Hydrogen Bonds and Biological Activities

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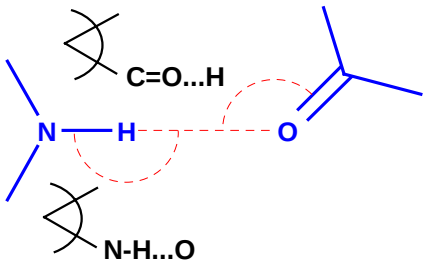
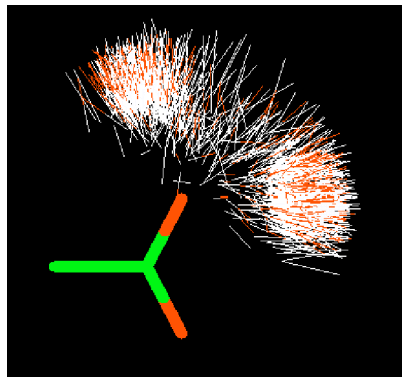
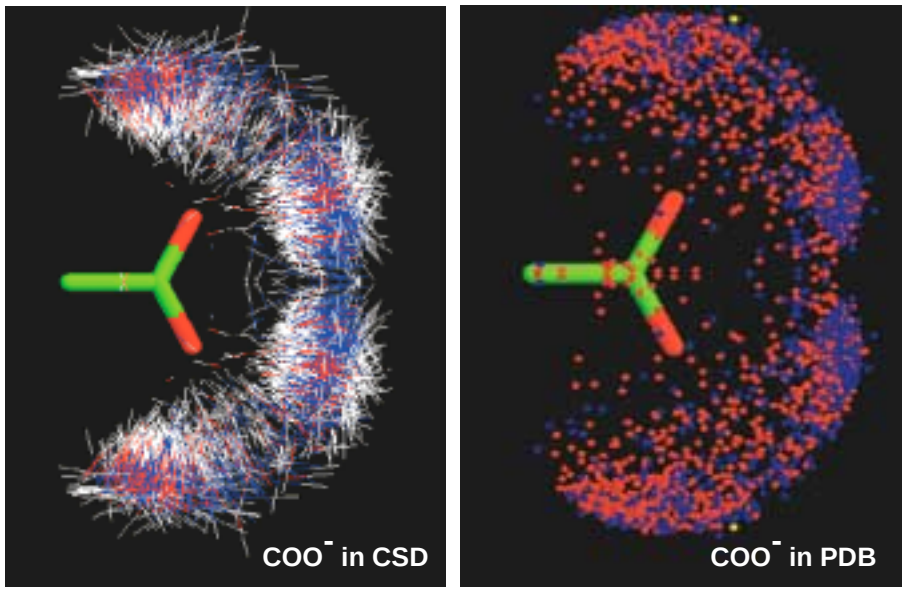
Nature of the Hydrogen Bond



a hydrogen bond is characterized by a shorter X-H ··· Y distance than the sum of the atom vdW radii



N-H...O distance	**2.8-3.2 Å**
N-H...O angle	**150-180°**
C=O...H angle	**100-180°**



O-N distances < vdW - 0.3; R. Taylor, Acta Cryst. D58, 879-888 (2002)

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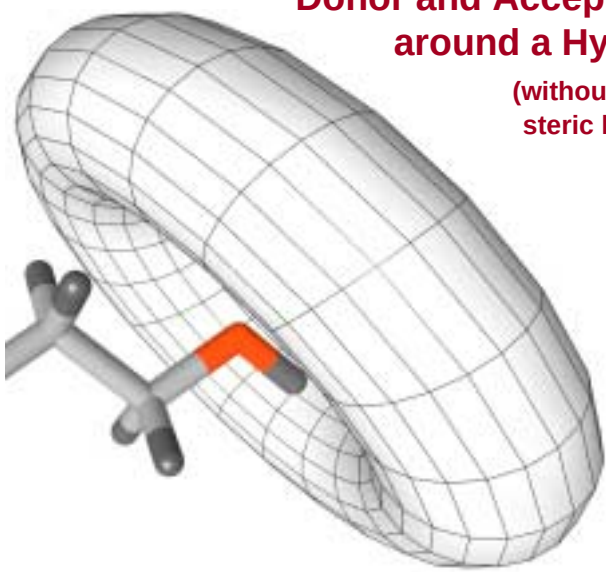
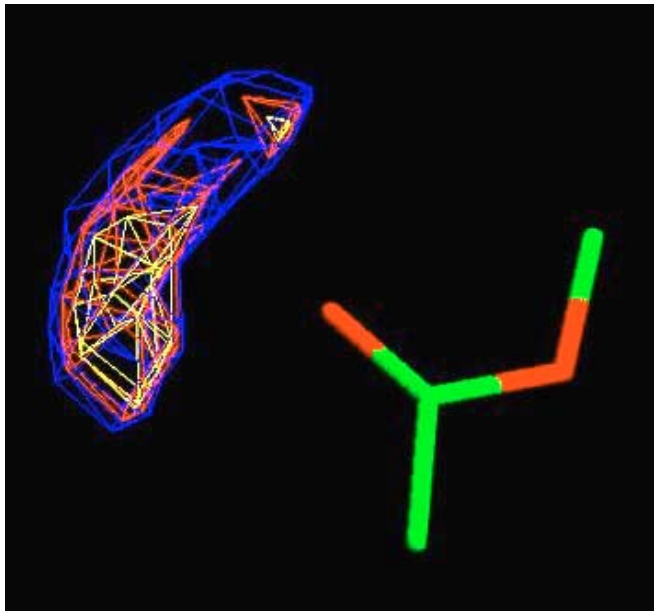
Donor and Acceptor Positions around a Hydroxy Group

(without consideration of steric hindrance)

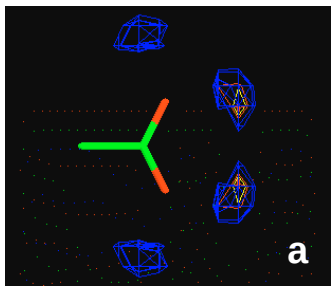


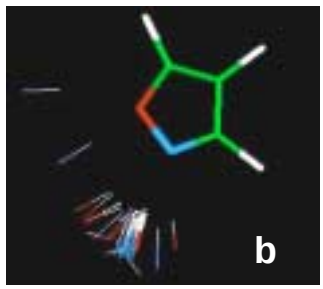
courtesy of
Dr. G. Wolber,
inte:ligand,
Vienna, Austria

