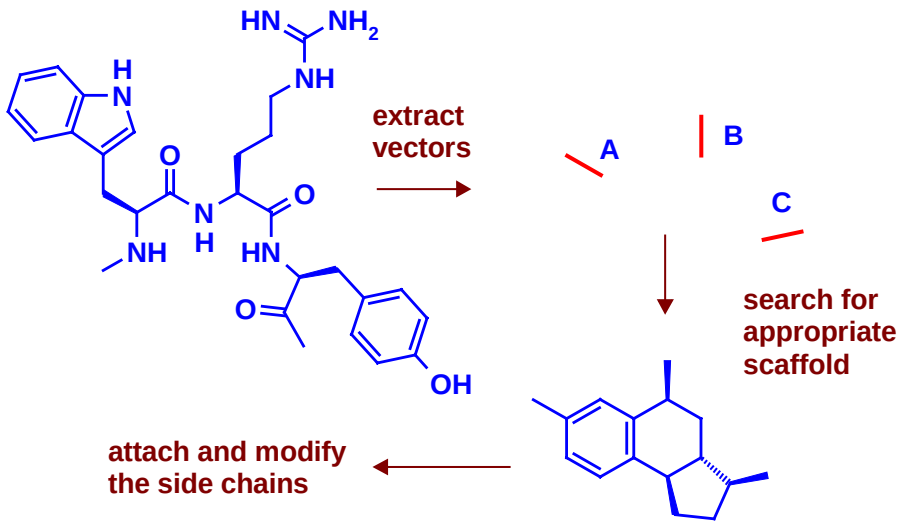
Computer-Aided Ligand Design

Hugo Kubinyi

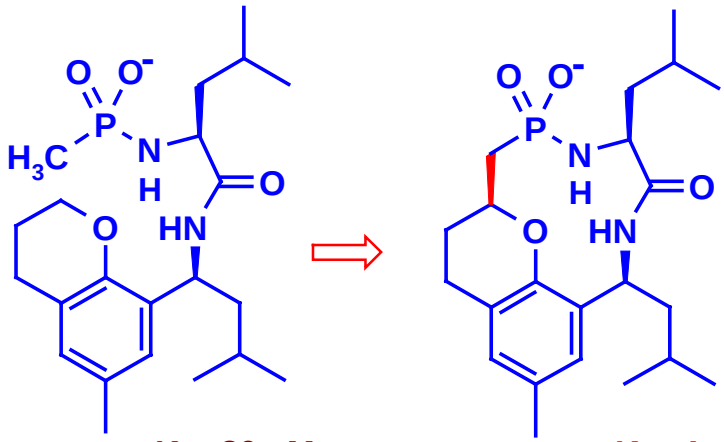
Germany

E-Mail kubinyi@t-online.de
HomePage www.kubinyi.de

CAVEAT - An Idea Generator for Peptidomimetics



Some Rigid Analogs are Highly Active Thermolysin Inhibitors

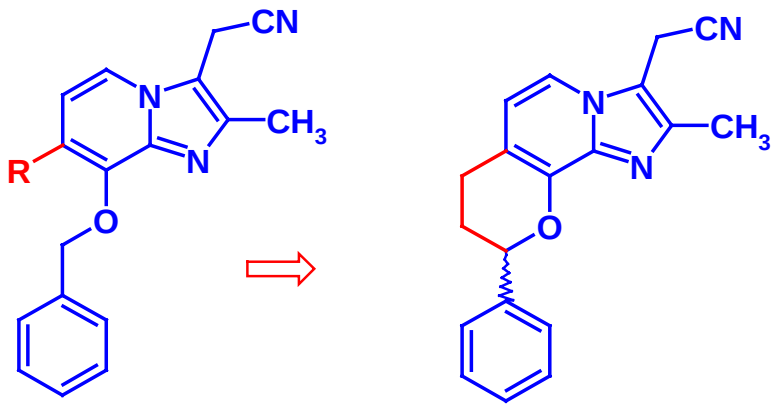


K_i = 80 nM

K_i = 4 nM

Hugo Kubinyi, www.kubinyi.de

Some Rigid Analogs are Highly Active H^+/K^+-ATPase Inhibitors



a, R = H, IC_{50} = 1.6 µM

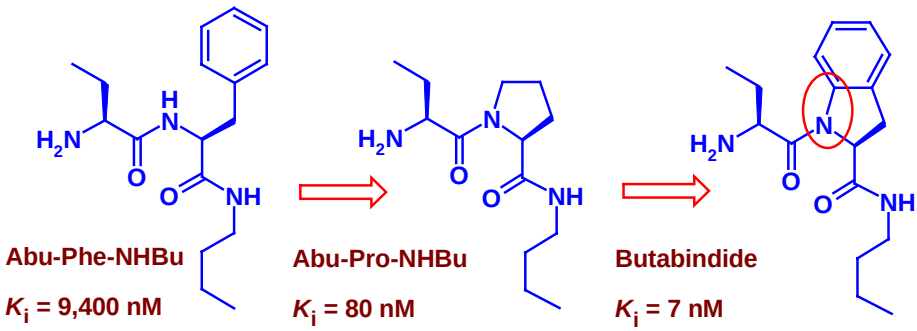
b, R = Me, IC_{50} = 13.7 µM

IC_{50} = 0.09 µM

Design of Butabindide, A Cholecystokinin-Inactivating Serine Protease Inhibitor

Enzymatic cleavage of sulphated CCK-8 :

Asp-Tyr(SO_3H)-Met-↓-Gly-Trp-Met-Asp-Phe-NH_2



Abu-Phe-NHBu — K_i = 9,400 nM

Abu-Pro-NHBu — K_i = 80 nM

Butabindide — K_i = 7 nM

C. R. Ganellin et al., J. Med. Chem. 43, 664-674 (2000)

Hugo Kubinyi, www.kubinyi.de

Femtomolar Carboxypeptidase Inhibitors

Cbz-Ala-Ala-PO_2^-O-Ala-OH
K_i = 76 nM

Cbz-Phe-Ala-PO_2^-O-Ala-OH
K_i = 56 nM

Cbz-Ala-Gly-PO_2^-O-Phe-OH
K_i = 0.7 nM

Val-Val-Val in PDB

Cbz-Ala-Ala-PO_2^-O-Phe-OH K_i = 0.003 nM

Cbz-Phe-Ala-PO_2^-O-Phe-OH K_i = 0.001 nM

Cbz-Phe-Val-PO_2^-O-Phe-OH K_i = 0.000 010 - 27 nM

(A. P. Kaplan and P. A. Bartlett, Biochemistry 30, 8165-8170 (1991)

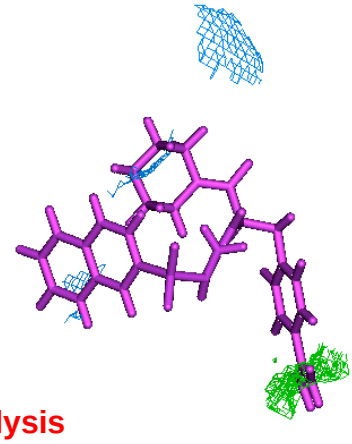
Structure Based Design with GRID (P. Goodford)

Calculates interaction energies between various atomic probes or functional groups and the surface of a protein at equally distributed grid points.

