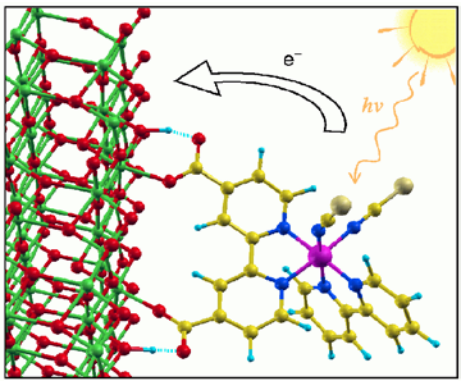
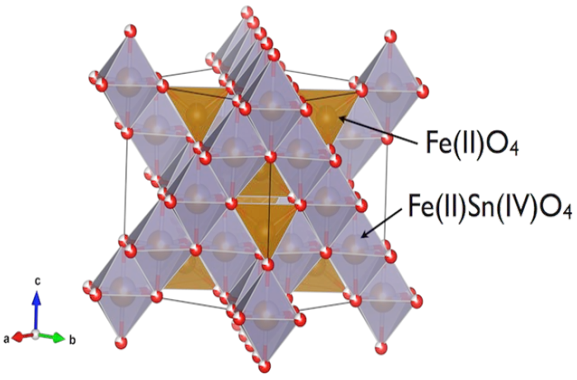
THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND

School of Chemical Sciences

SUMMER RESEARCH PROJECTS 2016-2017





Structure-activity relationship of polyamine-based antimalarials.

Assoc Prof Brent Copp,
Room 729B, Ph. 373-7599 x 88284, DDI 923-8284, b.copp@auckland.ac.nz

Why not come and join us in the hunt for a new cure for malaria? The world desperately needs new drugs to treat malaria infection. For our part, we've been investigating NZ marine organisms for new compounds that inhibit the growth of malaria parasites. We've found orthidine F (structure **1**) to be antimalarial with minimal toxicity – it's not a drug in itself, but does provide us with a valuable new idea on how to develop a drug. Since our initial finding, we've synthesized a lot of analogues, undertaking an extensive structure-activity relationship study. As a consequence, we now have several analogues that are close to cures for malaria in animal studies. In order to make these compounds into total cures, we're investigating new examples of polyamines that have multiple different antimalarial 'warheads' in their structures – type **2** in the Figure below. This summer project is designed to get you into the lab and making novel analogues in this series – all compounds will be tested against malaria with our collaborators. The research you undertake in this summer project can be extended into a BSc Hons project, and eventually into a PhD if you're interested.

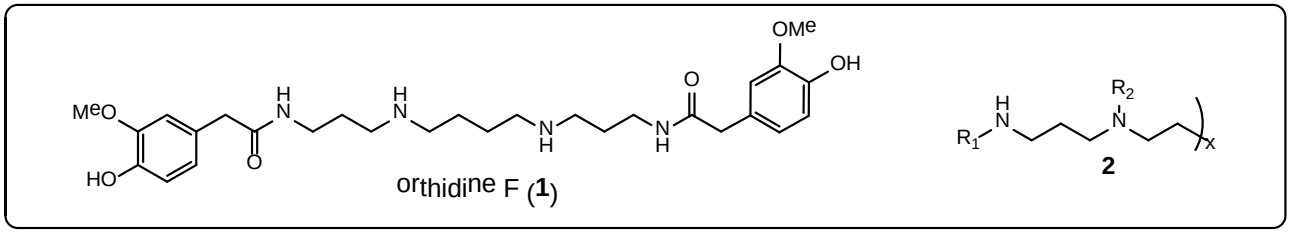


Figure. Structure of orthidine F and target polyamines.

Structure-activity relationship of new antimalarials.

Assoc Prof Brent Copp,
Room 729B, Ph. 373-7599 x 88284, DDI 923-8284, b.copp@auckland.ac.nz

In our search for new cures for malaria, we have been exploring not only natural products isolated from marine organisms but also screening of compound libraries. Recent data has identified new chemical scaffolds that exhibit potent activity towards malaria in vitro. Three of these scaffolds that we're particularly interested are shown in the Figure below. It's early days for this project – we don't know the structure-activity relationship of these scaffolds at all – we just know that they're active. Come and join my group to work on investigating the potential of these compounds to act as inspiration for new cures for malaria. You'll synthesize and characterize novel analogues and then they'll be tested by collaborators against drug resistant strains of malaria. The research you undertake in this summer project can be extended into a BSc Hons project, and eventually into a PhD if you're interested.

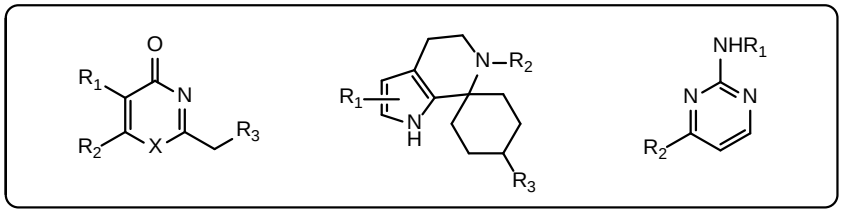


Figure. Scaffolds that can be studied in this project.

Exploiting marine natural products – antifouling polymer coatings.

Assoc Prof Brent Copp,
Room 729B, Ph. 373-7599 x 88284, DDI 923-8284, b.copp@auckland.ac.nz

Quorum sensing is a mechanism of chemical communication used by bacteria to coordinate communities of cells. Such coordination can include the formation of biofilms, considered to the initial step in the process leading to biofouling of marine surfaces. Halogenated furanones natural products, such as rubrolides and fimbrolides (see Figure below) are competitive inhibitors of quorum sensing, providing a template for the development of new antimicrobials and new antifouling agents. This project will lead to the synthesis and characterization of new analogues of these natural products: the functional groups to be included in the structures will include tethers that will allow them to be attached to polymers making them suitable for the preparation of antimicrobial films, paints and surfaces. The research you undertake in this summer project can be extended into a BSc Hons project, and eventually into a PhD if you're interested.

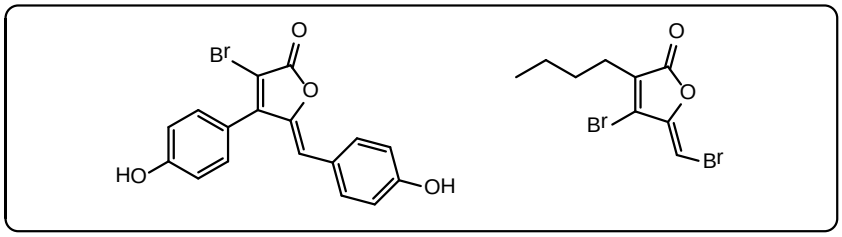


Figure. Structures of quorum sensing inhibitors.

Structure-activity relationship of new anti-tuberculosis agents.

Assoc Prof Brent Copp,
Room 729B, Ph. 373-7599 x 88284, DDI 923-8284, b.copp@auckland.ac.nz

We've been interested in developing new therapeutics for the treatment of tuberculosis for a number of years now. Our initial studies focused on marine natural products as the inspiration for bioactive scaffolds – more recently these studies have relied upon new structural classes of compounds identified by mass screening campaigns undertaken by big pharma. Two examples of bioactive hits coming from the GSK screen are shown in the figure below. This project will center on the synthesis of new analogues of these hits – all compounds will be evaluated for activity against *Mycobacterium tuberculosis* both here in NZ and also in the US. Our US collaborators are particularly talented at determining the mechanism of action of anti-tuberculosis agents and so that is also one of the aims of this project. The research you undertake in this summer project can be extended into a BSc Hons project, and eventually into a PhD if you're interested.

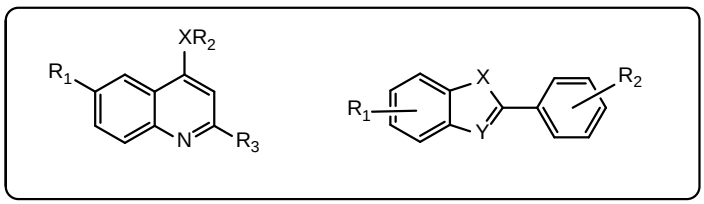


Figure. Examples of scaffolds that can be studied in this project.

New Zealand fungi as sources of new antibacterial lead compounds.

Assoc Prof Brent Copp, Assoc Prof Silas Villas-Boas, Dr Siouxsie Wiles (FMHS)
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Alexander Fleming's discovery of penicillin, an antibiotic produced by the fungus *Penicillium rubens*, saw the dawn of a golden age for humankind. The routine use of antibiotics has since prevented a great deal of suffering and saved countless lives. Worryingly, that era is now coming to an end whereby antibiotic resistance means that many antibiotics are no longer effective as bacteria have developed the mean to evade and/or destroy these life-saving medicines. We are searching for new antibiotics using a large collection of fungi, most derived from plants and soil from New Zealand and the South Pacific. We are screening this collection to discover new compounds that kill the superbugs causing the greatest clinical threat to New Zealand: *Staphylococcus aureus*, *Escherichia coli* and *Mycobacterium tuberculosis*. This project will have you undertaking metabolomics profiling of antibacterial extracts, using HPLC and NMR to investigate the natural product components. Bioassay-guided fractionation will then be used to purify the active component(s) of each extract – testing of which against our bacteria panel will then reveal if we have something worth pursuing. The research you undertake in this summer project can be extended into a BSc Hons project, and eventually into a PhD if you're interested.

Marine chemical ecology.

Assoc Prof Brent Copp,
Room 729B, Ph. 373-7599 x 88284, DDI 923-8284, b.copp@auckland.ac.nz

Marine chemical ecology is the science of investigating chemicals (natural products) produced by marine organisms and the roles they play in maintaining the evolutionary fitness of the organism. Such roles can include stopping biofouling (other things growing on top of the organism) or inhibiting predation. We've recently reported the first example of an alkyne containing amino alcohol lipid from a natural source – in this case, the sea squirt *Pseudodistoma opacum* which grows on rocks on West Auckland beaches. We're intrigued as to why the organism produces this compound, as well as several related alkyne containing structures, and seems to locate the compounds in its outer layers. In order to progress our studies, we plan to synthesise fluorescent compounds that will specifically tag the alkyne groups in these natural product. Once tagged, we'll be able to purify new analogues and we'll also be able to visualize where the compounds are specifically located in the organism. The research you undertake in this summer project can be extended into a BSc Hons project, and eventually into a PhD if you're interested.

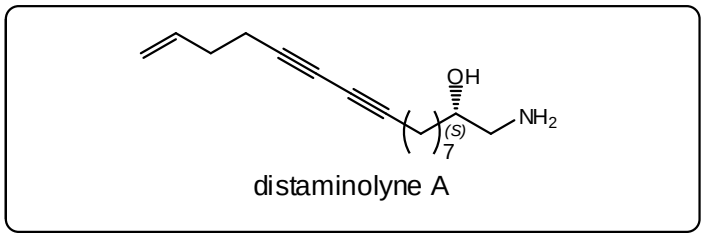

Figure. World's first example of a naturally occurring alkyne containing amino alcohol.

Sulfur compounds profiling in selected yeast strain fermentations.

Dr. Bruno Fedrizzi *b.fedrizzi@auckland.ac.nz*

Fermentative sulfur compounds (FSCs) are pivotal species in defining, tuning and spoiling wine quality. Their contribution to the overall wine bouquet is controversial and it seems to have both negative and positive implications. As the name suggests these molecules are generated from the yeast metabolism, putatively from amino acids or amino acidic precursors. Nowadays, the most important sulfur compounds can be quantified at the School of Chemical Sciences; this information could be successfully combined with the yeast genetic knowledge generated at the School of Biological Sciences in order to further our understanding on the formation of these species.
The project will aim at profiling FSCs in the fermentation trials carried out with particular yeast strains for which the genetic analyses are currently undergoing. Gas chromatography coupled to mass spectrometry will be applied to detect and quantify these molecules.

Bioorganometallic Anticancer Chemotherapeutics: Preparation of Ru Complexes with Bioactive Ligands

Prof. Christian Hartinger
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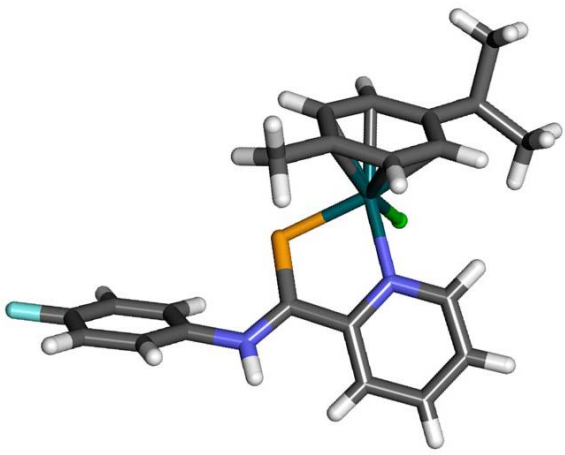
Phone 09 3737599 ext 83220; Room 301-629A

Medicinal bioinorganic chemistry is a relatively new but fervent area of research. It offers possibilities for the design and development of metal-based drugs for specific therapeutic needs that are not readily accessible to organic compounds. Currently, iron, ruthenium and osmium organometallic compounds have become the focus of interest and appear to be promising anticancer drug candidates. Some examples are at an advanced stage of preclinical development. Among the half-sandwich, piano-stool configured organometallic anticancer complexes, two most extensively studied approaches involve the coordination of ethylenediamine (en) and 1,3,5-triaza-7-phosphatricyclo[3.3.1.1] decane (pta) ligands to metal centres. *In vivo* studies on bifunctional RAPTA-C revealed excellent inhibition of metastasis growth. Monofunctional [Ru(η^6-arene)Ru(en)Cl]$^+$ type complexes were found to have *in vitro* anticancer activity similar to that of cisplatin, one of the most widely used anticancer drugs in clinics.
Within this project a series of organometallic metal-arene compounds (metal = ruthenium and osmium) will be prepared to feature bioactive ligands. We are currently focusing on *O*,*O*-, *N*,*O*- and *S*,*N*-chelating ligands which are chosen based on their intrinsic biological properties. The compounds that we will prepare in this project, will be evaluated for potential anticancer activity by *in vitro* assays. Experiments on biologically-relevant metabolisation including hydrolysis, interactions with proteins and DNA model nucleobases will be carried out.



