ligand efficiency in a typical project where we wish to obtain a compound with a potency of 10 nM and an upper MW of 500. Analysis of the Pfizer corporate screening data reveals that the mean molecular mass for a non-hydrogen 'heavy' atom in drug-like compounds is 13.286; thus, a compound with a 500 MW, contains on average 38 non-hydrogen atoms. Therefore, a 500 MW compound with a binding constant of 10nM (10.99 kcal mol^{-1}) possesses a ligand efficiency of 0.29 kcal mol^{-1} per non-H atom. Small differences in ligand efficiency (Δg) could have large consequences for the type of compounds that might be possible in a chemical series or against a particular target. For example, a compound with a $\Delta g = -0.27$ kcal mol^{-1} per non-H atom requires 41 atoms (541 MW) to bind with $K_d = 10$ nM, if ligand efficiency remains constant during optimization of the lead series (i.e. potency increase linearly with molecular weight). By contrast, a compound with a $\Delta g = -0.36$ kcal mol^{-1} per non-H atom requires only 30 atoms (405 MW) to bind with $K_d = 10$ nM. For the purposes of HTS follow-up, we recommend considering optimizing the hits or leads with the highest ligand efficiencies rather than the most potent, all else being equal.

Scaffold and lead series selection could be aided by considering a parameter that 'normalizes' the potency of a lead, with respect to MW, to enable comparisons between different series and scaffolds. Indeed, small compounds with low molecular complexity are predicted to have an improved probability of binding to the target of interest [2]. Medicinal chemists frequently work to produce compounds with properties constrained by many limits. We have considered MW, however, producing compounds with an acceptable logP while retaining potency can be challenging. It is of course trivial to extend the simple calculations we suggest here to encompass potency per logP unit for example.

The arguments presented here stress the value of low MW efficient leads. One might wish to respond to this by ensuring that HTS is able to detect such compounds. Comparison of lead compounds on the basis of ligand efficiency (binding energy per atom) rather than the potency alone could be useful in deciding the potential for further optimization for particular 'hits' and chemical scaffolds.

References

1 Sneader, W. (1996) *Drug Prototypes and their Exploitation*, John Wiley & Sons
2 Hann, M. *et al.* (2001) Molecular complexity and its impact on the probability of finding leads for drug discovery. *J. Chem. Inf. Comput. Sci.* 41, 856–864
3 Teague, S. *et al.* (1999) The design of leadlike combinatorial libraries. *Angew Chem. Int. Ed. Engl.* 24, 3743–3748
4 Oprea, T. *et al.* (2001) Is there a difference between leads and drugs? *J. Chem. Inf. Comput. Sci.* 41, 1308–1315
5 Lipinski, C. (2000) Drug-like properties and the causes of poor solubility and poor permeability. *J. Pharmacol. Toxicol. Methods* 44, 235–249
6 Lipinski, C. *et al.* (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Del. Revs.* 23, 3–25
7 Wenlock, M.C. *et al.* (2003) A comparison of physiochemical property profiles of development and marketed oral drugs. *J. Med. Chem.* 46, 1250–1256
8 Blake, J.F. (2003) Examination of the computed molecular properties of compounds selected for clinical development. *BioTechniques* 34, S16–S20
9 Lahana, R. (1999) How many leads from HTS? *Drug Disc. Today* 4, 447–448
10 Andrews, P. *et al.* (1984) Functional group contributions to drug-receptor interactions. *J. Med. Chem.* 27, 1648–1657
11 Kuntz, I. *et al.* (1999) The maximal affinity of ligands. *Proc. Natl. Acad. Sci. U. S. A.* 96, 9997–10002

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Promiscuity: what protects us, perplexes us

Molecular promiscuity plays a key role in the recognition, metabolism and elimination of xenobiotics and other harmful compounds. The human drug metabolism and recognition machinery evolved to detect compounds that vary widely in shape, size and chemical character. Utilizing promiscuous proteins for such processes frees the cell from having to maintain an enormous array of xenobiotic metabolism proteins, each specific to a small region of chemical space. Promiscuous proteins pay a significant penalty for their promiscuity. For example, non-promiscuous enzymes perform specific catalytic events with high k_{cat} and low K_m values. Promiscuous enzymes, in contrast, can handle compounds from a wide region of chemical space but exhibit relatively low k_{cat} and high K_m values for substrates.