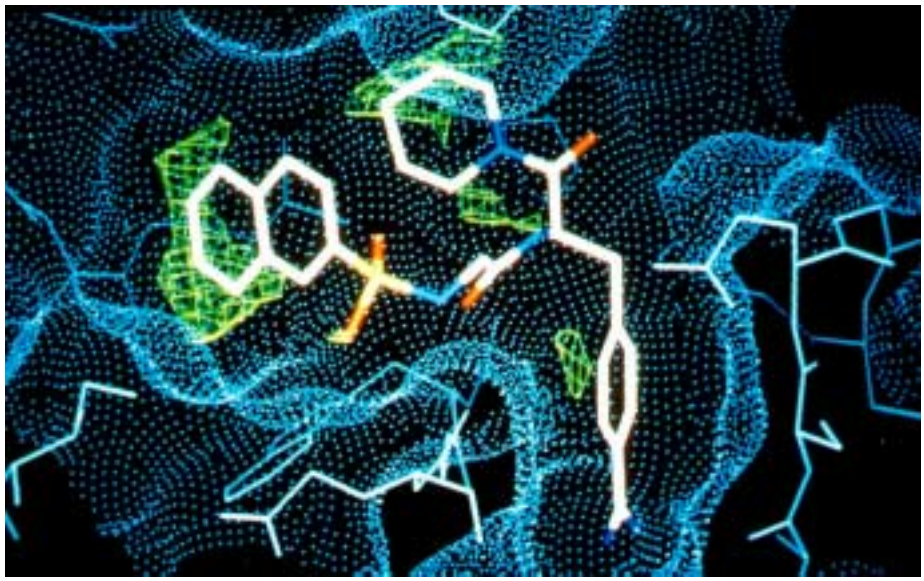
Considers force field parameters like van der Waals and electrostatic interactions.

Contains basic concepts to include side chain flexibility.

Can be used for binding site analysis and for lead structure optimization.

