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Abbott Physicochemical Tiering (APT)—A unified approach to HTS triage

Philip B. Cox *, Robert J. Gregg, Anil Vasudevan

Hit to Lead Group, Advanced Technology, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064, USA

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ABSTRACT

The selection of the highest quality chemical matter from high throughput screening (HTS) is the ultimate aim of any triage process. Typically there are many hundreds or thousands of hits capable of modulating a given biological target in HTS with a wide range of physicochemical properties that should be taken into consideration during triage. Given the multitude of physicochemical properties that define drug-like space, a system needs to be in place that allows for a rapid selection of chemical matter based on a prioritized range of these properties. With this goal in mind, we have developed a tool, coined Abbott Physicochemical Tiering (APT) that enables hit prioritization based on ranges of these important physicochemical properties. This tool is now used routinely at Abbott to help prioritize hits out of HTS during the triage process. Herein we describe how this tool was developed and validated using Abbott internal high throughput ADME data (HT-ADME).

1. Introduction

It is well recognized that the physicochemical profile of a drug candidate can have a significant influence on its probability of success, both in terms of favorable DMPK characteristics and reduced attrition due to off-target toxicity.[1–3] Given the high similarity between drug candidates and leads, it is imperative that the quality of starting points for lead generation and lead optimization be carefully considered to yield candidates in drug-like space with the desired pharmacological profile. A typical high throughput screen (HTS) of focused/diversity collections or legacy compounds can result in the identification of large numbers of ligands capable of modulating the target with a range of physicochemical properties. It is important therefore to have a system that enables a rapid and effective triage of these hits to identify ligands with favorable physicochemical profiles. We have devised a practical tool, coined Abbott Physicochemical Tiering (APT) that we use to systematically triage every HTS performed at Abbott. This tiering process enables the medicinal chemist to prioritize hits based on multiparametric physicochemical properties, which can then be used in conjunction with ligand and lipid efficiencies to identify the most promising starting points for lead generation activities.

2. Results and discussion

There have been many publications over the past several years which correlate physicochemical properties to drug-like characteristics or properties of molecules.[4–13] The aims of this current study were twofold:

1. Correlate multiple physicochemical property ranges to determine their influence on overall in house in vitro ADME properties, and then to identify optimal physicochemical property space with respect to superior overall ADME performance.
2. Based on these correlations develop a convenient and effective tool to aid in drug design and the triage of HTS hits.

3. Optimal physicochemical property space determination

In order to define optimal property space, a broad spectrum of physicochemical parameters was considered. Given the multitude of publications around the negative and positive effects of modulating physicochemical properties on drug-like properties, we focused our attention on what we considered to be the most important parameters—lipophilicity (*Clog*P), molecular weight, number of hydrogen bond donors and acceptors, total polar surface area, number of aromatics rings (NAR), and fraction of sp3 carbons (Fsp3). These parameters describe the overall greasiness (*Clog*P), size (MWt), polarity (tPSA, HBD, HBA), aromaticity (NAR), and three-dimensionality, or level of saturation (Fsp3) of a molecule, and as such should adequately describe the overall physical behavior of a molecule. Note that Leeson's 'flatness' descriptor (Ar-sp3) was published subsequent to our initial analysis.[14] This could have been integrated into this analysis however given that Ar-sp3 is inversely proportional to Fsp3 we reasoned that the overall contribution to flatness or saturation is adequately described by either descriptor.

* Corresponding author.
E-mail address: phil.cox@abbott.com (P.B. Cox).

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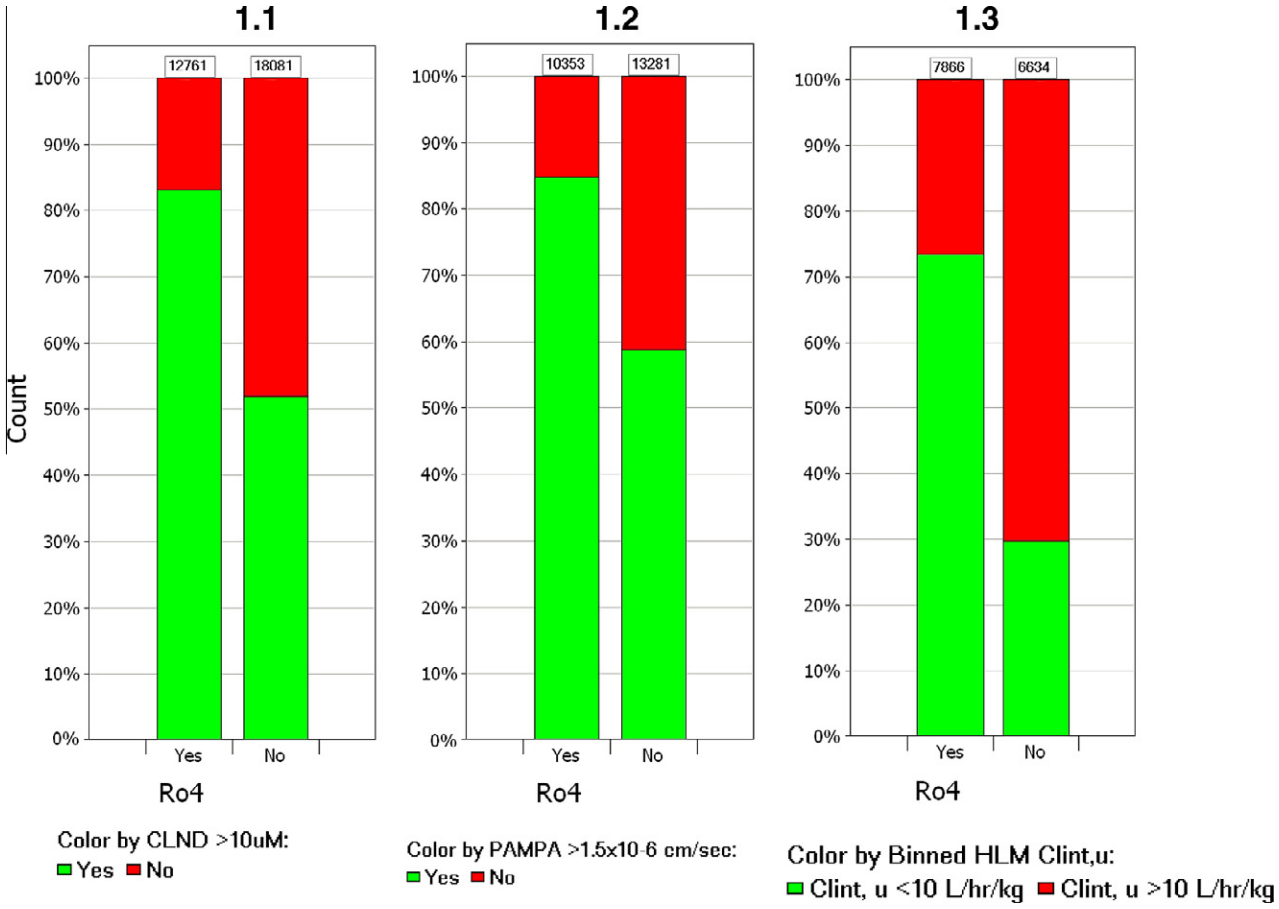

Figure 1. Ro4 compliance and effect on solubility (30.8 K compounds), PAMPA effective permeability (23.6 K compounds) and HLM Cl $_{int,u}$ L/h/kg (14.5 K compounds).

