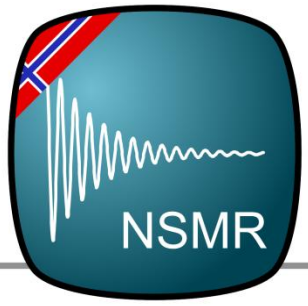

Norsk selskap for magnetisk resonans

Norwegian Society for Magnetic Resonance

MR 2012

12th Norwegian National MR Meeting

January 11 & 12, 2012
Radisson Blu Nydalen, Oslo




MR 2012 - Organizing Committee

The 12th National MR Meeting, MR 2012, is organized by

Frode Rise (UiO: University of Oslo), Øystein Bech Gadmar (OUS: Oslo University Hospital), Aud Bouzga (SINTEF), Eddy Walther Hansen (UiO), Sissel Jørgensen (SINTEF, UiO), Wibeke Nordhøy (OUS), Daniel Sachse (UiO / OUS), Anne Spurkland (UiO), Lili Zhang (OUS)

SINTEF Materials and Chemistry

SINTEF Materials and Chemistry is working closely with industry to develop advanced materials, products, processes and new tools. New, environmental friendly processing methods increase productivity and raise quality standards.

Institute for Experimental Medical Research

The IEMR was established in 1951 to create an environment that promoted research in collaboration with the clinical departments at Oslo University Hospital - Ullevål. The institute has developed a strong focus on cardiovascular research in addition to continued activity in biliary and pancreatic research.

University of Oslo NMR Center

University of Oslo NMR Center

The University of Oslo NMR Center services the NMR needs for Organic Chemistry, but is also serves academic and commercial research in polymer chemistry, nuclear chemistry, organometallic chemistry, homogeneous catalysis, organic analytical chemistry, inorganic chemistry, medicinal chemistry, material- and nano science, galenic pharmacy, medicinal pharmacy, botany, natural product identification, brain metabolism research, metabolomics studies, algae toxin research, protein structure elucidation and many other research fields.

Letter of Welcome

Dear conference participants and speakers

It is our great pleasure to welcome you on behalf of the Norwegian Society for Magnetic Resonance and the local organizing committee to the 12th Norwegian National MR Meeting – MR 2012 – in Oslo.

Our aim is to provide a meeting place for everyone working with
Magnetic Resonance for scientific and technical exchange and for the establishment of new contacts across this vast field. We continue the successful integration of animal and clinical MRI and MRS science from the 11th National NMR meeting together with the NMR science of biochemistry, organic chemistry, natural substance identification and many other fields.

We are particularly happy to welcome our dear and valued Corporate members to this meeting. NSMR started to recruit Corporate members in 2011 and we are happy to see so many present.

We hope you will enjoy the scientific program, divided into five sessions:

- NMR in Metabolomics
- Clinical and Preclinical MR Imaging and Spectroscopy
- Marine, Biomolecular and Bioactive Molecule NMR
- NMR on Solid and Porous Materials
- Macromolecular NMR

Each of these will start with a general introduction inteded to make the session accessible to those not working in the same field. We want to encourage you to take this opportunity and learn about your colleagues' work, and hope that this approach will inspire and strengthen collaboration.

In the early evening of January 10th you will also have the opportunity to visit MR labs at the Oslo University Hospital (Ullevål Hospital and Rikshospitalet), the SINTEF solid state NMR laboratory as well as the University of Oslo NMR Center at Blindern.

The poster presentations will be up during the whole conference and the official presentation of the posters will take place just before the conference dinner on Tuesday.

The conference dinner is sponsored by Bruker Biospin AB and wine will be covered by Agilent Technologies.

Best wishes and hoping for a great conference,

For the organizing committee
Frode Rise and Daniel Sachse

Aker BioMarine

Aker BioMarine is an integrated biotechnology company and has a wide set of capabilities within nutraceuticals (dietary supplements and functional foods) and is an experienced player in nutraceutical applications of lipids, product development, and intellectual property rights (IPR), R&D and product commercialization.

Drug Discovery Laboratory AS

Drug Discovery Laboratory AS has the knowledge, facilities and equipment for drug discovery and development, including synthesis and characterisation, chemical analysis, drug formulation and larger scale production.

EWOS Innovation

EWOS Innovation is the R&D Company of EWOS and Cermaq, and consists of people dedicated to be the worlds best R&D Company in aquaculture. We are constantly seeking to make new and better solutions for our customers. We want to reach our goals through knowledge, team-work ,and by the attitude that nothing is impossible. Our working tools are our people, unique R&D facilities, and our network with other industries and R&D institutions through-out the world.

Painted by JOTUN

Did you know that the Eiffel Tower is 300 metres high and was built to commemorate the centenary of the French Revolution? The tower was completed for the 1889 World's Fair and is still one of the world's best known landmarks. It is no coincidence that Jotun supplied the paint.

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MR2012 – Program

08.00 -9.00	Registration and Coffee
09.00 - 09.10	Welcome (Prof. Svein Stølen, head of the Dept of Chemistry, University of Oslo)
Session: NMR in Metabolomics (Chair: Daniel Sachse)	
09.10 - 10.00	Plenary Lecture. General Introduction, illustrated by presentation: NMR based Metabonomics approach: from food quality control to clinical applications (Eberhard Humpfer, Bruker Biospin)
10.00 - 10.20	Cancer tissue metabolomics (Tone Frost Bathen, NTNU)
10.20 - 10.50	Coffee Break
10.50 - 11.10	13C NMR spectroscopy elucidates novel biochemical pathways in the brain (Bjørnar Hassel, OUS / NDRE)
11.10 - 11.25	NMR profiling of biofluids (Daniel Sachse, UiO/OUS)
11.25 - 11.45	NMR Spectroscopy in Identification of Secondary Metabolites (Karl Egil Malterud, UiO)
11.45 - 12.45	Lunch
Session: Clinical and Preclinical MR Imaging and Spectroscopy (Chair: Ingrid Gribbestad)	
12.45 - 13.35	Plenary Lecture. General Introduction, followed by presentation: MRI and the human brain (Renate Grüner, Haukeland University Hospital / University of Bergen)
13.35 - 13.55	Using MRI and MRS for studying cancer treatment in animal models (Ingrid Gribbestad, NTNU)
13.55 - 14.15	Diffusion-weigthed MRI - basic prinicples and clinical applications (Therese Seierstad, OUS)
14.15 - 14.45	Coffee Break
Session: Marine, Biomolecular and Bioactive Molecule NMR	

(Chair: Chris Miles)	
14.45 - 15.25	Plenary Lecture. General Introduction, followed by presentation: NMR studies of phospholipid bilayers and brain tissue (Willy Nerdal, UiB)
15.25 - 15.45	NMR in Mycochemistry (Silvio Uhlig, NVI)
15.45 - 16.05	NMR studies of small antimicrobial peptides (Johan Isaksson, UIT)
15.05 - 16.20	Rangiputamide from Prorocentrum lima: Structure elucidation by NMR (Chris Miles, NVI)
16.20 - 16.40	Real-Life Possibilities for Parallel Receivers in Liquids NMR (Dimitris Argyropoulos, Agilent Technologies)
16.50 – 18.30	Excursions to the MR labs
18.30 - 19.30	Poster Session
20.00 ---	Conference Dinner

Wednesday, January 11th 2012

08.30 - 09.30	Registration
08.30 - 09.30	General Assembly of the Norwegian Society for Magnetic Resonance
Session: NMR on Solid and Porous Material (Chair: Eddy W. Hansen)	
09.30 - 10.20	Plenary Lecture. General Introduction, illustrated by presentation: NMR Spectroscopy of Solid and Soft Materials (Dick Sandstrøm, Bruker Biospin)
10.20 - 10.40	Easy Access to the Comonomer Content in Ethene/α-Alkene Copolymers Using Solid State 1H-MAS NMR Spectroscopy (Eddy W. Hansen, UiO)
10.40 - 11.00	Ageing of XLPE probed by High MAS 1H-NMR and Relaxation (Jobby Paul, UiO)
11.00 - 11.30	Coffee Break
11.30 - 11.50	Defects and Si/Al ratios in CHA type zeolites (Bjørnar Arstad, SINTEF)

11.50 - 12.10	Using Diffusion-weighted NMR to Characterize Porous Media. (John Georg Seland, UiB)
12.10 - 12.30	Progress and Challenges in Proton NMR of Solids: Fast Spinning, Multipulse Sequences, Indirect Detection (Vadim Zorin, Agilent Technologies)
12.30 - 13.30	Lunch
Session: Macromolecular NMR (Chair: Anne Spurkland)	
13.30 - 13.35	Announcement of the Poster Prize
13.35 - 14.15	Plenary Lecture. General Introduction, followed by presentation: A vitellogenin polyserine cleavage site: highly disordered conformation protected from proteolysis by phosphorylation (Øyvind Halskau, UiB)
14.15 - 14.35	NMR investigations of structural and functional properties of Co-containing mammalian methionine sulfoxide reductase B1 (Olena Dobrovolska, NTNU)
14.35 – 14.50	The intriguing Cyclophilin A -HIV-1 Vpr interaction: prolyl cis/trans isomerisation catalysis and specific binding (Torgils Fossen, UiB)
14.50-15.20	Coffee Break
15.20 - 16.00	Insights to enzymatic mechanism of Chitin-binding protein 21 (CBP 21) Serratia marcescens by NMR spectroscopy (Finn Aachmann, NTNU)
16.00 – 16.15	Structural analysis of the conserved ubiquitin-binding motifs (UBMs) of the translesion polymerase iota in complex with ubiquitin (Daniel Burschowski, UiO)
16.15 - 16.30	Protein-protein interaction in T cell signalling (Anne Spurkland, UiO)
16.30 – 16.40	Closing remarks

Abstracts for MR2012

NMR based Metabonomics approach: from food quality control to clinical applications

Eberhard Humpfer, Manfred Spraul, Hartmut Schäfer, Birk Schütz, Fang Fang

Bruker BioSpin GmbH Germany

NMR becomes more and more important as one of the key analytical technologies in Metabonomics applications. A wide range of applications could be covered which span from the investigation of body fluids and tissues of humans and animals to the quality and safety control of food materials. A strong pint of NMR is the analysis of mixtures NMR, especially due to its unmatched intra- and inter-laboratory reproducibility , which allows to safely visualize even smallest variations in the concentrations of a large set of metabolites at the same time. Additionally the NMR technique unifies the power of targeted and non-targeted screening within one experiment, such delivering a multitude of parameters describing a sample. Even unknown deviations can be identified comparing the spectrum of the actual sample to a standard model. Examples of this approach are given for a study using urine sample for metabonomic phenotyping by NMR, quality control for unfractionated heparin, health relevant adulteration of milk powder in baby food and some other examples from food chemistry like wine and oil analysis.

CANCER TISSUE METABOLOMICS

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Abstract
Metabolism comprises the integrated network of biochemical reactions that supports life in a living organism, and metabolomics is the systematic study of small-molecular compounds from metabolism. The metabolism of cancer cells is changed compared to normal cells due to high proliferation rates and malignant transformation. Metabolomics, using high resolution magic angle spinning MR spectroscopy (HR MAS MRS), may establish detailed tumor portraits reflecting diagnostic status or therapeutic response, thus potentially leading to the discovery of useful biomarkers in a clinical context. HR MAS MRS enables investigation of tissue samples with minimal sample preparation and keeps the sample intact after analyses. This talk will cover some of the practical issues of HR MAS MRS, and results from published an ongoing studies will be presented.

Foto: Geir Mogen/NTNU

Figure 1: MR Metabolomics Lab, NTNU, Trondheim.

^{13}C MRS IN NEUROBIOLOGY. ITS USE IN MONITORING BRAIN ENERGY METABOLISM AND NEURON-ASTROCYTE INTERACTIONS, AND IN IDENTIFYING NOVEL METABOLIC SUBSTRATES AND METABOLIC PATHWAYS.