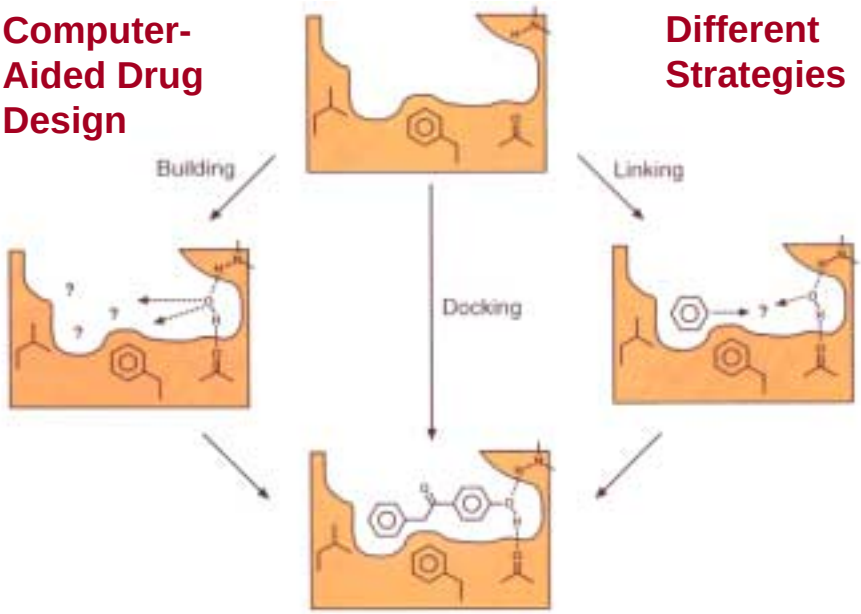


GRID Analysis of the Thrombin Binding Site



Computer-Aided Drug Design

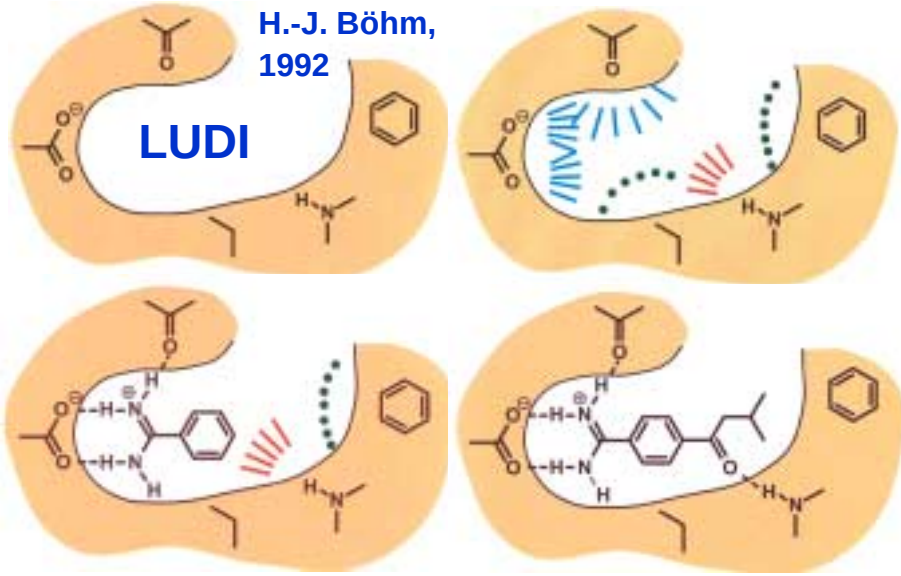
Different Strategies



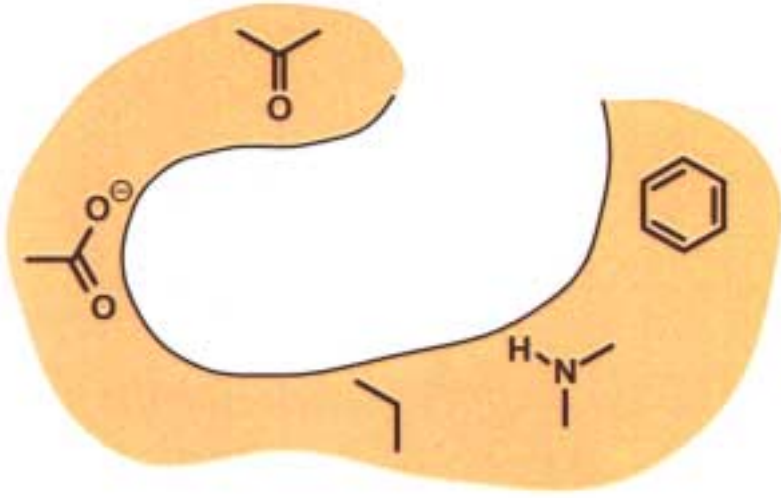
Computer-Aided Drug Design

H.-J. Böhm, 1992

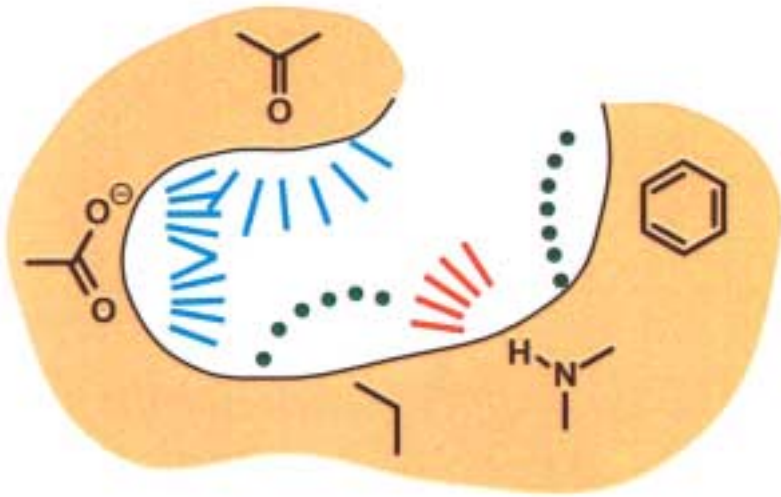
LUDI



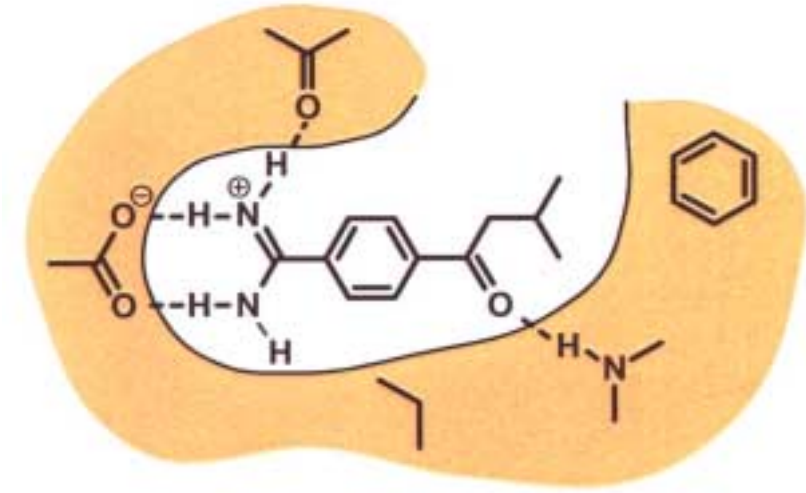
Ligand Docking into a Protein Binding Site



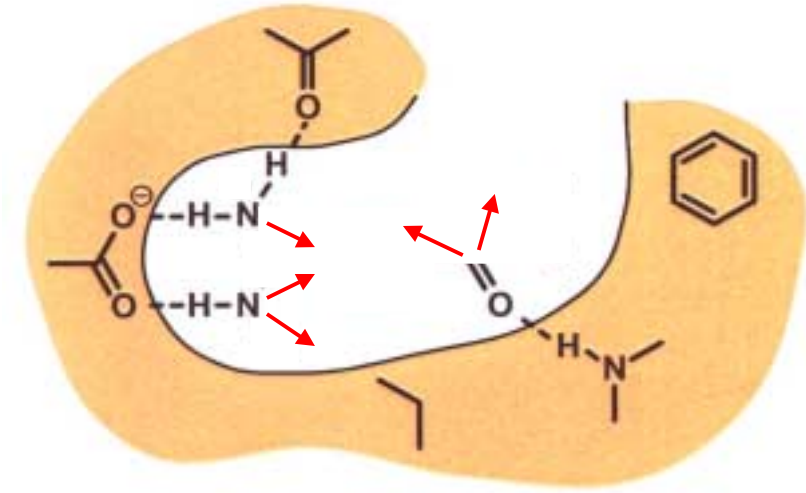
Assignment of Interaction Sites (H.-J. Böhm, 1992)



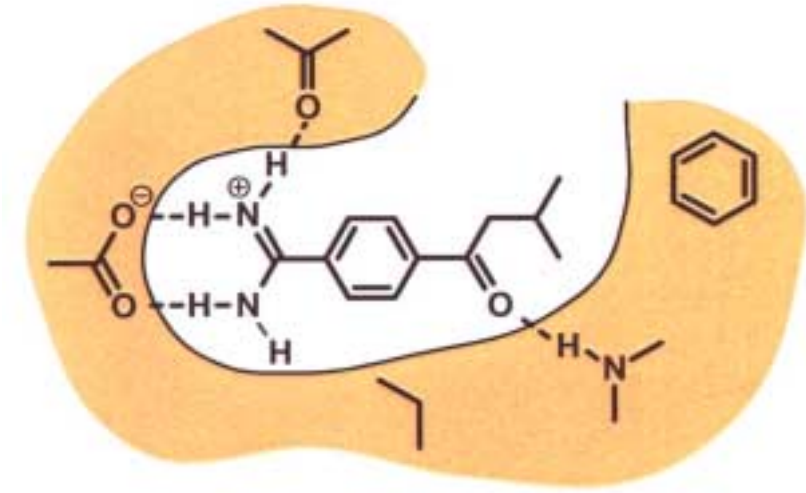
A Perfect Ligand



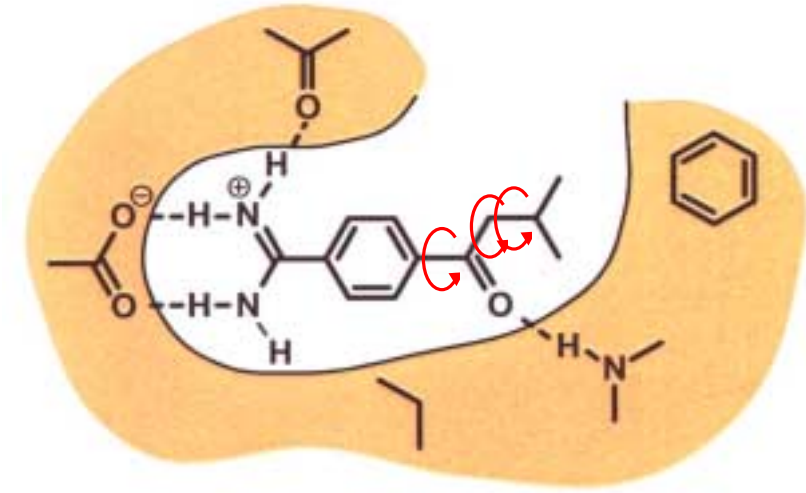
De Novo Construction of a Ligand



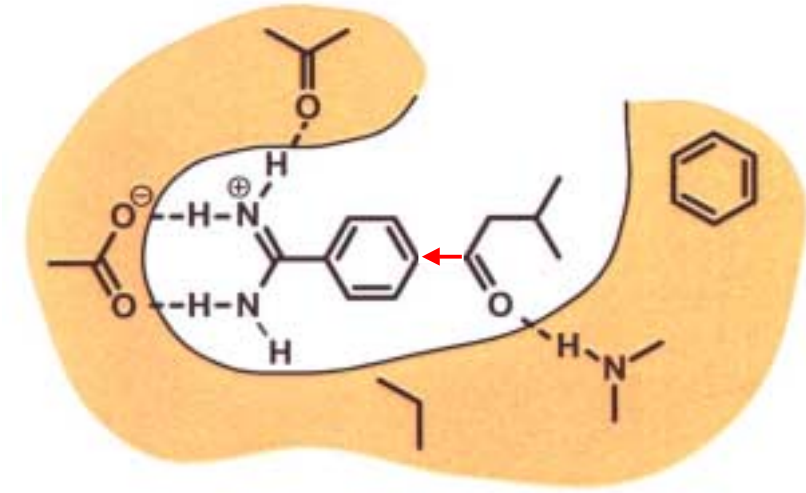
Rigid Docking (e.g. LUDI)



