



Lipophilicity in drug discovery

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Lipophilicity in drug discovery

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Importance of the field: The role of lipophilicity in determining the overall quality of candidate drug molecules is of paramount importance. Recent developments suggest that, as well as determining pre-clinical ADMET (absorption, distribution, metabolism, elimination and toxicology) properties, compounds of optimal lipophilicity might have increased chances of success in development.

Areas covered in this review: The review covers aspects of methods of prediction of lipophilicity in frequent use and describes the most relevant literature analyses linking individual ADMET parameters and more composite measures of overall compound 'quality' with lipophilicity.

What the reader will gain: The aim is to provide an overview of the relevant literature in an attempt to summarise where the optimum region of lipophilicity lies and to highlight which particular issues and risks might be expected when operating outside this region.

Take home message: The review of the data shows that this optimal space is defined by a narrow range of logD between ~ 1 and 3. Some of the implications of this for medicinal chemistry optimisation are discussed.

Keywords: ADMET properties, compound quality, lead optimisation, lipophilicity, permeability, pharmacokinetic properties, physicochemical properties, solubility, toxicology

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1. Introduction

The importance of lipophilicity on the pharmacological responses of compounds has been known for over a century. In 1893, the observation was made by Richet that the toxicity of simple ethers, alcohols and ketones was inversely related to their solubility in water [1]. In 1899, Overton and Meyer discovered independently that for many compounds their anaesthetic potency correlated with their oil/water partition coefficients [2-5]. The introduction of more sophisticated quantitative structure-activity relationships (SARs) pioneered by Hansch in the 1960s continued to show the importance of the lipophilicity term in many individual cases [6]. This concept rose to greater prominence in the late 1990s with the rise of high-throughput molecular biology and combinatorial chemistry, which often shifted the distribution of synthesised compounds to higher lipophilicity. A very influential review by Lipinski highlighted the issues with this shift and the desirability of targeting a lower lipophilicity range [7]. Moreover, Lipinski suggested that the desired lipophilicity values for drug candidates are universal to a degree, specifically highlighting the desirability of clogP values (the base 10 logarithm of the calculated octanol/water partition coefficient) < 5.

Since then an increasing body of literature has emerged highlighting the importance of lipophilicity on individual ADMET (absorption, distribution, metabolism, elimination and toxicology) parameters and on overall compound 'quality'. It has been suggested that areas of optimum lipophilicity should be targeted for the design of libraries [8] and for more advanced lead optimisation campaigns [9]. This manuscript aims to provide an overview of the relevant literature in an attempt to summarise where the optimum region lies and to highlight which particular issues and risks might

Article highlights.

- Currently available methods for calculation of lipophilicity possess a reasonable degree of error. The impact of ionisation (use of logD rather than logP) adds a further complication that must be considered.
- Lipophilicity plays a crucial role in determining ADME parameters. Solubility and metabolism are more likely to be compromised at high lipophilicity values whereas permeability and renal clearance are more likely to be problematic when lipophilicity is too low. The impact on more complex parameters such as distribution and bioavailability are less apparent due to their more complex nature.
- General toxicology and promiscuity as well as more specific toxicology issues of hERG inhibition, phospholipidosis and CYP inhibition are more likely to be problematic for compounds of high lipophilicity.
- Designing sufficiently potent compounds in the optimal lipophilicity range may be challenging than it is at higher lipophilicity but should still be possible for all common target classes.
- Compounds of high overall quality as judged by a variety of parameters such as surpassing multiple individual parameters or overall developmental progression are more likely to be found in an intermediate range of lipophilicity.
- The optimal range of lipophilicity highlighted by combining all of these considerations lies in a narrow range of logD between ~ 1 and 3.

This box summarises key points contained in the article.

be expected when operating outside this region. The intention is not to produce a systematic review (the body of literature is far too large for this to be possible in the allotted space); rather, the most definitive and influential studies have been selected where possible. Preference has been given in particular to those studies on larger, more diverse datasets so as to maximise their general applicability and to those studies that allow the definition (intentionally or otherwise) of where guideline limits for desirable properties lie.

2. Methods of prediction

The majority of literature on the impact of lipophilicity on drug properties is based on octanol/water partition coefficients (logD and logP values) and uses calculated rather than measured data. There exist a plethora of different computational methods for prediction of logP and logD [10]. A potential drawback of using calculated lipophilicity is that the methods of calculation predict the measured logD/logP values with a reasonable degree of error and often this error is systematic. For example, the commercially available clogP algorithm [11] predicts a subset of neutral compounds measured in the AstraZeneca logD assay with an average error of 0.87 and a mean bias of -0.14 ($n = 4,564$) [12]. A study of 18 different methods of calculating logP for a set of 96,691 compounds from Pfizer and Nycomed revealed average prediction errors

> 1 log unit with only 50% performing better than an arbitrary arithmetic average model [13]. One of the reasons for this discrepancy is that the molecules being predicted are dissimilar to those in the training sets of the models [10] and this has led many organisations to create bespoke models trained on their own data, which are more relevant to the compounds of interest [14]. These problems must be borne in mind when considering the literature analysis of lipophilicity dependent parameters and also when generating calculated data on potential compounds for synthesis. In principle, if a computational algorithm predicts logP with a given error, it should not be able to predict other dependent parameters with any greater accuracy.

Perhaps more significantly, there remains a question of whether the partitioning of the neutral form (logP) or the inclusion of the ionised form (logD) is the more appropriate parameter. This clearly will depend on the property being modelled. It has been more common to use calculated logP, in particular clogP, in these types of analysis. This is probably due, in part, to the ready availability of the algorithm. In addition, the ability to calculate logD depends on the accuracy of the pK_a calculation that introduces further error. However, it would seem unreasonable to expect to deal with molecules of different ionisation classes on a continuous logP scale since the interactions of the molecule with non-polar lipophilic species and with aqueous environments are critical to the majority of the processes in question, and ionised molecules are likely to interact with such species differently to neutrals.

Many reports in the literature do not validate the calculation method with measured data for the molecules in question. This introduces a potential caveat when comparing across studies since different algorithms have different associated errors for different compound sets. For simplicity and to allow cross-comparison of different studies, this review makes the assumption that the systematic error in the calculation is zero and hence attempts to compare across datasets on a continuous scale. Hence, logD and logP data are referred to generically regardless of the method of calculation employed or the systematic error they may include.

