# Abstract

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Title of Doctoral Thesis Design and Synthesis of New Compounds Active Especially against Multidrug-Resistant Mycobacterial Strains

This work is focused mainly on the field of searching of new potential antimicrobial agents, particularly against multidrug-resistant *Mycobacterium tuberculosis* strains, based on the modification of the salicylanilide (2-hydroxy-(*N*-phenyl)benzamide) group. The second research topic is a study of the rearrangement in the series of salicylanilide amino acids esters to form 2-hydroxy-*N*-[2-oxo-2-(phenylamino)-alkan-2-yl]benzamides called "diamides".

At the beginning, the thesis summarizes some basic facts about tuberculosis, a very important and serious bacterial infectious disease caused by *Mycobacterium tuberculosis* complex, about its treatment and related troubles and limitations. Proper attention is given for the problematic of drug-resistant tuberculosis, especially multidrug-resistant and extensively drug-resistant forms, their epidemiology and therapy.

The development of new drugs against multidrug-resistant tuberculosis is largely discussed, including requirements for them, recent advances and present status of some perspective molecules in clinical and preclinical stages of the investigation and the specific targeting on mycobacteria, a promising contemporary approach.

Salicylanilides have revealed a wide spectrum of pharmacological activities including antiviral, antifungal and antibacterial ones and their mechanism of the action seems to be complex and multiple; new targets have been found. The thesis describes some facts about biological properties of salicylanilides and their ester prodrugs, as well as about prodrug formation, which may bring some advantages, e.g. a higher activity, better passing through mycobacterial cell wall or a decreased toxicity.

In the experimental part, the rearrangement of the salicylanilide amino acids esters after liberation of amino group to form 2-hydroxy-*N*-[2-oxo-2-(phenylamino)-alkan-2-yl]benzamides ("diamides") was investigated to propose a new mechanism of the rearrangement *via* five-membered imidazoline ring.

The thesis reports the facts about salicylanilide modification based on the esterification *via* *N,N´*-dicyclohexylcarbodiimide as an activating agent or by direct acylation of salicylanilide salts. The synthesis, physico-chemical properties, spectral characteristics and mainly antimycobacterial, antifungal and antibacterial activities are presented and discussed. Five series of salicylanilide esters were designed, synthesized and evaluated – esters with *N*-acetyl-L-phenylalanine, benzoic acid, 4-(trifluoromethyl)benzoic acid, pyrazine-2-carboxylic acid and benzenesulfonic acid – and the series of sulfonamide derivatives containing 5-chlorosalicylamide and 5-chlorosalicylaldehyde scaffolds. Many of newly described derivatives exhibited excellent *in vitro* activity towards mycobacteria (minimum inhibitory concentrations ≥ 0.25 μmol/L, for drug-resistant strains even ≥ 0.125 μmol/L), Gram-positive bacteria and moulds (≥ 0.49 μmol/L). The structure-activity relationships are also discussed.

Moreover, some synthesized compounds were investigated as potential inhibitors of two essential mycobacterial enzymes, isocitrate lyase and methionine aminopeptidase. The results which revealed moderate inhibition of both these enzymes are reported.

**Keywords**

Antimicrobial agents; biological activity; multidrug-resistant tuberculosis; rearrangement; salicylanilides; salicylanilide esters; targeting.