RSC Organic Chemistry Community Scottish Regional Meeting 2025

Perkin Meeting

23rd June 2025

University of Edinburgh

Organised by Dr Andrés García-Domínguez and Dr Benjamin N. Bhawal

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Registration desk will be located in the ground floor of the Nucleus building.

Talk and Poster Sessions

Talks will take place in the Oak Lecture Theatre, which can be accessed from the first floor. Poster sessions will run break in the Alder Lecture Theatre during the lunch and afternoon coffee breaks.

Catering & Drinks reception

Catering and drinks reception will be provided by BlueSky and served in the ground floor area. Please, inform the catering staff if you have a specific food allergy or dietary requirement.

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Please refrain from taking photos of slides, speakers or poster presenters during their presentations without their prior consent.

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There is a baby changing toilet facility in the ground floor. Please, do not hesitate to ask the servitors for directions if required

Quiet Rooms

There is a quiet area on the top floor of the Nucleus Building.

PROGRAM

09:00 – 10:00	**Arrival & Registration**
10:00 – 10:05	**Welcome & Opening Remarks** Prof. Colin Campbell, University of Edinburgh
10:05	**Session 1** Chair – Dr Benjamin N. Bhawal, University of Edinburgh
10:05 – 10:35	Dr Dominic R. Willcox, Heriot-Watt University *Accessing Silicon-Switch Chemical Space*
10:35 – 11:05	Prof. Andrew Sutherland, University of Glasgow *Design and Synthesis of Fluorescent Unnatural α-Amino Acids for Biological Chemistry*
11:05 – 11:35	Dr Kirsten McAulay, University of Dundee *Identification of KRAS PROTACs Targeting GTP-loaded Alleles*
11:35 – 12:05	Prof. R. Alan Aitken, University of St Andrews *New Reactions Based on the [1,2]-Wittig Rearrangement of o-Benzyloxybenzamides*
12:05 – 14:00	**Lunch & Poster Session**
14:00	**Session 2** Chair – Dr Andrés García-Domínguez, University of Edinburgh
14:00 – 14:30	Dr Joshua Barham, University of Strathclyde *New Concepts in Visible Light-Powered Catalysis: Organophotocatalytic Dyads and Auto-Photoredox Catalysis*
14:30 – 15:00	Dr Emmanuel T. Oluwabusola, University of Aberdeen *Isolation and Characterisation of Bioactive New Chlorinated Natural Products from the Deep-Sea Streptomyces acrimycini B188M101*
15:00 – 15:30	Dr Emma King-Smith, University of Edinburgh *Little Big Data: Machine Learning Strategies for Experimental Chemistry*
15:30 – 16:15	**Coffee Break & Poster Session**
16:15 – 17:15	**Plenary Lecture** Prof. Harry Anderson FRS, University of Oxford *Synthesis of New Carbon Allotropes*
17:15 – 17:30	**Presentation of Poster Prizes & Closing Remarks**
17:30 – 18:30	**Drinks reception**

Talks - Abstracts

ACADEMIC TALK

Accessing Silicon-Switch Chemical Space

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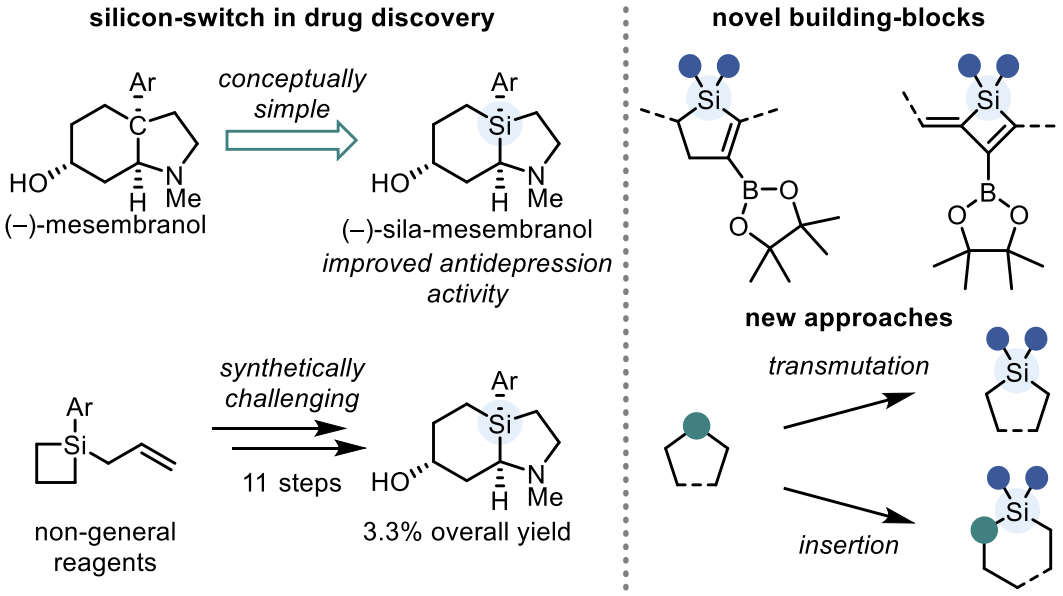
The chemical space of drug-like molecules has been estimated at 10^{60} different structures, which is more stars than the observable universe.[1] The overwhelming majority of approved drug molecules are made-up of a combination of hydrogen and three main-group elements (C, O, and N), as living organisms are principally made up of the same elements. Incorporation of silicon into drug molecules as a non-classical bioisostere of carbon, called a "silicon-switch", has been used in drug discovery to manipulate pharmacokinetically important parameters and expand the accessible chemical space.[2] The synthetic inaccessibility and poor structural diversity of existing silicon-switch molecules limits general uptake by medicinal chemists. In the Willcox group we seek to develop operationally simple methodologies to access new building-blocks containing silicon and explore new synthetic approaches to silicon-switch molecules.[3]



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ACADEMIC TALK

Design and Synthesis of Fluorescent Unnatural a-Amino Acids for Biological Chemistry

Andrew Sutherland*

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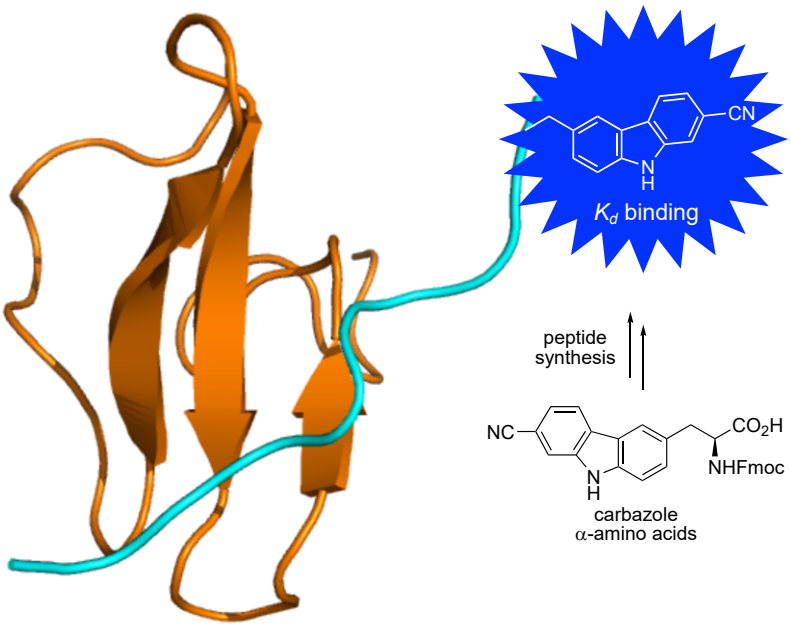
Abstract: Unnatural fluorescent amino acids are important analytical and diagnostic tools in many areas of biological and medical science.[1] Despite recent progress in the development of amino acid-based fluorescent probes, there is still a need for novel chromophore-containing amino acids that can be easily incorporated into proteins and peptides, retaining structure and function without the use of a spacer.[2]

Over the last 10 years, we have developed various classes of fluorescent unnatural a-amino acids designed to act as mimics of proteinogenic analogues.[3] Using transition metal-catalysed methods, rigid chromophores have been created that possess high quantum yields and display strong brightness. This presentation will describe the design and synthesis of amino acids that exhibit environment-sensitive fluorescence and have been used in assays to measure protein-protein binding and enzyme kinetics.[4]



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3. (a) J. D. Bell, A. H. Harkiss, D. Nobis, E. Malcolm, A. Knuhtsen, C. R. Wellaway, A. G. Jamieson, S. W. Magennis and A. Sutherland, *Chem. Commun*., 2020, **56**, 1887. (b) A. C. Dodds, H. G. Sansom, S. W. Magennis and A. Sutherland, *Org. Lett*., 2023, **25**, 8942.
4. (a) R. Clarke, L. Zeng, B. C. Atkinson, M. Kadodwala, A. R. Thomson and A. Sutherland, *Chem. Sci*., 2024, **15**, 5944. (b) O. Marshall, R. McGrory, S. Songsri, A. R. Thomson and A. Sutherland, *Chem. Sci*., 2025, **16**, 3490.

ACADEMIC TALK

Identification of KRAS PROTACs Targeting GTP-loaded Alleles

Vesna Vetma[a], Sohini Chakraborti[a], Emelyne Diers[a], Enrico Girardi[b], Natalia Karolak[a], Shakil Khan[a], Giorgia Kidd[a], Ross Mclennan[a], Suzanne O'Connor[a], Ilaria Puoti[a], Nicole Trainor[a], Claire Whitworth[a], Andre Wijaya[a], Jeff Wong[a], David Zollman[a], Will Farnaby[a], Johannes Popow[b], Alessio Ciulli*[a], Peter Ettmayer*[b], **Kirsten McAulay***[a]

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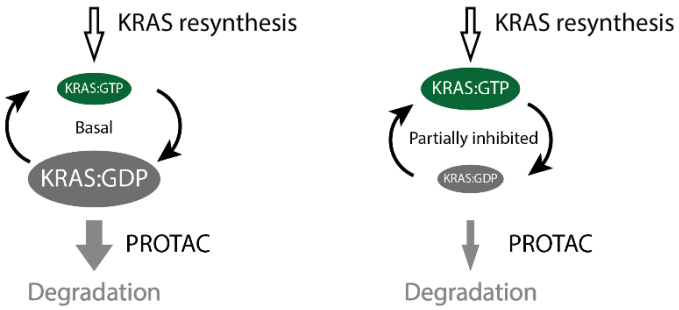
Kirsten rat sarcoma viral oncogene homolog (KRAS) is a frequently mutated in many cancers and is therefore a high priority drug target for oncology. Several mutations are capable of driving tumorigenesis, however, small molecules capable of tackling multiple mutations at once have not yet reached patients. Thus far, small molecule interventions have predominantly targeted only one mutation as well as affecting only 'inactive' GDP-loaded KRAS. However, several mutations are known to favour the GTP-loaded 'active' state. Building on the teams' previous work[1] and guided by biophysical data, we identified heterobifunctional VHL-based PROTACs capable of engaging 'active' KRAS. Such PROTACs can address a wider range of KRAS mutations. This talk will discuss the identification, synthesis and profiling of a highly efficacious 'KRASon' PROTAC which forms a very stable ternary complex between VHL and GTP-loaded KRAS, and which can degrade all KRAS variants leading to improved anti-proliferative effect *in vitro*.



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ACADEMIC TALK

New Reactions Based on the [1,2]-Wittig Rearrangement of *o*-Benzyloxybenzamides

R. Alan Aitken*, Argan Beaujean, Ryan A. Inwood, Lucy S. T. Jones, Ryan McHugh, Maurine Mongeot, Robert W. H. Ratsey and Josephine M. Stewart

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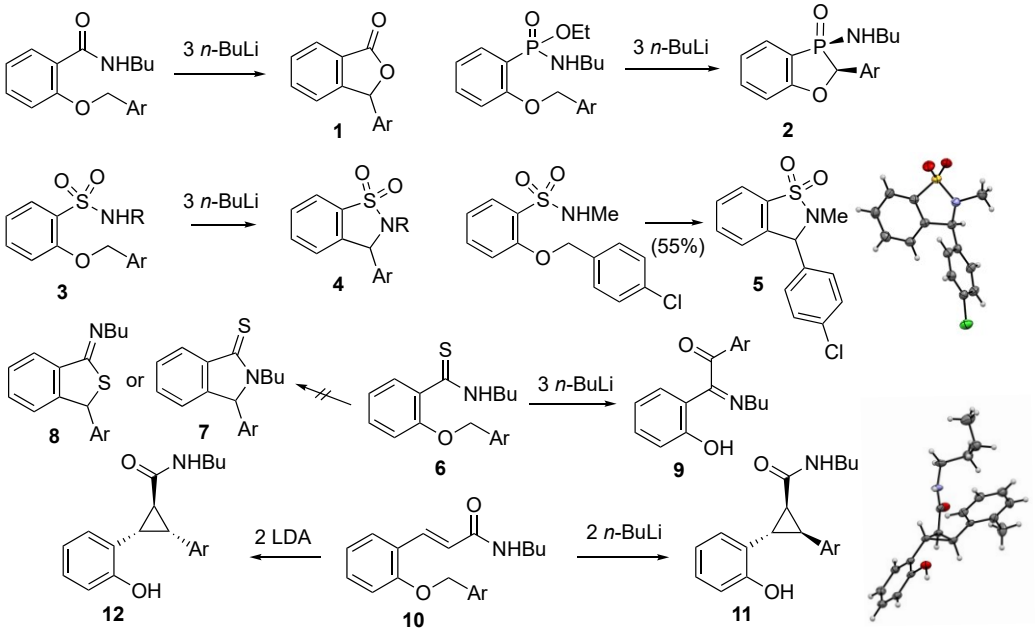
In recent work we have discovered the *N*-butylamide, CONHBu to be an effective facilitating group for the [1,2]-Wittig rearrangement of aryl benzyl ethers.[1] It is effective in *o*-, *m*- and *p*-positions to give diarylmethanol products with further cyclisation in the *o*-case giving 2-arylphthalides **1**. This chemistry has recently been applied to synthesis of a simple natural product and, with oxidative workup, to formation of hydroxyisoindolinone anticancer agents.[2] The corresponding phosphonamidates behave similarly leading to Wittig rearranged products for *m*- and *p*-cases,[3] but cyclisation occurs without rearrangement giving **2** for the *o*-series.[4]

In this talk I will present new unpublished results in three related areas:

1. Extension to *N*-alkyl benzyloxyarylsulfonamides which also gives Wittig rearranged products, and in the *o*-case **3** formation of benzisothiazoline dioxides **4**, including application to synthesis of an anti HIV agent **5**.

2. The reaction of *N*-butyl-2-(benzyloxy)phenylthioamides **6** which might be expected to give **7** or **8** but leads unexpectedly to 2-hydroxybenzil monoimines **9**.

3. Reaction of the vinylogous *N*-butyl-2-(benzyloxy)cinnamamides **10** which results in a new stereoselective synthesis of (2-hydroxyphenyl)cyclopropanecarboxamides **11** and/or **12**.



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4. R. A. Aitken, K. Ait Moulay, D. B. Cordes, R. A. Inwood, F. G. Jamieson, A. J. B. Nelson and A. P. McKay, *Organics*, 2024, **5**, 12–31.

