13th International Symposium

on the Synthesis and Application of Isotopically Labelled Compounds

Prague, Czech Republic

June 3rd – 7th 2018

Symposium Scientific Programme

and

Collection of Abstracts

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Welcome to Prague the City of Hundred Spires

It is a great honour and at the same time a great pleasure to welcome you on behalf of the Local Organising Committee to the 13th IIS International Symposium on the Synthesis and Applications of Isotopes and Isotopically Labelled Compounds held in Prague on June 3-7, 2018.

This series of international symposia is known to alternate between Europe and North America every three years. Strictly speaking until the year 1989 it has been alternating between Western Europe and North America. The first symposium of this series held east of the Iron Curtain was the 7th one held in the year 2000 in Dresden, in the already united Germany. The fact that this year international meeting of IIS is held in Prague is evidence that Czech Republic is firmly planted in European Union.

We are happy to see the professionals of all kinds - from academia and state research institutes through researchers in industry to specialists from instrument producing companies - coming to meet in Prague to discuss the subject that they all have in common - exploiting the unique qualities of isotopes and isotopically labelled compounds in all branches of science, applied research and quite often in daily life applications.

I would like to thank here for the great support from Institute of Organic Chemistry and Biochemistry of Czech Academy of Sciences and to my colleagues in this institute especially for the time I was able to dedicate to the organisational work. The organisation of the symposium would not be possible without the support of the president of Czech Chemical Society Jan John and hard work of the office of Czech Chemical Society, namely Helena Pokorná and Alena Vlková.

The members of the Scientific Advisory Board have done a tremendous job in securing top lecturers to provide high level Scientific Programme and many thanks to all of them.

My personal thanks to Jens Atzrodt for his invaluable advice and inspiring impulses when the work was losing tempo.

And last but not least, many thanks to our Symposium sponsors and exhibitors. Without their lavish contributions it would not be possible to maintain the high level of this symposium series established by previous meetings.

I wish everyone to enjoy the lectures, discussions with colleagues from all over the world as well as the City of Hundred Spires.

Tomáš Elbert

Chairman of the Local Organising Committee

Welcome note from IIS President 2018

On behalf of the Board of Trustees of the International Isotope Society, I have the great pleasure to welcome you to the International Isotope Society Symposium on the Synthesis and Applications of Isotopes and Isotopically Labelled Compounds, Prague, Czech Republic, June 3–7, 2018.

This conference is already the 13th symposium in a series going back to 1982. Again the organizers chose a venue in a European town with an excellent scientific and cultural reputation and a rich history. I hope you will take some time to explore the beautiful city of Prague.

Over the past years we have seen dramatic changes within the isotope science community. Isotope labs in the pharmaceutical industry have undergone major changes, including considerable headcount reductions, budget constraints and increased externalization of isotope chemistry. However, isotope chemistry will continue to play an important role in academic research but also in pharmaceutical drug discovery and in many other areas of life sciences.

This is also reflected by an impressive scientific program with key-notes from world famous scientists and scientific sessions covering a broad range of research and development in the field of isotopes and isotopically labelled compounds. I'm particularly happy to see a continuous tendency for increased academic interest in isotope science resulting also in higher student participation and more contributed oral presentations from young scientists. As in previous years, special sessions are dedicated to the Melvin Calvin and Wiley Young Scientist Award winners. Another highlight of the conference will be the banquet with the presentation of the IIS Award 2018. The poster session and exhibition will showcase new developments in isotope research and will provide additional opportunities for scientific exchange and networking.

The conference wouldn't have been possible without the dedication and engagement of the main organizer. Therefore first and foremost I would like to thank Tomáš Elbert who has worked very hard over the last three years to make this symposium a success. He was strongly supported by the Czech Chemical Society and the Institute of Organic Chemistry and Biochemistry of Czech Academy of Sciences. Particularly, I would also like to thank Prof. Jan John, Prof. Pavel Dražar, Dr. Ondřej Lebeda, Helena Pokorná, Alena Vlková and Aleš Marek.

I also want to thank all sponsors and exhibitors who by their generous contribution are again extremely important to the success of the IIS symposium. Since active participation is essential many thanks go also to the chairs, speakers and all other scientific contributors.

Once again, welcome to Prague. This should be a wonderful week for science but also for the delights that Prague can offer.

Jens Atzrodt,

IIS President 2018

Organisers

Local Organising Committee

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Dr. Ondřej Lebeda	*chairman of Session 3*
	co-chairman **Dr. Alfred Morgenstern**
Prof. František Tureček	*chairman of Session 4*
Prof. Jana Roithová	
Dr. Brad Maxwell	*chairman of Session 5*
	co-chairman **Dr. Charles Elmore**
Dr. Martin Sandvoss	*chairman of Session 6*
Prof. William Lockley	*chairman of Session 7*
	co-chairman **Dr. David Hesk**
Dr. Thomas Hartung	*chairman of Poster Session*
	co-chairmen **Dr. Boris Czeskis, Dr. Dieter Muri**

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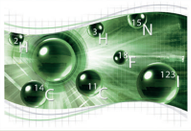

Journal of
Labelled Compounds and Radiopharmaceuticals

The Official Journal of the International Isotope Society

Chemické listy

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List of Exhibitors

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Since 1993, C/D/N Isotopes Inc. has provided its customers with superior quality and exceptional service. Researchers from around the world depend on C/D/N Isotopes as the company for deuterium labelled compounds. We currently have more than 3300 products in stock. Over the years, we have developed and expanded our expertise in the preparation of deuterated compounds. Check our NEW PRODUCTS listing as we regularly add more products. Our extensive Custom Synthesis capabilities allow us to develop chemicals that our customers need in a timely manner, reasonable price, isotopic enrichment and chemical purity.

Curachem, a Korean-based, full-service synthesis company, is a global provider of $^{14}C/^{3}H$ custom radiolabeled molecules as well as custom stable isotope labeled products. We also provide non-isotopically labeled syntheses of metabolites, impurities components and reference standards as requested. Our expertise spans across virtually all investigational molecules including small molecules, peptides, polysaccharides, oligonucleotides, pesticides, proteins and complex antibody drug conjugate. We have recently added capabilities and expertise for the manufacture GMP-grade radiolabeled APIs (Drug Substances) and Investigational Medicinal Products (IMPs, Drug Products) suitable for global drug registrations. See **www.curachem.com.**

Cambridge Isotope Labs, Inc. is the world leader in the separation and manufacture of stable isotope products ^{13}C, ^{2}H or D, ^{15}N, ^{17}O, ^{18}O. CIL has the largest ^{13}C and one of the largest 18O separation facilities in the world and the only commercial D_2O re-enrichment columns. CIL offers over 15,000 products and decades of experience in the manufacture of deuterated synthetic intermediates and ^{13}C APIs. CIL adheres to quality management systems including cGMP, ISO 13485, and ISO 17025. Custom synthesis projects are reviewed by a team of experts to ensure customer and regulatory satisfaction.

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Hidex provides a variety of manual and automatic gamma and liquid scintillation counters, microplate readers as well as sample preparation equipment for different life science and radiation monitoring field.

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Pharmaron is a premier R&D service provider supporting the life science industry with diverse and well-established drug R&D service capabilities, from early discovery to clinical development. With operations in China, US and UK staffed by over 5,500 employees, Pharmaron has an excellent track record in the delivery of R&D solutions to its partners in North America, Europe, Japan and China.

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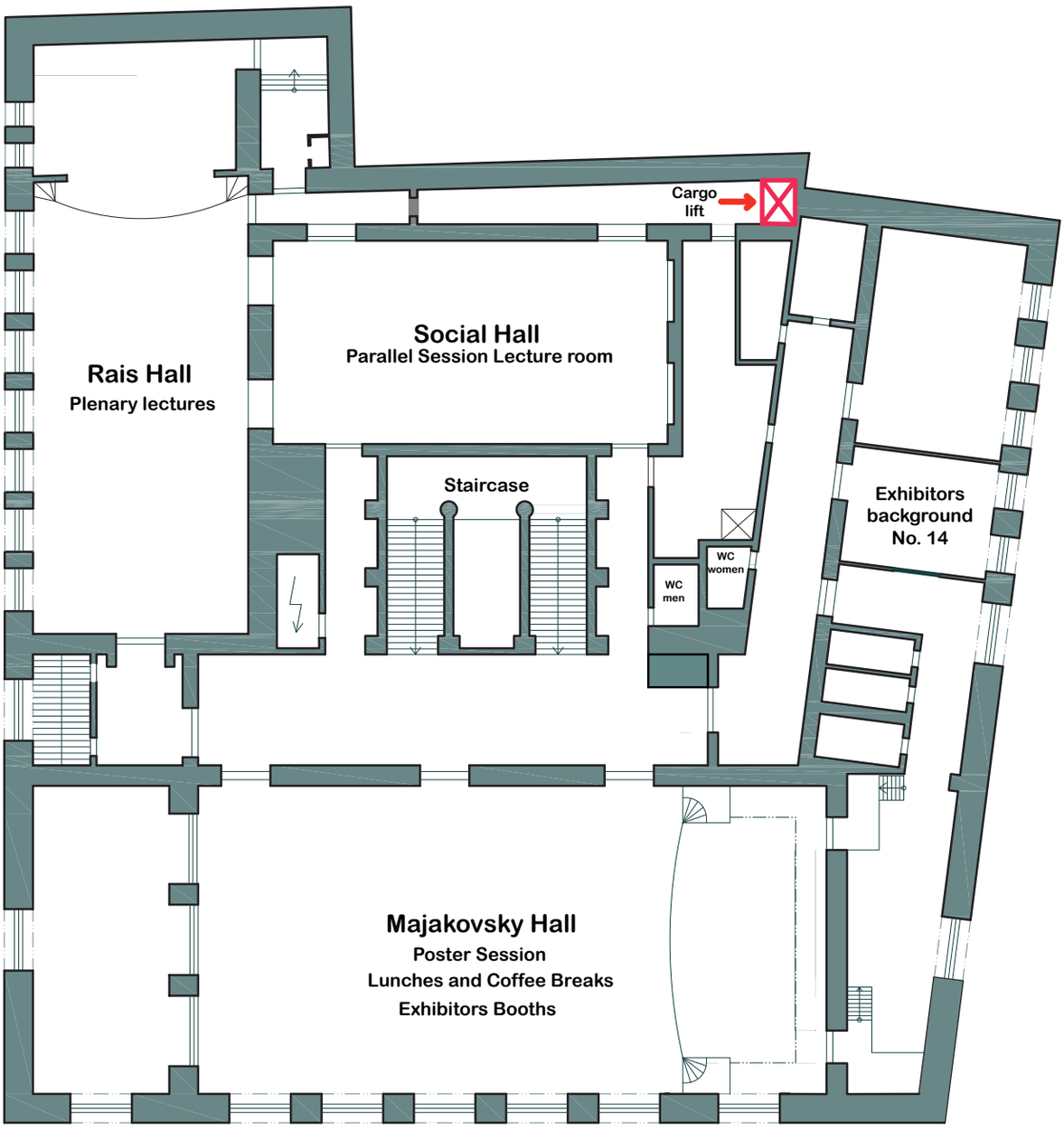
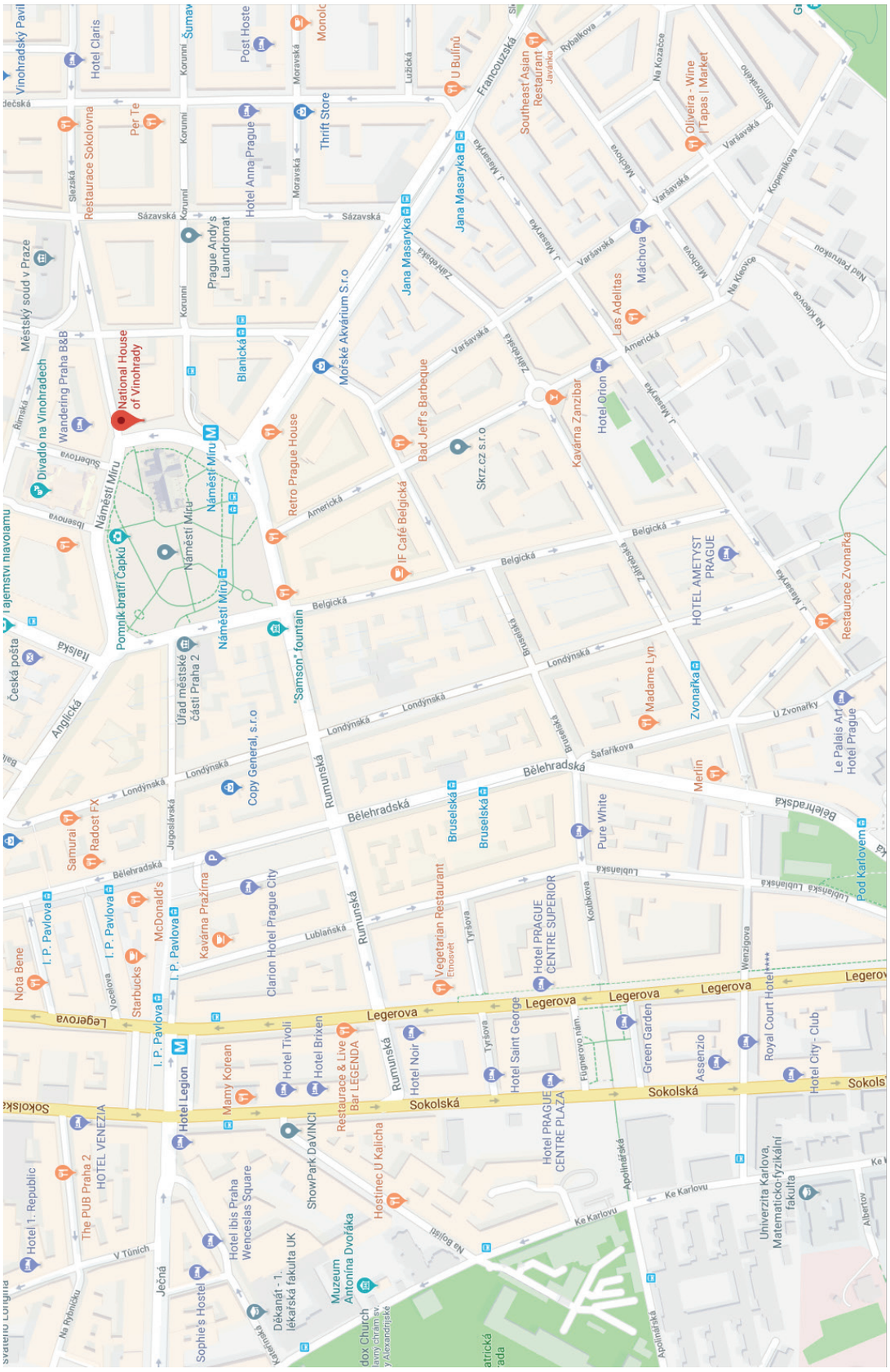
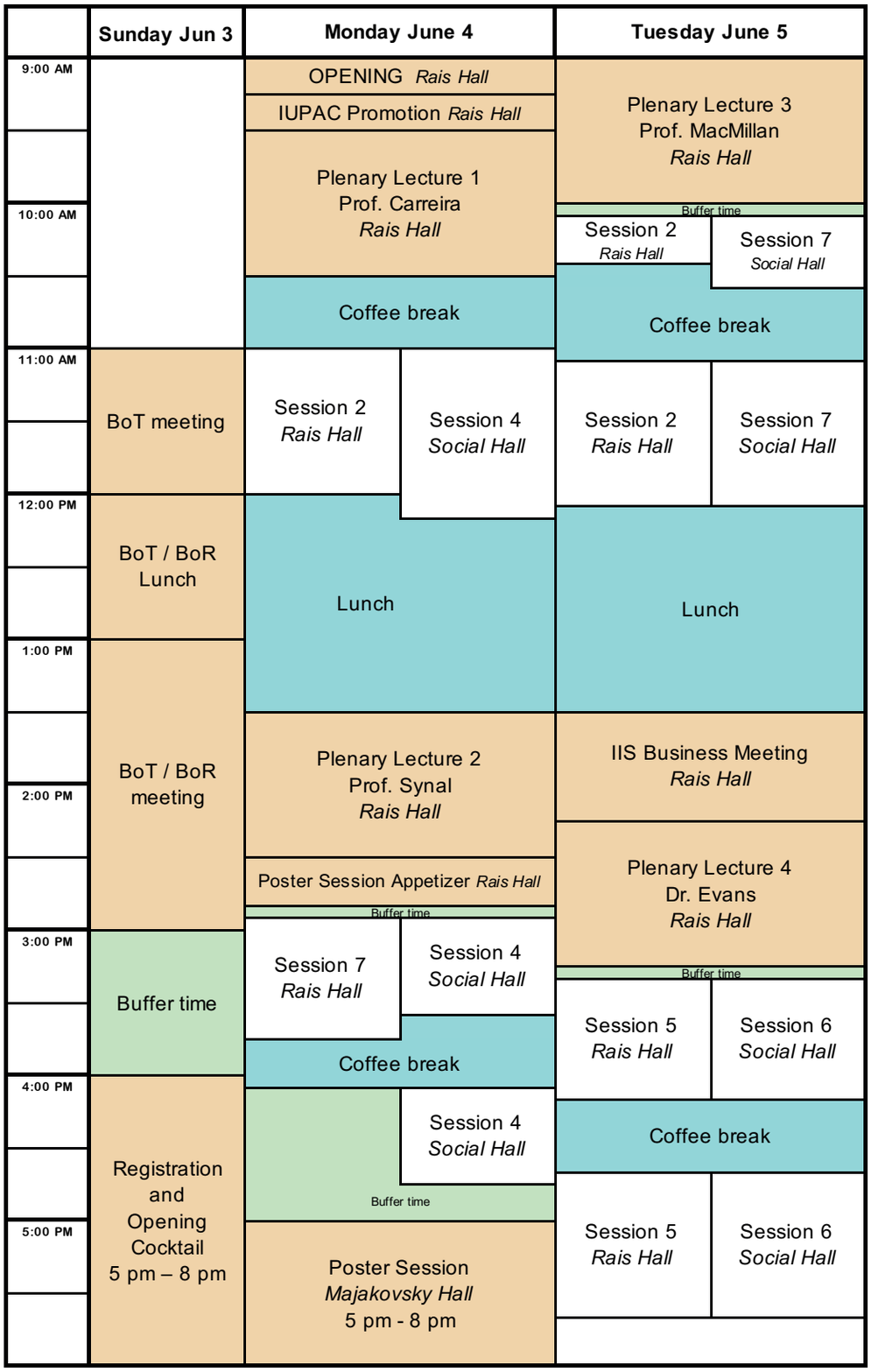


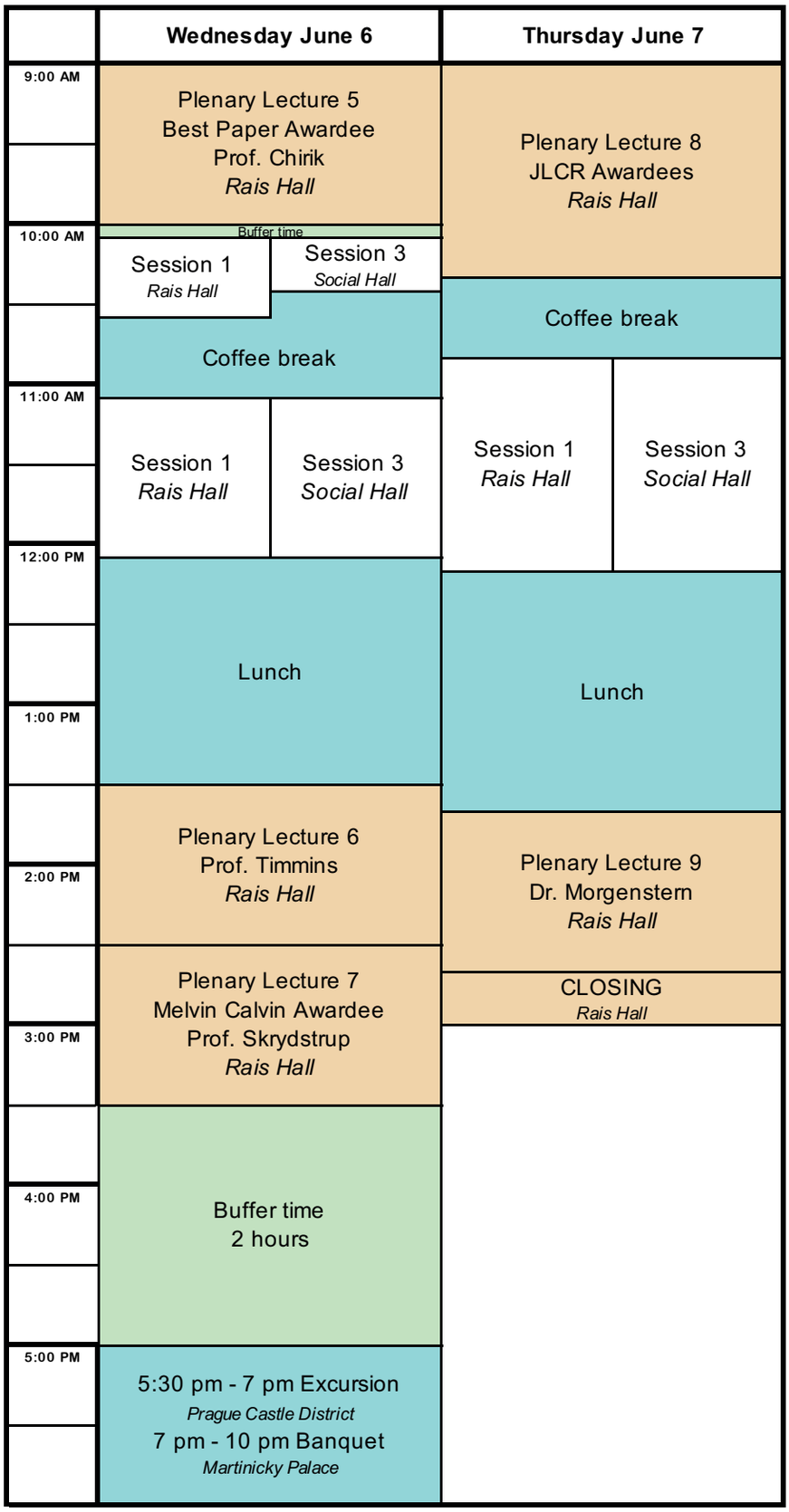
Map of NHV Surrounding Area



Final Scientific Programme

IIS Prague 2018 Time Schedule




Wednesday June 6
Thursday June 7
9:00 AM
Plenary Lecture 5
Best Paper Awardee
Prof. Chirik
Rais Hall
Plenary Lecture 8
JLCR Awardees
Rais Hall
10:00 AM
Buffer time
Session 1
Rais Hall
Session 3
Social Hall
Coffee break
Coffee break
11:00 AM
Session 1
Rais Hall
Session 3
Social Hall
Session 1
Rais Hall
Session 3
Social Hall
12:00 PM
Lunch
Lunch
1:00 PM
2:00 PM
Plenary Lecture 6
Prof. Timmins
Rais Hall
Plenary Lecture 9
Dr. Morgenstern
Rais Hall
Plenary Lecture 7
Melvin Calvin Awardee
Prof. Skrydstrup
Rais Hall
CLOSING
Rais Hall
3:00 PM
4:00 PM
Buffer time
2 hours
5:00 PM
5:30 pm - 7 pm Excursion
Prague Castle District
7 pm - 10 pm Banquet
Martinicky Palace

Sunday June 3rd, 2018

11:00 am–12:00 pm *Meeting room on 1 floor*	BoT Meeting
12:00–1:00 pm *Meeting room on 1 floor*	BoT / BoR Lunch
1:00–3:00 pm *Meeting room on 1 floor*	BoT / BoR Meeting
4:00–8:00 pm *Reception desk on 1 floor*	Registration of participants
5:00–8:00 pm *Majakovsky Hall*	***Opening Cocktail*** Sponsored by TJADEN BIOSCIENCES "Quality Catalogue and Custom Radiochemicals"

Monday June 4th, 2018

8:00 am–8:00 pm
Reception desk on 1 floor

Registration of participants

9:00–9:15 am
Rais Hall

Welcome and Opening
Local Organising Commitee Chairman: Dr. Tomáš Elbert
President of IIS: Dr. Jens Atzrodt

9:15–9:30 am
Rais Hall

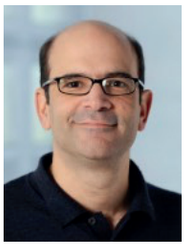
Presentation of IUPAC activities
Prof. Jiří Vohlídal (Charles University, Prague), Associate member of Chemical Nomenclature and Structure Representation Division (VIII) of IUPAC

Plenary Lecture 1

Chairman ***Dr. Jon Bloom*** *(Pharmaron, United Kingdom)*

9:30–10:30 am
Rais Hall
PL–1

Prof. Erick M. Carreira (ETH Zürich, Switzerland)



New Insights in Catalysis

Sponsored by SANOFI

10:30–11:00 am

Coffee break

Session 2: ***Synthesis and application of compounds labelled by ^{14}C***
Rais Hall

Chairman ***Dr. Jon Bloom*** *(Pharmaron, United Kingdom)*

11:00–11:20 am
O-1

Dr. Neil Geach (Selcia Ltd., USA)
Radiosynthesis of [^{14}C]Dasotraline for Pre–Clinical and Clinical Studies

11:20–11:40 am
O-2

Dr. Juhee Park (Curachem, Republic of Korea)
Bringing Understanding to Large Molecule Radiolabeling Including Biologics

11:40 am–12:00 pm
O-3

Antonio Dell'isola (Almac Sciences, United Kingdom)
Synthesis of [^{14}C]-Labelled Peptides

12:00–1:30pm
Majakovsky Hall

Lunch
Sponsored by Boehringer Ingelheim

Session 4: ***Stable isotopes of biogenic elements - chemistry of labelling and applications***
Social Hall

Chairman ***Prof. František Tureček*** *(University of Washington, Seattle, USA)*

11:00–11:30 am ***Invited Lecture***

O-4 **Prof. Jeroen S. Dickschat** (University of Bonn, Germany)
Tracing terrestrial terpenes with isotopes

11:30–11:50 am **Gary J. Knox** (University of Strathclyde, United Kingdom)
O-5 Computationally Guided Rational Ligand Design for the Development of Highly Active Iridium(I) Complexes in Hydrogen Isotope Exchange Processes

11:50 am–12:10 pm **Dr. Kateřina Bišová** (Institute of Microbiology CAS, Czech Republic)
O-6 Microalgae Grown in Stable Isotopes

12:10–1:30 pm ***Lunch***
Majakovsky Hall Sponsored by Boehringer Ingelheim

Plenary Lecture 2
Chairman ***Prof. František Tureček*** *(University of Washington, Seattle, USA)*

1:30–2:30 pm
Rais Hall

Prof. Hans-Arno Synal (ETH Zürich, Switzerland)
PL–2

Present and Future: What Can We Expect from Next Generation AMS Systems

Sponsored by ALSACHIM a Shimadzu Group Company

2:30–2:50 pm ***Poster Session Appetizer***
Chairman ***Dr. Thomas Hartung*** (F. Hoffmann La Roche, Switzerland)
Rais Hall

Session 4: ***Stable isotopes of biogenic elements - chemistry of labelling and applications***
Social Hall

Chairman ***Prof. František Tureček*** *(University of Washington, USA)*

2:55–3:15 pm **Dr. Sumei Ren** (Merck Sharp & Dohme, USA)
O-7 ^{34}S: A New Oportunity for the Efficient Synthesis of Stable Isotope Labeled Compounds

3:15–3:35 pm O-8

Dr. Ronghui Lin (Janssen R&D, Johnson & Johnson, USA)
Synthesis of Isotope-Labeled 1-Butyl-3-Chloro-4-(4-Phenyl-1-Piperidinyl)–(1*H*)-Pyridone (JNJ-40411813), a Positive Allosteric Modulator of the Metabotropic Glutamate 2 Receptor, and its Metabolites

3:35–4:05 pm

Coffee break

4:05–4:25 pm O-9

Dr. Charles S. Elmore (AstraZeneca, Sweden)
Synthesis of Di-Docosahexaenoyl (C22:6)-Bis (Monoacylglycerol) Phosphate in Unlabeled and C-13 Labeled Forms for Use as a Biomarker of Drug-Induced Phospholipidosis

4:25–4:45 pm O-10

Dr. Kunlun Hong (Oak Ridge National Laboratory, USA)
Designing Soft Materials With Desirable Properties by Selective Deuteration

Session 7:
Rais Hall

Emerging new fields in chemistry of isotopes and in isotope techniques applications

Chairman

Dr. David Hesk *(Merck Sharp & Dohme, USA)*

2:55–3:25 pm O-11

Invited Lecture
Sean Bew (University of East Anglia, United Kingdom)
Stable Isotope Hyperpolarisation in Metabolite Study and Disease Diagnosis: Why Do It? How Is It Done? What Is It Good For?

3:25–3:45 pm O-12

Dipl.-Ing. Martin R. Edelmann
(F. Hoffmann La Roche, Switzerland)
Radiolabeled IgG Antibodies – Potential Impact of Various Labels on Pharmacokinetics

3:50–4:20 pm

Coffee break

Session 8:
Majakovsky Hall

Poster Session and Exhibition

Sponsored by

International Isotope Society
Central European Division

Chairman

Dr. Thomas Hartung *(F. Hoffmann–La Roche, Switzerland)*

Co-chairmen

Dr. Boris Czeskis *(Eli Lilly & Co., USA)*
Dr. Dieter Muri *(F. Hoffmann–La Roche, Switzerland)*

5:00–8:00 pm

A buffet dinner and drinks will be served

Tuesday June 5th, 2018

Plenary Lecture 3

Chairman ***Dr. David Hesk*** *(Merck Sharp & Dohme, USA)*

9:00–10:00 am
Rais Hall

PL–3 **Prof. David W. C. MacMillan** (Princeton University, USA)
New Photoredox Reactions

Session 2: ***Synthesis and application of compounds labelled by ^{14}C***
Rais Hall

Chairman ***Dr. Jon Bloom*** *(Pharmaron, United Kingdom)*

10:05–10:25
O-13 **Dr. Ekaterina Parkhomchuk** (Novosibirsk State University, Russia)
^{14}C–Polystyrene Microspheres Detected by Accelerator Mass-Spectrometer for Biomedical and Aerosol Studies

10:25–11:05 pm ***Coffee break***

11:05–11:25 am
O-14 **Malvika Sardana** (AstraZeneca, Sweden)
Visible Light Enabled Carbonylation of Alkyl Iodides

11:25–11:45 am
O-15 **Dr. Bruce P. McKillican** (Syngenta, USA)
Syntheses of ^{14}C SYN545388: An Indazole Anthranilic Diamide Insekticide

11:45 am–12:05 pm
O-16 **László Orha** (Institute of Isotopes Co., Ltd., Hungary
Synthesis of ^{14}C-Labelled Sulfonylurea Type Pesticides

12:05–1:30 pm
Majakovsky Hall

Lunch
Sponsored by Roche

Session 7: ***Emerging new fields in chemistry of isotopes and in isotope techniques applications***
Social Hall

Chairman ***Prof. William Lockley*** *(University of Surrey, United Kingdom)*

10:05–10:35 am ***Invited Lecture***

O-17 **Prof. Chris Willis** (University of Bristol, United Kingdom)
Combining Isotopes, Synthesis and Synthetic Biology

10:35–11:05 am ***Coffee break***

11:05–11:25 am
O-18

Prof. Daniel E. Murnick (Rutgers University, USA)
Laser Based Radiocarbon Detection in the Laboratory; How Soon?

