Activity-Based Probes for Selective Targeting of Penicillin-Binding Proteins
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Antimicrobial resistance is a global health crisis, necessitating the discovery of new antibiotics and mechanisms for targeting resistant pathogens. Penicillin-binding proteins (PBPs) are a family of bacterial enzymes that are key components of cell wall biosynthesis and an important target of antibiotics such as penicillin and other β-lactams. Most microbial pathogens contain multiple PBP isoforms possessing high structural homology, making it difficult to target individual PBPs selectively. In order to fully understand bacterial cell growth and division, the individual roles of PBPs must be assessed in a spatial and temporal manner. To achieve this, we have developed several β-lactam and β-lactone activity-based probes that selectively target certain PBPs in E. coli, B. subtilis, and S. pneumoniae, allowing the visualization of both localization and activity of several PBPs at various stages of cell division. Development of the β-lactone scaffold is underway in an effort to further elucidate the roles and regulation of each individual PBP, which could lead to the discovery of new bacterial vulnerabilities that could be exploited in the fight against antimicrobial resistance.