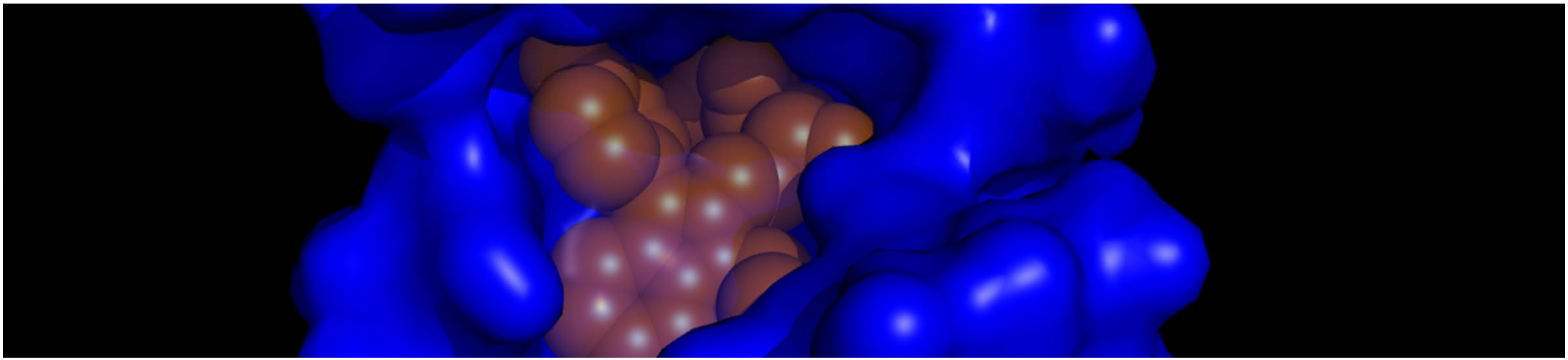
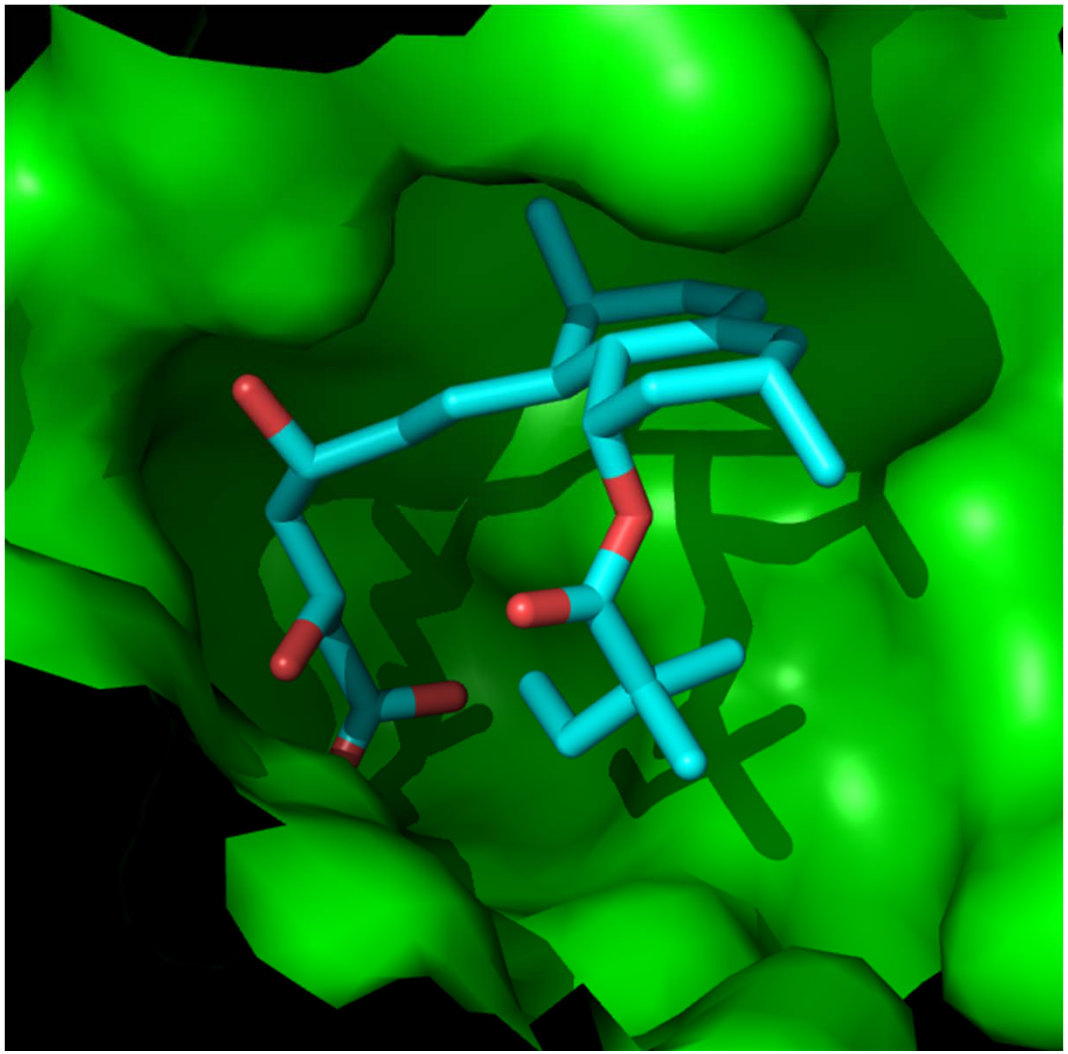
Thinking about Molecular Interactions in Drug Discovery

Martin Stahl, Roche Basel, March 2013



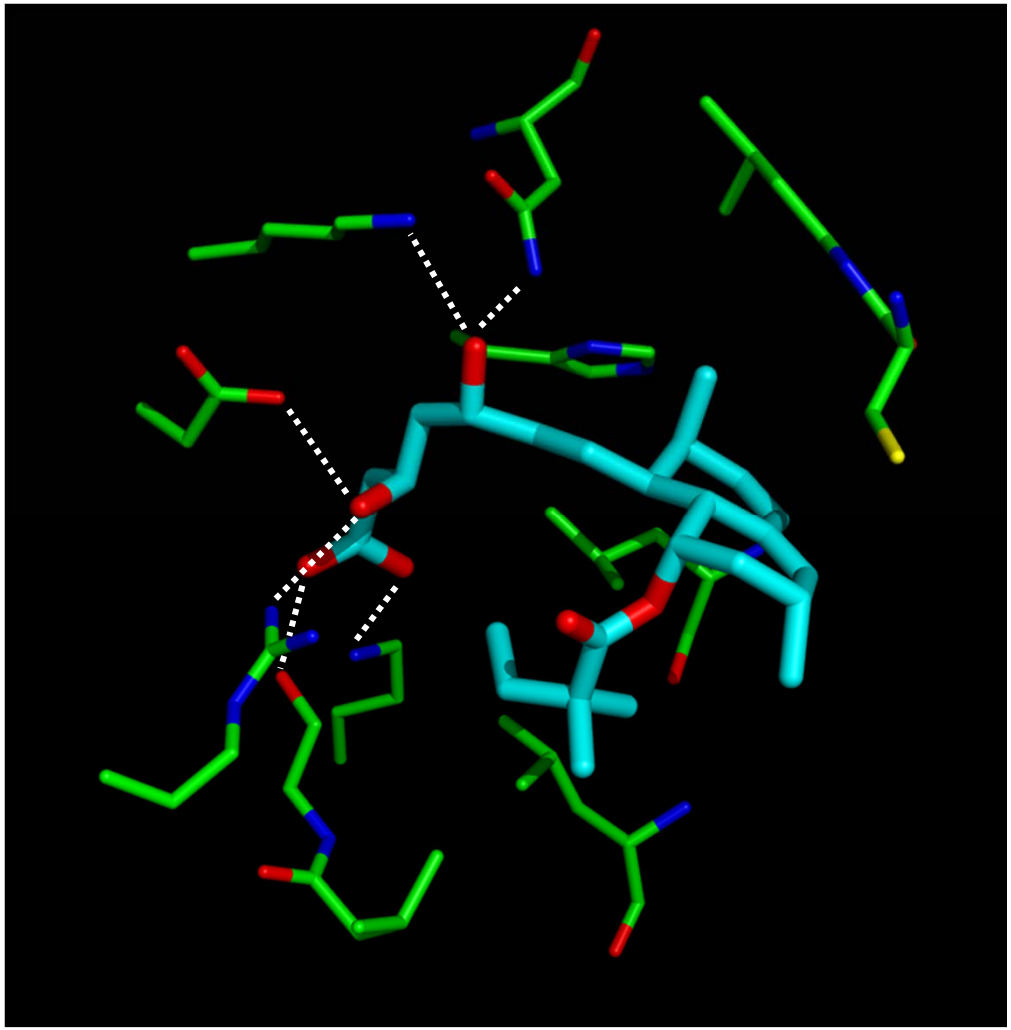
A Ligand in its Binding Site

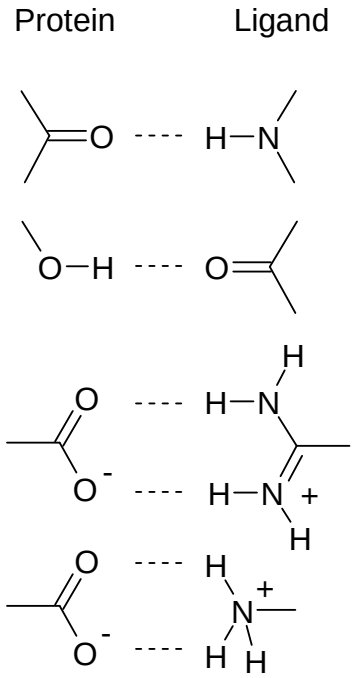
Shape Complementarity



Hydrogen Bonds

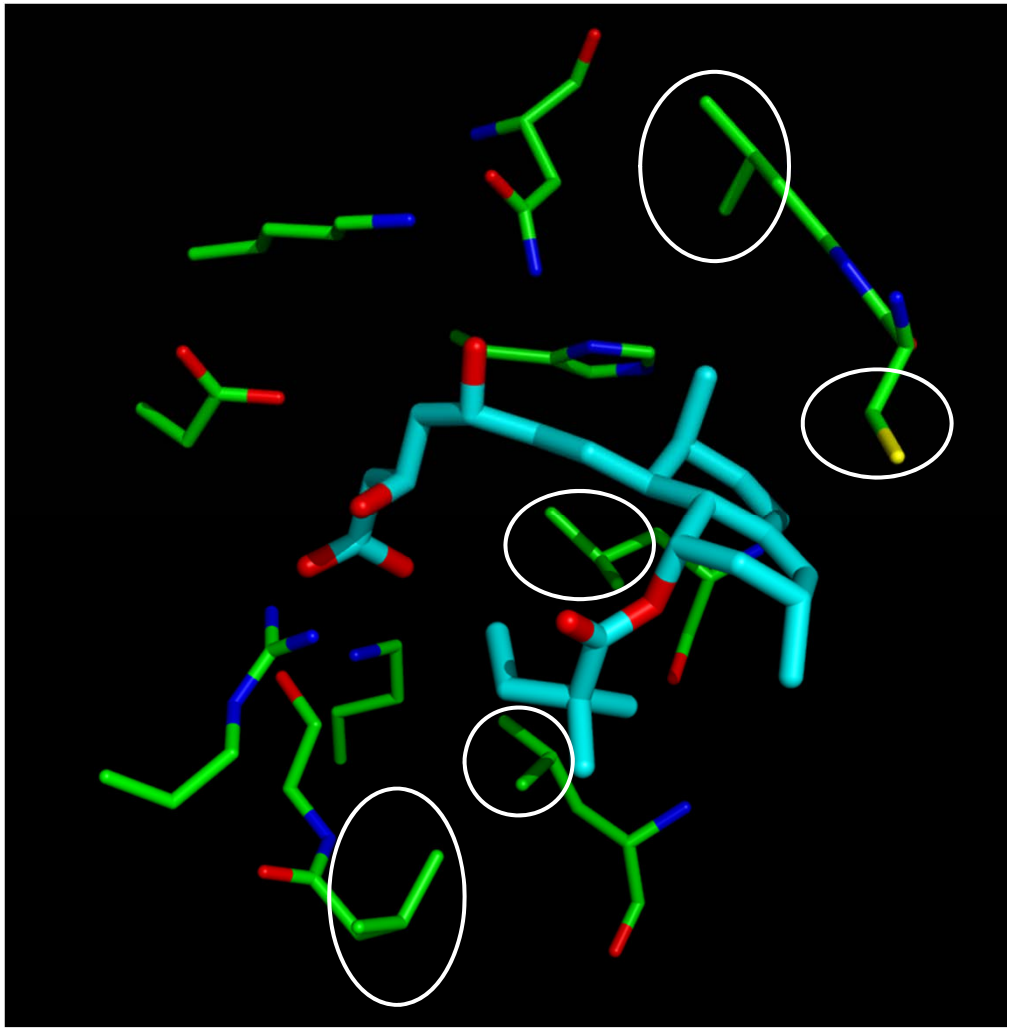
Specific and Directed

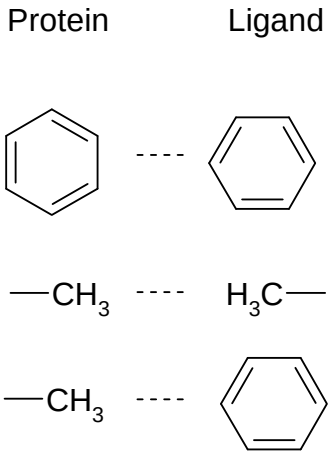




Hydrophobic Interactions

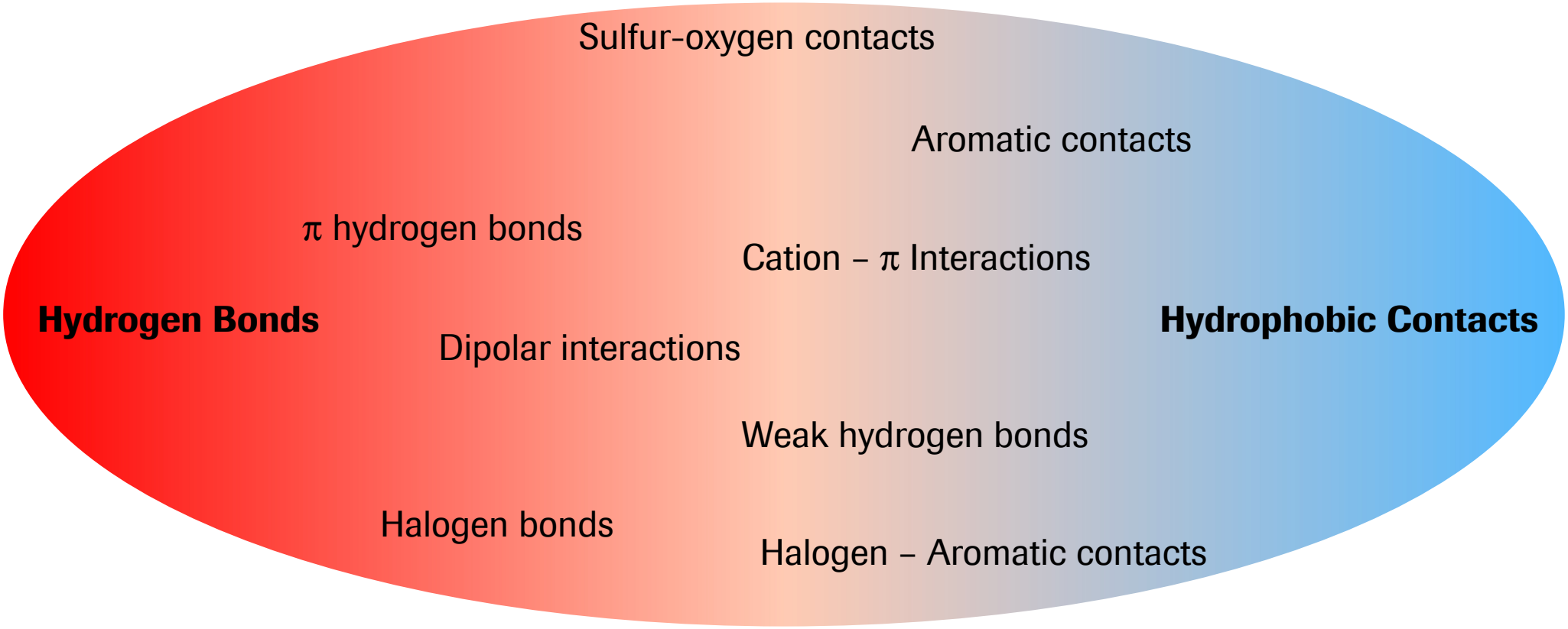
"Surface Contacts"



