



Virtual Screening - The Road to Success

Hugo Kubinyi

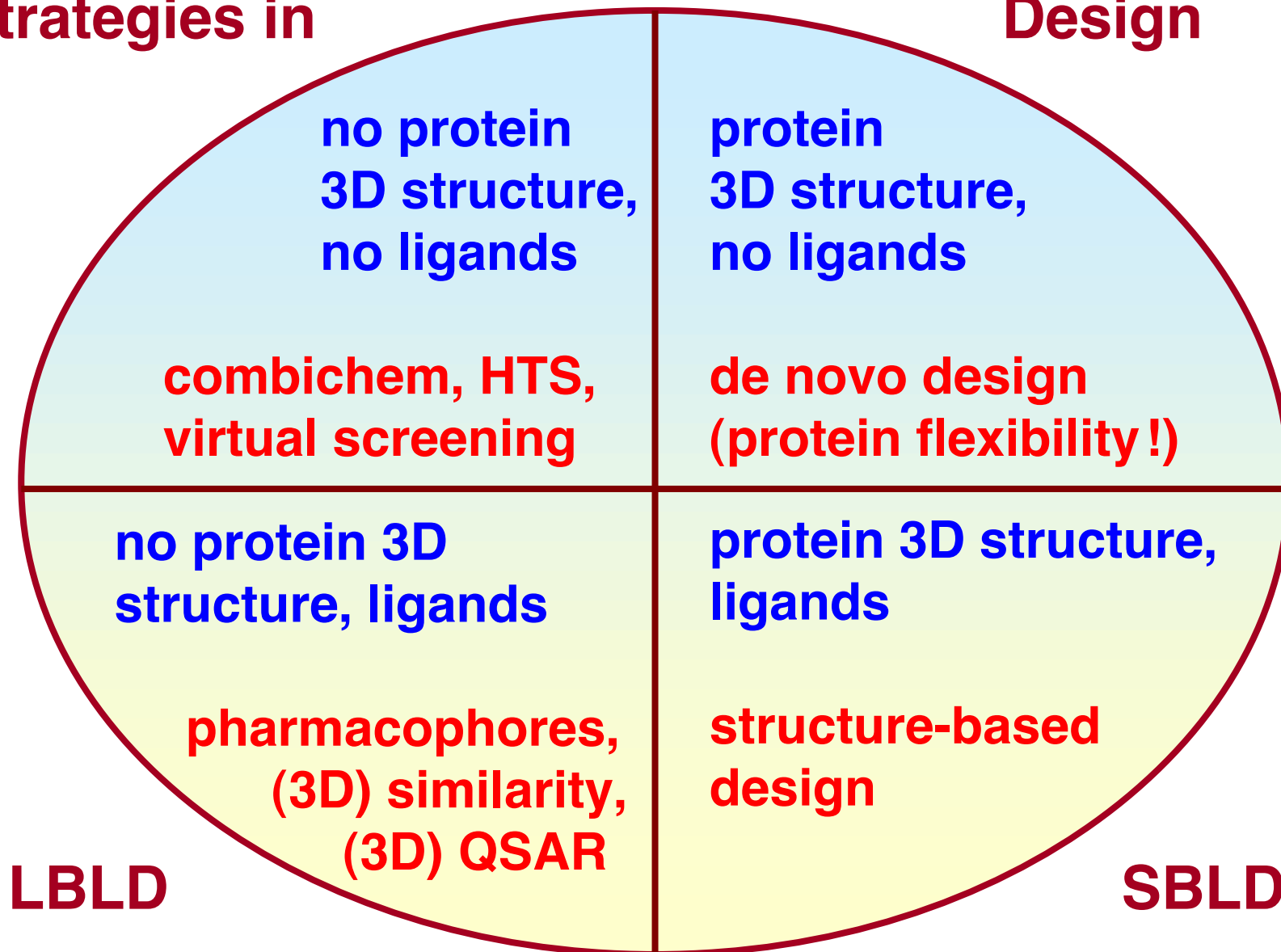
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August 29-September 02, 2006**

Strategies in

Design



Drug Research is



the Search for a Needle in a Haystack

Virtual Screening Reduces the Size of the Haystack by Selecting:

Compounds or libraries that are either
lead-like, or
drug-like, or have the
potential of oral bioavailability, or are
similar to a lead, or
fit the binding site of a certain protein
by rules (e.g. Lipinski bioavailability rules),
neural nets (e.g. drug-like character),
similarity analyses,
pharmacophore analyses,
scaffold hopping, or
docking and scoring

Chris Rescues CombiChem and Screening Collections



Advanced Drug Delivery Reviews 23 (1997) 3–25

advanced
drug delivery
reviews

Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings

Christopher A. Lipinski*, Franco Lombardo, Beryl W. Dominy, Paul J. Feeney

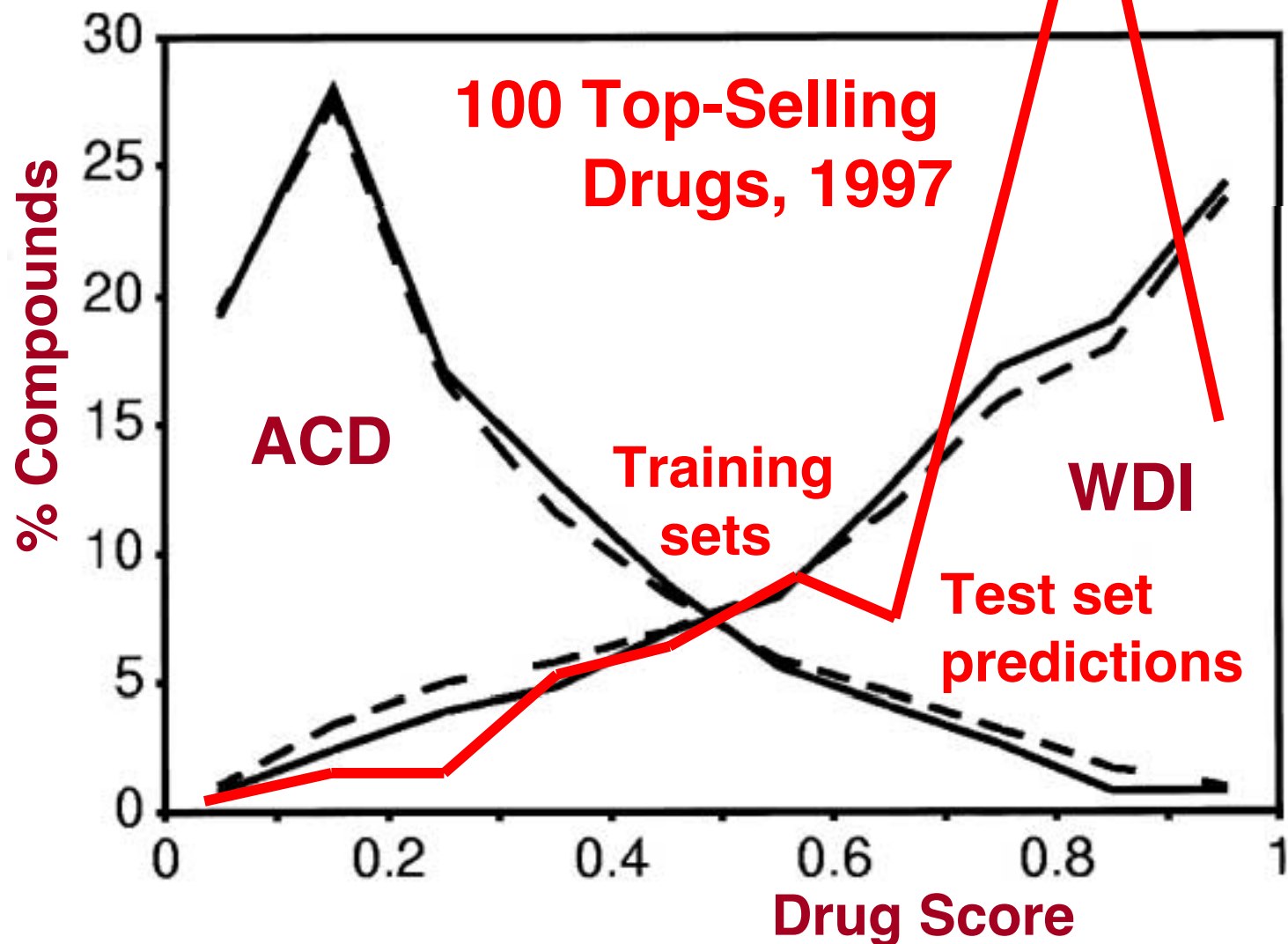
Central Research Division, Pfizer Inc., Groton, CT 06340, USA

Received 9 August 1996; accepted 14 August 1996

Abstract

Experimental and computational approaches to estimate solubility and permeability in discovery and development settings are described. In the discovery setting 'the rule of 5' predicts that poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight (MWT) is greater than 500 and the calculated Log P (CLogP) is greater than 5 (or MlogP > 4.15). Computational methodology for the rule-based Moriguchi Log P (MLogP) calculation is described. Turbidimetric solubility measurement is described and applied to known drugs. High throughput screening (HTS) leads tend to have higher MWT and Log P and lower turbidimetric solubility than leads in the pre-HTS era. In the development setting, solubility calculations focus on exact value prediction and are difficult because of polymorphism. Recent work on linear free energy relationships and Log P approaches are critically reviewed. Useful predictions are possible in closely related analog series when coupled with experimental thermodynamic solubility measurements.

„Drug-like“ Character



Filters for Virtual Screening

remaining

Garbage filter	90%
Druglike / Non-druglike	60%
Bioavailability	40%
Cytotoxicity	:
hERG channel inhibition	:
Antitargets	:
α 1a (orthostatic hypotension)	:
D2 (extrapyramidal syndrome)	:
5-HT _{2c} (obesity)	:
musc. M1 (hallucinations, memory)	:
CYP inhibition (3A4, 2C9, 2D6)	0% ?

Pharmacophore Generation and Searches

Catalyst (Accelrys)

established tool for hypothesis generation
and 3D searches

CATS topological pharmacophores (Roche)

no 3D structures required

FTree (feature trees; BioSolveIT)

no 3D searches required, ultrafast searches

LigandScout (inte:ligand)

automated generation of bioactive
pharmacophores from protein 3D structures

Problems in Pharmacophore Generation

Isomers, enantiomers, diastereomers

Superposition of flexible molecules

Ionisation and Dissoziation

(Sadowski rules, ACS Boston, 2002)

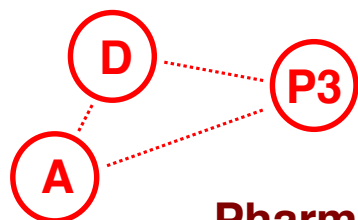
Tautomeric and protomeric forms

(program AGENT, ETH Zurich; ChemoSoft tautomer recognition, ChemDiv)

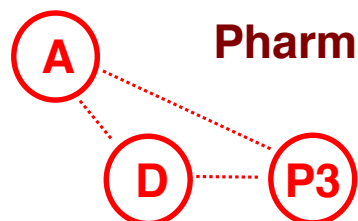
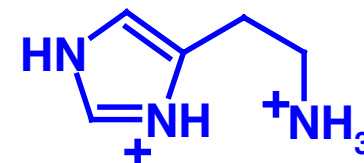
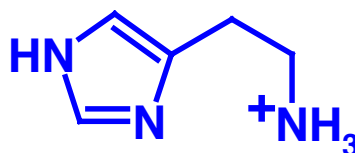
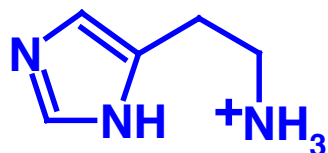
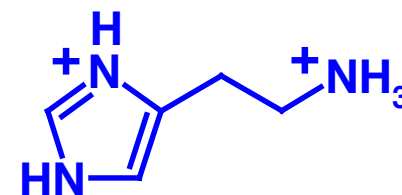
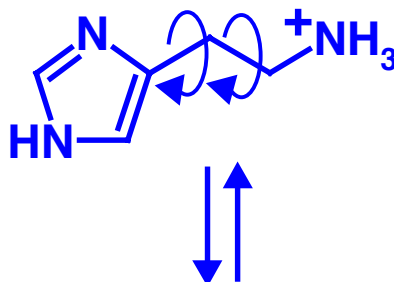
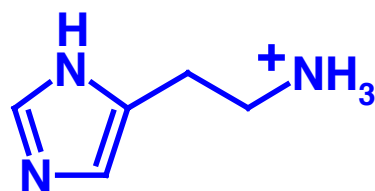
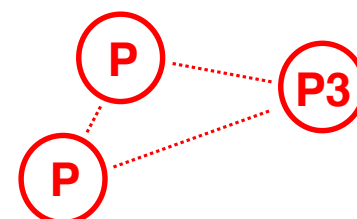
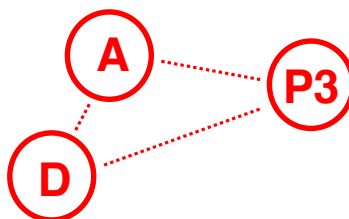
Acceptor properties of oxygen and sulfur atoms

(esters, aromatic ethers, oxazoles, isoxazoles, thiazoles, etc.)

