EPSRC Centre for Doctoral Training (CDT) in Molecular Sciences for Medicine (MoSMed)

Leveraging conformational control to access sp^2-rich 3D platforms for drug discovery

Newcastle University, School of Natural & Environmental Sciences

Supervisory Team

- **Dr Roly Armstrong (Newcastle University)**
- **Prof. Mike Waring (Newcastle University)**
- **Prof. AnnMarie O'Donoghue (Durham University)**

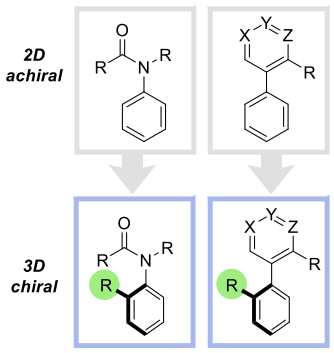
Project overview/context

The project will explore amides and biaryls, which are ubiquitous motifs in the pharmaceutical industry. We generally think of these molecules as flat, and two-dimensional, but in certain cases they can adopt a twisted, three-dimensional shape. Controlling the conformational preference of these molecules provides a unique opportunity to increase their binding affinity, and we want to study axially chiral analogues in which conformation is completely locked. The project will involve exploring new methods for the synthesis of these exciting new 3D templates, studying their 3D shape, and probing their ability to interact with biological targets (e.g. SARS-CoV-2 M^{pro}).

Research Project

21st century medicinal chemistry is increasingly seeking innovative 3D templates for drug discovery, which enable an "escape from the flatland" into unexplored areas of three-dimensional chemical space. This project will explore an exciting new approach by taking advantage of sp^2-rich amides and biaryls. These motifs are already ubiquitous in the pharmaceutical industry, but generally adopt a planar geometry. However, introducing a bulky *ortho*-substituent can "three-dimensionalise" such molecules, causing them to adopt a twisted (axially chiral) geometry, sufficient for the two enantiomers to be separable and stable. This is an ideal platform for the development of new 3D medicines, as it has the potential to produce structurally well-defined molecules with an enhanced enthalpic and entropic preference for binding to a given target. The aim of this project is to find new ways to make axially chiral templates for drug discovery, which will be showcased in the development of new 3D protease inhibitors targeting COVID-19.

Project overview: *ortho-substitution to access new 3D fragments for drug discovery*



The project will begin by developing efficient new synthetic chemistry to stereoselectively access *ortho*-substituted amides and biaryls. We are particularly interested in learning how to introduce medicinally relevant *ortho*-substituents, which have seldom been investigated in this context. A variety of different synthetic approaches will be employed to target these molecules as a single stereoisomer, including resolution-based methods as well as asymmetric reactions mediated by a chiral catalyst. The student will be trained to use a variety of specialized techniques and equipment to analyze the configurational stability and 3D shape of the products.

This chemistry will then be applied by the student to prepare analogues of an emerging class of amide-

based SARS-CoV-2 M^{pro} inhibitor. These inhibitors are able to block the processing of polyproteins produced by viral RNA translation, which is an important step in SARS-CoV-2 replication, and preparing more potent analogues holds potential for the development of new treatments. A library of *ortho*-substituted amides will be prepared, and their activity against SARS-CoV-2 M^{pro} will be assessed. A particular emphasis will be placed upon investigating the effect of their 3D shape and stereochemistry upon their potency.

Training & Skills

The project will provide in-depth training in the important fields of organic synthesis, molecular design, and medicinal chemistry, which will be highly desirable for a future career in medicinal chemistry or academia. The work will have a particular focus upon asymmetric synthesis, and 3D compound design, which are very important areas in the pharmaceutical industry.

The supervisory team will provide state-of-the-art training in the fields of organic synthesis and medicinal chemistry (at both Newcastle and Durham Universities). This will include expert training in routine synthetic chemistry techniques, as well as a variety of specialised analytical methods to study axially chiral molecules.

Co-funding for this project has been kindly contributed by the Bill and Milica Beck PhD Endowment Fund.

Further Information

Enquiries should be sent to Dr Roly Armstrong, roland.armstrong@newcastle.ac.uk, Tel. 01912080012

How to Apply

You must apply through the University's online application system.

When applying to Newcastle University please select the Course Code **8207F (PhD in Molecular Sciences)** You will need to:
- Insert the **programme code 8207F** in the programme of study section
- Select '**PhD in Molecular Sciences'** as the programme of study
- Input (only) the **studentship reference code (e.g. 22_15)** that you are applying for in the studentship/partnership reference field when prompted (all codes are outlined in the individual project adverts and can be found on the MoSMed website: https://research.ncl.ac.uk/mosmed/phdstudentships/)
- Attach all documents that are requested including a CV and cover letter. The cover letter must **clearly** state the project reference code, the full title of the studentship and state how your interests and experience relate to the project
- Attach degree transcripts and certificates and, if English is not your first language, a copy of your English language qualifications

Should you have any queries regarding the application process to Newcastle University please contact Selina McCarthy, MoSMed CDT Manager: Selina.McCarthy@newcastle.ac.uk or email mosmed.cdt@newcastle.ac.uk

Within the MoSMedCDT we are committed to building a diverse community based on excellence and commitment. To that end in our recruitment of Doctoral Researchers we welcome applications from outstanding candidates of all backgrounds regardless of ethnicity, disability, gender identity, sexual orientation and will consider all applications equally based on merit

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