University of Silesia, Katowice, Poland
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Ligand-receptor interactions

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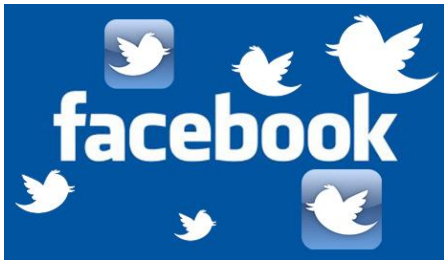
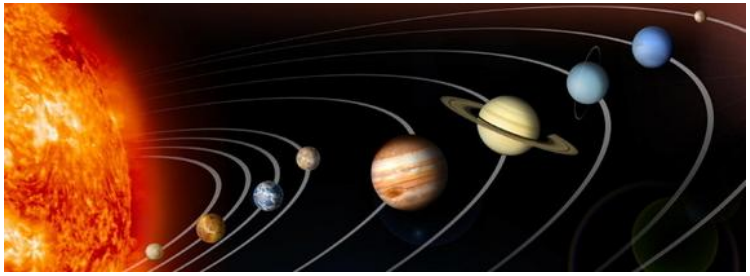
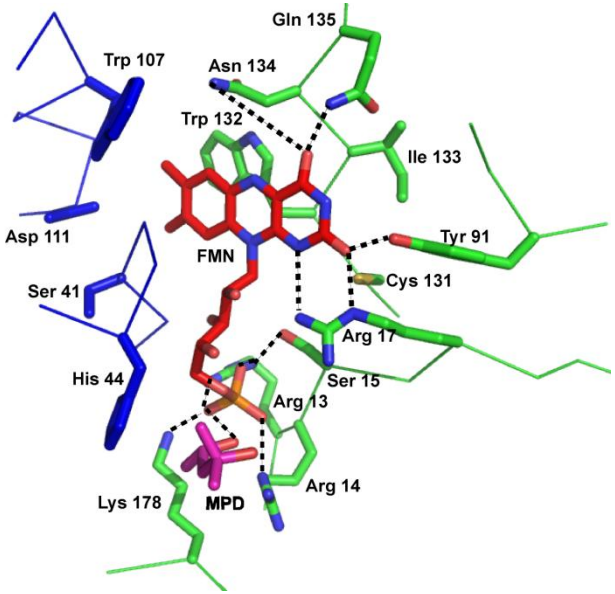
Interactions







Receptors and ligands

"Receptive substance"

Langley, 1878

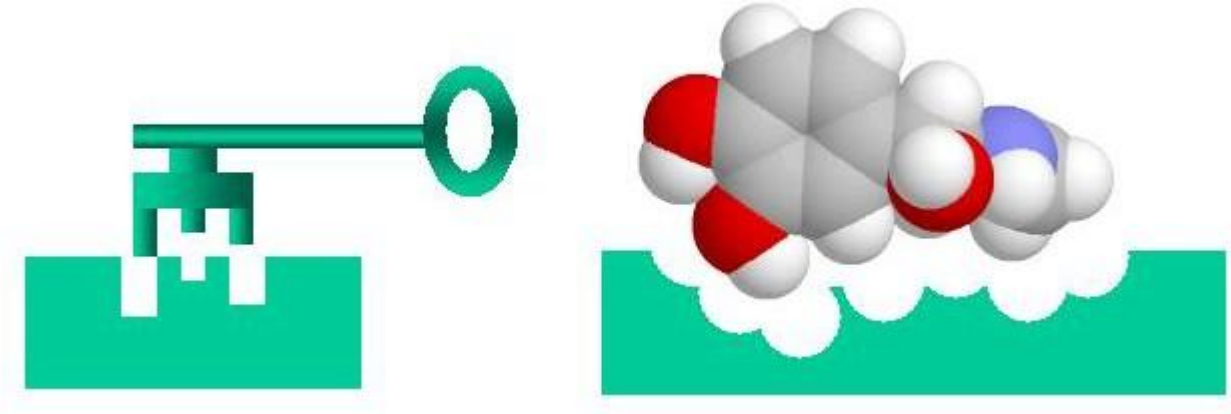
"Receptor",
"Pharmacophore"

Paul Ehrlich, 1900

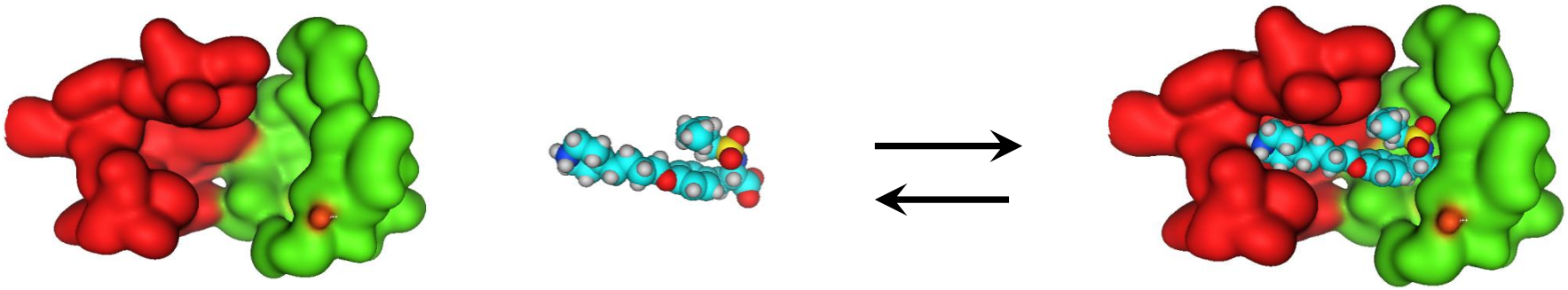
Lock-and-key paradigm

Emil Fisher, 1894

Lock-and-key paradigm



Ligand-receptor interaction



[R] [L] [RL]

$$K = \frac{[RL]}{[R][L]}$$

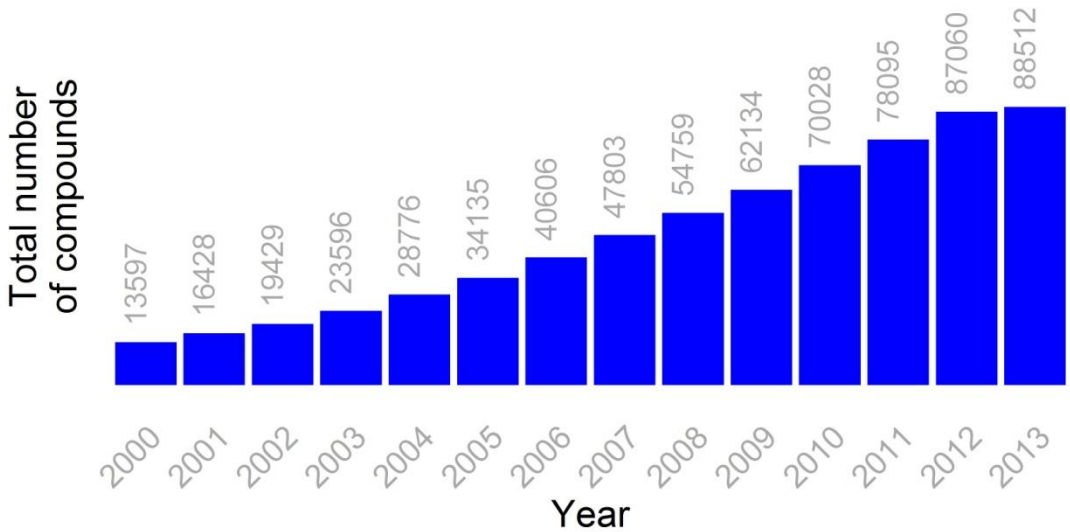
$$\Delta G° = -RTlnK = -2.303RTlogK$$

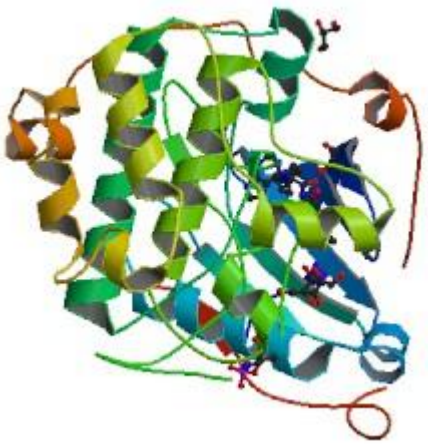
$$\Delta G° = 1.42logK$$ at 37°C

Protein Data Bank (PDB)

RCSB PDB PROTEIN DATA BANK http://www.pdb.org/pdb/home/home.do

Exp.Method	Proteins	Nucleic Acids	Protein/NA Complexes	Other	Total
X-RAY	72761	1440	3746	2	77949
NMR	8615	1022	192	7	9836
ELECTRON MICROSCOPY	342	41	123	0	506
HYBRID	46	3	2	1	52
other	147	4	5	13	169
Total	81911	2510	4068	23	88512



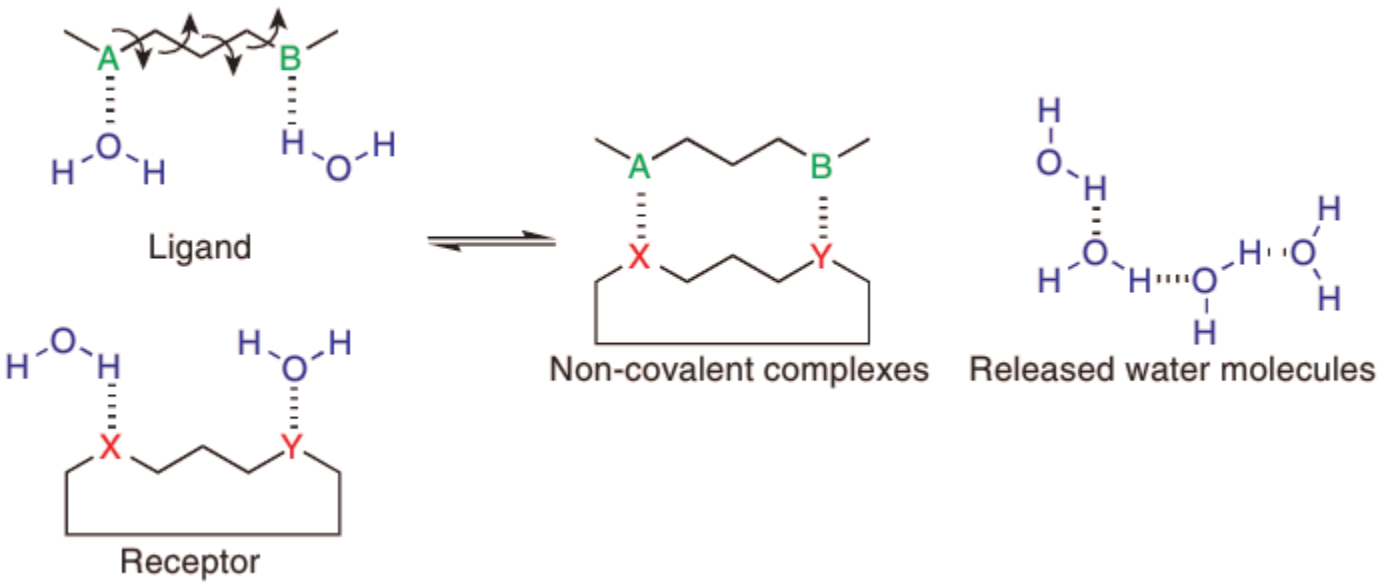


Enthalpy and enthropy

$$\Delta G = \Delta H - T\Delta S$$

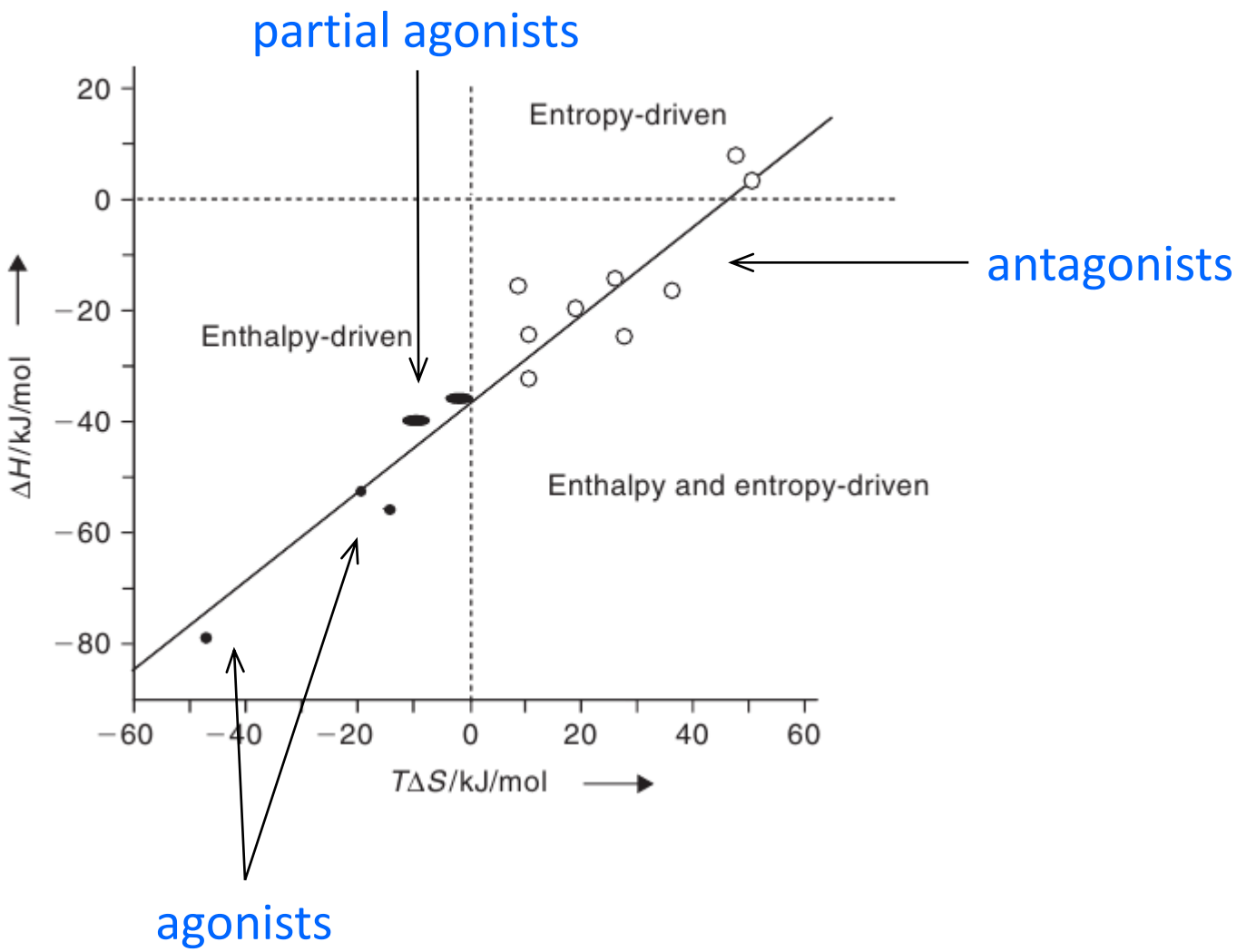
Entropy-enthalpy compensation

In short, the tighter and more directed an interaction, the less entropically favorable it is.
Bonding opposes motion, and motion opposes bonding.



