The Magic Behind SeeSAR:
Visual, Interactive 3D Lead Optimisation for Anyone

Webinar. 4:00 GMT, April 6th 2016

Marcus Gastreich and Nick Foster

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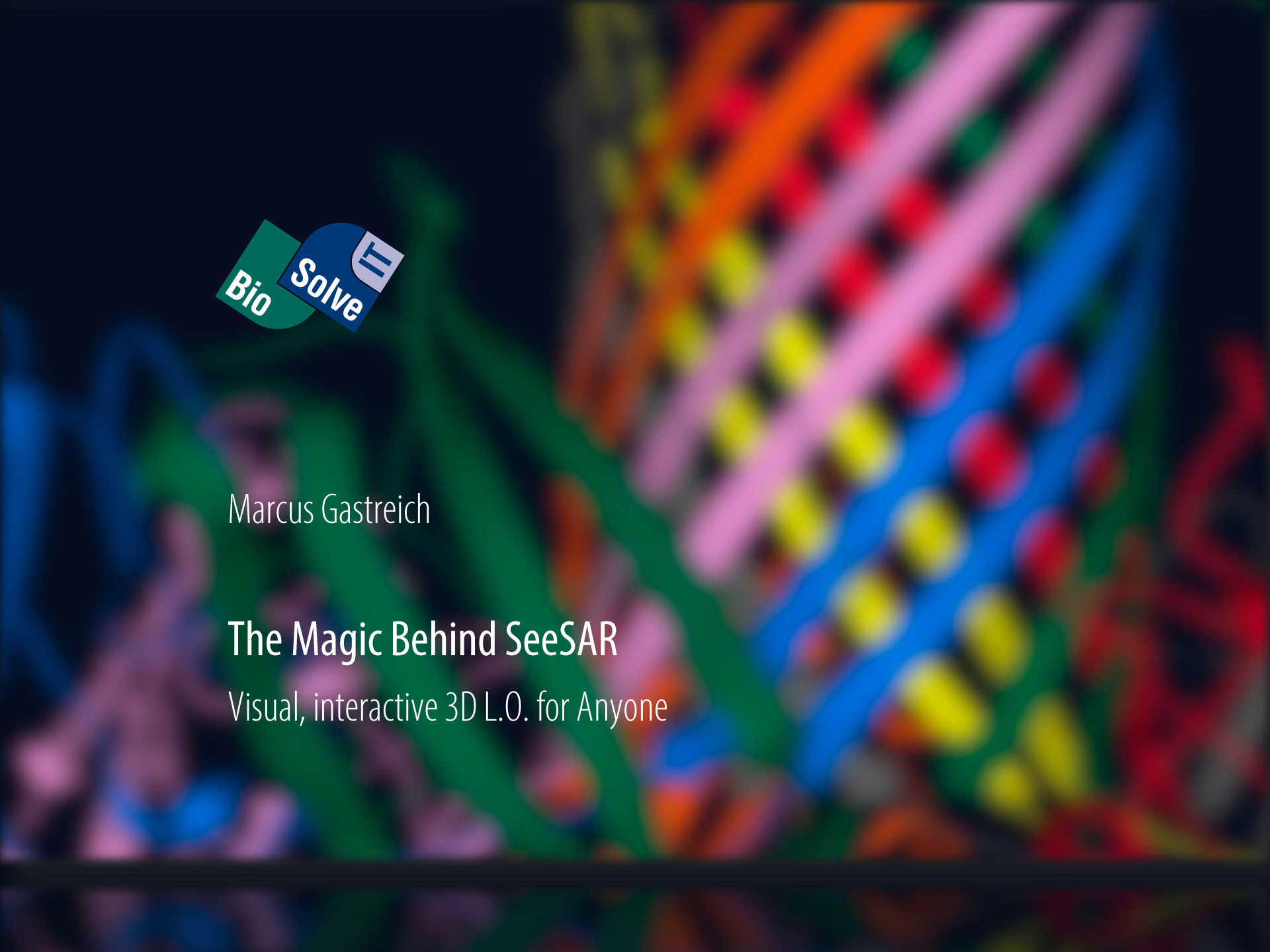


Marcus Gastreich

The Magic Behind SeeSAR

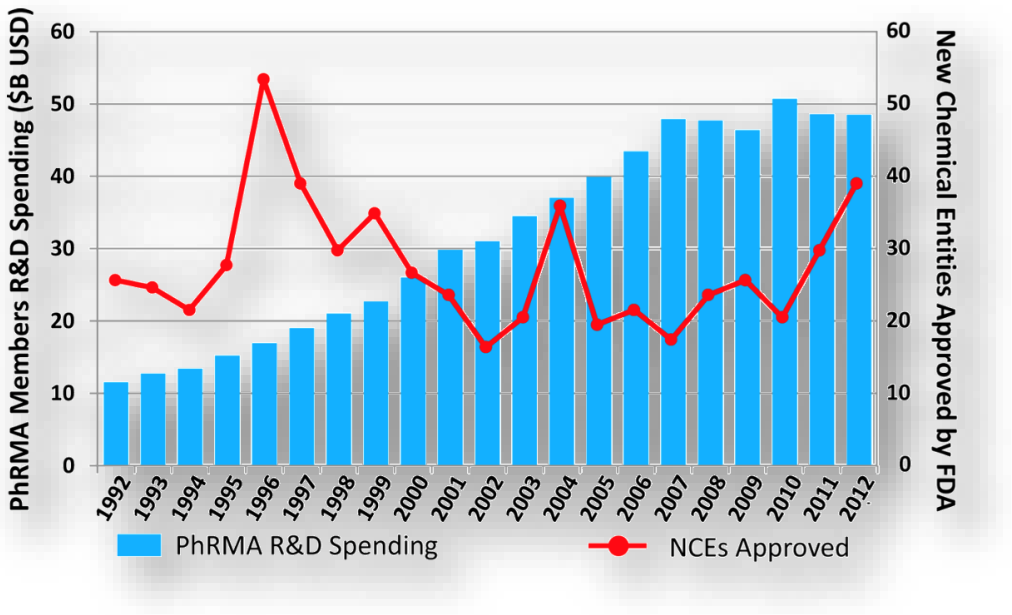
Visual, interactive 3D L.O. for Anyone

Times Have - and Are Still Changing…*

- Since 2000:
  Outsourcing, merging, 300.000+ layoffs in pharma

  PhRMA members:
  1998: 42
  2011: 11

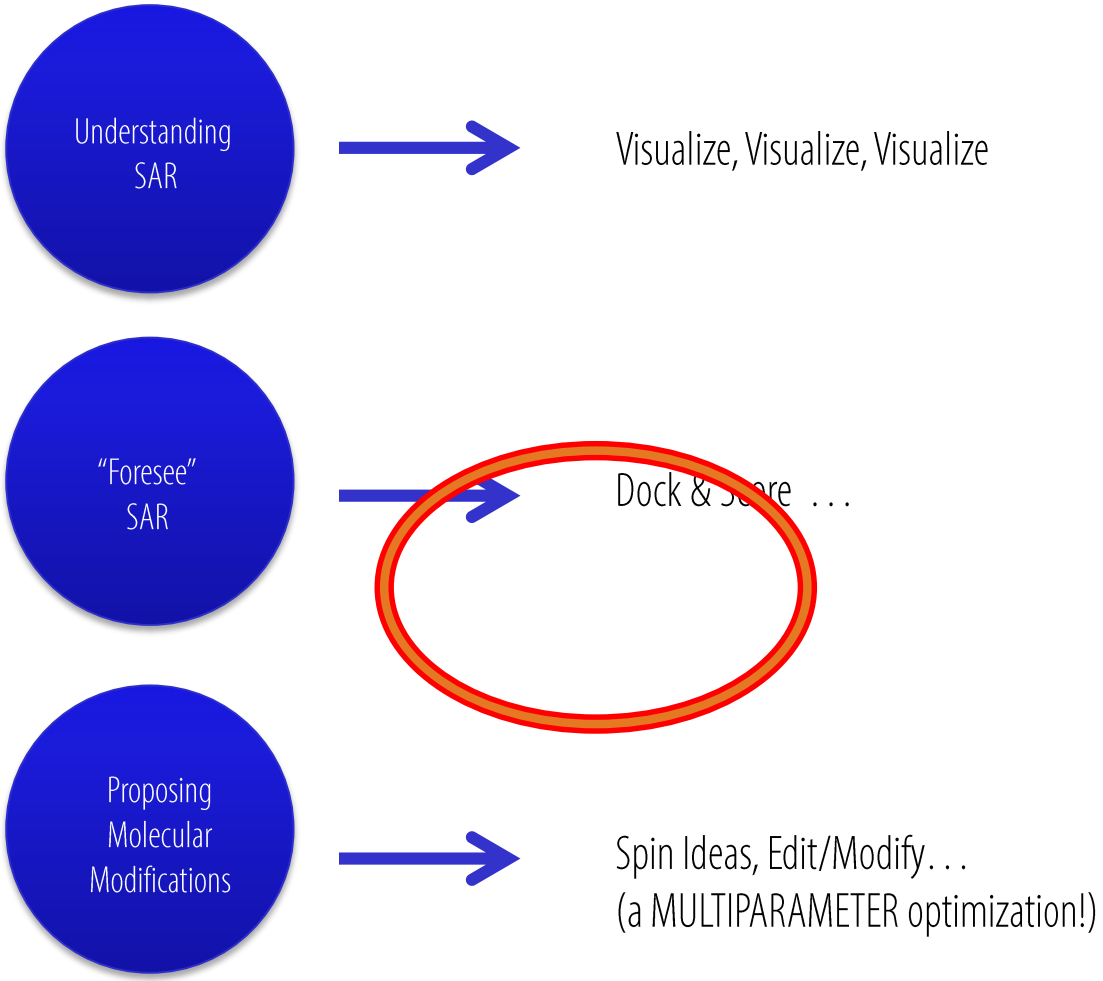
- Spending up, but approvals steady.
  (2015: 45)



- <u>MedChems take over basic computational tasks, esp. visualisation</u>

* Data & graphics from:
Abou-Gharbia et al, JMC 2013, dx.doi.org/10.1021/jm401564r

What is " Of Relevance " ? Our Daily Work:



What Does This Mean for SBDD?