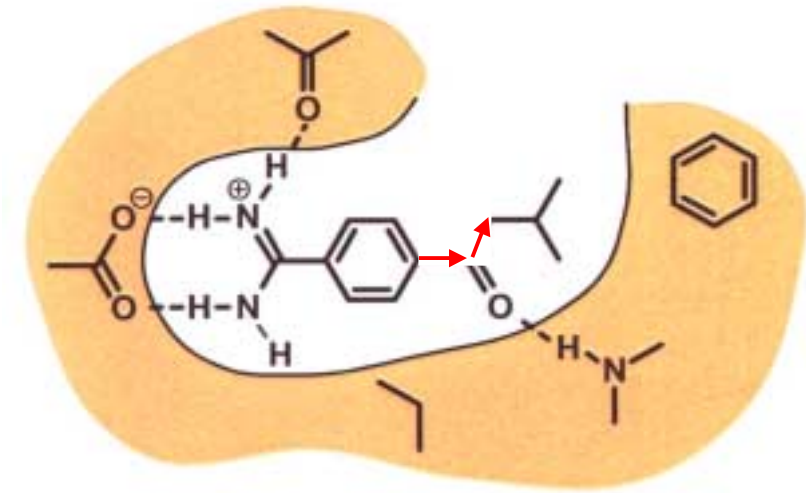
Multiple Conformations / Flexible Docking



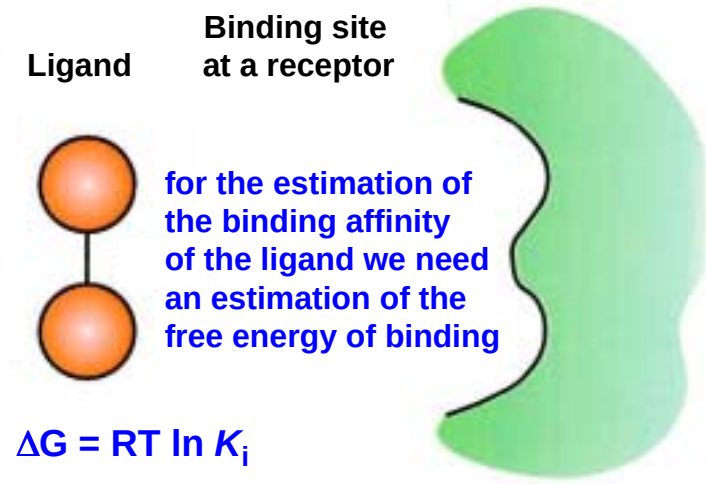
Linking (e.g. LUDI, SAR by NMR)



Flexible Incremental Docking (e.g. FlexX)



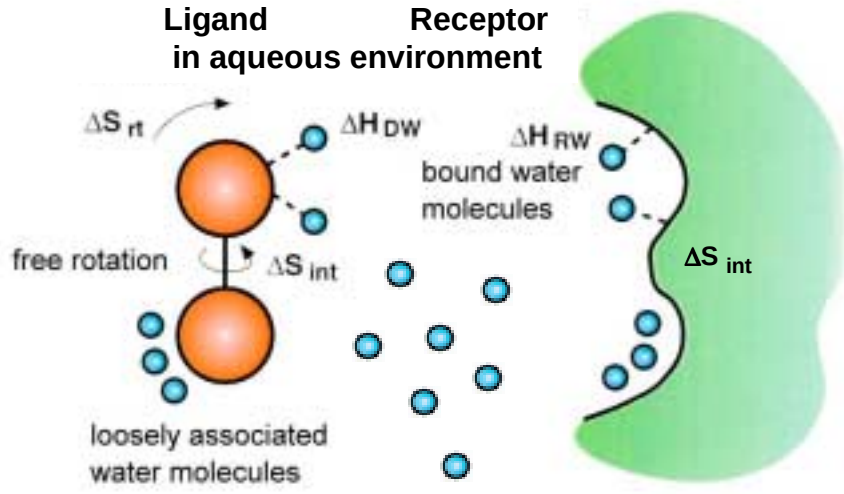
The Formation of a Ligand-Receptor Complex



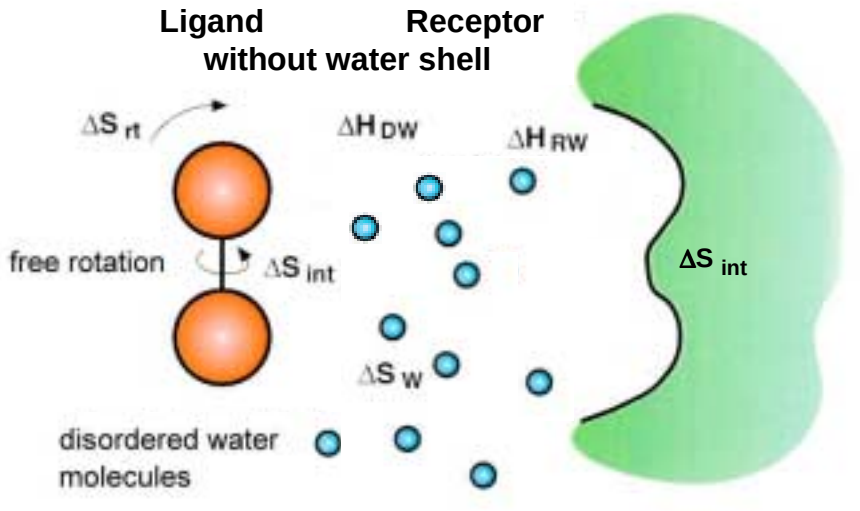
for the estimation of the binding affinity of the ligand we need an estimation of the free energy of binding

$$\Delta G = RT \ln K_i$$

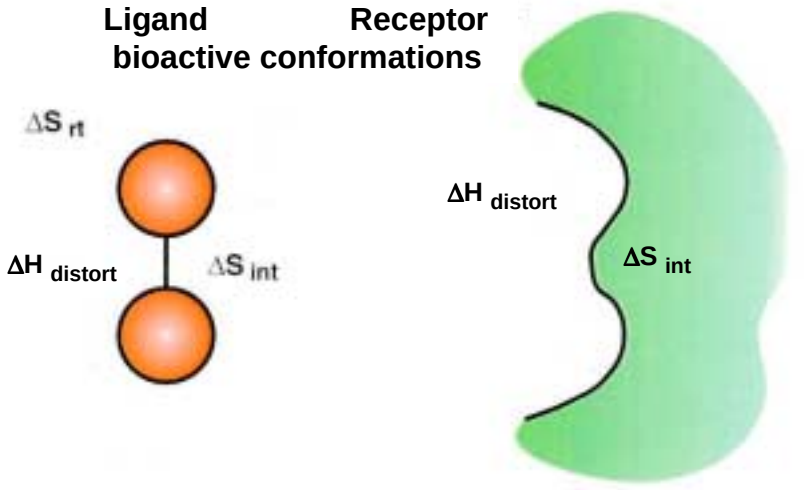
Consideration of Water, Flexibility and Mobility



