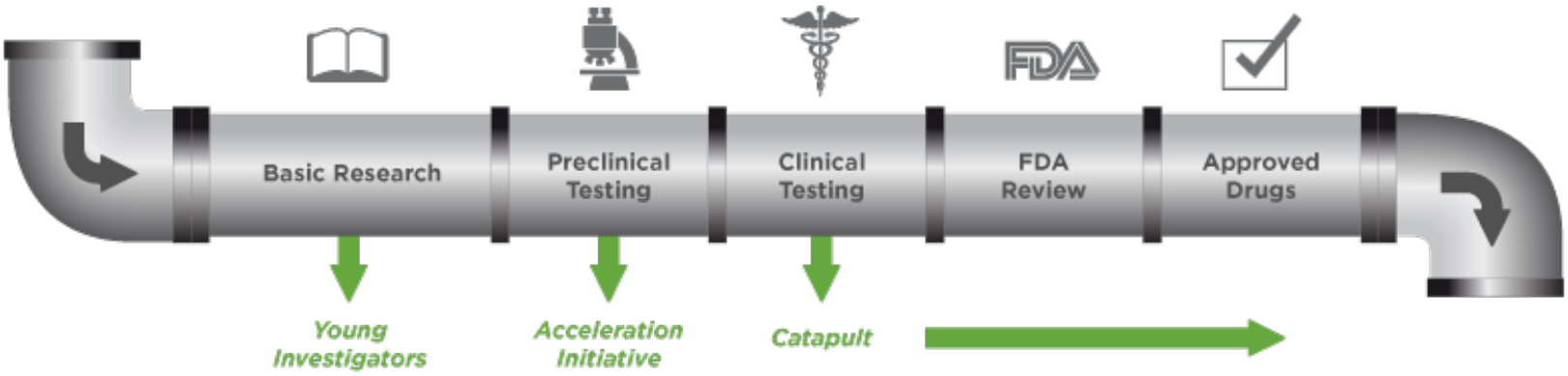
Modern Methods in Drug Discovery

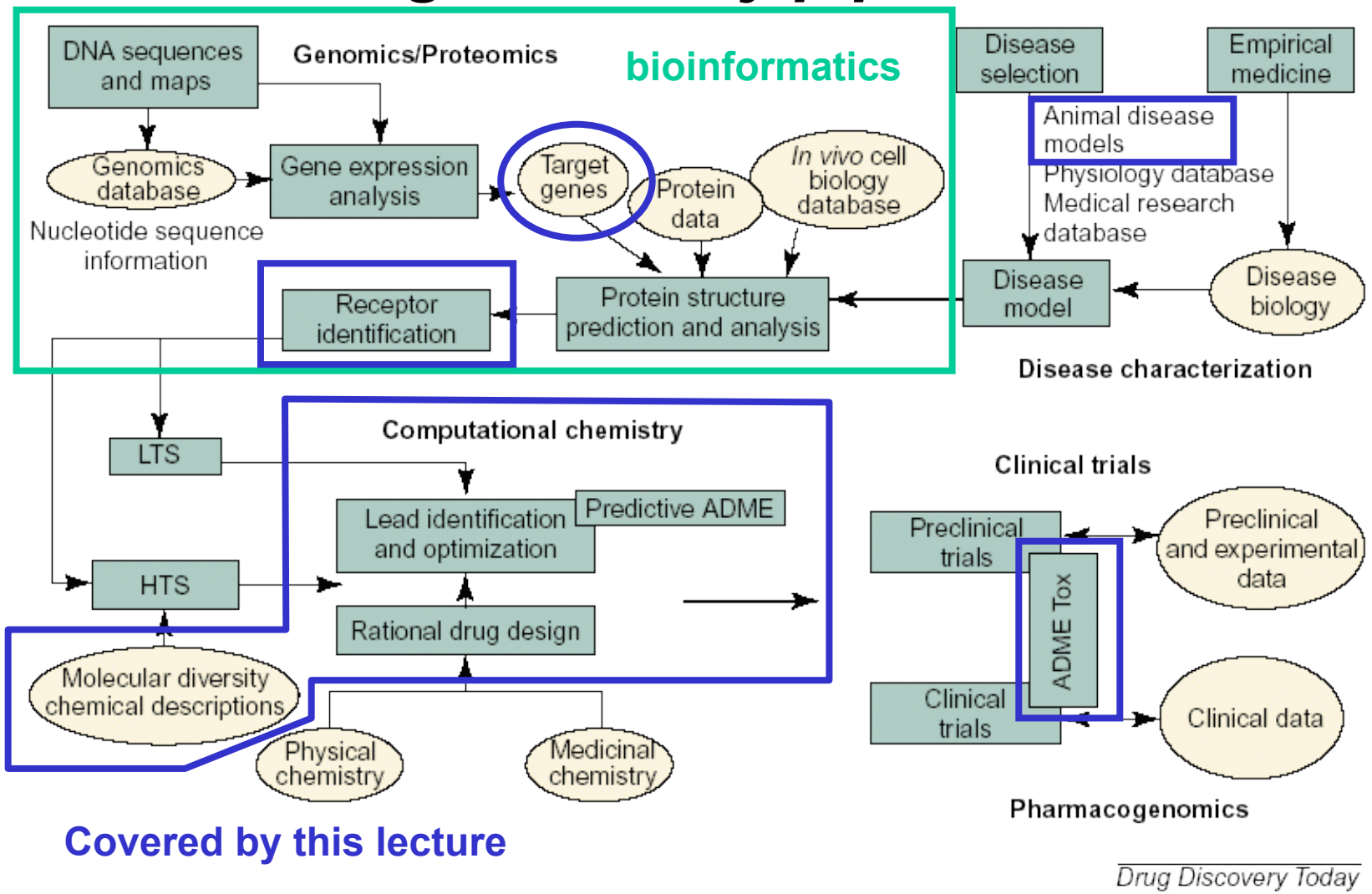
Aims of this course:

- comprehensive knowledge about all processes in the *drug discovery pipeline*
- in particular *in silico* methods of *drug design*
- perfoming substance queries in databases



Picture source:
https://curesearch.org/Impact-Report-Winter-2016/images/research-pipeline.png

Flow of information in a *drug discovery pipeline*



Related topics not covered by this lecture

medicinal chemistry
organic synthesis
biopharmaceutical aspects
(tissue models, non-oral administration)
immune system and monoclonal antibodies
clinical aspects
molecular modelling theory
homology modelling theory
docking basics and applications
computational chemistry
genome, proteome, metabolome
bioethics, legal aspects, regulatory issues, and patent law

Required knowledge

Use of tools for sequence analysis, e.g. BLAST, CLUSTALO
Use of visualizing tools, e.g. BALL, Rasmol, Pymol, VMD, SPDBV

recommended prior courses:

Softwarewerkzeuge der Bioinformatik
Computational Chemistry
Bioinformatics I + II
Structural Bioinformatics

Actual applications during the excerices and homework:

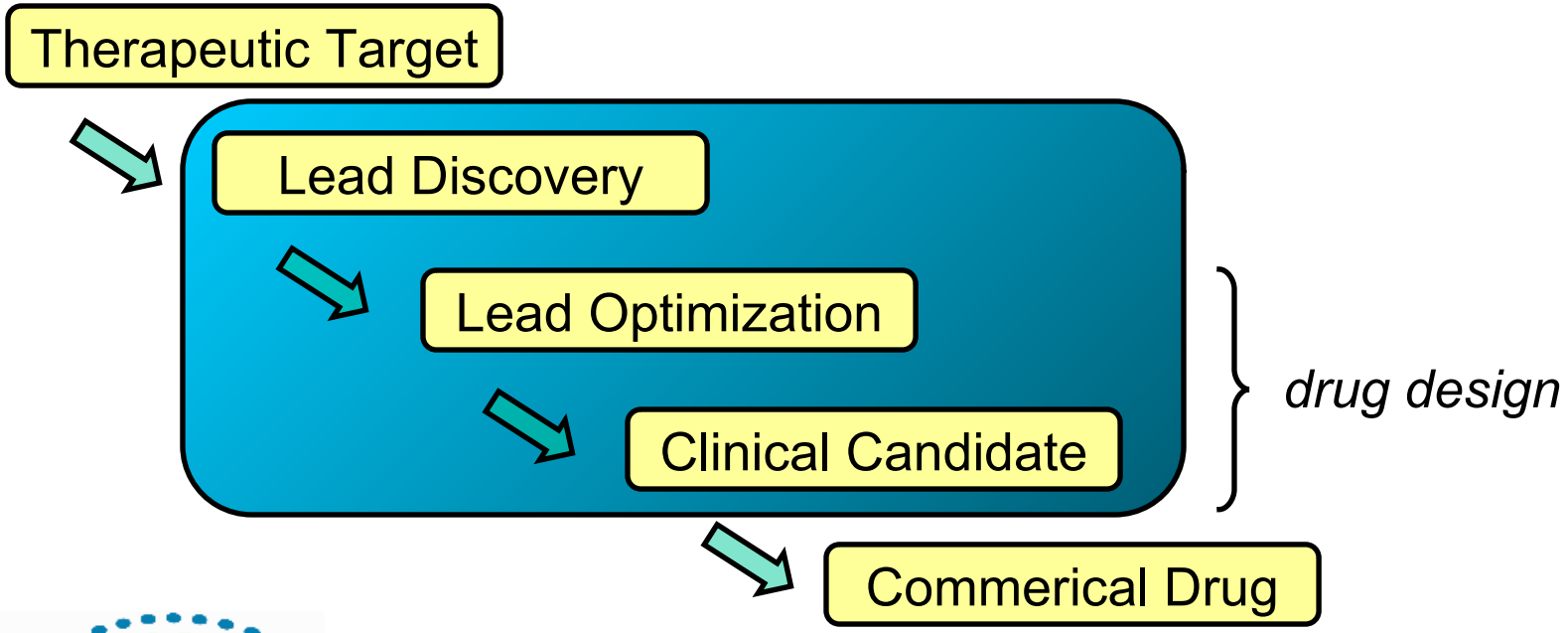
multiple sequence alignment, homology in sequences
analyzing protein-ligand interactions

