Chapter 14
Molecular Obesity, Potency and Other Addictions in Drug Discovery

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Abstract Achieving the right balance of properties in a candidate drug molecule is a very complex challenge as many of them are in conflict with each other. Structure Based Drug Design is a key tool in the medicinal chemists toolkit but can lead to an over dependence on potency if not used in conjunction with physical chemistry predictions and measurements to maintain the property balance needed.

14.1 Introduction

The title of this chapter is taken from our 2011 publication, with the same title as this chapter, and this should be read in conjunction with this chapter for further background [1].

   Drug discovery is a very complex activity that is often said to make rocket science look easy! Figure 14.1 attempts to summarize the journey that is required in both a multidimensional and multi-objective sense to attain the sweet spot where all the properties required of a safe and efficacious new medicine are appropriately balanced. Of course the view of the challenge of drug discovery presented in Fig. 14.1 can be over simplistic when we consider that there may not actually be a compromise that can be found between these conflicting properties. This may be because the target protein may actually be undruggable with a small molecule, or the window of specificity is vanishingly small.

   A consequence of the complexity of our challenge is the balance between the genuinely predictable scientific activities ("which needs maths") from the more chaotic activities ("which need experience and intuition"). Another way of thinking about this is embedded in the truism that "the interesting things in science are the differences between theory and experiment"!

   Protein crystallography and Structure-Based Drug Design (SBDD) have become key components of our toolkit to aid us on the journey, however using them without

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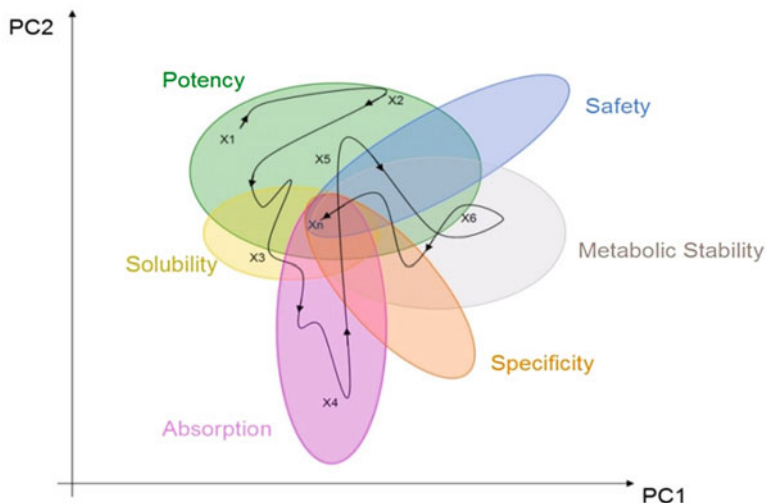e-mail: mike.m.hann@gsk.com

Fig. 14.1 A simplified 2D map of the challenge of drug discovery and the journey a project might take in starting from x1 and ending at xn

considering the bigger picture can lead to unfortunate consequences through the design of inappropriate molecules! This chapter aims to put in context some of the conflicts that a quality molecule needs to have in order to be a successful medicine and highlights the danger of seeking quick fixes through potency based on lipophilicity and other physiochemical influences.

While creativity in medicinal chemistry is at the heart of the drug discovery process it is often disciplines such as computational chemistry and structural biology that enable some of this creativity. The combined skill sets that are required for the identification of the best leads and then nurturing them through lead optimization on a complex landscape of constraints is often the defining characteristic of successful drug discovery campaigns.

14.2 What Are the Leading Causes of Failure in Drug Discovery?

It is clear from data compiled by Kola and Landis that comparison of cited reasons for drug discovery failures (e.g., attrition) in 1991 to those in 2000 showed a shift to an increase in failure attributed to toxicological reasons [2].

The issues of PK and bioavailability that were the leading cause of attrition in the 1991 data appear to have been largely controlled. It seems likely that this is due to both a better understanding of pharmacokinetic issues and also in the improved formulation of compounds that results in more chemical entities overcoming this

hurdle. Some of this improvement in getting compounds into the body (and keeping them there) is likely related to the rise in attrition due to toxicological issues as the body responds to chemical entities that are "forced" into the body. Thus by using formulation technologies to deliver inappropriate molecules we may have only delayed failure (i.e., the realization that a molecular series is inappropriate) to a more expensive part of the drug discovery activity.

