

**S-IN Soluzioni  
Informatiche**

*for Chemistry and Pharmaceutical Chemistry*

**MATH/CHEM/COMP 2008 Conference**

# **General and Independent Approaches for the Prediction of $\text{Na}^+, \text{K}^+$ -ATPase Inhibition at the Digitalis Receptor**

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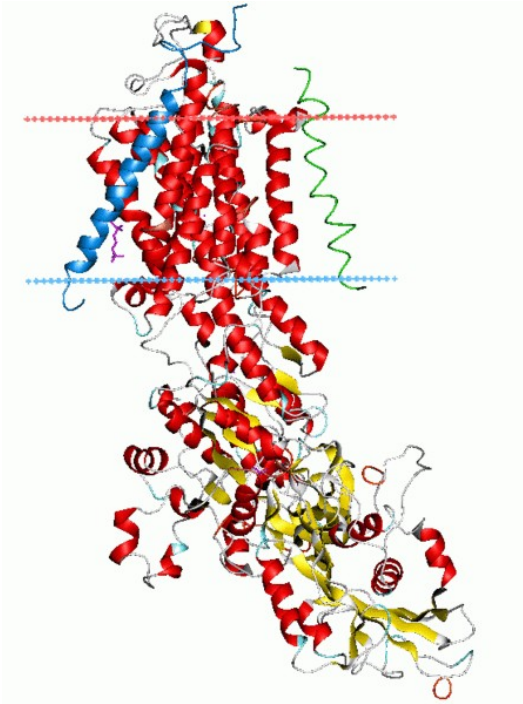
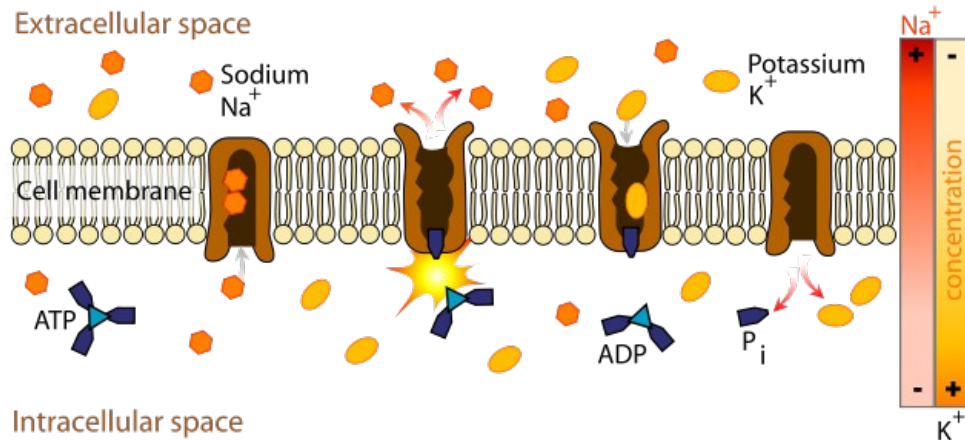
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# Outline

- Introduction
- Objective and Methods
- Dataset
- Results
- Conclusion

# Na<sup>+</sup>,K<sup>+</sup>-ATPase



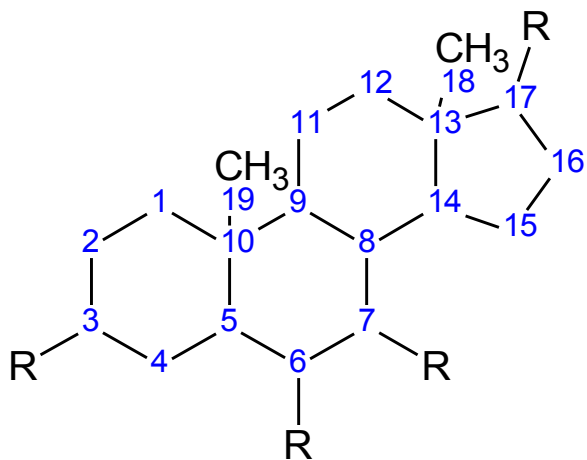
- Heterodimeric transmembrane protein complex
- Use hydrolysis of ATP to drive ion transport across cell membrane
- Cardiac glycoside binding inhibits the enzyme's ATPase activity, producing a positive inotropic action.

