A GUIDE TO DRUG DISCOVERY — OPINION

Finding the sweet spot: the role of nature and nurture in medicinal chemistry

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Abstract | Given its position at the heart of small-molecule drug discovery, medicinal chemistry has an important role in tackling the well-known productivity challenges in pharmaceutical research and development. In recent years, extensive analyses of successful and failed discovery compounds and drug candidates have improved our understanding of the role of physicochemical properties in drug attrition. Based on the clarified challenges in finding the 'sweet spot' in medicinal chemistry programmes, we suggest that this goal can be achieved through a combination of first identifying chemical starting points with appropriate 'nature' and then rigorously 'nurturing' them during lead optimization. Here, we discuss scientific, strategic, organizational and cultural considerations for medicinal chemistry practices, with the aim of promoting more effective use of what is already known, as well as a wider appreciation of the risks of pursuing suboptimal compounds.

Small-molecule drug discovery involves discovering what is often described as a lead compound and then optimizing its properties through structural modifications to achieve a profile that not only provides the desired efficacy at an acceptable dose but also minimizes any toxicological liabilities. As pointed out by Paracelsus[1] in the sixteenth century: "All things are poison, and nothing is without poison; only the dose permits something not to be poisonous."

Based on analyses comparing compounds that have become marketed drugs with those that failed during development, concepts of drug-like chemical property space emerged in the late 1990s and early 2000s[2–4]. Around the same time, it was realized that it is difficult to avoid property inflation — that is, increases in molecular properties such as molecular mass and cLogP (the computed octanol–water partition coefficient, which in general correlates well with experimental logP)[5] — during the progression from historical leads to the final drug molecule, and that the appropriate selection of starting points for leads was important[6–8]. Nevertheless, despite recognition of such issues, a recent analysis by Leeson and Springthorpe[9] of patent data from several pharmaceutical companies indicated that recent medicinal chemistry efforts are still often producing compounds with much higher molecular mass and cLogP values than historical drugs. These and other authors[10–13] have linked this trend to the likelihood of compounds failing in development as a result of poor ADMET (absorption, distribution, metabolism, excretion and toxicity) characteristics.

From these and many other analyses of what might be described as the metadata of medicinal chemistry efforts, it is apparent that a key challenge for successful drug discovery is finding a balance (or 'sweet spot') between two aspects: acknowledging the constraints on the physicochemical properties of drug candidates imposed by the higher risks of compound-related attrition outside the 'drug-like space'; and maintaining sufficient potency to provide an efficacious dose (BOX 1). Considering only two of the most important (although not completely independent) physicochemical properties — molecular mass and cLogP — it seems that sufficient potency usually requires a certain molecular mass (or complexity) and lipophilicity that could be in conflict with the constraints of drug-like space, as initially formulated in Lipinski's seminal paper[2]. The consequences of higher lipophilicity, its linkage to the quest for potency and the overall impact of these factors on the attrition of compounds during drug development have been termed 'molecular obesity'[14,15].

We would like to emphasize that attrition may be due to multiple reasons, including flaws in the therapeutic hypothesis being pursued (for example, owing to insufficiently rigorous target validation), insufficient efficacy and ADMET problems, as well as commercial and strategic issues. Although some of these reasons, such as therapeutic hypothesis validity and commercial strategy, are outside the control of medicinal chemistry teams and so are not considered further here, it is clear that problems related to insufficient efficacy and ADMET issues can be strongly influenced by compound quality. Ensuring that these aspects are effectively addressed by medicinal chemists will have an important role in reducing attrition rates overall.

With this goal in mind, it is becoming more widely accepted by medicinal chemists that it is important to identify good chemical starting points for lead optimization and then carefully monitor indices such as ligand efficiency[16] to avoid 'molecular obesity'[17]. Indeed, finding good-quality 'lean' starting points is necessary but not sufficient for achieving success, as it is easy to squander good starting points by pursuing an inappropriate 'diet' during lead optimization[18]. This is somewhat analogous to the debate on the role of nature and nurture in physical and behavioural traits in humans, with nature in this case being the chemical starting point and nurture being the medicinal chemistry optimization. The best outcomes in the identification of candidate drugs are likely to come from the effective combination of both a good starting point

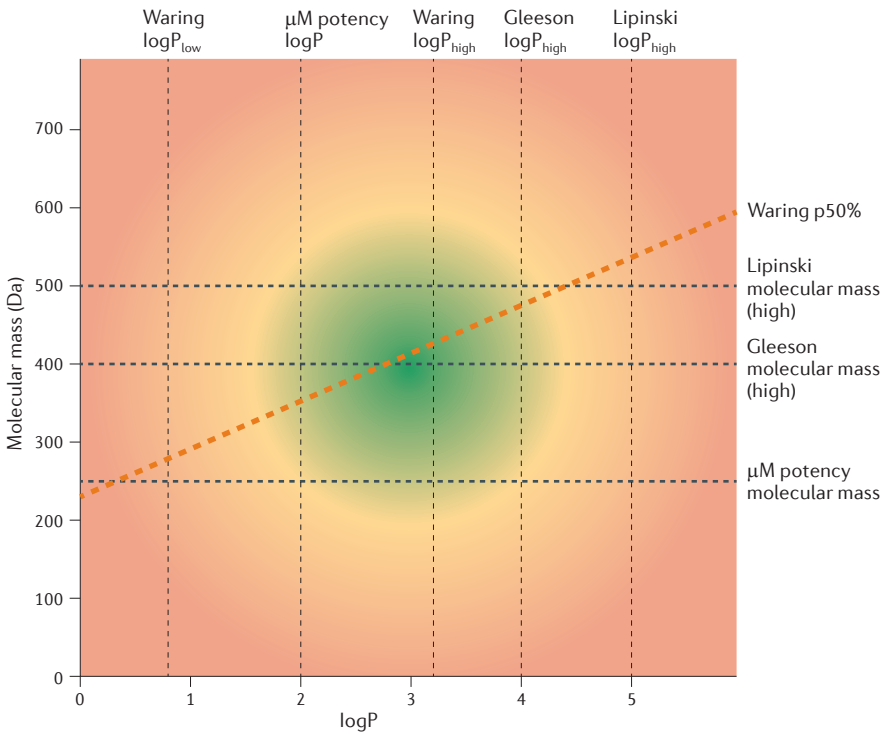
Box 1 | **The drug discovery 'sweet spot' defined in the molecular mass–logP space**

A key challenge in medicinal chemistry can be illustrated by highlighting the 'sweet spot' in the chemical space defined by the two key (although not fully independent) physicochemical properties: molecular mass and cLogP (the computed octanol–water partition coefficient). As shown in the figure, the influence of just these two properties on the ADMET (absorption, distribution, metabolism, excretion and toxicity) characteristics of the compounds narrows the range of values that are acceptable from a drug-like perspective. Given all the other bulk and molecularly specific interactions as well as other parameters — such as solubility, clearance and volume of distribution — that are relevant to the pharmacokinetics/pharmacodynamics profile of drug candidates, the extent of the challenge in identifying compounds in the 'sweet spot' is clear.

