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The Long and Rocky Road from a PDB File to a Protein-Ligand Docking Score

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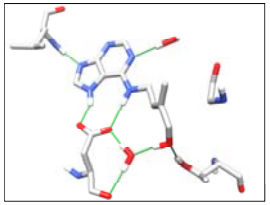

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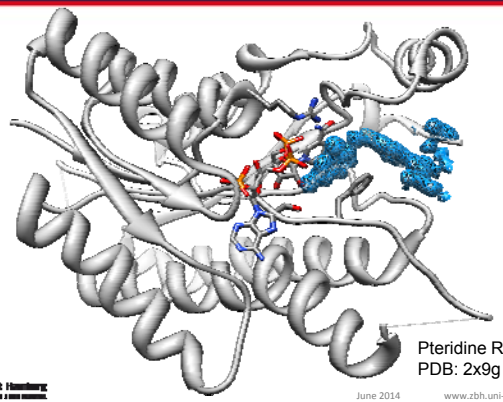
Protein Structures: The Starting Point for New Drugs



Pteridine Reductase
PDB: 2x9g

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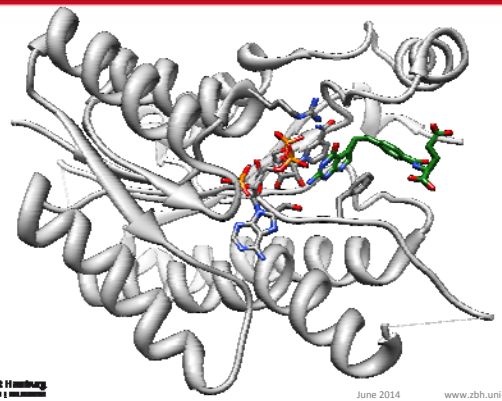
Protein Structures: The Starting Point for New Drugs



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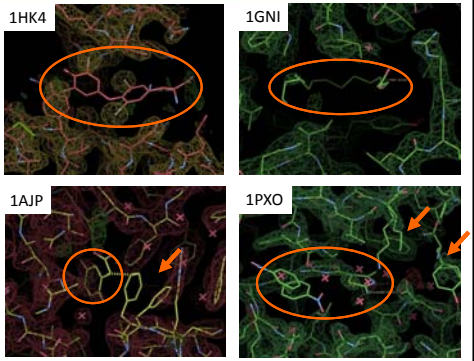
Detailed Structural Analysis of PDBbind 2007 by Consulting Electron Density Maps

- 107 complexes with structural deficiencies
  - Missing electron density
  - Alternative conformations
  - High temperature factors
  - Contact with symmetry related subunits



Protein Structures: The Starting Point for New Drugs

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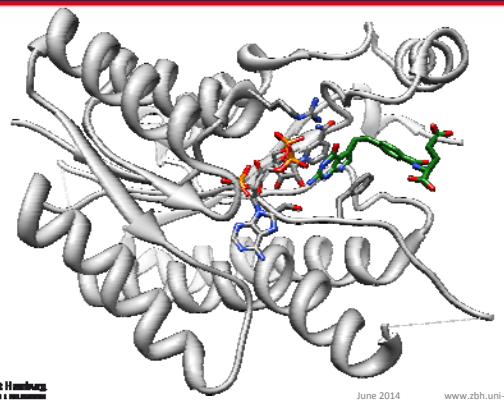

Protein Structures: The Starting Point for New Drugs

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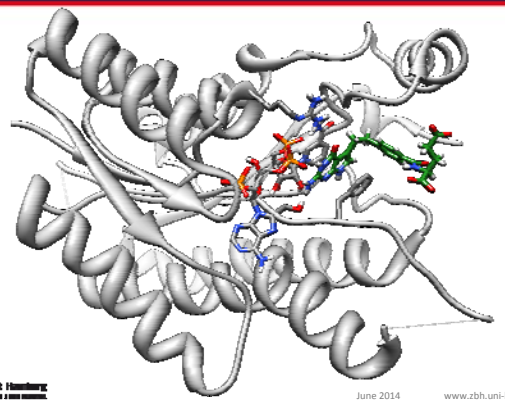

Does it Matter?