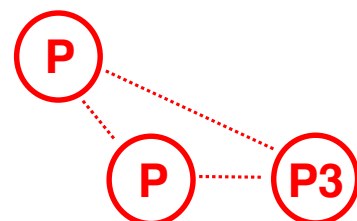
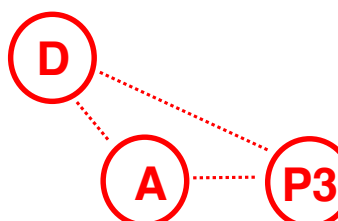
Pharmacophore Hypotheses - Histamine



Pharmacophores



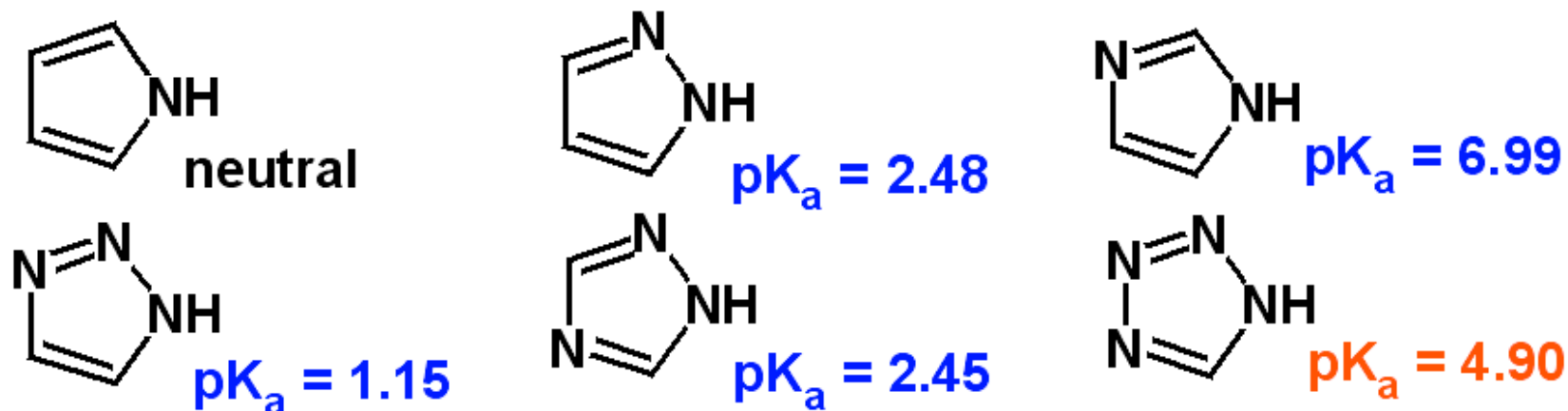
Pharmacophores



Dissociation of Acids and Protonation of Bases

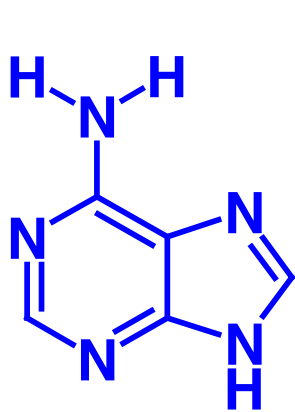
↑	strong acids	CF_3COOH
	acids	arom. + aliph. COOH , $\text{CF}_3\text{SO}_2\text{NH}_2$, tetrazole
	weak acids	arom. OH , arom. SO_2NH_2
	neutral	aliph. $-\text{OH}$, $-\text{CONH}_2$
	weak bases	arom. NH_2 , imidazole
	bases	aliph. NH_2
↓	strong bases	amidines, guanidines

pK_a Values of Selected Organic Compounds

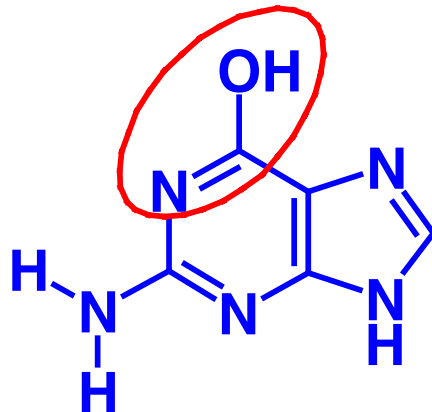


The Discovery of the DNA Double Helix

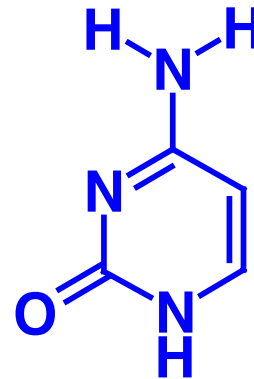
Summer 1952: Erwin Chargaff criticizes that Francis Crick and James Watson are ignorant about the structures of the bases



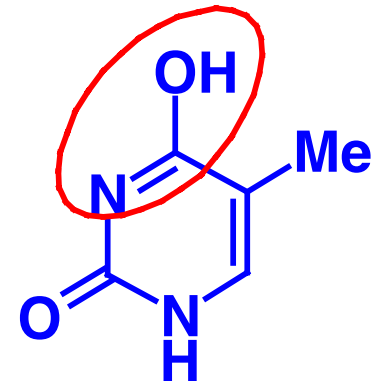
adenine



guanine



cytosine



thymine

J. N. Davidson, The Biochemistry of Nucleic Acids, London, 1950

early 1953: Pauling publishes a DNA model with a phosphate core

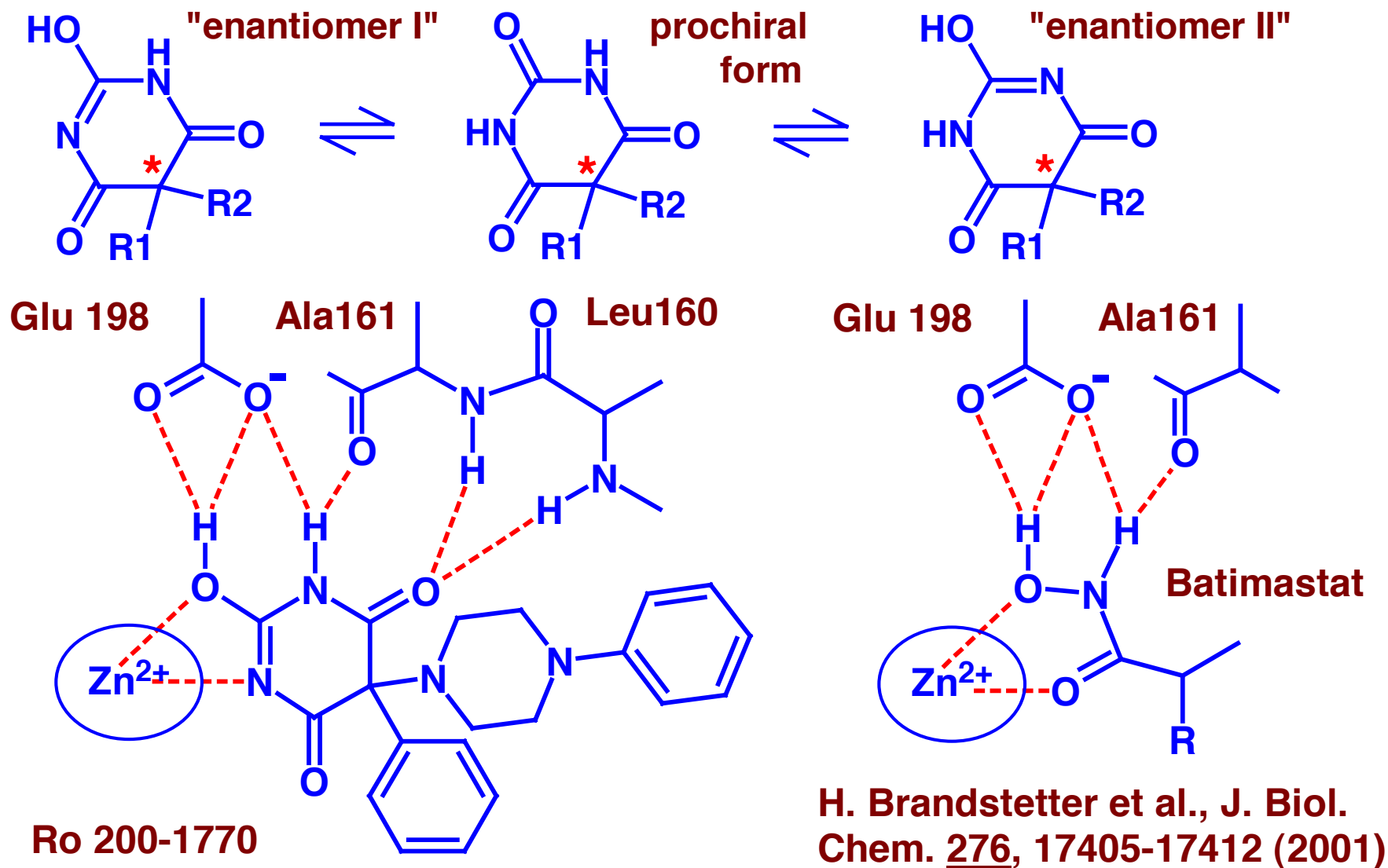
February 27, 1953: Jerry Donohue corrects the formulas of the bases

