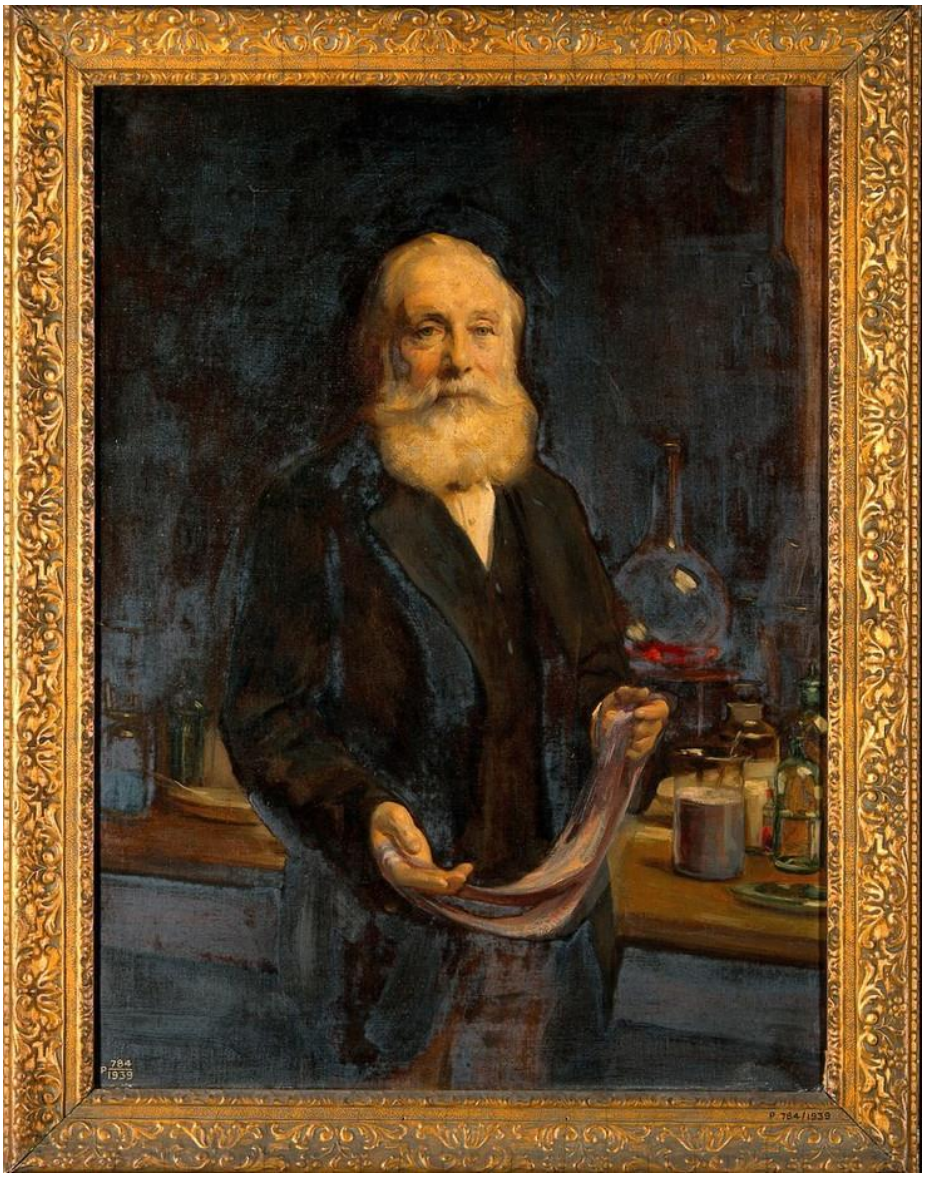
Science Teaching Hub
University of Aberdeen
21st June 2023

51st Scottish Regional Meeting, RSC Organic Chemistry Community Perkin Meeting



Credit: *Sir William Perkin. Oil painting after A.S. Cope. Welcome Collection. Public Domain Mark*

We sincerely thank the financial support from all our sponsors who made this meeting possible.

ROYAL SOCIETY OF CHEMISTRY

51st SCOTTISH REGIONAL MEETING, RSC ORGANIC CHEMISTRY COMMUNITY
WEDNESDAY, 21st JUNE 2023
SCIENCE TEACHING HUB, ABERDEEN

09.00 – 10.00 **Arrival, Coffee/Tea, Poster, and Exhibit Setup**

10.00 – 10.05 **Welcome and Opening Remarks (Dr Laurent Trembleau)**

10.05 – 12.15 **Session 1** **Chair: Dr Wael Houssen**

10.05 – 10.35 **Dr William Farnaby** (University of Dundee)
"Targeted Protein Degradation at the Academic-Industry Interface"

10.35 – 11.05 **Dr Rebecca Walker** (University of Aberdeen)
"Design and Synthesis of Liquid Crystalline Materials Exhibiting Polar and Modulated Nematic Phases"

11.05 – 11.35 **Dr O. Stephen Ojo** (University of Glasgow)
"Exploration of Transition Metal-Hydrides in Catalysis"

11.35 – 12.05 **Dr Benjamin Bhawal** (University of Edinburgh)
"Regiochemical Editing by Carbonyl Chain-Walking"

12.05 – 12.15 **Sponsor Flash Presentations**

12.15 – 13.55 **Lunch, Poster Session, and Exhibition**

14.00 – 15.30 **Session 2** **Chair: Prof. Hai Deng**

14.00 – 14.30 **Dr Rebecca Beveridge** (University of Strathclyde)
"Ion Mobility Mass Spectrometry Reveals the Effect of Small Molecules on Protein Conformation and Stoichiometry"

14.30 – 15.00 **Dr Ai-Lan Lee** (Heriot-Watt University)
"Decarboxylative Radical Functionalisations"

15.00 – 15.30 **Prof. David O'Hagan** (University of St Andrews)
"Exploring Properties of Partially Fluorinated Aliphatics and Alicyclics"

15.30 – 16.20 **Coffee/Tea, Poster Session, and Exhibition**

16.25 – 17.25 **Plenary Session** **Chair: Prof. Marcel Jaspars**

16.25 – 16.30 **Presentation of the RSC Merck, Sharp and Dohme Award 2022**

16.30 – 17.25 **Dr Katherine Wheelhouse, FRSC (GlaxoSmithKline)**
"Adventures in Pharmaceutical Catalysis"

17.25 – 17.30 **Poster Prizes and Closing Remarks (Dr Wael Houssen)**

17.30 – 18.30 **Wine Reception**

19:00 – 21.00 **Speakers' Dinner**

Oral Presentations

Targeted Protein Degradation at the academic-industry interface

William Farnaby, Christiane Kofink, Nicole Trainor, Barbara Mair, Melanie Wurm, Nikolai Mischerikow, Michael Roy, Emelyne Diers, Ross McLennan, Claire Whitworth, Manfred Koegl, Gerd Bader, Klaus Rumpel, Thomas Gerstberger, Moriz Mayer, Peter Ettmayer, Darryl McConnell, Simon Woehrle, Jorg Rinnenthal, Nicola Wiechens, Tom Oewn-Hughes, Harald Weinstabl, Alessio Ciulli

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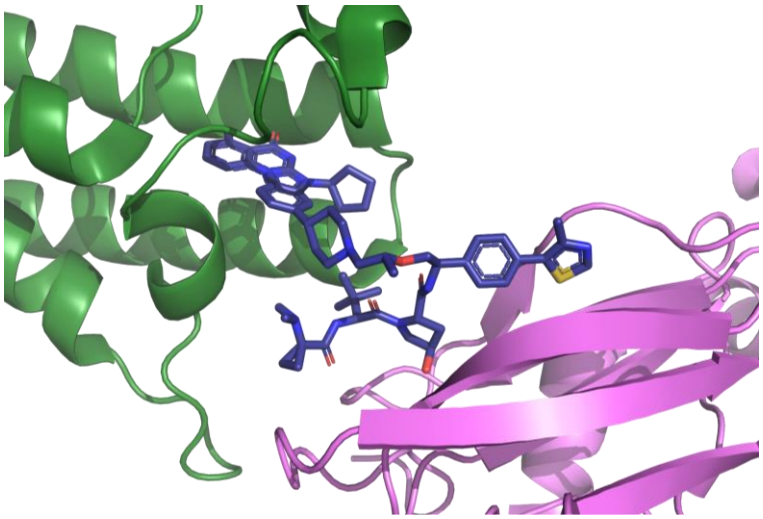
In this talk I will outline how we have approached the design of molecules to target the degradation of undrugged cancer disease drivers . I will then outline a future direction seeking to address opportunities in using targeted protein degradation in neurodegeneration research. Heterobifunctional degraders offer an alternative modality to classical inhibition and hold the promise of addressing previously undruggable targets. Here, we demonstrate the design of orally bioavailable molecules that selectively degrade the BAF Chromatin Remodelling complex ATPase SMARCA2 over its closely related paralogue SMARCA4, to allow *in vivo* evaluation of the synthetic lethality concept of SMARCA2 dependency in SMARCA4-deficient cancers. This required a combination of structure- and property-guided methods and the synthesis and validation of novel E3 ligase ligand conjugation points to access our chemical probe, ACBI2. Moving forward I now seek to use these learnings to investigate application of induced-proximity approaches in neurodegeneration.



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2. A selective and orally bioavailable VHL-recruiting PROTAC achieves SMARCA2 degradation in vivo. Christiane Kofink[$], Nicole Trainor[$], Barbara Mair[$], Melanie Wurm[$], Nikolai Mischerikow, Gerd Bader, Klaus Rumpel, Thomas Gerstberger…Harald Weinstabl*, William Farnaby*. *Nat Commun* 2022, **13**, 5969. https://doi.org/10.1038/s41467-022-33430-6

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Design & synthesis of liquid crystalline materials exhibiting polar & modulated nematic phases

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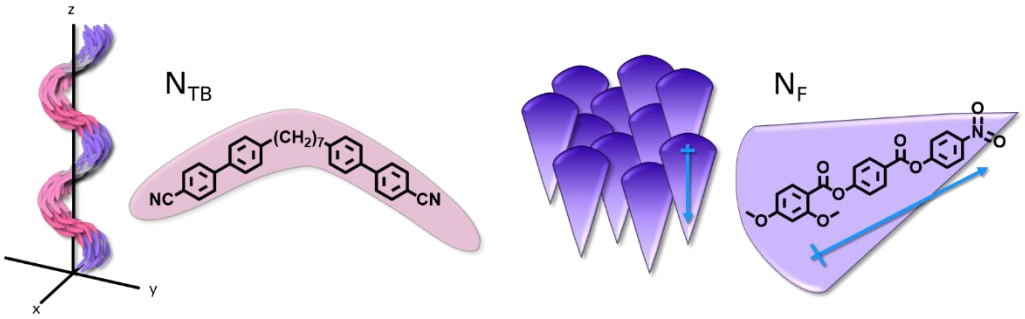
Liquid crystal is a state of matter with properties intermediate to those of solid crystals and isotropic liquids. Several liquid crystal phases are now known to exist, each with their own unique characteristics and applications.

The simplest liquid crystal phase – the nematic phase – is nowadays ubiquitous in our daily lives, and its ability to switch on application of an electric field underpins much of the multi-billion-pound liquid crystal display industry. Current LCD technology is limited by the speed at which the nematic phase can 'switch' and for this reason – and of course scientific curiosity – we seek new liquid crystal phases with the possibility of transformative applications in displays and beyond. Two such 'new' phases, for which primary studies appear to show incredible potential, are also nematic in nature – the twist-bend nematic phase, N_{TB},[1] and the ferroelectric nematic phase, N_F.[2]



From a chemist's perspective, understanding the molecular features influencing the formation and stabilisation of the N_{TB} and N_F phases is of paramount importance, and allows for the design of new materials that have targeted properties. As such, recent work in Aberdeen has had the primary aim of enhancing our current understanding of these relationships in dimeric[3] and low-molar-mass liquid crystals,[4] respectively, through the synthesis and characterisation of a diverse range of materials, including a selection of supramolecular liquid crystals.

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Exploration of transition metal-hydrides in catalysis

O. Stephen Ojo, and Hannah J. Steel

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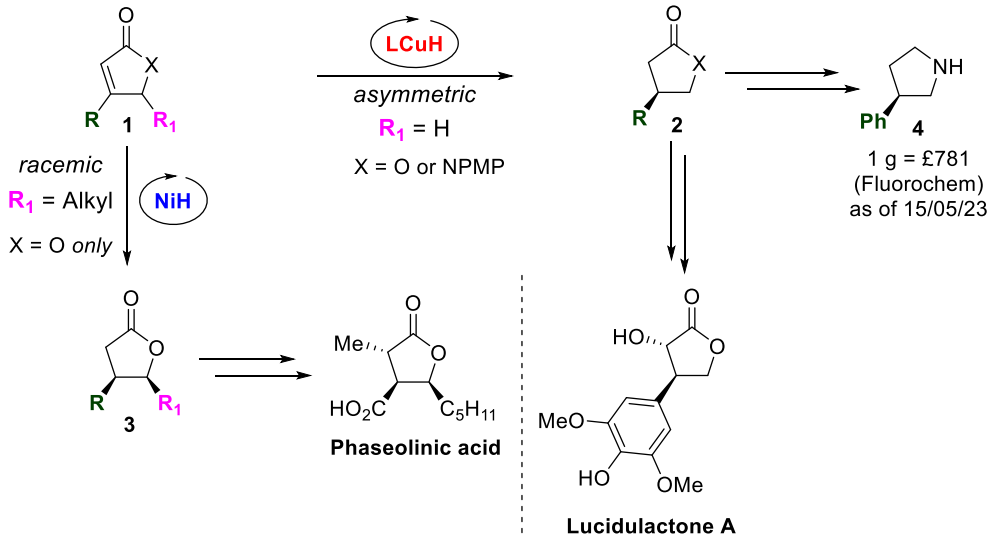
γ-Butyrolactone exists as a core architectural motif in numerous natural products and pharmaceuticals. Facile access to chiral or racemic γ-butyrolactone (**2** or **3**) can be achieved *via* hydrogenation or 1,4-reduction of β-substituted butenolides (**1**). The former requires expensive transition metal (e.g., Rh, and Ir) and extremely high pressure (50 atm). My talk will explain how a ligand that possesses planar chirality delivered **2** in excellent *ee*, an advancement from a previous study[4]. Also, I'll explain how *syn*-β-aryl, γ-alkyl disubstituted (±)-γ-butyrolactones **3** were generated *via* Nickel-hydride catalysis. The synthesis of (i) **3** provided the shortest synthetic route to Phaseolinic acid, and (ii) **2** (when X = O) enabled the first completed synthesis of Lucidulactone A and a high value chiral pyrrolidine **4** (when X = N).