Visualize, Visualize, Visualize

Meaningful & simple graphics

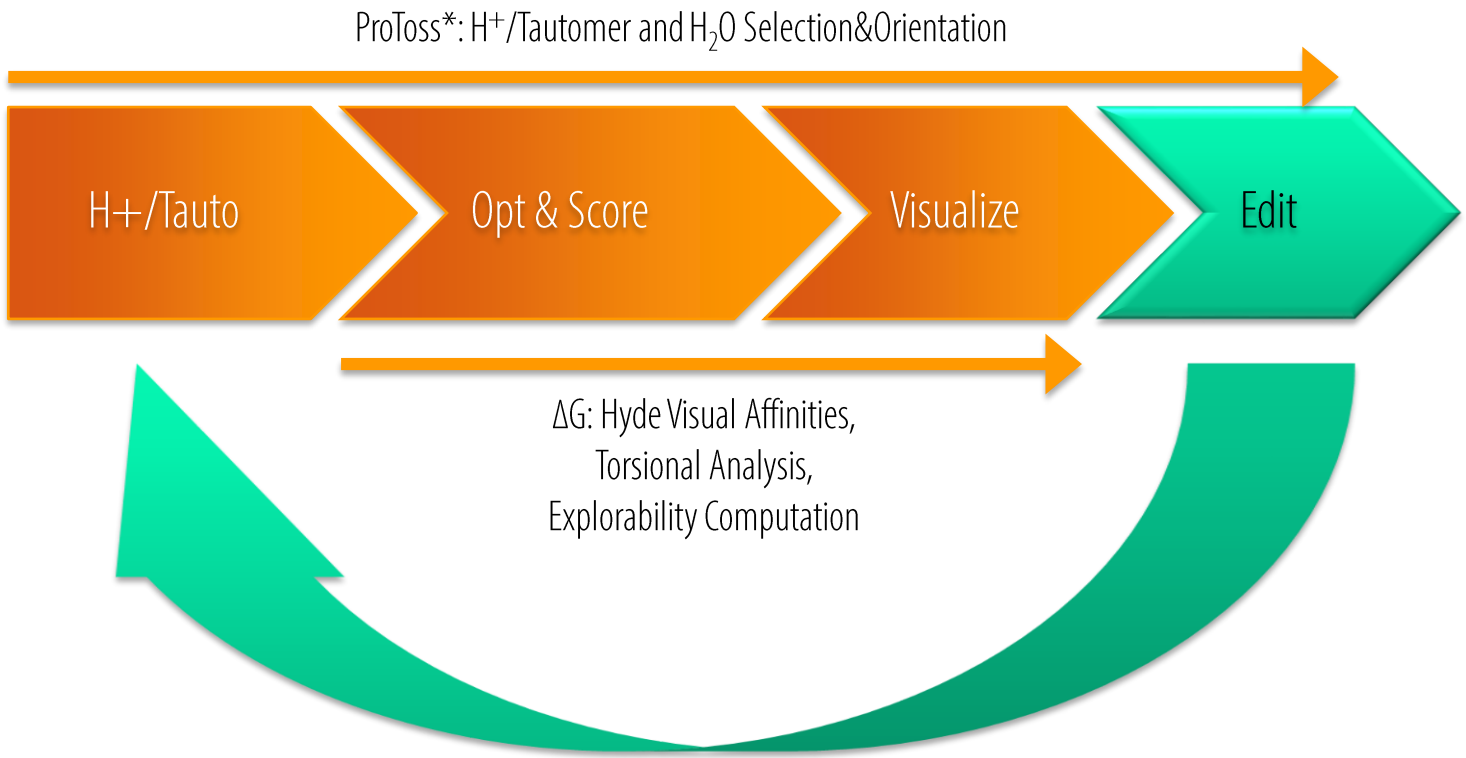
Docking & Scoring etc.

Sound, Relevant Science

Spin Ideas, Edit/Modify, . . .

Playful & Fast, Easy

The L.O. Workflow: What Happened So Far…

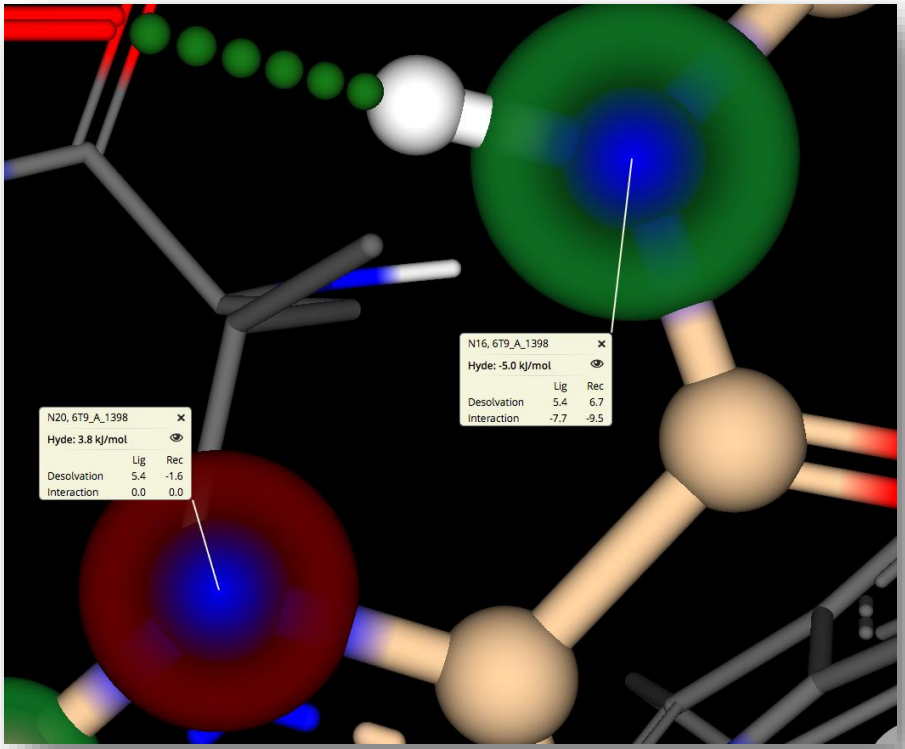


ProToss - Protonation, Waters, Tautomers proposed in millisecond time, Publication:
Bietz et al., Journal of Cheminformatics 2014, **6**:12

One Magic Behind: Hyde Affinities

Joint n Mio-$ Project:
- ZBH Hamburg University (Rarey)
- Bayer AG

HYDE Coronas™ Visualize ΔG Contributions



Green = good for affinity
Red = bad for affinity

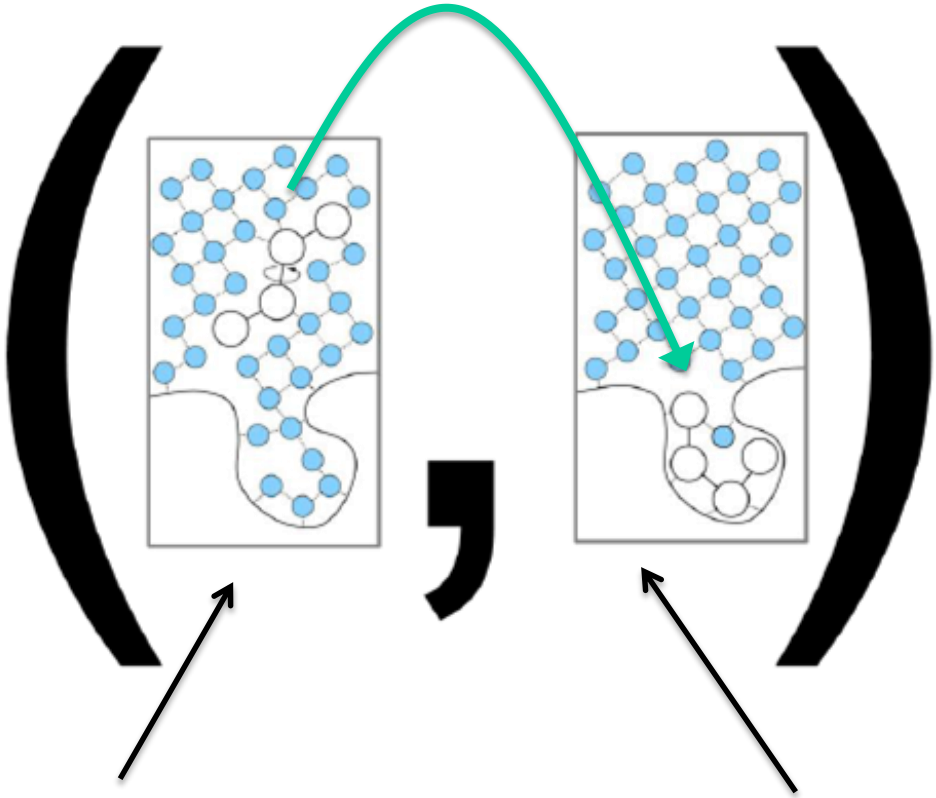
The larger the stronger the contribution.