So what defines inappropriate molecules? Clearly some of the toxicity of a molecule or series will be due to activity at the intended intervention target (or its pathway), which may only become apparent during development. However it is becoming increasingly clear that there are more generic influences behind a significant proportion of toxicology-related attrition. Much of this realization has come from recently published analyses of internal data from large pharma companies and this has led to the emergence of new guidelines aimed at hopefully controlling this aspect of attrition in the future (e.g., [3]).

The earliest of the rules of thumb that have become prevalent in contemporary drug discovery parlance is the Lipinski "rule of fives" which has been adopted, and often erroneously used, as defining the limits of drug like space [4]. Lipinski's rule actually refers to the likelihood of a compound having oral bioavailability, based on a set of compounds that made it to Phase IIa and were therefore assumed to be a good indicator of oral absorption. Thus compounds which have one or more of either CLogP greater than 5, Molecular Weight greater than 500, Number of H-bond acceptors greater than 10 or Number of H-bond donors greater than 5 are less likely to be orally absorbed. It is now becoming increasingly clear that a much more tightly defined set of rules are appropriate if we are considering drug space from the viewpoint of toxicological risk rather than the risk of a compound not being orally absorbed.

The publication from Leeson and Springthorpe at AstraZeneca on Receptor Promiscuity clearly highlighted (Fig. 14.2) the problem of excessive lipophilicity and they introduced the term Lipophilic Ligand Efficiency (LLE) (defined as pIC50 – cLogP) to help highlight likely promiscuous compounds [3]. If LLE >5, then the compound related toxicity risk is greatly reduced. The reason for this can be readily understood when it is remembered that the lipophilicity scales (such as cLogP) are logarithmic and therefore an increase of just one unit in cLogP means that there is now ten times more compound present in the highly lipophilic cellular membranes. These membranes are the home to many of the critical signaling systems and inappropriate triggering by local high concentrations of not very intrinsically potent compounds, can easily lead to unwanted effects leading to potentially toxicological events. While promiscuity of this non-specific type will be detrimental, there may be situations (e.g. for polypharmacology) where some degree of promiscuity is of course desirable.

In another study Hughes et al. at Pfizer showed (Fig. 14.3) that compounds with a cLogP <3 & Total Polar Surface Area TPSA >75 have a sixfold reduced in vivo toxicity compared to cLogP >3 and TPSA <75. This is known as the Pfizer 3/75 rule [5].
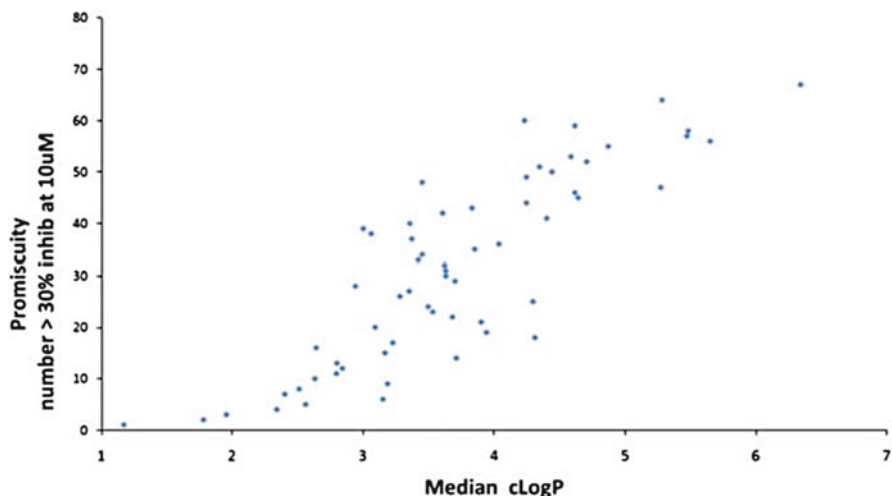
Fig. 14.2 Rise in promiscuity of compounds with cLogP (Data from Ref. [3])

Probabilities of toxicity vs ClogP/TPSA				
	based on [total drug]		based on [free drug]	
	TPSA>75	TPSA<75	TPSA>75	TPSA<75
ClogP<3	0.4	1.1	0.4	0.5
ClogP>3	0.4	2.4	0.8	2.6

Fig. 14.3 Toxicity probability matrix based on TPSA and cLogP criteria (Data from Ref. [5])

Another example (Fig. 14.4) of an analysis that has led to the emergence of a further set of guidelines is the GSK 4/400 rule which relates to compounds with a CLogP less than 4 and a MW less than 400 and how on average they have a more favorable ADMET profile [6]. This analysis by Paul Gleeson looked at ca. 30,000 neutral, basic, acidic and zwitterionic molecules that have been profiled in multiple physical chemistry and ADMET assays at GSK.