11:25–11:45 am
O-19

Renan Zorzatto (University of Strathclyde, United Kingdom)
Iridium(I) Complexes Bearing Chelating NHC/Phosphine Ligands: Synthesis and Application in HIE Processes

11:45 am–12:05 pm
O-20

Grant A. Johnston (Pharmaron UK, United Kingdom)
Recovery of High Specific Activity $^{14}CO_2$ from C14 Synthesis By-Products via Oxidation and Isotopic Enrichment

12:05–1:30 pm
Majakovsky Hall

Lunch
Sponsored by Roche

1:30–2:15 pm
Rais Hall

IIS Business Meeting

Plenary Lecture 4
Chairman

Dr. Brad Maxwell *(Vertex Pharmaceuticals, USA)*

2:15–3:15 pm
Rais Hall

Dr. David C. Evans (Janssen R & D, Johnson & Johnson, USA)
PL-4
Use of Isotopes in Drug Design and Mechanistic Drug Disposition

Session 5:
Rais Hall

Preclinical and clinical studies of drug candidates supported by labelled compounds

Chairman

Dr. Brad Maxwell *(Vertex Pharmaceuticals, USA)*

3:20–3:50 pm

Invited Lecture
Dr. Stephen R. Dueker (BioCore, Republic of Korea)
O-21
Performance Characteristics of WS-Cavity Ring Down Laser Spectroscopy System in Support of ^{14}C ADME Studies

3:50–4:10 pm
O-22

Dr. Andrew B. McEwan
The Human ADME Study: Past, Present and Future

4:10–4:40 pm

Coffee break

Chairman ***Dr. Charles Elmore*** *(AstraZeneca, Sweden)*

4:40–5:00 pm
O-23
Yong Gong (Janssen R & D, Johnson & Johnson, USA)
Biotransformation of Radio and Stable Isotopologues for Standard-Free Quantitation of Drug Metabolites

5:00–5:20 pm
O-24
Dr. Ad Roffel (PRA Health Sciences, Netherlands)
An Open Label, Single Dose Study to Assess the Excretion and Metabolism of [^{14}C]APD421 Administered via the Intravenous Route to Healthy Male Subjects

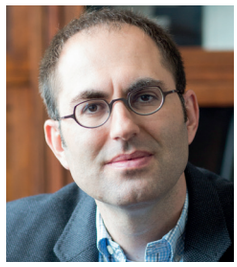
5:20–5:40 pm
O-25
Iain W. Shaw (Quotient Sciences, United Kingdom)
Application of ^{14}C Isotope to Gain a Comprehensive Understanding of Drug Disposition and Formulation Performance in Human Subjects

Session 6:
Social Hall

Analytical methods for characterisation of labelled compounds and developments in the field of formulation and storage of compounds with high specific activity

Chairman ***Dr. Martin Sandvoss*** *(Sanofi, Germany)*

3:20–3:50 pm
Invited Lecture



O-26
Prof. Joshua J. Coon (University of Wisconsin, USA)
Metabolic Labels for Multi-Plexed Protein Quantification

3:50–4:10 pm
O-27
Dr. Rhys B. Murphy (Australian Nuclear Science and Technology Organisation)
A New MS/MS Method to Determine Differences in the Metabolic Stability of Deuterated Molecules versus their Non-Deuterated Analogues together in the same Assay: A Case Study Using a Radiotracer Cold Standard

4:10–4:40 pm
Coffee break

4:40–5:00 pm
O-28
Dr. Aleš Marek
(Institute of Organic Chemistry and Biochemistry CAS, Czech Republic)
Storage and Stability of Organic Compounds Labeled with Tritium

5:00–5:20 pm
O-29
Dr. Tom Deakin (LabLogic Systems, United Kingdom)
Applications of Miniaturized Silicon Photomultipliers to Nuclear Medicine and Related Disciplines

5:20–5:40 pm
O-30
Roman I. Dralyuk (Novosibirsk State University, Russia)
Novel Simplified Absorption-Catalytic Method of Sample Preparation for AMS Analysis

Wednesday June 6th, 2018

Plenary Lecture 5

Chairman ***Dr. Brad Maxwell*** *(Vertex Pharmaceuticals, USA)*

9:00–10:00 am
Rais Hall

IIS Best Paper Award Address

PL–5 **Prof. Paul J. Chirik** (Princeton University, USA)
Iron, Cobalt and Nickel Catalysts for Hydrogen Isotope Exchange

Session 1: Synthesis and application of compounds labelled by ^{3}H.

Rais Hall

Chairman ***Dr. Jens Atzrodt*** *(Sanofi, Germany)*

10:05–10:35 am

Invited Lecture

Dr. Grégory Pieters (CEA, France)
O-31 Hydrogen Isotope Exchanges Catalyzed by Ruthenium Nanocatalysts

10:35–11:05 am

Coffee break

11:05–11:25 am

Sabina Doubková
(Institute of Organic Chemistry and Biochemistry CAS, Czech Republic)
O-32 Frustrated Lewis Pairs as a Novel Agent for Tritium Labeling – An Alternative to Hydride Reduction

11:25–11:45 am

Alberto Palazzolo (CEA, France)
O-33 Late Stage Deuterium and Tritium Labelling of Nucleobases Catalyzed by Ruthenium Nanoparticles

11:45 am–12:05 pm

Dr. Volker Derdau (Sanofi, Germany)
O-34 Tritiation of Azido-Labelled Diiodo Cabazitaxel (Jevtana) and Docetaxel (Taxotere) Derivatives to Generate ^{3}H-Photoaffinity Probes

12:05–1:30 pm
Majakovsky Hall

Lunch

Sponsored by

Session 3: *Synthesis and application of compounds labelled with medical radionuclides*

Social Hall

Chairman ***Dr. Alfred Morgenstern*** *(Joint Research Centre of EC, Germany)*

10:05–10:25 am
O-35
Prof. Tobias L. Ross (Hannover Medical School, Germany)
^{68}Ga-DOTA-Maltohexaose a New Infection Diagnostic Imaging Biomarker

10:25–11:05 am
Coffee break

11:05–11:25 am
O-36
Nigel R. Stevenson (Serena LLC, USA)
Sn-117m – A New Isotope for Treating Arthritis

11:25–11:45 am
O-37
Livia Chilug (IFIN-HH, Romania)
Preclinical Evaluation of Radiolabelled Peptides Targeting Neurotensin Receptor Subtype 1 as Theragnostic Agents In Colon Cancers

11:45 am–12:05 pm
O-38
Bayirta V. Egorova (Lomonosov Moscow State University, Russia)
Radiolabeling of Tetrapeptide by Bismuth and Europium and In Vitro Serum Stability of Formed Complexes

12:05–1:30 pm
Majakovsky Hall
Lunch
Sponsored by

Plenary Lecture 6

Chairman ***Dr. Jens Atzrodt*** *(Sanofi, Germany)*

1:30–2:30 pm
Rais Hall
PL–6
Prof. Graham S. Timmins (University of New Mexico, USA)
Stable Isotopes in Lung Infectious Diseases: Improved Drugs and New Breath Test Diagnostics

Sponsored by

Plenary Lecture 7

Chairman ***Dr. Jens Atzrodt*** *(Sanofi, Germany)*

2:30–3:30 pm
Rais Hall
Melvin Calvin Award Address

Prof. Troels Skrydstrup (Aarhus University, Denmark)
PL–7
The Development and Application of Two-Chamber Reactors for Isotope-Labeling

5:30–7:00 pm
Prague Castle District walking tour

7:00 pm
Symposium Banquet at Martinicky Palace *and* ***IIS Award Ceremony***

Thursday June 7th, 2018

Plenary Lecture 8
Rais Hall

Journal of Labelled Compounds and Radiopharmaceuticals Young Chemist Award

Chairman ***Dr. Ken Lawrie*** *(IIS)*

Sponsored by WILEY

9:00–9:20 am
PL-8-1

Mégane Valéro (University Paris-Saclay, France)
Iridium-Catalyzed Hydrogen Isotope Exchange (HIE) Method of Aliphatic sp^3-Centers in Unactivated Amides

9:20-9:40 am
PL-8-2

Gianluca Destro (CEA Saclay, France)
Carbon Isotopic Exchange for the Labelling of Carboxylic Acids

9:40–10:00 am
PL-8-3

Adele Queen (University of Strathclyde, United Kingdom)
Iridium-Catalysed Hydrogen Isotope Exchange of Amino Acid and Peptide Molecules

10:00–10:20 am
PL-8-4

Antonio Del Vecchio (CEA Saclay, France)
CO_2 Fixation for Late Stage Labeling of Drug Candidates

10:20–10:50 am ***Coffee break***

Session 1: ***Synthesis and application of compounds labelled by ^{3}H.***
Rais Hall

Chairman ***Dr. Volker Derdau*** *(Sanofi-Aventis, Germany)*

10:50–11:10 am
O-39
Viktor Pfeifer (CEA Saclay, France)
Tritium and Deuterium Labelling of Bioactive Molecules Catalyzed by Ruthenium Nanoparticles

11:10–11:30 am
O-40
Dr. Scott Ballentine (Janssen R & D, Johnson & Johnson, USA)
Selective Tritiation Reactions Using Heterogeneous Catalysts

11:30–11:50 pm
O-41
Dr. Břetislav Brož
(Institute of Organic Chemistry and Biochemistry CAS, Czech Republic)
The C–F Bond Activation Used for Deuterium Labeling

11:50 am–12:10 pm
O-42
Dr. David Hesk (Merck Sharp & Dohme, USA)
Ni-Catalysed Hydrogen Isotope Exchange of Pharmaceuticals

12:10–1:40 pm
Majakovsky Hall
Lunch

Session 3: ***Synthesis and application of compounds labelled with medical radionuclides***
Social Hall

Chairman ***Dr. Ondřej Lebeda*** *(Institute of Nuclear Physics CAS, Czech Republic)*

10:50–11:10
O-43
Dr. Emmanuelle Dubost (Université de Caen Normandie, France)
Access to Radiotracers through Site-Selective Palladium-Catalysed C-H Radio-Iodination

11:10–11:30 am
O-44
Dr. Tatiana A. Udalova (NRC Kurchatov Institute, Russia)
^{99}Mo Recoil Atoms Yield in the Reaction of ^{100}Mo(p,np)^{99}Mo under Irradiation of Mo Nanofilms in Cyclotron

11:30–11:50 am
O-45
Dr. Sviatoslav D. Brinkevich
(N.N. Alexandrov National Cancer Centre of Belarus, Republic of Belarus)
Autoradiolytic Decomposition of 2-[^{18}F]Fluorodeoxyglucose

11:50 am–1:40 pm
Majakovsky Hall
Lunch

Plenary Lecture 9

Chairman ***Dr. Ondřej Lebeda*** *(Institute of Nuclear Physics CAS, Czech Republic)*

1:40–2:40 pm
Rais Hall
PL–9
Dr. Alfred Morgenstern
(Joint Research Centre of EC, Germany)
Targeted Alpha Therapy with 225-Actinium and 213-Bismuth

2:40–3:00 pm

CLOSING REMARKS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Abstracts of presentations

Plenary Lectures

PL–1

NEW INSIGHTS IN CATALYSIS

Erick M. Carreira

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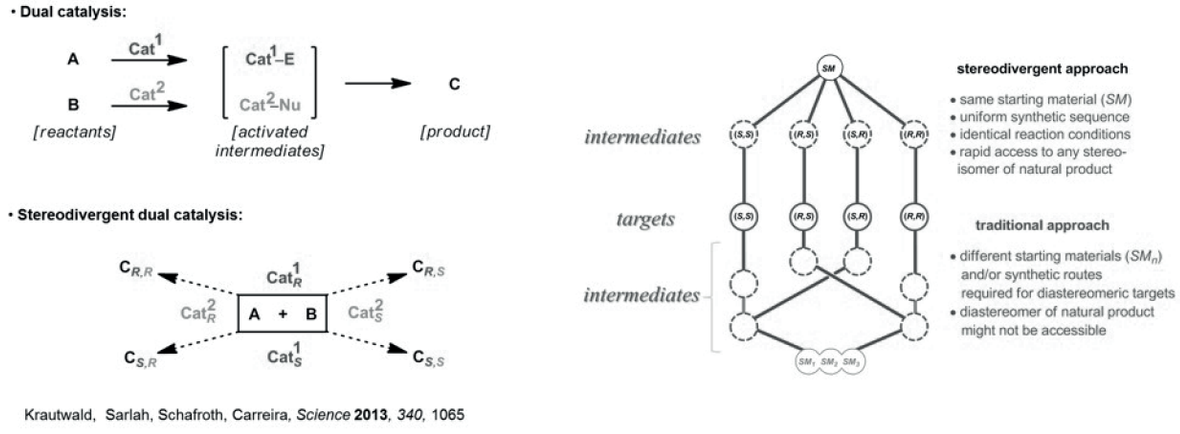
E-mail: carreira@org.chem.ethz.ch

The ability to readily access small-molecule building blocks at will has important consequences for the discovery and development of novel medicines and materials. It is particularly beneficial when the chemical methods are convenient while at the same time economically and environmentally tenable and sustainable. A focus of our research program at ETH-Zürich is the identification, study, and development of novel reactions and methods for preparation of functionalized structures. We are especially interested in catalytic processes that are easily executed and utilize readily available starting materials. We will discuss several new reaction processes that provide ready access to a host of fundamentally versatile building blocks for synthesis. The presentation will focus in part on the unique reactivity of Ir-complexes with a novel phosphoramidite-olefin ligand. We have found that these can activate allylic alcohols towards a wide range of direct displacement reactions, giving rise to optically active products; this has led to the development of fully stereo divergent processes. We will discuss the concept of stereodivergency and implications in drug discovery and manufacturing



Krautwald, Sarlah, Schafroth, Carreira, *Science* **2013**, *340*, 1065

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(1) S. L. Rössler, S. Krautwald, and E. M. Carreira *J. Am. Chem. Soc*. **2017**, *139*, 3603.
(2) T. Sandmeier, S. Krautwald *Angew. Chem. Int. Ed*. **2017**, *56*, 11515.
(3) D. A. Petrone, M. Isomura, I. Franzoni, S. L. Rössler, and E. M. Carreira *J. Am. Chem. Soc*. **2017**, *140*, 4697.
(4) S. Krautwald, D. Sarlah, M. A. Schafroth, and E. M. Carreira *Science* **2013**, *340*, 1065

PL–2

PRESENT AND FUTURE: WHAT CAN WE EXPECT FROM NEXT GENERATION AMS SYSTEMS

Hans-Arno Synal

Laboratory of Ion Beam Physics, ETH Zurich, Building HPK, Otto-Stern-Weg 5, 8093 Zurich, Switzerland
E-mail: synal@phys.ethz.ch

The technical evolution of Accelerator Mass Spectrometry (AMS) instrumentation over the last ten years is summarized. AMS is the most sensitive isotope selective detection method, capable of measuring, in specific cases, isotopic ratios of long-lived radionuclides as low as $1:10^{16}$. At present, ^{14}C is still the by far most important AMS nuclide but there is a great potential for applications of ^{10}Be, ^{26}Al, ^{36}Cl, ^{41}Ca, ^{129}I, and actinides measurements. A key characteristic of any AMS system is the destruction of molecular interferences and subsequent analyses of atomic ions. In the original designs of AMS instruments, highly charged ions (charge state 3+ or higher) were used for which no stable molecular exist. However, fairly high ion energies, and as a consequence, large accelerators are required to reach a sufficient yield of such ion species. Today, 1+ charge state is primarily used in case of ^{14}C detection, molecular interferences are destroyed in multiple collisions with stripper gas atoms or molecules, and a high yield of atomic ions is reached at energies of a few hundred keV, only. Thus, AMS instruments develop towards lab size or tabletop devices. The use of He as stripper gas has improved performance with respect to overall detection efficiency and reproducibility of measurement conditions. In parallel, implementation of permanent magnets into dedicated ^{14}C AMS systems has been progressed. This reduces complexity of the instruments and significantly reduces operation and installation costs.
He stripping has the potential to down size instruments for measurements of other radionuclides, too. For the $^{10}Be/^{10}B$ pair, a significant isobar separation capability can be achieved already at particle energies of less than 1 MeV, by using passive absorber techniques and exploiting the quite large difference in energy loss of these isobar. Apart from this, only nuclides that are not interfered by nuclear isobars can be detected with such compact instruments. Modern simulation technique allows to optimize their designs and replace traditional accelerator technology by high-voltage platforms driven by commercial HV power supplies. These developments have launched the wide spread use of AMS in various research fields and has resulted in a boom of new AMS facilities which impact the wide variety of applications of AMS in modern research.

PL–3

New Photoredox Reactions

David W. C. MacMillan

Merck Center for Catalysis
Princeton University
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Email: dmacmill@princeton.edu

Abstract. This lecture will discuss the advent and development of new concepts in chemical synthesis, specifically the application of visible light photoredox catalysis to the discovery or invention of new chemical transformations. This lecture will explore a strategy the discovery of chemical reactions using photoredox catalysis. Moreover, we will further describe how mechanistic understanding of these discovered processes has led to the design of new yet fundamental chemical transformations that we hope will be broadly adopted. In particular, a new catalysis activation mode that allows for the development of C–H abstraction and decarboxylative coupling reactions that interface with organometallic catalysis.

PL–4

USE OF ISOTOPES IN DRUG DESIGN AND MECHANISTIC DRUG DISPOSITION

David C. Evans

Janssen Research & Development, Johnson & Johnson,
1400 McKean Road, Spring House, PA 19477, USA

Dosing radiolabeled drug candidates to preclinical species and humans still represents the most expedient way of determining clearance mechanisms and quantifying drug-related material in plasma and excreta. When integrated with a range of mechanistic drug disposition studies performed in vitro, information so gained contributes to our understanding of potential for inter-patient variability and drug-drug interactions. Thoughtful discussions regarding the location of the isotope in a drug candidate remains important and largely depends upon the question at hand. Recent uses of deuterium to probe the kinetic isotope mediated impact on drug clearance provides insight into species differences in toxicity as well as in the design of next generation drug assets. In addition, radiolabeling drug candidates to understand their potential to label proteins and form immunogenic haptens can represent a component part of a weight of evidence approach to assessing potential for drug induced organ toxicity. Importantly, when this is encountered, having a mechanistic understanding of the metabolic activation event, which can often involve a novel biotransformation, is a prerequisite to providing a structure-based rationale for next generation drug design. Through these examples, I will convey why the appropriate use of isotopically labeled drug candidates remains an important part of the tool box for the contemporary drug metabolism scientist along with my implicit advocacy for their continued use in our discipline.

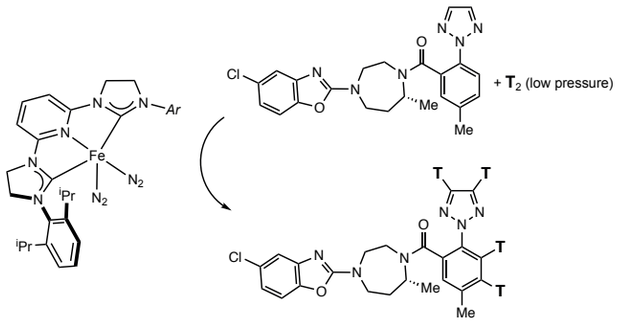
PL–5

IRON, COBALT AND NICKEL CATALYSTS FOR HYDROGEN ISOTOPE EXCHANGE

Paul J. Chirik

Department of Chemistry, Princeton University, Princeton, New Jersey, 08544 U.S.A.
pchirik@princeton.edu

Soluble, single site transition metal catalysts are attractive for the selective activation of carbon-hydrogen bonds. Coupling the C-H activation process with exchange of hydrogen isotopes, deuterium or tritium, finds application in the (radio)labeling of active pharmaceutical ingredients and is an important component of the drug registration and assay process. Precious metal catalysts, such as Crabtree and Kerr's iridium complexes are known to activate C(sp^2)-H bonds in arenes and heteroarenes. The selectivity in these reactions is often determined by directing groups – functionality that interacts with the transition metal and dictates the site of exchange. The unique redox properties of earth-abundant metals such as iron, cobalt and nickel present new opportunities for selective HIE in active pharmaceutical ingredients. We recently reported an iron dinitrogen complex, ($^{iPr}H_4$-CNC)Fe(N_2)$_2$ that offers complementary selectivity for HIE in a host of APIs [1]. The catalyst offers predictable sterically driven site selectivity and ignores directing groups typically used in iridium catalysis. Subsequent efforts have focused on understanding the mechanism of operation of this catalyst [2] as well as developing next generation technology to improve site selectivity and catalyst handling. Cobalt complexes have been discovered that alter selectivity to C(sp^3)-H sites and its stereospecific [3]. More recent efforts have been devoted to the development of air stable nickel catalysts and have offered unprecedented levels of activity and unique sites of HIE.



Other first row metals - unique activity and selectivity?

References

[1] Yu, R. P.; Hesk, D.; Rivera, N.; Pelczer, I.; Chirik, P. J. *Nature* **2016**, *529*, 195-199.
[2] Yu, R.P.; Darmon, J. M.; Semproni, S. P.; Turner, Z. R.; Chirik, P. J. *Organometallics* **2017**, *36*, 4341-4343.
[3] Palmer, W. N.; Chirik, P. J. *ACS Catal.* **2017**, *7*, 5674-5678.

PL–6

STABLE ISOTOPES IN LUNG INFECTIOUS DISEASES: IMPROVED DRUGS AND BREATH TEST DIAGNOSTICS

Graham S. Timmins [a,b]

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[b] *SpinCeutica Inc., 2778 Agua Fria, Suite C-B, Santa Fe NM 87505 USA.*
gtimmins@salud.unm.edu

We have been developing a range of diagnostics/biomarkers and new drugs using stable isotope enrichment. In diagnostics, we have developed a range of rapid breath test diagnostics based upon unique microbial metabolism of labeled tracers to labeled gasses. The most developed molecule, inhaled ^{13}C-urea, has been tested clinically in diseases including cystic fibrosis colonization with *Pseudomonas aeruginosa*, tuberculosis and bacterial pneumonias by Avisa Pharma. In drugs, we have utilized a range of isotope effects to improve antimicrobial activity of known and approved compounds. Our most developed compound, is a labeled isoniazid (INH) compound [*acyl*-^{13}C]INH, [1,2] utilizes the magnetic isotope effect (MIE) to increase the yield of the active metabolite, the INH-NAD adduct. The MIE increases coupling of the {INH· NAD·} radical pair formed upon KatG during INH activation. The compound shows enhanced activity against tuberculosis (TB) both *in vitro* and *in vivo* and is also highly active against the resistant strain with S315T KatG mutation. As predicted by MIE theory, the activity of [*acyl*-^{13}C]INH is potentiated by magnetic fields of the same magnitude as the ^{13}C hyperfine coupling (14mT). Our other molecules use the more conventional approach, drug deuteration and the kinetic isotope effect (KIE), to make drugs that are more resistant to metabolism, and so enhanced antimicrobial effects.

References

[1] G.S. Timmins, V. Deretic. US Patent **2013, #**8,394,839

[2] G.S. Timmins, S.W. Choi. US Patent **2017,** #9,579,381

Disclosures

Dr Timmins is co-founder of the companies Avisa Pharma (developing breath test technologies) and SpinCeutica (developing isotope enhanced antimicrobial drugs).

PL–7

The Development and Application of Two-Chamber Reactors for Isotope-Labeling

Troels Skrydstrup

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Gustav Wieds Vej 14, 8000 Aarhus C, Denmark
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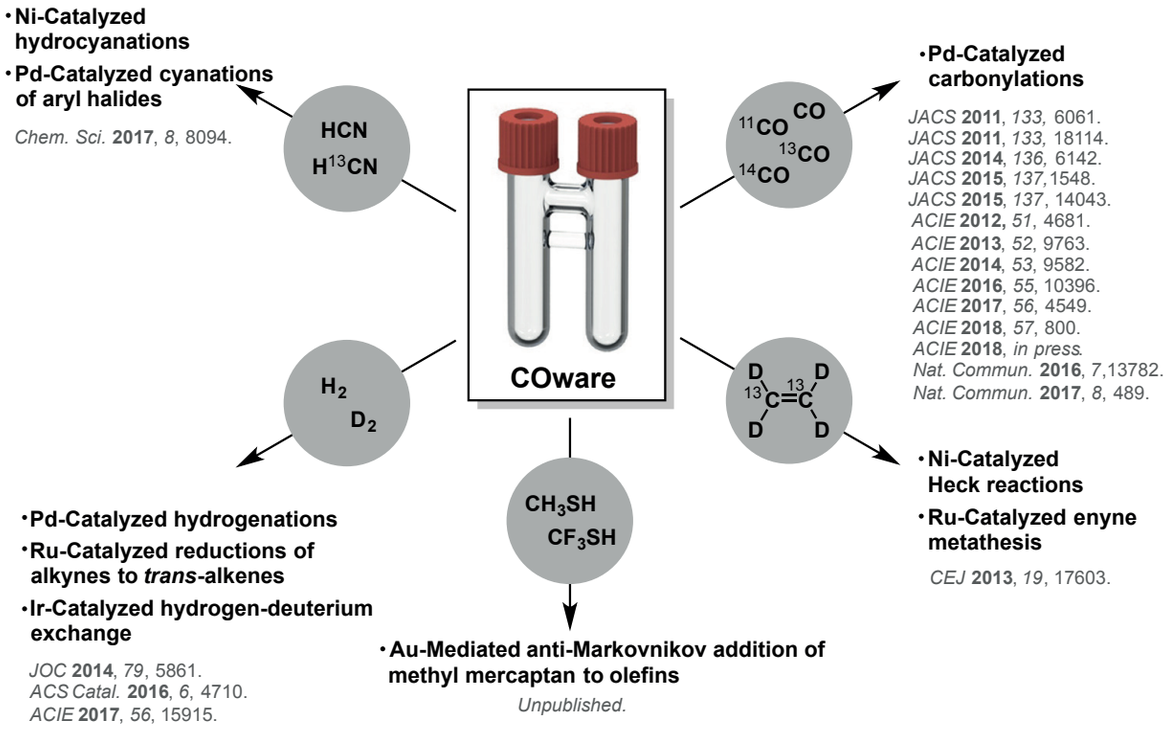
Carbon monoxide (CO) represents an important C1-building block for the construction of some of the most fundamental chemical functionalities carrying a carbon-oxygen double bond. Transition metal catalysis plays a key role in promoting such transformations. We have earlier shown that the combination of palladium catalysis with CO releasing molecules and our two-chamber reactor, COware®, provides a convenient and safe means for performing traditional Pd-catalyzed carbonylative couplings, but is also a platform for the discovery of new carbonylation transformations. Furthermore, the method can readily be adapted to ^{13}C- and ^{14}C-isotope labellng, and provides a suitable setting for developing efficient carbonylation reactions with ^{11}CO. In this talk, I will present a summary of our work, and also discuss our efforts to identify viable Ni-catalyzed carbonylations with aliphatic substrates, which can be performed efficiently under low CO partial pressures. Furthermore, I will present ongoing work with other small molecular weight gases, including carbon dioxide, hydrogen cyanide, ethylene and hydrogen.



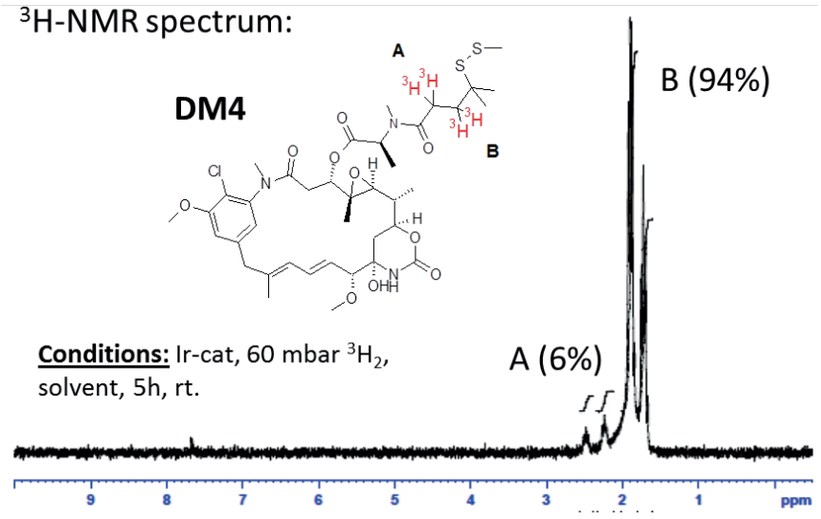
PL–8-1

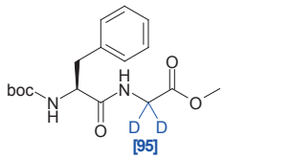
IRIDIUM-CATALYZED HYDROGEN ISOTOPE EXCHANGE (HIE) METHOD OF ALIPHATIC SP^3-CENTERS IN UNACTIVATED AMIDES

Mégane Valero[#], Remo Weck, Stefan Guessregen, Jens Atzrodt and Volker Derdau

Sanofi-Aventis Deutschland GmbH, R&D, Integrated Drug Discovery, Industriepark Höchst, 65926 Frankfurt, E-mail: Megane.Valero@Sanofi.com

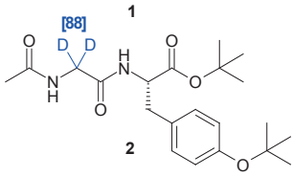
Hydrogen isotope exchange (HIE) allows the direct substitution of hydrogen by its isotopes (deuterium and tritium) at the target molecule itself and thus circumvents the need for additional chemical synthesis steps (e.g. precursor synthesis or a stepwise preparation from isotopically enriched starting materials). While direct HIE reactions on aromatic compounds have been heavily studied there is still a lack of useful protocols for selective aliphatic sp^3-labelling.[1,2] This is especially important for drug compounds lacking a reactive aromatic moiety. We present our results of ^{2}H/^{3}H-labelling of DM4, a cytotoxic drug presently being developed in antibody-drug conjugates (ADCs). Using the newly developed protocol a reaction sequence of five radioactive steps could be substituted with a single HIE reaction.