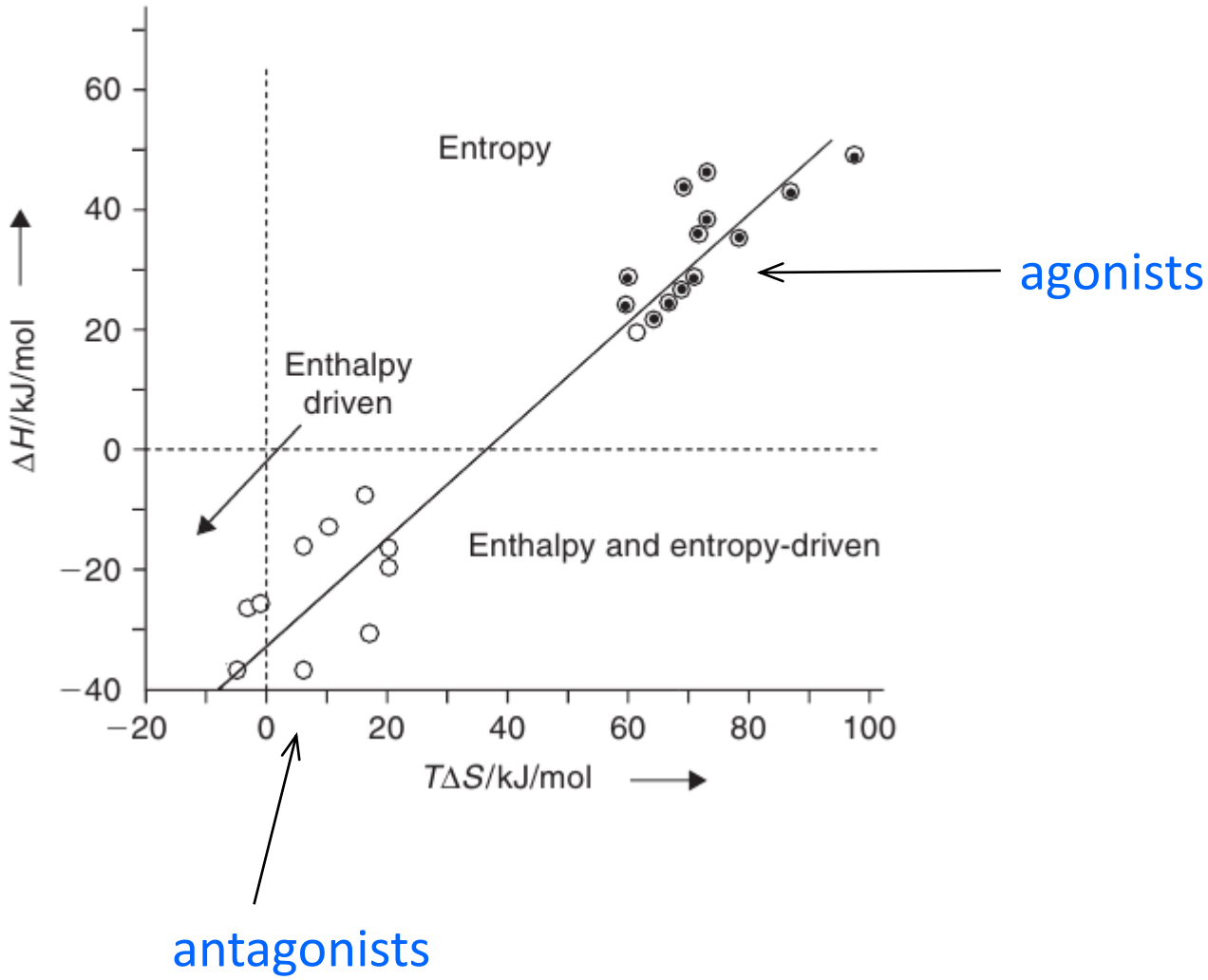
Entropy-enthalpy compensation: Example 1

β-adrenoreceptor ligands



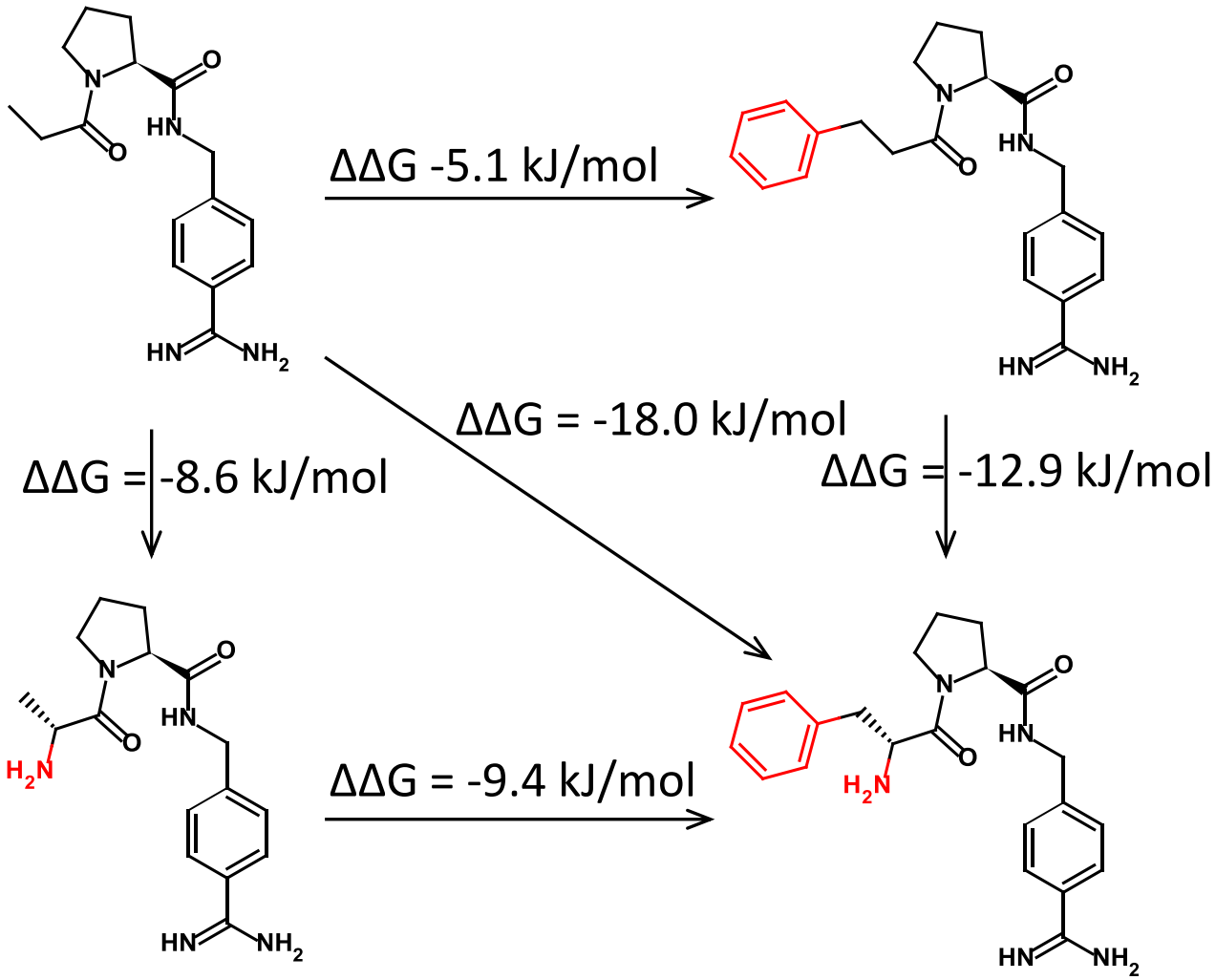
Entropy-enthalpy compensation: Example 2

adenosine A1 receptor ligands



Cooperativity

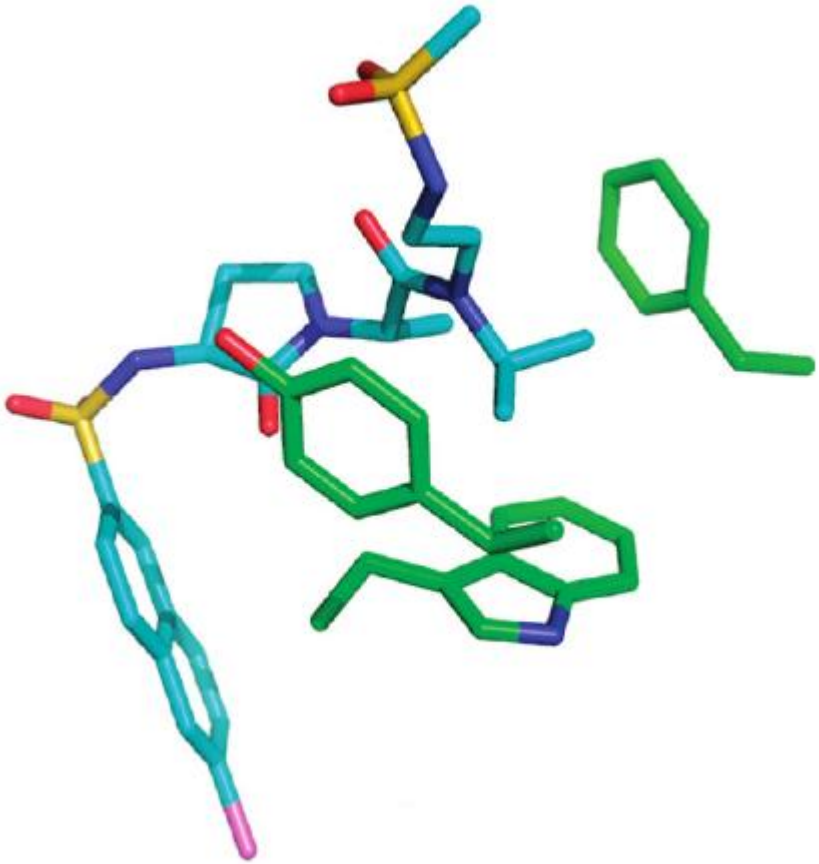
Thrombin inhibitors



Cooperativity = 18.0 – (5.1 + 8.6) = 4.3 kJ/mol

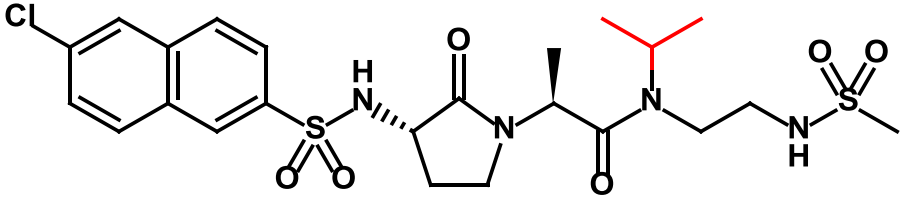
Muley L. et al, *J. Med. Chem.*, **2010**, *53* (5), pp 2126–2135

