ISSN 0790 4975

2009, Vol. 25, No.1

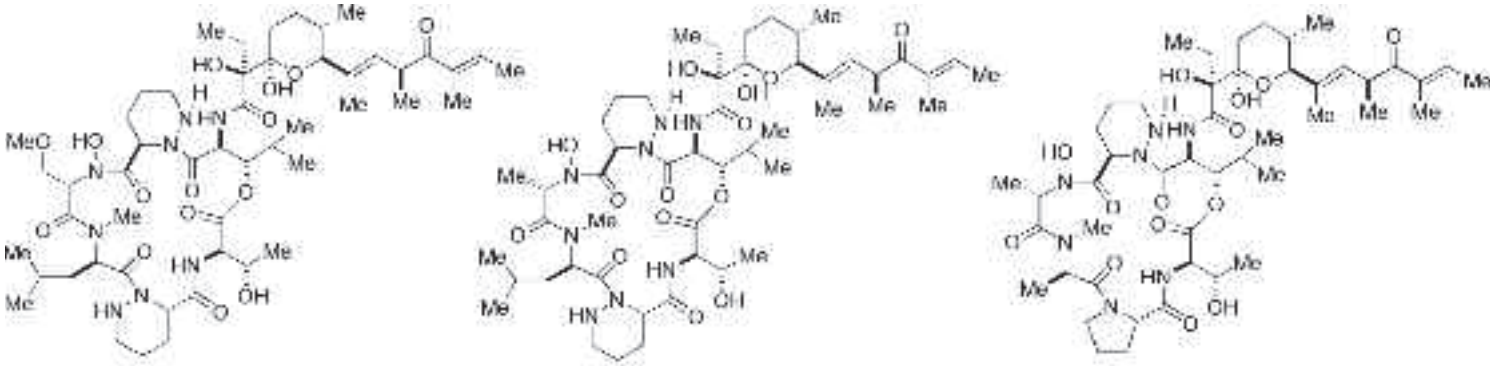
The Institute of Chemistry of Ireland

IrishChemicalNews

JOURNAL OF THE INSTITUTE OF CHEMISTRY OF IRELAND

FEATURE :

Molecules of the A83586C-Azinothricin-Kettapeptin and Agelastatin A Class; Their Synthesis, Mechanisms of Antitumor Action, and Potential For Counteracting β-Catenin Driven Cell Signalling



A83586C-Citropeptin Hybrid

A83586C-GE3 Hybrid

L-Pro-A83586C

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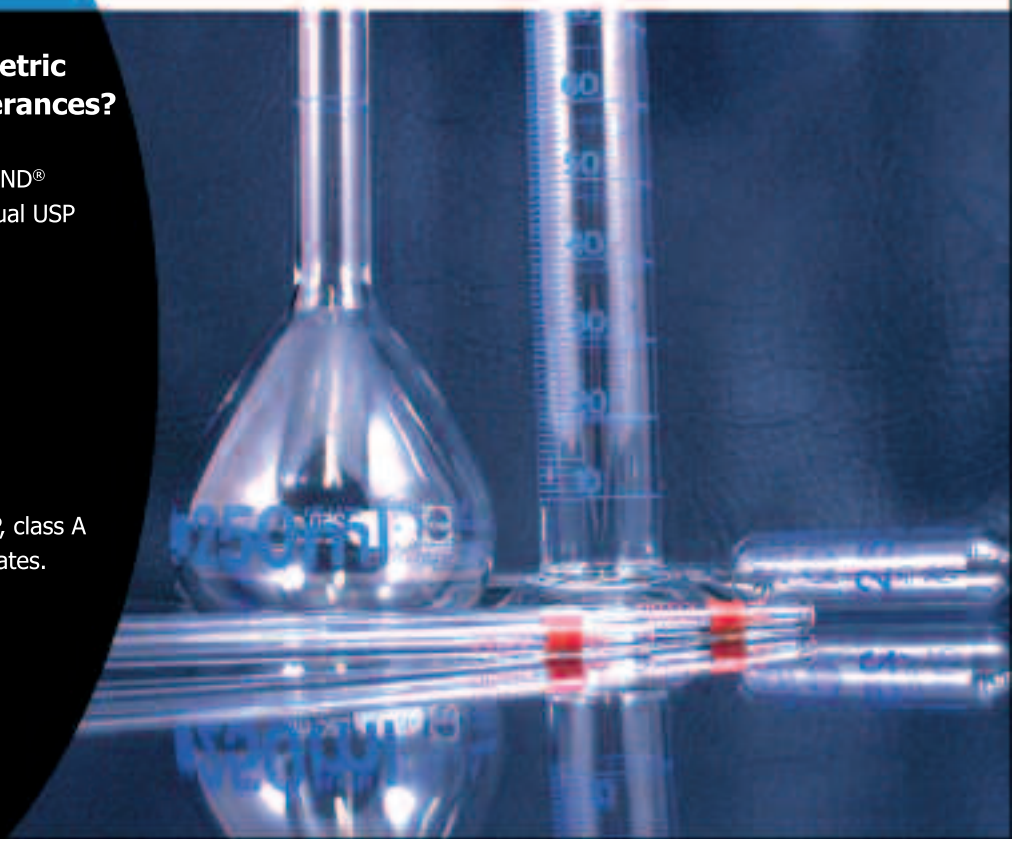

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Editorial

In this issue – we have a mix of regular items and contributions from chemists around the island of Ireland which hopefully has something of interest for everybody. In particular I would like to welcome a feature-article contribution from **Prof. Karl Hale,** the chair of Organic and Medicinal Chemistry and Chemical Biology at Queens University Belfast on some of his recent work in the field of both natural product synthesis and the modification of those materials with the aim of improving their biological potency. We are also pleased to have a research article contributed from an industrial research laboratory – **Dr. Stephen Hynes** has detailed the biomedical applications of cyanoacrylates – versatile materials being developed at Henkel in Dublin. Clearly there is much more to 'superglue' than I imagine most of us would have thought. From the nanoworld we also have an article written by **Prof. Michael Morris** from the Tyndall Institute and CRANN on the (chemical) engineering of small structures for the microelectronics industry. **Dr. Catherine Audley** and **Dr. John Mullane** have provided a profile of the Dept. of Chemical and Environmental Sciences at the University of Limerick. Our past president **Dr. Donal Coveney** has contributed the ICN crossword and an article on the alarming worldwide shortage of acetonitrile, and we have the usual roundup of meeting/event summaries and highlights from the chemical literature.

We welcome comments and suggestions on the balance and direction of the ICN - members are also strongly encouraged to submit essays, articles and correspondence on any issues/developments affecting chemistry, either globally or in Ireland.

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Meeting Report: The European Young Chemists Network

Colin Martin, *School of Chemistry, Trinity College Dublin, Dublin 2, Ireland*

As a satellite event associated with the 2nd EuCheMS Chemistry Conference (Torino Sept 2008) a one day EYCN-Young Chemists Event was held. An outline of the meeting is available at http://www.euchems-torino2008.it/site/other_scientific_events.asp.

Presentations on the topic of "Between science and Industry" were given by Prof. Michael Droscher (Head of Innovation EVONIC Industries) and Dr. Gernot Klotz (European Chemical industry council) outlining the current and future state of international young chemists from both an industrial and governmental viewpoint. The key message from both speakers was that the existence of the EYCN is seen as a key necessity in the future development of the European chemistry.

Following these talks an informal discussion was held in order to allow those attending the meeting who had no knowledge of the EYCN to discuss ideas and future strategies for developing the network in the future with those national delegates present at the Torino meeting.

The key aim of the satellite meeting was to further increase awareness of the EYCN throughout the wider chemistry community; this was achieved mainly through the 'Young chemist's reception' to which every delegate at the Torino conference under 35 was invited. Over 150 people attended this reception where delegates from different European young chemist associations were present (7 in total, myself from Ireland along with delegates from, Austria, Germany, Finland, Hungary, Portugal and the United Kingdom), in order to spread information about the EYCN.

The next meeting of the EYCN delegates is scheduled to take place at the German JCF symposium (similar to the Irish universities colloquium) from Wed March 11th- Saturday March 14th 2009 in Essen. http://www.jcf-fruehjahrssymposium.de/2009/index.htm

Meeting Report: UCD Chemical Society Inaugural Lecture

Secretary, *UCD Chemical Society, University College Dublin, Dublin 2, Ireland*

The 64th annual Chemical Societies Inaugural event was held on the 16th of April at University College Dublin. Following tradition, the evening was opened with a talk from an invited lecturer, followed by a food and drinks reception in the school. The event was kindly sponsored by the Institute of Chemistry of Ireland.

This year, the Chemical Society was privileged to have Professor Max Malacria from the University of Paris attend as our Inaugural Speaker, a researcher of note on the development of new selective and efficient approaches to complex polycyclic molecules, transition-metal-catalysed reactions, radical cyclisations, and asymmetric synthesis of natural compounds of biological interest. Professor Malacria gave a talk entitled "Platinum and Gold Catalysed Cycloisomerisation of Enynes, Allenynes and Allene Dienes.

Professor Malacria has been much lauded within his field and has won a number of awards, including the award of the Organic Division of the French Chemical Society and in 2000 he received the 'Grammaticakis Neumann' prize from the French Academy of Sciences, and in 2001 the "Médaille d'Argent" from the CNRS.

This Chemical Society event was attended by over 100 academic staff, postgraduate and undergraduate students from the university. Professor Malacria's research proved to be a very interesting and challenging topic for discussion, as it summarised a large section of his work and proved to be an excellent overview of the whole field, as well as highlighting his group's achievements and applications of his research, from potential new drugs and natural product syntheses to surface chemistry applications.

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Holy Rosary Primary School Science Week, 26th – 30th Jan 2009

Dr. Brian Murray, *Dept. of Science, IT Tallaght, Tallaght, Dublin 24*

Holy Rosary Science Week has proved to be a great success again this year. Now in its third year, the emphasis this year was on increased involvement by the students. A variety of activities were held in the school each day including the *Sustainable Energy Ireland (SEI) Guzzler workshop, BDI's Me and My Body (MAMBO) program, Bubble show, Science Show* and no Science week would be complete without a *mystery to investigate CSI style!* All classes from Junior Infants through to Sixth Class were involved. ITT Dublin facilitated a variety of class based experiments for 2nd, through to 6th classes. These experiments ranged from pH effects on plant growth, effects of noise on heart rate, growing crystals, sweat chromatography, and the determination of which foods grow the best moulds.

The highlight of the week was when the students presented projects on a variety of topics which they worked on themselves. These included building/launching rockets and constructing different types of working models. It was clearly evident from the excitement in the school that the event met its objective of raising the awareness of Science. Some of the Student's comments:

6th class: "The rocket workshop was excellent and it is the best thing that they have ever done in this school. It was cool and fun. They never thought rocket science would be so interesting. It was brilliant to see our rockets being launched in the school."

5th class: "The best thing was constructing our design and make projects and working with the electrical circuits. They were very proud when the items were put on display for the whole school to see."

4th class: "We loved trying to solve the CSI Ballycragh mystery. It brought great fun to the week and we felt like real detectives."

3rd class: "We really enjoyed the crystals and seeing them form. The MAMBO programme was also brilliant because we got to learn more about what happens inside our bodies." Junior infants were very excited by the bubble show and are still talking about it months later.

The teachers, parents and children agreed that Science Week was a great success in terms of both education and fun. The sponsors of the event, to whom we are deeply grateful, included Helsinn Birex Pharmaceuticals, Institute of Chemistry of Ireland (ICI), International Society for Pharmaceutical Engineers (ISPE) and ITT Dublin.

School Profile: The School of Chemical and Environmental Sciences at the University of Limerick

Dr. Catherine Adley and Dr. John Mullane, *Department of Chemical & Environmental Sciences, Plassey Park, University of Limerick*

The Department of Chemical and Environmental Sciences traces its provenance to the establishment, in 1979 of a B. Sc. Degree in Industrial Chemistry in what was then the National Institute for Higher Education, Limerick. The first graduates from this programme were conferred in 1983. The Institute expanded significantly throughout the 1980's and was awarded University status, by statute, in 1989. Continued development and considerable internal reorganisation followed this event, one result of which was the formation of the current Department of Chemical and Environmental Sciences. The twin aims of the new University were identified as excellence and relevance and the Department is committed to those standards in its teaching and research.

Courses

The Department of Chemical and Environmental Sciences (CES) is responsible for delivery of the following courses:

- B. Sc. in Environmental Science
- B. Sc. in Health and Safety
- B. Sc. in Industrial Biochemistry
- B. Sc. in Pharmaceutical and Industrial Chemistry
- Professional Diploma in Safety, Health and Welfare at Work
- Graduate Diploma in Chemical Engineering (Run jointly with the Department of Mechanical & Aeronautical Engineering)

The Department is also responsible for a range of modules delivered as service teaching to other Departments.

All the B. Sc. degree level undergraduate courses are of four years duration. The academic year is divided into two 15 week semesters: The Autumn Semester runs from early September to December and the Spring Semester runs from late January to May.

The academic programmes are organised on a modular basis. Generally each undergraduate takes 5-6 modules per semester. Each module comprises lectures plus an appropriate mix of tutorials, assignments, laboratory and fieldwork. Each module is individually assessed. All such assessments are then used to calculate the Quality Credit Average (QCA). A satisfactory score is required for progression from year to year. Final graduation level is decided on the basis of a weighted average of the scores for the final three years with modules from years three and four carrying twice the weighting of those from year two.

All the degrees feature a period of Cooperative Education, covering the sixth semester and the following summer period, wherein students are employed by participating companies. This not only provides students with valuable real-life work experience but, *via* feedback from students and employers, helps ensure that relevance of course material to job markets is maintained. The historical employment record of graduates from these programmes has, consequently, been consistently good.

The professional diploma and graduate diploma programmes are also organised on a modular basis and are assessed *via* the QCA system. The Department has a suite of modern, well-equipped laboratories available for teaching purposes.

The following is a brief description of each of these courses.

B. Sc. in Environmental Science (Course Director: Dr. Teresa Curtin)

This Programme aims to be distinctive in being immediately relevant to industry and business, through a focus on (a) environmental science - the application of fundamental sciences to environmental issues, (b) environmental management – how strategies can be developed and implemented in protecting all aspects of the environment, (c) clean technology – technologies and processes to minimise the negative impact of technology on the environment and (d) waste management - study of the physical methodologies and techniques for dealing with waste generated by the manufacturer and consumer.

B. Sc. in Health and Safety (Course Director: Dr. Tom O'Dwyer)

This is a new degree which will produce its first graduates in 2009. The main areas of study in the programme include, (a) toxicology & health - how occupational hazards potentially affect the health and well-being of the worker, (b) safety analysis - the design of safe operating systems & processes, (c) legislation - understanding the legal framework which underpins health & safety practice in both Ireland and Europe, (d) risk management - identifying safety hazards and quantifying and managing the associated risk, (e) ergonomics-assessing people in their physical environment in relation to levels of comfort, posture, manual handling, musculo-skeletal disorder and injury avoidance methods, and (f) occupational hygiene – designing monitoring programmes for the workplace, assessing potential worker exposure to dusts, vapours, noise, biohazards etc.

B. Sc. in Industrial Biochemistry (Course Director: Professor Gary Walsh)

The B.Sc. in Industrial Biochemistry is a degree program in biotechnology. The core subjects studied include: (a) biochemistry - study of the structure and biological function of cellular molecules such as proteins, carbohydrates, lipids and DNA, and how these molecules interact to form living cells, (b) industrial biochemistry - study of the applications of biological molecules for medical, industrial, environmental, agricultural or analytical purposes, (c) microbial technology - study of the biology and uses of bacteria, fungi, yeast and viruses, (d) genetic engineering - identification, isolation, engineering and expression of genes in order to gain new insights into gene function or for the generation of gene-mediated industrial/medical products, and (e) analytical science - methods and techniques used to detect and quantify biological molecules/chemicals in samples, for example measurement of hormone levels in blood or pesticide levels in water.

B. Sc. in Pharmaceutical and Industrial Chemistry (Course Director: Dr. Mathew Fanning)

The Pharmaceutical & Industrial Chemistry course is designed to qualify graduates for employment as professional chemists in a variety of industrial and professional positions, particularly, but not exclusively, in the pharmaceutical area. In common with the more traditional chemistry degrees it focuses on foundation chemistry (organic, inorganic, physical and analytical) in the first two years. It differs from the traditional courses, however, in a number of ways in the last two years of the programme. Thus in these two years a significant element of chemical engineering topics is covered as well as applied aspects of organic, inorganic, physical and analytical chemistry. These features of the course ensure that graduates are better prepared for the challenges of an industrial position immediately on graduation.

Professional Diploma in Safety, Health and Welfare at Work

This is a two-year, part-time multidisciplinary course designed to meet the academic competency requirements of the Safety, Health and Welfare at Work Act, 1989. The course is intended for persons with a professional interest in safety and health in the workplace, particularly safety advisors, occupational hygienists, physicians and nurses. The diploma is recognised by the Institution of Occupational Safety and Health (UK) for granting Corporate Membership of the Institution, subject to appropriate experience.

Graduate Diploma in Chemical Engineering (Course Director: Professor Toshko Zhelev)

The Graduate Diploma in Chemical Engineering is a conversion course for appropriately qualified graduates from Science or Engineering disciplines who wish to expand their employment horizons by obtaining a recognized qualification in chemical engineering. Being accredited by the Institution of Chemical Engineers, it offers an exceptional opportunity for science and engineering graduates to obtain a recognised qualification in chemical engineering in only one calendar year full-time, or two years part-time. The course comprises taught modules (primarily in chemical engineering subjects), two design projects, one on a continuous process and one on a batch (pharmaceutical) process, and a programme of industrial visits.

Chemical and Environmental Sciences Department Research Profile

The University of Limerick has an established reputation for being among Ireland's leading universities in industry-led research. This has resulted in significant research commercialisation activities and collaboration between our researchers and industry. The department staff has contributed significantly to this established research profile. All of the department key research indicators are showing strong growth, with increases in research applications, research income, and postgraduate numbers. Presently the department has 75 post graduate research students, complementing the strong gains in research outputs.