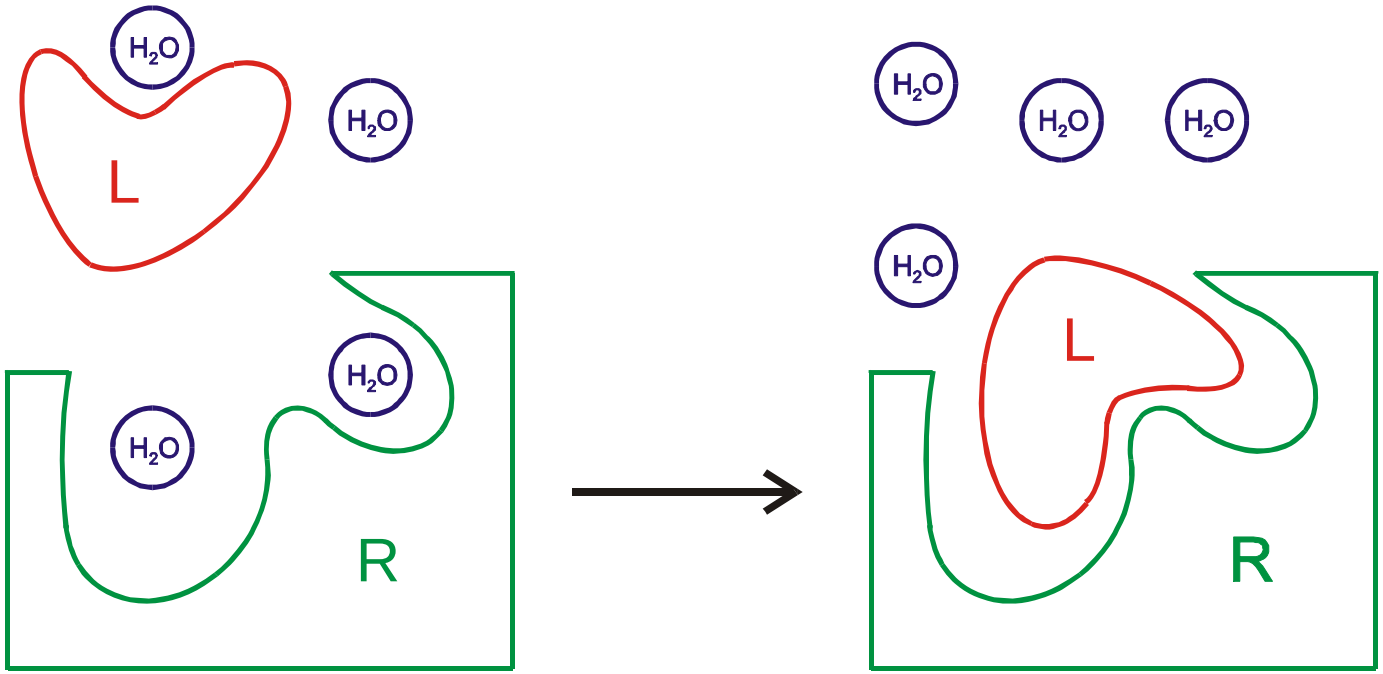


More Interactions!

A Continuum or Discrete Types?

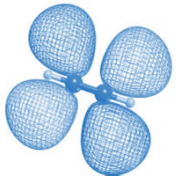


“Interactions” are only Part of a Complex Reality

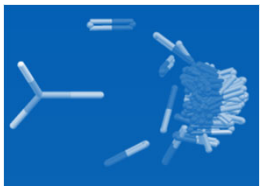


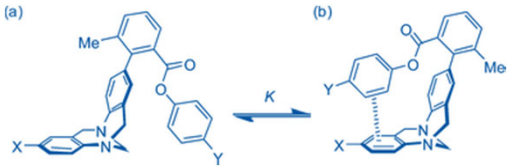
Learning about Interactions

From Theoretical to Experimental



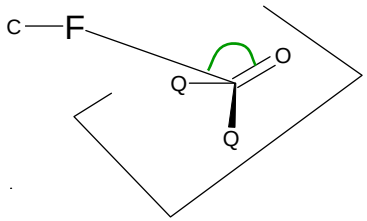
$$\Delta G = \sum_{i=0}^{n} \Delta G_i$$

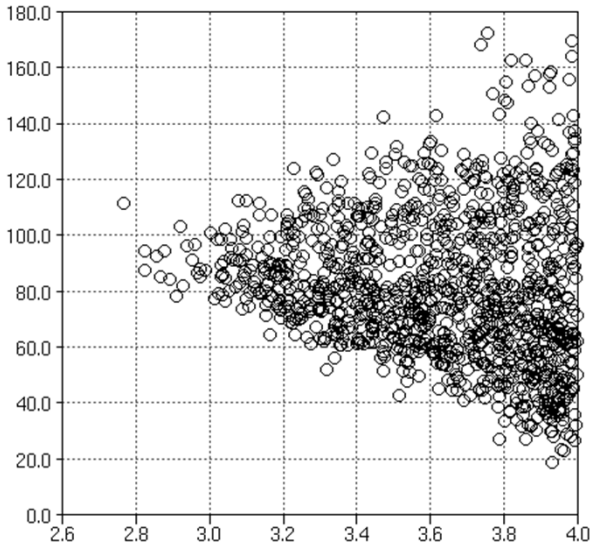


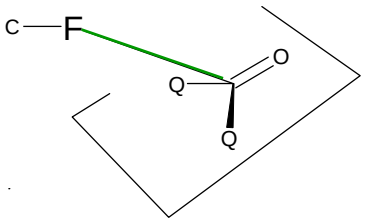


Method	Benefit	Caveat
Quantum chemistry	Exact energies & orientations	Gas phase only Complex interpretation
Empirical force fields, scoring functions	Fast estimates	Contributions to energy sum easily over-interpreted
Statistical X-ray analysis	Net energetic estimates & good geometries	Choice of reference states Sampling bias No total energy
Experimental model Systems	Good upper and lower bounds for an interaction	Tedious, many expt. parameters, Context dependent

Orthogonal Multipolar Interactions?



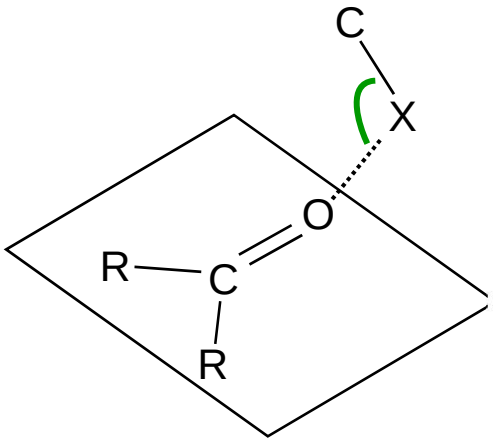




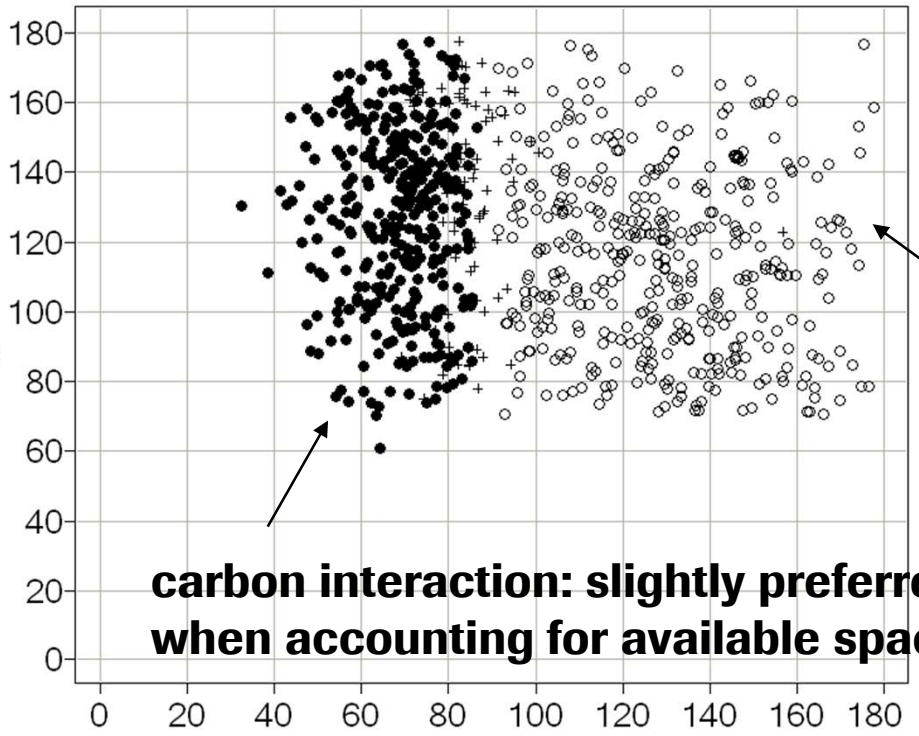
Paulini, R.; Müller, K.; Diederich, F. Angew. Chem. Int. Ed. **2005**, 44, 1788-1805.

Fluorine and Carbonyl Groups in the CSD

C vs. O Interactions

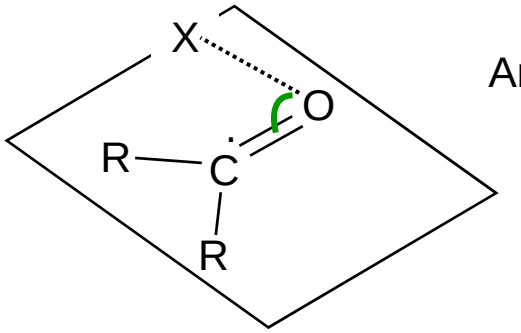


Angle C-X···O



oxygen interaction

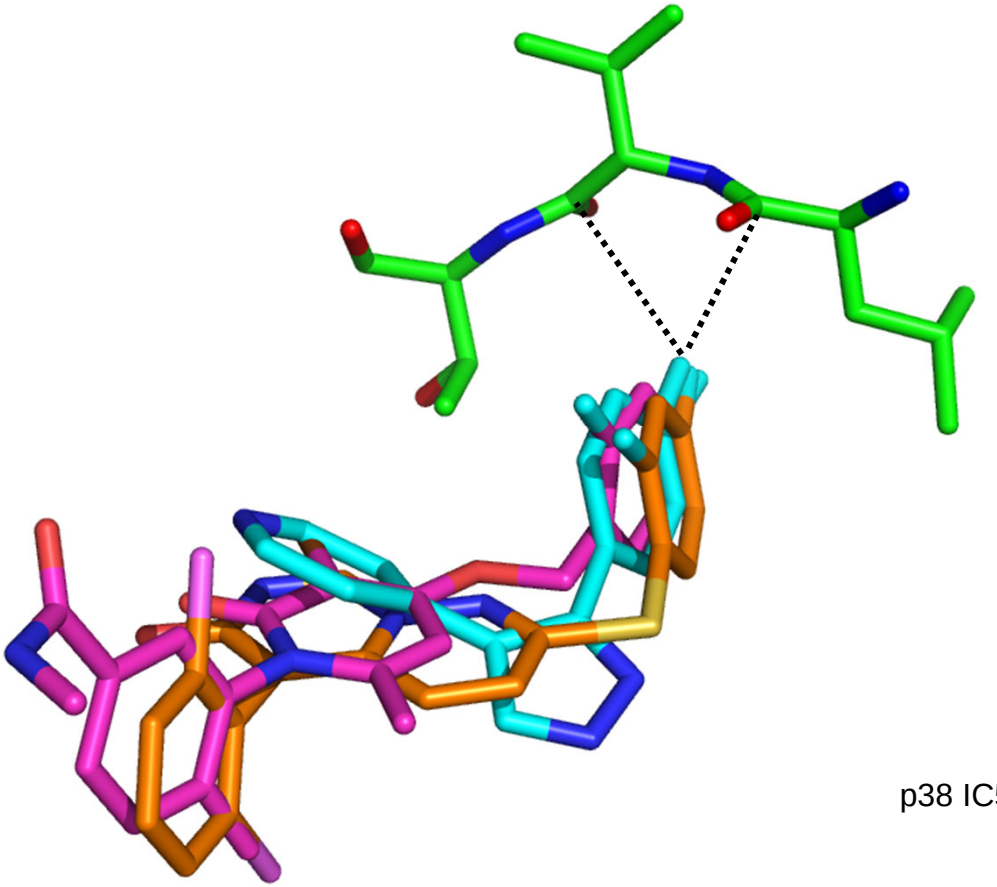
carbon interaction: slightly preferred when accounting for available space

