Journal of Labelled Compounds and Radiopharmaceuticals

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Abstracts of the 18th International Isotope Society (UK Group) Symposium: Synthesis & Applications of Labelled Compounds 2009

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MEETING SUMMARY

The 18th annual symposium of the International Isotope Society's United Kingdom Group took place at the Wellcome Genome Campus, Hinxton, Cambridge, UK on 12th November 2009. The meeting was attended by around 85 delegates from academia, the life sciences, chemical, radiochemical and scientific instrument suppliers.

Delegates were welcomed by Dr Ken Lawrie (GlaxoSmithKline, UK, chair of the IIS (UK group). The subsequent scientific programme consisted of oral and poster presentations on isotopic chemistry and applications of labelled compounds, or of chemistry with potential implications for isotopic synthesis. Both short-lived and long-lived isotopes were represented, as were stable isotopes. The symposium programme was divided into a morning and an afternoon session chaired by Prof Chris Willis (University of Bristol, UK) and Mr Mike Chappelle (Quotient Biosciences) respectively. In addition, a short presentation on the forthcoming 11th Triennial International IIS Symposium due to take place in Heidelberg in 2012 was given by Dr Jens Atzrodt (sanofi-aventis) on behalf of the international organising committee. The UK meeting concluded with remarks from Dr Ken Lawrie (GlaxoSmithKline, Stevenage, UK).

This year's UK symposium had a good attendance from students. Moreover, an excellent level of sponsorship was achieved, and the symposium proved self-financing. The Hinxton meeting venue again proved very popular. The next UK symposium is provisionally planned at the same venue for the 14th October 2010.

MEETING PROGRAMME

SYNTHESIS & APPLICATIONS OF LABELLED COMPOUNDS 2009

18th International Isotope Society (UK Group) Symposium, 12th November 2009, Francis Crick Memorial Lecture Theatre, Wellcome Trust Genome Campus, Hinxton, UK.

9:00 am Registration/Morning Coffee/Poster Viewing/ Manufacturers Exhibition
9:45 am Welcome: Ken Lawrie [GlaxoSmithKline, Stevenage, UK]
Morning Session: Chair:- Chris Willis [University of Bristol, UK]
9:50 am David Tanner [Tech. Univ. of Denmark, Denmark]
''*On the development of transannular Mannich (TAM) reactions for the synthesis of polycyclic alkaloids*''
10:20 am Ken Lawrie [GSK, Stevenage, UK]
''*Syntheses of [$^{13}C_6$] and [^{14}C]SB-480848 (Darapladib), an inhibitor of lipoprotein-associated phospholipase A_2*''
10:40 am Laura Marshall [University of St Andrews, UK]
''*Studies towards the synthesis of [^{13}C]anthocyanins*''
11:00 pm Posters Viewing / Manufacturers Exhibition / Coffee & Tea
11:20 am Mike Greaney [University of Edinburgh, UK]
''*New organopalladium chemistry for heterocycle synthesis*''
11:50 am Brian Warrington [University of Cambridge, UK]
''*Miniaturised flow systems and their application in PET*''
12:20 pm Posters Viewing/Manufacturers Exhibition/Buffet Lunch
Afternoon Session: Chair:- Mike Chappelle [Quotient Biosciences, UK]
1:35 pm Jens Atzrodt [sanofi-aventis & IIS]
''*The 11th international IIS symposium: Heidelberg 2012*''
1:40 pm Robin Bedford [University of Bristol, UK]
''*C-H activation and beyond*''
2:10 pm John Harding [AstraZeneca, UK]
''*The evolution of synthetic isotope chemistry support for DMPK*''
2:30 pm Denis Brasseur [sanofi-aventis, France]
''*Synthesis of labelled SR121463 (satavaptan), a vasopressin type 2 antagonist*''
2:50 pm Poster Viewing/Manufacturers Exhibits/Coffee & Tea
3:10 pm Colin Young [Charles River, UK]
''*Radioisotopes in drug development*''

3:40 pm Sophia Pascu [University of Bath, UK]
"Fluorescent copper(II) bis(thiosemicarbazonates): From synthesis to radiolabelling, in vitro cytotoxicity and confocal fluorescence microscopy"
4:10 pm Sean Kitson [Almac Sciences, UK]

"^{14}C-Radiosynthesis of 4-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyethyl)-6-(trifluoromethyl)-[4-^{14}C]quinolin-2(1H)-one, (XEN-D0401), a novel BK channel activator"
4:30 pm Concluding Remarks. Ken Lawrie [GlaxoSmithKline, Stevenage, UK]

ORAL PRESENTATION ABSTRACTS

ON THE DEVELOPMENT OF TRANSANNULAR MANNICH (TAM) REACTIONS FOR THE SYNTHESIS OF POLYCYCLIC ALKALOIDS

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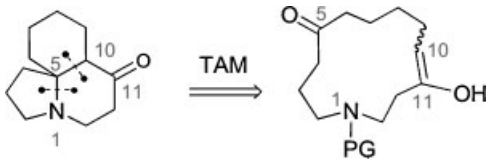
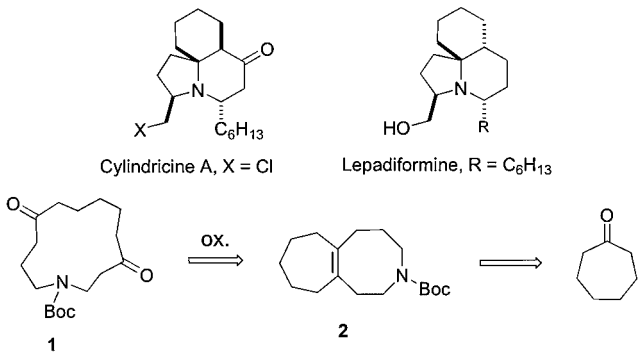
Transannular reactions[1] provide both challenges and opportunities for the rapid generation of molecular complexity, and can offer attractive and efficient solutions to problems encountered during the total synthesis of complex (polycyclic) molecules. We have recently[2] become interested in the idea of using transannular Mannich (TAM) reactions[3] of macrocyclic amino-diketones for the construction of azapolycycles characteristic of naturally occurring and biologically significant alkaloids, according to the general retrosynthetic scheme shown below.



