LigandScout

Automated Structure-Based Pharmacophore Model Generation

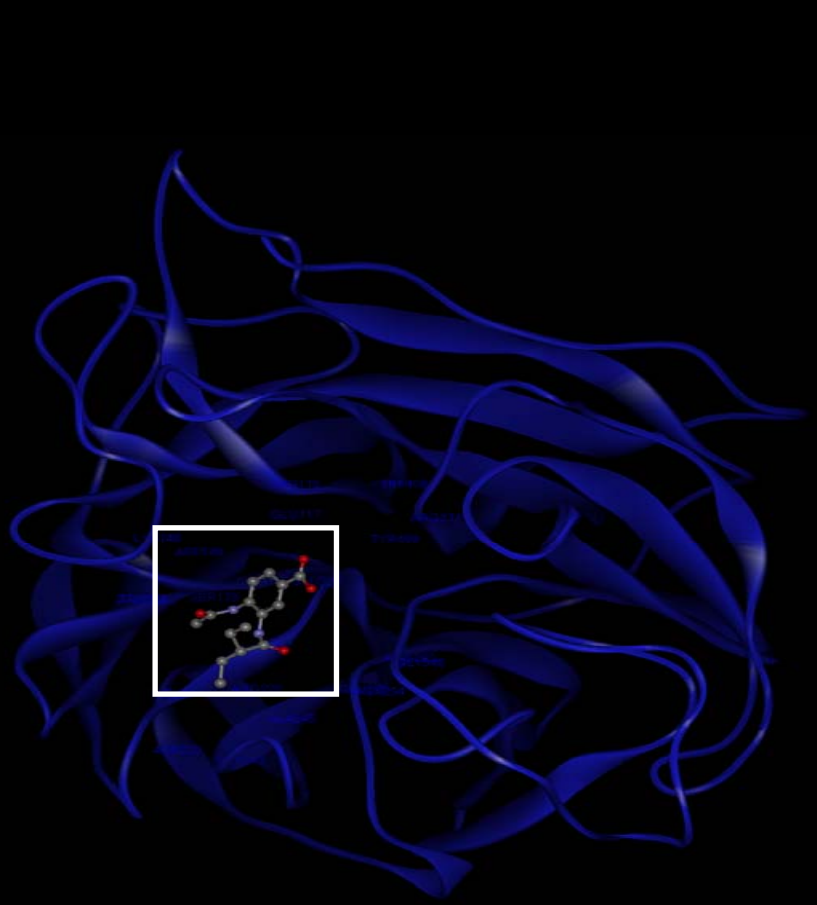
Gerhard Wolber*
and Thierry Langer

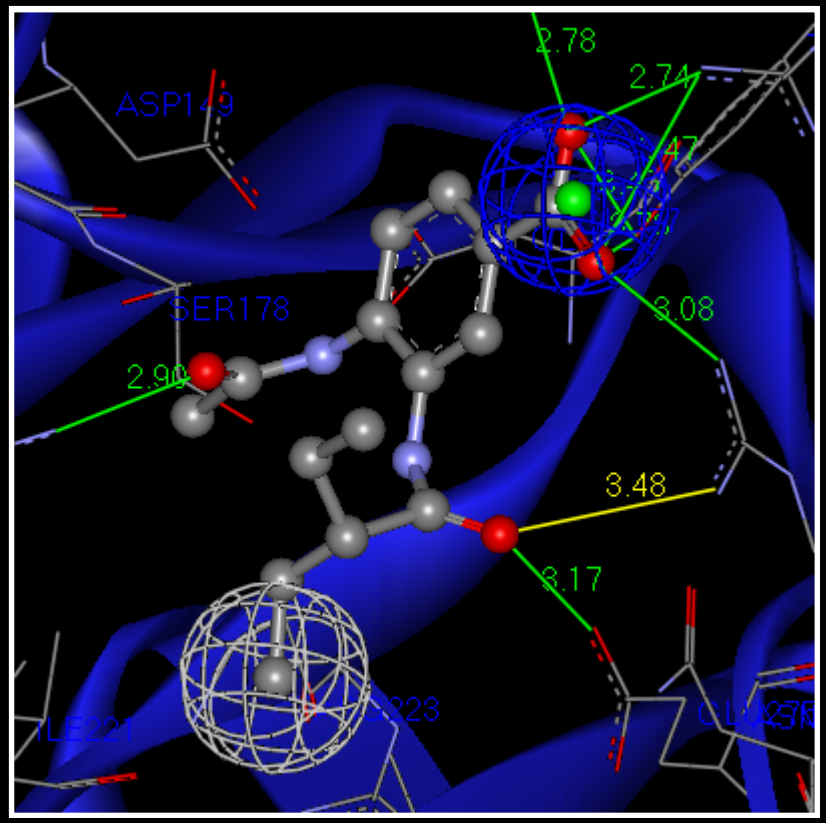
* E-Mail: wolber@inteligand.com

Pharmacophores from LigandScout

- **Pharmacophores & the Protein Data Bank**
  - 3D pharmacophore methodology
  - Primary data source: The Protein Data Bank
  - Why LigandScout?
- **LigandScout**
  - Ligand perception
  - 3D pharmacophore generation
  - Shared feature pharmacophores
- **Applications & Future Perspectives**

Ligand-Protein Interaction



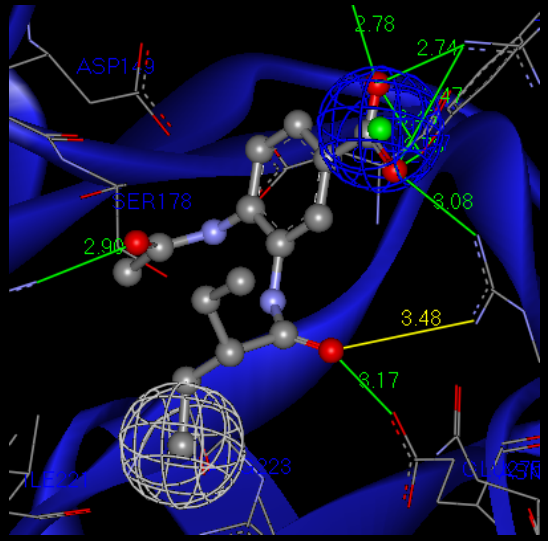


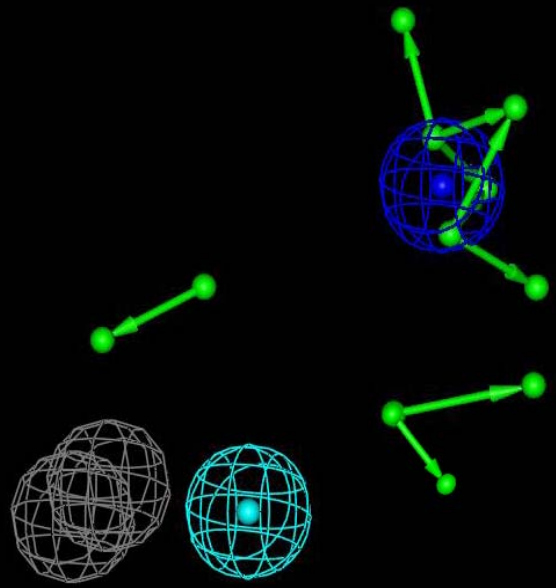
Influenza virus neuraminidase inhibition by ligand FDI
(4-(N-acetylamino)-3-[N-(2-ethylbutanoylamino]benzoic acid)

Pharmacophore Models

Definition: Ensemble of universal chemical features that represent a specific mode of action

Chemical Features: Hydrogen bonds, charge interactions, hydrophobic areas





Why Use Structure-Based Pharmacophores Instead of Docking?