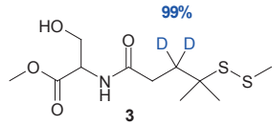
(L) Boc-Phe-Gly-OMe

1



2

(L)-Ac-Gly-Tyr(OtBu)-OtBu



3

We have discovered that this method can be applied much more broadly, and we have investigated its effectiveness on aliphatic amides like peptides, conjugates and drug precursors. To our great delight we found good deuterium incorporation and regioselectivities especially for glycine derivatives (**1, 2**) and linker side chains of type **3**. We are convinced this method will increase the possibilities for isotope chemists to label more complex aliphatic molecules in the future.

1. J. Atzrodt, V. Derdau, M. Reid, W. J. Kerr, *Angew. Chem. Int. Ed.* **2018**, doi: 10.1002/anie.201708903.
2. J. Atzrodt, V. Derdau, M. Reid, W. J. Kerr, *Angew. Chem. Int. Ed.* **2018**, 57(7), 1758-1784.

The ISOTOPICS project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement N°675071

PL–8-2

CARBON ISOTOPIC EXCHANGE FOR THE LABELLING OF CARBOXYLIC ACIDS.

Gianluca Destro,[1] Frederic Taran,[1] Thibault Cantat,[2] Davide Audisio[1]

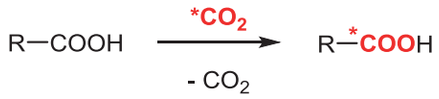
[1] SCBM, CEA, Université Paris-Saclay, CEA Saclay 91191 Gif-sur-Yvette, France
[2] NIMBE, CEA, CNRS, Université Paris-Saclay, CEA Saclay 91191 Gif-sur-Yvette, France
E-mail : gianluca.destro@cea.fr, Frederic.TARAN@cea.fr, thibault.cantat@cea.fr, davide.audisio@cea.fr,

Late stage isotope radiolabeling is a relevant topic both from a fundament research perspective and for health applications in academy and pharmaceutical and agrochemical industries. In this context, carbon-14 plays a basic role in drug development and ADME and toxicological studies.[1]

Traditional synthesis with radiocarbon, based on lengthy and multistep approaches, have hampered the sustainable development of such a strategy.[2] In addition, the price of carbon-14 building blocks and the disposal of long lived radioactive wastes ($T_{1/2}$ 5730 years) are nowadays major limitations to the use of this privileged isotope.

Isotope exchange is an intriguing powerful concept, routinely utilized in hydrogen\deuterium and hydrogen\tritium exchange for late stage labelling of active compounds; however, to the best of our knowledge, it is unprecedented in the field of carbon labeling.

We report the first carbon isotope exchange using $^{13}CO_2$ and $^{14}CO_2$, a fundamental and readily available source of radiocarbon. This new process expands the concept of late stage radiolabeling to carbon with substrates bearing carboxylic acid moiety.[3]



References

[1] a) N. Penner, L. Xu, C. Prakash *Chem. Res. Toxicol*. **2012**, *25*, 513−531; b) E. M. Isin, C. S. Elmore, G. N. Nilsson, R. A. Thompson, L. Weidolf, *Chem. Res. Toxicol*. **2012**, *25*, 532−542.
[2] R. Voges, J. R. Heys, T. Moenius, in "Preparation of Compounds Labeled with Tritium and Carbon-14", John Wiley & Sons, Ltd, **2009**, 393.
[3] G. Destro, T. Cantat, D. Audisio, *European patent to be filed*, **2018**

PL–8-3

IRIDIUM-CATALYSED HYDROGEN ISOTOPE EXCHANGE OF AMINO ACID AND PEPTIDE MOLECULES

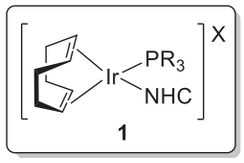
William Kerr,[a] David Lindsay, [a] Adele Queen,[a] David Hesk,[b] Colin Lam[b] and Ed Sherer[b]

[a]University of Strathclyde, Department of Pure and Applied Chemistry, Glasgow UK.

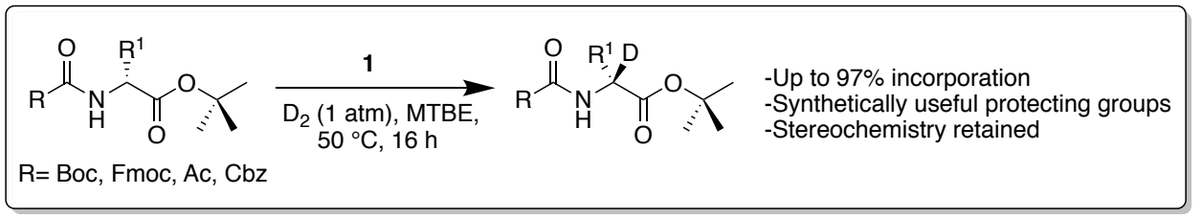
[b]Merck Research labs, 126 E. Lincoln Avenue, Rahway NJ 07065, USA.

w.kerr@strath.ac.uk

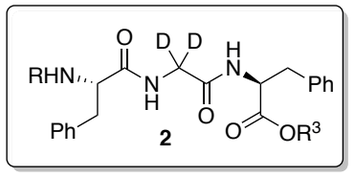
The persistence of high attrition rates within the drug discovery process has driven an increasing need for early metabolism studies to enable assessment of the properties of drug candidates. In this area, isotopic labelling *via* hydrogen isotope exchange (HIE) has played a central role; with additional uses in both mechanistic studies and labelled drug candidates.[1] Previous work within our laboratory has resulted in the development of a range of novel iridium(I)-based catalysts of type **1**, combining sterically encumbered *N*-heterocyclic carbene and phosphine ligands, to facilitate aryl HIE directed by a broad range of functional groups.[2-3] Although isotopically labelled aromatics are accessed effectively in metabolism studies, the emergence of peptidic drugs as therapeutics comes a requirement for isotopically labelled peptides and amino acids, however, this area remains relatively unstudied.[4]



Thus, we have initiated studies aimed at HIE of amino acids and peptides. Under our developed conditions, simple amino acids, bearing common protecting groups, are labelled with low catalyst loading. Further, mild reaction conditions enable retention of stereochemistry at extremely challenging tertiary centres.



Extension of our methodology has enabled the labelling of tripeptides such as **2**. Chemo-selective deuteration at the glycine residue through judicious choice of conditions offers the opportunity to selectively target specific residues within larger peptide molecules. The development of this practically convenient HIE process allows chemists access to novel, labelled peptide and amino acid compounds, which were previously challenging to access.



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PL–8-4

CO_2 FIXATION FOR LATE STAGE LABELING OF DRUG CANDIDATES

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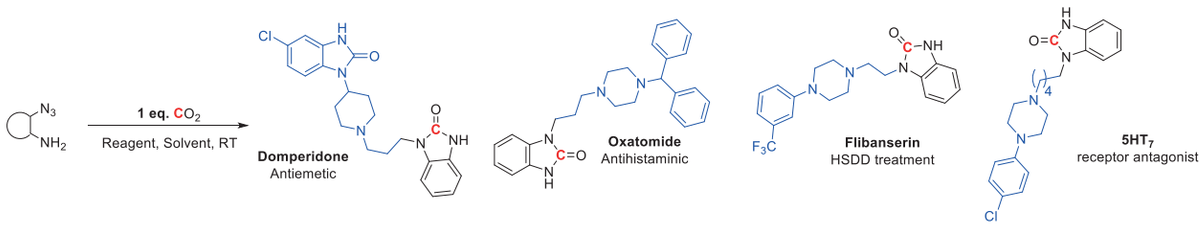
Carbon radiolabeling represents a milestone for the development of chemicals and agrochemicals in academic and industrial environments. In particular carbon-14 has no equal in ADME and toxicological studies [1], while carbon-11 is traditionally employed for imaging studies in humans and primates [2].

Heterocycles are a key framework in organic and medicinal chemistry. The importance of their synthesis is remarkable also in radiochemistry, where the need of a fast and efficient incorporation of the radioisotope is often required for new drugs or tracers. From a practical point of view, carbon-14 labeling is hampered by multistep procedures, with the subsequent production of expensive and polluting radioactive wastes. On the other hand, carbon-11, a short half-life isotope ($T_{1/2}$ 20.3 minutes), is produced in limited amounts and necessitates fast and efficient reactions for its valorization in a radio-synthetic process [3]. In order to overcome such limitations, we developed a Staudinger aza-Wittig cascade reaction using stoichiometric amounts of readily available [^{14}C]-CO_2, that allows a rapid and straightforward realization of different radio-labeled heterocycles, minimizing the generation of radioactive waste.

The methodology was successfully applied to the incorporation of both [^{14}C] and [^{11}C] isotopes into drug structures at the last stage of the synthesis, under very mild conditions and in good to excellent radiochemical yields [4].



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PL–9

TARGETED ALPHA THERAPY WITH 225-ACTINIUM AND 213-BISMUTH

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Targeted alpha therapy (TAT) is a promising approach for treatment of cancer. The use of alpha emitters for cancer therapy has two distinct advantages over conventional therapies. The short range of alpha radiation in human tissue (< 0.1 mm) corresponding to only a few cell diameters allows selective killing of targeted cancer cells while sparing surrounding healthy tissue. At the same time, the high energy of alpha radiation of several MeV and its associated high linear energy transfer leads to highly effective cell kill. Consequently, alpha radiation can kill cells which otherwise exhibit resistance to treatment with beta- or gamma-irradiation or chemotherapeutic drugs, and can thus offer a therapeutic option for patients resistant to conventional therapies. Recent reports of the remarkable therapeutic efficacy of ^{225}Ac-PSMA617 for therapy of metastatic castration-resistant prostate cancer have underlined the clinical potential of targeted alpha therapy. This presentation describes the current clinical experience with ^{225}Ac and ^{213}Bi with particular focus on recent studies of targeted alpha therapy of bladder cancer, brain tumors, neuroendocrine tumors and prostate cancer and discusses the current situation for supply of the alpha emitters.

Parallel Sessions Abstracts

O–1

RADIOSYNTHESIS OF [^{14}C]DASOTRALINE FOR PRE-CLINICAL AND CLINICAL STUDIES

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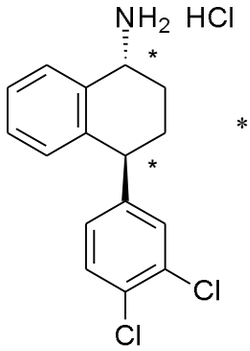

* denotes ^{14}C label
50:50 split across 1 & 4 positions

Dasotraline[1] [^{14}C]SEP-225289 is a novel inhibitor of dopamine and norepinephrine reuptake currently being investigated in clinical studies for the treatment of attention-deficit/hyperactivity disorder (ADHD). Uniquely, relative to current ADHD medications, dasotraline has a slow absorption and long elimination half-life.

[^{14}C]SEP-225289 was required for pre-clinical and clinical ADME[2] studies. This presentation will describe the route development, carbon-14 radiosynthesis from [^{14}C]succinic anhydride, stability study and GMP [^{14}C]drug substance manufacture of [^{14}C]SEP-225289.

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O–2

BRINGING UNDERSTANDING TO LARGE MOLECULE RADIOLABELING INCLUDING BIOLOGICS

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Due to the fact that radioactivity can offer the quantitative analysis of all drug-related substances in the complex systems of animals or human, radiolabeling remains the gold standard for ADME (absorption, distribution, metabolism, and excretion) studies during drug discovery and development stages although analysis technologies have been improved tremendously over last 20 years.

Despite advances in the development of biologics such as recombinant proteins, monoclonal antibodies, and oligonucleotides, the lack of appropriate tools to study pharmacokinetic profiles has resulted in a relatively high failure rate at the development of biologics. Attempts to overcome this hurdle have been made using a radiolabeling method, however technical difficulties in radiolabeling of large molecules compared to that of small molecules mainly arising from the difference in the molecular weight and the physicochemical property have been a bottleneck to become a gold standard for ADME studies during the biologics development. Years experience of large molecule radiolabeling in Curachem brought us understanding and generalized picture of radiolabeing methods in large molecules. Herein, key features of radiolabeling in large molecules including polyethylene glycol, polysaccharides, oligonucleotides, protein, and antibody will be presented.

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O–3

SYNTHESIS OF [^{14}C]-LABELLED PEPTIDES

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The radiolabelling group at Almac has significant experience in the manufacture of peptides labelled with carbon-14. The synthesis of these molecules provides a number of challenges: the Almac approach will be demonstrated by means of two case studies, one involving the preparation of a ^{14}C-labelled biotinylated 84-mer (Figure 1) and the other a selective oxidative folding of a 16-mer peptide in order to generate two disulfide bridges (Figure 2).

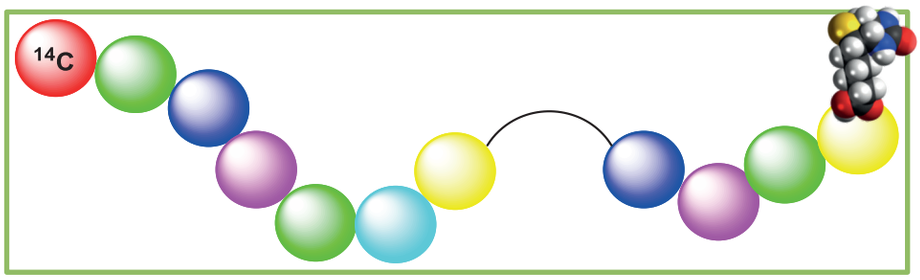

Figure 1. ^{14}C-labelled biotinylated 84-mer peptide

H-AA^{1}-AA^{2}-AA^{3}-Cys^{4}-AA^{5}-Leu(C^{14})^{6}-Cys^{7}-AA^{8}-AA^{9}-AA^{10}-AA^{11}-Cys^{12}-AA^{13}-AA^{14}-Cys^{15}-AA^{16}-OH

(AA= amino acid, disulfide bonds between Cys^{4} and Cys^{12}; Cys^{7} and Cys^{15})

Figure 2. Generic structure of 16mer peptide containing 2 disulfide bridges

O–4

Tracing terrestrial terpenes with isotopes

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The recent advances in genome sequencing have revealed a large number of terpene cyclases in bacteria,[1] fungi,[2] and eukaryotic microorgansism such as social amoebae.[3] Several of the encoded enzymes have been characterised during the past two decades by genome mining approaches. The terpene cyclase catalysed reactions frequently yield only one specific product with a high degree of stereocontrol. The complex mechanisms of terpene cyclisations can be addressed by quantum chemical calculations,[4] or experimentally by the use of isotopically labelled probes.

Among the uncharacterised enzymes, di- and sesterterpene cyclases are most interesting, because these enzymes usually make previously unknown compounds and their cyclisation mechanisms are generally more complex than those for mono- or sesquiterpene cyclases, as was impressively shown by the recent labelling studies on the fungal quiannulatene synthase[2c] and the bacterial cyclooctat-9-en-7-ol synthase.[1d] During the past few years my group has synthesised various isotopically labelled oligoprenyl diphosphates that can be used to efficiently unravel the cyclisation mechanisms of terpene cyclases.[5] Their application in mechanistic investigations on the most interesting newly discovered terpene cyclases will be discussed.

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O–5

COMPUTATIONALLY GUIDED RATIONAL LIGAND DESIGN FOR THE DEVELOPMENT OF HIGHLY ACTIVE IRIDIUM(I) COMPLEXES IN HYDROGEN ISOTOPE EXCHANGE PROCESSES

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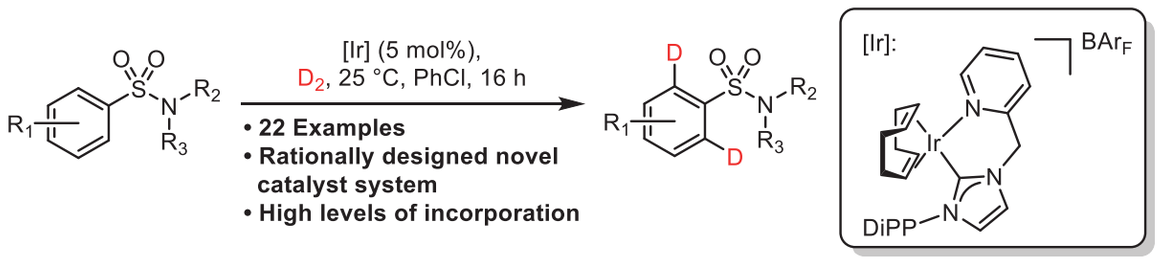
Drug molecules labelled with heavy isotopes have become indispensable throughout drug discovery. The installation of isotopic labels has been the focus of a significant body of research, particularly in recent years. [1] One such method of installing heavy isotopes into a molecule is directed hydrogen isotope exchange (HIE), wherein a functional group within the molecule is exploited to direct the activation of a C—H bond, and subsequent incorporation of a deuterium or tritium isotope. Notably, Iridium complexes have found widespread utility in this area. [2]



Through our understanding of the iridium complexes used in HIE, we aimed to develop a catalyst that can further improve upon the installation of heavy isotopes into substrates containing highly substituted sulfonamides. [3] Indeed, the use of DFT calculations has allowed computationally derived parameters to guide the design of a novel catalyst system, which has delivered excellent levels of isotope incorporations into sulfonamide substrates.

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O–6

MICROALGAE GROWN IN STABLE ISOTOPES

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Stable isotopes, the non-radioactive variants of elements with the same number of protons but with a varying number of neutrons, have been widely used for metabolic labeling to study metabolic fluxes as well as for quantitative proteomics. Deuterium, the heavy stable isotope of hydrogen, has strong isotopic effects and at high levels causes major defects in cell physiology. The borderline for its safe incorporation into plant and animal cells is 20 %. Yet some green algae are able to incorporate 100 % deuterium into their cells and are still able to grow and divide. It is not clear what mechanisms enable cells to tolerate high levels deuteration. Here, we study the effect of growth in deuterated water, D_2O, on two green algae, *Parachlorella kessleri* and *Chlamydomonas reinhardtii*. Of the two, *P. kessleri* is more resistant and can grow up to the 99% incorporated deuterium. In contrast, *C. reinhardtii* can only grow and divide until the ratio of D_2O/H_2O reaches 0.70, but can be acclimated to growth even to higher ratios. We compare *in situ* incorporation of deuterium into different biological molecules in the two microalgae by Raman microscopy. Furthermore, we performed a mutagenesis screen and isolated mutants allowing growth of *C. reinhardtii* to higher D_2O/H_2O ratios. The mutant identification is under way.

This work was supported by the GA CR (grant no. 17-06264S).

O–7

^{34}S: A NEW OPPORTUNITY FOR THE EFFICIENT SYNTHESIS OF STABLE ISOTOPE LABELED COMPOUNDS

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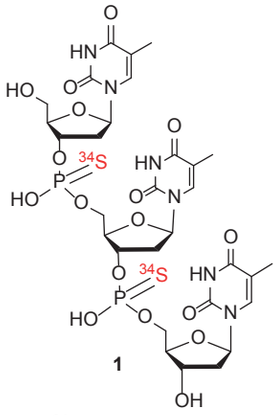
The synthesis of stable isotope labeled (SIL) complex drug molecules with ≥3 mass unit increase from the parent compound is essential for drug discovery and development. Typical approaches that rely on ^{2}H, ^{13}C, and ^{15}N isotopes can be very challenging or even intractable, and can delay the drug development process. Herein, we introduce a new concept for the synthesis of labeled compounds which relies on the use of ^{34}S. We demonstrated the synthetic utility of ^{34}S with the efficient synthesis of [^{34}S]phosphorothioates [$^{34}S_2$]-PS-ODNs-TTT and [^{13}C, ^{15}N, ^{34}S]-Ceftolozane. In addition, a procedure for the direct oxidation of phosphites to [^{34}S]phosphorothioates using elemental ^{34}S without isotope dilution was developed.



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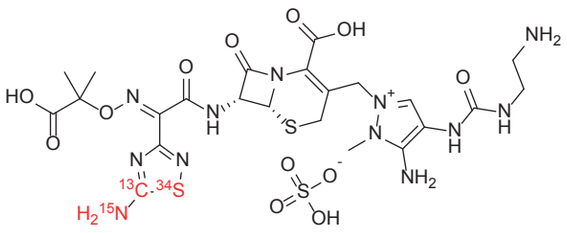
[$^{34}S_2$]-PS-ODNs-TTT



2

[^{13}C, ^{15}N, ^{34}S]Ceftolozane

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O–8

SYNTHESIS OF ISOTOPE-LABELED 1‑BUTYL-3-CHLORO-4-(4-PHENYL-1-PIPERIDINYL)-(1*H*)‑PYRIDONE (JNJ-40411813), A POSITIVE ALLOSTERIC MODULATOR OF THE METABOTROPIC GLUTAMATE 2 RECEPTOR, AND ITS METABOLITES

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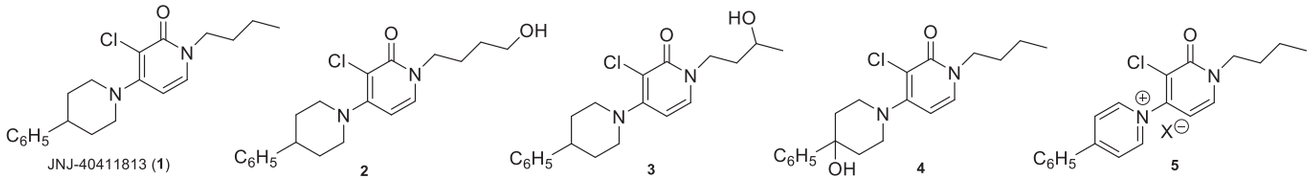
The metabotropic glutamate 2 receptor (mGlu2) represents a novel target for the treatment of CNS disorders, such as schizophrenia, anxious depression, and epilepsy. JNJ-40411813 (ADX71149), *i.e.* 1‑butyl-3-chloro-4-(4-phenyl-1-piperidinyl)-(1*H*)‑pyridone (**1**), was discovered as a novel positive allosteric modulator of the mGlu2 receptor and was selected as a clinical candidate for development.[1-5] Assessment of the preclinical drug metabolism identified hydroxylated compounds (**2-4**) and the pyridinium compound (**5**) as metabolites.

Isotopically-labeled compounds play an important role in the evaluation of drug metabolism-pharmacokinetics and bioanalysis of parent drug molecules and their metabolites in drug research and development. Herein we report various approaches and strategies directed to the synthesis of isotope labeled JNJ-40411813 and its metabolites (**2-5**) in support of its development.



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SYNTHESIS OF DI-DOCOSAHEXAENOYL (C22:6)-BIS(MONOACYL-GLYCEROL) PHOSPHATE IN UNLABELED AND C-13 LABELED FORMS FOR USE AS A BIOMARKER OF DRUG-INDUCED PHOSPHOLIPIDOSIS.

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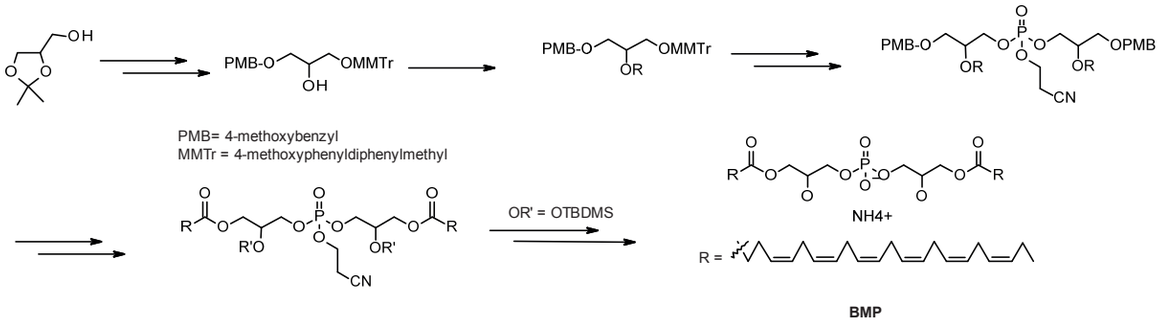
Di-docosahexaenoyl (C22:6)-bis(monoacylglycerol) phosphate (BMP) has been identified as a promising biomarker for drug-induced phospholipidosis (DIPL).[1] The compound is not commerically available and both unlabeled and stable isotope labeled versions of BMP were desired. Isopropylideneglycerol was converted to 4-methoxyphenyldiphenylmethyl-3-PMB-glycerol in three steps. The selection of protecting group of the 2-hydroxyl proved to be critical. Initially a diphenyl-t-butylsilyl protecting group was selected which proved difficult to remove without decomposition of the compound. The switch to a TBDMS protecting group resulted an intermediate that could be deprotected to the alcohol to give the target compound after salt exchange. The same procedure was used to prepare [$^{13}C_6$]BMP from [$^{13}C_3$]glycerol. All intermediate containing the docosahexaenoic side chain were unstable and required carefull manipulations. Administration of amiodarone (a compound known to induce DIPL[2]) has been demonstrated an increase the level of BMP in rat plasma supporting the potential of this compound to be used as a biomarker.



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O–10

DESIGNING SOFT MATERIALS WITH DESIRABLE PROPERTIES BY SELECTIVE DEUTERATION

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Abstract: Hydrogen has two stable isotopes, protium and deuterium. Selective incorporation of deuterium in place of protium in soft materials (organic compounds, polymeric materials) *for the most part* does not alter the physical and chemical properties of the compound, yet provides rich structural information using many characterization techniques, such as NMR, neutron scatterings. Accordingly, selective deuteration can provide a powerful approach to structural elucidation and chemical dynamics in soft materials. However, deuteration can sometimes introduce subtle changes in the properties of soft materials. In this presentation, we will discuss some examples of how selective deuteration can be used as a handle to tailor their properties of the targeted soft materials. We will also discuss using deuteration to design hydrogels with unique solution properties.

Acknowledgement: This research was conducted at the Center for Nanophase Materials Sciences, which is a DOE Office of Science User Facility.

O–11

STABLE ISOTOPE HYPERPOLARISATION IN METABOLITE STUDY AND DISEASE DIAGNOSIS: WHY DO IT? HOW IS IT DONE? WHAT IS IT GOOD FOR?

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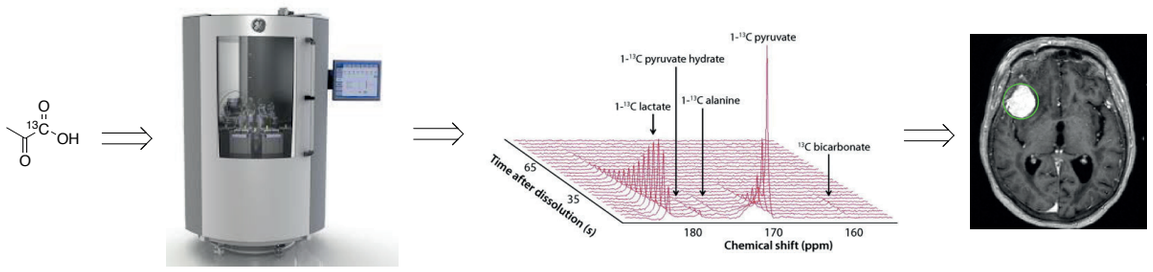

Magnetic resonance signals are relatively weak compared with other spectroscopic or imaging technologies such as acoustic, optical, emission, or transmission methods. Hyperpolarization is a novel technology that can dramatically increase signal to noise in magnetic resonance. The method is being applied to small injectable endogenous molecules, which can be used to monitor transient *in vivo* metabolic events, in real time.[1] The emergence of hyperpolarized ^{13}C-labeled probes, specifically ^{13}C pyruvate, has enabled monitoring and the ability to detect both precursors and downstream products of core cellular metabolic events.[2] Many more applications of this technology are envisaged with transformative potential in magnetic resonance imaging. This talk will highlight how hyperpolarization MRI has developed as a newly emerging technology, and how it has the potential to be transformative with significant benefits for patients. It will focus on what hyperpolarization is, how and which types of atoms/molecules are hyperpolarized and the advantages of hyperpolarization over, for example, PET techniques. Demonstrating application, we will discuss and focus on metabolite formation and the combined role of isotope labelled compounds and hyperpolarization for diagnosing disease, namely cancer.[3] It is hoped it will offer an overview and demonstrate the potential applications that may arise from harnessing the unique power of this technology.

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O–12

RADIOLABELED IGG ANTIBODIES – POTENTIAL IMPACT OF VARIOUS LABELS ON PHARMACOKINETICS

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Due to the fact that an increased number of complex antibodies like Fc-fusion, bispecific or multivalent formats are currently in pre-clinical and clinical development[1], there is a need for biodistribution studies with radiolabeled monoclonal antibodies in pre-clinical development. In parallel, the knowledge of antibody pharmacokinetics has been steadily gained. The neonatal Fc receptor (FcRn) plays a significant role in antibody turnover in endothelial cells (Figure 1), and thus it influences the systemic pharmacokinetics of immunoglobulin G (IgG).[2]

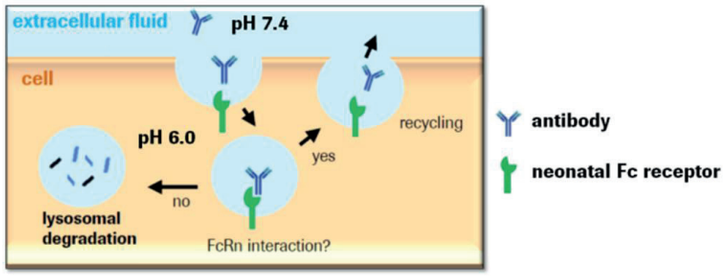

Figure 1: Schematic diagram of IgG - FcRn interaction.

Once antibodies are taken up into the endosome, they can be protected from degradation by binding to FcRn. This receptor binds antibodies in a strictly pH-dependent manner with high affinity at pH 6 in the endosome and negligible affinity at physiologic pH 7.4 in plasma.[3]

Radiolabeled antibodies which are used for *in vivo* imaging or biodistribution studies need a covalently bound label, e.g. a chelator complexed with a metallic radionuclide, radioactive iodine introduced by direct iodination on tyrosine/histidine or tritiated/iodinated small molecule conjugates on lysine or cysteine residues. The type of label can have an impact on FcRn binding which can lead to altered PK-properties compared to the unlabeled antibody. An FcRn affinity column was developed[4] and commercialized by Roche Diagnostics. This chromatography column allows the assessment of IgG samples with respect to their pH-dependent FcRn interaction. Therefore, this chromatography is regarded the most critical determinant in terms of disposition of IgG-based biotherapeutics. Due to shifts in retention time, the FcRn affinity chromatography can predict a higher antibody clearance after direct radioiodination or after conjugation with different chelator agents as well. Furthermore, increased conjugation ratio of chelator lowers the affinity to FcRn successively, and thus may impact the lysosomal degradation of the antibody in endothelial cells.

