

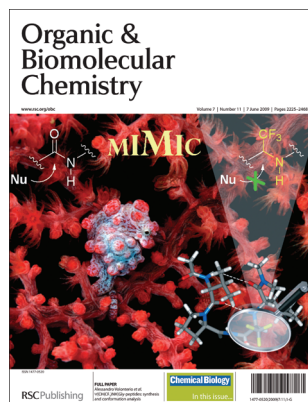
Organic & Biomolecular Chemistry

An international journal of synthetic, physical and biomolecular organic chemistry
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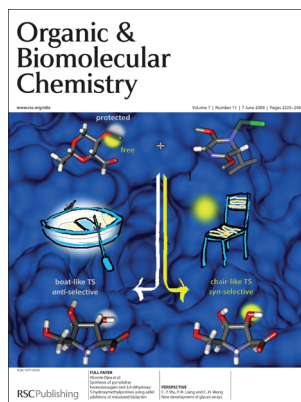
ISSN 1477-0520 CODEN OBCRAK 7(11) 2225–2468 (2009)



Cover

See Alessandro Volonterio *et al.*, pp. 2286–2296.
Mimicry is a fundamental concept for the chemist in designing useful peptidomimetics as well as for certain animals, like pygmy seahorses, in defending their own life. The authors thank Roberto Sozzani for providing the cover picture.

Image reproduced by permission of Alessandro Volonterio from *Org. Biomol. Chem.*, 2009, **7**, 2286.



Inside cover

See Vicente Ojea *et al.*, pp. 2310–2321.
The hydrophobic surface calculated for the active site of β -glucosidase A is depicted as the background image for aldol-based synthesis of pyrrolidine homoazasugars and polyhydroxylated prolines.

Image reproduced by permission of Vicente Ojea from *Org. Biomol. Chem.*, 2009, **7**, 2310.

CHEMICAL BIOLOGY

B41

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Chemical Biology

June 2009/Volume 4/Issue 6

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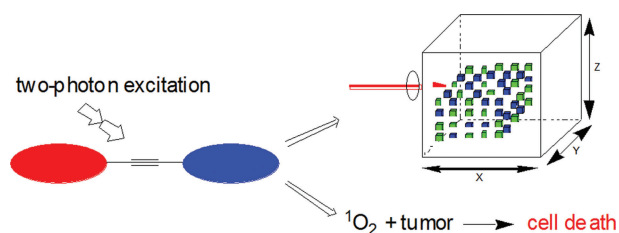
EMERGING AREA

2241

Design of two-photon absorbing materials for molecular optical memory and photodynamic therapy

Kazuya Ogawa* and Yoshiaki Kobuke*

Molecular design of two-photon absorption materials toward three dimensional high-density optical memory and highly selective photodynamic therapy at deep tissue sites is reviewed.



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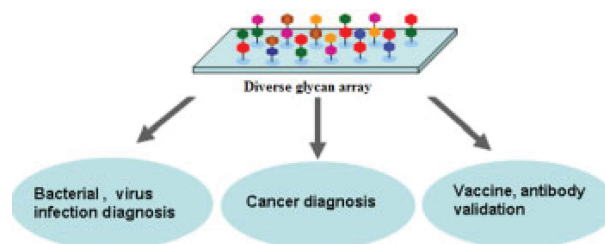
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2247

New development of glycan arrays

Chung-Yi Wu,* Pi-Hui Liang* and Chi-Huey Wong*

New fabrication and detection methods for glycan arrays, and their applications in biology and biomedical research, are described in this perspective article.



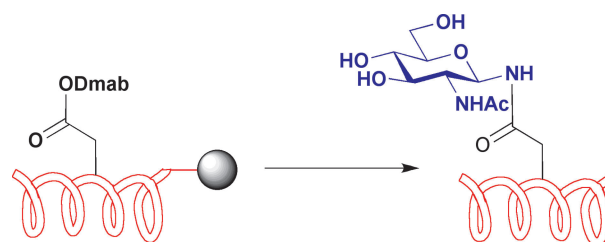
COMMUNICATIONS

2255

Efficient use of the Dmab protecting group: applications for the solid-phase synthesis of *N*-linked glycopeptides

Trent Conroy, Katrina A. Jolliffe and Richard J. Payne*

An efficient protocol for the chemoselective removal of Dmab esters on the solid phase is reported; this method has been successfully utilised for the convergent solid phase synthesis of *N*-linked glycopeptides.

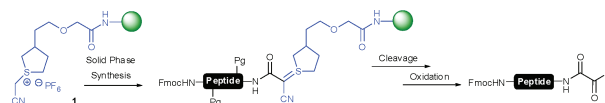


2259

A general strategy for the preparation of C-terminal peptide α -ketoacids by solid phase peptide synthesis

Lei Ju and Jeffrey W. Bode*

A new cyanosulfur-ylide based linker makes possible the synthesis of C-terminal peptide α -ketoacids by solid phase synthesis. The preparation of the requisite linker and its application to a variety of C-terminal peptide α -ketoacids with unprotected side chains is reported.

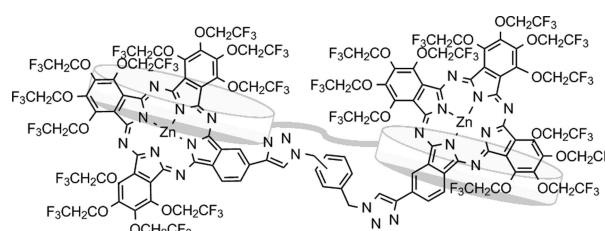


2265

Synthesis of trifluoroethoxy-coated binuclear phthalocyanines with click spacers and investigation of their clamshell behaviour

Hideyuki Yoshiyama, Norio Shibata,* Takefumi Sato, Shuichi Nakamura and Takeshi Toru

A series of trifluoroethoxy-coated phthalocyanine dyads with flexible click spacers were synthesized for investigation of intra- and intermolecular aggregation. UV-vis, fluorescence and electrochemical studies revealed that the trifluoroethoxy-coating stops their intramolecular aggregation.



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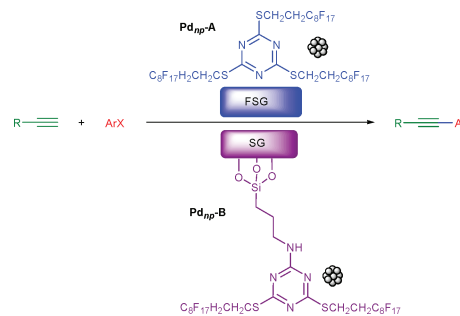
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2270

Alkynylation of aryl halides with perfluoro-tagged palladium nanoparticles immobilized on silica gel under aerobic, copper- and phosphine-free conditions in water

Roberta Bernini, Sandro Cacchi,* Giancarlo Fabrizi, Giovanni Forte, Francesco Petrucci, Alessandro Prastaro, Sandra Niembro, Alexandr Shafir and Adelina Vallribera

Perfluoro-tagged palladium nanoparticles immobilized on silica gel provide a solution to some of the problems of the alkynylation of aryl halides

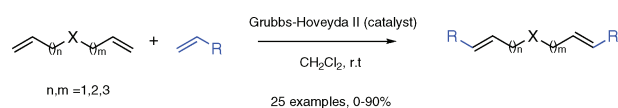


2274

Two-directional cross-metathesis

Annabella F. Newton, Stephen J. Roe, Jean-Christophe Legeay, Pooja Aggarwal, Camille Gignoux, Nicola J. Birch, Robert Nixon, Marie-Lyne Alcaraz and Robert A. Stockman*

Two-directional cross-metathesis of a range of α,ω dienes with a variety of electron deficient alkenes has been accomplished. It was found that the process is quite general and gives complete selectivity for the *E,E*-dienes, making this a very useful and high yielding protocol for two-directional chain elongation.



