



International Isotope Society UK Group

31st Annual Symposium

The Synthesis and Applications of
Isotopically Labelled Compounds

Friday, 14th November 2025
The Møller Institute, Cambridge

<https://www.iis-uk.org>

Sponsors

The organising committee would like to thank the following companies for their generous sponsorship:



Welcome & Acknowledgements

On behalf of the organising committee, it is my pleasure to welcome you to the 31st annual symposium of the International Isotope Society UK Group on the synthesis and applications of isotopically labelled compounds held, once again, at The Møller Institute in Cambridge.

Professor Jason Lewis from The Memorial Sloan Kettering Cancer Center, will open the meeting with a talk titled "*Radiopharmaceutical Chemistry – Precision Medicine in Cancer Treatment.*" Our afternoon session will be opened by Dr Katherine Wheelhouse from GSK with a talk titled "*Adventures in Pharmaceutical Catalysis.*"

Today's programme will also cover a multitude of topics including, radiopharmaceuticals, photochemistry, mechanochemistry, radiosynthesis with carbon-14 and tritium, catalysis, isotope exchange and the use of radiolabels in metabolism. I hope you'll find plenty of topics of interest.

I would like to thank all our speakers and those presenting posters for joining us today and taking the time to share their work. I'd also like to thank our sponsors and exhibitors for their generous support both this year and in years past. My thanks also go to our session chairs and to the staff of The Møller Institute for helping us to stage this event. This meeting would not have been possible without the dedication and enthusiasm of the organising committee — my thanks go to all involved.

Lastly, I have to thank you all for attending and helping to make this event so successful. I hope you have a very enjoyable day.

Chris Winfield.
Chair, IIS UK Group.

Organising Committee

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Scientific Programme

- 8:30 am Registration, morning coffee & manufacturers exhibition.
9:00 am Welcome: Dr Chris Winfield (Eurofins Selcia, Chair of the IIS UK Group).

Morning Session 1

Chair: Dr Graham Smith (University of Cambridge, UK).

- 9:05 am **Professor Jason Lewis** (Memorial Sloan Kettering Cancer Center, USA).
"Radiopharmaceutical Chemistry - Precision Medicine in Cancer Treatment."
- 9:55 am **Dr Susannah Coote** (University of Bath, UK).
"Making 'Difficult-to-Make' Molecules: Photochemistry as an Enabling Tool."
- 10:20 am *5-Minute Flash Presentations*
- Liam Raeside** (University of Strathclyde, UK)
"Iridium Catalysed Aryl Hydrogen Isotope Exchange Directed by Benzylic Amines."
- Lucy Pryde** (University of Strathclyde, UK)
"Iridium Catalysed Hydrogen Isotope Exchange of Amino Acids."
- Ksenia Stankevich** (University of York, UK)
"A Practical and General Method for Deuterium Labelling."
- Chris Otun** (University of Manchester, UK)
"Biocatalytic HIE for the Stereoselective Synthesis of Deuterated Reduced Nicotinamide Cofactors."
- Danny Ryder** (University of Southampton, UK)
"Aryl Halide Carboxylation via Decarboxylative Metal-Halogen Exchange."

- 10:50 am Manufacturers' exhibition, poster session, tea & coffee.

Morning Session 2

Chair: Dr Gregory Perry (University of Southampton, UK).

- 11:20 am **Dr Kevin Joly** (Eurofins Selcia, UK).
"Savolitinib: GMP Radiolabelled API Manufacture for a C-14 Human ADME Study."
- 11:45 am **Professor Duncan Browne** (University College London, UK).
"Mechanochemistry, an Opportunity for Isotope Chemistry?"
- 12:10 pm Buffet lunch, manufacturers' exhibition & poster session.

Scientific Programme

Afternoon Session 1

Chair: Dr David Lindsay (University of Strathclyde, UK).

- 1:25 pm **Dr Katherine Wheelhouse** (GlaxoSmithKline, UK).
"Adventures in Pharmaceutical Catalysis."
- 2:15 pm **Dr Grégory Pieters** (CEA, France).
"Nanocatalyzed Hydrogen Isotope Exchange: Applications in the Synthesis of Tritiated Pharmaceuticals."
- 2:40 pm Manufacturers' exhibition, poster session, tea & coffee.

Afternoon Session 2

Chair: Dr Helen Betts (University of Nottingham, UK).

- 3:15 pm **Associate Professor Miriam O'Duill** (University of Nottingham, UK).
"Methodology Development for Small Molecule Labelling."
- 3:40 pm **Ms Kathryn Webbley & Ms Claire Henson** (Pharmaron, UK).
"The Use of Radiolabels from a Metabolism Scientist's Perspective."
- 4:05 pm Concluding Remarks: Dr Chris Winfield (Eurofins Selcia, Chair of the IIS UK Group).

Presentation Abstracts

Radiopharmaceutical Chemistry – Precision Medicine in Cancer Treatment

Professor Jason S. Lewis.

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The use of Positron Emission Tomography (PET) for cancer imaging is a well-established and widely used molecular imaging modality both in clinical and research settings. Over the last 30 years, our ability to non-invasively diagnose, localize, and treat many forms of cancer has advanced tremendously. These diagnostic tools are now being combined with therapeutic isotopes to create "theranostics" - agents that allow for simultaneous imaging and treatment with the same drug. This talk will include both preclinical and clinical application of these cancer targeting drugs within the central premise of theranostics "see what you treat and treat what you see".

One area of emphasis for the Lewis Lab has been centered around the remarkable specificity and selectivity of antibodies for cancer biomarkers have made immunoglobulins some of the most flexible and adaptable tools in modern medicine. For therapeutic purposes, a wide range of non-labeled antibodies has now entered the clinic. Antibody-based PET and SPECT imaging agents are not far behind. For example, an array of ⁸⁹Zr-labeled radioimmunoconjugates has shown significant promise in both preclinical and clinical studies. Zirconium-89 has a number of distinct advantages which make it ideal for ImmunoPET including that the radioactive half-life of 78.4 h matches closely the extend times required for optimum biodistribution of intact mAbs. This presentation will review the current state-of-the-art on the use of radiometals with antibody constructs.

Making Difficult-to-Make Molecules: Photochemistry as an Enabling Tool

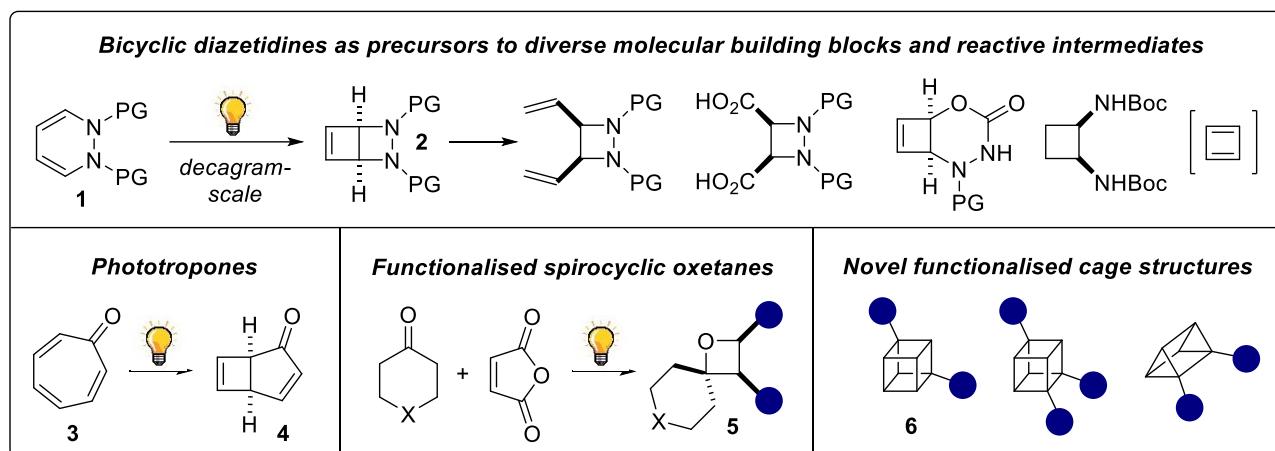
Dr Susannah C. Coote.

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Converting simple starting materials into complex products using only a light source (synthetic photochemistry) is especially attractive to organic chemists, particularly from the point of view of green chemistry: waste is minimised, and light is readily available. In addition, photochemical routes often allow efficient access to complex frameworks (particularly to strained molecules and intermediates) that cannot be generated using ground-state chemistry.