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O–13

^{14}C-POLYSTYRENE MICROSPHERES, DETECTED BY ACCELERATOR MASS-SPECTROMETER, FOR BIOMEDICAL AND AEROSOL STUDIES

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Reliable studies on the particle deposition in the respiratory tract and further particle translocation are of great value not only for risk assessment in the inhalation toxicology but also for improving the efficiency of drug delivery by inhalation therapies. But there is an important gap in health-particle matter (PM) investigations comprising low-dose exposures with organic aerosols. Polymeric monodisperse microspheres seem to be a perspective (or promising) model for aerosol investigations due to organic matter, nonbiodegradability, controllable size from several nm to several μm, possibility of surface modification by negative (-COOH) or positive (-NH_2) functional groups, as well as by designing core-shell structures with desirable chemistry. However ultra-small size, ultra-low concentrations and organic matter of the aerosol have made direct detection of particles inhaled under ambient conditions impossible to date. Due to strong analytical limitations the majority of PM health effect investigations are based on techniques that use intratracheal instillation instead of inhalation, and even when inhalation takes place PM concentrations are much greater 100 μg/m^3.

Accelerator mass spectrometry is firstly shown in this work to be applicable for studying the penetration of organic aerosols, inhaled by laboratory mice at ultra-low concentration [1]. We synthesized two series of polystyrene (PS) microspheres – 225 and 80 nm in size, prepared from ^{14}C-labeled styrene, for testing them as model organic aerosols. Styrene was synthesized from ^{14}C-methanol, ^{14}C-PS microspheres were obtained by emulsifier-free emulsion polymerization of ^{14}C-styrene initiated by $K_2S_2O_8$ in aqueous media. We have shown that particles 80 nm in size with a concentration of 10^4 pcs·cm^{-3} of inhaled air remained in the mice lungs for at least six months after exposure (data is not published yet).

This work was conducted within the framework of SB RAS program II.1 (project # AAAA-A17-117112870064-2)

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O–14

VISIBLE LIGHT ENABLED CARBONYLATION OF ALKYL IODIDES

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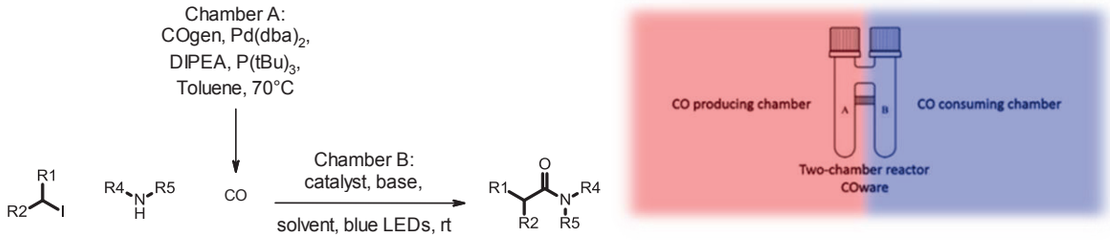
Palladium-catalyzed carbonylation is a standard method to incorporate labeled carbon monoxide (CO) into complex druglike molecules. In this reaction, aryl or vinyl halides are coupled with CO in the presence of an appropriate nucleophile to afford the corresponding carbonyl-labeled product.[1] The scope of this reaction was recently broadened to include alkyl halides as the electrophilic coupling partner for unlabeled CO using visible light.[2,3] Odell et al demonstrated that alkyl halides could be effectively carbonylated with $Pd(PPh_3)_4$ catalysis to generate ketones under low CO pressure (2-3 atm).[2]

While the methodology described by Odell et al is useful for the transformation of alkyl halides under "cold" conditions, using an excess of CO in radiochemical synthesis is not optimal. Using the procedure by Odell et al as a starting point, we have adapted the methodology to give moderate yields of carbonylated product with 1 equivalents of CO.



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O–15

SYNTHESES OF ^{14}C SYN388: AN INDAZOLE ANTHRANILIC DIAMIDE INSECTICIDE.

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The bisamide class of insecticides are activators of the ryanodin receptor (RyR) causing depletion of calcium stores. The anthranilic diamides show a high affinity for insect RyR receptors over those present in mammalian species, thus giving favorable toxicology profiles. This compound class has especially high activity against lepidopteran pests. Three separate ^{14}C labels were prepared to support environmental and metabolism studies required for product registration. The radiolabels were introduced using ^{14}C-cyanide, ^{14}C-barium carbonate and [2,3-$^{14}C_2$]-2,3-dichloropyridine. A unique iron reduction facilitated the formation of the aminoindazole carboxylic acid. An unusual coupling was used to prepare the bisamide linkage.

O–16

SYNTHESIS OF ^{14}C-LABELLED SULFONYLUREA TYPE PESTICIDES

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Sulfonylureas are widely used in medicine as antidiabetic drugs, as well as in agriculture as herbicides. With numerous compounds sulfonylureas are very popular among other pesticides.
Knowing the exact labeling position is a crucial part of the ADME (absorption, distribution, metabolism, excretion) studies. The synthetic methods start from $Ba^{14}CO_3$ or ^{14}C-labelled intermediates. After synthetizing the ^{14}C-labelled building blocks, the formation of sulfonylurea functional group by miscellaneous coupling methods is a key step.

The various synthesis routes of some ^{14}C-labelled sulfonylurea type herbicides (Tribenuron-methyl, Iodosulfuron-methyl, Metsulfuron-methyl, Oxasulfuron, Bensulfuron-methyl, Mesosulfuron-methyl, Nicosulfuron) will be presented.

O–17

Combining Isotopes, Synthesis and Synthetic Biology

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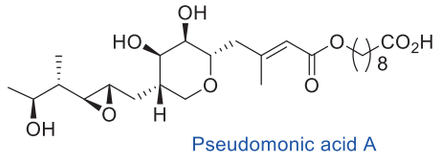
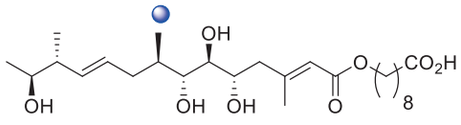
Polyketide-derived natural products isolated from bacteria exhibit a range of important biological activities making them attractive leads for the development of therapeutics and agrochemicals. They are assembled in the host organism *via* sophisticated multiple enzyme architectures – polyketide synthases. Our overall aim is to fully understand how polyketides are produced and thus enable rational engineering of the complex biosynthetic machinery to deliver novel antibiotics cleanly and efficiently in scalable amounts.

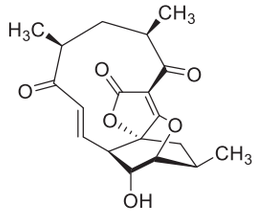
This lecture will focus on the use of organic synthesis, isotopic labelling and engineering biosynthetic pathways for the generation of libraries of biologically active targets and new biocatalysts of potential widespread value. Examples will be taken from our recent work on natural products isolated from both marine and terrestrial organisms such as mupirocin (a mixture of pseudomonic acids), the thiomarinols and abyssomicin C.



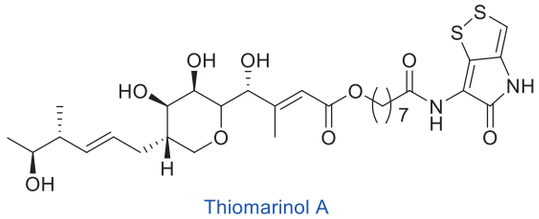
Pseudomonic acid A



[^{13}C]-Desepoxymupirocin W



Abyssomicin C



Thiomarinol A

These collaborative programmes are with scientists at the University of Bristol (Chemistry and Biochemistry) as well as the Universities of Birmingham and Newcastle.

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O–18

LASER BASED RADIOCARBON DETECTION IN THE LABORATORY; HOW SOON?

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Research over the past 25 years coupled with the use of Accelerator Mass Spectrometry (AMS) has demonstrated the benefits of single atom counting of ^{14}C compared to scintillation monitoring of ^{14}C radioactive decay for a multitude of applications in drug development studies. These include pharmacokinetics and metabolism studies, micro-dosing studies and quantification of DNA adducts among others. In the last decade, however, the possibility of single atom counting using lasers has been demonstrated, providing the possibility of simplified laboratory based systems which can equal or excel AMS sensitivity and provide scintillation system convenience without high levels of radioactivity[1,2,3]. To achieve the required sensitivity, optical storage cavities have been used to enhance the laser interaction to the low densities of radiocarbon under investigation. Two types of laser technologies have been used- cavity ring-down spectroscopy (CRDS) and intra-cavity opto-galvanic spectroscopy (ICOGS). Problems to be overcome to achieve routine use have included separation of the ^{14}C signal from ^{12}C and ^{13}C backgrounds, ruggedization of systems to achieve acceptable precision and accuracy, reduction of measurement times for small samples and improvement in the ease of use for the operator. Solutions to these problems have been based on improvements in laser design, electronic circuitry and data analysis. Both technologies have achieved impressive results to date using samples of order 10 mg with CRDS and 10 μg with ICOGS. Commercial development is the next step.

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O–19

IRIDIUM(I) COMPLEXES BEARING CHELATING NHC/PHOSPHINE LIGANDS: SYNTHESIS AND APPLICATION IN HIE PROCESSES

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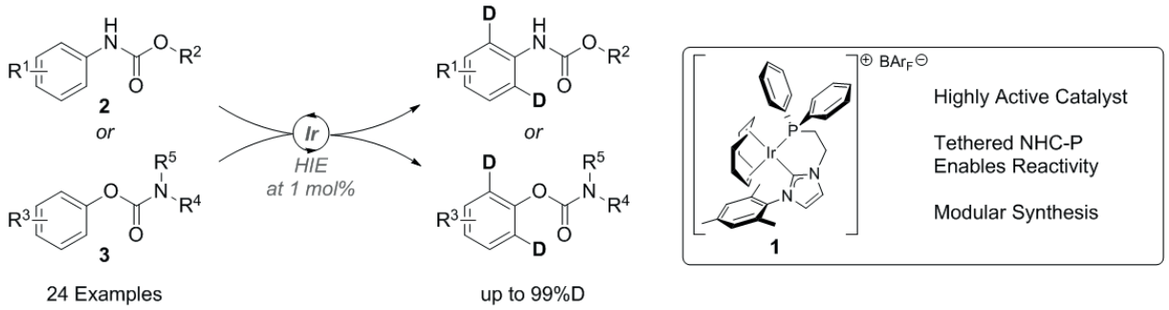
The continuing development of technologies that enable absorption, distribution, metabolism, excretion and toxicity (ADMET) studies to be performed in a timely and efficient fashion is a crucial factor in reducing the high attrition rates that hinder the drug discovery process.[1] In this context, hydrogen isotope exchange (HIE) has emerged as an efficient method to access isotopically enriched drug-like structures in late stage medicinal chemistry programmes. Iridium complexes are commonly employed in HIE[2] due to their catalytic activity and specificity for labelling sites adjacent to directing groups.[3] However, the poor performance of existing Ir complexes with sterically-hindered directing groups constitutes an important limitation. Herein we report a new class of Ir(I) complexes (**1**), bearing a chelating *N*-heterocyclic carbene-phosphine (NHC-P) ligand, and their application in the HIE of substrates with sterically demanding directing groups. Specifically, by conversion of anilines and phenols to their corresponding carbamates (**2** - **3**), high levels of incorporation were achieved with low catalyst loading under mild reaction conditions, establishing a new, successful strategy for HIE in these two important substrate classes. Additionally, the method's applicability to molecules of biological relevance was demonstrated by the efficient labelling of methyl salicylate and *L*-tyrosine. The mechanism of the reaction was also investigated, employing a combination of theoretical and experimental techiques, and an interesting interplay between substrate coordination and C-H activation as competing rate limiting steps was observed.



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O–20

RECOVERY OF HIGH SPECIFIC ACTIVITY $^{14}CO_2$ FROM C14 SYNTHESIS BY-PRODUCTS VIA OXIDATION AND ISOTOPIC ENRICHMENT

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The two reactors in the Ural region (Ozersk and Zarechny) which produce barium [^{14}C]carbonate have been operational since the 1950s and there are ecological problems in the areas around the reactor sites connected with radioactivity storage facilities and contamination of ground water. In 2011 a reduction in the supply of reactor-produced barium [^{14}C]carbonate from Russia which was accompanied by a significant price increase prompted us to undertake a general re-assessment of our C14 supply chain. Following the re-assessment exercise it was decided to begin a project to recover high specific activity $^{14}CO_2$ from the by-products of carbon-14 radiosynthesis.

The Pharmaron process brings together three established elements:

- Electrochemical oxidation to convert by-products of carbon-14 radiosynthesis cleanly to $^{14}CO_2$
- Reduction of $^{14}CO_2$ to $^{14}CH_4$
- Isotopic enrichment of $^{14}CH_4$ using Thermal Diffusion[1]

The presentation will give an overview of each of the above elements and will include descriptions of the process challenges we have found since initial commissioning and how they have been overcome.

Analytical data from batches of recovered, enriched $^{14}CO_2$ will be presented.

Options for the more general use of the Pharmaron process in carbon-14 waste recovery will be presented.

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O–21

PERFORMANCE CHARACTERISTICS OF WS-CAVITY RING DOWN LASER SPECTROSCOPY SYSTEM IN SUPPORT OF ^{14}C ADME STUDIES.

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Radiocarbon (^{14}C) is a near ideal tracer isotope for drug metabolism and distribution studies. This isotope brings high specificity (low natural background), stable, non-perturbing molecular inclusion, and an inherent means of quantitation when using decay counting (LSC/decay counting). Decay counting however for ^{14}C is limited by low efficiency; accordingly, relatively large quantities of radioactive "doses" must be administered for *in vivo* ADME studies. Conversely, Accelerator Mass Spectrometry brought several orders of magnitude improvement in sensitivity and speed by directly measuring atoms using high energy mass spectrometry relative. However, this "large and expensive" instrument was engineered for the difficult task of carbon dating and many current efforts are ongoing to simplify the platform. A technology that bridges the best of both platforms should be well received. Laser-based optical methods are poised to fill the measurement gap between AMS and LSC. Some experimental systems have already shown AMS sensitivity (SCARS[1], Optogalvanic effect[2]), while more rugged systems that present a balance between ease of use and sensitivity are closer to deployment[3]. One platform, Wavelength-scanned Cavity Ring-Down Spectroscopy (WS-CRDS)(developed at Picarro in collaboration with LLNL) builds open years of work with high precision mid and near IR lasers for quantification of isotopic signatures in small molecules with comparable precision to IR-MS (CRDS is not a new technology). An "alpha" phase instrument was set up at BioCore's AMS labs in Korea in 2017 for performance evaluation. As our lab had access to AMS and ^{14}C exposed biological samples (Animal tissue distribution, Human microtracer samples), a direct evaluation was possible between AMS and CRDS. Samples were measured over a large dynamic range from the natural ^{14}C background (1 Modern 98 amol/mg C) to ~16,000 Modern. Data on Accuracy and Precision of replicate measurements were within 5% for well mixed samples, with greater observed variance on difficult to homogenize tissue samples. In this talk will discuss the history, the theory, and application of CRDS to biomedical drug development and try to give the audience a clear picture of the current status of the technology. While we highlight data from a single instrument, several groups have systems under development. AMS and CRDS have greater importance than just being "better scintillation counters" and we expect CRDS to create greater demand for radiolabeled tool molecules in many areas of investigation.

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O–22

THE HUMAN ADME STUDY: PAST, PRESENT AND FUTURE

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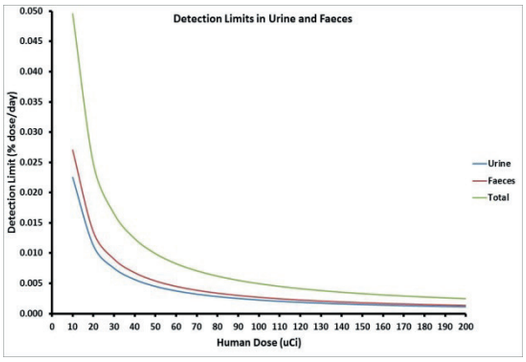
Mass balance studies using radiolabelled compounds in laboratory animals and man are an essential component of the drug development process. Current FDA [1] and ICH [2] guidelines addressing the safety of drug metabolites (commonly referred to as Metabolites in Safety Testing (MIST)) have placed the emphasis upon obtaining comparative human and animal metabolism data as early as possible in the development process. Although state-of-the-art LC/MS techniques are commonly employed for these studies, radiolabeled molecules are still preferred as they enable the quantification of metabolites and to assess the retention and excretion of all drug related material without relying on structural information and MS ionization properties.

The human ADME (hADME) study occupies a key position in the safety assessment. The accepted study design usually covers a range of objectives but the hADME study is essentially a metabolism study designed to investigate relative routes and rates of excretion, pharmacokinetics of drug related material in blood and plasma and to provide confirmation of the identity of major circulating metabolites.

In this talk the historical development, study design and data obtained from human mass balance studies will be reviewed and the advantages and disadvantages of using carbon-14 will be discussed.

Detection limits in the hADME study related to dose administered



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O–23

BIOTRANSFORMATION OF RADIO AND STABLE ISOTOPOLOGUES FOR STANDARD-FREE QUANTITATION OF DRUG METABOLITES

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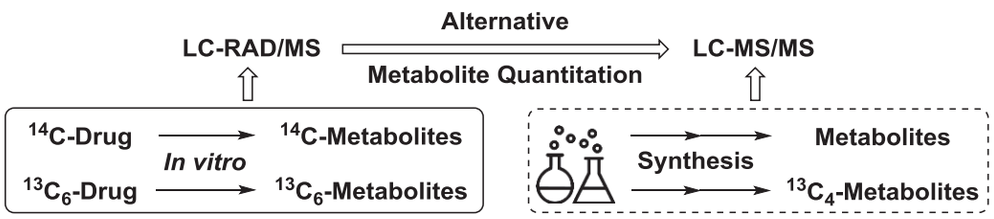
The conventional liquid chromatography-tandem mass spectrometry (LC-MS/MS) based metabolite quantitation approach[1] requires significant investment of time and resources in the synthesis of metabolite standards. This presentation describes a liquid chromatography coupled with radioactivity detection and mass spectrometry (LC-RAD/MS) method[2-3] that permits absolute quantitation of metabolites in biological samples without the requirement for reference metabolite standards.[4] This technique used radio- (e.g. ^{14}C) and stable- (e.g. $^{13}C_6$) isotopologues (RADIL and STIL) of a drug as substrates for *in vitro* biogeneration of the corresponding radio- and stable-isotope labeled metabolites. By supplanting the use of authentic metabolite standards, traditionally used to calibrate STIL metabolites via LC-MS/MS, STIL metabolites were radiocalibrated by radio quantified RADIL metabolites via LC-RAD/MS. The radiocalibrated STIL metabolites were in turn used to quantitate corresponding metabolites in rat plasma samples. The quantitation results were comparable to those from a valid LC-MS/MS method using authentic standards for calibration. Since authentic metabolite standards are not required under this new protocol, significantly fewer resources can be expected to support accurate metabolite quantitation in preclinical and clinical applications.



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O–24

AN OPEN LABEL, SINGLE DOSE STUDY TO ASSESS THE EXCRETION AND METABOLISM OF [^{14}C]-APD421 ADMINISTERED VIA THE INTRAVENOUS ROUTE TO HEALTHY MALE SUBJECTS

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Amisulpride is an established, atypical anti-psychotic for oral use. It selectively binds to dopaminergic D2 and D3 receptor subtypes and acts as a dopamine antagonist. APD421 is an intravenous (IV) formulation of amisulpride being developed for the prevention and treatment of nausea and vomiting, both in surgical patients and in patients receiving emetogenic cancer chemotherapy. The aim of the current study was to further understand the elimination pathways, metabolite profile and pharmacokinetic profile of APD421 after administration of [^{14}C]-APD421 to 6 healthy male subjects aged 18-65 years. All subjects received a [^{14}C]-APD421 solution (2.5 mg/mL) containing 1.784 MBq of ^{14}C (expected radiation burden 0.04 mSv) per 10 mg dose, administered as a single IV infusion over 4 minutes. Subjects were hospitalized in the clinical unit for at least 96 h after dosing; if needed, based on discharge criteria, hospitalization could be prolonged for another maximum 72 h. Drug product was manufactured on-site, under GMP, by dissolving unlabeled APD421 and [^{14}C]-APD421 (manufactured by Moravek Inc., USA) in water, followed by sterile filtration. APD421 parent drug analysis was conducted at LGC Ltd, UK; metabolism research was done by Sekisui XenoTech, Kansas City, USA; analysis of ^{14}C-radioactivity in blood, plasma, urine and feces was performed by PRA Bioanalytical Laboratory in the Netherlands. Results: the mean recovery of radioactivity in excreta was 96.4% (range 92.0-98.5%), indicating no significant retention of APD421 in the body. 73.6% (range 70.6-79.2%) of radioactivity was recovered from urine and 22.8% (range 18.9-25.7%) from feces. Excretion was initially rapid, with about two-thirds of the drug eliminated within 12 hours, primarily in urine. Urinary excretion was 94% complete after 24 hours. Thereafter, excretion was slower and predominantly in the feces, with 76% of fecal excretion occurring in the period 24-72 h. Excretion was essentially complete by 96 hours after dosing. [^{14}C]-APD421 was the only radioactive peak detected in plasma. [^{14}C]-APD421 and four related components (C1, C2, C3 and C4) were associated with detectable radioactivity in pooled human urine. [^{14}C]-APD421 and three related components (C1, C2 and C4) were associated with detectable radioactivity in pooled human feces. The radioactive components detected in excreta were formed by oxygenation (C1), N-dealkylation (C2), oxygenation plus di-dehydrogenation or methylation plus dehydrogenation (C3), and oxygenation plus dehydrogenation (C4). [^{14}C]-APD421 was predominantly excreted unchanged in urine and feces, accounting for 57.5% of the dose excreted in urine in the first 48 hours and 20.6% of the dose excreted in faeces in the first 96 hours. The four metabolites together represented 15.0% of the dose excreted in urine in the first 48 hours. Metabolite C3 was not detected in feces; the other three metabolites together represented 6.1% of the dose excreted in feces in the first 96 hours.

O–25

APPLICATION OF ^{14}C ISOTOPE TO GAIN A COMPREHENSIVE UNDERSTANDING OF DRUG DISPOSITION AND FORMULATION PERFORMANCE IN HUMAN SUBJECTS

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Introduction:

Intravenous microtracer (IVMT) studies and human mass balance (ADME) studies are well understood applications which help drug companies generate essential data to support drug development and registration. In recent years, integrated IVMT/ADME studies have become established as an efficient tool to enrich the data available from a single radiolabelled human study, and enable the generation of comprehensive datasets to understand and investigate factors influencing drug absorption and bioavailability.

Presentation:

Bioavailability from oral administration is influenced by a number of factors such as dissolution, solubility, absorption, gut metabolism, and first pass hepatic extraction. If drugs have a low oral bioavailability it could be due to any one of, or a combination of, these factors.

This presentation will provide case study examples of integrated IVMT/ADME studies which will highlight the value of such studies in teasing out the factors that influence bioavailability, and thus aid development of effective formulation strategies. The key factors in the establishment and conduct of these studies will be reviewed and details will be provided to demonstrate how the data resulting from comprehensive sample analysis can provide an understanding of absolute bioavailability, fraction surviving gut metabolism and fraction absorbed as well as mass balance and metabolite characterisation.

Conclusion:

The integrated IVMT/ADME study approach is a useful tool for providing a thorough understanding of drug disposition, including factors influencing oral bioavailability. Outcomes can be translated into a formulation ‘roadmap’ to recommend potential drug delivery strategies to overcome suboptimal performance and enhance outcomes within drug development programmes.

O–26

METABOLIC LABELS FOR MULTI-PLEXED PROTEIN QUANTIFICATION

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Proteome quantification has become an increasingly essential component of modern biology and translational medicine. Whether targeted or global, stable isotope incorporation with mass spectrometry (MS) analysis is a core technique for protein abundance measurement. There are numerous approaches to introduce stable isotopes into peptides, the most frequently used being stable isotope labeling with amino acids in cell culture (SILAC) and isobaric tagging. These methods incorporate heavy isotopes to increase mass by at least 1 Da. SILAC, the quantification gold standard, for example, typically utilizes a 4 Da spacing to limit the isotopic cluster overlap of the heavy and light peptides. This requirement limits the quantitative capacity of SILAC to triplex. We describe here a new and very different approach to protein quantification – one that exploits the subtle mass differences (mDa) that are induced by the varying energies of neutron binding in C, N, and H. We call this method neutron encoding (NeuCode). Here we describe this method, compare it to other techniques, and describe up to 9-plex NeuCode SILAC. NeuCode labeled amino acids can also be used to label mice as a strategy for multiplexed proteomic analysis in vivo. Using NeuCode we characterize an inducible knock-out mouse model of Bap1, a tumor suppressor and deubiquitinase whose in vivo roles outside of cancer are not well established. NeuCode proteomics revealed altered metabolic pathways following Bap1 deletion, including profound elevation of cholesterol biosynthetic machinery coincident with reduced expression of gluconeogenic and lipid homeostasis proteins in the liver. Bap1 loss increased pancreatitis biomarkers and reduced expression of mitochondrial proteins. These alterations accompany a metabolic remodeling with hypoglycemia, hypercholesterolemia, hepatic lipid loss, and acinar cell degeneration. Liver-specific Bap1-null mice present with fully penetrant perinatal lethality, severe hypoglycemia and hepatic lipid deficiency. This work reveals Bap1 as a metabolic regulator in the liver and pancreas, and establishes NeuCode as a reliable proteomic method for deciphering in vivo biology.

O–27

A NEW MS/MS METHOD TO DETERMINE DIFFERENCES IN THE METABOLIC STABILITY OF DEUTERATED MOLECULES VERSUS THEIR NON-DEUTERATED ANALOGUES TOGETHER IN THE SAME ASSAY: A CASE STUDY USING A RADIOTRACER COLD STANDARD.

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The deuterium isotope effect is well known to improve the metabolic stability of molecules such as drugs. When synthesising new molecules, it may not always be clear the position to deuterate to gain this advantage, without undertaking separate assays of both the deuterated and non-deuterated molecules, and in the case of radiotracers, the analysis of radiometabolites requiring specialist facilities.

Our previous work with the radiotracer [^{18}F]PBR111, a TSPO ligand showing potential for imaging neuroinflammation [1,2], demonstrated that [^{18}F]PBR111-d_4 (d_4 at a specific site) has slower metabolic breakdown and a decreased rate of formation of polar metabolites *in vitro* (rat and human liver microsomes) relative to non-deuterated [3]. However, this required the analysis of ^{18}F radiometabolites in separate assays of the deuterated and non-deuterated radiotracer.

Our new MS/MS method conveniently demonstrates the difference in metabolic stability without radiolabelling, by mixing equal concentrations of the deuterated and non-deuterated radiotracer together in a liver microsome assay, and examining the change in the ratio of the analogous MS transitions of intact tracer in multiple reaction monitoring (MRM) mode at different time points in the assay. As a control, we synthesised a second deuterated analogue, at a site significantly less metabolised than the first site [4]. In this case, the MS/MS method revealed minimal change in the ratio of the equivalent MS transitions, relative to the non-deuterated radiotracer.

We expect this method could be applied to any deuterated and non-deuterated analogues of molecules where the site of metabolism has not been comprehensively studied, to determine the suitability of the chosen site of deuteration. For radiotracers, there is no requirement to radiolabel until studies progress to *in vivo* PET imaging.

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O–28

STORAGE AND STABILITY OF ORGANIC COMPOUNDS LABELED WITH TRITIUM

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Application of tritium labeled compounds, mostly used as a tracers, demands on a very high purity of such tracer and misleading information derived from use of tracer contaminated by impurities need to be eliminated. Organic compounds labeled with tritium decompose on storage and the decomposition is accelerated by self-irradiation.(1, 2) The degree of decomposition is directly related to the storage conditions of the compound. Measures which can be taken into control and minimize the rate of self-radiolysis are perhaps not always so well known.
Almost complete total radiation energy of the tritium beta decay is absorbed by the compound itself of by its environs. If the former occurs, then the excited molecules may break-up in some manner; if the latter occurs the radiation energy can produce free radicals(3) which may then cause destruction of the labeled tracer. The methods of control - effect of temperature, diluent, free radical scavengers - providing best results for long term storage of tritium labeled compounds in our laboratory will be discussed at the meeting.
Examples of decomposition for a considerable number of compounds labeled with tritium and stored under various conditions will be presented. These general principles will be discussed with hope that this will lead to the best use being made of the available protective measures.
Preliminary studies of fate of organic molecule remnants after spontaneous tritium disintegration using EPR technique showing radical course of reaction will be disclosed.

Acknowledgement

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O–29

APPLICATIONS OF MINIATURIZED SILICON PHOTOMULTIPLIERS TO NUCLEAR MEDICINE AND RELATED DISCIPLINES

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For many years, the photomultiplier tube (PMT) and inorganic scintillation crystal has been the detection method of choice for the characterization of gamma radiation. However, recent advances in the development of silicon semiconductor-based photon detectors (commonly referred to as 'Silicon Photomultipliers' or 'SiPMs') have seen the technology become a dominant competitor to the established PMT-based state-of-the-art. In particular, improvements to the dark count rate, temperature-dependence and fill factor have resulted in SiPMs being implemented for a number of applications within nuclear medicine and, especially, imaging.

In this work, we describe a number of ways in which SiPMs have been applied successfully to applications within the pre-imaging sphere of nuclear medicine. Research into the development of a miniaturized quality control (QC) solution for the production of PET and SPECT radiotracers has resulted in the integration of SiPMs with microfluidic systems [1]. As well as exploiting the photon detection capability of SiPMs, sensitivity to key PET and SPECT radiotracers such as [^{18}F]FDG, [^{68}Ga]gallium-citrate and [^{99m}Tc]pertechnetate can be achieved via direct interactions between positrons and/or gammas with the semiconductor material. Such sensitivity allows for the scaling of the detector element to a few square centimeters and hence the potential to reduce the essential QC aspect of radiotracer production down to a single instrument can be realized. Additionally, the amount of radiotracer necessary for QC purposes can be reduced significantly, therefore lowering the radiation dose to laboratory staff per batch.

Also described are other applications of SiPMs to novel r-HPLC and r-TLC detection systems that are currently in development.

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O–30

NOVEL SIMPLIFIED ABSORPTION-CATALYTIC METHOD OF SAMPLE PREPARATION FOR AMS ANALYSIS

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Accelerated mass spectrometry (AMS) is the exquisite method for the detection of long-lived isotopes at part-per-quadrillion sensitivities with good precision. AMS is traditionally used for studying the past by means of radiocarbon dating. In the last decade biomedical applications based on tracing ^{14}C-labeled compounds through natural systems *via* AMS have been developing to elegantly solve complex problems including the metabolic fate of drugs up to several months, the formation of carcinogen-DNA adducts, the penetration of model aerosol particles inhaled at low dose by mice and cell renewal time.

