

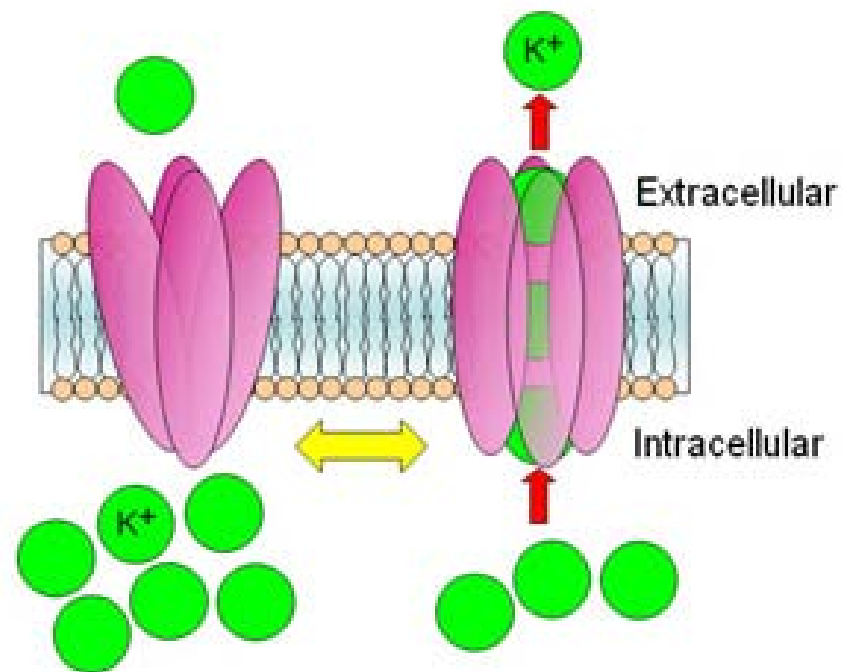
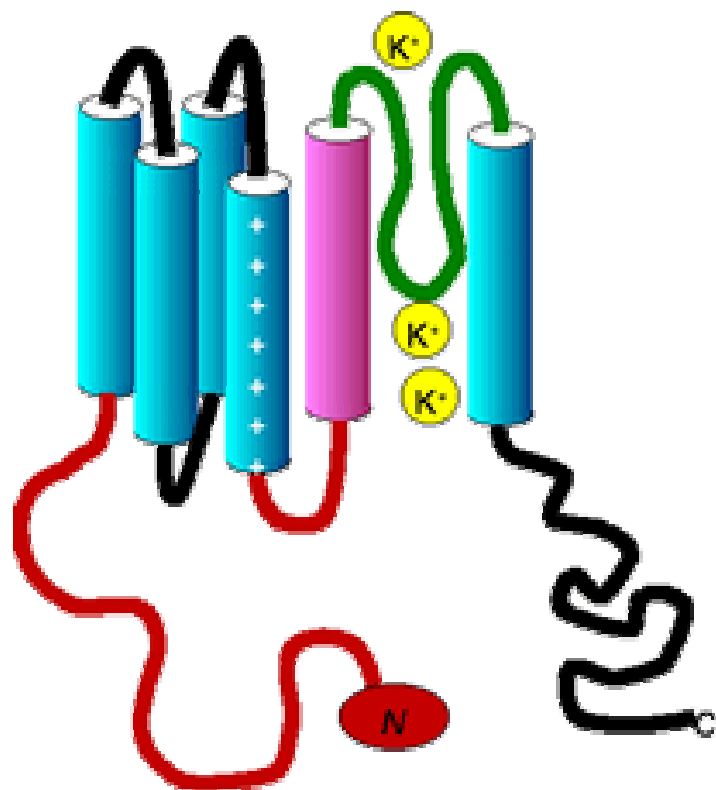
# Prediction of HERG affinity values using independent approaches