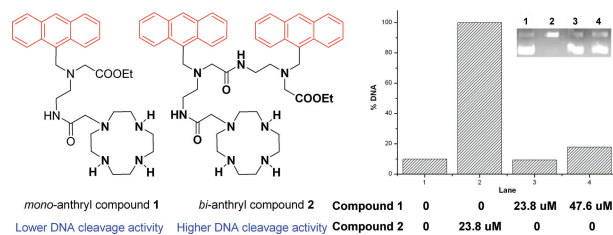
PAPERS

2278

Synthesis, DNA binding and photocleavage study of novel anthracene-appended macrocyclic polyamines

Yu Huang, Yu Zhang, Ji Zhang, Da-Wei Zhang, Qiao-Sen Lu, Jun-Liang Liu, Shan-Yong Chen, Hong-Hui Lin* and Xiao-Qi Yu*

The DNA binding and photocleavage activity of the anthryl dimer is more than twice that of the monomer. The structure of the compounds plays important role in the binding and photocleavage process.

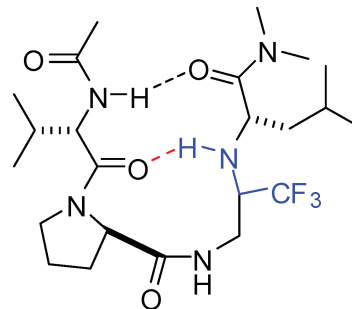


2286

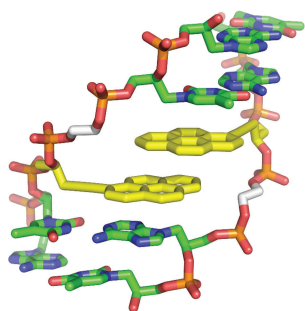
$\Psi[\text{CH}(\text{CF}_3)\text{NH}]\text{Gly-peptides}$: synthesis and conformation analysis

Marco Molteni, Maria Cristina Bellucci, Serena Bigotti, Stefania Mazzini, Alessandro Volonterio* and Matteo Zanda*

The synthesis and the conformation of selected $\Psi[\text{CH}(\text{CF}_3)\text{NH}]\text{Gly-peptides}$ have been investigated in this work. Notably, these peptides assume well defined secondary structures promoted by an intramolecular hydrogen bond involving the amionic proton of the trifluoroethylamino peptide bond surrogate.



2297

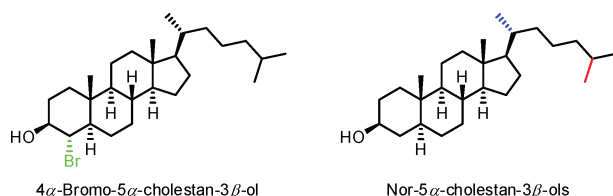


Pyrene acetylde nucleotides in GNA: probing duplex formation and sensing of copper(II) ions

Hui Zhou, Xiaoyan Ma, Jianpian Wang and Lili Zhang*

The synthesis and evaluation of GNA duplexes containing fluorescent pyrene and pyrene acetylde nucleotides is reported. Interestingly, only the pyrene acetylides, but not the related plain pyrene nucleotides, form strong excimers upon stacking in glycol nucleic acid (GNA) duplexes. The interstrand pyrene acetylde excimer formation was used to monitor GNA duplex formation and was applied to the design of a copper(II)-selective “turn-on” fluorescence sensor.

2303

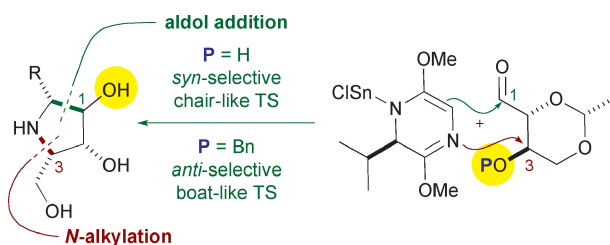


4 α -Bromo-5 α -cholestan-3 β -ol and nor-5 α -cholestan-3 β -ol derivatives—stereoselective synthesis and hormonal activity in *Caenorhabditis elegans*

René Martin, Ratni Saini, Ingmar Bauer, Margit Gruner, Olga Kataeva, Vyacheslav Zagoriy, Eugeni V. Entchev, Teymuraz V. Kurzchalia and Hans-Joachim Knölker*

We report the stereoselective synthesis of 4 α -bromo-5 α -cholestan-3 β -ol and nor-5 α -cholestan-3 β -ol derivatives and a preliminary study of their biological activity in *Caenorhabditis elegans*.

2310

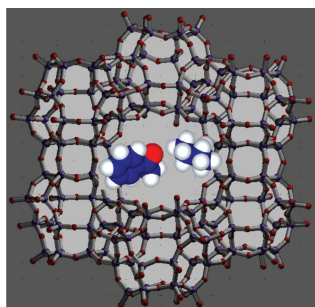


Synthesis of pyrrolidine homoazasugars and 3,4-dihydroxy-5-hydroxymethylprolines using aldol additions of metalated bislactim ethers to 2,4-*O*-ethylidene-D-erythroses

Olga Blanco, Cristina Pato, María Ruiz* and Vicente Ojea*

Stereocontrolled tin(II)-mediated aldol additions of bislactim ethers to 2,4-*O*-ethylidene-erythroses allow a direct access to pyrrolidine homoazasugars (R = CH₂OH) and polyhydroxylated proline derivatives (R = CO₂H).

2322



Radical pairs with rotational fluidity in the photochemical reaction of acetophenone and cyclohexane in the zeolite NaY: a ¹³C CPMAS NMR and product analysis study

Amme Amboya, Tina Nguyen, Hien T. Huynh, Ashley Brown, Gretchen Ratliff, Heather Yonutas, Deniz Cizmeciyan,* Arunkumar Natarajan and Miguel A. Garcia Garibay*

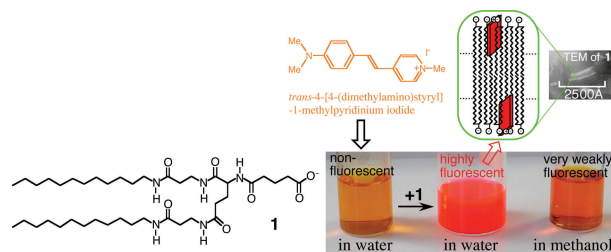
The photochemistry of acetophenone and cyclohexane co-adsorbed in the zeolite NaY revealed a very efficient cage effect with radical coupling products that take advantage of the relatively high rotational freedom of the pair.

2327

Molecular structural requirements, dye specificity, and application of anionic peptide amphiphiles that induce intense fluorescence in cationic dyes

Hiroshi Hachisako,* Naoya Ryu and Ryoichi Murakami

An anionic peptide amphiphile with several amide bonds per molecule was found to induce intense fluorescence in cationic dyes in water. The molecular structural requirements, dye specificity, and applications were investigated.

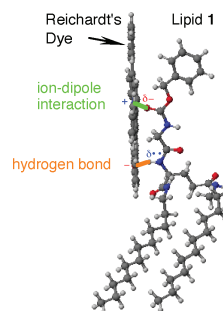


2338

Formation of specific dipolar microenvironments complementary to dipolar betaine dye by nonionic peptide lipids in nonpolar medium

Hiroshi Hachisako,* Naoya Ryu, Hiromi Hashimoto and Ryoichi Murakami

A nonionic peptide lipid with a Gly residue was found to capture dipolar betaine dye when self-assembled in chlorobenzene. The receptor site was specified, and the molecular structural requirements as receptors towards dipolar betaine dyes were investigated in detail.

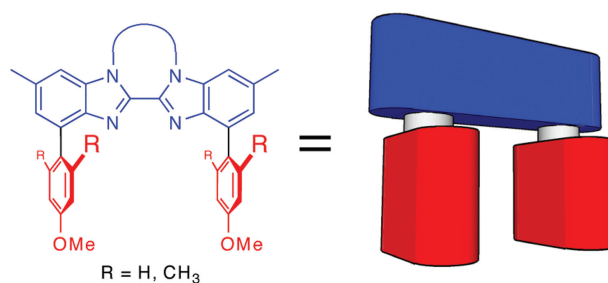


2347

Synthesis, X-ray crystal structures, and computational studies of 1,1'-bridged 4,4'-diaryl-2,2'-bibenzimidazoles: building blocks for supramolecular structures

Derik K. Frantz, Ashley A. Sullivan, Yoshizumi Yasui, Anthony Linden, Kim K. Baldrige* and Jay S. Siegel*

Molecular clips based on 2,2'-bibenzimidazole represent a new class of building blocks for supramolecular structures. Their crystal structures show a propensity to form intercalated molecular chains or include solvent molecules within their pincers.