A further perspective on attrition related parameters is given by a count of the number of aromatic rings. While clearly related in a non-linear manner to lipophilicity, the analysis of this property by Ritchie and MacDonald gives interesting insights which can be summarized as "the fewer aromatic rings in an oral drug candidate the better" with less than three being suggested as an appropriate target number [7]. This use of a count of aromatic rings has been extended (Fig. 14.5) by Young et al. at GSK to define a Property Forecast Index PFI as the sum of a chromatographically measured logD at pH 7.4 and the number of aromatic rings. If PFI is <6 then compounds are likely more soluble and have reduced ADMET risks [8].

Continuing this theme of the dangers of too much sp2 or aromatic character in molecules, Humblet et al. showed that the survival rate of compounds through the

neutral molecules	MW<400 & cLogP<4		MW>400 & cLogP>4	
solubility	average	intermediate	lower	bad
permeability	higher	good	average/higher	intermediate
bioavailability	average	intermediate	lower	bad
volume of distribution	average	intermediate	average	intermediate
plasma protein binding	average	intermediate	higher	bad
CNS penetration	higher/average	bad	average/lower	good
brain tissue binding	lower	bad	higher	bad
P-gp efflux	average	intermediate	higher/average	bad
in vivo clearance	average	intermediate	average	intermediate
hERG inhibition	lower	good	lower	good
P450 inhibition	lower 2C9, 2C19, 2D6 & 3A4 inhib	good	higher 2C9, 2C19 & 3A4 inhib	bad
	higher 1A2 inhib	bad	lower 1A2 inhib	good
			average 2D6 inhib	intermediate

Fig. 14.4 Effect of GSK 400/4 rule on properties effecting ADMET properties (Data from Ref. [6]). Good, Intermediate or Bad refers to criteria for a peripheral target

Assay/target value	PFI = mChrom log D7.4 + #Ar								
	<3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	>10
Solubility >200 μM	89	83	72	58	33	13	5	3	2
&HSA <95%	88	80	74	64	50	30	17	8	4
2C9 pIC50 <5	97	90	83	68	48	32	23	22	38
2C19 pIC50 <5	97	95	91	82	67	52	42	42	56
3A4 pIC50 <5	92	83	80	75	67	60	58	61	66
Clint <3ml/min/kg	79	76	68	61	54	42	41	39	52
Papp>200nm/s	20	30	46	65	74	77	65	50	33

Fig. 14.5 Property Forecast Index PFI and its effect on a number of ADMET properties. Numbers show percentage of compounds achieving defined target values in various developability assays (Data from Ref. [8])

drug discovery process is enhanced by an increase in the fraction of sp3 hybridized carbon atoms and the number of chiral centers present [9]. In addition to giving access to a greater diversity of compounds to explore it seems likely that one of the benefits of chirality in a drug is that it leads to increased complexity (and hence potential potency through appropriate complementarity) to a specific target without increasing the molecular weight of ligands [10].

Lipophilicity is well known to be the antithesis of solubility and lack of solubility has been a consistent problem for medicinal chemists [11]. As noted earlier improved formulation methodologies can somewhat mitigate this situation. However relying on formulation to get insoluble compounds on board is likely only to aggravate the body to work harder to eliminate them. The usual response of the body to lipophilic xenobiotics is to try to make them more polar via metabolism so they can be excreted. Medicinal chemists are then faced with the need to make their lipophilic and insoluble compounds more metabolically stable to prolong

their duration of actions. This can put enormous demands on a compounds profile, especially if once a day dosing is being sought as the target product profile. Blocked metabolism means the body will need to find more extreme ways of removing the compound, often inducing more high potential and thus intrinsically more reactive and toxic species.