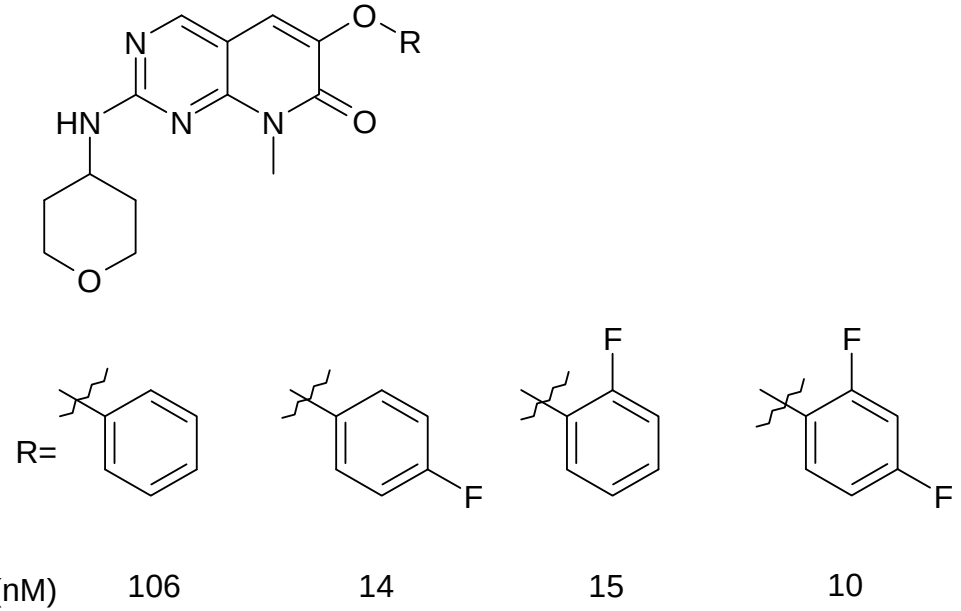


Angle C=O···X

P38 MAP Kinase Inhibitors

Role of F Substituents in Back Pocket



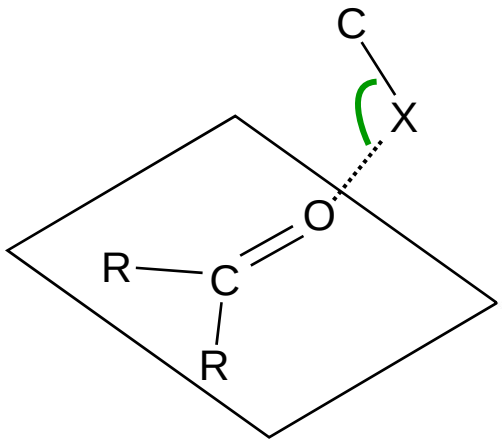


p38 IC50 (nM)	106	14	15	10

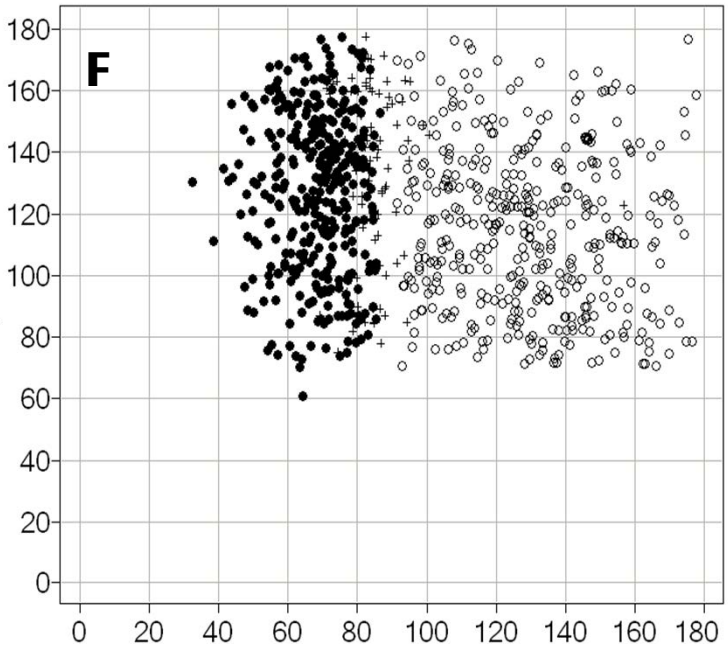
3fc1, 3hll, 3hvc

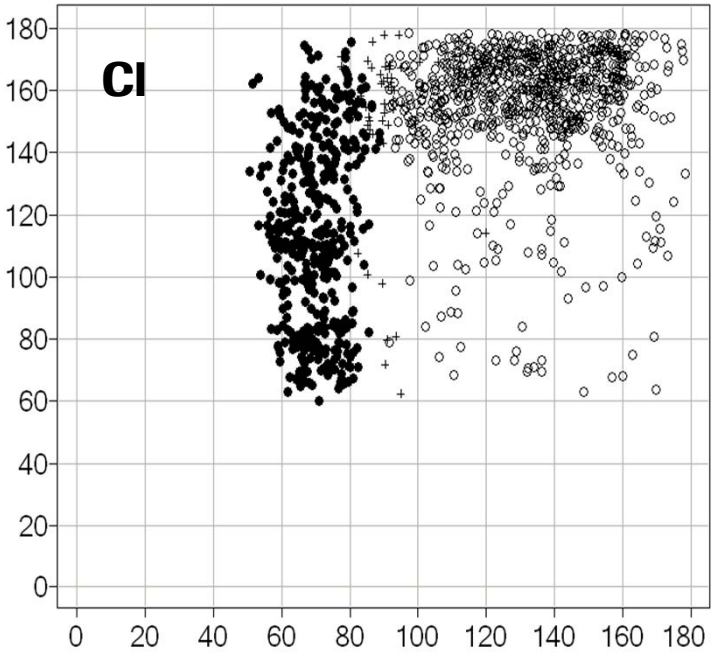
Chlorine vs. Fluorine

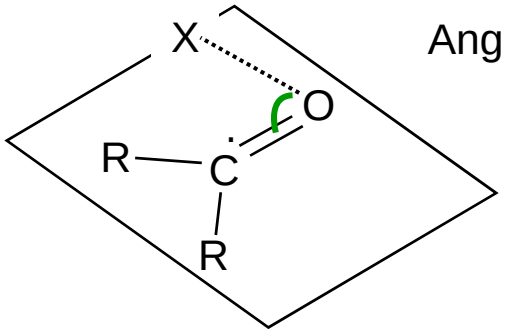
Halogen Bond more Frequent than Orthogonal Multipolar Interaction



Angle C-X···O

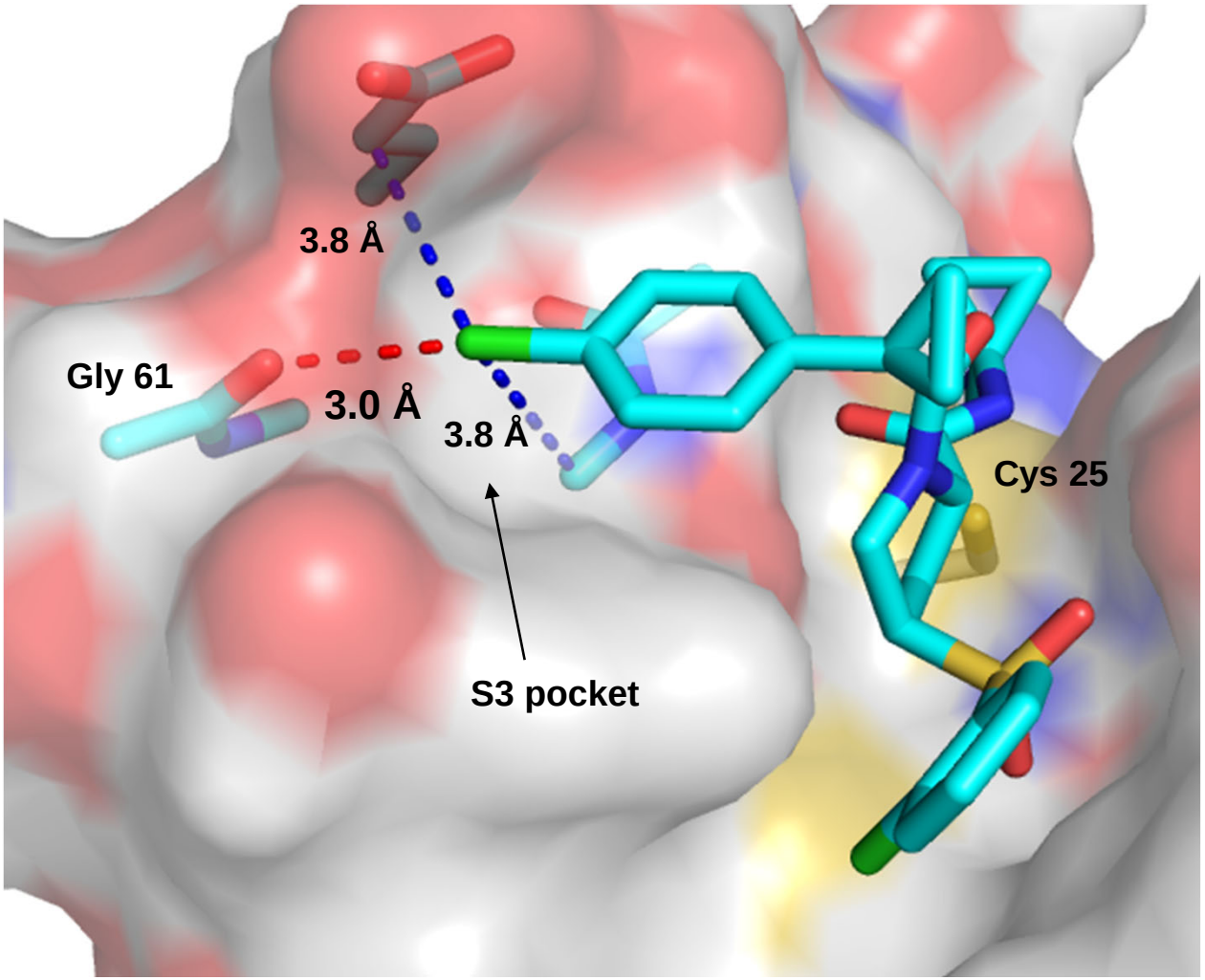


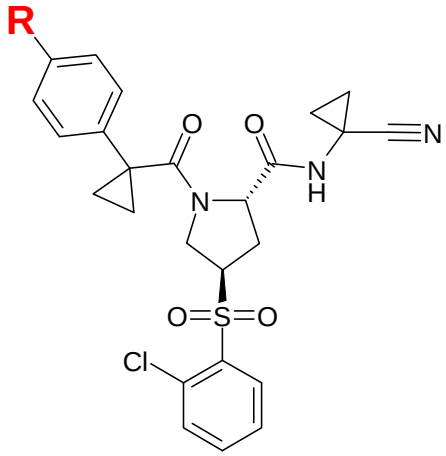




Angle C=O···X

Strong Halogen Bonding Effect in Cathepsin L

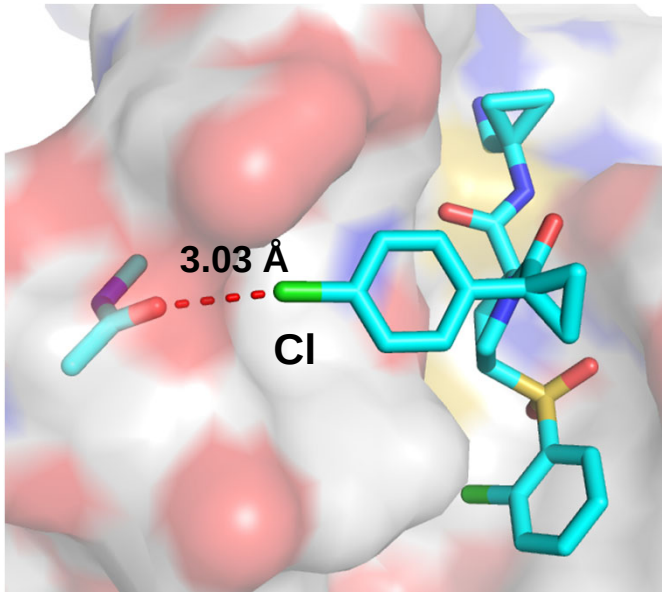


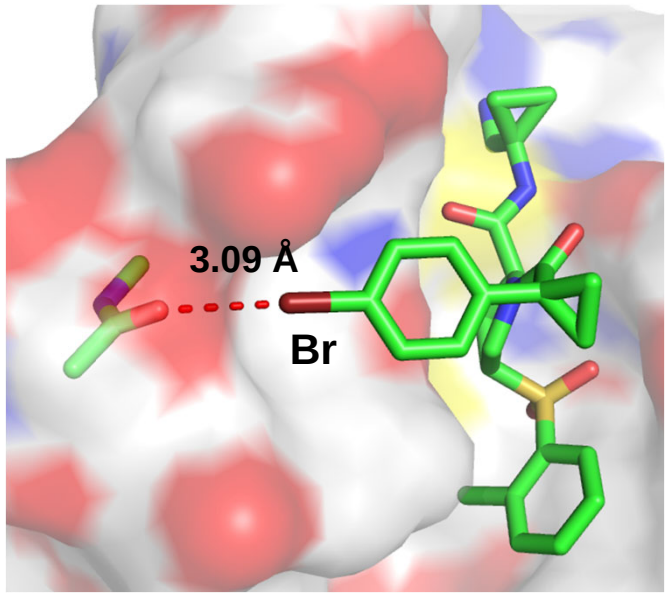


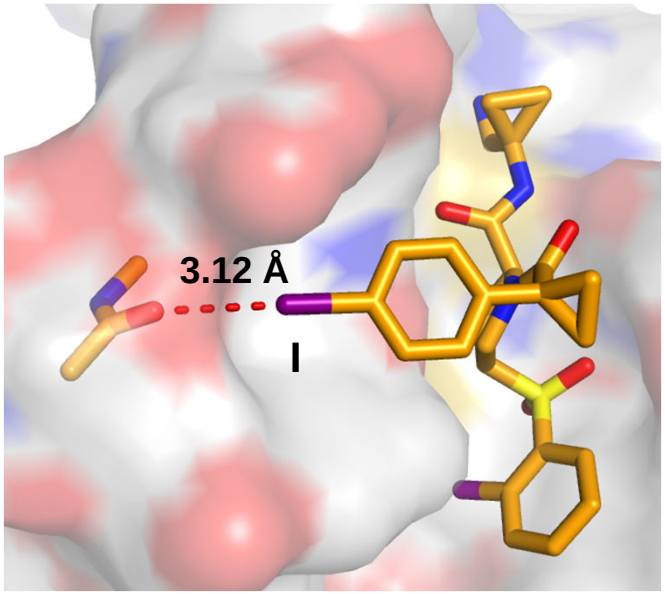
R	IC_{50}[nM]	
H	290	13-fold
Cl	22	
F	340	
Br	12	
I	6.5	
Me	130	

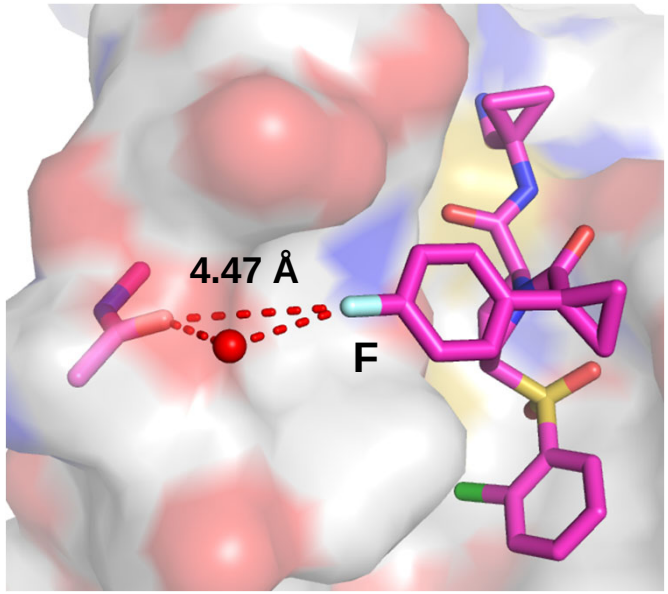
Hardegger et al, *Angew. Chem. Int. Ed.* 2011, *50*, 314

