Druggability & DruGUI

Ahmet Bakan

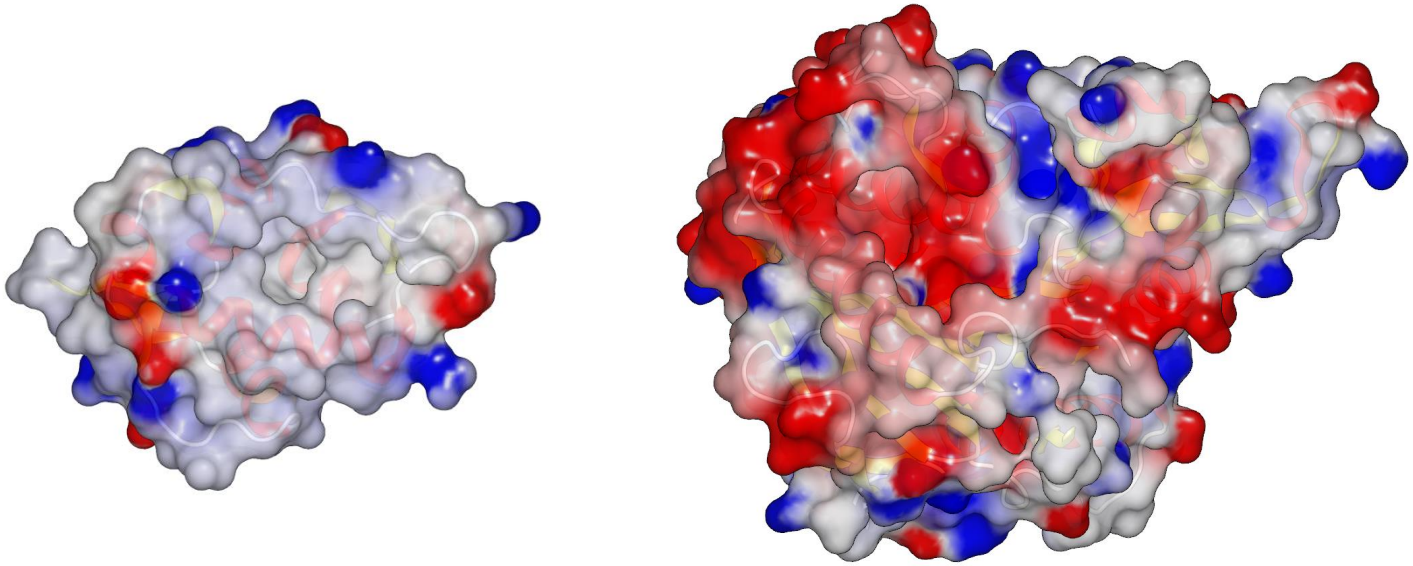
ahb12@pitt.edu

Department of Computational and Systems Biology

Target Druggability

Can a given biological target, such as a protein,

bind with *high affinity* to a drug?



Druggable or not?

Target Druggability

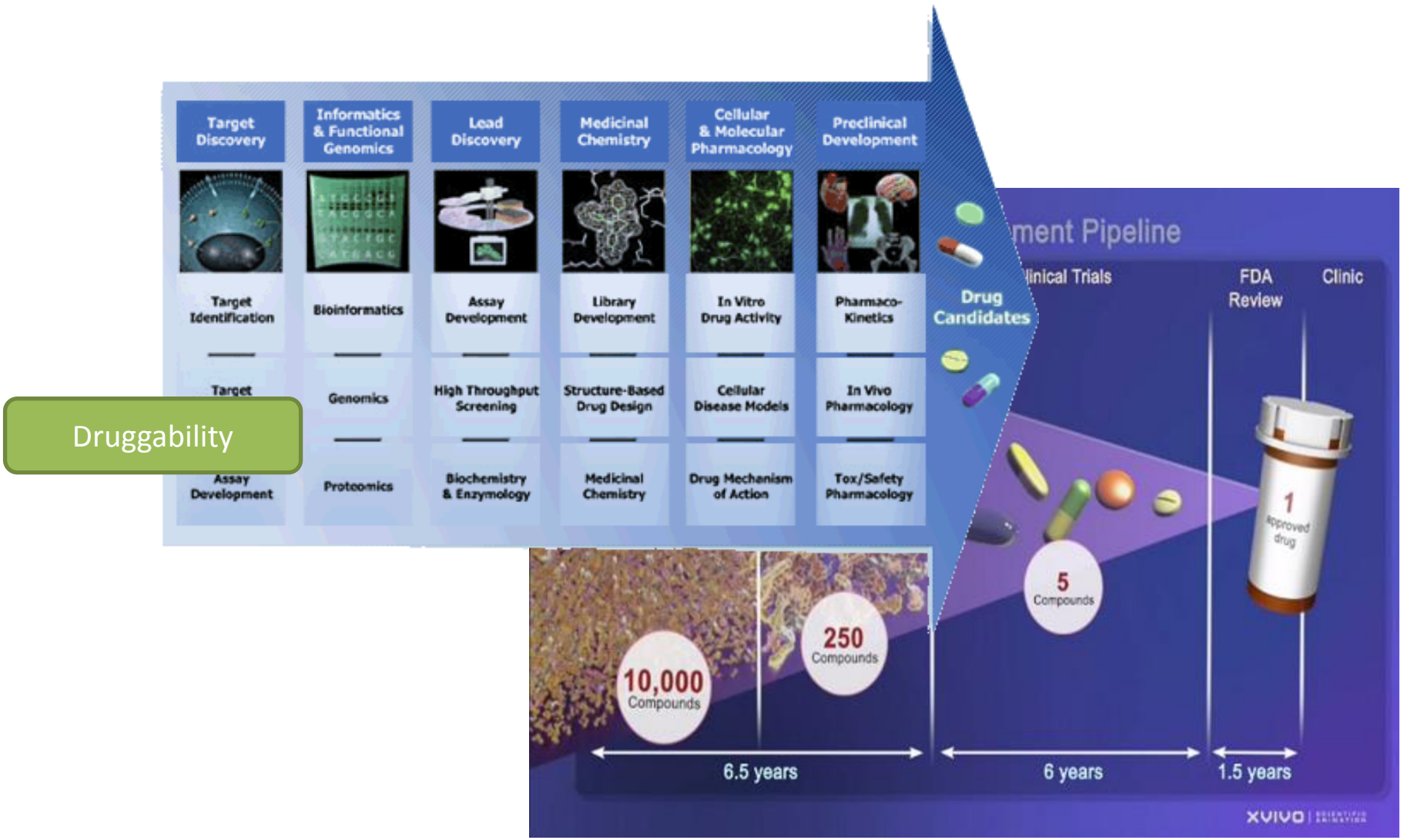
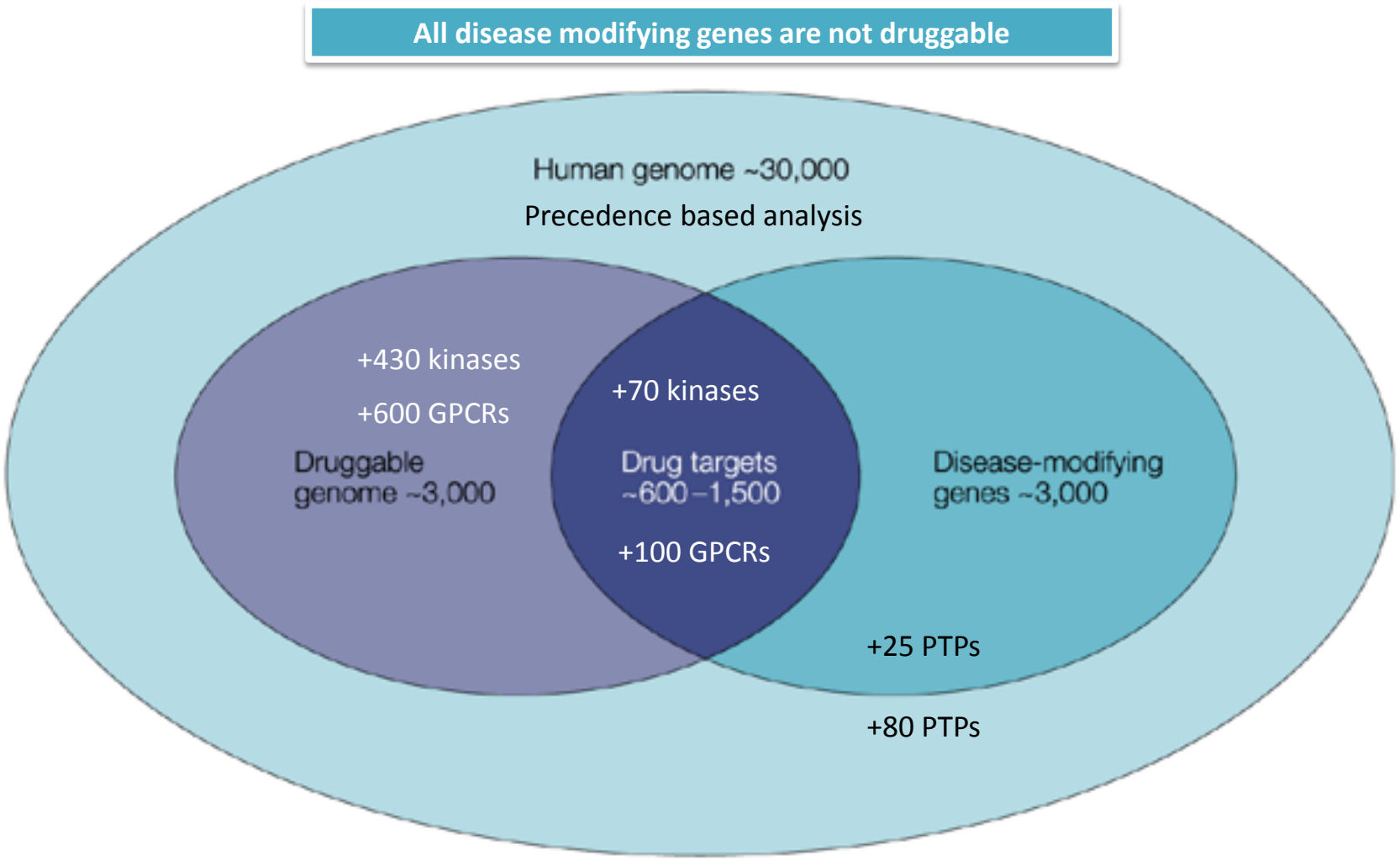


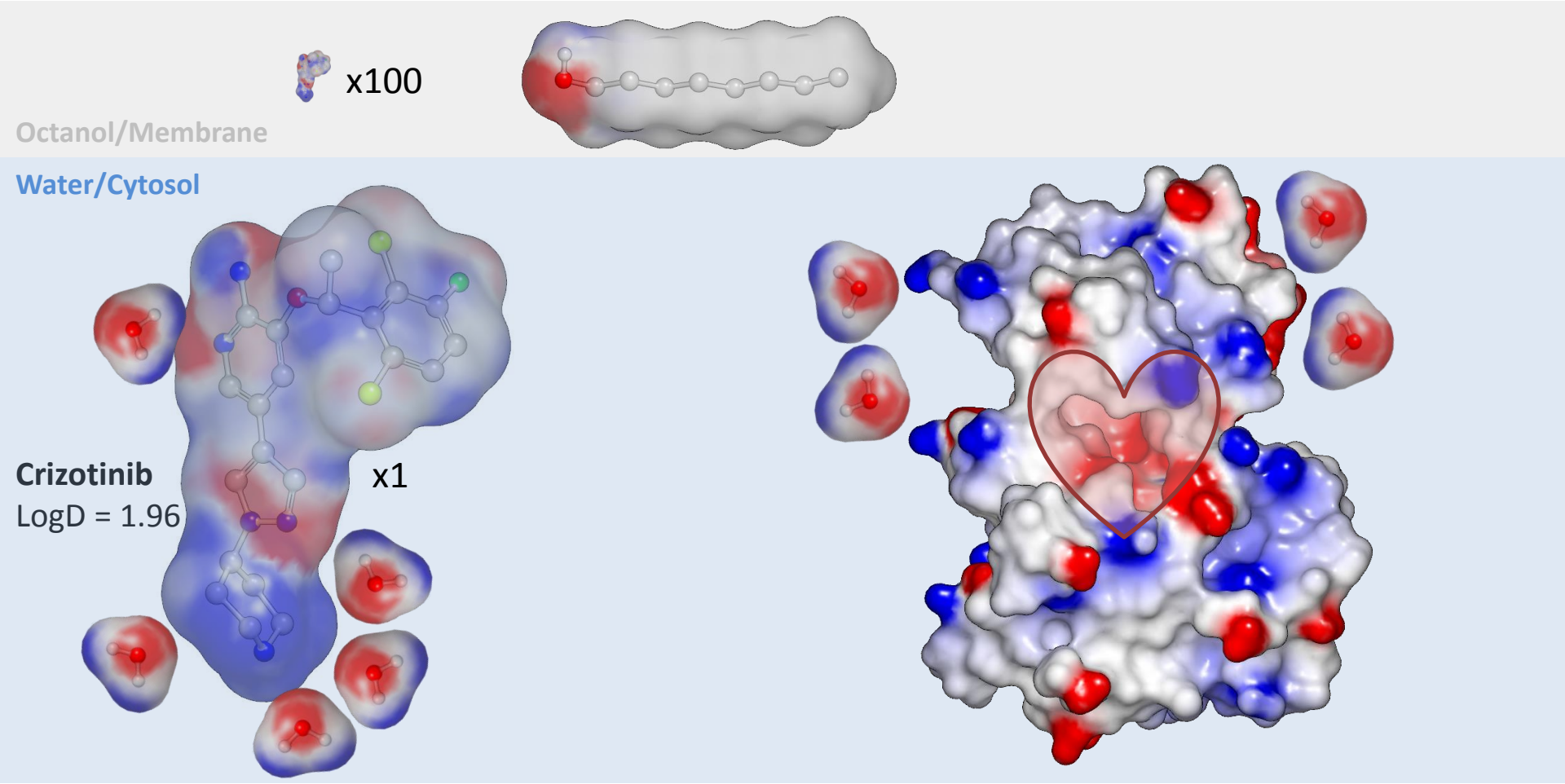
Figure: http://www.ncats.nih.gov/research/reengineering/timeline.html

