

4th Syngenta Organic and Biological Chemistry Postdoc Symposium

DP lecture theatre, Thursday 22nd March 2018

Programme

1.15-3.00 pm

Introductory remarks

Dr Michel Rickhaus (HLA group)

Flatten – Bend – Cyclize. Synthesis and properties of porphyrin nanorings linked by a single acetylene

Dr Venkaiah Chintalapudi (EAA group)

Validating predictive sequence analysis in polyketide stereochemistry: Towards the synthesis of stambomycin D

Dr Tom McAllister (AK group)

mRNA-Display selected cyclic peptide affinity probes for enzyme-substrate complex capture

Dr Manjeet Kumar (JWB group)

Studies towards the total synthesis of oxazolomycin A

3.00-3.30 pm: Tea break

3.30-5.00 pm

Dr Charlie FehI (BGD group)

In situ boronate activation for metallaphotoredox-initiated protein functionalization

Dr Lan-Gui Xie (DJD group)

Iridium-catalysed reductive functionalisation of tertiary amide

Dr James Morris (Syngenta)

Synthesis and reactivity of herbicidally active 1,8-naphthyridines and 1,8-naphthyridinones

5.00: Closing remarks

5.15 pm: Drinks reception and prizes

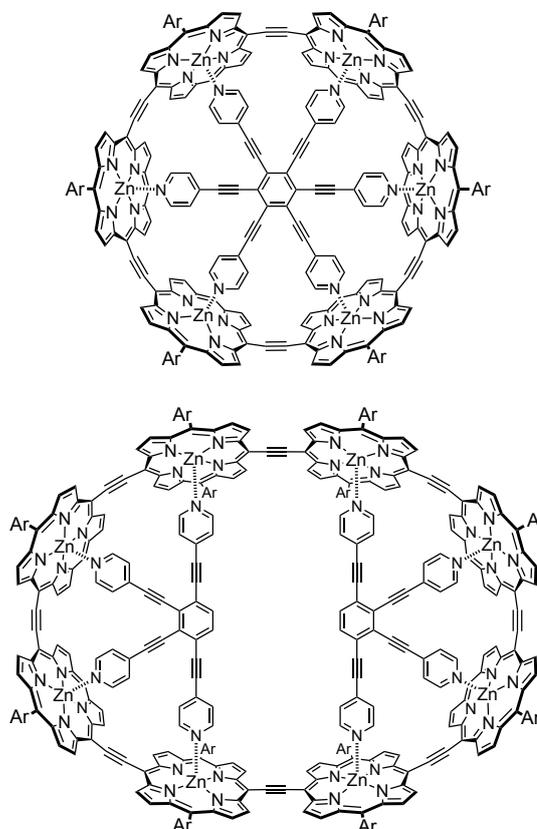
We thank Syngenta for generous sponsorship of this event

Dr Michel Rickhaus

Flatten – Bend – Cyclize. Synthesis and properties of porphyrin nanorings linked by a single acetylene

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π -Conjugated macrocycles are ideal models for testing the limits of aromaticity and electronic delocalization and are prototype materials for achieving efficient transport of charge and electronic excitation. The enhancement of electronic delocalization in ring structures explains why many natural light-harvesting systems consist of cyclic arrays of chlorophyll units. Amongst the systems that mimic these biological light-harvesters are conjugated macrocycles consisting of porphyrin units evenly spaced on the circumference. Porphyrins are famed for their Hückel-aromatic circuit and a multitude of these sizeable aromatic rings – each roughly the size of a fullerene – can be linked by polyacetylene spacers to yield conductive wires. In conjunction with a template, these wires can be cyclized to rings and related topologies. Phenomena such as energy migration, conjugation and coherence can then be studied on a nanometer scale.



The efficiency of these emergent phenomena is modulated by the relative distance between the chromophores: Further apart lessens electronic communication but allows the units to adopt any desired conformation. By bringing them closer, communication is enhanced but so are steric interactions leading to a restriction in the range of accessible conformers. An ideal playground to investigate this delicate distance-strain interplay are porphyrin rings linked by *single*-acetylenes. With shorter interchromophoric distances than any other related ring reported to date, they represent the most strained, conjugated nanorings we ever made. A key feature of the shorter linkage is the resulting twisted ground-state conformation with an accessible rotational barrier to allow planarization of the systems. We have recently introduced challenging synthesis, photophysical behavior and complexation behavior, which we complemented by DFT calculations. We have demonstrated that these rings adopt highly symmetric conformations leading to fully delocalized singlet excited states involving the entire ring π -system – with circumferences beyond 2 nm. Currently, we are engaged in exploring their coherent aromatic currents in the oxidized states.

