



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

Webinar. 4:00 GMT, April 6th 2016

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Marcus Gastreich

The Magic Behind SeeSAR

Visual, interactive 3D L.O. for Anyone

Times Have - and Are Still Changing...*

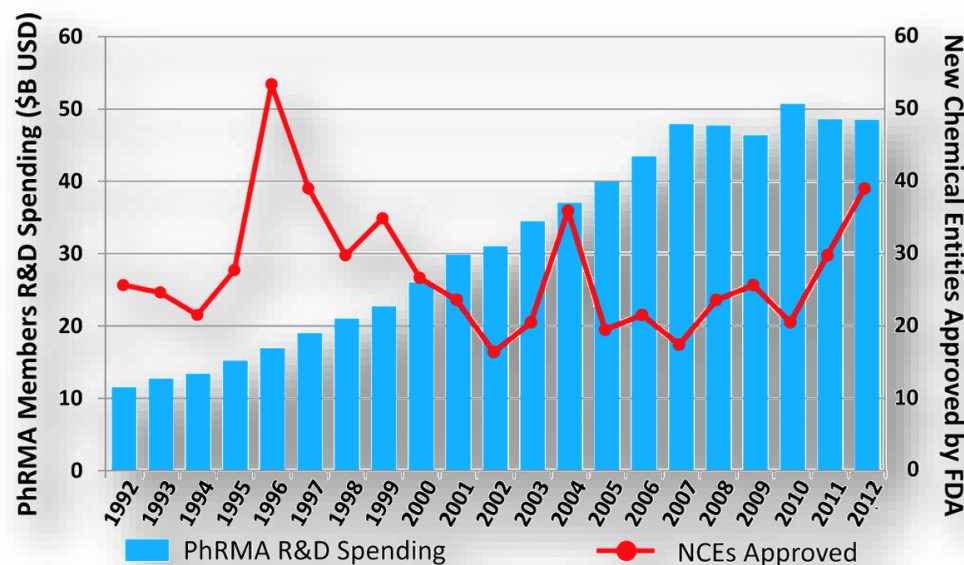
- Since 2000:
Outsourcing, merging, 300.000+ layoffs in pharma

PhRMA members:

1998: 42

2011: 11

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

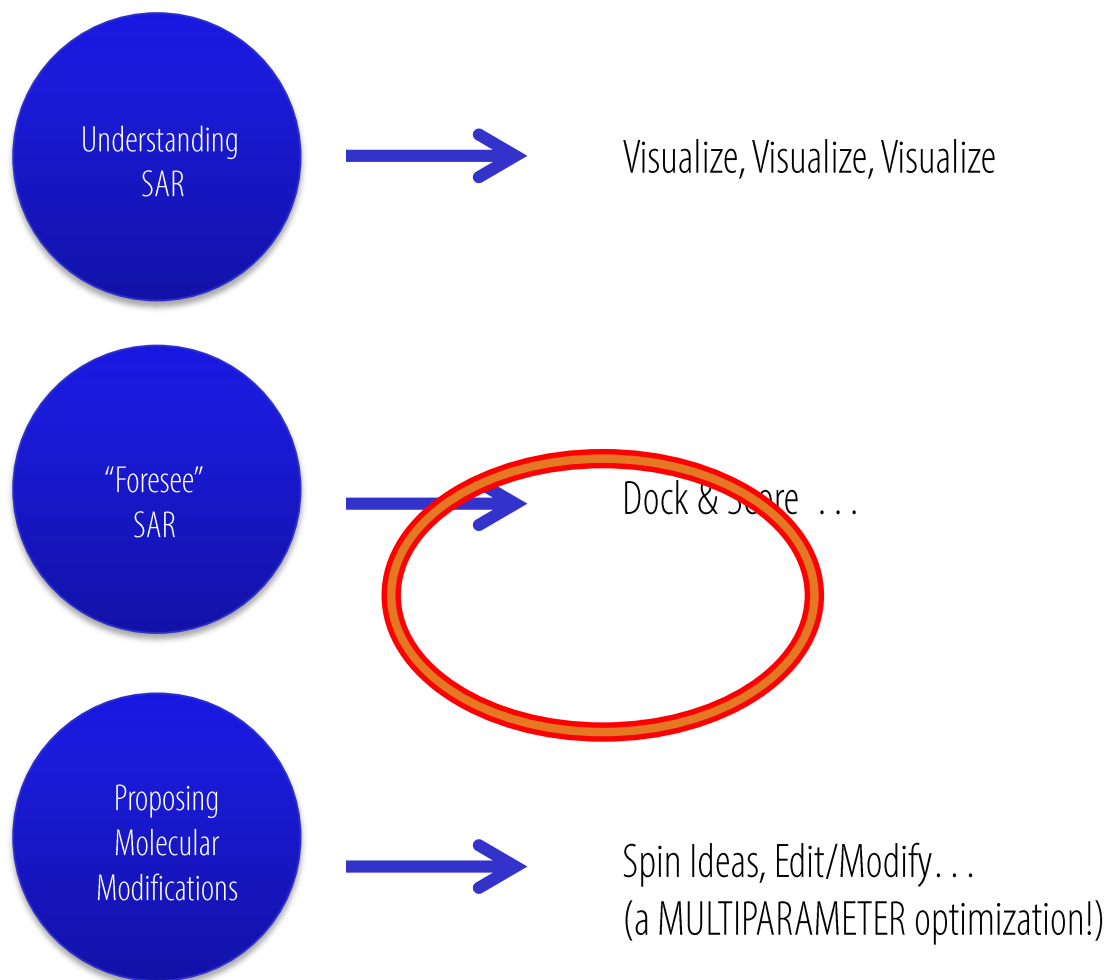


- MedChems take over basic computational tasks, esp. visualisation

* Data & graphics from:

Abou-Gharbia et al, JMC 2013, [dx.doi.org/10.1021/jm401564r](https://doi.org/10.1021/jm401564r)

What is "Of Relevance" ? Our Daily Work:



What Does This Mean for SBDD?

