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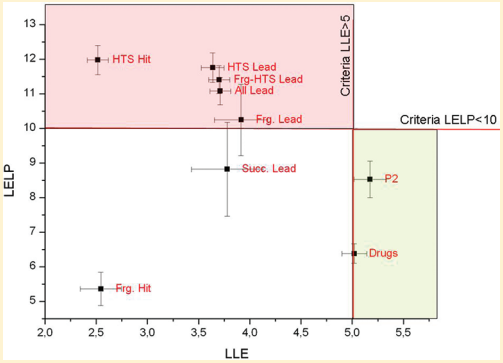
Impact of Lipophilic Efficiency on Compound Quality

Ákos Tarcsay, Kinga Nyíri, and György M. Keserű*

Discovery Chemistry, Gedeon Richter plc, 19-21 Gyömrői út, H-1103 Budapest, Hungary

Supporting Information

ABSTRACT: Lipophilic efficiency indices such as LLE and LELP were suggested to support balanced optimization of potency and ADMET profile. Here we investigated the performance of LLE and LELP on multiple data sets representing different stages of drug discovery including fragment and HTS hits and leads, development candidates, phase II compounds, and launched drugs. Analyzing their impact on ADME and safety properties and binding thermodynamics, we found that both LLE and LELP help identifying better quality compounds. LLE is sensible for the development stages but does not prefer fragment-type hits, while LELP has an advantage for this class of compounds and discriminates preferred starting points effectively. Both LLE and LELP have significant impact on ADME and safety profiles; however, LELP outperforms LLE in risk assessment at least on the present data set. On the basis of the results reported here, monitoring lipophilic efficiency metrics could contribute significantly to compound quality and might improve the output of medicinal chemistry programs.



INTRODUCTION

Lipophilicity is one of the crucial parameters used in drug discovery.[1] Measured as the logarithm of the octanol−water partition coefficient (log *P*) or as the pH-dependent distribution coefficient (log *D*), it contributes to potency,[2] has an inevitable role in selectivity and promiscuity,[3] affects compound solubility, determines the passive permeability of small molecules through biological membranes,[4] impacts drug metabolism and pharmacokinetics,[5] and influences adverse effects and compound-related toxicity.[6] It has been recently shown that lipophilicity has therefore a major impact on compound quality routinely assessed at the milestones of the discovery process including identification of chemical starting points, viable chemical leads,[7] and development candidates.[3] The low variance of lipophilicity over the past decade of drug candidates and marketed drugs also underscores its central role in drug discovery settings.[8] On the other hand, however, lipophilicity is, contrary to successful lead optimizations,[9] typically increasing along optimization paths, and this undesired shift is a major factor for the well documented inflation of physicochemical properties[2,3,7,10] observed in most medicinal chemistry programs. Because multidimensional optimization toward oral drug candidates should deliver compounds with log *P*/log *D* between −1 and 3[3−6] this relatively narrow range requires the effective control of lipophilicity. In addition to basic parameters such as log *P*/log *D* or related measures (e.g., log *k*), lipophilic efficiency indices provides a straightforward and meaningful way to control lipophilicity. A vast amount of project data indicate that the quality of hits and leads have a decisive effect on the fate of the chemotype in lead optimization and preclinical development. There is an increasing consensus[2,3,11,12] that efficacy indices typically used for ranking compounds or chemotypes can significantly support medicinal chemistry programs in delivering high quality candidates.

Lipophilic ligand efficiency (LLE) introduced by Leeson and Springthorpe is a typical example of efficacy indices.[3] Defined as the difference of log *P* (or log *D*) and the negative logarithm of a potency measure (pK_d, pK_i, or pXC_{50}), LLE describes the contribution of lipophilicity to potency. Compounds with reduced complexity (e.g., fragments and leadlike chemical matter) are typically polar compounds often with limited potency that makes their LLE less desirable. As a consequence, comparative evaluation of these compounds, that are otherwise considered to be promising, is challenging. This limitation of LLE is due to the neglected effect of ligand size that calls for an alternative metrics. The concept of lipophilicity-corrected ligand efficiency was first realized by LELP,[7] defined as the ratio of log *P* and ligand efficiency (LE) that therefore depict the price of ligand efficiency paid in log *P*. LELP is meaningful for log *P* values typical in most of the discovery programs and allows the evaluation of both fragments, leadlike and druglike compounds. Although LELP has its own limitation for compounds with log $P < 1$, due to the correlation of log *P* with molecular mass project compounds generally do not possess large heavy atom count with low log *P*. This might be the case for natural products that are therefore out of the scope of comparative LELP evaluations.

Efficiency metrics have been recently evaluated on a set of CNS drugs and candidates indicating[13] that unlike LE and LLE, LELP was able to discriminate development candidates and

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marketed drugs. Furthermore, these authors found that all of the investigated Pfizer candidates possessing suboptimal LELP values had been terminated along the drug discovery/development pathway. The unprecedented performance of LELP prompted us to investigate lipophilic efficiency metrics LLE and LELP in a large and diverse data set that includes fragment hits and corresponding leads, HTS hits and corresponding leads, successful leads, compounds that entered phase II trials, candidates, and drugs. These studies revealed that both LLE and LELP have a unique character when assessing the lipophilic efficiency at different stages of drug discovery and that these evaluations could contribute significantly to the overall quality of candidate drugs.

METHODS

Lipophilic efficiency metrics, LLE and LELP, have been evaluated from three different perspectives: (i) lipophilic efficiency in medicinal chemistry optimizations; (ii) impact of lipophilic efficiency on ADMET properties; (iii) the role of lipophilic efficiency in optimization strategies including conventional scheme guided and thermodynamics guided approaches.