The initial synthetic targets are the cylindricine and lepadiformine alkaloids,[4] and an efficient TAM process has now been developed for the synthesis of such tricyclic frameworks in a single step from 13-membered macrocycles such as **1**. The macrocycle is itself readily available via oxidative cleavage of the bicyclic alkene **2** which in turn can be accessed in a few synthetic steps from cycloheptanone.



References

[1] See, e.g., S. Phoenix, M. S. Reddy, P. Deslongchamps, *J Am Chem Soc*, **2008**; 130, 13989–13995.
[2] P. Vital, M. Hosseini, M. S. Shanmugham, C. H. Gotfredsen, P. Harris, D. Tanner, *Chem Commun*, **2009**; 1888–1890.
[3] For related work, see: D. A. Evans, J. R. Scheerer, *Angew Chem, Int Ed*, **2005**; 44, 6038–6042.
[4] Review: S. M. Weinreb, *Chem. Rev*., **2006**; 106, 2531–2549.

SYNTHESES OF [$^{13}C_6$] AND [^{14}C]SB-480848 (DARAPLADIB), AN INHIBITOR OF LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A_2.

GEOFF T. BADMAN, SIMON J. HARWOOD, KENNETH W. M. LAWRIE, JOHN J. NEWMAN, NICK J. SHIPLEY, DARREN SMITH, GLYNN D. WILLIAMS

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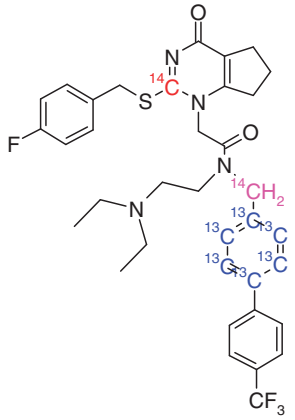
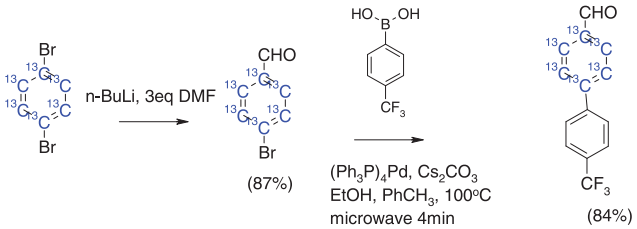
SB-480848, darapladib, is a highly potent selective inhibitor of Lp-PLA$_2$ (lipoprotein-associated phospholipase A$_2$) under development by GSK and is currently in late phase clinical trials. Syntheses of [$^{13}C_6$] and [^{14}C]SB-480848 are described.



High yielding, selective formylations of 1,4-dibromobenzene are disclosed.



The ''extreme'' radiolytic instability of high specific activity [^{14}C]SB-480848 and strategies to overcome this, particularly with regard to the preparation of clinical batches, are discussed.

STUDIES TOWARDS THE SYNTHESIS OF ^{13}C-LABELLED ANTHOCYANINS

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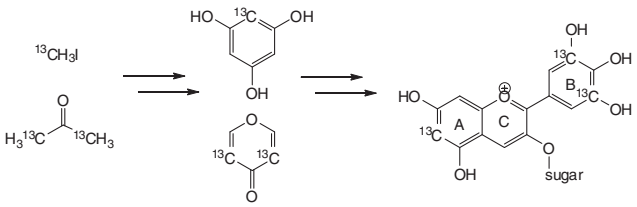
Polyphenols are an important group of compounds in natural product chemistry, producing a requirement for new synthetic routes to phenols. For the isotope chemist, these routes must be applicable to the incorporation of isotopically-labelled atoms, where the use of isotopically-labelled small molecules can allow the regioselective incorporation of labelled atoms into the structure.[1]

One class of polyphenols is the anthocyanins, with over 500 different anthocyanins being isolated from plants. The anthocyanin group consists of the sugar-free anthocyanidins and the water-soluble anthocyanin glycosides. Both are powerful antioxidants, and interest in their properties has intensified recently due to possible health benefits in humans.

Studies into the biological effects of anthocyanins will aid in the understanding of their properties and benefits. This requires accurate quantification of the compounds in plasma samples, with LC-MS and GC-MS being the common analytical techniques used. The use of stable isotope-labelled standards for calibration of the systems is required, as the standard will have similar chemical and physical properties to the analyte.[1] New synthetic routes to isotopically labelled anthocyanins are therefore required.

An efficient route towards the synthesis of delphinidin-3-glucoside is presented. This route builds on our strategy developed previously,[1,2] with regioselective incorporation of ^{13}C-labelled atoms in the B-ring using [1,3-$^{13}C_2$]acetone. The final ^{13}C-labelled atom is introduced into the A-ring using [^{13}C]methyl iodide.



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[1] L. J. Marshall, K. M. Cable, N. P. Botting, *Org Biomol Chem*, **2009**; 7, 785–788.
[2] L. J. Marshall, K. M. Cable, N. P. Botting, *Tetrahedron*, **2009**; 65, 8165–8170.

