

Benchmarking the Reliability of QikProp

Correlation between Experimental and Predicted Values

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Computational Methods

SCHRÖDINGER.

- **QikProp** Jorgensen *et al.* *Adv. Drug Del. Rev.*, 2002, **54**, 355.

- **CAChe 7.5**  THE POSSIBILITIES ARE INFINITE

- **ADME Boxes** Mannhold *et al.* *QSAR Comb. Sci.* 2003, **22**, 466.

Pharma
Algorithms

- **NIST** National Institute of Standards and Technology



QikProp V2.1.103 - Properties Predictions for
aspirin

Primary Metabolites & Reactive FGs:

> Reactive FG: unhindered ester

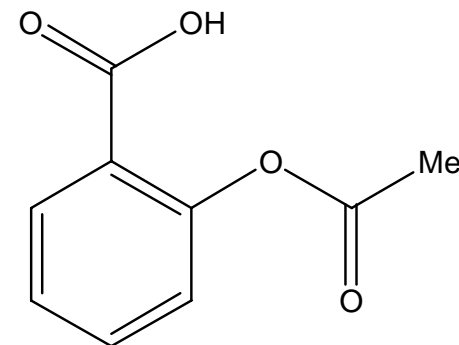
Principal Descriptors: (Range 95% of Drugs)

Solute	Molecular Weight	=	180.160 (130.0 / 725.0)
Solute	Dipole Moment (D)	=	1.800 (1.0 / 12.5)
Solute	Total SASA	=	386.215 (300.0 / 1000.0)
Solute	Hydrophobic SASA	=	88.966 (0.0 / 750.0)
Solute	Hydrophilic SASA	=	140.486 (7.0 / 330.0)
Solute	Carbon Pi SASA	=	156.763 (0.0 / 400.0)
Solute	Weakly Polar SASA	=	0.000 (0.0 / 150.0)
Solute	Molecular Volume (A ³)	=	614.017 (500.0 / 2000.0)
Solute	No. of Rotatable Bonds	=	2.000 (0.0 / 15.0)
Solute as Donor -	Hydrogen Bonds	=	1.000 (0.0 / 6.0)
Solute as Acceptor -	Hydrogen Bonds	=	4.500 (2.0 / 20.0)
Solute Globularity (Sphere = 1)		=	0.905 (0.75 / 0.95)
Solute Ionization Potential (eV)		=	9.589 (7.9 / 10.5)
Solute Electron Affinity (eV)		=	0.528 (-0.7 / 1.7)

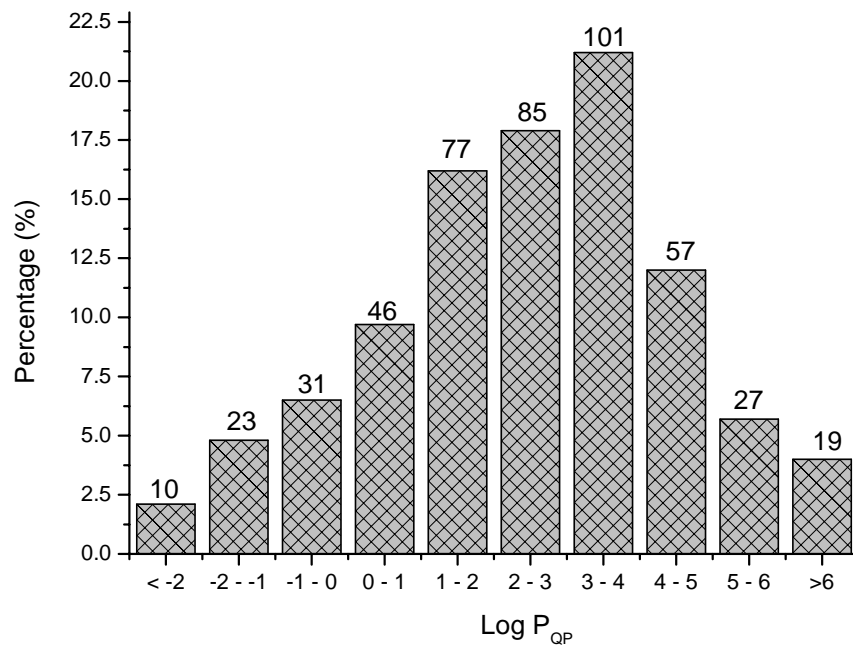
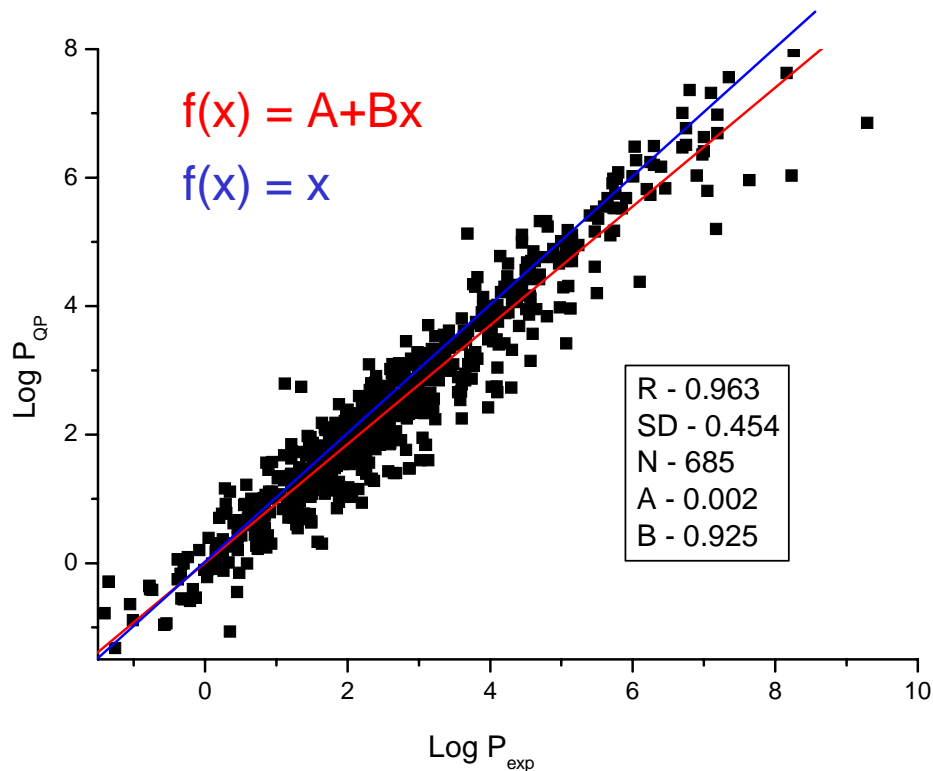
Predictions for Properties:

QP Polarizability (Angstroms ³)	=	18.632 (13.0 / 70.0)
QP log P for hexadecane/gas	=	6.256 (4.0 / 18.0)
QP log P for octanol/gas	=	9.759 (8.0 / 43.0)
QP log P for water/gas	=	8.162 (5.0 / 48.0)
QP log P for octanol/water	=	0.684 (-2.0 / 6.0)
QP log S for aqueous solubility	=	-1.648 (-6.0 / 0.5)
QP log S - conformation independent	=	-1.652 (-6.0 / 0.5)
QP log K hsa Serum Protein Binding	=	-0.754 (-1.5 / 1.2)
QP log BB for brain/blood	=	-0.723 (-3.0 / 1.0)
No. of Primary Metabolites	=	0 (1.0 / 8.0)*
Predicted CNS Activity (-- to ++)	=	-
HERG K⁺ Channel Blockage: log IC50	=	-3.515 (concern below -5)
Apparent Caco-2 Permeability (nm/sec)	=	92.316 (<25 poor, >500 great)
Apparent MDCK Permeability (nm/sec)	=	85.360 (<25 poor, >500 great)
QP log Kp for skin permeability	=	-3.364 (Kp in cm/hr)
Jm, max transdermal transport rate	=	1.750 (micrograms/cm ² -hr)