Eight compound sets have been compiled such as fragment hits, corresponding leads, HTS hits and corresponding leads, successful leads, compounds that entered phase II trials, development candidates, and marketed drugs. Fragment hits (N = 100) and leads (N = 95) were obtained from the literature,[14−17] and HTS hits (N = 319) and HTS leads (N = 319) were collected by Keserű and Makara.[7] Successful leads were reported by Perola et al. (N = 60).[9] Drugs and phase II (P2) compounds, which entered P2 trials, were collected from Thomson Reuters Integrity database[18] using the criteria of marketed drugs or the furthest trial being phase II, respectively, and having experimentally measured affinity on human "enzyme", "receptor", or "channel" targets and data that was published after 1960 (N = 210). Drugs downloaded from Thomson Reuters Integrity database were added to drugs reported by Perola et al.[9] and Wager et al.[13] Finally, this collection of marketed drugs was focused on those administered orally (N = 302). Data sets are available from the original papers and in Thomson Reuters Integrity database.

The octanol−water partition coefficient (log P) was calculated by the property calculator (cxcalc) of ChemAxon, version 5.3.6.[19] In the case of the ADME and safety analysis, we used the whole data set published by Wager et al., including LELP and LLE values, because the candidate structures were not disclosed. In all other cases, LELP was calculated by the number of heavy atoms times log P divided by the binding free energy. Binding free energies were calculated by the $\Delta G = RT \ln(\text{potency})$ formula, where potency was estimated by the available K_i or IC_{50} values. Graphs and statistical analysis was carried out by Origin 7 (OriginLab, Northampton, MA) and Statistica 9 (StatSoft, Tulsa, OK).

LIPOPHILIC EFFICIENCY IN MEDICINAL CHEMISTRY OPTIMIZATIONS

Hit to Lead Optimization. Our first objective was to investigate the two lipophilic efficiency metrics LLE and LELP, in preclinical settings. Five data sets such as fragment hits and leads, HTS hits and leads, and leads of marketed drugs, so-called successful leads, were collected from literature sources. Despite the sharp difference in the mean log P, low LLE values were found for both fragment and HTS hits (2.5 and 2.5, respectively; see Figure 1 and Supporting Information Table 1). Similar values are due to the generally lower potency and log P of fragment hits and the usually higher potency and log P of HTS hits. HTS leads had mean LLE values similar to that of the successful leads, while fragment leads possessed somewhat higher values, 3.6, 3.8, and 3.9, respectively. Both HTS and fragment hits had significantly lower mean LLE values

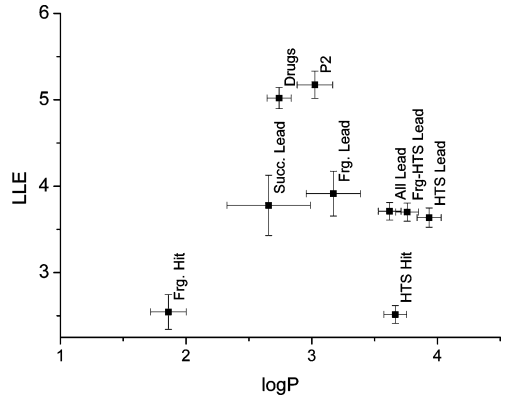

Figure 1. LLE−log P plot of the investigated subsets. All data are mean values with error bars representing standard errors.

compared to that of fragment, HTS, and successful leads. Hit-finding strategies investigated here provided similar LLE, because there was no separation between fragment hits and HTS hits, or fragment leads and HTS leads. Analyzing average LLE data on the horizon of a typical discovery project, we found that (i) mean LLE values were in line with research stages (hit and lead), (ii) LLE was not sensitive for hit discovery approaches, and (iii) LLE did not differentiate successful leads from other leads. Analysis of the corresponding LELP values revealed that the fragment hits have the lowest mean LELP value of 5.4, which was followed by successful leads (mean value of 8.8) and fragment leads (mean value of 10.2) (Figure 2). Somewhat higher mean LELP values were observed

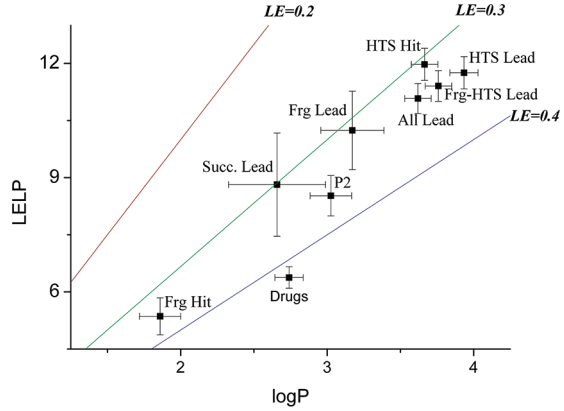

Figure 2. LELP−log P plot of the investigated subsets. All data are mean values with error bars representing standard errors. Lines marked as LE = 0.2, LE = 0.3, and LE = 0.4 are LE isovalues calculated from LELP and log P data.

for HTS leads (mean value of 11.8) and HTS hits (mean value of 12.0). A significant LELP difference ($p < 0.05$) could be observed as fragment hits were compared to fragment leads, HTS hits, HTS leads, and successful leads. Changes in LELP were also significant, comparing successful leads and HTS hits or HTS leads. Focus on the HTS hits and leads led to an improvement in the mean LE; meanwhile, log P was increased, and LELP did not change. On the contrary, hit to lead optimization of fragments slightly decreased the mean LE, increased log P, and consequently markedly increased the mean LELP. Increasing LELP values associated to hit to lead optimizations indicate that potency optimization at this phase

