# Substance Databases and Bioisosteric Compounds

Problems:

a) How to choose promising compounds for experimental/virtual screening?

b) How to automate screening (more compounds tested = more hits?)

1. step: choice of *target*

2. step: How much information about the *target* is available? Are there any *lead compounds* present already?

3. step: if yes, generate a virtual substance library based on the lead compound(s) → find/generate similar compounds

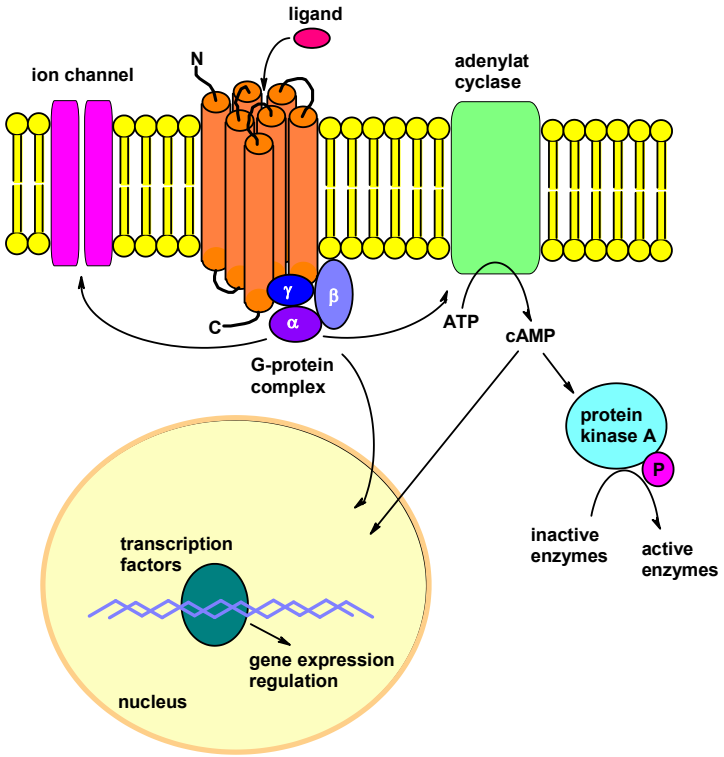
4. step: planning of synthesis (combinatorial chemistry)

# Setup of substance libraries for high thoughput screening (I)

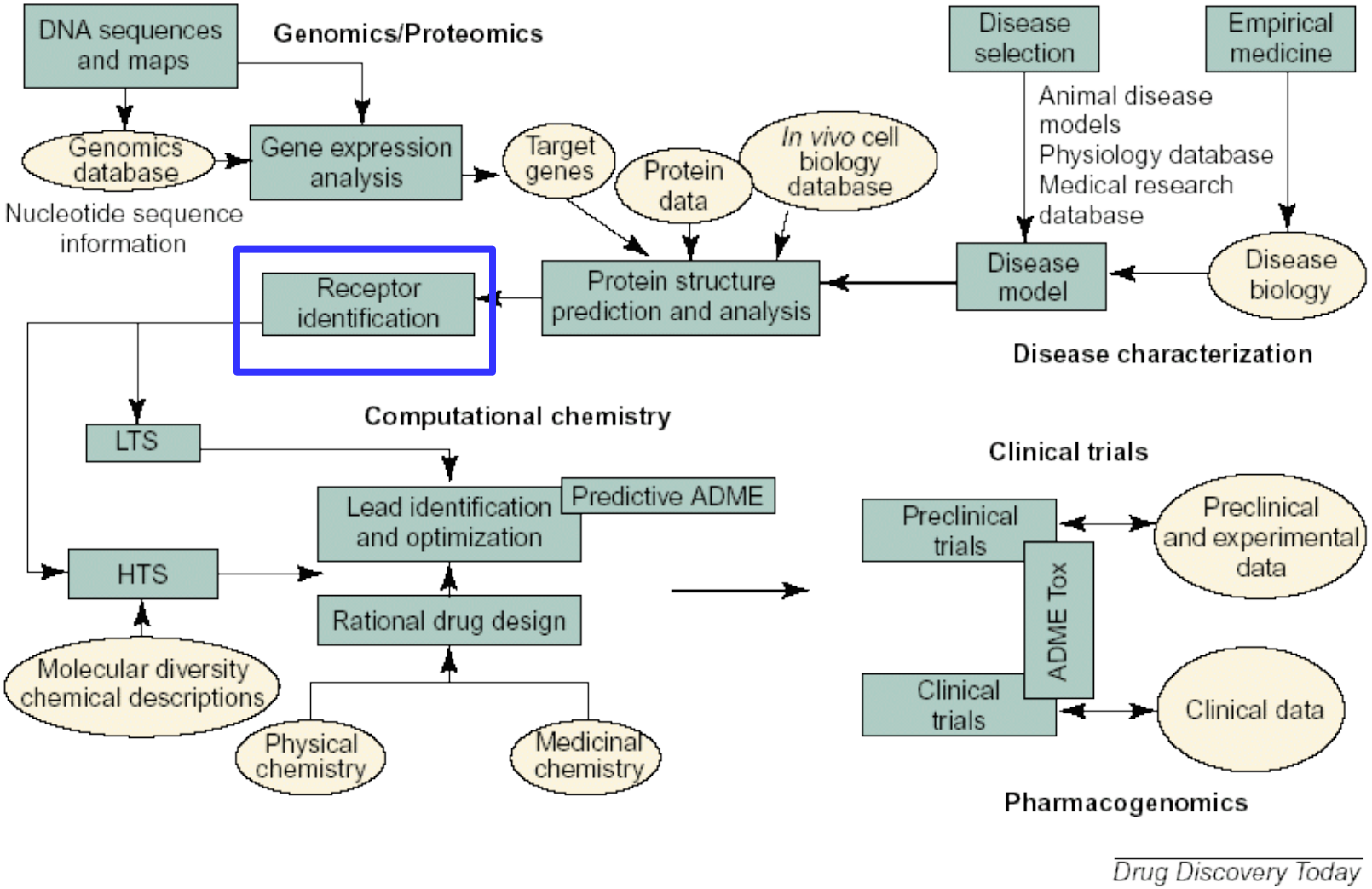
automated test of >1000 compounds on the *target*

Requires the synthesis of the according number of substances and processing of the results

1. step: choice of *target*



# Flow of information in a *drug discovery pipeline*



# Compound selection

How much information about the *target* is available?

increasing information

X-Ray with drug

X-Ray of protein

series of functional compounds

few *hits* from HTS

knowledge of enzymatic functionality (e.g. kinase, GPCR, ion channel)

*docking*

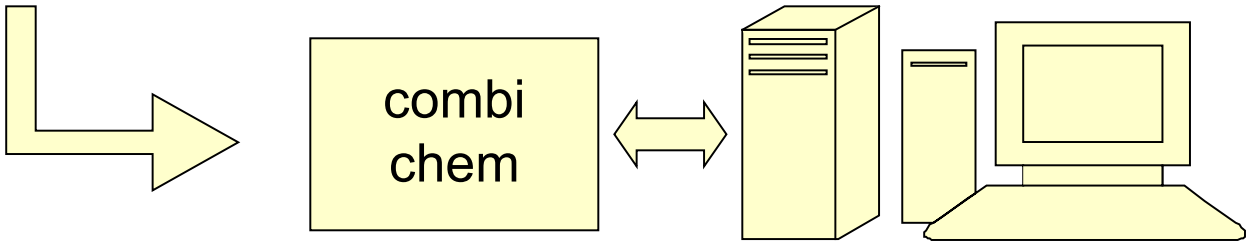
*HTS*

*active site*

*QSAR,*

*generate pharmacophore*

eADME filter




Setting up a virtual library

# Properties of combinatorial libraries

Combinatorial libraries are also tailored to their desired application:

| | |
|---|---|
| random libraries | drug-like / diverse scaffolds |
| focused libraries | lead-like / most comprehensive for a certain class of enzymes |
| targeted libraries | one single enzyme / substituents as diverse as possible |

**Chemogenomics**

aim: maximum diversity of substance libraries

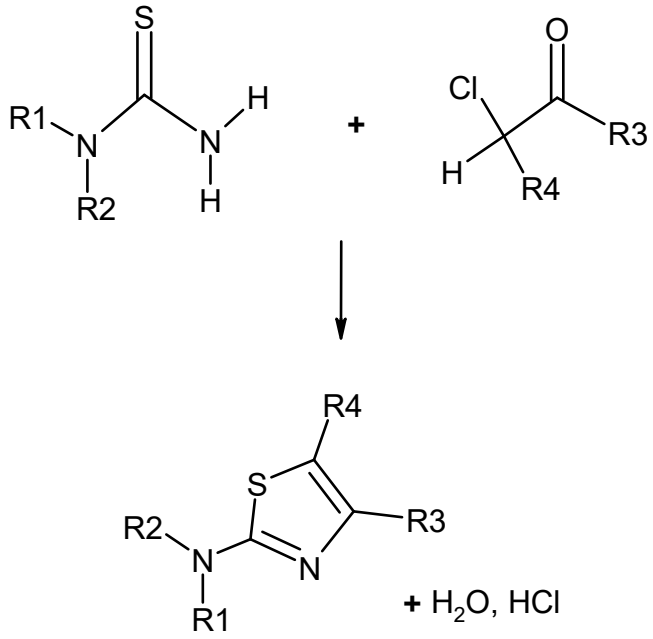
avoiding redundant compounds

improved propability of hits in the HTS

# Combinatorial approaches in rational drug design

automated tests of >1000 compounds on a single *target* require particularly effective synthesis and screening strategies:

- synthesis robots
- High Throughput Screening





Original idea: The more compounds being tested, the higher the likelihood of finding a lead compound *should* be.

# Setup of substace libraries for the High Thoughput Screening (IV)

Synthesis of a multitude of compounds based on a lead compounds required a change in paradigms.

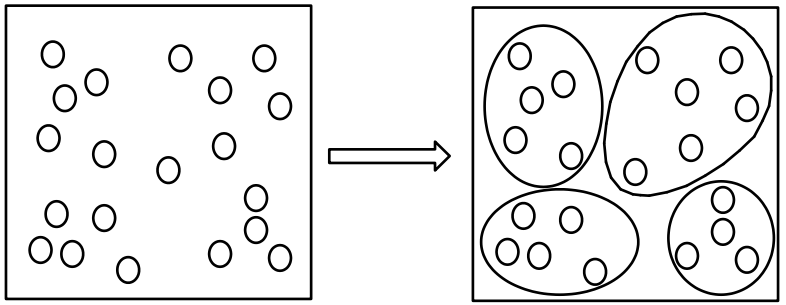
Until the late 80‘ substances selected for screening were synthesized one by one individually.

The principles of High Troughput Screening required, however, a different approach.

„If you are looking for the needle in the haystack, it is best not to increase the size of the haystack.“

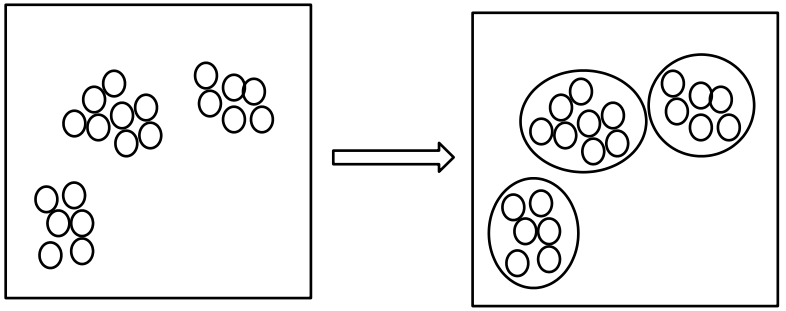
# Clustering in sets of data (I)

To evaluate the diversity of a data set, respectively a generated substance library, the obtained compounds have to be grouped to clusters.



diverse library

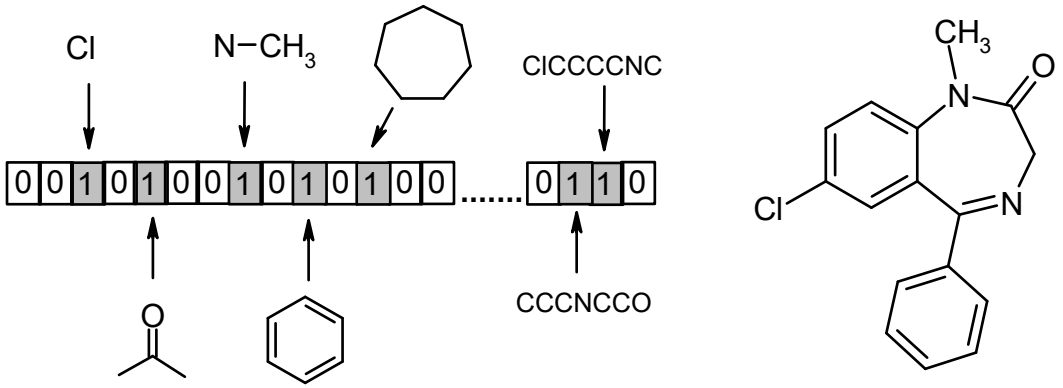
Test further molecules of the same cluster that produced a hit in the HTS



One molecule of each cluster selected for HTS

The assignment of the molecules is based on their pair-wise similarity. → Encode molecules in terms of features.