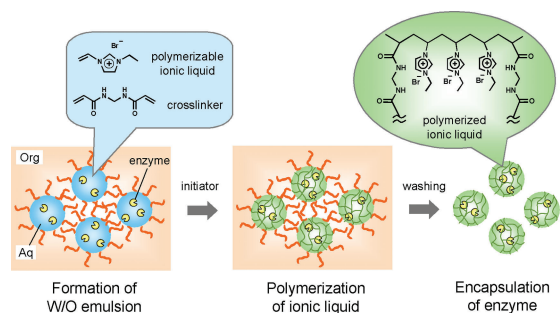


2353

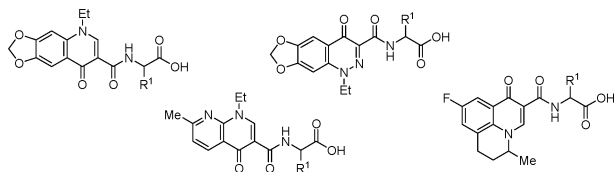
Enzyme encapsulation in microparticles composed of polymerized ionic liquids for highly active and reusable biocatalysts

Kazunori Nakashima, Noriho Kamiya, Daisuke Koda, Tatsuo Maruyama and Masahiro Goto*

Horseradish peroxidase is encapsulated in polymerized ionic liquid microparticles, which offer excellent biocatalytic activity and recyclability for repeated oxidation reactions.



2359

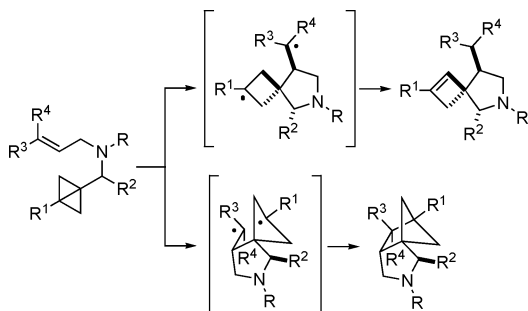


Synthesis of amino acid derivatives of quinolone antibiotics

Alan R. Katritzky,* Munawar Ali Munawar, Judit Kovacs and Levan Khelashvili

Optically pure conjugates of quinolone antibiotics with naturally occurring amino acids are synthesized in 40–98% yields.

2363

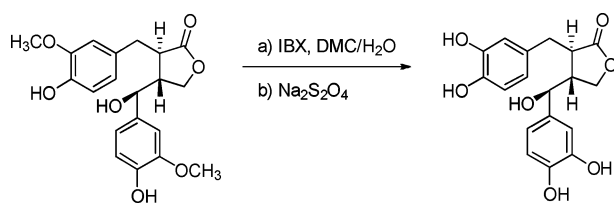


An ESR analysis of the mechanism of pericyclic reactions of bicyclobutane

Maciej A. A. Walczak, Byong-kyu Shin, Peter Wipf* and Sunil Saxena*

Experimental and simulated ESR data are in good agreement with a biradical mechanism for the intramolecular pericyclic reactions of bicyclo[1.1.0]butanes.

2367

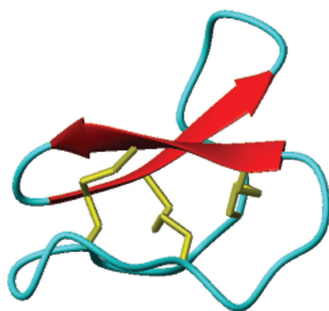


A selective de-*O*-methylation of guaiacyl lignans to corresponding catechol derivatives by 2-iodoxybenzoic acid (IBX). The role of the catechol moiety on the toxicity of lignans

Roberta Bernini,* Maurizio Barontini, Pasquale Mosesso, Gaetano Pepe, Stefan M. Willför, Rainer E. Sjöholm, Patrik C. Eklund and Raffaele Saladino*

New lignan derivatives have been prepared by IBX-oxidative procedure. The role of the catechol moiety on their cytotoxicity and genotoxicity has been investigated.

2378



Circular proteins from *Melicytus* (Violaceae) refine the conserved protein and gene architecture of cyclotides

Manuela Trabi, Joshua S. Mylne, Lillian Sando and David J. Craik*

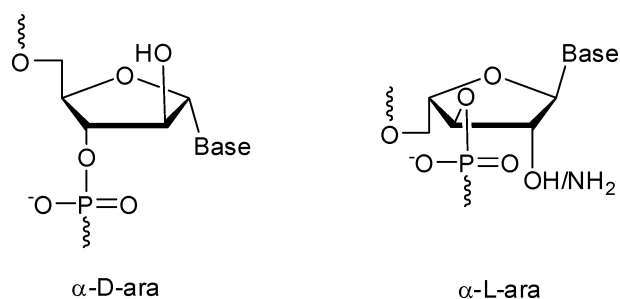
Cyclotides are ultra-stable peptides with a knotted pattern of disulfide bonds and a cyclic backbone. The novel cyclotides reported herein are from plants of the genus *Melicytus*.

2389

Synthesis and hybridization studies of α -configured arabino nucleic acids

Pankaj Gupta, Jyotirmoy Maity, Gaurav Shakya, Ashok K. Prasad, Virinder S. Parmar and Jesper Wengel*

Synthesis of α -L-arabino- and α -D-arabino-configured pentofuranosyl nucleosides of four of the natural bases is reported together with hybridization properties of oligonucleotides containing α -L-ara-T and -A, α -D-ara-T and -A, and 2'-amino- α -L-ara-T monomers.

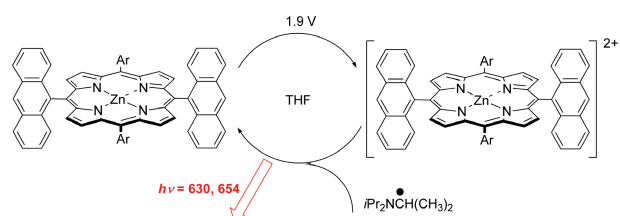


2402

Synthesis, photophysical, electrochemical, and electrochemiluminescent properties of 5,15-bis(9-anthracenyl)porphyrin derivatives

Chloè Sooambar, Vincent Troiani, Carlo Bruno, Massimo Marcaccio, Francesco Paolucci,* Andrea Listorti, Abdelhalim Belbakra, Nicola Armaroli,* Alessandra Magistrato,* Rita De Zorzi, Silvano Geremia and Davide Bonifazi*

Novel 5,15-bis(9-anthracenyl)porphyrin derivatives, showing uncommon electrooptical properties (ECL and NIR-centred IV-CT), are described.

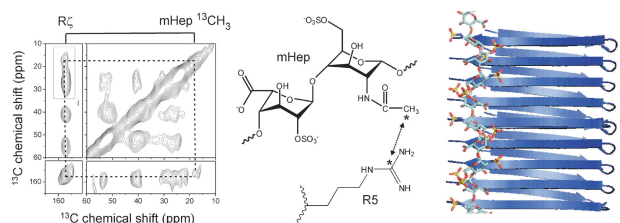


2414

Exploiting a ^{13}C -labelled heparin analogue for *in situ* solid-state NMR investigations of peptide-glycan interactions within amyloid fibrils

Jillian Madine, Jonathan C. Clayton, Edwin A. Yates and David A. Middleton

It is shown that contacts between a ^{13}C -labelled glycosaminoglycan and specific side groups of the Alzheimer's polypeptide $\text{A}\beta_{1-40}$ can be detected within amyloid fibrils using solid-state NMR spectroscopy.

