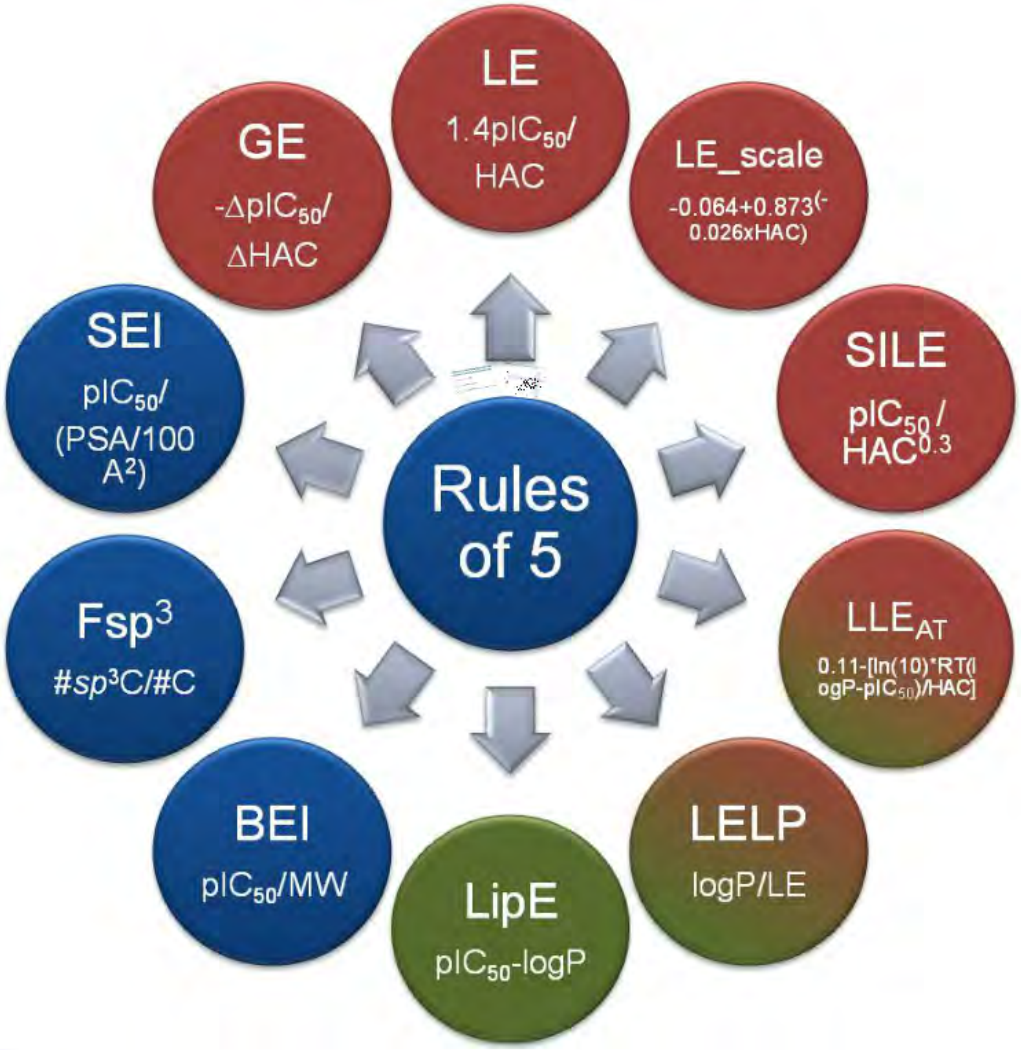
Improving the plausibility of success in drug discovery with inefficient metrics



Michael Shultz
19-March-2015

NOVARTIS

Which one of the following is the most probable description of an oral drug?

A. IC50 > 10,000 nM

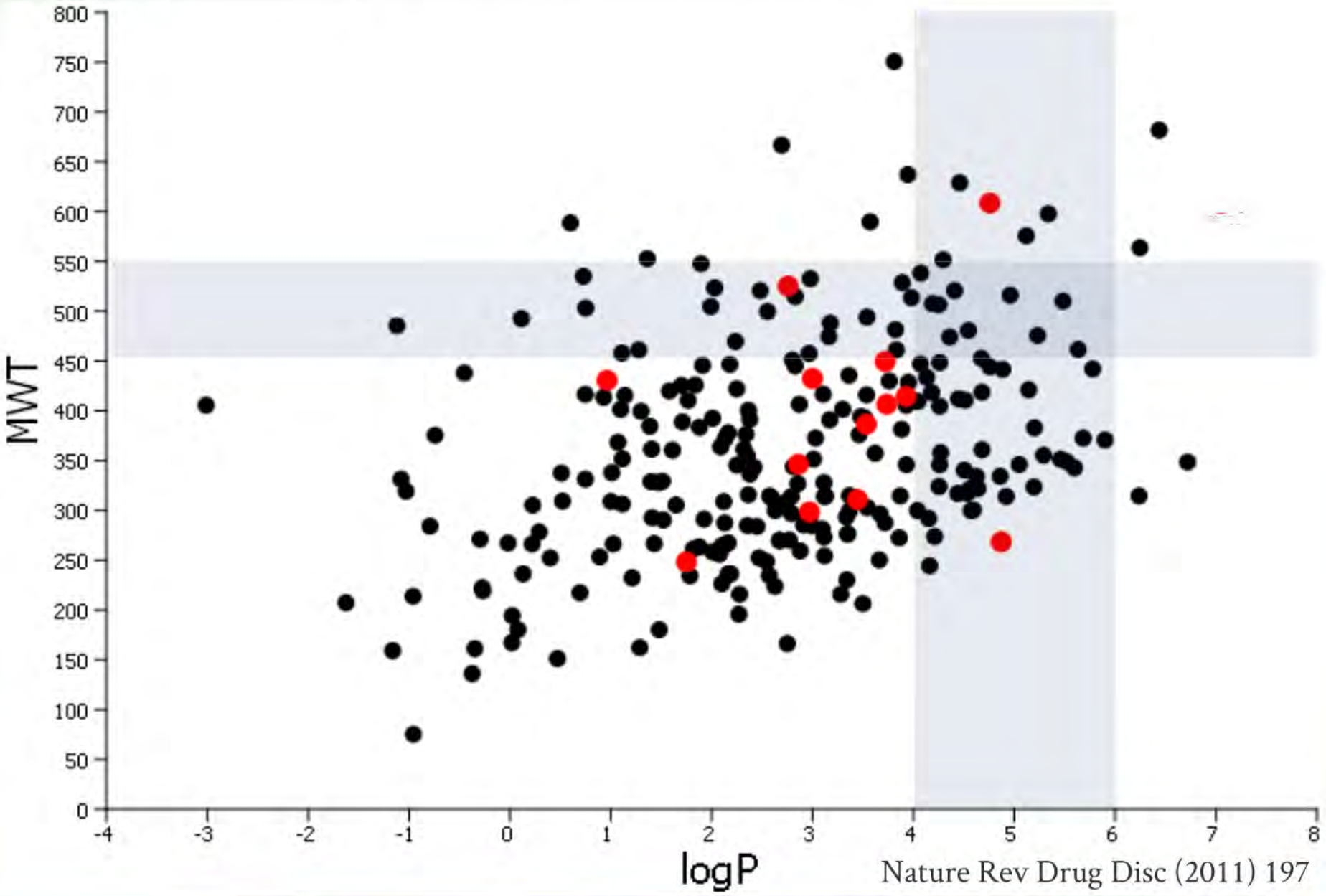
B. IC50 < 1 nM, clogP >4

C. IC50 0.1-1nM, MW 450-550, clogP 4.0 – 6.0

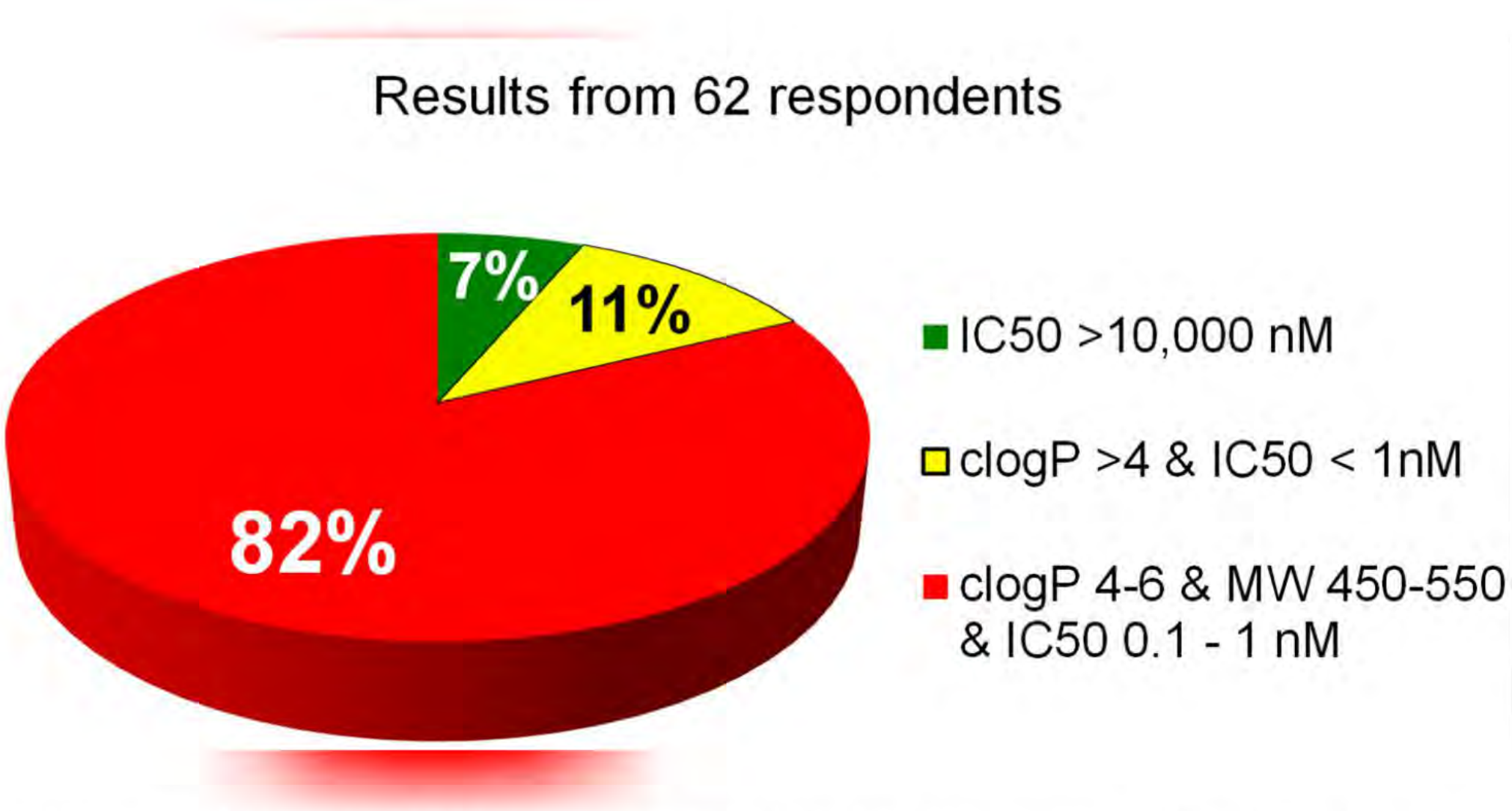
Oral Drugs

>10,000nM > clogP >4 + IC50<1nM > clogP 4-6 + MW 450-550 + IC50 0.1 -1nM

24 > 5 > 0



Nature Rev Drug Disc (2011) 197

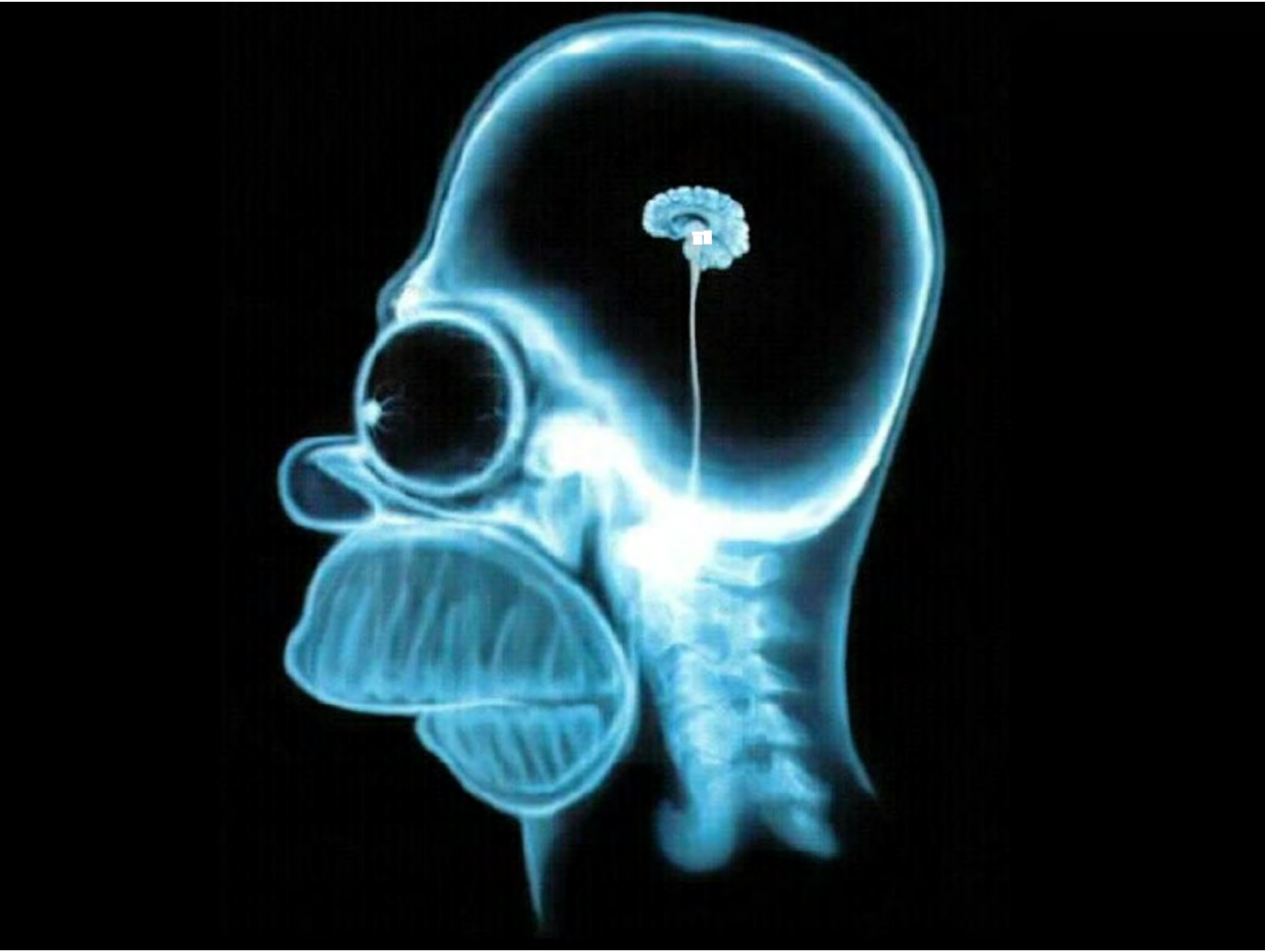


Attribute Substitution: Unconscious substitution of a more difficult problem with an easier problem

Probability: Hard

Plausibility: Easy

Kahneman (2011) Thinking, fast and slow



Confusing Probability with Plausibility?

Medicinal chemistry matters – a call for discipline in our discipline

Craig Johnstone, cjohnstone@rapier-research.co.uk

Drug Discovery Today • Volume 17, Numbers 11/12 • June 2012

FIGURE 2

Optimisation paths across LE and LLE space. The figure shows optimisation paths from different chemical spaces, which are typified by the hit-finding method. The suggested destination, high probability space (HPS), is a combination of good potency and high probability lipophilicity [7,17,18].

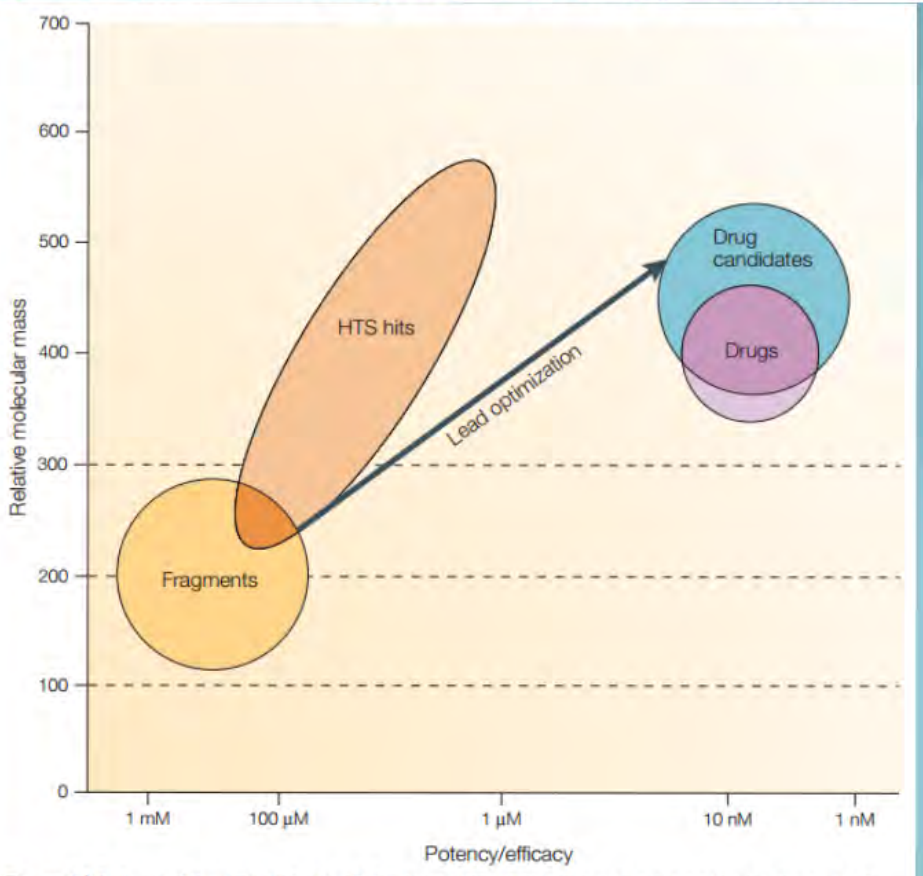
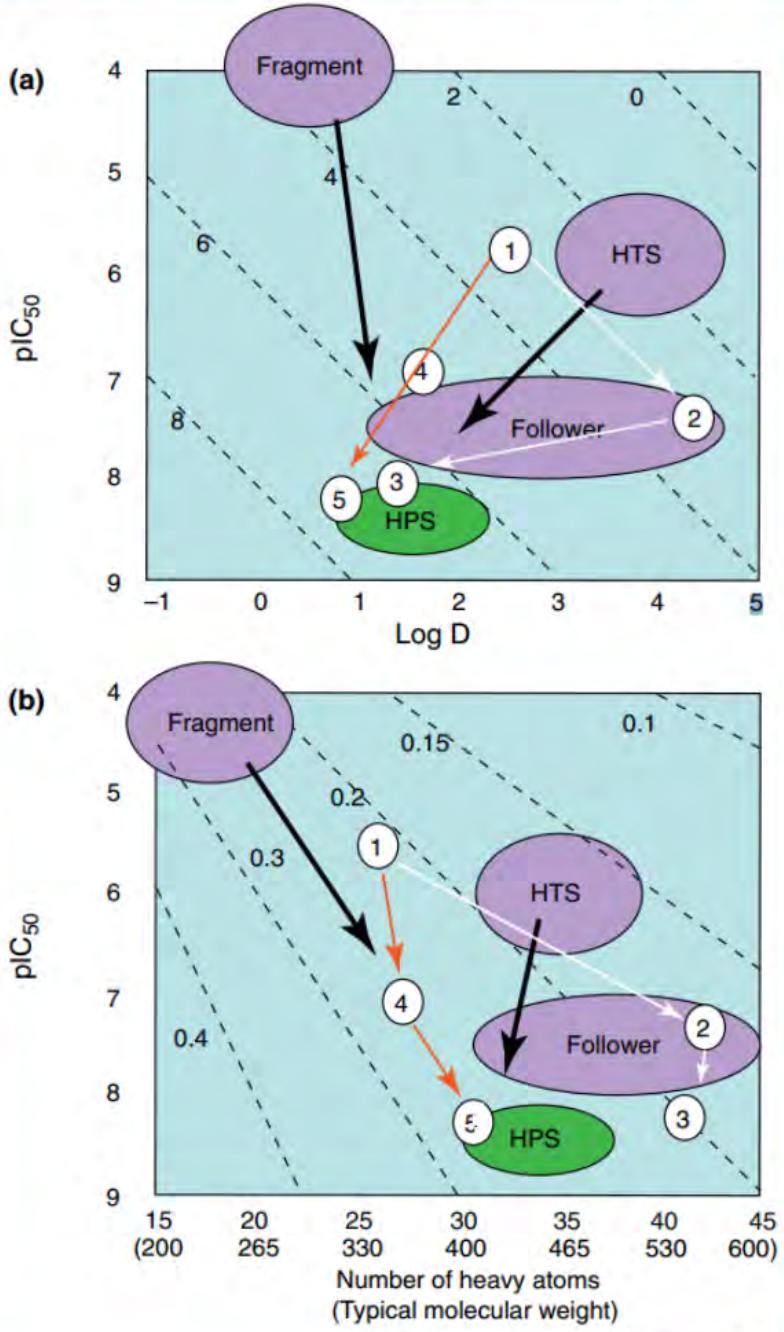
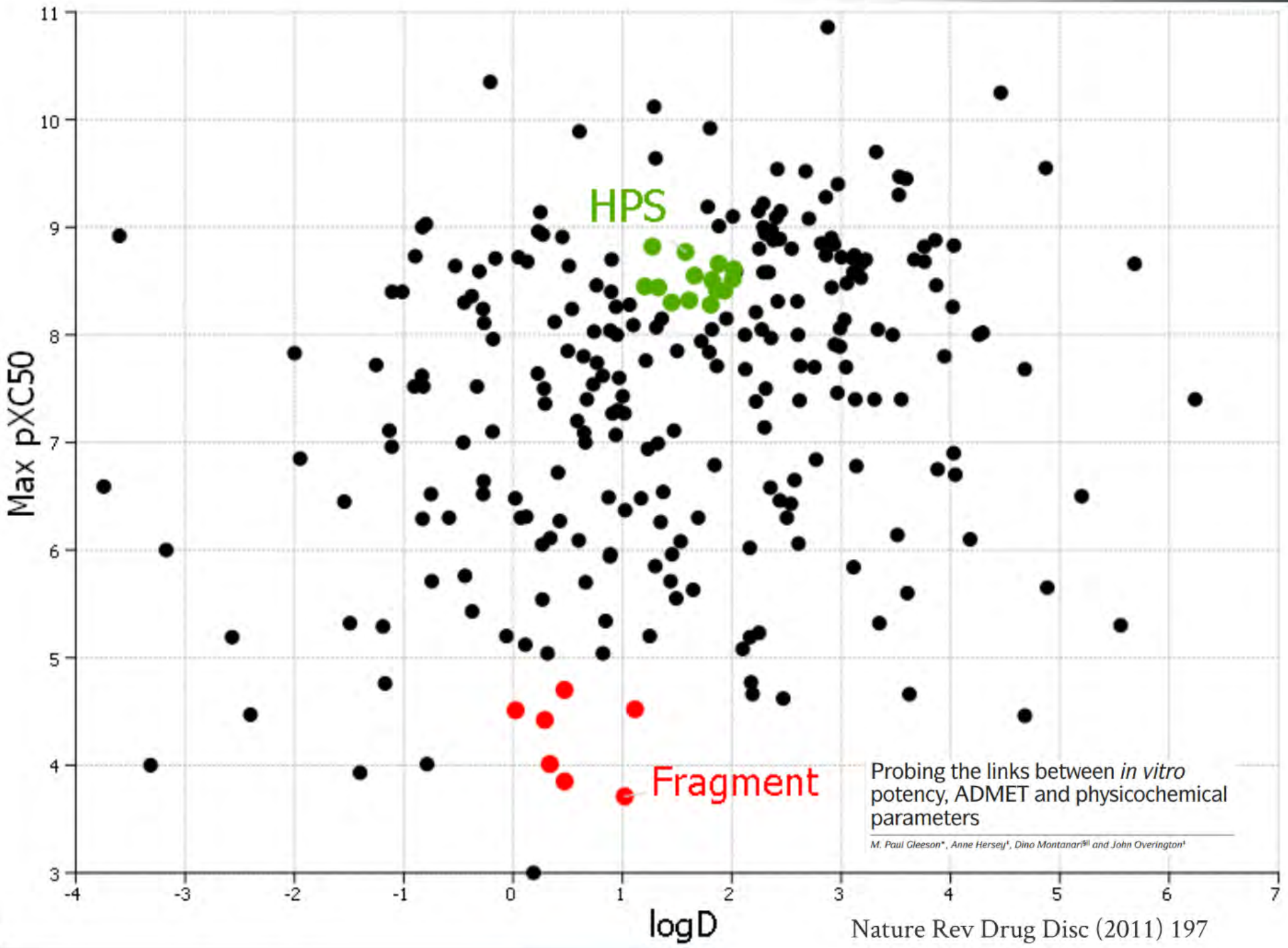