ACADEMIC TALK

New Concepts in Visible Light-Powered Catalysis: Organophotocatalytic Dyads and Auto-Photoredox Catalysis

Joshua P. Barham*[a,b]

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[b]Institüt für Organische Chemie, Universität Regensburg, Universitätsstr. 31, Regensburg 93040, Germany

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In this talk, two new concepts in visible light-powered catalysis are presented: **Topic 1:** Molecular dyads consisting of linked Donor-Acceptor (D-A) moieties find numerous applications as light-harvesting devices. Photoexcitation forms charge separated (CS) states that are advantageous or parasitic depending on the application. Building on previous learnings on pre-assembling electrogenerated radical ionic photocatalysts in our group,[1,2] we show how dyad CS states pre-assemble electronically-complementary substrates (Figure 1, top). Photoexcitating the resulting complex generates transient radicals which react selectively in close proximity for useful cross-couplings. **Topic 2:** Sulfonamides are ubiquitous in pharmaceuticals; for example cyclic biaryl sulfonamides (**BASN**s) in anticancer APIs. This talk reports a novel 'auto'-photoredox catalysis (auto-PRC) pathway to **BASN**s, an efficient process where the product itself acts as a photocatalyst[3] (Figure 1, bottom). We exemplify the power of auto-PRC in photocatalyst library construction and screening, identifying potent reductive photocatalysts for diverse organoradical precursors (60 synthetic transformations).

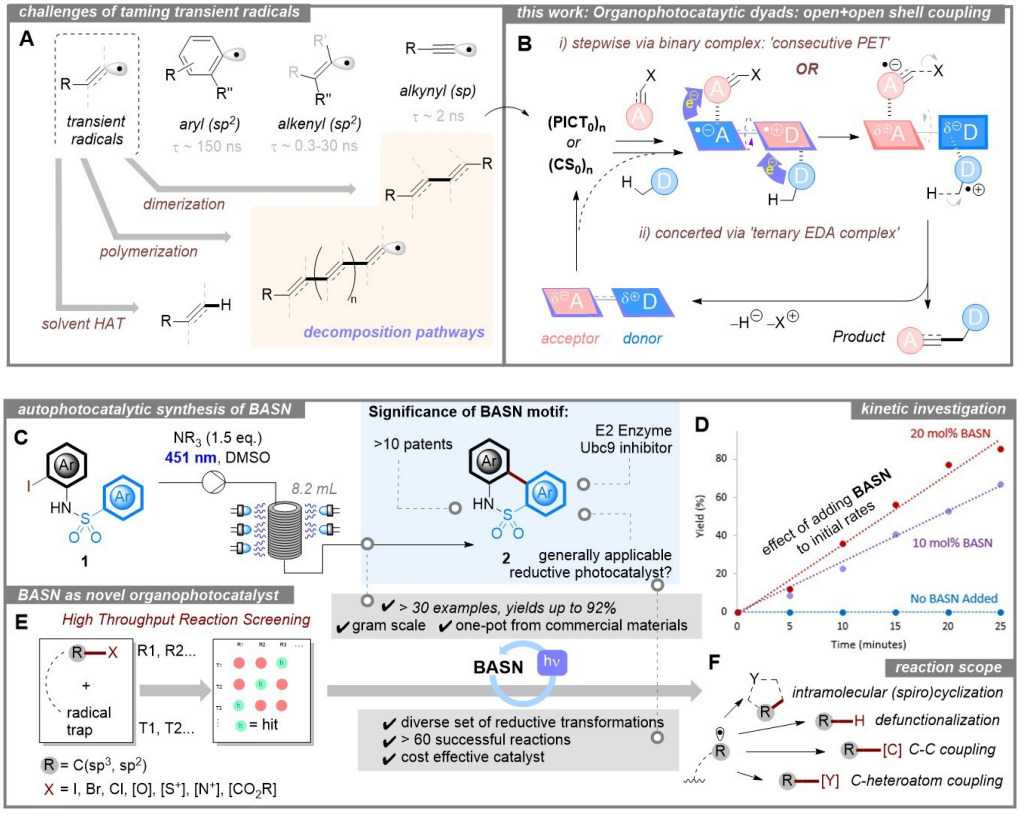

Figure 1: Top: challenges of transient radicals (**A**), organophotocatalytic dyad concept (**B**). **Bottom:** autophotocatalytic synthesis of **BASN**s (**C**), kinetic investigations (**D**), high throughput screening concept (**E**) and diverse scope of reactivity (**F**).

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ACADEMIC TALK

Isolation and Characterisation of Bioactive New Chlorinated Natural Products from the Deep-Sea Streptomyces *acrimycini* B188M101

Emmanuel T. Oluwabusola,[a] Stephen A. Jackson,[b] Stefanie Gackstatter,[a] Hannah Vedder,[a] Cristina Brunati,[c] Marianna Iorio,[c] David J. Clarke [b], Rainer Ebel, [a] Alan D.W. Dobson [b], and Marcel Jaspars[a]*

[a] Marine Biodiscovery Centre, Department of Chemistry, University of Aberdeen, Scotland, UK AB24 3FX.

[b] School of Microbiology, University College Cork, Cork, Ireland T12 K8AF.

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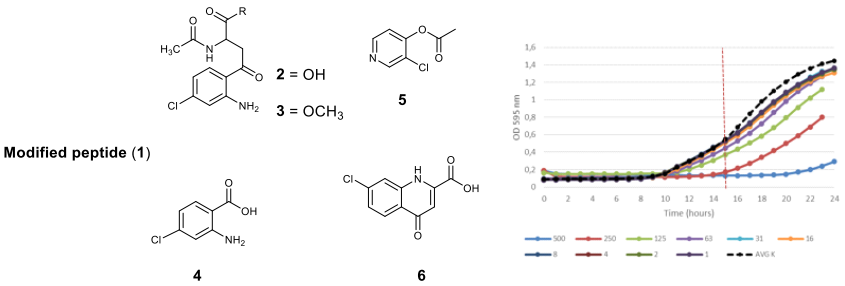
The European collaboration, the MARBLESS project, was established by 14 European consortiums with the goal of utilising marine microorganisms as a source of new bioactive compounds against fish, crop, and human pathogens and for the discovery and development of environmentally friendly natural products for aquaculture and agriculture.[1] Using the one-strain-many-compounds (OSMAC) culturing approach,[2] metabolomic studies and bioassay-guided purification,[3] we isolated and characterised four new chlorinated natural products (**2**-**5**) alongside the two known compounds, 'modified peptide' (**1**) and ageloline A (**6**), afforded by high-resolution mass spectrometry and 1D and 2D NMR analyses. The preliminary evaluation of compounds (**1**-**6**) against a panel of gram-negative bacteria, including the fish pathogens (*Yersinia ruckeri, Vibrio anguillarum, V. parahaemolyticus, V. harveyi, V. crassostreae, Aeromonas salmonicida)* and human pathogens, using a well-diffusion assay in duplicate, shows that compound **1** displayed significant activity against *A. salmonicida* and *P. aeruginosa* while the remaining compounds (**2**-**6**) were inactive at the highest concentration tested (500 µg/mL). Furthermore, a broth-microdilution growth-curves assay conducted to determine the antimicrobial potential of **1**-**6** against the human pathogen *Stenotrophomonas maltophilia* L2125 and *Staphylococcus aureus* ATCC6538P shows compound **2** displaying a moderate activity against both pathogens at the MIC value of 125 µg/mL and 250 µg/mL, respectively. Compounds **1** and **3** have not been tested at the time of this report. This is the first report of specific inhibition of *A. salmonicida* by compound **1**.



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ACADEMIC TALK

Little Big Data: Machine Learning Strategies for Experimental Chemistry

Emma King-Smith*

Joseph Black Building, School of Chemistry, University of Edinburgh

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Synthetic chemistry has many open challenges: how reaction yields change as reactants and conditions change, how molecules interact with the human body, or the full underlying mechanisms of some workhorse reactions. Machine learning (ML) has seen enormous strides in modelling the world's "black boxes": from image processing and recognition that rival human ability, consistently beating human players in a variety of games, to the amusing ruminations of the latest large language models. However, ML in chemistry is still a nascent field. Unlike our sister field of biology, the chemoinformatics community is not flush with big data. This is even more so when experimental data is the primary data source for modelling. This talk will examine how we can circumvent data restrictions in modern deep learning and classic ML techniques to yield state-of-the-art predictions on reaction outcomes and molecular properties.

1. E. King-Smith *et al.* "Predictive Minisci Late Stage Functionalization with Transfer Learning" *Nat. Commun.* 2024, 15, 426-438.
2. E. King-Smith* "Transfer Learning for a Foundational Chemistry Model" *Chem. Sci*. **2024**, *15*, 5143-5151.
3. W. McCorkindale *et al.* "Deconvoluting Low Yield from Weak Potency in Direct-to-Biology Workflows with Machine Learning" *RSC Med. Chem.* **2024**, *15*, 1015-1

PLENARY LECTURE

Synthesis of New Carbon Allotropes

Harry L. Anderson

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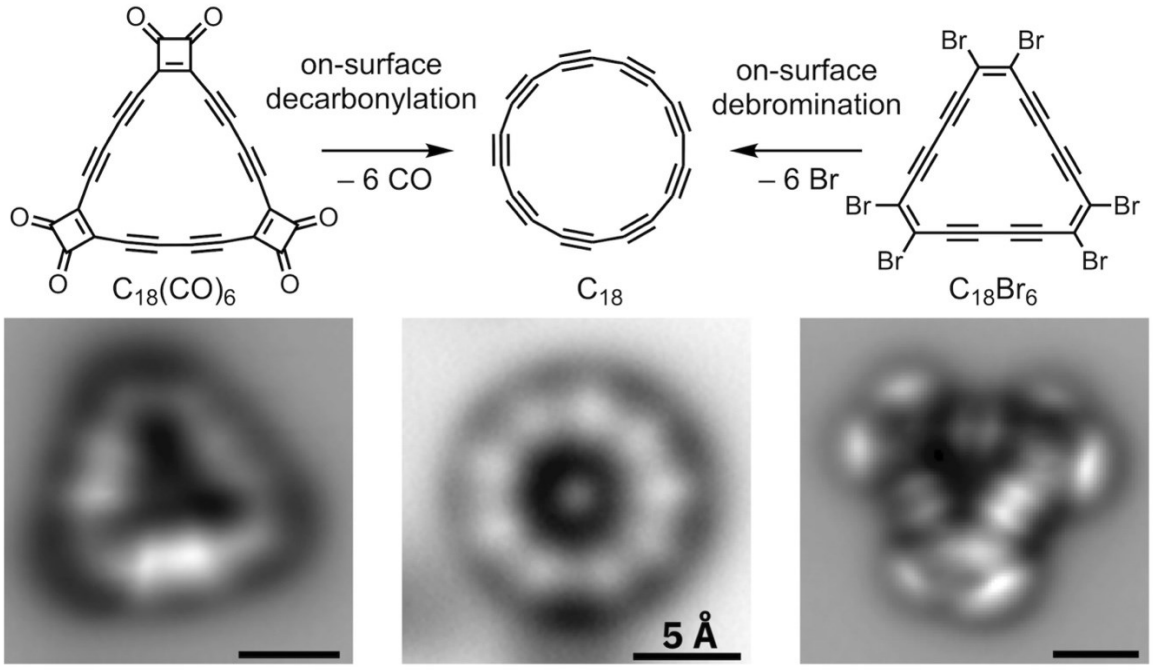
The cyclo[*N*]carbons are a family of molecular carbon allotropes consisting of rings of two-coordinate atoms. There has been much recent progress towards understanding the structures and properties of these carbon rings. The on-surface synthesis and characterization of cyclo[18]carbons, by low-temperature atomic manipulation and scanning probe microscopy (shown below),[1] heralded the preparation of many other cyclo[*N*]carbons (*N* = 10, 13, 14, 16 and 26).[2,3] Recent advances in this area will be presented, together with the synthesis of supramolecular cyclocarbon catenanes that are stable under ambient conditions. Previously cyclocarbons have only been studied in the gas phase or on surfaces as single molecules at cryogenic temperatures (4–10 K), but now they can be characterized in solution at room temperature.



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Posters - Abstracts

List of Poster Presentations

P1	Abigail Bidder	Heriot-Watt University
P2	Alessandra Salerno	University of Dundee
P3	Anna Stevenson	University of Dundee
P4	Aobo Gu	University of Edinburgh
P5	Ben Grills	University of Edinburgh
P6	Calum McLaughlin	University of Dundee
P7	Carina Schleidt	University of St Andrews
P8	Charlotte Bryson	University of Glasgow
P9	Dan Lambden	Heriot-Watt University
P10	Daniel Powell	University of Strathclyde
P11	Dongning Sheng	University of Edinburgh
P12	Faidra Batsaki	University of Edinburgh
P13	Fiona Gordon	Heriot-Watt University
P14	Francesca Kokkinos	University of Glasgow
P15	Fred Powell	Heriot-Watt University
P16	Gary Knox	University of Dundee
P17	James Luk	University of St Andrews
P18	Joe Walker	Heriot-Watt University
P19	Justin O'Yang	University of St Andrews
P20	Kristin Donnachie	University of Strathclyde
P21	Leonardo Amicosante	Heriot-Watt University
P22	Liam Raeside	University of Strathclyde
P23	Maria Rodriguez	University of Dundee
P24	Marta Kostadinova	University of Glasgow
P25	Mercy Gube-Ibrahim	University of Aberdeen
P26	Michael Malone	University of Glasgow
P27	Nico McVeigh	University of Strathclyde
P28	Nouf Alzahrani	University of Edinburgh
P29	Olivia Marshall	University of Glasgow
P30	Parul Parul	University of Glasgow
P31	Pedro Helou de Oliveira	University of Edinburgh
P32	Shubham Agrawal	University of St Andrews
P33	Sidra Faryal	University of Edinburgh
P34	Simone Montagna	University of Dundee
P35	Spyros Letsios	University of Edinburgh
P36	Stephanie Rowe	University of Strathclyde
P37	Sufiyanu Jiga	University of Aberdeen
P38	Swati Singh	University of Strathclyde
P39	Wang Yui Wylan Wong	University of St Andrews

POSTER

Click Chemistry at the Calix[4]arene Methylene Bridge

Abigail Bidder, Scott Dalgarno*

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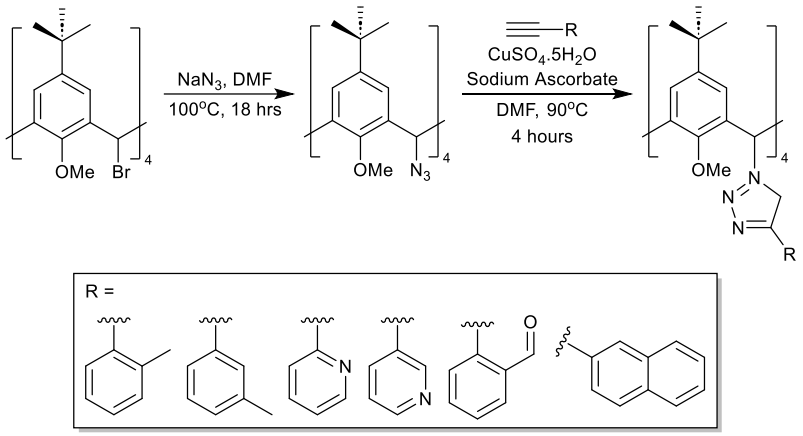
Previous studies within the Dalgarno group at Heriot-Watt University and others outwith[1] have illustrated that the substitution of azide groups onto the methylene bridge positions of calix[4]arenes with methyl ethers at the lower rim produce a variety of conformers (partial cone, 1,3-alternate, cone, alternate partial cone), with isomers resulting from stereocenters at the mono-substituted methylene bridge positions. Isolation of these conformers allows for further refinement of subsequent azide-alkyne click chemistry reactions[2] and higher degrees of control over the conformation of calix[4]arenes. A variety of functional groups can be "clicked" onto the methylene bridge positions and thus can give further control over potential binding sites. Some groups to be "clicked" onto the bridge positions include pyridyl moieties, fluorophores and other groups that can engage with hydrogen bonding or electrostatically charged interactions such as nitro groups and carbonyl derivatives. The aim for these structures is to bind nitroaromatic molecules and sense their binding via fluorescence, and to potentially function as ligands for metal clusters.[3]



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POSTER

Ferrocene: A Novel Organometallic Strategy for the Rational Design of PROTAC Linkers

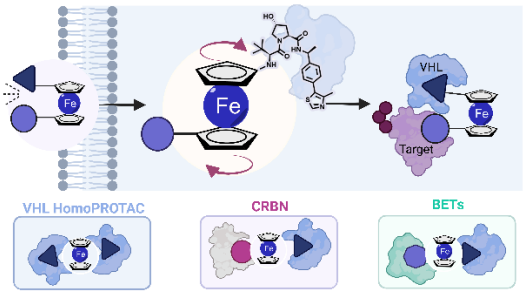
Alessandra Salerno,[a] Lianne H. E. Wieske,[a] Claudia J. Diehl,[a] Alessio Ciulli[a]*

[a] Centre for Targeted Protein Degradation, School of Life Sciences, University of Dundee, 1 James Lindsay Place, Dundee DD1 5JJ, Scotland, United Kingdom

Proteolysis Targeting Chimeras (PROTACs) are bifunctional molecules that facilitate the ubiquitination and degradation of target proteins by recruiting them to E3 ligases.[1] The linker is essential to various aspects of PROTAC functionality, such as cellular permeability, ternary complex formation, and target degradation. As a result, designing the linker has become a key focus for optimizing the molecular and pharmacokinetic properties of PROTACs.[2]

In this study, we present FerroTACs,[3] a novel PROTAC design strategy that leverages the ferrocene chemotype as a molecular hinge for linker development. This approach is demonstrated towards three distinct PROTAC systems: VHL-VHL (homo-PROTACs), VHL-CRBN, and VHL-BETs. The unique organometallic structure of ferrocene, consisting of freely rotating cyclopentadienyl rings around a central Fe(II), acts as a molecular hinge enabling structural adjustment to the environment that result in properties alteration, i.e., chameleonicity. NMR spectroscopy-based conformational analyses show that ferrocene fosters intramolecular interactions, promoting a more folded state in nonpolar environments. This feature improves cellular permeability and decreases efflux liabilities.

