

Synergy between advances in screening methodology and computational chemistry

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Outline

- Biology challenges
- Chemistry challenges
- Efficacy space and chemistry space
- Drug space is restricted
- Druggability vs. developability
- Experimental chemistry fixes
- Computational chemistry fixes

Drug discovery, 1970's, 1980's, 1990's, Now

- 1970's, phenotypic drug discovery
- 1980's, transition period
- 1990's and now, mechanistic screens
- Success rates stay constant with time
- Costs escalate in more recent times

My Medicinal Chemistry History

- 1970 in-vivo phenotypic screening
- 1977 first compound screened in-vitro
- 1970's everything was drug-like
 - never heard of ADMET
 - did not need rules and filters
- 1970's very difficult to start new projects
 - new ideas were extremely difficult

Biology Change and Drug Discovery

- 1960's 1970's biology in depth
 - breadth restricted by technology
 - in-vivo, phenotype filters
 - depth was great for target validation
- 1990's 2000's biology in breadth
 - breadth enhanced by technology
 - breadth great for knowledge base
 - breadth not great for target validation

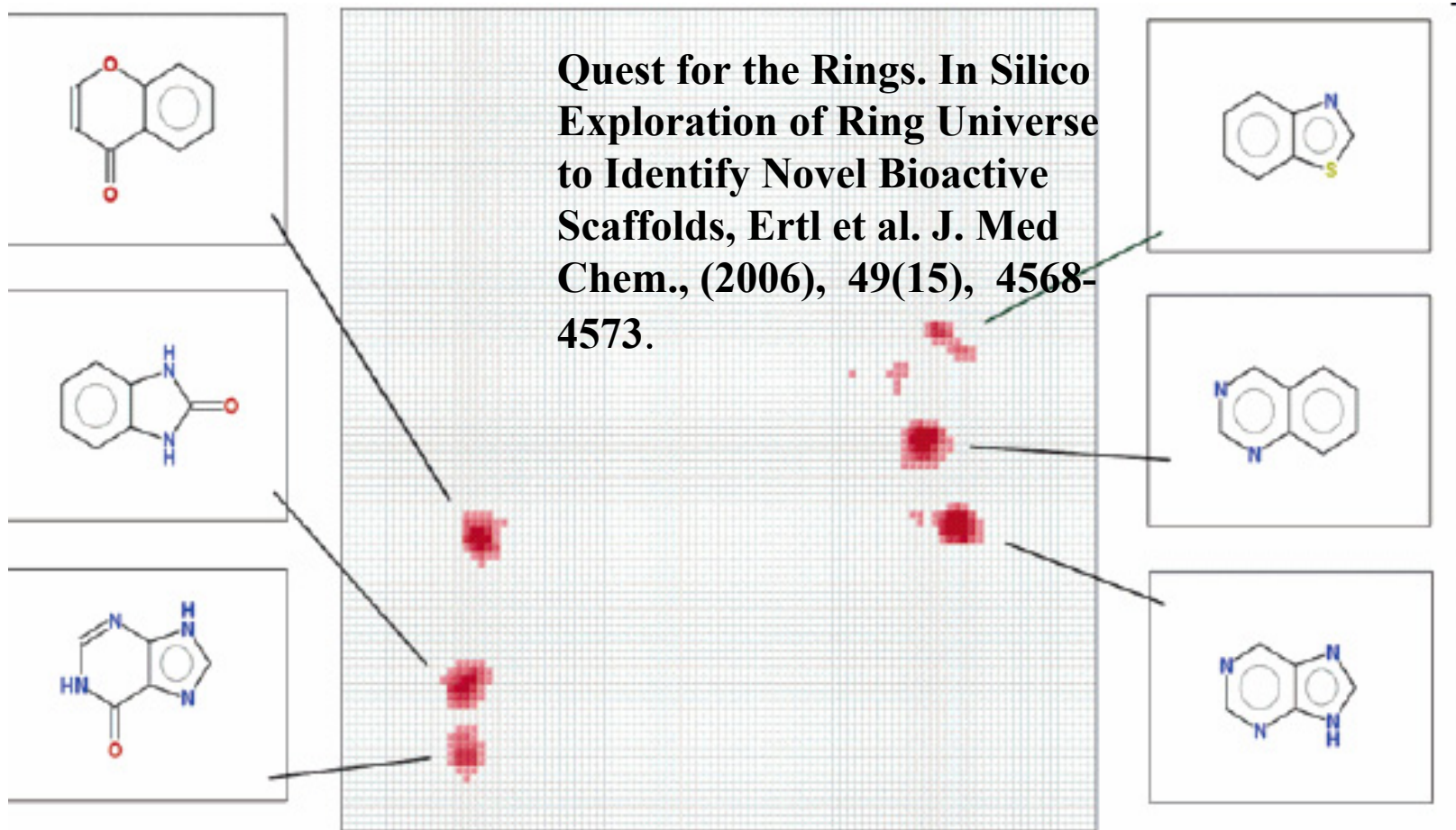
Biology and Drug Discovery

- Primarily a public policy, people issue
- Science knowledge needs breadth
- Drug discovery needs depth
- Change to depth is very difficult
 - dedicated careers
 - funding shortage
 - pharma has a negative public image
 - depth requires very tough choices
- Not optimistic about a solution

