The role of ligand efficiency metrics in drug discovery

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Abstract | The judicious application of ligand or binding efficiency metrics, which quantify the molecular properties required to obtain binding affinity for a drug target, is gaining traction in the selection and optimization of fragments, hits and leads. Retrospective analysis of recently marketed oral drugs shows that they frequently have highly optimized ligand efficiency values for their targets. Optimizing ligand efficiency metrics based on both molecular mass and lipophilicity, when set in the context of the specific target, has the potential to ameliorate the inflation of these properties that has been observed in current medicinal chemistry practice, and to increase the quality of drug candidates.

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The properties of small-molecule drugs, especially those that are orally bioavailable, are concentrated in a relatively narrow range of physicochemical space known as 'drug-like' space[1,2]. In studies of extensive data sets of small molecules, the fundamental properties of molecular size, lipophilicity, shape, hydrogen-bonding properties and polarity have been correlated — to varying degrees — with solubility[3], membrane permeability[4], metabolic stability[5,6], receptor promiscuity[7], *in vivo* toxicity[8,9] and attrition[10,11] in drug development pipelines.

Lipophilicity and hydrogen bond donor count seem to be key properties, as they have remained essentially constant in oral drugs over time[7,12–15]. The median and mean molecular mass of approved drugs has risen by only around 50 Da (15%) over the past three decades, whereas the median and mean molecular mass of synthesized experimental compounds has risen by over 100 Da (30%)[16]. By contrast, the molecules that are being published in the literature[15] and patented by the pharmaceutical industry[17], as well as those entering clinical development pipelines[10], are more lipophilic, larger and less three-dimensional[14,18] than approved oral drugs. However, analyses indicate that compounds that have a higher molecular mass and higher lipophilicity have a higher probability of failure at each stage of clinical development[10,19,20].

The control of physicochemical properties is dependent on the specific drug target, the mode of perturbation and the target product profile — all of which may justify developing compounds that lie beyond the norm — and it is also dependent on the variable drug discovery practices of originating institutions[7,17]. Individual drug discovery projects often justify the pursuit of molecules that have additional risks associated with suboptimal physicochemical properties, as long as experimental project goals and the target product profile criteria are met. However, when viewed in aggregate at a company portfolio level, the physicochemical properties of investigational drugs can have an important influence on the overall attrition rates[10,19,20] and therefore ultimately on the return on investment.

Three factors have been proposed to underlie the observed inflation in physicochemical properties[21,22] of investigational drugs over the past three decades. First, the discovery of initial hit compounds with inflated physicochemical properties has been linked to the rise of high-throughput screening (HTS)[23]. Larger and more lipophilic compounds, potentially with a higher binding affinity, are more likely to be detected in HTS assays, which are often based on a single affinity end point. Second, the tendency of HTS methods to identify large and lipophilic compounds is amplified by the observed tendency of the lead optimization process to inflate physicochemical properties[24,25]. Third, the portfolio of drug targets being tackled by the industry includes a growing number of targets that are less druggable than those pursued previously, which may justify the development of compounds with less optimal physicochemical properties[20].

We believe that the overemphasis on potency, as well as the associated tendency to inflate physicochemical properties, can be remedied by monitoring and

Box 1 | **Ligand efficiency metrics**

Ligand efficiency (LE) was first proposed as a method for comparing molecules according to their average binding energy per atom[26,27]. This concept has been extended to incorporate other properties such as lipophilicity[7], molecular mass[82], polar surface area[82], combinations of physicochemical properties[23,48] and functional group contributions[54]. The measures are focused only on *in vitro* binding affinity and not on *in vivo* properties. Commonly used efficiency metrics are described in equations 1–6, where HA denotes the number of non-hydrogen (that is, heavy) atoms. In equations 1–6, the negative logarithmic value of the half-maximal inhibitory concentration (pIC_{50}) can be substituted with the negative logarithmic values of the inhibition constant (pK_i), the dissociation constant (pK_d) or the effector concentration for half-maximum response (pEC_{50}; logarithms are to base 10) (see below). In equations 4–6, cLogP can be substituted by LogD. Each equation corresponds to a mathematically valid function, mapping either $\mathbb{R}\times\mathbb{N}\rightarrow\mathbb{R}$ (equations 1–3), $\mathbb{R}^2\rightarrow\mathbb{R}$ (equation 4) or $\mathbb{R}^2\times\mathbb{N}\rightarrow\mathbb{R}$ (equations 5,6), where $\mathbb{R}$ and $\mathbb{N}$ denote the spaces of real numbers and positive integers, respectively.

$LE = (-2.303(RT/HA)) \times \log K_d$ (1)

$LE = (1.37/HA) \times pIC_{50}$ (2)

$LEI = pIC_{50}/HA$ (3)

$LLE = pIC_{50} - cLogP$ (4)

$LLE_{AT} = 0.111 + 1.37(LLE/HA)$ (5)

$LELP = cLogP/LE$ (6)

Equation 1 (REF. 27) is derived from the Gibbs free energy of binding per heavy atom. The free energy of binding is defined as follows: $\Delta G^0 = -RT \times \ln(K_d/C^0) = -2.303RT \times \log(K_d/C^0)$, where R is the ideal gas constant (1.987×10^{-3} kcal/K/mol), T is the temperature in Kelvin (K), C^0 is the standard concentration and K_d is the dissociation constant. Varying the temperature and standard concentration will change the relative ΔG. Assuming standard conditions of aqueous solution at 300K, neutral pH and remaining concentrations of 1M, $-2.303RT\log(K_d/C^0)$ approximates to $-1.37 \times \log(K_d)$ kcal/mol. In other words, a change in Gibbs free energy of binding of –1.37 kcal/mol is equivalent to a tenfold increase in affinity. It follows that $LE = \Delta G^0/HA = -(2.303RT/HA) \times \log(K_d/C^0) \approx -(1.37/HA) \times \log(K_d) = (1.37/HA) \times pK_d$ kcal/mol/heavy atom. Following the common practice of substituting pK_d by pIC_{50} (or pK_i or pEC_{50}) values, LE can be expressed as $(1.37/HA) \times pIC_{50}$ (equation 2). As IC_{50} values for competitive inhibitors depend on the concentration of the competing ligand, ideally equation 2 should be used only to compare LE values under the same assay conditions. In this paper, all LE values are expressed as LE = (1.37/HA) × p(Activity) where p(Activity) is pK_i, pIC_{50} or pEC_{50} (note that in the studies of target LE values reported in this paper, checking all assay conditions for >200,000 compounds was not practical, but we treat published K_i, IC_{50} and EC_{50} values separately).

From equation 1 it follows that for a given LE, HA is linearly related to pK_d, with a slope of 1.37/LE. Therefore, the change in HA required to maintain constant LE for a tenfold increase in affinity (change in $pK_d = +1$) is 1.37/LE. There is no requirement that each change in HA that increases potency by tenfold should be constant for compounds with different LE values[29]. A simple approach has been adopted by some practitioners to define binding efficiency by simply dividing p(Activity) by HA to produce a unitless quantity referred to as the ligand efficiency index (LEI; equation 3). An alternative is to substitute HA with molecular weight to provide the binding efficiency index (BEI)[82].

Lipophilic ligand efficiency (LLE, equation 4) is simply the difference between p(Activity) and lipophilicity (cLogP or LogD) and is an estimate of the specificity of a molecule in binding to the target relative to partitioning into 1-octanol[7]. LLE is also referred to in the literature as LipE (lipophilic efficiency)[43]; LLE and LipE are defined identically and in this paper we use the term LLE.

Proposed acceptable values of LE and LLE (based on cLogP) for drug candidates are as follows: LE >~0.3 kcal per mole per heavy atom (REF. 26) and LLE >~5 (REF. 7), based on a K_d<10 nM molecule having a heavy atom count of 38 (~500 Da)[26] and a cLogP<3 (REF. 7). Published mean oral drug values that provide the benchmark we use for druggability assessment (FIG. 4; BOX 4) are as follows: LE = 0.45, LLE (based on cLogP) = 4.43 (n = 261, calculated from the *in vitro* potencies provided in the supplementary data in REF. 2). In another compilation[44] the values were similar: LE = 0.52, LLE (based on ChemAxon LogP) = 5.02 (n = 302). Supplementary information S3 (table) compiles potencies, LE, LLE and lipophilicity-corrected ligand efficiency (LELP) values of exemplar collections of drugs, hits and leads[44].

Equation 5 and equation 6 provide efficiency metrics that combine potency, lipophilicity and HA count in different ways, and are useful for fragment optimization. LLE_{AT} (LLE adjusted for heavy atom count; equation 5) is scaled to be comparable to LE (equation 1)[48]. LELP (equation 6) provides a metric that indicates the price of LE paid in lipophilicity[23]. Considering the acceptable lower limit of LE (0.3), and the lipophilicity range for lead-like compounds (–3 < LogP <3), the optimal LELP value in lead discovery should be in the following range[23]: –10 < LELP <10. It should be noted that LELP values will be less responsive to changes in size or potency as cLogP gets closer to zero. The LE metrics LLE, LELP and LLE_{AT} can be derived using measured 1-octanol–water or buffer partition coefficients or using calculated values of LogP (the partition coefficient) or LogD. Because of the risk of variability in calculating lipophilicity[46,83], it is recommended that confirmatory experimental data are obtained for exemplar molecules.

Size-independent ligand efficiency (SILE) measures and fit quality (FQ) are described in BOX 2, and group efficiency is described in BOX 3.

optimizing ligand efficiency metrics instead of potency alone. Ligand efficiency metrics, which are measures of the *in vitro* biological activity corrected for the physicochemical property 'load' of the molecule, quantify how effectively the molecule uses its structural features in binding to the target. The LE (equation 1; BOX 1) concept[26] was derived from the observation that the maximum affinity achievable by ligands is –1.5 kcal per mole per non-hydrogen atom ('heavy' atom), ignoring simple cations and anions[27], and from studies examining

Box 2 | **Size-independent measures of ligand efficiency**

Analysis of large numbers of protein–ligand complexes over a broad range of affinities[38,39] demonstrates that average or optimal ligand efficiency (LE) values are systematically higher for small ligands than for large ligands. By contrast, the relationship between lipophilic ligand efficiency (LLE) and cLogP is linear, with the gradient of the slope depending on the extent to which potency is driven by lipophilicity in the ligands used; a slope of –1 indicates that there is no relationship between potency and lipophilicity. Supplementary information S1 (figure) shows the nonlinear relationship between LE and heavy atom (HA) count, and the linear relationship between LLE and lipophilicity.

Lipophilicity-corrected ligand efficiency (LELP) and LLE adjusted for heavy atom count (LLE_{AT}; BOX 1) normalize lipophilic efficiency for molecular size. Two size-independent modifications of LE using only HA have been proposed: fit quality (FQ; equation 1)[39] and size-independent ligand efficiency (SILE; equation 2)[84].

$$FQ = [pIC_{50} \text{ or } pK_i \div HA] \div [0.0715 + (7.5328 \div HA) + (25.7079 \div HA^2) - (361.4722 \div HA^3)] \quad (1)$$

$$SILE = pIC_{50} \text{ or } pK_i \div HA^{0.3} \quad (2)$$

FQ normalizes LE by binning LE values for a large number of disparate complexes and using a scaling factor derived from a spline-fit of the most potent compounds in each bin. SILE does essentially the same thing with a different fitting function (that is, $\Delta G/HA^{0.3}$, where ΔG stands for the negative free energy of binding). In either case, the effect is to transform LE into a metric that is more consistent across broad ranges of molecular size. Similarly, this approach has been applied to derive size-independent enthalpy efficiencies, in which free energy is replaced by enthalpy[36].

Of course, this trend begs the question of why the HA count alone is not a more consistent normalization term for molecular size. At least three factors have been proposed to explain this result. First, the HA count is being used as a surrogate for molecular surface, as the latter would be expected to be more relevant to molecular recognition and binding. Second, analysis of the computed molecular surface as a function of molecular mass shows that although these two factors are generally related, the increase in molecular surface per additional HA declines with increasing size[39]. This is sensible given that larger molecules, by necessity, have a more buried (that is, internal) surface relative to small molecules. Third, beyond the breakdown in linearity between the number of atoms and surface area, there is also a fundamental problem with satisfying multiple binding subpockets simultaneously. As molecular structures are not infinitely adjustable (that is, bond distances and angles can only adopt very limited values without introducing strain), structural compromises are increasingly inevitable as ligand size increases. This was demonstrated with simple model systems[39] and is further supported by subsequent analysis of enthalpy and entropy efficiencies[42] showing that size dependency is related to enthalpy (see Supplementary information S2 (figure)).

functional group binding energy[28]. Kuntz *et al.* presented binding free energy (ΔG) per atom by dividing the free energy of binding by the number of heavy atoms, and postulated the potential use of the binding energy per heavy atom as a means to assess ligands throughout the drug discovery process[27].Treating the data in this way makes two assumptions: it assigns all of the intermolecular interaction to the ligand alone, and it assumes the binding energies per atom are additive. Thus for a given ligand efficiency (the gradient) there is a linear relationship between the free energy of binding and the number of heavy atoms, where it is assumed that a ligand with zero atoms has zero free energy of binding at standard conditions.

