Synthesis and chemical biology of natural product-like small molecules

Stephen Bartlett, Jamie Caryl, Christopher Cordier, Teresa Damiano, Adam Nelson, Catherine O'Leary Steele, Alexis Perry, Peter Stockley and Stuart Warriner

Introduction

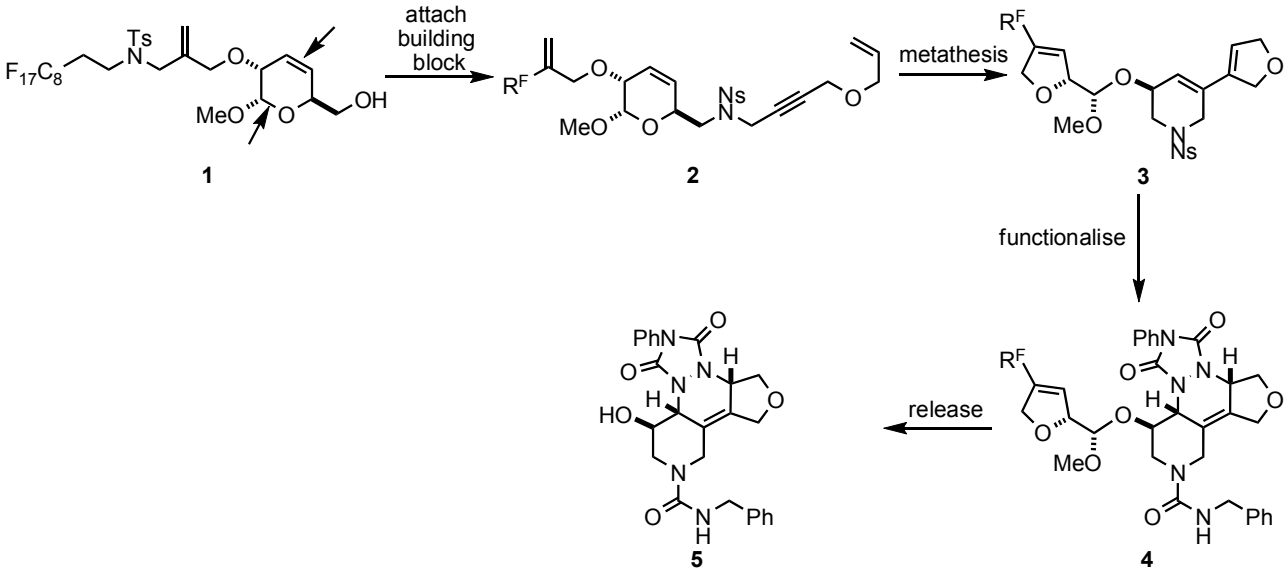
Synthetic organic chemistry is an immensely powerful tool for chemical biology, which we exploit in a wide range of biological problems. Our publications which were published in 2008 are provided in this report. You may like to browse our website at www.asn.leeds.ac.uk to find out more about what we do!

The synthesis of libraries of diverse natural product-like molecules

Historically, chemists have explored chemical space in an uneven and unsystematic manner: the organic chemistry "universe" is extremely top heavy, with half of molecules in the CAS database being based on just 0.25% of the known molecular scaffolds! A major challenge in chemical biology and medicinal chemistry is to prepare libraries of ligands that populate broad tracts of biologically-relevant chemical space. The development of methods that allow the systematic exploration of such chemical space is a major theme within our research group.

The synthesis of a small molecule library of unprecedented scaffold diversity was described in the 2007 annual report, and this research has recently been published as a VIP article in *Angewandte Chemie*. Our approach has received widespread attention: it was the subject of News & Views articles in *Nature* (Schreiber) and *Nature Chemical Biology* (Waldmann), highlights in *Angewandte Chemie* (Spring) and (on-line) in *Nature Chemistry*, and articles in *Science* and *C&E News*. It was also noted as "Exceptional" by the Biology Faculty of 1000.

More recently, we have described a fluorous-tagged "safety catch" linker which we have applied in the synthesis of skeletally-diverse small molecule libraries. The principles that underpin the design of the linker are outlined in Scheme 1. Crucially, cleavage of both of the bonds that are marked with an arrow (in structure **1**) is necessary for release of products from the linker.



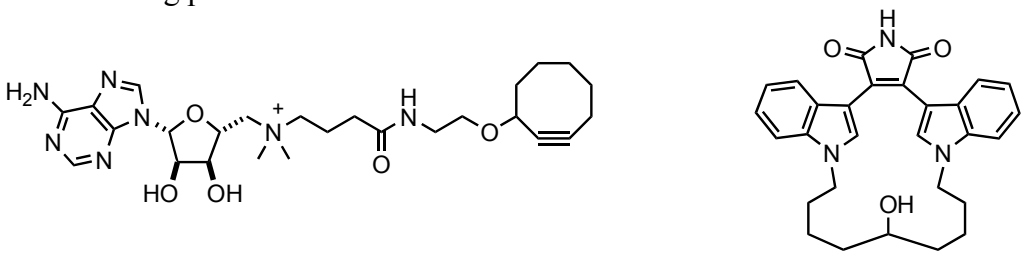
Scheme 1: A fluorous-tagged 'safety catch' linker for preparing skeletally-diverse small molecule libraries. Cleavage of both bonds marked with an arrow is necessary for release from the linker 1.

To start, a building block is attached to the linker **1** (e.g. to give **2**). A metathesis cascade process then leads to cleavage of the cyclic alkene in the linker (e.g. **2** → **3**). Further

functionalisation is possible at this stage (e.g. **3** → **4**). Finally, acid-catalysed acetal hydrolysis leads to release from the linker (→ **5**). Crucially, the design of the linker means that (a) fluorous–solid phase extraction alone is needed to purify the intermediates in the synthesis, and (b) only metathesis products are ever released from the fluorous tag.

Applications of chemical probes of biological systems

We have also reported some novel chemical tools that may be used to interrogate biological systems. We have used the SAM analogue **6** to modulate the function of the *E. coli* methionine repressor, MetJ. The strained cyclooctyne ring of **6** is a "bioorthogonal" tag which may allow the compound to be used as a tool in the purification and analysis of other SAM-binding proteins.



6 **7**

Scheme 2: Some novel probe molecules reported by the Nelson group in 2008.

In addition, the bisindolylmaleimide **7** is an example of a potent inhibitor of glycogen synthase kinase (GSK) 3. In collaboration with Prof. Melanie Welham, University of Bath, we have used such molecules to understand the role of GSK-3 in promoting the self-renewal of murine embryonic stem cells.

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Collaborators

We also thank our collaborators from outside the Astbury Centre. The research into GSK-3 function was undertaken in collaboration with Heather Bone, Julie Letchford and Melanie Welham from the Department of Pharmacy and Phamacology, University of Bath.

Publications

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