Bjørnar Hassel

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A wealth of information on brain metabolism has been gathered from studies in which ^{13}C-labeled metabolic substrates (often glucose; Fig. 1) have been administered to human subjects or experimental animals. ^{13}C Magnetic resonance spectroscopy (MRS) of the brain (or extracts of brain) has shown to what degree the ^{13}C-labeled compound has been metabolized by the brain, and, to some extent, along which metabolic pathways. The latter interpretation derives from the fact that ^{13}C MRS shows the ^{13}C labeling not of individual compounds, e.g. amino acids, but of individual carbon positions in those different compounds. Because some enzymes of amino acid metabolism have a cell-specific expression, it is possible to study the metabolic activity of individual cell types or the transfer of amino acids between them. Finally, ^{13}C MRS allows studies of a host of substrates to examine their potential as metabolic substrates for the brain.

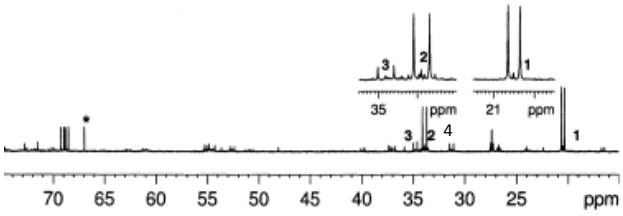

Fig 1. ^{13}C MR spectrum of a brain extract from a mouse that received 150 µmol [U-^{13}C] glucose intravenously and was sacrificed after 5 minutes. Peak numbers: 1, lactate C3; 2, glutamate C4; 3, GABA C2; 4: glutamine C4

The cellular complexity of the brain makes it desirable to study distinct cell types individually. By using ^{13}C-labeled substrates that are metabolized only by specific cell types a 'biochemical dissection' of the brain is made possible. For instance, [^{13}C]acetate is metabolized only by astrocytes, and will label glutamine strongly, because, in the brain, glutamine is formed only in astrocytes. Any labeling of the signaling substance γ-aminobutyrate, which is only formed in nerve cells, from [^{13}C]acetate will reflect transfer of [^{13}C]glutamine from astrocytes to nerve cells and subsequent formation of γ-aminobutyrate in nerve cells (Fig. 2).

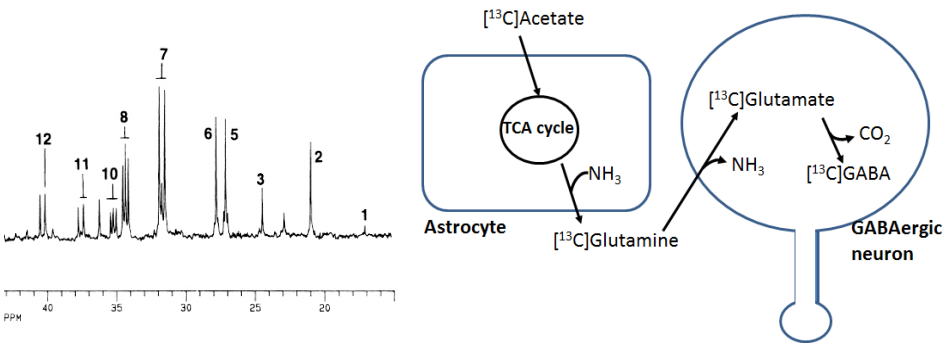

Fig 2. ^{13}C MR spectrum of a mouse brain extract that received [1,2-^{13}C] acetate. Peaks: 5, glutamine C-3; 6, glutamate C-3; 7, glutamine C-4; 8, glutamate C-4; 10, GABA C-2.

Interpretation: [^{13}C]acetate istaken up by astrocytes and converted into glutamine and transferred to neurons for conversion into

NMR PROFILING OF BIOFLUIDS

Daniel Sachse[1*]

[1] *Dept. of medical biochemistry, University of Oslo and Oslo University Hospital, Ullevål, Kirkeveien 166, 0407 Oslo*
[*] *daniel.sachse@medisin.uio.no*

Abstract
The department for medical biochemistry at Oslo University Hospital, in collaboration with the University of Oslo NMR Center, has been involved in NMR-based mixture analysis or profiling of biofluids since 2009. We have worked with a variety of substances ranging from human urine and blood serum and plasma and bronchoalveolar lavage fluid from pigs to bacterial and cell culture supernatants and attempted to measure, quantify and model the changes of levels of metabolites in these fluids. This presentation will showcase examples of successful and less successful projects and highlight our experiences and the challenges we faced.

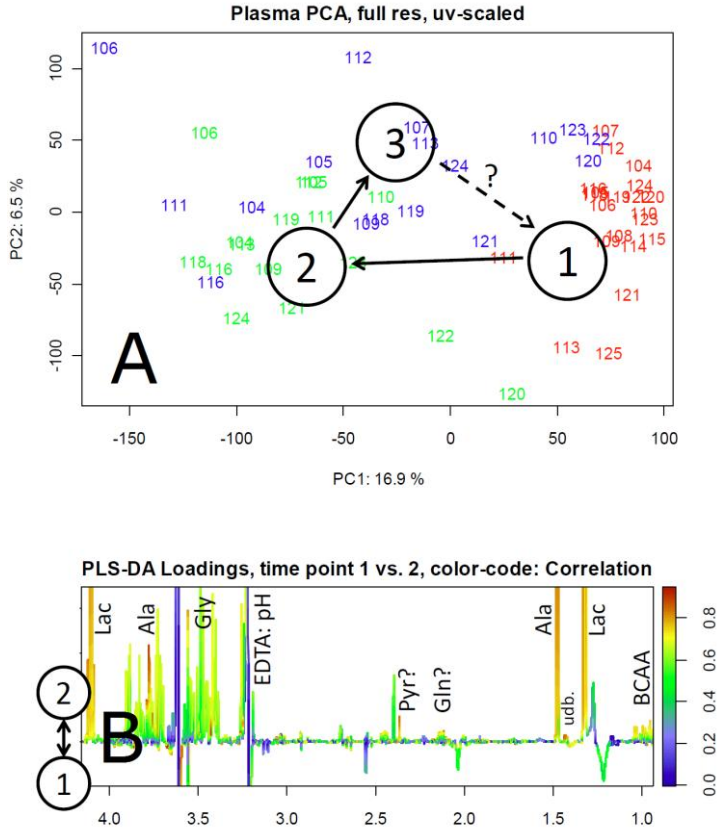

Figure 1: (A) PCA scores plot of [1]H-NMR spectra of plasma samples taken at different time points in a hypoxia study on pigs illustrates systematic changes in the metabolic profile. (B) PLS loading weights of the same spectra show which signals drive the group separation.

NMR SPECTROSCOPY IN IDENTIFICATION OF SECONDARY METABOLITES

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Abstract

Secondary metabolites are naturally occurring substances which are not found ubiquitously, as common lipids, proteins and carbohydrates which are necessary to all organisms are. It has been estimated that more than 100 000 secondary metabolites have been described in the scientific literature (Verpoorte, 1998 – the number has increased considerably since then). Secondary metabolites cover a very wide variety of structures, and many of them show interesting biological activities, making them of potential medicinal importance.

The branch of science that deals with bioactive natural products is known as pharmacognosy. This lecture will deal with the use of NMR spectroscopy as a means of identification and structural elucidation of secondary metabolites – mostly based on examples from the research group of the authors.

Reference

Verpoorte, R. (1998) Exploration of nature´s chemodiversity: The role of secondary metabolites as leads in drug development. *Drug Discovery Today* **3**: 232-238.

DIFFUSION WEIGHTED MRI -

BASIC PRINCIPLES AND CLINICAL APPLICATIONS

Therese Seierstad[1,2*]

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[2] *Faculty of Health Sciences, Buskerud University College, Drammen, Norway*

[*] *Corresponding author (set@ous-hf.no, Therese.Seierstad@hibu.no)*

Abstract

Diffusion-weighted magnetic resonance imaging (DWMRI) exploits the random movement of water molecules in the presence of magnetic field gradients for providing information on molecular displacements over distances comparable to the cell dimension. Signal intensity (SI) in DWMRI is inversely related to diffusivity and thus increase with the presence of macromolecules, membranes, fibres, vessels and cell organelles restricting diffusion. Since tumor tissue usually have higher cellular density that the tissue from which they originate the SI on DWMRI will be elevated compared to surrounding normal tissue. Differences in cellular density may reflect histological differences and biological aggressiveness – information that is important both for assessment of differentiation as well as for treatment planning. Therapeutic interventions causing disruption of cell membranes will increase water diffusion in the tissue. This increase has been shown to precede tumor volume regression. The quantitative apparent diffusion coefficient (ADC) is obtained by acquiring at least two DWMRI with different degrees of diffusion-weighting (b-values). When using two b-values (0 and, e.g., 850 s/mm^2) the ADC is determined as the log of the ratio of pixel intensities: i.e. ADC = -(1/b)*ln(SI_i/SI_o) with b = b-value for the diffusion weighted scan, SI_i the pixel intensity in the diffusion weighted scan, and I_o the pixel intensity of the non-diffusion weighted scan (b=0). Since diffusion weighting lowers signal intensity, the ratio in the log argument is less than one, and the ADC is in general >0.

References

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NMR studies of phospholipid bilayers and brain tissue

Willy Nerdal, Baichuan Deng, Linda Hanekam, Marit Schaathun
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Abstract

In this study ^{13}C Magic Angle Spinning (MAS) NMR spectra were acquired on phospholipid bilayer samples, on total lipid extract from pig brain[1] - see Figure 1, and on mouse brain tissue samples. Both ^{31}P experiments on non-spinning/static sample and MAS experiments have been carried out on the phospholipid bilayer samples, on total lipid extract from pig brain and on mouse brain tissue samples. Static ^{31}P NMR of phospholipid bilayers (lamellar) gives the chemical shielding anisotropy as the difference between the high ppm and the low ppm edges of the resonance due to rapid phospholipid motion around an axis perpendicular to the bilayer surface. In comparison, the powder pattern of an inverted hexagonal lipid phase has only half the width and the opposite sign of the powder pattern of the corresponding bilayer phase.

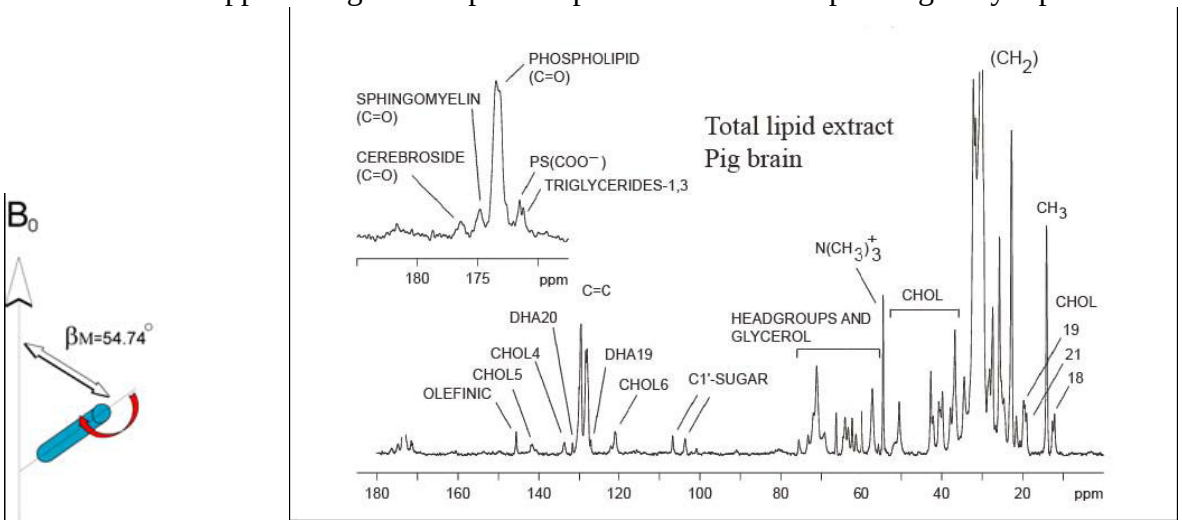

Figure 1. ^{13}C Magic Angle Spinning (MAS) NMR, Total lipid extract Pig brain.