What is Affinity?

$$\Delta G = \Delta G\,(\text{before, after})$$

What is Affinity?

$$\Delta G = \Delta G$$

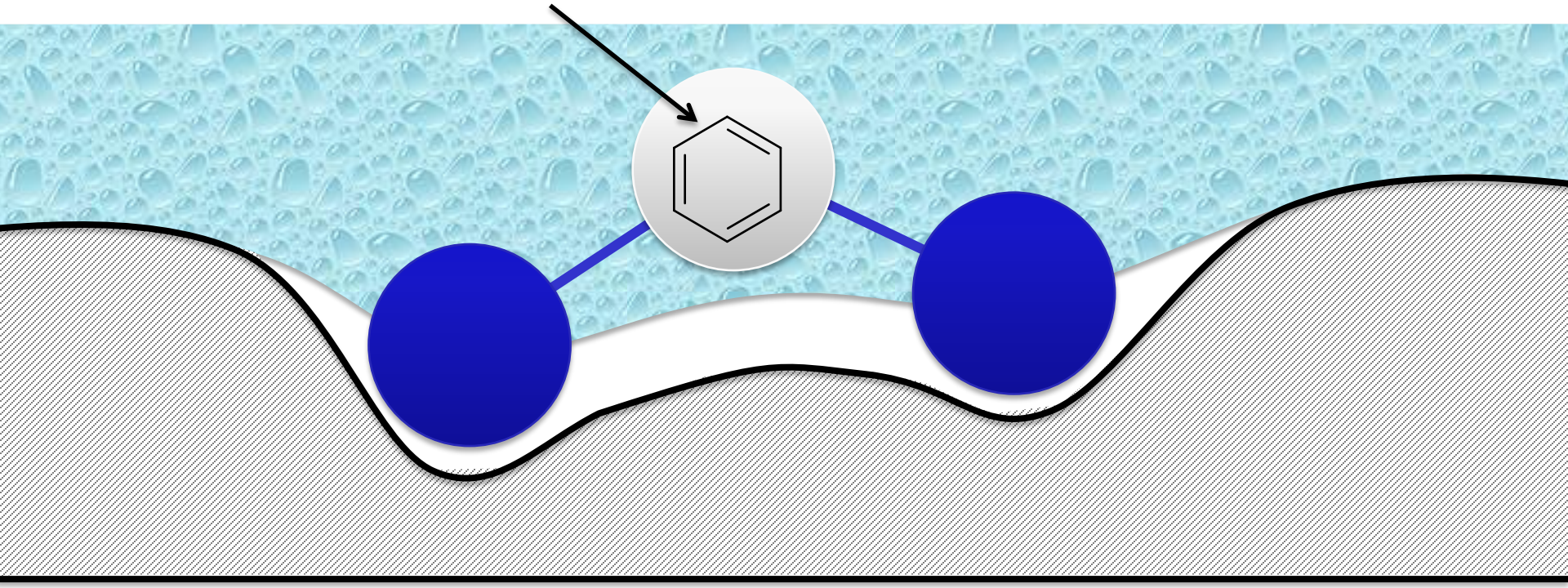


unbound,
in water

bound,
in complex

“Good” or “Bad” for Affinity??

an exposed, hydrophobic part of a ligand (ignore clash and torsions!)



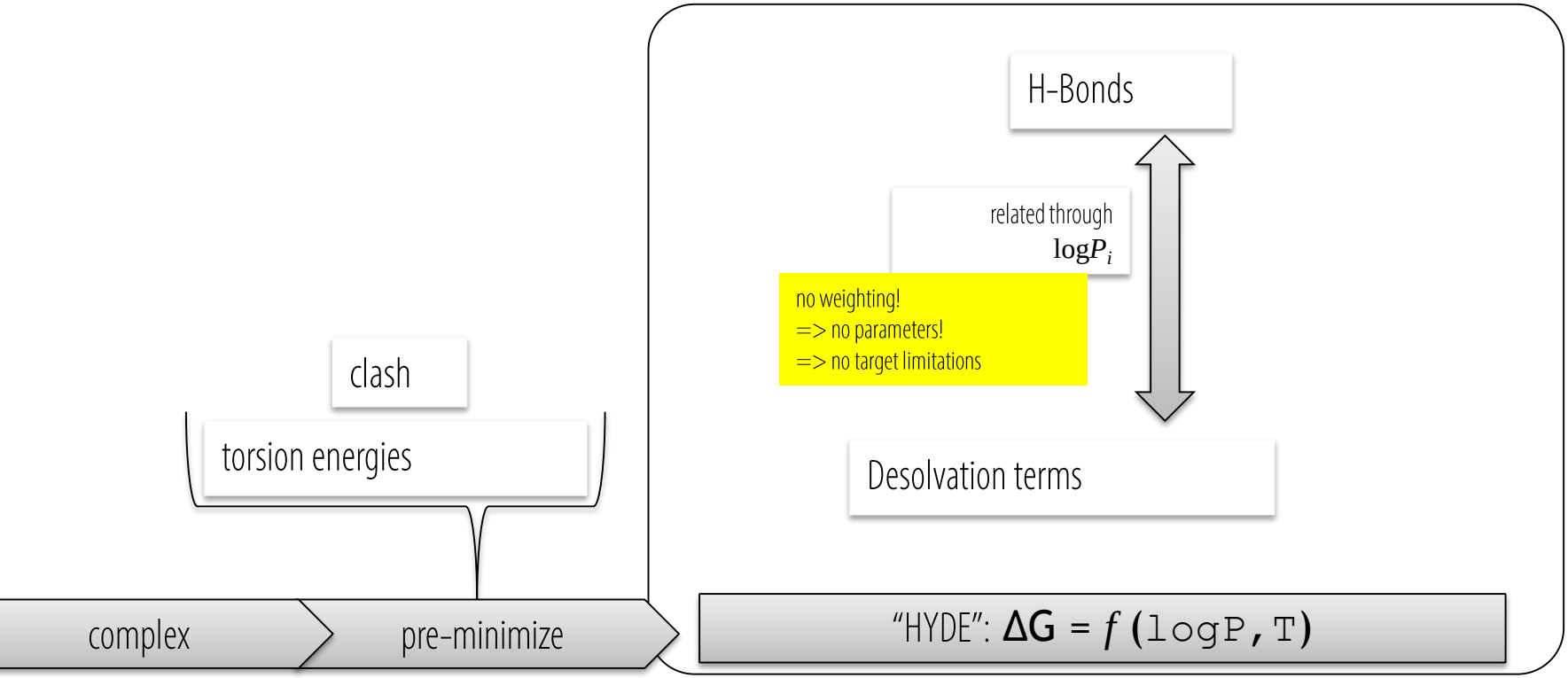
- The Phenyl was already ‘unhappy’ before binding.
- It still is unhappy after binding.

$\Rightarrow \Delta(\Delta G) \approx 0$

=> NO CONTRIBUTION to affinity (simplified view)

HYDE in a Nutshell

Lange et al, ICCS 2008; and: **Schneider et al, JCAMD 2013 27** 15 & refs. therein



- ONLY if clash and torsional strain are low, values are meaningful !
- subtle electronic effects cannot be captured !

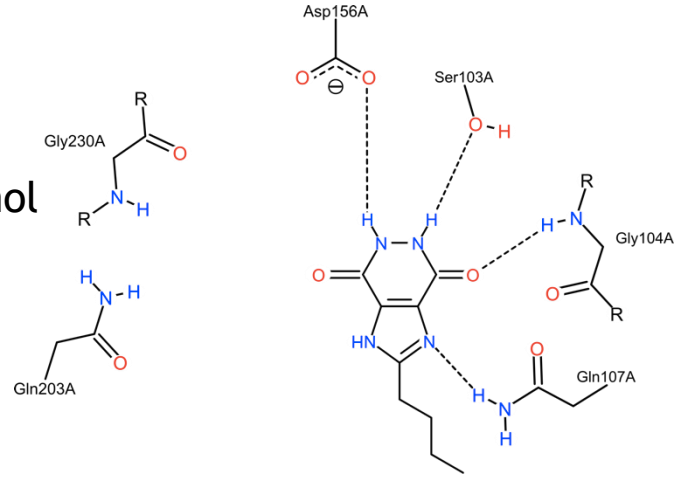
At a Glance - Advantages of SeeSAR & HYDE

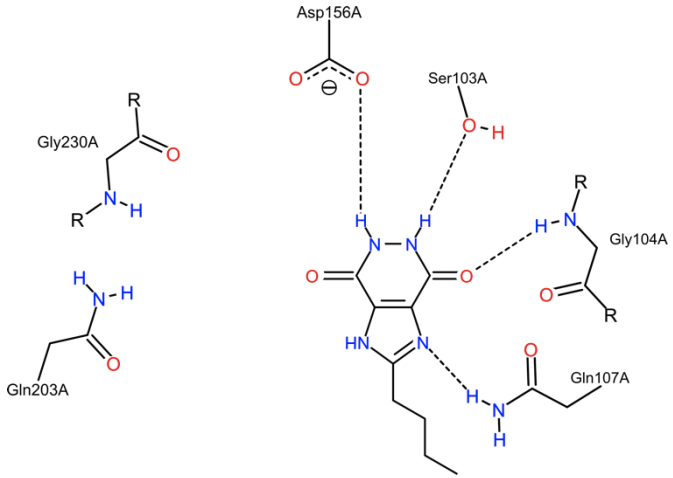
	FEP	MM-PB/SA	MMFF94 & similar	SeeSAR incl. HYDE
Non-Expert Usage?	🔴	🔴	🟢	🟢
Seconds fast?	🔴	🟡	🟢	🟢
Visually interpretable?	🟡	🔴	🔴	🟢
<10k $ per seat?	?	🟢	🟢	🟢
Affinity Predictiveness?	🟡	🟡	🔴	🟡
ADME on-the-fly?	🔴	🔴	🔴	🟢
Entropy included	🟢	🟢	🔴	🟢