Visualize, Visualize, Visualize

Meaningful & simple graphics

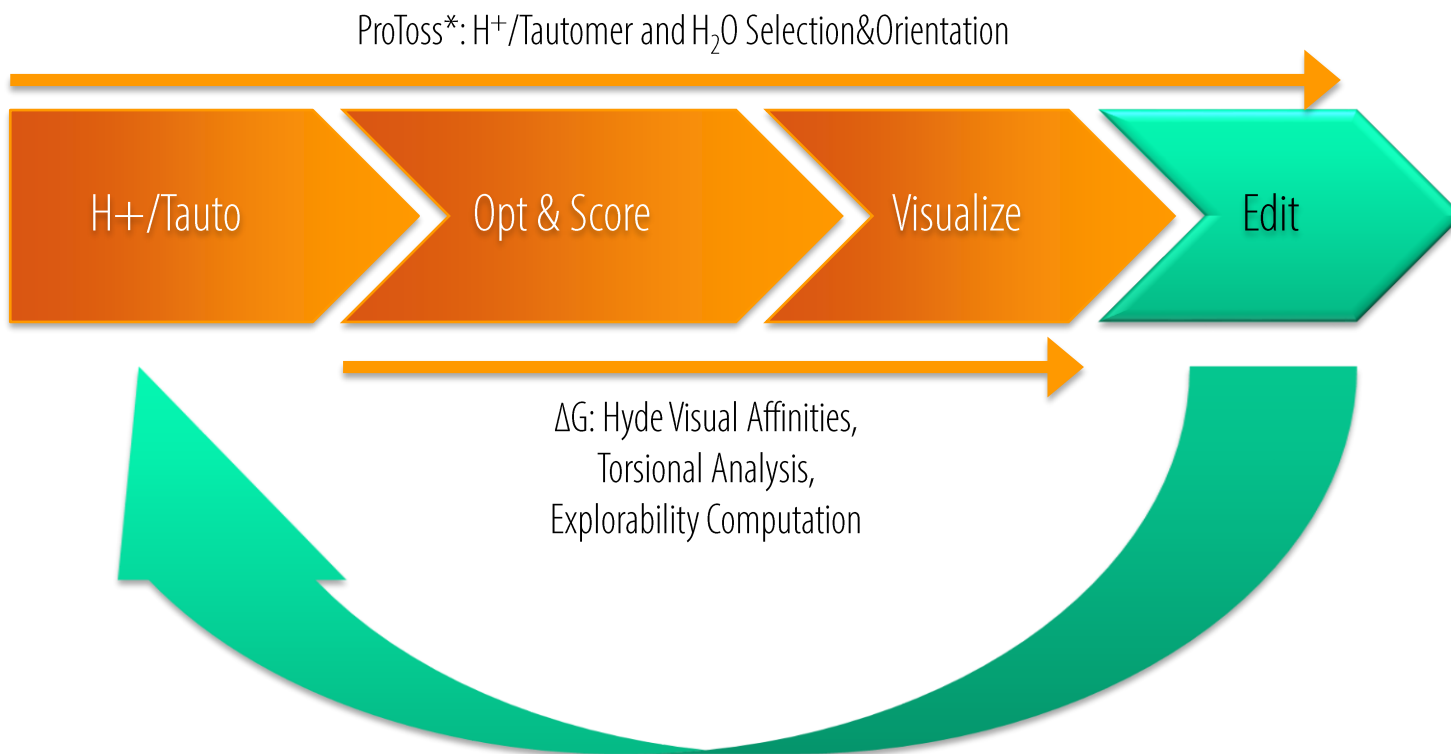
Docking & Scoring etc.

Sound, Relevant Science

Spin Ideas, Edit/Modify, . . .

Playful & Fast, Easy

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



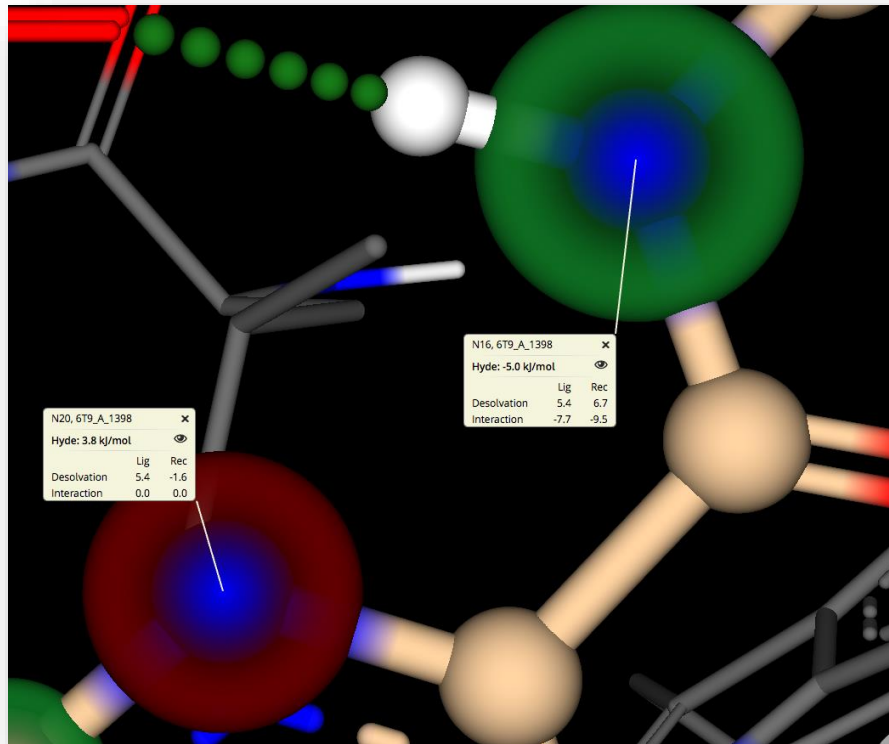
ProToss - Protonation, Waters, Tautomers proposed in millisecond time, Publication:
Bietz et al., Journal of Cheminformatics 2014, 6:12

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

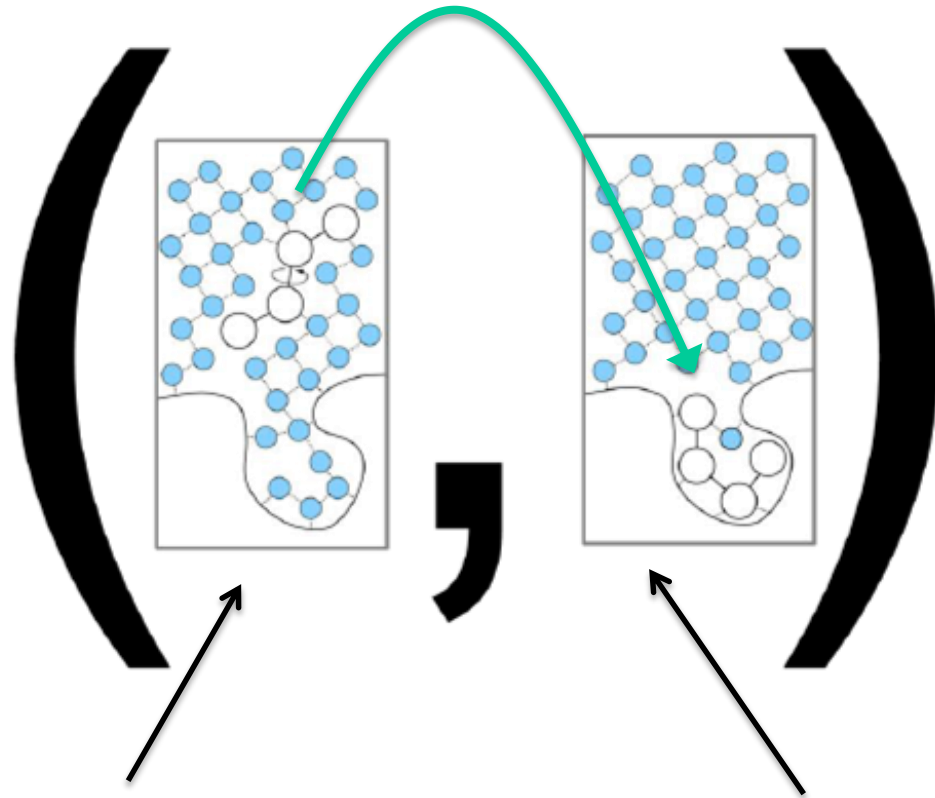
The larger the stronger the contribution.

What is Affinity?