We are particularly interested in the synthesis of four-membered rings, especially through the use of 4- π -photocyclisations and [2+2] photocycloadditions – atom-economical reactions that are generally under-used by synthetic chemists. For example, the 4- π -photocyclisations of dihydropyridazines **1**¹ and tropone (**3**)² produce cyclobutene products **2** and **4** respectively, which can both be converted into a variety of different derivatives. In addition, cyclic ketones react with maleic anhydride under irradiation to give complex functionalised spirocyclic oxetanes **5**³ that cannot be prepared any other way, and photocycloaddition reactions are key in the construction of caged compounds such as 1,3-cubanes **6**^{4,5,6} as well as ongoing projects directed towards other novel cubane and prismane derivatives.



References

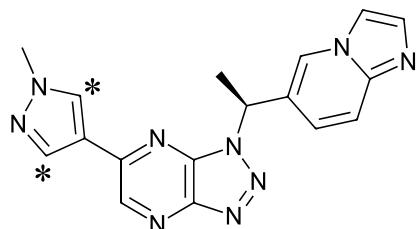
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Savolitinib: GMP Radiolabelled API Manufacture for a C-14 Human ADME Study

Dr Kevin Joly.

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[¹⁴C]Savolitinib

Savolitinib is a potent cMET inhibitor intended for the treatment of non-small cell lung cancer. As part of the clinical development of Savolitinib, a [¹⁴C]Savolitinib human ADME study was required to elucidate the drug's metabolism and disposition.

This presentation will describe the synthesis of [¹⁴C]Savolitinib GMP radiolabelled Drug Substance to support the human metabolism investigation.

The GMP starting material, [¹⁴C]AZ13791950, was synthesised in 5 steps from diethyl [¹⁴C]malonate and used to provide a non-GMP technical batch of [¹⁴C]Savolitinib for radio-stability testing and trial Drug Product (IMP) manufacture.

Two validated HPLC API release methods (radiochemical purity & chiral purity) as well as an NMR assay were formally transferred from AstraZeneca and adapted for GMP ¹⁴C-API release and radio-stability testing.

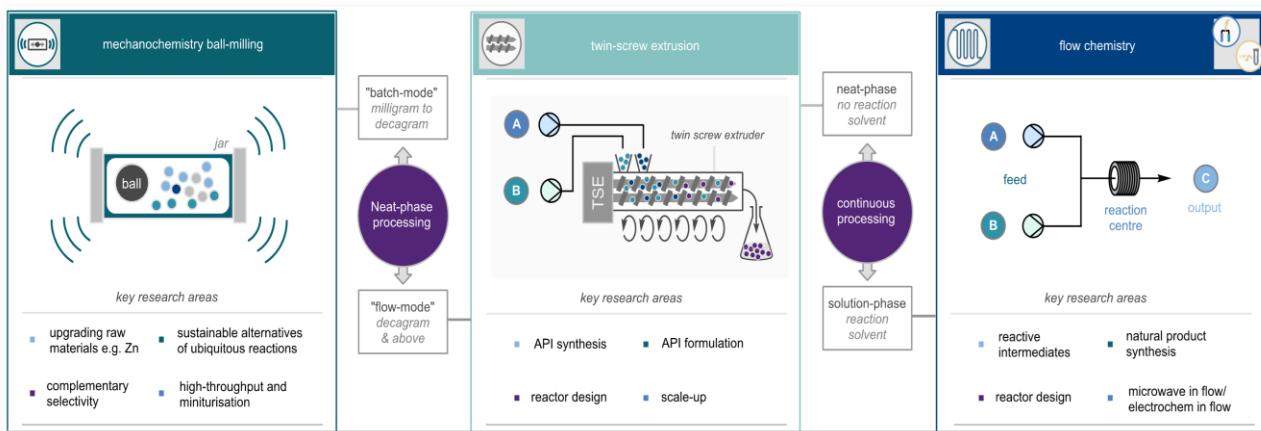
Radiosynthesis of GMP ¹⁴C-API from retained [¹⁴C]AZ13791950 was subsequently performed in a dedicated GMP radiosynthesis laboratory and supplied for use in the human ADME study in a time and material efficient manner.

Mechanochemistry, an Opportunity for Isotope Chemistry?

Professor Duncan L. Browne.

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The Browne research group focuses on the use of mechanochemistry and continuous processing for the making and breaking of organic molecules. This seminar will focus on the use of ball-milling methods to run reactions in the absence of a bulk reaction solvent. The ball-milling device inputs mechanical and thermal energy to elicit a chemical transformation. Whilst the use of mechanochemistry has been known for some time; in areas such as formulation, crystal engineering, forensics and geology, its use for the construction of organic molecules is relatively new. The potential solvent savings afforded by mechanochemistry techniques are particularly appealing at larger scales. This talk will focus on the concurrent development and discovery of new opportunities for molecular synthesis by small scale mechanochemistry (using a ball-mill device) and translation of these methods to larger scale solvent-minimised processes through continuous mechanochemistry using a twin-screw extruder.

References

For some examples of our groups work in mechanochemistry and extrusion see:

Research Articles

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Reviews

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- (2) Chem. Soc. Rev. **2022**, 51, 4243.
- (3) Chem. Sci. **2018**, 9, 3080.

Adventures in Pharmaceutical Catalysis

Dr Katherine M. Wheelhouse, FRSC.

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Chemical catalysis is a key technology in chemical synthesis, including pharmaceutical manufacture.

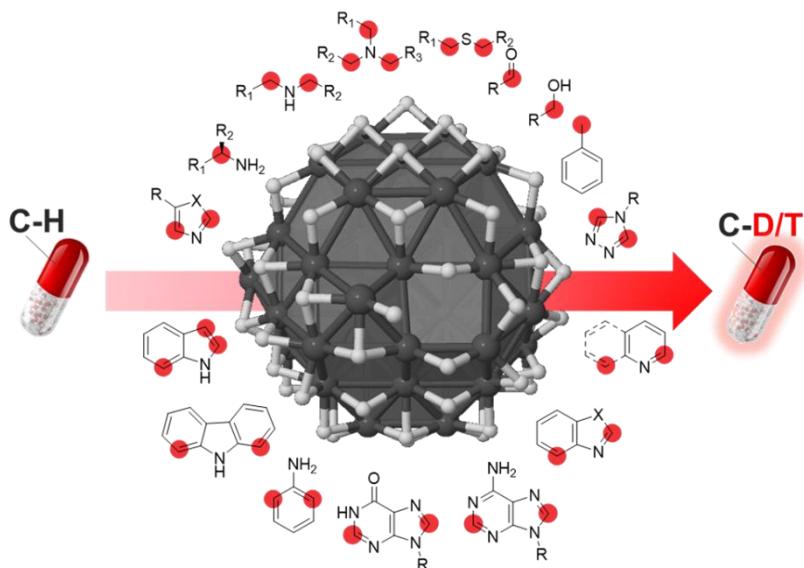
Application to manufacturing processes requires understanding of a range of factors beyond the reaction itself, from sourcing the specific catalyst required to understanding of the equipment, separation of the catalyst residues from the product and the equipment train and eventual recovery of the precious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

Nanocatalyzed Hydrogen Isotope Exchange: Applications in the Synthesis of Tritiated Pharmaceuticals

Dr Grégory Pieters.

Service de Chimie Bioorganique et de Marquage, Laboratoire de Marquage Isotopique, CEA Paris-Saclay, France.

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Deuterated and tritiated compounds play pivotal roles across diverse disciplines, including Chemistry, Biology, and Material Science.^[1a] Tritiated molecules serve as indispensable radiotracers in drug discovery, facilitating crucial Absorption, Distribution, Metabolism, and Excretion (ADME) studies.^[1b] Conversely, deuterated compounds are instrumental in metabolomics, enabling precise quantification through internal standardization. Moreover, strategic incorporation of deuterium into specific molecular positions can modulate metabolism rates, mitigate toxic metabolite formation *in-vivo*, and enhance the performance and stability of emitters essential in OLED devices and bioimaging. Therefore, the development of efficient and selective methods for the late-stage incorporation of hydrogen isotopes into complex molecules is of paramount importance.^[1c-d] In this context, the development of nanocatalyzed hydrogen isotope exchange (HIE) reactions^[1e] allowing the labelling of numerous substructures (alkylamines^[2a-b], thioethers^[2c], heterocycles^[2a, 2d-e]) in complex molecules through selective C-H activation processes using Ru nanoparticles will be summarized. Then, the potential to generate catalytically active nanoclusters (Ir^[3], Rh^[4], Ni^[5]) *in situ* from air-stable, commercially available precatalysts, as well as their application in the synthesis of tritiated pharmaceuticals, will be discussed.