HYDE Detects Subtle Binding Mode Differences

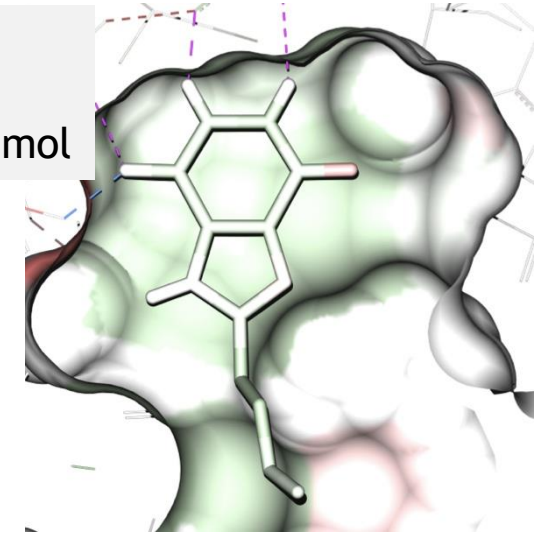
1n2v

$\Delta G_{experimental}$ -23kJ/mol

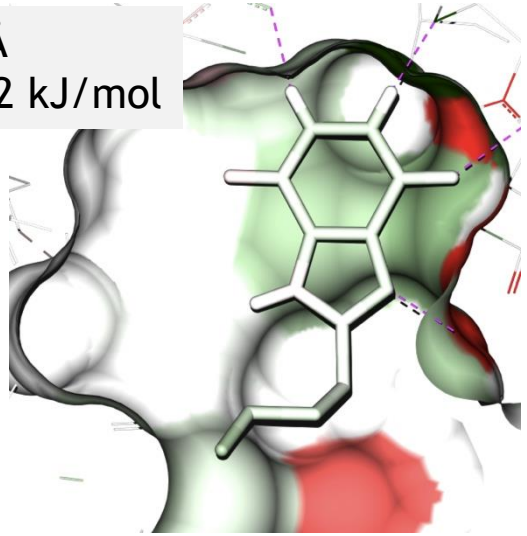




Best by scoring
RMSD 0.2 Å
ΔG_{HYDE} -23 kJ/mol

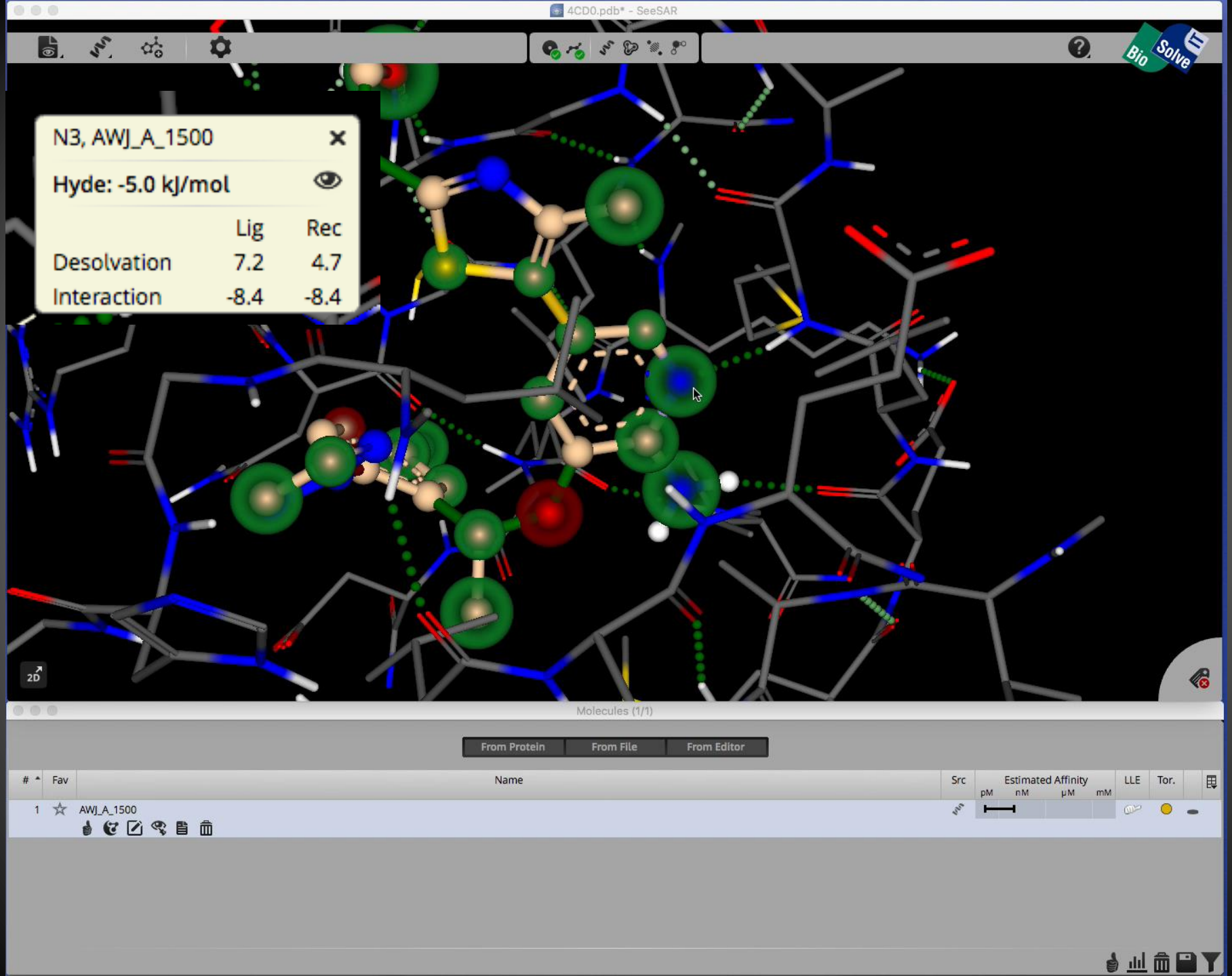


RMSD 2.3 Å
ΔG_{HYDE} -12 kJ/mol



tRNA-Guanine Transglycosylase

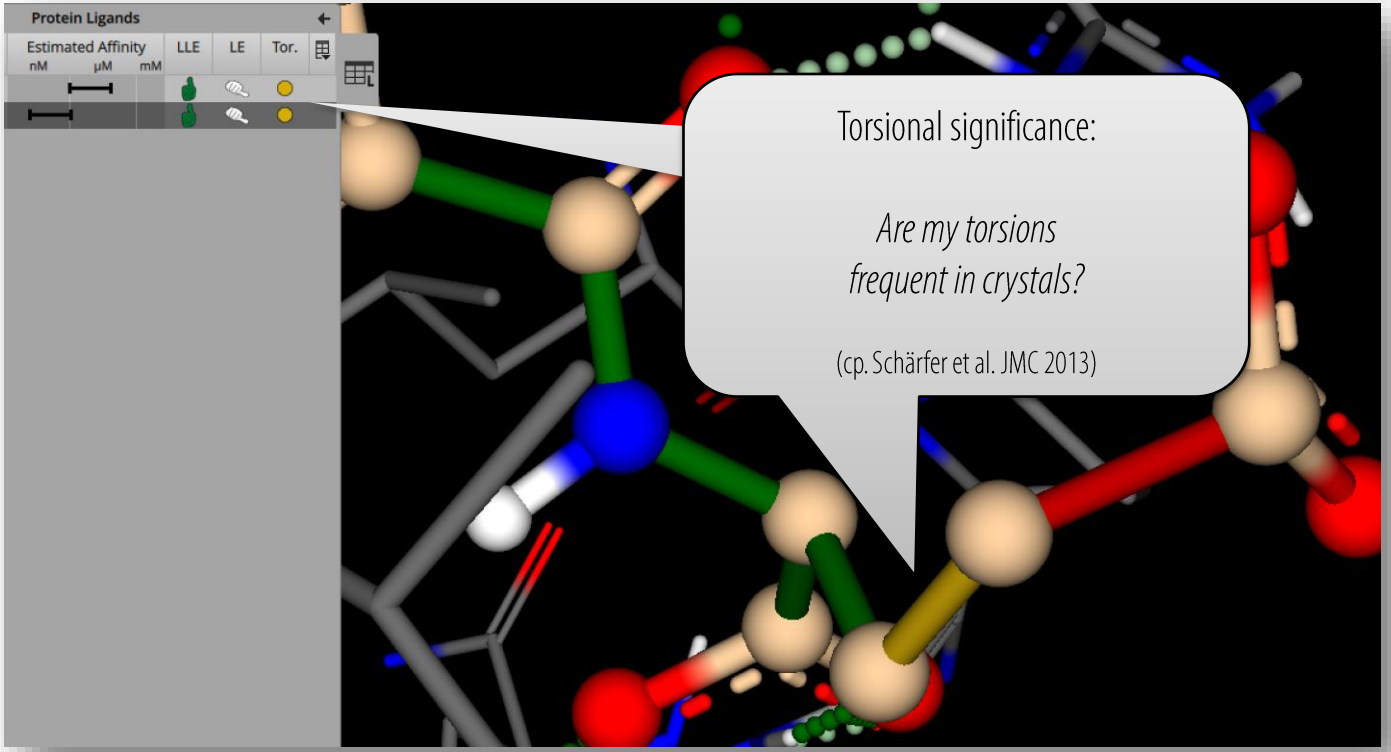
Drilling In. . .