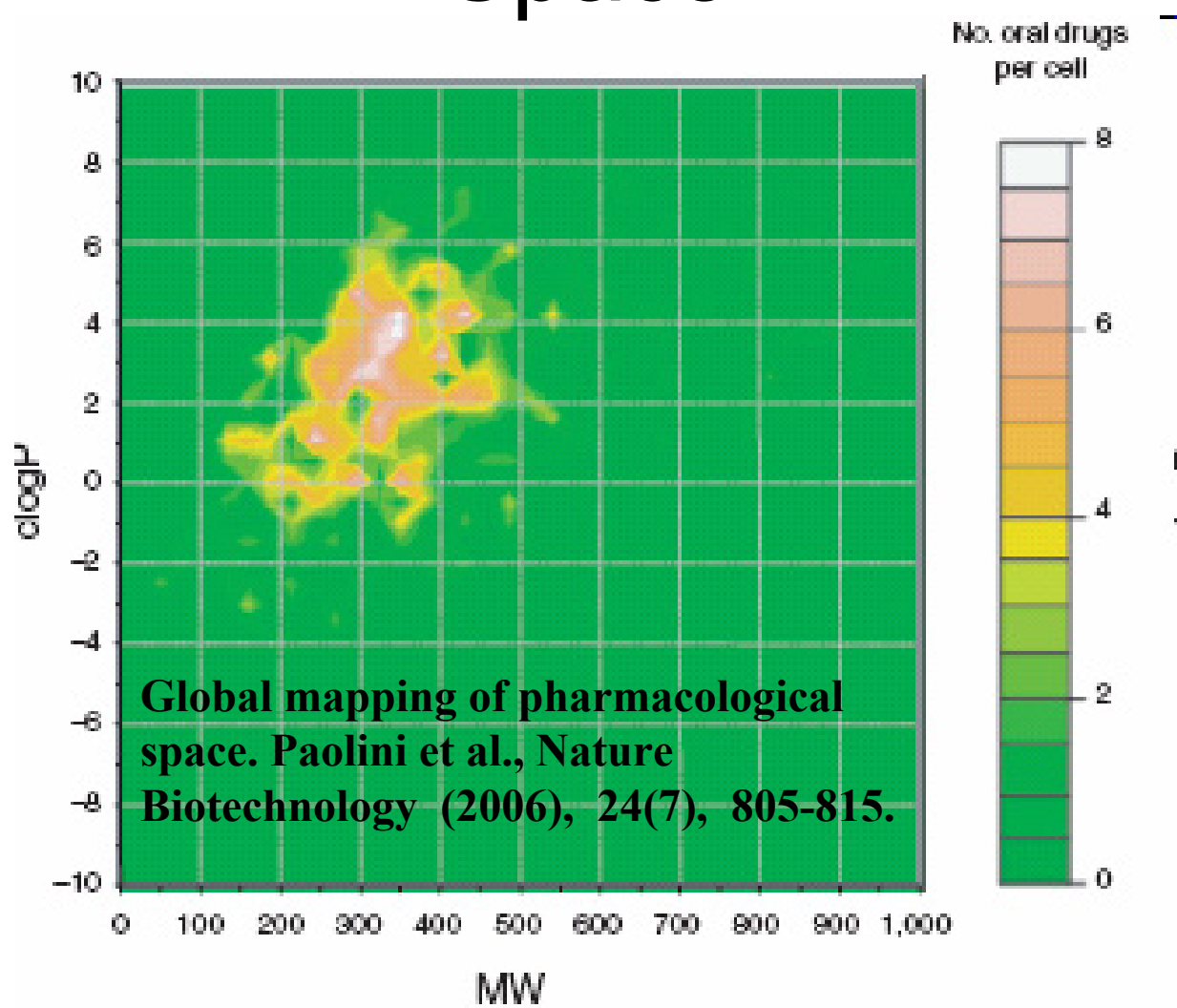
Mechanistic Screening is At Its Limits

- 186 targets for oral drugs
 - oral target poor landscape
 - limited pool of attractive targets for industry
 - high efficacy failure in clinical
- Biology approaches are non balanced
 - 95 % effort on mechanistic screening