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

What is Affinity?

$$\Delta G = \Delta G$$

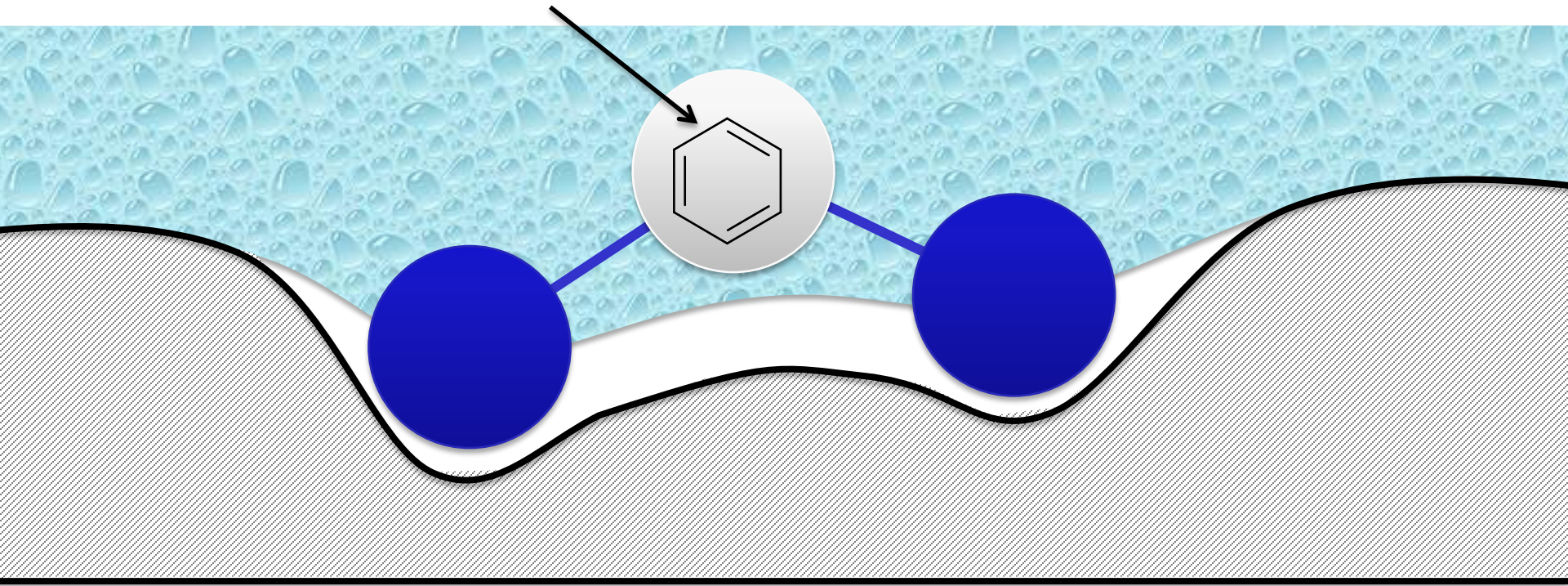


unbound,
in water

bound,
in complex

“Good” or “Bad” for Affinity??

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



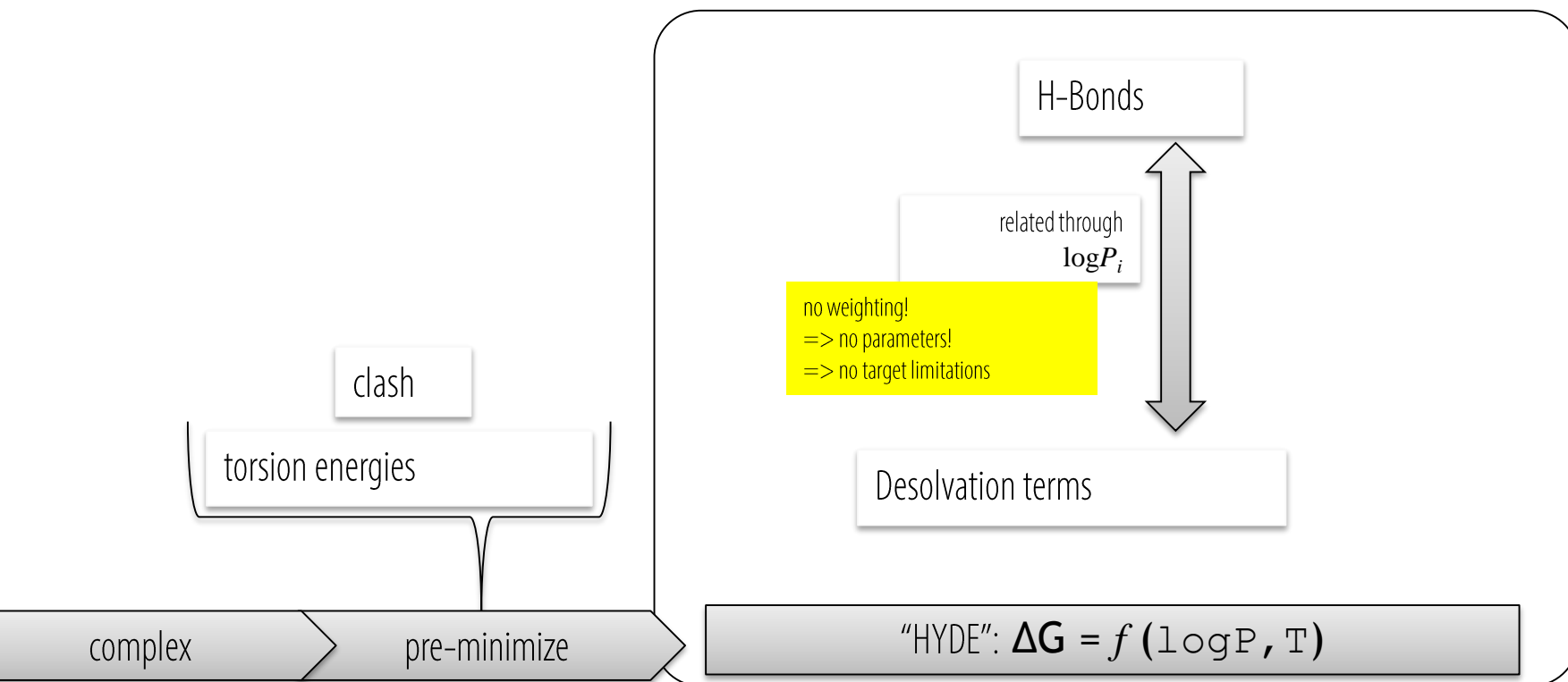
- The Phenyl was already ‘unhappy’ before binding.
- It still is unhappy after binding.

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

\Rightarrow 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 !

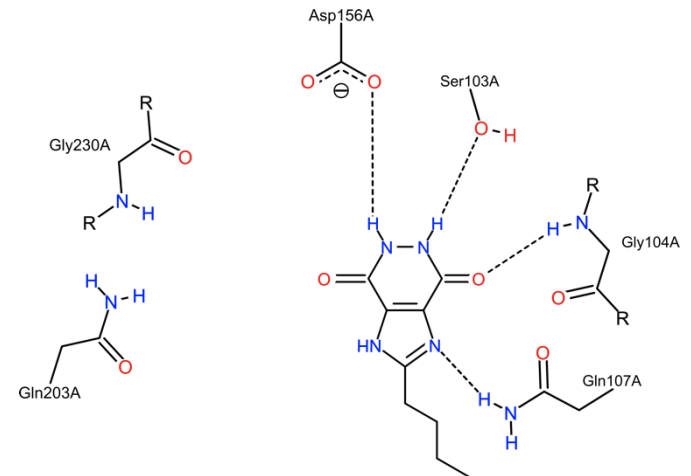
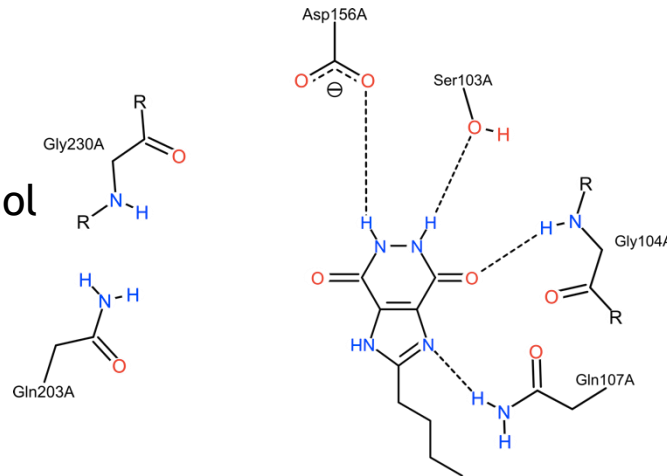
At a Glance - Advantages of SeeSAR & HYDE

