

Novel antibiotic deceives bacteria through mimicry

April 15 2021



Credit: Pixabay/CC0 Public Domain

Most antibiotics need to penetrate their target bacteria. But Darobactin, a newly discovered compound, is much too large to do so. Nonetheless, it

kills many antibiotic-resistant pathogens—by exploiting a tiny weak spot on their surface. Basel researchers have now revealed the amazing mechanism at play and thereby opened the door to developing completely new medicines.

An increasing number of bacterial pathogens are resistant to [antibiotics](#). And the most dangerous pathogens share a common feature: a double membrane that is difficult to penetrate. Even when antibiotic agents are able to break into this shell, the bacteria just pump them right out again. But a recently discovered compound called Darobactin manages to circumvent these protective measures and kill nearly all problem pathogens. Researchers have now been able to elucidate the mechanism of action in a project funded by the Swiss National Science Foundation (SNSF) under the National Research Program "Antimicrobial Resistance" (NRP 72).

Like a broken key

In a study published in *Nature*, the researchers describe how a deceptive maneuver enables Darobactin to work: its shape mimics a special three-dimensional structure normally found only in proteins produced by bacteria as building blocks for their outer membrane. The structure is the "key" for inserting the proteins into the outer shell at specific locations. Darobactin is a copy of this key. However, it does not act to penetrate the bacteria, but merely blocks the keyhole from the outside—like locking a door and then breaking off the key. As a result, the transport route for the bacteria's shell components is obstructed and they die.

Hard to detect by conventional means

Similar mechanisms are already known in microbiology and are used by other drugs. The targeted binding structures, or keyholes, are usually

quite large—at least in microbiological terms. In contrast, the target inhibited by Darobactin is very small and cannot be detected by conventional methods. At the same time, Darobactin is larger than most drugs and cannot get through the entry ports of the bacteria.

"At the beginning, we were puzzled by this," say Sebastian Hiller and Timm Maier of the Biozentrum of the University of Basel, the two principal authors of the study. Their teams immediately realized that Darobactin does not act inside the pathogens but rather on the surface. There it interferes with the function of a protein known as BamA, which plays a central role in the construction of the double-protective membrane. "But how exactly Darobactin interacts with BamA was completely unclear," says Hiller. It was only by combining several methods that the researchers finally identified the mechanism of action.

Spotting the perfect weak point

They discovered that Darobactin attacks a true Achilles heel of the pathogens: it binds directly to the most important site of BamA, the so-called backbone atoms. Because these atoms hold the protein together and determine its shape, it is nearly impossible to change them—though changing them would be the usual way for the [bacteria](#) to fend off a new antibiotic. In fact, Darobactin retained its effectiveness against all pathogens, for which Hiller and his team conducted laboratory tests that simulate resistance. In other words, the pathogens failed to change the broken lock.

Targeted drug development

These findings are a decisive step towards medical application, says infection biologist Dirk Bumann, who also conducts research at the Biozentrum in Basel. As co-director of the National Center of

Competence in Research (NCCR) "AntiResist," which like NRP 72 is funded by the SNSF, he closely follows activities in antibiotics research. "Identifying Darobactin's mechanism of action is a major achievement," he says, "because it will enable further targeted improvement of Darobactin and its development into an effective drug." That gives a boost to the long-cherished hope of finding a new generation of antibiotics to fight many of today's problem [pathogens](#).

More information: Hundeeep Kaur et al. The antibiotic darobactin mimics a β -strand to inhibit outer membrane insertase, *Nature* (2021). [DOI: 10.1038/s41586-021-03455-w](https://doi.org/10.1038/s41586-021-03455-w)

Provided by Swiss National Science Foundation

Citation: Novel antibiotic deceives bacteria through mimicry (2021, April 15) retrieved 27 April 2024 from <https://phys.org/news/2021-04-antibiotic-bacteria-mimicry.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.