Sandwich Laboratories, Worldwide Medicinal Chemistry

Overview of last 10 years: Successes and failures

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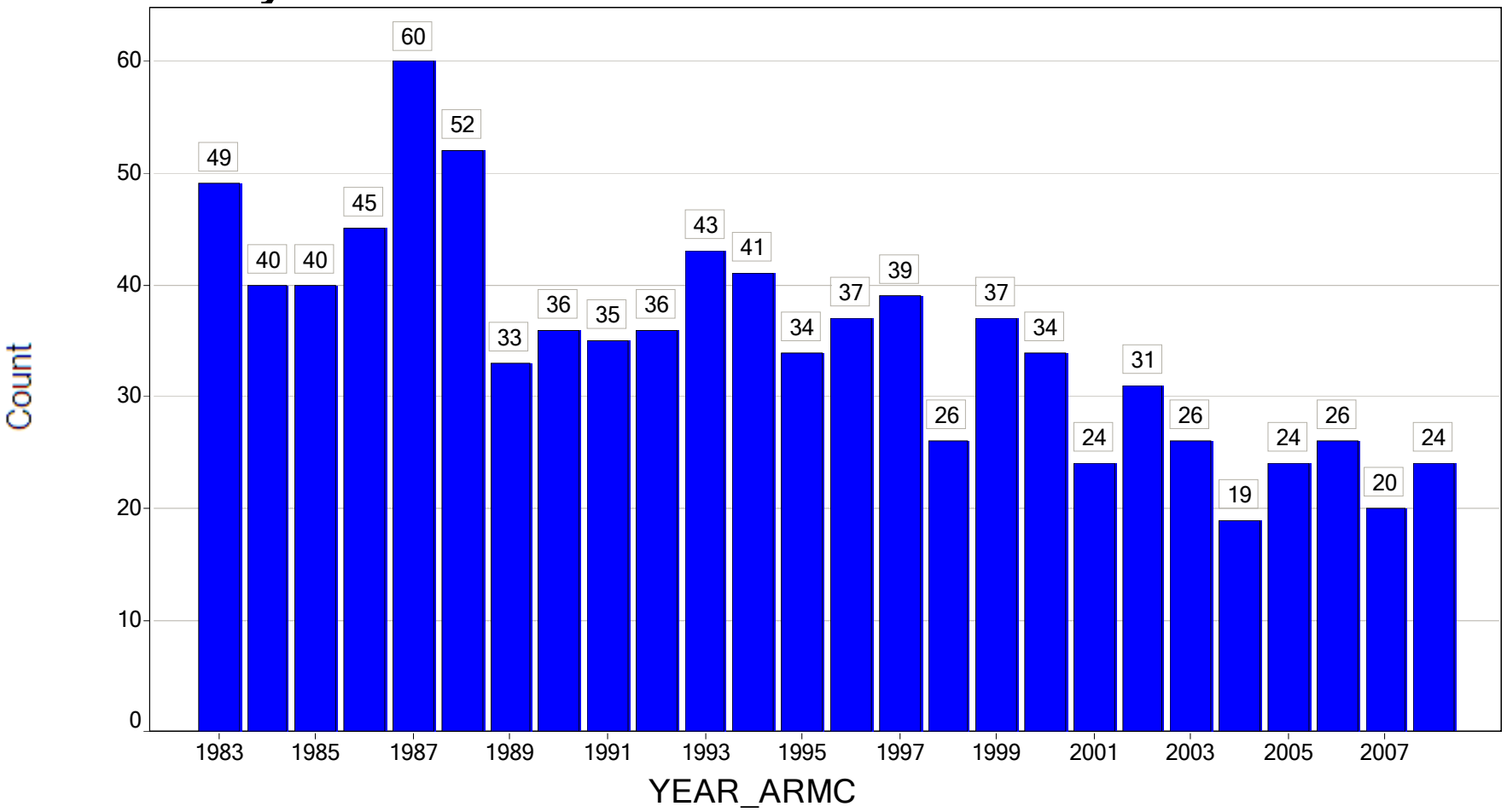
Lead Discovery Chemistry

11th November 2009, SCI meeting

Outline of the talk

- **Drug discovery success and failure**
- **Overview of Lead Generation**
- **HTS successes**
- **Role of combichem**
- **Successful Lead Generation strategies**
  - Ligand Efficiency (LE)
  - Fragment screening
  - Lipophilic ligand Efficiency (LipE/LLE)
  - Enzyme kinetics
- **Conclusions**

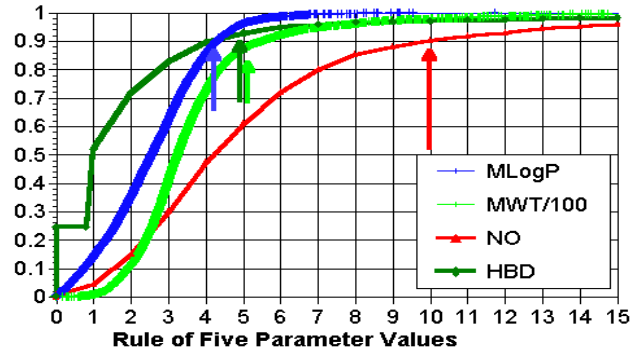
New Drugs Launches recorded In Annual Reports in Medicinal Chemistry

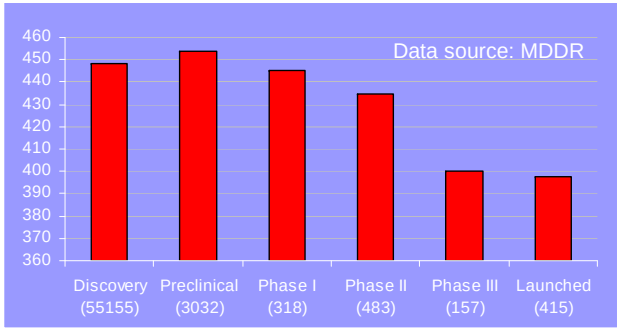


- Drug Launches show steady decline over the last 2 decades
- Fewer new approvals for each biological mechanism

Molecular Properties related to Compound Attrition

- Rule-of-Five: compounds outside the rule of five are less likely to be absorbed.
  - **C. Lipinski *et al*., Adv.Drug Del. Revs. 1997, 23, 3.**
- Strong trend for increasing molecular weight and clogP for 592 launched drugs between ’83 and ‘07.
  - **P.D. Leeson, B. Springthorpe, Nature Rev. Drug Disc. 2007, 6, 881.**
- Average molecular weight of drug candidates decreases from entering development to launch.
  - **Wenlock et al., J. Med. Chem. 2003, 46, 1250.**
- Molecular weight increases from leads to drug candidates by ~ 60 Dalton.
  - **T. I. Oprea et al.; J. Chem. Inf. Comp. Sci. 2001, 41, 1308.**
- Linear relationship between potency and MW in fragment to lead. Properties of the core fragment influence pharmacokinetics.
  - **P.J. Hajduk, J. Med. Chem. 2006, 49, 6972; Nat. Rev. Drug Disc. 2007, 6, 211. Vieth, Drug Discovery Today 2007, 12, 71.**





We need to improve lead discovery

Alex

A few definitions

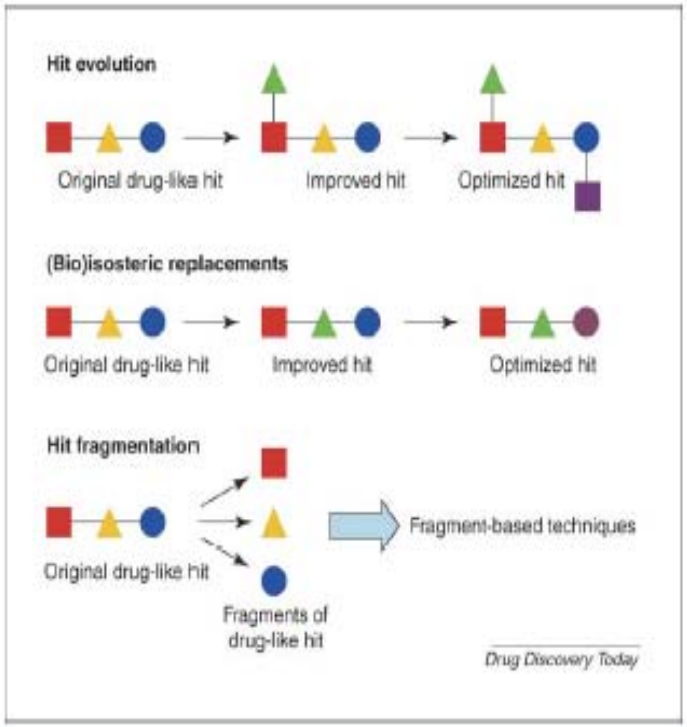


FIGURE 1

Schematic representation of hit-to-lead approaches for drug-like hits. The most common approach for evolving drug-like hits is hit evolution, a systematic SAR-driven analoging process. The strategy of (bio)isosteric displacement is mostly used for improving the pharmacokinetic or pharmacodynamic profile of the lead molecule. Hit fragmentation can be applied when the initial hit is a large molecule that cannot be significantly processed by hit evolution or (bio)isosteric displacement.

Review: Keseru & Makara
Drug Discovery Today Volume 11, Numbers 15/16 August 2006

HTS; Snowden & Green; Current Opinion in Drug Discovery & Development 2008 11(4):553-558

Non-HTS Approaches: Bleicher et al Nature Reviews in Drug Discovery 2003, 2, 369

Compound collection: **Jacoby et al**; *Current Topics in Medicinal Chemistry* 2005, 5, 397-411

Lead Criteria: Steele et al; *Current Topics in Medicinal Chemistry* 2005, 5, 421-439.

Fragment based Drug Discovery: de Esch et al; Drug Discovery Today Volume 14, Numbers 13/14 July 2009

ACS Chemical Biology:Expert Response (J Inglese)

- Are there currently any drugs on the market or in the late clinical phase developed using HT platforms?

  HT platforms have aided in the progression of countless compounds to the chemist's bench for optimization, and then on to early clinical trials, with an expected smaller number progressing to the late clinical phase. However, a number of notable drugs and late stage candidates have emerged from this. The requirement to develop new and effective drugs in shorter time periods will only be possible with the aid of advanced automated technologies. HTS and variations thereof are permeating all steps of drug discovery and development, and the more likely question in the next decade will be, "What newly approved drugs were *not* created with the aid of HT technologies?"

http://community.acs.org/ChemBiol/AsktheExpert/ExpertResponse/tabid/72/Default.aspx?webEditionid=27&qid=5215

Drugs with Origin in Screening and HTS.

Drug	Indication	Launch Year	2008 Sales	Origin
Montelukast (Singulair)	**Anti-asthma**	**1997**	**$7240MM**	**Merck.**
Tipravier (Aptivus)	**HIV (protease)**	**2005**	**$62MM (2007)**	**Boehringer Ingelheim**
Sorafenib (Nexavar)	**Renal cell Carcinoma**	**2006**	**$878MM**	**Bayer**
Sitagliptin (Januvia)	**Anti-hyperglycemic**	**2006**	**$2507MM**	**Merck**
Raltigravir (Isentress)	**HIV (integrase)**	**2007**	**$563MM**	**Merck**
Maraviroc (Selzentry)	**HIV (CCR5 Ant.)**	**2007**	**£46MM**	**Pfizer**
Rivaroxaban (Xarelto)	**Thromboembolism**	**2008**	**n/a**	**Bayer**
Eltromopag (Promacta)	**TPO Mimetic**	**2008**	**n/a**	**GSK-Ligand**

Reference: J. Inglese, Expert Response, *ACS Chemical Biology,* 2008

Any others that you're aware of?

