QSAR

Quantative Structure-Activity Relationships

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?Why QSAR

- The number of compounds required for synthesis in order to place 10 different groups in 4 positions of benzene ring is 10^4
- Solution: synthesize a small number of compounds and from their data derive rules to predict the biological activity of other compounds.

QSAR and Drug Design

Compounds + biological activity

New compounds with improved biological activity

?What is QSAR

- A QSAR is a mathematical relationship between a biological activity of a molecular system and its geometric and chemical characteristics.
- QSAR attempts to find consistent relationship between biological activity and molecular properties, so that these “rules” can be used to evaluate the activity of new compounds.

Statistical Concepts

Input: n descriptors $P_1,..P_n$ and the value of biological activity (*EC50* for example) for m compounds.

	Bio	P_1	P_2	...				P_n
Cpd1	0.7	3.7						
Cpd2	3.2	0.4						
…								
Cpdm								

Statistical Concepts

- The problem of QSAR is to find coefficients $C_0, C_1, \ldots C_n$ such that:

  $$\textit{Biological activity} = C_0 + (C_1 * P_1) + \ldots + (C_n * P_n)$$

  and the prediction error is minimized for a list of given m compounds.

- Partial least squares (PLS) is a technique used for computation of the coefficients of structural descriptors.

3D-QSAR

- Structural descriptors are of immense importance in every QSAR model.
- Common structural descriptors are pharmacophores and molecular fields.
- Superimposition of the molecules is necessary.
- 3D data has to be converted to 1D in order to use PLS.

3D-QSAR Assumptions

- The effect is produced by modeled compound and not it's metabolites.
- The proposed conformation is the bioactive one.
- The binding site is the same for all modeled compounds.
- The biological activity is largely explained by enthalpic processes.
- Entropic terms are similar for all the compounds.
- The system is considered to be at equilibrium, and kinetics aspects are usually not considered.
- Pharmacokinetics: solvent effects, diffusion, transport are not included.

QSAR and 3D-QSAR Software

- Tripos – CoMFA, VolSurf
- MSI – Catalyst, Serius

Docking Software

- DOCK – Kuntz
- Flex – Lengauer
- LigandFit – MSI Catalyst

3D molecular fields

- A molecular field may be represented by 3D grid.
- Each voxel represents attractive and repulsive forces between an interacting partner and a target molecule.
- An interacting partner can be water, octanol or other solvents.

Common 3D molecular fields

- MEP – Molecular Electrostatic Potential (unit positive charge probe).
- MLP – Molecular Lipophilicity Potential (no probe necessary).
- GRID – total energy of interaction: the sum of steric (Lennard-Jones), H-bonding and electrostatics (any probe can be used).
- CoMFA – standard: steric and electrostatic, additional: H-bonding, indicator, parabolic and others.

Comparative Molecular Field Analysis (CoMFA) - 1988

- Compute molecular fields grid
- Extract 3D descriptors
- Compute coefficients of QSAR equation

