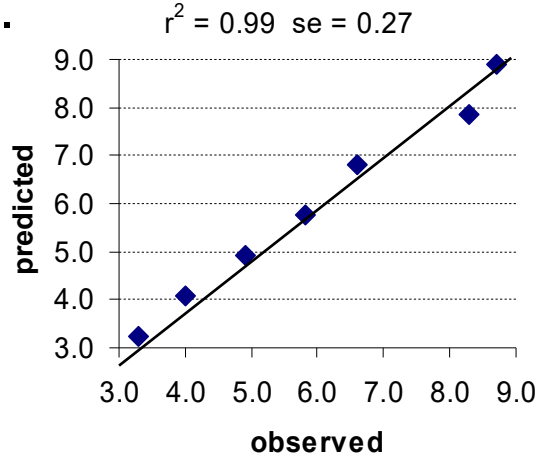
QSAR, QSPR, statistics, correlation, similarity & descriptors

The tools of trade for the computer based *rational drug design*, particularly if there is no structural information about the *target* (protein) available.

QSAR equations form a quantitative connection between chemical structure and (biological) activity.

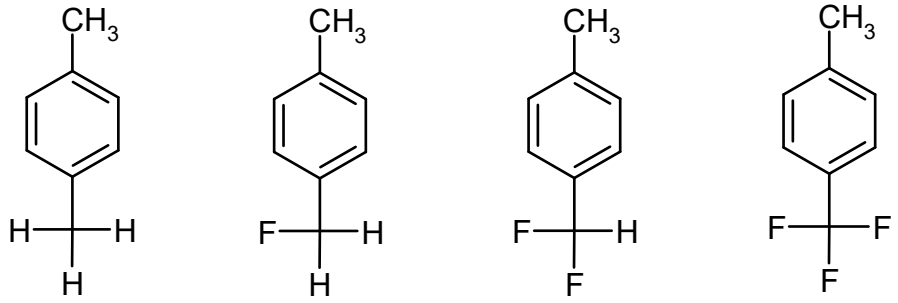
$$\log(1/C) = k_1 \cdot P_1 + k_2 \cdot P_2 + \ldots + k_n \cdot P_n$$



The presence of experimentally measured data for a number of known compounds is required, e.g. K_i or IC_{50} values taken from assays.

Introduction to QSAR (I)

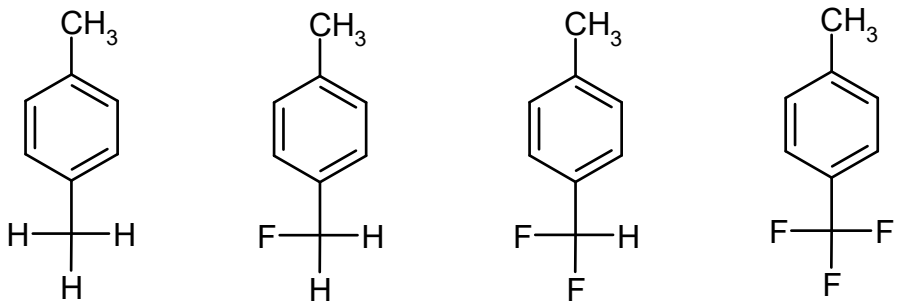
Suppose we have experimentally determined the binding constants for the following compounds



K_i [10^{-9} mol l^{-1}]	1550	250	5.0	2.0

Which feature/property is responsible for binding?

Introduction to QSAR (II)

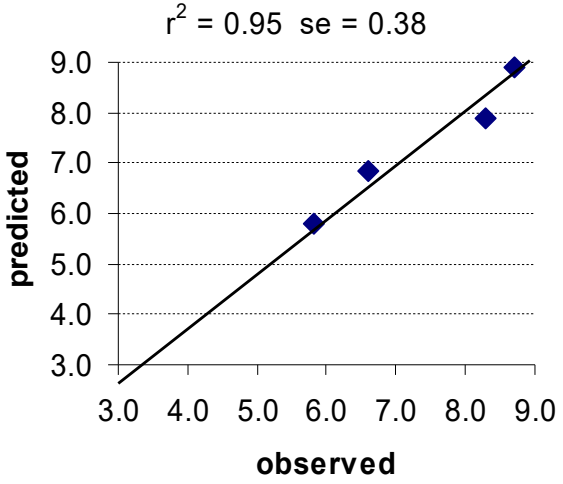


K_i [10^{-9} mol l^{-1}]	1550	250	5.0	2.0

Using the number of fluorine atoms as descriptor we obtain following linear regression equation:

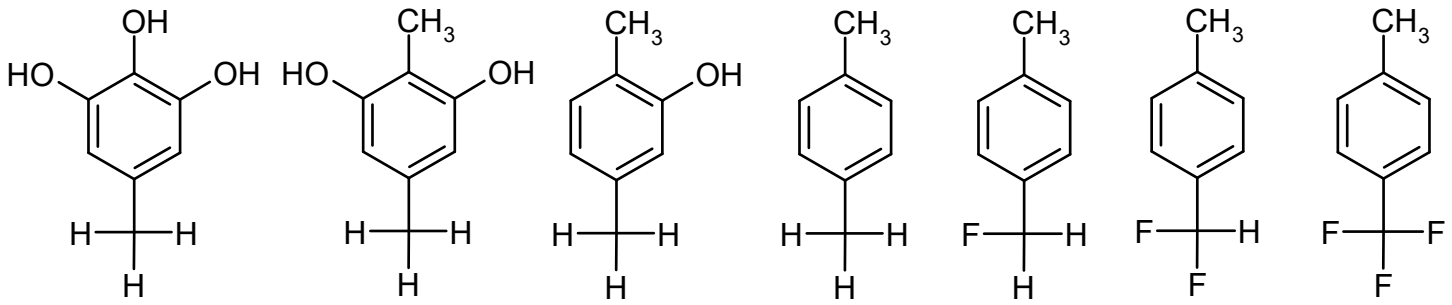
$$\log(1/K_i) = a \cdot n_{fluorine} + b$$

$$\log(1/K_i) = 1.037 \cdot n_{fluorine} + 5.797$$



Introduction to QSAR (III)

Now we add some additional compounds

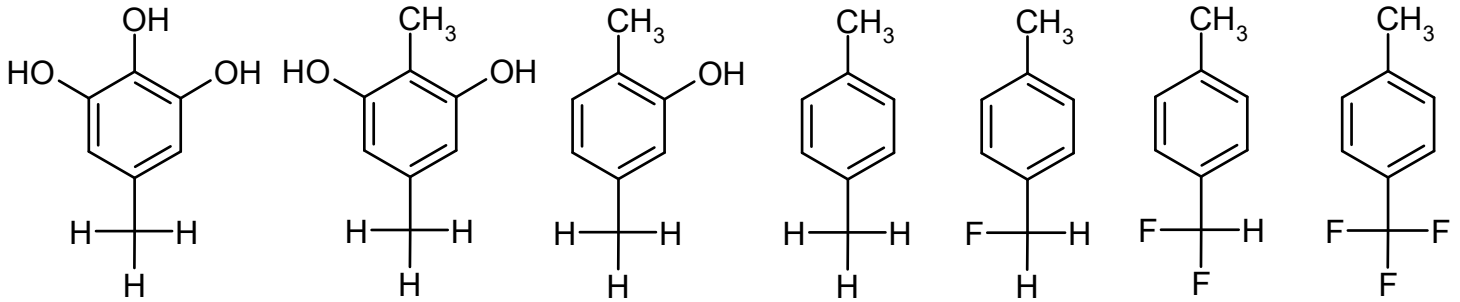


500000 100000 12500 1550 250 5.0 2.0

K_i [10^{-9} mol l^{-1}]

Which features/properties are now responsible for binding?