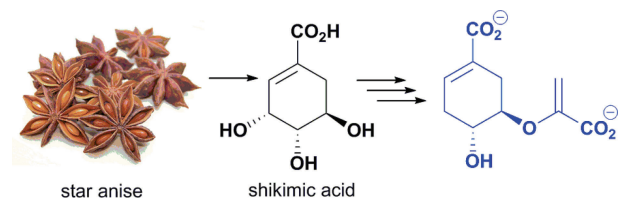


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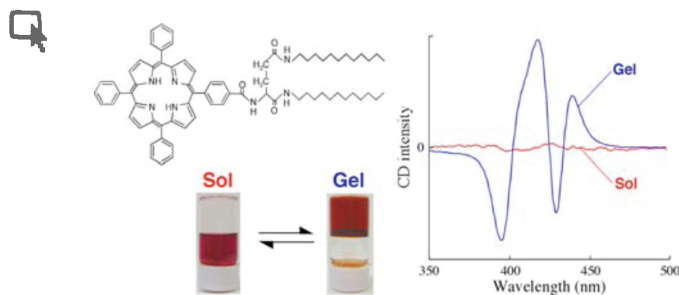
Synthesis and evaluation of 2,5-dihydrochorismate analogues as inhibitors of the chorismate-utilising enzymes

Richard J. Payne,* Esther M. M. Bulloch, Miguel M. Toscano, Michelle A. Jones, Olivier Kerbarh and Chris Abell*

A library of 2,5-dihydrochorismate analogues were designed as inhibitors of the chorismate-utilising enzymes anthranilate synthase, isochorismate synthase, salicylate synthase and 4-amino-4-deoxychorismate synthase. The compounds, synthesised from shikimic acid, showed differential enzyme inhibition.



2430

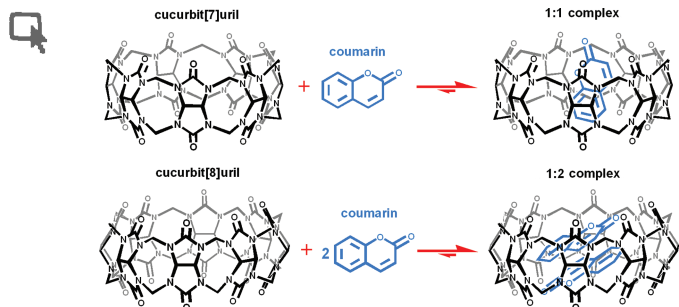


Chirally self-assembled porphyrin nanowires assisted by L-glutamide-derived lipid for excitation energy transfer

Hirokuni Jintoku, Takashi Sagawa, Makoto Takafuji and Hirotaka Ihara*

An L-glutamide-functionalized tetraphenylporphyrin (**1**) has been newly synthesized and its self-assembling behavior in organic solvents is reported.

2435

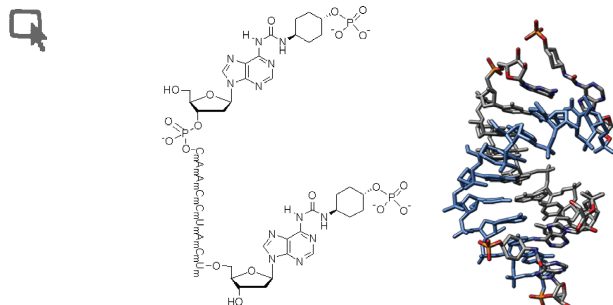


Inclusion complexes of coumarin in cucurbiturils

Ruibing Wang,* David Bardelang,* Mélanie Waite, Konstantin A. Udachin, Donald M. Leek, Kui Yu, Christopher I. Ratcliffe and John A. Ripmeester

Coumarin was found to form stable 1 : 1 and 1 : 2 host-guest inclusion complexes with cucurbit[7]uril (CB[7]) and cucurbit[8]uril (CB[8]) respectively as evidenced by ¹H NMR and UV-vis studies and further supported by *ab initio* calculations and single crystal X-ray diffraction.

2440

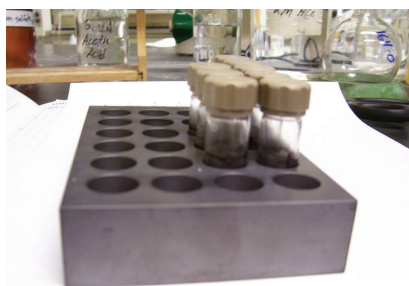


Synthesis of terminally modified oligonucleotides and their hybridization dependence on the size of the target RNAs

Kohji Seio,* Yusuke Takaku, Kazuya Miyazaki, Sayako Kurohagi, Yoshiaki Masaki, Akihiro Ohkubo and Mitsuo Sekine*

We have developed oligonucleotide probes having bulky negatively charged substituents at the termini and have demonstrated their selective binding of short RNA targets. This selectivity seems applicable to the detection of short RNAs, such as matured-miRNAs.

2452



Assessment and use of two silicon carbide multi-well plates for library synthesis and proteolytic digests using microwave heating

Lauren M. Stencel, Chad M. Kormos, Keri B. Avery and Nicholas E. Leadbeater*

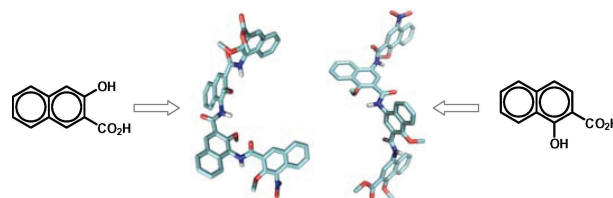
The use of two silicon carbide plates is reported for the preparation of three libraries of organic molecules and proteolytic digests using microwave heating.

2458

Sterically controlled naphthalene homo-oligoamides with novel structural architectures


Panchami Prabhakaran, Vedavati G. Puranik,
Jima N. Chandran, P. R. Rajamohanan,*
Hans-Jörg Hofmann* and Gangadhar J. Sanjayan*

This article describes the design, synthesis, and structural investigations of naphthalene homo-oligoamides derived from naphthalene building blocks. Our findings extend the utility of steric interactions as an efficient tool for modulating conformational features in synthetic oligomers.



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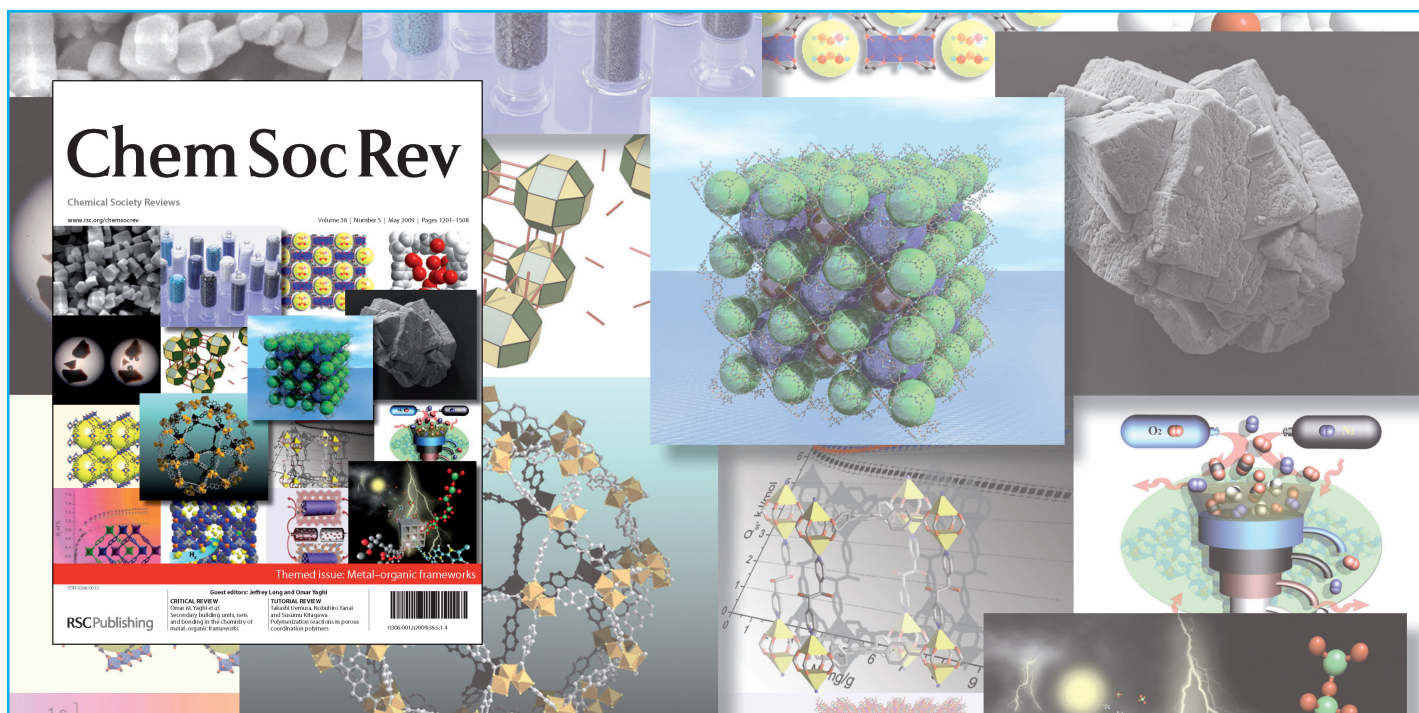
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Themed issue: Metal–organic frameworks

Metal–organic frameworks (MOFs) combine chemistry and geometry to produce technology-generating properties in a way that is rarely experienced in science. The vast expanse of possibilities that MOF chemistry offers has allowed many researchers from around the world to emerge as important leaders for their own unique contributions. This issue showcases some of these contributions, while presenting a diverse range of exciting recent developments in the field.