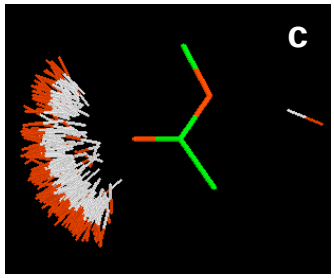


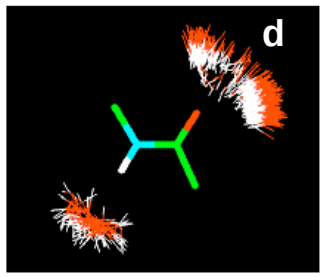
Donor contacts around an ester group

O and N as Hydrogen Bond Acceptors









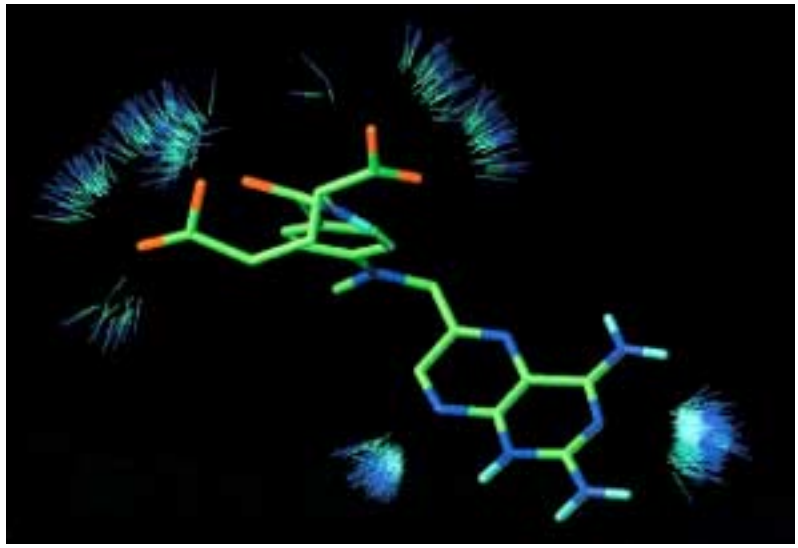
a) -COO$^-$, contour map

b) isoxazole, H bonds

c) ester group, H bonds with OH

d) amide group, H bonds with OH

Isostar: NH Contacts Around Methotrexate



M. L. Verdonk et al., J. Mol. Biol. 307, 841-859 (2001)

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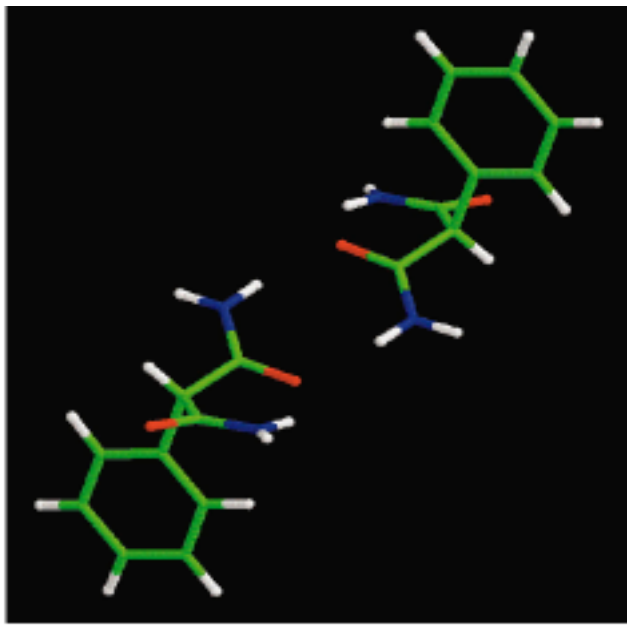
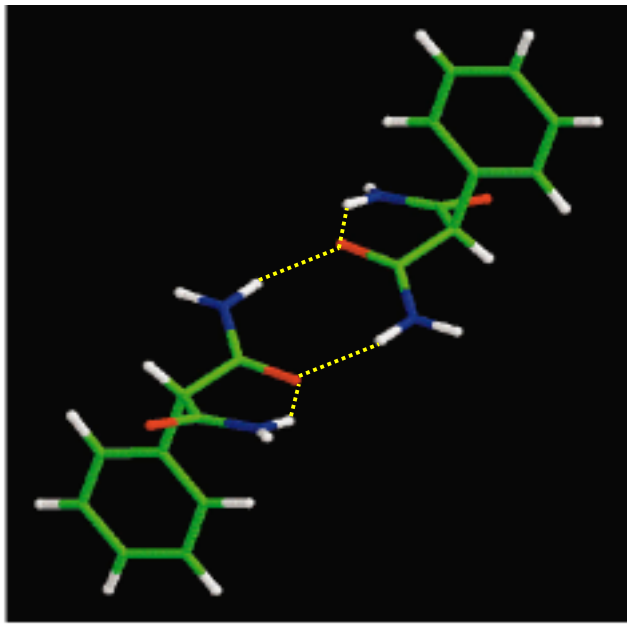


Typical Inter- and Intra-molecular Interactions Between O and NH in Amides

R. Taylor, Acta Cryst. D58, 879-888 (2002)



Typical Inter- and Intra-molecular Interactions Between O and NH in Amides

R. Taylor, Acta Cryst. D58, 879-888 (2002)

Lipophilicity of Hydrocarbons, Ethers and Secondary Amines

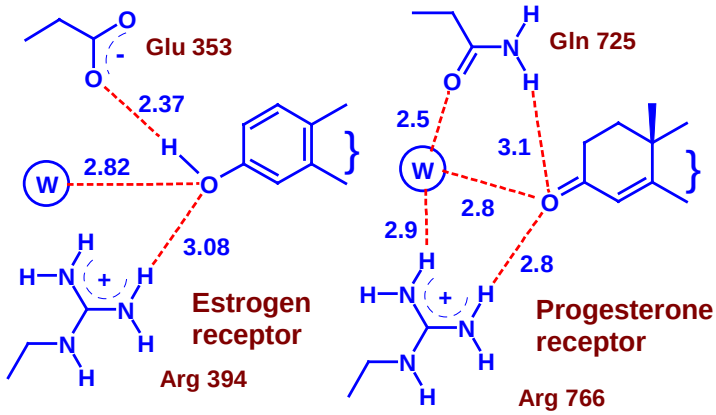
n-Octanol/Water log P* values

(MedChem-Database, Daylight Chemical Information Systems, Mission Viejo, CA, USA)