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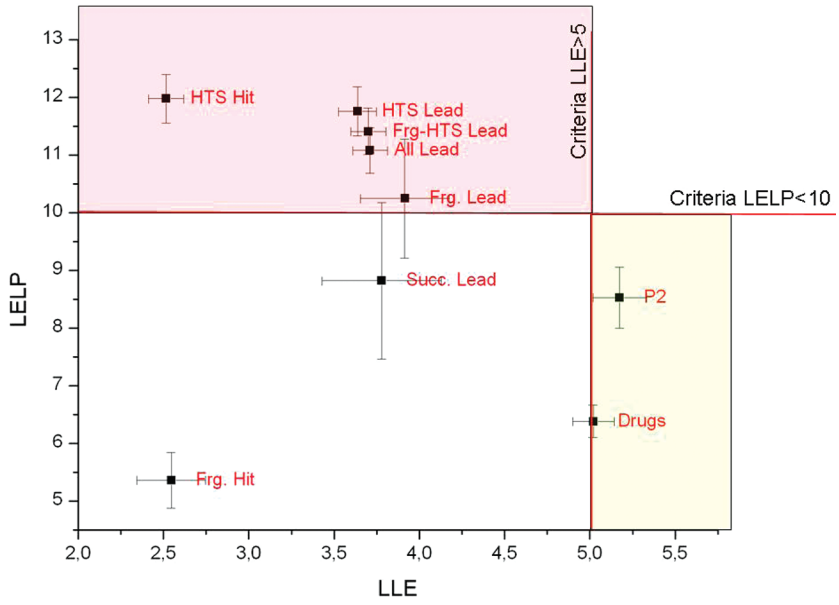

Figure 3. LELP versus LLE for the different subsets investigated. All data are mean values with error bars representing the standard error values.

is typically performed at the expense of lipophilicity. Our analysis points out that hit and lead data sets can be categorized into three groups including fragment hits, successful leads, and the most populated group consisting HTS hits, fragment leads, and HTS leads. Our interpretation is that (i) fragment hits have unique and desirable lipophilic efficiency, (ii) successful leads still have proper mean LELP values and they can be distinguished from HTS and fragment hits and fragment leads, (iii) fragment leads have LELP typically better than that of the HTS leads, (iv) lipophilic efficiency of HTS hits is pretty much similar to that of the HTS leads.

Lead Optimization. Starting from a viable lead, the primary objective of lead optimization is the identification of a development candidate suitable for a first in man study. Investigating the impact of lipophilic efficiency on lead optimization, we considered further subsets including compounds that had entered phase II trials (P2 compounds) and marketed drugs both having an acceptable ADME and pharmacokinetic profile in man. At this stage of the analysis, we used the following subsets: (i) successful leads, (ii) fragment leads, (iii) HTS leads, (iv) fragment + HTS leads, and (v) all leads (fragment + HTS + successful leads). Successful leads, fragment leads, fragment + HTS leads, and all leads had mean LLE values of 3.8, 3.9, 3.3, 3.7, and 3.7, respectively, while the P2 compounds and launched drugs possessed LLE values of 5.2 and 5.0, respectively (Figure 1). Figure 1 indicates that P2 compounds and marketed drugs have LLE much better than that of the leads from any source. Interestingly, we found that LLE does not discriminate between successful leads and all leads, and P2 compounds and drugs. Focusing on the discovery process, we clearly distinguished the development stages by their LLE values, but mean LLE shows virtually no difference between the lead subsets considered in this study. In the case of LELP, successful leads, fragment leads, HTS leads, fragment + HTS leads, and all leads had mean values of 8.8, 10.2, 11.8, 11.4, and 11.1, respectively (Figure 2). P2 compounds and marketed drugs showed mean LELP of 8.5 and 6.37, respectively. From a process perspective, a gradual, monotonic decrease in LELP can be observed in the course of HTS leads, fragment + HTS leads, fragment leads, all leads, successful leads, P2 compounds, and marketed drugs. Most importantly, successful leads had a mean LELP value significantly lower than that of the fragments leads, HTS leads, and their combination. The mean LELP of successful leads was similar to that of the P2 compounds and strikingly higher than that of the marketed drugs. In fact, the latter's have a LELP profile similar to that of the fragment hits. In summary, both LLE and LELP showed strong correlation with the development phase, and despite LLE, LELP was able to discriminate between lead discovery strategies and could differentiate successful and all the other leads. Consequently, LLE and LELP monitor the improvement of compound quality along the discovery path effectively. Pairwise comparison of corresponding LLE and LELP values separates leads, successful leads from P2 compounds, and marketed drugs (Figure 3), suggesting that LLE- and LELP-based assessment of compound quality directs discovery programs toward the desirable drug space.

Impact of Lipophilic Efficiency on ADMET Properties. Analyzing Pfizer candidates and marketed drugs, Wager et al. conducted an elegant study to explore the chemical space of CNS drugs.[13] This work spanned from descriptive analysis of physicochemical profiles via alignment of ADME and safety attributes until comparison of efficiency indices of the two databasets. These authors found that LELP, unlike LLE and LE, was able to discriminate drugs from candidates. This observation prompted us to investigate the impact of lipophilic efficiency on ADMET properties in depth. To achieve this goal, the in vitro ADME and safety attributes of all compounds mentioned in ref 13 were pooled together. Lipophilic ligand efficiency metrics (LLE and LELP) were analyzed in the context of three pharmacokinetic and three safety parameters such as passive apparent permeability, P-glycoprotein efflux liability, unbound intrinsic clearance and inhibition of CYP2D6 or CYP3A4 enzymes, inhibition of the hERG potassium channel, and cell viability. In fact, we challenged LLE and LELP in separating the compounds with attractive or undesirable in vitro properties, as these features are crucial when selecting candidates with favorable pharmacokinetic and safety profile.