# Objective & Methods

- Objective: Generation of different QSAR models able to predict Na<sup>+</sup>,K<sup>+</sup>-ATPase inhibition based on different sets of descriptors.
- Methods:
  - DRAGON Descriptors
  - QSDAR model with simulated 1D-HNMR spectral data
  - 3DQSAR model with PHASE

# Dataset

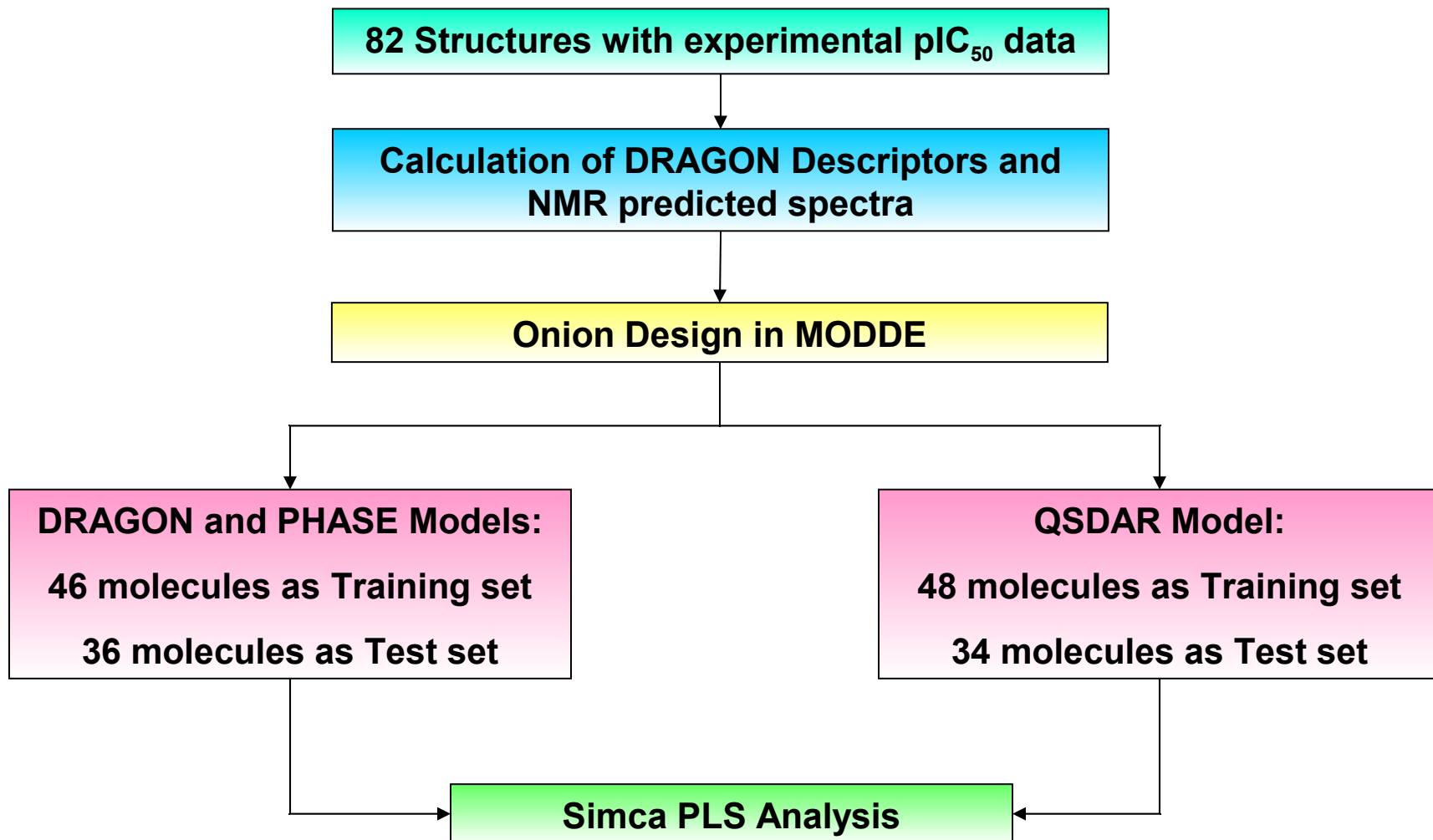
- 82 Structure with experimental  $pIC_{50}$  data
- Activity range from 4.2 to 8



