Young Career Focus: Dr. Matthew J. Fuchter (Imperial College London, UK)

Background and Purpose. From time to time SYNFORM meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Matthew J. Fuchter (Imperial College London, UK).

Biographical Sketch

Dr. M. J. Fuchter

Matthew Fuchter obtained his first class honors degree (MSci in Chemistry) from the University of Bristol (UK) in 2002, where he was awarded the Richard N. Dixon Prize as well as an undergraduate scholarship and several faculty commendations. In January 2006 he completed his PhD research entitled 'Synthetic Studies on Porphyrazines: Biological Applications and New Preparative Methods' under the supervision of Professor Anthony G. M. Barrett, FRS FMedSci (Imperial College London, UK) and in close collaboration with Professor Brian Hoffman (Northwestern University, USA). Following a short spell as a Research Associate at Imperial College, Dr. Fuchter was appointed as a CSIRO Research Fellow at the Commonwealth Scientific and Industrial Research Organisation, Australia as well as a Visiting Fellow at the University of Melbourne (Australia), where he worked with Professor Andrew B. Holmes, AM FRS FAA FinstP. He briefly took up an independent Fellowship position in 2007 at the School of Pharmacy, University of London (UK), before being appointed as a Lecturer in Synthetic and Medicinal Chemistry at Imperial College London (UK) in July 2008. He was subsequently promoted to Senior Lecturer in July 2012, and Reader in September 2015. He is currently additionally the co-Director of the Imperial College MRes course in Drug Discovery, a Research Board member of the Imperial College Institute of Chemical Biology, an Associate Editor of the Royal Society of Chemistry (RSC) journal MedChemComm and an Appointed Member of the RSC Organic Division Council. In 2014 he was awarded the Royal Society of Chemistry's Harrison-Meldola Memorial Prize, as well as being admitted to the RSC as a Fellow. In 2015, he was selected as a Thieme Chemistry Journal Awardee by the Editorial Boards of the Thieme Chemistry journals and received a Diploma for being the 'most meritorious runner-up' of the European Federation for Medicinal Chemistry (EFMC) Prize for a Young Medicinal Chemist in Academia (2015). The Fuchter group has a wide-ranging track record in the design, synthesis and application of organic molecules in chemistry, medicine and materials.

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Dr. M. J. Fuchter Broadly speaking, research in my group aims to use expertise in chemical synthesis to impact molecular science in chemistry, biology and materials. This means that while we are interested in the development and/or application of state-of-the-art organic synthetic procedures and strategies, our efforts in these areas are aligned to multidisciplinary and collaborative projects. Representative examples of research projects include the design and development of novel bioactive probes to be used in chemical biological and medicinal chemistry programs, and the design and development of novel chiral semiconducting molecules for application to unique organic electronic devices.

SYNFORM *When did you get interested in synthesis?*

Dr. M. J. Fuchter During my undergraduate degree in chemistry, the problem solving and creative nature of organic synthesis captivated me. The ability to design brand new molecules, even using only a basic understanding of molecular reactivity, seemed very powerful to me, and still does! I continue to be inspired by the fact that synthesis can deliver a wealth of fascinating molecular materials, which create vast opportunities for science and for society.

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SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

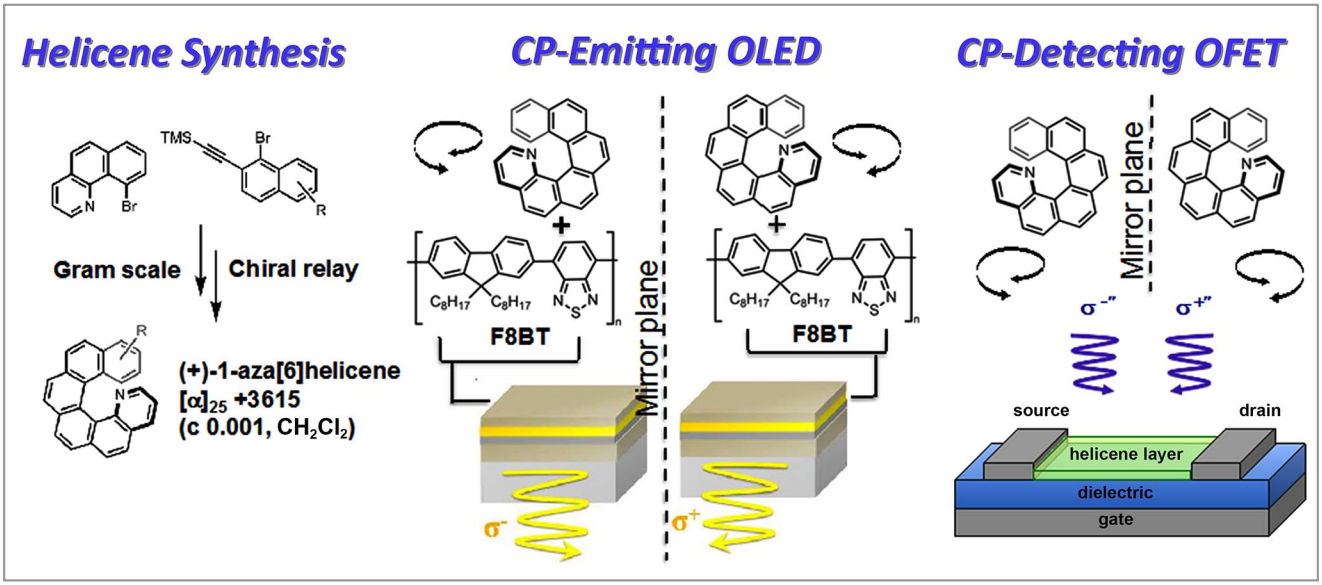
Dr. M. J. Fuchter Organic synthesis continues to deliver a whole range of wide-value products including pharmaceuticals, agrochemicals, plastics and organic electronics. The value of organic synthesis to society is therefore undeniable. Personally, I am really interested in how to design organic molecules to perform specific and unique tasks, from perturbing protein function, to modulating light signals, to conducting charge: to control molecular function via smart design. For many years, organic chemistry was concerned with the development and application of organic synthesis to better understand molecular structure. Now that we have a very good understanding of molecular structure, I think it is the turn of molecular function. Others have advocated such an idea too (for example: G. M. Whitesides, J. Deutch *Nature* **2011**, *469*, 21). For me, such studies involve collaborative efforts with other scientists in physics, materials, biology and medicine. I truly believe that the 'molecular vision' of chemists is rather unique and so chemists can provide strong leadership in such collaborative multidisciplinary projects.