First, we focused on pharmacokinetics-related features such as permeability, microsomal stability, and active transport

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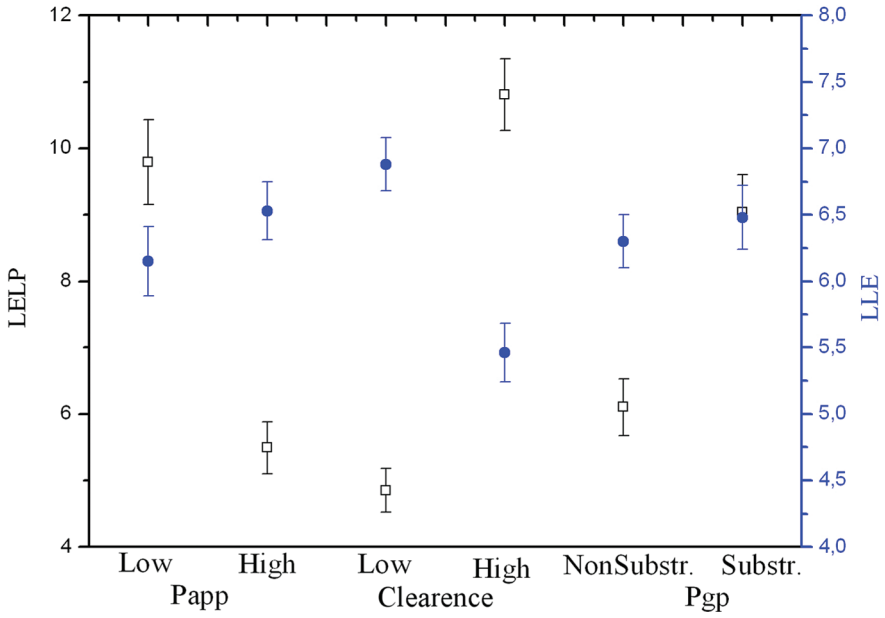

Figure 4. Lipophilic efficiency metrics (LELP and LLE) versus in vitro measured pharmacokinetic parameters. All data are mean values with error bars representing the standard error values.

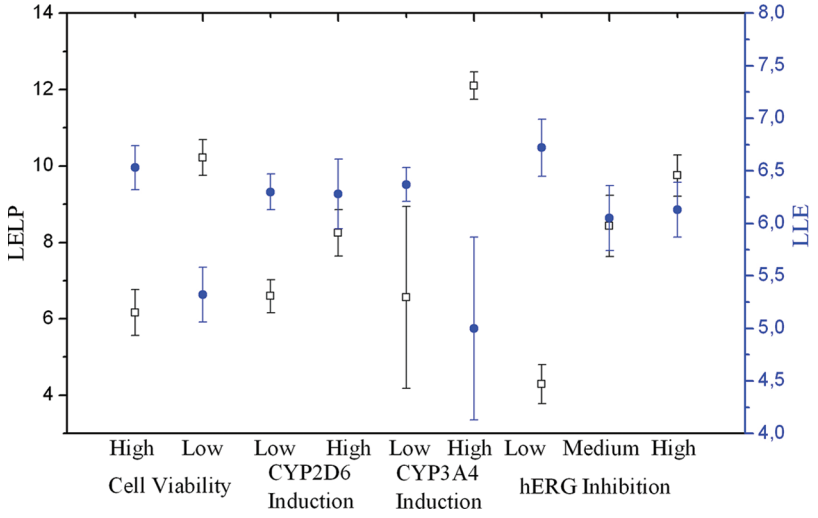

Figure 5. Lipophilic efficiency metrics (LELP and LLE) versus in vitro measured safety parameters. All data are mean values with error bars representing the standard error values.

properties. Permeability has a dominant role in adsorption and distribution. It is routinely assessed in vitro using epithelial cell lines that spontaneously form a confluent polarized monolayer, thereby serving as a feasible model for the assessment of epithelial transport. Wager et al. classified compounds as having low, moderate, and high permeability based on their P_{app} values < 2.5, 2.5 < P_{app} < 10 and P_{app} > 10 (units are 10^{-6} cm/s), respectively.[13] Here, compounds with low and moderate permeability have been pooled together to yield statistically relevant populations in each class. We found that compounds with high permeability have a mean LELP (5.5) much lower than those in the moderate or low permeability group (5.5 and 8.9, respectively; see Figure 4 and Supporting Information Table 3). Mean LLE values, however, were found to be pretty much similar in the two groups (6.3 and 6.5, respectively), showing no correlation with the permeability data.

Metabolic clearance, commonly estimated by the in vitro intrinsic clearance observed during incubation with liver microsomes, limits the maximal concentration and half-life of compounds and might hamper their development. Analysis of LLE and LELP values in the low and high clearance groups revealed that compounds with high metabolic stability are characterized by a mean LLE and LELP (6.9 and 4.8, respectively) significantly better than those observed in the high clearance group (10.8 and 5.5, respectively; see Figure 4 and Supporting Information Table 4).

A transport ratio higher than 2.5 measured in opposite directions, apical to basolateral and basolateral to apical, is an indicator of the active transport mainly mediated by P-glycoprotein. Classification of compounds as transporter substrates and nonsubstrates and evaluating them by their LLE and LELP values resulted in a significant difference in the case of LELP (mean 6.1 and 9.0, respectively) but no difference in LLE values (median 6.3 and 6.5, respectively; see Figure 4 and Supporting Information Table 5).

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Next, we focused on in vitro safety measures including CYP inhibition, hERG blockade, and cellular toxicity. Compounds perturbing clearance mechanisms might have potential for drug−drug interactions (DDI) that is routinely assessed by assessing the inhibition of CYP2D6 and CYP3A4 enzymes.[13] In the Pfizer study, compounds were classified having low (<25%), moderate (25% < inhibition < 75%), and high (>75%) inhibition. Compounds with moderate and high inhibition potential have been pooled together to yield statistically relevant populations in each class (Figure 5 and Supporting Information Tables 6 and 7). LELP values were higher for compounds with moderate and high CYP2D6 inhibition (8.25) than for those with low inhibitory potential (6.6), although the difference was not significant. LLE values were similar (mean values 6.3, 6.3) in the two groups of compounds (Figure 5 and Supporting Information Table 6).