- **Universal**

  Pharmacophores represent chemical functions, valid not only for the currently bound, but also unknown molecules

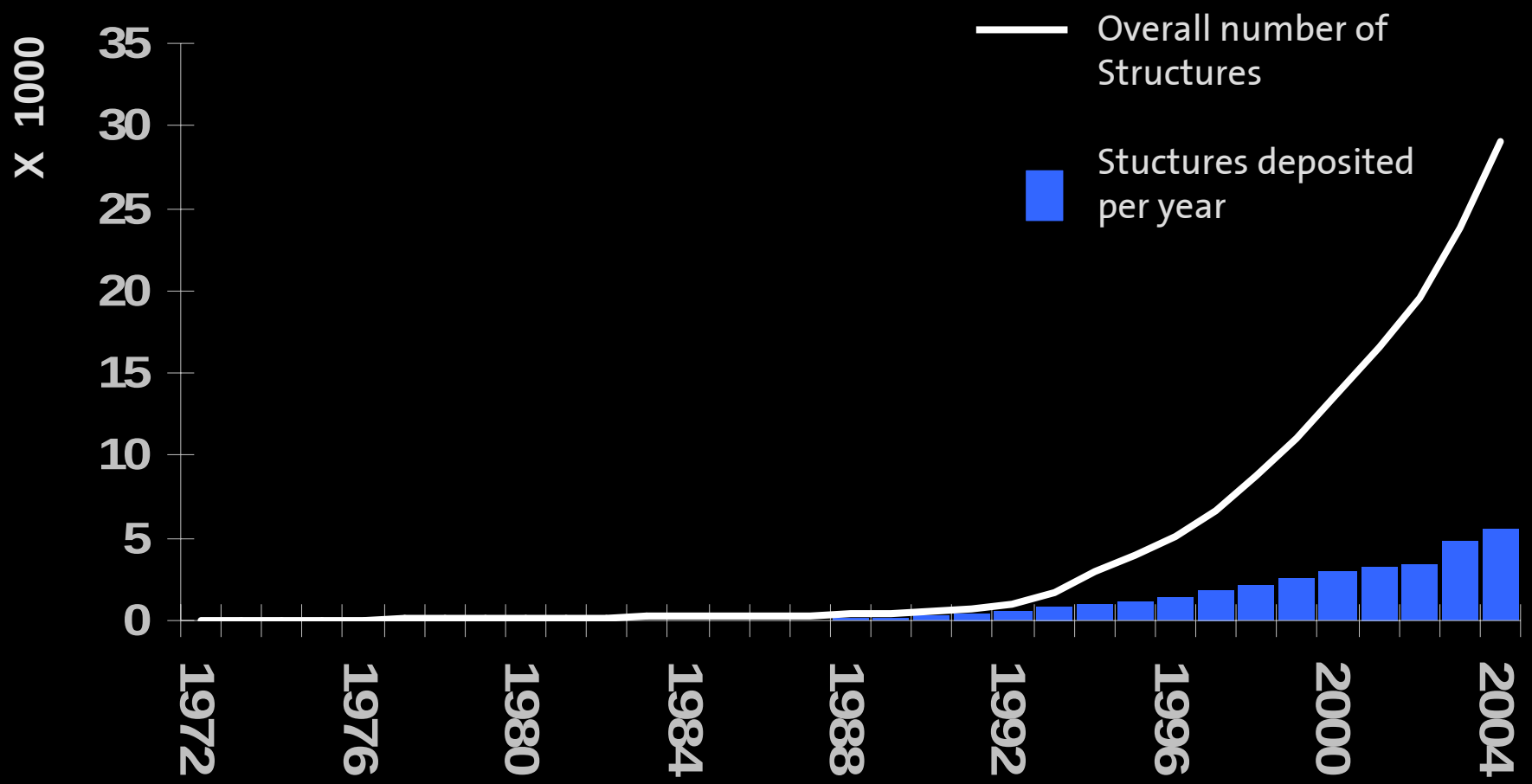
- **Comprehensive**

  selectivity-tuning by adding or omitting feature constraints

- **Computationally efficient**

  due to simplicity (suitable for virtual screening)

PDB Age and Content



Why LigandScout?

Structure-based pharmacophore creation from all PDB complexes:

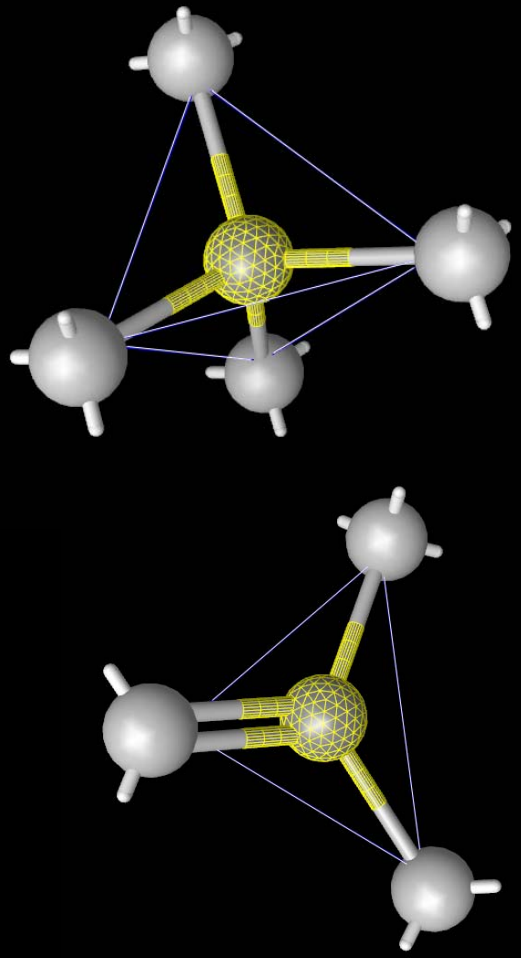
1. Identification & extraction of ligands
2. Interpret ligands (hybridization states, bond types)
3. Create pharmacophores
4. Visualize, allow user interaction and export for virtual screening

