Crystallographic Studies of Novel Inhibitors of β-Lactamases

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Bacterial expression of β-lactamases is the most widespread resistance mechanism to β-lactam antibiotics. There is a pressing need for novel, non-β-lactam inhibitors of these enzymes [1]. Our efforts to overcome bacterial resistance mechanisms have been directed towards novel, non β-lactam inhibitors of AmpC β-lactamase, a class C enzyme responsible of resistance to antibiotics treatment in gram-negative bacteria.

Through a structure-based approach, we discover novel inhibitors for this enzyme, with covalent mechanism of action such as boronic acid derivatives and with no-covalent, competitive mechanism of action, such as thiophene-2-carboxylic acid derivative [2].

In one case we were able to extend the inhibitory activity towards class A β-lactamases, obtaining a broad spectrum, highly potent inhibitor.

Some inhibitors were active in cell culture, reversing resistance to the third generation cephalosporin ceftazidime in bacterial pathogens expressing AmpC and did not up-regulate β-lactamase expression in cell culture.

The structure-based design, synthesis, biological evaluation and the crystallographic studies of such novel inhibitors will be described.

[1] Cosgrove S., Carmeli Y., *Clin. Infect. Dis.*, 2003, **36**, 1433-1437. [2] Tondi D., Morandi F., Bonnet R., Costi M. P., Shoichet B. K., *J. Am. Chem. Soc.*, 2005, **127(13)**, 4632-4639.

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