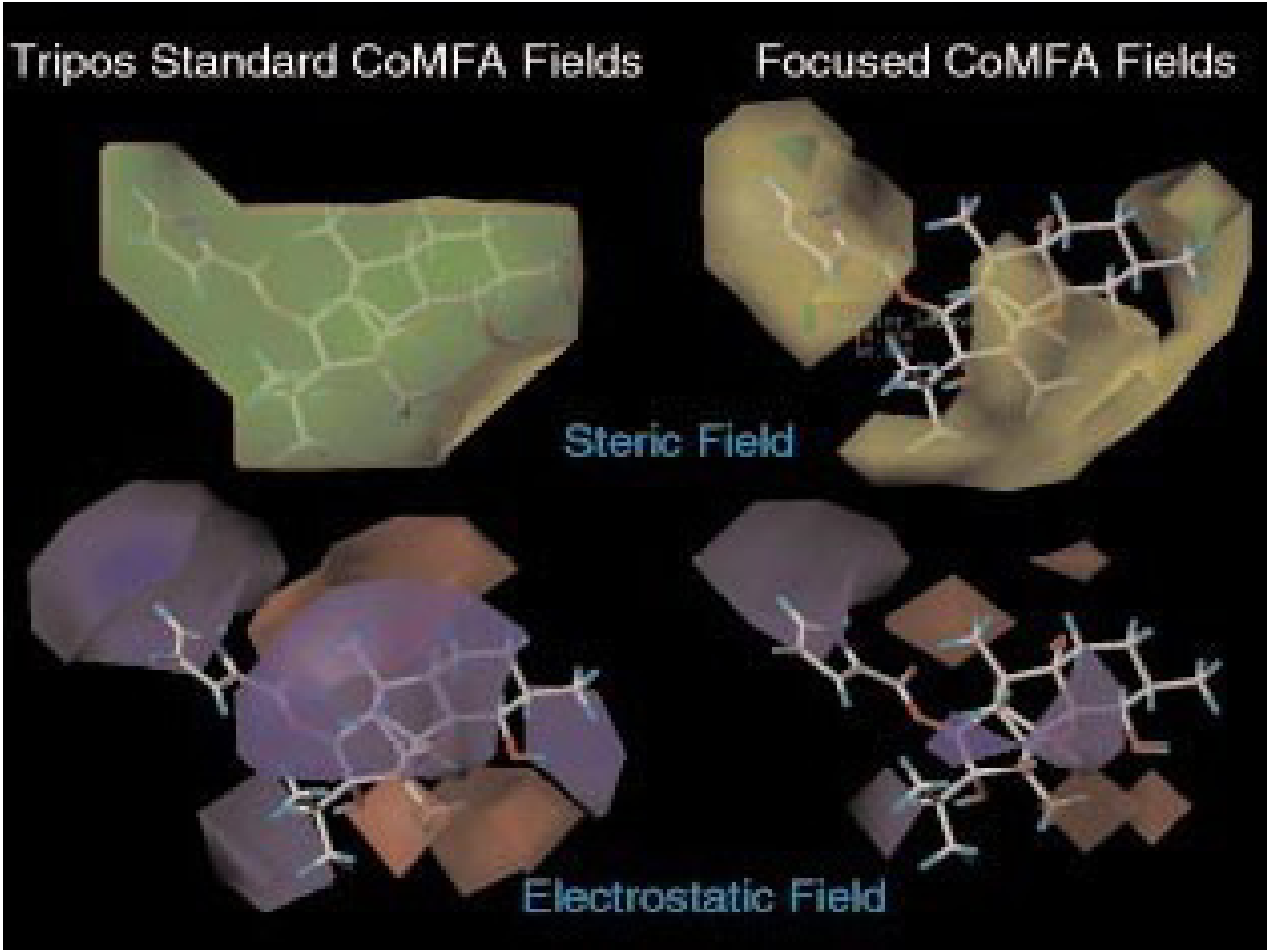
CoMFA molecular fields

- A grid wit energy fields is calculated by placing a probe atom at each voxel.
- The molecular fields are:

  Steric (Lennard-Jones) interactions

  Electrostatic (Coulombic) interactions

- A probe is sp^3 carbon atom with charge of +1.0


Tripos Standard CoMFA Fields
Focused CoMFA Fields
Steric Field
Electrostatic Field

CoMFA 3D-QSAR

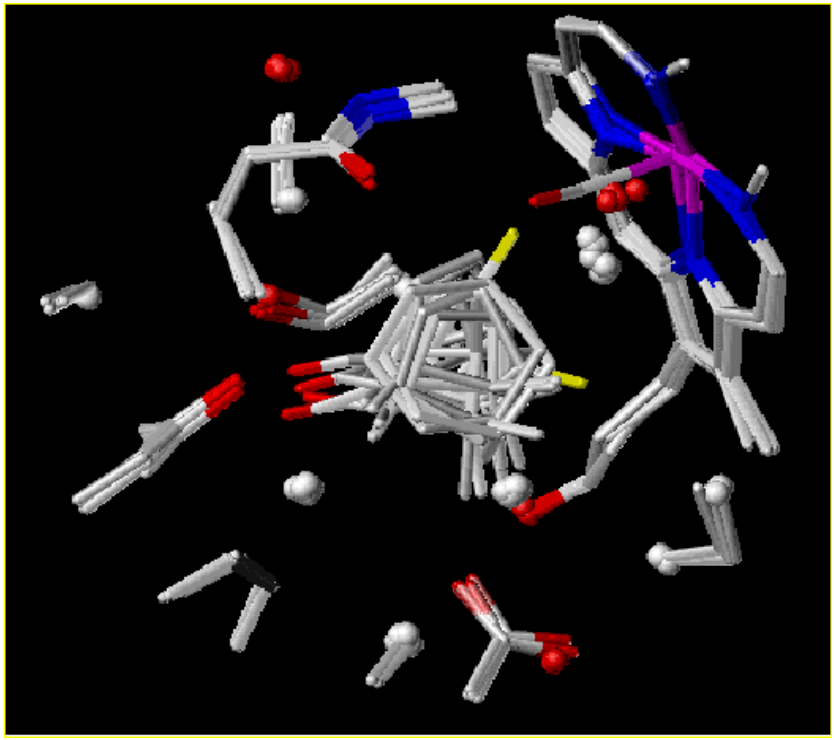
- Each grid voxel corresponds to two variables in QSAR equation: steric and electrostatic.
- The PLS technique is applied to compute the coefficients.

Problems:

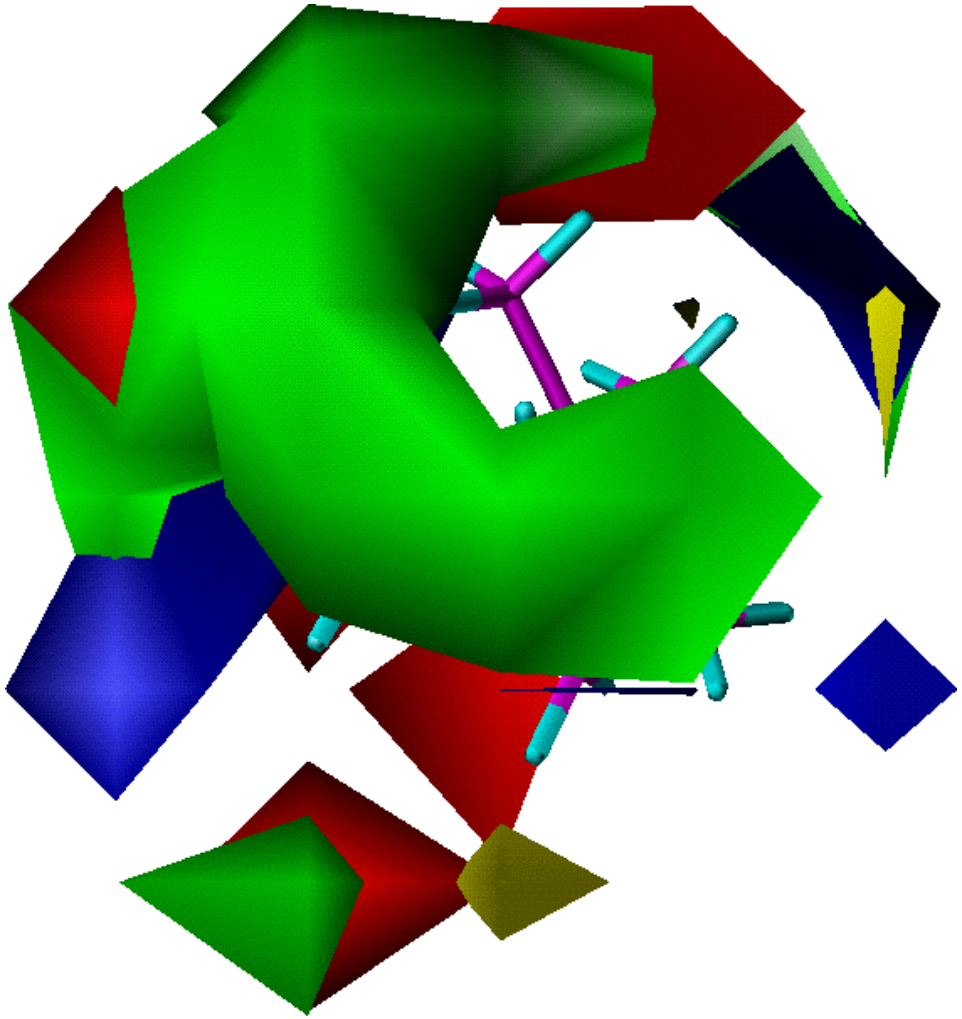
- Superposition: the molecules must be optimally aligned.
- Flexibility of the molecules.

3D-QSAR of $CYP450_{cam}$ with CoMFA

- Training dataset from 15 complexes of CYP450 with different compounds was used.
- The alignment of the compounds was done by aligning of the CYP450 proteins from the complexes.



3D-QSAR of $CYP450_{cam}$ with CoMFA



Maps of electrostatic fields:
BLUE - positive charges
RED - negative charges

Maps of steric fields:
GREEN - space filling areas for best Kd
YELLOW - space conflicting areas

VOLSURF

The VolSurf program predicts a variety of ADME properties based on pre-calculated models. The models included are:

- drug solubility
- Caco-2 cell absorption
- blood-brain barrier permeation
- distribution

