remarkably important within chemistry. Properties of different spin states will surely continue to serve as a challenge for theory, and also as a guiding principle for molecular design by computational and experimental chemists. ❐

Miquel Costas is in the Departament de Química, Universitat de Girona, Facultat de Ciències, Campus de Montilivi, 17071 Girona, Spain. Jeremy N. Harvey is in the Centre for Computational Chemistry and School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK.
e-mail: miquel.costas@udg.edu; jeremy.harvey@bristol.ac.uk

References

1. Schröder, D., Shaik, S. & Schwarz, H. *Acc. Chem. Res.* **33,** 139–145 (2000).
2. Xue, G., Hont, R. D., Münck, E. & Que, L. *Nature Chem.* **2,** 400–405 (2010).
3. Ye, S. & Neese, F. *Proc. Natl. Acad. Sci.* **108,** 1228–1233 (2010).
4. Siegbahn, P. E. M. *Acc. Chem. Res.* **42,** 1871–1880 (2009).
5. Subrata Kundu, E. M. *et al. J. Am. Chem. Soc.* **134,** 14710–14713 (2012).
6. Harvey, J. N. *Phys. Chem. Chem. Phys.* **9,** 331–343 (2007).
7. Liptak, M. D., Wen, X. & Bren, K. L. *J. Am. Chem. Soc.* **132,** 9753–9763 (2010).
8. Ye, S. & Neese, F. *Inorg. Chem.* **49,** 772–774 (2010).
9. Boguslawski, K., Marti, K. H., Legeza, Ö. & Reiher, M. *J. Chem. Theory Comput.* **8,** 1970–1982 (2012).
10. Deeth, R. J., Anastasi, A. E. & Wilcockson, M. J. *J. Am. Chem. Soc.* **132,** 6876–6877 (2010).

DRUG DISCOVERY

Nature's pieces

Natural products contain a range of chemical structures optimized for biological interactions. Fragmenting these compounds could help to combine this diversity with the broad coverage of chemical space offered by fragment-based drug discovery, and help to improve the efficiency with which screening hits can become successful drugs.

Brian K. Shoichet

If the ship of drug discovery has seemed recently adrift, it is not for lack of strong winds of opinion to fill its sails. In chemistry, different views of what are good starting points for drug leads have been hotly contested. Among these are fragment-based drug design (FBDD) and screening libraries from diversity-oriented synthesis (DOS). Fragments are small organic molecules, no greater than 250 to 300 Da that typically bind weakly to proteins. From an initial fragment hit, more potent molecules are elaborated for optimized fit and 'ligand efficiency' — which measures binding energy per non-hydrogen atom. DOS, inspired by natural products, develops stereochemically rich scaffolds, already drug-like in size (for example, 350–500 Da). Partisans of fragmentation-based approaches argue that DOS compounds will struggle to solve the chemical space problem in ligand discovery and often have physical properties that are associated with poor drug-likeness, whereas advocates of DOS say that fragments lead only to the same flat molecules that have characterized the last two decades of discovery, and are suitable only for screens against soluble proteins[1]. Writing in *Nature Chemistry*, Herbert Waldmann and co-workers investigate libraries composed of fragments of stereochemically rich scaffolds derived from natural products[2]. This approach combines favourable features of both techniques.

A romance with high-throughput screening (HTS) of large compound libraries, and a flirtation with combinatorial chemistry led, by the mid-1990s, to hit-lists choked with molecules with unfavourable properties; a substantial number of campaigns found essentially no active molecules that were not artefacts[3,4]. This inspired efforts to define drug-likeness, beginning with the 'Rule of Five' for oral drugs[5], which suggested that screening hits should, among other features, be <500 Da. There was a subsequent move towards 'lead-like' compounds in screening (<350 Da), because a screening hit was rarely suitable as a clinical candidate, and would inevitably require optimization[6]. Also, investigators began to realize that even the chemical libraries of the great pharmaceutical companies (containing 10^6 to 10^7 molecules), captured only a tiny fraction of chemical diversity space; there are thought to be more than 10^{60} possible organic structures with molecular mass <400 Da (ref. 7). Given this under-sampling, the fact that HTS did return real hits may be a reflection of the bias of screening libraries towards biogenic molecules[8]. In the fragment range (<250 Da) the coverage of chemotypes in commercial libraries is perhaps 45-log orders better than at the drug-like range[9] (Fig. 1). Logically, this means that chemical libraries were far more likely to contain