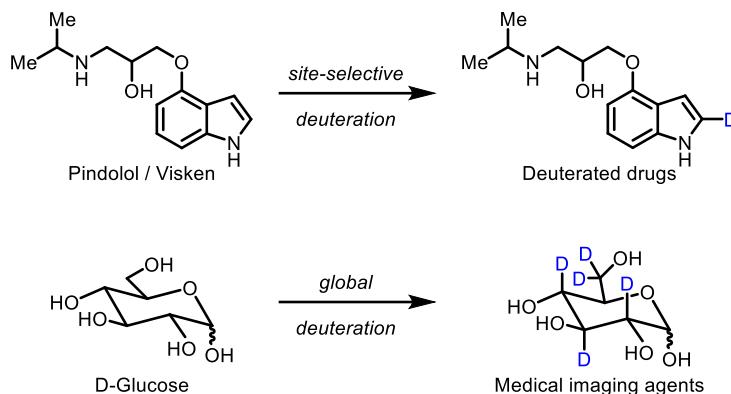
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- (5) Tatol, C. *et al.*, submitted.

Methodology Development for Small Molecule Labelling

Associate Professor Miriam O'Duill.

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Deuteration is a crucial tool for drug ADME (absorption, distribution, metabolism, and excretion) studies and can improve the metabolic stability, pharmacokinetics, and toxicity profile of drugs.¹ Deuterated molecules also play an important role in medical imaging, providing metabolic and biological information on disease processes.² The development of new methods for deuterium incorporation into drug molecules and medical imaging probes has thus become an increasingly vital tool for medicinal chemistry, but the requirements for the two applications are very different: While single site-selective isotopic labelling is usually required for drug design, medical imaging probes provide more information the more isotopic labels they carry. In this talk, two examples of transition-metal catalysed methodology for (1) site-selective deuteration of indoles for drug design,³ and (2) global deuteration of sugars⁴ for medical imaging applications will be discussed.

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The Use of Radiolabels from a Metabolism Scientist's Perspective

Ms Kate Webbley and Ms Claire Henson.

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Understanding the fate of a drug candidate in humans and relevant toxicology species is a critical component of the drug discovery and development process. Throughout the development pipeline, a range of in vitro and in vivo studies are conducted to elucidate the drug's absorption, distribution, metabolism, and excretion (ADME) properties.

Although advanced LC/MS techniques are widely used for these investigations, radiolabelled molecules remain an integral part of the analytical toolkit. They enable precise quantification of metabolites and allow researchers to assess the retention and excretion of all drug-related material, independent of structural information or MS ionization efficiency.

From a metabolism scientist's perspective, radiolabels are powerful molecular tools that reveal the hidden intricacies of biological systems. This presentation highlights the collaborative synergy between radiochemists and metabolism scientists, where chemistry becomes a lens to decode biology.

Flash Presentation Abstracts

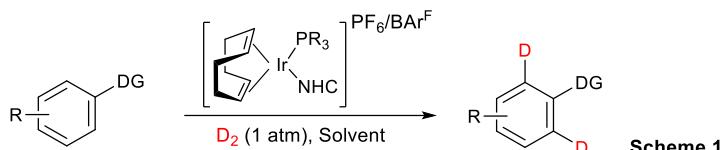
Iridium Catalysed Aryl Hydrogen Isotope Exchange Directed by Benzylic Amines

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

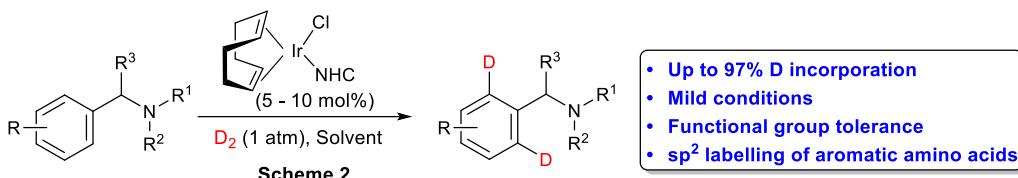
^aDepartment of Pure and Applied Chemistry, University of Strathclyde, Glasgow, G1 1XL, Scotland, UK.

^bMedicinal Chemistry, GSK Medicines Research Centre, Gunnels Wood Road, SG1 2NY, Stevenage, UK.

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Absorption, distribution, metabolism, excretion, and toxicity (ADMET) studies are essential to the assessment of the 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) is an approach which furnishes selectively labelled molecules without the expensive and time-consuming re-synthesis of labelled analogues. Iridium(I) catalysts of the type $[\text{Ir}(\text{COD})(\text{PR}_3)(\text{NHC})]\text{X}$, 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).



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 benzylic amines 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 $\text{C}(\text{sp}^2)\text{-H}$ 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 also includes aromatic amino acid examples labelled at the *ortho*-position of the arene, a labelling pattern which has, to date, not been demonstrated using transition metal catalysed HIE methods. Reaction optimisation will be described, along with competition studies related to other Lewis basic functionality.

References

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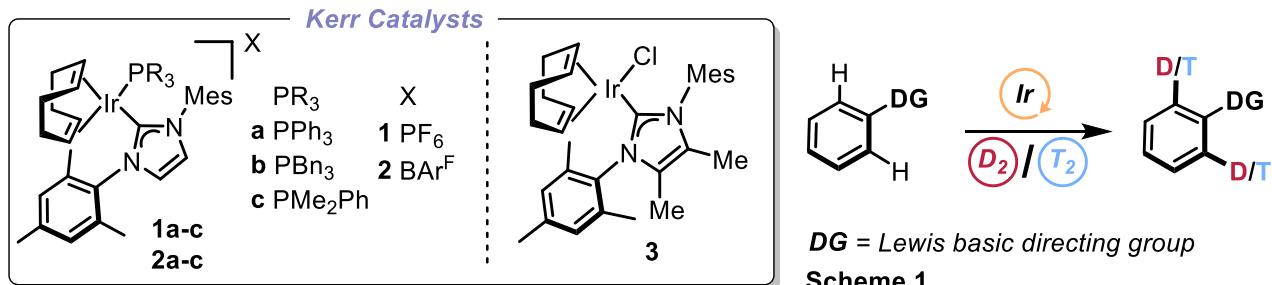
Iridium Catalysed Hydrogen Isotope Exchange of Amino Acids

Lucy V. Pryde,^a Megan Cuthbert,^a Adele E. Queen,^a Sumei Ren,^b Neil Strotman,^b David M. Lindsay^a and William J. Kerr.^a

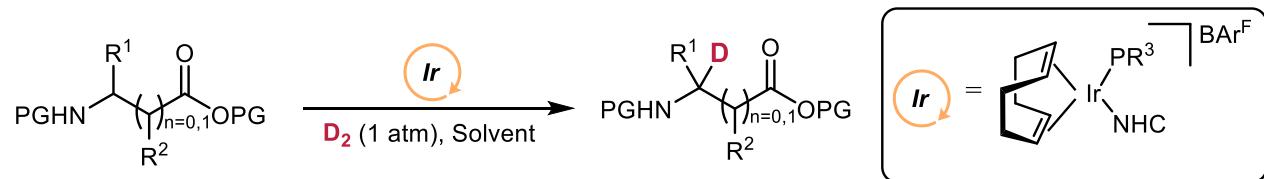
^aDepartment of Pure and Applied Chemistry, University of Strathclyde, Glasgow, G1 1XL, Scotland, UK.

^bDepartment of Process Research & Development, Merck Research Laboratories (MRL), MerckSharp&Dohme Corp, Rahway, USA.

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An understanding of the adsorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of pharmaceuticals is crucial to bringing a new drug to the market. Incorporating isotope labels into drug candidates is a method of investigating their ADMET properties without significantly altering their physical characteristics.¹ Hydrogen isotope exchange (HIE) is a robust technique frequently used for labelling, with catalysts of the type $[\text{Ir}(\text{COD})(\text{PR}_3)(\text{NHC})]\text{X}$, already extensively developed within our laboratories (Scheme 1).² These catalysts have proven to be highly active, and operate under mild conditions, utilising a variety of Lewis basic directing groups for the C-H activation required for HIE.



- Up to 99% D
- Mild conditions
- >40 examples
- Stereoretentive

Scheme 2

C-H activation is an attractive methodology for late-stage functionalisation reactions, including HIE. Amino acids are fundamental building blocks in biology and medicine, however, examples of amino acid HIE are rare and often require harsh reaction conditions with high catalyst loadings or have very limited substrate scopes.³ This work describes the application of cationic iridium catalysts in the HIE of α - and β - amino acids (Scheme 2). This methodology has been applied to a range of natural and unnatural amino acids, giving high levels of deuterium incorporation, under mild reaction conditions. Notably, the scope includes a range of protecting groups frequently employed in peptide chemistry. Reaction optimisation will be described, along with an extensive substrate scope.