SMILES and SMARTS notation of chemical structures
using SMARTS with Open Babel

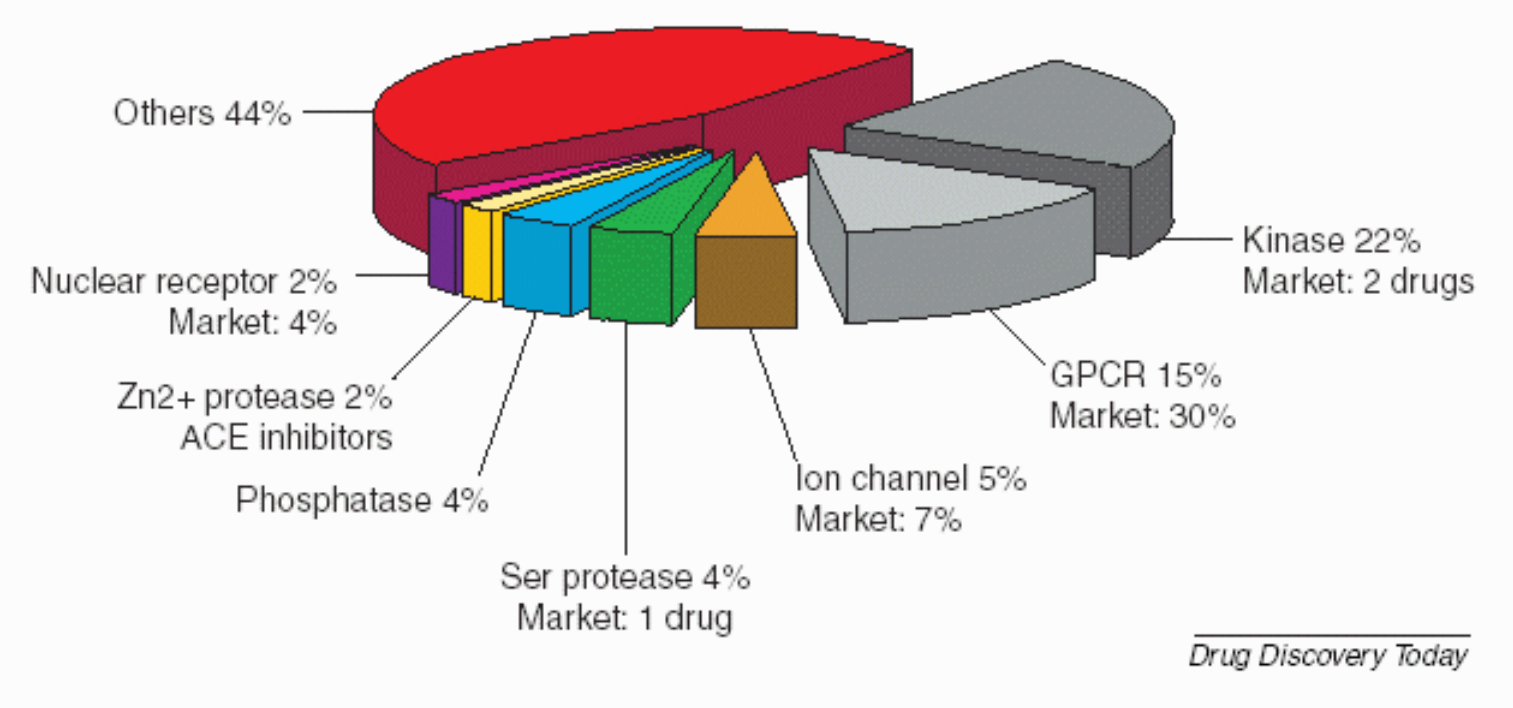
Database queries (PubChem, ChEMBL, DrugBank, ZINC, UniProt,...)

What is *drug discovery* ?

rational and targeted search for new drugs

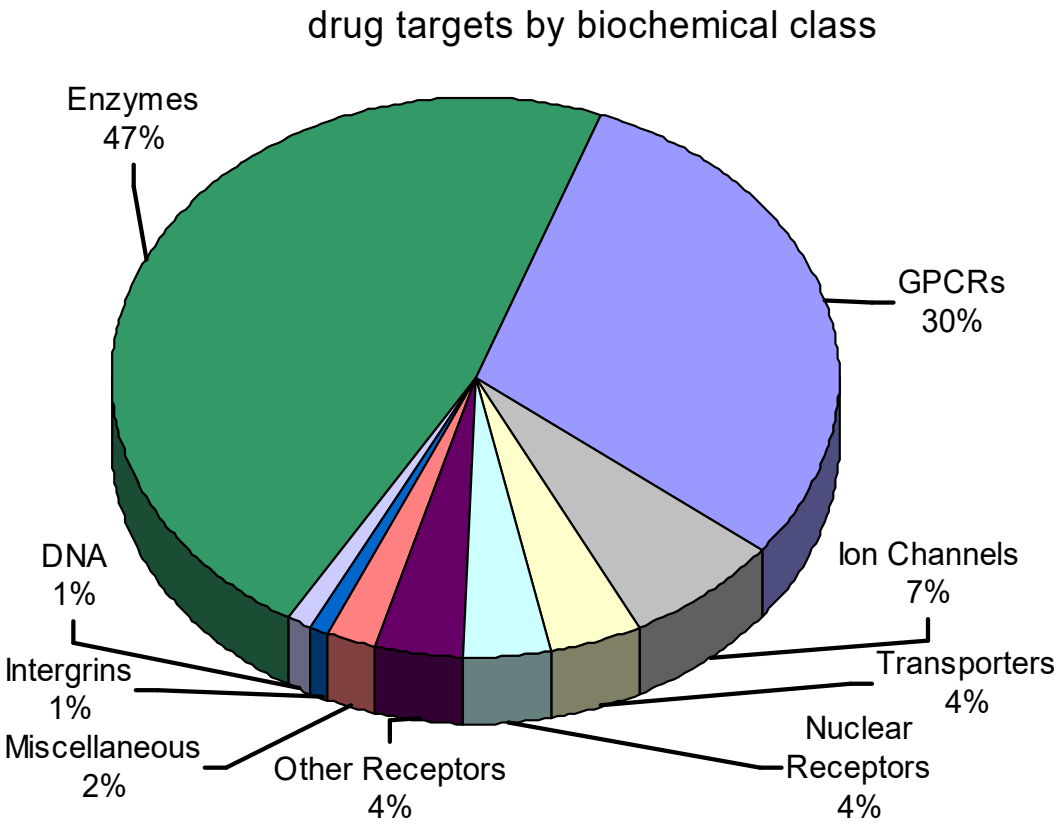


Typical targets (I)



contribution to the human genome and marketed drugs

Typical targets (II)



Fractional content of marketed drugs according to their biochemical targets

data: Hopkins & Groom, *Nat.Rev.Drug.Disc.* **1** (2002) 727

Preliminary schedule (lectures/topics)

1. Introduction, overview, recap of chemical structures
2. typical diseases
3. properties of drugs and their mode of action
4. Substance databases and bioisosteric compounds
5. QSAR, statistics and descriptors
6. More about QSAR and statistics
7. ADME models
8. metabolism and toxicology
9. target identification, animal models
10. cytochrome P450, polymorphisms, transporters
11. more complex diseases malaria, obesity, current trends

Preliminary schedule (exercises/tutorials)

Biweekly online via MS-Teams meeting

→ register for this course in the moodle system

https://lms.sulb.uni-saarland.de/moodle/?lang=en

Naturwissenschaftliche Fakultät/ Biowissenschaften/
Bioinformatik(Helms)/Modern Methods in Drug Discovery
use „Selbsteinschreibung“ (self enrolement)
I will add you to the corresponding MS-Team

- discussion of the assignments
- chemical structures of drugs: SMILES and SMARTS
- substance databases and SMARTS queries
- enzyme-ligand interactions, analysis of .pdb files
- using PubChem and ChEMBL databases
- ortholog targets in model organisms

Requirements to obtain the certificate and the credit points

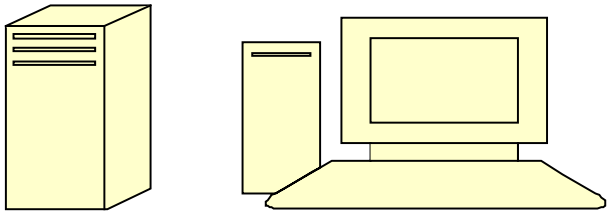
1. Register for this course in the moodle system.
2. Passing the two online tests (will be available in the moodle system) covering the topics of the previous assignments.
   → You don‘t have to hand in the assignments!
3. 50% of all accomplishable points from the final exam taking place at the end of the lecture period. If necessary, repeated (written) exam or oral exam (subject to the corresponding study regulation).
   Applies only to students enroled in Bioinformatics:
   Please register for the exams in the LSF timely.

Compound Databases

Size of typical substance libraries (2022)

ACD	12,000,000 chemicals	commercial
World Drug Index	80,000 compounds	
USAN	<10,000 in clinical trials	
virtual library	≈100,000 compounds	company, in house

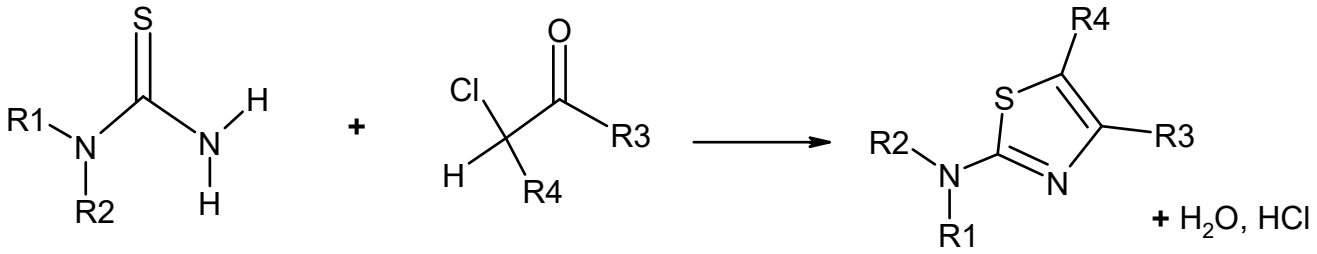
PubChem	> 112,000,000 compounds	NCBI	academic
ChEMBL	> 2,200,000 compounds	EMBL	
DrugBank	> 500,000 drugs	Uni. Alberta	
ZINC15	>750,000,000 compounds	UCSF	