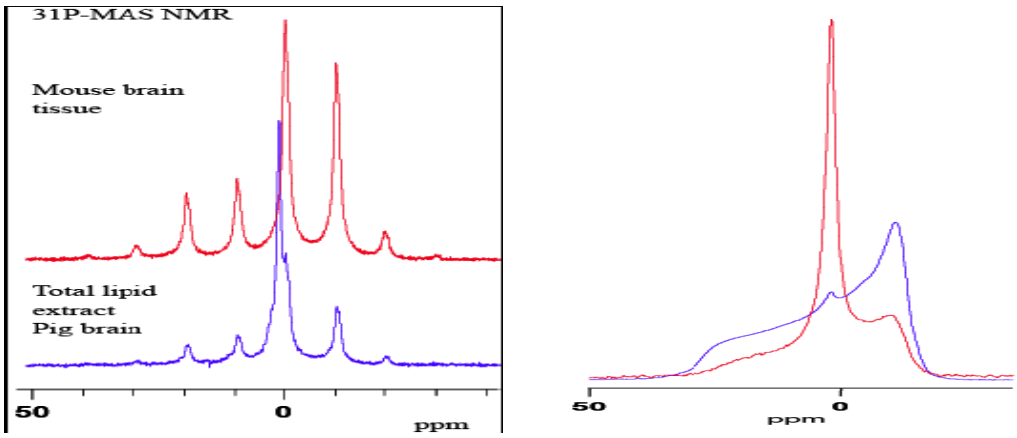

Figure 2. Left: Magic Angle Spinning ^{31}P MAS spectra, Right: ^{31}P spectra on static/non-spinning samples.

References

Jensen, M., Nerdal, W. Anticancer Cisplatin Interactions with Bilayers of Total Lipid Extract from Pig Brain: A ^{13}C, ^{31}P and ^{15}N Solid-State NMR Study. *European journal of pharmaceutical sciences.* 2008 , 34, 140–14.

NMR IN MYCOCHEMISTRY

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Abstract

Natural toxin chemistry and toxicology is the major research subject at the institute's Chemistry & Toxicology section. Being a team of scientists with background in different disciplines, NMR spectroscopy is an important tool whenever the structure of a biomolecule needs to be determined. As the purification of target toxins is a tedious and expensive operation the quantities of the substances that demand structural characterisation is often rather low, commonly around 1 mg and sometimes much less. Three examples will demonstrate our approach:

1) Ergot fungi (*Claviceps* spp., "meldrøye" in Norwegian) are parasites on more than 600 grass species, including forage grasses and leading cereals worldwide: wheat, rice, barley, sorghum, oats, rye and millet. The resting stage of the fungus ("sclerotium") contains a highly complex mixture of different alkaloids with effects on the nervous system. During our LC-MS-based screenings we became aware of an ergot alkaloid in sclerotia collected in the Oslo Nordmarka with a molecular mass that was higher than any of the previously reported natural analogues. The compound was isolated and NMR spectroscopy showed that the compound indeed was a new natural analogue.

2) *Fusarium* fungi are the most important fungal field pathogens in cereal grain worldwide. Several species produce toxic secondary metabolites ("mycotoxins") resulting in large economic losses every year. Fumonisins are polyketide-derived mycotoxins produced by at least two common *Fusarium* species. A biosynthetic pathway for fumonisin production has been proposed based on a combination of biochemical and genetic evidence, including production of fumonisin analogues by mutant strains of *Fusarium* in which individual genes have been inactivated. Although there is good evidence for most of the steps in the pathway, the products of the first two steps have not yet been identified. Our recent analyses of metabolites produced by a knockout mutant strain cast new light on fumonisin-biosynthesis.

3) Biosynthesis of a violet-blue pigment in the perithecium of the filamentous fungus *Fusarium graminearum* is dependent on the polyketide synthase *PGL1*. Over-expression of the *PGL1* cluster resulted in the production of the specific pigment and related intermediates in the vegetative mycelium. Structural characterisation of the dominating new metabolite shows that it is a novel polyaromatic polyketide, called purpurfusarin.

NMR STUDIES OF SMALL ANTIMICROBIAL PEPTIDES

Johan Isaksson[1], Geir Villy Isaksen[2], John S. Mjøen Svendsen[1], Bjørn Olav Brandsdal[2]

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[2]*The Norwegian Structural Biology Centre, Department of Chemistry, University of Tromsø, N-9037 Tromsø, Norway*
[3] *The Centre for Theoretical and Computational Chemistry, Department of Chemistry, University of Tromsø, N-9037 Tromsø, Norway*
[*]*Corresponding author (johan.isaksson@uit.no)*

Abstract
Synthetic antimicrobial peptides (SAMPs) with increased stability against proteolytic degradation and good efficacy and selectivity for methicillin-resistant staphylococci over human erythrocytes have been developed over the last decade[1, 2].

The pharmacophore of this class of molecules is intimately related to its general mode of action. This relationship has been investigated by liquid NMR and computer simulations both in pure solvent and in small unilamellar vesicles (SUVs)[3]. The role of the three dimensional structure in general, and the role of the positively charged arginines in particular, in solution as well as inside the lipid membrane and its effect on the solvatization energy of the SAMPs have been studied, resulting in a new refined pharmacophore able to successfully predict the efficacy of other antibiotics targeting the bacterial membrane, even ones not strictly belonging to the peptide class.

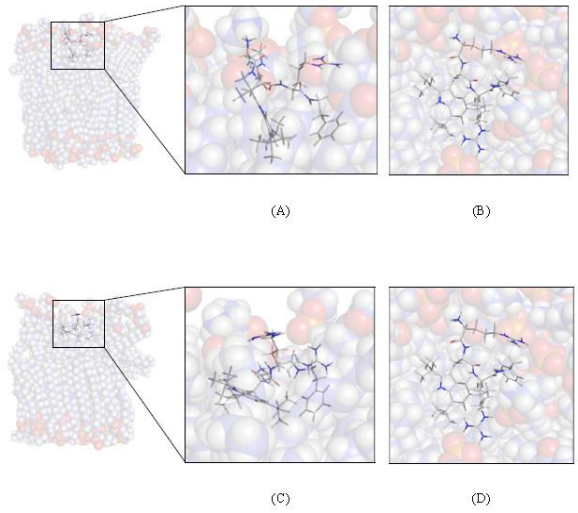

Figure 1. Representative snapshots from the MD simulations of the LLL stereoisomer of LTX 109 seem from the side (A) and top (B), and the LLD stereoisomer of LTX 109 seen from the side (C) and top (D).

References

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RANGIPUTAMIDE FROM *PROROCENTRUM LIMA*: STRUCTURE ELUCIDATION BY NMR

Christopher O Miles[1,*], Alistair L Wilkins[2], Patrick T Holland[3], Paul McNabb[3], Lesley R Rhodes[3], Pat Edwards[4], Kristofer Larsen[5], Frode Rise[5]

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[2] *Chemistry Department, University of Waikato, Private Bag 3105, Hamilton 3240, New Zealand*
[3] *Cawthron Institute, Private Bag 2, Nelson, New Zealand*
[4] *Institute of Fundamental Sciences, Massey University, Private Bag 11222, Palmerston North, New Zealand*
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[*] *Corresponding author (chris.miles@vetinst.no)*

Abstract
Prorocentrum is a genus of benthic dinoflagellate microalgae with a world-wide distribution. *P. lima* is a species commonly found in northern harbours of New Zealand and produces okadaic acid analogues. During LC-MS (ESI+) screening of *P. lima* culture extracts, several strains including one isolated from Rangiputa, Rangaunu Harbour, were noted to produce an unusual N-containing compound MH^+ 856 that eluted amongst the diol esters of okadaic acid. These strains were bulk-cultured and extracts of the cell pellets were fractionated by column chromatography, and the N-compound was isolated by preparative C18-HPLC in high purity (4.2 mg, MF $C_{50}H_{81}NO_{10}$ from HRMS of MH^+, 11 rings/double bonds). Acetylation followed by LC-MS indicated the presence of 4 reactive OH groups. The structure of rangiputamide (**1**) (1 mg) was deduced from an extensive array of 2D NMR experiments in CD_3OD and d_6-DMSO using double-solvent suppression. 1D and 2D NOESY and ROESY data is being analyzed to obtain stereochemical information. DMSO as solvent was useful in revealing the amide and hydroxyl protons and assigning some of the ether linkages and the epoxide.

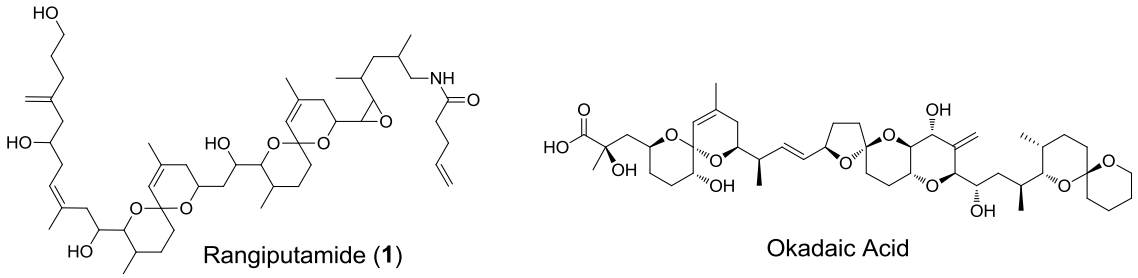

*Figure 1: Structure of rangiputamide (**1**).*

Prorocentrum spp. can produce several macrolides as well as okadaic acid, but this polyether structure is unprecedented. The matched pair of linked spiroketal 6-membered rings are similar to those in okadaic acid but with different substituent and linking groups. Rangiputamide was not detected in cultures of a strain of *P.lima* from Spain. It was non-toxic in mouse bioassay (i.p. injection) and not appreciably cytotoxic to Vero or P388 mammalian cells. The physiological or potential ecological function for **1** remains unknown.

REAL-LIFE POSSIBILITIES FOR PARALLEL RECEIVERS IN LIQUIDS NMR

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Abstract
Parallel receivers have been widely used in Magnetic Resonance Imaging for quite some time now offering unique capabilities and time savings when applied. It has only been in the past 6 years or so that applications with parallel receivers started appearing in high resolution liquids NMR.

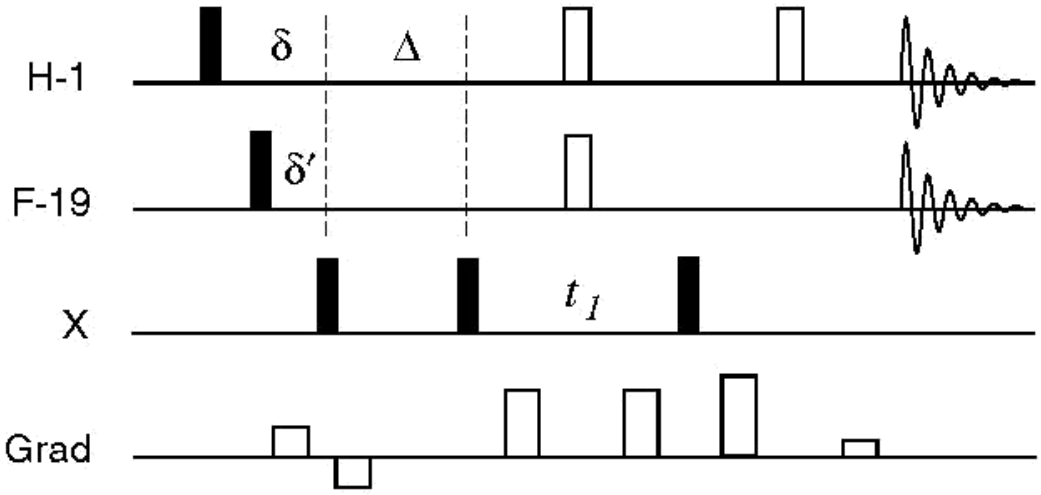

Figure 1: Pulse sequence of a ^{1}H, ^{19}F –{X} gradient HMBC experiment with parallel recording of the ^{1}H and ^{19}F resonances.