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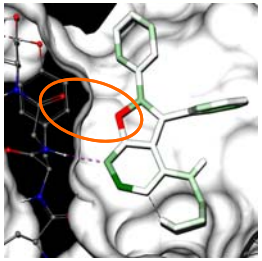
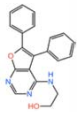
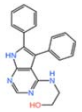


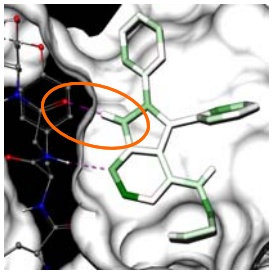
2BRB



ΔG= -28 kJ/mol



ΔG= -34 kJ/mol



* Foloppe N. et al., JMedChem 2005

Contribution of a Single Hydrogen Bond to Binding Affinity

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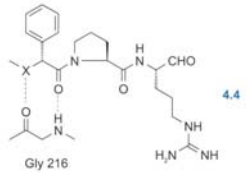
- Example: Thrombin/Trypsin-inhibitor complexes
- Exchange NH → CH_2:
  - slight loss in IC_{50}
- Exchange NH → O:
  - loss of two hydrogen bonds upon dehydration
  - no formation of a new hydrogen bond
  - IC_{50} drops by about three orders of magnitude

Abb.: G. Klebe, Wirkstoffdesign Spektrum Akad. Verlag, 2009

Tabelle 4.4 Bindung von **4.4** an die Serinproteasen Thrombin bzw. Trypsin



Enzym	IC_{50}-Werte in mg/ml X = -NH-	-O-	$-CH_2-$
Thrombin	0,009	52	0,07
Trypsin	0,009	43	0,018

Urbaczek et al, JCIM (2013), 53, 76-87

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PHASE 1: Perception of Chemical Structure

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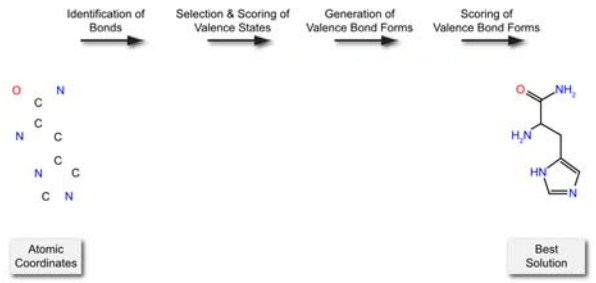

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Urbaczek et al, JCIM (2013), 53, 76-87

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Valence States

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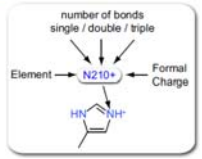
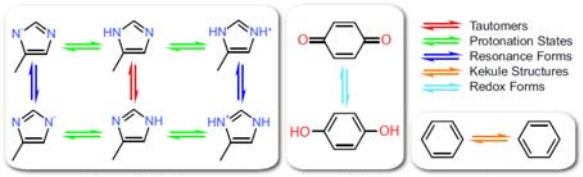
- Valence state: Chemically valid combination of bond orders and formal charge for a particular element.
- Aim: Find a valid valence state combination (VSC)





Forms of Histidine A | Forms of Chinon B | Kekule Structures C

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Urbaczek et al, JCIM (2013), 53, 76-87

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Valence States

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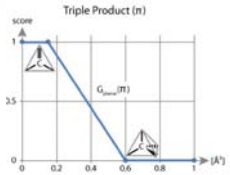
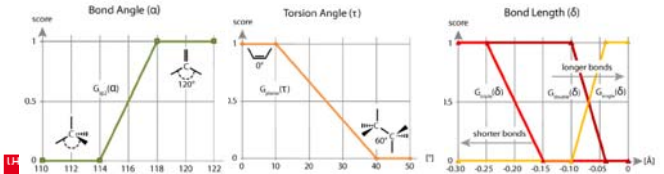
- Atoms get sets of all valence states compatible to the detected bond structure
- Each valence state is scored by the geometry of surrounding covalent bonds





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From Valence States to Valence Bond Structures

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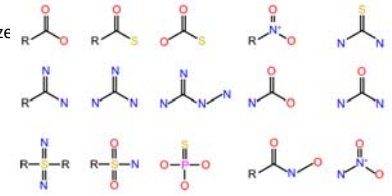
- Valence states get probabilities converted to scores
- Iterative refinement by removing valence states incompatible to those of neighboring atoms
- Partitioning of the molecules into zones of covalently bound atoms with yet undefined valence state
- Branch&Bound procedure enumerating and selecting highest scoring valence states
- Consider aromaticity, favorize certain functional group topologies in case of nearly equal scores