Analysing the effect of lipophilicity on ADMET properties, Waring[10] concluded that sufficient membrane permeability and renal clearance requires a logP >0.8. Permeability is another important aspect, as statistical observations suggest[11] that the higher the molecular mass of compounds undergoing passive diffusion, the higher the logD of the compounds needs to be. This dual effect of molecular mass and lipophilicity is more significant than the weak correlation found between these parameters in the drug-like space. Compounds above the Waring line in the figure below have a lower probability of cell permeability compared to those below it.

A set of simple and interpretable rules has been identified by Gleeson[12], who analysed the ADMET-related data set of 30,000 compounds at GlaxoSmithKline; this data set comprised solubility, permeability, bioavailability, volume of distribution, plasma protein binding, central nervous system penetration, brain tissue binding, P-glycoprotein efflux, hERG (also known as KCNH2) potassium channel inhibition and inhibition of the cytochromes P450 CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. These rules, often referred to as the GlaxoSmithKline 4/400 rule, suggest that compounds with a cLogP >4 and molecular mass >400 Da have a less favourable ADMET profile[12]. Large-scale analysis[13] of more than 200,000 compounds (available from the ChEMBL database) revealed that compounds with micromolar potency have a molecular mass >250 Da and a cLogP >2. These limits indicate that sufficient potency usually requires a certain level of complexity and lipophilicity that can often be in conflict with concepts of drug-likeness.

The figure is based on data from REFS 10–13. Waring $logP_{low}$ and $logP_{high}$ limits are the lower and upper logP limits obtained from REF. 10, and the 50% probability line of cell permeability (Waring p50%) is derived from REF. 11. The tendency for increased lipophilicity to enable the passage of larger molecules is represented by the diagonal line (which is the line of best fit to Waring's data). Gleeson molecular mass and logP are the upper limits (derived from REF. 12), average molecular mass and logP values related to micromolar potency (μM potency) are derived from REF. 13, and Lipinski molecular mass and logP limits are derived from REF. 2.



(nature) and appropriate optimization (nurture), rather than being dogmatic about the importance of one over the other.

In this article, we integrate the findings from a range of analyses of the physicochemical properties that are important for successful drugs to provide a basis for discussing why current medicinal chemistry practices may still be producing compounds with suboptimal drug-like characteristics, and consequently increasing the risk of compound-related attrition in development. We also propose strategies and guidelines that could help in improving the quality of compounds for clinical development.

Why we get into bad property space

Several studies on different data sets have reported undesired shifts in physicochemical properties for drug candidates. However, only a few have considered the reasons behind such shifts, and suggestions for strategies to combat them have been even rarer. Below, we discuss various issues that contribute to the observed inflation of physicochemical properties, and suggest strategies to avoid or reduce property inflation.

Target-related issues. The target dependency of the physicochemical profiles of compounds produced in discovery programmes was first quantified by Morphy[19] in 2006, based on an analysis of 1,680 medicinal chemistry optimizations. This revealed that the average molecular mass of compounds increases as the target class changes from transporters through to ion channels, aminergic G protein-coupled receptors (GPCRs), kinases, nuclear receptors, proteases, transferases and peptidergic GPCRs. A trend in average compound lipophilicity (as assessed by cLogP) was also observed: it was lowest for ion channels and proteases and increased for kinases, aminergic GPCRs and transporters. Compounds targeting peptidergic GPCRs and nuclear receptors had the highest average cLogP value. Similar conclusions have been drawn from the analysis of marketed oral drugs[20]. These observations suggest that targeting certain types of binding sites might increase the risk of undesirable physicochemical profiles for lead compounds. Indeed, lead discovery efforts on protein targets with large and apolar binding sites typically result in starting points with higher molecular mass and higher lipophilicity[19,21].

Here, we underline the importance of using medicinal chemistry knowledge and experience in target selection and feasibility

assessment. Understanding the likelihood of finding a lead-like compound that interacts effectively with the target (often based on an assessment of the characteristics of the putative ligand-binding pocket) should be a key step in setting up a new project. This is defined here as assessing the chemical tractability or 'ligandability' of a target, which is distinct to the druggability — a term that should be reserved for the likelihood of an efficacious drug eventually being discovered. Ligandability can be assessed by reference to knowledge on homologous structures[22] or by *in silico*[23] or fragment screening[24,25] to look for appropriate cavities. Instead of pushing targets that have inherently poor tractability through the discovery pipeline, it may well be more appropriate to explore other points that have higher tractability in a pathway. Investigation of unexplored kinetic, conformational or redox mechanisms of action of known tractable targets may also provide new therapeutic options[26].

It should be emphasized that we are not advocating that the difficult targets be ignored, but that medicinal chemists should be more aware of the problems associated with them. If it is deemed essential to work on a target that is likely to need compounds that go beyond the established drug-like space, then the consequences of this should be understood at the outset[27]. Design strategies should then be implemented to reduce the risks wherever possible — for example, through the use of intramolecular hydrogen bonding to improve membrane permeability and increase the absorption of larger molecules[28].

Although the physicochemical profile of compounds is certainly affected by the target, the data set compiled by Morphy[19] allows the investigation of shifts in molecular mass and logP that are associated with medicinal chemistry optimizations for different target classes. Interestingly, there was a significant shift in both the molecular mass and cLogP (42 Da and 0.4 logP units, respectively) independently of target family. Consequently, target-dependent differences in the physicochemical profile can be attributed to the properties of the chemical starting points, whereas optimization resulted in similar and target-independent shifts in physicochemical properties.

This finding is in line with the recent analysis of Leeson and St. Gallay[29], which demonstrates that in addition to differences in screening decks and starting points, behavioural and organizational effects are at least comparable to the effects of the target class in determining the physicochemical profile of optimized compounds. A limited impact of the target class has also been confirmed by Tyrchan *et al.*[30] in a study using more than three million structure–activity relationship data points collected for 898 human targets. By comparing marketed drugs and clinical candidates with bioactive compounds, these authors found that more than 90% of the targets are affected by property inflation. This inflation is independent of target class, although different target classes do need compounds with specific physicochemical profiles.

The impact of chemical starting points. Much has been written about the fragment-based drug discovery approach[31], which is based on identifying smaller, lower-affinity compounds (typically with a molecular mass of ~150–250 Da and with target affinity in the high micromolar to low millimolar range) than those used in conventional high-throughput screening (HTS). These fragments are then grown or linked to produce high-affinity leads, often with the aid of structural information on the protein target. This approach is now established as a part of the lead generation capabilities in most companies.

The advantages of this method can be summarized as follows[15]. First, the 'combinatorial explosion' of chemical space means that fragments can more effectively sample the available chemical space (at that level of complexity) than is possible with more complex molecules. Second, at a lower level of complexity, there is a higher probability of compounds matching the receptor, even though they may be harder to detect. More complex molecules are statistically more likely to have more 'clashes' and thus not fit or bind to the binding site. Third, medicinal chemists like to build molecules, and so starting small with fragments is the natural feedstock for structure-based design. Fourth, by starting small and selecting the most ligand-efficient compounds — that is, those compounds that provide the highest binding affinity to the target for a given number of non-hydrogen atoms (see below) — more lead-like starting points are found, which enhances the chances of successful lead optimization. Fifth, by reducing the number of pharmacophoric elements in the initial lead, only the necessary interactions are built into the compound as it is optimized. This helps to ensure that the resulting candidates have good developability properties and also provides the opportunity to integrate relevant polypharmacology if this is needed.

