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

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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.1,3 However they are underrepresented in pharmaceutical compound collections and pose significant challenges in terms of synthesis and pharmacokinetic compound collections and offer remarkable target affinity and selectivity.3

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-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.

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.

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References