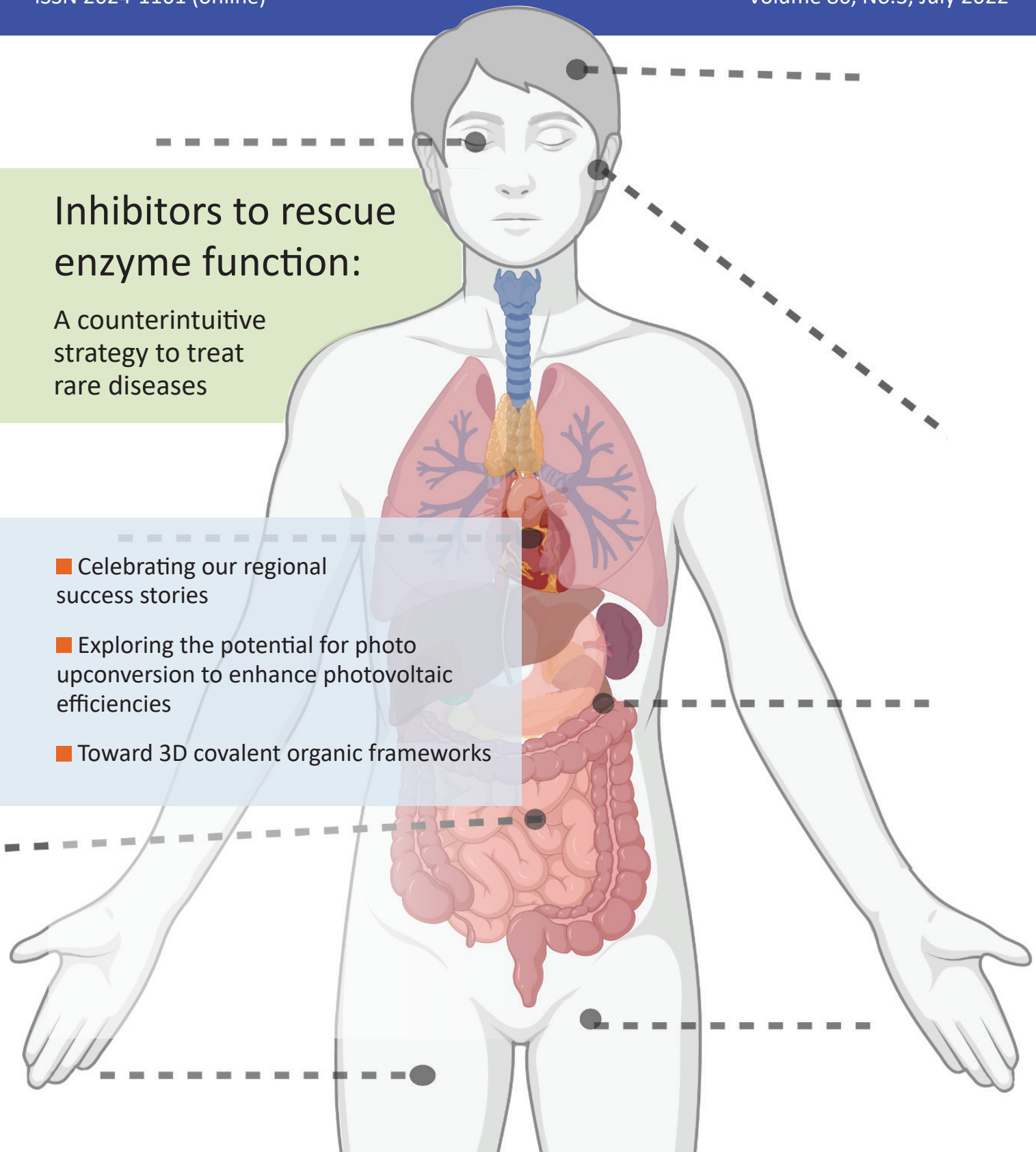
Chemistry in New Zealand

ISSN 2624-1161 (online)

Volume 86, No.3, July 2022

Inhibitors to rescue enzyme function:

A counterintuitive strategy to treat rare diseases



- Celebrating our regional success stories
- Exploring the potential for photo upconversion to enhance photovoltaic efficiencies
- Toward 3D covalent organic frameworks

Published on behalf of the New Zealand Institute of Chemistry in January, April, July and October.

The New Zealand Institute of Chemistry Incorporated

PO Box 33124
Barrington
Christchurch 8244

Email: nzic.office@gmail.com

Editor

Dr Catherine Nicholson
C/- BRANZ, Private Bag 50 908
Porirua 5240

Phone: 04 238 1329
Email: catherine.nicholson@branz.co.nz

Publishing designer

Natalie Bould
Email: gnatnz@yahoo.com

Advertising Sales

Email: nzic.office@gmail.com

Printed by Graphic Press

Chemistry in New Zealand

Volume 86, No.3, JULY 2022

Articles and features

Other columns

Comment from the President

Kia ora koutou

Winter salutations to you all! I hope this issue finds you in good health as we complete over half the year of 2022!

In August the borders finally open and we can look forward to a hopefully less restricted flow of international students and international workers into the country. We also hope that the supply logistics will improve down the track. This has caused many a concern not only in research projects across chemistry and other physical or natural sciences but also in more humble quarters such as the supermarket!

In my last column, I talked about a new look NZIC website which was designed by Brendon Gill. This new style website is now live and you are encouraged, if you have not done so already, to re-register with it so you can access it and its new layout. When you do that, please ensure you use the exact same form of email address you used to register with the old site as that is what it will only recognise. It is a great improvement on our previous site and we are grateful to Brendon for putting in the time to develop this.

In local news, we were delighted to hear that two of our members were selected to become Fellows of the Royal Society of New Zealand (FRSNZ). We offer our heartiest congratulations to Professors Nigel Perry of Plant and Food Research and Department of Chemistry, University of Otago and Professor Christian Hartinger of the School of Chemical Sciences at the University of Auckland. These people have been recognised as being at the top of their fields.

I am pleased to announce we have a new Chemical Education Trust (CET) Trustee appointed. As you know this is a trust set up by NZIC to which schools can apply to cover chemistry-related supplies for teaching etc. Members are normally invited to contribute to the CET when renewing their membership, so I hope that this is a request that is considered seriously by members as it helps the younger members of our discipline to learn chemistry in schools with the benefit of the appropriate equipment and supplies. This in turn also helps our chemistry teachers in that they can demonstrate and deliver chemistry concepts in a more effective way to their students.

Our new CET Trustee will be Dr Suzanne Boniface from the Wellington branch. We extend a warm welcome to her and thank her for accepting our offer to be part of it.

In overseas news, there have been more appointments to the editorial board of the journal *Physical Chemistry Chemical Physics* (PCCP). The latest appointment is as Associate Editor (AE). When this is formally ratified (a candidate has already been formally elected), that announcement will be made.

In other news, we have just learnt that ACES has approved an Early Career Researcher (ECR) award for our Institute. One award per year per society is offered, so this will form part of our suite of awards to apply for this year. So ECRs please note this. The successful awardee will receive a generous prize of 1000 Euro and be expected to give a talk at the NZ national conference and will also be invited to submit an article to an ACES journal of their choice. The other news is that Paul Plieger from Massey University, and who is the NZ representative, has been elected the new President of ACES so we extend to him our congratulations on this honour.

On the Commonwealth Chemistry front, elections for a new President and Executive Board have concluded and have resulted in a new President elect who will be Neville Coville (South Africa) and two new Executive Board members, Naumih Noah (Kenya) and Ting Kueh Soon (Malaysia).

Hopefully many of you are putting in your abstracts for the next NZIC national conference to be held at the University of Auckland. Remember that Abstract Submission closes on 12 August 2022.

Take care everyone and keep warm.

Noho ora mai
Michael Mucalo, NZIC President

NEWS

AUCKLAND

University of Auckland

EVENTS

■ Approximatley 900 graduands received degrees or diplomas in the Science Graduation Ceremony in May. The ceremony was held in person at Spark Arena.

■ The Chemistry Society and Auckland University Women in Science in collaboration with NZIC held the IUPAC Global Women's Breakfast on 16 February.

SCHOOL OF CHEMICAL SCIENCES SEMINARS

The SCS at the University of Auckland hosted several seminars:

■ Professor Steven L. Castle (Brigham Young University, Utah, United States): "New strategies for the synthesis of unusual peptides and alkaloids."

■ Dr Andrew Twidle (The New Zealand Institute for Plant & Food Research Ltd): "Semiochemicals – deciphering chemical conversations in nature."

■ Associate Professor Sallyann Harbison (University of Auckland): "Forensic genetics applied to crime investigation."

■ Dr Farhana Pinu (New Zealand Institute for Plant & Food Research Ltd): "Targeted and untargeted metabolomics in grape and wine research."

■ Dr Tristian de Rond (University of Auckland): "Terpenoid biosynthesis in the ocean: the search for an elusive class of enzymes."

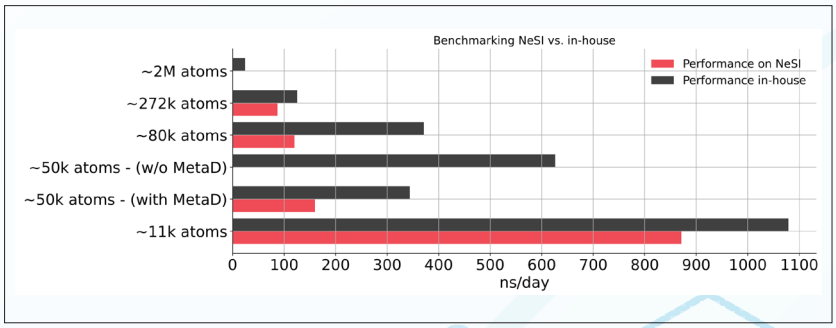
■ Dr Benjamin Dickson (University of Auckland): "Targeting the DNA damage response: PARP and DNA-PK, a tale of two targets and prodrugs to boot!"

THE CHEMISTRY OF ANCIENT BEAUTY TREATMENTS

Research in the School that investigates the chemistry of ancient beauty treatments gained recent media attention.

The research, being conducted by Erin Griffey (Art History), Cather Simpson, Michel Nieuwoudt and Ruth Cink, seeks to re-create and then analyse cosmetic treatments recorded during the period 1500-1700 AD.

For more, see: https://theconversation.com/remaking-history-how-we-are-recreating-renaissance-beauty-recipes-in-the-modern-chemistry-lab-176461



Benchmark NeSI vs In-house

STAFF SUCCESSES

■ Professor Christian Hartinger and Associate Professor SallyAnn Harbison are now Fellows of the Royal Society Te Apārangi.

Improved SCS computing capability

■ Great news for the Mercadante group with the addition of their new in-house GPU accelerated computing cluster. They will now be able to perform molecular mechanics calculations over longer timescales, making them highly competitive on the international stage.

The cluster features 7 dual-GPU nodes with an optimised coupling of central and graphical processing units, in order to extract the best performances from some of the latest nVIDIA GPU cards. Performances have been tested against the existing GPU acceleration offered by the New Zealand eScience infrastructure (NeSI) GPU computing nodes, showing a considerable speed of up of several nanoseconds/day – with a maximum increase in performance of up to 3x!

Orbis Technologies

■ Orbis Technologies, a startup company started by Cather Simpson, David Williams and Chief Technical Officer Matheus Vargas, has announced an agreement with the Green Cross chain (including Unichem and Life pharmacies) to have their testing platform available in pharmacies.

The initial product would allow customers to monitor their SARS-CoV-2 antibody levels (giving an indication of their immunity), while subsequent development could involve

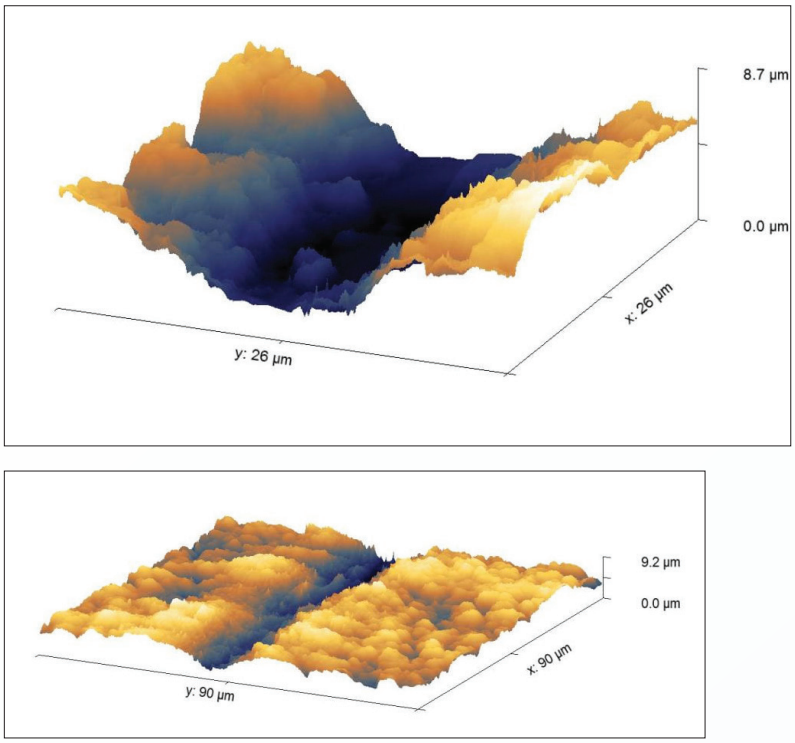
other health tests.

This initiative was featured in the NZ news media, including Radio NZ. For more, see: https://www.rnz.co.nz/news/national/463483/covid-19-immunity-level-tests-to-go-on-sale-at-pharmacies

IMPROVED AFM CAPABILITY IN SCS

■ The height range of SCS's Origin AFM has been upgraded to 40 µm which will allow it to image a larger range of samples. Example images are shown for a tungsten oxide air sensor that has been laser ablated to produce high surface area nanoparticles.

The ~9 µm deep channels that were produced are outside the height range of our Cypher AFM but well within that of the upgraded Origin; the Cypher, however, will continue to excel at higher resolution imaging and has fast scan times.



Improved AFM capability at the University of Auckland SCS will enable imaging of a larger range of samples

STUDENT SUCCESSES

■ Congratulations to Dr Shinji Kihara (supervisor: Duncan McGillivray) for winning the 2021 L H Briggs Memorial Prize for Best Doctoral Thesis. The Prize is awarded to the "person adjudged to be the most distinguished research worker in the School of Chemical Sciences who has submitted a thesis for the degree of PhD in Chemistry, PhD in Food Science, and PhD in Forensic Science during the calendar year of the award."

The judging panel noted that Shinji tackled a complex and topical problem, and that he had built a study from basic structural neutron scattering methods to study the interactions of proteins with nanoparticles, through studies of interactions with tethered bilayers as model membranes up to interactions with cells in cultu

PHD SEMINARS

■ Ali Lowrey, SCS PhD candidate gave a presentation entitled, "From the vineyard to the glass – what really goes into New Zealand wine?" in the "Raising the Bar Auckland seminar series."

PHD COMPLETIONS

■ Sutharsana Yathursan (supervised by Associate Professor Viji Saroni): "Studies towards the syntheses and analyses of short peptides as novel antimycobacterial agents."

■ Yann Hermant (supervised by Associate Professor Paul Harris and Distinguished Professor Dame Margaret Brimble): "Total synthesis and CLipPA derivatisation of antimicrobial lipopeptides."

■ Eva Antony (supervised by Dr Ivan Leung): "Biochemical and biophysical approaches to protein ligand and enzyme inhibitor discovery."

■ Zifei (Linna) Wang (supervised by Dr David Rennison in Margaret Brimble's group): "Nitrobenzoxadiazole and dipyrromethene boron difluoride derivatives of norbormide as fluorescent probes for live cell imaging."

■ Georgina Howard (supervised by Distinguished Professor Dame Margaret Brimble and Dr Dan Furkert): "Synthetic studies towards antimicrobial therapeutic agents: aspterric acid and malacidin A."

■ Thomas Grant (supervised by Dr David Rennison in Margaret Brimble's group): "Amphiphilic 2,5-diketopiperazines as novel, eco-friendly antifouling biocides."

■ Navneet Brar (supervised by Dr Cameron Weber and working in collaboration with Dr Laura Raymond, Dr Warren Grigsby and Dr Stefan Hill at Scion): "Understanding the effects of ionic liquids and deep eutectic solvents on extraction processes."

Massey University, Auckland

■ Congratulations to Distinguished Professor Peter Schwerdtfeger who was elected as a foreign member into

the Finnish Academy of Science and Letters: https://www.massey.ac.nz/about/news/acclaimed-massey-scientist-receives-rare-honour/

■ The only other New Zealand member is Distinguished Professor Gaven Martin and both are members of the New Zealand Institute for Advanced Study (NZIAS). Peter has also received the Hans Hellmann lecture series award by the Philipps University of Marburg. He is currently collaborating with the nuclear physics group at Michigan State (Distinguished Professor Witek Nazarewicz) and the atomic physics group at CNRS in Paris (Professor Paul Indelicato) on Gamow states.

■ Dr. Odile Smits (NZIAS) received a Sir Neil Waters Fellowship to work on superheavy element chemistry and physics and on phase transitions in bulk systems.

■ Zhirui Mao has recently joined the Massey Albany team as an MSc student working with Associate Professor John Harrison.

■ Earlier this year Jon Kitchen was promoted to Associate Professor and we farewelled two staff members - senior tutor Dr Marie-Anne Thelen, who has taken up a position at the University of Auckland, and technician Erin Moffet.

AUT

CONGRATULATIONS

■ Anau Lautaha was awarded a prestigious AUT doctoral scholarship and has started her PhD under the supervision of Professor Nicola Brasch. Her research will focus on elucidating the factors that determine the mechanism of photodecomposition for photoactive HNO donor compounds.

■ Dr Jack Chen has been awarded a faculty research grant to develop "Stimuli-responsive nanoscale containers."

■ Professor Nicola Brasch has received a faculty research grant to develop antimicrobial conjugates of vitamin B_{12}. This research is being carried out in collaboration with Dr Brent Seale and Associate Professor Yan Li at AUT, and Professor Greg Cook and Dr Scott Ferguson at the University of Otago.

Brian Palmer

■ Dr Cassandra Fleming, her PhD student Dóra Laczi, and Dr Mark Johnstone had their article entitled, "Photoresponsive small molecule inhibitors for the remote control of enzyme activity" published in *Chemistry - An Asian Journal*.

■ Dr Jack Chen, in work led by collaborators at Massey University, has published an article entitled, "Interfacial colloidal assembly guided by optical tweezers and tuned via surface charge" in the *Journal of Colloid and Interface Science*.

Auckland Cancer Society Research Centre (ACSRC)

STAFF NEWS

■ Associate Professor Brian Palmer retired from the ACSRC mid-2021. Brian is a PhD graduate from the Department of Chemistry at the University of Auckland and joined the Cancer Research Lab (CRL) in 1984.

His early work in the CRL/ACSRC involved the synthesis of hypoxia-activated cytotoxins, which set the chemistry foundations for work that continues through to today. His work led to the development of PR-104, which entered Phase 1 clinical trials and the next generation compound CP-506. He then worked on a series of collaborative projects funded by Warner Lambert/Parke-Davis/ Pfizer. He was involved in the medicinal chemistry programme that produced CI-1033, aka canertinib, the first irreversible tyrosine kinase inhibitor to go into human clinical trials for cancer. He then led a medicinal chemistry team for a series of multidisciplinary projects, preparing inhibitors of kinase enzymes involved in cell cycle control and cell signalling. This segued into studies of gyrase inhibitors as potential antibacterial agents.

Since 2005, Brian has led a medicinal chemistry group exploring anti-tubercular agents in very successful collaboration with the Global Alliance for TB Drug Development. This work has resulted in three new agents which are currently being evaluated clinically. In his spare time Brian has also developed a series of inhibitors of indole dioxygenases which are being developed by Antido Therapeutics as immune-modulating agents. Brian is an author of 114 research articles and 18 granted patents and has a very broad understanding of drug development. He continues his involvement with the ACSRC as an Honorary Associate Professor.

■ Associate Professor Gordon Rewcastle also retired mid-2021 from the ACSRC. Gordon is also a PhD graduate from the Department of Chemistry at the University of Auckland and joined the Cancer Research Lab in 1980 where he worked on the Warner Lambert/Parke Davis/ Pfizer

collaboration until 2004. He worked across a number of different projects from DNA intercalators, DMXAA and other immune modulators, through to kinase inhibitors.

Gordon's interest in kinase inhibitors expanded into looking at phosphoinosityl-3-kinases which are involved in cell signalling pathways and become dysregulated in cancer and metabolic disorders. He was the PI of three HRC projects and an AI on numerous other projects exploring this subject and which resulted in the commercialisation of PWT33597 through a University spin-out company, Pathway Therapeutics.

Gordon's knowledge of heterocyclic chemistry is encyclopaedic. Starting from a sabbatical with the legendary Alan Katritzky in Florida, Gordon has been responsible for four comprehensive reviews on aspects of heterocyclic chemistry, as well as the author on 108 research articles and 22 granted patents. Gordon also continues his involvement with the ACSRC as an Honorary Associate Professor.

Gordon Rewcastle (centre) with Michael Hay and Bill Wilson

Bill Denny with Governor-General Cindy Kiro

■ We are very pleased to welcome Dr Daniel Conole to the ACSRC in 2022. Daniel recently won a prestigious four-year HRC Sir Charles Hercus Health Research Fellowship to return to the ACSRC from Imperial College London. He will establish a next generation drug-screening research programme centred around DNA-encoded libraries.

This new high throughput screening technology is faster, cheaper and more convenient than conventional methods. Initially, this technique will be deployed to discover new chemical probes for an important class of deubiquitinase enzymes in cancer and inflammation, in collaboration with Professor Mike Waring (Newcastle, UK) and Dr Elton Zeqiraj (Leeds, UK). Further development will explore the ACSRC novel drug collection to increase productivity and success rates for drug discovery screens in collaboration with Associate Professor Michael Hay.

Daniel gained his PhD in medicinal chemistry at the University of Auckland. He completed postdoctoral research at the ACSRC, working with Associate Professor Brian Palmer, developing anti-TB agents in conjunction with the Global Alliance for TB.

Daniel moved to the UK and took up postdoctoral positions at the University of Oxford and University College London. Since 2018, Daniel has worked with Professor Edward Tate at Imperial College London to better understand the importance of deubiquitinase enzymes in health and disease.

■ Distinguished Professor Bill Denny recently received the honour of Knight Companion of the New Zealand Order of Merit at a ceremony at Government House. This is an exceptional honour and one that is truly deserved. Sir Bill has been a member of the Centre since 1972 and was Director/Co-Director for almost 40 years. Sir Bill is also an Officer of the NZ Order of Merit (2003), a member of the American Chemical Society

Hall of Fame, the first New Zealander to be so honoured, a recipient of the Rutherford Medal (1995), the Gluckman Medal (2006), the Vice Chancellor's Commercialisation Medal (2012), and has received many other prizes and honours.

Sir Bill's contributions to drug discovery, both academic and translational, have been phenomenal. He has published over 730 academic papers and 20 book chapters. He is responsible, in conjunction with a variety of academic and industry partners, for bringing 15 new drugs to clinical trial. Many of these were first-in-class drugs to reach clinical evaluation (e.g. amsacrine, DACA, vadimezan, canertinib, PR-104).

Sir Bill's productivity and the influence of his work reflects both the skills of the multidisciplinary team he has built in Auckland, and his extensive academic and industry partnerships, primarily in the US. He is a joint founder of the biotech companies Proacta Inc. and Pathway Therapeutics, which commenced in New Zealand before moving to the US, as well as Kea Therapeutics. In dedicating four decades of his life to cancer research at the ACSRC, Sir Bill has made a singular contribution to building one of the most respected cancer research centres in the world. Ina te mahi, he rangatira.

GRANT SUCCESSES

■ Jiney Jose, Peter Choi, David Ziegler, Maria Tsoli and Bill Denny: "Targeted therapy for treating paediatric high grade gliomas" - Cure Kids Foundation, $109,925. This research aims to develop optimal compounds to treat brain cancer with increased efficacy and decreased toxicity compared with currently available chemo- and radiotherapeutics.

■ Jiney Jose, Peter Choi, Thomas Park, Chae-Yong Kim, Michael Dragunow, Patrick Schweder, Richard Faull and Bill Denny: "Development of high-grade glioma targeted therapy to address tumour heterogeneity and recurrence" - Neurological Foundation, $253,257. The project aims to develop therapeutic agents that will improve survival outcomes and the quality of life of patients suffering from high-grade glioma. The specific objective is to design and synthesise multitargeted tumour-specific near-infra red-emitting drug-dye conjugates with the ability to cross the blood-brain barrier and specifically accumulate in brain tumours.

■ Andrew Thompson, Greg Cook and Veronica Playle: "Antibiotic hybrids to combat antimicrobial resistance" - Auckland Medical Research Foundation (AMRF), $159,991.

Following a lengthy career path largely funded by external collaborations with Pfizer, TB Alliance and the Drugs for Neglected Diseases initiative, Dr Andrew Thompson recently achieved a new milestone by gaining his first major academic grant as Principal Investigator. This will enable him to continue his infectious disease research through further development of an interesting class of antitubercular/antibacterial agents with both local and international collaborators.

■ CANTERBURY

University of Canterbury Department of Chemistry

SILK PURSE FROM A FOOD WASTE SOWS EAR

■ A research project led by University of Canterbury Environmental Science Professor Brett Robinson aims to find ways to turn waste products from New Zealand's food production industry, such as milk processing waste and grape marc (skins and stalks), into high-value soil conditioners and animal feed.

Details of the project can be found at: https://www.canterbury.ac.nz/news/2022/plan-to-transform-food-processing-waste-would-boost-nz-economy-and-environment.html

MICROPLASTICS

■ Sally Gaw, professor of environmental science, was on Breakfast on 7 April talking about microplastics. These are miniature plastics, generally smaller than 5mm in width. Sally commented on a European study published in the journal Environment International which had surveyed 22 people and found microplastics in the blood of 17.

Sally's interview can be found at: https://www.1news.co.nz/2022/03/29/theyre-everywhere-microplastics-found-in-human-blood/

■ A UC Connect public lecture on "Airborne microplastics and climate change" was presented by Associate Professor Laura Revell, Environmental Physics, School of Physical & Chemical Sciences, on 18 May.

New research led by Laura has found there could be ten times more airborne microplastics in New Zealand homes than outside. Synthetic materials used in carpets, curtains and clothing are to blame, and can be stirred up by walking around the house:

https://www.canterbury.ac.nz/news/2022/airborne-microplastics-and-climate-change.html and https://www.stuff.co.nz/environment/128687454/not-so-safe-at-home-new-research-points-to-higher-airborne-microplastic-levels-indoors

PHD DEFENCE

■ Liam Carroll successfully defended his PhD thesis on 27 April. Liam's thesis was titled, "Covalently-bound organic modification of transparent semiconducting oxides: effects on the electronic surface properties" and was carried out under the supervision of Professor Alison Downard with co-superviser Professor Martin Allen. The viva voce exam was conducted by Professor David Williams (Auckland) with Associate Professor Simone Ci-

ampi (Curtin University) as the external examiner and Vladimir Golovko as the exam chair.

■ Congratulations to Hayley Jensen (SPCS), who successfully defended her PhD thesis entitled, "A comparative assessment of lesser-studied trace elements in the soil plant system: implications for environmental quality." Hayley was supervised by Brett and Sally, as well as Nik Lehto and Peter Almond from Lincoln University.

■ MANAWATU

PHDs SUCCESSFULLY DEFENDED

■ Harikrishnan M. Kurup successfully defended his PhD thesis titled, "Design, synthesis, and evaluation of single-stranded DNAs as inhibitors of APOBEC3 enzymes." Harikrishnan was supervised by Associate Professor Vyacheslav V. Filichev, Dr Elena Harjes and Professor Emeritus Geoffrey B. Jameson. After finishing his PhD, Harikrishnan has continued working on the APOBEC3 project as a research officer funded by a grant from the HRC-breast cancer research partnership.

■ Sashikumar Ramamirtham successfully defended his PhD thesis titled, "Structure-rheology relationships of protein-polysaccharide complexes at oil/water interfaces." The outcome was a pass with minor emendations.

■ Arka Gupta successfully defended his PhD thesis titled, "Development of novel anthelmintics to overcome the drug resistance problem in nematode infested ruminants." The outcome was a pass with minor emendations.

■ Andy Li successfully defended his PhD thesis titled, "Characterisation of pseudogene-like EP400NL in chromatin remodelling and transcriptional regulation." The outcome was a pass with minor emendations.

Scenes from the Otago Chemistry Department Postgraduate Boot Camp.

■ OTAGO

■ On 22 April the second departmental Postgraduate Boot Camp was held. This was well attended with everyone presenting a 5-minute talk on their research. The quality of all the talks was extremely high, and the casual environment led to some great questions and discussions. The boot camp organisers are grateful to receive funding from NZIC to sponsor prizes.

The awards went to China Payne (Best Talk), Samuel Harris (People's Choice), Kathy Sircombe (Best Understanding of Project), Peter Remoto (Most Creative Talk) and Chris Mills (Prettiest Diagrams). Well done to everyone. A special mention must

University of Otago, Department of Chemistry

Professor Nigel Perry (Plant & Food Research and University of Otago Chemistry) was one of 23 new Fellows of the Royal Society Te Apārangi honoured on 28 April in Wellington.

Each has recorded a video about their work, available now on the Society's website at: https://www.royalsociety.org.nz/who-we-are/our-people/our-fellows/new-fellow-seminars/2021-new-fellow-seminars/

go to Ciaran Ward for his efforts behind the BBQ! The day was rounded off with some friendly competition, ranging from three-legged races and egg tossing, to a "pub" style quiz.

TRAVEL GRANT

■ *The Otago branch of the NZIC is really pleased to support student travel grants. The following is a travel report from Catherine Ross:*

"From the 22 to 25 November 2021, I attended the Federation of Asian and Oceanian Biochemist and Molecular Biologists 16th Congress online. This event brings together 7 societies that fall under FAOBMB's banner. This gives a varied program with speakers from many different specialties.

"Although some of these talks are outside of my research area, I tried to attend as many as I could. One talk I found really interesting was from Dr Emily Leproust of Twist Bioscience (a sponsor of the conference). She described how they are using DNA to store data, as due to the nature of DNA, it is a form of information storage that will always be able to be interpreted unlike other formats such as VCRs and DVDs which fade into obsolescence.