A * indicates a violation of the 95% range. # stars = 1



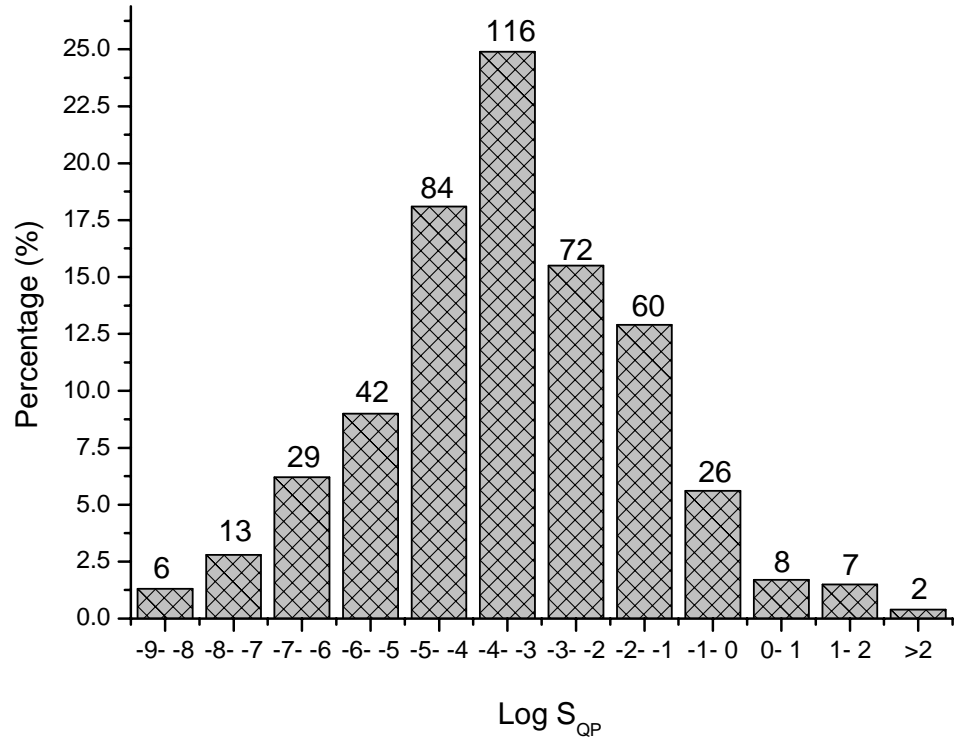
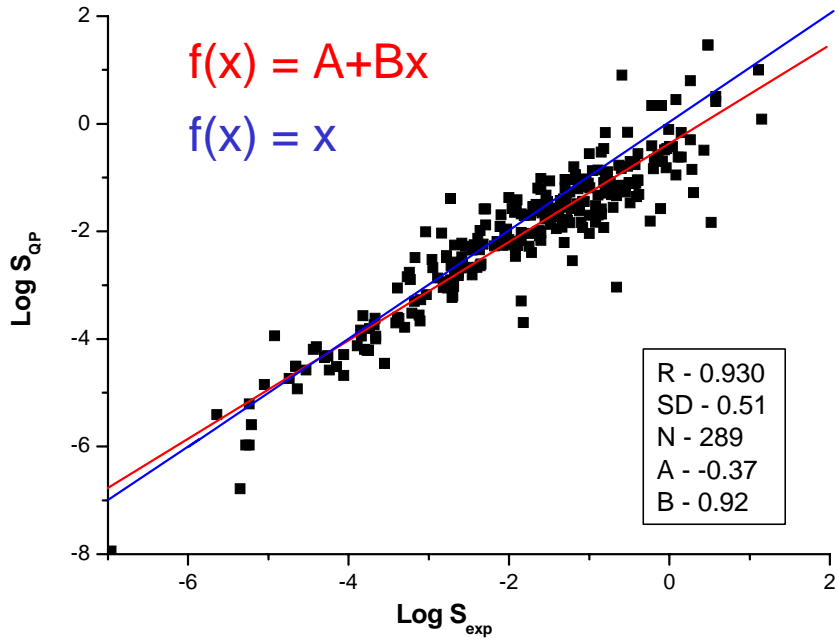
The Octanol-Water Partition Coefficient



$\text{Log } P: -2.0 - 6.0 \rightarrow 95\% (93.9\%)$

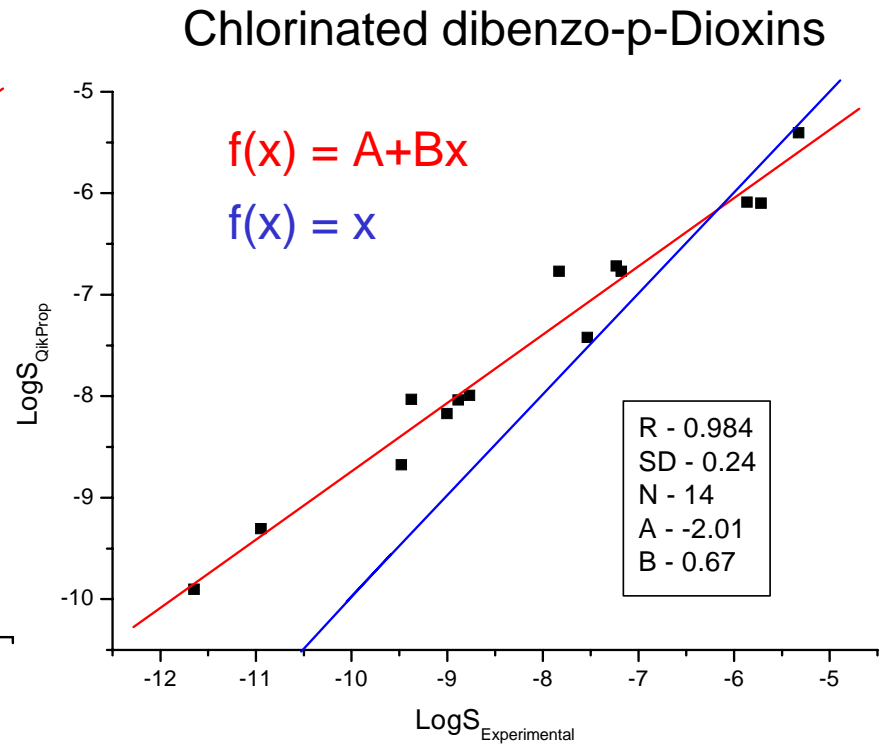
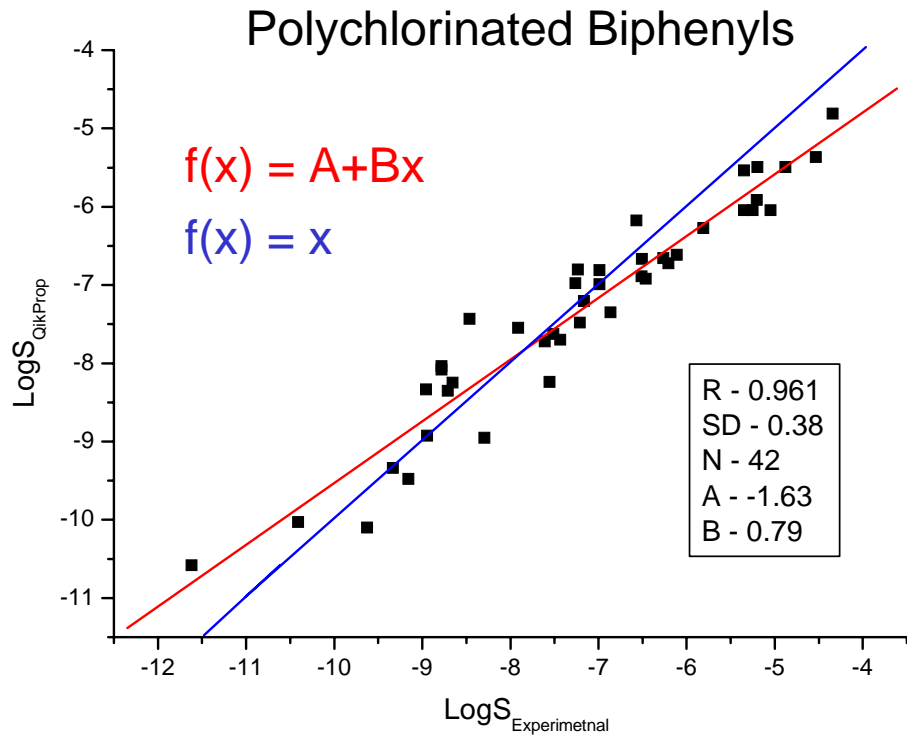
Sangster, J. Phys. Chem. Ref. Data 18 (1989) 1111.