Considering the CYP3A4 data set, LELP values were significantly higher (mean 12.1) for compounds with moderate and high inhibition than for those with low inhibition (6.56) (Figure 5 and Supporting Information Table 7), and a similar statistically significant difference was observed in LLE values (6.4 and 5.0, respectively).

Blocking the hERG potassium channel may result in prolongation of the QT interval of cardiac rhythm and has thereby emerged as one of the most important in vitro parameters of cardiotoxicity.[20] Mean LELP values decreased significantly for compound sets representing high (mean 9.8), moderate (8.4), and low (4.3) risk of inhibition. Mean LLE values changed periodically with no statistical significance (Figure 5 and Supporting Information Table 8).

THLE cell viability was the last safety parameter published by Wager et al.[13] Desirable compounds had to possess IC_{50} values higher than 100 μM (HighCv class) while compounds below the threshold had high risk to induce cellular toxicity (LowCv class). In this case, both LLE and LELP showed significant separation for low (mean LLE = 5.3, mean LELP = 10.2) and high (mean LLE = 6.5, mean LELP = 6.2) cell viability classes (Figure 5 and Supporting Information Table 9).

In summary, evaluation of pharmacokinetic and safety parameters revealed that LELP has benefits over LLE, as compounds with acceptable in vitro ADMET profiles are discriminated from compounds with significant liabilities. Consequently, the number of violated in vitro ADME or safety end-point criteria showed higher correlation with LELP than with LLE (Figure 6A,B). Compounds with low LELP value (around 4) have a high chance to pass all of the ADME and safety criteria, while compounds having a high LELP value, typically higher than 10, would have higher propensity to fail because of ADME and safety violations.

The most important difference between LLE and LELP is that the latter depends not only on log *P* but also on molecular size. LELP therefore combines the two most important physicochemical parameters, MW and log *P*, in a unique way. LLE is a linear function of log *P* while its correlation with LELP is nonlinear, but proportional, yielding increased penalty for compounds in the high log *P* space. Leeson et al. concluded that log *P* is the most important molecular property that changed less over time in launched oral drugs than other properties.[3] Hughes et al. also emphasized the role of lipophilicity in toxicological adverse effects studied on 245 preclinical Pfizer compounds,[6] and it is a general indicator of promiscuity.[2,3,21] Because desolvation terms change parallel with lipophilicity, it might rationalize the generally good

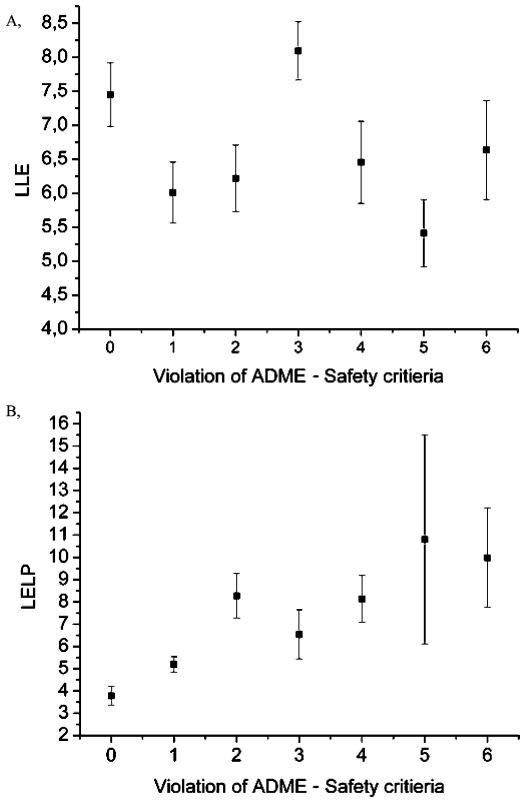

Figure 6. Mean LLE (A) and LELP (B) values for compounds violating a given number of in vitro ADME or safety end-point criteria (Papp, Clearence, Pgp substrates, CYP inhibition, hERG inhibition, and cell viability). Error bars represent the standard error values.

performance of lipophilic ligand efficiency metrics on predicting promiscuity. On the basis of our analysis, it seems that this effect is better represented in LELP than in LLE and is in line with the off-target effects of Pfizer compounds observed in in vitro ADMET profiling. Size dependency, that is also incorporated in other, recently published ADME scoring functions such as MPO[13] or ADMEScore,[2] strikingly distinguishes LELP from LLE. LE used in LELP is a more straightforward measure of protein−ligand interactions, and therefore ligand specificity, than potency (p*Act*) used in LLE, because the latter may increase simply by virtue of making many contacts.[22] Recently, Arrowsmith published a brief analysis on phase II failures within 2008−2010 concluding that 19% of the cases were still due to safety issues, a finding that urges the early evaluation of safety liabilities and decisions on chemical scaffolds.[23] Potency addiction[24] that results in high potency at the expense of undesirable log *P* and size should be controlled effectively. Our present results suggest that LELP may serve as a useful guide to realize candidates with balanced potency and ADMET profile.