Sorafenib: An Example HTS Drug

- **The introduction and refinement of rapid, high-throughput screening technologies over the past decade has greatly facilitated this targeted discovery and development process. Here, we describe the discovery and continuing development of sorafenib (previously known as BAY 43-9006), the first oral multikinase inhibitor that targets Raf and affects tumour signalling and the tumour vasculature. The discovery cycle of sorafenib (Nexavar; Bayer Pharmaceuticals) — from initial screening for a lead compound to FDA approval for the treatment of advanced renal cell carcinoma in December 2005 — was completed in just 11 years, with approval being received 5 years after the initiation of the first Phase I trial.**
- *Scott Wilhelm, Christopher Carter, Mark Lynch, Timothy Lowinger, Jacques Dumas, Roger A. Smith, Brian Schwartz, Ronit Simantov & Susan Kelley*
  - ***Nature Reviews Drug Discovery* 5, 835-844 (October 2006)**

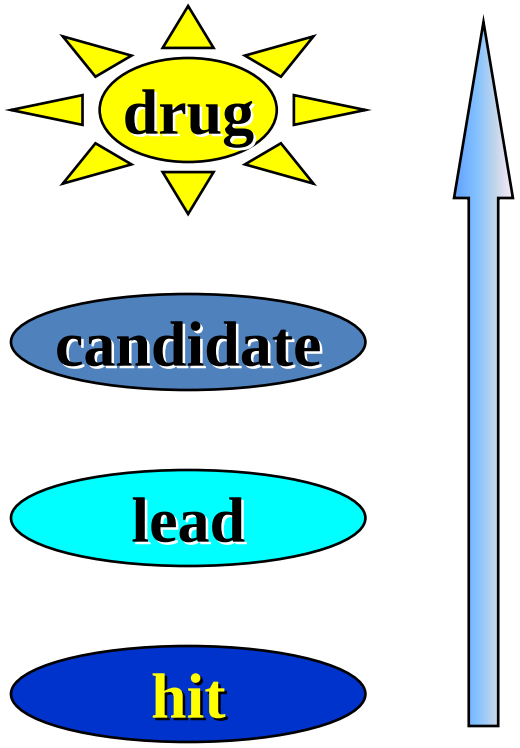
HTS at Pfizer 10 years ago

- **A 500,000 screening file**
  - Of mixed quality and purity
- **Drug discovery fails more often than it succeeds**
- **Fewer targets than before & some very difficult drug targets**
- **Some targets in the past, the industry has succeeded but Pfizer hasn't**
- **One possible cause**
  - Industry file said to be approx 3,000,000 in 1999
  - Pfizer file contained narrow range of structural types

- **Proposal to expand the Pfizer file through a "File Enrichment" Initiative**
- **Early days of parallel chemistry and automation in chemistry and purification**
  - Typical HTS gave 10% of lead matter being parallel chemistry friendly
  - Synthesis capacity > purification capacity

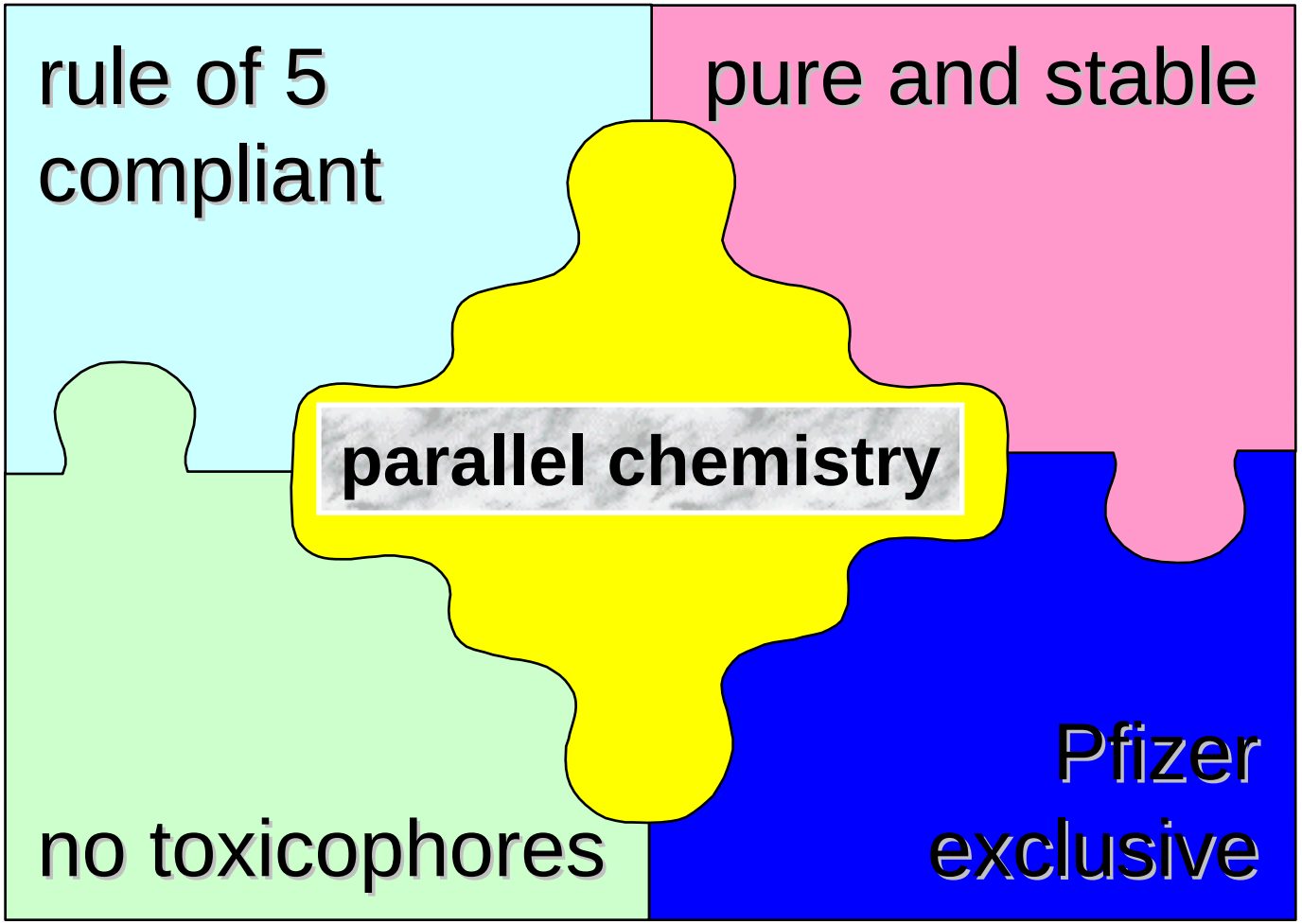
File Enrichment Strategy: consider attrition from outset

- We know what chemotypes are more likely to fail in development
- We know clinical candidates are similar to leads
- Build this knowledge into library design
  - ***Only make and screen drug-like or preferably lead-like compounds***



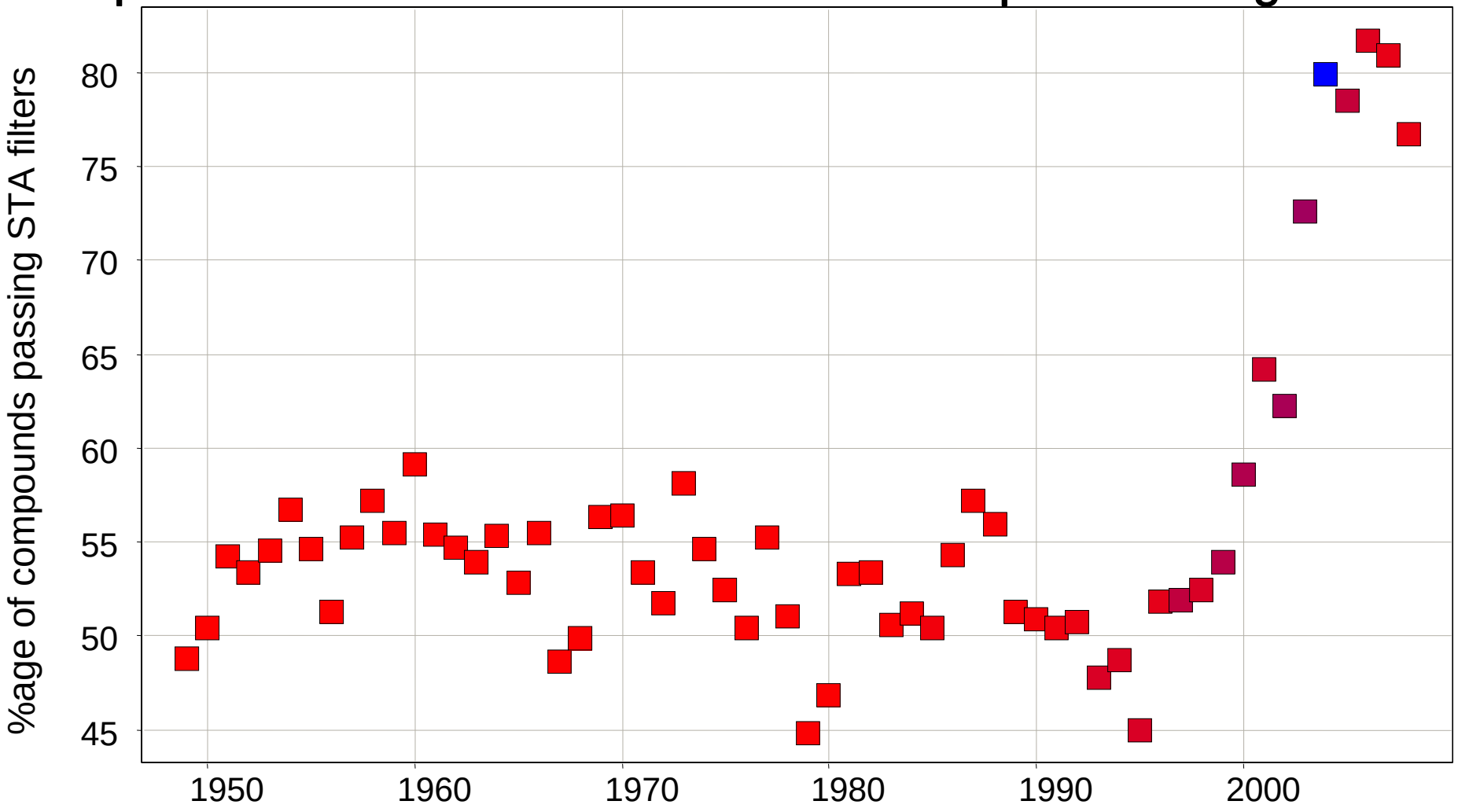
Develop methodology for synthesising compounds in sparse matrices