Compound	X = $-CH_2-$	X = -O-	Δ O/CH_2
Et-X-Et	3.39	0.89	-2.50
Phe-X-Et	3.72	2.51	-1.21
Phe-X-Phe	4.14	4.21	+0.07

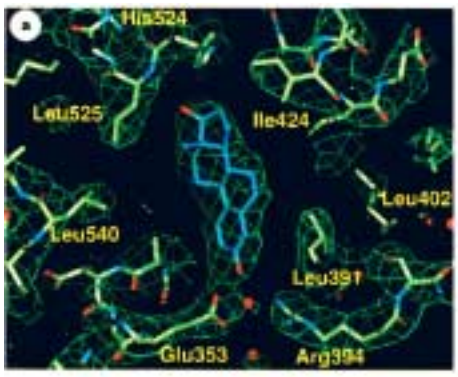
Compound	X = $-CH_2-$	X = -NH-	Δ NH/CH_2
Et-X-Et	3.39	0.58	-2.81
Phe-X-Et	3.72	2.16	-1.56
Phe-X-Phe	4.14	3.50	-0.64

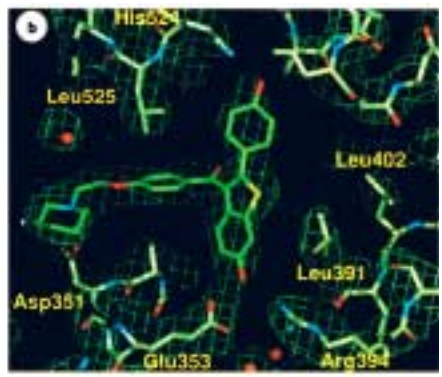
Ligand Recognition - Specificity of Estrogen and Progesterone Receptors



A. M. Brzozowski et al., Nature 389, 753-758 (1997)
S. P. Williams and P. B. Sigler, Nature 393, 392-396 (1998)

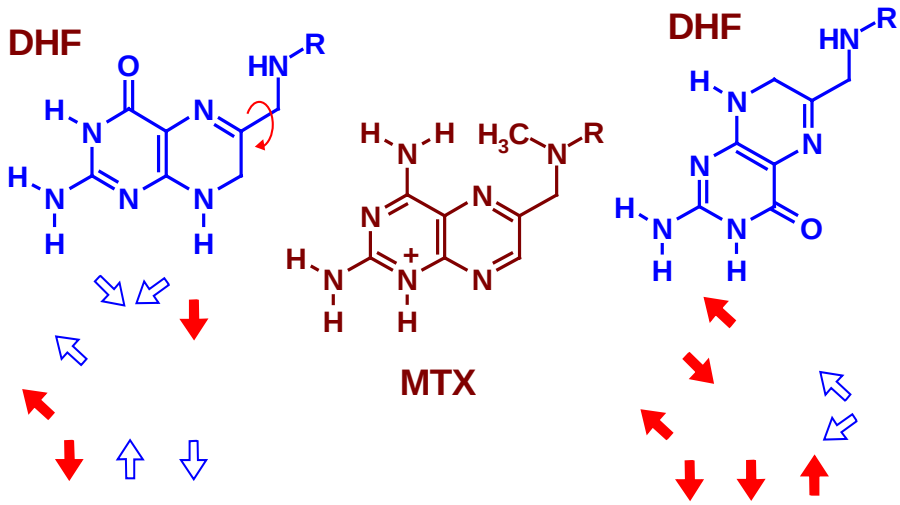
Estrogen Receptor



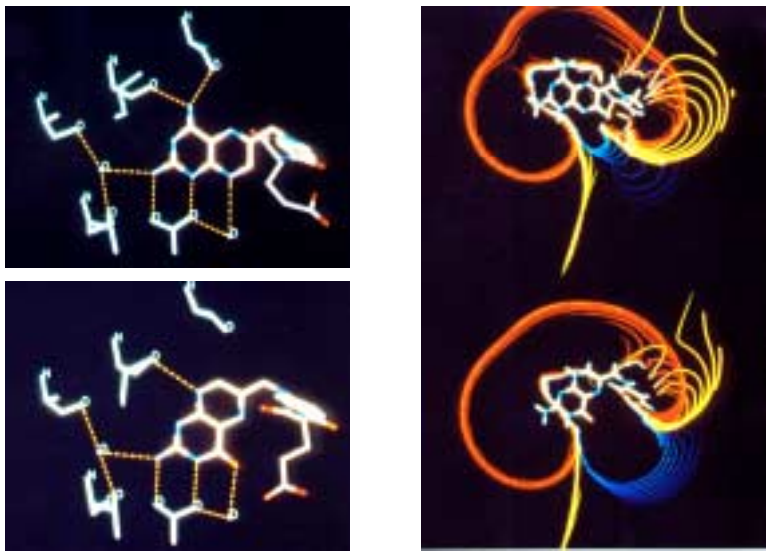


binding modes of oestrone (agonist) and raloxifen (antagonist)