The University of Limerick Key Research Strengths lie in six main areas - of which four have a significant input by staff from the Department of Chemical and Environmental Sciences, these include

- Energy and Sustainable Environment: with particular emphasis on biomass and biofuels, energy storage and materials, and monitoring, modelling and sustainability
- Materials & Surface Science: including composite materials, nano materials, solid-state pharmaceutical materials and biomimetic materials (for solar energy conversion and for biocatalysis)
- BioEngineering & Biosciences: including MicroFluidics, Biomedical Engineering and Structural Biology
- Applied Mathematics: with particular emphasis on mathematical modelling of fundamental problems in science, engineering and industry.

Professor Kieran Hodnett is director of the SFI funded Solid State Pharmaceuticals Cluster which investigates pharmaceutical solids and brings together complementary academic and industrial groupings from the disciplines of Chemistry, Pharmaceutics, Pharmaceutical Technology, Chemical Engineering and Mechanical Engineering. Department members have significant interests in additional SFI funded clusters including The SFI Strategic Research Cluster in Advanced Biomimetic Materials for Solar Energy Conversion (K. M. Ryan & T. Curtin).
The environmental research projects of members of CES branch into a myriad areas from mathematic modelling to membership of centres such as Carbolea, the Centre for Environmental Research and the Charles Parson Initiative on energy and sustainable environment. Projects include:

- Thermochemical processing of waste and energy crops (J. J. Leahy)
- Biorefinery and second generation biofuels and catalysts to upgrade bio-oils for the development of high value chemicals (M. Hayes)
- Efficient usage of energy, water and other resources in industrial processes. Chemical engineering optimisation. Process Integration, Process Systems Engineering (System Analysis, Synthesis & Optimisation) (T. Zhelev)
- Environmental impact assessments for industrial plants, landfills and quarries
- Ecological investigation of biodiversity and especially studies on the impact on biodiversity of human activities, such as management and pollution. Environmental impact assessments for industrial plants, landfills and quarries. (R. Moles/ B. O'Regan)

The department has an emerging centre in structural biology. The centre has been strengthened by the recent appointment of Dr. T. Soulimane. Additional biochemical projects include: highly stable enzymes of industrial and environmental interest (G. Walsh), mobile generic elements in particular ICE's and genomic islands in Enterobacteriaceae (T. Pembroke), biofilm research and persistence of in high purity water (C. Adley), beta-Lactam chemistry and the development of novel beta-lactamase dependent prodrugs (T. Smyth) and the use of mesoporous silicates to encapsulate proteins (E. Magner).

Our newest Health and Safety research programme is enhanced with the appointment of new staff members (P. Davern & F. Wixted) who contribute to our occupational exposure projects of indoor air quality and pollutant dispersion modelling and monitoring (T O'Dwyer). In addition the department members P. Childs and C. Adley contribute to the SIF funded UL National Centre for Excellence in Science Teaching and Learning with an aim of conducting best practice research into teaching and learning in science.

Information on all of our staff research interests can be obtained from our web page at www.ul.ie.

Update: Acetonitrile Shortage

Dr. Donal Coveney,
TopChem Laboratories Limited, 70 Western Parkway Business Park, Ballymount Drive, Dublin 12, Ireland

It is hard to believe but there is a world shortage of acetonitrile. Prices have been climbing steadily over the past year with many suppliers on back order and customers experiencing anxiety over the uncertainty in supply. Prices have shot up dramatically since 2008. In February, I received an unsolicited offer from a Florida based trader offering HPLC acetonitrile at an eye watering $110 per litre. Sure enough, on checking our purchasing records at TopChem, we were paying €13.13 per 2.5L bottle of HPLC acetonitrile in 2008. To be fair to our reputable and reliable supplier, they held this price all through 2008. However the New Year heralded an increase to €75 a bottle – a cool 471% increase. A 70 litre refill of diesel in my car costs less than that!

Why the shortage you ask? Well it is attributable to the falloff in demand for acrylonitrile. Commercial production of acetonitrile is actually a by-product of the manufacture of acrylonitrile. The main use of acrylonitrile is in acrylic fibres and resins which are used in the automotive, electronics and consumer goods sectors. Some acrylonitrile producers do not even commercialise the small amount of acetonitrile by-product, preferring to use it instead as fuel in their facilities.

Given the general economic downturn especially the collapse in car sales it is hardly surprising that the weak acrylonitrile demand is having a knock-on effect on acetonitrile supply. To make matters worse, one key supplier in the US shut one plant temporarily last year following hurricane damage and took another offline early this year for an expansion.

For chemists working in academia, this is certainly a nuisance if a literature or in-house procedure calls for acetonitrile. No doubt alternatives can be found if needs must, but we have enough things to challenges us these days. And so often reactions are influenced dramatically by solvents so that a direct replacement can be difficult to find.

For those of us working in the pharmaceutical industry, this is potentially quite serious. Acetonitrile is widely used in analytical methods and these methods are fixed either in the USP, EP or the companies own filings to the FDA, IMB and other regulatory agencies. Changing a method requires full validation and prior approval by the regulatory body prior to implementation. This is a lengthy and expensive procedure and prior to approval the old method must be used.

In a former life I had the experience of having to recrystallise an active pharmaceutical ingredient from acetonitrile which was not ideal as the allowed residual limits are relatively low for acetonitrile relative to other common solvents such as isopropanol, ethanol and acetone. Despite our best efforts, nothing else worked as well as acetonitrile. As far as I am aware, the company is still using acetonitrile for this commercial product which must be creating great tension in that parish!

This is a perfect example of the law of supply and demand. No doubt, the high prices will tempt manufacturers to supply the market leading ultimately we hope to a rebalancing of price and supply. We don't really think about bulk commodities do we, preferring to take such staples for granted, assuming these will always be readily available.

Simon Owens, Chemical Specialist of Fisher Scientific– a leading supplier of acetonitrile into the Irish market advises that, "The last 18 months has seen great volatility in the availability of acetonitrile and rather than introduce blanket rationing, Fisher Scientific Ireland has worked closely with each of our customers to ensure critical processes have not been affected during this time. We are pleased that due to our global purchasing power as part of Thermo Fisher Scientific, the availability situation is improving and having a UK based laboratory chemicals plant allows us to quickly respond to customer needs, not only in terms of supply, but also assured quality."

So next time you pick up a bottle of a common solvent or reagent think for a moment of the legions of chemists and engineers slaving away in the background delivering these products cheaply and in high quality without a word of thanks!

Feature Article

Molecules of the A83586C-Azinothricin-Kettapeptin and Agelastatin A Class; Their Synthesis, Mechanisms of Antitumour Action, and Potential For Counteracting β-Catenin Driven Cell Signalling

Prof. Karl J. Hale and Dr. Soraya Manaviazar

School of Chemistry & Chemical Engineering, Queen's University Belfast, Stranmillis Road, Belfast, BT9 7AG, Northern Ireland

Introduction

The total synthesis of complex, pharmacologically-active, natural products and their analogues continues to play a central role in the field of organic synthesis - not only for the unique contributions it makes to new chemical reaction development, but also for the many important and powerful insights it provides into the functioning of genes and proteins of relevance to human disease, through its ability to deliver natural and artificial small molecules that can modulate the workings of eukaryotic cells.[1]

A survey of the vast amount of small molecule chemical biology literature that has appeared over the past twenty years very quickly reveals the enormous impact that this type of endeavour has had on the isolation, purification and identification of novel proteins of fundamental significance to biology and medicine. This is a fact that has not gone unrecognised by the strategists at the US National Institutes of Health who, when formulating their recent NIH Roadmap,[2] placed small molecule deconvolutional biology at the very forefront of research effort aimed at converting genomic discoveries into therapeutic insights of relevance to human disease. Significant also is their recognition that natural products (and their analogues) will continue to play an important role in much future chemobiological interrogation work.

For some time now, our group[3] at Queen's University Belfast has been heavily engaged in chemical genomics research in order to expedite our anticancer drug discovery efforts, with several of our complex natural product total synthesis programmes having underpinned major target validation efforts, through their provision of various highly sophisticated small molecule probes for biological interrogation purposes. In many instances, the molecules that we have prepared have given significant biological insights that would otherwise have not been garnered, had we relied solely on gene knockouts in mice, RNA interference, or mutational analysis. We have been particularly fortunate in many of our endeavours inasmuch as nearly all of the natural product targets that we have synthesised to date have had unique and fascinating molecular architectures which, rather fortuitously, have conferred upon them unprecedented and quite specific biological effects at different drug concentrations. As a consequence, we have been able to employ some of these novel molecular tools to study various cell signalling pathways and proteins of relevance to cancer cell growth and metastasis, and we have been able correlate specific biological events with inhibition of cancer cell growth or the modulation of certain metastasis-inducing proteins.

The A83586C, azinothricin, kettapeptin antitumour macrolides

In the mid-1980s, the natural product screening group of F. Hoffmann-La Roche in Nutley, New Jersey, reported their discovery, isolation and structure determination of a potent new antibiotic in the culture filtrates of *Streptomyces sp. X14950*. They termed the molecule (+)-azinothricin,[4] on account of the two rather striking α-hydrazino-acid units (piperazic acids) it contained within its cyclodepsipeptide core. It later transpired that (+)-azinothricin was the prototype of a totally new class of natural product[5] in which there is a highly functionalised pyran ring connected to an unusual 19-membered cyclodepsipeptide ring system *via* a hydroxyleucine amide residue. Since this seminal discovery by Maehr and coworkers back in 1986, many other azinothricin family members have now been identified (see Fig 1); some with more elaborate pyran side-chains and cyclodespipeptides, others with less complex constituents.

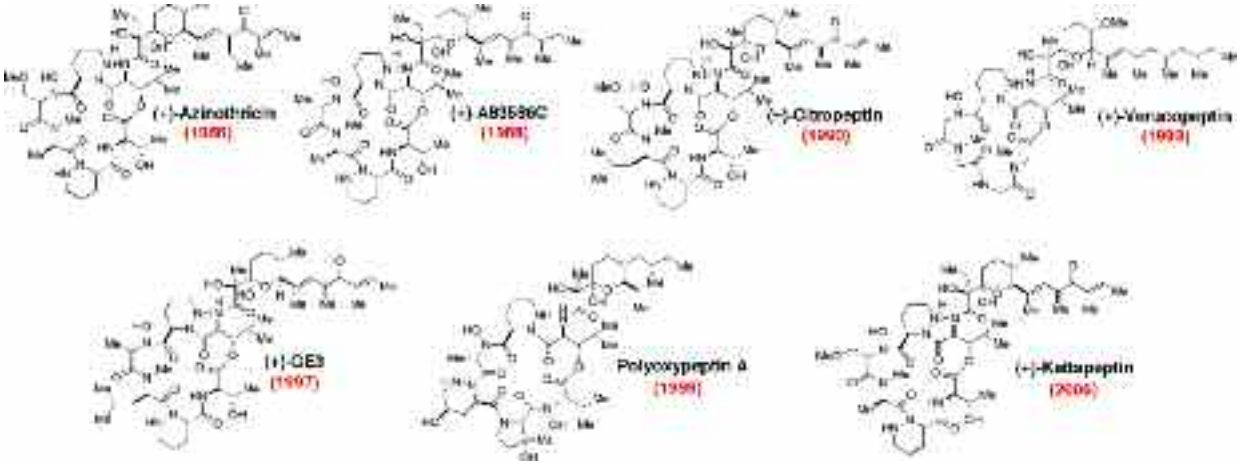


Figure 1. The azinothricin/A83586C/kettapeptin family of antitumour cyclodepsipeptides.

Collectively, each of these molecules has powerful antibiotic effects allied with strong antitumour properties.[5] In the case of GE3 (Fig. 1),[5d] the Kyowa Hakko Kogyo team of Sakai and coworkers reported that a single intraperitoneal dosage of GE3 at 2 mg/kg was sufficient to bring about a 47% reduction in tumour volume in mice xenografted with the (incurable) human PSN-1 pancreatic carcinoma within 11 days of treatment, without any serious toxic side effects. GE3 also displayed potent growth inhibitory effects against a range of human tumour cell lines at low drug concentration including HeLa S3 cervical carcinoma cells (IC_{50} = 6 nM), A431 human lung cancer cells (IC_{50} = 16 nM), and Saos-2 osteosarcoma cells (IC_{50} = 3.6 nM). In terms of a mechanism for the observed antitumour effects, GE3 was originally suggested to operate through inhibition of E2F transcription factors, although no specific details were given by Sakai on either precisely how it functioned in this way, or on its level of potency.

In order to shed new light on this biological behaviour (which was unique in 1997), and because related family members such as A83586C, citropeptin, verucopepin, polyoxypeptin A and kettapeptin were also reported to be powerful antitumour agents, we decided to explore how molecules of this class might be operating, in collaboration with Drs Alexander Wood and Ying-Nan Chen of the Novartis Institutes for Biomedical Research in Boston. The work was very much a follow on of our group's first generation asymmetric total synthesis of A83586C.[6]

We commenced our joint research effort[7] by first of all establishing whether synthetic A83586C could inhibit cancer cell growth through blockade or disruption of the actions of functionally active E2F transcription factors. E2F transcription factors are heterodimeric protein complexes formed from the association of one of eight E2F proteins (E2Fs 1-8) with one of two DP proteins (DPs 1 and 2). Deregulated E2F transcription factor activity, involving E2Fs 1-6, is thought to be a major contributor to the onset of human malignancy. Indeed, E2F1 overexpression is not generally encountered in normal human tissue, but it is in cancer tissue. Elevated E2F1 levels are often associated with aberrant retinoblastoma protein (pRb) function.

Ordinarily pRb is a tumour-suppressing (gatekeeper) protein found in all human cells which, when it lies in its "resting" unphosphorylated state, binds to, sequesters, and inactivates functionally active E2F transcription factors, to counteract their effects at promoting cell growth and proliferation.

Initially we examined whether A83586C could inhibit E2F transcription factor complexes by disrupting the all-important E2F-DP interaction, which is known to be critical for effective E2F transcription factor functioning. This was done by performing 'pull down' experiments with GST-E2F1 and ^{35}S-labelled DP1 protein in the presence of A83586C. Our results pointed to A83586C not perturbing this interaction in any way. We next examined whether A83586C could downregulate E2F1 protein expression within HCT116 human colon carcinoma cells and significantly, at a concentration of 0.3 mM, we observed that it did indeed downregulate E2F1 after 24 h of cell exposure to the drug. In order to assess whether A83586C had the ability to counteract cyclin D and E and cyclin-dependent kinase mediated phosphorylation of the pRb tumour suppressor protein, which renders it oncogenic and tumour-promoting, we next examined whether A83586C could induce dephosphorylation of hyper-phosphorylated pRb within HCT116 cells, to convert it to the tumour-suppressing dephosphorylated pRb form, which binds E2F-DP transcription factors and functionally inactivates them. Importantly, we showed that at 0.3 mM concentration, A83586C could very effectively cause hyperphosphorylated, oncogenic, pRb to undergo dephosphorylation to become E2F-complexing and thereby tumour-suppressing. Thus, we demonstrated that A83586C has the capacity to counteract the effects of upregulated cyclins D and E and their associated cyclin-dependent kinases, which are often overexpressed in many malignant cancers. It will thus be appreciated that molecules of the A83586C/kettapeptin/GE3 family can serve as E2F transcription factor inhibitors within human cancer cells by two distinct mechanisms: one involving E2F downregulation in the case of E2F1; the other involving dephosphorylation of hyperphosphorylated pRb (although the latter effect might actually be responsible for the former).[7]

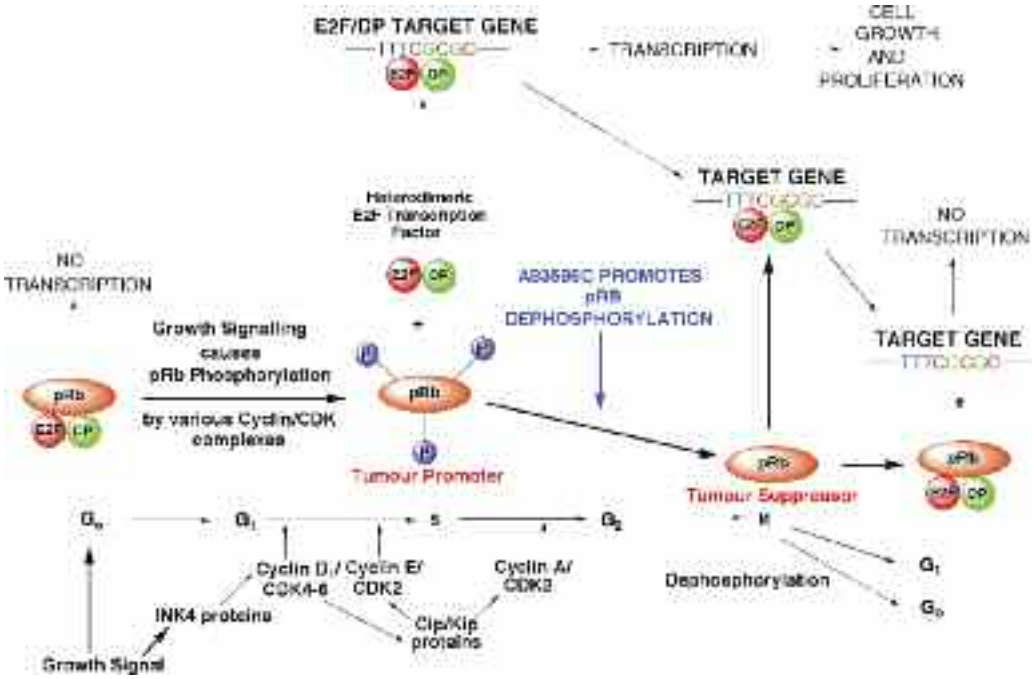


Figure 2. E2F Transcription factors, cyclins, cyclin-dependent kinases and the retinoblastoma protein (pRb), play an important role in initiating cell growth and proliferation, and are deregulated in many cancers. A83586C has the ability to promote the conversion of tumour-promoting hyperphosphorylated pRb into its tumour-suppressing dephosphorylated form within human cancer cells; this then binds to and inactivates functionally active E2F transcription factors to switch off cancer cell growth and proliferation. A83586C is also able to inhibit E2F1-DP transcription factor mediated gene transcription through its downregulation of E2F1 protein expression within cancer cells.