Hybridization State Determination

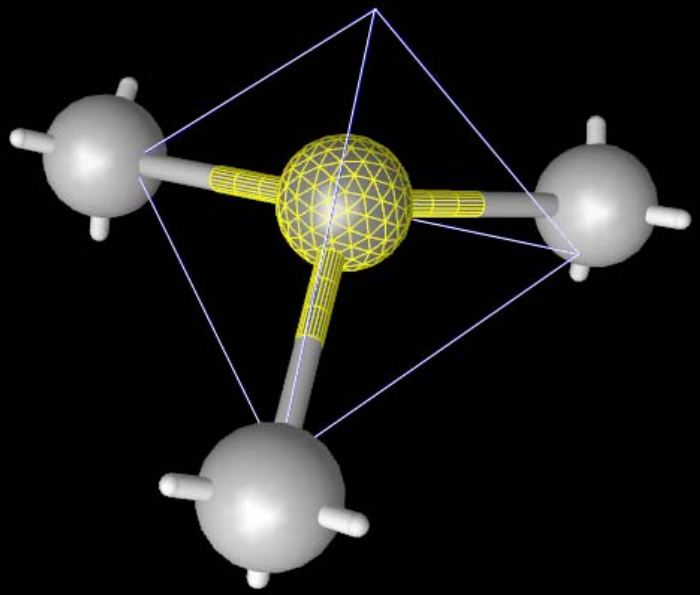
Quantitative Geometry Templates for all geometry types:

- sp^3: tetrahedral
- sp^2: trigonal planar
- sp: linear

Align along the first two points, numerically turn to match the third point



Geometry Templates: Better Than Bond Angles?



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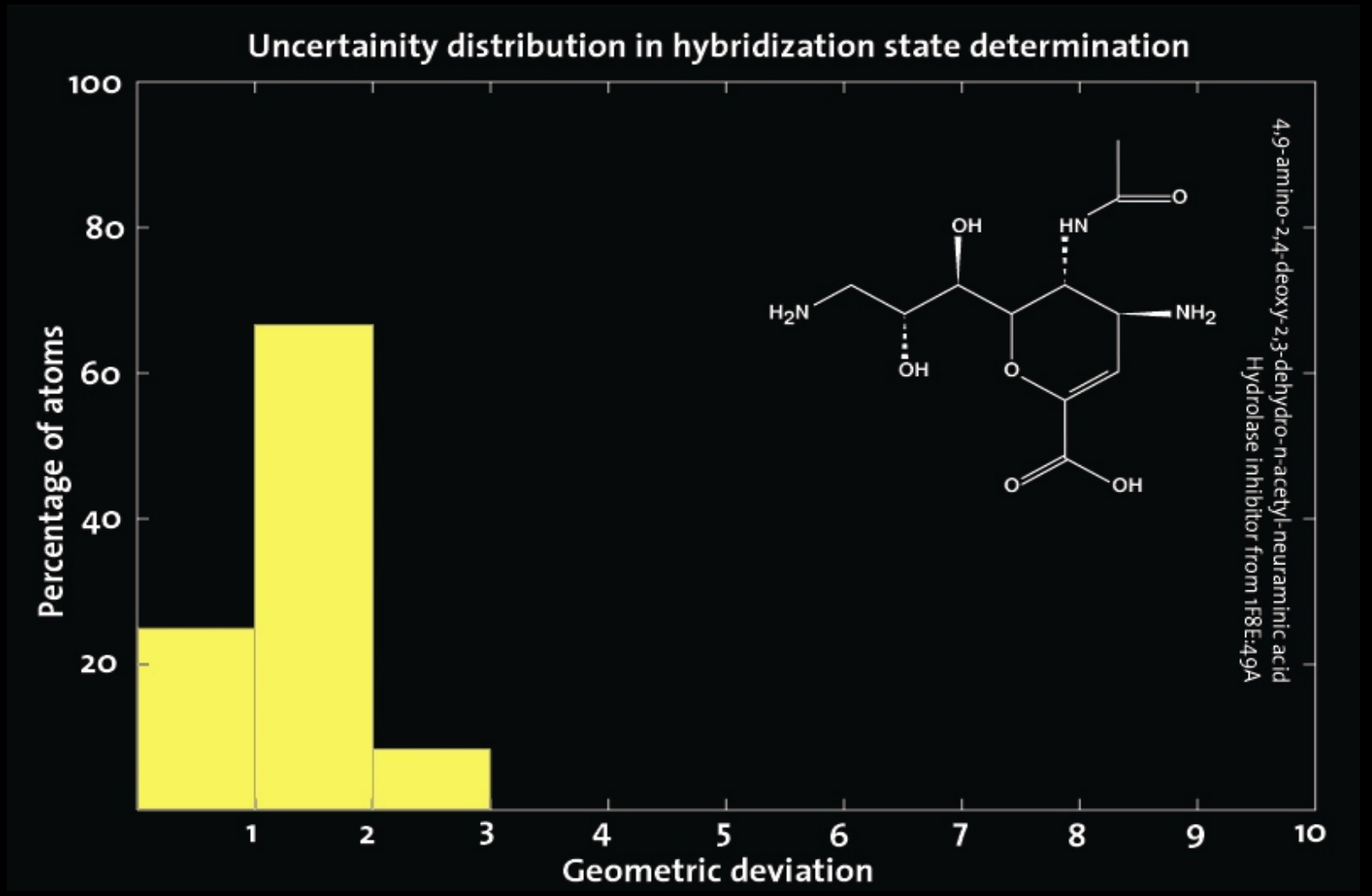
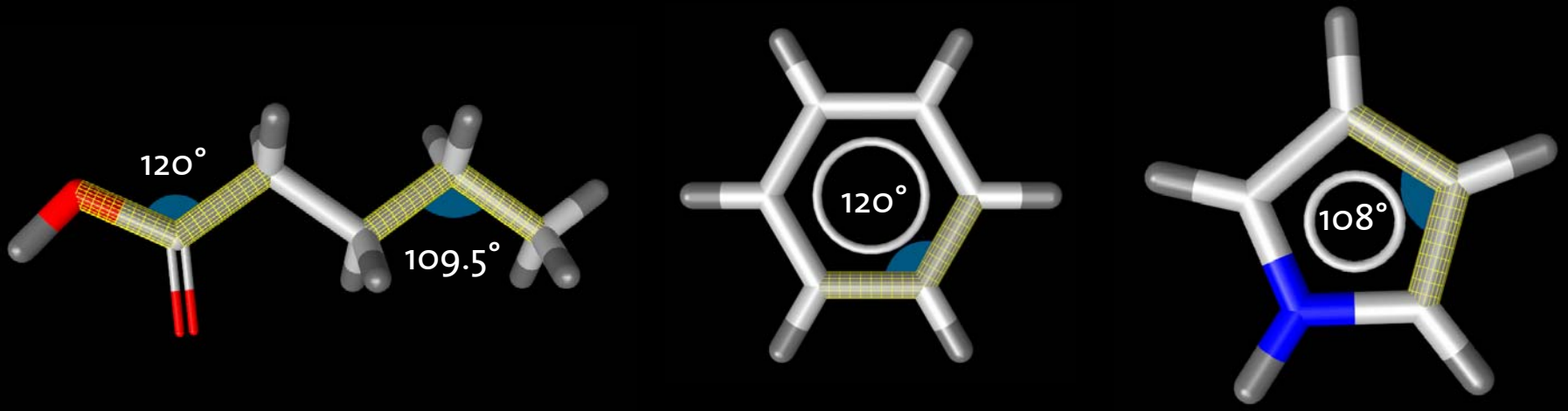
Hybridization State: Error Determination