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Urbaczek et al, JCIM (2013), 53, 76-87

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Results: Quality of Chemical Structure Perception

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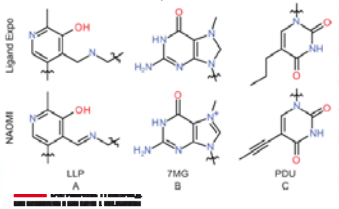
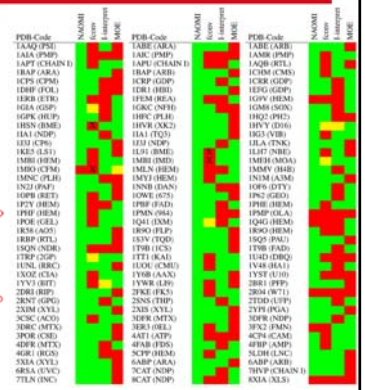
- 363 PDB files with hand-curated structures, 563 ligands in total
- NAOMI vs. Ligand Expo:
  - 92% identical structures
  - differences found: (NAOMI structure validated by literature):





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PHASE 2: Prediction of Protonation

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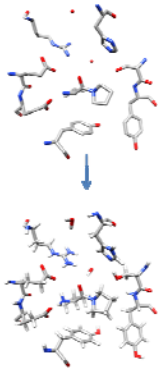

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Prediction of Hydrogen Coordinates

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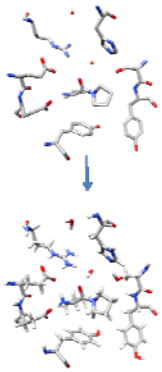
- Existing hydrogen placing tools:
  - WHAT IF[1]
  - Protonate3D (MOE)[2]
  - HINT Comp. Titration[3]
  - Protoss[4]
  - YASARA[5]



[1] R.W.W. Hooft *et al.* Proteins, 26(4):363–376, 1996.

[2] P. Labute *et al.* Proteins, 75(1):187, **2009**.

[3] A.S. Bayden *et al.* Journal of Computer-Aided Molecular Design, 23(9): 621–632, **2009**.

[4] **T. Lippert *et al.* Journal of Cheminformatics, 1(1):13, 2009.**

[5] E. Krieger *et al.* Computational Drug Discovery and Design, 819:405–421, **2012**.

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Prediction of Hydrogen Coordinates

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	proteins: rotatable hydrogens	proteins: tautomers	proteins: protonation states	proteins: side chain flips	proteins: water orientations	ligands: rotatable hydrogens	ligands: tautomers	ligands: protonation states	ligands: side chain flips
WHAT IF	✓	✓	✓	✓	✓				
Protonate3D	✓	✓	✓	✓	✓	✓	(✓)	(✓)	
HINT CT	✓	✓	✓	✓	✓	✓	(✓)	(✓)	
Protoss v2009	✓	✓	✓	✓	✓	✓	(✓)	(✓)	
YASARA	✓	✓	✓	✓	✓	✓	(✓)	(✓)	✓

Error Case Examples

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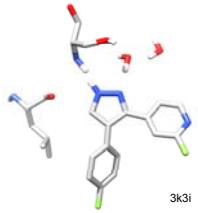
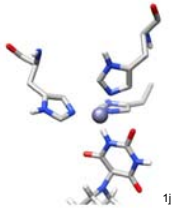


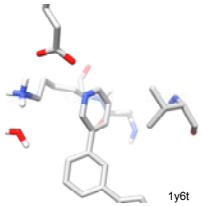
Repulsive donor interactions

YASARA



Hydrogen-metal clashes

Protonate3D



Unsaturated donors / acceptors

Protoss v2009

Frequency of Tautomerism

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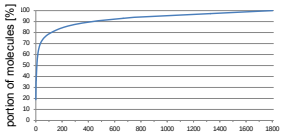
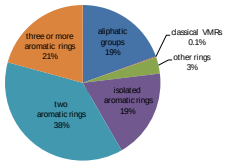
- Ligand Expo[6]: 17,563 small molecules[7]
- According to the ProToss protonation model
  - 81 % exhibit alternative tautomers or / and protonation states
  - 17 % only contain commonly used groups (primary amines, carboxylats, imidazoles)
  - Only 19 % do not show variability
  - 1802 structurally different variable mode regions (VMRs)





different VMR type portions

[6] Z. Feng *et al.* Bioinformatics, 20(13):2153-5, 2004
[7] Downloaded from http://ligand-expo.rcsb.org (01/03/2014)

