Understanding Compound Quality

Focus on Molecular Property Design

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A high level view

Oral small molecules

Guiding Optimal Compound Design and Development, Boston, 19th March 2015

Success rates: Preclinical-Phase III **4.3%**; Phase II **23%**

*Evidence for progression of **unoptimised compounds***

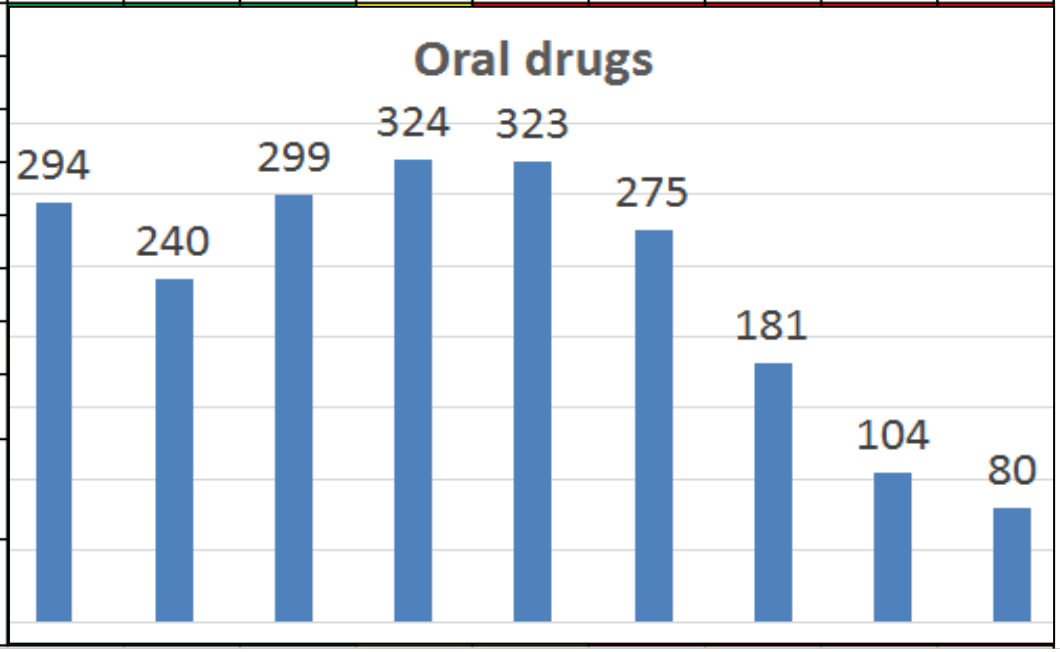
- **Pfizer: '4 Pillars' for phase II success** *(44 phase II projects, 2005-9)*
  - **Exposure at target; Binding to target; Pharmacological response; Target linked clinically to disease modification**
  - Low confidence in *exposure* in 18/34 non-progressing molecules: **"cannot conclude mechanism tested adequately in 43% of cases"**
- **AstraZeneca: '5Rs'** *(>114 preclinical to phase II projects, 2005-10)*
  - **'Right': Target & Tissue (4Ps); Safety; Patient; Commercial potential**
  - 29% Clinical efficacy failures **"dose limited by compound characteristics or tissue exposure not established"**
  - **Decision making process:** eg, 38% projects advanced to clinic had *low confidence in safety* & 78% of these eventually failed due to toxicity
- **GSK: solubility-limited candidates** – *BCS II/DCS class IIb*
  - **Add 2 years to development:** "lack of efficacy owing to lack of exposure"
- **FDA submissions** *(302 NMEs, 2000-12; 151 (50%) unsuccessful 1st time)*
  - 29% Unsuccessful 1st submissions had **dose or clinical end point issues**

Success rates: Thomson Reuters, 2006-10; **4 Pillars:** Morgan et al, *Drug Discovery Today* 2012, **17**, 419; Bunnage, et al *Nat. Chem. Biol*. 2013, **9**, 195; **5Rs:** Cook et al, *Nat. Revs. Drug Disc.* 2014, **13**, 419; **Solubility:** Hann & Keserű, *Nat. Rev. Drug Disc*. 2012, **11**, 355; **FDA:** Sacks et al, *JAMA* 2014, **311**, 378; **Pharma's problems:** Scannell et al, *Nat. Rev. Drug Discov*. 2012, **11**, 191

A Significant Body of Evidence links Physical Properties to *Probability* of ADMET Risk

Key properties: lipophilicity + ionisation. ***Property forecast index (PFI)***

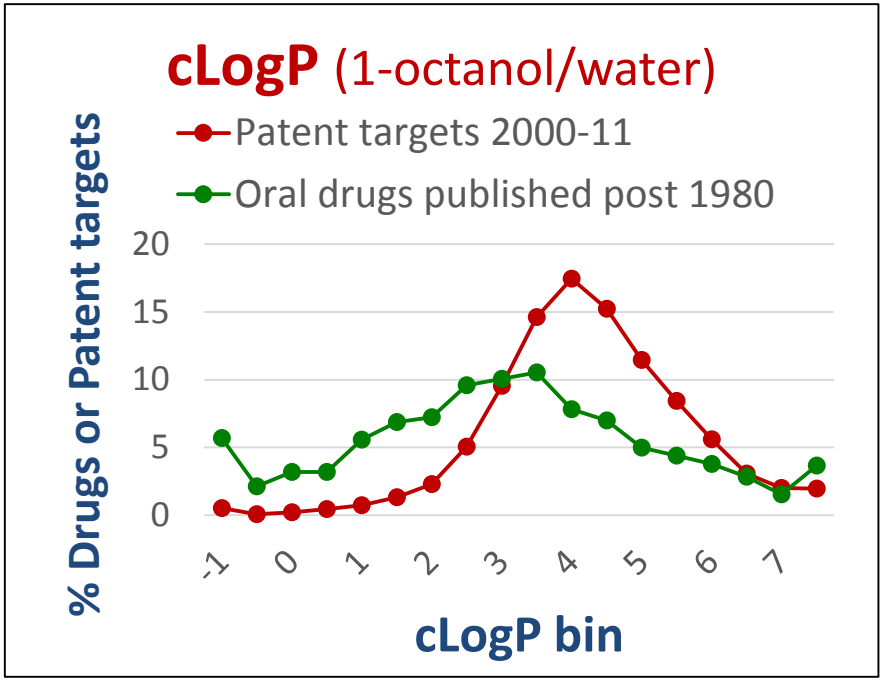
	PFI = Chrom $LogD_{pH7.4}$ + #Ar rings								
Assay / target value	**<3**	**3-4**	**4-5**	**5-6**	**6-7**	**7- 8**	**8-9**	**9-10**	**>10**
Solubility >200 µM									
%HSA <95%									
2C9 pIC_{50} <5									
2C19 pIC_{50} <5									
3A4 pIC_{50} <5									
Cl_{int} <3 ml/min/kg									
P_{app} >200 nm/s									
hERG pIC_{50} <5 (+1 charge)									
Promiscuity <5 hits with pIC_{50} >5									

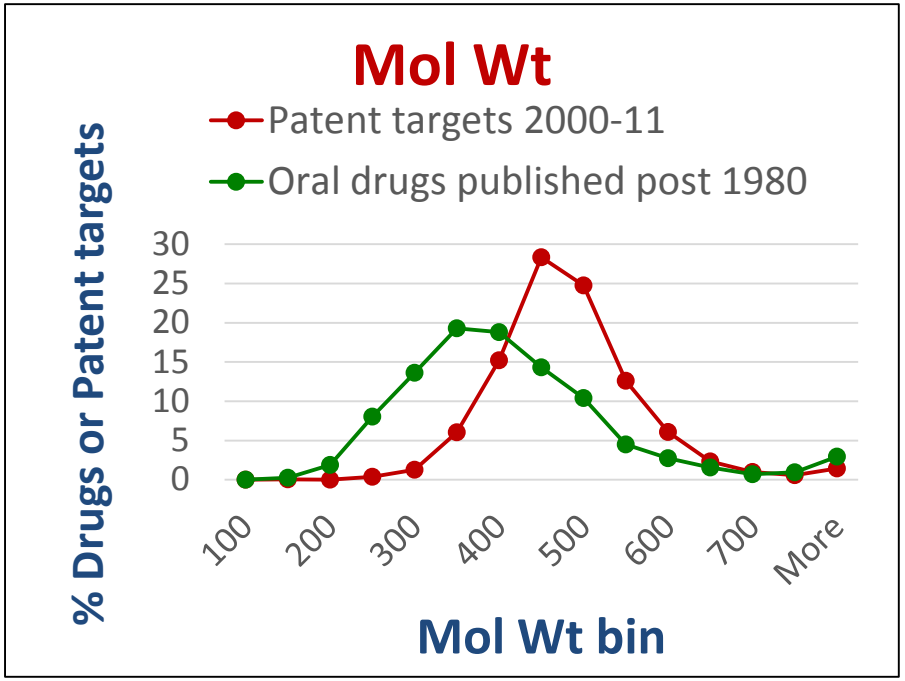


≥67% 34-66% <33% % chance of achieving target in particular bin

PFI: Young et al, *Drug Disc. Today* 2011, **16**, 822; **Physical property reviews**: Meanwell, *Chem. Res. Toxicol*. 2011, **24**, 1420; Young, *Top Med. Chem*. 2015, **9**, 1; Gleeson et al, in *The Handbook of Medicinal Chemistry: Principles and Practice*, eds A.M. Davis and S. Ward, RSC, 2015, p1-31; Hann & Keserű, *Nat. Rev. Drug Disc*. 2012, **11**, 355; Gleeson et al. *Nat. Rev. Drug Disc*. 2011, **10**, 197**; Lipophilicity:** Waring, *Exp. Op. Drug Disc*. 2010, **5**, 235; **Ionisation**: Charifson & Walters, *J. Med. Chem.* 2014, **57,** 9701; **Ar rings review**: Ritchie & Macdonald, *J. Med. Chem.*, 2014, **57**, 7206; **Critique - statistics**: Kenny & Montanari, *J. Comp.-Aid. Mol. Des*. 2013, **27**, 1; **Critique - toxicity data**: Muthas et al, *MedChemCommun*. 2013, **4**, 1058