The most common approach for biological sample preparation is the conversion of organic samples to graphite as follows: solid or liquid tissue is dried, oxidized to carbon dioxide, CO_2 gas is separated from impurities and reduced to graphite. Dried organic samples are typically combusted in sealed quartz tubes containing CuO at 900°C for 1–5 h. Carbon dioxide purified by means of passing through a series of cryogenic traps followed by the conversion to graphite commonly produced by the "overnight" reduction of CO_2 by hydrogen or zinc over an iron catalyst. Multi-stage graphite production is time and resource consuming step of AMS analysis.

To update the procedure mentioned above we suggest a simplified absorption-catalytic method of sample preparation. The main features of novel approach are rapid and complete catalytic combustion of the sample and "inverted" carbon dioxide purification representing one-step CO_2 separation from oxidation products by means of the selective solid absorbent based on CaO. The sample is burned in O_2 flow at 600–950°C followed by afterburning over the ICT-12-8 catalyst allowing carbon, CO and other pyrolysis products to be completely oxidized in 10-15 min even in the presence of chlorine and sulfur compounds. The products of complete combustion pass through the trap of water and heavy-boiling compounds representing a U-shaped tube placed into snow/NaCl mixture having the temperature of -20°C. The further separation of combustion products is carried out by selective absorption of carbon dioxide on CaO at 550–650°C followed by the system mild evacuation to remove the impurity gases mixture near the sorbent. Then the absorbent is moved to the high temperature zone (T > 900°C) to completely desorb accumulated CO_2. Carbone dioxide is collected in the quartz graphitization reactor, loaded with Fe catalyst and equipped with a water trap, by means of liquid nitrogen cooling. The reactor is filled with H_2 in a double excess, sealed and moved to the furnace preheated to 560°C for converting CO_2 to graphite. The graphitization is a rate-limiting step of the sample preparation and requires about 5.5 h. However, the independence of the graphitization from the rest procedures allows several samples to be accumulated and simultaneous graphitized in the furnace. To sum up, the suggested method allows producing graphite targets from organic samples faster and cheaper making it perspective for biomedical applications.

Acknowledgements

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O–31

HYDROGEN ISOTOPE EXCHANGES CATALYZED BY RUTHENIUM NANOCATALYSTS

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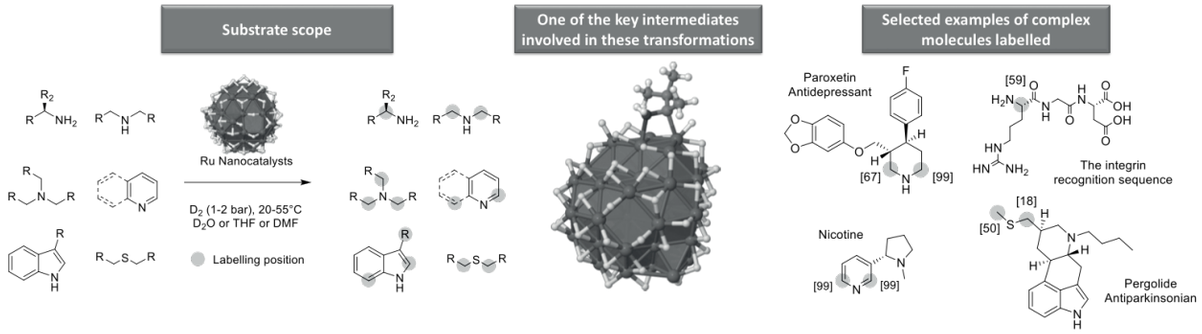
Deuterated and tritiated compounds are widely used in numerous applications in chemistry, biology and material science.[1] In the drug discovery and development process for example, tritiated molecules are often employed as radiotracers for Absorption, Distribution, Metabolism and Excretion (ADME) studies. In metabolomics and related fields of research, deuterated molecules are essential for absolute quantification through internal standardization. Therefore, the development of efficient late-stage processes enabling selective incorporation of deuterium and tritium into complex molecules is of paramount importance. In this context, we have recently developed hydrogen isotope exchange reactions using Ru nanoparticles as catalyst and D_2/T_2 gases as isotopic sources (see figure below).[2] In this presentation substrate scopes, limitations and mechanistic aspects related to these transformations will be discussed.



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O–32

FRUSTRATED LEWIS PAIRS AS A NOVEL AGENT FOR TRITIUM LABELING

- AN ALTERNATIVE TO HYDRIDE REDUCTION

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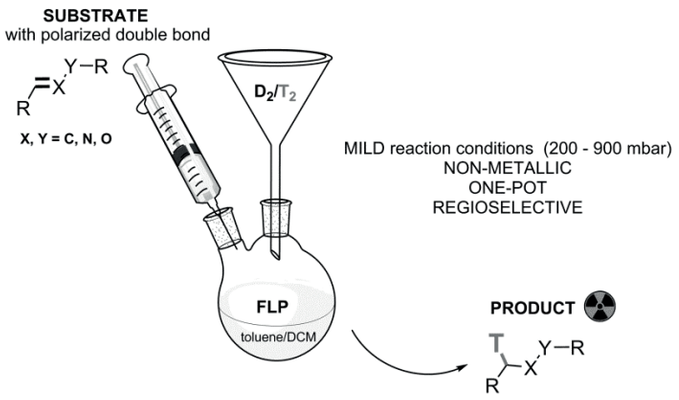
The principal aim of our laboratory is focused on labeling of organic compounds by heavy isotopes of hydrogen, which will be then used as radiopharmaceutical tracers. Up to now, there is available a limited line of reagents generally useable for tritium labeling, moreover they are very often disqualified from routine application because of theirs instability, low specific activity or metallic character of such reagent. In the last decade many studies using chemistry of Frustrated Lewis pairs (FLP) for the activation of molecular hydrogen have been published.[1] In general, the FLP-assisted labeling provide excellent regioselectivity and satisfactory yield under very mild reaction conditions (very low pressure, room temperature), and, moreover, potential contamination of synthesized radioligand by traces of noble metals is hereby totally eliminated. The FLP reagent seem to fulfill the lack of suitable reagents used at tritium labeling. The suitability of FLP reagent for tritium labeling was proved many times in our laboratory since first ^{3}H-labeled compound was synthesized that way and published in 2015.[2] That success had launched our efforts to improve and utilize this elegant one-pot synthesis in conventional labeling of small pharmaceutically relevant organic compounds by heavy isotopes of hydrogen. Our results show specific activity of isolated alcohols and amines up to 27.1 Ci/mmol. We feel privileged to announce that reactivity of FLP reagent works similarly at wide range of tritium pressure used for reduction (200-900 mbar), which has significant effect on cost of labeling as well as radioactive waste reduction.



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LATE STAGE DEUTERIUM AND TRITIUM LABELLING OF NUCLEOBASES CATALYZED BY RUTHENIUM NANOPARTICLES.

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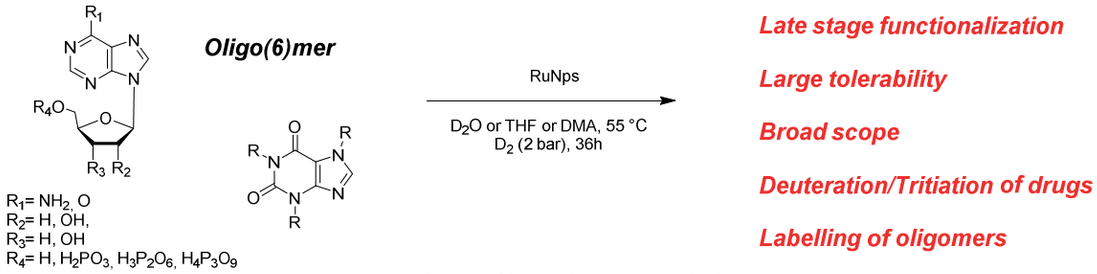
Hydrogen isotope labelled compounds possess a broad range of application in the early pre-clinical phases of drug development process. For instance, deuterated compounds are ordinarily applied as internal standard in quantitative LC-MS techniques while tritiated molecules are often the preferred radioactive tracers for the investigation of molecular absorption, distribution, metabolism and excretion studies.[1] Employed from pulmonary diseases to antiviral therapy and cancer treatment, nucleobases represent an essential class of therapeutic agents whom deuteration and/or tritiation appear attractive but challenging to achieve. As a matter of fact, they are mostly labelled via (radio) synthesis,[2] H/D-T exchange of labile hydrogen atoms[3] or reduction of double bonds.[4] To date, only one heterogeneous palladium catalyzed example has been reported involving a C-H activation process in deuterated water, nevertheless harsh conditions are mandatory.[5] Herein we propose a mild and selective method to perform late stage deuteration and tritiation of variously functionalized nucleobases, included drugs, catalyzed by ruthenium nanoparticles. Moreover, this reaction has been successfully applied to achieve the first deuteration reaction, involving non exchangeable protons, on a complex and fragile high molecular weight oligomer.



Scheme1: H/D exchange on nucleobases

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O–34

TRITIATION OF AZIDO-LABELLED DIIODO CABAZITAXEL (JEVTANA) AND DOCETAXEL (TAXOTERE) DERIVATIVES TO GENERATE ^{3}H-PHOTOAFFINITY PROBES

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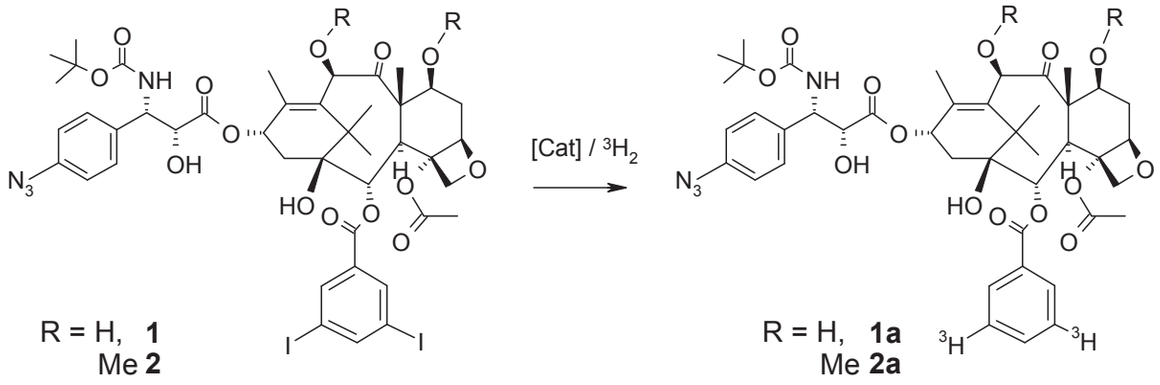
Cabazitaxel was developed in the clinic due to its activity in preclinical taxane-resistant human cancer models. To study the differences in P-gp transporter affinity for Docetaxel and Cabazitaxel radiolabeled azidophenyl analogues of both compounds were needed (**1a, 2a**), as these can make powerful photoaffinity probes for the identification of molecular targets. Initial approaches using H/T-exchange reactions[1] on intermediates and the final compound failed to meet the neccessary biological experiment criteria. Therefore a long precursor synthesis with a late-stage tritiation by iodine/tritium exchange with diiodo precursors **1, 2** was initiated. We report the different challenges overcome in finally synthesizing the required materials **1a** and **2a** with >50 Ci/mmol specific activity.[2]



With the prepared [^{3}H]-azido-taxane analogues we calculated a dissociation constant (K_d) value of 1.7 µM for [^{3}H]-azido-docetaxel **1a** and ~7.5 µM for [^{3}H]-azido-cabazitaxel **2a** for a 4.4-fold difference. We concluded that the improved activity of Cabazitaxel in MDR cancer models that express P-gp is due to its reduced affinity for P-gp transporter compared to Docetaxel.[3]

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O–35

^{68}GA-DOTA-MALTOHEXAOSE: A NEW INFECTION DIAGNOSTIC IMAGING BIOMARKER

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Introduction: The differentiation between bacterial infections and aseptic inflammations is one of the major challenges in post-operative patient care in clinical routine. Current diagnostic tools only poorly address this issue. A promising approach is to target bacteria specifically by their unique energy substrate maltohexaose, which is taken through maltodextrin-transporters, expressed by bacterial and not mammalian cells. Following this concept, we developed a radiolabeled maltohexaose and evaluated it *in vitro* and *in vivo*.

Methods: An azido-functionalized maltohexaose was linked to the DOTA-chelator via Cu(I)-mediated click-chemistry, and labeled with ^{68}Ga. The new ^{68}Ga-DOTA-maltohexaose (DMALTO) was evaluated *in vitro* in cultured *E. coli*, *B. subtilis* and human macrophages (negative control). Three mouse models were established based on C57BL/6 mice: healthy mice, hind limb infection with wildtype *E. coli* (107 CFUs) and hind limb sterile inflammation induced by lipopolysaccharides (LPS, 1 mg/kg). 24h after an intervention, DMALTO (11.0±1.6 MBq) was injected via a tail vein, and dynamic PET was acquired over 60 min (Siemens Inveon µPET/CT). In another group of hind limb infected and inflamed mice ^{18}F-FDG scans (8.3±0.8 MBq) were acquired as reference and for comparison. *In vivo* metabolites of DMALTO were analyzed in blood and urine by radio-TLC and radio-HPLC. Morphology and cell content of the calf muscle were determined by immunohistology.

Results: DMALTO was radiolabeled with ^{68}Ga in excellent radiochemical yields of ≥ 95%. Cultured wildtype *E. coli* and wildtype *B. subtilis* show specific uptake of DMALTO, whereas negligible uptake was found in human macrophages. PET studies in healthy mice demonstrated favourable pharmacokinetics, including rapid renal clearance, low background signal and the absence of radiometabolites in blood or urine (60 min p.i.). In mice with a hind limb infection of wildtype *E. coli* and *B. subtilis* (both confirmed by histology), DMALTO clearly distinguished significant ($P<0.001$) between the infected and non-infected injection site (ratio of up to 5.8). By contrast, the clinically used standard ^{18}F-FDG (non-specific) could identify the infection, but had a lower infected to non-infected muscle ratio than DMALTO. Moreover, the specificity of the DMALTO signal was tested in the sterile inflammation model (confirmed by histology). While FDG uptake remained prominent (LPS: 1.48 %ID/cc, saline: 0.67 %ID/cc, $P<0.01$), reflecting the local inflammation, DMALTO uptake was similar to the non-inflamed contralateral muscle (LPS: 0.38 %ID/cc, saline: 0.25 %ID/cc, $P>0,05$).

Conclusions: A new infection diagnostic imaging biomarker was developed, capable of distinguishing between wildtype *E. coli* and *B. subtilis* infection and sterile inflammation *in vivo*. Moreover, DMALTO identifies gram(-) (*E. coli*) as well as gram(+) (B. subtilis) bacteria. Further exploration of the potential of DMALTO as specific bacterial infection marker in other animal models and the translation into humans are warranted.

O–36

SN-117M – A NEW ISOTOPE FOR TREATING ARTHRITIS

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Introduction

Joint disorders, including rheumatoid arthritis (RA) and osteoarthritis (OA), are common in every society and represent some of the largest medical burdens to human healthcare today. Osteoarthritis in dogs is the leading cause of pain and discomfort that can be so extreme as to even lead to the need for euthanasia. These serious issues are now starting to be addressed with a novel Sn-117m based colloid that can be used in joint radiosynoviorthesis (RSO, aka radiosynovectomy) procedures. Additionally, systemic problems can also be addressed with a Sn-117m labeled molecule that targets CD-206 macrophages abundantly found in the inflammatory RA joints.

Discussion

Sn-117m has been incorporated into a novel and unique homogeneous colloid. We employ a technique where the slow decomposition of urea releases ammonia uniformly throughout the colloid solution and raises the pH in a very reproducible and controlled manner. This results in a colloid with a tight particle size distribution (around 5 μm). This colloid has very high retention (>99.8% after 5 half-lives) in the injected joint and has demonstrated efficacious treatment of arthritis in animal models. An ideal size range of the colloid (2-20 μm) results in no leakage from the joint (or the need for joint splinting to prevent leakage) and complete phagocytosis of the particles by migrating macrophages which allows for the engulfed colloid to irradiate the deeper inflamed synovium. The colloid has demonstrated suitability for treating both small and medium sized joints and may even be useful in larger joints. This cGMP product has completed several successful canine OA trials and will be commercially available in the US as a veterinary product later this year. Multi-national human trials for this product are also set to begin.

High specific activity Sn-117m has been used to label a mannosyl-dextran macromolecule. A similar imaging molecule ([Tc-99m]-tilmanocept) has demonstrated great specificity for RA. Initial attempts found that the DTPA in this construct did not retain Sn-117m in a physiological pH environment. To overcome this, the molecule was modified to accommodate Sn-117m using a DOTA chelate which is known to be stable *in-vivo*. This novel theranostic molecule mimics the biodistribution of [Tc-99m]-tilmanocept and allows for a therapeutic effect similar to the Sn-117m colloid product, but on a systemic basis that is particularly suitable for treating RA.

Conclusions

Joint disorders such as RA and OA represent some of the world's largest medical problems. A Sn-117m homogeneous colloid has been developed for the RSO treatment of canine OA. This commercial product is also ideal for treating human arthritis and multi-national clinical trials are underway. A [Sn-117m]-DOTA-mannosyl-dextran composition under development also shows promise to image and treat RA systemically.

O–37

PRECLINICAL EVALUATION OF RADIOLABELLED PEPTIDES TARGETING NEUROTENSIN RECEPTOR SUBTYPE 1 AS THERAGNOSTIC AGENTS IN COLON CANCERS

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Neurotensin is a natural peptide, pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu, produced mainly in the central nervous system and in N-endocrine cells of the gastrointestinal tract. As it is involved in the proliferation of many types of cancers, an overexpression of neurotensin receptors is an early event that occurs in many tumors compared to normal tissues. Targeting neurotensin receptors for both detection and treatment is envisaged for tumors showing an increased level of NTSR1 subtype of neurotensin receptor NTR: colon, breast, lung cancers and ductal pancreatic adenocarcinomas.

DOTA-neurotensin, DOTA(pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu) and several analogs based on neurotensin peptide fragments (6-13) and (8-13) were developed for targeting neurotensin receptors of colonic tumors, thus radiolabelled with Ga-68 (imaging/diagnostic) and Lu-177 (therapeutic). Comparative preclinical testing of the cellular uptake-retention on tumor cell lines HT29 and CaCo2 was performed, as indicator of protein- cell receptor interaction that can provide useful information regarding the dosage, latency and duration of effect of the radiolabelled compound.

Radio-synthesis method was optimized, resulting in a rapid, automated and robust process (25 min, yield > 85%, radiochemical purity >99%). The bio-affinity profile of ^{68}Ga/^{177}Lu-DOTA-NT and ^{68}Ga/^{177}Lu-DOTA-NT fragments analogs show rapid and high uptake of the radiolabelled peptide in HT29 tumor cells up to 80%, stable over 30 h followed by a slow decrease of 20%, compared with only 30% retention on CaCo2 cells, stabilized after a fast fall down of the initial retention value. *In vivo* binding of the radiolabelled peptides to colon tumor, was confirmed by PET scans in mice. The preliminary *in vivo* investigations of apoptosis triggering and the radiotoxicity induced by ^{177}Lu-radiolabelled neurotensin and analogs, gives promising results and recommends the radiolabelled peptides for targeted systemic radionuclide therapy of the colon cancer.

This work was supported by the grant of the Romanian Ministry of Research and Innovation CCCDI - UEFISCDI project number PN-III-P1-1.2-PCCDI2017-0769, within PNCDI III.

O–38

RADIOLABELING OF TETRAPEPTIDE BY BISMUTH AND EUROPIUM AND IN VITRO SERUM STABILITY OF THE FORMED COMPLEXES

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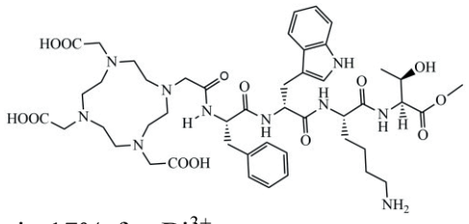
Nowadays bismuth and rare earth elements (REE) radioisotopes are very perspective for application in therapy. Besides that gadolinium is already used for magnetic resonance imaging and europium is well-known fluorescence probe. In this work radiolabeling of tetrapeptide by ^{207}Bi and ^{152}Eu (as representative of REE) radionuclides with DOTA as chelator was studied. All experiments were carried out with ^{152}Eu and ^{207}Bi. For labeling optimization variation of pH, temperature and concentration of ligand was performed. Thin layer chromatography followed by autoradiography and gamma-spectrometry and high performance liquid chromatography were used for analysis of labeling efficiency.



At lower pH values 2-3 the maximal labeling efficiency is 17% for Bi^{3+} and 11% for Eu^{3+}. Increasing of pH facilitates ligand's deprotonation and consequently leads to increase of labeling yield and rate of chelation. According to obtained results labeling takes 20-30 min at 90°C and 60-120 min at 60°C. Bismuth chelation is regularly slower that could be caused by its high tendency to hydrolysis (constants of Bi^{3+} hydroxide complexes are higher by 6-7 orders of magnitude than that of REE) and competition of DOTA-tetrapeptide with hydroxide-ions. For both cations labeling yield of 90-95% at 37°C is achieved after 1 day of interaction. Under same conditions (pH, temperature, ligand concentration) DOTA itself chelates 98-99% of cations. The possible reason for the difference between the labelling yield with DOTA and DOTA-tetrapeptide is lower stereochemical availability of the chelator's molecule for cation. Tetrapeptide sequence can partly shield macrocycle from cation. The obtained complexes with Eu^{3+} and Bi^{3+} were tested for stability in 100 times volume excess of fetal bovine serum. By precipitation of serum proteins it was shown that 15-20% of complex dissociate during first 30 min and further this value doesn't increase for both cations.

This work was supported by the RFBR project №18-03-00891.

TRITIUM AND DEUTERIUM LABELLING OF BIOACTIVE MOLECULES CATALYZED BY RUTHENIUM NANOPARTICLES

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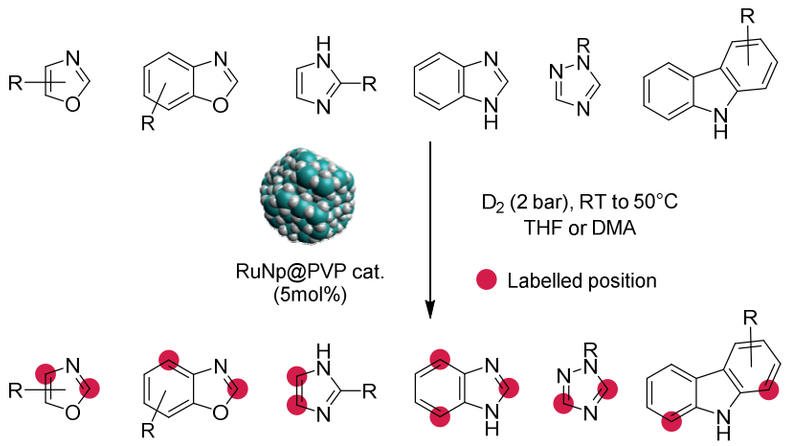
Drug Discovery and Development is constantly confronted with drug candidates that could not be labelled in a rapid, efficient and easy way using **hydrogen isotope exchange reactions (HIE)** which permit the labelling of a target of interest in one step with deuterium or tritium. Many cases are known, in which **HIE's** were still not attempted or would not succeed, due to low solvent or functional group tolerance of common existing methods. Among those bioactive representatives, several complex *N*-heterocyclic derivatives are of large abundance for example in environmental studies[1] and ligand-protein affinity assays[2]. Herewith, we present an efficient way for the controlled deuteration in α, β and γ positions relative to a nitrogen atom on sp^2- and sp^3-carbons of *N*-containing heterocycles which are recurrent patterns in many drug structures. Numerous *N*-heterocyclic model compounds, one agrochemical, one natural product and several drugs from the **oxazole**, **imidazole**, **triazole** and **carbazole** families were successfully deuterated using ruthenium nanoparticles as a catalyst and deuterium gas as isotopic source. Later on, the method was extended to the tritiation of pharmaceutics being difficult to label, to the present day. Tritiated analogues of the structurally complex **Fluconazole** and **Astemizole** were obtained under mild reaction conditions, with a specific activity exceeding the requirements for ADME studies.



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O–40

SELECTIVE TRITIATION REACTIONS USING HETEROGENEOUS CATALYSTS.

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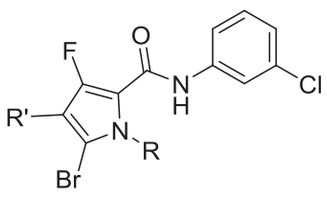
Hydrogen Isotopic Exchange (HIE) is a powerful methodology in the arsenal of radiolabeling techniques. It allows for the rapid, late-stage introduction of tritium labels oftentimes directly onto the unlabeled API. A drawback of this method results in label installation over a wide variety of locations. As the desire in late discovery/early development moves toward ever faster decisions, biologists often need radiotracers that can answer questions at a more granular level. Tritio-dehalogenation can often provide the regiochemical control of a carbon-14 synthesis coupled with a shorter timeframe. The following work describes three case studies that may be of interest to radiochemists.



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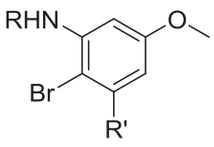

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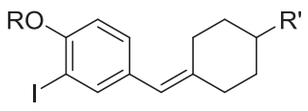

3

O–41

THE C-F BOND ACTIVATION USED FOR DEUTERIUM LABELING

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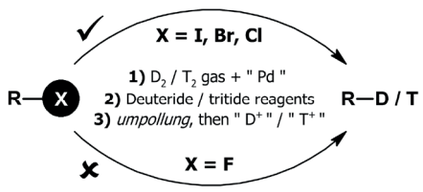
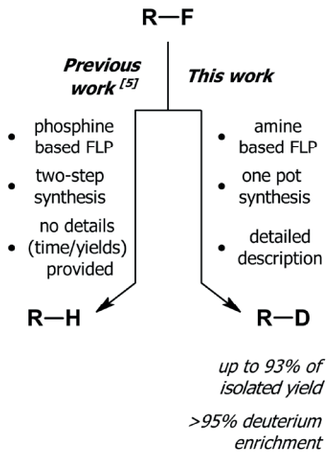
One of the frequently used methods for an incorporation of heavy isotopes of hydrogen into target molecule is the noble metal catalyzed reductive dehalogenation of organic halides. The obvious and major advantages of this versatile and massively used methodology are especially a late stage of such labeling, usually very good accessibility of starting material, rather high certainty of regioselectivity and often achievement of high specific activities of labeled material.[1] In general, an organic compound substituted by halogen (Cl, Br and I) can be used for dehalogenation comprising one of following procedures:[2,3]

1) catalytic reduction using gaseous D_2 or T_2
2) deuteride / tritide reagents (e.g. $^{n}Bu_3SnD/T$)
3) *via umpollung* (generation of distinct Grignard or organolithium species subsequently quenched by appropriate source of D^+/T^+)





On the other hand, the carbon-fluorine bond is due to its very high energy (485 kJ/mol) persistent to oxidative addition and therefore the reductive dehalogenation does not proceed at all.[2]

Despite the C–F bond is rather unreactive, few methods for its activation have been already reported.[4] Our attention attracts the non-metallic activation of aliphatic fluorides by in advance synthesized phosphine-based frustrated Lewis pairs (FLPs) added into reaction in presence of $B(C_6F_5)$.[5]

We have focused on an idea of fluorine ↔ deuterium exchange *via* one pot preparation of amine-based FLP and substrate activation. Detailed conditions and results will be discussed.

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O–42

NI-CATALYSED HYDROGEN ISOTOPE EXCHANGE OF PHARMACEUTICALS

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Tritium labelled compounds are of critical importance in supporting a series of studies in the process of drug discovery and development, including the study of drug absorption, distribution, metabolism and excretion (ADME) and protein receptor-ligand binding assays. Transition metal mediated hydrogen isotope exchange (HIE) emerges as one of the most attractive option for tritium labelling, as it allows for tritium incorporation at a late and/or final stage of the drug molecule, eliminating the need for multistep handling and synthesis of precursors. While several methods of HIE are well described in the literature and have been extensively used in tritium labelling, many of these methods are limited to specific reaction solvents, have limited functional group tolerance and often use tritiated water as the isotope source.

This presentation will introduce the exploration of Ni based catalysts for H/T exchange of drug molecules in combination with use of T_2 gas as isotope source, which is safer and easier to handle compared to tritiated water. Both the easily accessible in *situ* Ni catalyst and its isolated active species, α-diimine nickel hydride complex, were found to be capable of efficiently catalyzing hydrogen isotope exchange of drug molecules containing nitrogen based heteroarenes, such as pyridine, pyrazine, pyrimidine and nucleobase analogues. Hydrogen isotope was incorporated not only at the α-position to the heteroatom but also at the ortho-directed position, a regioselectivity different from that displayed by known catalysts such as rhodium black. The Ni based catalyst enables rapid access to tritium labelled pharmaceuticals that are not easily labeled by existing methods and thus add another valuable option to the labelling “toolbox”.

O–43

Access to Radiotracers through Site-Selective Palladium-Catalysed C-H Radio-Iodination

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Labelling of (bio)molecules with radioactive isotopes is of high interest to the scientific community, as it strongly impacts the discovery process in life science and nuclear medicine. Radiolabelled molecules have been extensively used to assess biochemical reactions, to measure in vivo distribution of a substance or to perform RIA (RadioImmunoAssay). In nuclear medicine, radio-therapeutics for RIT (RadioIsotope Therapy) and radio-tracers for molecular imaging experiments such as PET (Positron Emission Tomography), SPECT (Single Photon Emission Computed Tomography) or scintigraphy have been described. Several useful isotopes of iodine can be used for both diagnosis and therapy: ^{123}I for SPECT imaging, ^{124}I for PET imaging, ^{125}I for biological assays and nuclear medicine and ^{131}I for radio-therapy and scintigraphy. [1]

Our group has recently developed a method to radio-iodinate *N*-acylsulfonamides through a room temperature palladium catalysed C-H activation.[2] This original strategy allows radiolabelling of model substrates in very mild conditions without the use of chemical precursors.

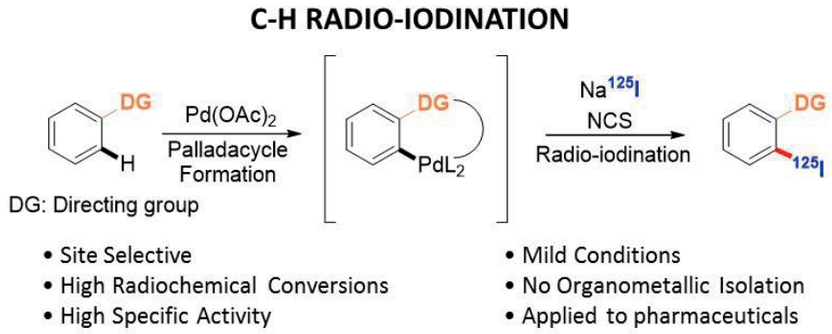

Figure: General strategy of C-H radio-iodination

In this context, we have enlarged the scope of this methodology toward the radio-iodination of antitumoral agents containing a *N*-acylsulfonamide group, as well as other directing groups reported in classical C-H methodology. Here, the radio-iodination methodology and its application will be presented.