Pos 17: carbonyl or OH group

Pos 3: oxime group

# Dataset



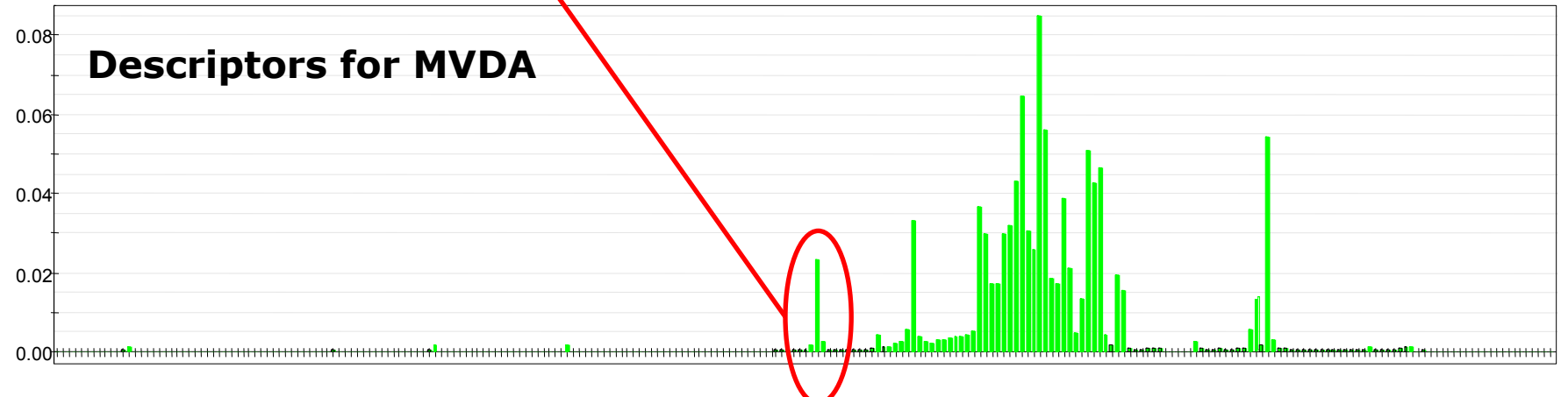
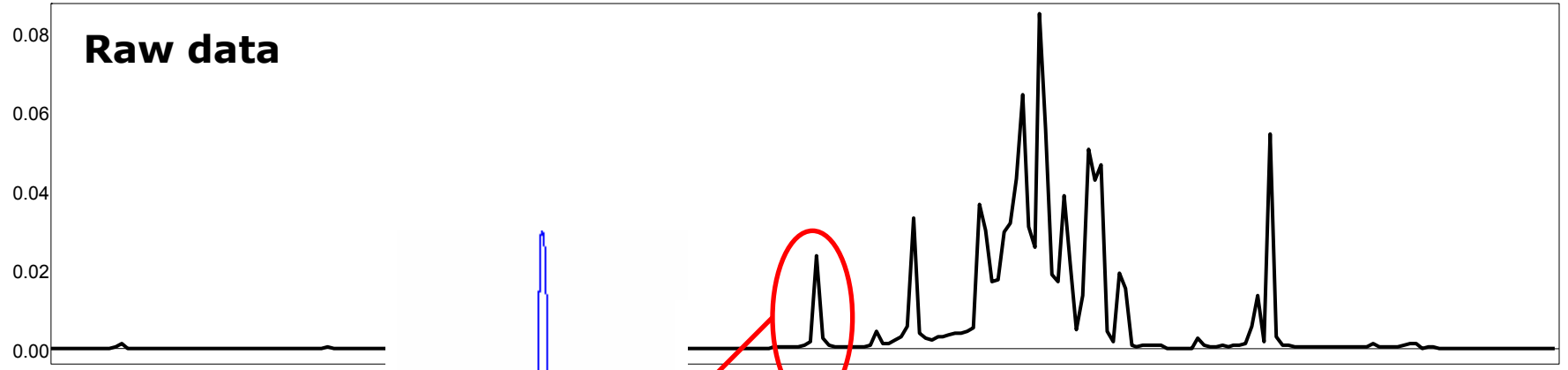
# DRAGON Descriptors

- DRAGON is an application for the calculation of molecular descriptors originally developed by the Milano Chemometrics and QSAR Research Group.
- In Version 5.4 about 1600 descriptors are available:
  - Constitutional descriptors
  - Randic molecular profiles
  - Topological descriptors
  - Geometrical descriptors
  - Walk and path counts
  - RDF descriptors
  - Connectivity indices
  - 3D-MoRSE descriptors
  - Information indices
  - WHIM descriptors
  - 2D autocorrelations
  - GETAWAY descriptors
  - Edge adjacency indices
  - Functional group counts
  - BCUT descriptors
  - Atom-centred fragments
  - Topological charge indices
  - Charge descriptors
  - Eigenvalue-based indices
  - Molecular properties

# QSDAR

- Quantitative Spectral Data Activity Relationship
- Finding relationships directly between molecular spectra (NMR) and biological effects.
- use of computer-predicted, rather than instrumentally acquired spectra, for model building purposes (Faster)