Properties of Patented Compounds & Oral Drugs

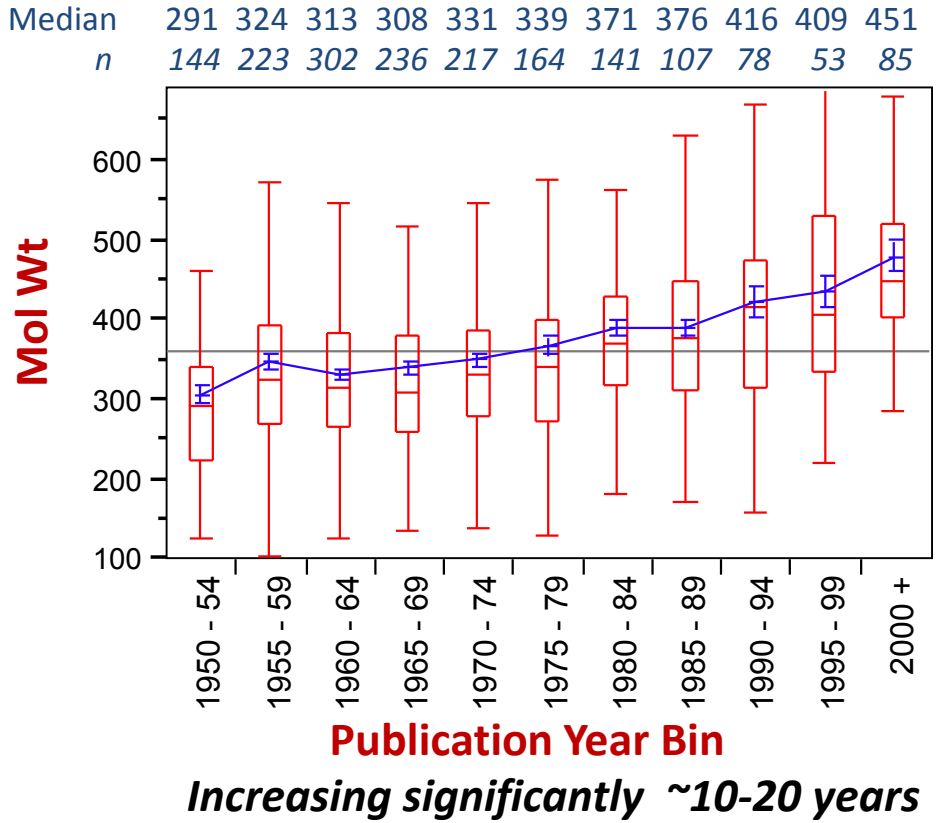




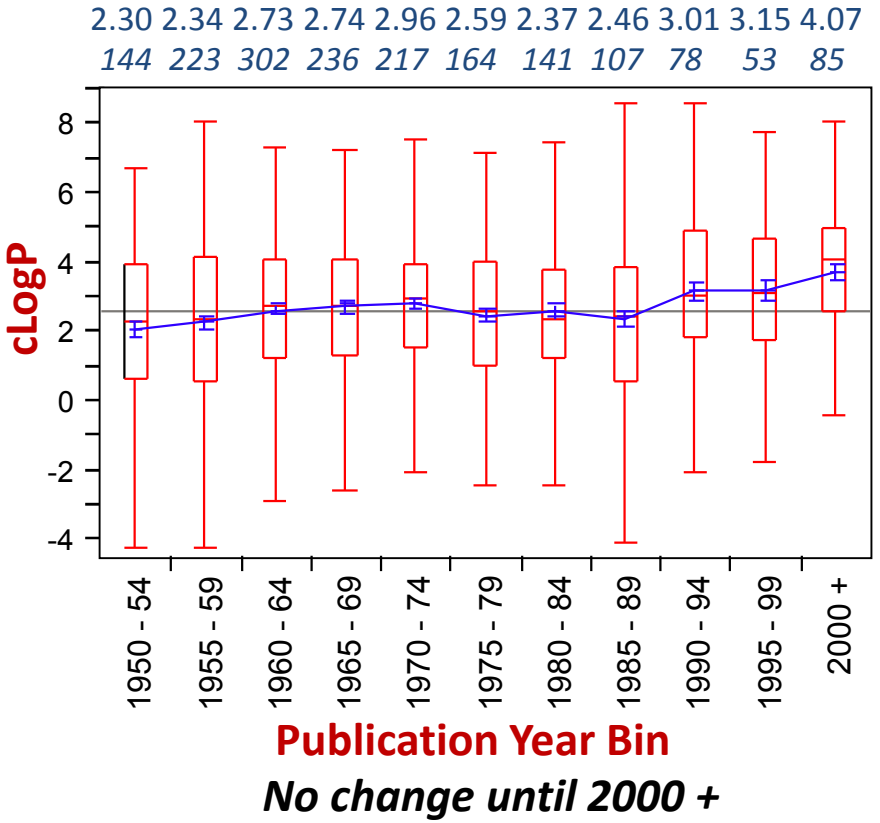
- 'Inflated' patented compounds are likely to possess increased ADMET risks vs recently marketed drugs → **pipeline attrition?**
- Will the **probability of success in a portfolio** of drug candidates increase as its balance of biological and physicochemical properties more closely resembles that of successful marketed drugs?
- What other viable strategies exist for medicinal chemists to improve productivity?
- **Compound quality is a medicinal accountability.** Fixed at the point of design, controllable in optimisation, **must not be the root cause of clinical attrition**

Drug data: Leeson et al, *Med. Chem. Comm*. 2011, **2**, 91, updated to 2014
Patent data: Leeson & St-Gallay, *Nature Revs. Drug Disc.* 2011, **10**, 749

Oral ‘Druglike’ Properties: Changes over Time



Increasing significantly ~10-20 years



No change until 2000 +

- **Least change:** cLogP, HBD, %PSA, Fsp3 & chiral atoms
- **Most change:** Mol Wt, HBA, RotB, PSA & Ar; *all increasing*

Hypothesis: drug properties changing least are more important

Global oral drug approvals to end 2014. **Property vs time publications**: Leeson & Davis, *J. Med. Chem* 2004, **47**, 6338; Proudfoot, *Bioorg. Med. Chem. Lett.* 2005, **15**, 1087; Leeson & Springthorpe, *Nat. Rev. Drug Disc.* 2007, **6**, 881; Walters et al, *J. Med. Chem*. 2011, **54**, 6405; Leeson et al, *Med. Chem. Comm*. 2011, **2**, 91; **Phase I-III data**: Wenlock et al, *J. Med. Chem*. 2003, **46,** 1250

Does Size Matter?

neutral molecules	MWT < 400 and clogP < 4	MWT > 400 and/or clogP > 4
solubility	average	lower
permeability*	higher	average/higher
bioavailability	average	lower
volume of Dist.**	average	average
plasma protein binding	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
P450 inhibition****	higher 1A2 inhibition	lower 1A2 inhibition
P450 inhibition****		average 2D6 inhibition

GSK: ADME '4/400' rule

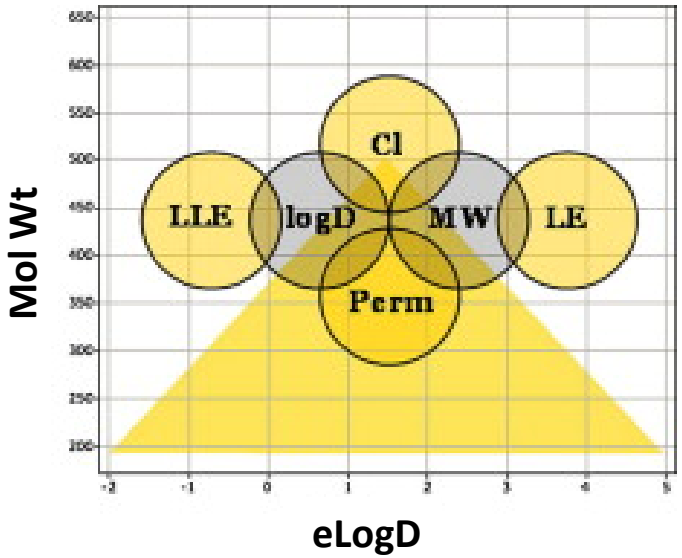
Gleeson, *J. Med. Chem*. 2008, **51**, 817

AZLogD limits required to achieve >50% chance of high permeability for a given Mol Wt

Mol Wt	AZLogD
<300	>0.5
300-350	>1.1
350-400	>1.7
400-450	>3.1
450-500	>3.4
>500	>4.5

AZ: Mol Wt & LogD dependent permeability

Waring, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2844

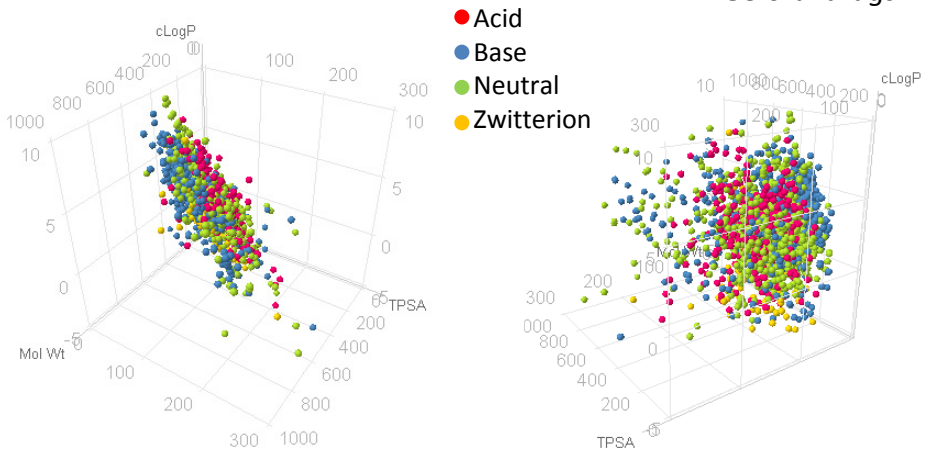


Pfizer: 'Golden triangle'

Johnson et al, *Bioorg. Med. Chem. Lett*., 2009, **19**, 5560

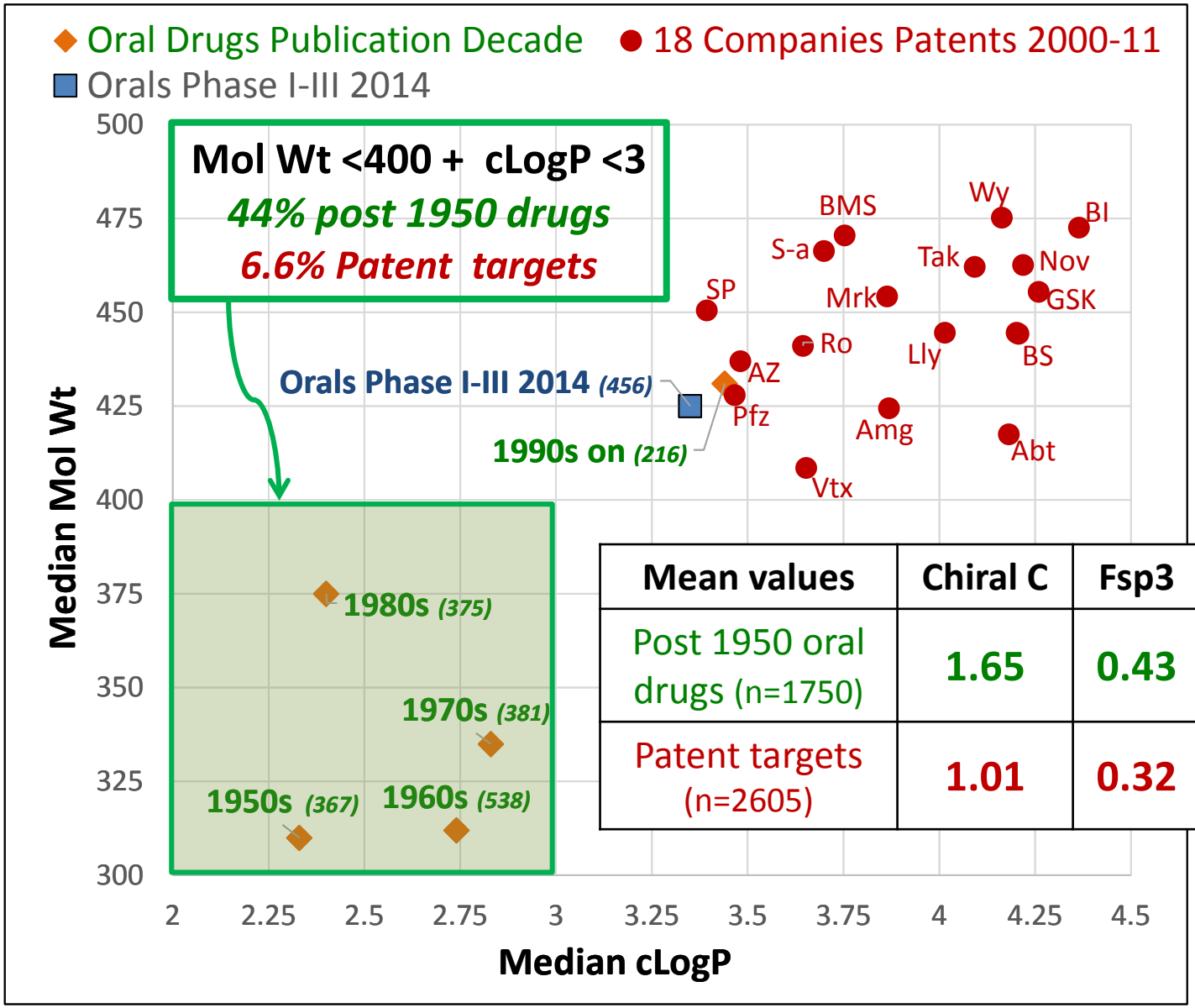
Mol Wt vs cLogP vs TPSA

n= 2138 oral drugs



Ro5 QSAR: cLogP = 0.0173 **Mol Wt** - 0.564 **O+N** - 0.439 **OH+NH** + 0.246 *n=2138, r^2 = 0.616*