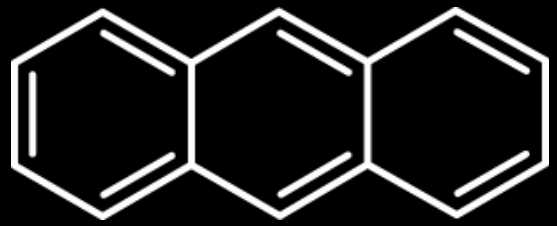
Hybridization State: Planar Rings



Planar rings show different bond angles than non-ring sp^2 atoms: all planar ring atoms are to be sp^2 hybridized

Hybridization State: Ring Perception

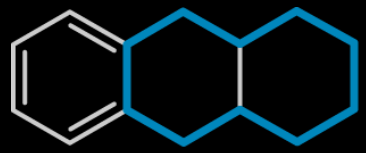
- Ring recognition must match graph-theoretical and chemical view



3 out of 6

- Smallest set of smallest rings (SSSR) [Figueras 2000]

(4)



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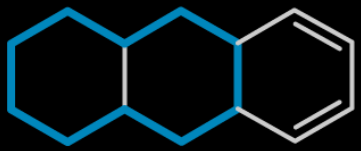
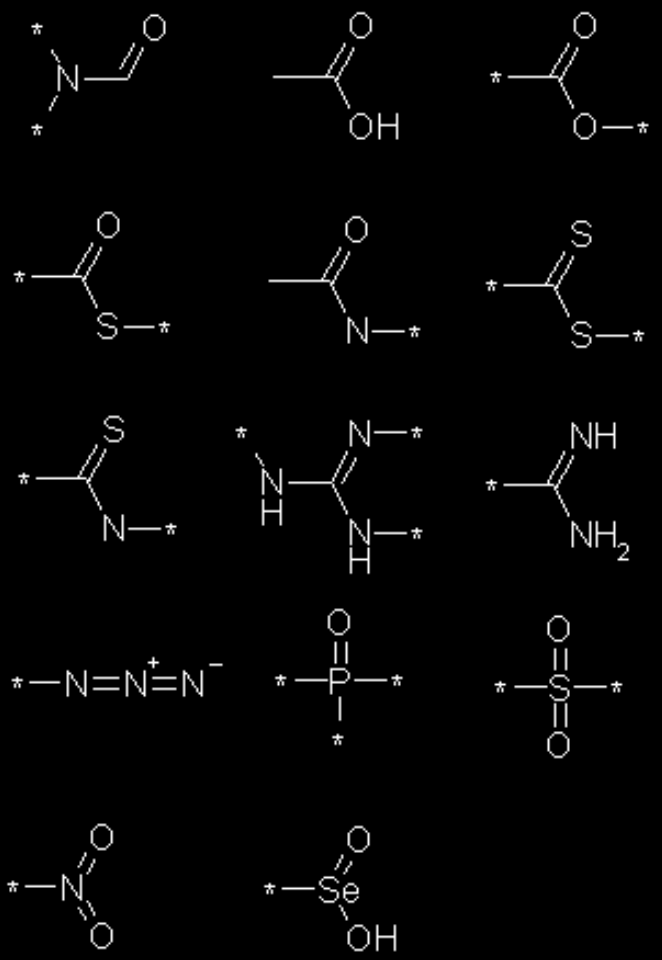


(6)

- Empirical discrimination between planar and non-planar rings (Porphyrine pyrroles vs. pyrrolidines)

Double Bond Distribution Among sp² Atoms

- No exact solution in many cases (e.g. Keto-enol tautomers)
- Use of patterns explicitely covering all known cases from the view of a central atom
- Greedy (recursive) scoring algorithm covering the rest of the cases



Patterns by Roger Sayle: Bioinformatics Group, Metaphorics LLC, Santa Fe, New Mexico, see http://www.daylight.com/meetings/mug01/Sayle/m4xbondage.html

Distributed Batch Extraction and Interpretation

- **Extraction and Interpretation is computing-intense**
  - Distance comparison of macromolecular atoms to each ligand atom
  - Ring detection
  - Bond distribution
- **Requirements**
  - Client can join or leave any time
  - Scalable
- **Solution**
  - Central HTTP server distributes PDB files
  - Central application server collects ligands
  - Computational clients can arbitrarily join or leave at any time

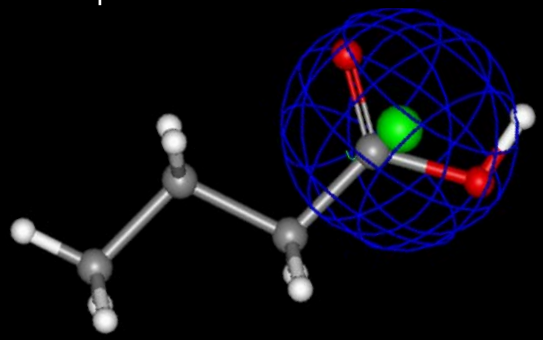
Chemical Feature Constraints

Distance Constraints

Relation between two points, one located on ligand side, one on macromolecular side.

Feature Type	Distance
H-Bond	2.5-3.8 A
Charge Transfer	1.5-5.6 A
Hydrophobic	1.0-5.8 A

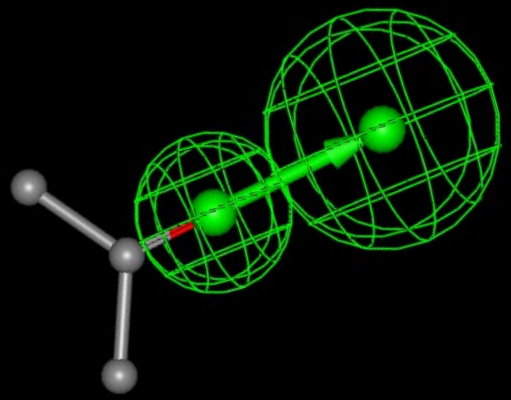
Result: one tolerance sphere on ligand side