# Encoding of Molecules for Data Base Storage




Each present feature set the corresponding bit on

→ binary *fingerprint* of the molecule

Pro : Resulting bit string allows efficient storage, retrival and comparison (bit-wise AND, OR, EOR operations)

Con: Choice of predefined features is abitrary and may lead to bias of predefined features

# Classification of compounds (I)

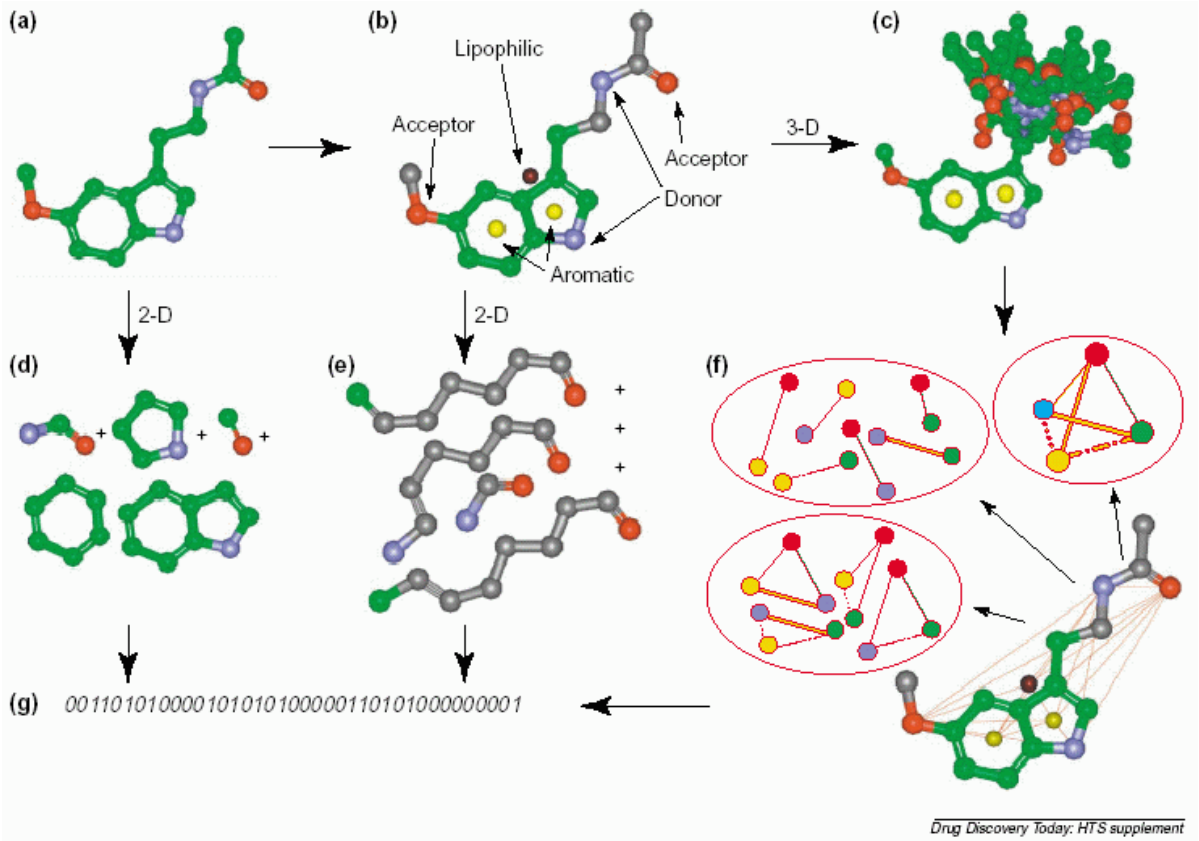



**Figure 2.** Schematic illustration of primary methods used in molecular fingerprint creation. **(a)** Create 2-D and 3-D model of molecule; **(b)** deconstruct the molecule into pharmacophoric elements; **(c)** generate conformational models; **(d)** deconstruct the molecule into topological/substructural 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.

Using pharmacophoric features to obtain a binary *fingerprint* of a molecule

# Fingerprints (I)

Similarity of two molecules A and B represented as fingerprints is computed (most frequently) via the Tanimoto coefficient/index (Jaccard index)

$$J(A,B) = \frac{|A \cap B|}{|A \cup B|} = \frac{|A \cap B|}{|A| + |B| - |A \cap B|}$$

common bits of A and B (intersection)

all bits of A and B (union, length of fingerprint

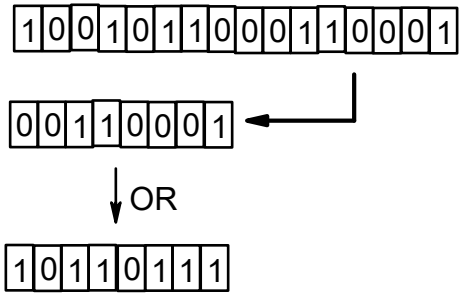
Inherent problem: with increasing length of a fingerprint the chance of common bits is decreasing; so does the information density. As a consequence similarity values become lower than expected. Thus the discriminatory power in virtual screening worsens.

Lit: M.Vogt & J.Bajorath *F1000 Research* **9** (2020) 100.

# Fingerprints (II)

How to „increase“ similarity scores

**Folding** of fingerprints: perform a logical OR operation on both halves, which yields a shorter fingerprint.



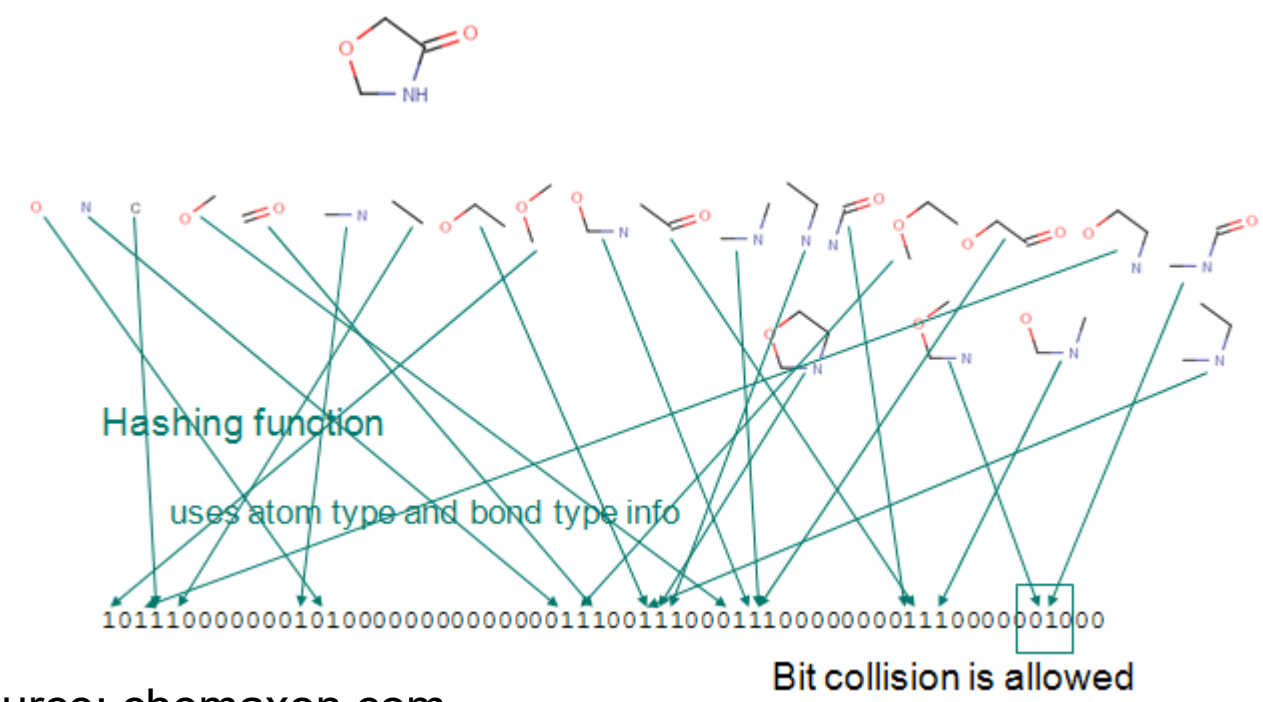

Pro: results in higher bit density and likewise higher similarity Tanimoto coefficients

Con: increases the number of false positive hits (features that are not actually present in the molecule)

# Fingerprints (III)

How to „increase“ similarity scores

**Hashing** of fingerprints: Like usual hashing functions single features are rearranged, resp. grouped together (bit collision)




Source: chemaxon.com

Con: A single feature can no longer be identified unambigously, but *similar substructures* can be grouped together.

# Classification of compounds (II)

Frequently applied fingerprint concepts are:

- Daylight fingerprint (1024 bits) → see also openbabel
- ISIS MOLSKEYS (atom types, fragments of molecules)
- Circular/Morgan/Extended Connectivity Fingerprints
takes the neighborhood of an atom into account
Lit: Rogers & Hahn *J.Chem.Inf.Model.* **50** (2010) 742.
- Topological Torsion
take 1-4 atom type sequences into account
Lit: Nilakatan et al. *J.Chem.Inf.Comput.Sci.* **27** (1987) 82.
- 2D-Pharmacophore Fingerprints
use predefined features
Lit: Gobbi & Poppinger *Biotech.Bioeng.* **61** (1998) 47.

see also RDKit for python implementation www.rdkit.org

Comparison of fingerprints and their performance:

Lit. H.Briem & U.Lessel *Persp.Drug Discov.Des.* **20** (2000) 231.

S.Riniker & G.A.Landrum *J.Cheminf.* **5** (2013) 26.

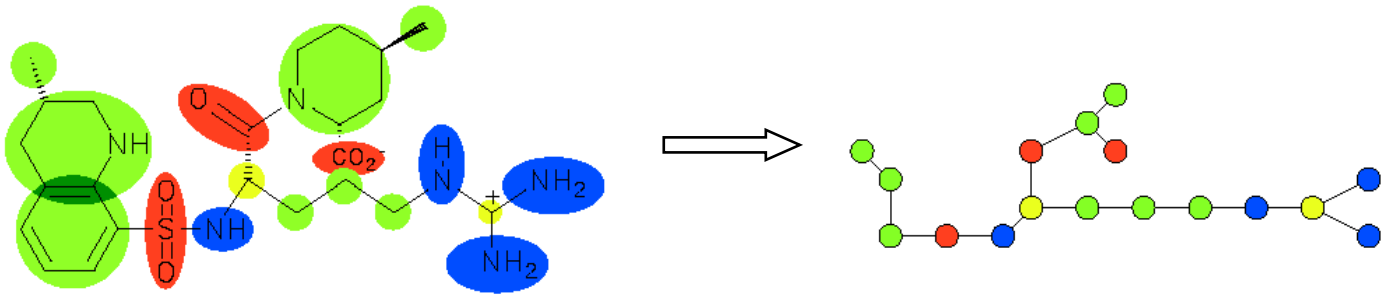
# Classification of compounds (III)

FTREES feature trees concept:
each node (in a molecule) represents a chemical feature

Lit. M.Rarey & J.S.Dixon *J.Comput.-Aided Mol.Des.* **12** (1998) 471.

Allows to search for chemically similar compounds in large virtual substance libraries

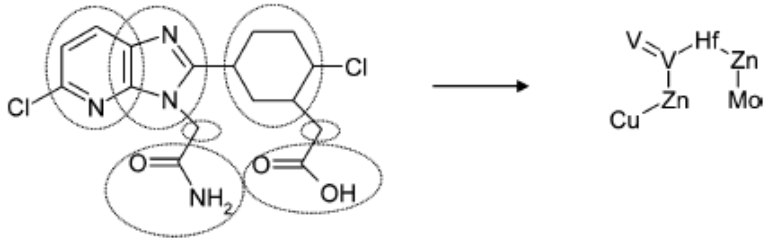
Lit. M.Rarey & M.Stahl *J.Comput.-Aided Mol.Des.* **15** (2001) 497.




→ the molecule is represented as reduced graph.
The FTREES concept furthermore allows (fast) matching of sub-trees to find similar compounds.

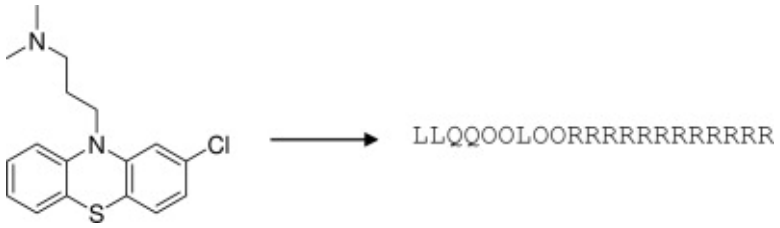
# Classification of compounds (IV)

Comparison of molecules using (reduced) graphs:




Lit: V.J.Gillet and co-workers *J.Chem.Inf.Model.* **46** (2006) 577.

Comparison of molecules using alignments: PhAST, LINGO




| LINGO freq. | | LINGO freq. | | LINGO freq. | |
|---|---|---|---|---|---|
| "N(C)" | 1 | "ccc(" | 1 | "c0Sc" | 1 |
| "0Sc0" | 1 | "cc00" | 1 | "0c0c" | 1 |
| "cccc" | 2 | ")CCC" | 1 | "CN(C" | 1 |
| "N0c0" | 1 | "L)cc" | 1 | "(L)c" | 1 |
| "C)CC" | 1 | "cc(L" | 1 | "CN0c" | 1 |
| "c(L)" | 1 | "Sc0c" | 1 | "(C)C" | 1 |
| "ccc0" | 1 | ")cc0" | 1 | "c0cc" | 2 |
| "0ccc" | 2 | "cc0S" | 1 | "CCN0" | 1 |
| | | "CCCN" | 1 | | |

Lit: G. Schneider and co-workers *J.Comput.Chem.* **30** (2009) 761.

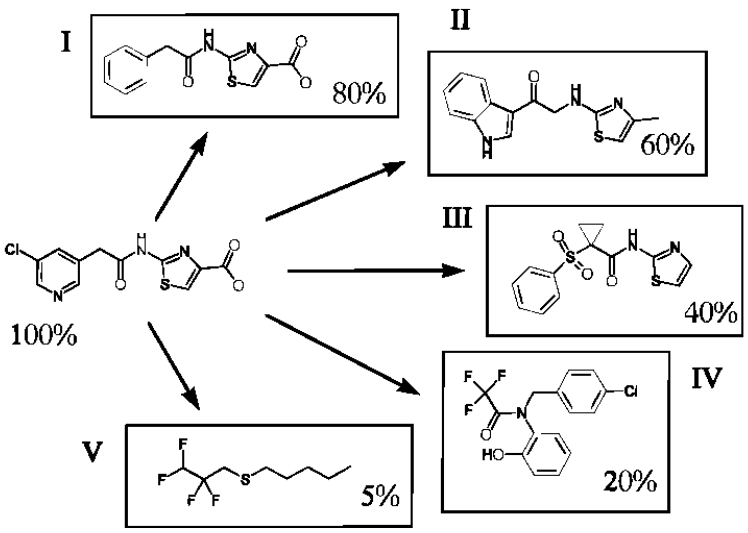
Lit: D. Vidal et al. *J.Chem.Inf.Model.* **45** (2005) 386.