Elena Fioravanzo

S-IN Soluzioni Informatiche, Vicenza

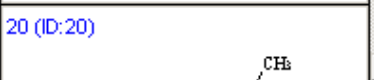
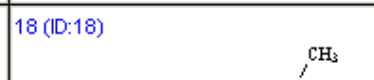
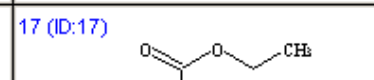
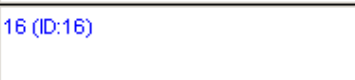
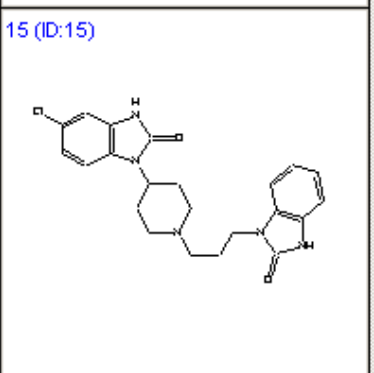
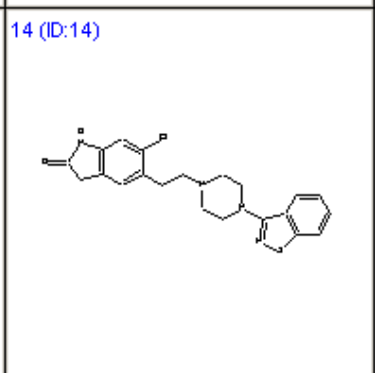
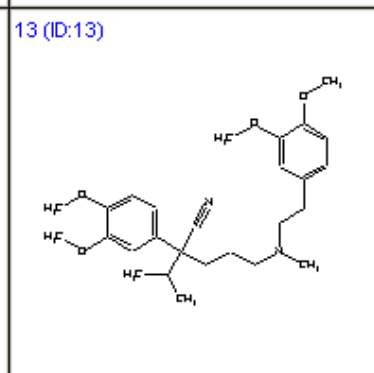
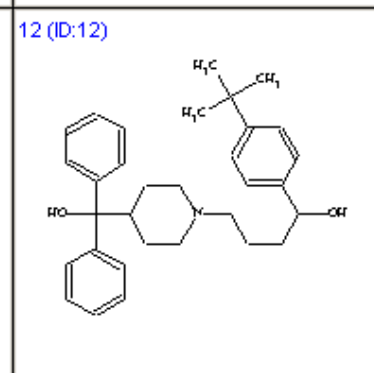
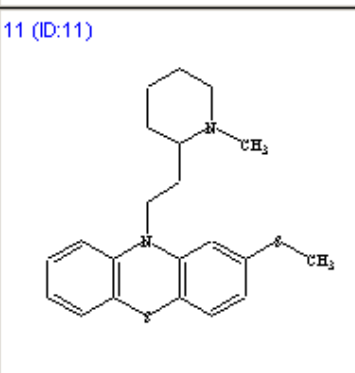
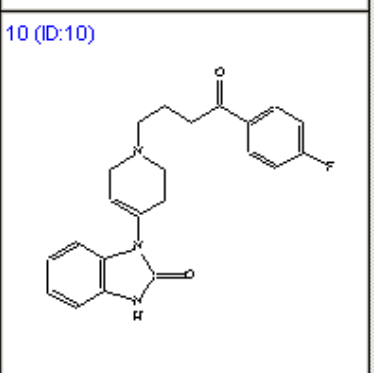
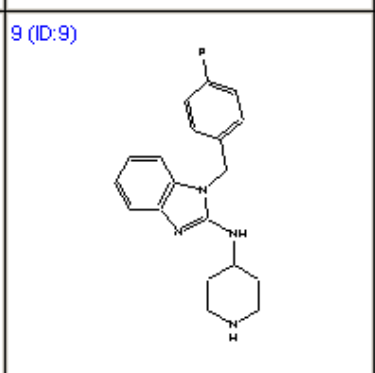
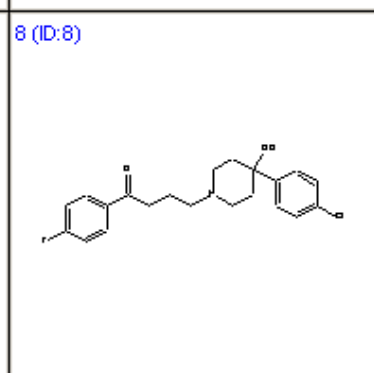
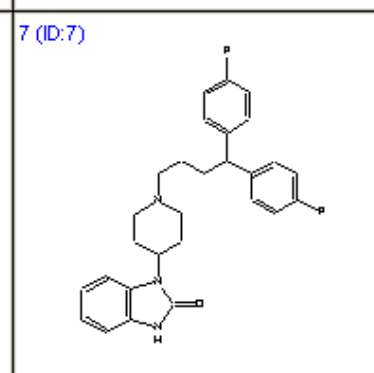
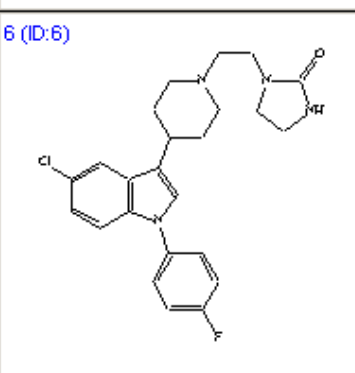
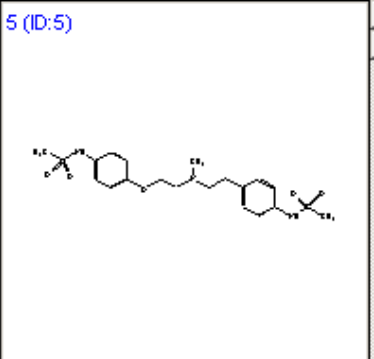
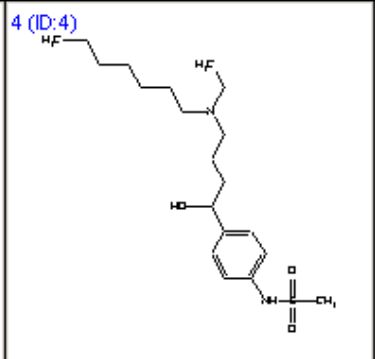
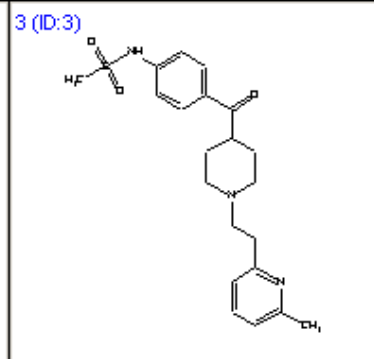
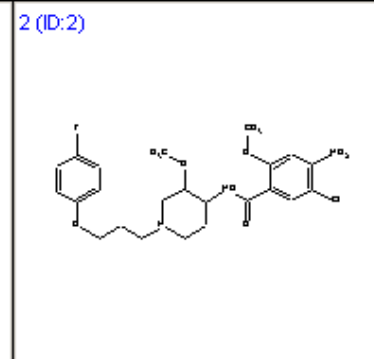
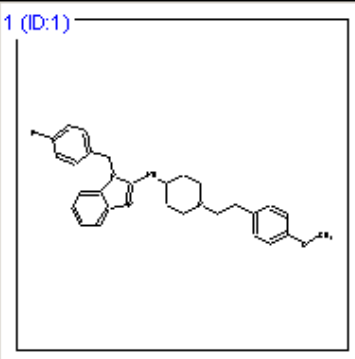
- hERG K<sup>+</sup> channels
- Data set
- Methods
  - Descriptors
    - EVA
    - DRAGON (Talete)
  - PLS models (SIMCA-P, Umetrics)
- Results
- Methods
  - PASS & QikProp (Schrödinger)
- Results