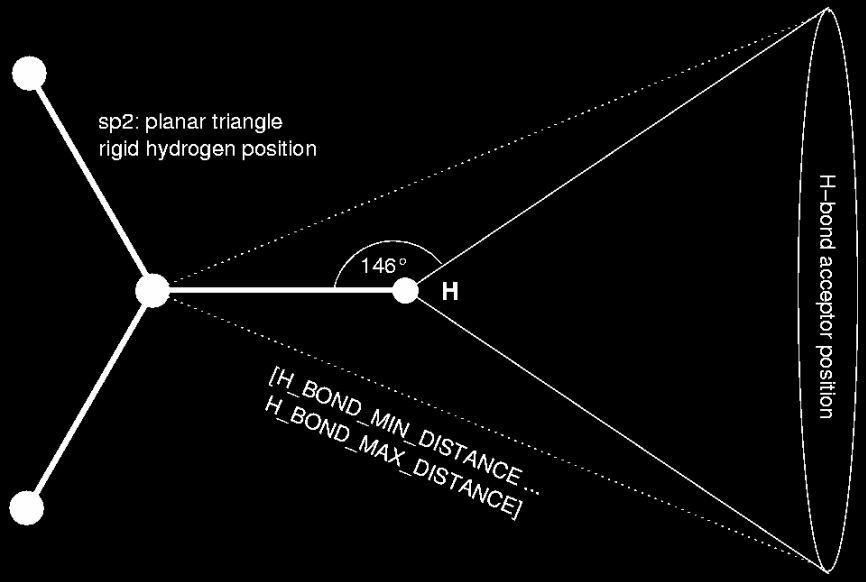
Direction Constraints

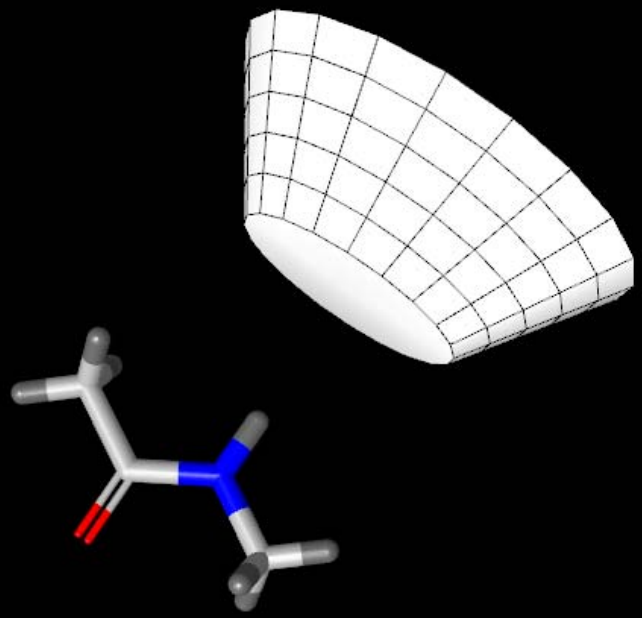
Relation between two atom groups, one located on ligand side, one on macromolecular side.

Groups form a rigid reference geometry, which are the basis for a directed vector.

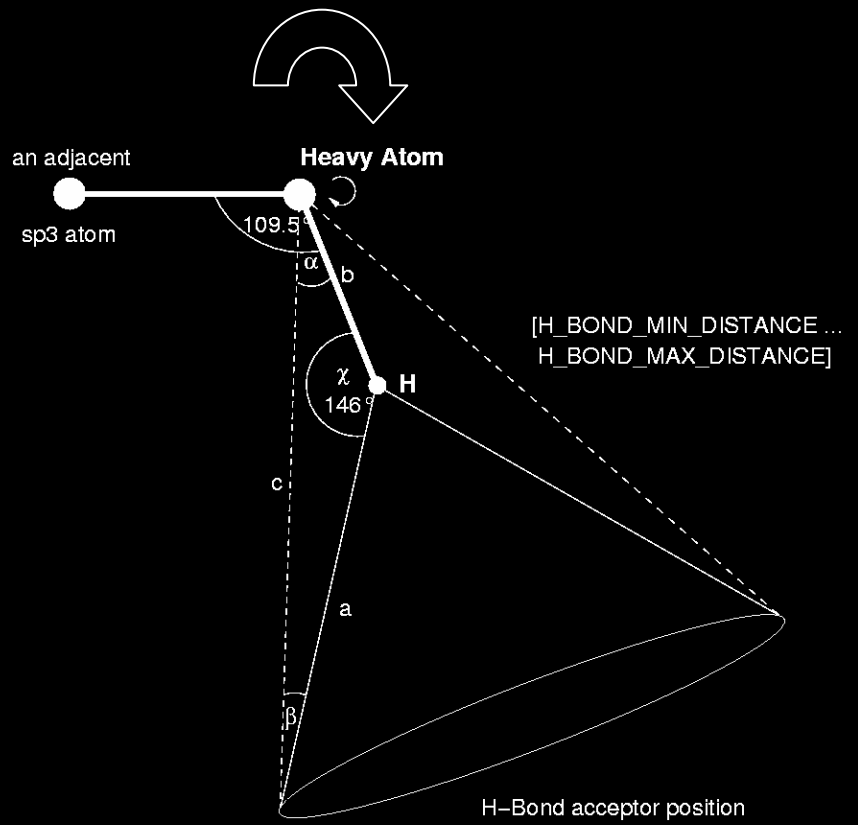


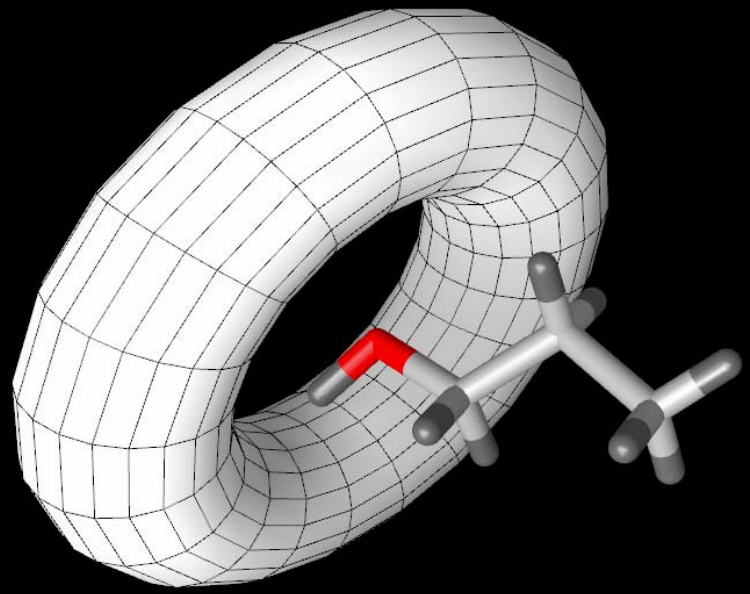
Chemical Feature Constraints: Rigid H-Bonds





Chemical Feature Constraints: Flexible H-Bonds





$$\alpha = \delta - inv\sin\left(\frac{b.\sin(\chi)}{c}\right)$$

Chemical Features Universality Layers

Layer 4	**Chemical Function**	Without geometry constraint	Lipophilic area, positive ionizable area
Layer 3		Including geometry constraint	Hydrogen bond donor/acceptor
Layer 2	**Subgraph**	Without geometry constraint	Hydroxylic group, phenol group
Layer 1		Including geometry constraint	Phenol group facing a parallel benzene

Why Universality?