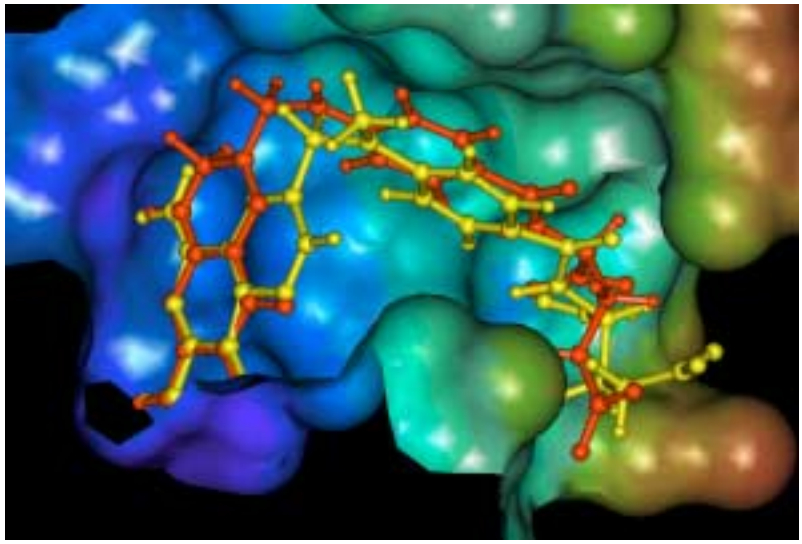
Ligand Orientation of Dihydrofolate Reductase Inhibitors



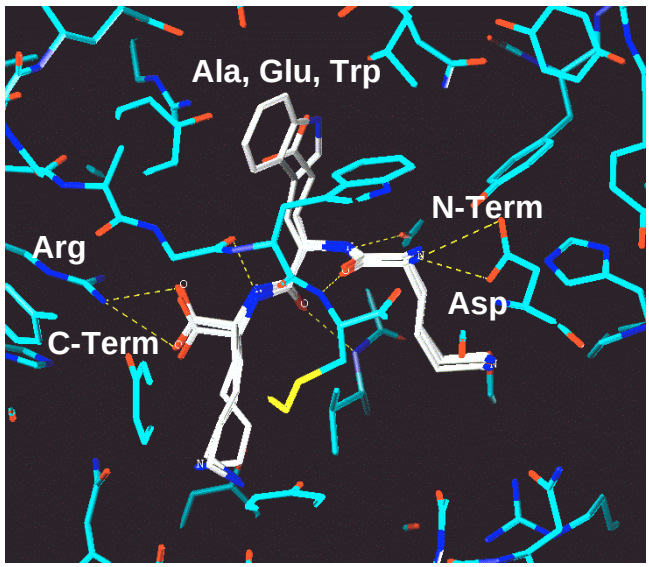
Ligand Orientation of MTX and DHF



Orientation of DHFR Inhibitors



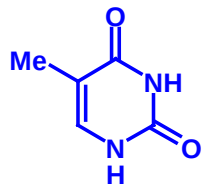
The OppA Transporter Recognizes Any Peptide



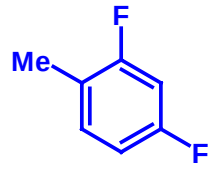
recognition of any di- to pentapeptide

binding pocket filled with water molecules, H-bond interactions only with COO^- and backbone NH and CO's.

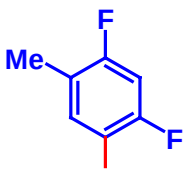
Ligand Recognition in DNA Replication



thymine

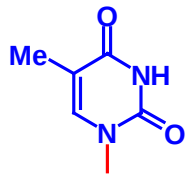


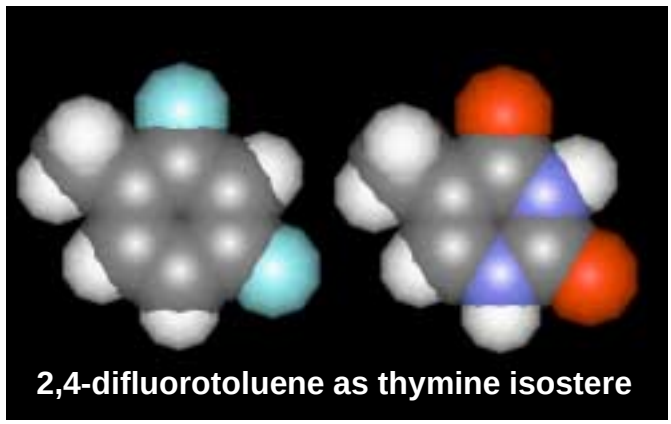
2,4-difluoro-
toluene



Ligand Recognition in DNA Replication

S. Moran et al., J. Am. Chem. Soc. 119, 2056-2057 (1997)

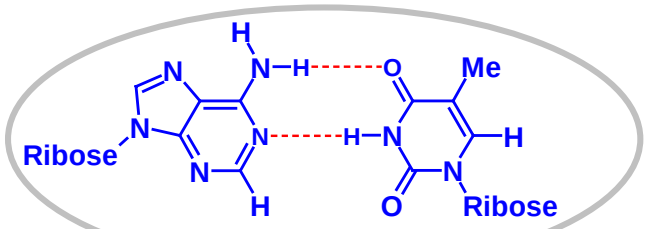




2,4-difluorotoluene as thymine isostere

A-T Pair in DNA

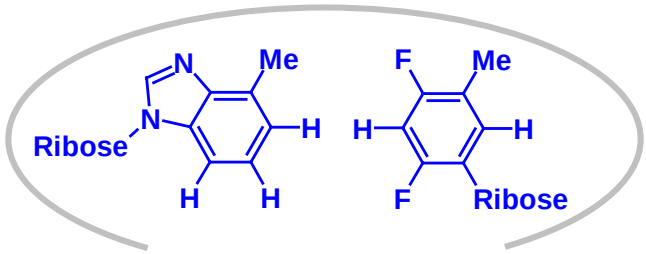
(Watson and Crick, 1953)