Water Solubility



$\text{Log } S: -6.0 - 0.5 \rightarrow 95\% (87.3\%)$

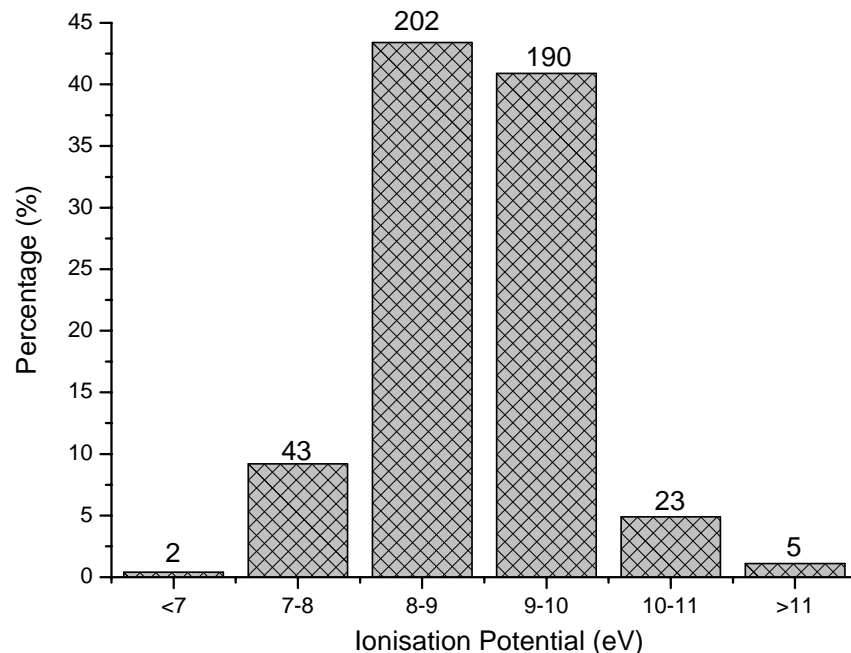
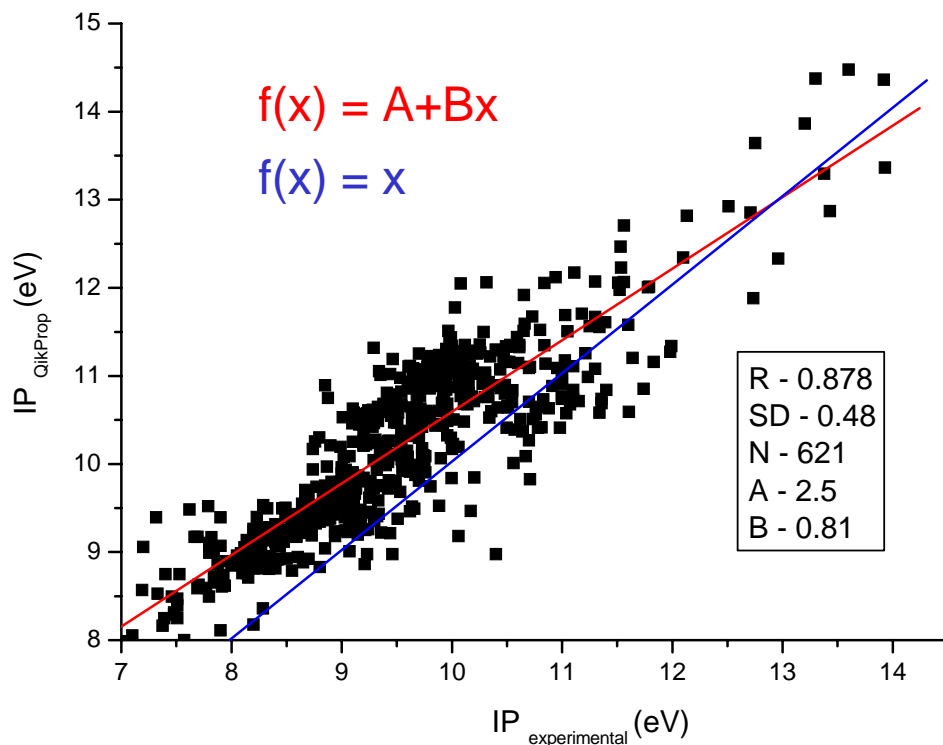
Water Solubility