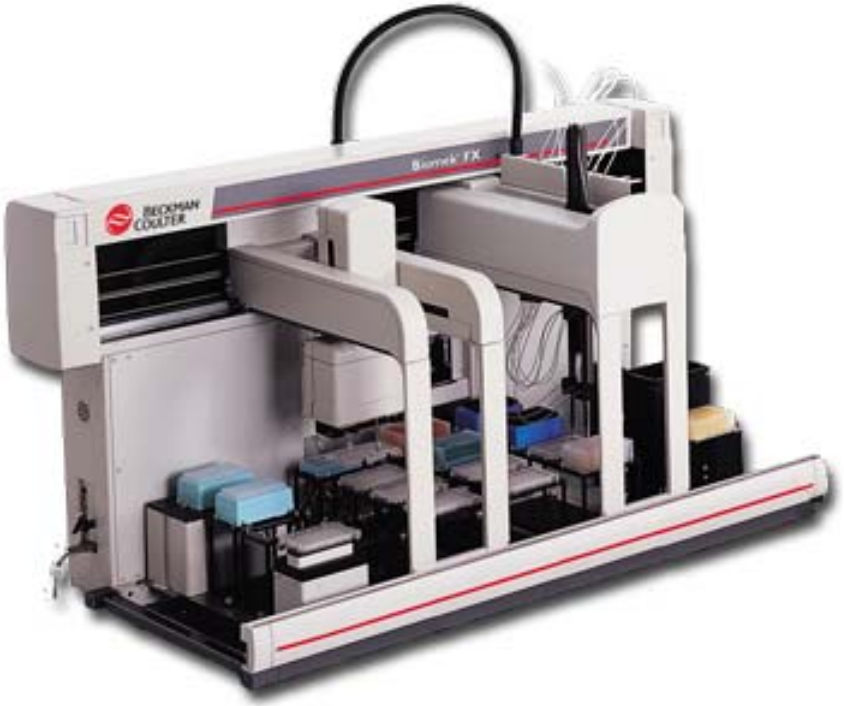


Investment per new chemical entity: >800,000 $

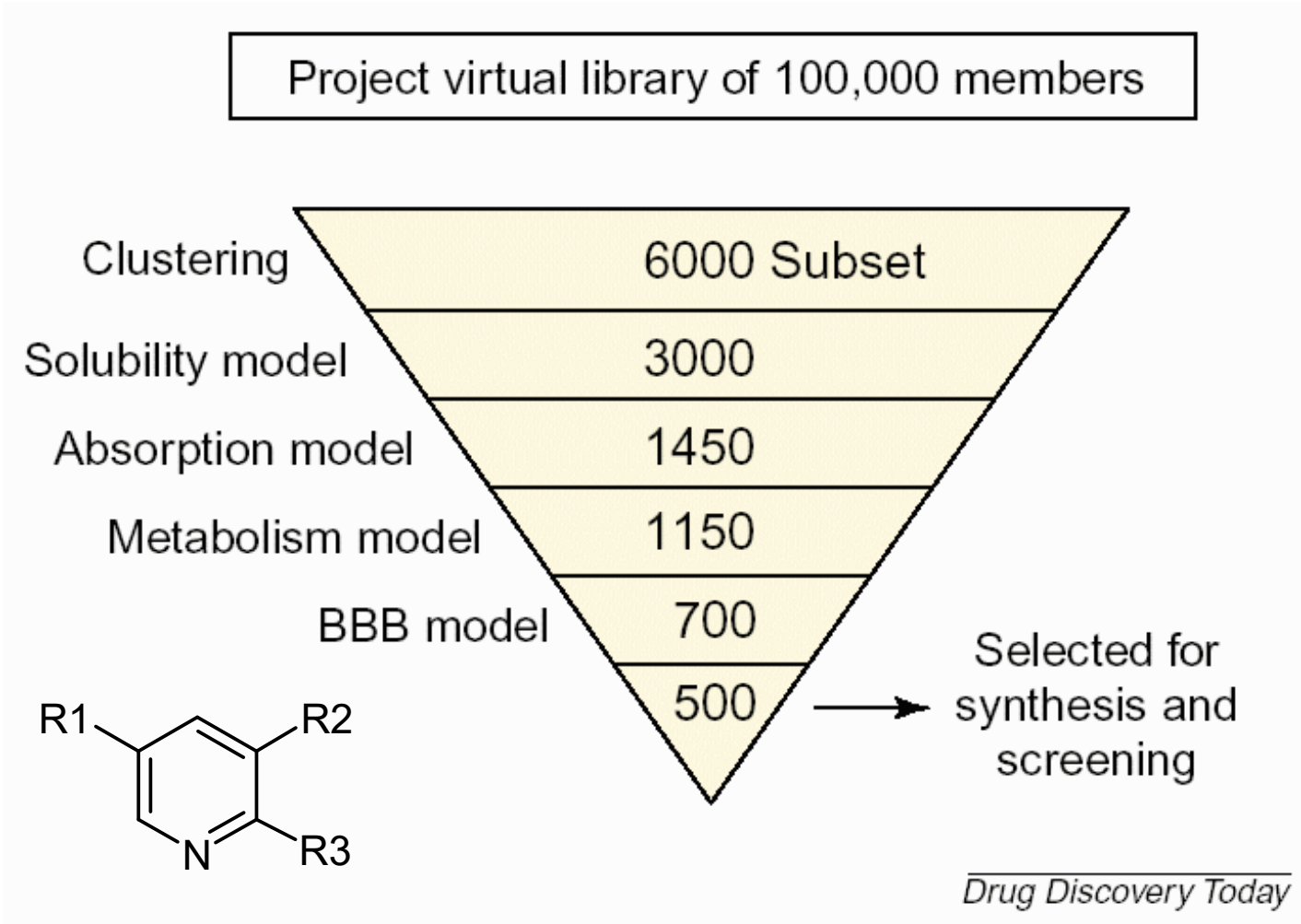
New chemical entities per year: ca. 15 strongly fluctuating

Methods of Combinatorial Synthesis for High Throughput Screening (HTS)





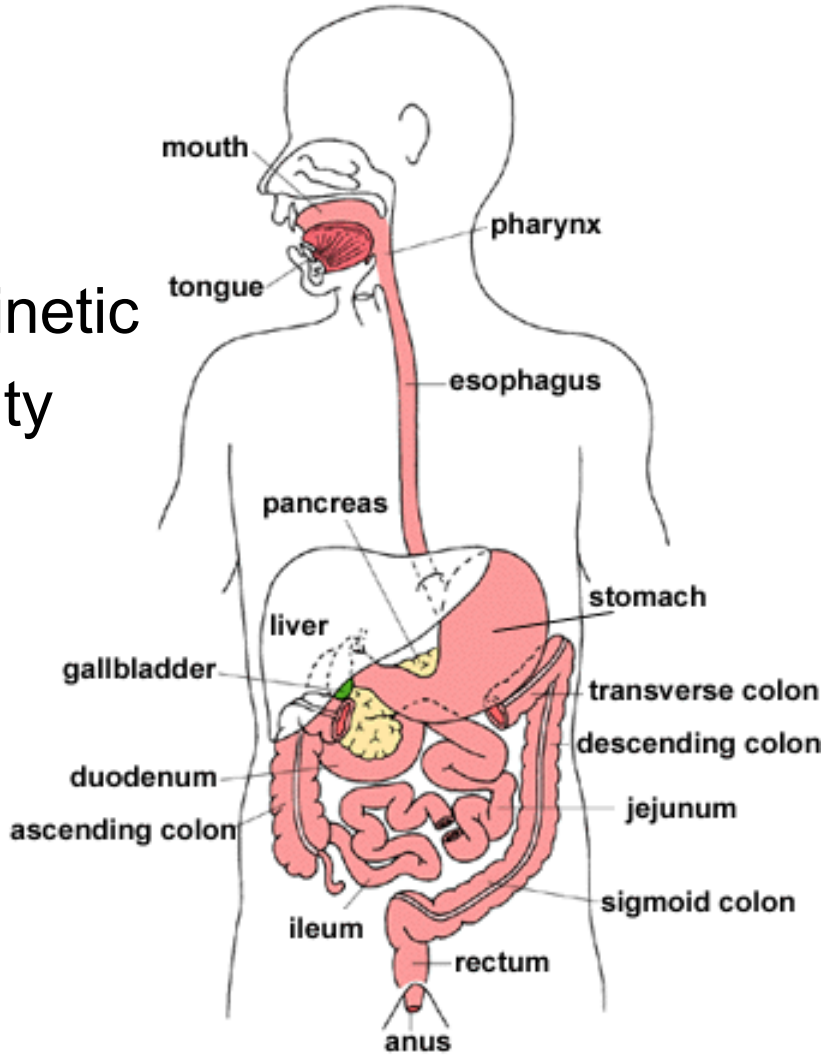
Selection of compounds for High Throughput Screening (HTS)



Predictive ADME

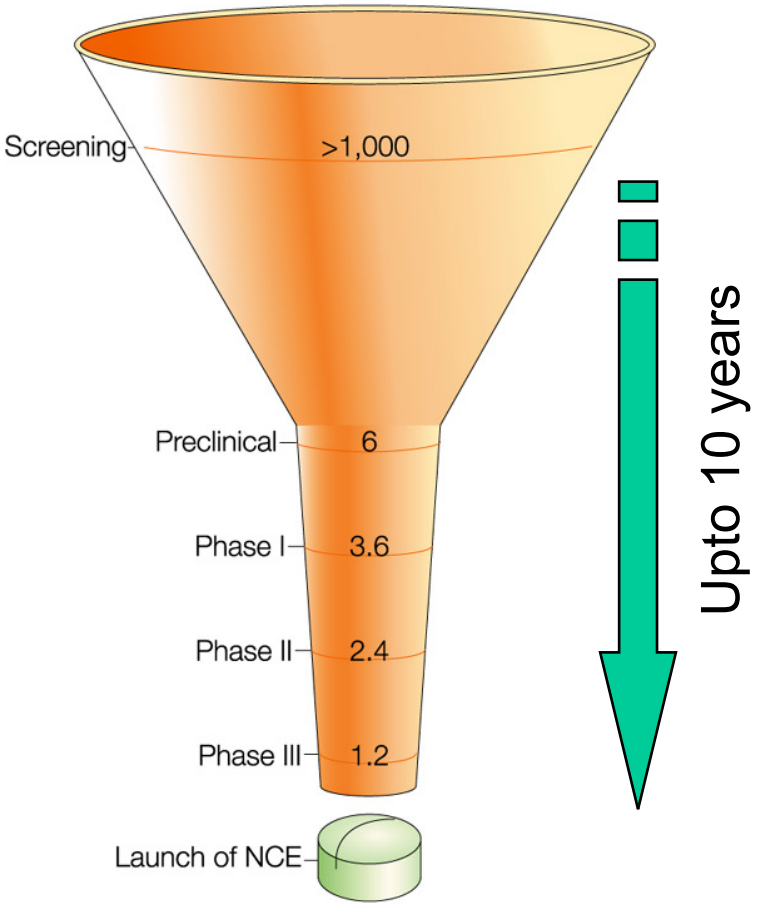
Absorption
Distribution
Metabolism
Elimination

} Pharmacokinetic Bioavailability

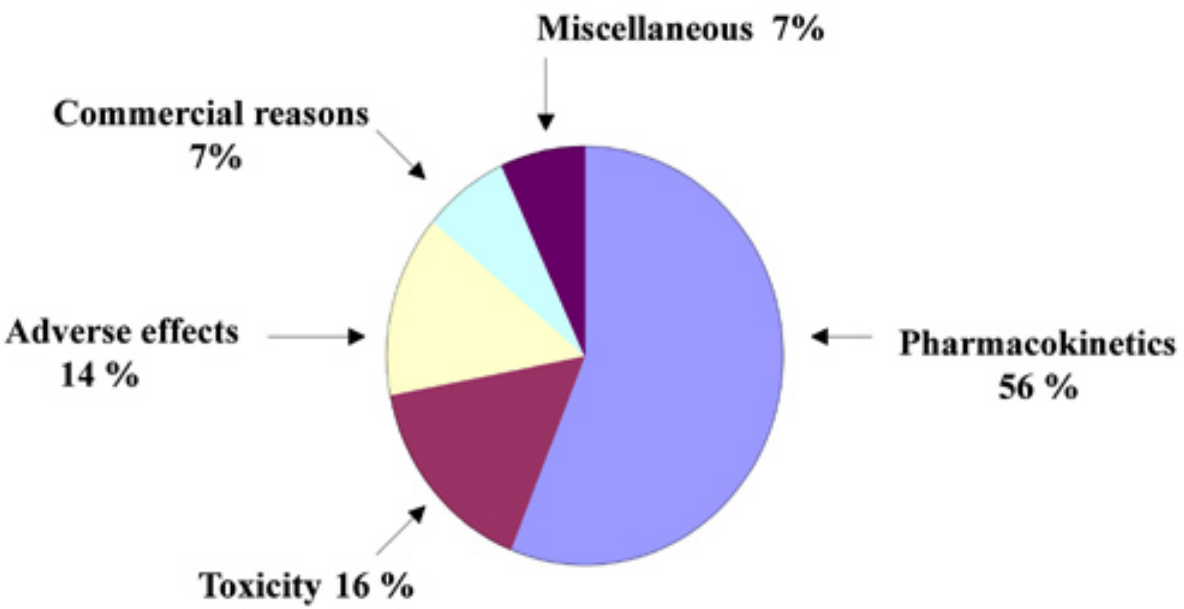


From the pipeline until the commerical launch

For each actual marketed drug (*new chemical enitity, NCE*) there have been more than 1000 substances that underwent screened *in vitro*. Without the use of available computer-based ADMET filters, this number would be even larger.

