**Small Molecule Approaches to Disarming Antibiotic Resistance Mechanisms**

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Antimicrobial resistance (AMR) is one of the leading global health and development threats to date. It was estimated that in 2019 antibiotic resistance was responsible for 1.27 million deaths worldwide. In addition, AMR poses a considerable economic burden, being responsible for an estimated $4.7 billion in additional health care costs in the United States alone. Specifically, the rise in antibiotic resistance poses a substantial threat to public health with alarming rates of resistance among common bacterial pathogens. Many of the greatest healthcare threats are the so-called ESKAPE (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) pathogens. The ESKAPE pathogens have been identified as multi-drug resistance (MDR) bacteria that can rapidly “escape” antibiotic action. This presentation will present the development of molecules that break resistance to conventional antibiotics is members of the ESKAPE pathogens and can be used to either probe antibiotic resistance mechanisms or provide a powerful combination approach to the treatment of MDR bacterial infections. Specifically, the focus will be on the identification and subsequent exploration of a clerodane diterpene that reverses -lactam resistance in methicillin-resistance S. aureus (MRSA) and the development of a benzimidazole series of compounds that potently reverse resistance to colistin, the antibiotic of last resort for the treatment of MDR gram-negative infections, across multiple gram-negative species.