NEW ORGANOPALLADIUM CHEMISTRY FOR COMPLEX MOLECULE SYNTHESIS

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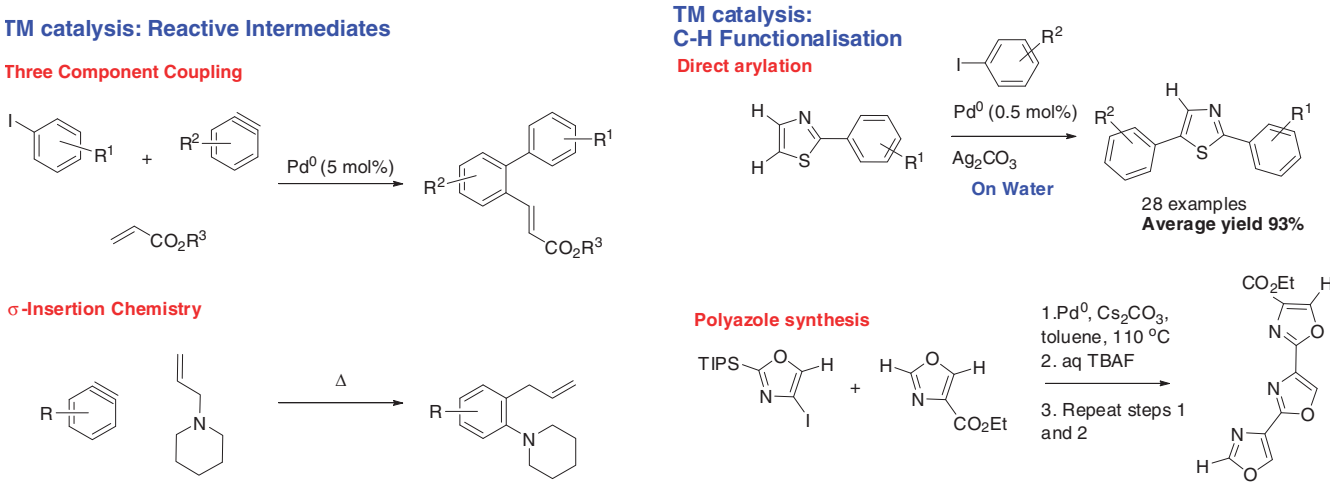
Transition metal (TM) catalysts can control a vast range of chemical reactivity. At one extreme, they can harness and modulate the reactivity of the most energetic reactive intermediates, such as arynes and carbenes. Contrastingly, they can be used to activate inert, unreactive functional groups such as C–H bonds. Both of these areas offer tremendous potential for the discovery of new reaction pathways that use catalytic metals for novel bond construction.

The successful manipulation of arynes under TM catalysis will depend on mild methods for generating the strained triple bond that are compatible with typical cross-coupling conditions. The fluoride-induced decomposition of 2-(trimethylsilyl)phenyl triflates is one such method, and has enabled the development of novel aryne multicomponent coupling processes in our laboratory (Scheme 1). Our work focuses on the discovery of new chemistries for carbon-carbon, and carbon-heteroatom formation at the aryne nucleus, a delicate business given the propensity for non-productive side reactions of this highly reactive intermediate. Using optimised TM catalyst systems, we can stabilise the aryne structure such that it undergoes selective coupling with electrophilic and nucleophilic components to produce highly functionalised aromatic compounds in a single step.



Scheme 1. TM-catalysed reactions of reactive intermediates and C-H bonds.

The activation of C-H bonds as sites for C-C bond formation using TM catalysis is an exploding area of research in the literature. Heteroarenes constitute one of the most important classes of substrates for C-H functionalisation, as they undergo efficient metallation at electron rich carbon atoms, providing a handle for subsequent C-C bond formation. When coupled with aryl partners, the resultant *direct arylation* provides an extremely fast and versatile synthesis of valuable aromatic heterocycles. We are designing reaction systems that capitalise on this highly efficient bond construction, and applying them to the rapid, modular synthesis of poly-heteroarenes under mild reaction conditions.

References

[1] A. A. Cant, G. V. H. Bertrand, J. L. Henderson, L. Roberts, M. F. Greaney, *Angew Chem Int Ed*, **2009**; 48, 5199–5202.
[2] J. L. Henderson, A. S. Edwards, M. F. Greaney, *Org Lett*, **2007**; 9, 5589–5592.
[3] G. L. Turner, J. A. Morris, M. F. Greaney, *Angew Chem Int Ed*, **2007**; 46, 7996–8000.

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MINIATURISED FLOW SYSTEMS AND THEIR APPLICATION IN PET

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An iterative use of emerging data to drive compound design is the most efficient strategy for lead discovery in that it minimises the number of molecules that need to be made to find the best molecule to be realised from an infinite number of virtual options. In addition, because the process is driven by emerging data, the chemical changes indicated are likely to be those that lead to a novel compound, rather than screening out a foreseen molecule in a pre-realised collection of limited diversity.

However, when performed at the macro scale, data-driven bespoke synthesis of molecules is extremely expensive making the theoretically inferior screening method an attractive option. The presentation will describe a no-loss, microfluidics-based iterative strategy for lead identification and optimisation. In addition, tools that allow bench top integration of the chemistry, biology and informatics and have a capability to overcome at low cost the logistical and diversity limitations of the current paradigms will be described.[1]

In this microfluidic systems the reduced size of the reaction zone reduces mixing times to a second or so hence reducing the reaction time of mass transfer limited reactions in an analogous fashion. In addition, the low Reynolds number environment of a micro flow system provides an opportunity for real time reaction optimisation. Clearly these reduced reaction times provided an opportunity for the synthesis of small amounts of PET ligand on a ''one-shot'' basis and alleviated the some of the difficulties of dealing with short-half life ^{11}C-labelled materials and opening up new uses for PET technology.

Reference

[1] B. H. Warrington, S. Y. F. Wong-Hawkes, J. C. Matteo, J. D. White, *Ernst Schering Found. Symp Proc*, **2006**; 39–55.

AROMATIC C-H ACTIVATION AND BEYOND

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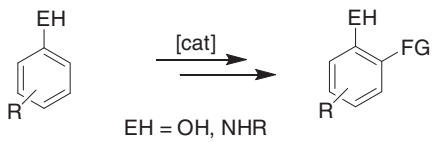
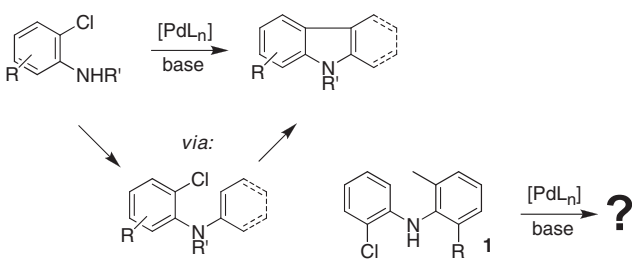
The presentation will focus on the development of organic reactions that proceed *via* catalytic aromatic C-H activation. In particular it will focus on the *ortho*-functionalisation of appropriately modified phenols and anilines (Scheme 1). Here we are particularly interested in both the synthesis of biologically relevant molecules and on simplifying catalytic methodology. Just how much, and what, can we remove from the reaction?