Beautiful compound concept - 2000



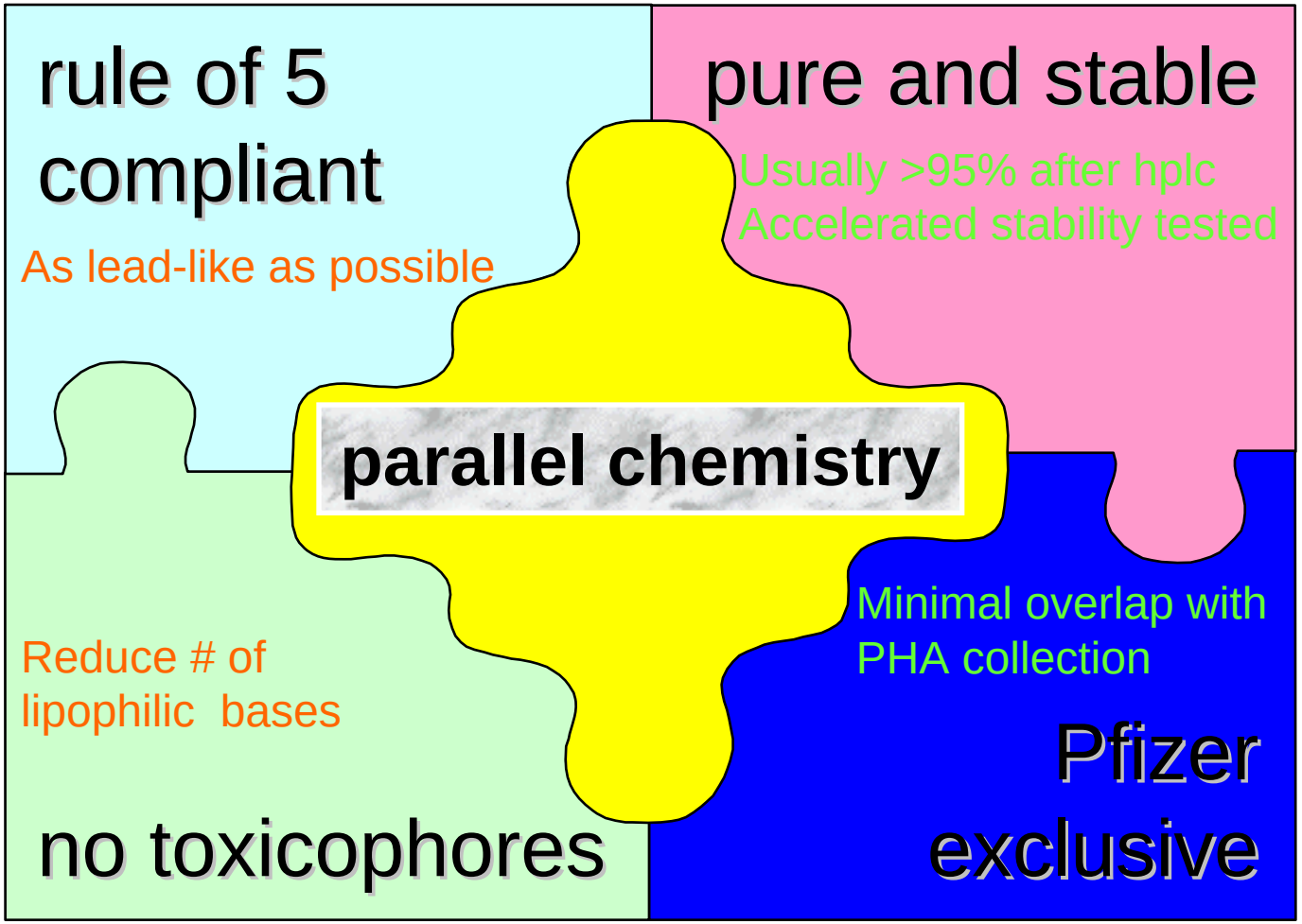
Lipinski, C.A. Chris Lipinski Discusses Life and Chemistry after the Rule of Five. *Drug Discovery Today* **2003**, *8*, 12-16.

Impact of Structural Alert Initiative on Compound Design



Loesel/ van Hoorn

Beautiful compound concept - by 2005



TPSA & cLogP correlate with IVT outcome

- **Combining low PSA and high cLogP exacerbates the risk**
  - (numbers in parentheses indicate number of outcomes in database)
- Odds Ratio* Matrix

Total-Drug	TPSA>75	TPSA<75
ClogP<3	0.39 (57)	1.08 (27)
ClogP>3	0.41 (38)	2.4 (85)

Free-Drug	TPSA>75	TPSA<75
ClogP<3	0.38 (44)	0.5 (27)
ClogP>3	0.81 (29)	2.59 (61)

Annual Reports in Medicinal Chemistry, 2006; Volume 41 pp 353

* Ratio of toxic to non-toxic outcomes

Blagg

Low PSA and High cLogP leads to Promiscuity

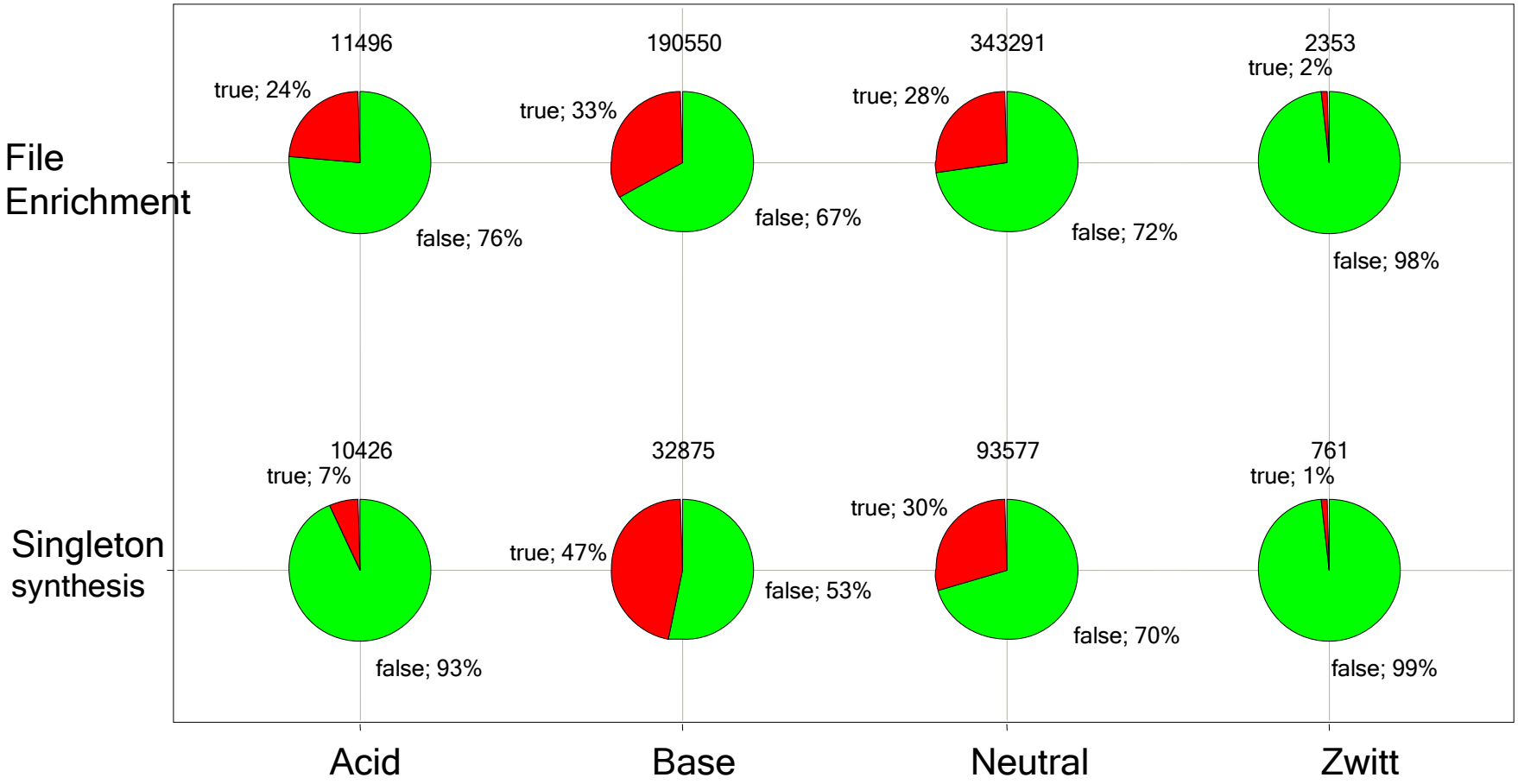
(As defined by activity in >2 Bioprint assays)

	TPSA>75	TPSA<75
ClogP<3	0.25 (25)	0.80 (18)
ClogP>3	0.44 (13)	6.25 (29)

* Ratio of promiscuous to non-promiscuous compounds

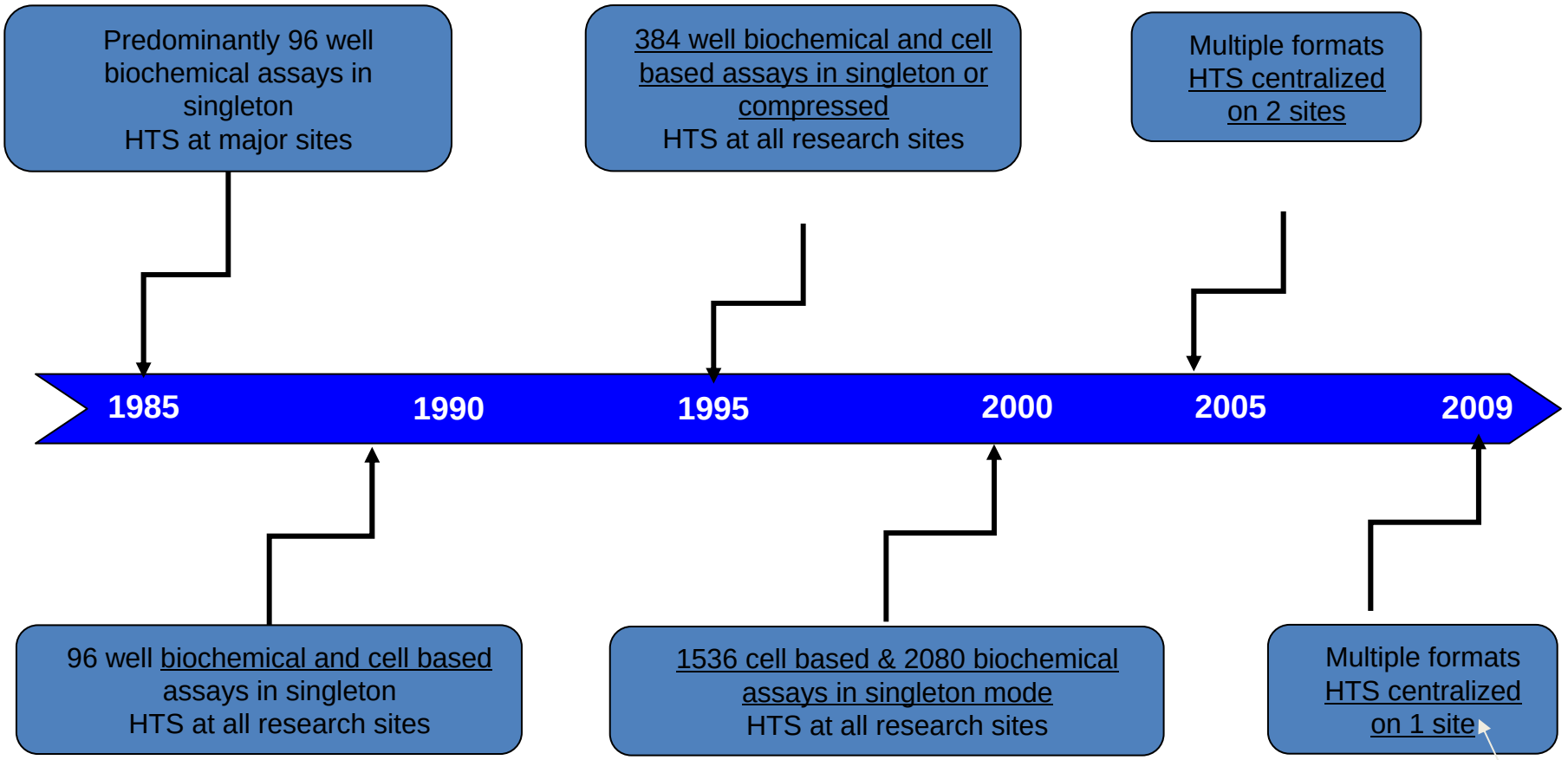
- **Promiscuity defined as >50% activity in >2 Bioprint assay out of a set of 48 (selected for data coverage only)**
- **Maybe be a surrogate for off-target potency and hence tox potential (?)**