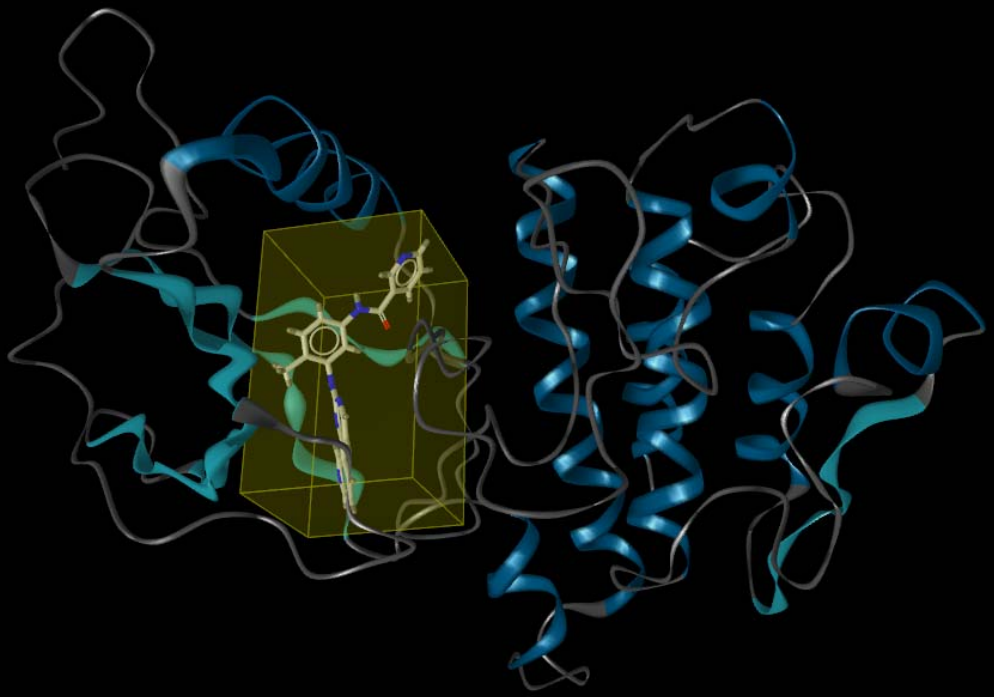
- **Semantic enhancement:**
  Allows the comparison of chemical features

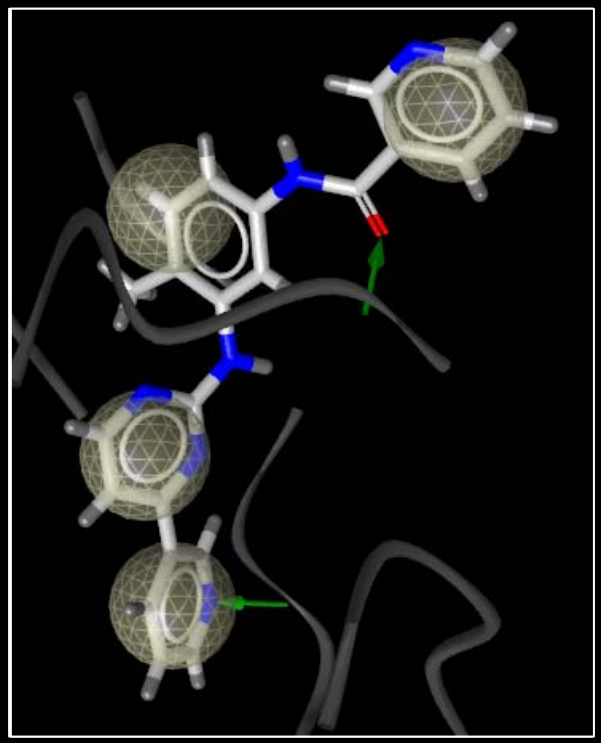
- **Categorization:**
  Prerequisite for the creation of **ontologies** (classification trees of chemical features)

- **Indexing capabilities:**
  Only categorized features permit **indexing**: Necessary for efficient pharmcophore search techniques

→ LigandScout creates pharmacophores using the universal Layer 3 and Layer 4 features

Application Example: Gleevec

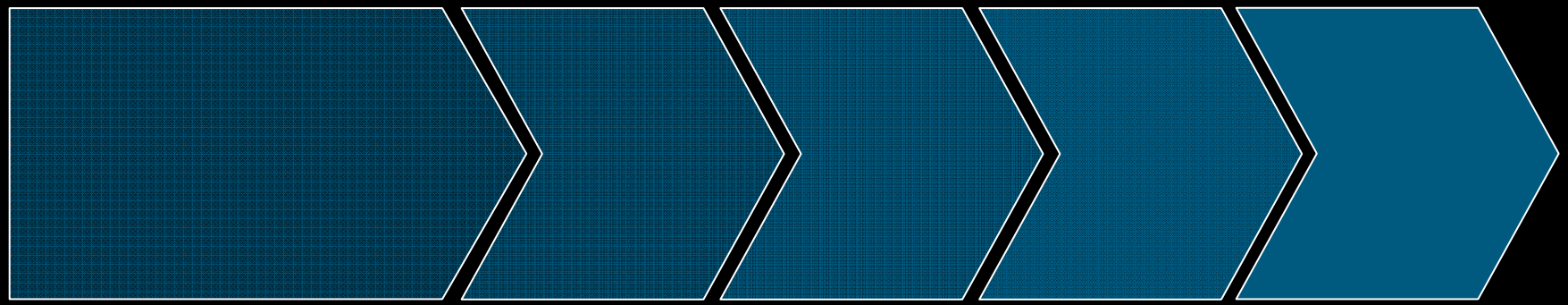




Gleevec modification
(PRC) from 1FPU

Pharmacophore Overlaying

Pharmacophore model derived from one single bound ligand may not be able to retrieve other related compounds ...



Starting set: Several ligand-protein complex pharmacophores

Creation of compatibility graphs

Maximum clique detection

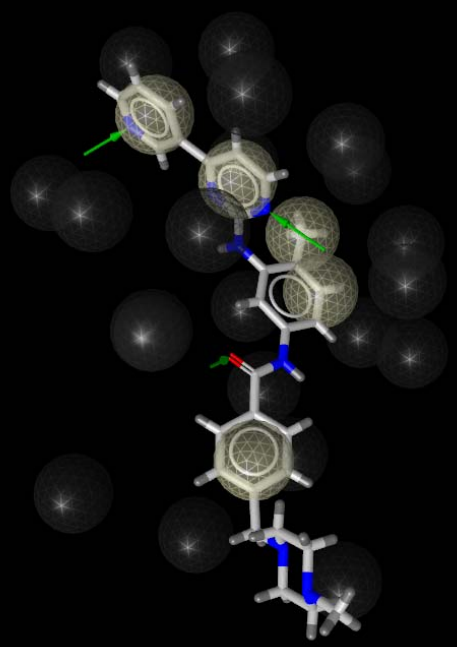
Feature alignment

Calculation of combined features

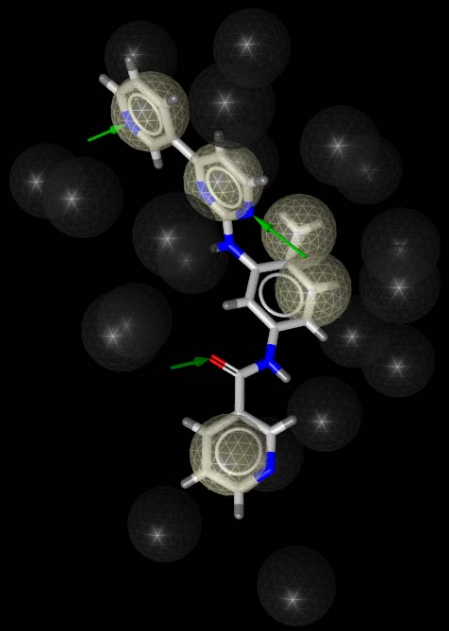
... new **common feature** pharmacophore