Shiu, *et al.* Env. Sci. Tech. 22 (1988) 651.

Shiu and MacKay, J. Phys. Chem. Ref. Data 15 (1986) 911.

Ionisation Potentials



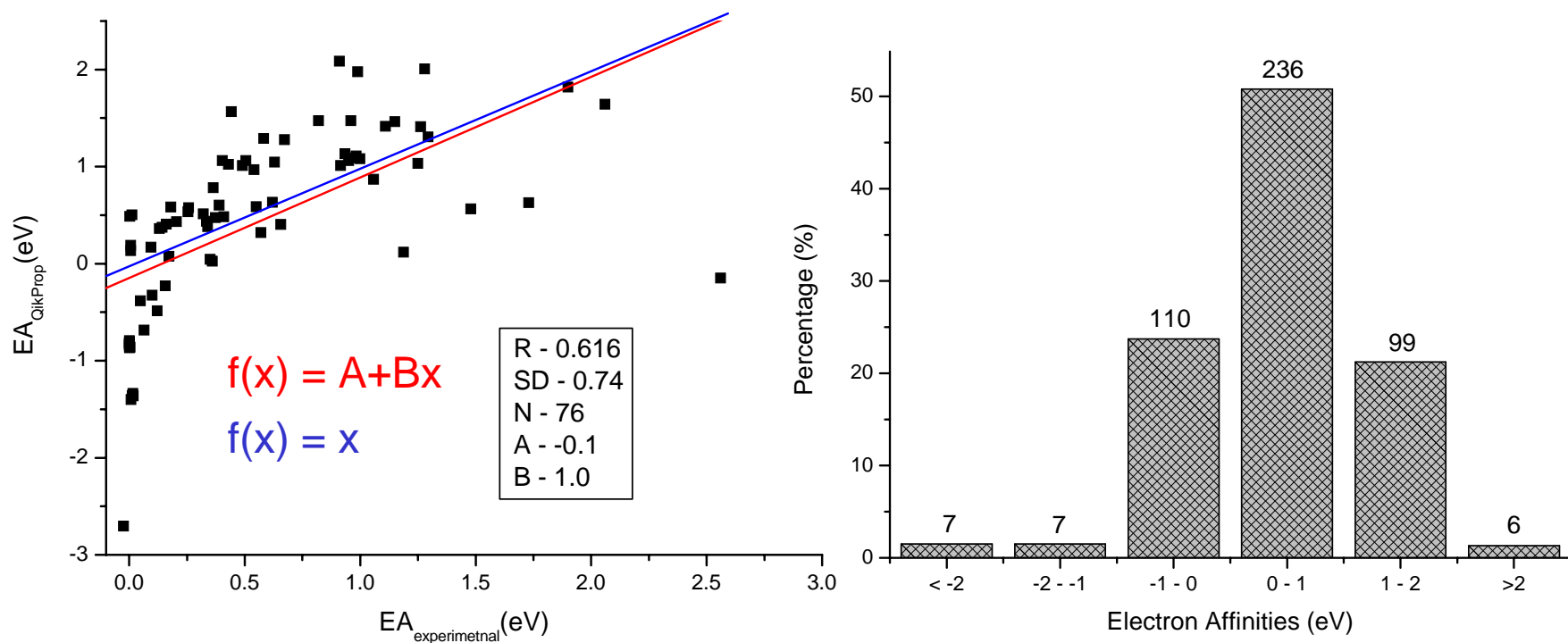
IP: 7.9 – 10.5 eV → 95% (92.5%)

PM3 semi-empirical calculations

Stewart, J. Comp. Chem. 10 (1989) 209.