# Bucket Integration



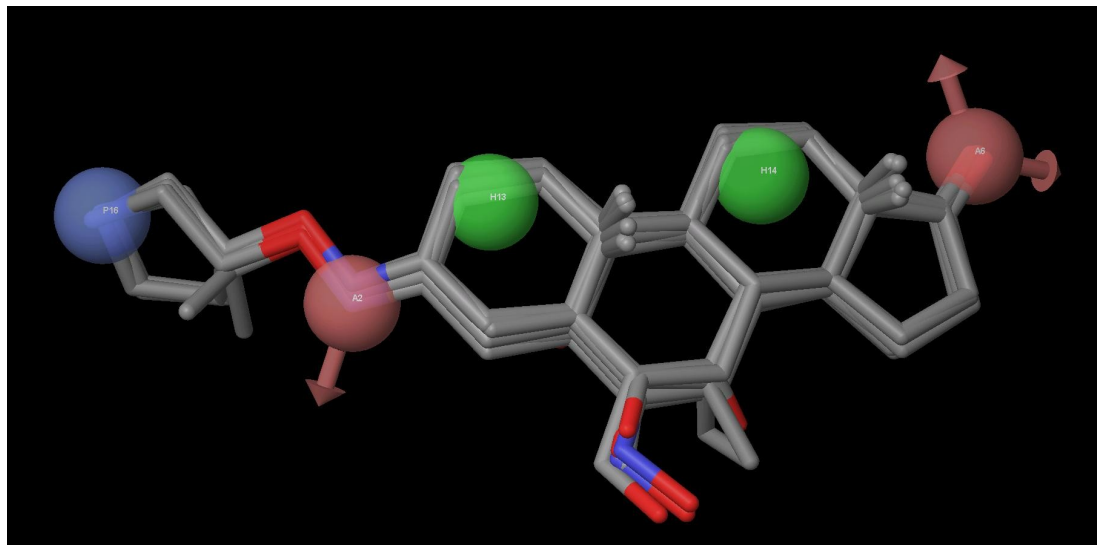
# QSDAR Methods

- Predicted 1D H-NMR spectra with ACD/H-NMR Predictor 11.01
  - Mixture of sample and benzene 1:1, solvent chloroform, 300 Mhz, predicted from  $-1.0$  to  $11.0$  ppm
- Bucket Integration with ACD/NMR Manager 11.01
  - Integration grid 0.4 ppm
  - Variable with less than 3 values different from 0 were excluded
    - To avoid models being influenced from single-value variables
    - Usual when working with fragmental descriptors that tend to produce scattered matrices

# 3D-QSAR with PHASE

- Common Pharmacophore Perception via PHASE
  - Conformers generation:
    - Mixed MCMM/LMOD with pre- and post-processing with Macromodel
    - Max 100 conf, 10 Kcal from minimum
  - Searches:
    - Most active molecules as reference ligands ( $pIC_{50} > 7.5$ )
    - Search 5,6,7 point pharmacophore
    - Standard feature set