Cellular assays confirm that FerroTACs demonstrate i) strong target degradation, ii) enhanced permeability, and iii) physicochemical properties either matching or surpassing the benchmark PROTACs (CM11, 14a, and MZ1). These results highlight the potential of ferrocene as a versatile linker design strategy, offering a platform to modulate molecular chameleonicity for the development of next-generation PROTACs.



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POSTER

Discovery of a Novel and Selective GPR151 Agonist and Its Therapeutic Validation as a Gastrointestinal Motility Target

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GPR151 is an orphan receptor which is preferentially expressed on enteric neurones and modulates peristaltic activity in the gut. Potential ligands for GPR151 were identified following a 25,000 small molecule library screen, which resulted in 52 potential agonist hits. After hit validation, 5 main compound series were chosen for progression. Initial follow up resulted in a no-go decision for series A-D (Figure 1), for reasons including cytotoxicity, failure to yield an improvement on the original hit and synthetic tractability.

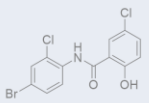
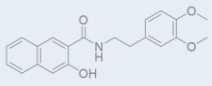
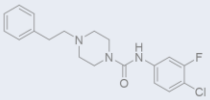
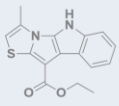
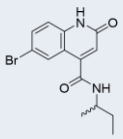
Series A DDD01836492	Series B DDD01837424	Series C DDD01896397	Series D DDD01833914	Series E DDD00013474
				

Figure 1: Compound Series A-E

However, Series E passed initial hit validation and was progressed to hit expansion. Over 300 analogues were synthesised, using late-stage functionalisation techniques and rapid purification. Details of this are discussed on the poster. Whilst changes to the hit compound suggested tight SAR, the physiochemical properties of our new lead compound DDD02465849 and the inactive match pair DDD02454281 (Figure 2) were adequate to be taken forward for target validation using an ex-vivo water perfused manometry system.

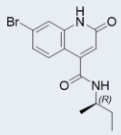
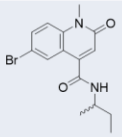
		DDD02465749	DDD02454281
			
Potency	pEC50 (>5)	6.4	<4.31
Toxicity	HepG2 pIC50 (<4)	<4	<4
Solubility	ReaSol (uM, >100)	38	190
DMPK	Clearance (m/h, <5 ml/min/g)	1.2	7.0
	MDCK (Papp, >50 nm/s)	150	166
Physiochemical Properties	MWt (<425)	323	337
	logP/CHI-logD (<3)	2.0/1.9	2.5/2.9

Figure 2: Structures of lead compound DDD02465849 and the inactive match pair DDD02454281

The novel agonist DDD02465849 was shown to exhibit receptor activity and effect gut motility, demonstrating proof-of-concept of GPR151 as a potential therapeutic target for inflammatory bowel disease (IBD), constipation and gastroparesis. Targeting GPR151 therefore has the capacity to deliver a new treatment for gastrointestinal motility for a large patient cohort.

POSTER

Total Synthesis of Pabmaragramin via Homochiral Dimerization

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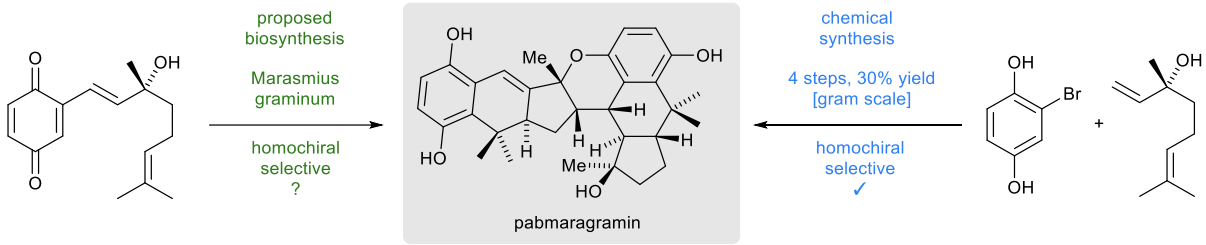
The first total synthesis of the dimeric meroterpenoid pabmaragramin has been achieved via a biomimetic Diels–Alder strategy. Pabmaragramin was isolated from *Marasmius graminum* as a scalemic mixture (30% e.e.), with both enantiomers showing α-glucosidase inhibitory activity.[1,2] We propose that the heptacyclic structure of pabmaragramin arises from spontaneous, homochiral selective dimerization of a scalemic precursor. Key steps of our total synthesis include a Heck reaction between linalool and bromohydroquinone, hydroquinone oxidation, and two [4 + 2] cycloaddition cascades,[3] forging eight bonds, five rings, and six stereocenters in four steps. The homochiral selectivity observed in this total synthesis supports a non-enzymatic biosynthetic pathway for pabmaragramin. Finally, the total synthesis of enantiopure (−)-pabmaragramin has been achieved by utilizing (−)-linalool as a chiral pool starting material.



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POSTER

Functionalised Phosphines for Bimetallic Catalysis

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With sustainability at the forefront of chemical research, Ni-catalysis has emerged as a powerful method of achieving a wide range of synthetic transformations.[1] However, there is growing evidence to suggest that Lewis acidic species - often present in Ni-catalysed reactions - can play a crucial role in the success of these transformations.[2]

To exploit the synergy between Lewis acids and Ni-catalysis, a series of phosphine ligands were designed to enable their incorporation into a bimetallic catalyst. These ligands contain a protic functional group that undergoes deprotonative metalation with an organometallic reagent, resulting in a Lewis acidic cation bound to the ligand. The catalysts were then applied to the development of the Miyaura borylation, a powerful method for producing highly functionalized boronic esters—key intermediates in organic synthesis. A 2D screen of ligands and organometallic Lewis acid sources identified a highly efficient system for the Miyaura borylation of widely available aryl chlorides under mild conditions.

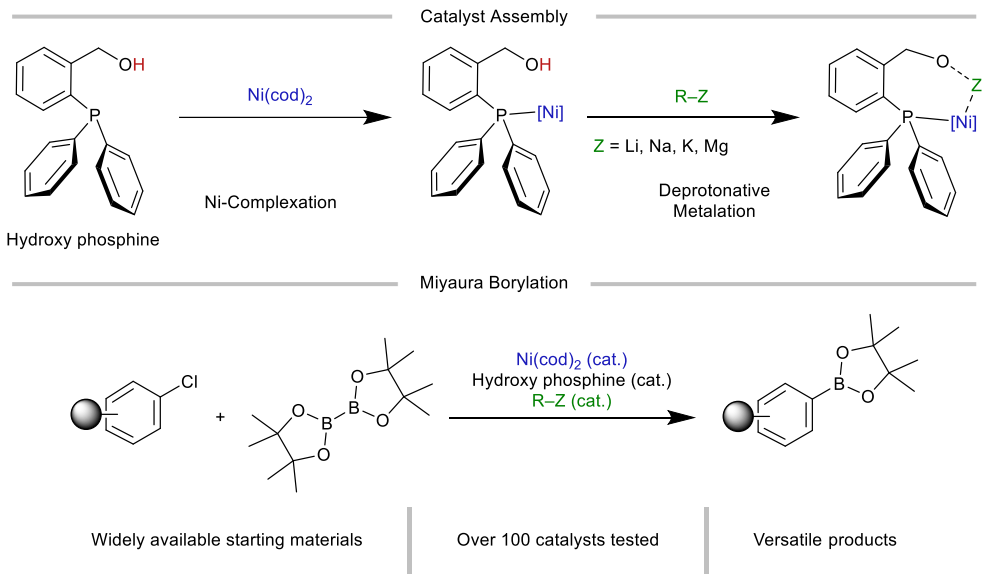

Figure 1. Bimetallic catalyst assembly and use in Miyaura borylation of aryl chlorides

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POSTER

PhosTACs: Heterobifunctional Molecules Inducing Targeted Protein Dephosphorylation

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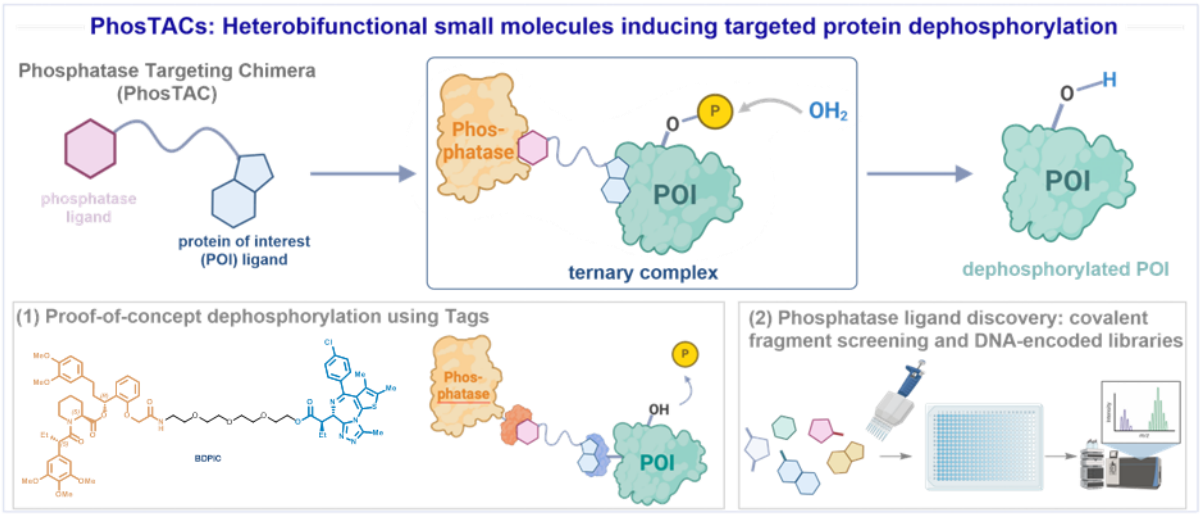
Dysregulated hyperphosphorylation of proteins, occurring when kinase enzymes are overactivated, is associated with many diseases. To attenuate elevated phosphorylation levels, >70 kinase inhibitors have been clinically approved for the treatment of cancers and inflammation. However, many proteins are targets of multiple kinases, whilst kinase inhibitors are promiscuous. As a result, target selectivity and off-target toxicity are significant problems associated with kinase inhibition.[1]

PhosTACs (Phosphatase TArgeting Chimeras) are novel heterobifunctional molecules composed of two ligands, one for a protein of interest (POI) and the other for a phosphatase enzyme, connected by a linker.[2] PhosTACs enable the selective dephosphorylation of specific targets by hijacking the natural enzymatic activity of phosphatases and inducing proximity between the POI and phosphatase. This alternative complimentary approach to inhibition has the potential to revolutionise therapy by allowing complete target dephosphorylation to be achieved without disturbing upstream kinase cellular signalling pathways.[3]

In this poster, we will describe two approaches towards the development of PhosTAC molecules for the targeted dephosphorylation of proteins: (i) demonstrating proof-of-concept dephosphorylation of various POI harnessing molecular dimerisers and Tags, and (ii) phosphatase ligand discovery through covalent fragment screening and DNA encoded libraries.



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POSTER

Enzymatic fluorination to an [^{18}F] -A_{2A} Adenosine Receptor Agonist for PET

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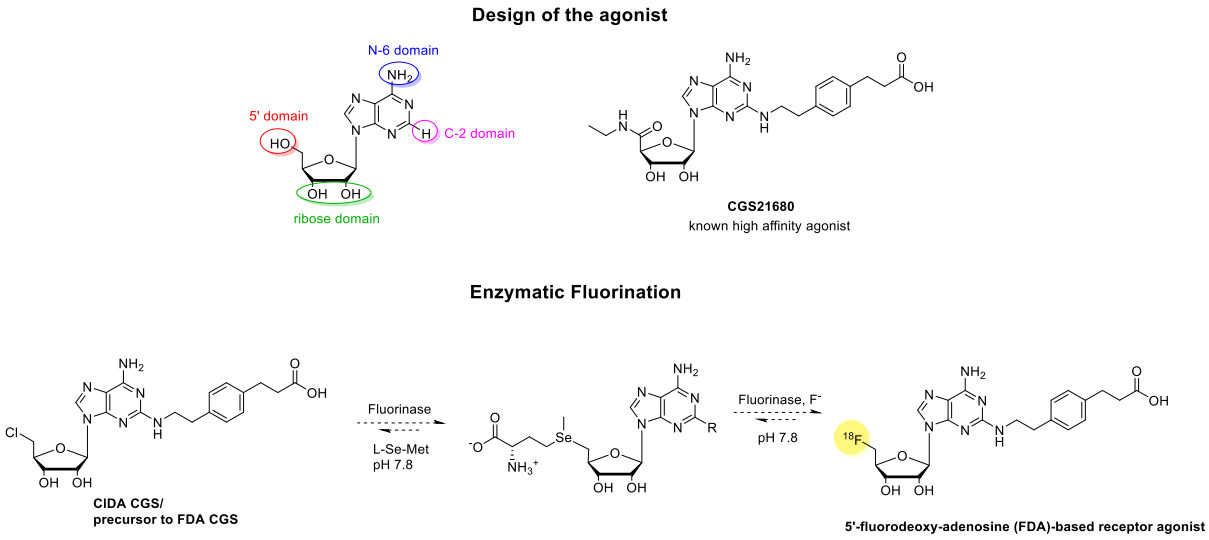
Adenosine receptors belong to the largest family of integral membrane proteins in the human genome, the G protein-coupled receptors. One subclass, the A_{2A} receptor presents, a potential therapeutical target for a variety of physiological processes and conditions ranging from dementia and Parkinson's disease to cancer immunotherapy and myocardial pre-conditioning.[1] Last step enzymatic [^{18}F]-fluorination of A_{2A} receptor agonists, using the fluorinase enzyme, has enabled the radiosynthesis of potential radiotracers for imaging using positron emission tomography (PET).[2]



Scheme 1: Design and enzymatic reaction scheme of the novel A_{2A} adenosine receptor agonist

A recent study has revealed a key substrate tolerance for NH-alkyl substitution at the C-2 position of substrates for the fluorinase.[3] Reported herein is the design and synthesis of a new 5'-fluorodeoxy-adenosine (FDA)-based receptor agonist with C-2 N-alkyl substitution. The design is inspired by the structure of the existing high affinity agonist CGS21680. Our strategy allows for the possibility of an enzymatic [^{18}F]-fluorination from a chlorinated precursor.[2] This work aims to prepare a new A_{2A} adenosine receptor agonist, which will be assessed for receptor binding. It will also be explored for radiolabelling (at Aberdeen Royal Infirmary) using the fluorinase enzyme.