Introduction to QSAR (IV)



500000	100000	12500	1550	250	5.0	2.0

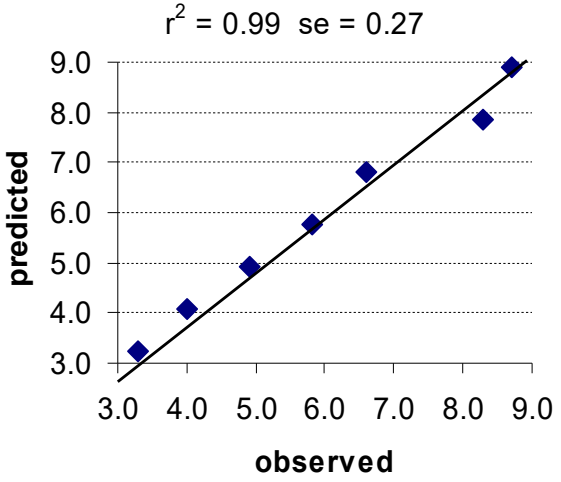
K_i [10^{-9} mol l^{-1}]

We assume that following descriptors play a major role:

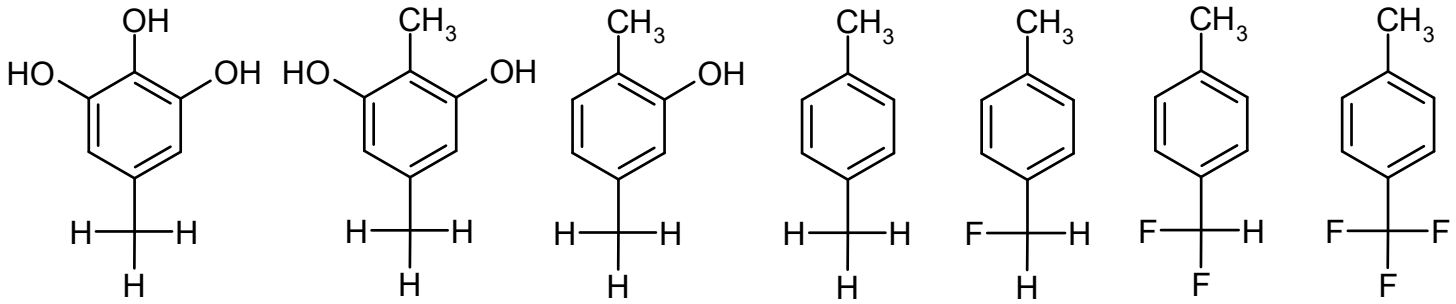
- number of fluorine atoms
- number of OH groups

$$\log(1/K_i) = a_1 \cdot n_{fluorine} + a_2 \cdot n_{OH} + b$$

$$\log(1/K_i) = 1.049 \cdot n_{fluorine} - 0.843 \cdot n_{OH} + 5.768$$



Introduction to QSAR (V)



500000	100000	12500	1550	250	5.0	2.0

K_i [10^{-9} mol l^{-1}]

$$\log(1/K_i) = 1.049 \cdot n_{fluorine} - 0.843 \cdot n_{OH} + 5.768$$

$$r^2 = 0.99 \quad se = 0.27$$

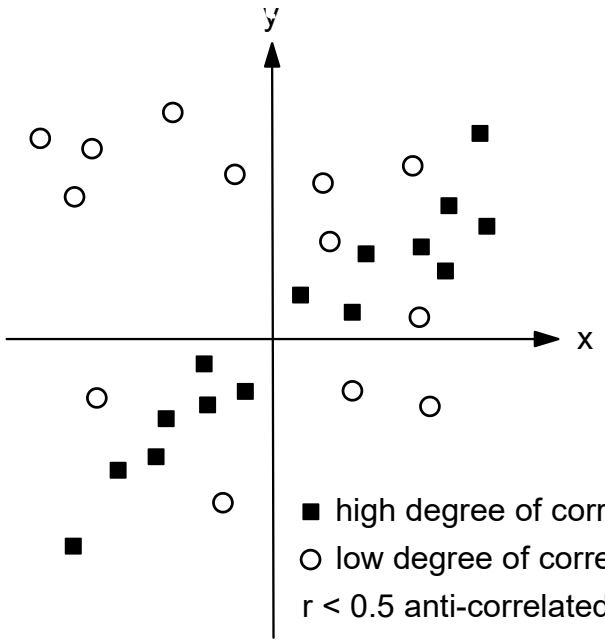
Is our prediction sound or just pure coincidence/random?

→ We will need statistical proof of our assumption (e.g. using a test set, χ^2-test, *p*-values, cross-validation, boots trapping, ...)

Correlation (I)

The most frequently used value is Pearson‘s correlation coefficient

$$r = \frac{\sum_{i=1}^{n} \left(x_i - \bar{x}\right)\left(y_i - \bar{y}\right)}{\sqrt{\left(\sum_{i=1}^{n} \left(x_i - \bar{x}\right)^2\right)\left(\sum_{i=1}^{n} \left(y_i - \bar{y}\right)^2\right)}} \in [-1 \ldots 1]$$



→ A plot tells more than pure numbers!
distribution of the data points, trends, potential outliers, indication of non-linear correlation...

Definition of terms

QSAR: quantitative structure-activity relationsship

QSPR: quantitative structure-property relationship

activity and property can be for example:

$\log(1/K_i)$ K_i constant of binding

$\log(1/IC_{50})$ IC_{50} concentration that produces 50% effect

also physical quantities, such as boiling point, solubility, … can be addressed.

aim: prediction of molecular properties from their structure without the need to perform the experiment.

→ *in silico* instead of *in vitro* or *in vivo*

advantages: saves time and resources

Development of QSAR methods over time (I)

1868 A.C.Brown, T.Fraser:
Physiological activity is a function of the chemical constitution (composition)

but: An absolute direct relationship is not possible, only by using differences in activity of already measured compounds.

remember:

1865 Suggestion for the structure of benzene by A. Kekulé. The chemical structure of most organic compounds at that time was still unknown!

1893 H.H.Meyer, C.E.Overton
The toxicity of organic compounds is related to their partition between aqueous and lipophilic biological phase.

Development of QSAR method over time (II)

1868 E.Fischer
Key and lock principle for enzymes. Again no structural information about enzymes was available!

1930-40 Hammet equation: reactivity of compounds
physical, organic, theoretic chemistry

1964 C.Hansch, J.W.Wilson, S.M.Free, F.Fujita
birth of modern QSAR-methods
Hansch analysis and **Free-Wilson analysis**

$$\log(1/C) = k_1 \cdot P_1 + k_2 \cdot P_2 + \ldots + k_n \cdot P_n$$

coefficients (constant) **descriptors or variables**

linear free energy-related approach

Descriptors

Approaches that form a mathematical relationsship between numerical quantities (descriptors P_i) and the physico-chemical properties of a compound (e.g. biological activity log(1/C)), are called QSAR or QSPR, respectively.