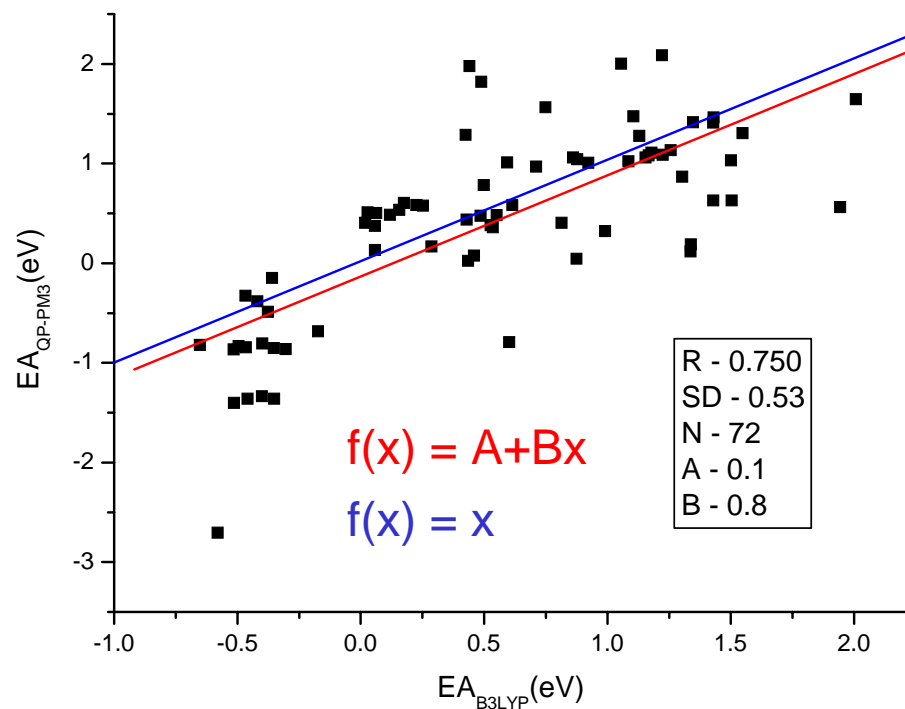
Stewart, J. Comp. Chem. 10 (1989) 221.

Electron Affinity



The computational prediction of electron affinities has always been a particularly difficult task for wave function based methods. Koch and Holthausen, A Chemist's Guide to Density Functional Theory Wiley-VCH, Weinheim, 1999, p. 166.

Electron Affinity

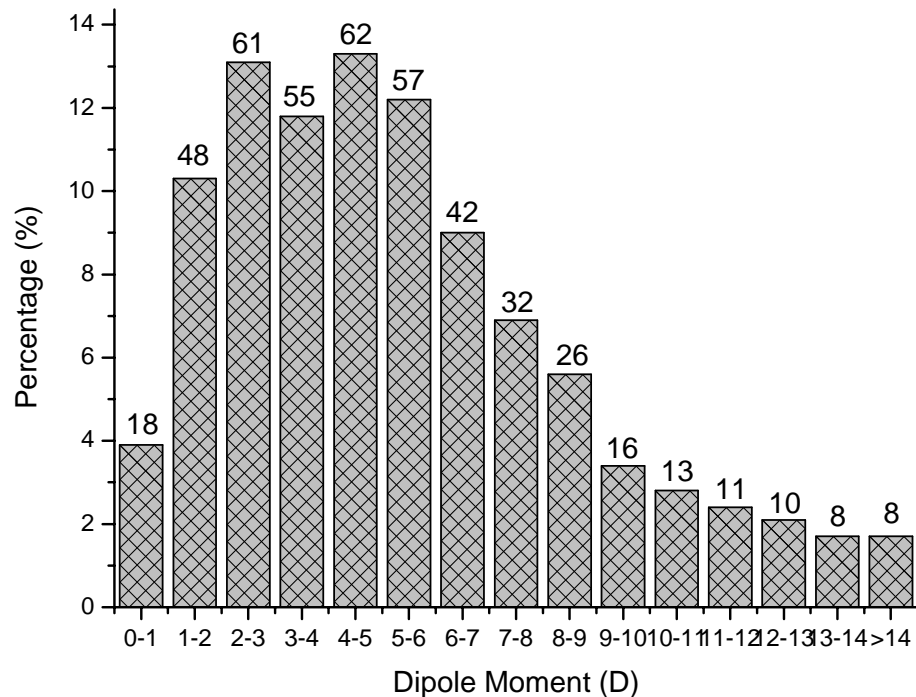
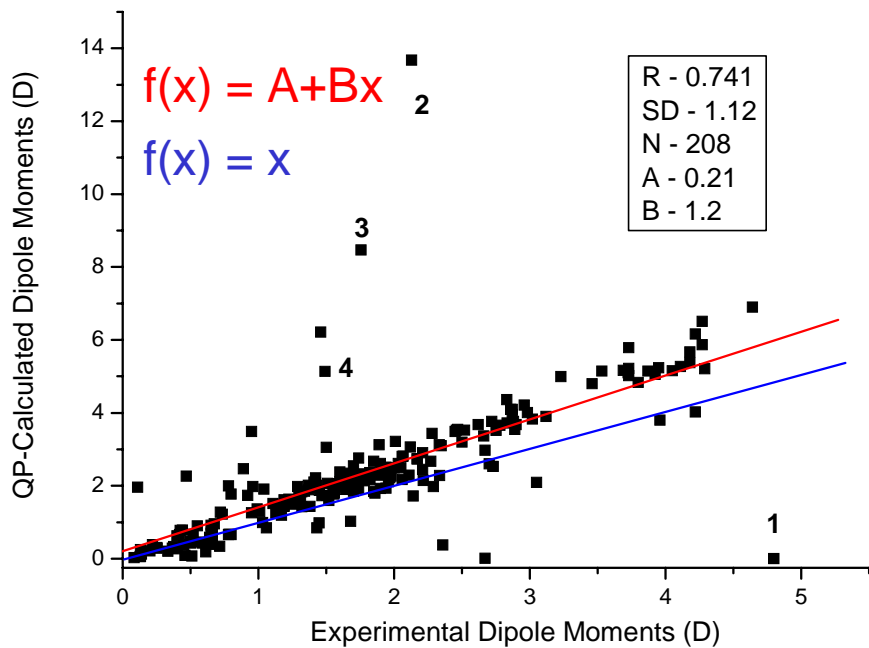


