HYDE - Scoring for Lead Optimization

HYDEing the False Positives

Nadine Schneider

Matthias Rarey

Center for Bioinformatics Hamburg

Christian Lemmen

Bayer CropScience

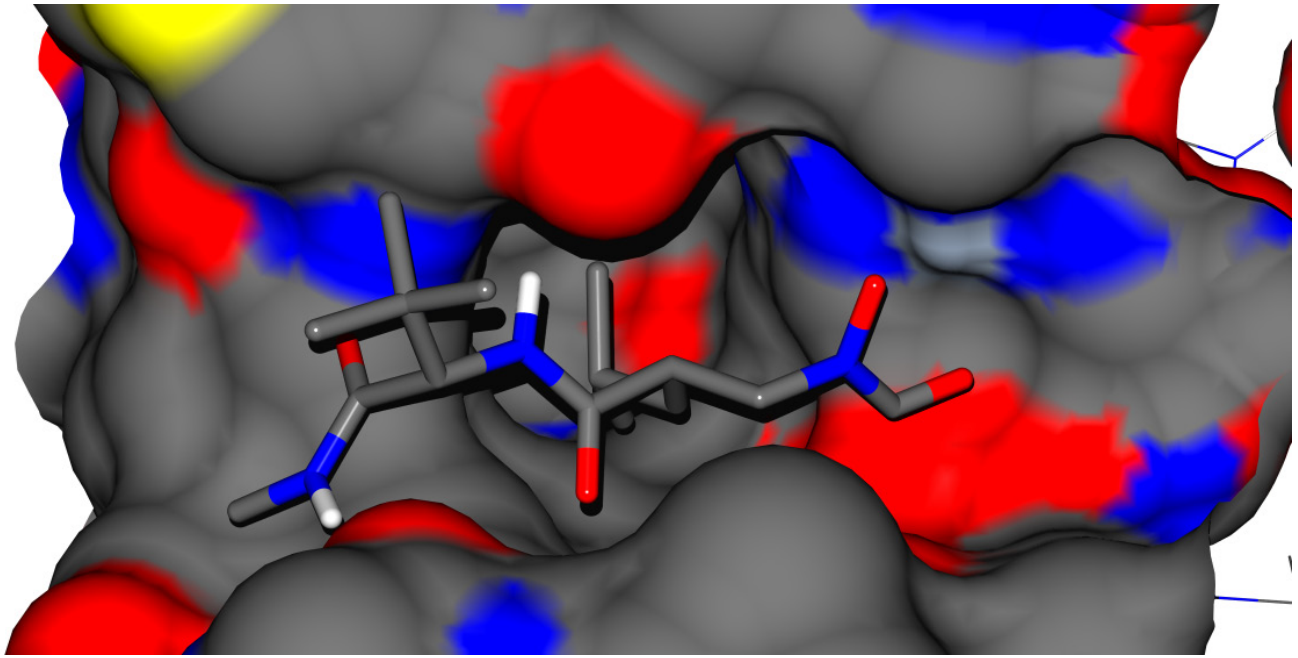
Gudrun Lange

Robert Klein

HYDE = **HY**drogen bonding and **DE**solvation

"Thus, a primary question in molecular design should be which donors and acceptors need to be satisfied and not how more hydrogen bonds can be formed."

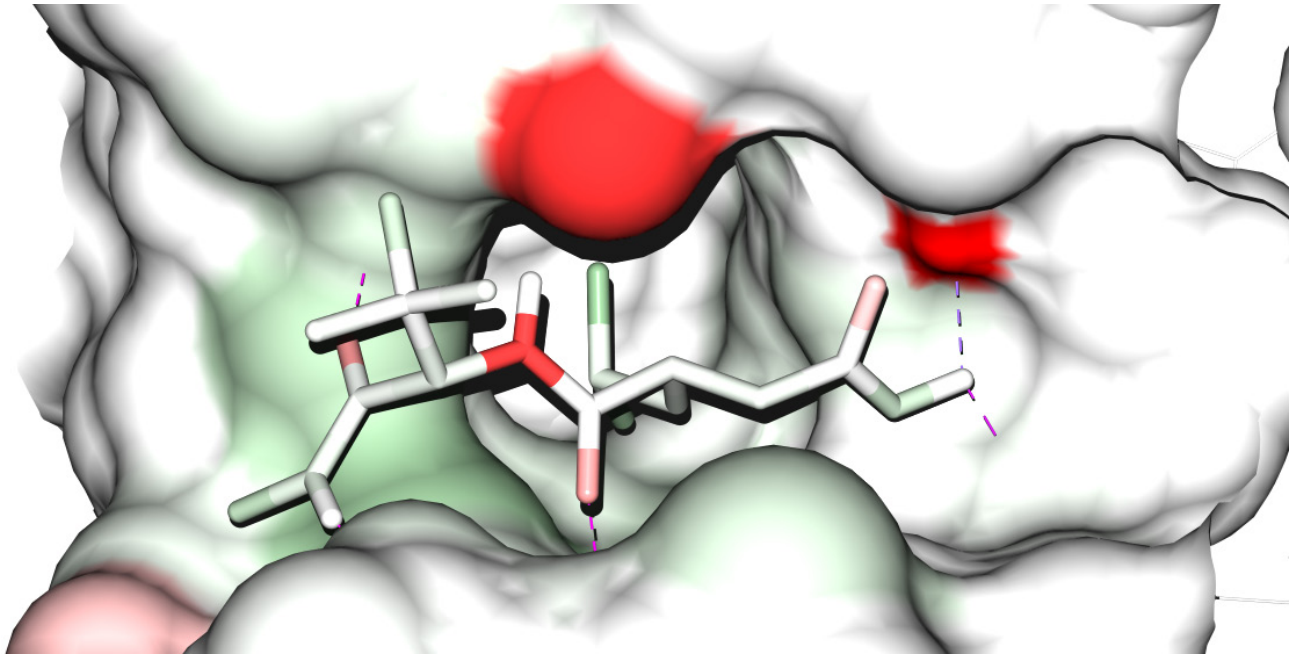
(Martin Stahl, A medicinal chemist's guide to molecular interactions, JMedChem, 2010)



PDB: 1GKC

HYDE = **HY**drogen bonding and **DE**solvation

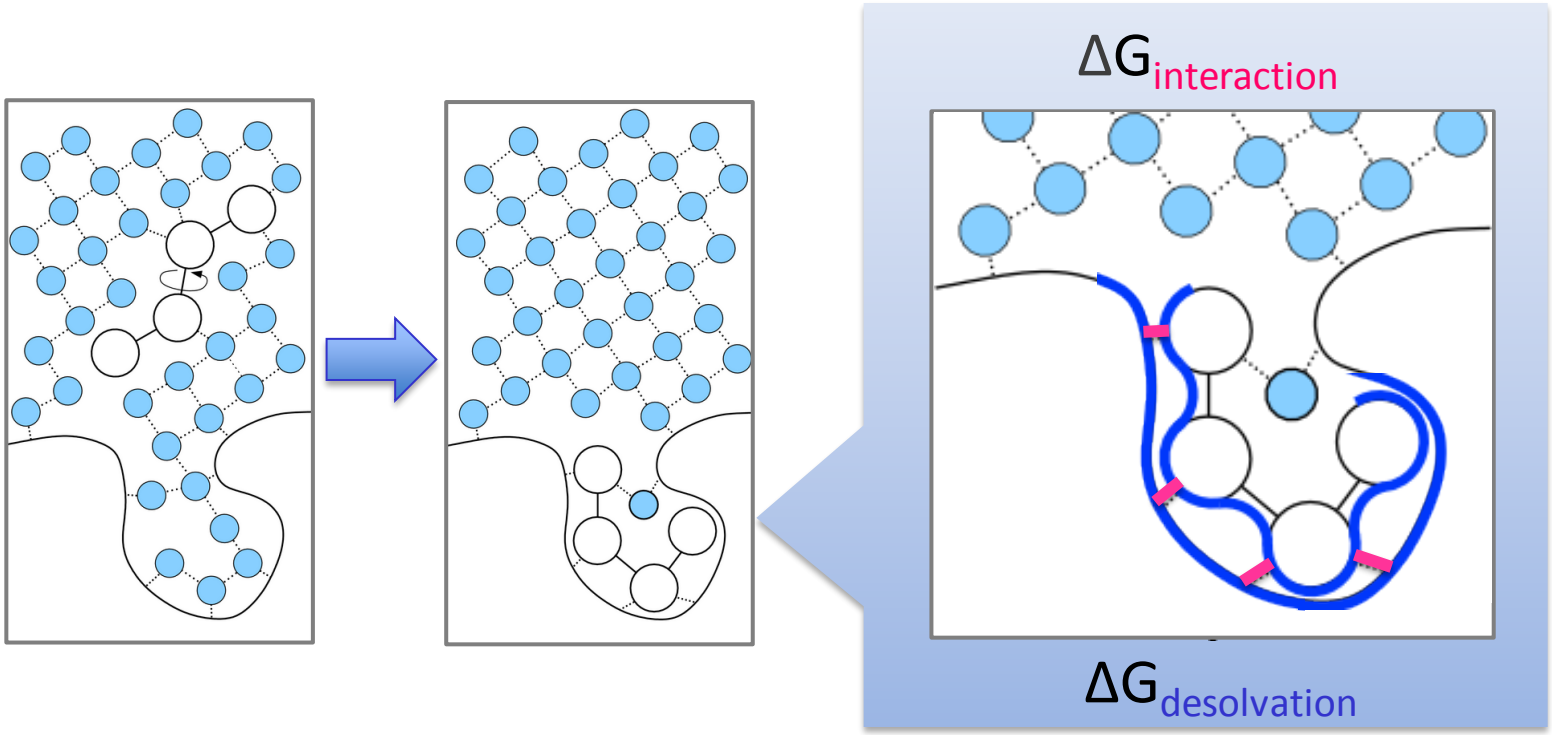
HYDE describes consistently hydrogen bonds, the hydrophobic effect and desolvation



PDB: 1GKC

HYDE Scoring Function* - Concept

*Reulecke et al., ChemMedChem, 2008



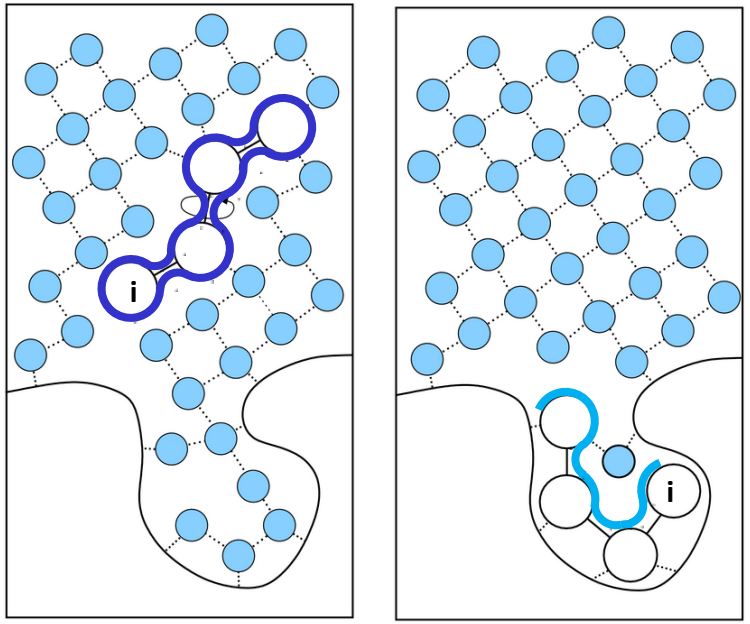
$$\Delta G_{binding} = \sum_{atom\ i} \Delta G^{i}_{desolvation} + \Delta G^{i}_{interaction}$$