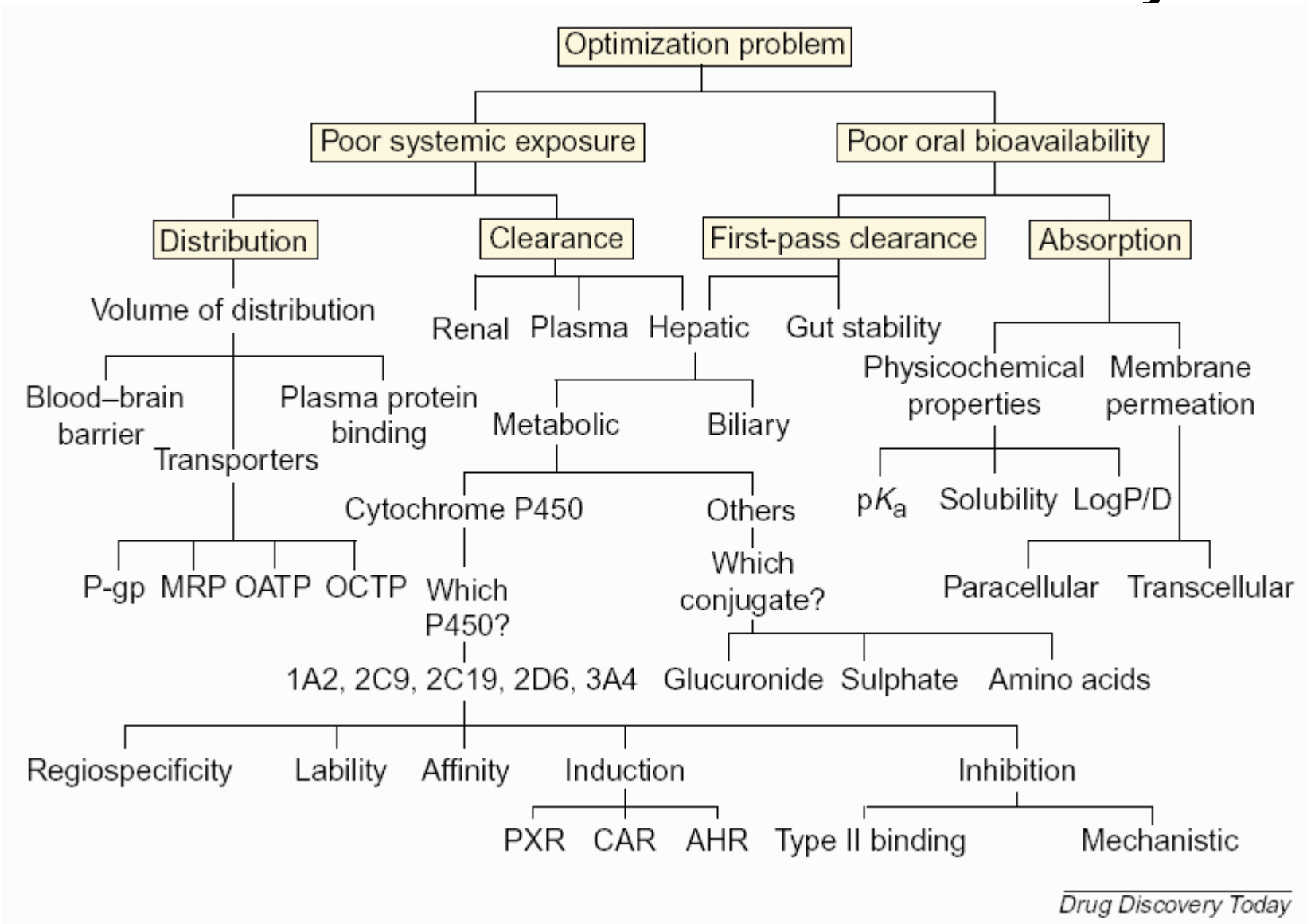


Why is the prediction of ADME parameters that important ?



Reasons that lead to failure or withdrawl of a potential drug by the mid 1990‘s

Pharmacokinetics and Bioavailability



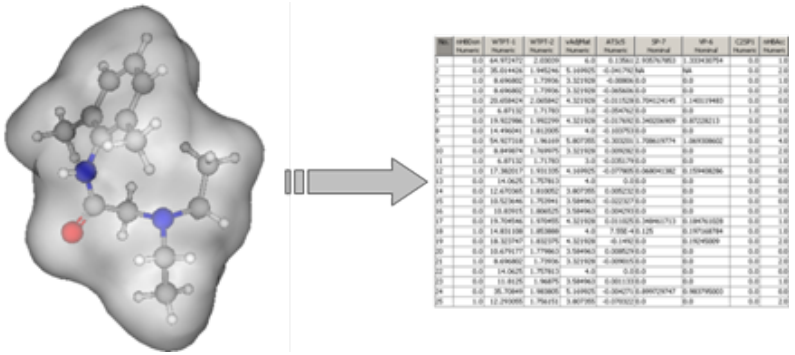
(Some) descriptors based on molecular properties used to predict ADME properties

logP water/octanol partitioning coefficient

topological indices

count of hydrogen-bonds

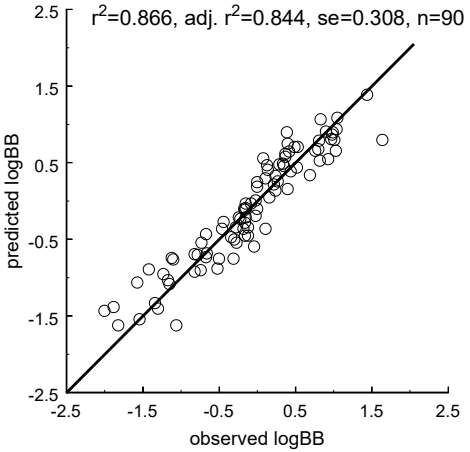
polar surface area



Multiple linear regression analysis

QSAR quantitative structure activity relationship

QSPR quantitative structure property rel.



Metabolism

(bio-)chemical reactions of xenobiotics in the body

First pass effect:

Extensive metabolization of mainly lipophilic molecules, such with MW>500, or those that have a specific affinity to certain transporters, during the first passage through the liver

Phase I:

Oxidation, reduction and hydrolysis → esp. cytochrome P450 enzymes

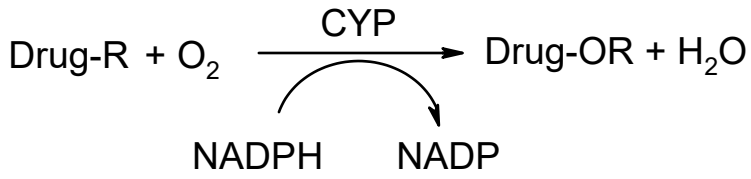
Phase II:

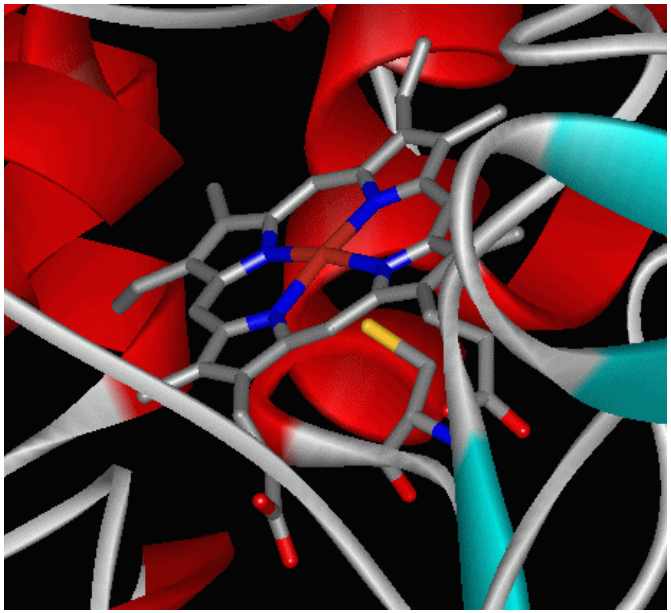
Conjugation with small molecules (e.g. glutamine) mediated by transferases

Phase III:

elimination by transporters

Cytochrome P450 Enzymes (I)





flavin monooxygenase isoenzyme (FMO)

monoamine dehydrogenase (MAO)

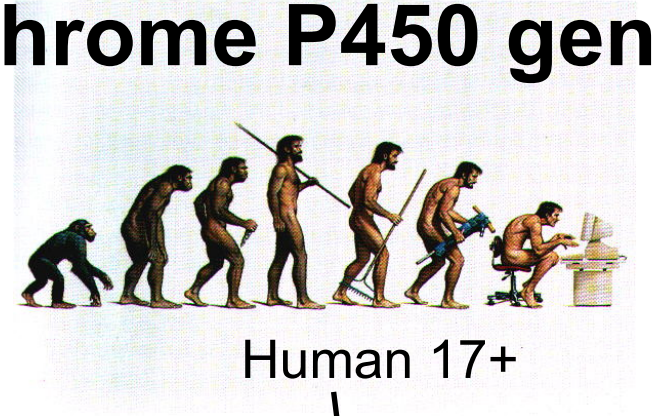
aldo-keto reductase (AKR)

alcohol dehydrogenase

aldehyde oxidase

} Further phase I enzymes

Cytochrome P450 gene families

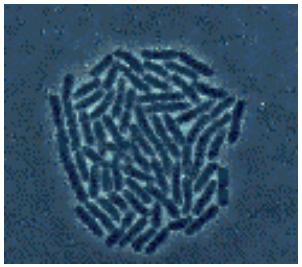


Human 17+

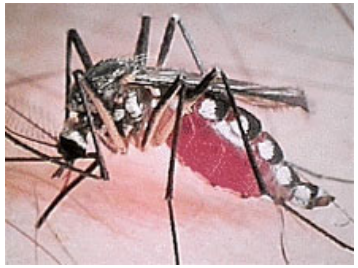
Molluscs 1

CYP450

Plants 22

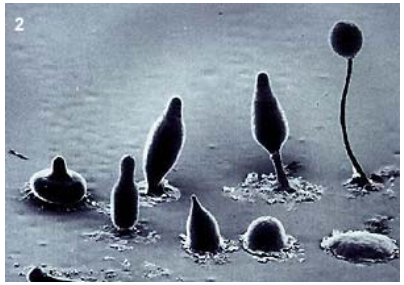


Bacteria 18

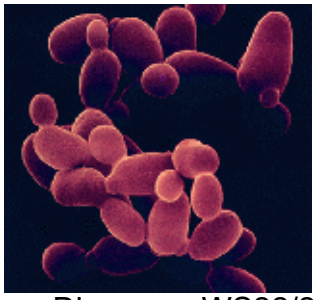


Insects 3

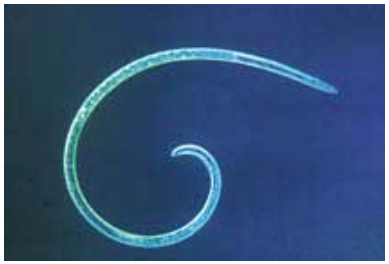
Fungi 11



Yeasts 2



Nematodes 3



Cytochrome P450 polymorphism

„Every human is (more or less) different“

Determination of the phenotype by the actual activity or the amount of the expressed enzyme.