References

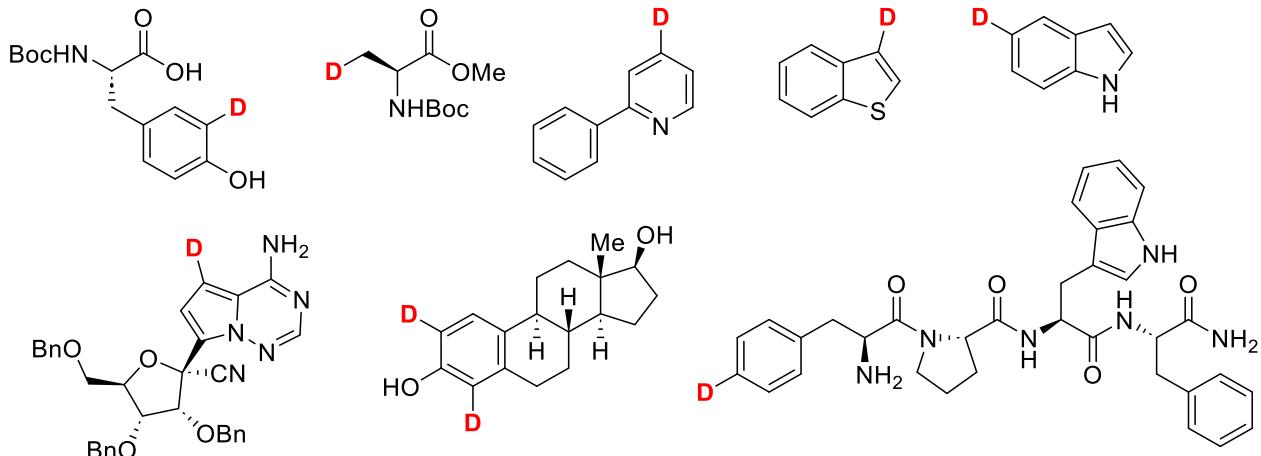
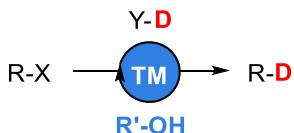
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A Practical and General Method for Deuterium Labelling

Ksenia Stankevich and Christopher Spicer.

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Deuterium labelling finds diverse applications in both research and industry. In particular, pharmaceutical companies are leveraging the properties of deuterium to enhance drug stability, safety, and efficacy, and more widely as a tool to study pharmacokinetics of lead compounds.¹ Although various strategies for deuterium incorporation are available, they often require the use of deuterated solvents or deuterium gas, forcing conditions, and specialist techniques or equipment.² This leads to a number of challenges, including the limited utility of these methods. For example, the site-specific deuteration of biological molecules, such as peptides and proteins, often results in the concomitant exchange of labile hydrogens with deuterium, which can significantly affect protein structure and biological activity. In this study, we present a deuteration strategy that enables the facile formation of $C(sp^2)$ -D and $C(sp^3)$ -D bonds in protonated solvents, such as water and alcohols, without the loss of deuterium labelling efficiency. The reaction is operationally simple and takes place within minutes in open flask at room temperature. This practical method enables site-selective deuterium labelling of complex and polar molecules such as peptides and proteins alongside common synthetic building blocks, pharmaceuticals, and natural products, with high yields and isotopic purity.

References

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Biocatalytic HIE for the Stereoselective Synthesis of Deuterated Reduced Nicotinamide Cofactors

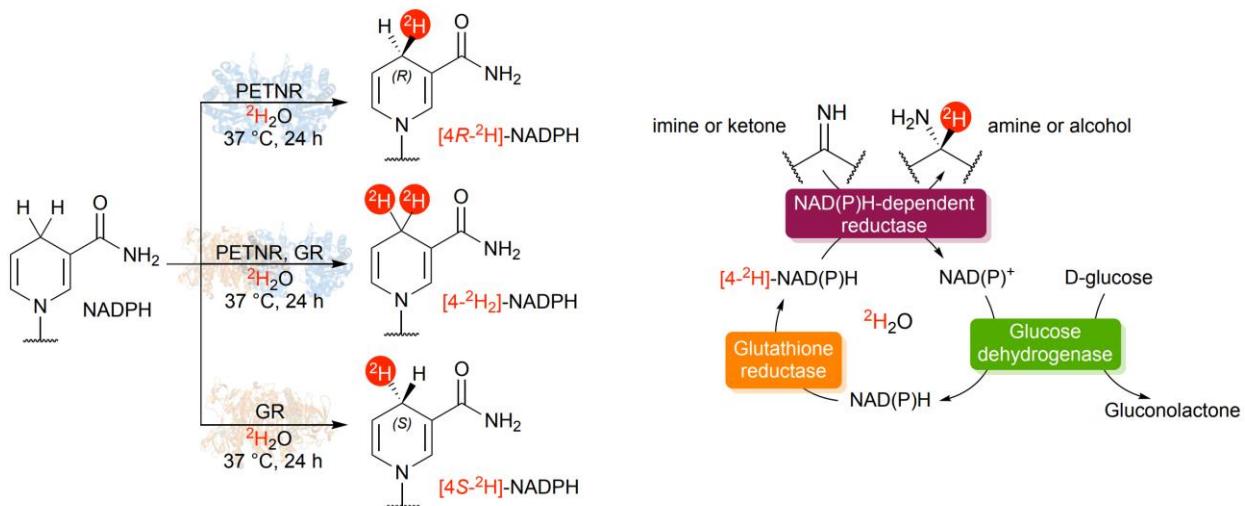
Christopher W. O. Otun,^a Francesco Falcioni,^b Ryan A. Bragg,^b Charles S. Elmore^c and Jack S. Rowbotham.^a

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The deuterium kinetic isotope effect (DKIE) can be exploited to increase the therapeutic value of pharmaceuticals which suffer from rapid oxidation or racemisation *in vivo*. By decreasing the rate of these attrition reactions using the DKIE, deuterated drugs can be administered in lower dosages and remain active in the body for longer durations compared to their undeuterated counterparts.¹ Thus, the interest in deuterated pharmaceutical agents has increased substantially in recent years, provoking the development of a range of chemical methods for their synthesis. Biocatalysis is a valuable option for installing deuterium atoms at targeted locations because enzymes are naturally selective and operate in aqueous conditions (enabling deuterium oxide ($^2\text{H}_2\text{O}$) to be used as the solvent and isotope source).² However, hydrogen isotope exchange (HIE) and reductive isotopic labelling methods, which are common in the field of chemocatalysis, are not currently well developed for enzymes. This poster presents new data on the ability of flavoenzymes to catalyse HIE for the synthesis of deuterated reduced nicotinamide cofactors ($[4\text{-}^2\text{H}]\text{-NAD(P)H}$). Moreover, the addition of flavoenzyme into C=N and C=O bond reductase/dehydrogenase-based cofactor recycling systems in $^2\text{H}_2\text{O}$ facilitates *in situ* (re)generation of $[4\text{-}^2\text{H}]\text{-NAD(P)H}$, providing a facile and selective route to chiral deuterated amines and alcohols for research, diagnostics and therapeutic applications. The commercial availability of the enzymes used in the $[4\text{-}^2\text{H}]\text{-NAD(P)H}$ recycling system enables this strategy to be implemented in any standard synthetic chemistry laboratory.

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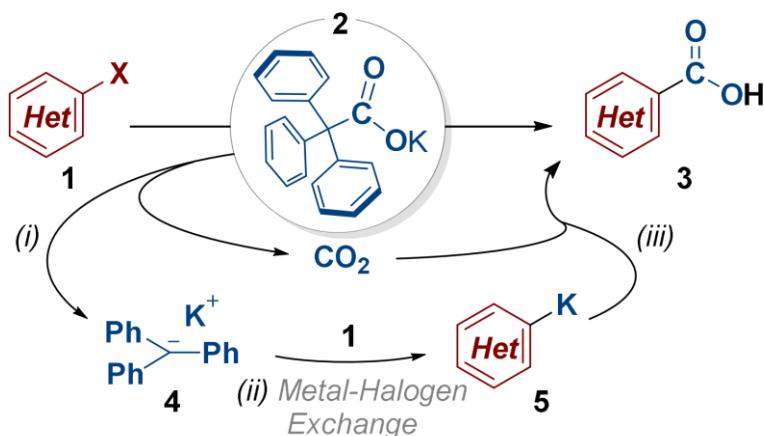
Aryl Halide Carboxylation via Decarboxylative Metal-Halogen Exchange

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Scheme 1: The carboxylation of aryl halides **1** by dual-function reagents **2**.

