Prof. Donal O'Shea
Department of Pharmaceutical and Medicinal Chemistry
Royal College of Surgeons in Ireland

Current Research Projects

New class of near-infrared (NIR) fluorochrome for real-time fluorescence guided surgery [1]

The use of real-time fluorescence imaging has potential in oncology as a guide for surgical resections. As over 50% of all non-skin cancers are first treated with surgery, the benefits of improved surgical outcomes are obvious. The use of longer wavelength NIR fluorochromes circumvents problems of background absorbance and auto-fluorescence from endogenous chromophores, allowing for better resolution, greater penetration of biological tissue and a reduction of light induced cellular damage. We have recently described the synthesis of a series of NIR fluorescent probes based upon the BF_2 chelated tetraarylazadipyrromethene structure, which have the potential to act as biologically switchable *off* to *on* NIR fluorescent imaging agents.

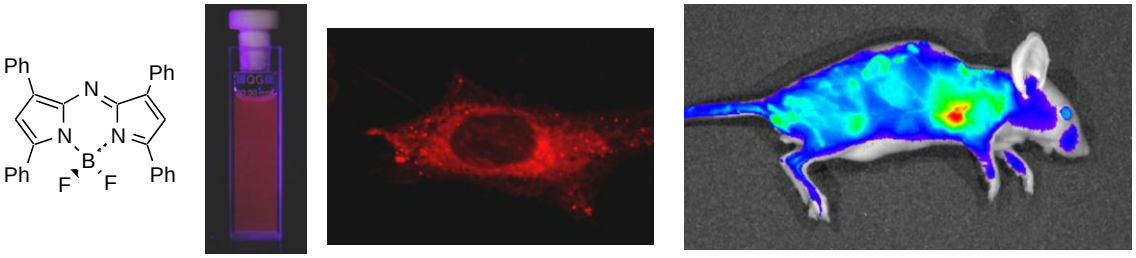


Figure. Near-infrared fluorescence of BF_2 chelated-azadipyrromethene, in saline solution, *in vitro* and *in vivo*.

On-going research is focused on tailoring of our class of imaging agent to allow for targeted real-time *in vivo* imaging. For example, synthetically controlled functionalization of nanoparticles with our fluorophore class has allowed us to develop the first cellular activated *off* to *on* responsive nanoparticle which switches fluorescence on only when taken up into cells.

1. Key publications:

(a) Palma, A.; Alvarez, L.A.; Frimannsson, D.O.; Grossi, M.; Quinn, S.J.; O'Shea, D.F. *J. Am. Chem. Soc.* **2011**, *133*, 19618. (http://www.youtube.com/watch?v=FjipbGTf8w4).
(b) Tasior, M.; O'Shea, D.F. *Bioconjugate Chem.* **2010**, *21*, 1130.
(c) O'Shea D.F. Novel fluorescent near-infrared (NIR) dyes. International Patent Application No: PCT/EP2010/065991.
(d) Wu Dan, O'Shea D.F. *Org. Lett.* **2013**, *15*, 3392.

New class of light activated anti-cancer and anti-microbial agents [2]

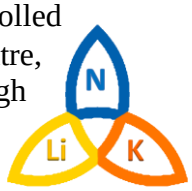
Photodynamic therapy (PDT) is a unique treatment modality for a range of disease classes, both cancerous and non-cancerous, which uses low energy light in conjunction with a photosensitizer to effect specific cell death. My research has developed a totally new class of PDT agent, the BF_2 chelated dibromo-tetraarylazadipyrromethenes. Optimised synthetic procedures have been developed to facilitate the generation of an array of specifically substituted derivatives to demonstrate how control of key therapeutic parameters such as wavelength of maximum absorbance and singlet oxygen generation can be achieved. Our lead compounds display nano-molar EC_{50} values across a broad spectrum of human cancer cell lines and excellent levels of tumour clearance in a pre-clinical *in vivo* efficacy study of human tumour bearing nude mice. In addition a new approach to achieving selectivity for photodynamic therapy based upon the reversible off/on switching of the key therapeutic property (singlet oxygen generation) of a supramolecular photonic therapeutic agent in response to an external microenvironment stimulus has been developed. Further work into this unique selectivity approach is on-going.