In contrast, the genotype is determined by the individual DNA sequence.

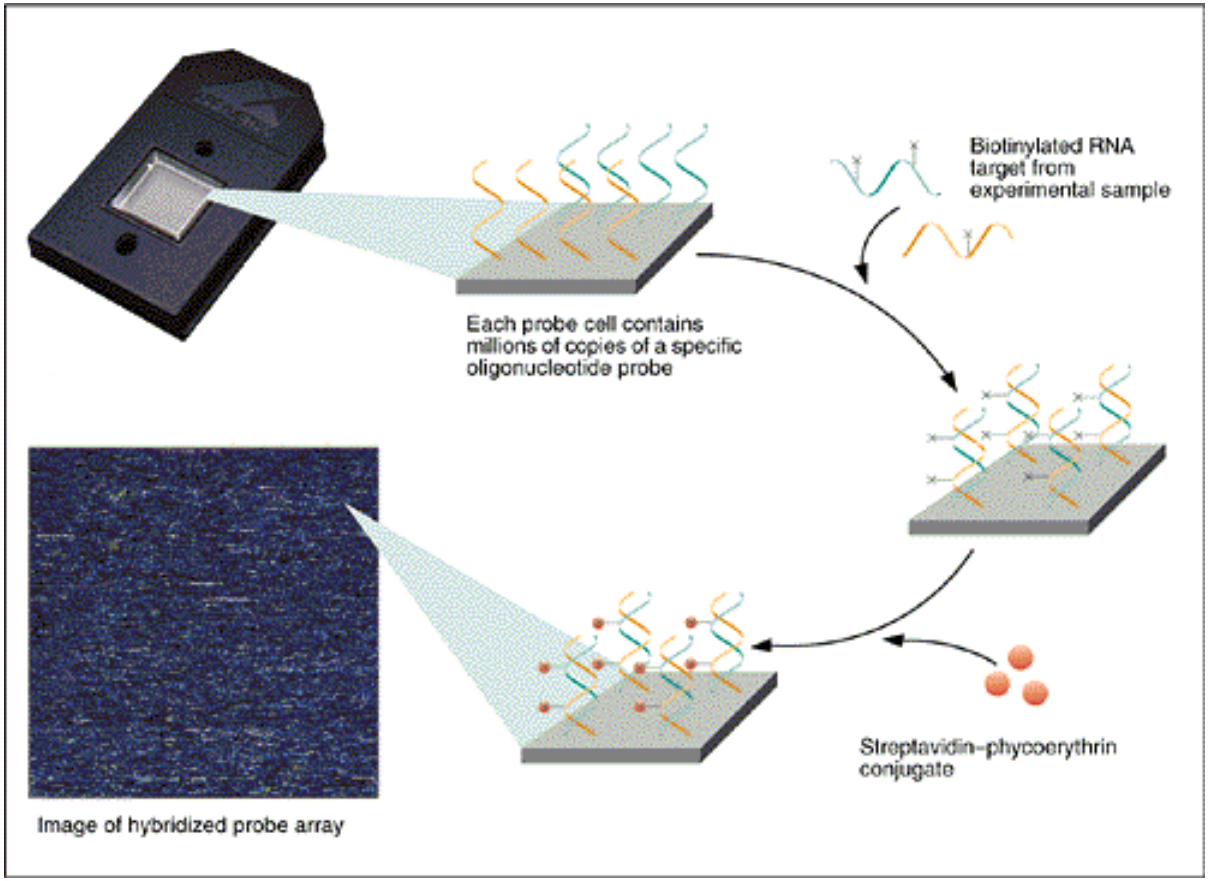
Thus, the same genotype enables several different phenotypes

According to their metabolic activity of CYP there is a classification into normal (*extensive metabolizer*), weak (*poor metabolizer*), und accelerated (*ultra-rapid metabolizer*) metabolism.

Lit: K. Nagata et al. *Drug Metabol. Pharmacokin* **3** (2002) 167

Genotyping of CYP P450 alleles

By using immobilized, synthetic copies of P450 nucleotides, the Affymetrix company (USA) has developped mircoarrays (gene chips) that allow the identification of all clinically relevant alleles.



Prediction of molecular properties (I)

The keynote of *rational drug design*

The general question is:

What is the connection between the biological space (activity) and the chemical space (structure) ?

How are we able to make structure-based prediction ?

→ QSAR and QSRP, regression analysis

→ decision trees, machine learning algorithms

→ other statistical methods

Prediction of molecular properties (II)

What are (physial) molecular properties?

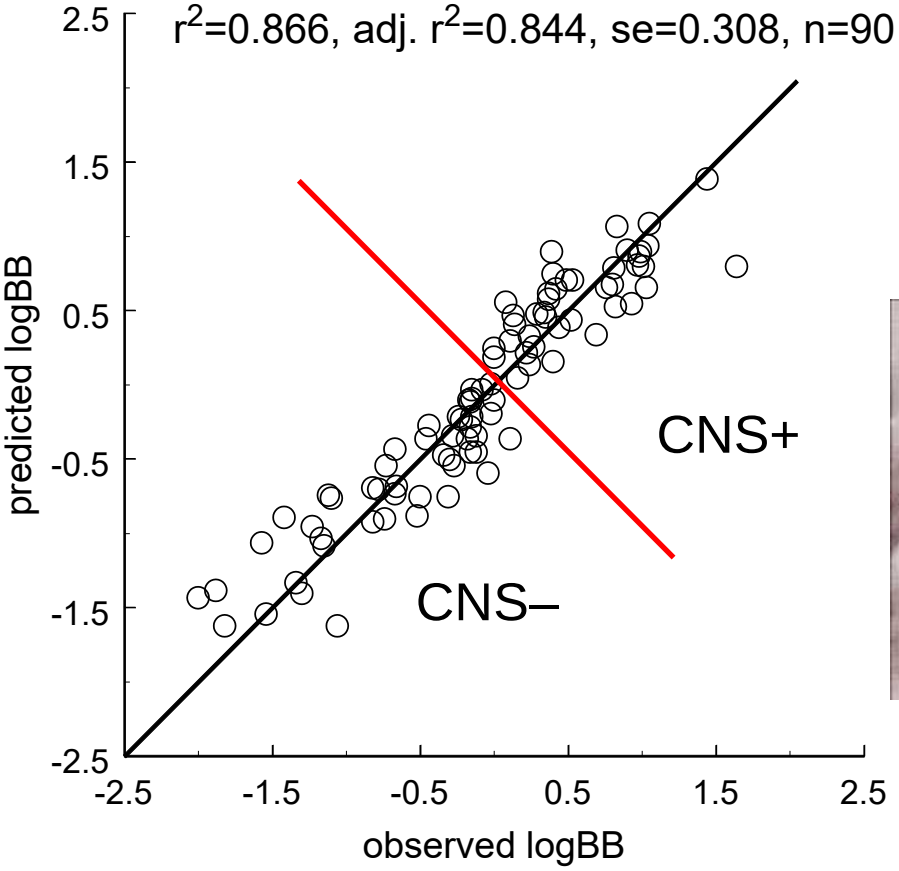
observables

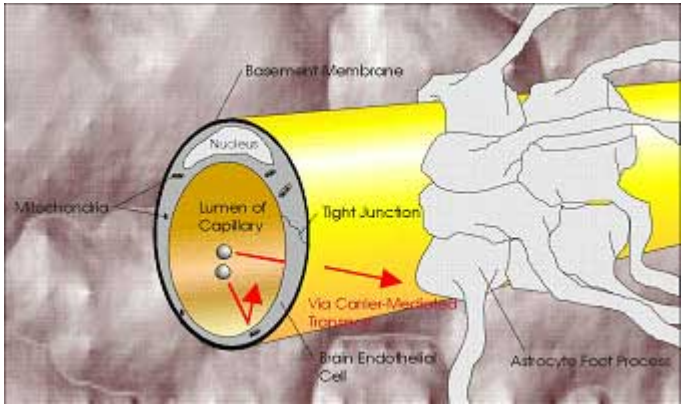
- molecular weight MW (from the sum formula $C_{12}H_{11}N_3O_2$)
- melting point
- boiling point
- vapour pressure
- solubility (in water)
- charge
- dipole moment
- polarizability
- ionization potential
- electrostatic potential

Directly computable from the electronic wave function of a molecule

BBB-model with 12 descriptors

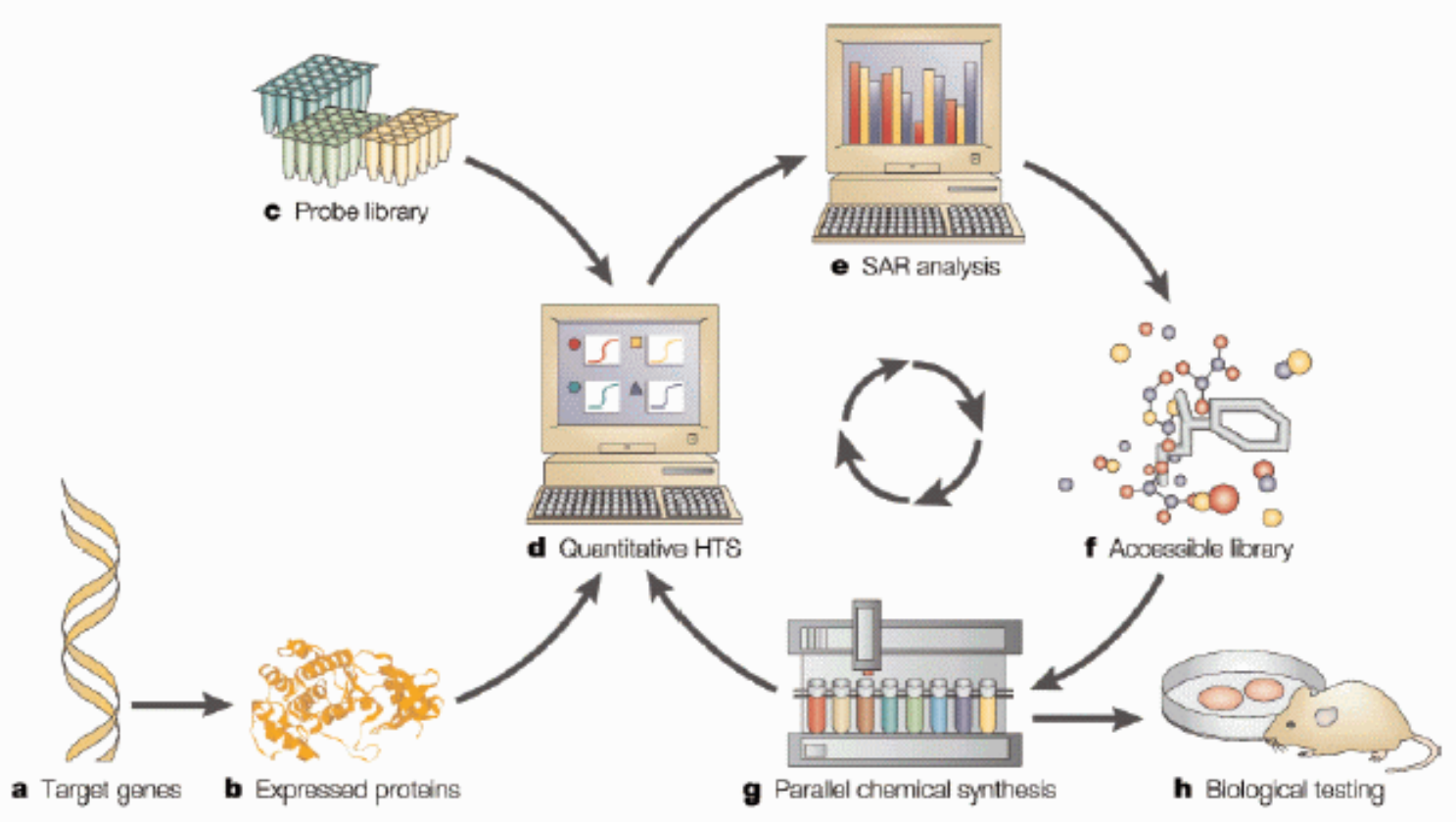
Descriptors mainly from QM calculations: electrostatic surface, principal components of molecular geometry, H-bond properties





Lit: M. Hutter *J.Comput.-Aided.Mol.Des.* **17** (2003) 415.