Carboxylic acids are widely used across multiple industries with numerous applications as synthetic building blocks or desired products. Current routes for aryl halide carboxylation often involve hazardous organometallic reagents or expensive transition metal catalysts.^{1,2} Excess gaseous CO₂ is also generally used which limits application in isotopic labelling.³ A controlled and efficient delivery of CO₂ would prove useful in the arena of carbon isotope chemistry.

We present a unique mode of metal-halogen exchange for the carboxylation of heteroaromatic halides with carboxylate **2** (Scheme 1).⁴ We describe carboxylate **2** as a dual-function reagent as it performs as a source of CO₂ and metalating agent.⁵ Mechanistic studies support our proposed decarboxylative metal-halogen exchange in which reagent **2** undergoes decarboxylation to give metalating agent **4** and CO₂ (step i) followed by metal-halogen exchange with aryl halide **1** (step ii). The metalated intermediate **5** then captures the *in-situ* generated CO₂ to give carboxylate product **3** (step iii). This provides a practical route for CO₂ delivery as it proceeds under mild conditions and does not require pressurised apparatus.

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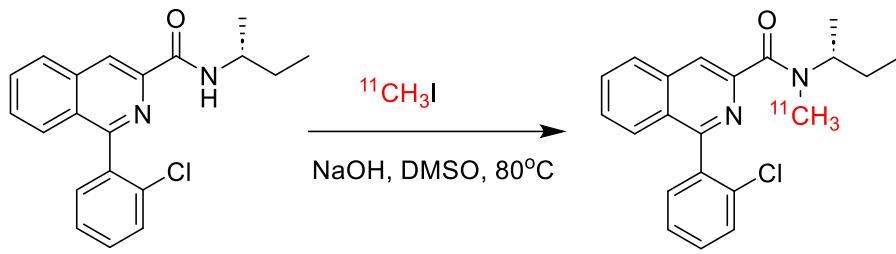
Poster Abstracts

Production of [¹¹C]PK11195 on Synthra MelPlus in a GMP Environment

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Radiosynthesis of [¹¹C]PK11195

[¹¹C]PK11195, is a PET is a first-generation translocator protein (TSPO) PET radiopharmaceutical revalidated at the Radiopharmaceutical Unit (RPU). Exempt from the issues associated with RS6971 polymorphism, it is used in clinical settings for diagnosis of neuroinflammation related disorders.

The Synthra Mel plus is used for the synthesis of [¹¹C]PK11195 via semi preparative HPLC purification. [¹¹C]CO₂ is produced from the GE PETtrace 800 cyclotron in 50-60 min. Irradiation produces ~45 GBq of starting [¹¹C]CO₂ radioactivity which on the module is converted via [¹¹C]CH₄ to [¹¹C]CH₃I. The radiosynthesis of [¹¹C]PK11195 proceeds via methylation of the PK11195 precursor (2 mg) in DMSO. After a 6-minute delivery to the reactor, the reaction is heated at 80°C for 3 minutes. The solution is cooled and diluted with water before being injected onto the semi-preparative column. The product peak is collected in 17mL of water and then trapped on an Oasis MCX cartridge. The cartridge is washed with water for injection (WFI) to wash off solvents and impurities into the waste bottle. [¹¹C]PK11195 is eluted from the cartridges with ~1 mL of Ethanol and 2 mL of PBS into a solution of 10 mL 0.9 % NaCl, then delivered to the dispensing system (Clio dispenser).

Currently in routine production at the RPU for one patient dose at a time. Typical synthesis time was 48 minutes, and average radiochemical yield was 10 %, 1.4 GBq (n = 5), with a molar activity average of 83.8 GBq/ μ mol (n= 5). This provides sufficient dose for imaging studies on site. A large percentage of [¹¹C]PK11195 (~40%) is currently stuck on the dispensing kit (due to lipophilicity of PK).

[¹¹C]PK11195 has been validated for clinical production in RPU. The manufacturing process is reasonably robust, semi-automated with minimal user interaction and provides enough radiotracer for 1 patient doses on-site.

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Switchable N–H vs C3–H Carboxylation of Indoles Using Dual-Function Reagents

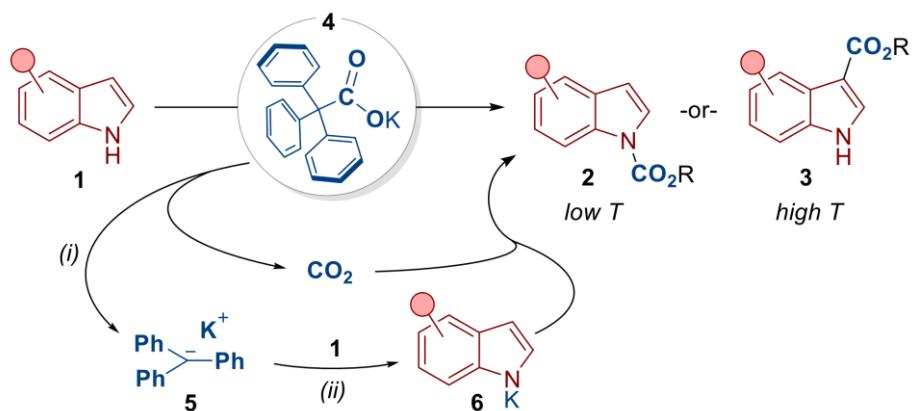
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Scheme 1. The selective carboxylation of indoles **1** by dual-function reagent **4**.

Indoles are widely known as attractive scaffolds, particularly in the pharmaceutical field. Both N–H and C3–H carboxylation of such compounds presents numerous applications, for example in drug/prodrug synthesis. Access to reactivity at either position on indoles generally requires excess reagents to tune reactivity or gaseous CO₂, limiting appeal of such methodologies to pharmaceutical use or ¹³C labelling.¹ Although reports on the carboxylation of indoles is known, a general method that allows the selectivity to be switched between N–H and C3–H carboxylation is not available.

Potassium triphenylacetate for the carboxylation of indoles is presented herein. Direct deprotonation and carboxylation *in situ* via dual-function reagent **4** showcases a unique methodology, that mitigates use of harsh conditions or pressurised CO₂.² Decarboxylation of reagent **4** gives CO₂ and triphenyl anion **5** (step i), which acts as a strong base to deprotonate indole **1** (step ii). At low temperatures, carboxylation and subsequent alkylation affords carbamate **2**, whereas high temperatures promote C3–H carboxylation, giving indole carboxylate **3**. Conditions are successfully optimised to access tuneable selectivity for the N–H and C3–H positions. This work is extended to include other N-containing substrates, such as anilines, azaindole and other amines, as well as relevant drug derivatives, providing clear medicinal relevance. Additionally, application towards ¹³C-labelled derivatives is showcased, allowed due to the use of a bench-stable, weighable carboxylating reagent.

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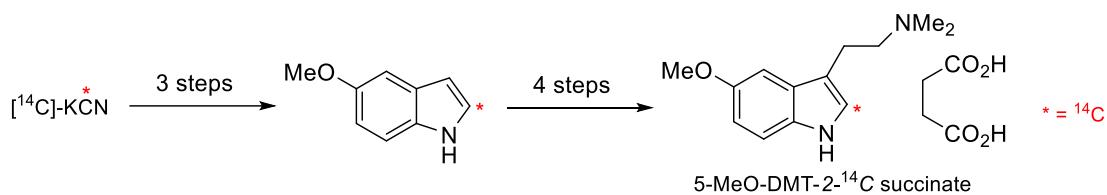
Synthesis of 5-Methoxy-N,N-Dimethyltryptamine-2-¹⁴C Succinate

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5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is a naturally occurring psychedelic drug. There is renewed interest in using 5-MeO-DMT to treat mental health conditions such as depression, anxiety and post-traumatic stress disorder (PTSD). This controlled drug requires a licence for manufacture and storage prior to undertaking any practical synthetic work. In this poster the synthesis of the novel isotopologue with a ¹⁴C-label at the indole 2-position, and isolation of the succinate salt with a specific activity of 173 µCi/mg will be described. The stability of this succinate salt was evaluated and data will be shown supporting its use for long-term in vivo ADME and behavioural studies in the path toward regulatory approval of 5-MeO-DMT for treating mental health disorders.

