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ESKAPE active antibiotics avoiding resistance development

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Infections caused by bacteria with developed resistance to nearly all antibiotic classes are critically spreading. They represent a major cause of mortality and morbidity worldwide, and urgently require new compounds into clinical practice. Here we present cyclic pseudomimetic antibiotics bactericidal against ESKAPE human multi-resistant clinical isolates and stable in human sera. Modified, unnatural amino acids are required for stability and antibacterial activity on infected mice. These novel antibiotics trigger bacterial deformity, induce cell wall dissolution and alter membrane permeability. Two are active against methicillin- and vancomycin resistant *Staphylococcus aureus* on a mice sepsis model and also on a skin infection model. Upon prolonged exposure to the antibiotics *in vitro* and in infected mice, multi-resistant *S. aureus* did not develop resistance. Three-dimensional structures of the lead compound with and without modified amino-acids provide structural insights on its activity.

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