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The thermodynamic basis for the use of lipophilic efficiency (LipE) in enthalpic optimizations

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ABSTRACT

Approaches to improve the efficiency of molecular optimizations have received great attention and numerous efficiency metrics have been introduced to assist in this effort. Optimization of properties is equally important to optimization of potency and therefore these metrics contain potency versus property calculations. Widespread use of a metric does not guarantee its accuracy and a further understanding of which, if any, metric increases the probability of success was sought. An analysis of LE, LELP and LipE based on theoretical and experimental data was performed demonstrating that LipE most strongly correlates with compound quality as defined by enthalpy-driven binding. The basis for the prioritization of LipE over other metrics in enthalpic optimizations is described.

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To assist in the optimization of drug-like molecules, multiple composite parameters (or efficiency indices) have been proposed (Table 1).[1–10] While the motivation for this effort is commendable and the need is great, it can be overwhelming for even highly experienced medicinal chemists to decide which metric, if any, to use and when. There has been a great deal of study on which physicochemical are most critical and from these studies lipophilicity ($\log P$ or $\log D$) appears most highly correlated with a variety of ADME and toxicological outcomes, with molecular weight (MW) or heavy atom count (HAC) having significant, but fewer correlations.[11–15] Therefore, controlling for lipophilicity and MW during optimizations has been a key goal of many medicinal and computational chemists.

Efficiency metrics are simple mathematical functions hypothesized to provide a measure of how efficiently potency is achieved relative to another calculated or measured variable (Table 1). They are hypothesized to enable chemists to increase the probability of success by shifting from potency-centric decision making to multi-parameter optimization. Three widely used metrics were examined: ligand efficiency (LE = $1.4^{*}\mathrm{pIC_{50}}$/HAC), lipophilicity dependent ligand efficiency (LELP = $c\log P$/LE) and lipophilic efficiency (LipE = $\mathrm{pIC_{50}} - \log \mathrm{D}$). While the hypothesis that binding energy per atom (LE) will normalize potency for molecular weight is plausible, the original LE function ($1.4^{*}\mathrm{pIC_{50}}$/HAC) has been disproven for a variety of reasons.[8,10,16–18] A size independent ligand efficiency (SILE) function has also been proposed and adopted, despite also having a size dependency.[18] Care must be taken when accepting any metric for which only positive data is published since there is a greater incentive for highlighting compounds that conform to these new metrics versus compounds that appear to be 'inefficient'. The resulting availability bias leads to an illusion of validity where these efficiency metric hypotheses are treated as fully validated theories. It is important that attempts to disprove all efficiency metrics are pursued so that improvements to these mathematical functions can be made. Those metrics that cannot be readily disproven and have been evaluated thoroughly may be used with greater confidence and understanding. This manuscript attempts to understand why LipE was resistant to previous invalidation efforts and probe additional limitations that were not previously described.[18] The result should be greater utilization or more validated metrics and the goal of enhancing the probability of success may eventually be realized.

It was during efforts to identify and optimizes tankyrase (TNKS) inhibitors that our project team at Novartis attempted to evaluate several composite parameters in real time and determine which, if any, could be disproven.[19] We quickly determined that the use of more efficiency indices was less efficient due to conflicting interpretations of data. This is in line with many observations where pursuing non-instrumental information decreases decision making.[20] We were likewise less comfortable utilizing metrics that were supposedly valid for only certain 'phases' of drug discovery as these 'phases' are corporate and not scientific taxonomies. Early on, we evaluated the use of LipE for decision making and concluded this to be the most robust, consistent and meaningful metric available, a view that has been supported by others.[21] Our efforts

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Table 1
Common composite parameters used as efficiency metrics. Note that lipophilic efficiency is the only metric not dependent on heavy atom counting.

	Efficiency metric	Potency-property function
LE	Ligand efficiency	$1.4*pIC_{50}$[a]/HAC
%LE	Maximal ligand efficiency	(LE/max LE)*100
SILE	Size independent ligand efficiency	$1.4*pIC_{50}$[a]/$HAC^{0.3}$
LE_scale	Scaled ligand efficiency	$0.0715 + 7.5328/HA + 25.7079/HA^2 - 361.4722/HA^3$
FQ	Fit quality	LE/LE_scale
BEI	Binding efficiency index	pIC_{50}[a]/MW
GE	Group efficiency	$-\Delta pIC_{50}$[a]/ΔHAC
SEI	Surface efficiency index	pIC_{50}[a]/(PSA/100 Å^2)
Fsp^3	Fraction sp^3	#sp3/total #carbon
LLE_{AT}	Astex ligand lipophilic efficiency	$0.11 - [\ln(10)*RT(\log P - pIC_{50})/HAC]$
LELP	Lipophilicity dependent ligand efficiency	$c\log P$/LE
LipE	Lipophilic efficiency	pIC_{50}[a] – $c\log P$[b]

[a] pIC_{50}, K_d, K_i are often used interchangeably.
[b] Log*P*, *c*log*D* and log*D* are often used interchangeably.

to disprove the hypothesis for utilizing LipE have been entirely unsuccessful and spurred questions as to why this metric appeared the most resilient. From TNKS and other internal programs, we observed that compounds with high LipE had the behavior of compounds with enthalpy-driven binding (highly[20] selective with favorable physicochemical and safety profiles) while low LipE compounds had small or unmeasurable enthalpy of binding and were typically highly promiscuous. A hypothesis for these observations and a rationale for the use of LipE during all phases of drug discovery is detailed herein.