"Another session I enjoyed was the drug discovery parallel session which included a talk from Prof Mark Blaskovich from the University of Queensland. His lab is looking at the development of octapeptins as novel antibiotics which can overcome polymyxin resistance.

"Although the conference was online there was a session where we could network. This involved being randomly sorted into a room with 3 others to chat. This was a nice way to round off the first day of the conference and I got to meet students from universities around New Zealand and discuss our research.

"On Wednesday evening I presented my poster in the medicinal chemistry category. In preparation I had also recorded a 2 min video discussing the poster. I did not have many people ask questions but I did connect via video call with Dr Jennifer Payne from Monash University and had a great discussion with her about her interest in our prodrug system and her similar work in attaching immune beacons to antibiotics to promote swift infection resolution.

"The creation of my poster was difficult due to intellectual property limitations on the data I could present. However, I feel this conference was a good introduction to presenting my work and gave me some ideas for how I would like to present at the future conferences."

WELLINGTON: Rose McLellan (supervised by Emily Parker) (left) and Thathsaranie Manthrirathna (supervised by Bridget Stocker, Emma Dangerfield and Mattie Timmer) (right, centre) have completed and defended their PhD theses and graduated in May. Special congratulations to Rose for making the Dean's List for Excellence.

■ WAIKATO

University of Waikato

■ Congratulations to Zahida Zia who has completed her PhD with Michael Mucalo. Her thesis was on the use of natural material composites to remove heavy metals from water and she was supported by a Pakistan HEC scholarship.

■ Sam Murray, supervised by Michèle Prinsep (with other supervisors, Tim Harwood and Jonathan Puddick at Cawthron), has successfully defended his thesis on characterisation of cyclic sulfated polyethers produced by toxic Gambierdiscus species.

■ Michèle Prinsep gave an invited webinar to the American Society of Pharmacognosy on "Probing the chemistry of nudibranch interactions with their prey."

■ WELLINGTON

Branch activities have largely been on hold during the Covid-19 wave, but at time of writing (May) we are making plans for the remainder of the year, with seminar presentations, a chemistry-related outing, our annual secondary schools quiz and the President's visit to look forward to.

VUW

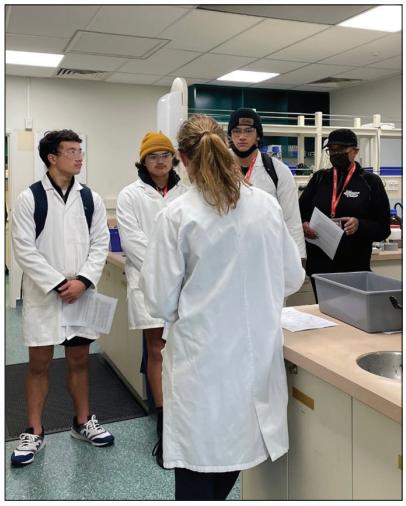
■ We've had a number of excellent seminars in the past few months, with PhD completion presentations

from Drs Anindita Sen (Colorimetric aptasensors for the detection of methamphetamine in saliva), Aleksandra (Sasha) Ilina (Ultrafast dynamics of the eumelanin pigment) and Rose McLellan (Unravelling the biosynthesis of aminoacylated indole diterpenes through heterologous pathway reconstruction). The May visit of Professor Steven Castle (Brigham Young University, Utah) was our first international speaker presenting in person for over 2 years. His seminar (New strategies for the synthesis of unusual peptides and alkaloids) described elegant chemistry for the synthesis of yaku'amide A and analogues, as well as incorporation of dehydroamino acids into peptides.

■ Drs Mat Anker and Nate Davis received VUW Early Career Research Excellence Awards – congratulations to both for this well-deserved honour!

■ The Ferrier Research Institute was involved in April's 'Tech Bootcamp', initiated by the Robinson Research Institute, in which Māori and Pasifika students eager to discover STEM careers spend a week doing hands-on work with scientists. The bootcamp was run in conjunction with the Tauhara North No.2 Trust (Ngāti Tahu and Ngāti Whaoa).

Students participating in Tech Bootcamp (Photos courtesy of Kath Beare)



Article

Inhibitors to rescue enzyme function: a counterintuitive strategy to treat rare diseases

LUCENA (LUCY) A. HUGHES,* SCOTT A. CAMERON AND FARAH LAMIABLE-OULAÏDI

The Ferrier Research Institute, Victoria University of Wellington, 69 Gracefield Rd, Lower Hutt, New Zealand (email: lucy.hughes@vuw.ac.nz)

Keywords: *enzyme, inhibition, metabolic disorder, pharmacological chaperone, protein*

Enzymes are the workhorses of biological systems, so it is not surprising that enzyme deficiencies due to genetic mutations are the cause of many inherited disorders. Such disorders have a wide range of observed pathologies: relatively mild symptoms are experienced for lactose intolerance, whereas disorders such as Krabbe disease result in death within the first couple of years of life. Over half of the mutations recorded for the human genome are missense mutations and result in numerous diseases as a consequence of protein misfolding.[1]

Pharmacological chaperones (PCs) are small molecules that act as molecular scaffolds to facilitate refolding of aberrant proteins with intact active sites to rescue their function. Proteopathies (protein misfolding diseases) are thus targets for treatment using PCs. This approach was first applied to the treatment of lysosomal storage disorders (LSDs) and is the focus of this brief review. PC therapeutic strategies will be discussed, using lysosomal enzymes to illustrate therapeutic mechanisms of action in the context of LSDs and beyond.

Lysosomal storage disorders and the shortcoming of current treatments

Lysosomal storage disorders (LSDs) are a subgroup of diseases arising due to enzyme deficiencies, consisting of over 70 different monogenic disorders.[2] Although the worldwide incidence of any one of these individual LSDs is rare, together they occur once in every 5,000 births,

Lucy Hughes is a PhD candidate at the Ferrier Research Institute, having graduated with BSc(Hons) in 2021 from the University of Otago. Lucy is working under the supervision of Drs Lamiable-Oulaïdi and Cameron on the preparation of pharmacological chaperones for galactosylceramidase. She is also working on solving the transition-state structure of this enzyme.

Scott Cameron undertook both his BSc(Hons) and PhD in chemistry at the University of Otago with Prof. Sally Brooker. After a postdoc with Prof. Vern Schramm at the Albert Einstein College of Medicine (New York), he returned to the Ferrier Research Institute in 2017. His research interests are focused on enzymatic transition-state analysis, inhibitor design, and building bespoke instruments. In his spare time, he is also the institute crystallographer.

Farah Lamiable-Oulaïdi undertook both her MSc(Hons) and PhD in chemistry at the University of Orleans (France) with Prof. Olivier Martin, investigating the use of iminosugars as pharmacological chaperones of multiple enzymes. This was followed by two postdocs and a temporary lecturer position. She now leads a team investigating chaperones of enzymes involved in lysosomal storage disorders. Her research interests are focussed on nucleoside and iminosugar enzyme inhibitor design and synthesis.

Te Kāuru
Ferrier Research Institute
VICTORIA UNIVERSITY OF WELLINGTON TE HERENGA WAKA

The Ferrier Research Institute – Te Kāuru investigates issues related to health, wellbeing, and the sustainability of our environment. Our science is all about nature-inspired new molecules and the ways they can be used to build a better world. Our expertise is in synthetic chemistry and analysis, synthetic and chemical biology, chemical immunology, and natural product isolation.

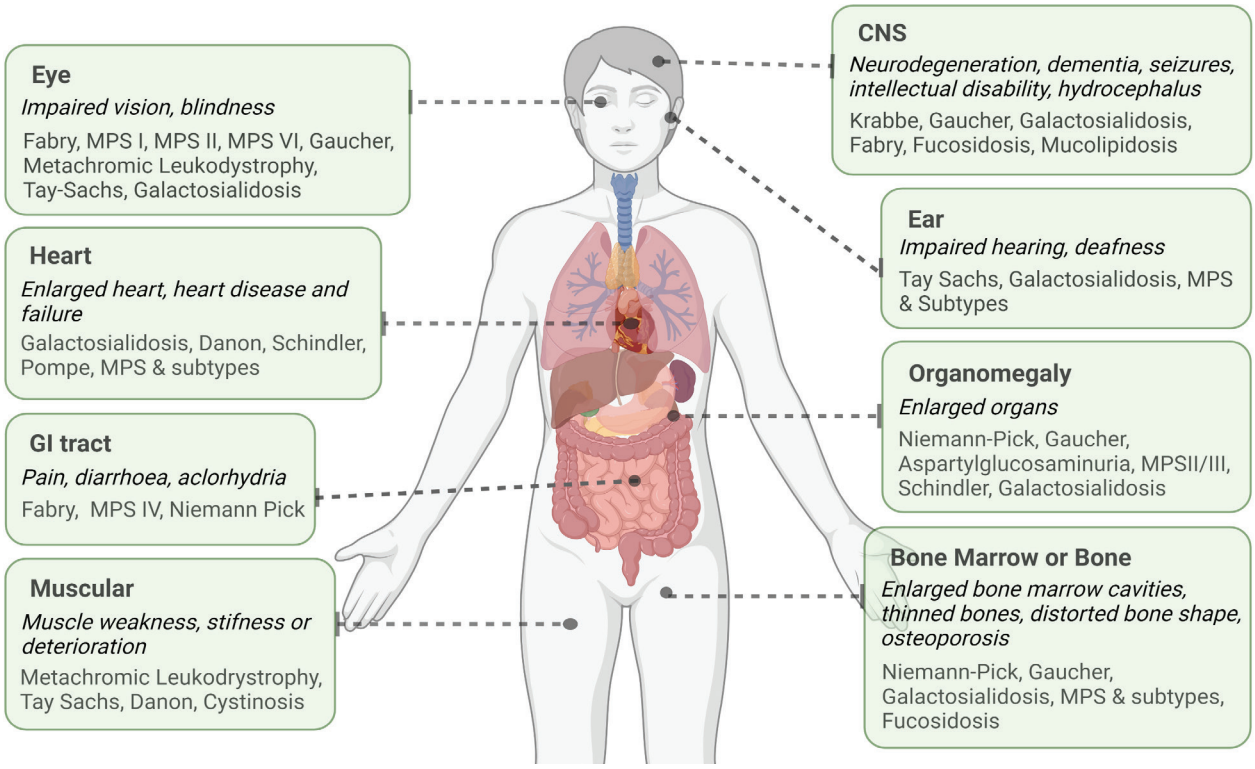


Fig. 1. Examples of organs impacted by different LSD subtypes, with the symptoms italicised. *Created with biorender.com.*

impacting a large proportion of the population. The lysosome itself is a cellular organelle considered to be the 'recycling centre' of the cell, primarily responsible for the breakdown of proteins, polysaccharides and lipids into their respective building blocks for destruction and reuse.[3] This breakdown is maintained by the balanced cooperation of over 60 different acidic hydrolases, lysosomal membrane proteins, activator proteins, transport proteins and non-lysosomal proteins.[4]

An inherited mutation in any one of the genes that encode this suite of lysosomal proteins can therefore lead to impaired processing and degradation of metabolites, giving rise to an LSD.

A common biochemical feature of this group of proteopathies is the accumulation of unprocessed metabolites inside organelles of the endosomal-autophagic-lysosomal (metabolic) system, hence the name, lysosomal storage disorder.[2] Lysosomes are ubiquitous across eukaryotic cells; consequently, the effect of an accumulated substrate in cellular compartments affects a wide variety of tissues (Fig. 1). The particular substrate that is stored and the associated site of accumulation varies between disorders as a result of different metabolic functions occurring within different tissues.[5] This storage impairs cellular functions, initiating a cascade of secondary downstream biochemical effects, including apoptosis.[2, 6]

There are a vast number of genetic mutations and associated LSD variations, making treatment of this diverse group of disorders difficult. Despite this and the rarity of these diseases, over the last few decades, we have seen the emergence of several therapeutic options that can decrease or relieve substrate build-up (Fig. 2).

The common drawback of these treatments is the limited capability to treat the most severe manifestations of LSDs that impact the nervous system, accounting for 75% of these disorders.[5] The blood-brain barrier (BBB), a layer of endothelial cells serving as a protective interface between the brain and systemic circulation, prevents several of these treatments from acting within brain tissue. For haematopoietic stem cell therapy (HSCT), one of the main advantages reported in many reviews is the ability for stem cells to cross the BBB to engraft and proliferate into the brain.

However, many studies suggest that HSCT only slows the progression of symptoms, and is not sufficient to totally prevent neurological damage.[7] Likewise, although small molecule inhibitors applied for use in substrate reduction therapy (SRT) can cross the BBB to act in the brain, inhibiting normal biosynthetic pathways used for the construction and catabolism of essential cellular components is not a desirable therapeutic approach for any LSD.[8]

The fact that all these treatments cannot be applied for the treatment of severe, neurological LSDs demonstrates a clear need for an alternative therapeutic approach.

Pharmacological chaperones for lysosomal storage disorders: inhibitors to the rescue

Lysosomal enzymes are synthesised in the rough endoplasmic reticulum in an unfolded state as precursor polypeptides. These polypeptides must be transported through the complex cellular environment, including the endoplasmic reticulum and Golgi apparatus, where they become functionalised, folded and further matured before being delivered to the lysosome to assume their catabolic function.[9] Some mutations may result in incorrect folding of these polypeptides; partially folded or misfolded proteins may expose hydrophobic amino acid residues that would normally be buried in the core of their native conformation.

These exposed regions drive the concentration-dependent formation of aggregates of aberrant proteins.[10-11] These aggregates are toxic, and their accumulation has been implicated in several neurodegenerative disorders such as Alzheimer's and Parkinson's disease.[12] Some mutant proteins may still retain partial or even full catalytic capability despite their mutations. However, such abnormal proteins are usually broken down by the cell's protein quality control process, via the endoplasmic reticulated-associated degradation (ERAD) pathway, which utilises the proteolytic activity of the proteasome.[10, 13]

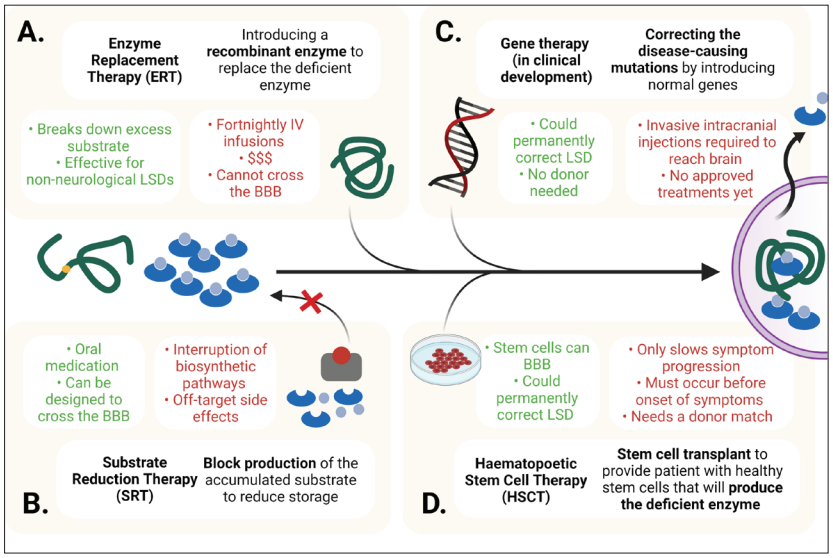


Fig. 2. Summary of LSD treatments (excluding PC therapy). *Black text = description of therapy, green text = advantage of therapy, red text = disadvantages of therapy.*

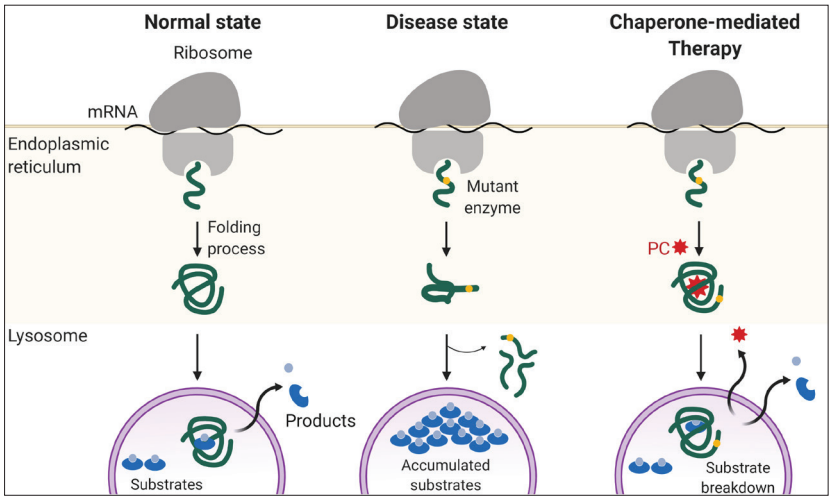


Fig. 3. Proposed mechanism of action for pharmacological chaperones enhancing enzyme activity in the lysosome. Made using BioRender.com

The hypothesis behind the PC therapeutic strategy is that if misfolded mutant proteins could acquire a near-native conformation and successfully pass through the cell's quality control process, then these proteins could still perform their catalytic roles if trafficked to their site of utility, in our case the lysosome. In 1999, Fan and co-workers published an article in *Nature Medicine*, showcasing the ability of a competitive enzyme *inhibitor* to *enhance* the function of a mutant enzyme.[14] They found that 1-deoxygalctonojirimycin (1-DGJ), a potent inhibitor of the lysosomal enzyme *α-galactosidase A,* was able to increase the activity of two mutant forms *of this enzyme by 7- or 8-fold.*[14]

This pioneering work was one of the first descriptions of what we now refer to as pharmacological chaperones (PCs). PCs are small molecules that selectively and reversibly bind to the active site of mutant proteins with high affinity.[15] In doing so, PCs act as molecular scaffolds that facilitate the folding of these proteins into their correct native conformation, thereby preventing them from being degraded by the ERAD pathway.[16-17] The mutant protein can then undergo further maturation, before finally being trafficked to the lysosome to assume its catabolic role. Once the enzyme-chaperone complex is there, the high concentration of accumulating substrate should displace the PC and subsequently be broken down (Fig. 3).[18-19] However, this PC strategy is only amenable to mutants that leave the protein catalytically active.

Fan and co-workers also reported that the residual activity of the targeted enzyme could only be increased

to a certain extent since at high PC concentrations undesired enzyme inhibition becomes dominant.[14] Therefore, potent competitive inhibitors should be administered at sub-inhibitory concentrations in order to act as PCs and enhance enzyme activity.[17, 20] Recently, a new class of PCs has emerged to overcome the challenging balance between inhibition and chaperone effect. In this case, PCs are designed to bind to allosteric binding pockets of misshaped enzymes, in contrast to the active-site binding PCs. Notably, detailed structural information used to guide the design and development of suitable PCs is more readily available for enzyme active sites compared to allosteric binding sites.[18]

Competitive inhibition is required for active-site targeted PCs, as the concentration-dependent exchange of inhibitor by the substrate is vital to achieve catabolic activity in the lysosome. This highlights a challenge faced by researchers developing PCs: the inhibitor must bind tightly enough to facilitate protein folding, but not so tightly that ligand exchange cannot readily occur. Despite this challenge, the use of small molecules offers the ability to tailor the design of compounds using medicinal chemistry drug discovery approaches to optimise both the inhibitory activity and biodistribution of the drug.[21]

In 2019, 19 years after it was first reported to rescue *α-galactosidase A (AGAL)* activity by Fan and co-workers, 1-deoxygalactonojirimycin (Fig. 4, 1-DGJ·HCl, Galafold®) became the first and, to date, only PC to be approved by the United States Food and Drug Administration. This oral drug is now available worldwide for the treatment of Fabry disease,[22] which is caused by a deficiency of AGAL activity, resulting in a build-up of its substrates, globotriaosylceramide and related glycosphingolipids.[23]
There are more than 1,000 known mutations in the GLA gene encoding the synthesis of AGAL that result in Fabry disease, and an estimated 35-

"... the serious renal and cardiac complications observed in Fabry patients are significantly reduced upon treatment with 1-DGJ, which is particularly important since the main cause of death arises from cardiac involvement."

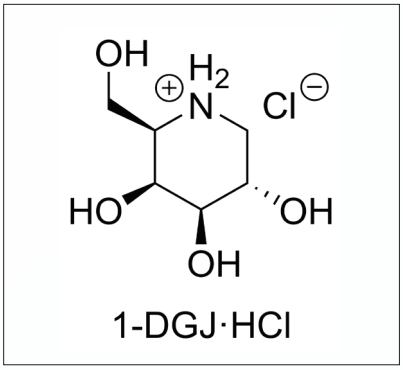


Fig. 4. Structure of the hydrochloride salt of 1-deoxygalactonojirimycin (1-DGJ), the active pharmaceutical component in Galafold®.

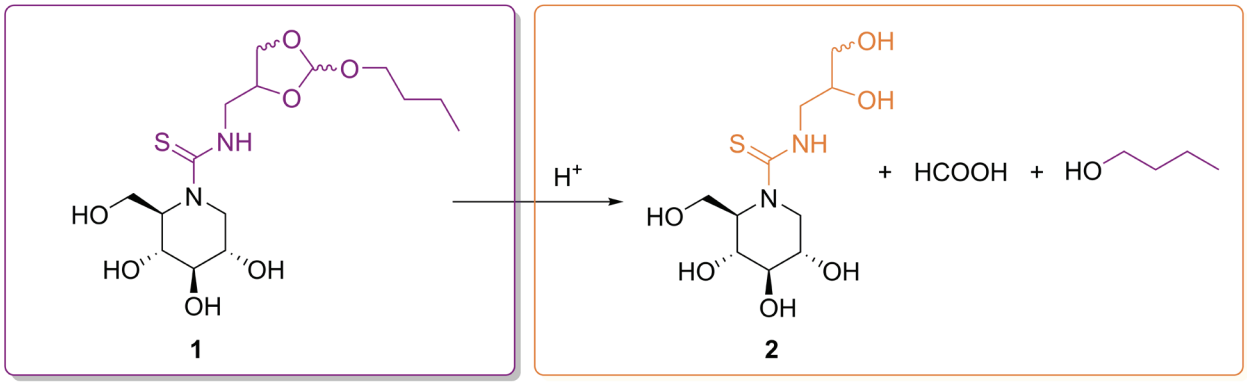
50% of these mutations are responsive to 1-DGJ treatment. For this subset of mutations, 1-DGJ can increase α-galactosidase A activity up to 48% of normal levels. Remarkably, only a 5-10% increase in residual enzyme activity is necessary to relieve and prevent the effects of disease, highlighting the efficacy of 1-DGJ's chaperone effect.[24] This small molecule increases α-galactosidase A enzyme levels in blood, skin, kidney, and brain, resulting in decreased substrate storage in these areas compared to baseline.

Notably, 1-DGJ can reach tissues that are not penetrated by enzyme replacement therapy (ERT), which was previously the only available treatment for Fabry disease. Furthermore, the serious renal and cardiac complications observed in Fabry patients are significantly reduced upon treatment with 1-DGJ, which is particularly important since the main cause of death arises from cardiac involvement.[25] The convenience (compared to ERT) and efficacy of 1-DGJ has established this PC as an important therapeutic for patients with amenable Fabry mutations, but more broadly validates PC therapy as an effective treatment strategy, particularly with respect to LSDs.

Using the acidic lysosomal environment to tailor PC activity

One consideration for the PC approach towards enzyme rescue is the potential of inhibition by the PC overpowering its therapeutic action. Initially, the high concentration of substrate enables ready exchange of the ligands, permitting substrate breakdown and relieving accumulation. However, as substrate concentration decreases the inhibitory action of the PC can begin to dominate within the lysosome, decreasing therapeutic efficacy. To overcome this, Galafold® capsules are taken every other day to allow inhibitor concentration to decrease, permitting substrate turnover. Although this regime is sufficient in this case, a more elegant approach to facilitate substrate binding is desirable.

An ideal PC would bind maximally to a protein within the endoplasmic reticulum (ER), where it facilitates protein folding, but would have decreased binding affinity within the lysosome, allowing enzyme substrate to easily displace the ligand. The lysosome possesses a key environmental difference that can be utilised for drug deactivation; lysosomes feature a low pH (5.2) relative to the rest of the neutral cell (7.0–7.4). An approach to exploit these pH differences with respect to PC design was first outlined by Mena-Barragán and co-workers in 2015.[26] They identified literature indicating that alkylated derivatives of 1-deoxynojirimycin (1-DNJ, an iminosugar



Scheme 1. Cleavage of the orthoester side chain under acidic conditions reveals the hydrophilic diol group, which deactivates the chaperone toward protein binding. The purple box represents a neutral environment, whereas the orange box represents an acidic environment.

of D-glucose) were able to act as PCs of β-glucocerebrosidase (GCase), the deficient enzyme in Gaucher disease.

Interestingly, the PC activity of these compounds was not observed when 1-DNJ was instead functionalised with hydrophilic groups.[27] This observation set the scene for the design of lysosomally deactivated PCs. Their approach uses orthoester functionality, which is stable at neutral pH in aqueous solution but essentially completely cleaved to the corresponding diol at pH 5. Specifically, thiourea conjugates of 1-DNJ were prepared, possessing an alkylated orthoester moiety, which is completely hydrolysed on exposure to the acidic lysosomal environment (Scheme 1).

All lipophilic orthoester functionalised analogues were able to inhibit two mutant forms of GCase in the micromolar to nanomolar range. Moreover, the corresponding diol cleavage product (**2**) showed no inhibitory activity toward these mutant forms.[26] Orthoester derivative **1** was able to increase GCase activity 2.5- to 6-fold at 20 μM and 60 μM, respectively. To challenge their deactivation hypothesis, the orthoester compounds were incubated with Gaucher patient fibroblast cultures, then washed and the cells lysed to investigate lysosomal contents. The fibroblast cell lysates showed the presence of compound **2** only, indicating that the orthoester was trafficked into the lysosome and subsequently hydrolysed.

To further test their approach, Mena-Barragán and co-workers then applied this conjugation strategy to 1-DGJ (Fig. 4), the marketed PC drug for Fabry disease. They found that an orthoester conjugate of 1-DGJ successfully restored *AGAL activity in several AGAL mutant models. Notably, 1-DGJ shifts from therapeutic to inhibitory at concentrations of 200* μM and above, which was not observed for their orthoester conjugate at the same concentrations and further validates their strategy. This approach to PC design is an elegant solution to one of the main drawbacks of this therapeutic approach.

PC therapy beyond LSDs

PC therapy is not limited to LSDs. For instance, protein misfolding and endoplasmic reticulum dysfunction are linked to many different diseases, many of which can be targeted for therapy using a pharmacological chaperone approach. This section will discuss the PC approach to treating endoplasmic reticulum dysfunction in Alzheimer's disease, and opioid tolerance and addiction.

Alzheimer's disease

Dementia impacts 55 million people worldwide, with Alzheimer's disease (AD) being the most common cause of dementia for people over 65.[28] The total cost of dementia in Aotearoa alone is around NZ$2.5B a year. There is no cure for AD, only medications to help manage symptoms.

AD is a slowly progressing neurodegenerative disease.

The exact pathological mechanisms leading to neurodegeneration in AD are not known and intensely debated, although protein misfolding and aggregation have long been pathological hallmarks of this devastating disease. This includes the two main neuropathological features of AD, neurofibrillary tangles (NFTs) and senile plaques. NFTs are abnormal filaments of hyper-phosphorylated tau protein that accumulate within the cytoplasm of the neuron, compromising its physical structure.[29, 30] Synaptic integrity is also affected by tau accumulation, resulting in memory impairments.[29] The other pathological indication of AD, senile plaques, are extracellular deposits of amyloid-beta (Aβ) protein. These plaques can have potent neurotoxicity and play a role in neuronal death.[31]

Li and co-workers published a study in 2020 detailing their use of a pharmacological chaperone to target vacuolar protein sorting 35 (VPS35), a component of the retromer complex system.[32] The retromer complex is a key component in the protein sorting machinery of the cell, which is responsible for trafficking proteins from the endosomes to other cellular compartments.[33] VPS35 was chosen as a therapeutic target for a number of reasons. AD patients are known to have lower levels of VPS35 in the brain.[34] This protein regulates amyloid precursor protein (APP) me-

tabolism, with APP downregulation increasing *in vitro* formation of Aβ.

In silico screening of VPS35 against a small molecule library revealed a lead compound TPT-172 (Fig. 5), which was then found to stabilise VPS35 against thermal denaturation in vitro.[35] Li and co-workers investigated the impact of TPT-172 on wildtype and 3xTG mice, a transgenic mouse model bearing memory impairments and neuropathological traits like AD (NFTs and senile plaques).

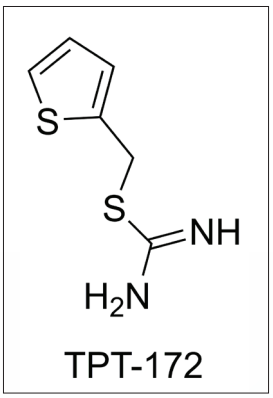


Fig. 5. Structure of TPT-172

"*In silico* screening of VPS35 against a small molecule library revealed a lead compound TPT-172, which was then found to stabilise VPS35 against thermal denaturation in vitro."

The 3xTG mice treated with TPT-172 showed a significant improvement in many of the major neuropathological and phenotypic characteristics of AD. VPS35 levels increased significantly, alongside an increase in the other two key proteins comprising the core of the retromer complex.[32] These treated mice showed decreased levels of Aβ protein compared to controls, likely due to upregulation of APP recycling.

An increase in cathepsin D protease and the mannose-6-phosphate receptor was also observed in treated mice compared to the control cohort. Both components are vital for the synthesis of proteins in the endosomes and for their consequent trafficking to appropriate cellular compartments.[9] Furthermore, an improvement in tau pathology and increased synaptic integrity was seen compared to control mice, as well as improvements in tests quantifying memory and behaviour.

These results indicate the significant role of retromer complex disruption in the pathological outcomes of AD and highlight its potential as a druggable target for future research.[32] Their research also highlights something exciting: small molecules have the potential to make huge changes in the numerous pathological pathways at play in diseases such as AD.

PCs for the δ opioid receptor

Interestingly, the application of PCs can go beyond regular protein-misfolding diseases and can be applied to G-protein coupled receptors (GPCRs). GPCRs are the most diverse and largest group of membrane receptors in eukaryotic cells, mediating many cellular processes. GPCRs have been of interest as druggable targets for a long time, and of note are the opioid receptors (ORs). The three OR isoforms (μ, κ and δ) are involved in several physiological processes but are most notably involved in the modulation of pain. When activated by an appropriate agonist μ- & κ-ORs result in analgesia, but are also associated with respiratory depression, dysphoria, and euphoria.[36]

The majority of marketed opioid receptor agonists bind to the μ-OR isoform.[37] However, chronic use of such opioids results in opioid tolerance, reducing the analgesic effects of these pharmaceuticals and causing opioid-induced pain sensitivity.[37, 38] δ-OR isoform activation is involved in the relief of chronic pain.[36] Notably, the role these isoforms play in mediating brain physiology is complex and goes beyond pain modulation, though the δ-OR isoform is of particular interest in the search for better pain management solutions.