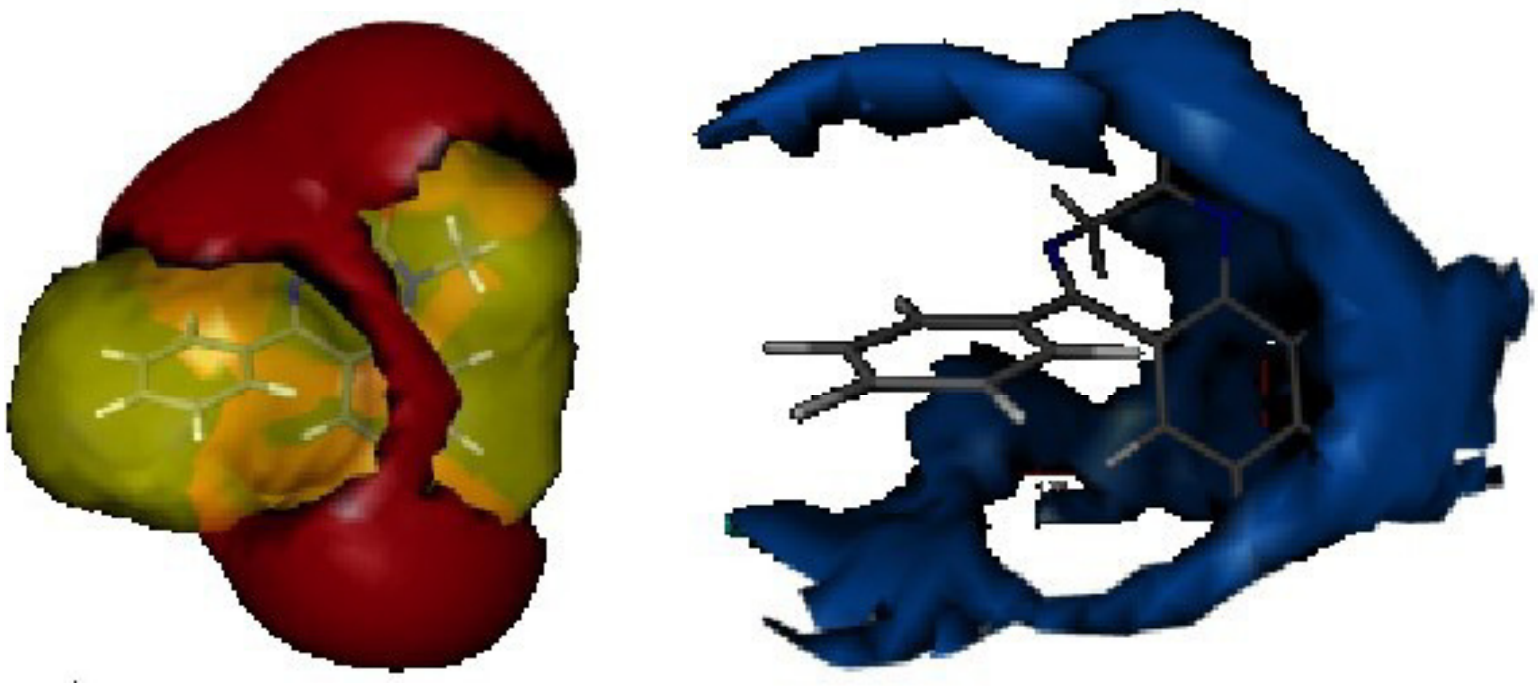
VOLSURF

- VolSurf reads or computes molecular fields, translates them to simple molecular descriptors by image processing techniques.
- These descriptors quantitatively characterize size, shape, polarity, and hydrophobicity of molecules, and the balance between them.

VOLSURF Descriptors

- Size and shape: volume *V*, surface area *S*, ratio volume surface *V/S*, globularity S/S_{equiv} (S_{equiv} is the surface area of a sphere of volume *V*).
- Hydrophilic: hydrophilic surface area *HS*, capacity factor *HS/S*.
- Hydrophobic: like hydrophilic *LS*, *LS/S*.
- Interaction energy moments: vectors pointing from the center of the mass to the center of hydrophobic/hydrophilic regions.
- Mixed: local interaction energy minima, energy minima distances, hydrophilic-lipophilic balance *HS/LS*, amphiphilic moments, packing parameters, H-bonding, polarisability.

VOLSURF



hydrophobic)blue(and hydrophilic)red(surface .area of diazepam

Catalyst

- Catalyst develops 3D models (pharmacophores) from a collection of molecules possessing a range of diversity in both structures and activities.
- Catalyst specifies hypotheses in terms of chemical features that are likely to be important for binding to the active site.
- Each feature consists of four parts:
  - Chemical function
  - Location and orientation in 3D space
  - Tolerance in location
  - Weight

Catalyst Features

- HB Acceptor and Acceptor-Lipid
- HB Donor
- Hydrophobic
- Hydrophobic aliphatic
- Hydrophobic aromatic
- Positive charge/Pos. Ionizable
- Negative charge/Neg. Ionizable

Catalyst HipHop

Feature-based pharmacophore modeling:

- uses ONLY active ligands
- no activity data required
- identifies binding features for drug-receptor interactions
- generates alignment of active leads
- the flexibility is achieved by using multiple conformers
- alignment can be used for 3D-QSAR analysis

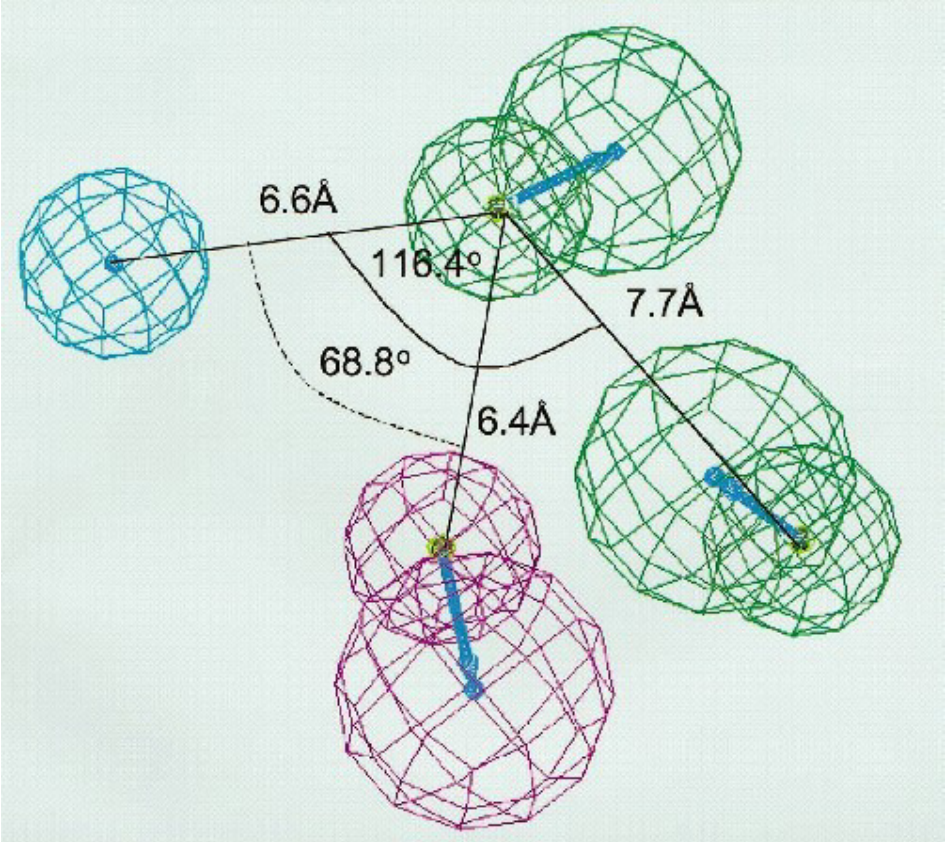
Catalyst HipoGen

Activity-based pharmacophore modeling:

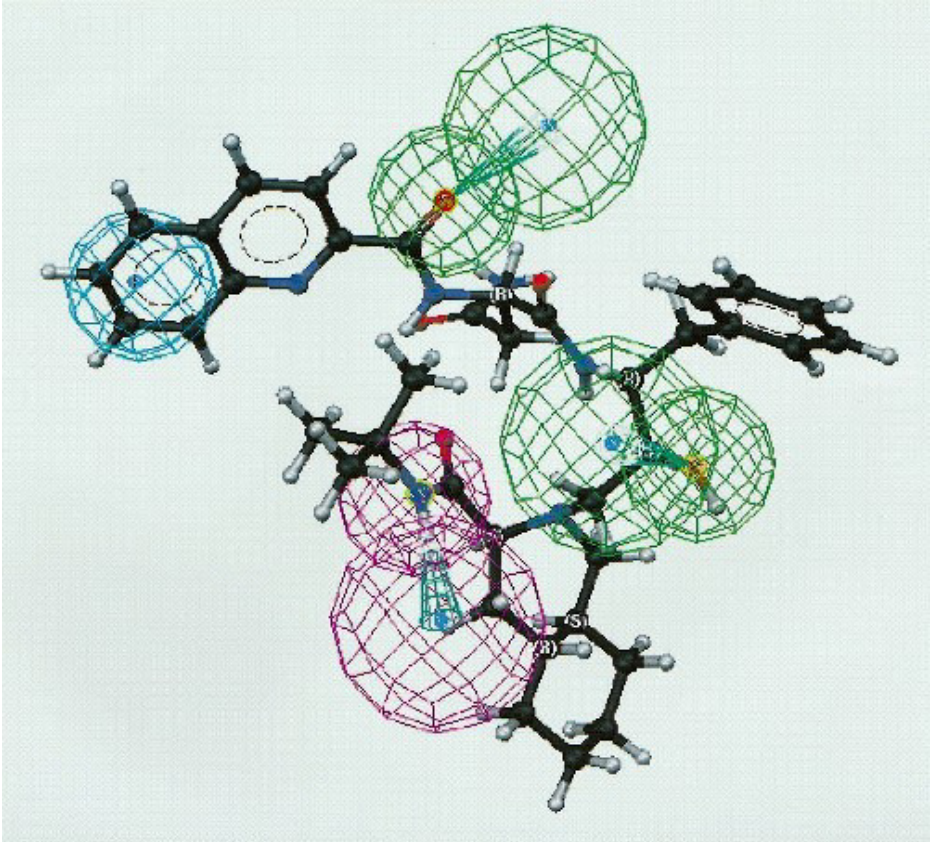
- uses active + inactive ligands
- activity data required (concentration)
- identifies features common to actives missed by inactives

