Chemistry

Name of PI: Dr Haitham Hassan

Project Title: DNA Encoded Chemical Libraries to Tackle Multidrug-Resistant Pathogens

Project Description:
In September 1928, Alexander Fleming discovered Penicillin, the first antibiotic, revolutionising bacterial infection treatment. However, bacteria have since developed resistance to Penicillin and most other antibiotics. The discovery of new antibiotics is declining, while bacterial resistance remains a significant threat.

β-Lactam antibiotics, including penicillin, cephalosporins, and carbapenems, are increasingly ineffective due to β-lactamase enzymes that hydrolyse these drugs. Inhibiting these enzymes can enhance treatment options for multidrug-resistant pathogens. Although several β-lactamase inhibitors, such as avibactam, have been developed, bacterial resistance continues to evolve. Identifying new pharmacophores or hit compounds against resistant pathogens is a key challenge.

DNA-encoded chemical libraries (DECL) are becoming crucial in this effort by providing a vast and diverse chemical space for hit identification. DECL involves synthesising DNA-tagged molecules, each uniquely coded by a DNA sequence, which can be screened rapidly against protein targets. This technique allows for the rapid synthesis and screening of millions of compounds, accelerating the discovery process.

The project aims to mimic chemical structures of key β-lactamase inhibitors by designing and synthesising a range of key fragments. These fragments will be incorporated into a DECL synthesis workflow, resulting in a library of approximately one million compounds to be screened against resistant bacterial targets.

Name of PI: Deborah Sneddon

Project Title: Exploring the Antimicrobial Activity of Lanthanide Complexes

Project Description:
Multidrug resistance has been cited by the World Health Organization as one of the biggest threats to global health, yet 75% of antimicrobials under clinical development are derivatives of known antibiotics, making resistance likely. Could metal compounds be the key to overcoming antimicrobial resistance? These three-dimensional scaffolds are readily tuneable and have access to unique modes of action, including ligand exchange/release, reactive oxygen species (ROS) generation, and more.

Ruthenium complexes have been widely studied for their antimicrobial properties, but several metals remain relatively unexplored, including those in the lanthanide series. A recent review analysing metal complexes as antibiotics highlighted a europium complex with antibacterial activity, though its mode of action remains unknown. Europium and its salts have low toxicity, making ligand selection critical for imparting antimicrobial activity.

Europium complexes offer an additional advantage: their luminescent properties can be exploited for potential imaging applications. This project aims to synthes

---

Name of PI: Ian Crossley

Project Title: Phosphorus Analogues of Biologically Important Cyano-Complexes

Project Description:
Phosphorus' ability to chemically 'mimic' carbon is well-established, particularly in the context of low-coordinate compounds such as phosphaalkynes (RCP), which are recognised chemical analogues of alkynes rather than nitriles, yet possess their own unique character. This is especially evident in the ‘cyaphide’ ligand (‘-CP’), a notional analogue of cyanide that resembles ethynyl (-CCH) but is electronically distinct.

An unresolved question is what implications this has for bio-inorganic complexes, such as analogues of vitamin B12 (cyanocobalamin) or within the haem coordination sphere.

My group, alongside others, has established reliable synthetic access to a range of transition metal complexes of cyaphide through several complementary routes. This project aims to apply these methods to prepare complexes of several biologically important metals (e.g., Fe, Co, Cu, Zn), supported by simple porphyrin ligands, as model systems. These will then be chemically investigated and characterised using techniques such as cyclic voltammetry and density functional theory (DFT) to determine their distinctions from natural analogues and evaluate their suitability for similar biological roles. Analogues involving simple phosphaalkyne ligands (RCP-MLn) will also be studied, providing a broad understanding of the CN/CP analogies and distinctions, with the results informing future target design.

Name of PI: Storm Hassell-Hart

Project Title: Synthesis Enabled Drug Discovery: Novel Methods for the Synthesis and Evaluation of Medicinally Important Heterocycles

Project Description:
Heterocycles are a key motif in drugs and medicines, with approximately 60% of all

FDA-approved drugs containing nitrogen heterocycles. Unfortunately, synthetic methods to prepare heterocycles are often limited, resulting in low yields and poor substrate scope. This restricts access to key compounds and impedes drug discovery.

This project aims to address these challenges by developing new, high-yielding methods for the preparation of traditionally difficult-to-synthesise heterocycles, enabling their use in screening and medicine development. For example, we have recently developed novel methods to access thiazoles from underexplored sulfoxonium ylide starting materials, employing acid or iridium catalysis. Screening the resulting novel thiazoles led to the identification of a new family of antibiotic-resistant gonorrhoea inhibitors.

Building on these findings, the project will further expand the range of heterocycles that can be synthesised. The resulting compounds will be screened against a variety of biological targets, forming the basis for novel fragment libraries and potentially even drugs. This research combines organic and medicinal chemistry, with the potential to pursue results in either field as the PhD progresses.