Table 1
Percentage, and overall odds, of compounds achieving acceptable levels of solubility (>10 μM), permeability (>1.5 × 10^{-6} cm/s) and HLM $Cl_{int,u}$ (<10 L/h/kg) as a function of Ro4 compliance

ADME Threshold	Solubility CLND >10	PAMPA >1.5	HLM Cl $_{int,\ u}$ <10
Ro4 (pass) %	83	85	73
Ro4 (pass) odds	4.9	5.7	2.7
Ro4 (fail) %	52	59	30
Ro4 (fail) odds	1.1	1.4	0.3
Fold odds advantage (pass vs fail)	4.5	4.1	9

In this analysis we examined the following broad spectrum of physicochemical properties and descriptors. Calculated physicochemical properties were employed in this analysis that could be quickly and conveniently calculated by the medicinal chemist.

(a) Rule of 4 and 5 (Ro4 and Ro5) (note that we adopted a conservative, no violations allowed, variation of Lipinski's rules[15] which includes Veber's addition of TPSA)[16]—since these rules capture a number of important physicochemical properties simultaneously (*C*log*P*, molecular weight, number of hydrogen bond donors (HBD), number of hydrogen bond acceptors (HBA) and total polar surface area (TPSA), we considered these to be critical descriptors to be included in our analysis. In our interpretation of Ro4 and Ro5 compliance, no violations were allowed and the following filters were adopted whereby Ro4/5 compliance was achieved only if the chemical matter satisfied the following criteria:
Ro4 compliance—*C*log*P* ⩽4, molecular weight ⩽400, HBD ⩽5, HBA ⩽10, tPSA <140.
Ro5 compliance—*C*log*P* ⩽5, molecular weight ⩽500, HBD ⩽5, HBA ⩽10, tPSA <140.

(b) Number of Aromatic Rings (NAR)—from the work of Ritchie et al and from our own analysis (described below), the number of aromatic rings has a significant effect on the physical behavior of a molecule.[17] For example solubility decreases significantly with increasing NAR and Log*D* (calculated and estimated). From this Hill and Young have shown that the sum of Log*D* and NAR can be used as a solubility forecast index (SFI) to predict the likelihood of a compound having acceptable solubility. In general if a compound has a SFI of less than five it will have acceptable solubility.[18]

(c) Fsp3—the number of sp3 carbons as a fraction of overall carbon count as described by Lovering et al gives an indication of the level of saturation and also a sense of the overall 'flatness' of a molecule.[19] The lower the value of Fsp3, the flatter a molecule is likely to be based on higher levels of unsaturation. Note that after we had developed this tiering system

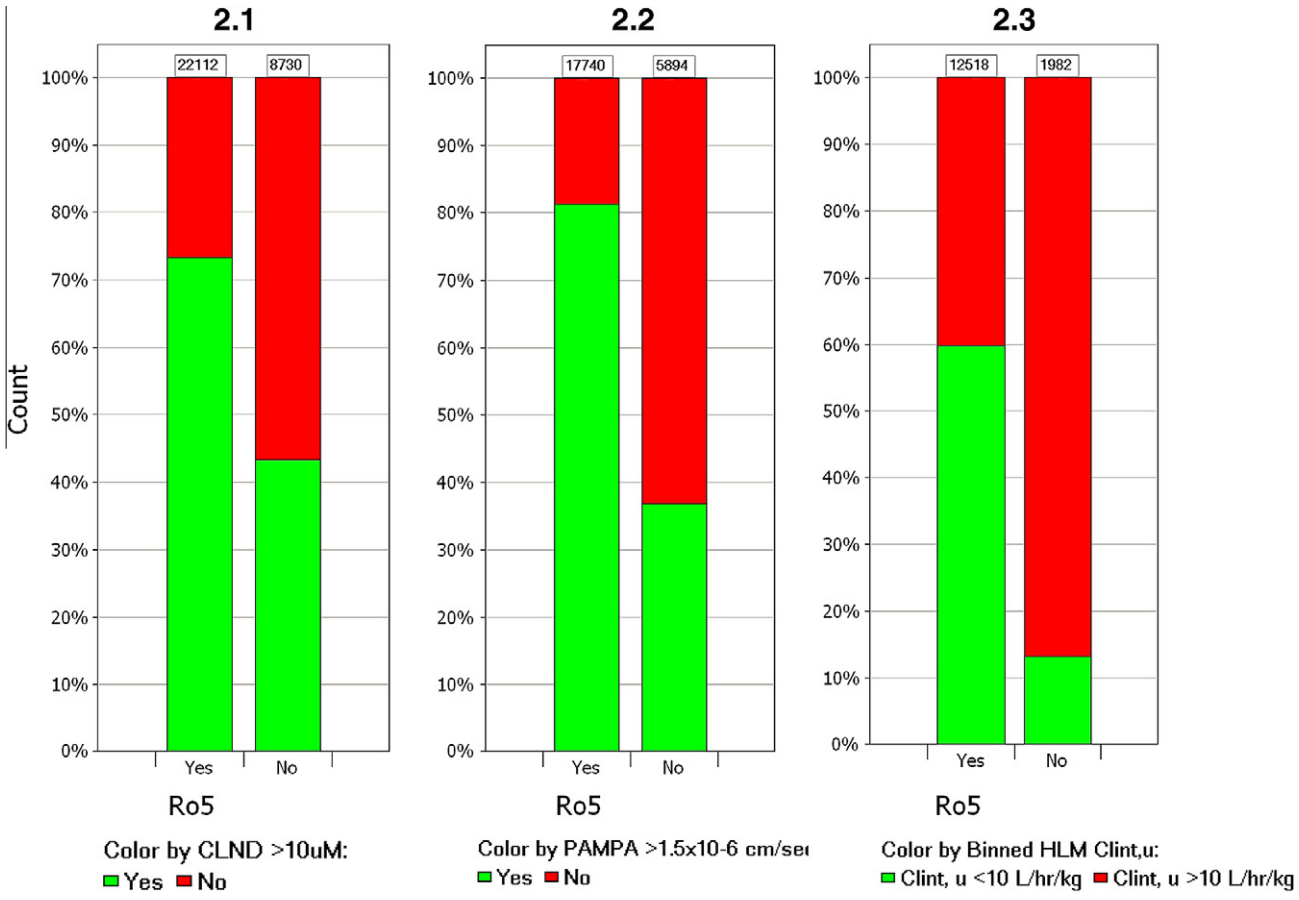

Figure 2. Ro5 compliance and effect on solubility (30.8 K compounds), PAMPA effective permeability (23.6 K compounds) and HLM $Cl_{int,u}$ L/h/kg (14.5 K compounds).