The second area of interest is in the construction of heterocycles from 2-haloanilines *via* sequential amination/C-H activation (Scheme 2). An interesting question arises with substrates of the type **1** – what reactivity will they undergo?



Scheme 1.



Scheme 2.

THE EVOLUTION OF SYNTHETIC ISOTOPE CHEMISTRY SUPPORT FOR DMPK

RYAN A. BRAGG, NICK BUSHBY, JOHN R. HARDING*, ANGELA JORDAN, DAVID A. KILLICK

Isotope Chemistry, Clinical Pharmacology and DMPK, Astra Zeneca UK Ltd, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK, e-mail: john.harding@astrazeneca.com

A synthetic isotope chemistry team has supported Drug Metabolism and Pharmacokinetics (DMPK) studies at Alderley Park for over 40 years. This presentation contrasts the original isotopic labelling requirements to those requested now and highlights the similarities and important changes over this period. Particular mention will be made of the:

1. increased sophistication of synthetic methods and the move towards 'greener'chemistry
2. introduction of improved vacuum manifolds that allow safer handling of carbon-14 and tritium in the laboratory
3. improvements in laboratory design and experimental risk assessment
4. advances in chromatography and NMR and MS technologies
5. introduction of electronic laboratory notebooks

Recent synthetic methodology from our laboratory will be used to illustrate new ways of working and how the use of isotopes can still provide new insights into reaction mechanisms.

Reference

[1] J. R. Harding, *J Label Compd Radiopharm*, **2007**; 50, 927–932.

SYNTHESIS OF LABELLED SR121463 (SATAVAPTAN), A VASOPRESSIN TYPE 2 ANTAGONIST

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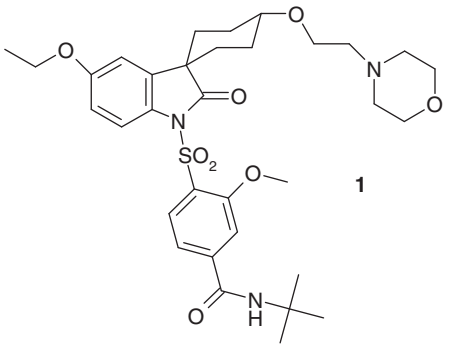
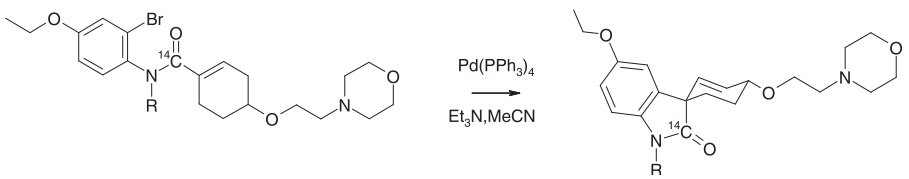
Patients under treatment with diuretic drugs lose mineral salts at the same time as water. Sanofi-aventis has been developing SR121463 **1**: a compound in a new class of Vasopressin type 2 antagonists which has the advantage of being an aquaretic drug which induces free water excretion.



SR121463

The presentation describes our investigations towards the labelling of this lead compound with carbon-14, tritium and stable isotopes. One synthesis uses a key Heck reaction to form the spiro cyclohexane ring.[1]



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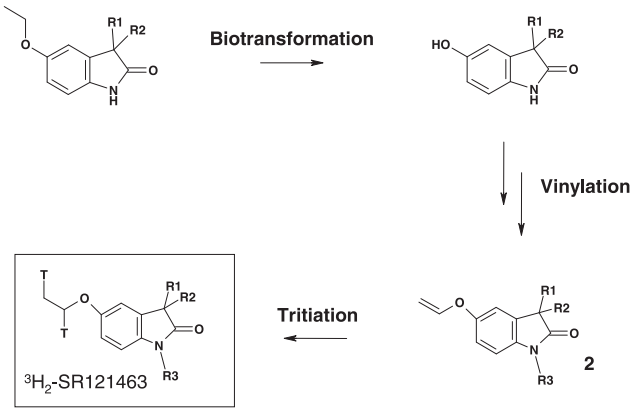
We have also developed a novel biocatalytic *O*-deethylation/vinylation sequence to give the vinyl enol ether **2**, the key precursor of tritiated SR121463.



Reference

[1] L. E. Overman, *J Org Chem*, **1992**; 57, 4571–4572.

RADIOISOTOPES IN DRUG DEVELOPMENT.

COLIN G. YOUNG

Charles River, Edinburgh, UK.

Ever since the early pioneers began to experiment with radioactive sources, the medical profession was quick to capitalise on the potential applications for the newly discovered properties of radioisotopes. Although some of the early products such as radon water and uranium blankets now seem somewhat misguided, radioisotopes are commonplace in the modern healthcare industry, being used in a wide number of applications from end-product sterilisation, diagnostics and treatment of disease.

Radioisotopes also play a valuable role in the development of new medicines, being used as tracers to aid quantification of drug and metabolite concentrations in biological matrices. In the field of drug metabolism and pharmacokinetics, isotopes such as carbon-14 and tritium are routinely used in studies designed to address the regulatory requirement for a full understanding of the fate of a drug molecule following administration of a therapeutic agent to a patient. Some of the key applications of radioisotopes in the investigation of the absorption, distribution, metabolism and excretion of a potential drug candidate will be discussed.