Bietz et al, JCheminf (2014), 6 (12):1-12

Challenges to an Advancement of ProToss

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- Find the tautomer / protonation state that leads to the best hydrogen bonding network in the protein-ligand complex
- Keep the runtime low

	protein: rotatable hydrogens	protein: tautomers	protein: protonation states	protein: side chain flips	protein: water orientations	ligands: rotatable hydrogens	ligands: tautomers	ligands: protonation states	ligands: side chain flips
WHAT IF	✓	✓	✓	✓	✓				
Protonate3D	✓	✓	✓	✓	✓	✓	(✓)	(✓)	
HINT CT	✓	✓	✓	✓	✓	✓	(✓)	(✓)	
Protoss v2009	✓	✓	✓	✓	✓	✓	(✓)	(✓)	
YASARA	✓	✓	✓	✓	✓	✓	(✓)	(✓)	✓
Protoss v2013	✓	✓	✓	✓	✓	✓	✓	✓	(✓)

Bietz et al, JCheminf (2014), 6 (12):1-12

Protoss Workflow

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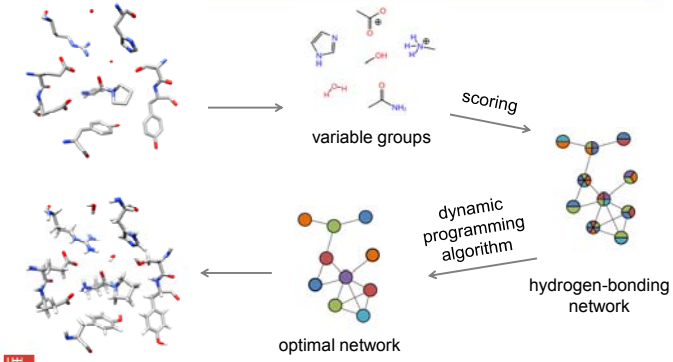

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Generation of Tautomers and Protonation States

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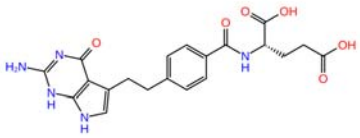

Pemetrexed (PTR1 inhibitor)

Urbaczek et al, J Chem Inf Model (2014), 45 (3):756-766

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Generation of Tautomers and Protonation States

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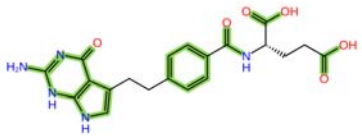
Step 1: Conjugated zone identification



Urbaczek et al, J Chem Inf Model (2014), 45 (3):756-766

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Generation of Tautomers and Protonation States

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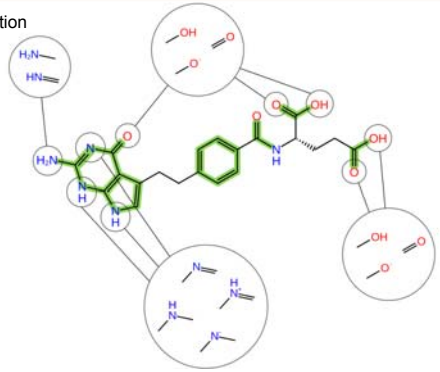
Step 2: Atom state selection



Urbaczek et al, J Chem Inf Model (2014), 45 (3):756-766

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Generation of Tautomers and Protonation States

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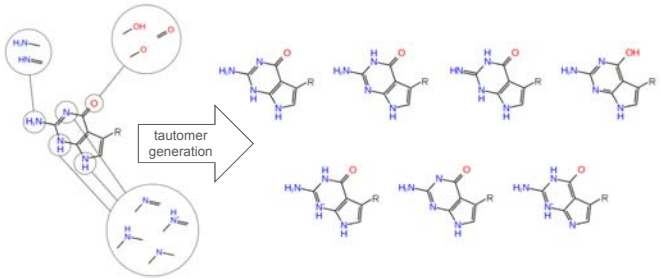
Step 3: Enumeration of tautomers and protonation states