Table 2
Percentage, and overall odds, of compounds achieving acceptable levels of solubility (>10 μM), permeability (PAMPA >1.5 × 10^{-6} cm/s) and HLM $Cl_{int,u}$ (<10 L/h/kg) as a function of Ro5 compliance

ADME threshold	Solubility >10	PAMPA >1.5	HLM $Cl_{int,u}$ <10
Ro5 (pass)%	73	81	60
Ro5 (pass) odds	2.7	4.26	1.50
Ro5 (fail)%	43	37	13
Ro5 (fail) odds	0.75	0.59	0.15
Fold odds advantage (pass vs fail)	3.6	7.2	10

another descriptor for flatness, Ar-sp3, was described which equates to the number of aromatic atoms minus the number of sp3 hybridized carbon atoms.[14]

Abbott high throughput ADME (HT-ADME) data was used to understand the effect of changing the above-mentioned physicochemical properties on drug-like in vitro ADME properties. 30,500 kinetic (CLND) solubility data points, 23,600 PAMPA effective permeability data points and 14,500 human liver microsomal unbound intrinsic clearance (HLM $Cl_{int,u}$) data points were analyzed. Data manipulation and calculations were performed using Pipeline Pilot and the data visualized using Spotfire. Reasonable thresholds for CLND solubility, PAMPA permeability and HLM $Cl_{int,u}$ were determined and used to assess the performance of physicochemical properties relative to the percentage of compounds that achieve these thresholds. For CLND solubility data, a threshold was determined based on the relative distribution of compounds in the Abbott data set. Given that the mean solubility in this collection = 27 μM and that approximately 36% of the compounds have CLND solubility less than 10 μM, this concentration seemed like a acceptable threshold for defining reasonable solubility as equating to >10 μM. A similar assessment was performed for both PAMPA permeability to determine a 1.5 × 10^{-6} cm/s threshold and for HLM $Cl_{int,u}$ to determine a 10 L/h/Kg threshold.

Throughout the course of this analysis we define both the percentage of compounds that achieve the acceptable ADME threshold, and also the odds of achieving this particular level, to provide a more meaningful assessment of the advantages/disadvantages of a particular property. Odds are calculated using the following expression:

Odds of achieving ADME threshold = number or percentage of compounds at desired level/number or percentage of compounds not at desired level.

Thus if 50% of compounds are at the desired ADME threshold then the odds of achieving this level are even (or odds = 1). Odds in this context gives us an idea of where in physicochemical space the likelihood of achieving a certain ADME threshold is more likely than not likely. Figure 1.1 shows the effect of Ro4 compliance on overall CLND solubility, with 83% of Ro4 compounds having a solubility >10 μM (odds of achieving acceptable CLND solubility >10 μM = 4.9) versus 52% (odds = 1.08) for non Ro4 compliant

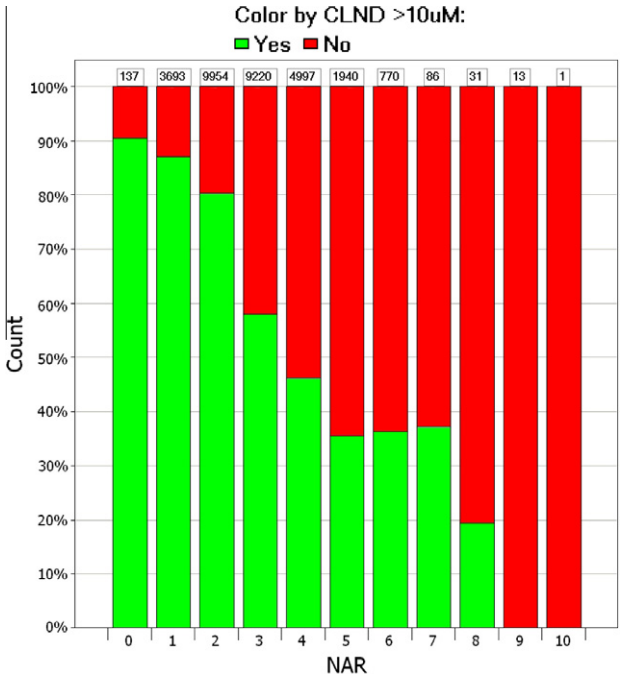

Figure 3. Effect of NAR on solubility-% of compounds with CLND solubility >10 μM shown in green (30.8 K compounds).

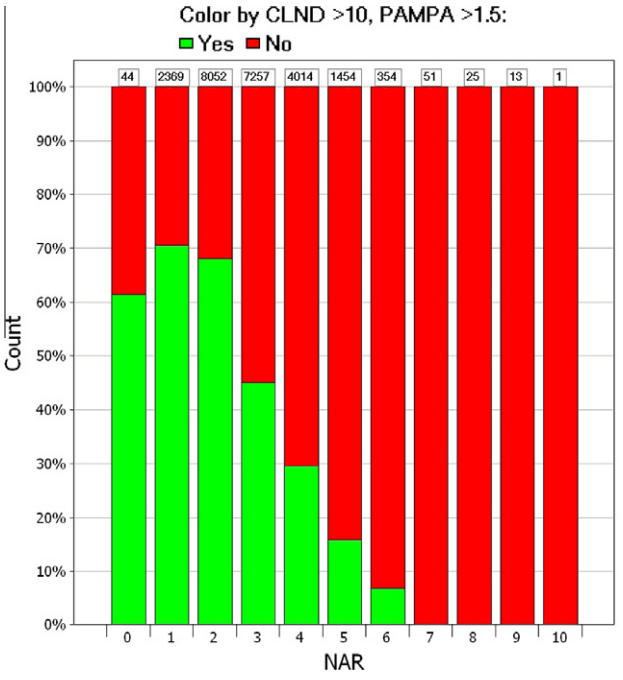

Figure 5. Effect of NAR on combined solubility and permeability-% of compounds with a combined solubility of 10uM and permeability of >1.5 × 10^{-6} cm/s shown in green (23.6 K compounds).

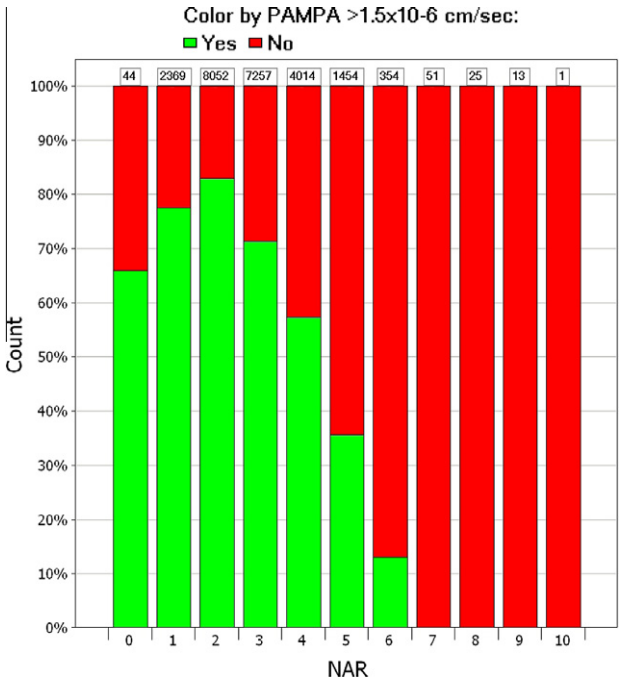

Figure 4. Effect of NAR on PAMPA permeability-% of compounds with PAMPA permeability >1.5 × 10^{-6} cm/s shown in green (23.6 K compounds)