FLUORESCENT COPPER(II) BIS(THIOSEMICARBAZONATES): FROM SYNTHESIS TO RADIOLABELLING, *IN VITRO* CYTOTOXICITY AND CONFOCAL FLUORESCENCE MICROSCOPY

SOFIA I. PASCU[a,b]*, PHILIP A. WAGHORN[b], RORY L. ARROWSMITH[a], SIMON R. BAYLY[b], JONATHAN R. DILWORTH[b], MARTIN CHRISTLIEB[b], REX M. TYRRELL[c], JULIA ZHONG[c], RADOSLAW M. KOWALCZYK[d], DAVID COLLISON[d], GRANT C. CHURCHILL[e], FRANKLIN I. AIGBIRHIO[f]

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[b]Siemens Oxford Molecular Imaging Laboratory, University of Oxford, OX1 3QR Oxford (UK)
[c]Department of Pharmacy & Pharmacology, University of Bath, BA2 7AY Bath (UK)
[d]EPSRC EPR Centre, Department of Inorganic Chemistry, The University of Manchester, Manchester (UK)
[e]Department of Pharmacology, University of Oxford, OX1 3TA (UK)
[f]Wolfson Brain Imaging Centre, University of Cambridge, Cambridge (UK).

Metal bis(thiosemicarbazonato) complexes have been a focus of interest over recent years owing to their potent biological activities, with attention more recently devoted to the use of ^{64}Cu(II) bis(thiosemicarbazonates) such as [Cu(ATSM)] (Figure 1) for the selective imaging of hypoxia by Positron Emission Tomography (PET).[1–5] Recent clinical trials have shown that the aliphatic bis(thiosemicarbazonato) copper complex [^{64}Cu(ATSM)] can be used to image head and neck tumours.[6] Although it has been demonstrated that this compound accumulates in hypoxic tissue, it suffers from high liver uptake, potentially related to kinetic

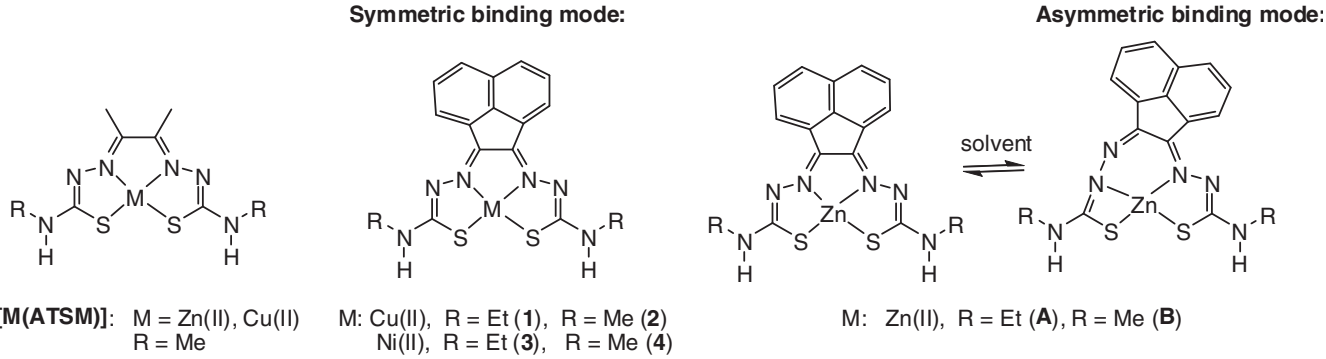

Figure 1.

instability in solution,[7] it is responsive only at very low oxygen concentrations and shows a poor hypoxic response to certain cancer cell types (e.g. prostate cancer cells).[8–10]

Copper bis(4-ethyl-3-thiosemicarbazonato) acenaphthenequinone (**1**) and copper bis(4-methyl-3-thiosemicarbazonato) acenaphthenequinone (**2**) were synthesized and characterized in solution and in the solid state and radiolabelled with $^{64}Cu(OAc)_2.2H_2O$. Serum protein binding radioassays showed good stability in solution and about 25% binding to protein over 1h, comparable to the hypoxia selective tracer [^{64}Cu(ATSM)]. Cyclic voltammetry showed fast and reversible reduction at redox potentials similar to the values known for hypoxia selective copper compounds. However, despite this, complex 1 did not show hypoxic selective uptake in HeLa cells over 1 h standard assays. Possible reasons for this were studied by using the intrinsic fluorescence of the Cu(II) complexes to determine the cellular distributions and uptake mechanism by confocal microscopy. The complexes were found to bind to the external cell membrane and disperse evenly in the cytoplasm only after a very slow cell internalisation (>1 h). No significant changes in distribution were observed by fluorescence imaging under hypoxic conditions. The rate of localisation in the cytoplasm contrasts with their Zn(II) analogues which are known to have fast cell uptake (up to 20 min) and a clear localisation in lysosomes and mitochondria. The cytotoxicity mechanism of 1 over 24 h against a number of adherent cell lines is by membrane disruption and is of a comparable magnitude to that of [Cu(ATSM)], as demonstrated by MTT and LDH assays.

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CARBON-14 RADIOSYNTHESIS OF 4-(5-CHLORO-2-HYDROXYPHENYL)-3-(2-HYDROXYETHYL)-6-(TRIFLUOROMETHYL)-[4-^{14}C]QUINOLIN-2(1*H*)-ONE (XEN-D0401), A NOVEL BK CHANNEL ACTIVATOR

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The drug candidate XEN-D0401 (Figure 1) has found application in the management of disease states arising from the dysfunction of cellular membrane polarization and conductance.[1] XEN-D0401 contains a 3-substituted-4-arylquinolin-2-one pharmacophore and is a novel, selective small molecule activator to open the large-conductance calcium-activated potassium channel known as the BK channel.[2]

Journal of Labelled Compounds and Radiopharmaceuticals

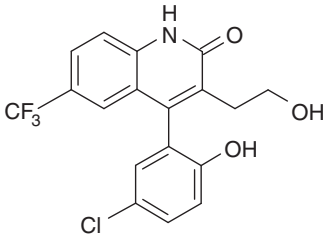

Figure 1. XEN-D0401

This drug candidate is currently in Phase I development for the treatment of overactive bladder (OAB).[3]

This presentation will describe the radiosynthesis of [^{14}C]XEN-D0401, having a single carbon-14 label in the quinolin-2-one ring as illustrated in Figure 2.