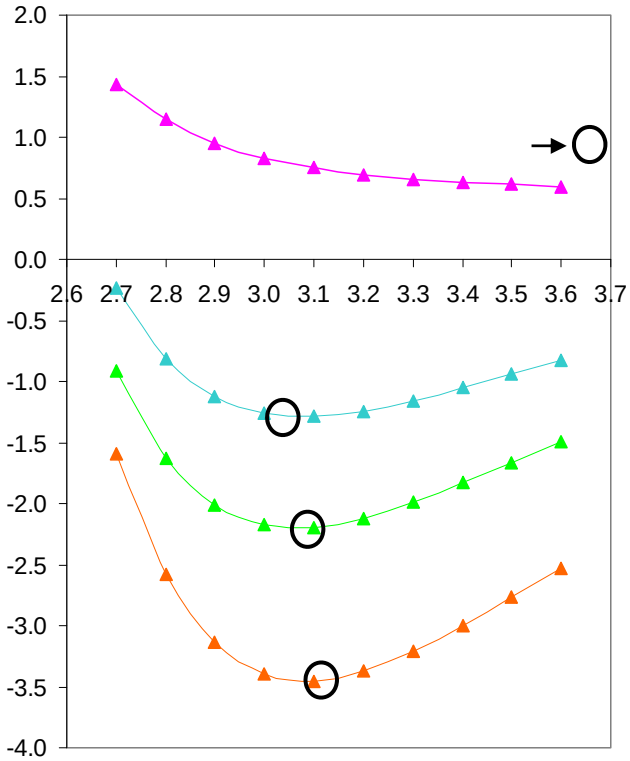
Binding Modes Adapt to Halogen Bonding



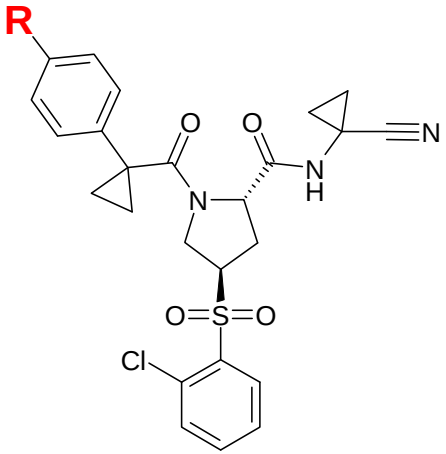


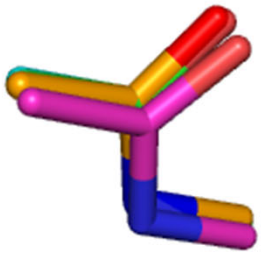


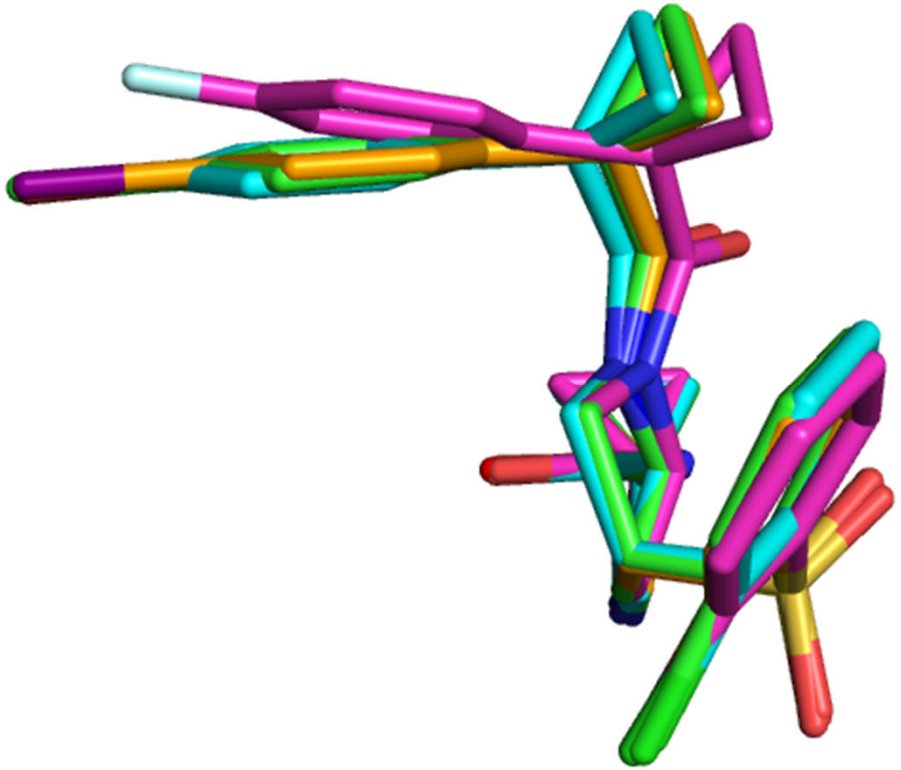




Flexible Pyrrolidine Ring Allows for Adjustment

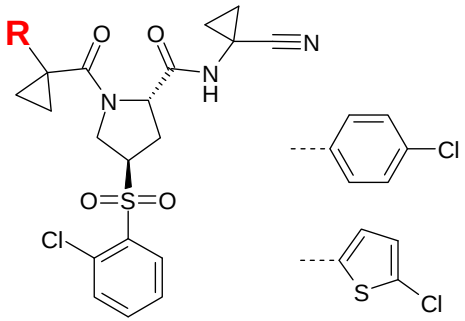




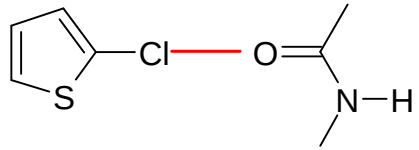


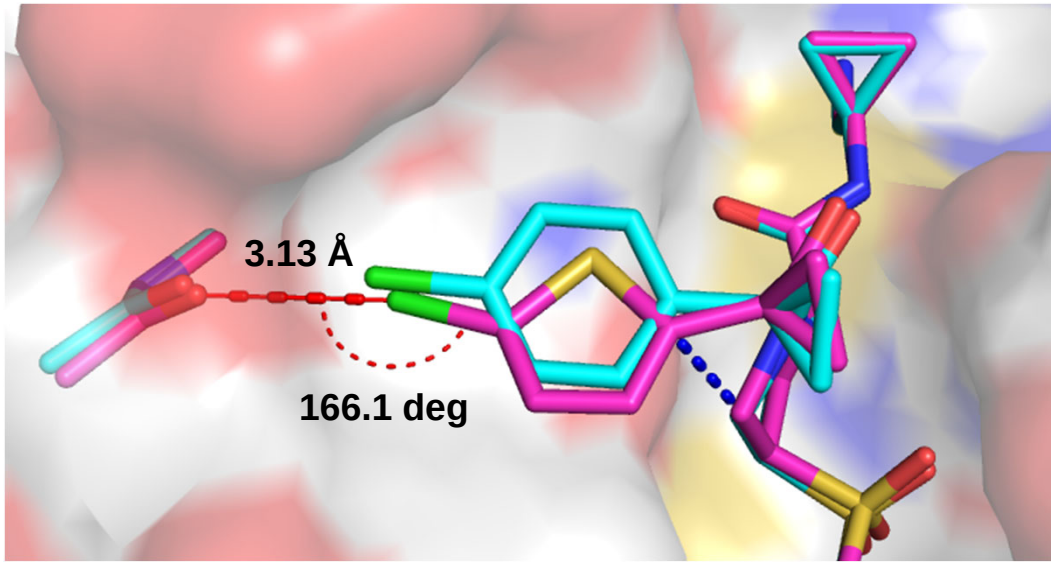
Changing the Halogen Bonding Angle

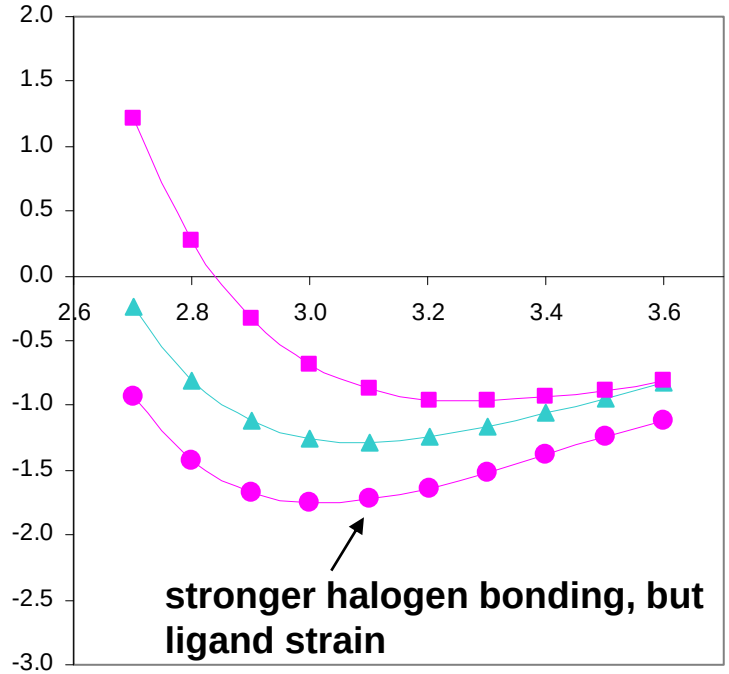
Interaction with Cl-substituted 5-membered Rings



	IC_{50}[nM]
	22
	160



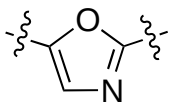




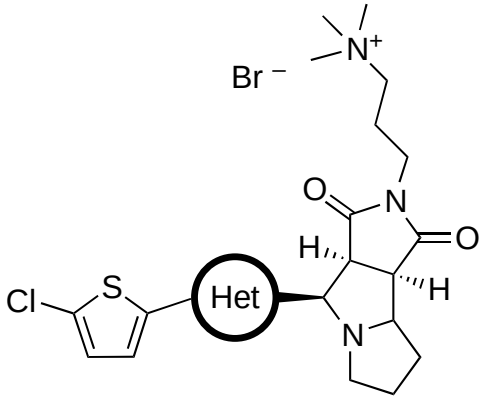
Conclusions: Halogen Bonding

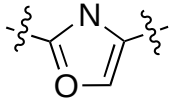
- Rigorous geometric requirements:
  - *d* (halogen···oxygen) ≤ sum of van der Waals radii
  - angle C–X···O ≈ 140°-180° (optimal): steep angle dependency
  - angle X···O=C can vary between 90° and 180°
- I > Br > Cl
- No halogen bonding for aryl fluorides
- Establishing a halogen bond might enhance protein–ligand interactions by as much as a factor of 74 (X = H vs. X = I) which translates into a gain in free enthalpy of $-\Delta\Delta G$ = 2.6 kcal/mol

SAR in S1 Pocket of Factor Xa

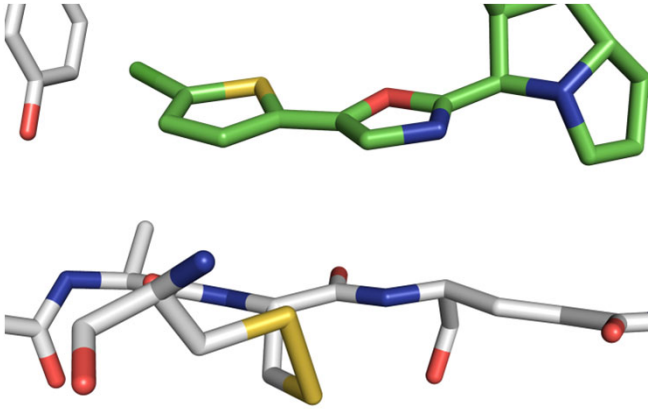


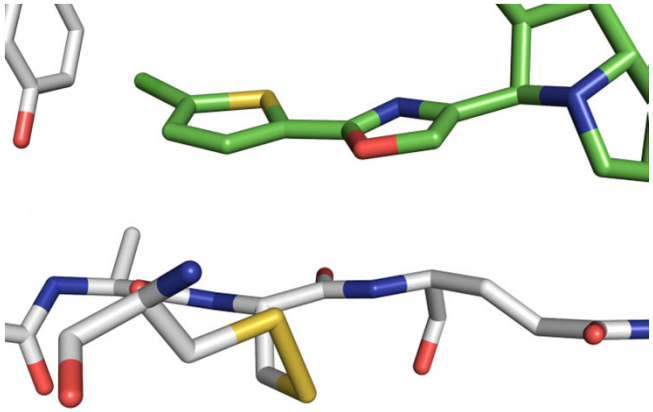
K_i = 146 nM





K_i = 1620 nM

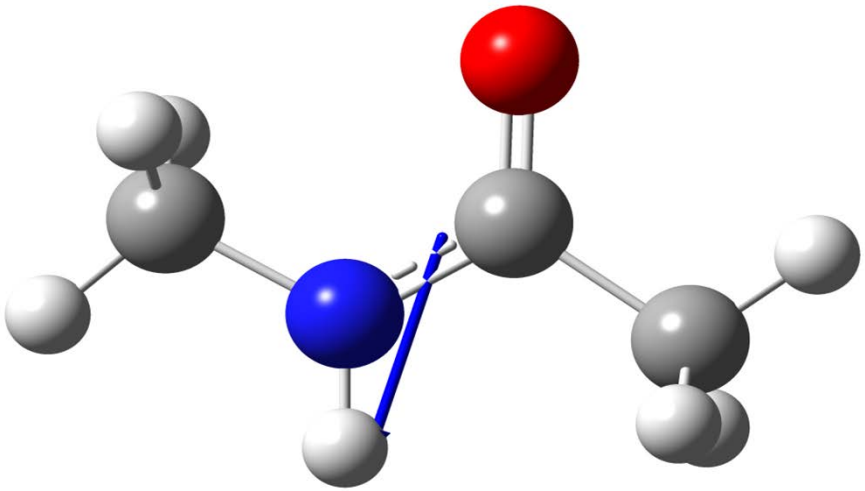




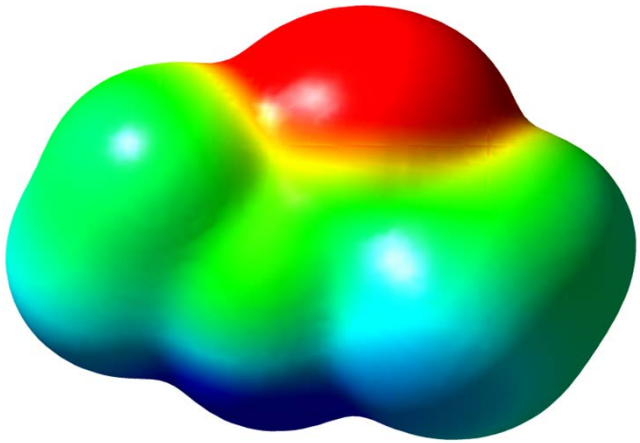
Salonen et al, *Chem. Eur. J.* 2012, *18*, 213