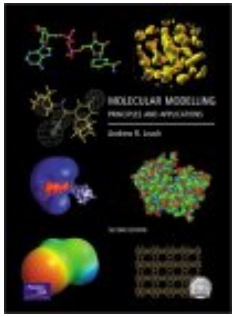
Cycle of optimization in the drug discovery pipeline



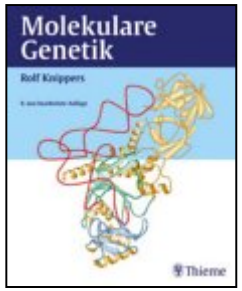
Source: D.K. Agrafiotis et al. *Nature.Rev.Drug.Discov.* **1** (2002) 337.

Accompanying books and further reading (I)

Andrew R. Leach*
Molecular Modelling. Principles and Applications
2nd edition, Prentice Hall, 2001

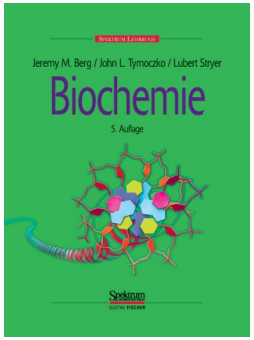


Rolf Knippers*
Molekulare Genetik
8. Auflage, Thieme, 2001



The Merck Index*
13th edition, Merck & CO., Inc., 2001

J.M. Berg, L. Stryer*
Biochemie, Spektrum Verlag
Biochemistry, W.H. Freeman & Co Ltd.



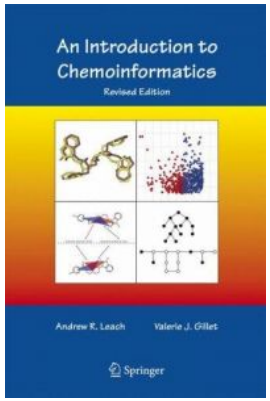
*Available in the „Semesterapparat“

Accompanying books and further reading (II)

Gerhard Klebe*
Wirkstoffdesign
2. Auflage, Spektrum Akad. Verlag, 2009

C.A. Orengo, D.T. Jones, J.M. Thornton*
Bioinformatics
Genes, Proteins & Computers
1st ed., Bios Scientific Publishers, 2003

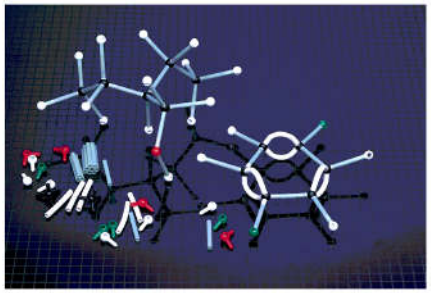
A.R. Leach, V. Gillet*
An Introduction to Chemoinformatics
revised ed., Springer, 2007

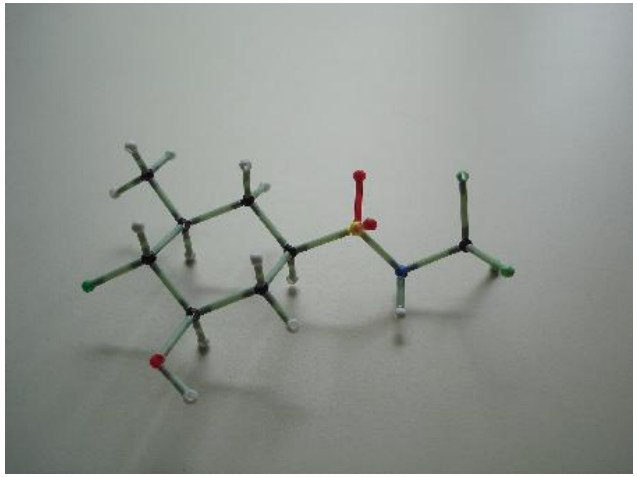


*Available in the „Semesterapparat“
located at the library in E2.3

Further hands-on tools

Molecular model sets / Molekülbaukasten





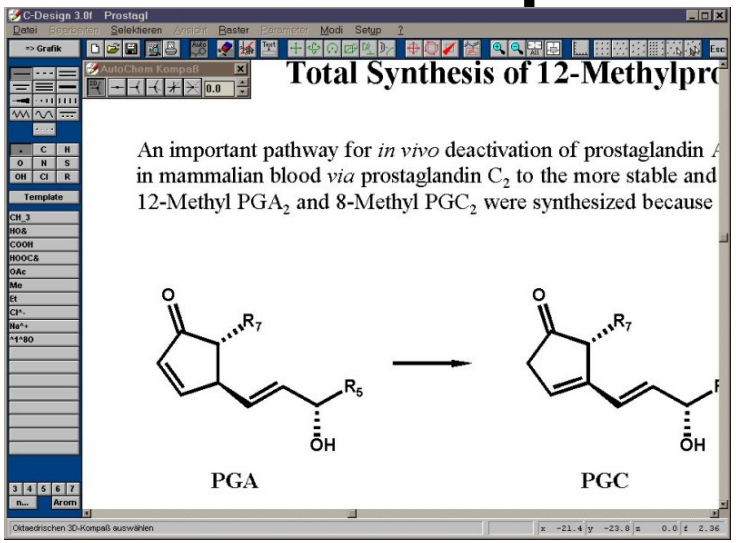
Commerically available at various price ranges

Other useful software to make nice pictures

Chemical structures and other objects:

C-Design 3.0f

Windows-Platform

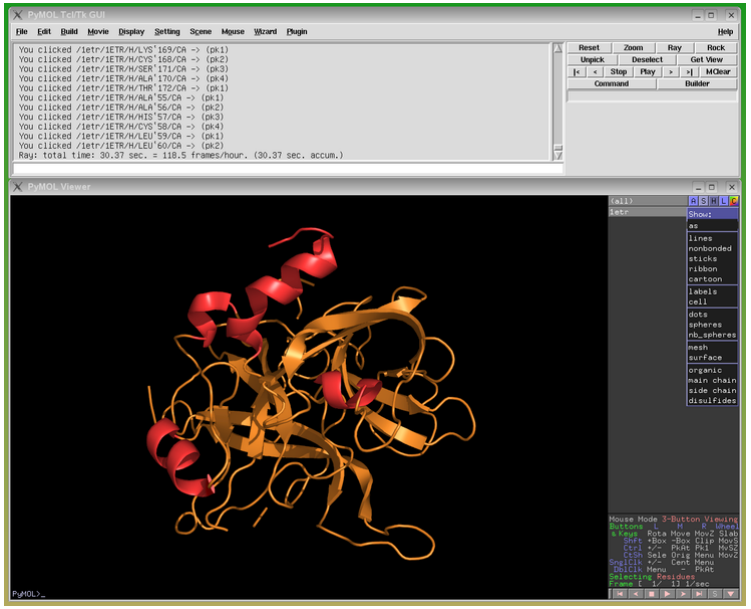


Protein structures:

PyMOL

www.pymol.org

Linux, Mac OS X, Windows



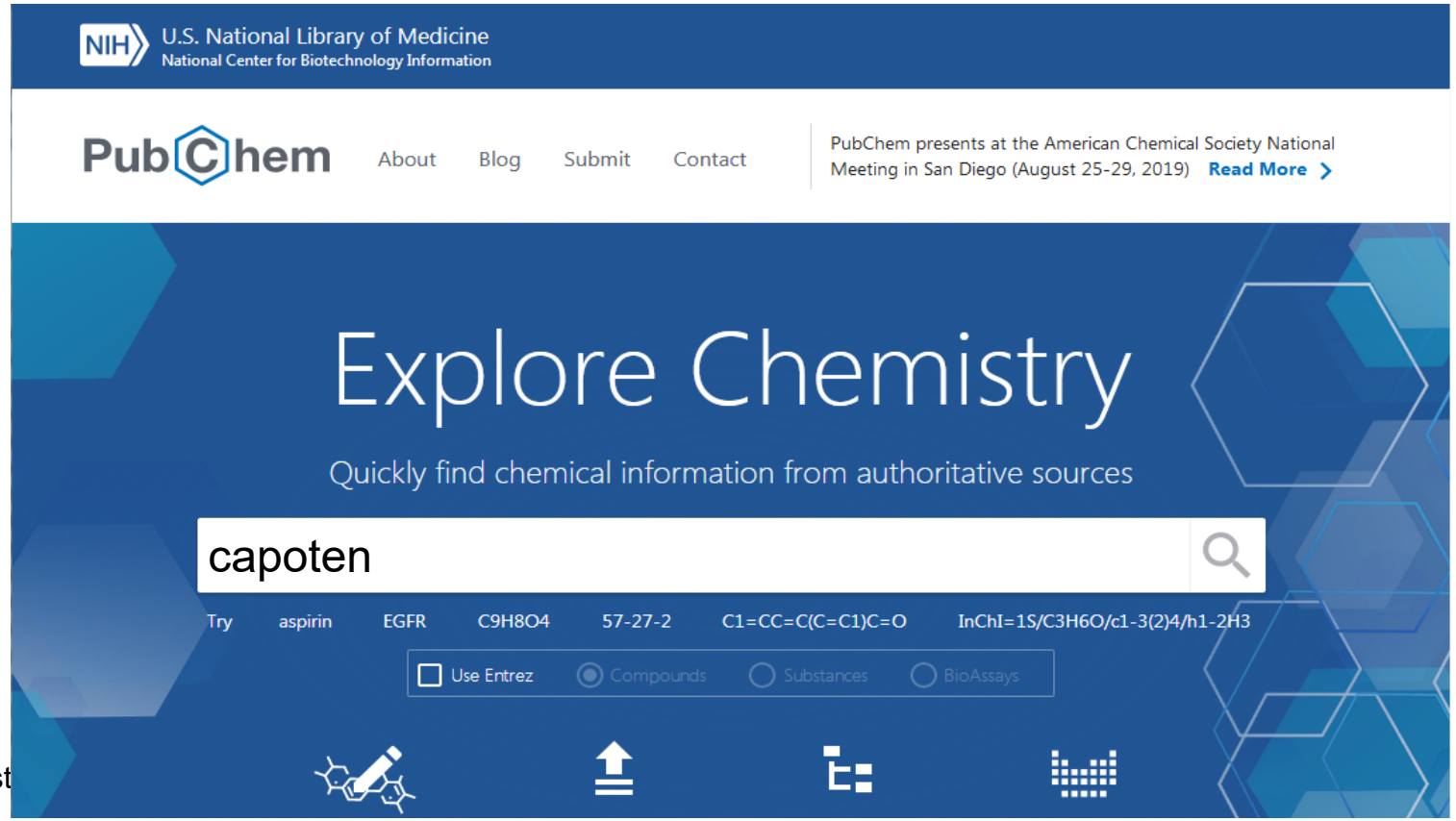
1st assignment (I)

Refer to a prescription medicine of your own choice

Write down the active ingridient

Try to find out its molecular structure:

https://pubchem.ncbi.nlm.nih.gov/



1st assignment (II)

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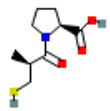
PubChem presents at the American Chemical Society National Meeting in San Diego (August 25-29, 2019) **Read More** >

SEARCH FOR

capoten

Treating this as a text search.