2. Key publications:

(a) O'Connor, A. E.; McGee, M. M.; Likar, Y.; Ponomarev, V.; Callanan, J. J.; O'Shea, D. F.; Byrne, A. T.; Gallagher, W. M. *Intern. J. Cancer* **2012,** *130*, 705.
(b) Frimannsson, D.O.; Grossi, M.; Murtagh, J.; Paradisi, F.; O'Shea, D.F. *J. Med. Chem.* **2010**, *53*, 7337.
(c) McDonnell, S.O.; Hall, M.J.; Allen, L.T.; Byrne, A.; Gallagher, W.M.; O'Shea, D.F. *J. Am. Chem. Soc.* **2005**, *127*, 16360.
(d) O'Shea, D.F., Killoran J., Gallagher W.M. United States Patent No. 7,220,732, May 22, 2007.

Mixed Li/K amides and enantioselective carbolithiations as effective synthetic tools [3]

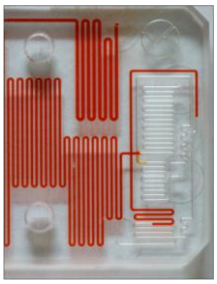
We have recently illustrated how mixed Li/K metal TMP amides (LiNK metalation conditions) are uniquely suited for selectively achieving challenging metalations. Specifically, the use of the reagent triad BuLi/KO*t*Bu/TMP(H) to *in situ* generate a mixed Li/K metal TMP amide has proven to be an efficient and general method to achieve direct vinylic and benzylic metalations with excellent and predictable regioselectivity. The scope of this novel methodology is currently being established and expansion of its synthetic utility for targetted synthesis is in progress. Enantioselective cascade reaction sequences are very powerful synthetic protocols for the assembly of complex organic architectures. The goal is to devise systems in which a facile transformation triggers the conversion of prochiral starting materials to chiral intermediates of high synthetic potential that can subsequently be converted *in situ* into products of increasing complexity. Our current approach is to exploit a chiral amine controlled enantioselective carbolithiation of *ortho*-substituted β-methylstyrenes. The chiral centre, formed in good enantiomeric excess in the carbolithiation step, can be carried through different reaction sequences thereby generating a collection of products. As the chiral centre generated during the carbolithiation step is carried through the subsequent reaction sequences to the final products, selectivity is solely dependent upon achieving an enantioselective alkyllithium addition.



3. Key publications:
(a) Blangetti M; Muller-Bunz H; O'Shea D.F. *Chem. Commun*. **2013**, *49*, 6125.
(b) Fleming, P.; O'Shea, D.F. *J. Am. Chem. Soc.* **2011**, *133*, 1698.
(c) Tricotet, T.; Fleming, P.; Cotter, J.; Hogan, A.M.L.; Strohmann, C.; Gessner, V.H.; O'Shea, D.F. *J. Am. Chem. Soc.* **2009**, *131*, 3142.
(d) Hogan, A.-M.L.; O'Shea, D.F. *J. Am. Chem. Soc.* **2006**, *128*, 10360.
(e) Coleman, C.M.; O'Shea, D.F. *J. Am. Chem. Soc.* **2003**, *125*, 4054.

Automated flow micro-reactors and parallel microwave-assisted synthesis [4]

Continuous flow chemistry has recently emerged as a productive technology for synthetic pharmaceutical chemists. It offers a new tool to accelerate lead discovery and development as it provides reliable control of reaction conditions, such as time, temperature, equivalents of reagents and mixing, and allows exothermic reactions to be performed without the need for cryogenics. In addition, by pressurising the system, reactions can be superheated to give reaction rates significantly faster than in open reflux. This gives microwave-like rate enhancement without the problems associated with microwave-based reactions. On-going research involves the application of fully automated flow micro-reactor systems to sequential compound library generation. The ability of microwave heating to funnel a spectrum of chemical reactivity found in a library into a very short time span has the potential to become a tool for high-throughput synthesis. My research has given rise to a new methodology that can overcome the technical problems associated with microwave parallel synthesis. As a proof of concept we have developed a diversity tolerant multi-component route to sulfanyl-imidazoles and have shown that a comparable microwave generated library can be achieved with a dramatic reduction in library generation time.



4. Key publications:
(a) Tricotet, T.; O'Shea, D.F. *Chem. Eur. J.* **2010**, *16*, 6678.
(b) Le Bas, M.-D.H.; O'Shea, D.F. *J. Comb. Chem.* **2005**, *7*, 947.
(c) Coleman, C.M.; MacElroy, J.M.D.; Gallagher, J.F.; O'Shea, D.F. *J. Comb. Chem.* **2002**, *4*, 87.