Common Feature Pharmacophore

1iep



1fpu



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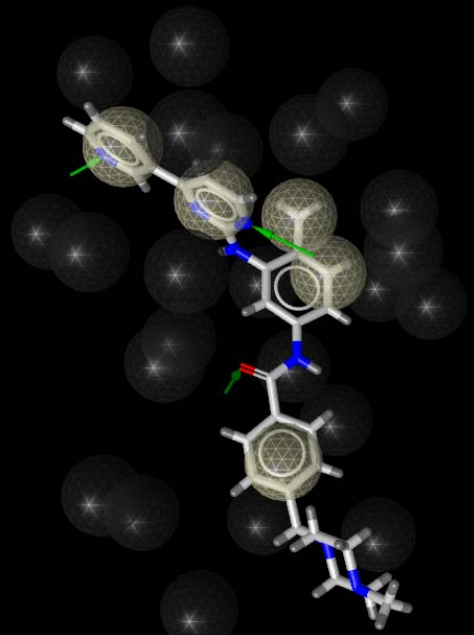
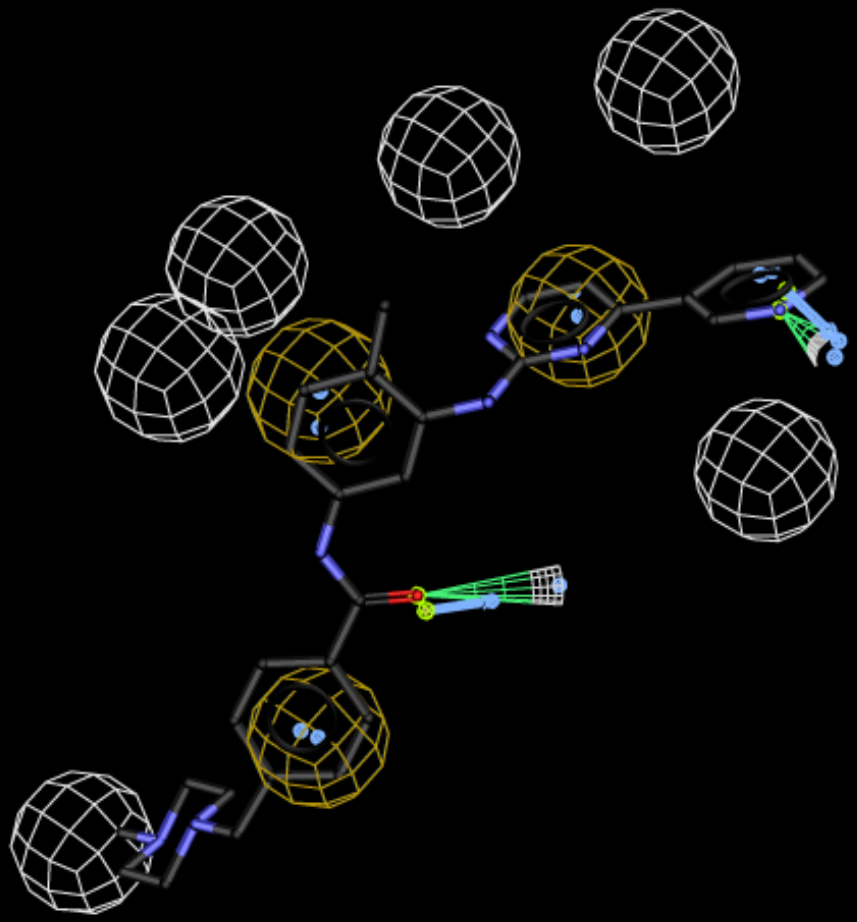