	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	●	●	●	●

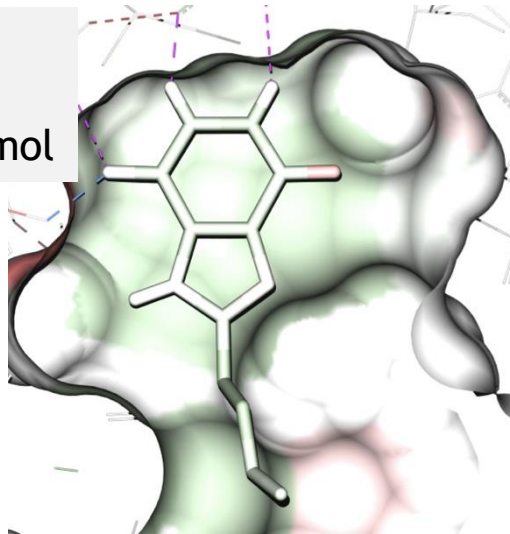
HYDE Detects Subtle Binding Mode Differences

1n2v

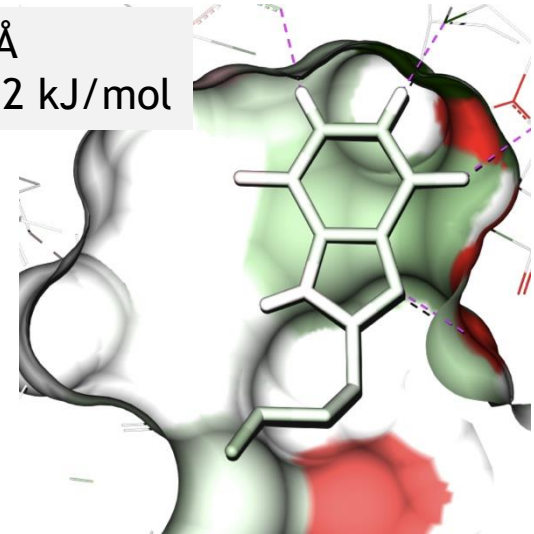
$\Delta G_{\text{experimental}} -23\text{kJ/mol}$



Best by scoring
RMSD 0.2 Å
 $\Delta G_{\text{HYDE}} -23\text{ kJ/mol}$



RMSD 2.3 Å
 $\Delta G_{\text{HYDE}} -12\text{ kJ/mol}$



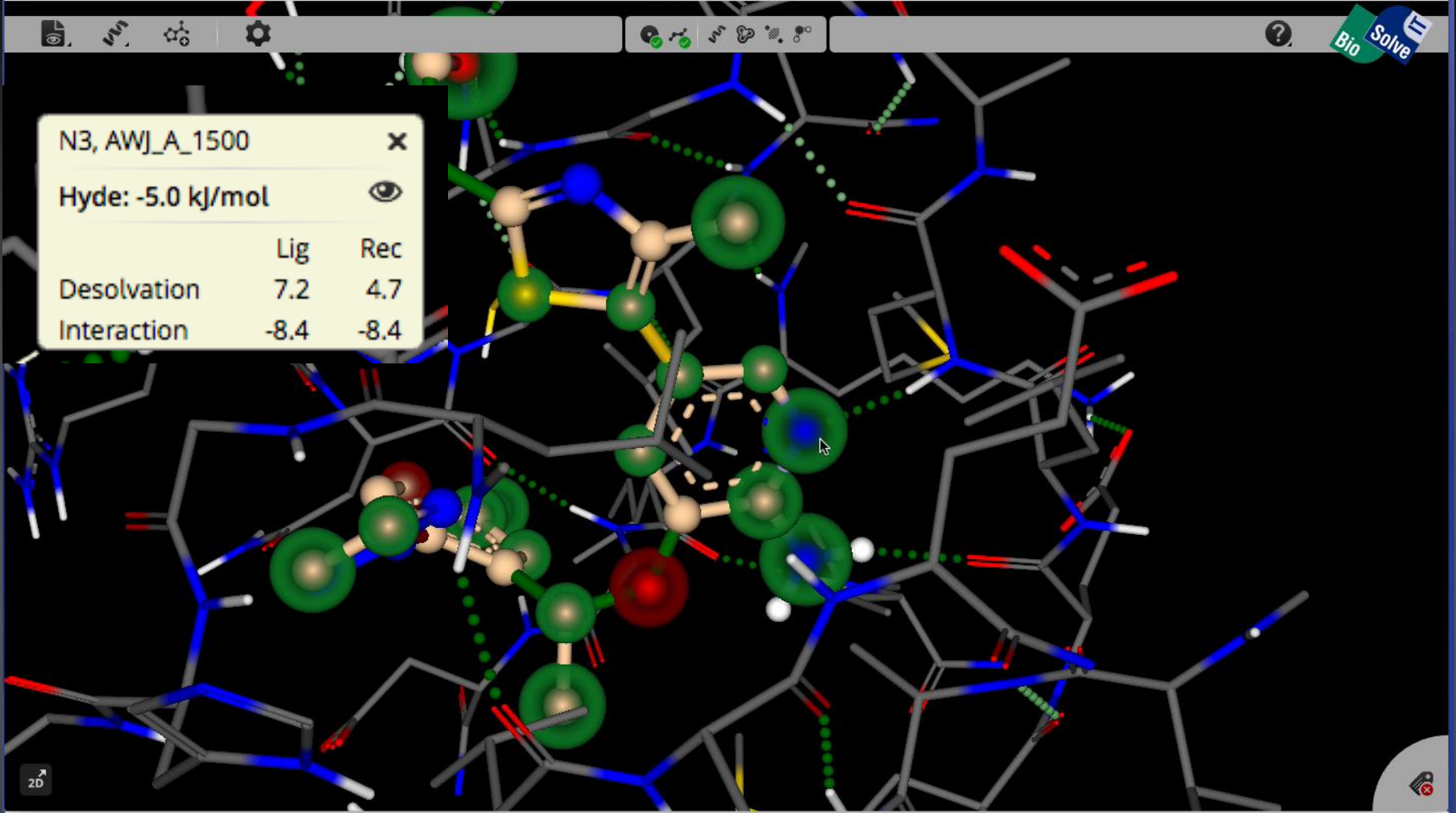
tRNA-Guanine Transglycosylase

Drilling In. . .