Inflation of ‘Druglike’ Physical Properties



Mean values	Chiral C	Fsp3	Ar ring
Post 1950 oral drugs (n=1750)	1.65	0.43	1.77
Patent targets (n=2605)	1.01	0.32	2.55

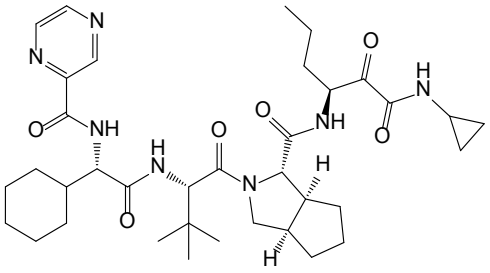
Drug data: Leeson et al, *Med. Chem. Comm*. 2011, **2**, 91, *oral drugs updated to 2014*; **Patent targets** 2000-11 from 18 companies: Leeson & St-Gallay, *NRDD* 2011, **10**, 749; **Phase I-III orals**: http://www. citeline.com/

Disease Risk/Benefit & Property Inflation

36% 2012-14 FDA approvals are orphan drugs

post-1990 Orals (n=216)	**Median cLogP**	**Median Mol Wt**	**≥2 Ro5 unmet**
Kinase, HIV prot., HCV (n=45)	**4.64**	**556**	**40%** (18)
Others (n=171)	**3.07**	**420**	**12%** (20)
			Pre-90: 6.5%

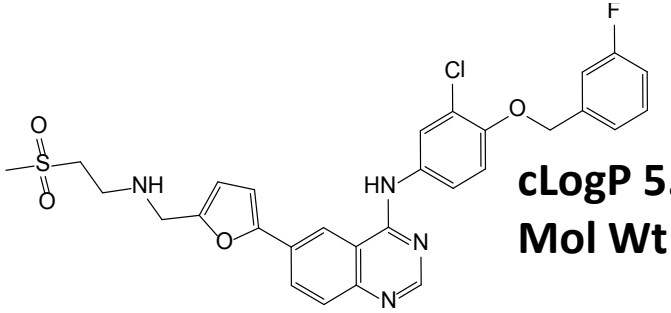
Telaprevir: HCV NS3 protease



cLogP 5.4
Mol Wt 680

Dose 750mg *tid*, high fat food; sol. 4.7 µg/ml, 'less than marble;' SDD formulation; **Black Box:** serious skin reactions; *efficacious, superceded*

Lapatinib: EGFR & ErbB2 kinases



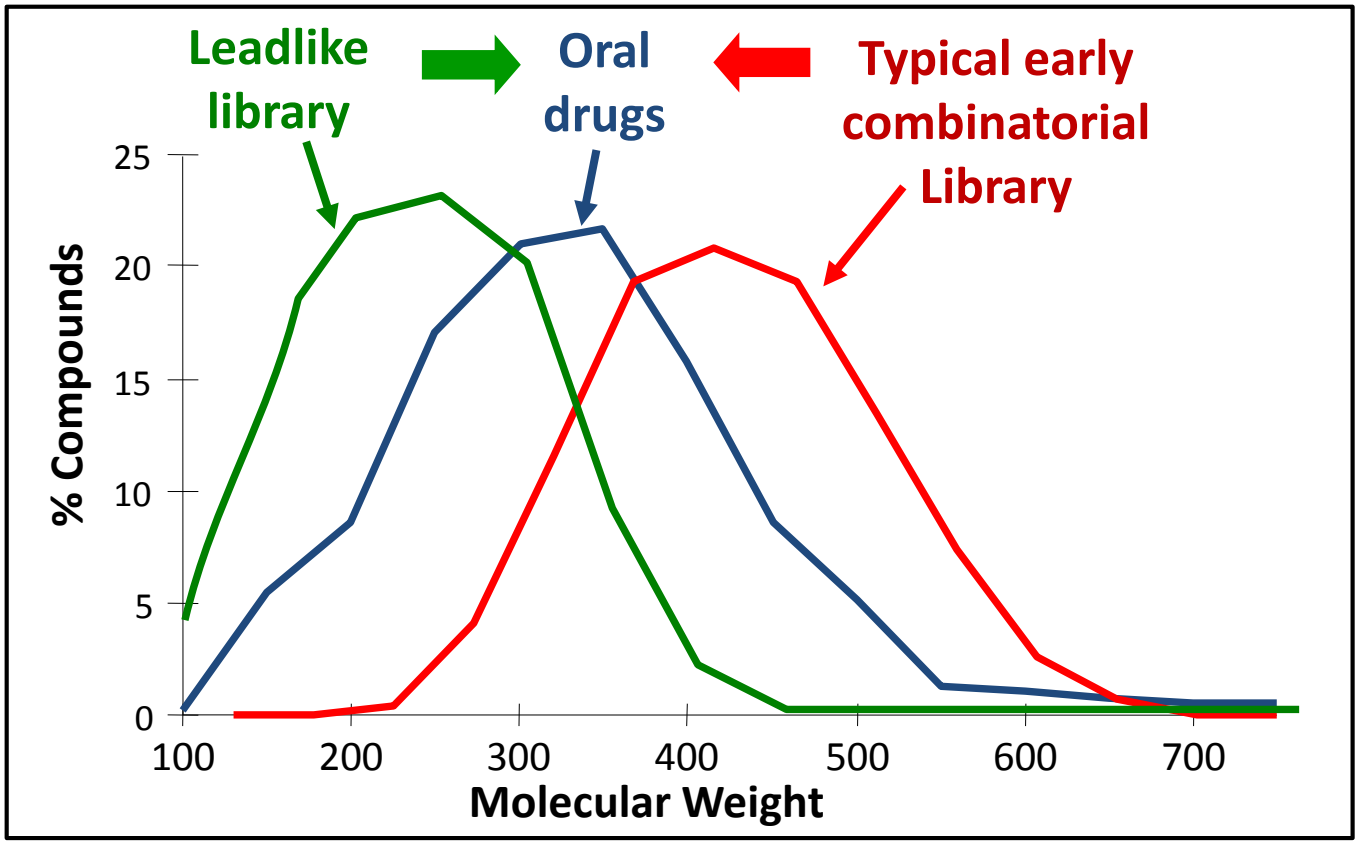
cLogP 5.8
Mol Wt 581

Dose 1500mg *uid*, 1hr before or after meal; sol. 7 µg/ml; hERG inhibitor; **Black Box:** hepatotoxic; *slow off-rate; standard treatment for breast cancer*

Medical need & efficacy can overcome risk & dosing inconvenience

Telaprevir: Kwong et al, *Nat. Biotech.* 2011, **29**, 993; **Lapatinib:** Lackey & Cockerell in *Kinase Inhibitor Drugs,* Wiley, 2009, p41; **Cancer drugs & food interaction:** Weitschies, *Clin. Pharm. & Therapeutics* 2013, **94**, 441

Physical Properties Tend to Increase in Optimisation: *the 'Leadlike' Hypothesis*

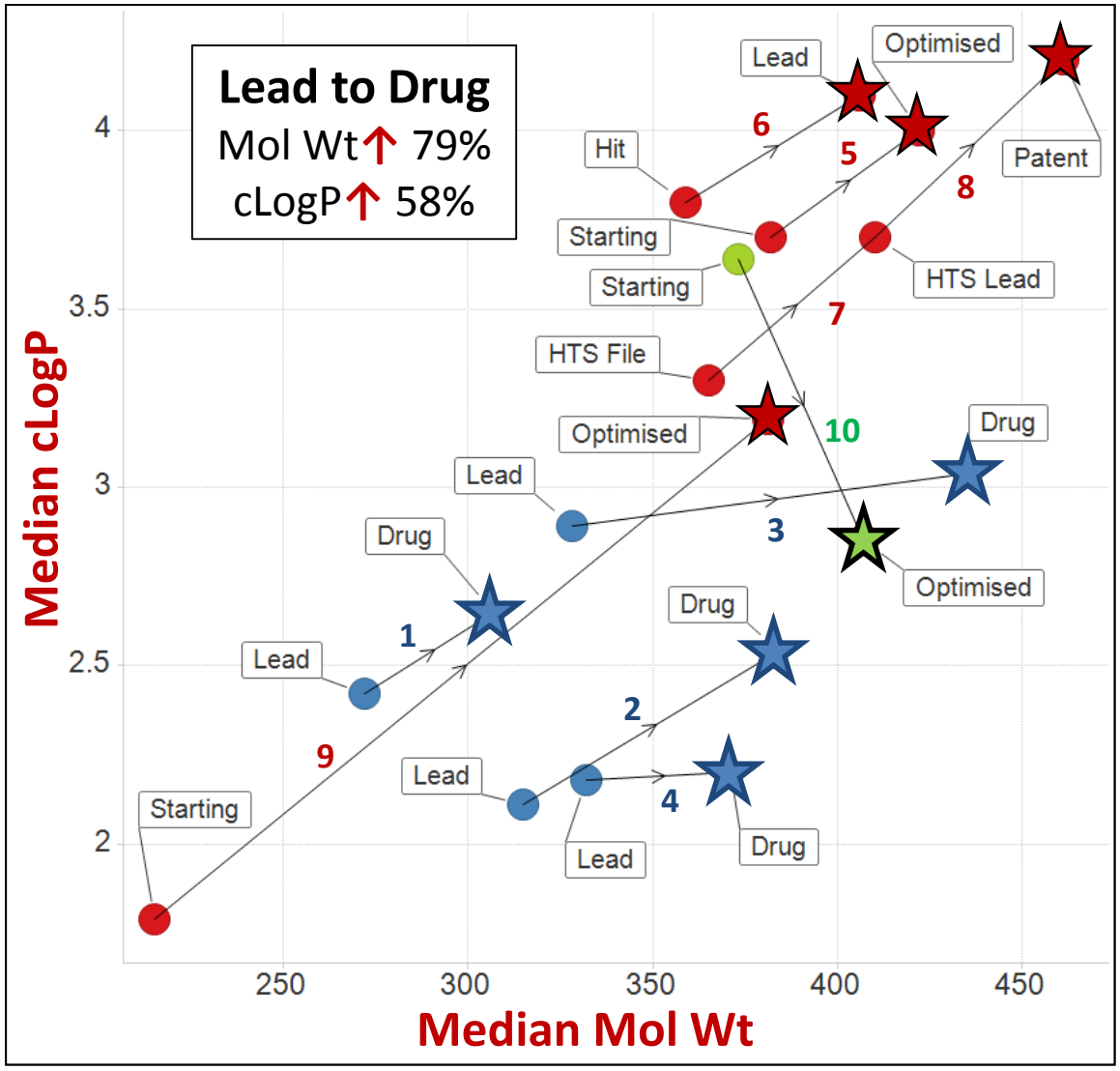


'Leadlike' lead: Affinity >0.1µM; Mol Wt 100-350; cLogP 1-3

Leadlikeness: Teague, Davis, Leeson & Oprea, *Angew. Chem. Int . Ed*. 1999, **38**, 3743; Oprea et al, *J. Chem. Inf. Comput. Sci*. 2001, **41**, 1308; Hann et al, *J. Chem. Inf. Comput. Sci.* 2001, **41**, 856; **Synthetic challenges:** Doveston et al., *Org. Biomol. Chem.* 2015, **13**, 859