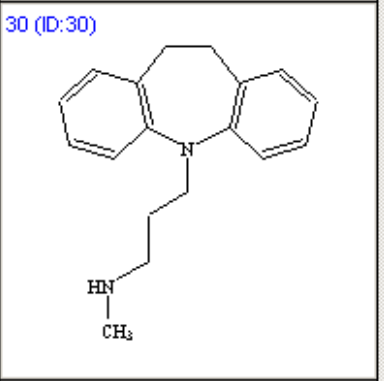
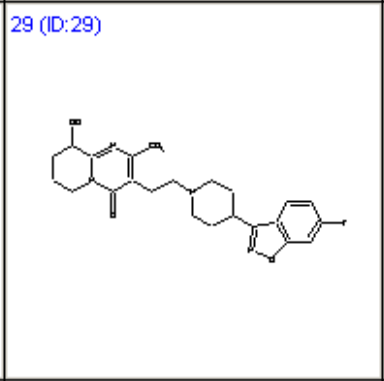
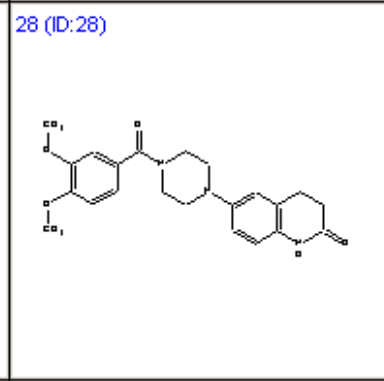
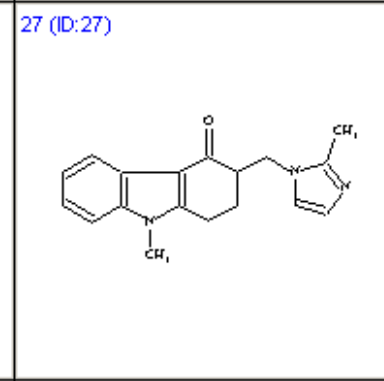
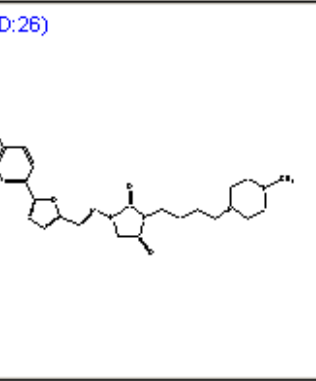
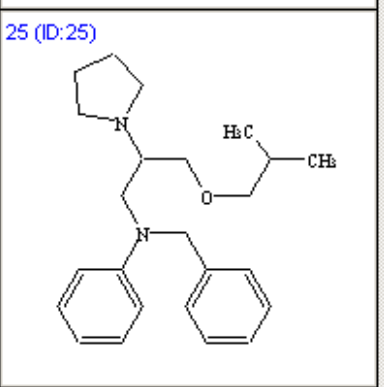
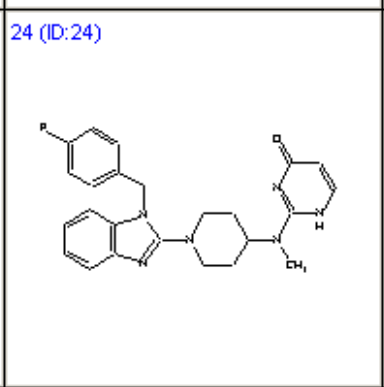
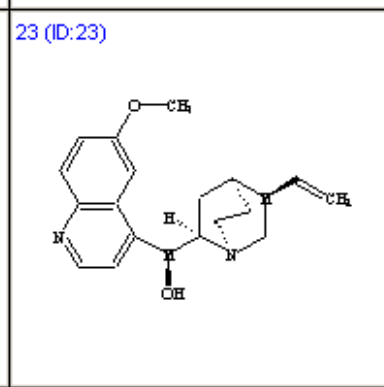
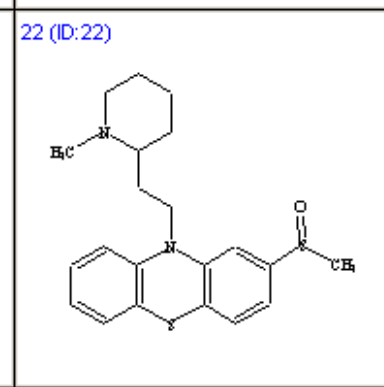
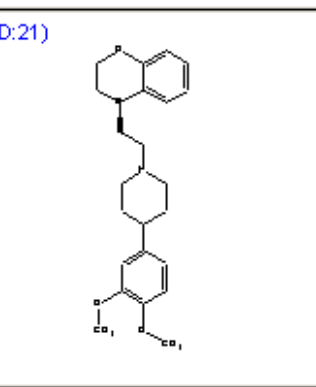
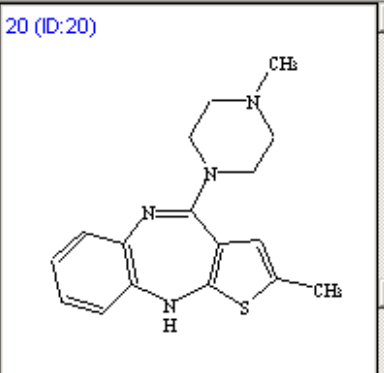
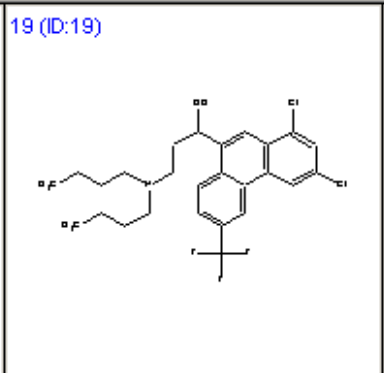
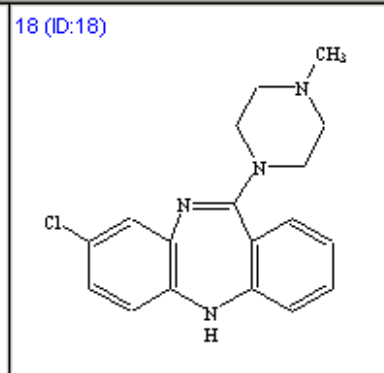
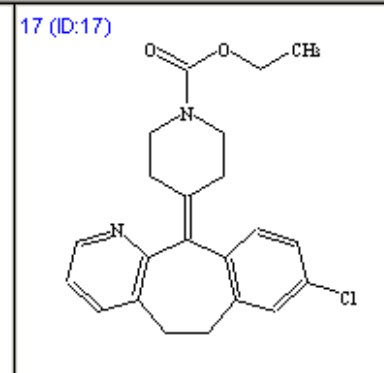
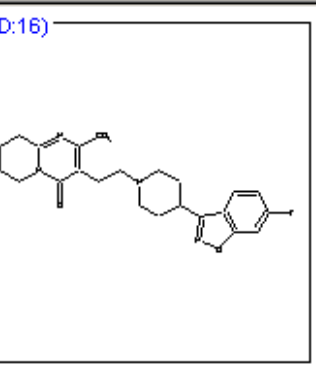
# hERG K<sup>+</sup> channels