The impact of the chemical starting point can be illustrated by comparative analysis of leads from different sources. Literature data on the average molecular mass and cLogP of HTS leads (416.0 Da and 4.0, respectively) indicate that these compounds have a higher molecular mass and cLogP than marketed drugs[17]. Although it was suggested that improvements made in the screening decks of large pharmaceutical companies could improve lead quality, recent data from three companies (with an average molecular mass of 405.9 Da and an average cLogP of 3.7) do not entirely support this hope[32]. The quality of HTS leads is still close to that of the general medicinal chemistry output (an average molecular mass of 458.6 Da and average cLogP of 4.0)[29].

The evidence for the benefits of fragment-based strategies, as opposed to supposition of benefit, is only now beginning to emerge. Thus the data of Leeson and St-Gallay[29] show that a fragment-based approach (as illustrated by patent data from Astex Pharmaceuticals) can consistently lead to candidate-quality compounds with a lower cLogP (2.8) and molecular mass (392.6 Da) than other programmes performed on the same set of targets (mainly kinases). This should be viewed in the context of the earlier data assembled by Keserü and Makara[17] across a range of companies' published fragment-based projects, which suggested that fragment-based approaches can also yield molecules that are no better than those derived from HTS. This clearly illustrates the need to stay focused on the goal of 'lean' and efficient molecules, and the data for Astex Pharmaceuticals suggest that this can be effectively done when the company culture is built around this mantra.

The role of the optimization strategy. The key parameter pursued in many lead discovery and optimization programmes is a high *in vitro* potency, typically set in the low nanomolar range. Although by the time the lead optimization stage is reached, medicinal chemists have usually gained an understanding of other aspects, such as solubility, selectivity, cellular activity and ADMET properties, the dominant role of high *in vitro* potency in selecting compounds for progression during the process could be detrimental, given that it may be in conflict with good ADMET characteristics, particularly when the increased potency is driven by lipophilicity[33].

Ladbury and co-workers[34] analysed 254 protein–ligand complexes, representing 29 proteins and 176 ligands that had both

structural and thermodynamic data. They found that the difference in maximal affinity between binding sites correlates with the apolar surface burial at the protein–ligand interface. This has been confirmed for a much larger data set by Durrant and McCammon[35], who demonstrated that the average number of ligand–receptor hydrophobic contacts increases with increasing potency. These observations suggest that the maximal affinity is target-dependent and requires significant hydrophobic interactions between the compound and its target. Consequently, ligands for proteins with large and highly apolar binding sites can be readily optimized into the nanomolar range; however, these compounds have suboptimal physicochemical profiles that are characterized by high molecular mass and high cLogP. The large-scale analysis by Gleeson *et al.*[13] supports this hypothesis. By analysing more than 200,000 compounds with reported biological activity from the ChEMBL database, these authors found that *in vitro* potency increases in parallel with both molecular mass and clogP.

By investigating the thermodynamic basis of ligand binding, we (and others) have been able to rationalize these observations[18,36]. In terms of thermodynamics, optimization of *in vitro* potency is equivalent to improving the free energy of binding, which can be done by changing the enthalpic and/or entropic components. Enthalpy-driven optimization requires the formation of specific, often directional, contacts between the ligand and its protein counterpart. These interactions are typically hydrogen bonds, salt bridges or van der Waals contacts that are typically well used by endogenous ligands. As most of the orthosteric binding sites were evolutionarily formed for the recognition of endogenous compounds, one can hypothesize that interactions at binding hotspots characterized by high-density contacts are basically enthalpic in nature. The recent analysis of Ladbury and colleagues[34] supports this theory as most of the natural ligands in the SCORPIO data set showed enthalpy-dominant binding.

Designing exogenous compounds with similar high enthalpic binding is considerably more challenging. The gain in binding enthalpy can only be realized by high-quality interactions in which the interaction partners have optimal geometry. However, the polar atoms of ligands represent a significant entropic penalty upon desolvation, and this is independent of the orientation of interacting partners. In contrast to enthalpy-driven optimization, entropy-driven optimization is often easily realized by increasing the lipophilicity of the ligand, but a direct linkage between lipophilicity and entropic binding should not be made as there are many complexities in this relationship that are only now being revealed at a structural level[37,38].

The ease of making lipophilic interactions is also enabled by the lack of directionality of such interactions. Lipophilic compounds desolvate more readily, resulting in significant entropic reward. Furthermore, these ligands can readily replace water molecules at lipophilic binding sites, resulting in further gain in the binding entropy. Consequently, the relative ease of entropic optimization can contribute substantially to property inflation. This finding suggests that monitoring binding thermodynamics with more emphasis on enthalpy-driven optimization should improve the quality of compounds produced by medicinal chemistry optimization programmes. The advantageous physicochemical profile of high-enthalpy compounds over high-entropy and high-affinity ligands is demonstrated in TABLE 1 (based on data from REF. 39).

Although enthalpy-driven optimization should result in better-quality compounds, it has certain limitations. We found that the maximal achievable binding enthalpy appears to decrease with increasing molecular size[39]. This is in contrast to maximal binding free energy, which increases with increasing molecular size until it reaches a plateau (FIG. 1a). We concluded that the simultaneous optimization of binding free energy and binding enthalpy becomes less feasible with increasing molecular size. This observation has several important implications. First, it suggests that the binding of compounds with less than 25–30 non-hydrogen atoms (the enthalpic size limit) is more likely to be enthalpy-driven. In other words, specific interactions needed for the gain in binding enthalpy could be more easily formed for smaller compounds. This finding is in line with the molecular complexity theory, which suggests that the probability of useful interactions falls dramatically with increasing complexity[7]. The data represented in FIG. 1 thus provide thermodynamic evidence to support the probabilistic complexity model, and explain the advantage of the enthalpic binding profile often found for fragments. In practical terms, these data suggest that specific interactions should be formed at an early stage, typically during early hit-to-lead optimization.

Second, potency optimization of compounds that are larger than the enthalpic size limit is typically entropy-driven. This finding provides a thermodynamic rationale for property inflation and suggests that late-phase medicinal chemistry optimizations should focus on high-enthalpy leads. Fragment-based approaches are best suited to this strategy, as small soluble fragments must have polar functionality to be included in the screening sets in the first place. Enthalpy-driven optimization of these compounds would continue to provide the highest possible binding enthalpy determined by the given molecular size. The resulting optimized compounds would have balanced potency and physicochemical profiles, and might be further optimized — entropically, if needed — but under strict control of lipophilicity.