4CD0.pdb* - SeeSAR
N3, AWJ_A_1500
Hyde: -5.0 kJ/mol
Lig Rec
Desolvation 7.2 4.7
Interaction -8.4 -8.4
2D
Molecules (1/1)
From Protein
From File
From Editor
Fav Name Src Estimated Affinity LLE Tor.
pM nM µM mM
1 AWJ_A_1500

Another Magic:
Torsional Significance

Joint Project:
- ZBH Hamburg University (M. Rarey)
- F.A. Hoffmann-LaRoche, Basle (M. Stahl)

The Idea: Color Torsions by Occurrence in CSD Crystals



Green = frequently observed

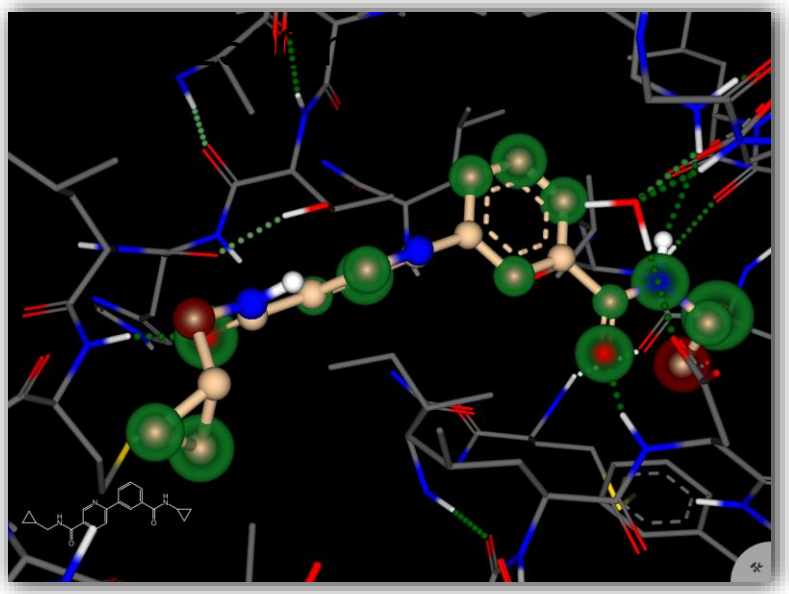
Yellow = unusual, however several times observed

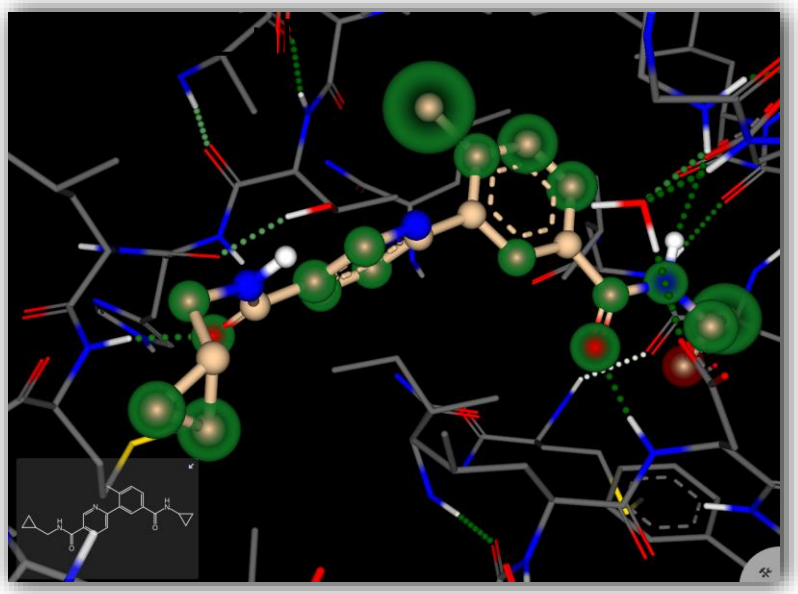
Red = very rarely observed

MIND: This is a STATISTICAL and NOT an energetic statement.

Detecting Magic Methyls With SeeSAR

PDB 3IPH (p38 Kinase)

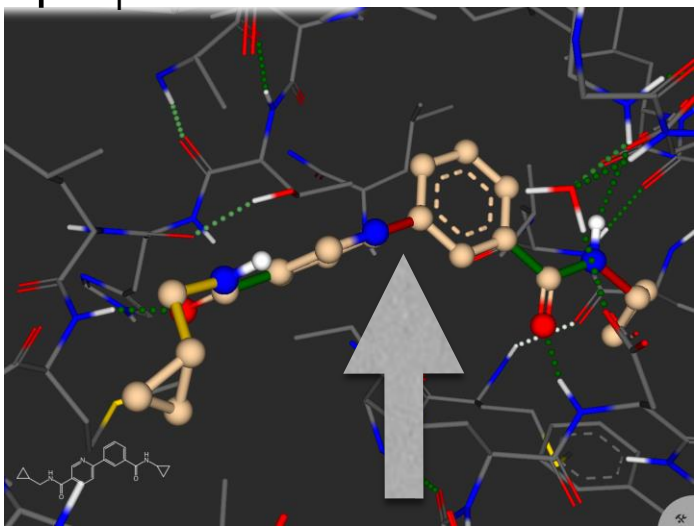




Bioorg. Med. Chem. Lett. 2008 **18** 4428–4432

Methyl Locks Torsion Into Preferred Arrangement

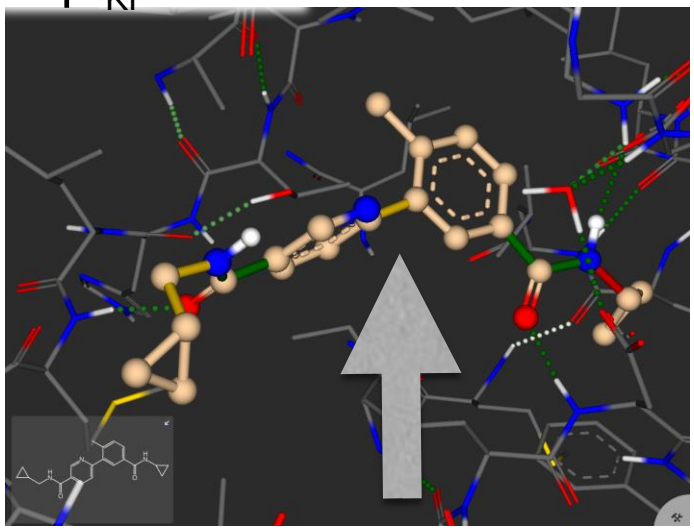
Exp K_i 2500 nM



red = very rare

likely: strain energy in here!