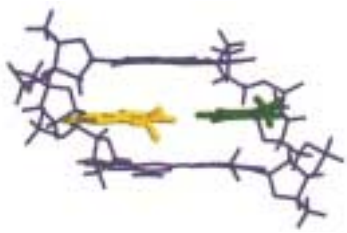
bases: adenine thymine

nonpolar „base pair“

J. C. Morales et al., J. Am . Chem . Soc. 122, 1001-1007 (2000)

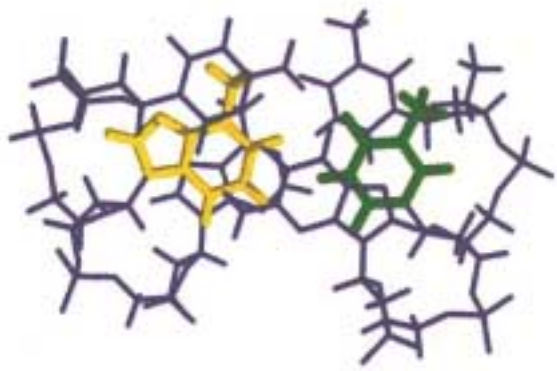


4-Me-benzimidazole 2,4-difluorotoluene



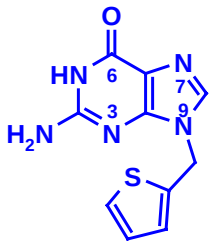
Insertion of nonpolar „bases“ into DNA

(NMR 3D-structure of a duplex DNA-12mer)

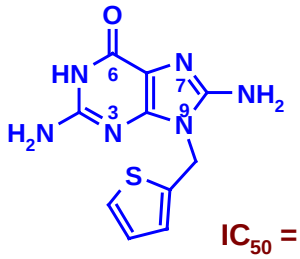


K. M. Guckian et al., J. Am . Chem . Soc. 122, 6841-6847 (2000)

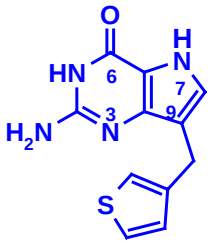
Purine Nucleoside Phosphorylase Inhibitors



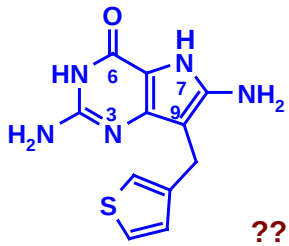
IC_{50} = 11 µM



IC_{50} = 0.16 µM



IC_{50} = 0.067 µM



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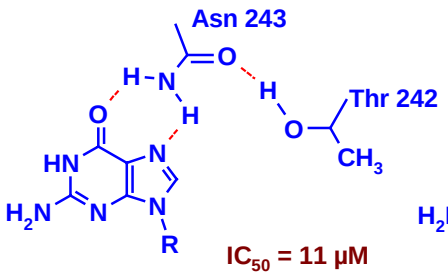
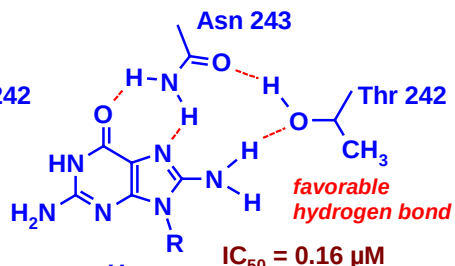
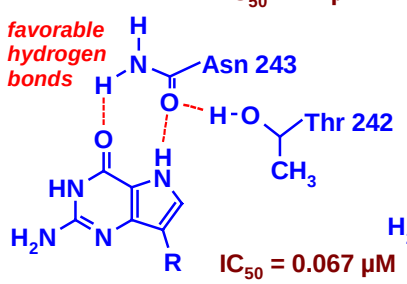
Purine Nucleoside Phosphorylase Inhibitors



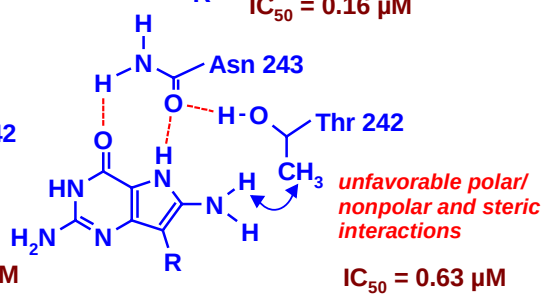
IC_{50} = 11 µM



IC_{50} = 0.16 µM

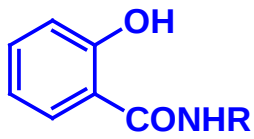


IC_{50} = 0.067 µM



IC_{50} = 0.63 µM

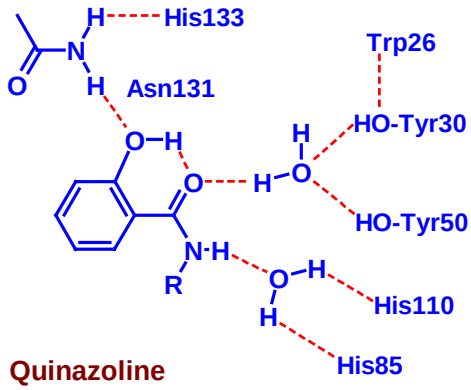
Pharmacophore Recognition of Scytalone Dehydratase Inhibitors



To be (similar)
or not to be (similar)
that‘s the question

... if William Shakespeare had been a medicinal chemist

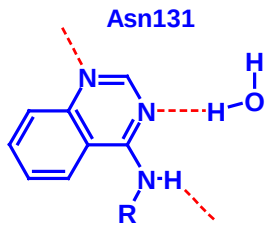
Recognition of Scytalone Dehydratase Inhibitors