Druggable Genome

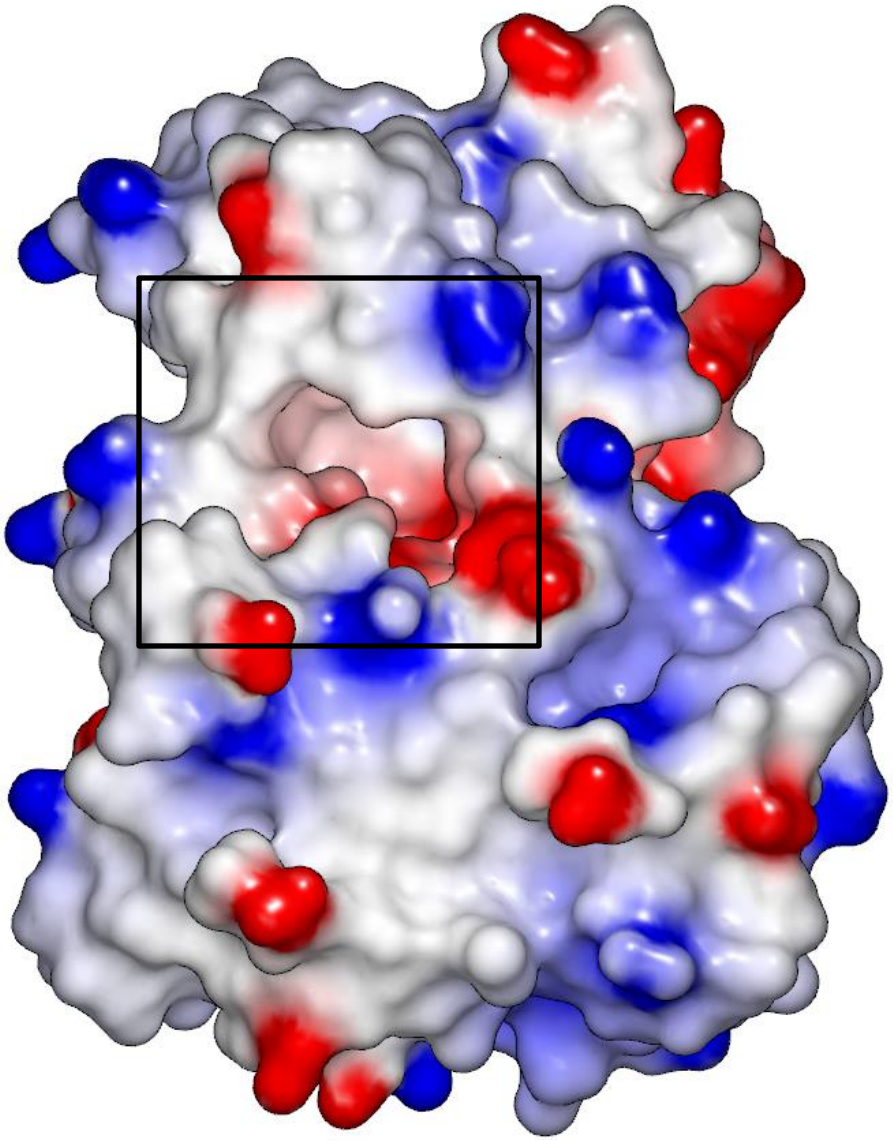


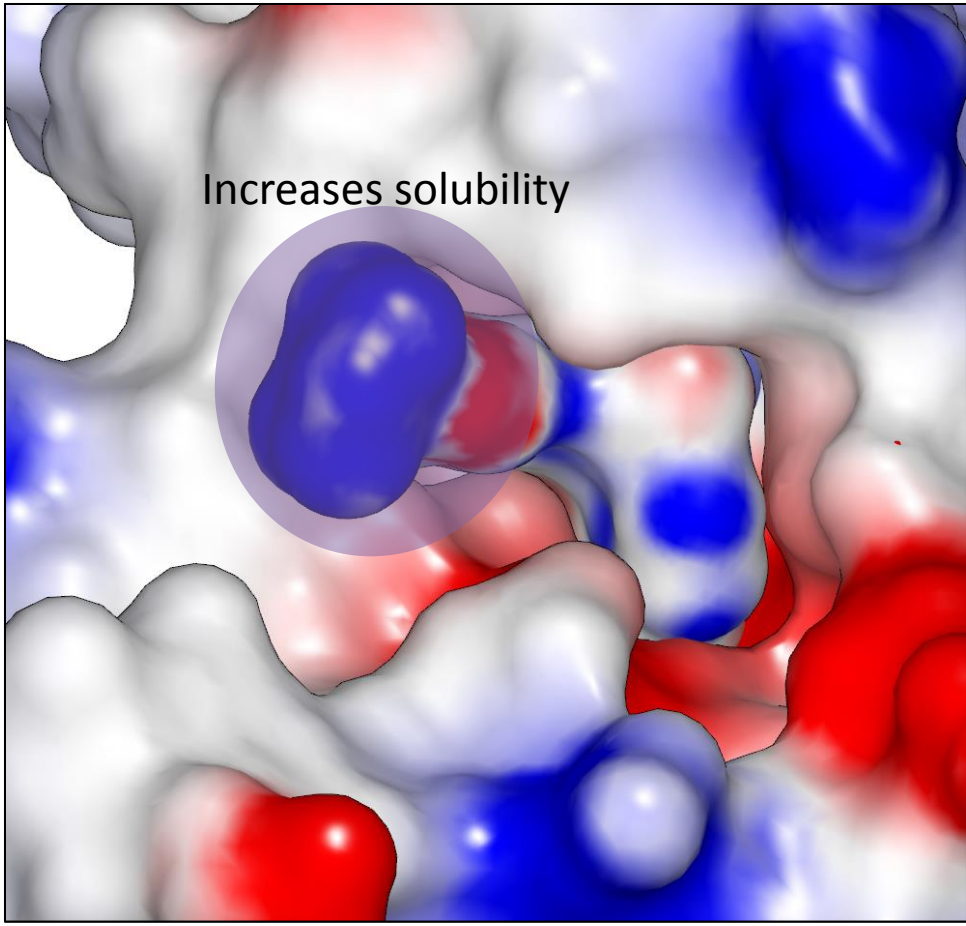
Hopkins and Groom, *Nat Reviews Drug Disc*, 2002

Why drugs bind proteins?



cMET and Crizotinib (FDA approval in 2011)

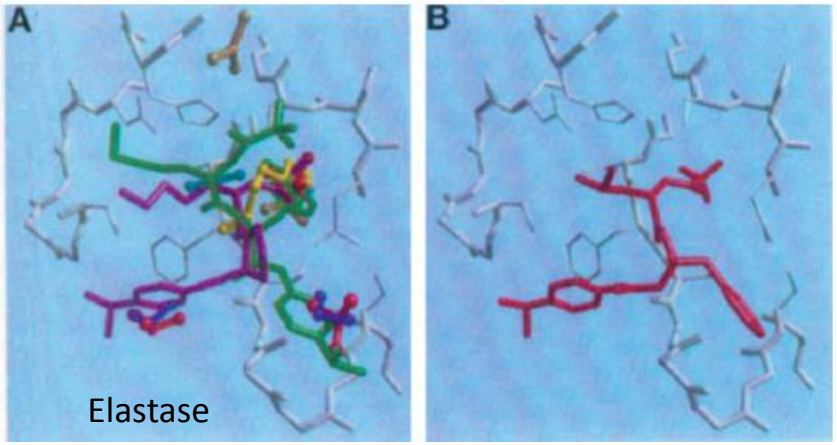




Druggability from Experiments

X-ray crystallography

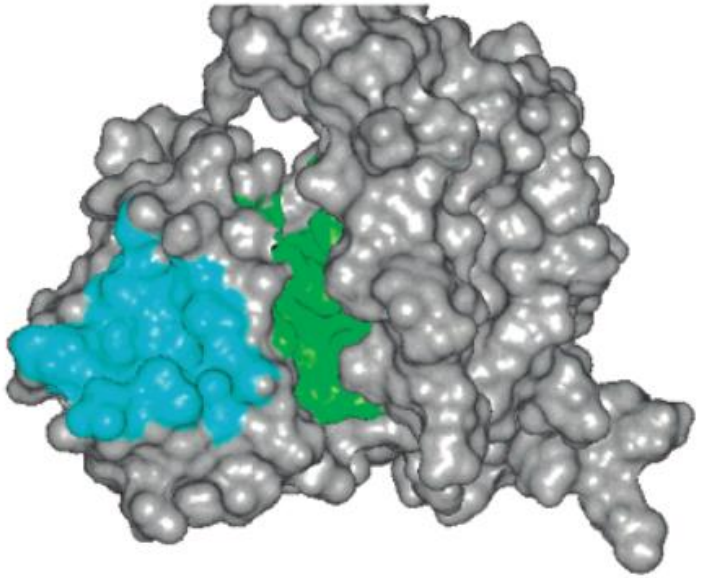
- protein structure is solved in presence of small organic molecules



Mattos and Ridge, *Nat Biotechnology*, 1996

NMR screening

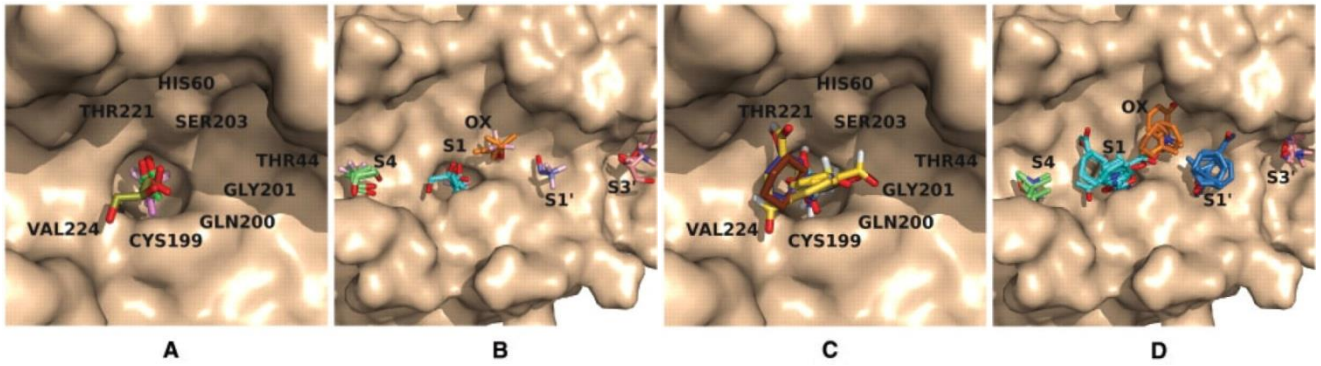
- compounds from a fragment-library are screened as mixtures of 20-30 compounds, druggability is calculated from chemical shift perturbations

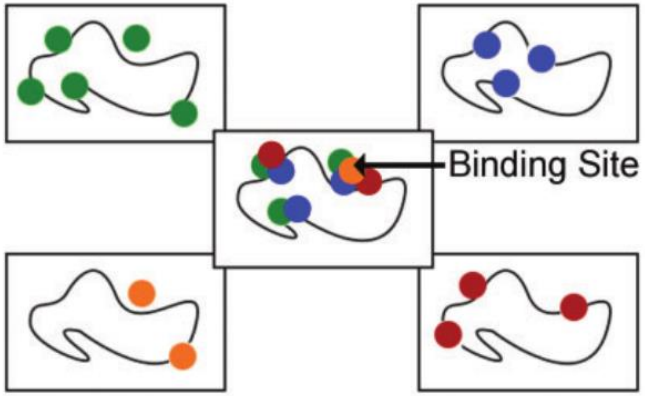


Hajduk et al., *J Med Chem*, 2005

Structure-based Druggability

- Solvent/Probe Docking
  - isopropanol, acetone, ethane, benzene, etc





Miranker and Karplus, Proteins, **1991**
Schmidtke and Barril *J Med. Chem.* **2010,** *53*, 5858-5867.
Brenke et al., *Bioinformatics* **2009,** *25*, 621-627.

Structure-based Druggability

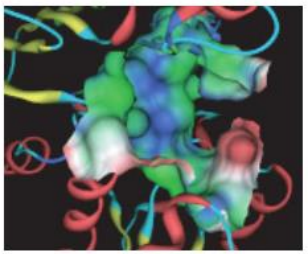
$$\Delta G_{MAP_{POD}} \approx \Delta G^{target}_{desolvation} + \Delta G^{ligand}_{desolvation} + \Delta G_{constant}$$

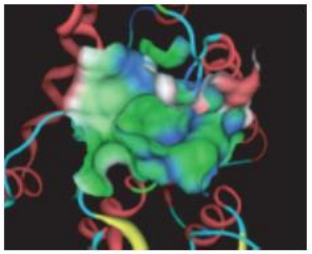
$$\Delta G_{MAP_{POD}} \approx -\gamma(r) A^{target}_{nonpolar} - \gamma_{constant} A^{ligand}_{nonpolar} + \Delta G_{constant}$$

$$\gamma(r) = \frac{\gamma(\infty)}{1 - \frac{1.4}{r}}$$

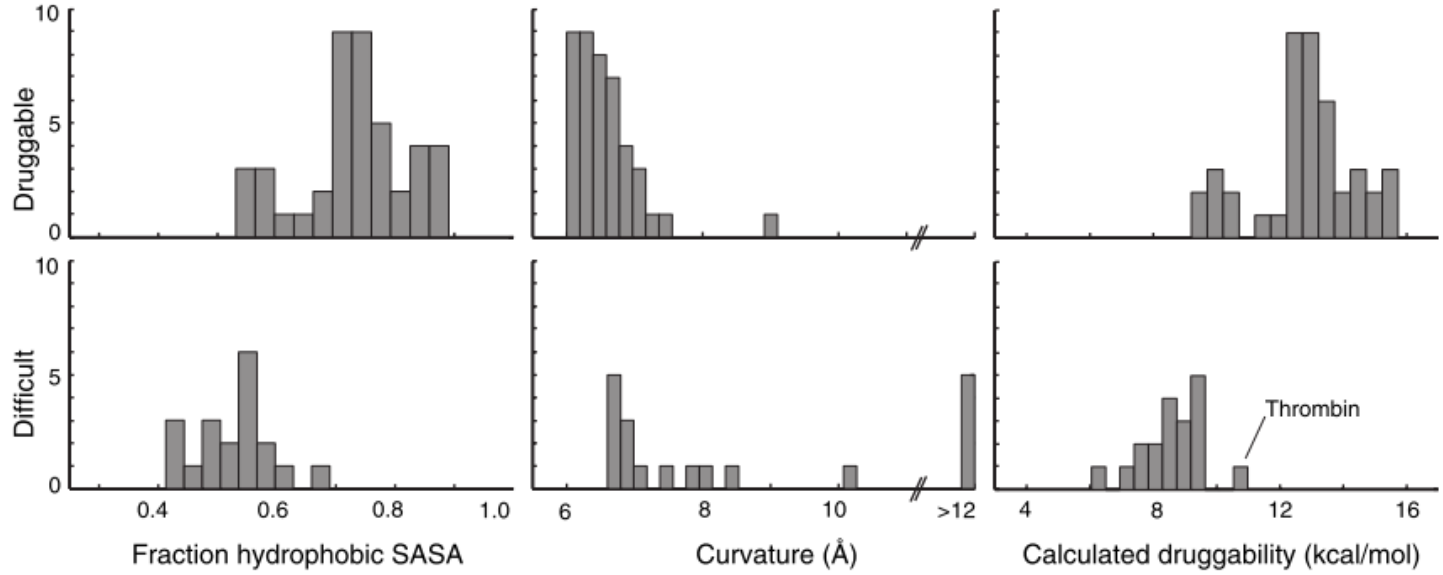
1.4 is radius of water,
smaller *r* more druggable

$$K_d = \exp\left(\frac{\Delta G}{RT}\right), \text{where } T = 298\text{K}$$



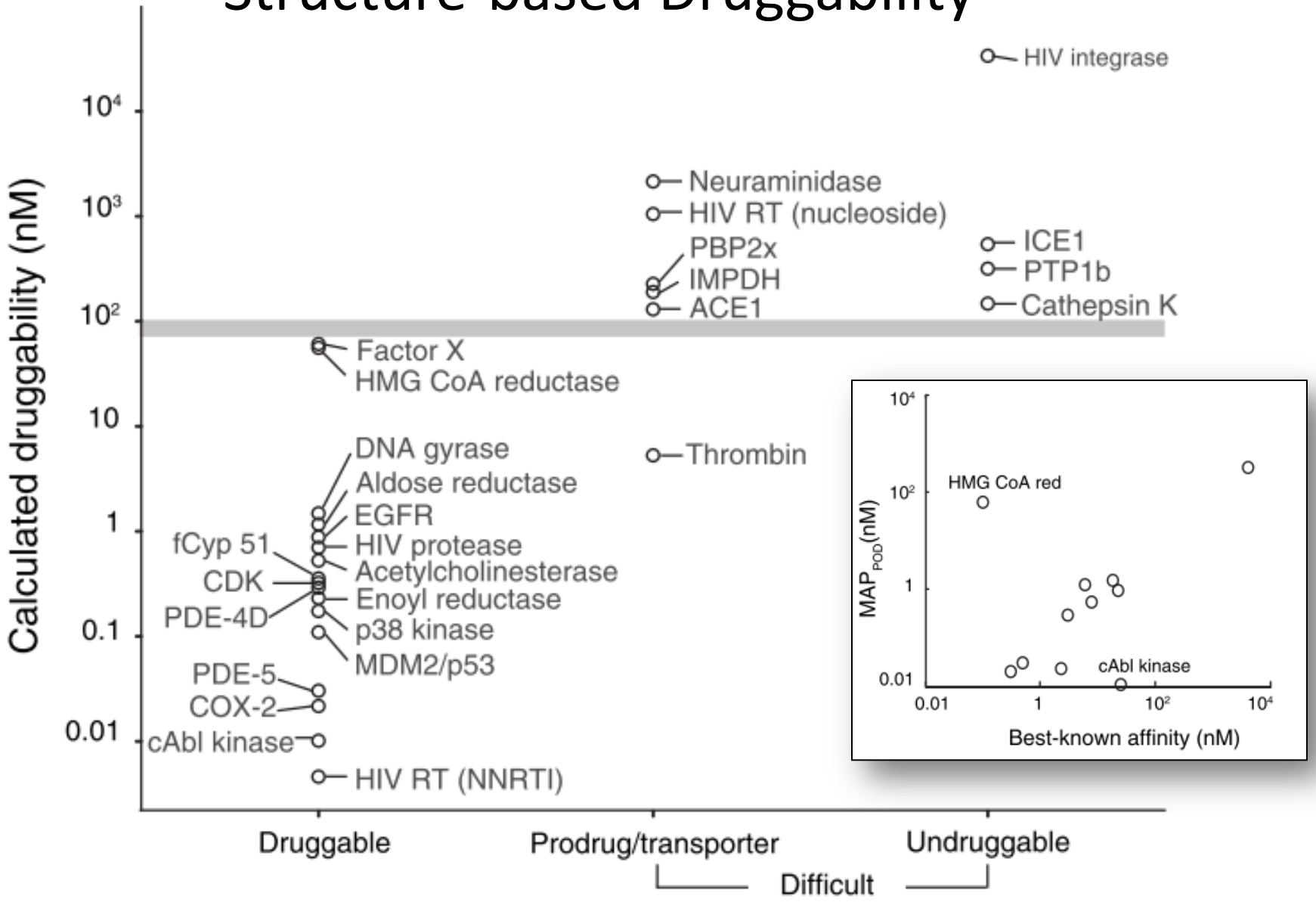


	Fungal HSD	H-PGDS
$MAP_{POD}K_D$	240 nM	30 nM
Primary HTS hits	16	200
Compounds with $IC_{50} \leq 5$ μM	2	33
Compounds with $IC_{50} \leq 1$ μM	0	11