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POSTER

Targeted Protein Degradation inside Bacteria as a Potential Novel Platform for the Treatment of Bacterial Diseases

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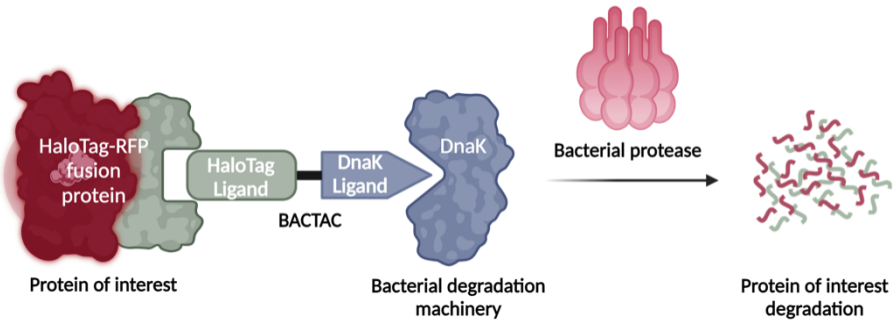
Antimicrobial resistance is the phenomenon where bacteria, viruses, parasites, and fungi mutate over time making them no longer susceptible to drugs which used to be effective against them. Rates of resistance against classes of antibiotics commonly used to treat bacterial infections have risen sharply which makes it more difficult to treat diseases caused by bacteria, leading to further spread of disease and rising mortality rates globally. Simultaneously, the number of new antibiotic approvals is declining, and this has led to a need for new classes of drugs which are active against bacteria.[1]

Targeted protein degradation is emerging as a useful tool for engaging previously undruggable proteins by inducing the degradation of a protein of interest by bringing it into proximity of an endogenous degradation pathway.[2] Many degrader molecules target proteins of interest to the eukaryotic ubiquitin-proteasome system for degradation. However, bacteria use different protein degradation pathways to eukaryotes, so this project aims to adapt eukaryotic degrader technology for use in bacteria by designing bifunctional degrader molecules which are able to recruit a chaperone protein, DnaK, which is known to be involved in bacterial protein degradation.

Originally FDA-approved for the treatment of Hepatitis C virus, the peptidomimetic small-molecule drug, telaprevir, has more recently been investigated as a ligand for DnaK.[3] Herein, the synthesis of a range of telaprevir analogues and their binding affinity for DnaK is reported which has allowed for the identification of analogues with improved ligand efficiency. Also reported is the conversion of the most promising DnaK ligands into bifunctional degraders and the initial biological evaluation of this first-generation of Bacterial Proteolysis Targeting Chimeras (BACTACs) for use as chemical tool compounds for studying bacterial proteins and for facilitating the development of a first-generation of degrader-based therapeutics to fight bacterial diseases.



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POSTER

Bisarylbutadiyne scaffolds for ratiometric pH_i sensing with Raman & SRS microscopy

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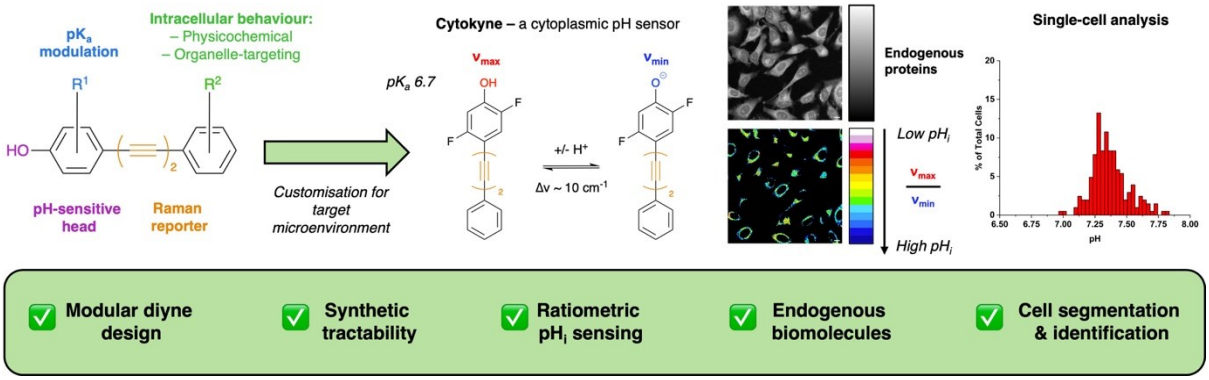

Stimulated Raman scattering (SRS) microscopy enables label-free visualisation of endogenous biomolecules with high spatiotemporal resolution. However, the profound advantages of Raman-based techniques are often eclipsed by the weak Raman scattering effect and consequential reduction of signal intensity in comparison to fluorescence-based technologies.[1] Bisarylbutadiyne (BADY) scaffolds have been established as a structural design-based solution to the low signal intensities of the Raman-active alkyne bond, with structure-signal relationship studies by Yamakoshi et al. revealing an amplification of up to x150 relative to terminal alkynes.[2]

BADY scaffolds have been commonly exploited in imaging strategies *via* functionalisation with organelle-targeting moieties and ratiometric sensing capabilities.[3] This poster will present the development and application of a modular diyne design for ratiometric sensing of intracellular pH (pH_i), with tuneable pK_a and capacity for tractable synthetic modifications to direct intracellular behaviour. Coupled with SRS, this design has been used to dissect and interrogate the cellular milieu, comparing organellar microenvironments, responses to apoptotic stimuli, and the physiology of different cell lines. Analytical depth has been further enhanced by a novel single-cell analysis (SCA) method, exploiting label-free imaging of endogenous proteins to enable cell segmentation in large populations and simultaneous evaluation of individual cellular features within single experiments. Consequently, this modular scaffold has established a versatile platform for tuneable chemical design in intracellular sensing.

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POSTER

Synthesis and Characterisation of High Nuclearity Cobalt-carboxycalix[4]arene Clusters

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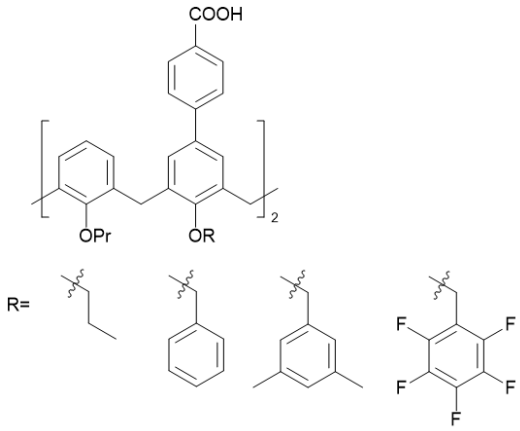
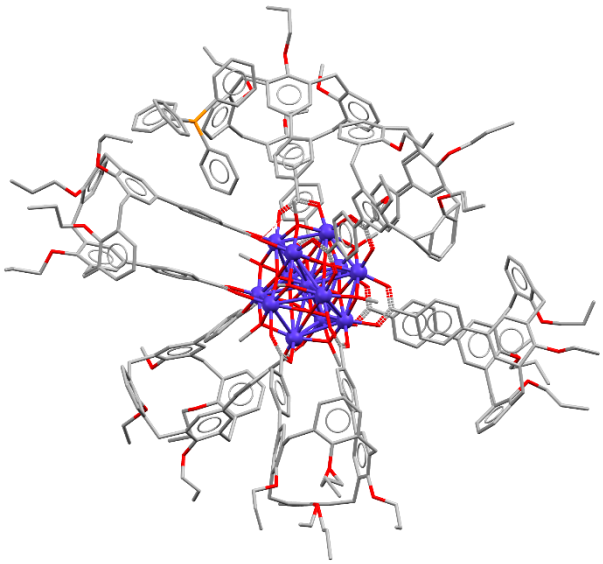
Through careful substitution of calix[4]arene, it is possibly to synthesise high nuclearity Cobalt clusters with interesting magnetic properties for applications as single molecule magnets (SMMs). Herein we report the synthesis and characterisation of several $Co_{13}L_6$ clusters, where L is a carboxycalix[4]arene based ligand. Characterisation by SCXRD and magnetic susceptibility show the effect of adding organic bases on the Cobalt oxidation state ratio as well as on the magnetic susceptibility of the clusters formed.

Synthetic challenges include minimising the formation of calix-ester, favouring $[Co^{II}_{12}Co^{III}_{1}]$ oxidation state ratio, and recrystallisation of the formed clusters.





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POSTER

Tyrosine Bioconjugation in a Nanopore

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Bioconjugation enables the precise re-engineering of proteins for exploring protein function and developing novel treatments, biosensors, and enzymes. The bioconjugation of hydroxy-containing amino acids is challenging due to their reduced reactivity, and the potential lack of selectivity and stability compared to approaches targeting lysine and cysteine. Here we introduce triazine reagents for rapid tyrosine bioconjugation under mild, biologically compatible conditions (aqueous solution, pH 3.8 – 5.0, room temperature). Triazine bioconjugation and disconnection at tyrosine was characterised at the single-molecule level inside individual α-HL nanopores. The reactive species was identified, and the reaction mechanism probed using model reactions and modified triazine reagents. We also demonstrated a linker-based approach in which tyrosine bioconjugation was used to incorporate an azide for subsequent modification with Cu(I)-catalysed azide–alkyne [3 + 2] cycloaddition. Our experiments reveal the potential for tuning the reactivity of triazines either to broaden applicability, or to target tyrosine residues in specific local protein environments. We aim to encourage the broader investigation of triazine reagents as a hitherto unexplored class of protein bioconjugation agent.

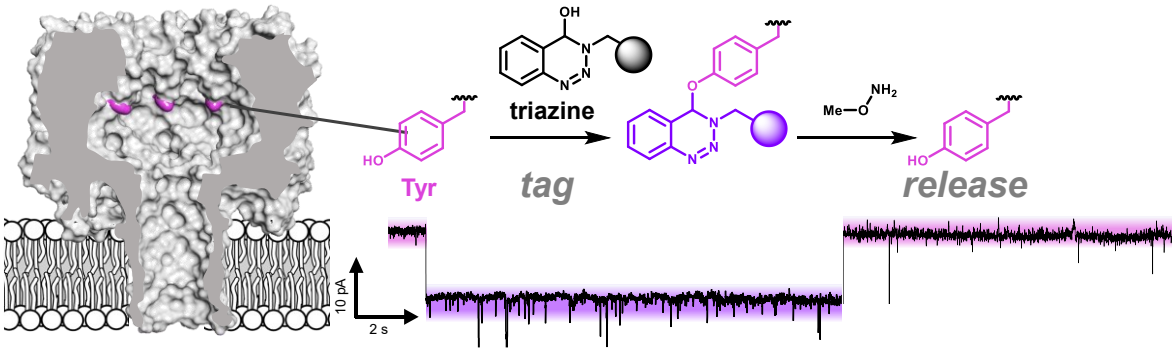

Figure 1. Tag-and-release Tyrosine Bioconjugation within α-HL nanopore.

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POSTER

Monitoring the early stages of protein aggregation as a diagnostic tool against neurodegeneration

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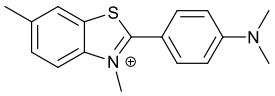
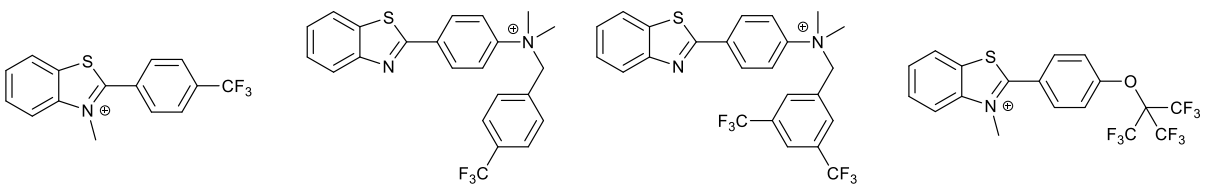
A hallmark of neurodegenerative diseases is protein misfolding and amyloidal aggregates (eg. α-synuclein for Parkinson's and amyloid-β for Alzheimer's). These aggregates are known to form via polymerisation of the corresponding protein but the fibrillisation mechanism, its kinetics, and intermediates still remain unknown. Recent evidence on α-synuclein aggregation, suggests that the oligomers formed during the first steps of the fibrillisation could be the most toxic species of the aggregation pathway. However, due to their small size and high heterogeneity these structures can not be monitored with the traditional fluorescence techniques, highlighting the urgency for development of new diagnostic tools that can map the entire aggregation window. Inspired by the structure of thioflavin T (ThT), a widely used amyloid dye that recognises the β-sheet structure of amyloidal aggregates and induces a fluorescence switch-on, we are aiming to design fluorinated fluorescent probes that maintain affinity for aggregates whilst allowing for the use of ligand-observed ^{19}F NMR studies. ^{19}F NMR is an emerging field in medicinal chemistry as it allows for high signal to noise ratio, high sensitivity, no background signals and easy analysis of biological samples. Investigating different fluorine functionalities and positions within the fluorescent probe we are aiming to explore the sensitivity of the ligands, variations for fibril affinity, the range of chemical shift anisotropy, as well as, determining the binding epitome of ThT and its fluorinated analogues. High fluorine content, enhanced sensitivity, and selective binding for amyloid aggregates, could allow for the development of the fluorinated ThT analogues as novel diagnostic tools against the early stages of neurodegeneration with either blood diagnostics analysis with the help of ^{19}F NMR or development into ^{19}F MRI probes with spatial recognition within the tissue.

Thioflavin T (ThT)



Fluorinated ThT analogues



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POSTER

Automating the Vortex Fluidic Device for Photocatalytic Transformations

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The Vortex Fluidic Device (VFD) is a microfluidic reactor that rotates a sample tube at speeds up to 9000 rpm with adjustable tilt angles (Figure 1).[1] This high-speed rotation creates thin films on the walls of the tube, generating high shear forces. The resulting mechanical energy accelerates the rate of chemical reactions. Additionally, the VFD eliminates the need for harsh conditions and enables reactions to occur at ambient temperatures and, in some cases, in a solvent-free environment.[1] Overall, this ensures safer synthesis for the chemist, minimised waste and improved energy efficiency, aligning with the green principles of chemistry.