The student will be exposed to different levels of the drug development process and will gain extensive training in a range of synthetic

procedures (both organic and inorganic synthesis) and separation/purification techniques. The prepared compounds will be characterised with state-of-the-art analytical methods (NMR, IR and UV/vis spectroscopy, electrospray ionisation mass spectrometry and X-ray diffraction analysis).

Design of Multimodal Organometallic Anticancer Agents

Prof. Christian Hartinger
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Since the discovery of cisplatin, the design of most metallodrugs has been based on the paradigm that DNA is the target in tumour cells. Such agents however cannot explicitly discriminate between healthy and cancerous cells. More recently this paradigm has shifted and a small body of research has been aimed at developing inhibitors of specific enzymatic targets via organometallic compounds. Late transition metals such as ruthenium and osmium are ideally suited for this purpose. Their (relatively slow) ligand exchange rates and versatile synthetic chemistry can be exploited to construct novel structural scaffolds (e.g. octahedral motifs) that are not generally accessible to purely organic small molecules, which are largely restricted to tetrahedral, planar, or linear geometries. This molecular complexity can be utilized for developing inhibitors of specific enzymatic targets by linking a metallopharmacophore to a ligand or to construct metal complexes that resemble the shape of substrates of such enzymes. In tumours, a number of proteins are upregulated, often to satisfy the increased demand of rapidly dividing cancerous cells for nutrients. These alterations in tumours can be successfully targeted for rational design of anticancer agents with high selectivity. One of such targets are zinc-containing histone deacetylases (HDACs) which are considered important targets for anticancer chemotherapeutics. In this project, we will design an anticancer active metal(arene) fragment with groups able to selectively chelate zinc in HDACs. Connecting two or more pharmacophore will result in a compound that can bind to more than one target and thereby provide a means to overcome drug resistance through multi-modal activity.

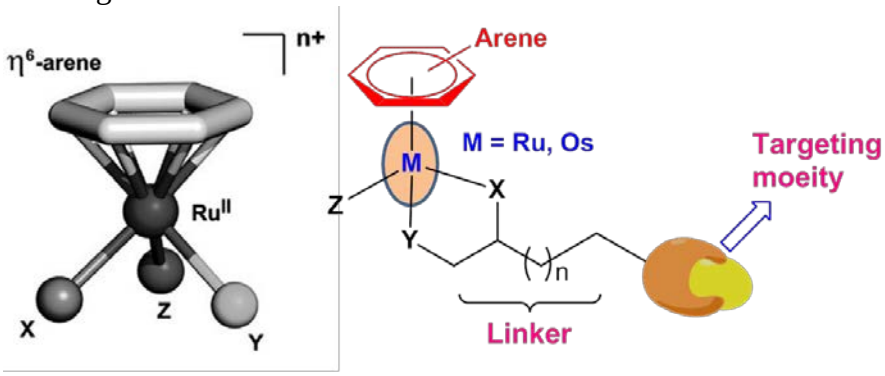

Figure. *General structures of half-sandwich, piano-stool metal(arene) complexes (left) and outline of the design strategy for multimodal organometallic anticancer agents (right).*

The student will be exposed to different levels of the drug development process and will gain extensive training in a range of synthetic procedures (both organic and inorganic synthesis) and separation/purification techniques. The prepared compounds will be characterised with state-of-the-art analytical methods (NMR, IR and UV/vis spectroscopy, electrospray ionisation mass spectrometry and X-ray diffraction analysis).

Design and Applications of Organometallic Complexes for Catalysis

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Prof. James Wright
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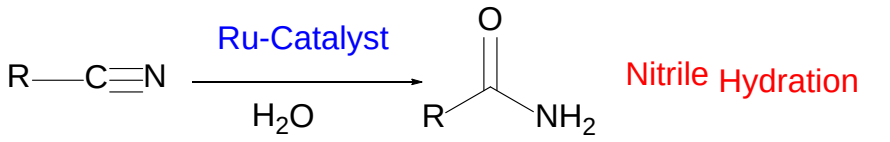
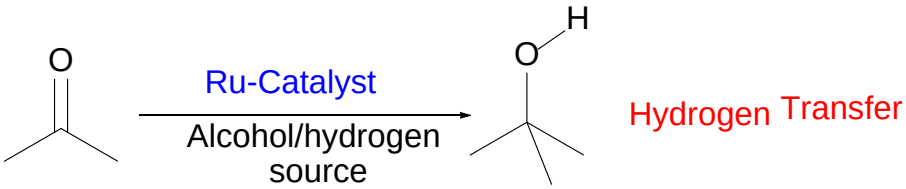
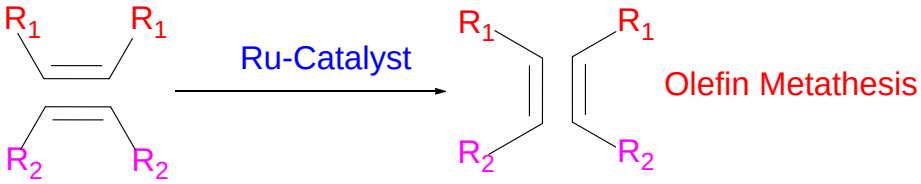
The production of everyday products, such as pharmaceuticals, fertilisers and functional materials, is reliant on efficient chemical transformations to yield high amounts of the desired products at low cost. Catalytic processes are often the only efficient option to prepare certain compounds. In recent years, we have designed a large variety of ruthenium complexes featuring ligands with phosphorus, nitrogen, oxygen and sulphur donor atoms.
In this project we want to explore the use of such ruthenium complexes as catalysts for different reactions. These will range from the hydration of nitriles, transfer hydrogenation of ketones to olefin metathesis. Each of these reactions has a very important role in the preparation of chemicals widely used in industry.







The student will gain extensive training in a range of synthetic procedures (both organic and inorganic synthesis) and analytical methods to characterize compounds and study their catalytic properties (TON, TOF). The methods employed will include NMR, IR and UV/vis spectroscopy, HPLC, GC and electrospray ionisation mass spectrometry.

Bioanalytical Mode-of-Action Studies of Metal-based Anticancer Agents

Prof. Christian Hartinger
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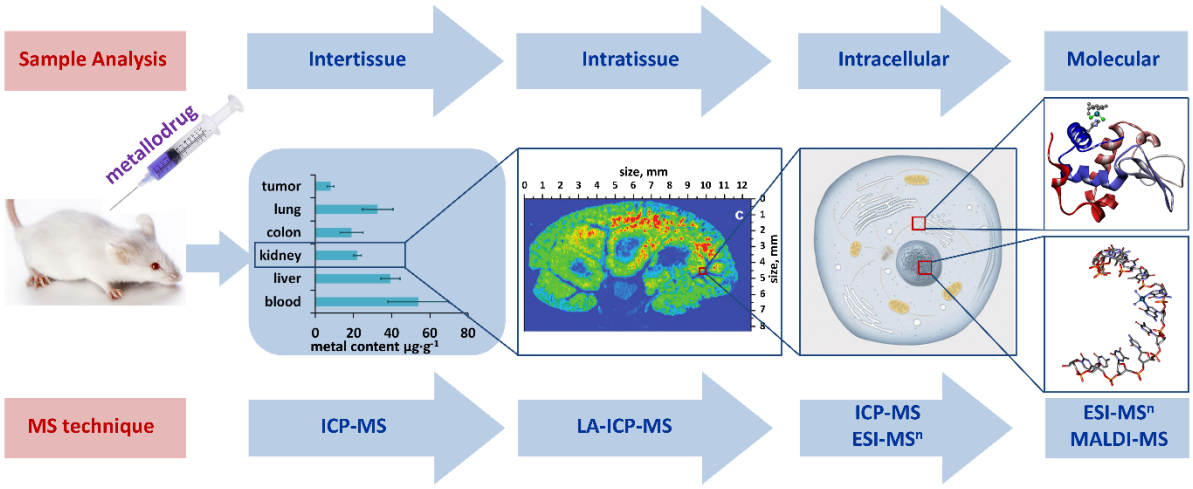
Phone 09 3737599 ext 83220; Room 629A

DNA has been identified as the target of Pt-based anticancer agents in tumour cells. However, until anticancer drugs reach DNA, they may interact with many other biological molecules. Therefore, we extensively study the binding of metal-based anticancer agents with amino acids and with proteins. For this purpose we use different analytical methods which include capillary electrophoresis, gel electrophoresis, high performance liquid chromatography, NMR spectroscopy and mass spectrometry (Figure).



In this project, the student will be learn about different levels of the drug development process and will gain extensive training in a range of analytical methods, especially NMR, CE and electrospray ionisation mass spectrometry. The project will involve studying the interactions of metal complexes designed as anticancer agents with biological binding partners. Studies with model proteins will be followed by experiments to elucidate the interaction with serum proteins. This studies will allow us identifying the influence of different structural components on the reactivity of metal complexes. This is important information to decide which compounds to put forward for further in depth preclinical studies as anticancer agents.

Thermal stability analysis of bioactive compounds from *Centella asiatica*

Prof Conrad Perera & Dr. Sudip Ray
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Phone 09 3737599 ext 83156

Centella asiatica (gotu kola) is a herbal medicinal plant recognized for its health benefits such as revitalizing the nerves and brain cells, memory enhancing, wound healing and anti-inflammatory properties (Vasantharuba *et al*,2012). A PhD project is currently being carried out on "The Extraction, characterization and in vitro testing of bioactive compounds from *Centella asiatica* (gotukola) and development of a suitable food matrix/nutraceutical to deliver potential functional properties. Quantity and bioactivity of phytochemicals present in plant materials are affected by processing and storage conditions (Negi, 2012). Therefore, the thermal stability of bioactive compounds is important for their potential applications as food products or ingredients.
This project is to study the thermal behaviour of the isolated bioactive compounds using DSC and TGA. The thermal degradation kinetics of reactions occurring in a given temperature range and glass transition temperature are important in interpreting thermal degradation of bioactive compounds (Brown, 1988; Ross, 2003). HPLC and FTIR will be used to quantify and to identify the changes in the known functional groups. The information obtained will help to establish a comprehensive understanding of the stability of the targeted bioactive compounds that will provide a base line in developing a suitable food matrix as a carrier.

References

Brown, Michael E. 1988. Introduction to Thermal Analysis: Techniques and Applications. New York, NY: Chapman and Hall.
Negi, P. S. (2012). Plant extracts for the control of bacterial growth: Efficacy, stability and safety issues for food application. International Journal of Food Microbiology, 156(1), 7-17.
Roos, Y. H. (2003). Thermal analysis, state transitions and food quality. Journal of Thermal Analysis and Calorimetry, 71(1), 197-203.
Vasantharuba Seevaratnam, Banumathi, P., Premalatha, M.R., Sundaram, S.P. and Arumugam, T. Functional properties of Centella asiatica (L.): A review. Int J Pharm Pharm Sci. 2012; 4: 8-14

Note:
Skills Required: Preferably a third year Chemistry or Food Science student with a good analytical Chemistry background.

Available during summer from middle of November till end of February.

Synthesis of biologically active lignan natural products

Associate Prof David Barker
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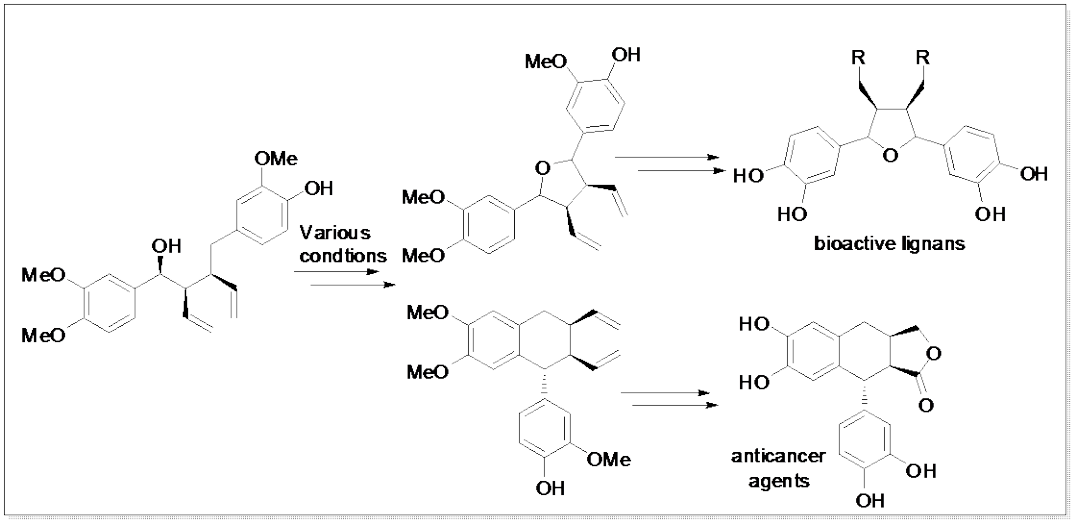
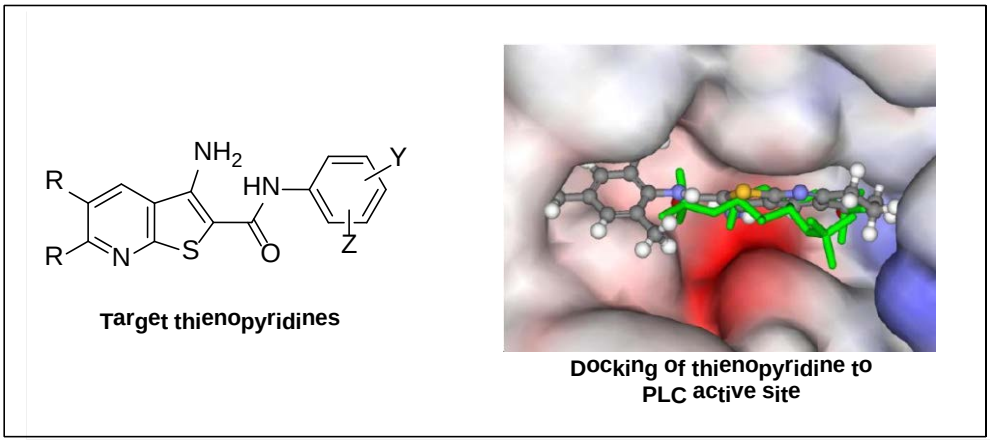
Lignans are a class of compound which has become the a target of particular interest to researchers, owing to their numerous biological activities including anti-cancer and cytotoxic properties and have also shown an array of pharmacological activities, including antifungal, antibacterial, antioxidant and anti-proliferative properties. In this project we will explore our recently developed methods to prepare a range of classes of lignan natural products using a common, easily made intermediate. This compound can be converted to both THF lignans and also aryl-tetralin lignans, both classes have highly bioactive members including clinically used drugs. The student undertaking this project will be involved in organic synthesis, purification and compound characterisation (NMR, MS, IR, etc).