Lead compound metabolism

What protects us also perplexes the drug discovery process. It would be great to be able to predict *a priori* whether a promising lead compound will serve as a substrate for drug metabolism enzymes or as a ligand for xenobiotic receptors that regulate the expression of drug metabolism genes. In a recent article in *Drug Discovery Today*, Sean Ekins provides an excellent review of the current state of the field's attempts to apply *in silico* muscle to the problem of predicting the metabolism of lead compounds and their potential for drug-drug interactions [Ekins, S. (2004) *Drug Discovery Today* 9, 276–283]. QSAR and functional data are typically combined with protein crystal structures (or models, if necessary) to predict the relative lability of compounds. For example, substrates for the highly promiscuous human cytochrome P450-3A4 isoform, which

metabolizes >50% of human drugs, and ligands for the nuclear xenobiotic receptor PXR seem to share key but enigmatic structural similarities. Not all targets to be avoided are drug metabolism proteins, however. Ekins also outlines efforts to understand why an array of structurally-distinct compounds can block the human ether-a-gogo cardiac channels (hERG), which causes potentially lethal long-QT cardiac syndromes in some patients.

Flexibility

A small number of generalities about molecular promiscuity has emerged. Most promiscuous proteins use a combination of hydrophobic and hydrogen-bonding interactions to bind to substrates and ligands, but most of these proteins are also highly flexible. This flexibility is particularly difficult to handle, as it adds tremendous complexity to the problem of *in silico* modeling of lead compound behavior.

One thing is clear: predicting the lability of compounds in humans is of critical importance to the use of current drugs, the development of new ones, and the potential for tailoring clinical regimen to individuals.

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Obituary of Dr Paul Janssen (1926-2003)

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Dr Paul Janssen passed away on November 11 last year while attending a conference in Rome. He died as he had wished to, suddenly and in the line of his work. He leaves behind a wife, five children and thirteen grandchildren. In the annals of medicinal chemistry he will be remembered as one of the greatest drug designers of all times. His track record is most impressive: 77 original medicines brought to the market and several more awaiting further development, over 850 scientific publications, more than 100 patents registered in his name, 22 honorary doctorates and a score of scientific and civil distinctions and awards. In 1953 he founded a research laboratory that became world famous for its inventiveness and productivity. During the past 50 years Janssen Pharmaceutica, acquired in 1961 by Johnson and Johnson, evolved into a multinational company in its own right, employing about 25,000 people in 43 subsidiaries spread over five continents.

Paul Janssen's major achievements are in the fields of analgesics, psychotropics,

anthelmintics, antimycotics, antihistaminics and gastro-intestinal compounds. He has saved millions of human lives and improved the quality of life of countless people. Five Janssen compounds have been included in the list of essential medicines of the World Health Organization. His products also found application in veterinary medicine, agriculture and material protection.

Many visitors to the Janssen laboratory have often wondered what might have been the key to its success. It certainly could not be found in the buildings and facilities, which were rather austere. Nor did it show in the laboratory equipment, which was home made to a great extent. Many of the initial researchers were self-made persons, often lacking extensive academic qualifications. To a large extent, the success of the laboratory can be attributed to the character and personality of Paul Janssen. He possessed a rare combination of talents, which made him a gifted pharmacologist and chemist, a compassionate clinician and an alert entrepreneur. He possessed the charisma to inspire his collaborators and make them feel part of an enterprise that gave meaning to their life. All addressed him affectionately as Dr. Paul. His memory was legendary, and so was his faculty to discern rapidly between what is important and what is not for bringing new and better medicines to

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