HYDE – Atom-based Desolvation

$$\Delta G^{i}_{\text{desolvation}} = -2.3RT\left(\text{acc}^{i}_{\text{free}} - \text{acc}^{i}_{\text{bound}}\right) \text{plogP}_{i}$$

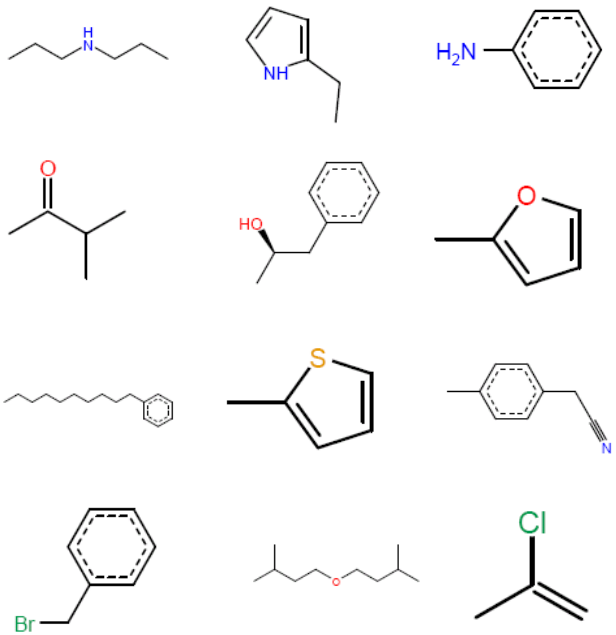
- **plogP$_i$**
  Atom solvation parameter derived from octanol/water partition coefficients

- **acc^i**
  Solvent accessibility of atom *i* with respect to the chemical model



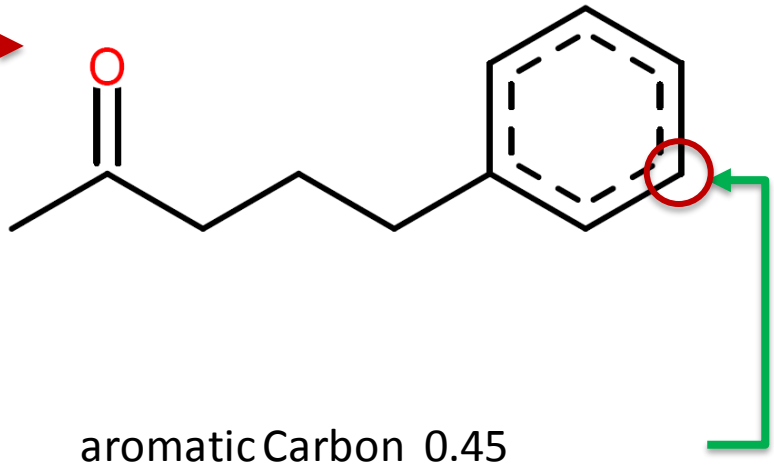
plogP$_i$ – Atom-based Hydrophobicity

- Calibration dataset:
  - 458 small, simple molecules taken from the Starlist*
  - 21 plogP descriptors used



Oxygen sp2 -1.42

$\Delta G_{desolvation}$ = 8.09 kJ/mol



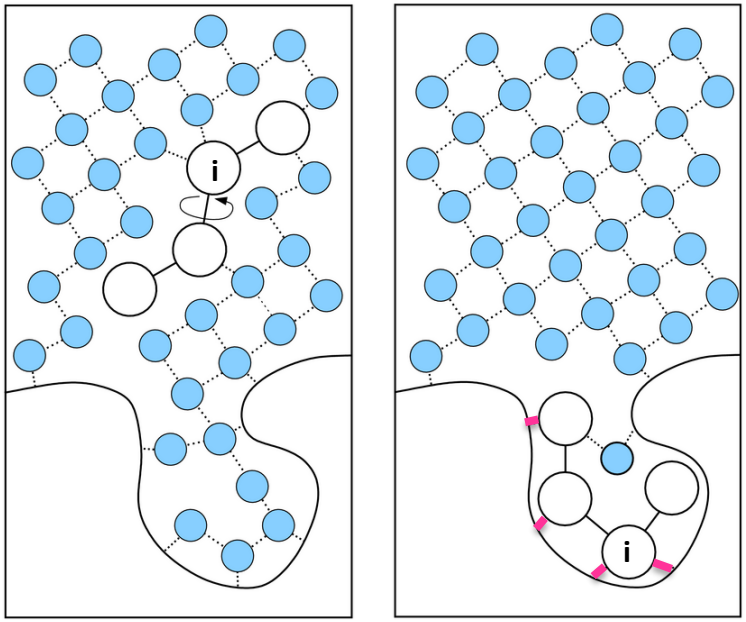
aromatic Carbon 0.45

$\Delta G_{desolvation}$ = -1.37 kJ/mol

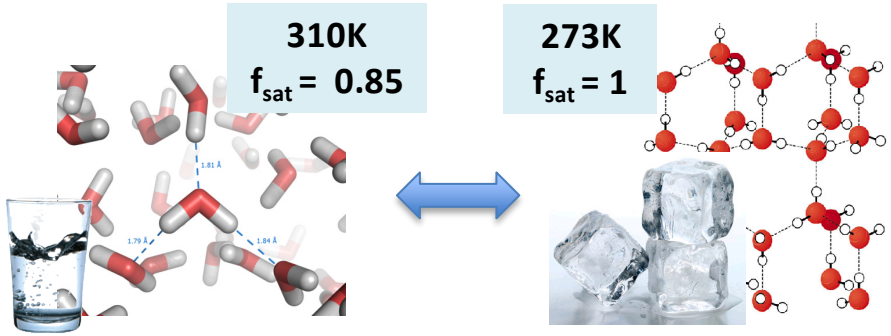
* Hansch C. et al., American Chemical Society, 1995

HYDE – Atom-based Interaction

$$\Delta G^{i}_{\text{interaction}} = \frac{2.3RT}{f_{\text{sat}}}\left(\text{sat}^{i}_{\text{bound}} - \text{sat}^{i}_{\text{free}}\right)\ \text{plogP}_{i}$$



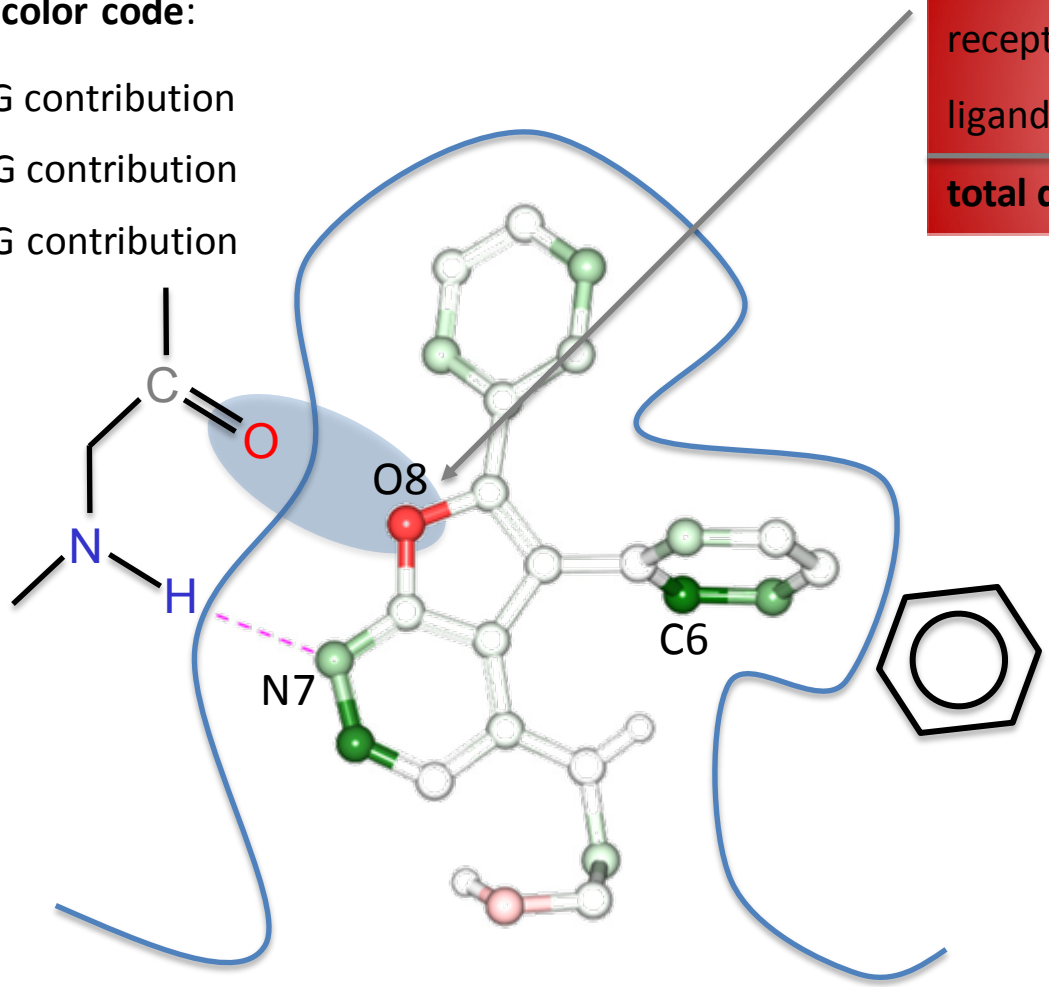
- **sat^{i}**
  Number of intermolecular and intramolecular interactions (degree of saturation)
- **f_{sat}**
  Saturation factor describing the incomplete saturation of the hydrogen bond network in solvent water



Binding Mode Analysis with HYDE

HYDE color code:

- +ΔG contribution
- -ΔG contribution
- no ΔG contribution

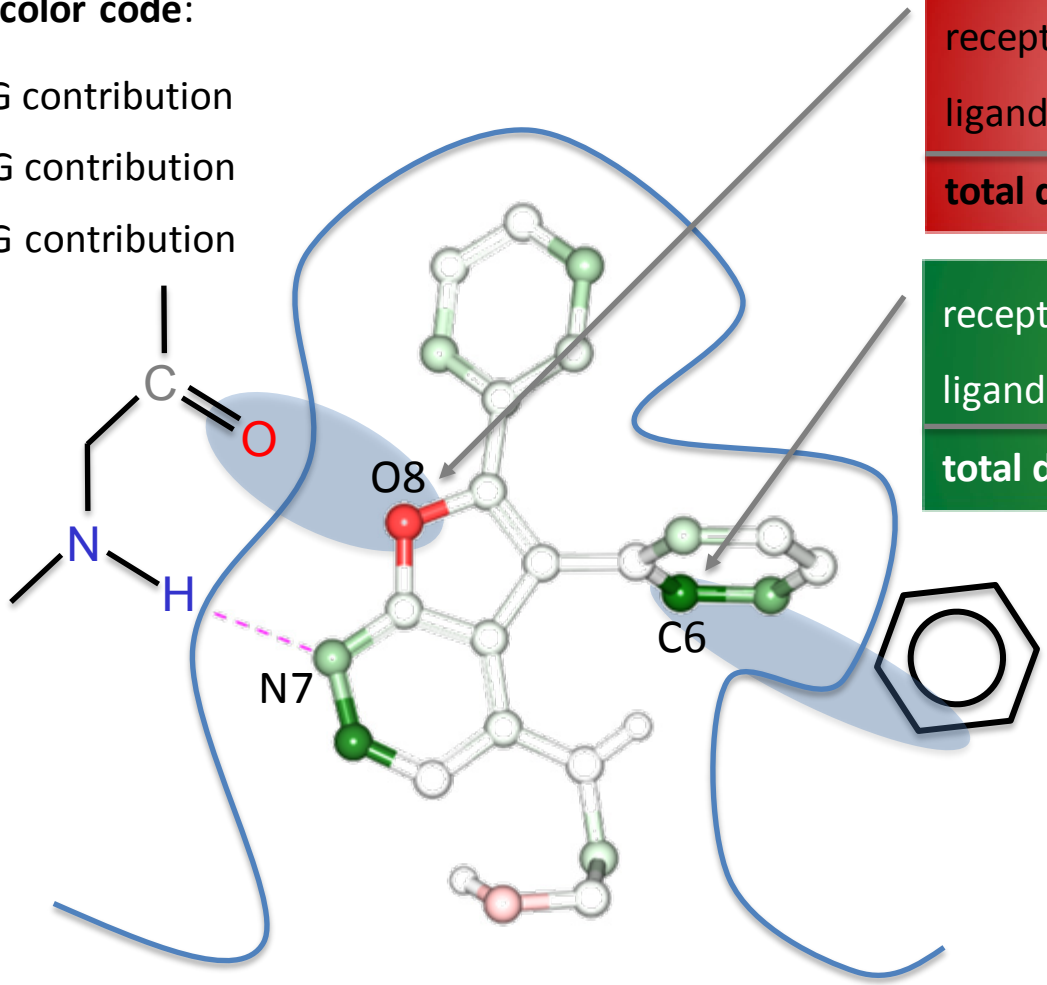


receptor carbonyl oxygen	8.2 kJ/mol
ligand aromatic oxygen	2.4 kJ/mol
total desolvation cost	10.6 kJ/mol

Binding Mode Analysis with HYDE

HYDE color code:

- +ΔG contribution
- -ΔG contribution
- no ΔG contribution



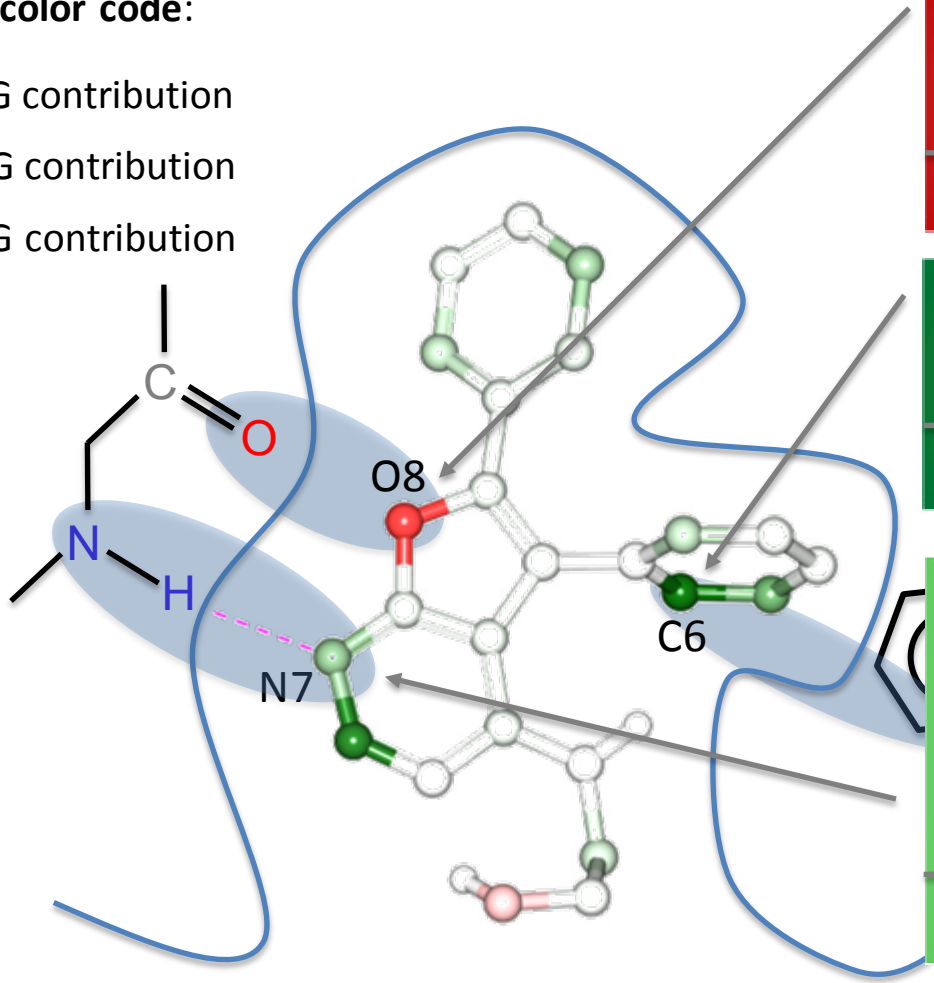
receptor carbonyl oxygen	8.2 kJ/mol
ligand aromatic oxygen	2.4 kJ/mol
total desolvation cost	10.6 kJ/mol

receptor aromatic carbons	-5.2 kJ/mol
ligand aromatic carbon	-2.0 kJ/mol
total desolvation gain	-7.2 kJ/mol

Binding Mode Analysis with HYDE

HYDE color code:

- +ΔG contribution
- -ΔG contribution
- no ΔG contribution



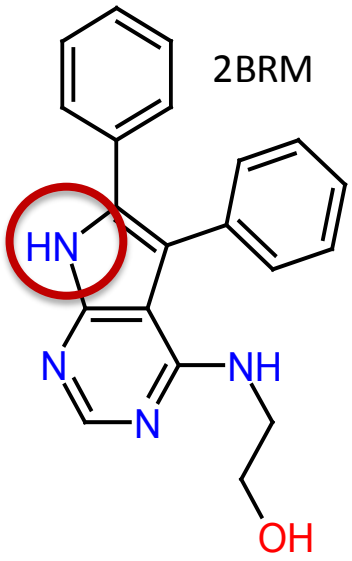
receptor carbonyl oxygen	8.2 kJ/mol
ligand aromatic oxygen	2.4 kJ/mol
total desolvation cost	10.6 kJ/mol

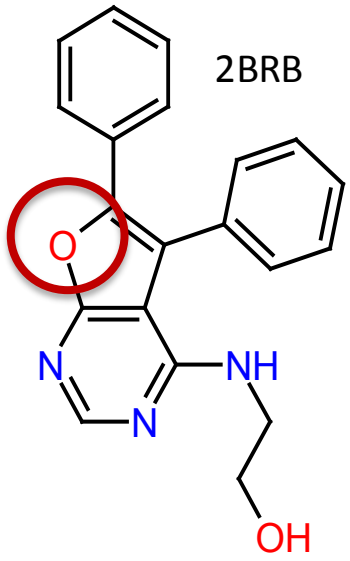
receptor aromatic carbons	-5.2 kJ/mol
ligand aromatic carbon	-2.0 kJ/mol
total desolvation gain	-7.2 kJ/mol

receptor amid nitrogen	6.3 kJ/mol
	-7.4 kJ/mol
ligand aromatic nitrogen	6.4 kJ/mol
	-7.5 kJ/mol
total energy	-2.2 kJ/mol

The Cost of a Hydrogen Bond

Structure-based design of novel Checkpoint kinase 1 inhibitors: Insights into hydrogen bonding and protein-ligand affinity *