Synthesis of Novel inhibitors of Phospholipase C, an enzyme involved in cancer cell proliferation

Associate Prof David Barker, Dr Johannes Reynisson and Dr Euphemia Leung, Auckland Cancer Society Research Centre)
d.barker@auckland.ac.nz

Phospholipase C is a promising biological target for anticancer drug therapy with compounds binding to PLC showing marked growth inhibition of haematological tumour cells. We have recently discovered a class of compounds which are potent inhibitors of cell growth. Morphology and motility assays using triple negative breast cancer cell lines lead to the conclusion that PLC is a probable bio-molecular target of these compounds however other important targets may be effected. The student working in this project will be involved in the design (computation modelling), synthesis and biological testing of novel compounds to treat cancer.



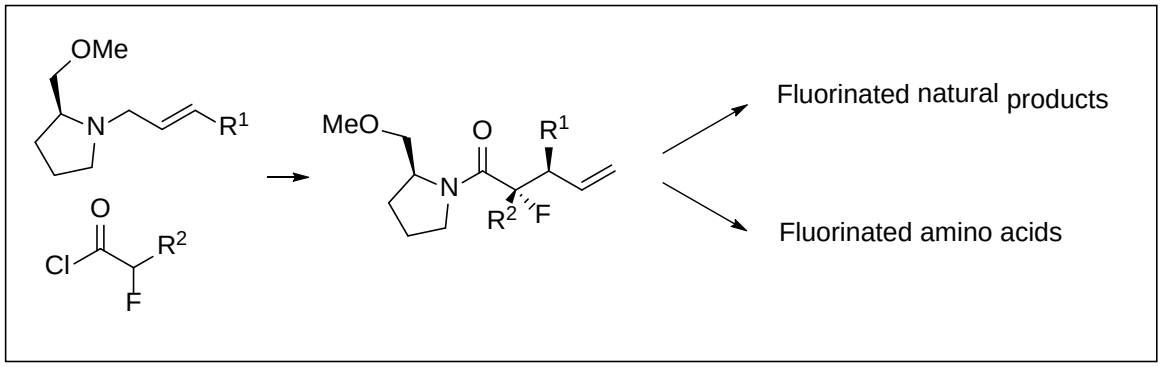
Target thienopyridines

Docking of thienopyridine to PLC active site

Exploring the effect of fluorination on Claisen rearrangement reactions

Associate Prof David Barker
d.barker@auckland.ac.nz

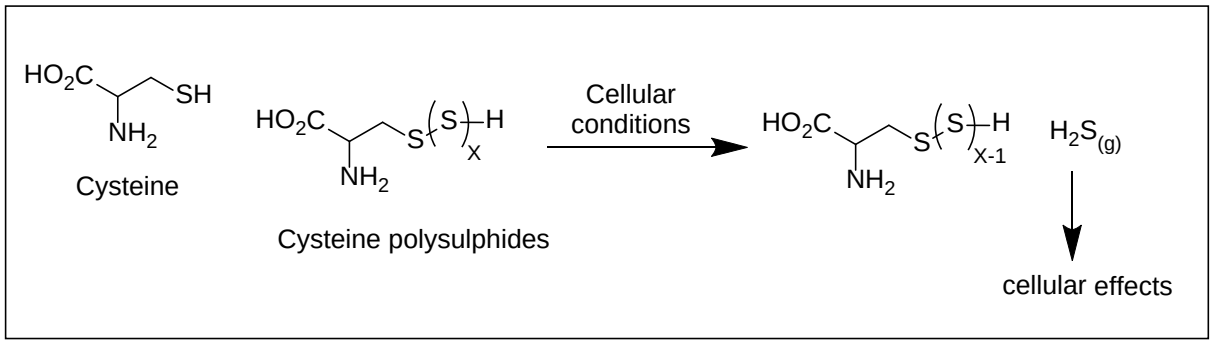
The Acyl-Claisen rearrangement is a modern derivative of a classical organic chemistry reaction and allows multifunctional compounds to be prepared which we have found are extremely useful for the synthesis of complex biologically active compounds. In this project we will further explore the use of fluorinated materials in this reaction and discover conditions that allow a variety of substrates to be employed. This will then allow access to a range of poly-functional fluorinated compounds that are otherwise difficult to obtain. Fluorinated compounds are of considerable interest in drug-like molecules and in amino-acids/peptides for the interesting way they effect both the shape and electronic properties of the molecules. The student undertaking this project will be involved in organic synthesis, purification and compound characterisation (NMR, MS, IR, etc).



Understanding the biogenesis of H2S in yeast and its role cell signalling

Associate Prof David Barker, Dr Bruno Fedrizzi
d.barker@auckland.ac.nz

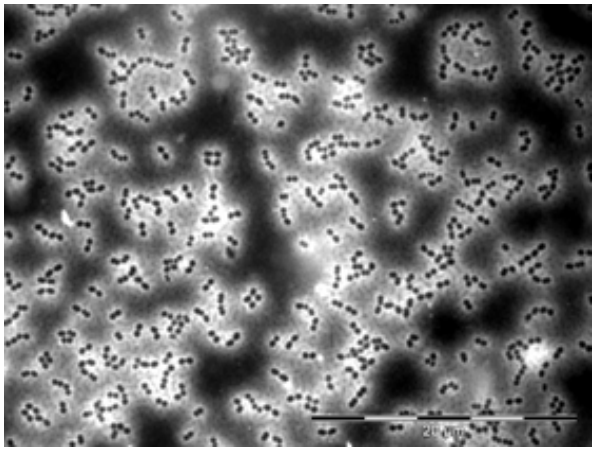
There is growing recognition that H_2S is a "gasotransmitter'' that plays critical roles in cellular signalling and hormonal regulation. In humans, H_2S has come under intense recent scrutiny because of its importance in cardiovascular diseases, cellular energetics and apoptosis. Since gaseous transmitters diffuse rapidly and with fine temporal control, understanding their modes and sites of synthesis is critical to understanding their biology. Several enzymes produce H_2S, but their roles and relative importance in H_2S signalling are not yet clear. In this project students will work on the synthesis of novel polysulphides, based on the amino acid cysteine, which act as H_2S donors. These molecules are reacted upon by enzymes to release H_2S and will be used study the effect of H_2S in the inter-species signalling. The student undertaking this project will be involved in organic synthesis, purification and compound characterisation (NMR, MS, IR, etc) and also analytical techniques such as GCMS and LCMS.



Synthesis of novel polymeric materials as surface active antimicrobial agents

Associate Prof David Barker; Prof. Jadranka Travas-Sejdic
d.barker@auckland.ac.nz

Due to the increase in bacterial resistance there is a need to develop new antibacterial agents, in particular in a hospital and medical environment. In this project we will synthesize novel fluorescent antimicrobial polymers which not only kill bacteria upon contact but allow visualisation of the bacterial killing. The polymers will be designed so they can be used in a either a solution to be applied where desired or could be attached permanently to a surface to give an antibacterial surface. The student undertaking this project will be involved in organic and polymer synthesis, purification and compound characterisation (NMR, MS, IR, etc).

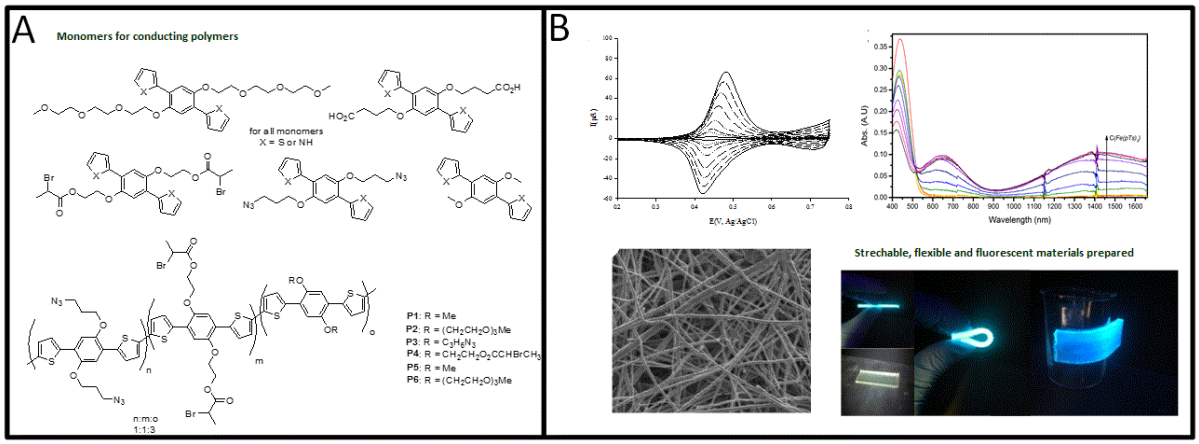


Staphylococcus aureus treated with fluorescent antibacterial polymers.

Synthesis of novel polymeric materials for modern electronic materials

Associate Prof David Barker; Prof. Jadranka Travas-Sejdic
d.barker@auckland.ac.nz

In this project the synthesis of novel polymeric materials will be undertaken with the prepared materials having the unique ability to not only conduct electricity but to also be adhesive and self-healing. The concept is that through appropriate design, materials can be made that are flexible, stretchy but also conducting. This can allow for the preparation of a new generation of conducting plastics for a wide range of applications, such as optoelectronics, bio-integrated electronic devices and conducting skin and soft robotics. The student undertaking this project will be involved in organic and polymer synthesis, purification and compound characterisation (NMR, Mass, IR, etc) as well as wide range of materials spectroscopy (AFM, SEM XPS etc).



Killing surface bacteria

Dr Duncan McGillivray
d.mcgillivray@auckland.ac.nz

Antimicrobial surfaces are extremely important to prevent contamination of materials used in everything from health care to food manufacturing. While a number of effective antimicrobial materials exist, attaching them to relevant surfaces so that they maintain their activity remains a challenge. This project will investigate methods of chemically attaching molecules to surfaces, and characterising the surfaces that are formed using ellipsometry, X-ray reflectometry, AFM and antimicrobial assays, towards optimising surface activity. Students will need to be comfortable with chemical laboratory skills.

Making better biominerals

Dr Duncan McGillivray
d.mcgillivray@auckland.ac.nz

Nature is extremely effective at creating hybrid hard/soft materials, combining the strength of minerals with the flexibility and lightness of biological materials. This project will investigate attempts to create equivalent materials chemically, and characterising the result at the molecular and microscopic scale using ellipsometry, X-ray reflectometry, AFM and SEM, as we attempt to produce room temperature biomineralisation to rival sea shells!

Understanding the mechanism of the copper-catalysed oxidative cross-coupling of amines and phosphates to yield phosphoramidates

Dr. Erin Leitao
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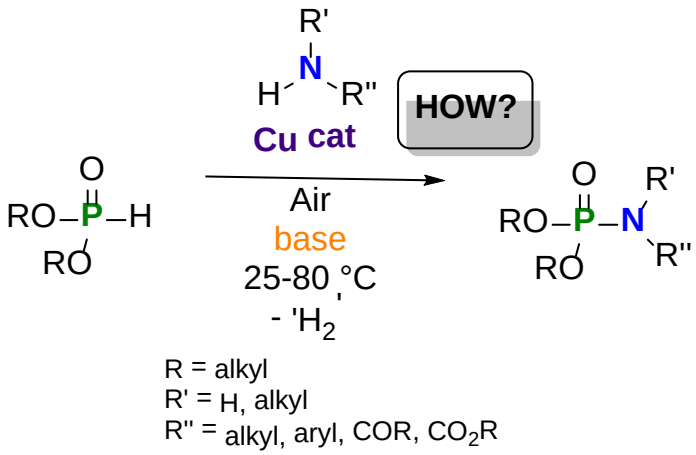
Compounds containing P-E bonds (E = N, S, O, P) expand a wide range of applications such as flame retardants, pesticides, coenzymes, as well as several bioactive molecules. Since the recent seminal reports of copper-catalyzed oxidative cross-coupling to furnish hypophosphates (P-P), pyrophosphates (P-O-P) and phosphoramidates (P-N) from H-phosphonates ($(RO)_2P(O)H$), there has been some expansion in the reaction scope using this methodology (including P-S bond formation), however, the mechanism(s) of the catalysis remain elusive. The seemingly simple and readily available catalysts (CuX_2 or CuX, *e.g.* X= halide, OAc, OMe) and substrates used in the majority of the transformations make this reaction attractive to study mechanistically (see Figure). Not to mention the elimination of byproducts such as H_2O (observed in some cases) and high selectivity in the P-N bond forming reaction (very little P-P, P-O-P products observed under the reaction conditions). Preliminary data suggests a homogeneous catalyst is in operation and forms

more readily from the Cu(II) salts. Straightforward isotopic labelling and kinetic monitoring using GC-MS will provide access to kinetic isotope effects (KIE) and temporal-concentration data. These studies along with the use of other techniques such as: stoichiometric reactions, control reactions (*e.g.* absence of Cu catalyst, absence of a reagent, changing the order of addition), solvent and temperature studies, attempted synthesis of postulated intermediates and use of model complexes/analogues, will reveal pertinent details concerning the rate-determining step, potential transition states, and intermediates. This project will involve the synthesis of phosphoramidates using a variety of copper-catalysts, as well as the potential synthesis of labelled substrates and/or new copper-catalysts, along with analysis and characterization using NMR spectroscopy and GC-MS.



