Exploring Chemical Space

Medicinally Relevant Chemical Space and Consequences for Synthesis

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CVGI Innovative Medicines
AstraZeneca

Exploring Chemical Space: Synthesising the Drugs of Tomorrow
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SCI HQ, London

AstraZeneca

Medicinally Relevant Space

Our understanding of medicinally relevant space

- Physical / bulk properties of desirable space
- The constraints this places on desirable structures
- Our attempts to evolve synthetic capability in this direction

Medicinally Relevant Space

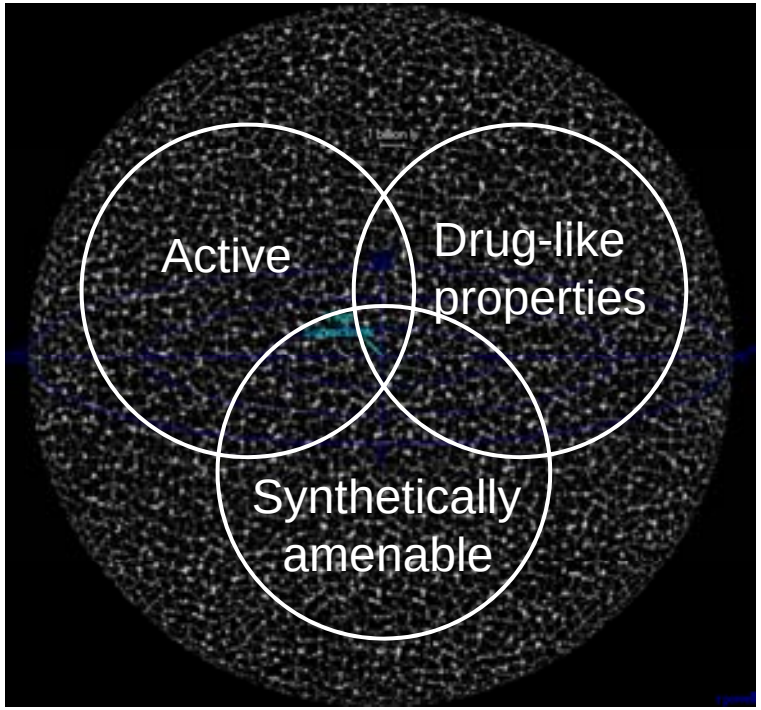
There are between 10^{62} and 10^{200} possible "drug-like" molecules[1,2]

10^{62} molecules of gas occupy ~2 cubes 10^{10} km wide

The sun is ~10^{8} km from earth

10^{200} molecules of gas occupy ~2 cubes 10^{43} lightyears wide

The visible universe extends 1.4×10^{10} lightyears from us



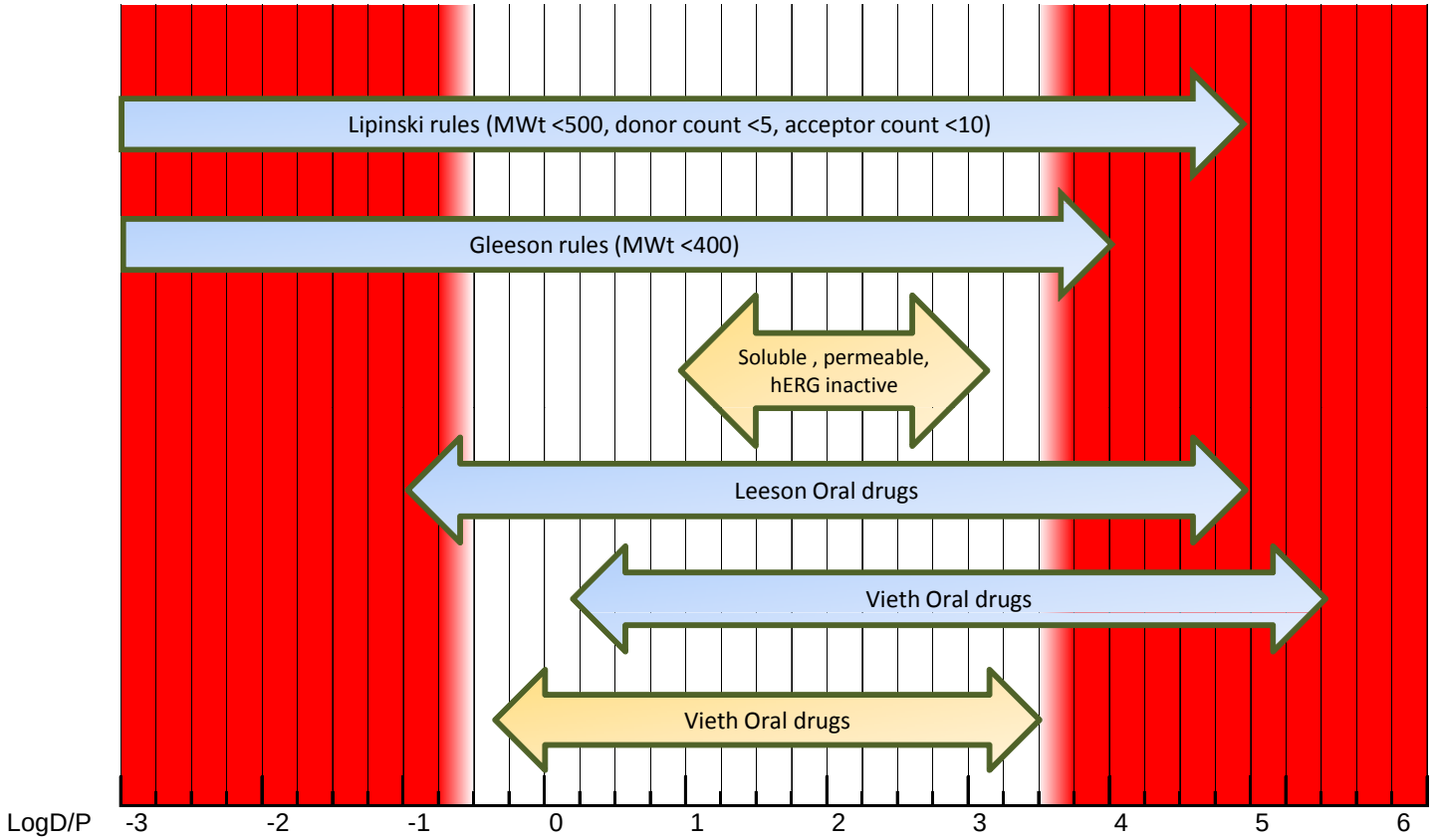
Medicinally relevant chemical space is defined by nature – substructures and bulk properties

Medicinally relevant chemical space is limited by the reactions we can do

"The size of the universe depresses many people but not me, I am delighted by it" – Alan Watts