Only a fraction of synthesised δ-OR precursors undergo folding and maturation before leaving the ER to emerge at the cell surface for function. The remaining δ-OR precursors are retained in the ER and targeted for degradation by the ERAD pathway.[39] Notably, despite not bearing mutations, which may cause misfolding or aggregation, these polypeptide intermediates are instead targeted for degradation as a result of poor folding kinetics.[39] In 2000, Bouvier and co-workers found that membrane-permeable opioid receptor ligands were able to increase the maturation and transport of synthesised δ-OR proteins to the surface of the cell, proposing that these ligands acted as PCs for these intermediates.[40] These compounds were hypothesised to interact with the δ-OR precursors in the ER, favouring a stable conformation and hence preventing their premature degradation.[40]

There are several implications of their findings: by increasing the incidence of the δ-OR at the cell surface, the δ-OR response to opioids is increased; PCs can be applied to proteins and conditions beyond those impacted by mutated proteins; and GPCR ligands can have important implications with regards to their ability to influence GPCR maturation and responsiveness downstream of the initial ligand interaction in the ER.

Opioid tolerance stems from several downstream biochemical pathways and is a complicated multifaceted mechanism. In 2020, Okuyama and co-workers reported evidence that ER stress plays a significant role in the development of morphine tolerance and that this stress could be decreased by treatment with PCs.[41] These PCs could attenuate morphine tolerance and restore analgesia in vivo, even after tolerance had developed. This research again shows the

ability of PCs to modulate physiological processes at cellular levels and give rise to improved pathological outcomes.

Summary

Pharmacological chaperone therapy is an exciting approach to treat diseases related to protein (mis)folding by rescuing the activity of the associated aberrant proteins. The application of PCs to treat LSDs, other proteopathies including AD, and opioid-receptor maturation highlights the potential of a small molecule to positively impact the pathological outcomes of a diverse range of complex disorders.

Although PC therapy is now well established for the treatment of amenable Fabry disease mutations, the development of clinically successful PCs remains challenging and has not yet been successful for the treatment of other LSDs such as Gaucher or Krabbe disease. With only one PC approved worldwide, there are many unexplored targets that should be suitable for PC therapy and are just waiting to be found.

References

1. Stenson, P. D.; Mort, M.; Ball, E. V.; Shaw, K.; Phillips, A. D.; Cooper, D. N. *Hum. Genet.* **2014,** *133* (1), 1-9.
2. Platt, F. M. *Nature Reviews Drug Discovery* **2018,** *17* (2), 133.
3. Xu, H.; Ren, D. *Annu. Rev. Physiol.* **2015,** *77*, 57-80.
4. Marques, A. R.; Saftig, P. *J. Cell Sci.* **2019,** *132* (2), jcs221739; Parenti, G.; Andria, G.; Ballabio, A. *Annu. Rev. Med.* **2015,** *66*, 471-486.
5. Segatori, L. *IUBMB life* **2014,** *66* (7), 472-477.
6. Vellodi, A. *Br. J. Haematol.* **2005,** *128* (4), 413-431.
7. Escolar, M. L.; Poe, M. D.; Provenzale, J. M.; Richards, K. C.; Allison, J.; Wood, S.; Wenger, D. A.; Pietryga, D.; Wall, D.; Champagne, M. *N. Engl. J. Med.* **2005,** *352* (20), 2069-2081; Allewelt, H.; Taskindoust, M.; Troy, J.; Page, K.; Wood, S.; Parikh, S.; Prasad, V. K.; Kurtzberg, J. *Biol. Blood Marrow Transplant.* **2018,** *24* (11), 2233-2238.
8. Coutinho, M. F.; Santos, J. I.; Alves, S. *Int. J. Mol. Sci.* **2016,** *17* (7), 1065.
9. Braulke, T.; Bonifacino, J. S. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* **2009,** *1793* (4), 605-614.
10. Cortez, L.; Sim, V. *Prion* **2014,** *8* (2), 197-202.
11. Hartl, F. U. *Annual review of biochemistry* **2017,** *86*, 21-26.
12. Jucker, M.; Walker, L. C. *Nature* **2013,** *501* (7465), 45-51.
13. Pereira, D. M.; Valentão, P.; Andrade, P. B. *Chemical Science* **2018,** *9* (7), 1740-1752.
14. Fan, J.-Q.; Ishii, S.; Asano, N.; Suzuki, Y. *Nat. Med.* **1999,** *5* (1), 112-115.
15. Liguori, L.; Monticelli, M.; Allocca, M.; Hay Mele, B.; Lukas, J.; Cubellis, M. V.; Andreotti, G. *Int. J. Mol. Sci.* **2020,** *21* (2), 489.
16. Beck, M. *IUBMB life* **2010,** *62* (1), 33-40.
17. Fan, J.-Q. *Biol. Chem.* **2008**.
18. Fan, J.-Q. *Trends Pharmacol. Sci.* **2003,** *24* (7), 355-360.
19. Biela-Banaś, A.; Oulaïdi, F.; Front, S.; Gallienne, E.; Ikeda-Obatake, K.; Asano, N.; Wenger, D. A.; Martin, O. R. *ChemMedChem* **2014,** *9* (12), 2647-2652.
20. Convertino, M.; Das, J.; Dokholyan, N. V. *ACS Chem. Biol.* **2016,** *11* (6), 1471-1489.
21. Sánchez-Fernández, E. M.; Fernández, J. M. G.; Mellet, C. O. *Chem. Commun.* **2016,** *52* (32), 5497-5515.
22. McCafferty, E. H.; Scott, L. J. *Drugs* **2019,** *79* (5), 543-554.
23. Germain, D. P. *Orphanet J. Rare Dis.* **2010,** *5* (1), 1-49.
24. Parenti, G. *EMBO Mol. Med.* **2009,** *1* (5), 268-279; Schueler, U.; Kolter, T.; Kaneski, C.; Zirzow, G.; Sandhoff, K.; Brady, R. *J. Inherit. Metab. Dis.* **2004,** *27* (5), 649-658.
25. Waldek, S.; Patel, M. R.; Banikazemi, M.; Lemay, R.; Lee, P. *Genet. Med.* **2009,** *11* (11), 790-796.
26. Mena-Barragán, T.; Narita, A.; Matias, D.; Tiscornia, G.; Nanba, E.; Ohno, K.; Suzuki, Y.; Higaki, K.; Garcia Fernandez, J. M.; Ortiz Mellet, C. *Angew. Chem.* **2015,** *127* (40), 11862-11866.
27. Luan, Z.; Higaki, K.; Aguilar-Moncayo, M.; Ninomiya, H.; Ohno, K.; García-Moreno, M. I.; Ortiz Mellet, C.; Garcia Fernandez, J. M.; Suzuki, Y. *Chembiochem* **2009,** *10* (17), 2780-2792; García-Moreno, M. I.; Díaz-Pérez, P.; Mellet, C. O.; Fernández, J. M. G. *Chem. Commun.* **2002,** (8), 848-849.
28. Gauthier, S.; Rosa-Neto, P.; Morais, J. A.; Webster, C. *World Alzheimer Report 2021: Journey through the diagnosis of dementia*; 2021.
29. Breijyeh, Z.; Karaman, R. *Molecules* **2020,** *25* (24), 5789.
30. Avila, J.; Lucas, J. J.; Perez, M.; Hernandez, F. *Physiol. Rev.* **2004,** *84* (2), 361-84.
31. Lublin, A. L.; Gandy, S. *Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine: A Journal of Translational and Personalized Medicine* **2010,** *77* (1), 43-49.
32. Li, J.-G.; Chiu, J.; Ramanjulu, M.; Blass, B. E.; Praticò, D. *Mol. Neurodegener.* **2020,** *15* (1), 1-11.
33. Seaman, M. N. *J. Cell Sci.* **2012,** *125* (20), 4693-4702.
34. Muhammad, A.; Flores, I.; Zhang, H.; Yu, R.; Staniszewski, A.; Planel, E.; Herman, M.; Ho, L.; Kreber, R.; Honig, L. S. *Proceedings of the National Academy of Sciences* **2008,** *105* (20), 7327-7332; Small, S. A.; Kent, K.; Pierce, A.; Leung, C.; Kang, M. S.; Okada, H.; Honig, L.; Vonsattel, J. P.; Kim, T. W. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **2005,** *58* (6), 909-919.
35. Mecozzi, V. J.; Berman, D. E.; Simoes, S.; Vetanovetz, C.; Awal, M. R.; Patel, V. M.; Schneider, R. T.; Petsko, G. A.; Ringe, D.; Small, S. A. *Nat. Chem. Biol.* **2014,** *10* (6), 443-449.
36. Stein, C. *Annu. Rev. Med.* **2016,** *67*, 433-451.
37. Darcq, E.; Kieffer, B. L. *Nature Reviews Neuroscience* **2018,** *19* (8), 499-514.
38. Chang, G.; Chen, L.; Mao, J. *Medical Clinics* **2007,** *91* (2), 199-211.
39. Petäjä-Repo, U. E.; Hogue, M.; Laperriere, A.; Walker, P.; Bouvier, M. *J. Biol. Chem.* **2000,** *275* (18), 13727-13736.
40. Petäjä-Repo, U. E.; Hogue, M.; Bhalla, S.; Laperrière, A.; Morello, J.-P.; Bouvier, M. *The EMBO journal* **2002,** *21* (7), 1628-1637.
41. Okuyama, Y.; Jin, H.; Kokubun, H.; Aoe, T. *Int. J. Mol. Sci.* **2020,** *21* (20), 7536.

Article

Exploring the potential for photon upconversion to enhance photovoltaic efficiencies

LARA D. BROWNE* AND NATHANIEL J. L. K. DAVIS

School of Chemical and Physical Sciences, Victoria University of Wellington, Wellington (email: lara.browne@vuw.ac.nz)

Keywords: *triplet-triplet annihilation, nanomaterials, hybrid organic/inorganic, photovoltaics*

Climate change

What allows the earth to be habitable is both its distance from the sun and greenhouse gases (GHG) within the earth's atmosphere.[1] GHGs trap and reflect radiation from the sun providing a naturally occurring warming of the earth's surface, this is known as the Greenhouse Effect. These atmospheric gases include water vapour (H_2O), nitrous oxide (N_2O), methane (CH_4) and carbon dioxide (CO_2), as well as man-made gases such as sulfur hexafluoride (SF_6) and chlorofluorocarbons (CFCs).[2] Although greenhouse gases are an important aspect of the earth's atmosphere, increased levels of these gases have been shown to cause unnatural warming of the earth's surface as more radiation from the sun is trapped within the atmosphere.[1] Changes in global climate can have dire consequences, including an increased likelihood of natural disasters such as droughts or flooding as well as rising sea levels due to melting ice caps.[3] Both cases pose a grave threat to ecosystems and societies.

Given this global crisis, immediate action needs to be taken; New Zealand has pledged net-zero carbon emission by 2050.[4] One such action is to reduce CO_2 emissions; this can be achieved through two main methods: carbon capture and sequestration (CCS) and zero-emission. Carbon capture involves capturing CO_2 and storing it underground before it can reach the atmosphere.[5] Zero emission, as the name suggests, is the complete elimination of CO_2 as a by-product of energy production. One such way of accomplishing zero-emissions is by the use of renewable energy.[3]

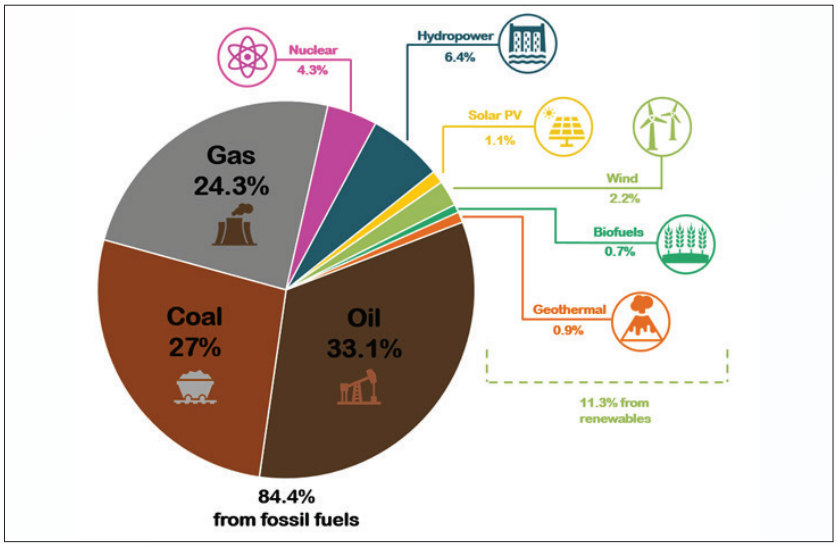


Fig. 1. Summary of global energy sources, based on 2019 data[6]

Renewable energy

Renewable energy refers to energy that is not obtained from a finite source, such as coal or oil, and is instead derived from an unlimited source such as the sun, wind, geothermal sites or water. Moreover, use of these sources does not generate CO_2 or other GHGs, making them suitable for achieving a 'net-zero emissions' future. In 2020, the global energy supply was largely sourced from fossil fuels, making up 84.4% of energy worldwide. Renewables on the other hand only constituted 11.3% (Fig. 1).[6]

List of abbreviations

CCS	Carbon capture and sequestration
DC	Downconversion
DPA	Diphenylanthracene
Eg	Bandgap energy
Fwhm	Full-width half-maximum
GHG	Greenhouse gases
ICS	Intersystem crossing
IR	Infrared
L-UC	Lanthanide upconversion
MEG	Multiple exciton generation
NC	Nanocrystal
NIR	Near infrared
PLQE	Photoluminescence quantum efficiency
PV	Photovoltaic
QD	Quantum dot
QY	Quantum yield
RE	Rare-earth
SQ	Shockley-Queisser
TET	Triplet energy transfer
TTA	Triplet-triplet annihilation
UC	Upconversion
UV	Ultraviolet

Major contributions to the global renewable energy supply have been made by photovoltaic (PV) technologies, and due to their boom in development over recent years, they have now become the cheapest source of renewable energy.[7] The switch to renewable energy sources is crucial for securing our future, and as such, optimisation of renewable energy harvesting technologies is key.

Photovoltaics

The sun is the primary energy source sustaining life on earth, emitting at a rate of 3.8 x 10^{23} kW per second, of which 60%, or 1.08 x 10^{14} reaches the earth's surface.[8] This amount of energy accounts for more than 7500 times the average energy consumption of the planet for one year,[8] making solar thermal energy the most abundant energy source known to humankind. Solar irradiation also has high versatility, acting as the fuel for photosynthesis, a process which can exploited in man-made systems, as well as providing heat and light to be converted into electricity.[9] Despite this wealth of energy, only 3% of this energy contributes to global energy demands.[10] This is due to the small number of photovoltaic (PV) cells currently in operation as a result of their relatively poor overall efficiency.

PV cells experience a number of loss mechanisms which limit efficiency (Fig. 2), thereby increasing operating costs to make up for the losses. The theoretical efficiency limit for single-bandgap devices is known as the Shockley-Queisser (SQ) limit. This states that for a single p-n junction type solar cell with a bandgap of 1.4 eV, the maximum solar conversion efficiency is ~34%.[11] The most significant power-loss mechanisms are spectral losses, as the sun emits a wide range of wavelengths of light and single junction p-n type solar cells are only capable of absorbing photons of a specific energy as dictated by their bandgap. This results in lower energy photons not being absorbed due to their energies being less than that of the bandgap, whereas higher energy photons experience thermalisation losses as their energies exceed that of the bandgap.[12] Strategies for circumventing the SQ limit and overcoming these losses are being investigated.

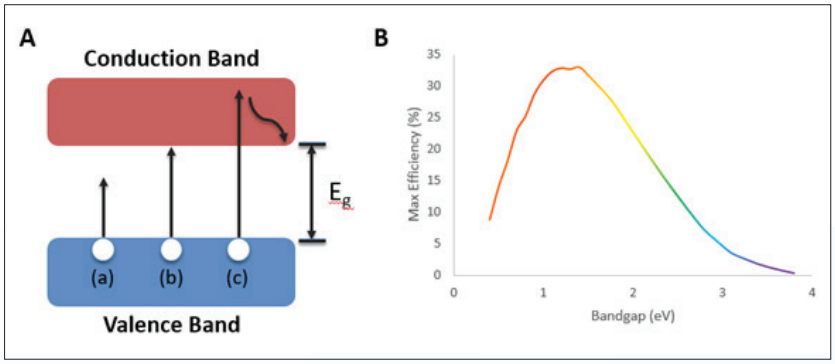


Fig. 2. **A:** Graphical representation of a solar semiconductor bandgap (E_g). Possible outcomes are represented by: (a) photons with energies less than E_g, which are not absorbed; (b) photons of energies equal to, or slightly greater than, E_g are utilised efficiently; (c) photons with energies greater than E_g which are absorbed, however, excess energy is lost by relaxation of the electron down to the minimum energy of the conduction band (thermalisation) **B:** The Shockley-Queisser theoretical limit for the efficiency of a solar cell as a function of the bandgap.[13]

"The most significant power-loss mechanisms are spectral losses, as the sun emits a wide range of wavelengths of light and single junction p-n type solar cells are only capable of absorbing photons of a specific energy as dictated by their bandgap."

Some of these strategies include multiple exciton generation (MEG)[14], multi-junction cells,[15] and spectral converters.[16] Spectral converters are technologies for adjusting incident solar light such that it is better matched to the bandgap of a given solar cell. The main two types of spectral conversion are upconversion (UC) and down conversion (DC). UC is a process by which two low energy (sub-bandgap) photons combine to give one higher-energy photon. DC is a process in which a high energy photon is converted into two lower-energy photons.[16] UC and DC are expected to be valuable contributors for surpassing the SQ limit,[17] with an anticipated increase in theoretical limit to 66% and 69% for DC and UC respectively in crystalline silicon cells.[18]

Upconversion in photovoltaics

UC can be used to recover sub-bandgap photons in solar cells and therefore boost maximum energy conversion efficiency. There are two main routes for the application of UC in photovoltaics; the first being rare-earth metal doping of nano-/micro-crystals and solid-state matrices, and the second is photochemical upconversion that utilises a process known as triplet-triplet annihilation (TTA).[19] Rare-earth metal upconversion (RE-UC), also referred to as lanthanide upconversion (L-UC), occurs as a result of the unique electron configuration of trivalent lanthanide ions where f-f transitions from the 4f shell and f-d transitions in the 4f-5d shell give rise to luminescence.[20] In general, RE-UC best captures light with wavelengths

above 800 nm,[21] however, this process can be tuned to a wide range of wavelengths from UV to NIR by consideration of lanthanide ion pairs and nanotechnology.[22] A major limitation for RE-UC and its use in PV cells is that extremely high excitation power densities are required to achieve upconversion efficiencies comparable with other upconversion methods.[23] TTA on the other hand, is able to achieve upconversion efficiencies up to 18% at low excitation power densities.[24] TTA makes use of organic/inorganic chromophores, in which a sensitiser and emitter pair to upconvert low energy light into higher-energy light.

Triplet-triplet annihilation upconversion (TTA-UC)

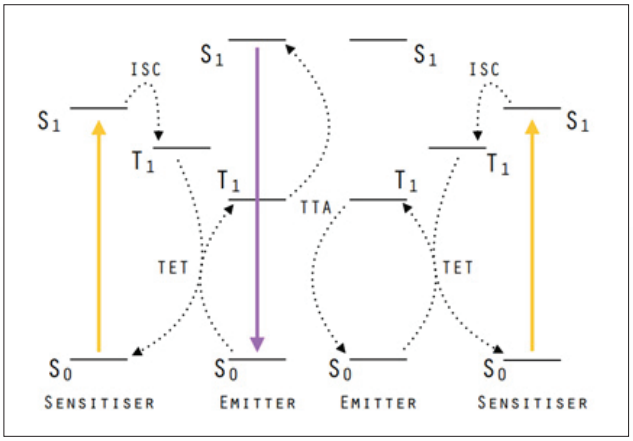
TTA-UC begins with the absorption of a photon by the triplet sensitiser. Upon absorption, a singlet excited state ($^1S \rightarrow {}^1S_n^*$) is formed and rapidly undergoes intersystem crossing (ISC) in which the singlet excited state ($^1S_n^*$) is converted to an excited triplet state ($^3S^*$).[25] This excited triplet state is then transferred from the sensitiser to the emitter through triplet energy transfer (TET). The longer-living triplet states, through collisional encounters, may then undergo TTA, another spin-allowed energy-transfer type process. Through TTA the triplets pair together to generate a singlet excited state in one emitter, and in another, the triplet relaxes down to the singlet ground state.[26-27] A single, high energy photon is then generated by the radiative relaxation of this singlet excited state.[28] This process is represented in Fig. 3.

The efficiency of the overall UC process is therefore determined by the efficiency of each mechanistic step. This can be expressed by Eq. 1:

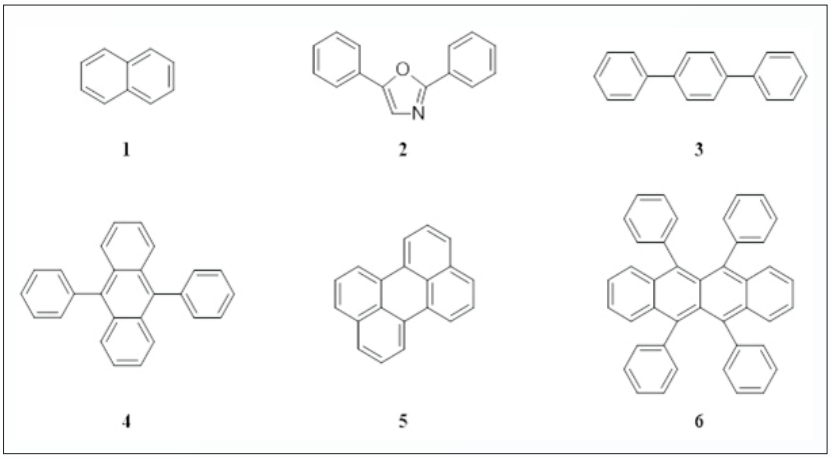
$$\Phi_{UC} = \tfrac{1}{2} f \Phi_{ISC} \Phi_{ET} \Phi_{TTA} \Phi_{FL} \quad \textit{(Eq. 1)}$$

In which Φ_{ISC}, Φ_{ET}, Φ_{TTA}, and Φ_{FL} represent the quantum efficiencies of ISC of the sensitiser, TET of the sensitiser triplet to the emitter, the statistical likelihood of two triplets undergoing TTA before decay, and the fluorescence quantum yield (QY) of the emitter, respectively.[25] The parameter *f* represents the statistical probability that a singlet excited state is obtained following the annihilation of two triplets via TTA. The factor of ½ accounts for stoichiometry of the TTA process, as two excited triplets are required to yield one higher-energy singlet excited state. This therefore limits the maximum achievable Φ_{UC} to 50%.[29]

An understanding of the TTA-UC mechanism, and how all components contribute to the process allows for an understanding of how to improve overall efficiency by tuning the properties of these components. For example, to ensure a viable energetic pathway for TET, there must be orbital overlap between the sensitiser and the emitter.[30] As such, the energy of the excited triplet state of the emitter must be either equal to or lower in energy than that of the sensitiser. Similarly, in order to facilitate TTA, the energy of the first excited singlet state of the emitter must be higher than, or at least equal to, double that of its excited triplet state.[31] As both TET and TTA processes are diffusion controlled, the triplet states must have lifetimes of at least several microseconds, such that there in an increased likelihood of an encounter between excited triplet states. Finally, the Φ_{FL} of the emitter and the Φ_{ISC} of the sensitiser should be near unity for efficient conversion of excited singlet energy to excited triplet energy, and optimal emission of the upconverted photon.[31] Examples of common emitter molecules used include naphthalene (**1**),[30] 2,5-diphenyloxazole (PPO) (**2**),[30] *p*-terphenyl (PT) (**3**),[30] diphenylanthracene (DPA) (**4**),[32, 33] perylene (**5**)[34] and rubrene (**6**),[35-38] as seen in Fig. 4.



Left, Fig. 3. TTA-UC mechanism.



Below, Fig. 4. Common emitter molecules.

In order to optimise the overall UC efficiency, the photophysical properties of the sensitiser and emitter should be considered. Numerous studies have been conducted on the synthetic tuning of the molecular properties of sensitisers and emitters. In this review article, modification of the sensitiser by use of semiconductor nanocrystal (NC) complexes is discussed.

Semiconductor NCs such as quantum dots (QD) were found to be particularly effective for use as sensitisers.[39-40] In comparison to common sensitisers such as lanthanides or palladium and platinum porphyrins, NCs are relatively easy to synthesise, and can be made from more abundant earth metals.[41] However, their main benefit stems from the tunability of their bandgap, allowing them to effectively harvest low energy photons, and their small singlet (S_1)-triplet (T_1) gap.[39, 40] This small energy difference between the two states allows for triplet sensitisation with little to no energy loss as a function of the bandgap.[42]

In conjunction with the sensitiser and emitter molecules, a third component which can be used is a mediator ligand. The mediator ligand is typically functionalised with a binding group such as a carboxylic acid for anchoring to a NC sensitiser.[43] An ideal mediator ligand has an excited triplet state less than that of the sensitiser but greater than that of the emitter, allowing for greater orbital overlap, thereby facilitating TET.

Different combinations of sensitisers and emitters allow for the ability to upconvert light across a broad spectrum, many of which have been investigated for optimisation.

Visible-to-UV TTA-UC

Upconversion of visible light to violet and UV light has been accomplished in a number of different TTA-UC hybrid nanomaterials systems.[24, 30, 32, 33, 35, 43-49] These systems typically include sensitisers with a wide bandgap and

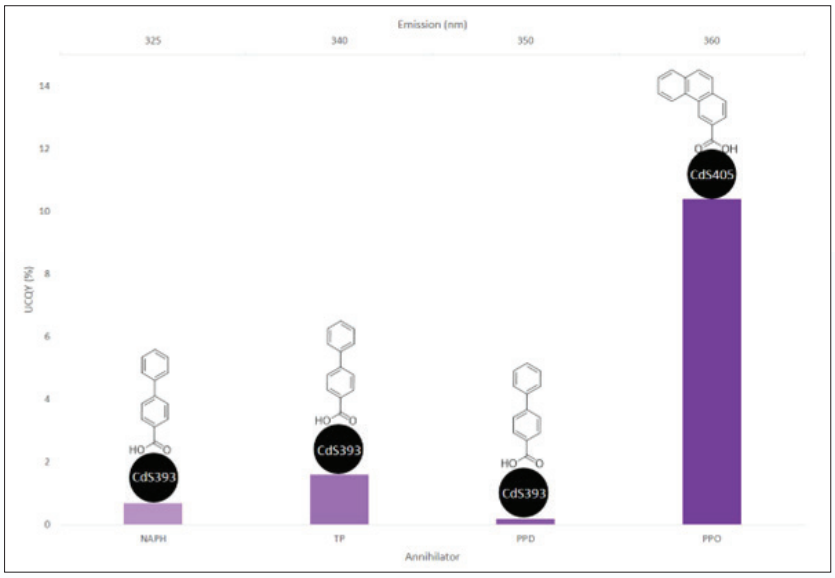


Fig. 5. Comparison of maximum UCQYs for emitters naphthalene (NAPH), *p*-terphenyl (TP), 2,5-diphenyl-1,3,4-oxadiazole (PPD), and 2,5-diphenyloxazole (PPO)[30]

"Different combinations of sensitisers and emitters allow for the ability to upconvert light across a broad spectrum, many of which have been investigated for optimisation."

that absorb light in the ~400-500 nm region. Examples of these nanomaterials include nanoparticle cadmium selenide/sulfide (CdSe/S)[30, 35, 43, 49] or zinc sulfide (ZnS), shelled indium copper sulphide ($CuInS_2$)[24] and perovskites such as caesium lead bromide ($CsPbBr_3$)[46] or caesium lead iodide ($CsPbI_3$).[45] Common mediator ligands are typically polyaromatic hydrocarbons such as naphthalene or anthracene, functionalised with a carboxylic acid group for anchoring to the nanocrystal. Mediator ligands often share similar structural scaffolding such that they have greater orbital overlap to facilitate TET.[43]

The two most favoured emitters for violet and UV upconversion are PPO and DPA (Fig. 4) for their high photoluminescence quantum efficiency (PLQE) and long-lived, low lying triplet states.[50] PPO and DPA have emission λ_{max} at 355 nm and 430 nm respectively.[30, 49]

In order to access the UV region, PPO is commonly used as an emitter, allowing for UC to ~355 nm. Mediator ligands for these systems are often naphthalene or naphthalene derivatives functionalised with a carboxylic acid anchoring group, anchoring to a QD such as CdS or $CsPbBr_3$.[30, 46]

In a more recent advancement, Hou et al.[30] conducted a thorough investigation of combinations of TTA-UC systems including four mediator ligands, four emitters and three differently sized CdS QDs to assess how changing each parameter can affect the upconversion quantum yield (UCQY). The different sizes of CdS QDs were defined according to their first exciton absorption peak, giving CdS393, CdS405 and CdS426, with diameters of 3.1, 3.5 and 4.3 nm respectively. The variation in size was achieved by careful control of the hot-injection and growth temperature, from which Hou et al. were able to obtain high quality CdS QD with high PLQEs, weak trap state emission and narrow full-width of half-maximum (fwhm). The different mediator ligands were benzoic

acid (BA), biphenyl-4-carboxylic acid (4-BCA), phenanthrene-3-carboxylic acid (3-PCA), and 1-napthoic acid (1-NCA). However, BA was eliminated as a viable mediator due to its high T1 state and was therefore thermodynamically unfavourable in all combinations. The emitters investigated were 2,5-diphenyl-1,3,4-oxadiazole (PPD), naphthalene (Naph), *p*-terphenyl (TP), and 2,5-diphenyloxazole (PPO), with PLQEs of 98%, 25%, 100%, and 95% respectively. This revealed that across all TET and TTA allowed combinations, PPO performed significantly better compared to the other emitters. This can be attributed to higher-lying triplet energies and short-lived triplet lifetimes of the other emitters, making it thermodynamically unfavourable for TET between the mediator and emitter to occur. Maximum reported UCQYs were 0.2% for PPD, 0.07% for naphthalene, 1.6% for TP, and 10.4% for PPO (Fig. 5).