Using catalysis to create new bioerodible materials useful in the construction of synthetic bone

Dr. Erin Leitao
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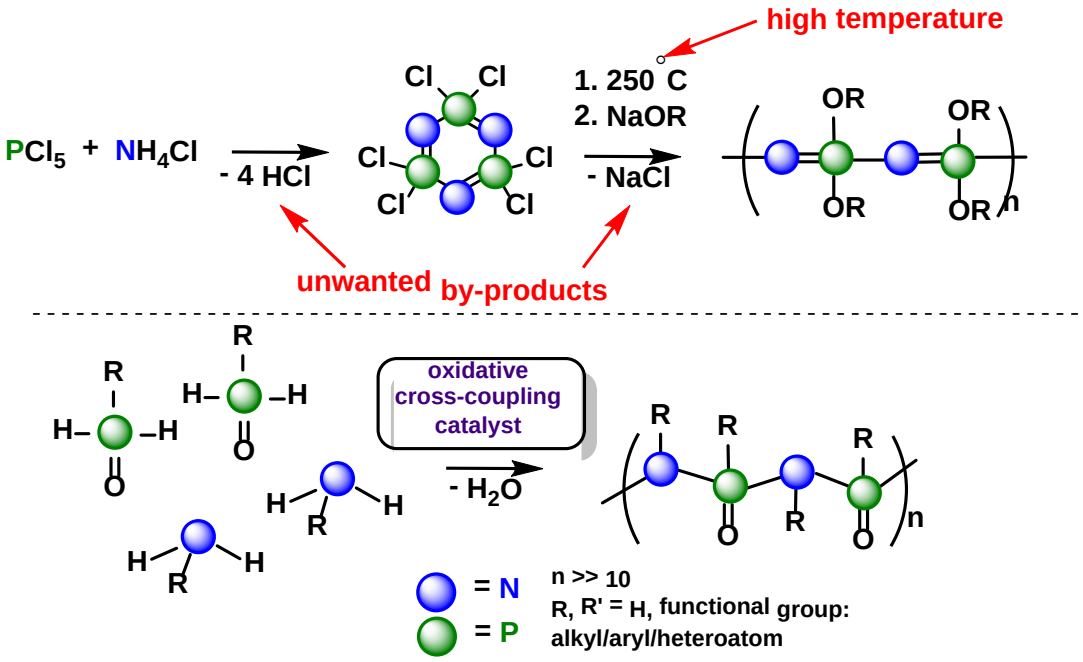
Recent research demonstrates that polyphosphazenes are attractive bioerodible polymers postulated to be useful in the construction of synthetic bone. Polyphosphazenes are made from the ring opening polymerization of hexachlorocyclotriphosphazene $(Cl_2P{=}N)_3$ at high temperatures followed by functionalization by replacing the Cl atoms (see top scheme below; *e.g.* with RO, NRH, etc.). This synthesis suffers from the use of high temperatures, toxic reagents and large amounts of unwanted by-products. Copper-catalyzed oxidative cross-coupling (see bottom scheme below) has recently been shown to be an effective way to make P-N bonds from H-phosphonates $((RO)_2P(O)H)$ and amines $(R'NH_2)$. Expansion of this method in an attempt to make phosphoramidate polymers will be explored. The project will involve inorganic synthesis using various Cu(I) and Cu(II) catalysts with analysis and characterization using NMR spectroscopy and GC-MS. The project may also include the synthesis of a new active homogeneous catalyst useful for this process.



Catalytic routes to robust polysilanes

Dr. Erin Leitao
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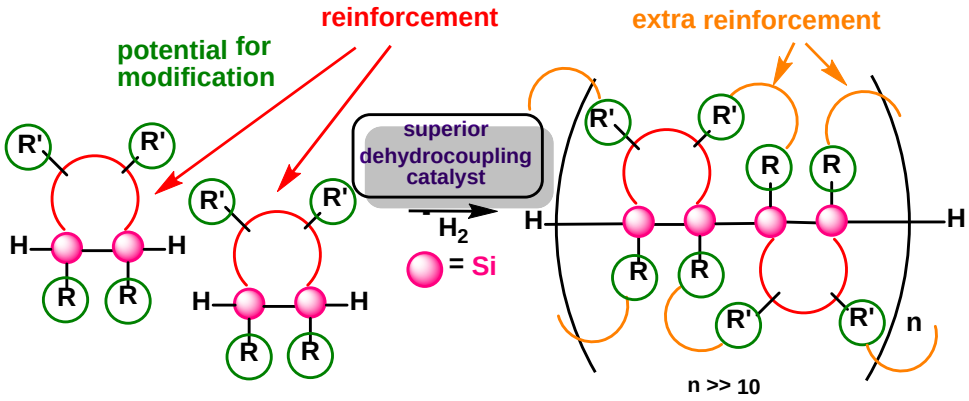
Polymers with a carbon backbone are ubiquitous. It is hard to go a day without coming in contact with one (polyethylene: *e.g. plastic bags, bottles, toys*; polypropylene: *e.g. dollar bills; thermal clothing*; polyisobutylene: *e.g. chewing gum, tires*). Polysilanes, polymers containing a Si-Si backbone, are in their relative infancy in terms of commercialization, but are highly sought after, as strong electronic σ-conjugation is achieved upon linear Si-Si chain formation giving rise to properties with a wide-range of potential applications (*e.g. photoconductors/initiators, explosive detecting materials, molecular recognition and information storage, semi-conductors suitable for modern energy generation*). Despite the first synthesis of polysilanes reported by Kipping nearly 100 years ago, and the growing interest in the utility of these materials, access to a mild and controlled synthetic method amenable to the large scale production of defect free (well-defined), strong (high molecular weight), high silicon content (extensive σ-conjugation) and tunable polysilane is non-existent. Of the current methods available to synthesize polysilanes, catalysis is the most promising. Catalytic dehydrocoupling is attractive because dihydrogen (H_2) is the only by-product and there is literature precedence for the formation of long chains of Si-Si atoms with primary silane substrates. To make robust polysilanes (see Figure), secondary silane substrates will need to be employed which is a significant challenge as strained Si-Si bonds are subject to disproportionation via Si-Si bond cleavage (much weaker than C-C bonds) producing low molecular weight oligomers. Furthermore, bulky substituents on the monomers can cause steric congestion at the metal-centre of catalyst as the chain grows limiting the chain length. A series of new catalysts will be assessed for this transformation using selected secondary silane substrates and the drawbacks illuminated during

detailed investigations of the catalysis. The project will involve inorganic synthesis and analysis using NMR spectroscopy and mass spectrometery.



Behaviour of fingermarks on ice

Associate Prof Gordon Miskelly
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We have reported that fingermarks can be deposited and recovered from ice and other difficult substrates, by staining with a dye that is soluble in fluorous solvents. This project will investigate the conditions under which this is possible, and also investigate what is happening to the fingermark components over time.

Hyperspectral imaging in chemical analysis

Associate Prof Gordon Miskelly
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We have constructed a hyperspectral line imager suitable for imaging objects in the 1 mm – 10 cm size range. This project will apply this hyperspectral imager to systems in which spectral changes occur along one dimension. This project will require calculations using the Matlab programming environment.

Production and purification of recombinant bacterial and human trimethyllysine hydroxylase for the treatment of ischemic heart disease

Dr Ivanhoe Leung; School of Chemical Sciences; i.leung@auckland.ac.nz

Ischemic heart disease is one of the most common causes of mortality in the Western society. During periods of ischemia, the lack of blood flow to the heart limits the supply of oxygen, and causes the usually tightly regulated glucose and fatty acid oxidation pathways to be compromised. During ischemia, glycolysis (an oxygen independent metabolic pathway) serves as the main source of energy (ATP) production. However, the restoration of blood flow after an ischemic episode (reperfusion) does not restore the balance between glucose and fatty acid oxidations. Instead, fatty acid oxidation dominates as the major pathway for ATP production. Fatty acid oxidation has a much greater oxygen requirement than glucose oxidation, this, together with the disturbances in ionic and chemical homeostasis during ischemia and in the post-ischemic period, lead to an overall decrease in cardiac efficiency of between 25% and 40%.

It is possible to pharmacologically restore the balance between fatty acid oxidation and glucose oxidation (and hence the cardiac efficiency of the ischemic/reperfused heart), for instance, by limiting the mitochondrial fatty acid uptake. The transport of fatty acids from the cytoplasm to mitochondria requires a small carrier molecule called carnitine. By controlling the availability of carnitine (e.g. by limiting its biosynthesis), one can shift the cardiac energy source from fatty acid oxidation to glucose oxidation by restricting the amount of fatty acid substrates in the mitochondria and thereby forcing the cells to utilise glucose as the energy source instead.

Four enzymes are involved in carnitine biosynthesis. We are interested in characterising the first enzyme (trimethyllysine hydroxylase, TMLH) in this pathway, which catalyse the hydroxylation of trimethyllysine. This information will be useful for future developments of TMLH inhibitors for the treatments of ischemic heart disease. This summer scholarship will be the first step of this project, which will include cloning, production and purification of recombinant TMLH from both humans and bacteria.

There is no formal prerequisites to this summer scholarship, although an understanding of basic molecular biology and an enthusiasm in chemical biology will be helpful. Training and supervision in molecular biology and enzymology will be given throughout the summer period. Please contact me by email if you require any more information.

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Development of novel inhibitors for *Mycobacterium tuberculosis* isocitrate lyase

Drs Ivanhoe Leung and Jonathan Sperry; School of Chemical Sciences; i.leung@auckland.ac.nz and j.sperry@auckland.ac.nz

Tuberculosis is an infectious disease that is caused by the airborne bacterium *Mycobacterium tuberculosis*. Once infected, *Mycobacterium tuberculosis* may exist in different metabolic states including a slow or non-growing ‘dormant’ state that is non-responsive to conventional anti-tuberculosis treatments. The failure to eliminate all populations of *Mycobacterium tuberculosis* from the patient may lead to the development of drug-resistant bacteria. It is estimated that about a third of

the world's population has latent tuberculosis, the control of which is therefore crucial to the management and eradication of the disease.
Isocitrate lyase (ICL) is the first enzyme in the bacterial glyoxylate cycle, which is an important pathway for latent *Mycobacterium tuberculosis* to synthesise carbohydrates and other biosynthetic products for survival. We are interested in the development of novel ICL inhibitors for the treatments of latent tuberculosis. This summer scholarship will form a key part of this project, which include the design and synthesis of ICL inhibitors, and *in vitro* characterisation of their inhibition potency against different isoforms of *Mycobacterium tuberculosis* ICL using biophysical techniques.
There is no formal prerequisites, although an interest and understanding of organic and medicinal chemistry and an enthusiasm in chemical biology will be helpful. Training and supervision will be given throughout the summer period. Please contact us by email if you require any more information.
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Biocidal and antifouling polymers for surfaces

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Note: Can include skills required, pre-requisites, timings, etc.

Antimicrobial and antifouling polymers have a potential to be used as permanent coating on surfaces. These can be synthesized by grafting of biocidial or antifouling polymers from pre-made functional polymer backbones. The biocidial/ antifouling polymers will be designed to firmly link to various surfaces, including metal, glass and plastic. The properties of the polymers, e.g. hydrophobicity, molecular weight, stability and biological activity will be characterised and controlled by the compositions of the polymers or block-copolymers. A student is sought, ideally with synthetic polymer chemistry skills, who would make such a proof-of concept polymer system, working alongside a post-doctoral fellow and a senior PhD student in the group of Prof. Travas-Sejdic. The project will be conducted in collaboration with Prof. Gillian Lewis from the School of Biological Sciences and supported by Biocide ToolBox programme.

Correlation between predicted and measured hydrogen bonding energies in model systems

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Hydrogen bonding is crucial biological systems, e.g., facilitating recognition between a substrate and an enzyme[1] as well as being the foundation of the genetic code.[2] It is therefore important that reliable theoretical methods are available to predict the hydrogen bonding energies such as the nucleotides in DNA.[3]
In this project a range of ab initio and density functional methods will be benchmarked against experimentally derived hydrogen bonding energies for model systems.[4-8] This will give us insight in the reliability of the quantum mechanical methods available for further application in biological systems.

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The redox potentials of pro-drugs activated with bio-oxidation/reduction as calculated with DFT

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School of Chemical Sciences, University of Auckland, New Zealand
It is well known that many of the drugs currently in clinical use are activated via bio-oxidation or reduction.[1] E.g., mitomycin is an anticancer drug that has been in use for more than fifty years is activated by bio-reduction.[2] Many tumours are hypoxic and therefore designing drugs that are DNA damaging agents in their reduced form is an excellent strategy for making new potent anticancer drugs.[3, 4] In this project all drugs in clinical use, which are redox activated will be collected and their ionisation potentials (one-electron oxidation) and electron affinities (one-electron reduction) derived using the density functional theory (DFT). This will define a region in chemical property space that is acceptable and can be used for design purposes.

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[2] P. A. Hume, M. A. Brimble, J. Reynisson, Comp. Theo. Chem. 2013, 1005, 9-15.
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The physicochemical parameters of veterinary drugs. A comparison study

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The concept of known drug space (KDS) is now well established for design of screening libraries and decision making in drug discovery projects.[1, 2] This volume in chemical space is characterised by the physicochemical parameters of the drug compounds as well as with certain unwanted chemical moieties.[3, 4] In this project veterinary drugs will be collected and analysed for their properties and functional groups. This will create a reference volume in chemical space to KDS and will give an idea of its positioning, i.e., is KDS unique or does it share the same/similar region as KDS?