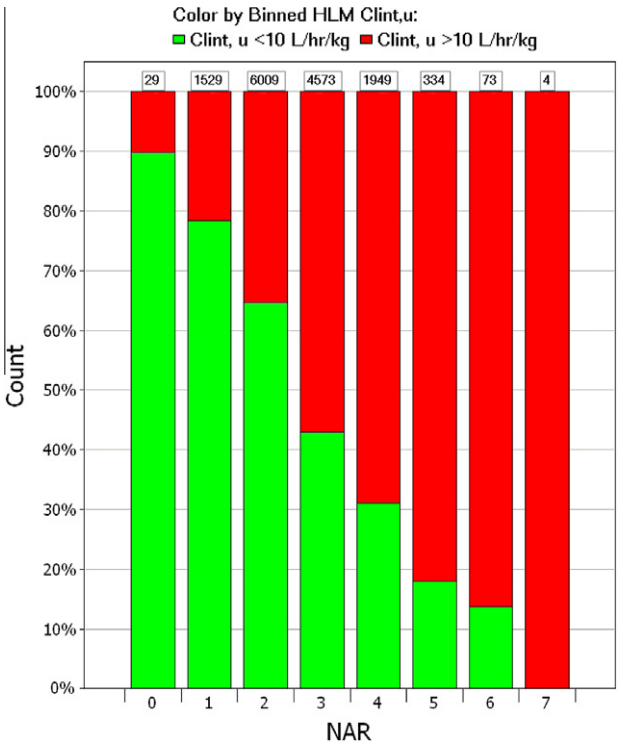

Figure 6. Effect of NAR on HLM $Cl_{int,u}$ L/h/kg (14.5 K compounds).

compounds. For effective permeability (PAMPA) shown in Figure 1.2, 85% of Ro4 compliant compounds have PAMPA permeability >1.5 × 10^{-6} cm/s (therefore odds of achieving acceptable permeability = 5.7) versus 59% for non Ro4 compounds (odds = 1.4). As seen in Figure 1.3, we see a very similar trend for HLM $Cl_{int,u}$ with 73% of Ro4 compliant compounds having a reasonable value (<10 L/h/Kg) (odds = 2.7) versus just 13% for Ro4 failures (odds = 0.15).

Table 1 shows the overall breakdown of the percentage and the odds of compounds falling within acceptable levels of solubility (CLND >10 μM), effective permeability (PAMPA >1.5 × 10^{-6} cm/s) and HLM $Cl_{int,u}$ (<10 L/h/Kg) for both Ro4 and non Ro4 compliant compounds. Clearly, there is a significant advantage for compounds that pass Ro4 versus fail, with the largest odds advantage for Ro4 pass versus fail seen for unbound intrinsic clearance.

Table 3
Percentage, and overall odds, of compounds achieving acceptable levels of solubility (CLND >10 μM), permeability (PAMPA >1.5 × 10^{-6} cm/s) and combined solubility, permeability (CLND >10 μM and PAMPA >1.5 × 10^{-6} cm/s) and HLM $Cl_{int,u}$ (<10 L/h/kg) as a function of NAR

NAR	0	1	2	3	4	5	6	7	8	>8
% CLND >10	91	87	80	58	46	36	36	37	19	0
Odds CLND >10	10.1	6.7	4	1.4	0.9	0.6	0.6	0.6	0.2	0
% PAMPA >1.5	66	78	83	71	57	36	13	0	0	0
Odds PAMPA >1.5	1.9	3.2	4.9	2.5	1.3	0.6	0.2	0	0	0
% CLND >10 and PAMPA >1.5	61	71	68	45	30	16	7	0	0	0
Odds CLND >10 and PAMPA >1.5	1.6	2.4	2.1	0.8	0.4	0.2	0.1	0	0	0
% HLM $Cl_{int,u}$ <10	90	78	65	43	31	18	14	0	0	0
Odds HLM $Cl_{int,u}$ <10	9	6.7	1.9	0.8	0.4	0.2	0.2	0	0	0

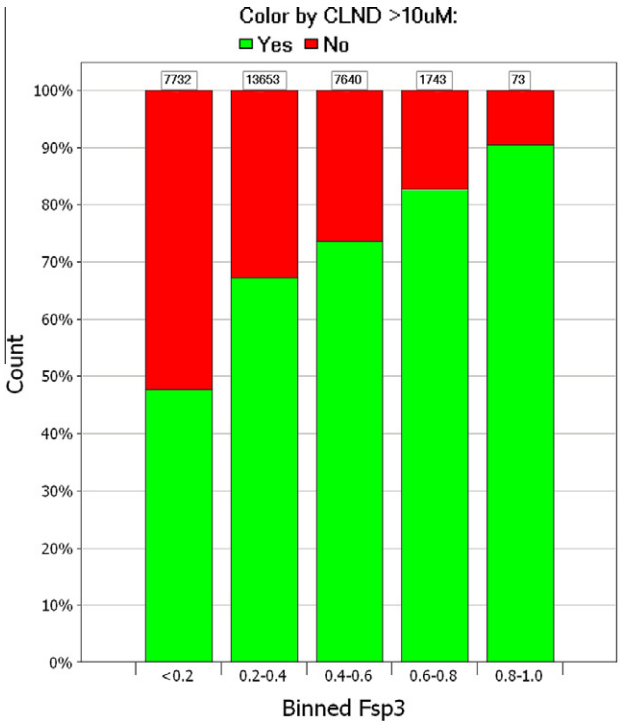

Figure 7. Effect of Fsp3 on solubility-% of compounds with CLND >10 μM shown in green (30.6 K compounds)

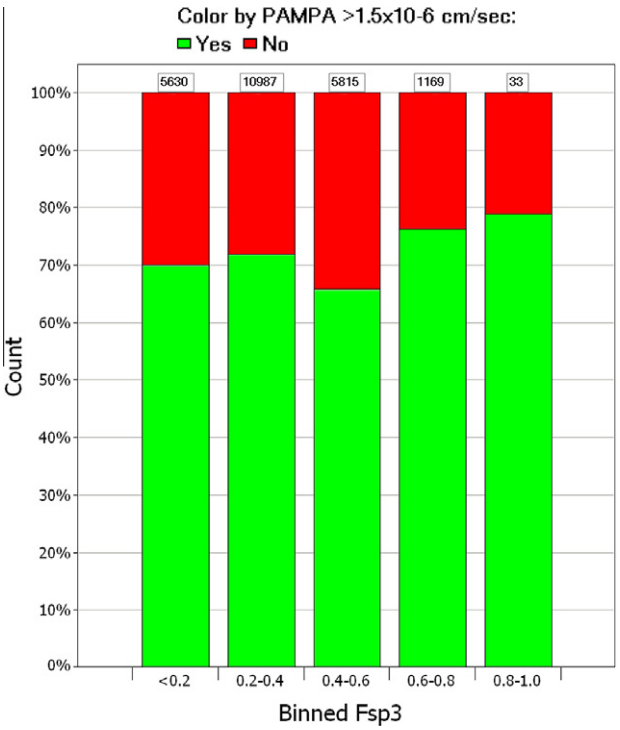

Figure 8. Effect of Fsp3 on PAMPA permeability-% of compounds with PAMPA permeability >1.5x10^{-6} cm/s shown in green (23.6.3 K compounds)

A similar analysis of Ro5 compounds is shown in Figure 2. Again the trend is very much the same observed for Ro4 with a commensurate decrease in overall percentage of compounds achieving acceptable levels of solubility, permeability and HLM $Cl_{int,u}$ as function of Ro5 compliance. Note that the overall fold odds advantage is similar to that of Ro4 with the exception of PAMPA permeability where there is a significant increase in fold odds advantage for compounds that pass Ro5 versus Ro4—see Table 2.