Salicylamide

R = -CH(CH$_3$)C$_6$H$_4$-p-Br

***K*$_i$ = 0.14 nM**



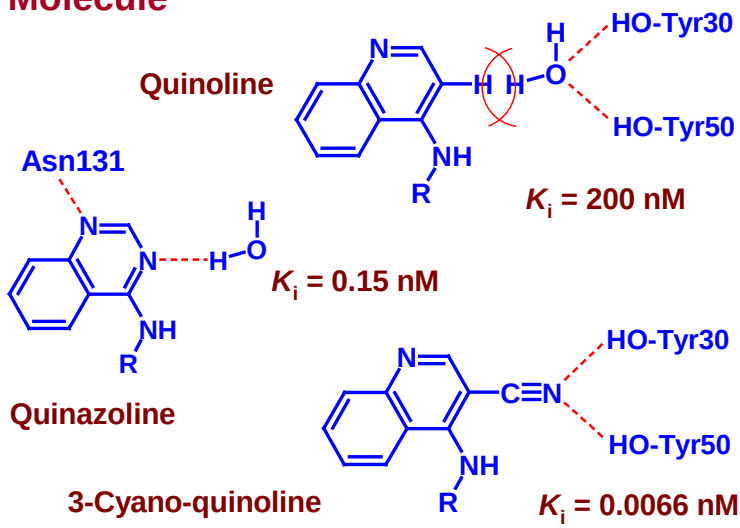
Quinazoline

R = -CH$_2$CH$_2$CH(C$_6$H$_5$)$_2$

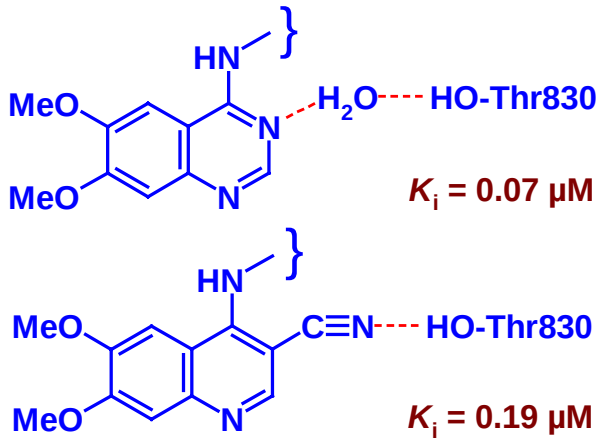
***K*$_i$ = 0.15 nM**

J. M. Chen et al., Biochemistry 37, 17735-17744 (1998)

Favourable Replacement of a Water Molecule

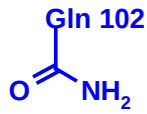


Bioisosteric Replacement of a Water Molecule in the Binding Site of EGFR Kinase

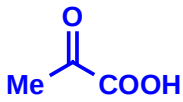


A. Wissner et al., J. Med. Chem. 43, 3244-3256 (2000)

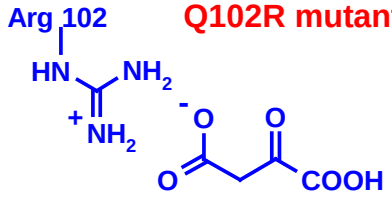
Change of Substrate Specificity of an Enzyme



wild type enzyme



pyruvate



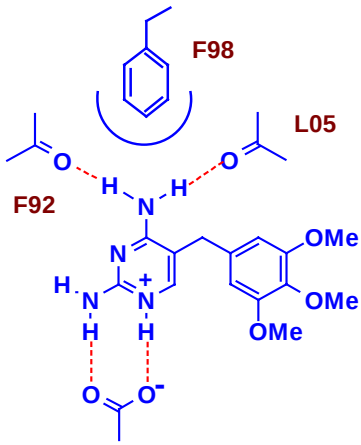
Q102R mutant

oxalacetate

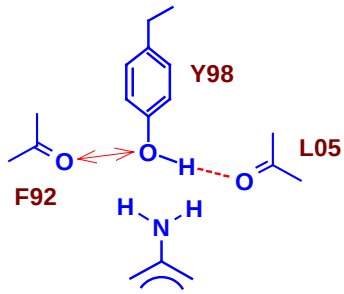
native enzyme $\frac{k_{cat}/K_m \text{ oxalacetate}}{k_{cat}/K_m \text{ pyruvate}} = 0.001$

Q102R mutant $\frac{k_{cat}/K_m \text{ oxalacetate}}{k_{cat}/K_m \text{ pyruvate}} = 10{,}000$

Trimethoprim Resistance of Staphylococcus aureus



trimethoprim, K_i = 0.01 µM

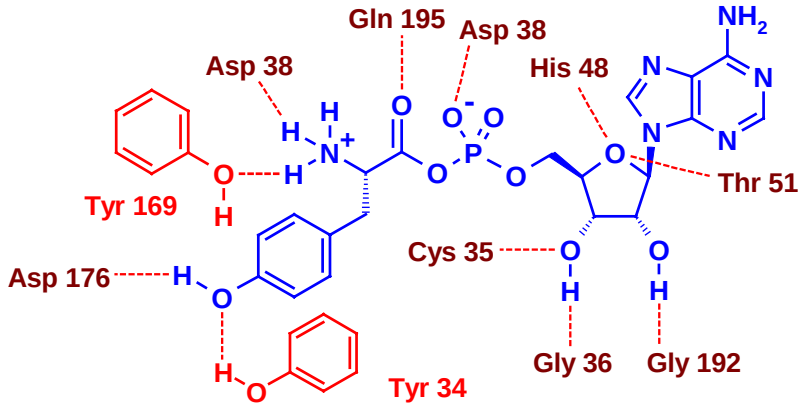


F98Y mutant, K_i = 4.1 µM

F98Y double and triple mutants (H30N, H149R, L20V, N59I), K_i = 2.8-24 µM

G. E. Dale et al., J. Mol. Biol. 266, 23-30 (1997)

Hydrogen Bonds and Ligand Affinities



In tyrosyl-tRNA synthase, the exchange of Tyr 34 or Tyr 169 against Phe leads to a loss of one hydrogen bond and, correspondingly, to lower binding affinities.

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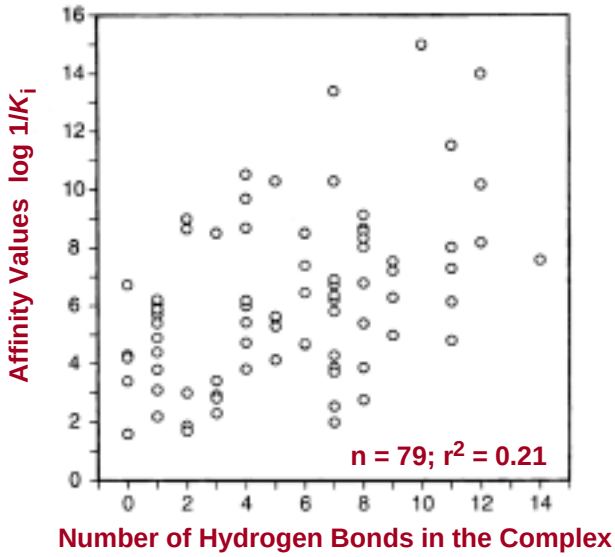
Hydrogen Bonds and Ligand Affinities



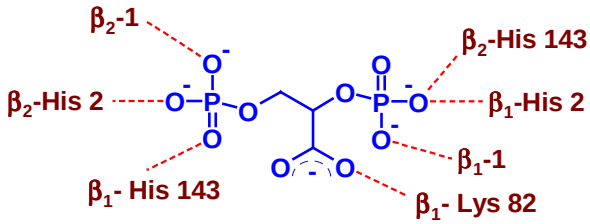
Correlation of Hydrogen Bonds and Ligand Affinities: Mean Energy Values, Ionic and Neutral Hydrogen Bonds

Neutral hydrogen bonds **2-6 kJ/mol**
(increase affinities by a factor 2-15)
Ionic hydrogen bonds **up to 20 kJ/mol**
(increase affinities up to a factor 3,000)

Many exceptions, e.g.

