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Ligand efficiency: a useful metric for lead selection

Potency is not the only consideration when selecting a lead compound for further optimization into a drug, but it does hold a powerful attraction to the medicinal chemist. As a general observation, during the process of optimizing a lead to a clinical candidate, the compound usually increases in molecular weight [1–4].

Indeed, potency within a chemical series is often strongly correlated with molecular weight (MW). Interestingly, Lipinski has observed an inexorable rise in molecular weight for both Pfizer (http://www.pfizer.com) and Merck (http://www.merck.com) clinical candidate compounds over the past 30 years [5] and this could represent a general industry trend following the introduction of HTS and structure-based drug design.

Despite the inexorable rise in the molecular weight of clinical candidates, the mean MW of drugs (and other 'rule-of-five' [6] violations) in clinical development declines in each subsequent stage to market [7,8]. Therefore, reducing the MW of leads and clinical candidates might have an important role in reducing attrition rates in drug development. Potency is an important criteria for assessing leads (or 'hits') discovered in HTS, however, potency alone is often a false prophet. Indeed the screening parameters, reagent concentrations and false-positive filters make the detection of weak, low MW leads unlikely in the configuration of many high-throughput screens. The bias of the screen towards high MW compounds has often confounded further optimization because increases in potency often track increases in MW, resulting in compounds falling outside of the profile for acceptable absorption and permeability properties [3,9]. Thus, a simple 'ready reckoner', which could be used to assess the potential of a weak lead to be optimized into a potent, orally bio-available clinical candidate, can be of use to the practicing medicinal chemist.

We propose that the simple concept of the binding energy per atom or binding 'efficiency' of a ligand could be a useful parameter in the selection of a lead compound and in the optimization process. The concept of analyzing ligand binding in terms of the free energy per atom was first proposed by Andrews *et al*. [10]. The 'Andrews binding energy' of a compound indicates a theoretical binding potential based on the particular functional groups present, from a statistical analysis of a limited set of drugs. However, for practical use in 'hit' and lead assessment we recommend the application of the actual experimental binding affinity per atom proposed by Kuntz *et al.* [11]. The calculation of the binding energy of the ligand per atom, or 'ligand efficiency' (Δg) is a simple parameter, which might be useful in lead assessment and which can be calculated by converting the K_d into the free energy of binding [Eqn 1] at 300K and dividing by the number of 'heavy' (i.e. non-hydrogen atoms) atoms [Eqn 2]:

Free energy of ligand binding:

$$\Delta G = -RT.\ln K_d \qquad \text{[Eqn 1]}$$

Binding energy per atom (ligand efficiency):

$$\Delta g = \Delta G / N_{\text{non-hydrogen atoms}} \qquad \text{[Eqn 2]}$$

The logarithmic relationship between free energy of binding and dissociation constant potency means that every ΔG change of –1.4 kcal mol^{-1} results in a 10-fold change in potency. Kuntz *et al.* surveyed the dissociation or IC_{50} values of ~150 ligand complexes and concluded that the maximum affinity per atom for organic compounds is –1.5 kcal mol^{-1} per non-hydrogen atom. The medicinal chemistry phenomenon of 'magic methyls', the addition of a single methyl group increasing potency by 10-fold, is explained in terms of the maximum achievable from burying the surface area of a single 'heavy' atom. Ligand efficiency is a way of normalizing the potency and MW of a compound to provide a useful comparison between compounds with a range of MWs and activities. Thus, ligand efficiency might be a more useful concept than Andrews binding energy in assessing the druggability of leads and targets. In practice, we have found that IC_{50} and extrapolated IC_{50} values from percentage inhibition can be substituted for K_d for the purpose of relative comparison.

The vast majority of medicinal chemistry compounds have efficiencies far below the observed maximal affinity per atom. A simple calculation can define the lowest limits acceptable for

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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.

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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