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Domestic Production of Radionuclides via Fusion

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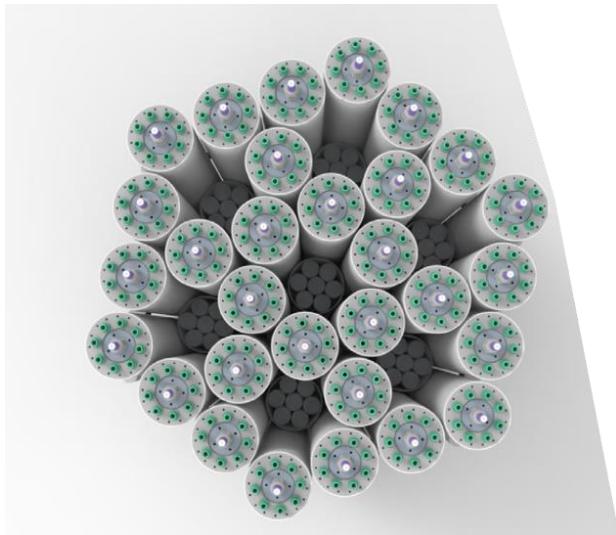


Figure 1. An array of 30 compact fusion devices arranged in a honeycomb configuration.

The United Kingdom currently lacks domestic capability for the manufacture of neutron-produced radionuclides, which are essential for a range of therapeutic and diagnostic applications.¹ This poster presents the design and development of a fusion neutron facility by Astral Systems, aimed at enabling local production of diverse range of radionuclides.² The proposed facility will utilise an array of 30 compact fusion devices arranged in a honeycomb configuration to maximise neutron flux, housed within a shielded bunker to safely contain high-energy neutron emissions. Performance data for Mark 1 and Mark 2 reactor iterations demonstrate significant improvements in neutron yield and flux, supporting the efficient irradiation of targets for radionuclide production. The facility is designed to produce a wide spectrum of radionuclides, including Sc-47, Cu-64, Cu-67, Tb-161, Pb-212, and Ac-225, among others, through various nuclear reactions such as (n,2n), (n,p), and (n,α). Cross-section analyses indicate favourable production rates for key radionuclides using high-energy neutrons. The establishment of this facility will address a critical gap in UK healthcare infrastructure, enabling reliable, domestic supply of medical radionuclides and advancing the field of nuclear medicine.

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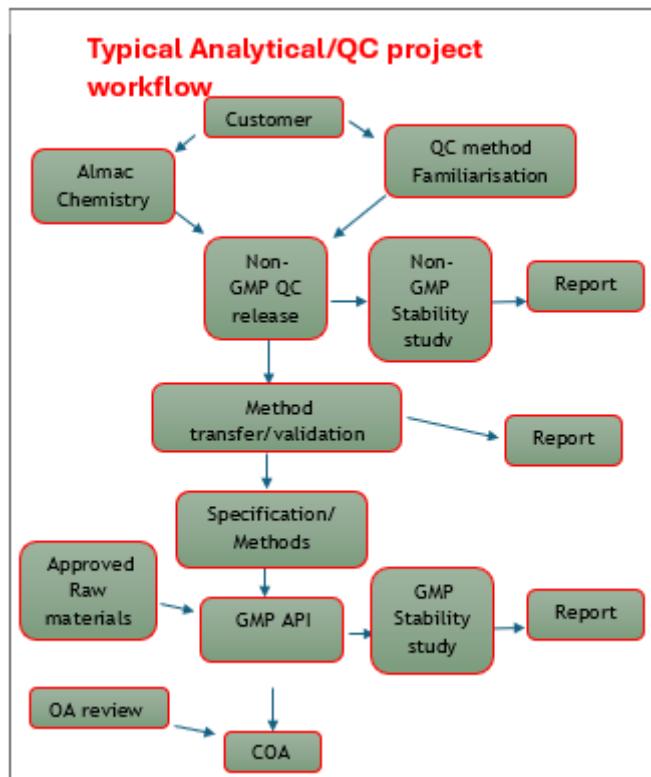
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Quality Control Analysis and Release of ^{14}C APIs

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Radiolabelled active pharmaceutical ingredients (APIs) are essential for A(D)ME (absorption, (distribution), metabolism, and excretion) studies, with ^{14}C often being preferred due to the long half-life. Within Almac a range of ^{14}C APIs are produced for customers including controlled drugs and peptides alongside traditional Non-GMP and GMP compounds. During drug substance (DS) manufacture and release an array of activities, teams and personnel are required to successfully release a ^{14}C GMP API to the customer. This poster outlines the typical workflow of a radiolabelled project within Almac; it shows the roles of various departments and teams in manufacture, release and dispatch of ^{14}C APIs. From a quality perspective the requirements of accurate quality control testing are discussed, along with steps to ensure analytical methods used are fit for purpose and meet the challenges faced during testing and release. A case study is included - demonstrating the detection limits, equipment sensitivity and testing performed on a ^{14}C API manufactured within Almac Sciences.

Photoredox Catalysed Reductive Cleavage of Dibenzothiophene Dioxides Enabled by a 3D Printed Photoreactor

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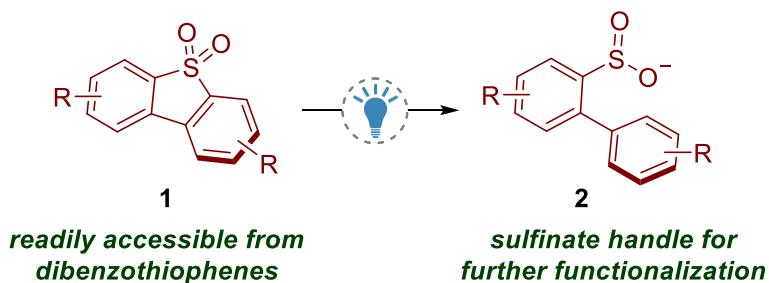
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Scheme 1: Photoredox catalysed reductive cleavage of dibenzothiophene dioxides **1**.

Dibenzothiophene dioxides **1** are a class of relatively unactivated sulfones that can be easily accessed through routine oxidation of dibenzothiophenes. Recent investigations into the deconstruction of dibenzothiophene dioxides has resulted in a variety of useful C–S bond cleaving transformations that have found applications in neighbouring fields.¹ The processing of dibenzothiophenes also holds benefits in the desulfurization of petroleum products as they are impurities in crude oil that are stubbornly resistant to removal. If left untreated, dibenzothiophenes lead to acidic impurities that damage refineries and contribute to air pollution.² The cleavage of C–S bonds in dibenzothiophene dioxides **1** under reductive photoredox catalysed conditions is reported.³ The reaction affords sulfinates **2**, which can be used in a variety of subsequent transformations for diversification. In addition to fluorination, we also present the utility of the sulfinate products by accessing sulfones and performing a palladium catalysed desulfinylative cross-coupling to give ortho-terphenyl.⁴ The process tolerates the presence of oil (dodecane), highlighting a possible application in the desulfurization of petroleum products.² Reactivity of some substrates is highly dependent on reaction temperature, hence reaction screening was performed using a versatile and inexpensive 3D printed photoreactor that allows for precise control of reaction temperature.

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From Copper(I)-Catalyzed Reduction of Esters With H₂ to Molecular Recognition

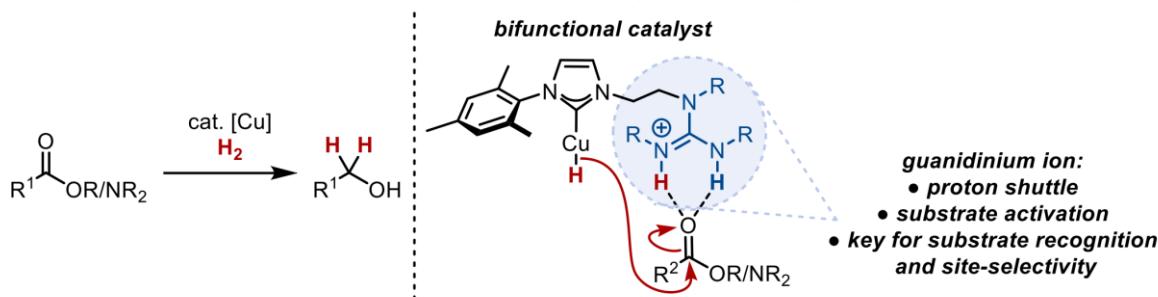
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catalytic reduction of carboxyl compounds with a copper(I)/guanidinium catalyst



The reduction of carboxyl compounds such as esters or amides is an important transformation in organic chemistry that generally requires the use of "hard" stoichiometric metal hydrides.¹ These stoichiometric reducing agents are associated with the generation of metal waste and tedious work-up procedures. Therefore, catalytic hydrogenation of carboxylic acid derivatives, which circumvent the commonly employed stoichiometric reducing agents, are highly desirable.²

Recently, we have disclosed a new approach to catalytic ester hydrogenation facilitated by a bifunctional copper(I)/N-heterocyclic carbene complex.³ In this strategy we employ an intrinsically not sufficiently nucleophilic copper(I) hydride from H_2 while the actual ester reduction is enabled through hydrogen bonding by a second organocatalytic⁴ unit within the same catalyst. Herein, we present the exploitation of bifunctional catalysts moving from simple control of chemoselectivity towards molecular recognition.⁵ In our approach, the hydrogen bonding unit is now employed to select one carboxylic acid derivative over another, structurally closely related one. In this manner, not only a catalytic reduction of amides becomes feasible, but also site-selectivity⁶ is achieved.