The Effect of Ligand and Protein Desolvation

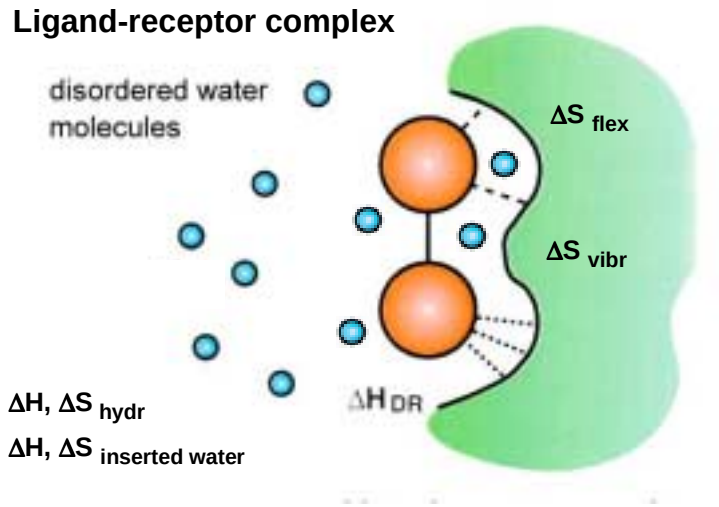


Freezing the Bioactive Conformations

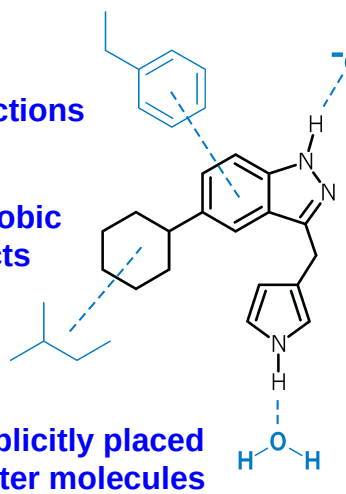


Free Energy of Complex Formation

Ligand-receptor complex



Terms Contributing to Ligand Binding



π interactions

hydrogen bonds (directed interactions)

hydrophobic contacts

ligand and protein flexibility

steric clashes

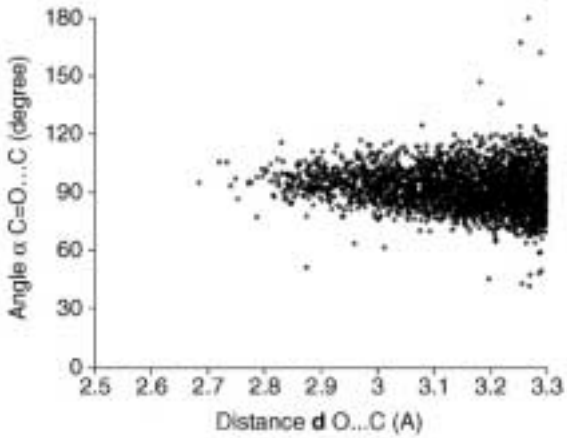
explicitly placed water molecules

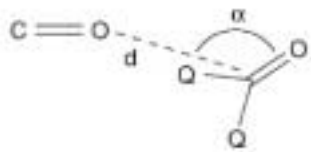
T. Schulz-Gasch, DDT Europe 2003, Stuttgart, Germany

Factors to be Considered in Scoring Functions

Desolvation enthalpy and entropy (ligand and protein)
Protonation state of the ligand and the binding site
Distortion energy of the ligand and its binding site
Loss of translational and rotational degrees of freedom of the ligand
MEP + dielectric constant at the binding site
Dipole moment of the ligand and local dipole moment at the binding site
Binding enthalpy of the ligand-protein complex
Repulsive effects (e.g. -O···O-)
Inserted water molecules
Solvation enthalpy and entropy of the complex

Unrecognized Favorable Interactions

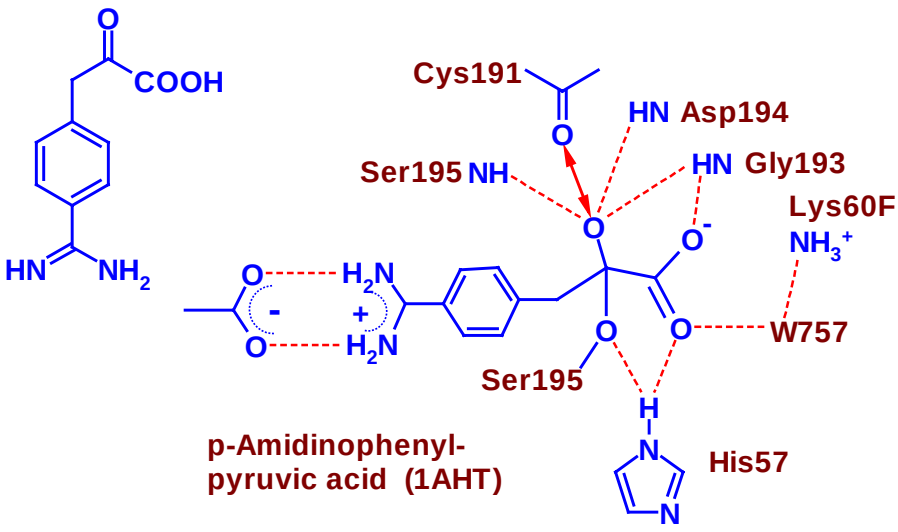




derived from 2,850 high-resolution CSD structures

T. Schulz-Gasch and M. Stahl, Drug Discov. Today: Technologies 1, 231-239 (2004)

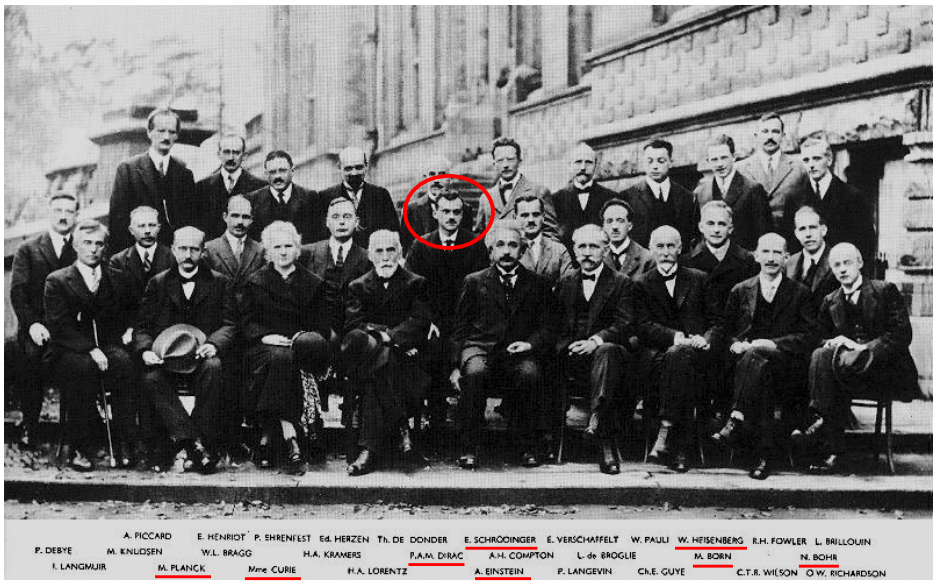
... But There Are Also Other Contributions



The Dilemma of Computer-Aided Drug Design

The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble.