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Dr Jonathan Sperry

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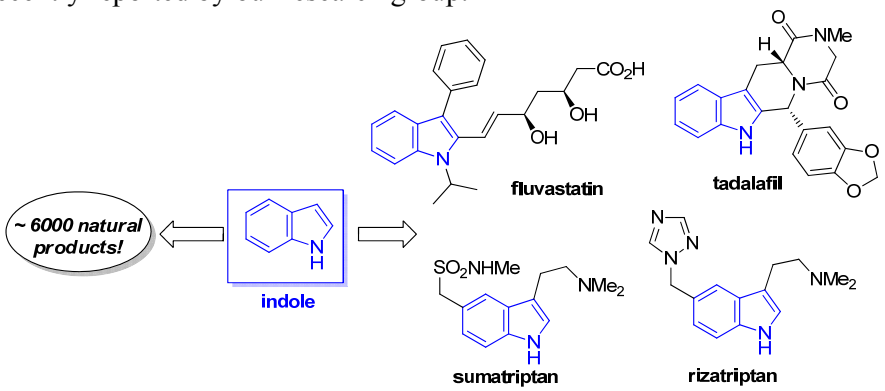
1. Novel Synthetic Methods for Indole Construction

The indole ring system represents one of the most abundant and important heterocycles in nature, with over 6000 natural products possessing this ring system. Additionally, drugs containing the indole heterocycle below accounted for nearly US$8 billion in sales annually. In keeping with their importance, the development of new routes towards indoles is a central theme and ongoing challenge in contemporary organic synthesis.[1] This project aims to develop a novel indole synthesis using some intriguing transition metal chemistry recently reported by our research group.[2]



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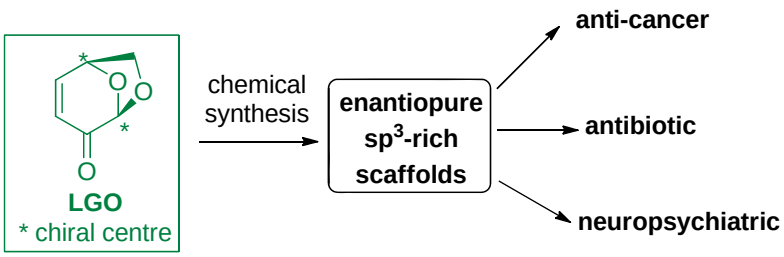
2. Sustainable Medicinal Chemistry with Biomass-Derived Building Blocks

Recent advances in sp^2-couplings have resulted in the synthesis of 'flat' molecules becoming the mainstay of drug discovery programmes. As a result, the field is slowly moving away from the 'flatlands' and towards saturated, sp^3 rich compounds capable of exploring novel, three dimensional chemical space. Molecules containing a high fraction of sp^3-hybridised carbon atoms and numerous stereocentres have a lower rate of attrition during the drug discovery process, thus providing higher-quality lead compounds. When also considering that the global chemistry community must reduce its reliance on fossil fuels and employ molecules derived from biorenewable sources in the production of society enhancing chemicals, sustainable methodologies that provide stereodefined, "sp^3-rich" scaffolds will underpin future advances in small molecule drug design. The summer research student will investigate the cellulose-derived molecule levoglucosenone (LGO) as a platform for the synthesis of several biorenewable sp^3-rich scaffolds. All of the new compounds synthesised in this project will be subjected to a detailed biological evaluation for anti-cancer, anti-microbial and neuropharmacological properties through international collaborators.



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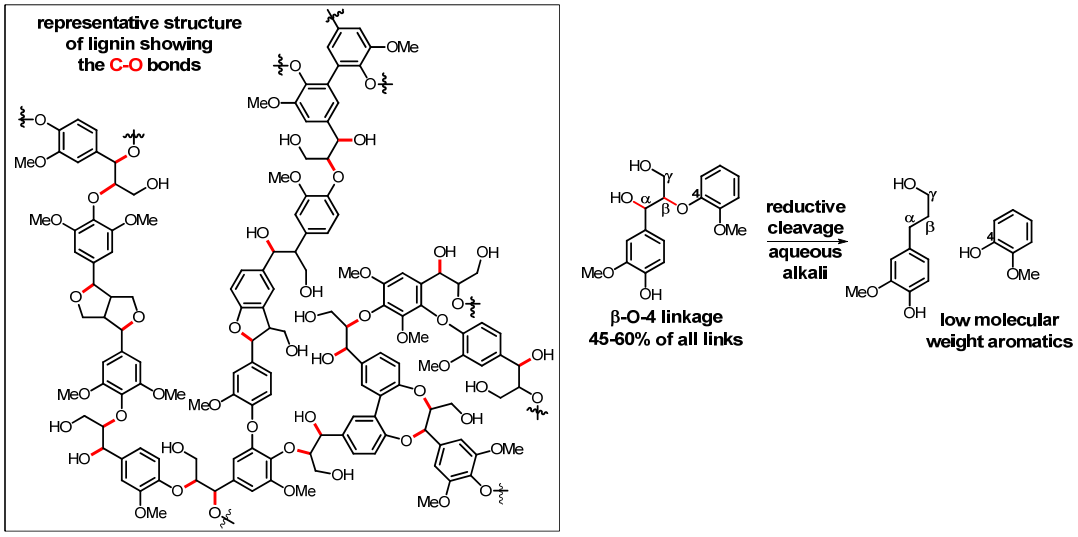
3. New Chemical Technologies for the Depolymerisation of Lignin

Fossil fuels are the carbon feedstock that modern society relies upon for the production of fuels and fine chemicals. Besides the environmental impact from their extraction and processing, fossil fuels are a finite resource for which there are currently no sustainable alternatives. Biomass is the only renewable carbon feedstock that could potentially replace fossil fuels and the efficient conversion of biomass into fuels and fine chemicals on a global scale is one of the great scientific challenges of the 21st century. Lignocellulosic biomass (dry plant matter) is the most abundant renewable carbon resource on earth, with an annual growth in the region of 200 billion tonnes. The separation of lignocellulosic biomass (wood pulping) produces the cellulosic fraction and the lignin fraction. The cellulosic fraction is amenable to chemical and enzymatic degradation techniques and its conversion into useful monomers is relatively well advanced. On the other hand, the large-scale potential of lignin is mostly limited to use as a low value fuel in pulp mills. As an aromatic biopolymer, lignin is an ideal candidate to meet future demand for aromatic commodity chemicals (phenols, benzene, xylenes, BTX etc) and other marketable aromatic products. This project will investigate novel reductive methods for the depolymerisation of lignin, specifically targeting the β-O-4 linkage that comprises up to 60% of the lignin linkages.



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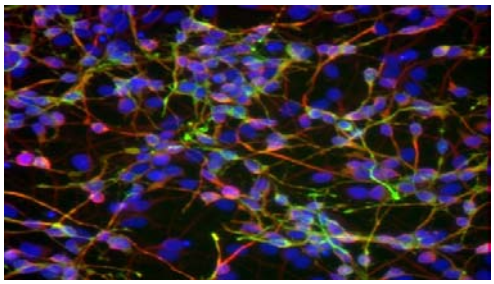
4. Synthesis of Small Molecules that Influence PSA-NCAM: Potential Therapeutics for the Prevention of Glioblastoma Metastasis

Neural cell adhesion molecules (NCAM) are involved in neural plasticity, cell migration, cell-cell adhesion etc. When attached to a polysialic acid (PSA) motif, the resulting PSA-NCAM complex promotes cell migration and is thought to play a pivotal role in the metastasis of glioblastomas (brain tumours).[1] In collaboration with the Centre for Brain Research at the University of Auckland, we have developed a library of small molecules that lower PSA-NCAM levels, but by an (as yet) unknown mechanism. This project will involve the chemical synthesis of further compounds that will help unravel the exact mechanism of action, an important step towards the goal of developing therapeutics that target the PSA-NCAM complex.



(neural stem cell derived neurons; PSA-NCAM in red)

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Dr Jonathan Sperry

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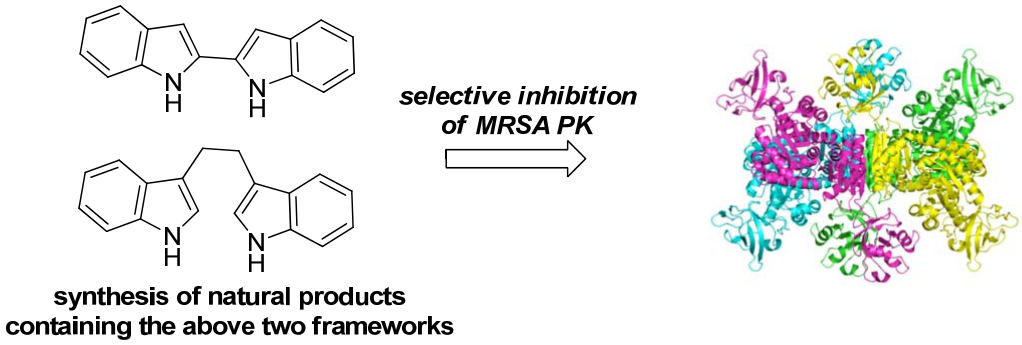
5. Targeting Methicillin-Resistant *Staphylococcus Aureus* (MRSA) with bisindole natural products

Methicillin-resistant *Staphylococcus aureus* (MRSA), a bacterium that has evolved immunity to conventional antibiotics, is responsible for several difficult-to-treat infections in humans that often have a devastating outcome.[1] MRSA infections are typically treated with the glycopeptides vancomycin and/or teicoplanin but worryingly, strains resistant to these antibiotics have recently emerged [Vancomycin intermediate-resistant *Staphylococcus aureus* (VISA)]. Accordingly, there is an urgent need for new antibiotics in the clinic, in particular those that are not based on existing therapies. In collaboration with the University of British Columbia, we have recently shown that bisindole natural products selectively inhibit the pyruvate kinase (PK) of MRSA over human PK isoforms. This project will involve synthesising bisindole natural products of modest complexity for MRSA PK inhibition studies, which will increase our understanding on how this inhibition occurs with this class of compounds.



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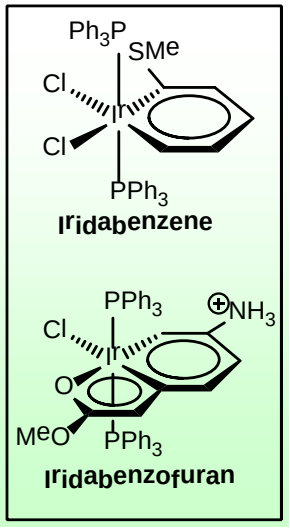
Metallabenzenes as building blocks for new materials

Supervisor: L. J. Wright (http://www.che.auckland.ac.nz/staffsites/WrightJ/index.html)

Contact: lj.wright@auckland.ac.nz, ph 373 7599 ex 88257, Room 627A (301)

Metallabenzenes are compounds in which one of the CH groups of benzene has been formally replaced by a transition metal with its ancillary ligands. The first example of a metallabenzene, an osmabenzene, was synthesised at the University Auckland. We are interested in exploring the syntheses, reactivity and bonding of this intriguing new class of compounds and have an active research programme in this area. Summer Scholarship projects will involve the investigation of routes to functionalised metallabenzenes that will serve as precursors for the fabrication of new materials. Particular targets are conducting polymers that contain the metallabenzene unit as part of the polymer backbone and two-dimensional sheets that are comprised of fused-ring metallabenzenes that can be viewed as nascent metallagraphenes. The projects will enable experience to be gained in a broad range of areas including synthesis, spectroscopy (especially NMR, IR, ESMS), and X-ray crystallography.



Water purification by catalytic oxidation of pollutants

Supervisor: L. J. Wright (http://www.che.auckland.ac.nz/staffsites/WrightJ/index.html)

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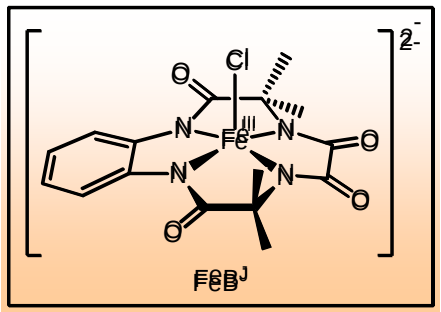
Oxidation chemistry plays a central role in many key processes including fine chemical and commodity chemical manufacture, bleaching, waste remediation and disinfection. The use of the environmentally benign oxidant hydrogen peroxide in these processes is very attractive, but it reacts very slowly with most organic compounds under ambient conditions. Appropriate oxidation catalysts are therefore needed. In a joint Green Chemistry programme with Carnegie Mellon University in the USA, we are investigating the applications of a series of new iron complexes (TAMLs) that efficiently catalyse hydrogen peroxide oxidations. The Summer Scholarship project involves studies of these iron compounds as catalytic oxidants in a new solid state technology we have developed for the oxidative destruction of dilute organic pollutants in water. Oxidative removal occurs without



contamination of the water with hydrogen peroxide, catalyst or base. The project will enable experience to be gained in a broad range of areas including synthesis, spectroscopy and analysis (especially using NMR, IR, UV-vis, ESMS and HPLC).

CO-Releasing Molecules with Targeted Pharmacological Activity

Supervisors (joint): L. J. Wright and C. Hartinger

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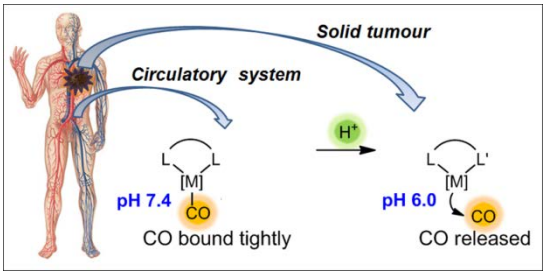
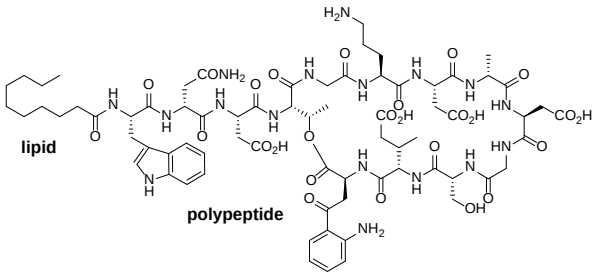
It has recently been established that carbon monoxide (CO) plays a key role as a gaseous messenger in the human body. At very low concentrations CO has been shown to elicit protection and beneficial outcomes against inflammation, apoptosis (including cancer cells), cell proliferation, and oxygen reperfusion damage. Accordingly, there is rapidly growing interest in the potential therapeutic applications of CO. Since administration of CO gas through inhalation is not feasible because of its lack of selectivity and high general toxicity when overdosed, there is a strong research drive to develop water soluble transition metal (TM) compounds that can bind CO and release it inside the body in a controlled way. Current CO-releasing molecules (CORMs) of this type release CO either by hydrolytic or photolytic processes. There is a clear need for the development of CORMs that are selectively activated by certain tissue types. We are currently developing special ligands for metal carbonyl complexes that will show this tissue selectivity and only release CO in target tissues such as those found in solid tumours or in the heart after cardiac arrest. The project will involve the synthesis of selected examples of these special ligands, the formation of metal carbonyl complexes of these ligands and the study of CO release from these. The project will enable experience to be gained in a broad range of areas including synthesis, spectroscopy and analysis (especially using NMR, IR, UV-vis, ESMS and HPLC).



