MEDICINAL CHEMISTRY

Exploring the third dimension

The importance of certain key properties of molecules, such as molecular mass and lipophilicity, for their potential to be suitable drug candidates has been increasingly appreciated since the publication of Lipinski's 'Rule of 5' guidelines on limits for these drug-like properties in 1997. However, as Lovering and colleagues note in the *Journal of Medicinal Chemistry*, one property that so far has not been directly considered is molecular complexity. By analysing a database of more than two million compounds, sampled from each stage of the drug development process, the authors provide evidence that the complexity of a molecule is a key determinant of success in the transition from discovery, to clinical testing, to approved drugs.

The authors chose two measures to reflect molecular complexity: the extent of bond saturation and the number of chiral centres. The rationale behind this choice was that increased levels of saturation — defined by the fraction of sp^3 hybridized carbons (Fsp^3) — makes the compound more three-dimensional in shape and an increased number of chiral centres increases the number of potential isomers of the compound. Such effects on molecular shape might allow for improved interactions with the target protein, enhancing the potency and/or specificity of the drug candidate and increasing the probability that it will lead to a successful drug. Importantly, these effects are achieved without substantially increasing molecular mass — a key consideration for drug-likeness noted in the Rule of 5.

Using these measures, the authors analysed the GVK BIO database of compounds in various stages of drug development. They found that Fsp^3 increased by 31% from discovery, to Phase I–III clinical trials and eventually to drug status. A comparable increase over the course of development was seen for chiral centres, even when molecules that violated any one of the Rule of 5 parameters were excluded from the analysis. Finally, saturation was shown to correlate with solubility, a physical property that is known to be important for success in drug discovery.

Overall, this study identifies Fsp^3 as a surrogate for molecular complexity that could be used to improve the success of drug development programmes. It also highlights a key limitation of synthesizing chemical libraries for screening by using reactions that link flat aromatic moieties, which have been popular in recent years owing to their amenability to high-throughput parallel synthesis. So, it provides support for the broader application of approaches such as diversity-oriented synthesis to produce architecturally complex candidate drug molecules. Emphasis should therefore be placed on developing further reactions that allow the efficient preparation of such molecules.

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ORIGINAL RESEARCH PAPER Lovering, F., Bikker, J. & Humblet, C. Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **52**, 6752–6756 (2009)

FURTHER READING Leeson, P. D. & Springthorpe, B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nature Rev. Drug Discov.* **6**, 881–890 (2007)