3. ADME properties

3.1 Solubility

The link between solubility and lipophilicity is perhaps the most obvious of all. At a theoretical level, the solubility of a molecule in solution is determined by its activity coefficient and this is an indication of its hydrophobicity [15]. Hence, Yalkowsky *et al.* have proposed the empirically derived General Solubility Equation [16] that describes the solubility of a compound as a function of logP and melting point, in which the melting point describes the lattice energy that is lost on dissolution. A recent version [17] of this equation for organic compounds is:

$$\log \text{Sol}_{\text{aq}} = 0.5 - \log P - 0.01(\text{MP} - 25)$$

where MP is the melting point in degree centigrade.

Hence, for a typical drug-like molecule melting at 150°C to achieve a solubility of > 100 µM, a typical desirable value for drug molecules [18], it requires a logP value < 3.25. Consistent with this, the reduction of lipophilicity within a series is well established as a successful means of improving solubility. Clark *et al.* have published a consistent dataset of kinetic solubilities for 711 commercial compounds that are believed to be drug-like [19]. In this study, a clear dependence of solubility on logP was shown although the direct correlation is weak. For compounds with logP > 3, only 1% were soluble (having kinetic solubility > 250 µg/mL, 500 µM for a compound of molecular weight 500 Da); conversely, for logP < 3, 50% were soluble.

In principle, the discussion presented earlier neglects the role of ionisation in solubility. The solubility of an ionisable compound increases exponentially with the difference between pH and pK_a [20]. Hence, in considering equilibrium solubility, the relationship for ionisable compounds is more complex and introduction of ionisable groups is a well-exploited strategy for increasing solubility. However, the intrinsic solubility of the compound still depends on logP and for high logP compounds, low intrinsic solubility can still manifest in issues with pH dependent solubility and compromised absorption. Hence, reduction of logP is always likely to be desirable in targeting improved solubility [20]. Indeed, Gleeson has shown that the chances of achieving high solubility are increased significantly for logP < 3 for a set of 44,584 GSK compounds and that below this value the dependence of solubility on ionisation is much less significant [21].

3.2 Permeability

One of the origins of the use of logD/P as a descriptor was as a means of mimicking the partitioning of a compound between an aqueous phase and a cell membrane. It would, therefore, be expected that lipophilicity would play a role in cellular permeability and, hence, in absorption *in vivo*. In general, it is accepted that in the majority of cases the neutral form of an ionisable compound is the most significant contributor to permeability [22], although studies by van de Waterbeemd have established that the ionised forms of some compounds are also capable of crossing membranes [23,24].

It has been known for some time that permeability within a series diminishes with increasing polarity but the possibility of a lower lipophilicity limit based on permeability is often overlooked in optimisation. This problem was mentioned by Lipinski [7] but permeability is accounted for in the Lipinski rules using other descriptors (donor count < 5, acceptor count < 10, molecular weight < 500 Da) rather than logP.

A considerable number of other studies have been conducted in this area using *in vitro* cellular permeability data and the dependence on lipophilicity has been established although other factors such as size and hydrogen bonding also play a role. The relationship between permeability and lipophilicity has been reported to be linear [25], hyperbolic [26-29], sigmoidal [23,30-32], parabolic [6] and bilinear [25,33]. Of course all of these relationships imply diminishing permeability at the lower

end of the lipophilicity scale. For polar compounds there exists a substantial energy penalty for desolvation of the molecule coupled with reduced affinity for the phospholipid bilayers forming the cell membrane. At the upper end, these differing relationships are likely to arise from the greatly increased affinity for the phospholipid phase and hence a diminished propensity for the molecules to exit the cell membrane and pass into the aqueous phase on the basolateral side. However, this is likely to occur at very high logD values and the other issues with high lipophilicity are likely to impact on a molecule's overall profile before this is observed. Hence, permeability issues are most commonly encountered at the lower end of the scale.

Egan has developed a computational model that discriminates high, medium and low levels of absorption [34]. This model uses logP and polar surface area (PSA) as key descriptors with well-absorbed compounds grouping in a region of logP ranging from -1 to 5.9 and PSA < 132 Å². More recently, it has been shown based on AstraZeneca Caco-2 data that the lower limit of the region that should be optimally targeted for high permeability occurs much higher than these values and the precise position of the limit is dependent on molecular weight [35]. Specifically, to achieve a >50% probability of attaining an apical to basolateral P_{app} value of > 100 nm/s (a value typically representing unambiguously high permeability) a logD value of > 1.7 is required for compounds of molecular weight 350 – 400, > 3.1 for molecular weight 400 – 450, > 3.4 for molecular weight 450 – 500 and > 4.5 for molecular weight > 500 (Figure 1).

3.3 Clearance and metabolism

The clearance of a drug is a very complex process involving metabolism by a variety of different enzymes in different tissues and elimination by a variety of organs and processes. Reduction of lipophilicity has often been suggested as a valid strategy for reducing metabolic clearance of lipophilic compounds [20,36,37]. Within a series, clearance has often been observed to reduce with reducing logD. However, like many other parameters, these observations must be treated with caution since the structures are changing as well as the lipophilicity and so the reduction in clearance may equally be due to reduced recognition by metabolising enzymes, removal/blocking of sites of metabolism or a combination of these factors. Nevertheless, it seems reasonable to expect that more lipophilic compounds should, on average, be more prone to metabolism. Many metabolising enzymes have evolved to convert lipophilic substrates into more polar compounds to assist with their removal from the body. Moreover, it has been suggested that the binding sites of CYP enzymes (responsible for a significant proportion of drug metabolism) are generally lipophilic in nature and so their affinity for lipophilic substrates is greater [37,38] although the common CYPs have been shown to metabolise substrates with low logP values (0 – 1) as well as more lipophilic substrates [20,39].