After the first "proof of concept" publications people started exploring the real life possibilities for experiments with parallel receivers. This did not prove to be as straightforward as initially thought as unexpected complications presented new challenges in pulse sequence design as was the case for the ^{1}H-^{19}F-{X} gradient HMBC experiment shown in Fig. 1.
In this presentation we will review the use of parallel receivers for the simultaneous recording of ^{1}H and ^{19}F heteronuclear correlation experiments, the recording of multiple types of correlations spectra within one experiment as well as the potential applications to bio-NMR. We will also examine the options for the use of more than two receivers.

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NMR SPECTROSCOPY OF SOLID AND SOFT MATERIALS

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Abstract
One of the most important objectives in science is to advance our understanding of the relationships between molecular structure, dynamics, and function. We know for example that each type of protein has a very specific three-dimensional conformation which is required for its biological activity. The two most useful experimental methods for studies of structure and dynamics have been liquid-state nuclear magnetic resonance (NMR) and X-ray diffraction. Unfortunately, neither of these techniques is feasible when the molecules are immobilized in membranes, tumble slowly, or tend to aggregate without forming well-defined crystals. These materials include membrane-bound peptides and proteins, inorganic glasses, liquid-crystalline systems, many polymers, and tissue samples.

Solid-state NMR methodology has emerged as a powerful tool for investigations of these "difficult" materials. Its usefulness derives from the fact that it allows for molecular identification, estimation of crucial parameters such as internuclear distances, torsional angles, and correlation times without the necessity of rapid tumbling or microscopic periodicity.

The aim of this presentation is to demonstrate the utility of solid-state NMR techniques for the study of molecular structure and dynamics, and its application as a method for routine chemical analysis of solid and soft materials. I will briefly discuss the spin interactions that give rise to the broad NMR signals in these systems, and the tools designed to remove this broadening. The spectrometer hardware necessary for carrying out these experiments will also be reviewed.

EASY ACCESS TO THE AMOUNT OF SHORT CHAINS IN ETHENE/α-ALKENE COPOLYMERS FROM SOLID STATE ^{1}H-MAS NMR

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Abstract
Solid state ^{1}H-MAS NMR is shown to be an attractive experimental technique for determining the comonomer content in ethene-α-alkene copolymers. Its advantage is associated with: a) no particular need for sample preparation, b) non-destructive, c) short overall acquisition time of the order of a few minutes. d) no need for calibration and finally e) the copolymer content in cross-linked LDPE may be determined, which is otherwise not easily accessible, as these samples are non-soluble in most liquids.

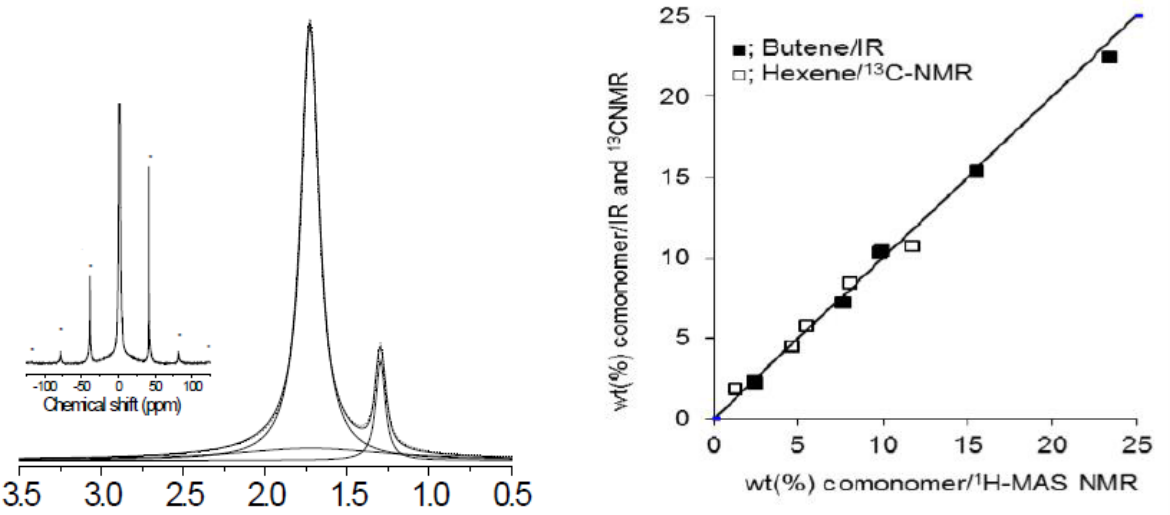

Figure (left:) ^{1}H- MAS (20 kHz) NMR spectrum of an ethylene-hexene copolymer. The solid curve represents a non-linear least squares fit to a sum of four individual Lorenzian functions of which one is assigned to the CH3-protons ($\delta \approx 1.35$ ppm). The insert shows the overall spectrum including spinning side bands (*). No apodization was applied.
Figure (righ): Weight-% of butene and hexene in ethylene-butene and ethylene-hexene copolymers, as determined by solid-state ^{1}H-MAS NMR and IR/^{13}C-NMR, respectively.

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E. W. Hansen, J. Paul, S. Jørgensen, B. Arstad and A. Bouzga, IJRRAS, 2011, 6, 382–390.

Ageing of crosslinked low density polyethylene monitored by high MAS ^{1}H-NMR and relaxation

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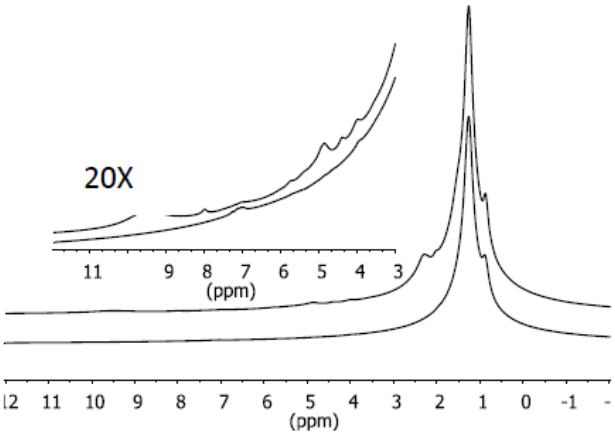
Thermal oxidation in a chemically cross-linked low density polyethylene exposed to high temperature is monitored by solid state ^{1}H- NMR techniques. Solid state NMR has special advantage in studying cross-linked polymers with respect to sample preparation and has short acquisition time compared to ^{13}C-NMR. Solid state ^{1}H-NMR spectrum of the degraded XLPE acquired at a MAS rate of 20 kHz shows new resonance peaks which are assigned to various functional groups formed during the course of ageing. The functional groups identified in degraded XLPE are acid, ester, lactone, vinyl and aldehyde. The onset and extent of degradation with ageing time is monitored by observing changes in the phase composition and relaxation parameters determined by ^{1}H - solid echo and relaxation experiments.



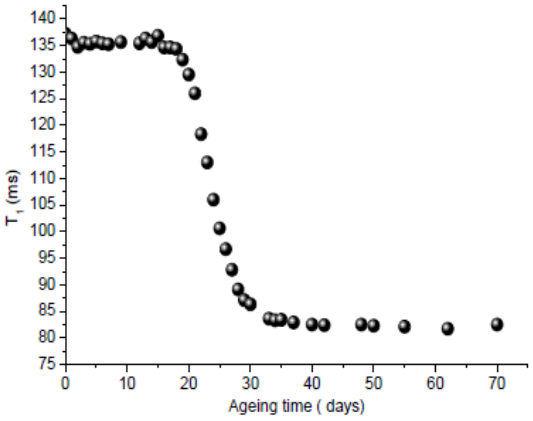


Figure (Left): Solid state ^{1}H- MAS (20 kHz) NMR spectra of degraded (top) and non-degraded (bottom) XLPE exposed to air at 130 ^{o}C. The inset shows the same spectra from 12 to 3ppm.
Figure (right): ^{1}H- spin lattice relaxation time of XLPE aged at 130^{o}C measured for different ageing time.

DEFECT'S INFLUENCE OF THE DETERMINATION OF SI/AL RATIOS BY ^{29}SI NMR IN HIGH SILICA CHA ZEOLITES

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Abstract

A series of high silica CHA zeolites with a true single parameter variation has been synthesized, where only the Si/Al ratio changes. The materials have been synthesized with high crystallinity, and with a Si/Al ratio ranging from 20 to infinity, i.e. pure SiO_2. Powder XRD shows that the unit cell parameters increase with increasing amount of Al incorporated into the framework, while BET and SEM shows that the specific surface area and the particle size is fairly independent of the Si/Al ratio. For high silica materials one must be careful when the Si/Al ratio is quantified directly from the ^{29}Si MAS NMR spectra. In this work we suggests that the reported disagreement in Si/Al ratio determined by elemental analysis and ^{29}Si MAS NMR could also be due to defects in the structures.

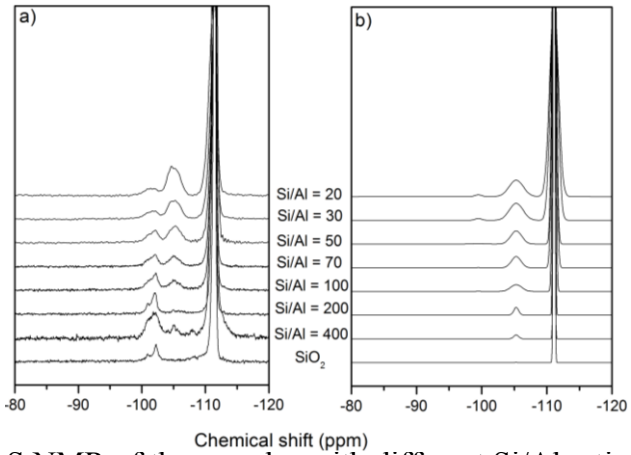

Figure A: ^{29}Si MAS NMR of the samples with different Si/Al ratios. Experimentally data on the left panel, (a). The right panel, (b), corresponds to theoretically calculated spectra of ideal samples with a random distribution of Al and no defects.

USING DIFFUSION-WEIGHTED NMR TO CHARACTERIZE POROUS MEDIA

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Abstract

Diffusion-weighted NMR is a powerful tool in porous media research. Time-dependent restrictions in the observed diffusivity of liquid molecules are caused by diffusion barriers in the porous systems and can be related to the local geometry [1].

Commonly, diffusion-weighted NMR is performed using the Pulsed Gradient Spin Echo (PGSE) method, where two separate gradient pulses label the position of the molecules, and where the diffusion coefficient is related to the mean square displacement in the time interval between the pulses. An alternative method is the Modulated Gradient Spin Echo (MGSE) method, where diffusion is measured through a rapid oscillation of the gradients and thus of the spin phase [2,3]. The MGSE method enables diffusion measurements at a shorter time scale than can be obtained by the PGSE method.

We present examples from applications of diffusion-weighted NMR in liquid-saturated rock cores using PGSE methods, and in micro-emulsions using the MGSE method. PGSE methods enable a characterization of the porous structure and surface interactions in rock cores [4]. The MGSE method enables characterization of the droplet sizes in micro-emulsions [5].

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PROGRESS AND CHALLENGES IN PROTON NMR OF SOLIDS: FAST SPINNING, MULTIPULSE SEQUENCES, INDIRECT DETECTION

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Abstract
Liquid-state NMR of protons is a widely used technique since the early days of NMR. However, proton NMR of static solid samples suffers from strong homonuclear dipolar coupling which causes significant line broadening. Typically the broadening exceeds the chemical shift separation of the NMR signals which prevents the interpretation of such spectra in terms of the sample structure. Many modern methods of multidimensional NMR or indirect detection rely on the chemical information available from the high-resolution proton spectra; the lack of this information in typical solids significantly restricts the applicability of these methods.
Several approaches have been proposed to tackle the problem. In this presentation we will discuss progress and challenges of the modern proton NMR in solids. Applicability of fast magic-angle spinning, multipulse techniques, NMR in ultra-high magnetic field will be presented. Many of these new techniques strongly benefit from the progress in NMR hardware. In recent years new RF technologies and NMR probe designs continue to improve and simplify NMR of protons.