Polarity of Amide Groups

N-methylacetamide as model system



dipole moment: 3.8 Debye

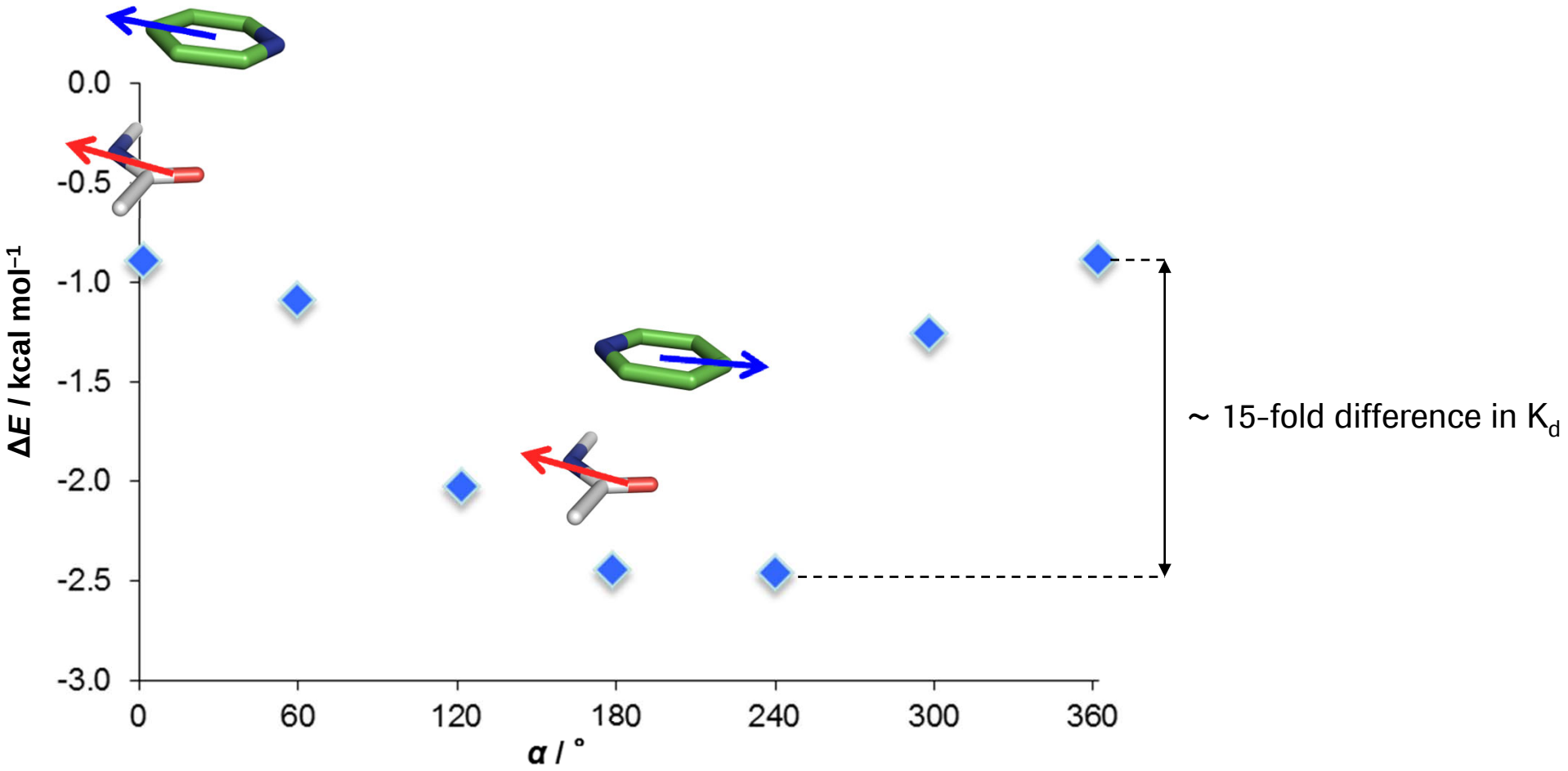


electrostatic potential

M. Harder et al., ChemMedChem **2013**, in press

Rotational Scan of Pyridine…N-methylacetamide

Interaction energy vs. dipole moment angle

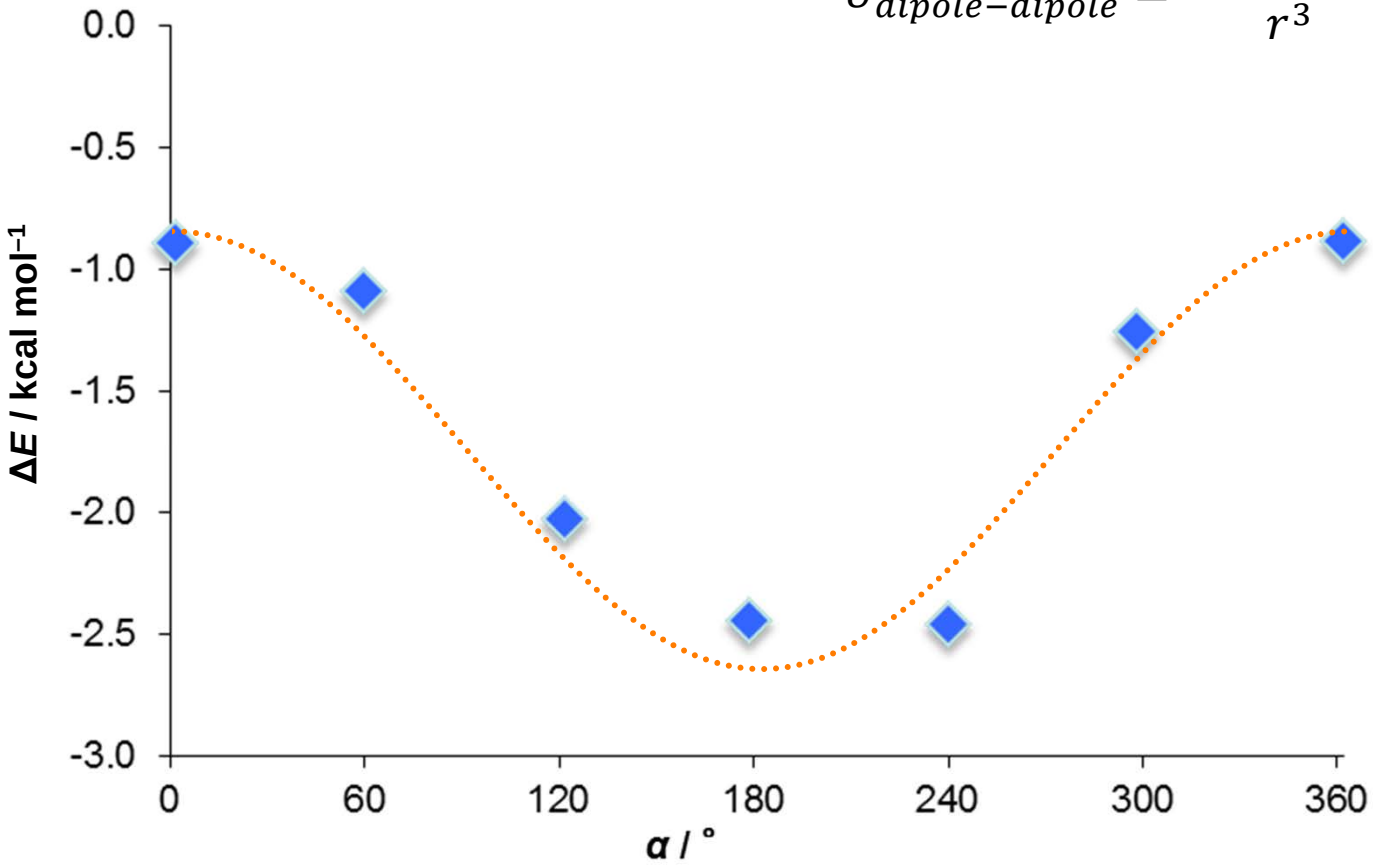


preference for close to anti-parallel alignment

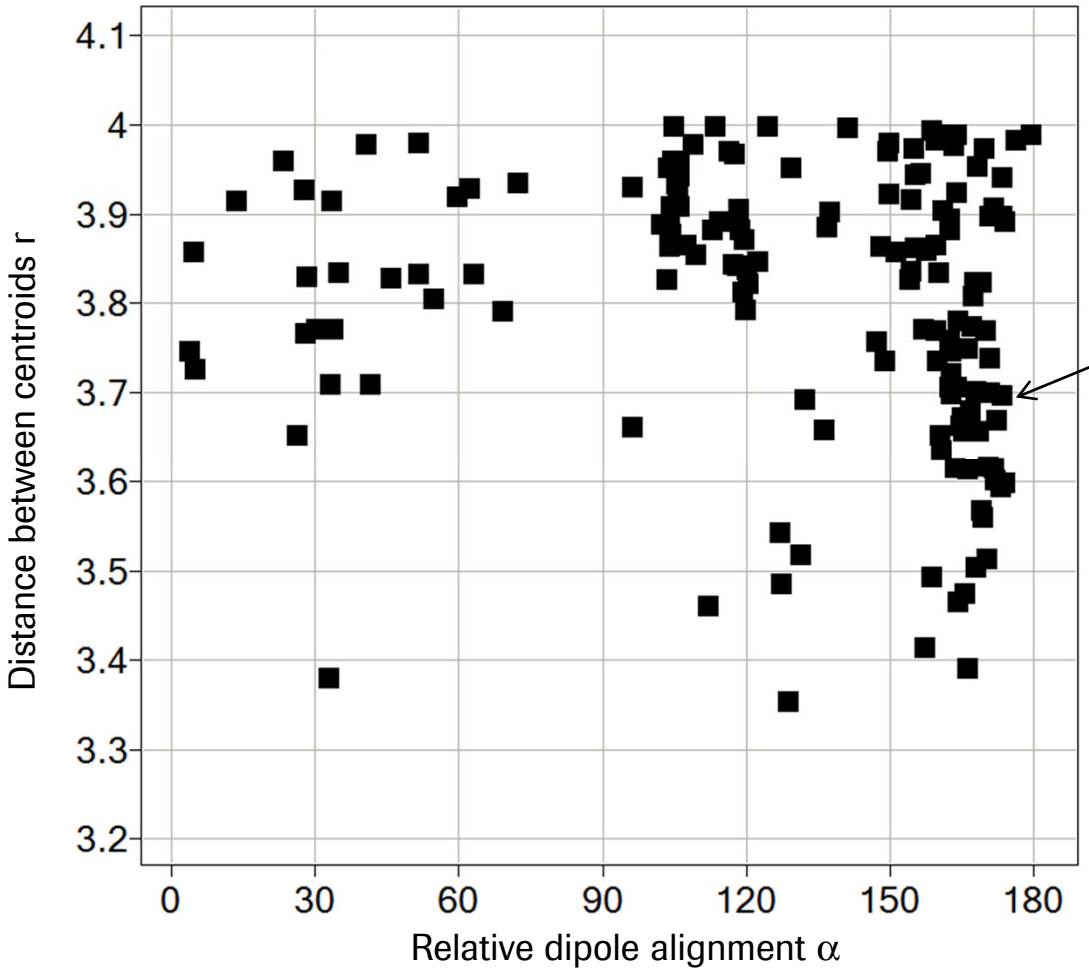
Dipole-dipole Interaction

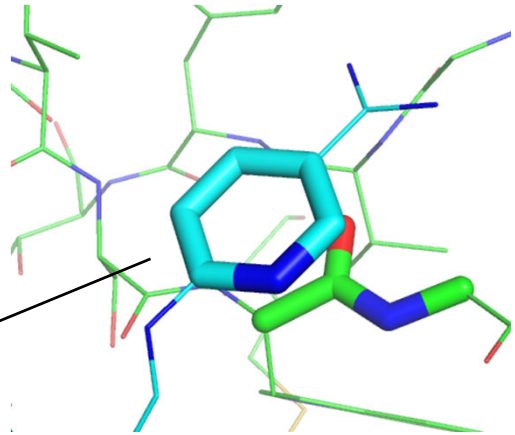
parallel dipoles, on top of each other:

$$U_{dipole-dipole} = \frac{f * \mu_1 * \mu_2}{r^3} * \cos\alpha$$



PDB Database Analysis Confirms Antiparallel Preference

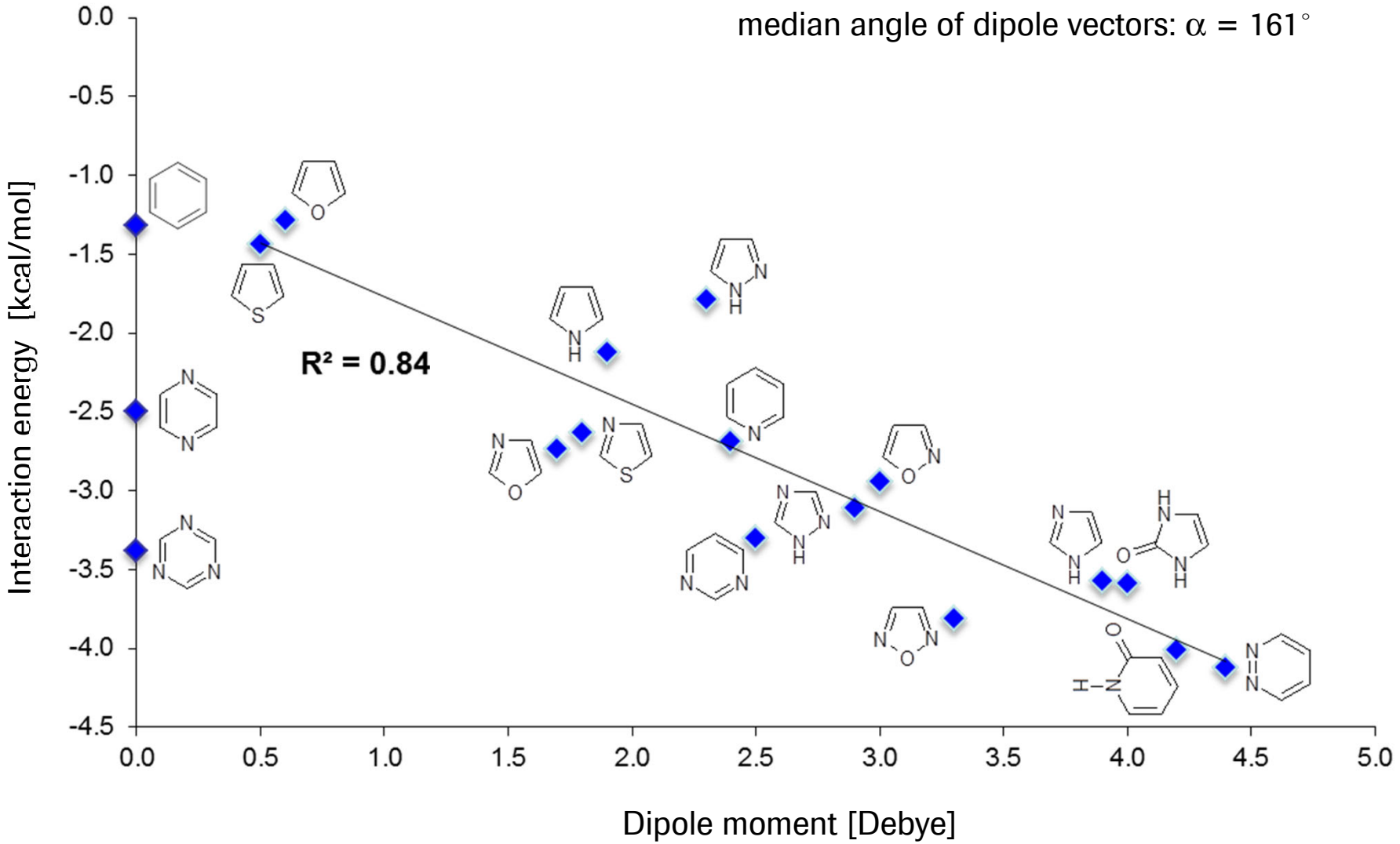




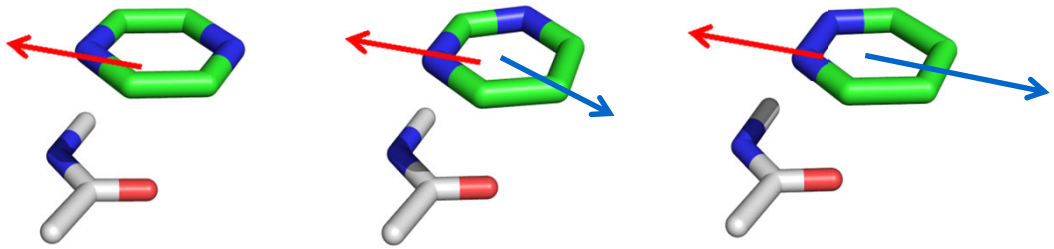
2ec9 (factor 7a)

angle between planes: 0-30 °

Correlation between Interaction Energy and Dipole Moment



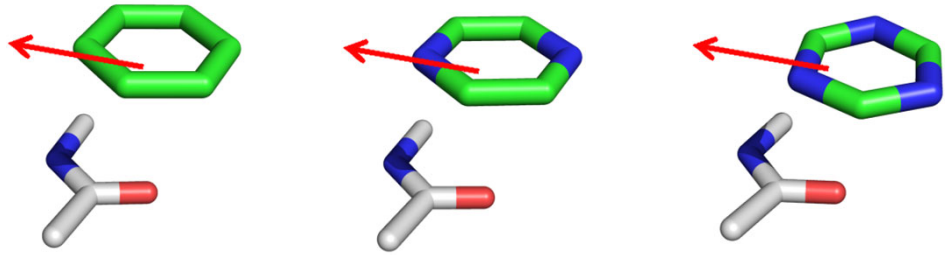
Trends in Interaction Energies



ΔE (dimer) in kcal/mol	-3.67	-4.34	-5.31
Dipole moment in Debye	0.00	2.47	4.38

Stacking interaction is improved with increasing dipole moment of the heterocycle

Trends in Interaction Energies

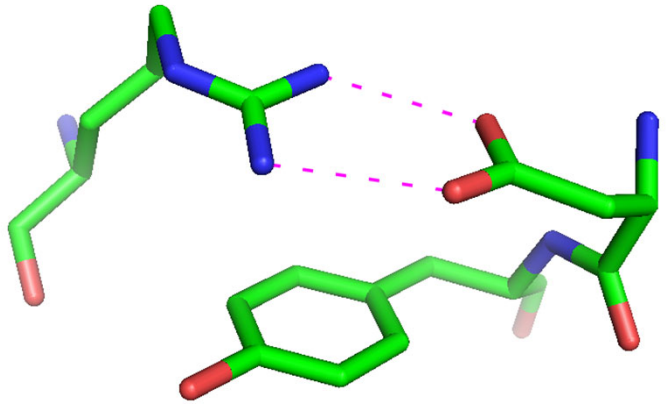


ΔE (dimer) in kcal/mol	-2.50	-3.67	-4.91
Dipole moment in Debye	0.00	0.00	0.00

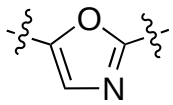
Stacking interaction is improved with decreasing π-electron density

Conclusions: Amide–π Stacking

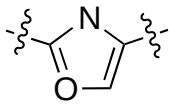
- Stacking energies of heteroarenes on amide π systems can be improved by:
  - proper orientation of the dipole moment vectors in an anti-parallel fashion
  - increasing the dipole moment of the heterocycle
  - decreasing its π-electron density.
- Ideal distances between both planes: 3.4-3.8Å
- Guidelines can be extended to other π systems, e.g. H-bonding arrays