N3, AWJ_A_1500 ✕

Hyde: -5.0 kJ/mol 👁

	Lig	Rec
Desolvation	7.2	4.7
Interaction	-8.4	-8.4



Molecules (1/1)

From Protein From File From Editor

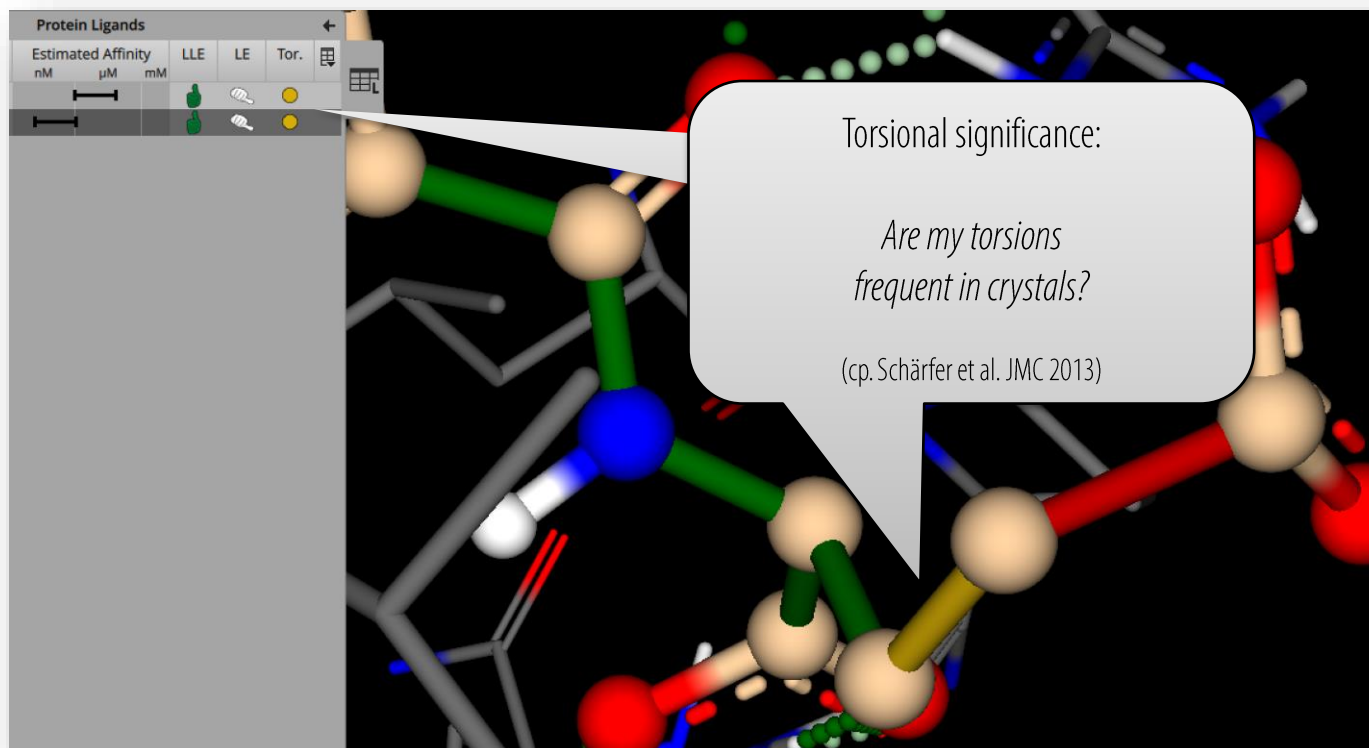
#	Fav	Name	Src	Estimated Affinity				LLE	Tor.	🗄
				pM	nM	μM	mM			
1	☆	AWJ_A_1500	mm	[Bar chart showing affinity scale]						👍 🔄 📄 🗑

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

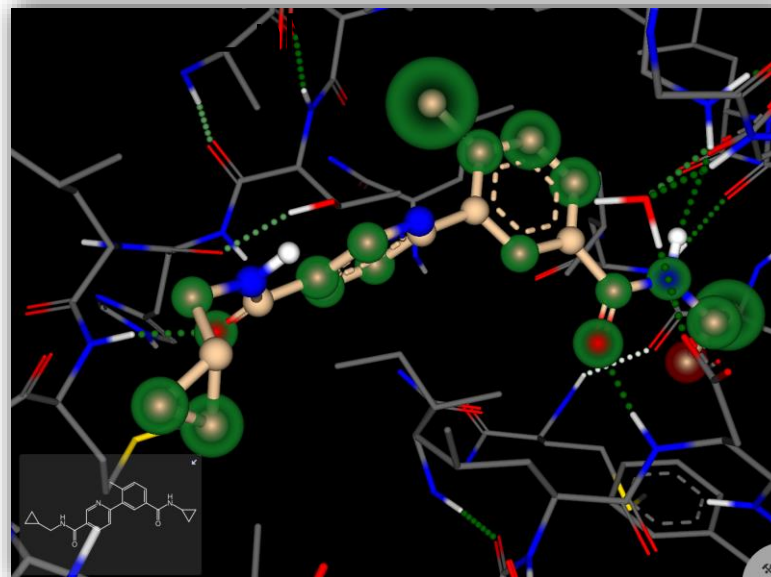
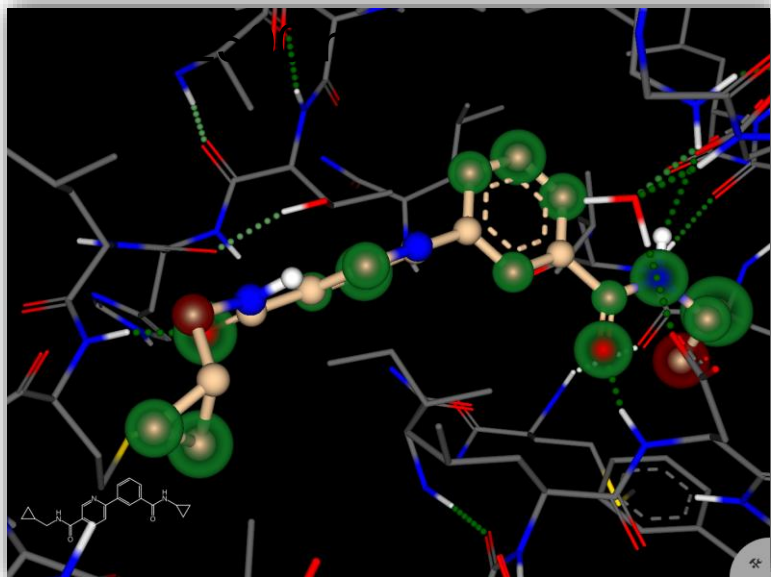
Yellow = unusual, however several times observed

Red = very rarely observed

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

Detecting Magic Methyls With SeeSAR

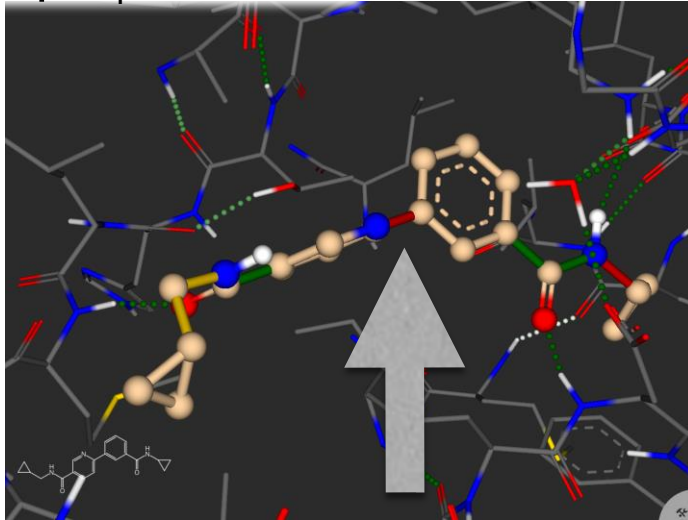
PDB 3IPH (p38 Kinase)



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

Methyl Locks Torsion Into Preferred Arrangement

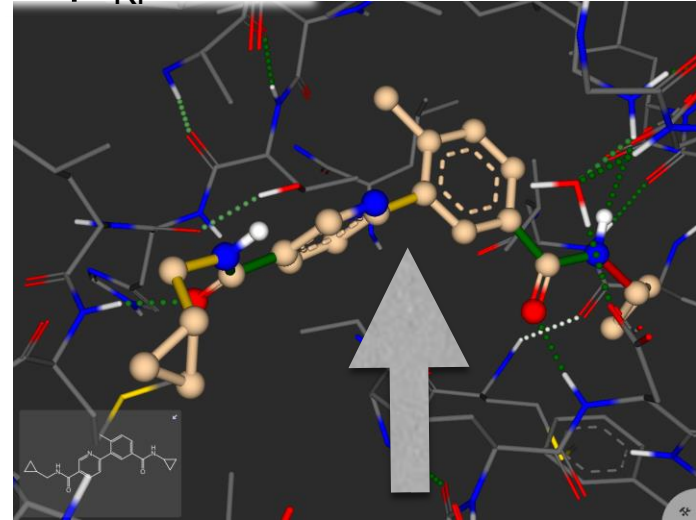
Exp K_i 2500 nM



red = very rare

likely: strain energy in here!

