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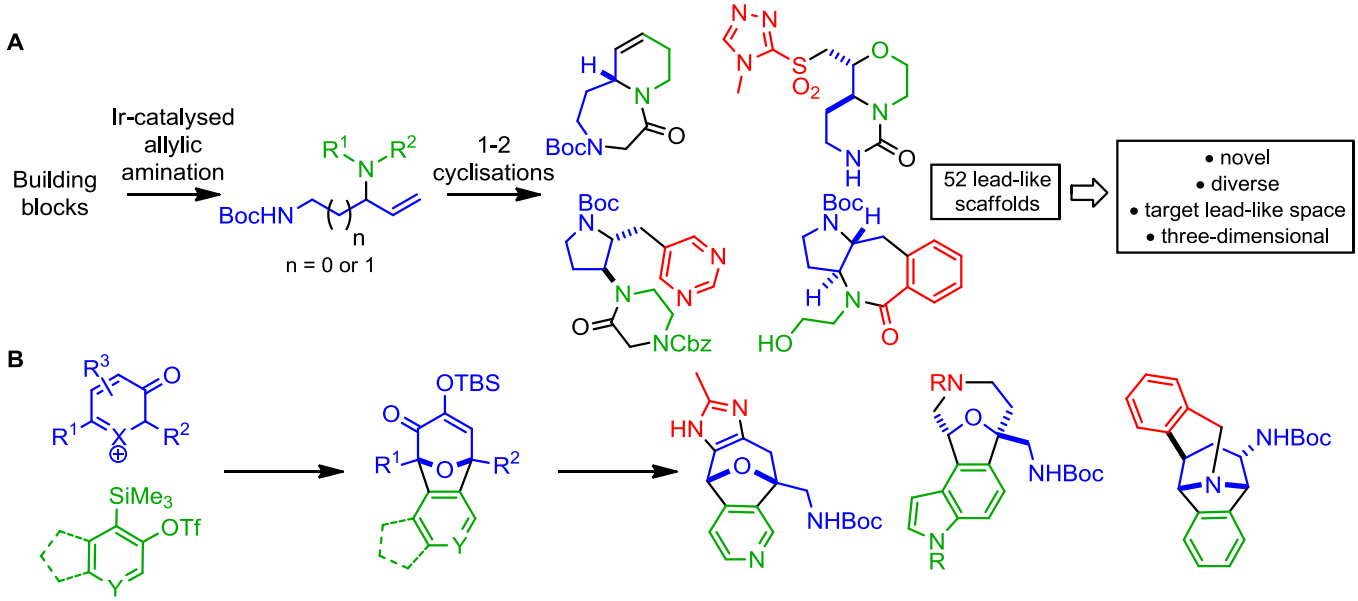
Synthesis of Diverse Small Molecules with Controlled Molecular Properties

Screening collections of compounds is often a key step in the discovery of functional small molecules. Molecules in such collections need to be diverse and distinctive, and to have controlled properties. For example, the properties of molecules that would provide a good starting point for drug discovery – such as lead-like molecules and fragments – have been clearly defined.[1] Similarly, clear guidelines have been defined in other discovery sectors such as agrochemicals. Unfortunately, sourcing large numbers of diverse and novel compounds with appropriate molecular properties is often extremely challenging.

Our collaborative research programme has led to the development of unified synthetic approaches that facilitate the systematic exploration of biologically-relevant chemical space. To date, we have largely targeted lead-like chemical space i.e. that would provide good starting points for early-stage drug discovery.[2] For example, we developed a "bottom-up" strategy in which pairs of building blocks were combined and then cyclised to yield 52 diverse and lead-like molecular scaffolds (Scheme 1, Panel A).[2a] Throughout this work, we have used computational tools help us to focus on reactions that have the potential to target novel lead-like chemical space.



Scheme 1: Our complementary unified approaches to lead-like scaffolds. Panel A: Our "bottom-up" approach from building blocks to diverse scaffolds. Panel B: Our envisaged "top-down" approach in which complex polycyclic molecules converted into alternative scaffolds.

This project will involve the development of a complementary "top-down" strategy for preparing diverse scaffolds with controlled molecular properties. Here, complex bridged structures will be rapidly prepared, and then converted (e.g. by bond cleavage, ring expansion, ring fusion etc) into alternative small molecule scaffolds (Panel B). Throughout, the synthetic programme will be informed by analysis that is possible using our recently-launched open-access tool, LLAMA (llama.leeds.ac.uk). Thus, the new synthetic approach will yield diverse molecular scaffolds with appropriate properties for discovery applications.

References

(1) For specific requirements of lead molecules and fragments, see (respectively): *Angew. Chem. Int. Ed.* 2012, **51**, 1114; *Angew. Chem. Int. Ed.* 2015, DOI: 10.1002/anie.201506783.

(2) (a) *Org. Biomol. Chem.* 2015, **13**, 859; (b) *Bioorg. Med. Chem.* 2015, **23**, 2629; (c) *Bioorg. Med. Chem.* 2015, **23**, 2736; (d) *Bioorg. Med. Chem.* 2015, **23**, 2613; (e) *Synthesis* 2015, **47**, 2391; (f) *Chem. Commun.* 2014, **50**, 10222; (g) *Org. Biomol. Chem.* 2014, **12**, 2584; (h) *Org. Lett.* 2014, **16**, 4718; (i) *Drug Discov. Today* 2013, **19**, 813; (j) *Chem. Commun.* 2013, 2383; (k) *Org. Lett.* 2013, **15**, 6094; (l) *Org. Biomol. Chem.* 2012, **10**, 17; (m) *Org. Biomol. Chem.* 2012, **10**, 3147; (n) *J. Org. Chem.* 2011, **76**, 5495. (o) *New Frontiers in Chemical Biology: Enabling Drug Discovery*, ed. M. E. Bunnage, RSC Publishing, Cambridge, 2011; (p) *Adv. Synth. Catal.* 2010, **352**, 3153; (q) *Tetrahedron* 2009, 65, 9002; (r) *Org. Lett.* 2008, 10, 4117; (s) *Chem. Commun.* 2015, **51**, 11174.