Within a set of 47,018 Pfizer compounds, Johnson *et al.* have shown a broad trend of an increasing proportion of

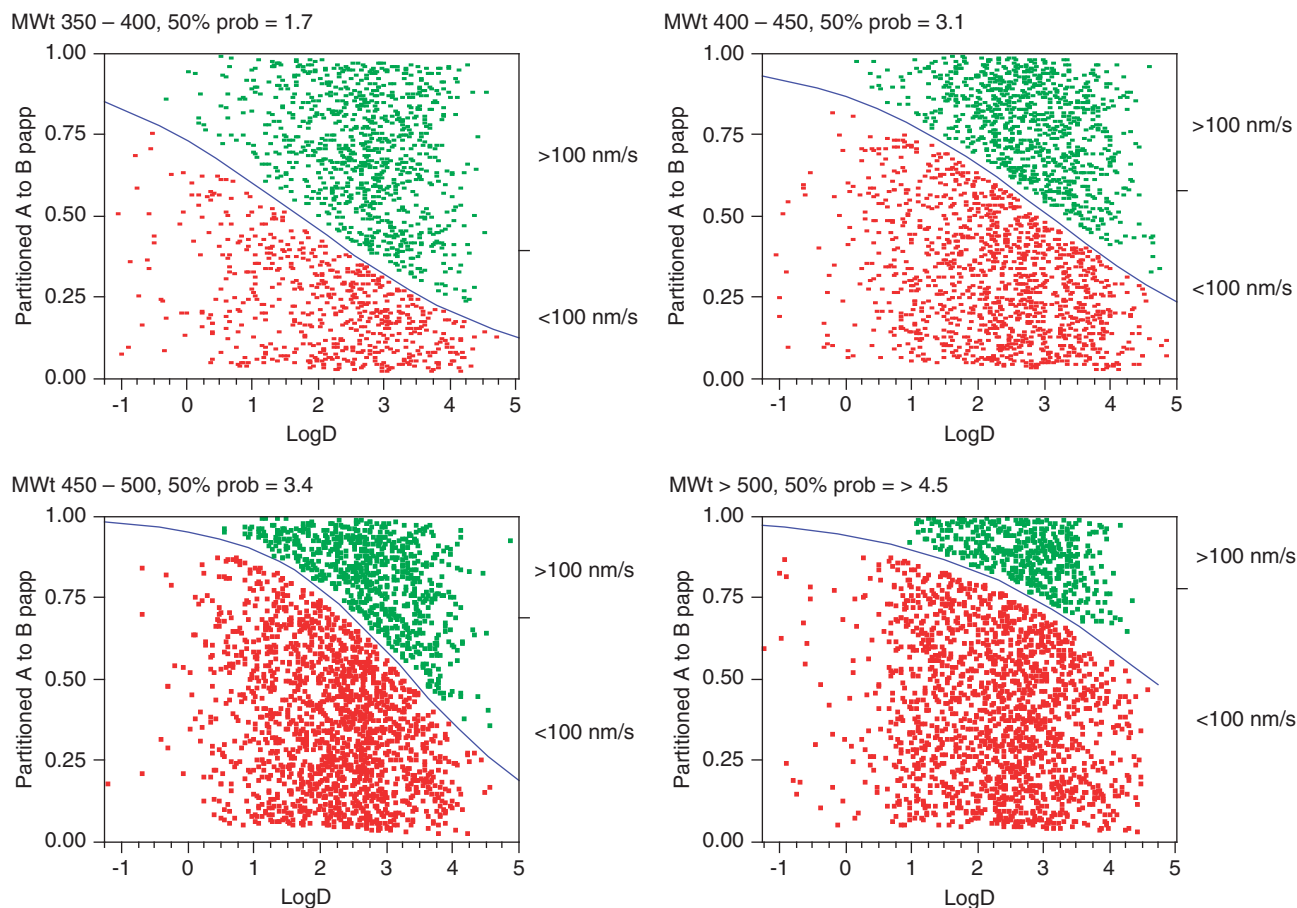


Figure 1. The change in probability of achieving high permeability (Caco-2 P_{app} 100 nm/s) with logD for molecular weight bands between 350 and 500. Permeable compounds are coloured green, non-permeable are red, the data points are drawn at their logD value in the x direction, and in y position they are jittered randomly within the range corresponding to their permeability category. The blue line indicates the probability of high permeability as a function of logD.

Data are derived from those in the literature [35].

compounds with human liver microsomal intrinsic clearance values < 8.6 mL/min/mg (corresponding to a scaled extraction ratio of 0.5) with decreasing logD. It is apparent from this analysis that to stand a reasonable chance of meeting this threshold, a logD < 3 is desirable [40]. They suggest that the exact position of this cut off is molecular weight dependent but the trend is apparent in all molecular weight bands.

For very polar drugs, it is believed that renal elimination of the parent compound can contribute to a significant proportion of the total clearance. It has been suggested that this is because the reabsorption across the kidney tubule becomes much less facile the more polar a compound becomes [36]. This has been illustrated for a series of β -adrenoceptor antagonists that show increasing renal clearance with reducing logD. In this case, renal clearance becomes significant for compounds with logD values < 0 [41]. More recently the role of transporters in these processes is becoming better understood and a study of 391 more diverse compounds tested in humans reveals weaker correlations with logD [42]. Nevertheless, the increasing

propensity for compounds with lower logD (or logP) values to undergo renal clearance is still apparent in this study; 50% of the compounds that showed net renal secretion had calculated logD values < 0, whereas 50% of the compounds that showed net renal reabsorption had logD values > 1.2. While this study does not analyse the data in this way, it seems likely from this that the chances of a compound showing significant renal clearance increase to > 50% for compounds with logD values in the < 0 – 1 region.

Gleeson has shown that for 11,490 GSK compounds, rat *in vivo* clearance values show a very weak but statistically significant trend, increasing with increasing logP [21]. The effects are different for different ionisation types with more lipophilic bases and neutral compounds showing slightly increased mean clearance values compared to those of lower logP but the trend is reversed for acids and zwitterions with mean clearance decreasing with increasing logP. These differences may well be due to different plasma protein binding characteristics in the different ionisation types (see Section 3.5).

However, it also highlights the complexity of this parameter both in terms of the number of processes that are contributing to the value and also the number of different structural and physicochemical factors that govern each of these processes. As highlighted by Gleeson, it may point to the fact that clearance is influenced more by chemical structure than lipophilicity and that across differing chemical structures, the effect of logP is difficult to observe.