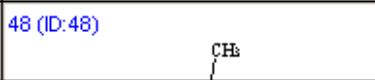
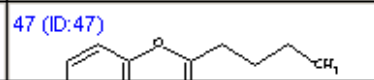
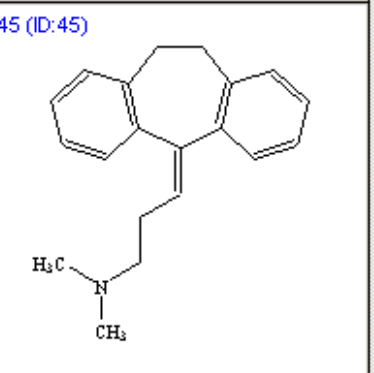
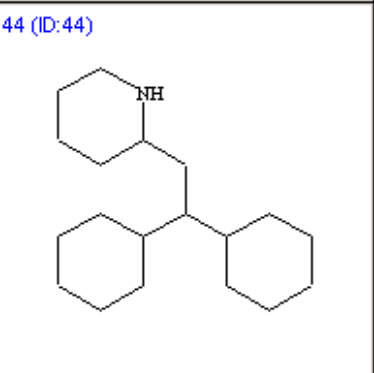
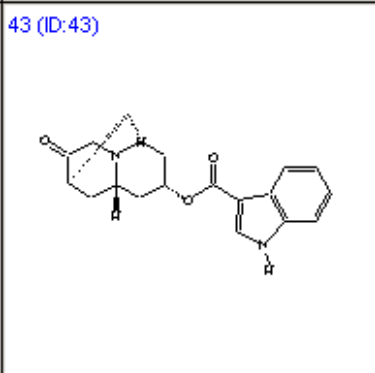
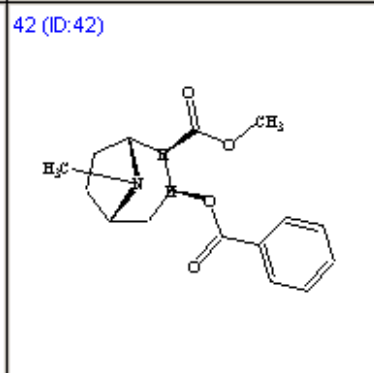
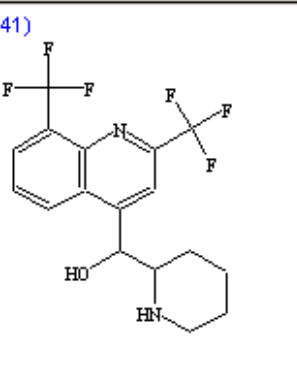
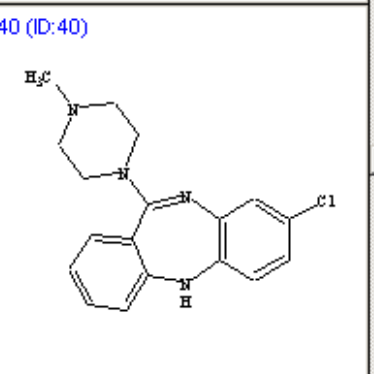
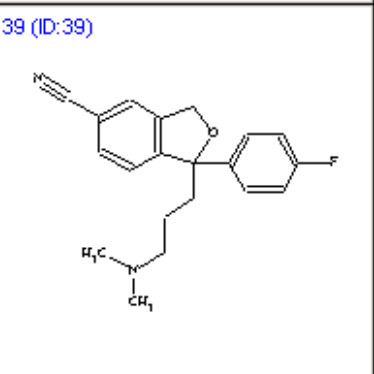
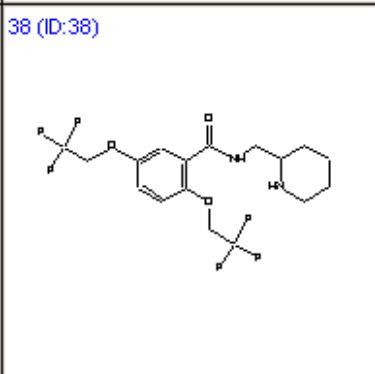
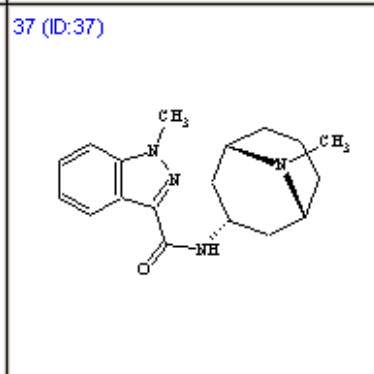
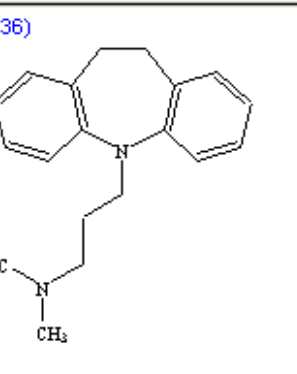
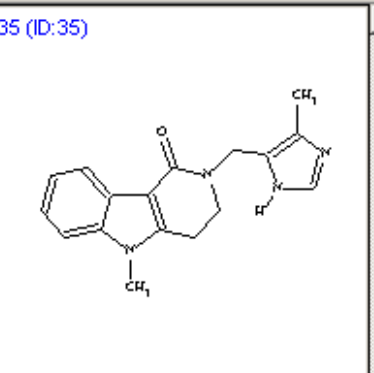
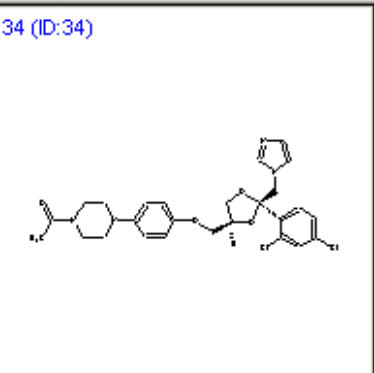
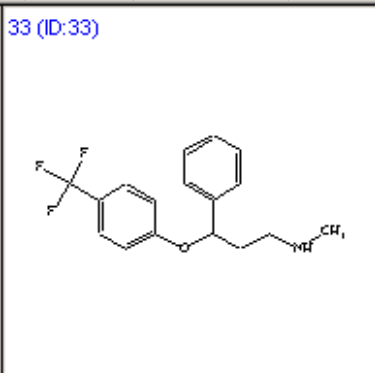
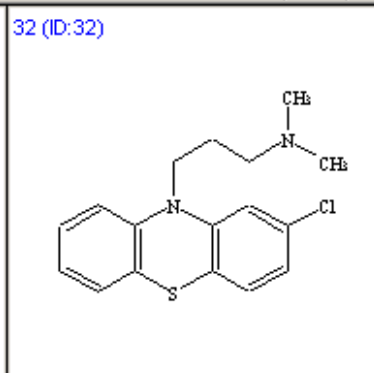
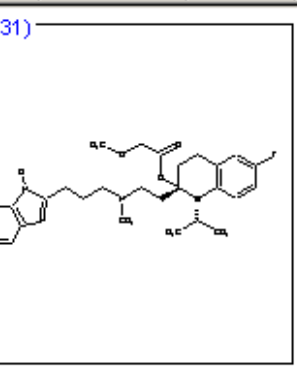
Ion Channel Schematic of Potassium (K<sup>+</sup>) channel