Desolvation and hydrophobic effects

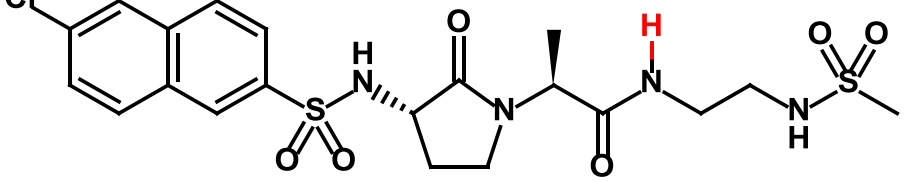


PDB: 2J4I

Factor Xa inhibitors

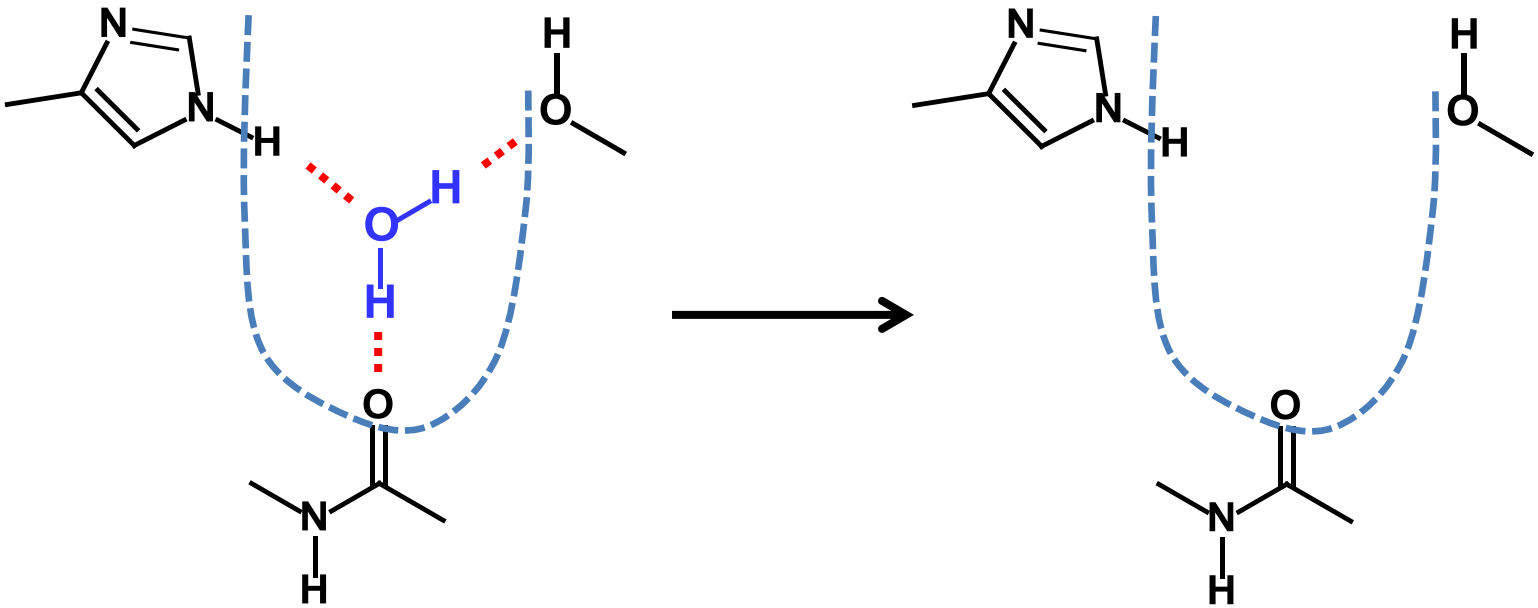


K_i = 1 nM



K_i = 39 µM

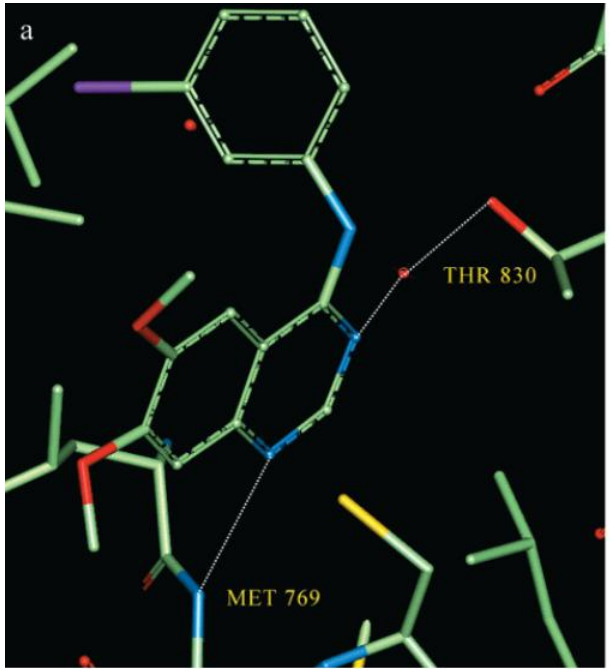
Structural water

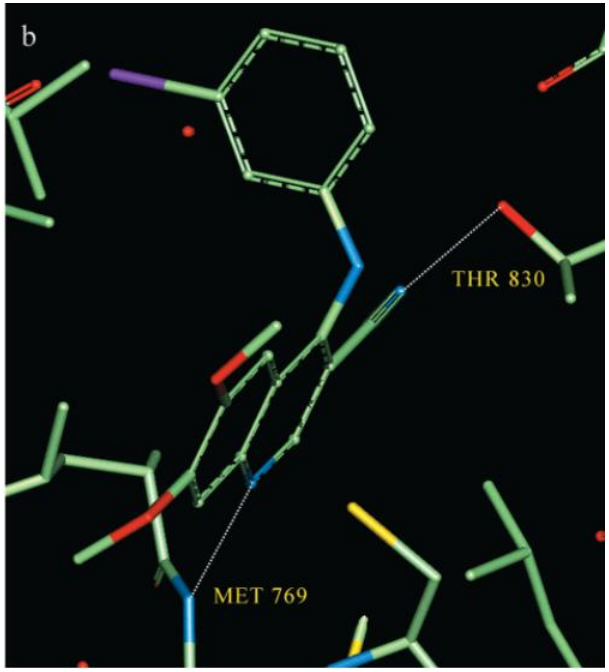


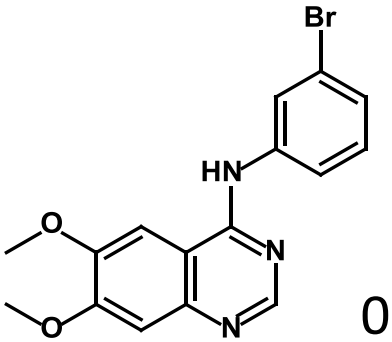
Entropy gain up to 2 kJ/mol

Structural water

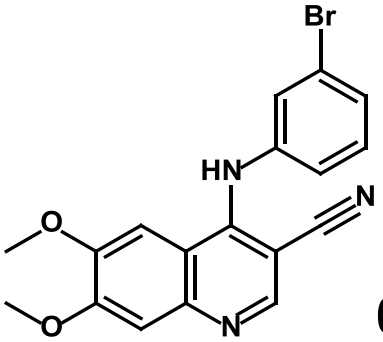
Inhibitors of Epidermal Growth Factor Receptor (EGFR) Kinase







IC_{50}
0.07 μM

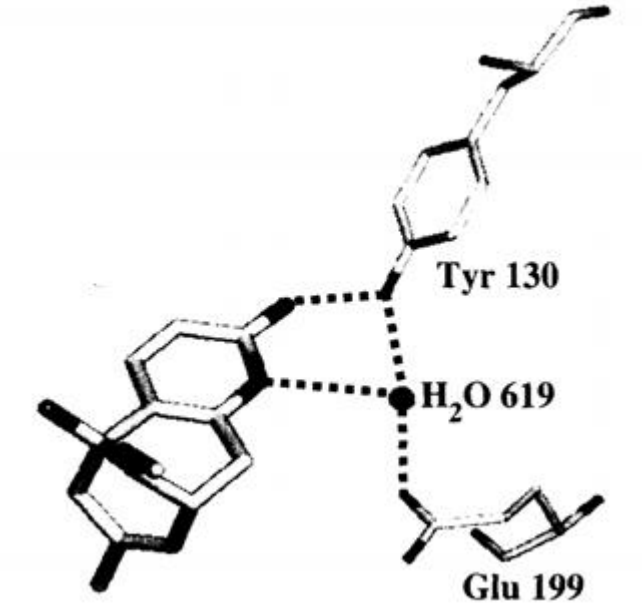


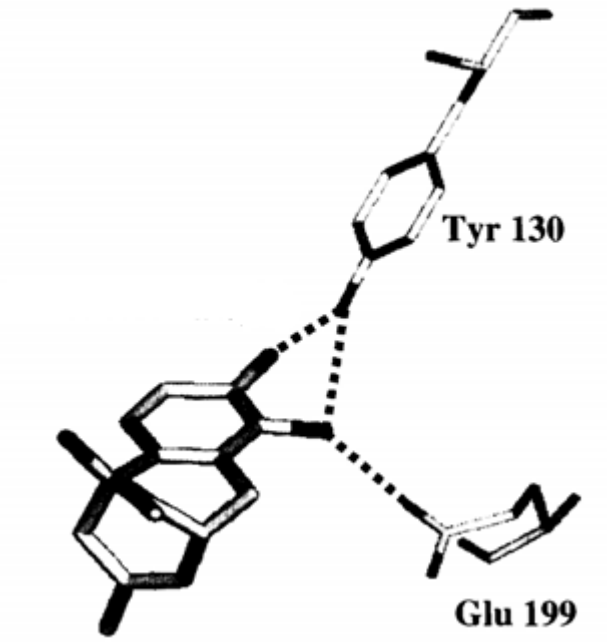
IC_{50}
0.19 μM

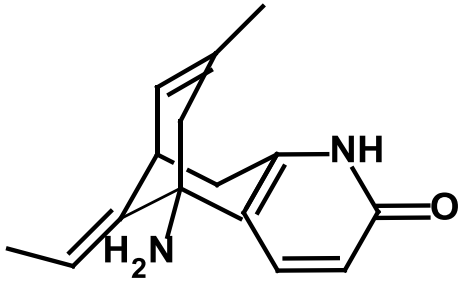
Wissner A. et al, J. Med. Chem., **2000**, *43* (17), pp 3244–3256

Structural water

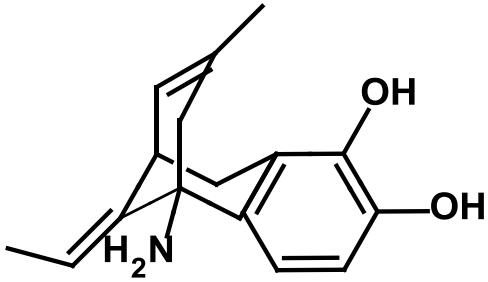
Inhibitors of acetylcholinesterase (AChE)







Huperzine

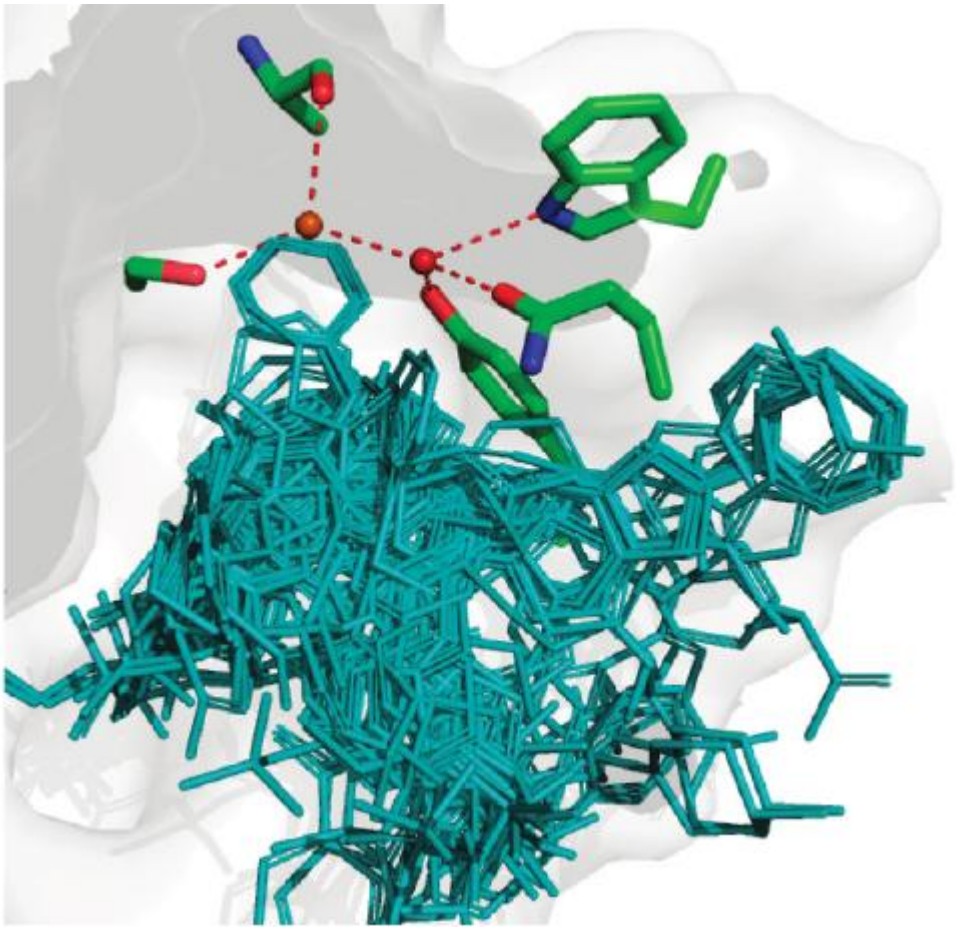


Catechol Analogue

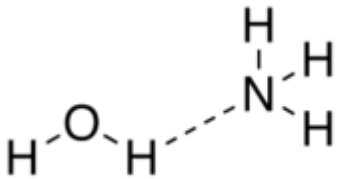
Campiani G. et al, Bioorganic & Medicinal Chemistry Letters, 1998, 8 (11), 1413-1418

Structural water

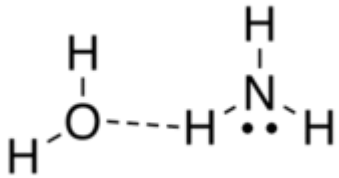
Overlay of 15 PDE10 inhibitors



Specific interactions. Hydrogen bonding.