$$\log(1/C) = k_1 \cdot P_1 + k_2 \cdot P_2 + \ldots + k_n \cdot P_n$$

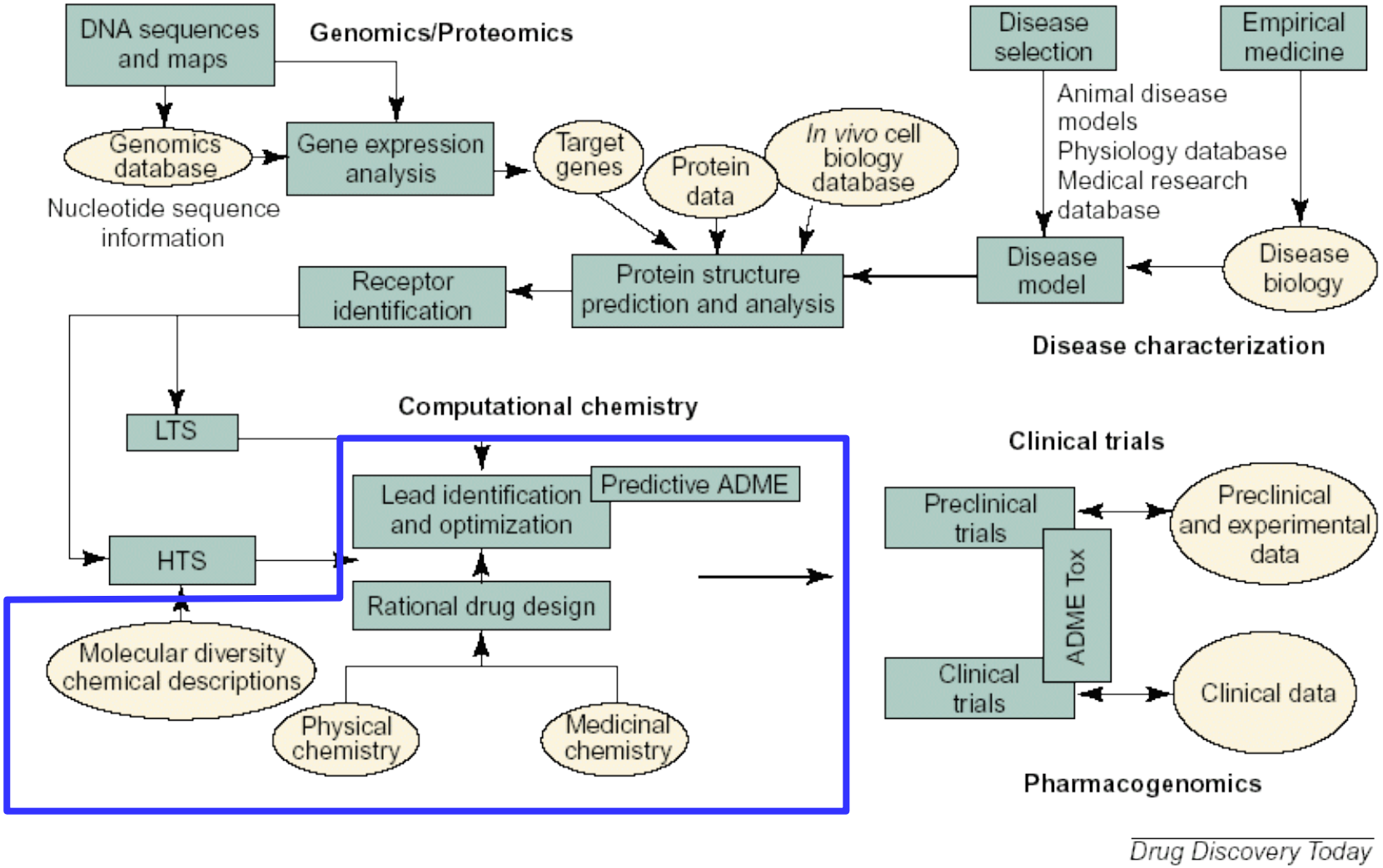
Furthermore, descriptors are used to quantify molecules in the context of diversity analysis and in combinatorial libraries.

In principle any molecular or numerical property of the compound can by used as descriptors.

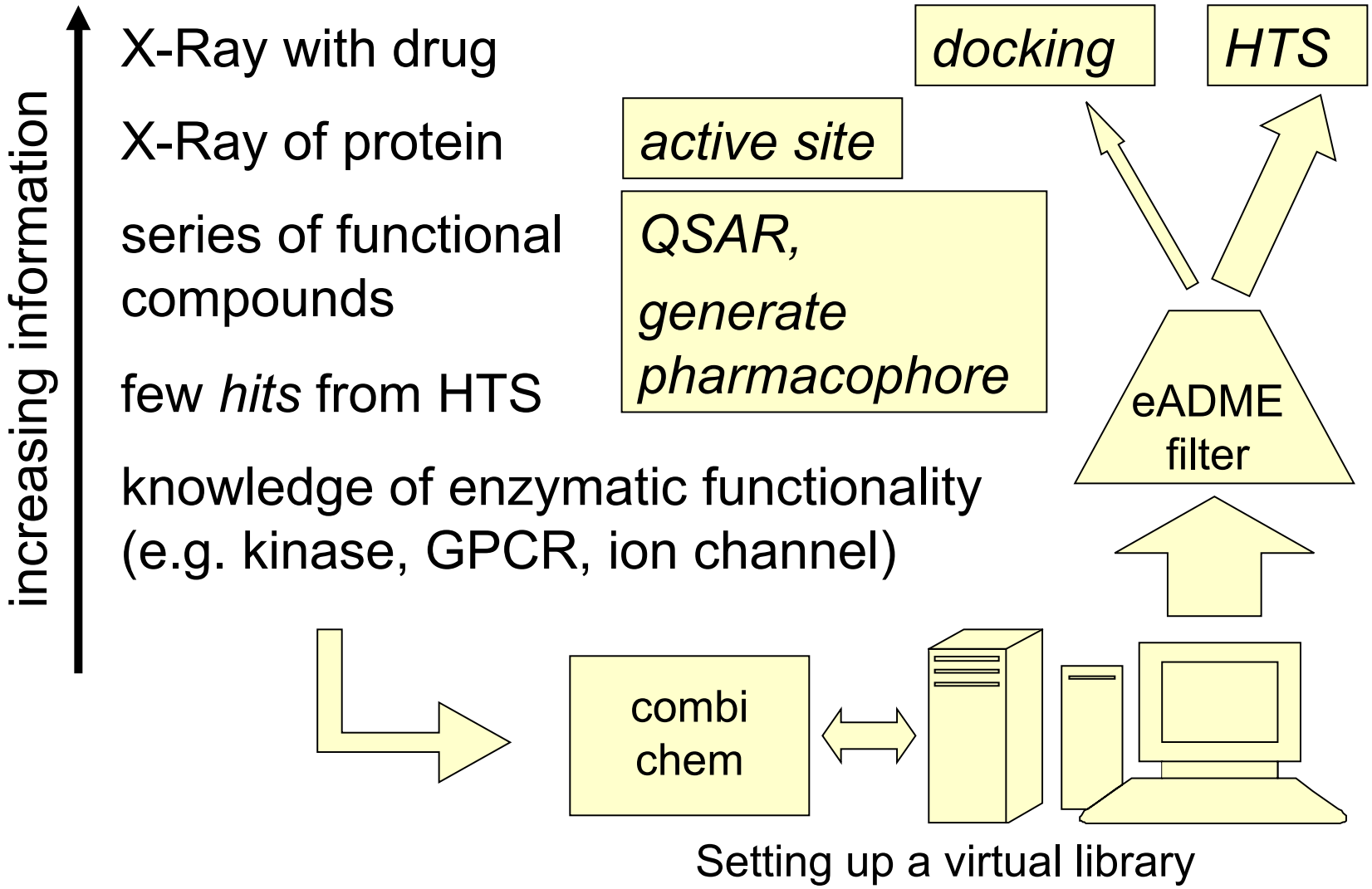
More about descriptors and their classification see

http://www.codessa-pro.com/descriptors/index.htm

Flow of information in a *drug discovery pipeline*



Compound selection



Setting up a virtual library

(Some) descriptors based on molecular properties used to predict ADME properties

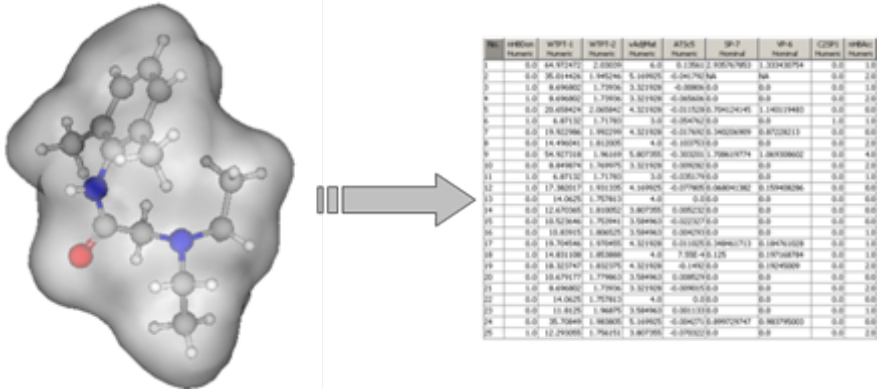
logP water/octanol partitioning coefficient

Lipinski‘s rule of five

topological indices

polar surface area

similary / dissimilarity



QSAR quantitative structure activity relationship

QSPR quantitative structure property rel.

„1D“ descriptors (I)

For some descriptors we need only the information that can be obtained from sum formula of the compound. Examples:

molecular weight, total charge, number of halogen atoms, ...

