Identification and optimisation of small molecule inhibitors as chemical tools

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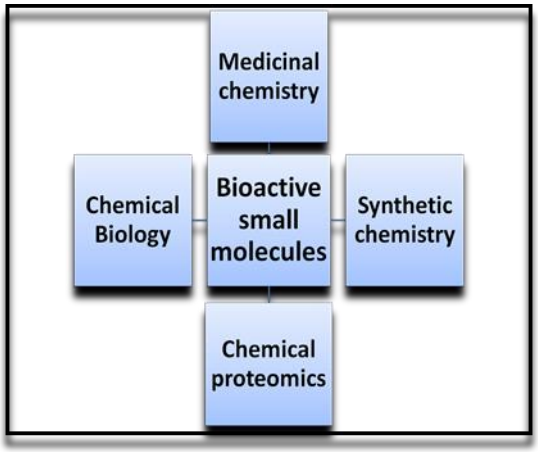
Introduction

Our group is interested in the design, synthesis and optimisation of small molecules for therapeutic application or their use in the elucidation of biological function. By combining tools and techniques in medicinal chemistry, computer-aided drug design and chemical genetics we identify and optimise small molecules as key modulators of specific biological function to support both basic target validation of proteins implicated in disease and as potential starting points for future drug discovery.



The group has capabilities in a number of areas for which bioactive molecules may be identified, optimised and/or targeted, including:

Medicinal chemistry, probe synthesis and chemical genetics

- Bio-targeted small molecules
- Targeted imaging agents
- Small molecule microarrays

Computational-aided drug design

- Ligand- and structure-based design
- Virtual screening

High-throughput screening

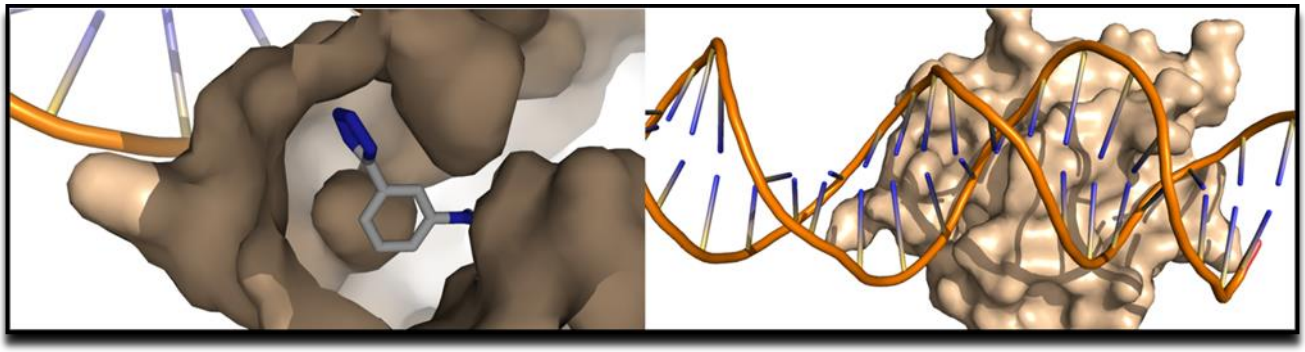
- 36k member diverse lead-like small molecule library
- 4k drug library for repurposing of chemical leads
- Fragment library
- Assay transfer/assay development expertise – to 384-well format incorporating a variety of assay formats and readouts

The activities are managed through the Medicinal Chemistry and Chemical Biology (MCCB) Technology Group as part of the Biomedical Health Research Centre (BHRC) at Leeds. Several projects in the cardiovascular and cancer disease areas have been progressed during 2014.

Development of a novel anticoagulant with minimal bleeding risk

We have identified potent, novel small molecule inhibitors of a key enzyme involved in regulation of the coagulation cascade with exceptional *in vivo* efficacy. The inhibitors have been

identified by a number of parallel approaches incorporating virtual drug design, chemical synthesis and HTS of drug-like small molecule libraries and fragments. Presently, we are optimising the inhibitors for target potency, specificity and drug-like physicochemical properties using iterative rounds of medicinal chemistry development and screening using a panel of orthogonal bioassays. *with Helen Philippou, Robert Ariens, Colin Fishwick*



Identification of novel inhibitors of TRP ion channel function as potential therapeutics
We have identified a series of novel inhibitors of a number of TRP ion channels implicated in cardioprotection. The compounds have been developed as agents to support detailed understanding of the role of the protein target and its relevance in disease as well for future development of small molecule-based therapeutics. These dual aims are being achieved through iterations of directed chemical synthesis aided by pharmacophore-based design and screening *via* a panel of orthogonal assays. The current inhibitors are novel, potent and selective and demonstrate lead-like properties consistent with the potential for further development. *with Lin-Hua Jiang, David Beech, Rao Sivaprasadarao*

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