Figure 2 | **Schematic comparison of the usual molecular mass and potency ranges of high-throughput screening hits with fragments as starting points for lead identification and drug discovery.** The figure shows graphically a broad generalization of the range of molecular

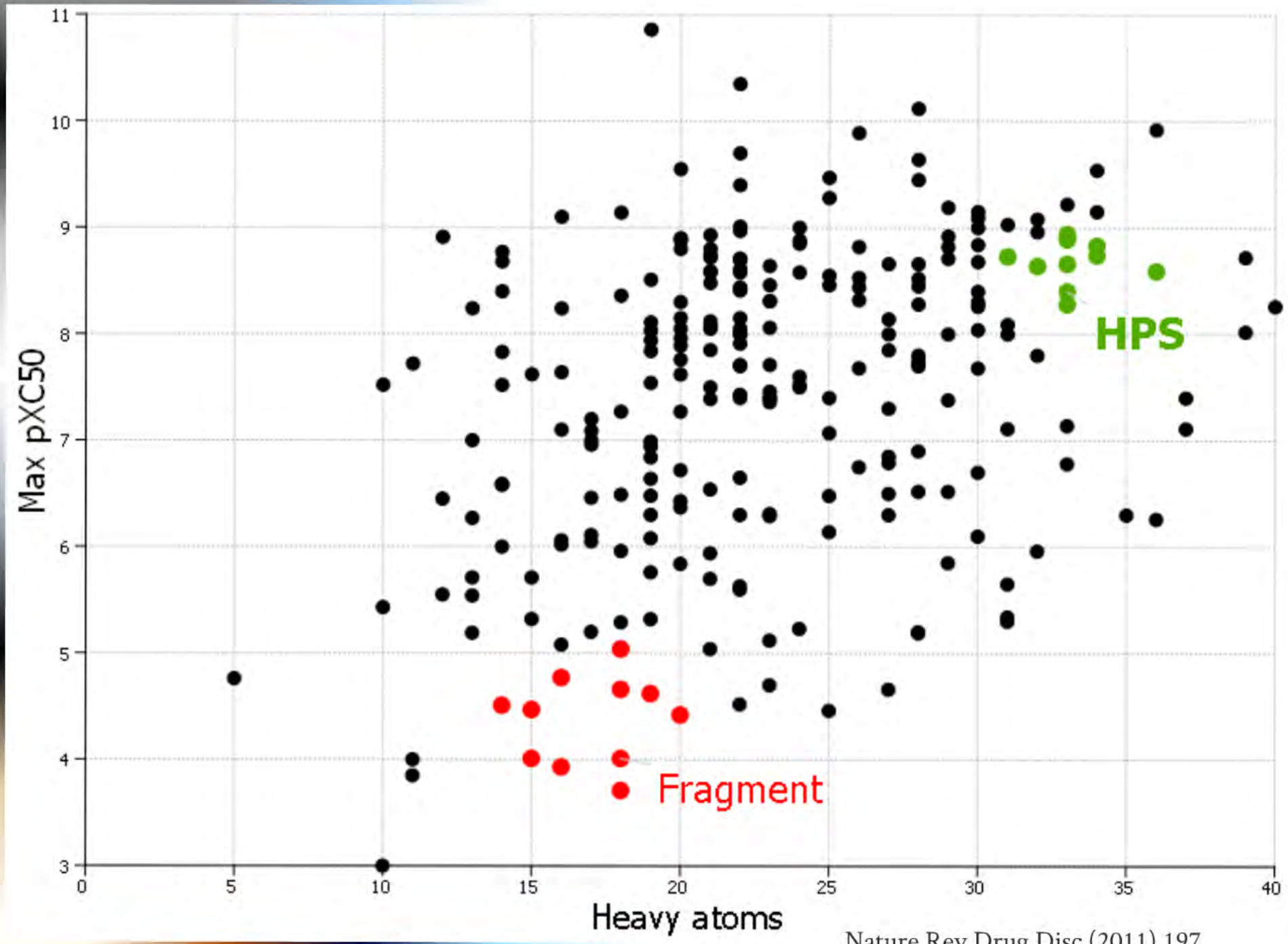




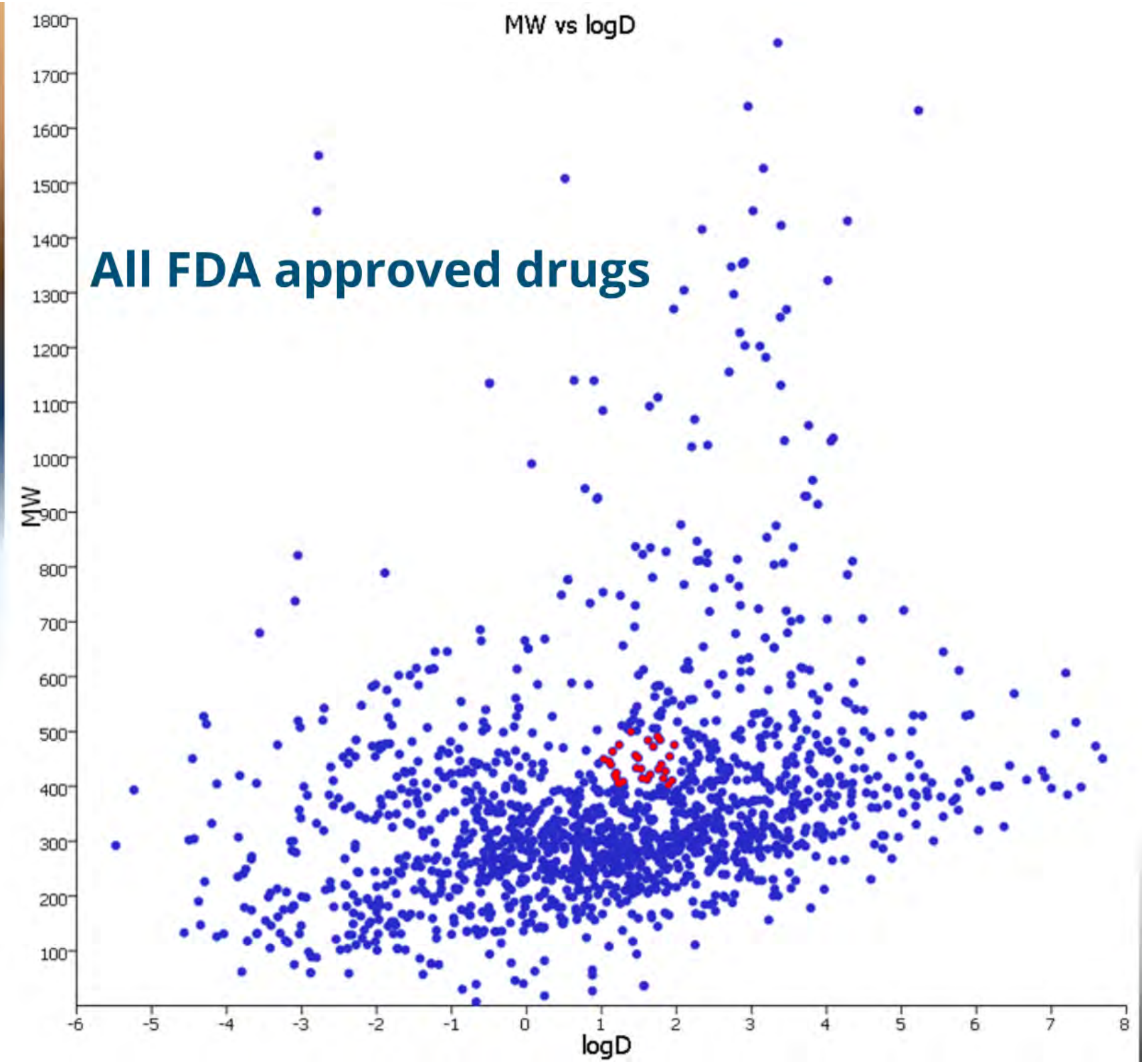
Probing the links between *in vitro* potency, ADMET and physicochemical parameters

M. Paul Gleeson*, Anne Hersey†, Dino Montanari‖ and John Overington†

Nature Rev Drug Disc (2011) 197

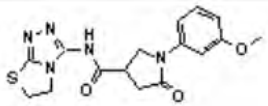
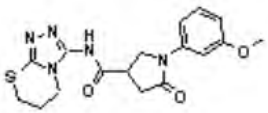
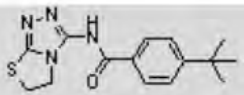
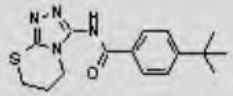
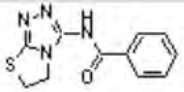
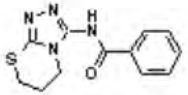
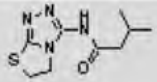
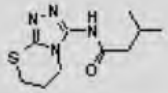


Nature Rev Drug Disc (2011) 197

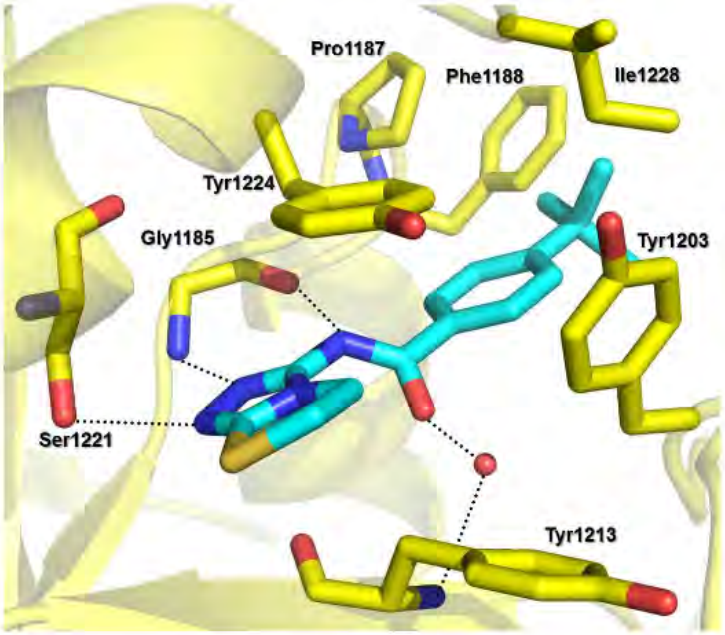


All FDA approved drugs

Why are some efficiency metrics inconsistent?

Structure	clogP	TNKS2				ΔLipE	ΔLE	ΔLELP
		IC_{50} (μM)	LipE	LE	LELP			
	1.8	0.630	4.4	0.33	5.5			
						1.1	0.05	-1.6
	2.0	4.71	3.3	0.28	7.1			
	3.1	0.031	4.3	0.50	6.2			
						1.1	0.09	-1.8
	3.3	0.353	3.2	0.41	8.0			
	1.3	0.250	5.3	0.54	2.4			
						1.2	0.11	-1.1
	1.5	2.76	4.1	0.43	3.5			
	1.3	0.103	5.7	0.66	2.0			
						1.1	0.13	-0.6
	1.4	0.980	4.6	0.53	2.6			

J. Med. Chem. (2013), 56, 7049



Each matched pair:

- ΔHAC = 1
- ΔclogP ~0.2
- ΔpIC_{50} ~1

LE = 1.4*pIC50/#HA
LELP = clogP/LE
LipE = pIC50 - clogP

Questions to invalidate efficiency metric hypotheses

	LE (SILE, FQ)	LELP (LLE_{AT})	LipE
Is it rational?	Can it be used for decision making? Normalizing potency versus property		
Is the equation valid?	Does the equation do what it's hypothesized to do? Test to see if equation normalizes potency for property		
Is the underlying assumption correct?	Relationship between the property, potency and ADMET		
Correlates with successful optimizations?	Separate possibility and plausibility from probability		

Bioorg. Med. Chem. Lett. (2013) 5980

The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Steve Carney, Editor, *Drug Discovery Today*, e-mail: S.Carney@elsevier.com

Ligand efficiency: a useful metric for lead selection

Potency is not the only consideration when selecting a lead compound for further optimization into a drug, but it does hold a powerful attraction to the medicinal chemist. As a general observation, during the process of optimizing a lead to a clinical candidate, the compound usually increases in molecular weight [1–4].

Indeed, potency within a chemical series is often strongly correlated with molecular weight (MW). Interestingly, Lipinski has observed an inexorable rise in molecular weight for both Pfizer (http://www.pfizer.com) and Merck (http://www.merck.com) clinical candidate compounds over the past 30 years [5] and this could represent a general industry trend following the introduction potency alone is often a false prophet. Indeed the screening parameters, reagent concentrations and false-positive filters make the detection of weak, low MW leads unlikely in the configuration of many high-throughput screens. The bias of the screen towards high MW compounds has often confounded further optimization because increases in potency often track increases in MW, resulting in compounds falling outside of the profile for acceptable absorption and permeability properties [3,9]. Thus, a simple 'ready reckoner', which could be used to assess the potential of a weak lead to be optimized into a potent, orally bio-available clinical candidate, can be of use to the practicing medicinal chemist.

We propose that the simple concept of the binding energy per atom or binding 'efficiency' of a ligand could be a useful parameter in the selection of a lead compound and in the optimization

binding energy of the ligand per atom, or 'ligand efficiency' (Δg) is a simple parameter, which might be useful in lead assessment and which can be calculated by converting the K_d into the free energy of binding [Eqn 1] at 300K and dividing by the number of 'heavy' (i.e. non-hydrogen atoms) atoms [Eqn 2]:

Free energy of ligand binding:

$$\Delta G = -RT.\ln K_d \qquad \text{[Eqn 1]}$$

Binding energy per atom (ligand efficiency):

$$\Delta g = \Delta G / N_{\text{non-hydrogen atoms}} \qquad \text{[Eqn 2]}$$

The logarithmic relationship between free energy of binding and dissociation constant potency means that every ΔG change of –1.4 kcal mol^{-1} results in a 10-fold change in potency. Kuntz *et al.* surveyed the dissociation or IC_{50} values of ~150 ligand complexes and concluded that the maximum affinity per atom for organic compounds is –1.5 kcal mol^{-1} per non-hydrogen atom. The medicinal chemistry phenomenon of 'magic methyls', the addition of a single methyl group increasing potency by 10-fold, is explained in terms of the maximum achievable from burying the surface area of a single 'heavy' atom. Ligand efficiency is a way of normalizing the potency and MW of a compound to provide a useful comparison between compounds with a range of MWs and activities. Thus,

ould be
weak
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can be of
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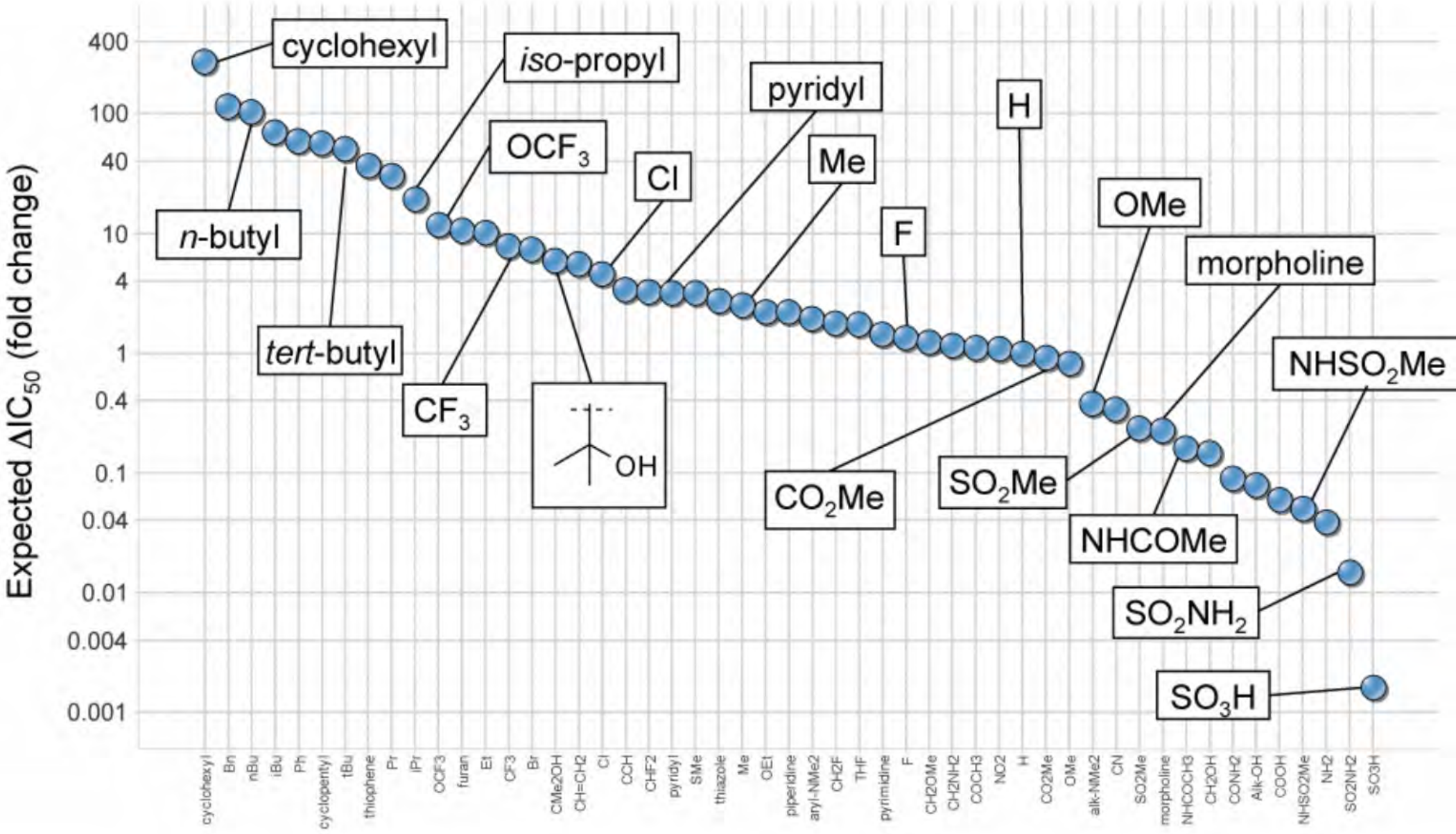
Thought experiment for LE, LLEAT and LipE



Ligand Efficiency IS dependent on MW

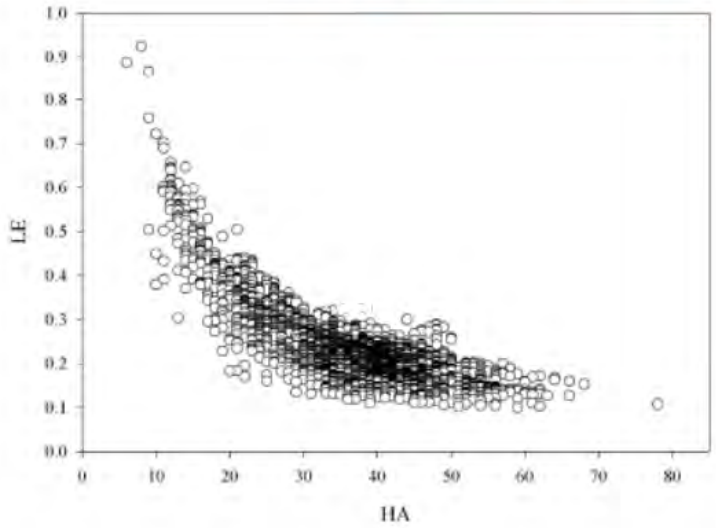


Figure 4. The ligand efficiency (pK_i/HA) as a function of number of heavy atoms for the K_i dataset. Ligand efficiency falls off dramatically between 10 and 25 heavy atoms.

