ACS Medicinal Chemistry Letters

In This Issue

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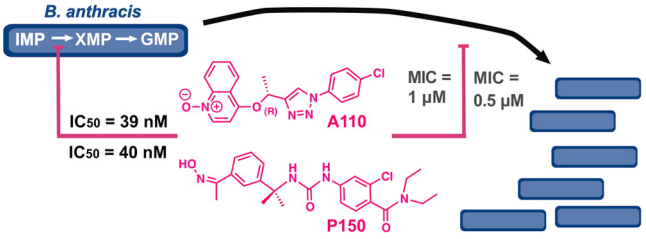
IMPDH AS AN ANTIBIOTIC TARGET (FEATURED LETTER)

The increasing obsolescence of the current antibiotic arsenal creates an urgent need for new drugs to treat bacterial infections. Inosine 5′-monophosphate dehydrogenase (IMPDH) is an attractive target for new antibiotics as this enzyme catalyzes the rate-determining step in guanine nucleotide biosynthesis.

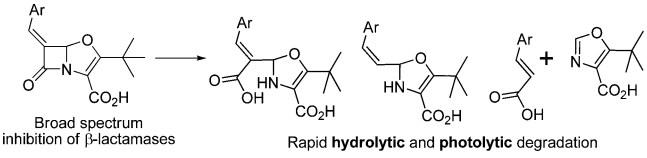
In this issue, Mandapati et al. (DOI: 10.1021/ml500203p) report that inhibitors of IMPDH have activity against the Gram-positive bacteria *Bacillus anthracis*, the causative agent of anthrax, and *Staphylococcus aureus*, which is a major cause of hospital-acquired infections. This Featured Letter demonstrates the potential of IMPDH as an antibiotic target and lays the foundation for the development of moderate spectrum antibiotics.



REVISITING AN OLD CLASS OF β-LACTAMASE INHIBITORS

The β-lactam antibiotic is one of the oldest and most widely used classes of antibacterial agents. However, resistance to the class is widespread, primarily due to expression of β-lactamase enzymes that proficiently hydrolyze the β-lactam to an inactive metabolite. Thus, resistance can be overcome by inhibition of the β-lactamase enzymes.

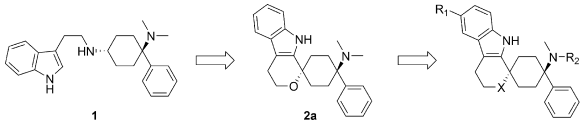
Herein, Miller et al. (DOI: 10.1021/ml5001855) revisit an old class of β-lactamase inhibitors, the oxapenems. The authors show that oxapenems possess an unprecedented broad spectrum of activity against all classes of modern serine β-lactamases, but suffer from poor stability as they are rapidly degraded by water or light. The authors developed computational models to predict the hydrolytic and photolytic stability, showing that these stability issues cannot be overcome. Thus, the activity of oxapenems makes them great tool compounds to study broad spectrum inhibition of β-lactamases, but their poor stability precludes their development into drugs.



THE DISCOVERY OF CEBRANOPADOL

Recent literature indicates that small molecules activating both nociceptin/orphanin FQ peptide (NOP) and mu opioid peptide (MOP) receptors may have therapeutic potential as innovative analgesics.

In this issue, Schunk et al. (DOI: 10.1021/ml500117c) present a series of studies aimed at optimizing a previously identified lead compound acting as mixed NOP and MOP agonist, and ultimately disclosing the discovery of a novel NOP and MOP agonistic compound, cepranopadol, which is currently in clinical development for the treatment of severe chronic nociceptive and neuropathic pain. Its superior efficacy and improved tolerability as compared to standard opioids are described.



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