  used to “predict” or estimate activity of new ligands

Catalyst CYP3A4 substrates pharmacophore

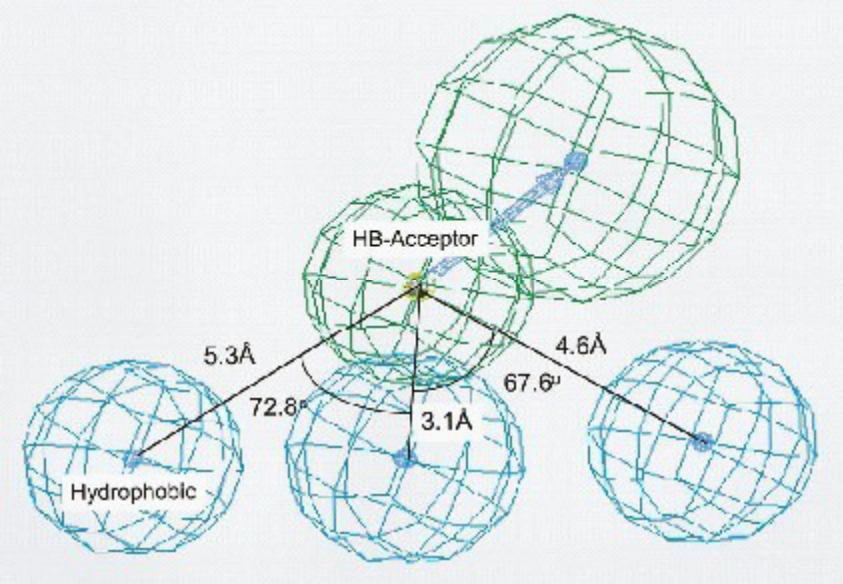


Hydrophobic area, h-bond donor, 2 h-bond acceptors

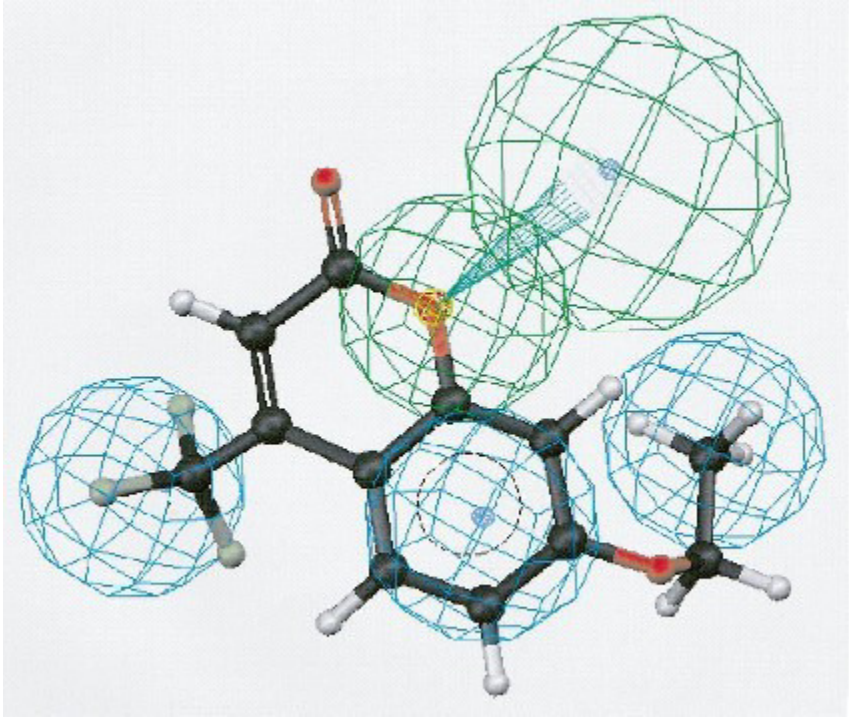


Saquinavir (most active compound) fitted to pharmacophore

Catalyst CYP2B6 substrates pharmacophore



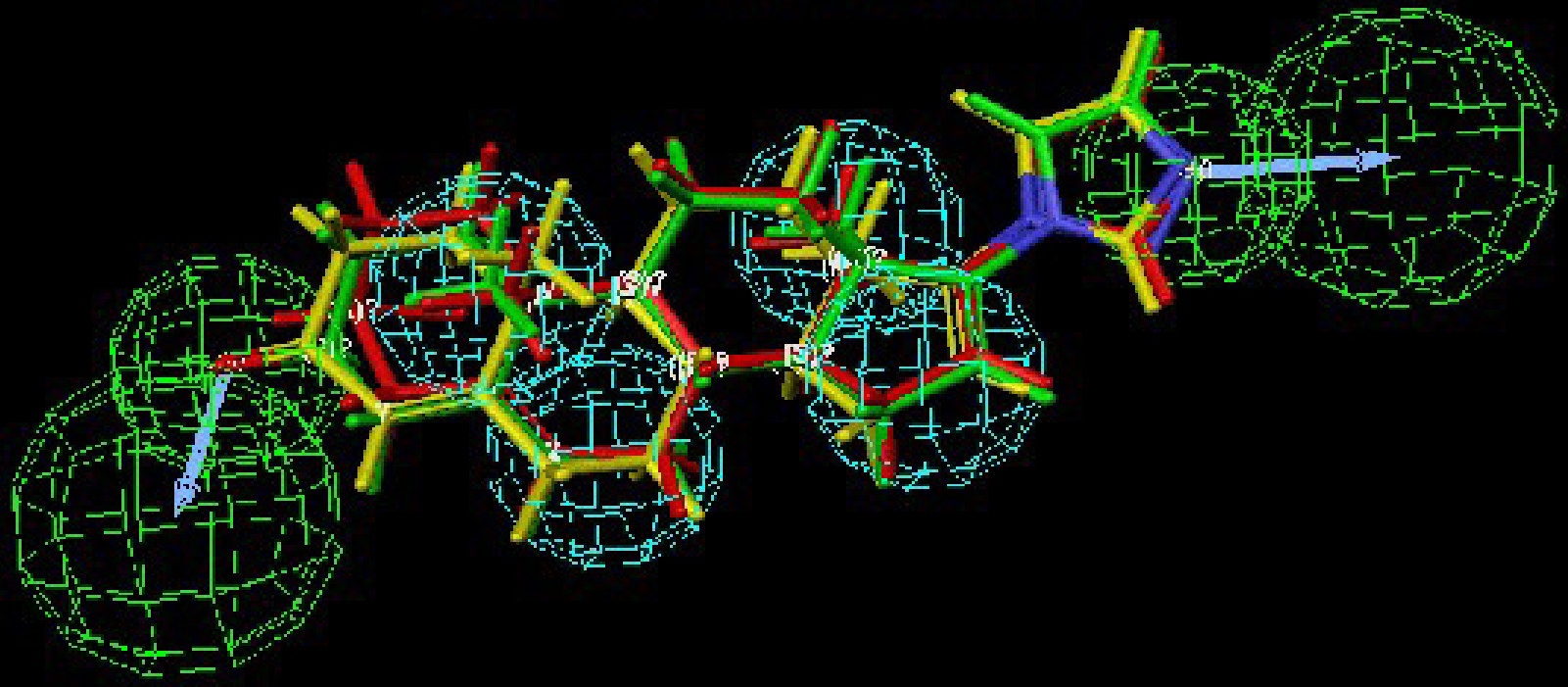
hydrophobic areas, h-bond 3 acceptor



ethoxy-4-trifluoromethylcoumarin-7 fitted to pharmacophore

CATALYST®-generated pharmacophore models

- CYP17 inhibitors



Highly active 17-Lyase inhibitors aligned onto model

Clement, Njar and Brodie; *manuscript in preparation*

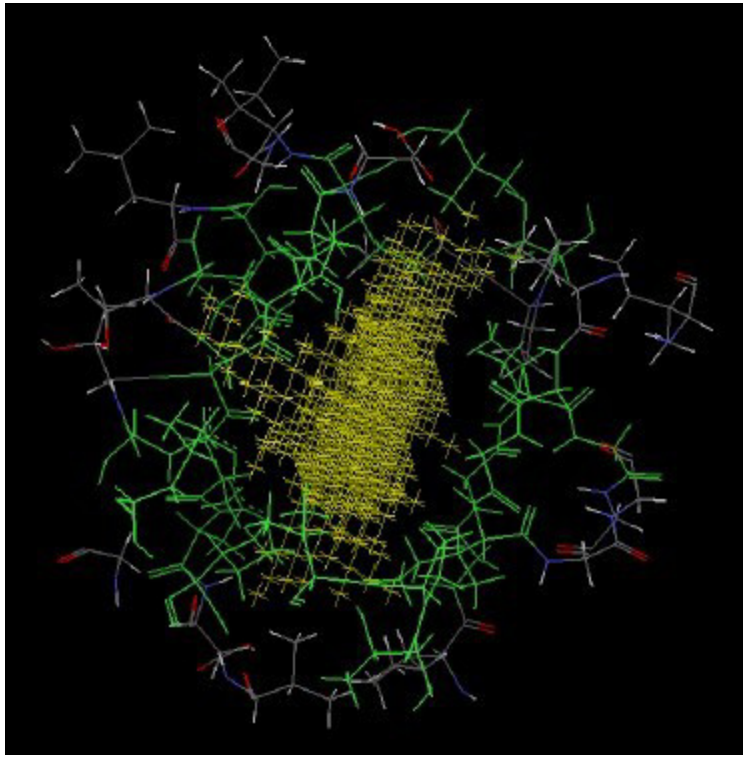
Catalyst Docking – Ligand Fit

- Active site finding
- Conformation search of ligand against site
- Rapid shape filter