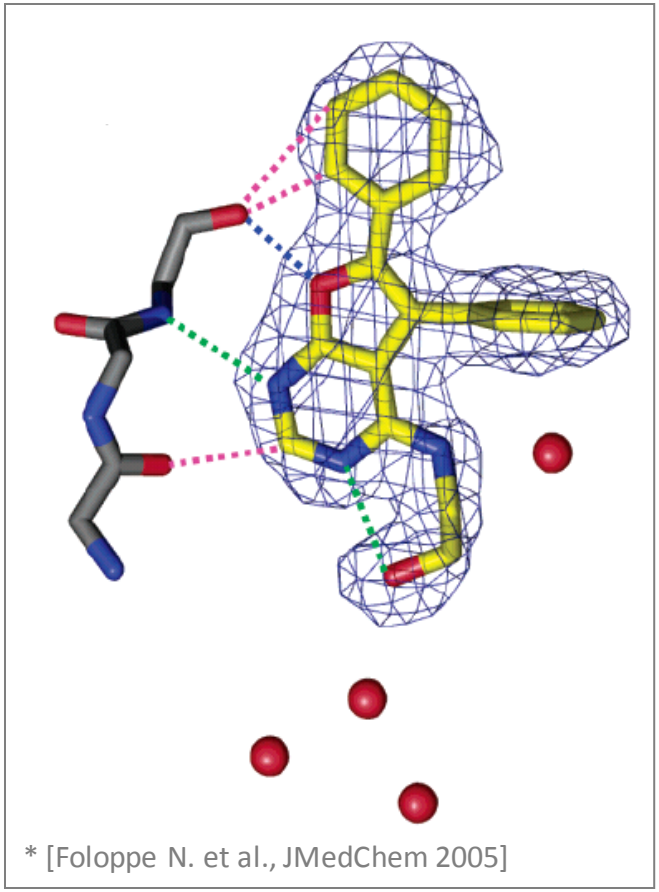




K_i = 1.3 µM SD ± 1.3 µM

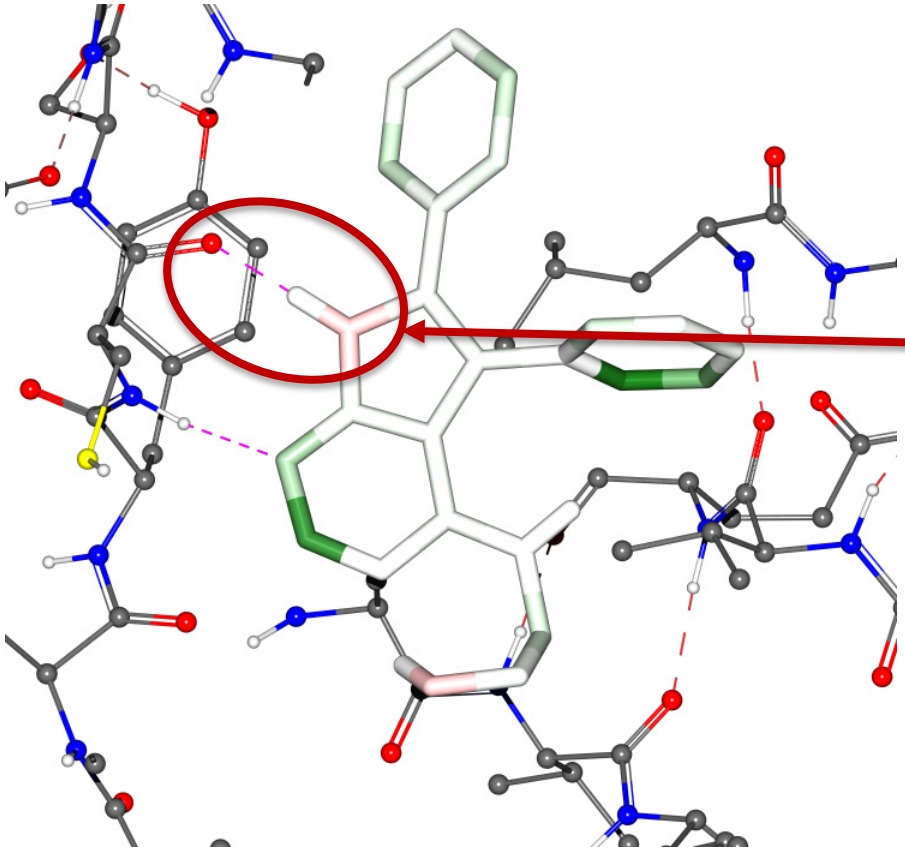
K_i = 13.7 µM SD ± 4.5 µM

ΔΔG 6 kJ/mol



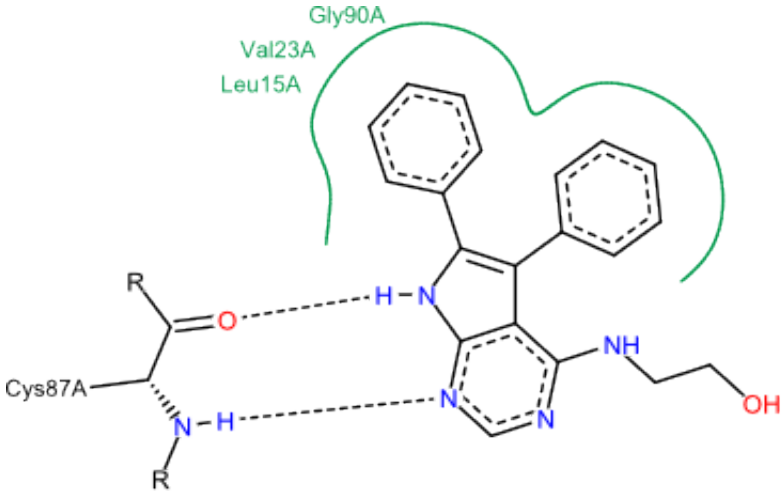
* [Foloppe N. et al., JMedChem 2005]

The Cost of a Hydrogen Bond

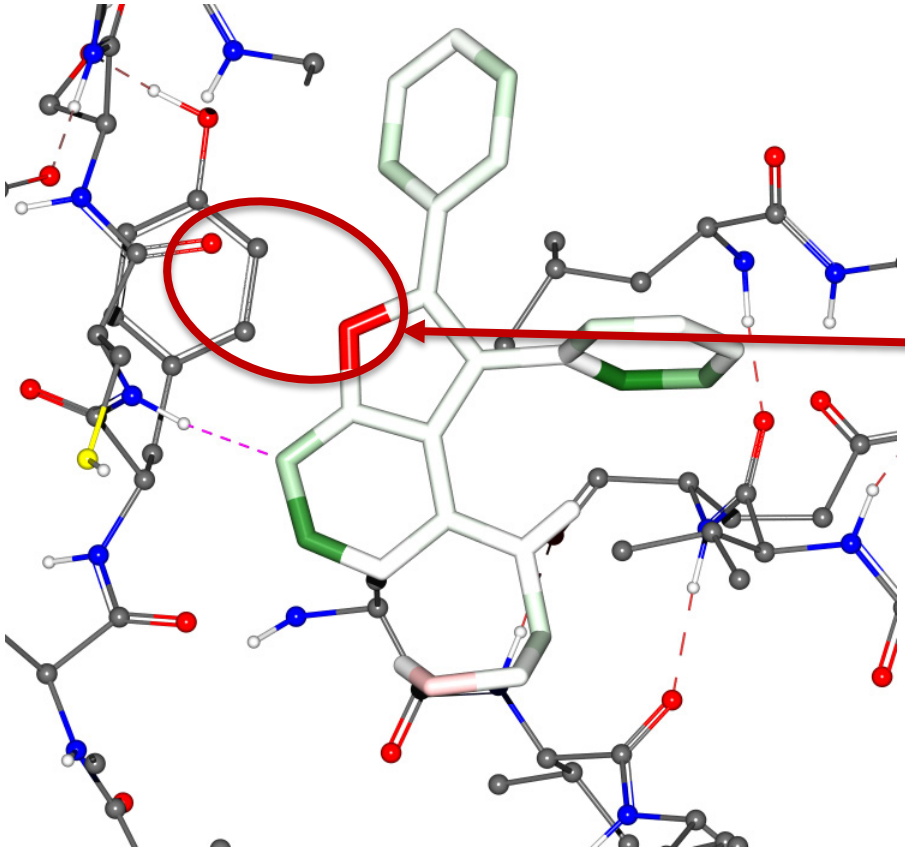


$\Delta G_{experimental}$ -34 kJ/mol

ΔG_{HYDE} -30 kJ/mol



The Cost of a Hydrogen Bond

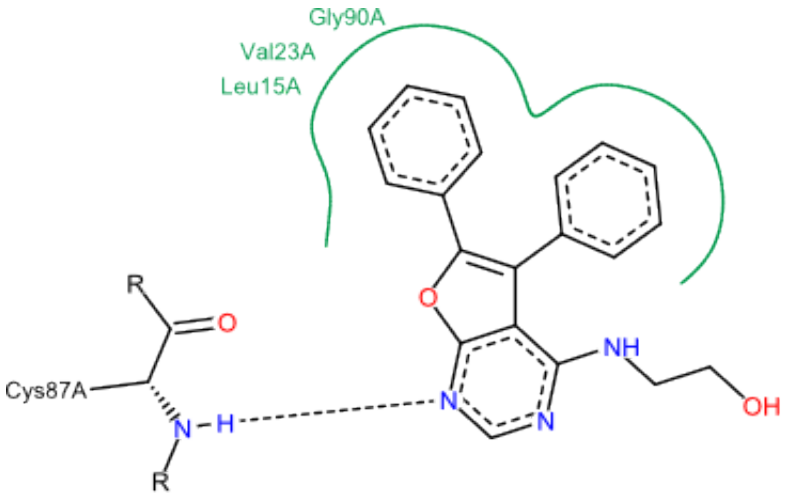


$\Delta G_{experimental}$ -28 kJ/mol

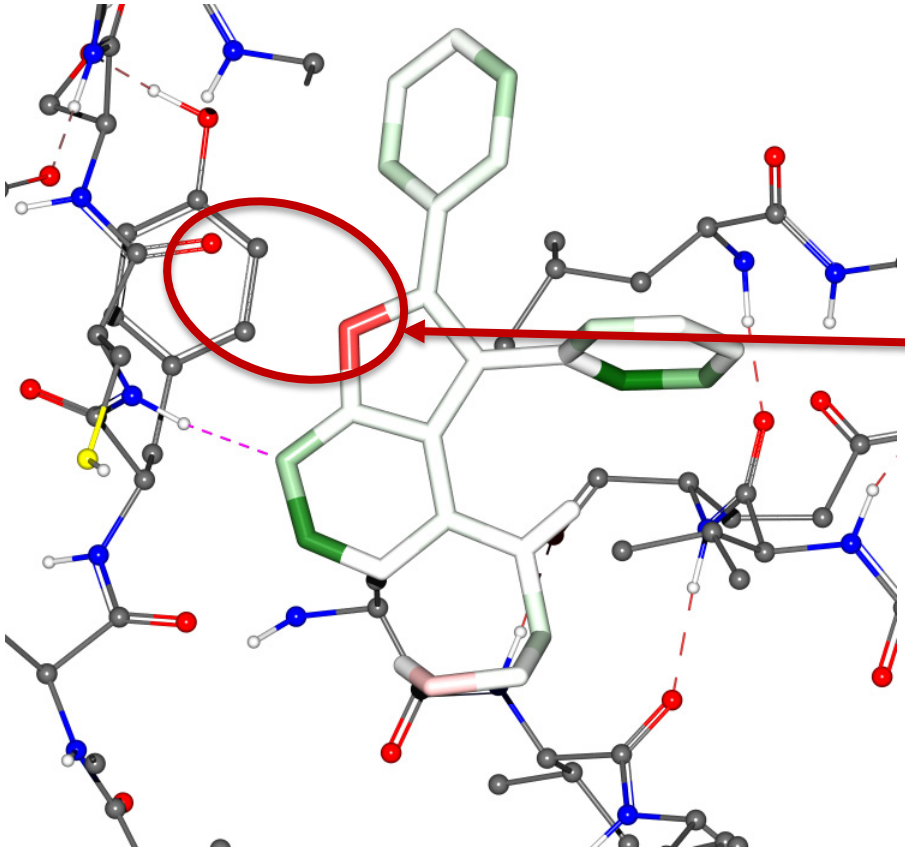
ΔG_{HYDE} -22 kJ/mol

Lost hydrogen bond:

ΔG_i = +10 kJ/mol



The Cost of a Hydrogen Bond

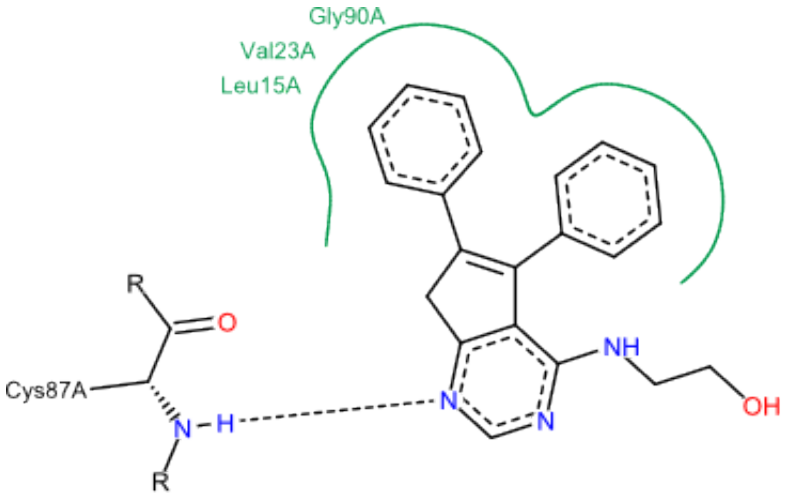


$\Delta G_{experimental}$

ΔG_{HYDE} -28 kJ/mol

Lost hydrogen bond:

ΔG_i = +6 kJ/mol



HYDE – Ranking Power

* Cheng T et al., JChemInfMod, 2009

Table 4. Success Rates of 16 Scoring Functions in "Ranking Power" Evaluation on the Primary Test Set *

scoring function[a]	success rates (%) on original complex structures	success rates (%) on optimized complex structures
X-Score::HSScore	58.5	52.3
DS::PLP2	53.8	46.2
DrugScore^{CSD}	52.3	49.2
SYBYL::ChemScore	47.7	52.3
SYBYL::D-Score	46.2	46.2
SYBYL::G-Score	46.2	36.9
GOLD::ASP	43.1	49.2
DS::LUDI3	43.1	43.1
DS::Jain	41.5	35.4
DS::PMF	41.5	35.4
SYBYL::PMF-Score	38.5	33.8
GOLD::ChemScore	36.9	41.5
DS::LigScore2	35.4	47.7
GlideScore-XP	33.8	35.4
by NHA[b]	32.3	32.3
SYBYL::F-Score	29.2	36.9
GOLD::GoldScore	23.1	38.5

[a] Scoring functions are ranked by their success rates based on original complex structures. [b] Ranking by the number of heavy atoms on each ligand.