February 28, 1953: Watson and Crick derive the correct DNA model

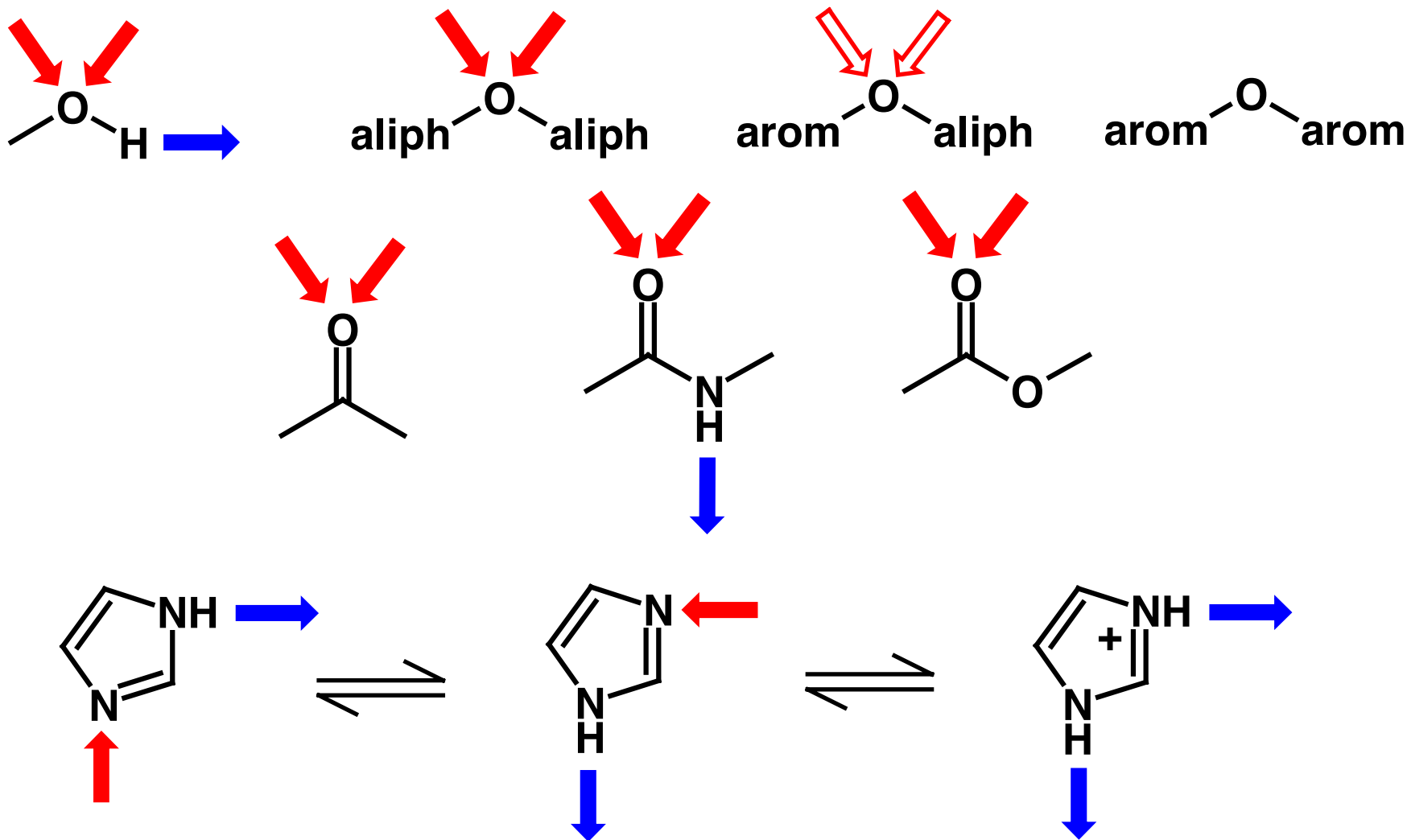
April 02, 1953: Manuscript sent to Nature; published **April 25, 1953**

cited from: J. Watson and A. Berry, DNA. The Secret of Life, 2003

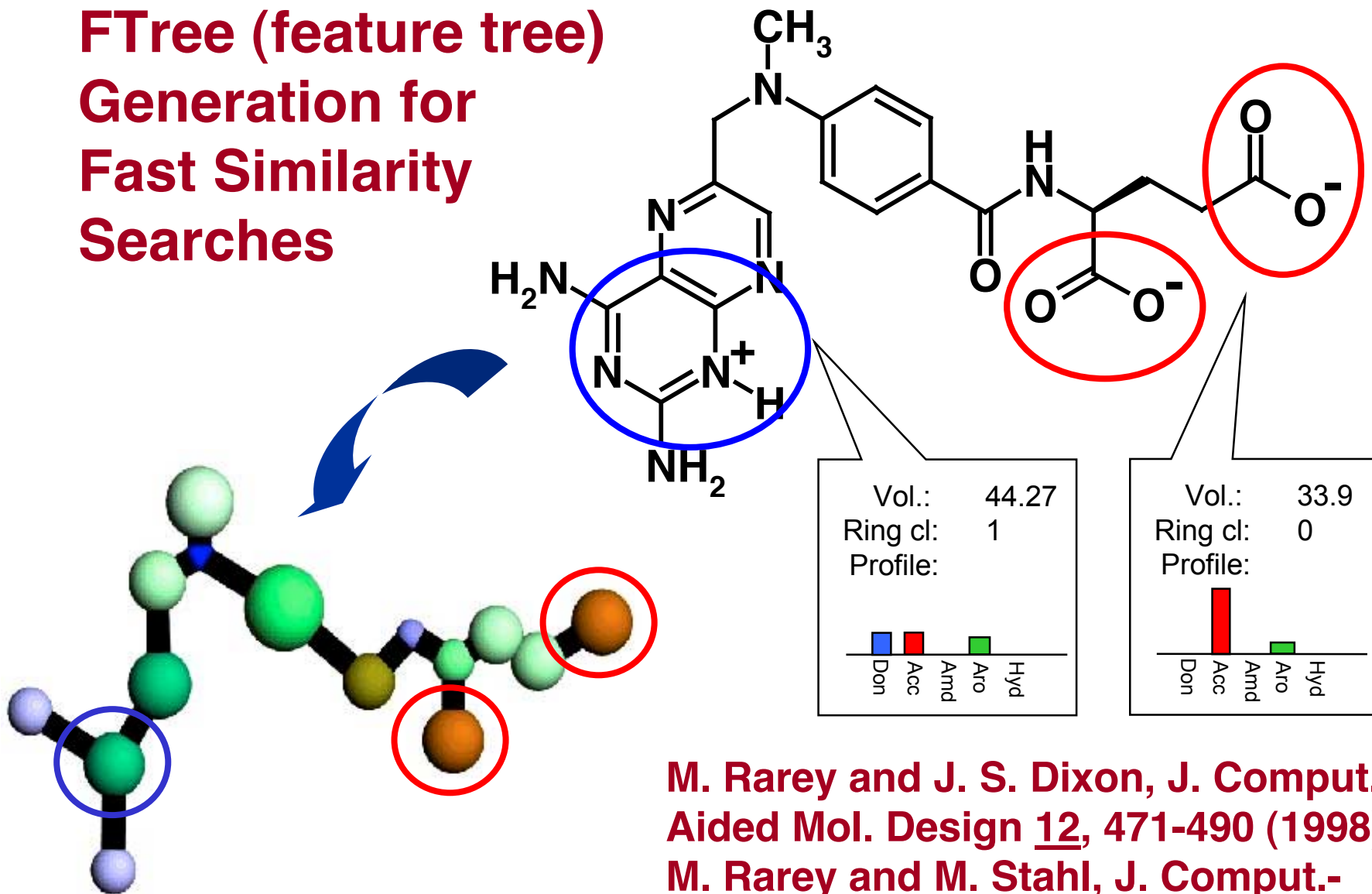
Tautomeric Forms of an MMP-8 Inhibitor (1jj9)



Donor and Acceptor Properties of O and N

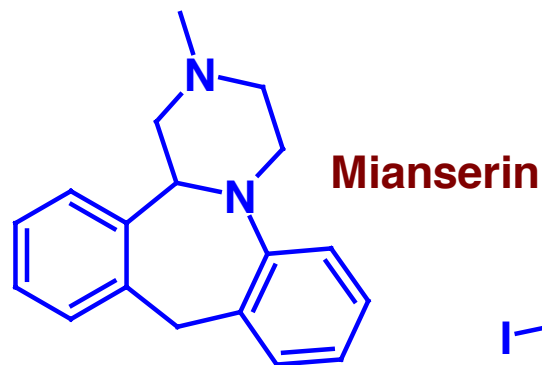
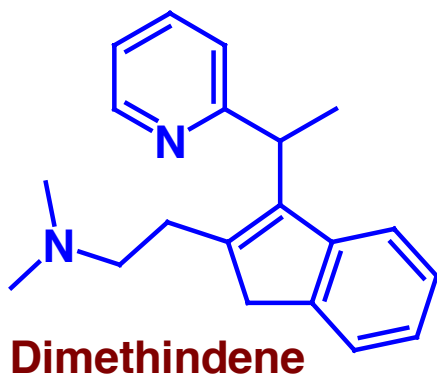


FTree (feature tree) Generation for Fast Similarity Searches

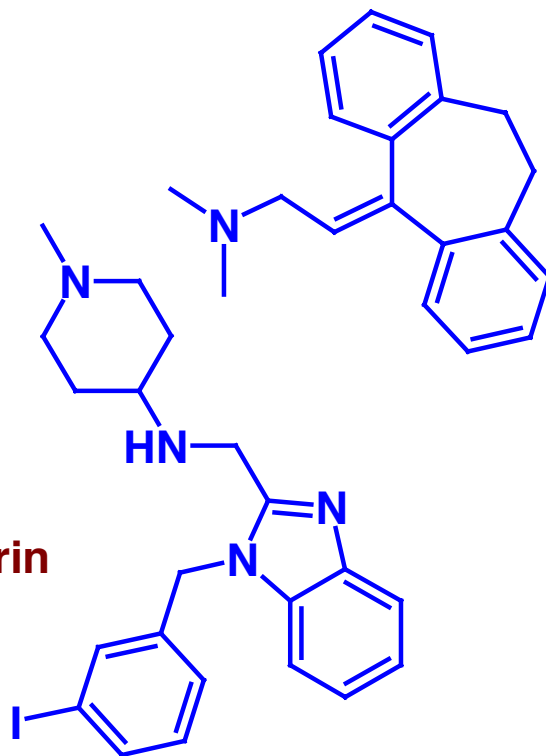


M. Rarey and J. S. Dixon, J. Comput.-Aided Mol. Design 12, 471-490 (1998);
M. Rarey and M. Stahl, J. Comput.-Aided Mol. Design 15, 497-520 (2001)

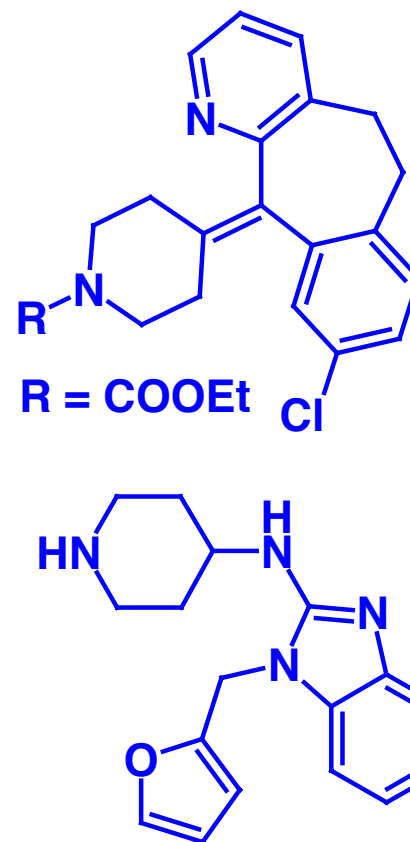
FTree Query Results for H1 Antagonists and Antidepressants