We also examined the effect of increasing the number of aromatic rings (NAR) on solubility, permeability, and HLM $Cl_{int,u}$, (see Figs. 3–6 and Table 3). Consistent with the observations of Ritchie et al., we see a distinct drop off in solubility as a function of NAR with the crossover of even odds of achieving solubility level (CLND >10 μM) at NAR = 3 (i.e., for compounds with NAR >3 the odds of achieving desired solubility is less than achieving poor solubility (CLND <10 μM)). Similarly there is an even odds crossover in achieving the desired level of permeability at NAR = 4. It should be noted that the crossover in even odds of achieving acceptable combined solubility and permeability (CLND >10 μM and PAMPA >1.5 × 10^{-6} cm/s) occurs at NAR = 2—see Figure 5. This trend is also manifested for HLM $Cl_{int,u}$ where the cross over in even odds of achieving acceptable levels (<10 L/h/kg) occurs at NAR = 2—see Figure 6. These observations lend further credence to Ritchie's conclusions indicating that NAR should be restricted to less than three in order to achieve the best possible outcome in terms of overall drug-like properties.

Lastly we looked at the effect of Fsp3 on solubility, permeability, and HLM $Cl_{int,u}$. Not surprisingly we saw a reciprocal relationship to the effect seen on increasing NAR. Figure 7 shows the effect of increasing Fsp3 on solubility; clearly increasing Fsp3 leads to a commensurate increase in solubility. This makes sense given that higher Fsp3 relates to a greater level of saturation and therefore a lower NAR. For example, for compounds with an Fsp3 >0.8, the maximum NAR in this cohort of compounds is 1, thus explaining the superior solubility of these compounds. Note that the average *C*log*P* is actually higher than for compounds with Fsp3 (0.6–0.8) thus showing that higher saturation is helping drive higher solubility despite higher lipophilicity! The effect of Fsp3 on permeability is less pronounced but it does trend towards higher Fsp3 having improved permeability—see Figure 8. A more pronounced improvement in HLM $Cl_{int,u}$ is seen with increasing Fsp3—see Figure 9. In general, increasing Fsp3 has a favorable effect on the drug-like properties of a molecule and it is, therefore, not surprising that oral drugs on average have an Fsp3 >0.5.[19]

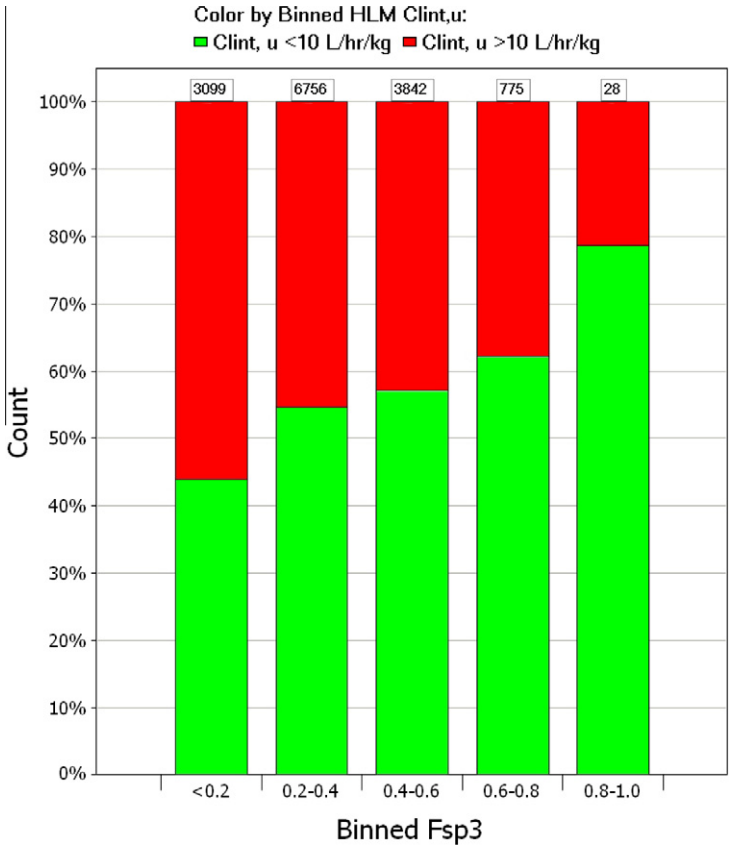

Figure 9. Effect of Fsp3 on HLM Cl $_{int,u}$ -% of compounds with HLM Cl $_{int,u}$ <10 L/h/kg shown in green (14.5 K compounds)

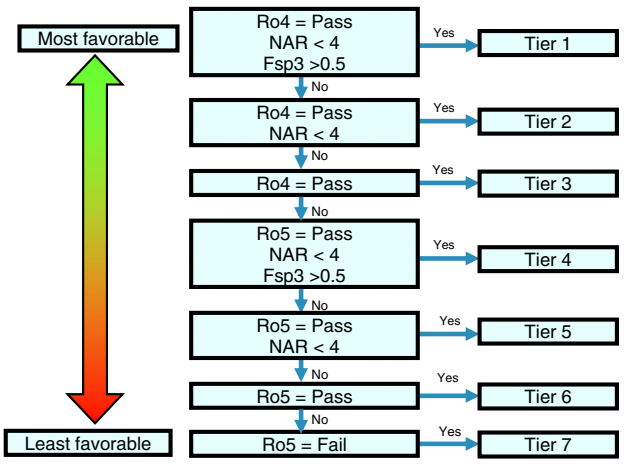

Figure 10. Tiering decision tree—spectrum of physicochemical properties.

From the analysis above we concluded that optimal physicochemical space may be defined by the following criteria; Ro4 compliance, NAR $\leq$3 and Fsp3 >0.5. Compounds within this physicochemical space will have very good drug-like properties as defined by overall ADME performance.

4. Developing the Abbott Physicochemical Tiering tool

Having determined optimal ADME space in the context of overall physicochemical properties, we then proceeded to develop a set of data-driven bins or tiers as a means to prioritize HTS hits. We designated optimal physicochemical ADME space as Tier 1 and then used this as the starting point to develop a range of seven tiers (or bins) across a spectrum of physicochemical properties from the

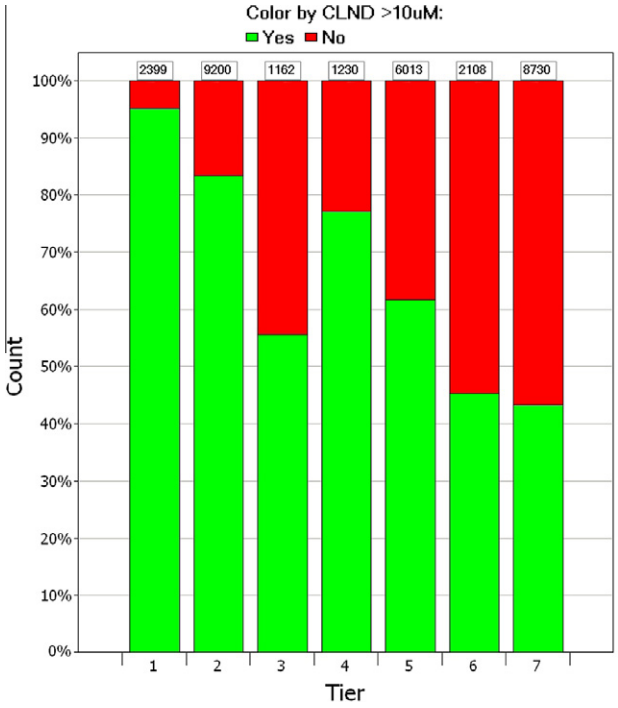

Figure 11. Tiers and CLND solubility-% of compounds with CLND solubility >10 μM shown in green (30.8 K compounds).

