



Target Affinity, PhysChem & ADMET properties: *Is there a need for a better balance?*

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Computational & Structural Chemistry

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Overview

- Typically compound profiling based on literature data (GSK, Pfizer, AZ, Lilly, Roche..) and limited to relatively small drug datasets ranging from 100s-1000s¹⁻⁸.
- Analyses here have been performed on;
 - >100,000 GSK molecules with expt. ADMET data
 - >1,000 GSK molecules with expt. affinity/selectivity data
 - >100 of oral drugs with affinity & dose

1. Sneader, W. *Drug Prototypes and their Exploitation* John Wiley and Sons Ltd. **1996** 2. Lipinski et al, *Adv. Drug Deliv. Rev.* **1997**, 23, 3-25
2. Teague et al, *Angew. Chem., Int. Ed. Engl.* **1999**, 38, 3743-3748. 3. Hann et al., *J. Chem. Info. Mod.* **2001**, 41, 856-864.
4. Oprea et al, *J. Chem. Inf. Comput. Sci.* **2001**, 41, 1308-1315. 5. Wenlock et al, *J. Med. Chem.* **2004**, 46, 1250-1256.
6. Hann et al, *Curr. Opin. Chem. Biol.* **2004**, 8, 225-263. 7. Lajiness, et al *Curr. Opin. in Drug Disc. & Dev.* **2004**, 7, 470-477.
8. Oprea et al, *J. Comput. Aid. Mol. Des.* **2007**, 21, 113-117.

GSK ADMET Datasets

- **Absorption**

- Solubility (Phosphate buffer)
- Permeability (MDCK / AM)
- Bioavailability (Rat)

- **Distribution**

- Volume of Distribution (Rat)
- Plasma Protein Binding (Rat)
- Brain Tissue Binding (Rat)
- CNS Penetration (Rat)
- PGP Efflux (Rat)

- **Metabolism**

- Clearance (Rat, in-vivo)
- Clearance (Rat, in-vitro)

- **Excretion**

- **Toxicity**

- hERG Inhibition
- P450 1A2 Inhibition
- P450 2C9 Inhibition
- P450 2C19 Inhibition
- P450 2D6 Inhibition
- P450 3A4 Inhibition

Data

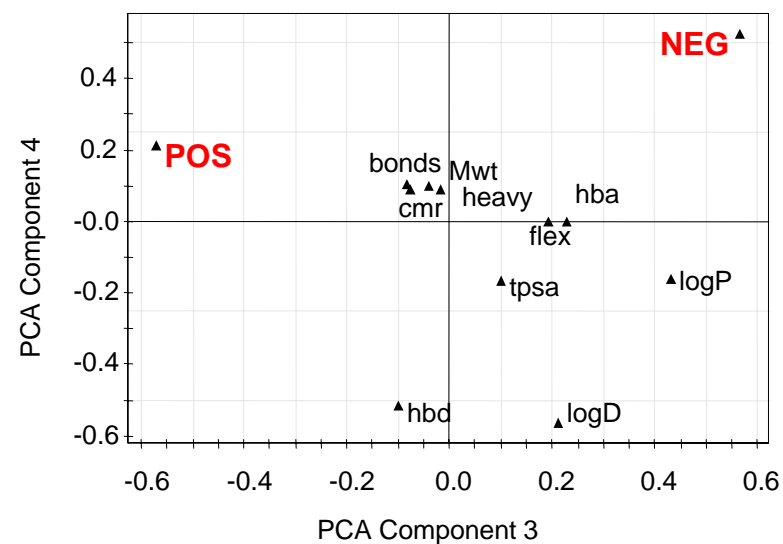
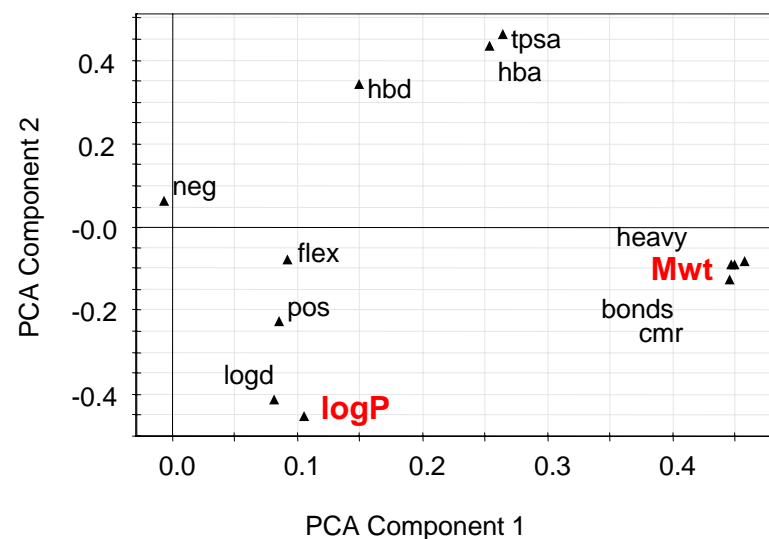
- Numerous, large, diverse ADMET datasets, obtained almost exclusively from single assay sources.
- N ranging from ~1000 - 50000
- In house in-silico QSAR models available on each endpoint.

Simple SAR Generation

- Want simple interpretable rules to guide chemistry and allow facile assessment of inter relationships.
- Focus on (a) a small number of non-redundant descriptors for simplicity and (b) ANOVA statistical method?

Which Molecular Descriptors?

- PCA model built on a diverse dataset of ~30,000 molecules with key computed descriptors
 - 81% of variance explained
 - PC1/2 = 60%
 - PC3/4 = 21%
- Significant redundancy in the descriptors commonly used for profiling
 - Mwt & logP and ionisation state are quite representative of axes – represent a good compromise between No. and description.