Another quite remarkable property that we have uncovered for A83586C lies in its ability to very potently counteract the effects of upregulated β-catenin signaling within HCT116 human colon carcinoma cells by disrupting the β-catenin/TCF_4 protein-protein interaction.[7] In this regard, A83586C is the most potent Wnt/β-catenin/TCF_4 signalling antagonist so far identified (IC_{50} = 3 nM) using TOP-FLASH/FOP-FLASH luciferase reporter assaying in this same cancer cell line. Upregulated β-catenin signalling has been suggested to be a major contributor to cancer onset in a variety of cancers, the β-catenin/TCF_4 interaction being known to initiate transcription from a number of genes critically involved in cancer cell growth and metastasis. Some of the more important β-catenin/TCF_4 gene targets and their roles are shown in Figure 3.

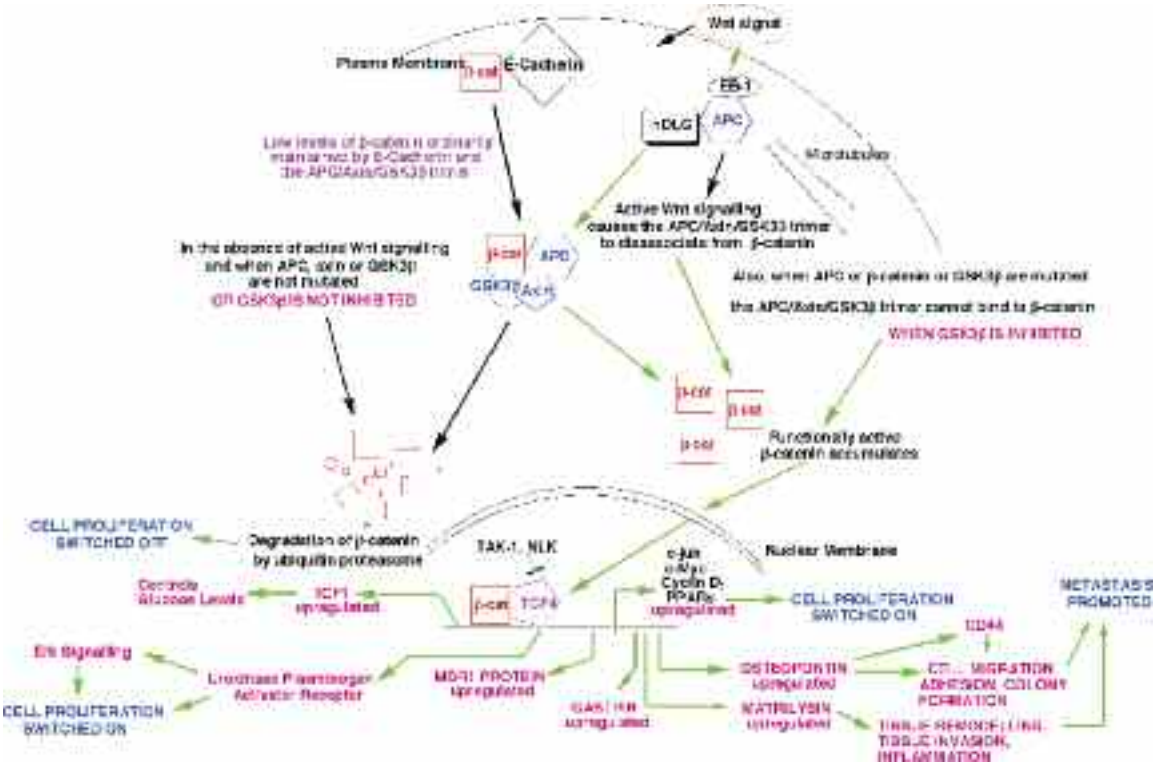
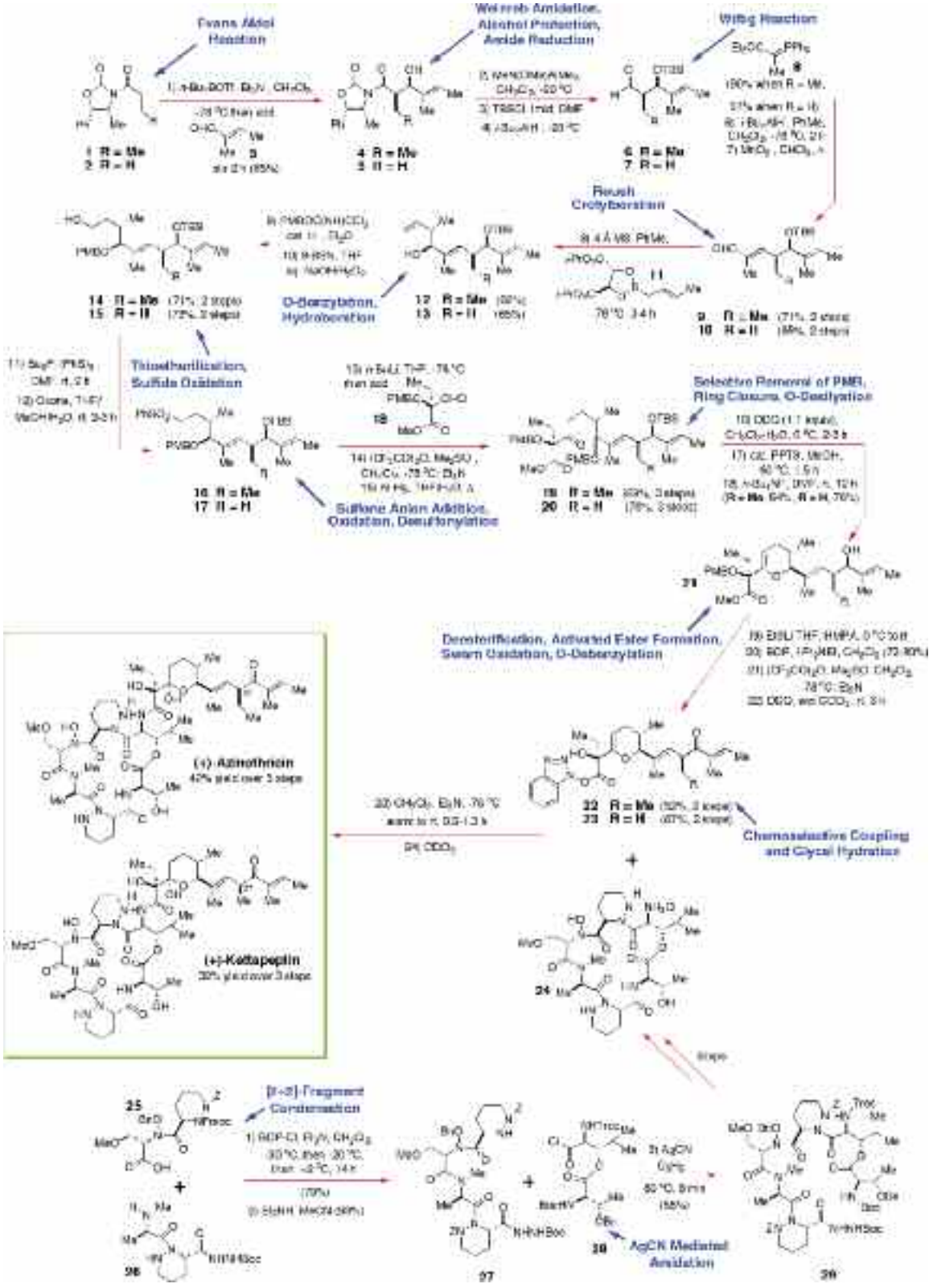


Figure 3. The Wnt/β-catenin/TCF4 cell signaling pathway and its potential contributory role to cancer cell growth, proliferation, and metastasis when deregulated. In many metastatic cancers, β-catenin signaling is upregulated, and this stimulates gene transcription from the TCF4 promoter. Some of the genes transcribed are shown. A83586C family members have the ability to disrupt or blockade this interaction of the β-catenin protein with TCF4.

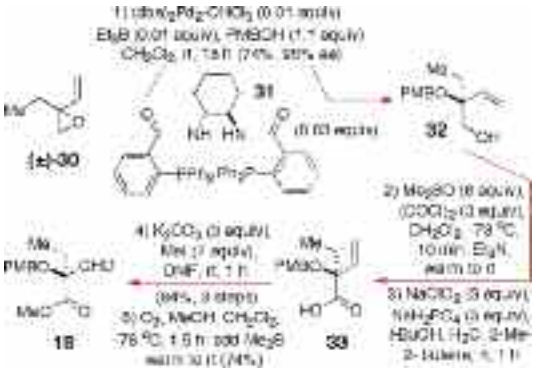
Based upon these novel biological findings, Novartis very generously sponsored our group to develop an improved second-generation synthesis of molecules of the A83586C/ Kettapeptin/Azinothricin class for the purpose generating simplified analogues for biological evaluation and, quite recently, we were successful in achieving this goal with the new route shown in Scheme 1.[8] Key steps in this considerably shortened pathway were the Evans asymmetric aldol reactions used to build up **4** and **5**, the stereocontrolled Wittig processes on **6** and **7** en route to **9** and **10**, and the Roush asymmetric crotylborations that were used to build up the remaining chiral centres in sulfones **16** and **17**, prior to their respective unions with aldehyde **18**.

Further transformations on **19** and **20** thereafter elaborated them into the desired activated esters **22** and **23** needed for the syntheses of kettapeptin, A83586C and azinothricin respectively.

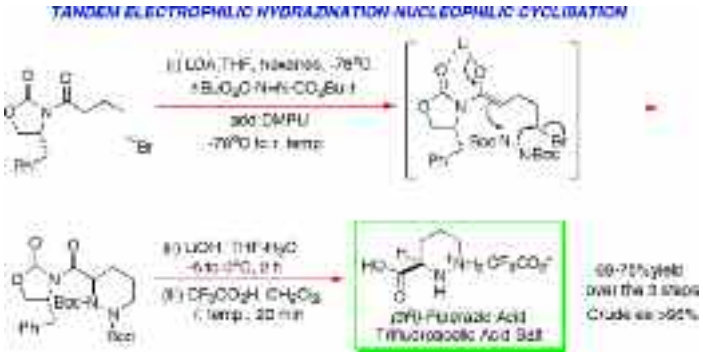
A particular highlight of the new route to **22** and **23** lay in the considerably improved pathway that was put in place to the aldehyde **18** which featured a Trost Pd(0)-catalysed asymmetric epoxide ring-opening/dynamic resolution[9] on (±)-epoxide **30** with *p*-methoxybenzyl alcohol to secure the alcohol **32** which was obtained in virtually single enantiomer form (Scheme 2). Another important methodological contribution was the tandem Evans hydrazination/nucleophilic cyclisation pathway that we conceived[10] in the early 1990s for construction of the two piperazic acid enantiomers of these targets (Scheme 3), which critically underpinned the cyclodepsipeptide synthesis work that was being undertaken (Scheme 1). The latter were then utilised for a [2+2+2]-fragment condensation sequence involving **25, 26** and **28** to give **29** which, after due structural adjustment, ultimately allowed a Carpino HATU cyclisation to be used to close the 19-membered macrolactam ring. After protecting group removal cyclodepsipeptide salt **24** was eventually obtained.


Evans Aldol Reaction
Weinreb Amidation, Alcohol Protection, Amide Reduction
Wittig Reaction
Roush Crotylboration
O-Benzylation, Hydroboration
Thioetherification, Sulfide Oxidation
Sulfone Anion Addition, Oxidation, Desulfonylation
Selective Removal of PMB, Ring Closure, O-Desilylation
Deoxidation, Activated Ester Formation, Swern Oxidation, O-Debenzylation
Chemoselective Coupling and Glycal Hydration
[3+2]-Fragment Condensation
AgCN Mediated Amidation
(+)-Azinothricin
42% yield over 3 steps
(+)-Kettapeptin
35% yield over 3 steps

Scheme 1. The 2009 Hale-Manaviazar Route to (+)-azinothricin and (+)-kettapeptin



Scheme 2 Our improved second generation synthesis of aldehyde **18** via Trost epoxide ring-opening.



Scheme 3. The tandem electrophilic hydrazination-nucleophilic cyclisation reaction for piperazic acid synthesis.

Probably the most spectacular accomplishment of our respective total syntheses of (+)-kettapeptin and (+)-azinothricin[9] were the highly chemoselective couplings that we effected between the fully elaborated cyclodespipeptide **24** and activated esters **22** and **23** which proceeded very cleanly to give the two natural products in respectable overall yield for each of these last three steps. When one considers the great complexity of the two fragments that are being joined together in this union, alongside the absence of protecting groups in both reaction partners, the great success of both these sequences is noteworthy.

On the back of this new second-generation strategy, we were able to conveniently prepare significant quantities of both natural products as well as several hundred milligram batches of sophisticated analogues such as the A83586C-citropeptin hybrid.[7] An A83586C-GE3 hybrid and an analogue known as L-Pro-A83586C were also prepared by the new strategy.[7] In every case the new pathway allowed 12 synthetic steps to be cut off the overall sequence needed to these molecules. As such, the new strategy represents a considerable improvement on our 1997 strategy.

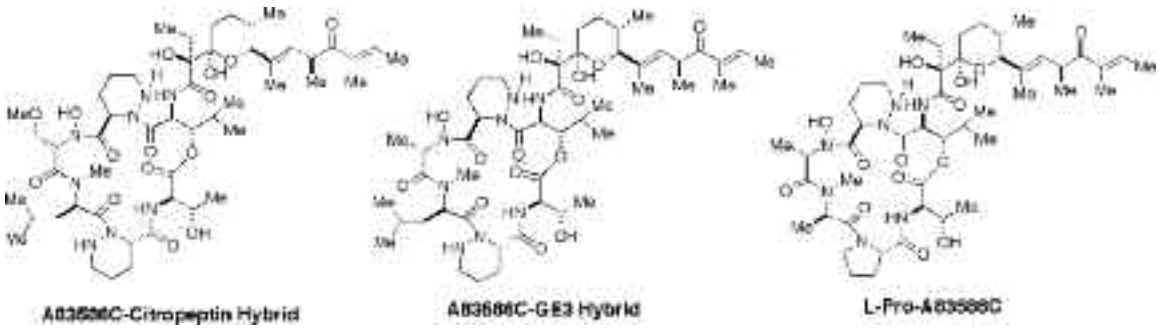
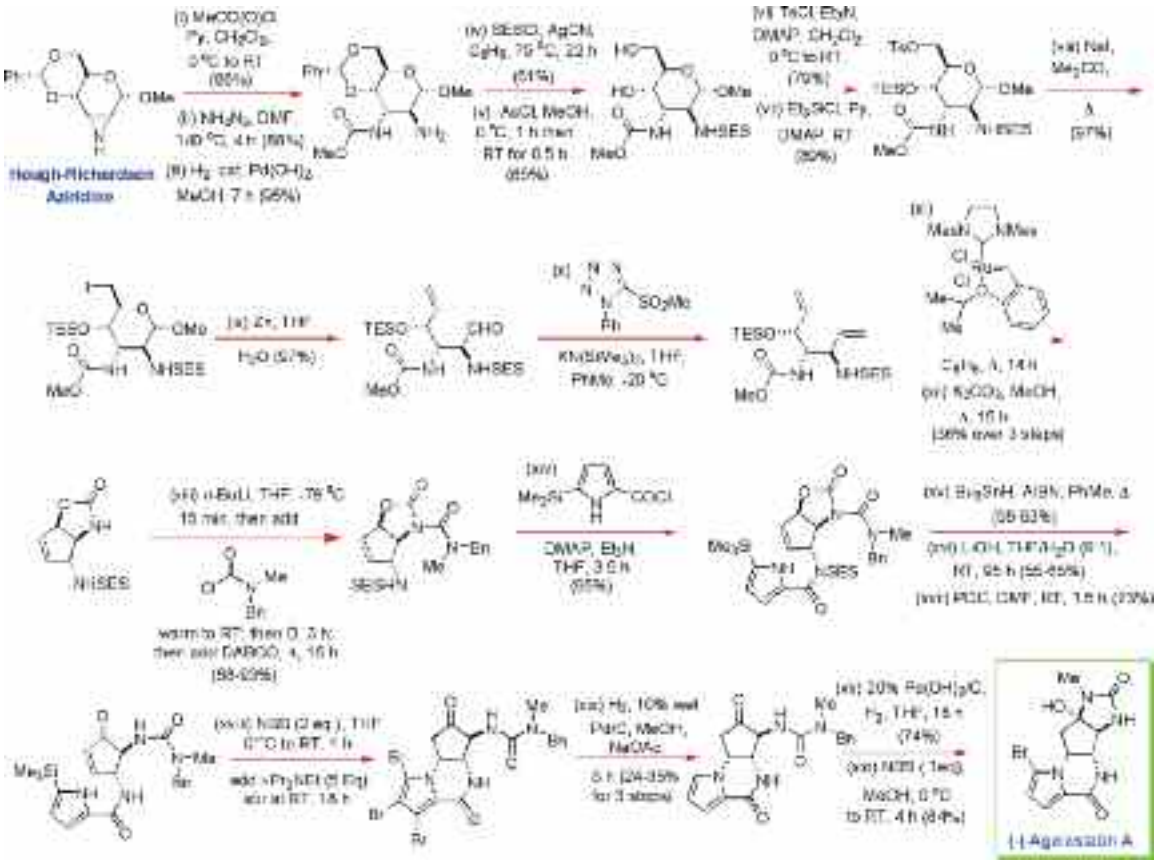


Figure 4 Some of the many analogues that we have prepared by our new, improved, second-generation synthetic strategy for molecules of the A83586C/azinothricin/kettapeptin class.