known actives

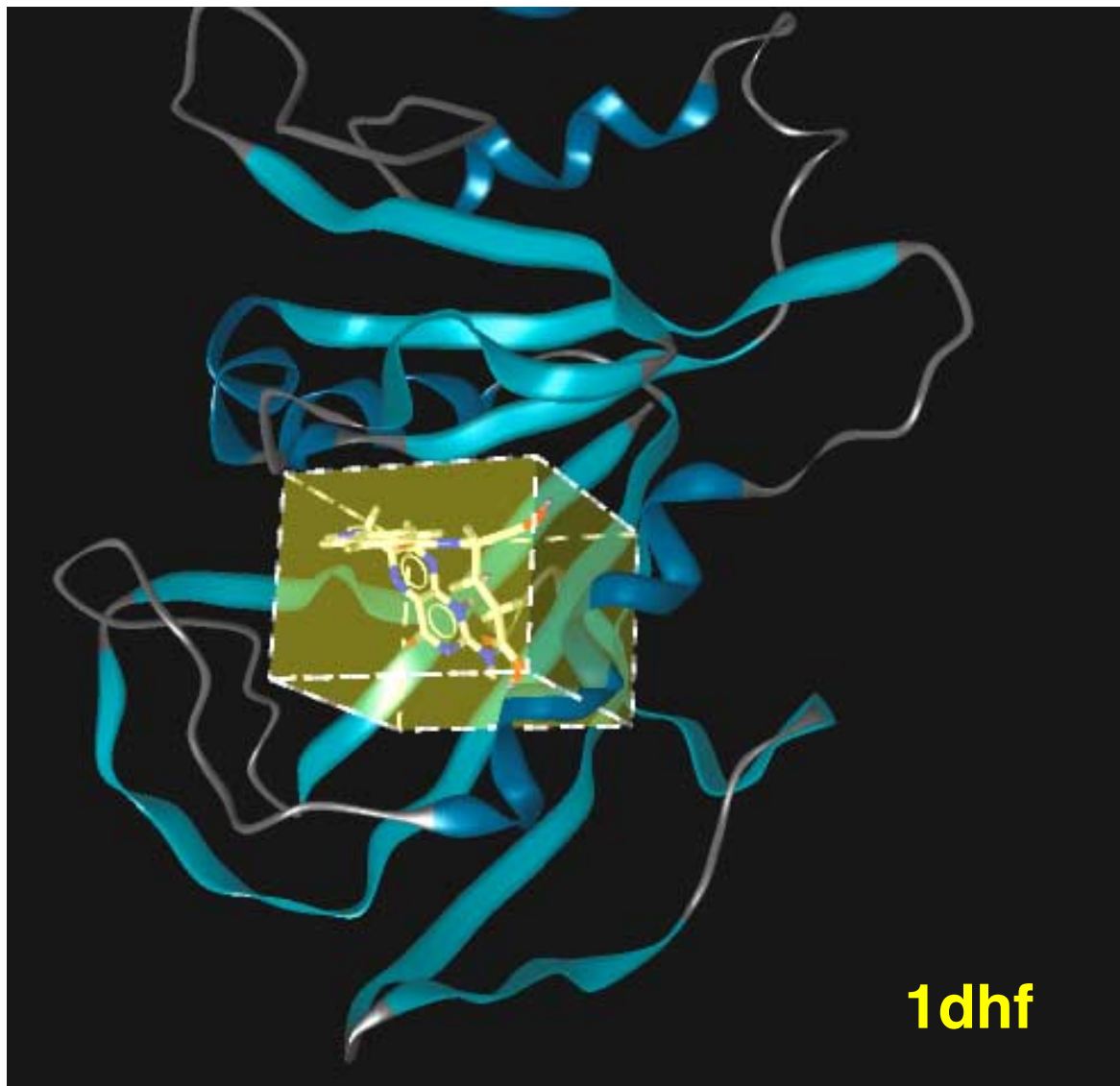


plausible hits



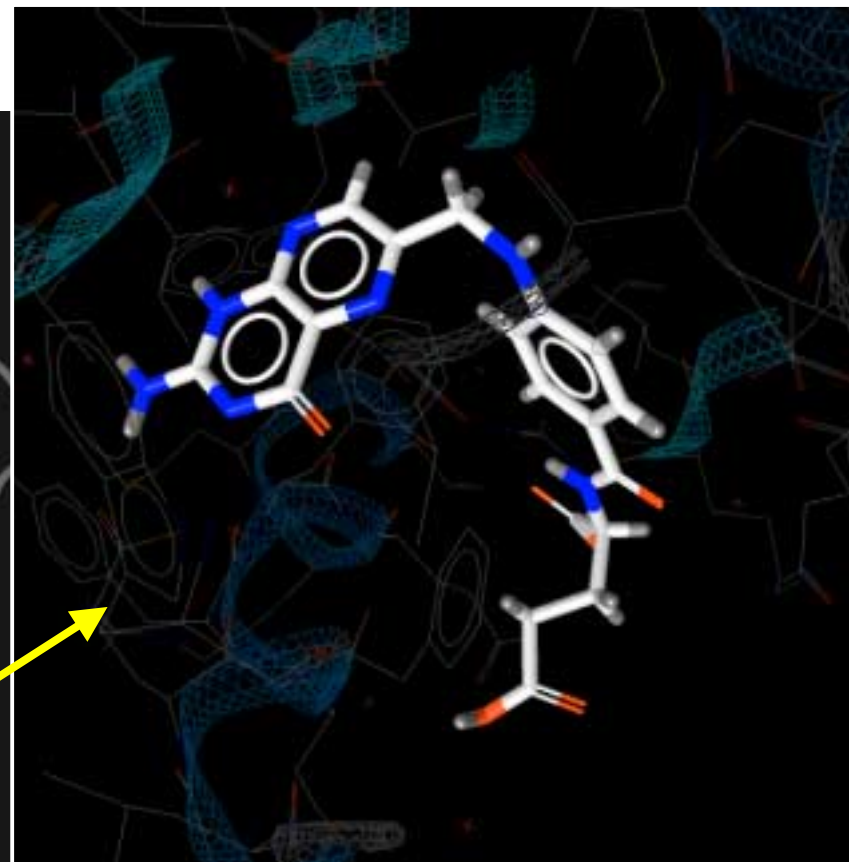
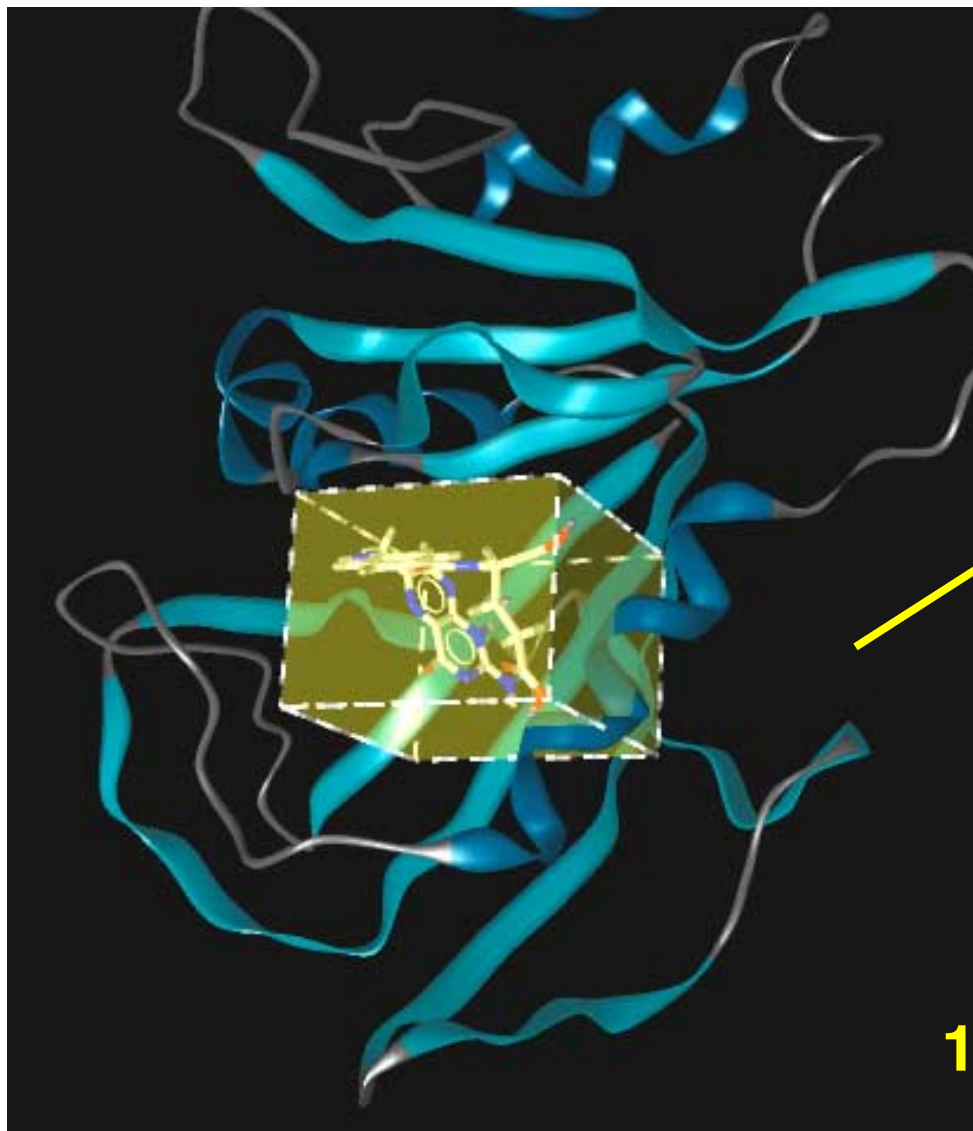
known actives related
to the plausible hit

LigandScout (inte:ligand)



G. Wolber and T. Langer,
J. Chem. Inf. Model. 45,
160-169 (2005)

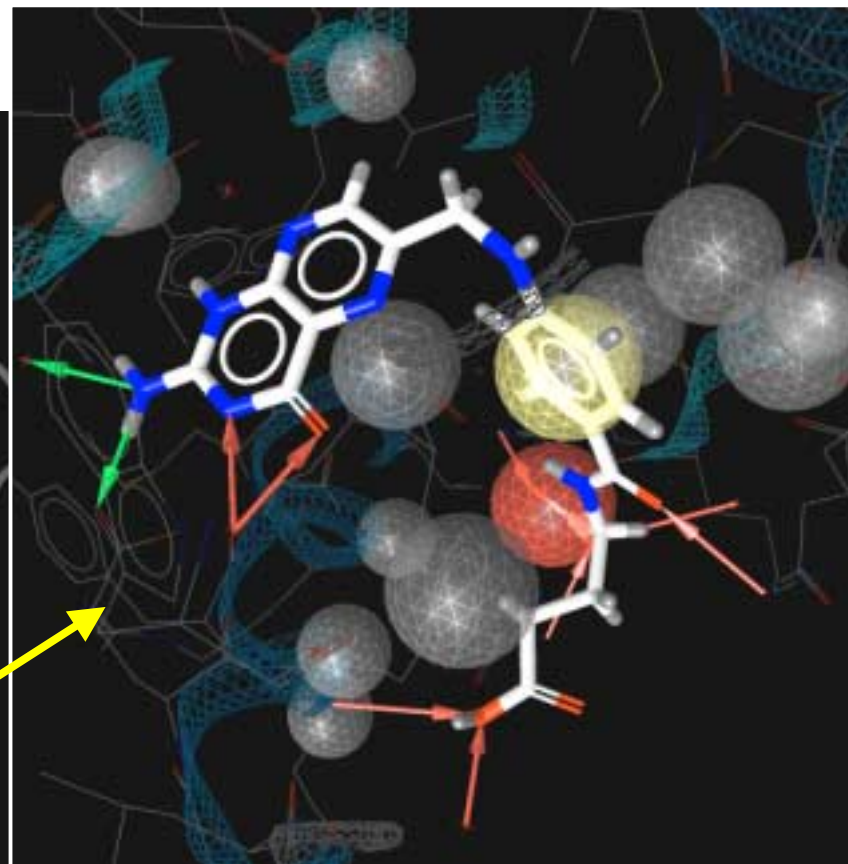
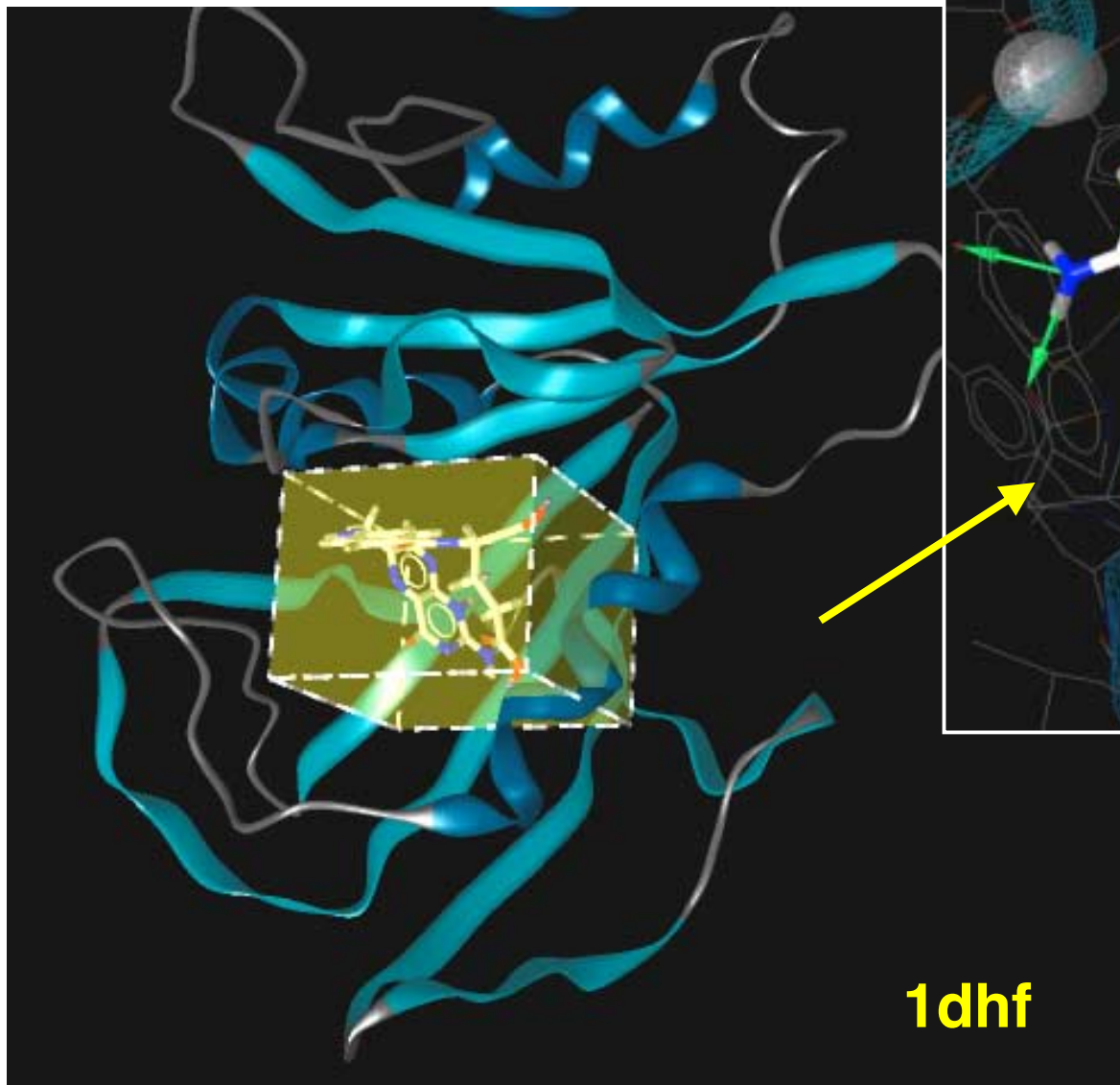
LigandScout (inte:ligand)