Synthesis of New Generation Lipopeptide-based Antibiotics

Distinguished Professor Margaret Brimble, Dr Paul Harris
Room 731B, 7th floor, building 301; Phone: 09-9238259, Email: *m.brimble@auckland.ac.nz*



Antibiotic resistance has been recognised by the WHO as one of the greatest threats to humanity and infectious diseases rank as the second most common cause of death worldwide. This is further compounded by the observation that development of new structural classes of antibiotics has all but ceased in the past 40 years.

An emerging subset of peptide based antibiotics e.g. daptomycin are cyclic peptides containing a lipid or fatty acid. They have been shown to be clinically relevant and are used as the "last line of defence" against otherwise untreatable bacterial infections. The challenge remains, however, to efficiently produce new antibiotics based on a cyclic peptide scaffold incorporating the crucial lipid motif.

Using our newly devised method of installing a lipid onto a peptide (a thiol-ene reaction), this projects aims to exploit and develop this chemistry to generate a chemical library of peptide based antibiotics, which will undergo biological testing against the most antibiotic resistant strains of bacteria.

Successful candidates will be using organic synthesis techniques and modern methods of solid phase peptide synthesis.

Synthesis of the Novel Macrocyclic Peptide, Streptide

Distinguished Professor Margaret Brimble, Dr Dan Furkert, Dr Paul Harris
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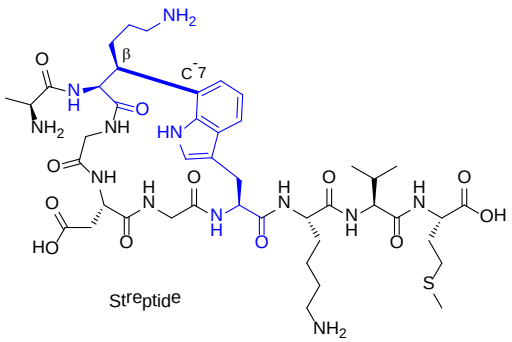

Quorum sensing is a system of intercellular communication by which some species of pathogenic bacteria coordinate the regulation of gene expression and production of virulence factors in order to have maximum impact on their environment. As a result, quorum sensing has significant implications in the pathogenicity of disease-causing bacteria. Understanding the transcription products involved in quorum sensing systems provides insight into the regulation of these systems and may help identify potential biological targets for the development of novel antibiotic compounds that inhibit quorum sensing.

Streptococcal bacteria use peptide signals as a means of intraspecies communication. These peptides can contain unusual post-translational modifications, providing opportunities for expanding our understanding of nature's chemical and biosynthetic repertoires. Streptide is a novel macrocyclic peptide produced by *Streptococcus thermophilus*, a non-pathogenic streptococcal model strain that is used in the fermentation of dairy products. Although it does not express the virulence factors of its pathogenic relatives (which include *Streptococcus mitis*, *Streptococcus pyogenes* and *Streptococcus pneumoniae*), it does harbour a new, recently identified quorum sensing system common to many streptococci, including pathogenic strains.

Streptide contains an unprecedented tryptophan-lysine cross-link (C-7 to β) in the macrocycle. In combination with solid phase peptide synthesis, C-H activation will be used to install the tryptophan-lysine cross-link and synthesise the unnatural amino acid (blue) required to complete an initial total synthesis of streptide.

A successful synthesis will allow evaluation of the biological activity of streptide and will provide the basis for future syntheses of related cross-link-containing macrocyclic peptides.

Synthesis and Development of Antimicrobial Peptides containing the rare amino acid enduracididine in the Fight Against Bacterial Resistance

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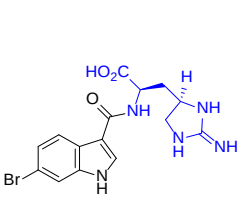
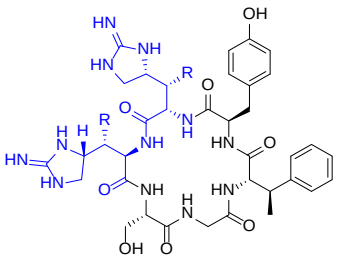


ascidian metabolite **1**



mannopeptimycin **2**

The emergence and spread of multi-drug-resistant bacteria is becoming a great threat to the health of humankind. The rate of bacteria developing resistance to both frontline and 'last line of defence' antibiotics is currently greater than the introduction of new compounds into clinical practice. This poses a severe problem as simple routine medical procedures will become life threatening as any resulting bacterial infection will not be easily and effectively treated.

Naturally-occurring antimicrobial peptides (AMPs) are the tools by which many living organisms employ to defend themselves against bacterial attack. These unique compounds therefore show great potential as new source of antibiotics.

The ascidian metabolite **1** and mannopeptimycin **2** have been show to possess antimicrobial activity and contain the rare cyclic amino acid enduracididine (highlighted in blue).

This project will involve two aspects of modern synthetic chemistry. Firstly, an organic synthesis of enduracididine and secondly, solid phase peptide chemistry to incorporate End into synthetic polypeptides. A successful synthesis of enduracididine will not only allow access to the above antimicrobial peptides and therefore the development of more potent analogues though SAR studies, but provide the basis for investigation of other peptides containing this intriguing amino acid e.g. teixobactin.

Synthesis of Amylin Mimics (Pramlitide) as a Treatment for Diabetes

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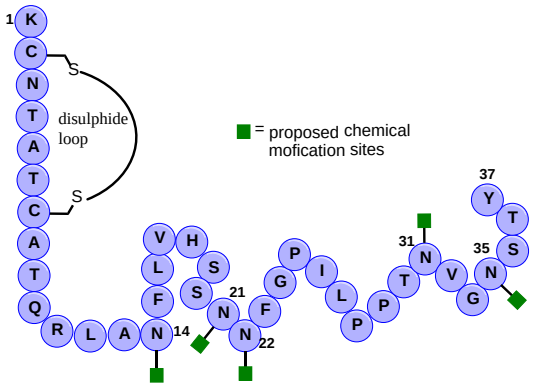

Diabetes Mellitus (DM) is a vast worldwide medical problem. The associated medical complications lead to heart disease, stroke, renal failure, premature blindness, amputation and significant mortality rates.

Existing therapies revolve around maintaining glucose at an appropriate level by administration of pramlitide (below), a 37 amino acid residue polypeptide a structurally related but non-toxic analogue of Amylin. However, pramlitide therapy suffers from several shortcomings such as low bio-availability and a half-life of just 48 mins thus necessitating a challenging 3 times daily injection.

Lipidation of polypeptides or glycosylation of polypeptides is known to increase both circulatory half-life and bio-availability whilst maintaining biological effects. Using click chemistry or thiol-ene chemistry, this research project aims to install lipids or sugars in a chemoselective manner on specific amino acid residues thereby synthesising modified pramlitide molecules that will be submitted to both biological evaluation (Prof. Debbie Hay, SBS) and estimation of half-life in the body by enzymatic hydrolysis.

Successful candidates will employ organic synthesis techniques to access suitable glycosylated amino acids, solid phase peptide synthesis to prepare polypeptides and be exposed to biological testing techniques.

The Impact of AGEs in Alzheimer's Disease

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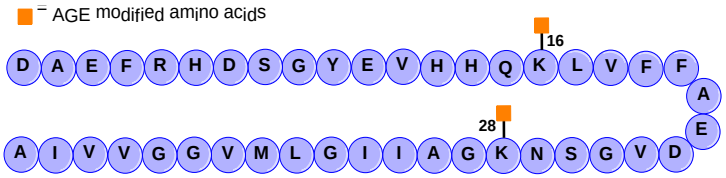

Alzheimer's disease (AD) is a complex neurodegenerative disorder that results in progressive cognitive impairment, loss of memory and changes in behaviour. In 2011, 33.9 million people worldwide were diagnosed with AD, and it is estimated that this figure will triple by 2050 due to an increasing ageing population. Despite vast research spanning more than a century, current treatments for AD are still limited to modest symptomatic relief and the precise causes of AD remain largely unknown.

Recently, new evidence has suggested that β-amyloid (Aβ) peptides (a hallmark of AD) that have been irreversibly modified by advanced glycation end products (AGEs) are more pathogenic than Aβ itself. However, the Aβ-AGE peptides used in these studies were prepared by the non-specific incubation of Aβ in glucose; this results in the formation of a complex mixture of Aβ-AGE peptides. Thus, the precise impact of individual AGEs on the biophysical properties of Aβ remains to be evaluated.

This project aims to prepare a small library of Aβ-AGE peptides, which will then undergo biological testing by Professor Michael Dragunow (FMHS). Successful candidates will employ organic synthesis techniques to prepare AGE building blocks followed by incorporation of the AGE building blocks into the Aβ peptide using solid phase peptide synthesis.

Antibody-Directed Cytotoxins (ADCs): Probing The Influence of Unnatural Amino Acid Components of Culicinin D

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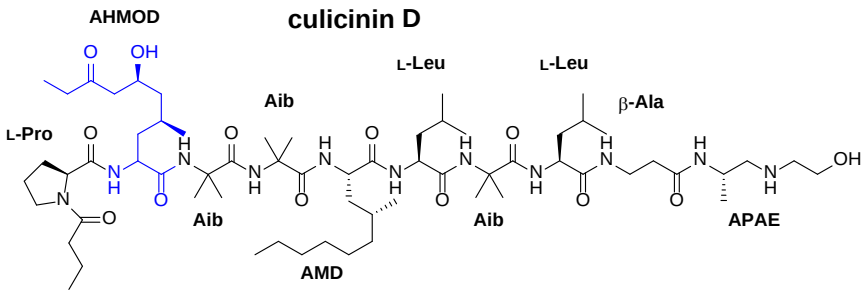

Antibody-directed cytotoxins (ADCs) are a promising class of drugs that aim to target specific cancerous tissues, by conjugation of a location-specific antibody to a highly toxic 'warhead' compound.

Culicinin D is the subject of a current ADC study underway in our research group, which involves both solid-phase peptide synthesis (SPSS) and asymmetric organic synthesis, based on our group's expertise in both areas.

The three non-natural amino acids that occur in culicinin D (AHMOD, AMD and APAE) have be prepared enantioselectively at SCS and incorporated into the natural product polypeptide chain using SPSS in the Brimble peptide laboratory at SBS. Following on from this platform, a series of chiral and heterocyclic AHMOD analogues will be synthesised, in order to identify culicinin D analogues with desirable activity/stablilty/solubility profiles for ADC development.

This project offers the opportunity to conduct high level asymmetric synthesis in the context of a medicinal drug discovery chemistry programme, based on a promising lead compound isolated from nature.

Synthesis and Medicinal Chemistry of Natural Product Shellfish Toxins

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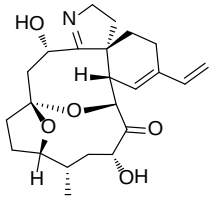

portimine

The production of shellfish toxins during dinoflagellate algal blooms ('red tides') poses a significant health risk. During these blooms the level of toxins within healthy shellfish can be harmful to humans, causing symptoms ranging from diarrhoea to extreme cardiovascular and neurotoxic effects, at exposures as low as a few parts per billion.

One of our research programmes is directed towards the synthesis and medicinal chemistry of complex shellfish toxins, with a specific focus on the newly-discovered spirocyclic imine, portimine. This compound was isolated in 2013 from algae collected in Northland.

Total and partial synthesis of the previously unknown structural motifs found in portimine will enable preparation of pharmacological probes for nicotinic acetylcholine receptors (nAChRs) and L-type calcium channels. nAChRs play an important role in signal

transmission in the nervous system and are implicated in the progression of Alzheimer's and Parkinson's diseases. In addition, regulation of L-type calcium channels is used to treat cardiovascular disorders such as hypertension and angina pectoris.

Portimine also exhibits promising anti-cancer activity (selective cytoxicity against mammalian P388 leukemia cells, LC_{50} 2.7 nM and apoptosis promotion *via* caspase 3 activation). The spiroimine macrocyclic structure of portimine poses an intriguing and demanding challenge to synthetic chemists, providing a unique opportunity to develop novel chemistry to enable efficient and stereoselective construction of the complex molecular architecture.

Asymmetric Synthesis of Benzannulated Spiroketals: Towards Novel Telomerase Inhibitors

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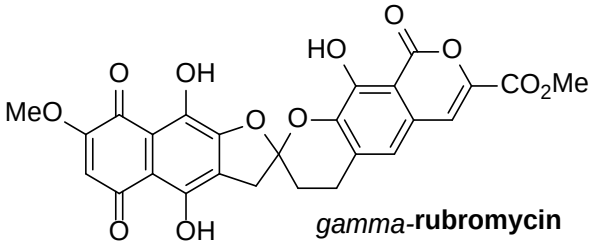

gamma-**rubromycin**

Telomerase inhibitors are of much current interest as a selective approach for the control of human cancer. The rubromycins are a unique class of antibiotics produced from a strain of *Streptomyces* that have been shown to inhibit human telomerase.

We have previously completed the synthesis of rubromycin, and are currently interested in novel catalytic methods for asymmetric synthesis of this unusual class of compound, that possess a single chiral centre at the spiroketal position.

We will investigate the asymmetric synthesis of benzannulated spiroketals using chiral Lewis acid catalysis, using a new route to prepare the necessary cyclisation substrates only recently identified in our group. In addition to probing the properties and stereochemistry of the compound class, we aim to develop new practical synthetic routes in order to assess the biological activity of chiral lead structures based on rubromycin.

This project offers the chance to work towards the development of new methods for chiral catalysis, based on the benzannulated spiroketal scaffold, as well as excellent general organic synthetic training.