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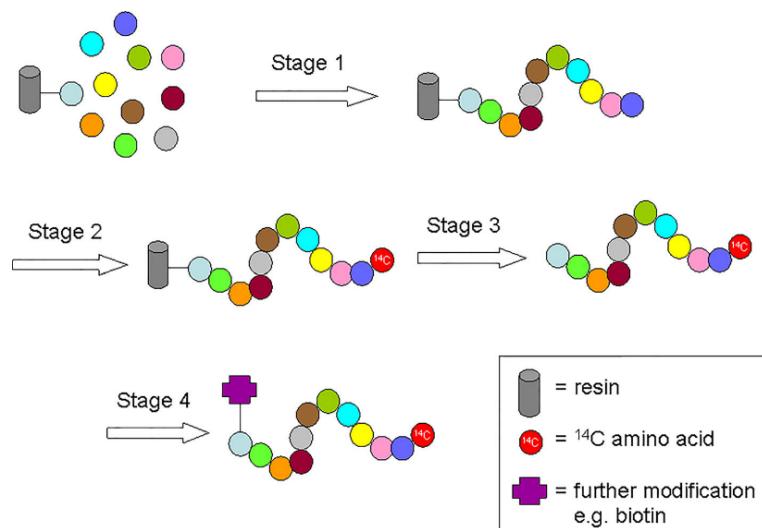
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Carbon-14 Labelled Peptides – Solid Phase Peptide Synthesis, Biotinylation and PEGylation

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The radiolabelling group at Almac have synthesised a number of peptide APIs containing carbon-14 amino acid residues using the solid phase peptide synthesis (SPPS) approach. Some of these carbon-14 labelled peptides were modified by the addition of polyethylene glycols (PEGs) to produce a new chemical entity with a different pharmacological profile. In other cases, carbon-14 labelled peptides can undergo biotinylation to provide targeted drug substances. This poster gives a general overview of Solid Phase Peptide Synthesis (SPPS), Biotinylation & PEGylation towards the synthesis of carbon-14 labelled peptides.

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GMP Radiosynthesis of [¹⁴C]Paxalisib to Support a Human AME Study

Gilles Raphy,^a David Carver,^a Jeremy Simpson,^b John Friend^b and Iain Shaw.^c

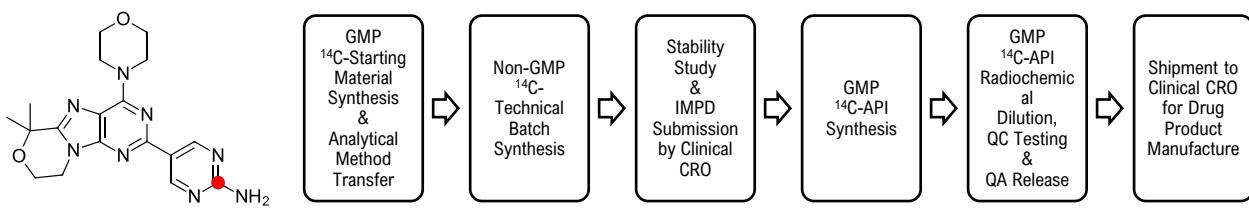
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Paxalisib, a potent, oral, selective small molecule inhibitor of PI3K and mTOR kinase, currently in Phase III clinical trials, is being developed as an anti-cancer therapeutic agent specifically aimed at treating glioblastoma. As part of the overall development programme the mass balance, pharmacokinetics, metabolism and excretion of Paxalisib were studied in an open-label, Phase I study in 6 healthy male subjects. This poster will describe radiosynthesis of [¹⁴C]Paxalisib as a GMP radiolabelled API for human use.



A typical process for radiosynthesis of C-14 Drug Substance under GMP

The designated GMP starting material, 5-Bromo-[2-¹⁴C]pyrimidin-2 amine, was synthesised from [¹⁴C]guanidine hydrochloride. After purification & analysis, a Certificate of Analysis and TSE/BSE statement were issued. An aliquot was held in storage at -20 °C for use in the GMP 14C-API preparation. The remainder was used to prepare, via successive Suzuki coupling reactions, a non-GMP batch of [¹⁴C]Paxalisib at medium specific activity (MSA) for use in stability studies. The MSA batch was diluted further to provide a low specific activity (LSA) technical batch for a trial Drug Product (IMP) manufacture at Quotient Sciences. A validated HPLC API release method (Radiochemical Purity & impurities) was formally transferred from Kazia Therapeutics and adapted for GMP 14C-API release and radio-stability testing.

Radiosynthesis of GMP 14C-API was repeated in a dedicated GMP radiosynthesis laboratory starting from retained 5-Bromo-[2-¹⁴C]pyrimidin-2 amine to provide 6.6mCi of GMP [¹⁴C]Paxalisib. QC release testing and QA review of the batch record confirmed the required specifications had been met.

This radiosynthesis process provided the necessary supply of GMP [¹⁴C]Drug Substance to support regulatory submission and Drug Product manufacture for a human AME study with Paxalisib in a time and material efficient manner.

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Contact: Andrew Ditchman
Tel: 01371 831611
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www.qmx.com

List of Delegates

The following attendees have agreed for their details to be included in the conference booklet.
 Delegates not wishing to share their information have not been included.

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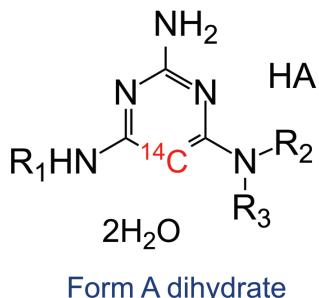
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- MHRA regulatory approved for ¹⁴C GMP manufacture of drug substance



Case Studies

Case Study 1 – ^{14}C GMP small molecule manufacture

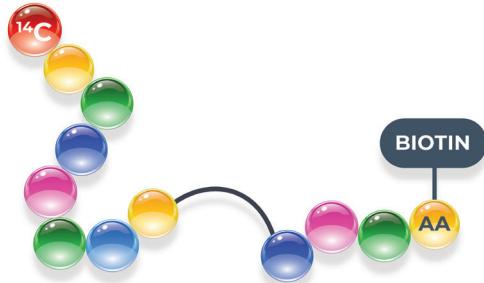


Our client required 3 mCi [^{14}C]-Drug substance as Form A (dihydrate)

The Almac Solution involved:

- GMP manufacture of the API, release analysis and completion of a stability study
- Desired polymorph was isolated via controlled crystallisation, drying, milling and controlled hydration
- Physical form of drug substance was confirmed by X-ray powder diffraction (XRPD)

Case Study 2 – ^{14}C synthesis of biotinylated 84mer peptide



Our client required 2 mg of ^{14}C labelled peptide

The Almac Solution involved:

- Integration of peptide and radiolabelling teams
- Redesign of the coupling step to minimise loss of expensive labelled amino acid

Case Study 3 – ^{14}C labelled PDC manufacture

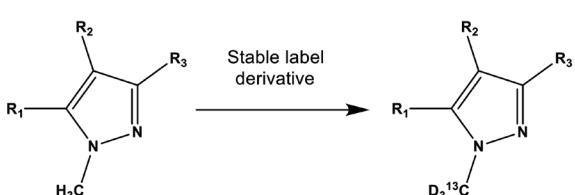


Our client required ^{14}C labelling of the linker technology followed by formation of the PDC

The Almac Solution involved:

- Integration of biology, purification and radiolabelling teams
- Prep-HPLC, HIC chromatography and ultrafiltration purification expertise

Case Study 4 – $^{13}\text{CD}_3$ labelling



Our client required 250 mg of $^{13}\text{CD}_3$ labelled material

The Almac Solution involved:

- Non-GMP synthesis of stable labelled product
- Prep HPLC purification expertise
- Isotopic purity determination by Mass Spectrometry to determine levels of isotopomers / unlabelled material

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years of excellence in
isotope labelling