P. A. M. Dirac, Proc. R. Soc. London 123, 714 (1929)



Fifth Solvay Congress, Brussels (1927)

Hugo Kubinyi, www.kubinyi.de

QSAR of Ligand-Receptor Interactions

P. R. Andrews et al., J. Med. Chem. 27, 1648-1657 (1984)

$$\text{AVERAGE } \Delta G = T\Delta S_{rt} + n_{DOF} \cdot E_{DOF} + \Sigma n_X \cdot E_X$$

$$= -59 - 3.0\, n_{DOF} + 3.0\, n_{C(sp^2)} + 3.4\, n_{C(sp^3)} + 48\, n_{N^+} + 5.0\, n_N + 34\, n_{COO^-} + 42\, n_{PO_4^{2-}} + 10.5\, n_{OH} + 14.2\, n_{C=O} + 4.6\, n_{O,S} + 5.4\, n_{Hal}$$

C. R. Beddell et al., Br. J. Pharmac. 65, 535-543 (1979)

$$\Delta G = -3.14\ (\pm 0.62)\ n_l - 6.78\ (\pm 1.39)\ n_C - 8.29\ (\pm 2.87)$$

$$(n = 29;\ r = 0.928;\ s = 3.34;\ F = 81.15)$$

R. S. Bohacek et al., J. Med. Chem. 35, 1671-1684 (1992)

$$\log 1/K_i = 0.624\ (\pm 0.10)\ \text{NPHO} + 0.217\ (\pm 0.08)\ \text{NHBOND} - 3.623\ (\pm 0.59)$$

$$(n = 9;\ r = 0.993;\ s = 0.228;\ F = 202.51)$$

LUDI Scoring Function

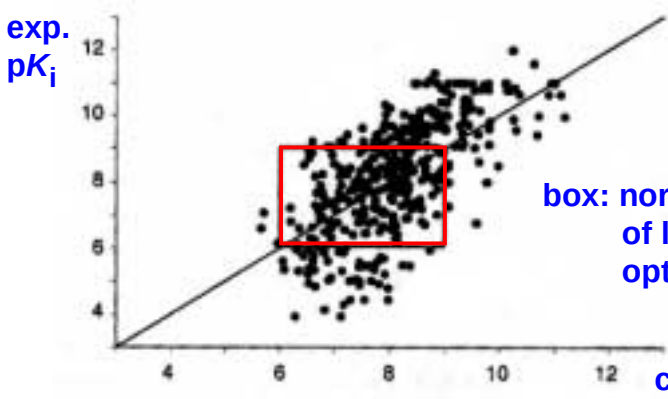
(H.-J. Böhm, J. Comp.-Aided Mol. Design 8, 243-256 (1994))

Log 1/K_i = 1.4 (±0.4) ionic hydrogen bonds
+ 0.83 (±0.3) neutral hydrogen bonds
+ 0.030 (±0.01) lipophilic contact surface area
- 0.25 (±0.1) number of rotatable bonds
- 0.91 (±1.4)
(n = 45; r = 0.875; s = 1.40; F = 32.8)

Consensus Scoring Functions

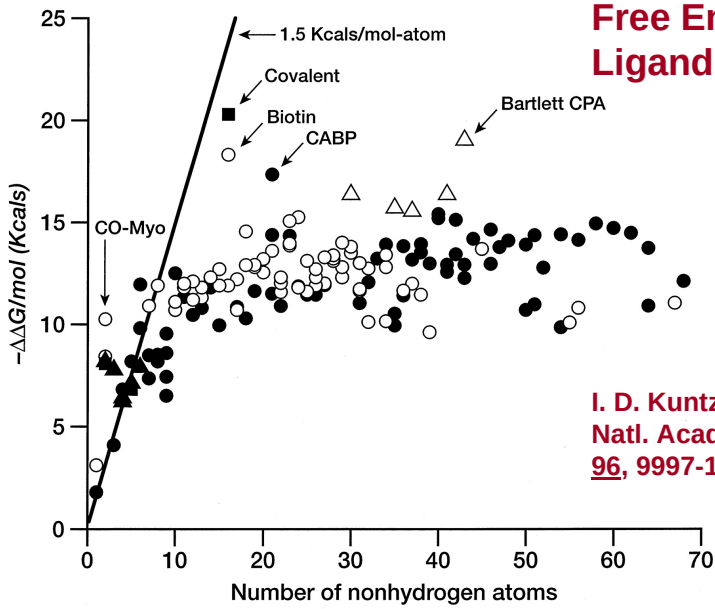
e.g. LUDI / FlexX score, DOCK score, GOLD score, ChemScore, PMF score, etc.
C. Bissantz et al., J. Med. Chem. 43, 4759-67 (2000);
R. D. Clark et al., J. Mol. Graph. Model. 20, 281-95 (2002);
www. tripos.com/software/cscore.html

pK_i values of HIV Protease Inhibitors: VALIDATE II Predictions



A. M. Davis et al., Angew. Chem. Int. Ed. Engl. 42, 2718-36 (2003); Angew, Chem. 115, 2822-2841 (2003)

Free Energy of Ligand Binding



I. D. Kuntz et al., Proc. Natl. Acad. Sci. USA 96, 9997-10002 (1999)

Hugo Kubinyi, www.kubinyi.de

De Novo Design Algorithms

BUILDER	HOOK	PRO-SELECT
CAVEAT	LEGEND	SKELGEN
CONCERTS	LUDI	SME
DLD	MCDNLG	SMOG
GENSTAR	MCSS	SPLICE
GROUPBUILD	MOLMAKER	SPROUT
GROW	NEWLF-AD	TOPAS
GROWMOL	PRO-LIGAND	

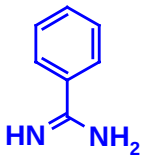
(G. Schneider and H.-J. Böhm, Drug Discov. today 7, 64-70 (2002))

De Novo Design Algorithms

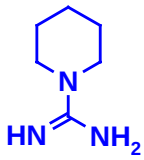
GENSTAR	Atom-based; grows molecules in situ based on an enzyme contact model
GROUPBUILD	Fragment-based, sequential growth, combinatorial search
GROW	Peptide design, sequential growth
GROWMOL	Fragment-based, sequential growth, stochastic search
HOOK	Linker search for fragments placed by MCSS
LEGEND	Atom-based, stochastic search
LUDI	Fragment-based, combinatorial search
MCSS	Fragment-based, stochastic sampling
MOLMAKER	Graph-theoretical 3D design
PRO-LIGAND	Fragment-based search
PRO-SELECT	Fragment-based, scaffold-linker approach
SKELGEN	Small-fragment based, Monte-Carlo search
SPROUT	Fragment-based, sequential growth, combinatorial search

(G. Schneider and H.-J. Böhm, Drug Discov. today 7, 64-70 (2002))

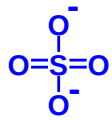
Small Molecules With High Affinity to their Target



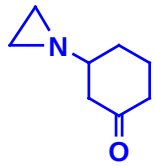
K_i = 18 µM (trypsin)



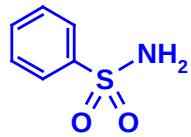
K_i = 150 µM (thrombin)



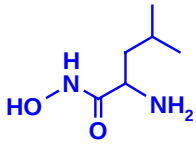
K_i = 0.12 µM (SBP)



K_i = 0.25 µM (FKBP)

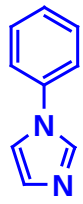


K_i = 0.1 µM (Carboanhydrase)



K_i = 190 µM (thermolysin)

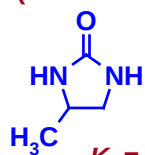
K_i = 1.6 µM (DHFR)



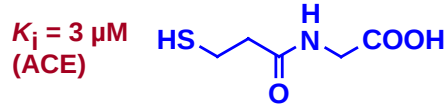
K_i = 0.1 µM ($CYP450_{cam}$)

$CF_3SO_2NH_2$

K_i = 2 nM (Carboanhydrase)

