MEDICINAL CHEMISTRY

Shades of chemical beauty

The concept of drug-likeness — which is based on the observation that physicochemical properties of drugs, such as molecular mass and lipophilicity, tend to fall within a relatively narrow range of the possible values — is widely used to prioritize compounds in early-stage drug discovery. Hopkins and colleagues, writing in *Nature Chemistry*, now present a novel approach for assessing drug-likeness that could overcome some important limitations of established approaches and might also better reflect the intuitive assessments of experienced medicinal chemists about the attractiveness of candidate compounds.

Standard approaches for assessing drug-likeness — which are widely used to filter large numbers of compounds to select those for inclusion in screening collections — typically apply several simple pass/fail cut-offs for individual physicochemical properties. For example, a compound would fail the classic Lipinski 'rule of 5' guidelines (Ro5) for oral bioavailability if two or more of the following criteria are met: molecular mass >500 Da; calculated octanol–water partition coefficient (cLogP; a measure of lipophilicity) >5, number of hydrogen-bond donors >5; number of hydrogen-bond acceptors >10.

However, the lack of discrimination of such approaches beyond simply passing or failing on particular properties means that compounds for which all properties are close to the cut-offs are considered to be equal to those that in fact may be much more likely to provide the starting point for a successful drug. Indeed, given that some properties such as lipophilicity may be more important than others, a compound that fails the Ro5 owing to a molecular mass slightly above the cut-off (for example, 502 Da) but has a favourable lipophilicity (for example, cLogP = 2) could be more drug-like than one that passes with properties just inside the limits (for example, molecular mass 499 Da, cLogP = 4.9).

To address this limitation, Hopkins and colleagues developed a measure named quantitative estimate of drug-likeness (QED), whose value ranges between 0 and 1, with 1 being the most drug-like. First, the numerical or categorical physicochemical descriptors of interest (measured on different scales) are described by a desirability function that reflects the extent to which the criterion in question is favourable. These are then integrated into the single dimensionless QED score, and — importantly — the weight that each descriptor has in the integrated value can be altered to reflect the relative importance of the descriptor to drug-likeness.

To assess how well QED could distinguish drugs from non-drugs, the authors compared its performance with other drug-likeness measures by using a set of 771 oral drugs from the DrugBank database as a positive group and small-molecule ligands from the Protein Data Bank as the negative set. QED outperformed the Ro5, as well as all other commonly used measures tested. An advantage of QED is that it provides a way to rank compounds whether they fail the Ro5 or not, and interestingly it was found that oral drugs that fail the Ro5 have QED values over a broad range, from nearly 0 to 0.8.

Additional research provided further support for the use of QED as a transparent and straightforward measure to allow compounds to be more effectively ranked by their relative merit. For example, a survey of medicinal chemists found that QED scores reflected their views on whether members of a large compound set were attractive or not for further progression if they were screening hits. Finally, the authors also suggest that this measure could be used to efficiently prioritize drug targets based on the potential to identify drug-like molecules (assessed by QED) that bind to a site on the target.

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ORIGINAL RESEARCH PAPER Bickerton, G. R. *et al.* Quantifying the chemical beauty of drugs. *Nature Chem.* 24 Jan 2012 (doi: 10.1038/nchem.1243)
FURTHER READING Gleeson, M. P. *et al.* Probing the links between *in vitro* potency, ADMET and physicochemical parameters. *Nature Rev. Drug Discov.* **10**, 197–208 (2011)