Reviews include:

Hydrogen storage in metal–organic frameworks

Leslie Murray, Mircea Dinca and Jeffrey Long

Recent advances on simulation and theory of hydrogen storage in metal–organic frameworks and covalent organic frameworks

Sang Soo Han, José L. Mendoza-Cortes and William A. Goddard

Polymerization reactions in porous coordination polymers

Tadashi Uemura, Nobuhiro Yanai and Susumu Kitagawa

Large breathing effects in three-dimensional porous hybrid matter: facts, analyses, rules and consequences

G rard F rey and Christian Serre

Industrial applications of metal–organic frameworks

Alexander U. Czaja, Natalia Trukhan and Ulrich M ller

Design and synthesis of metal–organic frameworks using metal–organic polyhedra as supermolecular building blocks

John J. Perry IV, Jason A. Perman and Michael J. Zaworotko

Guest editors



Jeffrey R. Long
University of California,
Berkeley, USA



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"The purpose of this themed issue is to... inform readers about a selection of topics in the field that are currently the subject of intense research."

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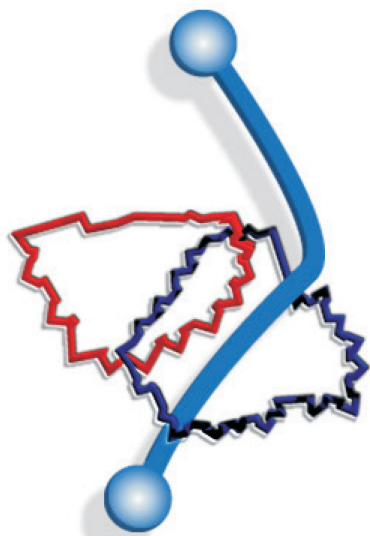


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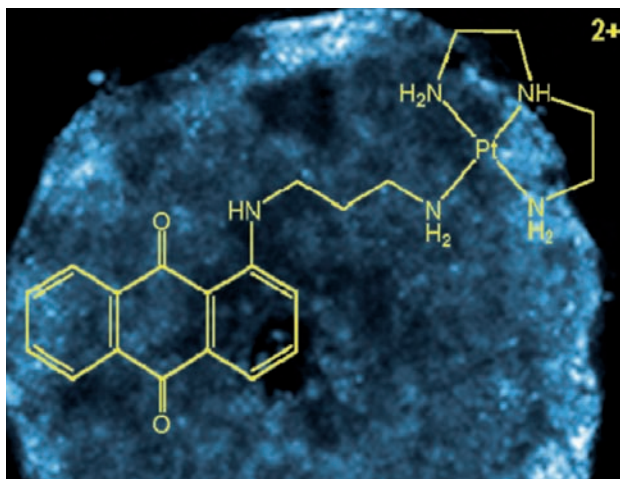


Chemical Biology

The competition between cell uptake and tumour penetration of anticancer drugs Slow uptake for effective drugs?

Anticancer drugs that enter cancer cells quickly may be less effective, according to work from Australian chemists. The University of Sydney team has demonstrated that rapid uptake of anticancer compounds by cells could limit how well they penetrate tumours.

Using a spheroidal culture of cancer cells as a tumour model, Trevor Hambley and co-workers investigated the rate of cellular uptake and penetration of some model anticancer drugs. Their results suggest that competition between cell uptake and penetration deeper into a tumour means that drugs that rapidly enter cells near the surface are less able to penetrate deeper into and affect cells near the tumour centre. They found that one drug candidate with slower cellular uptake showed greater penetration into a cancer cell spheroid. In contrast, a model drug with a high cellular uptake rate rapidly entered cells near the spheroid surface, allowing much less of the drug to diffuse to, and then be taken up by, cells at the centre of the



cancerous tissue.

The researchers suggest that, in the light of their results, the balance between cellular accumulation and tumour penetration may need to be shifted for some current anticancer agents. 'Rapid cellular uptake is usually considered highly desirable, but we have shown that slowing uptake can improve penetration,

Slow cellular uptake of a platinum compound allows it to penetrate inside a model tumour rather than just accumulating at its edge

Reference
N S Bryce *et al.*, *Chem. Commun.*, 2009, 2673 (DOI: 10.1039/b902415h)

which is also important,' says Hambley. Cells buried within tumours can have the most aggressive and drug resistant phenotypes, but as they are often not well supplied by blood vessels, it can be difficult for anticancer drugs to reach them. 'Poor penetration may be a major contributor to the failure of cancer chemotherapy,' Hambley says.

The work is welcomed by Sofi Elmroth, an expert in biochemistry, at Lund University, Sweden. She says that the research 'demonstrates in an elegant way that molecules with an improved tendency for cellular accumulation are typically less efficient when tissue permeability is measured. This observation highlights the need for tissue-like model systems in a relatively early phase of drug screening – and particularly so for anticancer active drug candidates – where efficient targeting of the central part of, for example, a tumour may well be the difference between an efficient cure and propagation of the disease.'
Russell Johnson

In this issue

Ruthenium probe puts the spotlight on RNA

Fluorophores join forces for cell imaging

Nanoparticles nurse neurological diseases

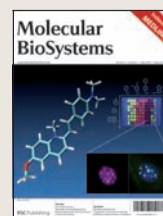
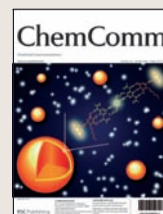
Silica-based gene delivery stimulates nerve cell formation in the brain

Bearing fruit

In this month's interview, Alan Crozier talks about flavonoids, David Bellamy and good wine

Squashing cancer cells

Could stretching cells be the way to diagnose cancer? June's Instant insight looks at the biomechanical approach to medicine



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Research highlights

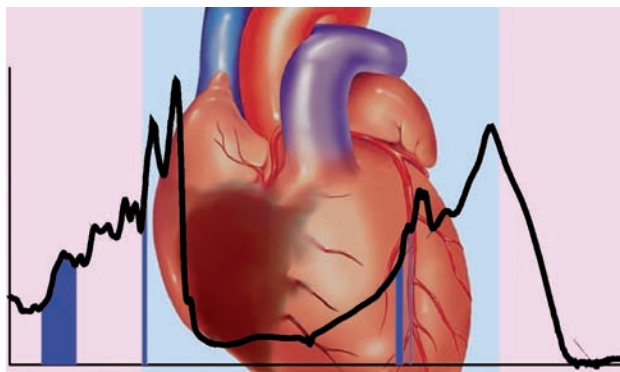
Infrared spectra used to account for chest pain symptoms

Recognising the signals of heart attacks

In a study involving over 100 patients, international scientists have used spectroscopy to find the cause of patients' chest pain.

'We started the study [as if looking] through the eyes of a doctor saying there is a symptom,' says Wolfgang Petrich from Roche Diagnostics, Mannheim, who led the investigation. The international team – from Germany, the US, Canada, Austria, Sweden and Spain – analysed serum samples using a combination of mid-infrared spectroscopy and statistical techniques. They found that they could identify particular shapes in the spectra of samples from patients with acute myocardial infarction (AMI) – heart cell death or damage brought about by a heart attack. This was in contrast to spectra from samples taken from patients with the same symptom of acute chest pain, but without AMI.