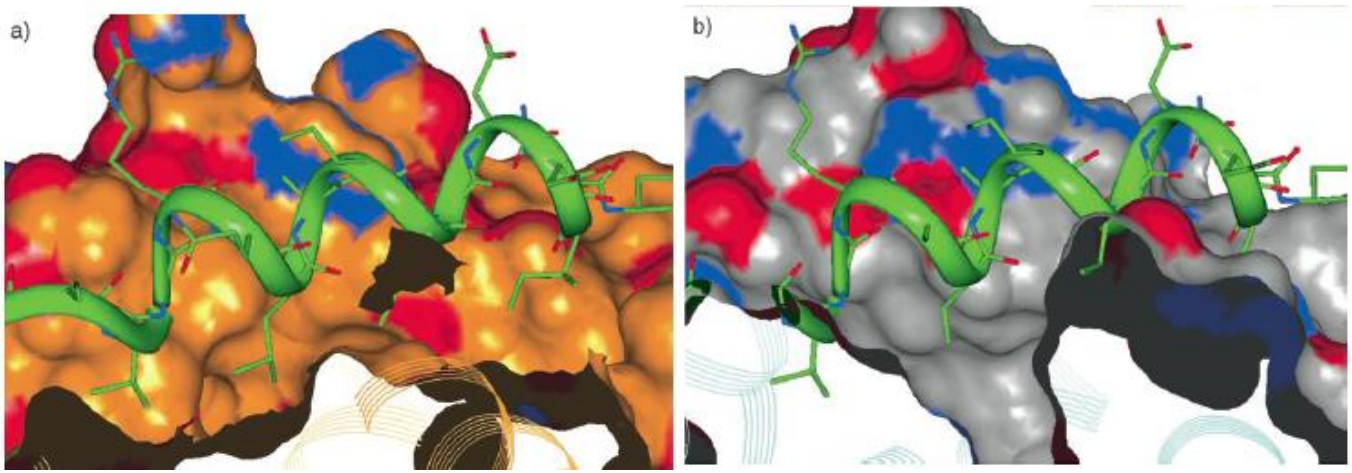
Cheng, A. C. et al. (2007). *Nature biotechnology*, *25*(1), 71–5.

Structure-based Druggability



Cheng, A. C. et al. (2007). *Nature biotechnology*, *25*(1), 71–5.

MD snapshot evaluation

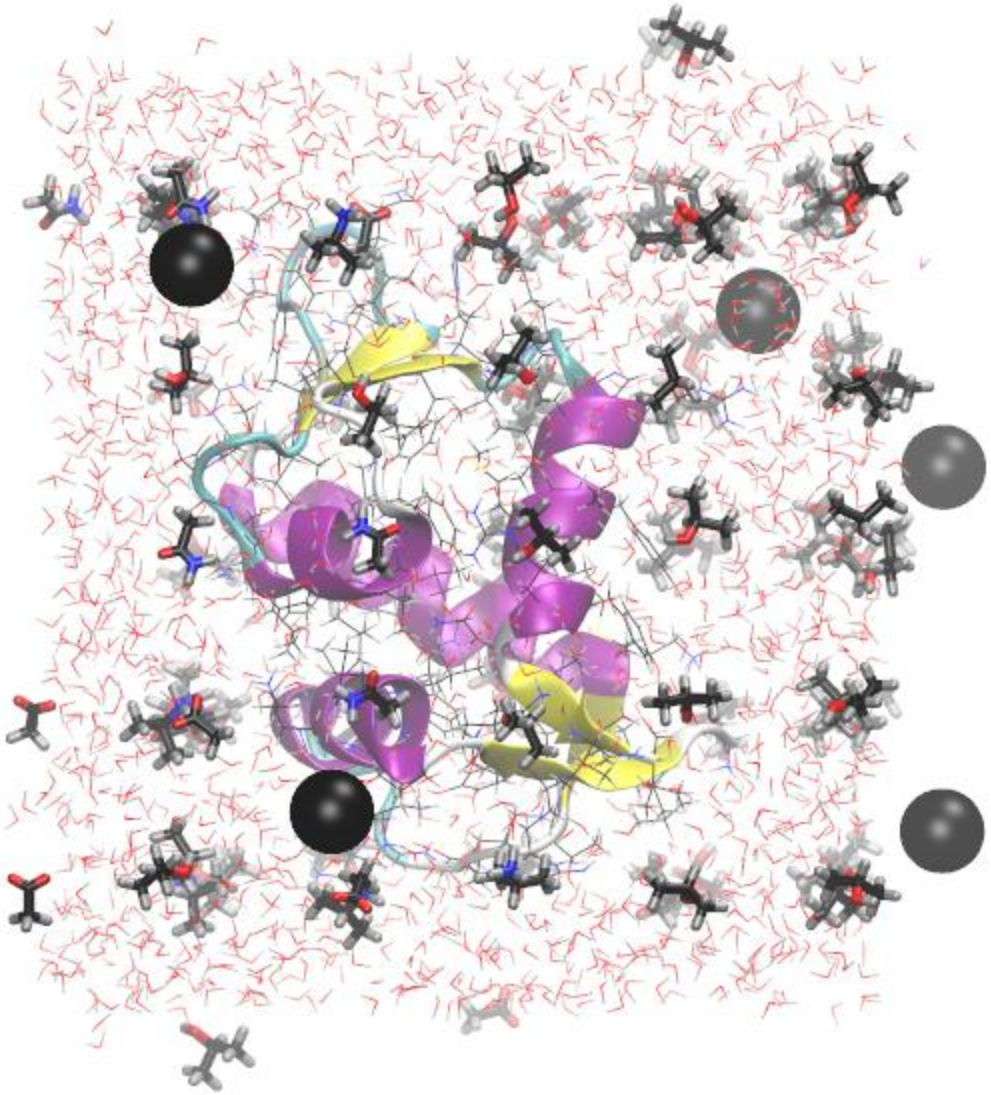


Not druggable

Druggable

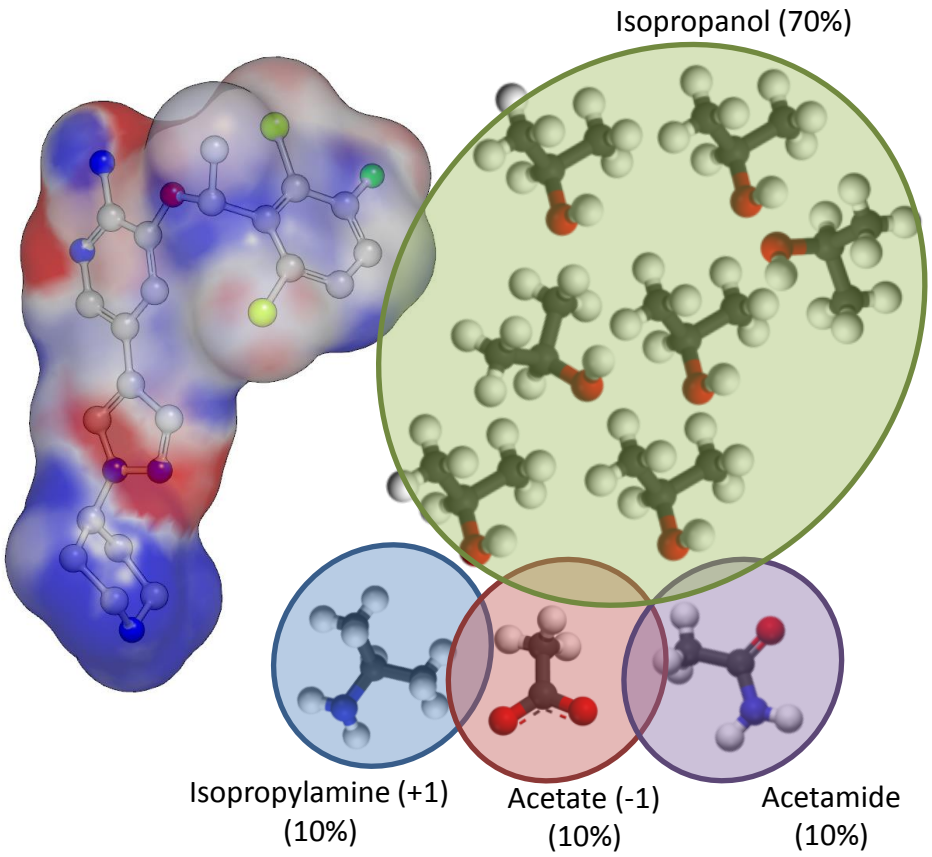
Brown and Hajduk, *Chem Med Chem*, 2006
Lexa and Carlson *J Am. Chem. Soc.* **2010,** *133*, 200-202.
Ivetac and McCammon *Chem. Biol Drug Des* **2010,** *76*, 201-217.

Probe Simulations



Mimicking Drugs

Fragment name	1341 approved drugs
Isobutane	1022 (76%)
Isopropanol	**768 (57%)**
Isopropylamine	**337 (25%)**
Acetic acid	**284 (21%)**
Acetamide	**280 (21%)**
Acetone	239 (17%)
Urea	61 (5%)
DMSO	37 (2%)

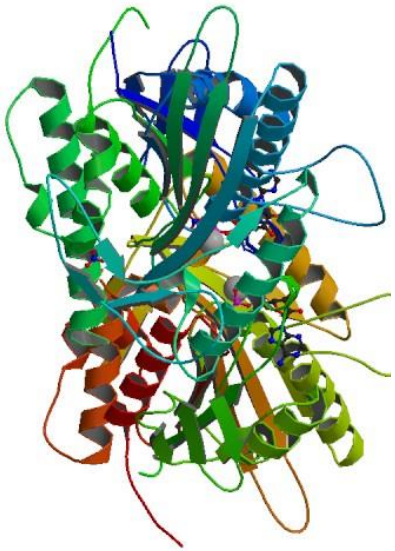


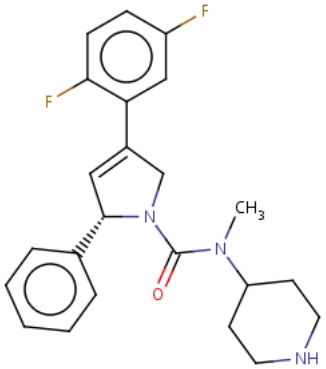
35% of orally available drugs are neutral
65% are charged or zwitterionic

Leeson, P. D.; St-Gallay, S. A.; Wenlock, M. C. *Med. Chem. Commun.* **2011,** *2*, 91-105.

eg5 Kinesin Simulations

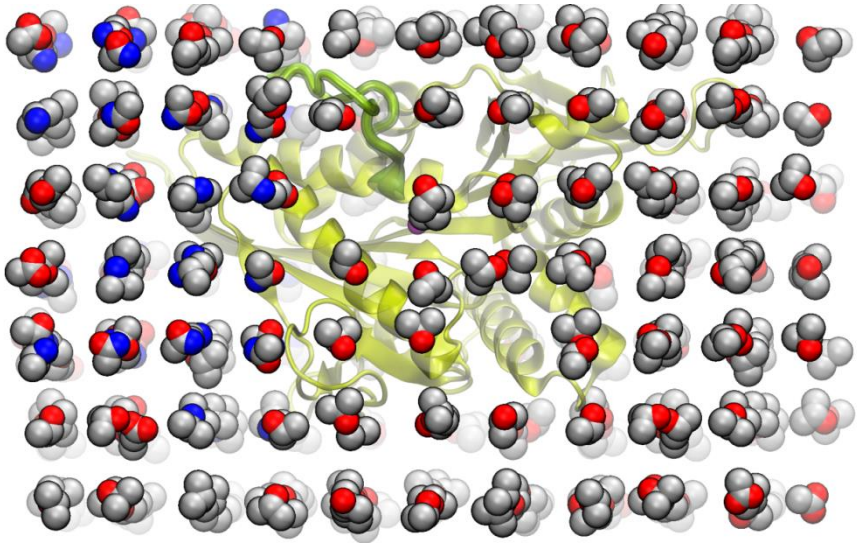
eg5 and an allosteric inhibitor

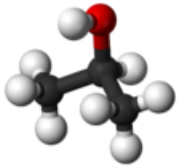




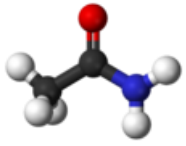
eg5 has a role in cell division and is an anti-cancer target

eg5 structure immersed in probes and water

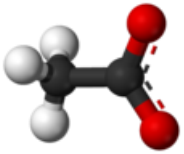




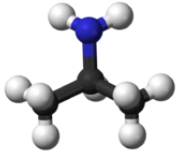
252



32



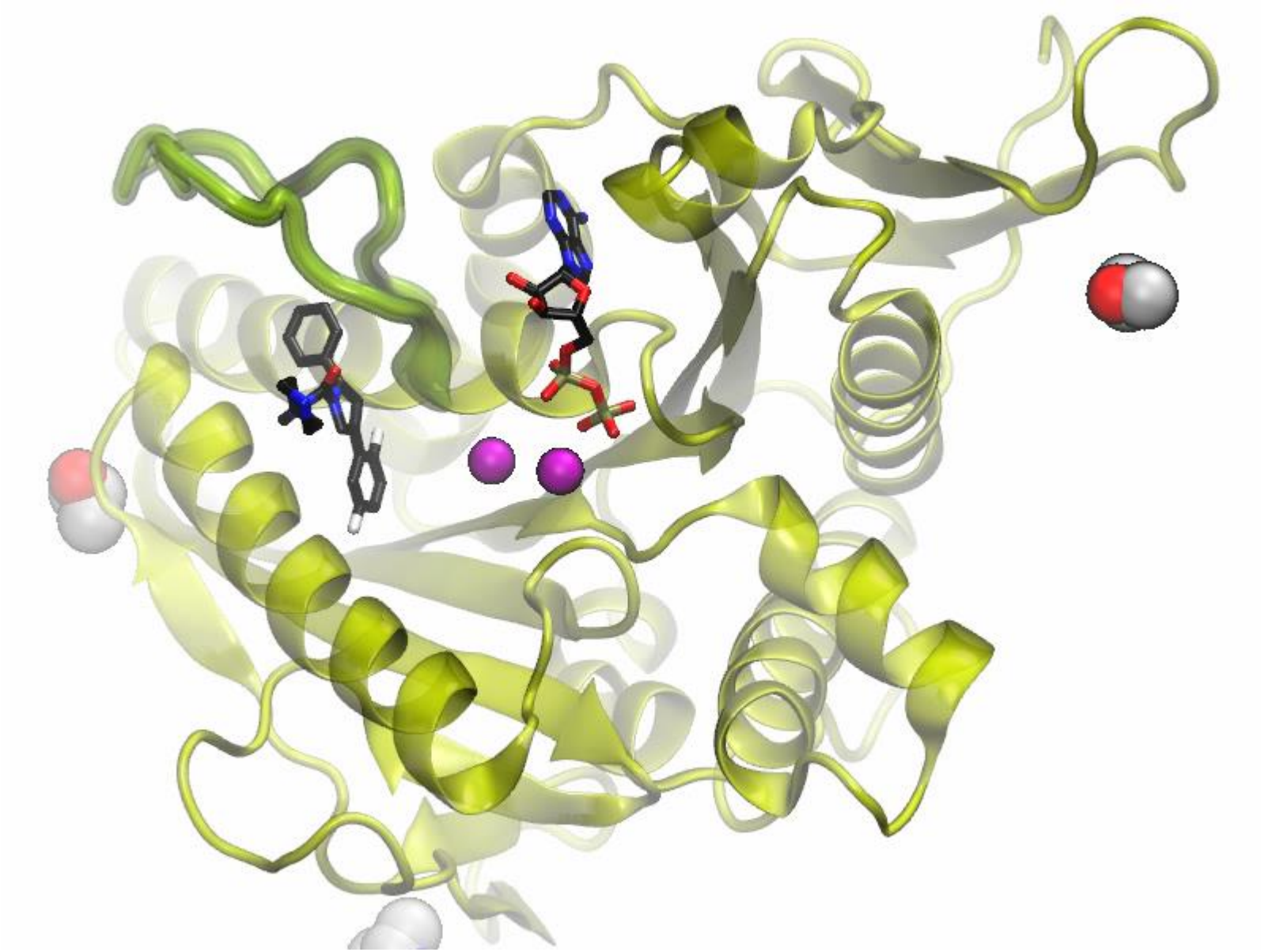
32



32

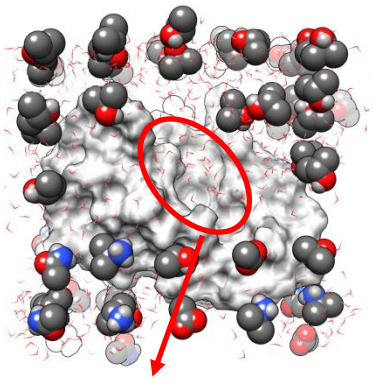
7200
20 per probe
(not shown)