Third, considering that the binding free energy determines the potency, whereas its components reflect the physicochemical profile, compounds under the size limit have a higher chance of possessing balanced properties. Interestingly, the size distribution of marketed drugs reaches its maximum at the heavy atom number close to the enthalpic size limit. Analysing the binding thermodynamics of compounds with various potencies, it seems that the binding of compounds with a higher potency is more likely to be significantly entropy-driven than of those with a lower potency (FIG. 1b). This represents another limitation of enthalpic optimization, as the binding enthalpy becomes less dominant for compounds with a pK_d (the logarithm of the dissociation constant) >8. In other words, the potency that could be realized by specific interactions is limited. This observation is in accordance with the enthalpic size limit and can be explained by the limited number of interaction partners available at binding sites. The ingenuity of chemists in finding ligand structures that can maximize these enthalpic interactions at the early stages of lead optimization is crucial to success.

One of the most important consequences of this finding is that single-digit nanomolar potency is usually realized by significant entropic optimization. A presentation including Astex's internal data (490 isothermal titration calorimetry data points) from several fragment-based lead finding and optimization programmes supported this conclusion (G. Williams, personal communication; relevant slides are available from Glyn.Williams@astx.com), in that it suggested that there is a trend towards increasing entropic contributions during the later stages of lead optimization, whereas enthalpic improvements tend to drive the progression of hits to leads and early-lead

Table 1 | **Profile of high-affinity, high-entropy and high-enthalpy compounds***

Physicochemical property	High affinity (pK_d>8, *n* = 172)	High entropy (pK_S>8, *n* = 123)	High enthalpy (pK_H>8, *n* = 188)
pK_d	9.19	8.07	6.66
Molecular mass	557.30	596.60	384.99
LogP	3.36	3.29	1.56
Number of non-hydrogen atoms	39.56	42.47	26.72
Number of rotatable bonds	11.26	12.59	7.44
Number of charged atoms	0.08	0.10	0.30
Number of hydrogen-bond acceptors	6.44	6.84	6.59
Number of hydrogen-bond donors	3.95	4.56	3.34
Apolar surface area	404.55	444.58	240.86

n, number of compounds; pK_d, the negative logarithm of the dissociation constant K_d (the total binding affinity); pK_S, the entropy-related binding affinity ($pK_S = -\Delta S \div (2.303 \times R)$); pK_H, the enthalpy-related binding affinity ($pK_H = -\Delta H \div (2.303 \times RT)$). *High-affinity, high-entropy and high-enthalpy compounds were collected from the supplementary material of REF. 39. Physicochemical parameters were calculated by the ChemAxon suite.

optimization work. The nonspecific apolar interactions needed to reach high potency seem to require larger and more lipophilic compounds. However, as discussed elsewhere, entropic optimization has its own limitations, such as decreasing solubility, as well as increased protein binding and requiring clearance (after metabolism) of lipophilic compounds.

The limitations of both enthalpic and entropic optimization on the maximal achievable potency question the potency expectations set up by drug discovery teams. Overington *et al.*[40] reported that the median potency (pXC_{50}) of marketed drugs is 7.7. More recently, Gleeson[13] reported the median pXC_{50} of oral drugs in another data set as 7.3. In-house data from GlaxoSmithKline[15] suggested an even lower median pXC_{50} (of 6.7) for oral drugs. Interestingly, these potency values are close to the potency limit of enthalpic optimizations (FIG. 1b), which underlines the importance of balanced *in vitro* potency, ADMET and physicochemical parameters. The moderate potency values observed for successful drugs suggest that the present level of potency expectations might be too high. A key point to consider is whether an effective dose could be achieved with compounds that have a more moderate potency but have balanced physicochemical profiles that ensure a better overall ADMET profile. In addition to such single-target compounds with desirable ADMET properties, ligands that are designed to interact specifically with multiple targets could also help achieve the required therapeutic efficacy[41]. Importantly, high potency does not necessarily result in low clinical doses. In fact, Gleeson *et al.*[13] found a very low correlation ($r^2 = 0.26$) between *in vitro* potency and the therapeutic dose level of 261 oral drugs. Furthermore, it was interesting to see that the range of clinical doses was up to two orders of magnitude for high-potency drugs compared with less than one order of magnitude for compounds with moderate potency. This supports the notion that potency addiction contributes substantially to the inflation of physicochemical properties, and that the advantages of high-potency compounds cannot necessarily be realized in clinical settings in which it is the dosage that is important.

Overall, these observations suggest that project teams should limit their quest for potency and focus on a more balanced optimization of compounds. This is supported by the emergence of new optimization metrics that focus on dose as well as potency (see below). Considering the challenges of getting into the narrow chemical space around the 'sweet spot', we advocate that compounds meeting these criteria should be investigated in greater depth to include detailed biophysical characterization of their thermodynamic and kinetic properties.

It should be noted that the use of thermodynamic and kinetic data to understand potency and efficacy in specific projects has not generally proved to be easy. The analysis of binding thermodynamics is often complicated by the consequences of enthalpy–entropy compensation and by large swings from entropy-driven to enthalpy-driven binding (or vice versa) that are associated with minor structural changes[42]. Similarly, owing to changes in biochemical efficiency (defined as the ratio of the binding affinity and the functional response), it is difficult to use the evaluation of binding kinetics and its effect on efficacy in a predictive sense, although this is clearly something that should be explored and it is an area of evolving understanding[26,43,44]. However, these issues are different to those that involve looking for and developing compounds that have maximal enthalpic interactions with the target, or compounds that have beneficial residence time at the target if such a choice is available. We are confident that such data might add further guidance to the identification of higher-quality drug candidates.

The use of optimization metrics. As potency alone is not an appropriate driver for medicinal chemistry optimization, multi-dimensional approaches considering physicochemical and ADMET parameters, together with efficacy, are preferred. This kind of optimization is based on parallel evaluation of optimized properties that are effectively realized by different optimization metrics or indices (TABLE 2). Although we see these metrics as helpful, in our view project teams should not use them slavishly, as they cannot be completely substituted for other (for example, true experimental) data generated through discovery screening activities.

Ligand efficiency (LE), defined as the Gibbs free energy of binding per non-hydrogen (heavy) atom[16], is a crucial concept that aids in the selection of compounds with substantial optimization potential. Reynolds *et al.*[45] demonstrated that LE depends on the size of the ligand, and introduced the maximal ligand efficiency (LE_{max}). Consistent with our results[39], Reynolds and Holloway concluded[46] that the size dependency of LE is almost entirely enthalpic. Comparing the actual LE of the optimized compound to LE_{max} therefore allows the potential for further enthalpic optimization to be estimated. The unbiased comparison of compounds of different size can be achieved using the size-independent ligand efficiency (SILE) metric[47].

Thermodynamic data can be used to derive enthalpic and entropic efficiencies, of which the former might effectively support early-phase optimizations. Owing to the size dependency of binding enthalpies, however, evaluation of enthalpic efficiencies requires size-independent metrics such as size-independent enthalpic efficiency (SIHE)[39].