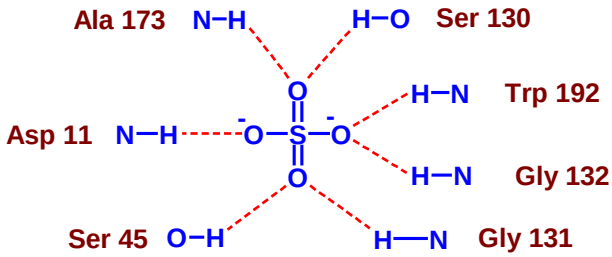
Affinity of 2,3-diphosphoglycerate to hemoglobin
seven ionic hydrogen bonds, but only
millimolar affinity to hemoglobin
Affinity of sulfate to a sulfate-binding protein (SBP)
seven neutral hydrogen bonds, but
nanomolar affinity to the sulfate-binding protein from
Salmonella typhimurium

Binding of 2,3-Diphosphoglycerate to Hemoglobin



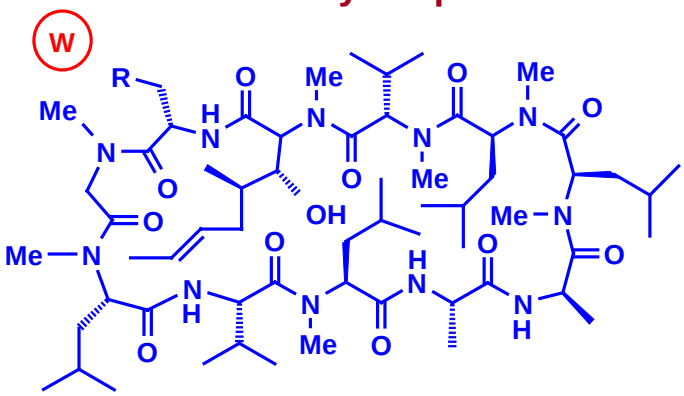
K_m ca. 1 mM

Binding of Sulfate to a Sulfate-binding Protein (SBP)



K_i = 120 nM

Unfavorable Replacement of a Water Molecule in Cyclosporin A

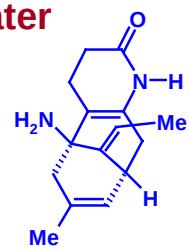


(5-Hydroxynorvaline)-2-cyclosporin A, R = CH_2CH_2OH, exerts a 8-9-fold lower affinity than cyclosporin A (R = CH_3)

(Mikol *et al*., J. Med. Chem. 38, 3361-3367 (1995))

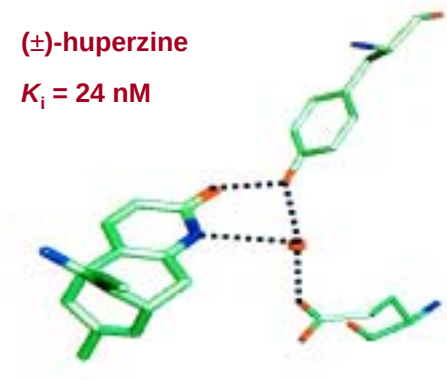
Hugo Kubinyi, www.kubinyi.de

Unfavorable Replacement of a Water Molecule in Huperzine



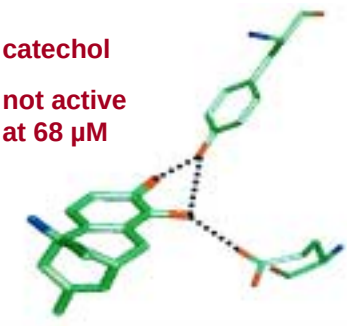
(±)-huperzine

K_i = 24 nM



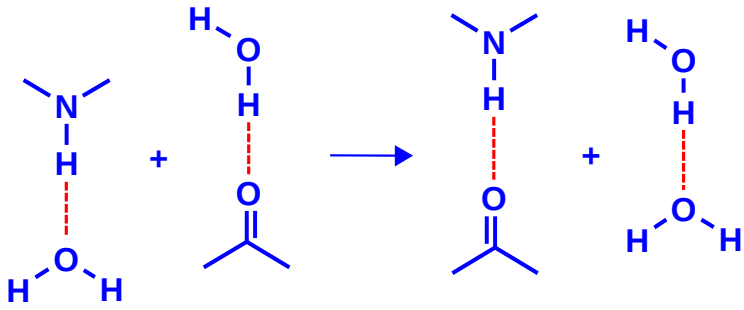
catechol

not active at 68 µM



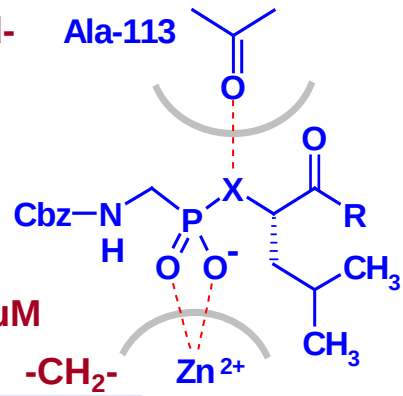
G. Campiani *et al*., Bioorg. Med. Chem. Lett. 8, 1413-1418 (1998)