A dataset of human *in vivo* clearances for 670 compounds has been published by Obach [43]. This dataset was analysed with respect to logP. In general, lower average clearance values are observed with lower logP with the median human clearance value for very hydrophilic (logP < 0) drugs being 2.2 mL/min/kg (10% hepatic blood flow), and 7.8 mL/min/kg (37% hepatic blood flow) for logP > 4. Of course, this dataset consists only of compounds for which the human kinetics are acceptable for their given indication but a large proportion show parameters that would be unacceptable for once-daily dosing. If the desire is to target once-daily dosing, it would seem reasonable from this analysis to target logP values < 4. The trend becomes more apparent when considering the unbound clearance values (clearance corrected for plasma protein binding); however, analyses of this type must be treated with caution due to the additional relationship between protein binding and lipophilicity (see Section 3.5) [44].

3.4 Bioavailability

Achieving good *in vivo* bioavailability can be considered to be a composite of the parameters discussed earlier requiring a combination of high solubility and permeability to maximise absorption, and low hepatic clearance to minimise first pass extraction. Hence, it might be expected that a balance of lipophilicity would be optimal: too low and permeability would become a problem, too high and solubility and metabolism will be limiting. Lipinski's rules state that oral bioavailability is more likely for logP < 5 but a lower limit is not introduced since, at the time, too low lipophilicity was less of a problem than values that were too high. Nevertheless, a lower logD limit based on compromised permeability does exist (see Section 3.2). It has been suggested that the optimal range is between 0 and 3 for logP [20], however, for solubility and permeability it might be expected that logD rather than logP is a more relevant parameter and it has been proposed that logD should be in the range 1 – 3 [45].

Based on a study of human oral bioavailability data for 232 structurally diverse drugs, Topliss *et al.* showed that by grouping the compounds into categories based on their human bioavailability data, the proportion of compounds in the logD (6.5) range -2 – 3 increase as bioavailability increases [22]. Notably, for those with > 80% bioavailability, 99% of the compounds fall in that range. More recently, other methods of selecting bioavailable compounds have been proposed. Veber *et al.* have proposed guidelines based on rat bioavailability that focus on polar surface area and rotatable bonds rather than on

lipophilicity directly [46]. Martin has shown that different rules can perform better for different ionisation types to predict rat bioavailability for a series of 553 Abbott compounds [47]. Notable in this study is the fact that no clear direct relationship between logD and rat bioavailability is shown. Gleeson has shown that the average bioavailability does not change significantly for compounds with logP < 3 relative to those > 3 regardless of ionisation type for a set of 4,431 GSK compounds [21]. This is perhaps consistent with the findings of Martin but does not address the concept of the lipophilicity window since the logP < 3 group will include compounds in optimal space and those that are too polar and, hence, have compromised permeability. It is possible that this subtlety is lost by considering average bioavailability values for the entire range of logP values in the group.

3.5 Distribution

Lipophilicity is also a factor in determining the distribution of compounds within the body. Critically, the extent to which compounds bind to plasma proteins, in particular serum albumin, has a profound effect on pharmacokinetic parameters such as clearance [48] and volume of distribution [49]. In addition, since the unbound drug concentration in plasma is usually the critical concentration for determining the pharmacological response, protein binding would be expected to be crucial for determining efficacy [50]. Lipophilicity is well established to be a major determinant in the degree of plasma protein binding. Valko *et al.* have shown a reasonable direct correlation between logP and the logK value for binding to human serum albumin for 135 diverse drugs and simpler organic compounds [51]. It is worthy of note that logP rather than logD predicts binding; serum albumin is rich in charged residues and transports endogenous fatty acids and, hence, can bind ionised and unionised molecules with similar affinity. Acids in particular tend to bind with greater affinity than would be expected from their logD values.

When considering aspects of the distribution of compounds within the body, such as volume of distribution and partitioning into specific effect compartments, the effect of protein binding is a determining factor. Direct lipophilicity relationships might not necessarily be expected, however, since lipophilicity is likely to also govern the extent of tissue binding as well as that to plasma protein and the balance between them is likely to be the key determinant of the extent of partitioning. For example, logD has also been shown to be a factor in determining the non-specific binding in tissues estimated from human volume of distribution data [52,53].

A special case of these considerations is presented by partitioning into the CNS. In this case, an additional hurdle is presented by the blood–brain barrier [20], the tight intercellular junctions of which are believed to present a more significant permeability hurdle than other membranes such as those of the intestines. In addition, the blood–brain barrier expresses a range of efflux transporters such as P-glycoprotein that are

not as easily saturable as those in the intestine. Hence, the CNS exposure of a drug relative to its plasma concentration is a function of the balance between its plasma protein and CNS tissue binding and its ability to permeate the blood–brain barrier, all of which are likely to increase with increasing lipophilicity. Many literature studies are based on total CNS drug levels that will be increased by greater CNS tissue binding relative to plasma protein yet it is likely that concentration of unbound drug in the CNS is responsible for driving efficacy.

A study of 50 marketed CNS drugs reveals that 75% of these compounds have logP values > 2 and that their *in situ* rat brain permeability is related to logP in a non-linear manner, reaching a plateau between logP values of 2 and 3 [54]. Of course, CNS drugs still need to satisfy the criteria for oral drugs. Indeed, maximising unbound plasma exposure of a drug is one obvious means of increasing exposure in the CNS [55]. Consistent with this, a summary of two literature studies reveals that for compounds to cross the blood–brain barrier, they should optimally have a logD between 1 and 3, a region very similar to that of oral drugs in general [20].

4. Toxicity

4.1 General toxicology

In principle, the ability of a compound to bind to any target is, in part, a function of its lipophilicity since a component of its binding affinity is hydrophobic collapse [56]. This contribution will be greater for more lipophilic compounds. These effects are likely to have poor specificity and will contribute to the affinity of a molecule to most, if not all, targets to a greater or lesser degree. Hence, it might be expected that more lipophilic compounds will be more promiscuous. Some of these additional targets in question are likely to give rise to unwanted pharmacology (anti-targets) and, hence, the more promiscuous compounds are likely to be more toxic.

