Compound may help in fight against antibiotic-resistant superbugs

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North Carolina State University chemists have created a compound that makes existing antibiotics 16 times more effective against recently discovered antibiotic-resistant "superbugs."

These so-called superbugs are actually bacterial strains that produce an enzyme known as New Delhi metallo-β-lactamase (NDM-1). Bacteria that produce this enzyme are practically impervious to antibiotics because NDM-1renders certain antibiotics unable to bind with their bacterial targets. Since NDM-1 is found in Gram-negative bacteria like *K. pneumoniae*, which causes pneumonia, urinary tract, and other common hospital-acquired infections, it is of particular concern.

"To begin with, there are fewer antibiotic options for treating infections caused by Gram-negative bacteria than for those caused by Gram-positive bacteria," says Dr. Roberta Worthington, NC State research assistant professor of chemistry. "Gram-negative bacteria with the NDM-1enzyme effectively neutralize the few weapons we have in our arsenal, making them especially difficult, if not impossible, to treat with existing antibiotic therapy."

Previously, NC State chemist Dr. Christian Melander had found that a compound derived from a class of molecules known as 2-aminoimidazoles "recharged" existing antibiotics, making them effective against Gram-positive antibiotic-resistant bacteria like the Staphylococcus strain MRSA. So Melander, Worthington and graduate students Cynthia Bunders and Catherine Reed set to work on a variety of

the compound that might prove similarly effective against their Gram-negative brethren.

In a paper published in ACS Medicinal Chemistry Letters, Worthington and Melander describe a compound that, when used in conjunction with the antibiotic imipenem, increased the antibiotic's effectiveness against the antibiotic-resistant *K. pneumoniae* 16-fold. The researchers believe that these early results are very promising for future treatments.

"We've demonstrated that we have the ability to take out the scariest superbug out there," Melander says. "Hopefully further research will allow us to make the compound even more effective, and make these infections little more than a nuisance."

The research was funded by the National Institutes of Health and the Jimmy V Foundation. The Department of Chemistry is part of NC State's College of Physical and Mathematical Sciences.

More information: "Small Molecule Suppression of Carbapenem Resistance in NDM-1 Producing Klebsiella pneumoniae" *ACS Medical Chemistry Letters*.

Abstract
The already considerable global public health threat of multidrug-resistant Gram-negative bacteria has become even more of a concern following the emergence of New Delhi metallo-β-lactamase (NDM-1) producing strains of Klebsiella pneumoniae and other Gram-negative bacteria. As an alternative approach to the traditional development of new bactericidal entities, we have identified a 2-aminoimidazole-derived small molecule that acts as an antibiotic adjuvant and is able to suppress resistance of a NDM-1 producing strain of K. pneumoniae to imipenem and meropenem, in addition to suppressing resistance of other β-lactam nonsusceptible K. pneumoniae strains. The small molecule is able to

lower carbapenem minimum inhibitory concentrations by up to 16-fold, while exhibiting little bactericidal activity itself.

Provided by North Carolina State University