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Structure-Based Design and In Parallel Synthesis of Boronic Acid Inhibitors of AmpC β-Lactamase

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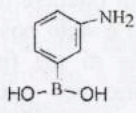
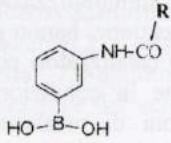
β-lactamases are the most common form of resistance to the penicillin and cephalosporin family of antibiotics. To overcome these enzymes, medicinal chemists have introduced β-lactam-based molecules that inhibit (e.g., clavulanate) or are stable to their action (e.g., aztreonam). These inhibitors and "β-lactamase-stable" molecules are themselves β-lactams, making it easier for bacteria to respond by adapting previously evolved mechanisms. Many bacteria are now resistant to these anti-resistance compounds[1].

Recent studies have found boronic acid derivatives to potently inhibit class A and class C of β-lactamases.[2] Presumably because these inhibitors do not have the β-lactam core structure, they were found to evade several of the mechanisms that are involved in resistance to more classic β-lactam-based inhibitors.

Starting from the crystal structures of the 3-aminophenyl-boronic acid (**1**) bound to AmpC β-lactamase[3,4], we designed and synthesized 28 new carboxamide (**2**) and sulfonamide boronic acid derivatives (**3**). In the attempt to rapidly optimize the activity, we used in parallel synthetic techniques, including a polymer-supported base in tandem with aminomethylated polystyrene as scavenger.



(1)



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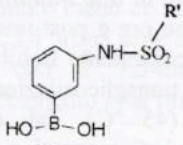

(3)

Among the 28 derivatives synthesized several molecules showed sub-micromolar inhibition constants (K_i) vs AmpC β-lactamase. The most active had a K_i of 0.040 μM, 175-fold better than the lead compound. Flexible ligand docking suggested a binding conformation for this inhibitor, in the R1-cleft of AmpC. A second focused library of twelve molecules was synthesized to improve solubility, inhibition, and to explore the SAR of the series. Subsequently, the x-ray structure of the best inhibitor in complex with AmpC was determined to 1.94 Å resolution, providing a template for further design in this new series of β-lactamases inhibitors [5].

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