Further 1-dimensional descriptors are obtained by the summation of atomic contributions. Examples:

sum of the atomic polarizabilities

refractivity (*molar refractivity,* M_R)

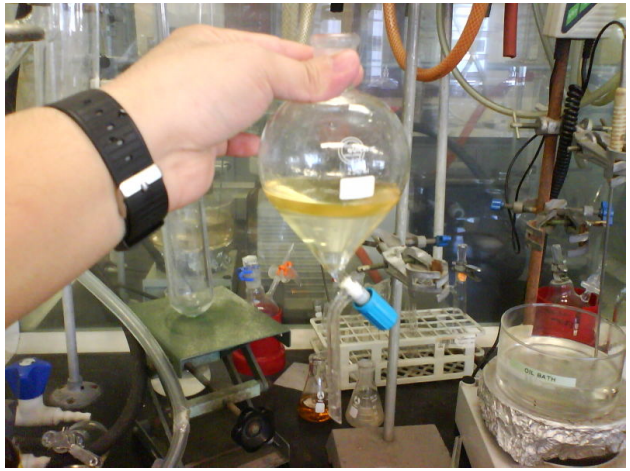
$M_R = (n^2 - 1)\, MW / (n^2 + 2)\, d$

with refractive index n, density d, molecular weight MW

Depends on the polarizability and moreover contains information about the molecular volume (MW / d)

logP (I)

The *n*-octanol / water partition coefficient, respectively its logarithmic value is called logP.



Frequently used to estimate the membrane permeability and the bioavailability of compounds, since an orally administered drug must be enough lipophilic to cross the lipid bilayer of the membranes, and on the other hand, must be sufficiently water soluble to be transported in the blood and the lymph.

hydrophilic –4.0 < logP < +8.0 lipophilic

glucose –3.24

„typical“ drugs < 5.0

flurbiprofene +4.16

logP (II)

An increasing number of methods to predict logP have been developed:

Based on molecular fragments (atoms, groups, and larger fragments)

ClogP Leo, Hansch et al. *J.Med.Chem.* **18** (1975) 865.
problem: non-parameterized fragments
(occur up to 25% of all compounds in substance libraries)

Based on atom types (similar to force field atom types)

SlogP S.A. Wildman & G.M.Crippen *J.Chem.Inf.Comput.Sci.* **39** (1999) 868.

AlogP, MlogP, XlogP...

Parameters for each method were obtained using a mathematical fitting procedure (linear regression, neural net,...)

Review: R.Mannhold & H.van de Waaterbeemd, *J.Comput.-Aided Mol.Des.* **15** (2001) 337-354.

logP (III)

Further logP prediction methods apply whole molecule properties, such as

- molecular surface (polar/non-polar area, or their electrostatic properties = electrostatic potential)
- dipole moment and molecular polarizability
- ratio of volume / surface (globularity)

Example: Neural net trained with quantum chemical data

logP T. Clark et al. *J.Mol.Model.* **3** (1997) 142.

„1D“ descriptors (II)

Further atomic descriptors use information based on empirical atom types like in force fields. Examples:

- Number of halogen atoms
- Number of sp^3 hybridized carbon atoms
- Number of H-bond acceptors (N, O, S)
- Number of H-bond donors (OH, NH, SH)
- Number of aromatic rings
- Number of COOH groups
- Number of ionizable groups (NH_2, COOH)

...

- Number of freely rotatable bonds (single bonds that are not in a ring)

Fingerprints as binary descriptors

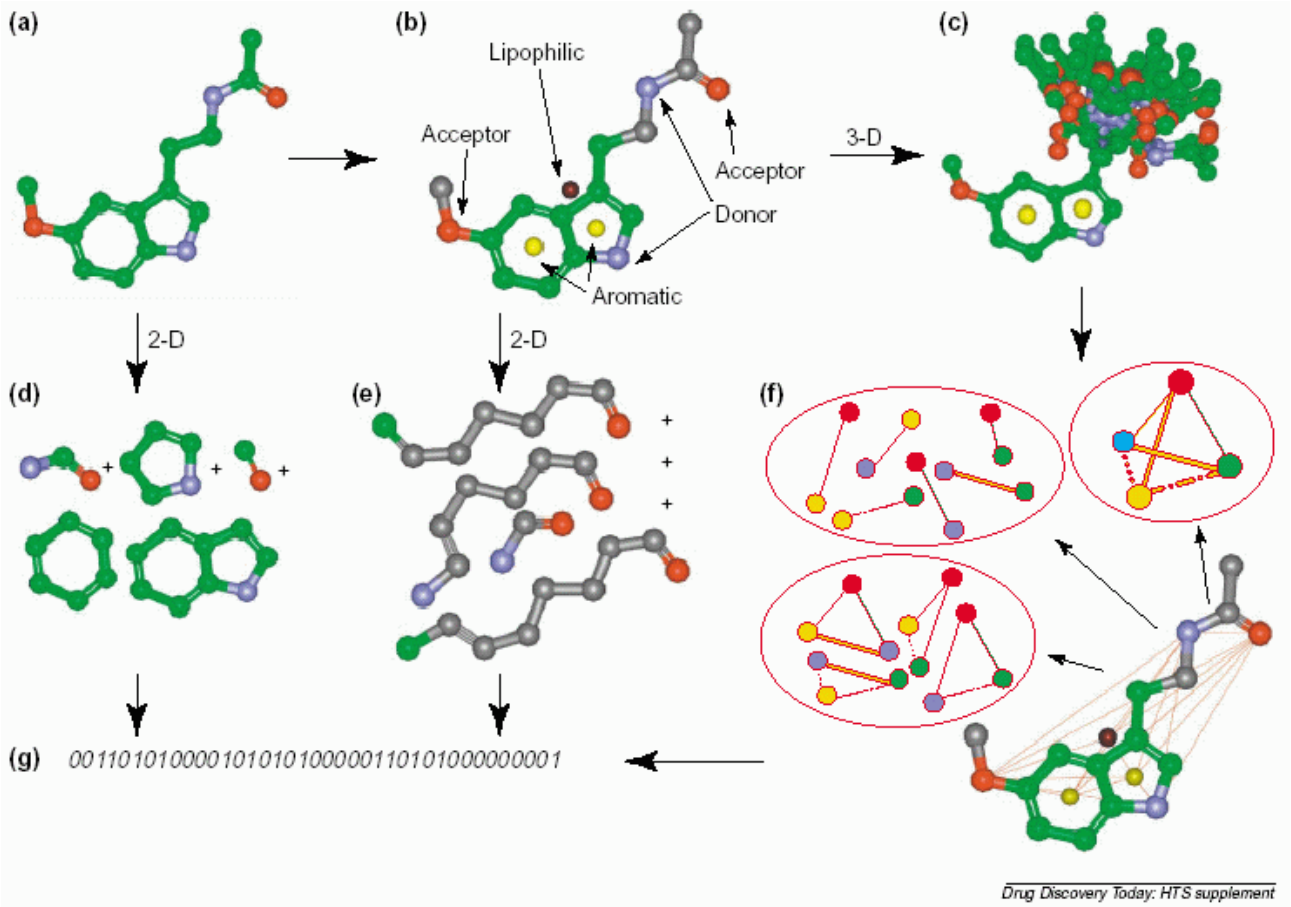
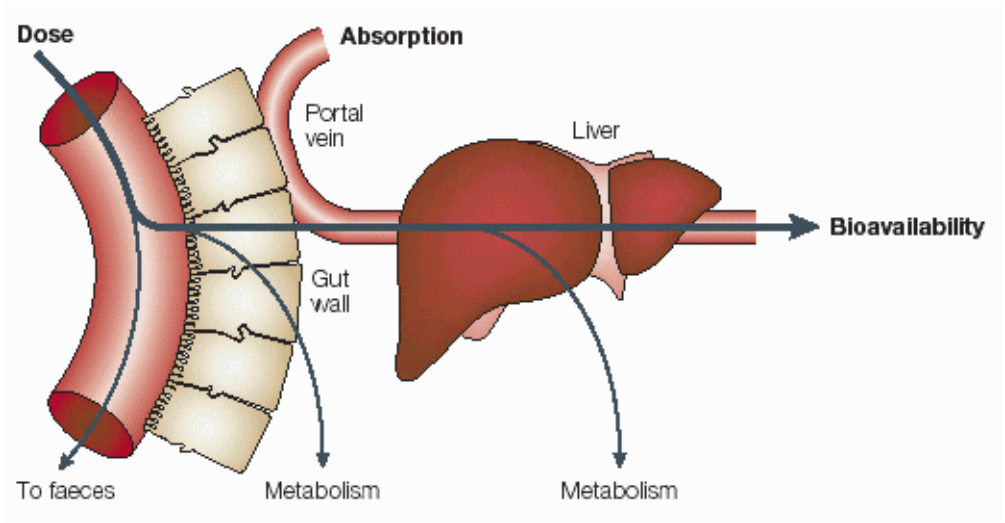


Figure 2. Schematic illustration of primary methods used in molecular fingerprint creation. **(a)** Create 2-D and 3-D model of molecule; **(b)** deconstruct the molecule into pharmacophoric elements; **(c)** generate conformational models; **(d)** deconstruct the molecule into topological/substructural elements; **(e)** determine distance between pharmacophoric groups using bond counts; **(f)** determine 2-, 3- or 4-center distance combinations of pharmacophoric groups for each conformer; and **(g)** determine the presence or absence of each descriptor element and combine to create a binary fingerprint.