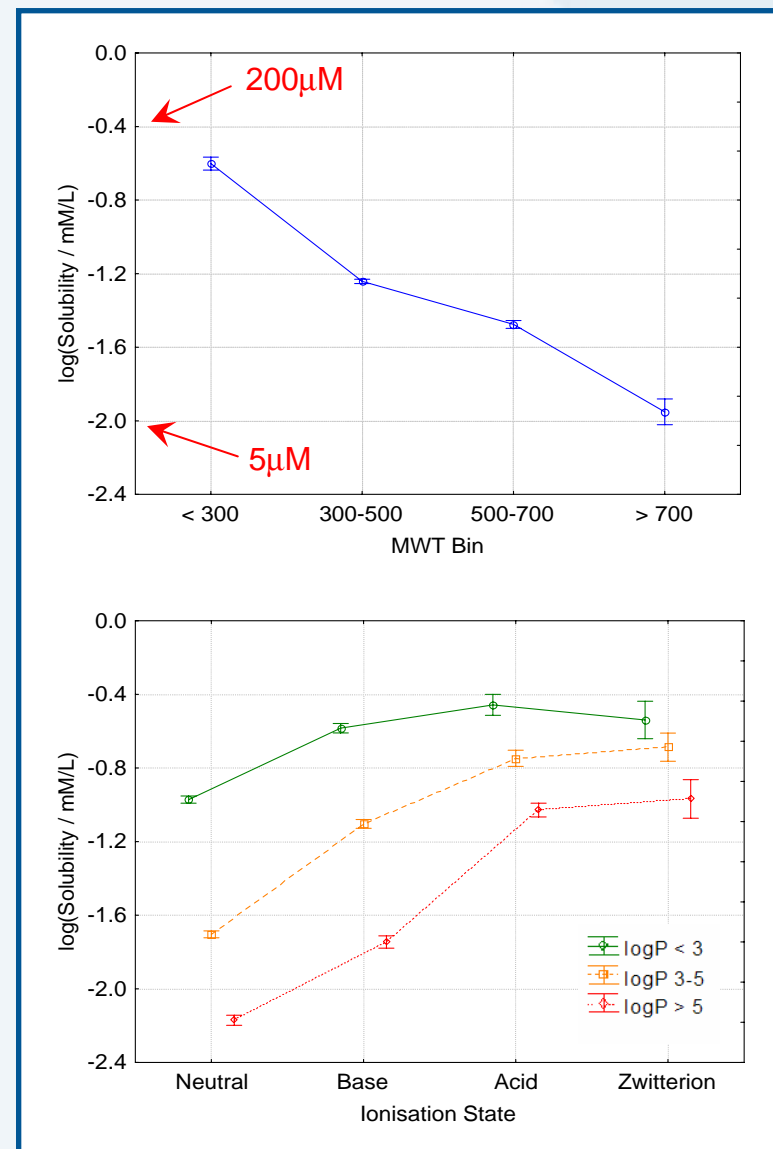


Solubility SAR (~45,000 Measurements)

- Solubility an important parameter for predicting absorption¹⁻³.

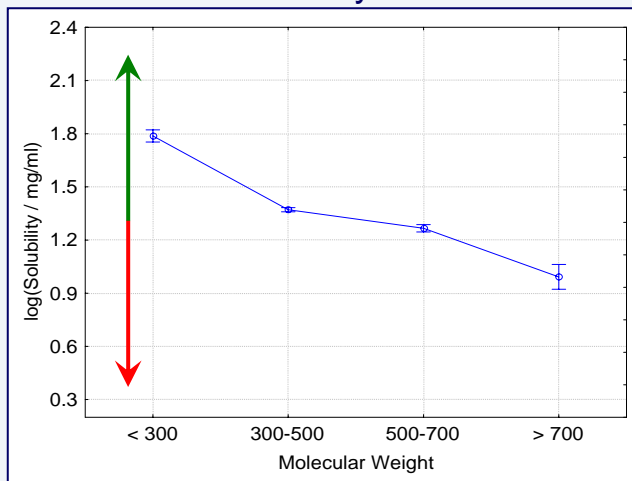
- Sol. ↓ with ↑ size
- Sol. ↑ with ↑ ionisation
- Sol. ↓ with ↑ clogP

1. Lipinski et al., *Adv. Drug Deliv. Rev.* **1997**, 23, 3-25
2. Abraham, et al., *J. Pharm. Sci.* **1999**, 88, 868-880
3. Votano, et al., *Mol. Diversity* **2004**, 8: 379–391.

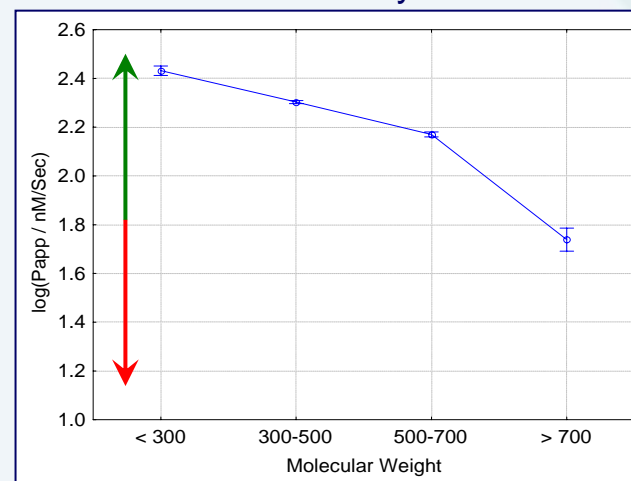


ADMET parameters vs Molecular Weight

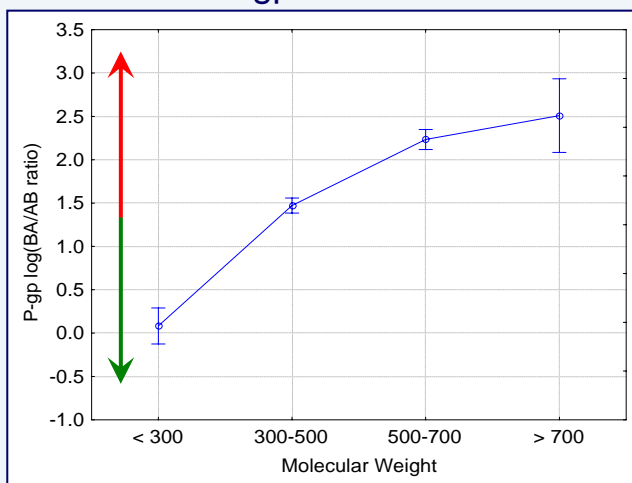
Solubility



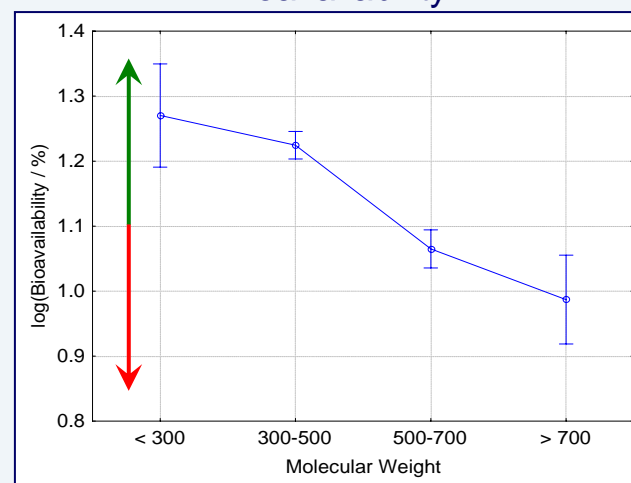
Permeability



P-gp Efflux



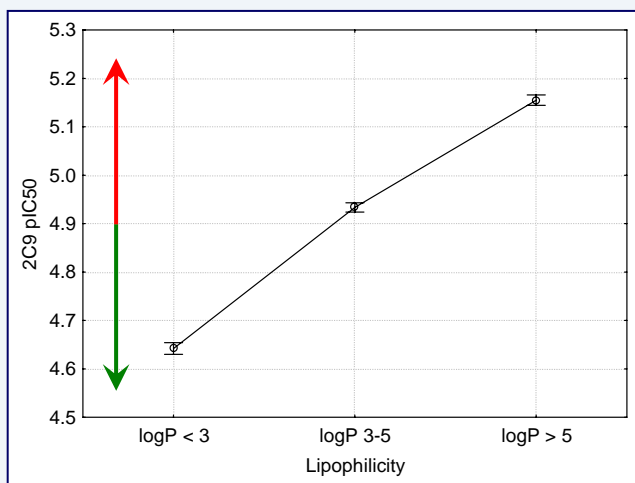
Bioavailability



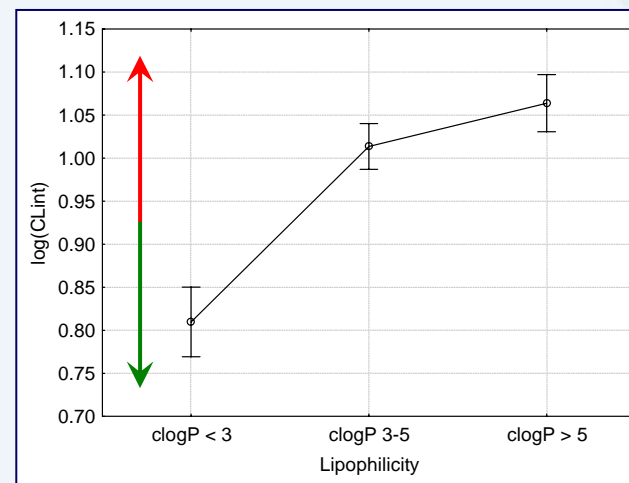
*can also be seen for PPB, BTB, hERG, P450 2C9, P450 3A4.

