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Practical application of ligand efficiency metrics in lead optimisation

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ABSTRACT

The use of composite metrics that normalise biological potency values in relation to markers of physicochemical properties, such as size or lipophilicity, has gained a significant amount of traction with many medicinal chemists in recent years. However, there is no consensus on best practice in the area and their application has attracted some criticism. Here we present our approach to their application in lead optimisation projects, provide an objective discussion of the principles we consider important and illustrate how our use of lipophilic ligand efficiency enabled the progression of a number of our successful drug discovery projects. We derive, from this and some recent literature highlights, a set of heuristic guidelines for lipophilicity based optimisation that we believe are generally applicable across chemical series and protein targets.

1. Introduction

The need to balance potency and physicochemical properties during medicinal chemistry optimisation is well established.[1–3] Undesirable values of simple physicochemical descriptors such as lipophilicity (logP, $logD_{7.4}$) and size (molecular weight, heavy atom count) are associated with poor absorption, distribution, metabolism, elimination and toxicity (ADMET) properties such as low solubility, high metabolic clearance and increased activity at toxicological targets such as the human ether-à-go-go-related gene (hERG) channel.[4] Nevertheless, medicinal chemists often continue to contend with large lipophilic compounds during optimisation because these typically bind well to protein targets and are therefore more likely to be found as a result of hit finding activities. This is not necessarily a catastrophic situation provided medicinal chemists are aware of the fact and can conceive of strategies to address the shortcomings of their leads and evolve them towards more desirable regions of physicochemical space.

Crude approaches to physicochemical optimisation involve the application of cut-off values for molecular weight and logP/D values such as Rule-of-5 criteria (MWt < 500, logP < 5).[5] Because potency often increases with lipophilicity and molecular weight, the concept of normalising a biological potency value by descriptors of size, such as heavy atom count (HA) in the case of ligand efficiency (LE, Eq. (1)), or lipophilicity (lipophilic ligand efficiency, LLE or LipE, Eq. (2)) have been introduced.[6] This initial concept has been expanded in an attempt to combine multiple parameters such as size and lipophilicity (ligand efficiency dependent lipophilicity, LELP, Eq. (3)).[7]

$$LE = -2.303(RT/HA) \times logK_d = (1.37/HA) \times pIC_{50} \quad (1)$$

$$LLE = pIC_{50} - logD_{7.4} \quad (2)$$

$$LELP = clogP/LE \quad (3)$$

These concepts have attracted some criticism, chiefly due to their lack of thermodynamic basis and their underlying assumptions about the baseline relationships between their components; for example that potency should increase linearly with heavy atom count in the case of LE and that the relationship between potency and logD is linear with a slope of unity for LLE.[8,9] These are valid considerations and make the combined assumptions that go into LELP hard to justify. The question about the validity of the metrics continues to attract debate.[10]

2. Selection of metrics

One important consideration is that composite metrics have been employed for two different purposes. Firstly, they have been used to facilitate comparison between different chemical series, for example to compare screening hits from different chemical series which differ from each other in their size or lipophilicity in order to determine which is most attractive. Secondly, they have been

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applied to the assessment of how a small structural change within a chemical series affects potency relative to its concomitant change in size or lipophilicity. Qualitatively, these are both reasonable and helpful questions to ask. We also contend that quantitative metrics such as LE and LLE are useful in informing these decisions and their application is valid provided one is aware of their assumptions and limitations.

The focus of the majority of the research we describe here relates to lead optimisation and so we are concerned primarily with the assessment of structural changes within a series. In that regard, we have found that LLE is the most helpful optimisation parameter since, in our experience, compound optimisation has primarily been concerned with the reduction in lipophilicity of compounds which were sufficiently potent, in order to improve their ADMET properties. In that regard, we have generally not been examining changes that significantly altered the size of the compounds and hence LE has been uninformative. Moreover, we were inherently attracted to the use of LLE as a metric because of the firm belief that muti-parameter optimisation can be greatly simplified by focussing on the design of potent compounds with low lipophilicity due to the propensity of the majority of ADMET properties to be compromised when lipophilicity is high.[4] Secondly, it is reasonable to assume that for a small molecule binding to a hydrophobic protein pocket, potency will show a positive, linear relationship with lipophilicity in the absence of any differences in polar interactions between compounds. This assumes that all compounds are within a suitable applicability domain, i.e. where the potency assay being used gives values that correlate with free energy and where lipophilicity can be measured accurately and is within an established range. It is critical to establish as far as is reasonably practical that this is the case for the compounds in question. Finally, the central assumption of the LLE parameter is that potency and lipophilicity not only correlate but do so with a slope of unity. We believe this to be a reasonable assumption but would emphasise that LLE values should not be interpreted in isolation and should be considered in the context of the absolute potency and lipophilicity changes for a given transformation within a series and an analysis of the overall trend in the data, considering compounds where lipophilicity is likely to change in the absence of other binding events.