Follow-on studies with these and other analogues have now confirmed that when one disrupts the TCF4/β-catenin interaction with a small molecule drug, one can very effectively downregulate expression of the TCF4/β-catenin target gene, osteopontin (OPN) (Fig. 3).[7] The latter encodes for the osteopontin protein which is a chemokine now heavily implicated in the metastatic spread of tumours, particularly when it is overexpressed (which it invariably is in most lethal, metastatic, tumours). As a result of our work, we have now shown, for the first time ever, that it is possible to downregulate the expression of osteopontin within metastatic cancer cells through use of a small molecule disrupter of the TCF4/β-catenin interaction, thereby validating this as a potentially viable approach to controlling OPN expression within tumours. Only time will tell whether these or other small molecules that can either disrupt or blockade this interaction will have the ability prevent or reduce metastatic spread *in vivo*. However, our discovery that molecules of the A83586C class can act in this way could go a long way towards proving that TCF4/β-catenin small molecule blockade is a clinically relevant method for preventing metastasis in an *in vivo* setting.

The (-)-agelastatin: A total synthesis story and its relevance to the wnt/β-catenin/TCF4 cell signalling pathway and the prevention of metastasis

Another rare antitumour natural product whose synthesis we have recently completed (see Scheme 4) is the marine bromopyrrole alkaloid (-)-agelastatin A, which was originally isolated by Pietra from the coral sea sponge *Agelas dendromorpha* in 1993.[11] As a result of our chemical synthesis,[12] 0.23 g of (-)-agelastatin A was prepared and thereafter biologically evaluated, in collaboration with our colleague, Dr Mohamed El-Tanani, of Queen's University Belfast CCRCB. Together we have shown that this novel *Oroidin* alkaloid can likewise downregulate OPN in invasive human breast cancer tissue at low drug concentrations.[13] However, in this particular instance, we demonstrated that this was achieved through a dowregulation of β-catenin and a simultaneous upregulation of TCF4 expression in these cells, which was a quite different and complementary OPN downregulatory mechanism to that seen previously for A83586C and its congeners. It is not currently known how (-)-agelastatin A is able to modulate the expression of these two proteins, but future affinity chromatography work with a suitably immobilised and tagged (-)-agelastatin A probe might shed some new light on this process, and potentially lead to a new regulatory protein being identified that is capable of controlling β-catenin and TCF4 levels within tumours. Further *in vitro* testing of synthetic (-)-agelastatin A by our group also showed that it was a powerful broad spectrum antitumour agent that is between 1.5 and 16 times more potent than cisplatin against 13 different human tumour cell lines. (-)-Agelastatin A also has respectable *in vivo* antitumour activity according to Pietra.[11]



Scheme 4. The 2004 Hale group total synthesis of the marine antitumour alkaloid, (-)-agelastatin A.

Conclusion

It will thus be appreciated that modern-day natural product total synthesis is no longer an enterprise conducted solely for the greater glory of organic chemistry. Although it does frequently spur and showcase many important new organic reaction developments, and it does lead to the introduction of many useful new protecting groups and reagents, it also often provides substantial quantities of many rare and highly important natural products for chemical genomics studies and/or clinical evaluation. The final syntheses that do eventually emerge also often allow all sorts of useful analogues and probes to be constructed which can, in some instances, prove highly valuable for the identification and characterisation of new proteins. In some settings, the small molecules that are produced can therapeutically validate important new therapeutic targets, in addition to providing insights into how we can build up other complex molecules of biological significance. It is hoped that this feature article has thus demonstrated that this branch of organic chemistry research is vibrant, multifaceted, and highly worthwhile, not only for the significant chemical dividends it can reap but also for the rich panoply of new biological insights it can provide.

Acknowledgements. We thank Novartis Pharma AG, AVERT, Ultrafine, and EPSRC for financial support of this work.

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10. K. J. Hale, J. Cai, V. Delisser, S. Manaviazar, S. A. Peak, G. S. Bhatia, T. C. Collins and N. Jogiya, *Tetrahedron* **1996**, *52*, 1047.
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Literature Focus

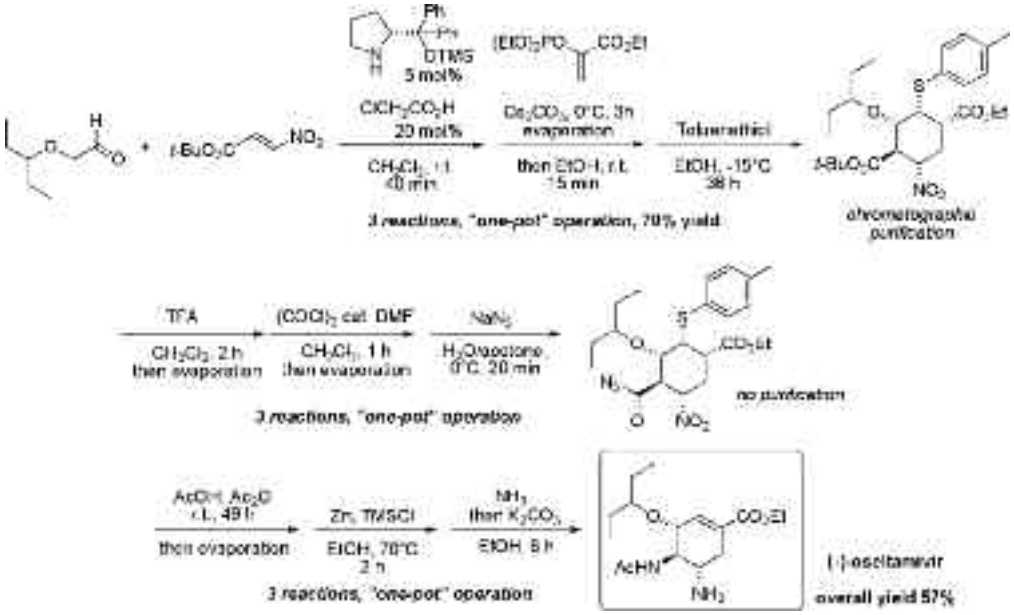
Claudio Cornaggia, Ronan Cullen, Kate Godinho, Emi Hashem, Amila Kahvedžić, Gunther Speichert.
School of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland.

Edited by Claudio Cornaggia and Amila Kahvedžić
Literature focus is a new feature consisting of short abstracts highlighting recent developments of interest in the literature selected by postgraduate researchers.
Stephen Connon MICI

Synthesis of (-)-Oseltamivir a.k.a. Tamiflu®

High-Yielding Synthesis of the Anti-Influenza Neuramidase Inhibitor (-)-Oseltamivir by Three "One-Pot" Operations

H. Ishikawa, T. Suzuki, and Y. Hayashi, *Angew. Chem. Int. Ed.* **2009**, *48*, 1304

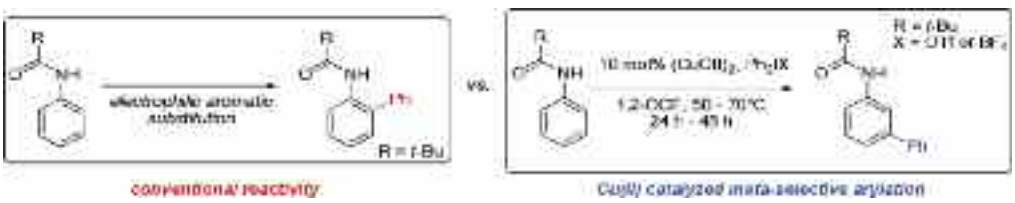


Hayashi and co-workers have developed a concise, inexpensive and efficient total synthesis of the anti-influenza therapeutic (-)-oseltamivir in three "one-pot" operations, one chromatographic purification and a total of nine reactions in an **3overall 57% yield.**

Arylation Reaction

A Meta-Selective Copper-Catalyzed C-H Bond Arylation

R. J. Phipps and M. J. Gaunt, *Science* **2009**, *323*, 1593

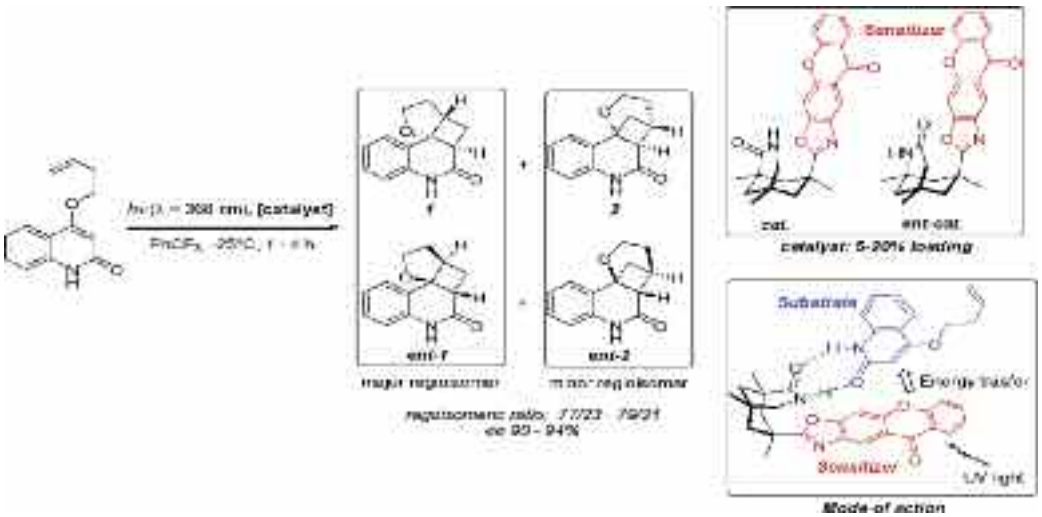


Gaunt and co-worker have disclosed a methodology to synthesise aromatic systems with unusual substitution patterns. A mild copper-catalyzed arylation onto electron-rich aromatic systems provides the direct formation of the elusive *meta*-isomer. **18 examples: Yields 11-93%**

Enantioselective Photochemical Reactions

Light-Driven Enantioselective Organocatalysis

C. Müller, A. Bauer and T. Bach, *Angew. Chem. Int. Ed.* **2009**, *48*, Early view - DOI: 10.1002/anie.200901603

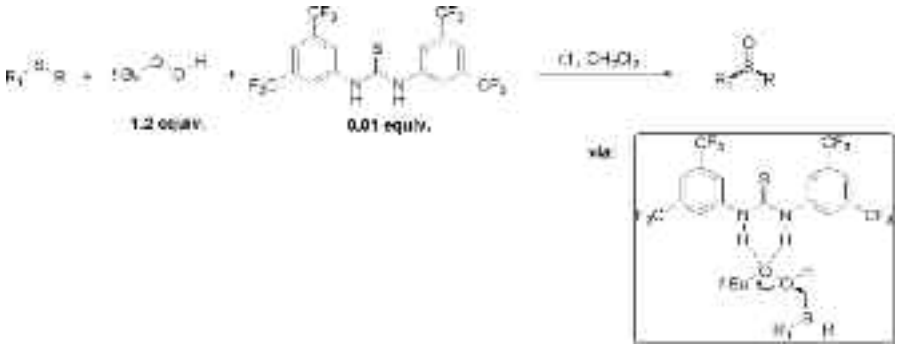


By attaching a sensitiser to a chiral organocatalyst able to bind to prochiral substrates via hydrogen bonding, Bach and coworkers accomplished an intramolecular enantioselective [2+2] photocycloaddition with very high enantioselectivity.

Oxidation of Sulfides

Hydrogen-Bonding Catalysis: Mild and Highly Chemoselective Oxidation of Sulfides

A. Russo and A. Lattanzi, *Adv. Synth. Catal.* **2009**, 351, 521

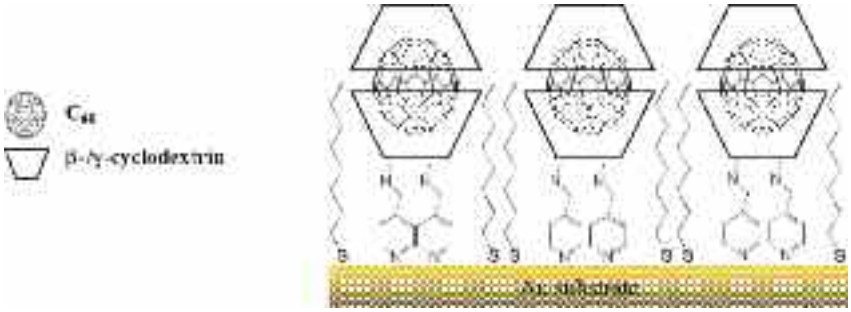


Lattanzi *et al.* have reported an efficient organocatalytic oxidation of sulfides to sulfoxides using tert-butyl hydroperoxide as the oxidising agent and proved that thiourea derivatives can catalyse this reaction at extremely low loadings. **13 examples: Yields 69-99%.**

Fullerene Assemblies

Interfacial Supramolecular Cyclodextrin-Fullerene Assemblies: Host Reorientation and Guest Stabilization

A. McNally, R. J. Forster and T. E. Keyes, *Phys. Chem. Chem. Phys.* **2009**, *11*, 848



Formation of a fullerene monolayer assembly encapsulated in cyclodextrin was achieved by McNally *et al.* and verified by SERS and cyclic voltammetry measurements.

Carbon Nanosheets

One Nanometer Thin Carbon Nanosheets with Tunable Conductivity and Stiffness

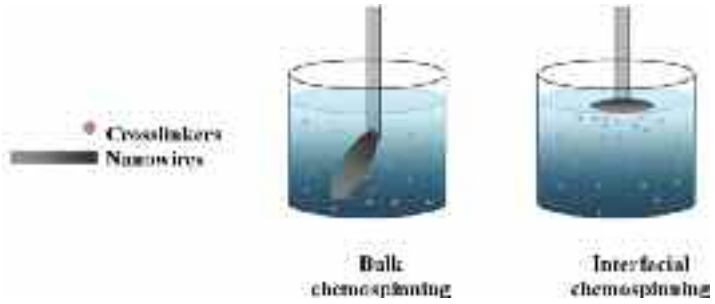
A. Turchanin, A. Beyer, C. T. Nottbohm, X. Zhang, R. Stosch, A. Sologubenko, J. Mayer, P. Hinze, T. Weimann and A. Gölzhäuser, *Adv. Mater.* **2009**, *21*, 1233

The preparation of ultra thin carbon nanosheets with tunable electronic and mechanical properties *via* molecular self-assembly, electron irradiation and pyrolysis has been reported.

Nanostructure Formation by Chemospinning

Cross-Linking Bi_2S_3 Ultrathin Nanowires: A Platform for Nanostructure Formation and Biomolecule Detection

L. Cademartiri, F. Scotognella, P. G. O'Brien, B. V. Lotsch, J. Thomson, S. Petrov, N. P. Kherani and G. A. Ozin, *Nano Lett.* **2009**, *9*, 1482

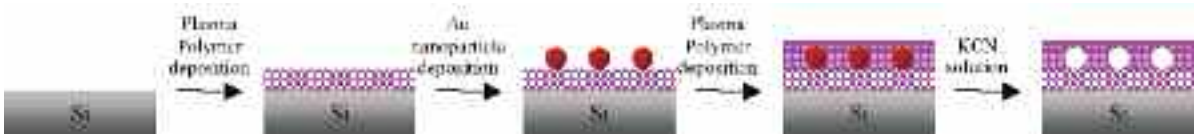


Cademartiri et al. describe the use of Bi_2S_3 colloidal nanowires for the fabrication of microfibers and nanomembranes and for the detection of small molecules.

Plasma Polymer Thin Films

Template-Assisted Generation of Nanocavities within Plasma Polymer Films

K. Vasilev, A. Casanal, H. Challougui and H. J. Griesser, *J. Phys. Chem. B* **2009**, *113*, 7059

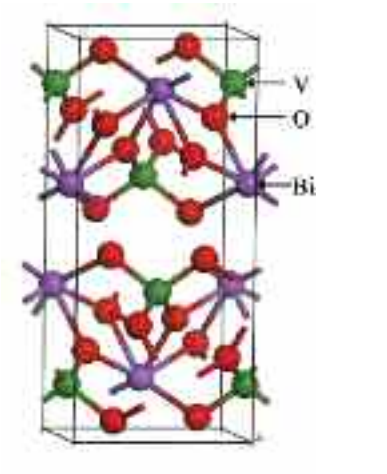


The incorporation of nanocavities into ultra thin plasma polymer thin films via a templating method has been reported by Vasilev *et al.* Such films could be used for applications such as delivery, storage, release systems and catalysis.

Electronic Structure of BiVO¬4

Band Edge Electronic Structure of $BiVO_4$: Elucidating the Role of the Bi s and V d Orbitals

A. Walsh, Y. Yan, M. N. Huda, M. M. Al-Jassim and S.-H. Wei, *Chem. Mater.* **2009**, *21*, 547

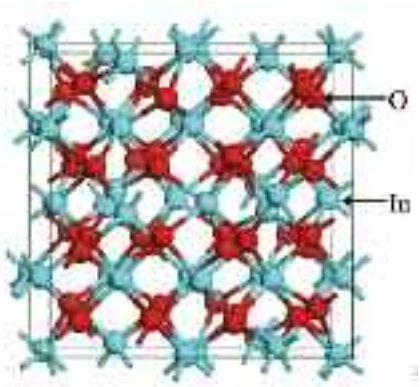


GGA-DFT calculations on $BiVO_4$, a promising novel photocatalyst, show it to be a direct gap semiconductor with light electron and hole effective masses for *p*- and *n*-type conductivity. The electronic structure requirements for design of photocatalysts for hydrogen production are discussed.

Intrinsic Defects in In2O3

Formation Entropies of Intrinsic Point Defects in Cubic In_2O_3 from First-principles Density Functional Theory Calculations

P. Ágoston and K. Albe, *Phys. Chem. Chem. Phys.* **2009**, *11*, 3226



Ágoston *et al.* have shown that the entropy contributions to intrinsic defect formation energies in In_2O_3 cannot always be neglected. Inclusion of entropy may cause variations in defect equilibria compared to static energy calculations.