Total Synthesis and Structural Elucidation of Callyspongiolide

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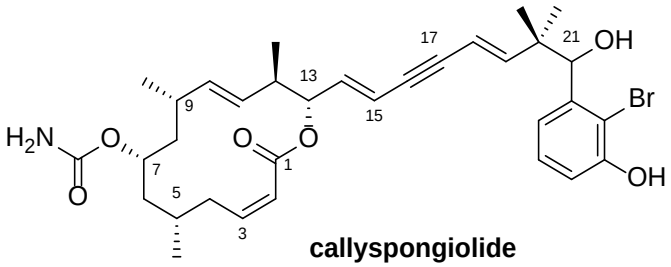

callyspongiolide

Callyspongiolide is a 14-membered macrolide isolated in 2013 from an Indonesian marine sponge of the genus *Callyspongia*. Sponges of this genus are known to produce a diverse variety of bioactive secondary metabolites, including polyketides, polyacetylenes, alkaloids and cyclic peptides, but to date, callyspongiolide is the only reported macrolide.

Callyspongiolide was found to exhibit potent cytotoxicity against a range of cell lines (L5178Y mouse lymphoma IC_{50} 320 nM, human Jurkat J16 T lymphocytes 70 nM, Ramos B lymphocytes 60 nM). Interestingly, addition of a caspase inhibitor (QVD-OPh) did not attenuate the activity of callyspongiolide, suggesting that it promotes cell death through a caspase independent mechanism.

The relative configuration of the C5, 7, 9 and 12 chiral centres was determined using a combination of 1D NMR proton coupling constants and transannular correlations in the 2D ROESY spectrum. Due to the extremely hindered nature of the secondary alcohol at C21, however, it did not prove possible to prepare any Mosher ester derivatives. As a result, the absolute stereochemistry of callyspongiolide, and the configuration at C21, has not been assigned to date.

The C14-19 yn-diene side chain linking the macrolide and bromoaryl domains is unprecedented in macrolide natural products reported to date, although known polyacetylenic algal metabolites are legion.

Total synthesis of the callyspongiolide will enable the complete structural elucidation of the natural product to be completed and permit convenient access to the key sub-structures for SAR investigation of the important biological activity observed.

This project will give an excellent introduction into the world of asymmetric synthesis, for those interested in the challenge of natural products and decoding their structure-activity relationships as pharmaceutical lead compounds.

Drug Discovery: Towards New Therapeutics for *Mycobacterium tuberculosis* (TB)

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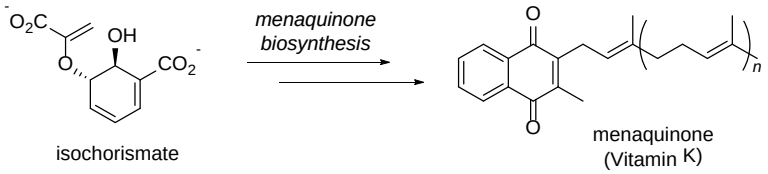

Tuberculosis (TB) affects tens of millions globally is a significant economic and health burden, especially in developing countries. The menaquinone (vitamin K) biosynthetic pathway offers a new drug development target, as menaquinone is essential for the survival of *Mycobacterium tuberculosis* through its role as a redox shuttle in the mycobacterial electron transport chain.

In collaboration with A/Prof Shaun Lott, Dr Jodie Johnston (UoA, SBS) and Prof Greg Cook (Otago), we are currently investigating potential inhibitors of the enzyme MenD, that uses isochorismate as a substrate in the first committed step in menaquinone biosynthesis (*above*). The study draws together our group's expertise in organic synthesis along with structural biology, enzymology and *in silico* computational methods for compound library screening and docking, in an effort to validate the menaquinone pathway as a target for new clinical TB treatments.

This project will provide an excellent introduction into the process of drug design in an academic context, with opportunities to work with specialists in related disciplines. The principal aim of the summer studentship will be to develop chemical methods to access novel inhibitor candidates, that will be characterised and evaluated for their activity against isolated MenD and whole cells.

Molecular Basis of Cannabinoid CB1 Receptor Binding for Modulation of CNS Cell Signalling Pathways

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Cannabinoid CB1 and dopamine D2 receptor signalling pathways are central to central nervous system (CNS) function and are implicated in neurobehavioural disorders. Evidence suggests that multi-receptor complexes involving the CB1 G-protein coupled receptor (GPCR), presently not well understood, play an important pharmacological role.

Current work in our group focuses on development of new ligands to target the CB1-D2 receptor complex, for investigation of cell signalling pathways and as lead compounds for new specific therapeutic agents for CNS disorders.

This research project will further explore the detailed nature of ligand binding to the CB1 receptor and resultant effects in downstream cell signalling pathways. The work will involve synthesis of a series of novel CB1 ligands, using chemistry that has been developed in our labs at SCS. These will then be investigated for receptor binding affinity, functional activity and signalling behaviour in the Glass lab in Pharmacology (FMHS).

The project would suit a student interested in the application of organic synthesis to the investigation of biological systems, ideally (but not necessarily) with some background in biological sciences or medicinal chemistry. Most of the time will be spent doing organic synthesis, but there will most likely be some opportunity to gain experience in pharmacology and the use of in silico molecular modelling.

Synthetic Studies towards Anticancer Opaliferin

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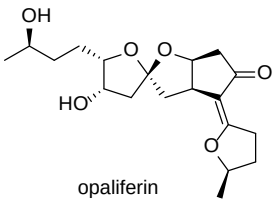
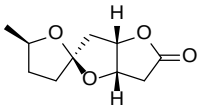


opaliferin



cephalosporolide F

Opaliferin was isolated from a culture of the pathenogenic fungus *Cordyceps* sp. NBRC 107954, which was collected from a cicada larva it had parasitised. The compound proved active against a number of cancer cell lines, and was isolated along with a number of biosynthetically related natural products from the cephalosporolide family, some of which have been the subject of previous study in our group.

The complex structure presents a number of challenges for asymmetric synthesis and also contains a spiroketal centre – a motif of particular interest to our research group.

Synthetic investigations will focus on access to the respective chiral building blocks required, and with these in hand, the assembly of the carbon skeleton. Work in the summer studentship will involve development of the key transformations to achieve these milestones, and progress permitting, advance to formation of the *cis* fused ring junction and the cyclic enol ether unit.

Characterisation of beverage antioxidants using cyclic voltammetry.

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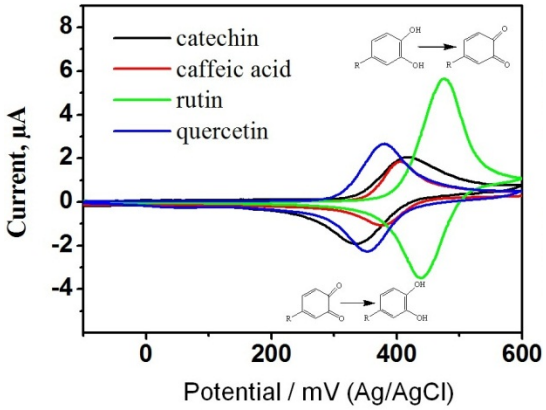
The antioxidants present in beverages can be quantified and information provided about their reducing strength using the electrochemical technique of cyclic voltammetry. This technique has been developed at the University of Auckland to profile wines, fruit juices, teas and coffees, and milk. In this project, the voltammetry procedure will be applied to the antioxidants present in a series of alcoholic beverages, including beer and fortified drinks. An examination of the most appropriate solvent for the measurement of the phenolic and other antioxidants present will be made, along with the electrode conditions needed to make a reliable quantification. Comparisons will be made with standard Food Science antioxidant assays, and a wide range of beverages of different strengths will be surveyed.



1. P.A. Kilmartin, H. Zou and A.L. Waterhouse, "Correlation of wine phenolic composition vs. cyclic voltammetry response", *American Journal of Enology and Viticulture* **53** (2002): 294-302.
2. P.A. Kilmartin and C.F. Hsu, "Characterisation of polyphenols in green, oolong, and black teas, and in coffee, using cyclic voltammetry", *Food Chemistry* **82** (2003): 501-512.
3. O. Makhotkina and P.A. Kilmartin, "Uncovering the influence of antioxidants on polyphenol oxidation in wines using an electrochemical method: cyclic voltammetry", *Journal of Electroanalytical Chemistry* **633** (2009) 165-174.
4. O. Makhotkina and P.A. Kilmartin, "The phenolic composition of Sauvignon blanc juice profiled by cyclic voltammetry", *Electrochimica Acta* **83** (2012) 188-195.

Localised interaction of PEDOT electrodes with antioxidants using Scanning Electrochemical Microscopy (SECM)

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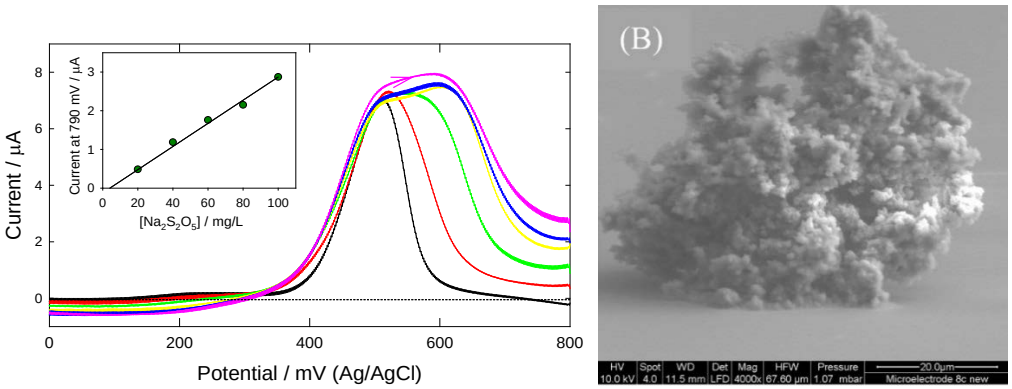
Conducting polymers are of considerable interest as plastics that conduct electricity. Their discovery by researchers including the New Zealander Alan MacDiarmid led to the award of the Nobel Prize in Chemistry in 2000. At the University of Auckland we have demonstrated that conducting polymers such as polyaniline are very efficient at scavenging free radicals, and in this sense act as solid antioxidant materials [1]. Further conducting polymers such as poly(3,4-ethylenedioxythiophene) (PEDOT) have been found to be highly suitable for separating out the analytical signal due to different types of antioxidants present in beverages [2-4]. In this project the technique of scanning electrochemical microscopy (SECM) will be applied to different types of PEDOT electrodes prepared on gold substrates, and the interaction between PEDOT and beverage antioxidants will be examined in situ. If available, in situ electrochemical AFM will be applied as a further means to profile the electrode surface properties.



Current resposne of sulfite at PEDOT electrodes, and "fractal" growth of PEDOT on microelectrodes

1. A.V. Nand, S. Ray, A J. Easteal, G.I.N. Waterhouse, M. Gizdavic-Nikolaidis, R.P. Cooney, J. Travas-Sejdic and P.A. Kilmartin, "Factors affecting the radical scavenging activity of polyaniline", *Synthetic Metals* **161** (2011) 1232-1237.
2. A. Türke, W.-J. Fischer, N. Beaumont, and P.A. Kilmartin, "Electrochemistry of sulfur dioxide, polyphenols and ascorbic acid at poly(3,4-ethylenedioxythiophene) modified electrodes", *Electrochimica Acta* **60** (2012) 184-192.
3. H. Karaosmanoglu, J. Travas-Sejdic and P.A. Kilmartin, "Designing PEDOT-based sensors for antioxidant analysis", *International Journal of Nanotechnology* **11** (2014) 445-450.
4. H. Karaosmanoglu, W. Suthanthangjai, J. Travas-Sejdic and P.A. Kilmartin, "Electrochemical analysis of beverage phenolics using an electrode modified with poly(3,4-ethylenedioxythiophene)", *Electrochimica Acta* (2016) in press.

The good without the bad: selective chelators for beryllium

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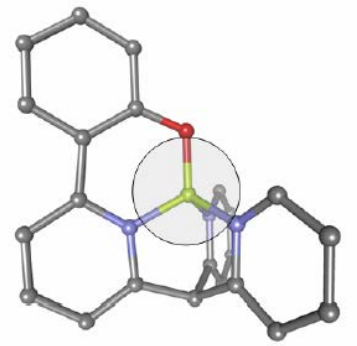

The element beryllium is increasingly utilised in consumer, scientific and commercial applications from mobile phones and speaker drivers, to golf clubs and the James Webb Space Telescope. The chemistry of this element has largely been overlooked due to its high toxicity. The non-toxic elements boron and aluminium will be used to model the chemistry of beryllium. We will develop selective agents for binding beryllium with the aim of finding new directions in detection, therapeutic and remediation technologies for beryllium.

Activities: chemical synthesis
Skills: Stage 2 or 3 organic or inorganic chemistry

Lighting up sugars – fluorescent probes for saccharides

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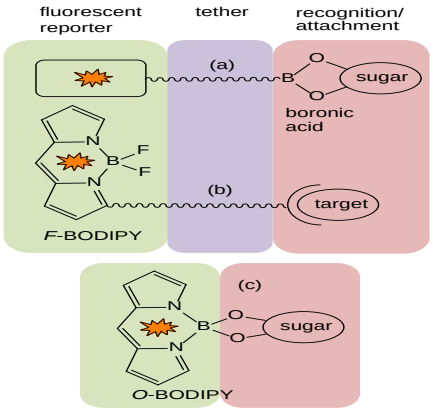

We have developed a method of attaching a fluorescent label directly to glucose. This allows for highly targeted, sensitive, fluorescent labelling of sugars which could be applied to the detection of specific sugar disease markers on cell surfaces, the labelling of saccharide capsules coating pathogenic bacteria, and the determination of polysaccharide fine structure in biology and materials science. The project will involve exploring the chemistry of the fluorescent BODIPY molecule and its chemistry with sugars.

Activities: chemical synthesis and spectroscopy
Skills: Stage 2 or 3 organic or inorganic chemistry

A new multi-analyte sensor platform

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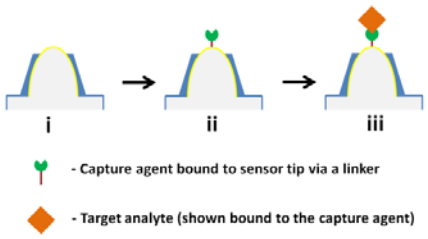

Traditional chemical sensors are designed for one analyte (or target) at a time. We are using a newly devised gold-tipped silicon array to develop a platform for multi-analyte sensors for use, for example, in the dairy industry. The project will involve using surface attachment chemistry to attach sensors to the gold tips and measuring the response to various analytes.