The most widely used ligand efficiency metrics are calculated in a simple way and are summarized in BOXES 1–3; they can be applied at all stages of drug discovery to evaluate fragments, screening hits, leads and candidate drugs. The use of molecular-size measures such as heavy atom count in LE metrics (for example, see BOX 1) has some caveats[29]. In particular, component atoms (that is, carbon, nitrogen, oxygen, sulphur and halogen) are treated equally even though their sizes and binding properties are different, and some atoms in a molecule may not participate in receptor binding interactions (BOX 2).

Nevertheless, monitoring ligand efficiency metrics during hit and lead optimization can highlight the price paid in physicochemical properties when modulating binding affinity. Depending on the binding affinity and the physicochemical properties of a lead molecule, ligand efficiency values may increase or decrease during optimization. This is exemplified by the changes in affinity that are needed to maintain constant LE (equation 1; BOX 1) values when substituting a lead molecule with various groups (BOX 3; FIG. 1). Applying ligand efficiency analyses has practical utility in guiding lead discovery — and, more importantly, lead optimization — towards drug-like chemical space. Here, we illustrate this with new analyses, including recent optimizations from the literature and surveys of ligand efficiencies of compounds for particular drug targets as well as recently approved oral drugs.

Spline fit
A statistical, numerical method for fitting a curve through a set of data points using a cubic polynomial.

Binding thermodynamics and ligand efficiency

Hit-to-lead efforts typically start from hits with micromolar affinity (or even low millimolar affinity in the case of fragment hits), and aim to identify submicromolar lead series with promising physicochemical and ADMET (absorption, distribution, metabolism, excretion and toxicity) profiles that are suitable for further optimization. Improving potency increases the negative free energy of binding (ΔG), which in turn is composed of two thermodynamic quantities: binding enthalpy (ΔH) and binding entropy ($T\Delta S$).

Predicting how structural modifications will affect the enthalpy or entropy of binding is extremely difficult, particularly given the well-known phenomenon of entropy–enthalpy compensation, but there are some

Box 3 | **Group efficiency**

Group efficiency (GE)[54] is used to show the contribution of different parts of a lead molecule to the overall binding affinity. It is analogous to ligand efficiency (LE), but GE refers only to the atoms that have been added onto an existing molecule.

GE provides a guideline of the gain in affinity that should be sought depending on the size of a group that is added to an existing compound. GE is the contribution to the negative free energy of binding (ΔG) per heavy atom (HA; the number of non-hydrogen atoms) of the added group[54]. So, if a group of atoms is added to compound 'A' to form compound 'B', the GE of the added group is defined by equation 1 (in which ΔΔG and ΔHA are defined as in equations 2 and 3):

$$GE = -\Delta\Delta G/\Delta HA \quad (1)$$

$$\Delta\Delta G = \Delta G \text{ (compound B)} - \Delta G \text{ (compound A)} \quad (2)$$

$$\Delta HA = HA \text{ (compound B)} - HA \text{ (compound A)} \quad (3)$$

GE is a more sensitive metric than LE when considering the change in affinity, as a fragment (or early lead) is optimized into a lead with a higher affinity and increased molecular mass, and it can be used to show 'hotspots' in terms of binding efficiency. Consider, as an example, an early compound A that has 25 atoms and an affinity of 1 μM. If a phenyl group is added to compound A and a tenfold increase in affinity is measured for the new compound B, the LE values for the two compounds are similar, 0.33 and 0.31 respectively (compound A: 6 × 1.37 ÷ 25; compound B: 7 × 1.37 ÷ 31). However, the GE of the phenyl group is only 0.23 (GE = [(7 × 1.37) – (6 × 1.37)] ÷ 6), which indicates that it is a relatively poor addition in terms of binding affinity. As shown in the table[54], if a phenyl group (HA = 6) is added and if the aim is to achieve a GE of 0.39 (or an overall LE of 0.39, which is in line with a candidate molecular mass of 400 Da and a half-maximal inhibitory concentration (IC_{50}) of 10nM), then a 46-fold increase in affinity is required.

GE is useful in fragment-based drug discovery (FBDD) during the optimization of the binding affinity of a millimolar or micromolar fragment into a nanomolar lead. It provides the chemist with a measure of whether atoms that are added onto the starting fragment justify their presence in terms of providing additional binding affinity (see the example in FIG. 3). Some of the limitations of GE are that it can only be determined if binding affinities have been measured for closely related compounds, and GE assumes that the structure–activity relationship of the groups being added is additive (that is, each one is independent of the other groups). Furthermore, GE, as with LE and related terms, is primarily intended for use when focusing on affinity optimization rather than on *in vivo* properties.

ΔHA	Fold-improvement in binding affinity required to maintain GE		
	GE = 0.31 (500 Da lead with IC_{50} = 10nM)	GE = 0.39 (400 Da lead with IC_{50} = 10nM)	GE = 0.52 (300 Da lead with IC_{50} = 10nM)
1	1.7	1.9	2.3
2	2.8	3.6	5.5
3	4.6	6.8	13
4	7.7	13	30
5	13	24	71
6	22	46	170
7	36	88	390
8	60	170	920
9	100	320	2,200
10	170	600	5,100
11	280	1,100	12,000
12	460	2,200	28,000

The table shows the affinity increase required when adding atoms onto a lead molecule in order to maintain overall LE[54]. For example, if a phenyl group, C_6H_5 (HA = 6), is added onto a molecule and the resulting affinity increase is 22-fold, this phenyl group has an LE of 0.31. This is referred to as the GE.

general trends[30,31]. Optimization of specific polar interactions between the target binding site and the ligand is usually associated with a more promising physicochemical profile (lower lipophilicity) and improvements in binding enthalpy. By contrast, increasing ligand size and lipophilicity to generate nonspecific interactions often leads to entropy-driven improvements in affinity[32], whereas specific lipophilic interactions can increase or decrease the binding enthalpy. The entropy-driven approach to improving affinity probably contributes to the well-documented inflation of physicochemical properties in hit and lead optimization[22–25].

Although this picture is qualitative, thermodynamics-based optimizations have recently been the subject of increasing interest[33,34]. Isothermal titration calorimetry (ITC) allows the determination of ΔH and TΔS[35], and ITC data have been analysed from more than 700 protein–ligand complexes, which were obtained from a literature survey covering both medicinal chemistry and

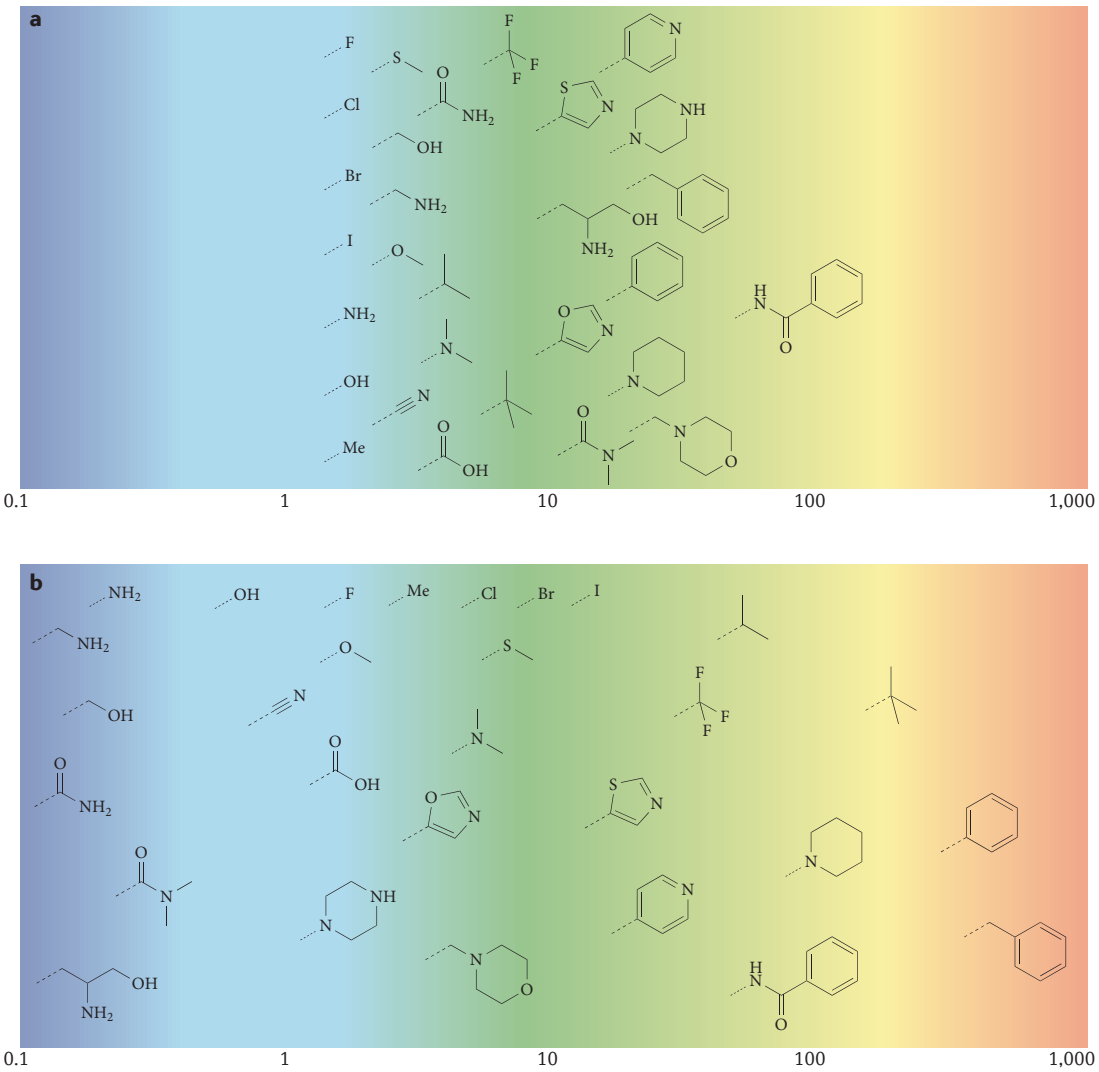


Figure 1 | **Maintaining acceptable ligand efficiencies during optimization of binding affinity.** **a** | The diagram shows the fold increase in affinity (on the horizontal axis) that is needed to maintain a ligand efficiency (LE; defined in BOX 1) value of 0.3 when adding the indicated groups to a lead molecule. Adding a methyl group (with a heavy atom (HA) count = 1) requires an approximately twofold increase in affinity, whereas adding a benzyl group (HA = 7) requires an approximately 30-fold increase in affinity. **b** | The diagram shows the fold increase (on the horizontal axis) in binding affinity that is needed to maintain a lipophilic ligand efficiency adjusted for heavy atom count (LLE_{AT}; defined in BOX 1) value of 0.3 when adding the indicated groups to an aromatic carbon of a lead molecule. Note the differences in the affinity increase required when adding a six-membered ring according to its cLogP value (piperazine versus morpholine versus pyridine versus a phenyl group)[48].

natural product-derived ligands[36]. In contrast to ΔG[27], ΔH decreases with increasing molecular size at a heavy atom count of 25 or greater[37].

As the number of heavy atoms increases, LE (BOX 1) decreases (see BOX 2 and Supplementary information S1,S2 (figures))[38,39]. It has been suggested that the less favourable $T\Delta S$ values for larger and more flexible ligands may contribute to the fall-off that is typically observed for LE in larger ligands[40]. However, in an analysis of the number of energetically accessible conformations for several thousand ligands of varying sizes and affinities, no trend was observed for increased conformational entropies with increasing ligand size[39]. It is clear from this analysis that many large molecules are much more conformationally constrained than might be expected from their overall size or from a simple count of the number of rotatable bonds. It also seems likely that any effect of conformational entropy on ligand binding may well be swamped by other contributions to the overall $T\Delta S$ of binding[40].

Thermodynamic data allow individual ligand enthalpic and entropic efficiencies per heavy atom to be calculated[35]. A size-independent version of enthalpic efficiency (SIHE)[36] can also be used. Analysis of experimental ITC data[33,41] across a broad range of chemotypes shows that the average entropic efficiency does not change significantly

with size (Supplementary information S2 (figure)), but it narrows when ligand size is increased[42]. By contrast, the enthalpic efficiencies show a much more dramatic trend with increasing size, which is similar to the trend seen with the overall LE values (that is, derived from ΔG). Very favourable enthalpic efficiencies are common for small ligands, but the average — and most favourable — enthalpic efficiencies for larger ligands are systematically reduced (see Supplementary information S2 (figure)). Hence the overall trend in ΔG-related LE is mainly a consequence of enthalpic efficiency[40,42]. These results suggest that the effects of conformational entropy may not be as significant as is commonly believed. In contrast to size, both lipophilic enthalpy efficiencies and lipophilic entropy efficiencies tend to decrease with increasing lipophilicity (see Supplementary information S2 (figure)). For individual protein targets, lipophilic ligand efficiency (LLE), also known as LipE (equation 4, BOX 1), might be a more useful surrogate than LE or lipophilicity-corrected ligand efficiency (LELP) for the enthalpic component of ligand binding, especially under circumstances where structurally similar series such as matched molecular pairs display similar specific lipophilic binding interactions[43].