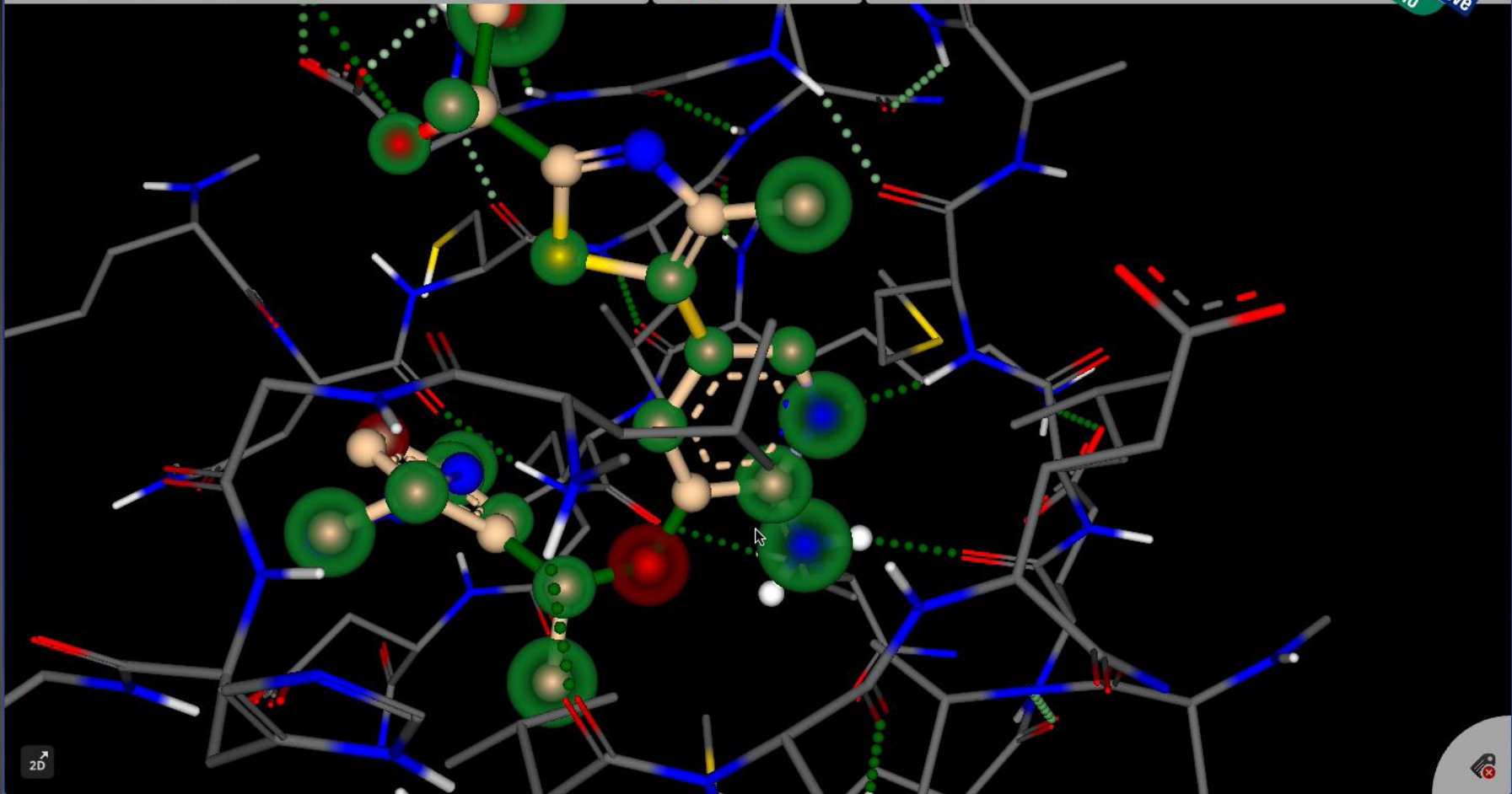
Exp K_i 12 nM



yellow = unusual

likely: more favorable

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

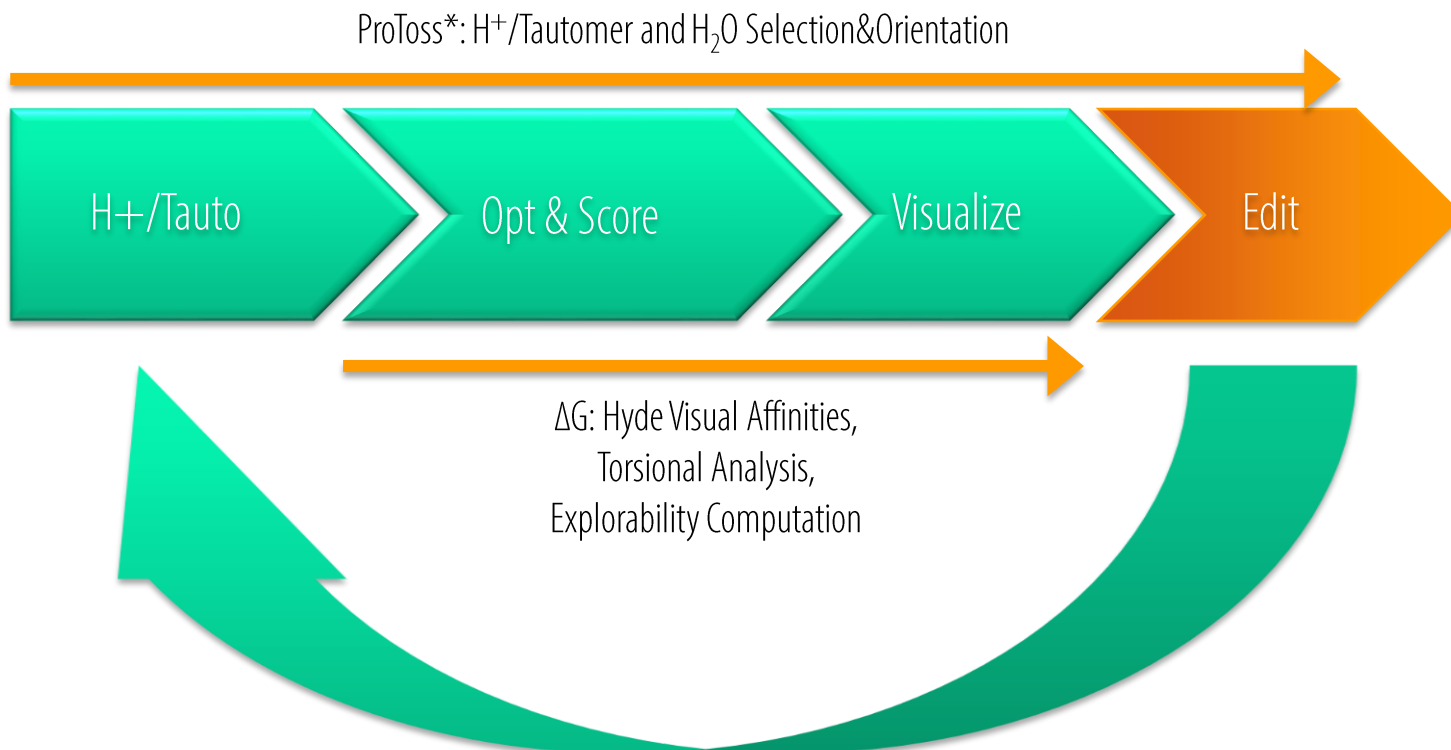


Molecules (1/1)