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Regiochemical editing by carbonyl chain-walking

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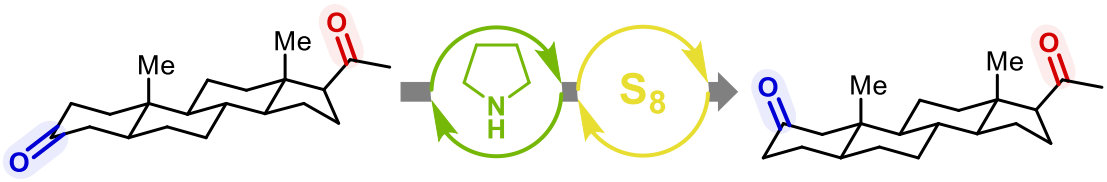
The relative position of functional groups plays a key role in determining the biological and physical properties of a molecule. Thus, being able to control the position of functional groups is a fundamental goal in organic synthesis. Multistep *de novo* synthesis enables accurate control of the regiochemistry of a molecule but, if another regioisomer is desired, then an entirely new synthesis, often entailing a new synthetic strategy, is required.[1] Isomerisation offers the opportunity to "correct" the regiochemistry in a single synthetic transformation.[2]

To address this challenge, we have developed a carbonyl chain-walking process that enables the isomerisation of ketones. This process exhibited a distinct thermodynamic and kinetic selectivity profile which subsequently proved critical in facilitating the regiochemical isomerisation of naturally occurring steroids to afford novel steroids bearing unnatural oxidation patterns.



♦ Simple and inexpensive catalysts ♦ Rare example of positional isomerization

♦ Reversible reaction ♦ Late-stage modification of steroids

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Ion mobility mass spectrometry reveals the effect of small molecules on protein conformation and stoichiometry

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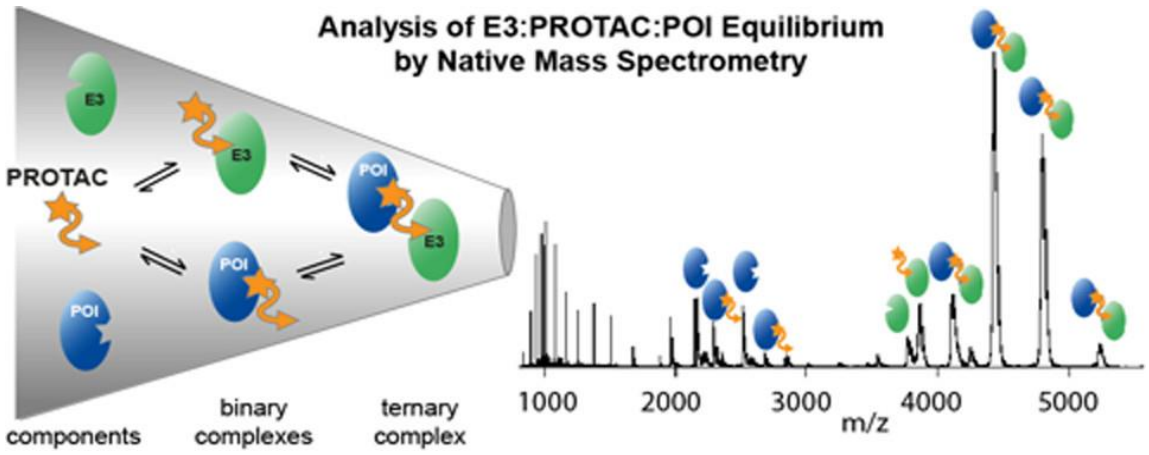
The effect of small molecules on protein structure can be challenging to delineate, especially when multiple binding events occur, when interactions are transient, and when molecule binding affects the stoichiometry of protein complexes. Native mass spectrometry (nMS) is a useful method for measuring protein-molecule interactions, and can provide information on structural rearrangements of proteins.

The strength of nMS in studying the stoichiometry of protein complexes is exemplified in its application to PROTACs, which are bifunctional ligands that bind to two proteins simultaneously. PROTACs bind an E3 ligase and a substrate protein that is targeted for degradation, bringing them into close spatial proximity. We show that nMS can monitor the formation of ternary E3-PROTAC-substrate complexes and detect intermediate species in a single experiment. A unique benefit of the method is its ability to reveal preferentially formed E3-PROTAC-substrate combinations in competition experiments with multiple substrate proteins, thereby positioning it as an ideal high-throughput screening strategy during the development of new PROTACs.

nMS can also be coupled with ion mobility, which is a useful method for studying intrinsically disordered proteins (IDPs) which are highly dynamic and rapidly interconvert between compact and extended conformations. It reveals the range of shapes in which IDPs exist, including those that are only populated to a low extent. It also reports on conformational changes induced upon complex formation with ligands and drugs. We have used IMMS to delineate the effect that drug leads have on the Androgen Receptor which is a key drug target in the treatment of prostate cancer.



Decarboxylative Radical Functionalisations

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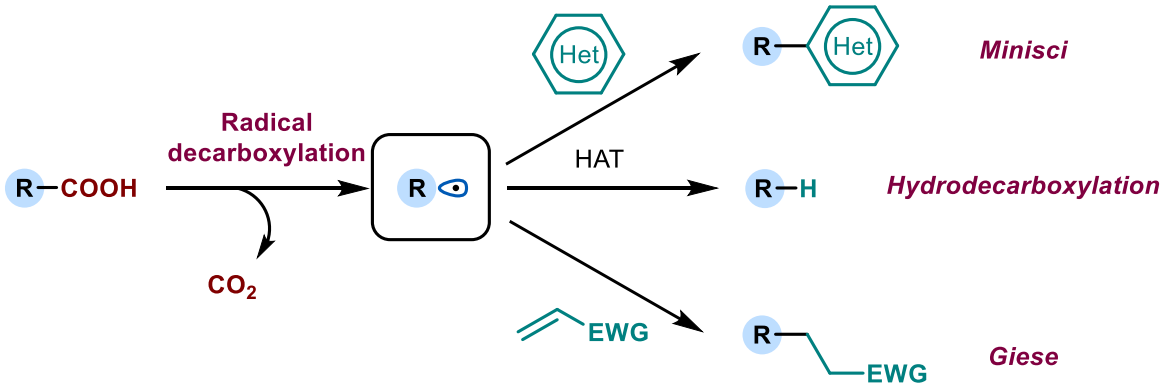
Direct decarboxylative C-H functionalisations of heterocycles (Minisci reaction) can now be readily achieved without requiring any conventional metal, photocatalyst or light activation, thus significantly improving on sustainability, costs, toxicity, waste and simplicity of the operational procedure.[1-4] These mild conditions are also suitable for gram-scale reactions as well as late-stage C-H functionalisations of complex molecules, including drug molecules, *N*,*N*-ligands, purine bases and light-sensitive molecules which would otherwise which degrade under photocatalytic conditions.

More recently, metal- and light-free methodologies have been developed alongside new photocatalytic methods for direct hydrodecarboxylation of alkylcarboxylic acids[5] and radical conjugate addition (Giese) reactions.[6]



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Exploring properties of partially fluorinated aliphatics and alicyclics

David O'Hagan

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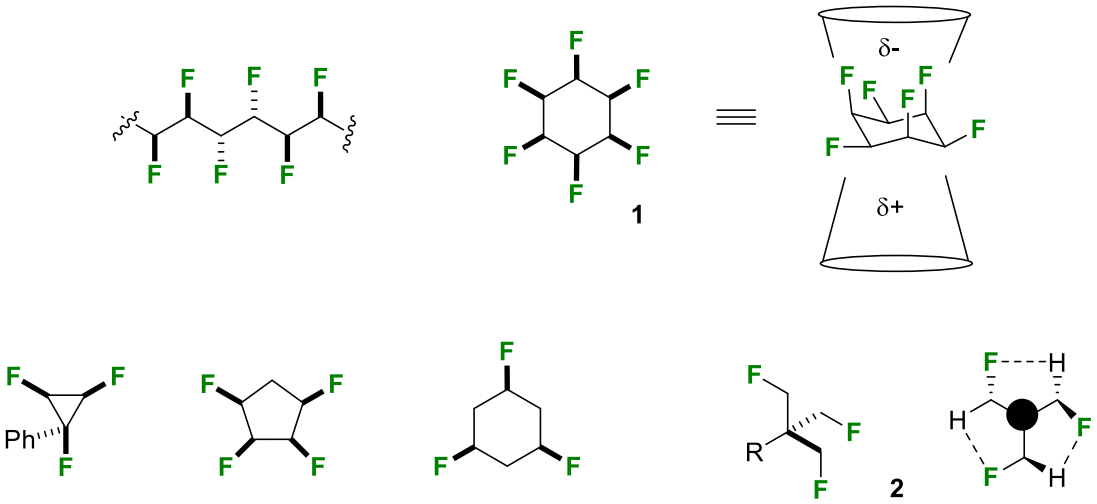
The presentation will describe the preparation and properties of selectively fluorinated alkanes generated by linking fluoromethylene (-CHF-) groups in chains and rings. The flagship molecule, all-*cis*-1,2,3,4,5,6-hexafluorocyclohexane **1**, emerged to be the most polar aliphatic compound recorded, with very different properties to hydrocarbons and perfluorocarbons.[1-4] The polarity arises because there are three co-aligned triaxial C-F bonds and the six fluorines occupy one face of the ring. Conversely the electropositive hydrogens occupy the other face. More generally the ($^{\delta+}$H-C-F$^{\delta-}$) arrangement polarises the hydrogens and increases molecular polarity eg. increasing electrostatic attractions and lowering Log P's and these features emerges as an attractive property for applications in organic materials and medicinal chemistry.

The lecture will also discuss the *tert*-(*β,β',β''*)-trifluoro)butyl (TFTB) group **2**.



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2022 Winner of the Organic Division mid-career Award: Merck, Sharp and Dohme Award

For contributions to the application and industrialisation of chemical catalysis in the pharmaceutical industry in the pursuit of more sustainable synthesis of medicines.

Dr Katherine Wheelhouse FRSC

GlaxoSmithKline

Dr Katherine Wheelhouse studied for her MChem at Jesus College, Oxford, graduating in 2004; her final year project was carried out under the supervision of Professor Timothy Donohoe in the area of ring-closing metathesis for heterocycle synthesis. She remained in the Donohoe group for her DPhil, developing osmium-mediated oxidative cyclisation reactions, before joining GlaxoSmithKline (GSK) as a process development chemist in 2008.

Since 2011 Katherine has specialised in the application of chemical catalysis to pharmaceutical development and manufacture, impacting around 100 projects across all stages of development through practical support or consultation. She currently leads GSK's global chemical catalysis community of practice. Throughout this time, she has been a champion of modernised approaches to chemical development, including automation, high-throughput experimentation and reaction monitoring. Katherine's role expanded in 2021 to encompass broader technology strategy and application within small molecule chemical development.

Katherine is a strong believer in collaboration for innovation, being active in a range of academic collaborations and multinational consortia throughout the last decade. She is a GSK scientific fellow, a member of the RSC Applied Catalysis Committee and of the editorial advisory board of the journal Organic Process Research and Development.

Adventures in Pharmaceutical Catalysis

K. Wheelhouse

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Chemical catalysis is a key technology in chemical synthesis, including pharmaceutical manufacture. Application to manufacturing processes requires understanding of a range of factors beyond the reaction itself, from sourcing the specific catalyst required to understanding of the equipment, separation of the catalyst residues from the product and the equipment train and eventual recovery of the precious metal. This talk will cover two case studies from GSK where difference in oxygen levels between lab development and the plant resulted in a difference in performance, necessitating careful selection of the equipment for lab experiments to generate appropriate data to predict what would happen for future plant campaigns.

Poster Presentations

Development of a high-throughput synthesis and direct to biology approach for rapid generation of a PROTAC library targeting the AMPK α1-subunit as a potential new treatment in cancer

M Wheldon*[1], JD Kumar*[1], SA Hawley[2], C Kerr[1], L Spinelli[2], C McGinnis[1], S Boomkamp[1], E Fordyce[1], F Cunningham[1], C Mackenzie[1], DA Cantrell[2], DG Hardie[2] and D Gray[1]

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[2]Cell Signalling and Immunology, School of Life Science, University of Dundee, UK

*Shared first authors

The α1-subunit of the AMPK (adenosine 5′ monophosphate-activated protein kinase) complex is frequently activated in tumour cells. To date, identifying a specific AMPK-α1 inhibitor has been challenging due to inhibitors targeting the generic ATP binding pocket resulting in promiscuity and off-target effects. Here we propose to use an activator specifically targeting the allosteric drug and metabolite (AdAM) site of AMPK-α1 as a start point to generate Proteolysis Targeting Chimeras (PROTACs) to drive targeted degradation of AMPK-α1. We successfully developed a high-throughput chemistry approach to synthesise a library of 123 crude PROTACs and used these in a “Direct to Biology” approach to test the degradation of AMPK-α1 in HEK293 cells. We will present the design of an E3 ligase-linker library and the development of the high-throughput chemistry to synthesise the PROTAC library in a format suitable for testing. We will demonstrate the use of automated Western Blot analysis to quantify the degradation of AMPK-α1. The screen identified 18 PROTACs showing ≥30% degradation of AMPK-α1, and these were re-confirmed in dose-response tests. Four of the potential PROTAC hits and one inactive PROTAC were selected for re-synthesis and purification by standard chemistry methods. These PROTACs were then further profiled and compared to “Crude” data to show reliability in the “Direct to Biology” approach used. Promising PROTAC molecules were taken forward for additional biological profiling and a summary of these results will be presented.

In summary, we report the successful use of a high-throughput, direct to biology approach for the synthesis and screening of PROTAC molecules which has led to the identification of a degrader of the AMPK-α1 protein.

Scaffold-Hopping Strategy and Bespoke Syntheses Towards a Clinical Candidate For Visceral Leishmaniasis

Peter Dodd

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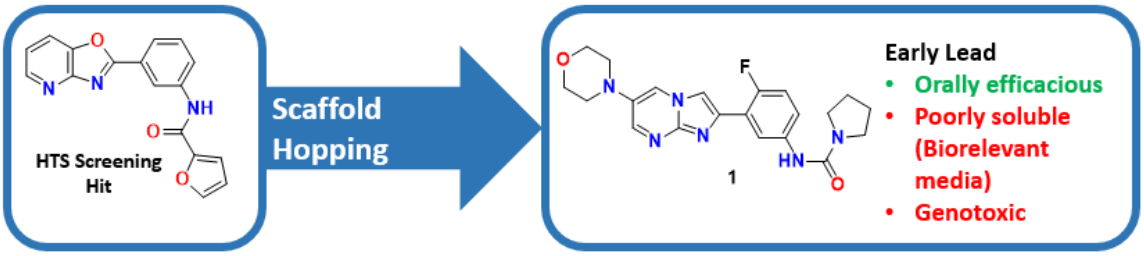
Visceral Leishmaniasis is a parasitic infection responsible for approx. 50,000 deaths a year. It mainly affects parts of Asia and East Africa. There is an urgent need for new treatments. Here we describe a scaffold-hopping strategy to find new soluble and efficacious scaffolds and their syntheses, for phenotypic screening against leishmaniasis.



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Development of a HTS assay and protein crystallography platform facilitating development of inhibitors of SARS-CoV-2 nsp14 methyltransferase activity

Sean O'Byrne[1], Anna Czarna[2], Jacek Plewka[2], Lesley-Anne Pearson[1], Irene Georgiou[1], Sandra O'Neill[1], Shamshad Ahmad[1], Fraser Cunningham[1], Nagakumar Bharatham[1], Xiao Hu[1], Leanid Kresik[2], Alex Matsuda[2], Abdulkarim Karim[3], Piotr Wilk[2], Magdalena Pachota[2], Grzegorz Popowicz[4], Paul Graham Wyatt[1], Grzegorz Dubin[2], Charlotte J. Green[1], De Lin[1], Alain-Pierre Petit[1], David W. Gray[1], Victoria H. Cowling[5], Duncan Scott[1], Euan A. F. Fordyce[1], Krzysztof Pyr[2], Ian H. Gilbert[1], Colin Robinson[1].