Activities: chemical synthesis, surface chemistry, spectroscopy, electrochemistry
Skills: Stage 2 or 3 chemistry

Porphyrin compounds for dye sensitised solar cells and new functional materials

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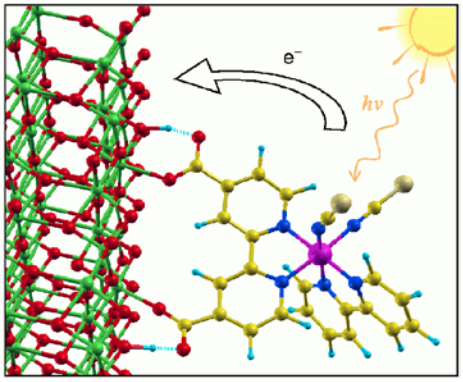

Porphyrins are the pigment which gives heme its red colour. These planar, electron-rich molecules are good absorbers of light and can also bond to small gas molecules. They are investigated widely as dyes for solar cells, as the active site in gas sensors, and for their ability to act as building blocks in new functional materials. This project will explore the synthesis of a range of porphyrins designed for these applications.

Activities: chemical synthesis, surface chemistry, spectroscopy, electrochemistry
Skills: Stage 2 or 3 chemistry

Cobalt complexes for catalytic hydrogen production

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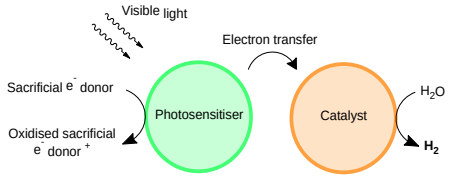

The efficient production of hydrogen from sustainable sources is an important goal in the search for new fuels. We have recently developed a cobalt-BODIPY dye complex which can be used for the photocatalytic production of hydrogen from water. This kind of technology is directed towards the use of sunlight to drive hydrogen production.

Activities: chemical synthesis, laser spectroscopy, electrochemistry
Skills: Stage 2 or 3 chemistry

Formation of Millard reaction products in sub-critical water extracted kiwifruit by-product fraction

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Subcritical water extraction (SWE) has already shown its great potential for extraction of phenolic compounds. However, concerns still remain on reactions that may occur during the extraction process, usually taking place at high temperature such as Millard reaction. The aim of this work is to study the formation of Millard reaction products (MRPs) from kiwifruit by-products during SWE. Experiments will be conducted to study the formation of MRPs in the sub-critical water extracted kiwifruit by-product fraction, taking into account the total reducing sugar, total free amino acid and 5-hydroxymethylfurfural (5-HMF) content.

Flavour improvement of noni juice

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Noni juice has a variety of functional properties including antioxidant, antimicrobial, anticancer and anti-inflammatory properties as reported in literature. Despite the potential health benefits, it is still not well accepted by some customers because of its strong distinctive odour which has been perceived as unpleasant. Flavour improvement is therefore necessary for the juice in order to gain market acceptance. This can be done by adding suitable flavour additives or food ingredients which can effectively mask the unpleasant flavour of noni juice. This summer project will include product formulation and sensory evaluation. An ethical approval has been gained for the work. Candidate must has good experience in food product development and sensory evaluation (has obtained good results in FOODSCI 3043 and FOODSCI 303).

THE CHEMICAL TRANSPORT AND CHARACTERISATION OF THE SOLID SOLUTION OF $Cu_2V_2O_7$ AND $Co_2V_2O_7$.

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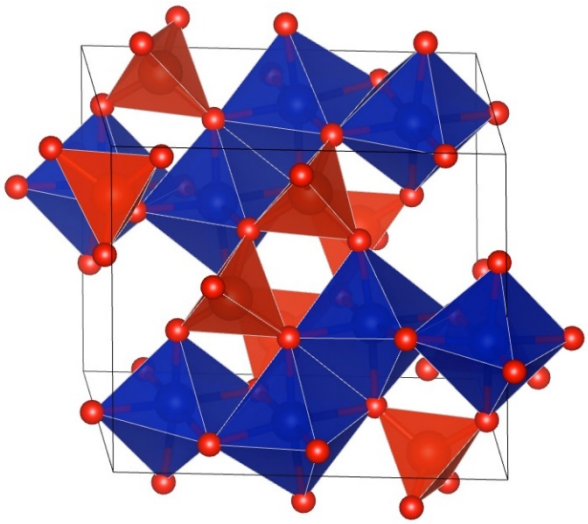
This project is in the field of solid-state materials and deals with the preparation and characterisation of vanadium-compounds with mixed transition metal content. Vanadium oxides show a large variety of crystal structures where the main building blocks are various extended units of vanadium–oxygen polyhedra, from low-dimensional (chains, sheets) to more complex three- dimensional blocks. These vanadium oxides show an impressive variety of functional properties whose origin is closely related to the structural and electronic peculiarities of the compounds. Therefore, they are widely used as advanced materials like phosphors, optical switches, chemical sensors, catalysts, in solid-state batteries.

The goal is to prepare solid solutions of $Cu_2V_2O_7$ and $Co_2V_2O_7$ to study the influence of doping on electric and magnetic properties on single crystals. These compounds are known to show different and complex magnetic arrangements and dielectric behavior at low temperatures.



For the preparation a number of different methods will be applied, ranging from classical high-temperature sintering to chemical transport reactions for the preparation of single crystals. Especially chemical transport reactions have been proven to be a very successful technique for the preparation of highly pure single crystals in many different systems, which is essential for the study of the physical properties.

PREPARATION AND PHYSICAL CHARACTERISATION OF $M_{2-X}Fe_XSnO_4$ MIXED METAL OXIDE PHASES

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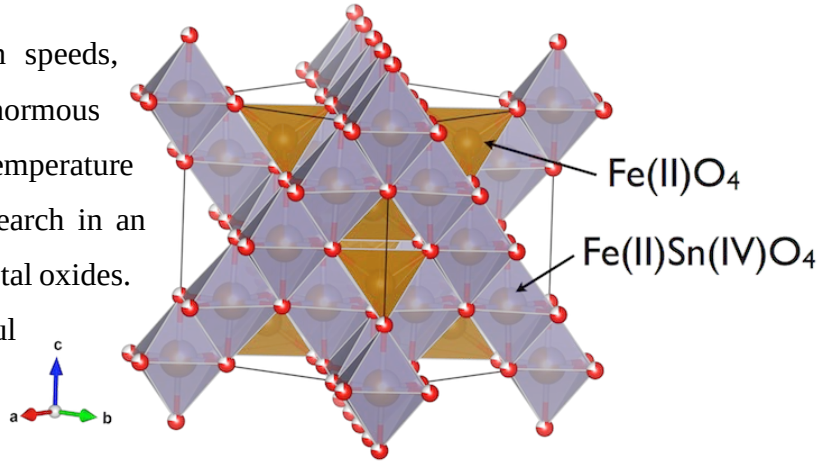
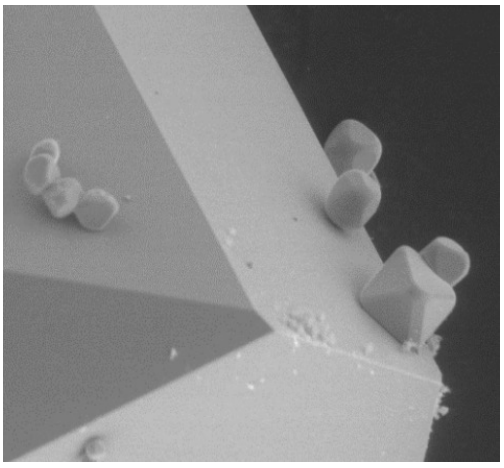


Modern life requires us to refrigerate our food, communicate and travel at high speeds, make precise measurements, and store enormous amounts of data. The discovery of high temperature superconductors triggered extensive research in an area of cluster materials and transition metal oxides. Researching new materials with useful magnetic and electrical properties is currently of great interest in solid state chemistry, cluster chemistry, and material engineering. The properties of simple binary oxides are now very well understood. Ternary and higher (doped) systems are, therefore, promising areas to investigate. Not only can it bring immense technological progress, but also change the way scientists and society think of science, and deepen our understanding of nature. Nonetheless, research of new materials is also a very difficult endeavour to justify since it represents a foray into the unknown.



This project focuses on synthesis and physical characterization of novel inorganic materials based on Fe-based spinel oxides $M_{2-x}Fe_xSnO_4$, which have not been systematically studied yet. The structural changes and the to the changes in properties will be studied upon doping with transition metals. By use of a wide range of spectroscopic and other analytical methods, we are hoping to go beyond a mere description of coordination and structure of the products. We are seeking evaluative answers to how do chemical, coordination, and structural changes influence the properties of Fe doped metal oxides with a strong emphasis on the influence of the dopant site preference to these properties.

New Enzymes for Water Treatment

Dr Viji Sarojini and Prof James Wright
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In developing as well as in industrialized nations, a growing number of contaminants are entering the aqueous environment from human activity. Organic herbicides/pesticides for controlling weeds, insects and fungi in agriculture comprise the largest group of xenobiotic compounds deliberately introduced into the environment. These compounds, and their metabolites end up in drinking water at concentrations exceeding the 0.1µg/L threshold of pesticide residues in drinking water. This translates into an immediate need for effective, low-cost, robust water treatment methods to remediate waters without further stressing the environment or endangering human health. This project aims to undertake the basic research to develop biodegradable peptide-based scavenger enzymes for water remediation applications. The summer student working in this project will be trained in Molecular Modelling, Solid Phase Peptide Synthesis, HPLC purification and residue scavenging techniques relevant to the project.

Anti-Biofilm Peptides for Water Disinfection

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Billions of people lack access to safe drinking water and millions die annually from diseases transmitted through the consumption of unsafe water. Waterborne infectious agents causing such diseases include bacteria, fungi, protozoa and viruses. Viruses are of particular concern and account for half of the emerging pathogens in recent times. The main water disinfectant used worldwide, free chlorine, is ineffective in controlling certain waterborne pathogens, particularly *Mycobacterium avium*, ubiquitous in biofilms found in water distribution systems. Growing of biofilms within ageing water distribution systems is a significant challenge facing infrastructure providers across the world. Using our previous experience in developing antimicrobial peptides for biofilm control, this project aims to develop antimicrobial peptides with potency and selectivity towards *Mycobacterium avium* biofilms found in water distribution systems. The summer student working in this project will be trained in Solid Phase Peptide Synthesis, HPLC purification and microbiology techniques relevant to the project.

Antifreeze Peptides for Preserving Texture in Frozen Food

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Antifreeze proteins (AFPs) enable organisms like polar fish to survive the freezing temperatures of their natural habitat. As well as being cryoprotective, AFPs have the ability to influence the size, morphology and aggregation of ice crystals which can be used in food technology, where the growth of ice crystals in frozen foods is of primary concern. AFPs expressed in yeast have been used in the ice-cream industry for creating a smooth texture and preserving ice crystal size distribution until consumption. However, infusing large protein molecules into fruits and vegetables is not a viable option and there are no analogous commercial products in the frozen fruit and berry industries. In this project we aim to develop tailor-made analogues of natural AFPs for fundamental mechanistic studies as well as potential applications in the frozen food industry. Ice crystal morphology studies and texture analysis of frozen fruits using the synthetic peptides will be done in collaboration with the Food Science group at UoA. This interdisciplinary project applies cutting edge peptide research to the needs of the frozen fruit industry which plays a major role in New Zealand's economy. The summer student working in this project will be trained in Solid Phase Peptide Synthesis, HPLC purification and food science techniques relevant to the project.

Lipopeptides with Broad Spectrum Antimicrobial and Antibiofilm Activities

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According to the World Health Organisation, the rapid emergence of multidrug resistant 'superbug' bacteria has created an urgent need to develop novel classes of antimicrobial agents. Unfortunately, over the last 30 years, no major types of antibiotics have been developed. Cationic antimicrobial peptides (CAPs) are promising therapeutics to address the challenge of bacterial resistance. The near success of MSI-78 (pexiganan acetate) and MX-226 or CPI-226 (Omiganan) in reaching the clinic, provide us with the enthusiasm to overcome the current roadblocks of CAPs (e.g. proteoclytic susceptibility) to achieve clinical implementation of AMPs. To this end, we have developed several linear and cyclic lipopeptides with nonprotein amino acids which have shown low micromolar activity against bacterial pathogens and the ability to lyse bacterial membranes. This project will develop stereoisomers of our potent lipopeptides through chemical synthesis and investigate their potency and mechanism of action. The summer student working in this project will be trained in Synthetic Organic Chemistry, Solid Phase Peptide Synthesis, HPLC purification and spectroscopic techniques such as NMR and Circular Dichroism.

Cell Penetrating Peptide Nanoparticles for Drug Delivery

Dr Viji Sarojini and Prof Jadranka Travas-Sejdic
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Increase in the number of new therapeutics that fails to reach the clinic due to poor delivery has made novel drug delivery systems an important consideration in therapeutic development. Cell penetrating peptides (CPP) are promising tools for delivering biologically active molecules like oligonucleotides and proteins into cells. The carrier-biomolecule (cargo) interactions are dictated by the sequence of the CPP. Mechanism of cellular drug internalization by CPPs is not well understood. This project aims to develop short synthetic peptides derived from the *trans*-activating regulatory protein (TAT) of the human immunodeficiency virus (HIV) which is the first known CPP ever. The TAT sequence will be synthesized by Solid Phase Peptide synthesis and conjugated to short oligonucleotide chains. It is expected that the peptide-oligonucleotide complex will form stable nanoparticles facilitating the entry of the drug into the cell through the plasma membrane. Morphological features of the CPP-oligonucleotide complex will be investigated by scanning electron microscopy (SEM) and light scattering measurements in collaboration with Prof Jadranka Travas-Sejdic. This project also involves collaboration with the Auckland Cancer Society Research Centre.