Optimization of enthalpy-driven binding efficiency appears to be an attractive strategy[37], but it is not yet clear whether this will lead to less attrition in drug candidate pipelines. Analysis of four targets from the literature suggests that as well as enthalpy efficiency, lipophilic ligand efficiency measures can provide practical guidance in designing ligands with improved molecular properties[44], as discussed below.

Lipophilic ligand efficiency

The mean lipophilicity of marketed drugs — measured by the partition coefficient (LogP) or the distribution coefficient (LogD) — has not changed substantially over several decades[7,12–15]. This important observation implies that lipophilicity is a fundamental property that affects the progress of drug discovery programmes and the ability to develop identified candidates. By contrast, it has been observed that the physicochemical properties of analogues in a chemical series, including molecular mass and lipophilicity, often increase during optimization from hit to lead[23] and from lead to drug candidate[24,25].

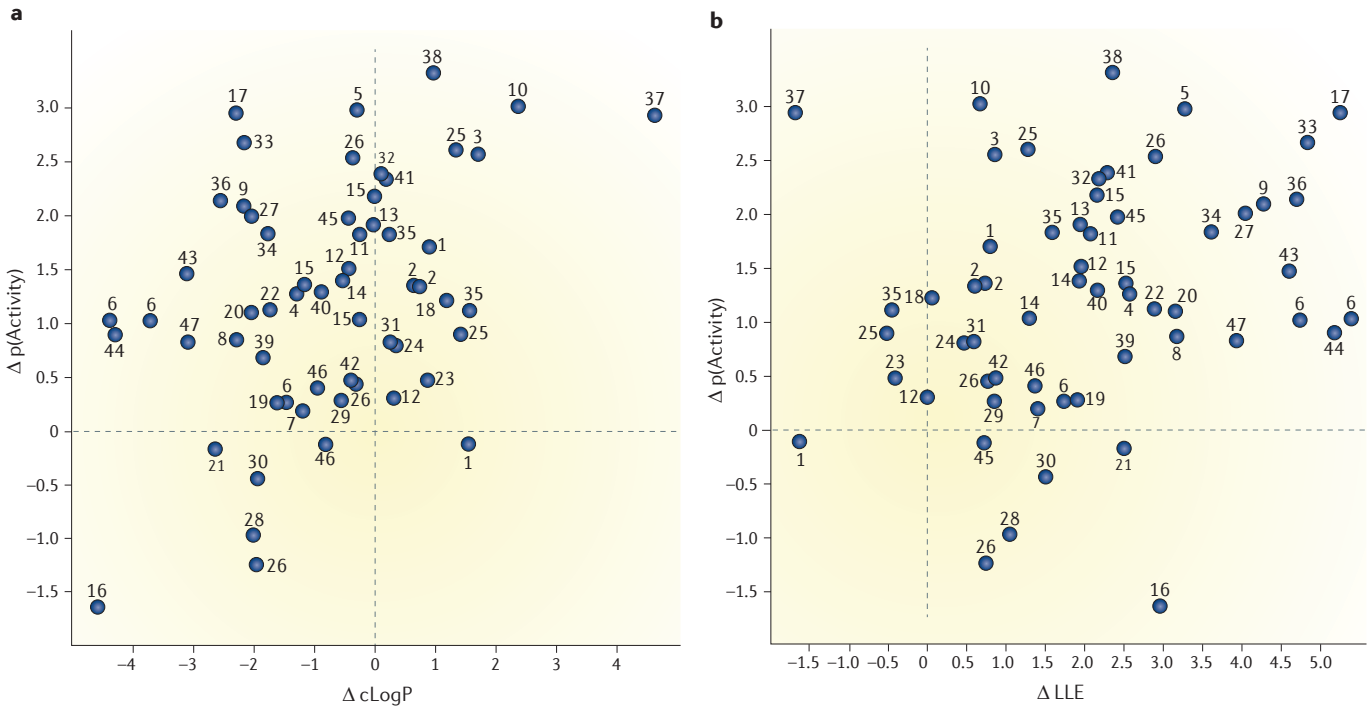
The concept of using minimal hydrophobicity in drug design is not new[45], and is supported by a wealth of recent evidence[46] showing that lipophilicity has an important effect on drug-like properties. In addition to its connection to solubility[3], lipophilicity affects many ADME properties as well as toxicity properties such as voltage-gated potassium channel hERG liability, phospholipidosis, cytochrome (CYP) inhibition and receptor promiscuity[46]. Owing to its central role in pharmacokinetics and safety, most of the empirical ADMET guidelines include lipophilicity, such as Lipinki's rule of five guidelines on absorption[47], GlaxoSmithKline's 4/400 guideline on ADMET properties[6] and Pfizer's 3/75 guideline on toxicological outcomes[8].

In addition to influencing ADMET properties, lipophilicity (LogP or LogD) is one of the key factors determining binding affinity to drug target proteins. High target potency combined with high lipophilicity may therefore also increase the risk of ADMET-related attrition[2]. As a result, medicinal chemistry optimization needs to be balanced and multidimensional[37], which is a difficult task but one that can be assisted by the use of efficiency metrics to control lipophilicity. LLE[7] (BOX 1) is a simple but important index combining *in vitro* potency and lipophilicity. A molecule with an LLE equal to zero based on LogP, where target affinity is equal to LogP, can be thought of as having the same affinity for its target as it does for 1-octanol, whereas a drug candidate with an LLE of 6 has a one-million-fold higher affinity for its target compared to 1-octanol. Negative LLE values are clearly unfavourable. Based on the properties of an average oral drug, with a calculated LogP (cLogP) of ~2.5–3.0 and potency in the range of ~1–10 nM, an ideal LLE value for an optimized drug candidate is ~5–7 units or greater[7]. Fragments or lead-like molecules that are used as chemical starting points generally cannot possess drug-like LLE values because they are not potent enough. Hits with LLE ≤2 are commonly found from HTS (that is, ≥1 μM affinity with cLogP ~4 (REF. 23)), and these will have to be improved by ~3 or more LLE units during optimization to a candidate. Additional metrics such as LE are useful for dealing with molecular size in fragment-to-hit and hit-to-lead optimizations.

Combining both size and lipophilicity into a single efficiency index is useful at the hit identification and hit-to-lead stages as well as in fragment-based drug discovery (FBDD; see the next section). Two such parameters — LELP[23] and LLE_{AT} (LLE adjusted for heavy atom count)[48] — have been developed (BOX 1). Although the full range of optimal LELP values[23] is −10 to +10, a desirable hit or lead against a tractable target in the early optimization stage — with an LE of >0.40–0.45 and a cLogP of 0–3 — would have an LELP value of 0–7.5 units. The LLE_{AT} was derived from experience in FBDD, and is scaled to be comparable in magnitude to LE[48]. Both LELP and LLE_{AT} can also be applied in lead optimization.

It has been shown[44] that increasing lipophilic efficiency, using LLE and LELP values, is associated with improved ADMET characteristics, probably as a result of both lowered lipophilicity and increased specificity. In one study, developmental candidates were successfully discriminated from marketed drugs by LELP but not by LE and LLE alone[49]. In addition, compilations of hits, leads, successful leads (those that produced marketed drugs)[50] and drugs are differentiated by their mean LLE and LELP values[44]; potency, LE, LLE and LELP values for these compound sets are given in Supplementary information S3 (table). An analysis presented below in the section titled 'Ligand efficiencies of oral drugs' shows that using LE and LLE together can differentiate between marketed drugs and other molecules acting at the same target.

The recent medicinal chemistry literature contains an increasing number of examples where LLE has been explicitly used in the optimization process; 59 examples, covering 47 different molecular targets, are summarized in FIG. 2 (see Supplementary information S4 (table) for



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Property	Mean difference	*P*
Ar ring	+0.14	0.172
p(Activity)	+1.23	<0.0001
cLogP	–0.77	0.0014
HA	+3.24	<0.0001
Molecular mass	+45.1	<0.0001
Topological polar surface area	+19.6	<0.0001
LE	+0.019	0.077
LLE	+2.00	<0.0001
Lipophilicity-corrected ligand efficiency (LELP)	–2.45	0.0018
Size-independent ligand efficiency (SILE)	+0.50	<0.0001
LLE_{AT}	+0.077	<0.0001

Figure 2 | **Examples from the literature in which lipophilic ligand efficiency was explicitly used in the optimization process on 47 different targets.** Changes in p(Activity) between the starting point and the optimized compound are plotted against the corresponding changes in LogP (part **a**) and lipophilic ligand efficiency (LLE) (part **b**) for the 59 examples. The upper left quadrant in part **a** contains examples where activity is increased and cLogP is lowered (34 out of 59 examples). The upper right quadrant in part **b** contains examples where potency and LLE are increased (48 out of 59 examples). Results from matched pair analysis of starting properties versus optimized properties for the 59 pairs are given in part **c**. Full data, including literature references, are available in Supplementary information S4 (table). The targets are as follows: 1, 11β-hydroxysteroid dehydrogenase; 2, acetyl-CoA carboxylase 1; 3, AKT; 4, MAPK/ERK kinase kinase 5 (also known as ASK1); 5, β-secretase 1; 6, cannabinoid 1 (CB_1) receptor; 7, CB_2 receptor; 8, CC-chemokine receptor 8; 9, MET–ALK (anaplastic lymphoma kinase); 10, diacylglycerol *O*-acyltransferase 1; 11, epoxide hydrolase; 12, free fatty acid receptor 1 (also known as GPR40); 13, formyl peptide receptor 1; 14, glycoprotein GP120; 15, G protein-coupled receptor 119; 16, growth hormone secretagogue receptor type 1a; 17, histone H4; 18, HIV integrase; 19, HIV reverse transcriptase; 20, human rhinovirus major capsid protein VP1; 21, Janus kinase 1; 22, UDP-3-*O*-acyl-*N*-acetylglucosamine deacetylase; 23, leucine-rich repeat kinase 2; 24, metabotropic glutamate receptor 1 (mGluR1); 25, mGluR2 and mGluR3; 26, mGluR5; 27, matrix metalloproteinase 13; 28, metallothionein 1 and metallothionein 2; 29, NMDA (*N*-methyl-D-aspartate) receptor subtype 2B; 30, *N*-myristoyltransferase; 31, NS4B protein; 32, OX2 membrane glycoprotein; 33, phosphodiesterase 8B; 34, phosphoinositide 3-kinase (PI3K); 35, PI3K p110β isoform; 36, serine/threonine protein kinase PIM1; 37, peptidyl-prolyl *cis-trans* isomerase NIMA-interacting 1; 38, protein kinase Cθ; 39, progesterone; 40, tankyrase; 41, G protein-coupled bile acid receptor 1; 42, tyrosine kinase 2; 43, vasopressin receptor V_{1A}; 44, vascular endothelial growth factor receptor; 45, β_1-adrenergic receptor; 46, γ-secretase; 47, σ1 receptor.