eg5 Kinesin Simulation



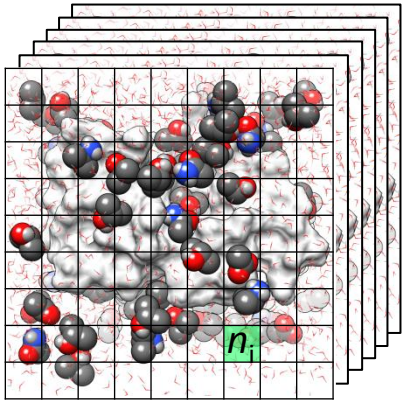
Trajectory Analysis

Initial state



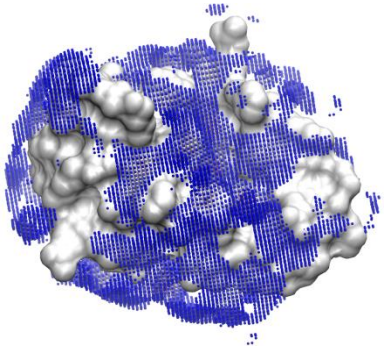
binding site

~10,000 snapshots



Voxels dimension is 0.5 Å

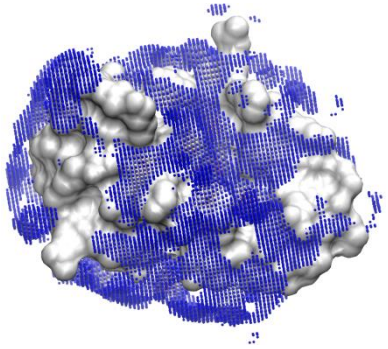
Voxels occupied by probes interacting with the protein



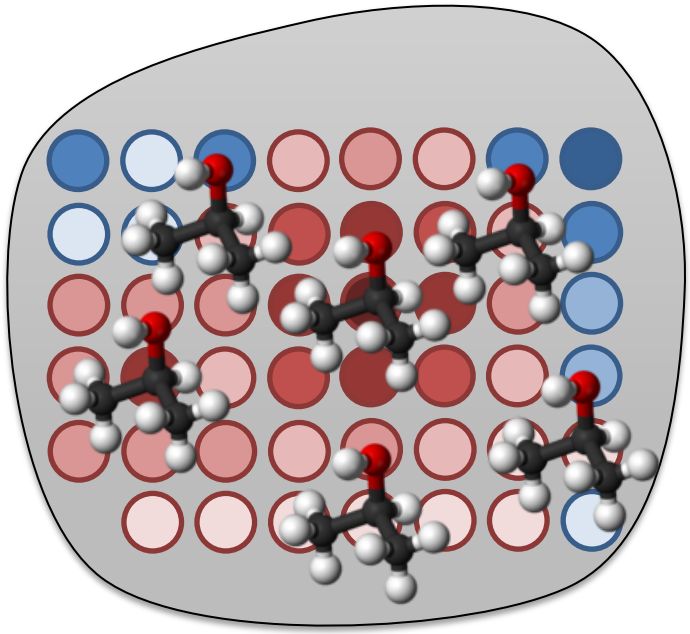
~50,000 voxels

Probe Binding Site Identification

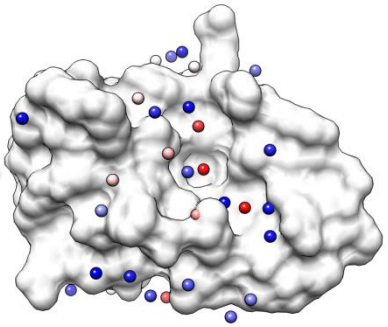
Voxels occupied by probes interacting with the protein



~50,000 voxels



Probe binding sites



~50 sites

Ligand Efficiency

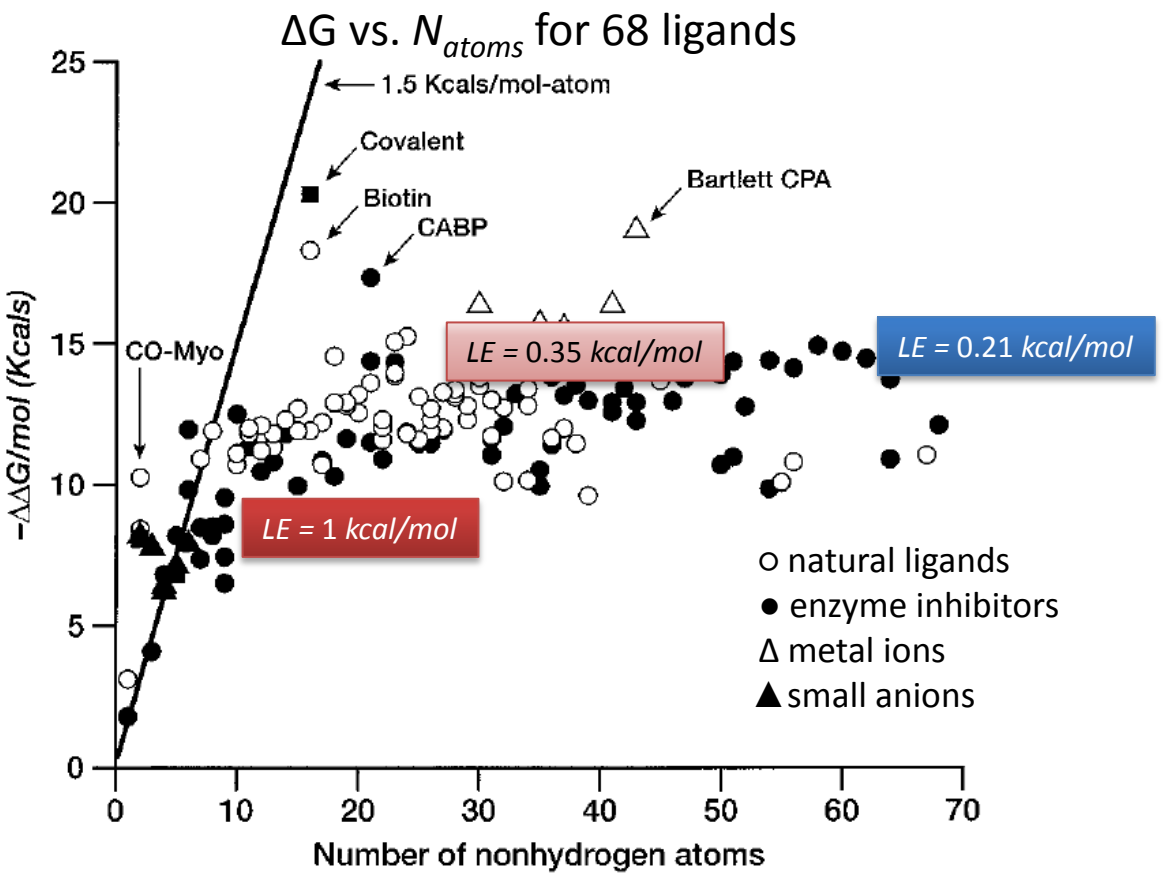
Ligand binding free energy:

$\Delta G = -RT \ln (K_d)$

Ligand efficiency or
free energy per atom

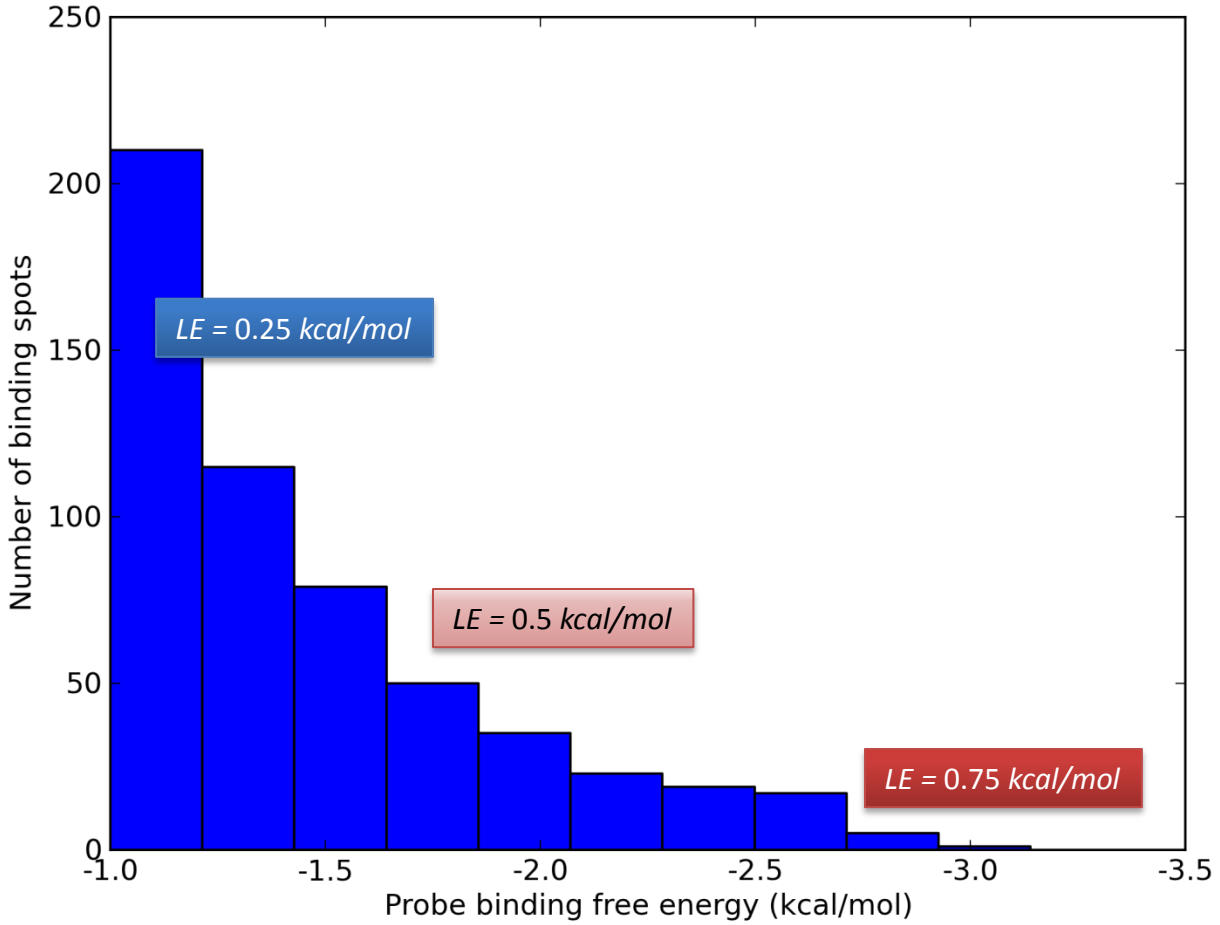
$\Delta g = \Delta G^* / N_{non\text{-}hydrogen\ atoms}$

*IC_{50}, EC_{50}, K_i can replace K_d

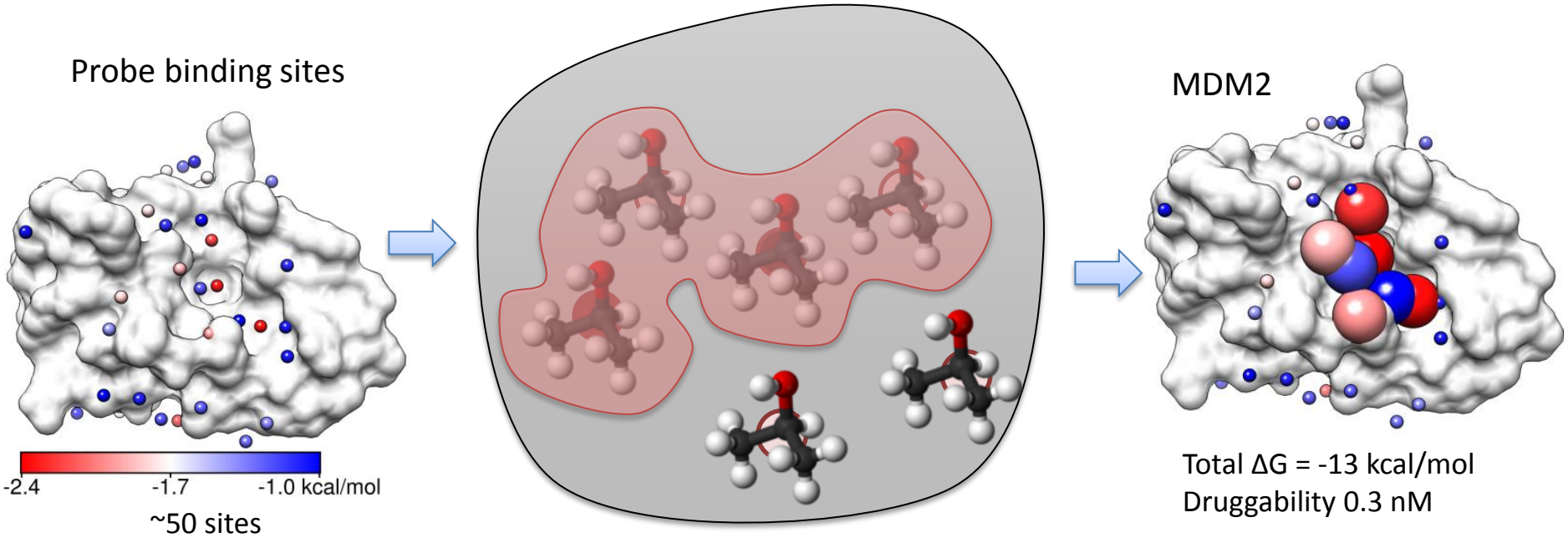


Hopkins, A., & Groom, C. (2004). Ligand efficiency: a useful metric for lead selection. *Drug Discovery Today*, *9*(10), 430-431.
Kuntz, I. D., Chen, K., Sharp, K. a, & Kollman, P. a. (1999). The maximal affinity of ligands. *PNAS*, *96*(18), 9997-10002.