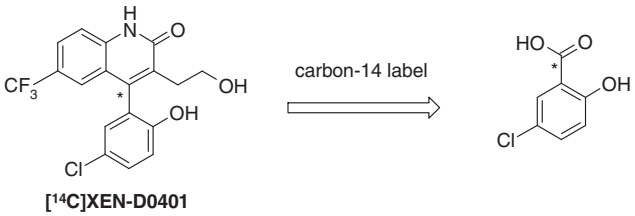

Figure 2. Position of carbon-14 label

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POSTER PRESENTATION ABSTRACTS

SYNTHESIS OF ^{14}C- AND ^{3}H-LABELLED L- AND D-SERINE DERIVATIVES.

DAVID HENDRY*, SHARON L. SMITH, JAMES S. JOHNSTON, ALAN J. SIMMONDS

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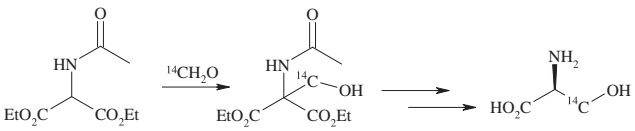
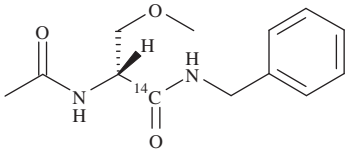
Natural and unnatural alpha-amino acids are required with specific labelling patterns for use in their own right and also for elaboration into derivatives that can be used as potential pharmaceuticals. The syntheses of L-[3-^{14}C]serine, L-[3-^{3}H]serine and D-[1-^{14}C] and L-[1-^{14}C]serine are described together with different methods for obtaining the desired optical isomer.

Details will be given of the synthesis of L-[3-^{14}C]serine from the reaction of diethyl acetamidomalonate with [^{14}C]formaldehyde.[1] Hydrolysis and decarboxylation lead to *N*-acetyl-DL-[3-^{14}C]serine. Resolution is achieved by enzymatic hydrolysis of the *N*-acetyl group by acylase I to give L-[3-^{14}C]serine.



The synthesis of L-[3-^{3}H]serine from diethyl acetamidomalonate and sodium boro[^{3}H]hydride will be presented. Details will also be provided of the synthesis of 3-methoxy-DL-[1-^{14}C]serine via a Strecker reaction[2] and its elaboration into a potential anticonvulsant[3–5] **1**, where the desired enantiomer is obtained by chiral preparative HPLC.



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THE SYNTHESIS OF STABLE ISOTOPE LABELLED TRIPHENYLACETIC ACID

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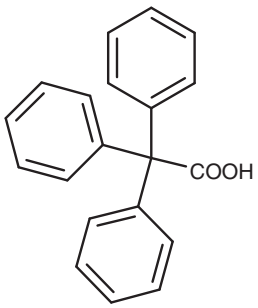
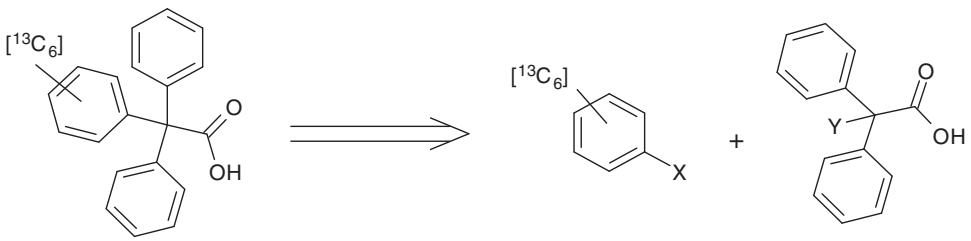
Triphenylacetic acid, **1**, figures amongst a range of acids being employed for the formation of crystalline salts of amines under development as potential drug candidates.



1

A requirement to prepare a stable isotope labelled (SIL) version of (1), incorporating a mass increase of at least 4 above parent, led to a retrosynthetic analysis wherein the addition of a suitable commercially-available [$^{13}C_6$] phenyl equivalent to a diphenylacetic acid derivative appeared attractive (Scheme 1).



Scheme 1.

A four step synthesis based on this retrosynthetic approach afforded the desired product; two of the steps involved the application of microwave irradiation to permit rapid heating of the mixtures above the boiling points of the solvents involved, offering significant time savings over the use of conventional heating methods in literature examples.

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A VERSATILE SYNTHESIS OF STABLE LABELLED *N*-ARYLPIPERAZINES

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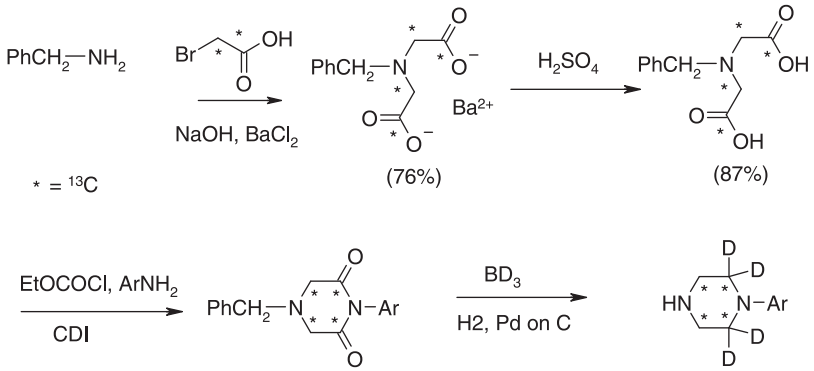
The *N*-arylpiperazine motif is commonly found in molecules of pharmaceutical interest, particularly in the field of neurosciences. Several approaches to stable labelled *N*-arylpiperazines have been described in the literature[1,2] and we present our work in this area.

We required a flexible approach giving access to a range of related *N*-arylpiperazines, and enabling introduction of 6–8 mass labels. The protocol is described in detail and alternative methods for ring closure and piperazinedione reduction are evaluated.



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ELECTRONIC EFFECTS IN THE *ORTHO*-^{2}H-LABELLED ANILIDE SYSTEM

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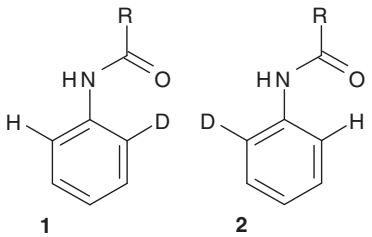
Deuterium isotope effects on conformation are of interest to isotopic chemists since they produce unexpected differences in spectroscopic properties (and possibly other physical behaviours) between the labelled and unlabelled compound.