# Similarity of chemical compounds

The pair-wise similarity of two molecules can be expressed by similarity indices computed from their binary fingerprints.

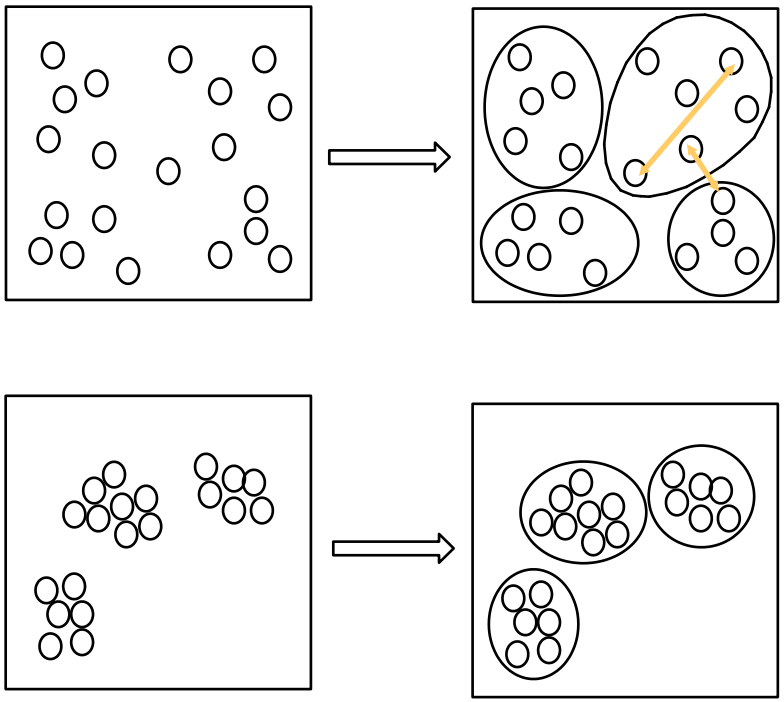
The comparison of binary data is computationally simple, but there are a number of different similarity indices. For the comparison of molecules the Tanimoto index is most frequently being used.

More about similarity indices in lecture 6




Lit. D.R.Flower *J.Chem.Inf.Comput.Sci.* **38** (1998) 379.

# Clustering in sets of data (II)



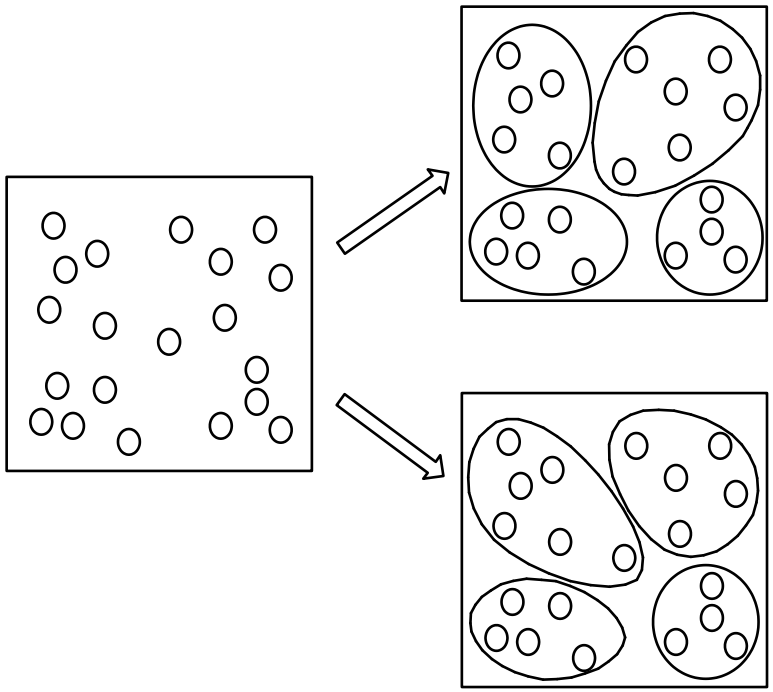
problem: The similarity of two molecules can be higher in between two different clusters than within the same cluster.

→ distance criteria (Eucledian, Manhattan, ...)

→ single linkage vs. complete linkage

# Clustering in sets of data (III)

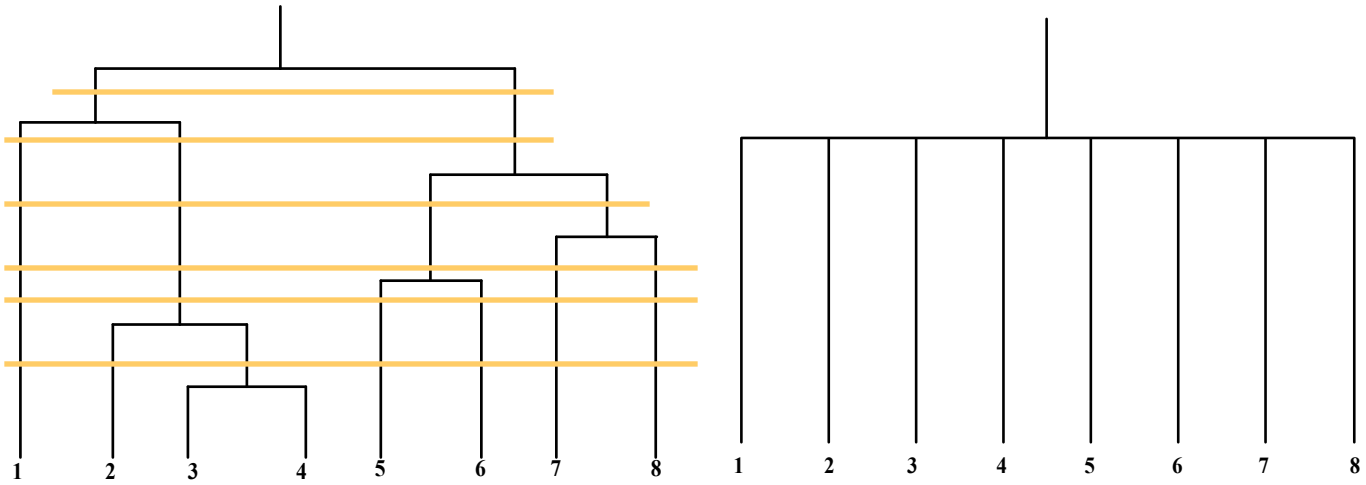
In general: Different algorithms for generating clusters will produce different clusters.



There is a „natural“ clustering in the data set, if different methods produce very similar looking clusters.

# Methods of clustering (I)

There are two large groups of clustering algorithms: hierarchical and non-hierarchical



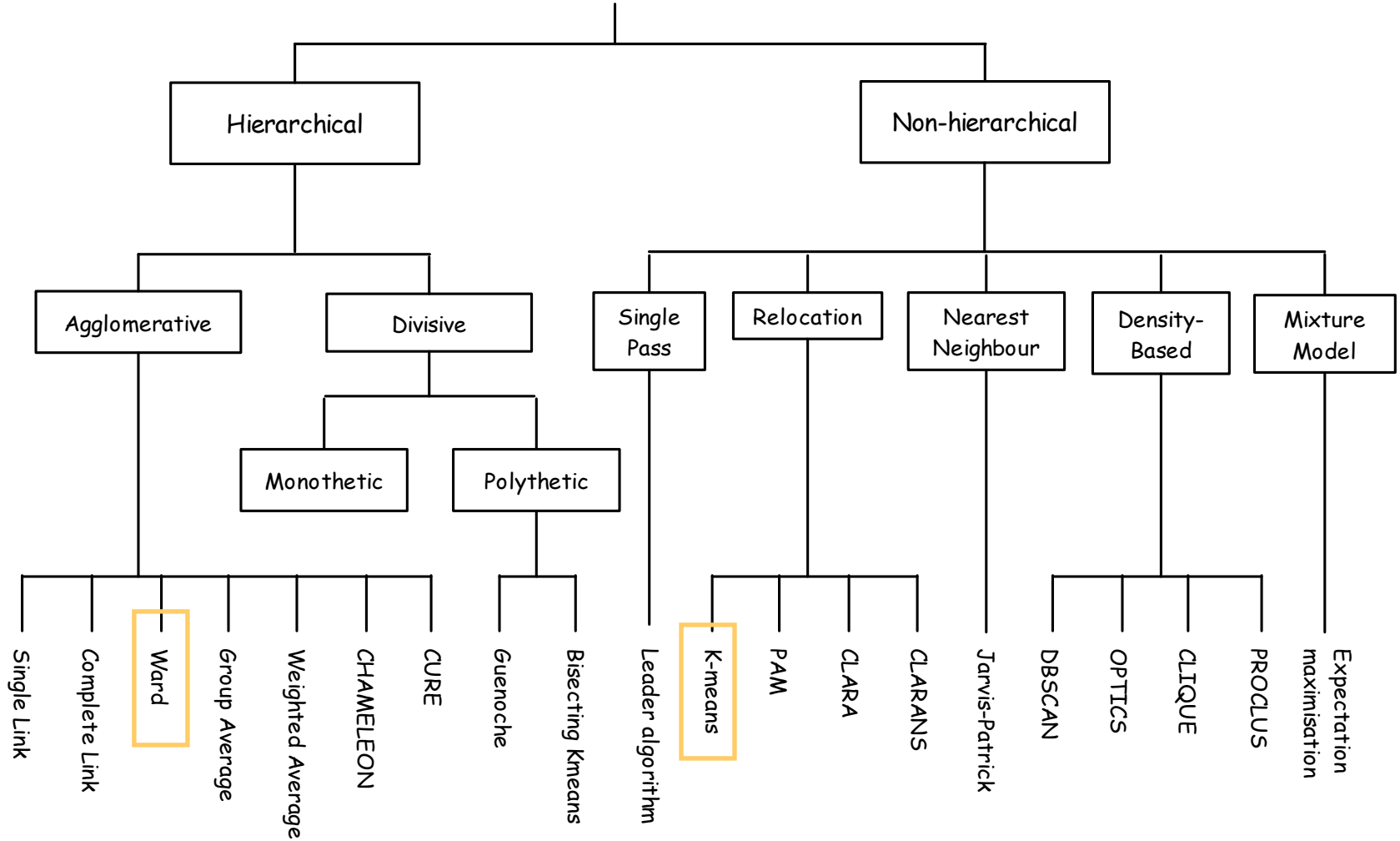

hierarchical clustering methods have the advantage of allowing access a each level.

all methods for clustering are computationally expensive !

runtime: O($nN$) to O($n^2N$) for $n$ out of $N$ molecules

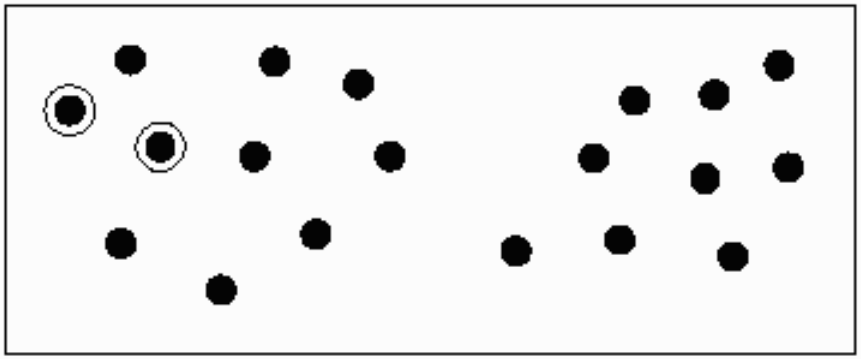
# Methods of clustering (II)

„Clustering of clustering methods“- a dendrogram

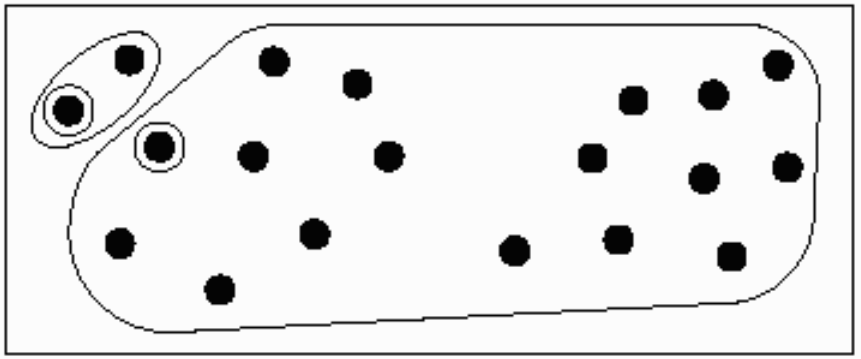



source: John Barnard, Barnard Chemical Information Ltd.

