

# High Throughput Virtual Screening

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# Overview

- Why use quantum mechanics ?
  - The NAO-PC model
- Binding vectors and pharmacophore maps
  - QSAR with a lead compound
  - QSAR using a grid pharmacophore
- Identifying binding features from real data

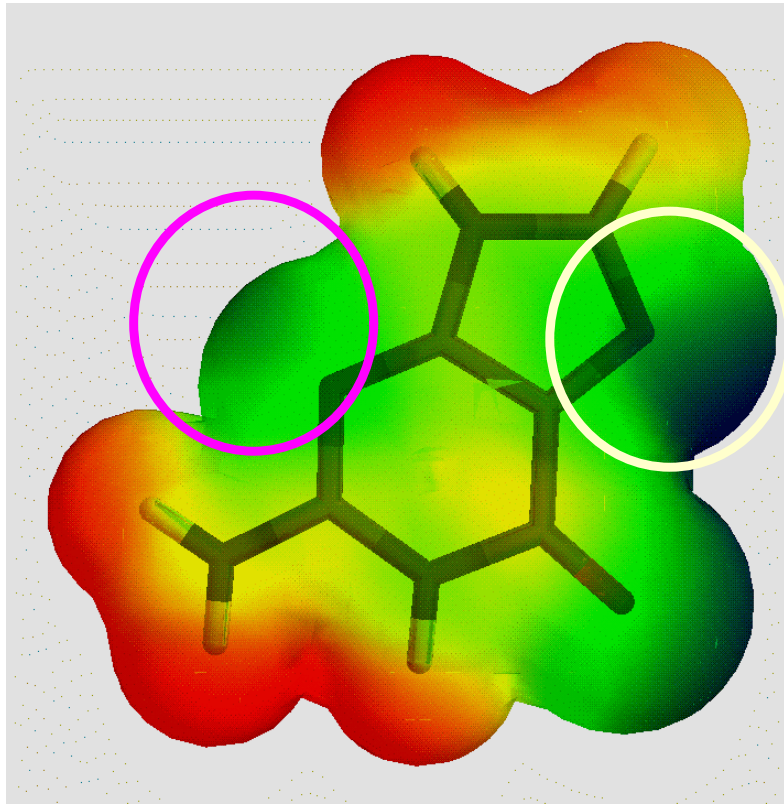


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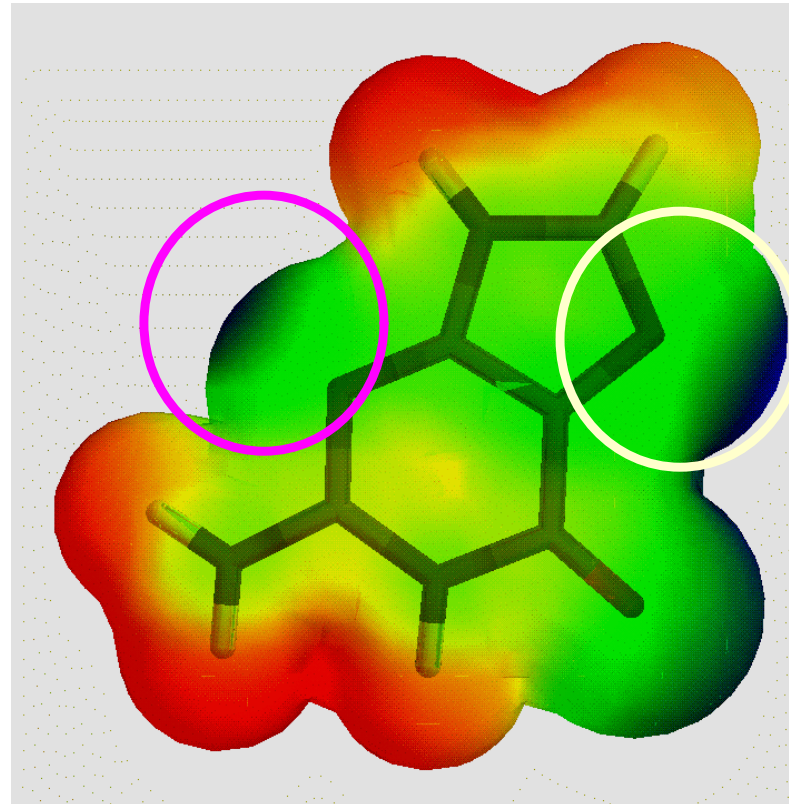
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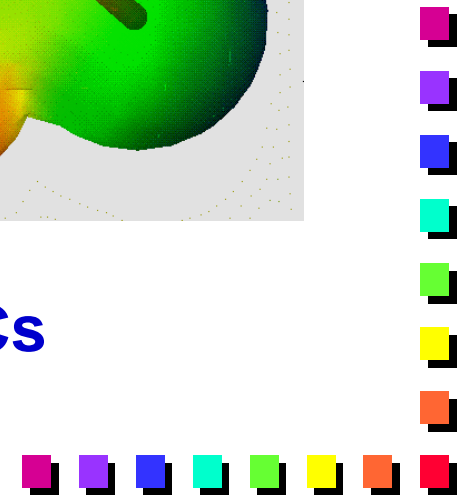
# NAO-PC: Guanine electrostatics