If as a result of our lead optimization we end up with excessively large and lipophilic molecules, it is clear that we have likely embedded other properties into these molecules that will limit their ability to become successful medicines. In effect they have become too large and too lipophilic for their own good and for this reason we introduced the term Molecular Obesity. As with medical obesity, which is measured by Body Mass Index (BMI), medicinal chemists have developed their own indices (Fig. 14.6 shows a summary of some of these) such as Ligand Efficiency LE (= binding affinity/number of heavy atoms) [12] and the already mentioned Lipophilic Ligand Efficiency LLE [3] to help identify and control the effects of molecular obesity, which are implicated in the premature demise of far too many drug candidates in recent years. Additional indices continue to emerge in the literature, all with the aim of restricting the tendency to Molecular Obesity. One such index is the LLE_{AT} index, which combines aspects of LE and LLE and adjusting so that the value is on the same scale as LE, so again 0.3 is a good target

- **Ligand Efficiency Index (LE)**
  Ligand efficiency: a useful metric for lead selection Hopkins et al.. DDT 2004;9(10):430-1
  LE=ΔG/#heavy-atoms
  Potency in kcal/mol (=-1.37logKd) normalised by dividing by the number of heavy atoms
  An *'idealised'* compound with 1nm pIC50 and 30 heavy atoms has LEI = 0.42
  An *'okay'* compound with 10nm pIC50 and 38 heavy atoms (MW 500) has LEI = 0.29
- **Lipophilic Ligand Efficiency Index (LLE)**
  The influence of drug-like concepts on decision-making in medicinal chemistry. Leeson and Springthorpe . NRDD 2007;6(11):881-90
  LLE = pIC50 – clogP
  Potency normalised by lipophilicity to ensure specific rather than non-specific effects.
  Typical good value are 5-7 for nanomolar potency compound
- **Ligand Ligand Efficiency (Astex version)**
  Assessing the lipophilicity of fragments and early hits. Mortenson and Murray JCAMD, 2011, 25 (7), 663-667
  $LLE_{AT} = 0.11*ln(10)*RT(logP-log(Kd))/HA$
  Combined LLE and LE index which is parameterised to be on same scale as LE, so 0.3 is considered a good target value. Particularly good for assessing fragment hits.
- **Binding Efficiency Index (BE)**
  Ligand efficiency indices as guideposts for drug discovery. Abad-Zapatero and Metz. Drug Discovery Today, 10(7), 2005, 464-469
  BE = pIC50/MW.   Potency (pIC50) normalised for MW
  An *'idealised'* compound with 1nm pIC50 and MW of 0.333 kDA has BEI = 27
- **Surface Binding Efficiency Index (SE)**
  Recent Developments in Fragment-Based Drug Discovery J. Med. Chem.; Congreve et al.. 2008; 10;51(13):3661-80;
  Potency normalised for Polar Surface Area
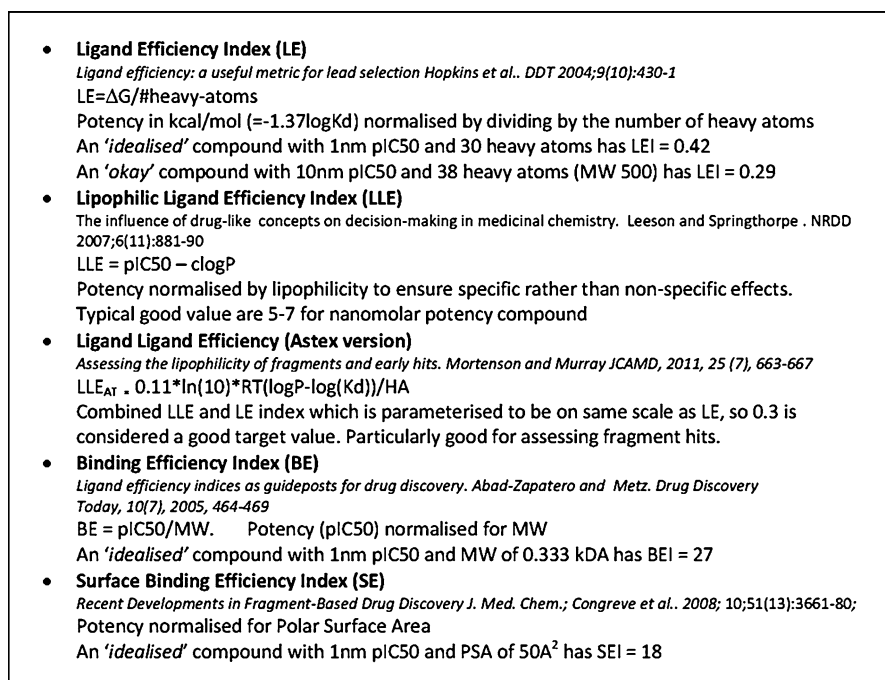 An *'idealised'* compound with 1nm pIC50 and PSA of $50A^2$ has SEI = 18

