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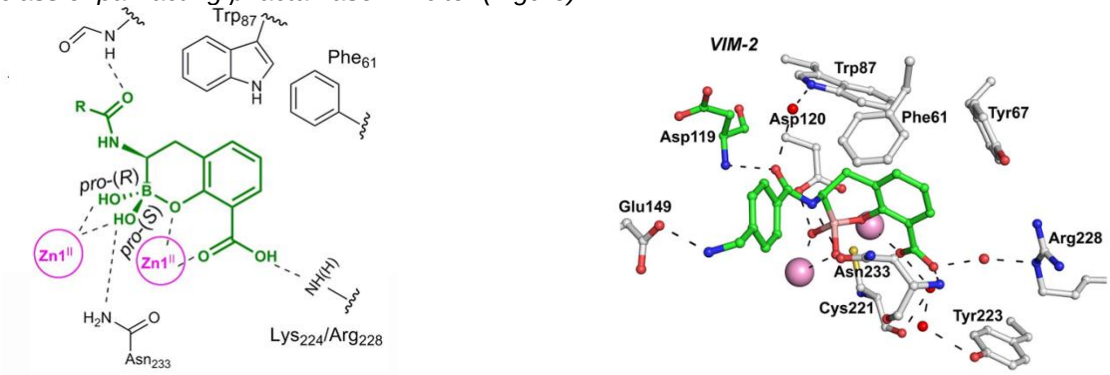
This proposal is representative of the projects currently on offer in our group. For more details of active research projects, please visit the Research and Publications sections of our webpage at: http://www.chem.leeds.ac.uk/People/Fishwick.html

New inhibitors of beta-lactamases- fighting antimicrobial resistance

The purpose of this project is to use computational drug design, medicinal chemistry, and biological assays, to identify new potential anti-infective drug leads. The position will suit students with a strong interest and background in synthesis who would also like to develop skills in computational molecular design and molecular and cellular biology. You will work in a vibrant, multidisciplinary research group consisting of medicinal chemists and molecular/cell biologists.

Recent surveillance data indicates that the incidence of serious Gram-negative infections are on the rise. Unfortunately, treatment options for these Gram-negative infections using β-lactam antibiotics has been seriously compromised by the presence of serine- and/or zinc metallo- β-lactamases in clinical strains of *E. coli, K. pneumoniae, A. baumannii* and *P. aeruginosa*. β-lactamases inactivate β-lactam antibiotics by hydrolyzing the β-lactam ring within the antibiotic, either via a serine protease or zinc metallo-protease mechanism. In fact, there are over 1800 known β-lactamases that can reduce or even eliminate the efficacy of most β-lactam antibiotics via lactam bond hydrolysis. To restore the activity of a β-lactam antibiotic against a Gram-negative strain containing one of these resistance-causing β-lactamases, the antibiotic is combined with a β-lactamase enzyme inhibitor. While this combination therapy approach has worked for many years, there are now strains that are completely resistant to available β-lactam/β-lactamase inhibitor combination therapy. There is therefore an urgent need for more treatment options to address this rising global health threat. *Recently, we have produced the cyclic boronate inhibitors (CBIs) as a new class of pan-acting β-lactamase inhibitor (Figure).*



(a) (b)

Figure. Crystal structural data for a CBI bound within the VIM-2 metallo β-lactamase (a*) summary of contacts between inhibitor and protein* (b) close-up view of crystallised inhibitor showing contacts to metal ions.

This project will build upon our knowledge of b-lactamase enzymes to develop highly potent and selective β-lactamase inhibitors to combat the threats posed by multidrug resistant bacteria and particularly those belonging to the Gram negative organism group.

The project will allow you to develop expertise and skills in a number of key areas linked to synthetic organic and medicinal chemistry including advanced aspects of structure-based molecular design, efficient synthesis of compound libraries to enable biological screening, the use of efficient assay methods to establish biological activity of inhibitors, and the use of ADMET data to improve drug likeness.

References

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