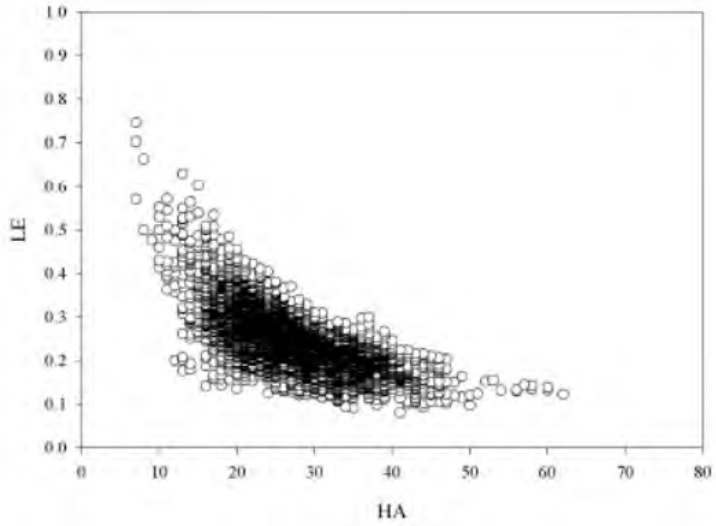


Figure 5. The ligand efficiency (pIC_{50}/HA) as a function of heavy atoms for the IC_{50} dataset. Ligand efficiency shows a similar precipitous decline between 10 and 25 heavy atoms.

There are many possible explanations for this observation. Andrews et al. explicitly included a crude entropy correction factor in their group additivity scheme. The assumption is that larger more flexible ligands might be forced to pay a larger entropic penalty for binding. It has also been suggested that as molecules become more complex the probability of fitting in an optimal way becomes smaller.[7,8] While beyond the scope of this paper, our own analysis indicates that a key factor is the lack of a linear relationship between the ligand surface area available for interaction with a protein and its atom count. Indeed, there are many factors that might contribute to this effect, but given the consistency we see across ligands and protein classes, we believe the empirical evidence for this general relationship between size and ligand efficiency is compelling.

"The fact that ligand efficiency is dependent on size makes direct comparison across wide size ranges problematic." Bembenek, Tounge and Reynolds. Drug Disc. Today 2009

Two additional possibilities:

- LE is not a valid mathematical equation for NORMALIZING size and potency
- There is no relationship between HAC and maximal potency

Reynolds, et al. Bioorg. Med. Chem. Lett. (2007) 4258

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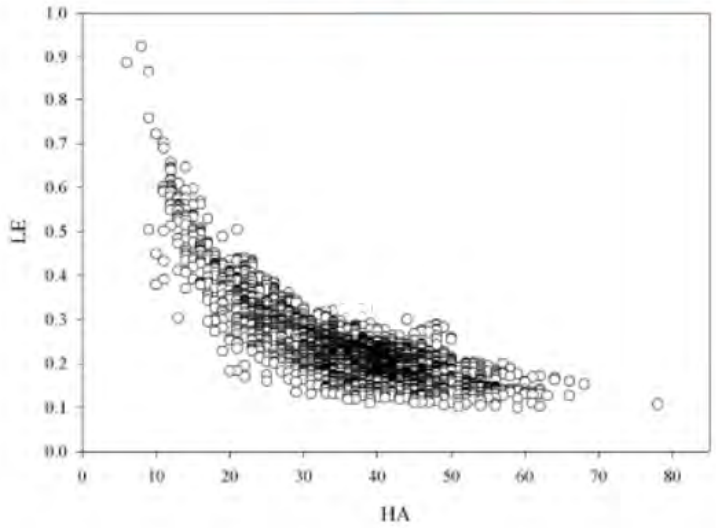

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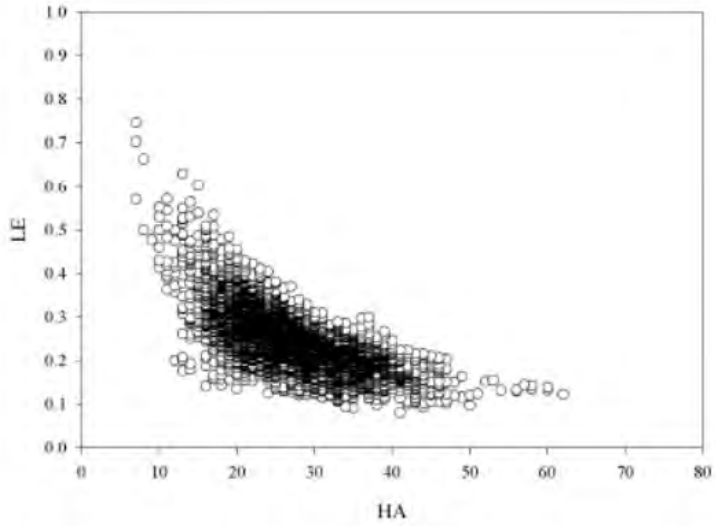

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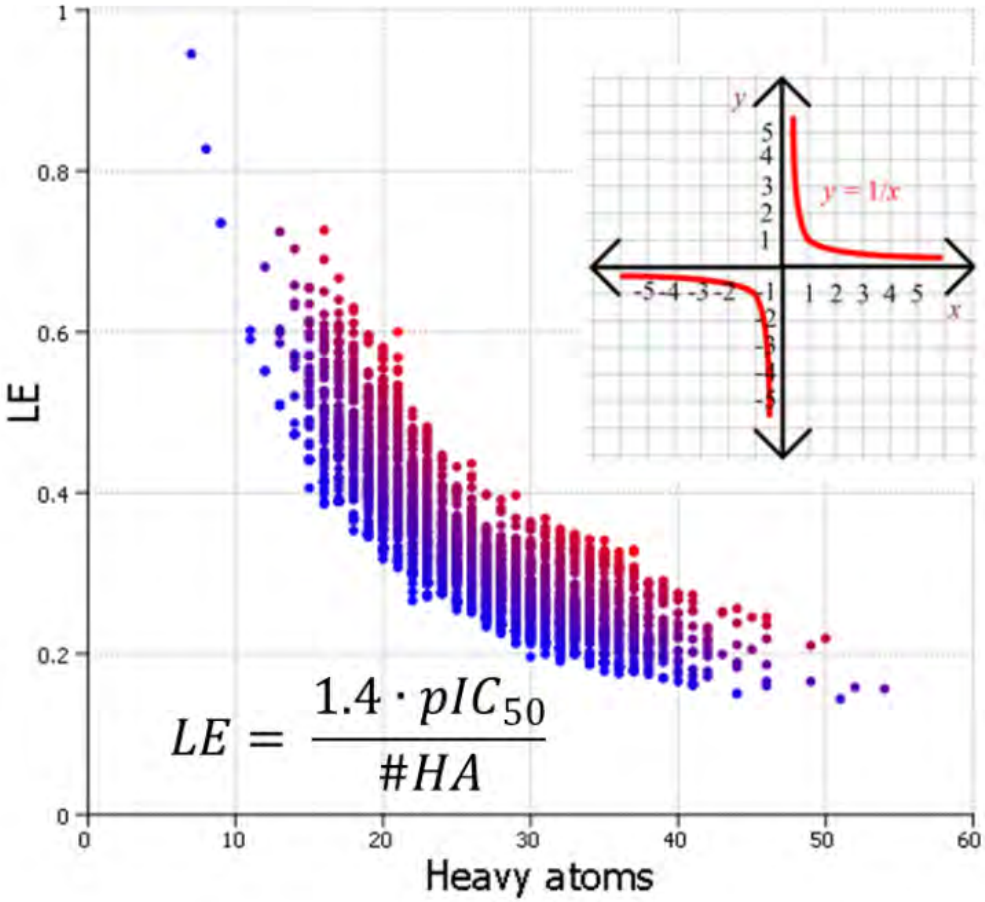
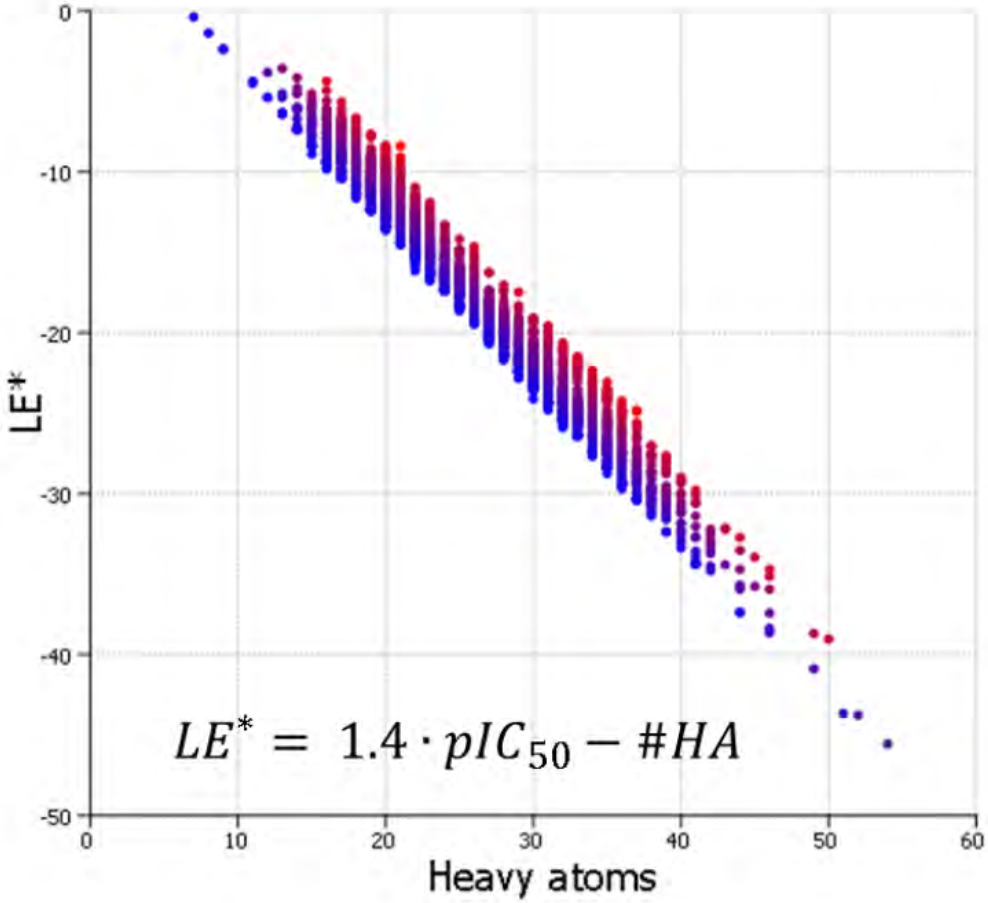
Reynolds, et al. Bioorg. Med. Chem. Lett. (2007) 4258

What if LE was calculated like LipE?

Novartis tankyrase IC50 data





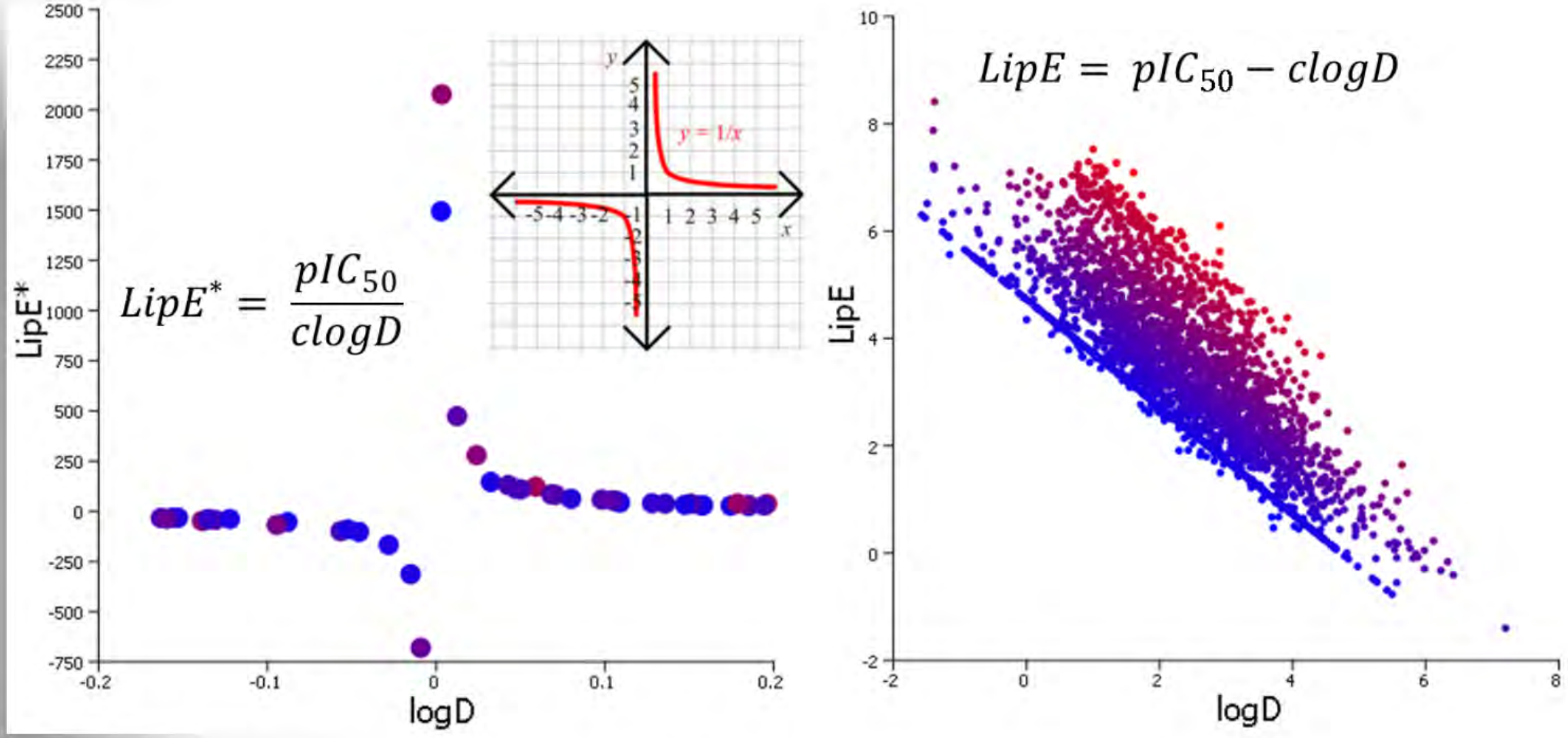
LE = 1.4*pIC50/#HA

LipE = pIC50 - clogP

Kenny et al.
J. Comput. Aided Mol. Des. (2014)

What if LipE was calculated like LE?

Novartis tankyrase IC50 data



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Mathiness

"A series of fervent gestures that gives the impression that mathematical ideas are being expressed, but doesn't actually deliver the goods."
- Jordan Ellenberg

$$A \rightarrow B$$

---

pIC50	pIC50 + y
HAC	HAC + y
clogP	clogP + y
logD	logD + y

Mathiness

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- Jordan Ellenberg

Quotient rule of logarithms:

$$log\left(\frac{A}{B}\right) = (logA - logB) \neq \frac{logA}{logB}$$

$$A \rightarrow B$$

pIC50	pIC50 + y
HAC	HAC + y
clogP	clogP + y
logD	logD + y

$$LE = \frac{1.4 * pIC50}{HAC} \neq \frac{1.4 * (pIC50 + y)}{(HAC + y)}$$

$$SILE = \frac{1.4 * pIC50}{HAC^{0.3}} \neq \frac{1.4 * (pIC50 + y)}{(HAC + y)^{0.3}}$$

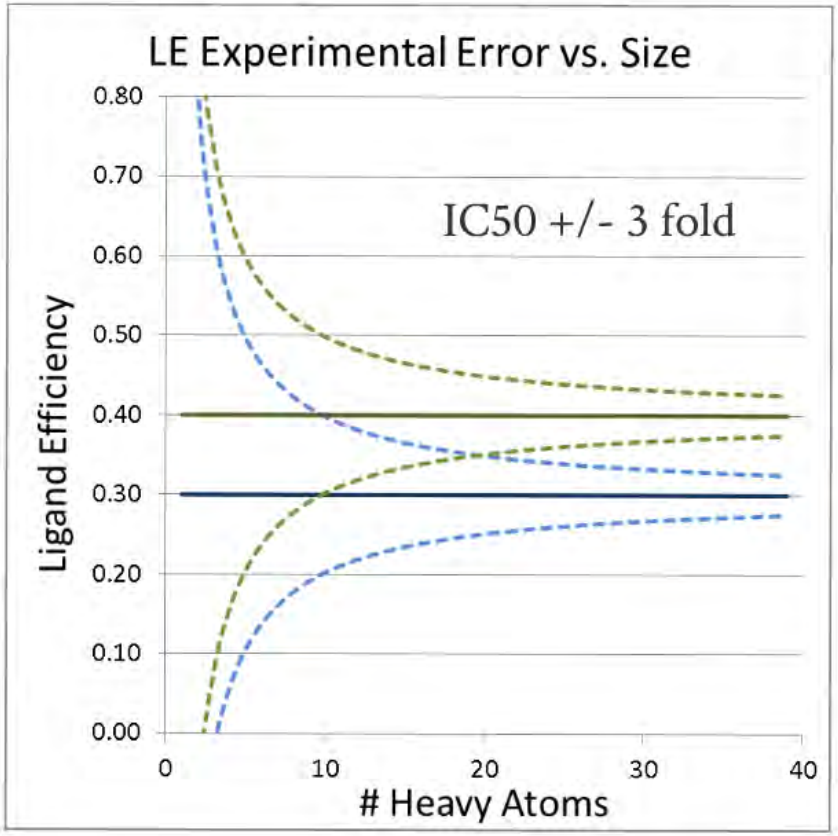
$$FQ = \frac{\left[\frac{1.4 * pIC50}{HAC}\right]}{LE\_Scale} \neq \frac{\left[\frac{1.4 * (pIC50 + y)}{(HAC + y)}\right]}{LE\_Scale}$$

$$LLE_{AT} = 0.11 - \left[\ln(10)^{\frac{RT(clogP - pIC50)}{HAC}}\right] \neq 0.11 - \left[\ln(10)^{\frac{RT\{(clogP+y)-(pIC50+y)\}}{(HAC+y)}}\right]$$

$$LELP = \frac{clogP * HAC}{1.4 * pIC50} \neq \frac{(clogP + y) * (HAC + y)}{1.4 * (pIC50 + y)}$$

$$LipE = pIC50 - logD = (pIC50 + y) - (logD + y)$$

$$LE^* = pIC50 - HAC$$



ACS Medicinal Chemistry Letters

Viewpoint

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Validity of Ligand Efficiency Metrics

Christopher W. Murray,*[,†] Daniel A. Erlanson,[‡] Andrew L. Hopkins,[§] György M. Keserü,[∥] Paul D. Leeson,[⊥] David C. Rees,[†] Charles H. Reynolds,[#] and Nicola J. Richmond[⊥]

ABSTRACT: A recent viewpoint article (Improving the plausibility of success with inefficient metrics. *ACS Med. Chem. Lett.* **2014**, 5, 2−5) argued that the standard definition of ligand efficiency (LE) is mathematically invalid. In this viewpoint, we address this criticism and show categorically that the definition of LE is mathematically valid. LE and other metrics such as lipophilic ligand efficiency (LLE) can be useful during the multiparameter optimization challenge faced by medicinal chemists.

However, there is no requirement for LE to remain constant for each additional heavy atom that increases potency by 10-fold. LE is simply an average and, *like any other average,* is not required to remain constant for each additional data point that differs by a fixed amount.

of a single 'heavy' atom. Ligand efficiency is a way of normalizing the potency and MW of a compound to provide a useful comparison between compounds with a range of MWs and activities. Thus,

$$X_{i,\,0\text{ to }1} = \frac{X_i - X_{Min}}{X_{Max} - X_{Min}}$$

Hopkins et al. DDT (2004) 430

Normalization scales all numeric values to bring all of the variables into proportion with one another, averaging does not.

averaged ≠ normalized

	LE (SILE, FQ)	LELP (LLE_{AT})	LipE
Is it rational?	N	N	Y
	1 H	2-103 NotH	consistent under all circumstances
Is the equation valid?	N	N	Y
	averaged ≠ normalized	Logarithm quotient rule: $\log(\frac{A}{B}) = \log A - \log B \neq \frac{LogA}{LogB}$	
Is the underlying assumption correct?	Relationship between the property, potency and ADMET		
Correlates with successful optimizations?	Separate possibility and plausibility from probability		

Checking Assumptions of Ligand Efficiency
Is there really a relationship between size and maximal potency?

Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 9997–10002, August 1999
Chemistry

The maximal affinity of ligands

I. D. KUNTZ*†, K. CHEN*, K. A. SHARP‡§, AND P. A. KOLLMAN*

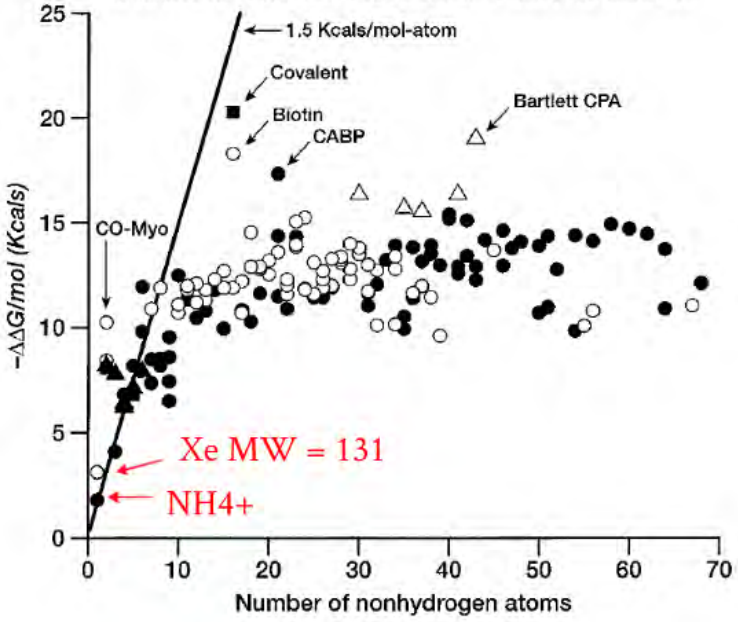
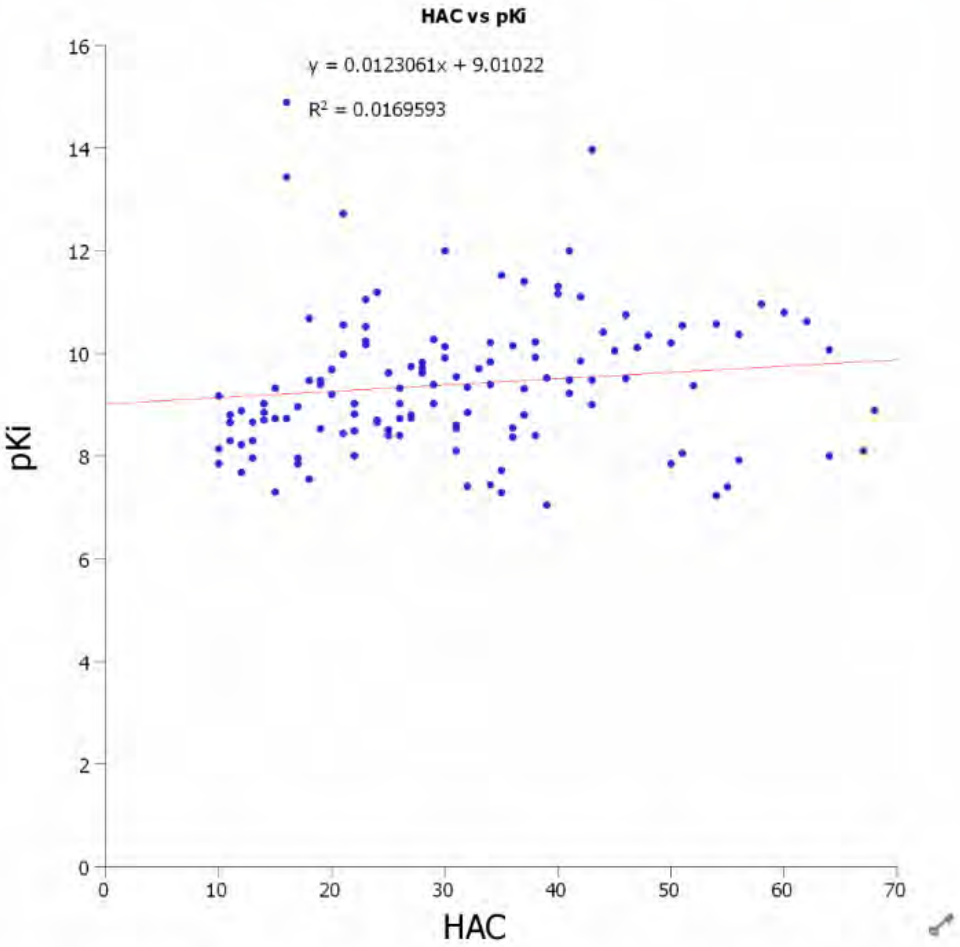


FIG. 1. Free energy of binding (in kcal/mol) for ligands and enzyme inhibitors plotted as a function of the number of nonhydrogen atoms in the ligand. See Table 1. A line with slope of 1.5 kcal/mol and an intercept of 0 is included as a visual aid to analysis. △, Metal ions or metalloenzymes; ▲, small anions; ○, natural ligands; ●, enzyme inhibitors.



Circular argument! A line forced through the origin assumes the hypothesis is true and this line is used to prove the hypothesis

Texas Sharpshooter Fallacy: The cluster in some data must be the result of a cause

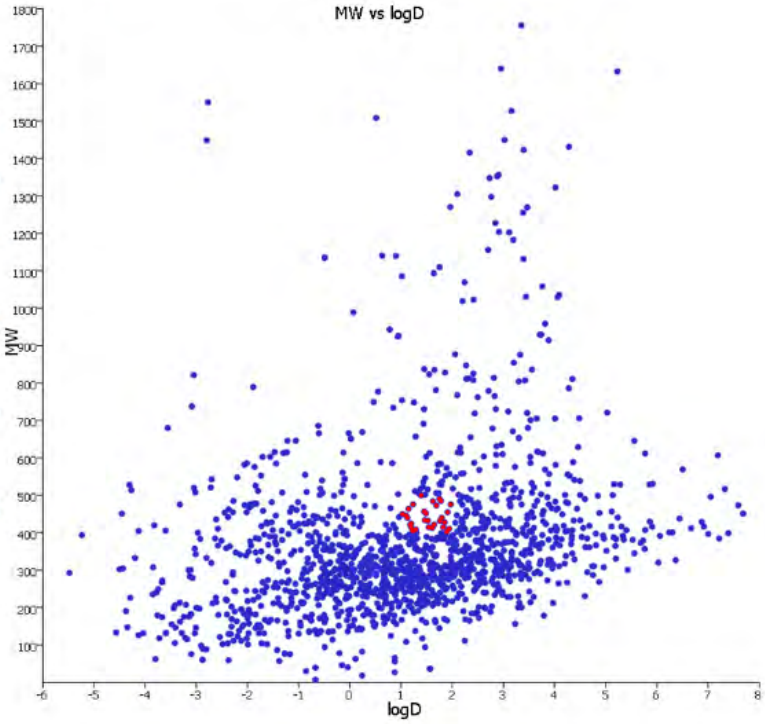
ARTICLES
PUBLISHED ONLINE: 24 JANUARY 2012 | DOI: 10.1038/NCHEM.1243
nature chemistry

Quantifying the chemical beauty of drugs

G. Richard Bickerton[1], Gaia V. Paolini[2], Jérémy Besnard[1], Sorel Muresan[3] and Andrew L. Hopkins[1]*

The concept of druglikeness provides useful guidelines for early stage drug discovery [1, 2]. Analysis of the observed distribution of some key physicochemical properties of approved drugs, including molecular weight, hydrophobicity and polarity, reveals they preferentially occupy a relatively narrow range of possible values[3]. Compounds that fall within this range are described as "druglike." Note that this definition holds in the absence of any obvious structural similarity to an approved drug. It has been shown that preferential selection of druglike compounds increases the likelihood of surviving the well-documented high rates of attrition in drug discovery[4].

$$\mathrm{QED}_{\mathrm{w}} = \exp\left[\frac{W_{\mathrm{MW}}\ln d_{\mathrm{MW}} + W_{\mathrm{ALOGP}}\ln a + W_{\mathrm{HBA}}\ln d_{\mathrm{HBA}} + W_{\mathrm{HBD}}\ln + W_{\mathrm{PSA}}\ln d_{\mathrm{PSA}} + W_{\mathrm{ROTB}}\ln + W_{\mathrm{AROM}}\ln d_{\mathrm{AROM}} + W_{\mathrm{ALE}}}{W_{\mathrm{MW}} + W_{\mathrm{ALOGP}} + W_{\mathrm{HBD}} + W_{\mathrm{PSA}} + W_{\mathrm{AROM}} + W_{\mathrm{ALERT}}}\right]$$



A Comparison of Physiochemical Property Profiles of Development and Marketed Oral Drugs

Mark C. Wenlock,* Rupert P. Austin, Patrick Barton, Andrew M. Davis, and Paul D. Leeson

Departments of Physical & Metabolic Science and Medicinal Chemistry, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leicestershire, LE11 5RH, United Kingdom

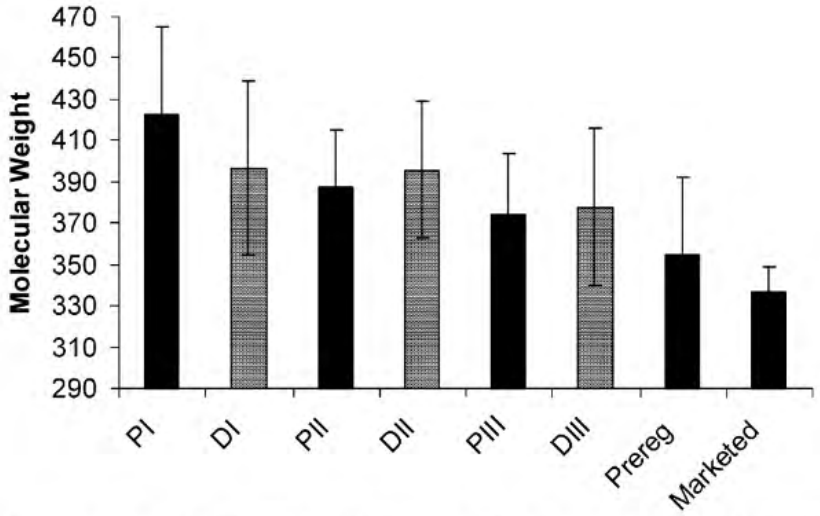


Figure 3. Mean molecular weight for drugs in different phases.

Discussion

One of the clearest findings that can be drawn from this study is that the mean molecular weight of orally administered drugs in development decreases on passing through each of the phases and appears to gradually converge toward the mean molecular weight of marketed oral drugs data set.

Conclusion

The properties showing the clearest influence on the successful passage of a candidate drug through the different stages of development are molecular weight and lipophilicity.

Time-Related Differences in the Physical Property Profiles of Oral Drugs

Paul D. Leeson*,† and Andrew M. Davis‡

Department of Medicinal Chemistry and Depart
Bakewell Road, Loughborough, Leicestershire L

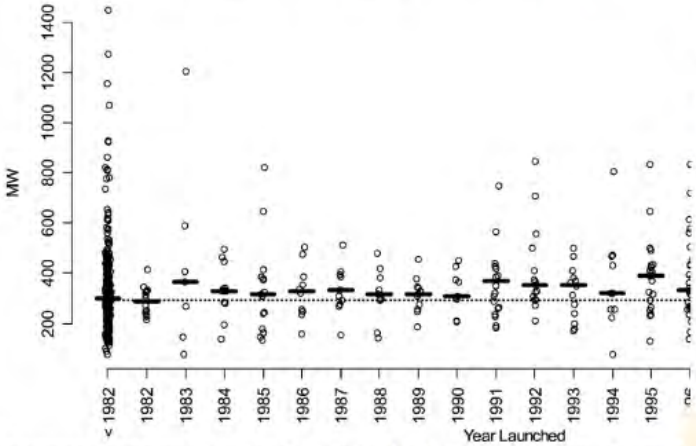


Figure 1. Molecular weight versus year of launch in the U.S. for oral drugs. The med
in each year from 1983 to 2002 are higher than those of the drugs launched prior to 198
Chem. **2004**, *47*, 224−232.[8]

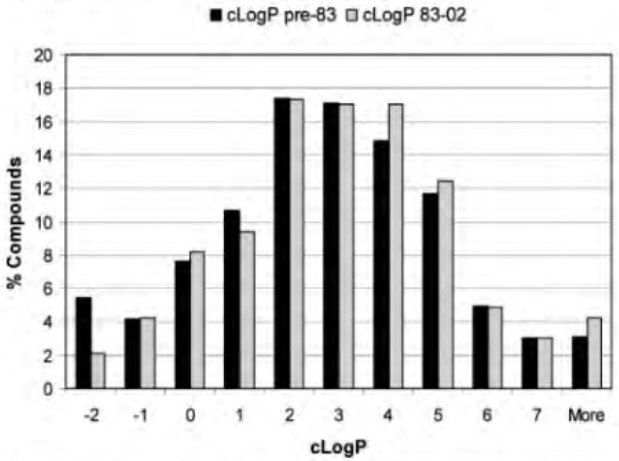
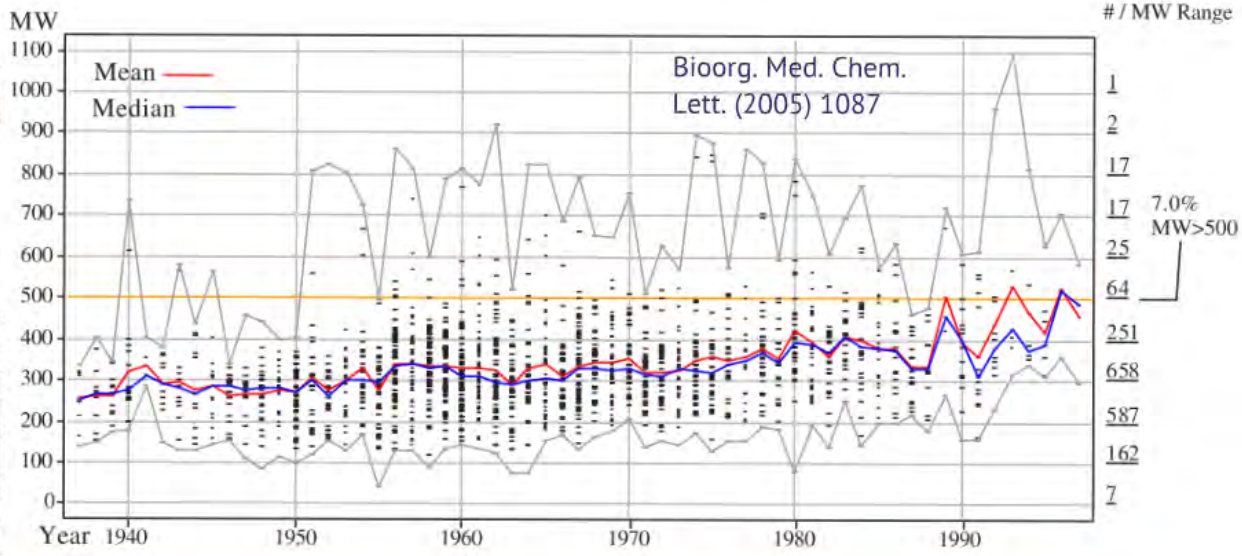


Figure 4. Distribution of lipophilicity (Daylight cLogP) in pre-1983 ($n = 864$)
(right) cumulative fraction. The differences in the lower 50% mean values a
0.0055 (two tailed, from two-sample t-test assuming unequal variances).



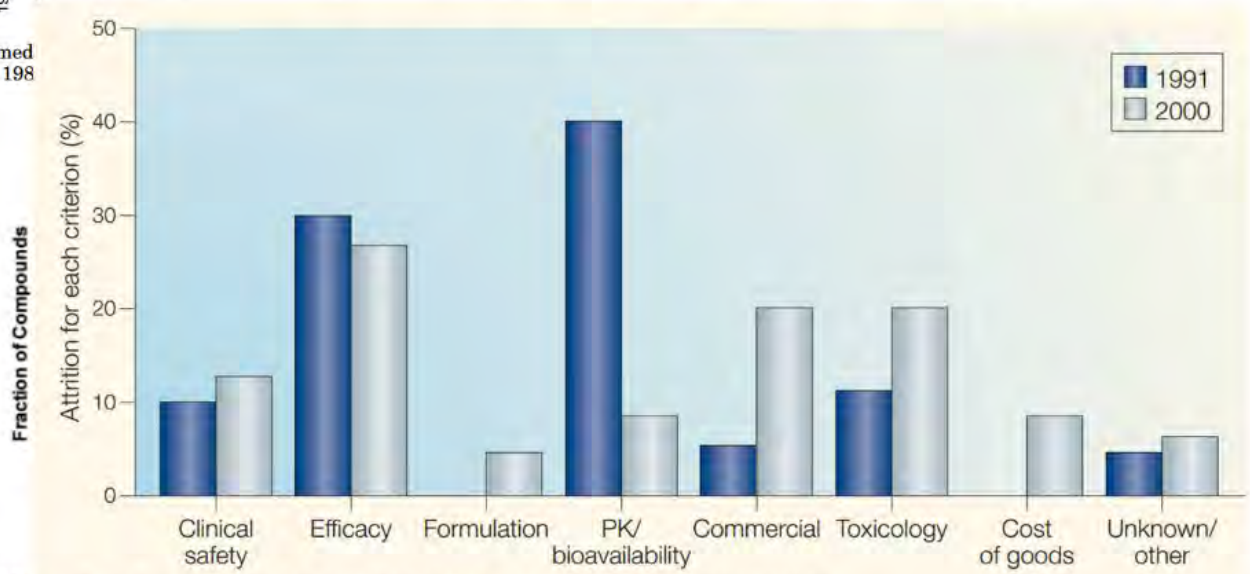


Figure 3 | **Reasons for attrition (1991–2000).** PK, pharmacokinetics.

Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings☆

Christopher A. Lipinski *, Franco Lombardo, Beryl W. Dominy, Paul J. Feeney

Central Research Division, Pfizer Inc., Groton, CT 06340, USA

This review deals only with solubility and permeability as barriers to absorption. Intestinal wall active transporters and intestinal wall

Role of molecular weight

One common factor that has long been thought to favor compound performance with respect to oral bioavailability is relatively low M_r[7,22]. This broadly-held belief can be objectively quantified through an analysis of the M_r distribution of all marketed drugs[16] (Figure 2a). The M_r distribution is seen to be roughly Gaussian in character in the range of 150 to 550 (x_o = 341; σ = 100), reflecting our ability, *de facto*, to meet the conflicting physicochemical requisites for drug bioavailability. This empirical observation can be

Base Rate Fallacy

When judging the probability of an event there are two types of information that may be available:

1. Specific information about the case in question
    e.g. MW distribution of all oral drugs

2. Generic information about the frequency of events of that type (Base rate)
    e.g. MW distribution of all possible organic molecules

When people have both types of information, they tend to make judgments of probability based entirely upon specific information, leaving out the base rate. This is the base rate fallacy.