COMPOUND BEST MATCH



Captopril; 62571-86-2; L-Captopril; Capoten; Lopirin; Captopryl; Cesplon; Tensoprel; ...

Compound CID: 44093

MF: $C_9H_{15}NO_3S$ MW: 217.29g/mol

InChIKey: FAKRSMQSSFJEIM-RQJHMYQMSA-N

IUPAC Name: (2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid

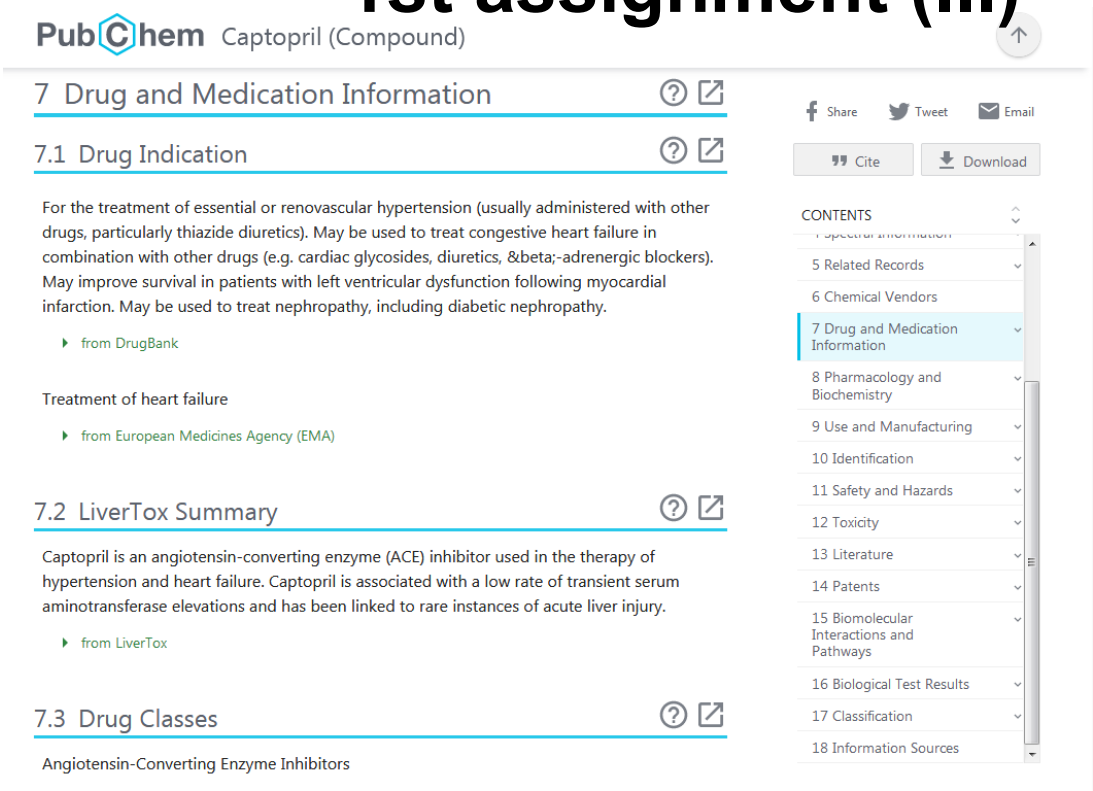
Create Date: 2005-06-24

Summary Similar Structures Search Related Records PubMed (MeSH Keyword)

Compounds (2) **Substances (19)** **Literature (80)**

Searching chemical names and synonyms including IUPAC names and InChIKeys accross the compound collection. Note that annotations text from compound summary pages is not searched. Read More...

1st assignment (III)

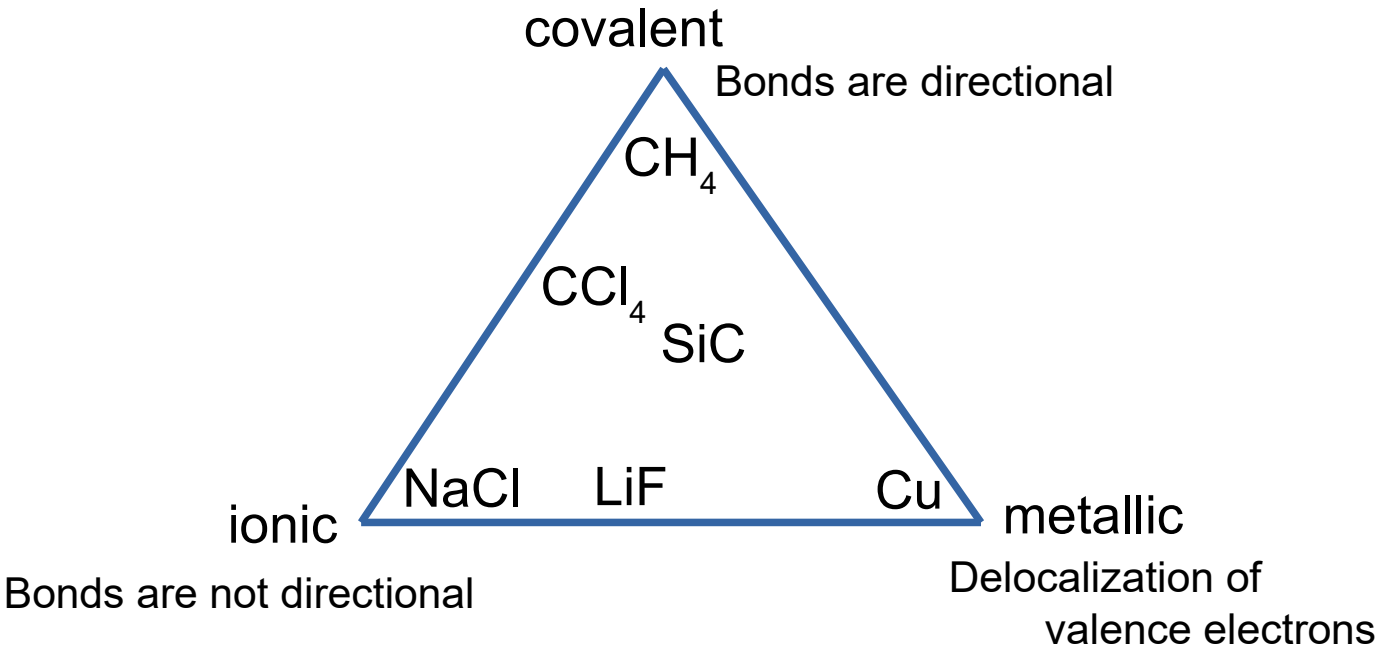


Explain why the medicine has a completely different name compared to the actual substance.

Try to find out some information about its actual *molecular target* (here: Angiotensin-Coverting Enzyme) e.g. using Wikipedia

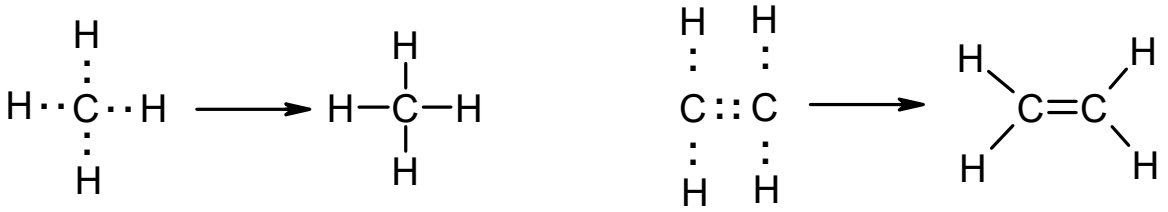
Recapitulation: The Chemical Bond

Entirely covalent, ionic, or metallic bonds between atoms are the extrem cases. More often the actual kind of bonding is somewhere in between and is subject to the difference in electronegativity of the atoms/elements involved.



Representation of chemical structures (I)

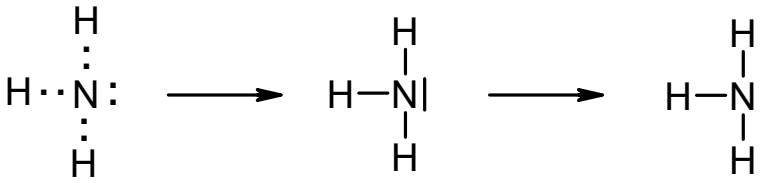
The valence electrons of the atoms are pairwise grouped together



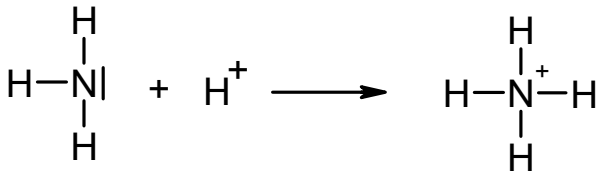
Such Lewis structures reflect covalent bonds between atoms in a molecule.
Therefore any molecule can be regarded as graph with the atoms being the nodes and the bonds as vertices.