# PHASE Pharmacophore



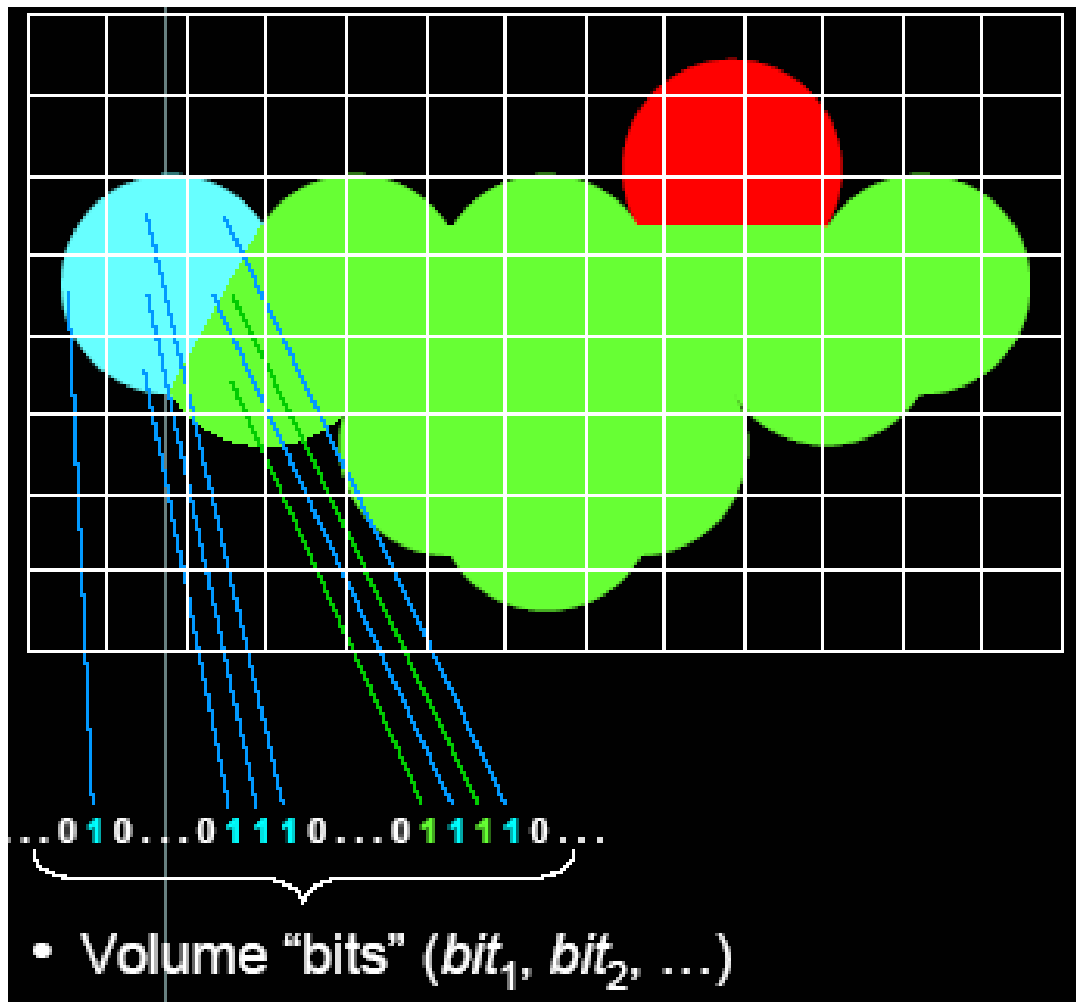
5 Features pharmacophore:

2 Hbond acceptor, 2 Hydrophobic, 1 Positive charge

# Build QSAR Model with PHASE

- Atom-Based Models
  - 6 atom categories (D, H, N, P, W, X)
  - Van der Waals radii
  - All atoms treated
- Pharmacophore-Based Models
  - Site categories (A, D, H, N, P, R)
  - Adjustable radii
  - Only matching sites treated

# Build QSAR Model



| Mol | Bit String              | Activity |
|-----|-------------------------|----------|
| 1   | 0 0 1 0 0 0 1 0 0 0 ... | 5.38     |
| 2   | 0 1 0 0 0 0 1 0 1 0 ... | 6.72     |
| 3   | 0 0 0 0 1 0 0 0 1 0 ... | 7.82     |
| 4   | 0 1 1 0 0 0 0 1 0 0 ... | 5.66     |
| .   |                         |          |
| .   |                         |          |
| .   |                         |          |



**PLS Regression**

# Build QSAR Model

- Generate Models for Multiple Hypothesis
  - Browse statistics
  - Visualize individual models
- Atom-Based Models
  - Requires clean overall alignments
  - Potential to identify excluded volumes due to steric clashes
- Pharmacophore-Based Models
  - Considers only pharmacophore sites that match hypothesis
  - Each matching site is a sphere with a user adjustable radius
  - Less sensitive to conformational variations in remainder of structure
  - Assumes that pharmacophore model explains SAR (i.e., no steric clashes)