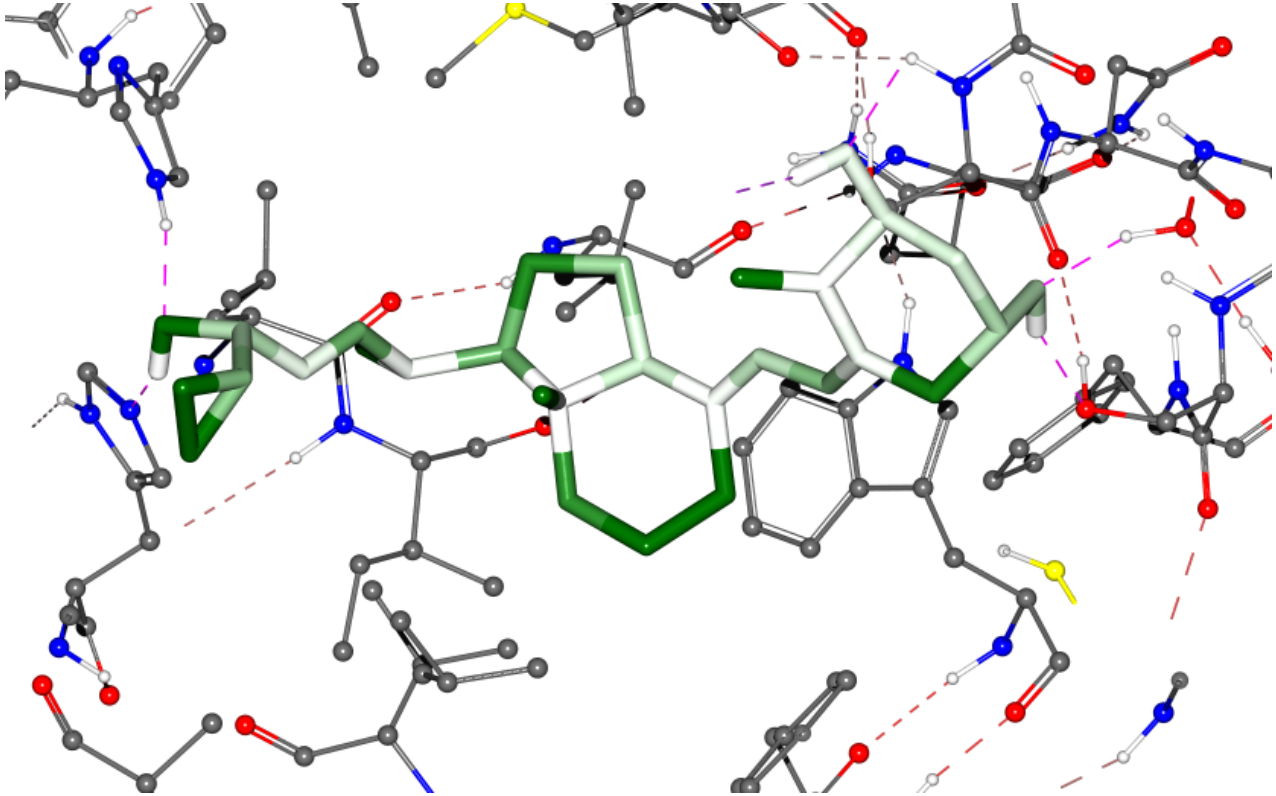
- PDBbind Coreset 2007:

  195 complexes with high resolution and measured K_i values

- HYDE ranks 29 of the 65 cases in the right order
- Sucuess rate: 45 %

HYDE on Astex Dataset*

*Hartshorn M. J. et al , JMedChem, 2007



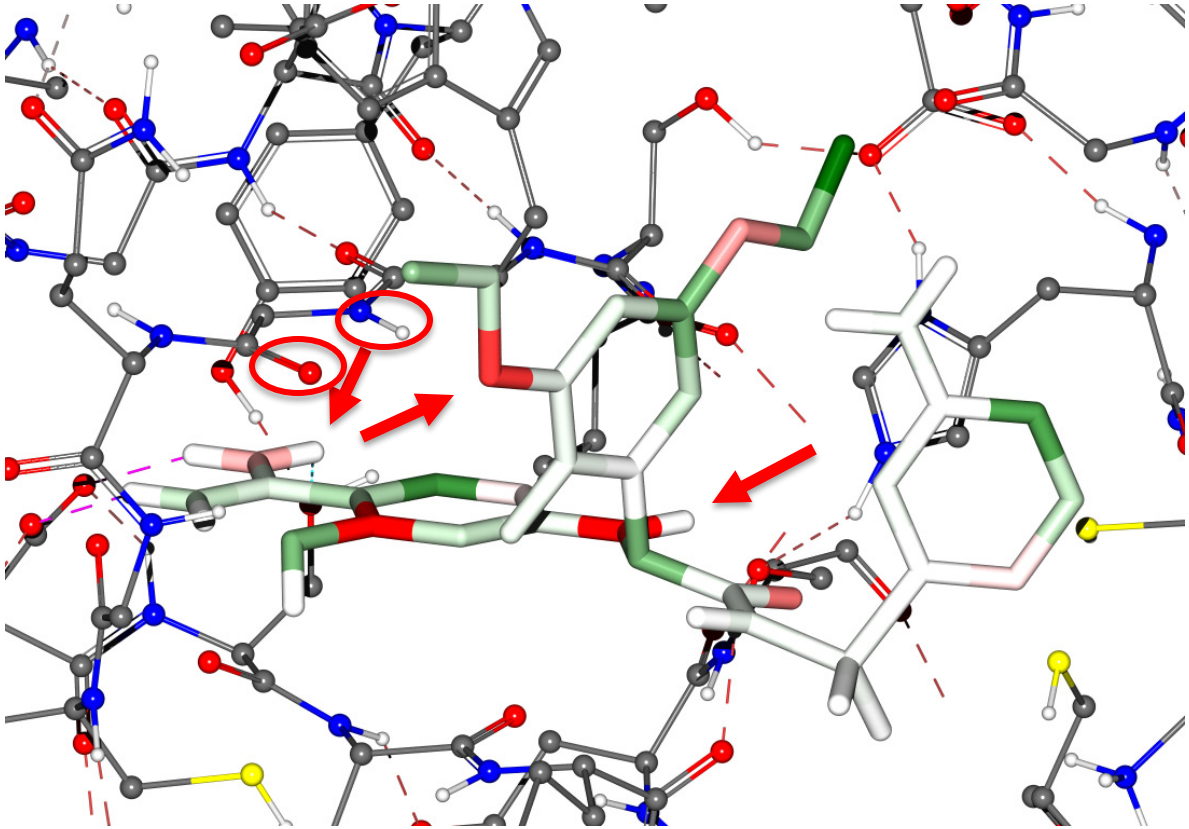
1S19

vitamin D nuclear receptor
Calcipotriol

$\Delta G_{experimental}$	-51 kJ/mol
ΔG_{HYDE}	-95 kJ/mol

huge hydrophobic ligand
perfect binding mode
EC50 value instead of K_i

HYDE on Astex Dataset



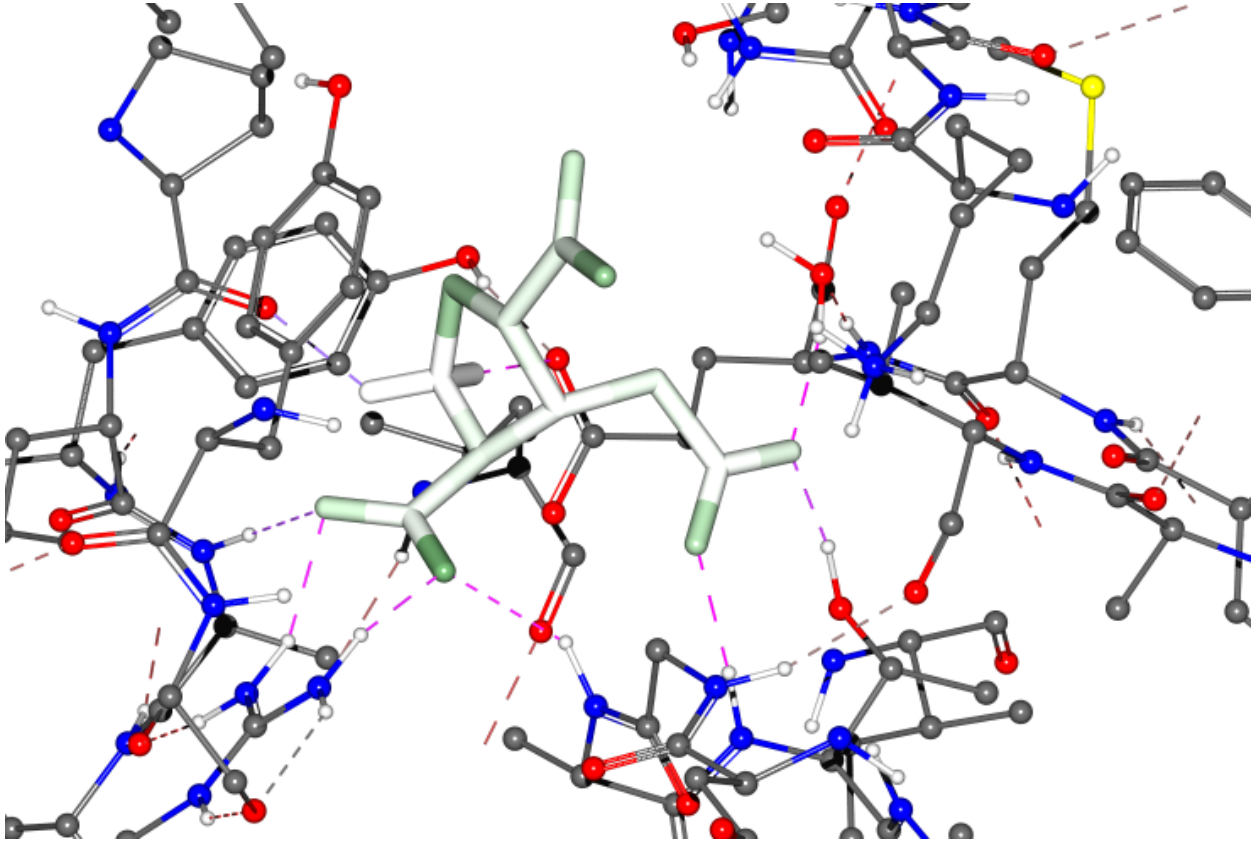
1YGC

factor VIIa
G17905

$\Delta G_{experimental}$	-54 kJ/mol
ΔG_{HYDE}	-18 kJ/mol

many unsaturated polar atoms in the interface

HYDE on Astex Dataset



1TT1

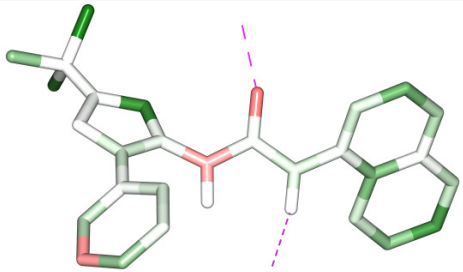
glutamate receptor 6
kainate

$\Delta G_{experimental}$	-23 kJ/mol
ΔG_{HYDE}	-26 kJ/mol

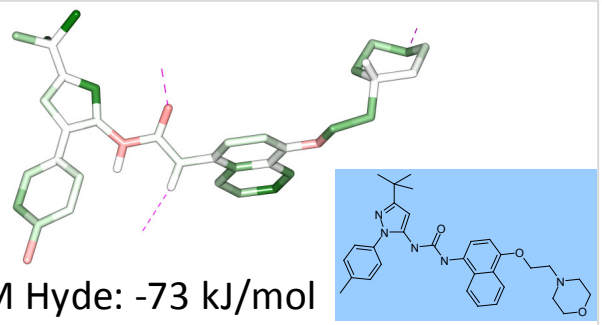
several excellent hydrogen bonds

HYDE – Compound Affinity Categorization

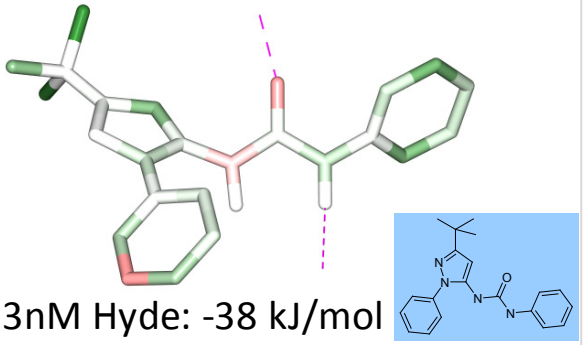
Regan et al., JMedChem, 2002



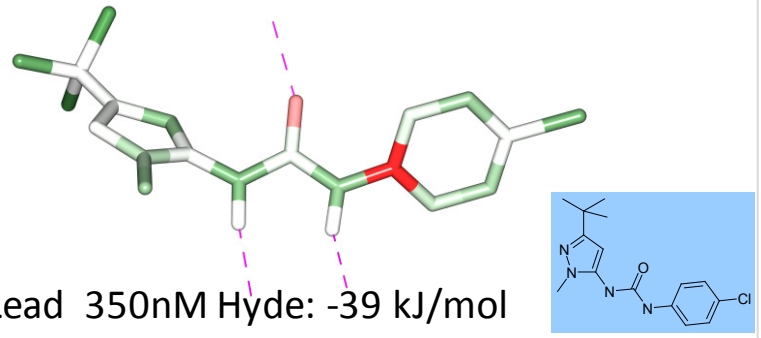
Cmpd72 10nM Hyde: -52 kJ/mol



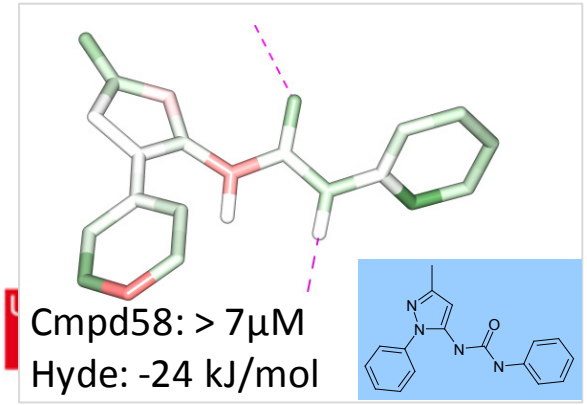
BIRB 0.1nM Hyde: -73 kJ/mol



