

Vancomycin Analog Shows Promise Pitted against Resistant Pathogens

Vancomycin-resistant *Enterococcus faecalis* is considered one of the most dangerous pathogens because of its

ability to withstand this antibiotic of “last resort.” However, a redesigned vancomycin analog could turn the tables on this pesky pathogen, effectively restoring sensitivity by molecularly tweaking vancomycin, according to a group of medicinal chemists at the Scripps Research Institute in La Jolla, Calif., and their collaborators.

“Our successful synthesis of a novel vancomycin analog could potentially lead to a new generation of antibiotics,” says organic chemist Dale Boger, who revamped vancomycin with the help of graduate student Brendan Crowley. “Vancomycin is a very complex molecule, yet we made a very subtle change.”

Based on a detailed understanding of what enables pathogens to develop resistance to this antibiotic, Boger and Crowley converted a vancomycin carbonyl group to a methylene. This seemingly simple chemical change required a challenging 24-step synthesis process to generate the new analog. “It’s amazing that one graduate student accomplished all of this,” Boger says. For the record, vancomycin is a

branched, tricyclic glycosylated peptide with a molecular weight of 1,449.

Vancomycin acts by mimicking, binding to, and blocking further synthesis of a peptidoglycan that makes up bacterial cell walls. Bacteria typically develop resistance to this antibiotic through a mutation that substitutes D-lactate for the usual D-alanine that is part of the peptidoglycan, reducing vancomycin’s effectiveness by about 1,000-fold. Boger attributes this reduced effectiveness to a loss in drug affinity through chemically localized destabilization caused by lone-pair electronic repulsion. Substituting a methylene for a carbonyl group in vancomycin counters this destabilizing lone-pair interaction, restoring binding affinity and biological activity that the parent antibiotic had lost.

Moreover, the methylene compound not only is effective against D-lactate-containing, vancomycin-resistant bacteria, but it also binds to and is effective against vancomycin-sensitive bacteria with D-alanine in their cell walls. When the researchers tested the methylene-containing analog against VanA *E. faecalis*, a highly resistant strain, they found that it proved 100-fold more powerful than vancomycin *in vitro*, whereas its potency was about 30-fold weaker against vancomycin-sensitive *E. faecalis*. Additional details are provided in the March 8, 2006, issue of the *Journal of the American Chemical Society*.

“For it to be an ideal drug, we need to increase its potency for sensitive bacteria at least 10-fold,” Boger says. Furthermore, because synthesizing the molecule from scratch is impractical for large-scale production, Boger plans to explore ways to produce the analog by chemically modifying vancomycin or by using a microorganism to generate the analog or a precursor.

Microbiologist Lynn Silver, an independent pharmaceutical consultant in Springfield, N.J., describes the redesign of vancomycin as “really excellent work.” The new analog, an agly-

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con, still needs to have its carbohydrate groups added, she notes, before the method is truly perfected. “The concept of changing the internal structure

of vancomycin is something that people have thought about for a long time,” she says. The approach changes the pathogen and drug interactions,

making it unlikely for resistance to occur again.

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