- 70 compounds with experimental hERG IC50 values from the literature
  1. A. Cavalli, E. Poluzzi, F. De Ponti, M. Recanatini, *J. Med. Chem.* **2002**, 45, 3844.
  2. G.M. Keserü, *Bioorg. Med. Chem. Lett.* **2003**, 13, 2773.
  3. S. Ekins, W.J. Crumb, R. Dustan Sarazan, J.H. Winkel, S.A. Wrighton, *J. Pharma. Exp. Therapeutics (JPET)* **2002**, 301, 427
  
- Data set for PLS: 60 compounds from ref. 2

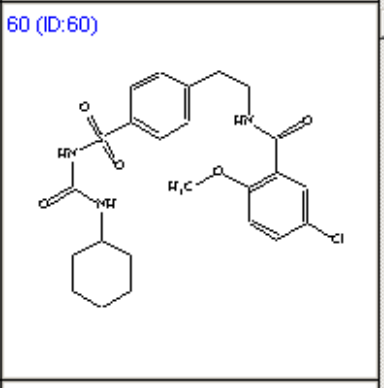
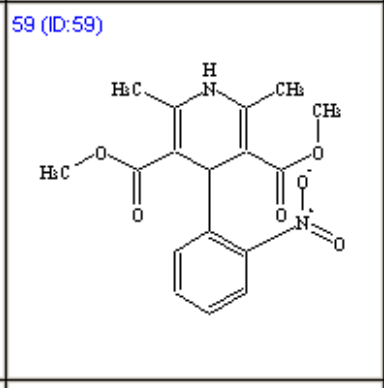
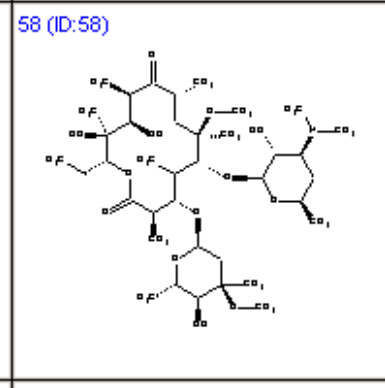
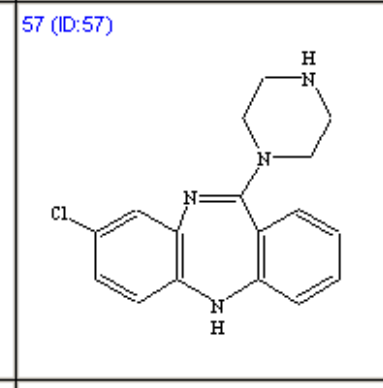
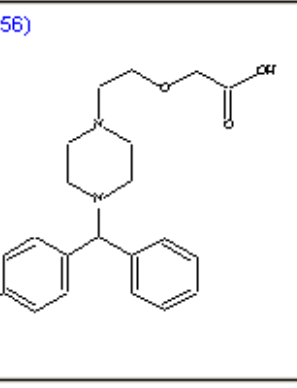
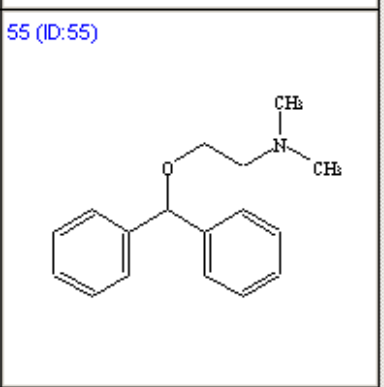
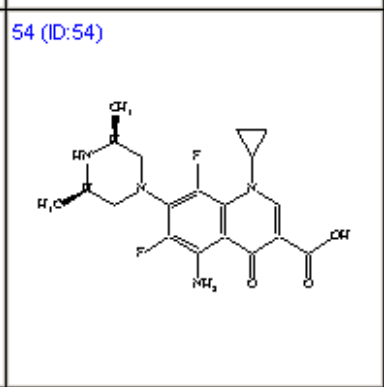
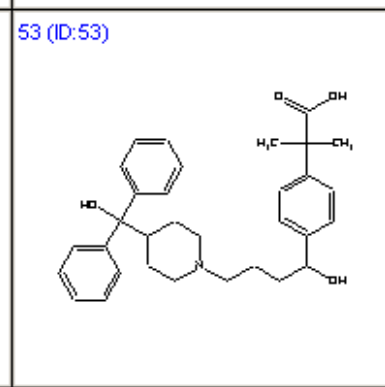
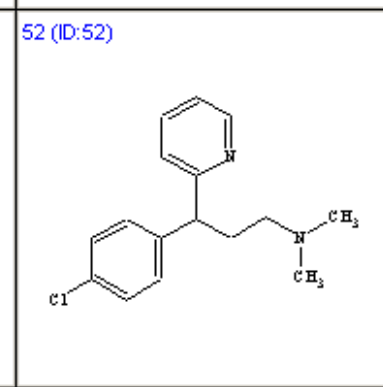
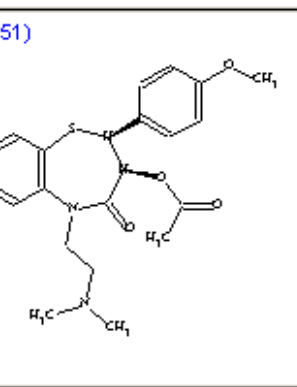
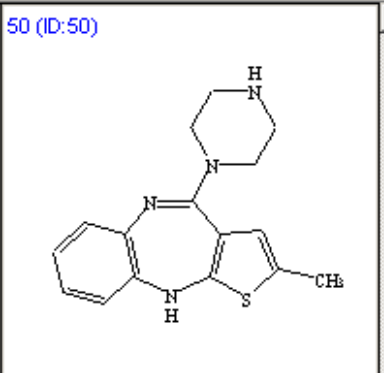
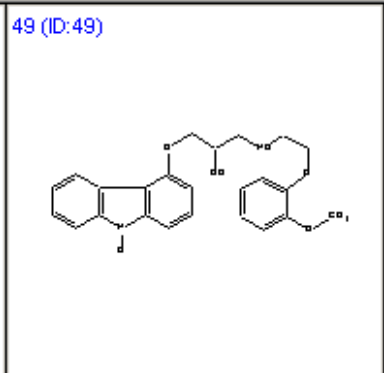
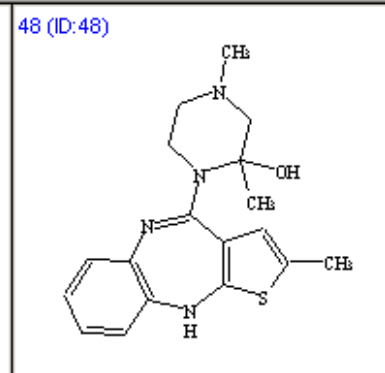
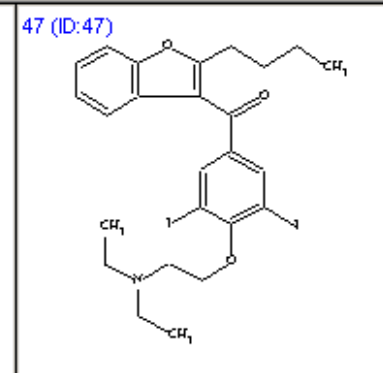
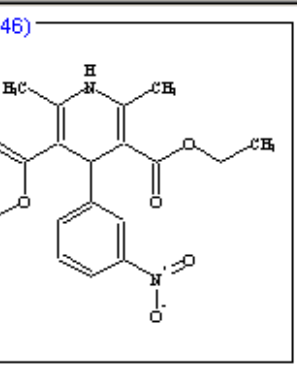