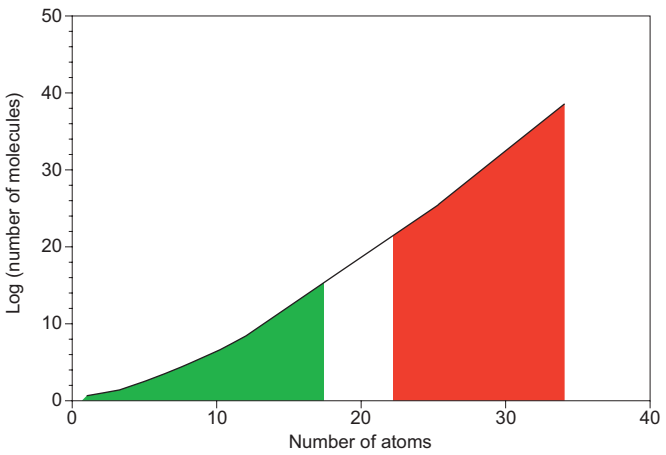

Figure 1 | Chemical space rises exponentially with molecular size. The growth of the number of possible molecules containing only carbon, nitrogen, oxygen, fluorine and hydrogen is extrapolated from explicit enumeration of molecules up to 11 non-hydrogen atoms in size, based on the method of Fink and Reymond[13]. Fragments fall into the green area whereas most DOS molecules fall into the red drug-like size range. Thus, similarly sized libraries of fragments can cover the available chemical space more effectively than libraries of drug-like molecules. If other common elements — sulfur, phosphorus and chlorine — are included, the growth of the number of molecules will be substantially steeper.

suitable fragments with weak affinities for a particular target than a drug-like lead[10,11]. Such fragment-based drug discovery has led to several investigational new drugs and, recently, the approved drug vemurafenib.

As HTS and FBDD were gaining traction, natural products were being abandoned by pharma. Today, with the exception of companies like Eisai and Novartis, it has largely disappeared from commercial research. Given the success of natural products in drug discovery over the past 60 years, this decision was met with bafflement by organic chemists[12]. The explanation was that natural products were often only active as mixtures, and were often not amenable to rapid synthetic optimization. Compounds produced by DOS seem well-suited to address these problems. They are stereochemically rich and so capture many of the properties of natural products. At the same time, they enable facile derivitization, making them suitable as early hits. The unstated hope is that their three-dimensionality will also solve the chemical space problem. It may be, however, that the unusual ability of natural products to modulate biological activity springs from their evolution as biological molecules[8], selected to modulate highly conserved proteins, and not their chemical complexity, as extraordinary as it is. If true, then the success of DOS-based approaches may face long odds.

The use of fragments of natural products by Waldmann and co-workers[2] combines the chemical space advantages offered by fragments (and their ability to fit optimally into new receptor sites), with the rich chemistry and geometry that natural products bring. They have the further advantage of being optimized for biological recognition and modulation.

What makes this paper a tour de force is that they not only identify natural product fragments that are commercially available, and synthesize others, they go on to screen 193 natural product fragments against P38 MAP kinase and several tyrosine phosphatases, determine P38–fragment complexes by X-ray crystallography, and finally synthesize optimized derivatives. Although some of the fragments discovered resembled known chemotypes, such as the flavenoids for the kinase, and several were weak even by fragment standards, others explored unusual chemotypes and had high ligand efficiencies. Intriguingly, fragments of cytisine — itself a recent triumph of natural product synthesis that led to the drug verenicline — were active against both the kinase and one of the phosphatases. Fragments are often found to be promiscuous — binding weakly to a number of different targets — and this suggests that natural-product-derived fragments fit this pattern. The binding to poorly explored pockets in the kinase by these fragments, revealed by crystallography, supports the idea that stereochemically rich cores can lead to molecules that explore new protein sites.