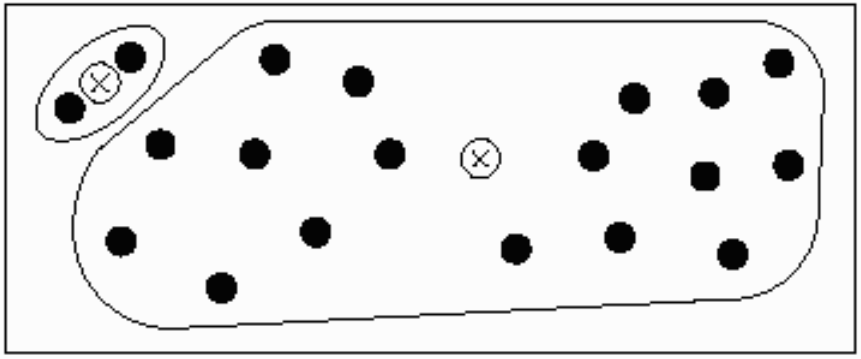
# K-means with mobile centroid (I)



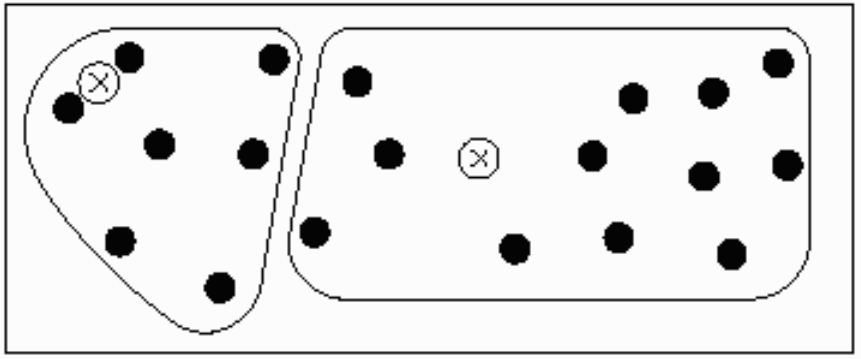
Step 1: K initial centroids are selected



Step 2: Clusters are constructed by affecting each molecule to the closest centroid



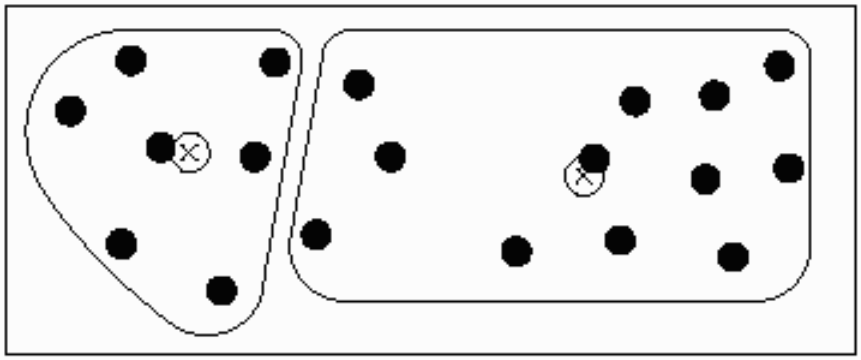
Step 3: Centres of gravity are calculated



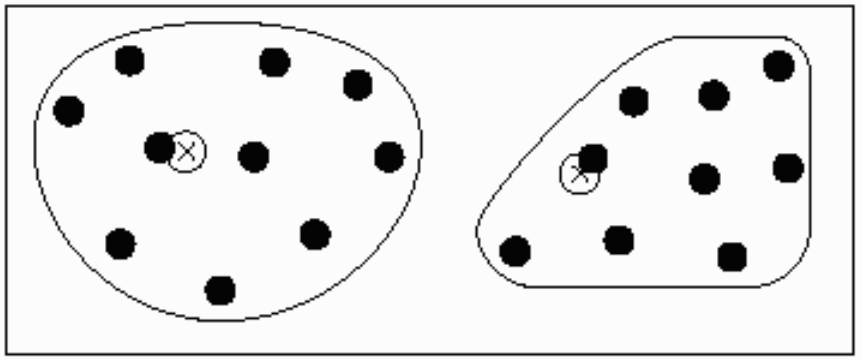
Step 4: Clusters are reconstructed

Lit: D.Gorse et al. *Drug Discovery Today* **4** (1999) 257.

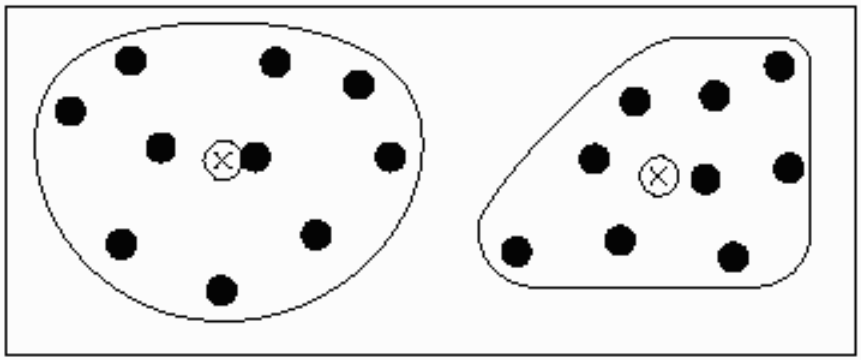
# K-means with mobile centroid (II)



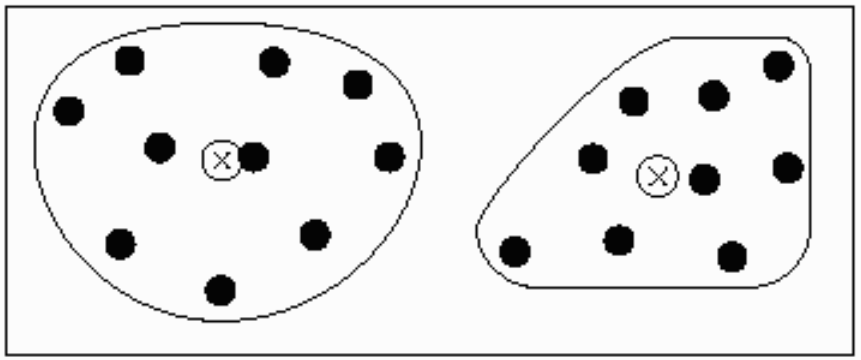
Step 3′: Centres of gravity are calculated



Step 4′: Clusters are reconstructed



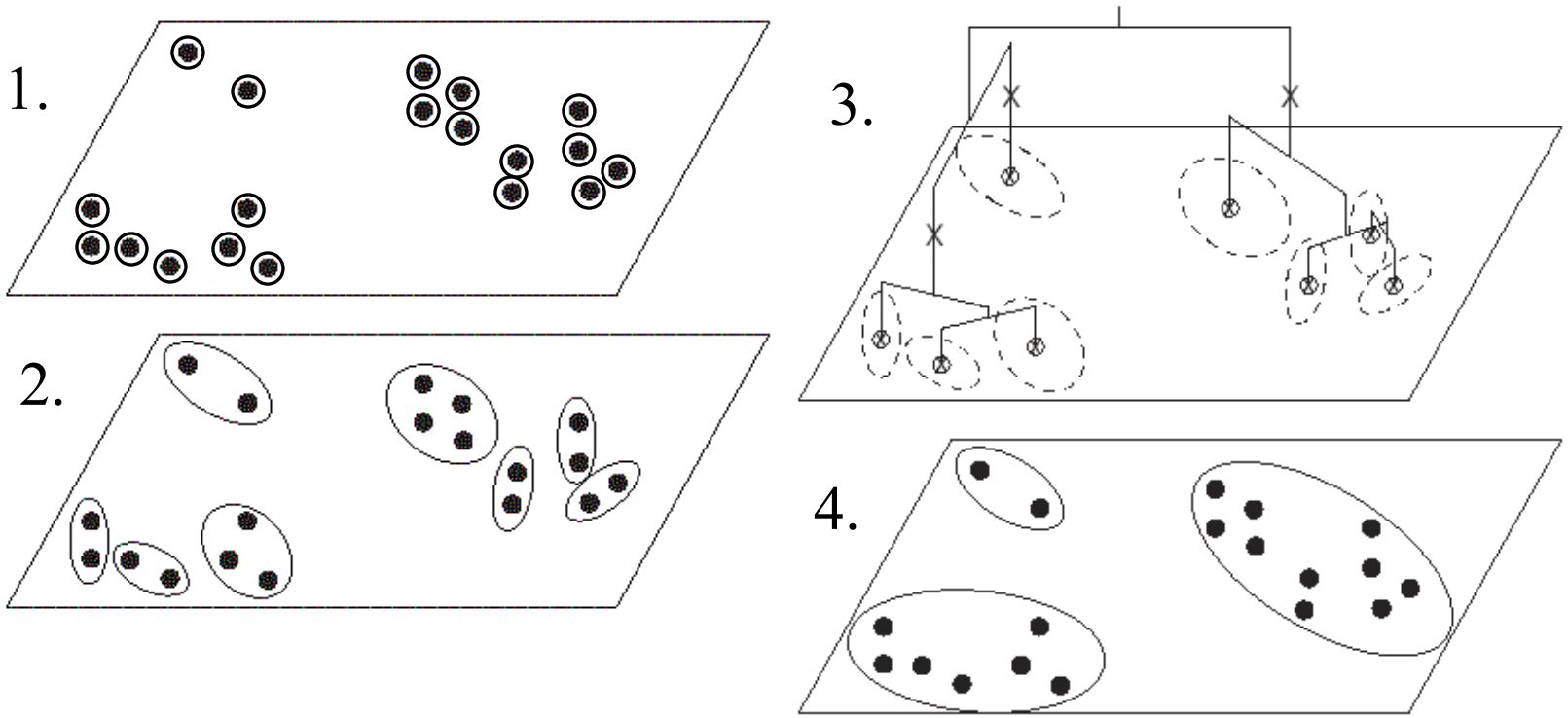
Step 3″: Centres of gravity are calculated



Step 4″: Clusters are reconstructed
Convergence is reached

Disadvantage: spherical clusters are often not adapted optimally regarding the distribution of the molecules in the chemical space

# Mobile centres with Ward classification

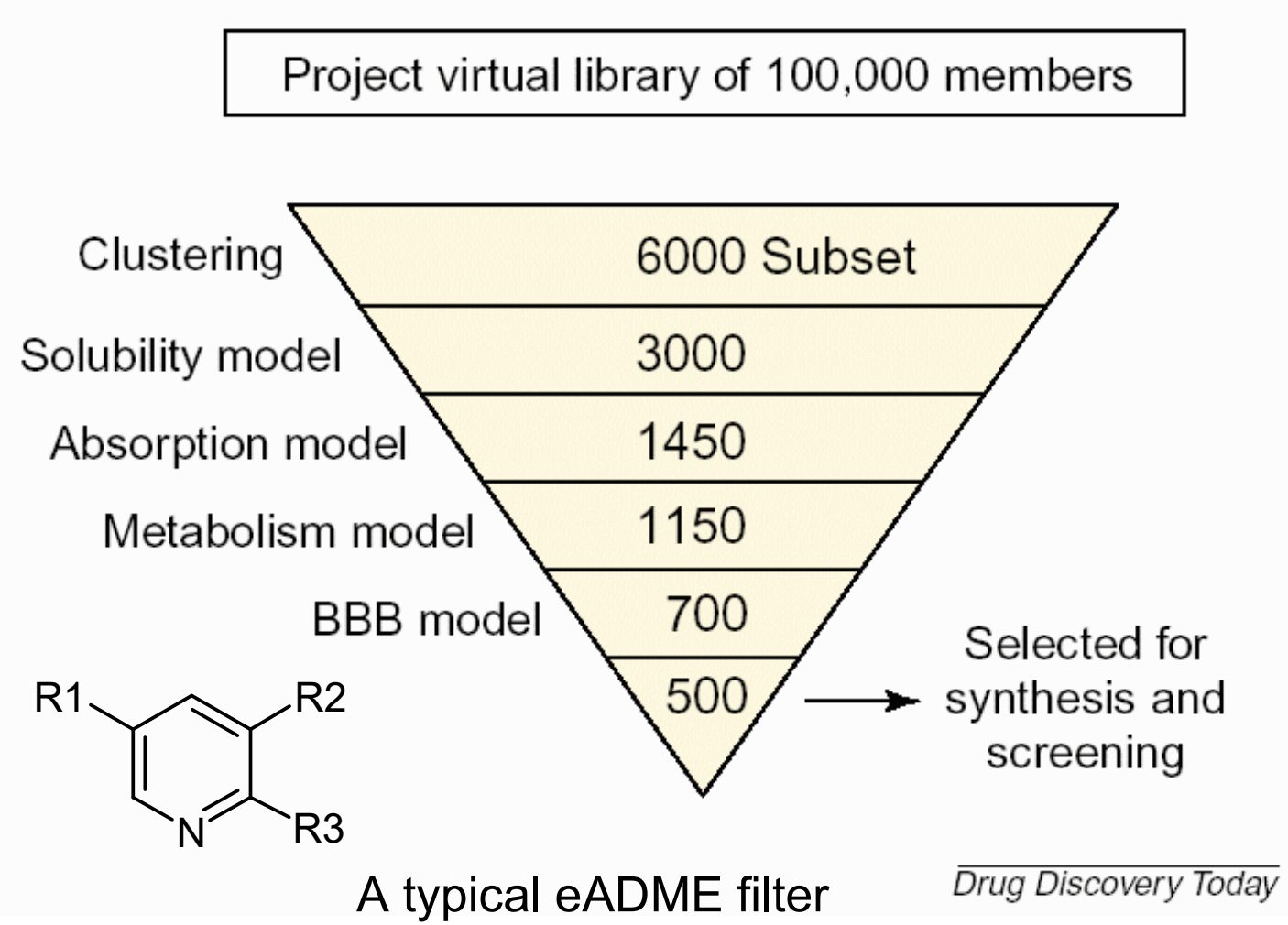



Most similar points of data are grouped to clusters step by step

Advantage: hierarchical, adapted shape of the clusters

Lit: D.Gorse et al. *Drug Discovery Today* **4** (1999) 257.