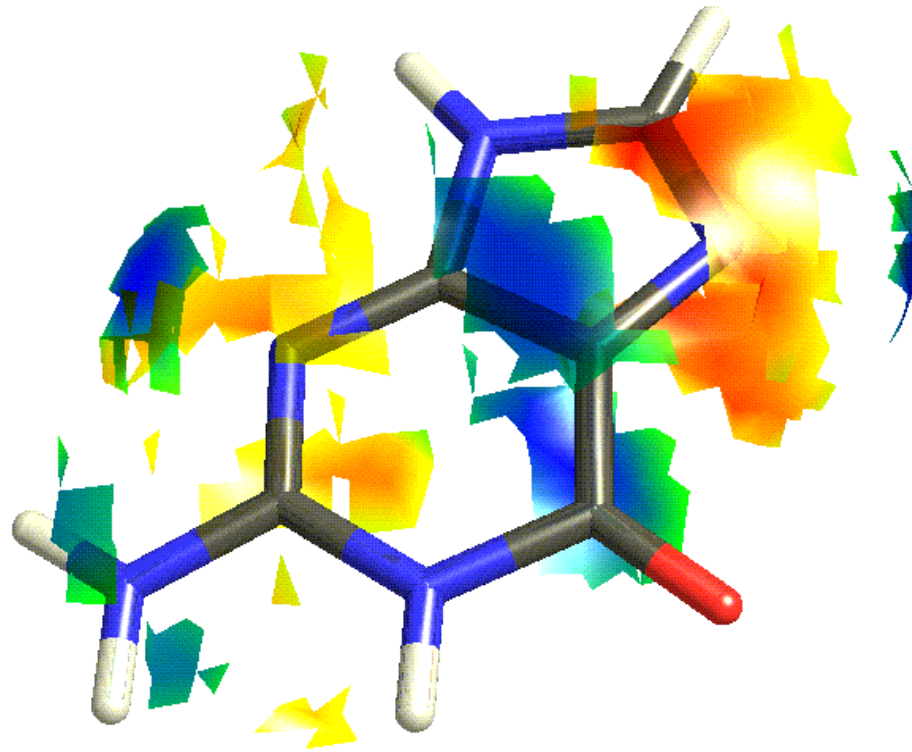
**MEP-derived atomic  
monopoles**



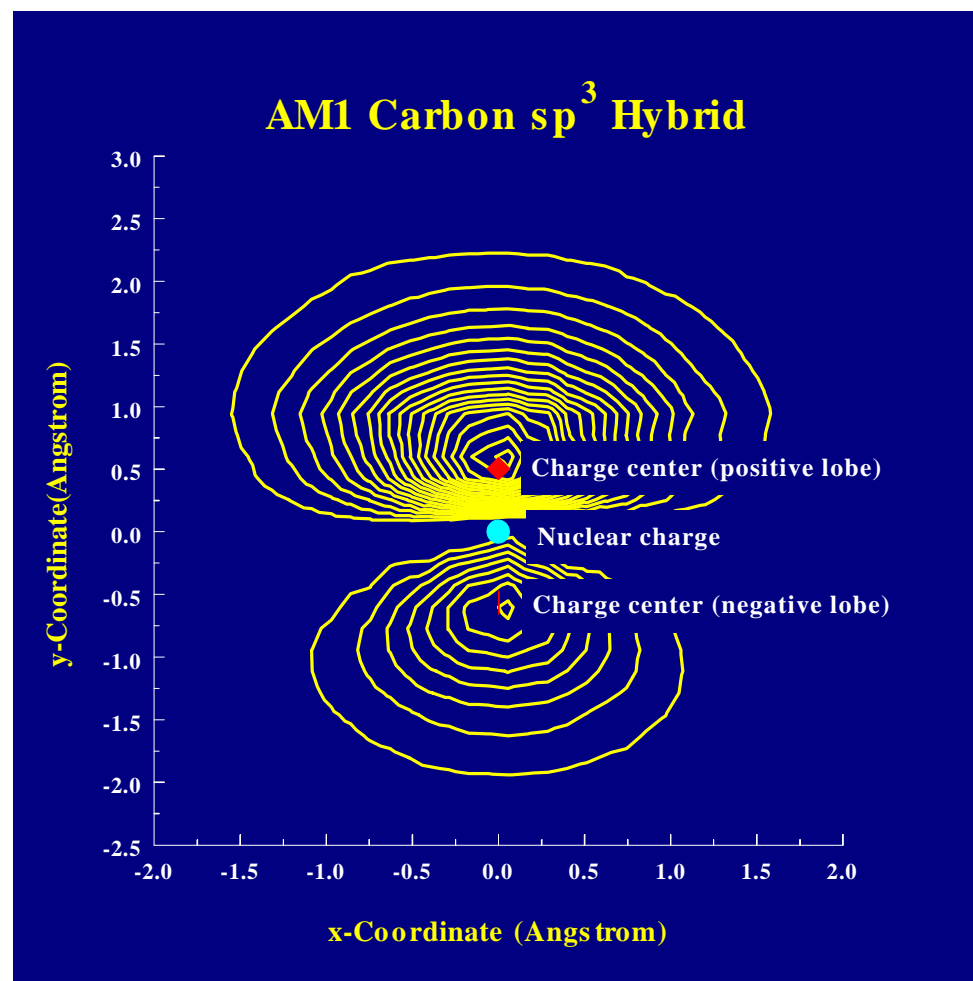
**NAO-PCs**



# NAO-PC: Guanine differences



# The NAO-PC model



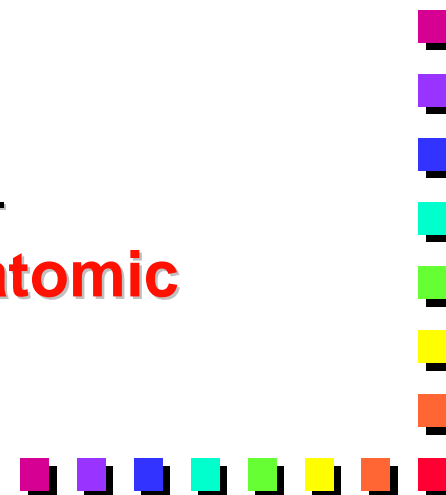
# The NAO-PC model

- Derive NAOs by diagonalization of the one-atom blocks of the density matrix
- Calculate NAO-point charges
  - Variables are the distance from the nucleus and the magnitude of the charge
  - These only depend on the hybridization and are therefore simple functions of the  $s$ -coefficient
- Use lookup tables and polynomials



# The NAO-PC model ...

- **... is sufficient to describe the quantum mechanics**
  - Reproduces Hamiltonian-based dipole moments within 0.1 Debye
- **... predicts experimental data**
  - Reproduces experimental quadrupole moments as well as MP2/6-31G\*
- **... is compact**
  - Can be stored in  $(10 \cdot N_{\text{heavy}} + N_{\text{hydrogen}})$  words.
- **... accurately describes molecular & atomic multipoles**
  - Used as QSAR descriptors in Prophet