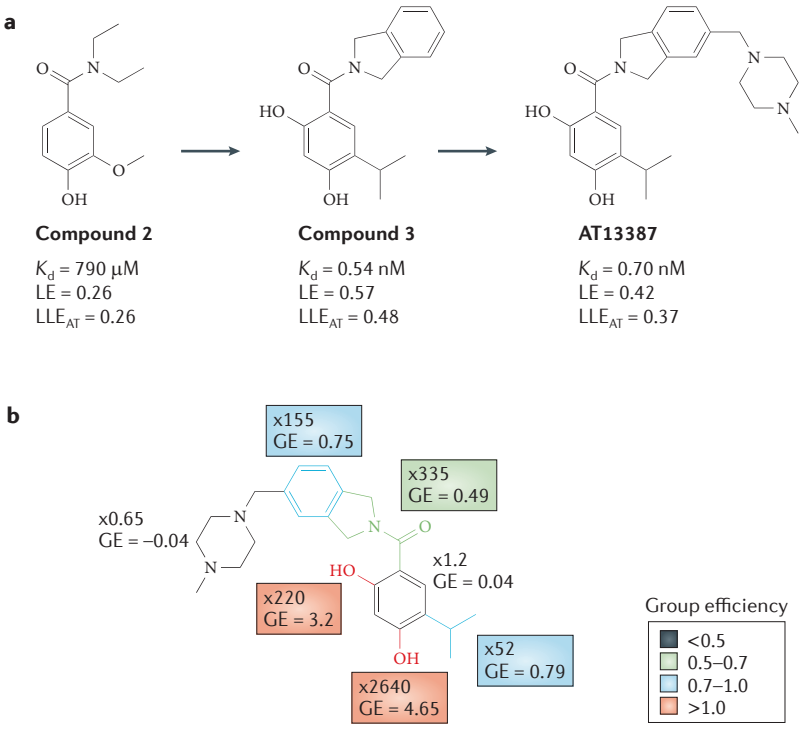


Figure 3 | **HSP90 inhibitors as an example of the application of ligand efficiency metrics in fragment-based drug discovery.** **a** | Fragment-to-clinical candidate for heat shock protein 90 (HSP90). Around 1,600 fragments were screened by NMR LOGSY (ligand observed by gradient spectroscopy), and 125 were progressed into X-ray crystallography studies[56]. The phenol (compound 2) has a low ligand efficiency (LE), 0.26 kcal per mol per heavy atom, which shows that its binding affinity (790 μM by isothermal titration calorimetry) is suboptimal. However, examination of its binding to HSP90 by X-ray crystallography, together with the binding interactions of previously reported chemically related inhibitors (such as radicicol), indicated three opportunities for improvement: filling a lipophilic pocket in the region of the methoxy group; incorporating a second hydroxyl group onto the phenol; and growing from the diethylamide into the region occupied by the conformationally flexible Lys58 side chain. Adding only six heavy atoms (non-hydrogen) to the phenol compound 2 led to compound 3 (with a dissociation constant (K_d) of 0.54nM), which has a >1,000,000-fold increase in affinity leading to a corresponding improvement in LE to 0.57 kcal per mol per heavy atom. Optimization of physicochemical, pharmacokinetic and *in vivo* properties led to AT13387 (K_d = 0.7 nM, LE = 0.41)[57], which is currently under evaluation in Phase II trials for the treatment of cancer. **b** | Group efficiency (GE; see BOX 3)[54] for the different parts of the HSP90 inhibitor, AT13387. The GE values are colour coded and illustrate the binding 'hotspots' for this compound. As expected from the fragment-to-lead structure–activity relationships and the X-ray crystal structure, each hydroxyl interacts with the protein via direct and water-mediated hydrogen bonds and has a very high GE (GE = 4.65 and 3.2, corresponding to a 2,640-fold and 220-fold increase in binding affinity, respectively), and the isopropyl group that fills a lipophilic pocket also has a high GE (0.79). The piperazine group improves the pharmacokinetic properties without directly binding to HSP90 and hence has a very low GE (–0.04).

p(Activity)
The negative logarithm of activity *in vitro* in published papers: for example, half-maximal inhibitory concentration (IC_{50}), inhibition constant (K_i) or effector concentration for half-maximum response (EC_{50}) values.

details). For each example, *in vitro* activities as well as LLE and LE values of the starting points and optimized molecules were collected. The median changes in p(Activity) and LLE were +1.22 and +1.96, respectively (P <0.001 from matched pair analysis). Median values of LELP (–2.74) and LLE_{AT} (+0.066) were also significantly reduced and increased, respectively. These results show that focusing on LLE in lead optimization facilitates the discovery of molecules with increased binding affinity without necessarily increasing lipophilicity at the same time. In fact, 48 of the 59 examples increased LLE in the optimization process, even though properties in addition to binding affinity were being optimized in many of the examples cited.

The importance of controlling lipophilicity in optimization is further exemplified in an analysis[50] of 60 recently marketed drugs and their leads, which showed that mean lipophilicity remained constant during the optimization process, whereas mean potency — and therefore mean LLE — increased by ~2 Log units. For these 60 drug examples[50], a high drug LLE is linked to a decreased lead cLogP, with the straight line fit being as follows: LLE drug = 7.93 – 0.78 × lead cLogP (n = 60, r^2 = 0.47, P < 0.0001). In the recent 59 LLE-aware optimizations shown in FIG. 2, the same trend is present, but — as expected — it is much less pronounced: optimized LLE = 6.15 – 0.30 × lead cLogP (n = 59, r^2 = 0.077, P = 0.033). Achieving high LLE values in optimized molecules is therefore more likely when starting with leads that have a low cLogP (ideally <3). These observations on newer drugs and on current practices contrast with earlier studies in the literature[24,25,51], largely pre-dating the application of LE concepts, in which lipophilicity increased — on average — during optimization. We conclude that the optimization of LLE values will guide projects towards potent molecules with lowered lipophilicity, which will — in turn — improve the ability to develop the emerging candidate compounds.

It is interesting to note that the mean LE did not change in either the lead to drug optimizations analysed in REF. 50 or in the LLE-based optimizations shown in FIG. 2. The conservation of LE during lead optimization supports the original premise of LE as a metric for aiding the selection of leads, as well as for comparing compounds for further optimization at the hit selection stage[20,26]. By contrast, median size-independent ligand efficiency (SILE; BOX 2) values were significantly increased by +0.48 (P <0.001) in the optimizations shown in FIG. 2. SILE is therefore a metric that could be useful for differentiating among molecules in the physicochemical property ranges where lead optimization commonly takes place.

FBDD and ligand efficiency

An important emerging area for the application of LE metrics is in FBDD. During the past decade, FBDD has been used to discover several compounds that have progressed into clinical trials[52] and onto the market[53]. Fragments are compounds that have molecular masses between 100 and 250 Da and are small relative to the compounds that are typically screened in HTS. As a consequence of their small size, fragment hits commonly have low binding affinities, usually in the range of 1 mM to 10 μM. LE itself is a useful metric for normalizing the affinities of hits to identify the best starting points for optimization — that is, those with the highest LE values, all else being equal.

Despite their low affinities, fragment hits that are selected for further optimization often have generally good (>0.4) or even excellent LE values. Developing

these fragments into leads is a challenge and often requires the addition of more than ~15–20 heavy atoms (corresponding to an increase of ~200–250 Da in molecular mass) to increase the affinity by several orders of magnitude (from the millimolar or micromolar range to the nanomolar range). This presents an opportunity to use the various ligand (BOX 1) and group efficiency (GE)[54] (BOX 3) metrics to carefully control chemical properties. This approach to FBDD, when practised by specialist teams, can result in optimized molecules with improved drug-like properties[17].

An example of a FBDD programme targeted at heat shock protein 90 (HSP90) — a chaperone protein that is a promising anticancer target[55–57] — illustrates the

Box 4 | **Ligand efficiencies and target druggability**

To examine physicochemical property and ligand efficiency (LE) trends at the drug target level, compounds acting at human drug protein targets and their affinities were assembled from the primary medicinal chemical literature using the GVK BIO database[85]. Important caveats in using the medicinal chemistry literature are that the bulk of the molecules reported are not fully optimized and, in contrast to potency optimization, physicochemical property-based optimization is not routine. For targets where mean LE values are currently relatively low, better molecules may not yet have been discovered.

The database contained 270,471 inhibition constant (K_i), half-maximal inhibitory concentration (IC_{50}) and effector concentration for half-maximum response (EC_{50}) values from 1,045 targets, predominantly from the *Journal of Medicinal Chemistry* (41% of values), *Bioorganic and Medicinal Chemistry Letters* (42% of values) and *Bioorganic and Medicinal Chemistry* (13% of values). Where compounds had more than one reported K_i, IC_{50} or EC_{50} value at a specific target, the mean value was determined. The physicochemical properties of all compounds were calculated as described previously[7,17], and LE and lipophilic ligand efficiency (LLE; based on cLogP) values determined; K_i, IC_{50} and EC_{50} values were treated separately for each target. Finally, weakly active molecules (>100 μM) and very large molecules (>70 heavy atoms (HAs)) were excluded, and the database (containing 228,265 compound–assay pairs) was analysed by target–assay type pairs. Out of a total of 1,690 target–assay pairs, only those for which there were ≥100 compounds were used, resulting in 480 target–assay pairs covering 329 different targets that represented 201,041 molecules (88% of the database; 127 targets had more than one assay type with ≥100 compounds). For the 480 target–assay pairs, median values are as follows: LE = 0.32, LLE (based on cLogP) = 2.83, HA = 29.75, cLogP = 3.89.

The median LE values of the 480 target–assay pairs span a broad range: ~0.2 to 0.6 for LE and ~ −3 to 9 for LLE (FIG. 4a). This is a consequence of intrinsic target druggability, combined with the properties of the actual molecules synthesized. For the purpose of comparing the druggability of target classes only, arbitrarily defined property and efficiency criteria were derived from oral drugs (FIG. 4b). For the property criterion, we use the percentage of published molecules at each target that meet both the size and lipophilicity criteria according to the rule of five guidelines (HA <38, equivalent to a molecular mass <500 Da, and cLogP <5)[47]. For the efficiency criterion, we use the percentage of published molecules at each target for which both the LE and LLE values are higher than the mean values of oral drugs (LE >0.45, LLE >4.43; see BOX 1). Although fewer molecules meet the efficiency criteria compared to the property criteria for the majority of targets, both of these measures clearly indicate the relative druggability of the target classes. The physicochemical property trends across the target classes in FIG. 4b are consistent with other studies[17,20,51,60]. The least druggable target classes, on both property and efficiency measures, are peptidergic and lipidergic G protein-coupled receptors and nuclear hormone receptors. Although the bulk (>60%) of the published molecules for the other target classes meet the rule of five criteria (FIG. 4b), there is greater relative variability in the percentages meeting the drug-like ligand efficiency criteria, from 2.8% for kinases to 14.8% for the most druggable target class — aminergic G protein-coupled receptors. The major challenge in finding active compounds for many targets is demonstrated by the fact that 120 of the 480 target–assay pairs have no published compounds with both LE and LLE values exceeding the mean values of oral drugs.

Reducing size and lipophilicity will tend to increase ligand efficiencies, and the individual target data suggest that doing so may not necessarily have a detrimental effect on affinity for many targets. Thus, among the 480 target–assay pairs, although straight line fits between activity and either HA count or lipophilicity are mostly statistically significant, they frequently have low r^2 (correlation coefficient) values and the slopes can be negative as well as positive (FIG. 4c, d). In agreement with reported data[2], there are broad trends towards increased activity with increasing size and lipophilicity if the full data set of >200,000 compounds is analysed without taking into account the targets, with the effect of size being greater than lipophilicity. Within individual series of structurally similar compounds that are typically investigated in lead optimization, correlations of potency with size and lipophilicity are often found, but when all of the published molecules acting at a target are taken into account, increasing these properties does not have a large effect on potency in most cases (FIG. 4c,d). The effects of size and lipophilicity are often different on each target, as indicated by the r^2 value of 0.14 for the correlation of the slopes of the potency-cLogP versus potency-HA target relationships for the 480 target–assay pairs (see Supplementary information S4 (table) for details).

A key conclusion, therefore, is that for targets that possess small-molecule binding sites there should be no need a priori to seek to increase bulk physicochemical properties in pursuit of increased activity. In practice, optimization across 59 targets for which LLE was used during potency and other optimizations (FIG. 2) resulted in a reduction in mean lipophilicity and an increase in mean size (resulting in an increase in mean LLE and a conservation of mean LE).