1. Drug Discovery Unit, Wellcome Centre for Anti-Infectives Research, School of Life Sciences, University of Dundee, Dow Street, Dundee DDI. 2. Virogenetics Laboratory of Virology, Malopolska Centre of Biotechnology, Jagiellonian University, Gronostajowa 7a, 30-387 Krakow, Poland. 3. Department of Biology, College of Science, Salahaddin University-Erbil, Kirkuk Road, 44002 Erbil, Kurdistan Region, Iraq. 4. Helmholtz Zentrum Munchen, Ingolstadter Landstrasse 1, 85764 Neuherberg, Germany. 5. Centre for Gene Regulation and Expression, School of Life Sciences, University of Dundee, Dundee, UK, 5EH, UK.

SARS-CoV-2 is responsible for the on-going COVID-19 global pandemic. SARS-CoV-2 is an enveloped virus belonging to the beta-coronavirus family and contains positive-sense single-strand RNA genome that encodes 20 proteins including non-structural proteins 1- 16. The non-structural proteins regulate viral RNA replication and transcription. The polyproteins formed from ORF1a/b translation are cleaved by two proteases PLpro (a domain of nsp3) and Mpro (nsp5). Once processed, the nsps have diverse functions including modulating host response, reducing host gene expression, formation of the replication-transcriptions complex.[1]

Non-structural protein 14 (nsp14) is a bi-functional protein, consisting of a C-terminal SAM-dependent guanine-N7-methyl transferase domain and an N-terminal 3'-5' exoribonuclease (ExoN) domain. Viral RNA can be recognised by host pattern recognition receptors, which activate interferon (IFN)-associated antiviral immune responses. Nsp14 catalyses the methylation of guanine N7 of the newly formed viral mRNA. By capping viral mRNA, viruses can evade the host innate immune system, delaying the antiviral response and stabilise RNA, preventing degradation by exonucleases.[2] Mutational studies have demonstrated the importance of nsp14 in the immune response and nsp14 mutated viruses are significantly attenuated *in vivo*, suggesting nsp14 is a valid drug target.[3]

Aiming to identify inhibitors of nsp14, we have developed a high throughput screening biochemical assay using RapidFire mass spectrometry.[4] The assay has been used to screen a library of FDA approved drugs and identified nitazoxanide as a selective inhibitor of nsp14 methyltransferase activity. In addition, the structure of nsp14 bound to co-factor SAH has been solved. Together these form a validated platform for further development of inhibitors of nsp14 methyltransferase activity.

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Designing Artificial Fluorinases: Using Unnatural Amino Acids to Desolvate Fluoride Anions

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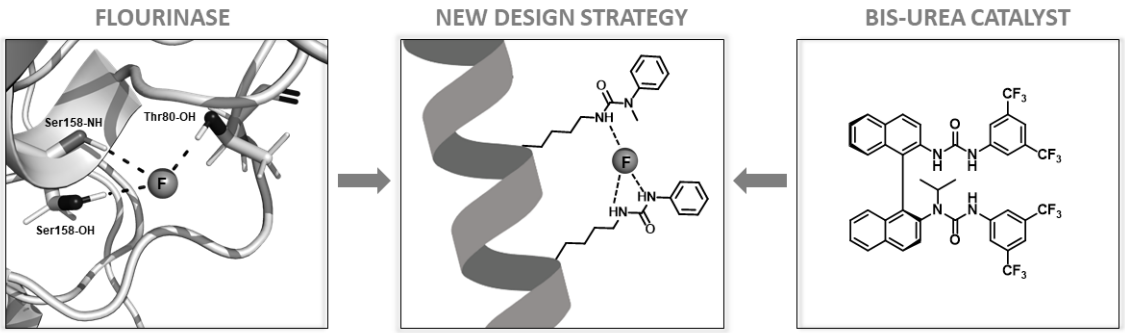
To date, only one enzyme is known in nature that can catalyse the formation of a C-F bond. This is because the fluoride anions that are used as fluorine source are mainly unreactive in an aqueous environment due to their high solvation in water. In 2002, the fluorinase of *Streptomyces cattleya* was discovered.[1] Since then no fluorinating enzymes other than fluorinase homologues have been identified, although it is suspected that there are other fluorinating enzymes.[2] Therefore, it is of great interest to develop new methods for enzymatic fluorination and to create an artificial fluorinase.

Here I present new design strategies to bind fluoride anions in proteins and peptides for nucleophilic fluorination aiming to extend biocatalysis for organofluorine synthesis. The design is based on the active site of fluorinase and urea receptors.[3,4] In view of this, peptides with incorporated unnatural amino acids with urea motifs and specific protein folds were explored to overcome the high desolvation energy of fluoride, with the aim of making them more reactive for the formation of a new C-F bond.



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Design and Optimisation of New Modalities for Migraine Treatment

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Migraine is a neurological disease that affects the day-to-day lives of 1 in 7 people and is ranked as the 6th most disabling disorder by the World Health Organization [1]. Migraine has a large global financial impact, costing £10 billion annually to the UK economy. Neuropeptides, such as calcitonin gene-related peptide (CGRP) have been implicated in migraine. Current migraine treatments, that block the binding of CGRP to its receptor in the peripheral nervous system, involve oral small molecules (Gepants) and intravenous antibody-based CGRP-receptor antagonists. Gepants and antibodies have limited efficacy (~60% of patients benefit), whilst early Gepants showed signs of hepatotoxicity. Our lab has identified truncated versions of the parent CGRP peptide, which can bind to the receptor but lack the amino acids required to active it. Here, we discuss the lead optimisation of our peptide-based antagonist series, using a combination of computational, synthetic and biological assay methods, aiming to improve blood serum half-life for pre-clinical studies. By making selected sequence modifications and conjugation to the peptide N-terminus, we have achieved an 47x increase in *in vitro* human serum half-life compared to the lead compound.

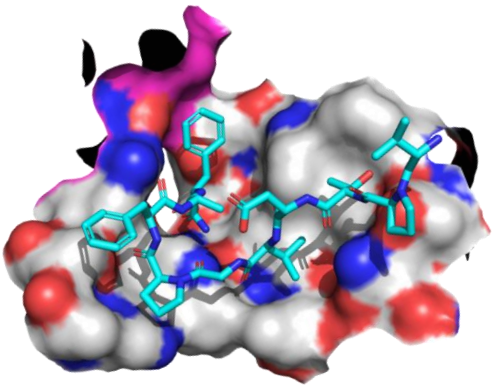

Figure 1 Lead compound (PYP006, blue sticks) interacting with extracellular domain region of CGRP receptor.

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A Convergent Synthetic Strategy Towards Brevianamide S

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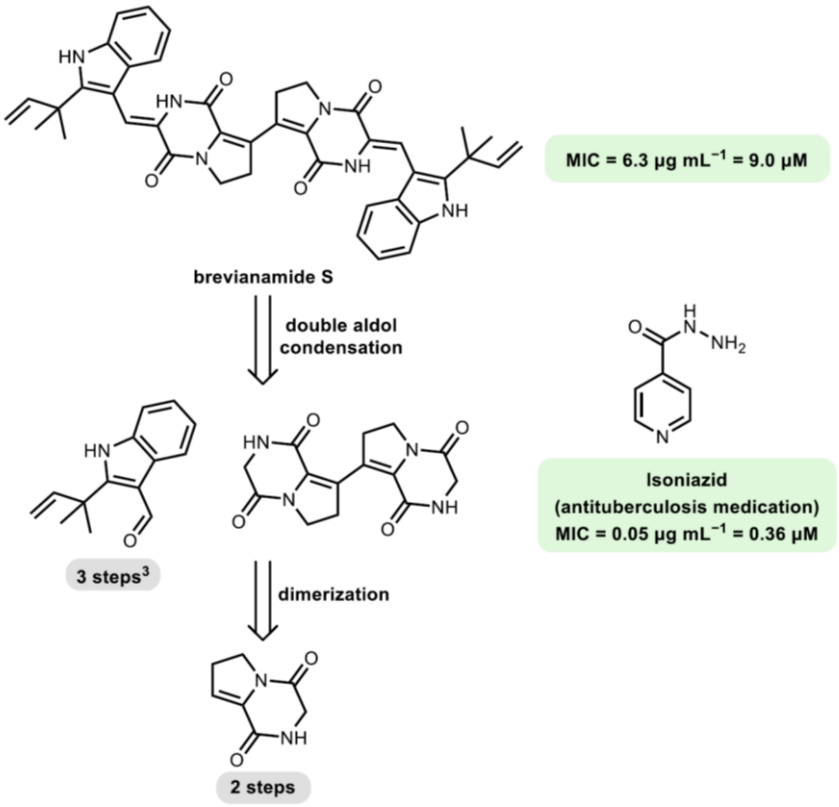
This presentation will be an account of our development of a convergent synthetic strategy towards a series of dimeric alkaloids.1 Brevianamide S was isolated from *Aspergillus versicolor* and exhibits selective antibacterial activity against a screening surrogate for *Mycobacterium tuberculosis* (MIC = 6.3 μg mL−1 = 9.0 μM).1a It has been proposed to act through a new mechanism of action, which could inform the development of next-generation antitubercular drugs.1a

Despite the appeal of pursuing a biomimetic strategy (*i.e*., dimerization of brevianamide monomers),2 we have elected to pursue a more pragmatic approach. A convergent strategy featuring a metal catalysed cross-coupling and a double aldol condensation was devised. It is envisaged that this will not only provide a short efficient route to the natural products but also present several opportunities to access a diverse collection of structural analogues.



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The Nickel-Catalyzed Ullman Coupling: A Well-Seasoned Reaction

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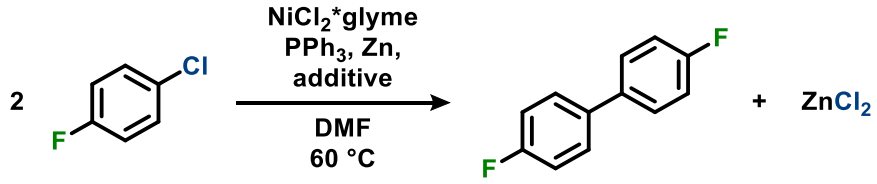
The Nickel catalyzed Ullman coupling has been the subject of many investigations due to its readily available and cheap starting materials and synthetic relevance. There are numerous reported applications and proposed mechanisms under various conditions, [1-3] however, why, and how these changes in conditions influence the reaction mechanism remains unclear. This study discusses the influence of various salts on the catalyst activation, the reaction rate and the kinetic profile observed by NMR spectroscopy. Possible interferences of these additives with the proposed mechanistic cycle are highlighted to guide the user when selecting and troubleshooting reaction conditions.



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Hidden Borane Catalysis

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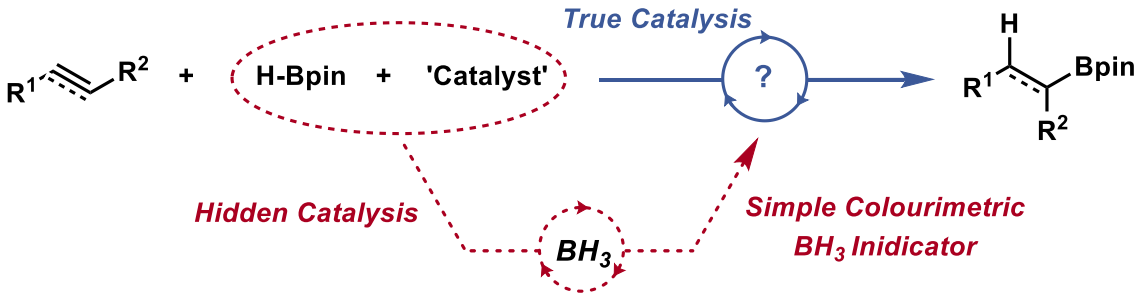
Hydroboration has become a go-to test bed for new catalyst structures from across the periodic table. Since 2010 there have been 600 publications on catalysed hydroboration reactions using pinacolborane (HBpin) alone.[1] Hydridoboranes, including BH_3, can be readily generated by the reaction of sub-stoichiometric nucleophiles, Lewis acids and bases with HBpin and these species have been shown to be active catalysts for hydroboration.[2] Therefore hidden borane catalysis is prevalent and often outcompetes the proposed catalyst reactivity. Our introduction of a series of tests to identify hidden borane catalysis has reduced the number of these cases, but adoption has not been universal. Prior to the introduction of these tests only 5% of publications tested for hidden borane catalysis, and even now this is only 13%.[3]

Here we introduce a colourimetric method for the determination of hidden borane catalysis. This simple method uses only bench stable reagents and has been shown to identify HBpin decomposition to boranes, including BH_3, with species from across the periodic table. This practical and quick method allows for the identification of hidden borane catalysis and is visible to the naked eye.

Quick and Easy Differentiation Between 'True' and 'Hidden' Catalysis



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Probing the UBE2D1:Ubiquitin non-covalent complex as a target for ligand discovery

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Ubiquitin-conjugating E2 enzymes (E2s) collaborate with E3 ligases to transfer the C-terminus of ubiquitin (Ub) from a cysteine residue in the catalytic site of the E2, to a lysine residue on a substrate protein. Further Ub's can be sequentially added to one of 7 lysines present in the initial "priming" Ub, to build polyubiquitin chains $(Ub)_n$ on the substrate. The substrate is directed towards a particular downstream signaling pathway based primarily on the $(Ub)_n$ topology [1]. After the E2 enzyme UBE2D1 is charged with Ub, the resulting species UBE2D1~Ub can self-assemble into chains $(UBE2D1\sim Ub)_n$. This is possible due to a non-covalent interaction (K_D ~ 300 μM) between the exposed hydrophobic surface of Ub and the "backside" of UBE2D1. This polymerisation enhances the binding affinity of UBE2D1 towards the E2-recognition subunit of RING E3 ligases, and triggers these E3 ligases to ubiquitinate a bound substrate in a processive manner (Figure 1A) [2]. Crystal structures of the non-covalently associated complex between Ub and UBE2D1 (UBE2D1:Ub) reveal that the vacant space between the contacting surfaces resembles a composite hydrophobic pocket (Figure 1B). Ubiquitin variants can exploit this pocket with a mutated Phe-Trp sequence (Figure 1C), making them potent inhibitors of both UBE2D1~Ub self-assembly and processive ubiquitination by RING E3 ligases [3]. Preliminary docking studies suggest that small synthetic molecules similar to the Phe-Trp sequence can access the native composite pocket. This provides a starting point for the design of ligands which could bind at the UBE2D1:Ub interface and act either as molecular glues, or as inhibitors of the interaction. A library of conformationally-constrained derivatives of Phe-Trp has been synthesised, and their effects on ubiquitination and processivity will be tested in collaboration with the Walden Lab at the University of Glasgow.