Fig. 14.6 Summary of medicinal chemistry indices and guidance on target values

value [13]. This index is particularly useful for assessing early fragment hits for follow up.

14.3   Driving Potency Through Molecular Obesity

We like potency in our molecules for a number of reasons and it is worth examining why this is. This is a particular problem when following a SBDD approach where the availability of compelling structural insights enable by progress in protein crystallography can lead to highly potent molecules designed and built to fit the protein target. While there is nothing intrinsically wrong with potent molecules, there is when other properties compromise their overall effectiveness!

One of the basic tenets of medicinal chemistry is that increasing ligand potency leads to increased specificity and hence to an improved therapeutic index [14]. This is true if the potency is based around directional (i.e., polar) interactions because the directionality implies specificity. In 2001, we introduced the concept of Molecular Complexity (Fig. 14.7) [10] and updated this in a further paper in 2011 [15]. The basic tenet of the idea is embedded in a simple and abstract model of molecular interactions between a ligand and receptor that gives insights into the probability of finding appropriate complementarity at different levels of molecular complexity. While we aspire to find very complex and thus potentially potent (and specific) interactions the chances of finding these all at once (i.e., in HTS) is highest when we only expect to get a few right initially. This is the basis of the fragments approach, which is based on finding weakly binding but small compounds with just a minimal number of correct interactions. We then iteratively grow the molecule to find new interactions and hence potency. However one of the easiest ways of gaining potency is through lipophilic interactions which are non-directional and therefore do not require precise engineering. In a recent book chapter we have developed an extension of the complexity model, which uses information content as a way of representing (Fig. 14.8) such non-directional interactions [16]. In the left hand representation, slippage is difficult as the complexity in the pattern makes slippage difficult. While on the right low information content (e.g., lipophilicity) can slip easily and in addition all the secondary interactions as attractive.

Of course high potency can allow reduction in the size of dosage especially if a compound has good pharmacokinetic properties. Low dosage not only helps reduce the cost of goods but it is also one of the only known predictors of low incidence of idiosyncratic toxicity [28]. Potency can compensate for low bioavailability in that the small portion of, for example, a poorly absorbed drug that does get into the circulation will at least have a chance of being efficacious if it has high molar potency. However this brings a high risk in that the part of the high dosage that is not being effectively utilized is available to cause off target issues.

So while there are many reasons why potency is a good thing, the problem is how we have often gone about achieving it. Ladbury and colleagues have shown by ITC studies that the Free Energy of interaction (i.e. potency) of synthetic ligands
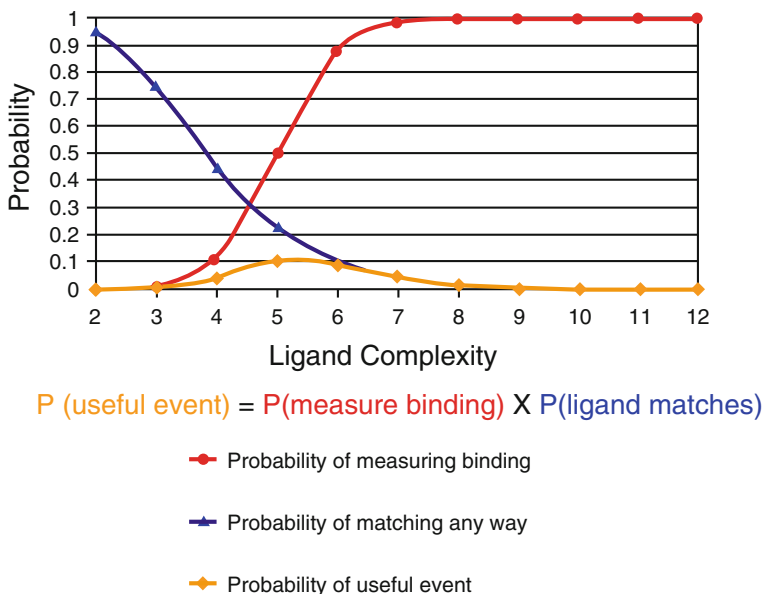
P (useful event) = P(measure binding) X P(ligand matches)