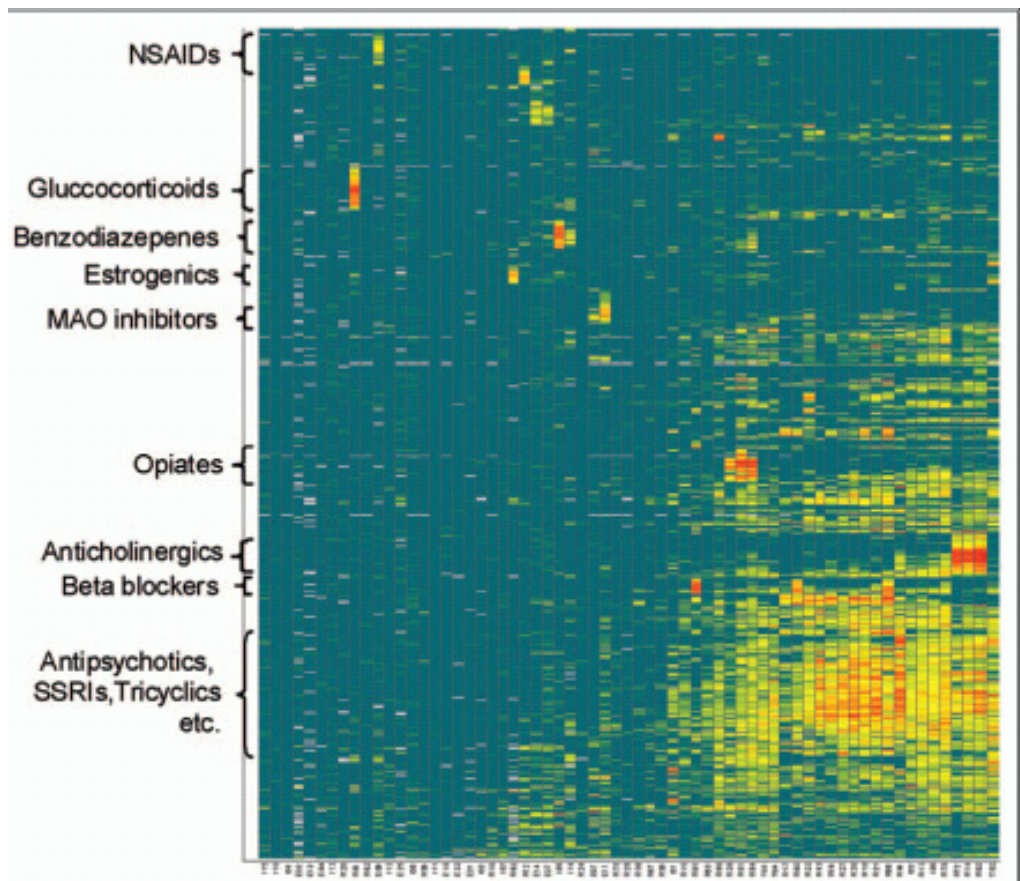
Sparse Activity in Chemistry Space



Sparse Oral Activity in Property Space



Promiscuous Drugs by Design

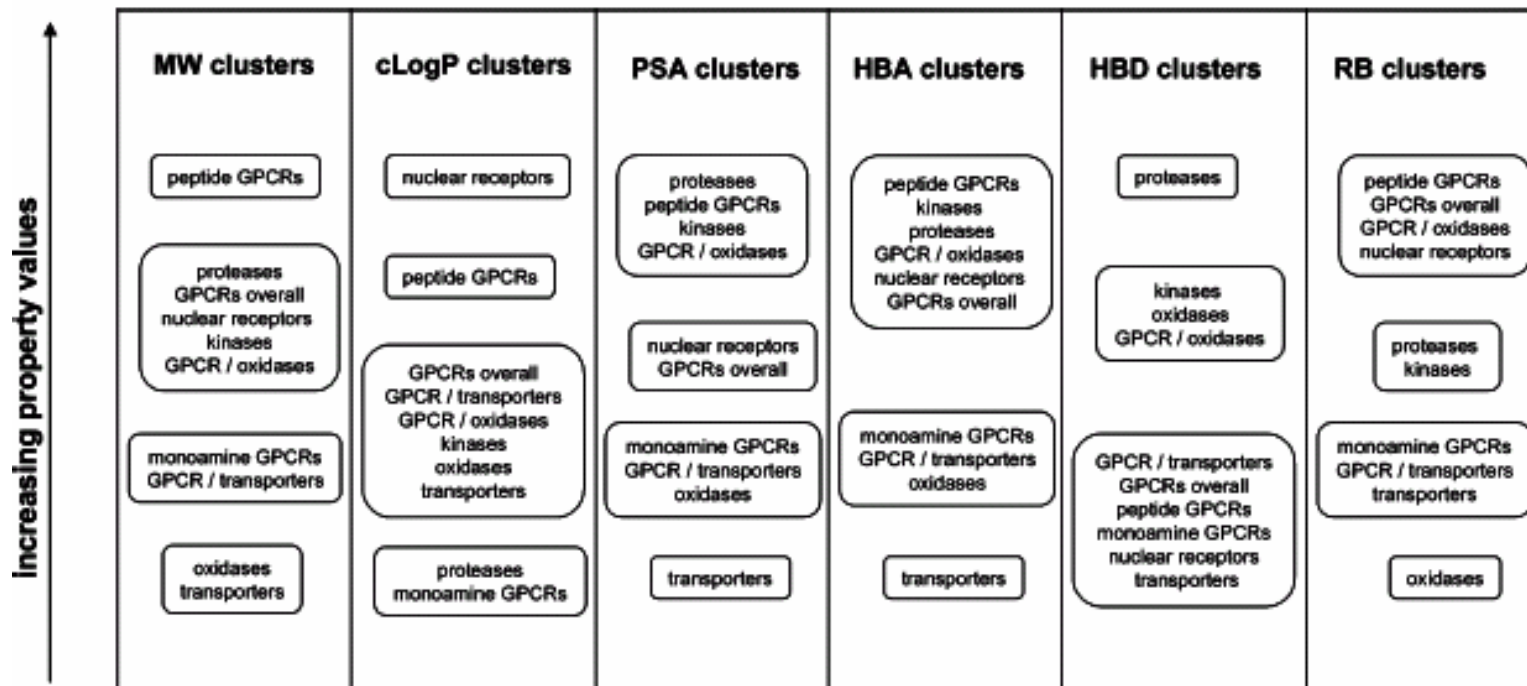


Hopkins et al.

**Current
Opinion in
Structural
Biology**

**16, 127-136,
2006**

Polypharmacology by Design



Morphy et al. *J. Med Chem.*, 49, 4961-70, 2006

Why is Biologically Active Chemistry Space So Small?

- Medicinal chemists are unimaginative?? **NO**
- Biological systems are designed to be robust and resistant to modulation
- Nature is conservative – motifs are re-used
- Protein folding motifs are limited
- Protein energetics are balanced for signalling
- Critical pathways are limited
- Biologists ideas on targets are wrong??
MAYBE