In particular, conformational changes occasioned by *ortho*-substitution with heavy hydrogen isotopes are interesting since the resulting labelled compounds are the products of catalytic *ortho*-directed isotope exchange, a widely utilised approach for the isotopic labelling of aromatic systems with deuterium and tritium.

One striking conformational effect resulting from a single *ortho*-substitution of deuterium for hydrogen is shown by *2*-deuterated anilides. These compounds show an unusually large shift[1] of the remaining *ortho* proton (the 6-proton) in the ^{1}H-NMR. This shift is ascribed to a preference for anilide conformer **1** over conformer **2**.



1 **2**

Early studies have suggested that this preference is not simply steric in nature.[2]

The poster will describe recent NMR investigations into the effect of varying the aromatic and acyl substituents within the [2′-^{2}H]anilide system.

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USING THE COLOGICA ISOTOPIC SYNTHESIS DATABASE: A COMPLEMENTARY APPROACH TO SEARCHING VIA THE MAJOR SEARCH ENGINES

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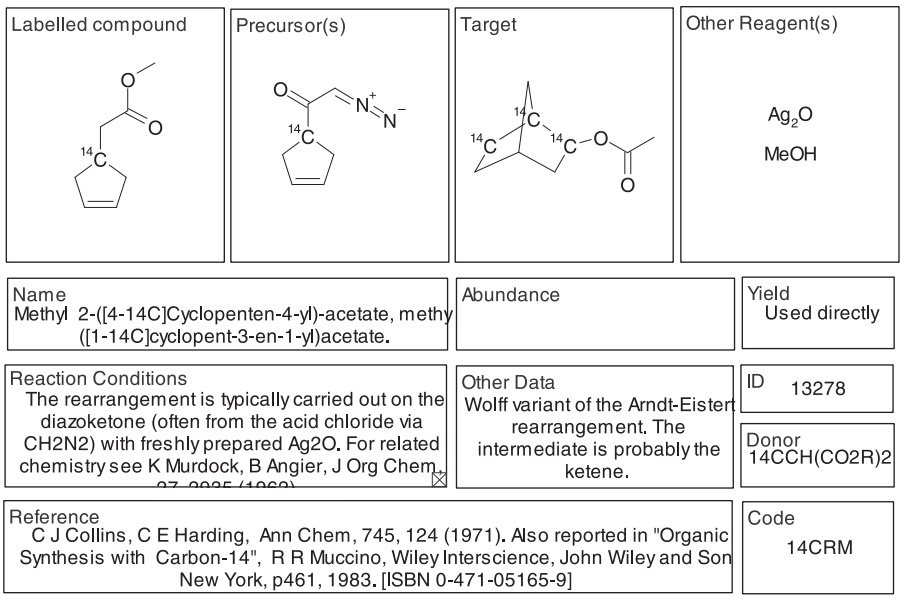
The poster describes examples of the use of an isotopic synthesis database covering compounds labelled with the isotopes ^{2}H, ^{3}H, ^{11}C, ^{13}C & ^{14}C. Four examples are given of the application of the database to isotopic synthesis via (a) searches for potential reactions, (b) searches for reaction conditions and reagents, (c) reconstruction of literature synthesis schemes, and (d) *de novo* route planning.

The database itself is PC-based and runs under Windows XP or Vista. It contains the main fields of interest to chemists involved in isotopic synthesis and is extensive but not comprehensive, currently containing ca. 20,000 records. It is comprised of abstracts from both the early and the recent isotopic synthesis literature, particularly concentrating on literature which is not easily retrieved by search engines. Included, for example, are many records from sources such as local and international IIS symposium proceedings and from the classic text books on isotopic synthesis, many of which are now out of print. The accent of the database is on molecules likely to be of use as synthetic intermediates. As such, it is a very rapid and complementary adjunct to researching isotopic synthesis pathways via the major search engines. A typical record is shown below.



THE SYNTHESIS OF CARBON-14 LABELLED 3H-QUINAZOLIN-4-ONE BUILDING BLOCKS.

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Over the past decade, 4-anilinoquinazolines have emerged as an important class of anticancer agents.[1] To support drug metabolism and distribution studies of this class of compound, a number of carbon-14 labelled materials were required. We detail here the synthesis of carbon-14 labelled, 5-, 6-, 7- and 6,7- substituted, 3*H*-quinazolin-4-one building blocks, the precursors of substituted 4-anilinoquinazolines (Figure 1).

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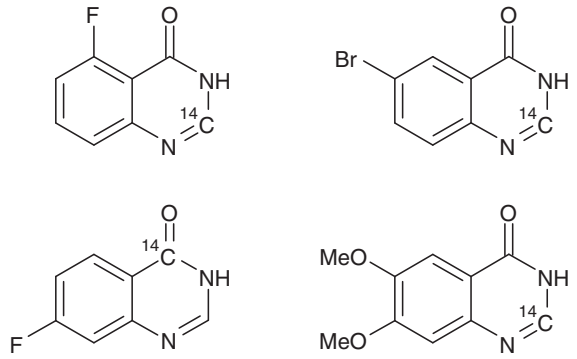

Figure 1. Substituted carbon-14 labelled 3*H*-quinazolin-4-ones

Reference

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AN INNOVATIVE SYNTHESIS OF A STABLE ISOTOPE LABELED *N*-METHYL-PYRAZOLE

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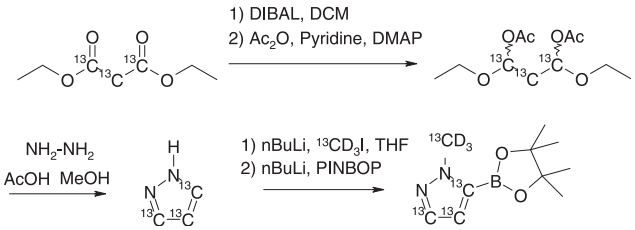
The synthesis of pyrazoles is of great interest due to the wide application of such heterocylic motifs in the pharmaceutical industry eg COX-2 inhibitor celecoxib (Celebrex®)[1], CB1 antagonist acomplia (Rimonabant®),[2] sildenafil (Viagra®).[3]

The synthesis of the 1,2-pyrazole moiety is classically achieved by either a 1,3-dipolar cycloaddition of diazo compounds and alkynes or by condensation of hydrazine with 1,3 difunctionalised molecules, generally diketones. Such syntheses of a SIL version of *N*-methylpyrazole appeared quite challenging, since the number of isotopically labelled starting materials for either route is quite limited.