Lipinski´s Rule of 5

Combination of descriptors to estimate intestinal absorption.
Insufficient uptake of compounds, if

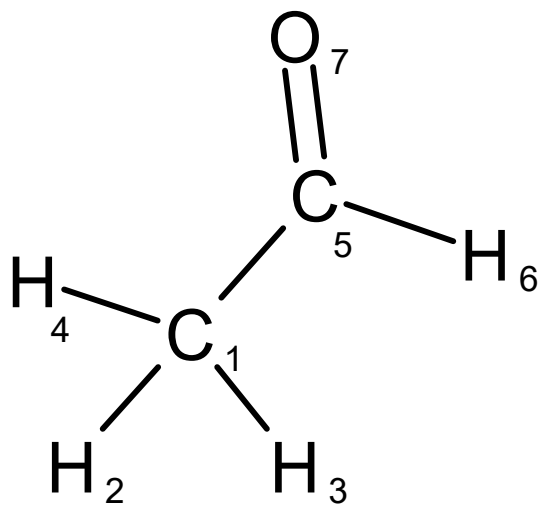
Molecular weight > 500	slow diffusion
logP > 5.0	too lipophilic
> 5 H-bond donors (OH and NH)	to many H-bonds with the head
>10 H-bond acceptors (N and O atoms)	groups of the membrane



C.A. Lipinski et al. *Adv. Drug. Delivery Reviews* **23** (1997) 3.

2D descriptors (I)

Descriptors derived from the configuration of the molecules (covalent bonding pattern) are denoted 2D descriptors . Since no coordinates of atoms are used, they are in general conformationally independent, despite containing topological information about the molecule. C.f. representation by SMILES



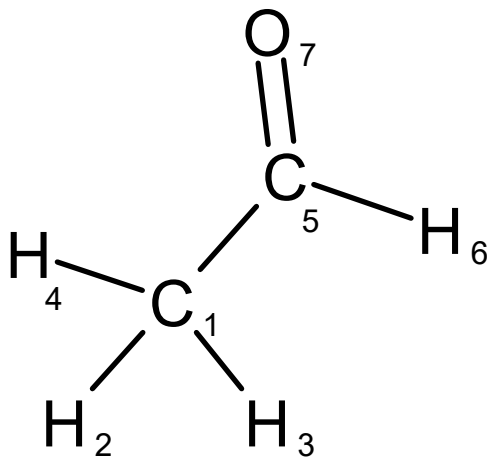
adjacency matrix M

*C*1	0	1	1	1	1	0	0	0	1	1	1	1	2	2
*H*2	1	0	0	0	0	0	0	1	0	2	2	2	3	3
*H*3	1	0	0	0	0	0	0	1	2	0	2	2	3	3
*H*4	1	0	0	0	0	0	0	1	2	2	0	2	3	3
*C*5	1	0	0	0	0	1	1	1	2	2	2	0	1	1
*H*6	0	0	0	0	1	0	0	2	3	3	3	1	0	2
*O*7	0	0	0	0	1	0	0	2	3	3	3	1	2	0

distance matrix D

2D descriptors (II)

The essential topological properties of a molecules are the degree of branching and the molecular shape.



An sp^3 hybridized carbon has got 4 valences, an sp^2 carbon only 3.

Thus the ratio of the actual branching degree to the theoretically possible branching degree can be used as descriptor because it is related to the saturation (double or aromatic bonds where hydrogens can be added). C.f. unsaturated fatty acids

2D descriptors (III)

Common definitions:

Z_i ordinary number (H=1, C=6, N=7, LP=0)

h_i number of H atoms bonded to atom *i*

d_i number of non-hydrogen atoms bonded to atom *i*

Descriptors accounting for the degree of branching and the flexibility of a molecule:

Kier & Hall Connectivity Indices

p_i sum of *s* and *p* valence electrons of atom *i*

$v_i = (p_i - h_i) / (Z_i - p_i - 1)$ for all non-hydrogen (heavy) atoms

Kier and Hall Connectivity Indices

Z_i ordinary number (H=1, C=6, LP=0)

d_i number of heavy atoms bonded to atom *i*

p_i number of *s* and *p* valence electrons of atom *i*

$v_i = (p_i - h_i) / (Z_i - p_i - 1)$ for all heavy atoms

Chi0 0th order $\chi_0 = \sum_i \frac{1}{\sqrt{d_i}}$ for all heavy atom with $d_i > 0$

Chi1 1st order $\chi_1 = \sum_i \sum_{j>i} \frac{1}{\sqrt{d_i d_j}}$ for all heavy atoms if i is bonded to j

Chi0v Valence index $\chi_{0v} = \sum_i \frac{1}{\sqrt{v_i}}$ for all heavy atoms with $v_i > 0$

Kier and Hall Shape Indices (I)

n number of heavy atoms (non-hydrogen atoms)

m total number of bonds between all heavy atoms

p_2 number of paths of length 2

p_3 number of paths of length 3 from the distance matrix **D**

Kappa1 $$\kappa_1 = \frac{n(n-1)^2}{m^2}$$

Kappa2 $$\kappa_2 = \frac{(n-1)(n-2)^2}{p_2^2}$$

Kappa3 $$\kappa_3 = \frac{(n-1)(n-3)^2}{p_3^2} \text{ for even } n$$

$$\kappa_3 = \frac{(n-3)(n-2)^2}{p_3^2} \text{ for odd } n$$

Kier and Hall Shape Indices (II)

Relating the atoms to sp^3-hybridized carbon atoms yields the Kappa alpha indices

$$\alpha = \sum_i^n \frac{r_i}{r_c - 1}$$

r_i covalence radius of atom *i*

r_c covalence radius of an sp^3 carbon atom

$$\kappa_{\alpha 1} = \frac{s(s-1)^2}{(m+\alpha)^2} \text{ with } s = n + \alpha$$

element	hybridi-zation	α
C	sp^3	0
C	sp^2	-0.13
C	sp	-0.22
N	sp^3	-0.04
N	sp^2	-0.20
N	sp	-0.29
O	sp^3	-0.04
P	sp^3	+0.43
S	sp^3	+0.35
Cl		+0.29

Balaban, Wiener, and Zagreb Indices

n number of heavy atoms (non-hydrogen atoms)

m total number of bonds between all heavy atoms

d_i number of heavy atoms bonded to atom *i*

$w_i = \sum_{i \neq j} D_{ij}$ Sum of the off-diagonal matrix elements of atom *i* in the distance matrix **D**

BalabanJ $\frac{m}{m-n+1} \sum^{m} \frac{1}{\sqrt{w_i w_j}}$

WienerJ (path number) $\frac{1}{2} \sum_{i}^{n} w_i$ Correlates with the boiling points of alkanes

Wiener polarity $\frac{1}{2} \sum_{i}^{n} w_i$ if $D_{ij} \geq 3$

Zagreb index $\sum_{i} d_i^2$ for all heavy atoms i

What kind of information do topological indices contain?

topological indices are associated with the

- degree of branching in the molecule
- size and spacial extention of the molecule
- structural flexibility

Usually it is not possible to correlate a chemical property directly by using only one single index.

Although topological indices encode the same properties as fingerprints do, they are harder to interpret, but can be generated numerically more easily.