Distribution of ΔG_{probe}

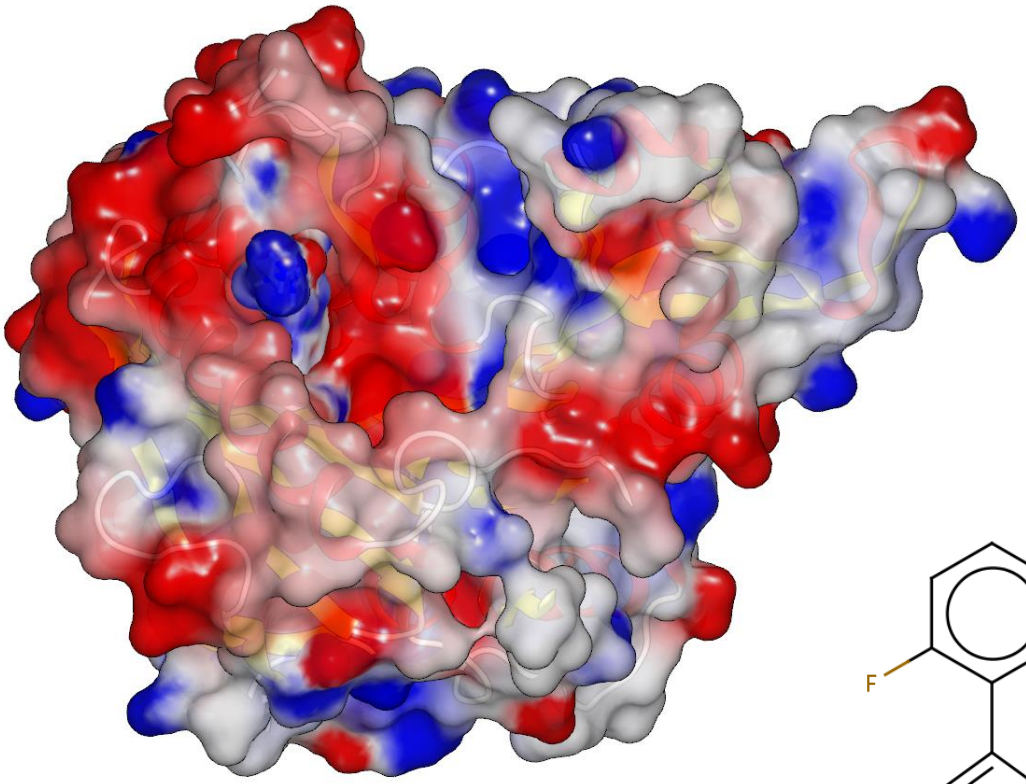


Druggability Index (or Maximal Affinity)



$\Delta G_{achievable\ by\ a\ drug}$ correlates with sum of $\Delta G_{probe\ binding}$ of 7-8 proximal probes

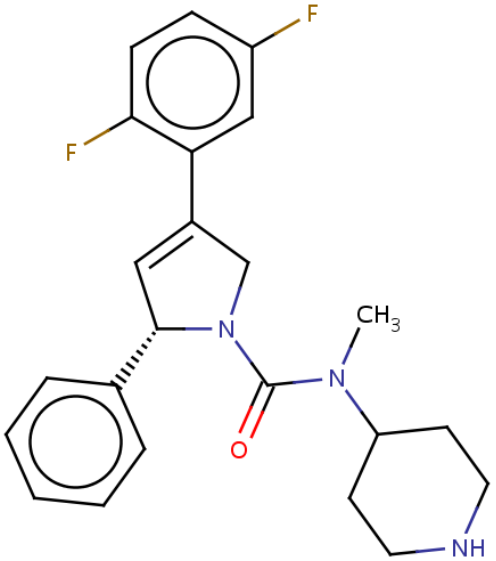
Druggable or not?

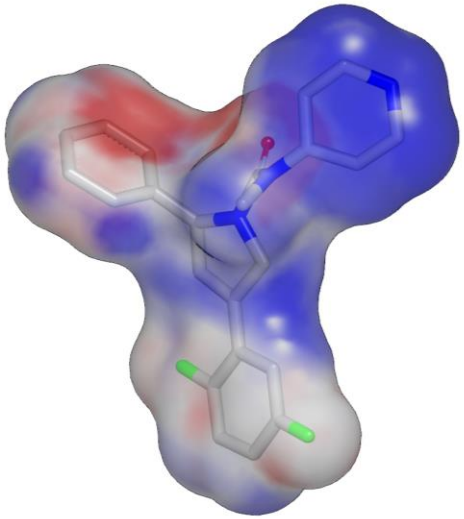


Kinesin Eg5 has a druggable allosteric site. eg5 has a role in cell division and is an anti-cancer target.

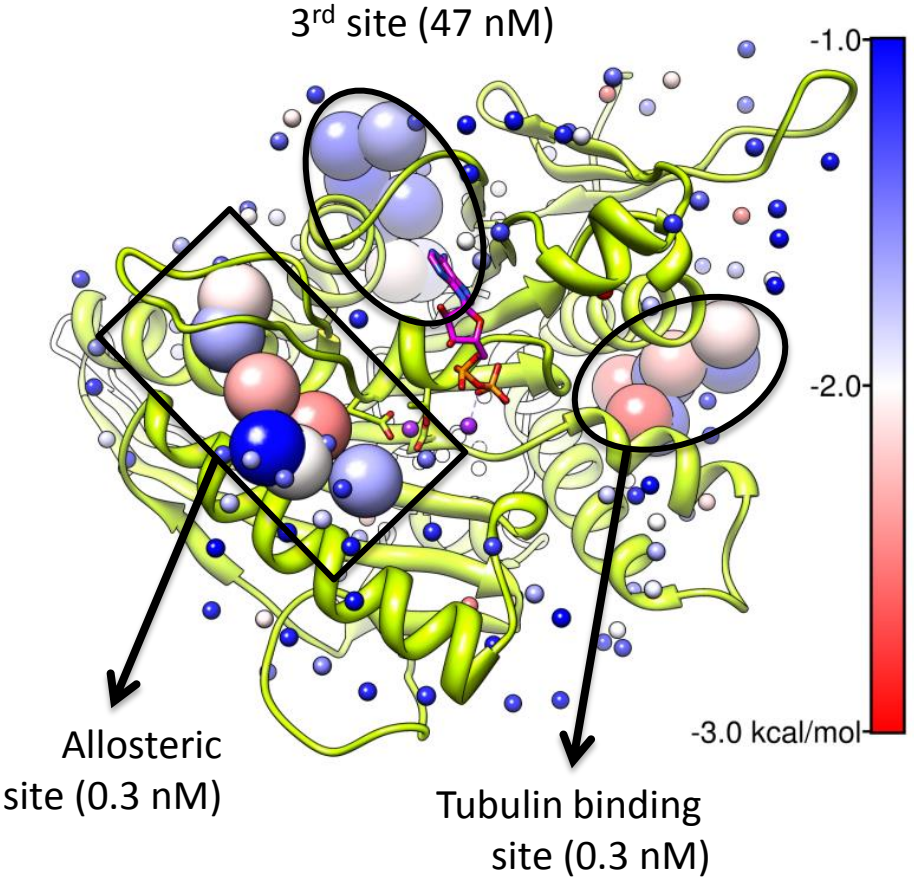
Druggability:

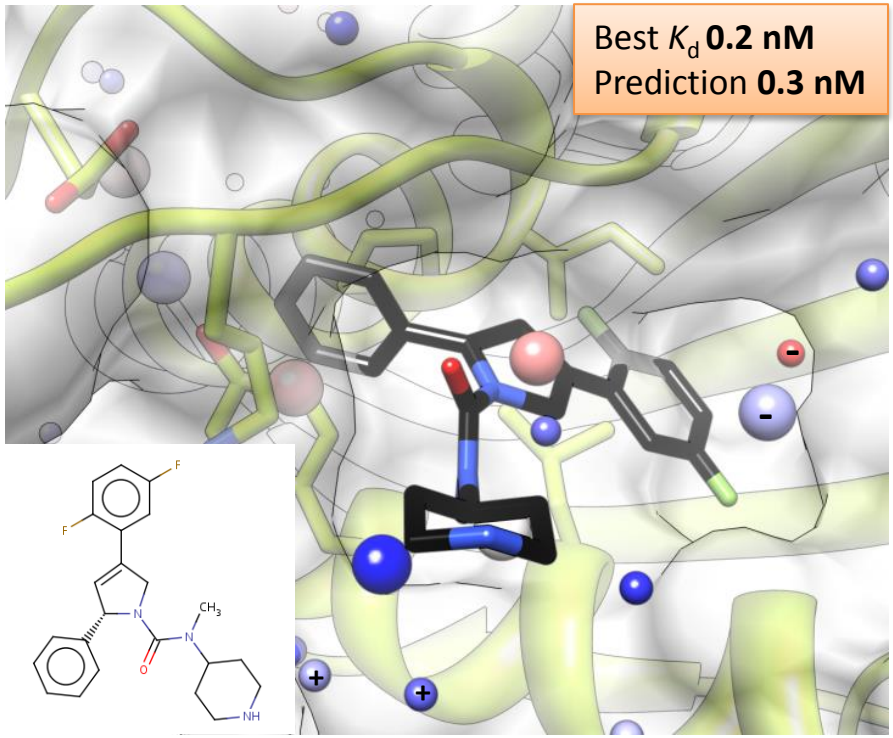
- Best known K_d 0.2 nM
- Simulation 0.3 nM





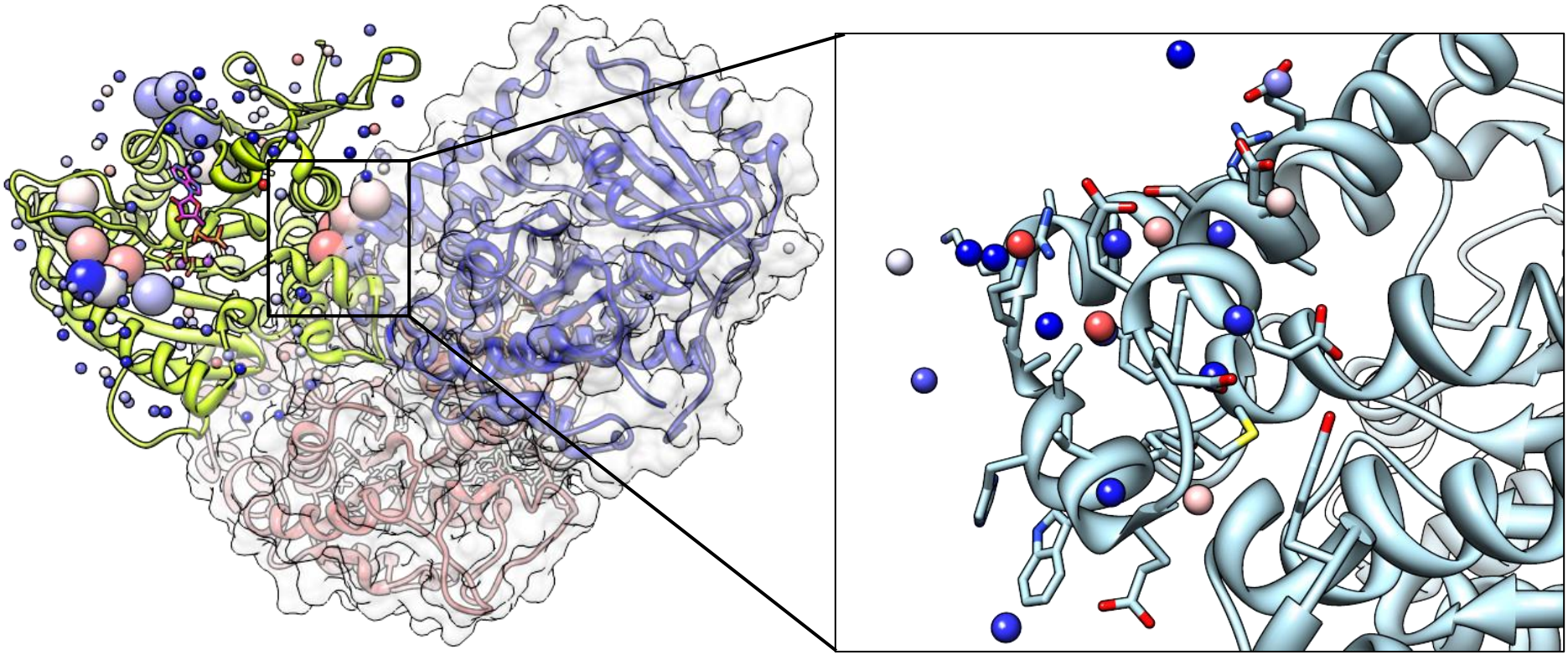
eg5 Druggable Sites





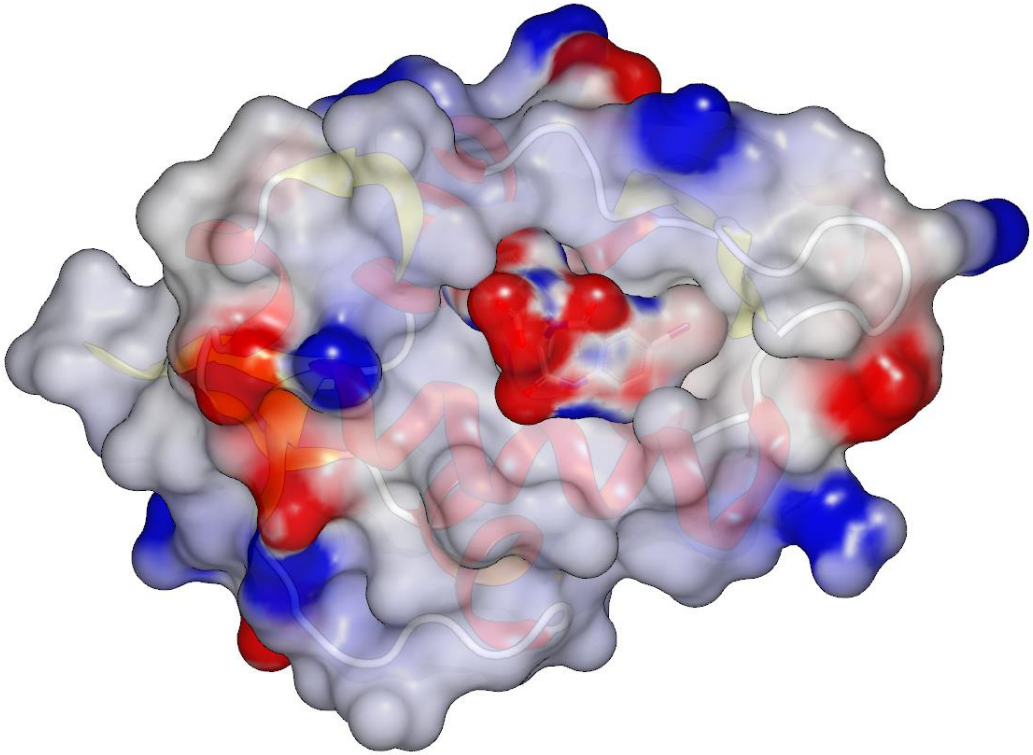
Bioorg. Med. Chem. Lett. **2007,** *17*, 5677-5682

Eg5-Tubulin Interface

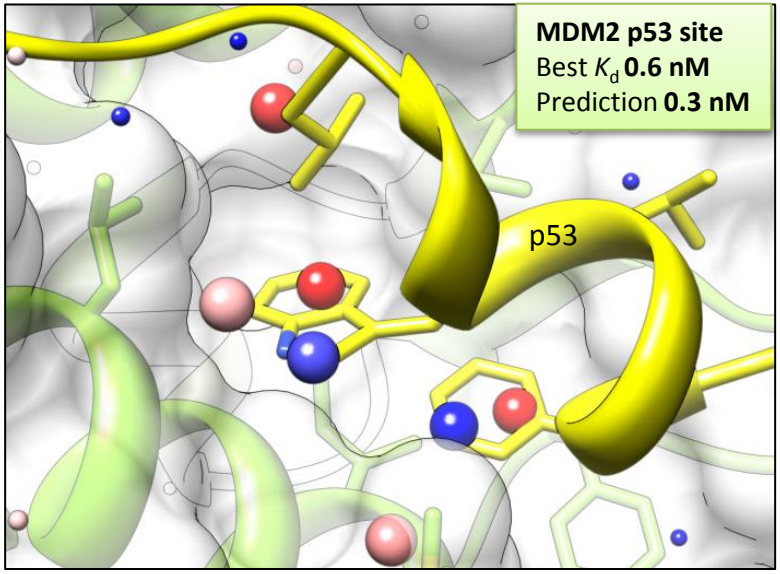


Human kinesin and tubulin structures
docked into an EM model at 9 Å resolution

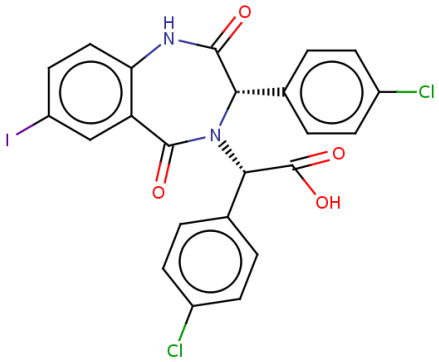
Druggable or not?