Lipophilicity can be effectively controlled using lipophilic ligand efficiency (LLE), which is defined as the difference between potency (pK_i; the logarithm of the inhibition constant) and logP[9]. As fragments are typically polar compounds with limited potency, they have an unusually low LLE that makes their evaluation challenging. Astex therefore

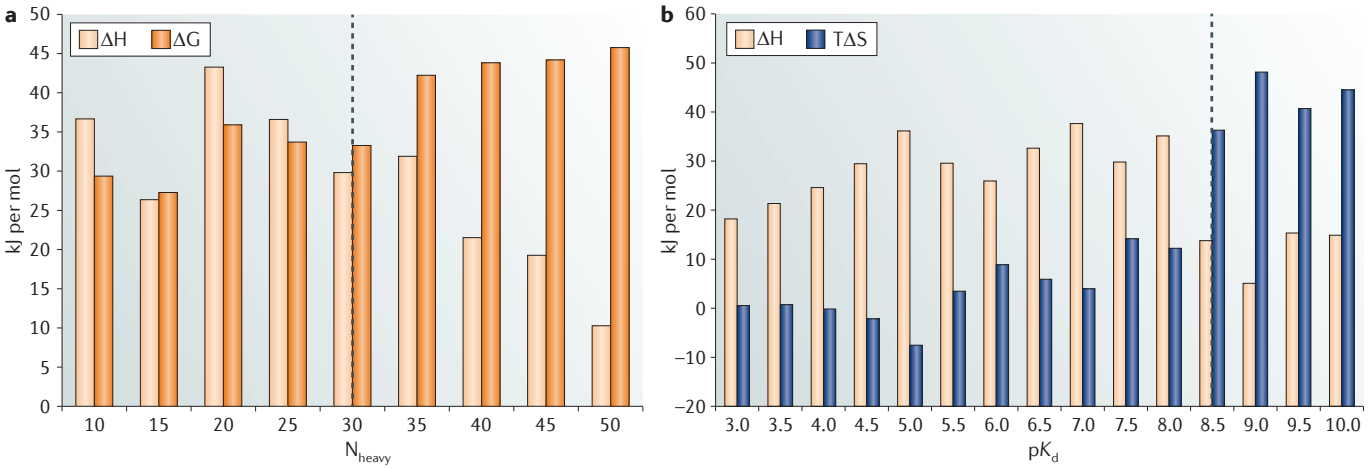


Figure 1 | **Binding thermodynamics in medicinal chemistry optimization.** The opportunity for enthalpy-driven optimization decreases with increasing molecular size (part **a**) and potency (part **b**). Consequently, highly potent and complex compounds are typically derived by entropy-driven optimization. Starting medicinal chemistry programmes from less potent and less complex starting points that have a strong enthalpic (rather than entropic) component to their binding could be advantageous. If optimized carefully, these compounds could be transformed into leads with beneficial binding enthalpy. Their beneficial physicochemical profile provides a higher chance for the discovery of a good-quality candidate in the subsequent lead optimization stage. Thermodynamic data are presented as averages binned over the size and potency ranges, respectively. The isothermal titration calorimetry data set used for this figure is based on supplementary material from REF. 39. N_{heavy}, number of non-hydrogen atoms; pK_d, negative logarithm of the dissociation constant K_d.

suggested a rescaled version of LLE for fragments[48]. Although LLE estimates how efficiently the ligand utilizes its lipophilicity, this measure contains no information on the ligand size. Addressing this issue, LELP, which is defined as the ratio of logP and LE, provides a lipophilicity-corrected metric[17] that indicates the 'price' of LE paid in logP. LELP is only meaningful for positive logP values (which is the norm for most discovery programmes) and allows the simultaneous evaluation of fragments, lead-like and drug-like compounds. Interestingly, a recent study indicated that unlike LE and LLE, LELP was able to discriminate between candidates in development and marketed drugs[49]. Furthermore, these authors found that all of the investigated candidates from Pfizer possessing suboptimal LELP values had been terminated along the drug discovery and development pathway.

In addition to simple metrics such as (size-independent) LE and LLE, the combined LELP metric is a useful post-synthesis parameter for the comparative evaluation of discovery compounds[50]. Multidimensional optimizations might be supported by other combined optimization metrics at the design phase. The CNS MPO (central nervous system multiparameter optimization) metric introduced by Wager *et al.*[51] is a typical example of this kind of measure; it combines six physicochemical parameters, including lipophilicity (cLogP), distribution at pH 7.4 (cLogD), molecular mass, topological polar surface area, the number of hydrogen-bond donors and pK_a (the logarithmic acid dissociation constant) for the most basic centre.

Although there has been a lot of discussion in the literature about the need to improve the physicochemical properties of candidate molecules, evidence has only recently emerged to indicate that this can have a positive effect on compound survival in a prospective sense, as opposed to drawing this conclusion based on analyses of compounds that have already succeeded or failed. Thus, in presentations on the use of their multiparametric descriptor called the compound safety evaluator (CSE)[52], scientists at Pfizer have disclosed that since introducing the CSE in 2007 they have observed a marked decrease in toxicity-related attrition. The CSE combines, into a single metric, information from a small panel of assays to assess promiscuity and toxicity (such as transfected human liver epithelial (THLE) cell cytotoxicity, the Ames test and hERG (also known as KCNH2) inhibition) together with physicochemical descriptors such as cLogP, topological polar surface area and pK_a. Scientists at Pfizer have claimed that CSE, combined with predicted or observed dosage information, has allowed them to make more effective decisions in lead optimization and in the selection of compounds to progress further.

This combining of multiple descriptors with dosage information also follows a trend in the use of concepts such as drug (or medicine) efficiency ($DRUG_{eff}$), which was first brought to prominence by Braggio *et al.*[53] from GlaxoSmithKline. $DRUG_{eff}$ is a simple parameter that accounts for all the factors influencing compound concentration at the site of action. Although simply defined as '$DRUG_{eff}$ (%) = (biophase concentration × 100)/dose', estimating the biophase concentration can be difficult as it needs to take into account the free fraction. However, the benefit of $DRUG_{eff}$ is that it takes an integrated view of the bioavailability, clearance, distribution volumes, half-life, and so on, and can be used — in combination with *in vitro* potency — to aid in the selection of compounds with optimized *in vivo* effectiveness. It thus de-emphasizes target potency in favour of effective or efficient dosage, as it is the actual dosage that is likely to be the arbiter of non-target-related issues. More recently, this group has extended this concept to define a drug efficiency index that recombines $DRUG_{eff}$ with the target potency, thus helping drug discovery teams to select and focus on those molecules that have the highest probability of interacting with the biological target and with the best balance between target affinity and ADME parameters[54].

A further recent example of the use of data fusion methods is in the quantitative estimation of 'drug-likeness' and the 'chemical beauty' of drug targets using the new quantitative estimate of drug-likeness (QED) measure[55]. This measure uses the similarity

of a compound to weighted distribution profiles of key molecular properties of known drugs. It claims to avoid the problem of step-typed indices, such as the Lipinski 'rule of five' guidelines, which do not penalize compounds as they approach the boundary conditions.