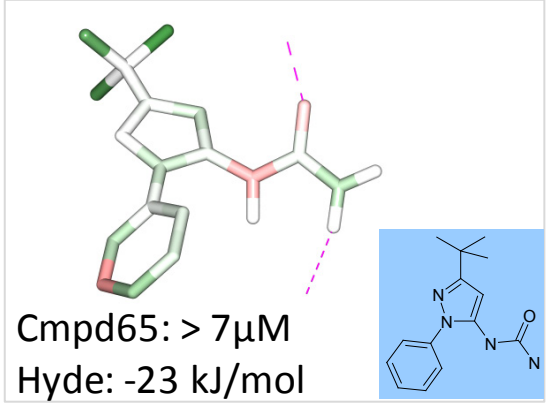
Cmpd46 13nM Hyde: -38 kJ/mol



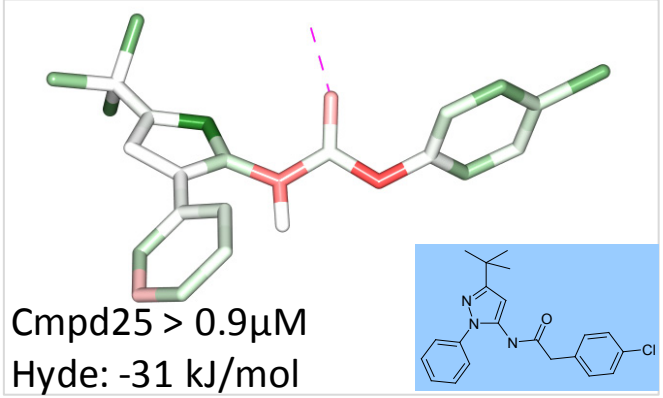
Lead 350nM Hyde: -39 kJ/mol



Cmpd58: > 7µM
Hyde: -24 kJ/mol



Cmpd65: > 7µM
Hyde: -23 kJ/mol

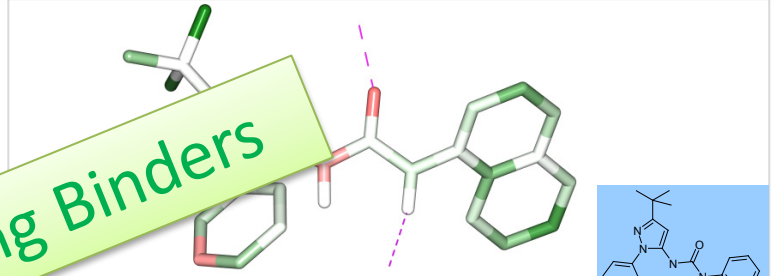


Cmpd25 > 0.9µM
Hyde: -31 kJ/mol

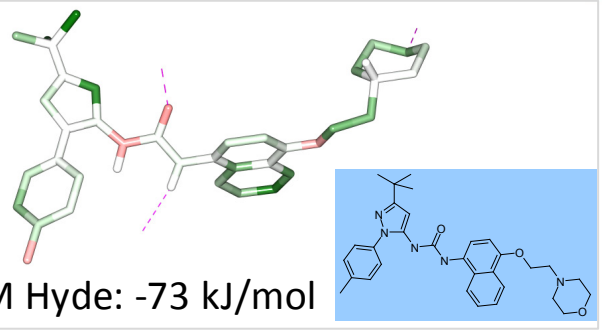
HYDE – Compound Affinity Categorization

Regan et al., JMedChem, 2002

Strong Binders

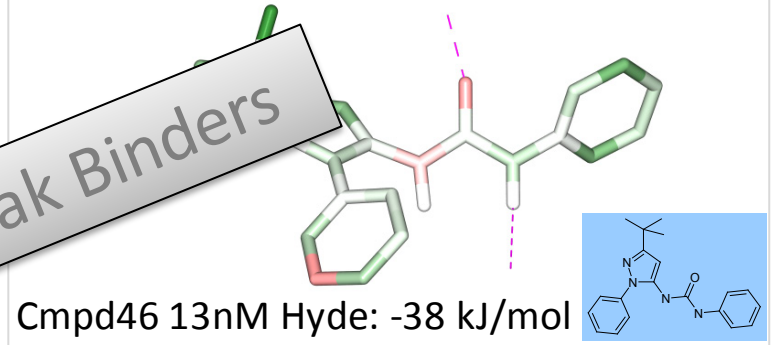


Cmpd72 10nM Hyde: -52 kJ/mol

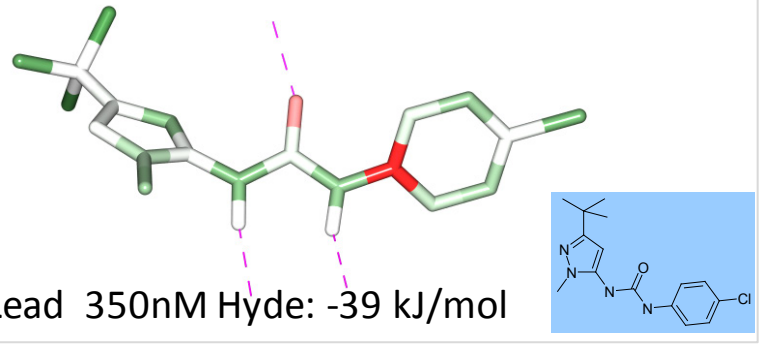


BIRB 0.1nM Hyde: -73 kJ/mol

Weak Binders

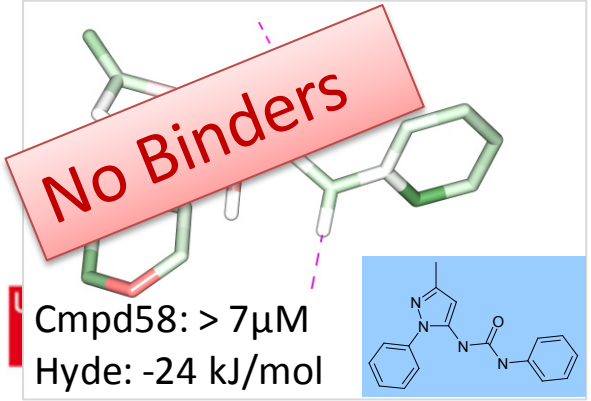


Cmpd46 13nM Hyde: -38 kJ/mol

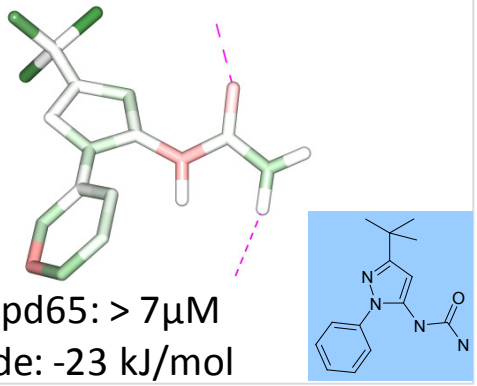


Lead 350nM Hyde: -39 kJ/mol

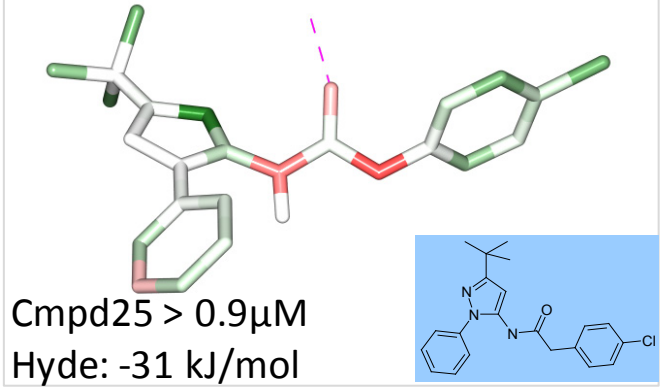
No Binders



Cmpd58: > 7µM
Hyde: -24 kJ/mol



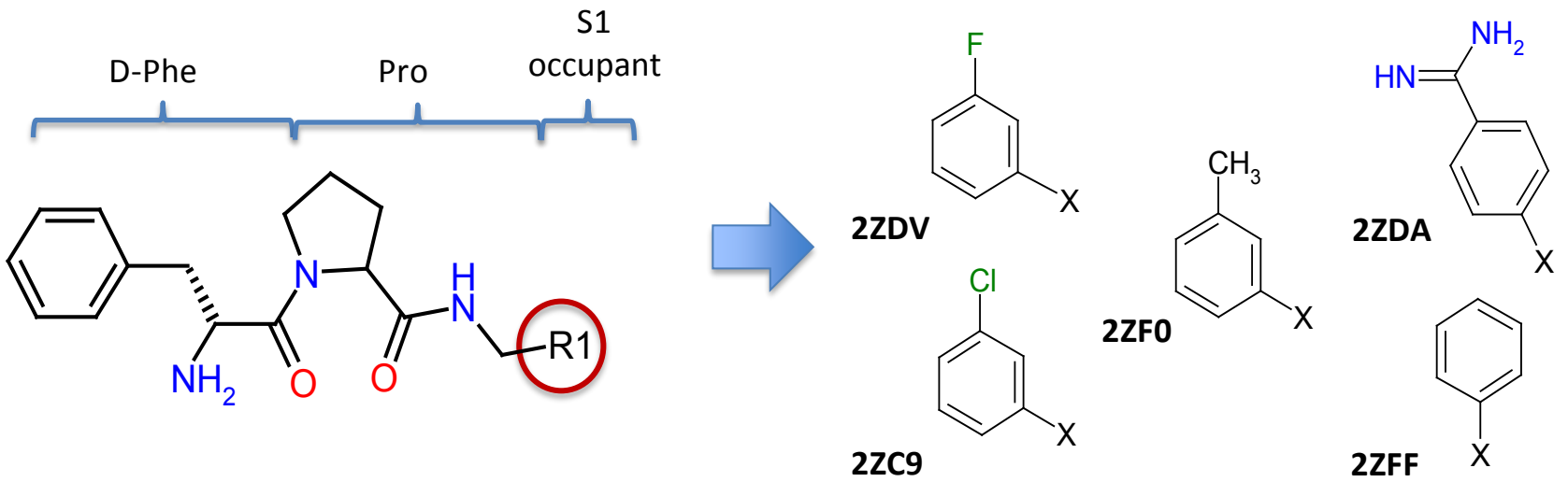
Cmpd65: > 7µM
Hyde: -23 kJ/mol



Cmpd25 > 0.9µM
Hyde: -31 kJ/mol

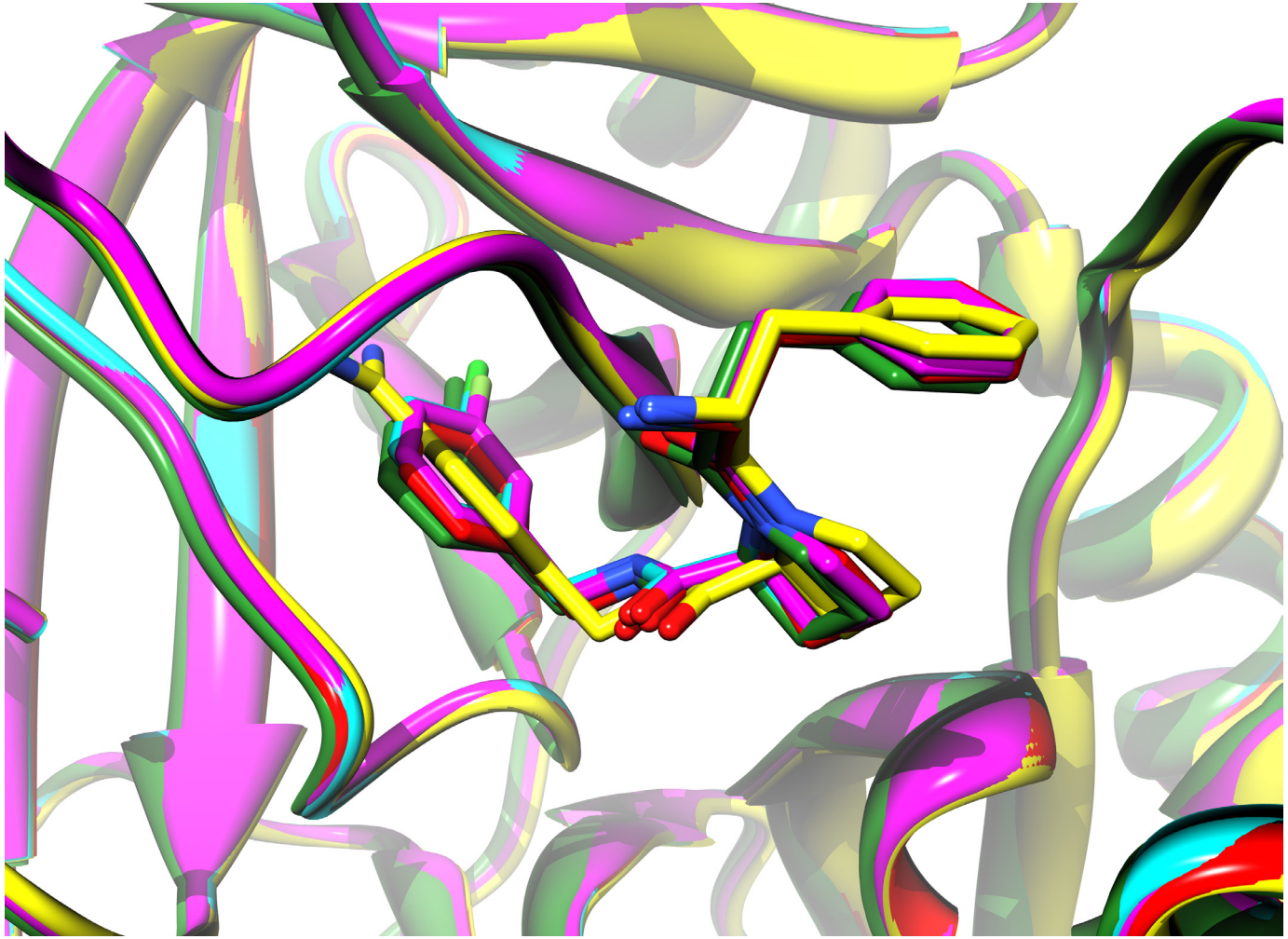
Thermodynamic Analysis of Thrombin Inhibitors

More than a Simple Lipophilic Contact: A Detailed Thermodynamic Analysis of Nonbasic Residues in the S1 Pocket of Thrombin [Baum et al., JMB, 2009]

