

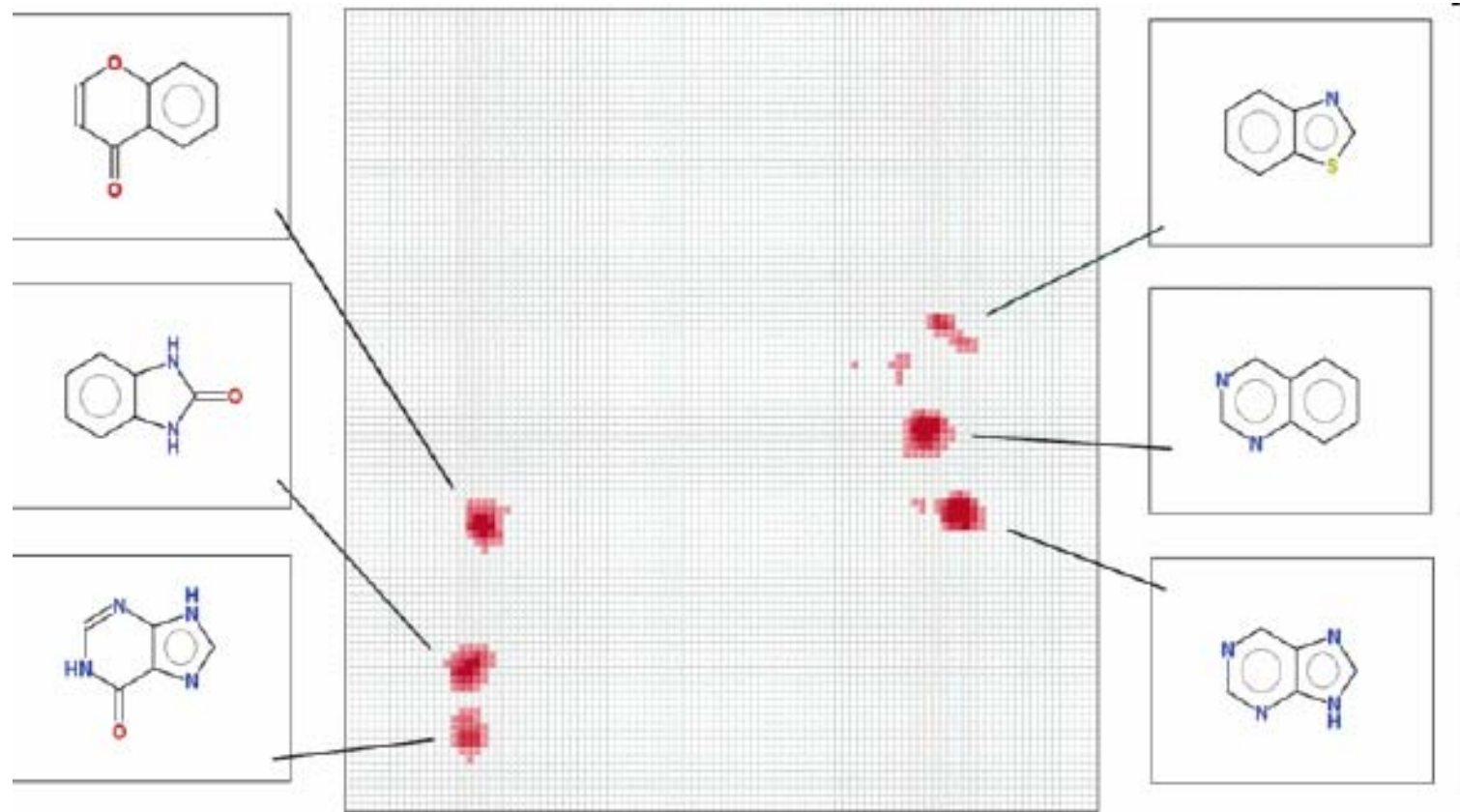
Hits to Leads to Drugs: What Makes a Chemical a Drug

