

N-aryl oxamic acid based inhibitors for Mycobacterium Tuberculosis Protein Tyrosine Phosphatase B (mPTPB)

Selective nanomolar inhibitors of tuberculosis virulence factor mPTPB with excellent drug properties.

Purdue University researchers developed highly potent and selective compounds for use in the treatment of tuberculosis. Tuberculosis (TB), an infectious disease caused by the bacteria *Mycobacterium tuberculosis* (Mtb), is one of the top 10 causes of death worldwide. This morbid fact is accentuated by the increasing prevalence of drug resistant TB strains. Therefore, development of new TB therapeutic agents with novel targets and mechanisms of action is a necessity in curbing the death toll. To meet this need, Purdue University researchers have developed a series of oxamic acid-based inhibitors for the TB virulence factor Mtb protein tyrosine phosphates B (mPTPB), a protein critical to the survival of TB in infected macrophages. The best inhibitors displayed an inhibition constant of less than 20 nM and over 2000-4500 fold selectivity for mPTPB over a panel of 25 mammalian protein tyrosine phosphatases. Kinetic, molecular docking, and site-directed mutagenesis analysis confirmed these compounds as reversible inhibitors that bind the active site of mPTPB. Macrophages expressing mPTPB displayed an expected dose-dependent increase in immunostimulatory signaling pathways upon inhibitor treatment. These inhibitors' properties also make them promising drug candidates. They possess molecular weights less than 400 Da, drug-like aqueous solubility, and excellent metabolic stability providing a starting point for further therapeutic development of second generation mPTPB inhibitors for use as TB treatments.

Technology Validation: Kinetic, molecular docking, and site-directed mutagenesis analysis confirmed these compounds as reversible inhibitors of mPTPB. mPTPB expressing macrophages displayed enhanced immunostimulatory signaling pathways upon inhibitor treatment. In addition, investigations into the physiochemical properties of these inhibitors make them promising drug candidates for TB therapeutic development.

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Category
Biotechnology & Life
Sciences/Biomarker Discovery &
Diagnostics
Pharmaceuticals/Drug Discovery
& Development
Biotechnology & Life
Sciences/Analytical & Diagnostic
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Advantages

- Potent mPTPB Inhibitors
- Selectively inhibitors mPTPB over other Mammalian Tyrosine Phosphatases
- Excellent Physiochemical Properties

Applications

- Tuberculosis Treatment
- Combating Anti-microbial Resistance

Related Publication:

Highly Potent and Selective N-Aryl Oxamic Acid-Based Inhibitors for Mycobacterium tuberculosis Protein Tyrosine Phosphatase B

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