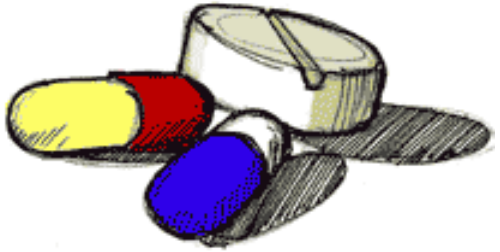
# eADME filter proceeding High Throughput Screening (HTS)

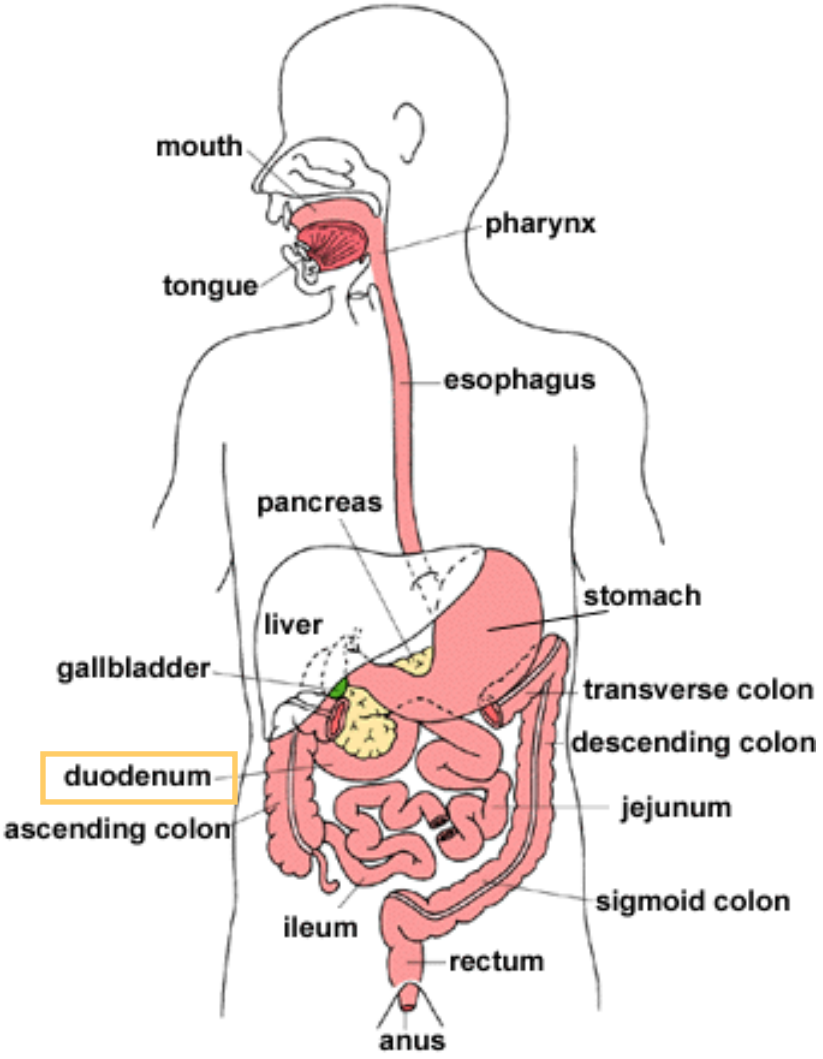


# Absorption

How does the drug reaches its destination ?

During the HTS the bioavailability is neglected first. To ensure the availability of the full dose in the assay, the substances are dissolved in a mixture of water and DMSO instead of pure water.



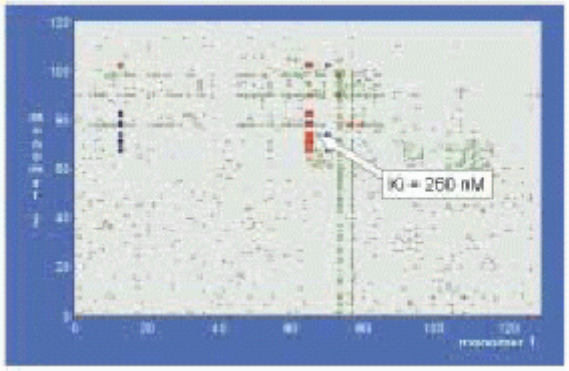


# Evaluation of HTS results

Original idea: Automated test of >1000 compound on the target

Requires the synthesis of the according number of compounds, as well as processing of the results.

Sources of uncertainties are:

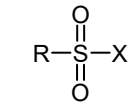



- purity and reliability of the compounds (false negatives)
- colored compounds (false positives)
- colloidal aggregation
- undesired covalent binding
- unspecifically binding compounds (false positives)
  e.g. ibuprofen is a promiscous binder

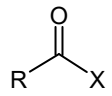
**P**an **A**ssay **In**terference **C**ompounds (PAINS) → in silico filtering

Lit: Aldrich et al. *J.Chem.Inf.Model.* **57** (2017) 387 and references therein

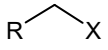
# Substructures to be avoided



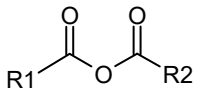
sulfonyl halides



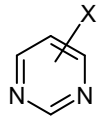
acyl halides



alkyl halides

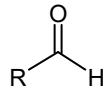


anhydrides

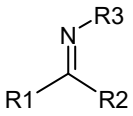


halopyrimidines

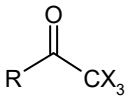
X at any of the carbon atom



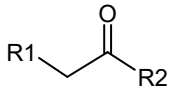
aldehydes



imines

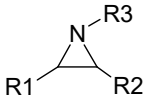


perhalo ketones

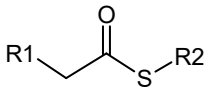


aliphatic ketones

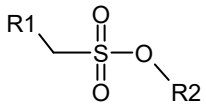
epoxides



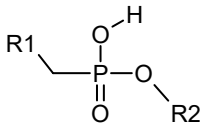
aziridines



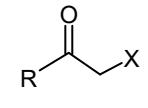
thioesters



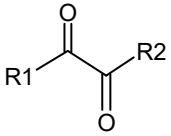
sulfonate esters



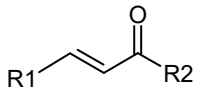
phosphonate esters



α-halocarbonyls



1,2-dicarbonyls



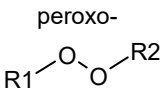
Michael acceptors

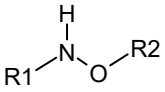
R = carbon

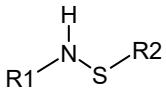
X = F or Cl or Br

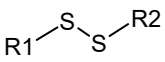
labile single bonds between hetero atoms (N, O, S)

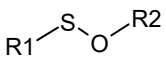
peroxo-

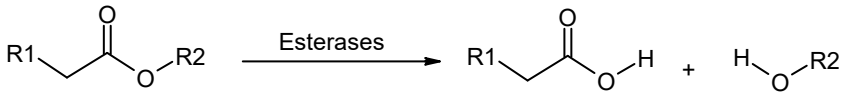


aliphatic esters

present in many prodrugs !

Reactive functional groups that produce false positive screening hits because they react with other substances

source: Hugo Kubinyi, www.kubinyi.de

# Setup of substance libraries for high thoughput screening (V)

3. step: if yes, generate a virtual substance library based on the lead compound(s)

systematic variation of the lead compound:

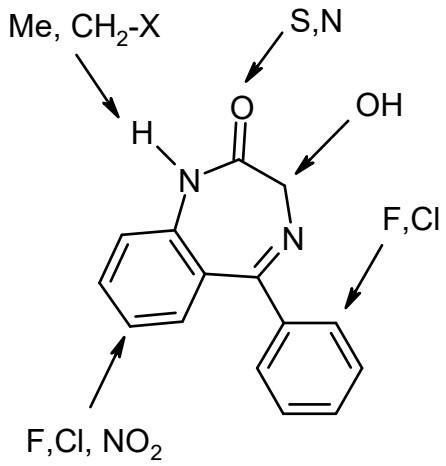
framework

side chains / substituents

bioisosters

⬇

Similar biological properties



# Publically Available Compound Databases

| | | |
|---|---|---|
| PubChem | > 112,000,000 compounds | NCBI |
| ChEMBL | > 2,200,000 compounds | EMBL |
| DrugBank | > 500,000 drugs | University of Alberta |
| ZINC15 | > 750,000,000 compounds | UCSF |

(this list is not comprehensive!)

| database | actual drugs | drug-like | lead-like | chemicals |
|---|---|---|---|---|
| PubChem | ++ | ++ | + | ++ |
| ChEMBL | ++ | + | + | - |
| DrugBank | ++ | + | - | - |
| ZINC | + | ++ | ++ | ++ |

Often compounds are hyper-linked to further information, such as targets and assays.

# Setup of substance libraries for high thoughput screening (VI)

During the optimization from the lead compound to the clinical drug, substances are usually getting larger and more lipophilic (extensive filling of the binding pocket with mostly hydrophobic parts).

Therefore these properties of lead compouds are desirable:

- molecular weight < 250
- low lipophilicity (logP<3) if orally administered
- enough possibilities for side chains
- sufficient affinity and selectivity

# Bioisosters (I)

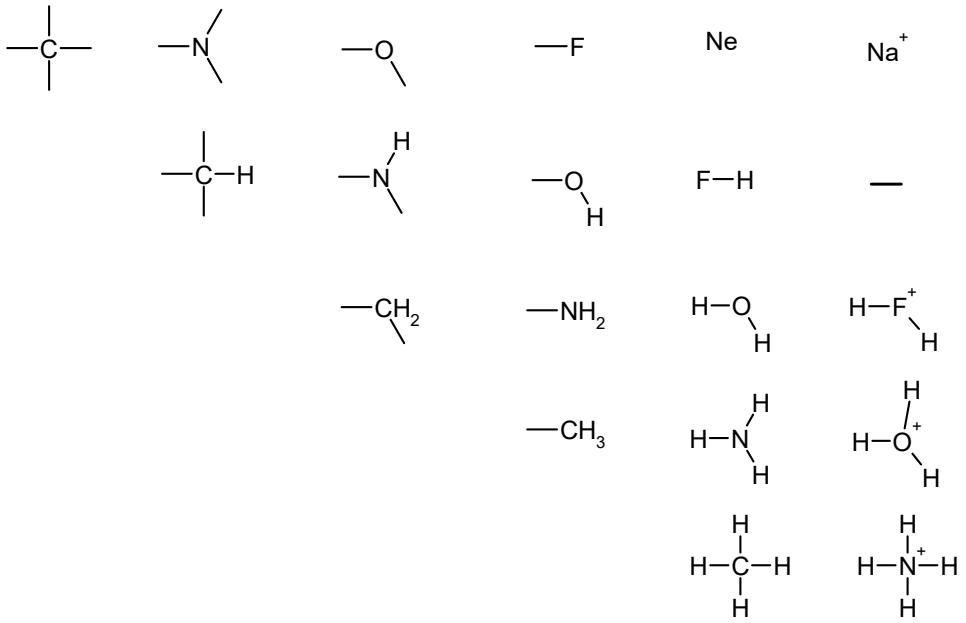
definition: Same number and arrangement of electrons (Langmuir 1919)

e.g. $N_2$ CO $CN^-$

$CO_2$ $N_2O$ $N_3^-$ $CNO^-$

$K^+$ $NH_4^+$ Ar

Grimm‘s hydride exchange law (1925)



# Bioisosters (II)

Definition:

Compounds or groups that possess near-equal, molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties.

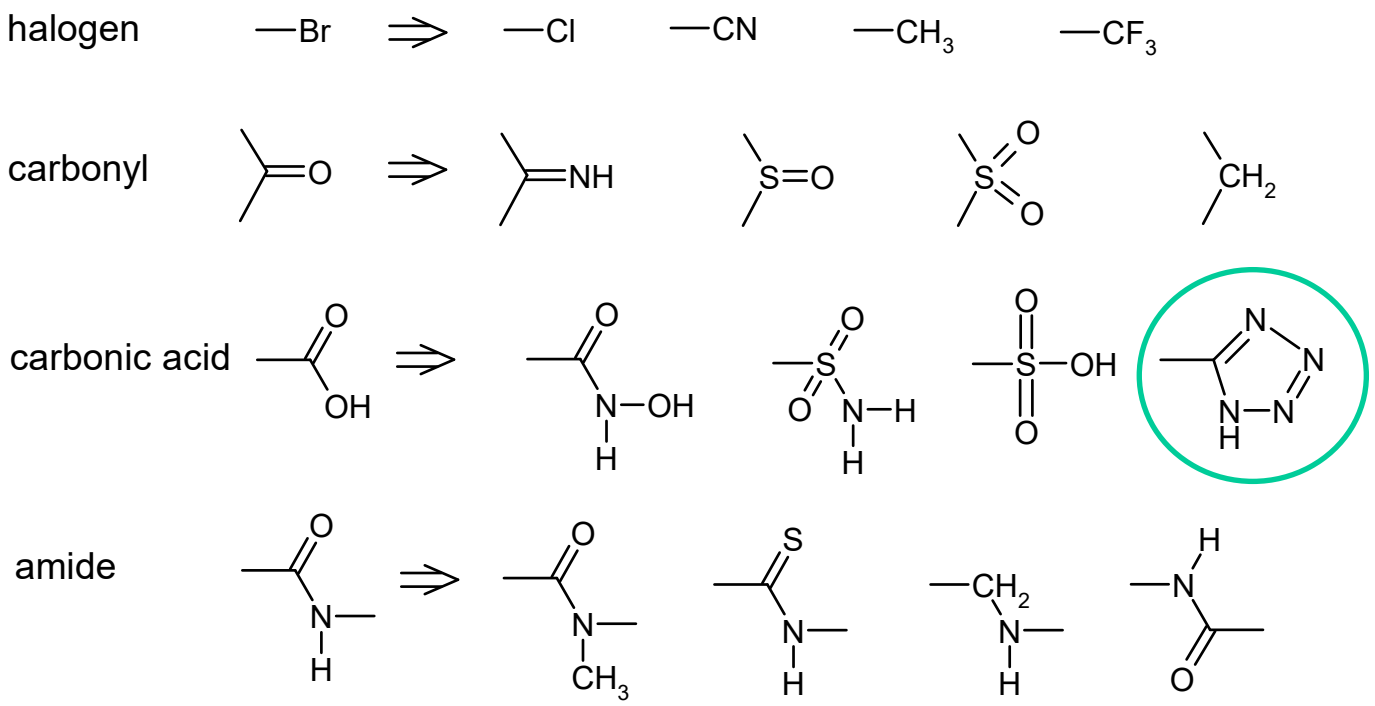
(A. Burger 1970)

| | | | |
|---|---|---|---|
| e.g. | -Cl | $-CF_3$ | -CN |
| | $-NO_2$ | $-COCH_3$ | $-SO_2CH_3$ |
| | $-CHCl_2$ | $-CH_2N_3$ | |

Review article: G.A. Patani, E.J. LaVoie, *Chem.Rev.* **96** (1996) 3147.

# Bioisosters (III)

classical (bio-)isosters are sterically and electronically similar




Non-classical isosters:

e.g. exchange of cyclic against linear structures

exchangeable groups (no apparent similarity)

# Bioisosters (IV)

In the rarest cases bioisosters (similar *chemical space*) will show the same activity profile (similar *biological space*) than the compound they have been derived from.