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My message

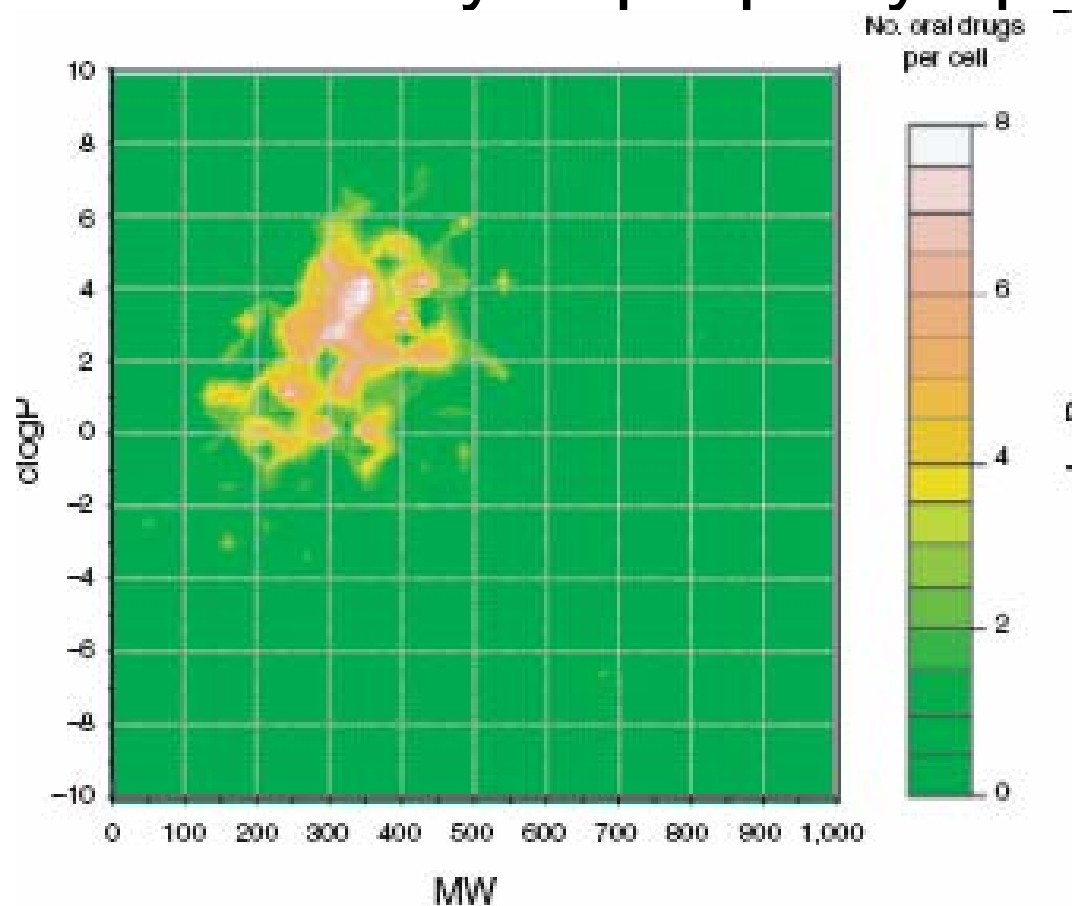
- Drug discovery is special
 - most of chemistry space is not drug-like
 - drug discovery is not chemical biology
 - drug discovery requires good chemistry structures
 - these cost a lot
 - targets require chemistry / biology cooperation
 - in-vitro optimization is the easy part
 - ADMET is the hard part
 - “hit to lead” to “lead optimization”
- CNS drug discovery is special
 - requires extra filters and effort

Sparse activity in chemistry scaffold space



Quest for the Rings. In Silico Exploration of Ring Universe to Identify Novel Bioactive Scaffolds, Ertl et al. *J. Med Chem.*, (2006), 49(15), 4568-4573.