From Protein From File From Editor

#	Fav	Name	Src	Estimated Affinity				LLE	Tor.	📄
				pM	nM	μM	mM			
1	☆	AWJ_A_1500	📄	▬				📄	🟡	🗑️

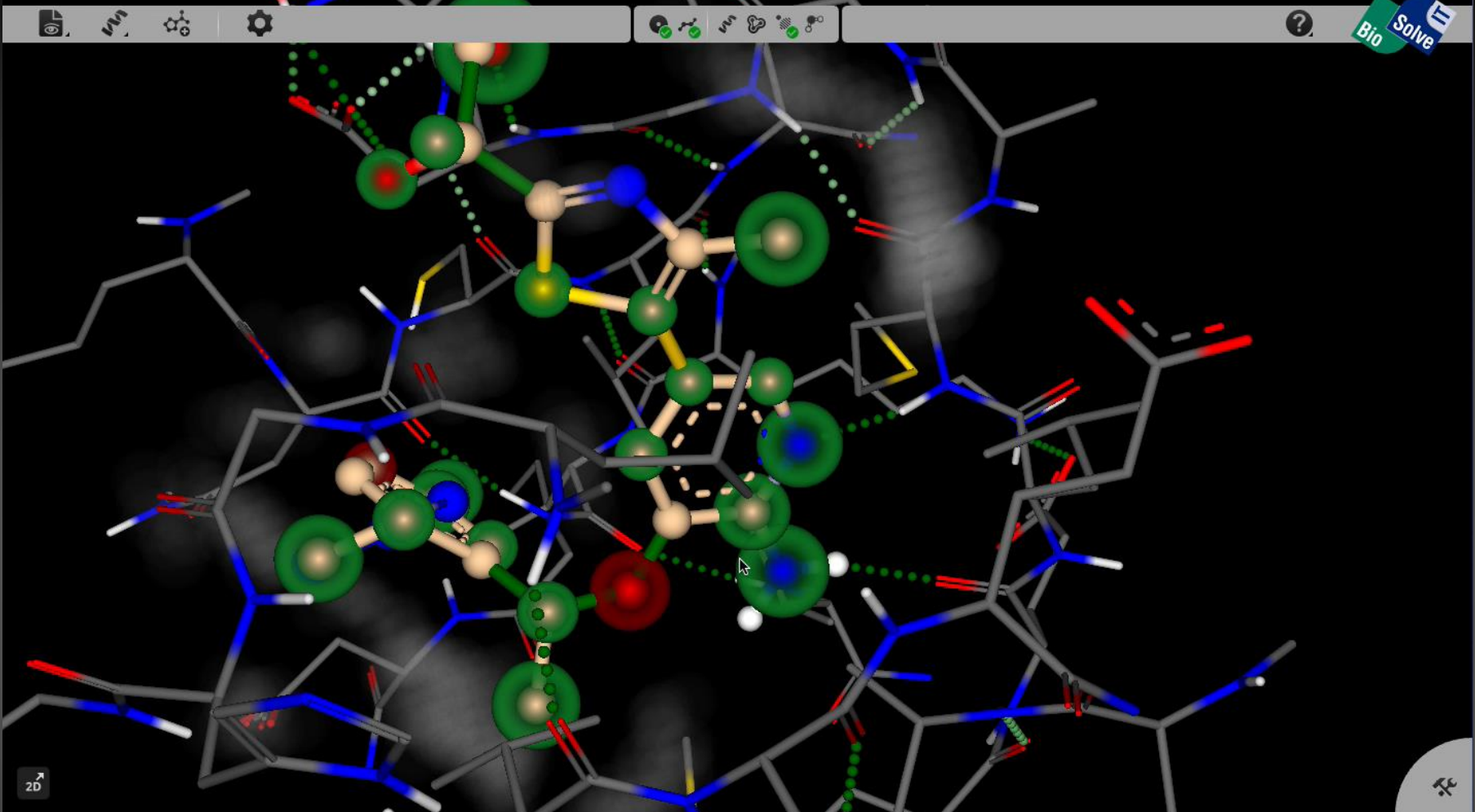
Editing in an MPO Context



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

Editor

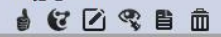




Molecules (1/1)

From Protein From File From Editor

#	Fav	Name	Src	Estimated Affinity				LLE	Tor.	hERG pIC5... optibrium	logS optibrium	🗄
				pM	nM	μM	mM					
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-parameter 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

which one should I make?
where can I optimize?
find me a "magic methyl!"
entropic vs. enthalpic binder?

#	Name	Estimated Affinity	LE	MW	LogP	TPSA
		nM				
1	3FUJ_B12_A_710	—	☁	283	2.40	37.9
2	3FTV_1...710_1	—	🌱	183	2.87	12.9
3	3FJN_7...A_710	—	☁	364	3.75	42.9
4	3FTU_RE2_A_710	—	☁	230	2.59	60.7
5	3F...	—	🔴	226	3.05	29.9

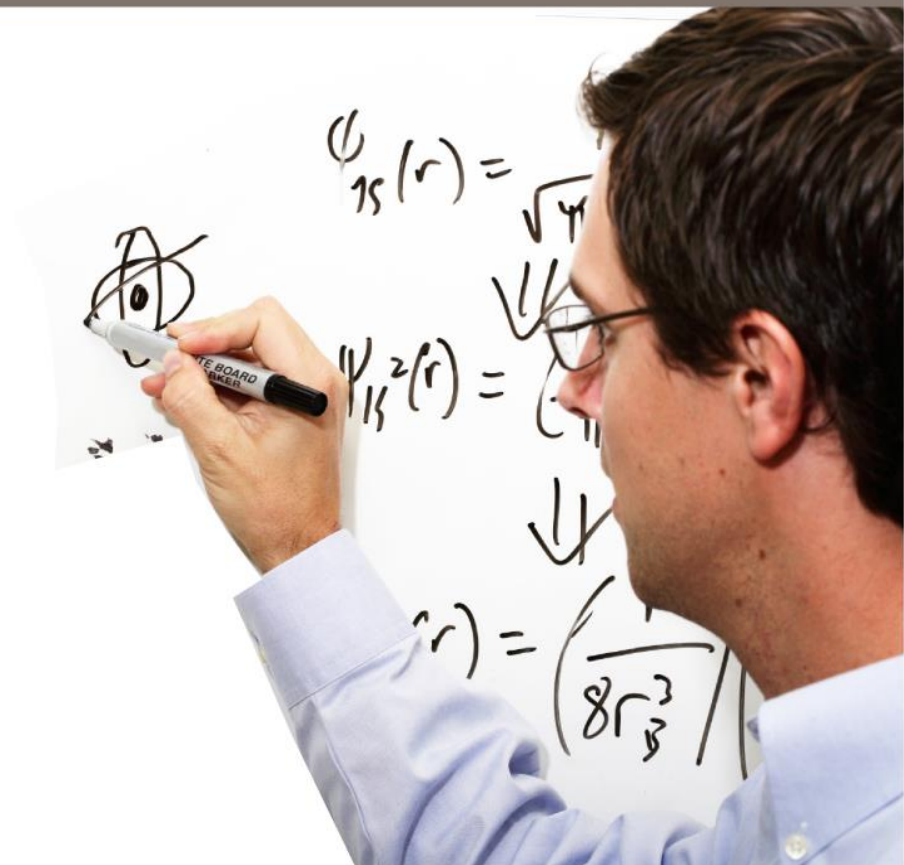
estimated ΔG ranges
rank sorted
visual feedback in 3D