Gaussian 03, uB3LYP/6-31+G(d,p)/6-31++G(2df,p)

Tschumper and Schaefer, J.Chem.Phys. 107 (1997) 2529

Vera and Pierine, PCCP, 6 (2004) 2899

Dipole Moments



DM: 1 – 12.5 D → 95% (94.6%)

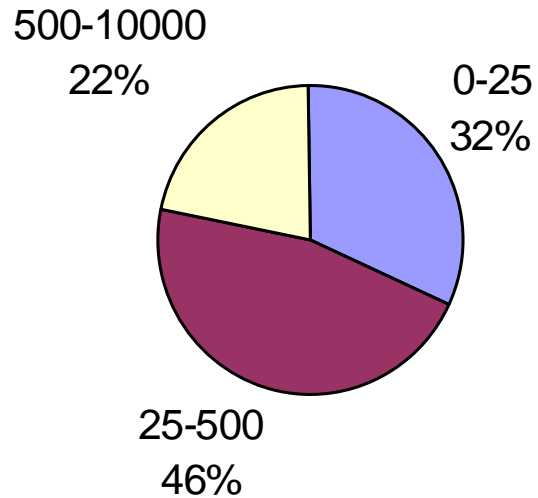
Lide, Handbook of Chemistry and Physics, Ed. Lide, CRC Press
London 1993, pp. 9-(42-45)

Application to a commercial compound collection

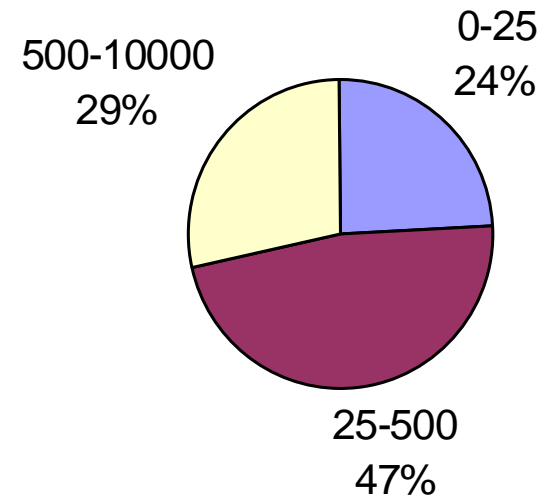
- $\sim 6 \times 10^5$ molecules from ZINC
- Log P: -2.0 to 6.0 \rightarrow **2.9%**
- Log S: -6.0 to 0.5 \rightarrow **15.1%**
- IP: 7.9 to 10.5 eV \rightarrow **5.3%**
- Dipole Moment: 1 – 12.5 D \rightarrow **4.1%**
- Combined reduction: **22.1%**

Predicted Cell Permeability Tested by Using 88 Anticancer Drugs (nm/s)