determines which conformations should be scored

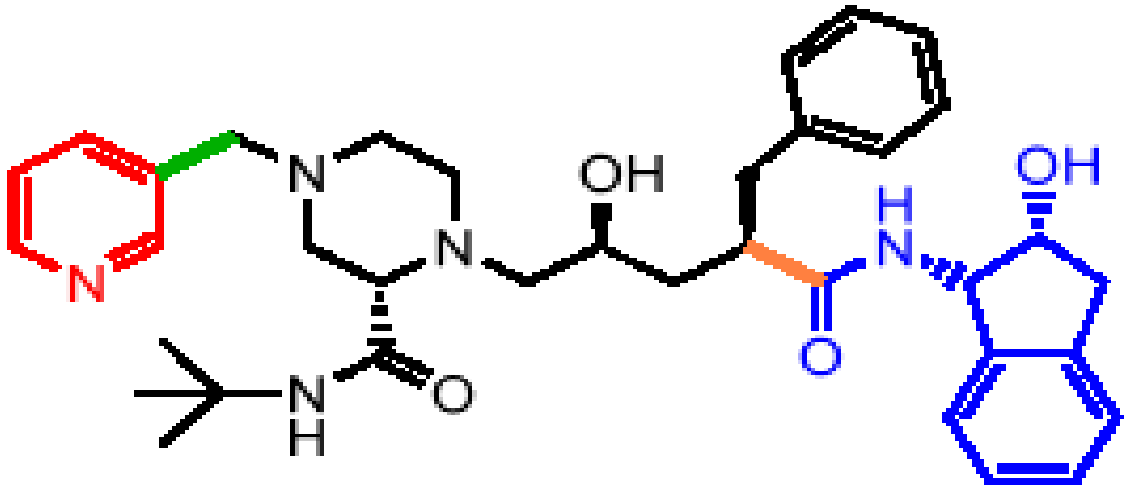
- Grid-based scoring for those

conformations passing the filter



Catalyst Docking – Ligand Flexibility

- Monte Carlo search in torsional space
- Multiple torsion changes simultaneously
- The random window size depends on the number of rotating atoms



Catalyst Docking – Scoring

pKi = – c – x (*vdW_Exact/ Grid_Soft*)
+ y (*C+_pol*)
– z (*Totpol^ 2*)

- ***vdW*** **=** softened Lennard-Jones 6-9 potential
- ***C+_pol*** **=** buried polar surface area involved in attractive ligand-protein interactions
- ***Totpol^ 2*** **=** buried polar surface area involved in both attractive and repulsive protein-ligand interactions

3D-QSAR of $CYP450_{cam}$ with DOCK

Goal:

- Test the ability of DOCK to discriminate between substrates and non-substrates.