Sparse oral activity in property space

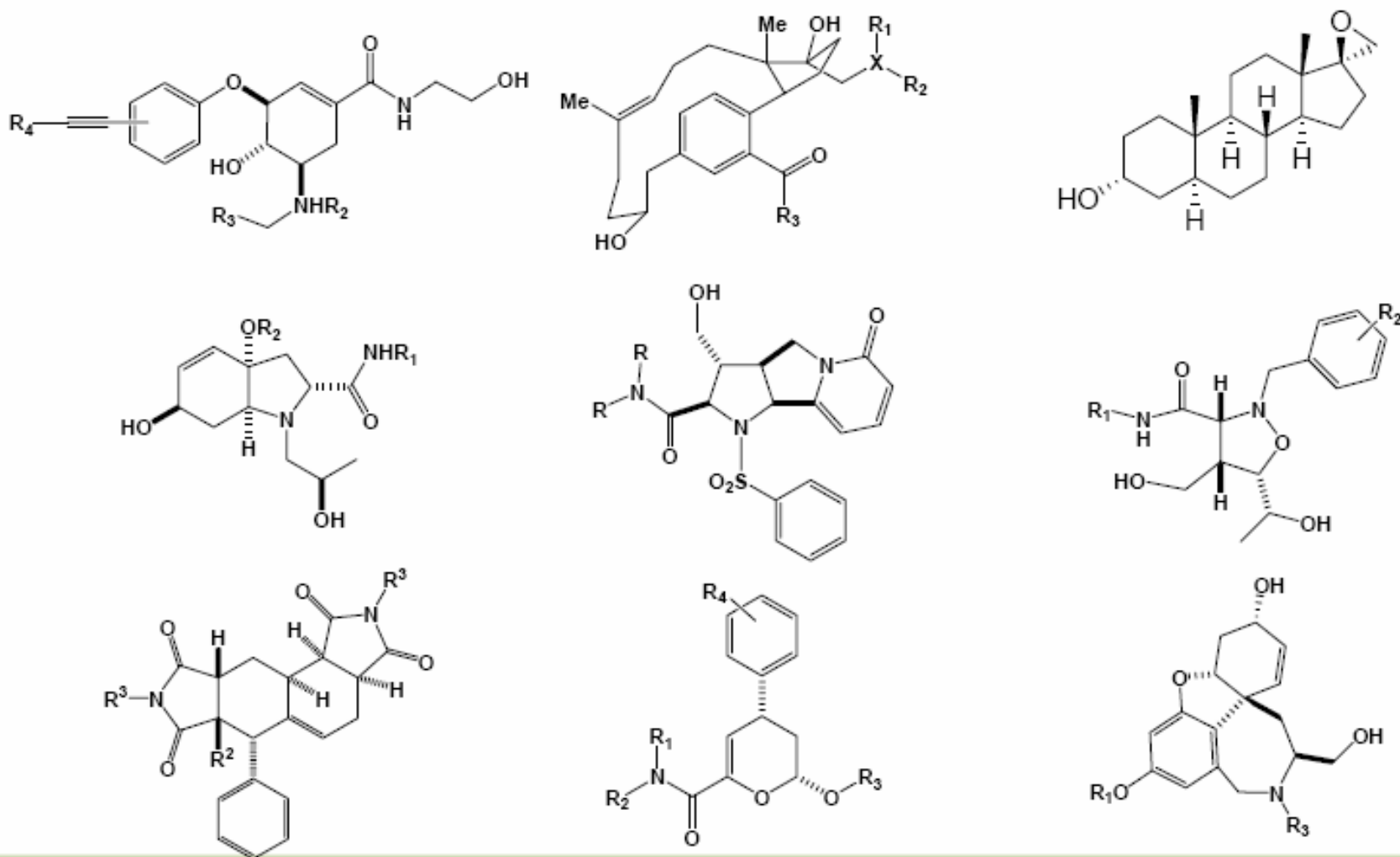


Global mapping of pharmacological space. Paolini et al.,
Nature Biotechnology (2006), 24(7), 805-815.