1dhf

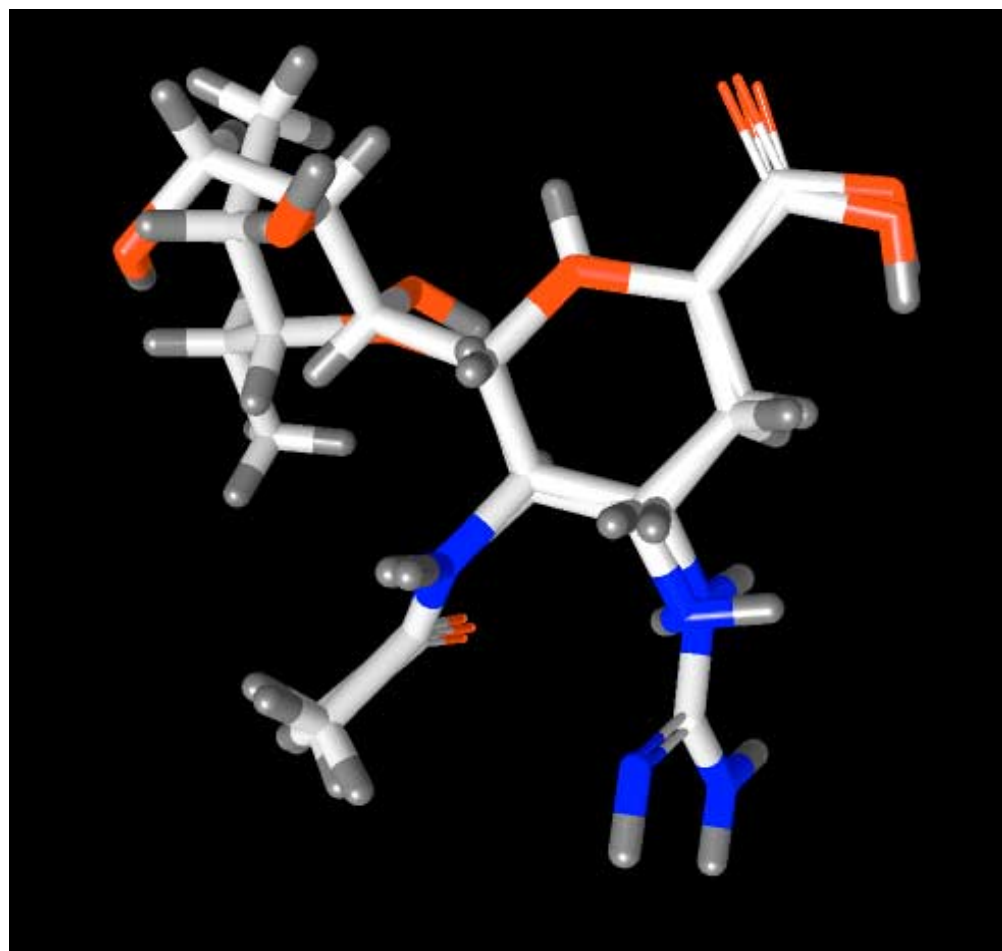
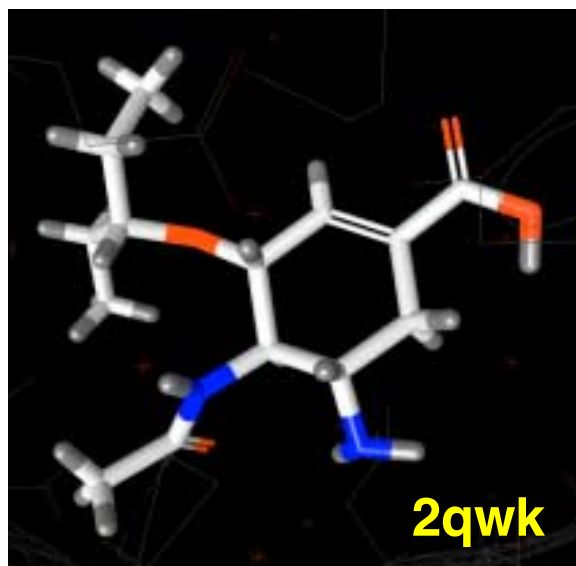
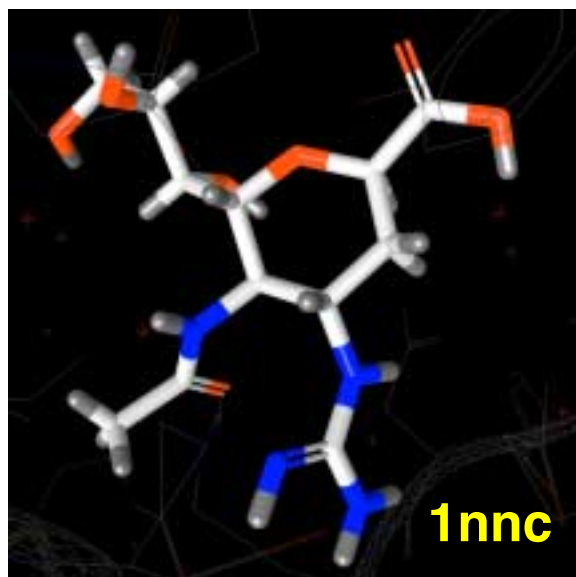
G. Wolber and T. Langer,
J. Chem. Inf. Model. 45,
160-169 (2005)

LigandScout (inte:ligand)

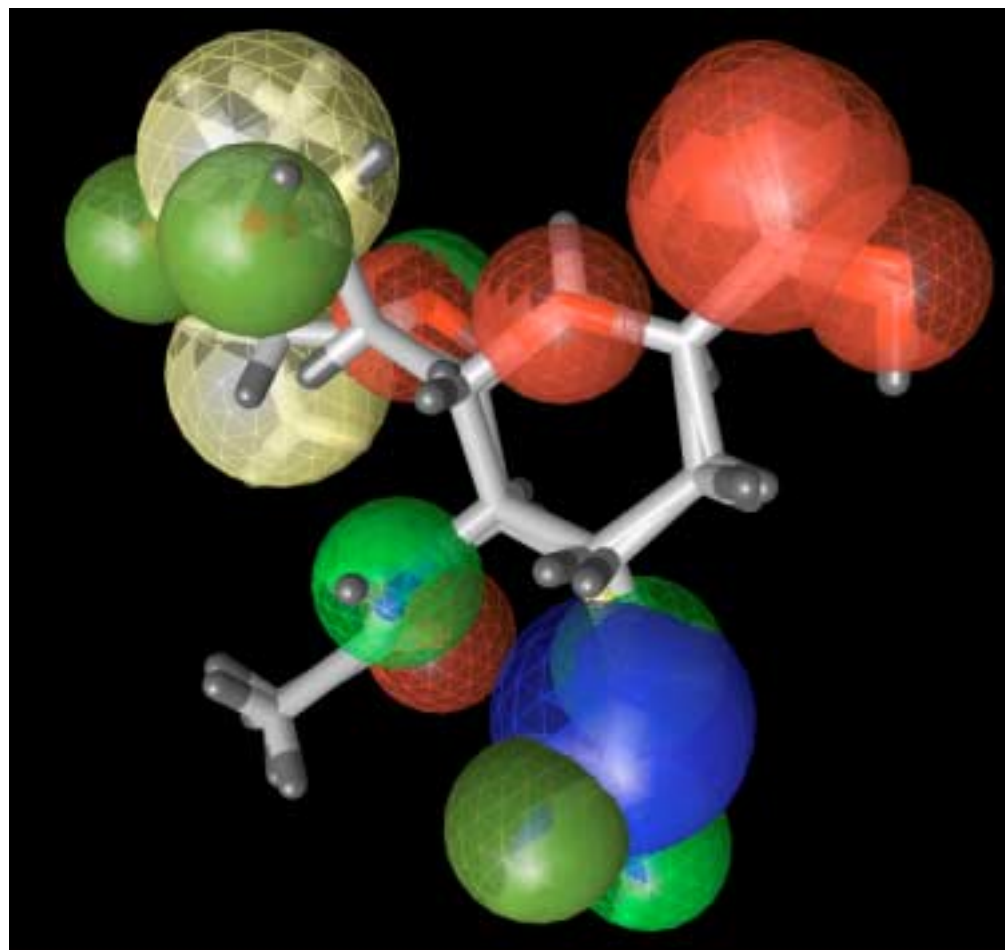
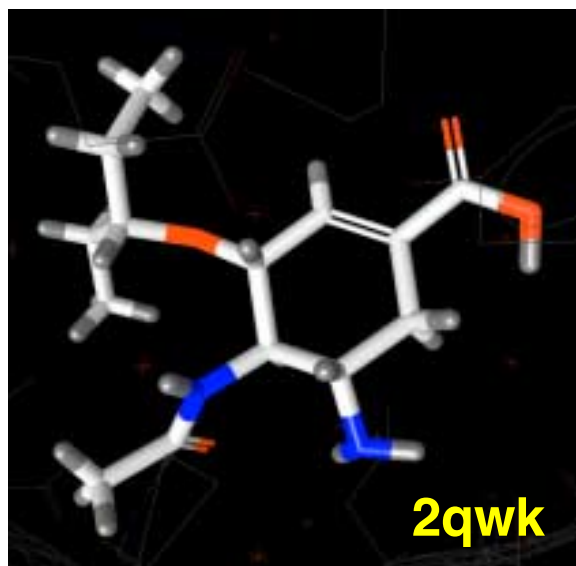
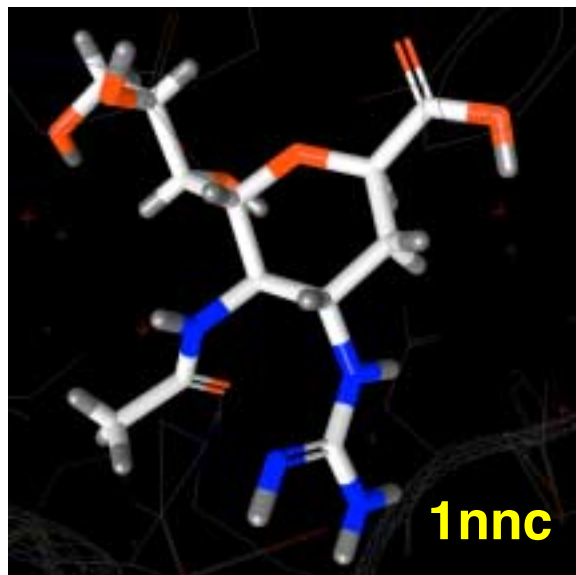