Assumption:

- Non-substrate candidate is a compound that doesn't fit to the active site of CYP, but fits to the site of it's L244A mutant.

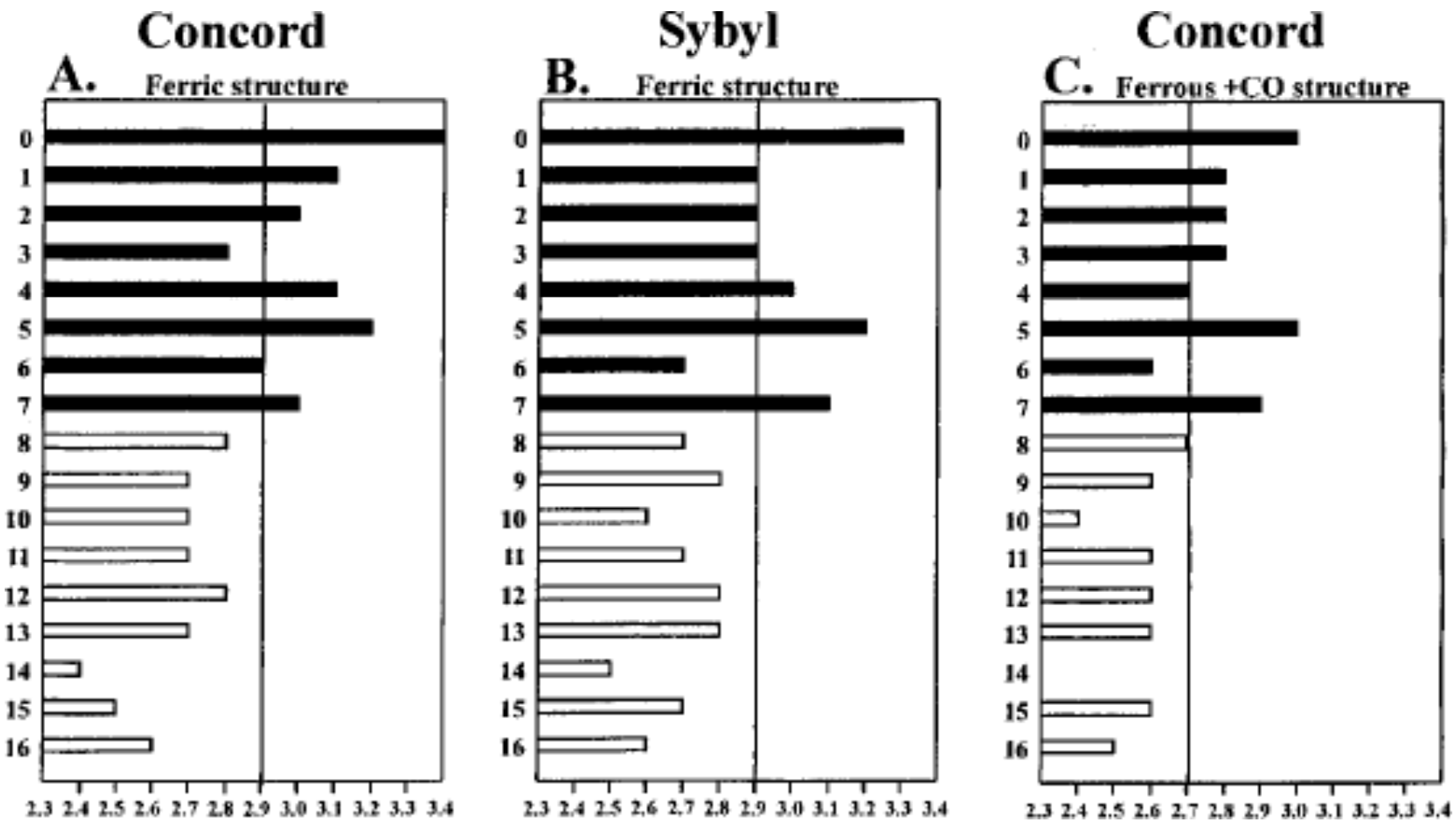
Methods

- Docking of 20,000 compounds to ‘bound’ structure of CYP and L244A mutant.
- 11 substrate candidates were selected from 500 high scoring compounds for CYP.
- 6 non-substrate candidates were selected from a difference list of L244A and CYP.
- Optimization of compounds 3D structures by SYBYL molecular mechanics program and re-docking. As a result 2 compounds move from “non-substrate” list to “substrate” list and one in the opposite direction.

Prediction Results

- All compounds predicted as “non-substrates” shown no biological activity.
- 4 of the 11 molecules predicted as “substrates” were found as non-substrates.
- The predictions of DOCK are sensitive to the parameter of minimum distance allowed between an atom of the ligand and the receptor (penetration constrains).

Prediction Results



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