Common Feature Pharmacophore

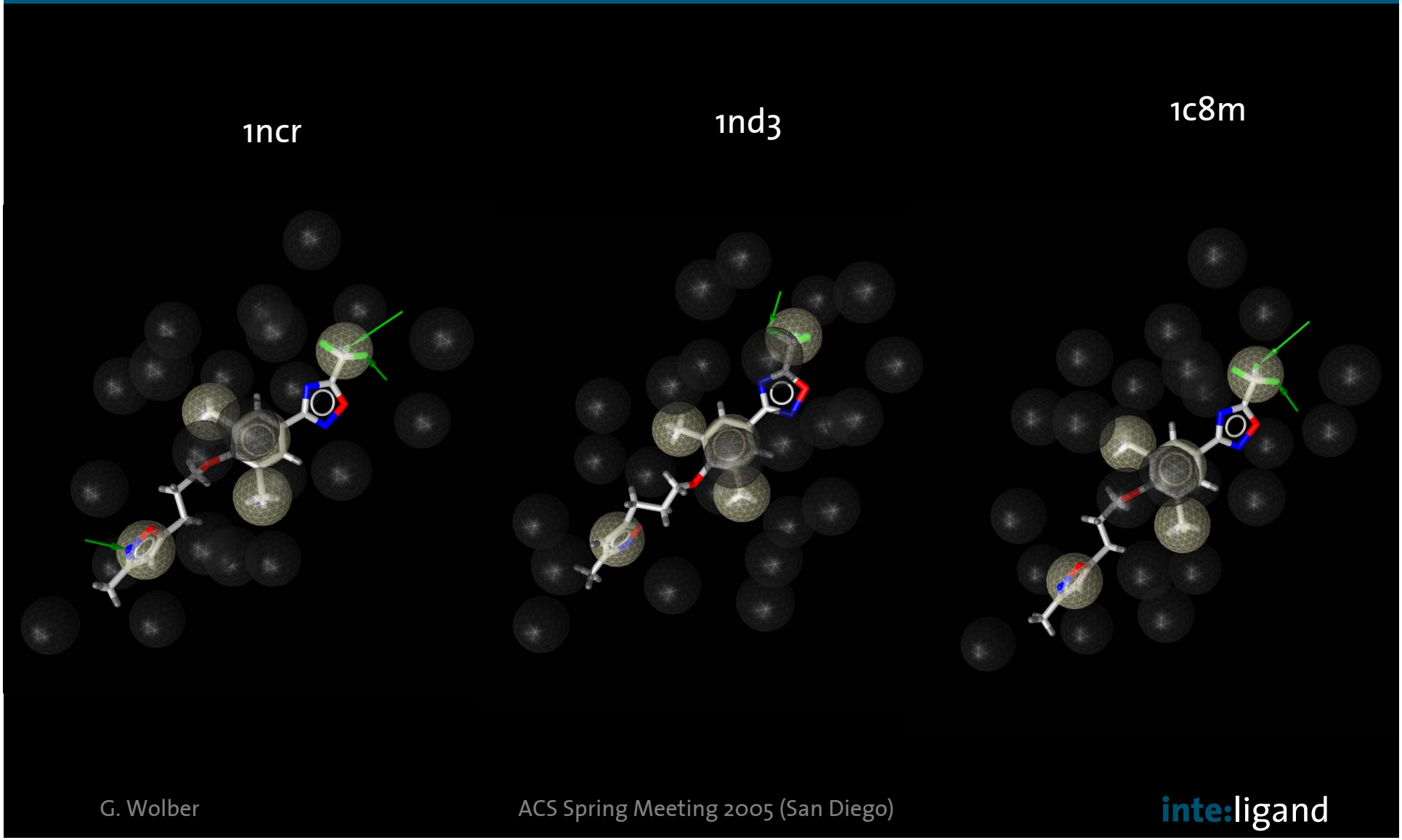


3 lipophilic aromatic areas
2 hydrogen bond acceptors

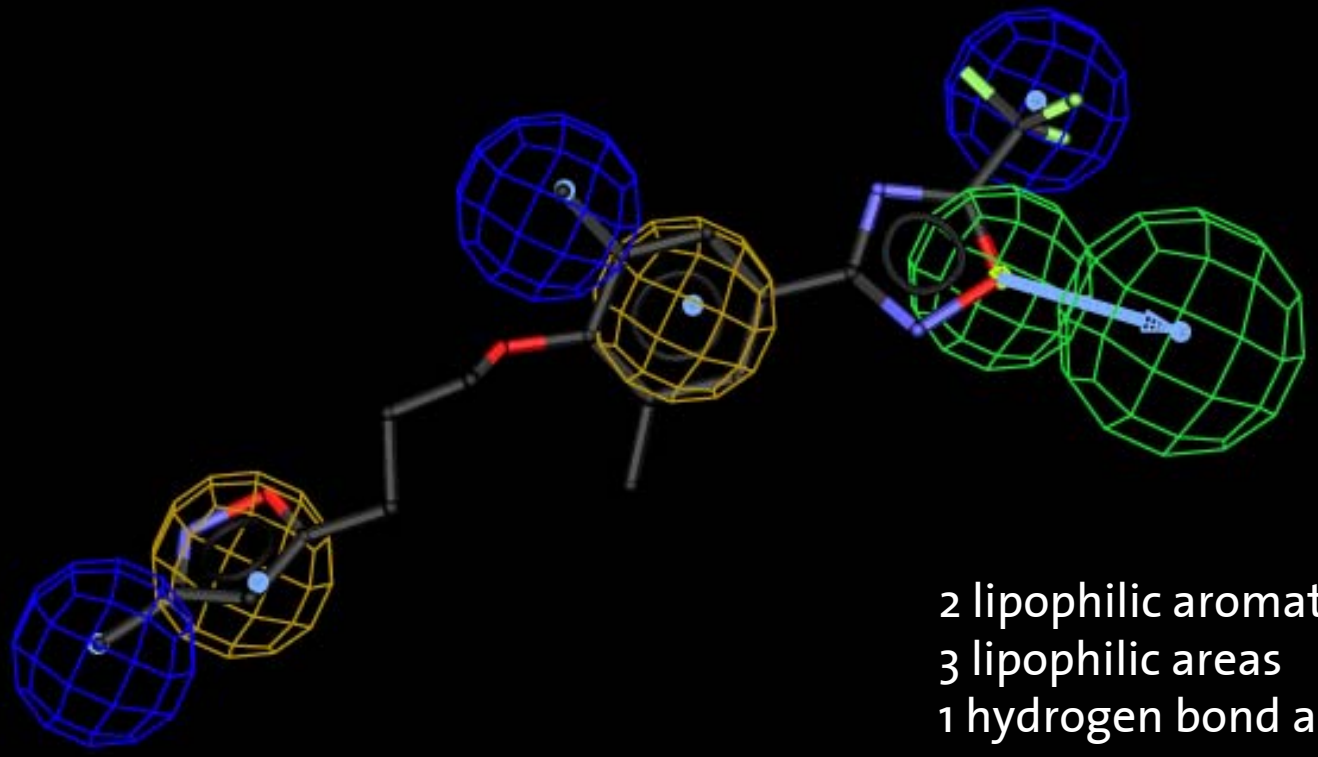
Virtual Screening Results

Database	Hits	Drug-like hits
PDB singleConf (~67k)	7	7
PDB multiConf (~7k)	2	2
Maybridge (~55k)	19	7

Application Example: HRV Coat Protein



Common Feature Pharmacophore



2 lipophilic aromatic areas
3 lipophilic areas
1 hydrogen bond acceptor

Virtual Screening Results

Database	Hits	Drug-like hits
PDB singleConf (~67k)	8	8
PDB multiConf (~7k)	1	1
Maybridge (~55k)	67	48

Summary

LigandScout

- Extracts ligands and their protein environment from PDB files
- Assigns bond characteristics to small molecule ligands in a fully automated and distributed way
- Creates and visualizes pharmacophore models that represent the interaction between protein and ligand in a universal way

Perspectives

The **collection of all pharmacophores** from the PDB can be used to ...

- ... develop 3D pharmacophore cascades in order to create computational models for biological pathways
- ... search all pharmacophores for the purpose of screening one compound against all its known biological effects ("activity profiling")

Literature

- G. Wolber and T. Langer. LigandScout: **3-D Pharmacophores Derived from Protein-Bound Ligands and Their Use as Virtual Screening Filters** *J . Chem. Inf. Model;* **2005**; 45; 160-169

- E. M. Krovat, K. H. Frühwirth, and T. Langer. **Pharmacophore Identification, in Silico Screening, and Virtual Library Design for Inhibitors of the Human Factor Xa.** *J. Chem. Inf. Model.;* **2005**; 45; 146-159

- T. Steindl and T. Langer. **Docking Versus Pharmacophore Model Generation: A Comparison of High-Throughput Virtual Screening Strategies for the Search of Human Rhinovirus Coat Protein Inhibitors.** *QSAR and Combinatorial Science;* **2005;** *in press*

Acknowledgements

inte:ligand

- Martin Biely
- Alois Dornhofer
- Robert Kosara
- Judith Rollinger

Thierry Langer

- Oliver Funk
- Johannes Kirchmair
- Eva Krovat
- Christian Laggner
- Daniela Schuster
- Theodora Steindl