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O–44

^{99}Mo RECOIL ATOMS YIELD IN THE REACTION OF ^{100}Mo(p,np)^{99}Mo UNDER IRRADIATION OF Mo NANOFILMS IN CYCLOTRON

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Tatiana M. Kuznetsova, Vladimir A. Zagriadsky

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The radionuclides formed in nuclear reactions, according to the Szilard-Chalmers effect, are able to leave the source material, penetrate into the environment and stabilize therein. Measurements of the ^{99}Mo recoil atoms yield are necessary to create an effective target for the production of this radionuclide, which is of high demand in nuclear medicine.

The design of such target assumes the yield of recoil atoms of ^{99}Mo from nanolayers or nanoparticles of molybdenum compounds, their fixation in buffer substance during irradiation, and subsequent separation of the parent and buffer material. Experiments for measuring the range of recoil atoms ^{99}Mo in the ^{100}Mo(p,np)^{99}Mo nuclear reaction were carried out by irradiating Mo metal nanofilms with 28 MeV protons in Cyclotron U-150. The energy of recoil atoms of ^{99}Mo in this reaction reaches the level of 280 keV.

Metallic molybdenum films with thicknesses of 30÷150 nm were used for measuring the yield of recoil ^{99}Mo atoms. These films were deposited on sapphire plates by magnetron sputtering. Aluminum films with the thickness of 200 nm were used as receiver on other sapphire plates. This receiver of recoil atoms of ^{99}Mo was placed at a distance of 0.2 mm from the molybdenum film.

After irradiation, the ^{99}Mo activity in the source and receiver was measured by gamma–ray spectrometer using the 140 keV line of ^{99m}Tc.

Conclusion:

The range of ^{99}Mo recoil atoms in natural metallic molybdenum was determined as 32±6 nm. The maximum yield of ^{99}Mo upon irradiation with protons of 28 MeV occurs at the molybdenum film thickness of 80±5 nm.

O–45

AUTORADIOLYTIC DECOMPOSITION OF 2-[^{18}F]FLUORODEOXYGLUCOSE

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2-[^{18}F]fluorodeoxyglucose (FDG) is the main diagnostic pharmaceutical for positron emission tomography (PET) accounting for about 70% of studies. During storage, FDG decomposes under the action of its own radiation worsening allocation of radioactive label between tumor and healthy tissues and increasing radiation exposure for the red bone marrow [1]. In the present work [^{18}F]fluoride-anion accumulation was investigated during storage of FDG at various conditions. The mechanism of defluorination was studied by the steady state radiolysis of 2-fluoroethanol (model compound) in aqueous solutions.

Samples of FDG were produced during a "standard" technological process. Quality control examinations were performed within 8 hours (designated shelf life) with two-hour intervals between sample openings. Radiochemical purity of FDG in 1.5 ml aqueous solutions with initial volumetric activities from 1 to 5 GBq/ml was monitored by radio-TLC and radio-HPLC. Complete quality control according to Eu. Ph. was also carried out after 8 hours of storage for 8 ml vial to confirm the designated shelf life. Concentrations of ethanol and acetaldehyde were measured by gas chromatography (GC) with a flame ionization detector.

It was shown that an increase in the initial volumetric activity from 1 to 5 GBq/ml accelerates the elimination of [^{18}F]fluoride – the main product of FDG autoradiolysis. Decrease in ethanol content (residual solvent) intensifies the decomposition of FDG. Moreover, accumulation of acetaldehyde was revealed during FDG storage indicating intensive radiation-induced oxidation of ethanol. Alteration of the storage temperature from 25 to 40°C does not an effect on the autoradiolysis rate. After 8 hours storage the specific activity of [^{18}F]fluoride in FDG was significantly higher in the vials with 8 ml, than with 1,5 ml of solutions with the same initial volumetric activity. This fact might indicate the important role of oxygen as an inhibitor of radiation-induced transformations of FDG. At irradiation of 2-fluoroethanol in aqueous solutions, it was shown that dehalogenation is induced by both electron and hydroxyl radicals. While the reaction with the latter is the major source of fluoride. Addition of organic compounds e.g. ethanol, tert-butanol significantly reduces the radiation-chemical yields of fluoride due to their ability to scavenge hydroxyl radicals, whereas oxygen exert the same effect via oxidation of hydroxyl-containing carbon-centered radicals of 2-fluoroethanol.

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Poster Abstracts

P–1

COST-EFFICIENT, SCALABLE PREPARATION OF ALPHA- AND BETA-DEUTERATED ALCOHOLS.

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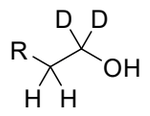
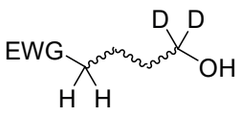
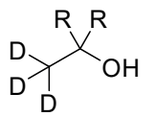
Deuterated alcohols play an increasingly important role in various applications of high commercial value, in particular pharmaceuticals and beverages. The growing importance of deuteration as a tool to increase drug efficiency is highlighted by the recent and first FDA approval for a deuterated drug, i.e., Teva's Austedo (deutetrabenazine) [1]. The negative effects of consuming alcohol in beverages may be strongly diminished by replacing conventional, non-labeled ethanol by deuterated ethanol [2]. Applications of hydrogen isotopes in the Life Sciences have been reviewed very recently [3]. With the relevance of deuterated compounds increasing steadily, the need for cost-efficient and scalable methods for their preparation far beyond laboratory scale amounts becomes more and more pressing. Ideally, readily available D_2O rather than much more expensive D_2 is used to that end. To meet stringent regulatory requirements, such methods also need to address very strict specifications on product purity. Development of suitable deuteration methods that meet all these requirements is often a challenging task that cannot be accomplished successfully by simply relying on reported literature methods. In this poster, we address some examples of our own work in this area. As part of the challenging selectivity requirements to be met, we developed highly selective, yet scalable, catalytic methods for the alpha-deuteration of primary alcohols not accompanied by any beta-deuteration, and for the alpha-deuteration of primary alcohols that also contain other C-H bonds prone to be exchanged by deuterium. A scalable method for the preparation of some beta-deuterated alcohols has also been developed.



alpha-Deuterated alcohols without *beta*-deuteration



alpha-Deuterated alcohols containing other exchangeable C-H bonds



beta-Deuterated alcohols

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P–2

SYNTHESIS OF 14C-LABELLED SQUALENE STARTING FROM SQUALENE

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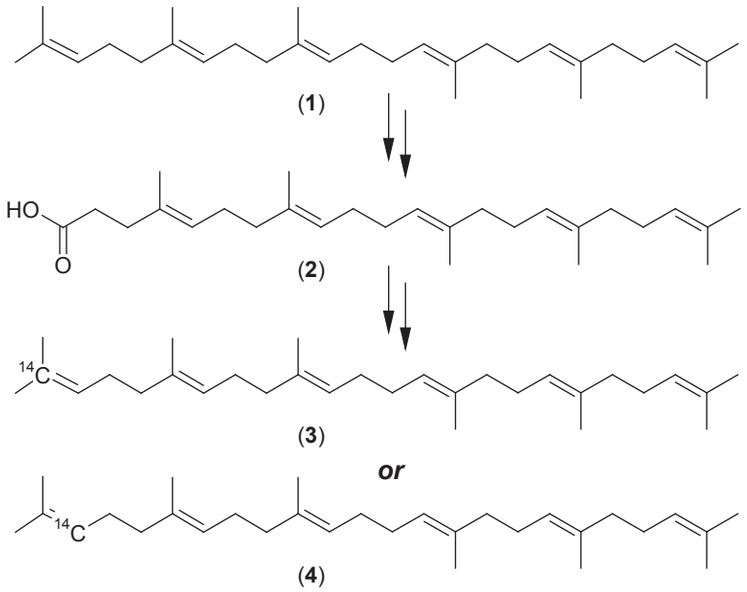
Squalene (***1***) is a naturally occuring triterpenoid widely found in nature, including in humans. This 30-carbon, polyunsaturated hydrocarbon chain consists of six consecutive isoprene units and plays an important role in the biosynthesis of sterols.[1] Moreover, numerous applications in nutrition, pharmacy and medicine have been reported for squalene, as adjuvant for stabilizing vaccines for instance.[2]

In order to conduct a biodistribution study within Sanofi, we were asked to provide ^{14}C-labelled squalene. Published syntheses of isotopically labelled squalene were based on coupling of labelled precursors,[3] with the notable exception of the *L. Cattel et al.*'s work on tritium labelled squalene.[4] In this poster we describe the synthetic efforts and the outcome of two syntheses starting from squalene itself, via turbinaric acid (***2***), its minus three carbon analogue, back to ^{14}C-labelled squalene (***3***) and (***4***).



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P–3

The Synthesis of Some Animal Health Compounds Labelled with Carbon-14

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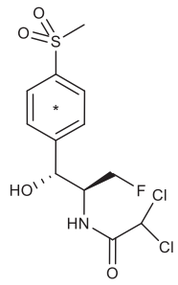

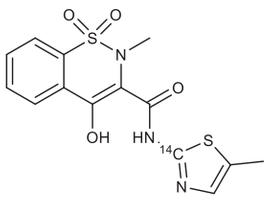

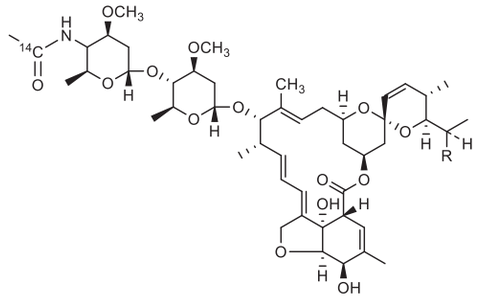

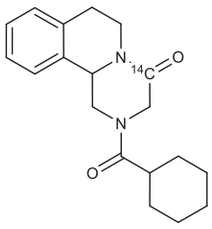

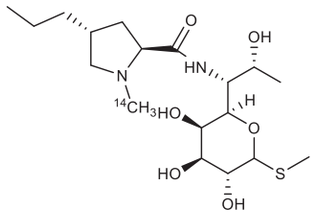

The health of domestic animals is of huge importance to humanity. Some drugs that have been developed for human use are useful for animals. Other drugs have been specifically developed for veterinary use. These drugs need to undergo similar tests as for human-use drugs. Carbon-14 label is the gold-standard for understanding the ADME characteristics of these compounds. In this poster we show how we have labelled some examples of these drugs. We describe the routes to [ring-U-^{14}C]Florfenical, [thiazole-2-^{14}C]Meloxicam, [acetyl-1-^{14}C]Eprinomectin, [ring carbonyl-^{14}C]Praziquantel and [methyl-^{14}C]Lincomycin.

P–4

TITLE. ACCELERATOR MASS SPECTROMETRY: CONTINUING DEVELOPMENT AND INNOVATION OF APPLICATIONS WITHIN DRUG DEVELOPMENT

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Accelerator mass spectrometry (AMS) has been used for quantitative analysis of analytes labeled with ^{14}C in a range of biological matrices since the early 1990s. Applications of the technique have progressed from total ^{14}C analysis in mass balance studies to specific analyte quantitation in microtracer studies, using LC fractionation with off-line analysis of the fractions (LC+AMS), i.e. bioanalysis. AMS is now an established complementary technology to conventional analytical techniques, and is routinely utilized during drug development.

In recent years, a number of advances in AMS technology and its applications have been explored and these will be considered here, including analysis of large molecules and analysis of less typical sample types. In addition, continuous development and improvement of analytical processes has allowed increased productivity with much faster sample turnaround time (reduced from 72 h – 24 h), while maintaining the improved currents of graphite as compared to CO_2 measurements. This decrease in turnaround time allows clinic release criteria to be assessed in real time (i.e. within 24 h of sample collection).

We look to provide an update on AMS applications and advancements, and its continued uptake across all stages of drug development.

P–5

THE SYNTHESES OF CARBON-14 AND STABLE ISOTOPE LABELLED SELECTIVE GLUCOCORTICOID RECEPTOR MODULATORS FOR THE TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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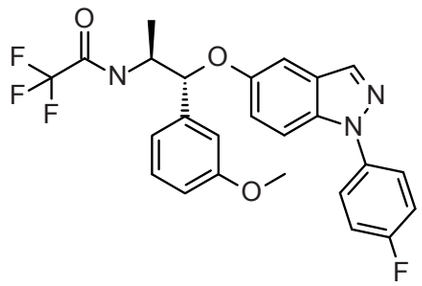
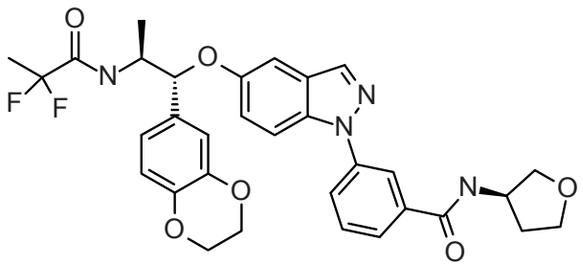
As part of a medicinal chemistry programme aimed at developing a selective glucocorticoid receptor modulator (SGRM) for the treatment of asthma and chronic obstructive pulmonary disease (COPD),[1] two compounds (AZD5423 and AZD7594) were required in both carbon-14 and stable isotope labelled forms. Whilst the 1st generation inhaled SGRM AZD5423 required lengthy syntheses for both labelled forms, subtle structural differences within the 2nd generation inhaled SGRM AZD7594 allowed for concise syntheses. The synthetic approaches used to access the labelled forms of the two compounds will be described.



AZD5423



AZD7594

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P–6

HIGH ENERGY GAMMA BEAM FORECASTED FOR PRODUCTION OF NEW AND EMERGING MEDICAL RADIOISOTOPES BY PHOTONUCLEAR REACTIONS

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The applications of radioisotopes in molecular nuclear medicine require high specific activities, which can be usually obtained using nuclear reactions induced by high-intensity accelerated beams or neutrons coming from nuclear reactors. These methods involve high reaction cross- sections, spanning from few barns to thousands of barns.

One of the alternative route for production of emerging radioisotopes for nuclear medicine employs (γ,n) nuclear reaction to produce such radioisotopes, with relevant quantity and quality. Gamma beams can efficiently excite a nucleon into an unbound state leading to photo- dissociation and creation of a new isotope. Using the new beam facilities compact targets could be exposed to the gamma radiation and undergo photonuclear reactions such as (γ, γ'), (γ, n), (γ, p) to form radioisotopes. The existing gamma beam facilities have flux densities below 10^{14}γ/cm^{2}s, leading to specific activities below 10^{-5} Ci/g.

At the new Extreme Light Infrastructure – Nuclear Physics (ELI-NP), the intense laser beam backscattered on high energy electron bunches is going to produce monoenergetic directed brilliant pulsed gamma-rays by the Compton backscattering process. Prospective radioisotopes to be produced by (γ,n) reactions simulations of the target geometry and estimation of activity of some radioisotopes of interest for nuclear medicine will be presented. Although the reaction cross- sections are as low as 0.1 barn for (γ,n) reaction, the flux densities and the narrow band at ELI- NP allows in the second stage the production of radioisotopes with higher specific activities. At ELI-NP, the spectral density is designed to be higher than $0.5 \cdot 10^4$ photons/s·eV, number of photons/s within FWHM bandwidth are 10^8-10^9 and linear polarization over 95%, while the energy of the photons will reach 19.5 MeV in the second phase of the project development. The reliable production of emerging radioisotopes using alternative routes will open the way for completely new clinical applications of radioisotopes. One of the envisaged radioisotope, ^{195m}Pt could be used to monitor the patient's response to chemotherapy with platinum compounds before a complete treatment is performed, using low-energy γ transition for SPECT imaging. At the same time, the short-range Auger and conversion electrons resulted from ^{195m}Pt decay could enable a very local radionuclide therapy. Other promising radioisotopes such as ^{62}Cu, ^{64}Cu, ^{186}Re and ^{225}Ra/^{225}Ac pair are also evaluated for production via this route, as their present production routes are difficult to access and expensive.

This work was supported by the grant of the International Atomic Energy Agency (IAEA) contract 22467, within the Coordinated Research Program.

P–7

ISOTOPIC LABELING FOR DRUG INNOVATION: THE "ISOTOPICS" EUROPEAN PROJECT*

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Nowadays, less than one drugable compound on ten entering clinical trials effectively reaches the market. This excessive drug attrition is due in part to insufficient ADMET investigations and PK/PD assessments during preclinical studies, resulting from the lack of straightforward methodologies for labeling drugs without altering their chemical integrity. Moreover the compelling rise of therapeutic biologics (proteins, peptides, nucleic acids, polysaccharides etc.) urges the need for chemically benign labeling methods working in soft conditions. There is also a demand for specialized chemists with deep knowledge in radiolabeling techniques and associated analysis, medicinal chemistry and engineering of biologics.

ISOTOPICS regroups 5 academic beneficiaries (CEA, CNRS, Univ. Oxford, Karolinska Instit., Univ. of Liège) and 3 big pharmas (UCB-BioPharma, AstraZeneca and Sanofi-Aventis) for 4 years. The project aims at the development of innovative chemical methods for the specific and selective late-stage labeling of small-molecule drugs and therapeutic biologics in order to help to derisk Drug Discovery & Development and to foster the emerging of new therapeutic solutions with reduced adverse effects. An associated training program for 15 PhD students includes a series of taught courses and lectures about chemical labeling, analysis and medicinal chemistry, complementary (soft) skills workshops and visit of Partner's premises, but also a secondments plan in order to expose the ESRs to both the academic and industrial sectors in different countries, and to give them a dual academic/industrial experience.

To date, research efforts produced by ESRs have led to the development of new isotopic labeling methods on model molecules but also real drugs and drugable compounds, with a particular interest for highly specific and selective late-stage labeling methods such as (to cite only a few) metal-catalyzed hydrogen exchange through C-H activation [1] and the very first dynamic carbon exchange reaction [2] on small-molecule drugs, but also the selective trifluoromethylation of tryptophan residues in peptides and proteins [3].

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* The ISOTOPICS project was granted by the H2020-MSCA-ITN-2015 European program, grant N°675071.

P–8

NOVEL PYRIDINE-CONTAINING AZACROWN-ETHERS FOR THE CHELATION OF THERAPEUTIC BISMUTH RADIOISOTOPES: COMPLEXATION STUDY, RADIOLABELING, SERUM STABILITY AND BIODISTRIBUTION

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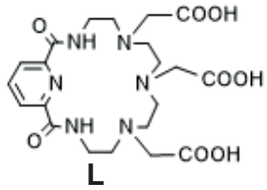
Nowadays alpha-emitting bismuth isotopes are very perspective for targeted alpha therapy. This work is focused on the complex formation of Bi^{3+} cations with series of new pyridine-containing amide azacrown ethers with or without pendant functional groups including evaluation of leading complex for in vitro serum stability and in vivo behavior.

All studied azacrown-ethers form complexes with Bi^{3+} which stability constants linearly correlate with ligand's affinity to proton. Ligands without carboxylic arms form two types of complexes with M:L=1:1 and 1:2. Upon pH increasing for all ligands except **L** formation of $LM(OH)_n$ species was observed. Ligand **L** possessing three carboxylic groups forms the most stable complex with Bi^{3+} (logK=21.3±0.2) through the studied ligands. According to DFT calculations Bi^{3+} is located in the macrocyclic cavity holding by two carboxylic arms on one side and one from the other. The calculated Interatomic distances are in agreement with EXAFS measurement of the complex.



L

Complex BiL demonstrates stability in 100 times volume excess of fetal bovine serum: during 3 h 50% dissociated vs BiEDTA complex >95% after 2 h. Moreover biodistribution in the normal BALB/c mice showed 2-3 times lower accumulation in all organs and faster clearance compared to BiEDTA. This indirectly confirms in vivo stability of the complex.

The results of *in vitro* serum stability and *in vivo* biodistribution studies suggest that this ligand can be promising as bifunctional chelator for the preparation of radiopharmaceutical with ^{213}Bi.

This work was supported by RSF 16-13-10226 and RFBR 16-33-00642.

P–9

RECOVERY OF [18O] H_2O USED AS A TARGET INTO THE CYCLOTRON

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Aim: 18F is produced by the (p,n) nuclear reaction via proton bombardment of highly enriched water ([^{18}O] H_2O) (at greater than 95% of [^{18}O] enrichment) in particle accelerators called cyclotron. If this irradiated [^{18}O] H_2O can be recovered, it can be re-used for the production of 18F. In this recovery process the most important issue is the purification of [^{18}O] H2O, which is contaminated with inorganic and organic impurities (such as absorption, irradiation, separation, etc.) during the processes without lowering the enrichment ratio. In this study we aimed to develop a purification method of irradiated [^{18}O] H_2O without lowering the enrichment ratio. **Material and Methods:** The purification method consists of advanced combined distillation techniques. **Results**: Inorganic and organic impurities can be completely removed with 5-10% rate of wastage (Fig-1,2). Moreover 1-2% increase enrichment was achieved with the developed method (Table 1). **Conclusion:** There are many purification methods for the recovery of the of irradiated [^{18}O] H_2O such as: UV, Ozone, and Sonochemical. However these methods cause secondary impurities and decrease the rate of O-18enrichment (1)(2)(3)(4).

Analysis Results (µg/L)

Li	-	Fe	76,5	Ag	-
Be	-	Co	338,4	Cd	-
Na	131489	Ni	528,4	Cs	-
Mg	56,3	Cu	11,8	Ba	12,8
Al	237,6	Zn	383,7	Hg	10,4
K	7393	Ga	-	Tl	-
Ca	455,1	As	-	Pb	301
V	-	Se	38,1	Bi	-
Cr	214,1	Rb	-		
Mn	11,4	Sr	-		

Before purification

Element \ Numune	01
Na (mg/L)	0.5
Si (mg/L)	0.5
B (mg/L)	0.4
Li (µg/L)	0.4

After purification

Fig-1 ICP-MS Results

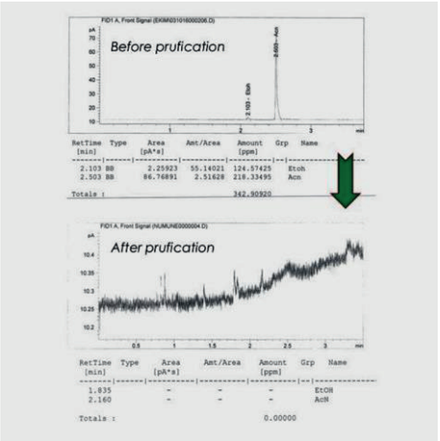

Fig-2 GC Results

Before Purification	After Purification
pH ≈ 5-6 Conductivity ≈12-20µS/cm O-18 Content % 95 Radioactivite	pH ≈ 7 Conductivity ≤ 3 µS/cm O-18 Content % 96.9 Not Radioactive

Table 1. Spesifications

Literature

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P–10

Synthesis of ^{14}C-labelled AAI101, a novel extended spectrum β-lactamase inhibitor

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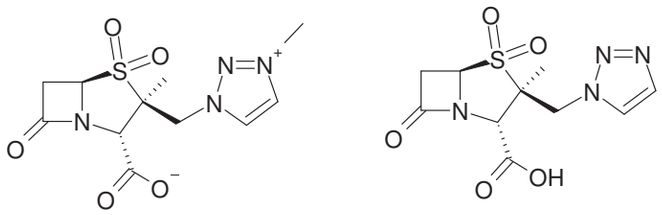
AAI101 is a novel penicillanic acid sulfone ß-lactamase inhibitor (BLI), active against a broad range of ß-lactamases including extended-spectrum ß-lactamases (ESBLs), and capable of enhancing substantially the antibacterial activity of ß-lactam antibiotics such as penicillins, cephalosporins, and carbapenems[1]. ESBLs constitutes the principal mechanism of resistance to β-lactam antibiotics in clinically isolated Enterobacteriaceae[2,3]. AAI101, or (*2S*,*3S*,*5R*)-3-methyl-3-((3-[^{14}C]methyl-*1H*-1,2,3-triazol-3-ium-1-yl)methyl)-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylate 4,4-dioxide), is structurally related to tazobactam (see Figure 1) but has significantly improved microbiological and pharmacokinetic properties. AAI101 has recently been studied in combination with cefepime is in Phase 2 clinical trials. In order to investigate the Absorption Distribution Metabolism and Excretion (ADME) profile of AAI101, it was necessary to prepare a radiolabelled version. As the starting material for the synthesis of AAI101 is tazobactam, we have identified a practical approach to introduce carbon-14 into the structure of AAI101 starting from commercially available [$^{14}CH_3$]methyl nosylate. In this poster we present and discuss the procedure that was developed and used to obtain [$^{14}CH_3$]-AAI101 in high radiochemical yield and purity.



AAI101 **Tazobactam**

Figure 1

References

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P–11

COMPOUND-SPECIFIC ISOTOPIC ANALYSIS FOR INVESTIGATING THE FATE OF ORGANIC CONTAMINANTS IN THE ENVIRONMENT

FAINA GELMAN

GEOLOGICAL SURVEY OF ISRAEL

Significant amounts of industrially produced organic compounds are used today in various fields of our life such as fuels, pesticides, flame retardants etc., resulting in their wide presence in the environment. Many of those anthropogenic organic compounds are classified as toxic/carcinogenic pollutants. Therefore, the knowledge on their fate in the environment is of a high importance.

Attenuation of organic pollutants in the environment may occur through degradative and/or non-degradative transformations. Degradation of the contaminant as a result of biological or chemical processes may result in its mineralization in transformation to other organic compounds. However, in some cases, the degradation products may be even more dangerous than the initial contaminant. Through recent decades compound specific isotope analysis (CSIA) has undergone a rapid development toward important applications in contaminant hydrology and organic biogeochemistry providing evidence of pollutant degradation. This approach is based on the fact that chemical bonds between the heavier isotopes are slightly stronger and broken slower than the bonds between the lighter isotopes. As a result of that, the remaining (still non-reacting) fraction of the substrate becomes enriched by the heavier isotopes. Isotope enrichment factor (ε), a characteristic parameter for a specific transformation, can be calculated using Rayleigh equation connecting between the changes in contaminant concentration and its isotope composition.

In our research projects we aim to develop and apply multi-elemental isotope analysis for investigating the fate of organic contaminants in the environment. In the focus of our research are groundwater contaminations by gasoline hydrocarbons, brominated hydrocarbons, and chlorinated hydrocarbons.

P–12

MASS-TRANSFER PERFORMANCE STUDY OF A CRYOGENIC DISTILLATION COLUMNS CONTAINING STRUCTURED PACKING FOR ^{13}C ISOTOPE SEPARATION

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Because it is necessary to use thousands of theoretical plates to obtain ^{13}C isotope enrichment up to above 90%, which is the abundance value required by many applications, especially for urea[^{13}C] breath test(^{13}C-UBT) used to detect the helicobacter pylori infection,[1] this paper presents the high-efficiency structured packing, PACK-^{13}C, that reduce the difficulty of engineering implementation for ^{13}C isotope separation significantly.[2] After a systematical review of distillation and the BRF mass-transfer model of structured packing,[3] the optimized mass-transfer model for PACK-^{13}C is established according to the ^{13}C isotope separation experiment by cryogenic distillation. Based on the above model, the mass-transfer efficiency parameters of the distillation column containing PACK-^{13}C structured packing are received, which show better agreement with the experimental data comparing with the traditional BRF model. When the gas flow factor changes from 0.18 to 0.90 m/s$(kg/m^3)^{0.5}$, the average relative error of the HETP simulation values is 10%, and the one of the separation work values is 6%. Therefore, with respect to the mass-transfer efficiency simulation of ^{13}C cryogenic rectification columns, a more appropriate method is based on the optimized model, which should be used to design the larger scale industrial distillation columns for ^{13}C isotope separation. And it could be applied to other traditional distillation industry furtherly.

Key Words: isotope ^{13}C; mass-transfer; structured packing; cryogenic rectification

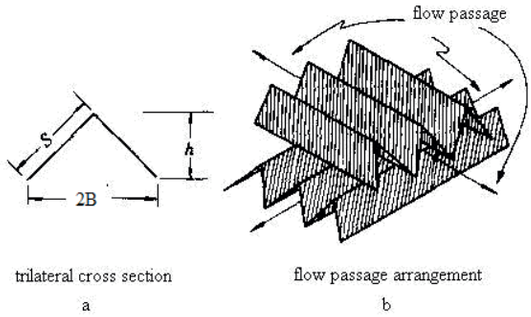

Fig.1 Geometry of corrugated structured packing

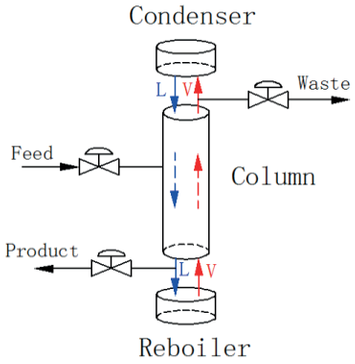

Fig.2 Schematic of ^{13}C isotope separation

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P–13

SYNTHESIS OF MRI PROBE [1-^{13}C]PYRUVATE

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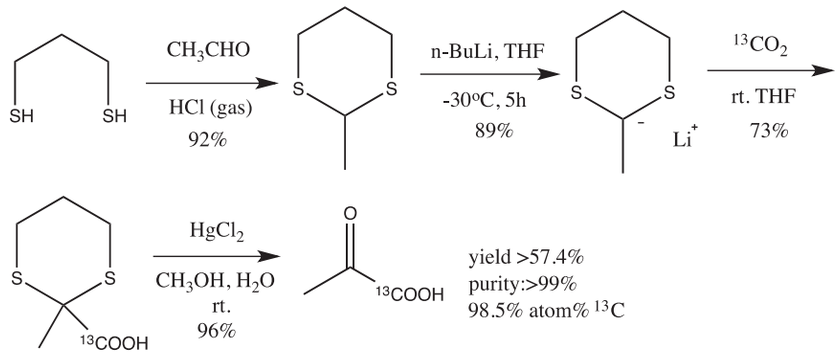
Metabolic Imaging of Patients with Prostate Cancer Using Hyperpolarized [1-^{13}C] pyruvate has been demonstrated to be a safety and feasibility technology, which can be applied to detect and stage cancer, as well as detect tumor progression and monitor response to therapy.[1] It was worth noting that the preparation and process development of the [1-^{13}C] pyruvate were still an extremely attractive yet challenging task. [2-5]

Herein, We explore here a four-step synthesis method to prepare the MRI probe [1-^{13}C] pyruvate, and then used the Uniform Design Experimentation to explore the synthetic process and obtain the optimized conditions, the yield was above 57.4%. Furthermore, the quality control was also studies according to the Chinese Pharmacopoeia and the related Appendix, the purity of three batches of samples was more than 99%, the isotopic abundance was greater than 98.5 atom%^{13}C.The optimized process reduced the production costs and energy consumption, which is suitable for the scale-up and industrial production of [1-^{13}C] pyruvate.