Influence of Beyond Structural Alert Initiative on Compound Properties



Increased focus on compound properties has helped ensure that new additions to the screen file minimise attrition

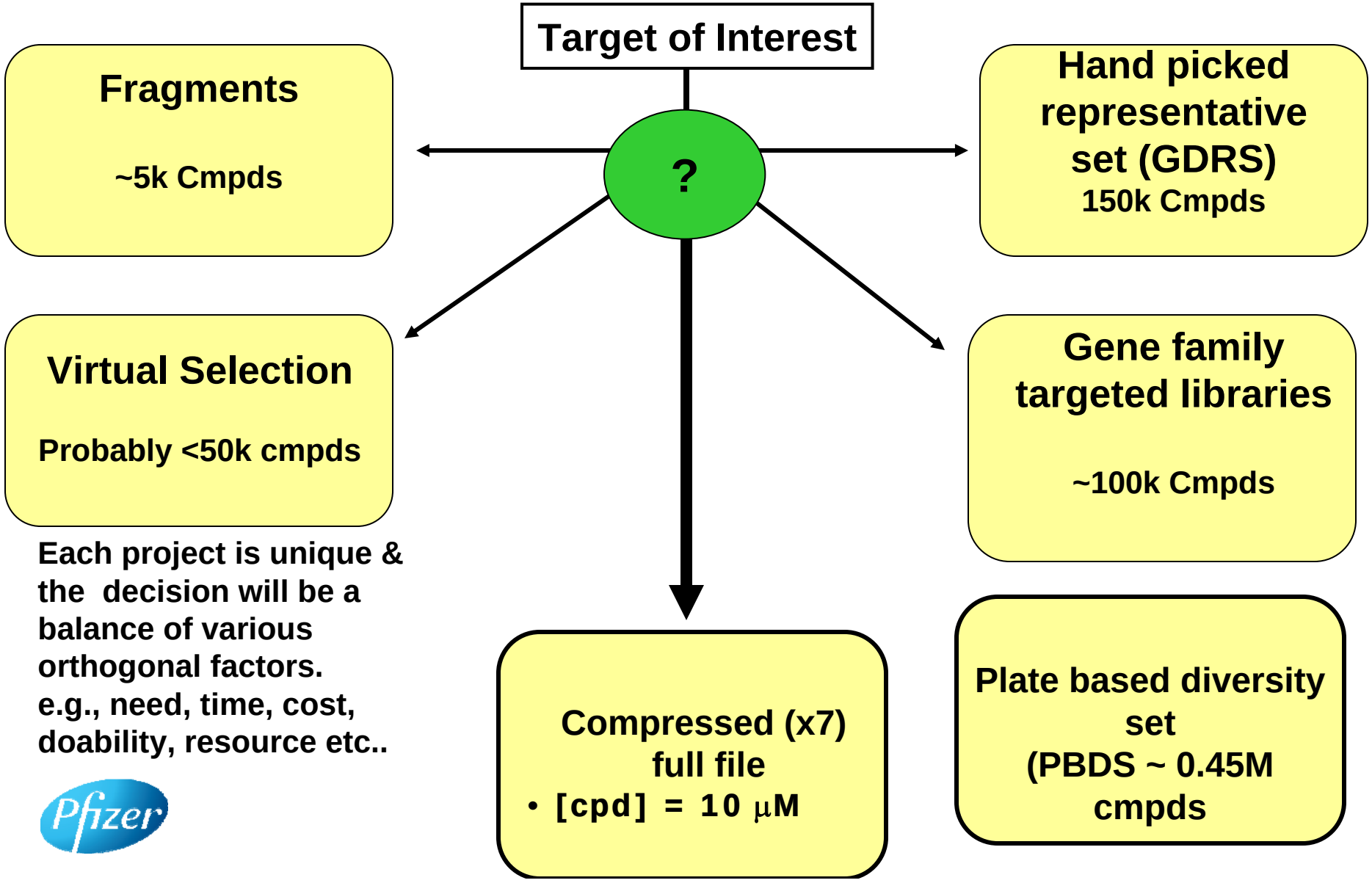
HTS at Pfizer



BMS Approach: Drug Discovery Today Volume 13, Numbers 1/2 January 2008

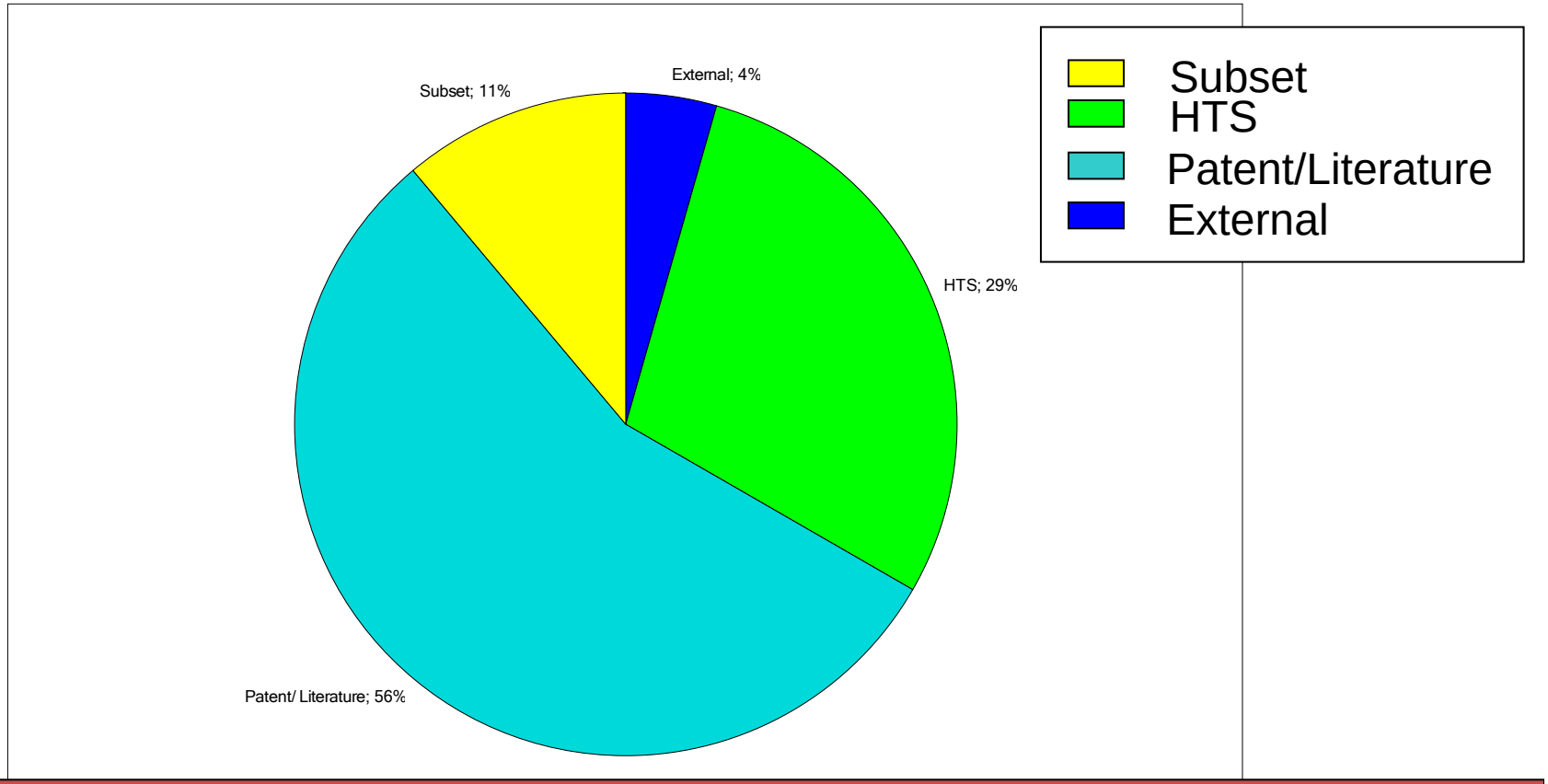
Williams

Screening Options



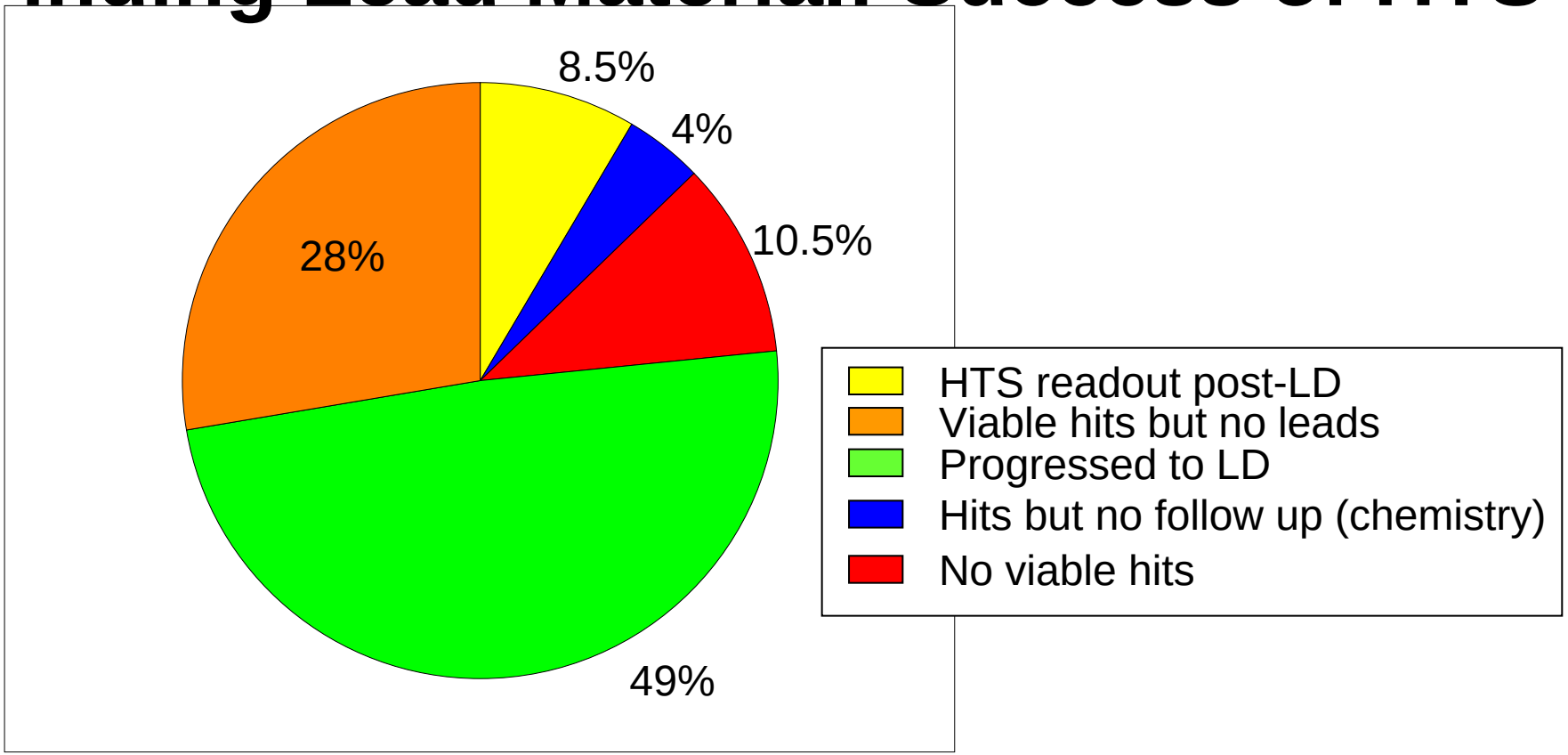
Each project is unique & the decision will be a balance of various orthogonal factors.
e.g., need, time, cost, doability, resource etc..

Finding Lead Material: Source of chemical matter



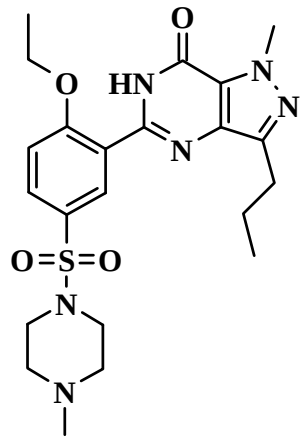
HTS + subset screening identified 40% of the leads nominated between 2005 & 2007.

Finding Lead Material: Success of HTS

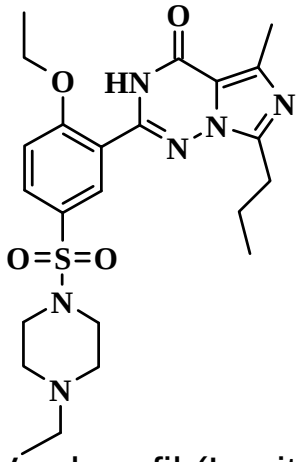


- In the 2005-2007 lead cohort, 90% of HTS identified viable hits & of these 55% were successful in generating leads

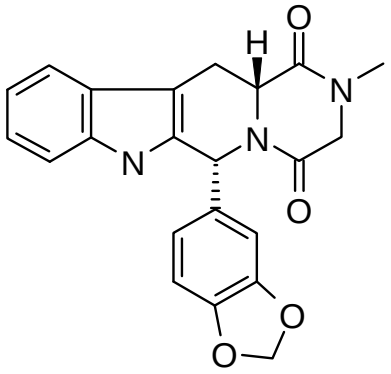
Discovery of 2nd generation PDE5i



Sildenafil (Viagra)
PDE5 IC_{50} 3.5nM
10-fold selective vs PDE6
780-fold selective vs PDE11
Human $T_{1/2}$ 3-5h



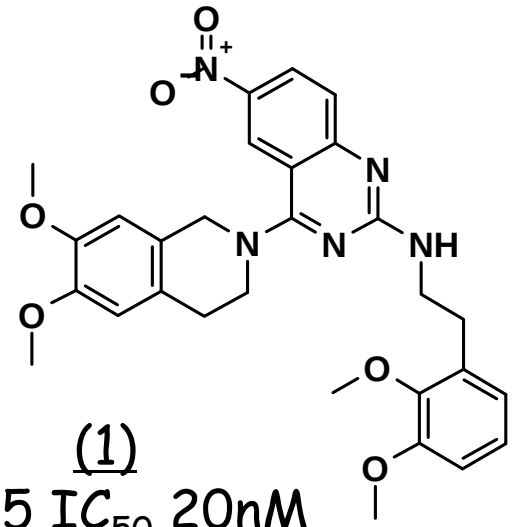
Vardenafil (Levitra)
PDE5 IC_{50} 0.1nM
25-fold selective vs PDE6
1000-fold selective vs PDE11
Human $T_{1/2}$ 3-5h



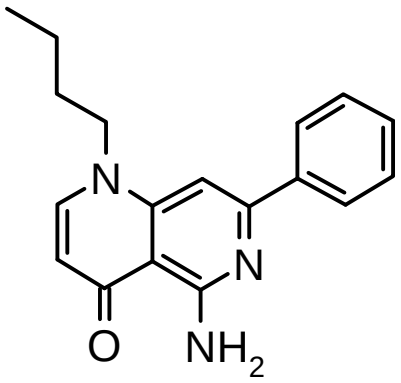
Tadalafil (Cialis)