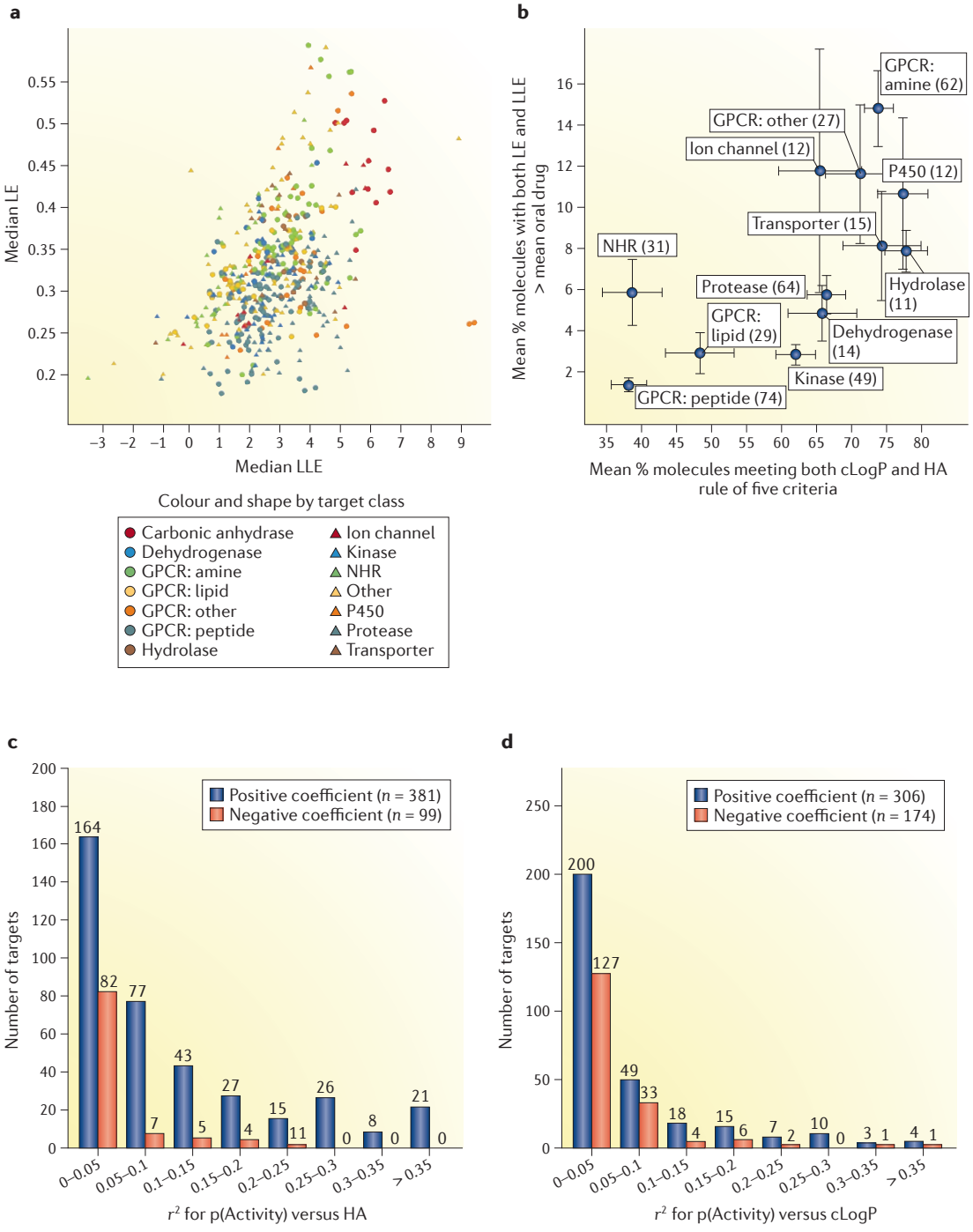


Figure 4 | **Druggability analyses.** Data from 480 target–assay pairs with more than 100 compounds covering 329 human drug targets, obtained from the GVK BIO database[85] (see BOX 4 for details). Target mean ligand efficiency (LE) values are widely distributed, as shown in the plot in part **a** of median target LE versus target lipophilic ligand efficiency (LLE; based on cLogP). Target class druggability assessment using physicochemical property and LE criteria based on marketed drugs (part **b**). The mean percentage of molecules for each target that meet physicochemical property criteria from the rule of five guidelines[47] is shown, with both cLogP <5 and heavy atom (HA) count <38 (HA count = 38 approximates to a molecular mass of 500 Da)[26], versus the mean percentage of molecules for each target that exceed the mean efficiency values of 261 oral drugs (see supplementary data from REF. 2), where LLE ≥4.43 and LE ≥0.446. Target classes and numbers of targets are shown. Error bars are standard errors of the mean. Correlations of potency versus size and lipophilicity within targets are often weak, and may be negative as well as positive. Distribution of the correlation coefficient (r^2) values from straight line fits for the 480 target–assay pairs in part **a** are shown in part **c** for p(Activity) versus HA count, and in part **d** for p(Activity) versus cLogP. Data are available in Supplementary information S4 (table). GPCR, G protein-coupled receptor; NHR, nuclear hormone receptor.

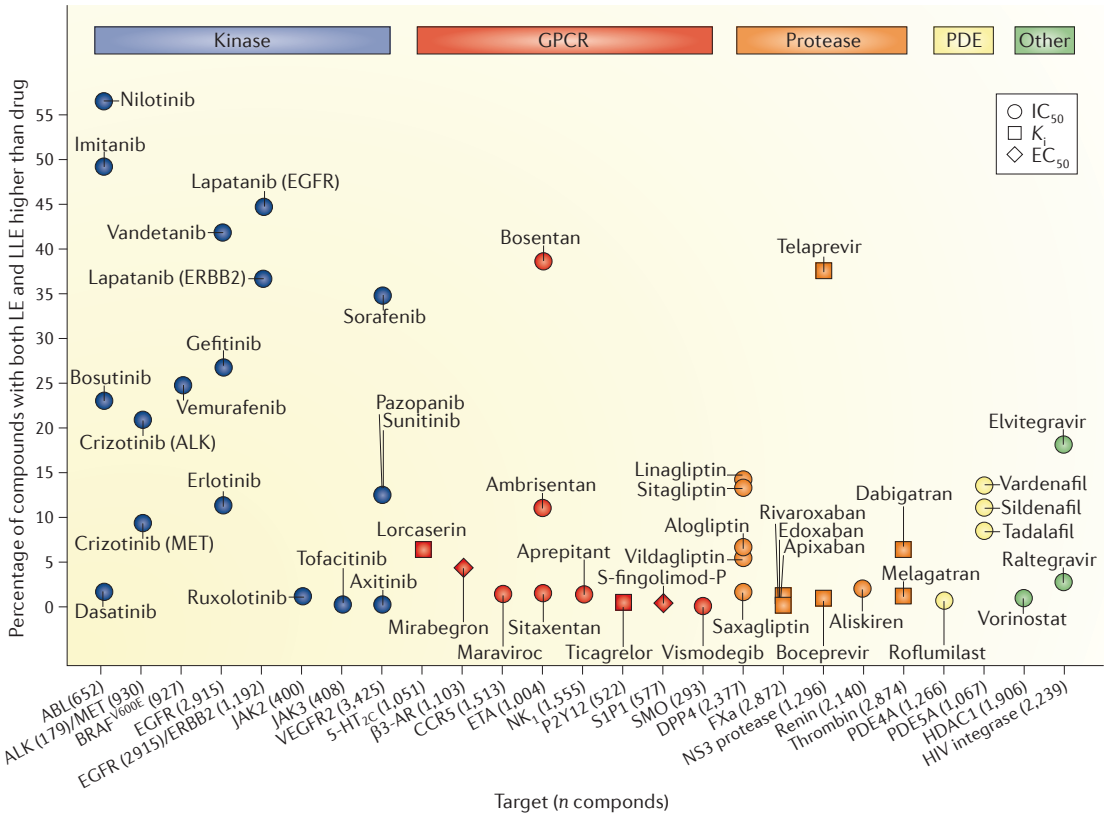
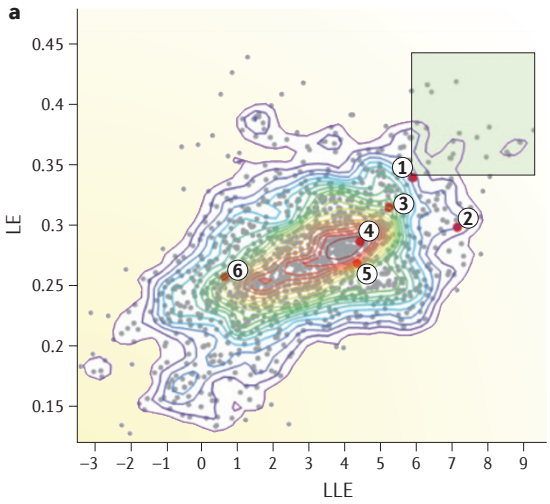
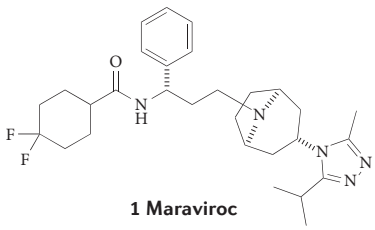


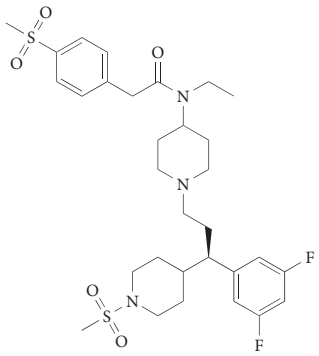
Figure 5 | **Relative ligand efficiencies of 46 oral drugs acting at 25 targets.** *In vitro* affinity data for oral drugs (half-maximal inhibitory concentration (IC_{50}), inhibition constant (K_i) or effector concentration for half-maximum response (EC_{50}) values) and for other molecules that were reported to be active (in the primary literature) at the specific human drug targets were collected from the ChEMBL database in late 2012. For compounds that had more than one reported IC_{50}, K_i or EC_{50} value, the mean value was used. Ligand efficiency (LE) and lipophilic ligand efficiency (LLE) values based on cLogP were calculated (BOX 1). The *y*-axis shows the percentage of compounds reported in the literature acting at the drug target for which both LE and LLE values are superior to the oral drug. The targets are arranged on the *x*-axis by target class and show the total numbers of compounds in the analysis. The active form of fingolimod is the S-O-phosphate; the parent molecules of the thrombin inhibitor prodrugs melagatran and dabigatran are used. Full data are available in Supplementary information S4 (table). $5\text{-}HT_{2C}$, 5-hydroxytryptamine receptor 2C; β_3-AR, β_3-adrenergic receptor; ALK, anaplastic lymphoma kinase; CCR5, CC-chemokine receptor 5; DPP4, dipeptidyl peptidase 4; EGFR, epidermal growth factor receptor; ETA, endothelin A receptor; FXa, factor Xa; GPCR, G protein-coupled receptor; HDAC, histone deacetylase; JAK, Janus kinase; NK_1, neurokinin 1 receptor; P2Y12, P2Y purinergic receptor 12; PDE, phosphodiesterase; S1P1, sphingosine 1-phosphate; SMO, Smoothened; VEGFR2, vascular endothelial growth factor receptor 2.

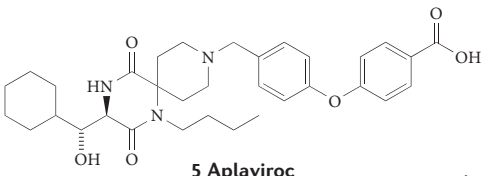
general principle of only adding atoms to the starting fragment that provide the desired increase in binding affinity (FIG. 3a). This example is a showcase, as six heavy atoms are added and the affinity increases by six orders of magnitude (from 0.79 mM to 0.70 nM)[56,57]. Careful attention to the experimentally determined X-ray crystal structure and overall chemical properties was crucial during this fragment-to-lead optimization. The LLE_{AT} metric is useful during this stage because it represents LLE normalized for size (BOX 1) and helps to ensure that an increase in affinity is not unduly driven by nonspecific lipophilic interactions. Ligand efficiency metrics are, by definition, useful for *in vitro* binding affinity, but the advantage of starting *in vivo* optimization with high LE is that additional atoms can be added to the lead compound to optimize *in vivo* efficacy, pharmacokinetics and safety while still resulting in a clinical candidate that is 'drug-like' in terms of molecular mass and lipophilicity.

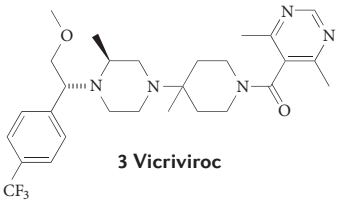
GE (BOX 3) is also particularly useful when growing fragments because it focuses on the efficiency of the atoms that are added to the original molecule. In the case of HSP90, the GE values for each group in the final molecule are determined by comparing matched pairs of related compounds. The groups with high GE values are those that appear in the X-ray crystal structure to form clear binding interactions. The GE values for the different parts of the HSP90 inhibitor, AT13387, were determined retrospectively by comparing the binding affinities of closely related compounds (FIG. 3b) (see BOX 3 for the method used). Several other published examples of fragment optimizations and the use of ligand efficiency metrics have been reviewed in the literature[58,59].