The Role of Lipophilic Efficiency in Optimization Strategies. Optimization strategies, exemplified here by the Topliss scheme,[25] provide qualitative and practical guidelines to achieve the desired improvement in potency. Exploitation of the SAR knowledge for potency in combination with the ADMET-sensitive LELP profile may provide novel viewpoints that would facilitate multidimensional optimizations. The procedure is illustrated on a prototype aromatic compound with log *P* = 3, p*Act* = 8, and N_h = 36 (see Figure 7, compound **1**) that is further optimized by introducing new substituents to

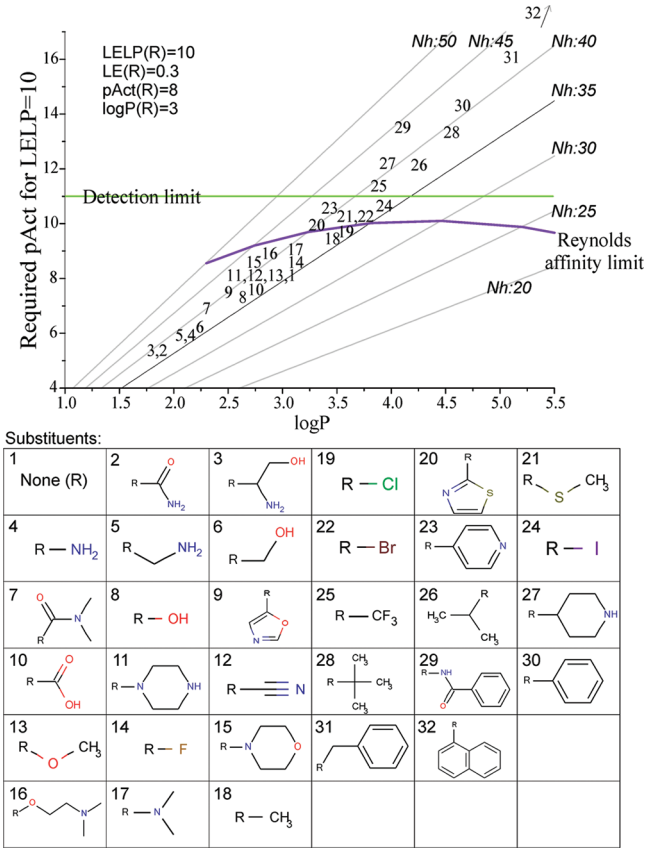

Figure 7. p*Act*(LELP = 10)−log *P* plot for the optimization of compound **1.** The graph depicts the potency required to maintain LELP = 10 for the optimized compounds (compounds **2**−**32**). Detection limit and the maximal achievable potency (Reynolds potency limit)[22] are colored green and violet, respectively. Heavy atom count isovalues (gray lines) were drawn using five-atom increments.

its aromatic ring. Considering the incremental log *P* contributions of the substituents, we calculated the necessary improvement in potency that was required to maintain the LELP value of 10. Reynolds et al. observed that the maximal achievable LE is size dependent.[22] We calculated maximal LE as a function of N_h to predict the maximal affinity ($pAct_{max}$) that represents a certain limit in potency optimization (Figure 7). Using the LELP value of 10, we plotted the $pAct_{max}$ as the function of log *P*, and the curve (Reynolds potency limit) separates the optimization space into feasible and nonfeasible regions. Next we collected the 30 substituents most common in medicinal chemistry programs that span a wide range of log *P*. Interestingly, compounds equipped with only 18 substituents were found below the maximal potency line, while for the remainder, an affinity higher than the actual Reynolds potency limit is needed to keep LELP equal to 10. On the other hand, introduction of the nine most polar substituents allows some limited decrease in potency. This reflects a situation well-known in medicinal chemistry programs that improvements in log *P* result in a simultaneous decrease in potency. We feel that the p*Act*−log *P* plot depicted in Figure 7 would facilitate the design of new compounds with balanced properties. Similar evaluation of group contributions by LLE, especially LLE_{AT}, has been published during the preparation of this manuscript.[26]

IMPLICATIONS ON BINDING THERMODYNAMICS

From a thermodynamic point of view, potency optimization can be realized by various strategies such as enthalpic or entropic optimizations.[27] Binding entropy relies primarily on hydrophobic effects and is typically optimized more readily than enthalpic contributions. The latter is a direct measure of the net change in the number and/or strength of the noncovalent, specific bonds formed upon binding.[28] Although changes in binding thermodynamics are difficult to predict, we were interested in whether lipophilic efficacy indices impact enthalpic or entropic components. Hypothetically, enthalpy-driven optimizations require the formation of novel specific interactions frequently realized by introducing polar groups that is reflected in LLE and LELP values. In the previous sections, we showed that LLE and LELP could support medicinal chemistry optimizations. Considering the increasing role of thermodynamics-guided medicinal chemistry programs,[27] we evaluated their performance using thermodynamic data from both early- and late-phase optimizations.

The potential of LLE and LELP is first highlighted in the early optimizations of renin inhibitors. Optimization of diaminopyrimidine-type renin inhibitors at Pfizer has been supported by crystallography and monitoring of binding thermodynamics.[29] Starting from the advanced hit, compound **33** (Figure 8), resulted in five leadlike compounds exemplified

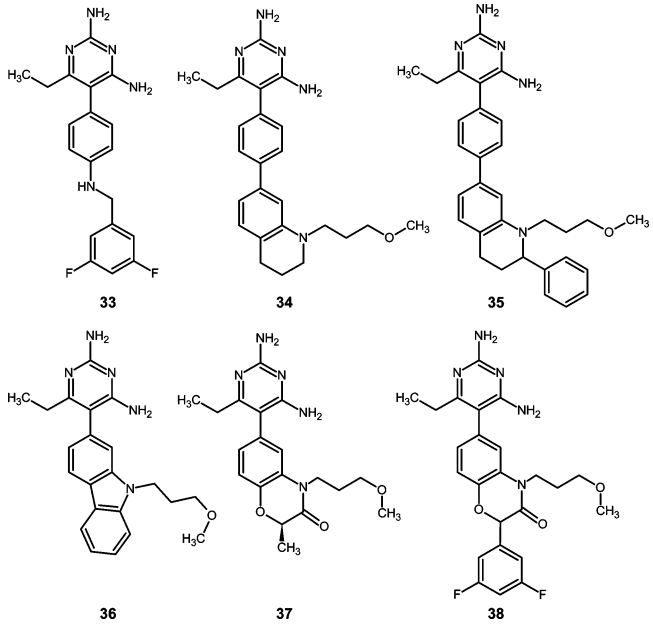

Figure 8. Diaminopyrimidine-type renin inhibitors (**33**−**38**).