Quantitative Estimation of Drug-Likeness (QED)

Specific information

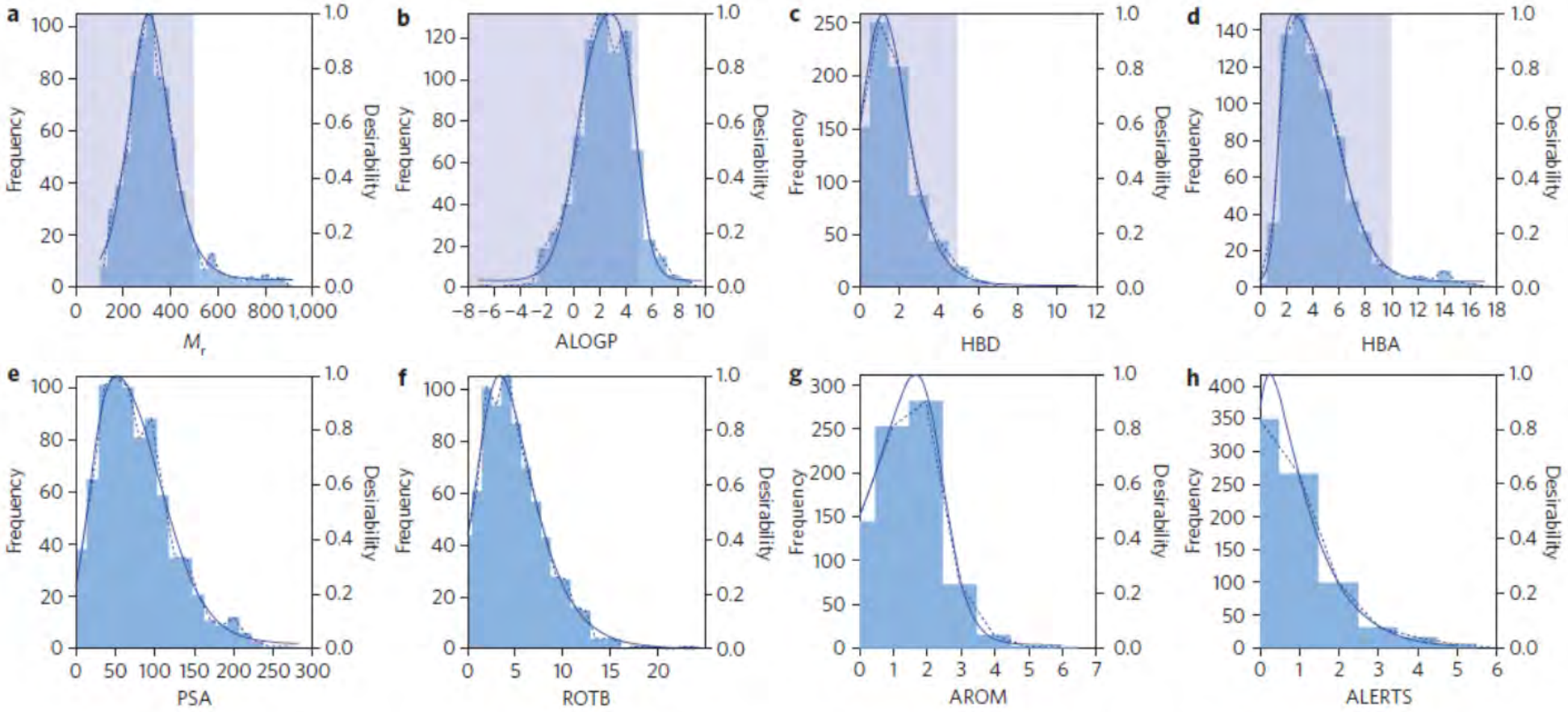
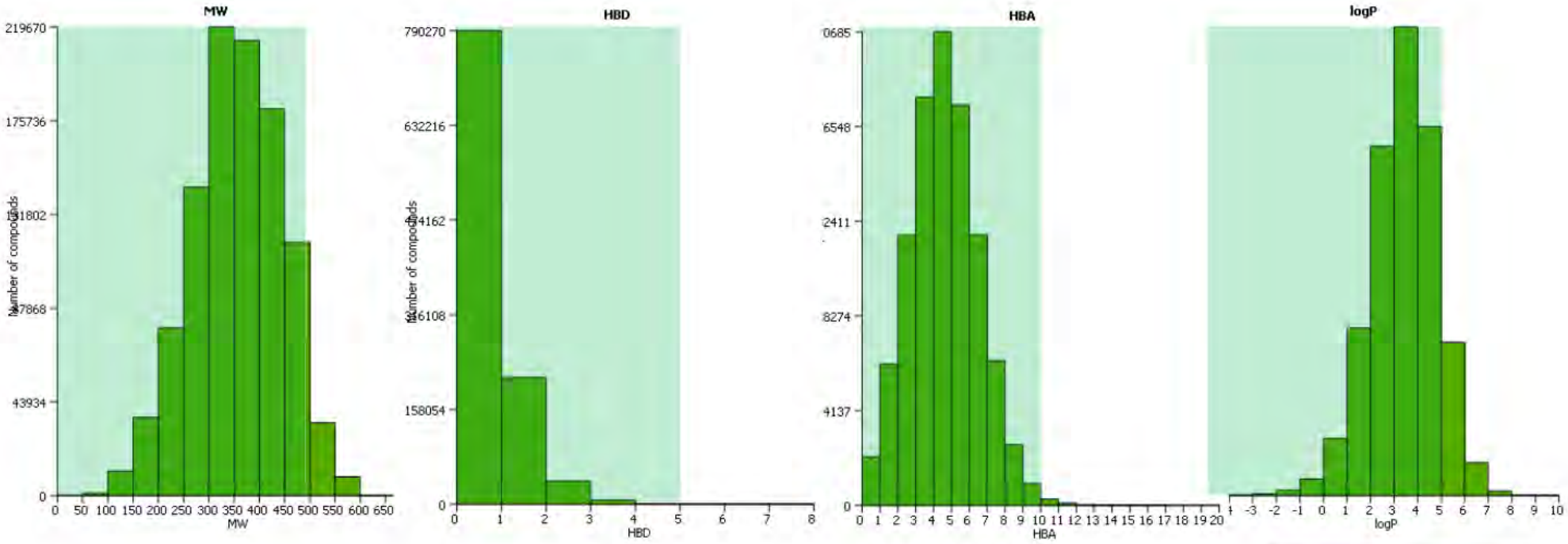


Figure 1 | Histograms of eight selected molecular properties for a set of 771 orally absorbed small molecule drugs. a–h, Molecular properties M_r (**a**), lipophilicity estimated by atom-based prediction of ALOGP (**b**), number of HBDs (**c**), number of HBAs (**d**), PSA (**e**), number of ROTBs (**f**), number of AROMs (**g**) and number of ALERTS (**h**). The Lipinski-compliant areas are shown in pale blue in (**a**), (**b**), (**c**) and (**d**). The solid blue lines describe the ADS functions (equation (2)) used to model the histograms. The parameters for each function are given in Supplementary Table S1.

J. Comput. Aided Mol. Des. (2011) 663

Quantifying the Chemical Ugliness of Non-Drugs

Generic information (base rate)



High probability space of non-druglike compounds

90% Cutoff of MW, HBD, HBA and logP

Costanza's Rules for non-drugs

MW < 500, HBD < 2, HBA < 8 (HBD+HBA <10), clogP <5

JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

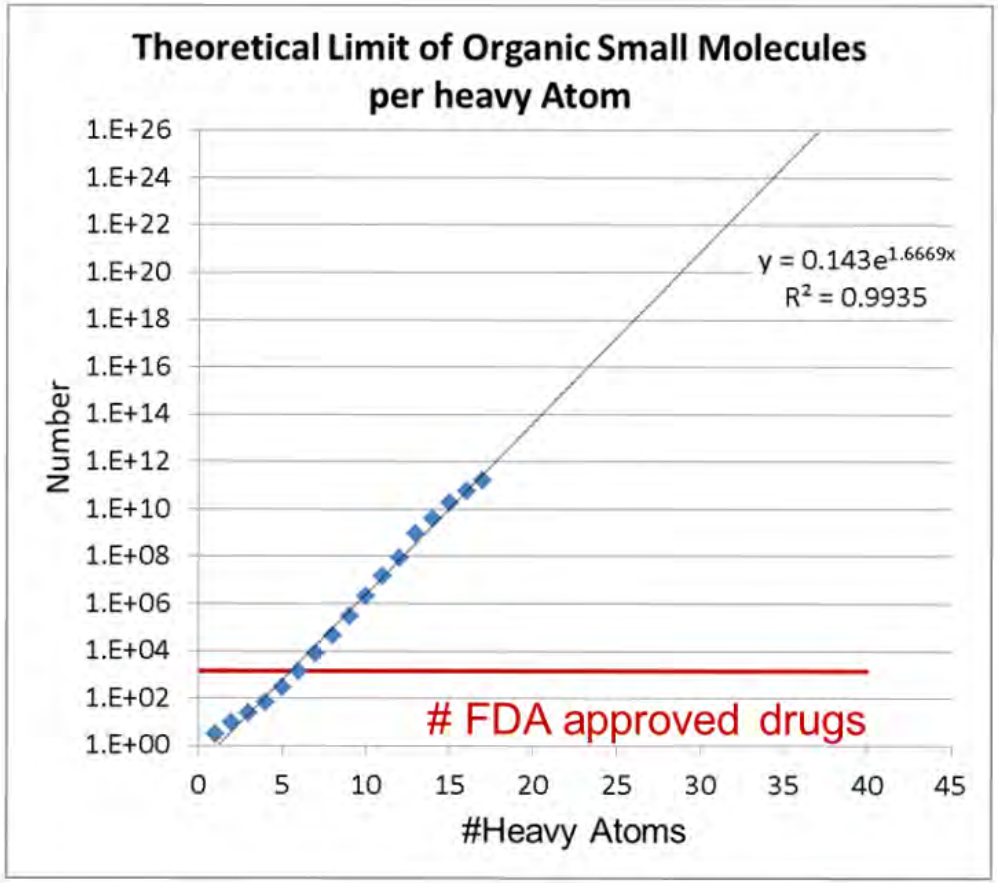
pubs.acs.org/jcim

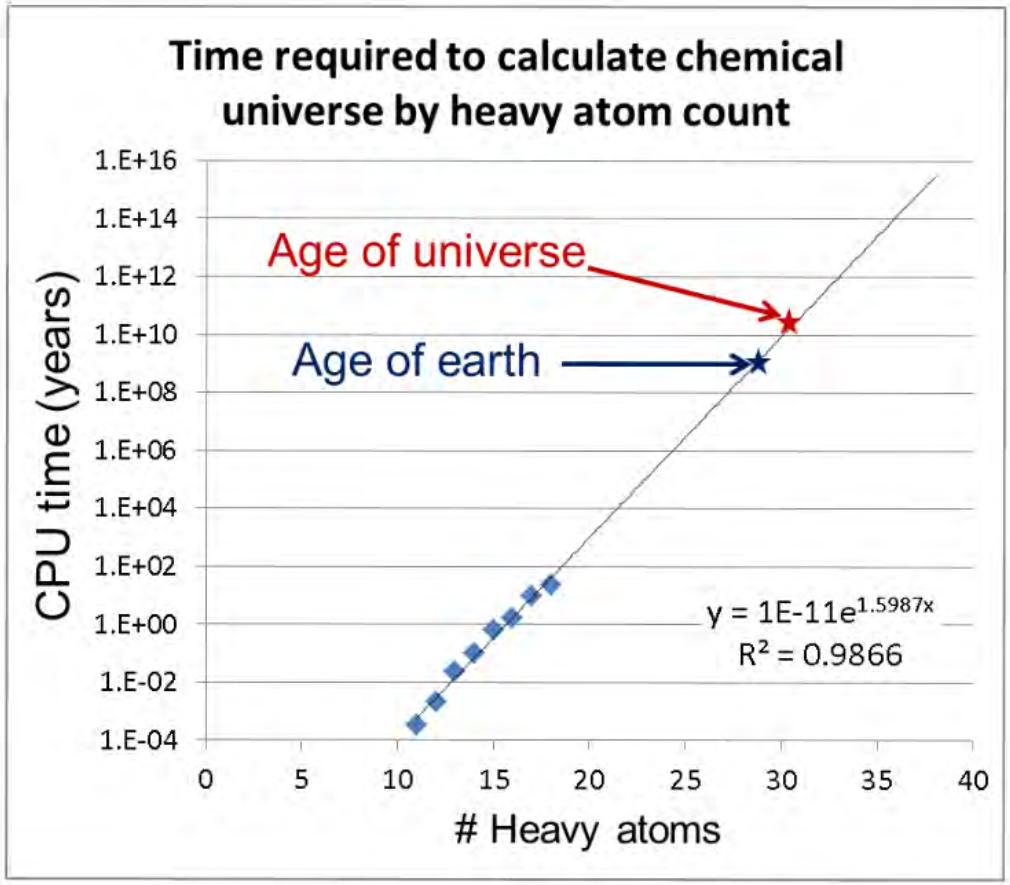
Enumeration of 166 Billion Organic Small Molecules in the Chemical Universe Database GDB-17

Lars Ruddigkeit,[†] Ruud van Deursen,[‡] Lorenz C. Blum,[†] and Jean-Louis Reymond*[,†]

[†]Department of Chemistry and Biochemistry, NCCR TransCure, University of Berne, Freiestrasse 3, 3012 Berne, Switzerland

[‡]Biomolecular Screening Facility, NCCR Chemical Biology, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland





Improving the Plausibility of Success

Efficiently targeting low probability space

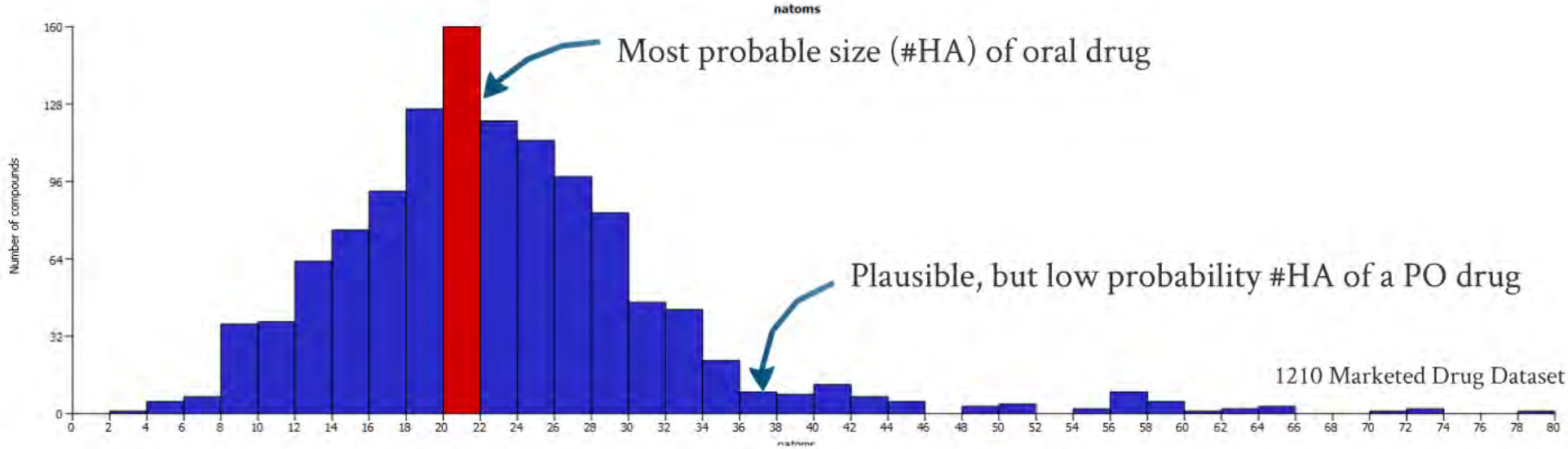


Table 1 Hypothetical progression from fragment to candidate

	HAC	IC_{50} (μM)	ClogP	LE	LLE_{AT}	LLE	LELP
Fragment	12	2,300	1.0	0.3	0.3	1.7	3.3
Hit	20	40	1.6	0.3	0.3	2.8	5.3
Lead	30	0.25	2.4	0.3	0.3	4.2	8.0
Candidate	36	0.01	3.0	0.3	0.3	5	10.0
Drug	22	0.063	2.5	0.42	0.38	4.7	6.0
Drug clogD	22	0.063	1.4	0.42	0.44	5.8	3.3

	LE (SILE, FQ)	LELP (LLE_{AT})	LipE
Is it rational?	**N**	**N**	**Y**
	$C \neq O \neq N \neq S \neq P \neq F$ $CO_2Me \neq CH_2CO_2^-$ $tBu \neq SO_3^{2-}$		consistent under all circumstances
Is the equation valid?	**N**	**N**	**Y**
	averaged ≠ normalized	Logarithm quotient rule: $\log(\frac{A}{B}) = \log A - \log B \neq \frac{LogA}{LogB}$	
Is the underlying assumption correct?	**N**	**N**	**?**
	Maximal potency, F%, 'drug-likeness' are ***not*** related to MW Base rate fallacy		
Correlates with successful optimizations?	Separate possibility and plausibility from probability		

Kenny and Montanari J Comput Aided Mol Des (2013) 1

An Analysis of the Binding Efficiencies of Drugs and Their Leads in Successful Drug Discovery Programs

Emanuele Perola*

Vertex Pharmaceuticals, 130 Waverly Street, Cambridge, Massachusetts 02139

J. Med. Chem. **2010,** *53,* 2986–2997
DOI: 10.1021/jm100118x

Lessons Learned and Suggested Guidelines for Lead Selection and Optimization. The key findings of this study can be summarized as follows:

(1) On average, drugs and corresponding leads have similar binding efficiencies but significant increases or decreases along the lead optimization path are common.
(2) 90% of leads have binding efficiencies over 12.4, and 90% of drugs have binding efficiencies over 14.7.
(3) Leads with efficiencies as low as 6.8 have been shown to be viable if there is a clear design rationale.
(4) On average, pK_i(drug) ≫ pK_i(lead) but ClogP(drug) = ClogP(lead), resulting in LLE(drug) ≫ LLE(lead): a significant increase in lipophilic ligand efficiency is one of the recurring trends of successful drug discovery programs.
(5) Increasing molecular weight to improve potency is often inevitable. Maintaining similar lipophilicity when increasing size is one of the keys to the success of lead optimization programs.

Percentage of successful optimizations where metric improves	
LE	58%
LipE	80%

Journal of Medicinal Chemistry

J. Med. Chem. 2013, 56, 2478−2486

Article

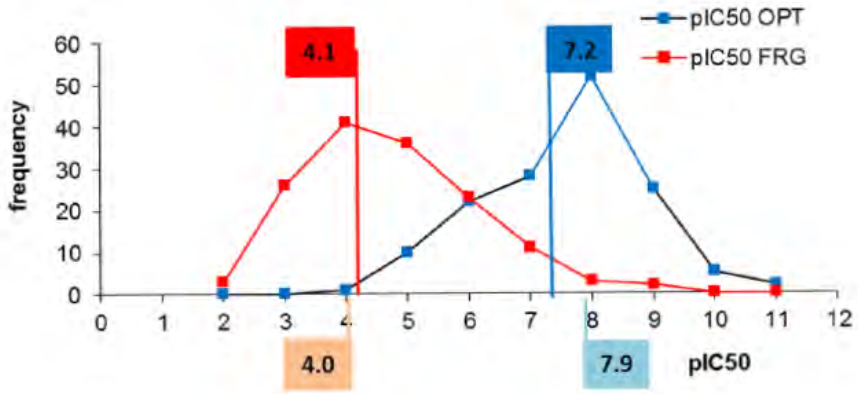
pubs.acs.org/jmc

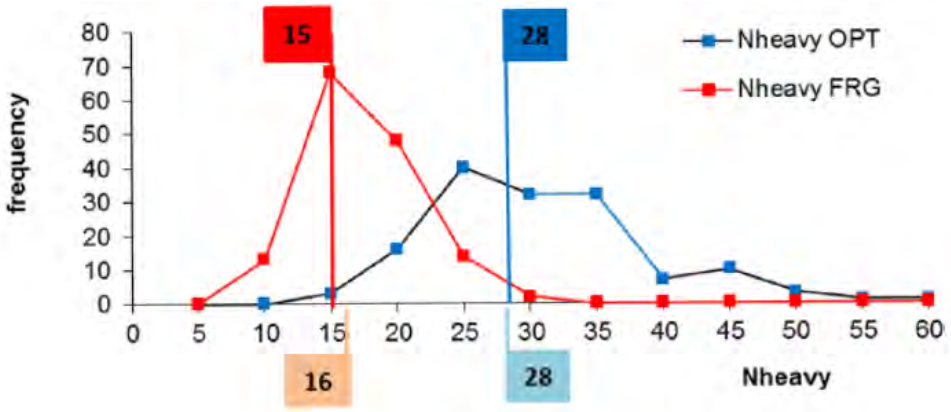
How Are Fragments Optimized? A Retrospective Analysis of 145 Fragment Optimizations

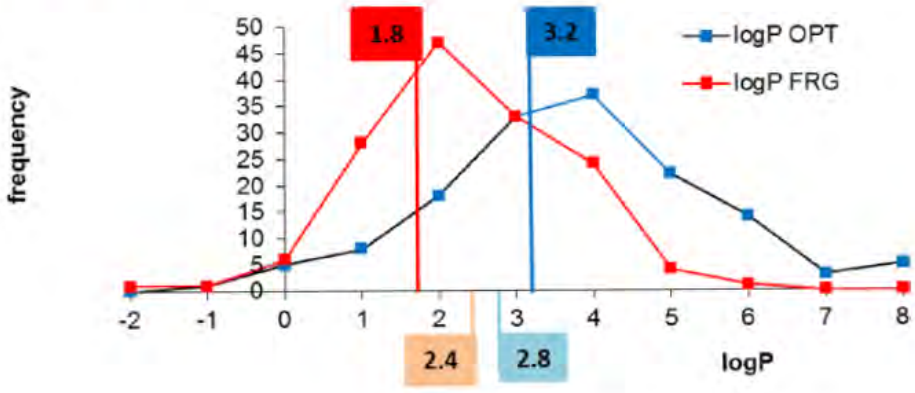
György G. Ferenczy*,† and György M. Keserű*,‡

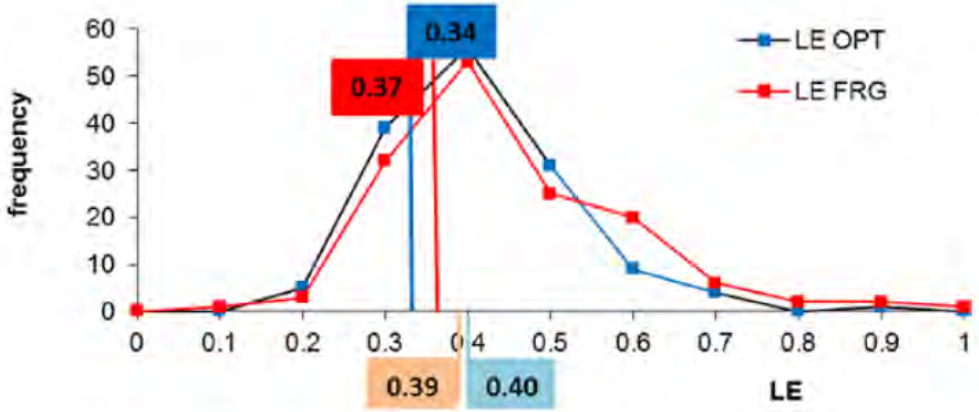
†MTA-SE Molecular Biophysics Research Group, Semmelweis University, Tűzoltó u. 37-47, H-1094 Budapest, Hungary

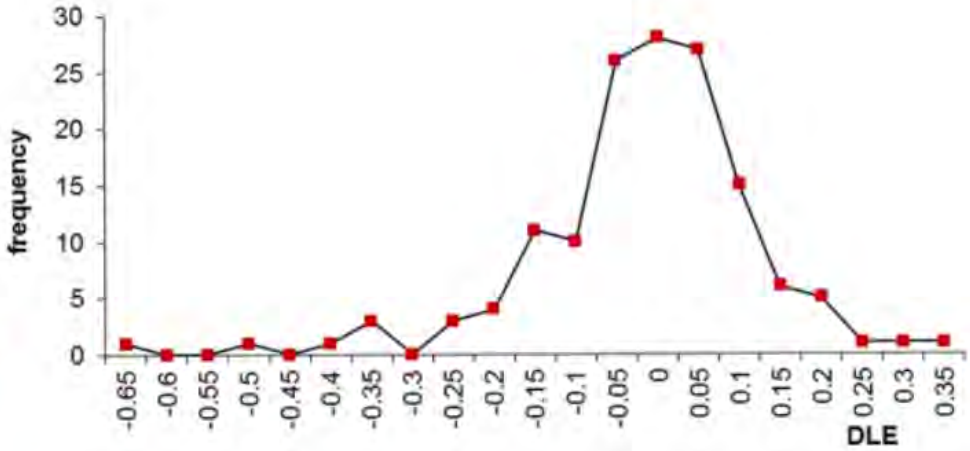
‡Discovery Chemistry, Gedeon Richter plc., Gyömrői út 19-21, H-1103 Budapest, Hungary