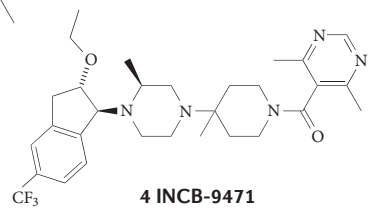


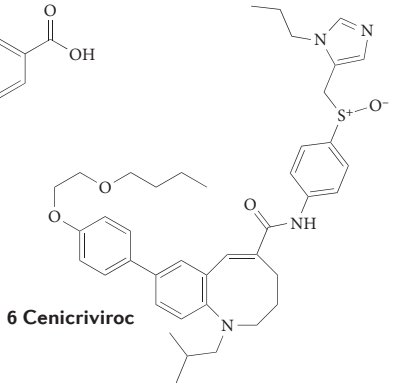


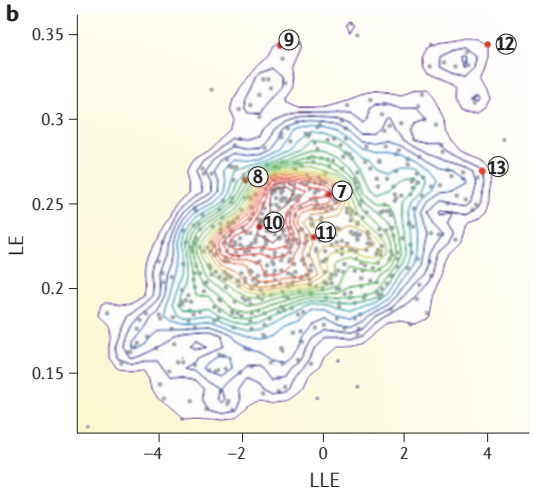


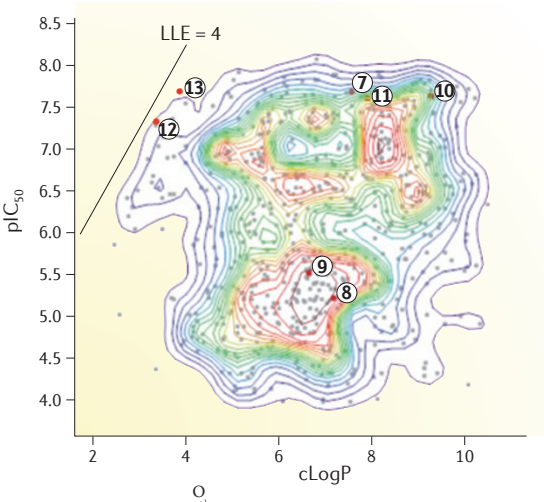


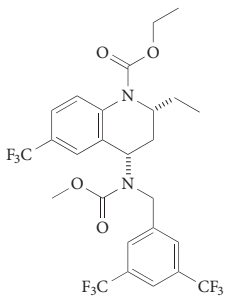


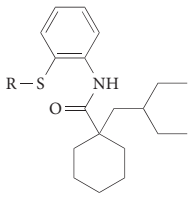


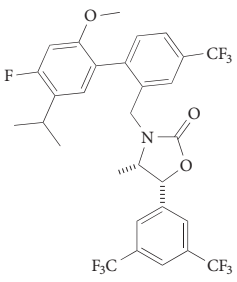


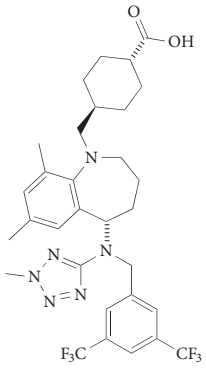


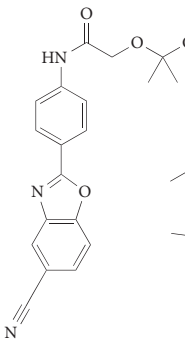












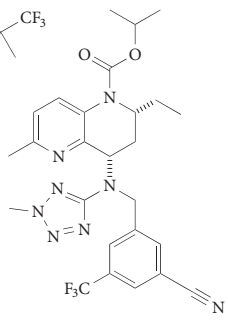


Figure 6 | **Examples of target ligand efficiency analyses. a** | Ligand efficiency (LE) versus lipophilic ligand efficiency (LLE) plot for compounds acting at CC-chemokine receptor 5 (CCR5; $n = 1,513$; half-maximal inhibitory concentration (IC_{50}) values). Although the mean affinity for the target is <100 nM, this comes at some cost in mean physicochemical properties. Mean values of all compounds are as follows: $pIC_{50} = 7.57$; heavy atom (HA) count = 38.6; cLogP = 4.65; LE = 0.27; LLE = 2.93. Compounds that are labelled are known clinical candidates[66,67,86], of which only maraviroc (compound 1) has reached the market. AZD5672 (compound 2)[67] was aimed at rheumatoid arthritis, whereas the others are used for HIV treatment. Cenicriviroc (compound 6)[86] is a dual CCR5 and CCR2 antagonist. The highlighted box on the top right of the plot shows the compounds that have better combined LE and LLE values than maraviroc (1.4% of the total, the value used for the analysis in FIG. 5). AZD5672 is comparable to maraviroc in balancing overall physicochemical properties (especially lipophilicity) and potency. **b** | Compounds that inhibit the cholesteryl ester transfer protein (CETP, $n = 721$; IC_{50} values). The left-hand panel, showing the LE versus LLE plot, and the right-hand panel, showing the pIC_{50} versus cLogP plot and the LLE = 4 boundary, exemplify recommended LE data analyses (along with potency versus size) that are applicable to any target. CETP[68,69] was chosen because there are several drug candidates targeting this protein in clinical trials and it is one of the most challenging in terms of achieving good physicochemical properties of inhibitors: mean values of all compounds are as follows: $pIC_{50} = 6.80$; HA count = 36.4; cLogP = 6.07; LE = 0.23; LLE = –0.73. The drug candidates have suboptimal LE and especially LLE values. Torcetrapib (compound 7) and dalcetrapib (compound 8; the deacylated active metabolite, compound 9, forms a disulphide bond with Cys13 on CETP) were discontinued in Phase III trials because of cardiovascular toxicity and inadequate efficacy, respectively. Anacetrapib (compound 10) and evacetrapib (compound 11) are currently in Phase III trials. Even with this poorly druggable target, it is possible to find molecules with better balanced properties, including a class of benzoxazoles (for example, compound 12)[70] that were identified from high-throughput screening. Notably, compound 13 (REF. 74) was discovered by lowering the lipophilicity of torcetrapib while retaining comparable affinity, resulting in an increase in LLE of 3.9 units. IC_{50} values were taken from the ChEMBL database, and LE and LLE (based on cLogP) values were calculated (BOX 1). The contours represent densities of points.

Ligand efficiencies of oral drugs

Target classes (for example, G protein-coupled receptors, kinases, proteases and nuclear hormone receptors) display differing molecular properties among their small-molecule ligands[17,20,51,60]. Measures such as LE and LLE (BOX 1) can be used in conjunction with physicochemical properties (such as cLogP and heavy atom counts) to assess the relative 'druggability' of human drug targets and target classes by analysing their known ligands (BOX 4; FIG. 4). The variability in LE and LLE values and in the physicochemical properties of targets evident from FIG. 4 is a consequence of the inherent differences in the relative druggability of targets combined with varying practices in drug discovery[7,17] that lead to published active compounds.

Drug molecules are the final result of the exhaustive optimization of chemical, biological, toxicological, pharmaceutical and clinical profiles of lead compounds. Can LE metrics help to distinguish drugs from non-drugs? We compared LE and LLE values of recently marketed drugs with other molecules that had shown reported activity at the same target (FIG. 5). The data set was compiled by searching the ChEMBL database for compounds with published human target affinity *in vitro* (half-maximal inhibitory concentration (IC_{50}), inhibition constant (K_i) or effector concentration for half-maximum response (EC_{50}) values), and by calculating LE and LLE values (BOX 1). The percentage of all compounds at each target where both LE and LLE values were superior to the oral drug was determined. This approach weights LE and LLE equally and, to achieve a low percentage score (the *y* axis of FIG. 5), a drug must rank highly on one or both of these efficiency measures. Based on their relative target rankings, both LE and LLE values make a similar overall impact on the percentage scores for the 46-drug set shown in FIG. 5 (see Supplementary information S4 (table)).

A group of first-in-class — and currently 'only-in-class' — drugs acting on single targets stands out as having notably better combined LE and LLE values than other compounds acting on the same primary targets. These drugs (FIG. 5) include aprepitant (a neurokinin 1 (NK_1; also known as substance P) receptor antagonist), aliskiren (a renin inhibitor), vorinostat (a histone deacetylase 1 (HDAC1) inhibitor), maraviroc (a CC-chemokine receptor 5 (CCR5) antagonist; see also FIG. 6), lorcaserin (a 5-hydroxytryptamine receptor 2C ($5\text{-}HT_{2C}$) agonist), roflumilast (a phosphodiesterase 4A (PDE4A) inhibitor), ruxolitinib (a Janus kinase 2 (JAK2) inhibitor), tofacitinib (a JAK3 inhibitor), vismodegib (a Smoothened antagonist), fingolimod (a sphingosine-1-phosphate 1 (S1P1) receptor antagonist; the active form is the *S*-phosphorylated metabolite) and ticagrelor (a P2Y purinergic receptor 12 (P2Y12) antagonist). Although these targets vary substantially in their druggability, with the relative druggability ranging from $5\text{-}HT_{2C}$ and HDAC1 at the higher end to renin and CCR5 at the lower end, the median percentage of molecules per target with superior combined LE and LLE values for these 'only-in-class' drugs is just 1.5%.

Among other targets shown in FIG. 5, two NS3 protease inhibitors — boceprevir and telaprevir — were both approved in 2011 for the treatment of hepatitis C virus infection. NS3 protease is a challenging target for developing inhibitors with good physicochemical properties, but boceprevir is clearly highly optimized in the class, with only 1.0% of NS3 inhibitors having better combined LE and LLE values. For telaprevir, which possesses a bicyclic structural moiety that is absent in boceprevir, 38% of NS3 inhibitors have a better LE and LLE profile. Both drugs are covalent inhibitors that have slow dissociation kinetics and require high doses (750 mg for telaprevir and 800 mg for boceprevir, both three times daily). However, the physicochemical properties of telaprevir result in very low solubility[61], requiring a non-standard formulation, and it also carries a boxed warning on the label for the risk of serious skin reactions.

Many anticancer drugs that inhibit kinases show non-optimal LE and LLE values for their targets (FIG. 5). The median percentages of compounds per target that have better LE and LLE values in FIG. 5 are 22% for kinase inhibitors and 2.7% for the other target classes. An example is vascular endothelial growth factor receptor 2 (VEGFR2) kinase, for which three drugs (sunitinib, sorafenib and pazopanib) are non-optimal but the newest drug (axitinib) is highly optimized. A recent study of clinical VEGFR inhibitors emphasizes the value of

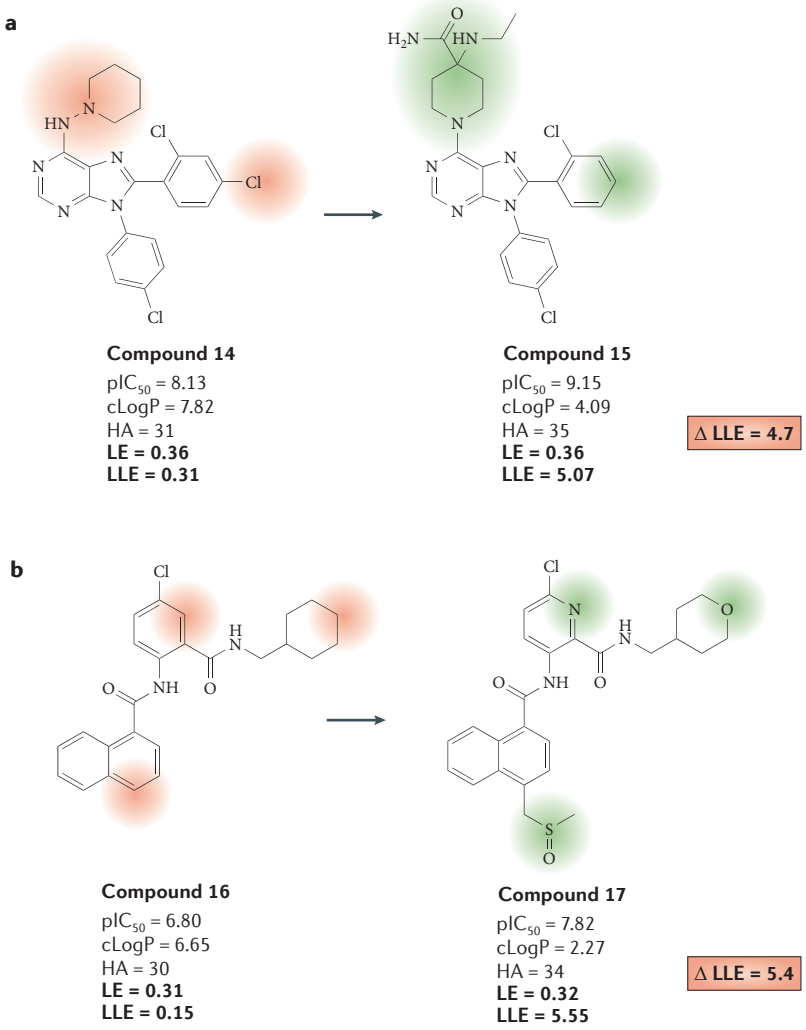


Figure 7 | **Explicit use of lipophilic ligand efficiency in optimizing compounds acting at the cannabinoid receptor CB_1.** For the cannabinoid 1 (CB_1) receptor, high affinity is often associated with high lipophilicity. In the ChEMBL database there are 3,606 p(Activity) values (negative logarithmic values of the half-maximal inhibitory concentration (pIC_{50}), effector concentration for half-maximum response (pEC_{50}) or inhibition constant (pK_i)) reported for the CB_1 receptor, with the following median values: p(Activity) = 7.1, cLogP = 5.8, lipophilic ligand efficiency (LLE; based on cLogP) = 1.2; only 2.7% of the compounds have LLE values >5. The optimization examples illustrate that increases in LLE of up to 5 units are possible, even when starting with unpromising leads (LLE <2), without reducing ligand efficiency (LE). Highlighted areas indicate the design approaches used: namely, the conversion of carbon atoms to non-carbon atoms, addition of new polar substituents and removal of lipophilic substituents. **a** | Candidate antagonist 15 from optimization of lead compound 14 (REF. 76). **b** | Agonist 17 with low central nervous system penetration, derived from screening hit 16 (REF. 77).

ligand efficiency analysis, showing that LLE correlates with kinase selectivity as well as clinical efficacy[62], with the latter probably driven by relative exposure levels. In the case of epidermal growth factor receptor (EGFR) kinase, all four drugs have non-optimal LE and LLE values. The difference between kinase inhibitors and other drug classes with respect the extent to which LE and LLE are optimized may be due to the primary pursuit in the discovery phase of selectivity[63] versus other kinases, and the acceptance of higher safety risk–benefit profiles for the treatment of cancer. Only one kinase inhibitor drug, the JAK3 inhibitor tofacitinib[64], is aimed at a non-cancer indication, and it has the best combined LE and LLE values of all reported JAK3 ligands. Among drug families (FIG. 5), highly optimal LE and LLE values are seen for all three factor Xa inhibitors[65], rivaroxaban, apixaban and edoxaban (only 0.2%, 0.9% and 1.1%, respectively, of reported molecules have better LE and LLE values), as well as for the non-prodrug parent molecules of the thrombin inhibitors melagatran and dabigatran (only 1.1% and 6.5%, respectively, of reported molecules have better LE and LLE values). For dipeptidyl peptidase 4 (DPP4) inhibitors, improvements in the most recently approved molecule (saxagliptin) are seen compared to the first-in-class molecule (sitagliptin); a similar trend is seen for endothelin A receptor antagonists.