Property Inflation in Optimisation

Leadlike hypothesis: Teague et al, *Angew. Chem. Int . Ed*. 1999, **38**, 3743

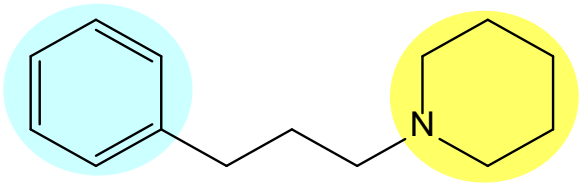


	n
1. Lead to drug - historical	469
2. Lead to drug - historical	62
3. Lead to drug, post 1990	60
4. 1st Drug to follow-on	74
5. Lit 2000s optimisation	1680
6. Lit 2000s HTS, hit-to-lead	335
7,8. HTS file/lead/patents 4 companies	
9. Fragment optimisation	145
10. Lit 2000s LLE opt'n **LLE** = p(Activity) – LogP/D	57

1. Hann, *J.Chem. Inf. Comput. Sci.* 2001, **41**, 856; **2.** Oprea, *J. Chem. Inf. Comput. Sci*. 2001, **41**, 1308; **3.** Perola, *J. Med. Chem*. 2010, **53**, 2986; **4.** Giordanetto, *DDT* 2011**,16**, 722**; 5.** Morphy, *J. Med. Chem.* 2006, **49**, 2969; **6.** Keseru, *NRDD* 2009, **8**, 203; **7.** Macarron, *NRDD* 2011, **10**, 188; **8.** Leeson, *NRDD* 2011, **10**, 749; **9.** Ferenczy *J. Med. Chem.* 2013, **56**, 2478; **10.** Hopkins, *NRDD,* 2014, **13**, 105

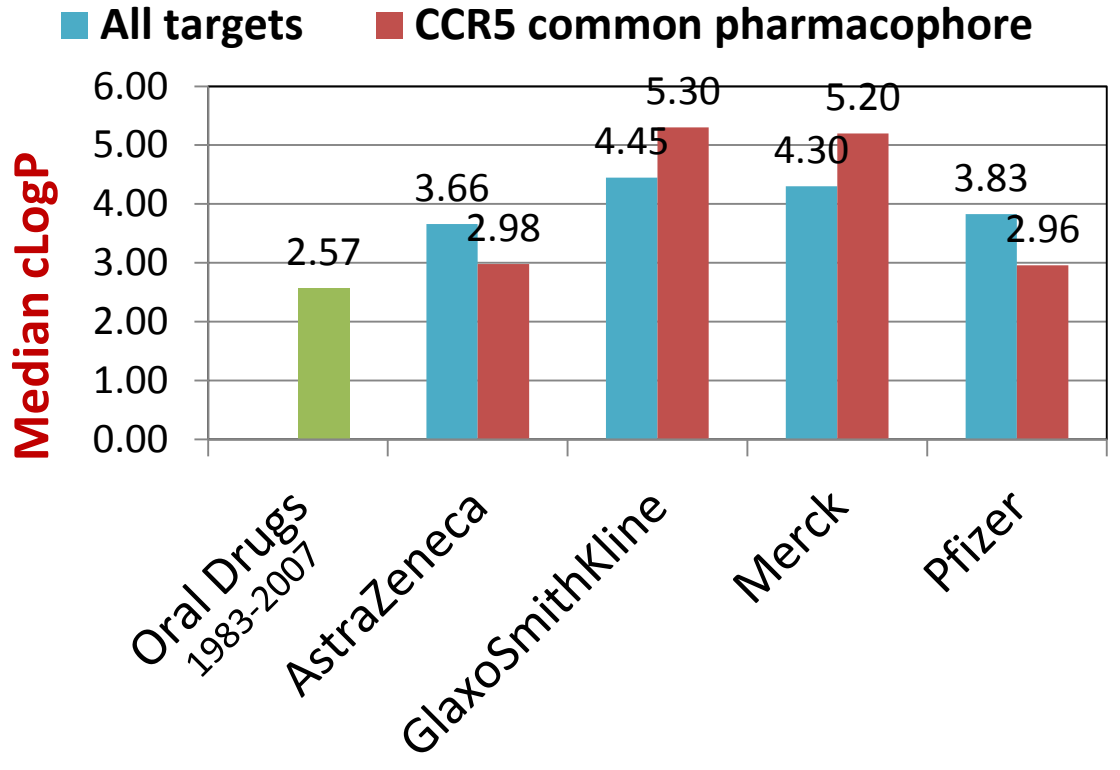
Divergent Company Design Practices

eg CCR5 Antagonists with a Common Pharmacophore



Phenylpropyl-piperidine

CCR5 antagonist pharmacophore pursued by all 4 Companies: AstraZeneca & Pfizer reached the clinic

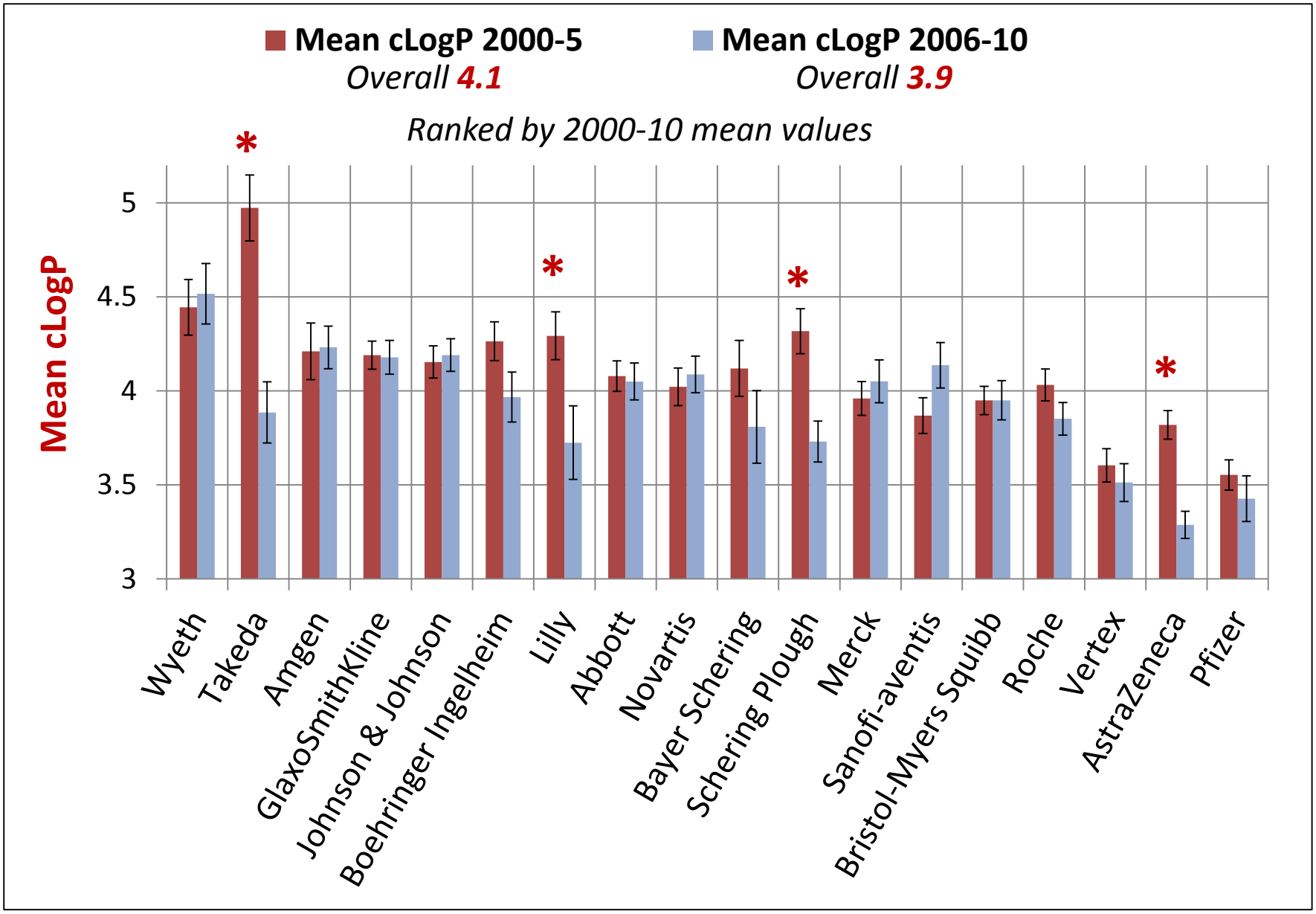


WO Patents 2001-6. *Source:* GVK BIO db

- **Company differences: comparable to target class differences**
- **Companies' design strategies: powerful impact of culture, history, experience, expertise; slow to change**

Leeson & Springthorpe, *Nat. Rev. Drug Disc.* 2007, **6**, 881;
18 Company target-unbiased 2000-11 analysis: Leeson & St-Gallay, *Nat. Rev. Drug Disc.* 2011, **10,** 749

Some Companies are Changing, Many are Not



Leeson & St-Gallay, *Nat. Rev. Drug Disc.* 2011, **10,** 749

Some Causes of Molecular Inflation

- **Increasing potency as the primary goal**
  - Often leads to increased cLogP & Mol Wt in a series
  - Medicinal 'obsession'?
- **Misinterpreting the 'rule of 5'**
  - Ro5 uses 90 percentile values
  - cLogP 4.5-5 + Mol Wt 450-500 is Ro5 compliant, *but occurs in only **1%** of oral drugs*
- **Hit selection**
  - Hit validation / selection is a critical step
  - Mean literature HTS hit: pAct 6.1 & **cLogP 3.7**
- **Synthetic feasibility**
  - Parallel chemistry mostly adds Mol Wt
  - Complex molecules & 'difficult' chemistry sometimes avoided?

Potency: Hann, *MedChemComm.* 2011, **2**, 349; **HTS hit selection:** Keserű & Makara, *Nat. Rev. Drug Disc.* 2009, **8**, 203; Dahlin & Walters, *Future Med. Chem.* 2014, 6, 1265; **Synthetic pragmatism:** Keserű et al, *Chem. Soc. Rev.*, 2014, **43**, 5387; **PPI**: Kuenemann et al, *J. Chem. Inf. Model.* 2014, **54**, 3067; **Company practice:** Leeson & St-Gallay, *Nat. Rev. Drug Disc.* 2011, **10,** 749; **Chemist behaviour**: Kutchukian, et al, *PLoS ONE*, 2012, **7**, e48476; **MPO:** Wager et al, *J. Med. Chem.* 2013, **56**, 9771

Some Causes of Molecular Inflation, contd.