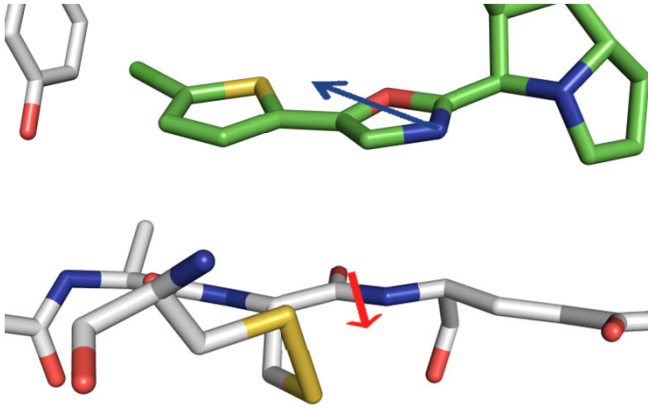
SAR in S1 Pocket of Factor Xa

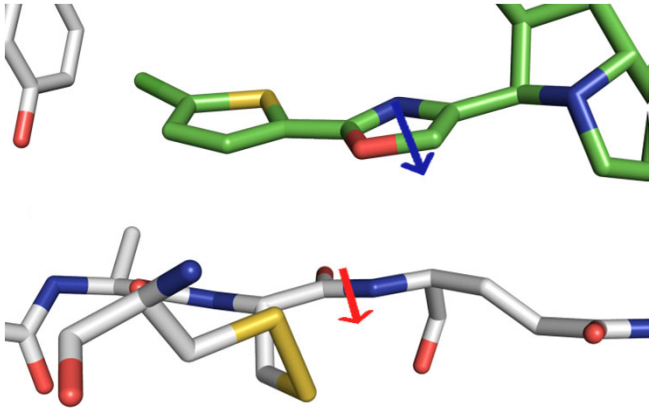


K_i = 146 nM



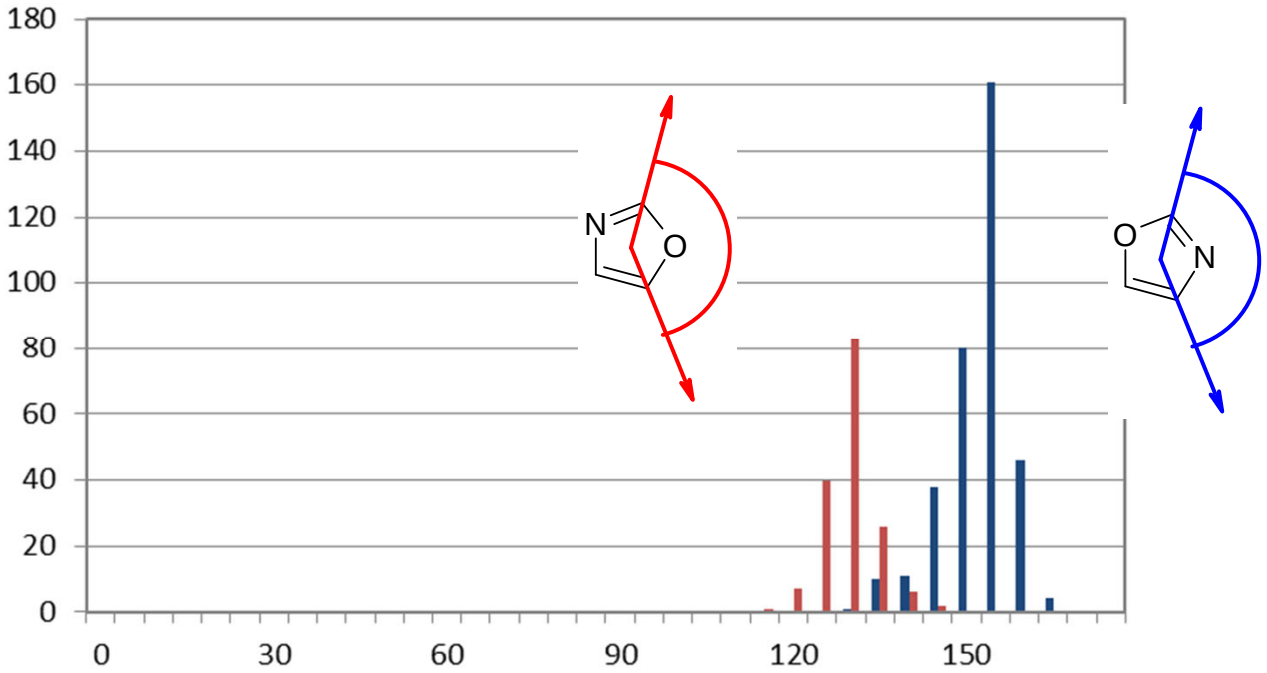
K_i = 1620 nM





There is Never Only One Explanation

Exit Vector Differences in Oxazoles

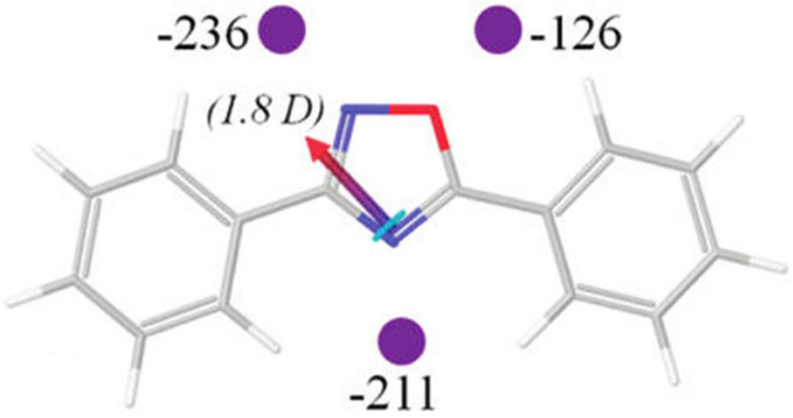


It's Never Only About Interactions

Dipole Moments and Physicochemical Parameters

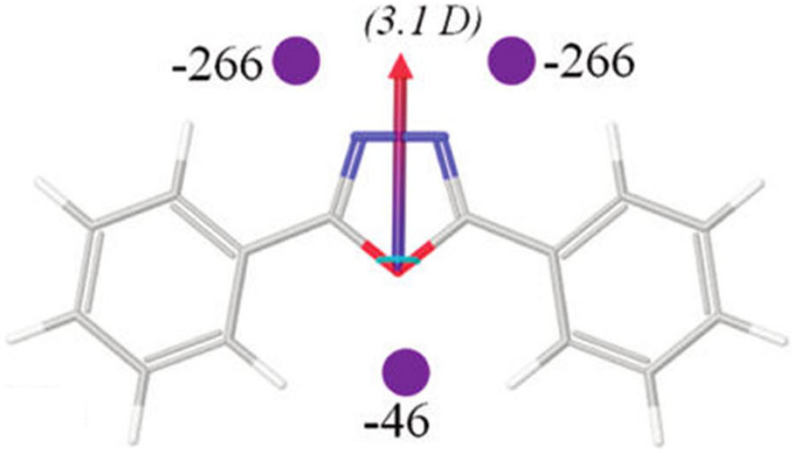
log D 5.9

solubility, 7 µM



log D 4.0

solubility, 26 µM

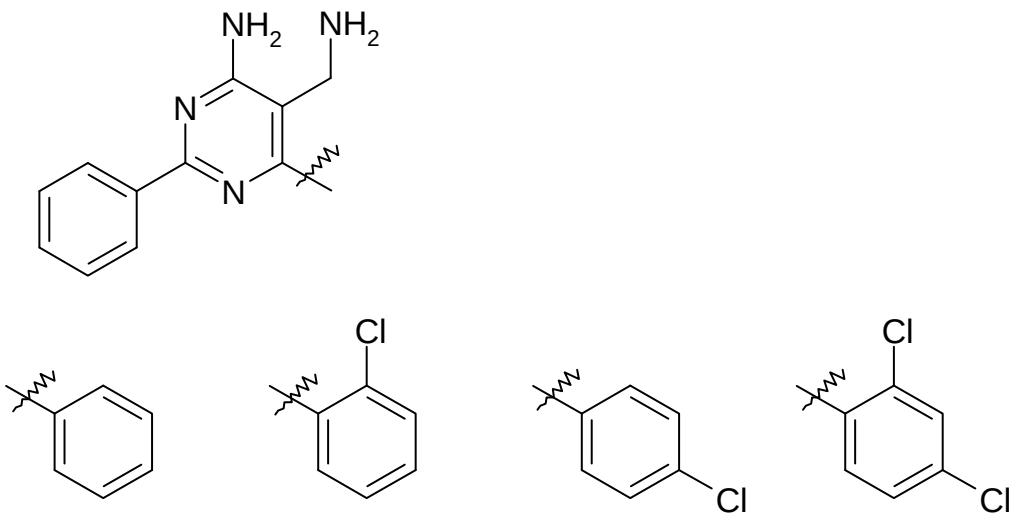


● V_{min} values

J. Boström et al., JMC 2012, 55, 1817–1830.

Non-Additivity

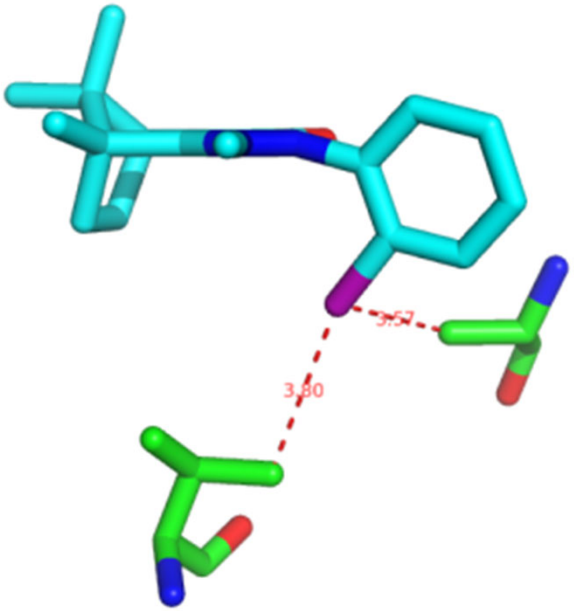
Aminopyrimidine DPPIV Inhibitors

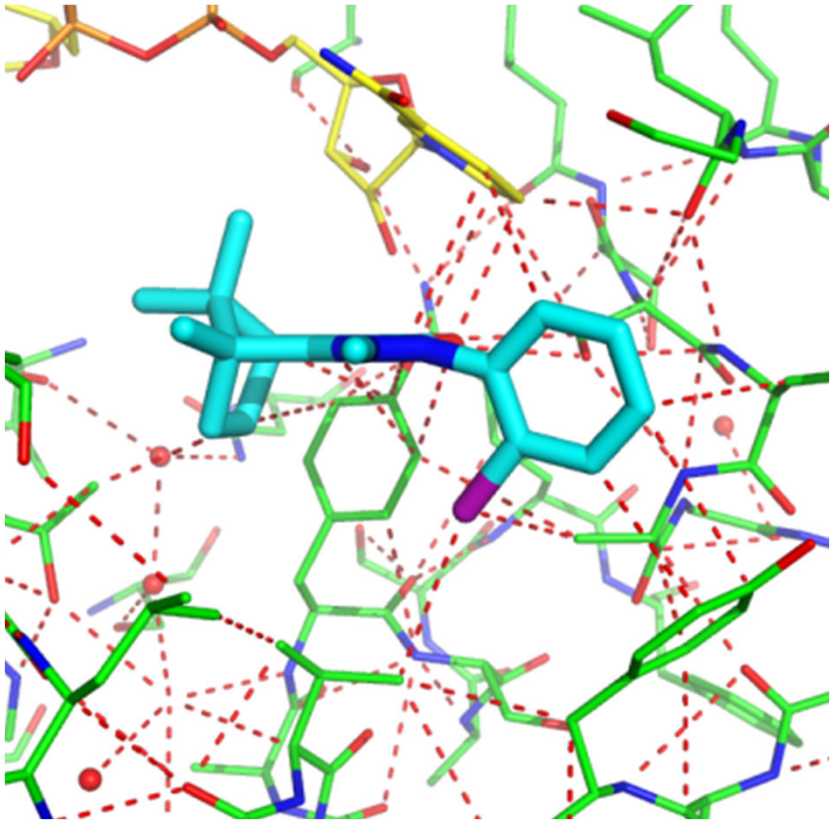


J.-U. Peters et al., BMCL 2004, 14, 1491

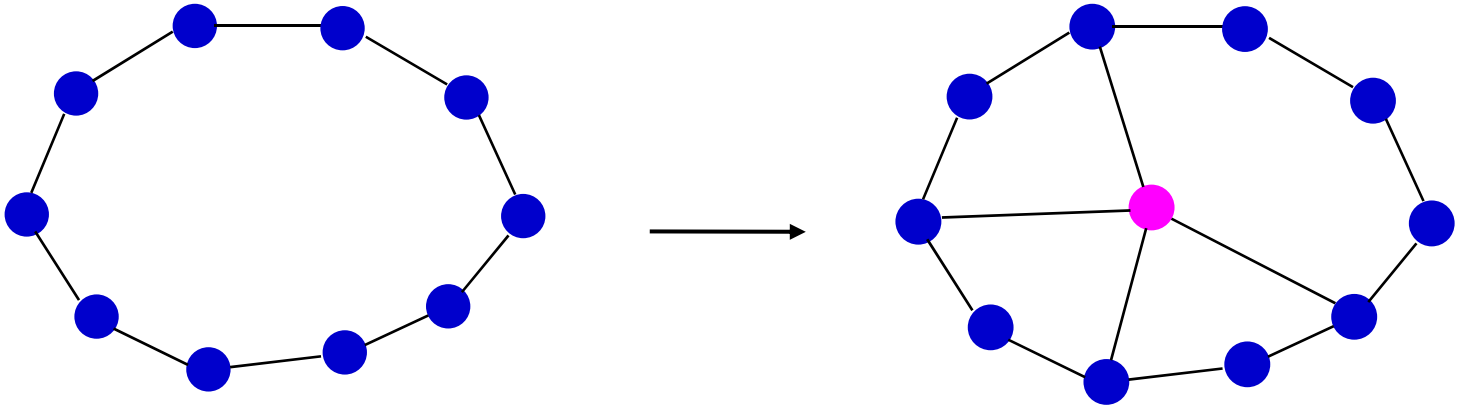
Directed Pairwise Interactions

… or Interaction Networks





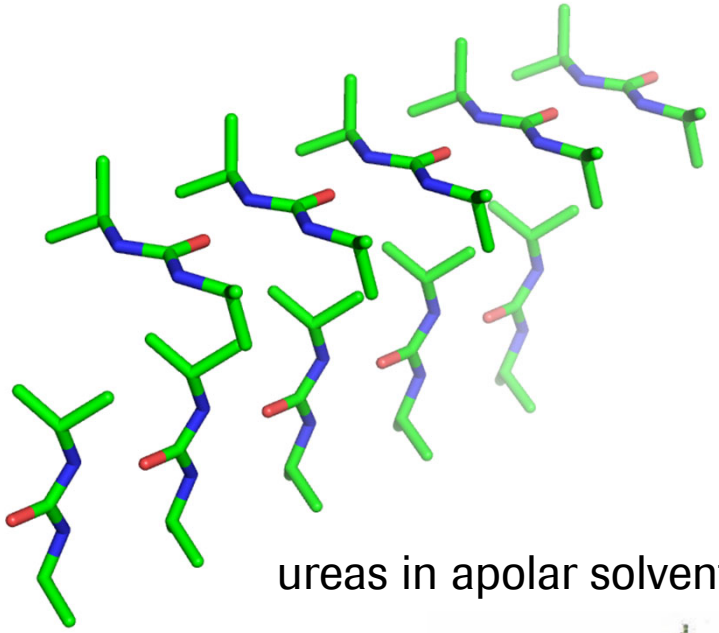
Protein-Ligand Complex Modeled as a Small World Network



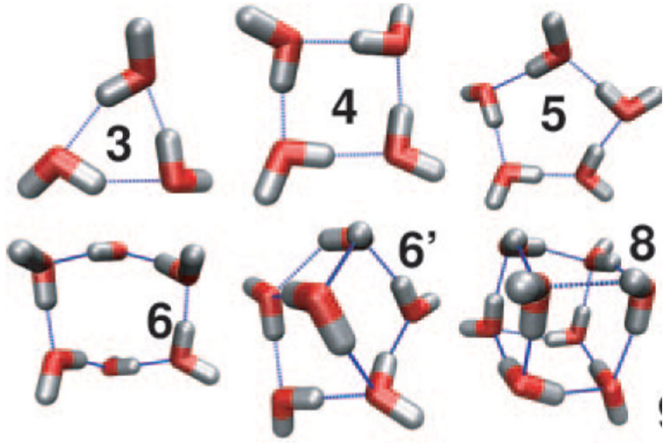
Addition of an extra node and just a few extra edges can reduce shortest path lengths between many pairs of nodes

Use network approach to capture cooperativity in protein-ligand complexes?