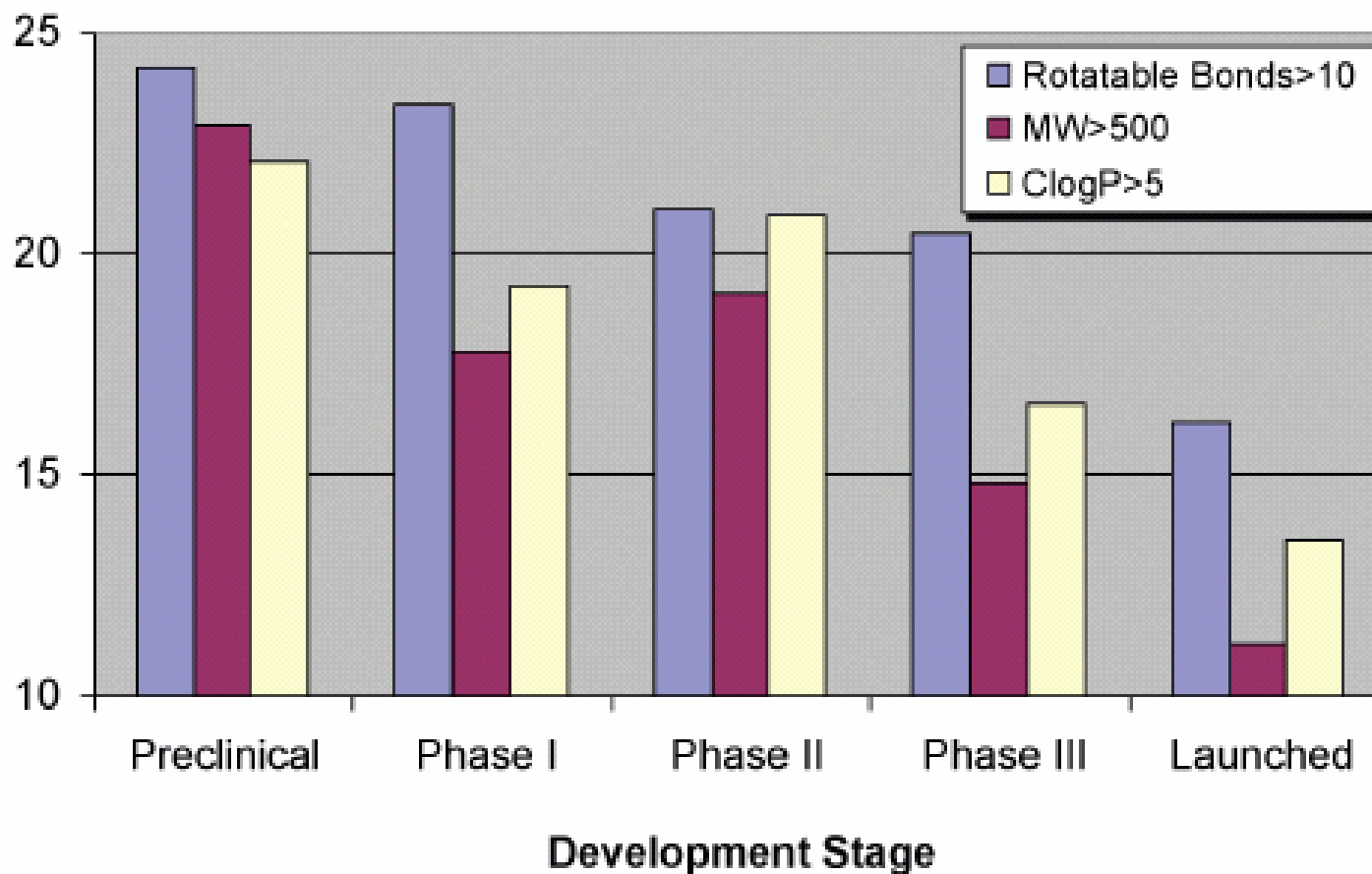
Chemistry Poor Properties

- Poor properties affect oral activity
 - eg. “rule of 5” non compliance
 - druggability
- Poor properties affect clinical
 - developability
- High log P tracks with useless promiscuity
 - eg. Corwin Hansch on toxicity
- High log P tracks with high attrition

Developability Observations

- Smaller drugs are approved
 - properties change throughout clinical
 - MWT 347 mean for FDA approved drugs
- Smaller drugs limit target choice
 - Acceptable
 - GPCR's aminergic, PDE's
 - Difficult
 - GPCR's peptidic, aspartyl proteases

Property Trends in Clinical



James F. Blake, *BioTechniques* 34:S16-S20 (June 2003)