Keywords: MRI probe; [1-^{13}C] Pyruvate; Prostate Cancer; Synthesis



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[4] US2007106085
[5] WO2008011033

P–14

INDUSTRIAL SEPARATION OF OXYGEN ISOTOPES BY OXYGEN DISTILLATION

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^{18}O-labeled water (Water-^{18}O) is widely used as a raw material of ^{18}F-labeled diagnostic agent in positron emission tomography (PET). Water-^{18}O has been separated by water distillation or nitric oxide distillation. [1] We developed a novel oxygen isotope separation process by cryogenic oxygen distillation in 2004. [2] We are now operating 3 separation units with the total capacity of 600 kg of Water-^{18}O per year in Japan.

Separation process of Oxygen-18

Oxygen isotope separation factor is so small that a long distillation cascade is required. Thereby, the cascade has a large liquid hold-up which results in a long start-up time. In order to solve this problem we developed a most efficient process comprising the following steps. (1) $^{16}O^{18}O$ is enriched around 50%. (2)$^{18}O_2$ is produced from $^{16}O^{18}O$ by isotope scrambling. (3)$^{18}O_2$ is enriched to product specification.

We developed a process simulator which enabled extensive design of enrichment and capacity. The 3 units designed by this process simulator achieved the target specifications of enrichment and capacity. Dynamic process simulation data and observed ones during the start-up ^{18}O enriching period showed good agreement.

Characteristics of No.3 unit

A new process was adopted for No.3 unit which started production in 2016. We succeeded in reducing energy consumption and improving yield compared to the previous 2 units. ^{17}O separation is also possible with this unit.

Separation unit	No.1	No.2	No.3
Enrichment (^{18}O)	> 98%	> 98%	> 98%
Capacity (Water)	100 kg/year	200 kg/year	300 kg/year
Start-up period	180 days	140 days	210 days
By-product	^{18}O 10%	^{18}O 10%	^{17}O 10%

References

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P–15

IRIDIUM (I) CATALYSIS FOR SITE SELECTIVE HYDROGEN ISOTOPE EXCHANGE OF AROMATIC ALDEHYDES

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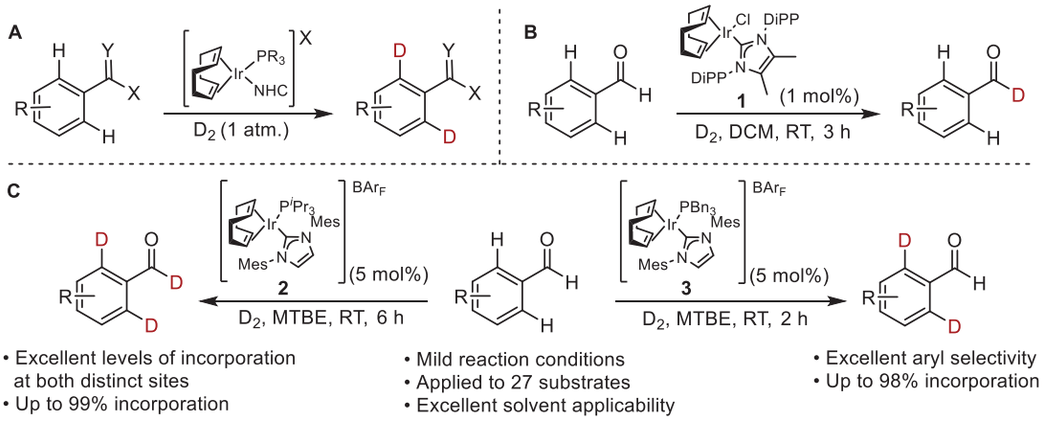
Transition metal-catalysed hydrogen isotope exchange (HIE) allows expedient access to isotopically enriched materials, and use of a directing group can allow high levels of regioselectivity in the process. Within our group, iridium (I) catalysts have been developed to enable HIE, directed by a wide range of directing groups such as ketones, nitro groups, pyridyl groups and primary sulfonamides (Scheme **1A**).[1,2]

Aromatic aldehydes are challenging substrates for selective HIE due to the presence of *ortho*-aryl and formyl C–H bonds, which can both undergo exchange. Recently, our group reported a highly selective formyl HIE of aromatic aldehydes, using an iridium (I) catalyst with a small ligand sphere consisting of a chloride and IPr^{Me} (Scheme **1B**, cat. **1**).[3] The complementary process of selective *ortho*-labelling, is currently unknown, with reported methods giving mixtures with formyl labelling.



Scheme 1

It was hypothesised that a larger ligand sphere – as is present in iridium (I) NHC/phosphine catalysts – would allow access to *ortho*- deuterated products. Through catalyst screening and optimisation, highly selective aryl labelling could be achieved with a wide range of substrates. Along with the optimisation of this process, serendipitous discovery led to development of a process for concurrent aryl *and* formyl labelling with high levels of incorporation (Scheme **1C**). The resulting deuterated products could be utilised further in common chemical transformations with retention of the label.

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P–16

THE SYNTHESIS OF ISOTOPOLOGUES OF AZD7307. A NOVEL, SELECTIVE β2-ADRENORECEPTOR AGONIST.

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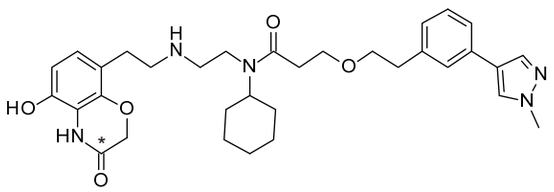
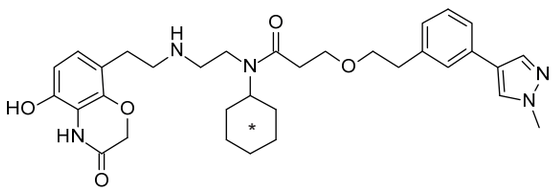
AstraZeneca has had a long standing interest in the investigation of compounds that are effective against asthma and chronic obstructive pulmonary disease (COPD). A research programme discovered a number of candidates and the compound AZD7307 was identified as a development candidate. In order to progress the development, a number of labelled compounds were required – namely a stable isotopically labelled (SIL) isotopologue to support bioanalytical studies and a radiolabelled species to investigate the fate of the compound in the body (ADME).

As the project evolved, a number of similar compounds were under investigation and shared a common structural motif. Recognising this, a strategy was devised utilising simple precursors which enabled the synthesis of common structural fragments; these could be elaborated further to afford the target structures.





* Denotes position of labelling.

P–17

C-14 LABELLING OF BENSULFURON-METHYL IN DIFFERENT POSITIONS

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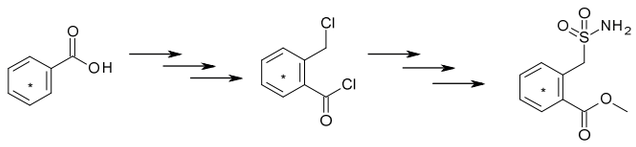
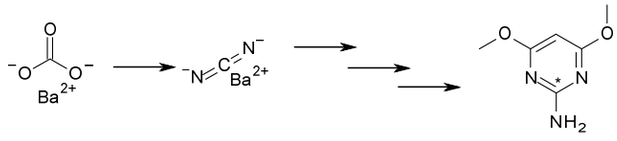
Bensulfuron-methyl (methyl-α-[(4,6-dimethoxypyrimidin-2-ylcarbamoyl)sulfamoyl]-o-toluate is an important member of the sulfonylurea herbicides. It is produced in industrial scale. However, we could not find any data of the synthesis of the C-14 labelled molecule in the literature. Therefore we aimed at the synthesis of the Bensulfuron-methyl, [phenyl ring-U-^{14}C] and the Bensulfuron-methyl, [pyrimidine-2-^{14}C]

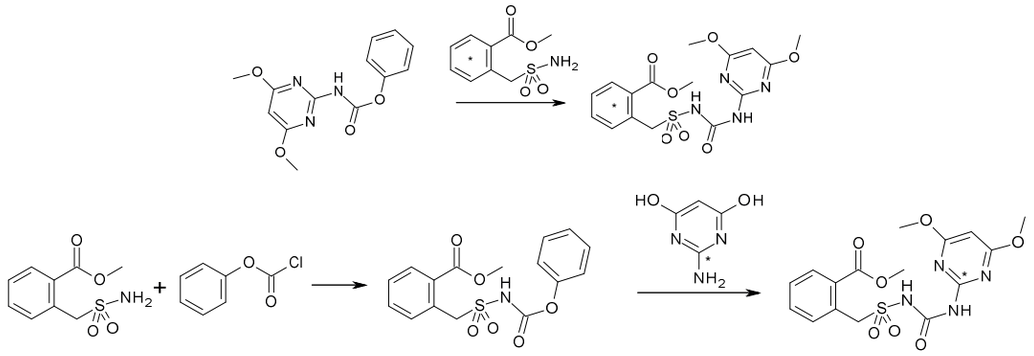
In the synthesis of the phenyl labelled molecule the production of unlabelled [(2-Methoxycarbonyl)phenyl]methanesulfonamide was described in the literature[1]. This way the key intermediate was the 2-Chloromethyl[ring-U-^{14}C]benzoyl chloride which was to be synthesized from [ring-U-^{14}C]benzoic acid.



The pyrimidine labelled molecule was prepared from barium [^{14}C]cyanamide which in turn was made from barium [^{14}C]carbonate.



The two differently labelled molecules were reacted with the unlabelled part in two different ways to reduce the number of active steps.



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Regioselective hydrogen deuterium exchange reaction by iridium catalyst at pyridyl-2-oxymethyl group

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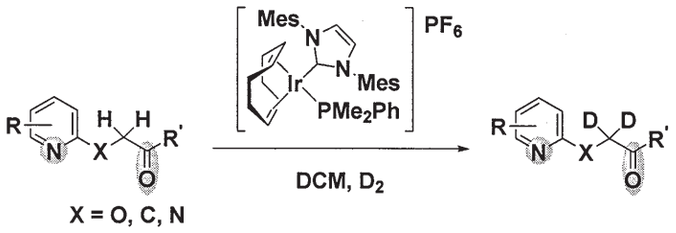
Stable isotope labeled compounds have been utilized for various experiments such as metabolism and toxicology studies. In development of pesticides, these compounds are effectively used as internal standards in residue trials for quick and easy quantitative measurement on trace amounts of pesticide in abundant impurities.

A hydrogen-deuterium exchange reaction using deuterium gas as a starting material is one of the most useful methods for productions of stable isotope labeled compounds. Especially, iridium catalysts are now commonly used for ortho-directed hydrogen-deuterium exchange of aryl compounds and many studies using these methods have been reported with various directing groups[1].

In this work, through our screening study on deuterium labeling of commercially available pesticides by iridium catalyst and deuterium gas, we obtained some pesticides D-labeled at α-position to pyridyl-2-oxy group connected with carbonyl functionality, although *O*-to-*N*-alkyl migration has been proceeded instead without carbonyl functionality in a previous study[2]. Based on this result, we investigated this reaction for model substrates and found a new regioselective hydrogen-deuterium exchange reaction. In the poster, potential utility of this reaction will be described.



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P–19

SYNTHESIS AND APPLICATION OF 125-I RADIOLIGANDS IN DEVELOPMENT OF INSULIN AND GLP-1 THERAPEUTICS

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Over decades, we have extensively applied ^{125}I-radio ligands in various discovery and development studies, comprising receptor binding assays, immunogenicity assessment as well as ADME studies.[1]

In this presentation we will focus on challenges related to synthesis, stability and formulation of ^{125}I-labeled insulin and GLP-1 analogs. More specifically, we will touch upon regioselectivity in iodination reaction, development of purification methods and recent applications of 125-I tracers.

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P–20

HYDROXYAPATITE NANOPARTICLES AS THERANOSTIC VECTORS FOR RADIOPHARMACY

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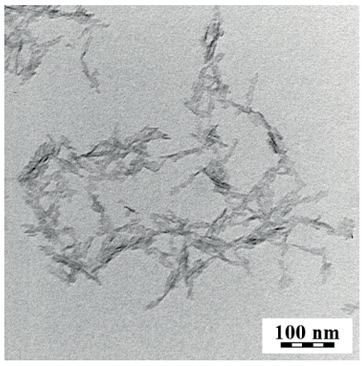
Hydroxyapatite nanoparticles (*HAp-NPs*) seem to be promising biocompatible material for radiopharmacy [1]. Radiolabeling of *HAp-NPs* with ^{18}F, ^{68}Ga, ^{99m}Tc and ^{223}Ra was studied and their in vitro stabilities were evaluated in saline, bovine serum/plasma and 5% albumin solution.

HAp-NPs were prepared as described previously [2]. The labelling was performed by contacting isotopes with NPs at particular pH for 30 min. Sodium [^{18}F]fluoride (UJV Řež, Czech Rep.), ^{68}Ga (IGG-100 generator, Eckert-Ziegler AG, Germany), ^{99m}Tc (GE Drytec generator, MGP Czech Rep.) were commercial Radium-223 was prepared inhouse, from an $^{227}Ac/^{227}Th/^{223}Ra$ generator, eluted as $Ra(NO_3)_2$ with the mixture of methanol and nitric acid and reconstituted in saline. IR and XRPD analyses confirmed *HAp-NPs* structure. Electron micrograph showed below revealed needle-like nanocrystals of *HAp* with significant aggregation.



While the radiolabelling yields for ^{18}F, ^{99m}Tc and ^{223}Ra were acceptable, relatively low yields were achieved with ^{68}Ga and therefore labelling strategy must be modified.

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A CONVENIENT SYNTHESIS OF DEUTEROSILANES BY DIRECT H/D EXCHANGE MEDIATED WITH EASILY ACCESSIBLE Pt(0) COMPLEXES

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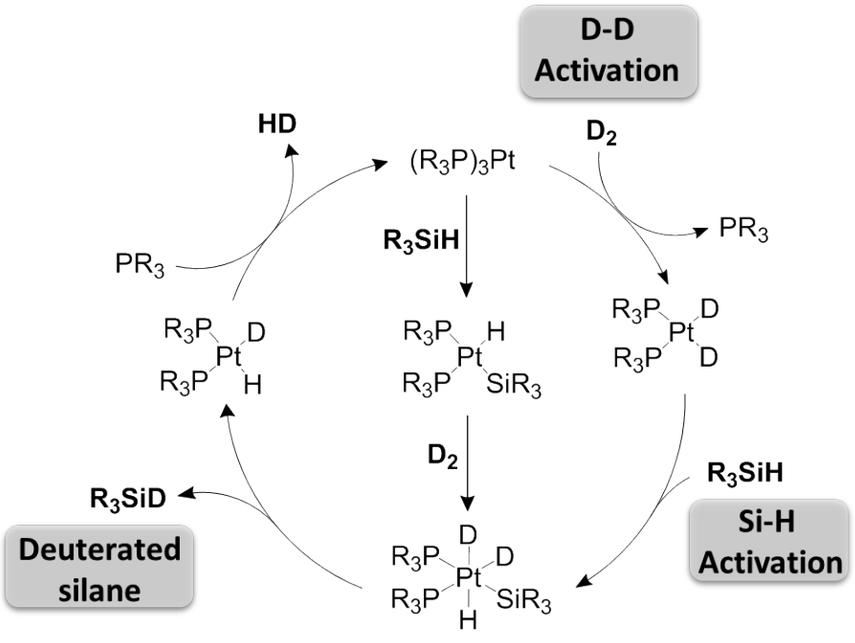
The rising interest in deuterium-labeled compounds stimulates the search for selective and catalytic methods for their preparation. Silanes are very useful reagents in synthesis and are environmentally friendly reductants alternatives to metallo-based or toxic tin derivatives, because of their tolerance to air, moisture and low toxicity. Despite these advantages, the use of deuterated silanes as isotopic labeling reagents is very limited, most probably due to the limited number of methods for their synthesis.

We report that easily accessible simple phosphino-platinum(0) complexes catalyze (0.1-1% mole equivalent) the deuteration of silanes in good yields under mild conditions (60°C, 1 atm). The catalysis is mediated by platinum(II) deuteride/hydride complexes which are in equilibrium with the precursor Pt(0) complexes (Scheme). The Pt(II) complexes can also insert into the Si-H bond of silanes to give intermediate Pt(IV) complexes (Scheme). The proposed mechanism for the catalysis is supported by DFT calculations.



Scheme

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DOTA DECORATED HYDROXYAPATITE NANOPARTICLES LABELLED WITH ^{68}Ga

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Hydroxyapatite nanoparticles (HAp-NPs) are widely used in medicine because of their biocompatibility and stability in various media [1]. The HAp-NPs also belong to promising drug carrier systems for medicinal radionuclides such as Ga-68 as the part of multipurpose theranostic system [2]. Diagnosis and therapy of some diseases is expected to be very accurate and beneficial. Commercial ^{68}Ge/^{68}Ga radionuclide generator (Eckert-Ziegler, Germany) was used to get ^{68}Ga without further purification. Elution was performed with 0.1 M HCl. The labelling was performed with ready-made HAp-NPs (5 mg) in 0.5 M Britton-Robinson buffer solution (5-6 ml) to cover studied pH range (5 - 9). Labelling was carried out with pristine NPs and NPs decorated with selected ligands: DOTA, NOTA, TETA and TRAP (0.05 mg). Experiments with pristine HAp-NPs have shown similar ^{68}Ga uptake with maximal yield of about 85 % at pH = 5 (30 min incubation) (Fig. 1.). Best result was obtained in a procedure when the ^{68}Ga was added to the NPs dispersion in the DOTA ligand solution heated to 70 ºC and incubated for 30 min. at pH = 5 resulting in 95 % yield (Fig. 1.). Further experiments have shown that uptake kinetics is quite fast (over 90% yield within 5 minutes). *In vitro* stability experiments have shown good stability of ^{68}Ga-DOTA-HAp-NPs nanoconstruct in a physiological saline (more than 95 % of activity remained bound to the NPs in 4 hours), but very poor results were obtained in bovine plasma and serum. Therefore, further experiments are needed to block the ^{68}Ga release (Fig. 2.).

Acknowledgment: AZV ČR - 16-30544A; TJ01000334.

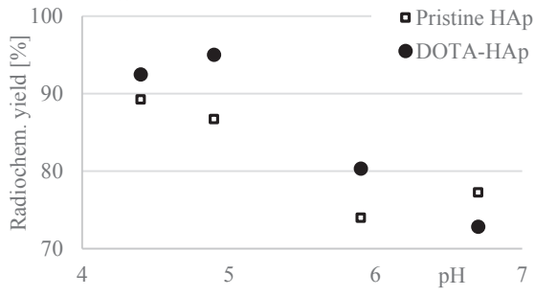

Fig. 1. Radiochemical yield vs. pH.

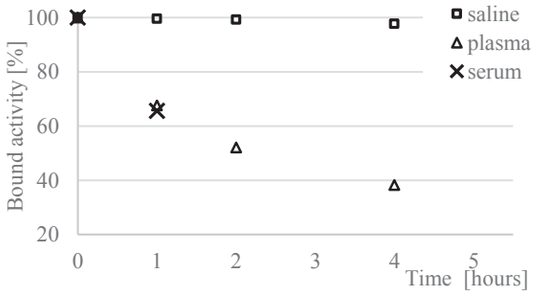

Fig. 2. *In vitro* stability of [^{68}Ga]-DOTA-HAp-NPs.

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P–23

Potent and Selective CC Chemokine Receptor 1 Antagonists Labeled with Carbon-13, Carbon-14 and Tritium

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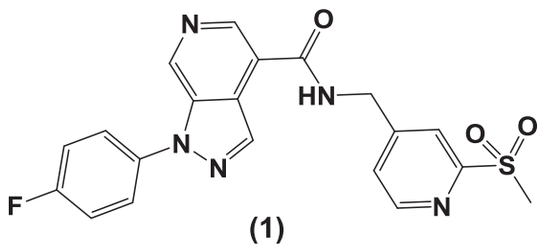
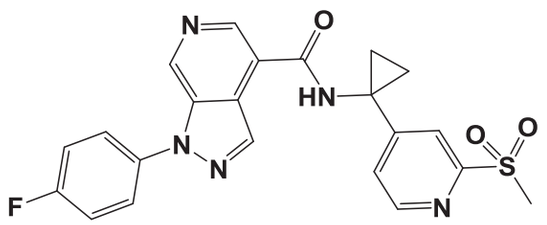
Abstract:

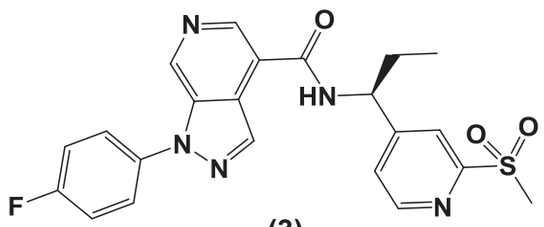
1-(4-Fluorophenyl)-1*H*-pyrazolo[3,4-c]pyridine-4-carboxylic acid (2-methanesulfonyl-pyridin-4-ylmethyl)-amide (**1**) and its analogs (**2**) and (**3**) are potent CCR1 antagonists intended for the treatment of rheumatoid arthritis. The detailed syntheses of these three compounds labeled with carbon-13 as well as the preparation of (**1**) and (**2**) labeled with carbon-14, and finally the tritium synthesis of (**1**) are described.



(1)



(2)



(3)

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THE EXPERIMENTAL STUDY ON THE TRANSFORMATION OF ZINC ISOTOPES IN CENTRIFUGATION

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Abstract: Diethylzinc is used as the gaseous feed medium for the centrifuge cascade. In this paper, the preparation of Diethylzinc and the conversion of Diethylzinc to zinc oxide were studied. The suitable technological route was selected to solve the key problems of the process and the process parameters and conditions were optimized. The yield of Diethylzinc is more than 95%, the yield of zinc oxide is over 99%, and the desired chemical form , zinc oxide is obtained.
Keywords: Diethylzinc; zinc oxide; zinc isotope; centrifuge

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ISOTOPE SCRAMBLING DURING DEUTERODECHLORINATION: CATALYST, SUBSTRATE AND INHIBITION STUDIES.

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The tritiodehalogenation of chloroaromatics is used less commonly than that of bromo- or iodo-aromatics since it often leads to less than optimal specific activity [1]. Dehalogenations are complex three-phase reactions and rate processes in any of the phases can affect the relative rates of the desired deuteration reaction and the unwanted isotopic scrambling reactions. We have studied a range of dehalogenation substrates (Figure 1) to identify important reaction parameters.

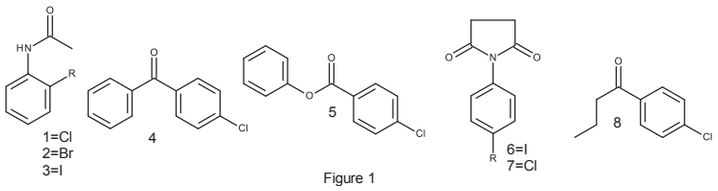

Figure 1

We observed that: (a) The degree of scrambling varied markedly across the range of chloro-substrates; (b) The scrambling was broadly similar for palladium on different supports, suggesting that spillover [2] is unlikely to be significant; (c) The scrambling increased with catalyst quantity and was marginally less with anhydrous catalysts than with catalyst pastes, though the former led to slower reactions; (d) Drying catalyst pastes over molecular sieve or silicagel reduced scrambling, whereas drying under heat and high vacuum gave no improvement, as observed previously[3]; (e) The scrambling was less for I or Br analogues (2,3,6), though the iodo-analogues reacted much more slowly [4]; (f) The scrambling reaction between catalyst-bound H_2O and D_2 gas was very strongly inhibited by iodo-compounds and less strongly by chloro-compounds; (g) The chloro-substrates (1,4,5,7) inhibited this scrambling to different extents; (h) In competitive deuterodechlorination reactions between substrates 5 (little scrambling) and 7 (extensive scrambling), substrate 7 did not react until the dechlorination of 5 was nearly complete, whilst under non-competitive conditions the reaction rates were similar. The difference may reflect the relative ease of oxidative-addition to Pd. This is fast [5] for electron deficient compounds such as 7. Alternatively, it may reflect differential physisorption.

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ISOTOPE SCRAMBLING UNDER DEUTERODECHLORINATION CONDITIONS: GAS PHASE ANALYSES.

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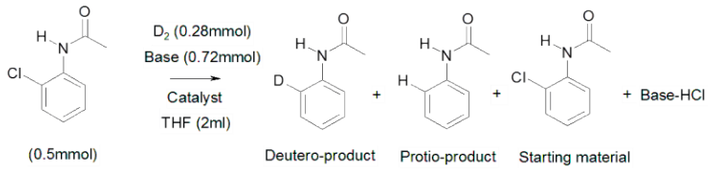
The dehalogenation of haloaromatics is commonly used to label aromatics with D or T. Usually bromo- or iodo-aromatics are used since dehalogenation of chloro-aromatics yields low isotopic abundance. Explanations for this "scrambling" have been briefly reviewed [1]. We have studied deuterodechlorination using the model system below [2].



Deuterodehalogenation reactions are complex single electron transfer processes [3] involving catalyst, solution & gas. Previously we have analysed the solution & the dehalogenation product. We now report studies of the gas phase using a mass spectrometer scanning the D_2/HD/H_2 region. These have shown that: (a) Isotopic scrambling [3] is rapid in the absence of the chloro-substrate. (b) The extent of scrambling was not significantly affected by the THF, the triethylamine, the reaction product, or the dryness of the reaction vessel. Instead, the scrambling was clearly associated with the catalyst. Moreover, the protium for the scrambling reaction arose from the catalyst's water content [4]. This finding is consistent with our previous ^{3}H-NMR analyses of tritiodehalogenation reactions in several solvents in which only HOT and no tritiated solvent was detected [5]. A similar HOT observation has been made by Filer [1].

The part played by isotopic hydrogen gas scrambling in the reduced abundance observed in dechlorinations still remains somewhat uncertain. However, the role of catalyst water is very significant. Utilising dried catalyst (& re-optimising the reaction time!) is advantageous, whilst adding the substrate prior to D_2 exposure avoids a drastic reduction in isotopic abundance.

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P–27

AUTORADIOLUMINOGRAPHY, A POWERFUL AND RELIABLE TOOL FOR DRUG DEVELOPMENT: ACCELERA'S EXPERIENCE

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Autoradiography is an excellent technique that allows to exploit the outstanding advantages of the use of radioisotopes in the drug discovery field.
The development of the phosphorimager technology and the use of autoradioluminography techniques (1) for drug disposition studies present many advantages, like the ease of detection the achievement of high sensitivity and the quantitative results of analyses.
Specifically, Quantitative Whole Body Autoradioluminography (QWBA) is employed for the preclinical studies where the aim is to obtain information about the tissue distribution of a drug candidate. Carbon-14 and tritium are the standard radioisotopes used to label small molecules, while ^{125}I labeling is preferred for biologicals such as antibodies, peptides, and proteins. Moreover, suitable approaches such as dual-labeling can be applied to allow overcoming the problems to investigate the distribution of some challenging drug candidates of new generation like e. g. Antibody Drug Conjugate (ADC) when the autoradiography technique is used.
Here following are summarized some of the WBA studies performed in our labs to provide qualitative as well quantitative information regarding a specimen:
- Determine drug candidate absorption, distribution, metabolism, and excretion;
- Distinguish site-specific drug localization and retention, identify penetration into specific targets (e.g., tumors), determine tissue binding (e.g., melanin), the crossing of the blood-brain barrier, placental transfer;
- Determine tissue distribution of biologicals;
- Track and monitor therapeutic cells *in vivo*;
- Measure the interaction/binding of a drug candidate with delivery devices.

In this poster, we present selected examples adopted in Accelera where autoradioluminography showed to be a key tool in the assessment of drug disposition as well as the validation of new experimental models.

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P–28

STABLE LABEL ACTIVE PHARMACEUTICAL INGREDIENTS: A SCIENCE BASED PROPOSAL FOR SYNTHESIS, ANALYSIS, AND CONTROL. PART 1: FRAMING THE PROBLEM

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The International Consortium for Innovation & Quality (IQ) in Pharmaceutical Development recently established a Working Group focused on the development of a guidance to address Stable Labeled Active Pharmaceutical Ingredients. Deuteration of an Active Pharmaceutical Ingredient (API) in some cases can retard and/ or alter API metabolism by exploiting the primary kinetic isotope effect.[1-2] A number of deuterated active pharmaceutical ingredients have entered into the clinic, and one has been approved.[3] In most cases it is very difficult to impossible to synthesize a 100% isotopically pure compound. This raises synthetic, analytical, and regulatory questions that warrant a science based assessment and proposal for synthetic methods, analytical methods, and specifications.

A cross functional team of scientists with expertise in isotope chemistry, process chemistry, analytical chemistry, and drug metabolism and pharmacokinetics have been meeting under the auspices of IQ to define and address these questions. This poster strives to frame chemistry manufacturing, and controls challenges.

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IN-SITU DETECTION AND CHARACTERIZATION OF ISOTOPICALLY LABELLED COMPOUNDS BIOSYNTHESIZED BY MICROALGAE: A CONFOCAL RAMAN MICROSCOPY APPROACH

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Isotopically labeled compounds needed for structural studies, proteomics, analysis of metabolic fluxes as well as medical applications can be prepared either chemically or biosynthesized *in vivo* by growing simple organisms, *e.g*. photosynthesizing microalgae, on inorganic sources of stable isotopes [1]. Since the cultivation of microalgae and biosynthesis of isotopically labeled compounds is often faced with various limitations resulting from isotopic effects, of which the most important is the detrimental effect of deuterium oxide in high concentrations needed for biosynthesis of fully deuterated compounds, rapid and simultaneous monitoring and quantification of biosynthesized compounds directly within living cells is of great importance for better understanding these effects at the cellular level. Besides nanoscale secondary ion mass spectrometry able to provide distribution of isotopes and isotopically labeled compounds *in situ*, a confocal Raman microscopy can be a method of choice for more dynamic and less laborious single cell studies. The method combines the advantages of molecular specificity and high sensitivity to isotopic substitutions inherent to Raman spectroscopy with spatial resolution of confocal optical microscopy, and can be performed in situ without any staining or complicated treatment and preparation of the specimen. Recent progress in application of confocal Raman microscopy for detection, visualization and quantification of isotopically labeled lipids, starch, proteins, and some microcrystalline inclusions within green microalgae grown on ^{2}H, ^{15}N and ^{13}C substrates will be presented. Advantages and perspectives, but also limitations and pitfalls of the method will be demonstrated and discussed.