Hydrogen Bonds in Ligand-Protein Interactions



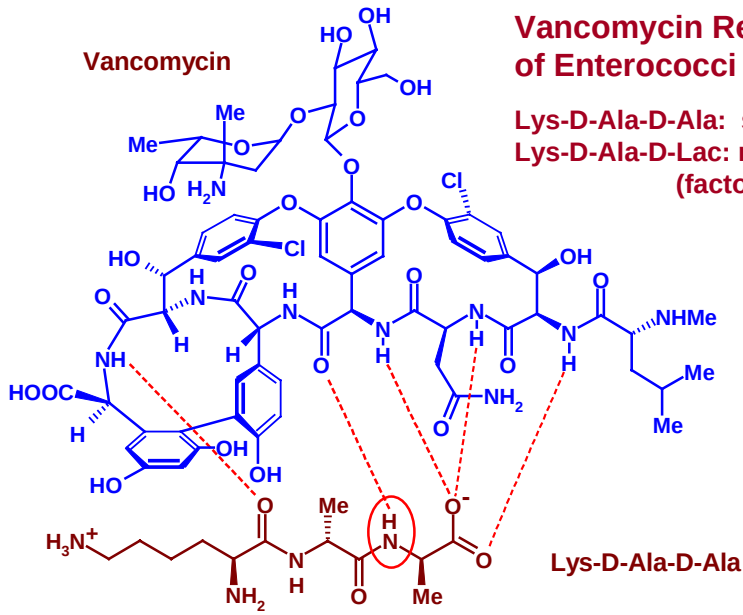
protein ligand ligand-protein complex

Hydrogen Bonds in Ligand-Protein Interactions



Inhibition Constants K_i in µM

R	X = -NH-	-O-	-CH_2-
-OH	0.76	660	1.4
-Gly-OH	0.27	230	0.3
-Leu-OH	0.01	9	0.01

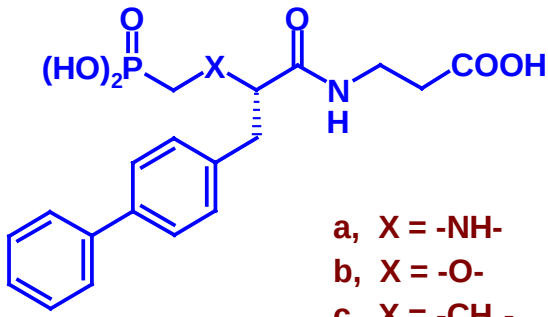


Vancomycin Resistance of Enterococci

Lys-D-Ala-D-Ala: sensitive
Lys-D-Ala-D-Lac: resistant
(factor 1,000)

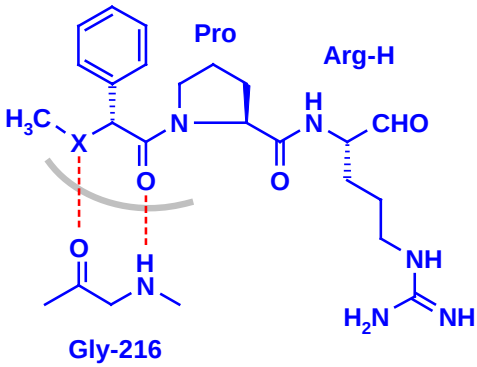
Hydrogen Bonds in Ligand-Protein Interactions

NEP 24.11 Inhibitors

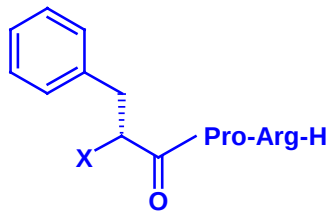


a, X = -NH- IC_{50} = 1.6 nM
b, X = -O- IC_{50} = 10 nM
c, X = $-CH_2-$ IC_{50} = 1 000 nM
d, X = -S- IC_{50} = 800 nM

Hydrogen Bonds in Ligand-Protein Interactions
Thrombin Inhibitors

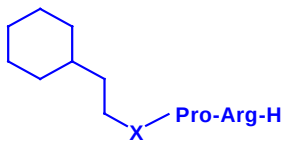


X = -NH- IC_{50} = 9 ng/ml
X = -O- IC_{50} = 130 ng/ml
X = -CH_2- IC_{50} = 70 ng/ml

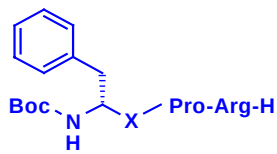


X = NH_2
IC_{50} = 49 nM
X = H
IC_{50} = 390 nM

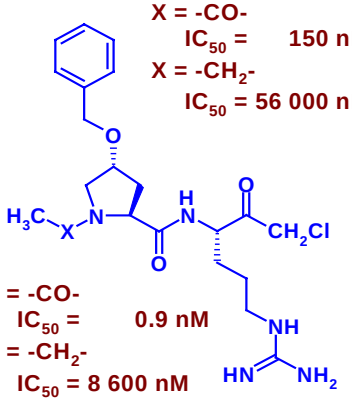
Hydrogen Bonds in Ligand-Protein Interactions



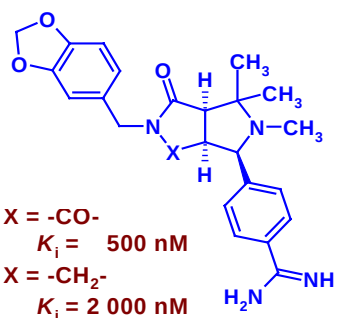
X = -CO- IC_{50} = 150 nM
X = -CH_2- IC_{50} = 56 000 nM



X = -CO- IC_{50} = 28 ng/ml
X = -CH_2- IC_{50} = 52 000 ng/ml

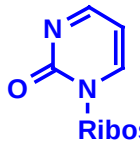


X = -CO- IC_{50} = 0.9 nM
X = -CH_2- IC_{50} = 8 600 nM



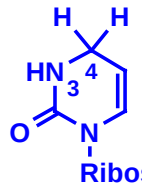
X = -CO- K_i = 500 nM
X = -CH_2- K_i = 2 000 nM

„Use“ of a Water Molecule in Cytidine Deaminase



zebularine

K_i = 0.0012 nM



3,4-dihydro-zebularine

K_i = 30,000 nM