M. D. Peeks, T. D. W. Claridge, H. L. Anderson, *Nature* **2017**, *541*, 200-203.

M. Rickhaus, A. V. Jentsch, L. Tejerina, I. Grübner, M. Jirasek, T. D. W. Claridge, H. L. Anderson, *J. Am. Chem. Soc.* **2017**, *139*, 16502–16505.

Dr Venkaiah Chintalapudi

Validating predictive sequence analysis in polyketide stereochemistry: Towards the synthesis of stambomycin D

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Stambomycins A-D are macrolide antibiotics with promising antitumour activity, identified as metabolites of *Streptomyces ambofaciens* by the Challis group using a genomics-driven approach. This method allows the connectivity and stereochemistry of the carbon skeleton to be predicted *via* sequence analysis of the modular polyketide synthase (PKS) enzymes responsible for stambomycin biosynthesis;¹ this approach allowed the configuration of 21 stereocentres in the 51-membered stambomycin macrolactone to be predicted, together with the nature of the appended sugar group. The Challis group also demonstrated that hydroxylation at C28 and C50 occurs *via* cytochrome P450 mediated oxidation,² and for these stereocentres no biosynthetic stereochemical prediction can be made. This project concerns synthetic validation of this biosynthetic hypothesis, which would have profound implications in the discovery and characterization of new polyketide natural products.

We have been working towards the synthesis of four diastereomers of the linear 51 carbon chain of stambomycin D, and/or the macrolactone aglycon. Retrosynthetic analysis of stambomycin D leads to four key building blocks at C1-C11, C13-C22, C23-C31 and C32-C51 which enables the formation of C1-C51 fragment of stambomycin *via* alkyne addition, hydroboration/oxidation and cross coupling sequences. My talk will focus on the late stage coupling of these fragments towards the synthesis of two diastereomers of the C1-C51 linear chain of stambomycin D.

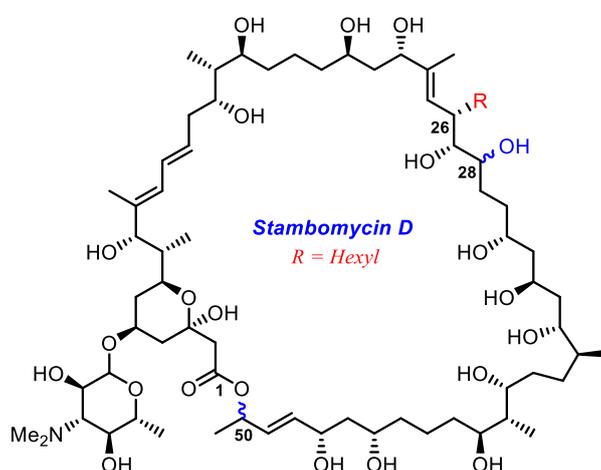


Fig 1

[1] L. Laureti, L. Song, S. Huang, C. Corre, P. Leblond, G. L. Challis and B. Aigle, *Proc. Nat. Acad. Sci.*, **2011**, *108*, 6258.