Bio Solve

SeeSAR www.biosolveit.de/SeeSAR

StarDrop™ including SeeSAR™

Estimated release Q2 2016



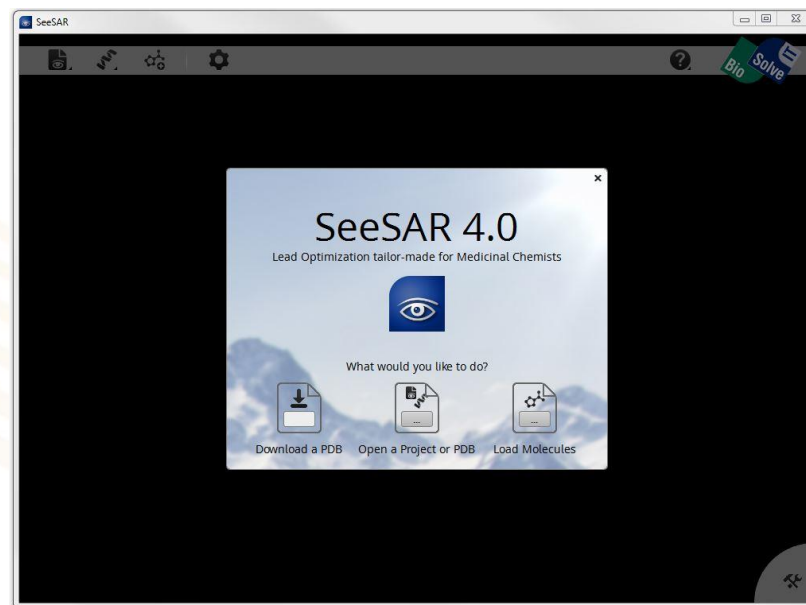
Collaboration with BioSolveIT

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

The screenshot displays the SeeSAR Viewer interface. On the left, a 3D ribbon model of a protein structure is shown in blue, with a yellow ligand docked in the binding pocket. Below the model, a 'Structure' panel shows a list of ligands, with the first one selected. On the right, a data table displays docking results for 10 rows. The table columns are: 'Hyde pKi + Oral Non CN' (with a bar chart), 'Structure' (with a chemical structure), 'ID', 'Hyde pKi estimate', 'logS', and 'logP'. The table is color-coded by 'Hyde pKi estimate' values.

	Hyde pKi + Oral Non CN	Structure	ID	Hyde pKi estimate	logS	logP
1	0.2905		Row731	8.142	3.837	2.126
2	0.139		Row3	8.011	3.078	3.705
3	0.3913		Row76	7.94	4.194	0.956
4	0.2637		Row6	7.928	4.501	1.976
5	0.3647		Row67	7.918	4.872	1.655
6	0.2537		Row137	7.676	3.286	2.559
7	0.1824		Row462	7.673	3.336	3.28
8	0.2824		Row139	7.671	2.141	1.959
9	0.2337		Row45	7.536	3.207	2.652
10	0.2337		Row46	7.536	3.207	2.652

Select between multiple poses

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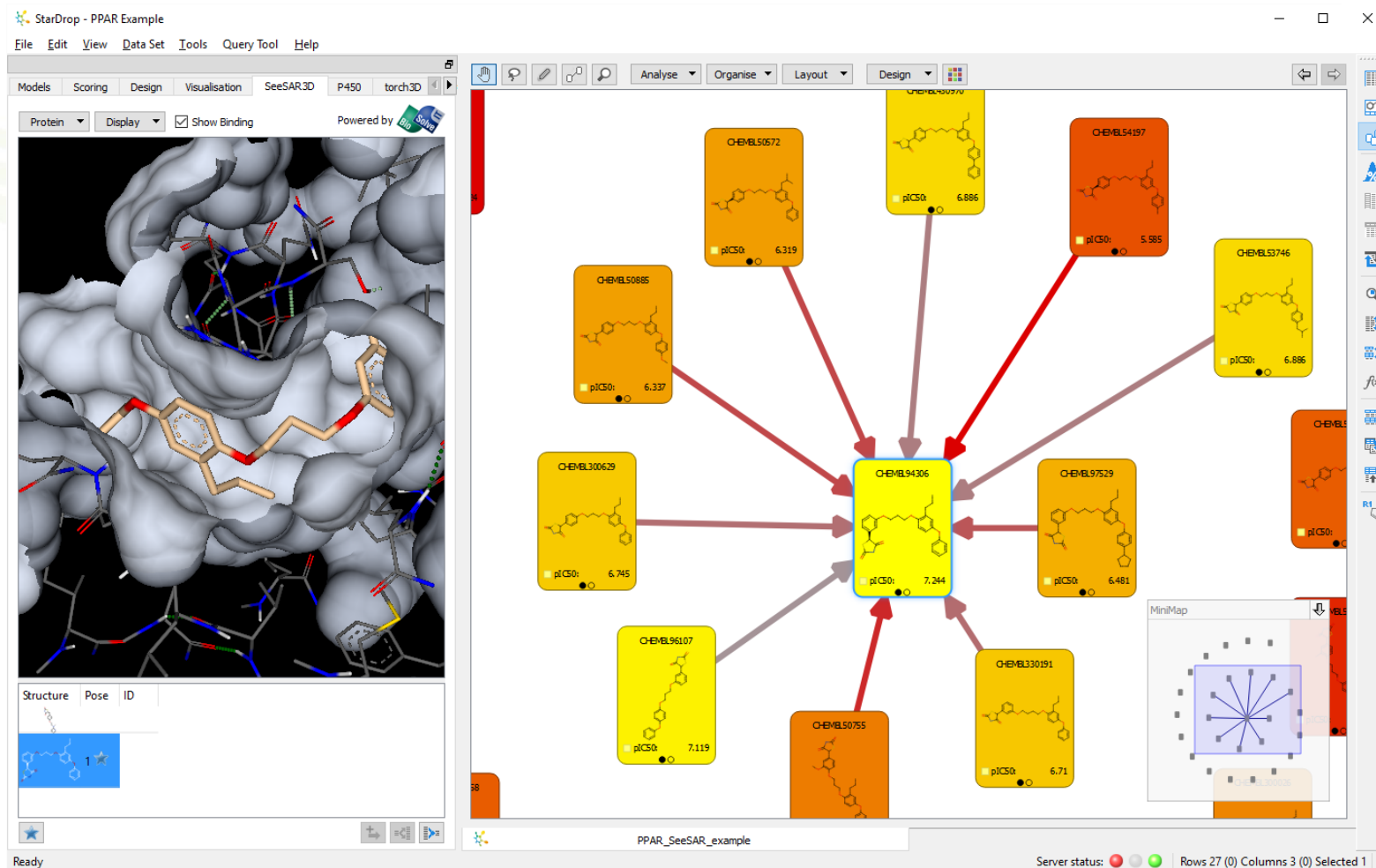
The screenshot displays the SeeSAR Viewer interface. On the left, a 3D molecular model shows a protein structure with a ligand docked in its binding pocket. Below the model, a 'Structure' panel shows a list of poses, with the first pose (Row7...) selected. On the right, a data table displays docking results for 10 rows. The table columns are: 'Hyde pKi + Oral Non CN' (with a bar chart), 'Structure' (with a chemical structure), 'ID', 'Hyde pKi estimate', 'logP', and 'logS'. The table is color-coded by 'Hyde pKi estimate' values.

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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