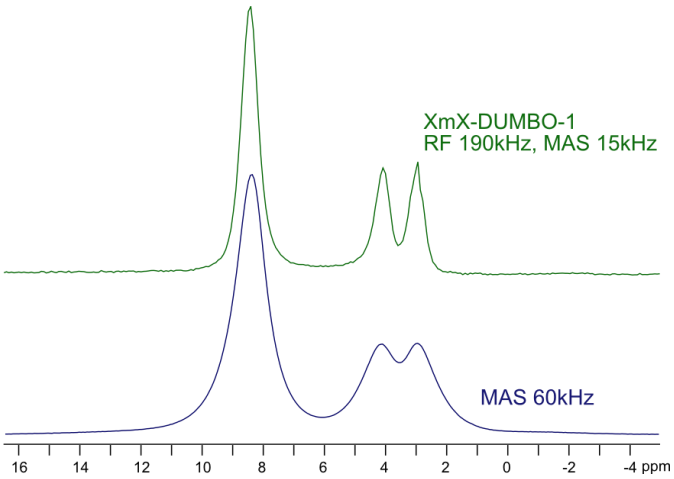

Figure 1: Solid-state NMR spectra of glycine measured with multipulse XmX-Dumbo-1 sequence and under fast magic-angle spinning conditions.

Some application examples of proton solid-state NMR will be presented. Prospects and challenges of indirect detection via protons in solids will be discussed.

HIGHLY EXTENDED AND EXPOSED DOMAIN LINKER INVOLVED IN VITELLOGENING REGULATION

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Abstract

Honey bee (*Apis mellifera*) vitellogenin is a multi-domain, large (1770 AAs) protein that has profound effects on the lifespan and task allocation in this social insect. We have recently identified tissue-specific cleavage of this protein into two parts. Cleavable protein domains are in some cases separated by a flexible linker region, and sequence based prediction suggests that such a region lies between the two parts of vitellogenin. This linker is a polyserine tract; rich in serine residues and found in variable lengths in nearly all insect vitellogenins, excluding certain species like *Nasonia vitripennis*. Due to the interesting evolutionary variation, the critical location between two domains that get cleaved and the expectation of the serine residues of the linker to act as a multiple phosphorylation site, we performed a structure-oriented study of the polyserine tract of honeybee and compared the tract to the corresponding region in *N. vitripennis*. Our results suggest that the polyserine linker is highly disordered in the bee, but less so in the wasp; a structural difference that might have lead to functional consequences. We also strengthen the assumption of multiple phosphorylation of the polyserine tract using mass-spectrometry and limited proteolysis assays and speculate that the phosphorylation might have a regulative role with respect to the vitellogenin cleavage.

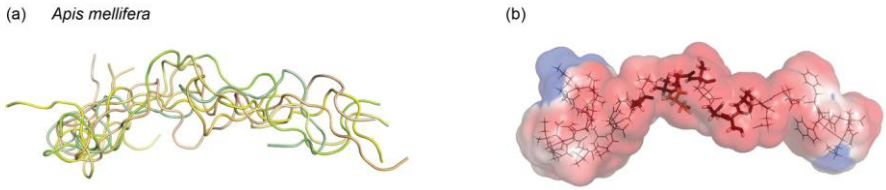

Figure 1: *Honeybee polyserine linker region. (a) Twenty calculated structures showing the outstretched random coil structure of the polyserine tract of AmVg(358-392). (b) An energetically minimized, averaged structure with surface electrostatics and with serine residues highlighted as thicker sticks.*

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NMR INVESTIGATIONS OF STRUCTURAL AND FUNCTIONAL PROPERTIES OF CO-CONTAINING MAMMALIAN METHIONINE SULFOXIDE REDUCTASE B1

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Abstract

Metal-containing proteins constitute about one third of all proteins and are widespread in nature. Among all metal ions zinc is the second, after iron, most abundant trace metal found in the human body [1]. Zinc-binding sites in proteins serve two main functions: structural and catalytic. The role of structural zinc site is to maintain the structure of the protein, which influence its function. The group of enzymes, containing structural zinc sites, includes carbonic anhydrase, Fpg protein, mammalian MsrB1 etc.

In mammalian MsrB1, which structure has been recently published [2], zinc ion is coordinated by four cysteines. MsrB1 catalyzes the reduction of methionine-R-sulfoxide (formed under the redox stress) back to methionine in the presence of thioredoxin [3].

We discovered that MsrB1 expressed in E.coli in Co^{2+}-containing LB medium uptakes both zinc and cobalt. The insertion of cobalt in MsrB1 was proved by observation of the paramagnetic signals in 1D proton NMR spectrum and the absorption bands in UV-visible spectrum of the protein (the protein was light blue).

Samples of MsrB1, obtained in several growth conditions were subjected to NMR analysis. The obtained data allowed us to conclude that there are two forms of MsrB1 expressing when both metals are present in the medium - Co-MsrB1 and Zn-MsrB1.

To characterize the metal-binding site in Co-MsrB1 UV-visible spectroscopy was used. The presence of absorption bands, characteristic for 4Cys coordination, has led to the suggestion that cobalt ion is tetrahedrally coordinated, as zinc in native MsrB1.

For comparative analysis of two MsrB1 forms several NMR spectra of MsrB1-Co were recorded (^{15}N-HSQC, ^{13}C-HSQC, NHCA, NHCO, CBCA(CO)NH, NHCACB, HBHANH, HBHA(CO)NH, HCCH-TOCSY). NMR data analysis revealed structural similarities between zinc- and cobalt-containing MsrB1. Although the question of biological significance of metal replacement remains open, MsrB1-Co and MsrB1-Zn activity was assayed using HPLC chromatorgraphy through the analysis of the enzyme product. MsrB1-Co was found to be as active as native MsrB1.

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The intriguing Cyclophilin A -HIV-1 Vpr interaction: prolyl cis/trans isomerisation catalysis and specific binding

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Cyclophilin A (CypA) represents a potential target for antiretroviral therapy since inhibition of CypA suppresses human immunodeficiency virus type 1 (HIV-1) replication, although the mechanism through which CypA modulates HIV-1 infectivity still remains unclear. The interaction of HIV-1 viral protein R (Vpr) with the human peptidyl prolyl isomerase CypA is known to occur in vitro and in vivo. However, the nature of the interaction of CypA with Pro-35 of N-terminal Vpr has remained undefined.
Characterization of the interactions of human CypA with N-terminal peptides of HIV-1 Vpr has been achieved using the powerful combination of nuclear magnetic resonace (NMR) exchange spectroscopy and surface plasmon resonance spectroscopy (SPR). NMR data at atomic resolution revealed that prolyl cis/trans isomerisation of the highly conserved proline residues Pro-5, -10, -14 and -35 of Vpr are catalyzed by human CypA and require only very low concentrations of the isomerase relative to that of the peptide substrates. Of the N-terminal peptides of Vpr only those containing Pro-35 bind to CypA in a biosensor assay. SPR studies of specific N-terminal peptides with decreasing numbers of residues revealed that a seven-residue motif centred at Pro-35 consisting of RHFPRIW, which under membrane-like solution conditions comprises the loop region connecting helix 1 and 2 of Vpr and the two terminal residues of helix 1, is sufficient to maintain strong specific binding.
Only N-terminal peptides of Vpr containing Pro-35, which appears to be vital for manifold functions of Vpr, bind to CypA in a biosensor assay. This indicates that Pro-35 is essential for a specific CypA-Vpr binding interaction, in contrast to the general prolyl cis/trans isomerisation observed for all proline residues of Vpr, which only involve transient enzyme-substrate interactions. Previously suggested models depicting CypA as a chaperone that plays a role in HIV-1 virulence are now supported by our data. In detail the SPR data of this interaction were compatible with a two-state binding interaction model that involves a conformational change during binding. This is in accord with the structural changes observed by NMR suggesting CypA catalyzes the prolyl cis/trans interconversion during binding to the RHFP35RIW motif of N-terminal Vpr.

Insights to enzymatic mechanism of Chitin-binding protein 21 (CBP 21) *Serratia marcescens* by NMR spectroscopy

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Abstract

In this project we have exploit the virtues of protein NMR to carry out structure-function studies for the chitin-active CBM33 (Carbohydrate Binding Module family 33), called CBP21 (Chitin Binding Protein 21). We have study the protein structure, dynamics, metal interaction and substrate interactions of CPB21.

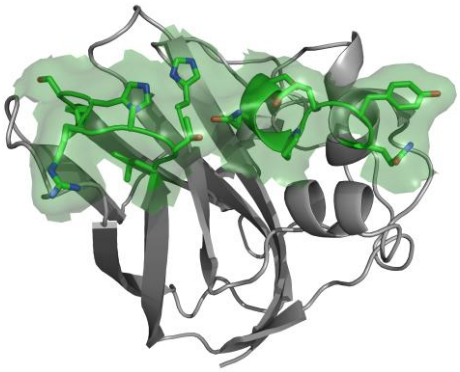

Figure 1: Chitin binding surface of CBP21.

STRUCTURAL ANALYSIS OF THE CONSERVED UBIQUITIN-BINDING MOTIFS (UBMS) OF THE TRANSLESION POLYMERASE IOTA IN COMPLEX WITH UBIQUITIN

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Abstract

The existence of many different types of ubiquitin-binding domains (UBDs) provides specificity and diversity to the ubiquitin system [1], which is also involved in translesion synthesis (TLS) in eukaryotic cells. In TLS the DNA lesions that are encountered by a replication fork are bypassed, rather than directly repaired, by specialized Y-family DNA polymerases. For recruitment of the TLS polymerase iota (Pol ι) to a stalled replication fork, its conserved UBDs (UBM domains) interact with monoubiquitinated proliferating cell nuclear antigen to regulate the interchange between processive DNA polymerases and TLS [2].

We performed a biophysical analysis and determined the solution structures of the two conserved UBM domains located in the C-terminal tail of murine Pol ι in complex with ubiquitin [3]. The domains consist of an approx. 35-amino acid core, which folds into a helix-turn-helix motif, which belongs to a novel domain fold. UBMs bind to ubiquitin on the hydrophobic patch delineated by Leu-8, Ile-44, and Val-70, similarly to most other UBDs. However, the interface is shifted towards Leu-8 and Val-70, which are inserted into a hydrophobic pocket on the UBMs. In contrast Ile-44 only interacts weakly with the hydrophobic surface (*Figure 1*). In addition, the interface is further stabilized by electrostatic interactions. Additional NMR and fluorescence spectroscopy studies revealed that UBMs do not bind Lys-48-linked ubiquitin chains, but can also not distinguish monoubiquitin from Lys-63-linked chains, where the binding surfaces are freely accessible.

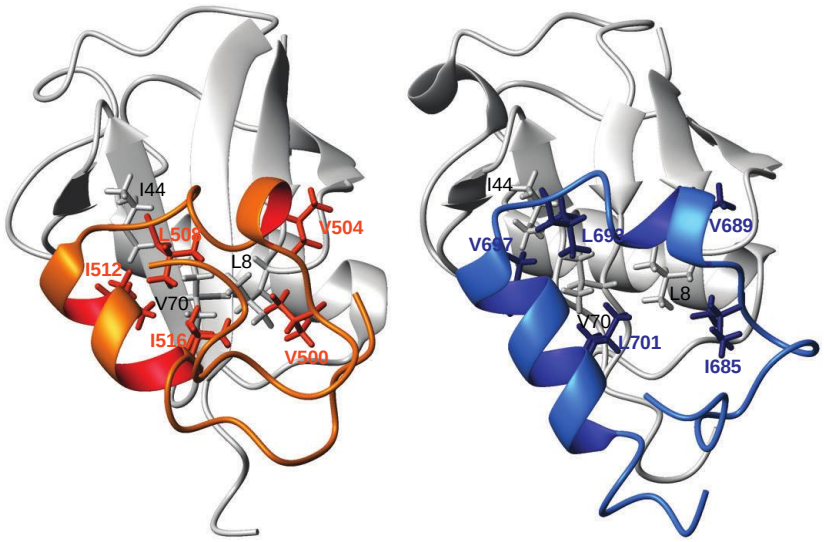

Figure 1: Binding interfaces of UBM1 (left, orange) and UBM2 (right, blue) with ubiquitin (grey). The side chains of the five conserved residues on the UBMs are in direct hydrophobic contact with the side chains of Leu-8, Ile-44 and Val-70 on ubiquitin.