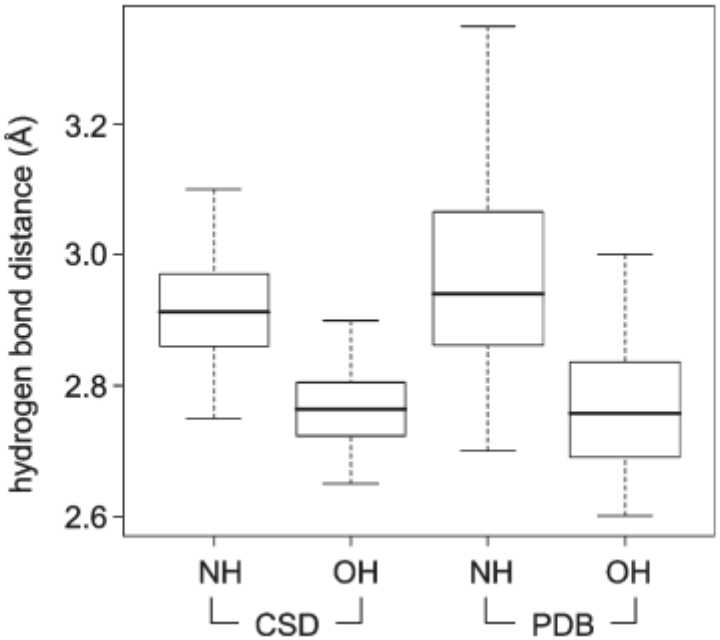


hydrogen bond **donor** hydrogen bond **acceptor**



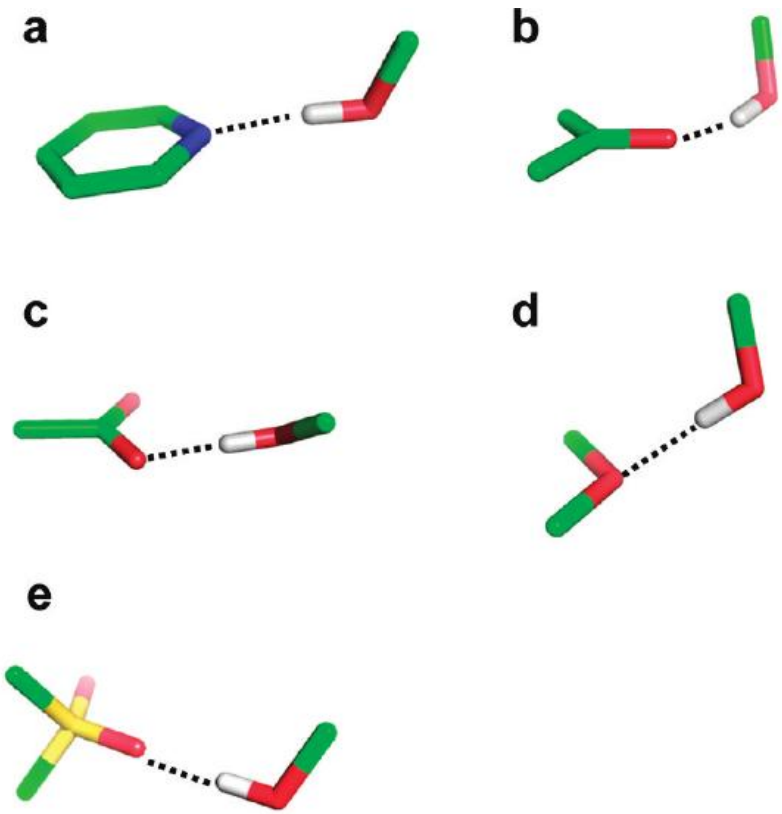
hydrogen bond **acceptor** hydrogen bond **donor**

Distance preference



Hydrogen bonding.

Angle preference



1. Donor – hydrogen • • acceptor
   > 150°

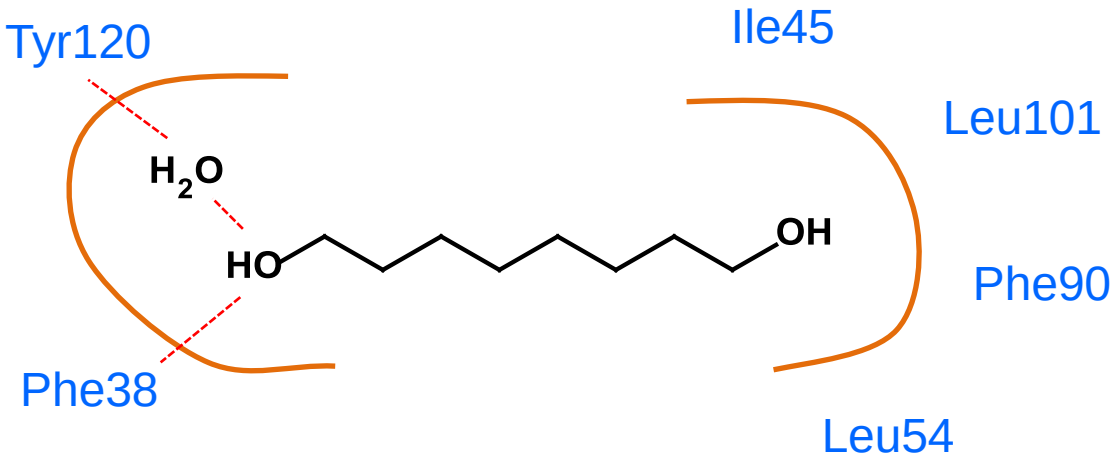
2. C=O • • H
   120°
   Exception: sulfonyl

3. Carboxyl groups
   syn orientation is preffered

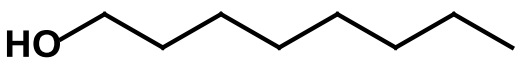
4. Aromatic acceptors
   deviation from the plane < 30°

Hydrogen bonding.

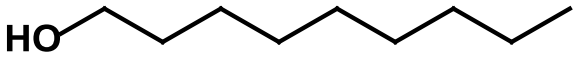
Major urinary protein



K_d = 1011 μM



K_d = 0.63 μM



K_d = 0.18 μM

Barrat E. et al, Journal of Molecular Biology, 2006, 362, 5, 994-1003

Hydrogen bonding.

Basicity ⟷ H-bond strength

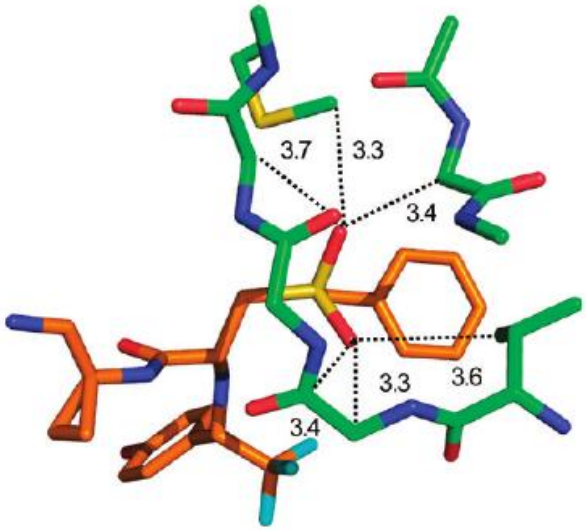
Hydrogen bonding: Empirical findings from CSD analysis

1. Cyclic amides and ethers are stronger acceptors than acyclic ones

2. Electron-donating substituents in aromatic rings increase acceptor strength

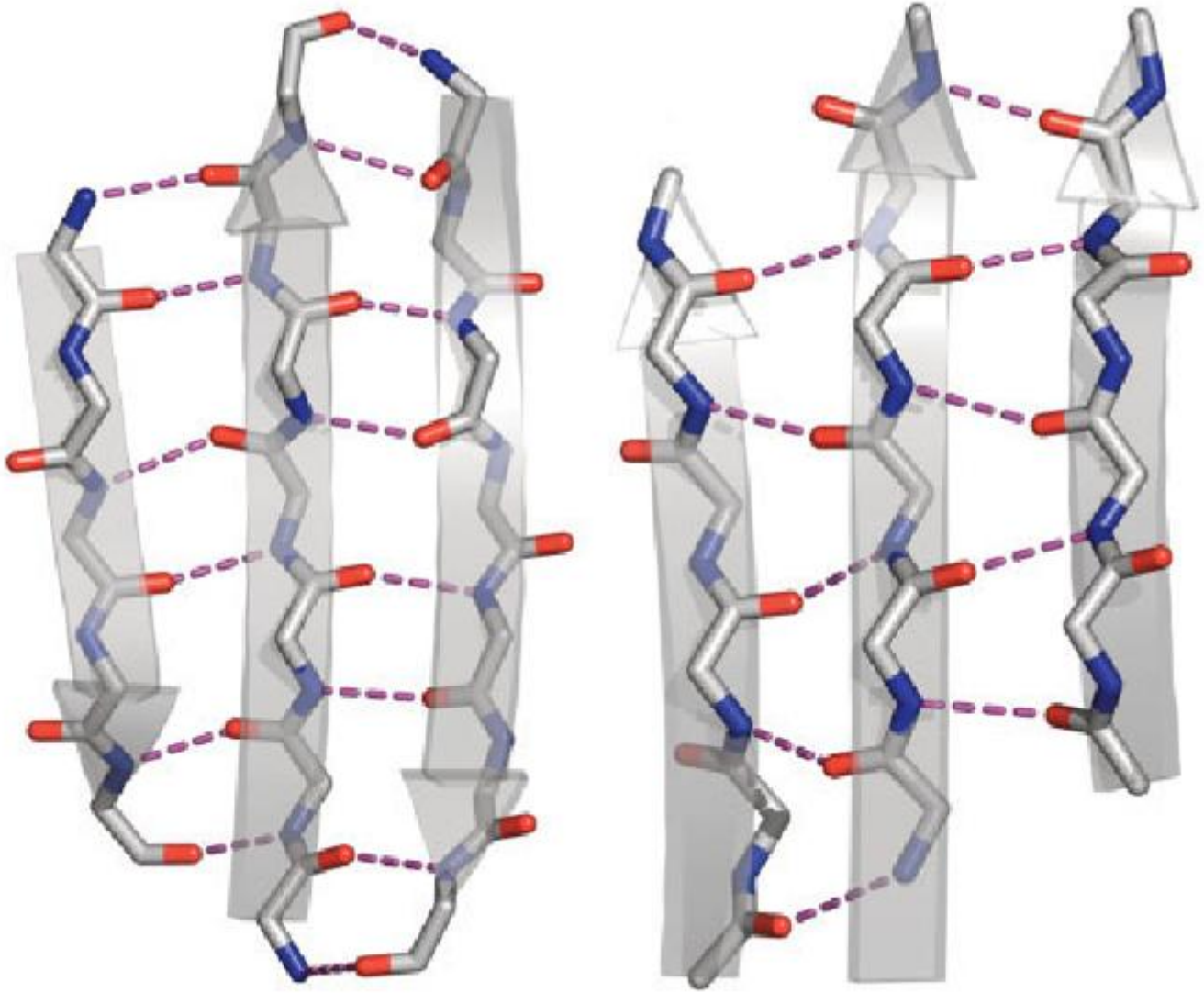
3. Aromatic ether are weaker acceptor than aliphatic.

4. Sulfones and sulfonamides are weak H-bond acceptors and they can be found more often in hydrophobic environment or form weak H-bonds with C-H.



PDB: 2FRA

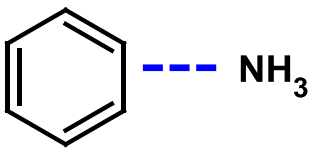
Cooperativity of H-bonds



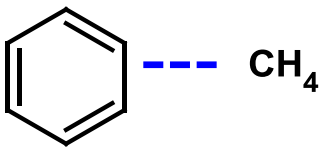
antiparallel β-sheet

parallel β-sheet

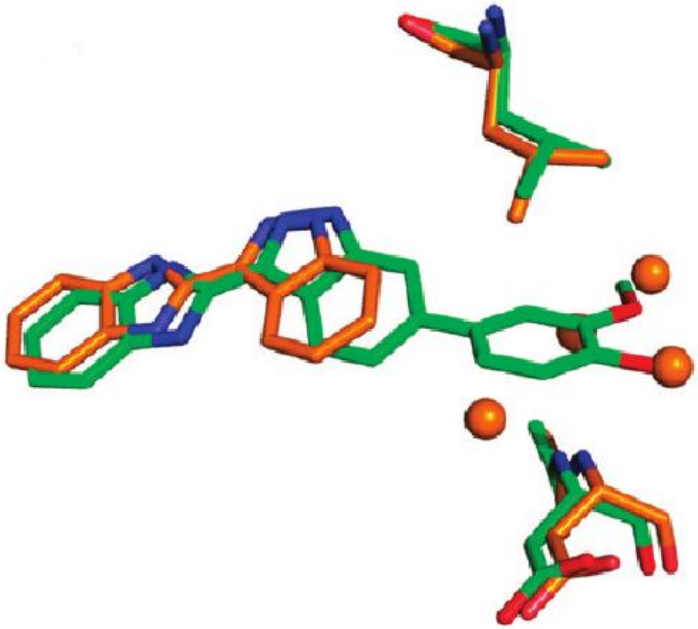
Weak H-bonds



2.2 kcal/mol
(in gas)



1.5 kcal/mol
(in gas)