1. R. S. Bohacek et al. *Med. Res. Rev.* **1996**, *16*, 3
2. M. J. Owen, *Biotech Advantage*, **2002**, *6*, 17
Image courtesy of www.altasoftheuniverse.com

Optimum Lipophilicity

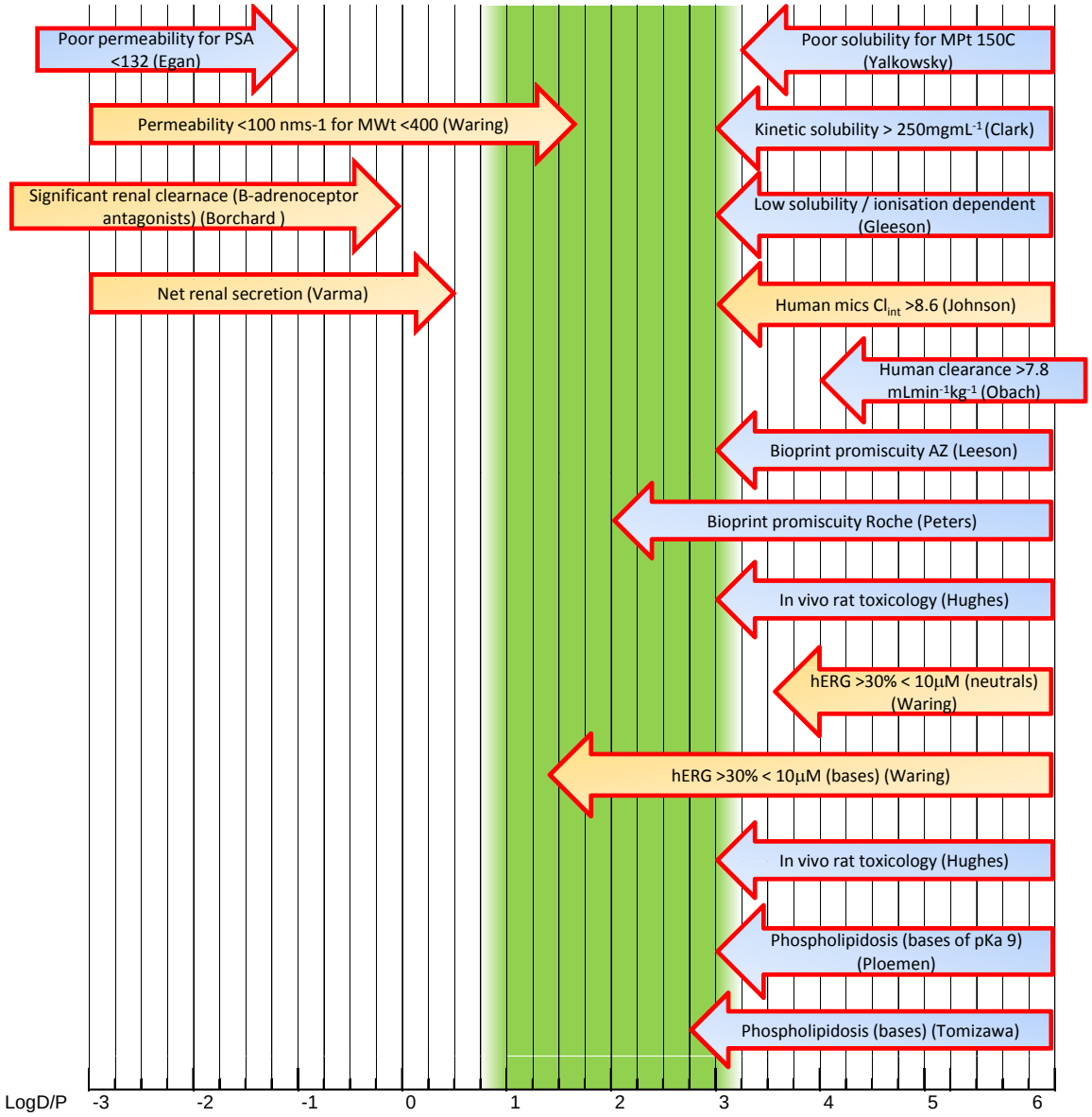


logP blue
logD orange

- Compounds of high overall "quality" occupy a window of lipophilicity

Waring, M. J. *Expert Opinion on Drug Discovery*, **2010**, *5*, 235

Optimum Lipophilicity



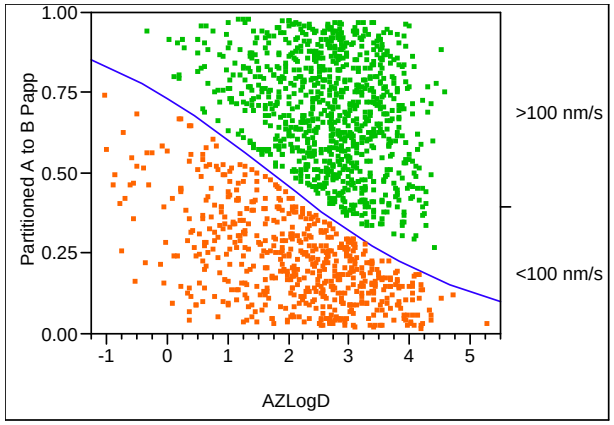
logP blue
logD orange

- Problems with high logD are myriad (and increasing)
- Problems with low logD permeability based primarily

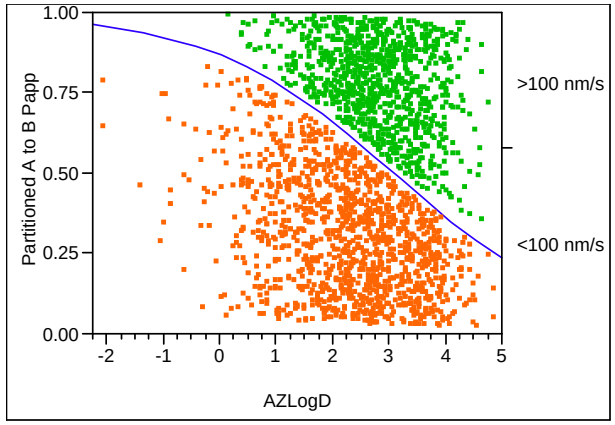
Waring, M. J. *Expert Opinion on Drug Discovery*, **2010**, *5*, 235