## 3D-QSAR with PHASE

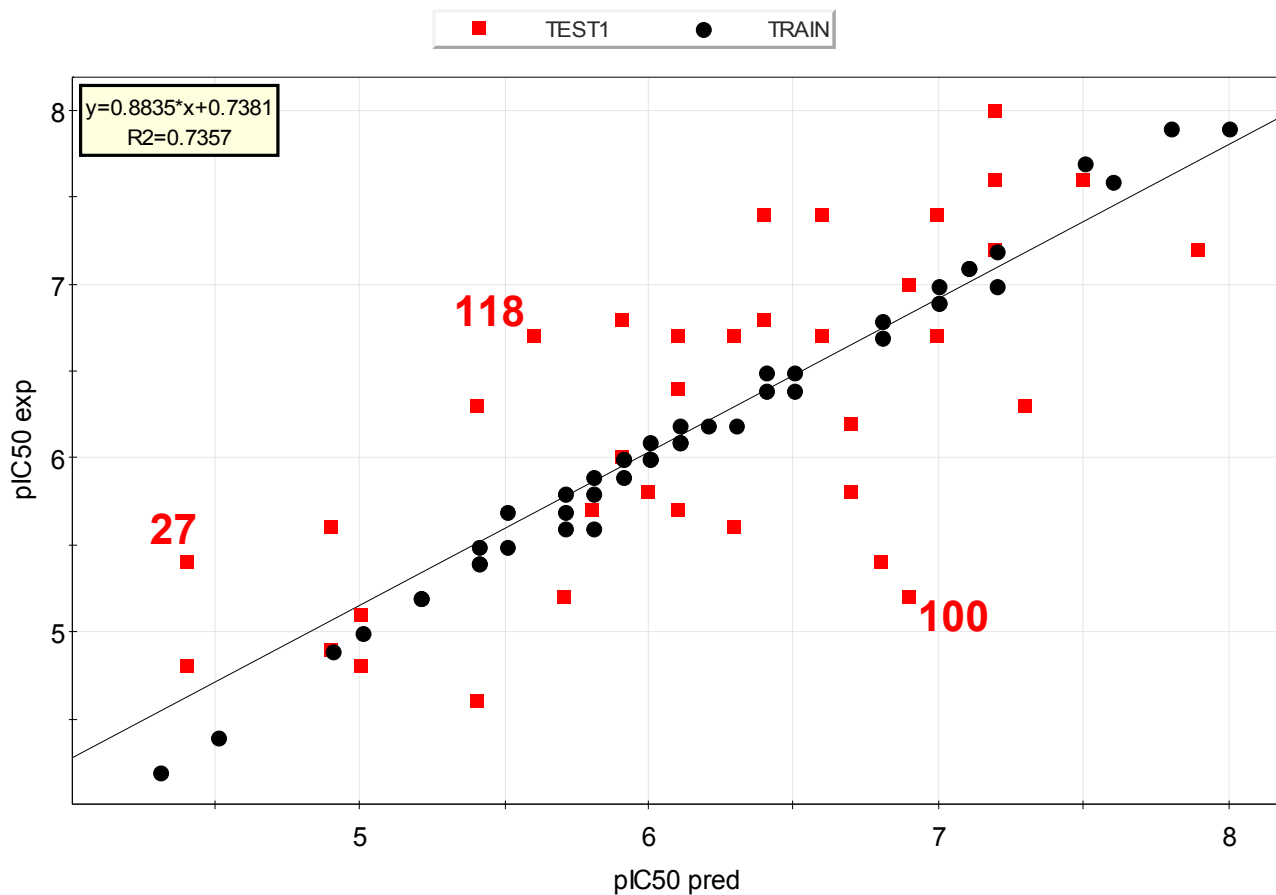
- 3DQSAR Model generation for ATPase
  - Atom based model with standard feature tolerances
  - Grid Spacing 0.5 Å
  - 3 PLS Components

# Results

| model               | R2   | Q2   | SDEC | SDEP |
|---------------------|------|------|------|------|
| <b>DRAGON - OSC</b> | 0.99 | 0.97 | 0.1  | 0.68 |
| <b>QSDAR - OSC</b>  | 0.83 | 0.82 | 0.37 | 0.64 |
| <b>PHASE 3DQSAR</b> | 0.77 | 0.76 | 0.42 | 0.66 |

- Orthogonal Signal Correction filter were applied to Dragon and QSDAR models
  - All variable were included for Dragon model
  - Variable with VIP > 1 for QSDAR model
    - Increase model stability in terms of Q2
- R2 and Q2 for Dragon and QSDAR are good as expected when OSC is applied
- Phase model also show good fitting and predictivity
- Predictive power towards external test set is similar between models

