Rational Design of Selective Adenine Based Scaffolds for Inactivation of Bacterial Histidine Kinases

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The exponential rise in antibiotic resistance and our inability to fight even common bacterial infections has prompted an urgent need for a new class of antibiotics that will not be susceptible to traditional resistance mechanisms. Most bacteria sense and respond to environmental changes through an autophosphorylation cascade using two-component systems (TCSs), which are composed of histidine kinases (HKs) and response regulators (RRs). Some TCSs or HKs have been implicated in the attenuation of virulence in multi-drug resistant microbes, such as SaeSR in *Staphylococcus aureus* and MtrAB in *Mycobacterium tuberculosis* but are not found to be essential for their growth. HKs are attractive antibacterial drug targets as multiple members are found in nearly all bacteria and inhibiting them simultaneously will block critical signaling pathways providing a novel strategy for antibiotic development. Most known HK inhibitors cause protein aggregation rather than inhibition and lack the potency desired in a drug candidate. We have identified nine small molecule-leads from a high-throughput screen that inactivate multiple HKs by targeting the conserved catalytic-ATP binding domain. Among these hits, a marked increase in potency was observed with adenine- or purine-like compounds. Currently, we are optimizing these leads by assessing the binding modes of inhibitors with a combination of molecular modeling, organic synthesis and biochemical assays. We have found that cyclic hydrophobic residues and deactivating groups on the purine ring substantially enhance inhibitor affinity. In addition to improved potency, efforts are underway to achieve selectivity over other ATP-binding proteins. Through a combination of docking studies, pharmacophore modeling and analog synthesis, we have identified chemical scaffolds that uniquely bind to bacterial histidine kinases. Such inhibitors provide the basis for novel antibiotics that will attenuate virulence and impede the development of resistance in harmful bacteria.