A TTA-UC system of CdS 405/4-BCA/PPO was found to be optimal, indicating that for efficient TET, the triplet level of the mediator must be at least 200meV lower than that of the NC and the emitter should have a similar or lower triplet level. The conclusions drawn by Hou et al. are significant for future development of not only Vis to UV TTA-UC but are also applicable for any TTA-UC hybrid system.

Visible-to-near-UV TTA-UC

An early example of visible to UV TTA-UC in a hybrid organic/nanocrystal system was demonstrated by Huang et al. in 2015.[43] They achieved upconversion of 532 nm light to 432 nm light by use of a CdSe/9-anthracenecarboxylic acid (ACA)/DPA system, with an overall upconversion quantum yield (UCQY) of 9 ± 2%.[43] Huang and co-workers also demonstrated a 10^3 fold increase in emission when using 9-ACA as a mediator ligand, setting a precedence for use of mediator ligands in TTA-UC. Similar 9-ACA/DPA systems have been investigated

"The conclusions drawn by Hou et al. are significant for future development of not only Vis to UV TTA-UC but are also applicable for any TTA-UC hybrid system."

but with a change in the sensitising nanoparticle; for example, copper indium sulfide ($CuInS_2$)[24] or indium phosphide (InS) based nanocrystals.[32] In both instances a "green" approach was taken in the design of the sensitiser, as more common sensitisers use toxic elements such as lead or cadmium. A ZnS shelled $CuInS_2$ sensitiser ($CuInS_2$/ZnS) was investigated by Han et al.[24] and was the first instance in which a non-toxic nanocrystal successfully sensitised the TTA-UC process, giving a UCQY of 18.6 ± 0.3%.[24] It was also in this study that Han et al. demonstrated that "self-trapped" excitons were able to be harvested by the mediator ligand, 9-ACA, to then undergo TTA in the DPA emitter molecule. This result gave valuable insight into how trap states pervasive in nanocrystals influence TET and therefore impact TTA-UC.

Another example of "green" TTA-UC was demonstrated by Lai et al.[32] with the development of an InP/ZnSe/ZnS core/shell QD. The purpose of the shells was to mitigate the picosecond hole trapping, which is often observed in 'core-only' QDs. The rate of TET for the shelled QDs was observed to be almost 10-fold slower than for core-only CdSe QD to 9-ACA,[51] possibly indicating that the shell acts as a tunnelling barrier for the flow of electrons between the QD and 9-ACA. Despite this, an 84% TET efficiency was calculated,[32] indicating that in these systems where the excitons are long lived, the rate of TET has no significant impact on its efficiency. This is consistent with the findings by Han et al., where they observed a relatively slow TET of 57.1 μs^{-1} but a high TET efficiency (~92%).[24]

A different approach was taken by Li et al.[33] with the introduction of flexible and ridged bridges between the carboxylic acid anchoring group and the main anthracene unit. Ridged bridges included 1-2 phenyl spacers and the flexible bridges consisted of a phenyl ring with an alkyl chain 3 or 8 carbons in length. From this investigation Li et al. were able to determine that by increasing the length between the anthracene unit and the CdSe NC, the UCQYs decreased, indicating a strong distance dependence for NC to mediator ligand TET efficiency.[33]

Li et al. noticed no discernible difference in the rate of TET between the two lengths of flexible aliphatic bridges, providing evidence to suggest that the flexible bridges bend on the surface of the NC, rather than extend, limiting the distance which the mediator ligand extends past the NC. However, for the ridged bridges, there was a dramatic change observed in the UCQY. A UCQY of 14.3% was observed for 9-ACA but the addition of one phenyl spacer caused the UCQY to drop to 3.9%, followed by a further decrease to 0.4% for two phenyl spacers. Li et al. concluded that, as a distance dependant mechanism, TET efficiency significantly decreases as a function of increased bridge length.

Near-IR-to-visible TTA-UC

Upconversion of near-IR (NIR) light to the visible region is of great interest for its applications in solar technologies. As typical silicon photovoltaics have a bandgap of 1.1-1.3 eV, integration of a TTA-UC system will allow access to sub-bandgap photons, thereby increasing PV efficiency above that of the SQ limit.[52] Common nanocrystalline sensitisers for NIR to Vis UC are PbS and PbSe for their tuneable absorptions, which span into the NIR region.[37, 38, 43, 53, 54] Tetracene scaffolds are favoured for mediators as their

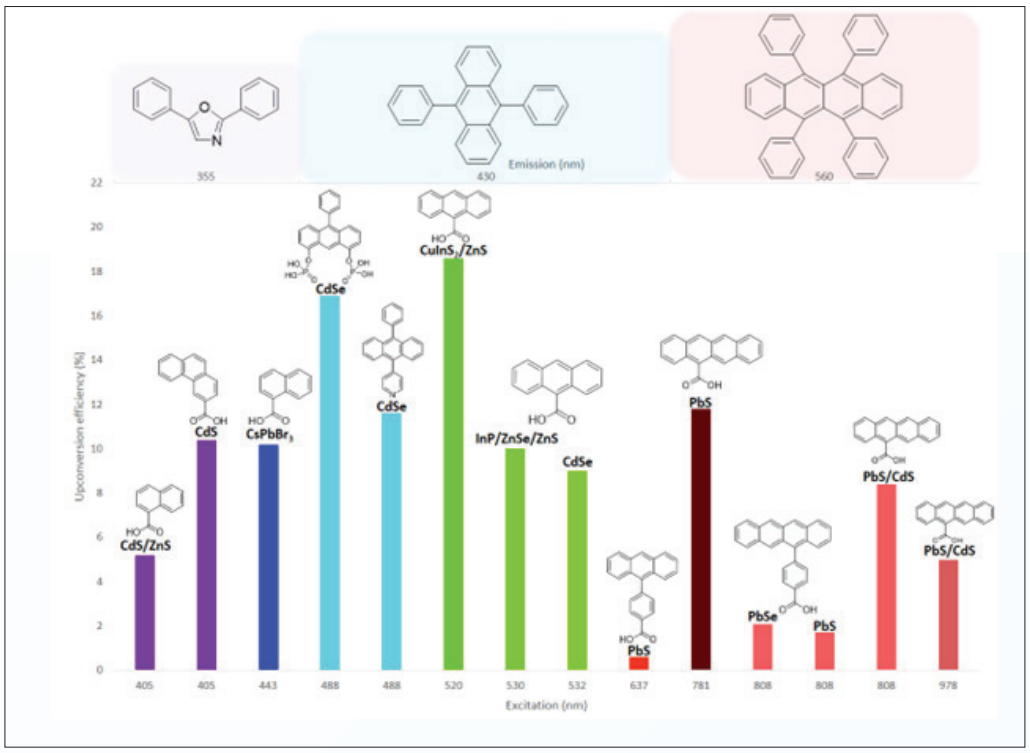


Fig. 6. Summary of literature TTA-UC hybrid nanoparticle/organic dye systems. From left to right: Gray et al.,[44] Hou et al.,[30] He et al.,[46] De Roo et al.,[49] Huang et al.,[35] Han et al.,[24] Lai et al.,[32] Huang et al.,[43] Imperiale et al.,[48] Huang et al.,[36] Huang et al.,[53] Huang et al.,[53] Mahboub et al.,[38] Huang et al.[37]

triplet energies are generally well-matched to the triplet energies of PbS/PbSe and the emitter rubrene, thereby facilitating an efficient TET. Rubrene, with an emission peak at ~550 nm, is a favourable emitter for its PLQE near unity, and long-lived, low-lying triplet states.[50]

The first prominent example of NIR-to-Vis TTA-UC was given by Huang et al.,[43] who demonstrated the upconversion of 980 nm light to 568 nm light by use of a PbSe/rubrene system. They achieved an UC efficiency of 0.01%, making this the first instance of TTA-based upconversion of 980 nm light in literature. While the UCQY fell short of those obtained from lanthanide-doped crystals, this research was an important first step for future optimisation of these systems. This further development can be seen in papers published by the same group; in 2016 Huang et al. [53] investigated how the addition of a mediator ligand can influence UC efficiency. In this study, functionalised and unfunctionalised PbS and PbSe QDs were compared. The QDs were functionalised with 4-(tetracen-5-yl) benzoic acid (CPT), this scaffold was chosen for its triplet energy level greater than that of rubrene but less than that of PbS/PbSe, allowing for thermodynamically favourable TET. Through this investigation, Huang et al. highlighted the benefit of using a mediator ligand, with an 84-fold increase in UCQY for PbS (0.021% without ligand, 1.7% with) and an 11-fold increase for PbSe (0.2% without ligand, 2.1% with).

Once CPT had been established as a good mediator ligand, optimisation of other components became of greater importance. One approach which was taken by Huang and co-workers,[36] was the improvement of the intrinsic qualities of the PbS QD sensitiser. Huang et al. determined that by optimisation of the NC synthesis, PLQEs could be greatly improved. A PLQE of 34.1% was achieved for PbS NCs which were synthesised using a N-(3,5-bis(trifluoromethylphenyl))-N'-phenylthiourea precursor, as opposed to the conventional sulfur source, bis(trimethylsilyl)sulfide. This increase in PLQE extended into an improvement of UCQY in a PbS/CPT/Rubrene system, achieving a UCQY of 11.8% for the upconversion of 781 nm light to 560 nm light. This increase in UCQY was attributed to reduced non-radiative decay, and extended triplet lifetimes on the surface of the QD.[36]

Hybrid nanoparticle/organic dye up-conversion systems are summarised in Fig. 6.

Conclusions

TTA-UC holds much promise for the future of photovoltaics for its ability to recover NIR low energy photons, which make up 53% of the sun's broad spectrum.[5] To be able to efficiently harness this process has significant efficiency implications for the future of high-performance next-generation solar PV cells. Improvement of the performance of solar PV cells will in turn have a positive impact on the efficiency of energy conversion and power generation.

References

1. Karl, T. R.; Trenberth, K. E. *Science* **2003,** *302* (5651), 1719-1723.
2. NIWA What are greenhouse gases? https://niwa.co.nz/atmosphere/faq/what-are-greenhouse-gases (accessed 16/03/2022).
3. Midilli, A.; Ay, M.; Dincer, I.; Rosen, M. A. *Renew. Sustain. Energy Rev.* **2005,** *9* (3), 255-271.
4. Climate Change Response (Zero Carbon) Amendment Act 2019. New Zealand Government: New Zealand, 2019.
5. Clean Growth: The UK Carbon Capture Usage and Storage deployment pathway. Growth, D. o. E. a. C., Ed. Crown: United Kingdom, 2018.
6. Ritchie, H.; Roser, M. *Energy mix*; Our World in Data: 2020.
7. IEA World Energy Outlook 2021. https://www.iea.org/reports/world-energy-outlook-2021 (accessed 16/03/2022).
8. Thirugnanasambandam, M.; Iniyan, S.; Goic, R. *Renew. Sustain. Energy Rev.* **2010,** *14* (1), 312-322.
9. Crabtree, G. W.; Lewis, N. S. *Physics Today* **2007,** *60* (3), 37-42.
10. Detollenaere, A.; Van Wetter, J.; Masson, G.; Kaizuka, I.; Jäger-Waldau, A.; Donoso, J., *Snapshot of Global PV Markets 2020 PVPS Task 1 Strategic PV Analysis and Outreach*. 2020.
11. Shockley, W.; Queisser, H. J. *J. Appl. Physics* **1961,** *32* (3), 510-519.
12. Conibeer, G. *Materials Today* **2007,** *10* (11), 42-50.
13. Rühle, S. Solar *Energy* **2016,** *130*, 139-147.
14. Klimov, V. I. *J. Phys. Chem. B* **2006,** *110* (34), 16827-16845.
15. Law, D. C.; King, R. R.; Yoon, H.; Archer, M. J.; Boca, A.; Fetzer, C. M.; Mesropian, S.; Isshiki, T.; Haddad, M.; Edmondson, K. M.; Bhusari, D.; Yen, J.; Sherif, R. A.; Atwater, H. A.; Karam, N. H. *Solar Energy Materials Solar Cells* **2010,** *94* (8), 1314-1318.
16. van Sark, W. G.; de Wild, J.; Rath, J. K.; Meijerink, A.; Schropp, R. E. I. *Nano. Res. Lett.* **2013,** *8* (1), 81.
17. van Sark, W. G. J. H. M.; Meijerink, A.; Schropp, R. E. I.; van Roosmalen, J. A. M.; Lysen, E. H. *Solar Energy Materials Solar Cells* **2005,** *87* (1), 395-409.
18. Richards, B. S. *Solar Energy Materials Solar Cells* **2006,** *90* (15), 2329-2337.
19. Tim, F. S.; Yuen Yap, C.; Tony, H. K.; Maxwell, C.; Bernd, S.; Klaus, L.; Timothy, W. S. *J. Photonics Energy* **2013,** *3* (1), 1-14.
20. Yu, Z.; Eich, C.; Cruz, L. J. *Front. Chem.* **2020,** *8*.
21. Shang, Y.; Hao, S.; Yang, C.; Chen, G. *Nanomaterials (Basel)* **2015,** *5* (4), 1782-1809.
22. Zhou, B.; Shi, B.; Jin, D.; Liu, X. *Nature Nanotechnology* **2015,** *10* (11), 924-936.
23. Richards, B. S.; Hudry, D.; Busko, D.; Turshatov, A.; Howard, I. A. *Chem. Rev.* **2021,** *121* (15), 9165-9195.
24. Han, Y.; He, S.; Luo, X.; Li, Y.; Chen, Z.; Kang, W.; Wang, X.; Wu, K. *J. Am. Chem. Soc.* **2019,** *141* (33), 13033-13037.
25. Gao, C.; Prasad, S. K. K.; Zhang, B.; Dvořák, M.; Tayebjee, M. J. Y.; McCamey, D. R.; Schmidt, T. W.; Smith, T. A.; Wong, W. W. H. *J. Phys. Chem. C* **2019,** *123* (33), 20181-20187.
26. Zhao, J.; Ji, S.; Guo, H. *RSC Advances* **2011,** *1* (6), 937.
27. Gertsen, A. S.; Koerstz, M.; Mikkelsen, K. V. *Phys. Chem. Chem. Phys.* **2018,** *20* (17), 12182-12192.
28. Ronchi, A.; Brazzo, P.; Sassi, M.; Beverina, L.; Pedrini, J.; Meinardi, F.; Monguzzi, A. *Phys. Chem. Chem. Phys.* **2019,** *21* (23), 12353-12359.
29. Schmidt, T. W.; Castellano, F. N. *J. Phys. Chem. Lett.* **2014,** *5* (22), 4062-4072.
30. Hou, L.; Olesund, A.; Thurakkal, S.; Zhang, X.; Albinsson, B. *Adv. Funct. Mat.* **2021,** *31* (47), 2106198.
31. Gray, V.; Dreos, A.; Erhart, P.; Albinsson, B.; Moth-Poulsen, K.; Abrahamsson, M. *Phys. Chem. Chem. Phys.* **2017,** *19* (17), 10931-10939.
32. Lai, R.; Sang, Y.; Zhao, Y.; Wu, K. *J. Am. Chem. Soc.* **2020,** *142* (47), 19825-19829.
33. Li, X.; Huang, Z.; Zavala, R.; Tang, M. L. *J. Phys. Chem. Lett.* **2016,** *7* (11), 1955-1959.
34. Wei, Y.; Wang, Y.; Zhou, Q.; Zhang, S.; Zhang, B.; Zhou, X.; Liu, S. *Phys. Chem. Chem. Phys.* **2020,** *22* (45), 26372-26382.
35. Huang, Z.; Xu, Z.; Huang, T.; Gray, V.; Moth-Poulsen, K.; Lian, T.; Tang, M. L. *J. Am. Chem. Soc.* **2020,** *142* (41), 17581-17588.
36. Huang, Z.; Xu, Z.; Mahboub, M.; Liang, Z.; Jaimes, P.; Xia, P.; Graham, K. R.; Tang, M. L.; Lian, T. *J. Am. Chem. Soc.* **2019,** *141* (25), 9769-9772.
37. Huang, Z.; Xu, Z.; Mahboub, M.; Li, X.; Taylor, J. W.; Harman, W. H.; Lian, T.; Tang, M. L. *Angew. Chem. Int. Ed.* **2017,** *56* (52), 16583-16587.
38. Mahboub, M.; Huang, Z.; Tang, M. L. *Nano Lett.* **2016,** *16* (11), 7169-7175.
39. Garakyaraghi, S.; Castellano, F. N. *Inorg. Chem.* **2018,** *57* (5), 2351-2359.
40. Scholes, G. D. *Adv. Funct. Mat.* **2008,** *18* (8), 1157-1172.
41. Landry, M. L.; Morrell, T. E.; Karagounis, T. K.; Hsia, C.-H.; Wang, C.-Y. *J. Chem. Ed.* **2014,** *91* (2), 274-279.
42. Nishimura, N.; Allardice, J. R.; Xiao, J.; Gu, Q.; Gray, V.; Rao, A. *Chem. Sci.* **2019,** *10* (18), 4750-4760.
43. Huang, Z.; Li, X.; Mahboub, M.; Hanson, K. M.; Nichols, V. M.; Le, H.; Tang, M. L.; Bardeen, C. J. *Nano Lett.* **2015,** *15* (8), 5552-5557.
44. Gray, V.; Xia, P.; Huang, Z.; Moses, E.; Fast, A.; Fishman, D. A.; Vullev, V. I.; Abrahamsson, M.; Moth-Poulsen, K.; Lee Tang, M. *Chem. Sci.* **2017,** *8* (8), 5488-5496.
45. Mase, K.; Okumura, K.; Yanai, N.; Kimizuka, N. *Chem. Comm.* **2017,** *53* (59), 8261-8264.
46. He, S.; Luo, X.; Liu, X.; Li, Y.; Wu, K. *J. Phys. Chem. Lett.* **2019,** *10* (17), 5036-5040.
47. Xia, P.; Raulerson, E. K.; Coleman, D.; Gerke, C. S.; Mangolini, L.; Tang, M. L.; Roberts, S. T. *Nature Chemistry* **2020,** *12* (2), 137-144.
48. Imperiale, C. J.; Green, P. B.; Hasham, M.; Wilson, M. W. B. *Chem. Sci.* **2021,** *12* (42), 14111-14120.
49. De Roo, J.; Huang, Z.; Schuster, N. J.; Hamachi, L. S.; Congreve, D. N.; Xu, Z.; Xia, P.; Fishman, D. A.; Lian, T.; Owen, J. S.; Tang, M. L. *Chem. Mat.* **2020,** *32* (4), 1461-1466.
50. Montalti, M.; Credi, A.; Prodi, L.; Gandolfi, M. T., *Handbook of Photochemistry*. 3rd Edition ed.; CRC Press: Boca Raton, 2006.
51. Mongin, C.; Garakyaraghi, S.; Razgoniaeva, N.; Zamkov, M.; Castellano Felix, N. *Science* **2016,** *351* (6271), 369-372.
52. Goldschmidt, J. C.; Fischer, S. *Adv. Opt. Mat.* **2015,** *3* (4), 510-535.
53. Huang, Z.; Simpson, D. E.; Mahboub, M.; Li, X.; Tang, M. L. *Chem. Sci.* **2016,** *7* (7), 4101-4104.
54. Xu, Z.; Huang, Z.; Li, C.; Huang, T.; Evangelista, F. A.; Tang, M. L.; Lian, T. *ACS Appl. Mat. Interfaces* **2020,** *12* (32), 36558-36567.

Article

A decade of main group chemistry research

MARTYN P. COLES

Victoria University of Wellington - Te Herenga Waka and MacDiarmid Institute for Advanced Materials and Nanotechnology, Wellington 6140 (email: martyn.coles@vuw.ac.nz)

Keywords: *main group*, *magnesium*, *bismuth*, *aluminium*

An accidental interest in main group chemistry?

I first became hooked on inorganic chemistry when I learned about d-orbitals and transition metals (TMs), taught to me during my undergraduate degree by Professor Vernon Gibson at Durham University in the UK. I was fascinated by the fact that a simple electrostatic model (crystal field theory) could be used to explain some of the fundamental properties of the TM complexes, including their colour and magnetic properties. I suspect that this had a lot to do with me choosing Prof Gibson as my PhD supervisor, with whom I spent three years studying the application of vanadium and chromium compounds for the polymerisation of ethylene (a hot topic in the 1990's).[1]

At that time, university classes on the chemistry of the main group elements were somewhat 'dry', especially when compared to the exciting reactions and catalytic processes in which the transition metals were involved. Most courses (and there weren't many) involved pouring over tables of physical data of the s- and p-block elements and their compounds and learning about the trends in various properties, not forgetting of course the 'exception to the rule' that had to be memorised and regurgitated at exam time.

My first foray into dedicated main group chemistry research was during my post-doctoral studies at the University of Iowa with Professor Richard Jordan. Although the originally funded NATO Post-Doctoral Research Fellowship involved the application of tetraaza-macrocyclic compounds of the group 4 metals in olefin polymerisation,[2] my poor organic chemistry skills and failure to make the ligand precursors caused a major rethink of the project after about 6 months.

Ultimately this led me to examine the potential for cationic aluminium compounds to polymerize alkenes, the first time this catalysis had been observed for non-transition metal or -lanthanide elements.[3]

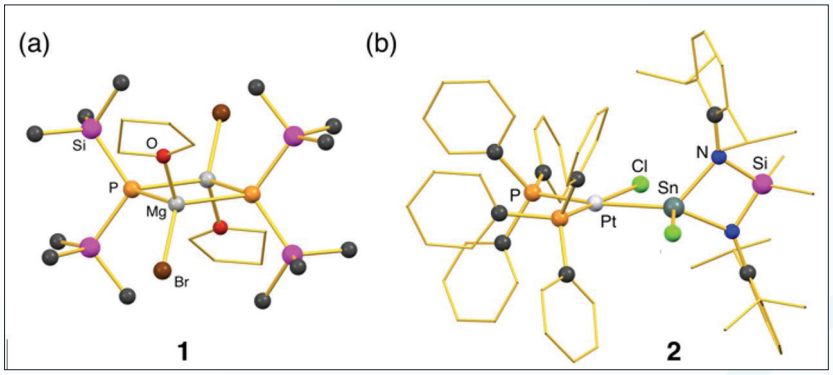


Fig. 1. X-ray structures of (a) a phospha-Grignard reagent (1) and (b) a platinum-tin catalyst for hydroformylation chemistry (2)

"Unbeknownst to me at the time, there was a renaissance taking place in main group chemistry research,[11] pushing the limits of compounds containing these elements such that legitimate parallels between their chemistry and that of the transition elements were being made.[12]"

As part of this study, we examined a number of anionic N,N'chelating ligand systems including the amidinate,[4] guanidinate[5] and β-diketiminate[6] ligands, a theme in ligand design that has featured heavily in my independent research career. So, truth be told, my initial research involving the chemistry of the main group elements was more 'accidental' than a carefully considered decision to explore this area of the periodic table.

Main group chemistry and me: the early years

During the start of my independent research career at the University of Sussex in the UK, I focused on the application of transition metal compounds for a number of catalytic applications including complexes of titanium[7] and scandium[8] for olefin polymerisation, copper[9] for atom transfer radical polymerisation (ATRP) and zinc for the production

of polylactide.[10] Unbeknownst to me at the time, there was a renaissance taking place in main group chemistry research,[11] pushing the limits of compounds containing these elements such that legitimate parallels between their chemistry and that of the transition elements were being made.[12]

The most significant discoveries that drove this new interest were (i) the existence of multiple bonds involving 'heavier' main group elements beyond the first period,[13] (ii) the isolation of stable compounds containing main group elements in low oxidation states (e.g. Al(I),[14] Si(II)[15]) and (iii) the isolation of radical species containing unpaired electrons centered at the p-block element.[16] Key to the success of these areas was the development of bulky ligands that were able to kinetically stabilise the main group element and protect it from unwanted reactivity.

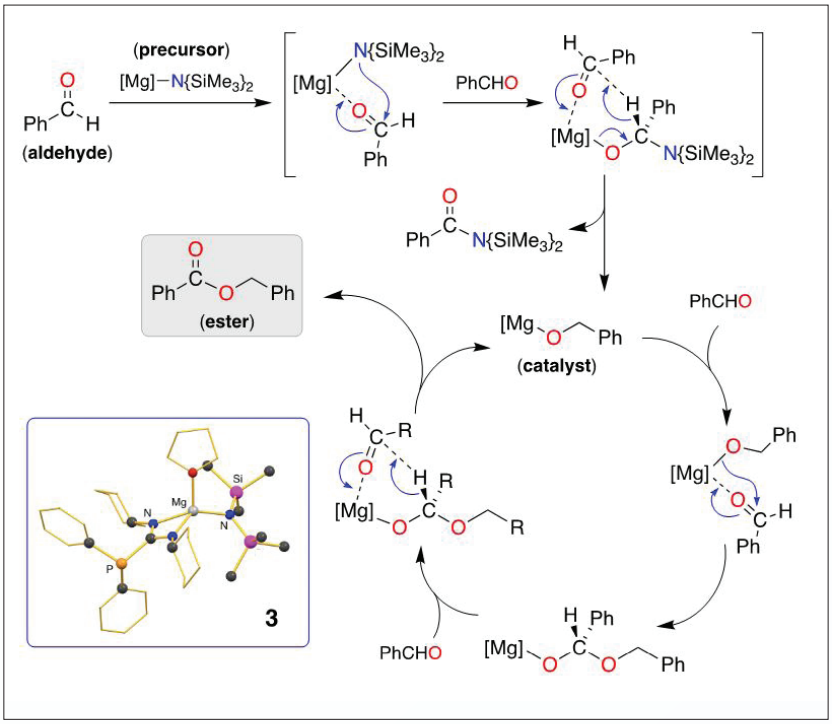
Aside from a few minor projects that involved elements from the s- and p-blocks of the periodic table, such as the development of an '(R_2P)MgBr' phospha-Grignard reagent (**1**, Fig. 1),[17] and the use of N-heterocyclic stannylenes as ligands in platinum hydroformylation chemistry **(2)**,[18] main group chemistry was not the focus of my research until the end of my time at Sussex. At that time a colleague, Prof Mike Hill, was breaking new chemical ground exploring the catalytic potential of the heavier group 2 metals calcium, strontium and barium in a wide range of chemical transformations.[19] To avoid overlap (and to be honest, as the starting materials were cheap…) we initiated a project investigating the potential for magnesium complexes to promote catalytic bond forming reactions.

Magnesium compounds in bond-forming reactions

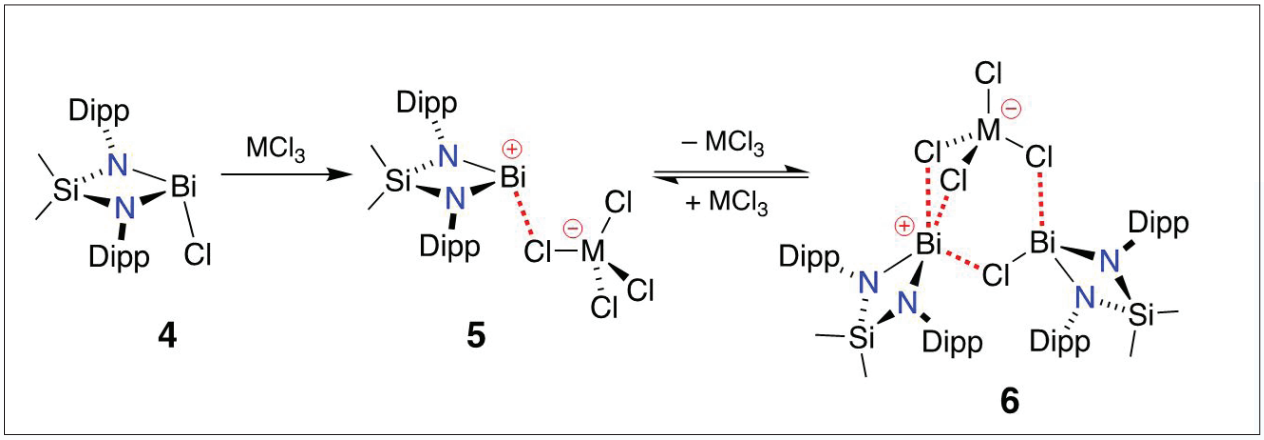
As a cheap, readily available, and essentially non-toxic metal (common justifications for research involving the earth abundant s- and p-block metals), magnesium offers several advantages over the transition metal elements for catalytic applications. However, unlike transition metals that typically engage in redox-based catalysis involving oxidative addition and reductive elimination steps, the +2 oxidation state of the magnesium is maintained during most if not all catalytic cycles. Productive conversion of starting materials into products is therefore achieved by a series of σ-bond metathesis and insertion steps at the metal, forming new bonds while preserving the Mg(II) centre.

The first reaction that we studied using magnesium-based catalysts was the dimerisation of aldehydes, known as the Tishchenko reaction. This industrially important process generates ester compounds via the simultaneous oxidation and reduction of two aldehydes (Scheme 1). We prepared a series of magnesium compounds with either an amidinate,[20] guanidinate[21] or phosphaguanidinate[22] ancillary ligand set to support the metal centre during the reaction, with an active magnesium-aryloxide or -amide group that is the site of initial reactivity. Strictly speaking, these compounds are catalyst precursors that are converted to an active magnesium alkoxide during an activation step. The best results for the dimerisation of benzaldehyde were achieved with the phosphaguanidinate compounds Mg(Ph_2PC{NCy}$_2$)(N{$SiMe_3$}$_2$)(THF) **(3)**, achieving a turnover frequency of up to 360 h^{-1} at 1% loading, with a 60% yield of benzylbenzoate produced in the first 10 minutes of the reaction.[22]

This series of magnesium compounds was also examined for the ability to promote the ring-opening polymerisation (ROP) of lactide to produce polylactic acid (PLA), a thermoplastic polyester derived from renewable resources.[22] Although these complexes were



Scheme 1. Proposed mechanism for the dimerisation of aldehydes (the Tishchenko reaction) promoted by magnesium amidinate, guanidinate and phosphaguanidinate compounds. Inset: X-ray structure of a catalytically active magnesium phosphaguanidinate catalyst precursor (3).