Table 4
Overall percentage of compounds and odds of achieving acceptable levels of solubility (CLND >10 μM), permeability (>1.5 × 10^{-6} cm/s) and combined solubility and permeability (CLND >10 μM and PAMPA >1.5 × 10^{-6} cm/s) and $Cl_{int,u}$ (<10 L/h/kg) as a function of tier

Tier	1	2	3	4	5	6	7
% CLND >10	95	83	56	77	62	45	43
Odds CLND >1	19	4.9	1.3	3.3	1.6	0.8	0.75
% PAMPA >1.5	80	86	86	82	78	68	37
Odds PAMPA >1.5	4	6.1	6.1	4.6	3.5	2.1	0.6
% CLND >10 and PAMPA >1.5	76	71	45	63	50	32	20
Odds CLND >10 and PAMPA >1.5	3.2	2.4	0.8	1.7	1	0.5	0.3
% HLM $Cl_{int,u}$ <10	84	72	58	44	38	30	14
HLM $Cl_{int,u}$ <10	5.3	2.6	1.4	0.8	0.6	0.4	0.2

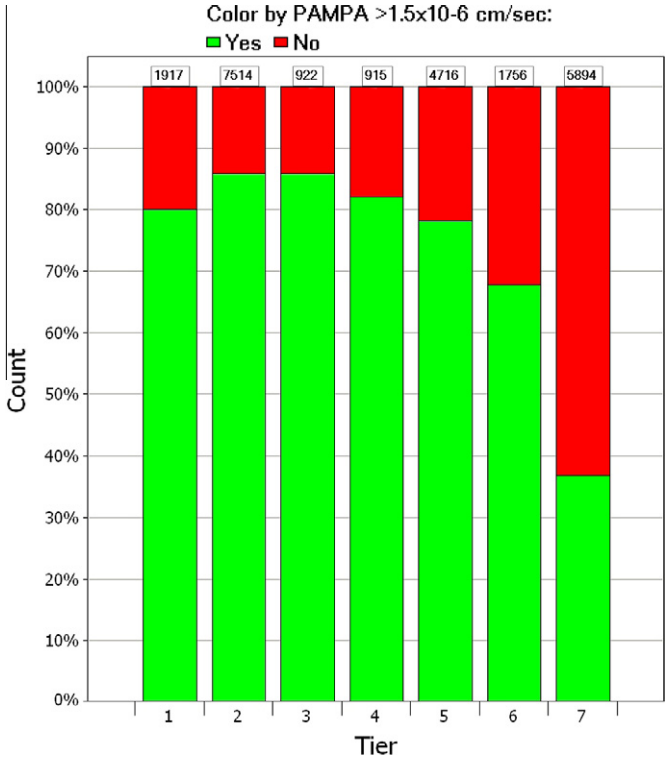

Figure 12. Tiers and PAMPA effective permeability-% of compounds with PAMPA permeability >1.5 × 10^{-6} cm/s shown in green (23.6 K compounds)

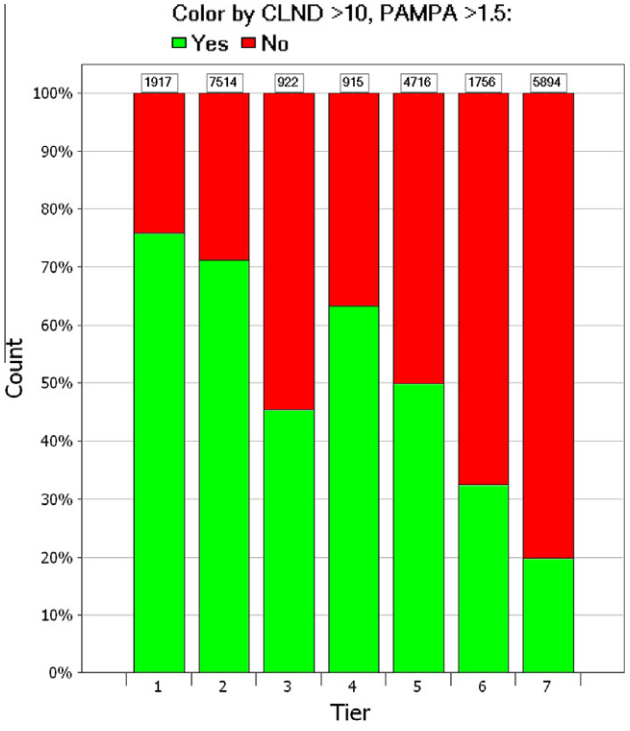

Figure 13. Tiers and combined solubility and permeability-% of compounds with a combined solubility of 10μM and permeability of >1.5 × 10^{-6} cm/s shown in green (23.6 K compounds).

more favorable Tier 1, to least favorable Tier 7 physicochemical properties. Starting from the Tier 1 classification, we sequentially relaxed the requirements for Fsp3 and NAR compliance—see Figure 10. Thus Tiers 1 through 3 represent Ro4 compliant compounds with Tier 2 having Fsp3 <0.5 and NAR ≤3 and Tier 3 having Fsp3 <0.5 plus NAR >3. This sequence is then repeated for Ro5 compliant compounds giving Tiers 4 through 6. Tier 7 contains compounds that fail Ro5 and should, theoretically, have most inferior drug-like properties.

We then proceeded to validate this tiering system in terms of CLND solubility, PAMPA effective permeability and unbound human liver microsomal clearance. Figure 11 shows the overall effect of tier occupancy on solubility. This analysis clearly shows the negative effect high NAR has on solubility, as Tier 3 compounds have lower odds of achieving the desired solubility level (CLND >10μM) compared to both Tiers 4 and 5 compounds—see Table 4. Therefore, despite the fact that Tier 3 compounds are Ro4 compliant, the high NAR, irrespective of low lipophilcity, contributes negatively to solubility. For PAMPA permeability, Tier 3 compounds actually demonstrate the highest odds of achieving the desired level of permeability—see Figure 12. This result indicates that permeability is driven more by lipophilicity than NAR. Indeed for Tier 3 compounds in general, the distribution of compound *C*log*P* is optimal for highest odds of achieving acceptable permeability (*C*log*P* 1–4) with 97% of compounds in Tier 3 within this *C*log*P* range (compared to 83% of compounds in Tier 1). Combining both solubility and permeability, Figure 13 shows that again Tier 3 is underperforming driven by high NAR with less than even odds (odds = 0.8) of achieving acceptable levels of both solubility and permeability.

For HLM $Cl_{int,u}$ there is a linear drop off in odds of achieving desired levels of clearance($Cl_{int,u}$ <10 L/h/kg) as a function of tier, with a crossover of even odds of achieving this level of clearance after Tier 3, suggesting that Ro4 compliance is key when considering the overall odds of effectively modulating unbound intrinsic clearance—see Figure 14. Undoubtedly this is due to the fact that Ro4 complaint compounds have both relatively low lipophilicity and molecular weight, which are two important determinants of low microsomal clearance.