- **Increase in less 'druggable' targets**
  - 'Low-hanging fruit' at the centre of drug-like space has been picked?
  - New, tougher targets – eg protein-protein interactions with large hydrophobic interfaces?
- **Disease risk/benefit**
  - Increased acceptance of safety risk & dosing inconvenience
- **Divergent design practices**
  - Search for new intellectual property; most targets are pursued by >1 organisation
  - Multiparameter optimisation used? Influence on medicinal chemists' decisions from **computational & ADMET** scientists?
- **It does not matter**
  - 'There are already highly lipophilic drugs on the market'

Potency: Hann, *MedChemComm.* 2011, **2**, 349; **HTS hit selection:** Keserű & Makara, *Nat. Rev. Drug Disc.* 2009, **8**, 203; Dahlin & Walters, *Future Med. Chem.* 2014, 6, 1265; **Synthetic pragmatism:** Keserű et al, *Chem. Soc. Rev.*, 2014, **43**, 5387; **PPI**: Kuenemann et al, *J. Chem. Inf. Model.* 2014, **54**, 3067; **Company practice:** Leeson & St-Gallay, *Nat. Rev. Drug Disc.* 2011, **10,** 749; **Chemist behaviour**: Kutchukian, et al, *PLoS ONE*, 2012, **7**, e48476; **MPO:** Wager et al, *J. Med. Chem.* 2013, **56**, 9771

Ligand Efficiency (LE) & Lipophilic LE (LLE or LipE)

'Bang for your buck' guidelines p(Activity) = pK_d, pK_i, pIC_{50}, pEC_{50}

LE = p(Activity)*1.37/HA

Units: kcal/mol/heavy atom

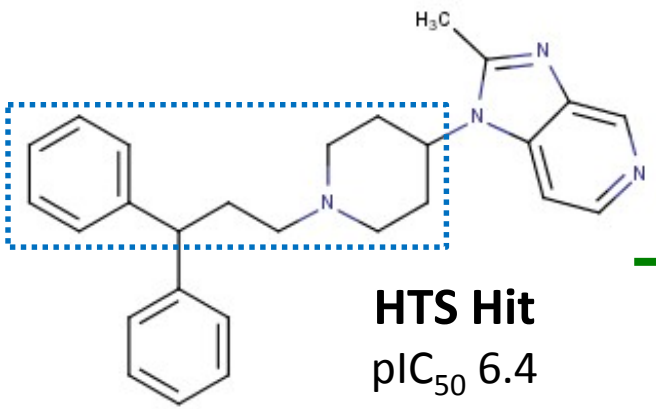
Mean oral drug LE = 0.45

LLE = p(Activity) – LogP/D

$[Drug]_{Target} \overset{k_d}{\rightleftharpoons} [Drug]_{Water} \overset{P\ or\ D}{\rightleftharpoons} [Drug]_{1\text{-}Octanol}$

Mean oral drug LLE (cLogP) = 4.4

Pfizer CCR5 Receptor Antagonist Optimisation



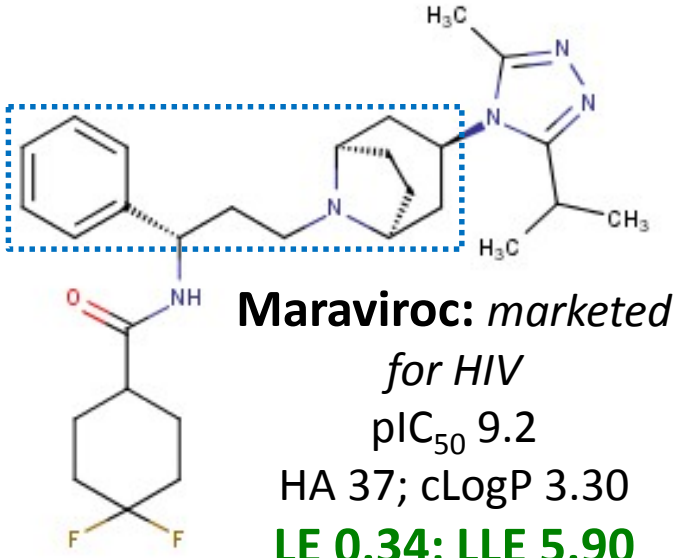
HTS Hit

pIC_{50} 6.4

HA 31; cLogP 4.56

LE 0.28; LLE 1.84

Δ LLE 4.1



Maraviroc: *marketed for HIV*

pIC_{50} 9.2

HA 37; cLogP 3.30

LE 0.34; LLE 5.90

Employed LE; issues addressed: **antiviral activity, P450 & hERG inhibition, permeability**

Wood & Armour, *Prog. Med. Chem.* 2005, **43**, 239; Price et al, *Bioorg. Med Chem Lett* 2006, **16**, 4633; Armour et al, *ChemMedChem* 2006, **1**, 706

Drug data (n=261) calcd. from: Gleeson et al. *Nat. Revs. Drug Disc.* 2011, **10**, 197; **LE:** Hopkins et al, *Drug Disc. Today* 2004 **9**, 430; **LLE**: Leeson & Springthorpe, *Nat. Rev. Drug Disc.* 2007, **6**, 881; **Review:** Hopkins et al, *Nat. Rev. Drug Disc.*, 2014, **13**, 105; **Debate:** Shultz, *ACS Med. Chem. Lett.* 2014, **5**, 2; Murray et al, *ACS Med. Chem. Lett.* 2014, **5**, 616; Kenny et al, *J. Comput. Aided Mol. Des* 2014, **28**, 699

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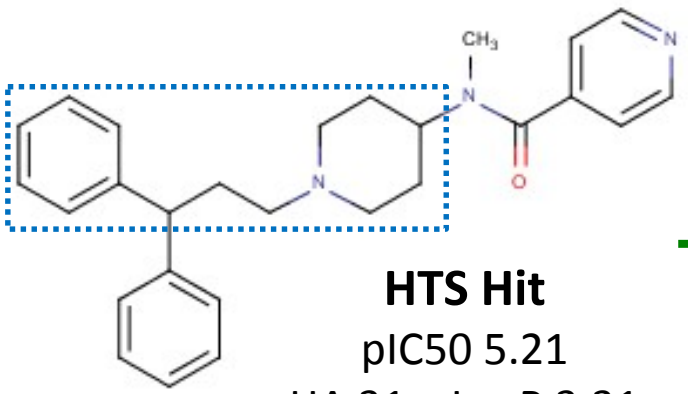
AstraZeneca CCR5 Receptor Antagonist Optimisation



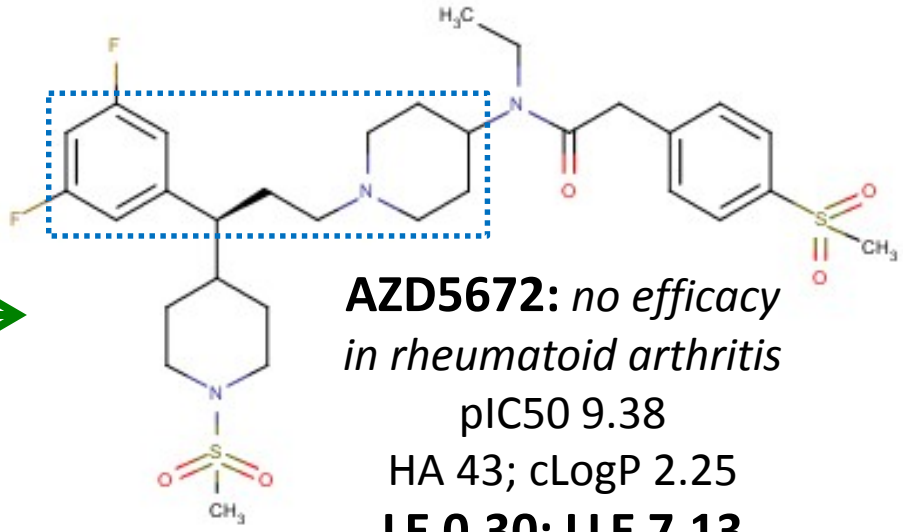
HTS Hit

pIC50 5.21

HA 31; cLogP 3.31

LE 0.23; LLE 1.90

Δ LLE 5.2



AZD5672: *no efficacy in rheumatoid arthritis*

pIC50 9.38

HA 43; cLogP 2.25

LE 0.30; LLE 7.13

Issues addressed: **affinity, hERG inhibition, absorption**

Cumming et al, *Bioorg. Med. Chem. Lett.* 2012, **22**, 1655; 2005, **15**, 5012; 2006, **16**, 3533

Drug data (n=261) calcd. from: Gleeson et al. *Nat. Revs. Drug Disc.* 2011, **10**, 197; **LE:** Hopkins et al, *Drug Disc. Today* 2004 **9**, 430; **LLE**: Leeson & Springthorpe, *Nat. Rev. Drug Disc.* 2007, **6**, 881; **Review:** Hopkins et al, *Nat. Rev. Drug Disc.*, 2014, **13**, 105; **Debate:** Shultz, *ACS Med. Chem. Lett.* 2014, **5**, 2; Murray et al, *ACS Med. Chem. Lett.* 2014, **5**, 616; Kenny et al, *J. Comput. Aided Mol. Des* 2014, **28**, 699

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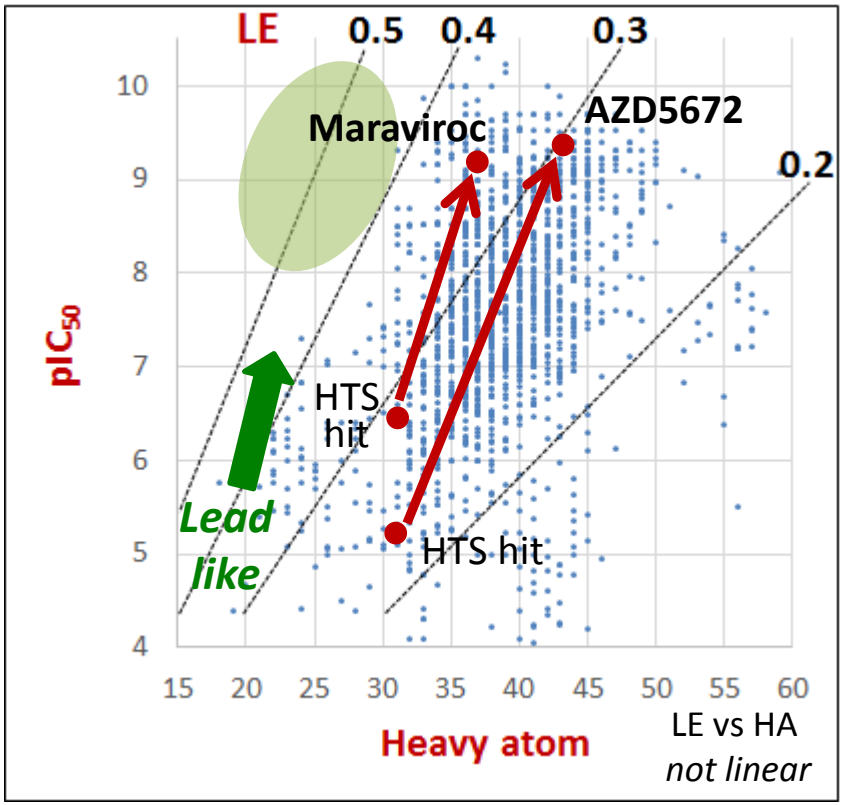
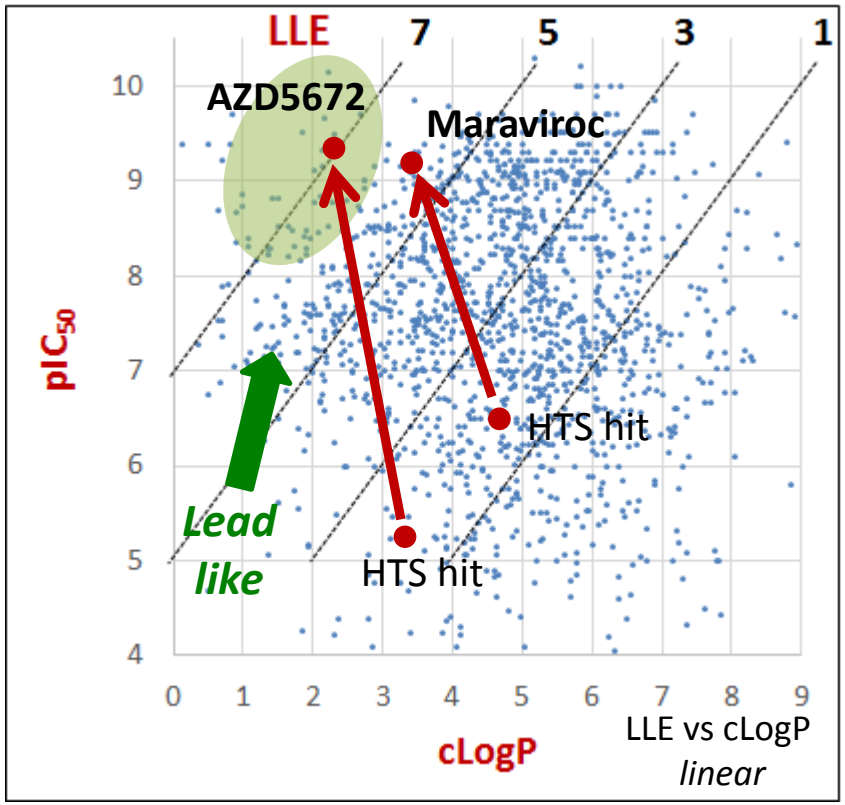
CCR5 Receptor Ligands: pIC_{50} values ex CHEMBL (n=1513)