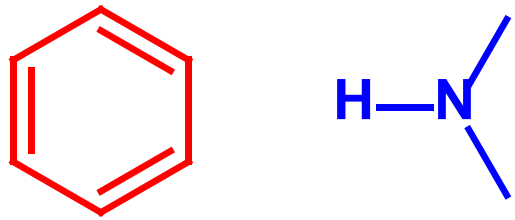


2C3L (orange): K_i = 8.5 μM

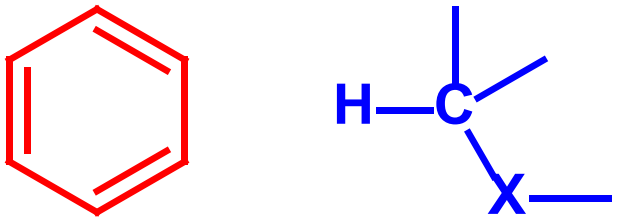
2C3K (green): K_i = 0.026 μM

Weak H-bonds

acceptor donor



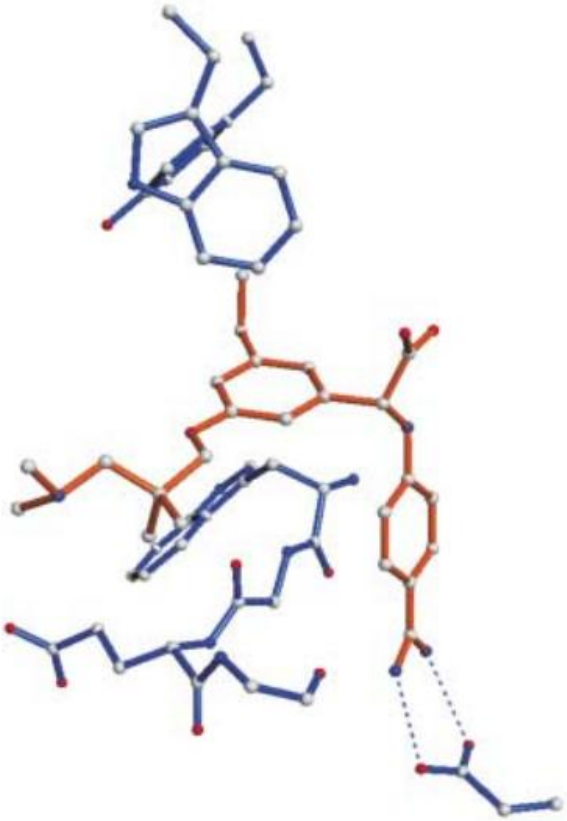
rare



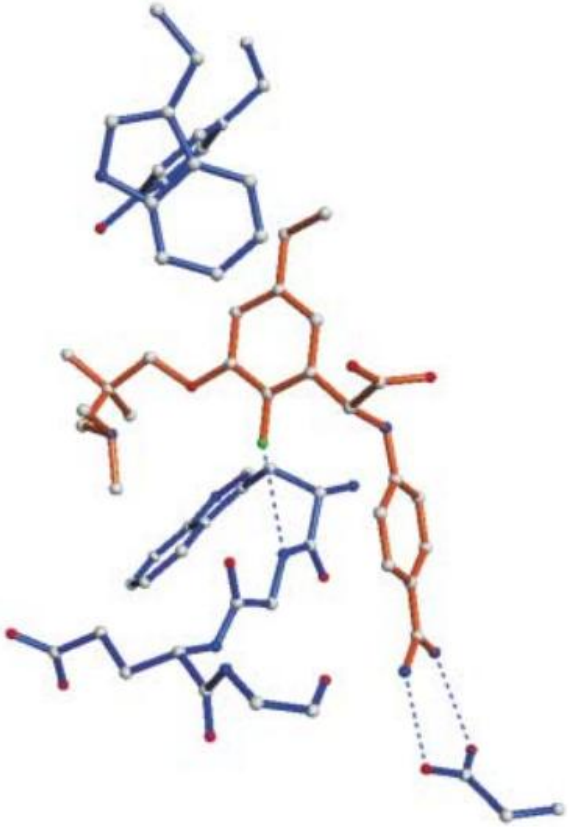
frequent

Weak H-bonds

Thrombin inhibitors



K_i = 1.6 μM

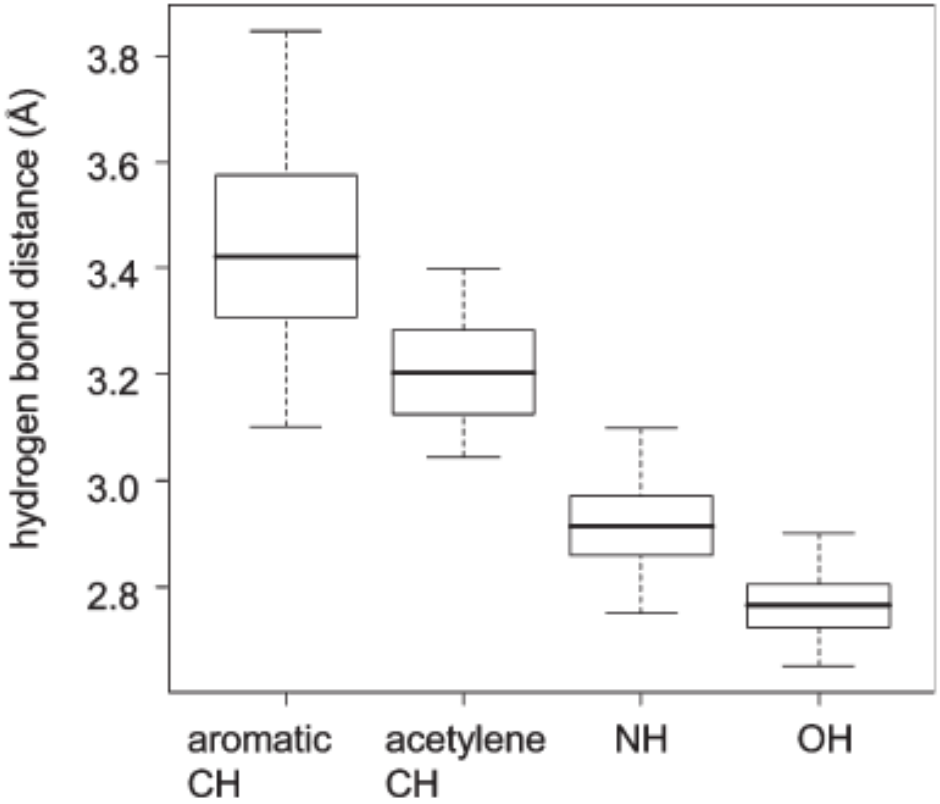


K_i = 0.26 μM

Böhm H. et al, ChemBioChem, 2004, 5 (5), 637-643

Weak H-bonds

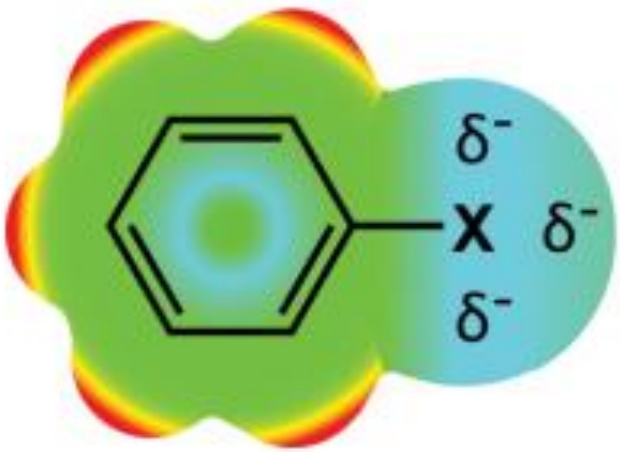
Distance preference



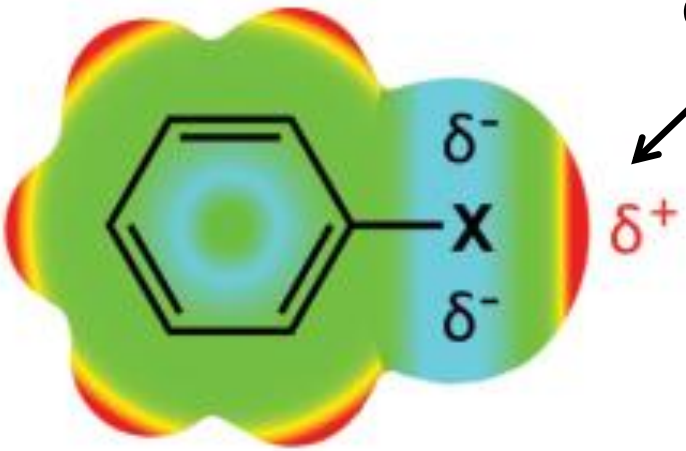
distance to oxygen atom of amide bond

Halogen bonding

Ph-F



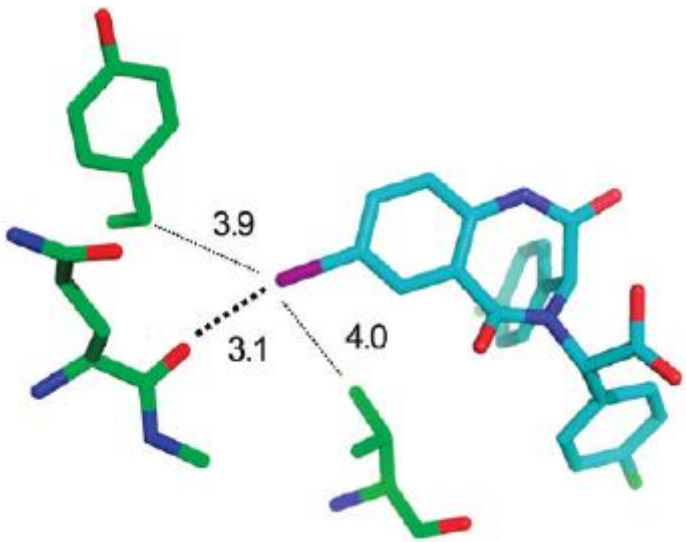
Ph-Cl, Ph-Br, Ph-I



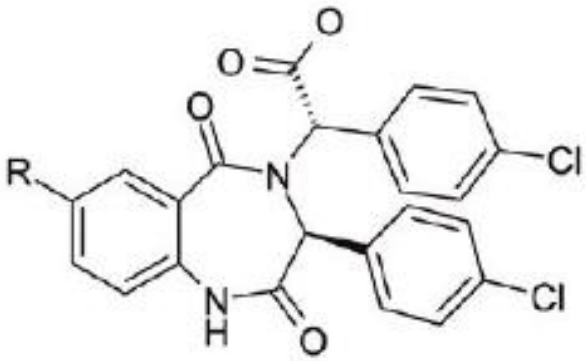
σ-hole

Wilcken R. et al, *J. Med. Chem.*, **2013**, *56* (4), pp 1363–1388

Halogen bonding



