

Chemical Tools to Fight Multiresistant Bacteria

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Multiresistant bacterial pathogens such as Methicillin-resistant *Staphylococcus aureus* (MRSA) are responsible for a variety of severe infections that pose a significant threat to global health. To approach this challenge new chemical entities with an unprecedented mode of action are desperately needed. This presentation will cover our latest efforts to identify new anti-bacterial targets and corresponding chemical inhibitors. In the first part a proteome mining approach will be presented to identify cofactor-dependent enzymes as novel antibiotic targets. Small molecule cofactor mimics infiltrate the bacterial metabolic machinery leading to their incorporation in PLP-dependent enzymes. Their analysis via mass-spectrometry revealed the function of uncharacterized proteins in important bacterial pathways as well as the mechanism of action of known antibiotics.

In a separate approach we identified a new compound class that effectively kills MRSA strains. Chemical synthesis of improved derivatives led to the identification of an active molecule with nanomolar potency and suitable metabolic stability. Its mode of action was investigated by affinity based protein profiling (AfBPP). The compound stimulates a signal peptidase correlating with enhanced secretion of extracellular proteins. These included essential cell-wall remodeling enzymes whose dysregulation likely explains the associated antibiotic effects. Strikingly, the compound turned out to be a promising therapeutic candidate as it did not induce in vitro resistance, exhibited optimal per oral bioavailability and in vivo efficacy in a mouse infection model.