Aimed are following properties:

- better mode of action
- improved selectivity
- increased bioavailability

} allows lower dosage

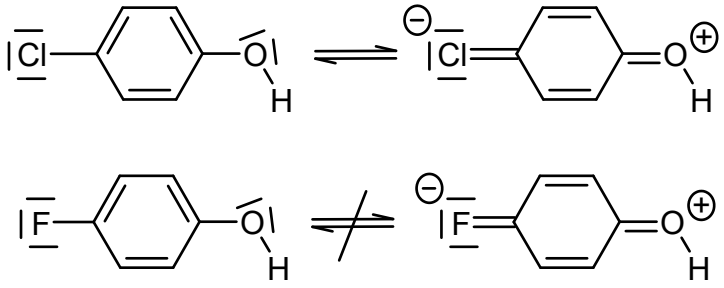
- less toxic
- fewer adverse side effects

# Monovalent Bioisosters (I)

## Exchange of (non-polar) H for F

Fluorine has a similar van der Waals radius compared to hydrogen and is thus about the same size. The lipophilic character is retained (fluorocarbons are even less soluble than hydrocarbons).

Fluorine is the most electronegative element, thus it produces an inductive effect (electron pulling) onto the neighboring C atom. In contrast to the other halogens, however, no mesomeric structures are possible. (attributed to the lack of *d*-orbitals)

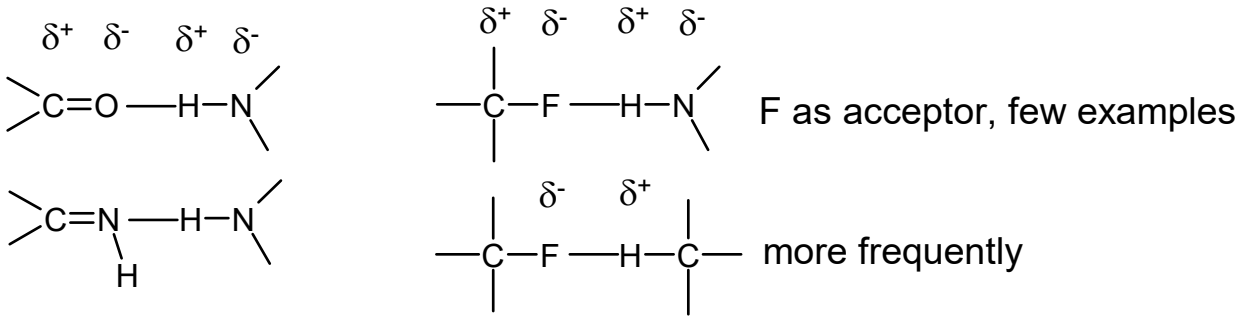


# Monovalent Bioisosters (II)

## Exchange of –H for –F

The C–F bond is stronger than the corresponding C–H, C–Cl, C–Br, and C–I bonds and therefore also more inert against metabolic reactions.

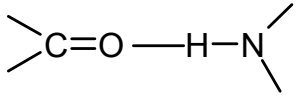
In principle, fluorine should also be a suitable H-bond acceptor like nitrogen or oxygen. However, in X-ray structures this is rarely seen.



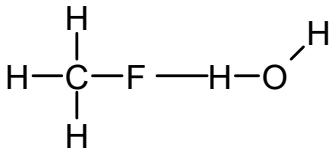

Lit: H.J. Böhm et al., *ChemBioChem* **5** (2004) 637.

# Fluorine in Hydrogen Bonds

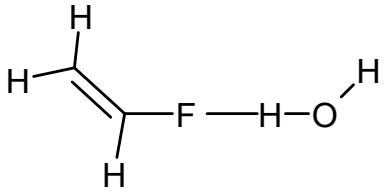
Electronegativity goes along with the tendency to accept electrons, not protons. Covalently bound fluorine is, however, a weak base and an extremely weak proton acceptor. Corresponding H-bonds are very weak.



ca. 5 kcal $mol^{-1}$



2.4 kcal $mol^{-1}$



1.5 kcal $mol^{-1}$

Thus, flourine is mainly used to block metabolically labile sites in drugs, or to increase lipophilicity without increasing the size at that spot.

Lit: J.A.K. Howard et al. *Tetrahedron* **52** (1996) 12613.
J.D. Dunitz, R. Taylor, *Chem.Eur.J.* **3** (1997) 89.

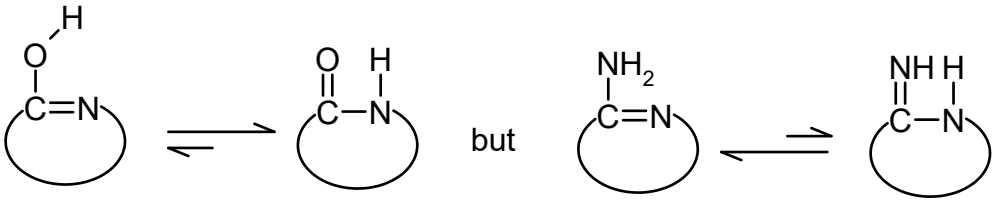
# Monovalent Bioisosters (III)

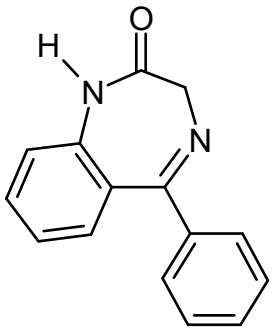
**Exchange of –OH for –$NH_2$**

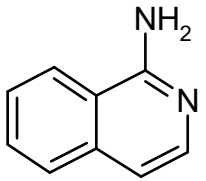
Both groups possess similar size and shape

Both are H-bond donors as well as H-bonds acceptors

In heterocyclic rings the equilibrium tautomer is shifted:



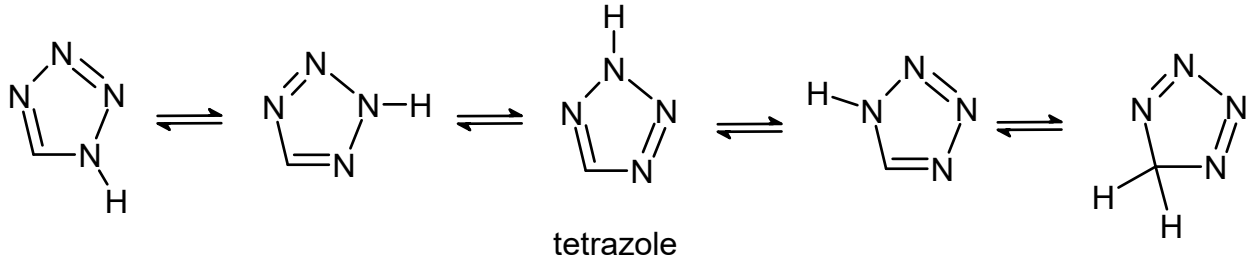



# Tautomers

Isomers that are interconvertible by the (formal) shift of a hydrogen (atom or proton) along the switch of a single bond and an adjacent double bond. In solution the equilibrium distribution of the possible tautomeric forms is dependend on pH, solvent, ions, ...


keto enol amine imine


lactam lactim enamine imine




tetrazole

# Monovalent Bioisosters (IV)

**Exchange of –SH for –OH**

Sulfur is much larger than oxygen

$R_{vdw}$(O) = 1.4 Ångstrom $R_{vdw}$(S) = 1.85 Ångstrom

and of lower electronegativity

O: 3.5 S: 2.4 - 2.6

Thus hydrogen bonds to SH are weaker.

Anyhow, thioles are more acidic and stronger dissociated than the corresponding alcoholes.

Cys-SH $pK_a$ 8.3

Ser-OH $pK_a \approx 13$

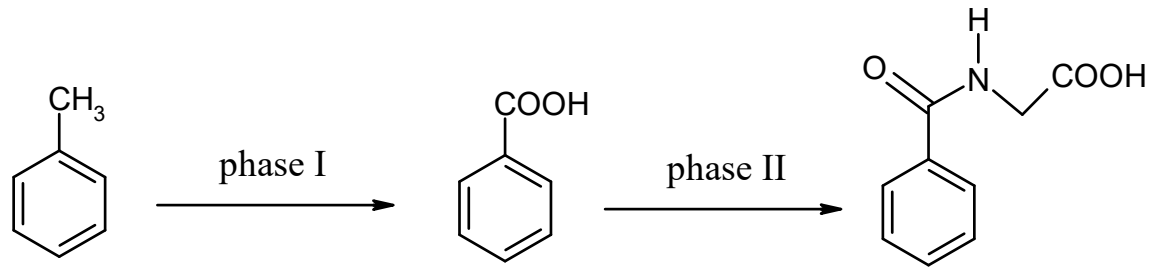
In heterocyclic rings the corresponding thiol can be formed by tautomerization similar to $–NH_2$

# Monovalent Bioisosters (V)

**Exchange of –Cl for –$CH_3$**

Chlorine and the methyl group possess the same size and lipophilicity.

In contrast to the C–Cl bond the corresponding C–$CH_3$ bond is metabolized and excreted more rapidly.



# Monovalent Bioisosters (VI)

**Exchange of $-CF_3$ or –CN for –Br**

The trifluoromethyl and the cyano (=nitrile) group have the same electronic properties, but the –CN group is much more hydrophilic. Bromine is similar in size and somewhat more lipophilic than the nitrile group.

Rule of thumb concerning **bioavailability**:

Lipophilic compounds are absorbed worse and are increasingly metabolized in the liver.

Usually hydrophilic compounds are easily absorbed but likewise being excreted by the renal pathway more rapidly.

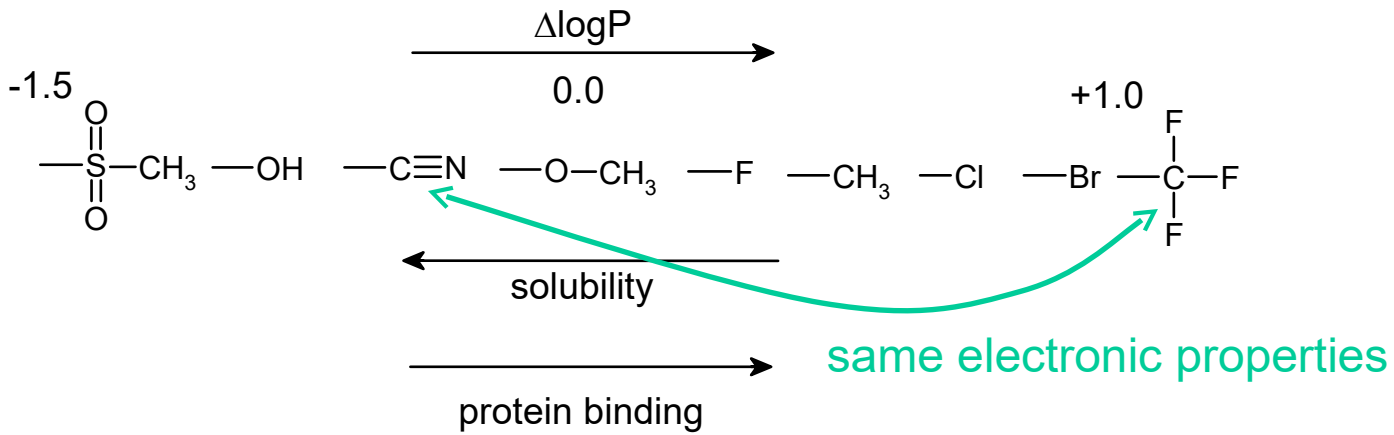
measure: logP = *n*-octanol / water partition coefficient

# LogP and Solubility

Rule of thumb concerning **solubility**:

Lipophilic compounds are less soluble than hydrophilic ones

measure: logP = *n*-octanol / water partition coefficient

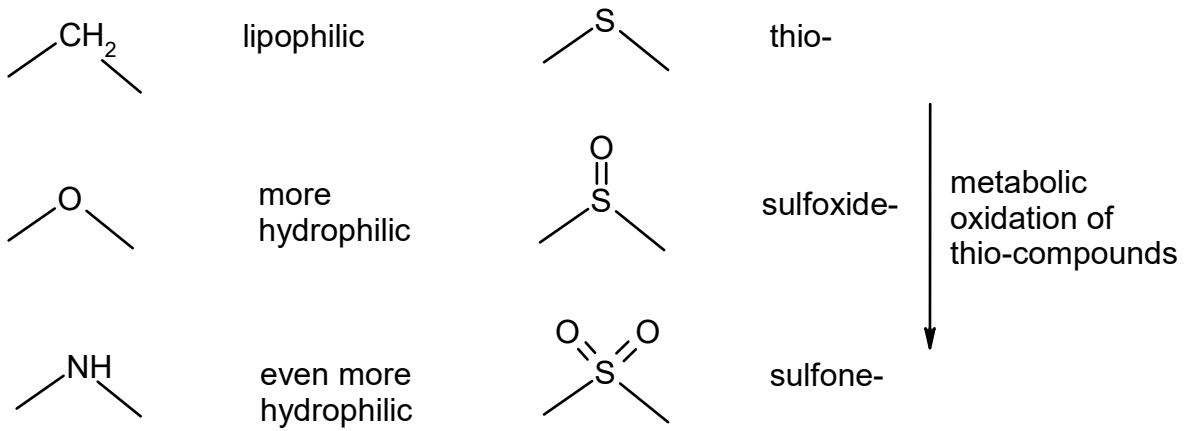



Fragmental contribution of substituents

Lit: A.G. Leach et al. *J.Med.Chem.* **49** (2006) 6672.