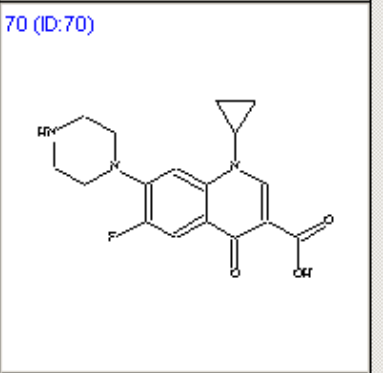
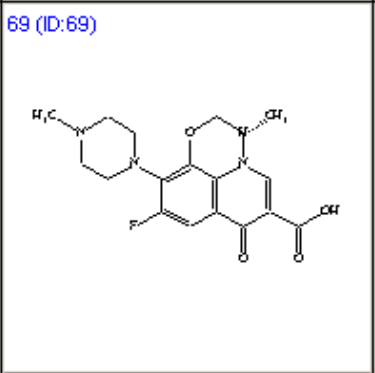
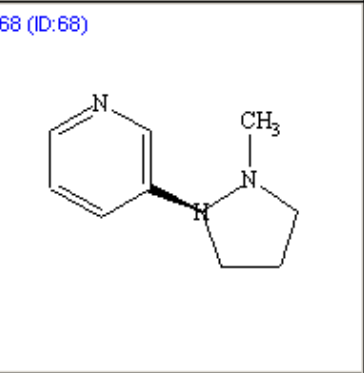
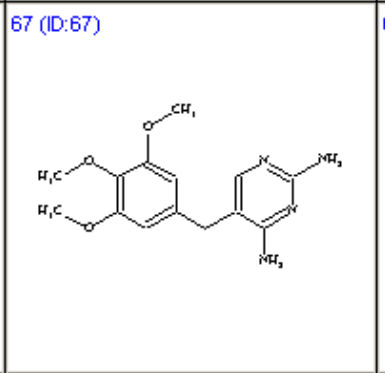
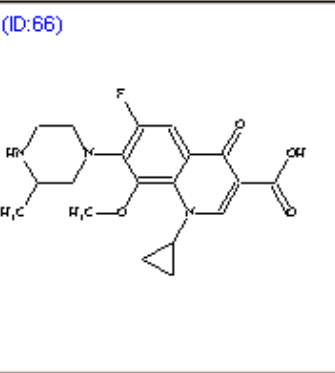
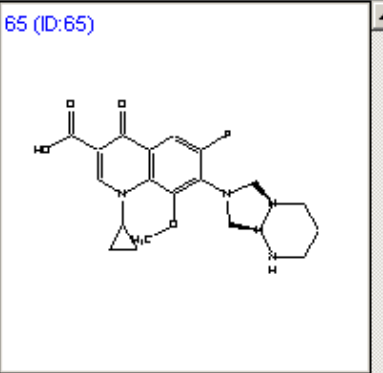
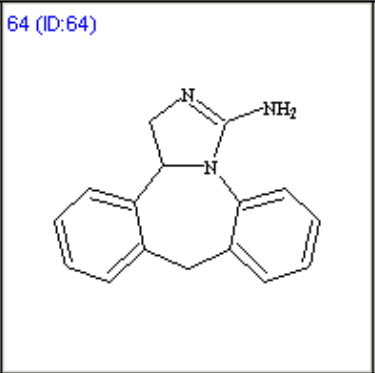
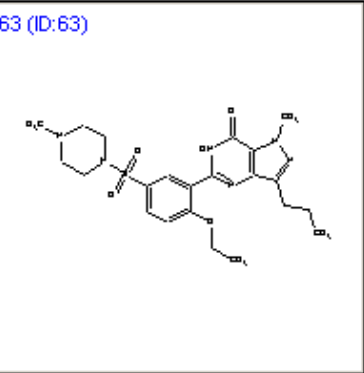
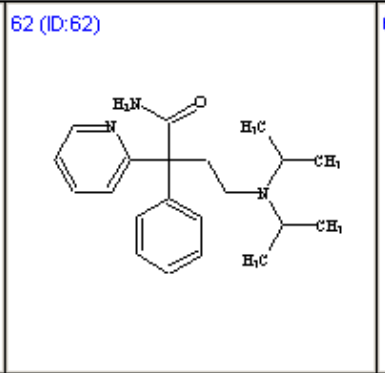
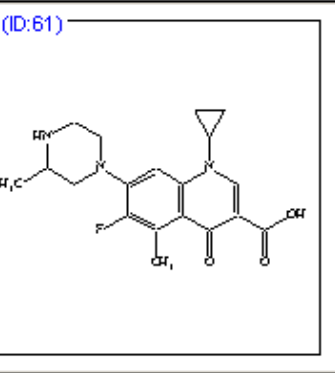