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Protein-protein interactions in T cell signalling

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Signalling in T cells is tightly controlled by kinases and adapter proteins. Some of these molecules are expressed primarily or uniquely in T cells. We have previously cloned and partially characterised the T cell specific adapter protein (TSAd), which is highly expressed in activated T cells. The role of TSAd in T cell signalling is still not well understood. We have found that both the Inducible Tec kinase (Itk) and the Lymphocyte specific kinase (Lck) interact with the proline rich region of the TSAd through their SH3 domains. Whereas Lck may also interact with TSAd through its SH2 domain, Itk may only interact with TSAd through its SH3 domain. To begin to understand on a molecular level how Lck-SH3 and Itk-SH3 interact with TSAd, we combined nuclear magnetic resonance spectroscopy (NMR) and biochemical analyses. We found that Itk- and Lck-SH3 domains both have two adjacent and overlapping binding sites within TSAd aa 242-268. Lck-SH3 displayed the strongest affinity for the N terminal site located around TSAd P250, whereas Itk-SH3 displayed weaker but equal affinity for both the N terminal site possibly defined by TSAd P247 and the C terminal site defined by TSAd P263. Both domains may bind simultaneously to TSAd aa242-268 as revealed by co-immunoprecipitation experiments. Molecular modelling based our results indicated that both Lck and Itk may interact with TSAd in a class I orientation.

as Vitas

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POSTER MR2012

RANGIPUTAMIDE FROM *PROROCENTRUM LIMA*: STRUCTURE ELUCIDATION BY NMR

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Abstract
Prorocentrum is a genus of benthic dinoflagellate microalgae with a world-wide distribution. *P. lima* is a species commonly found in northern harbours of New Zealand and produces okadaic acid analogues. During LC-MS (ESI+) screening of *P. lima* culture extracts, several strains including one isolated from Rangiputa, Rangaunu Harbour, were noted to produce an unusual N-containing compound MH^+ 856 that eluted amongst the diol esters of okadaic acid. These strains were bulk-cultured and extracts of the cell pellets were fractionated by column chromatography, and the N-compound was isolated by preparative C18-HPLC in high purity (4.2 mg, MF $C_{50}H_{81}NO_{10}$ from HRMS of MH^+, 11 rings/double bonds). Acetylation followed by LC-MS indicated the presence of 4 reactive OH groups. The structure of rangiputamide (**1**) (1 mg) was deduced from an extensive array of 2D NMR experiments in CD_3OD and d_6-DMSO using double-solvent suppression. 1D and 2D NOESY and ROESY data is being analyzed to obtain stereochemical information. DMSO as solvent was useful in revealing the amide and hydroxyl protons and assigning some of the ether linkages and the epoxide.

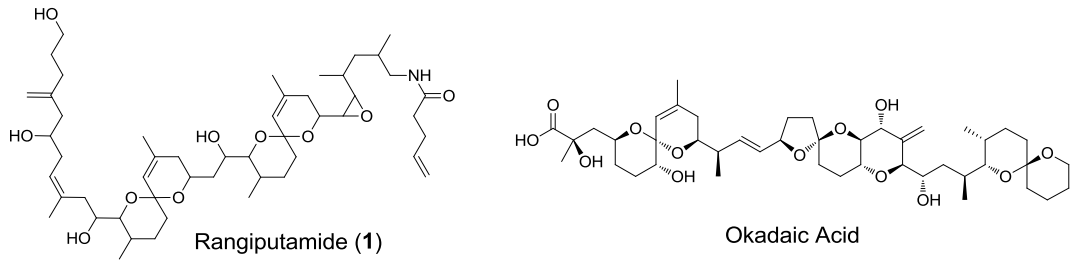

*Figure 1: Structure of rangiputamide (**1**).*

Prorocentrum spp. can produce several macrolides as well as okadaic acid, but this polyether structure is unprecedented. The matched pair of linked spiroketal 6-membered rings are similar to those in okadaic acid but with different substituent and linking groups. Rangiputamide was not detected in cultures of a strain of *P.lima* from Spain. It was non-toxic in mouse bioassay (i.p. injection) and not appreciably cytotoxic to Vero or P388 mammalian cells. The physiological or potential ecological function for **1** remains unknown.

PAKE DOUBLETS IN ^{1}H NMR SPECTRA OF ADSORBED WATER

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Abstract
Through careful sample preparation, using nonporous fumed silica particles, we show that water adsorbed on the silica surface can give rise to Pake doublets in ^{1}H NMR spectra [1]. This enables a detailed knowledge of water orientation near the solid-liquid interface. Such knowledge is scarce, despite decades of research, mainly due to lack of suitable experimental techniques. The arrangement of silica and water in the samples resulted in an orientation dependence of the doublet splitting with respect to the external magnetic field. Here, we use the orientation dependence of the Pake doublets, and T_1 and T_2 relaxation measurements to investigate the water properties. Relaxation values as a function of temperature is interpreted by the multiple-phase-relaxation model developed by Zimmerman and Brittin [2], and gave information on water environmental states, exchange between these states and molecular mobility. The frequency splitting of the Pake doublets can be explained by including two motional processes into the original model proposed by Pake [3], representing rotational and diffusive motions, respectively [4].

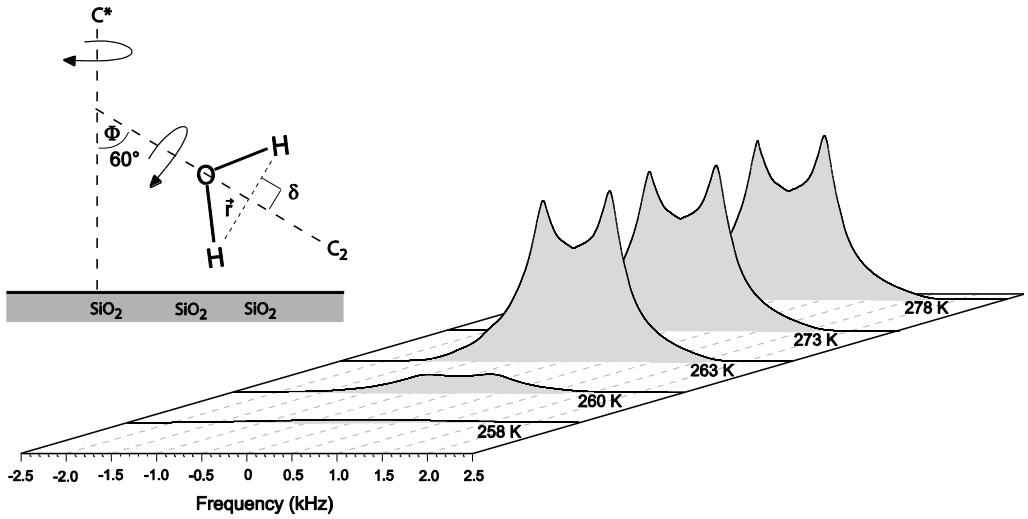

Figure 1: "Graphical abstract" illustration of current results from the Pake doublet orientation dependence (top, left) and recorded water ^{1}H spectra at varying temperatures, showing freezing of the sample water at approximately -13°C (bottom).

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CORRELATION BETWEEN PORE DIAMETER AND RELAXIVITY IN GADOLINIUM GRAFTED MESOPOROUS SILICA

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Abstract

Nanosized gadolinium modified mesoporous silica particles display promising properties as contrast agents (CA`s) for Magnetic Resonance Imaging (MRI) due to very high $r_1$ relaxivities compared to commercially available CA`s.[1-3] Unfortunately, few detailed studies have been performed on the underlying mechanisms explaining the high relaxivity obtained for these types of materials, complicating further progress in this promising field.

In this study, the gadolinium based mesoporous hybrid materials are obtained by the controlled grafting of the metalorganic precursor $Gd[N(SiHMe_2)_2]_3(THF)_2$ onto the surface of Periodic Mesoporous Silica (PMS) material SBA-15 with hexagonal topology. A full characterisation of the silica materials by powder x-ray diffraction, nitrogen physisorption, transmission electron microscopy, scanning electron microscopy and FTIR spectroscopy is presented. PMS materials with pore diameters in the range of 5.4 to 9.0 nm are used as support material for Gd.

The relaxivity is influenced by several different parameters and the key to a better understanding of the underlying mechanisms in these potentially new contrast agents is to use NMR to investigate the local dynamical interaction between water and the metal ion. This is achieved by performing dynamic NMR experiments (diffusion and relaxation) and examining temperature and field dependence (NMRD). To design improved contrast agents, every property of the silica materials that can potentially influence the relaxivity has to be optimized. The aim of this study is to examine the relation between r_1 relaxivity and the pore diameter of the mesoporous silica support.

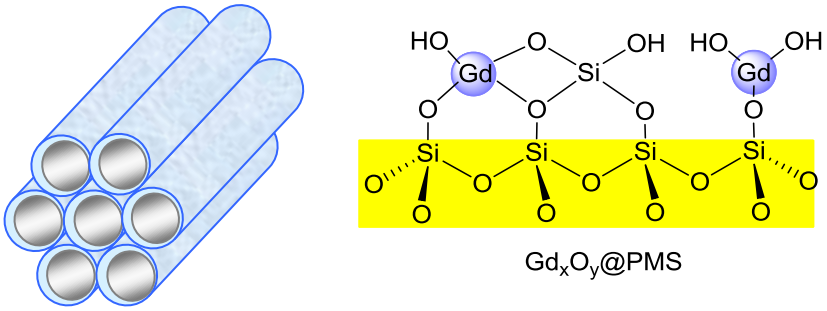

***Figure 1**: Periodic mesoporous silica SBA-15 with hexagonal topology and the proposed surface functionalisation with Gadolinium.*

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Synthetic Methods in Gold(III) Chemistry

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Abstract
The interest in organo-gold compounds continues to grow. Gold(III) complexes are being investigated as catalysts for organic transformations[1] as well as tested as potential anti-cancer drugs.[2] Despite this wide-ranging interest in the properties of such complexes, the synthetic methods for preparing them are underdeveloped.
AuCl2(tpy) (**1**) is an example of a compound that previously required the use of an organomercury reagent to achieve an acceptable yield with respect to gold.[3] Several gold(III) complexes with different bipyridine and pyridine ligands have now been prepared in our group using microwave heating and mercury-free conditions, see examples **1**-**3** below.[4, 5]

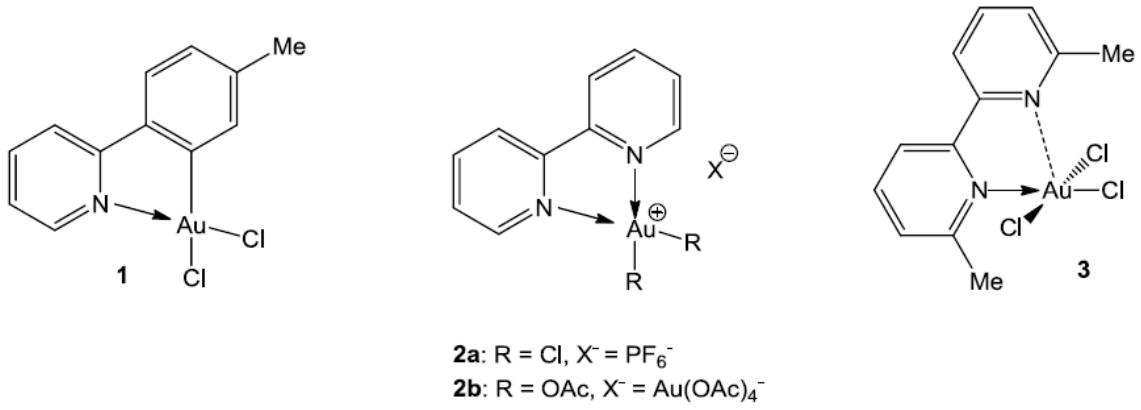

Figure 1: Examples of Au(III) complexes prepared in the group.