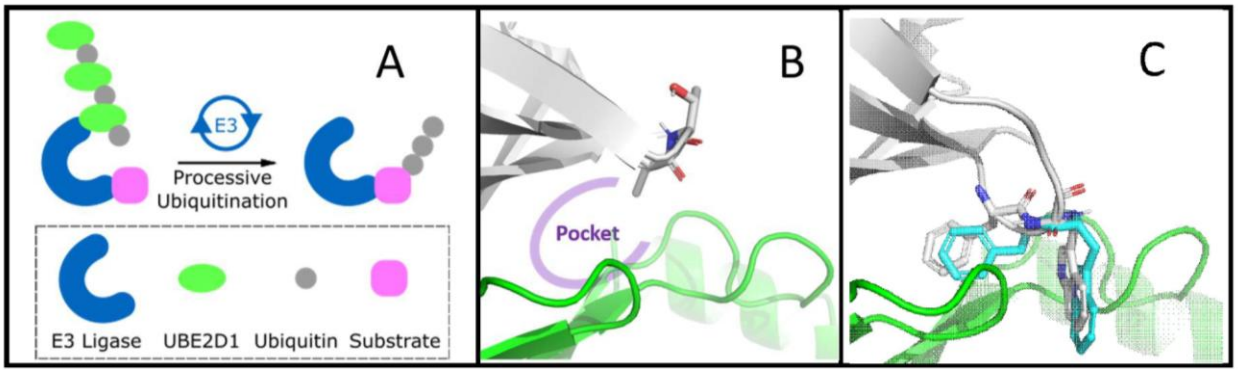

Figure 1. (A) $(UBE2D1\sim Ub)_n$ chain bound to RING-E3 ligase results in processive ubiquitination. (B) E2:Ub native interaction showing composite hydrophobic pocket (E2 = Green, Ub = Grey). (C) Phe-Trp Ubiquitin variant (Grey) with overlay of docked molecular glue (Cyan).

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Small molecule driven differentiation in osteosarcoma

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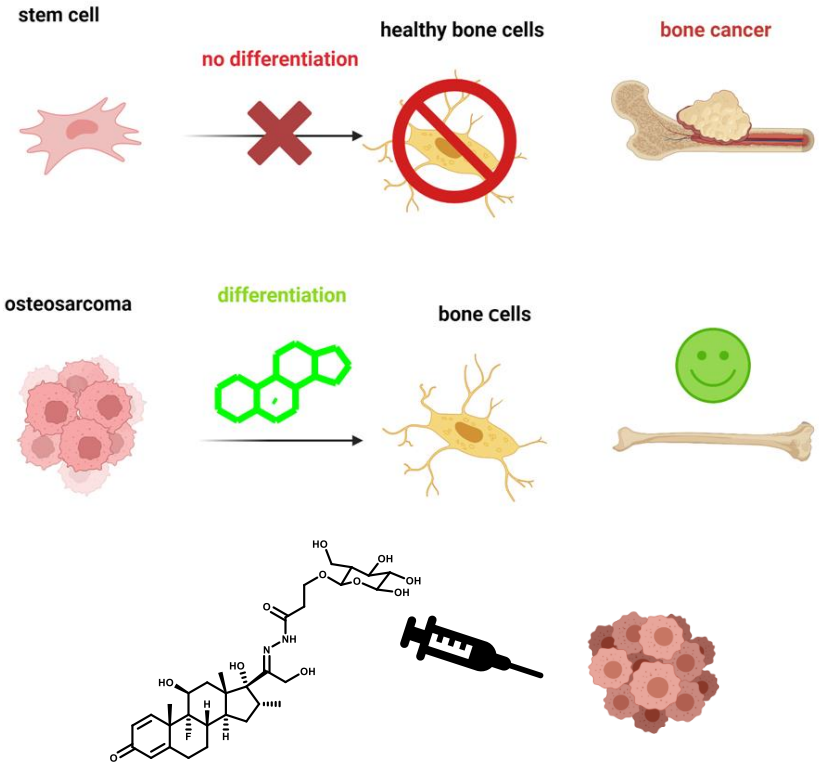
Osteosarcoma (OS) is a rare, aggressive primary bone cancer, with highest incidence in young people between the ages of 10-24. 80% of patients present defects in the osteogenic differentiation process, meaning incomplete conversion of stem cells to bone cells, which leads to immature, fast growing cancer cells. Differentiation therapy is a potential treatment, where instead of killing fast-growing cells, the aim is to push immature cancer sub-populations to maturity. The aim of this project is to study small molecule driven differentiation in osteosarcoma. Known osteogenic conditions for stem cells were applied on osteosarcoma cells, including a known osteogenic medium, as means of chemical stimulation, and nanokicking, as means of mechanical stimulation. Treatment led to an increase of certain osteogenic markers, which suggested that cells underwent differentiation. Small molecules were then identified through metabolomics and tested on the osteosarcoma cells. The molecules were tolerated, according to a viability assay, and were found to drive osteosarcoma differentiation in a dose dependent manner. Given the overconsumption of glucose in cancer cells, dexamethasone was tethered to glucose via a hydrazone linker to observe whether this can lead to enhanced differentiation, and a more targeted delivery to cancer cells. Future work includes testing this dexamethasone glucose conjugate, and expanding this strategy to different differentiation agents, as well as studying what signaling pathways are involved in differentiation.



Total Synthesis of Gymnocin B *via* a Novel Centrosymmetric Approach

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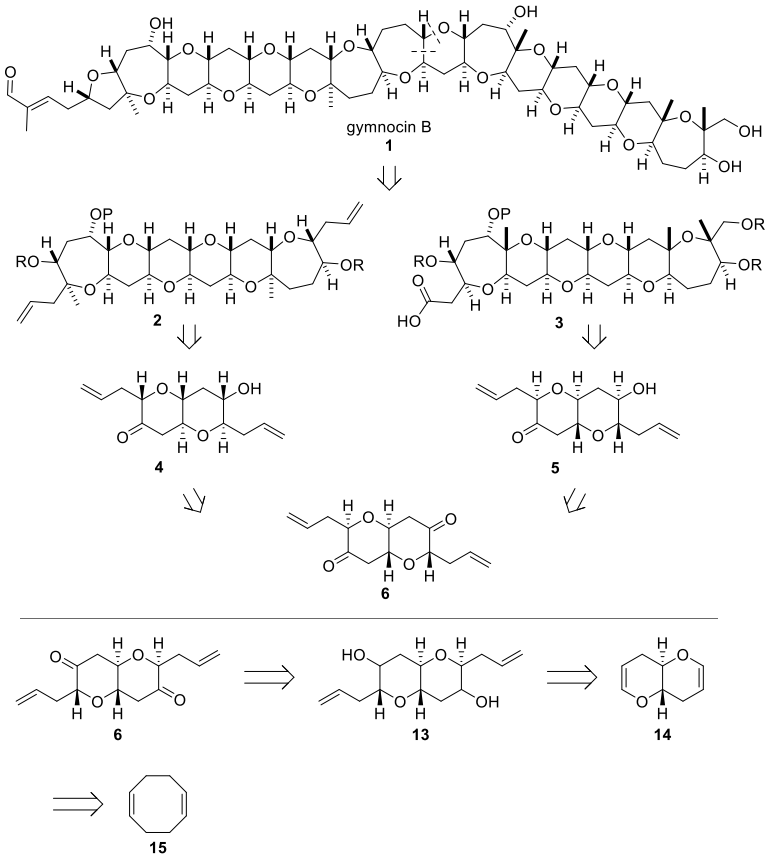
Gymnocin B **2** is a complex polycyclic ether toxin produced by *Karenia mikimotoi.*[1] It has shown cytotoxicity towards mouse leukemia P388 cells,[1] and there has only been on successful total synthesis reported in the literature thus far.[2] The bioactivity and complexity of the molecule makes it an attractive target for total synthesis.

This project aims to synthesise both gymnocin B and a variety of other polycyclic ether toxin fragments *via* a centrosymmetric approach. By taking advantage of the pseudosymmetry within the molecule, key symmetric intermediates can be built up in an efficient bidirectional manner, and then a key desymmetrisation step allows for distinctive functionalisations to be performed on either side of the molecule when required. The same key intermediate diketone **6** is used in the synthesis of gymnocin B and all of the other target fragments.



Scheme 1. Retrosynthetic analysis of gymnocin B **1**

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Synthesis of PEG-*b*-poly(cycloether): a poloxamer mimic containing a helical block

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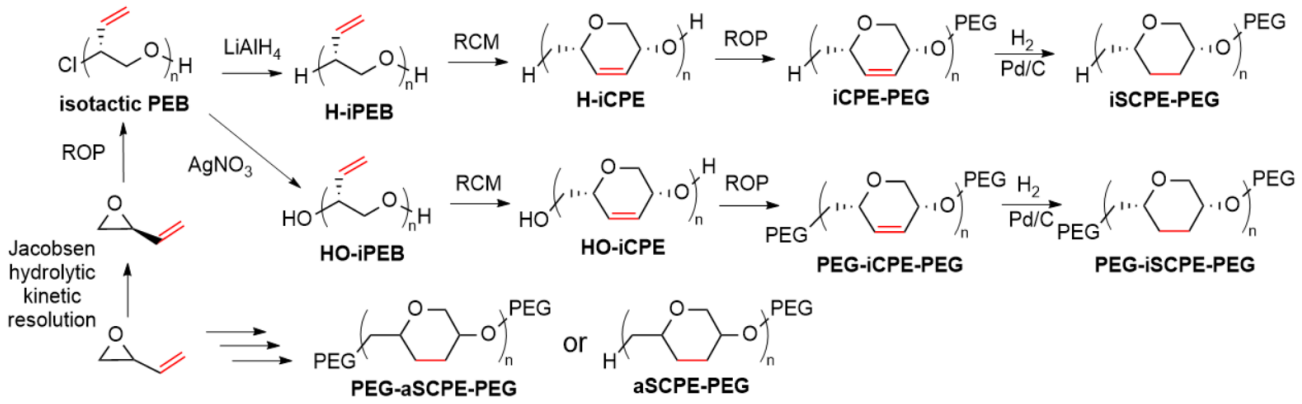
Poloxamers are amphiphilic triblock copolymers composed of a poly(propylene oxide) chain flanked by two poly(ethylene oxide) chains.[1] The physiochemical properties of poloxamers, as well as their biocompatibility and their self-assembly behaviour allow them to be used in a wide range of applications. Indeed, poloxamer-based materials have been employed in the field of cancer therapy, bioprinting, tissue engineering and drug delivery.[2] To tailor the properties of a poloxamer for a given application, the length of each block is modified.[3] To further explore the potential of this class of biomaterials without limiting oneself to modifying block lengths, a poloxamer mimic has been synthesised. PEG-*b*-poly(cycloether) contains the same hydrophilic block as a regular poloxamer but the hydrophobic block is a saturated cyclo(polyether) SCPE. This SCPE has the same carbon/oxygen ratio as poly(propylene oxide), the only difference is its unique polycyclic structure. Furthermore, the tacticity of the polymer can be controlled by using a racemic or enantiopure butadiene monoxide as the monomer. If an enantiopure butadiene monoxide is used, an isotactic polymer is obtained, leading to a helical cyclo(polyether).[4] When poloxamers were patented in 1973, they were designed as surfactants for the preparation of gels or emulsions.[1] In a similar fashion, to prove the surface-active properties of these poloxamer mimics as well as studying the knock-on effects of a stereocontrolled hydrophobic block, stable emulsions were successfully obtained and characterised.



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Development of orthogonal protection strategies for the synthesis of α-conotoxins

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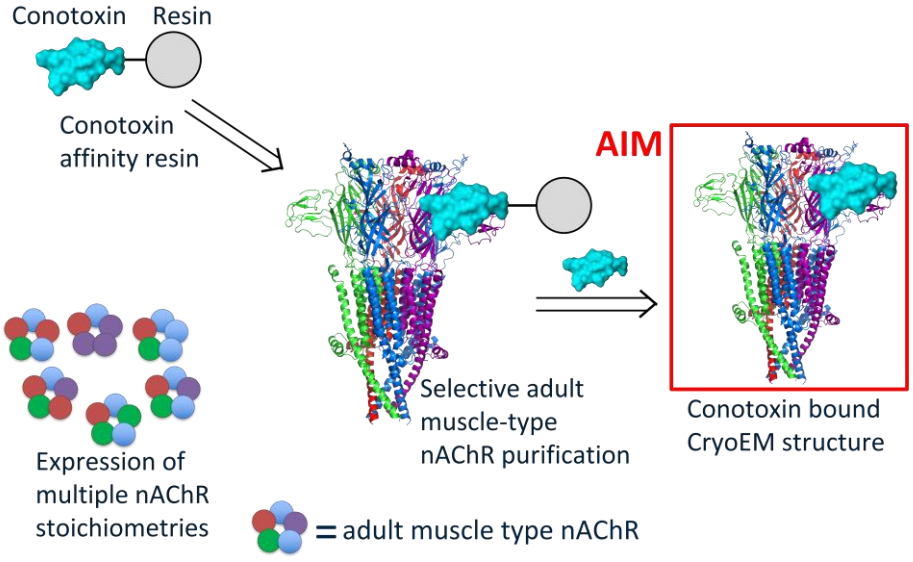
The nicotinic acetylcholine receptors (nAChRs) control muscle contraction and transmit signals in both the sympathetic and parasympathetic nervous systems. They are important therapeutic targets with implications in the treatment of chronic pain, Alzheimer's, schizophrenia, nicotine addiction, and myasthenic disease.

Conotoxins are disulfide-rich peptides produced by marine cone snails. α-Conotoxins act as competitive antagonists of nAChRs and are thus promising lead compounds for drug discovery and chemical biology studies.[1]

α-GI conotoxin has exquisite selectivity for muscle type nAChRs over the neuronal subtypes. However, our understanding of the molecular recognition event between conotoxins and the nAChRs is limited due a lack of structures that provide this information in a form that is physiologically relevant. Without this key information, rational drug discovery efforts are being impeded. Solving a structure of the muscle type nAChR complexed with α-conotoxin is also an important step in understanding the mechanism of action of the receptor.

The work presented in this poster will focus on an orthogonal protection strategy to synthesise α-conotoxins with careful control over the disulfide bond network. This strategy has been applied to produce an affinity resin functionalised with conotoxin α-GI which will be used to isolate the muscle type nAChR and facilitate Cryo-EM structural studies on this key receptor class in complex with conotoxin peptides. The knowledge gained from these structures and subsequent structure-based drug discovery has significant potential for the development of novel therapeutics for the treatment of myasthenia gravis and other myasthenic diseases.