PDE5 IC_{50} 5nM
187-fold selective vs PDE6
5-fold selective vs PDE11
Human $T_{1/2}$ 17h

- **Need for selective, long duration PDE5i for chronic diseases**
- **Current drugs considered not to be ideal starting points for 2nd generation series**
  - Sildenafil template not amenable to intrinsically long half-life.
  - Non-ideal selectivity over all other PDE's.

PDE5i HTS series



(1)
PDE5 IC_{50} 20nM
cLogP 5.4
MWt 547
LE 0.27
Nitro group



(2)
PDE5 IC_{50} 51nM
cLogP 3.0
MWt 294
LE 0.45
Synthetically challenging

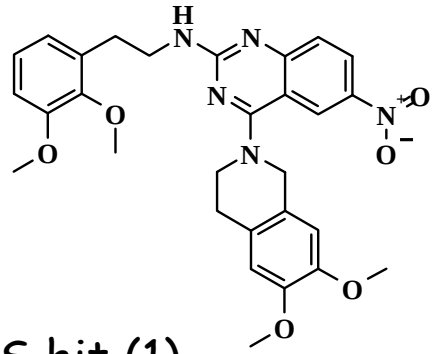
Ligand Efficiency (LE): A method for normalisation of MW & Potency

Useful property to rank lead series. How efficient is each (heavy) atom?

LE = -1.4logKi/n (n = # of non H atoms)

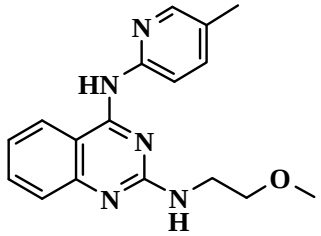
Drug Discovery Today, **2004**,9(10), 430

PDE5i Series 1 hit to lead



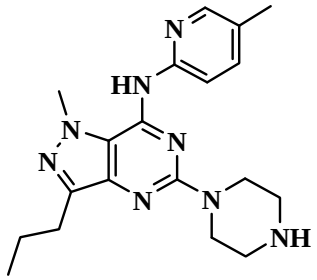
HTS hit (1)
PDE5 IC_{50} 20nM
cLogP 5.4
MWt 547
Nitro group
LE 0.27

Library 1:
SAR & scope



(2)
PDE5 255nM
cLogP 3.5
MWt 309
LE 0.4

Library 2:
Templates,
Phys chem



(3)
PDE5 71nM
cLogP 3.1
MWt 366
LE 0.37

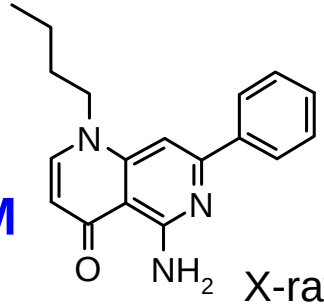
- ✓Unlike sildenafil series, piperazine was part of PDE pharmacophore.
- ✓Lead has evidence of selectivity.
- ✓Dog PK on lead demonstrated potential for od dosing
- ✓Subsequent candidate has 14h half-life in man