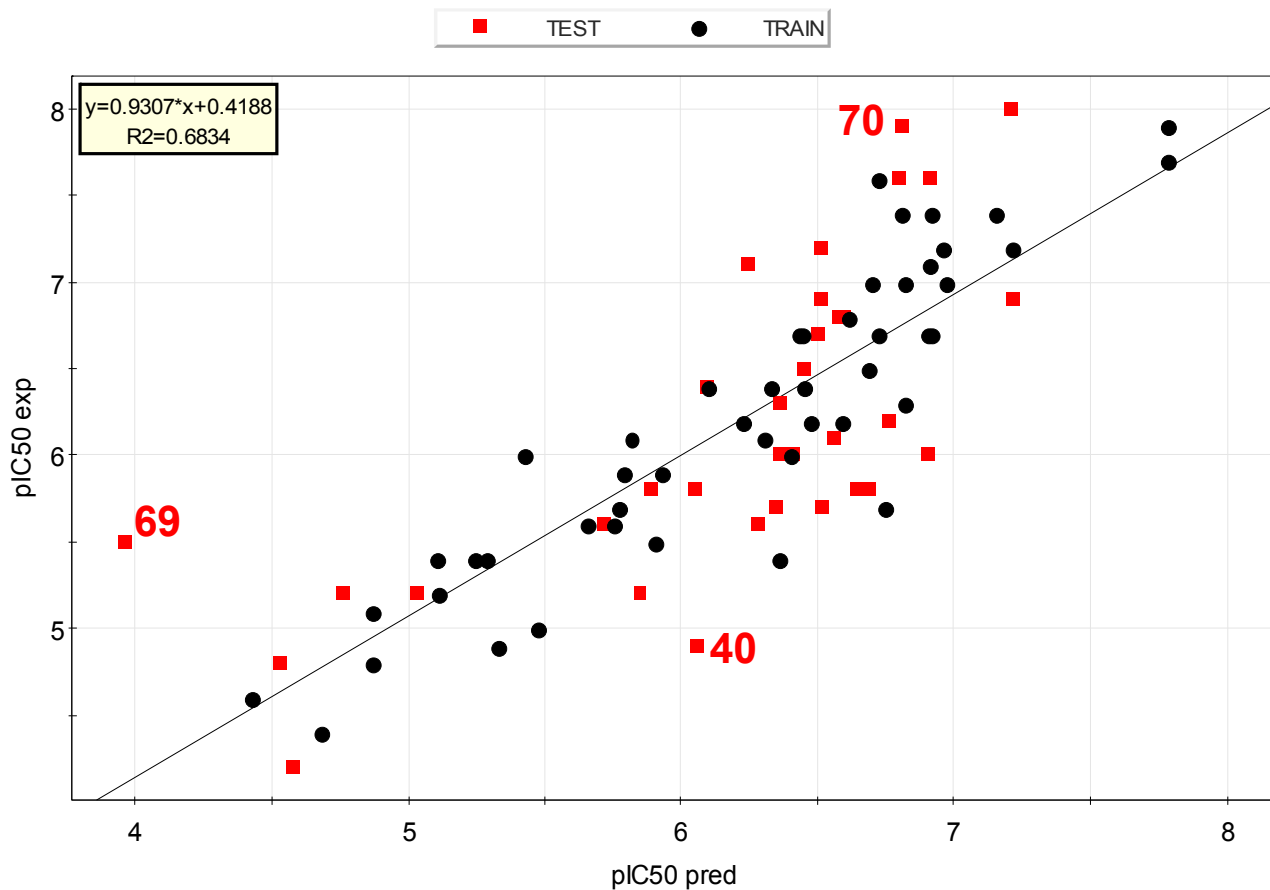
# Results - Dragon



| ID  | piC50 exp | piC50 pred | error |
|-----|-----------|------------|-------|
| 100 | 5.2       | 6.9        | 1.7   |
| 27  | 5.4       | 6.8        | 1.4   |
| 118 | 6.7       | 5.6        | 1.1   |