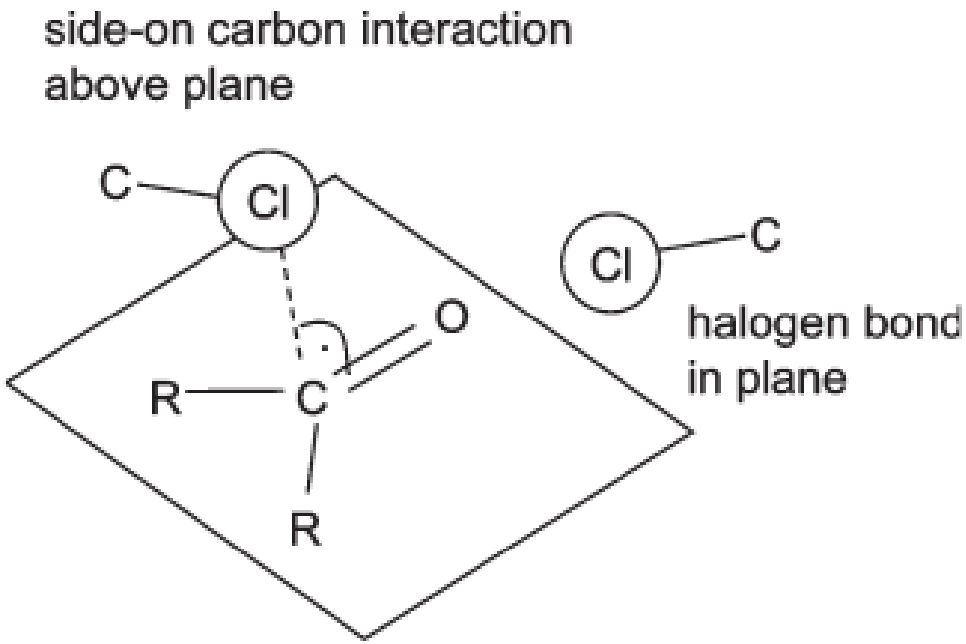
PDB: 1T4E

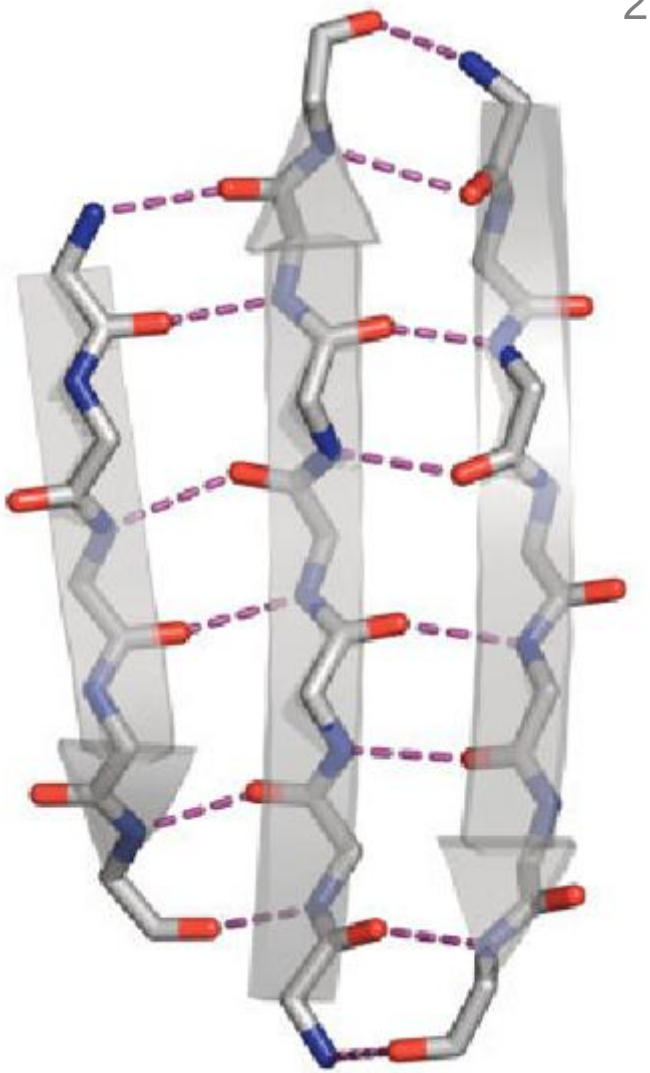


R	Kd (μM)
-H	7.69
-I	0.067
-Br	0.83
-CCH	0.25

Halogen bond ⟷ Weak H-bond

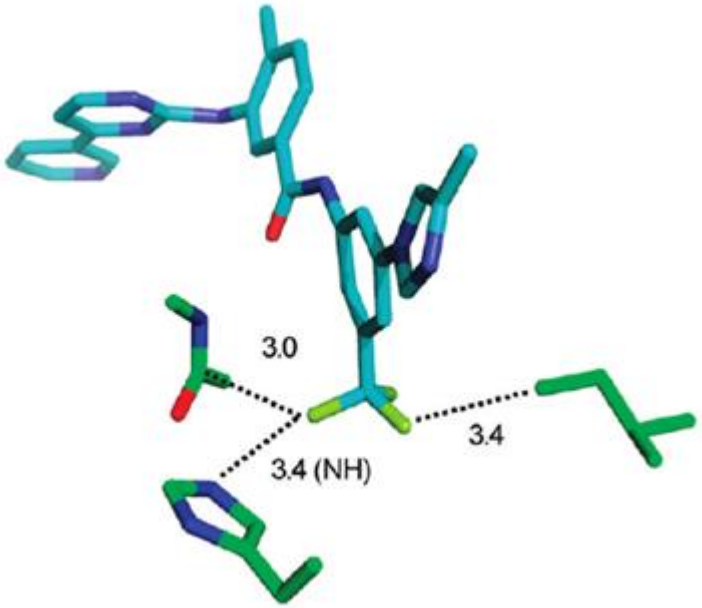
Orthogonal multipolar interactions



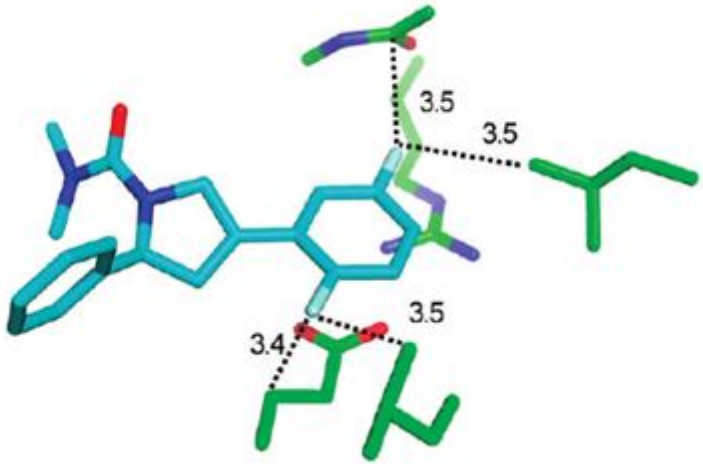


antiparallel β-sheet

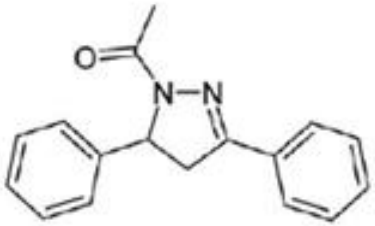
Orthogonal multipolar interactions



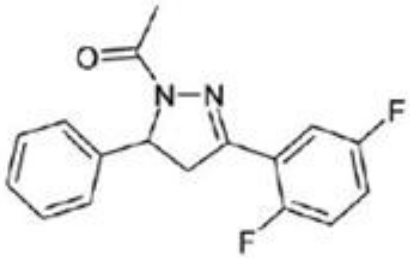
PDB: 3CS9



PDB: 2FL6

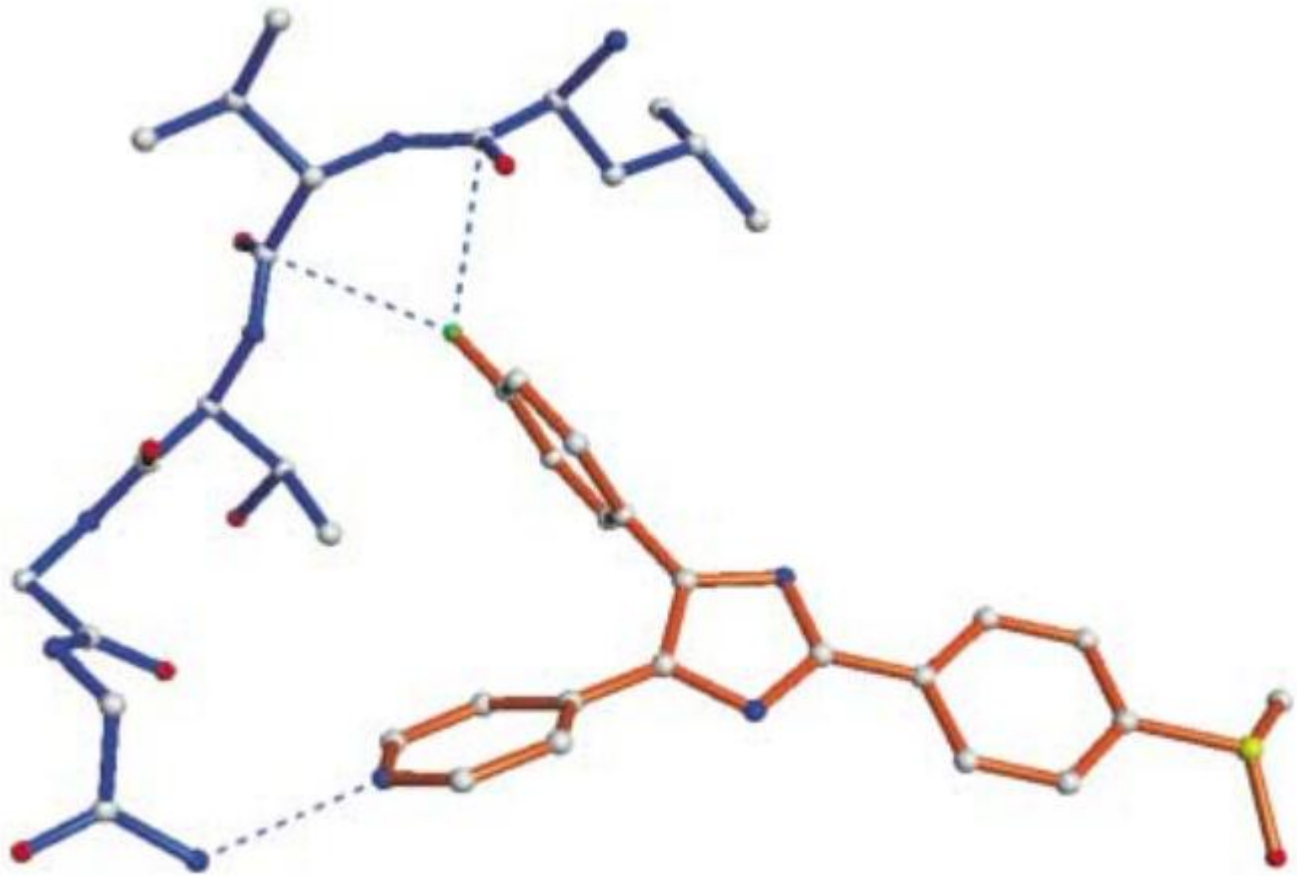


ATPase IC50 > 50 μM



ATPase IC50 = 94 nM

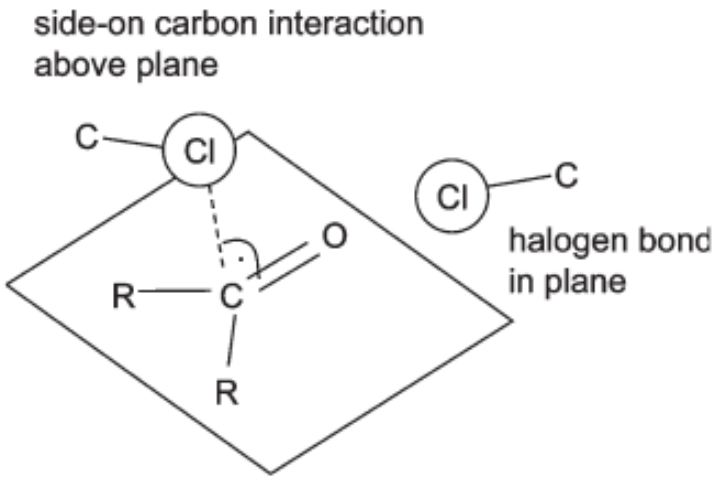
Orthogonal multipolar interactions

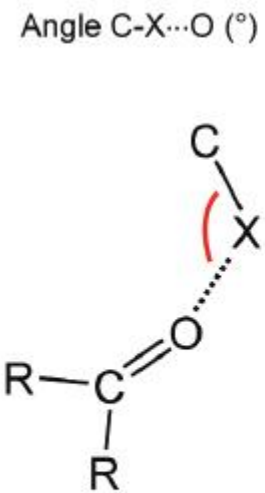


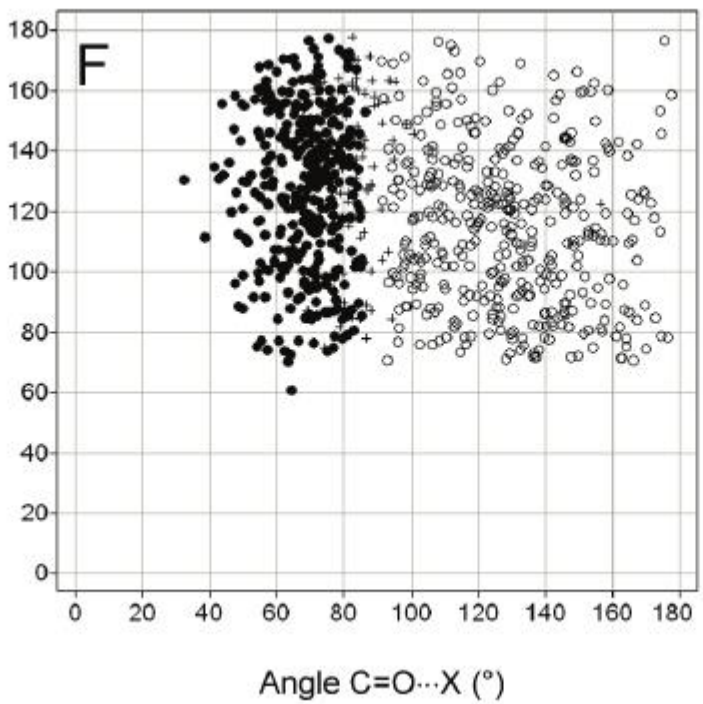
PDB: 1AU9

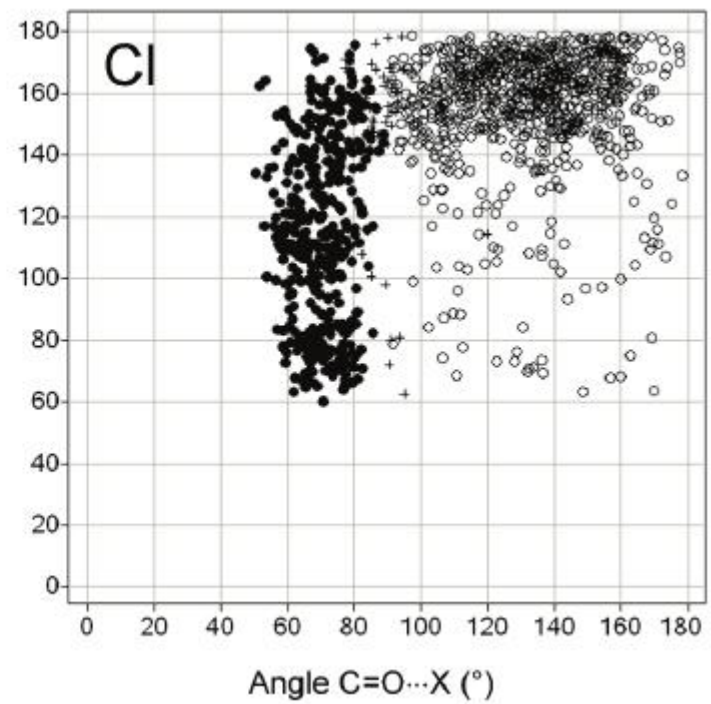
Böhm H. et al, ChemBioChem, 2004, 5 (5), 637-643