# Divalent Bioisosters

## Exchange of the –$CH_2$– (methylene) group



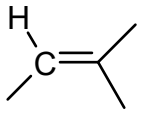

Compounds containing B-H or Si-H bonds are usually to sensitive against hydrolysis.
However, here are some examples of actual drugs

Boron: bortezomib, bosentan, dutogliptin, flovagatran

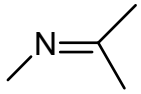
Silicon: flusilazol

# Trivalent Bioisosters

## Exchange of the –CH= group for –N= or –NH–

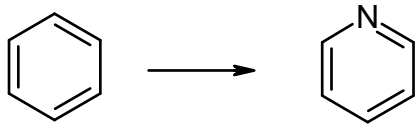



lipophilic

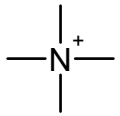



more hydrophilic,
H-bond acceptor

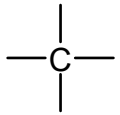
Important and successful especially in heterocyclic ring systems



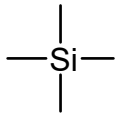
# Tetravalent Bioisosters



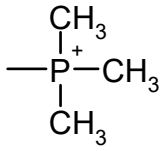

ionic, strongly hydrophilic

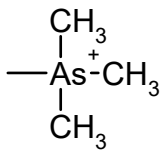



much more lipophilic




sensitive to hydrolysis
Si-C bond 20 % longer

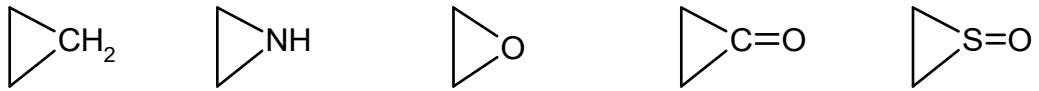


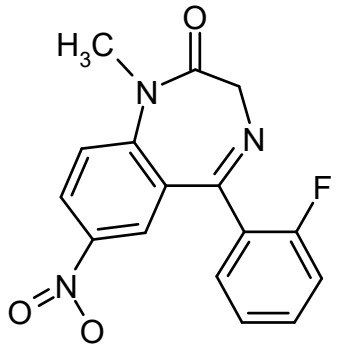

mostly toxic

# Divalent ring equivalents

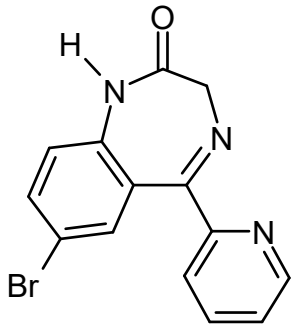
## Exchange of the –$CH_2$– group



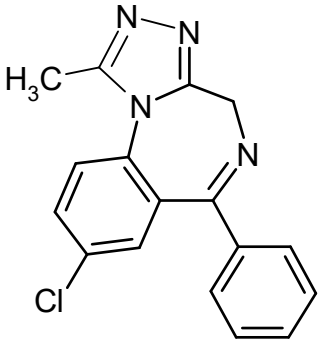

Also possible in larger ring systems (7-membered rings etc, see benzodiazepines):




flunitrazepam



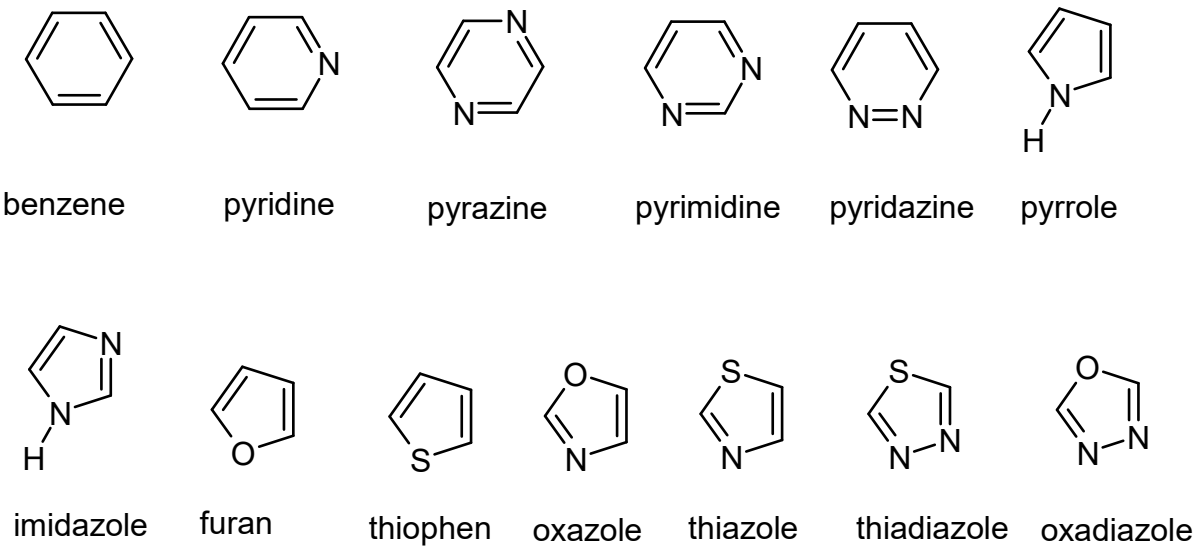

bromazepam




alprazolam

# Trivalent ring equivalents

## Exchange of the –CH= group

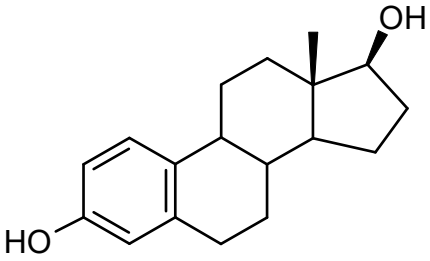



Enables frequently the fine tuning of the functional and ADME profile

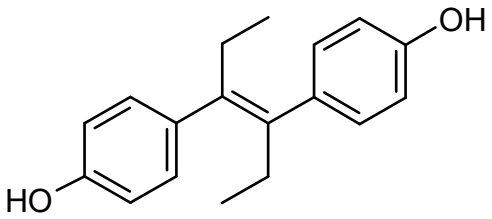
c.f. sildenafil versus vardenafil

# Non-classical Isosters (II)

## ring opening

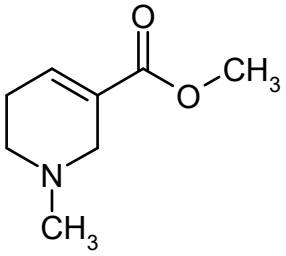


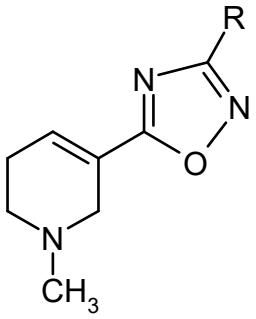

Estradiol

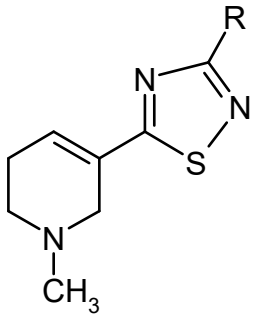



Diethylstilbestrol

## ring closure



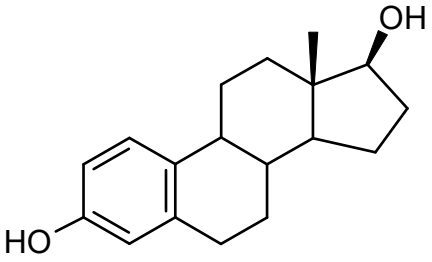



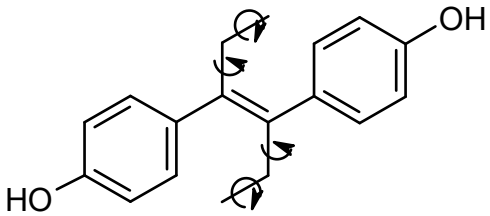

Frequently used to „freeze“ an active conformation

# Thermodynamic effects

**Ring opening:** Generates more degrees of freedom, thus loss of entropy upon binding to the enzyme

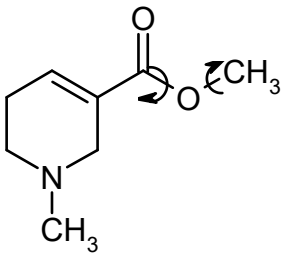


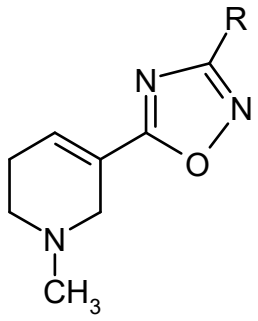

Estradiol

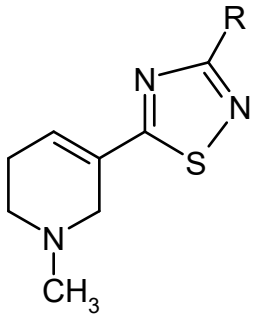



Diethylstilbestrol

**ring closure:** Reduced loss of entropy upon binding



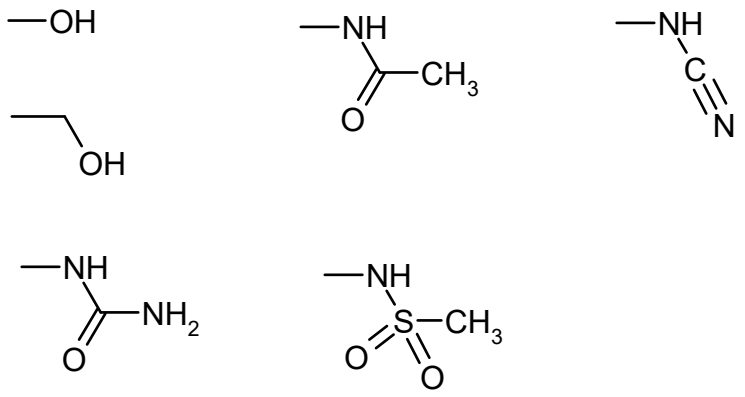



# Bioisosteric exchange of functional groups

**hydroxyl group –OH**

Here: Conservation of H-bond properties has priority

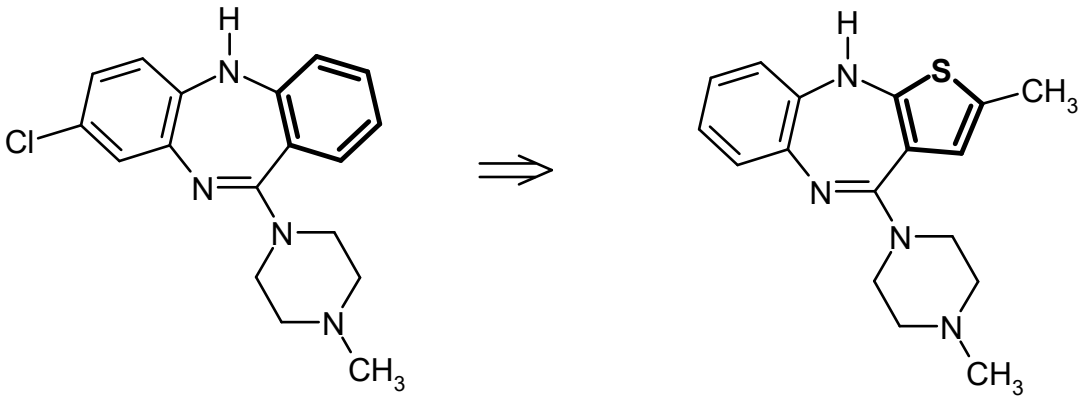



H-bond donors are more conserved than purely H-bond acceptors.

Lit: T.Fehlmann & M.C.Hutter *J.Chem.Inf.Model.* **59** (2019) 1314.

# Examples of Bioisosters (I)

## Exchange benzene-thiophene



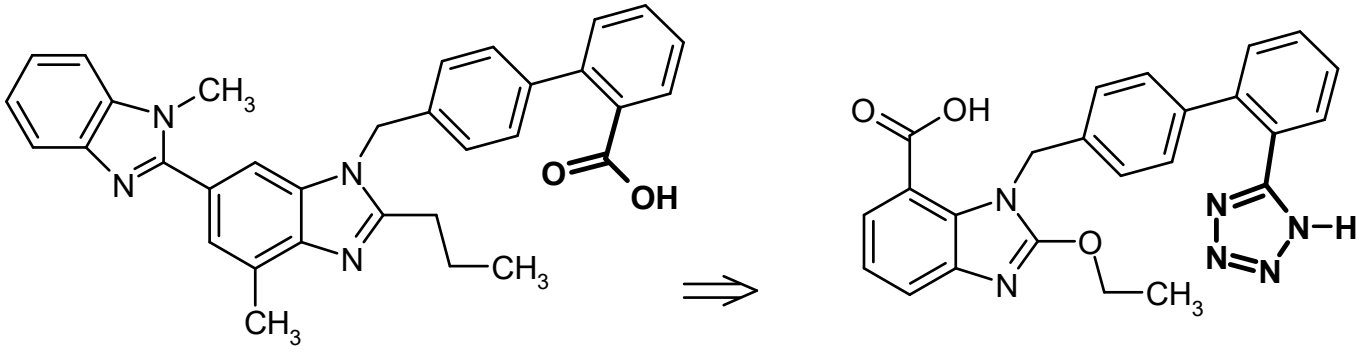

Clozapin

Olanzapin

Avoids expoxidation of the benzene ring, thus reduced hepatotoxicity

# Examples of Bioisosters (II)

## Exchange carboxylate-tetrazole



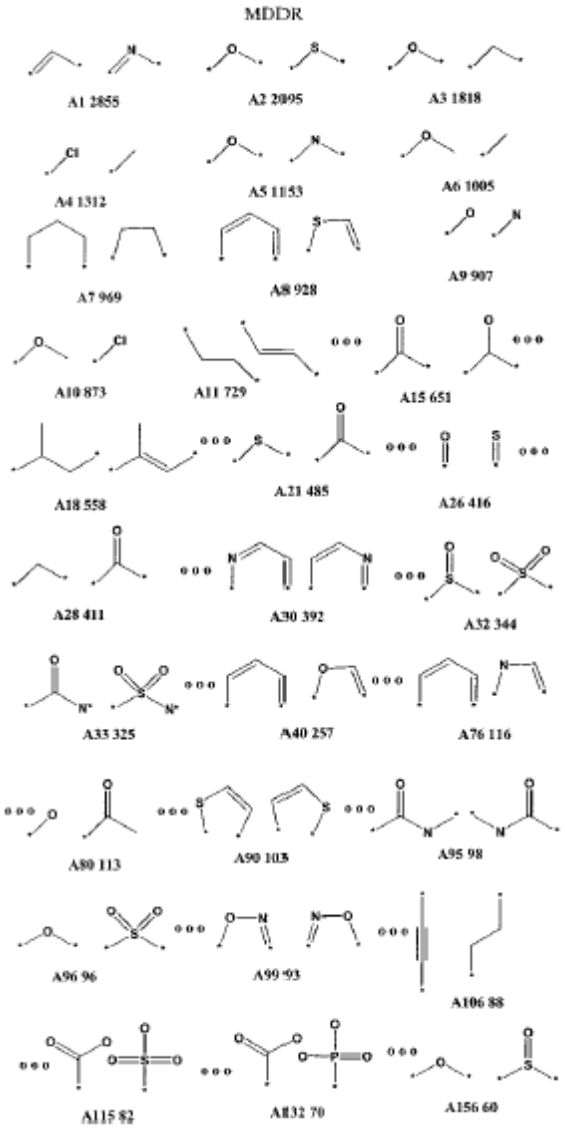

Telmisartan

Candesartan

Comparable acidity along improved solubility

Lit. C.D. Siebert *Chemie in unserer Zeit* **38** (2004) 320.