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Iron-Catalysed Regioselective C–H Thiocyanation of Arenes

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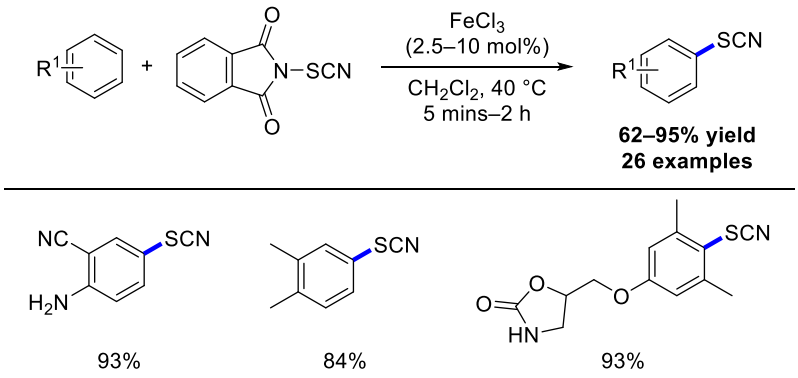
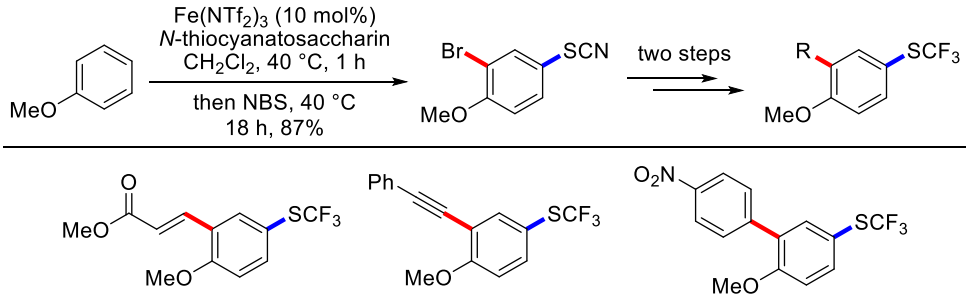
Aryl thiocyanates are important synthetic precursors for a wide variety of sulfur-containing compounds, including thioethers and the medicinally important trifluoromethyl thioether group.[1,2] As such, there is significant interest in the development of novel, sustainable and selective methods for the preparation of these valuable intermediates.[3] Herein, we present a mild and rapid method for the efficient regioselective thiocyanation of arenes using iron(III) chloride as a Lewis acid for the activation of *N*-thiocyanatosaccharin. The procedure was found to work well for a variety of electron rich arenes such as anilines and anisoles, and also for weakly activated arenes such as m-xylene. Reactions of more challenging substrates bearing electron withdrawing groups were significantly accelerated using a Lewis base co-catalyst, diphenyl selenide. The synthetic utility of the reaction was demonstrated in the formal synthesis of toltrazuril, an anticoccidial agent, and the functionalisation of biologically active compounds such as metaxalone, a muscle relaxant.



The thiocyanation procedure was also combined with a bromination reaction using NBS in a one-pot tandem iron-catalysed process resulting in dual functionalisation of an arene building block. The synthetic utility of this was demonstrated by conversion to a trifluoromethyl thioether using a Langlois-type reaction,[4] followed by various palladium-catalysed cross-coupling reactions using the bromide functionality.



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Ubiquitin binding peptides

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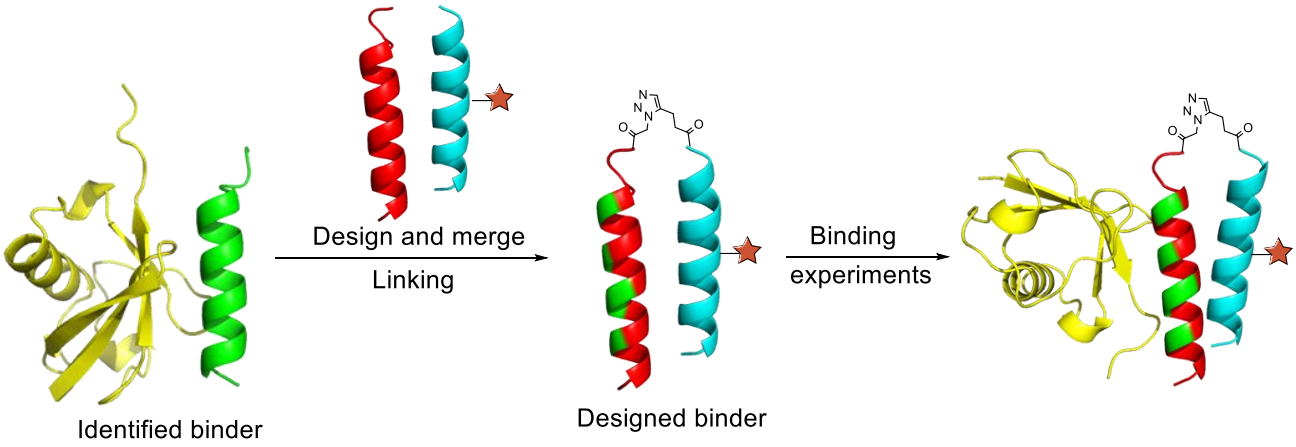
Ubiquitination is an important post-translation protein modification, linked to a large range of cellular processes. Ubiquitin (Ub) binding proteins generally bind through independently folded ubiquitin binding domains of 20-150 amino acids, which bind to the hydrophobic patch of the β-sheet of Ub through an α-helical structure.[1–3] The ubiquitin interacting motif (UIM) and the "reversed" motif interaction with ubiquitin (MIU) bind through single free standing α-helix. The UIM is a short 15 aa motif and is identified though a consensus sequence. UIMs generally bind to Ub with moderate affinities of 0.1-1mM.[3–5] MIUs bind Ub with a reversed orientation and some are known to have higher affinities compared to UIMs with k_D's of around 25 µM.[6,7]

This project aims to design stronger ubiquitin binding peptides based on UIM and MIUs. We present a short version of a UIM with improved binding compared to the literature. The project further investigates methods for improving binding though sequence design and by inducing structure via coiled coil formation of the single stranded binding helices.



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Direct Minisci-Type C−H Amidation of Purine Bases

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Purines are one of the most widely occurring *N*-heterocycles in nature.[1] As well as forming the building blocks for DNA and RNA, they are also significant components of important biomolecules such as ATP, GTP, cAMP, CoA, and NADH.[1] Purine bases are therefore unsurprisingly prevalent in biological and pharmaceutical applications (Figure 1). The ability to directly and selectively C-H functionalise these purine motifs would therefore be highly advantageous.

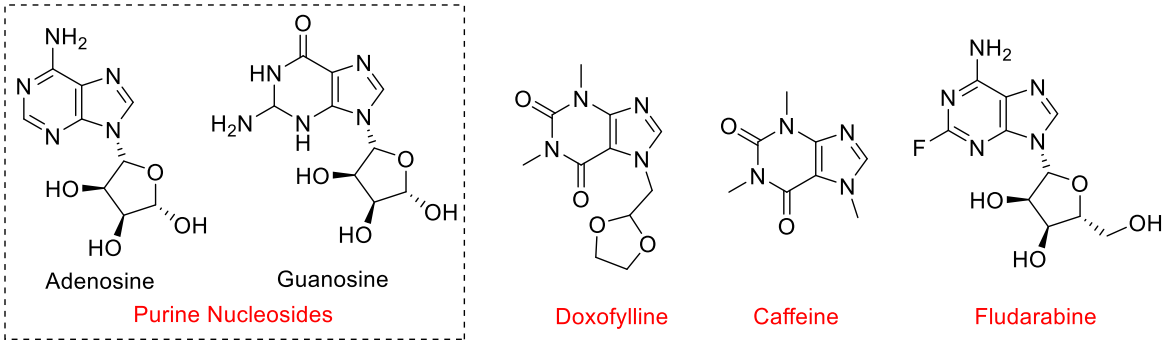
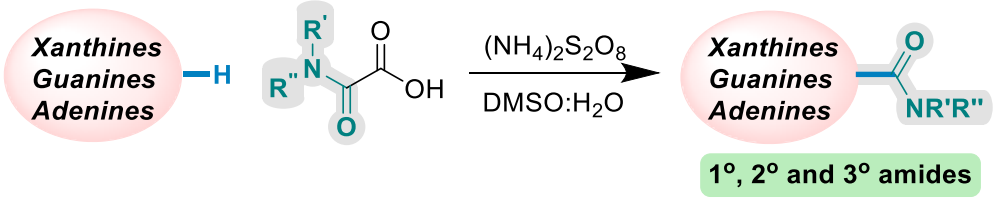


Figure 1: Examples of Purines Found in Nature and Purine Drugs

We present the first method for direct C-H amidation of purine bases for the functionalisation of a wide range of xanthine, adenine and guanine structures, including nucleosides and many well-known drug molecules (Scheme 1).[2] The protocol is capable of installing primary, secondary, as well as tertiary amides. Our variation of the Minisci reaction also has the advantage of being metal-, catalyst- and light-free, thus rendering it cheap, operationally simple, and scalable.[3, 4] By virtue of the tolerance of this protocol to many functional groups, we were also able to demonstrate further modifications of the amidated purine products.



Scheme 1: Minisci Amidation of Purines Protocol[2]

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Rare earth NHC complexes for biopolymer synthesis

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Polymerisation of cyclic esters is facilitated by the use of metal catalysts and the properties of the polymer product depend strongly on the characteristics of the metal centre and ligand set used. The most widely used biopolymer is currently polylactic acid and the industrially preferred catalyst is $Sn(Oct)_2$, however, $Sn(Oct)_2$ has poor control resulting in a broad range of polymer lengths and atactic chains.[1] Tin is also problematic as the reaction requires temperature of ca. 140°C and the natural reserves of elemental tin are critically low.[2]

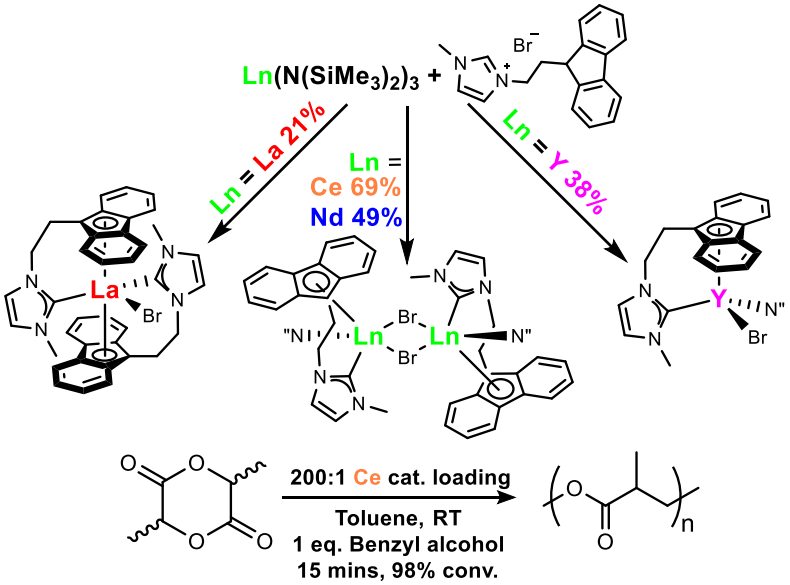

Figure 2 - Catalyst synthesis, yields and representative polymerisation conditions

Rare-earth metals despite their name are relatively abundant in the crust and have shown extreme activity towards lactide in polymerisation reactions so we are interested in their use. High catalytic activity will enable lower catalyst loadings, decrease reaction temperature requirements and enable polymerisation of more stable monomers such as γ-butyrolactone. The ligand developed by our group consists of a fluorenyl-tethered methyl N-heterocyclic carbene (NHC).[3,4] This should provide additional benefits to the synthesis and reactivity of the metal complexes including ring-slippage, low steric hindrance, NHC electron donation and chelation *via* the bidentate ligand preventing redistribution.

Synthesis of the yttrium, lanthanum, neodymium and cerium complexes has been successful, and all 4 tethered complexes have shown activity towards lactide with ca. 94% conversion of *rac*-lactide over 16 hours at 130°C. Initial experiments with the dimeric cerium catalyst have also shown promising conversion of >98% in 15 minutes at room temperature.

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Recent Synthesis From Lignin Derived Starting Materials

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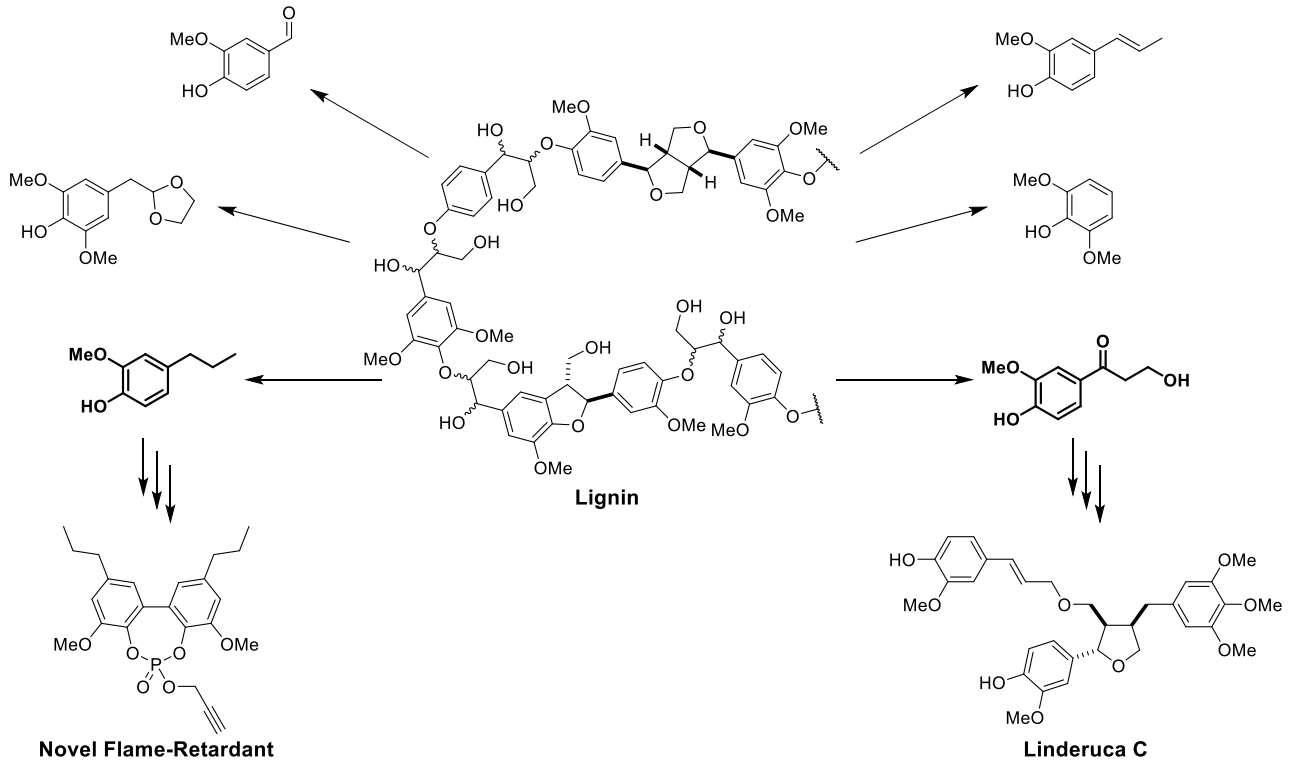
Lignin is a heterogenous bio polymer composed of aryl ring-containing monomers connected by various interunit linkages.[1] Lignin represents the most abundant renewable source of aromatic compounds, and depolymerisation of lignins using different methodologies leads to a large pool of aromatic monomers with a range of functional groups.[2] Some recent examples of synthesis starting from from these lignin derived monomers by the Westwood group is reported here, in particular the oxidative coupling of 4-propylguaiacol[3] towards a novel flame-retardant, and the synthesis of natural product Linderuca C[4] from various lignin derived monomers.