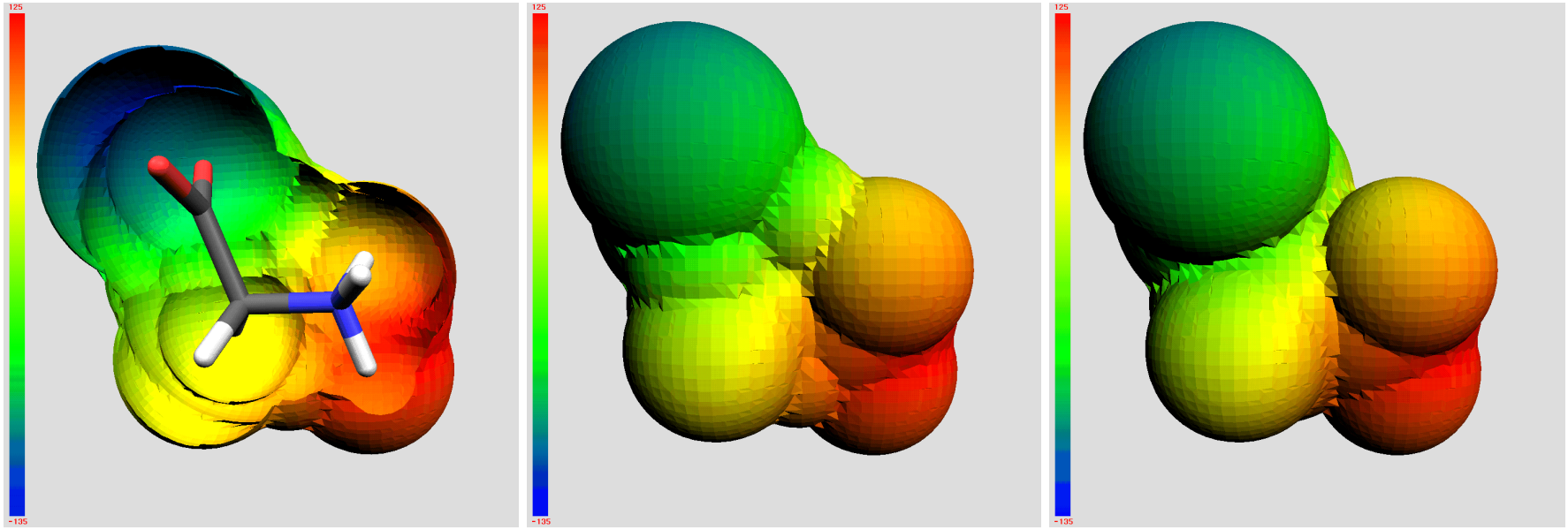
3D descriptors

Descriptors using the atomic coordinates (x,y,z) of a molecules are therefore called 3D descriptors.

As a consequence they usually depend on the conformation.
(rotation around single bonds causes leads to other conformations)

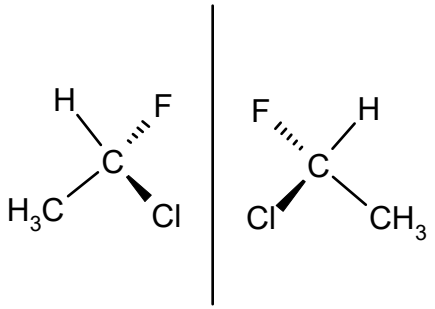
Examples:

van der Waals volume, molecular surface, polar surface, electrostatic potential (ESP), dipole moment



Chiralty Descriptors

Most biological interactions are stereospecific e.g. ligand binding



Stereoisomers share identical 1D and 2D-descriptors, because they have the same topology.

Ideas for including chirality:

- Using differences of the van der Waals volume or the electrostatic potential after superposition (rotation)
- Adding +1/-1 to chiral centers in the adjacency matrix while computing topological descriptors
- Modifying the sign of 1D-descriptors (electronegativity, size, polarizability,...) with respect to the enantiomer

Lit: G.M.Crippen *Curr.Comput.-Aided Drug Des.* **4** (2008) 259-264.

Quantum mechanical descriptors (selection)

Atomic charges (*partial atomic charges*) No observables!

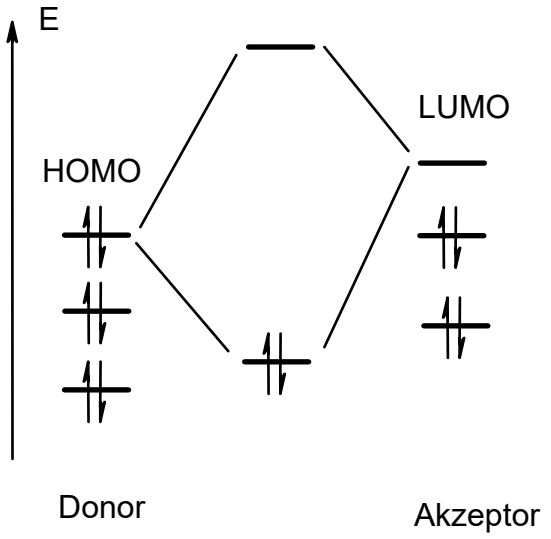
Mulliken population analysis, Gasteiger-Marsili charges, electrostatic potential (ESP) derived charges

dipole moment

polarizability

HOMO / LUMO

energies of the frontier orbitals given in eV



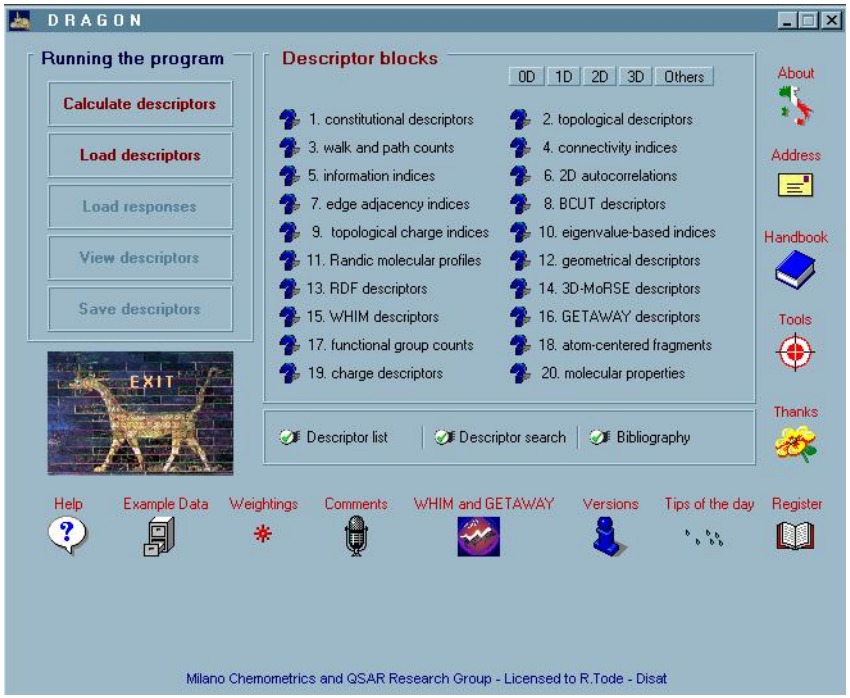
covalent hydrogen bond acidity/basicity

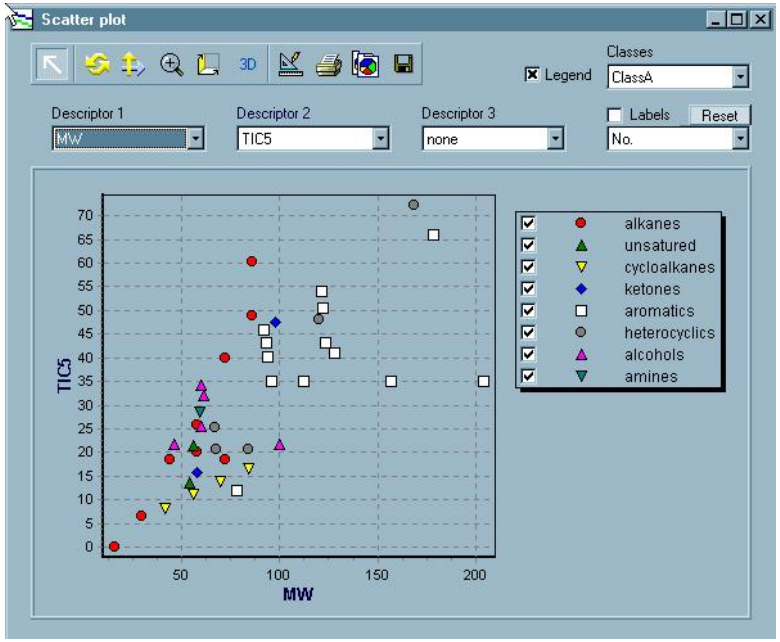
difference of the HOMO/LUMO energies compared to those of water → is the compound a better hydrogen-bond donor/acceptor than a water molecule?