Scheme 2. Formation of cationic bismuth compounds $[Bi(Me_2Si\{NDipp\}_2)][MCl_4]$ (M = Al, Ga) showing the interactions between cation and anion observed in the solid-state

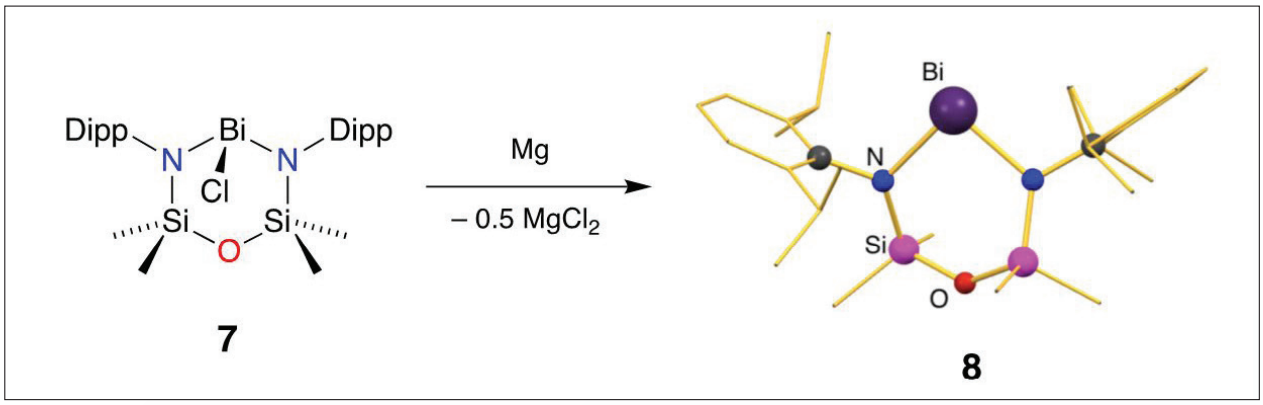
catalytically active for this reaction, with the best performing compound being the dimeric guanidinate complex $[Mg(hpp)(N\{SiMe_3\}_2)]_2$ (hppH = 1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidine) that converted 20 equivalents of lactide to PLA in < 5 minutes at room temperature, monitoring the reaction by ^{1}H NMR spectroscopy showed that the supporting $[hpp]^-$ ligand was released from the magnesium centre as the neutral guanidine hppH during this reaction. This was not ideal, as studies from other groups had shown that this guanidine was a highly active ROP catalyst in its own right,[23] and therefore the observed catalysis may not even be due to our magnesium complex!

The facile loss of the N,N'-chelating ligand from magnesium was an inherent problem with the application of this family of compound in catalysis, which we eventually proved in a series of studies on the hydroacetylenation of carbodiimides.[22,24] In this reaction, a terminal alkyne RC≡CH is coupled with a carbodiimide (R'N=C=NR') to form a propargylamidine RC≡CC(NR')(NHR'). Our initial work focussed on the application of catalyst precursors comprised of a magnesium amide supported by an amidinate ligand $Mg(MesC\{NCy\}_2)(N\{SiMe_3\}_2)(THF)$ (Mes = 2,4,6-$Me_3C_6H_2$), and we were pleased to observe catalytic turnover with this system. However, when we investigated this reaction further, we noted that the supposedly active amide group was not essential for the reaction to proceed and the corresponding bis(amidinate) compounds $Mg(MesC\{NCy\}_2)_2(THF)$ gave identical activity, implying the loss of an amidinate ligand from the metal during the catalysis. Furthermore, we noted that the amidinate ligand could be generated in situ from the insertion of a carbodiimide into a Mg–C bond (or the corresponding guanidinate ligand from the insertion of carbodiimide into a Mg–N bond), so in reality any organo-magnesium reagent has the potential to be used to initiate catalysis. In summary, our carefully designed catalysts were just a way of delivering a soluble magnesium centre with a reactive Mg–C or Mg–N bond, which could be achieved equally well using commercially available compounds such as $MgBu_2$ or MgMeBr. Although not exactly the outcome we anticipated when we started this project, it was an extremely satifying journey to reach these conclusions, and an interesting academic exercise along the way.

Bismuth and antimony: underrepresented heavy metals

Switching from the s-block to the p-block metals (and moving from one of the lightest metals to one of the heaviest), an area of research that began in Sussex but really took off in New Zealand was to study the synthesis, structure, and reactivity of bismuth(III) compounds. From a coordination chemistry standpoint, a major difference when compared to the Mg research described above was the requirement for a dianionic ligand scaffold to balance the charge and generate a reactive Bi–X bond in neutral Bi(III) complexes. As such, we initially examined the application of the silyl(bisamide) ligands $[Me_2Si\{NR\}_2]^{2-}$ that generate a pyramidal, tri-coordinate compound when coordinated to a bismuth(III) centre (**4**, Scheme 2).[25]

Our interest in this family of compounds derived initially from their potential application as Lewis acid catalysts,[26] and early on in this work we sought to enhance any potential catalytic properties by generating cationic bismuth species. This was readily achieved from **4** using $AlCl_3$ or $GaCl_3$ as a halide abstractor, affording salts of the type $[Bi(Me_2Si\{NDipp\}_2)][MCl_4]$ (M = Al, Ga; Dipp = 2,6-$iPr_2C_6H_3$) **(5)**.[27] However, we discovered that these compounds readily form intermolecular Bi···Cl interactions, a phenomenon that was even observed for the neutral compound $Bi(Me_2Si\{NDipp\}_2)Cl$ **(4)**, which formed a trimer in the



Scheme 3. Synthesis of the bismuth(II) radical, [Bi(NONDipp)]• (8)

solid-state.[25] Understandably this aggregation was more prevalent between the cations and anions in the charged $[Bi(Me_2Si\{NDipp\}_2)][MCl_4]$ systems (**5** and **6**, Scheme 2) and, although these interactions were predominantly characterised in the solid state, they suggested that such aggregation was possible in solution that would affect the targeted interaction between bismuth reagent and the substrate of interest.

I would love to claim that to overcome this problem we deliberately targeted a new ligand system that forms a larger metallacycle to increase the steric profile at bismuth, thereby reducing the extent of aggregation. However truth be told, we initially stumbled on a new ligand through an accidental hydrolysis reaction during a ligand preparation, demonstrating once again that serendipity has an important role to play in the physical sciences.

The new ligand system consisted of a bis(amidodimethyl)disiloxane group $[O\{SiMe_2NDipp\}_2]^{2-}$ (abbreviated as $[NON^{Dipp}]^{2-}$), which forms a six-membered OSi_2N_2Bi metallacycle when forming a N,N'-chelate (**7**, Scheme 3). Although this new ligand scaffold did not prevent Bi···Cl interactions between neutral and / or charged species as hoped,[28] it proved to be very good at stabilising highly reactive metals, both in group 15 (Bi, Sb) and more recently in group 13 (In, Al – vide infra).

"... truth be told, we initially stumbled on a new ligand through an accidental hydrolysis reaction during a ligand preparation, demonstrating once again that serendipity has an important role to play in the physical sciences."

Around that time a report appeared in the literature that described the reduction of bismuth(III) compounds supported by the bulky bidentate alkyl, 1,1,4,4-tetrakis(trimethylsilyl) butane-1,4-diyl ($[R_2]^{2-}$).[29] Although the monomeric $[R_2Bi]^{\bullet}$ radical could be detected in solution, it dimerised on crystallisation to form the corresponding dibismuthane $R_2Bi–BiR_2$ containing a Bi–Bi single bond. Using a similar procedure, we examined the reduction of **7** with magnesium to see whether we could isolate the corresponding reduced bismuth complexes. Fortunately for us, the bulk of the $[NON^{Dipp}]$-ligand was sufficient to prevent formation of the dimer and we were able to isolate the first example of a monomeric Bi(II) radical, $[Bi(NON^{Dipp})]^{\bullet}$ (**8**, Scheme 3).[30] To demonstrate that **8** existed as the proposed radical rather than the corresponding Bi(III) hydride $Bi(NON^{Dipp})(H)$ (with an elusive Bi–H hydride ligand), a wide range of techniques were employed including EPR spectroscopy, magnetic measurements and DFT calculations. The data from these analyses confirmed the presence of an unpaired electron that was located primarily at the bismuth atom in the solution and solid states. Indeed, attempts to isolate the proposed hydride failed, and it was shown that the Bi–H bond was unstable at room temperature and underwent bond homolysis to liberate H_2 and form the radical **8**.

Isolable radicals of the heavy main group metal elements are unusual, offering the opportunity to explore the novel reactivity of **8** towards the activation of small molecules. We focused our attention on how the radical interacts with inorganic substrates, including white phosphorus and elemental sulfur.

With the former reaction we observed a reversible activation of one of the P–P bonds of the P_4 tetrahedron, affording the $\mu,\eta^{1:1}$-bicyclo[1.1.0]tetraphosphabutane complex (**9**, Fig. 2).[31] When reacted with S_8, radical **8** gave mixtures of bimetallic $(NON^{Dipp})Bi(\mu\text{-}S_n)Bi(NON^{Dipp})$ (n = 1, 3, 5) compounds in which the bismuth atoms were linked with chains of sulfur atoms.[32] As part of this study we isolated a new derivative of the radical with an even

bulkier [NON^{R}]-ligand containing the 2,6-(Ph$_2$CH)$_2$-4-tBuC$_6$H$_2$ (Ar‡) groups.

When [Bi(NON^{Ar‡})]$^{\bullet}$ (**10** – not shown) is reacted with S_8 the resulting compound contains a group of eight sulfur atoms between the bismuth atoms (**11**). Analysis of the product using X-ray diffraction experiments and density functional theory calculations show that rather than forming a contiguous chain of eight S-atoms linked by S–S bonds, the best description of the S_8-unit is as two $[S_4]^{\bullet-}$ radical anion chains, with the two terminal S-atoms of each chain engaging in a side-on 'pancake' bond.

Once we had established efficient synthetic routes to these bismuth compounds, our attention turned to how we could apply them to catalytic reactions. The first (partial) success was with the hydrophosphination of isocyanates (RN=C=O), a reaction that corresponds to the addition of P–H bond across an unsaturated C=N bond.[33] The catalysts required for this process were well defined terminal phosphanides of general formula Bi(NON^{Dipp})(PR$_2$) (R = Ph, Cy).[31]

Although we were able to demonstrate each step of the catalytic cycle in stoichiometric reactions, extension to a catalytic regime was thwarted by facile homolysis of Bi–P (and/or Bi–H) bonds during the proposed cycle.

The second reaction that we examined was a catalytic oxidative coupling promoted by the bismuth complex, Bi(NON^{Dipp})(OTEMP) (12), which contains an anionic TEMPOxide ligand derived from the stable 2,2,6,6-(tetramethylpiperidin-1-yl) oxyl) radical (Scheme 4).[34] In contrast to the previous examples of catalysis with Mg and Bi that do not involve redox chemistry at the metal, this involves a 1 electron shuttle at the bismuth centre, predicated on the spontaneous homolysis of the Bi–H bond and formation of the radical 8.

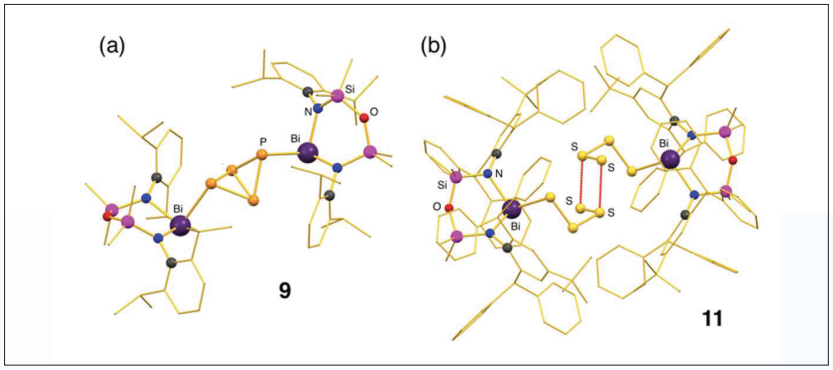
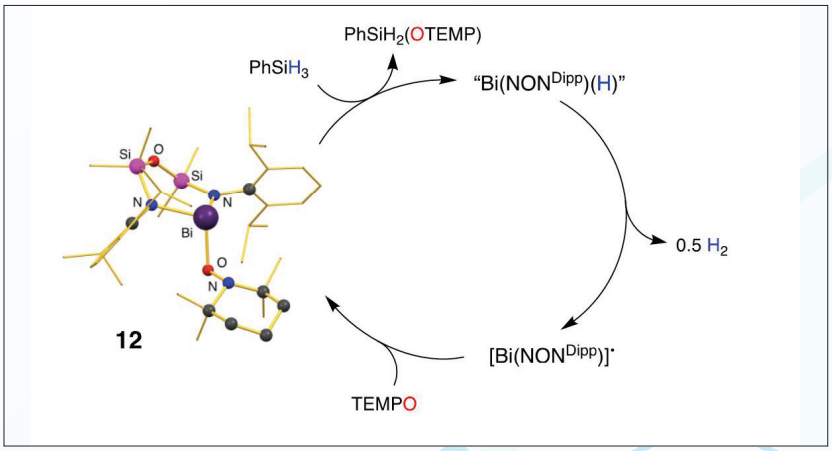


Fig. 2. X-ray structures of the products of the reaction of (a) [Bi(NONDipp)]• (8) with P4, (b) [Bi(NONAr‡)]• (**10**) with S8



Scheme 4. Oxidative coupling of TEMPO and PhSiH$_3$ catalysed by Bi(NON^{Dipp})(OTEMP) (12)

"The switch from bismuth to the lighter congener antimony may be considered as synthetically trivial, but we have discovered several important distinctions in the chemical behaviour of analogous 'Sb(NON^{Dipp}) X' compounds that, in favourable situations, gave improved catalytic performance."

The switch from bismuth to the lighter congener antimony may be considered as synthetically trivial, but we have discovered several important distinctions in the chemical behaviour of analogous 'Sb(NON^{Dipp}) X' compounds that, in favourable situations, gave improved catalytic performance. For example, all attempts at isolating an antimony(II) radical species analogous to [Bi(NON^{Dipp})]• (8) failed, instead generating distibanes with a single Sb–Sb bond between Sb(II) centres or distibenes with a single Sb–Sb bond between Sb(I) centres.[35]

The latter compounds (e.g. 13, Fig. 3) were synthesised when reducing Sb(III) compounds that have bulky R-substituents on the [NON^{R}]-ligand (e.g. R = Dipp, Mes) with Jones' Mg(I) reducing agent,[36] and structural characterisation showed a [NON^{R}]-ligand that bridges antimony and magnesium centres. With respect to catalytic applications, switching from bismuth to antimony allows catalytic turnover in the hydrophosphination of isocyanides.[37] We attribute this to

an increased stability of the Sb–P and Sb–H bonds towards homolysis, with proof of the latter stability obtained from a neutron diffraction study of the isolated antimony hydride Sb(NON^{Dipp})(H), containing a well-defined, terminal hydride ligand.[38]

Indium: low-valent group 13 anions

The isolation of the Bi(II) radical **8** and the interesting reactivity that it displayed towards small molecules sparked our interest in the chemistry of low-valent main group compounds. We switched our attention to group 13 and started a project investigating the chemistry of indium compounds supported by the [NON^{Dipp}]-ligand. Our attention was initially drawn towards a series of low-valent anionic group 13 compounds of general formula [E(L)$_x$]$^-$ (E = group 13 element in +1 oxidation state; (L)$_x$ = supporting dianionic ligand framework), where examples were known for E = boron and gallium. Although indium(I) compounds are relatively common as a consequence of enhanced stability of the low valent state due to the inert pair effect, only neutral In(I) compounds had been reported when we started our work. However, under the correct conditions we were able to show that reduction of the In(III) precursor In(NON^{Dipp})(μ-X)$_2$Li(L)$_2$ (X = Cl, Br; L = Et$_2$O, THF) with alkali metals afforded the indyl anion [In(NON^{Dipp})]$^-$ consisting of a two coordinate In(I) metal centre.[39]

Computational analysis showed that the highest occupied molecular orbital (HOMO) of the [In(NON)]$^-$ anion corresponded to a lone pair at the indium, with good directionality (Scheme 5, inset). Although this compound was initially isolated as the lithium salt (NON^{Dipp})In–Li(THF)$_3$, subsequent work developing the reactivity of this anion focussed on the potassium salt K[In(NON^{Dipp})] (**14**) that provided a more stable source of the anion.

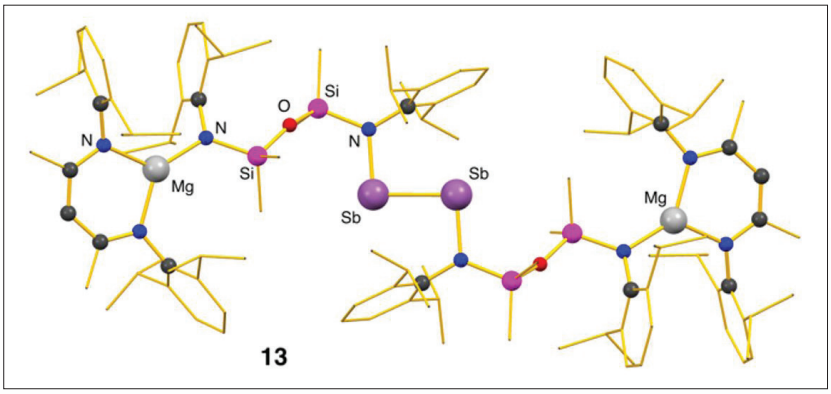
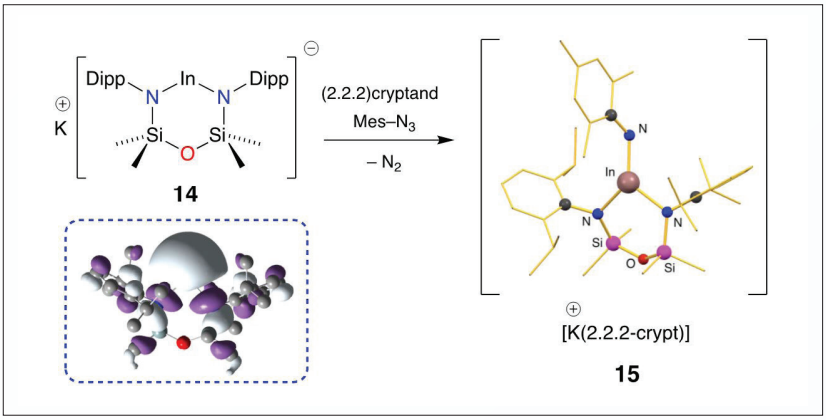


Fig. 3. X-ray structures of a distibene (**13**) containing a Sb=Sb double bond between Sb(I) centres and containing two bridging [NON^{Dipp}]-ligands to magnesium atoms



Scheme 5. Formation of indium-nitrogen multiple bonds from the reduction of organic azides by indyl anion K[In(NON^{Dipp})] (**14**). Inset: HOMO of the [**14**]$^-$ anion, showing lone-pair electron density at indium.

Investigating the reactivity of the indyl anion proved to be very challenging, with many of the compounds extremely sensitive to air / moisture, and possibly even light / temperature. As such we have only conducted preliminary reactivity studies with this system, but have been able to show that the potassium indyl, K[In(NON^{Dipp})] **14** reduces organic azides (R'N$_3$) to form compounds containing rare examples of In=NR' multiple bonds (e.g. **15**, Scheme 5).[40]

An approach that we have used to attenuate the reactivity of the indyl anion is to incorporate it as a ligand at another metal centre, generating heterobimetallic complexes with In–M bonds. We have achieved this with a range of transition metals, and briefly explored the chemistry of the bimetallic indium-zinc complexes (NON^{Dipp})In–Zn(BDI^R) (BDI = β-diketiminate [HC{C(Me)NR}$_2$]$^-$, R = Dipp, Mes) towards organic azides.[41]

The results show that both metals work cooperatively to form different products depending on the nature of the R'-substitute on the azide and the R-group on the [BDI^R]-ligand, with documented examples of reduction to form a bridging imide (R = R' = Mes), formation of a tetrazenido ring at aluminium (R = Mes, R' = Ph), and coupling of two azides via a new N–N bond to give the [PhNNNNNNPh]$^{2-}$ hexaazide ligand.

Aluminium: bond activation and bond forming chemistry of the aluminyl anion

The latest chapter in our research featuring the main group elements has focused on the chemistry of the aluminyl anion [Al(NON^{Dipp})]$^-$, which

is the lighter congener of the indyl anion described previously.[42] When discovered in 2018, this class of compound set a new precedent in aluminium chemistry by switching the mode of reactivity for this element from being typically associated with Lewis acidic behaviour, to displaying nucleophilic characteristics associated with the presence of the lone-pair of electrons at the metal centre.[43] The $[Al(NON^{Dipp})]^-$ anion is one of only six examples of this class of compound that has been isolated,[42,44] and displays the correct balance of kinetic stability imposed by the chelating $[NON^{Dipp}]$-ligand and reactivity of the accessible aluminium(I) centre.

We have isolated a series of compounds of general formula $[\{M(L)_x\}\{Al(NON^{Dipp})\}]_n$ (M = Li, Na, K, {Rb, Cs}; L = neutral donor; n = 1 or 2) that differ in the interaction(s) between the alkali metal (M) and the aluminyl anion (the contacted dimeric pairs $[M\{Al(NON^{Dipp})\}]_2$ (M = Rb, Cs) were synthesised in a collaborative project with Professor Robert (Rab) Mulvey at the University of Strathclyde, Scotland[45]). We have classified these different structural classes as being either contacted dimeric pairs (CDPs), monomeric ion pairs (MIPs) or separated ion pairs (SIPs),[45-46] shown in Fig. 4 for the series of potassium aluminyls, $[K\{Al(NON^{Dipp})\}]_2$ (CDP, **16**), $(NON^{Dipp})Al$–K(18-crown-6) (MIP, **17**), and [K(2.2.2)-crypt][$Al(NON^{Dipp})$] (SIP, **18**).

The most common structural variant is the CDP that has been isolated for all of the non-radiative alkali metals Li-Cs, and of this series the research has concentrated predominantly on the potassium salt. In addition to the solid-state structure that shows a dimeric structure in which the cations are held in place by flanking M···π(arene) interactions, diffusion ordered NMR spectroscopy has shown that the CDPs $[M\{Al(NON^{Dipp})\}]_2$ retain their dimeric structure in solution.

The MIPs have been isolated for M = Li, Na and K and contain highly polarised Al–M bonds within their structure. The most reactive of these three classes are those in which the cation is encapsulated to remove all of the Al···M interactions, generating a 'naked' aluminyl anion. We have achieved this using either two equivalents of TMEDA or 12-crown-4 (M = Li) or 2.2.2-cryptand (M = Na, K). Aside from the structural differences, we are beginning to gain an understanding of how the nature and extent of the Al/M interactions can influence the reactivity of the $[Al(NON^{Dipp})]^-$ anion.

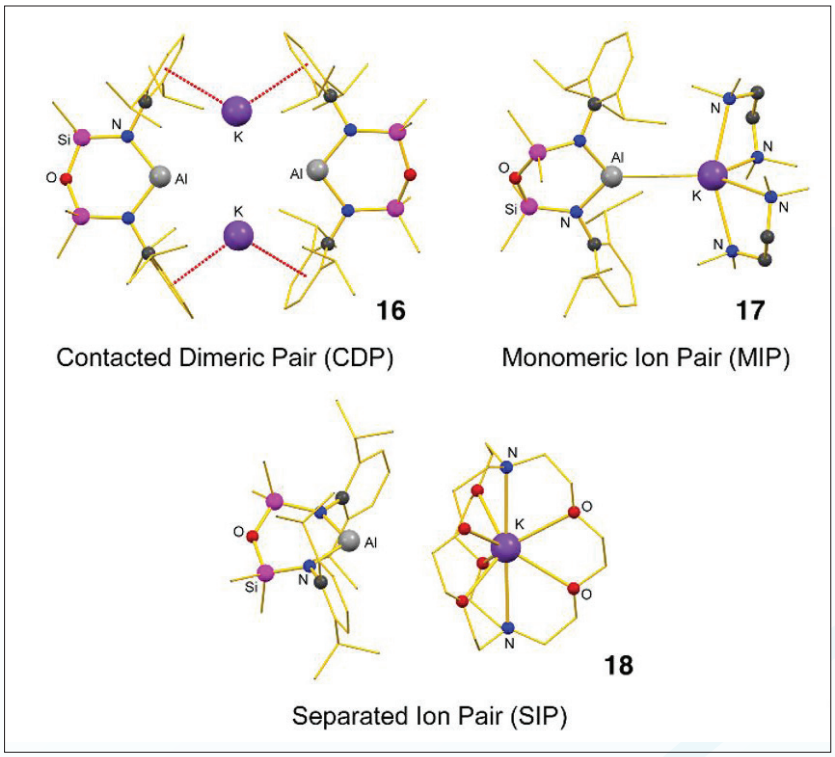


Fig. 4. A series of potassium aluminyls showing a contacted dimeric pair (CDP) $[K\{Al(NON^{Dipp})\}]_2$ (**16**), a monomeric ion pair (NON^{Dipp})Al-K(18-crown-6) (**17**), and a separated ion pair (SIP) [K(2.2.2)-crypt][$Al(NON^{Dipp})$] (**18**)

A readily accessed mode of activity at the low-valent Al(I) centre is oxidative addition to form the corresponding Al(III) compounds. We have focused our attention on E-H bonds and shown that this will occur independent of the polarity of the bond.[47] For example, the hydridic Si–H bond of $PhSiH_3$ will add effectively to the aluminyl anion in **16** to give $K[Al(NON^{Dipp})(H)(SiH_2Ph)]$ (**19**, Scheme 6) and the acidic N–H bond of $DippNH_2$ reacts in a parallel fashion to form $K[Al(NON^{Dipp})(H)(NHDipp)]$ (**20**).

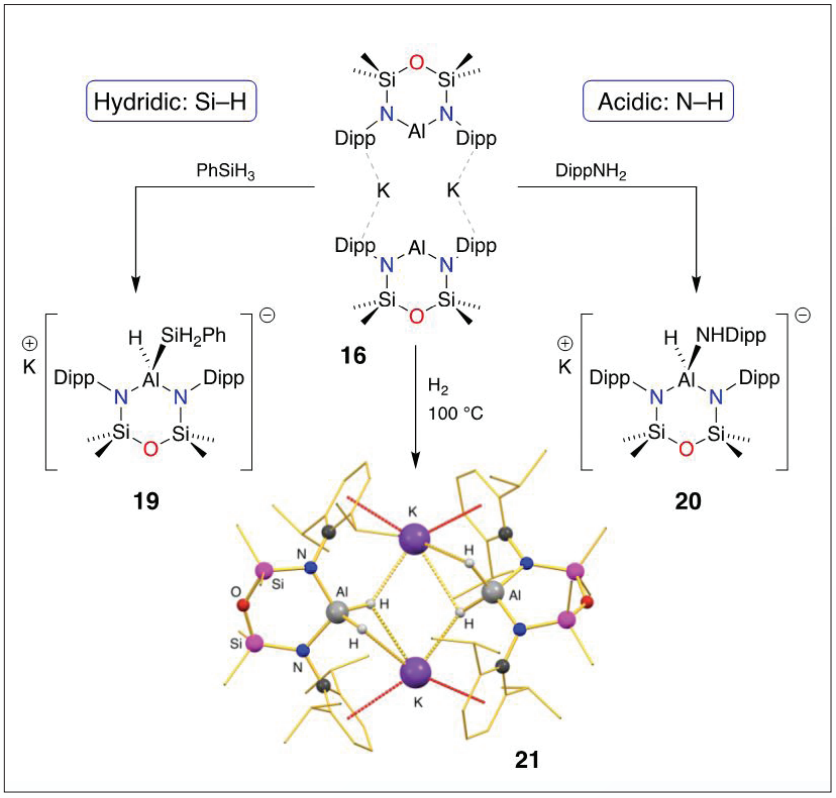
Turning our attention to non-polar bonds we investigated the reaction with dihydrogen, H_2. We found that although our aluminyls are reactive, they require considerably harsher conditions to activate the H–H bond.[46] This was quantified using the time taken for 50% conversion ($t_{1/2}$) as an approximate measure of the rate of the reaction, with the hydrogenation proceeding in the order Li ($t_{1/2}$ = 1.5 days) > Na ($t_{1/2}$ = 6 days) > K ($t_{1/2}$ = 12 days) at 100 °C. The dihydroaluminate products formed have been isolated as either the dimer (M = K (**21**), Scheme 6) or the solvated species $(NON^{Dipp})Al(\mu\text{-}H)_2Li(OEt_2)_2$, and a study of the reactivity of the Al–H bonds towards organic substrates is an ongoing area of interest.

Another new area that we have been able to explore with the aluminyl anions is the chemistry of well-defined Al–E multiple bonds. For the

group 15 element E = nitrogen, we have shown that, in an analogous reaction to that noted for the indyl anion (Scheme 5), CDP **16** reacts with $MesN_3$ to afford K[Al(NON^{Dipp})(NMes)] (**22** – not shown) containing a terminal aluminium imide bond.[48] DFT calculations indicated showed that the HOMO–1 is dominated by lobes orthogonal to the HOMO that extend across the Al–N_{imide} bond, indicative of multiple bond character. Furthermore, the reaction of **22** with CO_2 afforded the corresponding aluminium carbamate, K[Al(NON^{Dipp})(κO,N-OC{O}NMes)], consistent with a [2+2]-cycloaddition of a C=O bond from CO_2 with a Al=NMes group.

We have also developed synthetic compounds containing Al=E multiple bonds for the series of chalcogens, E = O, S, Se and Te. The synthesis of the heavier congeners E = Se,[49] Te[50] was achieved using a direct reaction with the elemental chalcogen, whereas the oxide (E = O) was formed when potassium aluminyl **16** reacted with N_2O,[51] and the sulfide (E = S) was accessed from a desulfurisation reaction of K[Al(NON^{Dipp})(cyclo-S_4)] using PPh_3.[52] Once again DFT calculations suggested multiple bond character, and the reaction with CO_2 (E = O, S, Se) afforded the aluminium carbonate derivatives K[Al(NON^{Dipp})(κE,O-EC{O}O)] consistent with [2+2]-cycloaddition (**23**, Fig. 5). Interestingly, when E = Te, we were unable to isolate the monoaddition product "K[Al(NON^{Dipp})(κTe,O-TeC{O}O)]", but instead the reaction proceeded to afford the bis-addition product K[Al(NON^{Dipp})(κO,O'-{OC(O)}$_2$Te)], containing a unique example of the tellurodicarbonate (telluramalonate) ligand (**24**).[50]

Most recently we have expanded this study to the addition of aldehydes and ketones to K[Al(NON^{Dipp})(E)] (E = S, Se), with a goal of developing reagents for the delivery of chalcogen atoms 'E' to organic compounds.[52] Work showed that the C=O bond of the aldehyde and ketone reacted in an analogous [2+2]-cycloaddition



Scheme 6. Oxidative addition chemistry of the potassium aluminyl, [K{Al(NON^{Dipp})}]$_2$ (**16**)

"We were extremely encouraged by the reaction described in Scheme 7 as it involves activation of the C≡O triple bond of carbon monoxide, acknowledged as one of the strongest bonds in nature."

mode to that observed for CO_2, with the product incorporating either one (e.g. benzophenone, Ph_2CO; **25**) or two (e.g. benzaldehyde, PhHCO; 26) equivalents in the product, corresponding to the formation of one or two new C–E bonds, respectively.