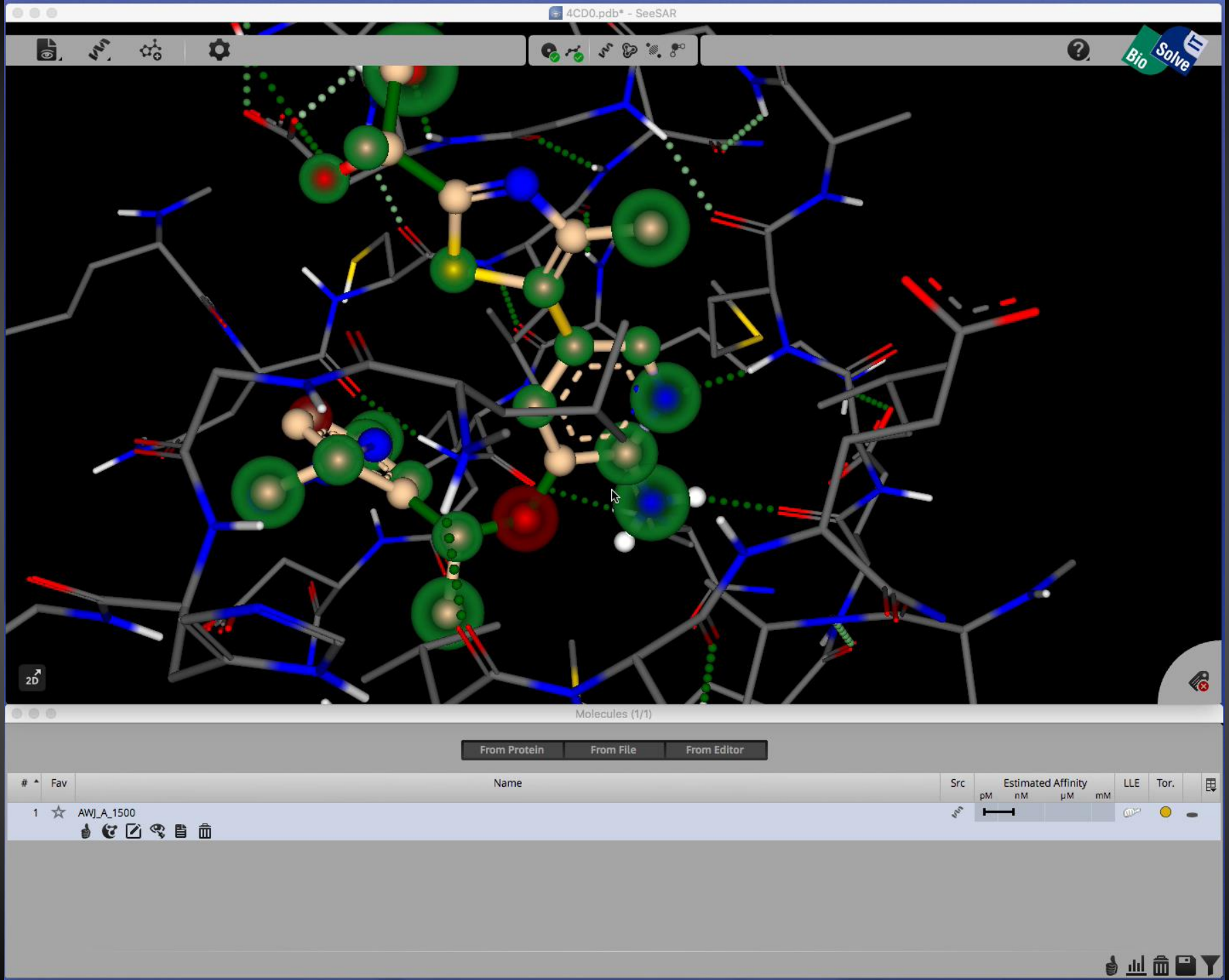
Exp $_{Ki}$ 12 nM



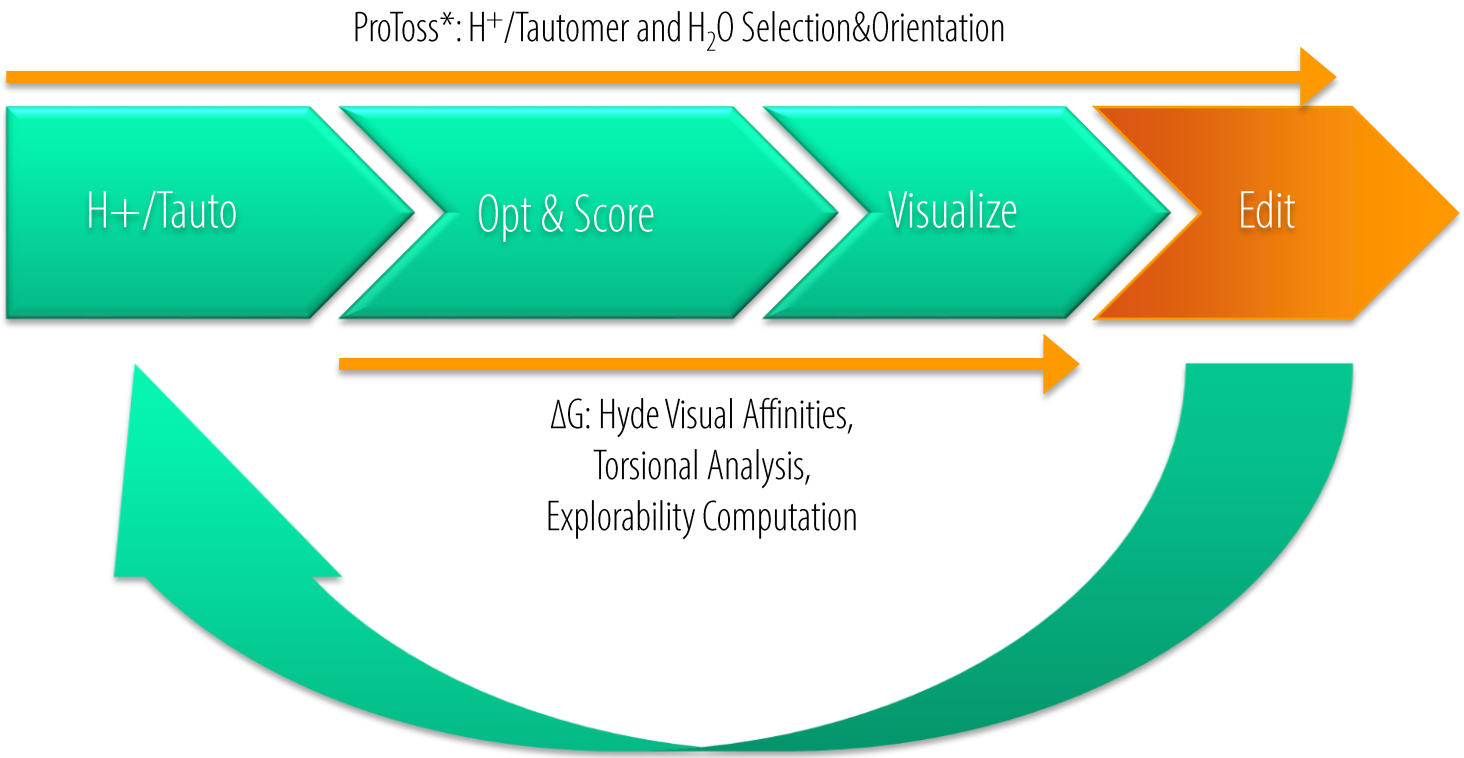
yellow = unusual

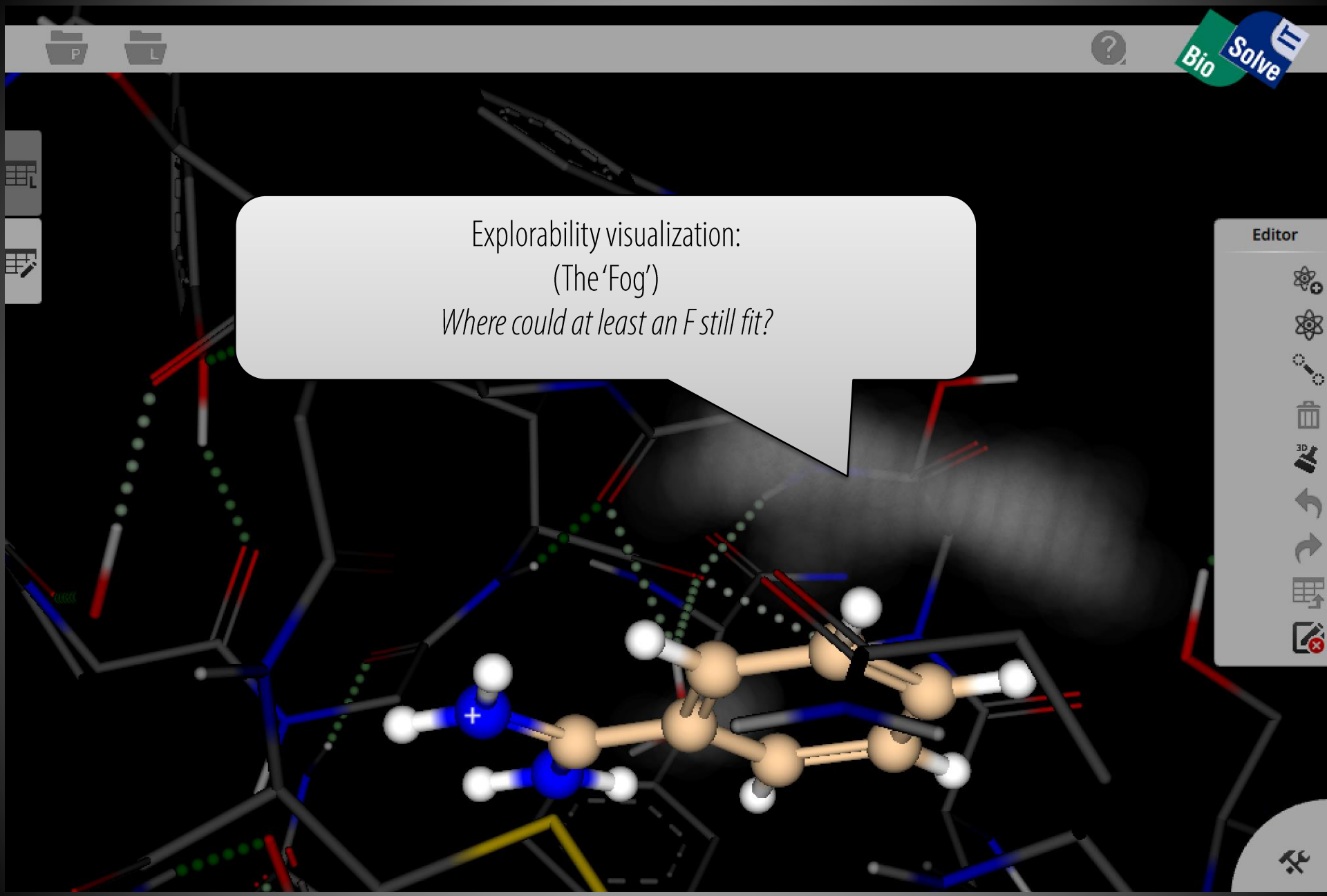
likely: more favorable

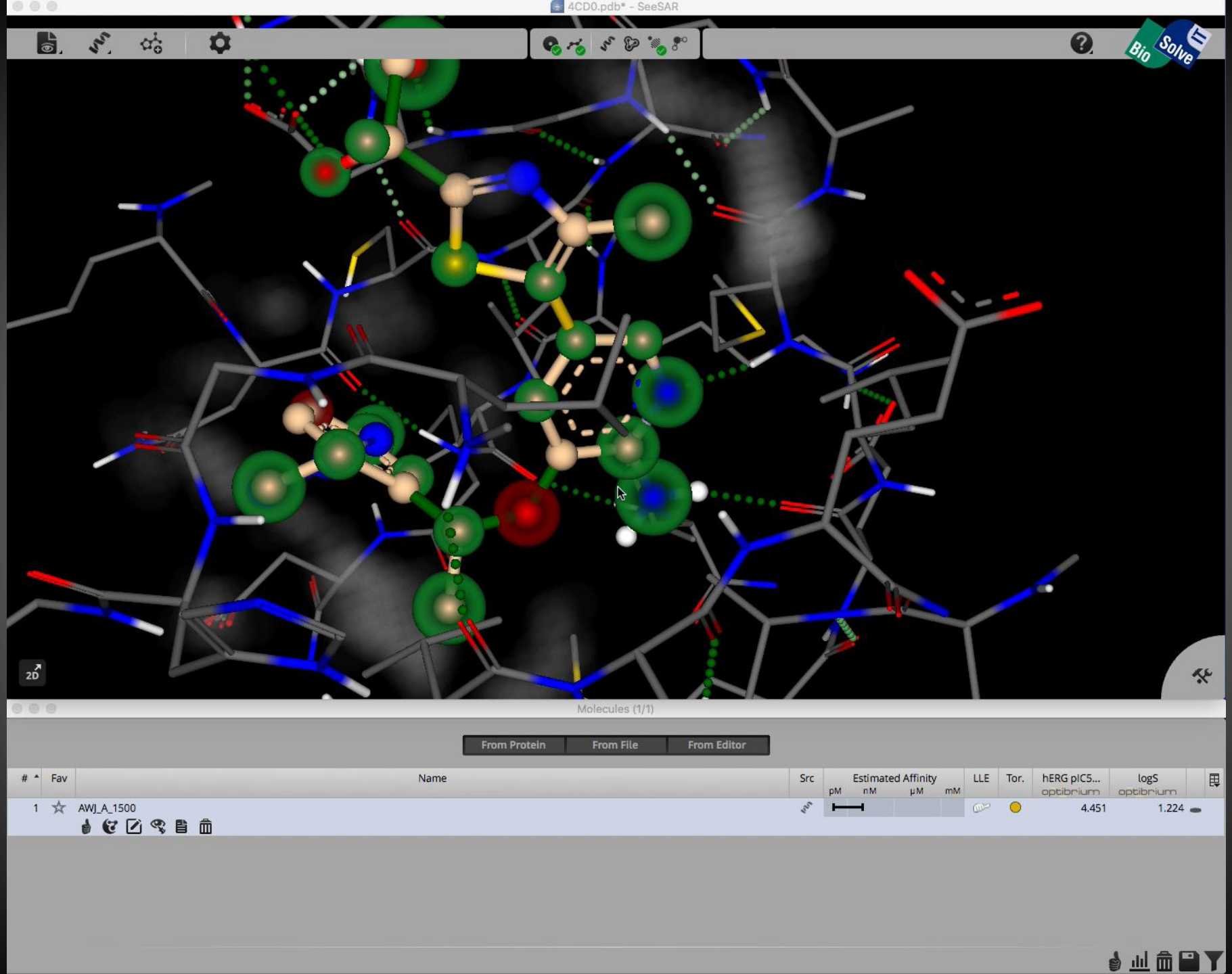
Another Magic:
“In-situ” **ADME by Optibrium™**