Orthogonal multipolar interactions



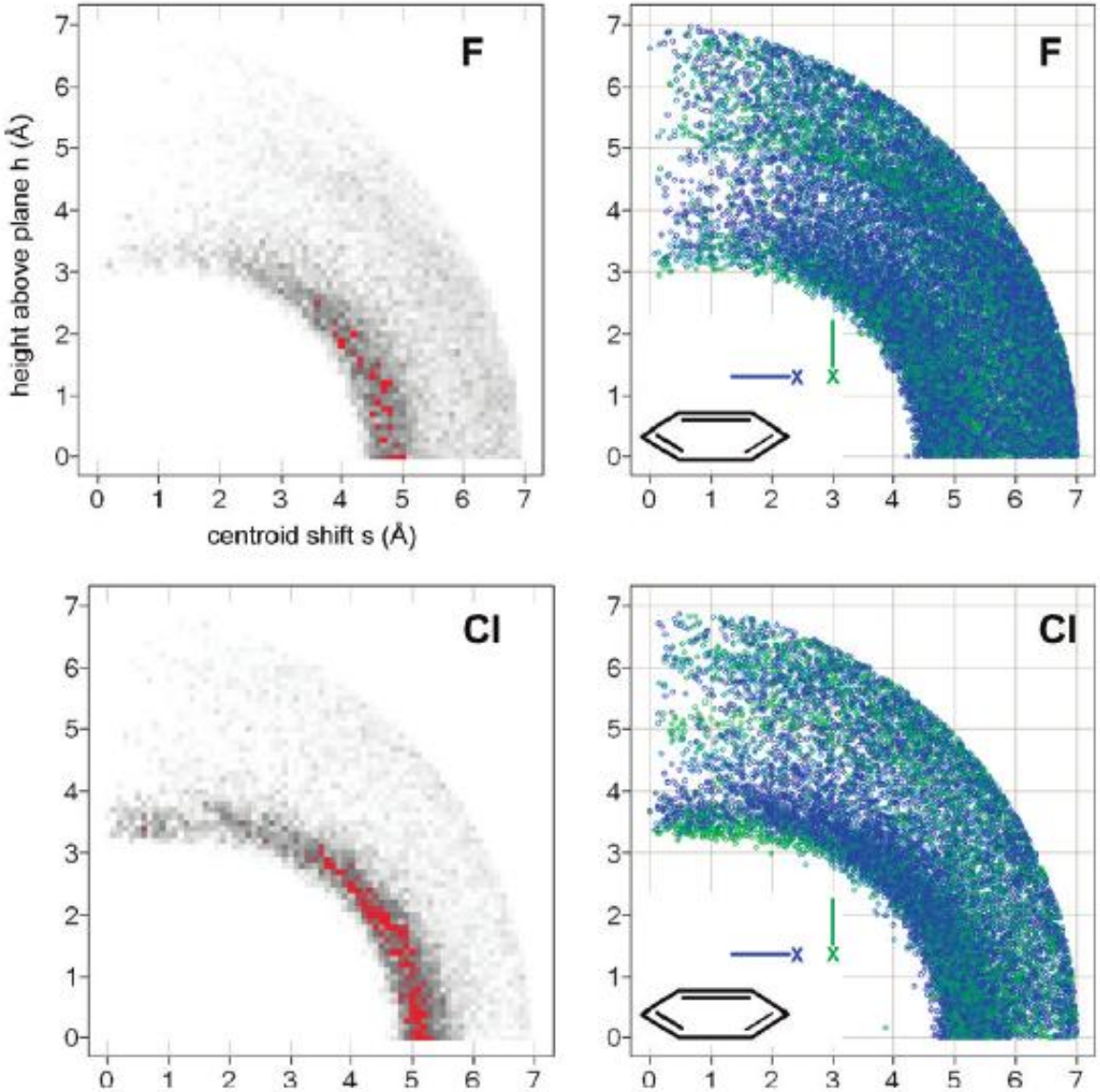




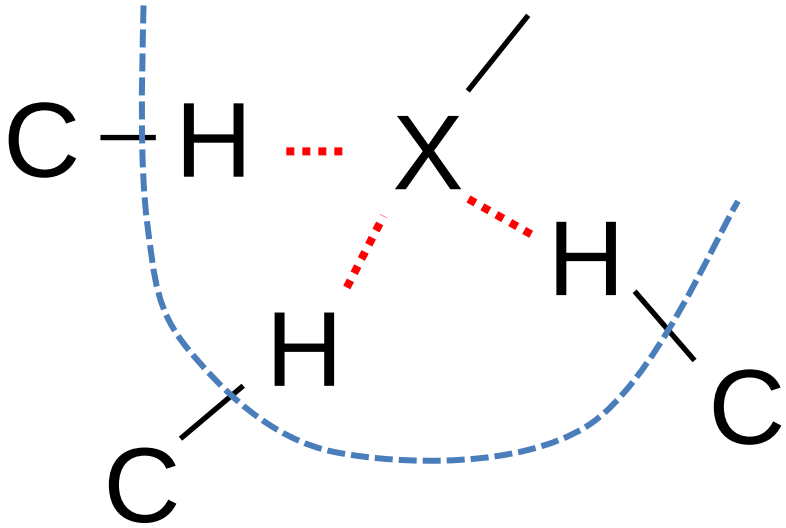


Halogen and aromatic rings

CSD statistics



Typical “good” environment for halogen



Hydrophobic interactions

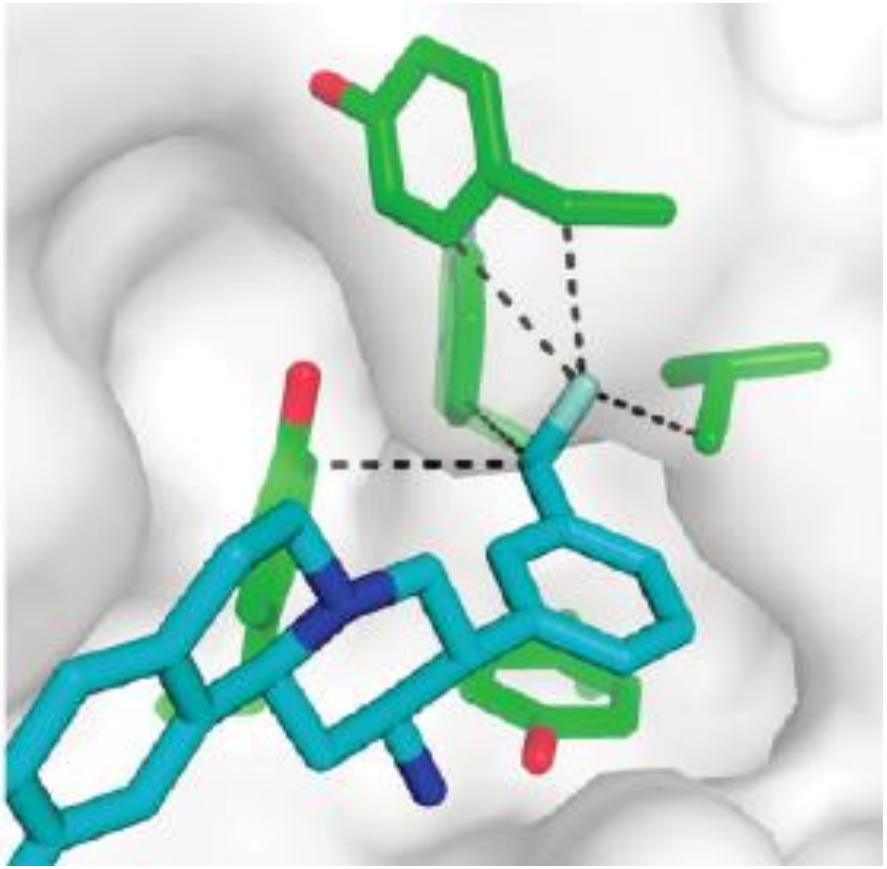
Hydrophobic effect 30 cal/(mol×Å^2)

for CH_3 0.7 kcal/mol (3.5-fold increase in affinity)

1. Desolvation and cooperative effects
2. Optimal filling of the hydrophobic pocket is ~55%. Residual flexibility is important!