Urbaczek et al, J Chem Inf Model (2014), 45 (3):756-766

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Generation of Tautomers and Protonation States

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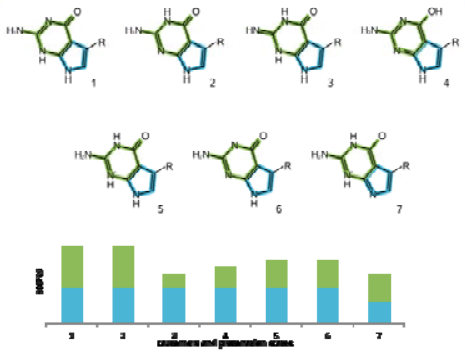
Step 4: State scoring



Bietz et al, JCheminf (2014), 6 (12):1-12

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ProToss Workflow Extended

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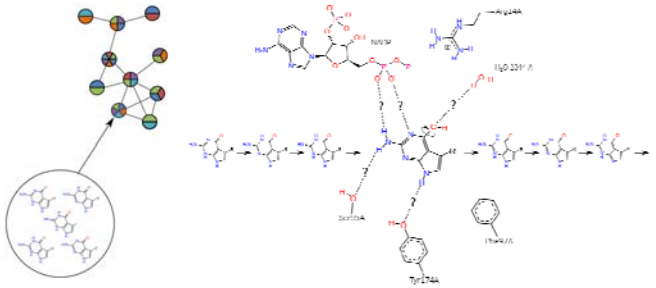
Step 5: Inclusion into ProToss' optimization procedure



Bietz et al, JCheminf (2014), 6 (12):1-12

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Results: Comparison on the sc-PDB

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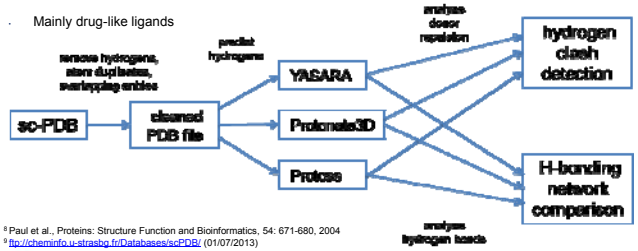
Dataset: sc-PDB[8-9]

- 8077 protein-ligand complexes (37 with errors excluded)
- Druggable binding-sites
- Mainly drug-like ligands



[8] Paul et al., Proteins: Structure Function and Bioinformatics, 54: 671-680, 2004
[9] ftp://cheminfo.u-strasbg.fr/Databases/scPDB/ (01/07/2013)

Bietz et al, JCheminf (2014), 6 (12):1-12

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Undesirable Donor Contacts in the Protein-Ligand Interface

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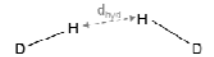
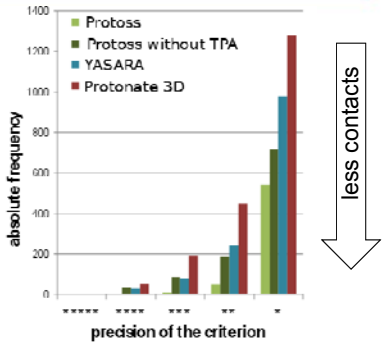


precision	d_{hyd} [Å]
*****	0.7
****	1.0
***	1.3
**	1.6
*	1.9



Bietz et al, JCheminf (2014), 6 (12):1-12

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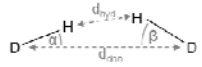
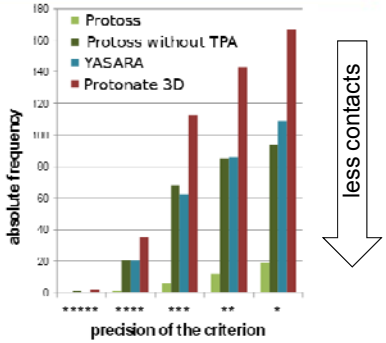
Undesirable Donor Contacts in the Protein-Ligand Interface

29



presision	d_{hyd} [A]	d_{don} [A]	α / β [°]
*****	0.7	2.6	30
****	1.0	2.9	30
***	1.3	3.2	30
**	1.6	3.5	30
*	1.9	3.8	30