→ Probability of measuring binding

→ Probability of matching any way

→ Probability of useful event

Fig. 14.7 The basis of the molecular complexity model

a High information content
e.g. slippage difficult

b Low information content
e.g. Slippage easy

Receptor   + − − + + − +

+ + + + + +

Ligand   + + − − +

− − − − − −

| = attractive primary interaction

/α\ = attractive secondary interaction

/α\ = repulsive secondary interaction
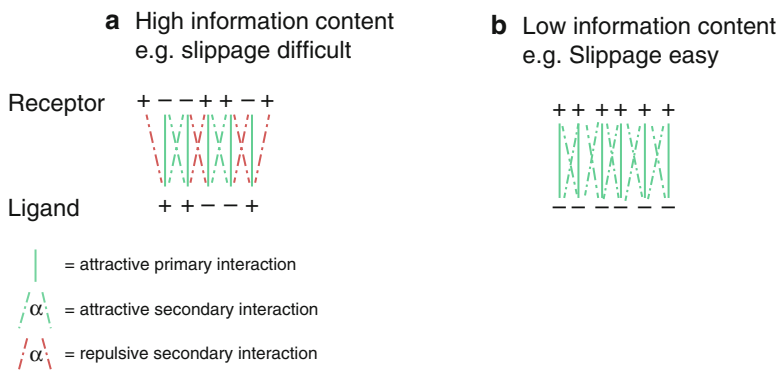
Fig. 14.8 Influence of information content on slippage ability in molecular complexity model

correlates well with the ligand's hydrated apolar surface area (i.e. lipophilicity) that is buried in the interaction [17]. This shows that we tend to use the easy gains of potency by adding lipophilicity.

Again using ITC data on a large number of compounds, Keseru et al. showed (Fig. 14.9) that as potency increases, enthalpic contributions tend to a maximum and then starts to fall while entropy starts to rise further in the most potent compounds [18, 19]. Broadly speaking enthalpy equates to polar interactions while a key contributor to entropy is lipophilic interactions. This suggests that if you do not
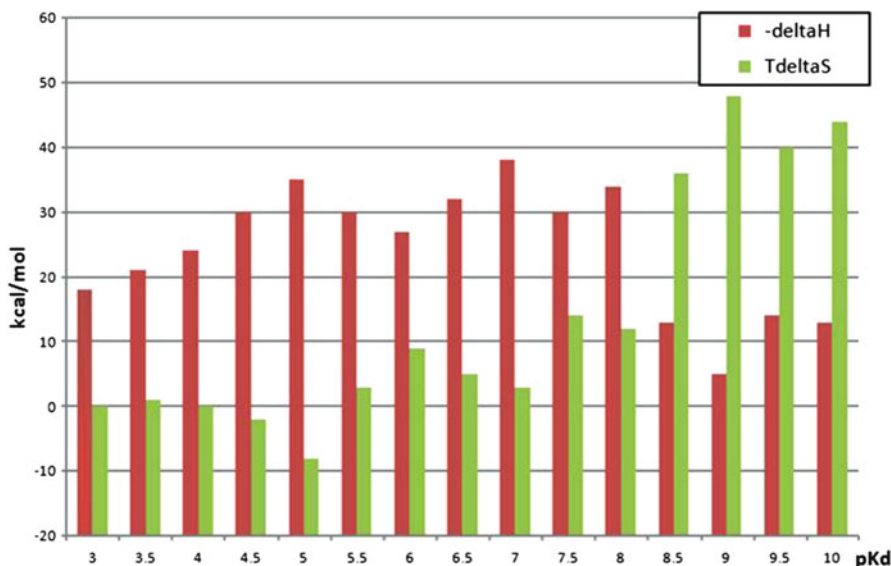
Fig. 14.9 Contribution of enthalpy (*light bars*) and entropy (*dark bars*) to overall potency of compounds (ordered by increasing potency) (Redrawn from original data used in Ref. [19])

get the maximum available enthalpic binding of a fragment or template to start with then you will end up having to use entropic interactions such as lipophilicity to get the desired potency. The use of indices such as LE and LLE are particularly useful for this purpose.