Provided it is the neutral form that is binding, it would be expected that logD rather than logP would be a better predictor of promiscuity. However, a number of anti-targets often screened have ionised compounds as endogenous substrates [57] and are likely to be capable of binding the ionised as well as the neutral forms of compounds with differing affinities. In this case, neither logD nor logP is an ideal descriptor but provided the contribution of lipophilicity to the binding is similar for the ionised and unionised form, logP would serve as a useful surrogate.

Evidence for increased promiscuity with high lipophilicity was provided by an analysis of a set of 2,133 drugs and reference compounds from the Cerep Bioprint database, carried out by Leeson and Springthorpe, that showed that promiscuity increases dramatically for logP > 3 [9]. Similar observations were made by Peters *et al.* on analysing Bioprint data for a set of 213 Roche compounds [57] who observed that promiscuity in this case increases for logP > 2. In both cases, the extent is different across ionisation types with basic compounds being more promiscuous than acids and neutral compounds. It is

possible, as stated by Peters *et al.* that this is an artefact of the enrichment of compounds targeted at monoamine GPCRs and their consequent activity at other targets in the same class.

A study at Pfizer considered the effect of logP and polar surface area on the outcome of *in vivo* toleration studies in rats and dogs [58] and found that compounds with logP < 3 and PSA > 75 Å² were 2.5 times more likely to be clean than toxic in these studies and conversely, compounds with logP > 3 and PSA < 75 Å² are 2.5 times more likely to be toxic than clean (Table 1). These findings were found to be consistent with analogous analysis of Bioprint promiscuity data.

4.2 hERG

The relationship between lipophilicity and hERG potency serves as a useful specific illustration of the earlier mentioned considerations. The hERG cardiac potassium channel is well known for its promiscuity and ability to bind a variety of different chemotypes at a level of potency that is likely to become problematic [59]. As a consequence, a number of studies have been conducted to establish SARs for hERG based on pharmacophores and molecular descriptors [60]. These studies suggest a strong contribution of lipophilicity to hERG binding.

The risk of compounds achieving problematic (IC₅₀ < 10 µM) levels of hERG potency have been quantified as a function of lipophilicity alone for different ionisation classes [61]. This study shows that the chances of compounds achieving hERG potencies of > 10 µM diminish significantly as logD increases for both neutral and basic compounds (Figure 2). To have a > 70% chance of a compound being less active than 10 µM requires a logD < 3.3 for neutrals and < 1.4 for bases. Similar findings have been reported across a range of other datasets [21,62].

On occasions, depending on the target class, it has been observed that a certain degree of lipophilicity has been required for target potency. In these cases, lipophilicity reduction may not be a valid strategy to avoid hERG activity since this may lead to a loss of target potency or, in other cases, low lipophilicity compounds may still retain unacceptable hERG potency. In such cases alternative strategies will be required to solve this more challenging problem [62,63,64]. Nevertheless, in the first instance, identifying potent compounds with low logD values within a series would seem the simplest and most established means of minimising hERG risk.

4.3 Phospholipidosis

Like hERG blockade, drug induced phospholipidosis is another specific toxicology that appears strongly linked to lipophilicity for basic compounds. In this case, it appears that it is the amphiphilicity that causes the problem and, hence, for a base, the more lipophilic it is the more amphiphilic it is likely to be. Ploemen *et al.* suggested that the risk of a compound causing phospholipidosis increases if the sum of logP² and pK_a² is > 90 [65]. Hence, for a base with a pK_a of 9, a logP of < 3 is desirable, whereas for weaker bases this limit should

Table 1. Ratio of toxic to non-toxic compounds based on *in vivo* toxicology studies categorised by logP and PSA.

	PSA 75	PSA 75
logP < 3	0.39	1.1
logP > 3	0.41	2.4

Data are derived from those in the literature [58].

PSA: Polar surface area.

increase. Tomizawa *et al.* have proposed a decision tree based on 63 drugs and proprietary Pfizer compounds that suggests the risk of a compound with a net charge of 1 causing phospholipidosis is high for logP > 2.75 [66]. All compounds in this category caused an effect in their assay.

4.4 CYP inhibition

CYP inhibition would be expected to exhibit a similar trend. Since substrates show increased affinity with increased lipophilicity [38,39], competitive inhibitors would be expected to show the same effect. Indeed, Gleeson has shown that for > 40,000 GSK compounds across the five most common CYP isoforms (1A2, 2C9, 2C19, 2D6 and 3A4), average IC₅₀ values are significantly lower for compounds with logP < 3 than for those > 3 [21]. The absolute value is ionisation state dependent and differs for different isoforms. This might be expected since the different isoforms have been shown to have different hydrophobicity factors for substrates [38] but, crucially, the average IC₅₀ for compounds with logP < 3 is consistently > 10 µM, a typically employed threshold above which drug-drug interactions are unlikely to be problematic. The same is not true for the more lipophilic compounds.

5. Effect on target potency

Primary target potency is another parameter that might give rise to a lower limit of lipophilicity. It is expected that, on average, more lipophilic compounds within a series will be more potent against their target. In some individual targets and target classes, this effect may be more prevalent than others. In some cases, the binding sites for compounds are characterised as being lipophilic in nature, thus leading to the reasonable hypothesis that lipophilic ligands will be required for potency.

An analysis by Vieth has shown that within oral drugs, different target classes have statistically significantly different average logP values [67]. One conclusion from this analysis (which is perhaps contentious) is that the need to balance bioavailability and affinity suggests that modified rules for drug likeness be adopted for certain target classes. However, if the compounds within this set are plotted in a one-way fashion to show the overall distribution rather than just the mean values and standard deviations (Figure 3, shown for logD as well as logP), two things become apparent. First, the statistical significance in the difference between mean values is as

much a function of the sample size as the absolute magnitude of the mean value; it would be expected that many other subsets would show significant differences if the sample size increased. Second, and more importantly, none of these distributions lie significantly outside optimal lipophilicity space. Compounds with logD values < 3 exist in all of the target classes and all overlap significantly with the overall distribution of oral drugs (see Section 6). It cannot be concluded from this, for instance, that working on a nuclear hormone receptor will require high lipophilicity to achieve the required potency. It may be true of individual targets within each class. An analysis of global pharmacophore space reveals that the distribution of average logP valued compounds active against individual targets within certain target classes can be as large as the variation between classes [68].