Because the majority of ADMET properties correlate negatively with lipophilicity, the compounds with the optimal overall profile within a series would be expected to be those that were the most potent with the lowest lipophilicity i.e. highest LLE. The one, and often only, exception to this trend is permeability, which generally decreases as lipophilicity decreases. Hence, a critical component of the strategy of lipophilic optimisation is to establish the lipophilicity limit, for the series in question, at which permeability becomes too low. The position of this limit is dependent on a number of factors including size and hydrogen bonding,[11] hence our primary strategies for compound optimisation have been based on the idea of achieving the highest possible potency with lipophilicity values as low as the permeability limit allows.

These concepts are easy to state and many articles have highlighted the value of property based optimisation and lipophilicity control.[2,12,13] There has been relatively little discussion, however, on how these principles might be implemented in practice within projects[14] with the majority of examples restricted to individual reported studies in which the focus of the discussion is the specific outcome of the optimisation and not the implementation of the approach. Here we discuss our implementation of LLE based optimisation across a range of projects, many of which led to clinical candidates. Importantly we highlight structural changes that led to improved LLE and were critical steps in project progression. We believe that many of these experiences are generically applicable and will be of use in future optimisations.

3. Measurement

One factor, which we consider of critical importance for LLE based analysis is to use measured lipophilicity values and not rely on calculated values. It is well established (but perhaps not widely appreciated) that calculated logP figures often vary significantly (with an average error of more than one log unit on average) from the true values.[14] This variation is sufficient to render LLE's derived from calculated values meaningless. The requirement to measure $logD_{7.4}$ values clearly requires extra experimental work, and the extra resource required may not be available to all researchers, but we would recommend that if possible, it is worth the investment for high resolution interpretation of structure activity relationships (SAR). The use of chromatographic methods for determining lipophilicity values[15] may reduce the resource requirement to obtain measured values.

We encountered a prominent example of this phenomenon in our optimisation of G-protein coupled receptor 119 (GPR119) agonists for which three oxadiazole isomers were shown to have very different $logD_{7.4}$ values, which were not predicted correctly (Fig. 1). In this case, using calculated (clogP) values would have led to the conclusion that compound **1** had the highest LLE, whereas the $logD_{7.4}$ values show that **2** has the highest. Consequently, we can conclude that **1** is gaining its superior potency through increased lipophilicity and that **2** and **3** should offer a better balance of potency and physicochemical properties. The lower $logD_{7.4}$ of **3** overall results in the most improved solubility and hERG potency.

The above example deals with predominantly neutral compounds (no significant ionisation at pH 7.4) and so the $logD_{7.4}$ values are not significantly different to their logP values. The difference between $logD_{7.4}$ and clogP is due solely to inaccuracies in the clogP calculation. Ionisation may be significant for some chemical series and this needs to be considered in the application of LLE. Use of $logD_{7.4}$ to derive LLE makes the assumption that binding of the ionised form to the target protein is negligible, which may be reasonable but needs to be considered if comparing compounds with differing pK_a values that are close to 7.4 (±1). This introduces a second problem with using calculated values because simple pK_a calculations can also carry significant errors.

4. Correlations

As stated in the introduction, a central assumption of the LLE metric, and a critical one to address if considering compounds across a range of lipophilicity values, is that the correlation between the selected measures of potency and lipophilicity is linear with a slope of unity, e.g. a unit increase in $logD_{7.4}$ leads to a unit increase in pIC_{50}, in the absence of any additional interactions. We believe this is a reasonable assumption for a drug binding to a lipophilic pocket, after all, logD is intended to quantify the energy associated with a compound transferring from an aqueous to a lipophilic environment, but it should always be remembered that the chosen organic phase in the logD experiment (usually 1-octanol) is only a crude surrogate of a protein pocket. It is necessary to analyse the SAR to build confidence that the assumption holds for the target in question. This is difficult, if not impossible, to do with absolute certainty because the majority of structural changes, such as additions of substituents to lead molecules, would be expected to change many other parameters to a varying degree in addition to lipophilicity and it is not possible to vary lipophilicity independently of other molecular properties – a significant problem with QSAR analyses in general. A recent analysis of >2000 pairwise changes demonstrated that addition of a single methyl group, perhaps the simplest structural change that can be made and one that would lead to an increase in logP of ~0.5 on