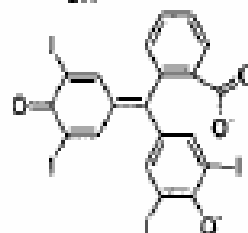
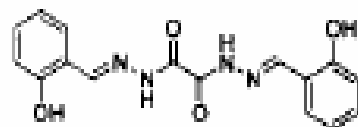
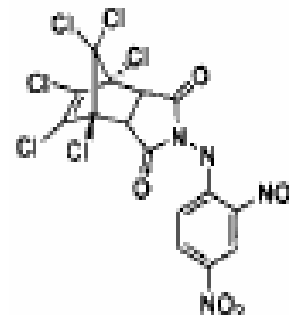
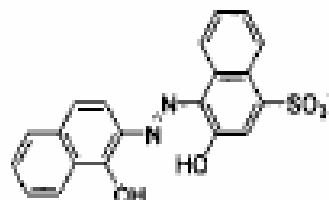
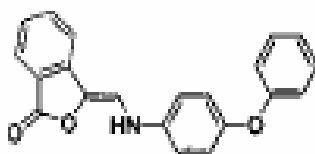
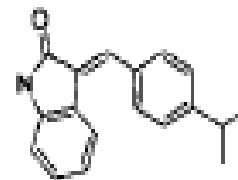
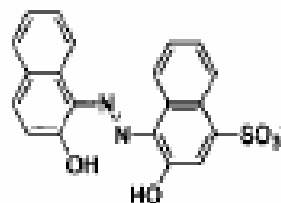
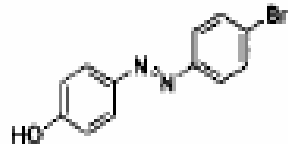
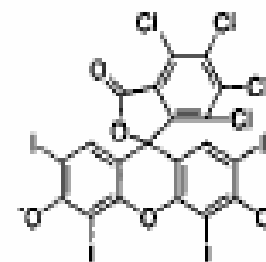
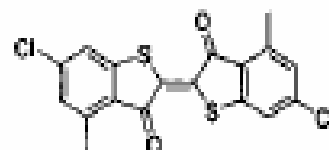
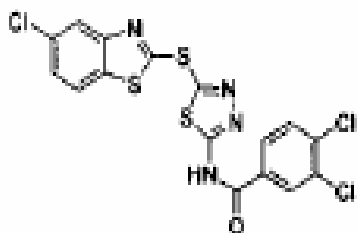
Drug discovery is not chemical biology

- Target validation
 - tool like compounds
 - relaxed chemistry criteria permissible
 - chemical biology
- Drug discovery
 - lead-like or drug-like compounds
 - strict chemistry criteria necessary
 - needs pharma skills

Nice chemistry



Horrible chemistry



These look good to biologists

Remove these types of compounds from any assays

Structures for drug screening cost a lot

- Use a chemical tool to probe biology
 - relaxed chemistry criteria permissible
 - chemical costs go down
 - \$16 for 10 mg of compound
 - 50,000 or fewer compounds in HTS
- Drug discovery
 - strict chemistry criteria
 - 30-50% of legacy compounds discarded by big pharma
 - cost as high as \$200-400 for 15 mg compound
 - 500,000 compounds in an HTS

Targets and chemistry / biology cooperation

- A good target has distinctly different meaning to biology and chemistry personnel
- In a biology sense, a good target is a biological pathway that can be intercepted in some way to give a useful therapeutic outcome
- In a chemistry sense, a good target is a biological pathway that can be intercepted in a useful sense by an orally active small organic molecule

Interplay of the disciplines leads to success

What is a good target

- Biology/genomics viewpoint
 - must be validated
- Chemistry viewpoint
 - low MWT ligand can be found
- Both viewpoints must be correct
 - non validated
 - chemistry succeeds - worthless
 - validated
 - chemistry fails - worthless