All of these indices point to greater integration of data from early clinical phases of drug discovery into the preclinical phases, when it is still possible to modify molecules to get the properties and, crucially, the required dose correct. A striking reminder of the benefits of this approach is that although assessment of — and avoidance of — compounds with reactive metabolites, cytotoxicity or specific on- and off-target-related toxicities is an essential strategy, the single most likely predictor of low propensity to idiosyncratic toxicity seems to be low total dosage[56].

Synthesis-related issues. As optimization strategies are realized by organic syntheses, it is obvious that synthetic chemistry has a substantial impact on compound quality. The chemistry of optimization includes specific reactions and building blocks applied for the synthesis of project compounds with different synthesis strategies. Most of these factors are typically determined by the core structure of the chemical starting point identified during lead generation. The chemotype of the starting points, as well as their hit-to-lead optimization, is therefore crucial from a synthetic chemistry perspective.

In the same way that automation in biology enabled the easy and speedy return of potency data from HTS assays, automation in chemistry (which favours robust reactions where a range of substituents can be tolerated) has provided speedier access to more chemical space. However, this reliance on automation to explore more biological and chemical space has, in effect, only allowed us to explore a limited amount of these spaces in greater depth; a greater breadth is also needed. All too often, pressure to make progress has been equated with making lots of compounds through readily available synthetic approaches and then rapidly testing them, rather than taking the time to make more difficult and complex compounds.

Consequently, early library syntheses typically used alkylations and acylations[57]. These reactions can be used in parallel synthesis strategies and can be readily automated, and this makes them popular in optimization programmes. Substantial improvements in palladium chemistry made carbon–carbon bond formation a popular reaction as well. However, such progress can be directly correlated with the increased aromaticity and lipophilicity of library compounds[57]. Contrary to this, the less inflationary functional group interconversions and redox reactions are rare at this stage. This is in line with the ease with which synthesis is facilitated by preformed or masked functional groups. Selectivity problems usually associated with redox chemistry are likely to be avoided in early-phase chemistry programmes.

Medicinal chemistry teams invariably have limited resources and time, leading to a focus on using known chemistries and readily available building blocks. However, the initial choice of chemotypes clearly determines the chemistry of later-phase optimizations. The types of reactions used in lead optimization[58,59] show a more balanced use of different chemistries. Alkylations, acylations and cross-coupling reactions still dominate but protective group chemistry, functional group interconversions and redox reactions are also becoming more widely used. However, the formation of heterocyclic rings is relatively rare. This is an indication that most of the heterocyclic rings are used intact in syntheses. It seems that the use of heterocycles is often determined by suppliers of fine chemicals, which provide a bias for particular scaffolds, as documented by Pitt and colleagues[60].

The most popular reactions are clearly those that result in a high yield of the desired product without requiring extensive purification or using expensive reagents and catalysts. These reactions do not need a long reaction time, extreme heating or cooling, and they are not dangerous or environmentally unsafe. From this technical perspective, the role of reaction temperature, pressure and the solvent is crucial. The temperature range of –80 °C to +250 °C and the pressure range of 0.1 to 10 define the operational limits of conventional medicinal chemistry. These limits, however, can be extended by emerging techniques, such as flow chemistry, that allow safe reaction temperatures far above the solvent's boiling point as a result of the ability to contain pressure[61]. Flow chemistry may therefore provide greater opportunities for new chemotypes using currently forbidden (for example, nitration, azides, and so on) or previously unknown chemistries[62].

A recent paper from GlaxoSmithKline[63] has introduced the concept of lead-oriented synthesis, which further expounds the issues of how synthetic chemistry practices have affected our ability to successfully prepare the kind of molecules that medicinal chemists now aspire to produce. One previously unreported consequence of automation and methodology is the observation[63] that reactions that succeed in synthetic arrays invariably have a higher logP than those that were initially designed. This drift in logP probably reflects the failure of monomers that are more functionalized, as well as the propensity to use organic work-up and extractions that favour more lipophilic molecules. It is worth speculating that as green chemistry principles prefer the use of water and green polar aprotic solvents, the application of green technologies may possibly support improvements in the solubility and other physicochemical properties of discovery compounds.

Thus the ease of synthesis can be added to the search for potency and bioavailability as another factor underlying the observed propensity to pursue 'molecularly obese' compounds. Based on our — and others' — experience, it seems that the ease of synthesis could be an even stronger driver than design. The current practices in organic chemistry make the design space seriously limited by synthesis capabilities, local traditions, organic chemistry knowledge and experience. Although access to new chemistries may help in the search for new molecules[64,65] with, for example, enhanced three-dimensional characteristics, strict control on physicochemical properties must remain the key driver in finding good-quality compounds.

The impact of process and corporate culture. Drug discovery is, by necessity, a series of triage events in which decisions as to what to do next are made based on evidence gathered to date. This is essential, as the 'combinatorial explosion' of all possible molecules versus all possible assays is clearly too large[8] to investigate each possible combination, and some sort of process must be used to navigate the chemical and biological space.

The question of which triage processes to use at the outset and at subsequent stages is heavily influenced by available technologies. Thus the advent of molecular biology and sequences from genomic studies have enabled the facile production of proteins that are suitable for the ultimate form of reductionist *in vitro* assays, in which protein targets are studied in a form in which they are isolated from their native environment. This has the advantage of enabling reproducibility, automation and miniaturization, such that assays can be used to assess millions of compounds in a HTS format rapidly and at an acceptable

Table 2 | **Lead optimization metrics**

Metric	Definition	Use	Refs
Ligand efficiency (LE)			
LE	$LE = \frac{-RT\ln(K_d \text{ or } pK_i)}{N_{heavy}}$	Prioritization of starting points; early-stage optimization	16
BEI	$BEI = \frac{(pK_i \text{ or } pK_d)}{\text{molecular mass}}$		73
Size-independent ligand efficiency (SILE)			
FQ	$FQ = \frac{LE}{\left(0.0715 + \frac{7.5328}{N_{heavy}} + \frac{25.7079}{(N_{heavy})^2} - \frac{361.4722}{(N_{heavy})^3}\right)}$	Size-unbiased comparison of compounds in early-stage optimization	45
%LE	$\%\,LE = \frac{LE}{(1.614^{\log2(\frac{10}{N_{heavy}})})} \times 100$		74
SILE	$SILE = \frac{-RT\ln(pK_i)}{(N_{heavy})^{0.3}}$		47
Lipophilic ligand efficiency (LLE)			
LLE	$LLE = pK_i - \log P \text{ (or } \log D)$	Control of lipophilicity in lead optimization	9
LLE_{Astex}	$LLE_{Astex} = \frac{0.11 \times \ln(10) \times RT(\log P - \log(K_d \text{ or } pK_i \text{ or } IC_{50}))}{N_{heavy}}$	Lipophilic efficiency assessment for fragments	48
LELP	$LELP = \frac{\log P}{LE}$	Control of lipophilicity in optimization, assessment of drug-likeness	17
Enthalpic efficiency (EE)			
EE	$EE = \frac{\Delta H}{N_{heavy}}$	Enthalpy-driven potency optimization	36
SIHE	$SIHE = \left(\frac{-\Delta H}{40 \times 2.303 \times RT}\right) \times (N_{heavy})^{0.3}$	Size-independent assessment of binding enthalpy contributions	39
Complex metrics			
MPO	logP, logD (pH=7.4), molecular mass, TPSA, H_{don} and pK_a	Supporting the optimization of CNS compounds	51
CSE	*In vitro* promiscuity and toxicity data, logP, TPSA and pK_a	Control of toxicity-related attrition	52
$DRUG_{eff}$	$DRUG_{eff} = \frac{\text{Biophase concentration}}{\text{dose}} \times 100$	Estimation of *in vivo* efficacy from *in vitro* potency	53
QED	$QED = \exp\left(\frac{\sum_{i=1}^{n} w_i \ln d_i}{\sum_{i=1}^{n} w_i}\right)$	Quantitative estimate of drug-likeness (QED)	55