98%

on average delivery
success rate

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molecules
synthesised

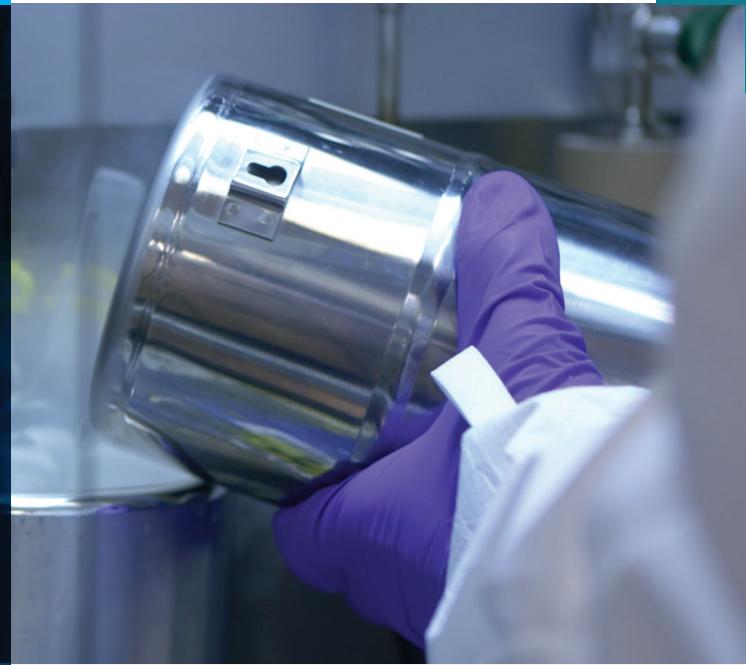
- **Supporting non-clinical and clinical studies.**
- **Available as a stand-alone service or as part of a holistic ADME programme delivered with Quotient Sciences.**

A proven track record of ensuring the highest precision and quality in radiolabelled compounds

Accelerate your non-clinical and clinical ADME studies with high-purity, fit-for-purpose ¹⁴C and stable isotope-labelled compounds, expertly designed to support metabolism studies and quantification in biological matrices. With over 40 years of on-site radiochemistry experience, Arcinova, A Quotient Sciences Company offer trusted consultancy and end-to-end delivery, backed by a 98% on-time success rate.

Our specialist chemists apply deep expertise in radiochemical, analytical, and synthetic chemistry to guide optimal label placement across a broad range of molecular entities.

Our approach is built for faster timelines, fewer handoffs, and reliable results that keep you on-track towards your development goals.





Expert-led labelling strategy

Optimal ¹⁴C label positioning in a metabolically stable part of the molecule is crucial to ensure key metabolites are identifiable to provide adequate ADME data. We offer upfront consultancy on labelling strategy, then design a synthetic strategy that delivers high isotopic purity and meets the requirements of your study.

Additionally, we support projects by synthesising non-clinical and clinical batches separately or by producing a preclinical intermediate for both. This integrated approach can eliminate re-synthesis, saving time and reducing costs for human ADME studies.

We are experts in the safe handling of highly potent, hazardous, and cytotoxic compounds and are licenced for Scheduled I-IV controlled substances, including cannabinoids, ketamine, and tryptamine.

Our experience also includes:

- Synthesis of stable-labelled compounds incorporating ²H, ¹³C, ¹⁵N or ¹⁸O, ensuring optimal label placement and high isotopic purity
- Expertise in polymorphic control, particle size reduction, lyophilisation, and polymer dispersion for poorly soluble radiolabelled drugs
- Synthesis of metabolites and reference materials tailored for bioanalytical and metabolism research

Synthesis-to-Clinic®: Integrated ¹⁴C-labelled drug substances and drug products with full ADME programme delivery

Our ¹⁴C-labelling capabilities are available as a standalone service through Arcinova or as part of an integrated human ADME programme delivered by the **Quotient Sciences**

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- Dedicated team including a technical chemist lead, analytical lead, and project manager to ensure consistent delivery
- Fully integrated support through our all-in-one facility – spanning isotopic labelling, drug substance development, formulation, IMP manufacture, and dossier preparation
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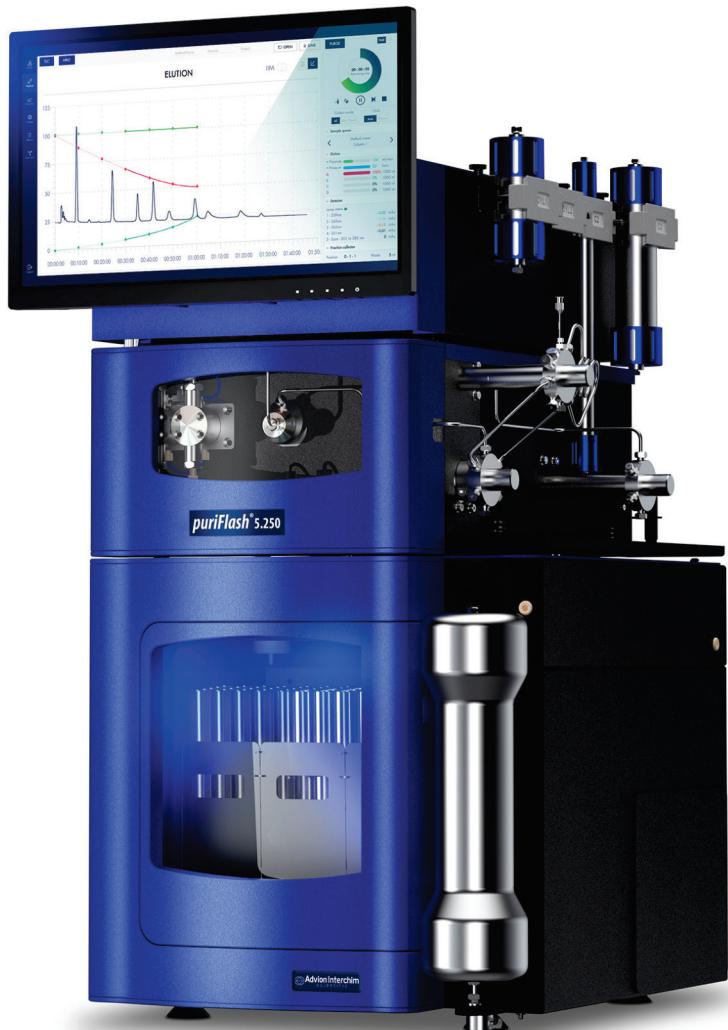
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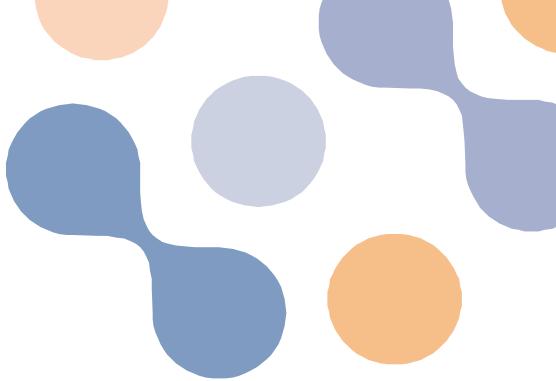
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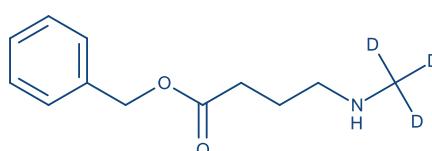
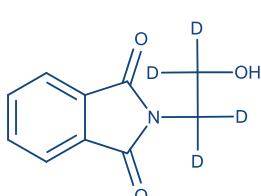
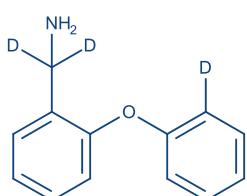
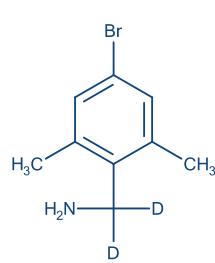
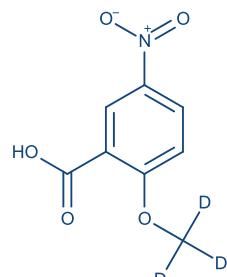
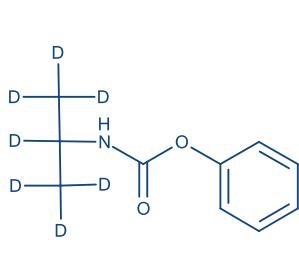
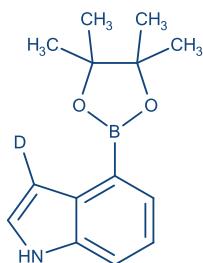


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- AMS (Accelerator Mass Spectrometry)
- High resolution mass spectrometry (HRMS) for MetID
- Bioanalysis and biomarkers (LC-MS/MS, immunoassay)

Non-clinical ADME & QWBA with Radiolabelled Compounds

- Pharmacokinetics, biliary excretion & excretion balance
- Tissue distribution (QWBA, mARG) and dosimetry
- Metabolite profiling & MetID
- Bioanalytical support (LC-MS/MS)

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- Physical chemistry
- Biodegradation
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