Bietz et al, JCheminf (2014), 6 (12):1-12

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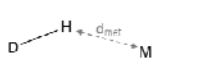
Undesirable Donor-Metal Contacts in the Protein-Ligand Interface

30



precision	d_{met} [A]
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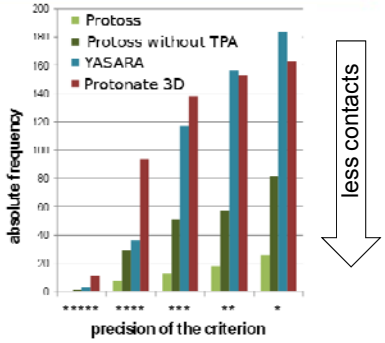
****	1.3
***	1.6
**	1.9
*	2.2



Bietz et al, JCheminf (2014), 6 (12):1-12

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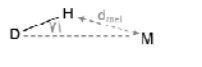
Undesirable Donor-Metal Contacts in the Protein-Ligand Interface

31



precision	d_{met} [A]	γ [°]
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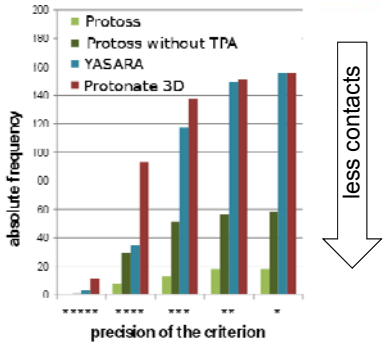
****	1.3	60
***	1.6	60
**	1.9	60
*	2.1	60



Bietz et al, JCheminf (2014), 6 (12):1-12

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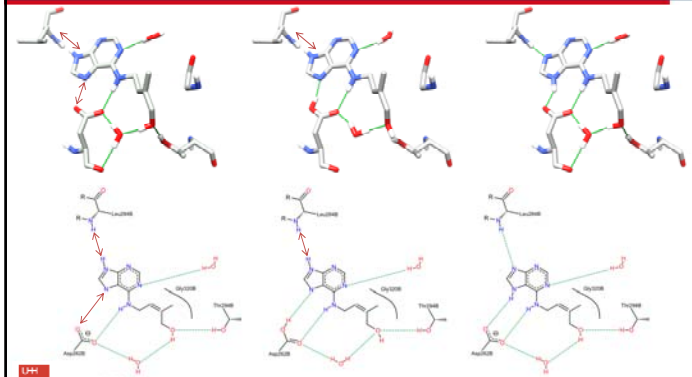
Undesirable Contacts in the Protein-Ligand Interface

32



Astex Diverse Set[9]: Protonation Comparison

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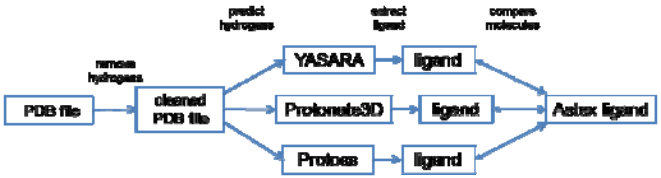

[9] Hartshorn et al., J.Med.Chem, 50(4): 726-741, 2007

Astex Diverse Set: Protonation Comparison

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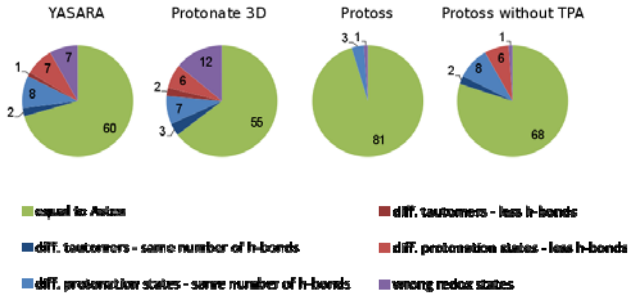

Astex Diverse Set: Protonation Comparison

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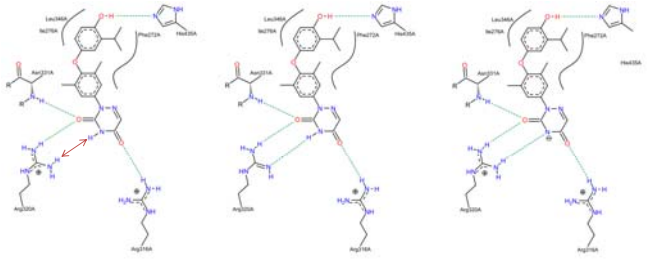