ADMET parameters vs Lipophilicity

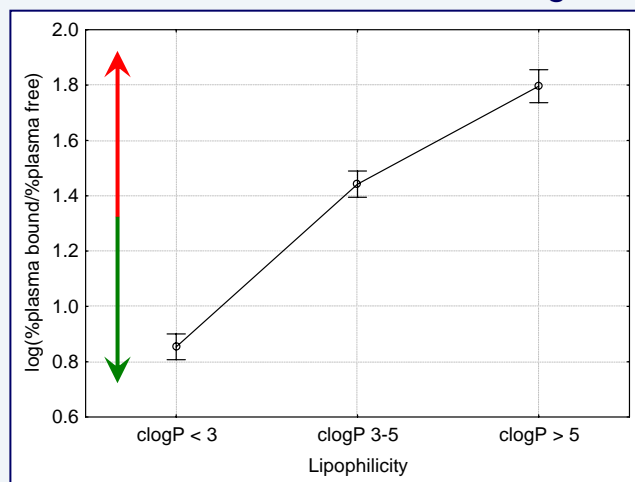
P450 2C9 Inhibition



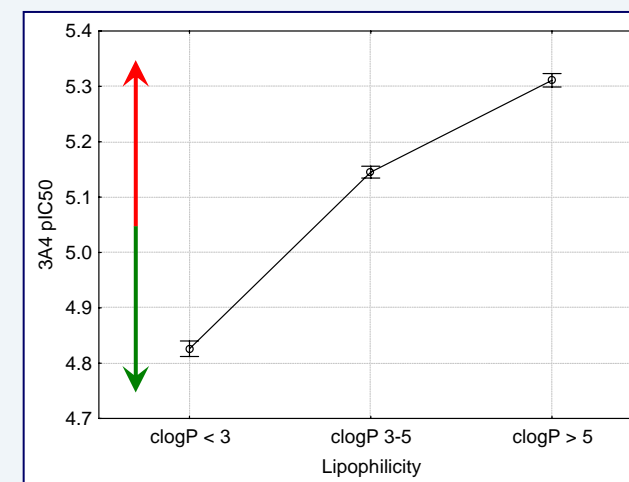
Intrinsic Clearance



Plasma Protein Binding



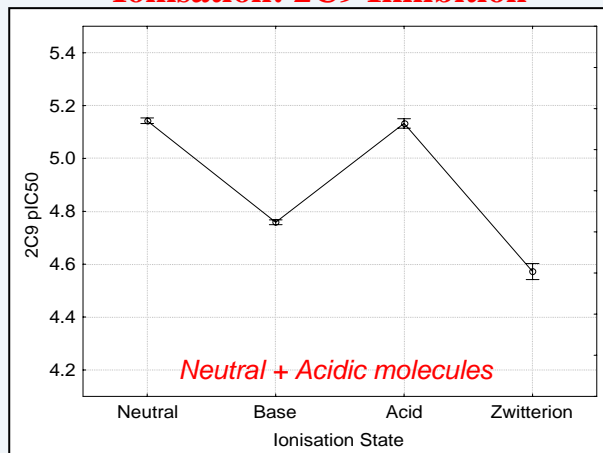
P450 3A4 Inhibition



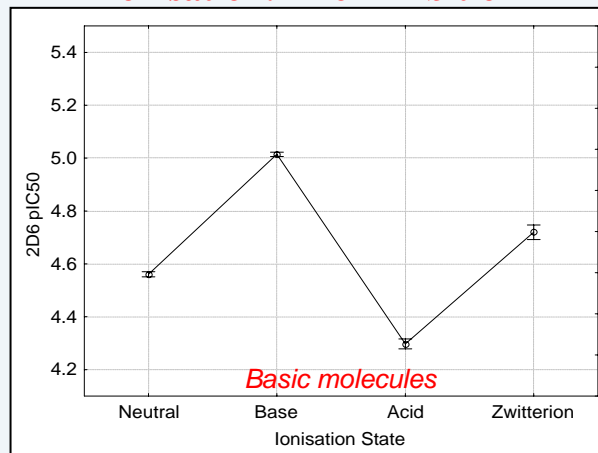
*can also be seen for Solubility, PPB, BTB, CNS, PGP, hERG, P450 all.