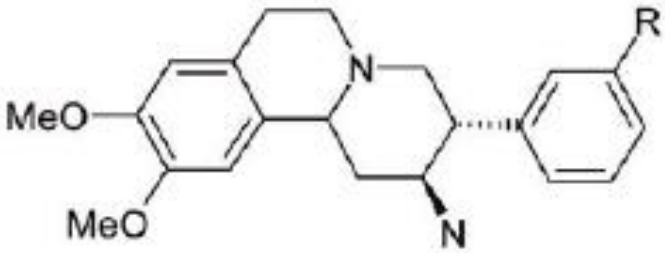
Hydrophobic interactions

Example of optimal filling of hydrophobic pocket



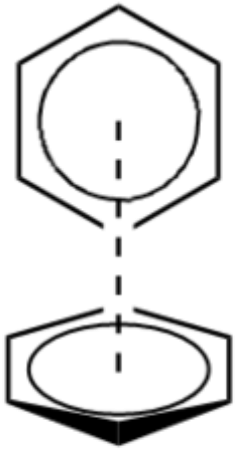
PDB: 3KWJ

Human serine protease DPP-IV inhibitors

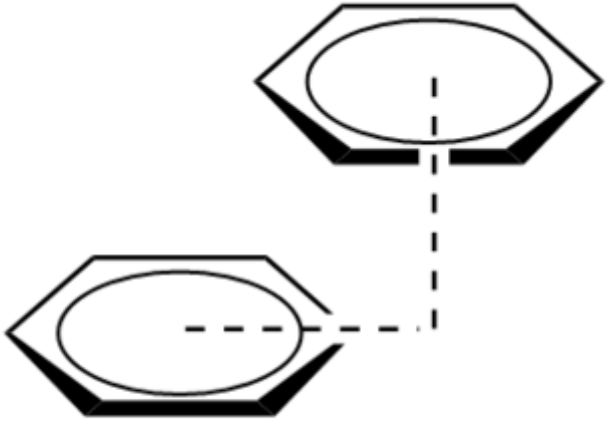


R	K_d (nM)
H	200
CH_3	4.6
CH_2F	0.5

Aryl-aryl and aryl-alkyl interactions



T-shaped



Parallel-dispaced

more often in proteins

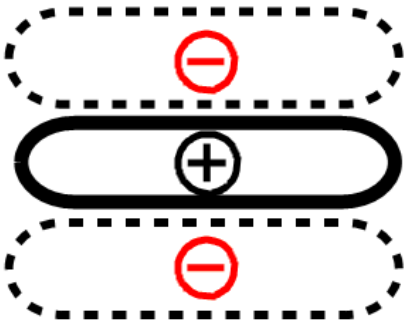
E_{calc} = -2.5 kcal/mol

E_{exp} = -1.6 … -2.4 kcal/mol

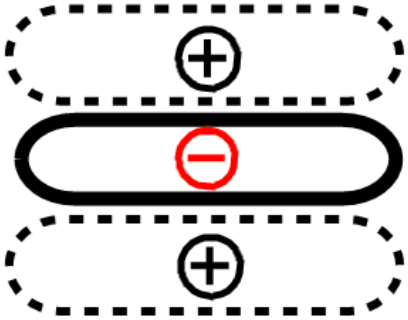
Aryl-aryl and aryl-alkyl interactions

Stacking

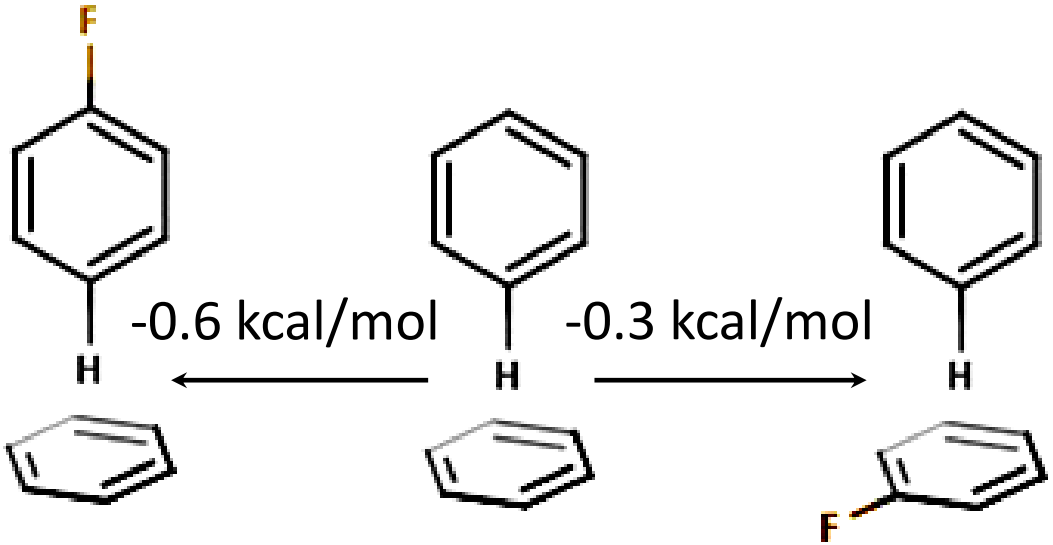
Quadrupole moments

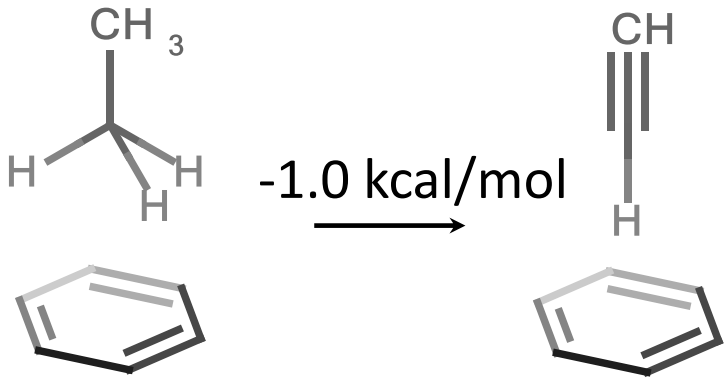


Benzene



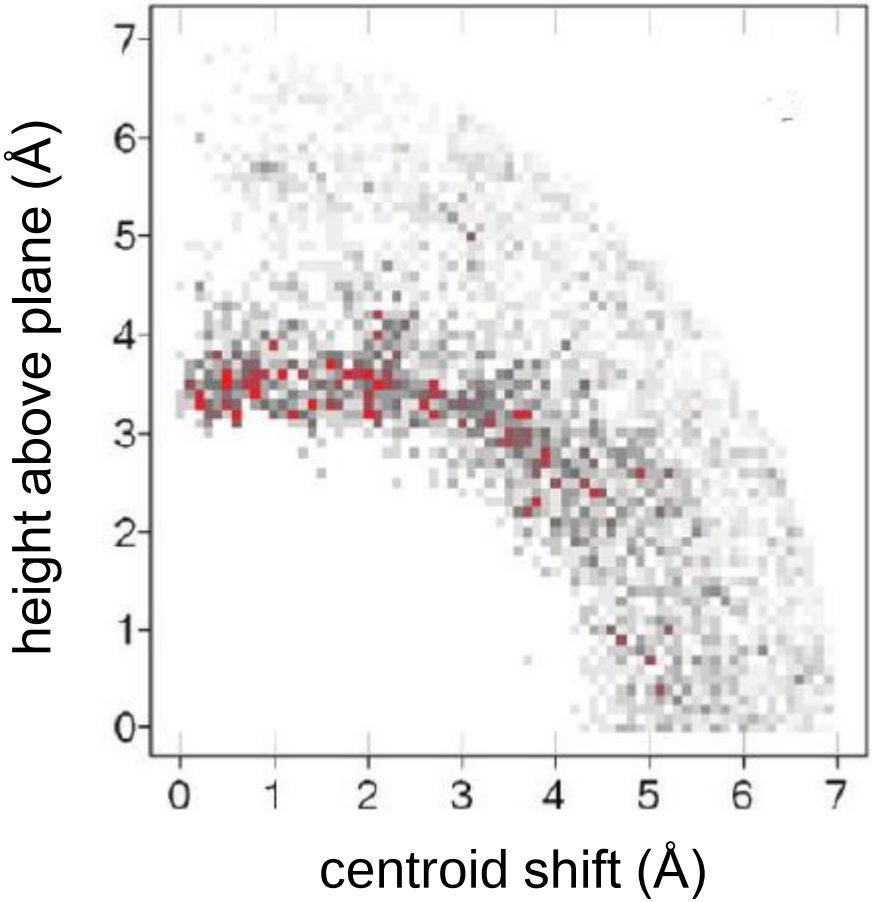
Hexafluorobenzene

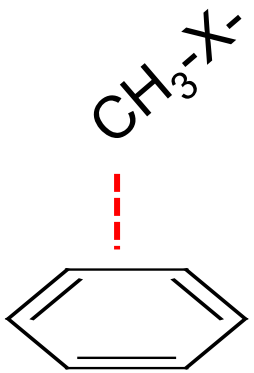




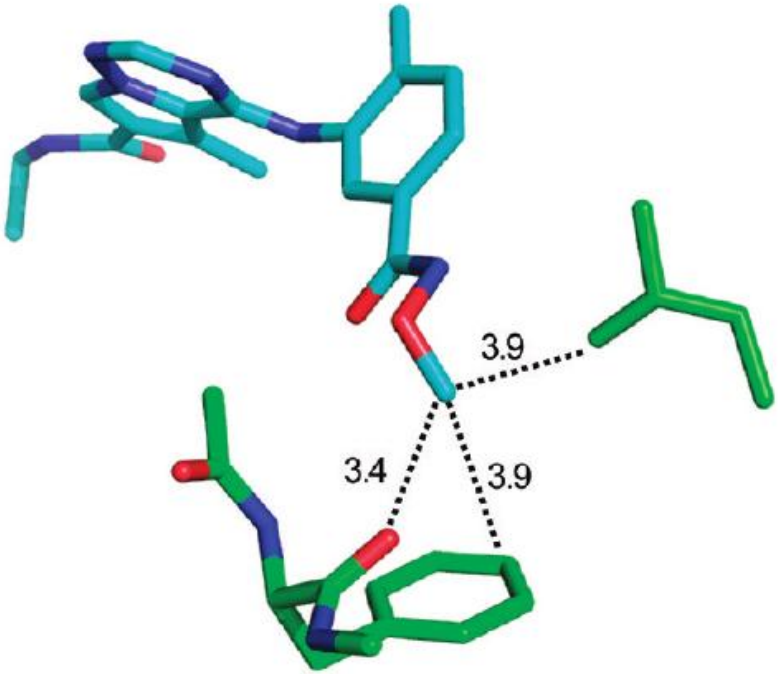
Aryl-aryl and aryl-alkyl interactions

PDB statistics



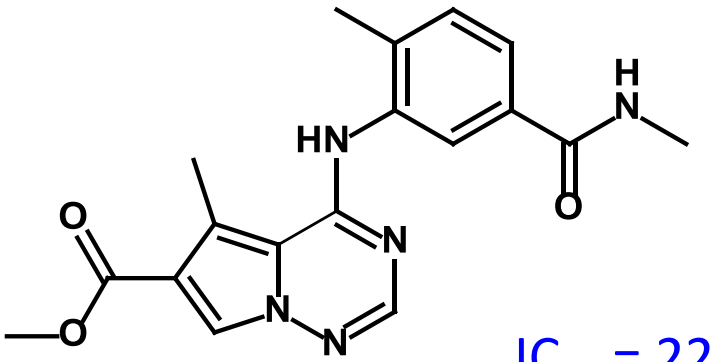


Aryl-aryl and aryl-alkyl interactions

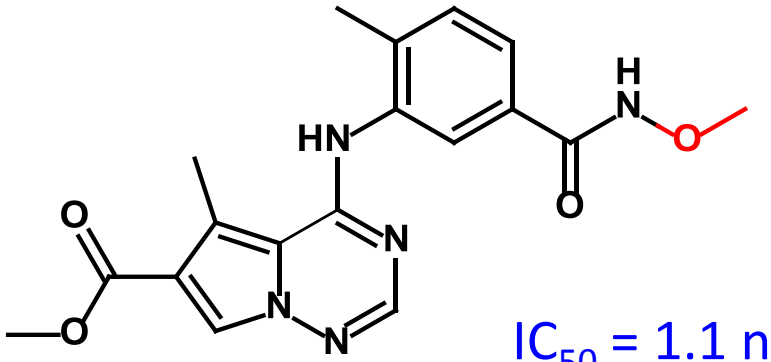


PDB: 2W26

p38 MAP kinase inhibitors



IC_{50} = 220 nM

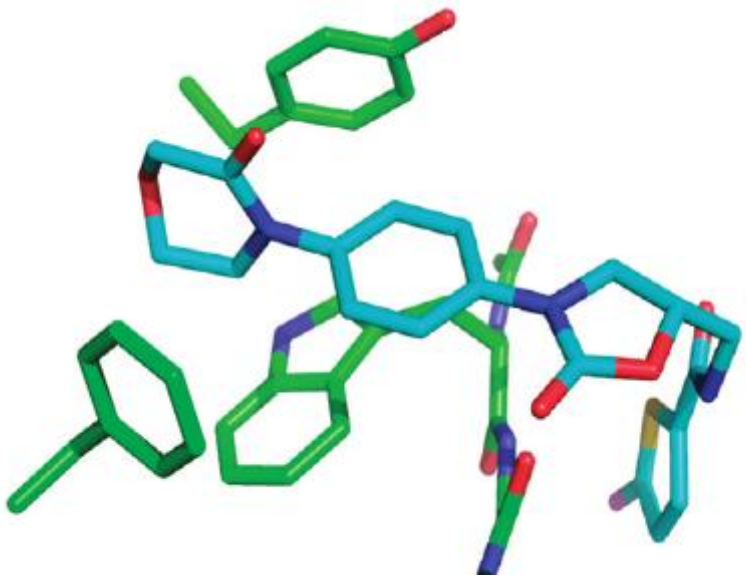


IC_{50} = 1.1 nM

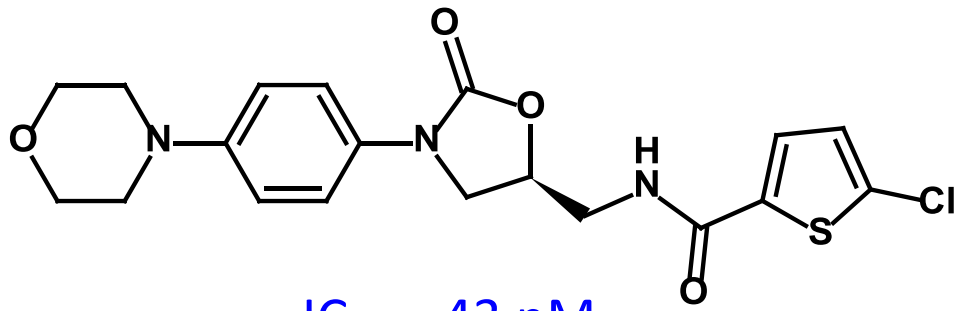
Hynes J. et al, *J. Med. Chem.* 2008, 51,4–16.

Aryl-aryl and aryl-alkyl interactions

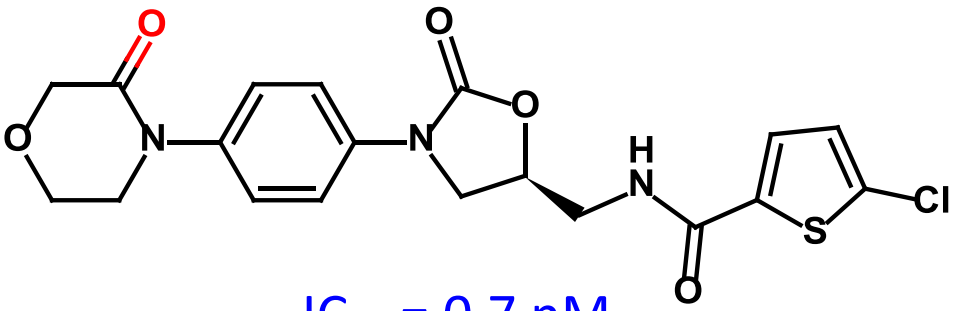
Factor Xa inhibitors



PDB: 2W26



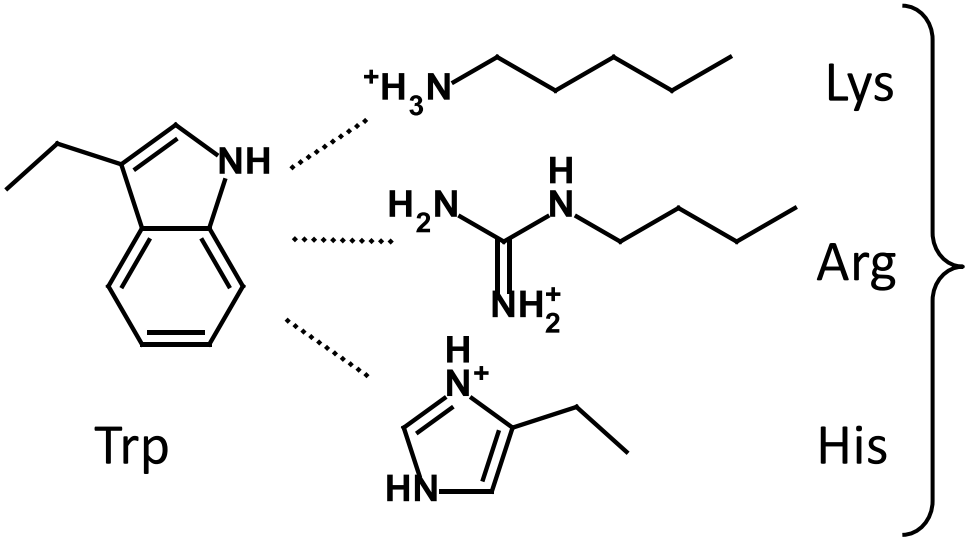
IC_{50} = 43 nM



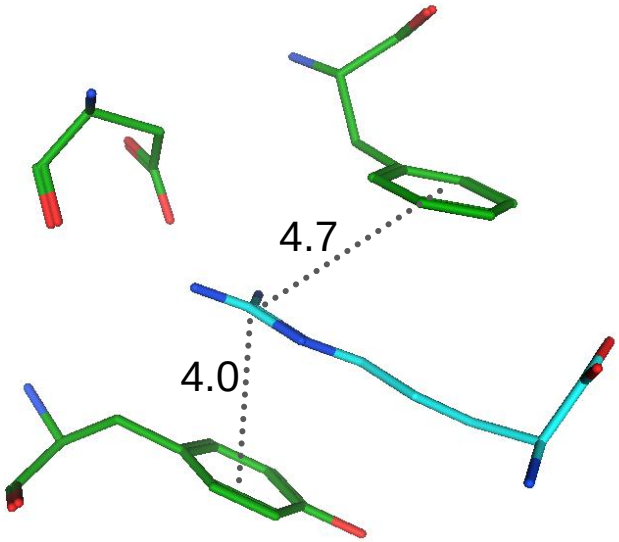
IC_{50} = 0.7 nM

Roehrig S. et al, *J. Med. Chem*. 2005, 48, 5900–5908.

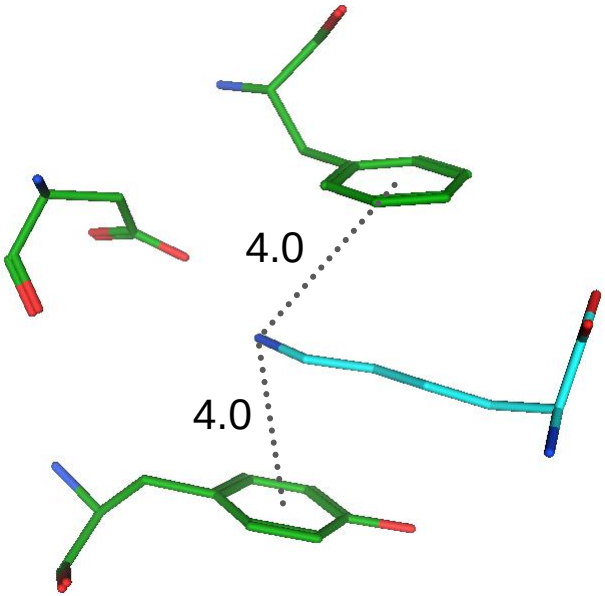
Cation – π interactions



-0.8 … -0.5 kcal/mol
(in buried pockets)

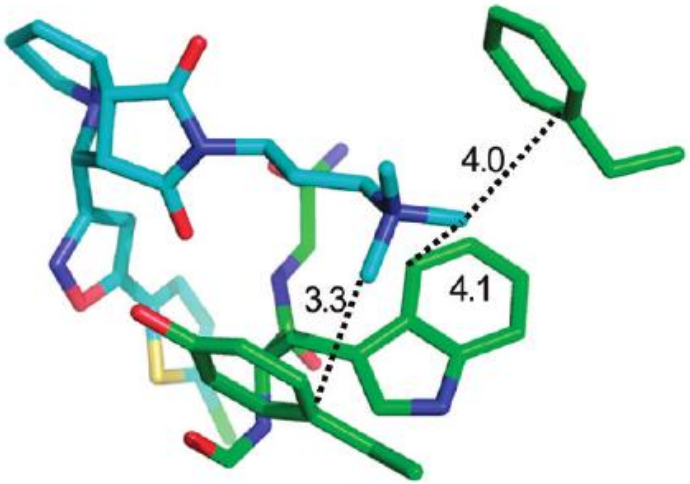


PDB: 1LAF



PDB: 1LST

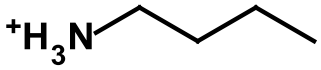
Cation – π interactions



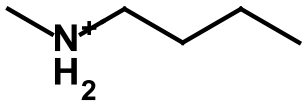
PDB: 2BOC

Factor Xa inhibitors

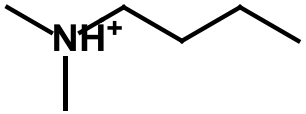
9800 nM



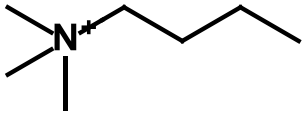
911 nM



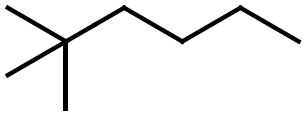
58 nM

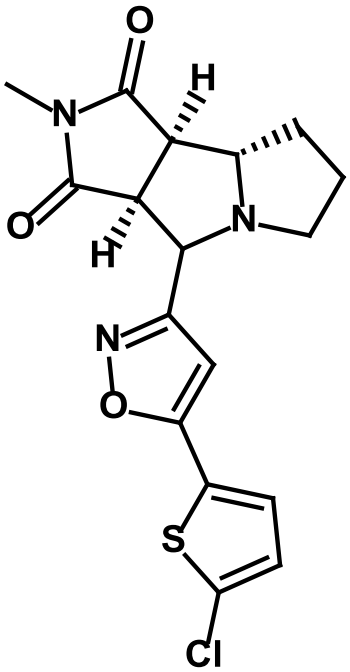


9 nM



550 nM





Improvement of binding affinity

1. Improving ligand-protein interactions over those with the solvent in order to obtain a favorable (negative) change in enthalpy.

2. Making the ligand more hydrophobic in order to make the solvation entropy large and positive.

3. Pre-shaping the ligand to the geometry of the binding site in order to minimize the loss of conformational entropy upon binding.

Recommended literature

Caterina Bissantz, Bernd Kuhn, and Martin Stahl
A Medicinal Chemist's Guide to Molecular Interactions
Journal of Medicinal Chemistry, 2010, Vol. 53, 5061-5084

Rainer Wilcken, Markus O. Zimmermann, Andreas Lange, Andreas C. Joerger and Frank M. Boeckler
Principles and Applications of Halogen Bonding in Medicinal Chemistry and Chemical Biology
Journal of Medicinal Chemistry, 2013, Vol. 56, 1363−1388