Application of efficiency metrics in optimization

The analysis of oral drugs in FIG. 5 indicates that plotting LE versus LLE values could be useful for analysing and tracking the progress of hit-to-lead and lead optimization projects, as well as for evaluating the relative properties of clinical candidates. In LE versus LLE plots, there is some level of redundancy as a potency-related term appears on both axes, but the purpose of using LE and LLE together is for data visualization rather than establishing quantitative correlations. In addition to assessing LE versus LLE, it is essential to separately examine the independent component parameters by constructing plots of potency versus both heavy atom count (or molecular mass) and lipophilicity (cLogP or LogD). The correlation between LE and LLE will increase when both size and lipophilicity influence potency to a similar extent. However, potency versus property relationships often have low correlation coefficients and vary according to the target and ligand chemotype (FIG. 4c, 4d).

An example of a plot of LE versus LLE is shown in FIG. 6a for CCR5 (REF. 66), for which there has been an intensive effort to find antagonists for the treatment of HIV and rheumatoid arthritis. CCR5 also proved to be a useful target for assessing different drug design practices in the pharmaceutical industry[7]. The only molecule to be approved for HIV so far is maraviroc, and its combined LE and LLE values are better than those of the other CCR5 antagonists that have been clinical candidates for HIV treatment (FIG. 6a). A major challenge associated with CCR5 ligands has been reducing unwanted cardiovascular risk due to inhibition of the hERG ion channel. This can be accomplished by reducing lipophilicity in combination with structure–activity optimization[67].

One of the most challenging targets, in terms of obtaining compounds with drug-like physicochemical properties, is the cholesteryl ester transfer protein (CETP)[68], which is a target for atherosclerosis as its inhibition raises high-density lipoprotein (HDL) cholesterol levels[69]. The co-substrates of CETP are the highly lipophilic cholesteryl ester and triglycerides, and inhibitors of this target — including four molecules

that have reached late-stage clinical trials — have low LE and very low LLE values (FIG. 6b shows LE versus LLE, and the negative logarithmic value of the half-maximal inhibitory concentration (pIC_{50}) versus cLogP, for CETP inhibitors). Nevertheless, HTS has identified a class of benzoxazoles[70–73], which are apparently not yet fully optimized, with markedly improved LE and LLE values compared to the clinical candidates. In addition, further optimization of the highly lipophilic candidate torcetrapib (which was discontinued in Phase III) has resulted in analogues that have a significantly lowered lipophilicity yet equal potency[74], and that increase LLE by ~4 units without having an adverse effect on LE (compare compounds 7 and 13 in FIG. 6b). In this example, a stated strategy was to "mitigate lipophilicity"[74], which was successfully achieved, although no LogP or LogD or LLE values were actually cited. Explicit use of quantitative LE and LLE measures during optimization, assisted by visualizations of LE versus LLE and potency versus lipophilicity and size, is the approach we recommend. By contrast, optimization of a class of diphenylpyridylethanamine CETP inhibitors[75], which was conducted without the obvious consideration of LE or lipophilicity, resulted in a lead compound, compound 20 in REF. 75, with an unfavourable negative LLE value ($pIC_{50} = 7.44$, cLogP = 8.96, LLE = –1.52).

The cannabinoid receptor CB_1 is another target with highly lipophilic endogenous ligands, where it has been challenging to control physicochemical properties. Specific application of the LLE concept has been successfully used in the optimization of both CB_1 receptor antagonists[76] and agonists[77] (FIG. 7). In these examples, unpromising LLE values (of close to zero) in the lead compounds were impressively increased by ~5 units while retaining constant LE values.

To conclude, even for the least tractable targets that appear to have highly lipophilic small-molecule binding sites, the search for compounds with improved properties is facilitated when the focus is placed on improving ligand efficiency values. The direction of optimization in LE versus LLE plots is towards the 'north east', whereas in potency versus lipophilicity (cLogP or LogD) or size plots the direction of optimization should proceed towards the 'north west'. In either case, property-based design should seek to extend the boundaries of these plots to new, unoccupied territory. In addition to LE versus LLE and potency versus size and lipophilicity, other visualizations that are useful for optimization purposes include potency versus LE, LLE, LELP and LLE_{AT}; LE versus cLogP or LogD; LLE versus heavy atom count or molecular mass; and the property forecast index[3] (PFI = LogP or LogD + aromatic ring count) versus LLE_{AT} (REF. 65). Lipophilic efficiency parameters for agonists can be adjusted if required to take into account intrinsic activity[78].

Overall, the retrospective analysis of successful drugs indicates that optimizing LE and LLE in concert is an important success factor for hit and lead optimization in drug discovery projects. Controlling lipophilicity is at the heart of successful optimization. Most of the medicinal chemistry designs used in the examples shown in FIG. 2 that led to increases in LLE did not require radical structural changes such as new core scaffolds. The examples of compound 7 to compound 13 in FIG. 6b, and those in FIG. 7, are typical. Tactics (FIG. 7) include replacing carbon atoms with oxygen or nitrogen atoms, especially converting phenyl rings to heteroaromatic rings, polar substitution, removing or replacing lipophilic substituents and templates and controlling the increase in the heavy atom count. Incorporation of polar functional groups that both lower lipophilicity and increase or retain binding affinity is probably due to new polar ligand–receptor contacts[79] (for example, hydrogen bonds), which will radically alter structure–affinity relationships and consequently provide new optimization opportunities. That said, finding the appropriate regions of a lead molecule that can be changed in these ways may be the biggest challenge; highly lipophilic hits or leads that are resistant to this approach should be quickly dropped. Finally, LLE correlates positively with the drug efficiency index (DEI)[80]. DEI is a very useful metric for application in lead optimization projects, as it combines the estimated fraction of the dose that is available freely in plasma with *in vitro* potency.

Conclusion

Ligand efficiency metrics provide an estimate of the price paid in terms of physicochemical property alterations when optimizing compounds to increase their affinity for a drug target. The use of efficiency metrics in optimization instead of potency alone is recommended at all stages of drug discovery, starting with the selection of a fragment or a screening hit. Oral drugs, especially those that are first-in-class in therapy areas with stringent risk–benefit requirements, frequently have highly optimized ligand efficiency values for their target.

A key consideration for drug designers is an awareness of the changes in potency that are required to keep ligand efficiency values at least constant when altering a lead structure. When all published molecules with activity at specific targets are considered, high correlations between affinity and size or lipophilicity are not frequent and so it is not always necessary to increase these physicochemical properties to increase affinity. The tendency to increase lipophilicity during the optimization of individual series of molecules can be countered by focusing on lipophilic efficiency. This is becoming recognized as a key strategy in lead optimization[43,81] and has been successfully used on many different targets.

We consider that the application of ligand efficiency principles, together with the synthesis of compounds with acceptable drug-like physicochemical properties, are key elements of best practice in drug design. We also believe this approach is applicable to any target containing a bona fide small-molecule binding site. Finally, we note that the hypothesis proposed by Hansch and co-workers[45] 25 years ago embraced the concept of LLE, and is withstanding the test of time: "Without convincing evidence to the contrary, drugs should be made as hydrophilic as possible without loss of efficacy."