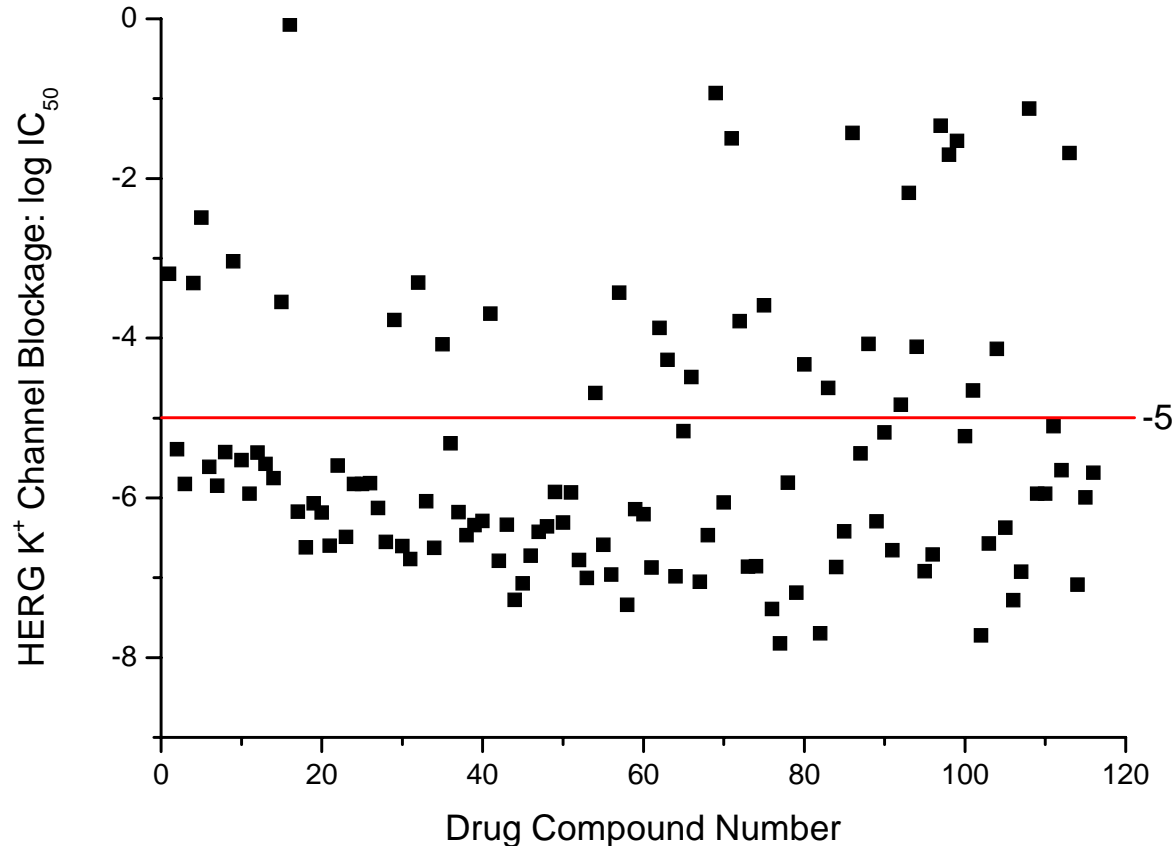
QP MDCK



QP Caco-2

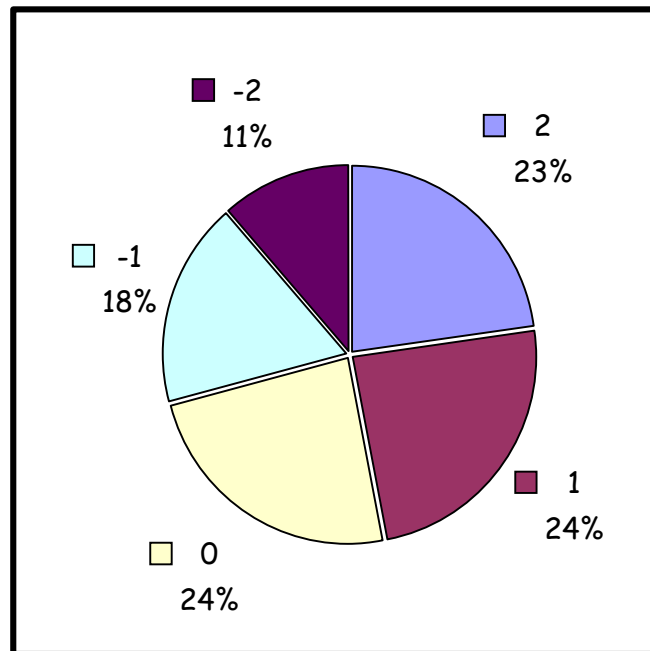


Testing of HERG K⁺ Channels Blockage Prediction Using 114 Cardiovascular Drugs



80 (70.2%) are below the critical limit

Testing the Central Nervous Systems Activity Module



181 drug molecules, which enter the CNS

Conclusions

- Log P, Log S, Ionisation Potentials and Dipole moments show good a correlation with experimental data
- A better benchmarking collection is needed for the Electron Affinity values
- More work is required on the ADME modules

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