Structure of Ice

A One-Dimensional Ice Structure built from Pentagons

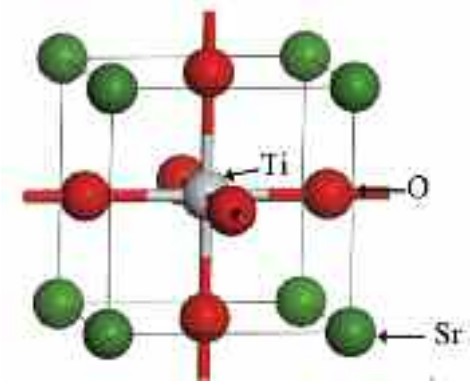
J. Carrasco, A. Michaelides, M. Forster, S. Haq, R. Raval and A. Hodgson, *Nature Materials* **2009**, *8*, 427

Carrasco *et al.* have carried out density functional theory calculations of ice nucleation on Cu (110) surfaces. Pentagonal chains are found to be favoured over other structures as they result in stronger water-metal interactions as well as a strong hydrogen-bonding network.

Doping of $SrTiO_3$

Combined Experimental and Computational Modelling Studies of the Solubility of Nickel in Strontium Titanate

A. M. Beale, M. Paul, G. Sankar, R. J. Oldman, C. R. A. Catlow, S. French and M. Fowles, *J. Mater. Chem.* **2009**, DOI: 10.1039/b902591j

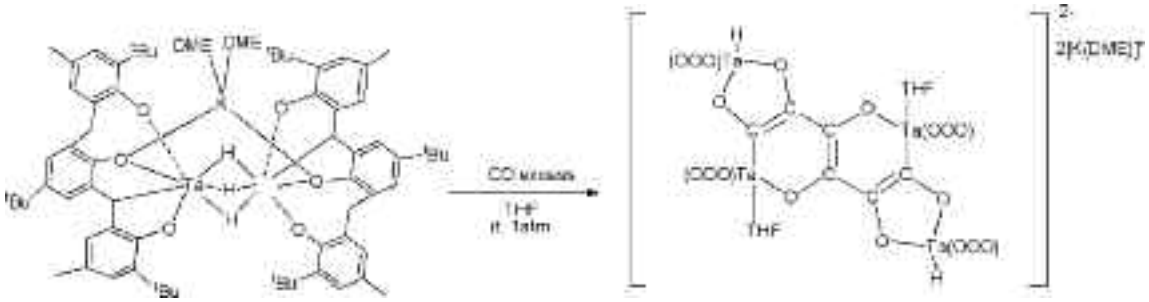


The doping of $SrTiO_3$ with Ni for use as a catalyst for the partial oxidation of methane was investigated using a combination of X-ray and computational methods. Ni^{2+} is indicated to substitute at the Ti^{4+} site with up to 5 atom % doping achieved.

Reduction of CO

Reductive Coupling of Six Carbon Monoxides by Ditantalum Hydride Complexes

T. Watanabe, Y. Ishida, T. Matsuo and H. Kawaguchi, *J. Am. Chem. Soc.*. **2009**, *131*, 3474

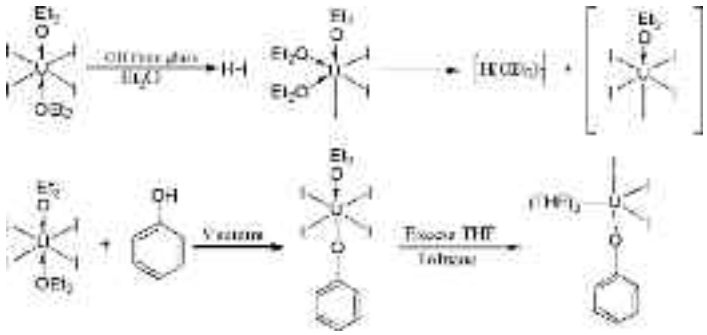


The high reductive potential of low-valent d-elements was applied to the coupling of CO; relatively stable C_6O_6 complex was achieved by the reduction of CO with ditantalum hydride complex and homologation of CO was prevented by the lack if d-electrons available for reduction. **Yield 31%**

Chemistry of Uranium

Reactivity of $UI_4(OEt_2)_2$ with Phenol: Probing the Chemistry of the U-I Bond

D. Schneers, G. Wu and T. Hayton, *Dalton Trans.* **2009**, 3681

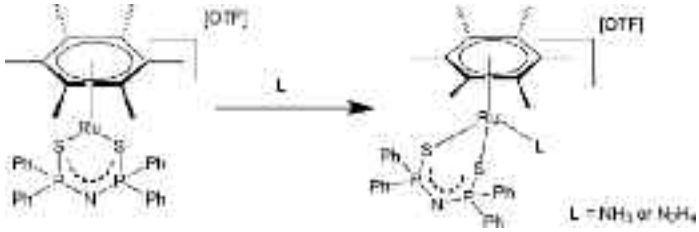


An easier route to the synthesis of uranium (III) and uranium (V) from uranium (IV) was reported by Schneers and co-workers. $UI_4(OEt_2)_2$, which is easily prepared and is highly soluble in organic solvents was used to prepare $UI_3(THF)_4$ and $UI_5(OEt_2)$ making it easier to study the relatively unknown chemistry of uranium (III) and uranium (V).

Ruthenium complexes

Ruthenium η^6- Hexamethylbenzene Complexes Containing Dichlorogenoimidophoshinate Ligands

W Cheung, W. Chiu, I. Williams and W. Leung, *Eur. J. Inorg. Chem.* **2009**, *279*

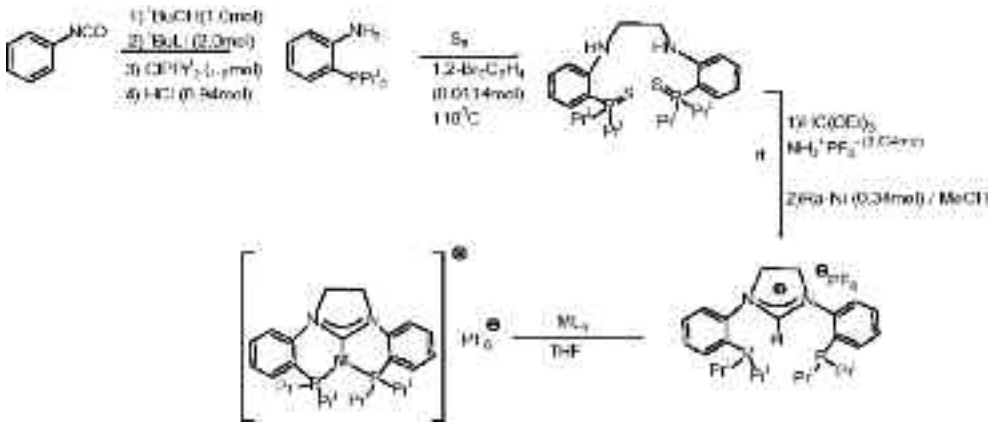


18-electron adducts were synthesised by crystallising the unsaturated 16-electron Ru (II) complexes with amine ligands such as NH_3 and N_2H_4. **Yield 87% and 79%.** Ruthenium hydride and ethyl complexes were also synthesised from $NaBH_4$ and $Li[BEt_3H]$ respectively. **Yield 78% and 82%.**

Tridentate Ligands

Synthesis and Coordination Chemistry of a Tridentate o-Phenylene-Bridged Diphosphine-NHC System

T. Steinke, B. Shaw, H. Jong, B. Patrick and M. Fryzuk, *Organometallics* **2009**, *28*, 2830

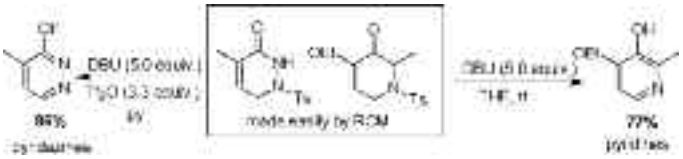


Tridentate ligand was incorporated onto the group 10 elements to generate square-planar metal hydride complexes such as PF_6 salts. Metal complexes of Ni (II), Pd (II), and Pt (II) were synthesised and fully analysed. **Yield 73.2%, 77.6% and 72.4%**

Ring Closing Metathesis

Synthesis of Substituted Pyridines and Pyridazines via Ring Closing Metathesis

T. J. Donohoe, L. P. Fishlock, J. A. Basutto, J. F. Bower, P. A. Procopiou and A. L. Thompson, *Chem.Commun.* **2009**, 3008

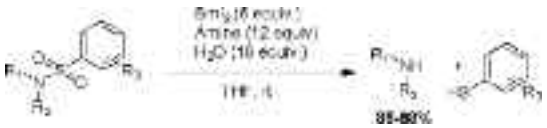


The use of ring closing metathesis (RCM) in the synthesis of aromatic nitrogenous heteorcycles, namely pyridines and for the first time pyridazines, has been reported. 11 examples: **Yield 60-93%.**

Deprotection Chemistry

Instantaneous Deprotection of Tosylamides and Esters with SmI_2/Amine/Water

T. Ankner and G. Hilmersson, *Org. Lett.* **2009**, *11*, 503

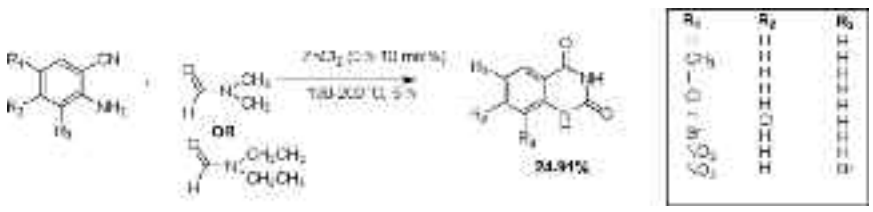


The instantaneous cleavage of highly hindered, sensitive and functionalised tosyl amides and tosyl esters using a solution of SmI2, amine (typically pyrrolidine, triethylamine or isopropyl amine) and water has been described. **19 examples: Yield 85-98%**

Quinazoline-2,4 (1*H*,3*H*)-Diones

A New and Facile Synthesis of Quinazoline-2,4 (1*H*,3*H*)-Diones

L. Jiarong, C. Xian, S. Daxin, M. Shuling, L. Quig, Z. Qi and T. Jianhong, *Org. Lett.* **2009**, *11*, 1193

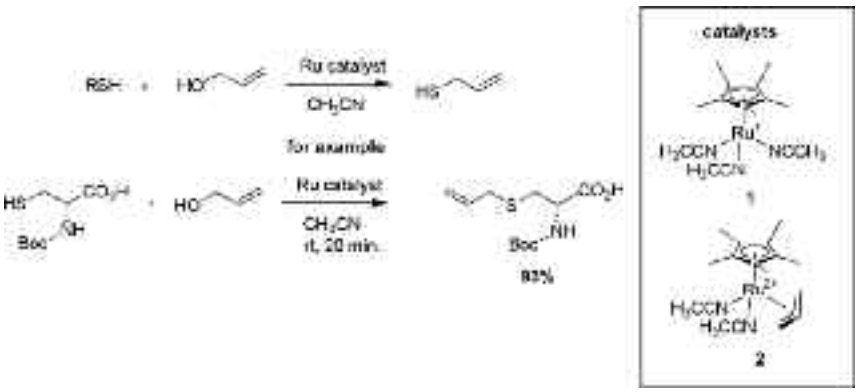


Jiarong and co-workers have reported a novel preparation of quinazoline-2,4(1*H*,3*H*)-diones via the condensation of aromatic *o*-aminonitriles with DMF or *N,N*-diethylformamide in the presence of $ZnCl_2$ in a sealed reactor. **8 examples: Yield 24-90%**

Allylation of Thiols

Fast Ruthenium-Catalysed Allylation of Thiols by Using Allyl Alcohols as Substrates

A. B. Zaitsev, H. F. Caldwell, P. S. Pregosin and L. F. Veiros, *Chem. Eur. J.* **2009**, DOI: 10.1002/chem.200900192

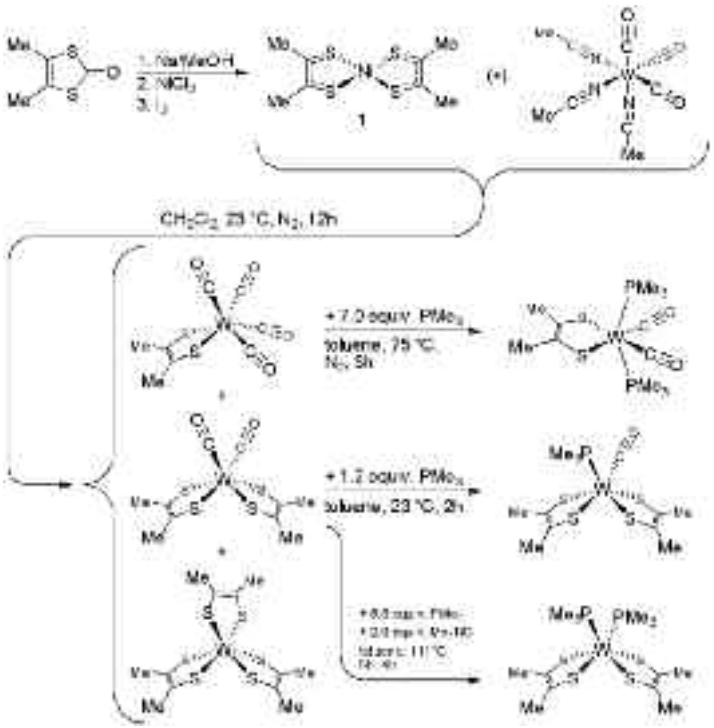


Aromatic and aliphatic thiols can undergo catalytic allylation within minutes at ambient temperatures by using a variety of alcohols as substrates with either a catalyst $[Ru(Cp^*)(\eta^3\text{-}C_3H_5)(CH_3CN)_2](PF_6)_2$ **(2)** (Cp*= pentamethylcyclopentadienyl), or a combination of $[Ru(Cp^*)(CH_3CN)_3](PF_6)$ **(1)** and camphorsulfonic acid.

Tungsten Dithiolenes

Synthesis, Structures, and Properties of Mixed Dithiolene-Carbonyl and Dithiolene-Phosphine Complexes of Tungsten

P. Chandrasekaran, K. Arumugam, U. Jayarathne, L. M. Pérez, J. T. Mague and J. P. Donahue, *Inorg. Chem.* **2009**, *5*, 2103

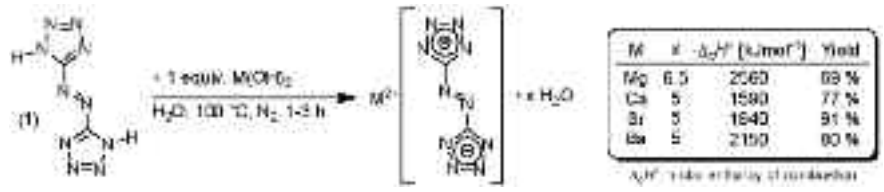


The authors present a new synthesis of $[Ni(S_2C_2Me_2)_2]$ **(1)** with high yield **(87%)** and purity. This precursor was used to synthesise various tungsten dithiolene compounds.

Pyrotechnics

Nitrogen-Rich Compounds in Pyrotechnics: Alkaline Earth Metal Salts of 5,5 '-Hydrazine-1,2-diylbis(1H-tetrazole)

K. Karaghiosoff, T. M. Klapötke and C. M. Sabaté, *Eur. J. Inorg. Chem.* **2009**, 238

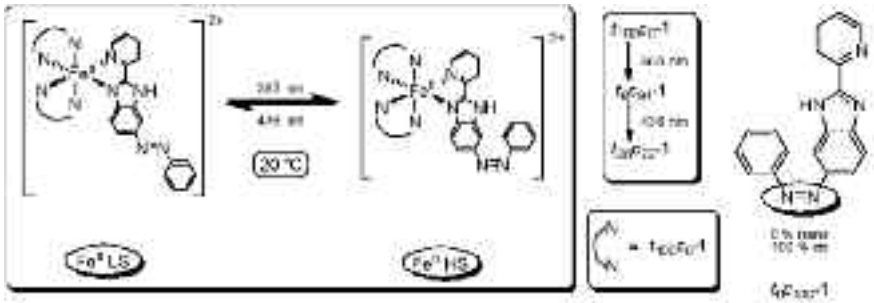


The synthesis of the high thermally stable alkaline earth metal salts of 5,5 '-hydrazine-1,2-diylbis(1H-tetrazole) **(1)** was improved and the salts were intensely analysed and spectroscopical investigated.

Magnetochemistry

Reversible light-induced magnetization change in an azobenzene-attached pyridylbenzimidazole complex of iron(II) at room temperature

Y. Hasegawa, S. Kume and H. Nishihara, *Dalton Trans.* **2009**, *2*, 280

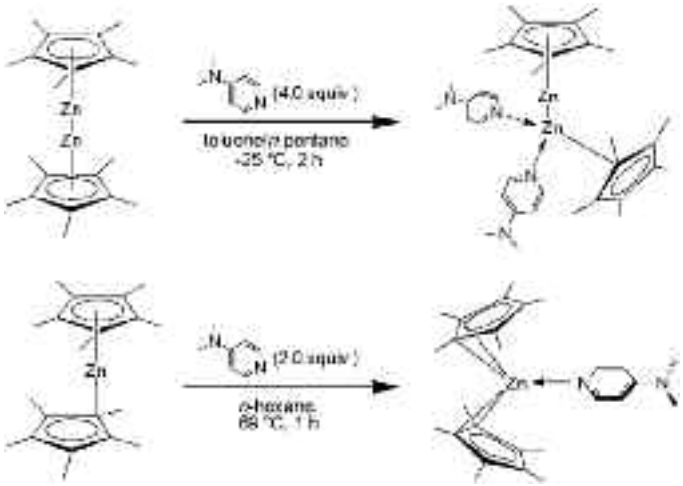


In this article the synthesis and properties of the first reversible LD–LISC Fe(II) complexes are described. The cis-trans isomerism of the new created ligand **(1)** has also been intensely examined. (LD-LISC = ligand-driven light-induced spin change).