Drug data (n=261) calcd. from: Gleeson et al. *Nat. Revs. Drug Disc.* 2011, **10**, 197; **LE:** Hopkins et al, *Drug Disc. Today* 2004 **9**, 430; **LLE**: Leeson & Springthorpe, *Nat. Rev. Drug Disc.* 2007, **6**, 881; **Review:** Hopkins et al, *Nat. Rev. Drug Disc.*, 2014, **13**, 105; **Debate:** Shultz, *ACS Med. Chem. Lett.* 2014, **5**, 2; Murray et al, *ACS Med. Chem. Lett.* 2014, **5**, 616; Kenny et al, *J. Comput. Aided Mol. Des* 2014, **28**, 699

Ligand Efficiency (LE) & Lipophilic LE (LLE or LipE)

'Bang for your buck' guidelines p(Activity) = pK_d, pK_i, pIC_{50}, pEC_{50}

LE = p(Activity)*1.37/HA

Units: kcal/mol/heavy atom

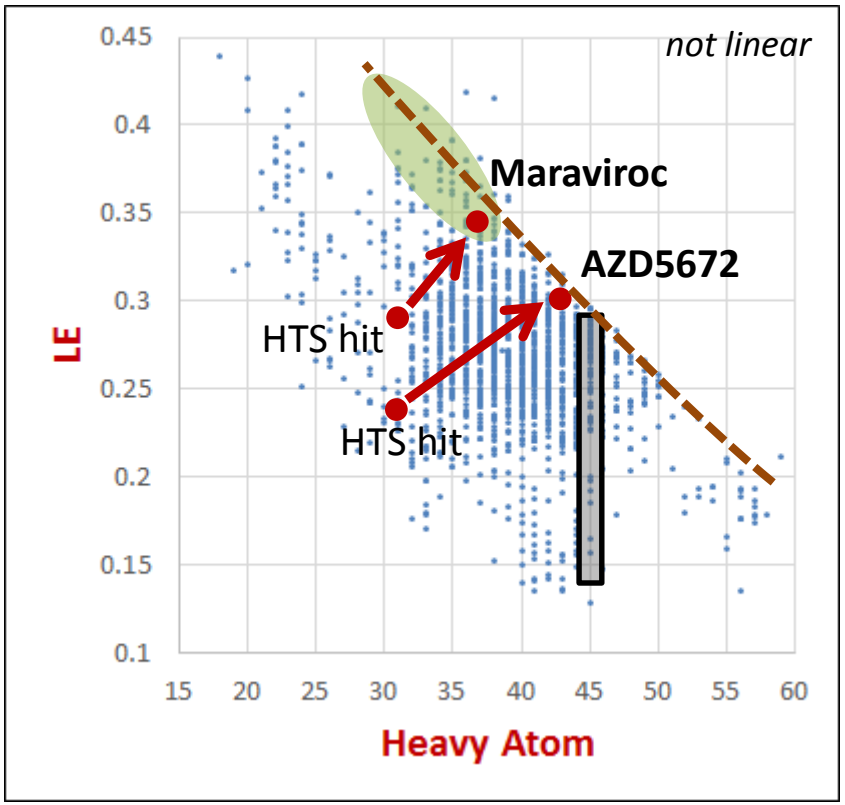
Mean oral drug LE = 0.45

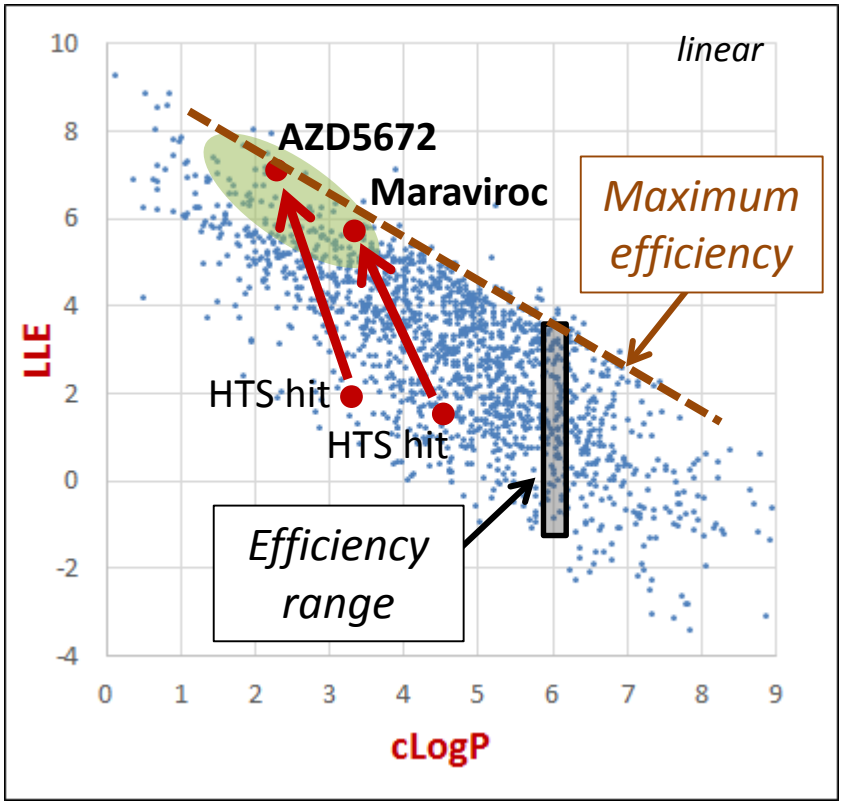
LLE = p(Activity) – LogP/D

$[Drug]_{Target} \overset{k_d}{\rightleftharpoons} [Drug]_{Water} \overset{P\ or\ D}{\rightleftharpoons} [Drug]_{1\text{-}Octanol}$

Mean oral drug LLE (cLogP) = 4.4

CCR5 Receptor Ligands: pIC_{50} values ex CHEMBL (n=1513)





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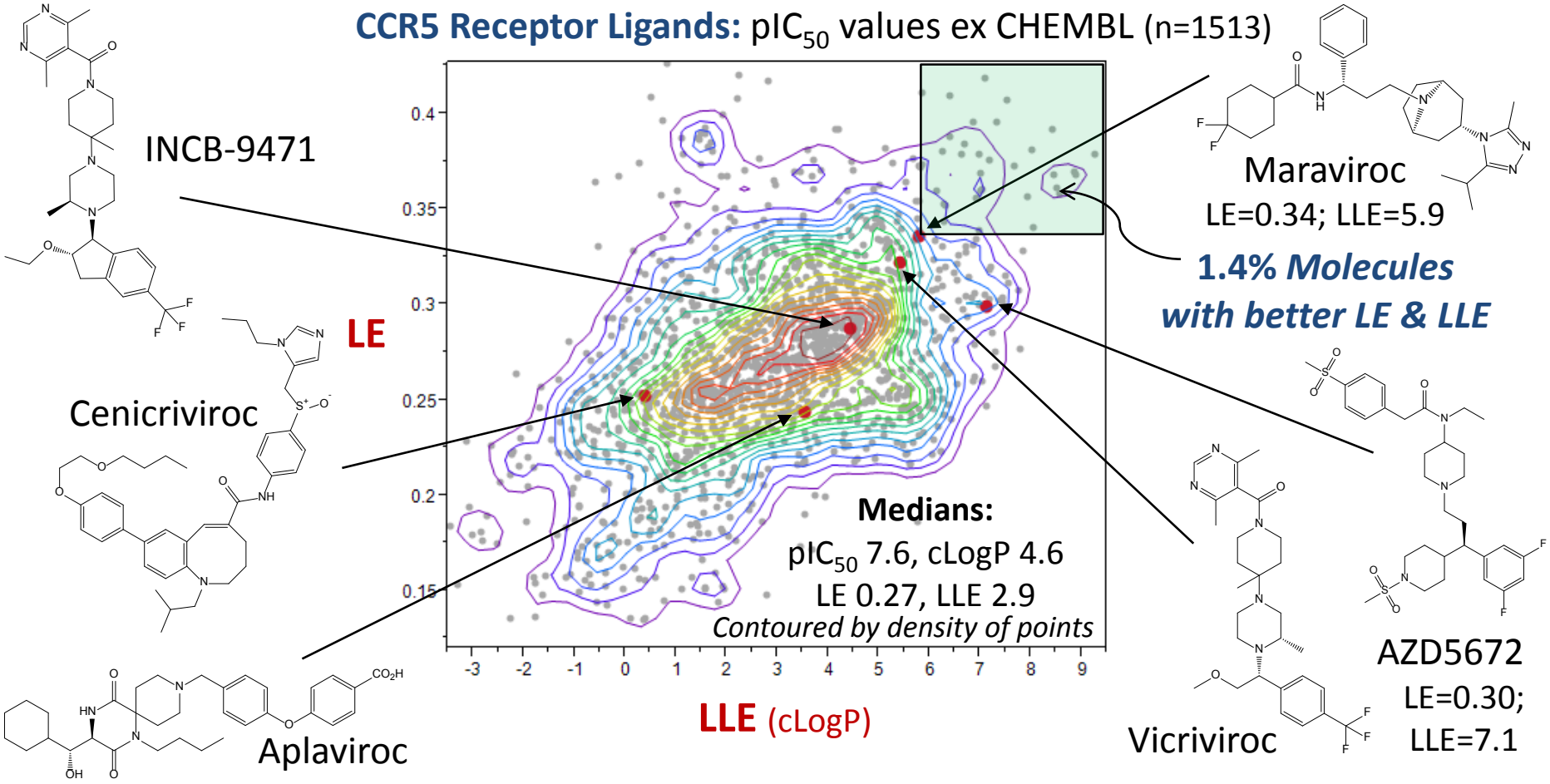
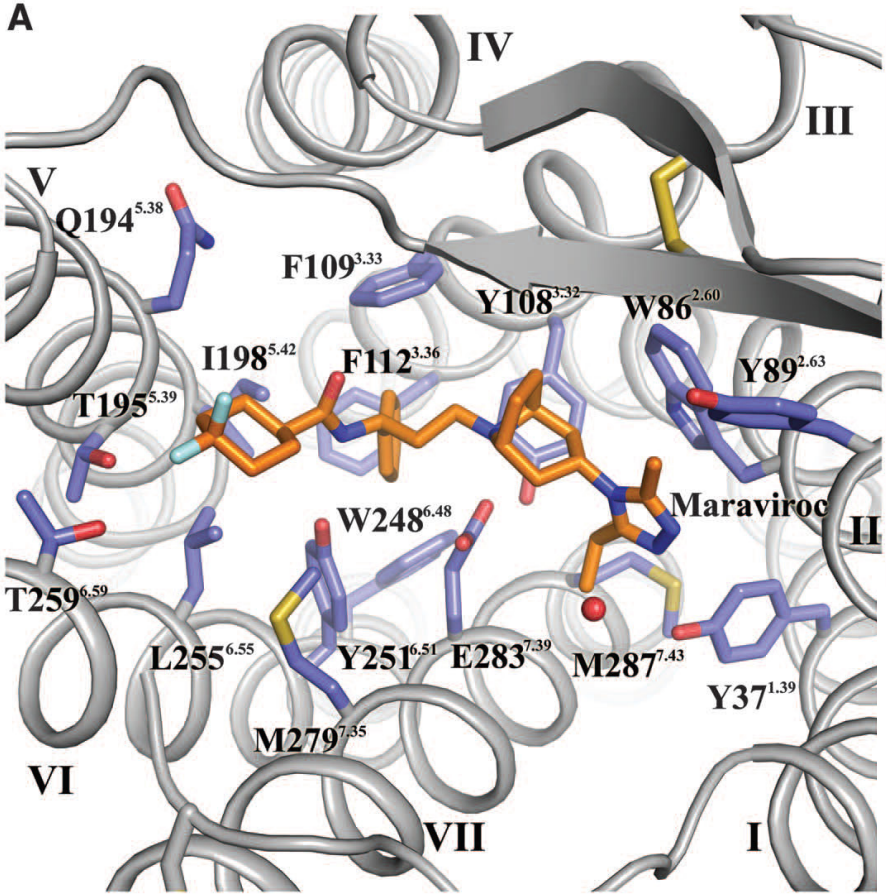
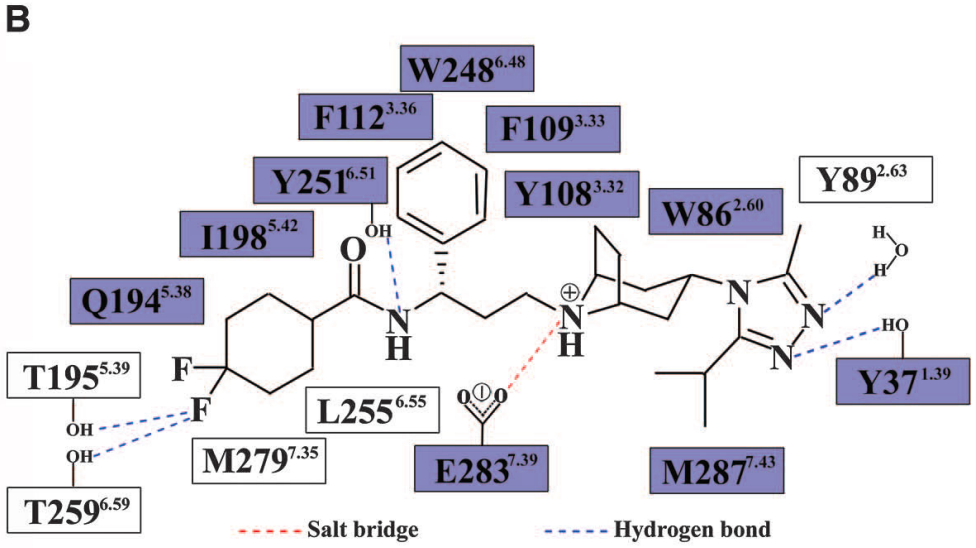