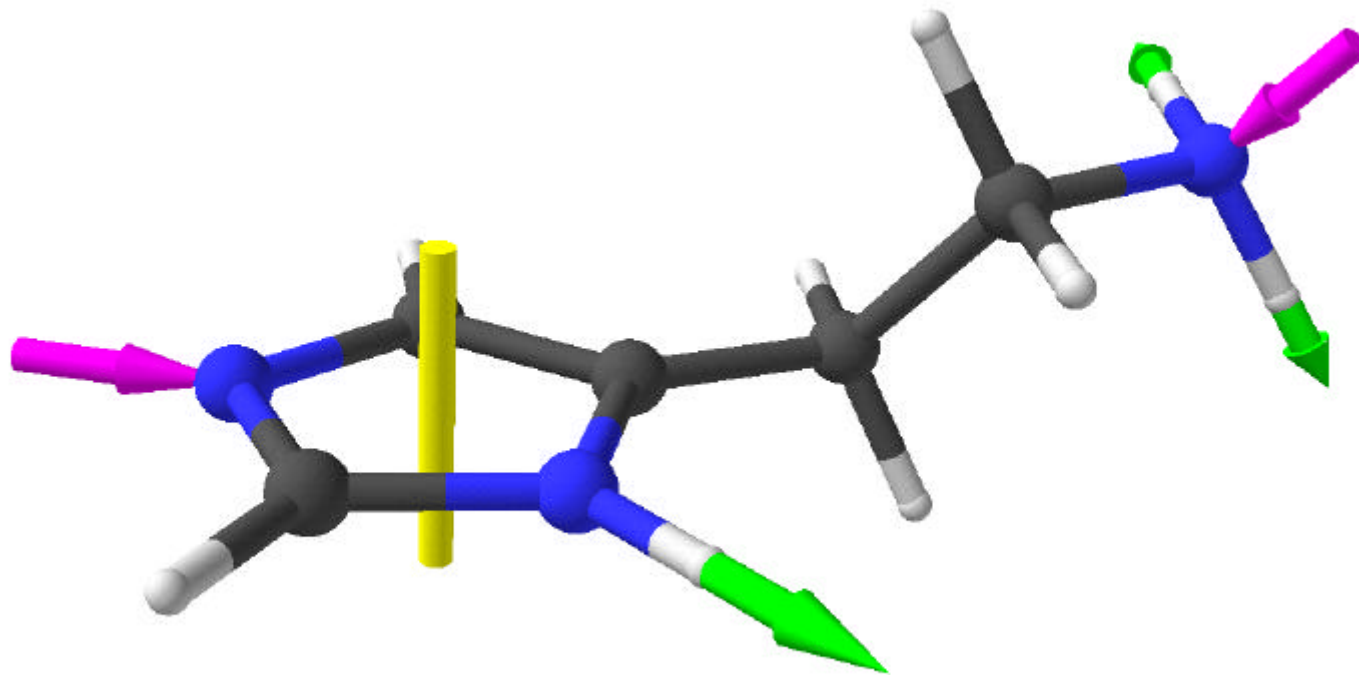


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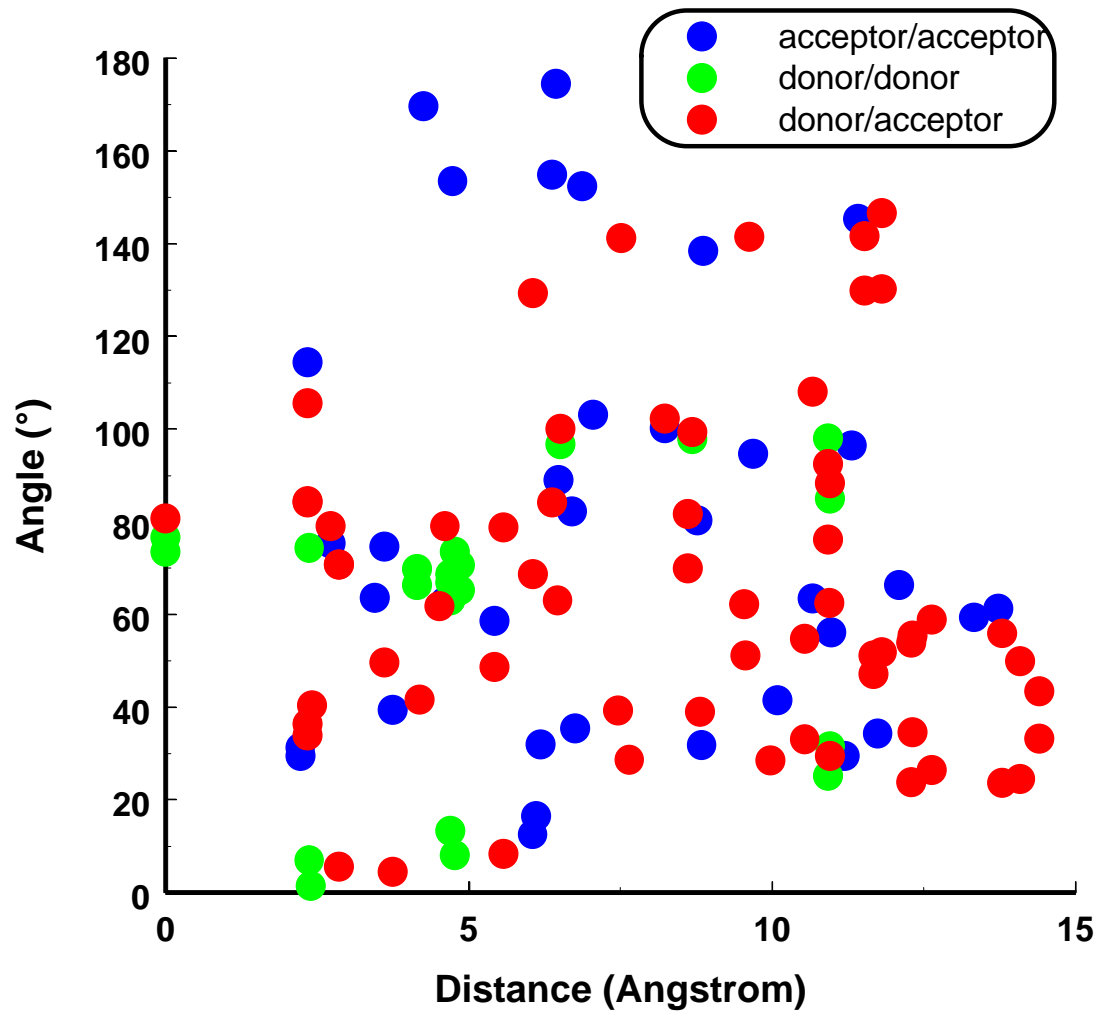
# Hydrogen-bonding vectors



**Histamine**



# Dipole-pair map: Methotrexate



# 3D-QSAR based on Quantum Mechanics

- Calculate dipole-pair maps
- Calculate Gaussian overlap for each pair with lead compound or pharmacophore
- Use the overlap vector for QSAR regression or perceptron filter