Swift and accurate diagnosis of the cause of chest pain is key to reducing mortality and Petrich's diagnostic



The infrared spectra of serum samples from patients with AMI show differences in some regions (dark blue)

Reference

W Petrich *et al*, *Analyst*, 2009, DOI: 10.1039/b820923e

pattern recognition method can recognise biochemical markers of AMI much earlier than the cardiac markers currently analysed. Another key benefit is that the patients' spectra can be stored and referred to retrospectively. This means they can not only be used to check against to see if a patient is responding positively to treatment but that clinical studies in the pharmaceutical industry could also use the results

of the study.

'Considering that myocardial infarction is a common presentation of ischemic heart disease, which is the leading cause of death in developed countries, this report might contribute significantly to a dissemination of the technique,' says Christoph Krafft from the Institute of Photonic Technology, Jena, Germany, who is an expert on the use of spectroscopy in medicine.

Petrich says that the starting point for the idea was a reagent-free analysis. 'You basically look at the sample without adding any reagents,' he says. 'You don't have to store reagents and you don't have to think about the waste, which you would have to in using radioactive tracers, for example.'

Petrich emphasises that the results still need to be confirmed on a larger scale. The next step will be to check for further factors which could have an impact on the results.

Jennifer Newton

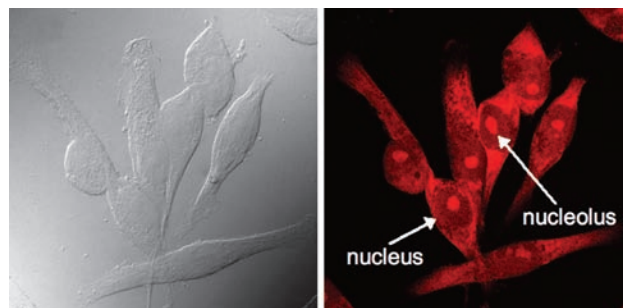
Fluorophores join forces for cell imaging

Ruthenium probe puts the spotlight on RNA

When using fluorescent probes to image inside the body the fluorescence signal must be strong enough and last long enough to distinguish it from the background fluorescence, otherwise the signal is undetectable. Now, by linking two fluorophores, US chemists have created a probe whose properties may make it superior.

Nicholas Turro at Columbia University, New York, and coworkers developed the fluorescent probe, RuEth, which can be used to image RNA-rich regions in cells.

The team made RuEth by attaching a ruthenium(II) isothiocyanate complex to a phenanthridine derivative. They then used the probe to image breast cancer cells using a combination of steady-state and time-resolved spectroscopy. Phenanthridines are known to have stronger fluorescence in regions of mammalian cells rich in nucleic



The RuEth probe shows stronger fluorescence (right) in the RNA-rich nucleolus than in the DNA-rich nucleus

Reference

N A O'Connor *et al*, *Chem. Commun.*, 2009, 2640 (DOI: 10.1039/b900290a)

acids, and this part of the probe allows it to highlight these regions rather than the rest of the cell. The ruthenium segment gives the probe long lasting fluorescence, overcoming the issue of background autofluorescence.

The team found that the probe had greater signal strength in cell regions where RNA is known to accumulate. This selectivity is the most impressive characteristic of

this probe, says Turro. 'We have developed a probe capable of specifically staining RNA over DNA.' Up to now this has proved difficult to achieve as other probes cannot usually distinguish between the nucleic acids.

Byeang Hyeon Kim, Pohang University of Science and Technology, Korea, an expert in the area of DNA/RNA probing, explains that 'by the simple combination of a phenanthridine moiety and a ruthenium(II) complex, the authors have developed an RNA probe with long-lived emission lifetimes.' RuEth fluoresces four times longer than other phenanthridine derivatives; its fluorescence intensity is also nine times stronger.

The researchers suggest that, given its selectivity, their probe could find potential applications as an *in vivo* probe for RNA.

Paul Cooper

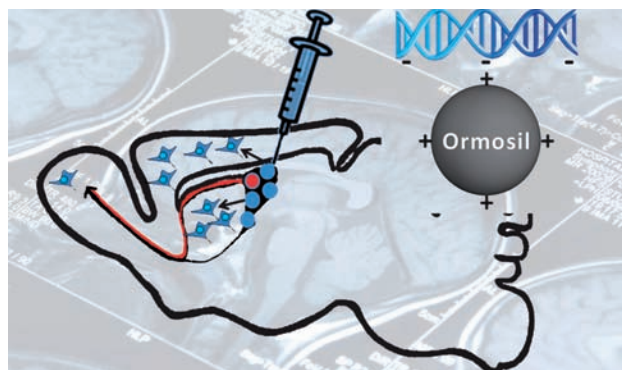
Silica-based gene delivery stimulates nerve cell formation in the brain

Nanoparticles nurse neurological diseases

Silica nanoparticles could potentially revolutionise treatment for neurodegenerative diseases such as Alzheimer's, Parkinson's and strokes, say US chemists.

Michal Stachowiak from the State University of New York, Buffalo, and colleagues have previously studied organically modified silica nanoparticles as gene delivery vehicles. From their results they have now designed nanoparticles that can be used to carry a gene for a form of protein FGFR1 into neuronal stem cells in mouse brains. The protein targets a signalling pathway in the cells, stimulating them to form mature neurons – a process called neurogenesis.

The group is looking at stimulating neurogenesis with a view to the therapeutic applications. Stachowiak explains that they want to see if it is



Injecting nanoparticle-bound DNA into the brain stimulates stem cells to differentiate into neurons

Reference
E K Stachowiak *et al*, *Integr. Biol.*, 2009, DOI: 10.1039/b902617g

possible to 'generate a wave of new neurons from stem cells and direct them to the affected areas.' In this way the technology could potentially be used to cure certain brain diseases, particularly in the case of a stroke, which happens as a single episode and is therefore not continuously

attacking the brain.

Injae Shin, an expert in genetics, from Yonsei University, Seoul, Korea, says that the work is 'exciting' and agrees it has the potential to treat neurological diseases. However, currently the procedure involves microinjecting the nanoparticles, which is a complicated process. Shin adds that for practical applications he hopes that future work will bring about an alternative way to deliver the genes.

The team has been looking at the signalling pathway in brain cells for over a decade, and has progressed its studies into rats, showing that the effects are not species-specific. The next step will be to assess the procedure in other species, with the eventual aim of using the particles in humans.

Ben Merison

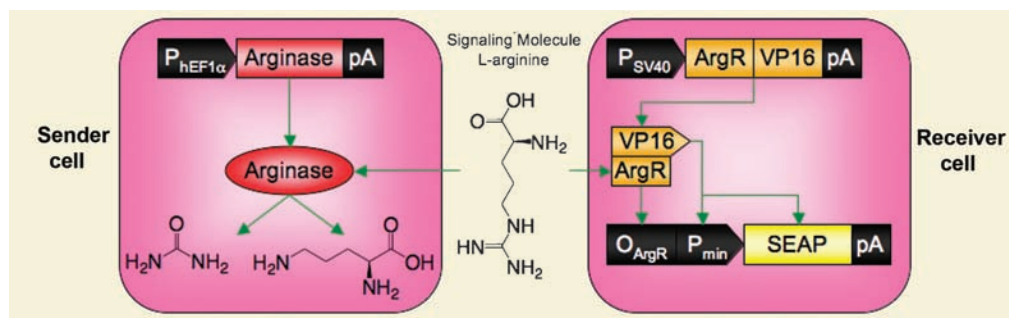
Synthetic biology provides route to amino acid responsive cell network

Cell-cell communication systems

Two-cell computers that transfer metabolic information from one cell to the other could lead to synthetic therapeutic hormone systems.

The field of synthetic biology exists at the interface between engineering and biology, where biological parts are connected to form systems with useful functions. Often this involves creating networks of genes that respond to a change in environment, behaving, for example, like a logic gate. However, it has been difficult to design such networks in mammalian cells, and until recently, most developments were limited solely to operate in individual cells.