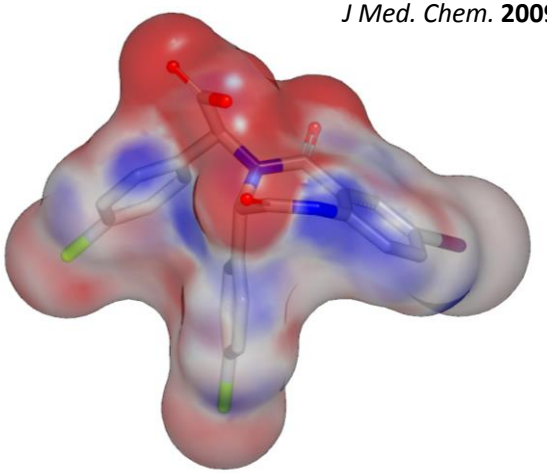


MDM2 is a negative feedback regulator of the p53 tumor suppressor.

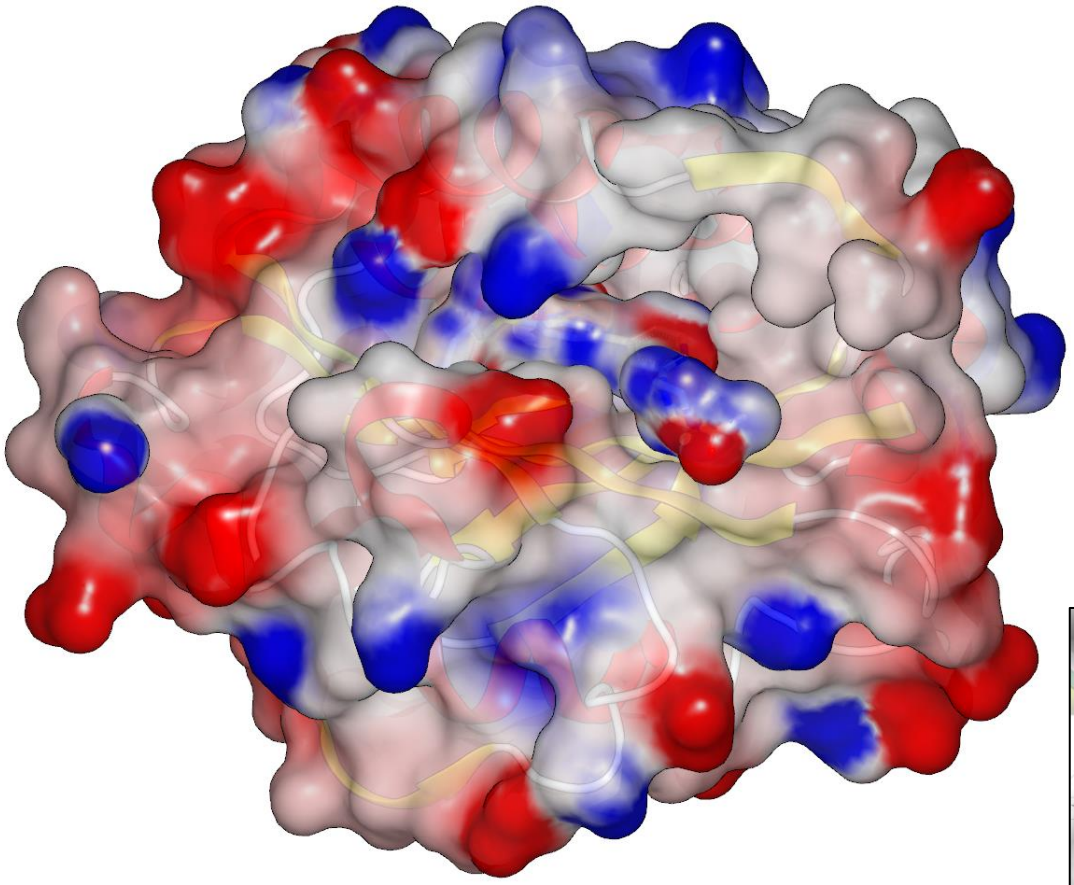


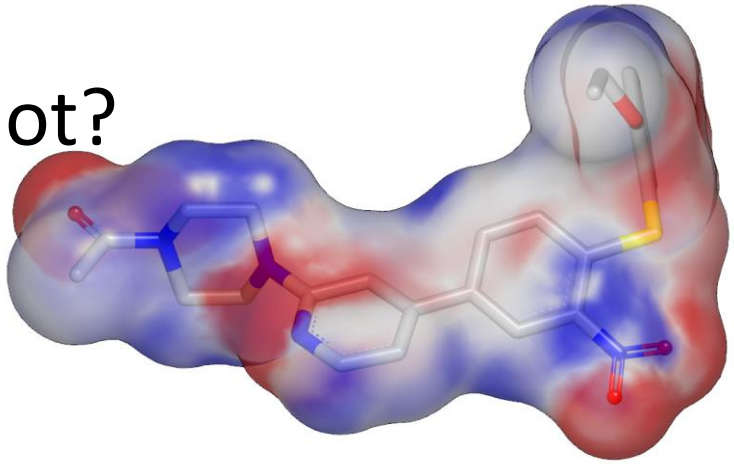
J Med. Chem. **2009,** *52*, 7970-7973

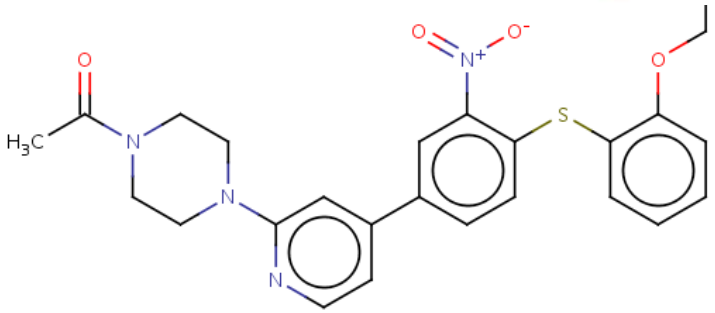


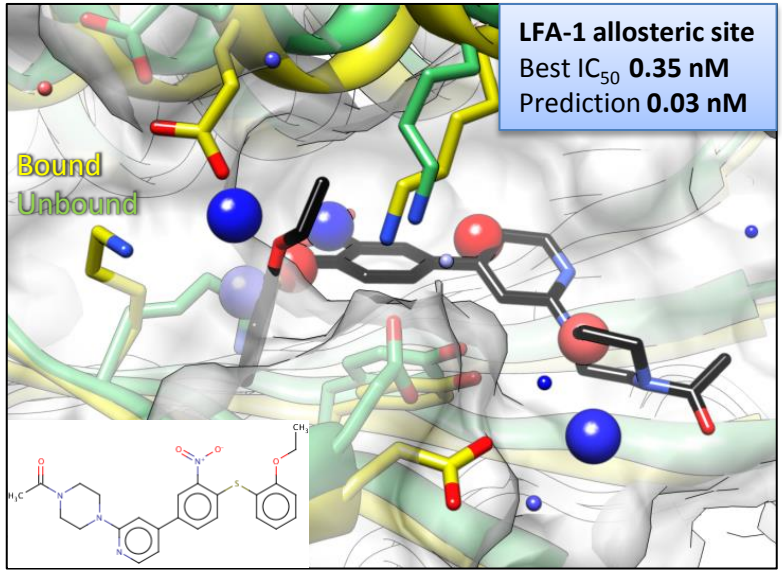


Druggable or not?





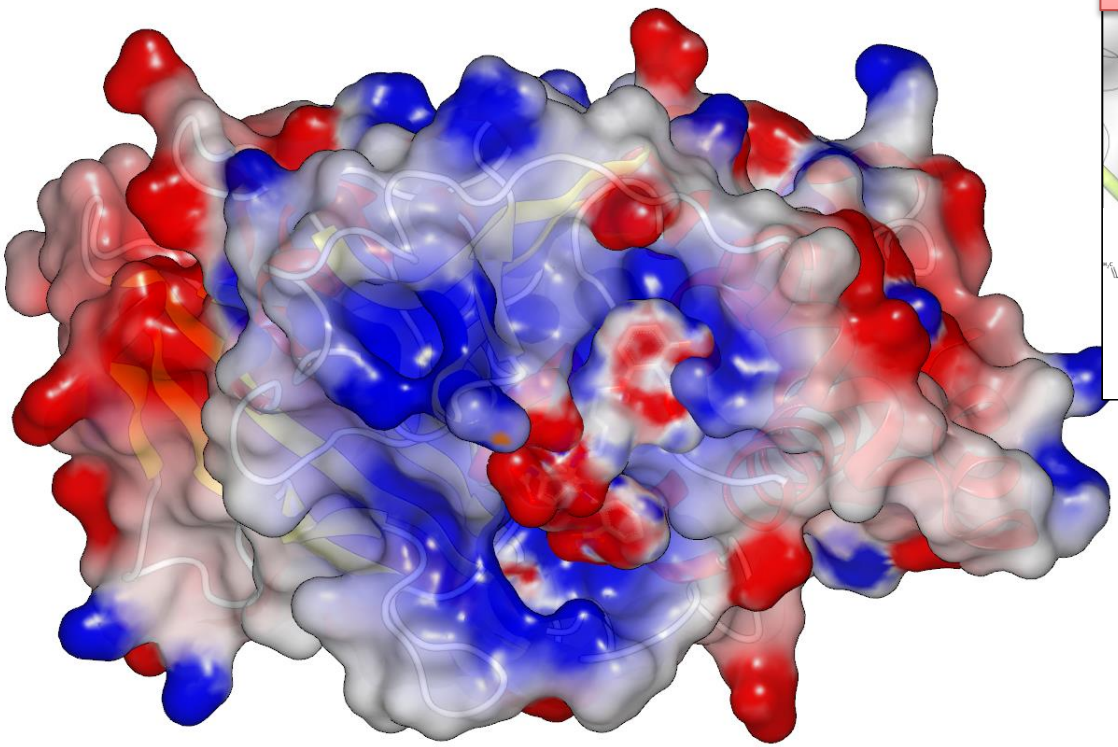


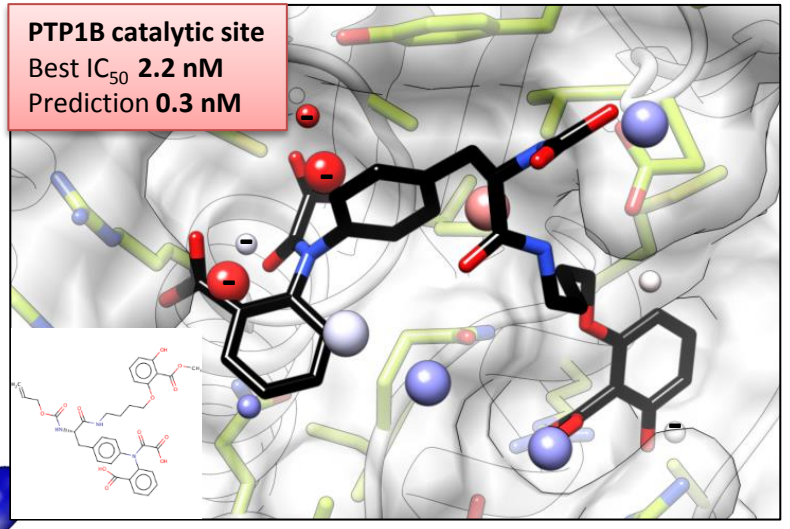


Lfa1 is a leukocyte cell surface glycoprotein that promotes intercellular adhesion and binds intercellular adhesion molecule 1

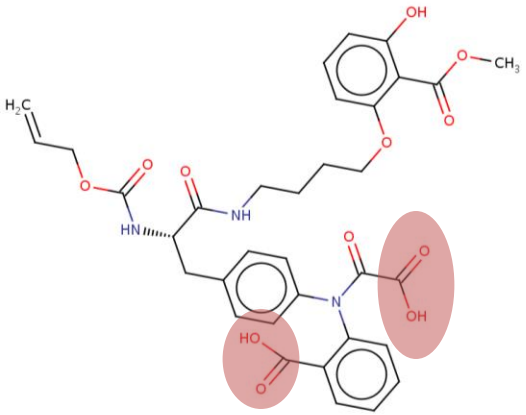
Biochemistry **2004,** *43*, 2394-2404

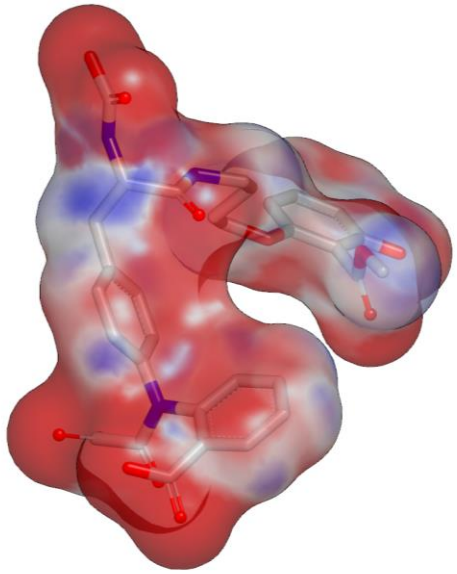
Druggable or not?





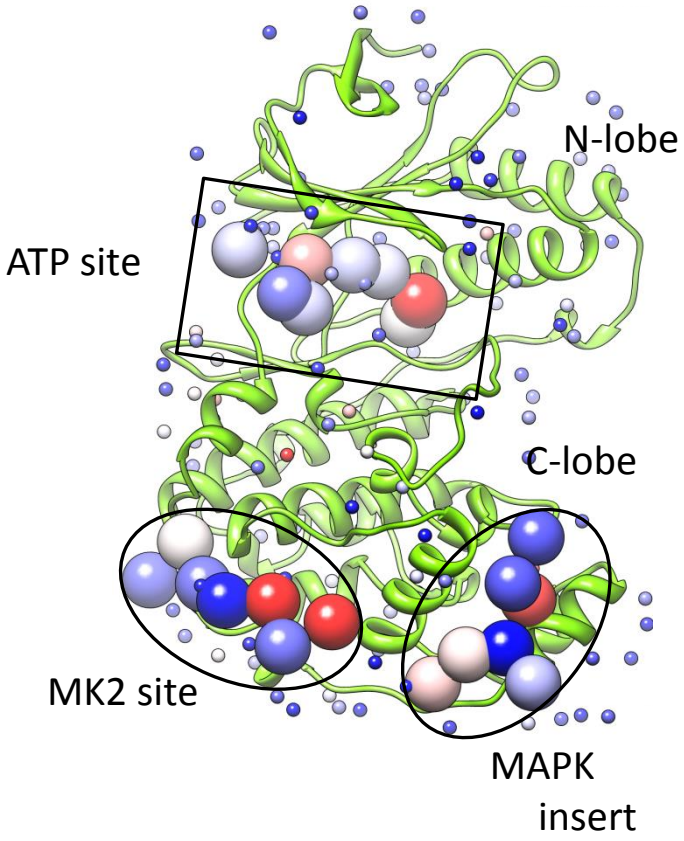
Bioorg. Med. Chem. Lett. **2003,** *13*, 3947-3950

