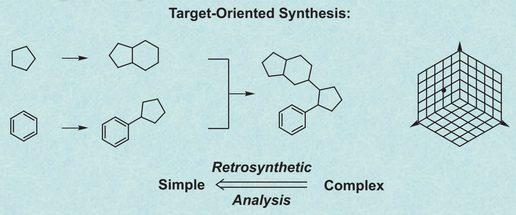
A new strategy for the diversity-oriented synthesis of drug-like macrocycles

Sean Bartlett, André Grossmann, Matej Janecek, James T. Hodgkinson and David R. Spring*

University of Cambridge, Department of Chemistry, Lensfield Road, Cambridge CB2 1EW

Diversity-oriented synthesis

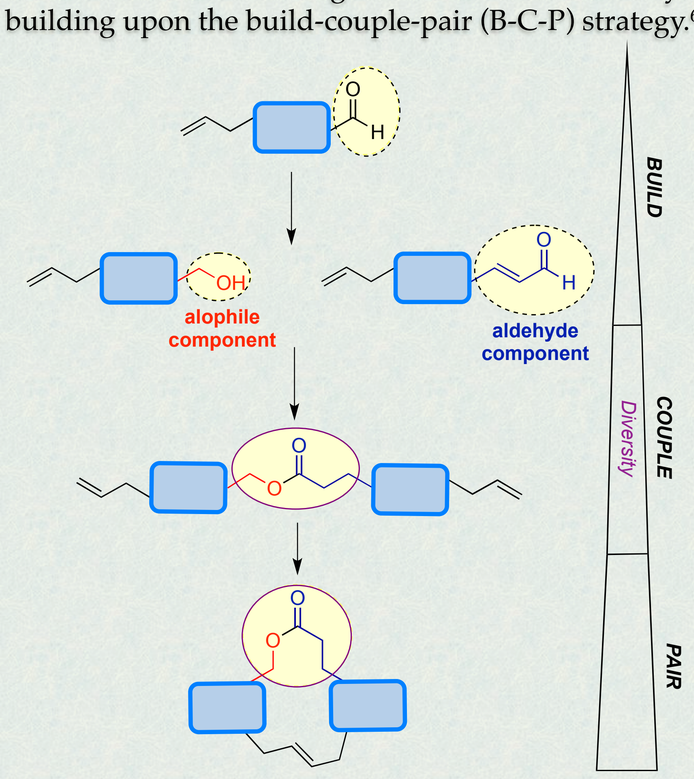
Small molecules are the cornerstone of biology and medicine. DOS aims to generate complex and diverse small molecules efficiently and effectively to probe and perturb biological systems.[1-2]



Macrocycles in drug discovery

Macrocycles are prominent motifs in natural products and offer remarkable target affinity and selectivity.[3] However they are underrepresented in pharmaceutical compound collections and pose significant challenges in terms of synthesis and pharmacokinetic modification.[4-5]

We conceived a new strategy for the synthesis of a library of macrocyclic drug scaffolds using orthogonal and chemoselective organo- and metal catalysis, building upon the build-couple-pair (B-C-P) strategy.[6-7]



Build phase – the expedient synthesis of a small number of pluripotent building blocks.