Molecular size and Permeability

MWt 350-400
50% prob = logD 1.7

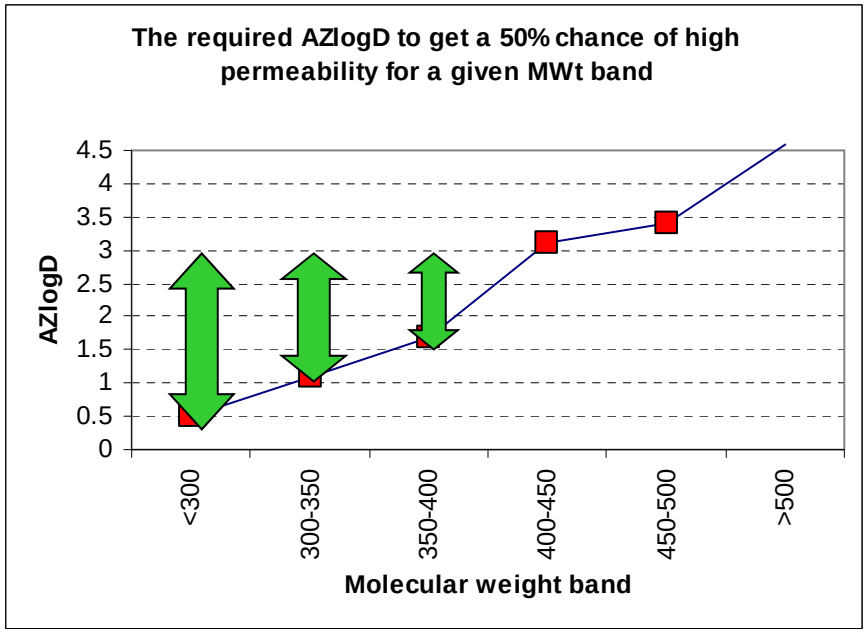


MWt 400-450
50% prob = logD 3.1



Guideline limits

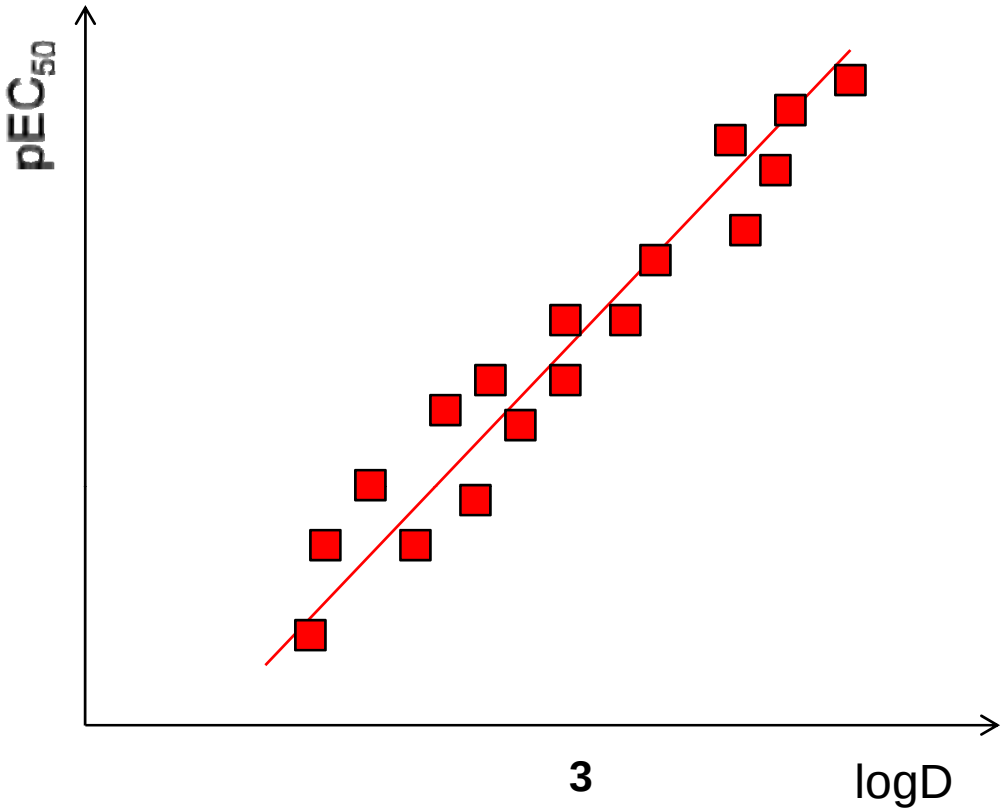
Molecular weight	AZLogD
< 300	> 0.5
300-350	> 1.1
350-400	> 1.7
400-450	> 3.1
450-500	> 3.4



Diminishing logD window as MWt increases

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

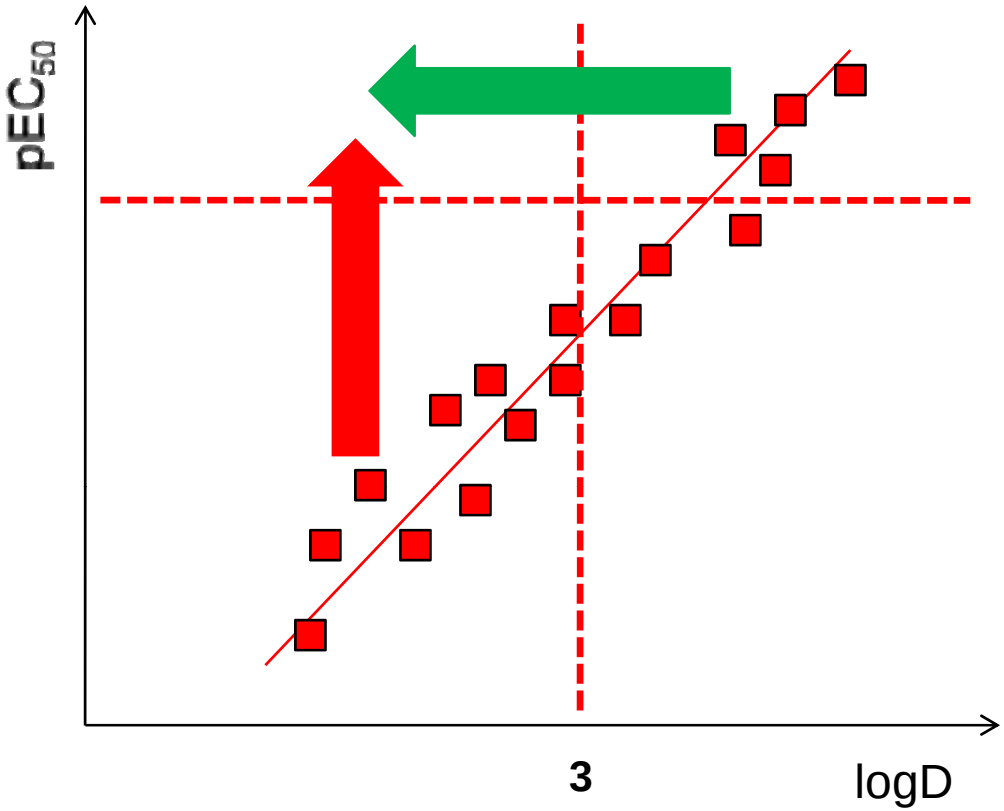
What about potency? - LLE and LE



- In the absence of additional specific interactions, series of compounds' potency will correlate with logD
- LLE (pEC_{50} – logD) stays constant
- LE used to ensure size increases achieve appropriate potency increases