P450 SAR: Ionisation State & Size

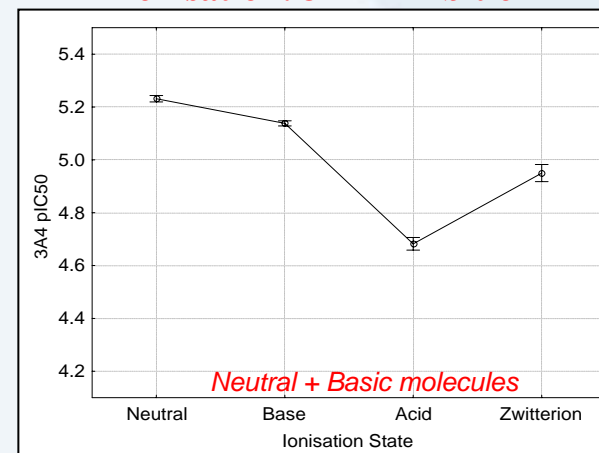
Ionisation: 2C9 Inhibition



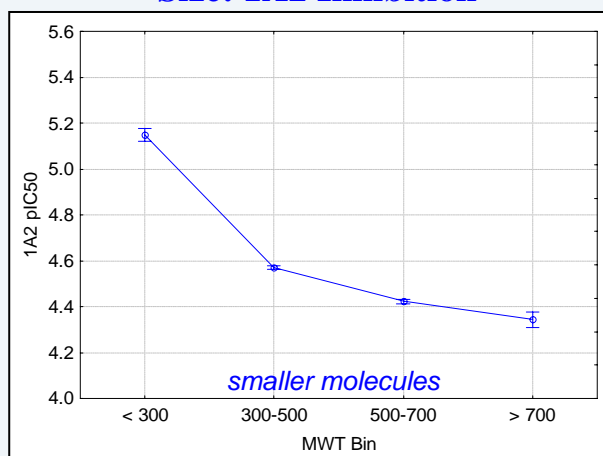
Ionisation: 2D6 Inhibition



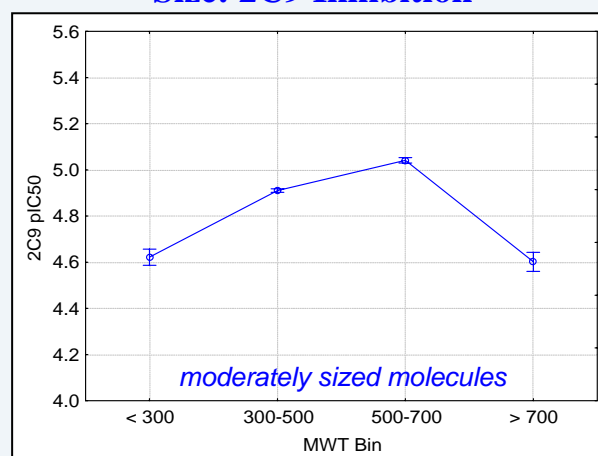
Ionisation: 3A4 Inhibition



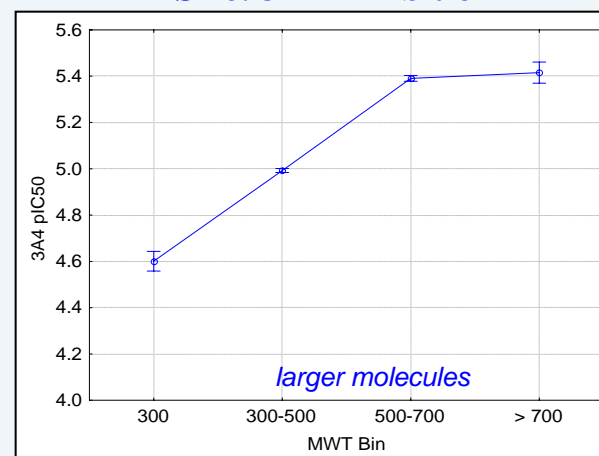
Size: 1A2 Inhibition



Size: 2C9 Inhibition



Size: 3A4 Inhibition



- 1A2:** Sansen et al., *J.Biol.Chem.* 2007, 282, 14348-14355 and Korhonen et al., *J. Med. Chem.* 2005, 48, 3808-3815
2C9: Lewis et al., *Drug Metabol. Drug Rev.* 2001, 18, 221-242 and Wester et al., M. R.; *J. Biol. Chem.*, 2004, 279, 5630-5637.
2D6: Rowland et al., *J. Biol. Chem.* 2006, 281, 7614-7622 and Snyder et al., *Quant. Struct. Act. Relat.* 2002, 21, 357-368
3A4: Ekroos et al., *PNAS* 2006, 103, 13682-13687 and Williams et al., *Science* 2004, 30, 683-686

Generic ADMET Rules of Thumb

- General ADMET rules to guide chemists at start of program
 - large diverse datasets
 - Consistent in-house data
- What ADMET issues are likely to be an issue for a given chemotype?
 - 2 Mwt/clogP groups
 - Mwt<400 & clogP<4
 - Mwt>400 &/or clogP>4
 - 4 Ionisation states
 - Neutral, Acidic, Basic & Zwitterionic

Neutral Molecules	Lower Mwt & logP	Higher Mwt &/or logP
Solubility	Average	Lower
Permeability*	Higher	Average/Higher
Bioavailability	Average	Lower
Volume of Dist.**	Average	Average
Protein Binding	Lower/Average	Higher
CNS Penetration***	Higher/Average	Average/Lower
Brain Tissue Binding	Lower	Higher
P-gp Efflux	Average	Higher/Average
In-vivo Clearance	Average	Average
hERG Inhibition	Lower	Lower
P450 Inhibition****	Lower 2C9, 2C19, 2D6 & 3A4 inhibition	Higher 2C9, 2C19 & 3A4 inhibition
"	Higher 1A2 inhibition	Lower 1A2 inhibition
"		Average 2D6 inhibition
Basic Molecules	Lower Mwt & logP	Higher Mwt &/or logP
Solubility	Average/Higher	Average/Lower
Permeability*	Average/Higher	Average
Bioavailability	Average	Lower
Volume of Dist.**	Average/Higher	Higher
Protein Binding	Lower	Average
CNS Penetration***	Higher/Average	Average/Lower
Brain Tissue Binding	Lower	Higher
P-gp Efflux	Average	Higher/Average
In-vivo Clearance	Average	Higher/Average
hERG Inhibition	Average/Higher	Higher
P450 Inhibition****	Lower 1A2, 2C9, & 2C19 inhibition	Lower 1A2 inhibition
"	Average 2D6 & 3A4 inhibition	Average 2C9, 2C19 inhibition
"		Higher 2D6 & 3A4 inhibition
Acidic Molecules	Lower Mwt & logP	Higher Mwt &/or logP
Solubility	Higher	Average/Higher
Permeability*	Lower	Lower/Average
Bioavailability	Average/Higher	Average
Volume of Dist.**	Lower	Lower
Protein Binding	Average/Higher	Higher
CNS Penetration***	Lower	Lower
Brain Tissue Binding	Lower	Higher
P-gp Efflux	Lower	Lower
In-vivo Clearance	Lower/Average	Average
hERG Inhibition	Lower	Lower
P450 Inhibition****	Lower 1A2, 2C19, 2D6 & 3A4 inhibition	Lower 1A2, 2C19, 2D6 & 3A4 inhibition
"	Average 2C9 inhibition	Higher 2C9 inhibition
Zwitterionic Molecules	Lower Mwt & logP	Higher Mwt &/or logP
Solubility	Higher	Average/Higher
Permeability*	Lower	Lower/Average
Bioavailability	Lower	Lower
Volume of Dist.**	Lower	Average/Lower
Protein Binding	Low/Average	Higher
CNS Penetration***	Average/Lower	Lower
Brain Tissue Binding	Lower	Higher
P-gp Efflux	Average	Average
In-vivo Clearance	Average	Average
hERG Inhibition	Lower	Average/Lower
P450 Inhibition****	Lower 1A2, 2C9, 2C19, 2D6 & 3A4 inhibition	Lower 1A2, 2C19 & 3A4 inhibition
"		Average 2C9, 2D6 inhibition

Generic ADMET Rules of Thumb

Neutral Chemotype with $\text{clogP} < 4$ and $\text{Mwt} < 400$

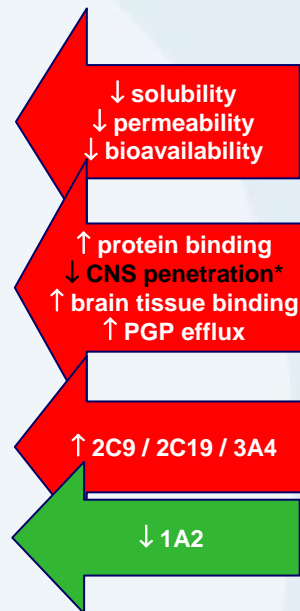
Neutral Molecules	Lower Mwt & logP	Higher Mwt &/or logP
Solubility	Average	Lower
Permeability*	Higher	Average/Higher
Bioavailability	Average	Lower
Volume of Dist.**	Average	Average
Protein Binding	Lower/Average	Higher
CNS Penetration***	Higher/Average	Average/Lower
Brain Tissue Binding	Lower	Higher
P-gp Efflux	Average	Higher/Average
In-vivo Clearance	Average	Average
hERG Inhibition	Lower	Lower
P450 Inhibition****	Lower 2C9, 2C19, 2D6 & 3A4 inhibition	Higher 2C9, 2C19 & 3A4 inhibition
"	Higher 1A2 inhibition	Lower 1A2 inhibition
"		Average 2D6 inhibition
Acidic Molecules	Lower Mwt & logP	Higher Mwt &/or logP
Solubility	Higher	Average/Higher
Permeability*	Lower	Lower/Average
Bioavailability	Average/Higher	Average
Volume of Dist.**	Lower	Lower
Protein Binding	Average/Higher	Higher
CNS Penetration***	Lower	Lower
Brain Tissue Binding	Lower	Higher
P-gp Efflux	Lower	Lower
In-vivo Clearance	Lower/Average	Average
hERG Inhibition	Lower	Lower
P450 Inhibition****	Lower 1A2, 2C19, 2D6 & 3A4 inhibition	Lower 1A2, 2C19, 2D6 & 3A4 inhibition
"	Average 2C9 inhibition	Higher 2C9 inhibition