Compounds that achieve their potency through lipophilic interactions are likely to possess a greater proportion of entropic rather than enthalpic contribution to their binding energy [56,69]. It might be postulated that compounds of this nature may be less selective and more promiscuous since entropic contributions to potency through hydrophobic collapse are less likely to be specific than enthalpic contributions. A recent study of marketed 'first in class' and 'best in class' HIV protease and HMG CoA reductase inhibitors has suggested that compounds with a greater enthalpic component to their binding affinity may be superior overall to those for which the entropic contribution is greater [56]. While this is by no means conclusive, the hypothesis appears sound and is worthy of further consideration.

6. Development attrition and overall quality

As part of optimisation, it is of course necessary to satisfy all of the individual parameters discussed in this review. It might, therefore, be expected that compounds that satisfy multiple criteria will occupy a mutually desirable lipophilicity range. For example, Lipinski's suggested limit of logP < 5 is based on compounds reaching Phase II clinical trials [7]. This was based on the assumption that these compounds must have the required solubility and permeability but will have satisfied many other additional requirements. Gleeson has suggested that compounds with logP < 4 (and molecular weight < 400) stand a much higher chance of success against a comprehensive set of ADMET parameters [21]. A set of AstraZeneca compounds proven to satisfy criteria for permeability, solubility and hERG binding (P_{app} > 100 nm/s, solubility > 100 µM and hERG IC₅₀ weaker than 10 µM) were found to occupy an intermediate range of logD values with 80% of them occupying a logD range between 1 and 3.1 (the 10th to 90th percentile range; Figure 4A) [12].

For similar reasons, it would be expected that oral drugs should fall into a similar range. An analysis of the properties of oral drugs over time by Leeson *et al.* showed that the average logP value for oral drugs has stayed roughly constant over time (by comparing drugs launched before 1983 to those launched after) with a mean value between 2.3 and 2.6 [70]. The range of logP

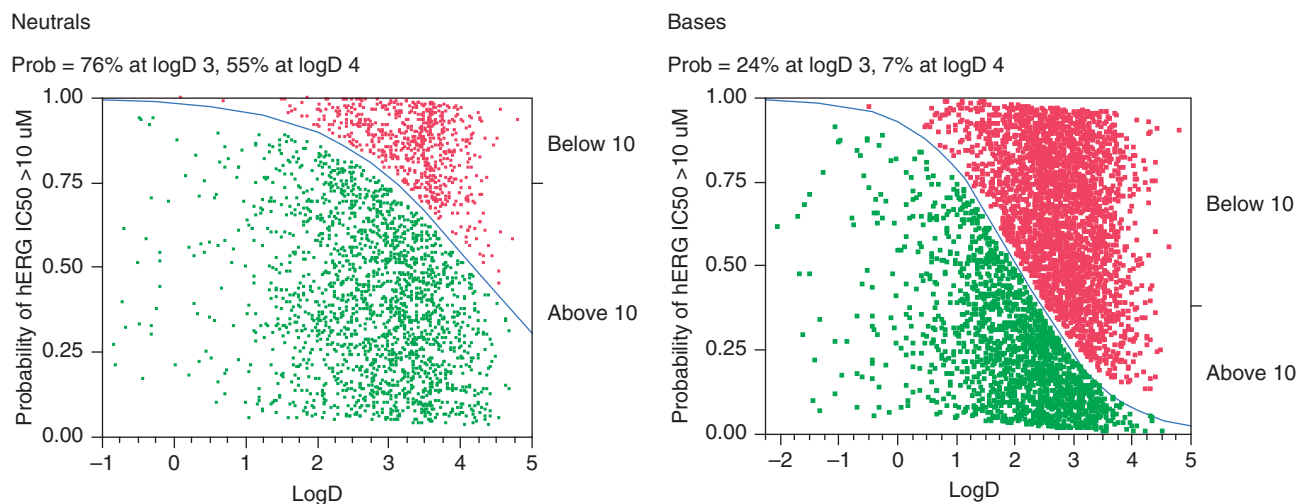


Figure 2. The change in probability of achieving hERG IC_{50} 10 μM with logD for neutral and basic compounds. The less active compounds are coloured green, more active are red, the data points are drawn at their logD value in the x direction, and in y position they are jittered randomly within the range corresponding to their hERG activity category. The blue line indicates the probability of achieving an $IC_{50} > 10 \mu M$ as a function of logD.

Data are derived from those in the literature [61].

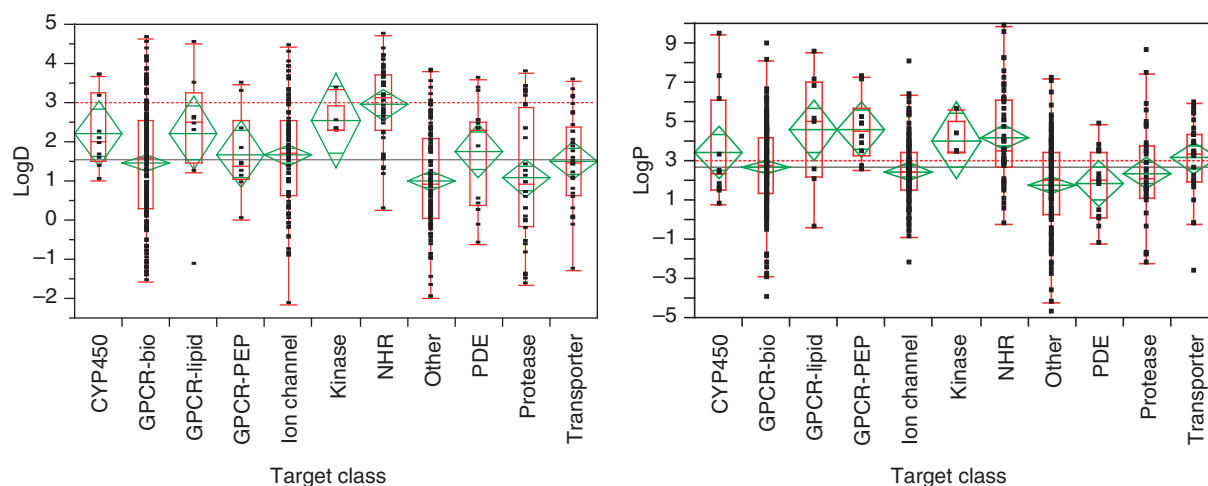


Figure 3. logD and logP distributions for compounds in the Vieth set broken down by target class. The dotted red line shows $\log D / \log P = 3$.

