ACS Infectious Diseases

In This Issue

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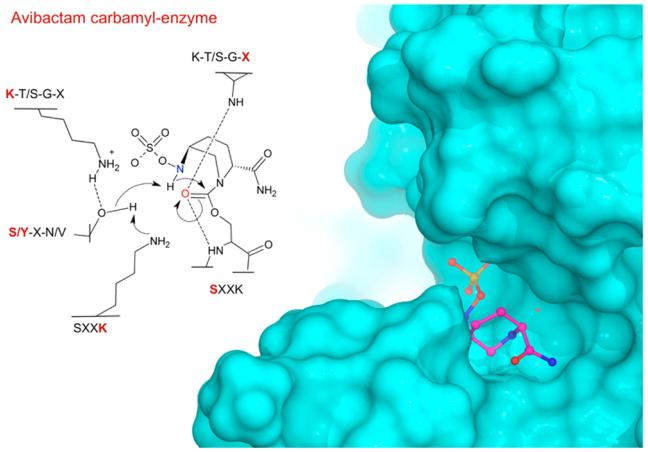
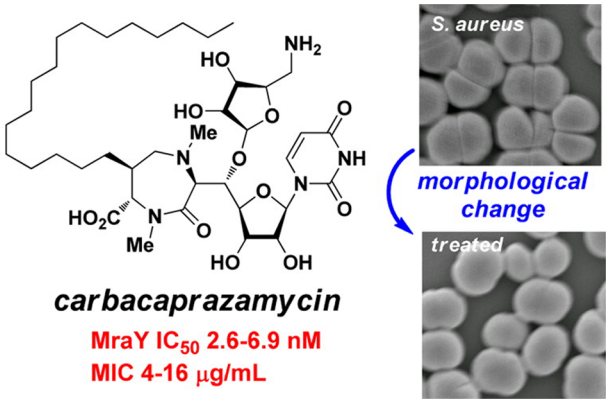
IDENTIFICATION OF AVIBACTAM'S MECHANISM OF INHIBITION



There are four distinct classes of β-lactamases (A–D), three of which are most clinically prevalent as they are involved in β-lactam hydrolysis, making serine β-lactamases a main threat to the most prominent class of antibacterial agents, the β-lactam drugs. Although combining β-lactams with β-lactam-based β-lactamase inhibitors has been somewhat successful, many pathogens have developed resistance to these combinations. Recent reports have demonstrated that avibactam, a non-β-lactam β-lactamase inhibitor antibiotic, utilizes a unique mechanism of inhibition.

In this issue, King et al. (DOI: 10.1021/id5b00007) address the molecular details of inhibition using structural, kinetic, and mutagenesis studies, revealing target active-site features that are likely responsible for the variable inhibition observed, and a possible mechanism for avibactam-mediated β-lactamase inhibition.

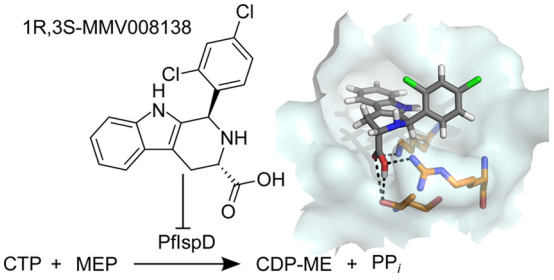
TOTAL SYNTHESIS OF CAPRAZOLE AND DERIVATIVES



Caprazamycin is a member of a class of naturally occurring antibiotics which have been shown to possess antimycobacterial activity against drug-susceptible and multi-drug-resistant *Mycobacterium tuberculosis* strains, which make caprazamycin and its derivatives of therapeutic interest. However, their syntheses are very onerous, and some moieties are unstable.

Here, Ichikawa et al. (DOI: 10.1021/id500047s) report the total synthesis of caprazole and palmitoylcaprazole using a less arduous strategy and show the antibacterial properties of these compounds against drug-resistant pathogens including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci* by interfering with an essential enzyme in peptidoglycan biosynthesis. Given the need for broad-spectrum antibiotics due to the rapid development of antibiotic resistance, these compounds could serve as leads for a novel antibacterial agent.

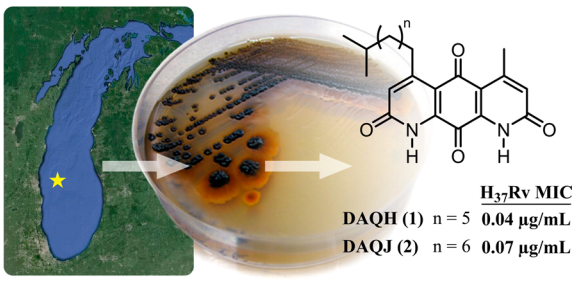
IDENTIFYING AN ANTIMALARIAL TARGET USING A MALARIA BOX COMPOUND



There remains a need to develop novel antimalarial therapies as drug resistance continues to emerge. Malaria enzyme IspD, found in the nonmevalonate isoprenoid biosynthesis pathway, was recently identified as an ideal target for an MMV Malaria Box compound. Targeting IspD is ideal because this pathway is not present in humans.

In this issue, Imlay et al. (DOI: 10.1021/id500047s) present data supporting the druggability of PfIspD using an MMV Malaria Box compound whose antimalarial action had been ascribed to PfIspD inhibition. The group also used enzymological studies and chemoinformatic modeling to explore the mechanism of inhibition of IspD. Our studies both chemically and genetically validate IspD as a target for the treatment of malaria and support MMV008138 as an antimalarial scaffold. With the rise and spread of artemisinin resistance, new therapies for malaria are a critical global health goal.

NATURAL PRODUCT CLASS OF TB INHIBITORS FROM A LAKE MICHIGAN-DERIVED BACTERIUM



Tuberculosis is caused by *Mycobacterium tuberculosis*, which usually attacks the lungs, but can also attack any part of the

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body such as the kidney, spine, and brain. If not treated properly, this disease can be fatal. With the rise of multidrug- and extensively drug-resistant strains, it has become a pathogen of global concern.

Featured on the cover is this study by Mullowney et al. (DOI: 10.1021/id5b00005), which highlights their effort in finding natural products from freshwater for novel molecule discovery. The group reports on the discovery of new bacterial compounds belonging to the diazaquinomycin class and their significant activity against the serious pathogenic bacterium *Mycobacterium tuberculosis*. The authors discuss the isolation and screening of a library of aquatic bacterial natural product fractions to subsequently determine the structure of two new natural products using spectroscopic data and the evaluation of biological activity. This report identifies a potent and selective class of *M. tuberculosis* inhibitors.

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