Generic ADMET Rule

**Increases
clogP &/or Mwt**

**Neutral Chemotype with
clogP<4 and Mwt<400**

Neutral Molecules	Lower Mwt & logP	Higher Mwt &/or logP
Solubility	Average	Lower
Permeability*	Higher	Average/Higher
Bioavailability	Average	Lower
Volume of Dist.**	Average	Average
Protein Binding	Lower/Average	Higher
CNS Penetration***	Higher/Average	Average/Lower
Brain Tissue Binding	Lower	Higher
P-gp Efflux	Average	Higher/Average
In-vivo Clearance	Average	Average
hERG Inhibition	Lower	Lower
P450 Inhibition****	Lower 2C9, 2C19, 2D6 & 3A4 inhibition	Higher 2C9, 2C19 & 3A4 inhibition
"	Higher 1A2 inhibition	Lower 1A2 inhibition
"		Average 2D6 inhibition
Acidic Molecules	Lower Mwt & logP	Higher Mwt &/or logP
Solubility	Higher	Average/Higher
Permeability*	Lower	Lower/Average
Bioavailability	Average/Higher	Average
Volume of Dist.**	Lower	Lower
Protein Binding	Average/Higher	Higher
CNS Penetration***	Lower	Lower
Brain Tissue Binding	Lower	Higher
P-gp Efflux	Lower	Lower
In-vivo Clearance	Lower/Average	Average
hERG Inhibition	Lower	Lower
P450 Inhibition****	Lower 1A2, 2C19, 2D6 & 3A4 inhibition	Lower 1A2, 2C19, 2D6 & 3A4 inhibition
"	Average 2C9 inhibition	Higher 2C9 inhibition



Generic ADMET Rules of Thumb

Neutral Chemotype with $\text{clogP} < 4$ and $\text{Mwt} < 400$

Neutral Molecules	Lower Mwt & logP	Higher Mwt &/or logP
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Brain Tissue Binding	Lower	Higher
P-gp Efflux	Average	Average
In-vivo Clearance	Average	Average
hERG Inhibition	Lower	Lower
P450 Inhibition****	Lower 2C9, 2C19, 2D6 & 3A4 inhibition	Higher 2C9, 2C19, 2D6 & 3A4 inhibition
"	Higher 1A2 inhibition	Lower 1A2 inhibition
"		Average 2D6
Acidic Molecules	Lower Mwt & logP	Higher Mwt &/or logP
Solubility	Higher	Average
Permeability*	Lower	Average
Bioavailability	Average/Higher	Average
Volume of Dist.**	Lower	Lower
Protein Binding	Average/Higher	Higher
CNS Penetration***	Lower	Lower
Brain Tissue Binding	Lower	Higher
P-gp Efflux	Lower	Lower
In-vivo Clearance	Lower/Average	Average
hERG Inhibition	Lower	Lower
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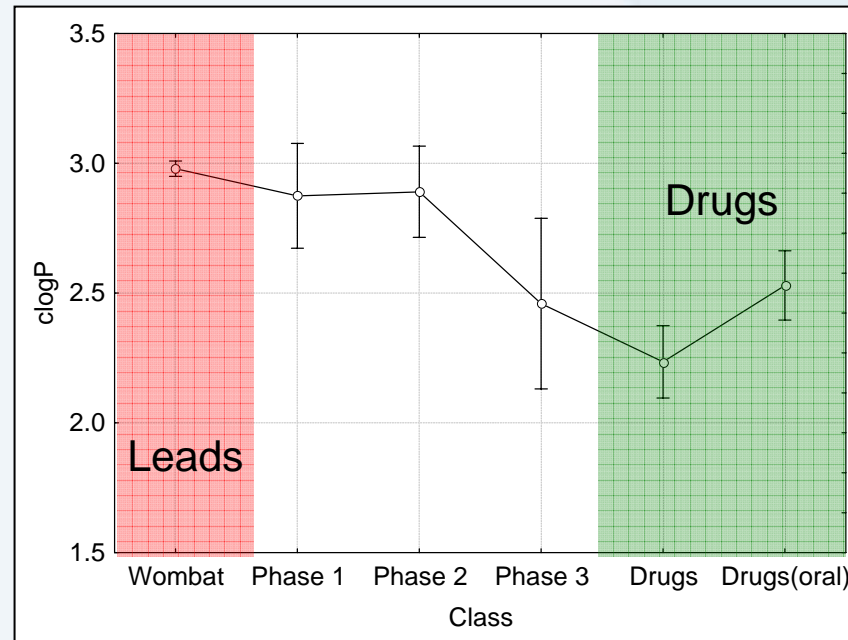
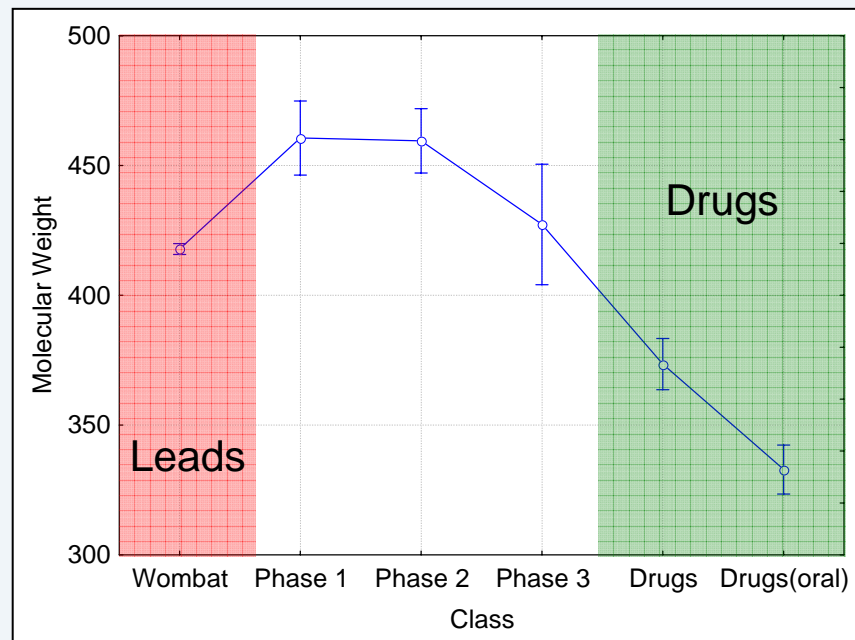
Add acidic center to chemotype

more variable effect on the various ADMET parameters

The Unsurprising Summary so far!

- Almost without exception, the 17 key ADMET parameters studied here deteriorate with either increasing molecular weight and/or clogP.
 - Ionisation state plays either a beneficial or detrimental effect depending on the ADMET parameter in question
 - Conclusions are in line with numerous literature QSAR studies on much smaller datasets.

Timeline – From Leads to Drugs



- Molecular weight and clogP must drop to reach the market as reported in the 2004 analysis by Wenlock³
 - Data illustrated here; Med. Chem Lit (91-05 - WOMBAT)², development¹ and drugs on the Market^{2,3}.
- Mean clogPs of ~2.5 and molecular weight of ~350 (data from ref 2)
 - 8% of oral drugs have both clogP>4 and Mol. Weight>400.