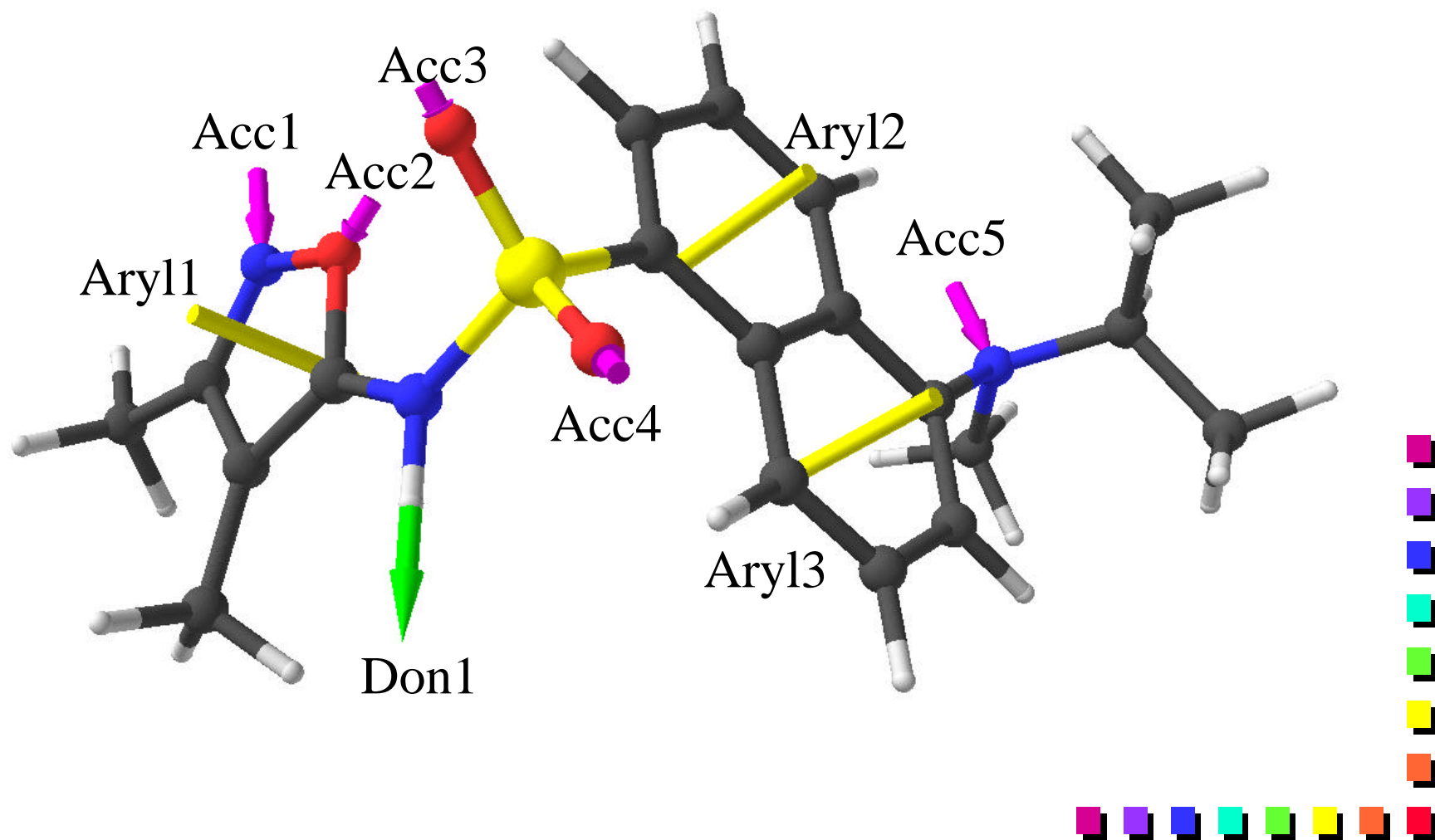


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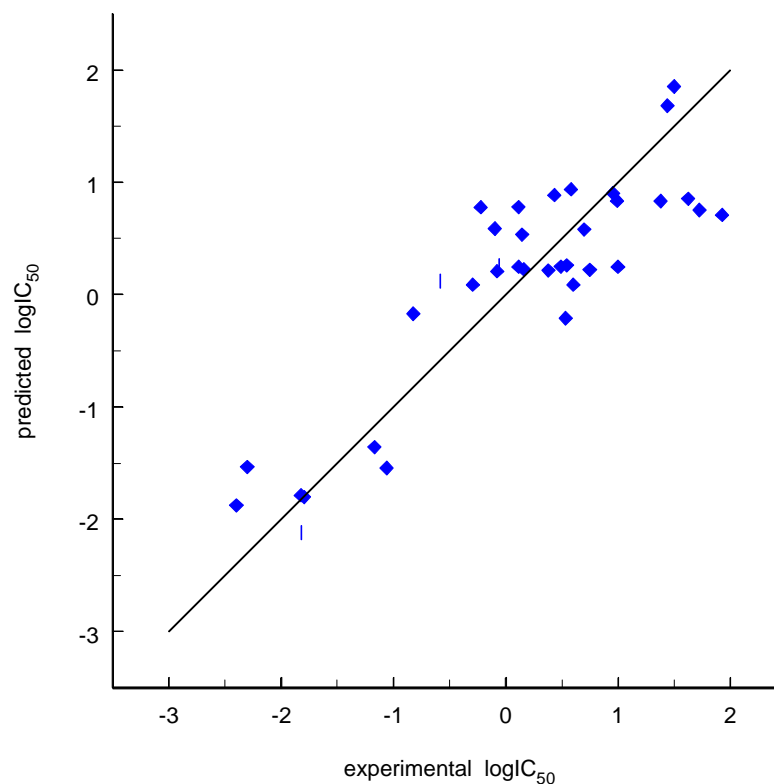
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# ET<sub>A</sub>-Antagonists

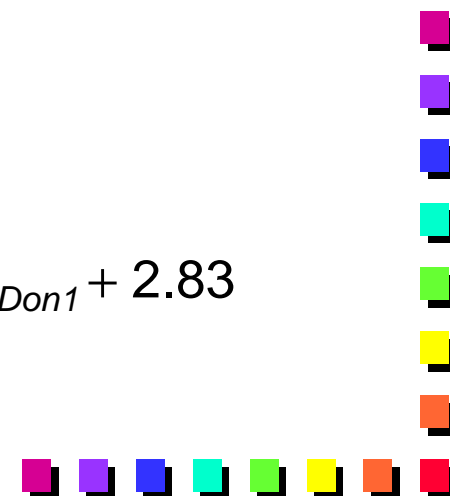


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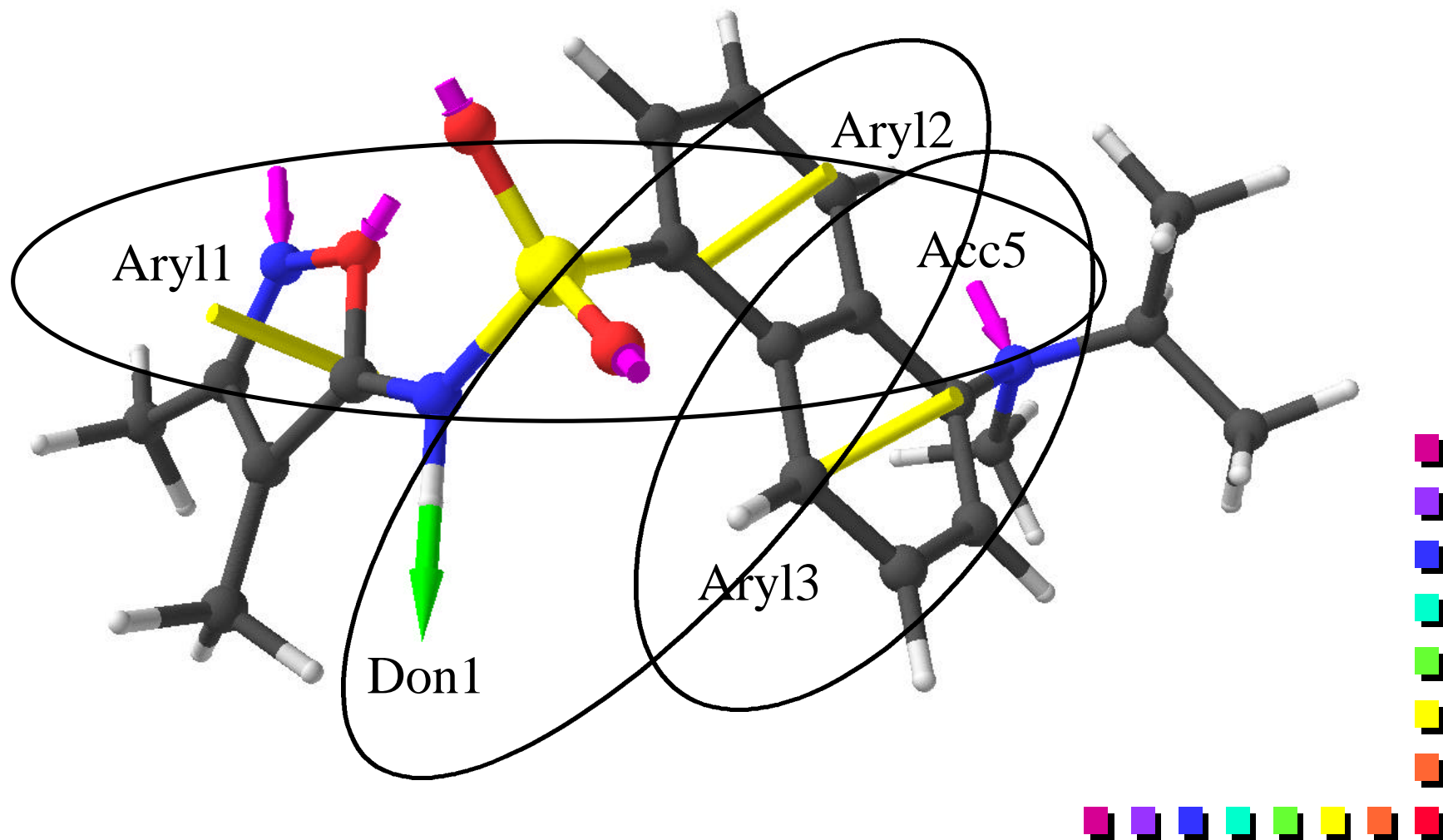