BEI, binding efficiency index; CNS, central nervous system; CSE, compound safety evaluator; $DRUG_{eff}$, drug (or medicine) efficiency; FQ, fit quality; IC_{50}, half-maximal inhibitory concentration; H_{don}, number of hydrogen-bond donors; K_d, dissociation constant; LELP, ratio of logP and ligand efficiency; LLE_{Astex}, lipophilic efficiency at Astex; MPO, multiparameter optimization; N_{heavy}, number of non-hydrogen atoms; pK_a, logarithmic acid dissociation constant; pK_i, logarithmic inhibition constant; SIHE, size-independent enthalpic efficiency; TPSA, topological polar surface area.

cost. However, although the rapidity and ease with which such HTS assays can be carried out has clearly enabled their widespread use and allowed HTS to have a real impact in drug discovery[32], there are downsides. Providing rapid turnaround of potency data fits in well with the medicinal chemists' synthetic work schedule and allows potency optimization to proceed in a highly efficient manner, but there is often pressure to show early signs of cellular *in vitro* (or even *in vivo*) activity, and this will invariably occur early in the screening cascade triage. One of the quickest ways to introduce cellular activity (and to help increase potency as well) is to increase lipophilicity to allow passage into and hence through membranes. The pressure for rapid progress can easily trump the appropriate balance of physicochemical properties, and clearly the order in which the screening cascade is built can have a profound effect on the outcome.

In the past, assays were based more on the use of tissues derived from animals, in which membranes were still present, and this may unknowingly have contributed to the progression of compounds with more balanced properties. The increasing availability of cellular assays based on immortalized cell lines, and ultimately derived from stem cells, may be helping to redress this balance.

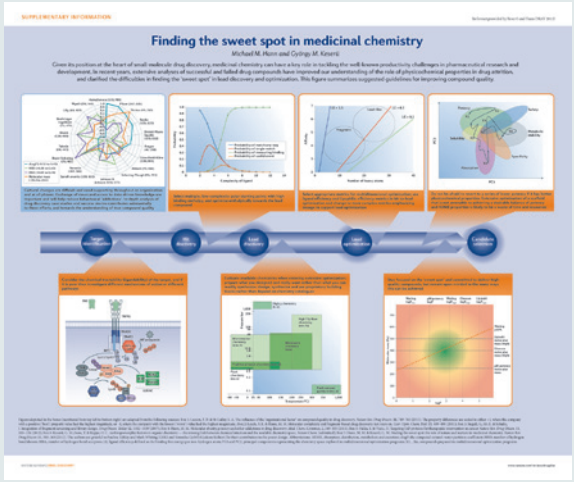
Certainly, it is interesting to note that in a recent analysis of the origin of the 45 first-in-class new molecular entities approved by the US Food and Drug Administration between 1999 and 2008, ~60% (28 out of 45) originated from phenotypic (that is, cellular) screens as opposed to ~40% that originated from reductionist target-based assays[26]. This may seem contrary to expectations, considering the investment into more reductionist *in vitro* technologies over the past 20 years, during which time these assets will have been created. This suggests that phenotypic screens punch above their weight in terms of providing good starting points for successful first-in-class drug discovery. However, the downside of such assays is that they are unlikely to be effective at identifying weakly active compounds of the type that provide the typical starting points for fragment-based approaches. This emphasizes the need for rigour and discipline in the fragment-based approach to avoid squandering good chemical starting points by allowing them to become just as 'obese' in the search for potency and early cellular activity.

Another aspect of *in vitro* assays is that they are often remarkably tolerant of high levels of organic co-solvent, which allows compounds with poor aqueous solubility to

Box 2 | **Proposed medicinal chemistry guidelines**

- Consider the chemical tractability (ligandability) of the target, and if it is poor then investigate different mechanisms of action or different pathways
- Select multiple, low-complexity polar starting points with high binding enthalpy, and optimize enthalpically towards the lead compound
- Select appropriate metrics for multidimensional optimization; use ligand efficiency and lipophilic efficiency metrics in hit-to-lead optimization and change to more complex metrics emphasizing dosage to support lead optimization
- Evaluate available chemistries when entering extensive optimization; prepare what you designed and really want rather than what you can readily synthesize; design, synthesize and use proprietary building blocks rather than depend on chemistry catalogues
- Do not be afraid to revert to a series of lower potency if it has better physicochemical properties. Extensive optimization of a scaffold that is not amenable to achieving a desirable balance of potency and ADME (absorption, distribution, metabolism and excretion) properties is likely to be a waste of time and resources
- Stay focused on the 'sweet spot' and committed to deliver high-quality compounds, but remain open-minded to the many ways this can be achieved
- Resist timelines that compromise compound quality

Cultural changes are difficult and need supporting throughout an organization and at all phases. Exchange of views and access to data-driven knowledge are important and could help reduce behavioural 'addictions'. In-depth analysis of drug discovery case studies and success stories contributes substantially to these efforts, and towards the understanding of true compound quality. The figure (available online as a full-size poster for downloading; see Supplementary information S1 (figure)) illustrates the above guidelines. Our hope is that displaying it in offices and laboratories could help highlight the importance and responsibility of medicinal chemists in drug discovery, as well as stimulate debate.



be tested — for example, by adding dimethyl sulfoxide (DMSO). As compounds are routinely stored in automated stores in DMSO, this also means that true solubility from crystalline material is rarely understood for compounds that are in the early stages of the lead discovery process. This can all too often lead to structure–activity relationship analyses being carried out in series that have intrinsically low solubility, which is often driven by high lipophilicity — the antithesis of solubility.

Attempts to predict the solubility of any given compound are difficult, but useful trends can be identified in series and across large data sets. The use of the solubility forecast index (which is equal to clogD (pH 7.4) plus the number of aromatic rings; if it is >5 then this indicates an increased risk of poor solubility) is a recent example of progress in understanding how to select and/or design molecules with improved solubility[66]. The logD term clearly indicates the lipophilic contribution to poor solubility, whereas the number of aromatic rings may reflect the contribution of planarity in enabling increased intermolecular interactions (for example, high lattice energies). Interestingly, similar trends have been identified in the related property forecast index, which again emphasize the relationship between lipophilicity and undesirable ADMET properties[67].