1. Wenlock et al, *J. Med. Chem.* **2004**, 46, 1250-1256

2. Oprea et al, *J. Comput. Aid. Mol. Des.* **2007**, 21, 113-117.

3. Proudfoot, *J. Bioorg. Med. Chem. Lett.*, **2005**, 15, 1087-1090

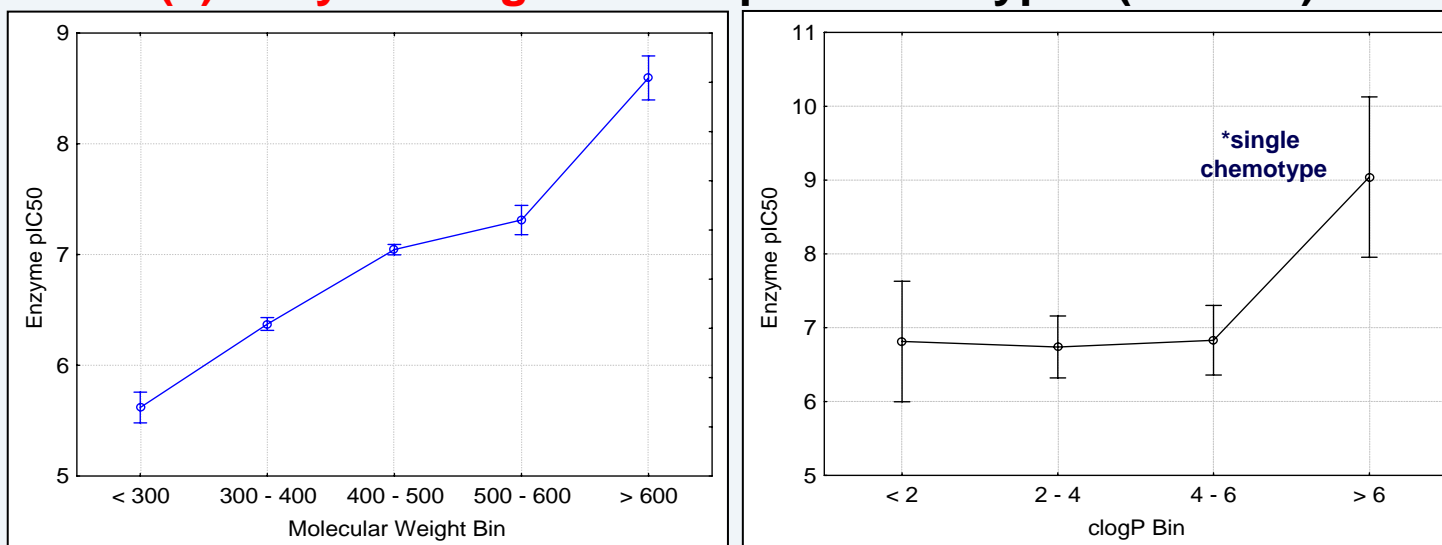
Is there a reason for making larger, more lipophilic molecules?

- Lead selection biases us to higher molecular weight¹⁻⁸.
 - Affinity key parameter used in lead selection.
- Lead optimization increases Mwt by 60da on average⁴.
 - Affinity the first readout after synthesis in lead optimization.
- Questions:
 - Is bias in PhysChem parameters down to affinity (selectivity/dose)?
 - Can we demonstrate this using GSK and literature data?

1. Sneader, W. *Drug Prototypes and their Exploitation* John Wiley and Sons Ltd. **1996** 2. Lipinski et al, *Adv. Drug Deliv. Rev.* **1997**, 23, 3-25
3. Teague et al, *Angew. Chem., Int. Ed. Engl.* **1999**, 38, 3743-3748. 4. Hann et al., *J. Chem. Info. Mod.* **2001**, 41, 856-864.
5. Oprea et al, *J. Chem. Inf. Comput. Sci.* **2001**, 41, 1308-1315. 6. Wenlock et al, *J. Med. Chem.* **2004**, 46, 1250-1256.
7. Hann et al, *Curr. Opin. Chem. Biol.* **2004**, 8, 225-263. 8. Lajiness, et al *Curr. Opin. in Drug Disc. & Dev.* **2004**, 7, 470-477.
9. Oprea et al, *J. Comput. Aid. Mol. Des.* **2007**, 21, 113-117.

Target Affinity

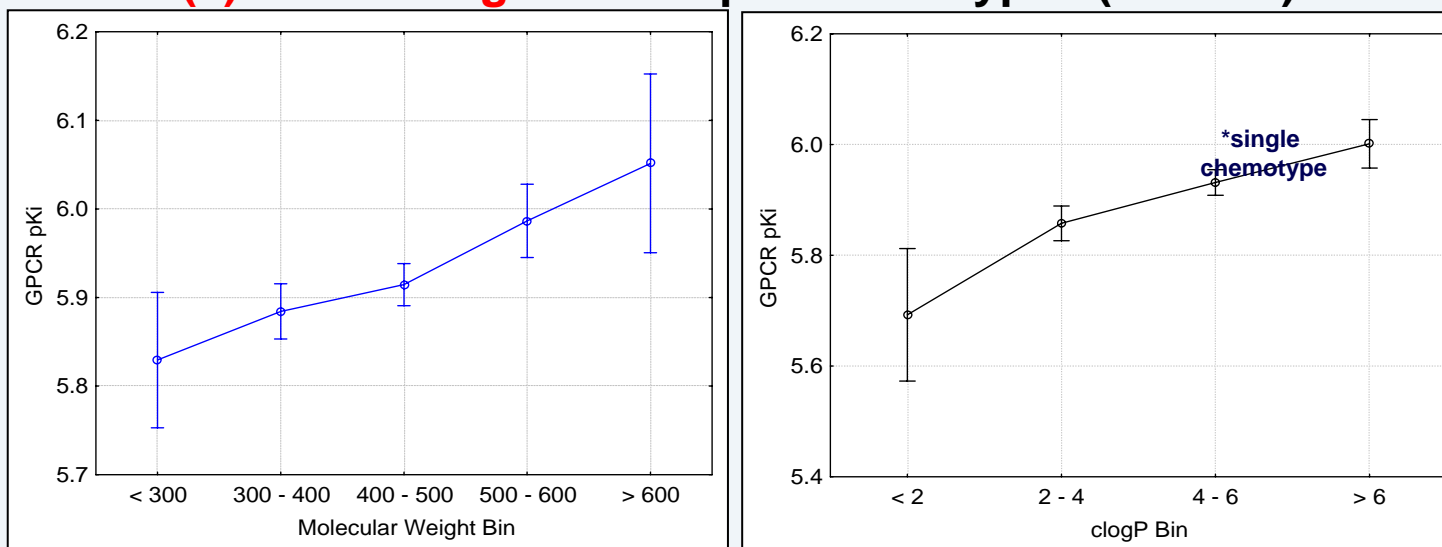
(1) Enzyme Target – multiple chemotypes (N=5037)



- Common for projects to want candidate molecule of nM affinity
- Increase molecular weight and logP to reach required affinity threshold^{1,2} (Enzyme, Kinase & GPCR illustrated).