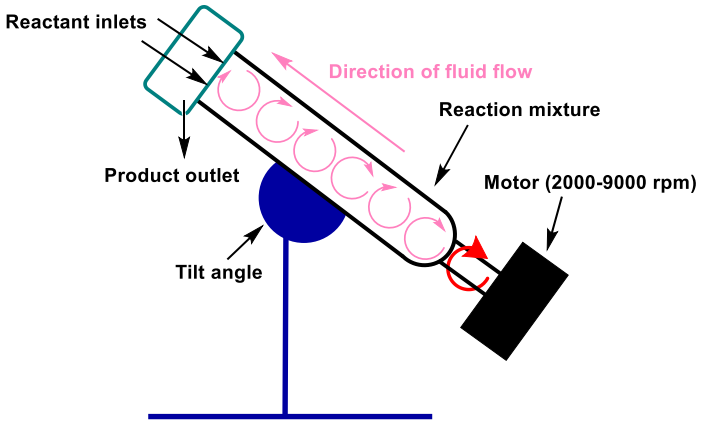
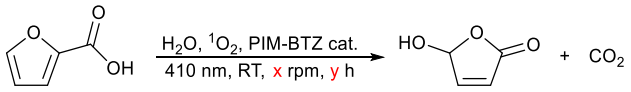


Figure 1: The Vortex Fluidic Device

This study will explore the VFD's use in photocatalytic experiments. The generation of singlet oxygen has great application in pollutant degradation and photodynamic therapy.[2] However, the oxidation of 2-furoic acid under singlet oxygen using a thin film coating of PIM-BTZ catalyst (Scheme 1) proceeds very slowly in batch leading to < 2% conversion after 7 days.[2] A comparison between batch, flow and VFD will be investigated.



Scheme 1: Adjusting the rate of rotation and reaction time for the photocatalytic oxidation of 2-furoic acid

Automation in chemistry improves safety by minimising the exposure of hazardous substances to the chemist and reducing human error through precise, automated measurement techniques. The chemist will then be able to focus on advancing their research rather than repeatedly performing the same experiments. The VFD features a simple control box. The first step of its automation is to incorporate computerised control. Ultimately the VFD will function as a continuous flow reactor in an automated setup with a syringe pump and inline analysis tools e.g. benchtop NMR and UV-Vis spectroscopy.

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POSTER

Small molecules for osteogenic differentiation of MSCs and the treatment of Osteosarcoma

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Osteosarcoma is the most common and frequent primary bone cancer in children and young adults. Osteosarcoma typically arises in areas of rapid bone growth and high bone turnover. Pathological and molecular features of most osteosarcoma tumours indicate the interruption of differentiation of mesenchymal stem cells (MSCs) to bone forming cells, known as osteoblasts. In addition, osteosarcoma tumours exhibit characteristics of undifferentiated osteoblasts, they are able to self-renew and proliferate. This provides a great therapeutic possibility by aiming to promote terminal differentiation of cancer thus making them more susceptible to apoptosis.

The differentiation of MSCs to osteoblasts, known as osteogenesis, can be controlled *in vitro* through the addition of exogenous growth factors and steroid hormones, such as the synthetic steroid dexamethasone, to culture media. However, the addition of such small molecules and growth factors greatly increases the production of off-target non-osteogenic differentiation. Cholesterol sulfate, an endogenous steroid, has been identified as a highly specific inducer of osteogenesis in MSCs. However, its potency is still far from some of the widely used and identified steroid hormones.

The aim of the project is to design and synthesise small molecules that will then be tested biologically as either inducers of osteogenic differentiation in MSCs and/or for the treatment of osteosarcoma. Due to the identified osteogenic potential of the steroid cholesterol sulfate, synthesis of more stable analogues of the natural steroid are investigated as a means of improving potency. Targeted delivery of steroids like dexamethasone is also explored for the treatment of osteosarcoma and a novel synthetic route for a bifunctional analogue is described. Alternatively, steroid sulfatase inhibitors have shown promising effects in a number of hormone-dependent cancers with Irosustat being the first to reach phase two clinical trials for the treatment of breast cancer. Herein, the synthesis of a cholesterol-based steroid sulfatase inhibitor is described. Initial results in the assessment of its biological activity in both breast and bone cancer cell lines indicate to its controlled ability to decrease cell viability with improved potency compared to Irosustat. Unprecedentedly, Irosustat is shown to be active in bone cancer cell lines and its activity is further assessed as a potential repurposing strategy for the treatment of osteosarcoma.

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POSTER

In Search of Enzyme Activation: A computational workflow for allosteric drug discovery

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Enzyme activation is an underexplored mode of pharmaceutical intervention which holds tremendous potential in the treatment of a variety of human diseases. In comparison to the more common concept of enzyme inhibition, the activation of enzymes is a delicate phenomenon, often exploiting intricate allosteric networks to increase the affinity of an enzyme for its substrate. We have undertaken a drug discovery project targetting activation of the cell-signalling enzyme EPAC1. This paves the way for novel therapies in cardiac, metabolic, inflammatory, and oncologic disorders.[1]

We first used protein-ligand docking modelling to advance our hit compound, I942 (a partial EPAC1 activator),[2] into a promising lead compound. We have since developed and applied a steered molecular dynamics (sMD) and Markov state model (MSM) based workflow for predicting the potency of allosteric enzyme modulators. Our workflow uses sMD to explore the conformational space of the target system. By employing sMD, we can sample conformational space that is inaccessible under routine MD timescales. Subsequently, we utilise intermediate conformations arrived at *via* sMD as the starting point for multiple short, equilibrium MD simulations. The resulting data is pooled and used to construct MSMs. This affords us insight into the probability of EPAC1 being active or inactive with a potential activator *in situ*. Our models have successfully demonstrated activation of EPAC1 by the endogenous activator, cyclic AMP, as well as partial activation by I942.[3] The mechanistic insights this afforded to us were used to guide development of a potent, selective EPAC1 activator.

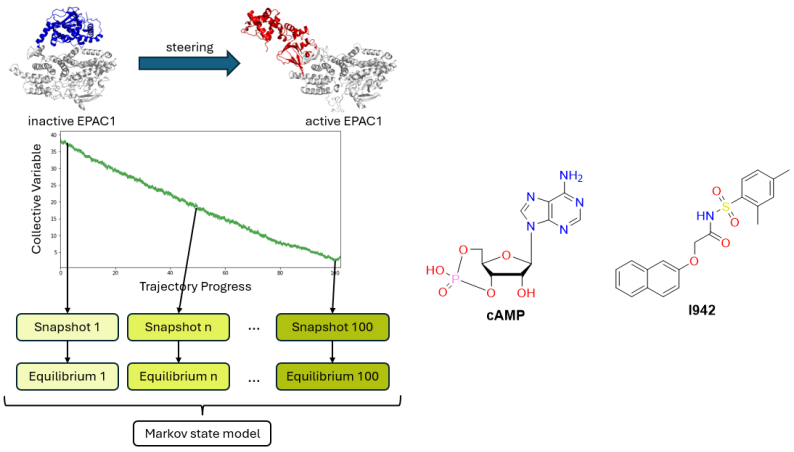

Figure 1: A schematic overview of our sMD/MSM workflow, alongside the structure of cyclic AMP and I942.

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POSTER

Assessment of a DEL Hit Series for Development Towards a Novel *Pf*IleRS Inhibitor

Gary J. Knox[a], on behalf of the SDDC team

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Despite significant progress towards an established strategy for the control of malaria, the latest WHO report showed that the number of cases rose by 11 million in 2023, with respect to the previous year.[1] Africa remains the area with the heaviest burden, representing 94% of the worldwide malaria cases, as well as 95% of deaths associated with the disease. In light of the requirement for improved treatments that can be applied alongside preventative measures, the Structure-guided Drug Discovery Coalition (SDDC) is dedicated to accelerating the drug development process by generating novel early lead compounds. In particular, the group aims to focus on identifying inhibitor molecules for disease-validated targets and, with the support of structural information, rapidly move from hit compounds to early leads which can be taken further in the drug discovery process.

One such enzyme which was recently identified as an attractive target for the potential treatment of malaria is isoleucine tRNA synthetase (IleRS).[2] The class of enzymes to which this target belongs are responsible for charging tRNA with their cognate amino acid. They are critical in protein synthesis throughout the parasite's life cycle and have multiple sites for substrate recognition, making them highly desirable targets for an antimalarial drug program.[3] In pursuit of a suitable inhibitor for *Pf*IleRS, we have identified a new chemical series, shown in **Figure 1** below, which appear to be a promising starting point for the development of a new early lead molecule. In this poster we outline some of our efforts to establish the developability of the series, and highlights the major challenges faced during the assessment of this new set of inhibitor molecules. More specifically, we discuss the endeavours towards improving the *in vitro* parameters influencing the pharmacokinetic profile of the molecules, in the hopes of studying the compounds in an appropriate model, as well as some highlights of the synthetic chemistry applied therein.

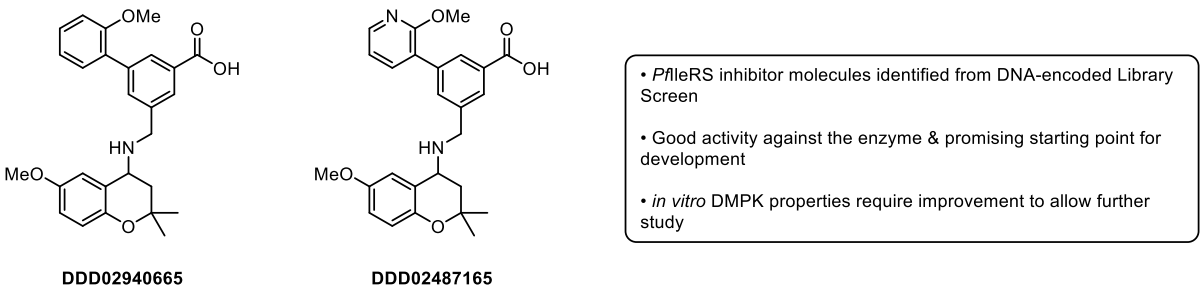

Figure 1

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POSTER

Rare earth fluorenyl-tethered NHC complexes for biopolymer synthesis

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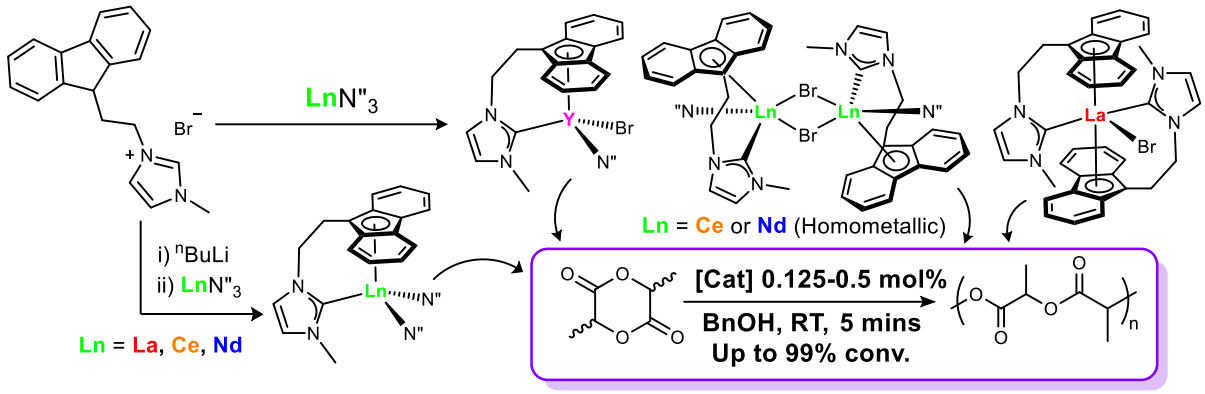
Industrial synthesis of the bio-derivable/degradable polymer polylactic acid *via* ring-opening polymerisation (ROP) requires use of inorganic initiators. Currently, $Sn(Oct)_2$ is widely used but has poor control over polymer properties e.g. tacticity and polydispersity. Elevated reaction temperatures of ≥ 140°C and limited natural reserves of tin are also evident sustainability concerns.[1] To alleviate these issues, development of new catalysts featuring various metals for ROP has been intensely researched.[2,3]

Interest in rare earth metal complexes for ROP has risen as elemental resources are relateively abundant in the crust; they are also highly Lewis acidic and oxophilic promoting catalytic activity in the ROP of lactide. Consequently, examples from the literature have displayed extreme reaction rates and new ligand systems are sought to further customise reactivity.[3]



We are interested in fluorenyl-tethered ligands which allow for the synthesis of heteroleptic lanthanide complexes – which is otherwise difficult due to the Schlenk equilibria. The use of a strongly electron donating NHC moiety, low steric hindrance of its methyl sidearm and the potential for ring slippage *via* the indenyl effect should produce highly active catalysts.

Subsequently, synthesis of a range of Y, La, Ce and Nd complexes has been achieved through two synthetic pathways. All display high activity in ROP of lactide at room temperature, with full conversion observed in as little as ≤ 5 minutes.

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POSTER

The Catalytic Enantioselective [1,2]- and [2,3]-Wittig Rearrangements of Allylic Ethers

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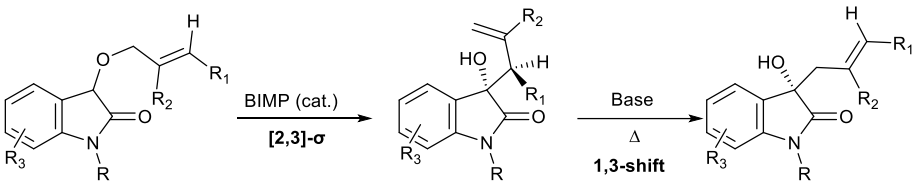
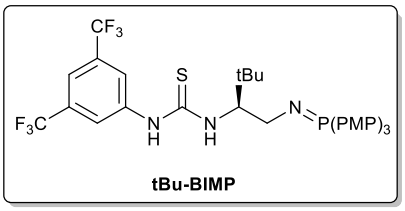
The [2,3]-Wittig rearrangement is a powerful tool to generate new carbon-carbon bonds and therefore has been extensively studied and widely applied in organic synthesis. This [2,3]-sigmatropic rearrangement transforms an allylic ether into a homoallylic alcohol, while simultaneously generating up to two contiguous stereocentres. This process is often competitive with the related [1,2]-Wittig rearrangement, with selectivity and stereocontrol of [2,3]- and [1,2]-Wittig rearrangements being a recognised challenge to the scientific community. While enantioselective [2,3]-Wittig rearrangements have been explored extensively in the past decade,[1] the corresponding [1,2]-Wittig rearrangements are much less developed.

This work demonstrates the highly enantioselective [1,2]-Wittig rearrangement of allyloxy-oxindole systems by application of a chiral bifunctional superbasic iminophosphorane catalyst (BIMP).[2–3] Mechanistic investigations revealed the presence of an initial diastereo- and enantioselective [2,3]-Wittig rearrangement (isolable [2,3]-Wittig compounds, 71:29 – 92:8 d.r., up to 98:2 e.r.) followed by a thermally-promoted enantioretentive 1,3-allyl shift to produce the formal [1,2]-Wittig products in high enantioselectivity (up to 95:5 e.r.). This talk will focus on the development of this process as well as ongoing work into similar rearrangements.





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POSTER

Computer Vision for Quantitative Comparison of Carbon Monoxide Surrogates

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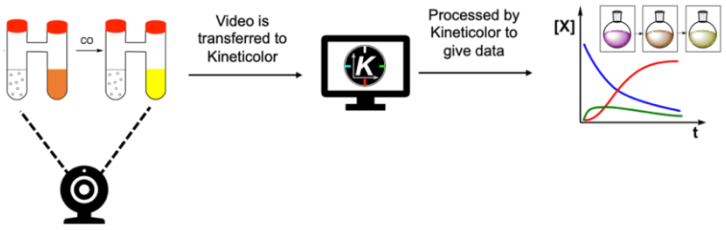
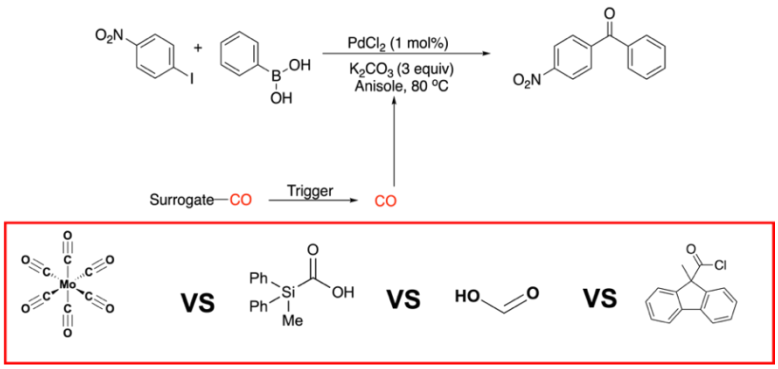
CO surrogates are molecules that enable controlled release of CO without ever having to handle the dangerous gas. The current gap in the literature is the quantitative analysis of the CO release rates from each surrogate. Such comparison of CO surrogates is a challenge in large part due to the structural diversity and range of conditions employed to trigger CO release.



