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β-lactam antibiotics are the most commonly prescribed antimicrobials. This class of antibiotics includes penicillin, cephalosporin, and carbapenem. In these drugs, there is a strained four membered ring with an amide bond known as a β-lactam ring that is important for the reactivity of β-lactams. β-lactam antibiotics act by inhibiting penicillin binding proteins (PBPs), an enzyme native to bacteria, and disrupt biosynthesis of the bacterial cell wall leading to cell lysis and death. Unfortunately, bacteria have developed mechanisms that eliminate the β-lactam's potency, subsequently leading to resistance.

Among the mechanisms bacteria employ for resistance, the expression of β-lactamases is the most common. These enzymes confer resistance to β-lactam antibiotics by hydrolyzing the lactam ring through a two-step acylation-deacylation mechanism. Once the β-lactam ring is hydrolyzed, it is inactivated. There are four classes of β-lactamases: A, B, C, and D. Classes A, C, and D employ a serine based mechanism to hydrolyze the β-lactam ring, while class B β-lactamases are metalloproteins that require zinc for their activity. Although all classes of β-lactamases are of clinical importance, class D β-lactamases, also known as OXAs, are the least understood. A particular subset of the class D enzymes is of particular concern: the carbapenem-hydrolyzing class D β-lactamases of which OXA-24 is a member. In OXA-24 mechanism, a carboxylated lysine is used to hydrolyze carbapenems, which is a troubling trend, as carbapenems are the newest antibiotics and often used as a last resort.

In an effort to combat antibiotic resistance against β-lactams, combination therapies consisting of a β-lactam antibiotic with a β-lactamase inhibitor have been employed. However, current β-lactamase inhibitors also contain a β-lactam ring. Due to this structural similarity to β-lactam antibiotics, inhibitors are also susceptible to existing resistance mechanisms of bacteria. Currently, there are no commercially available inhibitors for class D β-lactamases. The main objective of our research is studying class D β-lactamases to discover novel inhibitors that are structurally different from β-lactam antibiotics. In this effort, creating novel inhibitors would serve as an advantage against bacteria by circumventing the traditional β-lactam resistance mechanisms.

To discover a novel inhibitor for OXA-24, we took a structure-based approach to optimize an identified lead fragment. In the beginning stages, a molecular docking program, DOCK, identified a non-covalent fragment (Fragment #5) showing some signs of inhibition against OXA-24 with a Ki of 3.53 mM. For optimizing this lead, commercially available analogs were ordered and tested for inhibition against OXA-24. So far, nine analog compounds have been experimentally tested against OXA-24. Of the nine analogs, one inhibits with a Ki of 0.100 mM, showing improved binding affinity of 35 fold over the lead. As a continuing focus, we will look at further optimizing this series of novel inhibitors to improve binding, ultimately working towards developing a clinically-relevant novel inhibitor.