In the preceding manuscript it was determined that the expected change in potency for a matched molecular pair (MMP) was reproducible using a LipE analysis.[18] In contrast, HAC based composite parameters such as LE and LELP were found to have variable expectations for MMPs that were dependent on the MW, lipophilicity and potency of the reference compound of the MMP. Additionally, this analysis did not find a single case when LE, LELP or LipE were in agreement with one another as to how much potency should be expected when comparing identical transformations. When two or more composite parameters provide opposing interpretations of when a particular molecular modification is favorable, it begs the questions which composite parameter is 'correct' (if any) and why? For example if a polar group is added to a molecule that reduces potency tenfold, but decreases lipophilicity 100-fold, LipE would improve by an order of magnitude, while LE would necessarily diminish.[22] The lack of consistent expectations with HAC based composite parameters was found to be due to invalid mathematical functionas and flaws in the assumption of a potency-HAC relationship.[18] A useful efficiency metric would be one that identifies favorable modifications, defined as one that improves specific ligand–protein interactions, to be retained for subsequent rounds of molecular optimizations, especially if it is non-intuitive (e.g. decreased potency). LipE is more highly correlated with successful optimizations, has constant expectations under all optimization settings and has not (yet) been invalidated.[14,18,23–25] Therefore, there might be a more fundamental, thermodynamic basis for the utility of LipE.

Thermodynamic considerations of composite parameters: There is an emerging opinion that optimization of binding enthalpy will lead to higher quality drug candidates[26,27] but the rational optimization of enthalpy remains challenging.[28] The thermodynamics of protein–ligand interactions has been extensively covered and a simplified depiction is shown in Figure 1. The thermodynamic states of protein–ligand interactions are simple to visualize but incredibly difficult to predict with accuracy. Ligand solvation, or hydration energy, is a balance between a favorable enthalpic component between polar atoms, such as hydrogen bonding and dipolar interactions (ΔH_{solv}), and a negative entropic component due to the hydrophobic effect (ΔS_{solv}).[29–31] The hydrophobic effect is generally believed to be due to the increased entropy resulting from the release of an ordered solvation shell surrounding the ligand upon binding, but in reality the hydrophobic effect may still be an unresolved thermodynamic problem.[32–35] To leave the aqueous environment a molecule must dissociate from the surrounding bulk solvent with a corresponding enthalpic penalty and an entropic gain (ΔH_{solv} and ΔS_{solv}, respectively). Protein–ligand binding involves a favorable enthalpic component dominated mainly by hydrogen bond, electrostatic and favorable van derWaals interactions (ΔH_{bind}) and an entropic penalty due to reduced conformational, translational and rotational freedom upon binding (ΔS_{bind}). Depending on the protein of interest, there can be entropic and enthalpic components contributed by the protein due to loss of bound water molecules,[36,37] changes in conformational entropy, etc. but this will be ignored for simplicity.

Recent work has brought composite parameter analysis to bear on enthalpic optimization.[24,38,39] Previous studies demonstrated a non-linearity of ligand interactions as a function of molecular size[40] and Reynolds et al., have shown that there is no correlation between HAC and ΔH or ΔS of binding.[39] To account for size, Ferenczy et al. defined a size-independent enthalpic efficiency (SIHE) that accounts for their finding that enthalpic effects decrease and entropic effects increase with molecular size.[38] Their conclusions and the derivation of SIHE deserve further consideration. They started with the well-known relationship between binding free energy (ΔG_{assoc}) and K_d:

$$\Delta G_{assoc} = RT\ln K_d = \Delta H - T\Delta S \quad (1)$$

ΔG can be expressed in terms of enthalpy and entropy which results in:

$$\ln K_d = \frac{\Delta H}{RT} - \frac{\Delta S}{R} \quad (2)$$

Eq. (2) can then be rewritten as

$$pK_d = \left[\frac{-\Delta H}{2.303 \cdot RT}\right] + \left[\frac{\Delta S}{2.303 \cdot R}\right] \quad (3)$$

Using the definitions of Ferenczy et al. for the enthalpic component (pK_H) and the entropic component (pK_S)

$$pK_H = \left[\frac{-\Delta H}{2.303 \cdot RT}\right] \quad (4)$$

$$pK_S = \left[\frac{\Delta S}{2.303 \cdot R}\right] \quad (5)$$

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