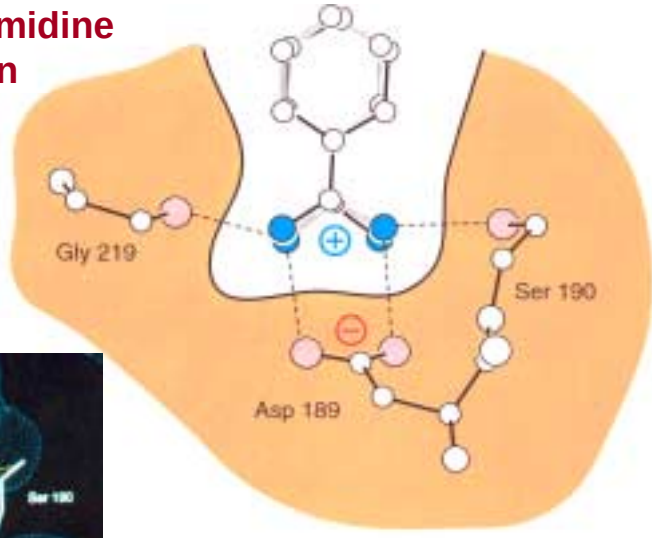


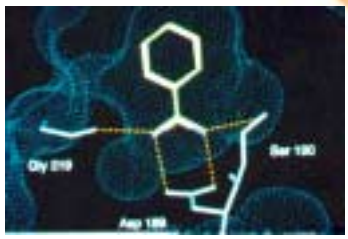
K_i = 34 µM (avidin)



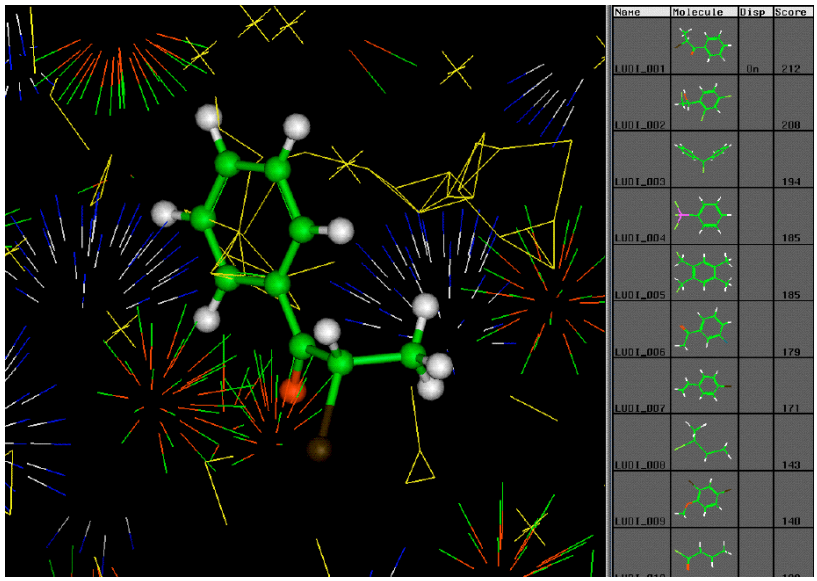
K_i = 3 µM (ACE)

LUDI: Benzamidine in the Trypsin Specificity Pocket

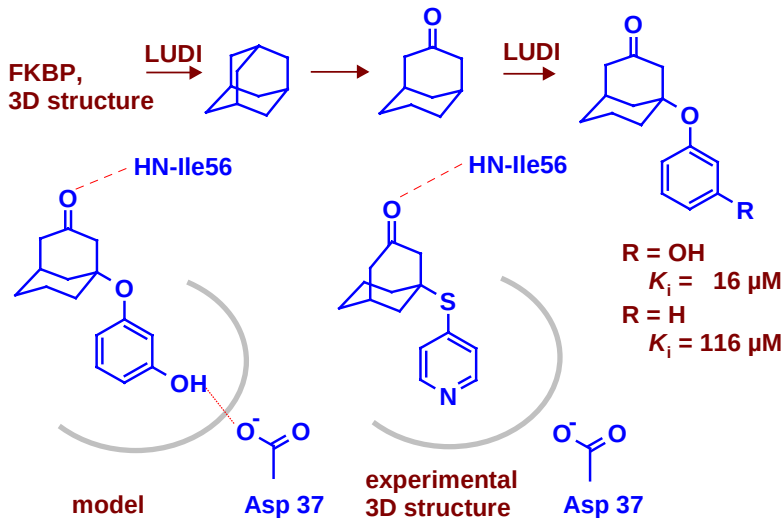




Results from a LUDI Search

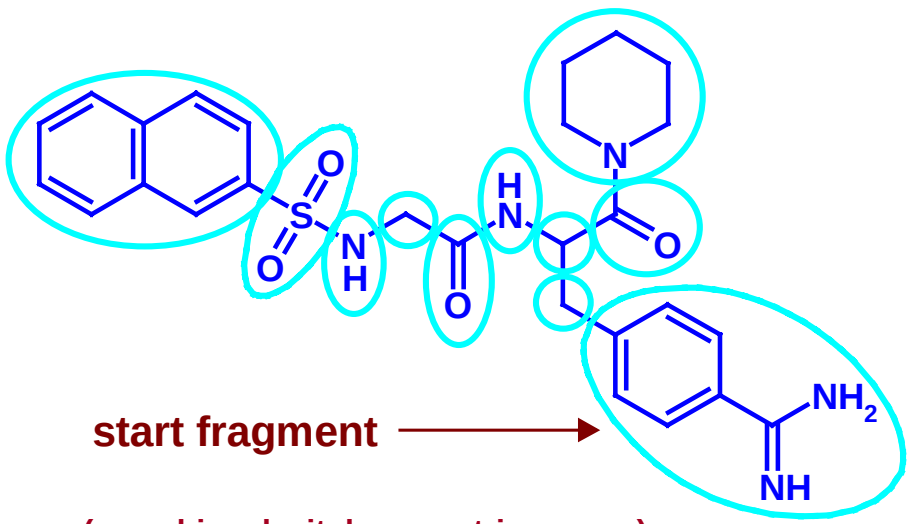


LUDI: Design of a FK-506 BP Ligand



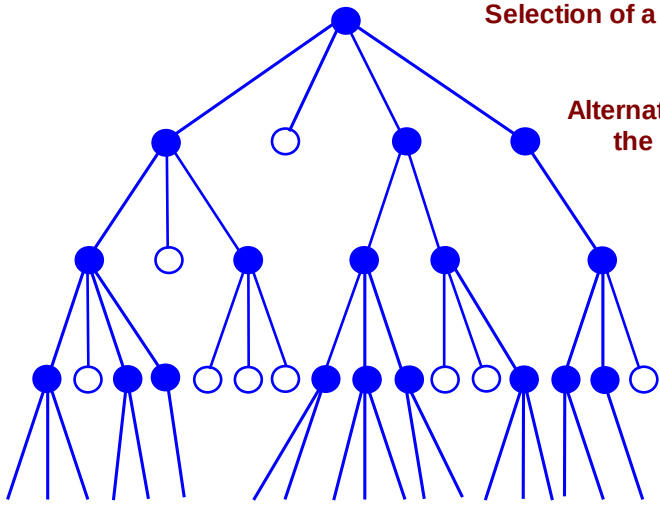
R. E. Babine et al., Bioorg. Med. Chem. Lett. 5, 1719-1724 (1995)