Review: Hopkins et al, *Nat. Rev. Drug Disc.*, 2014, **13**, 105

Structure of Maraviroc Bound to CCR5





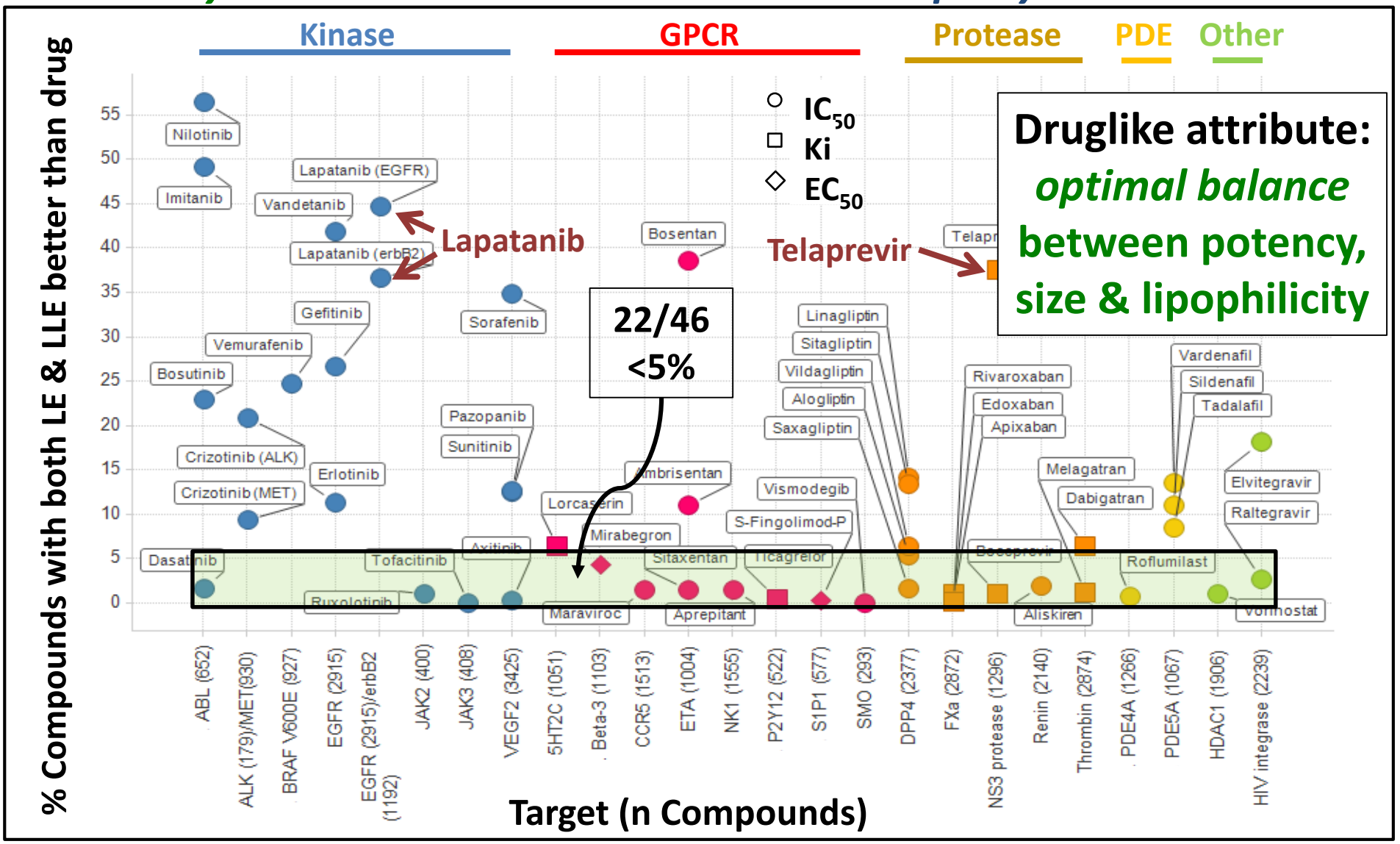
Maraviroc dissociation:
$t_{1/2}$ 6.4hrs

- **Efficient use of H-bonding atoms**
  - **7 Polar atoms make 6 polar interactions: enthalpy ↑**
- **Efficient local hydrophobic interactions**
  - **Phenyl, isopropyl, tropane & cyclohexyl binding pockets**

Tan et al, *Science*, 2013, **341**, 1387; **Polar contact review:** Higueruelo et al, *PLoS ONE* 2012, 7(12): e51742; **Kinetics**: Swinney et al *Br. J. Pharmacol*. 2014, **171,** 3364

Oral Drug Ligand Efficiencies: 46 Drugs, 25 Targets

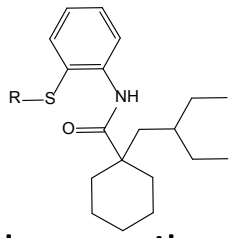
% LE + LLE better vs drug: kinases 22%; other targets 2.7%; only in class 1.5%. LE & LLE contribute equally to % score



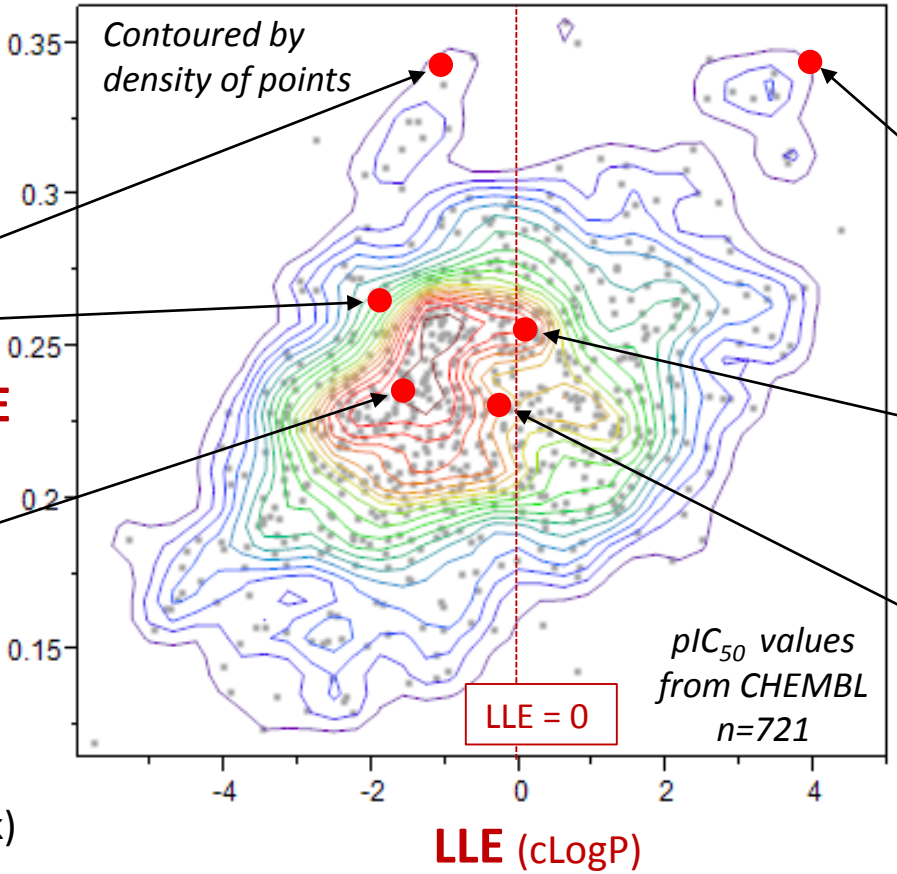
Hopkins et al, *Nat. Rev. Drug Disc.*, 2014, **13**, 105