G. Wolber and T. Langer,
J. Chem. Inf. Model. 45,
160-169 (2005)

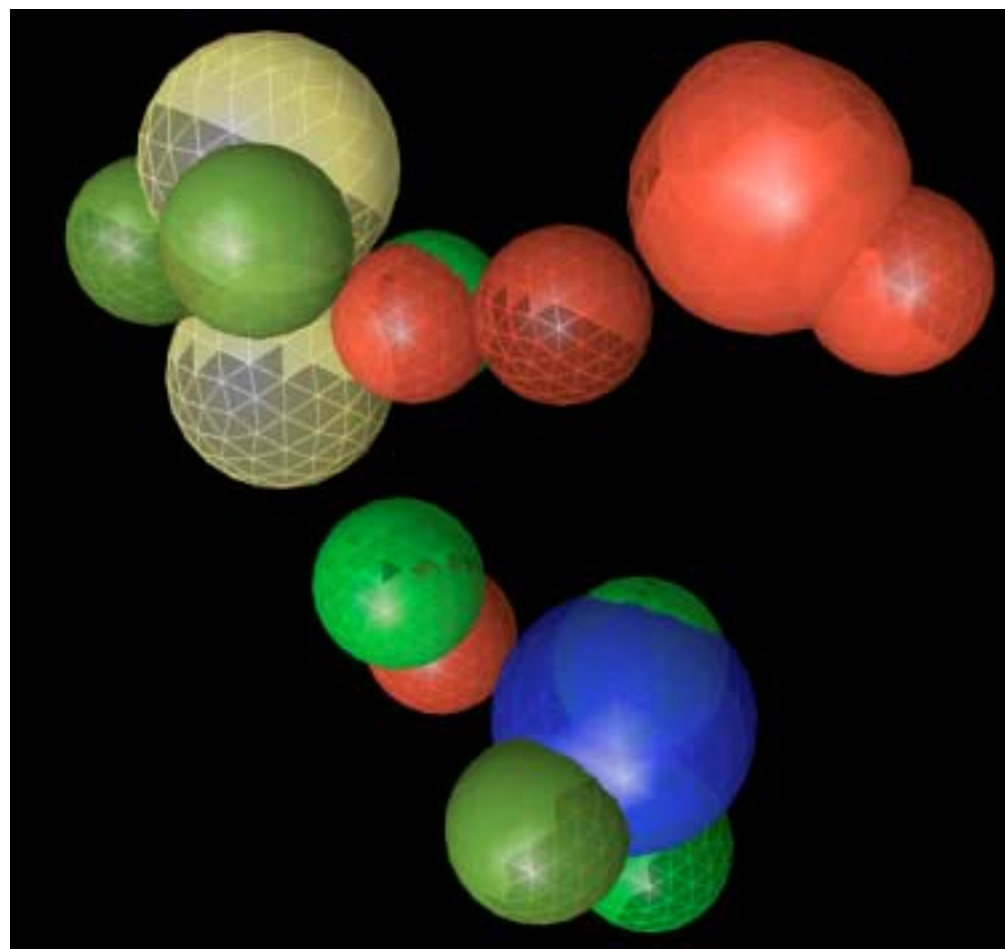
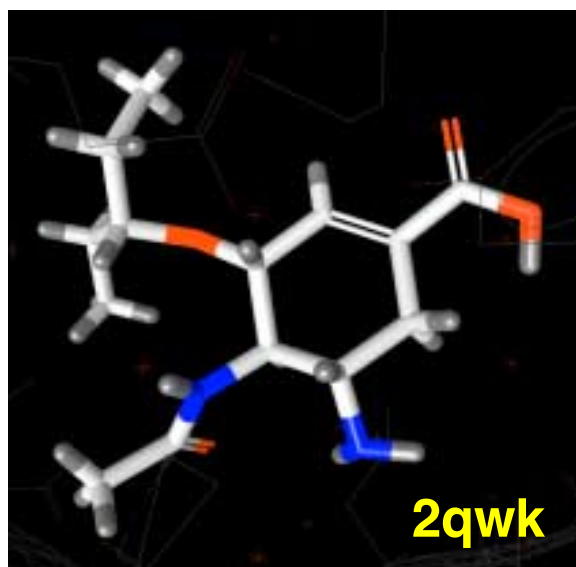
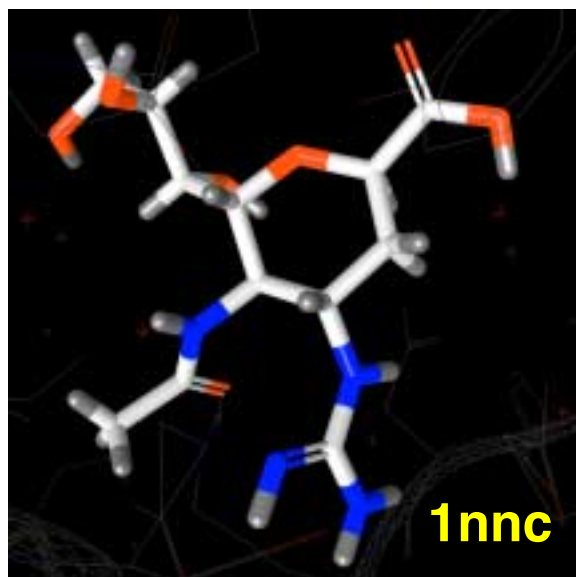
LigandScout Superposition: Zanamivir vs. GS 4071



LigandScout Superposition: Zanamivir vs. GS 4071



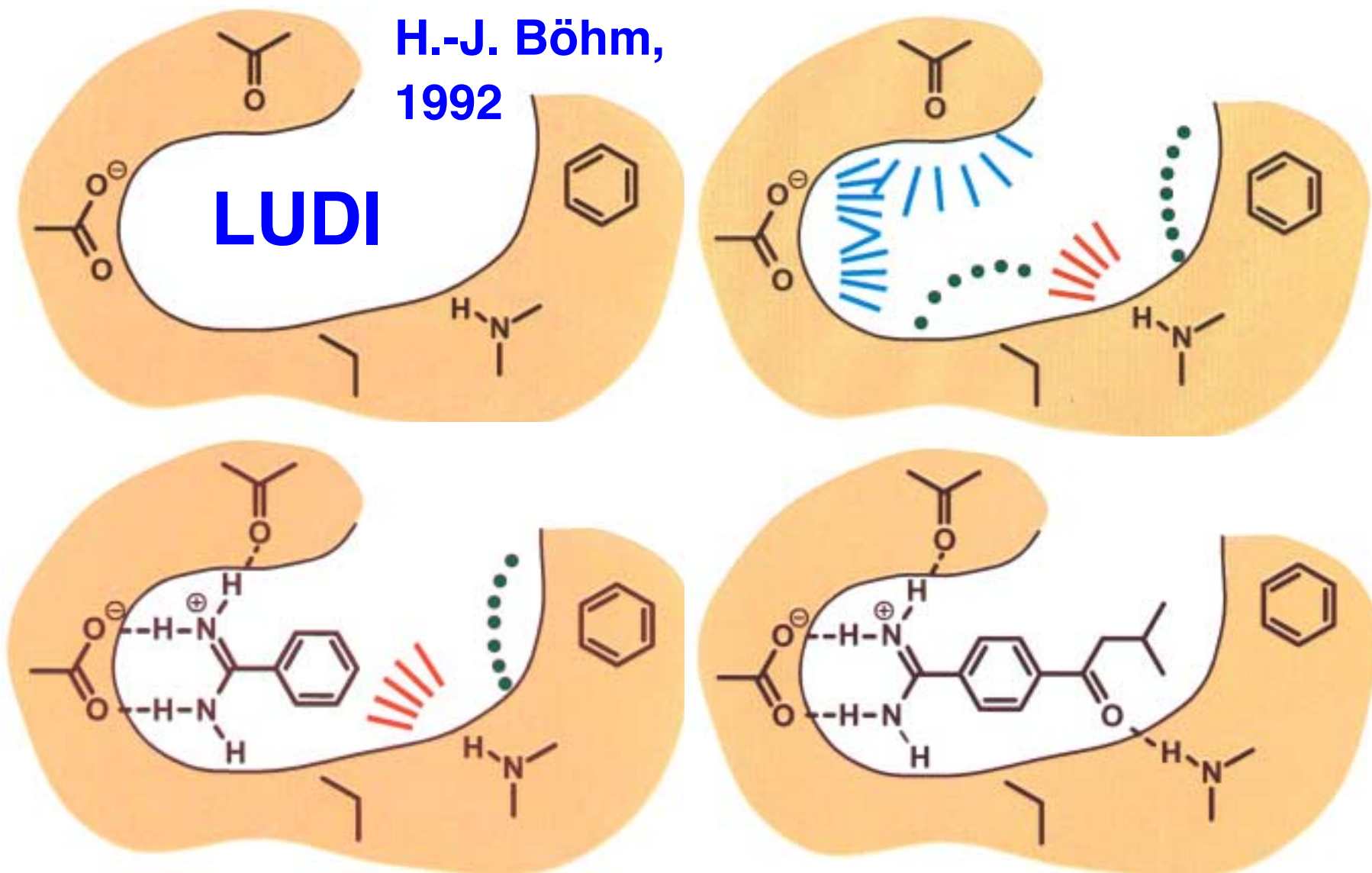
LigandScout Superposition: Zanamivir vs. GS 4071



Computer-Aided Drug Design

H.-J. Böhm,
1992

LUDI



Problems in Docking and Scoring

Pre-processing of the protein

lacking hydrogens, hydrogen bonds network,
protonation states of his, lys, asp, glu

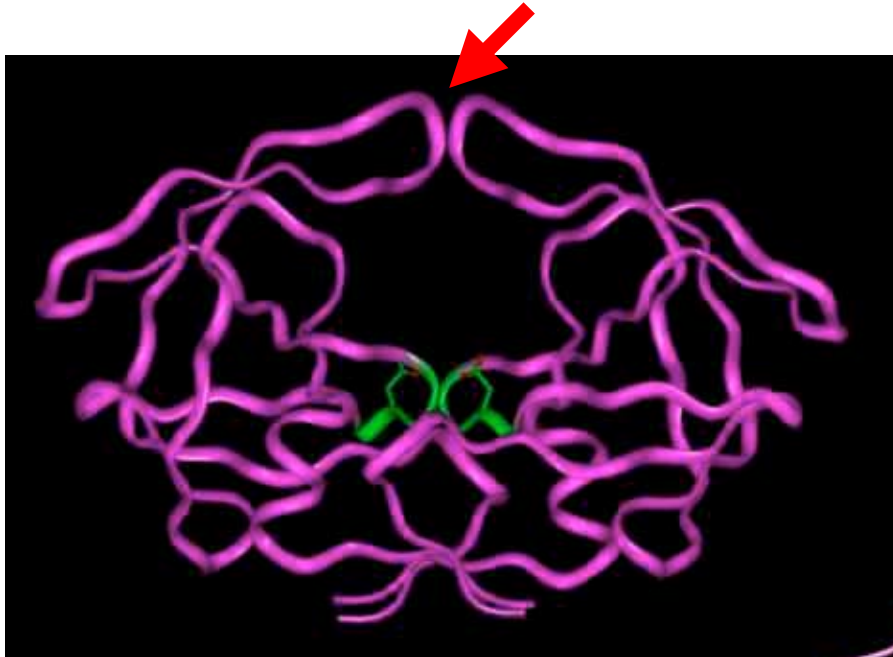
Pre-processing of the ligands

protonation states, tautomers

Flexibility of the ligand (no serious problem)