# Distribution of Chemical Replacements (I)



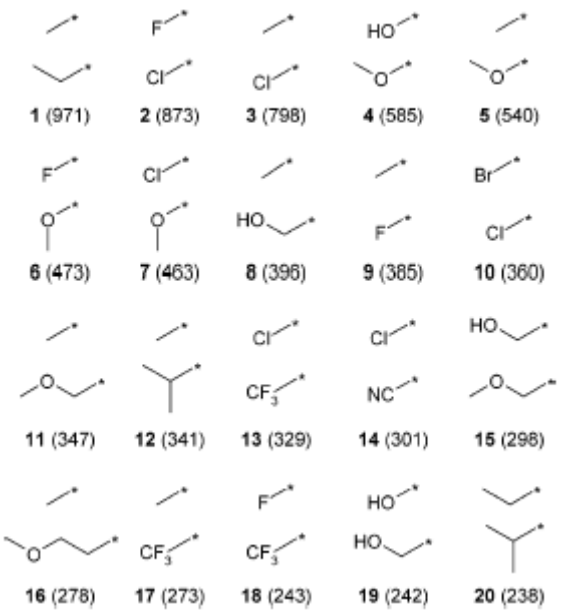

Analysis of the MDL Drug Data Report (>100,000 drugs)

The most common replacements of fragments (starting from top, left)

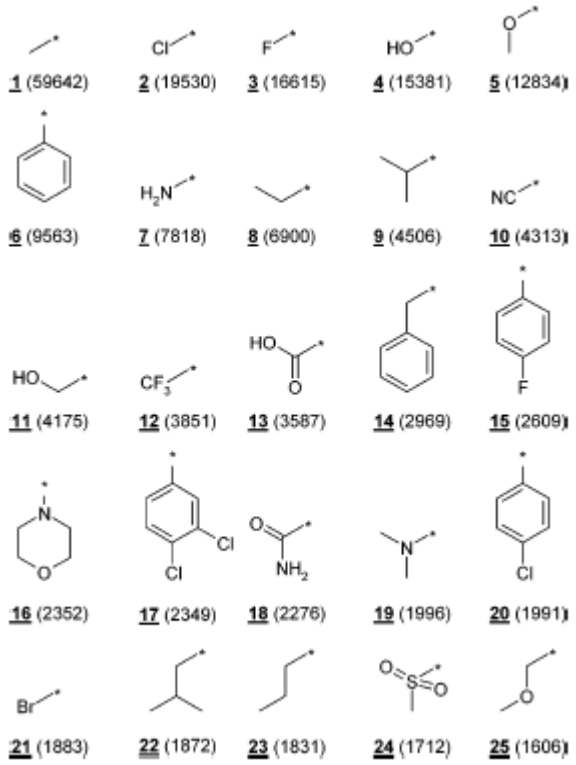
Lit. R.P. Sheridan
*J.Chem.Inf.Comput.Sci.* **42** (2002) 103.

# Distribution of Chemical Replacements (II)

In house database (50,000 drug-like compounds)




Most common replacements
**rank** (count)



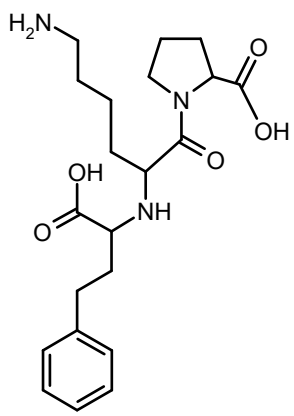

Most common sidechains
**rank** (count)

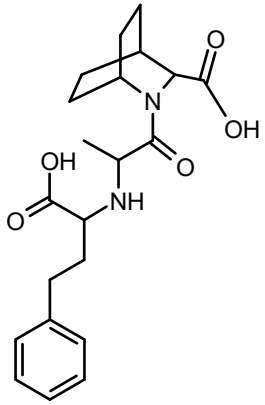
Lit. D.Y. Haubertin, P. Bruneau *J.Chem.Inf.Model.* **47** (2007) 1294.

# Statistical Evaluation of Bioisosteric Exchanges in Drugs

Align similar drugs of the same target (e.g. ACE-Inhibitors)

lisinopril



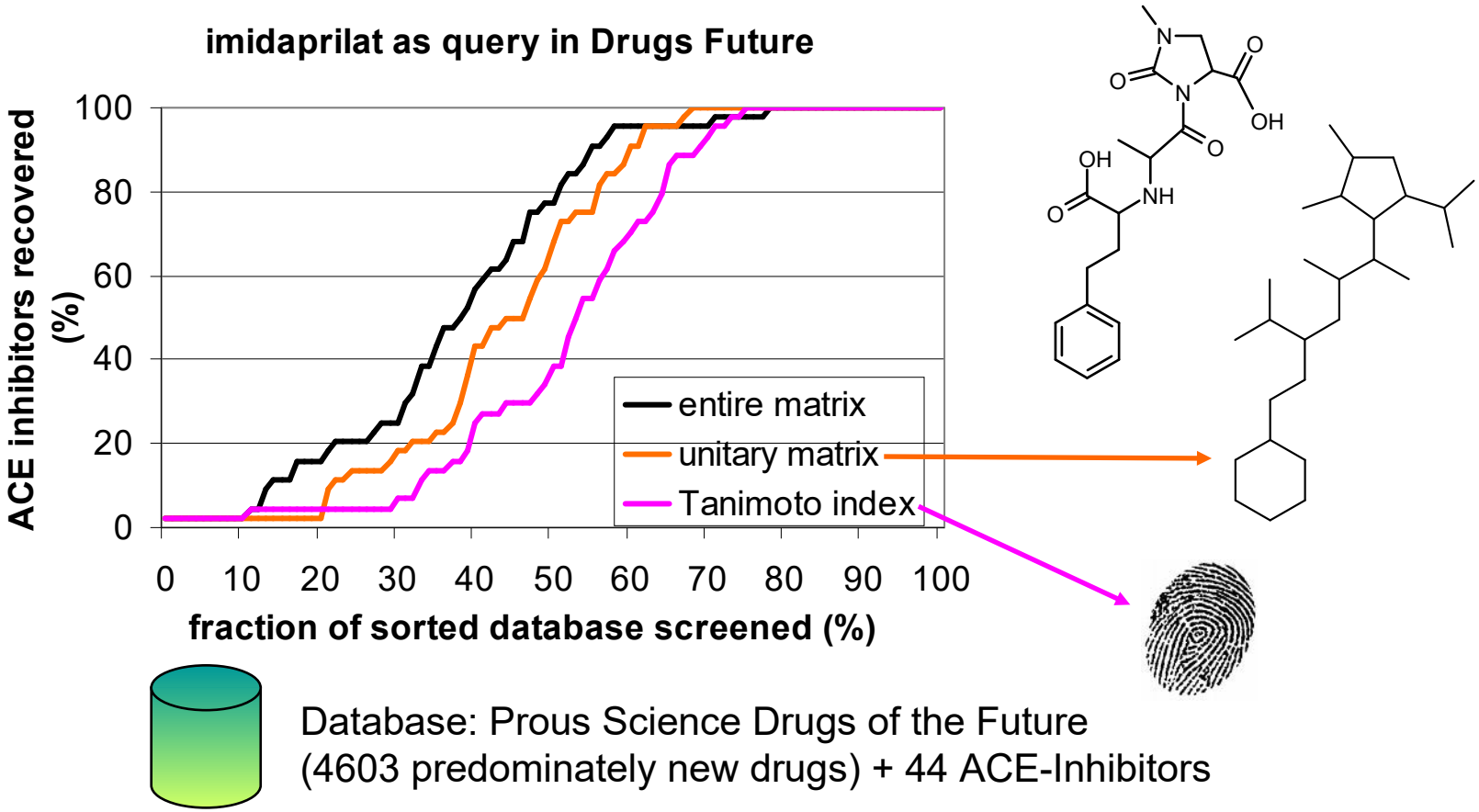

Statistical frequencies of chemical exchanges

Bioisosteric exchange matrix (similar to amino acid exchange matrices such as PAM250 or BLOSUM62)

Predict similarity of new compounds (in virtual screening)

Lit. M.Krier, M.C.Hutter *J.Chem.Inf.Model.* **49** (2009) 1280.

# Bioisosteric Similarity vs Substructure matching and fingerprints

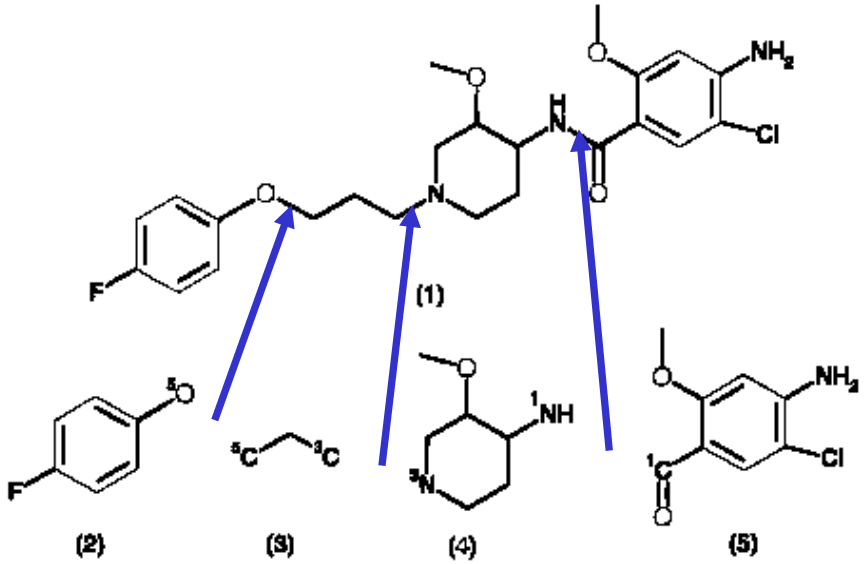



Database: Prous Science Drugs of the Future
(4603 predominately new drugs) + 44 ACE-Inhibitors

Lit. M.Krier, M.C.Hutter *J.Chem.Inf.Model.* **49** (2009) 1280.

# Systematic Variation – *in silico* approaches (I)

Analog to the approach used in the feature trees, each molecule is splitted into *nodes* and *linkers*. Each node corresponds to a chemical group and each linker to a bond between such groups.



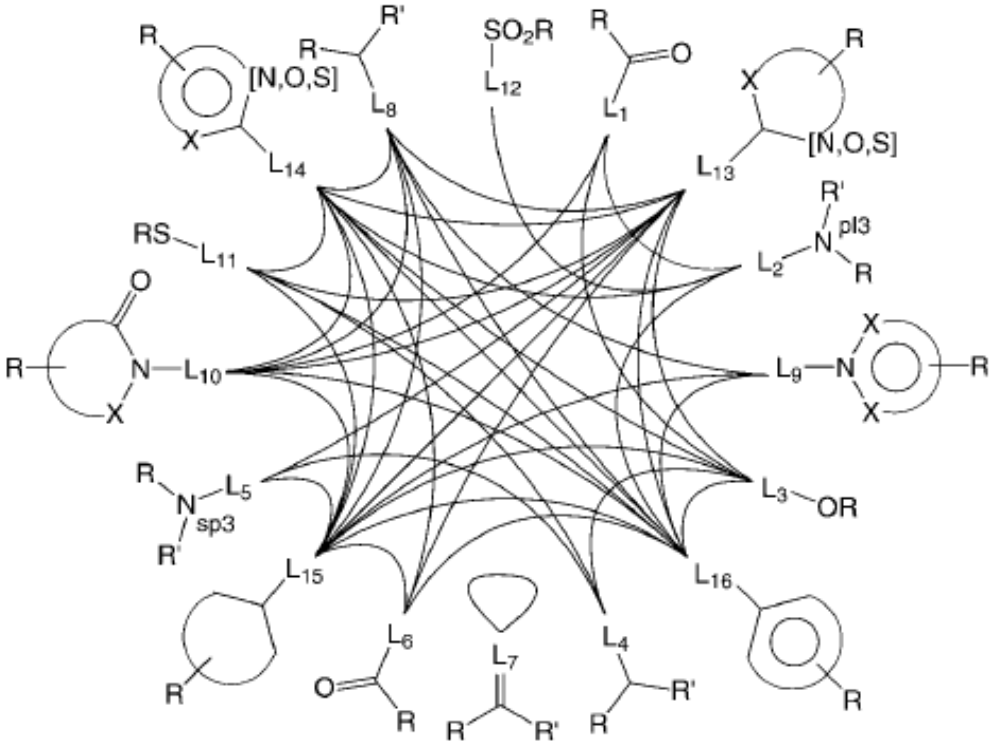

By using defined types of bond cleavages (retro synthesis), matching fragments can be searched in data bases and combined differently.

**RECAP** concept:

Lit. X.Q.Lewell et al. *J.Chem.Inf.Comput.Sci.* **38** (1998) 511.

# Systematic Variation – *in silico* approaches (II)

A more specific set of rules for bond cleavages and reformation of bonds is realized by the **BRICS** concept. Here, information for the synthesis of actual combinatorial libraries was compiled.




Lit. J.Degen et al. *ChemMedChem* **3** (2008) 1503.