A final reaction involving the alumoxane [K{Al(NON^{Dipp})(O)}]$_2$ (**27**) that extends this area to the formation of compounds containing new carbon-carbon bonds was the synthesis of the ethenetetraolate compound **28** from the reaction with CO gas (Scheme 7).[53] DFT calculations performed by our collaborator Dr Claire McMullin from the University of Bath in the UK showed that the reaction proceeded via an initial cycloaddition reaction at one of the aluminium centres in **27** to form a dioxocarbene species. This intermediate reacts with a second molecule of CO at the carbenic carbon atom to generate a bent aluminium ketene complex that undergoes a second cycloaddition reaction between the terminal C=O bond and the intact Al=O group. The resulting $[C_2O_4]^{4-}$ ligand is the first example of a tetraolate ligand in coordination chemistry.

We were extremely encouraged by the reaction described in Scheme 7 as it involves activation of the C≡O triple bond of carbon monoxide, acknowledged as one of the strongest bonds in nature. We therefore sought to see whether we could utilise this toxic gas in the direct carbonylation of unsaturated organic functional groups.

Accordingly, we have shown that adding CO to an alumincyclopropane complex **29** (formed on exposure of 16 to ethylene gas) gives the carbonylation product (**30**, Scheme 8).[54] Furthermore, heating **30** induces a 1,2-hydrogen shift and ring-expansion to afford **31** whilst maintaining the integrity of the C–C bonds formed in the initial step. This carbonylation is non-reversible and occurs at room temperature under 1 atmosphere of CO, showing that only mild conditions are required to promote this reaction.

Finally, we have very recently shown that CO will react directly with aluminyl compounds, forming a series of products containing the $[C_nO_n]^{n-}$ ligand (Fig. 6).[55] To date we have isolated three consecutive members of the series **32** (n = 3), **33** (n = 4) and **34** (n =5), representing a sequence in CO homologation. Once again this occurs under ambient conditions and is of potential importance in understanding chain growth in Fischer-Tropsch chemistry, an industrially important process that transforms CO and H_2 into liquid hydrocarbon and oxygenates.

Summary

In the last decade or so, we have been expanding the chemistry of selected main group elements and examining new areas of bond formation / cleavage, principally accessed through the isolation of compounds in unusual (low valent) oxidation states. We have developed new types of reactivity associated with the activation of very stable bonds and are beginning to apply these reactions in the formation of previously inaccessible compounds.

Along the way we have learned a great deal about the fundamental chemistry associated with these elements and hopefully have laid to rest the idea that these are 'boring elements that don't do anything exciting….'

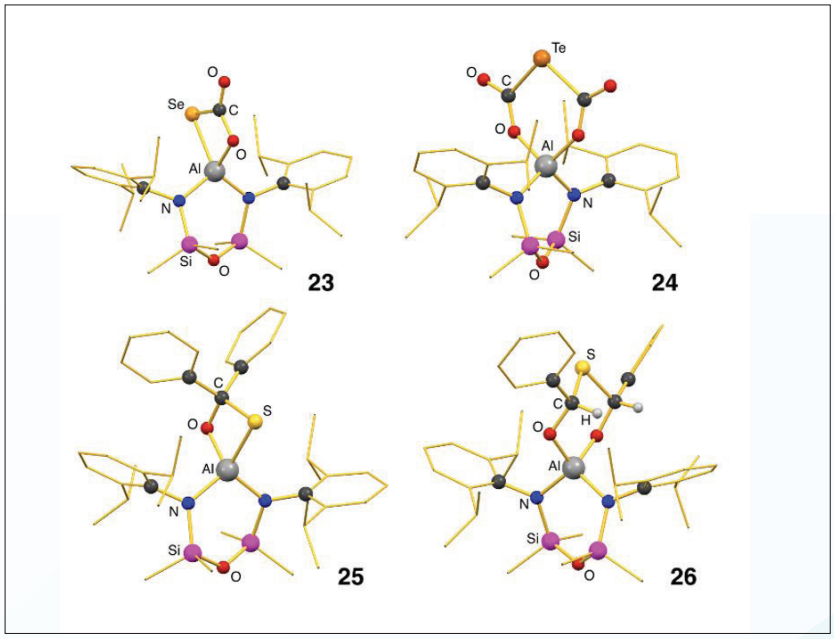
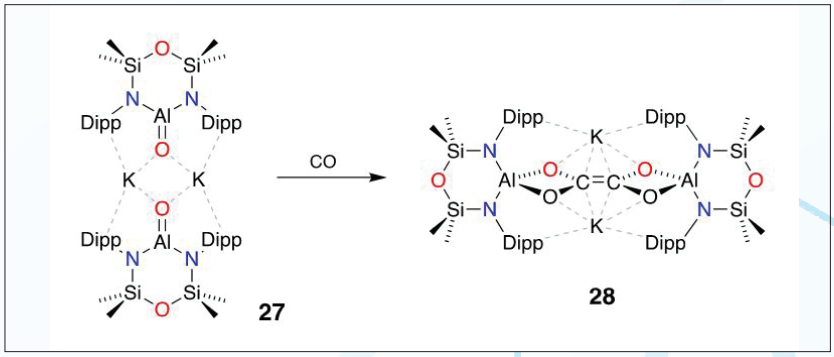
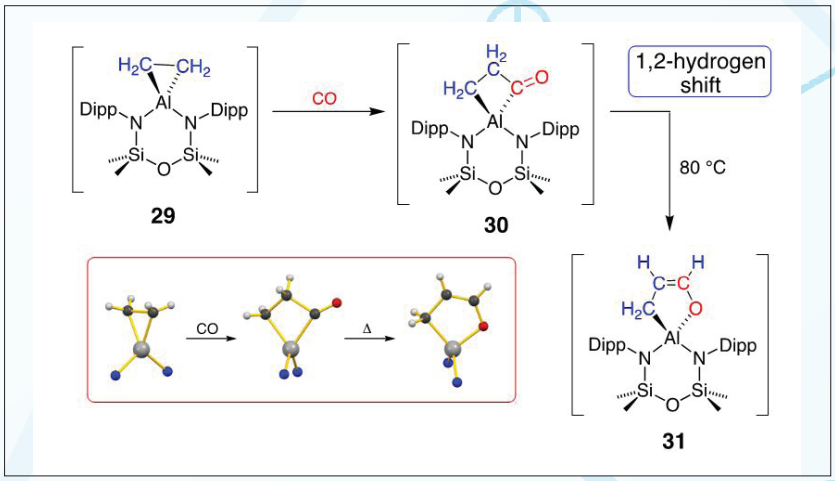


Fig. 5. Anionic components of the products of the addition of organic compounds containing C=O bonds to K[Al(NON^{Dipp})(E)] (E = S, Se, Te)



Scheme 7. Formation of the tetraolate ligand, $[C_2O_4]^{4-}$ from the reaction of a dimeric alumoxane (**27**) with carbon monoxide gas



Scheme 8. Carbonylation chemistry promoted by a potassium aluminyl species, (NON^{Dipp})Al-K(18-crown-6). Inset: Partial crystal structures showing the conversion of 'CH_2CH_2' (**29**) to 'CH_2CH_2CO' (**30**) to '$CH_2CH{=}CHO$' (**31**).

Acknowledgements

None of this work would have been achieved without the help of extremely talented students and collaborators. Special mention to the workers in the lab Dr Ben Day (Sussex), Dr Ryan Schwamm, Dr Mat Anker and Matt Evans (VUW) for their ability to synthesise, manipulate and characterise extremely reactive compounds.

Also, thanks to A/Prof Chris Fitchett whose crystallographic skills helped us to establish ourselves in this area when we first moved to New Zealand. Current collaborations with Dr Claire McMullin (computational) and Prof Rab Mulvey (Rb, Cs chemistry) will hopefully lead to many more exciting discoveries. Acknowledgement also to funding from the Marsden Fund Council, managed by Royal Society Te Apārangi (Grant Number: MFP-VUW2020) and the MacDiarmid Institute for Advanced Materials and Nanotechnology.

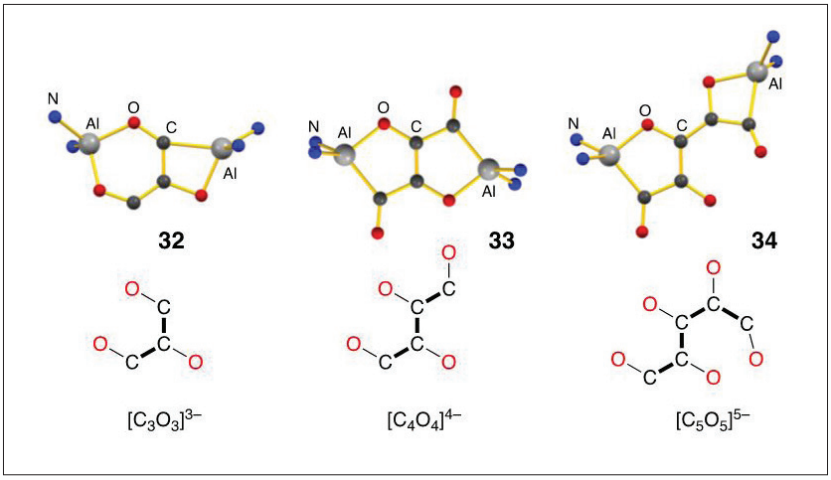


Fig. 6. Partial crystal structures of products containing $[C_3O_3]^{3-}$, $[C_4O_4]^{4-}$ and $[C_5O_5]^{5-}$ chains formed via CO homologation (anionic component only)

References

1. Coles, M. P.; Dalby, C. I.; Gibson, V. C.; Clegg, W.; Elsegood, M. R. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1709-1711. Coles, M. P.; Dalby, C. I.; Gibson, V. C.; Little, I. R.; Marshall, E. L.; Ribeiro da Costa, M. H.; Mastroianni, S. *J. Organomet. Chem.* **1999**, *591*, 78-87.
2. Uhrhammer, R.; Black, D. G.; Gardner, T. G.; Olsen, J. D.; Jordan, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 8493-8494.
3. Coles, M. P.; Jordan, R. F. *J. Am. Chem. Soc.* **1997**, *119*, 8125-8126.
4. Dagorne, S.; Guzei, I. A.; Coles, M. P.; Jordan, R. F. *J. Am. Chem. Soc.* **2000**, *122*, 274-289.
5. Aeilts, S. L.; Coles, M. P.; Swenson, D. C.; Jordan, R. F.; Young, V. G. *Organometallics* **1998**, *17*, 3265-3270.
6. Radzewich, C. E.; Coles, M. P.; Jordan, R. F. *J. Am. Chem. Soc.* **1998**, *120*, 9384-9385.
7. Coles, M. P.; Hitchcock, P. B. *Organometallics* **2003**, *22*, 5201-5211.
8. Evans, L. T. J.; Coles, M. P.; Cloke, F. G. N.; Hitchcock, P. B. *Inorg. Chim. Acta* **2010**, *363*, 1114-1125.
9. Oakley, S. H.; Coles, M. P.; Hitchcock, P. B. *Inorg. Chem.* **2003**, *42*, 3154-3156.
10. Coles, Martyn P.; Hitchcock, Peter B. *Eur. J. Inorg. Chem.* **2004**, *2004*, 2662-2672.
11. Arnold, J. *Dalton Trans.* **2008**, 4334-4335.
12. Weetman, C.; Inoue, S. *ChemCatChem* **2018**, *10*, 4213-4228. Power, P. P. *Nature* **2010**, *463*, 171-177.
13. Power, P. P. *Chem. Rev.* **1999**, *99*, 3463-3504. Fischer, R. C.; Power, P. P. *Chem. Rev.* **2010**, *110*, 3877-3923.
14. Hobson, K.; Carmalt, C. J.; Bakewell, C. *Chem. Sci.* **2020**, *11*, 6942-6956.
15. Bag, P.; Ahmad, S. U.; Inoue, S. *Bull. Chem. Soc. Jpn.* **2016**, *90*, 255-271.
16. Power, P. P. *Chem. Rev.* **2003**, *103*, 789-810.
17. Day, B. M.; Coles, M. P. *Eur. J. Inorg. Chem.* **2010**, *2010*, 5471-5477.
18. Day, B. M.; Dyer, P. W.; Coles, M. P. *Dalton Trans.* **2012**, *41*, 7457-7460.
19. Hill, M. S.; Liptrot, D. J.; Weetman, C. *Chem. Soc. Rev.* **2016**, *45*, 972-988. Barrett, A. G. M.; Crimmin, M. R.; Hill, M. S.; Procopiou, P. A. *Proc. R. Soc. A* **2010**, *466*, 927-963.
20. Day, B. M.; Knowelden, W.; Coles, M. P. *Dalton Trans.* **2012**, *41*, 10930-10933.
21. Day, B. M.; Mansfield, N. E.; Coles, M. P.; Hitchcock, P. B. *Chem. Commun.* **2011**, *47*, 4995-4997.
22. Schwamm, R. J.; Day, B. M.; Mansfield, N. E.; Knowelden, W.; Hitchcock, P. B.; Coles, M. P. *Dalton Trans.* **2014**, *43*, 14302-14314.
23. Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 4556-4557.
24. Schwamm, R. J.; Coles, M. P. *Organometallics* **2013**, *32*, 5277-5280.
25. Day, B. M.; Coles, M. P. *Organometallics* **2013**, *32*, 4270-4278.
26. Lopez, E.; Thorp, S. C.; Mohan, R. S. *Polyhedron* **2022**, 115765.
27. Schwamm, R. J.; Day, B. M.; Coles, M. P.; Fitchett, C. M. *Inorg. Chem.* **2014**, *53*, 3778-3787.
28. Schwamm, R. J.; Coles, M. P.; Fitchett, C. M. *Dalton Trans.* **2017**, *46*, 4066-4074.
29. Ishida, S.; Hirakawa, F.; Furukawa, K.; Yoza, K.; Iwamoto, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 11172-11176.
30. Schwamm, R. J.; Harmer, J. R.; Lein, M.; Fitchett, C. M.; Granville, S.; Coles, M. P. *Angew. Chem. Int. Ed.* **2015**, *54*, 10630-10633.
31. Schwamm, R. J.; Lein, M.; Coles, M. P.; Fitchett, C. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 14798-14801.
32. Schwamm, R. J.; Lein, M.; Coles, M. P.; Fitchett, C. M. *J. Am. Chem. Soc.* **2017**, *139*, 16490-16493.
33. Schwamm, R. J.; Fulton, J. R.; Coles, M. P.; Fitchett, C. M. *Dalton Trans.* **2017**, *46*, 2068-2071.

34. Schwamm, R. J.; Lein, M.; Coles, M. P.; Fitchett, C. M. *Chem. Commun.* **2018**, *54*, 916-919.

35. Schwamm, R. J.; Coles, M. P. *Chem. Eur. J.* **2019**, *25*, 14183-14191.

36. Jones, C. *Nat. Rev. Chem.* **2017**, *1*, 0059.

37. Schwamm, R. J.; Coles, M. P. *Eur. J. Inorg. Chem.* **2022**, e202200064.

38. Schwamm, R. J.; Edwards, A. J.; Fitchett, C. M.; Coles, M. P. *Dalton Trans.* **2019**, *48*, 2953-2958.

39. Schwamm, R. J.; Anker, M. D.; Lein, M.; Coles, M. P.; Fitchett, C. M. *Angew. Chem. Int. Ed.* **2018**, *57*, 5885-5887.

40. Anker, M. D.; Lein, M.; Coles, M. P. *Chem. Sci.* **2019**, *10*, 1212-1218.

41. Anker, M. D.; Altaf, Y.; Lein, M.; Coles, M. P. *Dalton Trans.* **2019**, *48*, 16588-16594.

42. Schwamm, R. J.; Anker, M. D.; Lein, M.; Coles, M. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 1489-1493.

43. Hicks, J.; Vasko, P.; Goicoechea, J. M.; Aldridge, S. *Angew. Chem. Int. Ed.* **2021**, *60*, 1702-1713.

44. Hicks, J.; Vasko, P.; Goicoechea, J. M.; Aldridge, S. *Nature* **2018**, *557*, 92-95. Schwamm, R. J.; Coles, M. P.; Hill, M. S.; Mahon, M. F.; McMullin, C. L.; Rajabi, N. A.; Wilson, A. S. S. *Angew. Chem. Int. Ed.* **2020**, *59*, 3928-3932. Kurumada, S.; Takamori, S.; Yamashita, M. *Nat. Chem.* **2020**, *12*, 36-39. Koshino, K.; Kinjo, R. *J. Am. Chem. Soc.* **2020**, *142*, 9057-9062. Grams, S.; Eyselein, J.; Langer, J.; Färber, C.; Harder, S. *Angew. Chem. Int. Ed.* **2020**, *59*, 15982-15986.

45. Gentner, T. X.; Evans, M. J.; Kennedy, A. R.; Neale, S. E.; McMullin, C. L.; Coles, M. P.; Mulvey, R. E. *Chem. Commun.* **2022**, *58*, 1390-1393. Evans, M. J.; Anker, M. D.; Gardiner, M. G.; McMullin, C. L.; Coles, M. P. *Inorg. Chem.* **2021**, *60*, 18423-18431.

46. Evans, M. J.; Anker, M. D.; McMullin, C. L.; Neale, S. E.; Coles, M. P. *Angew. Chem. Int. Ed.* **2021**, *60*, 22289-22292.

47. Evans, M. J.; Anker, M. D.; Coles, M. P. *Inorg. Chem.* **2021**, *60*, 4772-4778.

48. Anker, M. D.; Schwamm, R. J.; Coles, M. P. *Chem. Commun.* **2020**, *56*, 2288-2291.

49. Anker, M. D.; Coles, M. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 13452-13455.

50. Evans, M. J.; Anker, M. D.; McMullin, C. L.; Rajabi, N. A.; Coles, M. P. *Chem. Commun.* **2021**, *57*, 2673-2676.

51. Anker, M. D.; Coles, M. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 18261-18265.

52. Evans, M. J.; Anker, M. D.; McMullin, C. L.; Neale, S. E.; Rajabi, N. A.; Coles, M. P. *Chem. Sci.* **2022**, *13*, 4635-4646.

53. Anker, M. D.; McMullin, C. L.; Rajabi, N. A.; Coles, M. P. *Angew. Chem. Int. Ed.* **2020**, *59*, 12806-12810.

54. Evans, M. J.; Neale, S. E.; Anker, M. D.; McMullin, C. L.; Coles, M. P. *Angew. Chem. Int. Ed.* **2022**, *61*, e202117396.

55. Evans, M. J.; Gardiner, M. G.; Anker, M. D.; Coles, M. P. *Chem. Commun.* **2022**, *58*, 5833-5836.

Article

Nelliellosides: protein kinase inhibitory nucleosides from the understudied phylum Bryozoa

BROOKE D. NICHOLLS*, JOE BRACEGIRDLE, ROBERT A. KEYZERS AND JOANNE E. HARVEY

School of Chemical and Physical Sciences, Victoria University of Wellington, Wellington 6012 (email: nicholbroo@myvuw.ac.nz)

Keywords: *natural product, bryozoan, nucleoside, protein kinase inhibition*

Introduction

Aberrant protein kinase activity has been implicated in a wide range of diseases spanning the human body.[1-6] The development of inhibitors to ameliorate this behaviour is a growing area of research, with the majority of clinically approved protein kinase inhibitors used in cancer therapy.[1-5] Despite advances in computational tools[7] and diversity-oriented synthesis,[8] natural products remain a dominant source of new drug scaffolds.[9] Over half of small-molecule therapeutics approved since 1981 are natural compounds, their direct derivatives or compounds inspired by them.[9] Indeed, these categories contribute 79% of anticancer therapeutics.[9] Our recent isolation of two nucleoside natural products from a Pacific bryozoan and discovery of their kinase inhibitory activities[10-11] has prompted this review.

Protein kinases in disease

Adenosine triphosphate (ATP, **1**) is a critical metabolite employed by human cells to power essential life processes such as cell signalling,[3,12-13] using energy released by the cleavage of a high-energy phosphate bond (Fig. **1**).[14] ATP often adopts the role of organic cofactor in enzymes, the biomachinery in these important processes.[2,14] Protein kinases are enzymes that transfer a phosphoryl group to the awaiting hydroxyl of an amino acid residue (tyrosine, threonine or serine) on a signalling protein.[15-16] This modulates the protein substrate's behaviour and downstream effects.[13] The reverse process is catalysed by protein phos-

■ **Brooke Nicholls** completed her undergraduate studies (BSc, majoring in chemistry and cell and molecular bioscience) at Victoria University of Wellington (VUW). She recently submitted her MSc thesis in organic synthesis, focussing on the development of kinase inhibitors, under the supervision of Associate Professors Joanne Harvey and Robert Keyzers. Brooke is currently employed at VUW as a research assistant, working on the separation of enantiomers by diastereomeric salt formation.

■ **Joe Bracegirdle** completed his BSc(Hons) and PhD at Victoria University of Wellington, with research supervised by Associate Professor Rob Keyzers focusing on chemistry-guided isolation of new biologically active marine natural products. Joe has been undertaking post-doctoral work at University of South Florida with Prof Bill Baker and is about to take up a post-doctoral position at University of Western Australia working with Dr Heng Chooi studying the biosynthesis of complex natural products.

■ **Rob Keyzers** carried out his BSc(Hons) and PhD studies at Victoria University of Wellington. His thesis research, carried out under the guidance of Assoc. Prof. Peter Northcote, focused on spectroscopy-guided isolation of sponge metabolites. He then carried out post-doctoral research with Mike Davies-Coleman (Rhodes University, South Africa) and Raymond Andersen (University of British Columbia, Canada) before a short role as a flavour and aroma chemist at CSIRO in Adelaide, Australia. He was appointed to the faculty at his alma mater in 2009 where he is currently an Associate Professor.

■ **Joanne Harvey** completed a BSc(Hons) at VUW in 1995, including a research project in carbohydrate chemistry supervised by Professor Robin Ferrier, before heading to Canberra to undertake a PhD in chemistry (1997–2000) at the Australian National University under the supervision of Professor Martin Banwell, focussed on cyclopropane reactivity. Subsequent post-doctoral work in natural product synthesis with Professor Richard Taylor at the University of York, UK (2000–2004) was supported by Anglo-Australian and Sir William Ramsay Memorial Trust Post-doctoral Fellowships. In 2004, Joanne returned to Aotearoa NZ to take up an academic role at VUW, with teaching and research focused around organic synthesis.

phatases.[16-17] Together these operations result in complex patterns of phosphorylation found across all of life's Kingdoms,[18] regulating the innate and complex biochemical networks.[2-3,13,15,17] The human body relies on more than 500 protein kinases working in interconnected pathways to control the intricate details of our physiology.[13] As a result, human health can be jeopardised in a myriad of ways when the functional integrity of kinases is compromised.[2,15,17,19]

Mutation, overexpression or amplification of protein kinases resulting in increased or aberrant activity has been correlated with devastating phenotypic consequences.[3,17,20] Kinases exhibiting such detrimental behaviour may therefore be targeted by small-molecule therapeutics.[3,17,20-21] In 2002, Manning et al. mapped 244 protein kinases to loci and amplicons associated with disease.[13]

Developing inhibitors of these enzymes is a rapidly expanding research space, with kinases constituting up to one-third of all current therapeutic targets under investigation.[3-4,17,20] While new drug targets are continuously sought,[1] efforts are also needed to improve upon the antagonism of established kinase targets by either optimising the selectivity and/or potency of inhibition,[2,4,20,22] overcoming resistance to inhibitors,[23-24] and by reducing the costs of marketed pharmaceuticals.[25]

Protein kinases have an especially strong pathological association with cancer due to their comprehensive involvement in cell differentiation, growth, survival, and motility.[17,20] Kinase hyperactivity amplifies these processes and causes tumour formation and metastasis.[6,17,20]

The receptor tyrosine kinase (RTK) family is notorious for its involvement in this, with the majority of its members identified in mutant form spanning several cancers.[6] For example, increased activity by the epidermal growth factor receptor (EGFR) subfamily of RTKs occurs in non-small-cell lung cancers[26] and up to 50% of glioblastomas[27] and 82% of colorectal cancers.[6,28] Aside from cancer, destructive protein kinase activity is also linked to various metabolic,[29] cardiovascular,[30] neurological,[31-32] infectious[33] and immune-related conditions.[1,34]

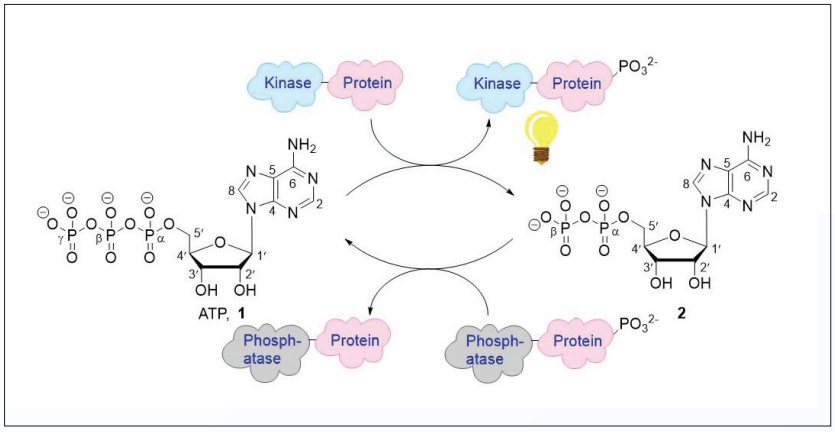


Fig. 1. Kinase-mediated protein phosphorylation using the coenzyme ATP

"Developing inhibitors of these enzymes is a rapidly expanding research space, with kinases constituting up to one-third of all current therapeutic targets under investigation."

Several of these conditions are listed in the top twenty most fatal diaseses by the World Health Organization,[35] notably including HIV and AIDS,[36] tuberculosis,[33] diabetes mellitus[29] and dementia.[37] Mitogen-associated protein kinases (MAPKs) and Janus kinases (JAKs) are two key kinase families involved in the immune responses and the repurposing of known inhibitors of these families continues to be investigated for treating COVID-19 symptoms in the on-going pandemic.[38-39]

However, despite the growing interest and extensive efforts to develop kinase inhibitors, just 20% of the human kinome is targeted by the 71 small-molecule inhibitors approved by the United States Food and Drug Administration as of mid-2021.[2] This leaves considerable room for growth in the development of kinase inhibitors.