Target Affinity

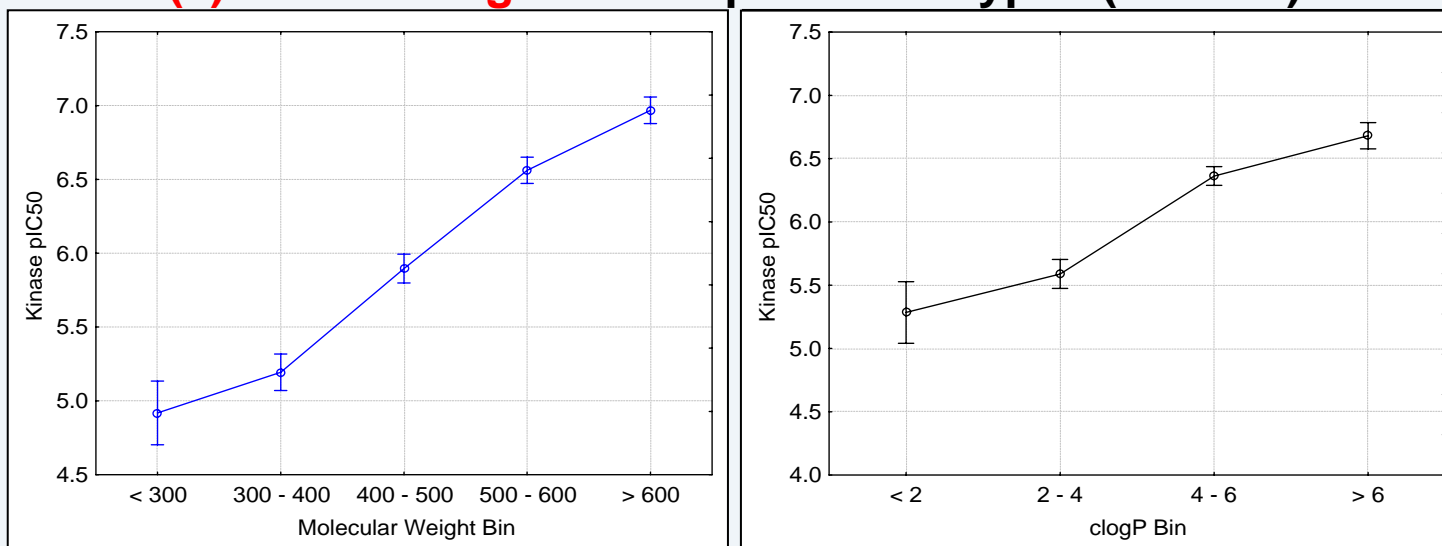
(2) GPCR Target – multiple chemotypes (N=3631)



- Common for projects to want candidate molecule of nM affinity
- Increase molecular weight and logP to reach required affinity threshold^{1,2} (Enzyme, Kinase & GPCR illustrated).

Target Affinity

(3) Kinase Target – multiple chemotypes (N=2266)



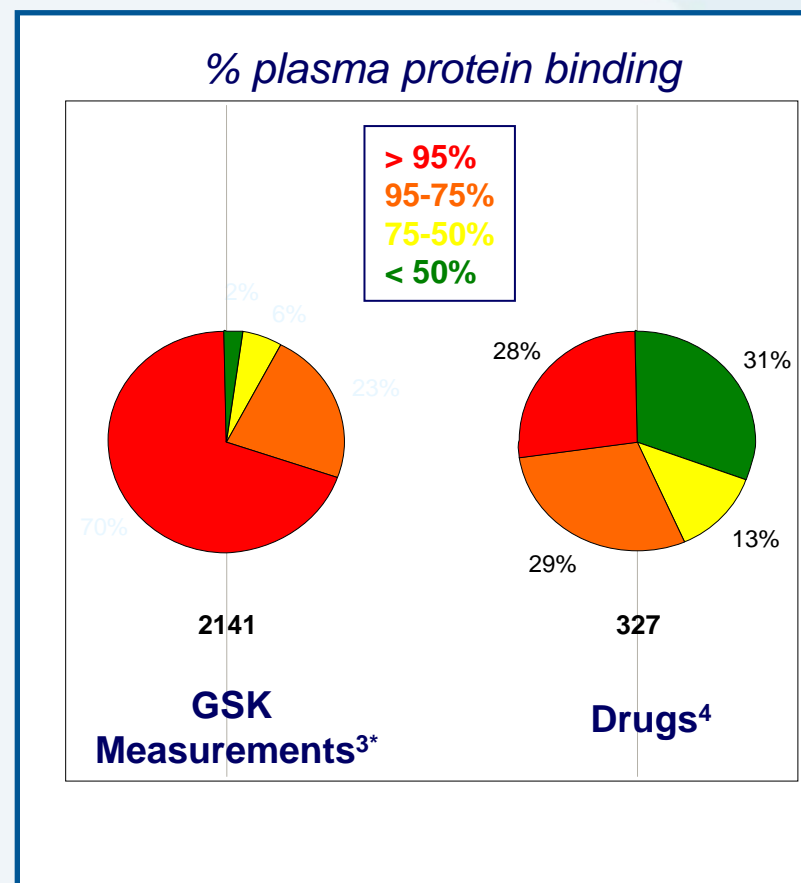
- Common for projects to want candidate molecule of nM affinity
- Increase molecular weight and logP to reach required affinity threshold^{1,2} (Enzyme, Kinase & GPCR illustrated).
- There are of course implications for ADMET since these have a diametrically opposed dependence on PhysChem parameters!

1. Andrews et al, *J. Med. Chem.*, **1984**, 27, 1648-1657.

2. Hajduk, *J. Med. Chem.*, **2006**, 49, 6972 -6976.

Affinity vs ADME Considerations

- Reports that ADME no longer a major issue might be a bit premature^{1,2}.
- Consider plasma protein binding (free fractions)
 - nM affinity threshold considerably greater than mean value of oral drugs
 - Countered by the ~10 times lower free fraction.



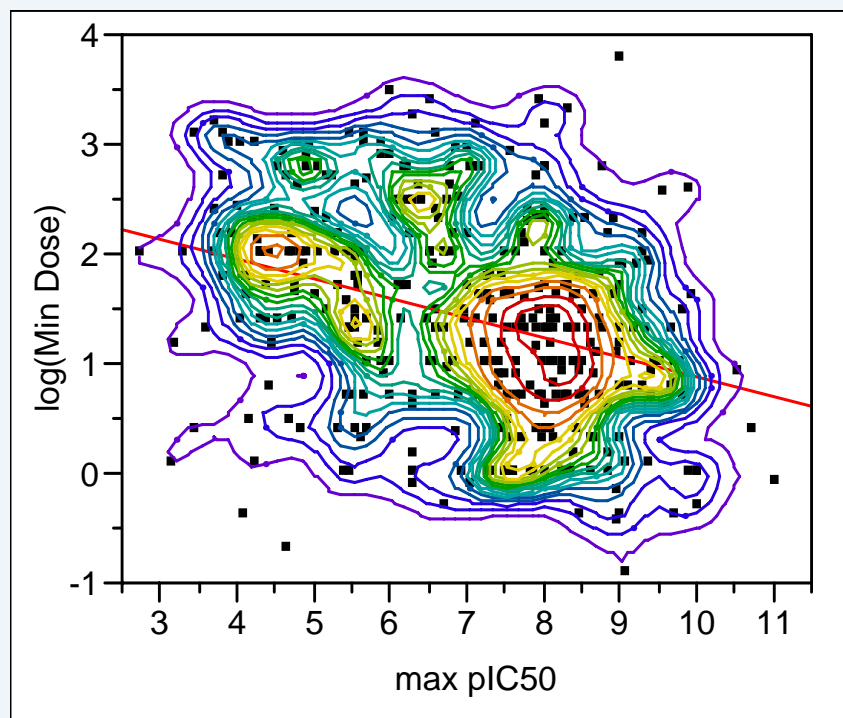
1. Kubinyi, *Nature Rev. Drug. Discovery* **2003**, 2, 665-668