In other surveys of specific and cross-series data it is also apparent that increasing molecular weight and complexity tend to correlate with increased potency [20]. This is consistent with adding either specific or non-specific interactions but it is also likely to be a consequence of the predilection of medicinal chemists, who invariably trained as synthetic organic chemists, to build molecules rather than take them apart. Interestingly the equivalent of retro-synthetic analysis, which is so critical to planning good syntheses, has only recently become more embedded into the medicinal chemistry sphere in terms of fragmenting hits to find the most ligand efficient and smallest critical part [21]. An additional aspect of synthetic chemistry that has only recently been shown is how even laboratory practices such as reaction work up actually bias the synthesis of more lipophilic compounds, presumably as they are more easily extracted from the aqueous reaction quench [22].

Another reason why it is all too easy to increase LogP in the early stage of drug discovery projects is that if the initial assay is a very specific target based assay (e.g., enzyme or artificially constructed complex) then as soon as hits have sufficient potency to be interesting, the screening cascade will require them to be looked at in cellular assays. In order to gain cellular potency it is all too easy to add lipophilicity as a quick way to get membrane permeability. Such compounds may have short-term benefits of demonstrating cellular activity but it is equally too easy to then just forge ahead with this "fattened ligand" in the desire to make further speedy progress

Likelihood (50% probability) of permeability based onAZlogD lipophilicity for binned MW ranges	
MW	AZlogD
<300	>0.5
300-350	>1.1
350-400	>1.7
400-450	>3.1
450-500	>3.4
>500	>4.5

Fig. 14.10 Lipophilicity required for maximising probability of passive permeability at different molecular weights (Redrawn for data in Ref. [11])

towards the project's next milestones. You should pause at this stage to re-evaluate the properties of the now current lead compounds. Of course, in previous eras of drug discovery when *in vivo* testing (or classical tissue pharmacology) was used much earlier in the discovery process this issue did not exist, because compounds that either showed no activity through lack of bioavailability or toxicity through inappropriate mode of action or side effects were dismissed or never found in the first place!

A study by Waring and colleagues of 9,598 AZ compounds has shown (Fig. 14.10) that on average larger molecules need more lipophilicity to be permeable through cell membranes [11]. Thus the apparent twin drivers of potency (MW = more interactions and LogP = increased permeability) are seen to be not truly independent variables in relation to bioavailability but increasingly linked as compounds get larger. In Lipinski's rule of five, the cutoff of MW of 500 is consistent with the experimentally observed upper limit of permeability of compounds through membranes without invoking active transport. What Waring's work now clearly shows is that the space below 500 is not binary, in the sense of being permeable with MW less than 500, but that it has an increasing LogP demand as 500 is approached.

14.4 Further Insight into Controlling These Addictions in Drug Discovery

While a typical medicinal chemistry publication will set out to show that a very logical process was followed towards achieving the project's objectives, it is clear that by any objective or subjective measure, the path that a drug discovery

project actually follows through a multi-dimensional property space is non-linear. Figure 14.1 illustrated this by showing a pathway that could be taken from a start point X1 which has been found by some potency based screening process. From there on, there are numerous pathways (only one of which is illustrated) that could be taken to finally reach Xn, which is the candidate drug. Whether there is overlap of the zones in any given project as implied in the figure is only found out by trial and error, although experience with a related target may well inform on such target tractability.