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Diversity-oriented libraries from benzylic boronic esters via a Pd-catalyzed Matteson reaction of arylboronic acids

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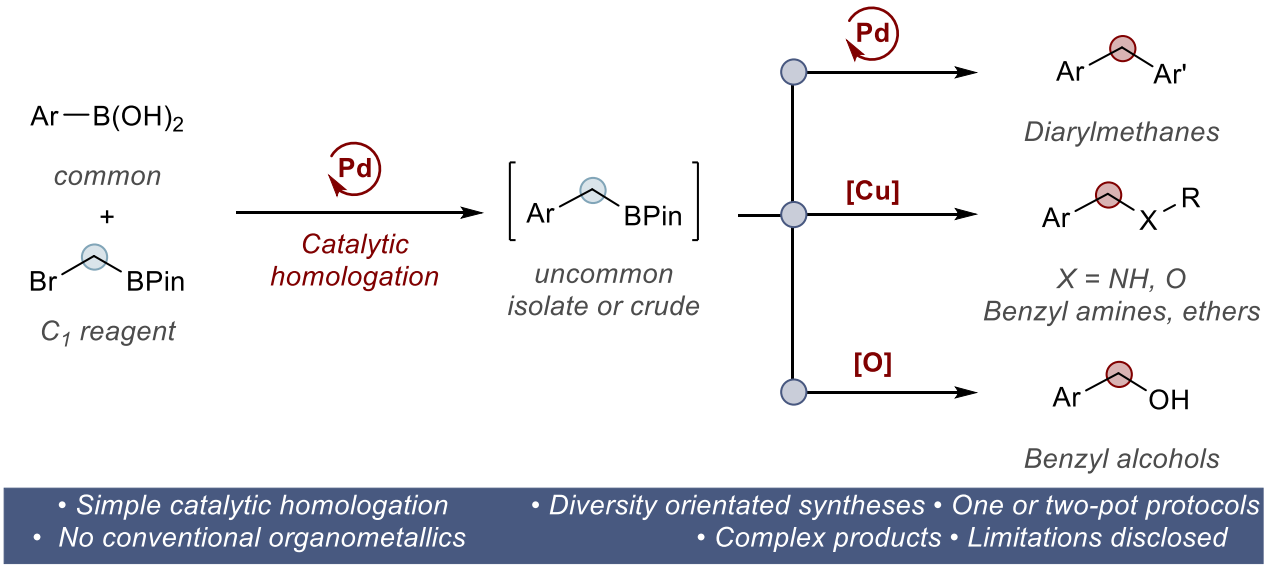
The rapid construction of small molecule libraries under mild conditions is a core facet of pharmaceutical research in both academic and industrial settings.[1] Approaches to the construction of classical organoboron linchpins, widely utilized in Suzuki–Miyaura and Chan–Lam couplings, typically require the use of stoichiometric organometallic reagents.[2] We have recently disclosed an alternative conceptual approach to the Matteson homologation by using a halomethyl boronic ester as a highly reactive surrogate carbenoid.[3] Under Pd catalysis, this reagent undergoes facile oxidative addition to generate bench stable benzylic BPin esters that are commercially limited due to the instability of the requisite boronic acid intermediate generated during conventional methodologies. With over 40 examples in hand, we demonstrate the synthetic utility of these C(sp^3)–B products in a variety of Pd and Cu– mediated protocols to assemble a diverse library of compounds bearing pharmaceutically desirable functional groups. Current limitations of the catalytic homologation are discussed.



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The tri-fluoro *t*-butyl (TBTF) motif

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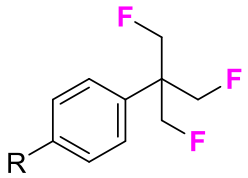
The tri-fluoro *t*-butyl group (TBTF) is a largely unexplored motif, with few syntheses and those reported involving multiple steps.[1] The TBTF group has potential value within bioactives design, where fluorine is often introduced into lead molecules in order to influence their lipophilicity (LogP) and improve pharmacokinetics. The t-butyl group is relatively common in pharmaceutical and agrochemical products, although it raises Log P.[2] Interestingly the TBTF significantly reduces Log P relative to t-butyl group and its synthesis and properties have become of interest to our group.

This poster will outline the synthesis and properties of the aryl-TBTF group, as well as elaborations to generate med-chem like products. The conformation of the TBTF group has also been explored through crystallography and computation. A synthesis incorporating the TBTF group into an existing t-butyl containing agrochemical molecule will also be outlined.



Aryl-TBTF motif

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Isothiourea-Catalysed Acylative Kinetic Resolution of Tertiary Pyrazolone Alcohols

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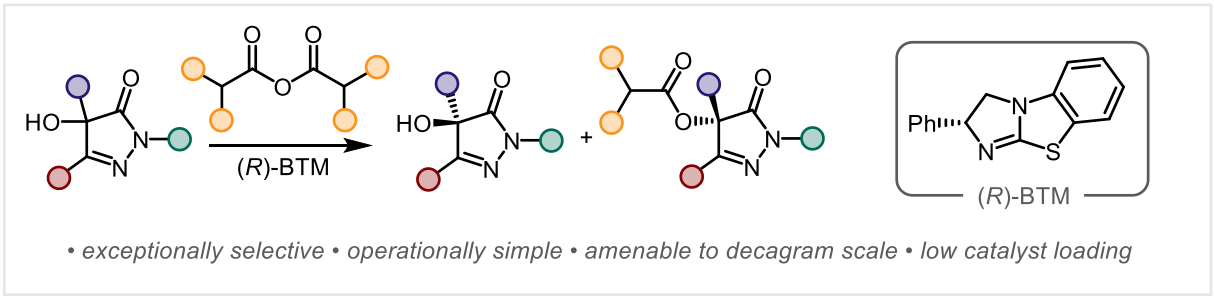
Pyrazolones are a widely prevalent heterocyclic motif in biologically relevant pharmaceutical and agrochemical compounds. However, routes to access enantioenriched pyrazolone derived tertiary alcohols remain scarce with the limited routes available possessing issues with both functional group tolerance and limited scope. The use of isothiourea organocatalysts has emerged as a powerful strategy in recent years, with their application for the acylative kinetic resolution of both secondary alcohols widely studied. A ***widely recognized remaining challenge*** is to develop the kinetic resolution of **tertiary alcohols** as (i) acylation is inherently difficult due to the sterically hindered nature of the alcohol; (ii) the acylation catalyst is required to discriminate between enantiomers bearing three non-hydrogen substituents at the carbinol centre.[1]

In this work we report the application of isothiourea catalysts in the kinetic resolution of pyrazolone tertiary alcohol derivatives. The reaction exhibits extremely high selectivity across a broad range of substrates (>30 examples, selectivity factors typically >200), including pyrazolones derived directly from several pharmaceutical compounds at low catalyst loadings. The reaction is also highly amenable to scale up, with decagram reactivity showing no drop in reaction efficiency.



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Enantioselective Access to α-Aryl Ketones by a Cobalt Catalysed Semipinacol Rearrangement

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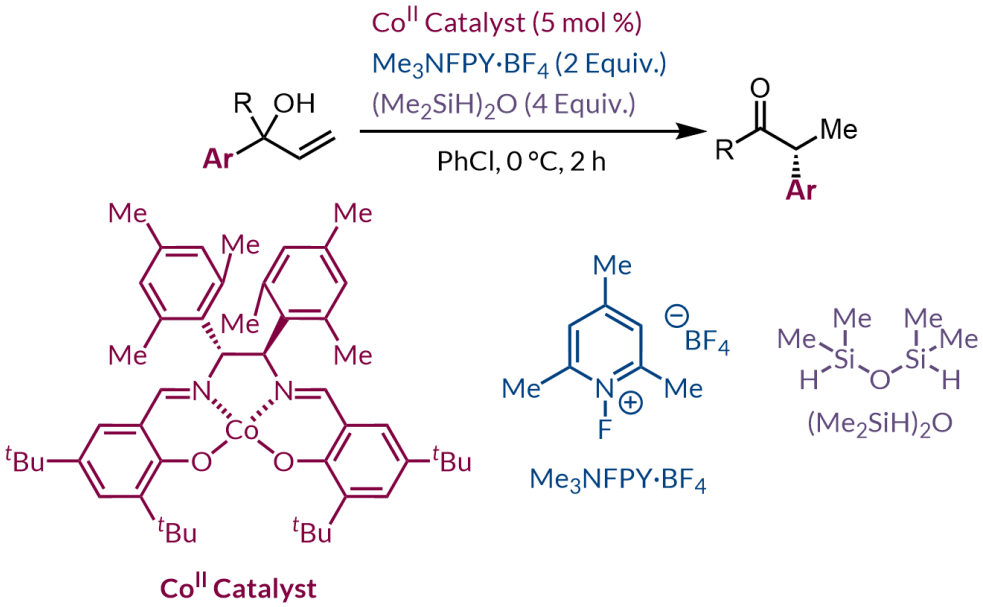
Enantioenriched α-aryl carbonyl compounds are useful synthetic targets in organic chemistry as they appear in a number of bioactive natural products and marketed pharmaceuticals.[1,2] The enantioselective synthesis of tertiary α-aryl ketones, through transition metal catalysed enolate arylation, poses challenges as products are prone to racemisation under basic conditions[3]. Our cobalt-catalysed methodology provides enantioselective access to this sensitive tertiary motif through a semipinacol rearrangement pathway using a tamed carbocation-like intermediate. The 1,2-aryl migration occurs after hydrogen atom transfer and a radical polar crossover event[4] with high yield (up to 95%) and enantioselectivity (up to 99 : 1 er) using a catalytic amount of an appropriate chiral cobalt salen complex.



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The development of oxaziridine-based methionine spin-labels for EPR

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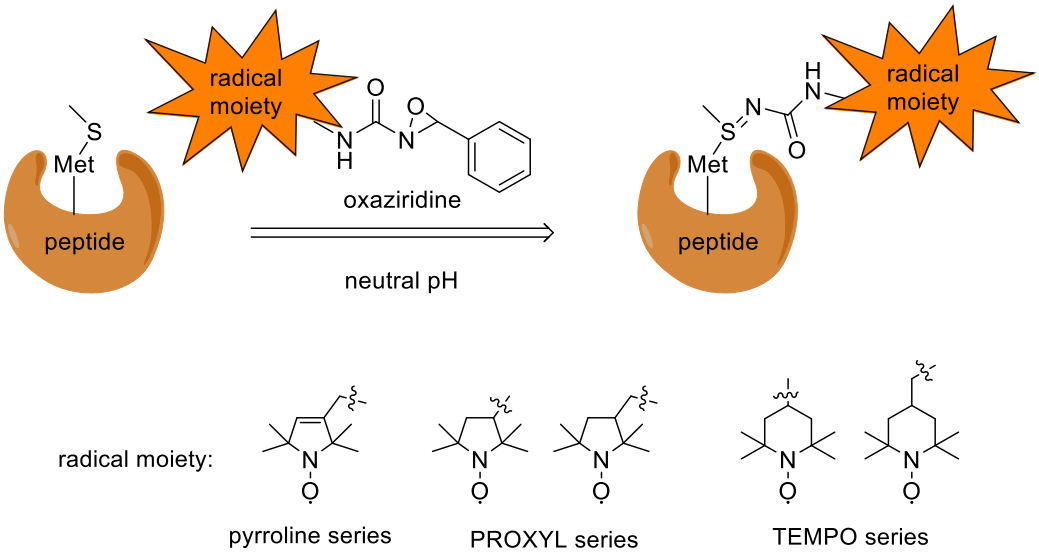
Methionine (Met) is a sulfur-containing proteinogenic amino acid playing various biophysical and biochemical functions. Due to its rare occurrence on the protein surface, Met has become a potentially great protein modification target without modifying and compromising other surface-accessible amino acid residues. Therefore, the physiological function of modified proteins will not be interfered with. Recently, redox-activated chemical tagging (ReACT) has become the first method to modify Met residues specifically over other nucleophilic amino acids at physiological conditions (**Scheme 1**).[1] A novel application of ReACT has been proposed in the Florence group: combining site-directed spin-label (SDSL) with Met-specific ReACT. Due to Met's rareness on the protein surface, ReACT will only modify Met residues introduced by site-directed mutagenesis of proteins with a low risk of affecting the protein's normal function. This offers potential advantages over the use of SDSL probes to modify cysteine (Cys) residues. This poster details synthetic access to a range of nitroxide radical-containing oxaziridine probes and assessment of their selectivity towards Met over Cys and other amino acid residues. Currently, pyrroline nitroxide radical oxaziridine has been found with a 100-fold selectivity on Met over Cys, and further chemical modifications will be carried out to improve the selectivity.



Scheme 1*. Schematic presentation of methionine selective ReACT*

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Your glassware matters! Imaging vessel shape and mixing profiles

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Reid Group Research at the University of Strathclyde is developing software, *Kineticolor*, to enable computer vision analysis of chemical and physical processes. This produces quantified and reproducible data from visual information captured in a video, allowing temporally and spatially resolved analyses of kinetics in a non-contact manner. The applications are numerous: enhanced forensic spot tests, tracking the photodegradation of materials, monitoring the degradation of catalysts, solid and liquid phase peptide synthesis and understanding of mixing phenomena.[1-4]

This poster reports the significance of mixing in chemical processes. A case study involved monitoring the activation of Crabtree's catalyst with hydrogen gas (Fig 1a). ΔE, a measure of average contrast change, shows that the activation is mass transfer limited (Fig 1b). Increasing the gas-liquid surface area increased the activation rate. This is one of many demonstrations which should emphasise to researchers the importance of considering the effects mass transfer has on their processes. Other case studies and computational fluid dynamic (CFD) models (velocity profiles, Fig 1c) show how mixing issues arise when trying to scale up a process for commercialisation.

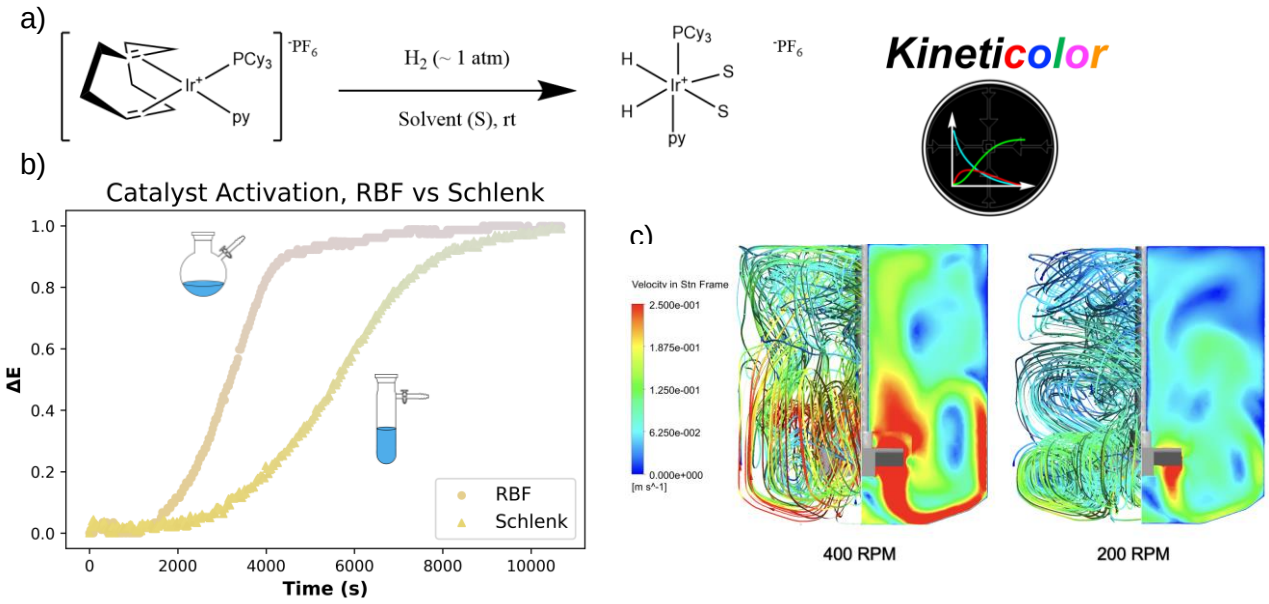

Figure 1: a) Chemical scheme of Crabtree's catalyst activation for hydrogenation. b) ΔE vs Time (s), tracking Crabtree's catalyst activation in different shaped vessels. c) CFD modelling results, quantifying and visualising the effects of reactor stirring speed on local velocity.