as compounds **34**−**38**. Comparison of compound **33** and compound **34** shows a favorable change in binding enthalpy that is rationalized by extending compound **33** with the methoxypropyl side chain toward the S3 subpocket. Compound **35**, a phenyl-substituted derivative of compound **34**, was more active due to beneficial changes in entropy, but its lipophilicity was increased detrimentally. In terms of LLE and LELP, we found similar trends; compound **34** has LLE and LELP values much better than that of compound **33**. Further, basically entropic optimization of compound **34** to compound **35**, however, was characterized by undesired changes in both of the lipophilicity indices. Compound **36** and **37** have somewhat lower but comparable binding enthalpy and improved potency

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Table 1. Binding Thermodynamics and Lipophilic Efficiency Indices of Compounds Delivered by Medicinal Chemistry Programs and Marketed Drugs

Optimization							
name	ΔG [kcal/mol]	$-T\Delta S$ [kcal/mol]	ΔH [kcal/mol]	N_h	log P	LELP	LLE
Renin Inhibitors							
33	−7.5	2.0	−9.5	26	3.6	12.6	1.8
34	−8.6	5.9	−14.5	25	2.8	8.0	3.4
35	−9.8	0.2	−10.0	31	4.3	13.5	2.9
36	−9.5	3.5	−13.0	28	3.5	10.3	3.4
37	−9.3	4.0	−13.3	27	1.4	4.0	5.4
38	−9.3	−0.4	−8.9	35	3.5	13.1	3.3
HIV Protease Inhibitors							
39	−14.9	−6.7	−8.2	54	2.3	8.4	8.6
40	−14.6	−2.5	−12.1	56	0.2	0.7	10.5
Plasmepsin II Inhibitors							
41	−10.6	−9.4	−1.2	44	4.7	19.7	3.0
42	−9.7	−3.7	−6	45	3.7	17.0	3.4
43	−12.7	−7.2	−5.5	45	3.7	13.0	5.6
Marketed Drugs							
name	ΔG [kcal/mol]	$-T\Delta S$ [kcal/mol]	ΔH [kcal/mol]	N_h	log P	LELP	LLE
Statins							
fluvastatin	−9	−9	0	30	3.8	12.8	2.7
pravastain	−9.7	−7.2	−2.5	30	1.6	5.1	5.4
cerivastatin	−11.4	−8.1	−3.3	33	2.6	7.5	5.7
atorvastatin	−10.9	−6.6	−4.3	41	5.4	20.3	2.6
rosuvastatin	−12.3	−3	−9.3	33	1.9	5.2	7.1
HIV Protease Inhibitors							
indinavir	−12.4	−14.2	1.8	45	2.8	10.2	6.2
saquinavir	−13	−14.2	1.2	49	3.2	11.9	6.3
nelfinavir	−12.8	−15.9	3.1	40	4.7	14.7	4.6
ritonavir	−13.7	−9.4	−4.3	50	5.2	19.1	4.8
amprenavir	−13.2	−6.3	−6.9	35	2.4	6.4	7.2
lopinavir	−15.1	−11.3	−3.8	46	4.7	14.3	6.3
atazanavir	−14.3	−10.1	−4.2	51	4.5	16.2	5.9
tipranavir	−16.6	−13.9	−2.7	42	7.8	19.8	4.3
darunavir	−15	−2.3	−12.7	38	2.8	7.1	8.1

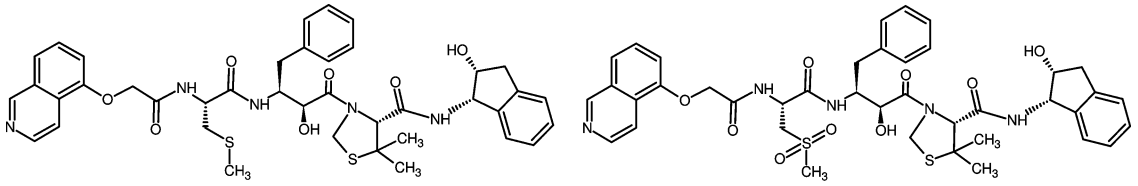

Figure 9. HIV-protease inhibitors (**39** and **40**).

as compared to compound **34**. Compound **37**, having the most favored LLE and LELP, shows a unique balance in potency, enthalpy and entropy contributions, and lipophilicity. Introduction of an additional phenyl group to compound **37** (compound **38**) increased the lipophilicity and enhanced the entropy contribution without significant improvement in potency that is in line with the unfavorable change in both LLE and LELP. In this particular set of compounds (**33**−**38**), binding enthalpy showed reasonable correlation with LELP (r^2 = 0.646) while the correlation with LLE was weaker (r^2 = 0.339), which is somewhat lower than that found with log P (r^2 = 0.388). Both LLE and LELP ranked the enthalpically most favored compound **34** at the top two positions. Interestingly, the most potent compound (**35**) had the highest lipophilicity (log P = 4.3) and the second most favored binding entropy; thus, it was ranked last by LELP and fifth by LLE.