In the last century, food scientists at the Reese corporation combined two food groups — peanut butter and chocolate — in the 'peanut-butter cup', apparently resolving a formerly intractable culture war (http://go.nature.com/nAWmgU). By adopting fragments of natural products as screening tools, Waldmann and co-workers combine two innovative techniques in modern drug discovery: fragments that can illuminate target sites with new chemotypes, and the ability of natural products and DOS compounds to escape from the 'flatland' into which most fragments fall. This method to identify accessible fragments from natural products may find broad use in bringing new, complex but biologically optimized chemotypes into screening. Although the fragments that result will remain unsuitable for cell-based or phenotypic screens — something that will remain the domain of DOS and other libraries, it is a welcome addition to our armamentarium of early discovery tools. Yum. ❐

Brian K. Shoichet is Department of Pharmaceutical Chemistry & California Institute for Quantitative Biosciences University of California, San Francisco, 1700 4th St., Byers Hall Room 508D, San Francisco, California 94158, USA.
e-mail: bshoichet@gmail.com

References

1. Hajduk, P. J., Galloway, W. R. & Spring, D. R. *Nature* **470,** 42–43 (2011).
2. Over, B. *et al. Nature Chem.* **5,** 21–28 (2013).
3. Payne, D. J., Gwynn, M. N., Holmes, D. J. & Pompliano, D. L. *Nature Rev. Drug. Discov.* **6,** 29–40 (2007).
4. Babaoglu, K. *et al. J. Med. Chem.* **51,** 2502–2511 (2008).
5. Lipinski, C. A., Lombardo, F., Dominy, B. W. & Feeney, P. J. *Adv. Drug Delivery Rev.* **23,** 3–25 (1997).
6. Oprea, T. I. *Mol. Divers.* **5,** 199–208 (2002).
7. Bohacek, R. S., McMartin, C. & Guida, W. C. *Med. Res. Rev.* **16,** 3–50 (1996).
8. Hert, J., Irwin, J. J., Laggner, C., Keiser, M. J. & Shoichet, B. K. *Nature Chem. Biol.* **5,** 479–483 (2009).
9. Hann, M. M., Leach, A. R. & Harper, G. *J. Chem. Inf. Comput. Sci.* **41,** 856–864 (2001).
10. Shuker, S. B., Hajduk, P. J., Meadows, R. P. & Fesik, S. W. *Science* **274,** 1531–1534 (1996).
11. Rees, D. C., Congreve, M., Murray, C. W. & Carr, R. *Nature Rev. Drug Discov.* **3,** 660–672 (2004).
12. Newman, D. J., Cragg, G. M. & Snader, K. M. *J. Nat. Prod.* **66,** 1022–1037 (2003).
13. Fink, T. & Reymond J. L. *J. Chem. Inf. Model.* **47,** 342–353 (2007).

BIOSYNTHESIS

Imaging cell-wall biosynthesis live

The biosynthesis of peptidoglycan is an important step in bacterial cell division and cell-wall maturation. Now it has been shown that fluorescent D-amino acids can be used to label the peptidoglycan cell wall of living bacteria, providing a new tool to study this important process.

Timothy D. H. Bugg

An important question at the interface between microbiology and biochemistry is how the complex machinery for bacterial cell division is controlled in three dimensions during the cell-division cycle. At the heart of this mystery is peptidoglycan, a polymer made from sugars and amino acids that is an integral part of the bacterial cell wall. A better understanding of the processes involved offers more than just fundamental insight, it could help in the design of new antibiotics: in 1965 penicillin's mechanism of action was discovered to involve inhibition of the final crosslinking step in peptidoglycan biosynthesis[1]. Now writing in *Angewandte Chemie International Edition*, Yves Brun, Michael VanNieuwenhze and co-workers report[2] a method for labelling peptidoglycan that should help scientists to study bacterial cell division.

The presence of D-amino acids in the pentapeptide sidechain of peptidoglycan is a unique feature of its structure. For many years it was believed that the -D-Ala-D-Ala terminus (recognized by the antibiotic vancomycin) was universal