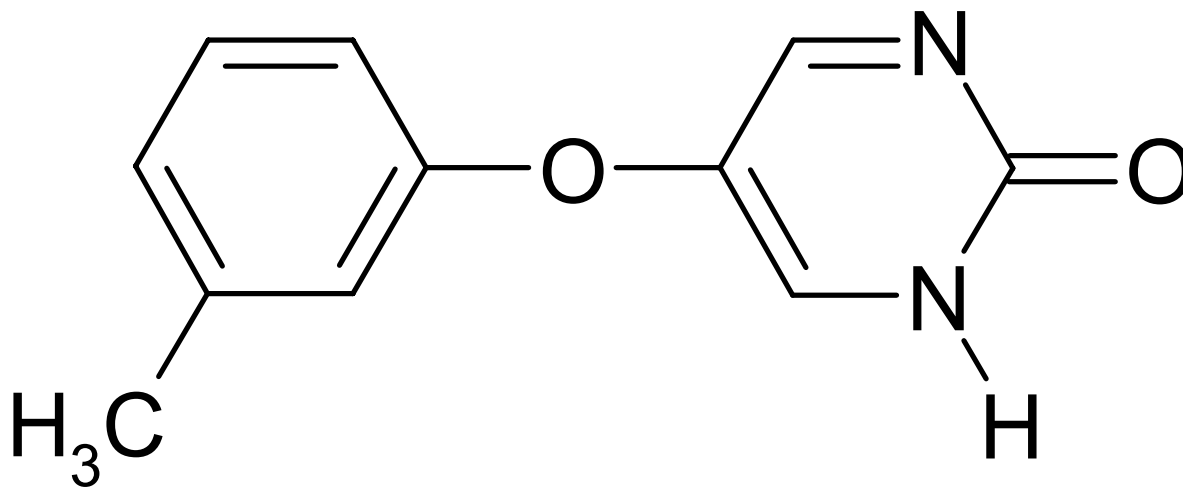
Phenotypic Screens and Mechanism

- Phenotypic screens increase opportunity
- FDA doesn't require mechanism.
- Drug company attitude change
 - eg. Sanofi-Aventis
- Phenotypic screens give an active but without mechanism.
- Progress on deciphering mechanism

Melior MLR-1023

- Antiulcer compound phase 3 from 1970's Pfizer
- New activity from phenotypic in-vivo mouse screens
- IND filed by Melior Discovery for type 2 diabetes/metabolic syndrome
- Lyn kinase activator with EC-50 63 nm
- MWT 202, LE 0.48 kcal/heavy atom

Simple Chemistry

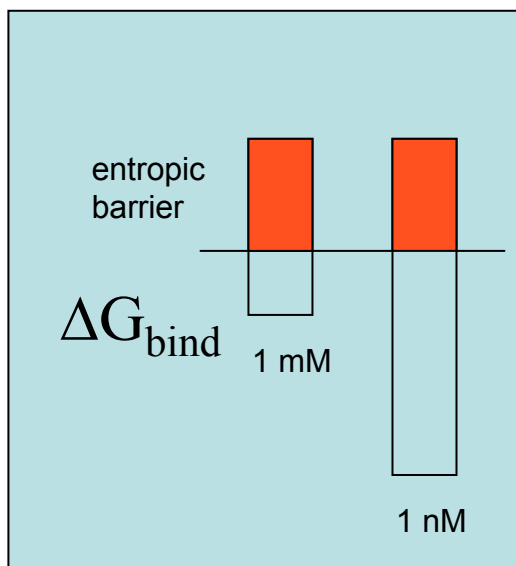


MLR-1023

Chemistry Technology

- Fragment screening
 - detects high binding efficiency
- Isothermal Calorimetry
 - detects high enthalpy of binding
 - MicroCal
- Library rules and filters
 - eg. rule of 5
- Ligand efficiency instead of IC50
- Corporate culture changes
 - Pfizer

Fragment Binding



Graphic courtesy of Prof
Chris Abell, Cambridge Univ

Murray and Verdonk, *J. Comput. Aided Mol. Des.* 2002, **16**, 741-53

Fragment Screening

- Isothermal calorimetry
- Surface plasmon resonance
- Target immobilized - Biacore
- Ligand immobilized – Graffinity
- Affinity MS, Novartis (Hartmut Zehender)
- SAR by NMR
- X-ray, soaking or crystallization