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Local Anesthetic Articaine Enantiomers interaction with Brain Lipids.

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Abstract

We have investigated the interaction of the R-and S-enantiomers of the local anesthetic articaine with monolayers of phospholipids by the Langmuir-Blodgett technique. The racemic mixture of articaine, and the isolated R-and S-enantiomers of articaine were added to the phospholipids DPPC, DPPS, POPS and total lipid extract from pig brain(TLPB). The differences of the enantiomers are assumed to cause different intercalation in phospholipid monolayers. Our results indicate that the R-enantiomer intercalates better in monolayers of POPS and TLPB than the S-enantiomer. That the R-enantiomer is a better intercalator might be the reason why the R-enantiomer shows more cardiovascular toxosity than the S-enantiomer(1). Our investigation shows that the Langmuir-Blodgett monolayer technique is a fast, inexpensive as well as powerful method to find model membranes to be studied by solid-state NMR. The monolayer experiments indicate that bilayers of POPS and TLPB with the R- and S-enantiomers are candidates for a solid-state NMR study. The POPS bilayer might give information about different bonding mechanism of R-and S-enantiomers into the serine containing headgroup, while the TLPB lipids should be investigated to get a good model of a biological bilayer. A solid-state NMR study of R- and S-articaine interaction with TLPB show that the R-articaine is located near the achylchain region, while the S-articaine is located near the headgroup region.

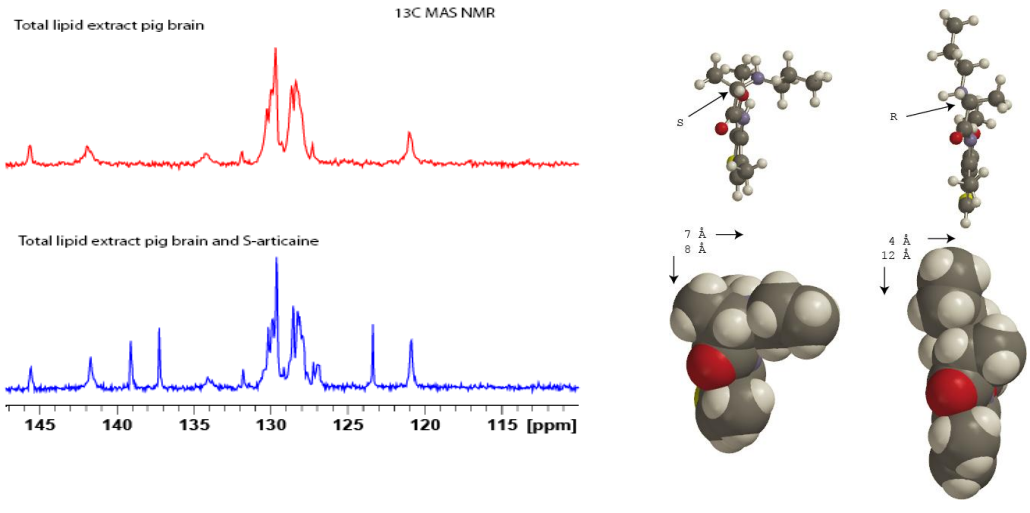

Figure 1:Left: The ^{13}C solid-state NMR spectrum of Total Lipid Extract from Pig Brain with and without S-articaine. Right: Models of the R-and S-enantiomers of articaine.

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THE USE OF NMR FOR TRACE LEVEL IDENTIFICATION OF COMPOUNDS RELATED TO THE CHEMICAL WEAPONS CONVENTION (CWC)

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Abstract
The chemical weapons convention (CWC) prohibits the development, production, acquisition and use of chemical weapons by state parties. The Organisation for the Prohibition of Chemical Weapons (OPCW) implements the conventions, and organises annual Proficiency Test for state parties to participate in. During the test laboratories have to identify and validate the presence of scheduled and related compounds at trace level in different matrixes (soil, water, organic, rubber etc), and report their findings within 15 days.

The Identification laboratory at FFI has participated in the Proficiency Test three times. GC-MS is an invaluable tool in the analysis of samples, because of high sensitivity and library search options. But NMR has shown to be valuable especially for analysis of phosphorous containing compounds. FFI uses NMR for screening of all samples/extracts for phosphorous and fluorine compounds, and 1D ^{1}H-^{31}P HSQC is used to screen for compounds with an alkyl group directly bound to phosphorous (Figure 1). The use of water suppression experiments is also important, and pulse sequences developed for analysis of trace amounts of chemicals have been used with success.

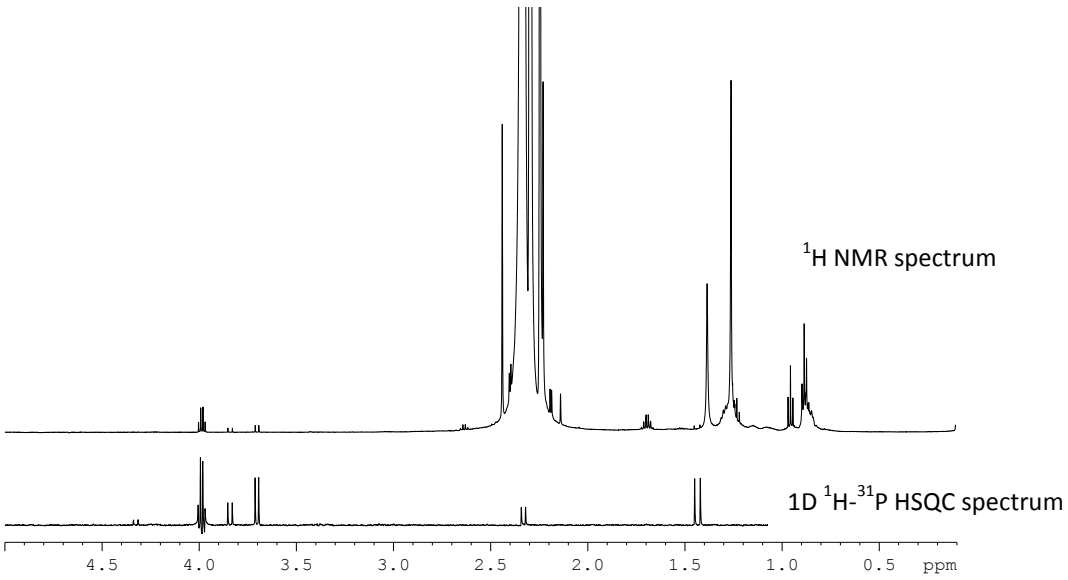

Figure 1: ^{1}H NMR spectrum and 1D ^{1}H-^{31}P NMR spectrum of a toluene sample containing dimethyl methyphosphonate and 2-methyl-1,2,3-dithiaphosphinane-2-sulfide

References

OPCW, http://www.opcw.org

THAXTOMIN ANALOGUES: SYNTHESIS, PHYTOTOXICITY AND NMR

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Abstract
Common potato scab affects potato farmers worldwide and costs the Tasmanian potato farming industry approximately $5 million dollars a year. The disease is caused in white potatoes by the common soil bacterium streptomyces scabies, from which several secondary metabolites have been isolated,[1] these are known as the thaxtomin class of phytotoxins. These compounds have been shown to cause scabs in potatoes in sterile conditions and are phytotoxic to cellulose based plants.

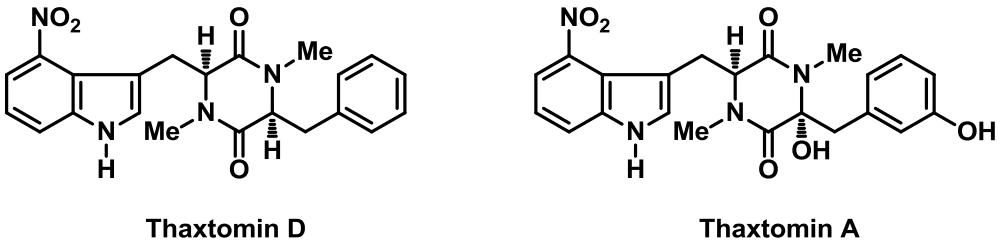

Figure 1: Two examples of the thaxtomin class of phytotoxins.

We present our work on the total synthesis of biologically active thaxtomin D analogues.[2] We also report the results of phytotoxicity screening in the search for new herbicides and NMR results of key intermediates.

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ALUM-TREATED WOOD: CHARACTERIZATION USING INFRARED SPECTROSCOPY AND SOLID STATE NMR

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The Oseberg find contains a large proportion of hardwoods that had been treated about 100 years ago with hot solutions of alum salts (potassium aluminum sulfate dodecahydrate, $KAl(SO_4)_2 \cdot 12H_2O$). Today, the wood is characterized by a high acidity (pH 1) and is structurally highly degraded. The observed deterioration is also active. The 'alum treatment' was a method of choice for the conservation of highly deteriorated waterlogged archaeological wood found from 1850 – 1950 and has since been replaced by treatment with polyethylene glycols (PEG). The alum treatment has been mainly used in Scandinavia but also in the USA, Japan and other European countries.

Attempts to chemically characterize the alum-treated wood from the Oseberg find is one phase in the research currently being undertaken at the Museum of Cultural History as a part of the Alum Research Project. Analyses using infrared spectroscopy and solid state ^{1}H and ^{13}C NMR were undertaken on selected alum-treated samples and compared with fresh woods as well as archaeological woods from the same find not treated with alum.

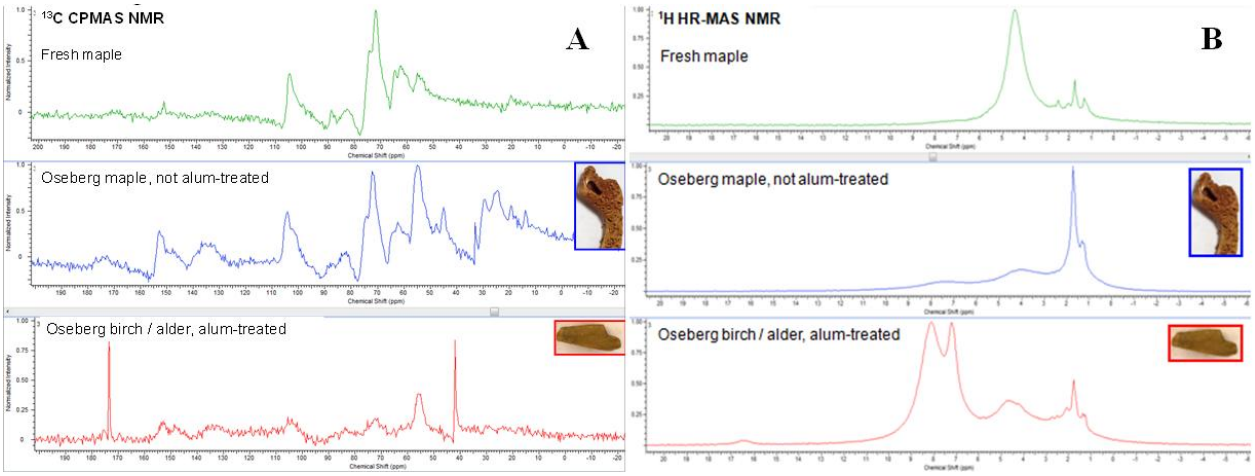

Figure 1: All alum-treated samples are highly degraded relative to archaeological wood from the same find not treated with alum salts. ^{13}C NMR (A) shows that in the non-alum-treated archaeological wood, carbohydrates are present, which are highly reduced in the alum-treated wood. ^{13}C NMR can also distinguish different lignin types, and has shown that syringyl lignin is more deteriorated than guaiacyl lignin in alum-treated samples. Remaining polymers in the alum-treated wood, dominated by lignins, are highly oxidized and contain carboxylic groups. ^{1}H NMR (B) shows a greater relative content of aromatic signals in the alum-treated wood, due to selective deterioration of the carbohydrate moiety.