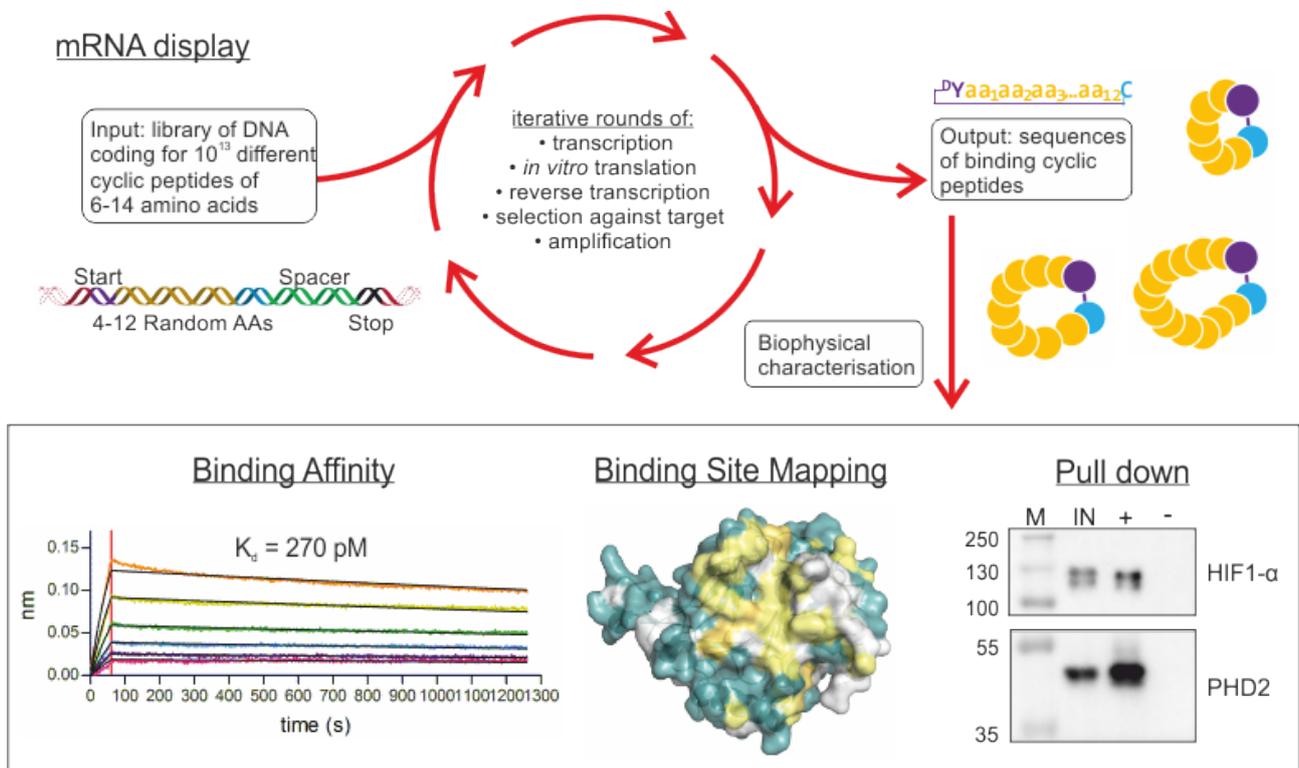
[2] L. Song, L. Laureti, C. Corre, P. Leblond, B. Aigle and G. L. Challis, *J. Antibiotic.*, **2014**, *67*, 71.

Dr Tom McAllister

mRNA-Display selected cyclic peptide affinity probes for enzyme-substrate complex capture

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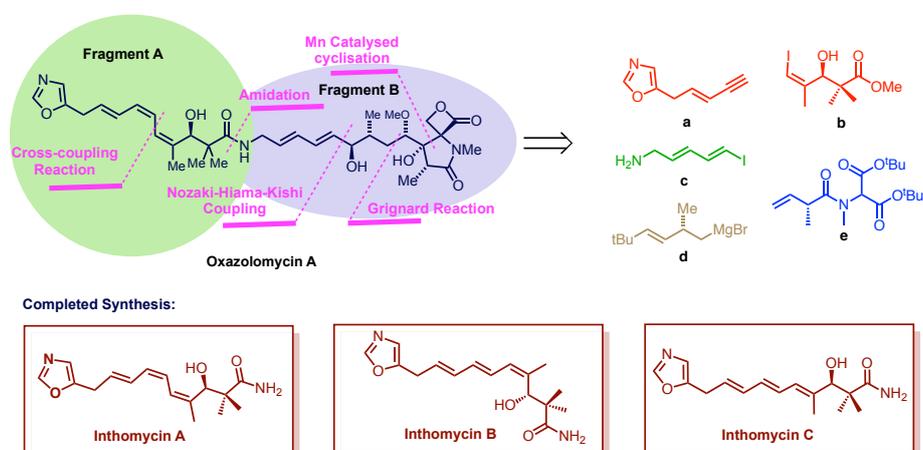
We have identified cyclic peptides through mRNA display, that recognise, the human hypoxia inducible factor prolyl hydroxylase 2 (PHD2) – the primary hypoxia sensor in the eukaryotic cell. One of these peptides was shown to bind with sub nM Kd in an allosteric site with no effect on enzyme activity. A version of this peptide derivatised with a biotin moiety can be used like an antibody to isolate all three members of the PHD family of human 2OG oxygenases while not binding to other related proteins. Furthermore, the peptide can capture endogenous levels of PHD2 from cell lysates as well as enzyme / substrate and enzyme / product complexes. This work highlights the potential for cyclic peptides to be used as an alternative to antibodies.