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Sensing Intracellular Esterase Activity Using Stimulated Raman Scattering

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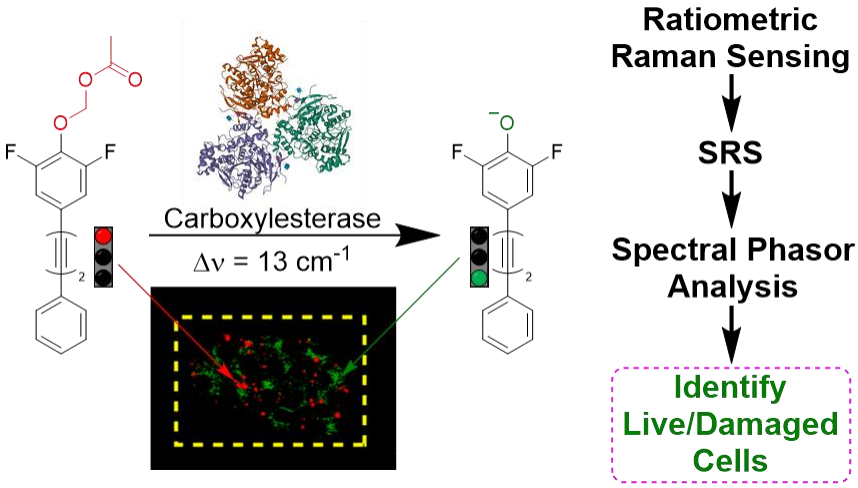
Carboxylesterases (CEs) are a class of enzymes that catalyze the hydrolysis of esters in a variety of endogenous and exogenous molecules. CEs play an important role in drug metabolism, in the onset and progression of disease and can be harnessed for prodrug activation strategies. As such, the regulation of CEs is an important clinical and pharmaceutical consideration.

In this poster we will describe the first ratiometric sensor for CE activity[1] using Raman spectroscopy based on a bisarylbutadiyne scaffold.[2] The sensor is highly sensitive and specific for CE detection and has low cellular cytotoxicity. In hepatocyte cells, the ratiometric detection of esterase activity is possible which was validated by multimodal imaging with standard viability stains used for fluorescence microscopy within the same cell population. In addition, the detection of localized ultraviolet damage in a mixed cell population proved possible using stimulated Raman scattering microscopy coupled with spectral phasor analysis. This sensor demonstrates the practical advantages of low molecular weight sensors that are detected using ratiometric Raman imaging and will have future applications in drug discovery and biomedical research.



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Photoredox Mediated Oxidation and Functionalisation of Aryl Alkyl Ethers

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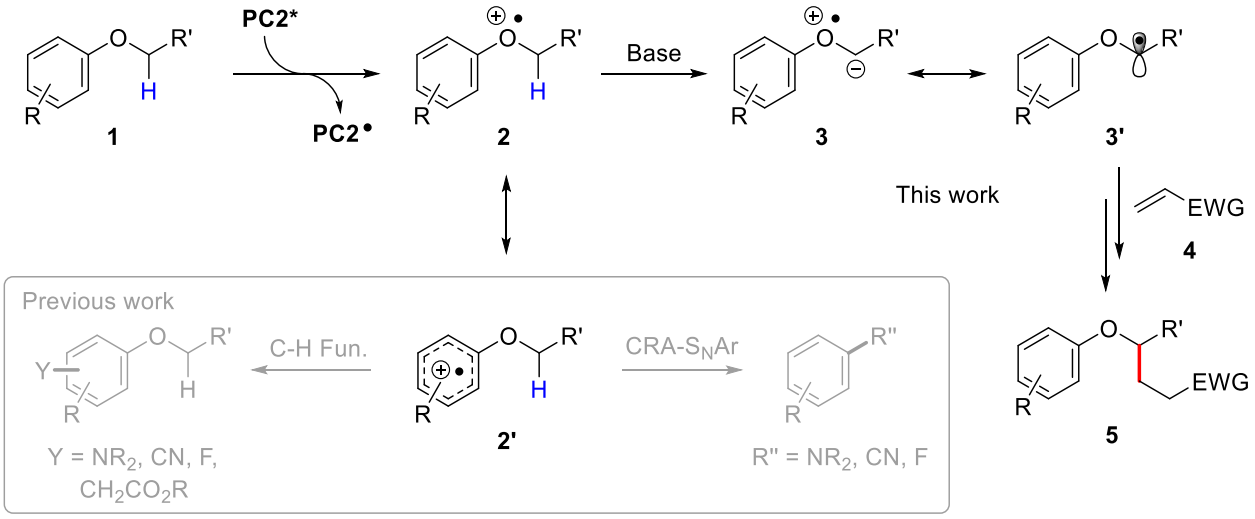
It has been widely reported that aryl alkyl ethers can be oxidized to their corresponding radical cations through single electron transfer using acridinium based salts as strongly oxidizing organic photocatalysts.[1] These radical cations have then been shown to enable facile functionalization of the aryl ring of these ethers either through C-H functionalization or cation radical-accelerated nucleophilic substitution (CRA-S_NAr).[1-9] However, a novel approach to the use of these aryl alkyl ether radical cations involves deprotonation of the α-carbon relative to the oxygen atom to furnish a neutral α-aryloxyalkyl radical (*Scheme 1*). This poster highlights the development and application of this chemistry.



Scheme 2: *Examples of previous work in this field and theoretical basis and proposed outcome for the work presented in this poster.*

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Development of a Molecular Reference Standard for Photoacoustic Imaging

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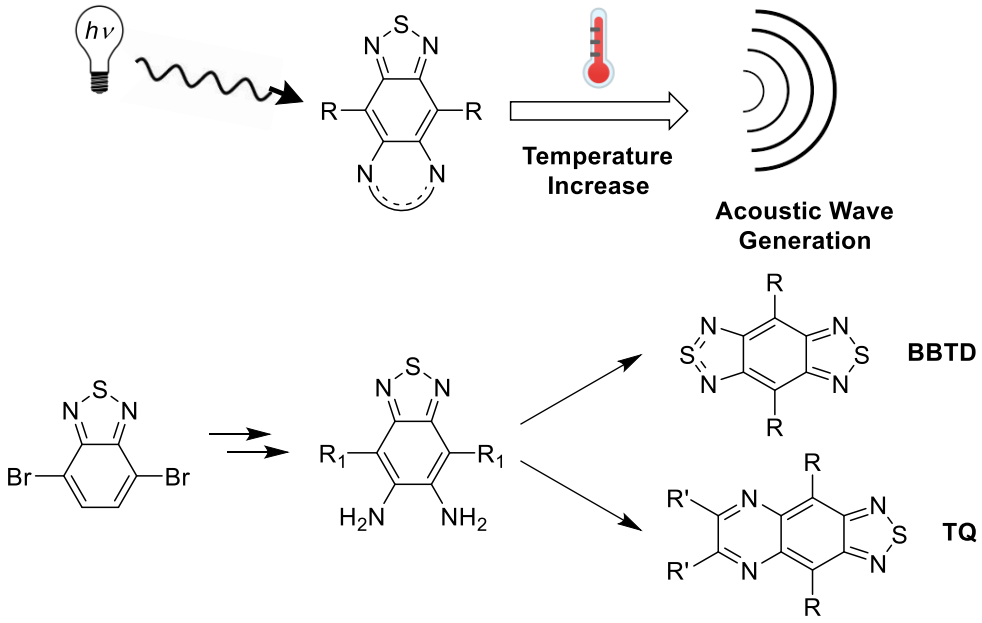
The photoacoustic (PA) effect refers to the process of light absorption followed by the production of an acoustic wave *via* localised pressure changes produced by heating.[1] The PA effect can be utilised in photoacoustic imaging (PAI), where images are generated from the acoustic signal. PAI offers a modality with improved penetration depths than optical imaging and improved resolution when compared to ultrasound imaging.[2,3]

Currently no standardised references currently exist for PAI making it difficult to compare proposed contrast agents. BBTDs have been previously reported for potential PA contrast agents due to their high rate of non-radiative decay and near IR absorption.[4,5] It was proposed that BBTDs and the related TQs could make attractive standards in PAI due to their relatively broadband absorption. Further improvements to the BBTD and TQ derivatives aim to improve water solubility for biologically relevant comparison.



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Computationally Guided Catalyst Design Towards Enhanced Iridium(I) Catalysts

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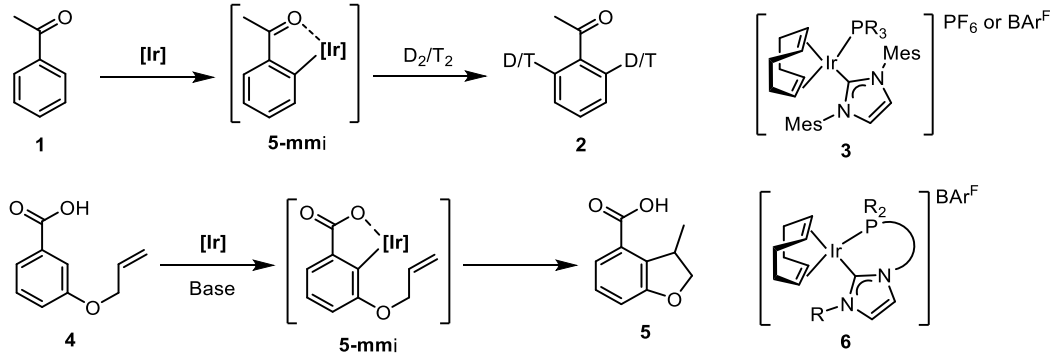
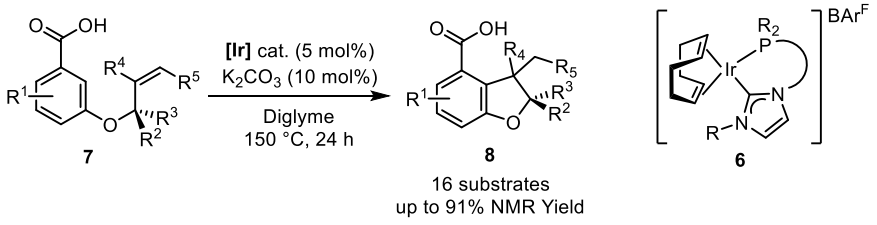
The activation and subsequent functionalisation of C-H bonds is a powerful transformation for the synthetic organic chemist. One of the simplest and most fundamental C-H activation and functionalisation processes is that of hydrogen isotope exchange (HIE). Over the past decade, the Kerr group have developed a range of monodentate iridium(I) NHC-phosphine catalysts (**3**) which are highly efficient HIE catalysts, capable of C-H activation *via* a 5-membered metallocyclic intermediate (**5-mmi**).[1,2] Most recently, we have applied bidentate iridium(I) NHC-phosphine Kerr catalyst (**6**) in the activation of C-H bonds for use within C-C bond formation. As shown in Scheme 1, bidentate catalyst (**6**) can undergo C-H activation *via* a **5-mmi**. Subsequent alkene coordination and migratory insertion of the aryl-iridium bond into the alkene affords cyclised dihydrobenzofuran products (**5**).



By undertaking a Design of Experiments (DoE) approach, in conjunction with the implementation of a synthetically tractable carboxylate directing group, a range of 2,3-dihydrobenzofurans (**8**) have been synthesized *via* an intermolecular hydroarylation process (scheme 2). In combination with these experimental studies, DFT calculations have also been conducted to probe the reaction mechanism for this process. Furthermore, *in silico* screening of alternative ligand motifs has been conducted in an attempt to identify enhanced catalysts which can, ultimately, improve the process and expand the substrate scope.



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The Effects of Tail Group Modifications on Antibacterial Activity of Strathclyde Minor Groove Binders (S-MGBs)

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The first-in-class S-MGB, MGB-BP-3[1], has completed Phase IIa clinical trials for the treatment of *Clostridioides difficile,* but also has strong activity against other Gram-positive bacteria, such as *Staphylococcus aureus*[2]. Although there has been an extensive optimization of S-MGB structures to generate potent antibacterial compounds, the 'tail group' moiety has been underexplored relative to its, now understood, importance[3,4]. Herein, a large panel (**Figure 1**) of S-MGBs was designed and synthesized to explore structure-activity relationships relating to the 'tail group' moiety. This panel explores the importance of aliphatic, aromatic and heteroatoms-bearing tail groups, by assaying them against several key bacterial pathogens and using a thermal shift assay to measure DNA binding affinity. This analysis shows that basic tail groups tend to promote DNA binding and antibacterial activity. However, potent S-MGBs can still be obtained even when lacking a traditional 'tail group'. This work is informing future designs of more potent S-MGBs.

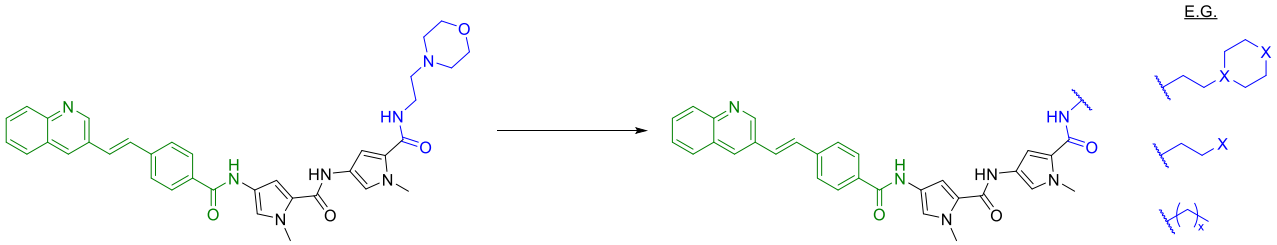

Figure 3 –Developing new tail groups with various moieties:- aliphatic chains/rings, aromatic rings, additional heteroatoms etc. Head Group (Green), Backbone (Black) and Tail Group (Blue)

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First-principles study of electronic and optical properties in 1-dimensional oligomeric derivatives of telomestatin

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The ground-state electronic structure and optical absorption profiles of a series of linear oligomers (n = 1-10) inspired by the macrocyclic natural product telomestatin (Figure 1) were investigated using real-space self-interaction corrected (time-dependent) density functional theory. The neutral species exhibits length-dependent formation of plasmonic excitations in the UV region, which is augmented by polaron-type absorption in the IR when the chains are doped with an extra electron/hole. When combined with a lack of absorbance in the visible region, these oligomers appear to be promising candidates for applications such as transparent antennas in dye-sensitised solar energy collection materials.