PDB code: 1n46

Astex Diverse Set: Protonation Comparison

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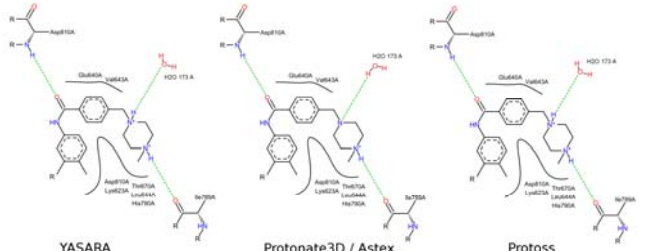

PDB code: 1t46

Astex Diverse Set: Protonation Comparison

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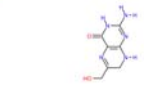
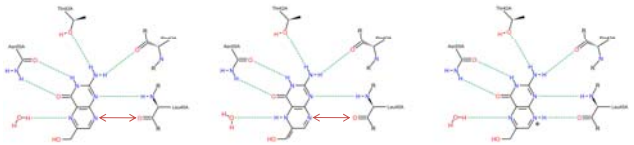


6-hydroxymethyl-7,8-dihydropterin



YASARA Protonate3D Protoss

PDB code: 1hq2

Astex Diverse Set: Protonation Comparison

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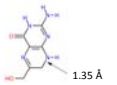
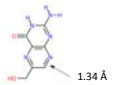
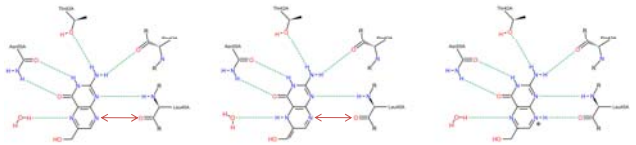


6-hydroxymethyl-7,8-dihydropterin (1hq2)



6-hydroxymethylpterin (3ip0)



YASARA Protonate3D Protoss

PDB code: 1hq2

Astex Diverse Set: Protonation Comparison

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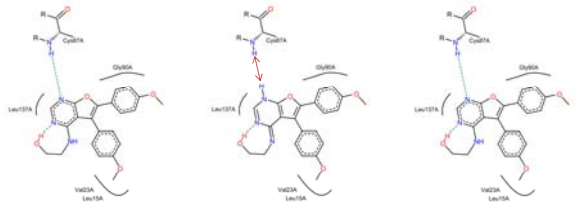

YASARA / Astex Protonate3D Protoss / Astex

PDB code: 2br1

ProToss Runtime Evaluation

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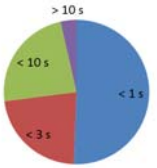
- Whole complex optimization on the Astex Diverse Set
  (including all ligands, co-factors and water molecules)
- Runtimes include
  - File IO
  - Complex preprocessing
  - Network optimization
- Intel® Core™ i7-2600 CPU (3.4 GHz)
  and 8 GB memory
- Mean: 2.47 s
- Median 0.93 s



PHASE 3: Scoring Protein-Ligand Complexes

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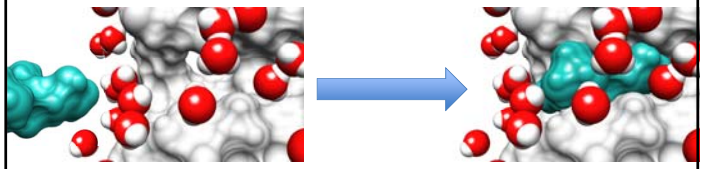

Schneider et al, *J. Comput. Aided Mol. Des.*, **27(1)**, 15-29 (2013)

HYDE – Towards a Consistent Description of Hydrogen Bonding, Dehydration and the Hydrophobic Effect