4CD0.pdb* - SeeSAR
Molecules (1/1)
From Protein
From File
From Editor
Fav Name Src Estimated Affinity LLE Tor.
pM nM µM mM
1 AWJ_A_1500

Editing in an MPO Context




Explorability visualization:
(The 'Fog')
Where could at least an F still fit?
Editor


4CD0.pdb* - SeeSAR
Molecules (1/1)
From Protein
From File
From Editor
Fav Name Src Estimated Affinity pM nM µM mM LLE Tor. hERG pIC5... optibrium logS optibrium
1 AWJ_A_1500 4.451 1.224

StarDrop™ ADME in SeeSAR™ is only
Step 1 out of more to come
in the Optibrium & BioSolveIT collaboration.

A Few Words of Caution

- For the MedChem:

  Experiments have error bars, too.
  HYDE is pretty strict regarding geometries.
  => Stay critical with your input,
  use esp. the local HYDE Coronas.

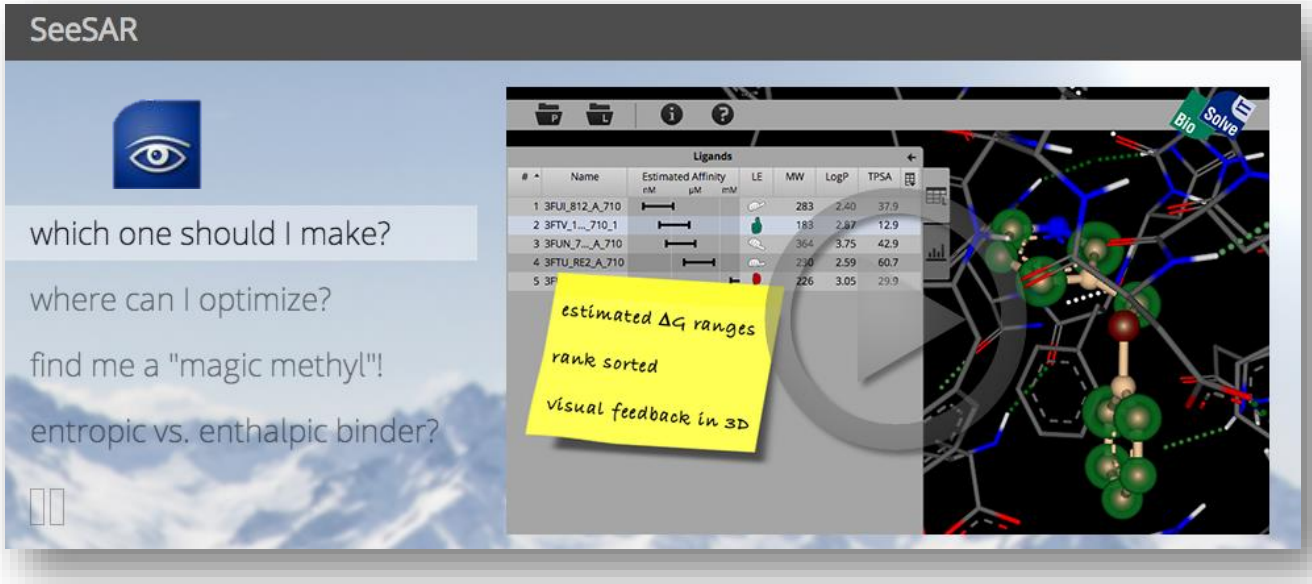
- For the CompChem:

  Exploit the unique visual character of the method, please try to not only script it, and do not discard the beauty of visualization.

Σ: Sound, Fast, and Visual SBDD

- An exciting new tool for multi-paramter L.O. that evolves rapidly
- All visual, rigorous physical & statistical models behind
- Free 7-day testing anytime - with admin-free install.

Optibrium & BioSolveIT: We are humming! - Watch this space ☺



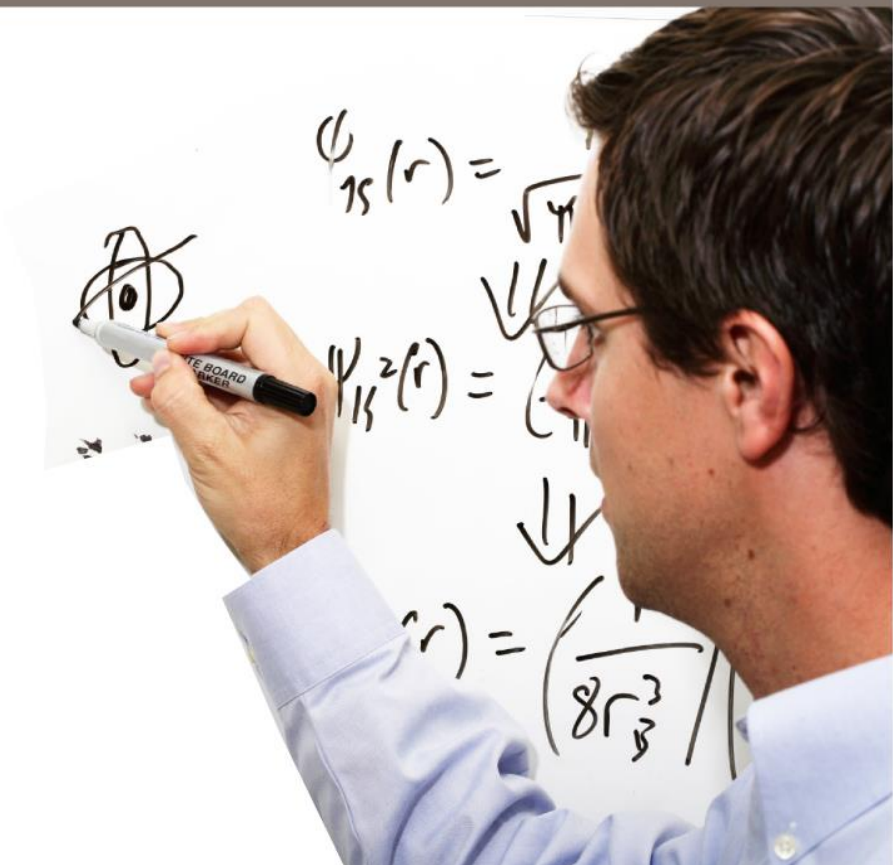
SeeSAR www.biosolveit.de/SeeSAR

StarDrop™ including SeeSAR™

Estimated release Q2 2016

optibrium

BioSolveIT



Collaboration with BioSolveIT
Integration of SeeSAR with StarDrop

- BioSolveIT's platform for structure-based design on chemists' desktops

- Applications include:
  - Crystal structure elucidation
  - Compound prioritization
  - Lead optimization and SAR exploration
  - Binding mode prediction
  - Virtual Screening

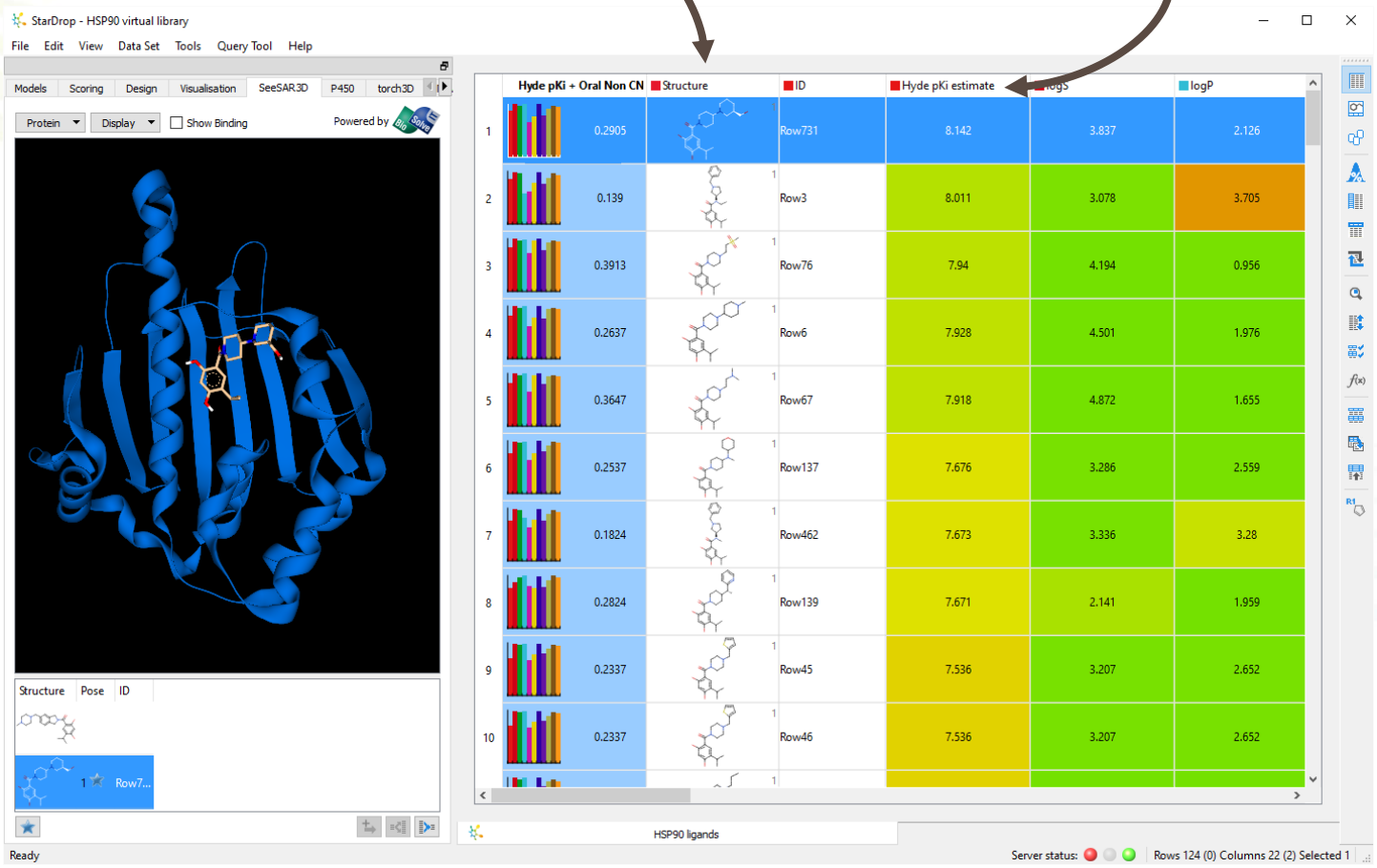
- **StarDrop 6.3 will include a 3D structure viewer based on SeeSAR**