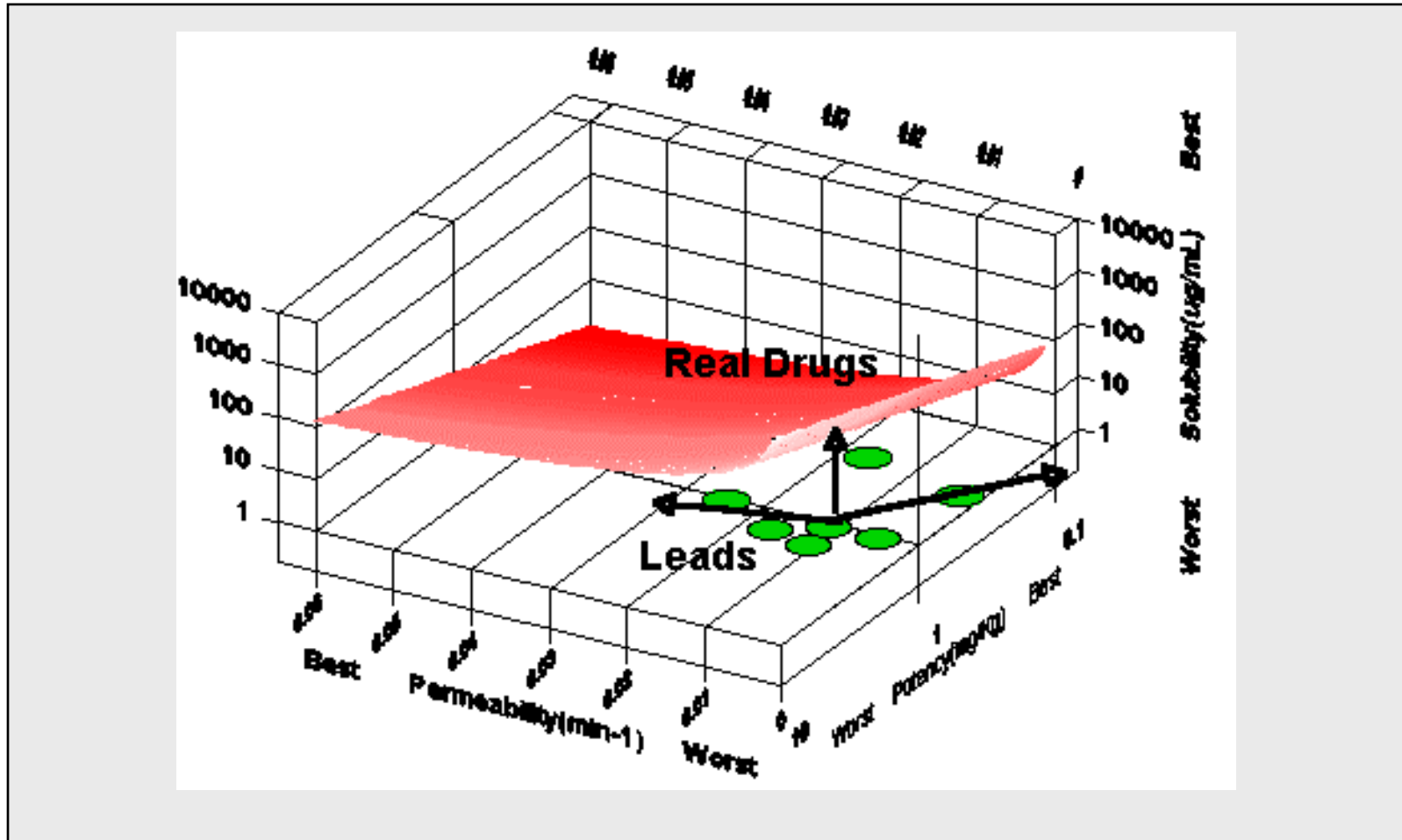
Biology and Chemoinformatics

Biology approach

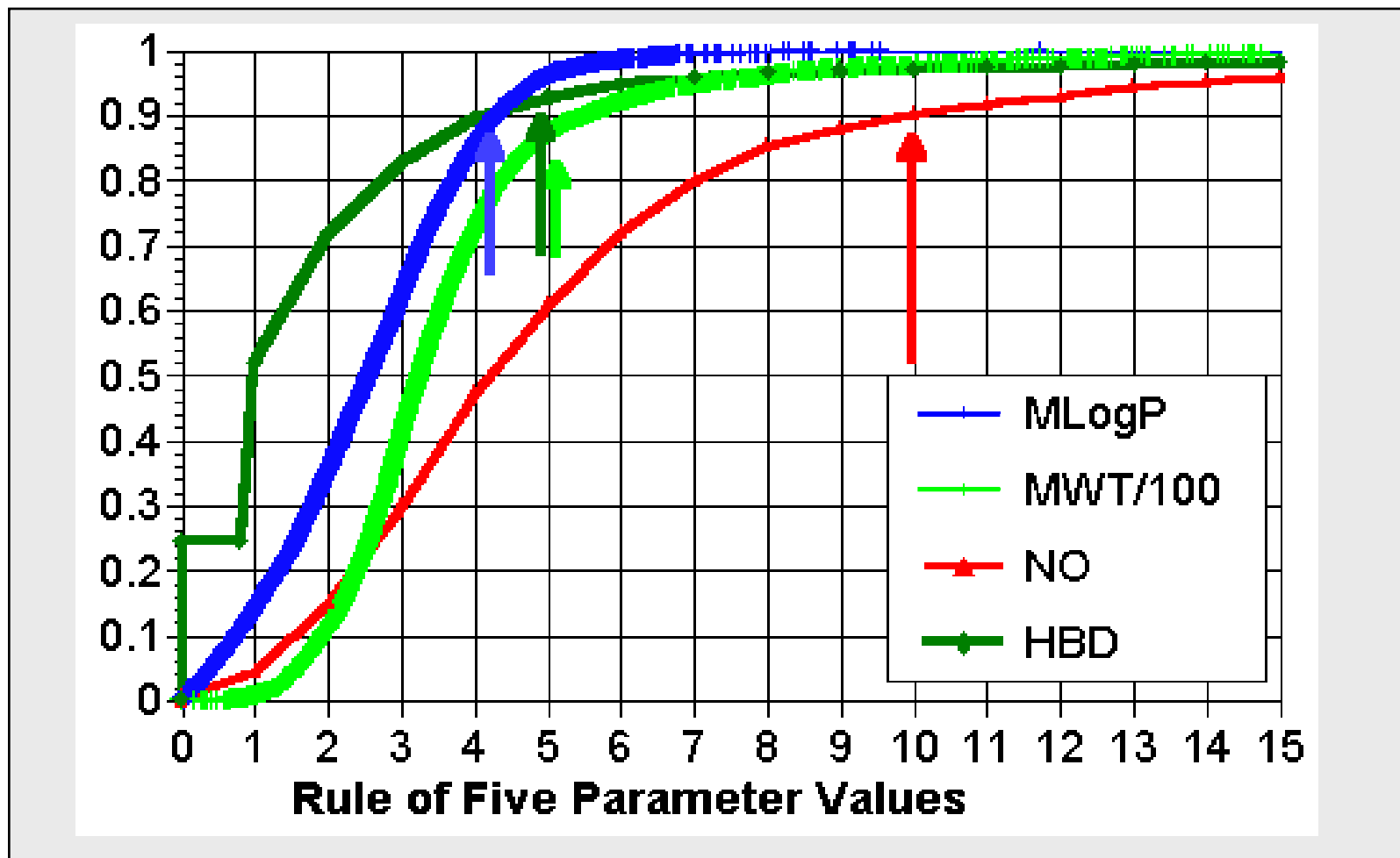


Is this target
druggable in
chemistry?

Aqueous Solubility and Permeability Data Must be Provided to Chemistry as Early as Possible to Avoid Oral Absorption Problems



Distribution Parameters for 7483 INN/USAN Drugs Define the 90% Limits Corresponding to Properties Unfavorable for Oral Drug Absorption.



The “rule of five” mnemonic

- Poor absorption or permeation are more likely when there are:
 - More than 5 H-bond donors.
 - The MWT is over 500.
 - The CLog P is over 5 (or MLOGP is over 4.15).
 - The sum of N's and O's is over 10.
- Substrates for transporters and natural products are exceptions.

Profiling in early discovery

- Is there chemistry SAR?
 - look for sharp activity changes
 - broad or narrow SAR?
- Where are the warts?
 - more than 3 things wrong gets difficult
- Freedom to operate
- Property profile?