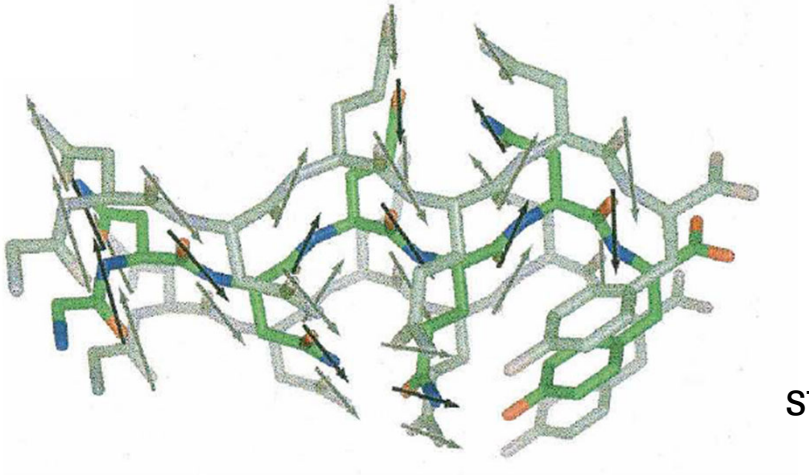
“Static” Cooperativity, e.g. Hydrogen Bond Networks



ureas in apolar solvents & crystal lattice

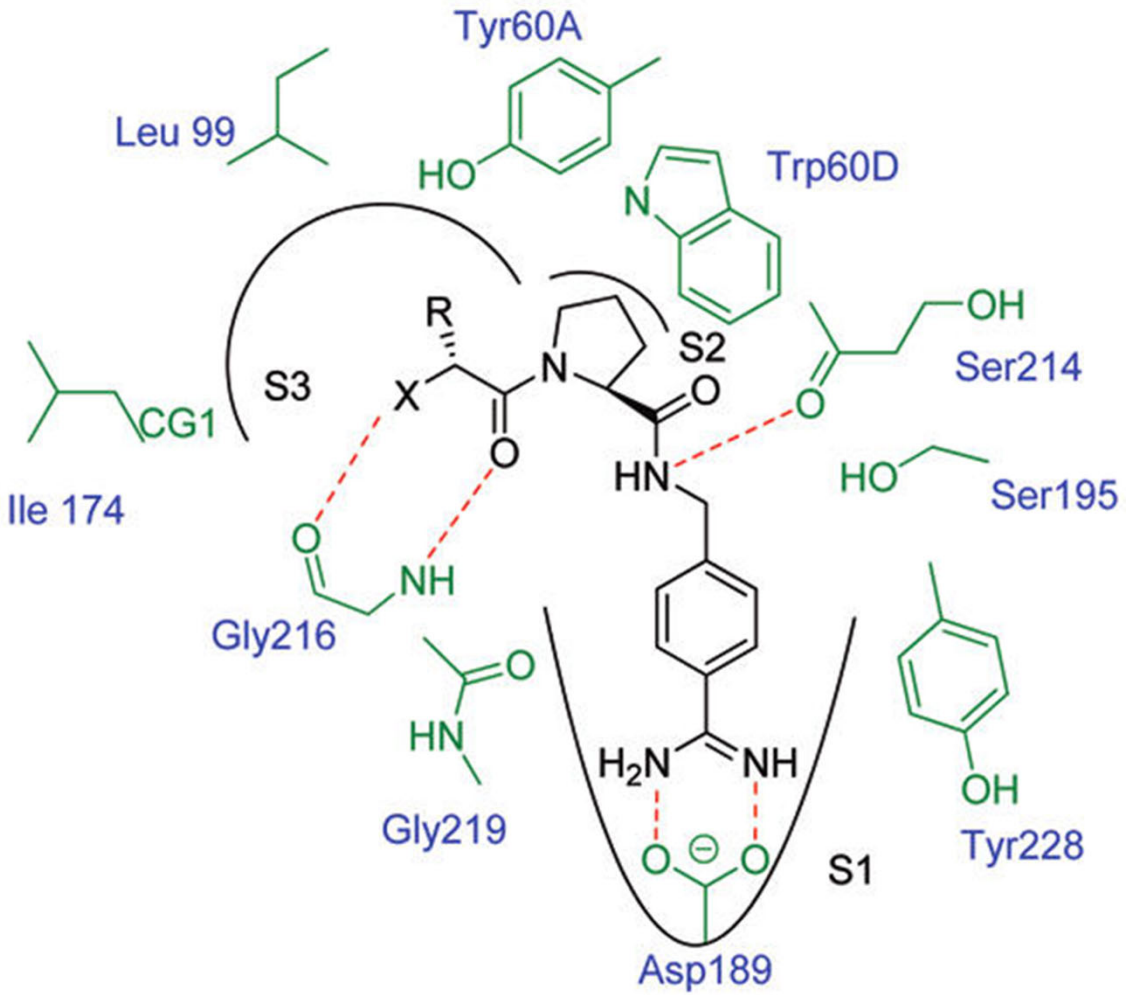


water clusters



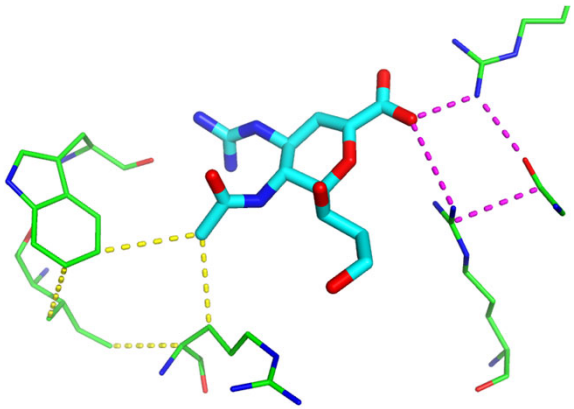
stacking of beta sheets

“Dynamic” Cooperativity



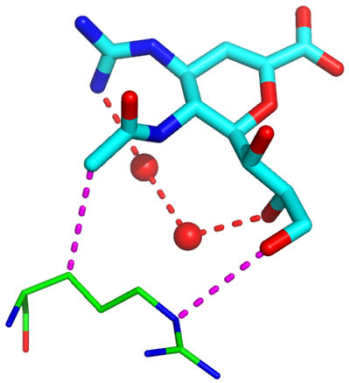
L. Muley et al. *J. Med. Chem.* **2010,** 53, 2126-2135.
B. Baum et al. *J. Mol. Biol.* **2010,** 397, 1042-1054.

Distinct Network Elements Involving Ligand and Protein Atoms



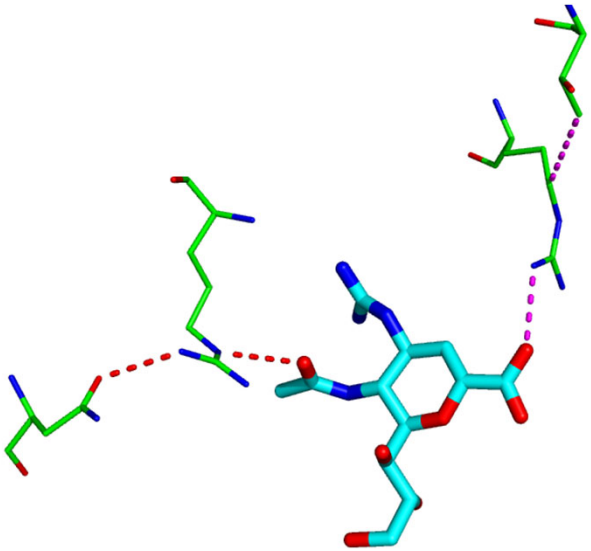
ligand-protein-ligand

“cycles”



ligand-protein-ligand

“loops”



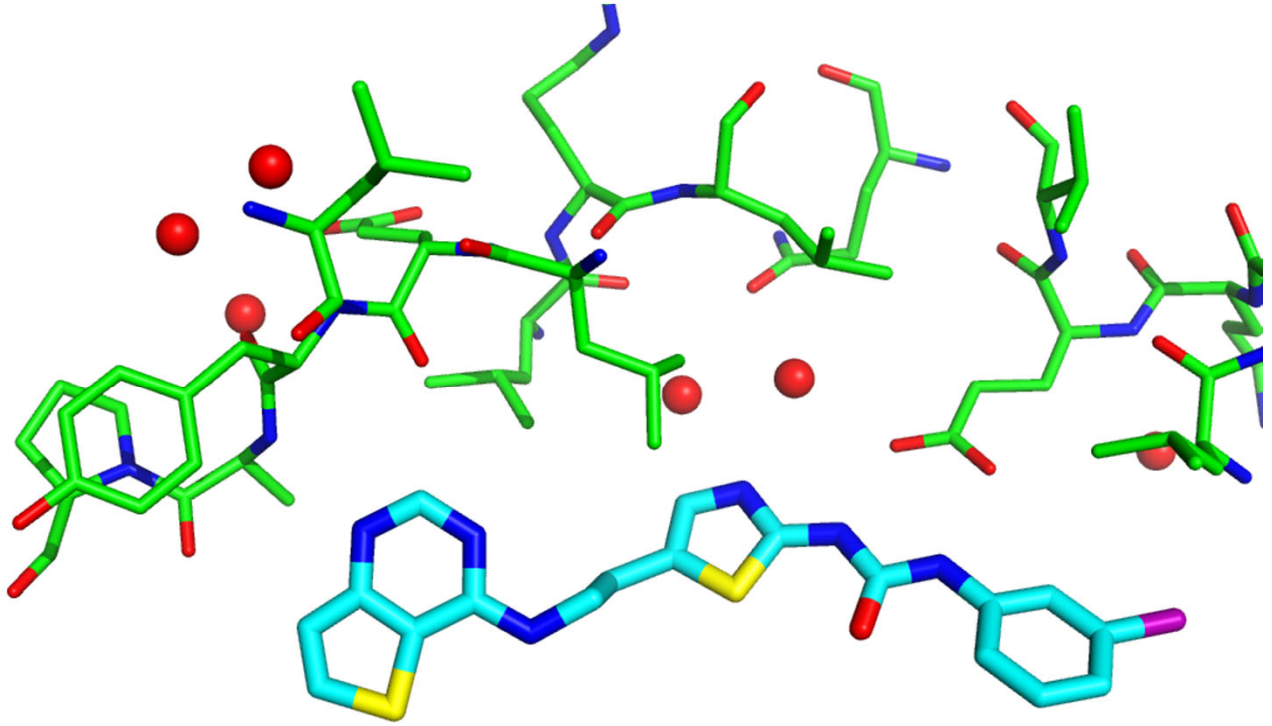
ligand-protein-protein

(subsets of larger loops)

1nnc

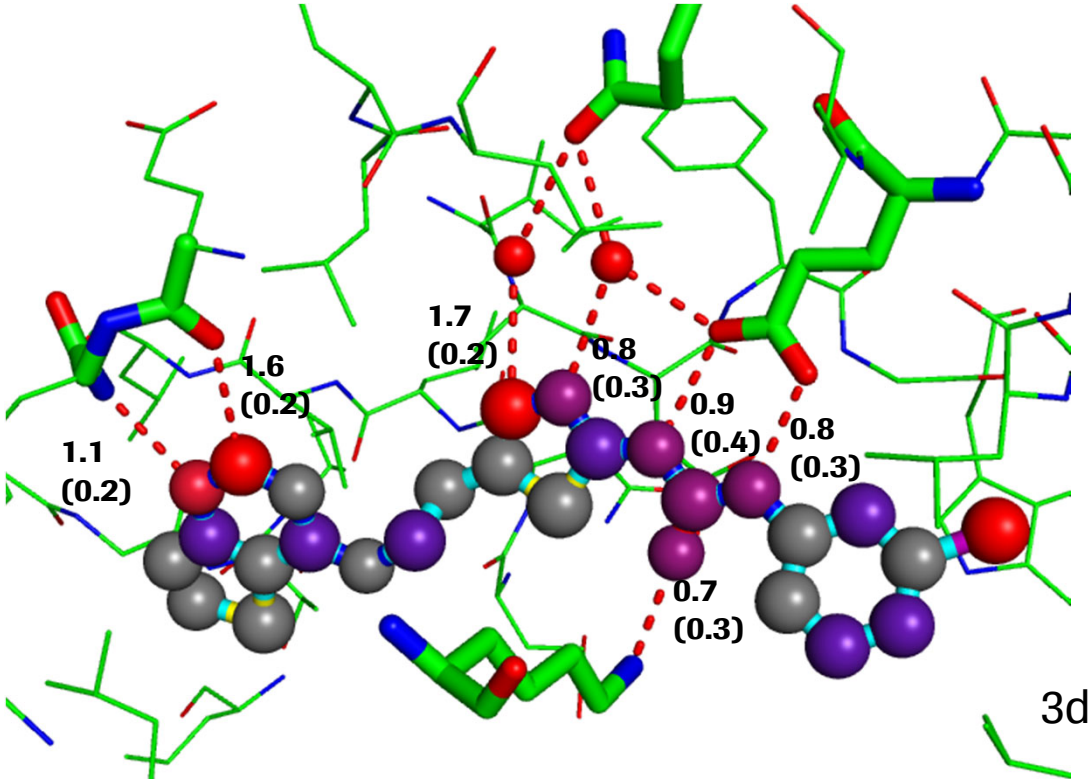
B. Kuhn et al., J. Chem. Inf. Model. **2011,** 51, 3180.

Aurora A Kinase Inhibitors

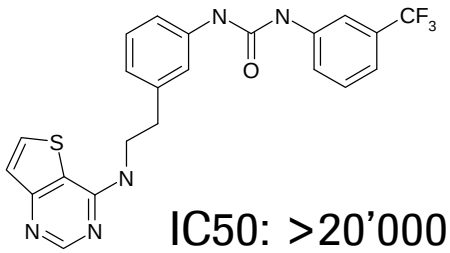


3d15

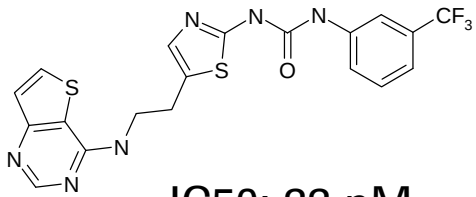
Aurora A Kinase Inhibitors



Aurora A Kinase Inhibitors

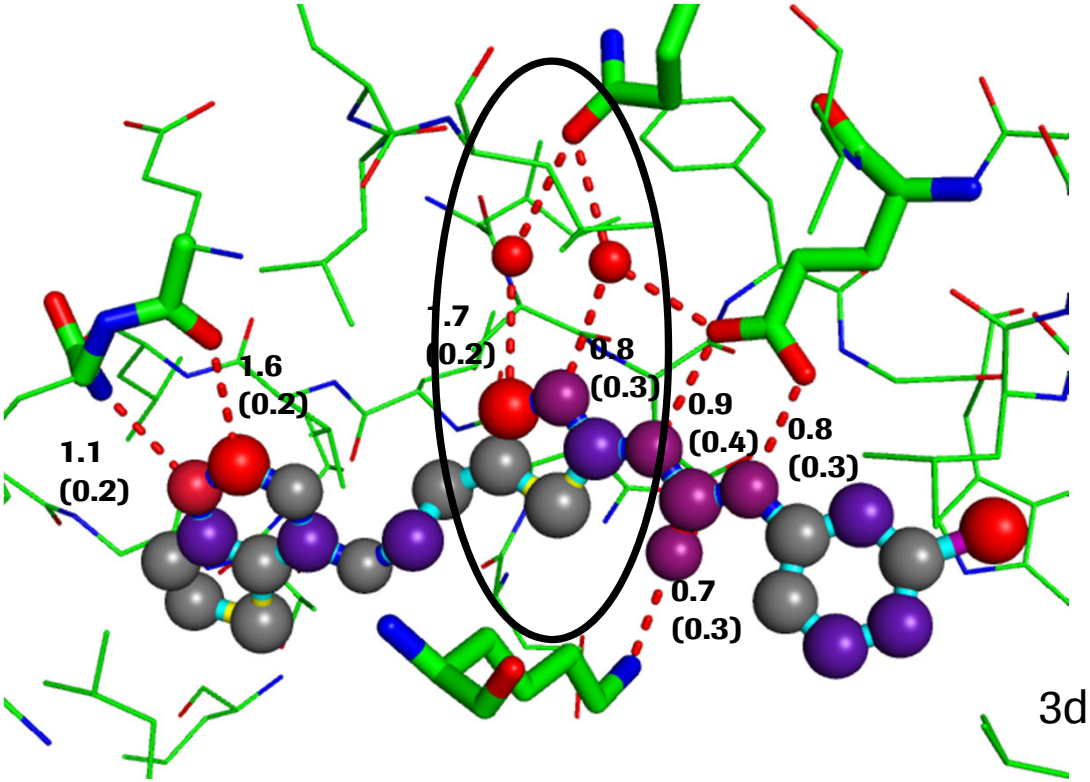


IC50: >20'000 nM



IC50: 22 nM

networked H-bonds with high score incl. network contribution



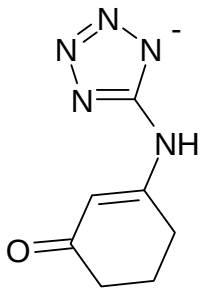
3d15

How Valid is the Network Concept?