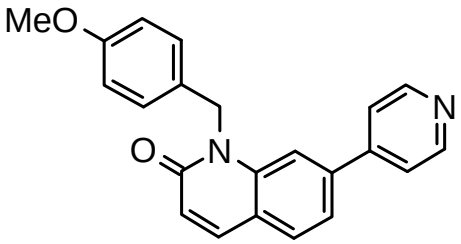
Palmer

PDE5i Series 2 - parallel enablement

PDE5 IC_{50} 51nM

PDE6 IC_{50} 150nM

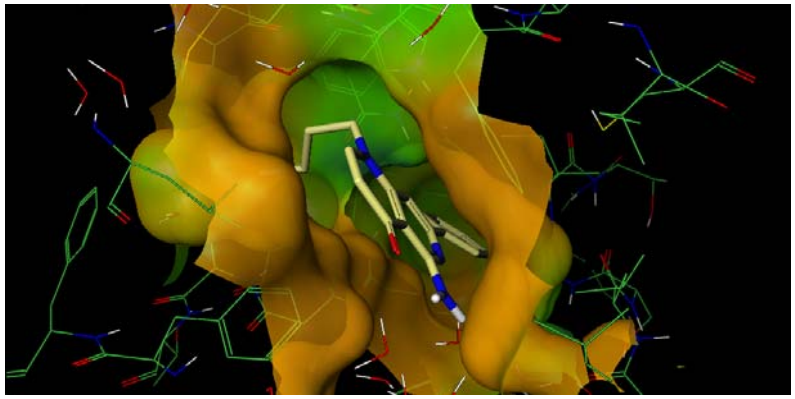


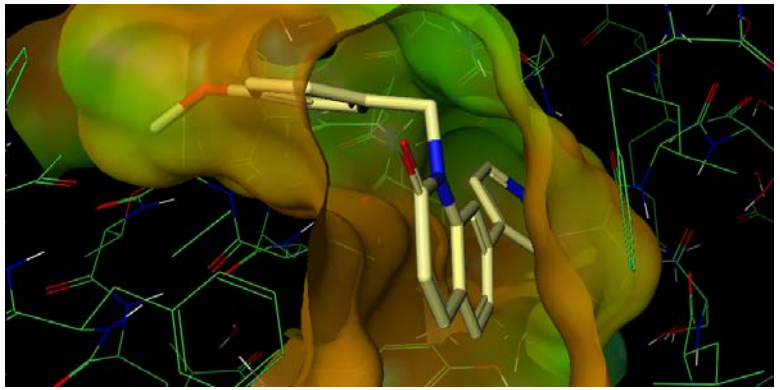


PDE5 IC_{50} 25nM

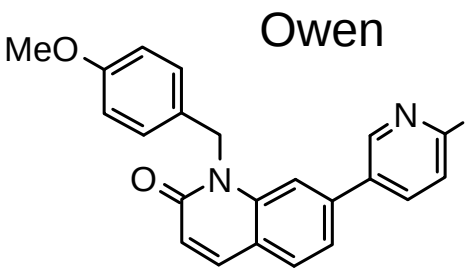
PDE6 IC_{50} 150nM

X-ray guided synthesis enablement





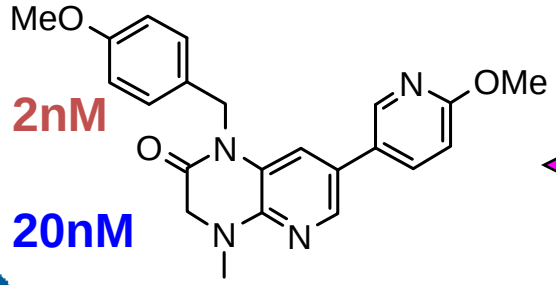
Owen



PDE5 IC_{50} 74nM

PDE6 IC_{50} 370nM

Parallel chem used to eliminate PDE11 activity

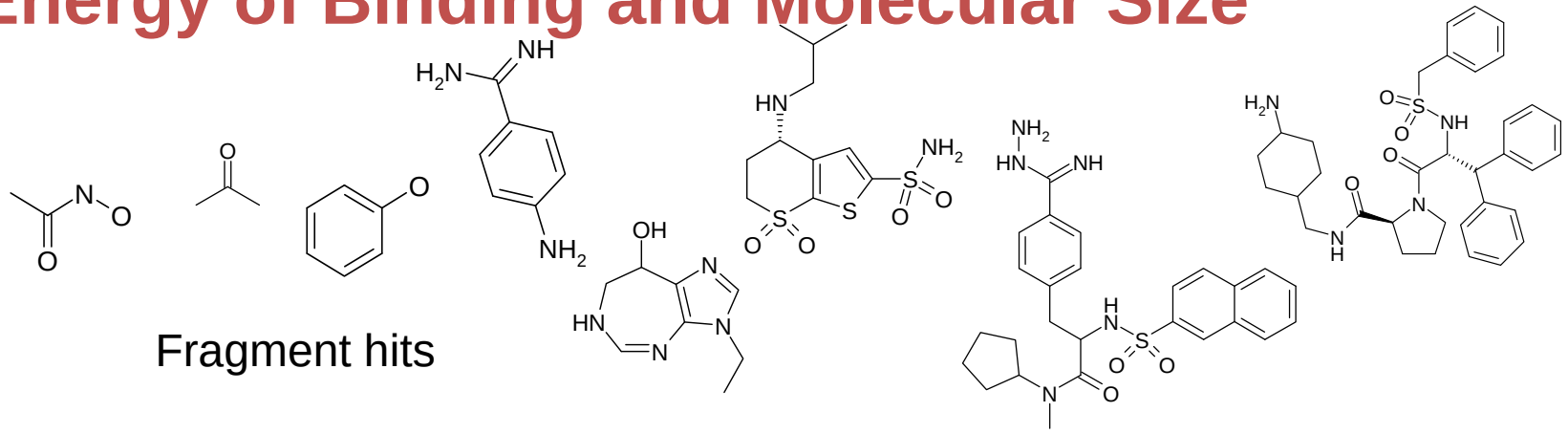


PDE5 IC_{50} 2nM

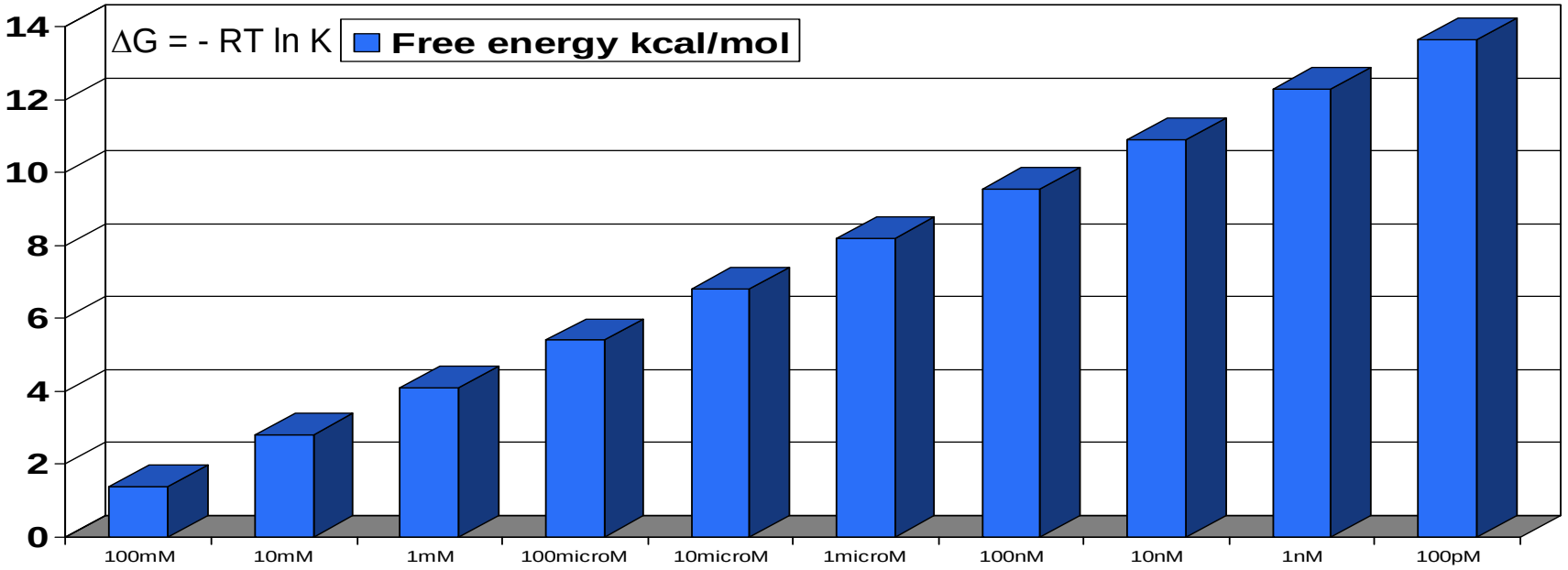
PDE6 IC_{50} 20nM

Alternative template to improve PK

Free Energy of Binding and Molecular Size



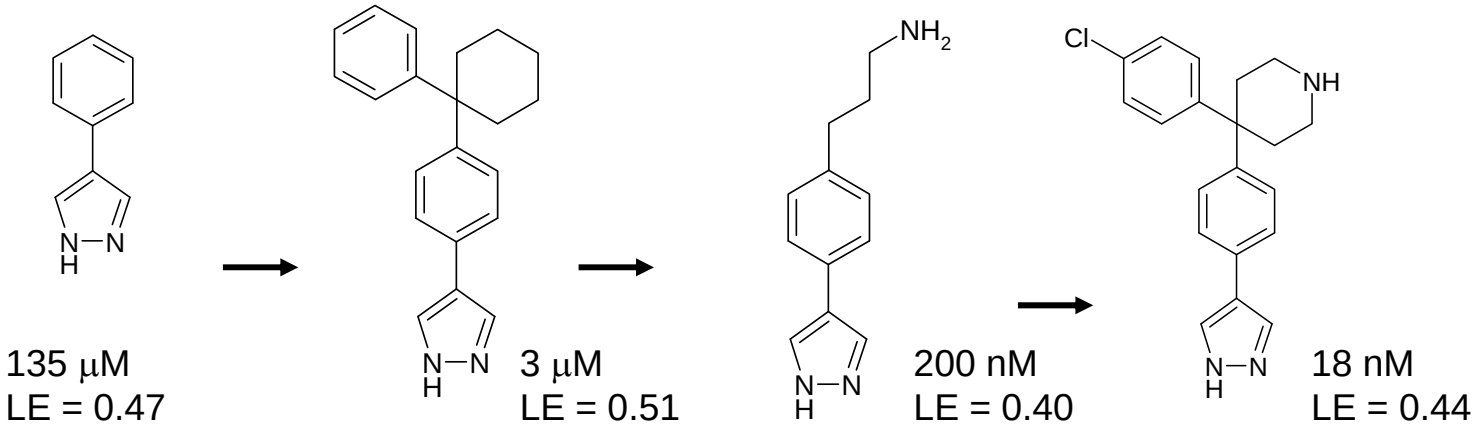
Fragment hits

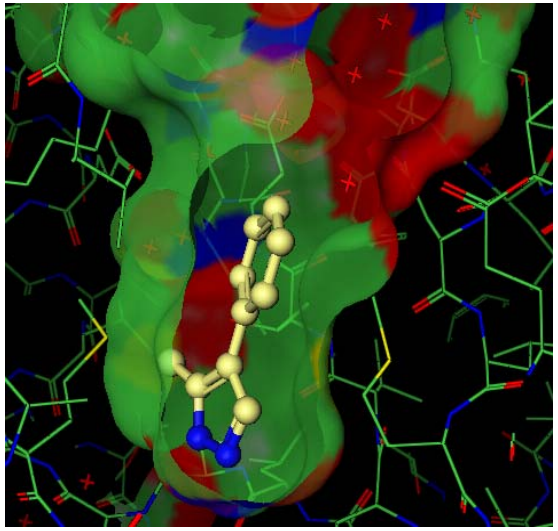


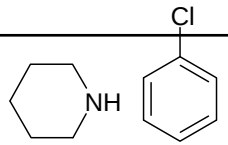
10 fold increase in potency = constant = -1.4 kcal/mol

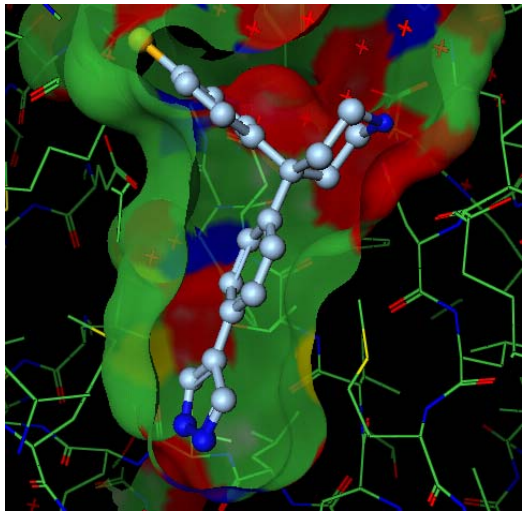
A.A. Alex, M.M. Flocco, Curr. Top. Med. Chem. 2007, 7, 1544-1567

Fragment Hit to Lead: Protein Kinase B (X-ray)