Ideally, a compound should have acceptable levels of solubility, permeability, and $Cl_{int,u}$ as it can be argued that these three parameters determine likelihood of good overall PK performance

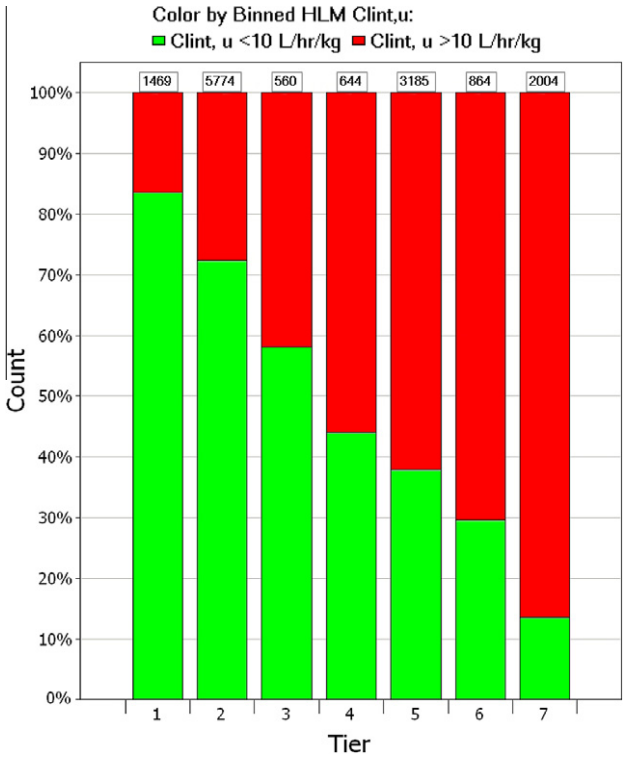

Figure 14. Tiers and HLM Cl $_{int,u}$ L/h/kg (14.5 K compounds)-% of compounds with HLM Cl $_{int,u}$ <10 L/h/kg shown in green (14.5 K compounds)

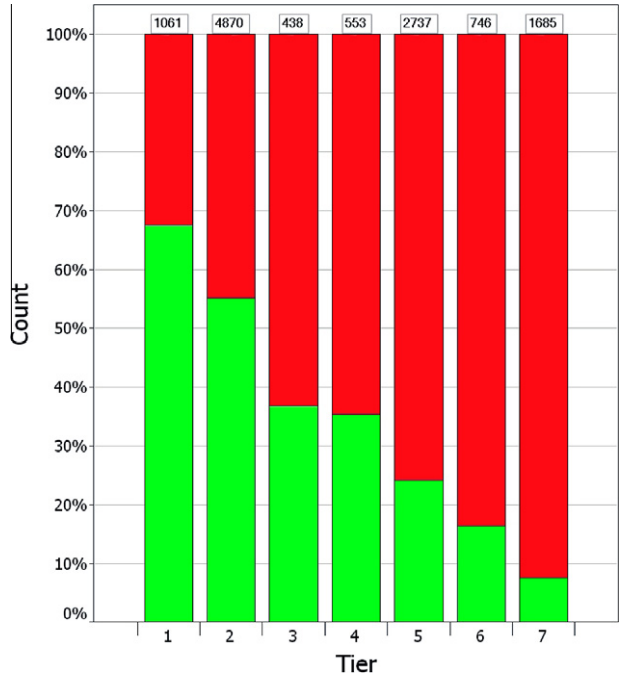

Figure 15. Tiers and combined solubility, permeability and unbound intrinsic clearance-% of compounds with a combined CLND solubility of 10 μM, permeability of >1.5 × 10^{-6} cm/s and with HLM Cl $_{int,u}$ <10 L/h/kg shown in green 12 K compounds).

(assuming that first pass metabolism is the predominant route of metabolism). In this analysis we identified compounds with acceptable levels of all three of these parameters (CLND >10 μM, PAMPA >1.5 × 10^{-6} cm/s and $Cl_{int,u}$ (<10 L/h/kg)) and examined the overall percentage of compounds in each of the tiers that fulfilled these criteria. In addition the odds of achieving this acceptable level of all three of the above mention parameters was calculated—see Table 5.

Table 5
Percentage of compounds and overall odds of achieving acceptable levels of solubility (>10 μM), permeability (>1.5 × 10^{-6} cm/s) and $Cl_{int,u}$ (<10 L/h/kg) as a function of tier (n = 12 K compounds)

Tier	1	2	3	4	5	6	7
# of compounds per tier	1061	4870	438	553	2737	746	1685
% CLND >10, PAMPA >1.5, and HLM $Cl_{int,u}$ <10	68	55	37	35	24	16	8
Odds CLND >10, PAMPA >1.5, and HLM $Cl_{int,u}$ <10	2.1	1.2	0.6	0.5	0.3	0.2	0.1

Overall Tier 1 was superior to all other tiers in terms of the odds of achieving the desired level of combined permeability, solubility, and unbound intrinsic clearance with only Tier 1 and 2 showing greater than even odds of achieving this targeted threshold. Overall, transition from Tier 1 through Tier 7 represents a reasonable spectrum of physicochemical properties that traverses a range from favorable to unfavorable drug-like properties—see Fig. 15.

In addition to comparing physicochemical tiers to internal ADME data we also investigated how oral drugs in general tier. We looked at 623 oral drugs used in an analysis performed by Hopkins—this cohort of drugs was approved from 1982 to 2004.[20] As shown in Figure 16, 61% of this collection of drugs reside in Tiers 1 and 2 thus indicating a predominant Ro4 compliance for oral drugs. What is surprising is the lack of Tier 3 drugs. Indeed we have yet to identify an oral drug that resides in Tier 3. This result suggests one of two things. Either statistically the likelihood of designing Tier 3 compounds is very low, which is a reasonable assumption given that only 4% of the compounds we analyzed in the Abbott ADME database reside in Tier 3, or Tier 3 compounds have very low odds of developability, and that's why there are no drugs of this ilk on the market. Moreover, it was also surprising to see only three Tier 6 drugs in this collection which suggests that designing drugs with NAR >3 within Ro5 is also statistically challenging. It could be argued that this is a result of good compound design, however given that most of these drugs were discovered well before physicochemical profiling was a major factor in drug design its hard to make this connection. Ultimately, NAR is the common denominator for this collection of oral drugs with very few having NAR >3, leading to low Tier 3 and 6 occupancy. This is not true, however, for all drug gene classes, such as kinase inhibitors, which typically have higher numbers of aromatic rings.