Herein, we report the use of computer vision-enabled kinetic analysis of CO release from a structurally diverse range surrogates by tracking CO uptake in organometallic CO chemosensors. To do this, we employ *Kineticolor®*, a software developed that empowers chemists to analyse video recordings of a reaction bulk to obtain information about rates of change of colour, shape, and mixing parameters.[1-5] This technology has now enabled the development of a reactor-specific scale of reactivity for CO surrogates for the first time.

The newly quantified information on the relative rate of CO release, reliability and reproducibility of each surrogate has now been applied to better inform the optimal choice of CO source in synthetic methodologies, including a carbonylative Suzuki coupling.



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POSTER

Green-light absorbing BTZ photocatalysts for phosphorylation of quinoline derivatives and automated Minisci coupling using flow

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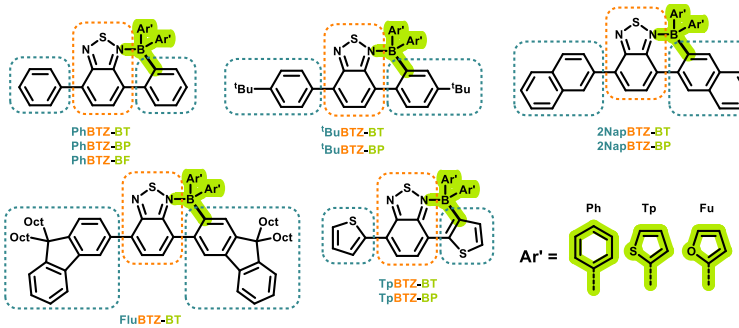
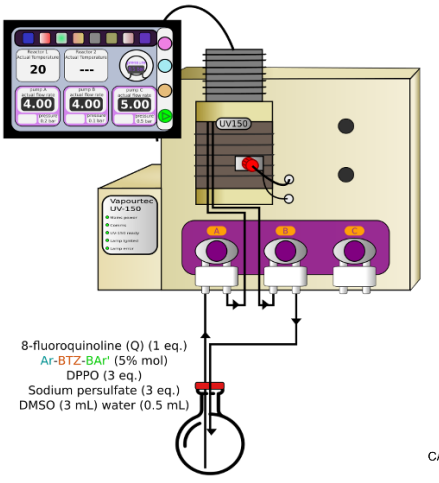
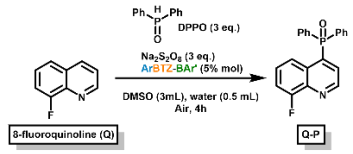
The widespread historical exploitation of non-renewable chemical feedstocks has driven increased focus towards solar light-harvesting technologies such as photocatalysts (PCs).[1] While efficient Ir and Ru-based PCs rely on expensive, scarce and toxic transition metals, all-organic PCs, such as those based on structures like the Benzo[c][2,1,3]thiadiazole (BTZ) heterocycle, are gaining popularity for their affordability and tunable optoelectronic properties. However, these organic PCs currently face limitations with lower efficiency and near-UV light absorbance.[2]

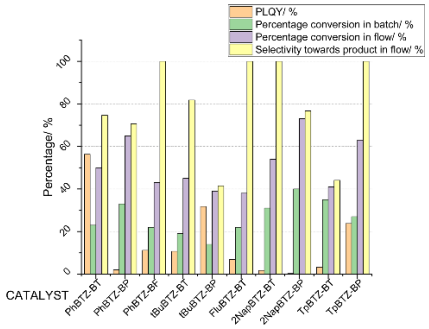
Herein, we introduce a targeted library of PCs that we have developed via selective ortho-borylation and ring fusion of Donor-Acceptor BTZ building-blocks,[3,4] achieving significant bathochromic shifts that extend the PCs' light absorption to lower-energy green wavelengths. These new PCs were tailored for contemporary photoredox catalysis reactions, such as the photocatalytic phosphorylation of quinoline derivatives, achieving up to 40% conversion in batch reactions and 73% in continuous flow set-ups within just 4 hours.[5]

To further demonstrate the versatility of these PCs, we also conducted a second reaction involving the Minisci C-C bond formation[4] in a flow setup, incorporating in-line UV-Vis monitoring for non-destructive tracking of reaction progress. The ability to initiate automated sequential reactions without purifying the initial step enables seamless process progression, reducing the need for human intervention and providing an efficient, low-cost approach for synthesizing valuable pharmaceutical intermediates and products.[6]









POSTER

Iridium Catalysed Aryl Hydrogen Isotope Exchange Directed by Benzylic Amines

*David M. Lindsay[a], *James D. F. Thompson[b], **Liam P. Raeside[a]**, Michael Field[a], Nathan M. L. Knight[a], and *William J. Kerr[a]

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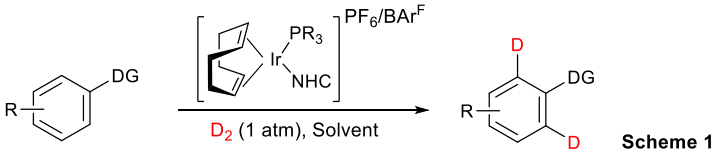
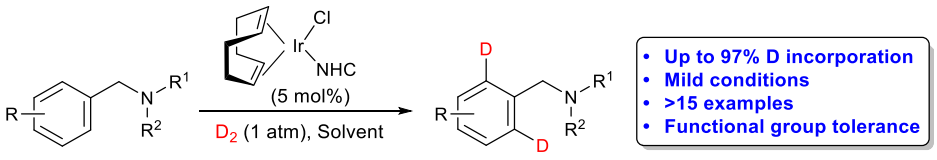
Absorption, distribution, metabolism, excretion, and toxicity (ADMET) studies are essential to the assessment of pharmacokinetics and pharmacodynamics of emerging drug candidates. These studies rely on isotopically labelled analogues, which allow incorporation of a traceable label without significantly altering the physical properties of the compound.[1] Late-stage hydrogen isotope exchange (HIE) has been explored to furnish selectively labelled molecules without expensive and time-consuming re-synthesis of labelled analogues. Iridium(I) catalysts of the type [Ir(COD)(PR_3)(NHC)]X, extensively developed within our laboratories, [2] have proven to be highly active HIE catalysts, operating under mild conditions, and utilising a variety of directing groups for the C-H activation required for HIE (Scheme 1).



Scheme 1

Benzylic amines are crucial motifs in a wide range of fields, including pharmaceuticals, organic building blocks, and in polymer chemistry. Considering the widespread utility of this functionality, C–H activation directed by the benzylic amine functionality would be particularly useful for late-stage functionalisation reactions, including HIE. However, examples of the *ortho*-directed HIE of secondary or tertiary benzylamines are extremely rare and either require harsh reaction conditions with high catalyst loadings or have very limited substrate scopes.[3] This work describes the application of pharmaceutically-ubiquitous benzylic amines for directed C(sp^2)-H functionalisation using a neutral Iridium(I) chloro-carbene complex (Scheme 2). This methodology has been applied to a range of benzylic amines, containing a variety of aryl substituents, giving high levels of deuterium incorporation. Notably, the scope includes Lewis basic functionality known to be competent as directing groups in HIE using cationic iridium(I) catalysts of the type [Ir(COD)(PR_3)(NHC)]X. Reaction optimisation will be described, along with competition studies related to other Lewis basic functionality.



Scheme 2

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POSTER

BromoCatch: a self-labelling protein tag platform for protein analysis and live cell imaging

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The Ciulli Lab pioneered the 'bump-and-hole' method for allele-selective small-molecule targeting of BET bromodomains.[1,2] The approach involves modifying a BET bromodomain ligand to incorporate a steric 'bump', such that it complements an engineered 'hole' at the target binding site, enabling it to bind with high affinity to the mutant protein with high selectivity over the wild type. Building from this initial work, a new protein fusion tag system called BromoTag® was recently developed, whereby the mutant bromodomain is used as a protein degron tag, for targeted protein degradation (TPD).[3] A bumped VHL-recruiting PROTAC (AGB1) was qualified as fast, potent and selective small-molecule degrader of proteins tagged with BromoTag® 3 Since its first disclosure, BromoTag® has been made commercially available and has been widely adopted and used for biomedical research.[4,5,6] Non-covalent degron tagging platforms such as BromoTag® are highly useful in the context of TPD and induced proximity, but the reversible binding limits broader applications in the analysis and labelling of proteins.

Here, we present the development of BromoCatch™, a self-labelling protein tag platform and demonstrate its utility for a number of applications. The development of this system leverages prior art from the original BromoTag®, utilising the same 'bump and hole' protein as the fusion tag. We introduced a nucleophilic cysteine in the protein fusion tag and designed a complementary 'bumped' electrophilic ligand tag that is capable of covalent binding the nucleophilic protein. Through extensive in vitro and *in cellulo* structure-activity relationship analysis (SAR), an optimal combination of ligand-mutant pairing was qualified. Successive conjugation of this ligand allowed the synthesis of a panel of bivalent probes for different applications including fluorescence imaging, biotin labelling or click conjugation. The platform was subsequently used *in vitro* and *in cellulo* of the resulting bifunctional probe molecules established BromoCatch as a versatile self-labelling tag platform for a broad range of applications.

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POSTER

Towards the targeted proteasomal degradation of the SARS-CoV-2 main protease

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Since the outbreak of SARS-CoV-2 in 2019 COVID-10 has infected more than 700 million people worldwide and taken the lives of more than 7 million. Swift global efforts have led to the production of vaccines and the repurposing of existing drugs to limit the spread of the infection. However, frequent mutations of SARS-CoV-2 have hindered the effectiveness of a significant proportion of the currently available treatments highlighting the necessity for new strategies to combat the virus. Efforts to tackle this issue have led to the identification of the main protease of SARS-CoV-2 – M^{pro}, which is highly conserved not only across the different variants of concern of SARS-CoV-2 but also shows high similarity to proteases of other members of the coronavirus, norovirus and picornavirus families. Furthermore, no close human analogue of M^{pro} has been discovered making the viral enzyme an attractive therapeutic target.

Nirmatrelvir is an orally available small molecule inhibitor developed by Pfizer for the treatment of mild to moderate COVID-19 that targets SARS-CoV-2 M^{pro} (figure below).[1] Despite the overall success of nirmatrelvir in preventing hospitalisation and the onset of severe symptoms, several mutations at the active site of M^{pro} have been found to hinder the binding of nirmatrelvir and therefore reduce its affinity. While none of these mutations are prevalent in nature it is nonetheless important to consider alternative strategies that would remain unaffected by the viral mutations in the future.[2]

One possible strategy is through the use of Proteolysis Targeting Chimeras (PROTACs).[3] PROTACs are bifunctional molecules that are composed of two ligands – for the cell's degradation machinery and for a protein of interest, joined via a linker. They exert their function by forming a transient ternary complex, which allows for labelling of the protein of interest for degradation thereby abolishing its function, including any downstream effects. Due to the nature of the ternary complex degradation is not dependent on the affinity of the protein of interest ligand which offers the potential to overcome issues arising from viral mutations.

The aim of this project was to develop and synthesise nirmatrelvir-based PROTACs and to assess their activity against M^{pro} in biological assays (figure below). Two PROTACs with different warheads – a nitrile and an aldehyde, were successfully synthesized over 13 steps. Their binding to M^{pro} was screened in an *in vitro* fluorescence intensity assay along with the monofunctional controls and nirmatrelvir. Future work involves performing cell penetration assays followed by M^{pro} degradation assays in various formats.

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POSTER

Gene Expression, and Cell-free biosynthesis of Ribosomally synthesised and post-translationally modified Peptides (RiPPs)

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Peptidyl natural products are increasingly being explored for new therapeutic agents. The emergence of genome mining and sequencing techniques, DNA libraries, and recombinant technologies enables the identification and production of peptides more efficiently, availing additional opportunities for drug discovery. Apart from heterologous gene expression, cell-free systems offer the advantage of assembling biosynthetic machinery that may otherwise be absent in specific hosts. A biosynthetic gene cluster (BGC) encoding a new bithionin ribosomally synthesised and posttranslationally modified peptides (RiPPs) from the culture broth of *Streptomyces Kurssanovii* NCIMB 12788 was identified through genome mining. The gene cluster comprises two precursor peptides, KurA1 and KurA2, including several post-translational modification (PTM) enzymes. KurA1 and KurA2 were biosynthesised through heterologous expressions. PTM enzymes: dehydratase and Kinase homologue KurC-D were co-expressed with KurA1 to provide the first post-translational modification to KurA1. Enzymatic cleavages for sequence determinations were carried out. LCMS analysis identified masses corresponding to expected fragments. Cell-free biosynthesis of Kur A1 confirmed a similar fragment identified from the LCMS analysis of enzymatic cleavage. Further modifications under varying reaction conditions are currently being explored.

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POSTER

The Development of Orthosteric GPR84 Antagonists Series

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With over 800 receptors reported, G-protein coupled receptors (GPCRs) comprise the largest family of proteins encoded by the human genome. By transducing an external stimulus to an intracellular response GPCRs play a pivotal role in cell signalling pathways. GPCRs are activated by a wide array of external stimuli such as: lipids, hormones, light, fatty acids, neurotransmitters and various other small molecules. Consequently, GPCRs are an attractive drug target with over 160 receptors validated as clinical targets and over 500 drugs Food and Drug Administration (FDA) approved.

GPR84 is predominantly expressed in immune cells across various tissue types including the heart, lung, pancreas, kidney, and intestine.[1] Medium chain fatty acids (MCFAs) are proposed to be the endogenous ligand for GPR84. However, the physiological concentration of MCFAs does not reach the threshold required to activate the receptor; consequently, the receptor is termed an orphan receptor.[1] Antagonism of the receptor, shows, in many instances, reduction of leukocyte concentrations and downregulation of proinflammatory markers.[1] Additionally, antagonism of GPR84 in an inflammatory bowel disease (IBD) mouse model displayed a decrease in neutrophil numbers.[1] Thus, antagonism of the receptor is being investigated as a potential route of treatment for diseases such as idiopathic pulmonary fibrosis (IPD) and IBD.[1]

There are 3 documented GPR84 antagonists in the literature. Of these, the only orthosteric GPR84 antagonist is the 1,2,4-triazine scaffold reported by our group.[2] The lead compound from this cluster displays a potent efficacy in a GPR84 GTPγS assay.[2] However, the inherent nature associated with the 1,2,4-triazine results in a discouraging lipophilicity, poor bioavailability and solubility.[2] Additionally, the lack of a regioselective routes to access 1,2,4-triazines further limits development of this chemical series.

This project, in collaboration with the Milligan group, focuses on the development of a novel GPR84 orthosteric antagonist series. The enhanced sp^3 nature of the core scaffold provides encouraging drug-like properties, owing to a favourable logD, high solubility and cell permeability. Synthetic accessibility and molecular modelling identified three potential areas of SAR exploration of the hit compound which will be discussed.

A library of over 80 compounds has been synthesised for pharmacological evaluation. Employing an orthogonal protection strategy allowed for late-stage diversification, facilitating SAR investigations. These molecules displayed excellent efficacy (EC_{50} < 100 nM), improved bioavailability and *in vivo* stability relative to the 1,2,4-triaizne series. Ultimately, this optimisation delivered a more drug-like series of GPR84 antagonists with improved potential for therapeutic development.