Now a team led by Martin Fussenegger, at the Swiss Federal Institute of Technology Zurich, has designed the first two-way network of communicating mammalian cells. The network is made up of a sender cell and a receiver cell. The receiver cell contains a previously developed expression system, which produces a fluorescent protein in response to raised arginine levels



Both sender and receiver cells respond to arginine allowing each cell to affect the other

Reference
W Weber *et al*, *Mol. BioSyst.*, 2009, DOI: 10.1039/b902070p

in the surrounding medium. These levels are regulated by the sender cell, which is engineered to express arginase, an enzyme that removes arginine by converting it to the amino acid ornithine. So, by controlling the amount of arginine, the sender cell transmits metabolic information to the receiver cell, which is converted to a fluorescent output.

Explaining his reasons for developing the system, Fussenegger says: 'We really dream of having prosthetic circuits that could be implanted into humans. These could sense pathological levels of

molecules and trigger a therapeutic response. Instead of having to take a pill every day this would be a one-time treatment, solving the problem once and for all.'

James Collins, a professor of biomedical engineering and co-director of the Center for BioDynamics, Boston University, US, says that the system is a brilliant achievement. 'This novel development opens up a number of bioengineering possibilities,' he adds, 'including the design of artificial hormone systems.'

Bailey Fallon

Peptides activated by enzymes in tumours allow selective treatment for diseased cells

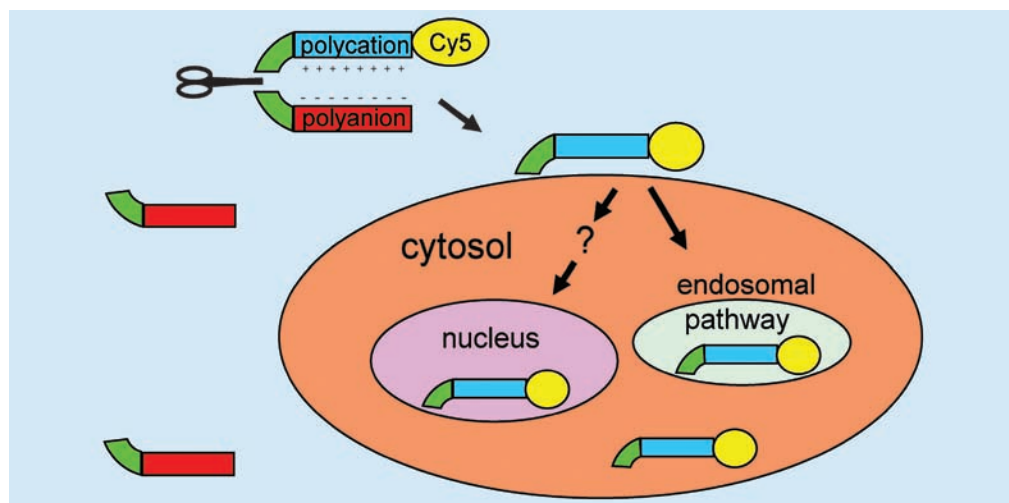
Activating peptides to target cancer

Activatable cell penetrating peptides (ACPPs) are unlocking new opportunities for targeted entry to cancer cells.

Cell penetrating peptides (CPPs) can be used to deliver molecular cargo, such as drugs or imaging agents, into cells. However, the uptake of these peptides is not limited to tumour cells and they are not suitable for widespread distribution in the body as they are naturally toxic.

Now Roger Tsien and colleagues at the University of California at San Diego, US, have made CPPs that are activated by diseased cells. This reduces the toxicity to healthy cells and allows different types of tumours to be targeted. 'The mechanism of binding and uptake of CPPs is rather non-specific, based upon electrostatic charge of amino acid residues,' comments Todd Aguilera, a member of the research team. Activatable CPPs (ACPPs) consist of a polycationic CPP connected via a linker to a matching polyanion. This reduces the overall charge to nearly zero and inhibits electrostatic uptake to cells. The linker can be cleaved by enzymes produced in cancerous cells (matrix metalloproteinases or MMPs). This turns on the cell penetrating properties of the peptide, allowing entry into the cancer cells.

While investigating the system



further, the team found that while polycationic CPPs are very toxic, ACPPs with linkers designed to be uncleavable - so they were not activated by the enzymes - were not toxic. This implies that designing disease specific cleavage systems could eliminate background toxicity to healthy cells, says Aguilera. The team also found that by linking the ACPPs to high molecular weight carriers they could improve the bio-distribution of the peptides.

Robin Polt, an expert in biological chemistry at the University of Arizona, Tucson, US, welcomes the research saying, 'Tsien's use

Enzymes present in tumors act as a scissor to cut the linker and allow CPPs to enter diseased cells.

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E S Olson *et al*, *Integr. Biol.*, 2009, DOI: 10.1039/b904890a

of MMPs to cleave a covalently attached polyanionic 'damper' which blocks the polycationic cell-penetrating moiety of the peptide is quite novel. In this way, the properties of the target cells 'turn on' the cell penetrating properties of the peptide when it becomes useful, but the polyanionic moiety keeps the CPP activity 'turned off' until acted upon by the cancer cell's MMPs. This work represents an important advance in the design of biologically active peptides that have the potential for systemic distribution.'

Russell Johnson

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(DOI: 10.1039/b900266a)

Active soft glassy rheology of adherent cells

Philip Kollmannsberger and Ben Fabry, *Soft Matter*, 2009, **5**, 1771
(DOI: 10.1039/b820228a)

A general map of iron metabolism and tissue-specific subnetworks

Valerie Hower *et al*, *Mol. BioSyst.*, 2009, **5**, 422
(DOI: 10.1039/b816714c)

Triggering cryptic natural product biosynthesis in microorganisms

Kirstin Scherlach and Christian Hertweck, *Org. Biomol. Chem.*, 2009, **7**, 1753 (DOI: 10.1039/b821578b)

Influence of amine ligands on the aquation and cytotoxicity of *trans*-diamine platinum(II) anticancer complexes

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Bearing fruit

Alan Crozier on flavonoids, David Bellamy and good wine. Carl Saxton investigates



Alan Crozier

Alan Crozier is professor of plant biochemistry and human nutrition at the University of Glasgow, UK. His research encompasses the absorption, metabolism and protective effects of dietary phenolics and flavonoids in fruits, vegetables and beverages.

What inspired you to become a scientist?

Pure serendipity. I was pushed in the right direction by David Bellamy who, before he became a TV botanist, taught plant ecology and all sorts of other topics with amazing enthusiasm at the University of Durham in the 1960s. His field trips, especially to southern Germany and the Dolomites, were an incredible experience. His encouragement convinced me to do a PhD at the University of London's Bedford College.

What motivated you to work in the field of biochemistry?

Once again there was no strategic plan. My research in biochemical aspects of human nutrition arose from a chance meeting in 1995 with the Rank Professor of Human Nutrition at the University of Glasgow, the appropriately named Mike Lean, who asked me if I could analyse flavonols. I said yes, little realising the exciting journey that would unfold for both of us.

What projects are you working on at the moment?

We are studying the fate of flavonoids and phenolic compounds in the body following the ingestion of fruit juices, green tea, rooibos tea, coffee and raspberries. And on a totally unrelated side line, I am investigating, with my colleague Professor Douglas Neil, the factors affecting the freshness of langoustines caught off the west coast of Scotland.

What are the current challenges faced in your research?

Assessing the efficacy of individual fruits and beverages in terms of their beneficial effects on human health is a current challenge. We need to identify the compounds involved and determine the bioactivity of their metabolites in vivo and how this impacts on the incidence of non-communicable diseases such as cardiovascular diseases, diabetes mellitus and cancer.

One of your areas of interest involves secondary metabolites in plants. What are these?

Plant secondary metabolites are a diverse and large group of organic compounds that in planta do not appear to have a direct role in photosynthesis, respiration or growth and development. They can accumulate in surprisingly high concentrations and are often distributed among limited taxonomic groups in

the plant kingdom. Caffeine is a typical example, being produced in substantial quantities by a very limited number of plant species. The function of many secondary metabolites is not known but it has recently been established using transgenic caffeine-producing tobacco plants that caffeine acts as a natural pesticide.¹ Flavonols, which are of significance in the human diet, are concentrated in leaf epidermal cells where they act as UV protectants.²

What is your favourite plant, and why?

