The exploration of biologically-relevant chemical space

Anthony Aimon, George Burslem, Ignacio Colomer, Philip Craven, Richard Doveston, Mark Dow, James Firth, Daniel Foley, George Karageorgis, Ho-Yin Li, Paolo Tosatti, Rong Zhang, Richard Foster, Stuart Warriner and Adam Nelson

Introduction

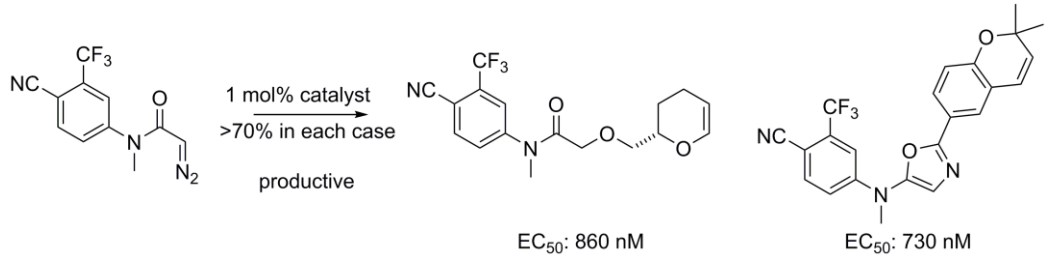
Chemists have explored chemical space in an uneven and unsystematic manner. An analysis of the scaffolds of the 25 million known cyclic small molecules (in 2008) revealed that one sixth of the compounds are based on just 30 (out of the 2.5 million) known molecular scaffolds! To address this historic 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 align with the requirements of drug discovery programmes. 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. 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.

Realisation of activity-directed synthesis

We have further developed activity-directed synthesis (ADS), our novel discovery approach in which bioactive small molecules emerge in parallel with associated synthetic routes. Unlike conventional discovery approaches, ADS exploits promiscuous reactions with many alternative outcomes, and enables the exploration of diverse regions of chemical space. The approach is iterative, exploiting diverse reaction arrays whose design is informed by the activity of product mixtures formed in previous rounds. Ultimately, promising reactions are scaled up to reveal, after purification, the structures of the responsible bioactive molecules. ADS is thus a function-driven approach in which the discovery of bioactive molecules occurs in parallel with the emergence of an associated synthetic route.



Scheme: Syntheses of androgen receptor agonists (with sub-micromolar activity) that emerged from our activity-directed approach. The chemotypes discovered did not have any previously annotated activity against the androgen receptor.

We have recently shown that intermolecular reactions greatly extend the scope of ADS. We exploited ADS in the discovery of diverse agonists of the androgen receptor: crucially, the chemotypes discovered did not have any previously annotated activity against the androgen

receptor; and high-yielding syntheses emerged in parallel (see Scheme for examples). In one case, a novel asymmetric reaction was discovered on the basis of biological activity alone. In another case, a heterocyclic peptidomimetic emerged from our ADS approach

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

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Collaborators

University of Leeds: S. Marsden.

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