Kinase inhibitors

Protein kinase inhibitors can be broadly assigned as reversible and irreversible (covalent) inhibitors[4,40-42] according to their interactions with the target, although the intermediate class of reversible covalent inhibitors is also noted.[2,21,43]

Reversible inhibitors, which constitute the majority of clinically approved kinase inhibitors, interact with the target binding site through non-covalent attractions and complementarity of size and shape.[4-5,21,41] This mode of inhibition is relevant for all protein kinases and gives an opportunity for both controlled and selective inhibition.[21]

The latter can, however, be challenging due to highly conserved features of protein kinases, particularly at the ATP-binding site where the majority of reversible inhibitors bind.[21,41-42] Conversely, irreversible kinase inhibitors form a covalent bond via a suitably positioned and compatible nu-

cleophilic residue that is accessible to the inhibitor.[1,21,44] These covalent inhibitors are typically Michael acceptors, soft α,β-unsaturated carbonyl electrophiles, most commonly acrylamides, due to their metabolic stability and tunable reactivity with soft cellular nucleophiles – predominantly cysteine residues.[2,21,43] An initial reversible association of other motifs in the inhibitor with the protein binding site positions the electrophile for covalent bond formation (Fig. 2).[1,5,21,43]

Each mode of inhibition carries its own advantages and disadvantages.[1,5,21,43] Covalent-binding kinase inhibitors are gaining prominence due to their benefits in binding strength and duration, with several gaining clinical approval in recent years.[1,5,21,43] These qualities confer several advantages over reversible inhibitors, such as potency and extended time prior to the restoration of kinase activity - the latter requires protein re-synthesis.[1,5,21,43] In turn, these benefits can reduce the necessary dosage and frequency of treatment.[5,21,43] Because the covalent bond has a more significant contribution to drug potency,[43] irreversible inhibitors may target more narrow and challenging sites, allowing the design of smaller inhibitors that are more synthetically tractable and more likely to exhibit favourable pharmacokinetic properties.[21]

Additionally, mutations at the kinase binding site (including those that modify the kinase conformation) may also be well-tolerated provided the covalently targeted residue remains available.[21] However, a drawback of covalent inhibitors is that they can suffer from a lack of selectivity, leading to side effects arising from off-target interactions.[5,21,43] These interactions result from the competitive reactivity of an inhibitor with similar amino acid residues in different proteins.[5,21] Furthermore, the covalent bond is a reason for trepidation in the development of irreversible inhibitors, as it can promote acquired resistance via the mutation of the (often susceptible) nucleophilic residue.[21,43] Undesired side-effects also arise from unpredictable immunogenic responses stemming from recognition of a covalently coupled peptide-inhibitor complex expressed at the cell surface by nearby antigen-presenting immune cells.[5,43,45] Reversible inhibitors participate exclusively in non-covalent interactions with the target binding site;[41] careful design can therefore confer a selectivity advantage at the expense of decreasing their tolerance to mutations at this site and generating drug-resistant kinase mutants.[21,43]

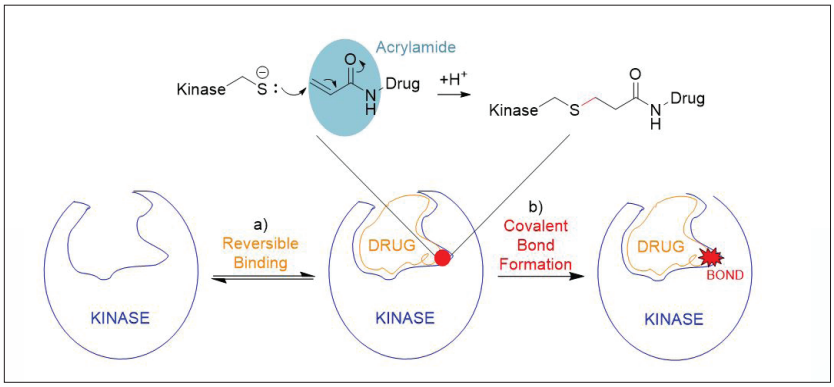


Fig. 2. Kinase-inhibitor interactions: a) reversible association of an inhibitor with a kinase; b) following reversible association, an inhibitor with a Michael acceptor reacts through covalent bond formation

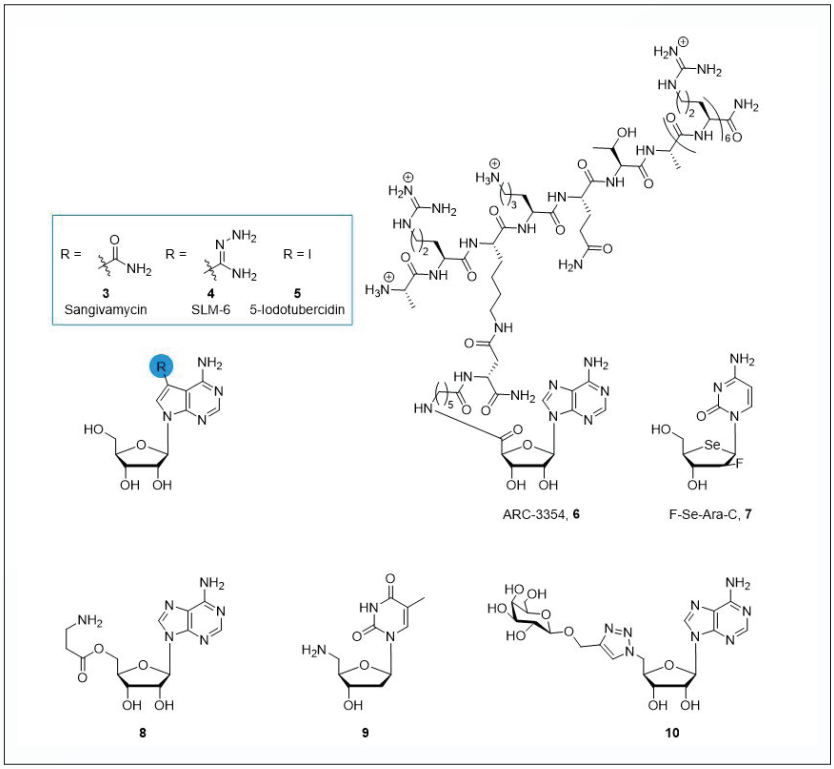


Fig. 3. A selection of kinase-inhibitory nucleosides

Nucleoside-derived kinase inhibitors

Adenosine (the nucleoside core of ATP) and other nucleoside scaffolds are important components of key cellular processes, including DNA replication, protein regulation and metabolism.[46] Given the prevalence

of reversible ATP-competitive kinase inhibitors,[41] it is perhaps unsurprising that several nucleoside derivatives have been identified that act in this way.[33,47-53] The anticancer potential of nucleoside-derived kinase inhibitors has had a particular focus on the inhibition of haspin,[49] a protein kinase overexpressed in cancers of the pancreas,[48] breast[54] and bladder.[55] One inhibitor is the bacterial natural product sangivamycin (**3**, Fig. 3), which additionally inhibits protein kinase C and paved the way to a range of sangivamycin-like molecules (SLMs).[50-51]

This led to the identification of SLM-6 (**4**) as a promising compound for the treatment of multiple myeloma through the inhibition of cyclin-dependent kinase 9.[51] Other examples of haspin inhibitors are 5-iodotubercidin (**5**) and the more specific, bisubstrate inhibitor adenosine analogue-oligoarginine conjugate ARC-3354 (**6**), which also binds to histone H3.[49] Fluorinated analogue F-Se-Ara-C (**7**) is an analogue of cytarabine (Ara-C), a sponge metabolite that was the first marine-derived pharmaceutical and is used in the treatment of acute myeloid leukaemia.[47,56-57] Unlike cytarabine, F-Se-Ara-C reduces the expression of MAPK-activated protein kinase 2 (MK2) and induces apoptosis in PC-3 cells (a prostate cancer deficient in p53).[47]

Several other useful therapeutic qualities are conferred by the inhibition of protein kinases using nucleoside analogues.[33,52-53] Adenosine derivative **8** reduces adenosine metabolism by adenosine kinase, the enzyme responsible for the phosphorylation of adenosine to adenosine monophosphate.[52] This inhibition is proposed to be useful in maximising the pharmacological benefits of adenosine for the reversal of hepatic fibrosis.[52] Capitalising on the inter-species molecular differences in kinases for selective inhibition is also on-going for antimicrobial purposes.[33,53]

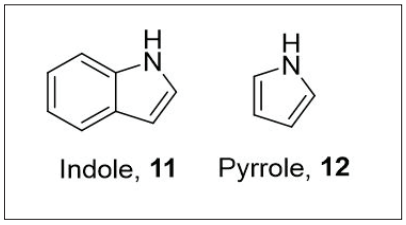


Fig. 4. The structures of indole and pyrrole

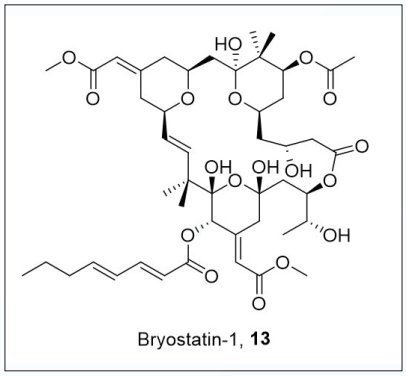


Fig. 5. The structure of bryostatin-1

Early success was shown with thymidine analogue **9** in the antagonism of thymidylate kinase in Mycobacterium tuberculosis,[33] the causative parasite of tuberculosis.[58] Thymidylate kinase is an enzyme essential to the survival of the pathogen but is not related (structurally or mechanistically) to the human variant of the protein.[58] Structure-activity relationship (SAR) studies have also revealed sugar-triazole-nucleoside **10** as an inhibitor of type III pantothenate kinase in Bacillus anthracis,[53] the underlying bacteria responsible for anthrax.[59]

This is an important protein for the essential biosynthesis of Coenzyme A.[53] The O-methylene triazole linker of **10** was proposed to resolve polarity and stability concerns of the charged and hydrolytically-sensitive phosphate linker of monophosphates studied in earlier work.[53,60]

Bryozoan-derived marine natural products

Bryozoans, also known as "moss animals" are aquatic invertebrates, found globally across environments varying in substrate surface, salinity, water depth and climate.[61-62] The individual animals (zooids) are primarily located in marine-based co-dependent colonies, arranging themselves into distinct growth forms.[61] Bryozoans are suspension feeders, utilising a crown of tentacles – their "lophophore" – to capture small particles of organic matter.[61] They in turn are a food source for other motile invertebrates such as nudibranchs, and provide a habitat for a variety of species including nematodes and small crustaceans.[61]

As highlighted in a recent article by Gris and Prinsep,[63] marine natural products (MNPs) have an important place in medicinal chemistry. This is of particular interest to island countries like New Zealand, which features approximately 15,000 km of coastline.[64] A comprehensive evaluation of natural product structures by Shang et al. emphasises that those of marine origin are expected to exhibit useful pharmacological properties.[65] The chemical space occupied by MNPs is distinct from those of other compound classes: generally, larger and more flexible ring systems as well as high proportions of halogens (especially bromine but also chlorine) and other heteroatoms such as nitrogen and sulfur are observed.[65]

Yet despite the recognised potential for lucrative and novel molecular discoveries,[10,61,65] reported MNP numbers are considerably fewer than their terrestrial counterparts.[62,66-68] This is largely attributed to the additional difficulties of collecting the producing organism from the marine environment.[67]

As seen with the similarly sessile tunicates[69] and sponges,[70] bryozoans generate a wealth of bioactive secondary metabolites (non-essential natural products that aid survival)[71] as a chemical form of defence.[61-62,72] Although natural products are frequently assigned to the macroorganism that forms the bulk of collected

organic matter, it should be kept in mind that the actual source of many bioactives is believed to be microorganisms they co-exist with.[62,73] Evidence of this already exists for some natural products derived from bryozoans[61,74] and many species of this phylum exist in symbiotic partnerships with microorganisms.[75]

However, despite boasting several thousand species this phylum is relatively underrepresented in databases of natural products.[61,68] In fact, from the (cautiously estimated) 450,000 isolated natural products[68] - 35,000 of them marine[66] – only 328 compounds from bryozoans have been reported, spanning just 30 or so species.[10-11,61,76] Of those bryozoan-derived compounds that have reported bioactivities, only a small handful were found with a noted affiliation for protein kinases.[61,77] Macrolides and nitrogenous heterocycles such as indole and pyrrole motifs (**11** and **12** respectively, Fig. 4) are commonly observed amongst bryozoan-derived bioactives.[61] Noted areas of biomedical relevance for these natural products include anticancer,[78] antiviral[77] and antiparasitic effects.[61,79]

A relatively well-known compound affiliated with bryozoans is bryostatin-1 (**13**, Fig. 5), one of several related macrolides isolated from samples of Bugula neritina[61,80] and which is administered in conjunction with paclitaxel to treat oesophageal cancer.[78] Ecological studies suggest bryostatins are concentrated in the vulnerable larval stage of B. neritina, to defend against predation by (in) vertebrates.[61,72,81] Diminished protection of larvae observed upon the administration of an antimicrobial agent supports bryostatin-1 synthesis by a bacterial symbiont ascribed to Candidatus Endobugula sertula.[61,72] One of the proteins regulated by bryostatin-1 is protein kinase C, which is activated at low dosages and inhibited with prolonged treatment.[82] Studies against various cancer cell lines have suggested promise for the use of bryostatin-1 in the treatment of various malignancies[82] and in vivo studies have shown the potential to enhance cognition in Alzheimer's disease.[61,83] Bryostatin-1 may also assist in reversing the latency of HIV-1, a required process to deplete reservoirs of the virus in afflicted individuals.[61,77]

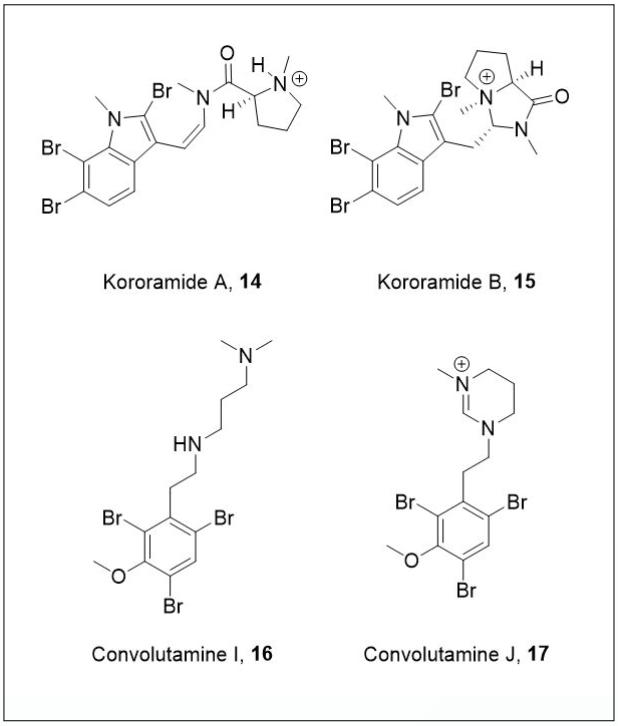


Fig. 6. The structures of kororamides A and B, and convolutamines I and J

Computational studies performed on kororamides A (**14**) and B (**15**), as well as convolutamines I (**16**) and J (**17**) – alkaloids isolated from Australian specimens of bryozoan Amathia sp.[84-85] – also support the favourable binding of these compounds to kinases implicated in Alzheimer's disease (Fig. 6).[61,86] Kororamide A and convolutamines I and J have also shown antiparasitic activity, antimalarial for the former and antitrypanosomal for the latter two compounds.[61,84-85]

Nelliellosides A and B

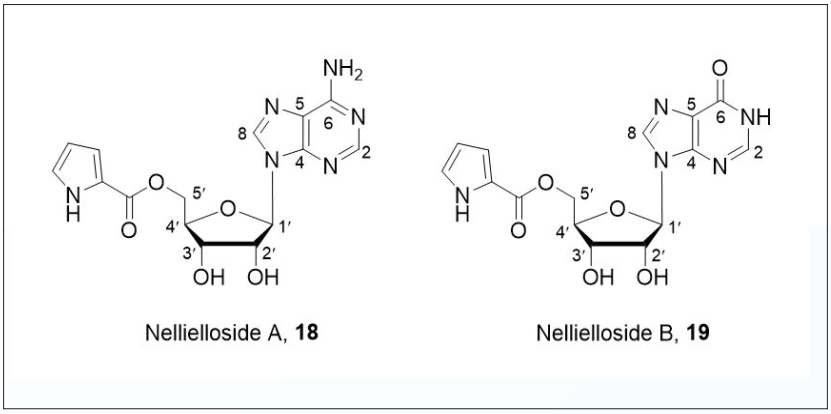
Recently, nelliellosides A and B (Fig. 7) were extracted from Nelliella nelliiformis, a Pacific bryozoan collected in the Kingdom of Tonga.[10-11] Both compounds show similar selective antagonistic activity against a small number of kinases relevant to human diseases.[10-11] Based on their structure, it could be envisaged that these natural products adopt an ATP-competitive reversible kinase-inhibitory binding mode.

Nelliellosides A (**18**) and B (**19**) feature nucleoside cores – adenosine for nelliellosides A and inosine for nelliellosides B – decorated with a 2-pyrrole carboxylate moiety at the 5′ position.[10-11] The two compounds were extracted from the bryozoan into methanol then separated from other constituents using reversed-phase column chromatography and high-performance liquid chromatography.[10-11] High-resolution mass spectrometry, tandem mass spectrometry and both one- and two-dimensional nuclear magnetic resonance spectroscopy were then used to propose their respective structural formulae.[10-11] Hydrolysis of nelliellosides A under acidic conditions released the furanose motif, which was derivatised as a peracetylated aldononitrile and compared to similarly derivatised furanose standards by chiral gas chromatography-mass spectrometry (GC-MS) analysis.[10-11] This confirmed the absolute and relative configurations of the furanose and therefore its identity as D-ri-

bose.[10-11] Similarities in the specific optical rotation values between nelliellosides A and B were initially used to assign the nellielloside B furanose as D-ribose, as insufficient material quantities prevented similar analysis by GC-MS.[11] Furthermore, comparing the characterisation data of synthetic material (produced via the route shown in Scheme 1, vide infra) and the natural products confirmed their assignment.[10-11]

A frequently encountered pitfall in the accessibility of natural products for pharmacological study is low and/or variable endogenous quantities of bioactive compounds,[11,66,87-88] necessitating extensive sacrifice of the producing life forms.[61] Indeed, only 18 grams of bryostatin-1 was obtained from approximately 12.7 tonnes of bryozoan (wet weight).[61] Relative bryostatin-1 levels can also vary dramatically between individual colonies of B. neritina and appear somewhat location-dependent,[88] which is proposed to reflect geography-related symbiotic relationships.[61,75] Some methods of meeting the material demand for MNPs include aquaculture, heterologous expression of biosynthetic gene clusters in chosen host organisms and chemical synthesis.[61] Molecular complexity plays a vital role in obtaining a marketable man-made synthetic compound – current synthetic routes to bryostatin-1 are composed of long, expensive sequences with a minimum of 29 steps.[61,89] These difficulties of acquisition have created barriers to the clinical use of bryostatin-1.[61,90]

It is therefore favourable that nelliellosides A and B can be achieved with a mere three-step synthesis from the relatively inexpensive and commercially available adenosine and inosine nucleosides (**20** and **21**, respectively, Scheme 1).[10-11] Protection of the 2′,3′-diol with an acetonide function using p-toluenesulfonic acid (p-TsOH), 2,2-dimethoxypropane (DMP) in acetone ensures regioselectivity at the 5′ position in the subsequent Steglich esterification, which utilised 2-pyrrolecarboxylic acid (**24**), N,N′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to install the 2-pyrrole carboxylate motif.[10-11] Hydrolysis of the acetonide group using trifluoroacetic acid (TFA) was used to obtain the final compounds.[10-11]



Nellielloside A, **18** Nellielloside B, **19**

Fig. 7. The structures of nellielloside A and nellielloside B

A 10 μM concentration of nellielloside A was tested against 485 kinases tied to various human diseases, with the activity of only a small number (13) of these kinases inhibited by greater than 80%.[10-11] Included in these 13 kinases were several members of the glycogen synthase kinase (GSK), ribosomal S6-kinase (RSK) and MAPK families, as well as haspin.[10-11] Nellielloside B was tested against seven of these kinases and exhibited a comparable degree of inhibition to nellielloside A against six.[10-11]

While early research on the GSK enzyme family related to the regulation of glycogen synthase,[91] the broad and multi-functional activity of this family is now recognised.[31-32] GSK-3 paralogues GSK-3α and GSK-3β are active in the brain's neuronal cells and influence cognitive development[31-32] and both were inhibited by nelliellosides A and B.[10-11] Inhibition of these paralogues is often looked at with applications to psychiatric treatment, with a particular focus on Alzheimer's disease.[31-32] GSK-3 kinases interact with over 100 native substrate molecules, and are overactive in various immunological, tumorigenic and neurological diseases.[31-32] As the two paralogues function in their own physiological niches, selective inhibition between them is an aspiration, however, as this has yet to be achieved with most small-molecule GSK-3 inhibitors.[32]

The MAPK family is ubiquitously expressed and helps regulate the motility of cells, their differentiation and cell cycle.[92] Nelliellosides A and B inhibit the p38α enzyme from this family,[10-11] commonly cited as a tumour suppressor protein with activity necessary for inducing apoptosis in some cancer chemotherapies.[93-94] However, evidence correlating p38 with proinflammatory, prosurvival and proangiogenic processes during carcinogenesis has led to the prescription of p38 inhibitors for a few types of tumour in inflammatory environments, e.g colon cancer.[94] Therefore, increasing or decreasing the selective inhibition of p38α by the nelliellosides could be desirable for medicinal applications.

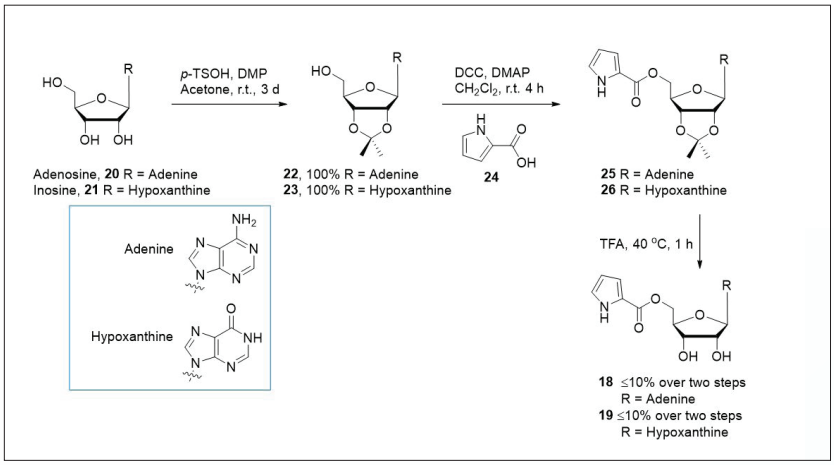
The four RSK isoforms (RSK1, RSK2, RSK3 and RSK4) are differentially expressed across human tissues.[95-96] These kinases are involved in regulating the responses of cells – including cell proliferation and survival - to growth factors, neurotransmitters and select hormones via the Ras-

MAPK pathway.[95-97] However, a thorough understanding of the disparate duties between the kinase subtypes is lacking,[98] and selectively inhibiting a single isoform has proven difficult.[97,99] Nonetheless, the development of RSK inhibitors is an exciting area of medicinal chemistry.[99] Inhibition of RSK2 and RSK4 – the two RSK enzymes inhibited by nelliellosides A and B[10-11] – has demonstrated anticancer potential in vivo and in vitro.[97,100] Promising therapeutic results have been found with RSK2 inhibition in head and neck squamous cell carcinoma[100] and with RSK4 inhibition in oesophageal squamous cell carcinoma.[97]

Nelliellosides analogues

Synthesising analogues of bioactive compounds is a common practice in the design of pharmaceuticals, enabling the optimisation of potency and selectivity for a biological target and the development of structure-activity relationships (SARs).[87,101-102] SAR studies produce one or more lead compounds to investigate further, which are ideally obtained through rapid and large-scale production with a short synthetic sequence featuring robust transformations.[61,87] Analogue synthesis is also used to address limitations of their parent compounds, such as the cost of synthesis,[9,61] poor stability,[53] and cellular resistance to drugs.[2,20]

Preparation of analogues of nelliellosides A and B is an attractive proposition to further increase the selectivity of their kinase inhibition, which in the larger picture could allow a more targeted treatment of medical indications. A considerable proportion of the molecular complexity held in these two nelliellosides, including all stereocentre configurations, is also provided by the commercially available nucleoside core. Therefore, new analogues of nelliellosides A and B should be readily obtained with relative ease, or at least few transformations.



Scheme 1. The synthesis of nelliellosides A and B by Bracegirdle et al.[10-11]

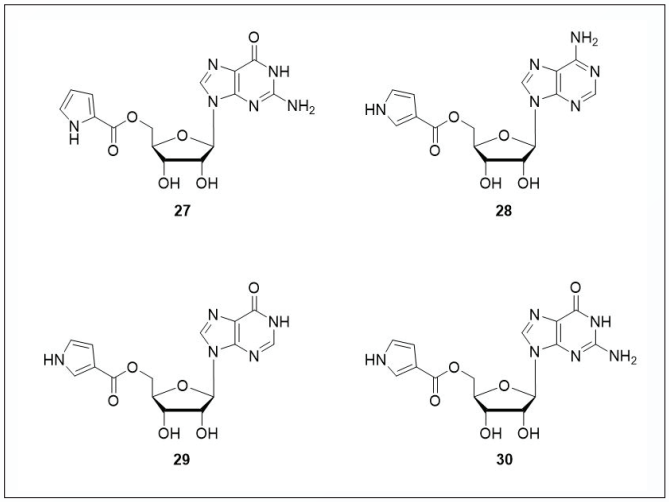


Fig. 8. The structures of nelliellosides **analogues 27-30**

Four synthetic analogues of nelliellosides A and B were prepared alongside the natural products (Fig. 8).[10-11] Their synthesis followed a similar sequence to that shown in Scheme 1: protection of the 2′,3′-diol, Steglich esterification, and deprotection.[10-11] Two analogues (**27** and **30**) feature a guanine purine motif and three (**28–30**) have 3-pyrrole carboxylate motifs.[10-11] The four analogues were submitted for kinase inhibition assays against the same kinases as nelliellosides B at 10 µM concentration, for which they showed similar levels of inhibition.[10-11] These results imply that minor changes to the purine and pyrrole motifs may be well tolerated by the kinase ATP-binding sites, and that more significant changes may be required to selectively target amongst the 13 kinases potently inhibited by nelliellosides A. Research into this area is on-going at Te Herenga Waka – Victoria University of Wellington.

Conclusions

Protein kinase inhibition is a large (and still growing!) sector of medicinal chemistry. Two new protein kinase inhibitors have been recently isolated from the Pacific bryozoan Nelliella nelliiformis and a series of analogues prepared, which have cores resembling those of ATP and other kinase-inhibitory nucleosides. The discovery of nelliellosides A and B from bryozoa serves as a timely reminder of the potential this vastly understudied phylum (and marine species as a whole) holds for yielding bioactive materials of interest to the medicinal chemist.

References

1. Ferguson, F. M.; Gray, N. S. *Nat. Rev. Drug Discov.* **2018,** *17* (5), 353-377.
2. Attwood, M. M.; Fabbro, D.; Sokolov, A. V.; Knapp, S.; Schiöth, H. B. *Nat. Rev. Drug Discov.* **2021,** *20* (11), 839-861.
3. Fabbro, D.; Cowan-Jacob, S. W.; Möbitz, H.; Martiny-Baron, G. *Kinase Inhibitors* **2012**, 1-34.
4. Roskoski, R. *Pharmacol. Res.* **2021,** *165*, 105463-105483.
5. Roskoski, R. *Pharmacol. Res.* **2021,** *165*, 105422-105437.
6. Regad, T. *Cancers* **2015,** *7* (3), 1758-1784.
7. Schneider, G.; Clark, D. E. *Angew. Chem. Int. Ed.* **2019,** *58* (32), 10792-10803.
8. Mortensen, K. T.; Osberger, T. J.; King, T. A.; Sore, H. F.; Spring, D. R. *Chem. Rev.* **2019,** *119* (17), 10288-10317.
9. Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2020,** *83* (3), 770-803.
10. Bracegirdle, J.; Gordon, D. P.; Harvey, J. E.; Keyzers, R. A. *J. Nat. Prod.* **2020,** *83* (2), 547–551.
11. Bracegirdle, J. Chemical Investigations of Pacific Marine Organisms. PhD Thesis, Victoria University of Wellington, 2020.
12. Ponnamperuma, C.; Sagan, C.; Mariner, R. *Nature* **1963,** *199*, 222-226.
13. Manning, G.; Whyte, D. B.; Martinez, R.; Hunter, T.; Sudarsanam, S. *Science* **2002,** *298* (5600), 1912-1934.
14. Neupane, P.; Bhuju, S.; Thapa, N.; Bhattarai, H. K. *Biomol. Concepts* **2019,** *10* (1), 1-10.
15. Duong-Ly, K. C.; Peterson, J. R. *Curr. Protoc. Pharmacol.* **2013,** *60*, 2-9.
16. Krebs, E. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* **1983,** *302* (1108), 3-11.
17. Bhullar, K. S.; Lagarón, N. O.; McGowan, E. M.; Parmar, I.; Jha, A.; Hubbard, B. P.; Rupasinghe, H. P. V. *Mol. Cancer* **2018,** *17* (1), 48-67.
18. Smith, C. A.; Toth, M.; Frase, H.; Byrnes, L. J.; Vakulenko, S. B. *J. Biol. Chem.* **2012,** *287* (16), 12893-12903.
19. Lahiry, P.; Torkamani, A.; Schork, N. J.; Hegele, R. A. *Nature Reviews Genetics* **2010,** *11* (1), 60-74.
20. Matthews, D. J.; Gerritsen, M. E., *Targeting protein kinases for cancer therapy*. John Wiley & Sons: 2011.
21. Abdeldayem, A.; Raouf, Y. S.; Constantinescu, S. N.; Moriggl, R.; Gunning, P. T. *Chem. Soc. Rev.* **2020,** *49* (9), 2617-2687.
22. Guo, Y.; Liu, Y.; Hu, N.; et al. *J. Med. Chem.* **2019,** *62* (17), 7923-7940.
23. Konieczkowski, D. J.; Johannessen, C. M.; Garraway, L. A. *Cancer Cell* **2018,** *33* (5), 801-815.
24. Roskoski Jr, R. *Pharmacol. Res.* **2015,** *100*, 1-23.
25. Hill, A.; Gotham, D.; Fortunak, J.; Meldrum, J.; Erbacher, I.; Martin, M.; Shoman, H.; Levi, J.; Powderly, W. G.; Bower, M. *BMJ Open* **2016,** *6* (1), e009586.
26. Riely, G. J.; Pao, W.; Pham, D.; Li, A. R.; Rizvi, N.; Venkatraman, E. S.; Zakowski, M. F.; Kris, M. G.; Ladanyi, M.; Miller, V. A. *Clin. Cancer Res.* **2006,** *12* (3), 839-844.
27. Hatanpaa, K. J.; Burma, S.; Zhao, D.; Habib, A. A. *Neoplasia* **2010,** *12* (9), 675-684.
28. Cunningham, D.; Humblet, Y.; Siena, S.; Khayat, D.; Bleiberg, H.; Santoro, A.; Bets, D.; Mueser, M.; Harstrick, A.; Verslype, C.; Chau, I.; Van Cutsem, E. *N. Engl. J. Med.* **2004,** *351* (4), 337-345.
29. Nikolic, I.; Leiva, M.; Sabio, G. *Nat. Rev. Endocrinol.* **2020,** *16* (12), 697-716.
30. Goette, A.; Staack, T.; Röcken, C.; Arndt, M.; Geller, J. C.; Huth, C.; Ansorge, S.; Klein Helmut, U.; Lendeckel, U. *J. Am. Coll. Cardiol.* **2000,** *35* (6), 1669-1677.
31. Beurel, E.; Grieco, S. F.; Jope, R. S. *Pharmacol. Ther.* **2015,** *148*, 114-131.
32. Sayas, C. L.; Ávila, J. *Cells* **2021,** *10* (4), 721-739.
33. Pochet, S.; Dugue, L.; Douguet, D.; Labesse, G.; Munier-Lehmann, H. *ChemBioChem.* **2002,** *3* (1), 108-110.
34. Raivola, J.; Haikarainen, T.; Abraham, B. G.; Silvennoinen, O. *Cancers* **2021,** *13* (4), 800-819.
35. World Health Organization - The Top 10 Causes of Death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death 2020 (accessed 27/04/2022).
36. Salerno, D.; Hasham, M. G.; Marshall, R.; Garriga, J.; Tsygankov, A. Y.; Graña, X. *Gene* **2007,** *405* (1), 65-78.
37. Law, A.; Gauthier, S.; Quirion, R. *Brain Res. Rev.* **2001,** *35* (1), 73-96.
38. Farahani, M.; Niknam, Z.; Mohammadi Amirabad, L.; Amiri-Dashatan, N.; Koushki, M.; Nemati, M.; Danesh Pouya, F.; Rezaei-Tavirani, M.; Rasmi, Y.; Tayebi, L. *Biomed. Pharmacother.* **2022,** *145*, 112420-112443.
39. Levy, G.; Guglielmelli, P.; Langmuir, P.; Constantinescu, S. *J. Immunother. Cancer* **2022,** *10* (4), e002838.
40. Fabbro, D.; Cowan-Jacob, S. W.; Moebitz, H. *Br. J. Pharmacol.* **2015,** *172* (11), 2675-2700.
41. Liu, Q.; Sabnis, Y.; Zhao, Z.; Zhang, T.; Buhrlage, Sara J.; Jones, Lyn H.; Gray, Nathanael S. *Chem. Biol.* **2013,** *20* (2), 146-159.
42. Roskoski, R. *Pharmacol. Res.* **2016,** *103*, 26-48.
43. Singh, J.; Petter, R. C.; Baillie, T. A.; Whitty, A. *Nat. Rev. Drug Discov.* **2011,** *10* (4), 307-317.
44. Leproult, E.; Barluenga, S.; Moras, D.; Wurtz, J.-M.; Winssinger, N. *J. Med. Chem.* **2011,** *54* (5), 1347-1355.
45. Henriot, S.; Lepoitrevin, J. P.; Trifilieff, E. *J. Pept. Sci.* **2001,** *7* (6), 331-337.
46. Jordheim, L. P.; Durantel, D.; Zoulim, F.; Dumontet, C. *Nat. Rev. Drug Discov.* **2013,** *12* (6), 447-464.
47. Song, J.; Yu, J.; Jeong, L. S.; Lee, S. K. *Cancer Lett.* **2021,** *497*, 54-65.
48. Bastea, L. I.; Hollant, L. M.; Döppler, H. R.; Reid, E. M.; Storz, P. *Sci. Rep.* **2019,** *9* (1), 1-10.
49. Amoussou, N. G.; Bigot, A.; Roussakis, C.; Robert, J.-M. H. *Drug Discov. Today* **2018,** *23* (2), 409-415.
50. Borowczak, J.; Szczerbowski, K.; Ahmadi, N.; Szylberg, Ł. *Med. Oncol.* **2022,** *39* (4), 39-53.
51. Dolloff, N. G.; Allen, J. E.; Dicker, D. T.; Aqui, N.; Vogl, D.; Malysz, J.; Talamo, G.; El-Deiry, W. S. *Mol. Cancer Ther.* **2012,** *11* (11), 2321-2330.
52. Hernández-Vázquez, E.; Chagoya, V. *Med. Chem. Res.* **2015,** *24*, 2325-2335.
53. Rowan, A. S.; Nicely, N. I.; Cochrane, N.; Wlassoff, W. A.; Claiborne, A.; Hamilton, C. J. *Org. Biomol. Chem.* **2009,** *7* (19), 4029-4036.