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POSTER

Probing the oxidative addition reactions of [Ni(COD)(dppf)] with aryl and vinyl triflates

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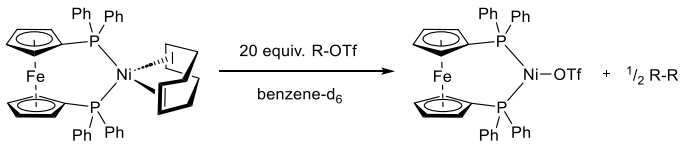
In a world where sustainability is becoming increasingly important, emphasis is being placed on developing efficient and environmentally friendly synthetic processes. The use of catalysis is a powerful tool that addresses many of the green principles of chemistry. However, currently, endangered precious metals such as palladium are typically employed in cross-coupling methodologies. With the aim of providing sustainable alternatives with similar reactivity, the earth-abundant, group 10 metal nickel has become a focus for organometallic chemists.

Whilst the metals exhibit similar properties, existing knowledge of palladium-based catalysts cannot be directly translated to nickel, and research has been complicated by their differing reactivity.[1] Nickel exhibits distinct behaviour with certain functional groups, inducing selectivity in cross-coupling reactions that aren't generally possible with palladium catalysts. Oxidative addition is a crucial step in catalysis, and understanding the mechanisms by which it works provides insight into catalyst ligand design and reaction selectivity. Our mechanistic understanding of the fundamental steps in nickel catalysis is made more challenging by nickel's ability to adopt a wide range of oxidation states, some of which are difficult to follow by standard analytical techniques such as NMR.

Our research is concerned with understanding the reactivity of oxidative addition to nickel(0) complexes and the rate at which these reactions occur. This is important for determining the feasibility of performing reactions on synthetically relevant timescales. Additionally, whilst the rate of oxidative addition does not linearly scale with reaction feasibility, studies have shown that substrates that undergo oxidative addition at slower rates tend to lead to poorer overall yields in cross-coupling. As products from the oxidative addition step serve as intermediates in subsequent reaction steps, understanding their structures and effects on reactivity is imperative.

Nickel(0) complexes are highly reactive to oxidative addition, and the rate of addition of different electrophiles to nickel(0) species has been previously investigated both experimentally and computationally.[2] In our work, the oxidative addition of aryl and vinyl pseudo-halides to a model nickel(0) complex, [Ni(COD)(dppf)], is probed. By investigating both vinyl and aryl substrates, we can alter both the ring size and electron-rich or electron-poor character to determine the effect these properties have on the rate of oxidative addition with [Ni(COD)(dppf)]. This work aims to provide insight into the mechanics of ligand displacement and oxidative addition to a zerovalent metal catalyst.



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POSTER

Neutrophil Elastase Induced Hydrogel Formation

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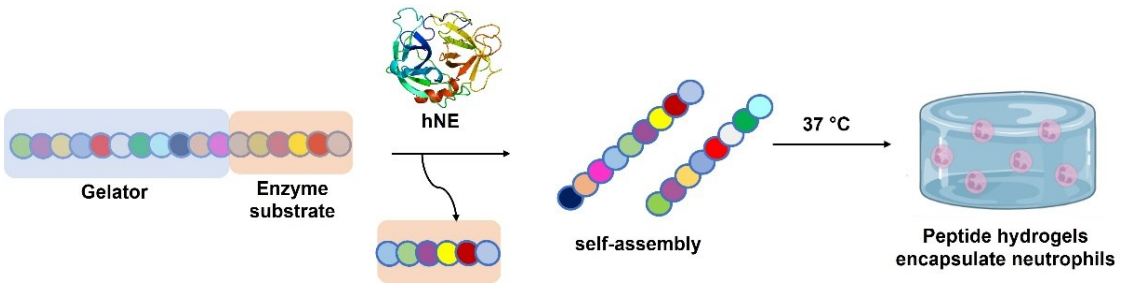
Human neutrophil elastase (hNE) is a serine protease enzyme found in neutrophils, which are the most abundant white blood cells. Neutrophils are among the first immune cells to be recruited to site of inflammation or infection, serving as the primary line of immune defence against pathogens or tissue damage, mainly by secreting hNE.[1] Although important part of the normal immune response, hNE overactivity is widely recognised as a main factor often hindering the normal healing process.[2] Thus, detecting and inhibiting hNE activity is fundamental to understanding the role of this enzyme in various pathologies, but particularly in inflammatory processes such wound healing. One innovative approach to achieve this is through the use of hydrogels. Peptide-based hydrogels have shown promise in various biomedical applications due to their biocompatibility, tuneable physical properties, and ability to create a controlled microenvironment.[3]

Here, we present hNE induced formation of a hydrogel from soluble peptide precursor, with the aim of encapsulating neutrophils at the site of inflammation, resulting in the entrapment of the cells and reduction in both the secretion and activity of hNE. An hNE substrate, containing a protease recognition/cleavage sequence linked to a hydrogelator sequence, was designed and optimised. The sequences were synthesised using Fmoc-based solid-phase peptide synthesis and characterised by MALDI-ToF MS and HPLC. The sequences were evaluated for the solubility, ability to form hydrogels, and finally for their enzymatic cleavage and hydrogel formation by hNE released from activated human neutrophils.



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POSTER

One-Pot Synthesis of Novel Biaryl Fluorescent Amino Acids and the Discovery of a Serine Protease FRET Probe

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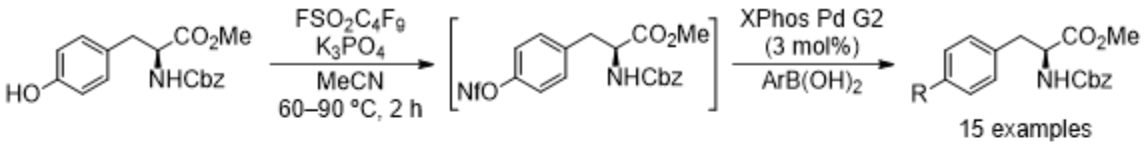
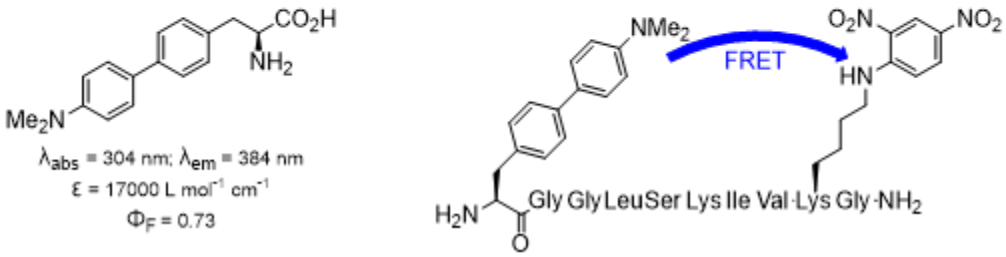
Fluorescent amino acids have recently received significant interest as non-invasive peptidic probes.[1] Compared to labelling with large, extrinsic fluorophores such as GFP,[2] fluorescent amino acids are low molecular weight fluorophores with tuneable photophysical properties that allow straightforward, selective incorporation into peptides *via* solid phase peptide synthesis. Despite several classes of fluorescent amino acids being reported,[1] there remains a desire for shorter synthetic routes to access larger libraries of fluorescent amino acids with distinct photophysical properties. This poster describes the development of a one-pot method involving activation of a commercially available tyrosine derivative by installation of a nonaflate leaving-group, followed by palladium catalysed Suzuki-Miyaura cross-coupling reaction to access novel biaryl α-amino acids.[3] Rapid access to a library of novel fluorescent α-amino acids enabled extensive evaluation of substituent effect on the photophysical properties. This led to the discovery of a dimethylaminobiphenyl analogue that displays strong charge-transfer based fluorescent properties as well as environmental sensitivity to solvent and pH. The dimethylaminobiphenyl analogue was subsequently utilised as a FRET donor and incorporated into a nonapeptide containing a 2,4-DNP-lysine fluorescent quencher. Emission of the dimethylaminobiphenyl amino acid could hence be used to evaluate the kinetic parameters of a serine protease, trypsin, during digestion of the decapeptide.





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POSTER

Design and synthesis of BODIPY fluorophores for radical detection in membranes.

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Reactive Oxygen Species (ROS) are known to play a pivotal role in the mitochondrial dysfunction which underlies cardiovascular diseases and neurodegeneration, and are implicated in ageing. Radical oxidation of the mitochondrial membranes is a major component of this disruption. We have designed (Figure) and synthesised novel BODIPY probes containing a complementary tag to the self-labelling protein, SNAP-tag, for quantification of lipid peroxidizing radicals at various sites within the membranes of the mitochondria. Synthesised probes show a significant shift in emission wavelength after reacting with ROS which allows ratiometric measurement.

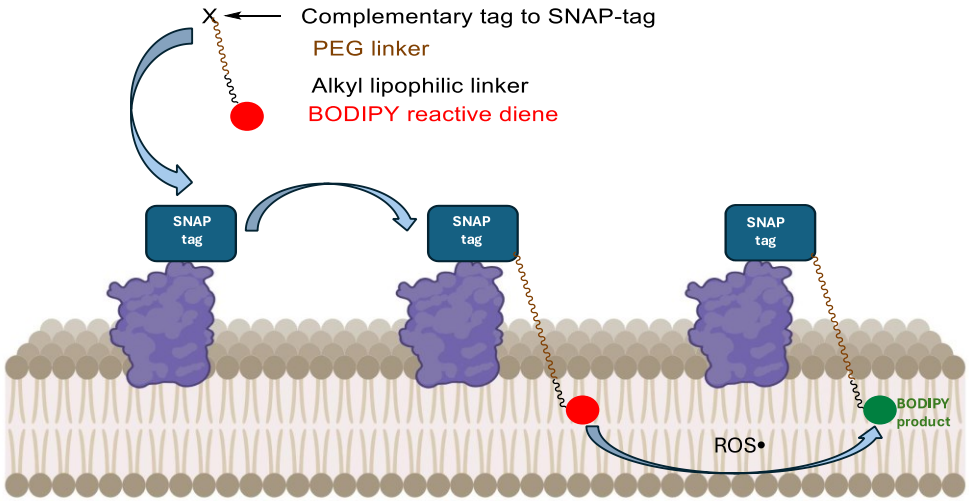

Figure: Probes are designed to be recognised by the self-labelling protein SNAP-tag, localized to various sites in the mitochondria through the expression of fusion proteins or use of a targeting sequence.

POSTER

Kinetic and mechanistic insights to the Petasis borono Mannich reaction by NMR monitoring

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Multicomponent reactions are a widely used method to access complex scaffolds with high atom-economy and selectivity.[1] The Petasis borono-Mannich (PBM) reaction involving formaldehyde, secondary amines, and vinyl boronic acids was first reported in 1993 for the synthesis of naftifine reported by Petasis and co-workers.[2] To obtain mechanistic insights on the transformation, we have conducted the first detailed kinetic studies on PBM reactions. Using a combination of $^{1}H/^{19}F$ NMR spectroscopy reaction monitoring, computational studies, isotopic labelling, and kinetic modelling, we present details for a PBM system comprising 5-fluorosalicylaldehyde, *N*-methyl-4-fluorobenzylamine, and pinacol (*E*)-(4-fluorostyryl)boronic ester, as well as on the subsequent side reactions.[3]

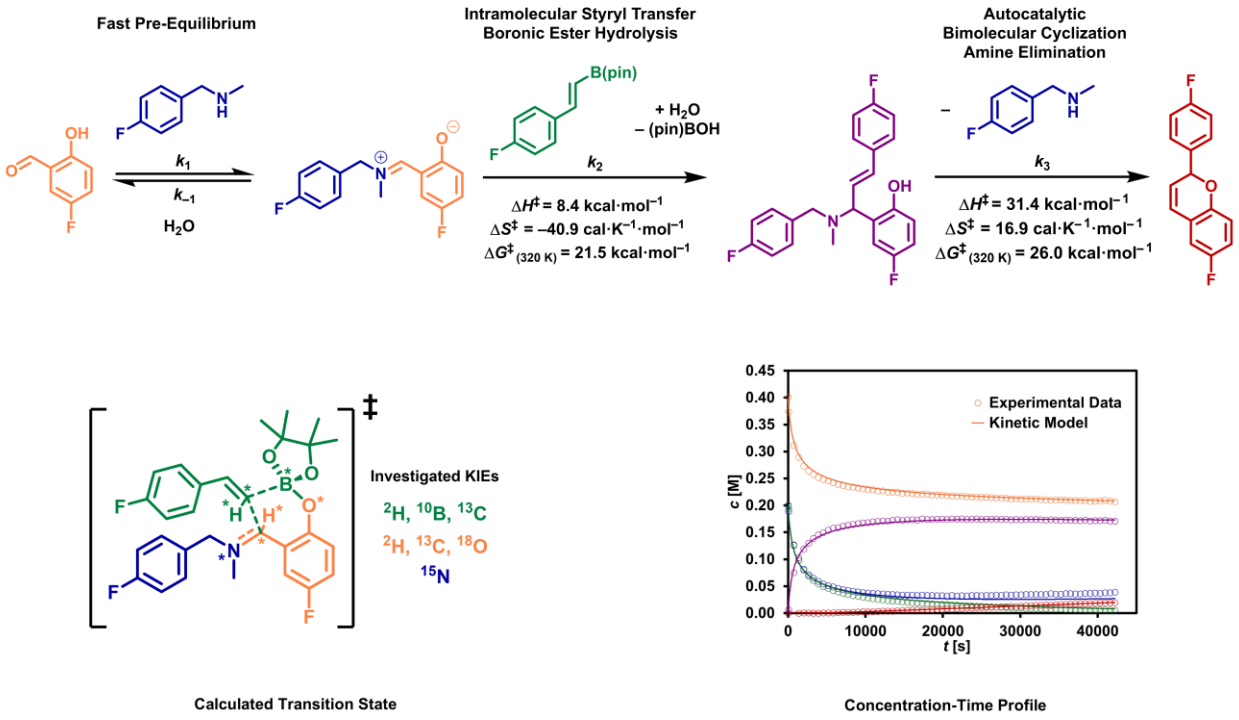

Figure 1. The model PBM system employed in the mechanistic study.

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POSTER

Dual Photo/Organocatalytic *E*/*Z* Isomerization Combined with Dynamic Kinetic Resolution

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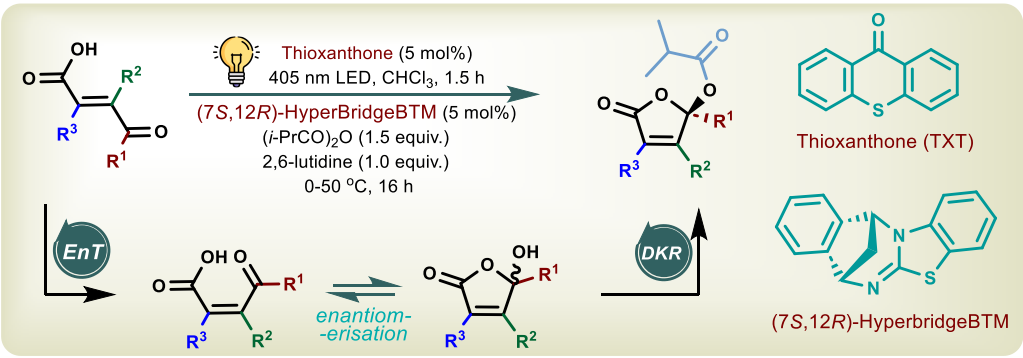
The γ-hydroxybutenolide motif is commonly found in drug molecules and natural products and exhibits a wide range of biological activities yet methods for their preparation in enantiopure form in a simple and mild manner remains challenging. A potential way to access these compounds in enantiopure form is through dynamic kinetic resolution that requires the alkene to be in *cis* configuration. Seminal work from Gilmour *et al* demonstrated the photocatalysed energy transfer *E*→*Z* isomerization of alkenes driven by $n_O \rightarrow p_{C=O}^*$ interactions. In recent work we have developed a dynamic kinetic resolution methodology for tetra-substituted 3-hydroxyphthalides using isothiourea catalysis, where reversible ring-opening and closing is used as an enantiomerisation strategy. Building on this work, we envisaged a one-pot dual photo/organocatalytic approach combining contra-thermodynamic *E*→*Z* isomerization with isothiourea catalysed dynamic kinetic resolution. However, utilising enantiopure tertiary amine catalysts with photocatalytic transformations is currently limited, due to the facile oxidation and subsequent degradation of the amine organocatalyst by the excited state photocatalyst. To address this, we have developed a conformationally constrained isothiourea catalyst, HyperbridgeBTM, that is stable to photocatalytic degradation and enables the dual cphoto/organocatalytic enantioselective synthesis of γ-butenolide esters in high yields and enantioselectivities. Mechanistically, the alkene is selectively isomerized by visible-light photosensitization to its contra-thermodynamic *Z*-form. This intermediate undergoes enantiomerization *via* reversible ring-opening and closing with selective acylation of one enantiomer promoted by the isothiourea catalyst producing enantiopure γ-butenolides esters.