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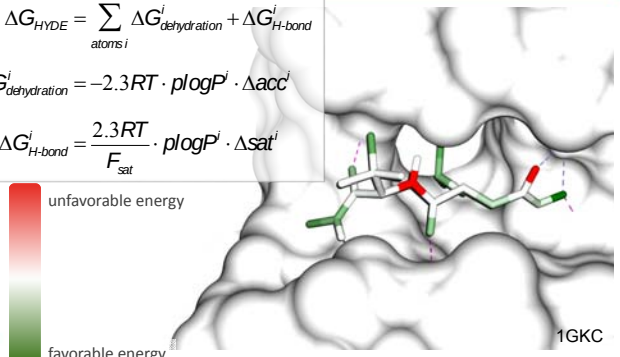
$$\Delta G_{HYDE} = \sum_{atoms\ i} \Delta G^{i}_{dehydration} + \Delta G^{i}_{H\text{-}bond}$$

$$\Delta G^{i}_{dehydration} = -2.3RT \cdot plogP^{i} \cdot \Delta acc^{i}$$

$$\Delta G^{i}_{H\text{-}bond} = \frac{2.3RT}{F_{sat}} \cdot plogP^{i} \cdot \Delta sat^{i}$$



Schneider et al, J.Comput.-Aided Mol. Des. **26** 2011: 701-723

HYDE Benchmarks

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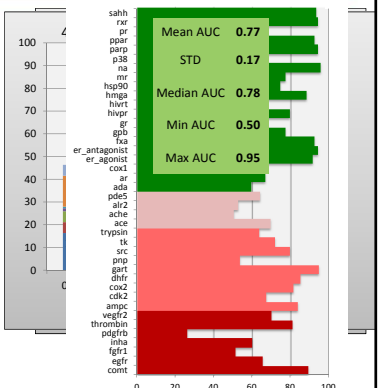
- PDBbind 2007 coreset[1] ➔ Binding affinity prediction
- Astex diverse set[2] ➔ Redocking experiments
- Dataset of Useful Decoy[3] ➔ Virtual screening study

[1] Wang R. et al, JMedChem, 2004, 2005
[2] Hartshorn M. J. et al , JMedChem, 2007
[3] Huang N. et al, JMedChem, 2006
[4] Schneider N. et al, JCAMD, 2011



Estimating the Cost of a Single Hydrogen Bond

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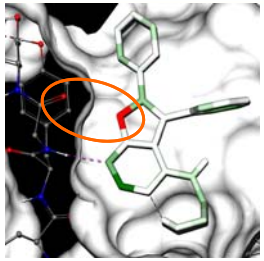
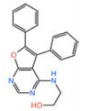
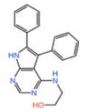


2BRB

ΔG= -28 kJ/mol

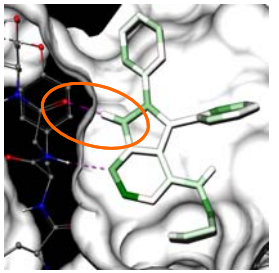
ΔG_{HYDE} = -22 kJ/mol





ΔG_{HYDE} = -32 kJ/mol

ΔG= -34 kJ/mol



* Foloppe N. et al., JMedChem 2005

A Few Things to Remember

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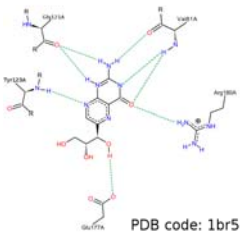
- PDB files are models – consult electron density.
- Perception of chemical structures from PDB is difficult – cross-check with literature.
- Assigning protonation and tautomeric states is not simpler
  - cross-check the results of automatic assignment procedures
- Tools like ProToss help in large scale applications in which manual curation is not possible.



Contributions / Acknowledgements

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- **Stefan Bietz**
  ProToss development
- **Sascha Urbaczek**
  Tautomer generation
- **Tobias Lippert**
  First version of ProToss
- **Nadine Schneider**
  Hyde development
- **Benjamin Schulz**
  ProToss development, testing and validation
- **Holger Claussen**
  Testing, testing …
- **Christian Lemmen**

Software Availability

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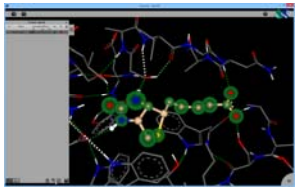

More on ProToss
http://protoss.zbh.uni-hamburg.de/
ProToss in action:
http://www.biosolveit.de/SeeSAR/

More on tools and servers from ZBH:
http://www.zbh.uni-hamburg.de/AMD
http://www.biosolveit.de/techtransfer