Development of tools and approaches to facilitate more systematic exploration of lead-like chemical space

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Introduction

Chemists have explored chemical space (using synthesis and biosynthesis) in an uneven and unsystematic manner. An analysis of the scaffolds of the 25 million known cyclic small molecules (in 2008) revealed that one sixth of the compounds are based on just 30 (out of the 2.5 million) known molecular scaffolds! To address this historic uneven exploration, we have developed a vibrant research programme focusing on the identification and development of synthetic methods that have potential to facilitate more systematic exploration of chemical space

Extension to lead-like chemical space

A strongly developed theme within the Nelson group has been to develop diversity-oriented synthetic approaches that map onto the requirements of drug discovery programmes. This programme has been undertaken in collaboration with scientists from major pharmaceutical companies. Established diversity-oriented approaches have tended to focus on small molecules that lie well outside drug-like space. It is now generally accepted that attrition rates in drug discovery are strongly linked to molecular properties such including molecular weight and lipophilicity. Optimisation almost always leads to increases in both molecular weight and lipophilicity, so it is important to control the properties of initial lead molecules.

In collaboration with GSK, we have developed computational tools that allow the value of alternative synthetic approaches to be assessed. Thus, before any optimisation work is undertaken, we now routinely assess synthetic approaches for their potential to target under-explored regions of lead-like chemical space. We then focus on optimising those reactions that are likely to have the greatest value. We are thus continuing to develop a robust and growing toolkit of synthetic reactions that address the challenges raised in the nascent field of lead-oriented synthesis. This research programme is now feeding into the €196M European Lead Factory in which Leeds is a partner.

Summary

The development of general strategies that are able to deliver skeletally diverse compounds – but within the boundaries of lead-like chemical space – is demanding. Publications from this programme, and other programmes under active development in the group are listed below. Further details of research within the Nelson group may be found at www.asn.leeds.ac.uk.

Publications

Dow, M., Fisher, M., James, T., Marchetti, F. & Nelson, A. (2012) Towards the systematic exploration of chemical space. *Org. Biomol. Chem.* **10:** 17-28.

Joce, C., White, R., Stockley, P., Warriner, S., Turnbull, W. & Nelson, A. (2012) Design, synthesis and *in vitro* evaluation of novel bivalent s-adenosylmethionine analogues. *Bioorg. Med. Chem. Lett.* **22:** 278-284.

Kinnell, A., Harman, T., Bingham, M., Berry, A. & Nelson, A. (2012) Development of an organo- and enzyme-catalysed one-pot, sequential three-component reaction. *Tetrahedron* **68:** 7719-7722.

Timms, N., Daniels, A., Nelson, A. & Berry, A. Directed Evolution and (Semi-)Rational Design Strategies for the Creation of Synthetically-Useful, Stereoselective Biocatalysts. (2012) ed. Turner, N. J., in *Comprehensive Chirality*.

Tosatti, P., Nelson, A. & Marsden, S. (2012) Recent advances and applications of iridium-catalysed asymmetric allylic substitution. *Org. Biomol. Chem.* **10:** 3147-3163.

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