Indeed we calculated the mean physicochemical properties of 623 oral drugs and compared with 14 marketed kinase drugs—see Table 6. In general, kinase drugs are rather more lipophilic (*C*log*P* increase of 2.5 log units) and have 2 aromatic rings more than other oral drugs with a mean NAR >3. The higher NAR translates into higher Tier 6 occupancy with 21% of kinase drugs in Tier 6 as compared to just 0.5% for other oral drugs. The large majority of kinase drugs reside in Tier 7 (43%) by virtue of high *C*log*P* (>5) and high molecular weight (>500). This bias towards kinase inhibitors occupying higher tiers can also be seen in the tier distribution of kinase targeted HTS campaigns. Indeed the tiering distribution for active molecules from HTS is, not surprisingly, related to the drug gene class. Thus another useful feature of the tiering system is that it can be used to build a picture of the physicochemical profile of drug target gene classes out of HTS. The active or hit tier profiles of multiple targets can be compared with similar distribution patterns seen based on gene class. A comparison of the tier distributions of hit sets from 7 GPCR and kinase HTS campaigns performed at Abbott is shown in Figure 17. The bar chart shows the

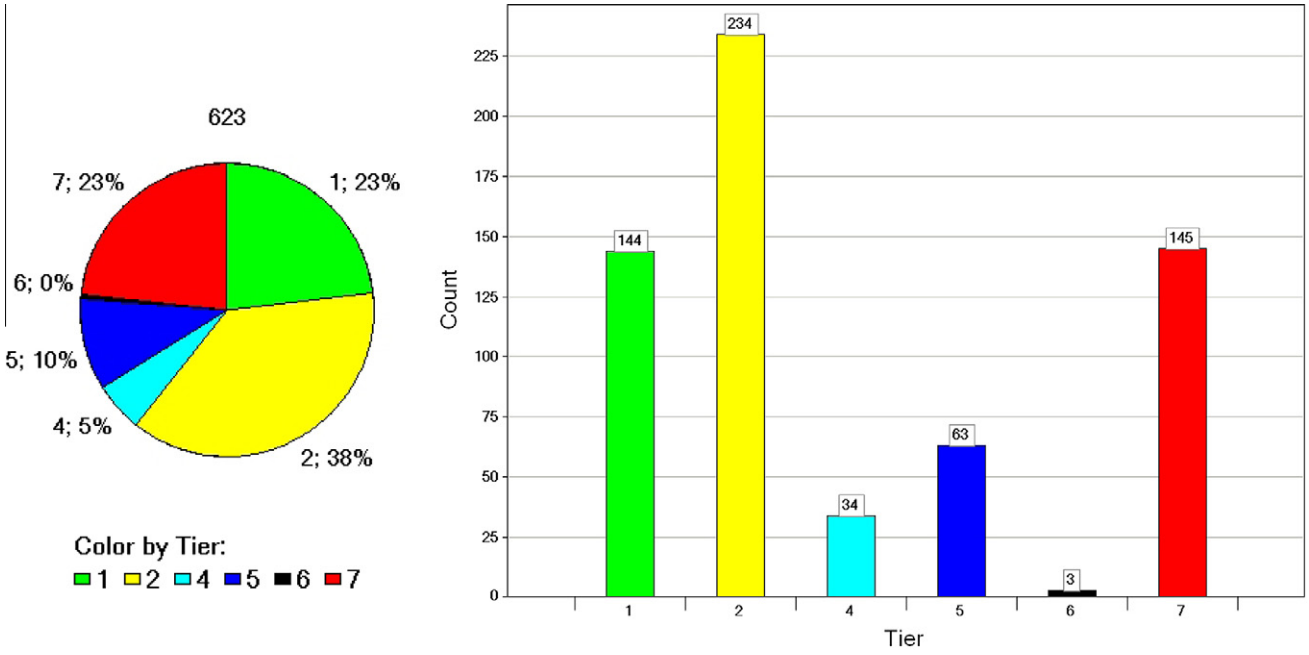

Figure 16. Tiering 623 oral drugs—61% of oral drugs reside in Tiers 1 and 2.

Table 6
Comparison of mean physicochemical properties of 623 oral drugs versus 14 marketed kinase drugs

Properties	NAR	*C*log*P*	MWt	Fsp3	TPSA	% in Tier 6
Oral drugs (n = 623)	1.4	2.2	344	0.44	79	0.5
Marketed kinase drugs (n = 14)	3.5	4.6	452	0.24	87	21

percentage of compounds within each tier for seven different kinase and GPCR targets with each color representing a different target. Clearly there is a similar fingerprint in terms of tier distribution for each gene class with GPCRs showing higher occupancy in the more favorable tiers (predominantly in Tiers 1, 2 and 5) compared to occupancy in the less favorable tiers for kinases (predominantly in Tiers 6 and 7). Interestingly, and consistent with observations made earlier, kinase inhibitors tend to be less saturated, hence the very low Tier 1 and 4 occupancy, and also tend to have higher NAR, hence higher occupancy in Tiers 3 and 6. Conversely, GPCR ligands (non-peptidic) tend to be more saturated, hence higher occupancy in Tiers 1 and 4, and have less NAR, hence low occupancy in Tiers 3 and 6. Gene class is therefore important and should be taken into consideration when assessing the overall physicochemical and tier profile of a hit set from HTS.

Another important observation from the tiering of oral drugs is that 23% of these compounds fall into Tier 7. This is due to violation of one of the criteria set out in the tiering filters. Thus, of the 145 drugs in Tier 7, 118 fail due to either high lipophilicity (*C*log*P* >5) or molecular weight (>500), with the remaining 27 drugs failing due to either high TPSA (>140) or number of HBD (>5). In general the nature of drugs that fall into Tier 7 are related to natural products based drugs such as Thyroxine and Reserpine and anti-infective drugs such as Erythromycin and Vancomycin.

In conclusion we have developed the Abbott Physicochemical Tiering (APT) tool based on a broad range of important physicochemical properties and subsequently validated this tool using internal HT-ADME data. Using already established criteria for determining overall drug-likeness we have developed a practical tool that the medicinal chemist can use to aid in compound design and to prioritize hits during HTS triage. This concept of 'tiering'

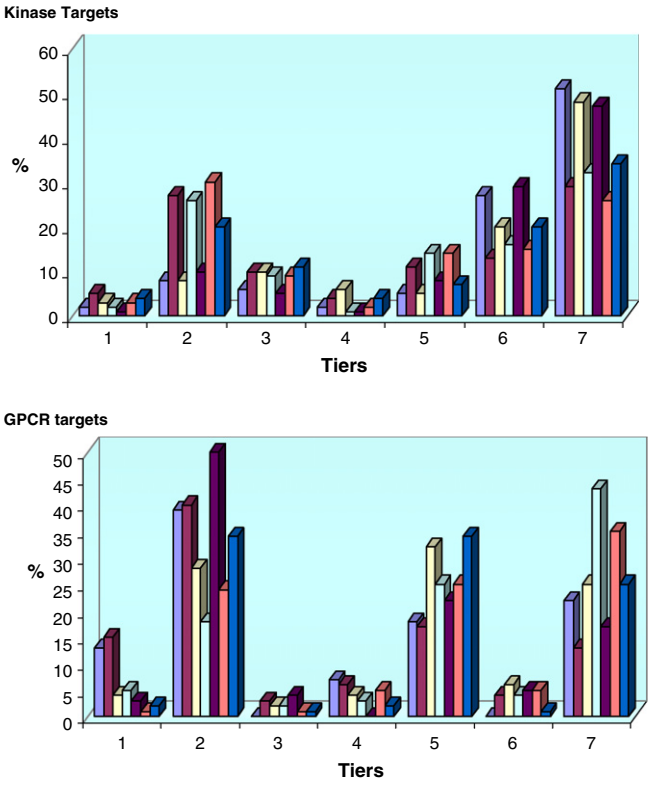

Figure 17. Comparison of triages across gene classes—Tier distributions of hits from kinase and GPCR targets from HTS. Each color represents a different target

chemical matter based on a spectrum of physicochemical properties we believe is new and represents another potential tool in the medicinal chemist's drawer to enable compound design and the prioritization of hits during HTS triage. This tool is now used not only to help facilitate all HTS triages at Abbott but also to further guide compound optimization in hit to lead and beyond.

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