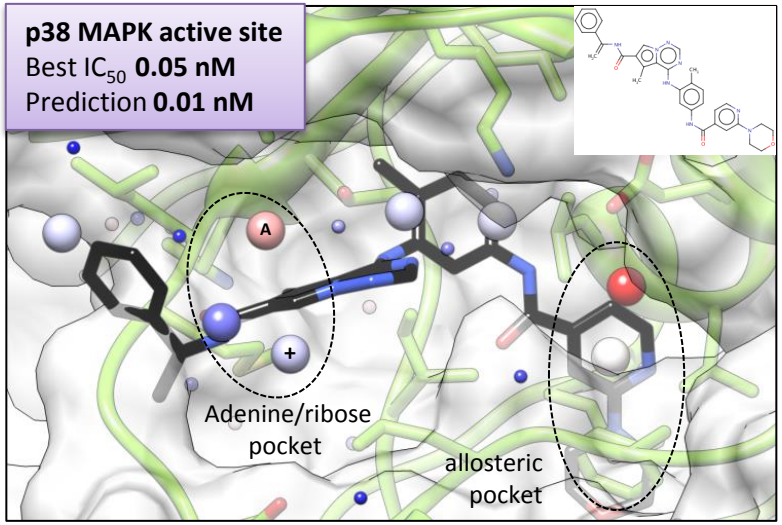




Protein tyrosine phosphatase 1B has a basic non-druggable (but **<u>ligandable</u>**) active site, also features an allosteric barely druggable site (not visible in this perspective).

p38 Binding Sites



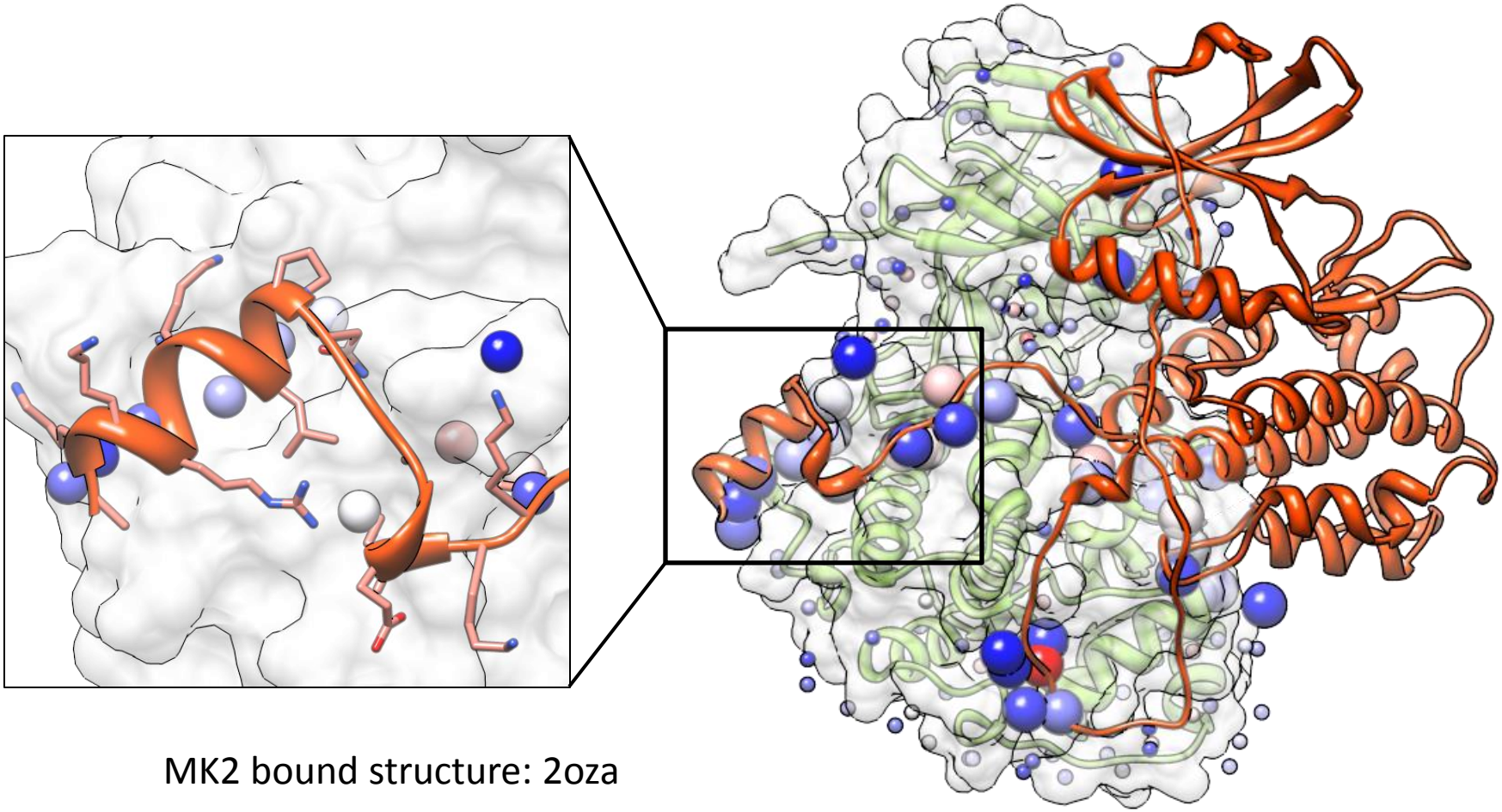


J Med. Chem. **2010,** *53*, 2973-2985

p38 MAP kinases are responsive to stress stimuli and are involved in cell differentiation and apoptosis.

Unbound PDB id: 1p38
Ligand bound: 3bv2

p38 – MK2 Interface

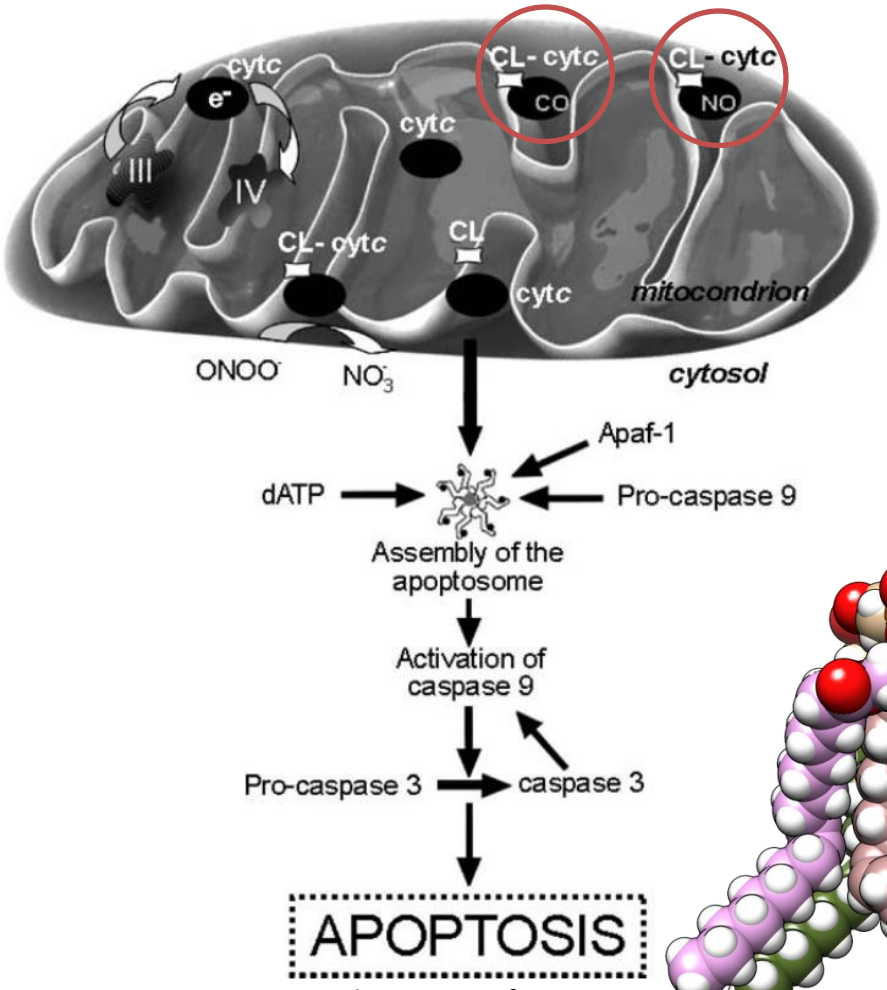


MK2 bound structure: 2oza

Druggability Index (or Maximal Affinity)

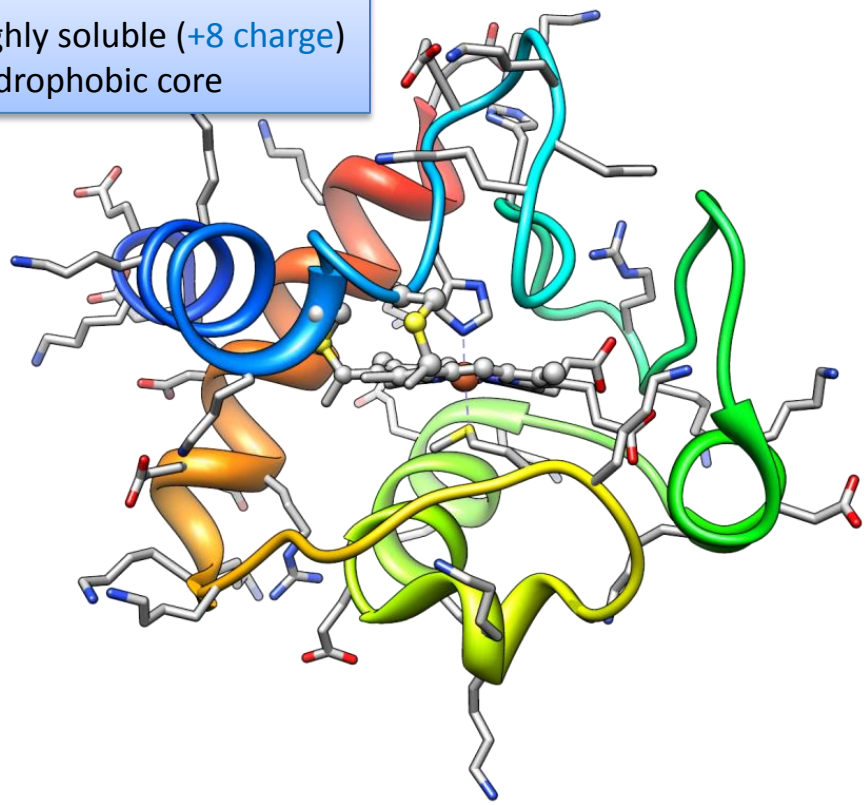
Target	Binding site	Best K_d /IC_{50}	Isopropanol	Probe mixture
MDM2	p53	**0.6 nM**	0.4-1.0 nM	**0.3-2.0 nM**
PTP1B	pTyr	**2.2 nM**	Nd	**0.3-0.9 nM**
	allosteric[d]	**8 µM**	0.2 µM	**6-72 µM**
LFA-1	induced	**18.3 nM**	0.5-0.8 nM	**0.03-0.5 nM**
Eg5	allosteric[d]	**0.2 nM**	27 nM	**0.3 nM**
	tubulin site	Na	2 nM	0.2 nM
p38	ATP	**0.05 nM**	1-2 nM	**0.01-0.12 nM**
	MK2 site	na	2-3 nM	2-3 nM
	MAPK insert	na	13-90 nM	5-210 nM

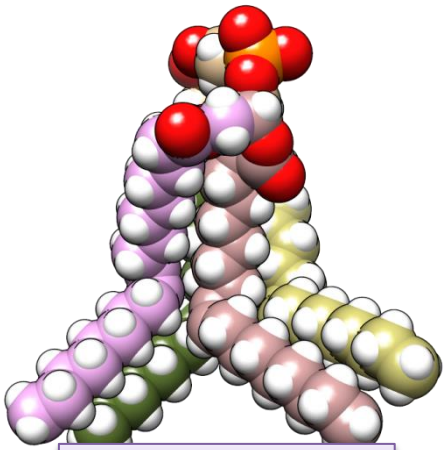
Cyt *c* Inhibitor Discovery



Ascenzi et al., *IUBMB Life*, 2011

Cyt *c*
- highly soluble (+8 charge)
- hydrophobic core



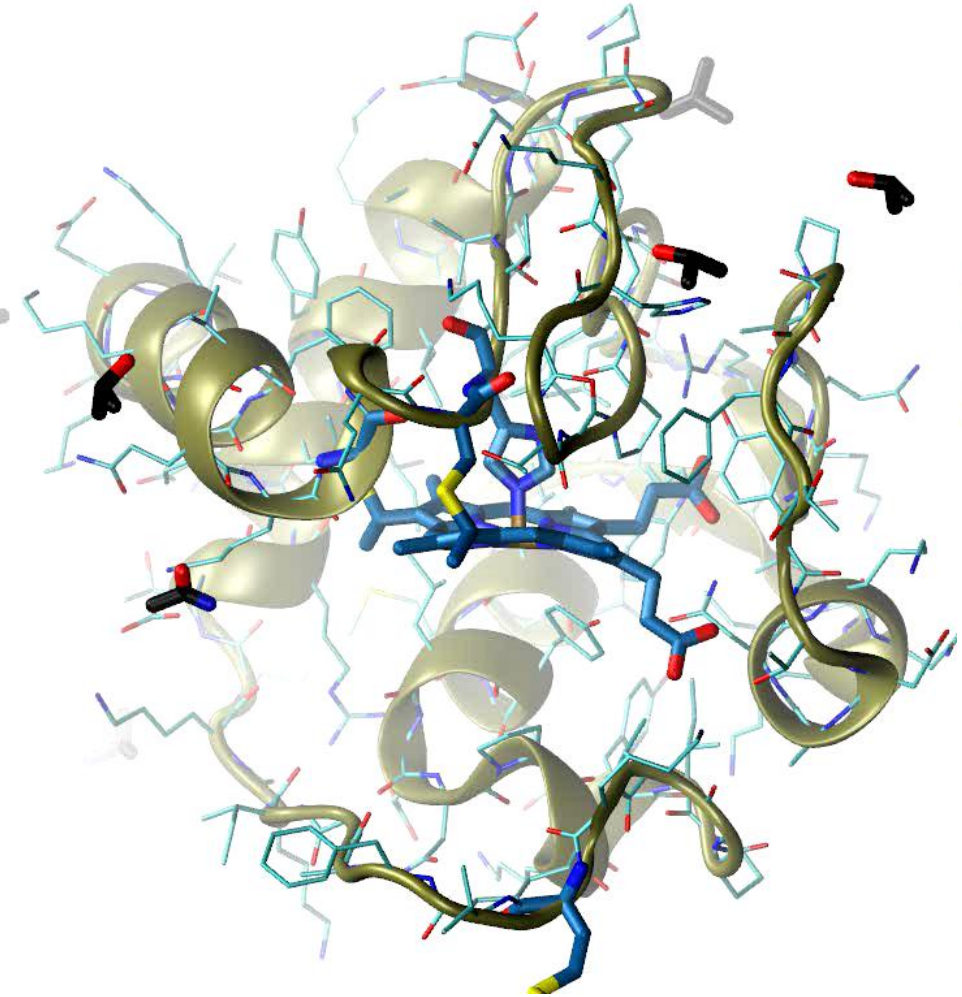


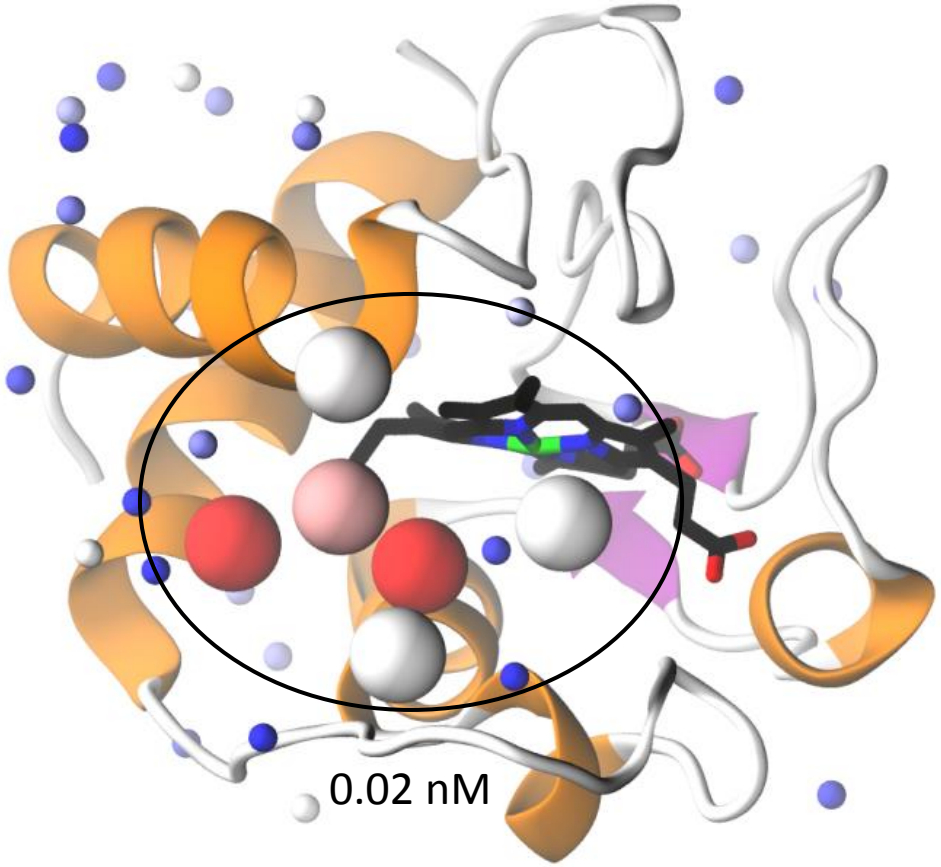
Cardiolipin (CL; $2e^-$)

When bound to CL, cyt c gains peroxidase activity that contributes its apoptotic release

Kagan et al., *Free Radical Biology and Medicine*, 2009

How Druggable is Cyt *c*?