Lit: M. Karelson et al. *Chem.Rev.* **96** (1996) 1027

(e)DRAGON

a computer program that generates >1400 descriptors



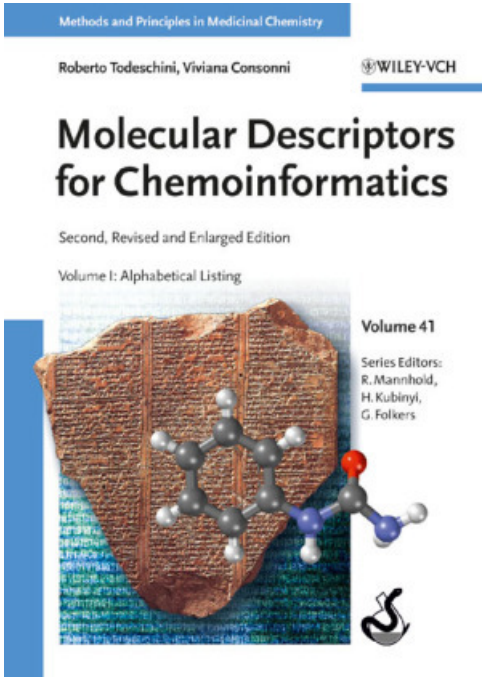


Roberto Todeschini

http://www.vcclab.org/lab/edragon/

Requires 3D-structure of molecules as input

Further information about descriptors



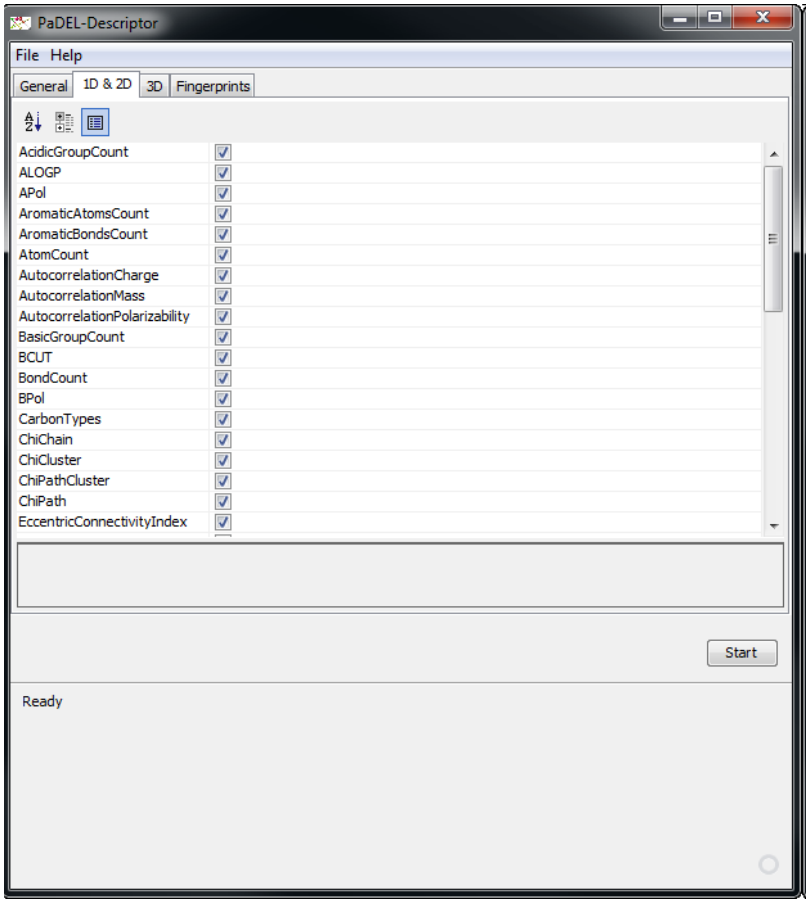
Roberto Todeschini, Viviana Consonni

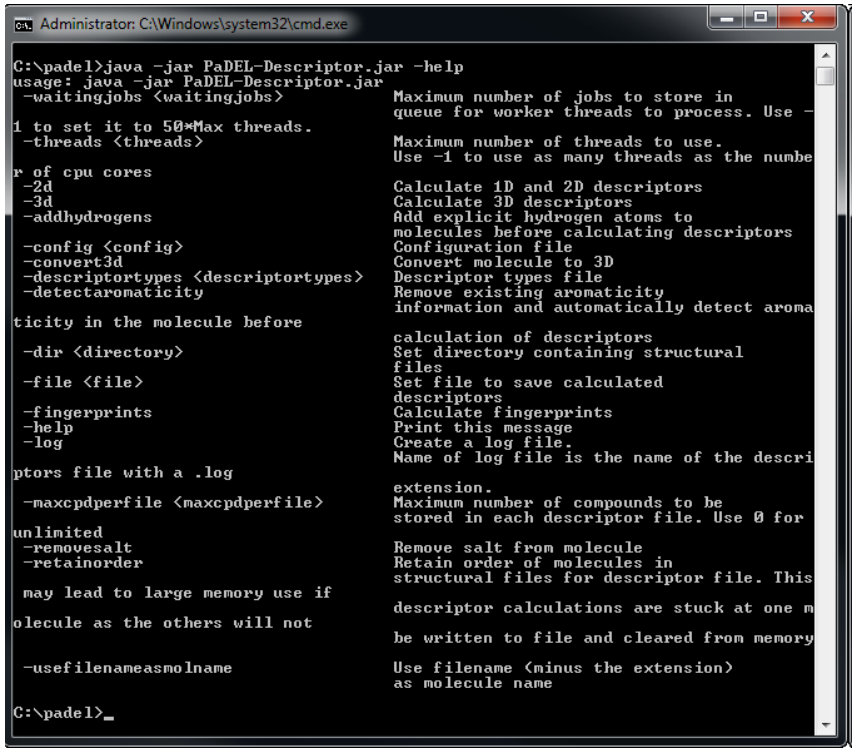
Handbook of Molecular Descriptors, Wiley-VCH, 2nd ed. (2009)
1257 pages

CODESSA Alan R. Katritzky, Mati Karelson et al.

http://www.codessa-pro.com

PaDEL-Descriptor





Open Source Software (JAVA)

Chun Wei Yap

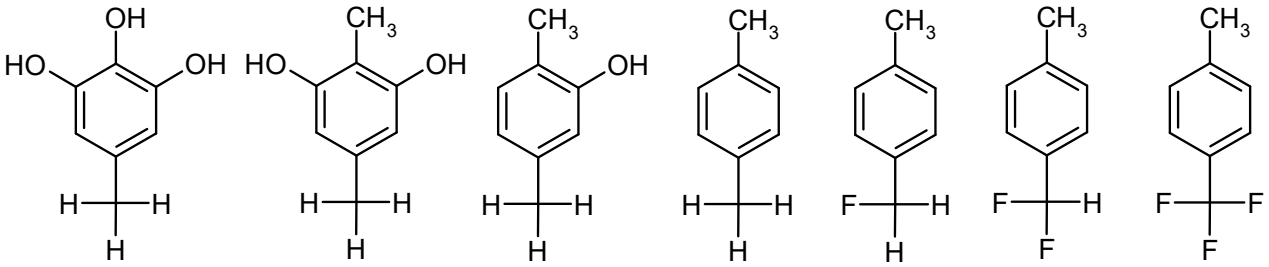
http://www.yapcwsoft.com/dd/padeldescriptor/

C.W. Yap *J.Comput.Chem.* **32** (2011) 1466-1474.

Chosing the right compounds (I)

To derive meaningful QSAR predictions we need

- A sufficient number of compounds — statistically sound
- Structurally diverse compounds — tradeoff between count and similarity



500000 | 100000 | 12500 | 1550 | 250 | 5.0 | 2.0

K_i [10^{-9} mol l^{-1}]

How similar are chemical compounds to each other?