MR PHASE CONTRAST VELOCIMETRY UTILIZING A NOVEL NINEPOINT BALANCED MOTION ENCODING SCHEME WITH INCREASED ROBUSTNESS TO EDDY CURRENT EFFECTS

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Introduction: Phase contrast magnetic resonance (PC-MRI) velocimetry is a well-established highresolution motion assessment tool. In PC-MRI, the motion of the spins are encoded into the complex MR signal by the introduction of motion encoding gradients into the MR sequence1. This family of techniques allows non-invasive measurement of three-directional motion in all four dimensions (3D+time) with a temporal resolution approaching that of echocardiography2. However, both high resolution and high motion sensitivity relies on the employment of strong and rapidly shifting magnetic gradients. Consequently, PC-MRI is prone to base line shift artifacts due to significant creation of eddy current in the system3, 4. In this study, we propose a novel PC-MRI velocity encoding strategy designed to be more robust to base line errors. The presented technique, entitled *nine-point balanced encoding*, allows for yet higher resolution and motion sensitivity than previously have been feasible.

Methods: The proposed nine-point method was validated in rotating phantom PC-MRI experiments. Additionally, computer simulation and i*n vivo* PC-MRI experiments were performed to investigate the accuracy of the strategy. In all cases, the performance of the nine-point approach was compared to two well established PC-MRI encoding schemes[1, 5].

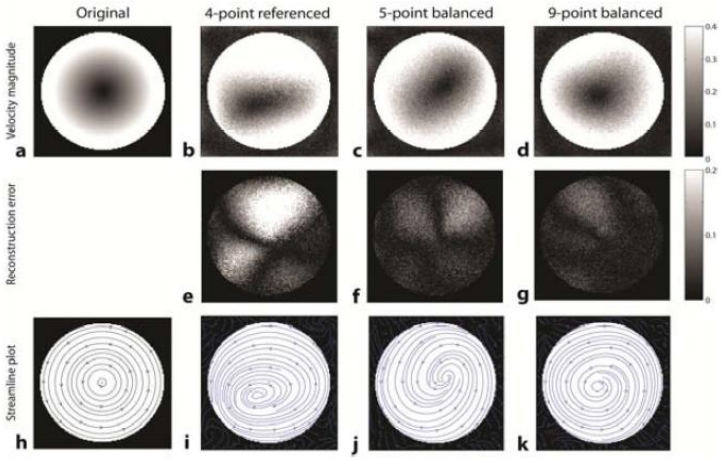

Figure 1: Results from the computer simulation. The nine-point method (right) demonstrates significantly less error in reconstruction (g) and geometrical distortion (k) than the four- and the five-point (e-f, i-j).

Results: The phantom experiments validated the accuracy of the method and demonstrated a significant reduction in deviation from the expected velocity distribution, compared to existing methods. Computer simulations (Fig. 1) yielded a 39-57% improvement in velocity-to-noise ratio (corresponding to a 27-33% reduction in measurement error), depending on which method was used for comparison. Moreover, *in vivo* experiments (Fig. 2) confirmed this by demonstrating a 36-55% reduction in accumulated velocity error over the R-R-interval.

Discussion: The nine-point balanced PC-MRI encoding strategy is likely useful for settings where high spatial and temporal resolution and/or high motion sensitivity is required, such as in high-resolution rodent myocardial tissue phase mapping.

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MANGANESE BASED MRI CONTRAST AGENT

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Abstract
In the early 1980s MRI contrast agents based on the endogenous paramagnetic metal, manganese were explored in parallel with gadolinium (1). Manganese proved to be similarly effective in providing a signal; however unstable chelates led to inferior tolerability and excretion properties as the manganese ion dissociated from the imaging agent.
We have now revisited the manganese concept and designed a manganese based contrast agent with a signal efficacy greater than that of commercially available gadolinium based agents, while dramatically improving the stability of the chelate (2).

Methods
A series of manganese chelates were synthesized and subjected to various in vitro tests, characterizing chelate stability and relaxivity. A lead candidate was further evaluated in vivo and tolerability, imaging and biodistribution properties were characterized.

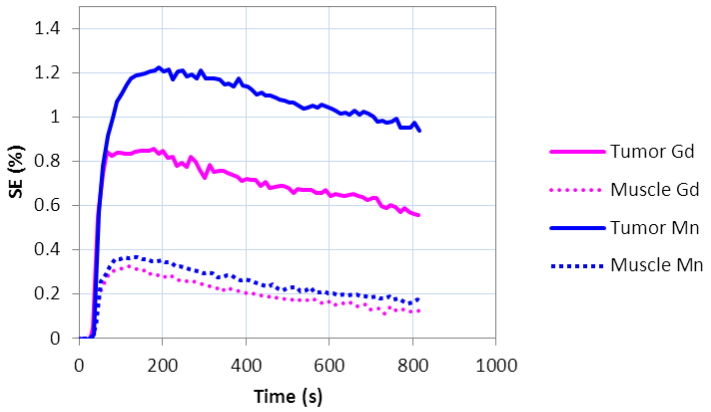

Fig 1. Greater signal enhancement over time of manganese agent vs commercial gadolinium agent exemplified in an animal model (3).

Results
Transmetallation assays indicate a very low dissociation rate for the manganese chelate and this was confirmed in vivo where renal excretion was the dominant pathway for the paramagnetic species. The high in vitro relaxivity was verified in imaging studies where the manganese agent maintained greater signal generating properties compared to a commercial gadolinium agent.

Conclusion
The efficacy and safety of the agent have been evaluated in vitro and in vivo, and the current lead candidate shows great promise as a general purpose contrast agent for MRI.

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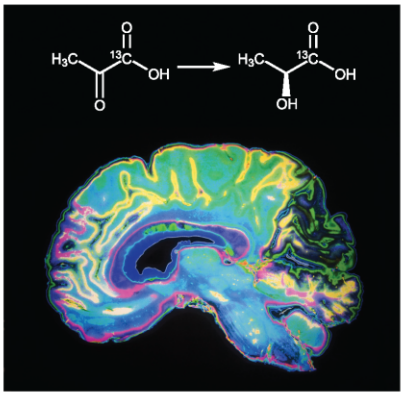
ALDRICH Chemistry

Hyperpolarization MRI/MRS Products

Two polarization techniques, dynamic nuclear polarization (DNP) and parahydrogen-induced polarization (PHIP), have been used to produce magnetic resonance spectroscopic and imaging agents containing polarized ^{13}C and ^{15}N nuclei. While operating by different mechanisms of polarization, DNP and PHIP both have succeeded in producing substrates with high levels of signal enhancement.



DNP

Hyperpolarization of a substrate to enhance the NMR signal can be achieved using DNP along with low temperature and high magnetic field.[1] Within the field of magnetic resonance imaging (MRI) and spectroscopy (MRS), DNP has been used to enhance the signal of labeled substrates allowing the real-time tracking of *in vivo* metabolism.[2] DNP has found use in the study of prostate tumors,[3] brain cancer,[4] tissue pH,[5] as well as further elucidation of the Krebs cycle.[6] Within this field, pyruvic acid has been the most heavily and successfully studied substrate due to its long T_1, ease of use and metabolic relevance.[3] Still, research into the development of additional substrates has shown the potential of other compounds as well.[5,7]

Cat. No.	Description	Isotopic Purity
729655	Acetylene-$^{13}C_2$ dicarboxylic acid	99 atom % ^{13}C
665223	Acetylene dicarboxylic acid-1-^{13}C disodium salt	99 atom % ^{13}C
704164	*N*-Acetyl-L-methionine-1-^{13}C	99 atom % ^{13}C
489867	L-Alanine-1-^{13}C	99 atom % ^{13}C
588741	4-Amino-TEMPO-piperidinyl-d_{17}	98 atom % D
683604	3-Bromopyruvic acid-1-^{13}C	99 atom % ^{13}C
722545	3-Bromopyruvic acid-3-^{13}C	99 atom % ^{13}C
679860	*tert*-Butan-1-^{13}C, d_9-ol	99 atom % ^{13}C 98 atom % D
488372	Butyric acid-1-^{13}C	99 atom % ^{13}C
609269	Choline chloride-^{15}N	98 atom % ^{15}N
720593	Ethyl pyruvate-2-^{13}C	99 atom % ^{13}C
676594	Ethyl pyruvate-3-^{13}C	99 atom % ^{13}C
492140	D-Fructose-2-^{13}C	99 atom % ^{13}C
749389	Fumaric acid-1,4-$^{13}C_2$	99 atom % ^{13}C
752576	Fumaric acid-1,4-$^{13}C_2$, 2,3-d_2	99 atom % ^{13}C 98 atom % D
552151	D-Glucose-$^{13}C_6$-1,2,3,4,5,6,6-d_7	99 atom % ^{13}C 97 atom % D
604968	L-Glutamic acid-1-^{13}C	99 atom % ^{13}C
605018	L-Glutamine-1-^{13}C	99 atom % ^{13}C
750506	L-Glutamine-4-^{13}C	99 atom % ^{13}C
604690	L-Glutamine-5-^{13}C	99 atom % ^{13}C

Cat. No.	Description	Isotopic Purity
705748	4-Hydroxy-TEMPO-^{15}N	98 atom % ^{15}N
487686	4-Hydroxy-TEMPO-d_{17}	97 atom % D
704334	2-Ketoglutaric acid-1-^{13}C	99 atom % ^{13}C
750832	2-Keto-4-methylpentanoic acid-1-^{13}C	99 atom % ^{13}C
487716	2-Keto-4-methylpentanoic acid-1-^{13}C sodium salt	99 atom % ^{13}C
738778	L-Lactic acid-1-^{13}C	99 atom % ^{13}C
606057	L-Lactic acid-1-^{13}C solution (85% w/w in H_2O)	99 atom % ^{13}C
703621	L-Malic acid-1-^{13}C	99 atom % ^{13}C
696471	4-Oxo-TEMPO-1-^{15}N	98 atom % ^{15}N
485268	4-Oxo-TEMPO-d_{16}	97 atom % D
487740	4-Oxo-TEMPO-d_{16},1-^{15}N	98 atom % ^{15}N 98 atom % D
591173	4-Oxo-2,2,6,6-tetramethylpiperidine-d_{17},1-^{15}N	98 atom % ^{15}N 97 atom % D
677175	Pyruvic acid-1-^{13}C (free acid)	99 atom % ^{13}C
692670	Pyruvic acid-2-^{13}C (free acid)	99 atom % ^{13}C
721298	Pyruvic acid-1,2-$^{13}C_2$ (free acid)	99 atom % ^{13}C
279293	Sodium acetate-1-^{13}C	99 atom % ^{13}C
279315	Sodium acetate-2-^{13}C	99 atom % ^{13}C
663859	Sodium acetate-$^{13}C_2$, S&P tested	99 atom % ^{13}C
372382	Sodium bicarbonate-^{13}C	98 atom % ^{13}C
299359	Urea-^{13}C	99 atom % ^{13}C

Medical Imaging Laboratory

The overall goal of MI Lab is to facilitate cost efficient health care and improved patient outcome through innovation in medical imaging, and to exploit the innovations to create industrial enterprises.

Synthetica is an efficient, flexible and independent synthesis laboratory. Our staff is capable of handling complex synthetic assignments and providing high quality, on-time, and confidential services. We are specialists in multi-step organic synthesis with many years of experience.

Pharma Marine

Pharma Marine AS , innovator in marine lipids, was established in 2007 by one of the most experienced teams in the marine omega-3 industry. The company s philosophy of using raw material and by-products from sustainable sources has lead the R& D team into the development of the CALAMARINE® (natural and concentrated DHA products) and **Oceans** marine ingredient lines. Pharma Marine`s new manufacturing unit is located on the west coast of Norway, near Ålesund, a region where marine oil refining dates back more than 130 years. In addition to advanced purification technologies, the facility houses a state-of–the art-research laboratory and is considered one of the most ecologically friendly production facilities in Norway.

www.pharmamarine.no

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