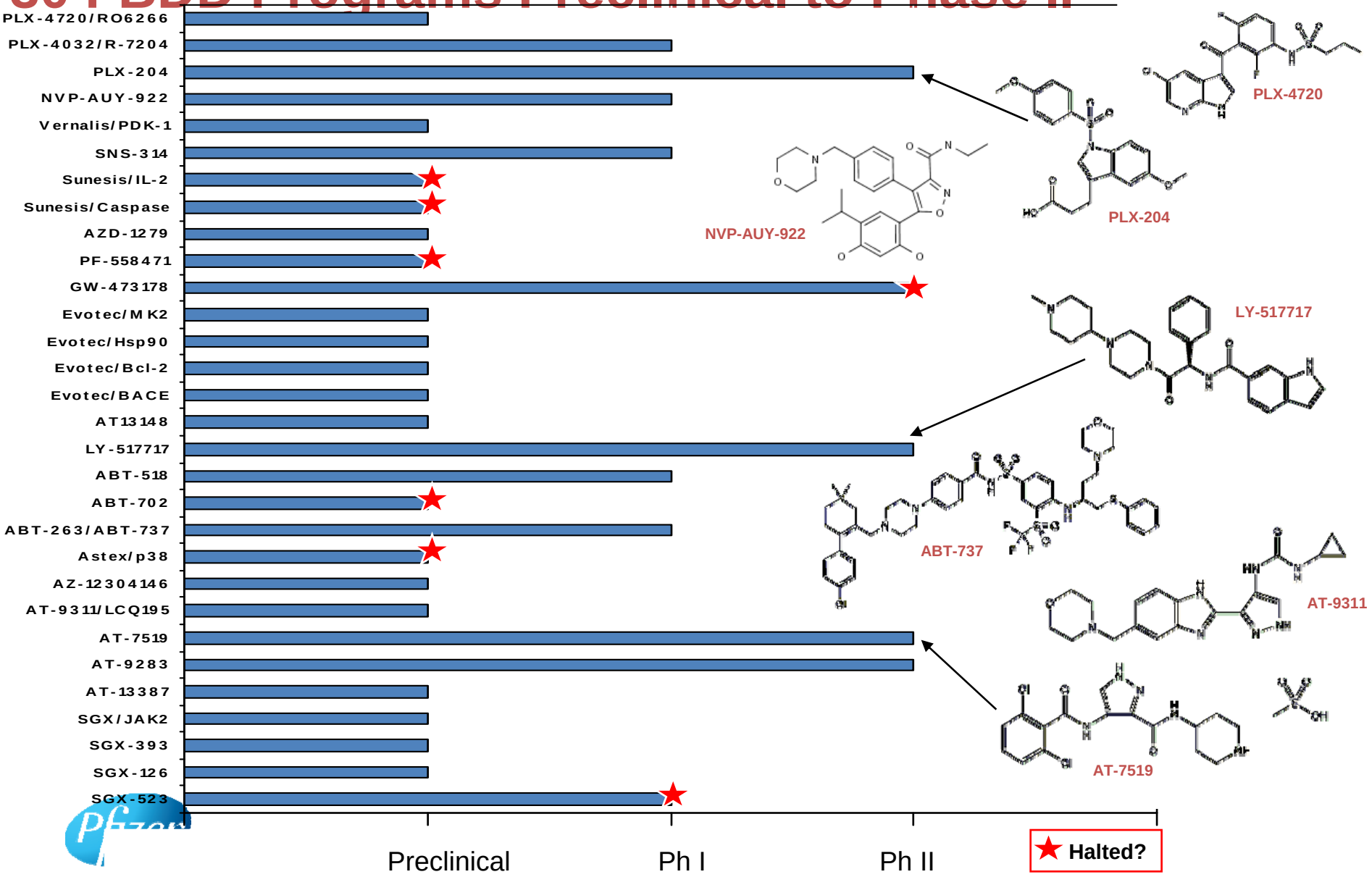


MW increase	**+ 193**
Potency increase	**+ 3.92 kcal/mol**
LE	**- 0.03**
clogP increase	**2.47**
Lipophilic binding increase	**3.36 kcal/mol**
Fragments added	



G. Saxty et al., J. Med. Chem. 2007, 50, 2293-2296, pdb 2uw3, 2uw4, 2uw5, 2uw6, 2uw7, 2uw8.

30 FBDD Programs Preclinical to Phase II



Focus on LipE - a measure of lipophilic ligand efficiency

- In theory, a one unit increase in LogD should result in a 10-fold increase in binding due to the hydrophobic effect.

  ΔG_H =
  - 0.03 kcal/mol/Å^2 buried hydrophobic surface
  - ~ 1.36 kcal/mol gain per unit LogP
  - 10 fold increase in potency
- However, increasing lipophilicity frequently detrimental to drug-like properties (PK, aqueous solubility, polypharmacology).

- LipE = -Log(activity) – LogD

- LipE Plot: graph of - Log(activity) vs. LogD(clogP)
  - a way to visualize the balance between lipophilicity and potency
- The compound with the highest LipE is the most efficient expression of potency for lipophilicity – the most bang for your buck

Edwards *et al*, Biorg. Med Chem. Lett., **2009**, 19, 4406

Progesterone Antagonist Hit-to-Lead

Hit compound

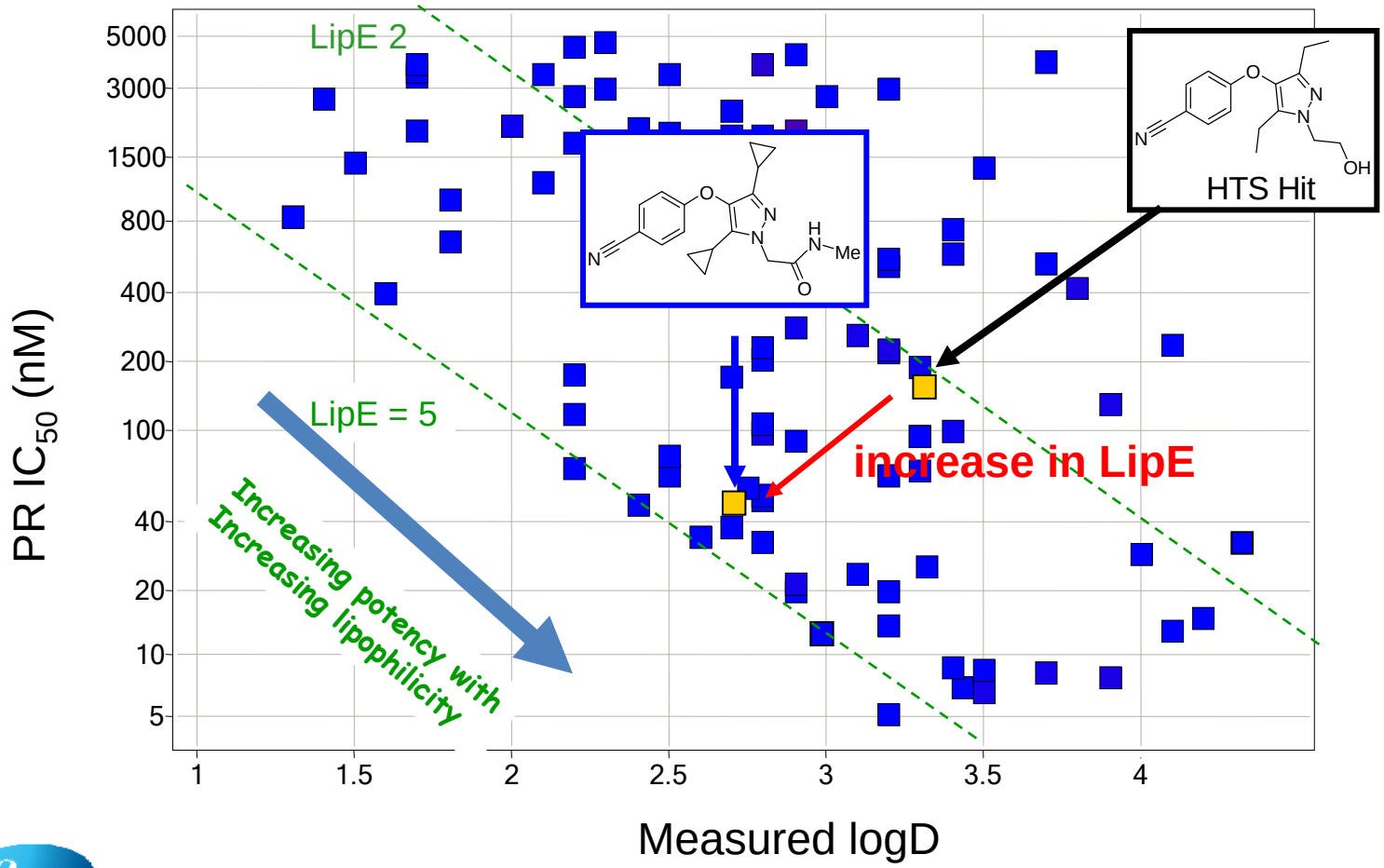
PR IC_{50} ~140 nM
logD 4.7
HLM Clint >50 µL/min/mg
<30x selective over AR

PF-2367982

PR IC_{50} 50 nM, K_b 26 nM
logD 2.6
HLM Clint 9 µL/min/mg
>100 fold selective over AR

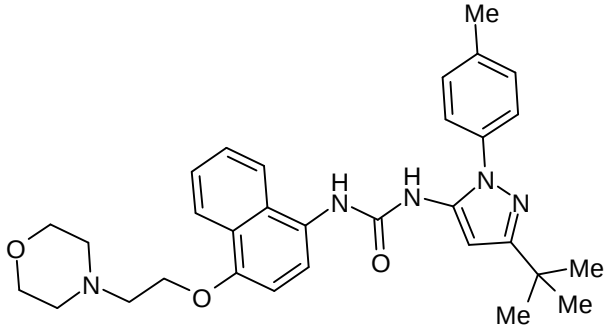
- Hit to lead (PF-2367982): use of optimised lipophilicity and polar groups to control logD, lower clearance & avoid selectivity issues.
- Compound binding efficiencies monitored by lipophilic ligand efficiency score (LipE).