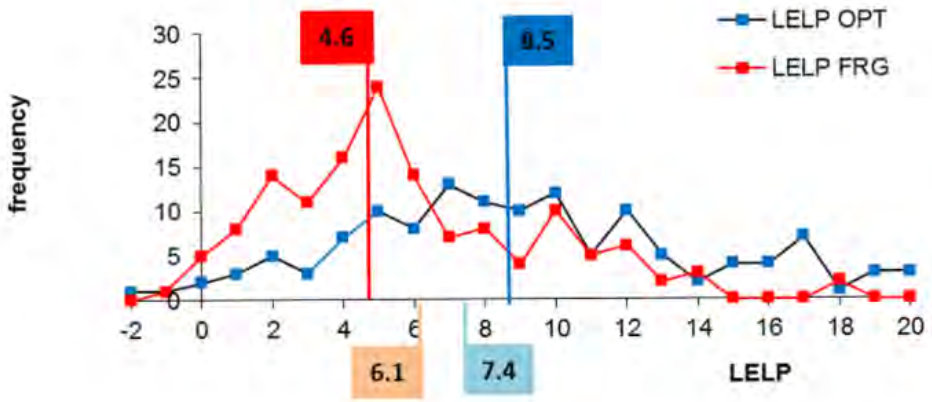


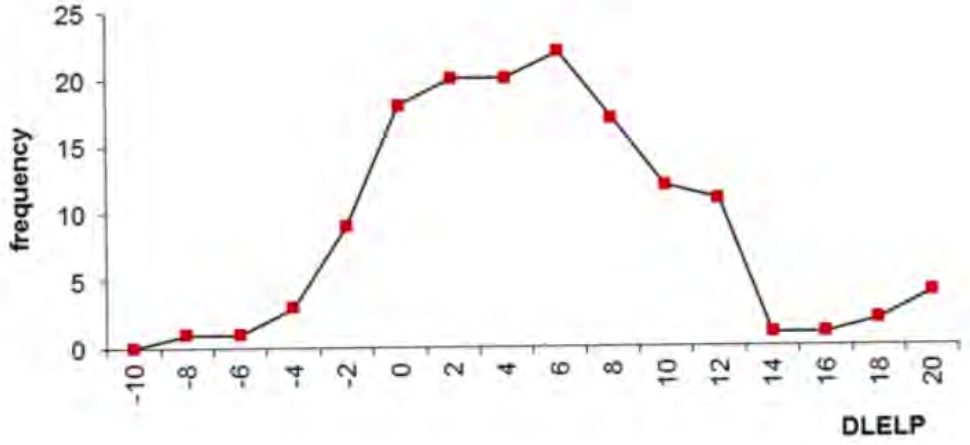


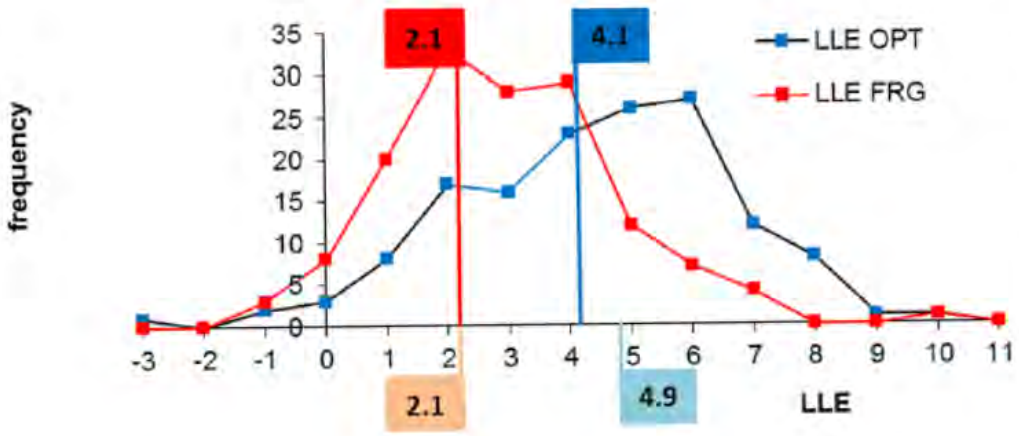


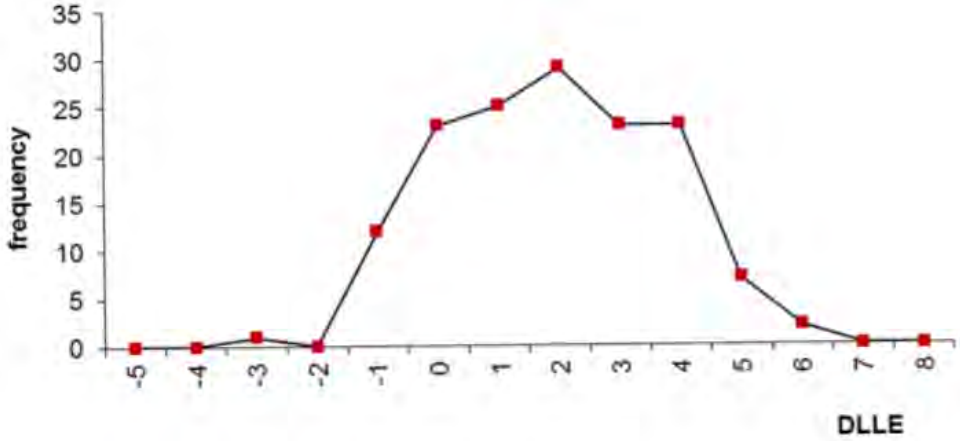

frequency
LE OPT
LE FRG
0.34
0.37
0.39
0.40
LE


frequency
DLE


frequency
LELP OPT
LELP FRG
4.6
9.5
6.1
7.4
LELP

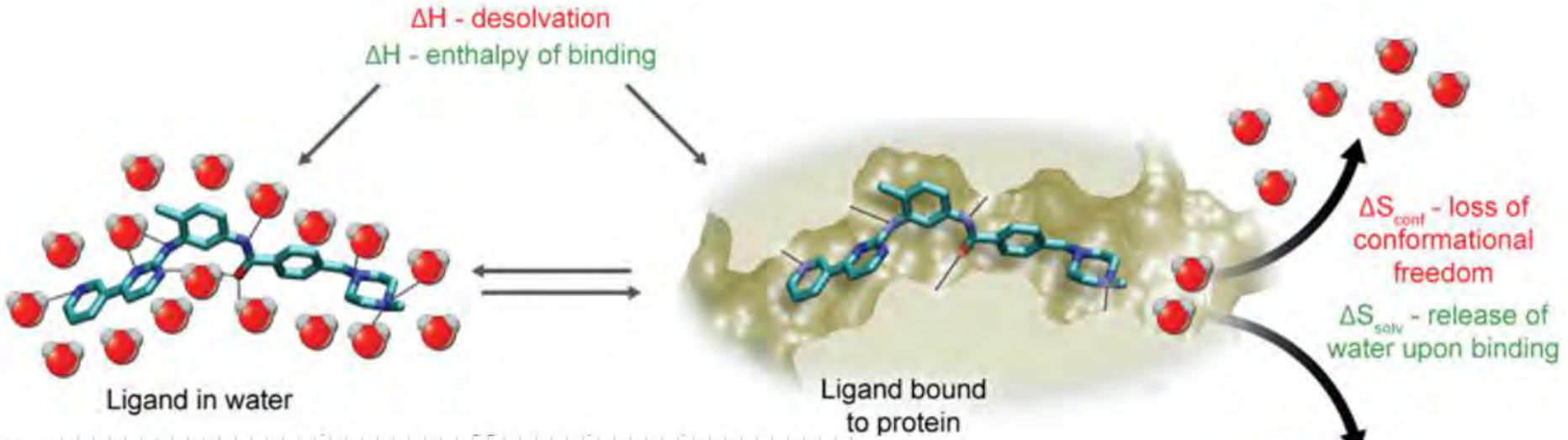

frequency
DLELP

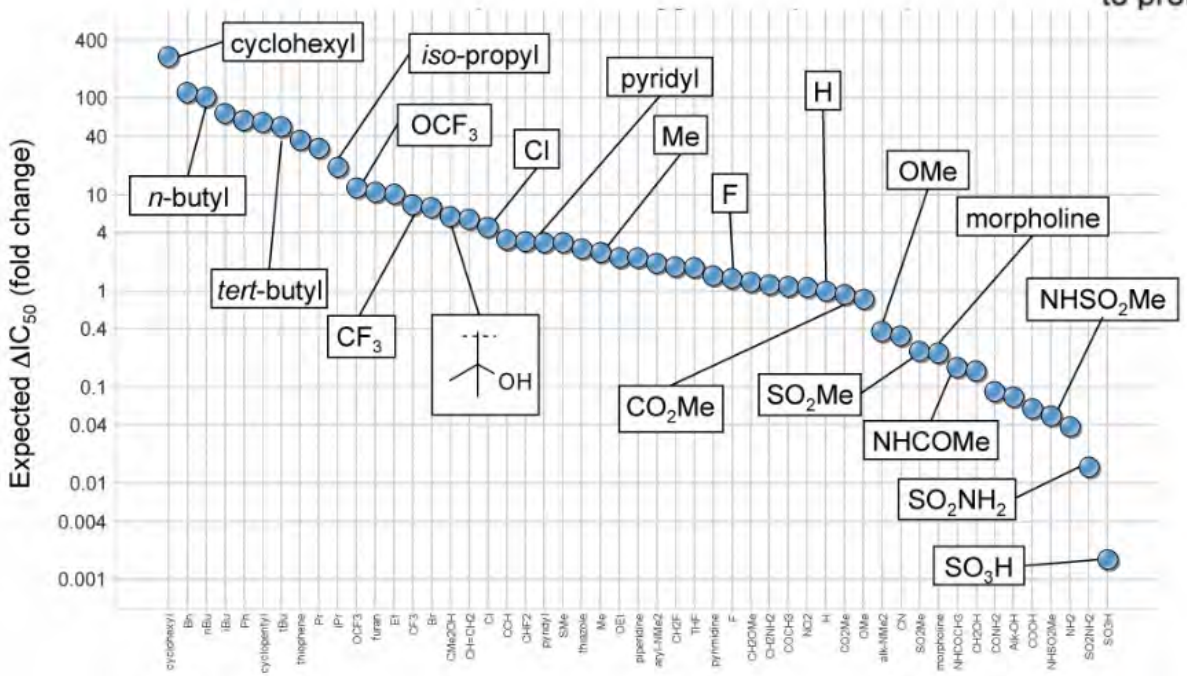

frequency
LLE OPT
LLE FRG
2.1
4.1
2.1
4.9
LLE


frequency
DLLE

	LE (SILE, FQ)	LELP (LLE_{AT})	LipE
Is it rational?	**N**	**N**	**Y**
	$C \neq O \neq N \neq S \neq P \neq F$ $CO_2Me \neq CH_2CO_2^-$ $tBu \neq SO_3^{2-}$		consistent under all circumstances
Is the equation valid?	**N**	**N**	**Y**
	averaged ≠ normalized	Logarithm quotient rule: $\log(\frac{A}{B}) = \log A - \log B \neq \frac{LogA}{LogB}$	
Is the underlying assumption correct?	**N**	**N**	**?**
	Maximal potency, F%, 'drug-likeness' are ***not*** related to MW Base rate fallacy		
Correlates with successful optimizations?	**N**	**N**	**Y (~80%)**
	Perola E., *J. Med. Chem.* **2010,** *53*, 2986 Tarcsay, A., et al., *J.Med.Chem.* **2012,** *55*, 1252 Bembenek, et al., *Drug Discov.Today* **2009**, *14*, 278		

Thermodynamics of protein-ligand interactions





$$\Delta G_{assoc} = RT\ln K_d = \Delta H - T\Delta S$$

$$pK_d = pK_H + pK_s$$

$$pK_H = pK_d - pK_s$$

$$\mathrm{LipE} = pK_d - \log P$$

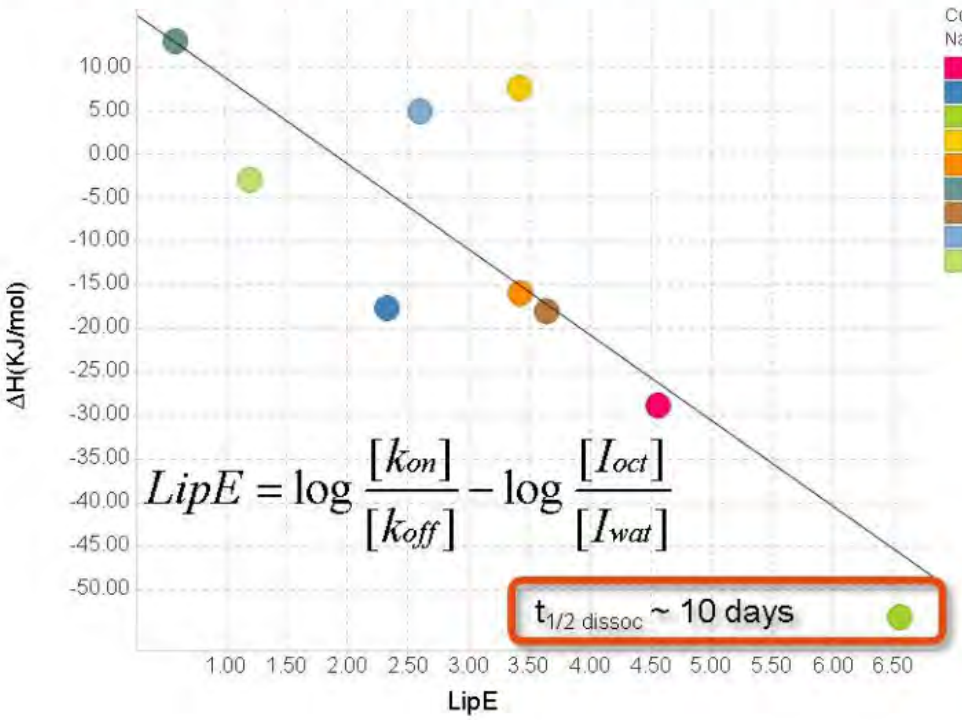
$$\Delta\mathrm{LipE} \propto \Delta pK_H \propto \Delta\Delta H$$

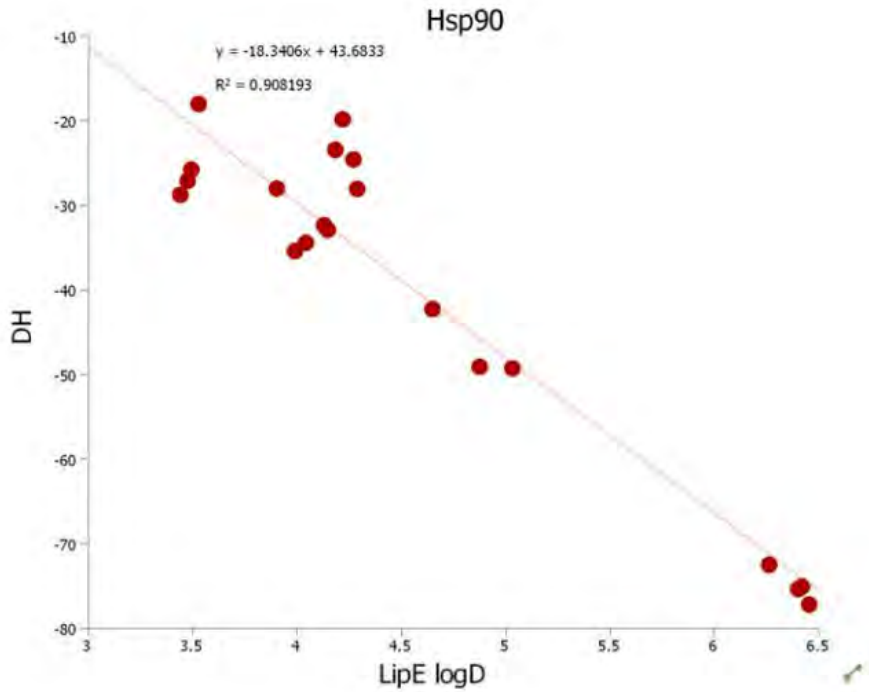
$$\mathrm{LipE} = \log\frac{[EI]}{[E][I]} - \log\frac{[I_{oct}]}{[I_{wat}]}$$

Bioorg. Med. Chem. Lett. (2013) 5992

How well do metrics trend with enthalpy?

Metric	Trends with ΔH	Avg slope (R^2)	No Trend	Trend is Opposite ΔH	Avg slope (R^2)
LELP	32 (54%)	2.7 (0.28)		21 (36%)	-10 (0.48)
LE	39 (66%)	-290 (0.38)	5 (8%)	15 (25%)	280 (0.39)
LipE	50 (85%)	-10.6 (0.57)	2 (3%)	7 (12%)	5.6 (0.24)

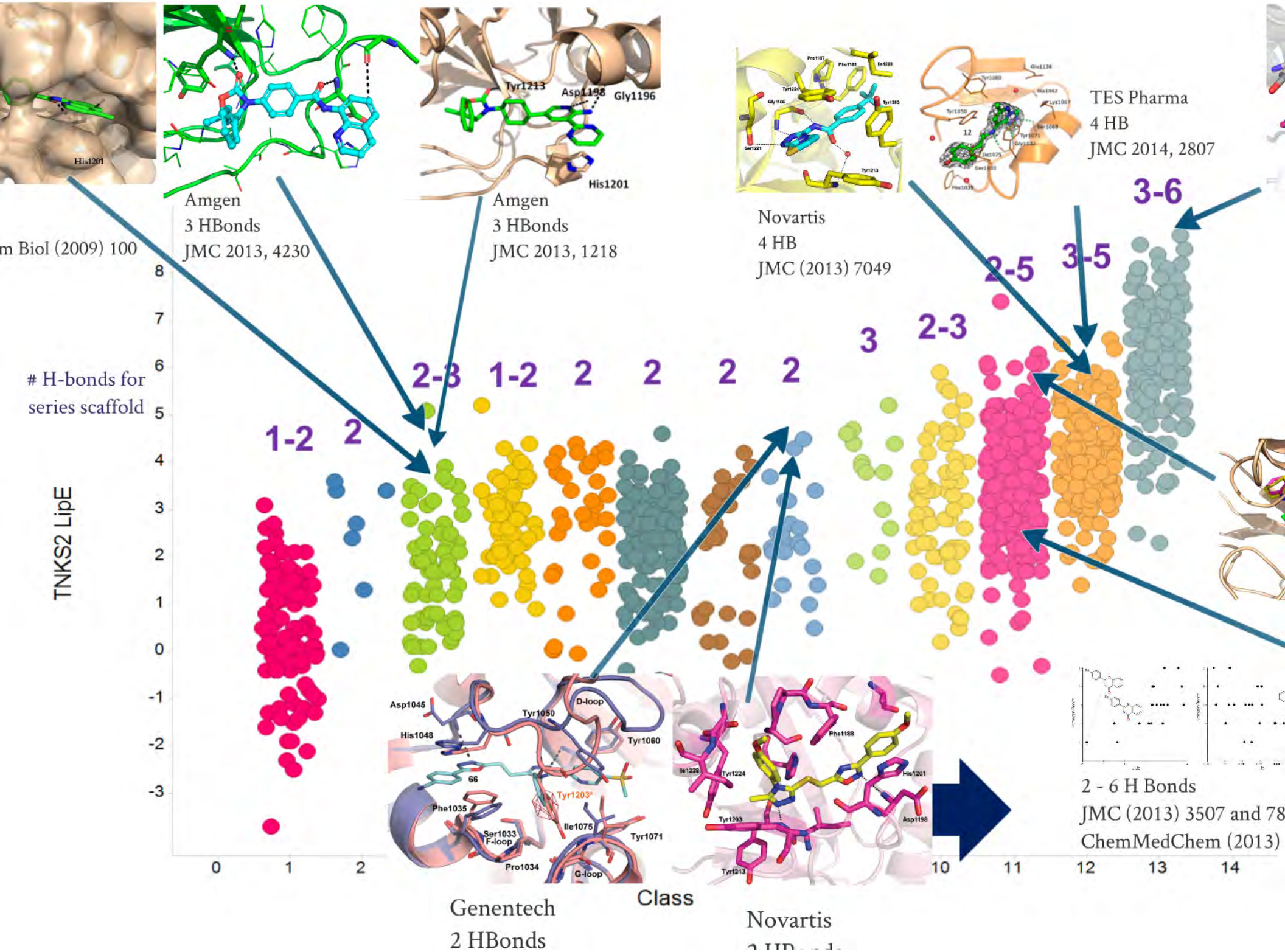


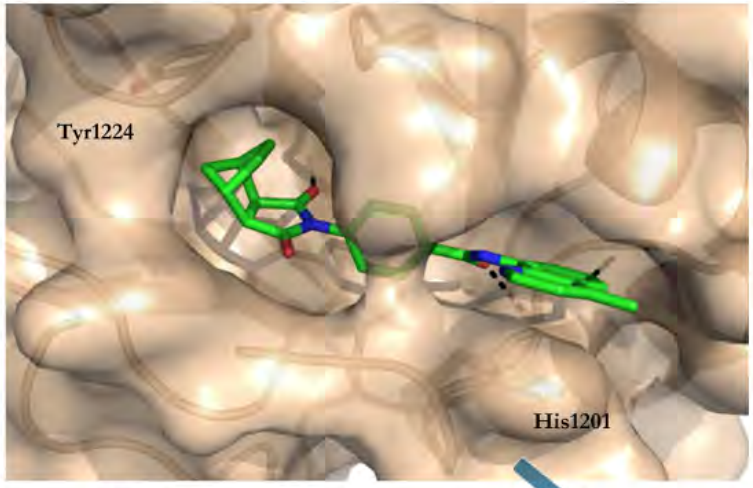


SCORPIO http://scorpio.biophysics.ismb.lon.ac.uk/

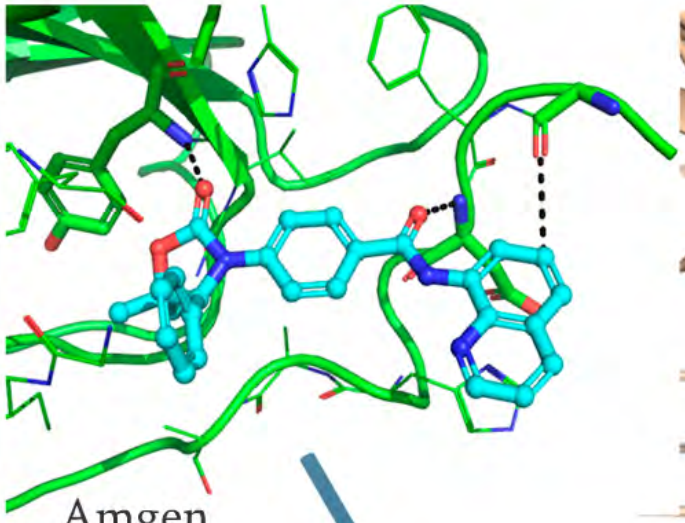
Tankyrase Hit Triage Summary
Prioritization of properties over potency

