New compound shown to be as effective as FDA-approved drugs against life-threatening infections

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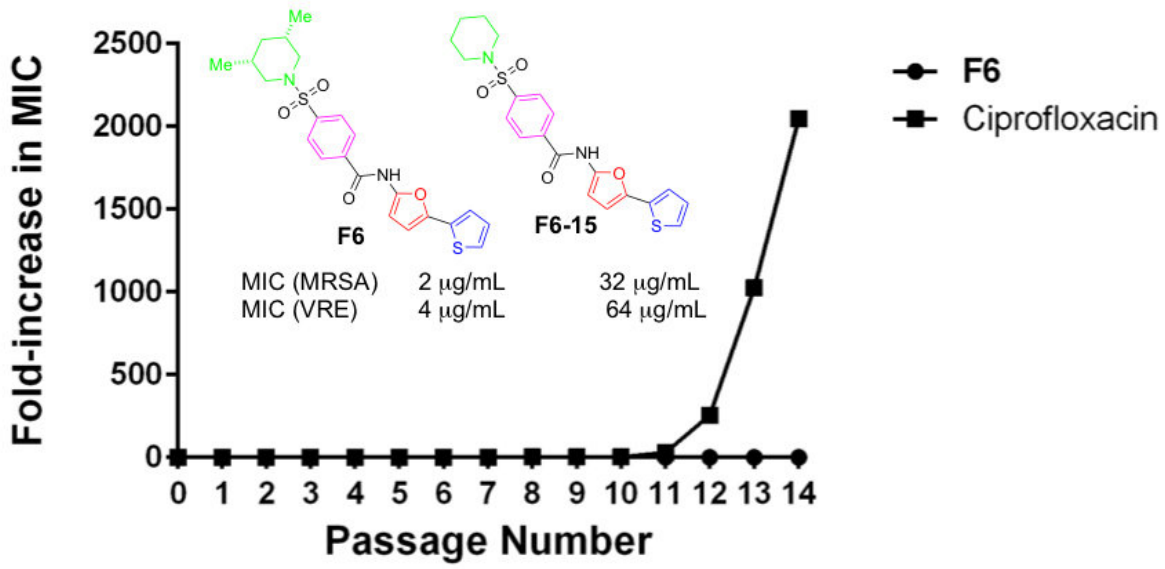

Purdue University researchers have developed a compound called F6 that is 16 times more potent than the closely related F6-15, highlighting the importance of piperidine modification on antibacterial activity. Credit: Purdue University

Purdue University researchers have identified a new compound that in preliminary testing has shown itself to be as effective as antibiotics approved by the Food and Drug Administration to treat life-threatening infections while also appearing to be less susceptible to bacterial

resistance.

The compound, called F6, has been potent against antibiotic-resistant pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), which is often found in hospitals and other health care settings, and vancomycin-resistant Staphylococcus aureus (VRSA), with vancomycin long considered a drug of last resort. The compound was tested against clinical isolates.

"This is very exciting," said Herman Sintim, drug discovery professor in Purdue's Department of Chemistry. "We are not the first to report of a new molecular entity that killed these drug-resistant pathogens. But what is unique about the compound that we found is that when we tried to generate resistance in the lab, we couldn't."

The results of the study were published Friday in the European *Journal of Medicinal Chemistry*.

Antibiotic resistance is a growing public health crisis. The World Health Organization has deemed antibiotic resistance one of the three greatest threats to human health because bacteria are becoming increasingly resistant and too few treatments are being developed. The Centers for Disease Control and Prevention reports that at least 2 million people a year in the United States become infected with bacteria resistant to antibiotics and at least 23,000 people die a year as a result. Studies have estimated that drug-resistant infections could be responsible for 10 million deaths a year worldwide by 2050.

Pharmaceutical companies have been reluctant to invest in antibiotics because it typically costs millions of dollars to develop a drug and the probability of bacterial resistance is high.

Purdue researchers identified F6 by screening a chemical library for

compounds with antibacterial activity. They tried to force bacteria resistance on F6, performing experiments to evaluate the ability of MRSA USA400 to develop resistance to F6 in vitro.

"The idea is that if you keep adding increasing concentrations to bacteria and then you keep regrowing the bacteria, after so many cycles you are going to develop resistance," Sintim said. "Scientists do this to figure out whether whatever they have created develops resistance quickly."

The minimal inhibitory concentration, or MIC, remained unchanged for F6 over nine passages and doubled on the10th passage. It then remained unchanged up to the 14th passage during a two-week period. By comparison, the MIC of the antibiotic ciprofloxacin tripled after the eighth passage and continued to rapidly increase to more than 2,000-fold by the 14th passage.

"We are not saying there will never be resistance to the F6 molecule or analogs thereof. What we are saying is that here is a new molecule that works and when we try to force resistance we couldn't generate resistance," Sintim said.

F6, which is nontoxic to humans and other mammals, works against bacteria in a group known as Gram-positive, but not against those that are Gram-negative. F6 was effective against MRSA, VRSA, Enterococcus faecalis, which lives in the human gut, vancomycin-resistant Enterococcus (VRE) and Listeria monocytogenes, often associated with unpasteurized dairy products.

Testing on mice also indicated F6 was as effective as fusidic acid in treating a wound infected with MRSA, further confirming its potent antibacterial effect.

More information: Clement Opoku-Temeng et al. N

-(1,3,4-oxadiazol-2-yl)benzamide analogs, bacteriostatic agents against methicillin- and vancomycin-resistant bacteria, *European Journal of Medicinal Chemistry* (2018). DOI: 10.1016/j.ejmech.2018.06.023