Data are derived from those in the literature [67].

values for oral drugs in this analysis range from $\log P$ -1 to 5 (10th and 90th percentiles). The set of oral drugs described by Vieth to analyse by target class has a similar $\log P$ distribution (mean 2.7, 0 – 5.3 for the 10th to 90th percentile range). This same dataset has a narrower $\log D$ distribution (mean 2.6, -0.3 – 3.5 for the 10th to 90th percentile range; **Figure 4B**) [12,67].

An analysis by Wenlock *et al.* showed that average $\log P$ values decrease throughout successive stages of development, implying that there is a link between development attrition and lipophilicity [71]. This observation is consistent with the premise that high lipophilicity is associated with

poorer DMPK and toxicological properties; however, it is not definitive since the reasons for compounds failing in development are complex and can often be based on commercial/portfolio decisions, issues with target validation and mechanism-related toxicity rather than the quality of the compound per se [72].

7. Summary

It is rare for strong direct correlations to exist between lipophilicity and any particular ADMET parameter, most likely

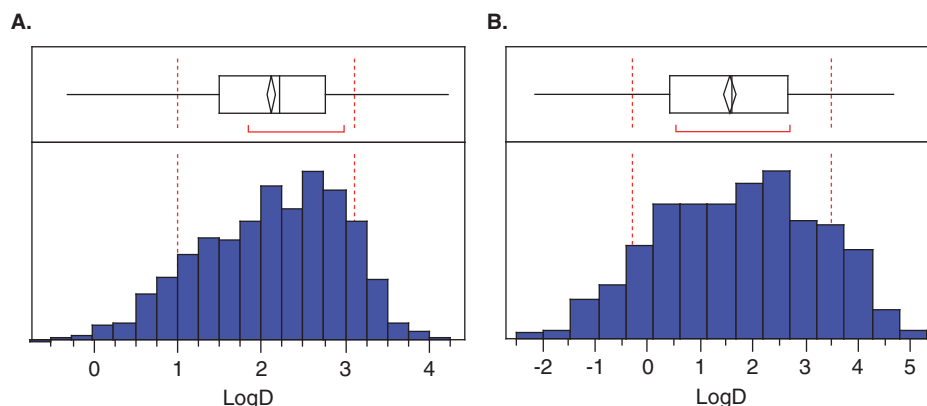


Figure 4. logD distributions for (A) AstraZeneca compounds with P_{app} 100 nm/s, solubility 100 μ M and hERG IC_{50} 10 μ M and (B) Vieth oral drugs. The dotted red lines indicate the 10th and 90th percentiles.

Data are derived from those in the literature [12,65].

because the influence of other physicochemical descriptors, such as size and hydrogen bonding, and, probably more importantly, the chemical substructures also have an effect. A better interpretation of these relationships is a probabilistic one. In this sense, the link between lipophilicity and many parameters is well established and it can be stated with confidence that, within a certain range of lipophilicity, compounds are significantly more likely to be successful against a given parameter.

Compromised properties are expected at both extremes of lipophilicity. As might be expected, the region where good overall compounds, defined in a variety of different ways, are distributed falls within these boundaries (Figure 5A). In different cases, logD or logP have been used to define limits as far as possible based on individual parameters to offer a guide for useful lipophilicity space to target. The positions at which these limits fall for various issues are quite similar (Figure 5B); those parameters that are compromised at high logP/logD values tend to have limits between values of 3 and 4 and those that are compromised at low values tend to have limits of $\sim 0 - 1$. Hence, the optimal range of lipophilicity lies between ~ 1 and 3.

8. Expert opinion

The optimal range of lipophilicity suggested here (logD/P between 1 and 3) is very narrow. However, it is expected that if projects can synthesise compounds within this window of opportunity, many parameters are less likely to present as issues and the complex problem of multi-parameter optimisation is greatly simplified. Moreover, not only is it easier to achieve acceptable values for these measurable parameters but from studies of toxicology and attrition, it might be expected that subsequent success in development against issues that are harder to assess in discovery might also be increased. The challenge then becomes finding compounds with appropriate lipophilicity values that are sufficiently potent. In this regard,

proposed composite measures potency per lipophilicity unit may be informative in assessing compounds and in analysing SAR within series [9,73].

Analysis of target classes individually reveals that certain target classes have different distributions of lipophilicity than others and it is likely that finding compounds of sufficient potency within the optimal lipophilicity range will be harder for certain target classes than others. However, since the Vieth data for every target class overlaps considerably with the optimal logD range, the existing data do not provide a compelling case that this is necessary for any of the target classes analysed thus far. It may be the case for individual targets within any class and, in extreme cases, there may be targets that are genuinely intractable for small molecule drug discovery. However, if medicinal chemists believe they must make very lipophilic compounds in order to achieve potency, then synthesised compounds will be biased towards this end of the range and the dogma will never be challenged sufficiently. Moreover, those compounds will still be expected to suffer against subsequent parameters in many cases and it might be argued that it is often easier to find potent compounds in optimal lipophilicity space than it is to find highly lipophilic compounds with acceptable ADMET properties given the numbers of other properties that are compromised in this region. This is not to say that it cannot be achieved, there are exceptions to these rules, some of which are very successful drugs, but rather to highlight where future success is more likely and where future attrition can be minimised.