Success in “hit to lead”

- Meets criteria for advancement
- Chemistry SAR is good enough to justify more expensive, more labor intensive chemistry

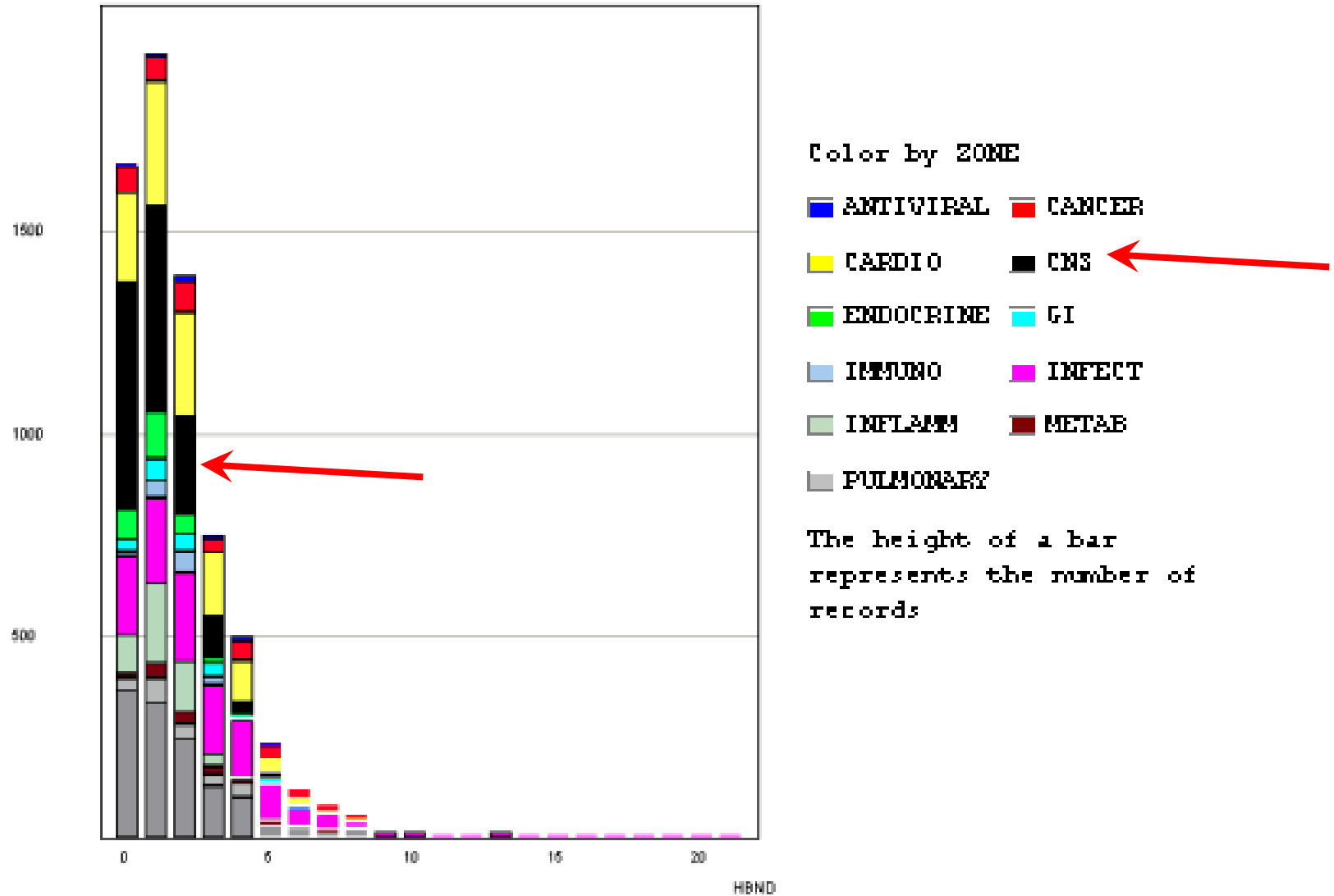
AstraZeneca "Generic Lead Target Profile" for progressing HTS hits to Leads (1)

Potency	100nM
Rat hepatocyte intrinsic clearance	< 14uL/min/10x6 cells
Human microsome intrinsic clearance	< 23ul/min/mg
Rat IV clearance	< 35ml/min/kg
	Volume > 0.5L/kg
	t _{1/2} > 0.5 hr
Rat PO bioavailability	> 10%
Plasma Protein binding	< 99.5%
Solubility	> 10ug/ml