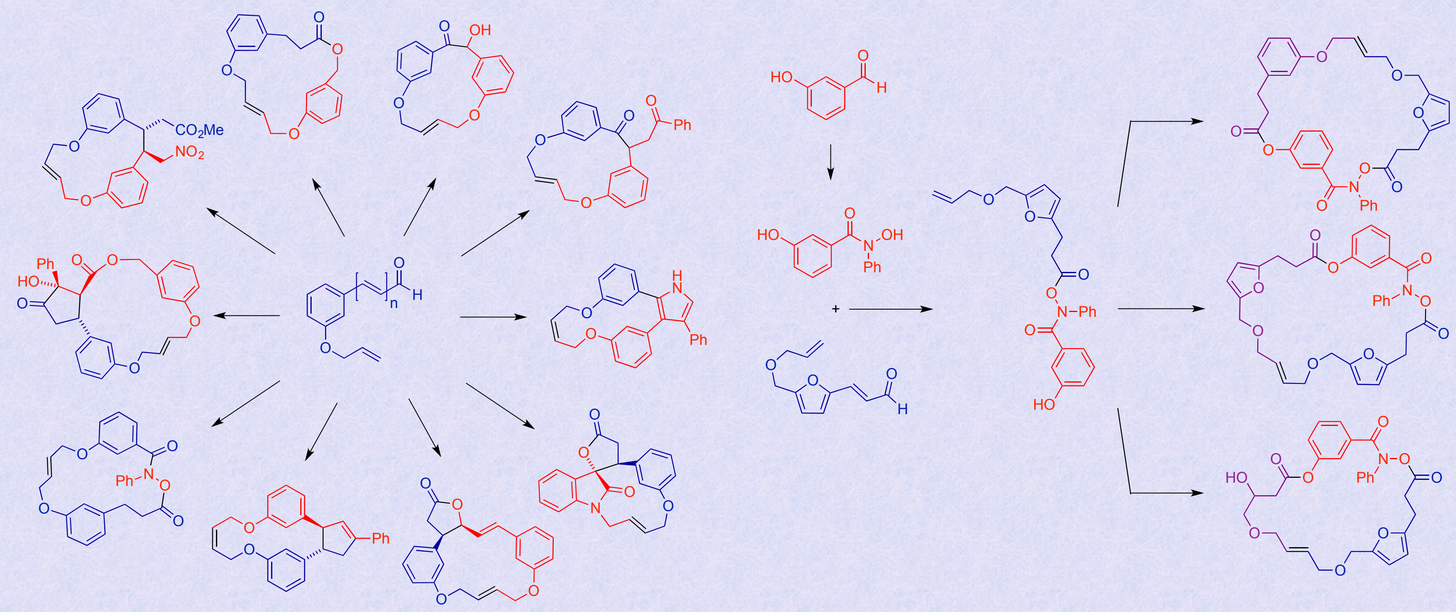
Couple phase – the selective coupling of building blocks *via* different linking motifs.

Pair phase – the cyclisation of the linear precursor.

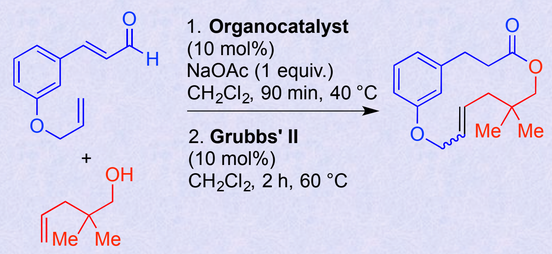
Library synthesis

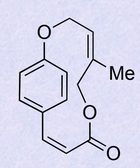
Using a number of complexity-generating organocatalytic coupling reactions, a small and diverse library of drug-like macrocycles was synthesised in as few as two steps from parent building blocks.

We have also demonstrated examples of B-C-C-P and B-C-C-C-P synthetic algorithms in the production of larger and more complex macrocycles, with skeletons up to 27 carbons in size.



Furthermore, we extended this methodology to the one-pot synthesis of natural product-like macrocycles through the optimisation of a one-pot sequential catalysis transformation.



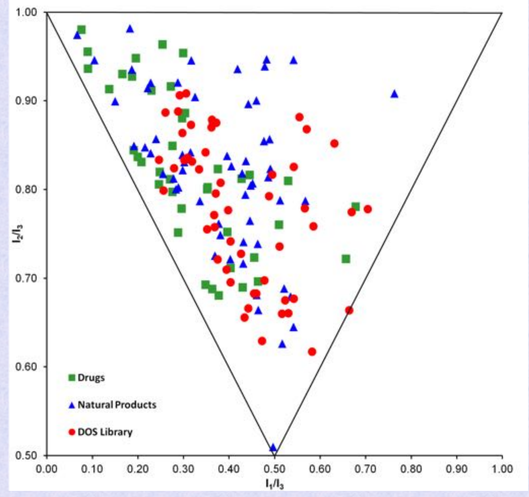


Pondaplin
(anti-cancer)

Diversity assessment

Principle component analysis of our library and two reference libraries (40 top-selling drugs and 60 natural products, respectively) revealed a high level of structural and physicochemical diversity and drug-likeness within our macrocycles, which is commonly one of the main sticking points of related methodology.