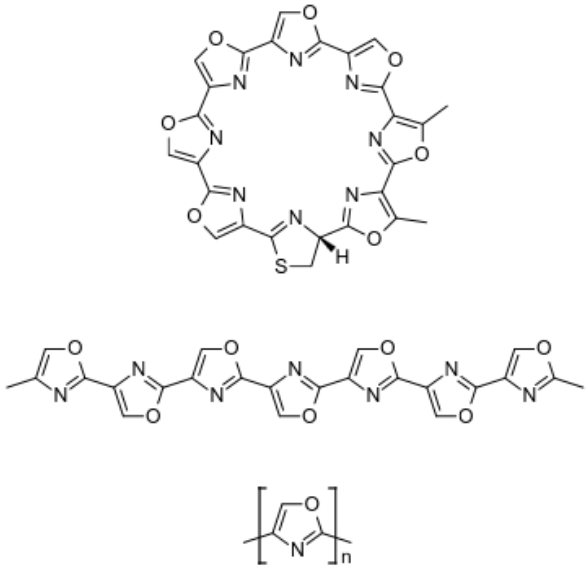

Figure 1. The all-cis natural product R-telomestatin (top), telomestatin-based linear all-trans model (middle), and overall schematic of the methyl-capped linear 1,4-polyoxazole oligomers explored in this study (bottom).

Design of cyclic peptide inhibitors to SARS-CoV-2 spike interaction with GRP78

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The Covid-19 pandemic has caused huge disruption over the last three years. The number of deaths has now risen to almost 7 million and the total number of new confirmed cases continues to rise.[1] New broad-spectrum antivirals are, thus, very much needed to combat the threat of new variants of the virus. Glucose Regulating Protein 78 (GRP78) is a molecular chaperone that typically resides within the endoplasmic reticulum but is translocated to the cell surface when cells are under stress.[2] Recent molecular docking studies found that a loop structure within the SARS-CoV-2 spike protein's receptor binding domain (RBD) had favorable binding affinities with cell surface GRP78, suggesting another route for virus entry to cells.[3,4] In this work we have designed and synthesised cyclic peptides that are derived from the wild-type and Omicron variants of this loop structure.[5] These peptides were tested for their ability to inhibit the binding of GRP78 with the wild type spike RBD and were found to both cause inhibition, with the Omicron variant showing higher binding affinity. This result was consistent with the greater transmissibility of the Omicron variant[5,6] opening the door for further development of these motifs, leading to a viable route to novel antivirals with activity against SARS-CoV-2.

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Synthesis of isovalery-dehydrobutyrine-proline thioester for bacterial pyrrolizidine biosynthesis

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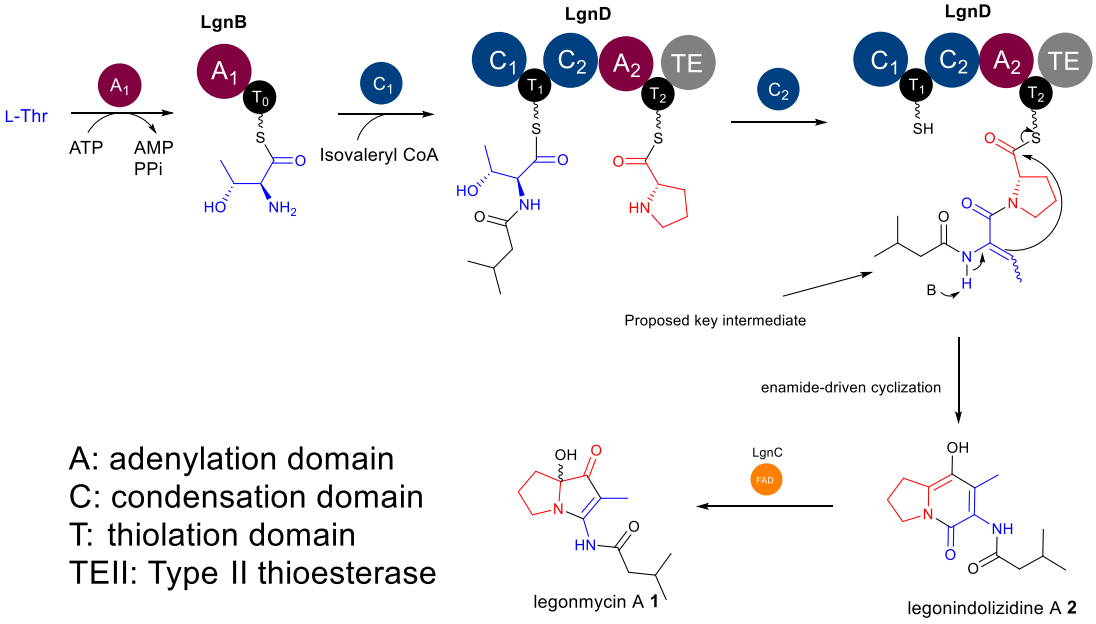
Pyrrolizidine alkaloids (PAs) are a group of naturally occurring alkaloids based on the structure of pyrrolizidine, and they are produced by plants as a defense mechanism against insect herbivores. More than 700 PAs have been identified in over 6,000 plants, and about half of them exhibit hepatotoxicity and they can result in damage to organs in the body, and could be a potential cause of cancer. PAs from bacterial origin are rare. In 2015, we discovered a new bacterial PAs called legonmycin A **1**. Biosynthetic investigation of legonmycins led a conclusion that legonmycin is biosynthesized from three building blocks (precursors/substrates) Pro, Thr and fatty acid CoA to form bicyclic legonindolizidine intermediate **2** (5+6), followed by multistep oxidation/rearrangement to decorate PA ring system (5+5) [1]. Recent studies indicated that two multidomain non-ribosomal peptide synthetases (LgnB and LgnD) together with the newly identified amino-acyl transferase/type II thioesterase (LgnA) are responsible for the assembly of **2**, the last intermediates of the **1** biosynthesis [2].



During the study, protein-tethered isovaleryl(IV)-dehydrobutyrine (Dhb)-Pro-thioester is likely to be the last intermediate for the encarbamide-driven heterocyclization by an unusual Type I thioesterase LgnD-Te to produce **2** [2]. However, the conformation of Dhb in this putative intermediate has remained elusive.
In this presentation, I will report the synthesis of the synthetic mimic IV-(E/Z)Dhb-Pro-SNAC. Once the synthetic molecules are produced, I will compare them with the biosynthetic intermediates with the aim of identifying the correct configuration.

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1,3-Dioxane synthesis using $TiCl_4$

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Cyclic acetal formation is a very well-known and widely used reaction. Recent advances in the liquid crystal area of studies and the discovery of the ferroelectric nematic phase for which a large molecular dipole is one of the prerequisites have employed the incorporation of the 1,3-dioxane ring into the structure of liquid crystalline materials.(1) One particular family of compounds branching from a molecule called DIO (see Fig. 1) all have 1,3-dioxanyl functionality within their structures. Moreso, desired liquid crystalline properties are only exhibited when a trans-1,3-dioxane is present in the structure.(2) Due to the challenges that arise from separation of the isomeric mixture of the products formed *via* conventional means of purification such as flash chromatography, we propose an alternative synthesis method of 1,3-dioxanes which allows some degree of control over the cis/trans isomer ratio of the ring which deviates from the current reported literature ratios.(2)

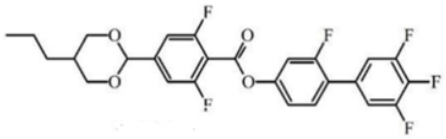

Figure 4 *The chemical structure of DIO.*

The alternative synthesis strategy capitalises on the Lewis acidity of $TiCl_4$ (**2**) which is reacted with a suitable the 1,3-diol (**1**) to form a cyclic complex intermediate (**3**) which subsequently reacts with the aldehyde (**4**) to produce the desired product (**5**) as shown in scheme 2:

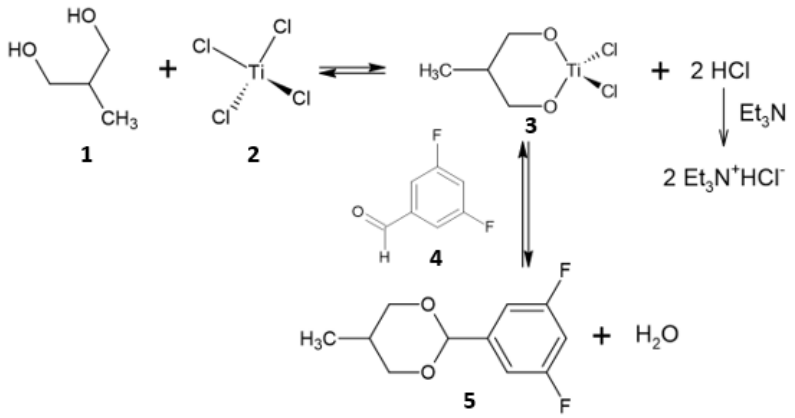

Figure 5 *The scheme of 1,3-Dioxane formation using $TiCl_4$.*

It should be noted that while similar reactions can be found in the literature (3), such synthesis method has never been used in order to form cyclic acetals or to control cis/trans ratio of the products formed. By changing the reaction conditions, the cis/trans ratio is found to vary from 72:28 to 85:15.

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Design and synthesis of novel peptidomimetic inhibitors of SARS-CoV2

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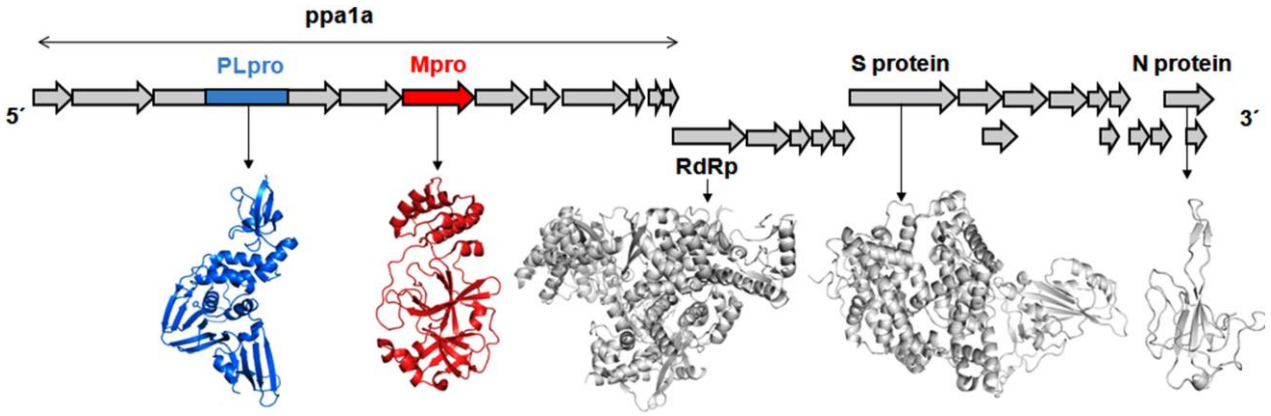
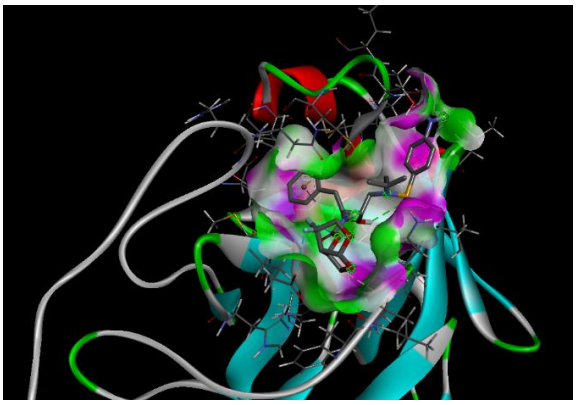
The objective of this project is to develop innovative peptidomimetic drugs targeting human coronaviruses. Given the resemblance of human coronavirus proteases, the inhibitors for the major protease (Mpro) and papain-like protease (Plpro) holds potential as effective therapeutics against SARS-CoV-2 and other related coronaviruses. In this poster, we present our work on the design, docking, and synthesis of potential novel Mpro inhibitors. Several of these compounds have been synthesized, and Mpro has been obtained through expression and purification techniques for conducting inhibition assays to assess their activity. Moving forward, our research will concentrate on synthesizing additional derivatives and evaluating the inhibitory activity of these compounds in vitro.





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List of Meetings

The RSC Scottish Regional Organic Division Meeting was first run in 1972 at the University of Edinburgh and was referred to as the Scottish Perkin Meeting - Perkin, referring to the Organic Division of the RSC named after Sir William Henry Perkin.

Meeting	Year	Location	Plenary Lecturer(s)
1	1972	University of Edinburgh	
2	1973	University of Strathclyde	
3	1974	University of Stirling	
4	1975	University of St Andrews	G. Maier
5	1976	Heriot Watt University	
6	1977	University of Glasgow	
7	1978	University of Aberdeen	
8	1979	University of Dundee	P. v R. Schleyer
9	1980	University of Edinburgh	R. A. Abramovich
10	1981	University of Strathclyde	(G. Ourisson) C.W. Rees
11	1982	University of Stirling	
12	1983	University of St Andrews	E. Vogel
13	1984	Heriot Watt University	H. Felkin
14	1985	University of Glasgow	P.D. Magnus
15	1986	University of Aberdeen	A. Van Leusen
16	1987	University of Dundee	W. Oppolzer
17	1988	University of Edinburgh	D. Arigoni
18	1989	University of Strathclyde	K. U. Ingold
19	1990	University of St Andrews	M. Regitz
20	1991	Heriot Watt University	A. B. Smith III
21	1992	University of Edinburgh	H. Prinzbach
22	1993	University of Aberdeen	M. Schlosser
23	1994	University of Dundee	R. W. Hoffman
24	1995	University of Glasgow	M.H. Zenk
25	1996	University of Edinburgh	L. N. Mander
26	1997	University of Strathclyde	A. G. Myers
27	1998	University of St Andrews	A. Hirsch
28	1999	University of Aberdeen	D. N. Reinhoudt
29	2000	Heriot Watt University	R. Ramage, E. J. Thomas
30	2001	University of Glasgow	L. S. Liebeskind, V. Snieckus
31	2002	University of Dundee	R. Schmidt
32	2003	University of Edinburgh	D. Hilvert
33	2004	University of St Andrews	L. F. Tietze
34	2005	University of Strathclyde	P. Renaud
35	2006	Heriot Watt University	F. Würthner
36	2007	University of Glasgow	E. Carreira
37	2008	University of Aberdeen	B. Gerwick
38	2009	University of Dundee	P. Kocienski
39	2010	University of Edinburgh	B. Feringa
40	2011	University of Strathclyde	M. Lautens, J. Lacour

Meeting	Year	Location	Plenary Lecturer(s)
41	2012	University of St Andrews	C. Hunter, GB Hammond
42	2013	Heriot Watt University	J. Bower
43	2015 (Jan)	University of Glasgow	M. Willis
44	2016 (Jan)	University of Aberdeen	A. Davis
45	2017 (Jan)	University of Dundee	T.Heightman
46	2018 (Jan)	University of Edinburgh	V. Aggarwal
47	2018 (Dec)	University of Strathclyde	J. Clayden
48	2020 (Jan)	University of St Andrews	V. Gouverneur
49	2021 (Jan)	Heriot Watt University (on-line)	W. van der Donk
50	2022 (Jun)	University of Glasgow	D. Procter, A. Hulme, D. MacMillan
51	2023 (Jun)	University of Aberdeen	K. Wheelhouse