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POSTER

Pituitary Adenylate Cyclase-Activating Polypeptide analogues as PAC-1 receptor antagonists

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Migraine is the most disabling neurological disease which affects ~15% people worldwide having a significant effect on the economy and society.[1] Neuropeptides, such as calcitonin gene-related peptide (CGRP), play a prominent role in the pathology of migraine. Blocking (antagonising) the CGRP receptor in the peripheral nervous system is validated for migraine treatment. However, they exhibit limited efficacy (~60% of patients benefit). In recent years, other neuropeptides have gained interest due to their involvement with migraine and could be other potential therapeutic targets.

Pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide that activates the G-protein coupled receptor, PAC1R. A recent clinical trial showed a monoclonal antibody (mAbs) (AG09222) binds to PACAP and prevent the onset of migraine.[2] However, the capture of PACAP using mAbs did not provide the expected benefits.[3] Therefore, the actual receptor which PACAP binds and triggers migraine is still unknown. In this study, amino acids from the N-terminus of PACAP were systematically truncated using solid phase peptide synthesis (SPPS), to explore the effect upon antagonist potency against PAC1. Overall, about 50 truncated analogues ranging from PACAP 6-38 to as short as PACAP 28-38 were synthesized and purified by preparative HPLC to high homogeneity by analytical HPLC. In order to probe the effect of replacement of each amino acid of PACAP 28-38 with alanine computational (BUDE) and experimental alanine scanning mutagenesis evaluation has performed. Another cell-based assay was performed using Fluorescence resonance energy transfer (FRET) in which the cAMP accumulation was studied which confirmed their action as antagonists. In order to improve the pharmacokinetic profile, hydrocarbon stapling is performed at various positions after careful analysis of binding interaction and possible steric hinderance by using computational drug design. Circular dichroism (CD) has confirmed the improvement of helicity of the stapled peptides. Future aim is to make sequential structural modifications to probe the effects of antagonism of a family of receptors: PAC1, VPAC1 and VPAC2 to further develop SARs.

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POSTER

An Acoustic Chemistry Platform for Nanoscale High Throughput Synthesis of Protacs

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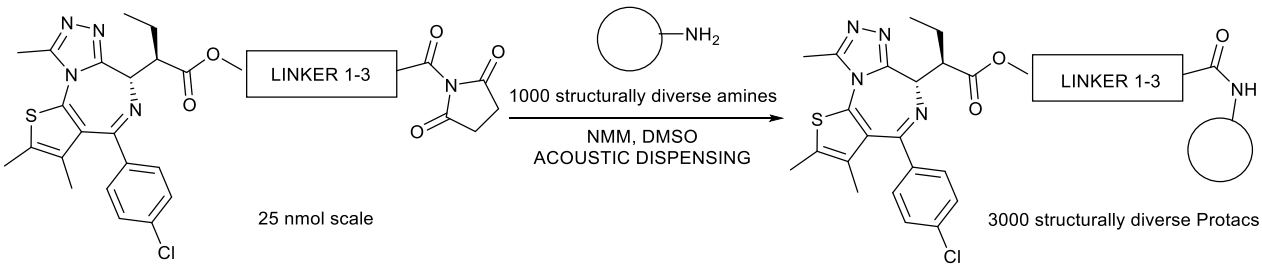
Synthesis of Protacs is often challenging due to complex chemical routes and expensive building blocks. Setting up structurally diverse libraries of Protacs for target identification is further complicated by the high number of compounds needed to cover wide chemical space and maximise the chances of identifying hits. In this work, we have developed a semi-automated platform for high throughput synthesis of Protacs in microplates, using acoustic dispensing of nanomolar amounts of starting materials. The platform allowed us to set up 3000 reactions of which QC showed 80% success. The resulting designed crude Protac library was screened in a positive selection degradation assay aimed at identifying ligandable E3 ligases in *Leishmania donovani*. The nanomolar scale used for this approach was crucial to enable the synthesis of such a large collection of compounds in a rapid and cost-effective manner. The screening of this library identified multiple hit compounds that are currently being followed up for resynthesis, activity confirmation and progression to target identification experiments.



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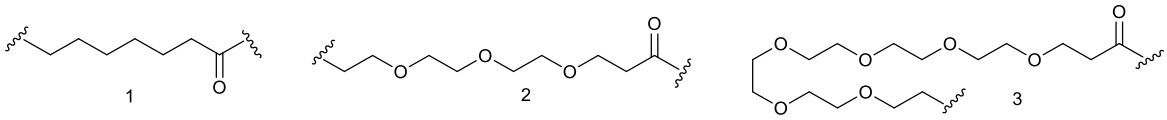

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POSTER

Generating Potent Raman-Active BRD4 Degrader Probes for Cellular Imaging

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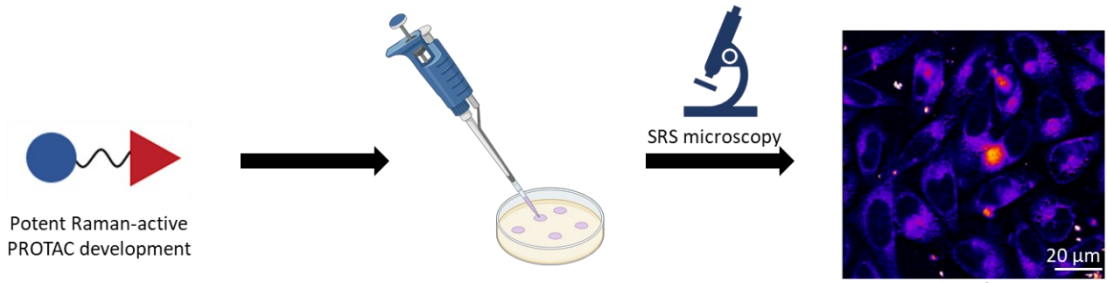
Despite advances in drug development, nearly 90% of small molecules in trials fail. Cellular imaging reveals crucial details in drug discovery, helping select molecules with favourable properties. Recently, Stimulated Raman Scattering (SRS) microscopy has become a valuable tool for drug imaging, detecting molecular vibrations with spatial resolution and high speed, offering quantitative imaging.[1] The aim of this work is to track and image the uptake of Proteolysis Targeting Chimeras (PROTACs) in cells using SRS microscopy, providing insights into their uptake and distribution for the first time.

Our lab has developed bio-orthogonal Raman labelling strategies that minimally impact drug activity.[2] This project focuses on creating Raman-active BRD4 degraders based on the molecule (+)-JQ1.[3] The synthesized heterobifunctional molecules demonstrated rapid and significant BRD4 degradation at low nanomolar concentrations via the ubiquitin-proteasome system. Their selectivity and binding properties were examined using advanced analytical techniques. These potent degraders were successfully imaged during cellular uptake.



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POSTER

New Metal-mediated Cyclisation Methods for the Generation of Heteroatom Functionalised Cyclic Systems

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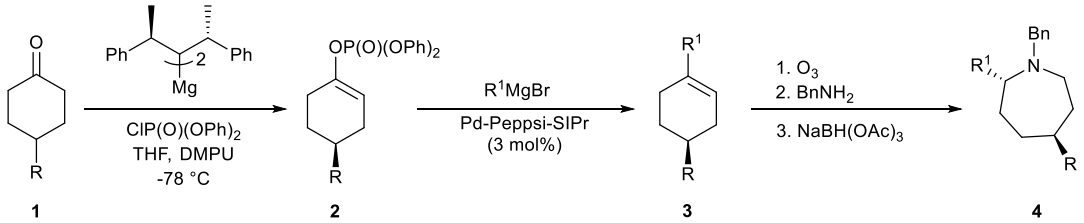
In recent years, the pharmaceutical industry has highlighted that introducing a higher degree of sp^3-character and stereogenic centres into developing drug candidate molecules has provided an increased chance of success of transitioning from drug discovery, through clinical trials, and to drugs that reach the market.[1] This is credited to the several advantages that are associated with sp^3-rich scaffolds in drug molecules, these being lowering compound melting points and decreasing lipophilicity, which subsequently improves solubility, as well as, reducing promiscuity and toxicity. On account of this, the synthesis of chiral, sp^3-rich small molecule scaffolds has continued to grow in popularity. Having stated this, in spite of the physiochemical advantages associated with these scaffolds, asymmetric synthetic routes required for the preparation of enantioenriched sp^3 molecules remain an area of active investigation.

As aligned with the above, and in order to access new regions of chemical space, we have established a sequence to allow conversion of achiral 4-substituted cyclohexanones to chiral azepane scaffolds. The azepane structural motif was a particular target of interest due to the varying potential points of diversity and its three-dimensional character has specific relevance as a pharmaceutically significant core.



- 10 azepane examples
- Up to 70% overall yield and 98% ee.
- Diasteroselective ozonolsis/reductive amination
- Generally mild conditions
- Broad substrate scope

The synthetic procedure initiates by employing chiral magnesium amide base chemistry to desymmetrise 4-substituted cyclohexanones (**1**), delivering a variety of chiral enol phosphates (**2**) in good to excellent yields (58%-97%) and with high levels of enantioselectivity (68%-98% *ee.*).[2,3] The chiral enol phosphates are then subjected to a palladium-catalysed cross-coupling reaction with a variety of alkyl and aryl Grignard reagents to form the corresponding trisubstituted alkenes (**3**) in moderate to excellent yields (43%-95%) whilst maintaining the high levels of enantiomeric integrity. Finally, a telescoped diastereoselective ozonolysis/reductive amination sequence forms a series of 7-membered rings (**4**) in moderate yields (27%-54%). Overall, this sequence provides both a practicable and synthetically efficient method for the construction of the targeted scaffolds.

The full scope of this developing methodology will be disclosed within the poster presentation.

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POSTER

Action of Tailoring Enzymes in RiPPs Biosynthesis: A Review

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Multinuclear non-heme iron-dependent oxidases (MNIOs), previously classified as the domain of unknown function 692 (DUF692), are metalloenzymes crucial for the post-translational modifications in ribosomally synthesized and post-translationally modified peptides (RiPPs). To the best of our knowledge, only a few of these enzymes have been fully characterized to date, among which only a small number are non-cysteine-modifying MNIOs. A common feature of cysteine-modifying MNIOs is their ability to modify Cys-rich precursor peptides through four-electron oxidative rearrangements in the absence of external reductants, resulting in the formation of thioamides, 5-thiooxazoles, heterocycles/macrocycles, or β-carbon excision.

POSTER

Skeletal rearrangement through photocatalytic denitrogenation: access to C-3 aminoquinolin-2(1*H*)-ones

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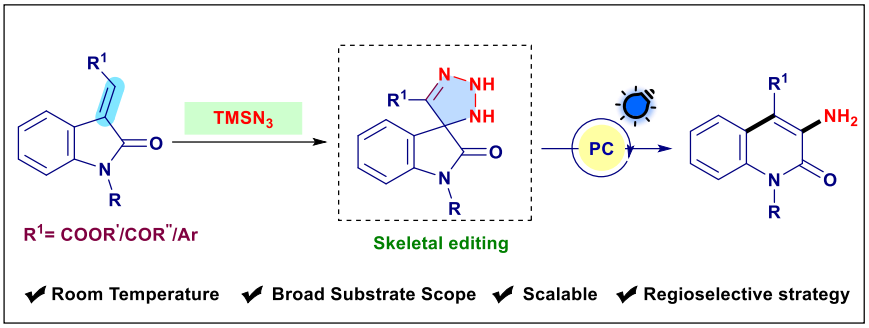
Selective introduction of an amino group on heterocyclic moiety is a crucial step for manufacturing various bioactive compounds.[1] It became essential to move beyond the limitations of conventional approaches that utilize elevated temperatures or extreme acidic conditions, ensuring site selectivity.[2] This research article discussed the skeletal editing approach for regioselective denitrogenative amination to access C-3 aminoquinolin-2(1*H*)-ones.[3] This strategy explored various 3-ylideneoxindoles substituted with sensitive functional groups as synthetic precursors for quinolin-2(1*H*)-one backbone. This protocol also manifests compatibility with benzoyl and aryl groups on the olefinic bond of 3- ylideneoxindoles. Detailed mechanistic experiments were conducted using several spectroscopic studies to corroborate the photocatalytic involvement in the skeletal editing of the triazoline intermediate. The practical utility of this approach was depicted by scale-up experiments and efficient synthesis of pharmaceutically active compounds.



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POSTER

Whole-cell Photobiocatalytic Cyclic Deracemisation of Secondary Benzylic alcohols

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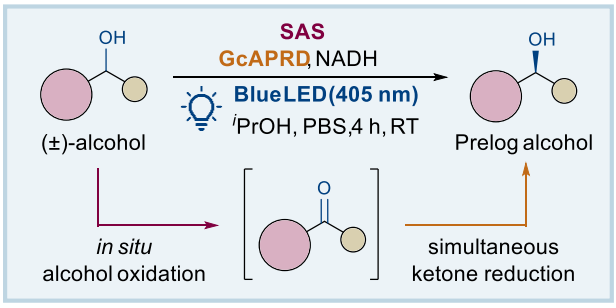
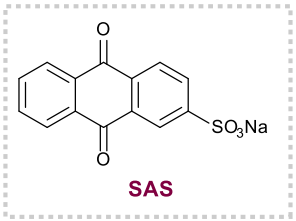
Photobiocatalysis is emerging as a sustainable synthetic approach offering unique synergistic reactivities, yet its practical implementation remained underexplored due to inherent incompatibilities, most notably photodamage of enzymes.[1] Deracemization of secondary alcohols is a key model reaction for photobiocatalytic protocols due to the importance of the enantioenriched products. However, current strategies rely on temporal separation of catalytic cycles to circumvent incompatibilities, precluding photobiocatalytic transformations that require the *in situ* generation of reactive intermediates.[2,3] We report a single-step cyclic deracemization protocol by combining a water-soluble photocatalyst (sodium anthraquinone-2-sulfonate) with a promiscuous alcohol dehydrogenase (*Geotrichum candidum* acetophenone reductase) encapsulated in lyophilized microbial whole-cells. This represents a modular and potentially generalizable strategy to developing photobiocatalytic cascades operating under mutually compatible conditions, wherein spatial separation mitigates photodamage and enables simultaneous dual catalytic turnover. Molecular docking and kinetic modeling further elucidated enzyme selectivity and system dynamics to inform optimization of this multi-component system.





- Up to 98 : 2 er
- Docking studies
- Kinetic modelling
- Biocatalyst protection
- Operationally simple

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