Navigation icons: Home, Back, Forward, Print, Copy, Paste, Undo, Redo, Find, and other utility icons.

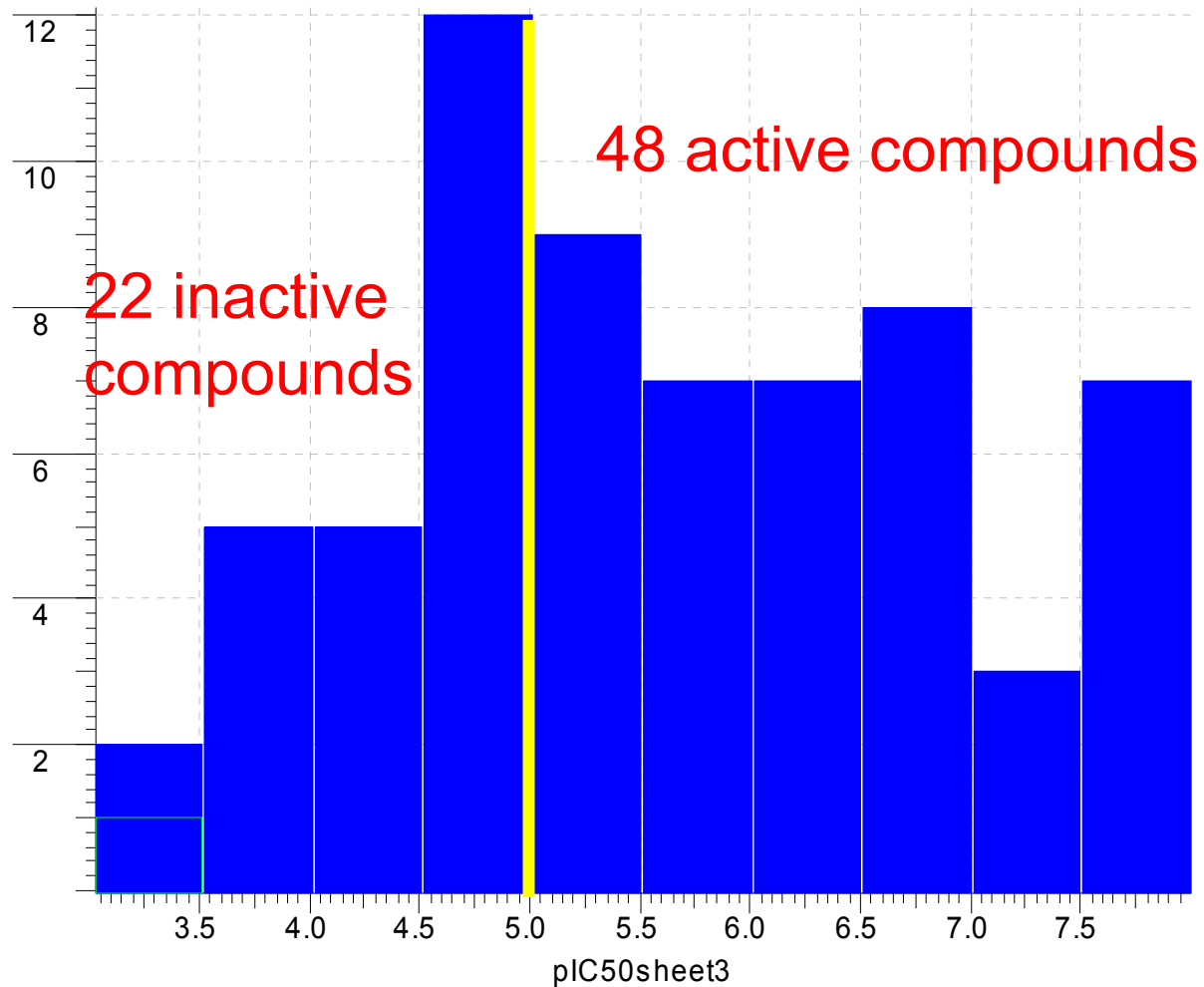


Office Microsoft





# Data set: pIC50



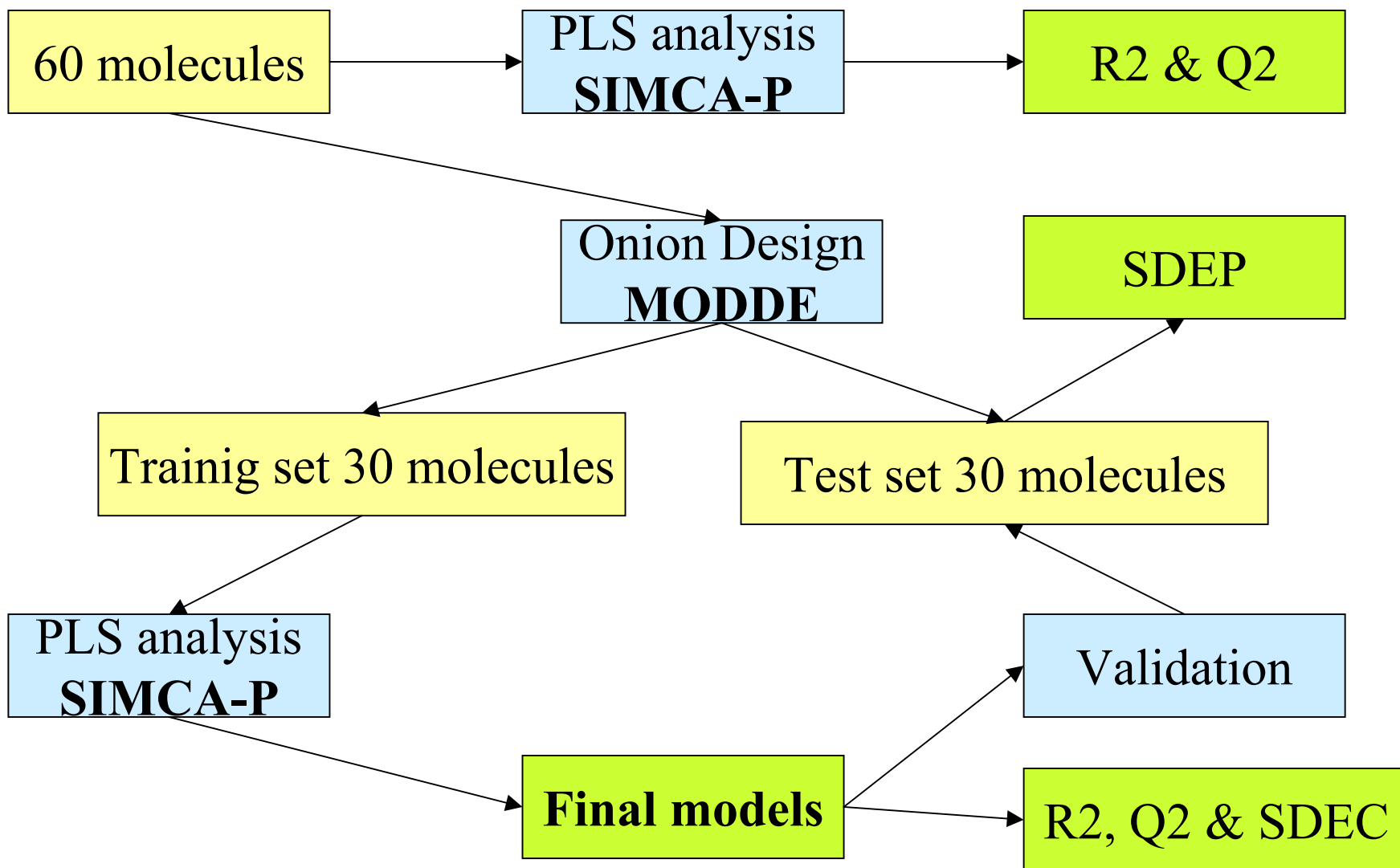
A descriptor of molecular structure based on theoretically derived normal coordinate EigenVAlue

A.M. Ferguson, T. Heritage, P. Jonathon, S.E. Pack, *J. CAMD* **11**, 143-152, 1997.

## IR Spectrum

- Characteristic of entire molecule
- Bands at or near the same frequency for certain groups of atoms
- Fundamental vibrations influenced by steric and electrostatic effects: nature & size of neighboring atoms.

- 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



Descriptors	X	PCs	Obj.	R2	Q2	SDEC	SDEP
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### Initial models

DRAGON ALL	418	3	60	0.817	<b>0.678</b>		
DRAGON 2Dautocorr.	48	2	60	0.657	<b>0.527</b>		
EVA	182	2	60	0.665	<b>0.533</b>		

### Final models (R2 Q2 SDEC for training and SDEP for test set)

DRAGON ALL	329	3	30	0.831	0.703	0.523	<b>0.939</b>
DRAGON 2Dautocorr.	34	2	30	0.727	0.572	0.663	<b>0.827</b>
EVA	86	2	30	0.745	0.615	0.669	<b>0.985</b>

## PASS

### *(Prediction of Activity Spectra for Substances)*

- Prediction of **Activity Spectra** for Substances