54. Nishida-Fukuda, H.; Tokuhiro, K.; Ando, Y.; Matsushita, H.; Wada, M.; Tanaka, H. *PLoS One* **2021,** *16* (4), e0249912.
55. Chen, Y.; Fu, D.; Zhao, H.; Cheng, W.; Xu, F. *Aging (Albany NY)* **2020,** *12* (10), 8858-8879.
56. Capizzi, R. L. *Invest. New Drugs* **1996,** *14* (3), 249-256.
57. Katanaev, V. L.; Di Falco, S.; Khotimchenko, Y. *Mar. Drugs* **2019,** *17* (8), 474-499.
58. Sukumar, S.; Krishman, A.; Khan, M. K. A. *Front. Biosci.* **2020,** *25*, 1636-1654.
59. Passalacqua, K. D.; Bergman, N. H. *Future Microbiol.* **2006,** *1* (4), 397-415.
60. Wlassoff, W. A.; Finlay, R. M.; Hamilton, C. J. *Synth. Commun.* **2007,** *37* (17), 2927-2934.
61. Ciavatta, M. L.; Lefranc, F.; Vieira, L. M.; Kiss, R.; Carbone, M.; van Otterlo, W. A.; Lopanik, N. B.; Waeschenbach, A. *Mar. Drugs* **2020,** *18* (4), 200-231.
62. Figuerola, B.; Avila, C. *Mar. Drugs* **2019,** *17* (8), 477-499.
63. Gris, L.; Prinsep, M. R. *Chemistry in New Zealand* **2021,** *85* (3), 31-38.
64. Walls, K. *Parks* **1998,** *8* (2), 5-10.
65. Shang, J.; Hu, B.; Wang, J.; Zhu, F.; Kang, Y.; Li, D.; Sun, H.; Kong, D.-X.; Hou, T. *J. Chem. Inf. Model.* **2018,** *58* (6), 1182-1193.
66. De Rop, A.-S.; Rombaut, J.; Willems, T.; De Graeve, M.; Vanhaecke, L.; Hulpiau, P.; De Maeseneire, S. L.; De Mol, M. L.; Soetaert, W. K. *Mar. Drugs* **2022,** *20* (1), 6-28.
67. Dayanidhi, D. L.; Thomas, B. C.; Osterberg, J. S.; Vuong, M.; Vargas, G.; Kwartler, S. K.; Schmaltz, E.; Dunphy-Daly, M. M.; Schultz, T. F.; Rittschof, D. *Front. Mar. Sci.* **2021,** *7*, 614766.
68. Ntie-Kang, F.; Svozil, D. *Phys. Sci. Rev.* **2020,** *5* (8), 20180121.
69. Schmidt, E. W.; Donia, M. S.; McIntosh, J. A.; Fricke, W. F.; Ravel, J. *J. Nat. Prod.* **2012,** *75* (2), 295-304.
70. Skropeta, D.; Pastro, N.; Zivanovic, A. *Mar. Drugs* **2011,** *9* (10), 2131-2154.
71. Petersen, L.-E.; Kellermann, M. Y.; Schupp, P. J. *Secondary metabolites of marine microbes: From natural products chemistry to chemical ecology*. Springer, Cham.: 2020.
72. Lopanik, N.; Lindquist, N.; Targett, N. *Oecologia* **2004,** *139* (1), 131-139.
73. Gerwick, W. H.; Fenner, A. M. *Microb. Ecol.* **2013,** *65* (4), 800-806.
74. Davidson, S. K.; Allen, S. W.; Lim, G. E.; Anderson, C. M.; Haygood, M. G. *Appl. Environ. Microbiol.* **2001,** *67* (10), 4531-4537.
75. Lopanik, N. B. *Funct. Ecol.* **2014,** *28* (2), 328-340.
76. MarinLit. https://marinlit.rsc.org/ 2022 (accessed 27/04/2022).
77. Mehla, R.; Bivalkar-Mehla, S.; Zhang, R.; Handy, I.; Albrecht, H.; Giri, S.; Nagarkatti, P.; Nagarkatti, M.; Chauhan, A. *PLoS One* **2010,** *5* (6), e11160-e11160.
78. Lu, W.-Y.; Li, H.-J.; Li, Q.-Y.; Wu, Y.-C. *Bioorg. Med. Chem.* **2021,** *35*, 116058-116087.
79. Davis, R. A.; Sykes, M.; Avery, V. M.; Camp, D.; Quinn, R. J. *Bioorg. Med. Chem.* **2011,** *19* (22), 6615-6619.
80. Pettit, G. R.; Herald, C. L.; Doubek, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982,** *104* (24), 6846-6848.
81. Lindquist, N.; Hay, M. E. *Ecol. Monogr.* **1996,** *66* (4), 431-450.
82. Kortmansky, J.; Schwartz, G. K. *Cancer Invest* **2003,** *21* (6), 924-36.
83. Schrott, L.; Jackson, K.; Yi, P.; Dietz, F.; Johnson, G.; Basting, T.; Purdum, G.; Tyler, T.; Rios, J.; Castor, T. *Curr. Alzheimer Res.* **2015,** *12* (1), 22-31.
84. Carroll, A. R.; Wild, S. J.; Duffy, S.; Avery, V. M. *Tetrahedron Lett.* **2012,** *53* (23), 2873-2875.
85. Dashti, Y.; Vial, M.-L.; Wood, S. A.; Mellick, G. D.; Roullier, C.; Quinn, R. J. *Tetrahedron* **2015,** *71* (41), 7879-7884.
86. Llorach-Pares, L.; Nonell-Canals, A.; Avila, C.; Sanchez-Martinez, M. *Mar. Drugs* **2018,** *16* (10), 386.
87. Paterson, I.; Anderson, E. A. *Science* **2005,** *310* (5747), 451-453.
88. Davidson, S. K.; Haygood, M. G. *Biol. Bull.* **1999,** *196* (3), 273-280.
89. Wender, P. A.; Hardman, C. T.; Ho, S.; Jeffreys, M. S.; Maclaren, J. K.; Quiroz, R. V.; Ryckbosch, S. M.; Shimizu, A. J.; Sloane, J. L.; Stevens, M. C. *Science* **2017,** *358* (6360), 218-223.
90. DeChristopher, B. A.; Loy, B. A.; Marsden, M. D.; Schrier, A. J.; Zack, J. A.; Wender, P. A. *Nat. Chem.* **2012,** *4* (9), 705-710.
91. Embi, N.; Rylatt, D. B.; Cohen, P. *Eur. J. Biochem.* **1979,** *100* (2), 339-347.
92. Cargnello, M.; Roux, P. P. *Microbiol. Mol. Biol. Rev.* **2011,** *75* (1), 50-83.
93. Olson, J. M.; Hallahan, A. R. *Trends. Mol. Med.* **2004,** *10* (3), 125-129.
94. Wagner, E. F.; Nebreda, Á. R. *Nat. Rev. Cancer* **2009,** *9* (8), 537-549.
95. Zeniou, M.; Ding, T.; Trivier, E.; Hanauer, A. *Hum. Mol. Genet.* **2002,** *11* (23), 2929-40.
96. Yntema, H. G.; van den Helm, B.; Kissing, J.; van Duijnhoven, G.; Poppelaars, F.; Chelly, J.; Moraine, C.; Fryns, J.-P.; Hamel, B. C.; Heilbronner, H. *Genomics* **1999,** *62* (3), 332-343.
97. Yuan, Y.; Xu, J.; Jiang, L.; Yu, K.; Ge, Y.; Li, M.; He, H.; Niu, Q.; Shi, X.; Fan, L.; Chen, Z.; Zhao, Z.; Li, S.; Xu, Y.; Wang, Z.; Li, H. *J. Med. Chem.* **2021,** *64* (18), 13572-13587.
98. Anjum, R.; Blenis, J. *Nat. Rev. Mol. Cell Biol.* **2008,** *9* (10), 747-758.
99. Youn, M.; Gomez, J. O.; Mark, K.; Sakamoto, K. M. *Biomedicines* **2021,** *9* (7), 726-740.
100. Kang, S.; Elf, S.; Lythgoe, K.; Hitosugi, T.; Taunton, J.; Zhou, W.; Xiong, L.; Wang, D.; Muller, S.; Fan, S.; Sun, S.-Y.; Marcus, A. I.; Gu, T.-L.; Polakiewicz, R. D.; Chen, Z. G.; Khuri, F. R.; Shin, D. M.; Chen, J. *J. Clin. Investig.* **2010,** *120* (4), 1165-1177.
101. Davison, E. K.; Brimble, M. A. *Curr. Opin. Chem. Biol.* **2019,** *52*, 1-8.
102. Liang, C.; Tian, D.; Ren, X.; Ding, S.; Jia, M.; Xin, M.; Thareja, S. *Eur. J. Med. Chem.* **2018,** *151*, 315-326.

Article

Toward 3D covalent organic frameworks

EMILY R. STEPHENS* AND LUJIA LIU

MacDiarmid Institute for Advanced Materials and Nanotechnology, School of Chemical and Physical Sciences, Victoria University of Wellington, Wellington 6012 (email: stephens.emily@vuw.ac.nz)

Keywords: *covalent organic framework, materials science, porous materials*

Covalent organic frameworks (COFs) are an emerging class of porous materials which have the potential to front a new wave of environmental technologies.[1] Using principles of reticular chemistry (working backwards based on the geometry of the desired framework),[2-3] COFs are synthesised via precise covalent bonding of organic monomers to build highly porous and highly structured networks, akin to a 'molecular sponge'.

The use of reticular chemistry results in highly modifiable frameworks with customisable characteristics such as pore size, surface area, density, and pore functionality, making COFs ideal materials for a vast range of practical applications.

Porous materials like inorganic zeolites and ordered mesoporous oxides held much interest in the past but their structures are not entirely modifiable and structural control can be difficult. Metal-organic frameworks (MOFs) were first developed in the 1990s to address these issues. Also dictated by reticular chemistry, MOFs contain coordinated inorganic clusters combined with organic linkers to create highly porous frameworks. MOFs have fronted research on highly structured porous materials,[4] but although breakthroughs have led to MOF materials which are stable in harsh conditions, covalently bonded materials offer innate stability in comparison with their metal coordination equivalent (Fig. 1).[5-6]

The design of an organic-equivalent ordered framework subsequently led to the new and promising COFs in 2005, thus mitigating stability issues while maintaining the modifiability of the framework.[7]

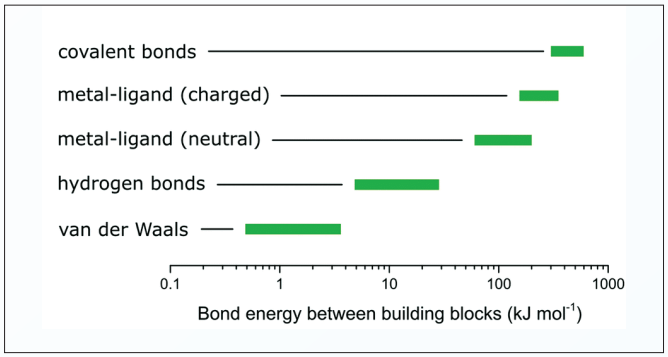


Fig. 1. Relative strengths of different bonds.[8] Reprinted with permission.

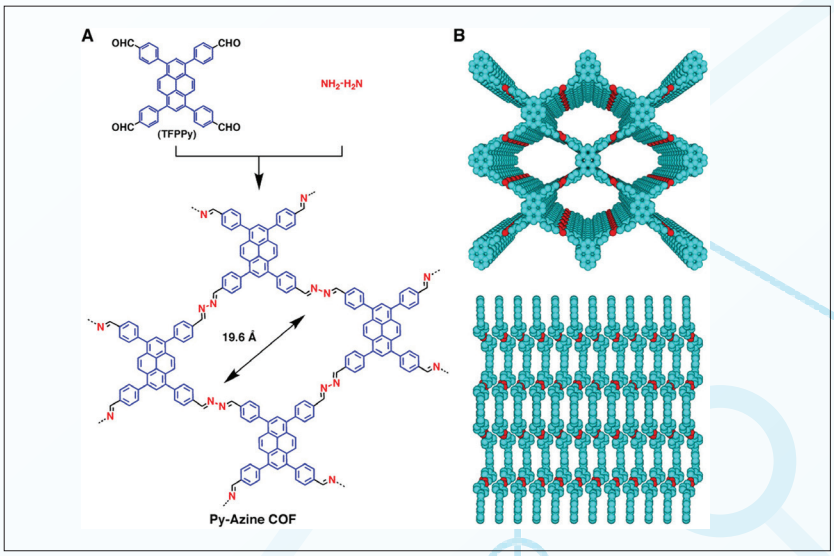


Fig. 2. A: The formation of a 2D COF, Py-Azine COF, from monomers. B: 3D depiction of a 2D COF. The monomers and oligomers are held together via strong covalent bonding whereas the layers are held together via weaker π-π stacking. The highly porous channels are uni-directional and the area where the atoms stack is incredibly dense.[9]
Reprinted with permission.

COF research over the past 16 years has primarily focused on 2-dimensional COFs, perhaps due to their relative ease of synthesis, processability, and simple structural determination. 2D COFs are comprised of stacked sheets of highly ordered 2D organic polymers. While the monomers within each layer are covalently linked, the layers themselves are held together with weaker π-π stacking. This results in an overall highly porous framework consisting of 1-dimensional channels of high porosity coupled with densely packed walls where the atoms stack (Fig. 2).

2D COFs are limited in how the structure is arranged through 3D space (called a 'topology', represented by three lower-case letters in bold) because of their shape and uni-directional pore channels.

In comparison, the relatively underdeveloped 3D COFs contain a 3-dimensional organic skeleton held together entirely through strong covalent bonds. The 3-dimensional framework allows for a larger diversity of pore sizes, shapes, and channel accessibilities, further generating a larger number of potential topologies and a higher degree of modifiability (Fig. 3). 3D COFs are more difficult to obtain than their 2D counterparts due in part to stricter crystallisation conditions, resulting in the lack of research in this area.

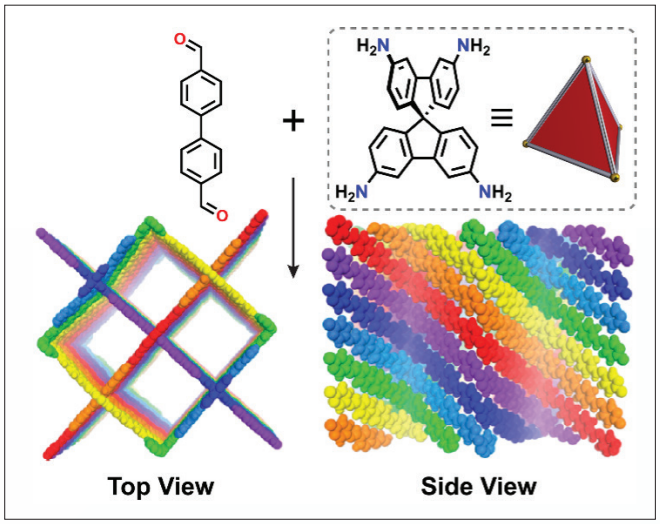


Fig. 3. Synthesis and structure of a 3D COF with an interpenetrated diamond (**dia**) network topology.[10] Adapted with permission.

Both 2D and 3D COFs are being used in the development of environmental technologies that can minimise or remedy environmental pollution. The highly accessible and size-adjustable pore systems of COFs make them suitable for gas storage, release, and separation (such as in the use of fuel cells[11-12] and CO_2 capture[13-14]), their large surface area makes them suitable for catalysis[15–18] and sensing,[19–22] and their highly ordered structure is suitable for charge carrier transport (such as in optoelectronics).[23] With properties that meet many application requirements, COFs may be put in use more frequently while older and less suitable technologies are phased out (Fig. 4).

Reticular chemistry is a key characteristic of COF design and synthesis, in which smaller building blocks are linked to create crystalline open frameworks.[3] Fig. 5 illustrates the steps of reticular synthesis.[25] Firstly, the desired framework and its topology is identified. Here, topology is a term borrowed from mathematics with a specific meaning in the realm of reticular chemistry. A topology defines how building units (COF monomers, metal clusters, MOF ligands) are linked and arranged periodically in space.[26]

Next, the framework is broken into smaller building blocks, focusing on the geometry and connectivity (number of points of linkage) that will yield the correct topological framework. These building blocks must also account for properties, such as linker length or steric bulk, required to selectively form the desired topology. Following this is the identification of molecular equivalents that will 1) fit the desired unit geometry, 2) fit the desired connectivity, and 3) form appropriate linkages to its neighbouring units. Finally, the augmented net is derived and the framework is synthesised. Because reticular chemistry works backwards, the building blocks chosen determine the properties of the framework at all scales (monomer, geometry, and topology).

The use of reticular chemistry would seemingly correspond to a large number of unique framework topologies. In MOFs this is certainly the case, with the number of unique MOF topologies sitting at over 100 and the building blocks showing a connectivity up to 24 (i.e. one building block connects to 24 neighbouring blocks).[28] However, 3D COFs lag

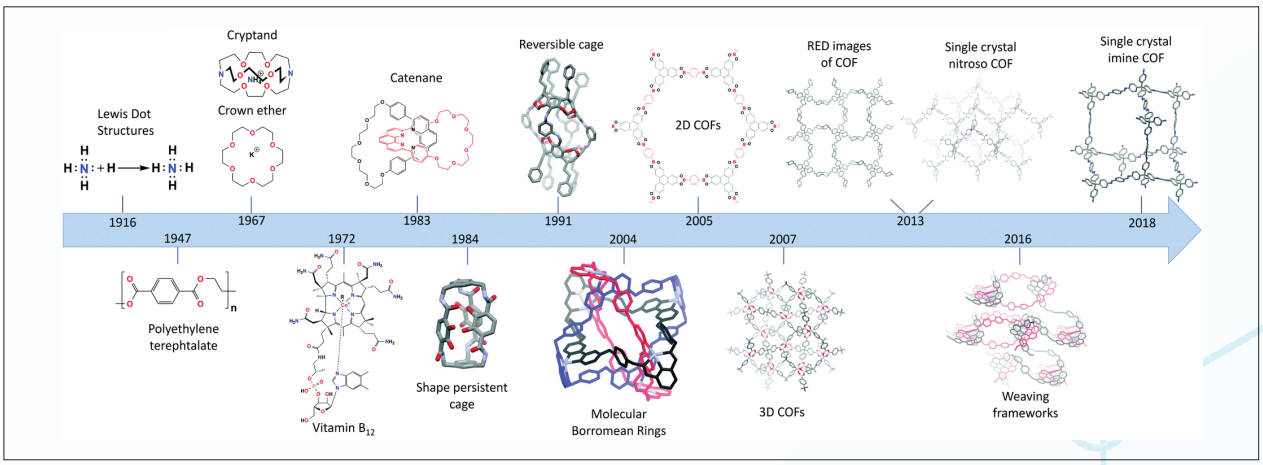


Fig. 4. A timeline of porous organic materials research.[24] Reprinted with permission.

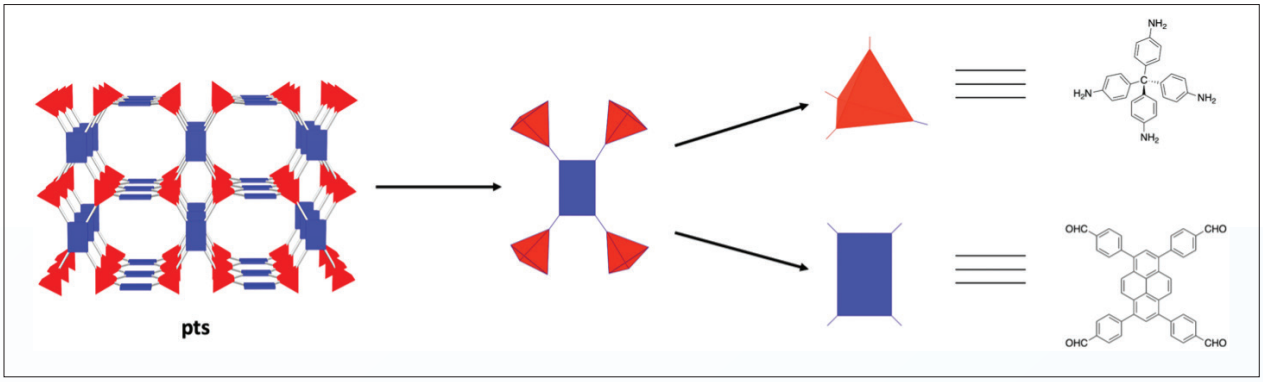


Fig. 5. Steps of reticular synthesis, based on the pts topology. Firstly, the desired framework topology is identified. Next, the geometry and connectivity of the building blocks are determined (4-c planar rectangular and 4-c tetrahedral). Then, molecular equivalents are identified for each geometry.[27] Adapted with permission.

far behind with only 15 topologies and a maximum of 8-connectivity to date. The primary reason for this lack of COF topologies is due to carbon's restricted bonding ability of sp, sp^2, and sp^3 hybridisations – an obstruction that metallic building blocks do not face. This limits the number of geometries available for covalent building blocks, further restricting the number of topologies available for 3D COFs.

The number of building blocks available for use in 3D COFs is currently very limited (Fig. 6). Conceptually, a 3-dimensional COF would require at least one building block that extends into 3-dimensional space – for carbon, this would instinctively be the 4-connecting tetrahedral building block. During early COF synthesis this mode of thinking was prominent, and consequently only three topologies were discovered during the first decade of 3D COF synthesis. All were reliant on the tetrahedral block paired with a planar 2, 3, or 4 connected linker.[29]

However, there are two recent strategies which are beginning to utilise more creative modes of thinking. The first is combining linear or 2D monomers to form 3D "organic clusters" of higher connectivities, which further form 3D COFs. For instance, the trigonal prismatic (6-connecting, or "6-c", Fig. 6d) building block in particular is gaining considerable interest as it relies on a group of covalently bonded organic elements, cleverly bypassing the geometry limitations of common organic molecules.

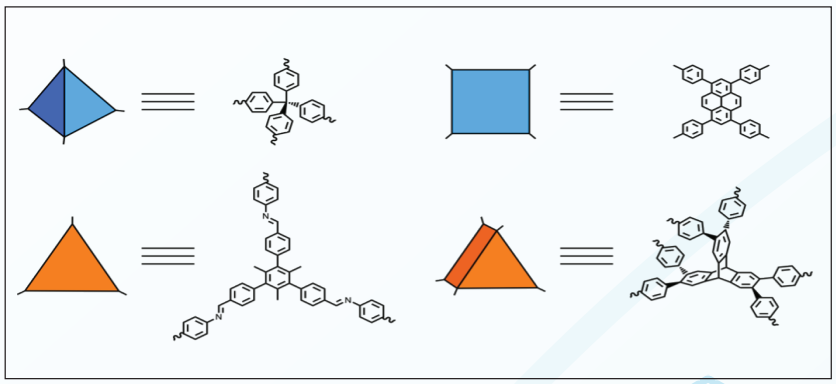


Fig. 6. Four geometric building blocks used in 3D COFs, and an example of each's molecular constituent. **a:** tetrahedral; **b:** square/rectangular planar; **c:** trigonal planar; **d:** trigonal prismatic.

"... there is a need for a more innovative and wider mindset among porous material engineers to truly test the limits of COF design."

The second strategy to synthesise 3D COFs is by using 2D monomers which have properties that force themselves into a 3D framework. In this strategy, a common occurrence is that the same combination of building block geometries can form numerous different topologies, based on monomer size, steric bulk, and symmetry. While a *square* planar/triangular planar geometry combination will form the **ffc** topology, a *rectangular* planar/triangular planar geometry combination will form the **tbo** topology.

To date, only two 3D cluster geometries have been identified, and only two sets of 2D monomer combinations have been utilised. Topology design can allow for tailoring of COFs to give specific properties (e.g. surface are, density), and thus can be utilised in COFs for specific applications. Because of this, there is a need for a more innovative and wider mindset among porous material engineers to truly test the limits of COF design.

References

1. Wang, J.; Zhuang, S. *Coord. Chem. Rev.* 2019, *70*, 213046.
2. Freund, R; Canossa, S.; Cohen, Sm.M.; Yan, W.; Deng, H.; Guillerm, V.; Eddaoudi, M.; Madden, D.G.; Fairen-Jimenez, D.; Lyu, H.; Macreadie, L.K..; Ji, Z.; Zhang, Y.; Wang, B.; Haase, F.; Wöll, C.; Zaremba, O.; Andreo, J.; Wuttke, S.; Diercks, C.S. *Angew. Chem. Int. Ed.* **2021**, *60*, 23946.
3. Yaghi, O. *J. Am. Chem. Soc.* **2016**, *138*, 15507 – 15509.
4. I. M. Hönicke, I. Senkovska, V. Bon, I. A. Baburin, N. Bönisch, S. Raschke, J. D. Evans, S. Kaskel, *Angew. Chem. Int. Ed.* **2018**, *57*, 13780.
5. Zhou, H. C.; Long, J. R.; Yaghi, O. *Chem. Rev.* **2012**, *112*, 673-674.
6. O'Keeffe, M. *Chem. Soc. Rev.* **2009**, *38*, 1215-1217.
7. Côté, A. P.; Benin, A.I., Ockwig, N.W.; O'Keeffe, M.; Matzger, A.J.; Yaghi, O. *Science* **2005**, *310*, 1166-1170.
8. Haase, F. & Lotsch, B. *Chem. Soc. Rev*. **2020**, *49*, 8469-8500.
9. Dalapati, S.; Jin, S.; Gao, J.; Xu, Y.; Nagai, A.; Jiang, D. *J. Am. Chem. Soc.* **2013**, *135*, 17310-17313.
10. Wu, C.; Liu, Y.; Liu, H.; Duan, C.; Pan, Q.; Zhu, J.; Hu, F.; Ma, X.; Jiu, T.; Li, Z.; Zhao, Y. *J. Am. Chem. Soc.* **2018**, *140*, 10016-10024.
11. Yang, Y.; He, X.; Zhang, P.; Andaloussi, Y.H.; Zhang, H.; Jiang, Z. *Angew. Chem. Int. Ed.* **2020**, *59*, 3678-3684.
12. Furukawa, H; Yaghi, O. M. *J. Am. Chem. Soc.* **2009**, *131*, 8875-8883
13. Olajire, A. A. *J. CO2 Util.* **2017**, *17*, 137-161.
14. Zeng, Y.; Zou, R.; Zhao, Y. *Adv. Mater.* **2016**, *28*, 2855-2873.
15. Liu, Y.; Wu, C.; Sun, Q.; Hu, F.; Pan, Q.; Sun, J.; Jin, Y.; Li, Z.; Zhange, W.; Zhao, Y. *CCS Chem.* **2021**, *3*(4), 2418-2427.
16. 16 Kang, X.; Wu, X.; Han, X.; Yuan, C.; Liu, Y.; Cui, Y. *Chem. Sci.* **2020**, *11*, 1494-1502.
17. Liu, H.; Chu, J.; Yin, Z.; Cai, X.; Zhuang, L.; Deng, H. *Chem* **2018**, *4*, 1696-1709.
18. Yusran, Y.; Li, H.; Guan, X.; Fang, Q.; Qiu, S. *EnergyChem* **2020**, *2*, 100035.
19. Li, Z.; Zhang, Y.; Xia, H.; Mu, Y.; Liu, X. *Chem. Comm.* **2016**, *52*, 6613-6616.
20. Li, W.; Yang, C.X.; Yan, X.P. *Chem. Comm.* **2017**, *53*, 11469-11471.
21. Qian, H.L.; Dai, C.; Yang, C.X.; Yan, X.P. *ACS Appl. Mater. Interfaces* **2017**, *9*, 24999-25005.
22. Zhang, X.; Li, G.; Wu, D.; Zhang, B.; Hu, N.; Wang, H.; Liu, J.; Wu, Y. *Biosens. Bioelectron.* **2019**, *145*, 111699.
23. Keller, N.; Bein, T. *Chem. Soc. Rev.* **2021**, *50*, 1813-1845.
24. Bourda, L.; Krishnaraj, C.; van der Voort, P.; van Hecke, K. *Mater. Adv.* **2021**, *2*(9), 2811-2845.
25. Diercks, C. S.; Yaghi, O. M. *Science* **2017**, *355*(6328), 1585.
26. Li, M.; Li, D.; O'Keeffe, M.; Yaghi, O. M. *Chem. Rev.* **2014**, *114*, 1343-1370.
27. Gui, B.; Lin, G.; Ding, H.; Gao, C.; Mal, A.; Wang, C. *Acc. Chem. Res.* **2020**, *53*, 2225-2234.
28. Yuan, D.; Zhao, D.; Zhou, H.C. *Inorg. Chem.* **2011**, *50*, 10528-10530.
29. Guan, X.; Chen, F.; Fang, Q.; Qiu, S. *Chem. Soc. Rev.* **2020**, *49*, 1357-1384.