Abstract

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Doctoral Degree Program Bioorganic Chemistry

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Title of Doctoral Thesis: Synthesis of purine derivatives with potential antimycobacterial activity

The theoretical part of this dissertation briefly summarizes basic data on tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis* (*Mtb.*). The epidemiological data published in the annual report of the World Health Organization (WHO) and the structure of drugs used in current TB therapy are presented. The theoretical section also gives a brief overview of the treatment of TB and mentions four compounds that are currently in phase II clinical trials. The mechanism of action of these compounds is inhibition of the enzyme decaprenylphosphoryl-β-D-ribose-2'-epimerase, specifically the DprE1 subunit. This enzyme plays an important role in the synthesis of mycobacterial call wall. The next part of the dissertation summarizes the results of research on potential purine and pyrrolo[3,2-*d*]pyrimidine antituberculosis agents derived from purine-6-one **10**. Compound **10** was identified as derivative with moderate anti-TB activity (MIC_{99}(*Mtb*) = 4 μM) in a high-throughput screening of pharmaceutical company Eli Lilly. Structure-activity relationships (SARs) in both purine and pyrrolo[3,2-*d*]pyrimidine series were elucidated with respect to antimycobacterial activity against *Mtb*, *Mycobacterium kansasii*, *Mycobacterium avium*, multidrug-resistant *Mtb* strains (MDR-TB) and extensively drug-resistant *Mtb* strains (XDR-TB). and is commented. Results of antibacterial activity (against G+ and G- bacteria), microsomal stability, plasma stability, cytotoxicity and water solubility of the most active compounds are also presented.

In the purine series, three most active compounds **53**, **61** and **72** with identical anti-TB activity (MIC_{99} = 1 μM) were identified. For the purine series, the exact mechanism of their antimycobacterial action, which is inhibition of the DprE1 enzyme, was determined. The

mechanism of action was determined by using whole-genome sequencing of *Mtb* strains resistant to compound **10**. In addition, target was confirmed by monitoring the fate of the radiolabeled substrate ([C^{14}]acetate) in *Mtb* in the presence or absence of compound **10**. In the pyrrolo[3,2-*d*]pyrimidine series, we identified two highly potent derivatives **151** and **152** with identical anti-TB activity against the drug-sensitive *Mtb* strain and also against MDR/XDR-TB strains (MIC_{99} = 0.06 μM). Moreover, these derivatives also showed significant activity against G+ bacteria. Furthermore, their cytotoxicity, solubility, microsomal stability was determined and their mechanism of action is currently being studied. The above-mentioned results led to the design of a new pyrimidine type of potential anti-TB agents, which is currently being intensively studied at our institute.