Abstract

Salicylanilides are an important class of aromatic compounds with a wide range of pharmacological activities, such as antibacterial, antifungal and anti-inflammatory, among others. Furthermore; several studies reported their potent antimycobacterial effect. Their activity results from multiple mechanisms. They are therefore interesting compounds for medicinal chemists. As phenolic-containing drugs, we hypothesised that a prodrug approach will make possible the improvement of the pharmaceutical, pharmacokinetic and/or pharmacodynamic properties of salicylanilides.

This thesis describes the development of new potential antimycobacterial active agents based on this group that have shown interesting antimycobacterial activity against *Mycobacterium tuberculosis*, and some atypical strains.

As the starting point for our research, the different strategies used in order to overcome the limited bioavailability of phenolic drugs were reviewed. Then new potentially antibacterial active prodrugs of salicylanilides, particularly *N*-benzyloxycarbonyl-ester and alkyl-carbamate derivatives of salicylanilide, active against *M. tbc.*, MDR-TB strains or non-TB strains such as *M. avium* and *M. kansasii*, were prepared. Finally the physicochemical and pharmacokinetic properties of the most active synthesised compounds were explored. For the esterification, *N*-protected, mainly *N*-benzyloxycarbonyl amino acids were used. The synthesised esters result to have comparable activity to the starting salicylanilides. In the course of our research, we have also investigated and elucidated the mechanism for the unexpected formation of novel seven-membered ring benzoxazepines and 2-hydroxy-*N*-(1-(oxo-(phenylamino)-alkan-2-yl)benzamides. All the studied alkyl-carbamate derivatives of salicylanilide exhibited higher activity against *M. tbc.*, *M. kansasii* and *M. avium* compared to the starting salicylanilide and promising activity against five MDR-TB strains, with MIC values between 0.5-2 □mol/L. Furthermore, as prodrug forms, they seem to fulfil better conditions than the corresponding synthesised esters, due to the increment of the half time of hydrolysis to several hours and to the stability in acidic environment.

All these results have been submitted, accepted or already published in several impact-scientific journals and presented in different national and international symposia.