Potent and Selective Inhibitors against a Novel Tuberculosis Target Protein

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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.

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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People:

- Zhang, Zhong-Yin (Project leader)
- Ruddraraju, Kasi Viswanatharaju

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Contact OTC:

Purdue Office of Technology Commercialization
The Convergence Center
101 Foundry Drive, Suite 2500
West Lafayette, IN 47906

Phone: (765) 588-3475

Fax: (765) 463-3486
Email: otcip@prf.org