Hopkins, A. L., Groom, C. R.; Alex, A. *Drug Discov. Today*, **2004**, *9*, 430

What about potency? - LLE and LE

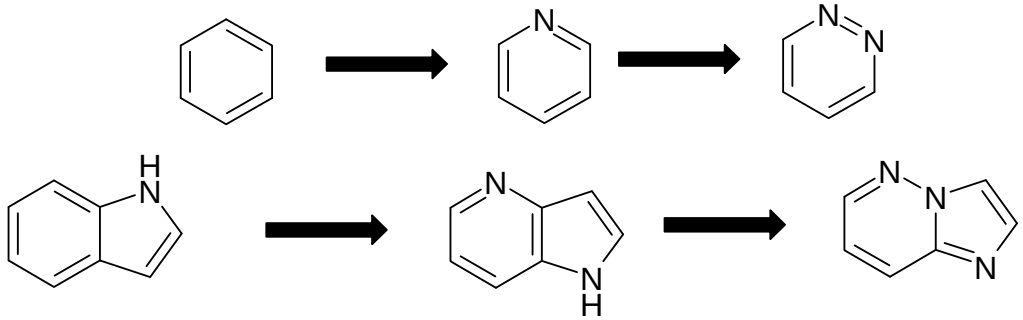


- Typical lead series likely to fall short of ideal space in terms of potency / logD
- Strategies for optimisation:
- Reducing logD with constant potency
- Increasing potency with constant logD
- Recent report suggests most commonly increase MWt and potency with constant lipophilicity going from lead to drug candidate[1]

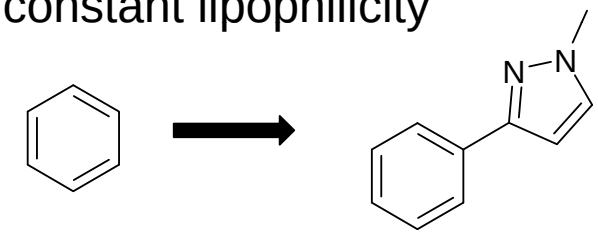
1. Perola, E. *J. Med. Chem*. **2010**, *53*, 2986

Increased Synthetic Challenge

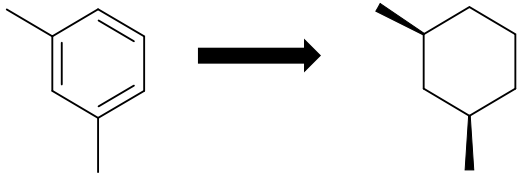
Reduced logD with constant size



Increased size with constant lipophilicity



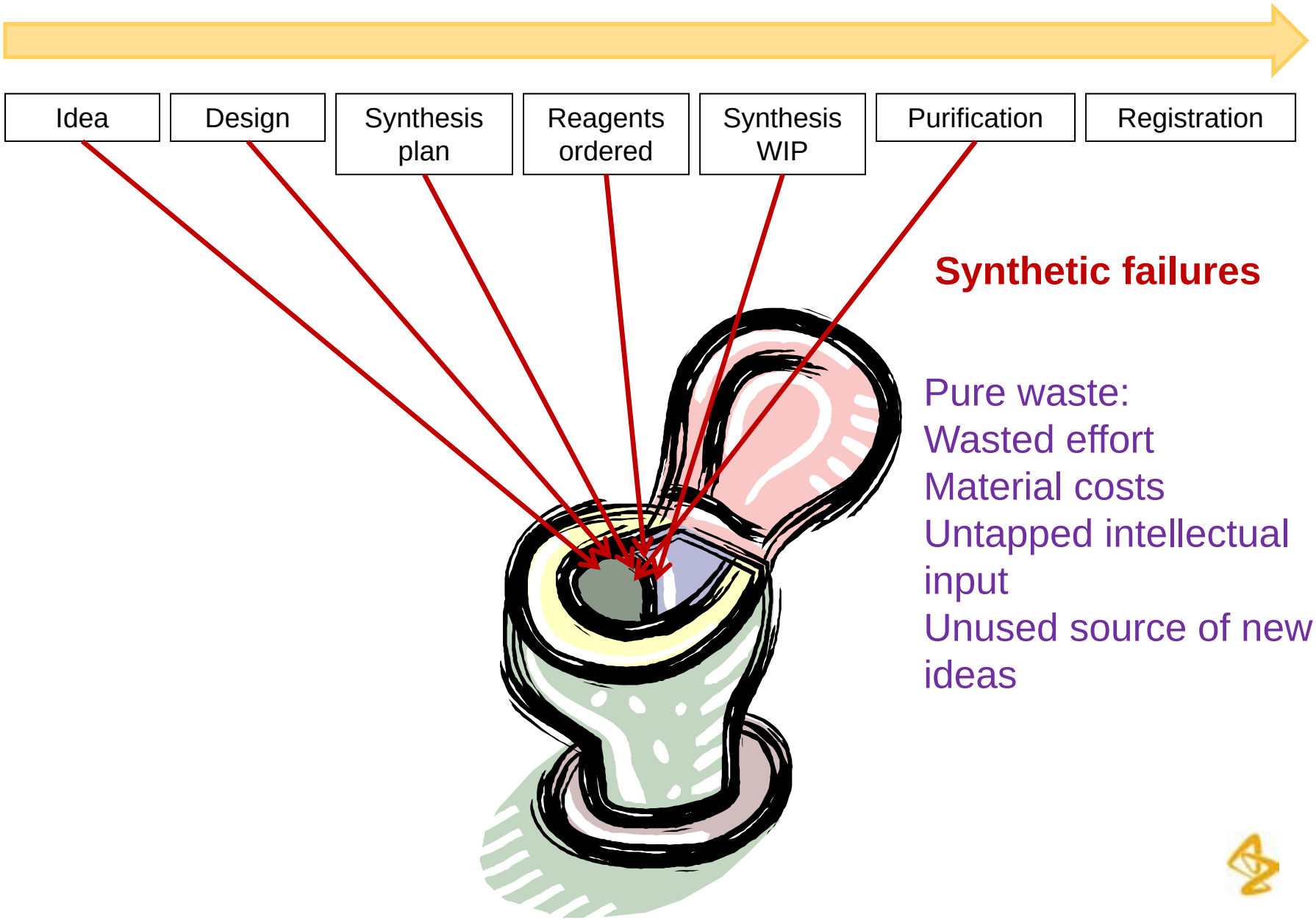
Escaping “flatland”[1] / reduced aromatic ring counts[2]