Another important way to diminish the negative effects of potency is to be more realistic about what level of potency we should aspire to. Again surveys of literature data can help reset expectations. Analysis of a data set of known drugs by Overington et al. shows (Fig. 14.11) that the median affinity for current small-molecule drugs is ca. 20 nM ($pIC_{50} = 7.7$) (24) Unpublished in house data from GSK suggests that for oral drugs the affinity median is even less potent ($pIC_{50} = 6.7$). These average levels of potency for successful drugs are considerably lower than the often aspired to pK_i or pIC_{50} values of 9. Different target classes (e.g., ion channels vs. GPCRs) and whether agonists or antagonists (which will likely require differing levels of receptor occupancy for efficacy) will affect the aspirational potency at the outset of a project but as efficacy is, at the end of the day, what is needed, greater emphasis on the factors that can enable overall drug efficacy need to be more to the fore in the earliest stages rather than just potency at the target. Thus, while the desire for potency is understandable, the tendency to choose the most potent compounds in lead selection and then let it remain the primary driver through early stage lead optimization remains a strong and inappropriate attractor and must be resisted [24]. The fact that potency is often easy to measure (once the assay is established) can often mean that this is the data most likely first returned to the project team. The team (or individual) then tends to react to it by making synthesis decisions about what to make next without waiting for a fuller profile of data. So reducing the desire for potency in favor of better ADMET properties is
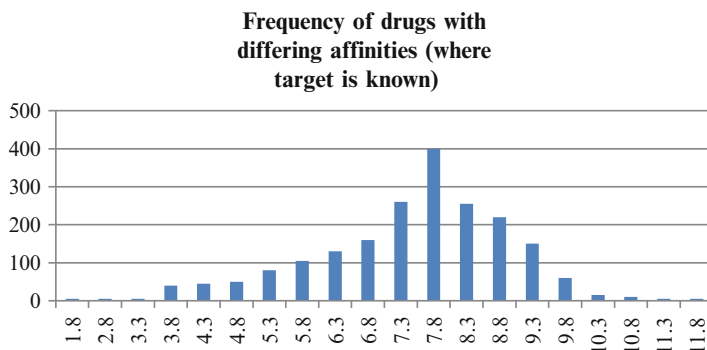

Fig. 14.11 Distribution of marketed drug affinities at target where target is known (Redrawn from data in Ref. [23])

one way of subjugating the potency attractor and its potentially fatal relationship to molecular obesity.

A useful tool to help maintain a balance of potency vs. ADMET properties is the Drug Efficiency concept, which tells you how much of your dose actually is available in the biophase of interest ($DRUG_{eff}$ = Biophase Concentration * 100/Dose) [25].

These authors more recently introduced the related Drug Efficiency Index DEI as a strategy towards low therapeutic dose (DEI = Log[$DRUG_{eff}$(%)] + pK_D) [26]. DEI is in effect a correction of the *in vitro* affinity (i.e. pK_D) by the *in vivo* pharmacokinetic potential. This simple descriptor directly connects efficacy and therapeutic dose with the potential to probe the balance between *in vitro* affinity and ADMET properties.

Finally a recent paper from Pfizer is worth highlighting [27]. It addresses the issue of what is the typical efficacious concentration (C_{eff}) of a drug that successfully passes through animal tox studies. For a series of 56 extensively studied compounds, the answer is <250 nM for total drug concentration and <40 nM for free drug. Interestingly 250 nM equates to 10 mg total dose in a human being, if we assume that we are just water! Clearly this is not the case, as we know drugs partition at an organ, tissue, cellular, organelle, lipid and target level. However it has long been known that idiosyncratic toxicology is rarely seen if the total daily dose of a drug is kept below 10 mg [28]. This only goes to emphasize the importance of getting the optimum balance between potency and bioavailability at the site of action. Traditionally bioavailability has been measured as the free concentration in plasma however this is not necessarily the free concentration inside a cell or some sub-cellular organelle. To enable this more appropriate measurement, MS based methods for understanding the local cellular concentration of drugs (as introduced by Per Artursson et al.) are evolving for use early in a drug discovery program and so there is increasingly no excuse for not being able to understand the issues on both sides of the balance before it is too late in a project [29].

Three excellent reviews that include further in depth discussion of physicochemical related attrition issues are recommended for further reading [30–33].

14.5 Summary

Molecular obesity and its inappropriate use to drive potency and get ligands through membranes have been killing too many drug discovery projects. Starting with the smallest possible lead (i.e. fragments) and striving to maintain their fitness through the use of various indices is now accepted as a key approach in a more holistic approach to contemporary drug discovery. The absolute need for potency should not be as dominant an attractor as we often allow it to become at the expense of other characteristics of a good drug.

There will always be some compounds that make it all the way to drugs and which lie outside of the known preferred space for likely success. However unless

truly forced to by circumstances that are fully understood, it is not appropriate to set out with the mentality that my project will be the "exception that proves the rule" as a risk mitigation strategy!

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