

NOTE: This proposal was written before it was decided that no chemistry students would be allowed in the labs for research projects over the summer. Although my project has a very similar aim and all the relevant chemistry is identical, I am carrying it out remotely and so many changes have had to be made. Please see the other documents on the Laidlaw Network for updated details.

Ring expansion approaches to 'NICE' molecular building blocks for pharma

Summary. The pharmaceutical industry has highlighted an urgent need to explore new chemical space for next-generation drugs. However, there is a disconnect between academia and industry, making it challenging for molecules made in Universities to be translated into the pharmaceutical industry. Companies like Redbrick Molecular bridge this gap, providing opportunities for academics to commercialise compounds. In project, we will build on an established collaboration between the Unsworth research group here in York, with Redbrick (an SME based in Sheffield), to design and make 'macrocycles' (large ring molecules) using novel ring expansion cascade reactions. If successful, the macrocycles made will one day be commercialised through Redbrick, allowing them to make a real impact in drug discovery research (providing a clear link to University research theme 'Health and wellbeing').

Project. Since the publication of the paper "Escape from Flatland" [J. Med. Chem. 2009, 52, 21, 6752], there has been great excitement and interest in developing drug compounds with greater 3-dimensional shapes due to their better fit for binding to proteins and their enhanced pharmaceutical properties. Macrocycles have historically been underexplored in the pharmaceutical industry and can have diverse 3D spatial properties, hence have much potential in this context. In the last 10-15, macrocycles have become increasingly prominent in medicinal chemistry [J. Med. Chem. 2011, 54, 1961; J. Med. Chem. 2014, 57, 278]. However, they are difficult to make using traditional synthetic methods, and this can serve as a major barrier to their uptake in pharmaceutical R&D programmes. A major research focus in the Unsworth group is the development of new, practical methods to prepare functionalised macrocycles using ring enlargement cascade reactions. Macrocycles have been highlighted by Redbrick as being highly attractive to their customer base in view of their chemical spatial geometries, useful synthetic handles and metabolic stability. **The main question that we are seeking to address during this 6-week project is whether ring enlargement cascade reactions can be used to make macrocycles relevant to pharmaceutical R&D.** If successful, the molecules made will be passed on to Redbrick Molecular for commercialisation (using established MTAs). The chemistry will be broadly based on that in the Unsworth group's published paper [Angew. Chem., Int. Ed. 2019, 58, 13942–13947], but it is likely that many of the targets will require us to develop new variants of the cascade reactions, known colloquially within the group as 'NICE' reactions (Nucleophile Induced Cyclisation/Expansion).

Timescales. The first 1-2 weeks will be spent on training, safety, familiarising myself with the group's methods and repeating known procedures. Alongside this, I will start planning new routes, informed by the Unsworth group's previous work, but they will be fundamentally novel processes. I will be fully supported by Dr Unsworth and members of his team in all aspects. The remaining time will focus on testing if the planned routes work and new macrocycles can be made. If even one novel macrocycle building block can be made in the project, then it will be considered a success. More ambitiously, we hope that a general method that can be applied to multiple derivative molecules can be established.