Lipophilicity can be calculated prior to synthesis although improved accuracy of prediction would still be desirable. However, the accuracy of these predictions can easily be verified by measuring the logD (and pK_a in some instances) of the compounds once synthesised and, if necessary, the predictions can be refined based on measured data. The narrowness of the lipophilicity window probably requires this in many cases since, if the average prediction error is > 1 log unit and the window

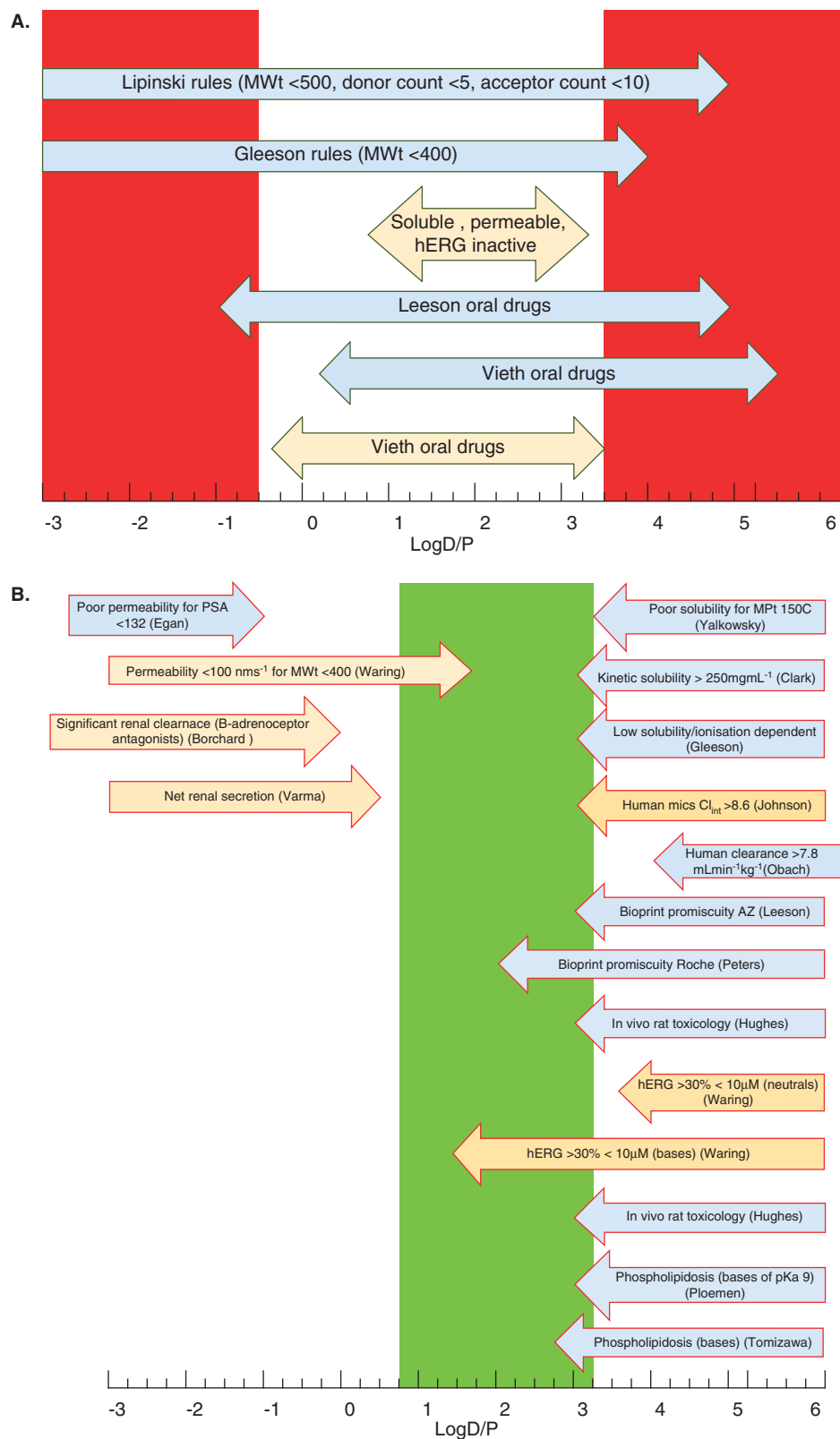


Figure 5. Summary charts showing the regions of lipophilicity where (A) good overall compounds are distributed and (B) properties are compromised for logD (orange) and logP (light blue).

of opportunity could be as narrow as 2 log units, generic algorithms may not be very discriminating in targeting this narrow window.

However, it is possible to manipulate lipophilicity in a predictable and understandable way by structural modification enabling greater application at the compound design stage, and with appropriate measured data the optimal range can be targeted within an optimisation series provided the effects of sub-structural changes on logD are understood.

One possible consequence of this is that lead generation libraries focus on optimal lipophilicity space [8]. This would appear a laudable aim, however, at the lead stage, compounds with low lipophilicity are less likely to show the required potency in a high throughput screen. In the absence of other binding interactions, a lead series should be expected to show a correlation between logP and potency. If a high throughput screen was run with an absolute potency cut off, only the more lipophilic compounds might be detected and these compounds are more likely to lie outside of the optimal range. Such compounds may still be valuable screening hits since lipophilicity of potent compounds can be reduced as part of the optimisation programme. This might still represent a tractable optimisation problem since the changes that reduce lipophilicity are well known and understood. It might, therefore, make sense for upper lipophilicity limits for library design to be increased slightly relative to the optimal space provided this increase is not too great. Although it has been shown that optimisation usually adds lipophilicity [74], provided medicinal chemists are aware of the issues, it is eminently feasible to

focus an optimisation programme on reducing lipophilicity and maintaining potency. The magnitude of the reduction required to access the optimal range could be taken as an assessment of the value of lead compounds and of the likely timescales and risks associated with an optimisation campaign.

The optimal lipophilicity range derived here is intended to be general and within individual series this optimal window may be different, sometimes smaller, sometimes larger but in our experience the range of logD 1 – 3 is typical. This allows very little room to manoeuvre in terms of structural modification, hence, the success of medicinal chemists in the future might be increased if ways to increase this window of opportunity were developed. Along these lines, it has been suggested that reduction of molecular weight [21,35,40], removal of aromatic rings [75] and increased saturation or added chirality [76] might offer generic means of achieving this. Within a series, more subtle sub-structural effects may be exploitable if the parameters defining the boundaries of the window can be identified and SAR developed.

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Declaration of interest

The author is an employee of AstraZeneca.

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