$$\log\text{IC}_{50} = -3.47 S_{\text{Aryl1-Acc5}} + 1.62 S_{\text{Aryl3-Acc5}} - 2.86 S_{\text{Aryl2-Don1}} + 2.83$$

$$N = 36, r^2 = 0.77, r_{\text{cv}}^2 = 0.72, \sigma = 0.57$$



# ET<sub>A</sub>-Antagonists



# Database searching

## ■ HOBO

- Calculates local dipoles from NAO-PCs
- Calculates Gaussian overlaps between lead and target
- Applies regression or perceptron QSAR model

■ 2,200 molecules  $\text{min}^{-1}$  processor $^{-1}$  (SGI 90 MHz R8000 Power Challenge)

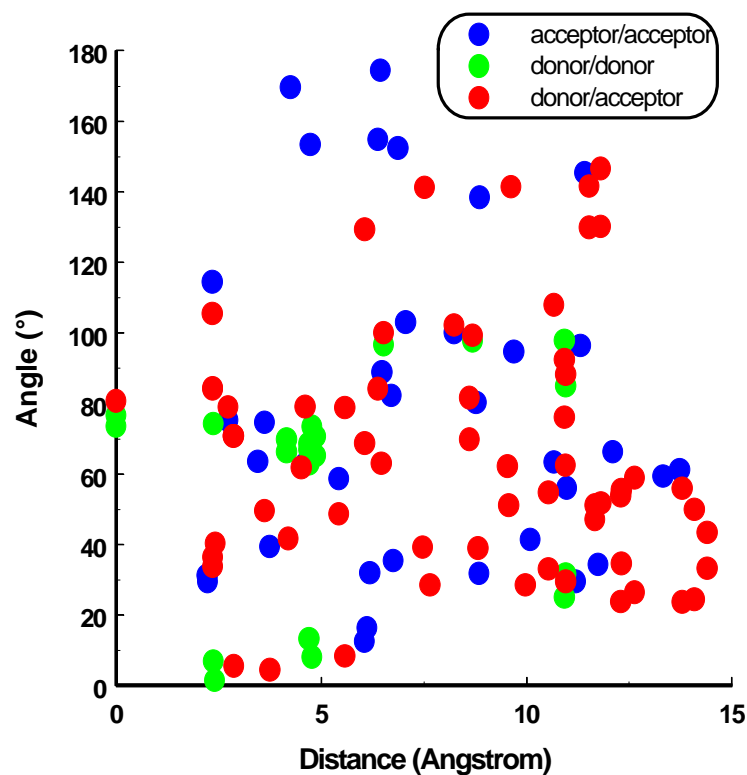


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# Dipole-pair map: Methotrexate



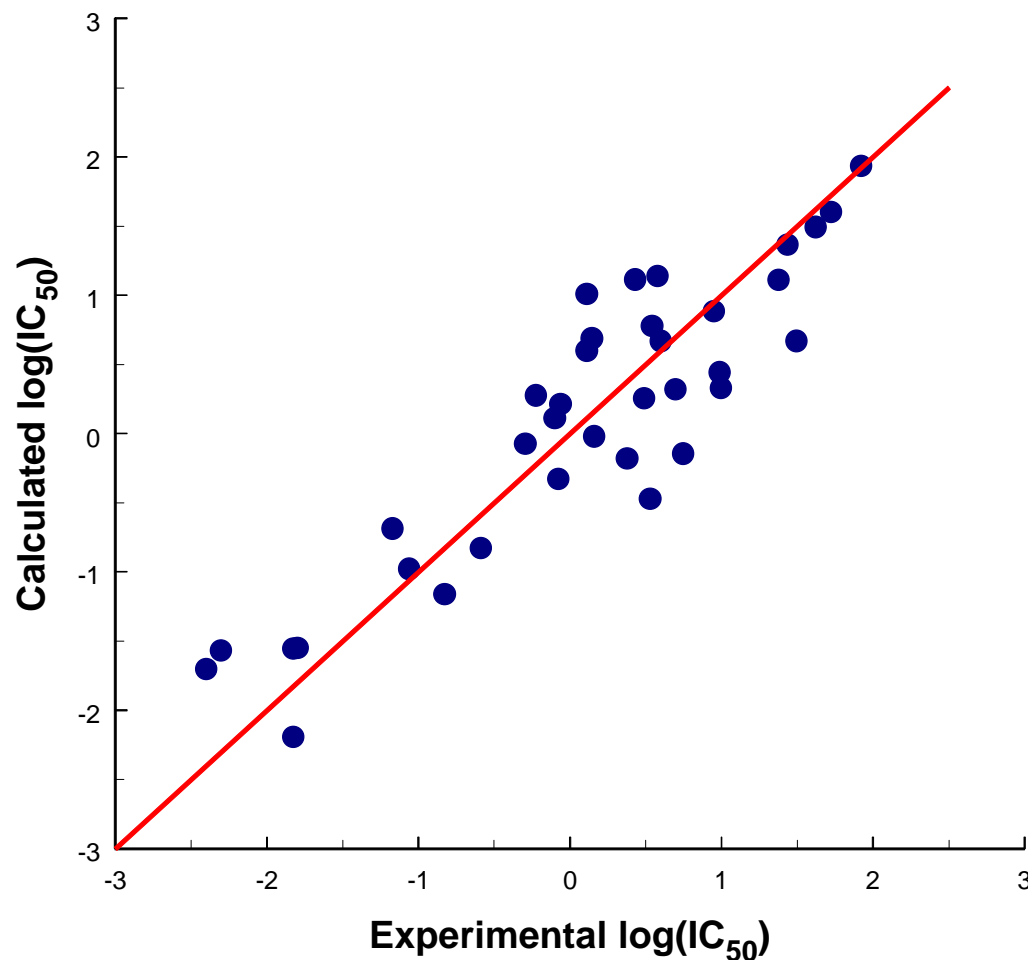
1. Lay a grid ( $15^\circ$ ,  $0.5 \text{ \AA}$ ) over the map

2. Calculate overlaps with dipoles situated at the grid points

3. Use PLS as in CoMFA<sup>TM</sup>



# ET<sub>A</sub>-Antagonists



$$N = 36$$

$$r^2 = 0.723$$

$$r^2_{cv} = 0.669$$

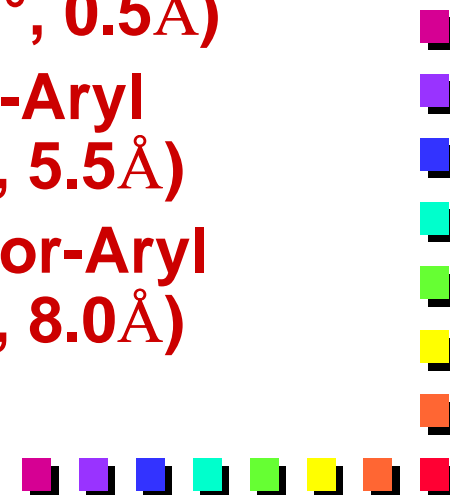
$$s = 0.49$$

3 grid points:

**Donor-Acceptor**  
**(115°, 0.5Å)**

**Aryl-Aryl**  
**(60°, 5.5Å)**

**Donor-Aryl**  
**(30°, 8.0Å)**



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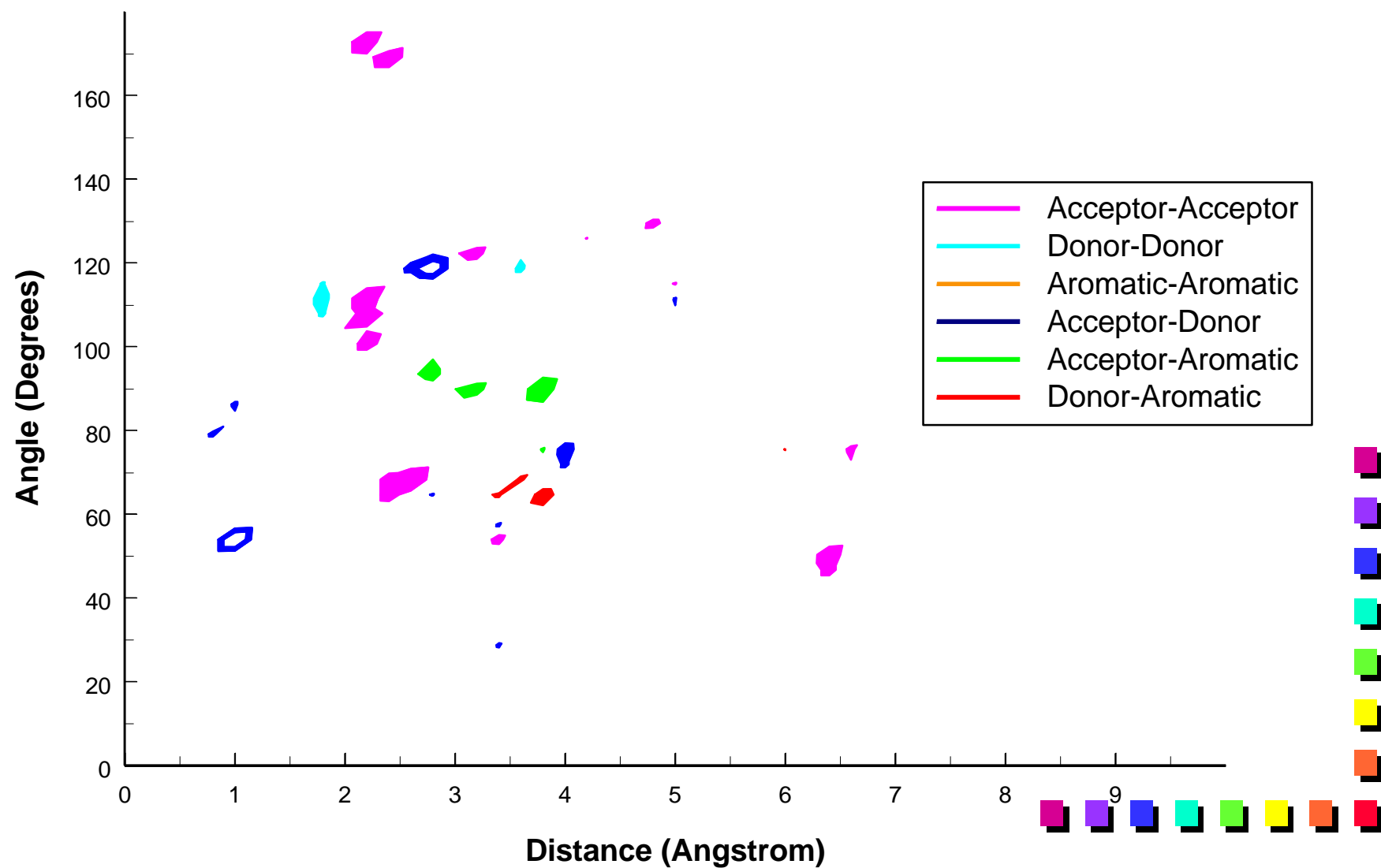
# Pharmacophore Generation

- Dataset of 3,682 compounds from the World Drug Index, all with one clear indication (Mike Snarey and Peter Willett)
- Calculate the dipole maps and:
  - Sum the actives for a given indication
  - Subtract the normalised background from the entire dataset