All serve to increase synthetic complexity

1. Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52,* 6752
2. Ritchie, T. J.; MacDonald, S. J. F. *Drug Discov. Today* **2009**, *14*, 1011; Ritchie, T. J.; MacDonald, S. J. F.; Young, R. J.; Pickett, S. D. *Drug Discov. Today* **2011**, *16*, 164

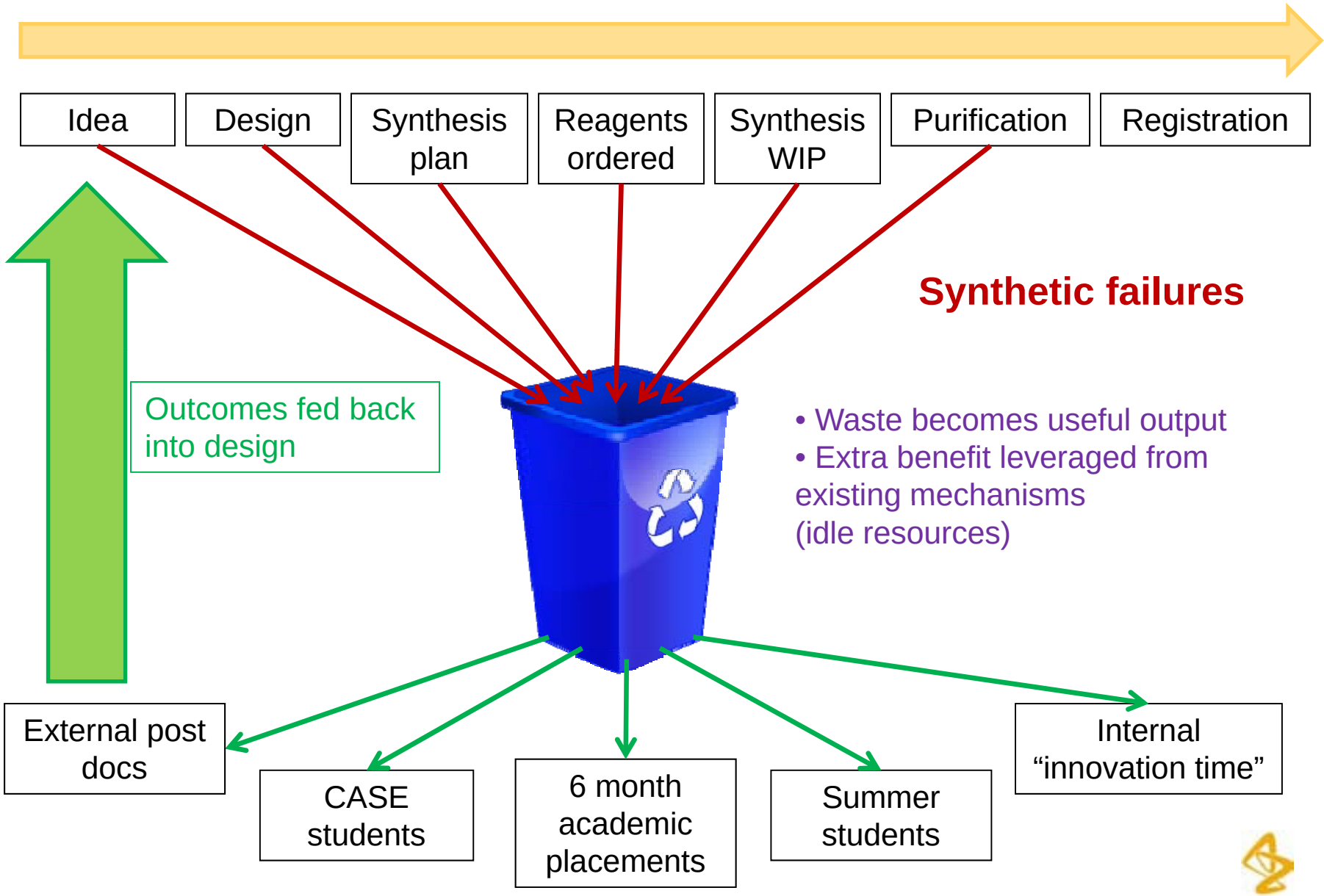
Synthesis process - The present situation



Synthetic failures

Pure waste:
Wasted effort
Material costs
Untapped intellectual input
Unused source of new ideas

Synthesis Process – Future Vision



The Directed Call for Proposals

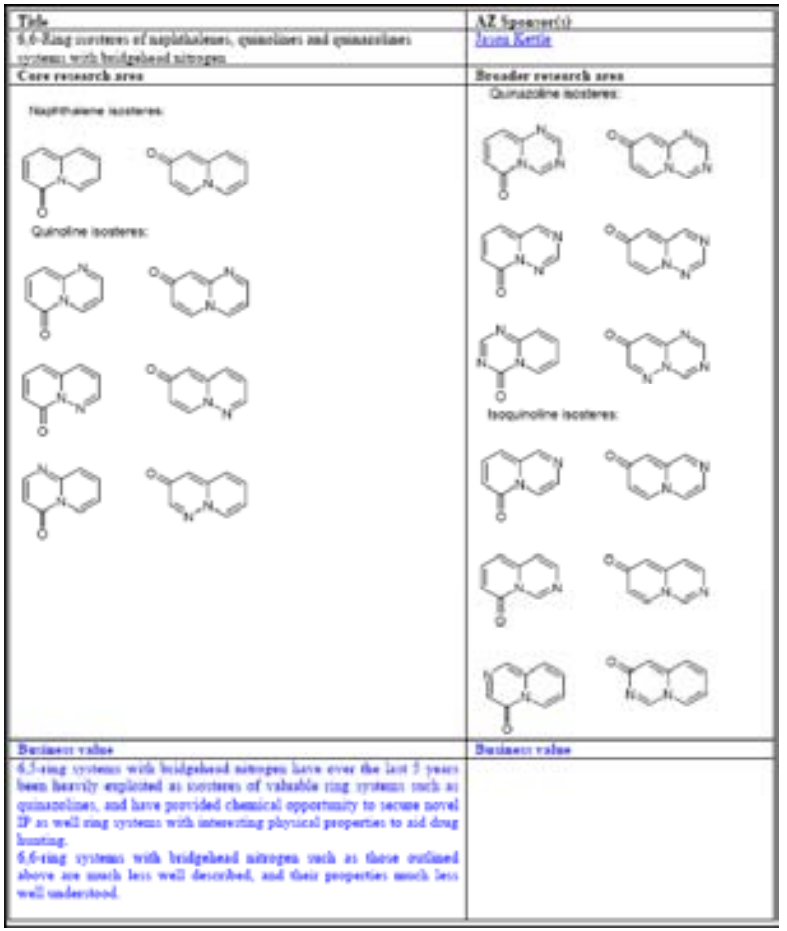
- To raise awareness of AZ problems in academia
- To maintain financial support by maximising business relevance for synthetic collaborations
- Ensure future access to difficult med chem space

