5. SUMMARY

This thesis deals with the synthesis of antimicrobial active compounds from the group of salicylanilide derivates that were found to be highly antituberculosis active compounds against atypical and resistant strains of *Mycobacterium tuberculosis*. These derivates served as the starting substances for the synthesis of prodrugs of acetic acid and amino acid esters, with the aim to reduce toxicity and to optimize physico-chemical properties and transport to the site of action. The second group under investigation was new modifications of some contemporary antituberculosis drug (isoniazide and pyrazinamide), the combination of either of these two compounds with second active molecule through an easily splitting methane bridge, which together could serve as depot forms, after release of both parts they may act as synergists.

The outcomes of a literary search, that forewent synthesis, were published as survey articles in scientific papers. They deal with: a) cyclization forms of prodrugs (**paper I**), b) salicylanilides and their research trends (**paper II**) and c) isoniazide, its mechanism of activity and structure modifications published till now (**paper V**).

The main scope of the thesis is experimental parts whose results were parcially published and belong to enclosed articles (**paper III**, **IV** and **VI**). Unpublished experimental results from chapter 3, that is supplemented with the results of biological evaluation and experimentally determinate values of the liphophilicity parameter. After receiving biological evaluation results from TAACF, this part will be completed and sent to scientific journal.

Within the frame of this dissertation 126 compounds were prepared, 112 are original till this time in literature blank organic adducts. The structures of all prepared compounds were electronically checked by Beilstein Commander and SciFinder Scholar electronic version of Chemical Abstracts. Esterification of α-amino acids with salicylanilides was not easy. Firstly, esters of acetic acid and salicylanilides were prepared by various modifications of the reaction. These procedures were applied on several chosen amino acid. The method from peptide chemistry where carboxylic group of *N*-benzyloxycarbonyl-α-amino acid was activated with *N,N´*-dicyclohexylcarbodiimide was found to be optimal one. In some cases, unexpected benzoxazepine-2,5-diones were formed. Unfortunately, these compounds did not report any antitubercular activity. In those cases, where esterification of *N*-benzyloxycarbonyl protected α-amino acid was successful, the following amino group liberation led to an unexpected hydroxy-*N*-(phenylamino)-oxo-alkyl benzamides formed by quick nucleophilic attack of the free amino group on amidic carbonyl and rearrangement. Identical compounds were also the products of reaction where both protection of amino group and activation of carboxylic group of amino acid were done in one step by Leuchs anhydride preparation, which reacted with appropriate salicylanilides. This way confirms the predicted cyclic mechanism of rearrangement. *N*-Protected esters and hydroxy-*N*-(phenylamino)-oxo-alkyl benzamides have shown very high activity against atypical strains of *Mycobacterium*. This group is still under intensive research, where the aim is the preparation of di- respectively tri peptide esters.

The synthesis of isoniazid and pyrazinamide *N*-hydrazone derivates has started in the University of Ljubljana as an international *Socrates/Erasmus* program. The combination of INH and pyrazinamide with other antitubercular agents or other molecules which are *N*-nucleophiles has led to the preparation of depot forms with possible synergetic action known from the literature. Results of biological evaluation show this group of compounds as perspective for finding other possible combinations, which will be highly active against a wide range of Mycobacterial strains.