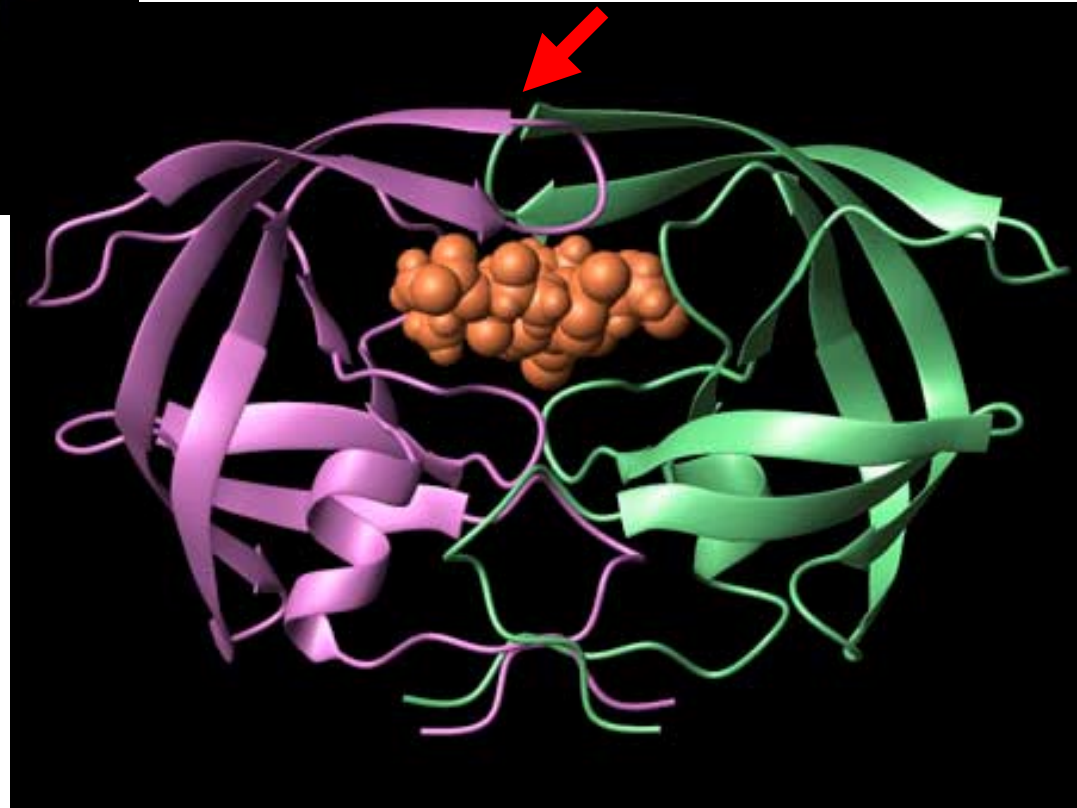
Flexibility of the protein / binding site (the real problem)

Fuzzy scoring functions (the biggest problem)

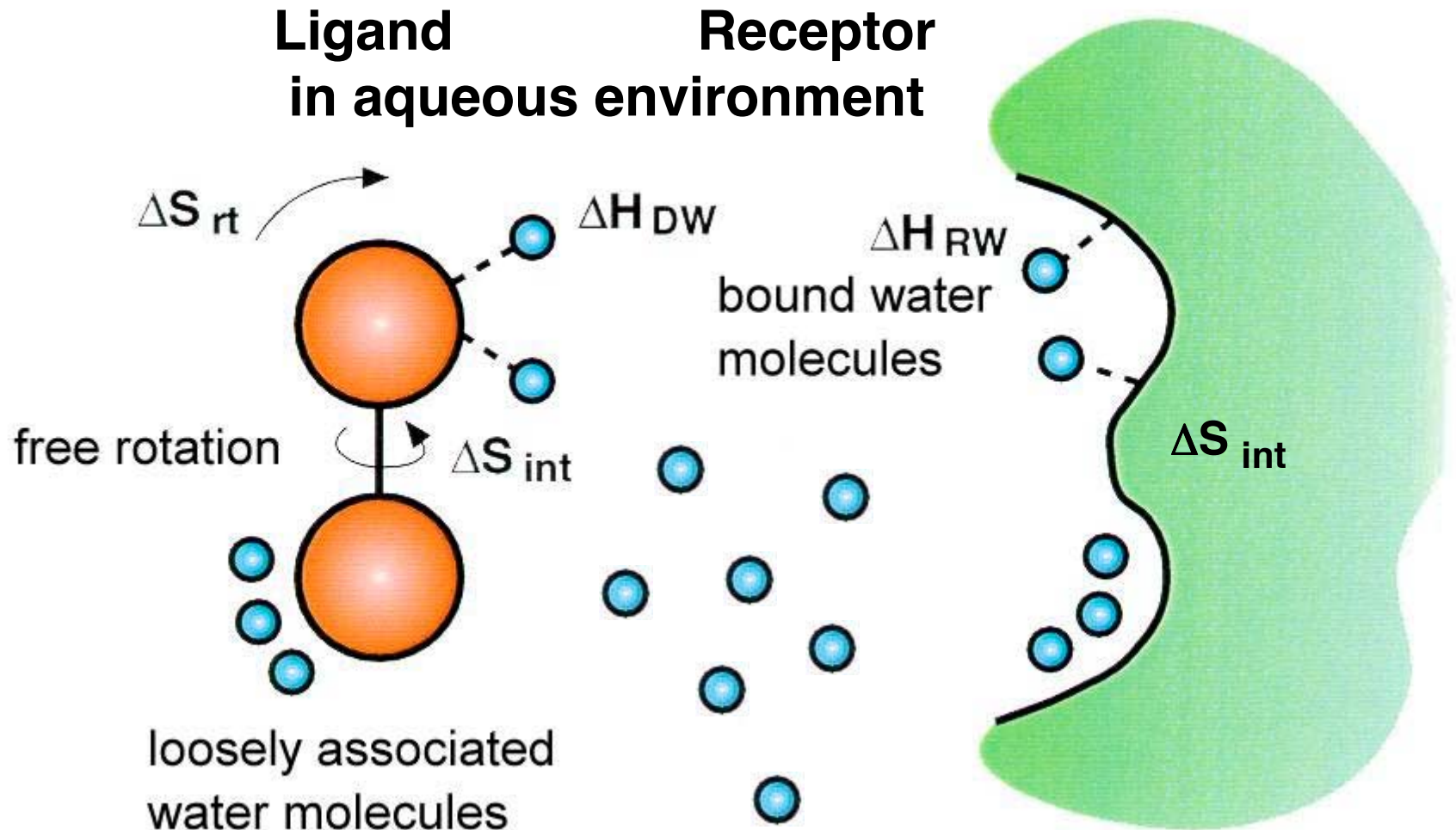


**HIV Protease,
without a ligand**

**HIV Protease,
with a ligand**



Consideration of Water, Flexibility and Mobility



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. $\text{-O}\cdots\text{O-}$)

Inserted water molecules

Solvation enthalpy and entropy of the complex

Virtual Screening vs. High-Throughput Screening

Comparison of the performance of high-throughput screening and virtual screening of potential leads of protein tyrosine phosphatase 1B (PTP1B):

- a) **High throughput screening** of 400,000 compounds from a corporate collection → 300 hits < 300 μM ,
85 validated hits with IC_{50} < 100 μM
= 0.021 % hit rate (many violate Lipinski rules)

- b) **Virtual screening** of 235,000 commercially available compounds, using DOCK, version 3.5
→ 365 high-scoring molecules are tested
127 with IC_{50} < 100 μM
= 34.8% hit rate (hits are more drug-like?)

T. N. Doman et al., J. Med. Chem. 45, 2213-2221 (2002)

Stepwise Virtual Screening

560,000 compounds (subsection of AstraZeneca repository)

199,000 hits

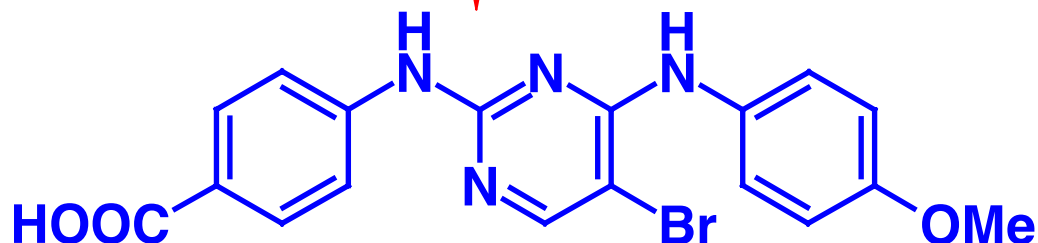
MW, rot-bond filter, presence of hinge region
binding motif

250 highest-scoring hits

FlexX-Pharm docking into ATP binding site

visual inspection for unrealistic conformations

103 compounds tested, 36 hits in the range 110 nM to 68 μ M



Checkpoint kinase 1
(Chk-1) inhibitor
 $IC_{50} = 450$ nM

P. D. Lyne et al., J. Med. Chem. 47, 1962-1968 (2004)

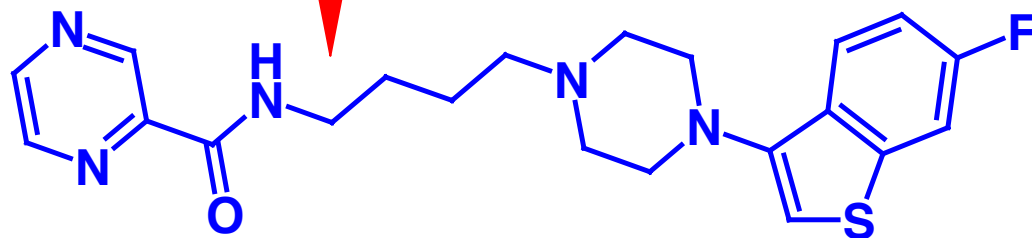
Stepwise Virtual Screening

Aventis in-house compound repository

■ MW, rot-bond filter, 3D pharmacophore search
22,950 compounds

■ docking into an α_1A receptor model
(GOLD, PMF)
300 top-scoring compounds

■ clustering, diversity selection
80 compounds tested, 37 hits with $K_i < 10 \mu\text{M}$



α_1A adrenergic receptor antagonist, $K_i = 1.4 \text{ nM}$

A. Evers and T. Klabunde, J. Med. Chem. 48, 1088-1097 (2005)

Stepwise Virtual Screening

250,251 NCI compounds (3D database)



3D pharmacophore search

6,727 hits



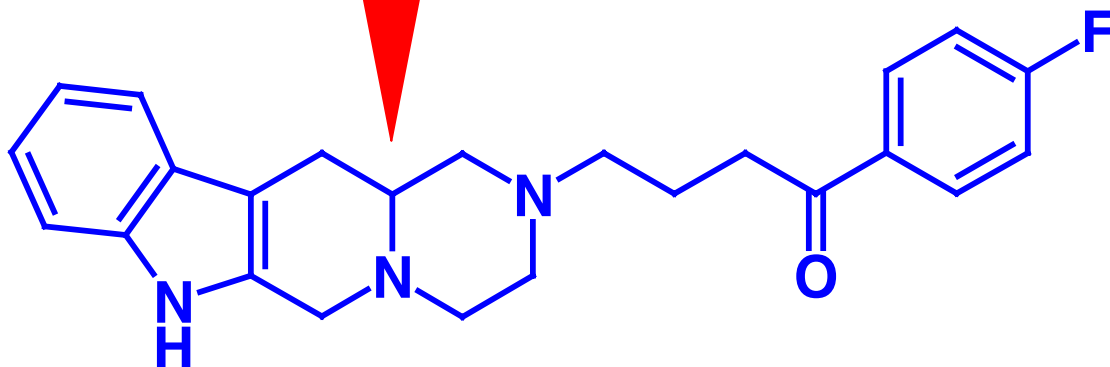
docking into four conformational clusters
of a D₃ receptor homology model