Pyrazole series : LipE Plot



LipE = -log(IC_{50})-logD

Role for enzyme kinetics in lead generation

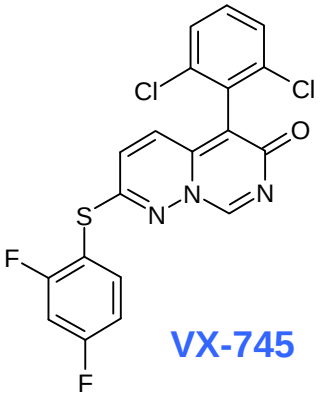


BIRB-796 (oral)

Boehringer Ingelheim

- **Oral p38 MAP kinase inhibitors are anti-inflammatory in humans and have progressed to advanced PhII-PhIII trials (RA, psoriasis, etc)**
  - e.g. BIRB-796 (doramapimod)
- **p38 expression and activation is increased in the lungs of COPD patients**
- **Oral p38i appear to be dose limited due to likely mechanism-based AEs**
- **Inhaled p38 inhibitors could maximise efficacy and TI for treatment of COPD**

p38 Inhibitor leads – looking beyond the Ki



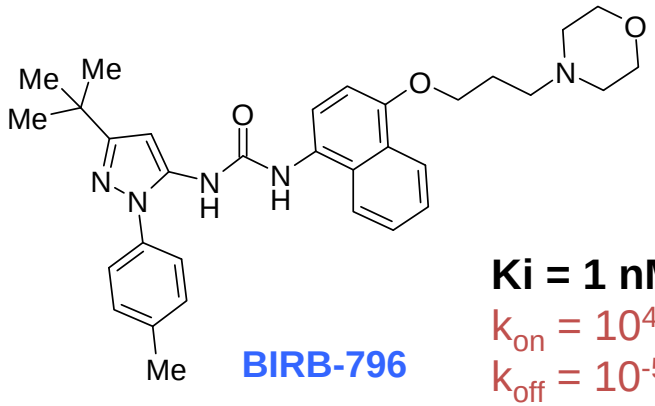
VX-745

Ki = 1 nM

k_{on} = 5 x 10^{7} $M^{-1}s^{-1}$

k_{off} = 5 x 10^{-2} s^{-1}

t1/2 ~ 30 s



BIRB-796

Ki = 1 nM

k_{on} = 10^{4} $M^{-1}s^{-1}$

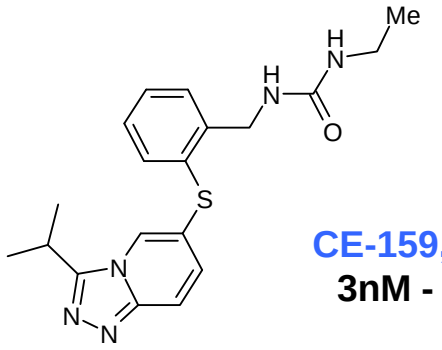
k_{off} = 10^{-5} s^{-1}

t1/2 ~ 23 hours (69,120 s)

- **VX-745 binds at ATP site in DFG-IN mode**
  - fast association & fast dissociation
- **BIRB-796 binds into pocket created by DFG-OUT loop movement & then enters ATP site**
  - slow association & slow dissociation
- **Potential for inhaled anti-inflammatory kinase inhibitor with once-daily dosing driven by slow offset kinetics ?**

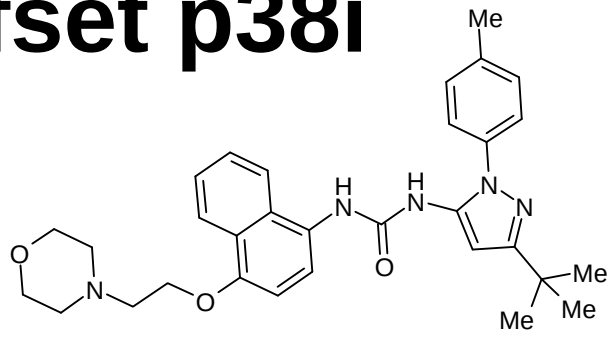
Mathias/Millan/Lewthwaite

Design of slow offset p38i

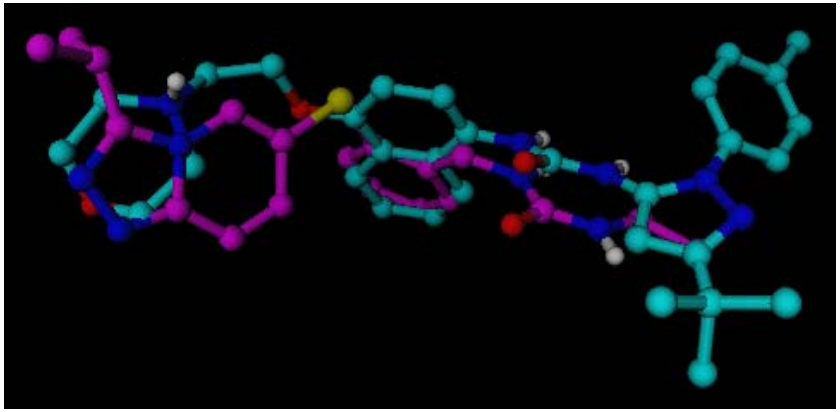


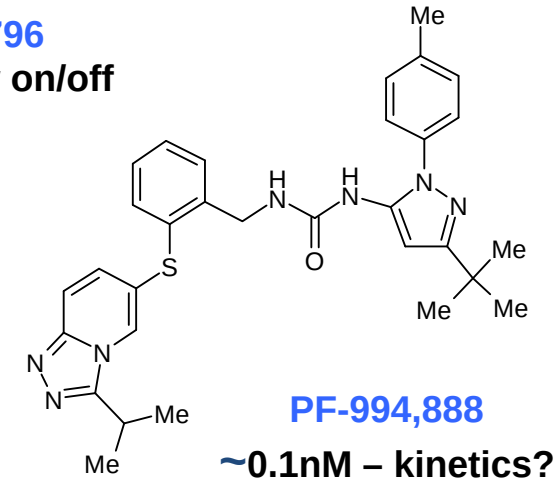
CE-159,167 (Pfizer)
3nM - fast on/off

+



BIRB-796
1nM - slow on/off

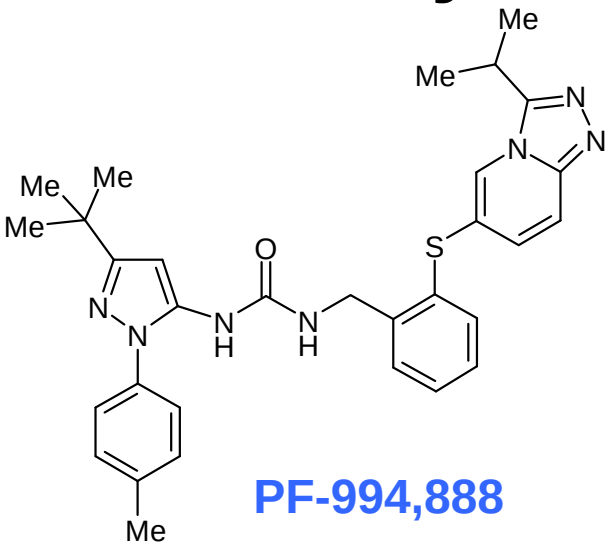




PF-994,888
~0.1nM – kinetics?

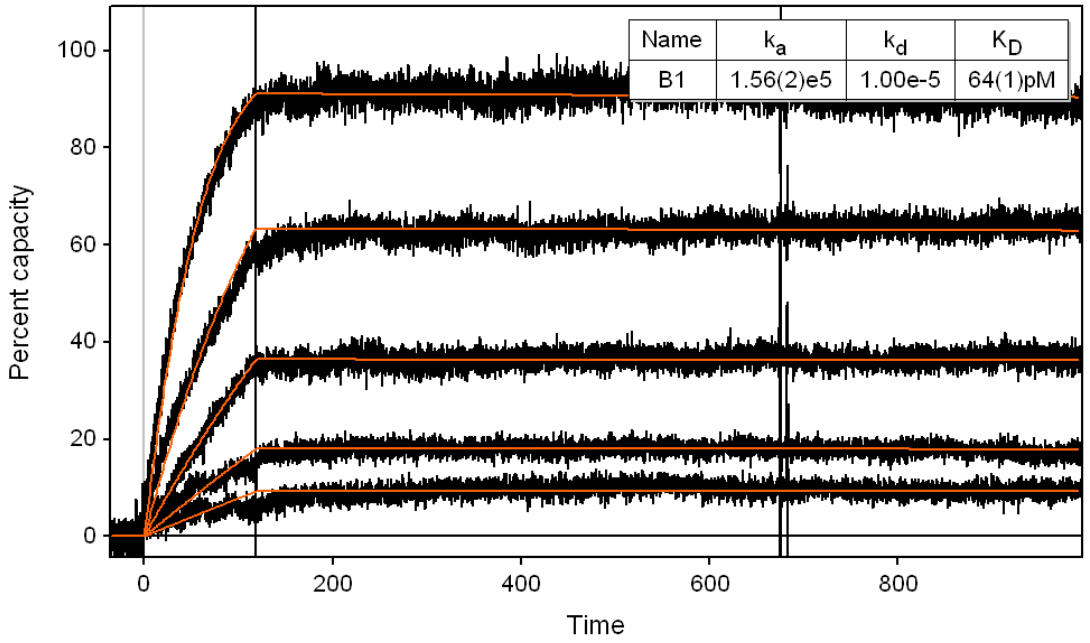
- **Slow offset by design?**
  - use p38 crystal-structure overlays to combine BIRB aryl pyrazole motif (DFG-out & slow offset) with Pfizer p38i triazolopyridine group (ATP site potency & selectivity)

SPR Analysis of PF-994,888



PF-994,888

K_D (p38) ~0.1 nM
kon ~10^5 $M^{-1}s^{-1}$
koff ~ 10^{-5} s^{-1}

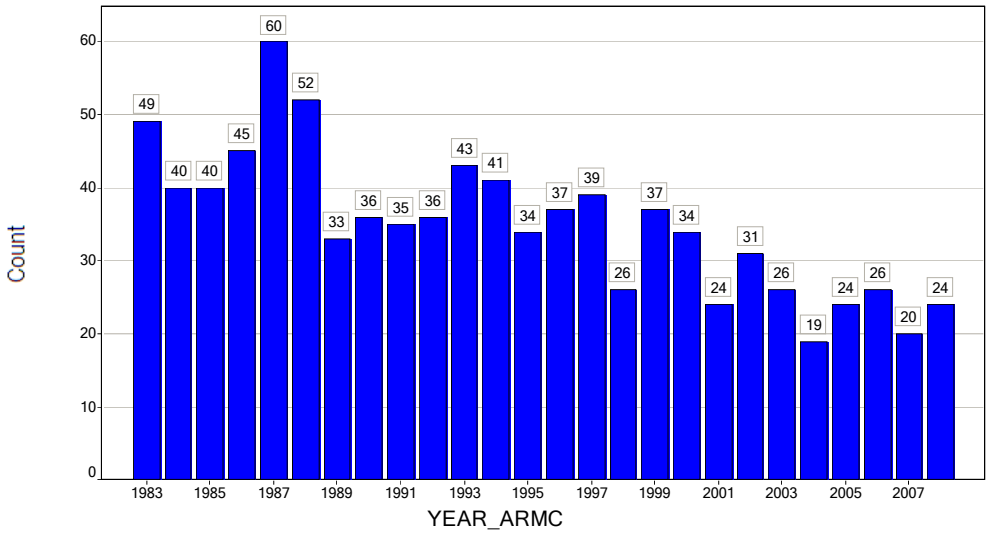


- **Slow offset (t1/2 ~24hr) established by SPR and confirmed using classical enzyme kinetic studies**

Conclusions

- Greater focus on lead generation technologies has increased chances of HTS success
- Considerations of LE and LipE have resulted in higher quality leads than earlier HTS
- Evolution of combinatorial chemistry as a tool
- Plenty of opportunity for further development (kinetics, PK…….)

Bar Chart



Add your comments here.

The height of a bar represents the number of records.

The labels show the height of each bar.