1. Leeson, P. D. & Oprea, T. I. in *Drug Design Strategies: Quantitative Approaches* Ch. 2 (eds Livingstone, D. J. & Davis, A. M.) (Royal Society of Chemistry, 2012).
2. Gleeson, M. P., Hersey, A., Montanari, D. & Overington, J. Probing the links between *in vitro* potency, ADMET and physicochemical parameters. *Nature Rev. Drug Discov.* **10**, 197–208 (2011).
3. Young, R. J., Green, D. V., Luscombe, C. N. & Hill, A. P. Getting physical in drug discovery II: the impact of chromatographic hydrophobicity measurements and aromaticity. *Drug Discov. Today* **16**, 822–830 (2011).
4. Waring, M. Defining optimum lipophilicity and molecular weight ranges for drug candidates — molecular weight dependent lower logD limits based on permeability. *Bioorg. Med. Chem. Lett.* **19**, 2844–2851 (2009).
5. Johnson, T. W. *et al.* Using the golden triangle to optimize clearance and oral absorption. *Bioorg. Med. Chem. Lett.* **19**, 5560–5564 (2009).
6. Gleeson, M. P. Generation of a set of simple, interpretable ADMET rules of thumb. *J. Med. Chem.* **51**, 817–834 (2008).
7. Leeson, P. D. & Springthorpe, B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nature Rev. Drug Discov.* **6**, 881–890 (2007).
   In this paper, LLE is proposed as a measure of specificity.
8. Hughes, J. D. *et al.* Physiochemical drug properties associated with *in vivo* toxicological outcomes. *Bioorg. Med. Chem. Lett.* **18**, 4872–4875 (2008).
9. Luker, T. *et al.* Strategies to improve *in vivo* toxicology outcomes for basic candidate drug molecules. *Bioorg. Med. Chem. Lett.* **21**, 5673–5679 (2011).
10. Wenlock, M. C., Austin, R. P., Barton, P., Davis, A. M. & Leeson, P. D. A comparison of physiochemical property profiles of development and marketed oral drugs. *J. Med. Chem.* **46**, 1250–1256 (2003).
11. Leeson, P. D. & Empfield, J. R. Reducing the risk of drug attrition associated with physicochemical properties. *Ann. Rep. Med. Chem.* **45**, 393–407 (2010).
12. Leeson, P. D. & Davis, A. M. Time-related differences in the physical property profiles of oral drugs. *J. Med. Chem.* **47**, 6338–6348 (2004).
13. Proudfoot, J. R. The evolution of synthetic oral drug properties. *Bioorg. Med. Chem. Lett.* **15**, 1087–1090 (2005).
14. Leeson, P. D., St-Gallay, S. A. & Wenlock, M. C. Impact of ion class and time on oral drug molecular properties. *Med. Chem. Commun.* **2**, 91–105 (2011).
15. Walters, W. P., Green, J., Weiss, J. R. & Murcko, M. A. What do medicinal chemists actually make? A 50-year retrospective. *J. Med. Chem.* **54**, 6405–6416 (2011).
16. Bickerton, G. R., Paolini, G. V., Besnard, J., Muresan, S. & Hopkins, A. L. Quantifying the chemical beauty of drugs. *Nature Chem.* **4**, 90–98 (2012).
17. Leeson, P. D. & St-Gallay, S. A. The influence of the 'organizational factor' on compound quality in drug discovery. *Nature Rev. Drug Discov.* **10**, 749–765 (2011).
18. Lovering, F., Bikker, J. & Humblet, C. Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **52**, 6752–6756 (2009).
19. Blake, J. F. Examination of the computed molecular properties of compounds selected for clinical development. *Biotechniques Suppl.* 16–20 (2003).
20. Paolini, G. V., Shapland, R. H., van Hoorn, W. P., Mason, J. S. & Hopkins, A. L. Global mapping of pharmacological space. *Nature Biotech.* **24**, 805–815 (2006).
21. Keserü, G. M. 5th Drug Design Lead Discovery Conference 2009: lead finding strategies and optimization case studies. *Drugs Fut.* **35**, 143–153 (2010).
22. Hann, M. M. Molecular obesity, potency and other addictions in drug discovery. *Med. Chem. Comm.* **2**, 349–355 (2011).
23. Keserü, G. M. & Makara, G. M. The influence of lead discovery strategies on the properties of drug candidates. *Nature Rev. Drug Discov.* **8**, 203–212 (2009).
24. Oprea, T. I., Davis, A. M., Teague, S. J. & Leeson, P. D. Is there a difference between leads and drugs? A historical perspective. *J. Chem. Inf. Comput. Sci.* **41**, 1308–1315 (2001).
25. Hann, M. M., Leach, A. R. & Harper, G. Molecular complexity and its impact on the probability of finding leads for drug discovery. *J. Chem. Inf. Comput. Sci.* **41**, 856–864 (2001).
    This paper explains why small compounds such as fragments have a higher probability than larger compounds (for example, those in a typical HTS library) of binding to protein targets.
26. Hopkins, A. L., Groom, C. R. & Alex, A. Ligand efficiency: a useful metric for lead selection. *Drug Discov. Today* **9**, 430–431 (2004).
    This paper defines the LE concept and proposes it as a measure to help prioritize screening hits.
27. Kuntz, I. D., Chen, K., Sharp, K. A. & Kollman, P. A. The maximal affinity of ligands. *Proc. Natl Acad. Sci. USA* **96**, 9997–10002 (1999).
    This seminal article lays the foundations for the derivation of LE metrics.
28. Andrews, P. R., Craik, D. J. & Martin, J. L. Functional group contributions to drug–receptor interactions. *J. Med. Chem.* **27**, 1648–1657 (1984).
29. Shultz, M. D. Setting expectations in molecular optimizations: strengths and limitations of commonly used composite parameters. *Bioorg. Med. Chem. Lett.* **23**, 5980–5991 (2013).
30. Freire, E. Do enthalpy and entropy distinguish first in class from best in class? *Drug Discov. Today* **13**, 869–874 (2008).
31. Ferenczy, G. G., Keserü, G. M. in *Physico-Chemical and Computational Approaches to Drug Discovery* Ch. 2 (eds Luque, J. & Barril, X.) (Royal Society of Chemistry, 2012).
32. Olsson, T. S. G., Williams, M. A., Pitt, W. R. & Ladbury, J. E. The thermodynamics of protein–ligand interaction and solvation: insights for ligand design. *J. Mol. Biol.* **384**, 1002–1017 (2008).
33. Freire, E. A thermodynamic approach to the affinity optimization of drug candidates. *Chem. Biol. Drug Des.* **74**, 468–472 (2009).
34. Ferenczy, G. G. & Keserü, G. M. Thermodynamics guided lead discovery and optimization. *Drug Discov. Today* **15**, 919–932 (2010).
35. Ladbury, J. E., Klebe, G. & Freire, E. Adding calorimetric data to decision making in lead discovery: a hot tip. *Nature Rev. Drug Discov.* **9**, 23–27 (2010).
36. Ferenczy, G. G. & Keserü, G. M. Enthalpic efficiency of ligand binding. *J. Chem. Inf. Mod.* **50**, 1536–1541 (2010).
37. Hann, M. M. & Keserü, G. M. Finding the sweet spot — the role of nature and nurture in medicinal chemistry. *Nature Rev. Drug Discov.* **11**, 355–365 (2012).
38. Reynolds, C. H., Bembenek, S. D. & Tounge, B. A. The role of molecular size in ligand efficiency. *Bioorg. Med. Chem. Lett.* **17**, 4258–4261 (2007).
39. Reynolds, C. H., Tounge, B. A. & Bembenek, S. D. Ligand binding efficiency: trends, physical basis, and implications. *J. Med. Chem.* **51**, 2432–2438 (2008).
    This paper demonstrates that LE has a significant size-dependence that can be explained in terms of simple molecular principles.
40. Loving, K., Alberts, I. & Sherman, W. Computational approaches for fragment-based and *de novo* design. *Curr. Top. Med. Chem.* **10**, 14–32 (2012).
41. Liu, T., Lin, Y., Wen, X., Jorissen, R. N. & Gilson, M. K. BindingDB: a web-accessible database of experimentally determined protein-ligand binding affinities. *Nucl. Ac. Res.* **35**, D198–D201 (2007).
42. Reynolds, C. H. & Holloway, M. K. Thermodynamics of ligand binding and efficiency. *ACS Med. Chem. Lett.* **2**, 433–437 (2011).
43. Shultz, M. D. The thermodynamic basis for the use of lipophilic efficiency (LipE) in enthalpic optimizations, *Bioorg. Med. Chem. Lett.* **23**, 5992–6000 (2013).
44. Tarcsay, A., Nyiri, K. & Keserü, G. M. Impact of lipophilic efficiency on compound quality. *J. Med. Chem.* **55**, 1252–1260 (2012).
45. Hansch, C., Bjoerkroth, J. P. & Leo, A. Hydrophobicity and central nervous system agents: on the principle of minimal hydrophobicity in drug design. *J. Pharm. Sci.* **76**, 663–687 (1987).
46. Waring, M. Lipophilicity in drug discovery. *Exp. Opin. Drug Discov.* **5**, 235–248 (2010).
47. Lipinski, C. A., Lombardo, F., Dominy, B. W. & Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **23**, 3–25 (1997).
48. Mortenson, P. N. & Murray, C. W. Assessing the lipophilicity of fragments and early hits. *J. Comput. Aided Mol. Des.* 663–667 (2011).
49. Wager, T. T. *et al.* Defining desirable central nervous system drug space through the alignment of molecular properties, *in vitro* ADME, and safety attributes. *ACS Chem. Neurosci.* **1**, 420–434 (2010).
50. Perola, E. An analysis of the binding efficiencies of drugs and their leads in successful drug discovery programs. *J. Med. Chem.* **53**, 2986–2997 (2010).
    This analysis of leads of 60 recently launched drugs shows that mean potency and LLE increased in optimization, whereas mean lipophilicity did not.
51. Morphy, R. The influence of target family and functional activity on the physicochemical properties of pre-clinical compounds. *J. Med. Chem.* **49**, 2969–2978 (2006).
52. Baker, M. Fragment-based lead discovery grows up. *Nature Rev. Drug Discov.* **12**, 5–7 (2013).
53. Tsai, J. *et al.* Discovery of a selective inhibitor of oncogenic B-Raf kinase with potent antimelanoma activity. *Proc. Natl Acad. Sci. USA* **105**, 3041–3046 (2008).
54. Verdonk, M. L. & Rees, D. C. Group efficiency: a guideline for hits-to-leads chemistry. *ChemMedChem* **3**, 1179–1180 (2008).
55. Drysdale, M. J. & Brough, P. A. Medicinal chemistry of Hsp90 inhibitors. *Curr. Top. Med. Chem.* **8**, 859–868 (2008).
56. Murray, C. W. *et al.* Fragment-based drug discovery applied to Hsp90. Discovery of two lead series with high ligand efficiency. *J. Med. Chem.* **53**, 5942–5955 (2010).
57. Woodhead, A. J. *et al.* Discovery of (2,4-dihydroxy-5-isopropylphenyl)-[5-(4-methylpiperazin-1-ylmethyl)-1,3-dihydrois oindol-2-yl]methanone (AT13387), a novel inhibitor of the molecular chaperone Hsp90 by fragment based drug design. *J. Med. Chem.* **53**, 5956–5969 (2010).
58. Ferenczy, G. G. & Keserü, G. M. How are fragments optimized? A retrospective analysis of 145 fragment optimizations. *J. Med. Chem.* **56**, 2478–2486 (2013).
59. Jhoti, H., Williams, G., Rees, D. C. & Murray, C. W. The 'rule of three' for fragment-based drug discovery: where are we now? *Nature Rev. Drug Discov.* **12**, 644–645 (2013).
60. Vieth, M. & Sutherland, J. J. Dependence of molecular properties on proteomic family for marketed oral drugs. *J. Med. Chem.* **49**, 3451–3453 (2006).
61. Kwong, A. D., Kauffman, R. S., Hurter, P. & Mueller, P. Discovery and development of telaprevir: an NS3-4A protease inhibitor for treating genotype 1 chronic hepatitis C virus. *Nature Biotech.* **29**, 993–1003 (2011).
62. McTigue, M. *et al.* Molecular conformations, interactions, and properties associated with drug efficiency and clinical performance among VEGFR TK inhibitors. *Proc. Natl Acad. Sci. USA* **109**, 18281–18289 (2012).
    This paper shows that LLE values of VEGFR inhibitors correlate with clinical efficacy.
63. Davis, M. I. *et al.* Comprehensive analysis of kinase inhibitor selectivity. *Nature Biotech.* **29**, 1046–1051 (2011).
64. Soth, M. *et al.* 3-amido pyrrolopyrazine JAK kinase inhibitors: development of a JAK3 versus JAK1 selective inhibitor and evaluation in cellular and *in vivo* models. *J. Med. Chem.* **56**, 345–356 (2013).
65. Young, R. J. The successful quest for oral factor Xa inhibitors; learnings for all of medicinal chemistry? *Bioorg. Med. Chem. Lett.* **21**, 6228–6235 (2011).
    This article proposes a general approach for assessing compound quality, exemplified by clinically available factor Xa inhibitors, which have a lower hydrophobicity and higher LLE_{AT} values than other published inhibitors.
66. Lemoine, R. C. & Wanner, J. Small molecule antagonists of the chemokine receptor CCR5. *Curr. Top. Med. Chem.* **10**, 1299–1338 (2010).
67. Cumming, J. *et al.* Balancing hERG affinity and absorption in the discovery of AZD5672, an orally active CCR5 antagonist for the treatment of rheumatoid arthritis. *Bioorg. Med. Chem. Lett.* **22**, 1655–1659 (2012).
68. Charles, M. A. & Kane, J. P. New molecular insights into CETP structure and function: a review. *J. Lipid Res.* **53**, 1451–1458 (2012).
69. Mantlo, N. B. & Escribano, A. Update on the discovery and development of cholesteryl ester transfer protein inhibitors for reducing residual cardiovascular risk. *J. Med. Chem.* **57**, 1–17 (2014).

70. Hunt, J. A. *et al.* 2-arylbenzoxazoles as CETP inhibitors: substitution and modification of the α-alkoxyamide moiety. *Bioorg. Med. Chem. Lett.* **20**, 1019–1022 (2010).
71. Sweis, R. F. *et al.* 2-(4-carbonylphenyl)benzoxazole inhibitors of CETP: attenuation of hERG binding and improved HDLc-raising efficacy. *Bioorg. Med. Chem. Lett.* **21**, 2597–2600 (2011).
72. Kallashi, F. *et al.* 2-arylbenzoxazoles as CETP inhibitors: raising HDL-C in cynoCETP transgenic mice. *Bioorg. Med. Chem. Lett.* **21**, 558–561 (2011).
73. Harikrishnan, L. S. *et al.* 2-arylbenzoxazoles as novel cholesteryl ester transfer protein inhibitors: optimization via array synthesis. *Bioorg. Med. Chem. Lett.* **18**, 2640–2644 (2008).
74. Fernanadez, M.-C. *et al.* Design, synthesis and structure-activity-relationship of 1,5-tetrahydronaphthyridines as CETP inhibitors. *Bioorg. Med. Chem. Lett.* **22**, 3056–3062 (2012).
75. Harikrishnan, L. S. *et al.* Diphenylpyridylethanamine (DPPE) derivatives as cholesteryl ester transfer protein (CETP) inhibitors. *J. Med. Chem.* **55**, 6162–6175 (2012).
76. Griffith, D. A. *et al.* Discovery of 1-[9-(4-chloro-phenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4 ethylaminopiperidine-4-carboxylic acid amide hydrochloride (CP-945,598), a novel, potent, and selective cannabinoid type 1 receptor antagonist. *J. Med. Chem.* **52**, 234–237 (2009).
77. Plowright, A. T. *et al.* Discovery of agonists of cannabinoid receptor 1 with restricted central nervous system penetration aimed for treatment of gastroesophageal reflux disease. *J. Med. Chem.* **56**, 220–240 (2013).
78. Darout, E. *et al.* Design and synthesis of diazatricyclodecane agonists of the G-protein-coupled receptor 119. *J. Med. Chem.* **56**, 301–319 (2013).
79. Higueruelo, A. P., Schreyer, A., Bickerton, G. R. J., Blundell, T. L. & Pitt, W. R. What can we learn from the evolution of protein–ligand interactions to aid the design of new therapeutics? *PLoS ONE* **7**, e51742 (2012).
80. Valko, K., Chiarparin, E., Nunhuck, S. & Montanari, D. *In vitro* measurement of drug efficiency index to aid early lead optimization. *J. Pharm. Sci.* **101**, 4155–4169 (2012).
81. Freeman-Cook, K. D., Hoffman, R. L. & Johnson, T. W. Lipophilic efficiency: the most important efficiency metric in medicinal chemistry. *Future Med. Chem.* **5**, 113–115 (2013).
82. Abad-Zapatero, C. Ligand efficiency indices for effective drug discovery. *Exp. Opin. Drug Discov.* **2**, 469–488 (2007).
83. Mannhold, R., Poda, G. I., Ostermann, C. & Tetko, I. V. Calculation of molecular lipophilicity: state-of-the-art and comparison of logP methods on more than 96,000 compounds. *J. Pharm. Sci.* **98**, 861–893 (2009).
84. Nissink, J. W. M. Simple size-independent measure of ligand efficiency. *J. Chem. Inf. Model.* **49**, 1617–1622 (2009).
85. Southan, C., Boppana, K., Jagarlapudi, S. A. & Muresan, S. Analysis of *in vitro* bioactivity data extracted from drug discovery literature and patents: ranking 1654 human protein targets by assayed compounds and molecular scaffolds. *J. Cheminform.* **3**, 14 (2011).
86. Klibanov, O. M., Williams, S. H. & Iler, C. A. Cenicriviroc, an orally active CCR5 antagonist for the potential treatment of HIV infection. *Curr. Opin. Investigat. Drugs* **11**, 940–950 (2010).

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Competing interests statement
The authors declare no competing interests.

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