Zinc(I)-Compounds

The Reaction of Dizincocene with Preservation of the Zn-Zn Bond

D. Schuchmann, U. Westphal, S. Schulz, U. Flörke, D. Bläser and Roland Boese, *Angew. Chem. Int. Ed.* **2009**, *48*, 807



Schumann *et. al.* have reported the first reaction of $[Cp_2^*Zn_2]$ with preservation of the Zn-Zn-bond and compared it with the reaction of $[Cp_2^*Zn]$ using the same reactant.

Biomedical Applications of 2-Cyanoacrylates

Dr. Stephen J. Hynes, *Henkel Technology Centre Europe, Tallaght Business Park, Dublin 24*
(stephen.hynes@ie.henkel.com)

Introduction
Among the wide variety of synthetic polymers with medical applications[1] polymerising medical devices are those non-pharmaceutical medical aids which are based on monomers which can be polymerised after (or during) application to the body. The resultant polymers perform roles in wound management, repair, stabilisation and hemostasis. They can also support tissue re-growth, as well as being used for drug delivery. The synthetic systems most commonly used are based around acrylic ester chemistries, analogous to their non-medical uses as plastics and adhesives.

Acrylate and methacrylate esters are olefinic monomers, which undergo radical or redox -initiated polymerisation and have many medical applications. For example in the areas of bone and dental cements, polymethylmethacrylate (PMMA) is used as a two-part mixture of monomer/stabiliser and pre-polymer/initiator which undergoes radical-initiated polymerisation upon mixing. This can be used as an aid to anchoring prosthetic joints, such as hip replacements and as a bone filler.[2]

Figure 1. Useful acrylate monomers

2-Cyanoacrylates
2-Cyanoacrylates are related monomers that are the main constituents of the well known 'Superglue' instant adhesives. They are also used extensively as medical devices - however the applications differ from those associated with acrylates and methacrylates due to the differing chemistries of the monomers. It is the biomedical applications of these 2-cyanoacrylates (CAs) which will form the basis of this article.

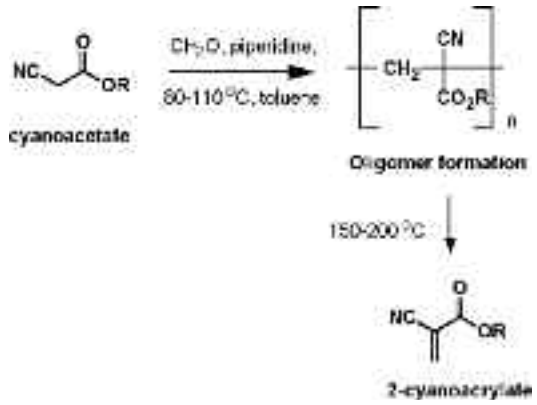
History:
Ardis patented alkyl-2-cyanoacrylates as adhesives in 1949.[3] However it was not until the 1960s that suitable synthetic procedures were developed to isolate and stabilise the monomer. The most important feature of 2-cyanoacrylates is their spontaneous and rapid polymerisation in seconds at room temperature particularly when placed between two surfaces. This, in addition to their excellent 'wetting' ability and low viscosity results in a strong adhesive bond when applied to most surfaces. They are thus invaluable as structural adhesives to virtually every industry with many different formulations and monomers tailored to suit each application.[4] Ethyl-2 cyanoacrylate has found the most notoriety as the SuperGlue® consumer adhesives.

Figure 2. Indermil® tissue adhesive: Designed, developed and manufactured in Ireland.

In an interesting Irish angle to the cyanoacrylate story, some of the seminal work on the elucidation the mechanism of polymerisation of CAs was carried out at Trinity College Dublin by Prof. D.C. Pepper[5] and more recent investigations have been carried out at the University of Limerick.[6] Also many of the early formulations for consumer and industrial applications were developed in Dublin at Loctite (now Henkel).[7] An example of the strength of these superglue bonds was displayed recently by the suspending of a world record 5 ton load from an adhesive bond made from just nine drops of Ethyl CA based adhesive (Figure 3).[8]

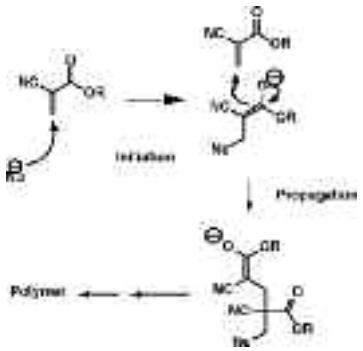
Figure 3. Guinness World Record - 5 tonne truck lifted with just 9 drops of Superglue

Cyanoacrylates are generally synthesised by the base-catalysed Knoevenagel condensation of cyanoacetates with formaldehyde. The water produced is removed by azeotrope and the resulting oligomers are 'cracked' at high temperatures to free the monomer, [1] (Scheme 1) which is then distilled on to a mixture of stabilisers. The monomer is redistilled to purity and can be stored for long periods in the refrigerator.



Scheme
1. Knoevenagel condensation of cyanoacetates with formaldehyde

The polymerisation mechanism is usually anionic/zwitterionic in nature and can be initiated by trace amounts of almost any nucleophile (< 1 ppm in unstabilised CA) including water, alcohols, phosphanes and ammonium salts.[8] Termination is due to the presence of a cationic species, usually deriving from a strong acid. Otherwise the polymerisation continues until the monomer supply is exhausted in the manner of a 'living polymer' – polymerisation can be reinitiated by addition of more monomer.[4] A strong exotherm is produced due to the rapid nature of the polymerisation. There is also a radical-promoted mechanism for polymerisation similar to that found using other acrylates. Cyanoacrylates must be mixed with appropriate acidic stabilisers (usually SO_2 or BF_3) and radical stabilisers (e.g. hydroquinone) to prevent polymerisation during storage. Their low viscosity (similar to water) means thickeners are employed in most formulations.



Scheme 2. Anionic polymerisation of 2-cyanoacrylate

Cyanoacrylates in medicine

Tissue adhesives

There are three general routes to the closure of surgical incisions or wounds - stapling, suturing or adhesive bonding. Suturing and stapling can be painful to the patient and normally require the use of an anaesthetic. Anyone who has ever used superglue can testify to its ability as a skin bonder. It is in this area that cyanoacrylates found their initial medical application as tissue adhesives for wound closure.[9,10] CAs hold several advantages over other tissue adhesives such as fibrin and collagen glues. These include cost, faster cure rates, spontaneous curing without initiation under physiological conditions and stronger bond formation. Cyanoacrylates also possess some antimicrobial properties,[11] which help prevent post-procedure wound infection without antibiotics. CA tissue adhesives are one-treatment, pain free wound closing medical devices and are increasingly common both in surgical and A&E environments.

Historically their first medical use was to prevent blood loss in field hospitals during the Vietnam War. However, subsequent trials with the commonly used consumer and industrial monomers (ethyl- and methyl-CA) failed to gain regulatory approval due to instances of tissue necrosis and inflammation in clinical trial patients. These reactions were ascribed to the toxic by-products of biodegradation *in vivo*. CA degradation pathways have been investigated both *in vivo*[12] and *in vitro*.[13] Two pathways have been proposed, which are thought to work in concert. First is the random hydrolytic chain scission, leading to retro-Knoevenagel condensation and formaldehyde formation. The second is cleavage of the ester linkage (both enzymatic and hydrolytic) to afford water-soluble acid residues and alcohols.[14,15,16] The combination allows bio-absorption and excretion of the component parts, but the associated by-products, particularly formaldehyde, cause the adverse tissue reactions.

The tissue response to biodegradable materials is regulated by the toxicity of the degradation products and the rate of degradation of the polymer. In the case of CAs, **the rate of degradation of polymers with longer chain alkyl groups is much slower when compared to methyl or ethyl derivatives**. The slower degradation rate results in slower release of formaldehyde, or other toxic by-products such as alcohols.[17] This allows their removal by natural systems resulting in a reduced tissue response. However, this slower rate of degradation results in the presence of the polymer long after wound healing is complete. The *lack* of degradation of such polymers *in vivo* can result in other complications, such as tissue necrosis and foreign-body giant cell reaction. This has obvious implications for internal applications of CAs. However, development of these longer-chain analogues did lead to the FDA approval of CAs as topical tissue adhesives in 1998 as the residual CA sloughs off the skin surface.[18] CA's have been approved for use as *topical* tissue adhesives in Europe and Canada since the 1970's. Internal applications of CA are still rare.

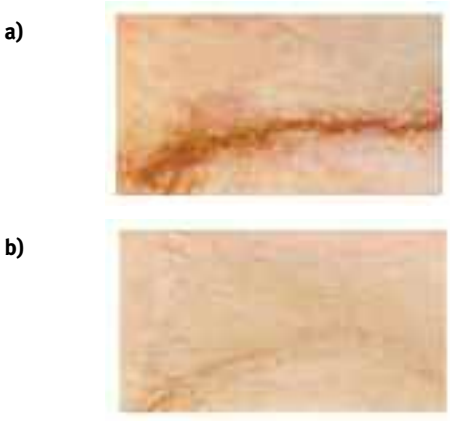


Figure 4. Wound closure with minimal scarring using cyanoacrylate adhesive at a) day of closure and b) three months after closure

Sterilisation of cyanoacrylates for medical use The sterilisation of medical devices is an important requirement and poses interesting issues for CAs due to their relative instability. Indeed, most sterilisation methods would promote polymerisation of the monomer. These problems have been overcome by careful selection of stabilisers and packaging materials to protect the monomer. Tissue adhesives available on the market have been sterilised by filtration, heat, electron-beam and gamma radiation.

Internal cyanoacrylate applications
As mentioned above due to the poor degradation rate of long chain alkyl-2-cyanoacrylates, these are not commonly approved for internal use. However, there are a number of surgical procedures where they have been used 'off-label'.

A. Sclerotherapy
Sclerotherapy is the closure of varices (distended veins). The procedure may be cosmetic (varicose veins) or lifesaving (bleeding intestinal or oesophageal varices). Sclerotherapeutic methods involve the injection of the agent (sclerosant) into the vein causing thrombosis or fibrosis and ultimately destruction of the venous channel. The procedure is common in Europe and Asia but less so in the US. 2-Cyanoacrylates such as Histoacryl are among the agents which have been successfully employed in this procedure.[19]

B. Surgical sealants
An attractive potential use for CA is as surgical sealants during operations. Again due to toxological issues this has not generally found favour. However, the advantages over suturing or stapling are even more obvious than for topical applications, as demonstrated by Lumsden and coworkers.[20]

Figure 4. Topical application of tissue adhesive – adhesive is placed on top of the skin and not into the wound.

Current and Future Research
As shown, the current medical market for CAs is mainly based around topical (skin) tissue adhesives. A push to advance the technology to internal applications has been hampered by the unsuitability of the degradation rate of the existing monomers. Thus in more recent years there has been much interest in generating new monomers and formulations which modify the rate of absorption of the polymer or the reduce the effects of the toxic by-products.

Given the limited scope for changing the basic structure of the cyanoacrylate monomer, research on novel biodegradable cyanoacrylates has focused on two areas. Firstly, increasing the hydrophilicity of the alkyl side chain, thereby altering its rate of *in vivo* degradation, and secondly, incorporating degradable polymer chains into the adhesive formulation to increase flexibility and degradation rate of the resulting polymer matrix. Regarding the first approach, alkoxyalkyl monomers **2** have proved to be much more degradable than higher alkyl chain monomers such as butyl-CA, 3-methoxybutyl has been shown to be one of the most promising of these alternatives, with a degradation rate greater than that of n-butyl CA but with lower levels of tissue response.[21] Alternative examples include 1,2-glyceryl 2-cyanoacrylate **3**, which replaces the alkyl chain with a glycerol ketal moiety. This rapidly degrades under physiological conditions to afford glycerol and acetone, both of which are non-toxic metabolites. Bond strength of the adhesive exceeded that required for tissue adhesives.[22]

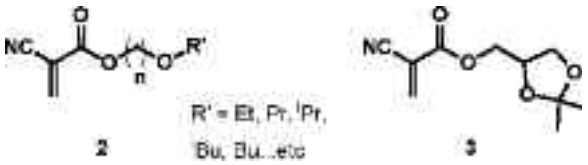


Figure 5. Biodegradable CAs

Secondly, there have been several recent patents aimed at increasing the biodegradability of cyanoacrylate-based adhesives by incorporating polymeric fragments into CA formulations. The majority of these have focused on using copolymers of common bio-absorbable materials.[23] These provide both the increased flexibility and degradability of the polymer bond without significantly reducing bond strength. These polymeric fragments are generally polyester in nature, formed from mixtures of lactide, glycolide, ε-caprolactone, trimethylene carbonate, and *p*-dioxanone. Polyoxalate[24] and PEG based formulations have also been reported.

These innovations have shown great promise, however none have thus far reached the marketplace.

Cyanoacrylate nanoparticles as drug delivery systems
The desire for targeted drug delivery arises from the inefficiency of current chemotherapeutic methods, which often result in poor selectivity and unwanted side effects. Increased drug resistance, the need for control of the release rate of the active agent into the bloodstream and protection of pharmaceutical agents sensitive to adverse physiological conditions prior to uptake by the target tissues have all heightened the search for ways to disguise existing drug molecules from cell and microbial defences and enhance their efficacy. Drug-containing nanoparticles have been seen as a possible way to accomplish this by encapsulating the drug in a suitable degradable shell. Many colloidal systems have been tested as vehicles for targeted delivery, such as liposomes and biodegradable polymers.[25] Polyalkylcyanoacrylate (PACA) nanoparticles first emerged as drug delivery candidates in the early 1980s.[26]

Their ease of polymerisation in water, facile encapsulation of a wide variety of drug products, the biodegradability of the nanoparticles[27] and relatively low toxicity *in vivo* have made them among the most popular substrates in this large and expanding area of medical research. An example of the spectacular results that can be obtained using PACA nanoparticles can be found in cancer therapeutics. Couvreur and co-workers dramatically enhanced the efficacy of doxorubicin. Association with PACA nanoparticles reduced the IC50 of doxorubicin for normally resistant breast cancer cells by a factor of 130.[28] These doxorubicin–PACA nanoparticles have undergone clinical trials.[29] Cytotoxicity studies have shown that the make-up of the monomer side-chain of these nanoparticles influences their toxicity at the cellular level in the same way as described for tissue adhesives above, i.e. that cells display increased sensitivity towards nanoparticles of monomers with shorter chain length whereas those of longer chain length are less toxic, again due to the slower rate of degradation. However there are issues with long-term effects on the cell of the virtually non-degradable long chain esters such as 2-octyl CA. The make-up of the nanoparticle can also determine the level of absorption by a particular tissue; this has implications for cytotoxicity of the nanoparticle and accuracy of targeting with the pharmaceutical agent. Recent research has included coating the CA nanoparticles with biodegradable materials such as dextran to improve tolerance and targeting of tissues.[30]

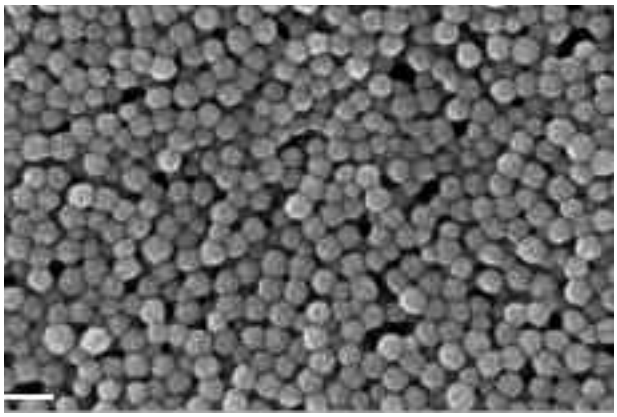
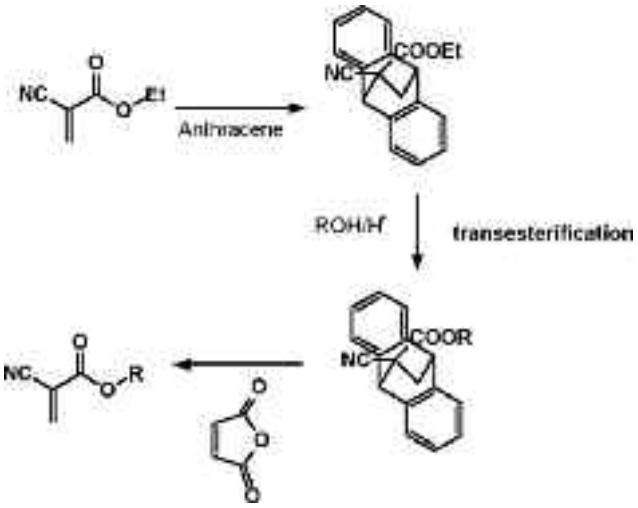


Figure 6. SEM image of PIBCA nanoparticles prepared by anionic emulsion polymerisation (the scale bar represents 100nm).[31]

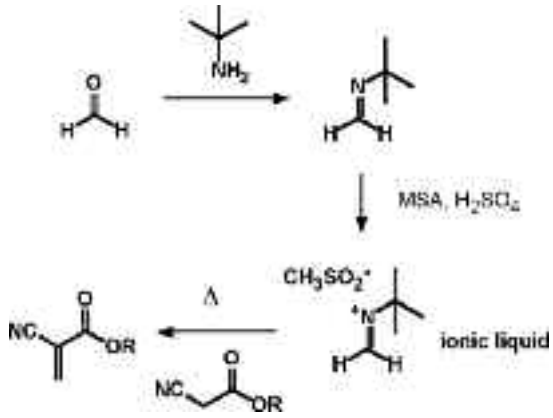
Future potential

One of the main inhibitors to the generation of new CA monomers for biomedical applications is the method of synthesising the CA itself. As described above the conditions required are relatively harsh, with temperatures of up to 200 oC required to thermally depolymerise the intermediate oligomer to afford the monomer. Also to purify the monomer it must be distilled in the presence strong acid. Thus it is impossible to use the standard method to synthesise CAs with side chains of high molecular weight and/or those containing thermal- or acid-sensitive functional groups. There are several other methods which can be used to synthesise unusual CAs,[32] most notably via 'protection' of the sensitive methylene group as a Diels–Alder adduct and subsequent transesterification followed by 'deprotection' using a superior dienophile such as maleic anhydride.[33]



Scheme 3. Transesterification of ethyl CA via a Diels-Alder adduct

Some patents detail methods to generate cyanoacrylic acid[34] and esterify with an appropriate alcohols usually *via* the acid chloride.[35] However it is not commercially practical to use any of these methods to synthesise CAs. This dramatically limits the pool of structures available. From this point of view a new method of CA synthesis recently developed at Henkel, Dublin may go some way to improving the scope of structures available for biomedical purposes. Using iminium-ion based ionic liquids generated from formaldehyde and a high boiling amine and an organic acid,[36] the Knoevenagel reaction can be carried with rapid distillation of the monomer without the need to depolymerise an oligomer. This and other methods under development should allow the synthesis of monomers which canexpand the range of applications of CAs in medicine.