Poorly soluble compounds can often be 'rescued' by formulation chemistry, but this will only mean that the human body is being forced to take on board a compound with intrinsically poor solubility and other dubious properties. The normal response of the body to such a compound is to metabolize it in order to make it soluble enough to be excreted. If this metabolism abrogates the required binding to the target macromolecule, then medicinal chemists will often try to block such metabolism. If the new compound remains lipophilic and/or insoluble, then even higher energy processes will be invoked to make the compound less lipophilic and hence more soluble. The danger of the formation of reactive metabolites (such as carbenium ions) by such processes is thus increased as a consequence of forcing insoluble and/or highly lipophilic compounds into the body.

Evidence of the influence of differing degrees of company culture and rigour in medicinal chemistry has emerged in the study of Leeson and St-Gallay[29] who, using data extracted from the 2000–2010 patent literature, looked at pairs of pharmaceutical companies that have worked on the same targets and analysed the differences between each company's output. They have shown how some companies have been able to influence the properties of patented molecules (as demonstrated through calculated physicochemical descriptors) more effectively than others by actively focusing on and reinforcing their medicinal chemistry towards preferred regions of descriptor space. Particularly striking is how companies such as Takeda, Lilly, Schering-Plough and AstraZeneca shifted the logP profiles of their compounds in the later part of the decade compared to the earlier part. Although some of this may be due to target choices, it is also clear that companies such as AstraZeneca have responded to internal advocacy such that the logP profile of their compounds matches that of Pfizer, which has advocated and practised a more stringent control over a longer period[68].

Much has been written about the risk factors in drug discovery and how the overall low probability of success in such an expensive process is best handled. One such example is the study by Paul *et al.*[69] from Lilly, who provided a comprehensive analysis of research and development (R&D) productivity based on a model that is normally associated with manufacturing process improvements. The model combined estimates of work in progress (*WIP*), probability of technical success (p(TS)), value (V), cycle time (CT) and cost (C) for different stages of the R&D process ($P = WIP \times p(\mathrm{TS}) \times V/CT \times C$) to estimate productivity (P). The authors then carried out a sensitivity analysis to see the effect of increasing or decreasing (by 50%) each of these terms at different chronological phases (such as lead identification, lead optimization and clinical

studies) on the overall cost of R&D. In their sensitivity analysis, it is quite clear that taking more time during the early stages (for example, during hit to lead optimization, and lead optimization) adds little to overall costs, but if this improves the later-stage *p*(TS) then the benefits are enormous.

A recent cost-benefit probabilistic analysis gives further support to this conclusion, revealing that despite the high cost, clinical phases are typically more productive than earlier phases (particularly lead optimization)[70]. Thus, in general, if it is possible to de-risk a project in the earlier and cheaper stages, this is far more cost-effective than in the post-candidate selection stage, where there is — by definition — no opportunity to modify the molecule being considered for development without returning to earlier stages. This indicates that we should spend more time and/or be more effective in the research phase to get things right.

The consequences of relying on, for example, formulation to solve problems with suboptimal ADME characteristics of lead compounds can be illustrated by looking at the developability classification system (DCS) of oral drugs, which uses permeability, solubility and dose as key descriptors to classify compounds as follows: 'high solubility, high permeability' (DCS1); 'dissolution limited' (DCS2a); 'low solubility, high permeability' (DCS2b); 'high solubility, low permeability' (DCS3); or 'low solubility, low permeability' (DCS4)[71]. Data from GlaxoSmithKline (J. Butler, personal communication) indicate that, on average, for compounds that are classified as DCS2b (that is, highly limited by lack of solubility) it takes almost twice as long to reach a decision indicating that the compound is not suitable to progress further. This additional time (which is ~2 years) is often expended on carrying out expensive clinical studies only to discover that the compound cannot be progressed because of, for instance, lack of efficacy owing to lack of exposure of the compound to the target. This then leaves questions about the actual validity of the target hypothesis unanswered. This could have been avoided if a compound with better ADME properties had been identified in preclinical studies.

In addition to a better understanding of the reasons for, and the bounds of, small-molecule drug space, there is the inevitable desire to explore the unknown on the basis that we might find something valuable there. As an example, Bennani[72] has argued that the only way to salvation for large pharmaceutical companies is through innovation. Although this is easy to propose, it comes with inherent dangers in that it could mean working outside the known drug space — whether this is known targets, known chemistries or known rules linking the two. However, if innovation is to be effective, it is still subject to the productivity equation proposed by Paul and colleagues[69]. Therefore, because the *p*(TS) is, by definition, very low in an unknown area, it is even more essential that it is de-risked (that is, that the *p*(TS) is improved) as early and as cost-effectively as possible; investing too much, too early, in half an idea is likely to be disastrous but starving it of resources so it cannot improve its *p*(TS) is equally disastrous. Science and technology develop by a clear understanding of the past, while looking for unusual and unexpected observations[70]. It is at the edge of our knowledge or, expressed another way, as a result of differences between theory and experiment, that important discoveries are often made. The challenge to all working in drug discovery is to know when to comply with 'rules' that are based on what has been deductively discovered at considerable expense, and when to ignore them.

Perspectives and conclusion

The phenomenon of molecular obesity affects development risks and could contribute substantially to the limited productivity of drug discovery programmes. Despite the number of analyses that have been published that identify the problem, evidence suggests that too many medicinal chemistry programmes (in industry and academia) continue to deliver obese compounds, which prompted us to explore the possible underlying reasons.

It is becoming increasingly clear that binding thermodynamics seem to provide an underlying explanation for molecular obesity, and this helps to rationalize the property inflation observed in medicinal chemistry programmes. Highly potent compounds are fundamentally predisposed to conflict with an optimal ADME profile. A better understanding of these thermodynamic considerations should help medicinal chemists to identify better-quality starting points with improved optimization potential, and enable the identification of the best balance between potency and ADME through simultaneous optimizations rather than through optimizing potency followed by addressing ADMET issues. The initial focus of medicinal chemistry should be to select good-quality starting points and then to control shifts in physicochemical properties effectively during optimization. This can be aided by selecting and using appropriate metrics or indices. This should be coupled with more emphasis on design through the use of thermodynamic data, as well as structural and physicochemical information, rather than on synthetic accessibility. Organizational factors such as project strategy and screening cascade structure, communication and management, as well as an understanding of how timelines and objectives can have unforeseen consequences, need to be considered more transparently to make medicinal chemistry more successful in the delivery of high-quality compounds. It is for this reason that we chose to use the phrase 'nature and nurture' in the title of the article to emphasise the interplay of what we can and cannot influence in the evolution of an idea into a drug.

Finally, as a result of intensive research on, and publication of, factors influencing compound attrition, as well as the drug discovery experience gained by us and many other colleagues, guidelines can be formulated to improve the quality of candidates in development. We present such guidelines in BOX 2 and in an accompanying poster (Supplementary information S1 (figure)), with the aim of helping to enhance the effectiveness of the key contribution of medicinal chemistry in drug discovery and development.

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Competing interests statement

The authors declare competing financial interests: see Web version for details.

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