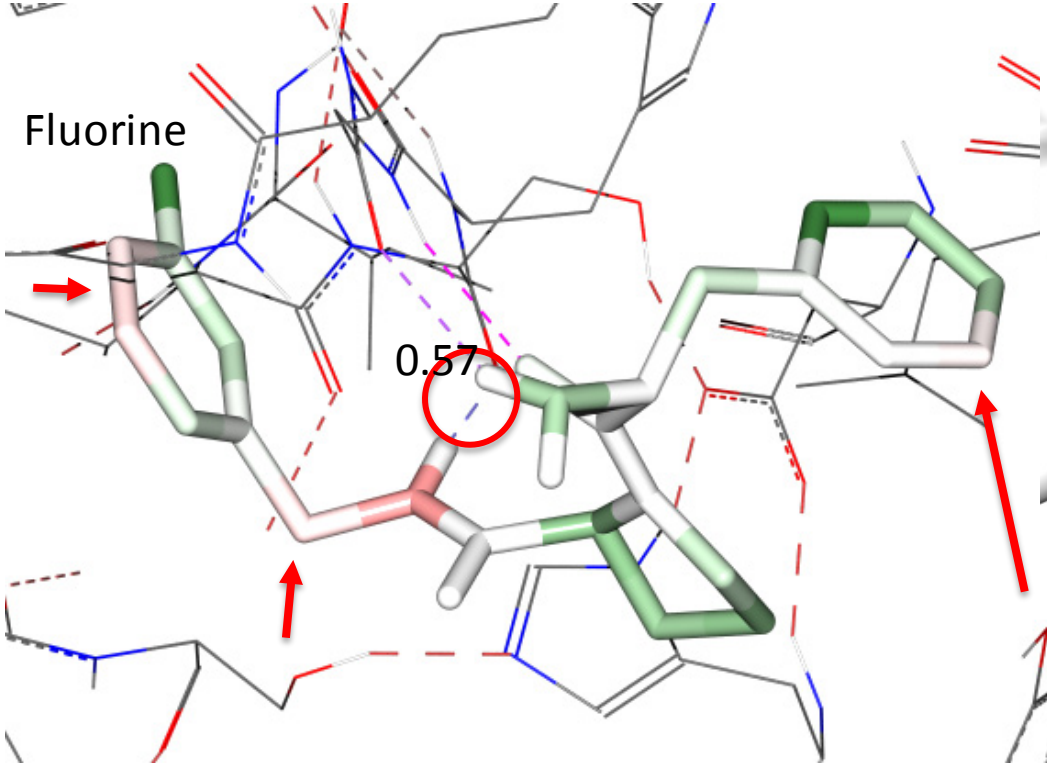


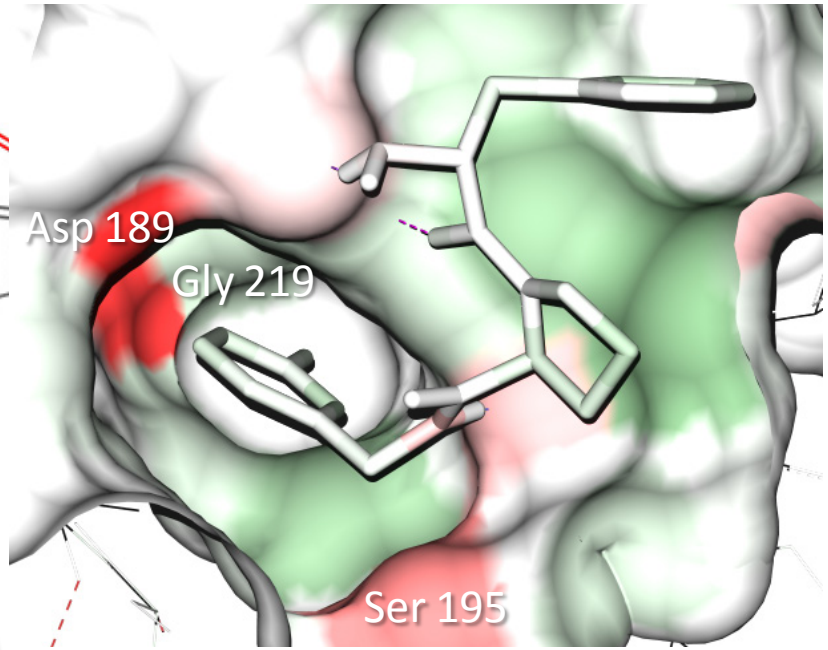
Superposition of Thrombin Inhibitors

2ZFF
2ZDV
2ZF0
2ZC9
2ZDA



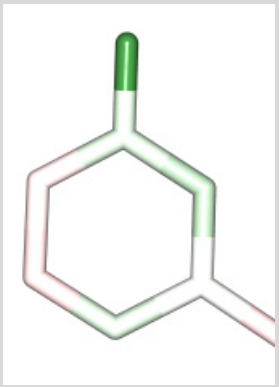
HYDE Analysis of Thrombin Inhibitors



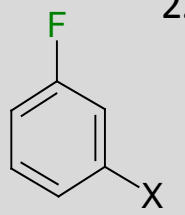


2ZDV	
$\Delta G_{experimental}$	-31.3 kJ/mol
ΔG_{HYDE}	-33.8 kJ/mol

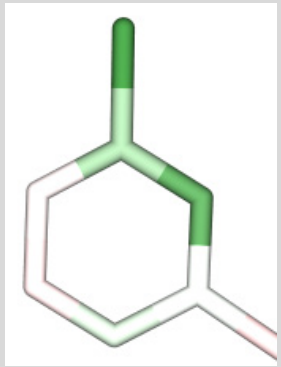
HYDE Analysis of Thrombin Inhibitors



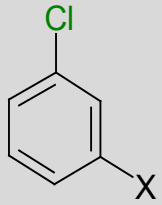
2ZDV



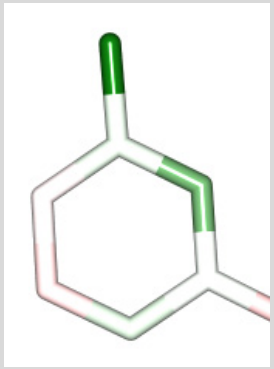
ΔG_{HYDE} **-9** kJ/mol



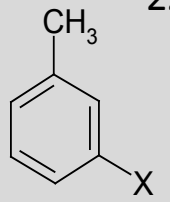
2ZC9



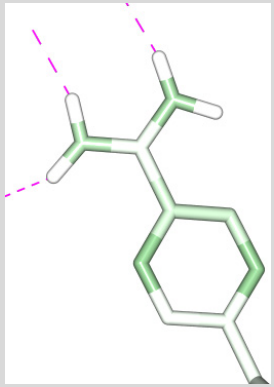
ΔG_{HYDE} **-14** kJ/mol



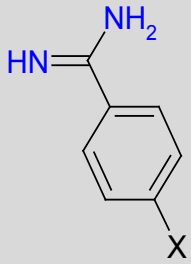
2ZF0



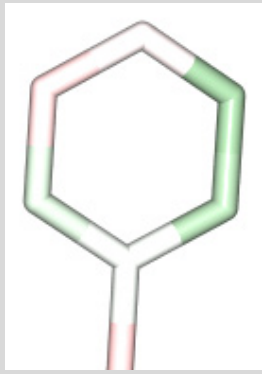
ΔG_{HYDE} **-13** kJ/mol



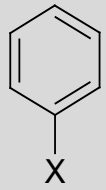
2ZDA



ΔG_{HYDE} **-20** kJ/mol

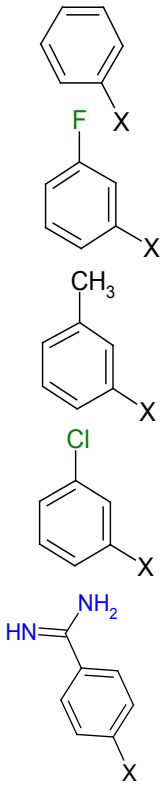


2ZFF



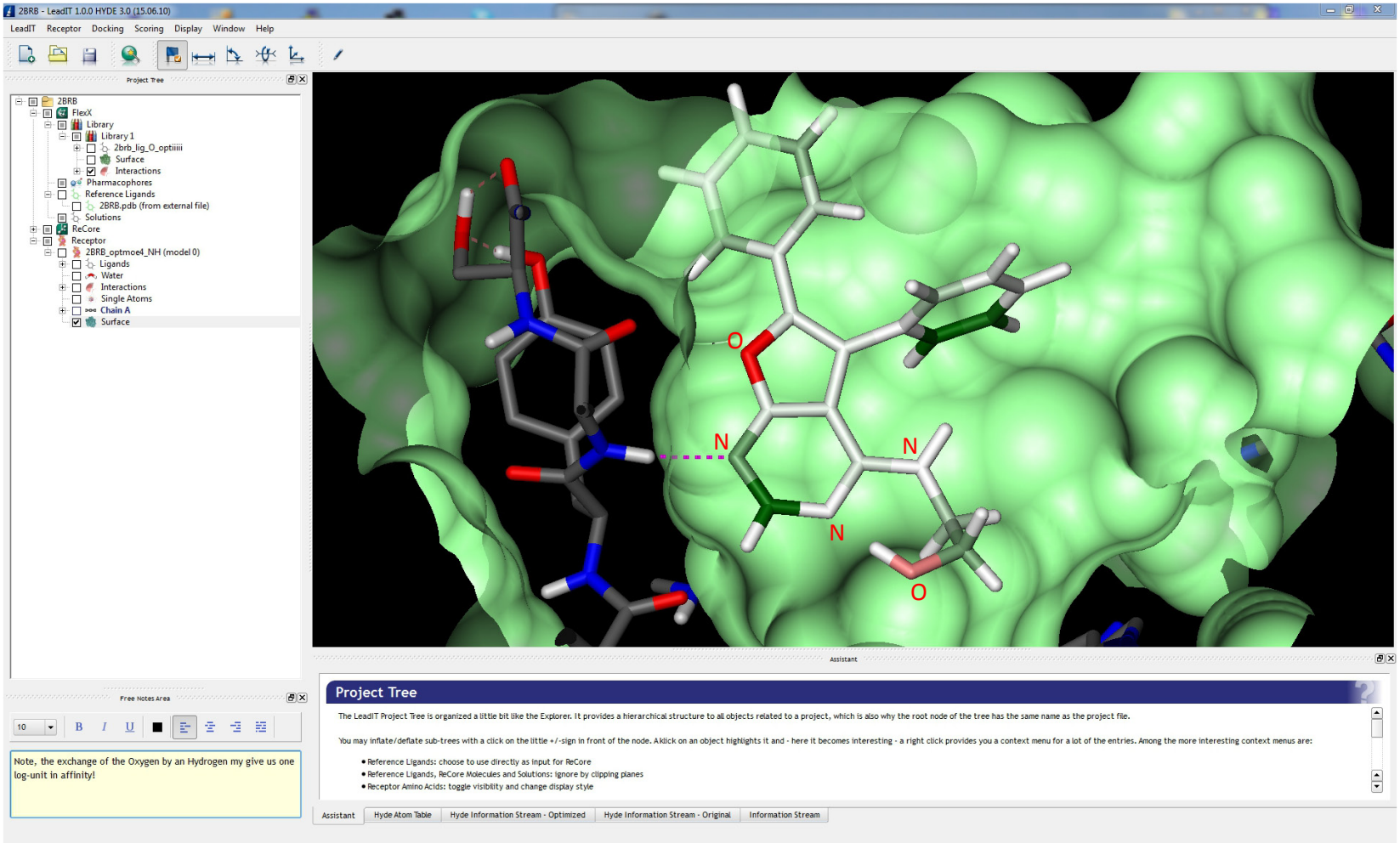
ΔG_{HYDE} **-5** kJ/mol

HYDE Analysis of Thrombin Inhibitors

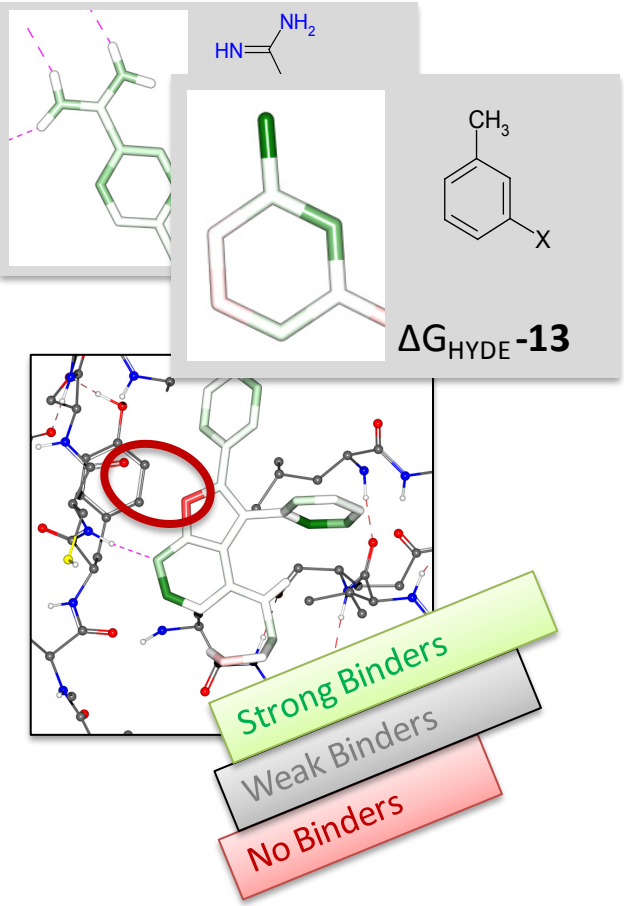


	$\Delta G_{experimental}$	ΔG_{HYDE}	D-Phe + Pro	S1 occupant
2ZFF	-32	-30	-25	**-5**
2ZDV	-31	-34	-25	**-9**
2ZF0	-35	-30	-17	**-13**
2ZC9	-35	-36	-22	**-14**
2ZDA	-46	-40	-20	**-20**

HYDE Analysis Tool: LeadIT GUI



Conclusions



HYDE …

- describes consistently hydrogen bonds, the hydrophobic effect and desolvation
- scores single atom exchanges correctly
- avoids false positives due to desolvation penalties
- facilitates the analysis of lead structures

Outlook

- HYDE specific geometric optimization of protein-ligand complexes

Acknowledgement

Bayer CropScience

- Gudrun Lange
- Robert Klein

Bayer HealthCare
Bayer Schering Pharma

- Hans Briem
- Kristin Engels

BioSolveIT

- Sally Hindle
- Martina Brümmer
- Holger Claußen
- Marcus Gastreich
- Christian Lemmen

- Matthias Rarey
- Katrin Stierand
- Lennart Heinzerling
- Sascha Urbaczek

Thank you

for your attention