Analysis of principal moments of inertia (PMI) highlights the broad structural diversity generated in such a small library. This is a direct consequence of powerful organocatalytic coupling reactions of pluripotent enals, which generates functionally complex coupling motifs and skeletal diversity.



Phenotypic screening

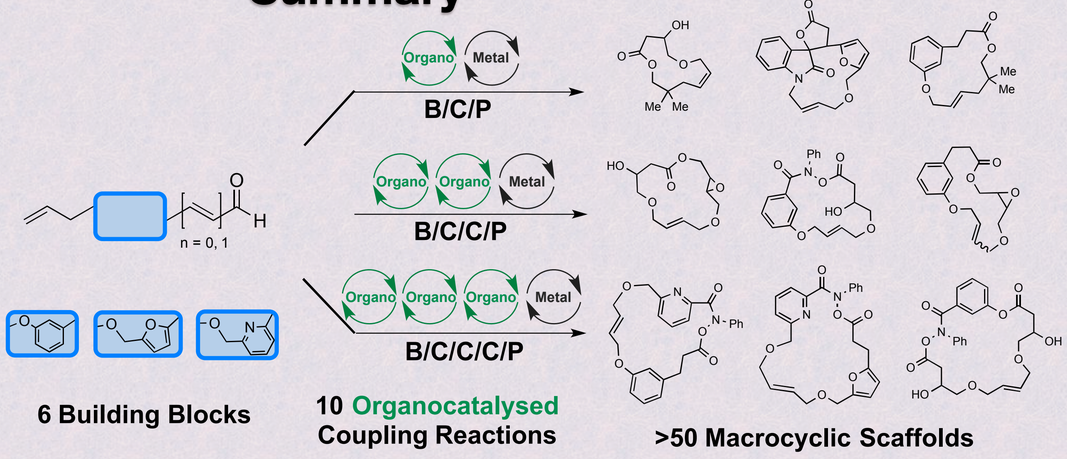
Preliminary phenotypic screening of this library has identified a number of compounds with biological activity, and further investigations in this area are ongoing. Other library members are being elaborated within the Spring group in the development of new inhibitors of biologically important protein–protein interactions.

Summary

New synthetic methods are needed to access biology-relevant chemical space, of which macrocycles comprise a disproportionate area.

We report a new strategy for the synthesis of drug-like macrocycles. These scaffolds are synthetically tractable, physicochemically and structurally diverse.

Hits found by phenotypic screening are now subject to further investigation.



References

1) S. L. Schreiber, *Science*, 2000, **287**, 1964.
2) C. J. O' Connor, *et al.*, *Chem. Soc. Rev.*, 2012, **41**, 4444.
3) E. M. Driggers *et al.*, *Nat. Rev. Drug. Discov.*, 2008, **7**, 608.
4) N. K. Terrett, *Drug. Discov. Today. Technol.*, 2010, **7**, e97.
5) C. M. Madsen and M. H. Clausen, *Eur. J. Org. Chem.*, 2011, 3107.
6) A. Grossmann *et al.*, *Angew. Chem. Int. Ed.*, 2014, **126**, 13309.
7) T. E. Nielson and S. L. Schreiber, *Angew. Chem. Int. Ed.*, 2008, **47**, 48.

Acknowledgements

Our laboratory is supported by the EU, EPSRC, BBSRC, MRC, Frances and Augustus Newman Foundation, Wellcome Trust and Isaac Newton Trust. S.B. thanks the Herchel Smith Fund for a Ph.D. studentship and Corpus Christi College Cambridge for financial support. A.G. thanks the German Research Foundation for a postdoctoral fellowship (GR4429/1-1).

UNIVERSITY OF CAMBRIDGE