Series	Structure	Dynamic SAR?						
		TNK	Cell	Solubility	Stability	hERG	DDI	Safety/kinase
'Zero Series' >four scaffolds **(JW67)**	N	N	N					
1	Y	N	N	N	N			
2	Y	Y	Y	Y/N	N	N	N	N
3 **(IWR-3)**	Y	Y	Y	N	N			
4	Y	Y	Y	N	N			
5	Y	Y	Y	Y/N	Y/N	Y/N	Y	N
6	Y	Y/N	Y	Y/N	Y	Y	N	Y/N
7	Y	Y	Y	N	Y	N	Y	N
8 **(JW74)**	Y	Y	Y	Y/N	N	Y	Y	N
9	Y	Y	Y	N	Y/N	Y	Y	
10 **(IWR-1)**	Y	Y	Y	N	N	Y	Y	Y
11 PARPi **(XAV939)**	Y	Y	Y	Y/N	Y/N	Y	Y	Y
12	Y	Y	Y	Y	Y	Y	Y	Y
13	Y	Y	Y	Y	Y	Y	Y	Y

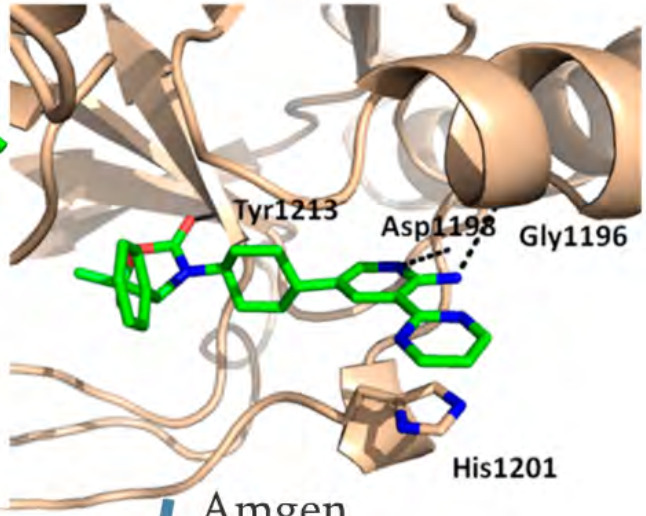

His1201
Amgen
3 HBonds
JMC 2013, 4230
Tyr1213
Asp1198
Gly1196
His1201
Amgen
3 HBonds
JMC 2013, 1218
Novartis
4 HB
JMC (2013) 7049
TES Pharma
4 HB
JMC 2014, 2807
m Biol (2009) 100
H-bonds for
series scaffold
TNKS2 LipE
1-2
2
2-3
1-2
2
2
2
2
3
2-3
2-5
3-5
3-6
8
7
6
5
4
3
2
1
0
-1
-2
-3
0
1
2
10
11
12
13
14
Class
Asp1045
His1048
Tyr1050
D-loop
Tyr1060
66
Tyr1203*
Phe1035
Ile1075
Ser1033
F-loop
Tyr1071
Pro1034
G-loop
Phe1188
Tyr1224
His1201
Asp1198
Tyr1203
Tyr1213
Genentech
2 HBonds
Novartis
2 - 6 H Bonds
JMC (2013) 3507 and 78
ChemMedChem (2013)