Scheme 4. Synthesis of CA *via* ionic-liquid intermediate

As we have shown, alkyl 2-cyanoacrylates perform an important role in medicine as rapid setting tissue adhesives. Their unique properties have made them an attractive alternative to sutures or staples as a method of topical wound closure. There is still scope for improvement however, to expand the application of these useful medical devices to the field of internal medicine where their unique advantages over other methods of wound closure would be further enhanced. CAs are still the subject of a large amount of interest in the area of targeted drug delivery. Further development in both of these areas depends on obtaining new monomers with novel functionalities which enhance the biocompatibility of the technology.

Acknowledgements
Thanks to Dr. Kenneth Broadley for useful discussion regarding content and Dr. C. Vauthier who supplied the SEM image of the PACA nanoparticles. We also would like to thank Dr. Liam O'Dwyer, Department Manager of Instant Adhesives, for supplying the photograph of the successful world-record attempt.

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3. A. Ardis US patent, **1949**, 2467926
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Future Scaling in the Microelectronics Industry: Engineering meets Chemistry

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Background

Photo-lithography has been the cornerstone of the electronics industry since the advent of the first silicon devices.[1,2] Briefly, light sensitive compounds (commonly polymeric or oligomeric materials called photoresists) deposited on a substrate are irradiated through a mask allowing the mask pattern to be transferred to the surface by selective removal of the sensitised (or non-sensitised) resist. The light effectively initiates polymerisation or crosslinking, or alternatively causes degradation in the resist so that solubility can be changed locally. A secondary chemical etch is then used to strip exposed silicon oxide (present at all silicon substrates exposed to oxygen) revealing elemental silicon.[3] The exposed silicon is used for transistor development (device level). In subsequent photo-lithographic processes, patterning and material depositions are then used to form metal interconnects/vias as well as dielectrics which allow individual transistors to be contacted and wired into device structures for development of complex electronic circuitry.[3] The photo-lithographic process has been continually developed to allow the size of devices to be decreased and the density of devices constantly increased so that individual transistor sizes have shrank from cm type sizes to *ca.* 50 nm. This miniaturisation (resolution enhancement) is frequently described by Moore's Law which states that the number of devices on a dye (or integrated circuit) increases by a factor of 2 every 18-24 months.[4] The result of miniaturisation is an increase in speed, *i.e.* the number of device operations per unit time and, probably more importantly, a reduction in power since the current and voltage needed to operate the transistor reduces with dimension.[5]

The trend in resolution enhancement was for many years achieved by reducing the dimensions of the mask patterns whilst simultaneously decreasing the wavelength of the radiation (light).[6] Currently, techniques such as immersion technologies whereby a liquid (usually water) is placed directly between the final lens and photoresist surface resulting in a resolution enhancement defined by the refractive index of the liquid have allowed device engineers to pattern transfer feature sizes (65/45 nm generation) less than the wavelength of light used (193 nm).[6] Patterning requirements beyond the 32 nm node will require additional steps to fulfil device density and lower power consumption. Techniques such as double patterning nano-imprinting and extreme UV (13 nm) are all viable options. There have also had to have been improvements in photoresist and mask materials and processing to allow these feature sizes to be realised.[7] To date, silicon chips have been produced at ever decreasing costs due essentially to mass production methods despite the increasing cost of the light sources and masks and post-processing equipment that are required to produce faster, more accurate and reliable electronics.[4] Whilst there may be novel device geometries under development that can improve performance and lower power[8] it appears likely that device performance is ultimately limited by the density of transistors on the chip.[9] Thus, the continuation of the improvements of device performance we have seen for the last 40 years will continue to require patterning at ever smaller dimensions. Ultimately, diffraction limits will prohibit the continued miniaturisation which the semiconductor industry has become dependent on for device evolution.

Nevertheless, whilst photolithography can potentially be used to create sub 10 nm device structures for high volume manufacturing processes, it will necessitate the use of deep UV (13 nm) and X-ray sources and these are associated with high costs and materials implications to the masks and resists.[10] Due of these factors, self-assembly may be of importance for transistor manufacture beyond the 22 nm node.[11] The advantages of self-assembly over conventional and non-lithographic methods include: i) the reduction of source costs, ii) elimination of masks and photoresists, iii) non-existence of proximity affects, iv) the possibility of developing 3-D patterning techniques, v) absence of diffraction restrictions to resolution and vi) they can be used to pattern materials with precision placement techniques by availing of templating (*i.e.* deposition of materials within the structure, known as graphoepitaxy) or a chemical pattern (alternating surface chemistries).

Self-assembly vs. lithographic techniques

Self-assembly contrasts with both conventional and non-conventional lithographic methodologies quite dramatically. Self-assembly follows the rules of a spontaneous chemical reaction (*i.e.* thermodynamic favourability) and the patterned material formed represents a local free energy minimum of a distribution of particles or molecular entities.[12] Lithographic methods produce patterns which are frequently thermodynamically and kinetically unfavourable since enthalpy changes can be positive (*i.e.* additional surface area created) and entropy changes negative (*i.e.* order increases due to pattern formation). Lithographic patterns form only because of the energy input. Because of the stability of the materials used in conventional lithography, pattern and structural defects largely derive from pattern transfer errors. In self-assembly errors are usually a representation of the thermodynamic limitations of the pattern formation process as the pattern typically results from the balance of enthalpic and entropic contributions. Note that in both conventional lithography and self-assembly there will always be a statistical (Bolzmann) distribution of defects - the number of which will reflect the energy differences between the defect state and the ideal structure. More detail of the nature of these defects is given elsewhere.[13] Very briefly, from the Gibbs Free energy equation,

$$\Delta G = \Delta H - T\Delta S \quad \text{.....(1)}$$

(where ΔG is the Gibbs free energy, H is the enthalpy, T is temperature (K) and S is the entropy term) it can be concluded that the disorder in the system can be minimised by maintaining as high as possible ratio of the enthalpy to entropy driving forces and this is frequently difficult at higher temperatures because of the weak intermolecular interactions frequently found in self-assembly. The thermodynamic nature of the assembled nanopatterns results in an order-disorder phase transition at elevated temperatures.14 The progress of the disordering process will be governed by a rate defined by an activated process expressed as an Arrhenius-type equation. The process of self-assembly will also be similarly defined (see Figure 1) and often limited by mass-transport of materials.[15] In this way, a temperature range is defined where well-ordered patterns can be formed.

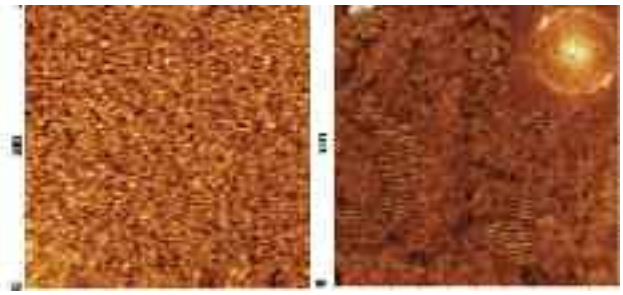

Figure 1. Effect of (solvent) annealing temperature on the phase separation of a cylinder formig polystyrene-β-polyethylene oxide (PS-β-PEO) block copolymer (tapping mode AFM phase images). Left is treatment at room temperature showing highly disordered phase separation. Right after treatment at 40 °C large phase separated domains. The inset shows the Fourier transform of the image and indicates random distribution of domain alignment.

The other important difference between lithographic methods and self-assembly is the limitations in structural motif that can be achieved using the chemistry of self-assembly. Generally, in self-assembly the system moves to separate or arrange components so that favourable interactions are maximised and unfavourable minimised. For 2-D films the structures that can be achieved are essentially limited to high symmetry patterns (stripes and dots[14]). Although arbitrary patterns can created using block copolymers on chemical patterns,[15] the chemical patterns must first be written by X-ray interference lithography. For practical use as an alternative to lithography designers will need to carefully consider what device structures and in which applications can these emerging methodologies be used for maximum impact.

Block copolymer (BCP) microphase separation

The microphase separation of block copolymers is emerging as the most promising method of assembling highly ordered nanopatterns at dimensionalities and regularity approaching the future device dimension requirements. These requirements are extremely challenging for self-assembly and lithography alike and include sub-nm line edge roughness and sub-4 nm positioning (of a feature expressed from the overlay registry requirements) accuracy for the 16 nm technology node.[16] In BCP systems the formation of ordered nanopatterns results from the interactions that exist between different blocks within the polymer molecule and has been well reviewed.[17] For the most part, several ordered structures can be formed for diblock copolymers but for templating or pattern formation the lamellar (stripe patterns of alternating blocks) and hexagonally arranged cylinders of one block within a matrix of the other block(s) are most applicable.[14] The structure formed is determined by the composition of the polymer (fraction of each block). Figures 1 and 2 show typical examples of these structures.

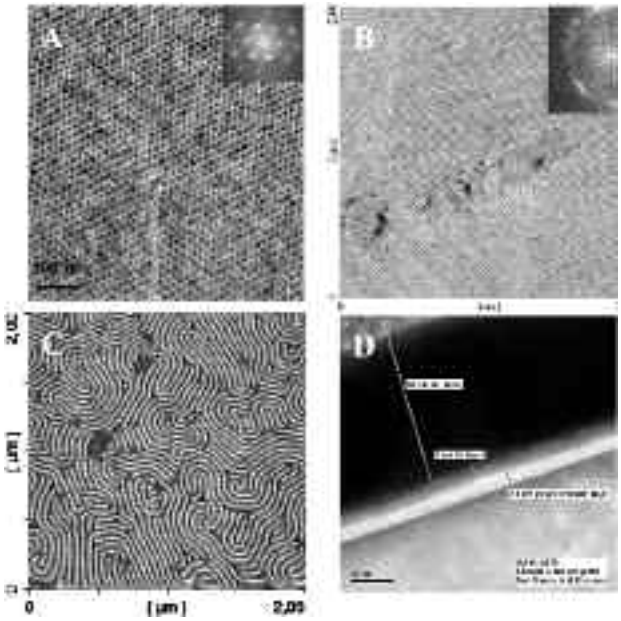

Figure 2. Tapping mode AFM phase images showing typical structures. A shows cylindrical arrangement of PS-β-PEO (PEP cylinders) with the cylinders orientated perpendicular to the surface. B is the same material with a parallel (to the substrate surface) arrangement of cylinders. C is a polystyrene-β-polymethylmethacrylate (PS-PMMA) lamellar system. The formation of the correct structure is often dependent on thin brush layers that 'neutralise' the surface energy so that neither block is favoured over the other. D is a TEM image of a brush layer on a silicon substrate. The gold shown is used for topographical patterning of the substrate.

The tendency for a BCP to microphase separate is governed by the Flory-Huggins interaction parameter, denoted χ, which essentially measures the enthalpic cost of placing chemically distinct and dissimilar individual copolymer units in contact. The entropy cost associated with pattern formation is very largely configurational in form and can be controlled by the length of the polymer chains (molecular weight) and the compositional ratio (molar fraction) of the individual blocks with the BCP. In a blend system the corresponding homopolymers would macrophase separate but in the BCP the macroscopic phase separation is prevented by the chemical bonds between the blocks.

Experimental evidence as well as theoretical predictions suggest that χ/N (where N is the degree of polymerisation) must be greater than ~10 to form ordered structures. χ has a temperature dependence and together with the temperature dependence of the entropy term in equation (1) the system will undergo an order-disorder phase transformation at temperature (100-200°C) as outlined above.

However, it is clear that to achieve well-ordered and temperature stable microphase separated systems, χ should be as large as possible (*i.e.* very chemically distinct blocks). Figures 1 and 2 provide indicative data from films that are very defective and contain a number of defects including grain boundaries, edge dislocations and various disclinations.[18] In pivotal work Harrison and co-workers provided clear insight into the understanding of these defects.[19] Grain boundaries are formed from the random orientation of patterns at unconfined surfaces coupled to classical nucleation and growth behaviour. Ostwald-type ripening can be used to describe grain growth with the total length of grain boundaries reducing with temperature/time because of strain at the grain boundary interfaces. Harrison *et al.* showed that annihilation of the point defects required concerted collision of multiple disclinations and that ordering followed an approximate time dependence of $t^{1/4}$ observed. As a result, block copolymer films will never achieve perfect order regardless of annealing time or temperature and the defects present are the result of thermodynamic equilibrium with the concentration being dependent on the magnitude of χ and the rigidity/mobility of the polymer system.

It is also important, when discussing the possible role of these materials in substrate patterning for microelectronic circuitry generation, to emphasise that the physical dimension of the polymer region has considerable significance to the degree of ordering present. Because the system ordering represents a local free energy minimisation, any defects present raise the local energy increasing strain and resulting in compressive/tensile stresses around the defect. In larger systems these strains can be de-localised through the whole system but in small localised areas the local energy increase is significant and so very less thermodynamically probable. This size dependence and the need for orientational control of the patterns provide a key motivation to pre-patterning of the surface and are discussed further below.

Interfacial effects in BCP systems

In any system, surfaces and interfaces will perturb structure extension from the bulk and in multi-component systems there will be a tendency to alter the structure and composition at the interface to minimise energy. In a block copolymer systems this is often manifest by formation of wetting layers of one component at the interface and preferred orientation of the structure.

When casting these BCPs from solvent great care is necessary to adjust the interfacial surfaces to create the desired structure. Indeed, control of interfacial energies through the use of 'brush' layers of random block polymers has become central to providing ideal morphological and structural alignment of BCP films.[15,17,23] One of the simplest means of controlling pattern formation at the substrate is 'tuning' the solvent chemistry to the BCP chemistry. The Hildebrand Solubility Parameter (HSP) is the simplest means of rationalising this chemical tuning as the HSP (δ) is the square root of the cohesive energy density of a solvent or polymer system. The HSP is related to the enthalpy of vaporization (per unit volume) and is a measure of the strength of the intermolecular forces in solution.[20] The value of δ can be used to estimate solubility because only polymers and solvents of very similar δ form true solutions. Polystyrene-β-poly(4-vinylpyridine) (PS-β-P4VP) is a BCP that has attracted much interest because of the metal complexing properties of the vinylpyridine group towards metals allowing surface patterning[21]. PS-b-P4VP has a strong tendency to form micelles in solution and we have shown that good phase separated structures are only reproducibly formed when the HSP of the solvent and the BCP (22.2 $MPa^{1/2}$) are in harmony. Figure 3 illustrates some of the recent data from our laboratories and shows a series of surface structures for a lamellar forming PS-b-P4VP as a function of solvent HSP (varied by mixing solvents of different δ values).

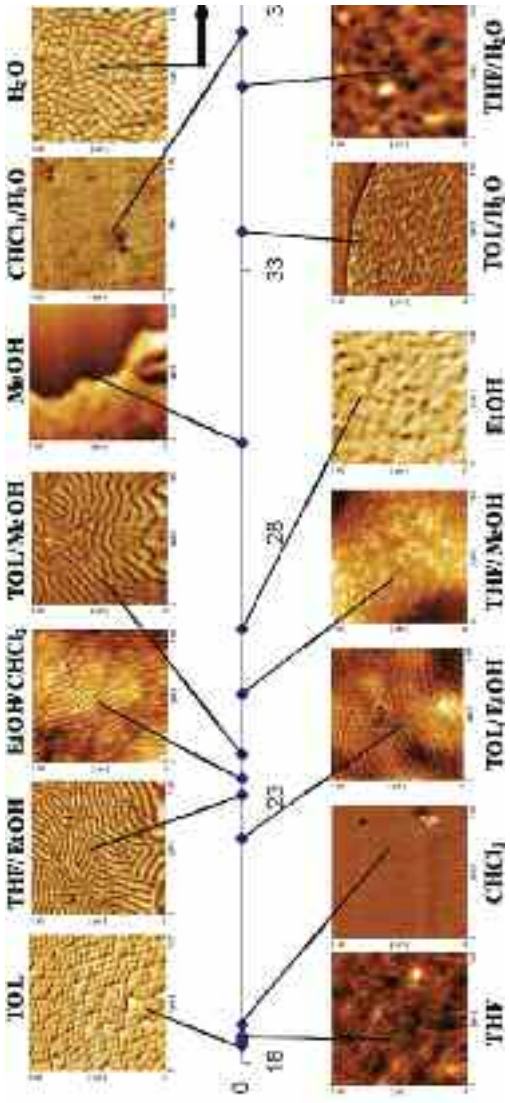

Figure 3. Tapping mode AFM phase images showing typical structures of PS-β-P4VP in different solutions (of differing Hildebrand Solubility Parameter). Phase separation is only seen around δ = 22 $MPa^{1/2}$ the value of the BCP. At lower (hydrophobic) and higher (hydrophilic) values micelle and inverse micelle structures are formed.