- Inputs solicited from across AZ
- Discovery inputs based on analysis of common failed reactions and desired design targets that failed due to synthetic tractability
- Very positive response from academia

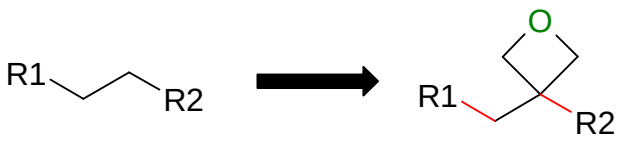
  2011 call:

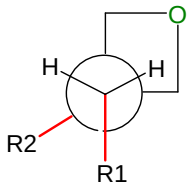
  43/112 submitted proposals targeted at directed call

  ~50-60% of collaboration starts will be from these



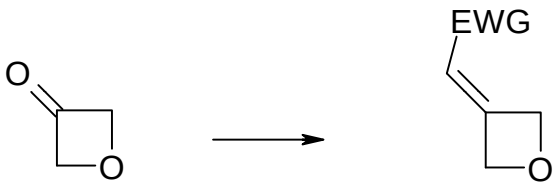
Oxetanes and Azetidines

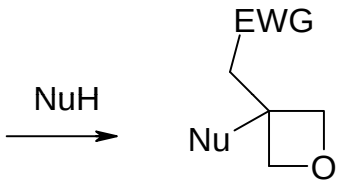




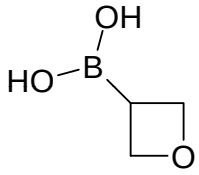
LogD lowering ~1log
Metabolically robust
Favoured Gauche conformer

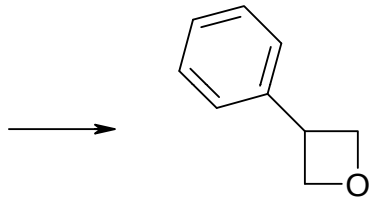
Cf. gem-dimethyl
More susceptible to metabolism
Equal populations of 3 conformers





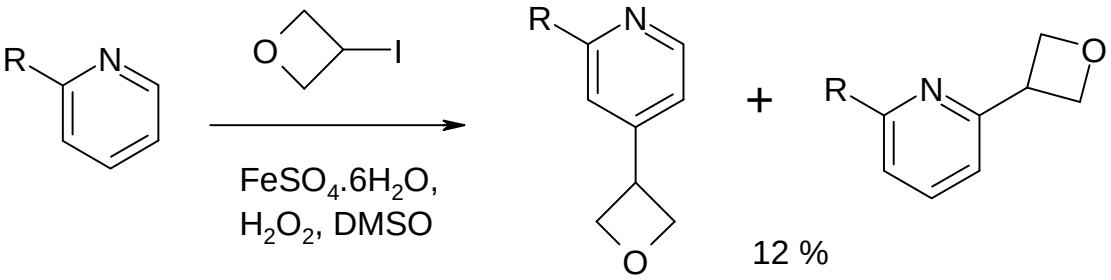
Roche / Carreira[1]





Pfizer / Evotec[2]
ΔlogP -0.7

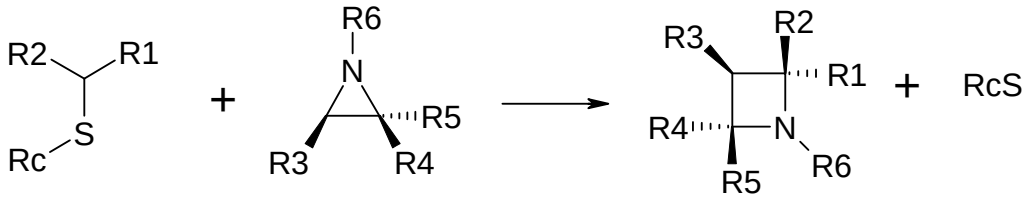
Minisci reaction[3]



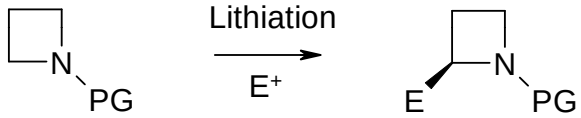
Nat Martin

1. Carreira, Rogers-Evans, Muller et al. *J. Med. Chem*. **2010**, *53*, 3227 and refs. therein
2. Duncton, M. A. J. et al. *Org. Lett*. **2008**, *10*, 3259
3. Duncton et al. *J. Org. Chem.*, **2009**, *74*, 6354

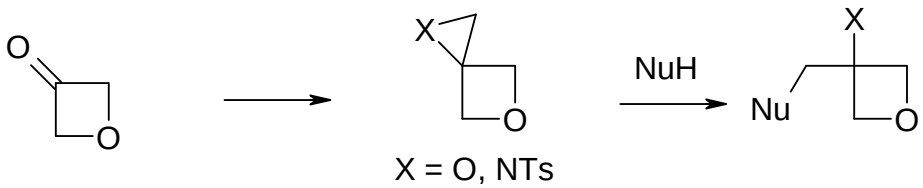
Oxetanes and Azetidines – AZ collaborations



Joe Sweeney



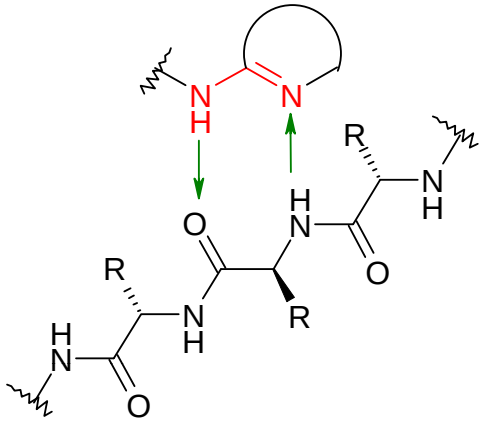
David Hodgson



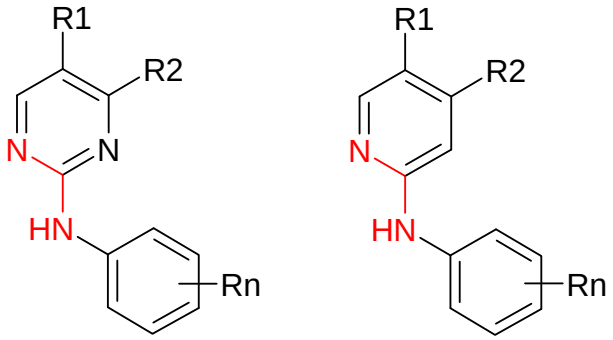
Mike Shipman

Geminal donor-acceptors

Privileged fragments due to productive bidentate H-bonding with peptide backbone

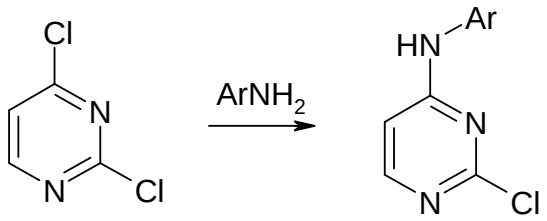


For example, anilinopyrimidines and pyridines as kinase inhibitors



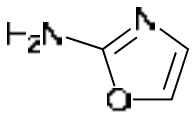
Compound issues often associated with lipophilicity of phenyl ring
Heterocyclic (esp. 5-membered systems) potentially appealing