A bonsai, Japanese black pine (*Pinus thunbergii*), that I brought back from Japan 16 years ago and which is thriving in Glasgow. This plant summons up happy memories of beautiful bonsai gardens in Japan. A closely run second is *Vitis vinifera* because of my love of a good red wine.

What's hot at the moment in the field of human nutrition?

The work of Jim Joseph at Tuft's University in Boston showing that consumption of blueberry and strawberry extracts improves cognitive function of elderly rats.³ When coupled with the results of the Kame study, which suggests that long-term, moderate consumption of fruit and vegetable juices by elderly humans can reduce the incidence of Alzheimer's disease,⁴ the door is open to some exciting possibilities linking diet to an improved quality of life as well as longevity.

Eating five portions of fruit and vegetables per day is said to be beneficial to one's health. From your research are there any fruits or vegetables that are better than others?

Although it is far from proven, I suspect that in terms of efficacy and potential protective effects, those near the top of the league table will include flavonol-rich onions, cocoa products with a high flavan-3-ol monomer and procyanidin content, green tea which is an extremely rich source of flavan-3-ol monomers, pomegranates because they contain unusually high levels of ellagitannins, coffee because of the high levels of chlorogenic acids and last, but not least, a full bodied red wine produced from Tannat grapes which will contain high concentrations of many flavonoids and phenolic compounds.

If you weren't a scientist, what would you be?

In my dreams, originally a footballer but now a successful professional golfer!

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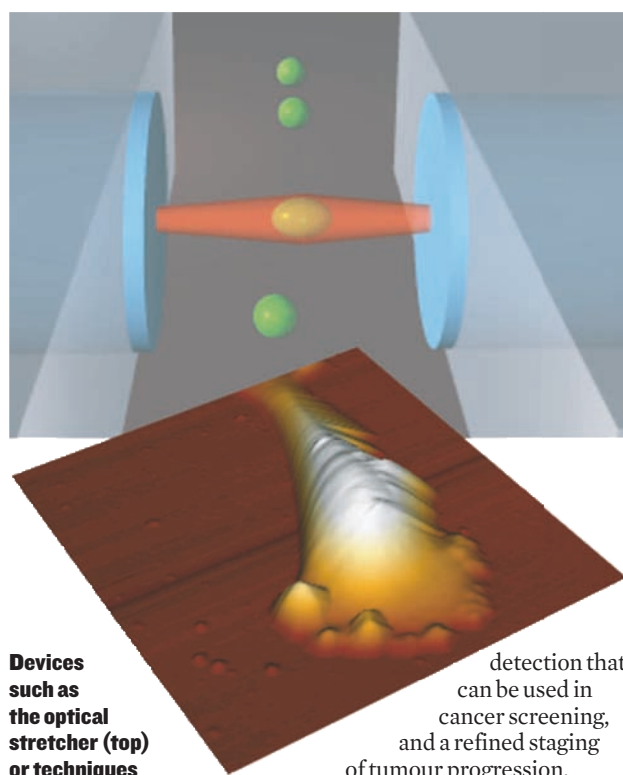
Could stretching cells be the way to diagnose cancer? Claudia Brunner at the University of Leipzig, Germany, takes a biomechanical approach to medicine¹

The 1991 Nobel laureate in physics Pierre-Gilles de Gennes stressed that the importance of results in biological physics can be measured by their medical impact, since any important biological finding must also influence medicine. Studies of cellular biomechanics are on the verge of fulfilling de Gennes' ambitious demand.

Over the past 20 years techniques to measure cell biomechanics have improved tremendously. So too has theoretical insight into the behaviour of worm-like biopolymers such as those found in the cell cytoskeleton – the mixture of microtubules and filaments that provide scaffolding for the cell. The result is that distinguishing cells by their functional biomechanical properties has become a valuable cell marker.

For example, it is now possible to use biomechanical studies to investigate such important phenomena as cancer. During the cancerous descent of a cell its cytoskeleton regresses from an ordered and fairly stiff structure to a more irregular and compliant state. Phenotyping individual cells according to their mechanical properties is a novel approach to identifying cancerous cells by correlating these cytoskeletal changes with malignancy.

However, there is no benefit in only recognising a cancer cell by its biomechanical properties. Imaging techniques are so refined that even small-sized tumours can be easily recognised and conventional pathology of these tumours can safely diagnose cancer. Biomechanical measurements have to provide information that cannot be delivered by normal diagnosis. Here, the two main requirements for state-of-the-art cancer diagnosis are earlier



Devices such as the optical stretcher (top) or techniques such as scanning force microscopy (bottom) can be used to measure cells' biomechanical properties

detection that can be used in cancer screening, and a refined staging of tumour progression.

In both cases biomechanical measurements show great promise.

The optical stretcher is one tool for quantifying biomechanical properties such as cell elasticity. The system takes measurements from a single cell by using a pair of laser beams to manipulate and stretch the cell in a microfluidic setup. Recently the device has been used to diagnose dysplasia (a pre-cancerous change in cells and tissues) in the mouth.² This could one day lead to screens for oral cancer at routine dental check-ups; cells could be extracted from the lining of the mouth with specially designed brushes (cytobrushes) and then analysed.

Biomechanical measuring systems, such as the optical stretcher or scanning force microscopes, also have the potential to be used in breast cancer diagnosis. Conventional pathology of breast tumours provides no conclusive information about metastasis – the cancer's spread. Instead, the sentinel lymph node – the lymph node closest to the tumour – is typically removed during breast cancer surgery to look for signs of breakaway cells. By detecting metastatic cells directly in the primary tumour, biomechanical measuring systems may avoid the need to remove the lymph node.

Cancer cells' ability to migrate shows how important it is to have a deeper understanding of cell motility and how this movement is generated. That means, besides investigating changes in passive biomechanical properties, the integration of active biomechanics is needed. A quantitative comprehension of how cells move may lead to new strategies in reducing metastasis by inhibiting cancer cell motion.

Isolating cells according to their biomechanical signature has the potential to be a key technique in emerging scientific fields. This novel approach to precisely distinguish different cell types has promise for cancer diagnostics, as well as for isolating rare cells such as stem cells more accurately. The growing success found in using a cell's biomechanical properties as a marker illustrates how novel insights into the physics of semiflexible polymers can lead to important applications in biomedicine and biotechnology.

Read more in the review 'Passive and active single-cell biomechanics: a new perspective in cancer diagnosis' in Soft Matter.

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Experimental Biology 2009, New Orleans, US, 18–22 April, saw the perfect opportunity for RSC Publishing to display its impressive bioscience journals portfolio. Visitors to the RSC picked up free copies of recently launched journals *Integrative Biology* and *Metallomics*, as well as the established *Molecular BioSystems*, *Organic & Biomolecular Chemistry*, *Photochemical & Photobiological Sciences* and *Natural Product Reports*. RSC staff were also available to provide online demonstrations of enhanced HTML articles via *RSC Prospect*. Many visitors also entered the competition to win an iPod Touch, and the lucky winner, drawn at random from the entries, is Abu-Bakr Al-Mehdi, University of South Alabama, Mobile, US.



Also at this event, *Integrative Biology* celebrated its 2009 launch in style on 19 April with an evening reception. Guests were welcomed with refreshments and the editor, Harp Minhas, was on hand to provide details and answer questions regarding this

exciting new journal. *Integrative Biology* focuses on quantitative multi-scale biology using enabling technologies and tools to exploit the convergence of biology with physics, chemistry, engineering, imaging and informatics.

'Integrative Biology is looking great – just hits the mark and all the articles are innovative, highly of interest and thought provoking.'
Philip Day, University of Manchester, UK

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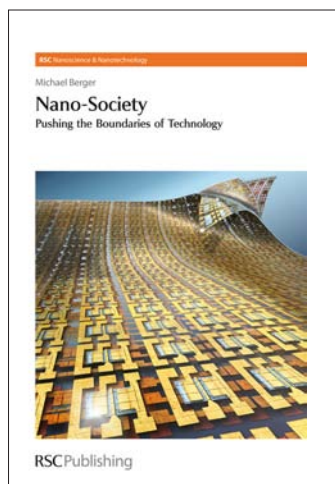
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