New SeeSAR 'Viewer' Module

Visualise 3D structure information

Import docking results or crystal structures, from SD/PDB files

Include docking scores or affinity predictions in MPO



Select between multiple poses

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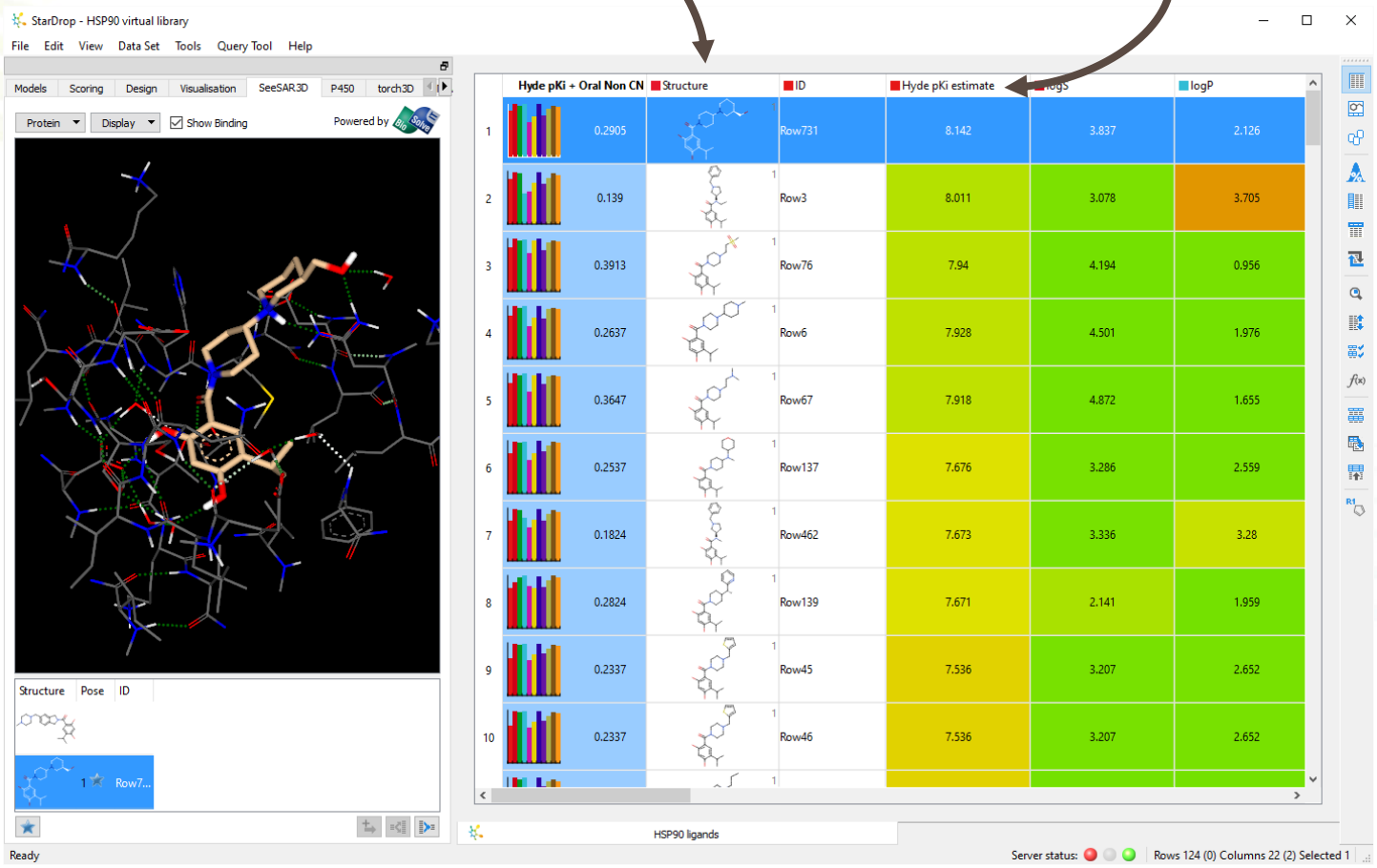
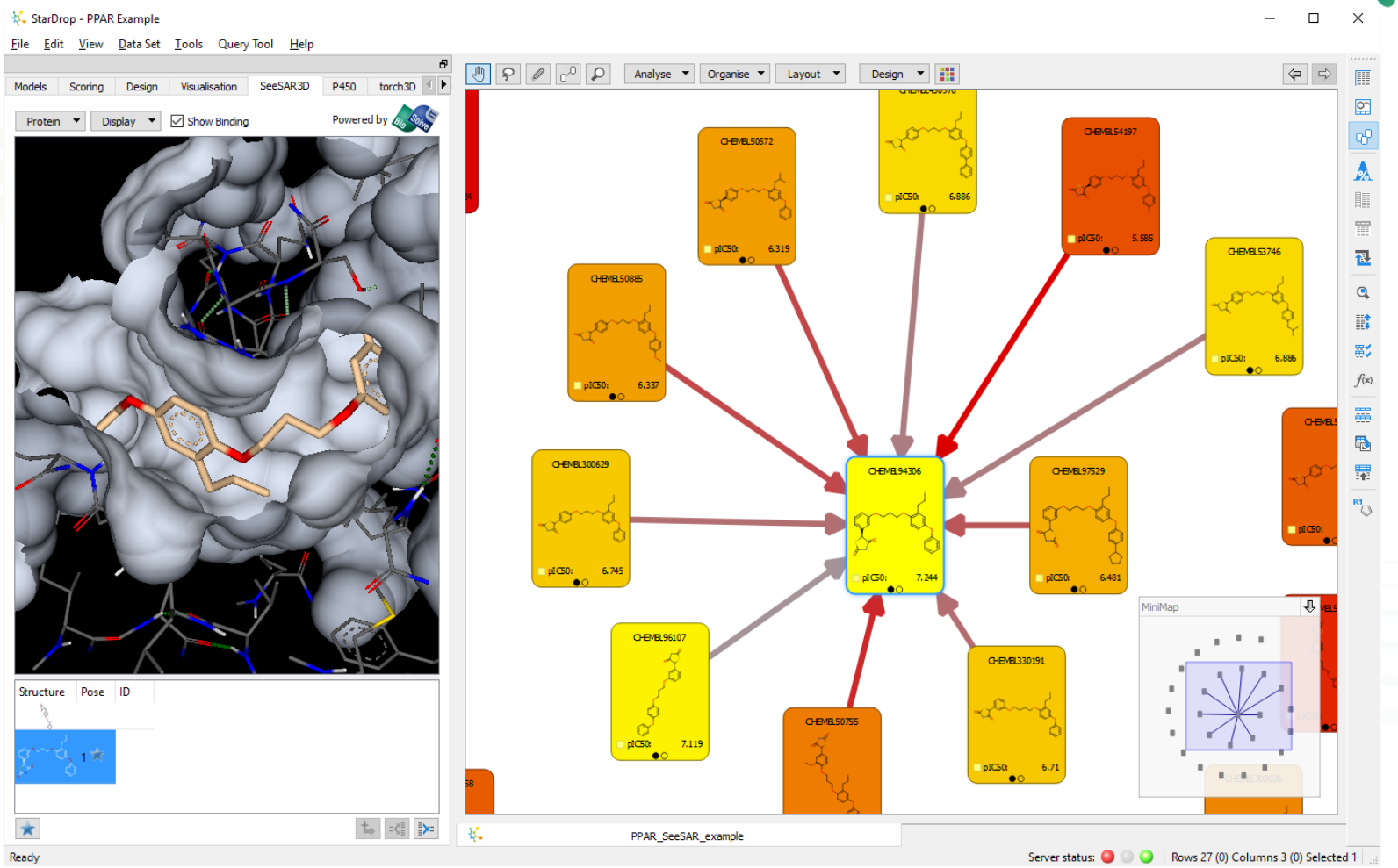


Select between multiple poses

Linking 2D and 3D SAR Analyses
E.g. Activity Neighbourhood



Demonstration

Questions and Answers

optibrium

Bio Solve IT