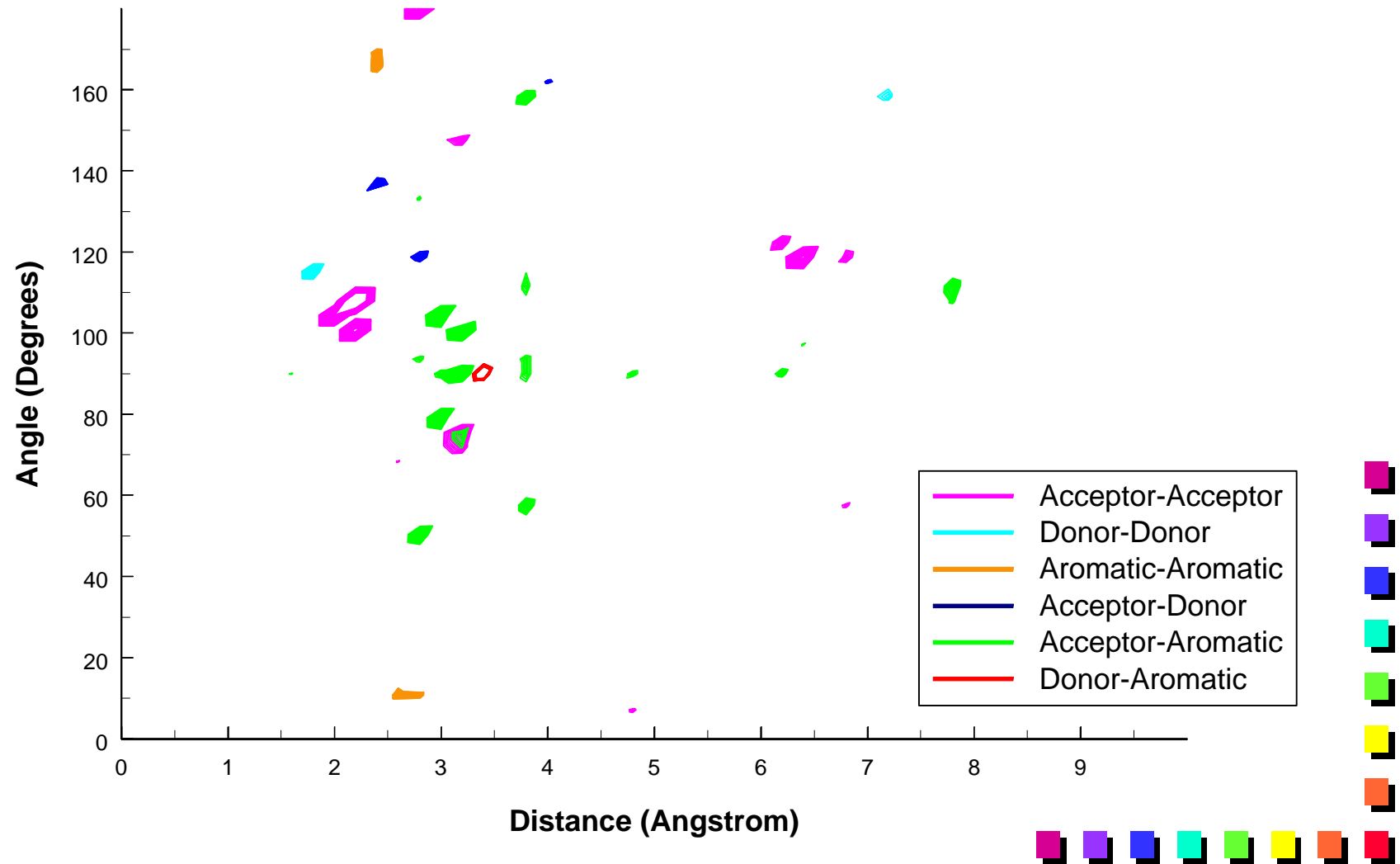
# Hypotensives : Pharmacophore Map

(10% countour threshold)



