Common "Ghost Trends" Due to Lipophilicity

influence of substituents on ΔLogD and expected "lipophilic potency"

Common Observation	Erroneous Conclusion	More Likely	Better Analysis
Activity of 100 inhibitors against enzyme A correlates with activity against enzyme B	Enzyme A and enzyme B must have a very similar receptor shape / pharmacophore	Activity of inhibitors vs. enzyme A and enzyme B both correlate with LogD	Re-analyze data normalizing activity for lipophilicity (e.g. $pIC50_A$/LogD vs. $pIC50_B$)
Compounds w/ lipophilic functional group R (e.g. t-Bu, Ph) show undesirable properties (e.g. CYP TDI)	Lipophilic functional group R is the cause of undesirable properties (e.g. bioactivated to a reactive species that causes CYP TDI)	Lipophilic functional group R increases compound LogD, increasing affinity/ K_M for off-target (e.g. CYP), and hence increases rate of inactivation	Compare "matched pairs" of compounds w/ R replacements of comparable lipophilicity, or normalize off-target activity for LogD
Compounds w/ polar functional group Y show more favorable properties (e.g. lack of CYP TDI)	Polar functional group Y is uniquely disfavorable to off-target binding and analogs including Y should be prioritized	Polar group Y lowers LogD, reducing affinity/K_M for off-target (e.g. CYP), and hence decreases rate of inactivation	Compare "matched pairs" of compounds w/ Y replacements of comparable lipophilicity, or normalize off-target activity for LogD
Replacement of lipophilic core A (e.g. phenyl, thiophenyl, pyridiyl) w/ less lipophilic core B (e.g. pyrimidyl, pyrazoyl) results in lower intrinsic clearance	Lipophilic core A is the likely site of metabolism for CYP3A4 because core B has a lower oxidation potential	Compounds containing core A have higher LogD and increased affinity/K_M for CYPs, resulting in faster metabolism	Compare again, normalize intrinsic clearance for LogD, or using sets of compounds with comparable overall LogD
Compounds with lipophilic moiety Z have high in vitro clearance, but total drug clearance in vivo is much lower	There is an in vitro/in vivo disconnect, and lipophilic moiety Z is important for in vivo exposure	Lipophilic moiety Z significantly increases plasma protein binding, resulting in lower total drug clearance in vivo	Compound in vivo unbound drug clearance to in vitro clearance and reassess whether there is a disconnect
Changes leading to significant reductions in undesired (e.g. hERG activity) almost always come with significant reductions in desired target activity	Desired target and hERG have very close pharmacophores, and scaffold should be deprioritized	hERG is promiscuous, and changes leading to reduced hERG activity also significantly reduce LogD, simultaneously lowering on-target activity	Use lipophilic efficiency metrics to evaluate changes, and focus on improving LLE against desired target rather than reducing hERG activity