Acinetobacter baumannii is one of the species most commonly isolated from clinical specimens and it can be the cause of severe and sometimes lethal, nosocomial infections. It colonizes patients in Intensive Care Units and contaminates inanimate hospital surfaces [1].

Antibiotic resistance to clinically employed β-lactam antibiotics currently is recognized as the most important risk factor for multiresistance. Described resistance mechanisms include hydrolysis by β-lactamases, alterations in outer membrane proteins and penicillin-binding proteins, and increased activity of efflux pumps.

β-lactamases can be divided into four classes (A, B, C, and D) according to their sequence similarities [2]. On the basis of their different catalytic mechanisms, two groups have been established. β-lactamases of classes A, C and D own in its active site serine groups, while class B β-lactamases are metalloproteins that require zinc for their activity. Metallo-β-lactamases often have mosaic structures with additional domains but in general all of them are small enzymes sharing a common four-layer αββα motif with a central β-sandwich and two α-helices on either side. This motif has an intrinsic metal-binding site located at an edge of the β-sandwich and it is occupied by a divalent zinc ion having a tetrahedral array of three histidines and a water molecule. The importance of the zinc ion to β-lactam substrate binding is unquestionable [3].

We present the three-dimensional structure of a new zinc metallo-hydrolase enzyme, extracted from a clinically epidemic multidrug-resistant *A.baumannii* strain. Crystals were grown using the vapour diffusion technique. They belong to space group P1, with cell dimensions a=60.04, b=64.55, c=69.37 Å; α=82.12, β=81.46, γ=75.89 º and four molecules in the asymmetric unit, which diffracted beyond 2.4 Å. We solved the phases by a SAD experiment. Our goal is to understand the role of the two metals ions in the catalytic pathway and get some insights into the mechanism of metallo-β-lactamase hydrolysis. This information could serve as a starting point for the development of new antimicrobial agents given that there is clearly a specific need for new potent class B β-lactamase inhibitors to bridge the existing therapeutic void.

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Keywords: A. baumannii, β-lactamase, zinc.

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Fragment-based drug discovery applied to heat shock protein 90 (HSP90)

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Heat shock protein 90 (HSP90) is a chaperone which guides the folding of proteins into functional configurations affecting stabilisation and activation. Many of these proteins are oncogenes regulating tumour cell growth, survival and apoptosis. Therefore, inhibitors of HSP90 are potentially useful as chemotherapeutic agents in cancer. This poster describes an application of Astex Pyramid™ fragment screening to the ATPase domain of HSP90. The screening identified an aminopyrimidine with affinity in the high micromolar range and subsequent structure-based design allowed its optimisation into a low nanomolar series with good ligand efficiency. A phenolic chemotype was also identified with affinity close to one millimolar. This fragment was optimised using structure based design into a resorcinol lead which has sub-nanomolar affinity for HSP90, excellent cell potency, and good ligand efficiency. This fragment to lead campaign improved affinity for HSP90 by over 1,000,000 fold with the addition of only 6 heavy atoms. Subsequent lead optimisation of the resorcinol lead produced AT13387, a compound that is now in clinical trials for the treatment of cancer.

Keywords: drug, fragment, chaperone

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Structure and binding analysis of active site inhibitors targeting HIV-1 RNase H

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Human immunodeficiency virus (HIV-1) reverse transcriptase (RT) is a multifunctional enzyme containing both polymerase and RNase H functionalities. RNase H is required to generate specific RNA primers and subsequently break down intermediate RNA/DNA hybrids during reverse transcription. This activity is dependent on binding of two divalent metal ions in the active site. Pyrimidinol carboxylic acid and *N*-hydroxy quinazolinedione inhibitors were designed to coordinate these metal ions at the active site. High resolution (1.4Å-2.1Å) crystal structures were determined with the isolated RNase H domain and RT that permit accurate assessment of the metal and water environment. The geometry of the metal coordination suggests that the inhibitors mimic a substrate state prior to phosphodiester catalysis. The inhibitors also engage His539 *via* π stacking interactions and form a polar interaction with Arg557. Surface plasmon resonance studies confirm metal-dependent binding to RNase H and demonstrate that the inhibitors do not bind at the polymerase active site of RT. Comparative analysis of human RNase H1 bound to RNA/DNA substrate suggests that there are differences in the position of the equivalent residues at His539 and Arg557 in human RNase H1. This provides a rational for why these inhibitors selectively target the HIV enzyme over the human enzyme. Additional evaluation of the active site reveals an open protein surface with few additional interactions to optimize inhibitors.

Keywords HIV, antiviral therapy, reverse transcriptase

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Structural basis of fosmidomycin's action on *Plasmodium falciparum*

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The human malaria parasite *Plasmodium falciparum* is responsible for the death of more than a million people each year. The emergence