SYNFORM *Your research group is active in the areas of organic synthesis, medicinal chemistry and organic materials. Could you tell us more about your research and its aims?*

Dr. M. J. Fuchter I would like to highlight two representative areas in which my group is active. It is worth noting, though, that enabling synthetic organic chemistry underpins all the ongoing research in the group, from natural product (semi-synthesis) to asymmetric methods to construct helically chiral aromatics. In many cases, this results in published outputs focused on synthetic methodology development (although not highlighted here).

1) Stereochemistry in chemistry, materials and devices. Chirality is a fundamental symmetry property of elemental particles, molecules or even macroscopic objects like human hands. Chirality is a significant theme in the group and we have published novel synthetic methods to control/install a number of forms of molecular chirality including point (*Org. Biomol. Chem.* **2012**, *10*, 512), axial (*Synlett* **2013**, *24*, 2365; *invited submission for the EuCheMS Young Investigators Workshop Special Issue*) and helical (*Org. Lett.* **2013**, *15*, 1706) chirality. Such methods give us unique access to interesting chiral small molecules and polymers, which we explore in a range of applications in materials science.

A representative application area for our chiral materials is in the development of unprecedented chiroptical organic electronic devices. Circularly polarized (CP) light is central to a large range of current and future display and photonic technologies, including highly efficient LCD backlights, optical quantum information processing and communication, and optical spintronics. There is therefore high interest in constructing CP-light-emitting devices, however to date, no highly efficient and broadly applicable methods for fabricating such devices have been reported. In collaboration with Dr. Alasdair Campbell (Physics, Imperial) we were the first to



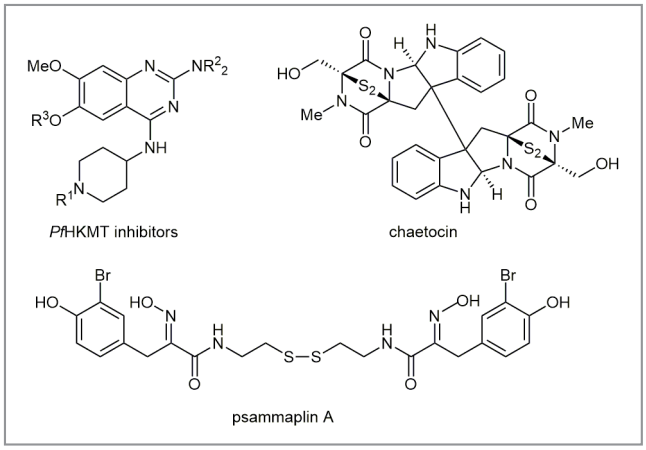
use a chiral small molecule dopant (in this case an enantiopure azahelicene) to induce solid-state circularly polarized (CP) electroluminescence from a conjugated polymer (Adv. Mater. **2013**, *25*, 2624). Simple blending of 1-aza[6]helicene or [7]-helicene, with a conventional (achiral) light-emitting polymer (F8BT), led to morphologically distinct thin films whose photoluminescent (PL) and electroluminescent (EL) emission was observed to become significantly circularly polarized. The sign of the CP emission was directly determined by the enantiomer of the helicene dopant, and the magnitude of the response competitive with, or better than, the state of the art. This highly translational approach allowed the fabrication of organic light-emitting diodes that directly emit CP light – a high-interest area for the preparation of energy-efficient displays.