The relationship between lipophilic efficiency metrics and binding thermodynamics was then further investigated on late-phase optimizations published by the Freire group.[30−34] The first example is a pair of HIV inhibitors with high structural similarity but markedly different thermodynamic profiles. Oxidation of the thioether moiety in **39** (KNI-10033) changed enthalpy and entropy contributions significantly but kept the potency constant (Table 1, Figure 9). The enthalpy-driven binding of **40** (KNI-10075) is characterized by better LLE and LELP values relative to the enthalpically less favored analogue **39**. Crystal structure of the complexes revealed that the binding enthalpy can be attributed to an additional hydrogen bond formed between one of the sulfonamide oxygens of **40** and the

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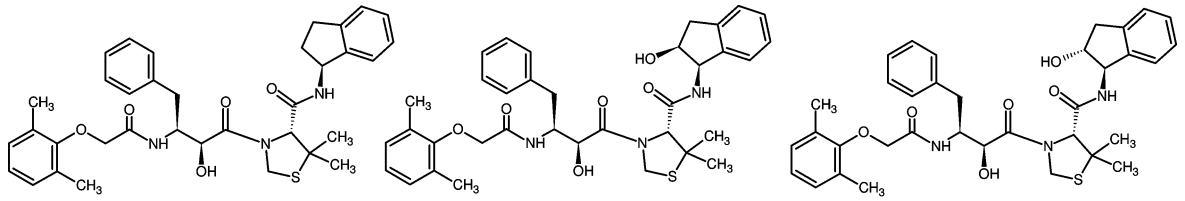

41 42 43

Figure 10. Plasmensin II inhibitors (**41**–**43**).

amide nitrogen of Asp 30B at the binding site of HIV-1 protease. The introduction of a polar, hydrogen bond acceptor into **39** decreased the log *P* but has virtually no effect on the potency, though this example shed light on the benefit of using lipophilic efficiency indices over ligand efficacy or potency alone. The suggested p*Act*–log *P* scheme may aid the design of such modifications. The next example is the thermodynamics-guided optimization of plasmepsin II inhibitors (Table 1, Figure 10), an aspartic protease considered as a promising antimalarial target.[34] The binding of **41** (KNI-10026) is entropy-driven; consequently, both LLE and LELP ranked this compound low. KNI-10007 (**42**) and KNI-10006 (**43**) have better lipophilic efficiency indices and improved binding thermodynamics. In fact, **43** having the highest affinity with significant enthalpic contribution was ranked first. The same number of heavy atoms and the same log *P* predicted for **42** and **43** results that LLE and LELP of these compounds are only influenced by potency. Accordingly, the difference in binding enthalpy is marginal, while for **43** there is a significant improvement in binding entropy due to the additional burial of hydrophobic atoms, increased desolvation, and by the release of unstable water molecules from the binding pocket.

The evolution of FDA-approved drugs in certain drug classes such as HIV-1 protease inhibitors and statins was studied from a thermodynamic point of view.[31−34] These data sets represent another challenge for investigating the relationship of binding thermodynamics and lipophilic efficiency. In the statin class, rosuvastation, having the highest LLE (7.1) and the second best LELP (5.2), binds enthalpically. On the other hand, the entropic fluvastatin is characterized by poor LLE and LELP values. Among the marketed HIV protease inhibitors, the binding of darunavir and amprenavir is enthalpy-driven. These two drugs have clearly the best LLE and LELP in the class. Note that entropic HIV protease inhibitors tipranavir and lopinavir had affinity higher than that of the enthalpic darunavir or ampreavir, representing an unbiased situation for the evaluation of lipophilic efficiency indices.

In summary, the analysis of a limited set of thermodynamic data suggests that lipophilic efficiency might have an impact on the binding thermodynamics profile. This is in line with the relationship identified between lipophilic efficiency measures and safety data. Enthalpy-driven binding typically provides higher specificity and better LLE and LELP. On the contrary, entropy-driven binding that basically relies on desolvation effects is mostly achieved by higher log *P*; thus, it increases the promiscuity of the ligand and gives suboptimal LLE and LELP. Although we emphasize that the thermodynamics of protein–ligand binding is far more complex,[35,36] similar trends in binding thermodynamics and lipophilic efficiency indices give further support to the comparative analysis of LLE and LELP at the decision points of discovery programs.

CONCLUSIONS

The attractiveness of increasing potency in medicinal chemistry optimizations can be more detrimental than prosperous without the adequate control of physicochemical parameters, especially log *P* or log *D*. The documented addiction to potency calls for a feasible measure that combines potency and lipophilicity that is useful for postsynthesis evaluations, supports prospective design, and facilitates identifying high quality compounds at discovery milestones. Lipophilic efficiency indices such as LLE and LELP are allowing this concept to be realized. In this work, we investigated these measures in several aspects such as comparison of data sets representing different stages of drug discovery, ADME and safety status, and binding thermodynamics. The results suggest that monitoring LLE and LELP both have clear benefits; however, these metrics possess different characteristics: (i) LLE is sensible for the development stages and does not prefer fragment-type hits that are otherwise considered to be promising starting points for lead discovery; (ii) LELP incorporates molecular size and penalizes the increase in log *P* more than in LLE; therefore, it has an advantage for both ADME- and safety-related issues over LLE, (iii) case studies highlighted that both LLE and LELP support enthalpy-driven optimizations. As a consequence, we recommend the use of LELP in the early-phase optimizations, especially where fragment-sized hits are compared to more complex structures, and for the early selection of desirable lead scaffolds, and the use of both LLE and LELP in later-phase optimizations that are characterized by lower fluctuations in molecular size.

ASSOCIATED CONTENT

Supporting Information

LLE and LELP values calculated for the studied subsets and the data set used in the ADMET-related analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Phone +361-431-4605, +361-432-6002. E-mail: gy.keseru@richter.hu.

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ABBREVIATIONS USED

ADMET, adsorption, distribution, metabolism, excretion, toxicology; CNS, central nervous system; DDI, drug–drug interaction; hERG, human ether a go-go related gene; HTS, high throughput screening; LE, ligand efficiency; LLE, lipophilic ligand efficiency; MPO, multiparametric optimization

score; P2, phase II clinical trials; Papp, apparent permeability; Pgp, P-glycoprotein

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