2,478 potential ligands



elimination of known chemotypes by similarity

20 compounds tested, 8 hits with $K_i < 0.5 \mu\text{M}$



dopamine D₃ receptor antagonist, $K_i = 11 \text{ nM}$

J. Varady et al., J. Med. Chem. 46, 4377-4392 (2003)

Stepwise Virtual Screening

259,747 ACD compounds

12,545 candidates

Ro5 filter with MW < 350 and rot-bond < 9,
presence of -COO⁻ or equivalent

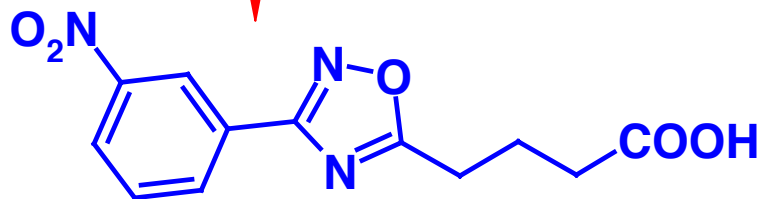
1,261 hits

3D pharmacophore search (derived from
binding site analysis)

216 highest-scoring compounds, after

FlexX docking into 0.66 Å aldose reductase
3D structure

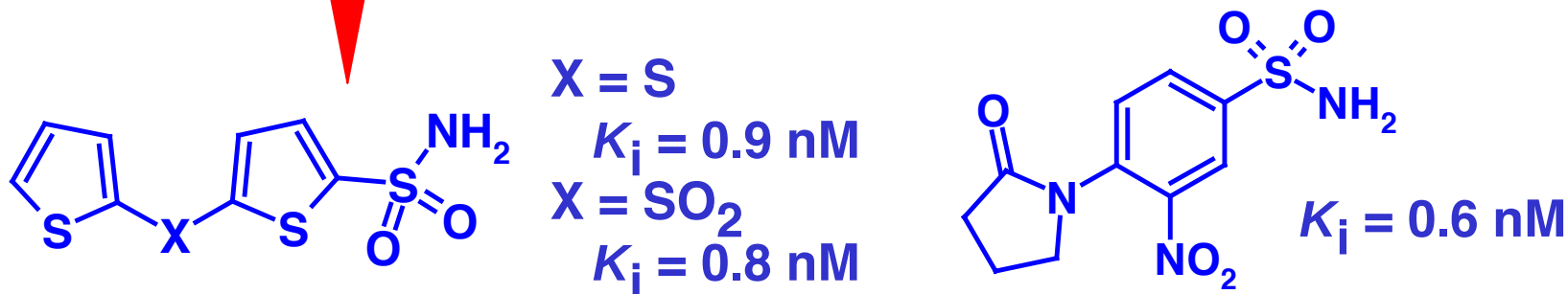
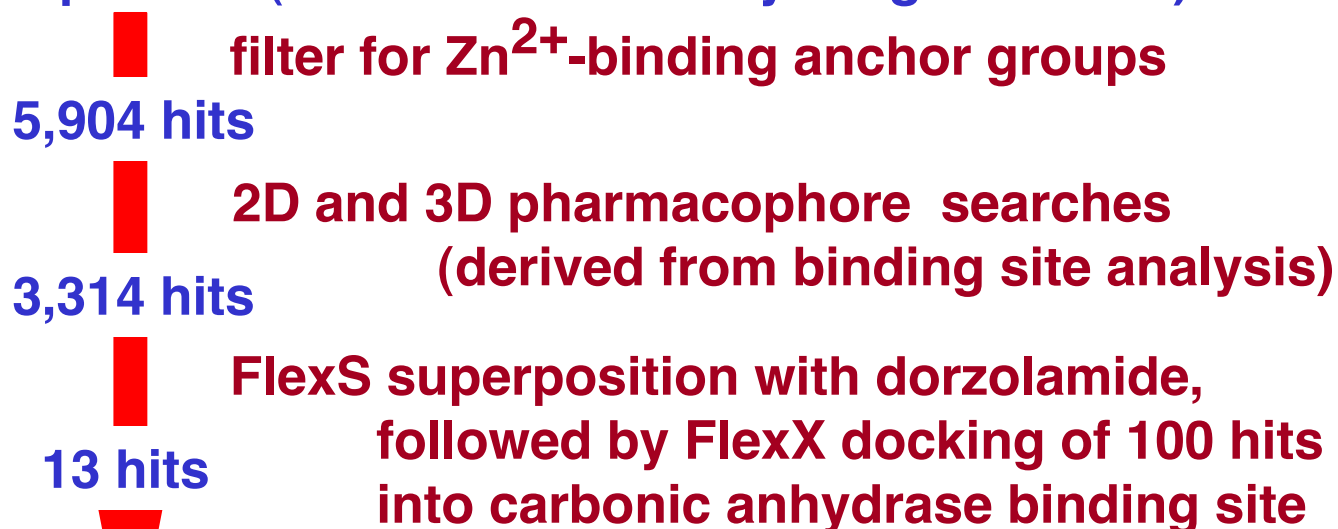
clustering and visual inspection:
9 hits for biological testing



aldose reductase inhibitor, IC₅₀ = 2.4 μM

Virtual Screening of Carbonic Anhydrase Inhibitors

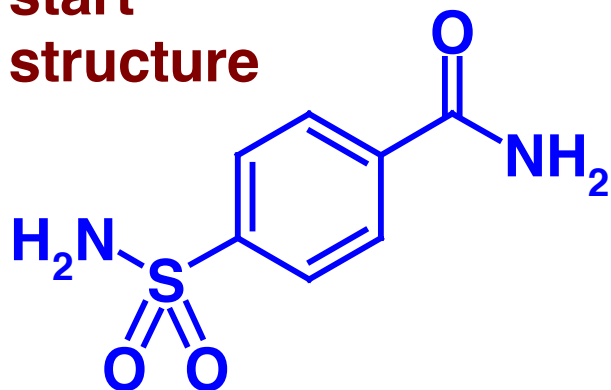
98,850 compounds (LeadQuest and Maybridge libraries)



S. Grüneberg et al., Angew. Chem., Int. Ed. Engl. 40, 389-393 (2001);
S. Grüneberg et al., J. Med. Chem. 45, 3588-3602 (2002).

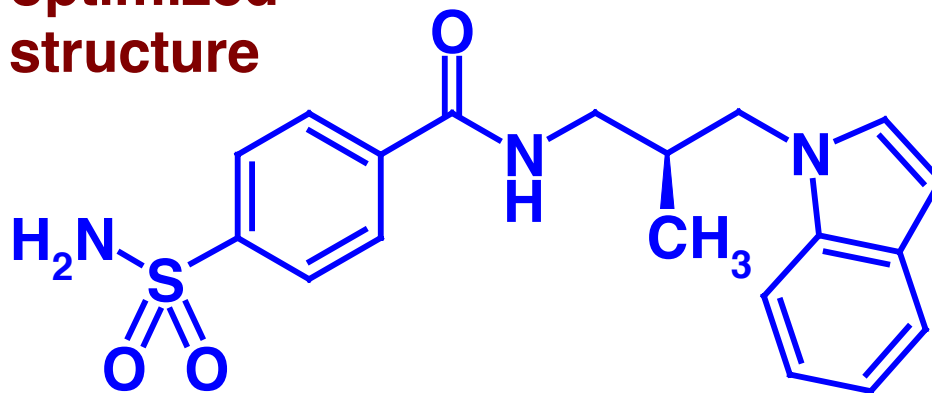
Combinatorial Design of Carbonic Anhydrase Inhibitors

start
structure



$K_d = 120 \text{ nM}$

optimized
structure



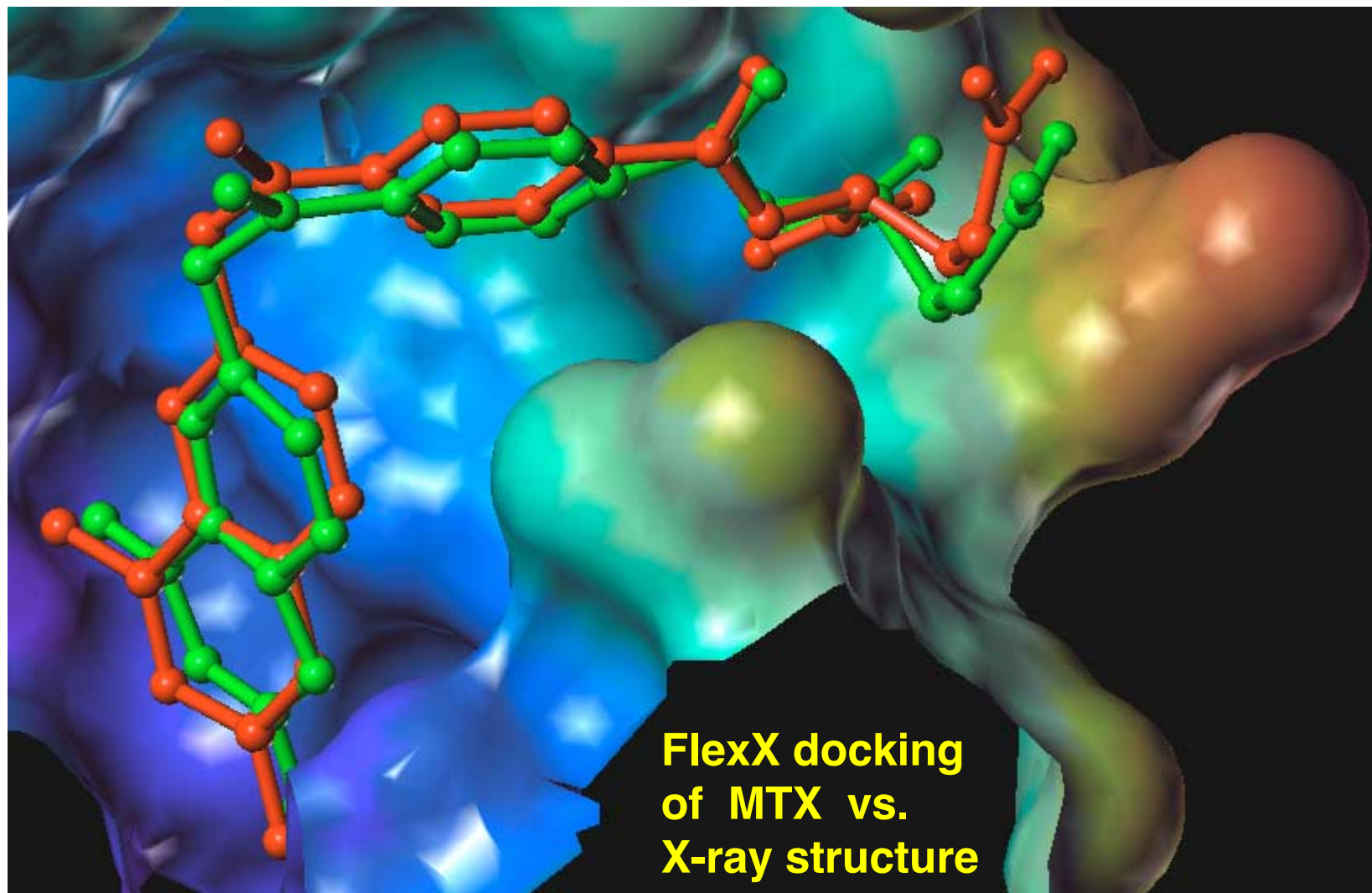
R enantiomer, $K_d = 30 \text{ pM}$
(*S* enantiomer: $K_d = 230 \text{ pM}$)

Program CombiSMoG, „best“ N-substituents from 100,000 candidates (20 scored by knowledge-based potentials)

B. A. Grzybowski et al., Acc. Chem. Res. 35, 261-269 (2002);

B. A. Grzybowski et al., Proc. Natl. Acad. Sci. USA 99, 1270-1273 (2002)

The Future: Combinatorial Drug Design



Summary and Conclusions

Virtual screening is a powerful tool to enrich libraries and compound collections

A proper preprocessing of the compound database is of utmost importance

Further experimental data and theoretical investigations are needed for better pK_a estimations and better scoring functions

Stepwise procedures (filters, pharmacophore searches, docking and scoring, visual inspection) are most efficient

Fragment-based approaches are a promising new strategy in lead structure search and optimization

Further progress needed in the understanding and scoring of ligand-receptor interactions

References

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