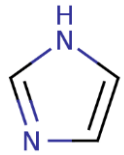


Partially unfolded form

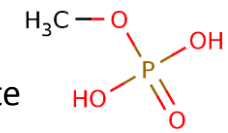
Probes molecules to Cyt *c*'s taste

Probe content

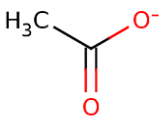
48x imidazole



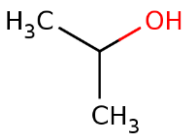
24x methly phosphate



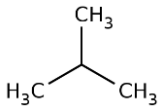
12x acetate

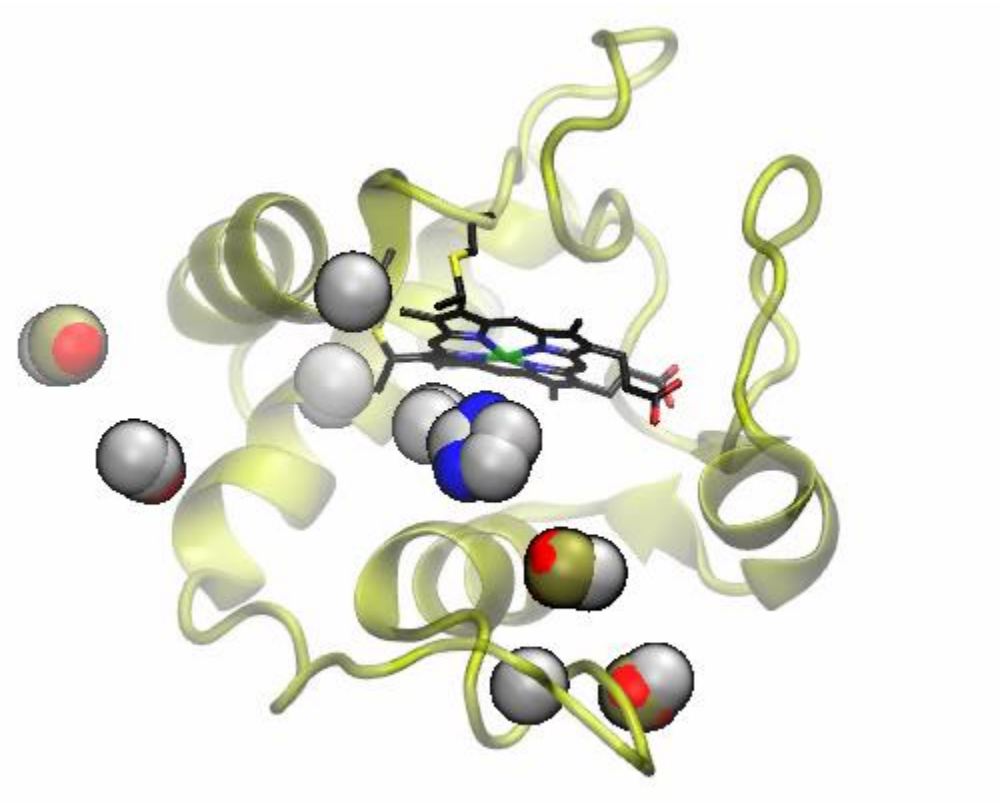


12x isopropanol

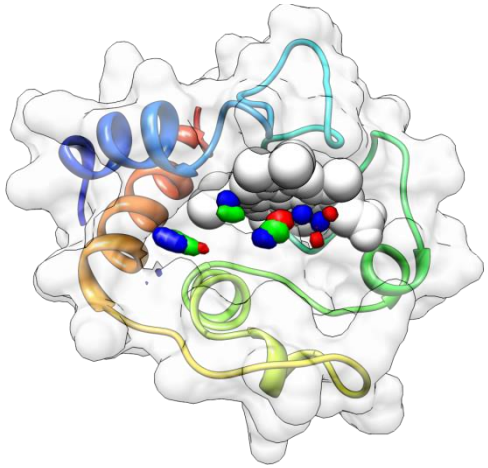


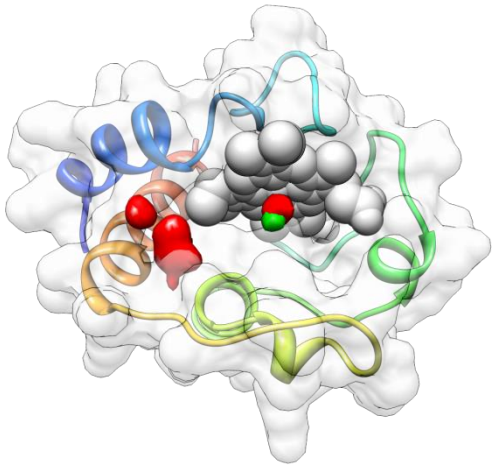
24x isobutane



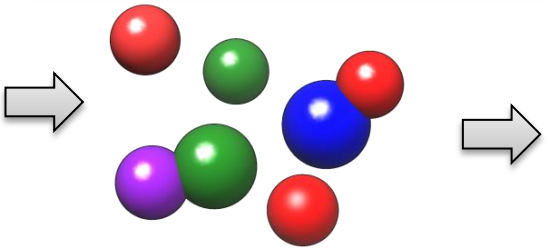


In silico screening



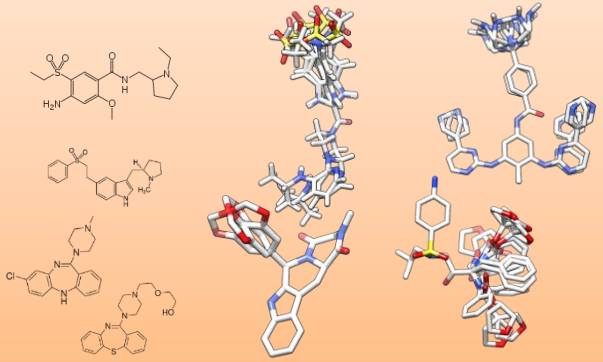


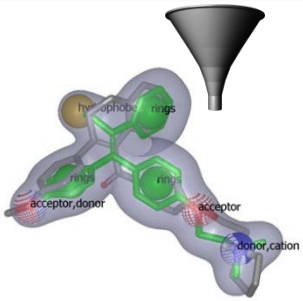
Build a consensus pharmacophore model



DRUGBANK ZINC

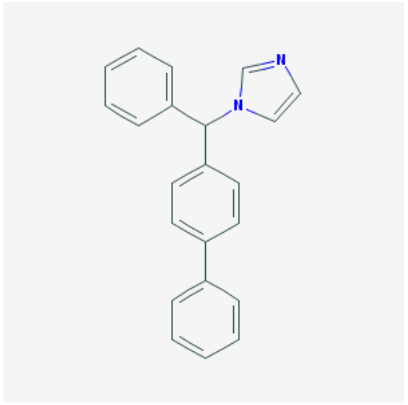
Screen virtual libraries
~6,000 approved or investigational drugs
7.5 million purchasable compounds



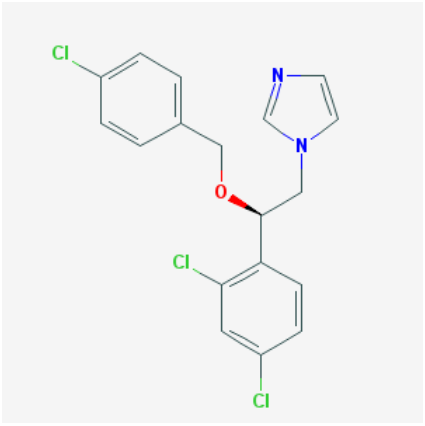


Test ~100 compounds

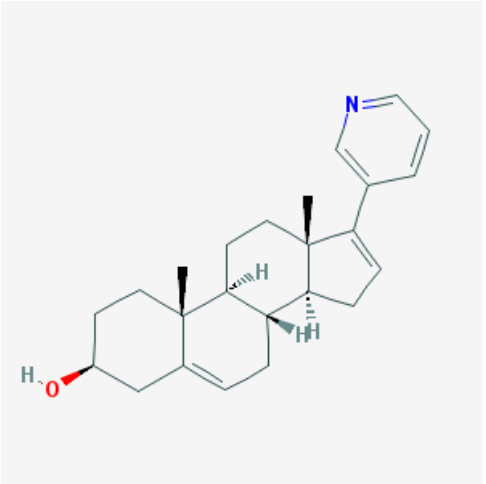
Bifonazole

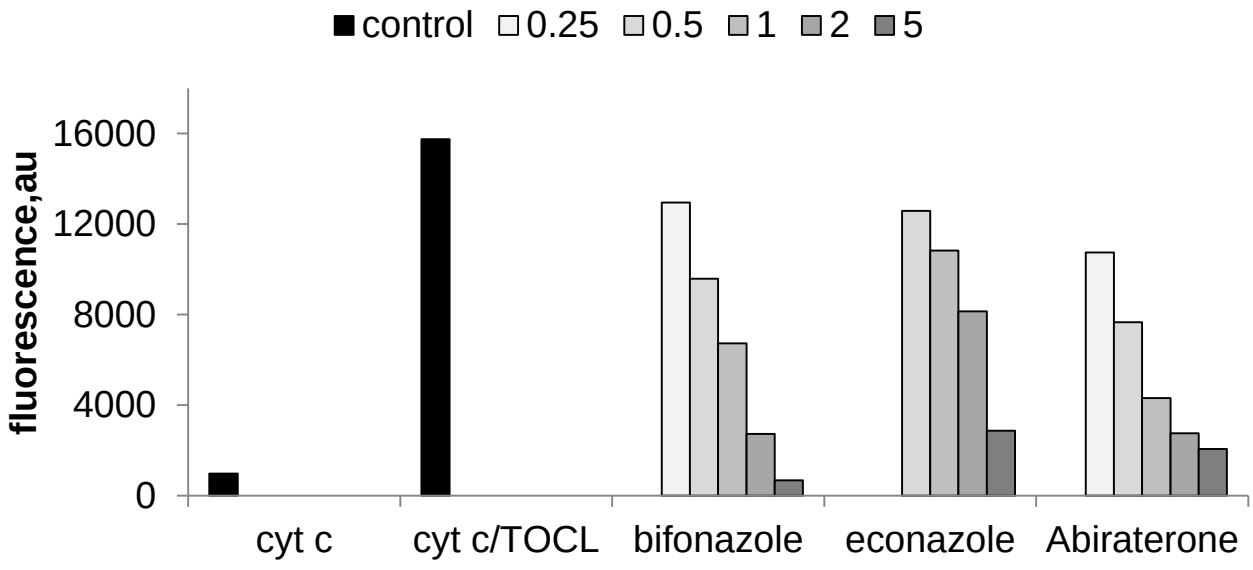


Econazole



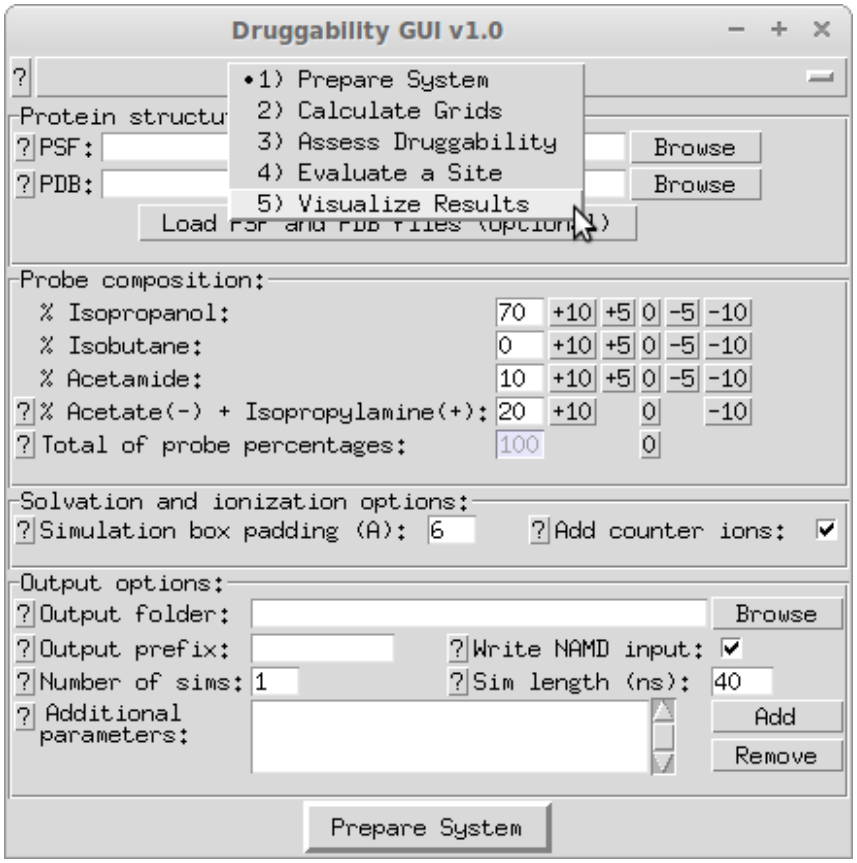
Abiraterone





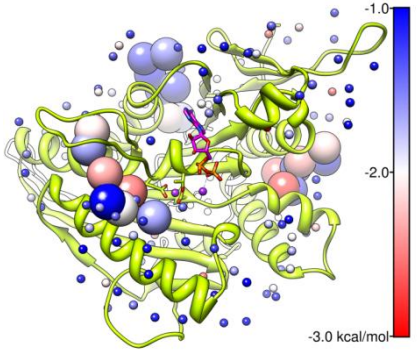
DruGUI Demo

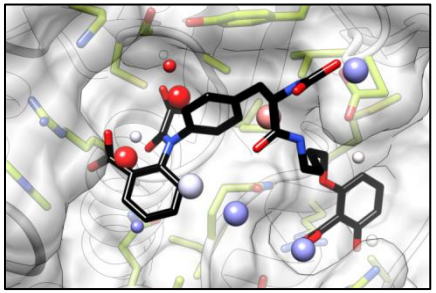
DrugGUI



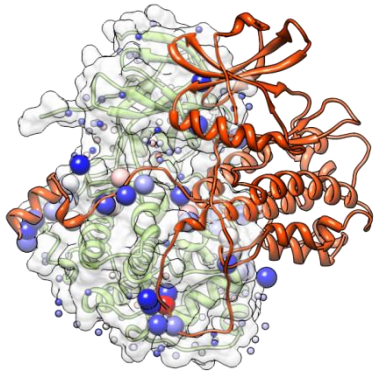
Potential use cases

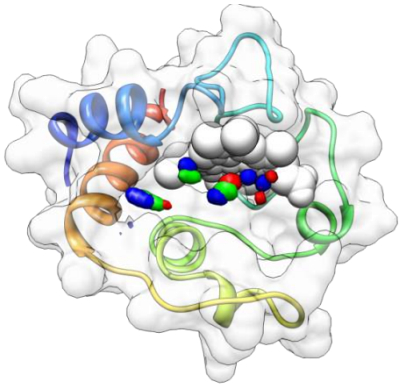
Identify druggable or ligandable sites





Identify protein interfaces





Develop pharmacophores