Abstract

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Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), remains a substantial global health burden. Regardless of the availability of modern antibiotics, the incidence and mortality rates of TB continue to advance due to drug resistance, highlighting the need for innovative strategies to combat this persistent disease.

The introductory part of this doctoral dissertation briefly describes TB and current challenges in the treatment regimen and the need for novel antibacterials to combat drug resistance. Mycobacterial prolyl-tRNA synthetase (mtProRS) is an essential enzyme for protein synthesis and it was our main cellular target of interest to combat TB, hopefully without effecting human homologue hsProRS. Aspartate decarboxylase (PanD) was an auxiliary target for some specific final compounds due to structural similarity to previously reported inhibitors.

The design of antimycobacterial compounds and potential inhibitors of mtProRS in this research was based on confirmed inhibitors of human-ProRS (hsProRS) containing a pyrazine scaffold. The final compounds exhibited firm structure-activity relationships (SAR) with MIC values ranging from 1.95–31.25 μg/mL against Mtb with consistent activities against multidrug-resistant Mtb strains with low toxicity on HepG2 cells. Several pyrazine-containing cyclic derivatives were synthesized within the main synthetic framework, and tested for antimycobacterial properties. These compounds are prone to metabolize to their respective pyrazinoic acids and open the door to the prodrug approach for PanD inhibitors. This dissertation also contains commentary on my work in complementary publications (co-author) focused on antimicrobial research.