Our successful approach to overcome this issue led us to a novel SIL synthesis of this fragment, starting from commercially available diethyl [$^{13}C_3$] malonate. By appropriate adjustment of the oxidation level,[4] a SIL malonaldehyde equivalent was prepared, which could be converted to the labelled pyrazole (see Scheme below).



References

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THE SYNTHESIS OF VERY HIGH SPECIFIC ACTIVITY PEPTIDES WITH ONE OR MORE CARBON-14 LABELLED AMINO ACIDS

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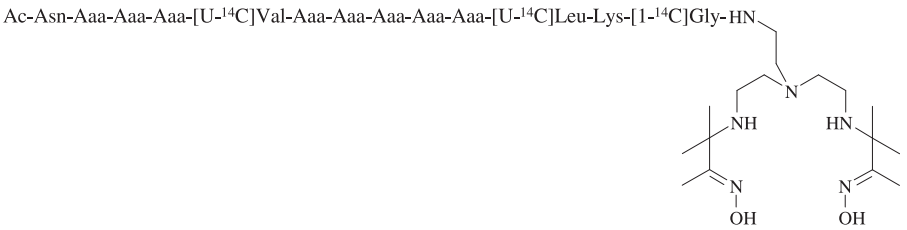
[c]GE Healthcare, The Grove Centre, White Lion Road, Amersham, HP7 9LL, UK

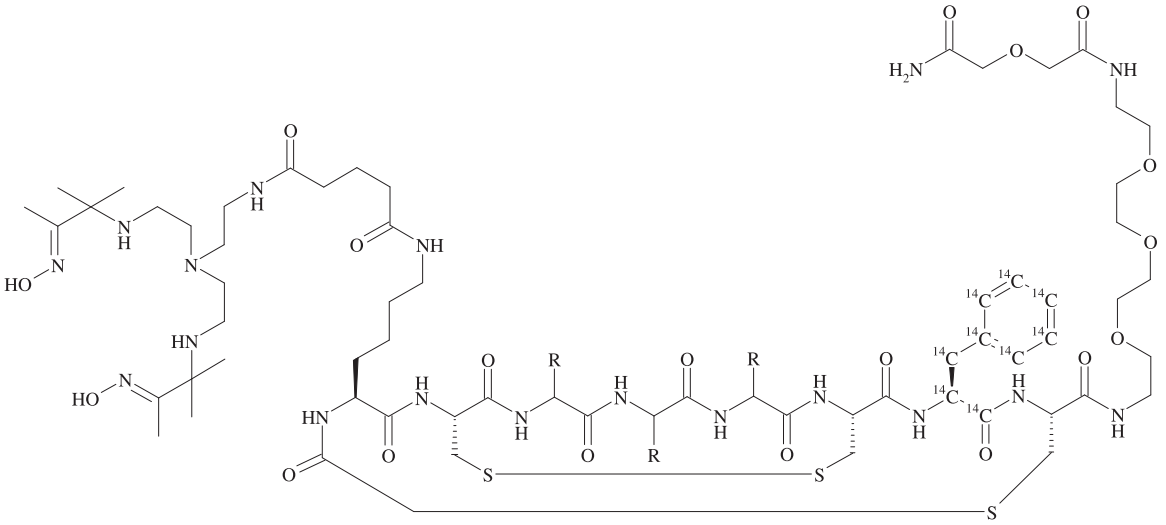
Objectives and methods: Due to the relatively high molecular weight of many peptides and their low dosage, labelled peptides often require a specific activity in excess of the single labelled 50–60 mCi/mmol. We required three peptides attached to a

technetium chelator and labelled with carbon-14 at high specific activity. The peptides were prepared by solid phase peptide synthesis using the Fmoc methodology and labelled amino acids prepared and protected in house. They were purified and converted to the acetate form by HPLC.



Results: TT 106 required three amino acid to be labelled and was produced by a two stage process. Firstly, the fully protected and purified peptide was prepared. This was coupled to the technetium chelator and the product deprotected and purified to give [^{14}C]TT 106 with a specific activity of 554 mCi/mmol.

NC100671, a close analogue of TT 106, was required with the label in the N-terminus asparagine. Since [U-^{14}C]asparagine is not readily available, the Fmoc-[U-^{14}C]Asn(Trt)-OH required for this peptide was synthesised from [U-^{14}C]aspartic acid. The previous two stage process was used to produce the desired product with a specific activity of 183 mCi/mmol.



NC100692 is a C-terminus modified, bicyclic peptide with a technetium chelator attached via the side chain of the N-terminus lysine. The first step in the synthesis was to attach the acid form of the C-terminus chain to an amide resin. The [U-^{14}C]phenylalanine was coupled manually and then the remainder of the peptide was prepared using an automated solid phase peptide synthesiser. The peptide was cleaved from the resin and partially deprotected, leaving the protecting groups on the cysteine residues. The thioether linkage was then prepared in two steps, followed by the disulphide bridge formation. Finally, the technetium chelator was added via an amide linkage. The [^{14}C]NC100692 had a specific activity of 438 mCi/mmol.

Conclusion: A combination of manual and automated solid phase peptide synthesis was used to prepare three peptides at very high specific activity with good radiochemical purity. These syntheses required a combination of multiple residue labelling, side chain protection of a labelled amino acid, C-terminus, N-terminus and side chain peptide modification and thioether and disulphide bridge formation.

