



ANTIBACTERIAL DRUGS

Pinpoint attack on resistance

Bacteria have developed numerous ways to resist the effects of antibiotics; in the case of vancomycin — currently one of the few antibiotics that is active against many potentially lethal bacteria — resistance can result from a small but crucial change in the structure of bacterial cell-wall precursors. Now, rationally counter-attacking by making a corresponding small change in the structure of vancomycin through chemical synthesis, Crowley and Boger have produced a compound that is active against vancomycin-resistant bacteria.

Vancomycin inhibits bacterial cell-wall biosynthesis by binding strongly to bacterial cell-wall precursors terminating in D-Ala-D-Ala. However, some bacteria have acquired the capacity to biosynthesize precursors that terminate in D-Ala-D-Lac — a deceptively simple change that greatly reduces the affinity of vancomycin for the modified cell-wall precursor by eliminating an attractive hydrogen-bond interaction between vancomycin and the precursor, and introducing a strongly repulsive interaction instead. This loss in affinity leads to a ~1,000-fold drop in antibacterial activity.

With the aim of counteracting this change, Crowley and Boger set out to construct a derivative of vancomycin in which a carbonyl group of the antibiotic that is involved in both the attractive hydrogen bond to D-Ala-D-Ala and the repulsive interaction with D-Ala-D-Lac was replaced with a non-polar methylene group. Because this group is in the core of the highly complex vancomycin structure, the authors used total synthesis to create the derivative, building on previous synthetic strategies for vancomycin and related antibiotics developed by the Boger group.

As anticipated, the new vancomycin derivative had considerably enhanced affinity for D-Ala-D-Lac, while affinity for D-Ala-D-Ala was reduced to around the same level owing to the loss of the hydrogen-bonding interaction. And excitingly, when tested against bacteria that resist vancomycin by switching from using D-Ala-D-Ala precursors to using D-Ala-D-Lac precursors in the presence of the antibiotic, the derivative showed significant antimicrobial activity reflective of its dual binding characteristics.

The activity of the derivative is not quite high enough for it to be considered a potential replacement for vancomycin, and the current need for total synthesis would also present considerable challenges for drug development. Nevertheless, both limitations are being addressed at present, and the results show that an understanding of the mechanisms of action of, and resistance to, antibiotics can be used to rationally design new agents that overcome resistance, and offer the hope of providing a fast track to much-needed new antibacterial drugs.

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