IWR
3 HBonds
Nature Chem Biol (2009) 100

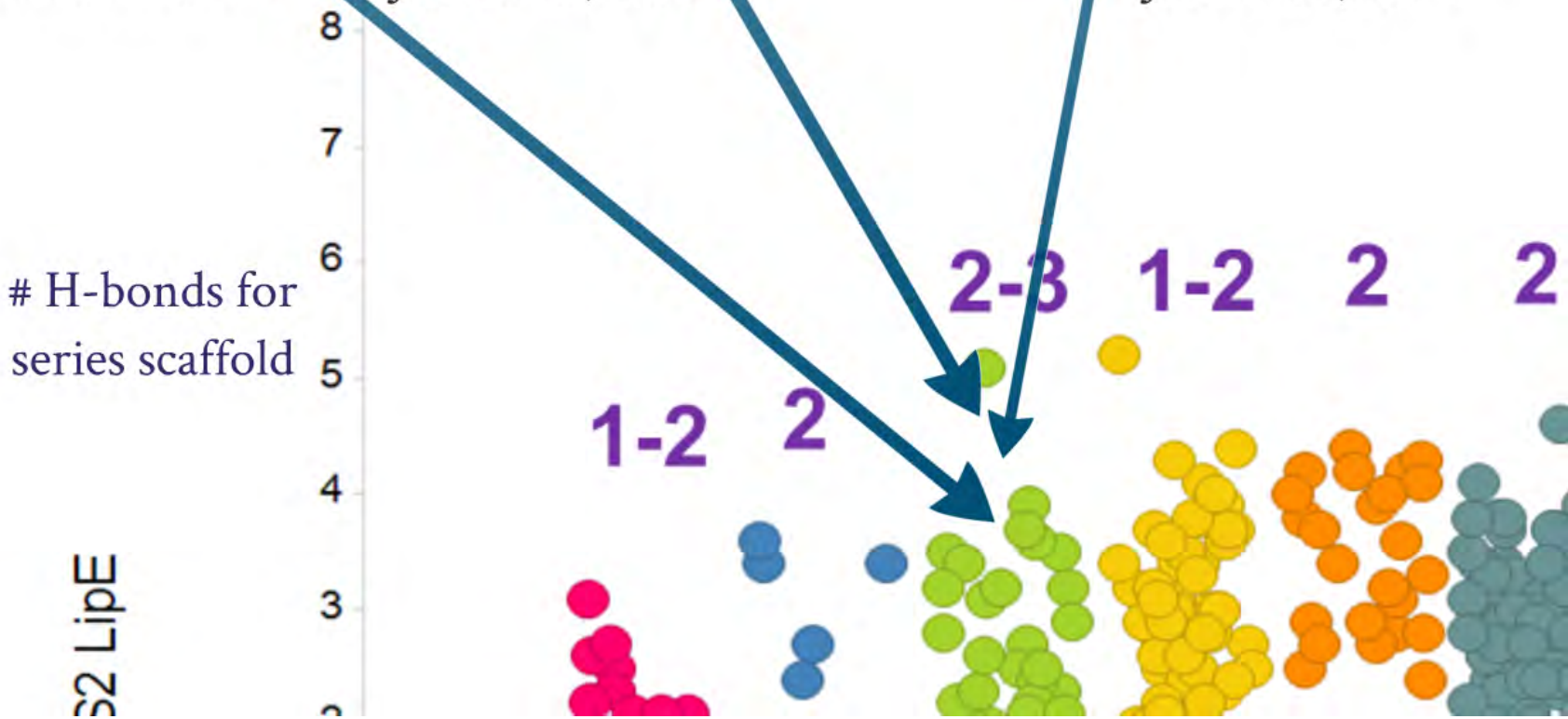


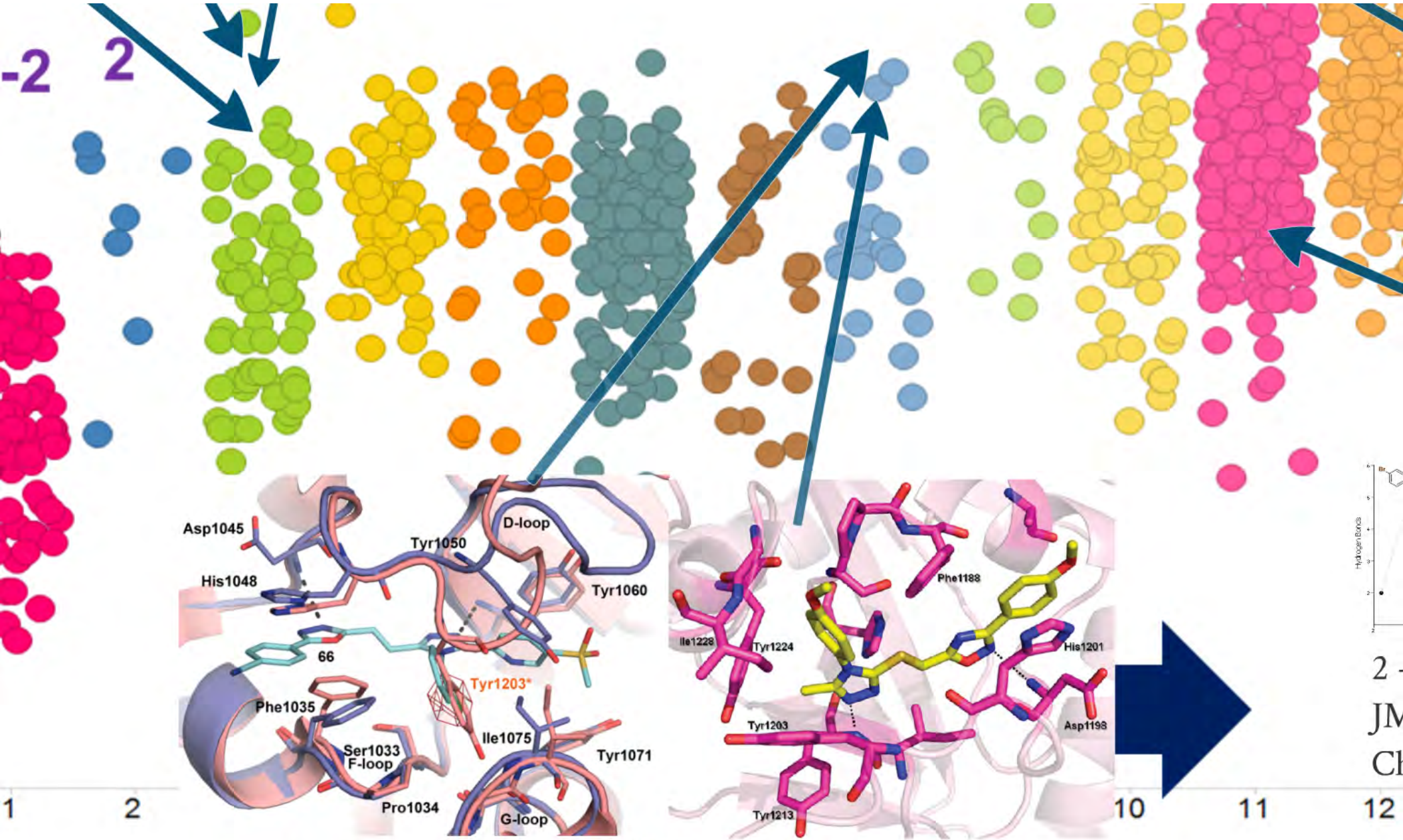
Amgen
3 HBonds
JMC 2013, 4230



Amgen
3 HBonds
JMC 2013, 1218

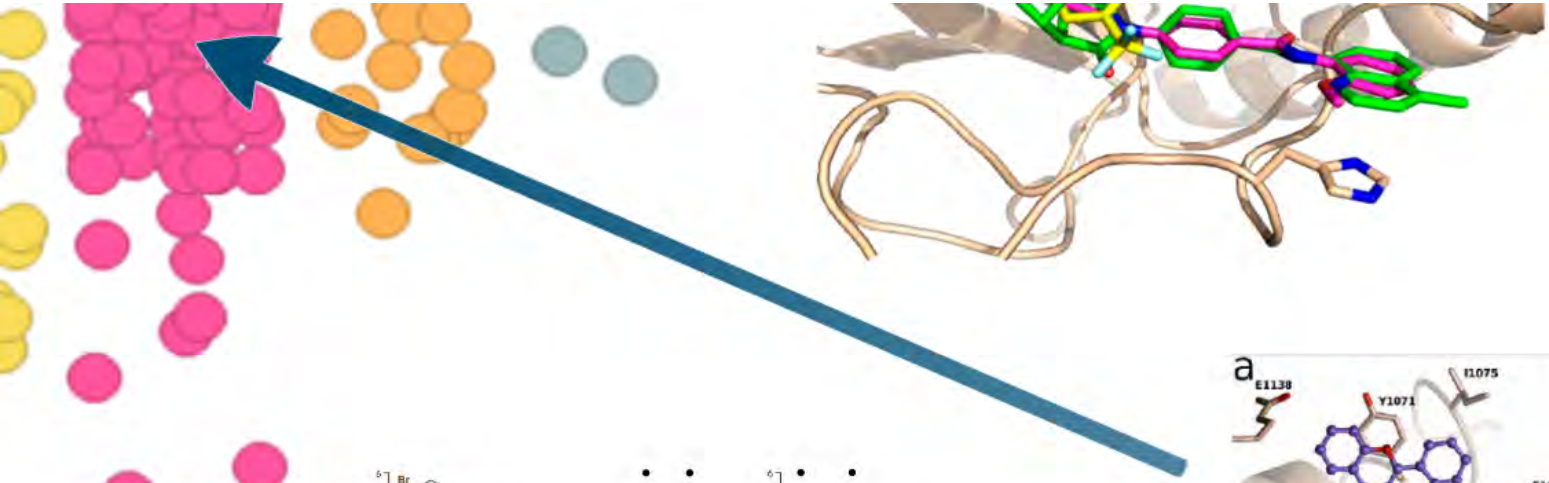
H-bonds for series scaffold

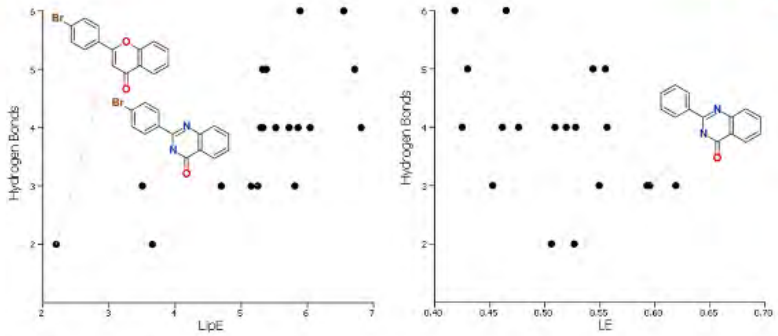




Genentech
2 HBonds
JMC (2013) 3012

Novartis
2 HBonds
JMC (2012) 1127



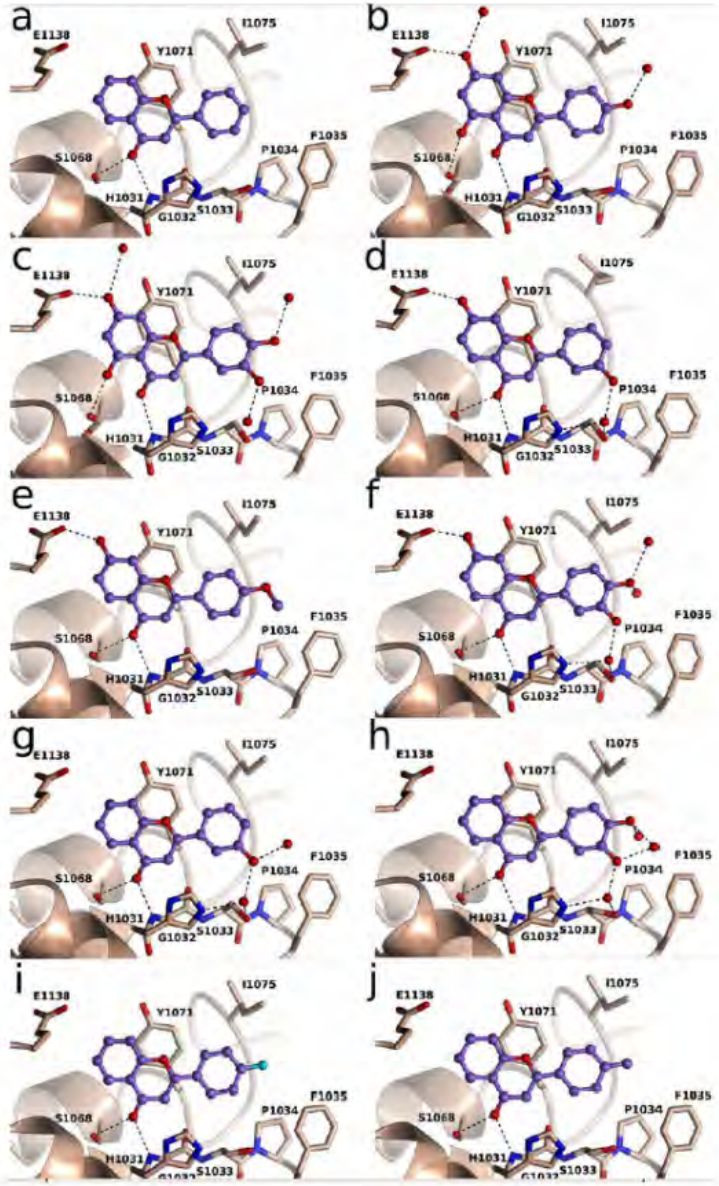


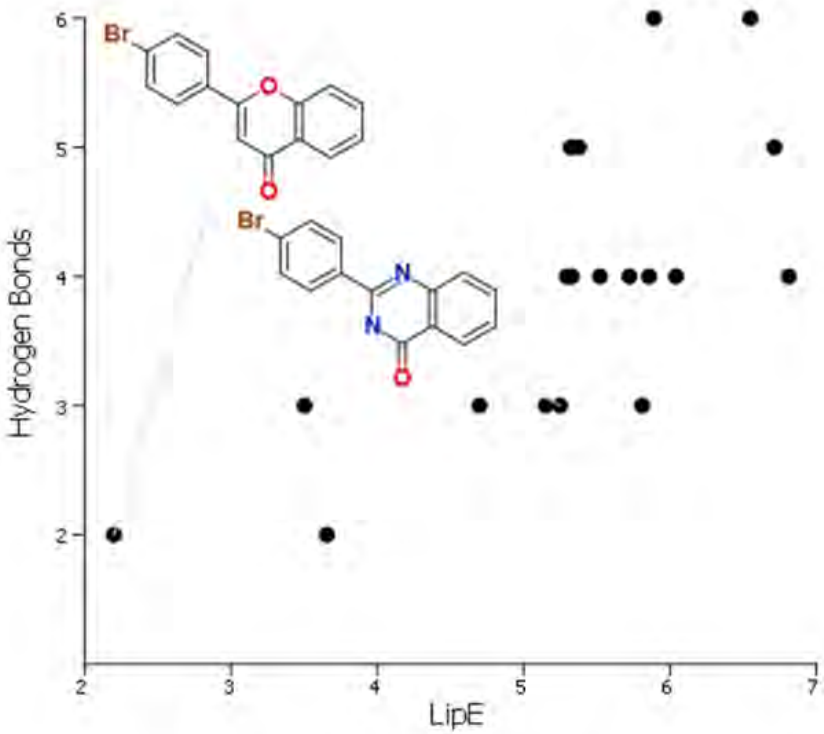
2 - 6 H Bonds

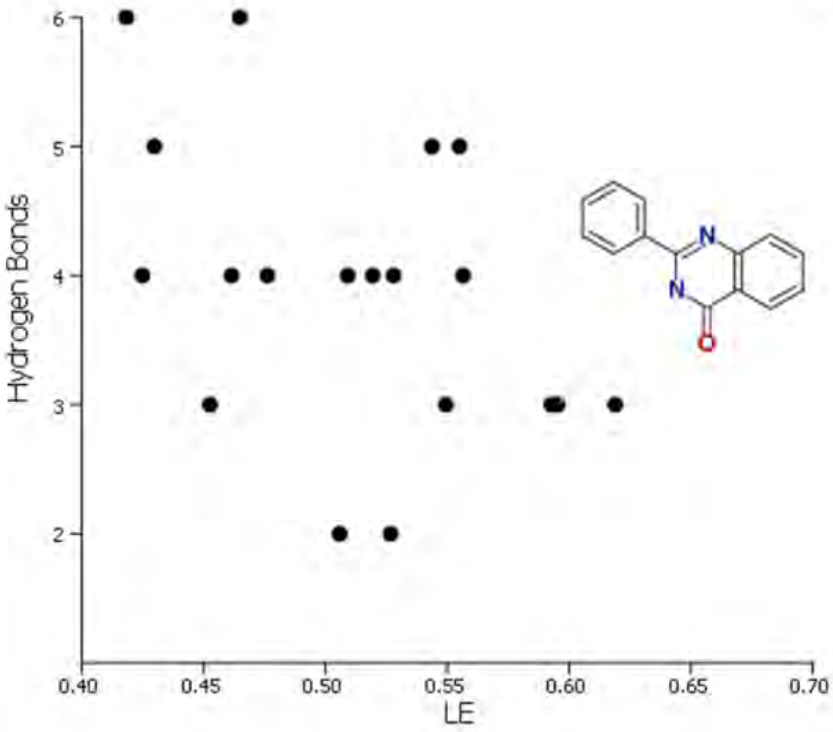
JMC (2013) 3507 and 7880

ChemMedChem (2013) 1978

11 12 13 14







2 - 6 H Bonds

JMC (2013) 3507 and 7880

ChemMedChem (2013) 1978

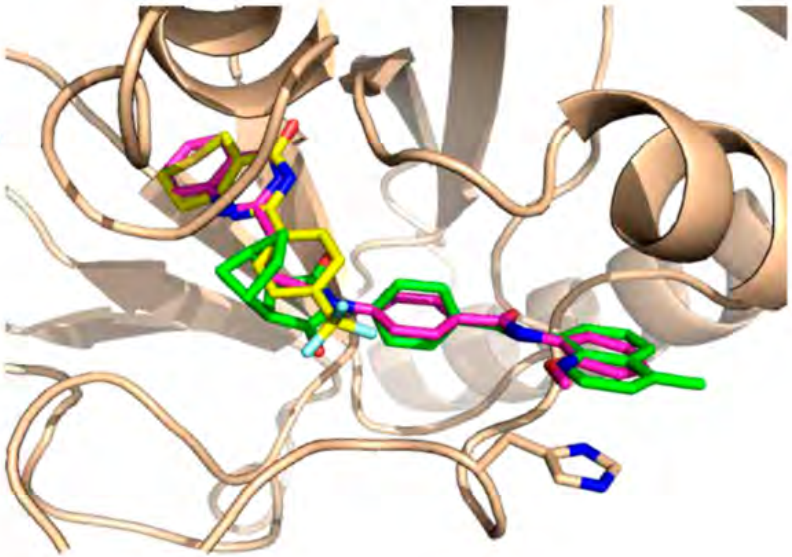
JMC (2013) 6495

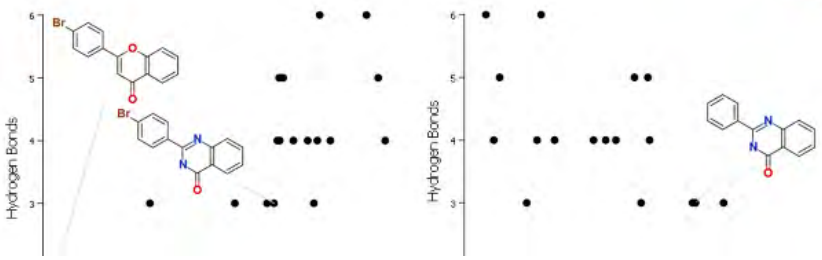
2-3

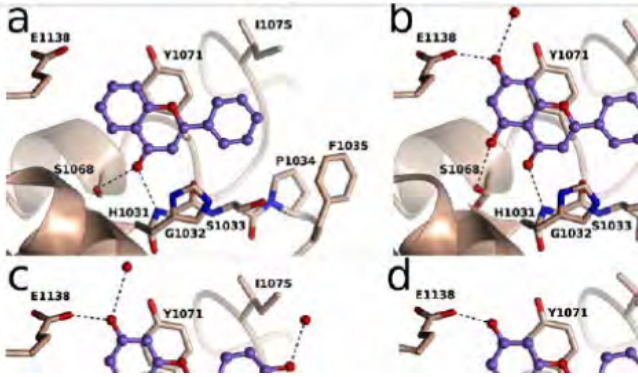
Amgen

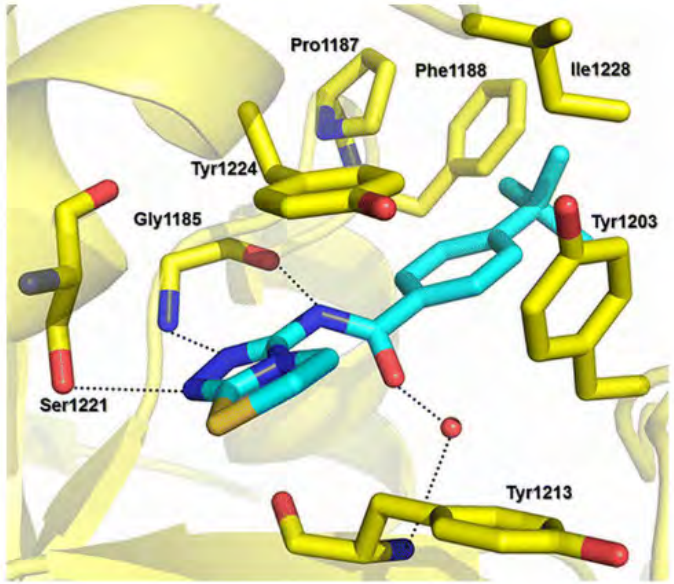
5 HB

JMC 2013, 1341

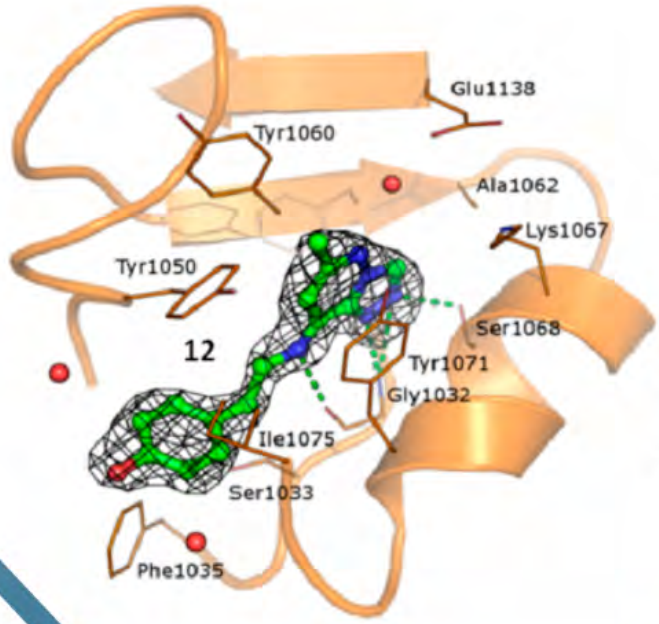




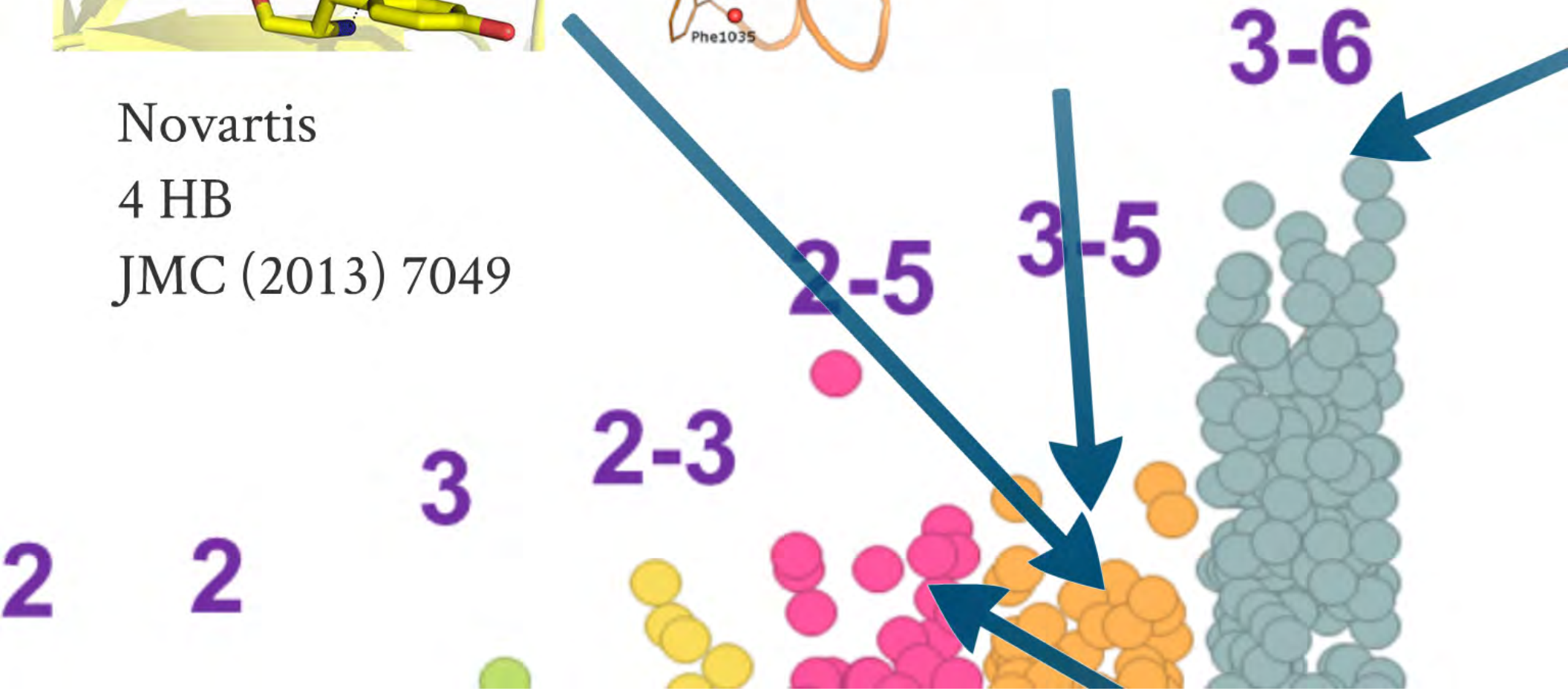




Novartis
4 HB
JMC (2013) 7049



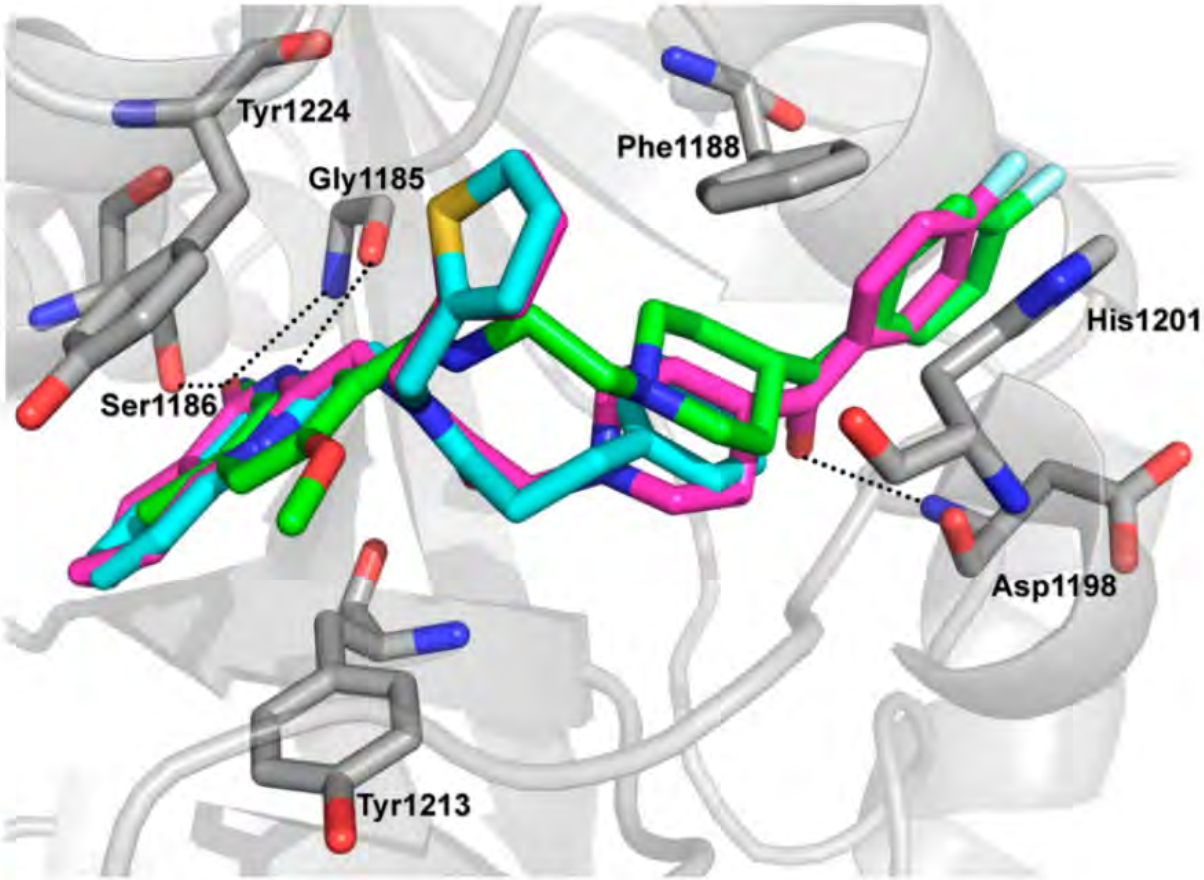
TES Pharma
4 HB
JMC 2014, 2807



S Pharma

IB

C 2014, 2807



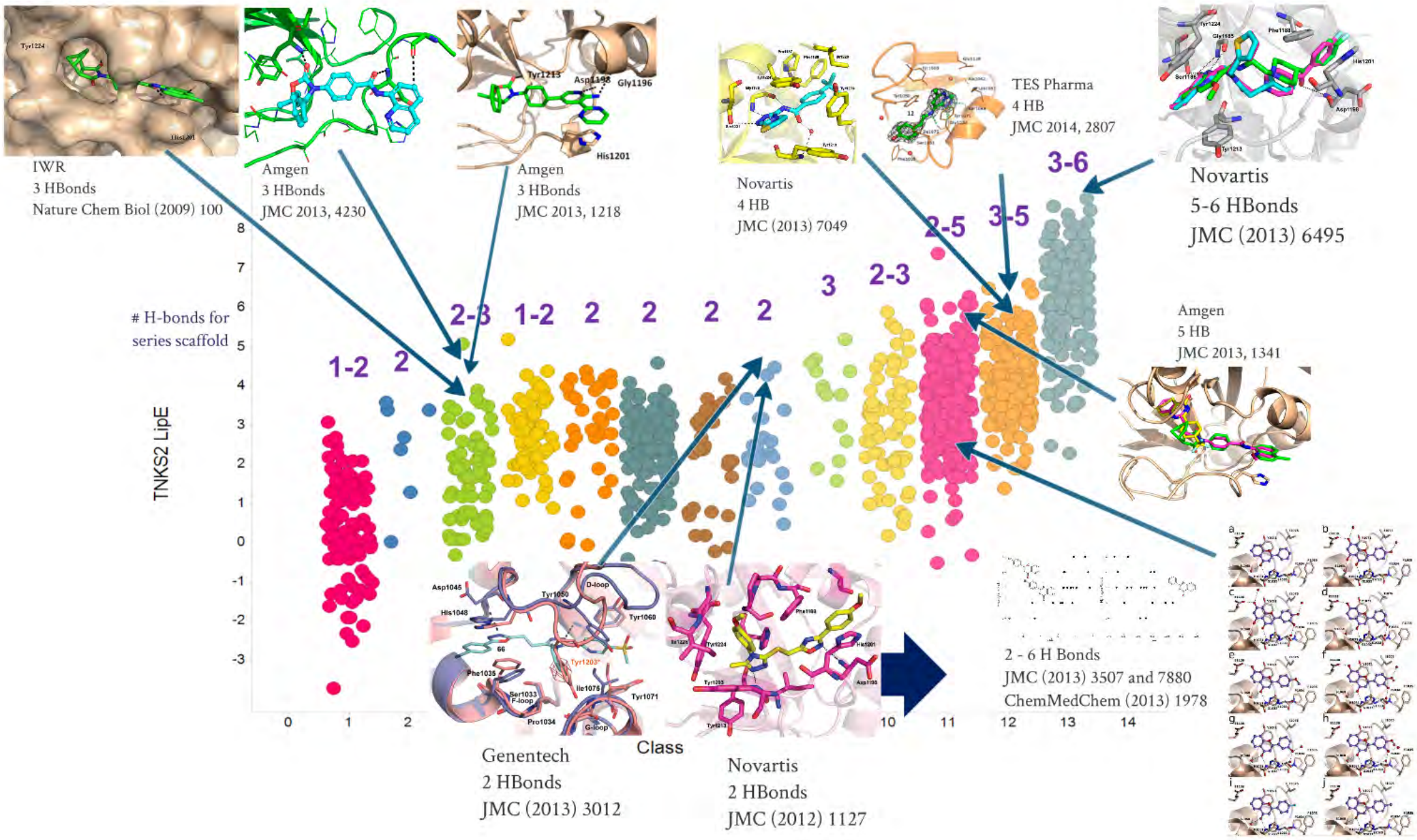
3-6

Novartis

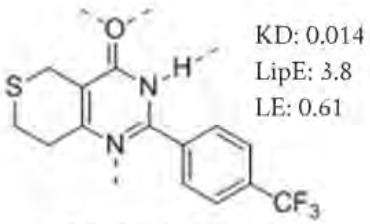
5-6 HBonds

JMC (2013) 6495

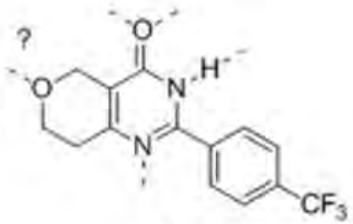
LipE is suitable for hit triage and trends with number of H-bonds across many series



Enthalpic Optimization Followed LipE Optimization



1 XAV939



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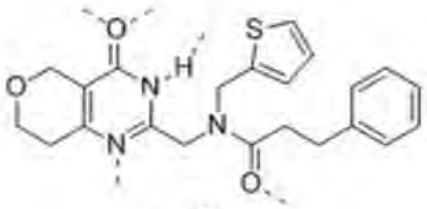

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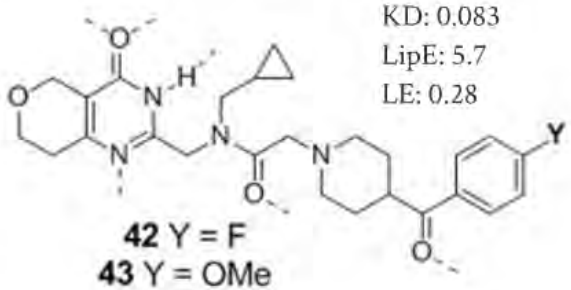
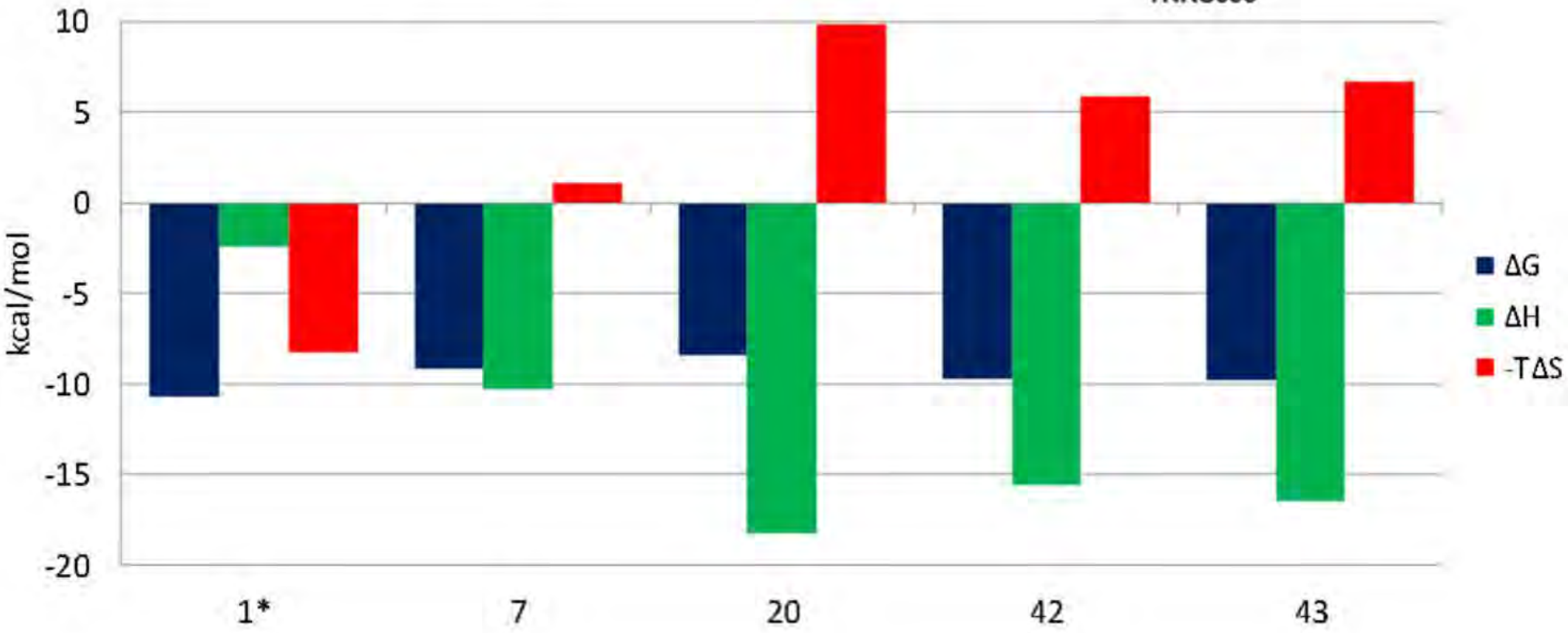


42 Y = F
43 Y = OMe
TNKS656



* J. Med. Chem. 2010, 53, 5352
J. Med. Chem. 2013, 56, 6495

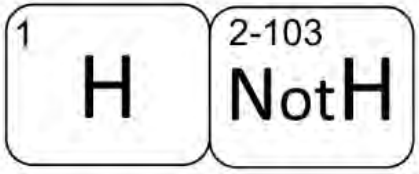
Summary and Conclusions

Ability to characterize what is 'drug-like' is highly overestimated

- We swap probability and plausibility

LE metrics are invalid

- Mathematically valid for averaging
- Mathematically invalid for normalization
- Not all heavy atoms are created equal



LipE has more substantial correlation with success and enthalpy

Scientists are not immune to irrational behavior

- Base rate fallacy, attribute substitution, Texas Sharpshooter fallacy, theory induced blindness, anchoring effect, confirmation bias

All models are wrong, some are useful

LipE was not validated by anything presented today

Kenny et al. J. Comput. Aided Mol. Des. (2014) 699

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