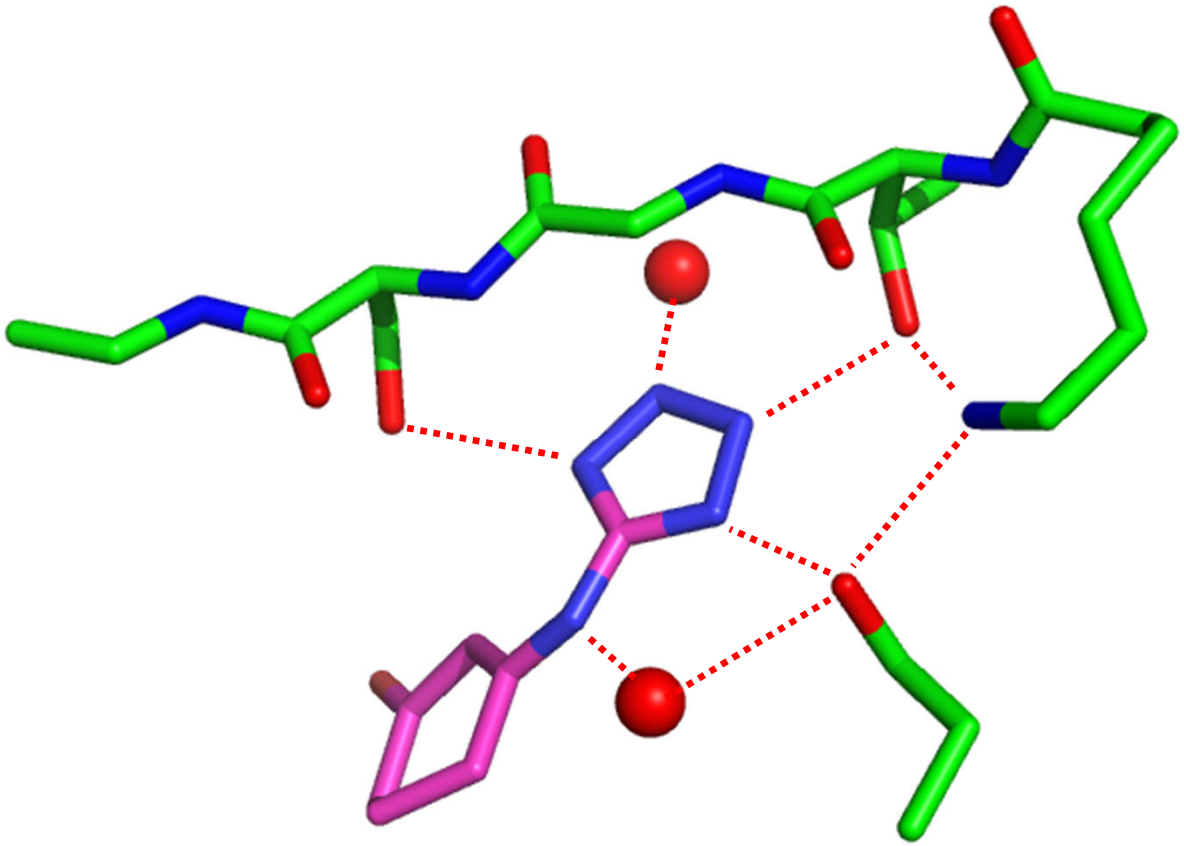
- Forces to consider the complexity of molecular interactions
- Visualization is Key
- A template against which to judge reality

- Scoring function derived to get a feeling for relative magnitude of parameters
- Need far more examples (positive and negative) for robust selection of terms
- Alternatively, use as an expert system (highlight what's been observed before)
- A good network may just mean there is a good fit – true even for fragments
- Current model still treats cooperativity as a very local phenomenon

Beta-Lactamase Inhibitors



~4 mM

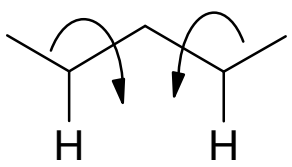


3g2z

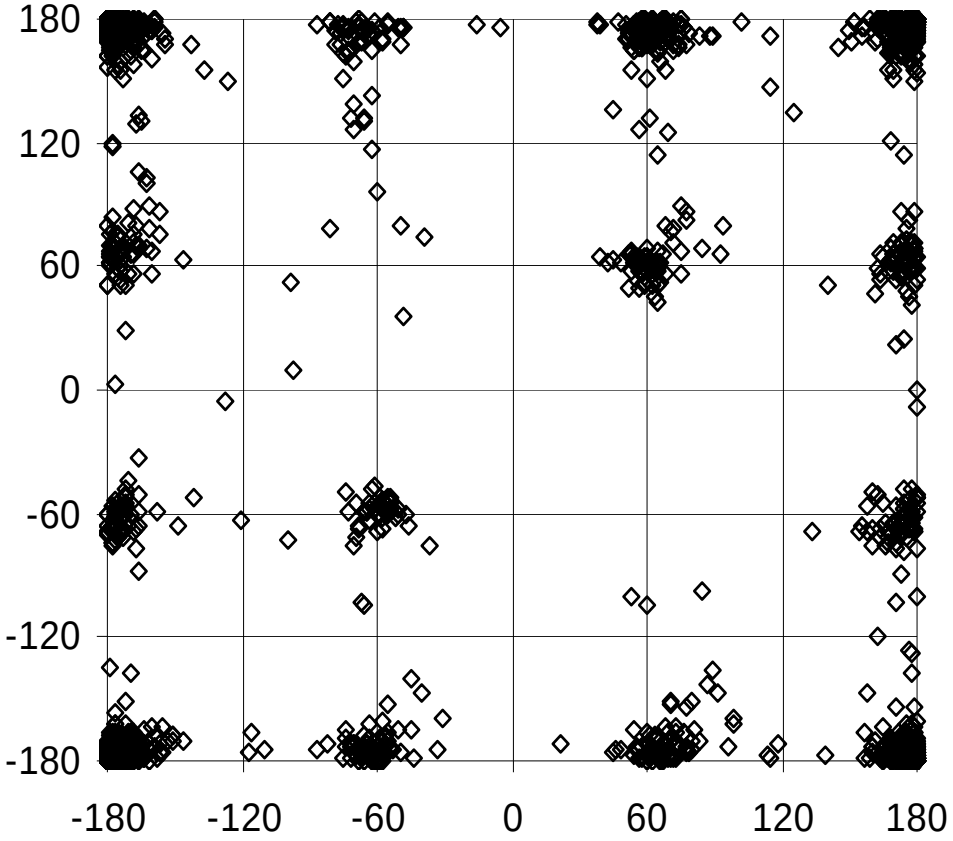
Y. Chen, B. Shoichet, Nature Chem. Biol. 2009, 5, 358

Syn-Pentane Interactions

Strongly Avoided

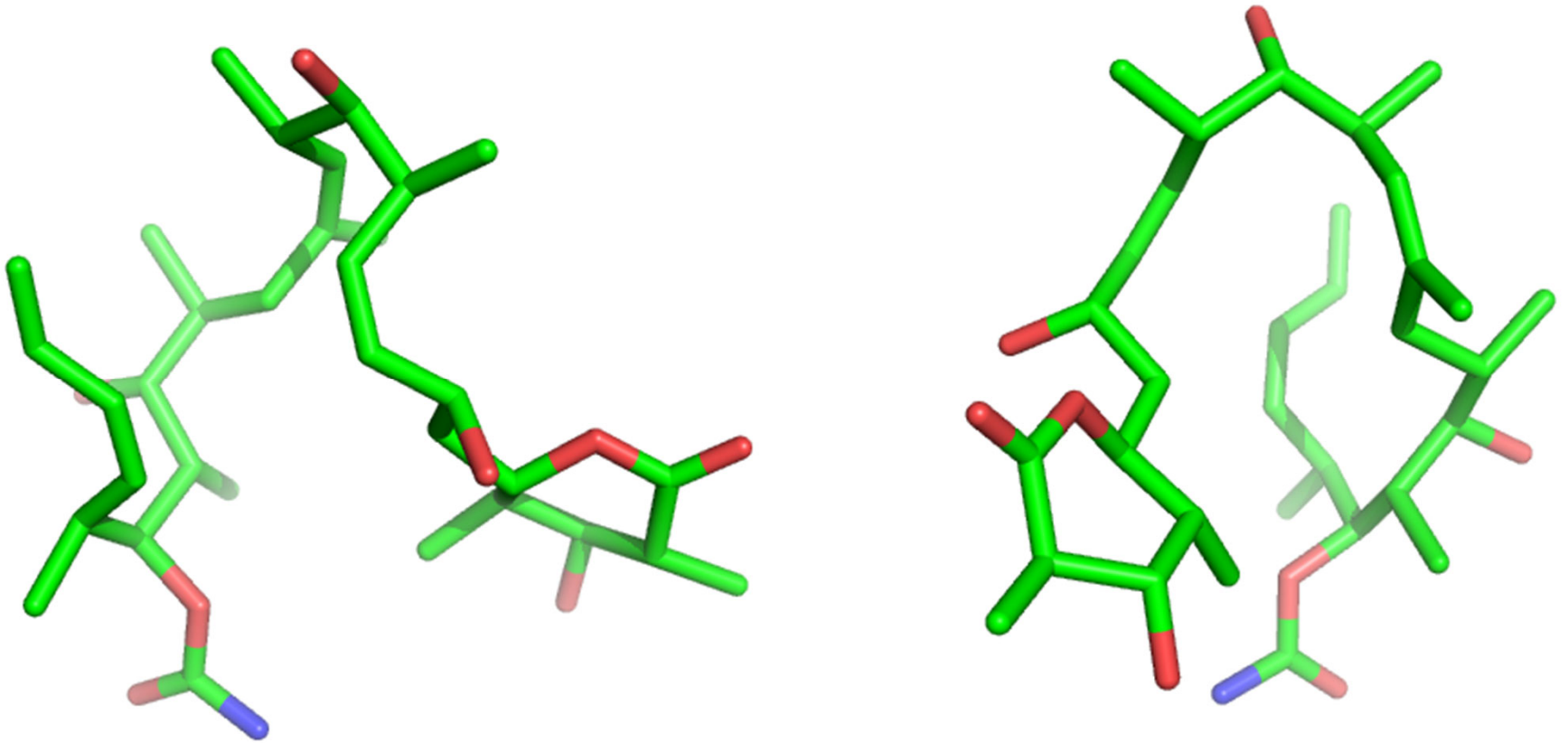


all C sp3



1,5-repulsion
destabilization ~2 kcal/mol

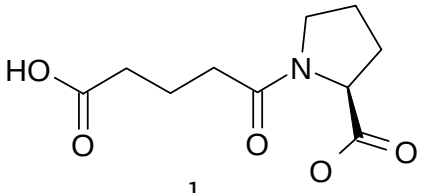
R. W. Hoffmann et al., Chemistry 1998, 4, 559-65.



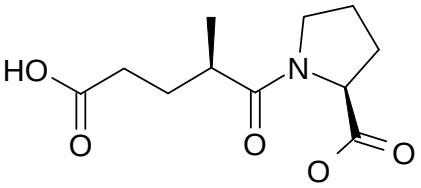
VINTAN01 – Discodermolide

Enalapril SAR

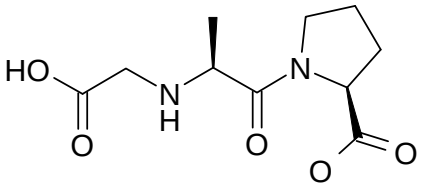
Conformational Locking Avoiding Syn-Pentane Interactions



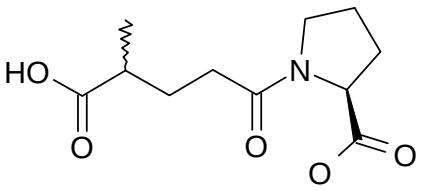
70 μM [1]



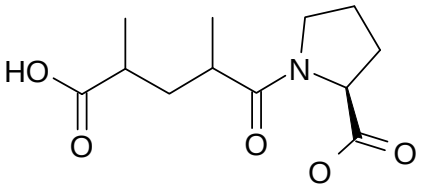
4.9 μM [1]



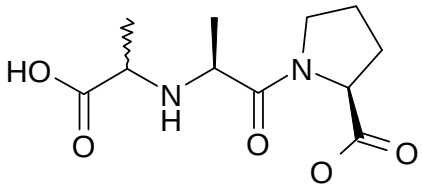
2.4 μM [2]



260 μM [1]



4.8 μM [3]



0.09 μM [2]

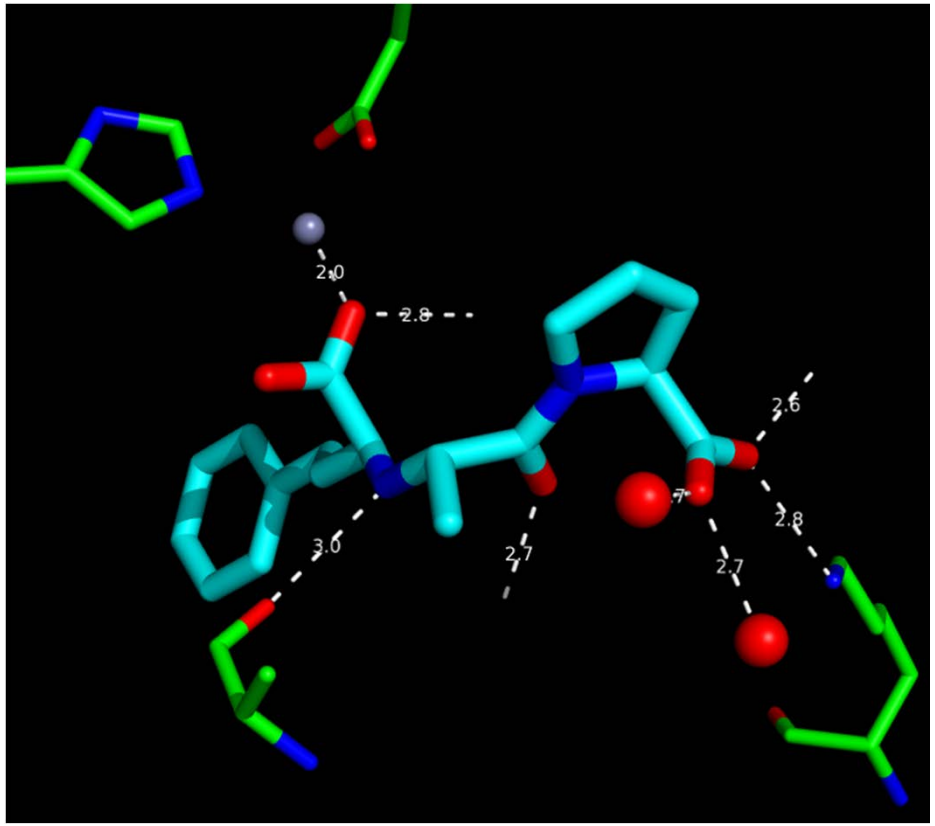
1. D. W. Cushman, et al., *Biochemistry* **1977,** 16, 5484-5491.

2. A. A. Patchett, ACS: Washington DC, 1993; Vol. 3, pp 125-163.

3.. P. Shi, P.; Wang, H. *Shandong Yixueyuan Xuebao (Acta Academiae Medicinae Shandong)* **1984,** 22, 44-48.

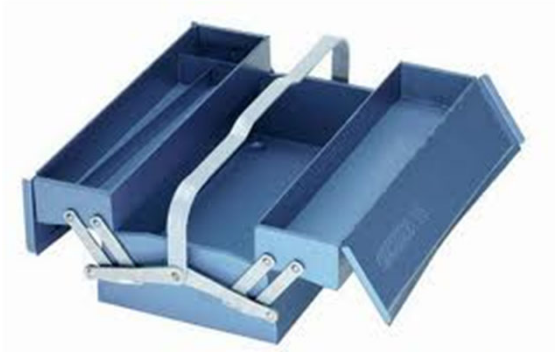
Enalapril / ACE Cocrystal Structure

No Direct Interaction formed by Methyl Group



1uze Enalaprilate – human testicular ACE1

Using the Tools



Best Practices

- Molecular Design is interactive work, it needs to be practiced like an instrument.
- Besides optimizing attractive interactions, monitor repulsive ones.
- Target rigid portions first.
- Conformations and interactions cannot be separated.

- Carefully assess experimental structures:
  - Electron densities
  - Invest into solving apo structures
  - Carefully analyze water networks
  - Assess key properties of pockets: rigid / induced two-state / induced with multiple conformations
  - Use overlays to solidify assessments (water / flexibility)

- Deconvolute larger ligands: Make compounds that lead to understanding which pockets, which moieties are giving what binding affinity
- Consciously push the boundaries of your models.

Acknowledgments

Bernd Kuhn

Jens-Uwe Peters

Wolfgang Haap

Michael Harder

François Diederich

We Innovate Healthcare