Problematic Buchwald-Hartwig Couplings

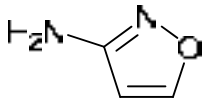


77% success rate

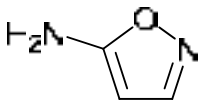
Oxazole and isooxazole the worst but others also proved challenging:

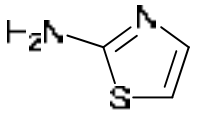


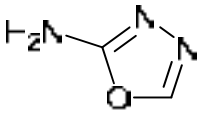
ΔlogP -2.2

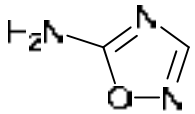


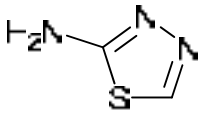
ΔlogP -1.9

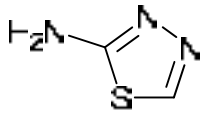








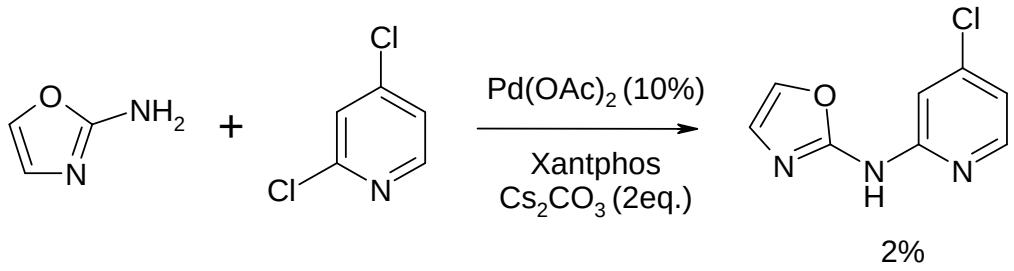




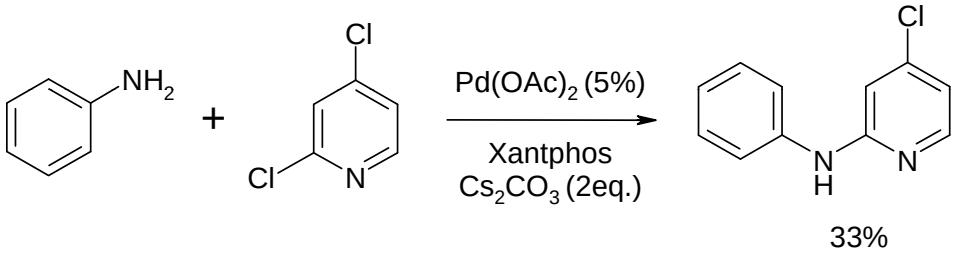
- Coupling reactions of these substrates poorly precedented[1,2]

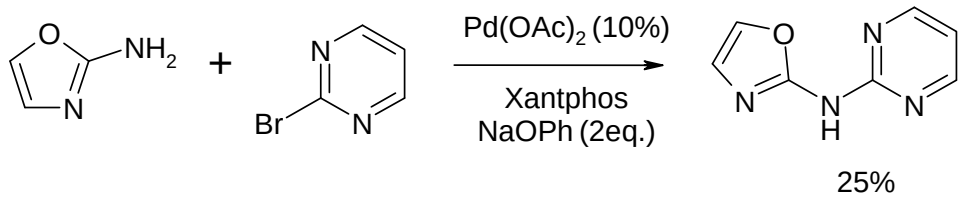
1. Buchwald, S. L. *Chem. Sci*. **2011**, *2*, 27
2. Buchwald, S. L. et al. *Angew. Chem. Int. Ed*. **2006**, *45*, 6523

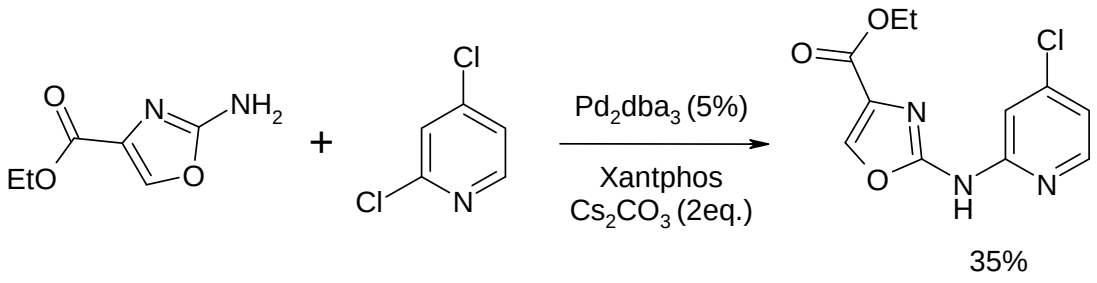
Model Coupling



Tried Pd_2dba_3, BINAP, Josiphos, NaOPh, NaO^tBu, different solvent and temperatures
Cu catalysis



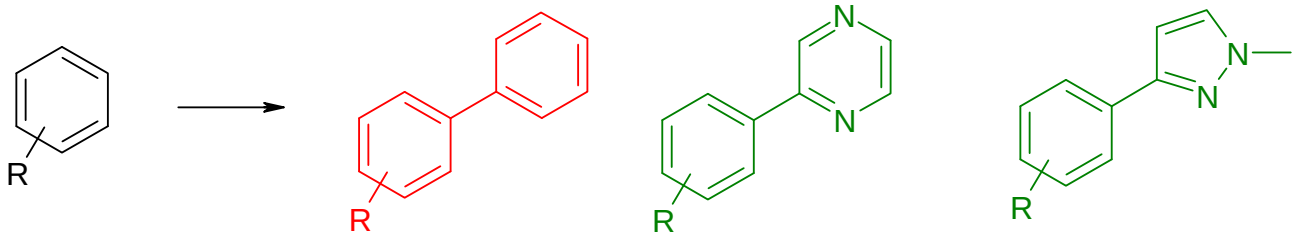




Gary Noonan

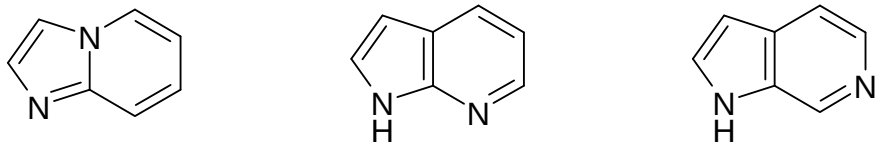
CH-Functionalisation

CH-functionalisation potentially useful in increasing potency of small, less active leads
Ideally need iso-lipophilic changes:

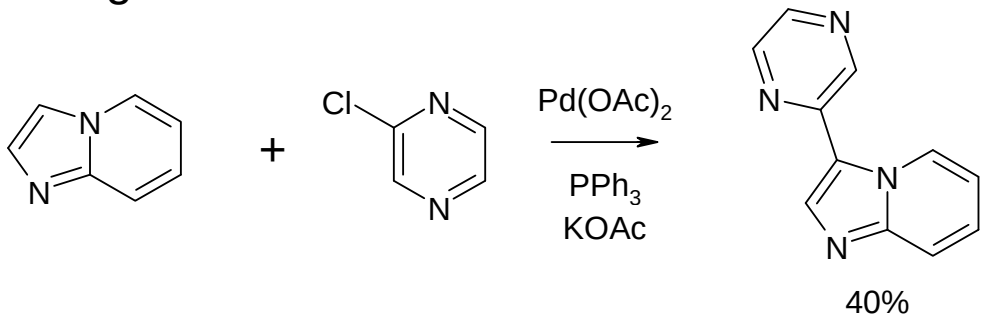


ΔlogP +1.9 ΔlogP -0.3 ΔlogP +0.2

Additional benefits with heterocycles as the CH partner where boronates / bromides not accessible, eg. poly-aza bicyclic systems:



Bringing the two together:

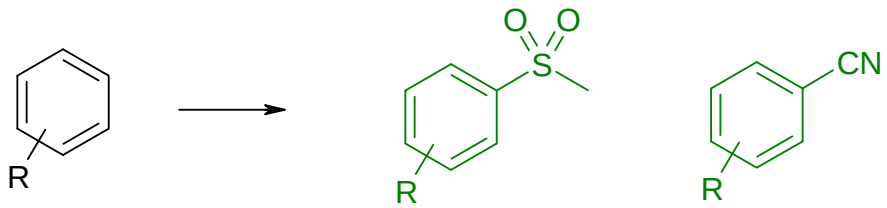


40%

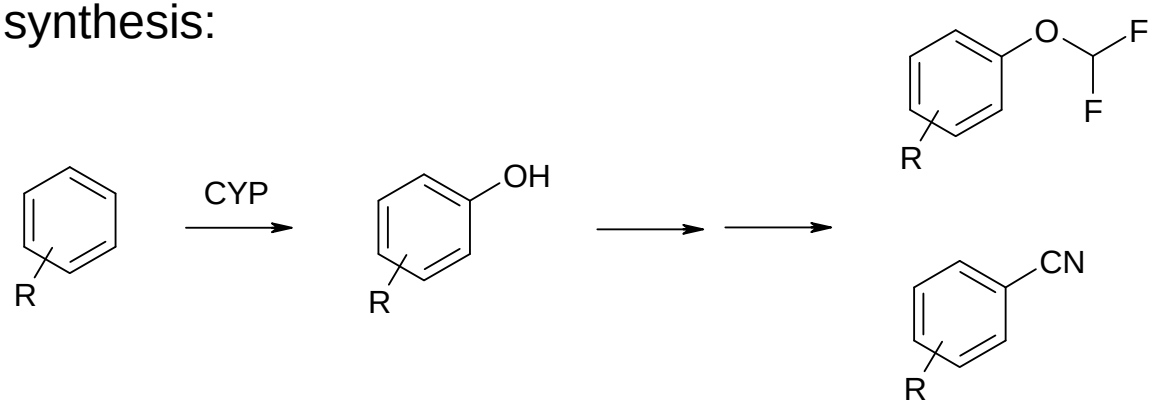
Rose Krawczuk

CH-Functionalisation

What if you could introduce classical drug-like substituents:



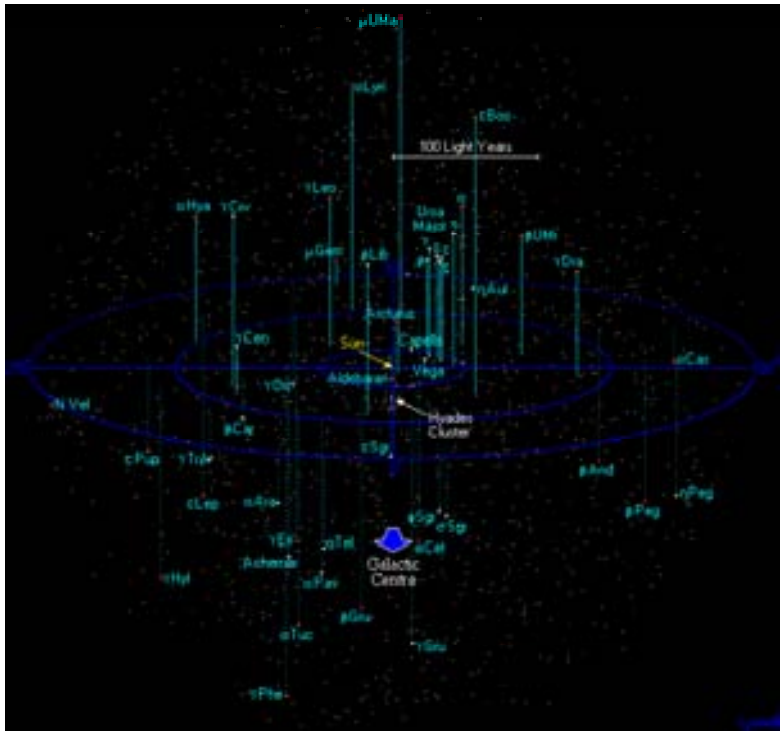
CYP450s in synthesis:



Elaine O'Reilly, Rob Davies, Nick Turner

Summary
A Final Thought

Our exploration of chemical space is at a similar level of maturity to our exploration of actual space. The challenge is to know where to go.



"The universe is full of magical things, patiently waiting for our wits to grow sharper"
– Eden Phillpotts

Image courtesy of www.altasoftheuniverse.com

Thank You
Acknowledgments