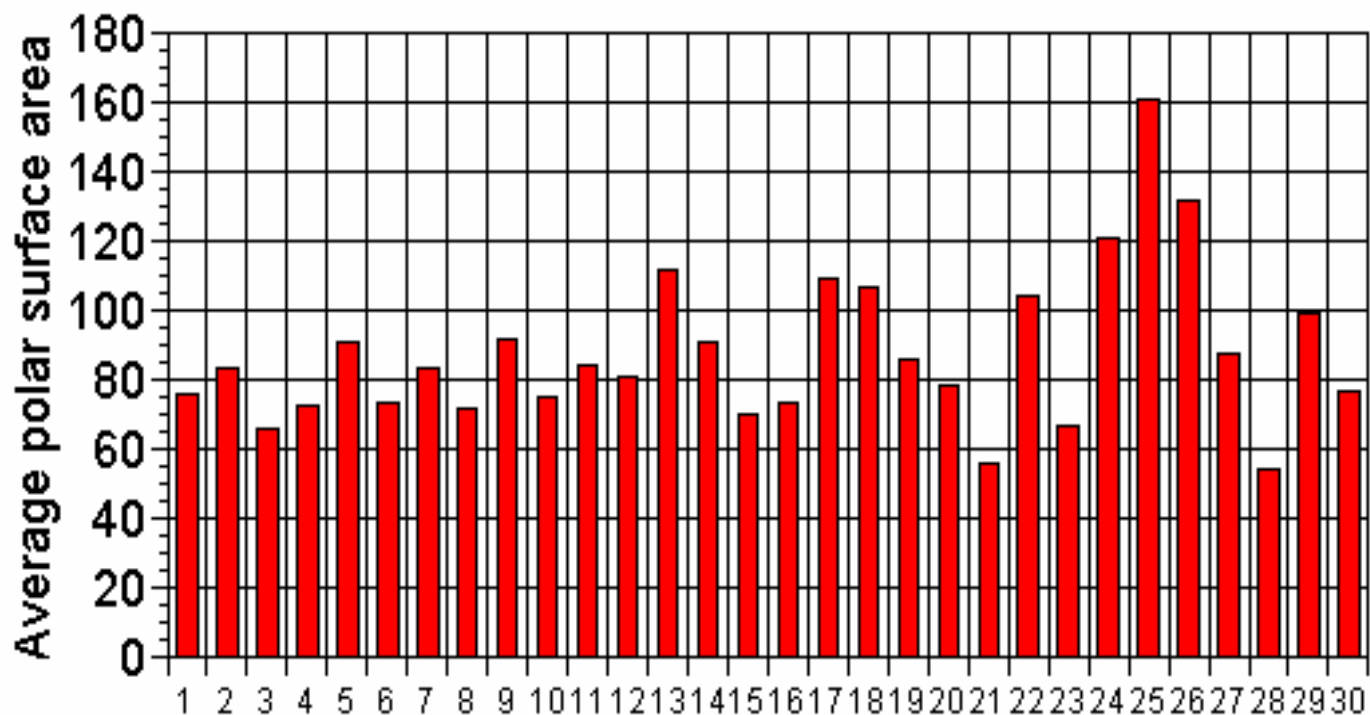
AstraZeneca "Generic Lead Target Profile" for progressing HTS hits to Leads (2)

ClogP	< 3
LogD	< 3
Mol Wt	< 450
P450 inhibition IC50	> 10uM for 5 major isozymes
HERG screening	Early toxicity in vitro screens
Clear SAR around potential lead	
Selectivity - Use PanLabs/Cerep batteries	
Structure must provide patent opportunities	
Need <i>in vivo</i> biological validation	

Distribution of H-Bond Donors by Therapy



Many combichem libraries are unsuited for CNS penetration



Set of 47,680 combinatorial compounds from the same commercial source made according to 30 different synthesis protocols. There is little variation in average polar surface area across the protocols.

CNS drugs require different parameters

- Six or fewer H-bond acceptors
- Three or fewer H-bond donors
- MWT of 400 rather than 500
- Differences are likely linked to physical chemical properties related to p-glycoprotein affinity