This paper was published in Drug Discovery Today 18(13-14), pp. 659-666 (DOI 10.1016/j.drudis.2013.02.008). In the paper we review the strengths and weaknesses of different definitions of 'drug-like' properties and measures of 'drug-likeness.' We propose an alternative metric the Relative Drug Likelihood (RDL) that identifies the properties with the greatest impact on a compound's likelihood of success for a drug discovery objective.

Abstract

Many definitions of ‘drug-like’ compound properties have been published, based on analysis of simple molecular properties of successful drugs. These are typically presented as rules that indicate when a compounds properties differ significantly from those of the majority of drugs, which may indicate a higher risk of poor outcomes for *in vivo* pharmacokinetics or safety. We review the strengths and weaknesses of these rules and note, in particular, that overly rigid application of hard cut-offs can introduce artificial distinctions between similar compounds and runs the risk of missing valuable opportunities. Alternatively, compounds can be ranked according to their similarity to marketed drugs using a continuous measure of ‘drug-likeness’. However, being ‘similar’ to known drugs does not necessarily mean that a compound is more likely to become a drug and we demonstrate how a new approach, utilising Bayesian methods, can be used to compare a set of successful drugs with a set of non-drug compounds in order to identify those properties whose values give the greatest distinction between the two sets, and hence the greatest increase in the likelihood of a compound becoming a successful drug. This analysis further illustrates that guidelines for ‘drug-likeness’ may not be generally applicable across all compound and target classes or therapeutic indications. Therefore, it may be more appropriate to consider specific guidelines for ‘drug-likeness’ dependent on the objectives of a project.

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