FlexX (GMD, BASF): Dissection of a Ligand

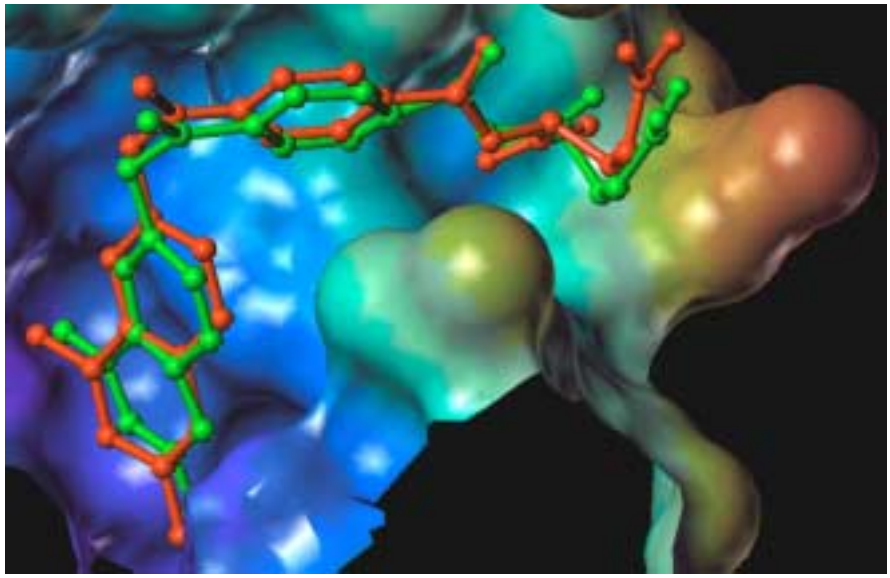


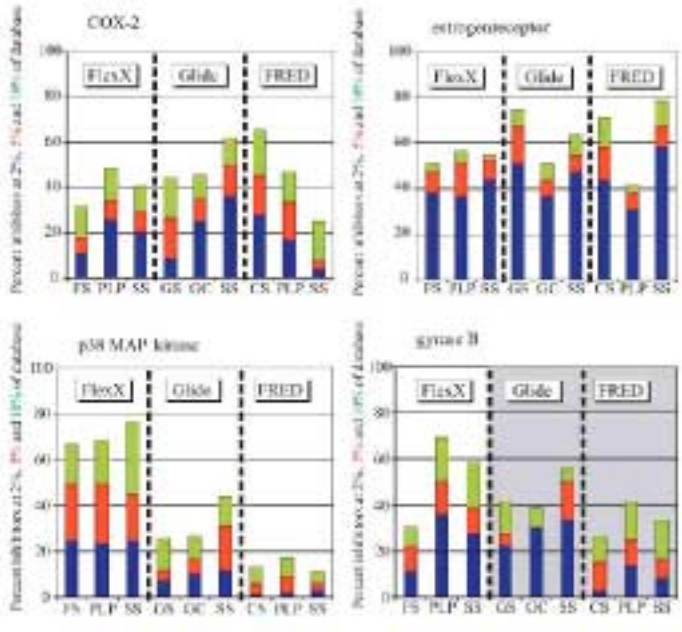
(www.biosolveit.de, www.tripos.com)

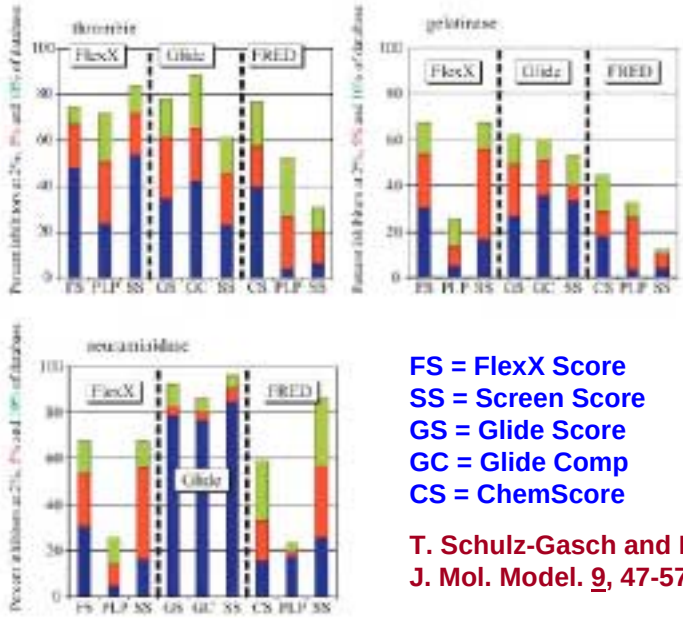
FlexX: Search Tree for Ligand Docking



Binding of Methotrexate to DHFR



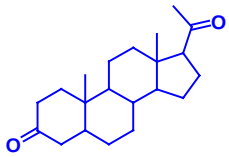




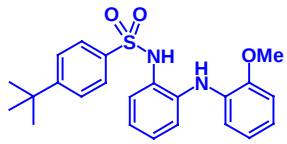
FS = FlexX Score
SS = Screen Score
GS = Glide Score
GC = Glide Comp
CS = ChemScore

T. Schulz-Gasch and M. Stahl,
J. Mol. Model. 9, 47-57 (2003)

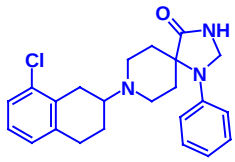
Success Stories in Computer-Aided Drug Design



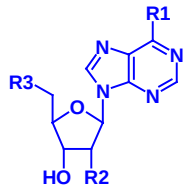
FKBP ligand
(docking and scoring)
P. Burkhard et al., J. Mol. Biol. 287, 853-858 (1999)



K^+ channel (kv 1.5) blocker
(fragment-based evolutionary design)
G. Schneider et al., J. Comput-Aided Mol. Design 14, 487-494 (2000)

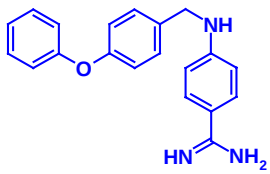


Ca^{2+} antagonist / T-channel blocker
(pharmacophore similarity search)
G. Schneider et al., Angew. Chem. Int. Ed. Engl. 39, 4130-4133 (2000)

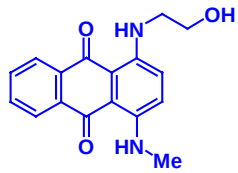


Glyceraldehyde-phosphate DH inhibitors (combinatorial docking)
J. C. Bressi et al., J. Med. Chem. 44, 2080-2093 (2001)

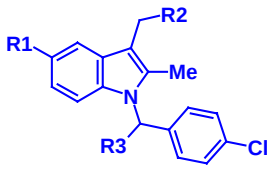
Success Stories in Computer-Aided Drug Design



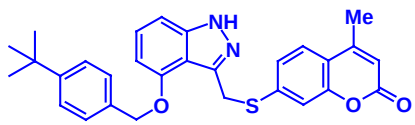
Thrombin inhibitor
(docking, de novo design)
H.-J. Böhm et al., J. Comput.-Aided Mol. Design 13, 51-56 (1999)



HIV-1 RNA TAR inhibitor
(docking, database search)
A. V. Filikov et al., J. Comput-Aided Mol. Design 14, 593-610 (2000)



Aldose reductase inhibitors
(3D database searching)
Y. Iwata et al., J. Med. Chem. 44, 1718-1728 (2001)



DNA gyrase inhibitor
(structure-based virtual screening)
H.-J. Boehm et al., J. Med. Chem. 43, 2664-2674 (2000)