Prof Colin Fishwick

c.w.g.fishwick@leeds.ac.uk
phone: 0113 343 6510

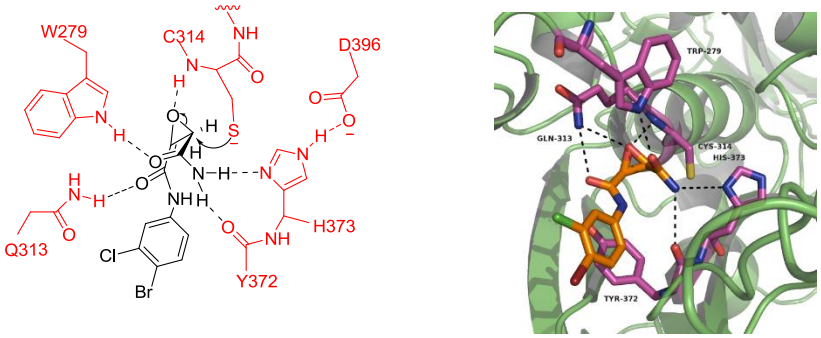
This proposal is representative of the projects currently on offer in our group. For more details of active research projects, please visit the Research and Publications sections of our webpage at: http://www.chem.leeds.ac.uk/People/Fishwick.html

Achieving the "Holy Grail" in the prevention of thrombosis

The purpose of this project is to use computational drug design, medicinal chemistry, and biological assays, to identify new potential drug leads for the treatment of thrombosis. 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.

During vascular injury blood clots are generated to stem bleeding, a process known as haemostasis. In some pathological conditions, inappropriate generation of clots occur (thrombosis) that can yield fatal outcomes such as myocardial infarction (heart attacks), ischaemic strokes, deep vein thrombosis and pulmonary embolism. The first phase of blood clot formation involves the activation and aggregation of platelets followed by activation of the coagulation system that results in a fibrin mesh that serves as a scaffold to help stabilise the forming blood clot. There are two ways to prevent blood clots and these are anti-platelet agents that inhibit the activation or aggregation of platelets and anticoagulants that prevent fibrin formation.

All anticoagulants and anti-platelet therapeutic on the market have an inherent risk of bleeding. The dogma to date has been that to achieve an anti-thrombotic action these drugs are balanced by a potential risk of bleeding. This project challenges this dogma by attempting to develop novel therapeutic anticoagulant oral small molecule compounds based on a principle that has shown proof of concept of achieving anticoagulation with minimal risk of bleeding using an antibody and peptide based approach.



(a) (b)

Figure. An example of recent modelling work performed at Leeds to produce novel inhibitors of blood coagulation enzymes (a) schematic of inhibitor showing predicted contacts to protein residues (b) graphic of predicted protein-inhibitor complex

The key aims of this project are;
1) to use in silico computational chemistry to design novel inhibitors to the target of interest (see Figure for example)
2) to employ medicinal chemistry to synthesis novel small molecules
3) to test the synthesised small molecules in models of coagulation and thrombosis.

.

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

David A. Lane, Helen Philippou, James A. Huntington. Directing thrombin, *Blood*, 2005, **106**, 2605 – 2612.

For a recent example of this approach in the development of antithrombotics, see Craig A. Avery, Richard J. Pease, Kerrie Smith, May Boothby, Helen M. Whitwood, Peter J. Grant, and Colin W.G. Fishwick. (±) cis-Bisamido epoxides: A novel series of potent FXIII-A inhibitors. *Eur. J. Med. Chem.*, 2015, **98**, 49 – 53.