

Draining the Moat: A Natural Product-Inspired Approach to Combat Bacterial Biofilms

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The importance of natural products as anticancer and antibiotic compounds is undisputed due to their wide application as potent and effective pharmaceuticals. In contrast, the investigation of natural products toward biofilm-implicated bacterial infections, a rising concern among scientists and medical professionals, has been significantly understudied. Biofilm formation is the first line of defense for many bacteria similarly to how a moat protects a castle, and it is this defense that makes them so hard to combat. Bacterial biofilms have been estimated to cost society in excess of \$200 billion/yr, affecting everything from human health to water purification. Furthermore, biofilms are increasingly resistant to antibiotic treatment and are responsible for persistent infections. Over the past four years our group has looked to Nature for inspiring chemical scaffolds and have identified promising candidates that perturb bacterial biofilms. Two ongoing projects, which focus on two disparate premises, will be discussed in detail.

The development of species-specific, “narrow-spectrum” antibiotics would be of interest to both the medical and environmental communities as these compounds could serve as either novel therapeutics or chemical probes. Promysalin, a secondary metabolite of *P. putida* isolated from the rhizosphere microbiome, possesses unique species-specific activity against a range of *Pseudomonads*. Our group has recently completed the first total synthesis of the natural product, established the relative and absolute stereochemistry, and identified previously unknown anti-virulence properties. Current studies focus on decoupling the multitude of biological activities from the chemical architecture to better understand the mechanisms of action. In stark contrast, broad-spectrum antibiofilm agents are also of great need and of significant interest to both industrial and healthcare partners. Inspired by earlier reports that indicated that the polyamine norspermidine possessed interesting antibiofilm activity, our group sought to expand these findings to a class of quaternary ammonium compounds (QAC) constructed in collaboration with the Minbiole Group at Villanova University. Over the past two years we have synthesized and evaluated over two hundred synthetic analogs and identified some of the most potent biofilm-eradicating compounds to date. Furthermore, we have utilized these tool compounds to better understand how QAC-resistance protects pathogenic bacteria from society’s most ubiquitous antiseptics (i.e. Lysol). This led to the discovery of multiQAC scaffolds that are equipotent against both resistant and susceptible strains. The talk will highlight the conceptualization of the research hypotheses of both projects, the synthesis and evaluation of each class of analogs, and the current progress toward utilizing each set of molecules as chemical probes to better understand the chemical biology of bacterial biofilms.