3. Gleeson et al, *J.Med.Chem.* **2007**, 50-101-112

2. Frank et al. *Nature Rev. Drug. Discovery* **2003**, 556-580

4. Yamakazi, et al. *J. Pharm. Sci.* **2004**, 93, 1480-1494.

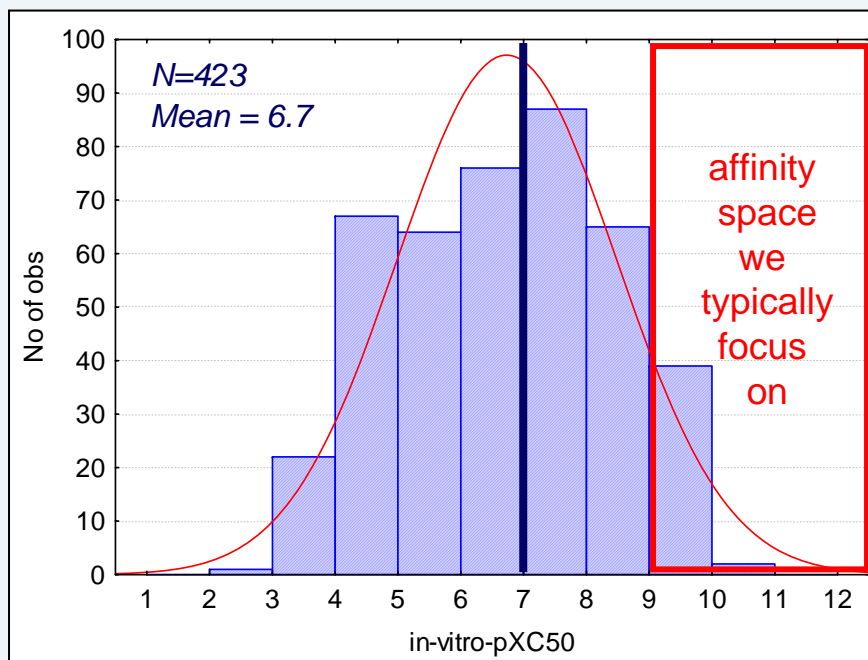
Target Affinity vs Therapeutic Dose



$$\log(\text{Min Dose}) = 2.68 - 0.18 * [\text{max pIC50}], \\ r^2 = 0.11, N = 370$$

- What level of affinity for a low therapeutic dose?
 - 370 oral drugs in-vitro potency and therapeutic dose¹.
- Correlation between affinity and dose¹ weak
 - Unsurprising given the importance of ADME parameters²⁻³.

What level of Affinity do we Need?



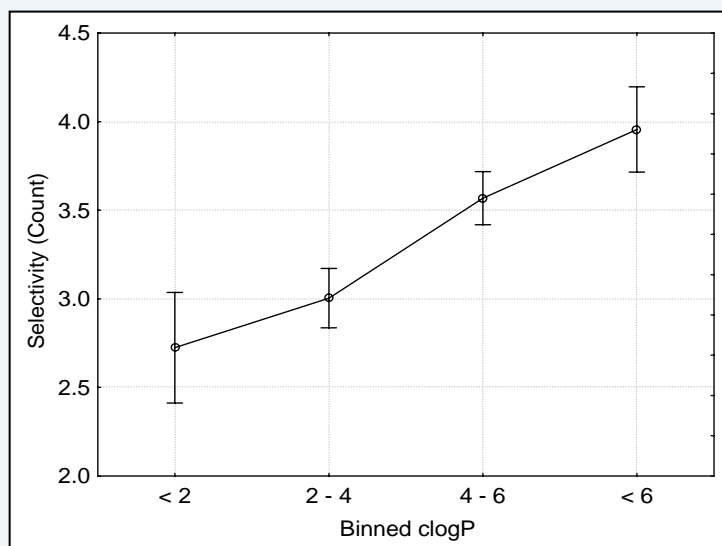
oral drugs¹ mean ~6.7
drugs^{1,2} mean ~7.8

1. GSK compiled dataset: Dana Scarborough et al (affinity, Drugdex, Martindales, PDR, integrated Index etc)

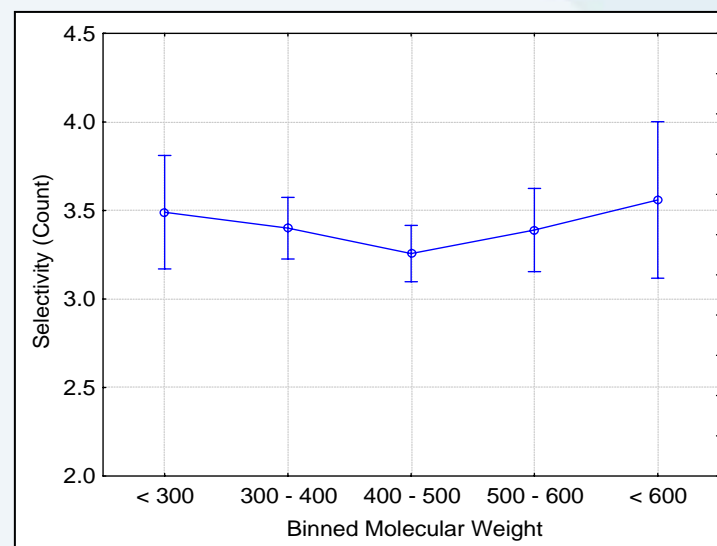
2. Overington et al. Nature Rev. Drug. Discovery, 2006, 5, 993-996

- 423 oral drugs with in-vitro affinity data!
- Oral drugs are seldom nM potent – closer to μM .
 - Are we correct in biasing to ever greater molecular weight/logP?
 - ... especially given invitro-in vivo correlation not always that strong?

Off Target Selectivity



*Selectivity defined as:
 $pXC50 > 6$
where
no other hit
within 1 log
unit of max.



- More potent molecules are generally more selective - but selectivity decreases with increasing clogP.
 - Negligible effect with molecular weight - not a good surrogate for molecular complexity¹.
 - Differs from Hopkins³ et al where selectivity defined as $pIC50 > 5$.

1. Hann, M. et al., *J. Chem. Info. Mod.* **2001**, *41*, 856-864.

2. Hopkins, A. et al, *Curr. Opin. Struct. Biol.* **2006**, *16*, 127-136.

3. Abad-Zapatero et al, *DDT*, **2005**, *10*, 464-569 ;

Conclusion

- Desire for nM affinity candidates drives molecular weight and clogP higher.
 - Mean pIC50 of oral drugs is 6.7 not nM.
 - Low therapeutic dose not guaranteed by nM affinity.
 - Selectivity increases with decreasing clogP.
- Almost without exception ADMET liabilities increase with increasing molecular weight &/or clogP.
 - Lipinski's cut-offs are not universally ADMET relevant, and are known to be too lax (only 8% of oral drugs lie outside tighter 400 & 4 cut-offs).

Acknowledgments

- Anne Hersey
- Dino Montanari
- Andrew Leach
- Colin Edge
- Mike Hann
- Andrew Brewster
- Iain Mclay
- Sandeep Modi
- Tudor Oprea
- GSK Comp. Chem.
- GSK Psy. CEDD