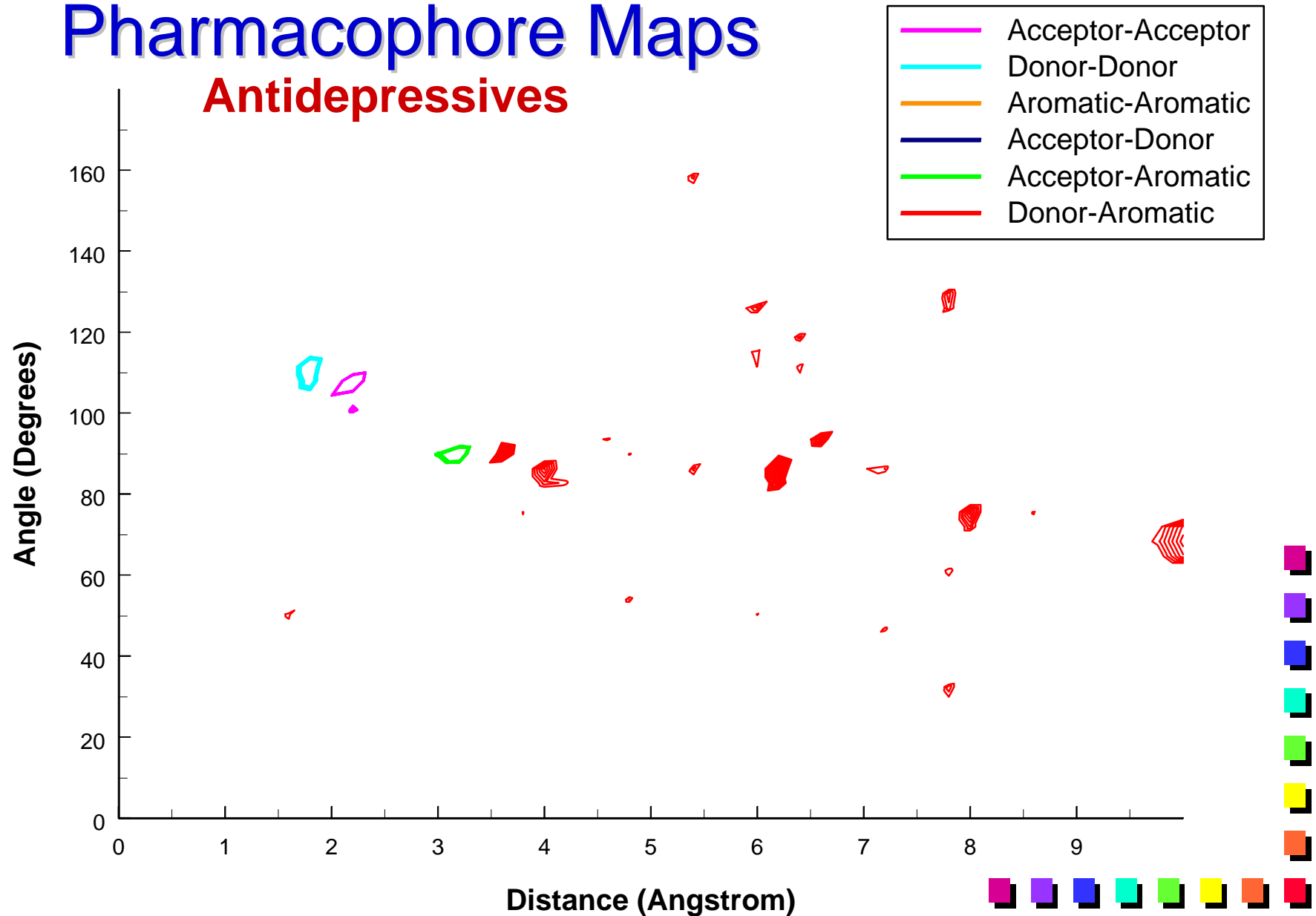
# Pharmacophore Maps

## Neuroleptics



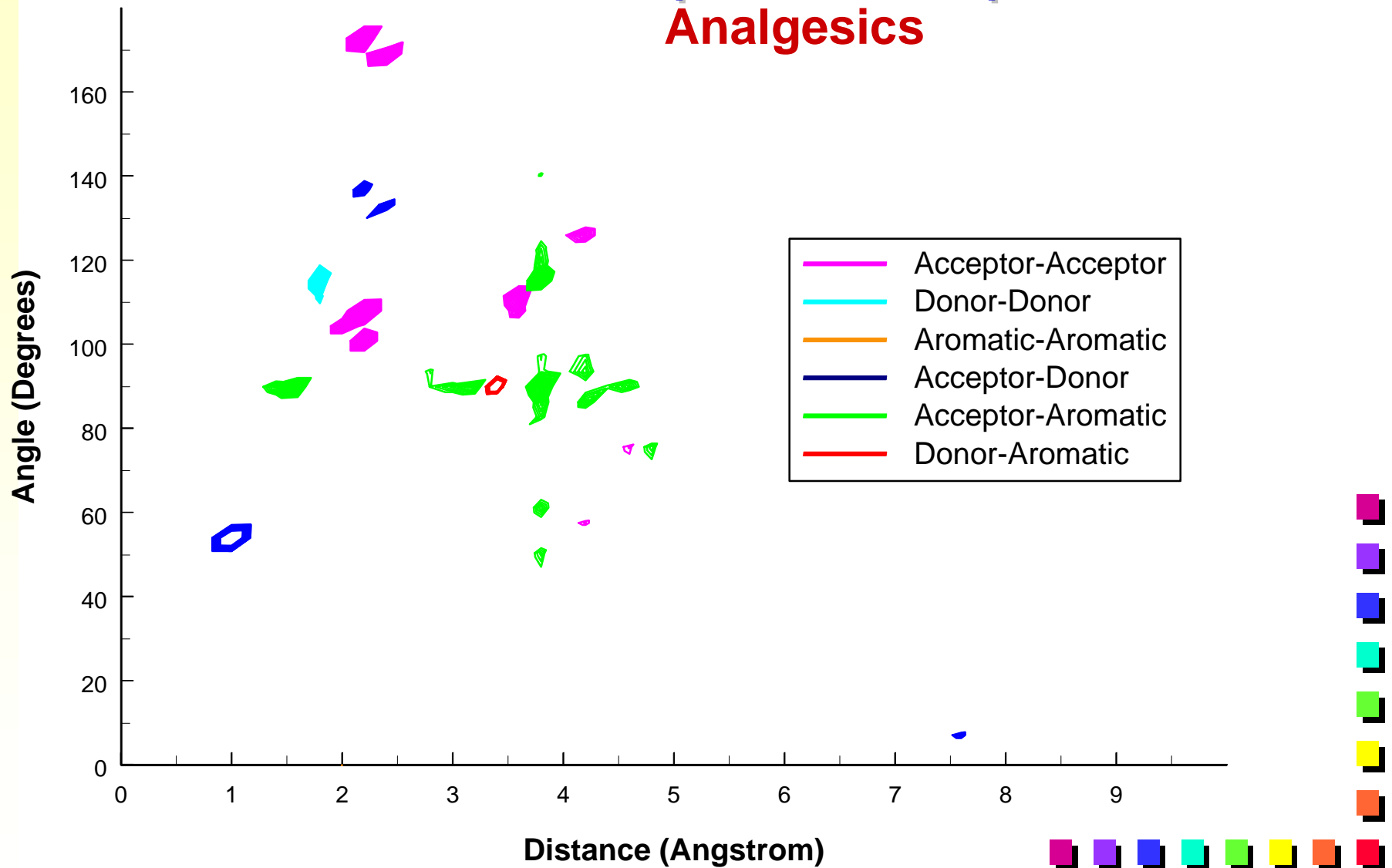
# Pharmacophore Maps

## Antidepressives



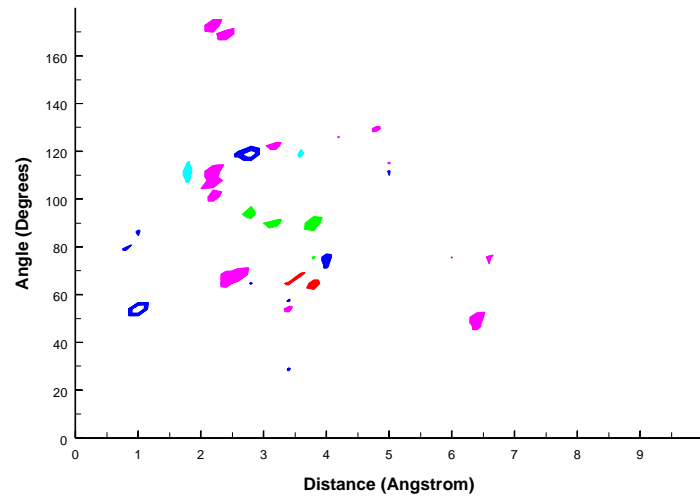
# Pharmacophore Maps

## Analgesics

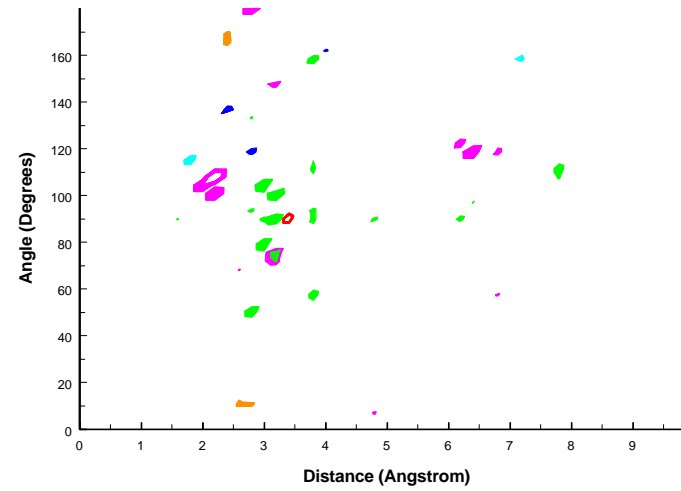


# Pharmacophore Maps

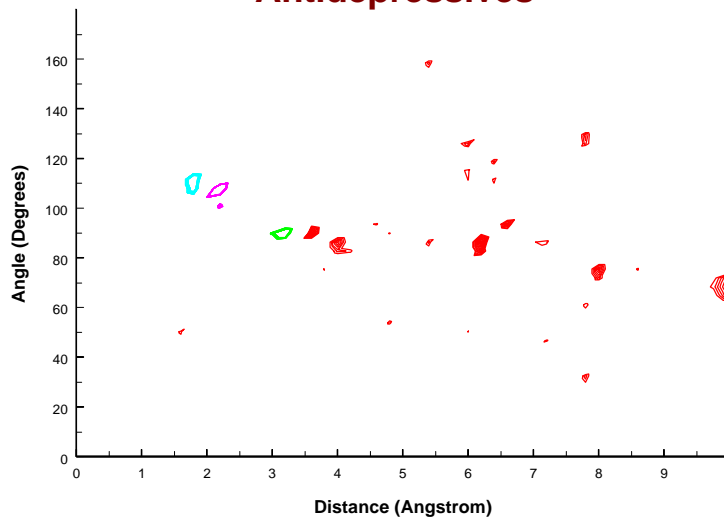
## Hypotensives



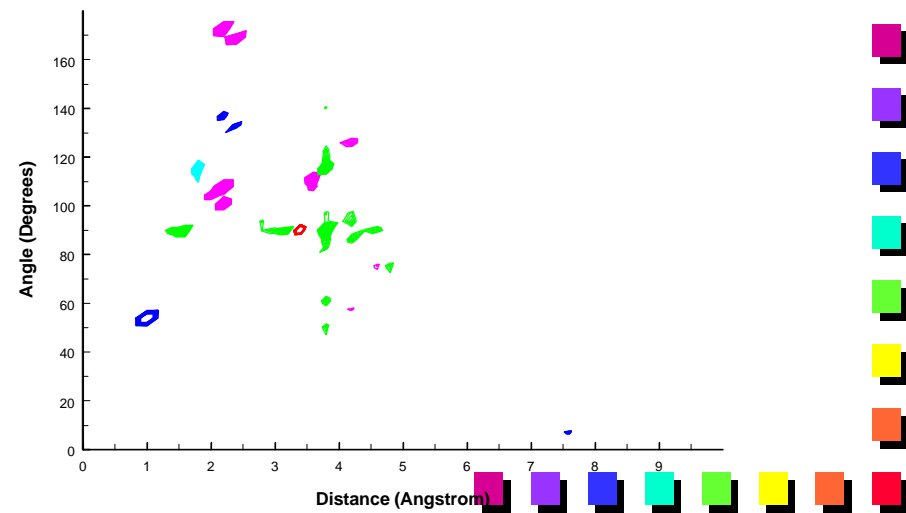
## Neuroleptics



## Antidepressives



## Analgesics



# Acknowledgments



**Oxford Molecular**  
*Solutions for Discovery Research*



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Dr. Peter Gedeck

Dr. Harald Lanig

