Novel Boronic Acid Inhibitors of the Class D β-lactamase OXA-24

The most common approach to treating a bacterial infection is the use of β-lactam antibiotics. However, antibiotic resistance has become a challenge in the clinical setting. The primary mechanism of bacterial resistance is the destruction of the β-lactam ring via hydrolysis of the cyclic amide by β-lactamase enzymes. To combat this hydrolysis mechanism, inhibitors (such as clavulanic acid, tazobactam, and sulbactam) have been developed to inhibit the β-lactamase and allow β-lactam antibiotics to continue to be useful. Class D β-lactamases – such as OXA-24 – are known to hydrolyze the last-resort carbapenem antibiotics and are not inhibited by current clinical inhibitors, creating a need to discover an inhibitor for this class of enzymes. Boronic acids are novel compounds that lack the classic β-lactam ring, and they have been known to inhibit class A and C β-lactamases. Ten boronic acid compounds were tested for inhibition of OXA-24, resulting in K_i values ranging from 23 to 1500 μM. Crystal structures of OXA-24 in complex with boronic acids were obtained, which will aid in studying the structural relationship of these inhibitors in the active site. Boronic acids show a promising future for the inhibition of class D β-lactamases.

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