- List of probabilities for a given compound to be active or inactive towards specific **macromolecular targets** and **pharmacological effects**.
- The probabilities **Pa** and **Pi** are the measures of belonging to the subsets of "active" and "inactive" compounds.
- The program **PASS** was trained to predict the probability of hERG activity, using a set of molecules with  $pIC_{50}$  values greater than or equal to 5.0.

## Properties

- Log Po/w
- Caco-2 and MDCK permeability (consensus score)
- Log S
- log BB
- Skin permeability
- logIC50 HERG K<sup>+</sup> channel blockage
- Log K hsa
- CNS activity
- Free energy of solvation
  - hexadecane
  - octanol
  - water
- Polarizability

■ Threshold value  $pIC_{50} = 5$

■ QikProp

- Correctly predicted: **96% of active**
- Correctly predicted: **45% of inactive**
- **12 false negative and 6 false positive**

■ PASS ( $p_a = 3$ )

- Correctly predicted: **75% of active**
- Correctly predicted: **73% of inactive**
- **2 false negative and 12 false positive**

## ■ S-IN Soluzioni Informatiche

- Dott. Massimo Mabilia
- Dott. Marco Parenti
- Dott.ssa Cristina Ferrari

## ■ A.C.R.A.F.

- Dott. Nicola Cazzolla
- Dott.ssa Lucia Durando
- Dott.ssa Rosella Ombrato