Graphoepitaxy

Graphoepitaxy is a method of 'forcing' or directing the phase separated polymers to align to topographical patterns at a substrate surface.[22] As such it represents the combination of top-down and bottom-up methodologies. Chemical patterning by material deposition22 or via X-ray interference lithography[23] has also been used as a means of guiding the BCP self-organisation process. Graphoepitaxy has been successfully applied to a number of systems and typical results are shown in figure 4 for a cylinder forming polystyrene-β-polyisoprene-β-polystyrene (PS-β-PI-β-PS) BCP which is spun cast from toluene solution into channels at a silicon wafer surface.[24] PS-β-PI-β-PS shows a remarkable tendency to self-align and provides high registry with the topography and it is only at the narrowest channel widths (165 nm) that the ideal structure is disturbed and this is related directly to the presence of sidewall defects which precipitate structural defects in the polymer self-organisation. A number of key learnings have now been acquired in terms of generating well-aligned and ordered BCP patterns in topographical surfaces. Ideally, the width of the channel must be closely related to an integer number of BCP structure repeat distances.[25] Whilst the polymer structure can tolerate some strain in terms of ideal spacings this is limited to a few percent and if too great structure deformation is defined by the topography, defect formation and misalignment will result. Secondly, sidewall and channel base interfaces ensure require 'tuning' of their chemistry to satisfactorily direct the polymer self-organisation and the use of topographies in alternative materials (to silicon) such as channels in metals or resists etc has been used to optimise structural control, [26] for instance, in an ideal system the sidewalls might be modified to have affinity for only one BCP. Control of these chemistries is a challenge because of the need to produce very regular films for this purpose.

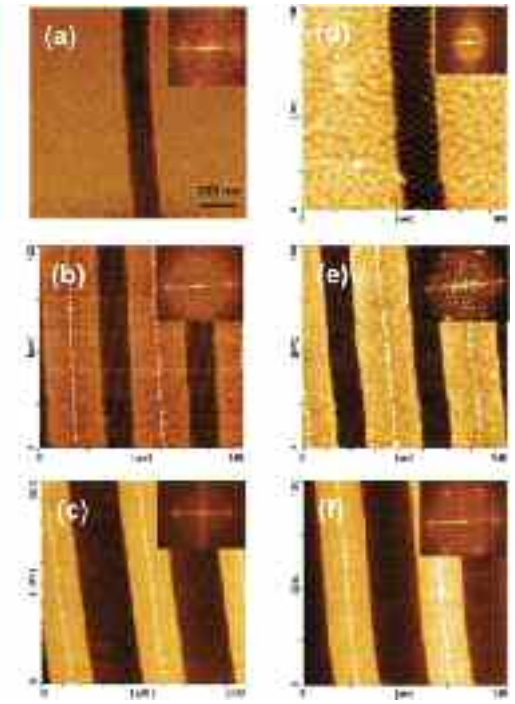

Figure 4. Tapping mode AFM phase images showing typical structures of cylinder forming PS-β-PI-β-PS at topographically patterned substrates.[24] Channel width varies from top to bottom (165 (a) and (d), 280 (b) and (e) and 430 nm (c) and (f)) and the orientation of cylinders (parallel – left and vertical – right) can be varied by control of polymer film thickness.

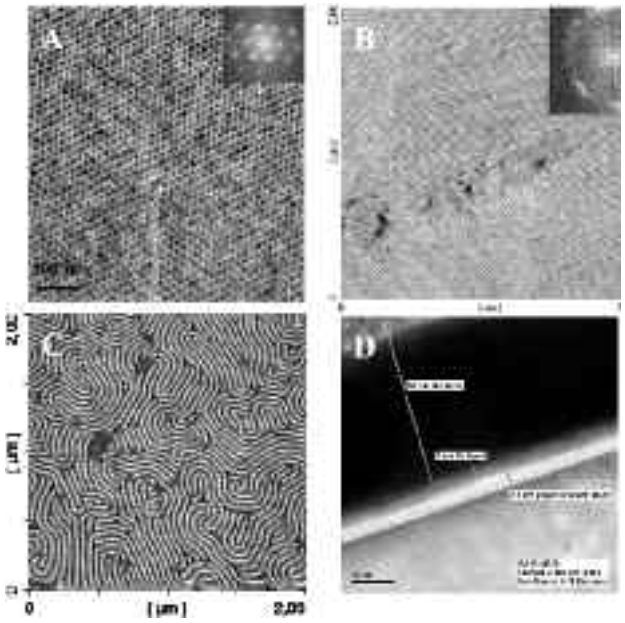

Figure 5. SEM data from a PS-β-PEO BCP (following PEO removal) deposited into topography at silicon substrates. The present of sidewall defects can cause packing and alignment errors in the self-organised patterns. It can also result in agglomeration of features as misalignment brings features into close proximity. In more complex topographies careful consideration of the extension of structure in new directions is required (lower images) or defective arrangements are precipitated.

As outlined above, when the topography and the sidewall chemistry are not ideal, the system will tend to produce significant defect densities. This is illustrated in Figure 5 for thin film (~50 nm) cylinder forming polystyrene-β-polyethylene oxide (PS-β-PEO) BCP. In these micrographs contrast has been enhanced by removal of PEO cylinders via a selective dry etch procedure to essentially reveal a porous PS system. In the upper images it can be seen that defect exist in both narrow (200 nm) and broader (475 nm) channels. In the former the high defect density is related to the roughness of the sidewall which results in significant variation of the channel width and the structure will perturb by rotational misalignment to accommodate the imposed strain. In the broader channels the sidewalls have less effect because the strain in the polymer imposed by sidewall roughness can be spread through a larger volume of the polymer.

There are local effects where features merge to produce isolated larger pores. In all systems grain boundary type dislocations are possible because the polymer structure can be rotated (azimuthally) to allow exact fitting of an integer number of polymer unit cells into channel (which is seen to slightly vary in width). Similarly, formation of extended defects such as dislocations and twins will also be possible. The presence of these defects simply reflects the nature of any self-assembly/organisation process and returns to the original point of this article in that the enthalpy term in the free energy equation (equation 1) is not that much greater than the entropy term.

Concluding Remarks

The microphase separation of block copolymers can provide nanopatterns at and beyond the current achievable limits of photolithography. However, the advantages of scale that can be achieved are balanced by a greater propensity to form defects than can be realised in lithographic methods. However, reducing dimensions to the nm region will tend to produce lower defect densities because the systems will be so small that the statistical contribution of defects into a small region will become less important. Further, incorporation of a defect will raise the local energy of the system significantly. In graphoepitaxial methods for aligning BCP patterns the defect density appears to be largely related to imperfections in the topography rather than a thermodynamic limitation. Obtaining the very precise topography required to direct self-organisation in a defect-free manner is a significant challenge but one that will require meeting by the industry if current scaling trends are to be maintained by top-down or bottom-up methodologies.

Further challenges for BCP self-organisation besides pattern regularity and placement remain. Pattern transfer to the substrate and formation of circuitry is in its infancy and much more extensive work is required for these techniques to challenge conventional fabrication. The issue of scale progression must also be addressed. In BCP systems scale is controlled by the length of the polymer blocks but as these decrease the systems become mobile and the order-disorder temperature is reduced below practical limits. Approaches such as low temperature synthesis have not been attempted to date and these will also need to be combined with, e.g. cross linking initiators so that desirable structures can be 'locked-in' for post processing.

These reservations and challenges aside it can be concluded that BCP systems afford the most likely self-assembly method to challenge lithographic techniques. The field of research has moved quickly and shown remarkable progress in the last 5 years. Similar progress will be required if these methods are to be integrated into industrial fabrication.

Acknowledgements

The authors would like to thank SFI for the provision of the CRANN CSET grant which has supported this work. We would also like to thank Intel for provision of substrates, transmission/secondary electron microscopy support and technical assistance through the researcher-in-residence programme. Staff and students at UCC and CRANN (including N Petkov, T Fitzgerald, S O'Driscoll, C O'Mahony and D Borah) are thanked for data.

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- pH extreme tolerance without dissolution or hydrolysis, both limitations of silica-based sorbents.

This combination of physical and chemical properties makes PoraPak Rxn cartridges ideal for synthesis cleanup. The polymers characteristics and particle size maintain gravity, pressure -or vacuum - assisted flow; even when reaction mixtures contain precipitate that may contribute additional resistance to flow. The sample will still pass through the cartridge.

The polymer used in PoraPak Rxn products is resistant to shrinking or swelling in the organic solvents typically used in synthetic reactions. Tests with the following solvents demonstrate that the packed bed maintains good flow properties:

- DCE
- DCM
- DMSO
- DMF
- THF
- Acetone

Some Medicinal Chemists are familiar with silica-based chromatographic products for reaction cleanup. One of the limitations of these silica-based ion-exchange materials is pH. Silica will dissolve at high pH, while bonded phases are hydrolyzed at low pH; both conditions result in loss of sample and/or impurities (silica and bonded phase) collected in product fractions. PoraPak Rxn polymer-based chromatographic phases are stable at extreme pH. This feature permits using pH as a very powerful tool to create a separation, particularly in ion-exchange mode.

WATERS: A WORLD LEADER IN SEPARATIONS SCIENCE PROVIDING SEPARATIONS SOLUTIONS

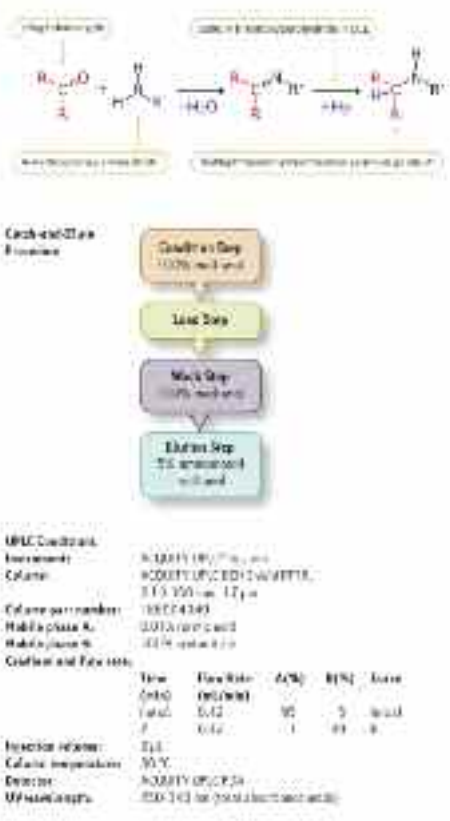
Waters is highly respected world wide for its expertise in chromatography. Coupled with our ability to seamlessly link critical instrumentation, chemistries, separation technologies, and software, this expertise puts us in a unique position to deliver value-added solutions to our customers.

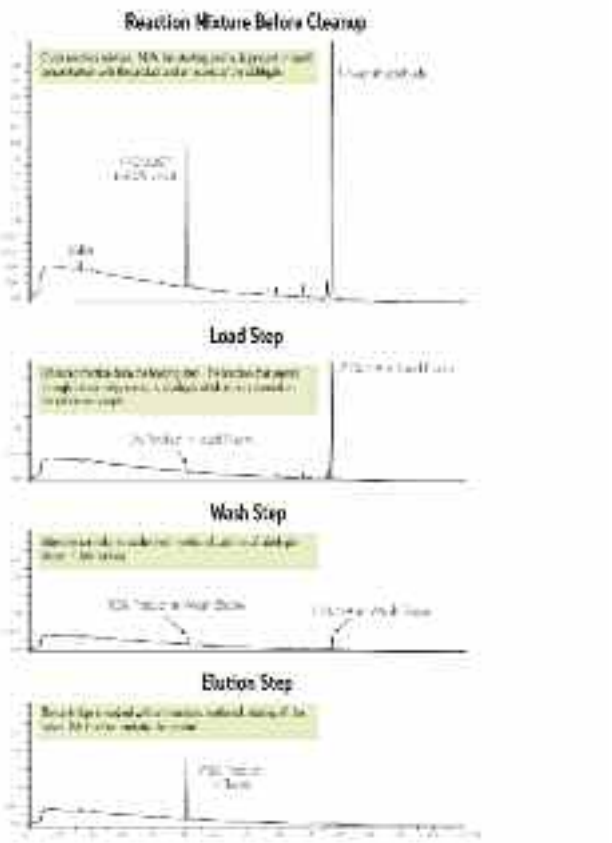
MANUFACTURING

Our world-class manufacturing facilities are continuously expanded and upgraded to keep pace with market demand for our new and existing products. We manufacture under the highest quality standards in the industry, including ISO-9001:2000, ISO 13485:2003 and Current Good Manufacturing Practices (cGMP).

CLEANUP OF A REDUCTIVE AMINATION MIXTURE

Reductive amination is a common reaction carried out in medicinal chemistry laboratories. In this example, a PoraPak Rxn CX cartridge is used to fractionate the reaction mixture.





[FAST CLEANUP OF SYNTHESIS REACTIONS]

- Efficient Fractionation
- Cost Effective

PoraPak™ Rxn products are designed to ensure fast and thorough cleanup of most synthesis reactions. The polymer used in PoraPak Rxn material is tolerant of pH extremes, shows low hydraulic resistance and displays very little shrinking or swelling in organic solvents. This combination of physical and chemical properties makes PoraPak Rxn an ideal solution for your most challenging synthesis cleanup.

PoraPak™ Rxn
Post Synthesis Cleanup

www.waters.com/porapak

Waters
THE SCIENCE OF WHAT'S POSSIBLE.™

Industry News

Dr. Donal Coveney,
TopChem Laboratories Limited, 70 Western Parkway Business Park, Ballymount Drive, Dublin 12, Ireland.

Do we hear anything else other than bad news in these days of doom and gloom? For those of us old enough to remember 16% mortgage rates things don't seen quite so bad with the ECB pushing rates lower and lower, but with over 400,000 now on the dole there is a haunting echo of the grim eighties. There is some positive news thankfully from the Industrial sector.

Generic Sector

Unlike the multinational research driven pharmaceutical companies, the generic sector is thriving. The market was stunned with the June 2008 announcement of Daiichi (Japan) agreeing to acquire Ranbaxy for a price of $3.4-$4.6 billion. Apart from the intriguing clash of Japanese and Indian cultures, the acquisition of a major generic player by a prescription medicine company is a new development.

Not long after the acquisition, Ranbaxy got into hot water with the US FDA leading ultimately to an FDA ban of over 30 Ranbaxy products. This led to a slide in Ranbaxy share price which triggered a $3.6 billion loss in Q3 2008 by Daiichi. The CEO of Ranbaxy has more recently stepped down bringing to an end one hell of a year for the two companies.

With Sanofi-Aventis stumping up $2.6 billion for the Czech generic maker Zentiva, perhaps we have a new trend here? With flagging pipelines and a burgeoning generic sector, this is not so surprising after all. Maybe the next bandwagon looms for Big Pharma?

Hot off the press in yet another move in the generic sector see the US based Watson acquiring the UK Arrow generics group for $1.75 billion. Arrow founder Tony Tabatznik certainly has hit the right formula having done the same trick in the nineties by selling his Generics UK business to the Merck kGA group for £200 million.

Domestic News

Good news from Pfizer with the welcome news for Cork of a biological facility investment of over €300 million with hundreds of jobs in the pipeline. The well established Portuguese API manufacturer Hovione has taken over the Pfizer Loughbeg facility preserving at least some of the jobs on that site. The Inchera Little Island facility is not so lucky however and is due to close.

Genzyme in Waterford are expanding further with a €130 million investment leading to an additional 170 jobs. Although like the Pfizer expansion, this is in the area of biologics. I am not sure how many organic chemists they will be looking for!

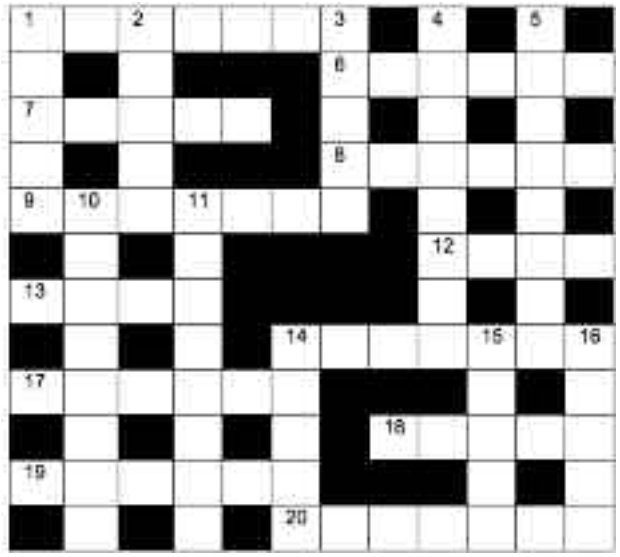
The latest CSO figures show a rise in April of 6% for the pharmaceutical and chemical manufacturing sector exports, adding to an overall growth of 2.6% in 2008 to €44.17 billion – an impressive 51% of the national total. At least our sector is showing some resilience in marked contrast to almost all others.

It is clear there are trends emerging in our domestic sector: the API manufacturers are struggling while the investment in biologics is growing. Maybe we should all be upskilling and learning some protein chemistry!

The ICN Crossword

Dr. Donal Coveney FICI,

TopChem Laboratories Limited, 70 Western Parkway Business Park, Ballymount Drive, Dublin 12, Ireland



Down

1 Old resin (5)
2 Measure the leaden depth? (5)
3 St. Patrick missed these (5)
4 "W" makes light? (8)
5 "....." baby, where did you get those eyes! (8)
10 You just can't eat it (8)
11 Cries of I are heard for openings (8)
14 A sine of an aromatic plant (5)
15 Bonus (5)
16 Particular nickel (5)

Across

1 Common analgesic (7)
6 Prolific US inventor seen in 4 Down (6)
7 Bear the ..... of (6)
8 Assam, Darjeeling, Earl Grey - all end up here (6)
9 Combine boss with ire for RNA framework? (7)
12 French waters (4)
13 Abominable leg pull (4)
14 Definitely not a pro (7)
17 Less evolved but real unlike 13 across! (6)
18 Rock climbers little metal friend (5)
19 Young eels (6)
20 River meets sea (7)

Last Issue Solution

Across.

Thunder, 6 Accord, 7 Niche, 8 Ionise, 9 Sacrcoid, 12 Item,

13 Soap, 14 Stomata, 17 Barium, 18 Villi, 19 Ritual, 20 Theatre

Down.

1 Tongs, 2 Ulcer, 3 Rabid, 5 Crescent, 10 Aromatic, 11 Capsicum,

14 Smelt, 15 Allot, 16 Azide