This work was supported by the Czech Science Foundation (grant no. 17-06264S).

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P–30

DEVELOPMENT OF A RADIOLABELED ANTIBODY DRUG-CONJUGATE (TAK-264) FOR DMPK AND IMAGING STUDIES

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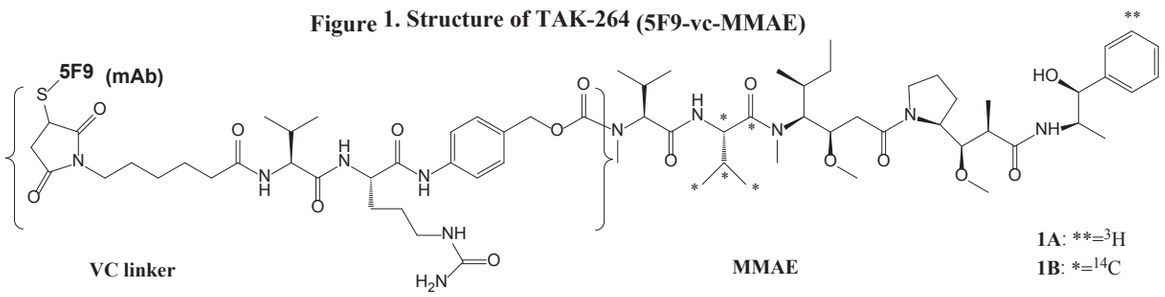
TAK-264 is an antibody-drug conjugate (ADC) containing a monoclonal antibody directed against guanylyl cyclase C (GCC, 5F9) conjugated to monomethylauristatin E (MMAE), an auristatin derivative and potent microtubule disrupting agent (Figure **1**). The monoclonal antibody moiety of TAK-264 selectively binds to GCC, a transmembrane receptor over-expressed in gastrointestinal cancers. The radiolabeled ADC was prepared to support DMPK studies and for later imaging studies with dual labeling on the antibody (using a short half-life isotope, indium-111) and tritiated MMAE (as a long half-life isotope). Preparation began with tritiation of an MMAE brominated derivative with inexpensive tritium gas. The Seattle Genetics-licensed conjugation method was then optimized to handle the small amount of [^{3}H]-MMAE ethanolic solution and to prevent protein precipitation. In order to overcome the possibility of tritium loss via exchange, a carbon-14 version of MMAE was also synthesized.[1] Due to the high molecular weight of the final ADC (~150 kDa), five [^{14}C] were incorporated in order to achieve a measurable specific activity for the ADC. TAK-264 was further investigated *in vivo* by dual-isotope cryo-imaging quantitative autoradiography (CIQA).[2]

Figure 1. Structure of TAK-264 (5F9-vc-MMAE)



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TEMPO-MEDIATED RADIOFLUORINATION OF PYRIDINYL IODONIUM SALTS FOR THE PREPARATION OF 3/5-[^{18}F] FLUOROPYRIDINES

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Objectives: The pyridine moiety is encountered in numerous drugs, and some PET radiotracers contain a [^{18}F]fluoropyridine framework.[1] Although advantageous for stability, introduction of [^{18}F]-fluorine atom at positions 3 or 5 remains challenging. Radiofluorination of pyridinyl iodonium salts using microfluidics was found to efficient but no scope was reported so far.[2] The radical scavenger TEMPO is known to be a very efficient agent for the enhancement of diaryliodonium [^{18}F]radiolabellings.[3,4] Herein, we report a study of the optimization of TEMPO-mediated radiofluoration of pyridinyl iodonium salts.

Methods: We prepared a series of pyridinyl iodonium salts (tetrafluoroborates, bromides, tosylates or triflates) from the corresponding iodopyridines and either anisole, mesitylene or thiophene. Radiofluorination reactions were conducted with [^{18}F]FK-K2.2.2 complex in different solvents (ACN, DMF or DMSO) for 10 to 60 min, at temperature between 85 and 150°C, in the presence of TEMPO (0-5 equiv) and K_2CO_3 (Figure 1). [^{18}F]Fluoropyridines were identified by coelution with reference compounds on analytical HPLC. RCYs were determined after purification on semi-preparative HPLC.

Results: Efficiency of radiofluorination reaction was strongly dependent on the starting iodonium salts and the amounts of TEMPO and K_2CO_3. The optimal RCYs (24-83%) were obtained by treatment of pyridinyl iodonium triflates containing an anisole group in the presence of TEMPO (1 or 3 equiv, depending on the amount of K_2CO_3) in DMF at 130°C for 30 min.

Conclusion: TEMPO-mediated radiofluorination of pyridinyl iodoniums has been proven to be useful for the synthesis of 3/5-[^{18}F]fluoropyridines. Application to the development of new radiotracers is underway.

Acknowledgements: we thank the ANRT (Association Nationale de la Recherche et des Technologies), CIFRE grant 2015/0665. We thank Florent Antoni for his preliminary work on the synthesis of pyridinyl iodoniums.

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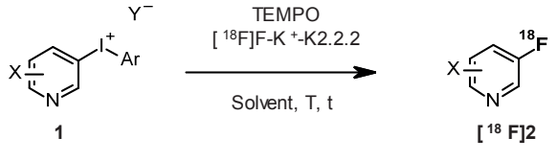

-X = -H, -Cl, -CN, -OMe, -CO2R (in position 2,4 or 6)
Y = BF_4, Br, OTs, OTf
Ar = Anisole, mesitylene, thiophene

Figure 1 : Radiosynthesis of **[^{18}F]2**.

P–32

In vitro and *in vivo* studies of ^{223}Ra labelled HAp nanoparticles modificated with phosphonic acids

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Alpha emitters might be used for palliative treatment of oncologic diseases, e.g. ^{223}Ra in the form of $^{223}RaCl_2$ (Xofigo®) is used for the treatment of bone metastases originating from castration-resistant prostate cancer, thanks to its self-targeting to bones. Precise targeting by appropriate carrier should ensure efficient and accurate destruction of target cancer tissue while keeping healthy tissues intact. Hydroxyapatite in the form of nanoparticles was selected as potential carrier in our studies. This material is biocompatible and its surface modification should lead to better targeting and/or to stabilized nanocomposite dispersions.

Experiments with selected phosphonic acids attached to HAp surface were performed. Hydroxyapatite nanoparticles were prepared by precipitation of $Ca(NO_3)_2$ with $(NH_4)_2HPO_4$ at pH = 11. The precipitate was washed, dried and crushed subsequently. Stabilized nanoparticle dispersions were prepared by ultrasound dispergation of ready-made HAp-NPs in corresponding phosphonic acid solution. The hydrodynamic size distributions of studied stabilized particles were determined using dynamic light scattering. Prepared composite carriers were labelled with ^{223}Ra eluted from ^{227}Ac/^{227}Th/^{223}Ra generator. The labelling yields ranged to some 90 %.

In vitro studies were performed in saline, bovine plasma, bovine serum and 5% albumin solution. Measurements of released activity revealed that stability of prepared carriers decreased in line: saline (released activity of about 7-14 %), bovine serum (15-30 %), albumin solution (30-40 %) and the lowest stability was shown to be in blood plasma (released activity of about 20-45 %). *In vivo* studies were performed with selected composite compounds, which were applied intratumorally into mice with colorectal carcinoma. *Ex vivo* biodistributions in selected organs was measured after 4 and 24 hours.

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P–33

HEAD-TO-HEAD COMPARISON OF BIODISTRIBUTION OF [^{14}C]DAROLUTAMIDE VERSUS [^{14}C]ENZALUTAMIDE IN RATS USING WHOLE BODY AUTORADIOGRAPHY

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Introduction: The risk of seizures is a recognized neuronal adverse event (AE) of androgen receptor (AR) antagonists possibly due to γ-aminobutyric acid A current inhibition in the CNS, which is a common off-target activity in this drug class [1]. In clinical studies with enzalutamide, a 2nd generation AR antagonist, CNS events have been reported in prostate cancer patients [2, 3]. Darolutamide is a novel, investigational oral AR antagonist which is structurally distinct from enzalutamide. Preclinical PK studies demonstrated previously very low blood-brain-barrier penetration for this drug, suggesting a minimal risk of CNS effects as e.g. fatigue, cognition impairment and seizures [4]. To better understand the effects of compound differences, we performed a head-to-head comparison *in vivo* biodistribution study in rats with [^{14}C]-labeled darolutamide and enzalutamide using quantitative whole-body autoradiography (QWBA).

Methods: The radiosynthesis of [^{14}C]darolutamide and [^{14}C]enzalutamide were each performed in 2 steps, introducing the carbon 14 isotope in the cyano group or imidazoline moiety, with a radiochemical yield of 13% and 22%, respectively. Male Wistar rats were orally dosed with 10 mg/kg [^{14}C]darolutamide or [^{14}C]enzalutamide in the same formulation, administration volume, and radioactive dose (specific activity 4.9 MBq/mg and 4.8 MBq/mg). One animal per time point was sacrificed at 1h and 8h following [^{14}C]darolutamide administration, and 4h and 8h following [^{14}C]enzalutamide administration, and processed for QWBA. The time points reflect the drug's specific time of maximum concentration (t_{max}) in either blood or brain, based on previous investigations. Quantitative evaluation was based on internal blood standards spiked with [^{14}C].

Results: At 8 h post dose, [^{14}C]enzalutamide was 3-5 times higher in several adipose tissues vs. blood, and showed almost similar concentration in brain vs. blood. In contrast, [^{14}C]darolutamide was near detection limit at 8 h post dose (brain/blood ratio of 0.08) without any hints for retention in any organs/tissues. In general, both compounds showed good absorption and homogenous distribution with highest concentration in excretion organs liver and kidneys. [^{14}C]darolutamide was rapidly eliminated from all organs/tissues until 8 h post-dose, whereas [^{14}C]enzalutamide remained constant in the whole animal body.

Conclusions: The present head-to-head QWBA study clearly demonstrated the different behaviors in biodistribution of [^{14}C]darolutamide and [^{14}C]enzalutamide. [^{14}C]darolutamide displayed only low blood-brain-penetration ([^{14}C]enzalutamide remained constant in the brain at blood level). This may lead to a reduction in the risk of CNS-related AEs with darolutamide vs. enzalutamide. In addition, the retention of enzalutamide in adipose tissue might be the reason for the long elimination half-life observed in humans (5.8 days) vs. darolutamide (11.5-16 h).

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P–34

FGFR2-TARGETED THORIUM-227 CONJUGATE IN PRECLINICAL MODELS OF COLORECTAL, GASTRIC AND TRIPLE-NEGATIVE BREAST CANCER

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Introduction: Overexpression of fibroblast growth factor receptor 2 (FGFR2) is involved in cancer progression, promotion of oncogenesis, and resistance to targeted therapies [1]. Combined with the low cell surface expression of FGFR2 in healthy tissues, FGFR2 is an attractive candidate for targeted alpha therapy (TAT), including targeted thorium-227 conjugates (TTCs). In this compound family a 3,2-HOPO chelator, which binds thorium-227 with high affinity, is covalently attached to an antibody. This enables the specific delivery of the alpha particle emitter thorium-227 to tumor cells. Thorium-227 has a half-life of 18.7 days and decays via emission of an alpha particle to radium-223 (half-life of 11.4 days), a calcium-mimetic used in the treatment of CRPC [2]. TTC have been previously demonstrated to induce clustered DNA double-strand breaks (DSB) [3]. We herein describe structure, *in vitro* and *in vivo* potency of the FGFR2-TTC.
Methods: Radiochemical purity was determined by instant thin layer chromatography and radio-HPLC analysis. *In vitro* cytotoxicity experiments were performed on FGFR2-positive cancer cell lines using Cell Titer Glo. Induction of DNA DSBs were measured by detection of phosphorylated histone protein H2AX. *In vivo* potency of the fully human mouse cross-reactive FGFR2-TTC was evaluated in subcutaneous xenograft mouse models of human colorectal (NCI-H716), gastric (SNU-16), and triple-negative breast cancer (MFM-223) (single iv dose: 0.14 mg/kg, 500 kBq/kg). Accumulation of FGFR2-TTC in tumor and various organs was evaluated by quantitative whole body autoradiography (QWBA) or a high purity germanium detector.
Results: FGFR2-TTC had a radiochemical purity of 95% with a radiostability of >48h. Binding experiments to recombinant human FGFR2 demonstrated similar affinity between radiolabeled FGFR2-TTC and non-radiolabeled FGFR2 antibody-chelator conjugate. *In vitro*, FGFR2-TTC reduced the viability of FGFR2-expressing human SUM-52PE cells, induced DNA DSBs and cased a cell cycle arrest in the G2/M phase. The immunogenic cell death marker calreticulin was detected on the cell surface on SUM-52PE cells after exposure to FGFR2-TTC. *In vivo*, FGFR2-TTC inhibited tumor growth in human colorectal and gastric cancer xenograft models. Specific accumulation of FGFR2-TTC was observed in human gastric cancer mouse model, determined by QWBA, as well in a human colorectal cancer model, determined by organ counting.
Conclusions: FGFR2-TTC is a novel TAT using thorium-227 as alpha emitting radionuclide. FGFR2-TTC efficiently decreased viability *in vitro* in FGFR2-positive cell lines. Its MoA was demonstrated to induce DNA DSBs and cell cycle arrest. FGFR2-TTC induced the expression of the immunogenic cell-surface death-marker calreticulin. FGFR2-TTC specifically distributed into tumor, whereas radium-223 into bone marrow/bone, in a xenograft gastric mouse model.

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P–35

Novel Synthesis of Deuterium-labelled Alternariol- and Alternariol monomethylether-Standards for the HPLC-MS/MS-Analysis in Food and Feed

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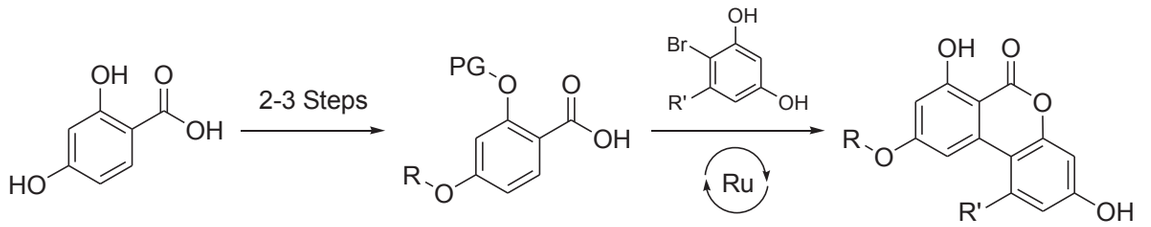
Abstract

Alternariol (AOH) and Alternariol monomethylether (AME) are two secondary metabolites of *Alternaria* fungi which can be found in various foodstuffs like tomatoes, nuts and grains.[1] Due to their toxicity and potential mutagenic activity[2] the need for the development of high-throughput methods for the supervision of AOH- and AME-levels is of increasing interest.[3] As the availability of both native and labelled AOH and AME analytical standards is very limited we herein wish to present a novel concise approach towards their synthesis employing a ruthenium-catalyzed *ortho*-arylation[4] as the key step.



R=H or CD_3

R=H, R'=CD_3: AOH-d_3
R=CD_3, R'=CH_3: AME-d_3

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P–36

COMPLEXES OF STIGMASTEROL HEMIESTERS WITH L, D-TRYPTOPHAN

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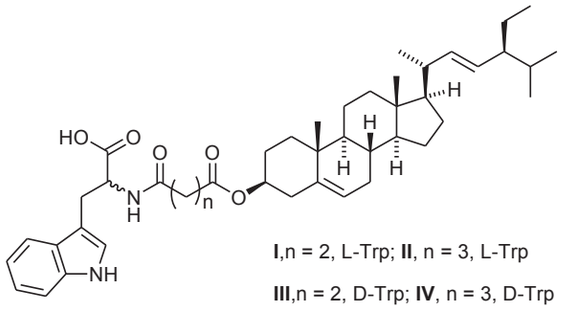
Various biological activities of steroid compounds have been well known for decades now. When labelled with the appropriate radionuclide, steroids can be applied in diagnostics and treatment of different hormone-dependent tumors. Specific receptor binding assures selective distribution of radiolabelled steroid in the body. In this work we present synthesis of four conjugates of stigmasterol hemiesters with L,D-tryptophan and their complexes with platinum (II). Furthermore, we introduce preliminary results of labelling one of DOTA-modified ligands with ^{68}Ga. Synthesis of stigmasterol-based ligands was carried out in three steps. Reaction of stigmasterol with succinic anhydride or glutaric anhydride in dry pyridine was followed by a coupling of stigmasterol hemiester with L,D-tryptophan benzyl ester in the presence of propylphosphonic anhydride [1]. Debenzylation of prepared conjugates resulted in desired products (**I** - **IV**) in 74-88% yields [2].



I,n = 2, L-Trp; **II**, n = 3, L-Trp
III,n = 2, D-Trp; **IV**, n = 3, D-Trp

Platinum (II) complexes of obtained conjugates **I** - **IV** were prepared by a reaction of steroidal ligand with potassium tetrachloroplatinate in DMF [3]. Structures of prepared complexes were confirmed by means of high resolution mass spectroscopy together with other experimental methods. Cytotoxic activities of prepared compounds are yet to be investigated. A preliminary labelling experiment with ^{68}Ga was made with conjugate of stigmasterol hemiglutarate with D-tryptophan **IV**. Steroidal ligand was modified by its reaction with a DOTA derivative in the presence of T3P. Labelling of obtained ligand with ^{68}Ga was performed using eluate from ^{68}Ge/^{68}Ga generator in citrate buffer during 30 min at 80°C. Yield of radiolabelling (about 50%) was determined by HPLC.

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P–37

UTILIZATION OF ROMANITE AMBER ORIGINATING FROM BUZAU COUNTY ROMANIA AS AN AMS BACKGROUND MATERIAL

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Amber deposits can be useful as a source of material to be used as AMS Background for carbon-14 measurements. In Romania, due to the uncertainty in obtaining samples of fossil coal deposits accessible and guaranteed in time, the exploitation of amber lodes in the Colti - Buzau quarry can offer a viable alternative to the current practices at RoAMS IFIN – HH Romania. Romanite is internationally recognized, and the exploits in the Buzau area have been known for thousands of years. In this respect, its physical and chemical properties recommend it as a good alternative to coal and graphite (better stability over time under certain conditions, large percentage of carbon, nitrogen lack, $\delta^{13}C$ values comparable of those of organic matter derived from samples to be analyzed), itself being a part of many artifacts involved in "amber route" that ran from the Baltic Sea, whether the time of the pharaohs, the Iron Age in Romania or Roman Age. Preliminary characterization of samples using instrumental chemical analysis methods will establish the type of amber, origin and also estimate its age by determining a number of parameters using Fourier transform infrared spectroscopy - variable angle reflectance (FTIR-VAR) and Fourier transform Raman spectroscopy (FT-Raman).

The experience gained from previous scientific projects such as grant no. 91-019 / 2007, ROMANIT research project entitled "Prestige and Power. Romanian Museums' Antique Items of Trade. Non-metallic adornments, with an archaeometrical study on the origin of amber beads", as well as from the RoAMS Laboratory practices have determined the optimal conditions for pre-treatment, storage and use of those samples from very old deposits.

AMS measurements have shown that the forecasts are correct, both for old amber and for the more recent sources (in this latter case, the value of the Background being increased), C-14 / C-12 ratio values obtained on a series of 20 different amber samples ranging between 10^{-15} and $2.5 \cdot 10^{-14}$.

In addition to the AMS data obtained at the 1 MV Cockroft-Walton Tandetron HVEE Netherlands accelerator coupled with mass spectrometer, the paper also presents a comparative experimental study performed by FTIR spectroscopy for contaminants occuring on storage of graphite, fossil and semi-fossil coals, commonly used in the AMS technique.

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P–38

SEMI-AUTOMATIC COMBUSTION OF ENVIRONMENTAL AND BIOLOGICAL SAMPLES AND DETERMINATION OF THEIR CONTENT IN TRITIUM AND CARBON-14 BY THE QUANTULUS 1220 ULTRA-LOW BACKGROUND ANALYZER; NEW SOLUTIONS TO REDUCE THE BACKGROUND FOR OXIDIZER M307 AND EQUIVALENTS

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The presentation aims to introduce and characterize a new experimental demonstrative model contributing to the increase of measurement accuracy, in terms of minimum detectable activity (MDA), in the analysis of samples with low concentrations of tritium (^{3}H) and radiocarbon (^{14}C) by the liquid scintillation beta spectrometry. The clue of this attempt is related to the qualitative and quantitative differences between ^{3}H and ^{14}C inventories of the cellulose used to manufacture the cups necessary for the immobilization of materials to be processed as sample – by their combustion in an oxidation device (combuster, oxidizer) – in which to be then measured the concentration of these radionuclides by liquid scintillation beta spectrometry, depending on the temporal origin of the wood from which it was extracted and contributing to the threshold level of the minimum detectable activity for the beta-emitting radionuclide. Finally, the aim of the research is to create and to use such combustion cups in the current practice of determining low concentrations of tritium and radiocarbon even in the limiting conditions offered by some equipments dedicated to liquid scintillation beta-spectrometry. The new solution proposed to be experimented represents an alternative embodiment of a consumable existing on national and international market. This new product will be obtained by an adapted technology following some of the variants described in the literature data.

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P-39

CARBON-14 RADIOLABELING OF ASPALATHIN: A POTENTIAL ANTIDIBETIC COMPOUND ISOLATED FROM ROOIBOS TEA.

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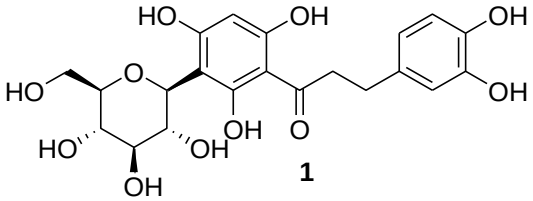
The natural product aspalathin **1** is a bioactive dihydrochalcone-*O*-glucoside, which was isolated from the leaves of *Aspalathus linearis*, a rooibos plant that grows in the mountainous areas of South Africa. It has been reported to show potential antioxidant and radical scavenging activities as well as having good in vitro activities against sugar diabetes type-II. Although preliminary research has focused on the synthesis of the nonlabeled aspalathin and developing it into a completely new medicine that can combat diabetes, carbon-14 labeled aspalathin has not been synthesized yet. Thus, there is a need to synthesize the C-14 labeled version of aspalathin in order to understand it's *in vivo* tissue distribution pattern. The successful incorporation of C-14 into aspalathin will speedily facilitate the *in vivo* biodistribution and pharmacokinetics studies of this compound, thereby accelerating it into the clinical phase and subsequently its entry into the market. The synthesis of aspalathin was achieved in a seven step radiochemical synthesis starting from the cyanation of 3,4-dibenzyloxy iodobenzene with C-14 CuCN. This step was followed by hydrolysis with sodium hydroxide, reduction with lithium aluminium hydride and oxidation with manganese dioxide to form 3,4-dibenzyloxy benzaldehyde. Subsequent aldol condensation followed by hydrogenation delivered the desired C-14 labeled aspalathin. This poster will focus on strategies towards radiolabeling aspalathin **1** with the C-14 isotope.



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GALIUM-68 LABELLING ON THE MICROFLUIDIC SYSTEMS.

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The use of the microfluidic systems in the production of the radiopharmaceuticals is a new direction to obtain a product of high purity and high specific activity. Increasing employing of gallium-68 radiopharmaceuticals in nuclear medicine for tumor imaging by positron emission tomography require to find a new and efficient synthetic strategies.

The aim of this research was verify the possibilities of new gallium-68 labelling procedure with microfluidic system. The radiolabelling of the precursor of DOTA-Substance P was performed on microfluidic chips, produced at the Department of Radiopharmaceuticals of the Nuclear Physic Institute of the ASCR, v.v.i. in Řež. The experiments are focused on preliminary experiments and prove of the functionality of the designed microfluidic system concerning to optimize production of the labelled product using small amounts of the precursor (μg) achieving a highest specific activity.

Radiolabelling procedure was performed on a system consisting of high-pressure HPLC pumps, connected with two manual Rheodyne valves, joined to microfluidic chip plugged in heating device with temperature sensor. Microfluidic chips were made from PMMA matrix with the column (approx. 10×4 mm) containing C18 sorbent. Radiolabelling was carried out using two approaches. In the homogeneous labelling, precursor was mixed in the reactor with generator eluate containing gallium-68 (30 MBq) and then was trapped on the sorbent. In the heterogeneous labelling, precursor was trapped on the sorbent and then was labelled with eluate containing gallium-68 (58 MBq). For both: Free gallium-68 went into the waste and the labelled product and the unlabelled precursor was washed with ethanol from the microfluidic chip into a vial. Analysis was carried out LC/MS system.

Experiments proved feasibility of the proposed procedure, but it is still necessary to optimize labelling conditions, especially pH value. The yield of gallium-68 labelled precursor of DOTA-Substance P was 41 %.

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THERANOSTIC SUPERPARAMAGNETIC IRON OXIDE NANOVECTORS

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Superparamagnetic iron oxide nanoparticles (*SPIONs*) are being widely studied as contrast agents and radionuclide carriers in nuclear medicine and radiology, advantaging of simple preparation, low toxicity, biocompatibility and superparamagnetic properties. Further**,** *SPIONs* can be vectorised by an external magnetic field to a target tissue [1]. The scope of our work was the synthesis and characterization of *SPIONs* and their labelling with: PET radionuclide ^{18}F, ^{99m}Tc useful for SPECT diagnostics and with ^{223}Ra for alpha-particle therapy.

SPIONs were prepared by co-precipitation method [2] and stabilised with 0.1 M sodium citrate. Such prepared *SPIONs* were labelled subsequently. The structure and composition of the synthesised nanoparticles was checked by using TEM, FT-IR, Raman and XRPD. The size-distribution of the nanoparticles in aqueous dispersions was determined by dynamic light scattering (DLS) and the stability of the nanoparticles was determined by the measurement of Z-potential. Labelled *SPIONs* were prepared by contacting the suspension of 1-2 mg *SPIONs* with generator eluates containing $Na^{99m}TcO_4$ 200-250 MBq eluted from commercial generator in physiological saline. Labelling with $^{223}Ra(NO_3)_2$ 100 – 50 kBq was performed in PBS buffer at pH = 7, contacting with reconstituted aqueous methanol-nitric solution (0.7 M HNO_3 in 80% CH_3OH) eluted from generator. Labelling SPIONs with $Na^{18}F$ 150 MBq was performed in aqueous solution.

The magnetite nanoparticles were labelled with ^{18}F (109,7 min), ^{99m}Tc ($T_{1/2}$ = 6 h) and ^{223}Ra ($T_{1/2}$ = 11,43 d) with excellent yields and their stability was studied for a period of five half-lives in physiological saline, plasma, serum and albumin solution.

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SYNTHESIS OF STABLE ISOTOPE D LABELED DIPHENYL PHTHALATE

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Diphenyl phthalate is one of the most widely used plasticizers in plastics industry. It is mainly used to increase the elasticity, ductility and softness of polymer plastics. Diphenyl phthalate is fat-soluble substance which can accumulate in adipose tissue of human. Toxicological experiments show that phthalates have the effect of estrogens, which can lead to male decrease in sperm numbers and female precocious puberty.

Internationally analysis method for detecting diphenyl phthalate mainly included gas chromatography (GC), liquid chromatography (LC), gas chromatography-tandem mass spectrometry (GC/MS), liquid chromatography- tandem mass spectrometry (LC/MS) etc. But there have been some defects on these methods, such as dealing with complex and matrix interferences. To avoid these problems, the current method is IDMS (Isotope Dilution Mass Spectrometry) to detect the content of diphenyl phthalate in food.

There are no reports about the synthesis of stable isotope D labeled diphenyl phthalate and as a stable isotope labeled compounds detected the content of diphenyl phthalate in food. Combined with the industrial synthesis route of diphenyl phthalate , this study reports that o-xylene-D_{10} as a starting raw material oxidized by potassium permanganate, then esterification with phenol to get diphenyl phthalate-D_4, which can be used as a stable isotope internal standard reagent. (Scheme Figure 1)

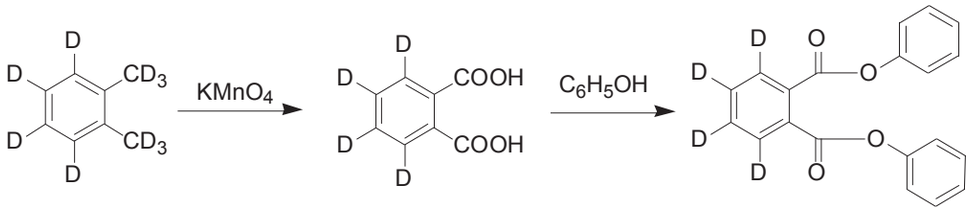

Fig.1 The Synthesis route of stable isotope D labeled diphenyl phthalate

After the two steps to give a white powder in a yield of 65.3% (in terms of o-xylene) with liquid purity of 99.3% and the abundance of 99.0atm% D.

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Acetic acid [^{3}H] sodium salt	15-30 Ci/mmol	Methyl iodide [^{14}C]	50-60 mCi/mmol
Aniline [^{14}C(U)] hydrochloride	80-100 mCi/mmol	Methyl iodide [^{3}H]	85-87 Ci/mmol
Barium carbonate [^{14}C]	50-60 mCi/mmol	Methyl nosylate [^{14}C]	50-60 mCi/mmol
Benzene [^{14}C(U)]	80-120 mCi/mmol	Methyl nosylate [^{3}H]	60-80 Ci/mmol
Benzoic acid [carboxyl-^{14}C]	50-60 mCi/mmol	Potassium cyanide [^{14}C]	50-60 mCi/mmol
Benzoic acid [ring-^{14}C(U)]	60-80 mCi/mmol	Sodium borohydride [^{3}H]	80-90 Ci/mmol
Bromoacetic acid [1-^{14}C]	50-60 mCi/mmol	Sodium cyanohydride [^{3}H]	30-50 Ci/mmol
Bromoacetic acid [2-^{14}C]	50-60 mCi/mmol	Sodium cyanide [^{14}C]	50-60 mCi/mmol
Bromobenzene [^{14}C(U)]	80-100 mCi/mmol	Sucrose [^{14}C(U)]	500-700 mCi/mmol
Chloroacetic acid [1-^{14}C]	50-60 mCi/mmol	Thiourea [^{14}C]	50-60 mCi/mmol
Cuprous cyanide [^{14}C]	50-60 mCi/mmol	Tritium gas [^{3}H]	2.6 Ci/cc
Diethylmalonate [2-^{14}C]	50-60 mCi/mmol	Urea [^{14}C]	50-60 mCi/mmol
Formaldehyde [^{14}C]	50-60 mCi/mmol	Zinc cyanide [^{14}C]	100-120 mCi/mmol

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