SIMCA-P+ 11 - 14/05/2008 12.32.02

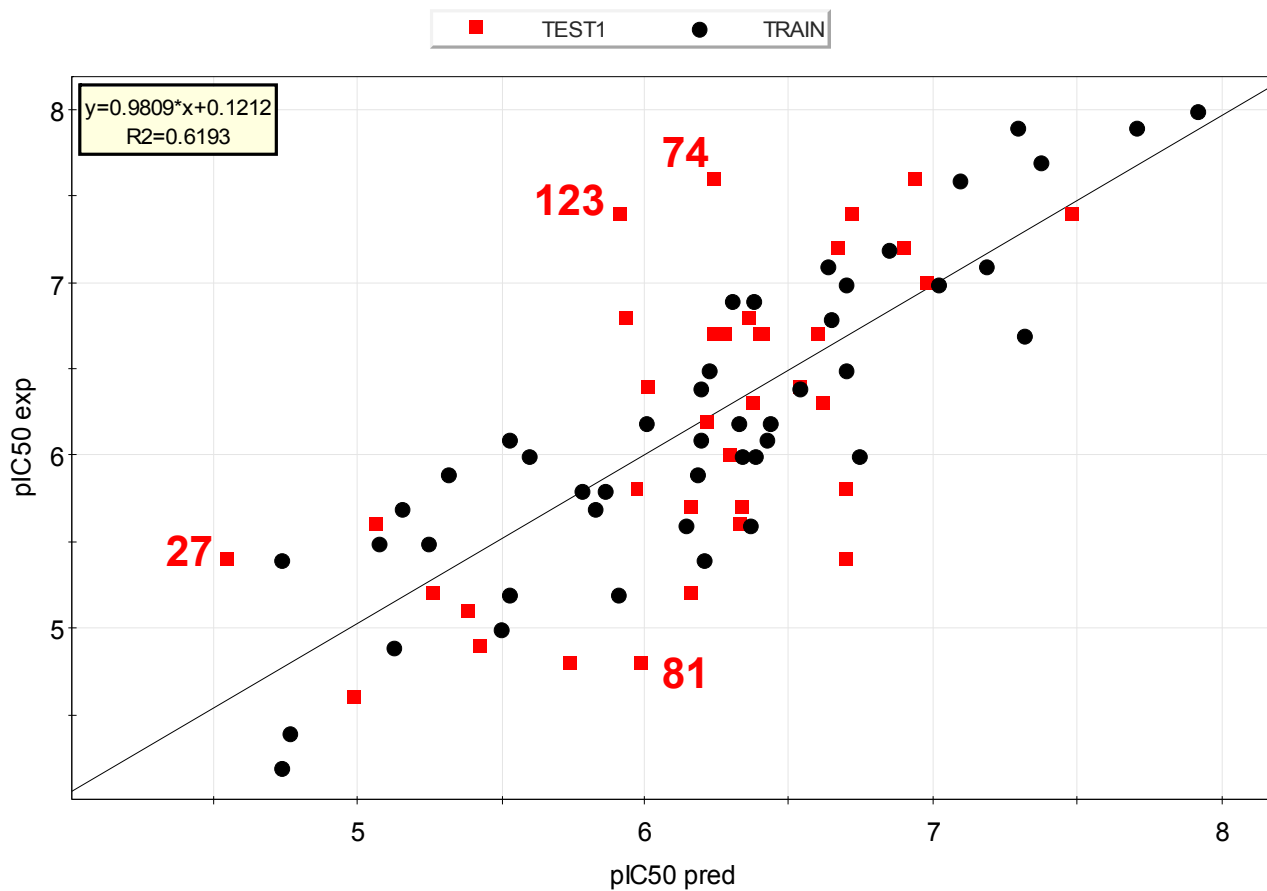
# Results - QSDAR



| ID | pIC50 exp | pIC50 pred | error |
|----|-----------|------------|-------|
| 69 | 5.5       | 4.0        | 1.5   |
| 40 | 4.9       | 6.1        | 1.2   |
| 70 | 7.9       | 6.8        | 1.1   |

SIMCA-P+ 11 - 14/05/2008 12.35.26

# Results - Phase



| ID  | pIC50 exp | pIC50 pred | error |
|-----|-----------|------------|-------|
| 123 | 7.4       | 5.9        | 1.5   |
| 74  | 7.6       | 6.2        | 1.4   |
| 27  | 5.4       | 6.7        | 1.3   |
| 81  | 4.8       | 6.0        | 1.2   |

SIMCA-P+ 11 - 14/05/2008 12.37.06

# Results

- The Dragon and the QSDAR models are sensitive to presence/absence of particular functional groups
- Errors in these models are mainly due to particular substitutions not well represented in training sets, or when the activity is related to chirality
- The Phase model is more sensitive to alignment of the molecules to the pharmacophore than presence/absence of particular features
  - Pharmacophoric features are common to all structures, SAR could be explained only with atom-based model

# Results - Consensus

- Consensus method:
  - Average between pIC50 predicted from Dragon and Phase
    - Suitable for all molecules, because Training set and Test set are the same for both models
  - Average of all 3 models
    - Suitable only for 13 molecules included in test set in each model
- Results:

| model                                   | R2   | Q2   | SDEC | SDEP |
|---|------|------|------|------|
| Average Dragon - Phase                  | 0.93 | 0.93 | 0.23 | 0.61 |
| Average Dragon - Phase - QSDAR (13 mol) |      |      |      | 0.44 |

- Slight improvement of SDEP for both consensus models...

# Conclusions

- ATPase inhibition could be predicted with good level of accuracy using different QSAR models
- The consensus between different approaches leads to better prediction
  - Dragon and NMR descriptors are related to chemical structure/fragment
    - But Interpretation is difficult...
  - The Pharmacophore is sensitive to alignment and conformation
    - Interpretation is straightforward
- Other kind of descriptors could be used for prediction, e.g EVA (IR spectra) or PASS

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