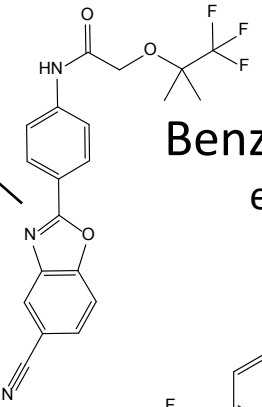
CETP: A High Value 'Lipophilic' Target

Medians: pIC_{50} 6.7; LLE -0.9 & LE 0.23

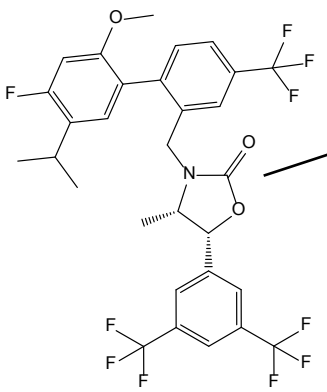


Dalcetrapib (Roche)
Metabolite, R=H
R = COiPr

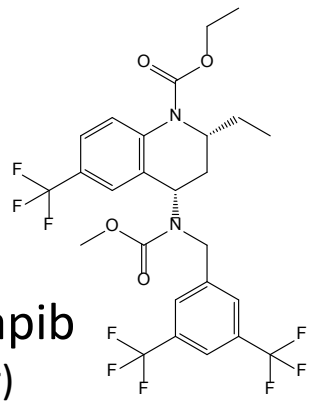




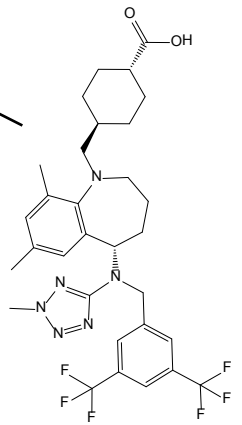
Benzoxazoles
ex HTS



Anacetrapib (Merck)



Torcetrapib
(Pfizer)



Evacetrapib
(Lilly)

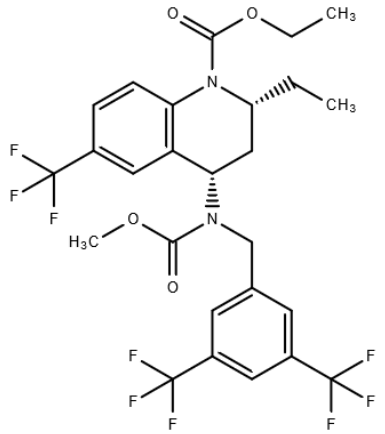
- 4 Phase III clinical candidates have **LLE ≤ 0**
- Torcetrapib (b.p. ↑) & dalceptrapib (efficacy) discontinued
- Anacetrapib: levels are ~40% of treatment after 12 weeks; detectable in plasma four years after last dose

LE & LLE data: Hopkins et al, *Nat. Rev. Drug Disc.*, 2014, **13**, 105; **CETP review:** Mantlo & Escribano. *J. Med. Chem.* 2014, **57**, 1; **Anacetrapib:** Gotto et al, *Am. J. Cardiol.* 2014, **113**, 76; **Benzoxazole**s, eg *Bioorg. Med. Chem. Lett*. 2010, **20**, 1019

CETP: Designing Less Lipophilic Inhibitors

C → N & O, hydrophilic substituents, control HA

Fernandez et al (Lilly), *Bioorg. Med. Chem. Lett*. 2012, **22**, 3056



Torcetrapib (Pfizer) pIC_{50} 7.7

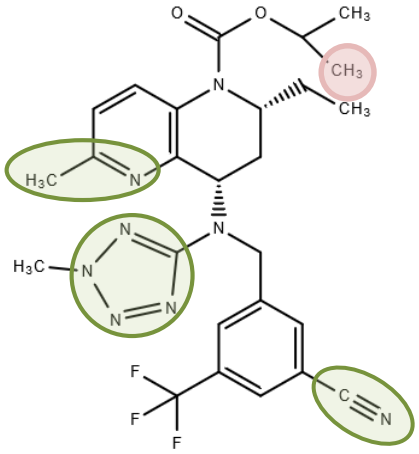
cLogP 7.6; HA 41; **LLE 0.1; LE 0.26**

'Mitigate lipophilicity'

LogP values not cited

Δ LLE = 3.8

Δ LE = 0.01

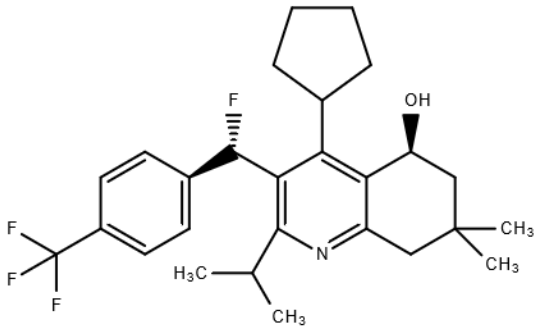


Lilly lead pIC_{50} 7.7

cLogP 3.8; HA 39; **LLE 3.9 LE 0.27**

LE + LLE % better **1.4%**

Trieselmann et al (BI), *J. Med. Chem.* 2014, **57**, 8766



BI hit pIC_{50} 6.6

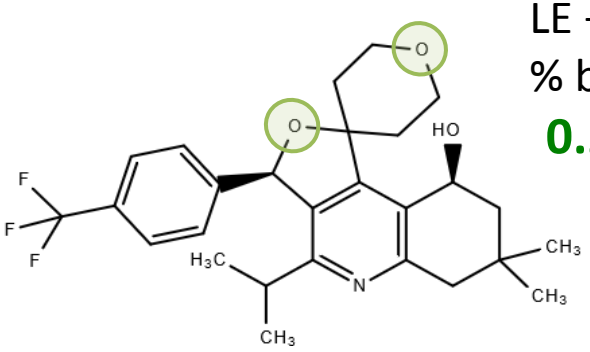
cLogP 7.6; HA 33; **LLE -1.0; LE 0.27**

'Reduce lipophilicity'

LogP values tracked

Δ LLE = 4.1

Δ LE = 0.04



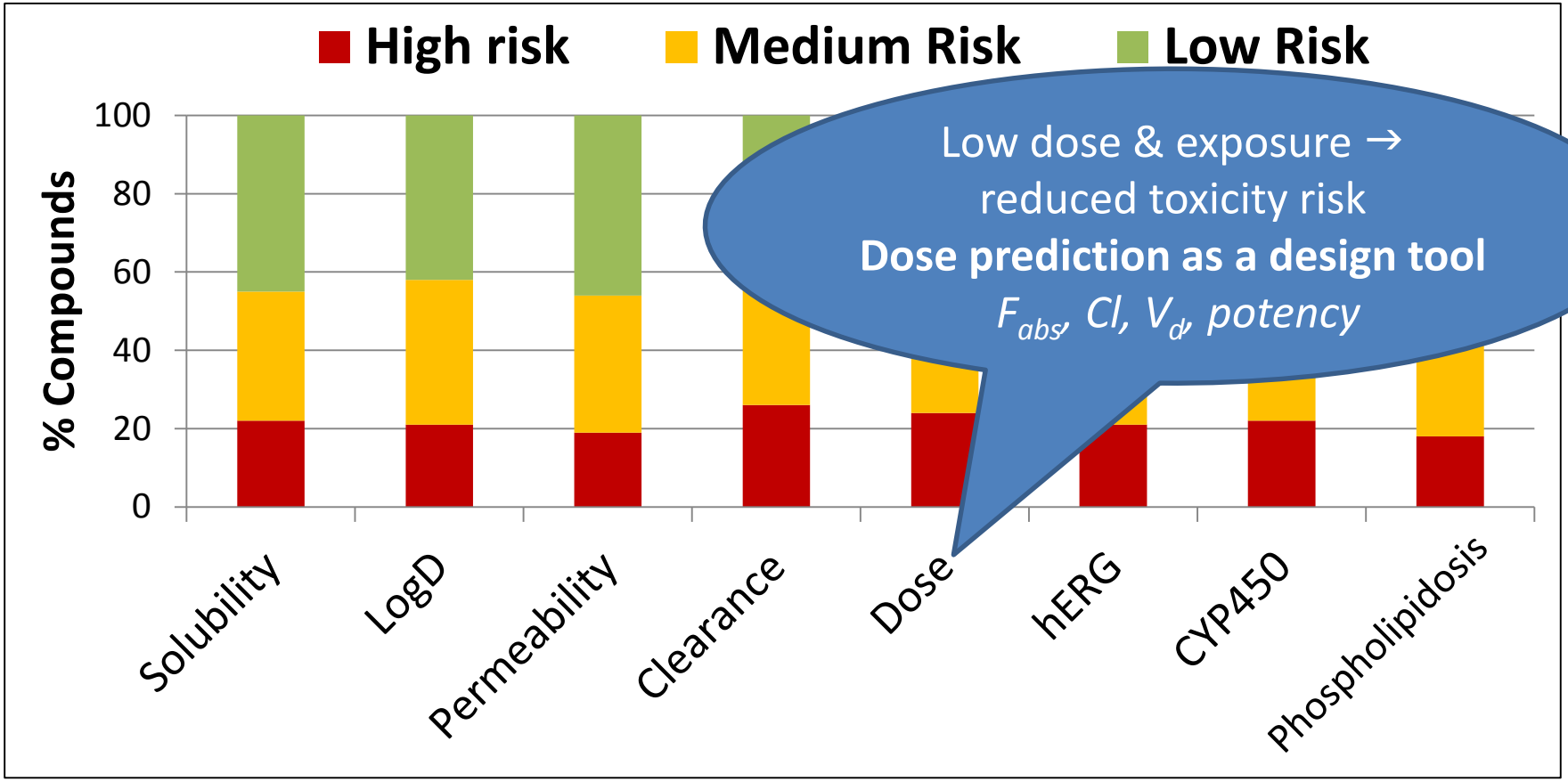
BI lead pIC_{50} 7.7

cLogP 4.6; HA 34; **LLE 3.1; LE 0.31**

LE + LLE % better **0.28%**

Controlling Risk: Compound Quality Guidance

Global & project predictive ADMET models: use pre-synthesis



- **If prediction is poor, why synthesise?**
- Using predictive models, AZ improved candidate drug **solubility**
- **'Virtual medicinal chemist' – Σ tools using existing knowledge**

Predictive chemistry: Cumming et al, *Nat. Rev. Drug Disc.* 2013, **12**, 948; **Dose prediction:** Grime et al, *Mol. Pharmaceutics*, **2013**, *10*, 1191; **Multi parameter opt'n:** Segall, *Curr. Pharm. Des.*, 2012, **19**, 1292; **Matched pairs:** Dossetter et al, *Drug Disc. Today* 2013, **18**, 724; **Automated design**: Besnard et al, *Nature*, 2012, **492**, 215

Designing Better Compounds

- Conduct multi parameter biology/ADMET optimisation
- Engage computational chemists & ADMET experts in design decision-making
- Seek leadlike starting points. Drop unpromising series; have back-up hit & lead generation plans
- Control physicochemical properties, especially lipophilicity; optimise ligand efficiencies & solubility
- Employ advanced computational chemistry tools; don't make compounds with poor predicted properties
- Reduce reliance on 'easy' synthesis & catalogue building blocks
- Learn constantly from past experience, avoid bias, consult others, challenge dogma
- **Never compromise on candidate compound quality**
- ***…and persist***

Acknowledgements

GlaxoSmithKline

Martin Bayliss
James Butler
Paul Feldman
Darren Green
Mike Hann
Alan Hill
Mike Palovich
Anthony Taylor
Rob Young
GSK Chemistry Council
GSK Scientists

AstraZeneca

Andy Davis
John Dixon
David Payling
Jan-Erik Nyström
Brian Springthorpe
Steve St-Gallay
Simon Teague
Mark Wenlock
AZ Global Chemistry Forum
AZ Scientists
CXCR2 team

Academia & Industry

Paul Gleeson
Andrew Hopkins
György Keserű
Tudor Oprea
David Rees
Chuck Reynolds

'Minimal hydrophobicity' in drug design. "Without convincing evidence to the contrary, drugs should be made as hydrophilic as possible without loss of efficacy."

C. Hansch, J.P. Björkroth & A. Leo, *J. Pharm. Sci.* 1987, **76**, 663-687