Studies towards the total synthesis of oxazolomycin A

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Oxazolomycins, the microbial metabolites isolated from a *Streptomyces strain*,¹ are well known for their protonophoric properties and thus possess a wide variety of interesting biological activities including antibiotic, anti-tumour and anti-viral activities.² In addition to the biological importance, these natural products contain particularly challenging structural features and functionalities including a spiro β -lactone- γ -lactam moiety bearing three stereocentres, a methylene interrupted oxazolyl-triene fragment and a chiral allylic β -hydroxy carbonyl centre. Moreover, the fragment A is a substructure of the inthomycin natural products isolated from the same species and found to be potent inhibitors of prostate cancer cell proliferation.³



In order to formulate the synthesis of oxazolomycin A, we have developed a flexible and modular route that resulted in the synthesis of all three inthomycins (A-C) using cross-coupling of **a** with the geometric isomers **b**. Next, the synthesis of eastern pyrrolidine section of fragment B utilising a manganese(III) mediated radical cyclization was developed in our group. The future end-game will involve the coupling of the eastern part of fragment B with **c**, **d** and fragment A to complete the synthesis of oxazolomycin A.

[1] T. Mori, K. Takahashi, M. Kashiwabara, D. Uemura, C. Katayama, S. Iwadare, Y. Shizuri, R. Mitomo, F. Nakano, A. Matsuzaki, *Tetrahedron Lett.* **1985**, 26, 1073.

[2] P. A. Grigorjev, R. Schlegel, U. Grafe, *Pharmazie* **1992**, 47, 707.

[3] (a) T. Henkel, A. Zeeck, *Liebigs Ann. Chem.* **1991**, 367; (b) M. Kawada, Y. Yoshimoto, K. Minamiguchi, H. Kumagai, T. Someno, T. Masuda, M. Ishizuka, D. Ikeda, *Anticancer Res.* **2004**, 24, 1561.

Dr Charlie Fehl

In situ boronate activation for metallaphotoredox-initiated protein functionalization

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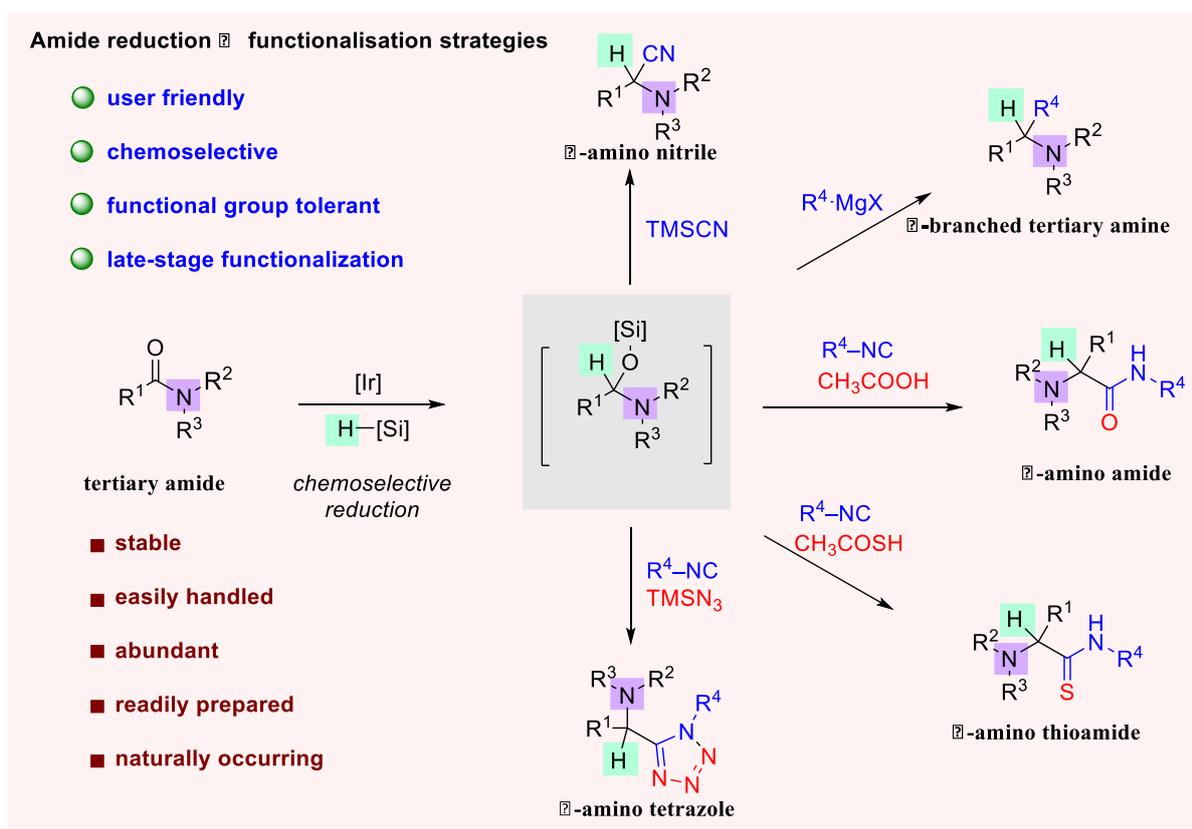
The development of bioorthogonal chemical activation manifolds for selective macromolecular modification is an intriguing challenge in chemical biology. In particular, site-specific methods for the installation of modified amino acid sidechains are useful for understanding the effects of the diverse modifications cells perform on natural proteins by enabling the synthesis of chemically-defined species.

