

Nitrogen Dense Heterocycles as Antibiotic Adjuvants

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The emergence of resistance to multiple antimicrobial agents in pathogenic bacteria has become a significant global public health threat. Drug resistant bacterial infections cause considerable patient mortality and morbidity, and rising antibiotic resistance is seriously threatening the vast medical advancements made possible by antibiotics over the past 70 years. The Centers for Disease Control and Prevention (CDC) estimates that over two million people acquire antibiotic resistant bacterial infections each year in the United States, and more than 23,000 people die as a result.

While the development of new antibiotics is one approach for the treatment of multi drug resistant pathogens, the fact remains that bacteria invariably develop resistance to any introduced therapy that relies solely upon a single bacteriostatic/bactericidal mechanism. For example, daptomycin was introduced into the clinic in 2003, and less than a year later the emergence of resistance was observed. As a result, alternative approaches to controlling bacterial infections are sorely needed and underexploited. One such approach is the identification of genes and pathways that play an important role in bacterial resistance to currently approved antibiotics, and the identification of small molecule adjuvants that target and block these pathways, thereby repotentiating the activity of the antibiotic when administered as a combination therapy. Efforts in our lab towards the development of such adjuvants based upon functionalized 2-aminoimidazoles will be presented, focusing on examples of breaking antibiotic resistance in multidrug resistant Gram-negative pathogens.