To develop CP-based technologies to their full potential would require the realization of miniature, integrated devices that are capable of detecting the chirality of CP light. Organic field-effect transistors (OFETs), in which the active semiconducting layer is an organic material, allow the simple fabrication of ultrathin, compact devices. Also together with Dr. Campbell, we have recently shown, for the first time, that OFET based on enantiomerically pure 1-aza[6]helicene can detect and differentiate CP light, acting as a CP-electrical switch (*Nature Photon.* **2013**, *7*, 634). OFETs with a semiconductor layer of helicene were solution-processible, leading to a self-organized crystalline morphology, and have well-behaved device characteristics. Critically, a highly specific and reversible photo-response to CP light was observed, which is directly related to the enantiomer of the helicene molecule. We believe this proof-of-concept device opens up a unique possibility for CP-light sensing in highly integrated photonic technologies. For example, patterning techniques available for solution-processible organic semiconductors, such as high-resolution ink-jet printing, should allow the creation of arrays of micrometer-scale CP-light-sensitive devices, as well as integration with CMOS electronics.

Aside from our interest in helicenes and related compounds, we have an active interest in stereochemical determination, particularly for natural products. Indeed, emerging from our natural product chemical biology studies on chaetocin (see below), we used state-of-the-art chiroptical methods to unambiguously establish the stereochemistry of 3,6-epidithio-diketopiperazine (ETP) desulfurization. This has led to stereochemical reassignment of the desulfurized natural product dehydrogliotoxin (*Chem. Eur. J.* **2011**, *17*, 11868) as well as a unified mechanism for the stereochemical course of this reaction for all chiral ETP compounds (*J. Org. Chem.* **2013**, *78*, 11646).

2) The medicinal chemistry and chemical biological study of epigenetic processes in disease.

'Epigenetic' describes the heritable changes in gene expression that occur without changes in DNA sequence. Epigenetic processes underpin fundamental physiology and are implicated in the aetiology of many diseases, particularly cancer. As such, epigenetics is an exponentially growing and exciting area of interest for scientific study. Through hypothesis-driven medicinal chemistry, my group has made significant progress in the discovery of unique and unprecedented small-molecule inhibitors of epigenetic enzymes; published outputs include highly ligand-efficient HDAC inhibitors (*ChemMedChem* **2013**, *8*, 149), highly isoform-selective SIRT inhibitors (*MedChemComm* **2012**, *3*, 373; *ChemMedChem* **2015**, *10*, 69), quinazoline dual EZH2/EHMT2 HKMT inhibitors (*Clin. Epigenetics*, in press) and quinoline EHMT1/2 inhibitors (*MedChemComm* **2014**, *5*, 1821; *invited submission to a special epigenetics edition*).



Working closely with expert collaborators, we have used these molecules to provide novel opportunities in therapy. Perhaps the best example of this is our work targeting epigenetic pathways in malaria. This work is in collaboration with Professor Artur Scherf (Pasteur Institute, Paris, France), a leader in parasite epigenetics. Together we were the first to discover *Plasmodium* histone methyltransferase (*Pf*HKMT) inhibitors that result in blood-stage independent parasite killing (*Proc. Natl. Acad. Sci. USA* **2012**, *109*, 16708; *ChemMedChem* **2014**, *9*, 2360; *Antimicrob. Agents Chemother.* **2015**, *59*, 950). We also discovered that our inhibitors have the unprecedented ability to 'reawaken' dormant liver-stage parasites (*Nature Med.*

2014, *20*, 307). Dormant and largely drug-resistant *Plasmodium* parasites (in *P. vivax*) cause recurrent malaria and are a significant and largely untreatable clinical problem; this drug-induced 'awakening' approach holds much hope for tackling such a limitation and therefore provides a potential new therapeutic option for this disease.

My group has also used enabling synthetic medicinal chemistry and biochemistry to unambiguously determine the mechanism of action of several epigenetically active natural products, including the fungal metabolite chaetocin (*Nature Chem. Biol.* **2013**, *9*, 136; *J. Med. Chem.* **2013**, *56*, 8616) and the marine natural product psammaplin A (*J. Med. Chem.* **2012**, *55*, 1731). Based on this work, we were invited to publish a critical perspective (*Nat. Prod. Rep.* **2013**, *30*, 605, *cover article*), which covers some of the challenges in this area.

SYNFORM What is your most important scientific achievement to date and why?

Dr. M. J. Fuchter Given that I am at the earlier stage of my career, I hope there will be significant achievements to come. This is especially true in the area of medicinal chemistry: while many of our medicinal chemistry efforts are at an early stage, I hope one day at least one project will reach a stage where a clear benefit to patients is recognized. Perhaps the area I am currently most proud of is our work on chiral organic materials for organic devices highlighted above (*Nature Photon.* **2013**, *7*, 634; *Adv. Mater.* **2013**, *25*, 2624). For me, this project has a nice blend of fundamental and applied science, and is a technology reliant on a key enabling organic material. Furthermore, the organic material in question – a helicene – is a challenging synthetic target and so it is a project area where innovation in synthesis is a requirement for success!