Here, we constructed a system to utilize visible light as a mild form of chemical energy for alkyl radical-based functionalization of alkene residues on proteins. Key to enabling the photochemical generation of carbon-based radicals was overcoming the insufficient redox potentials of tris(bipyridine)ruthenium(II) [Ru(bpy)₃] and related catalysts for common organic radical precursors. We find that redox-active (1,2-)orthoquinones including catechol facilitate alkyl boronic acid oxidation by Ru(bpy)₃ in aqueous, biomolecule-compatible conditions. Exploring a brief substrate scope of alkyl boronic acid derivatives revealed chemoselectivity for the homolytic oxidation of the C—BR₃⁻ bond (R = F, OH, and/or pinacol) even in the presence of other radical precursors (halides) and radical-reactive groups (alkenes). This enables us to install a variety of natural and non-natural protein modifications in a site-specific manner. In this talk, we detail the development, mechanistic investigation, and potential applications of this bioorthogonal photoredox manifold.

Iridium-Catalysed Reductive Functionalisation of Tertiary Amide

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Amides are a significantly under-exploited class of nitrogen-containing compound that are commonplace within the fine chemical, agrochemical and pharmaceutical industries. They are widely available, are easily prepared and, through their low reactivity and high chemical stability, are essentially inert to all but the harshest chemical reagents and to the vast majority of chemical transformations routinely used in contemporary synthesis. Accordingly, the development of new, efficient and highly chemoselective carbon-carbon bond forming methodologies arising from the functionalization of amides should find widespread use across academia and industry. We have developed an [Ir]-catalysed reductive methodology for the transformation of amide/lactam into hemiaminal/iminium synthon¹. Herein we present our findings on [Ir]-catalysed reductive C-C bond formations by combining tertiary amide with the coupling of cyanide, Grignard reagent or isocyanide respectively². These transformations tolerate broad range of the reaction partners, and are applicable to late stage functionalization of various bioactive molecules and pharmaceutical compounds.



[1] A. W. Gregory, A. Chambers, A. Hawkins, P. Jakubec, D. J. Dixon, *Chem. Eur. J.* **2015**, *21*, 111.

[2] (a) Á. L. Fuentes de Arriba, E. Lenci, M. Sonawane, O. Formery, D. J. Dixon, *Angew. Chem. Int. Ed.* **2017**, *56*, 3655; (b) L.-G. Xie, D. J. Dixon, *Chem. Sci.* **2017**, *8*, 7492; (c) L.-G. Xie, D. J. Dixon, *Manuscript in preparation*