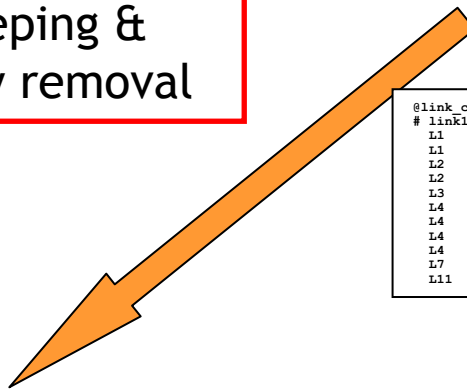
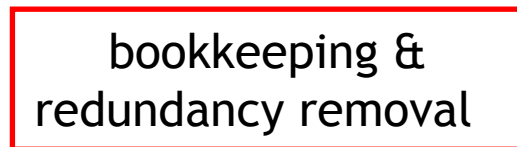
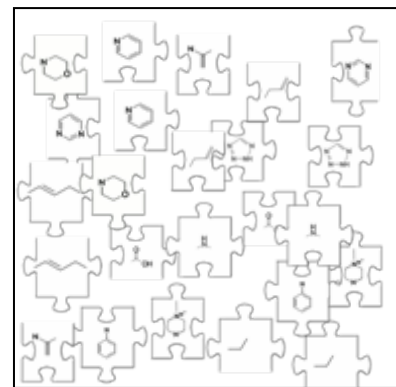
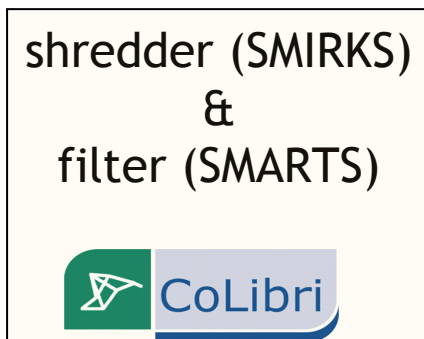
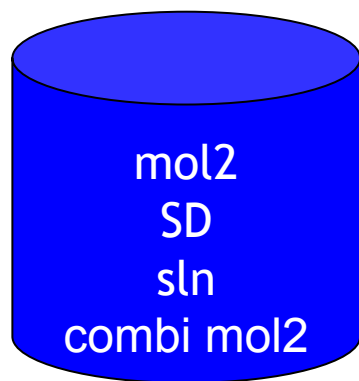
Less
Structural
data

More
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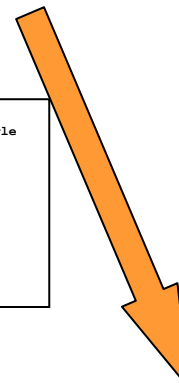
Computational Synergy

- List of biological actives
- Shred apart in a chemically sensible way
 - recap technology
 - software enabled recently
- Fuzzy fragment pattern recognition
 - generate new fragments
 - reassemble fragments

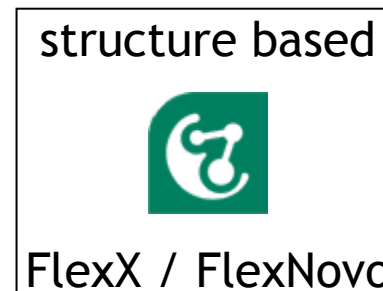
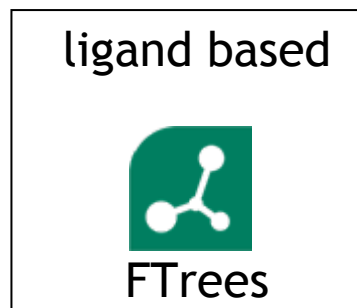
Fragment Generation



```
@link_connects
# link1 link2 bond blen tangle
L1 L2 am 1.355 180
L1 L3 1 1.362 *
L2 L6 am 1.355 180
L2 L12 1 1.656 *
L3 L4 1 1.362 *
L4 L5 1 1.469 *
L4 L8 1 1.469 *
L4 L9 1 1.469 *
L4 L10 1 1.469 *
L7 L7 2 1.316 180
L11 L11 1 1.473 180
```



BioSolveIT



What Chemists Should Do

- Tell the truth.
- Do not be afraid to talk to biologists.
- Calling a putative target undruggable is not being negative. The ligand matters.
- Telling a biologists that a target validation chemical tool or probe is unacceptable for drug discovery is not being negative.
- Hard debate and critical thinking in discovery is not lack of optimism.