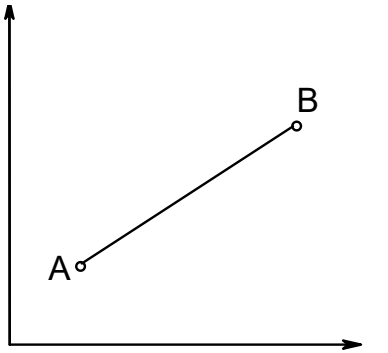
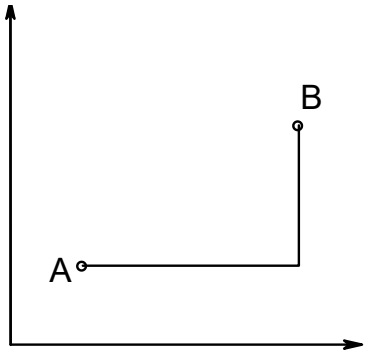
→ Clustering using distance criteria that are based on the descriptors

Distance criteria and similarity indices (I)

χ_A fullfilled property of molecule *A*

$|\chi_A \cap \chi_B|$ intersection of common properties of *A* and *B*

$|\chi_A \cup \chi_B|$ unification of common properties of *A* and *B*

	Euclidian distance	**Manhattan distance**
		
formula	$D_{A,B}=\sqrt{\sum_{i=1}^{N}\left(x_{iA}-x_{iB}\right)^2}$	$D_{A,B}=\sum_{i=1}^{N}\lvert x_{iA}-x_{iB}\rvert$
definition	$D_{A,B}=\sqrt{\lvert\chi_A\cup\chi_B\rvert-\lvert\chi_A\cap\chi_B\rvert}$	$D_{A,B}=\lvert\chi_A\cup\chi_B\rvert-\lvert\chi_A\cap\chi_B\rvert$
range	∞ to 0	∞ to 0
other names	–	City-Block, Hamming

Distance crtiteria and similarity indices (II)

Soergel distance

$$D_{A,B} = \sum_{i=1}^{N} |x_{iA} - x_{iB}| / \sum_{i=1}^{N} \max(x_{iA}, x_{iB})$$

$$D_{A,B} = |\chi_A \cup \chi_B| - |\chi_A \cap \chi_B| / |\chi_A \cup \chi_B|$$

1 to 0

–

Tanimoto index

$$S_{A,B} = \left(\sum_{i=1}^{N} x_{iA} x_{iB} \right) / \left(\sum_{i=1}^{N} (x_{iA})^2 + \sum_{i=1}^{N} (x_{iB})^2 - \sum_{i=1}^{N} x_{iA} x_{iB} \right)$$

$$S_{A,B} = |\chi_A \cap \chi_B| / |\chi_A \cup \chi_B|$$

–0.333 to +1 (continous values)
0 to +1 (binary on/off values)

Jaccard coefficient

For binary (dichotomous) values the Soergel distance is complementary to the Tanimoto index

Distance criteria and similarity indices (III)

Dice coefficient

$$S_{A,B} = \left(2 \sum_{i=1}^{N} x_{iA} x_{iB} \right) / \left(\sum_{i=1}^{N} \left(x_{iA} \right)^2 + \sum_{i=1}^{N} \left(x_{iB} \right)^2 \right)$$

$$S_{A,B} = 2 |\chi_A \cap \chi_B| / \left(|\chi_A| + |\chi_B| \right)$$

–1 to +1
0 to +1

Hodgkin index
Czekanowski coefficient
Sørensen coefficient

monotonic with the Tanimoto index

Cosinus coefficient

$$S_{A,B} = \left(\sum_{i=1}^{N} x_{iA} x_{iB} \right) / \sqrt{\sum_{i=1}^{N} \left(x_{iA} \right)^2 \cdot \sum_{i=1}^{N} \left(x_{iB} \right)^2}$$

$$S_{A,B} = |\chi_A \cap \chi_B| / \sqrt{|\chi_A| |\chi_B|}$$

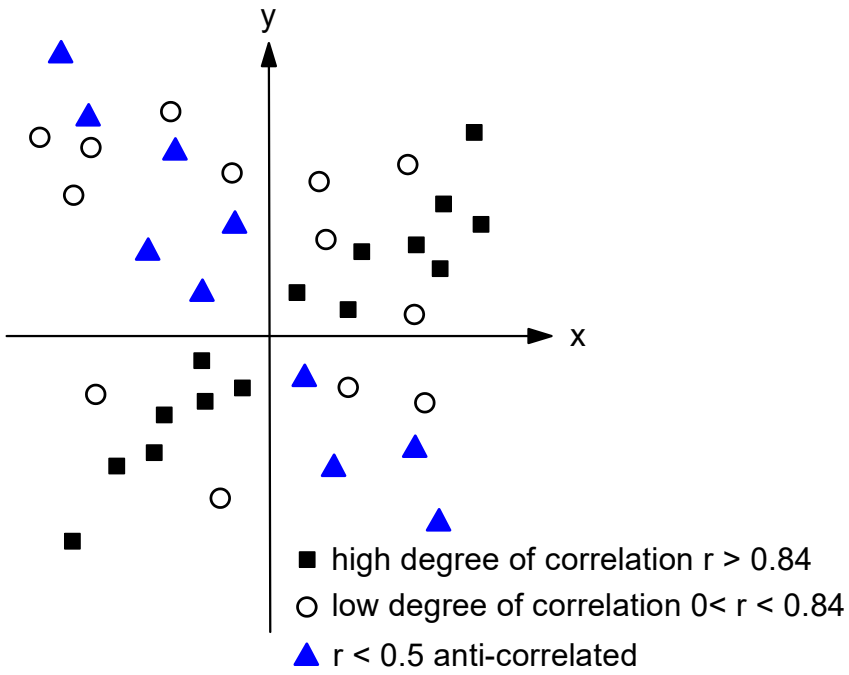
0 to +1 (continous values)
0 to +1 (binary on/off values)

Carbo index
Ochiai coefficient

Highly correlated to the Tanimoto index

Correlation between descriptors (I)

Descriptors can also be inter-correlated (colinear) to each other
→ redundant information should be excluded



Usually we will have a wealth of descriptors (much more than the available molecules) to chose from. To obtain a reasonable combination in our QSAR equation, multivariate methods of statistics or other selection procedures must be applied.

Correlation between descriptors (II)

How many descriptors can be used in a QSAR equation before overfitting sets in?

Rule of thumb:

per descriptor used, at least 5 molecules (data points) should be present

otherwise the possibility of finding a coincidental correlation is too high (as we will see later).

≥10 molecules → 2 descriptors
≥15 molecules → 3 descriptors...

(Ockham‘s razor: it‘s possible to fit anything to anything)
Therefore: Principle of parsimony; use the most simple explanation.

William of Ockham (1285 - 1347)

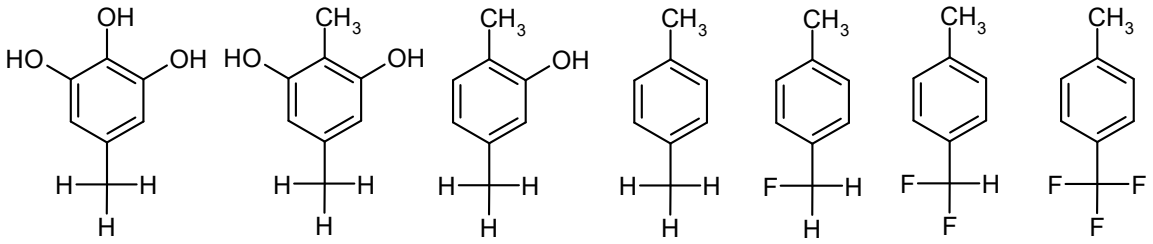
Deriving QSAR equations (I)

After removing the inter-correlated descriptors, we have to determine the coefficients k_i for those descriptors that appear in the QSAR equation.

Such multiple linear regression analysis (*least square fit* of the according coefficients) is performed by statistics programs.

There are several ways to proceed:

1. Using the descriptor that shows the best correlation to the predicted property first and adding stepwise descriptors that yield the best improvement (**forward regression**)



500000	100000	12500	1550	250	5.0	2.0

K_i [10^{-9} mol l^{-1}]

$$\log(1/K_i) = 1.049 \cdot n_{fluorine} - 0.843 \cdot n_{OH} + 5.768$$

Deriving QSAR equations (II)

2. Using all available descriptors first, and removing stepwise those descriptors that worsen the correlation fewest.
(**backward regression/elimination**)

3. Determining the best combination of the available descriptors for given number of descriptors appearing in the QSAR equation (2,3,4,...) (**best combination regression**)

This is usually not possible due to the exponential runtime.

Problem of forward and backward regression:

Risk of local minima

Problems: Which descriptors are relevant or significant?
Which descriptors are easy to understand?

Determination of such descriptors see lecture 6