Name of PI: Hazel Cox

Project Title: Development of New Methods for Few-Particle Quantum Systems

Project Description:
Numerical Tensor Methods (NTM) have emerged as a prominent area of scientific research due to their potential to revolutionise any field that requires matrix-based computation. By leveraging the power of multilinear algebra, these methods reduce computational costs and time, greatly enhancing our ability to perform high-level quantum chemical calculations.

The aim of this project is to develop novel numerical tensor methods to solve the time-independent Schrödinger equation for few-particle systems. The focus will be on explicitly treating the correlated motion of all the particles, using the most suitable tensor decompositions to ensure high-accuracy calculations.

Name of PI: Hazel Cox

Project Title: Exploring the Fundamental Interactions in Few-Particle Coulomb Systems

Project Description:
Technological and scientific advances are underpinned by fundamental science. This project aims to provide new knowledge and understanding of quantum systems, focusing on the key physical properties that affect the stability of quantum mechanical

systems, such as atoms or molecules, with a fixed number of particles interacting via Coulomb forces. These properties include mass and charge.

For instance, studying the critical nuclear charge for binding and the analytic properties of energy as a function of nuclear charge provides insights into correlation effects in real physical systems. The project seeks to solve the Schrödinger equation with explicitly correlated wavefunctions, using in-house code to generate high-accuracy data. This data can then be used to derive formulae that may improve conventional quantum chemistry methods, such as developing a correlation functional for use in density functional theory.

Name of PI: Haitham Hassan

Project Title: The Power of DNA Encoded Chemical Libraries in Tackling Multidrug-Resistant Pathogens

Project Description:
In late September 1928, Alexander Fleming, Nobel laureate, discovered Penicillin, the first antibiotic, which revolutionised bacterial infection treatment. However, over time, bacteria have developed resistance to Penicillin and most other antibiotics. The discovery of new antibiotics is declining, while bacterial resistance remains a significant threat.

β-Lactam antibiotics, such as penicillin, cephalosporins, and carbapenems, are widely used but are increasingly ineffective due to β-lactamase enzymes that hydrolyse these drugs. Inhibiting these enzymes can enhance treatment options for multidrug-resistant pathogens. Although several β-lactamase inhibitors have been developed (e.g. avibactam), bacterial resistance continues to evolve. One of the key challenges is identifying new pharmacophores or hit compounds against resistant pathogens.

DNA-encoded chemical libraries (DECL) are becoming crucial in this effort by providing a vast and diverse chemical space for hit identification. DECL involves synthesising DNA-tagged molecules, each uniquely coded by a DNA sequence, which can be screened rapidly against protein targets. This technique allows for the rapid synthesis and screening of millions of compounds, accelerating the discovery process.

The first aim of this project is to mimic the chemical structures of key β-lactamase inhibitors. To achieve this, we will design and synthesise a range of key fragments. The chemical synthesis will utilise both established methods and novel approaches developed throughout this project. The synthesised fragments will be incorporated into a DECL synthesis workflow, with the resulting DECL, containing approximately 1 million compounds, being screened against different resistant bacterial targets.

Name of PI: Mark Bagley

Project Title: New Synthetic Methods for the Production of Heterocycles of Biological Importance

Project Description:
The wide range of biological properties exhibited by heterocycles, such as pyridines, indoles, thiazoles, and quinolines, continues to demand the development of new and improved synthetic methods for their production. Cleaner, greener synthetic approaches require high chemical yields, a broad substrate scope, readily available precursors, the use of less hazardous methods, and reduced or no waste products.

This project will focus on developing new methods using state-of-the-art technologies such as flow chemistry, mechanochemistry, and photochemistry for the synthesis of heterocyclic scaffolds of biological interest.

You will gain experience in modern methods for the synthesis, purification, and analysis of chemical species, applying these skills to discover new and improved methods for nitrogen and oxygen-containing frameworks. The research will incorporate a range of enabling technologies and green processing methods to discover more efficient and sustainable synthetic processes. The outcome of these studies will be new knowledge and understanding, novel methods and technologies, and improved capabilities for chemical synthesis.

Name of PI: Mark Bagley

Project Title: New Technologies for the Synthesis and Isolation of Natural Products

Project Description:
Natural products continue to provide a rich diversity of clinical agents and important chemical leads for the medicines of the future. Despite their significant value, new methods for their synthesis and isolation have largely relied on traditional technological approaches—until recently.

This project will apply exciting developments in emerging and enabling technologies to natural product chemistry, exploring how mechanochemistry, flow chemistry, and photochemistry can be used to access structures of biological interest.

As part of the programme, you will learn modern methods for the synthesis, purification, isolation, and analysis of chemical species from natural sources, applying your skills to access natural products more efficiently for biological evaluation.