

MS9-P7 Novel inhibitors of beta-lactamase

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Beta-lactam antibiotics represent the most widely used group of antibacterial agents with broad-spectrum activity. However, bacteria can develop antibiotic resistance, often mediated by beta-lactamases. These enzymes render antibiotics inactive through the hydrolysis of the beta-lactam ring, resulting in the degradation of the drug. This process can be inhibited, but due to frequent mutations in the active site of the enzyme, inhibitors become ineffective at an accelerating rate. Thus, the identification of alternative means of beta-lactamase inhibition and the development of improved inhibitors is a priority.

To address this challenge, we used a computational approach specifically developed for this purpose, ViCi (<http://www.embl-hamburg.de/vici>), which uses a number of mathematical descriptors of molecular shape and charge distribution in a search for compounds that are similar to a template inhibitor. We screened a database of eight million compounds using four known low-affinity beta-lactamase inhibitors as a starting point. Recombinant TEM-171 beta-lactamase was expressed and used to kinetically assay the top 500 compounds from the ViCi screening. The best lead inhibitor, targeted to the allosteric site of TEM-171, had an order of magnitude higher in vitro affinity compared to the known inhibitors.

Using these potential novel inhibitors, we synthesised a number of chemically modified compounds; aiming for their higher activity, solubility and reduced toxicity compared to the known inhibitors. We have identified several new derivative compounds with promising characteristics.

Moreover, we have initiated X-ray crystal structure determination and have determined the structure of recombinant TEM-171 to a resolution of 2.0 Å. A series of inhibitor soaks have been initiated to decipher the mode of ligand binding.

Keywords: non-covalent inhibitors, beta-lactamase, computational drug design

MS9-P8 The crystal structure of a common allergen in complex with its specific patient-derived antibody

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In recent decades, the incidence of allergy, an immune disorder mediated by immunoglobulin E (IgE), has become more common¹. According to the European Federation of Allergy (EFA), the incidence of allergy in Europe has rapidly increased, with allergic rhinitis affecting approximately 20% of the population². More than 50% of these cases are associated with allergy to grass pollen³. The symptoms of this disease not only cause discomfort to patients, but may also lead to fatal anaphylaxis. The aetiology of allergy is debated, but it is widely accepted that the initiation of the allergic response involves the crosslinking of IgE with its high affinity receptor complexes on mast cells by allergens, which requires at least two epitopes on the allergen. This triggers the early phase of the allergic reaction, involving mast cell degranulation and the release of mediators. Interactions between IgE and allergens are poorly understood, mainly due to insufficient structural information on IgE-allergen complexes. A structure-based strategy provides insights into the nature of allergens and promotes engineering of new hypoallergenic proteins for therapeutic intervention in allergic disease. To that end, we present here the crystal structure of a grass pollen allergen *Phl p 7* and its complex with a specific Fab. The allergen has undergone conformational changes, which did not allow for a straightforward molecular replacement structure determination, making the project crystallographically challenging.

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