Representation of chemical structures (II)

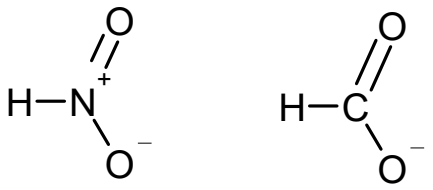
(electron) lone pairs are often not shown for visual clarity



octet rule and hypervalent atoms

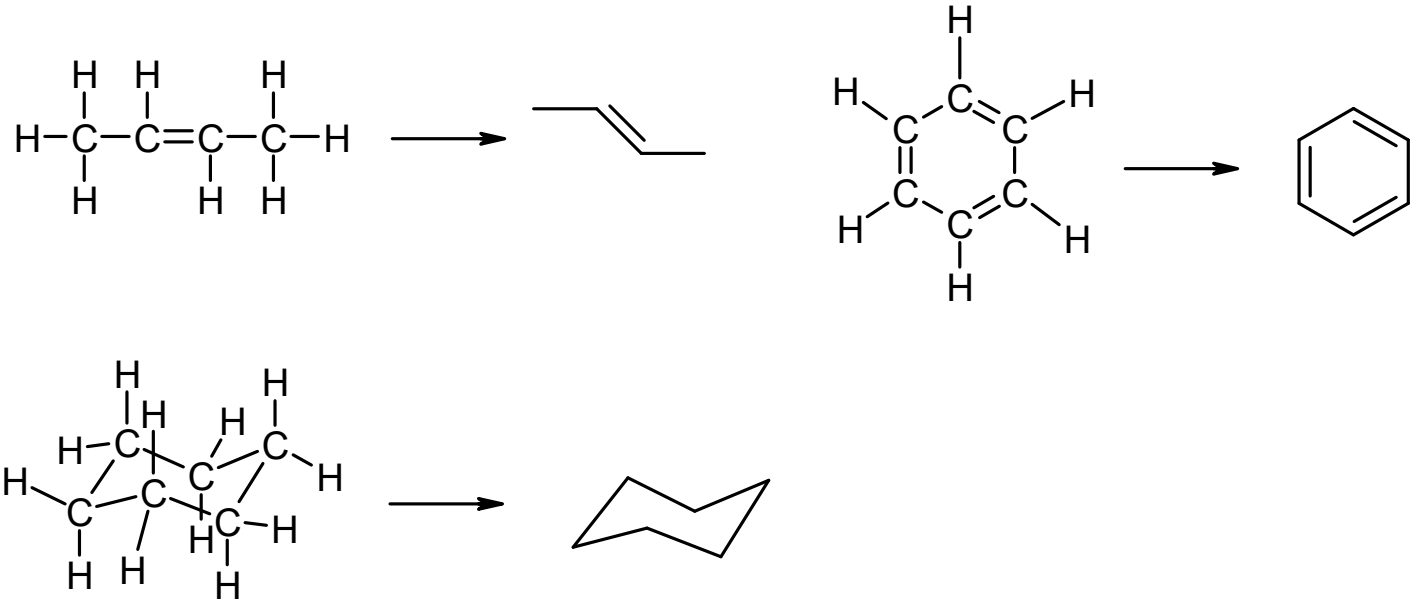


Equal bond lengths!



Representation of chemical structures (III)

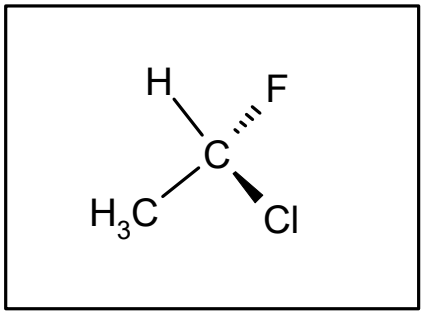
Also carbon atoms are often omitted



Corners and end of lines denote carbon atoms saturated with the appropriate number of hydrogen atoms

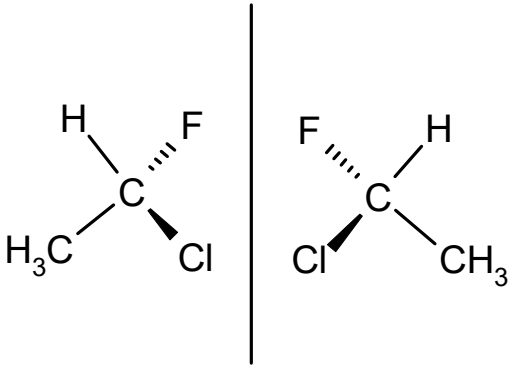
Representation of chemical structures (IV)

Stereochemistry



Solid wedges denote atoms in front of the plane,dashed wedges denote atoms behind

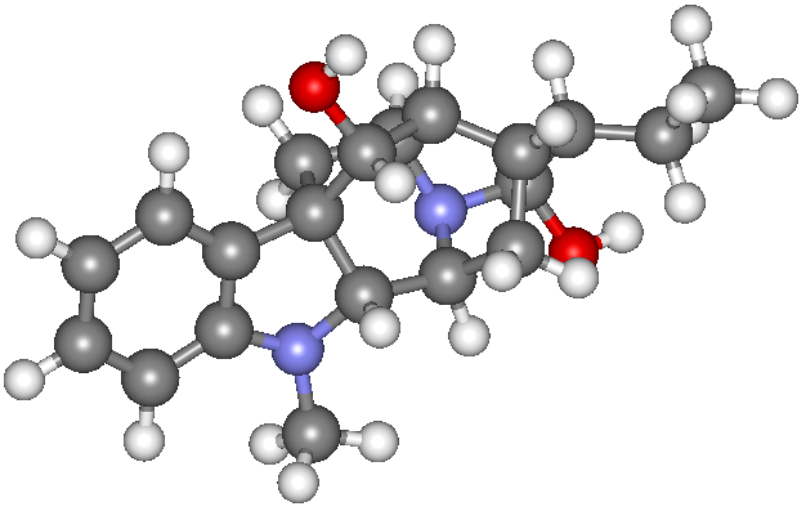
Four different substituents at a carbon atom cause chirality. Similar: silicon, sulfur, phosphorus,...

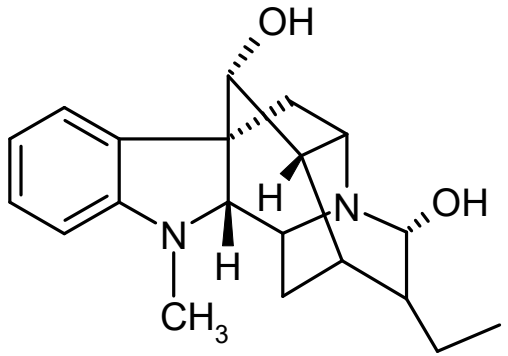


Examples: Most amino acids, sugars, many natural compounds,...

Representation of chemical structures (V)

Particular for more complex molecules, these 2D structural drawings provide more clarity than a picture of an actual 3D representation does.

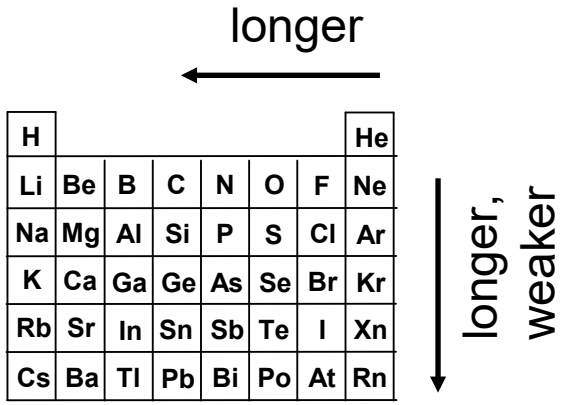




Exercise: Construct this molecule using a molecular model set. Specify the chiral carbon atoms.

Bond distances and bond dissociation energies (I)

bond	distance [Å]	D_o [kJ/mol] (homolytic cleavage)	
H–H	0.742	432	e.g. H• •H
C–H	1.09 ± 0.01	411 ± 7	
C–C	1.54	345	
C=C	1.34 - 1.40*	602 ± 21	*aromatic bond
C≡C	1.20	835	
C–N	1.47	305	
C=N	1.35	615	
C≡N	1.16	887	
C–O	1.43	358	
C=O	1.20	526	
C–Si	1.85	318	
C–P	1.84	264	
C–S	1.82	272	
C=S	1.60	577 ± 21	



Adapted from: J.E.Huheey *Inorganic Chemistry,* Wiley.

Bond distances and bond dissociation energies (II)

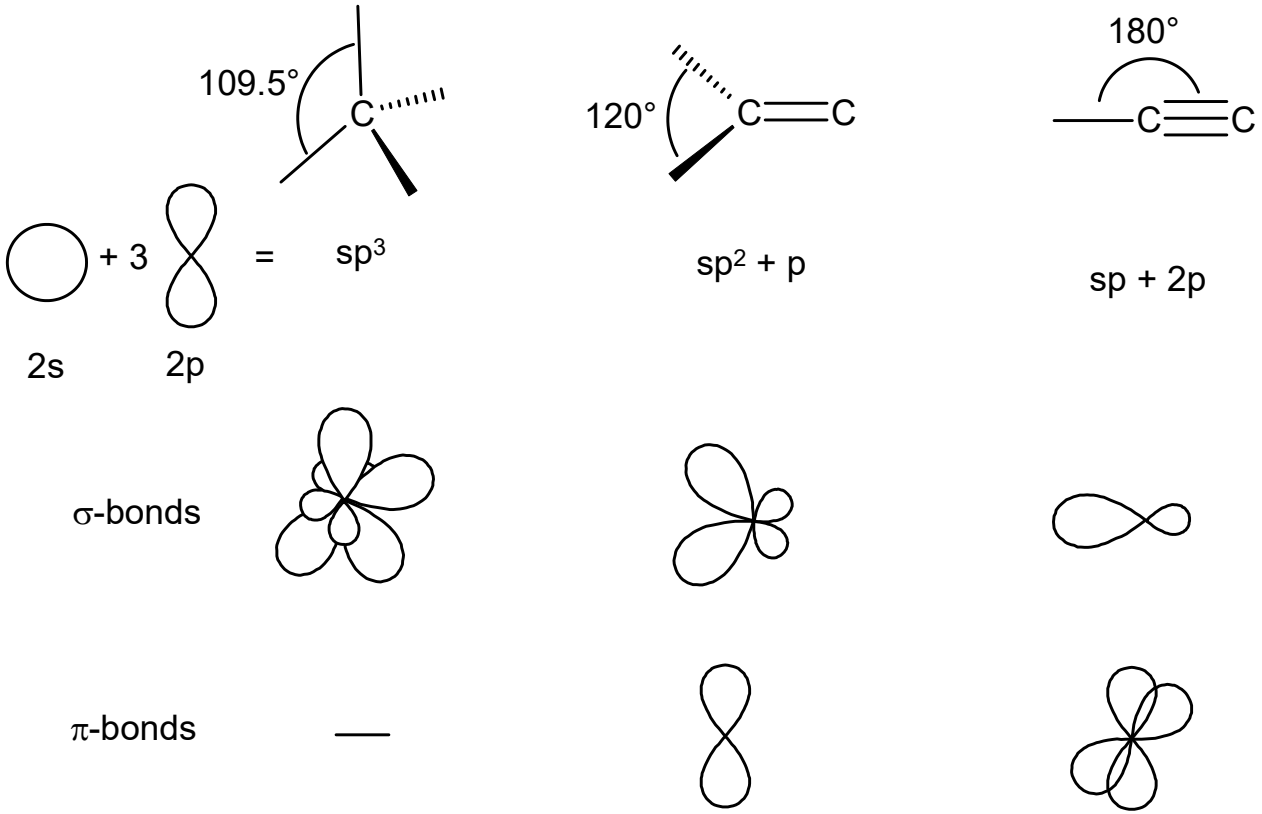
bond	distance [Å]	D_o [kJ/mol]	
C–F	1.35	485	
C–Cl	1.77	327	
C–Br	1.94	285	
C–I	2.14	213	
C–H	1.09	411	non-polar hydrogen
O–H	0.96	459	polar hydrogens, exchangable in polar solvents, e.g. water
N–H	1.01	386 ± 8	
S–H	1.34	363 ± 5	
N–N	1.45	247 ± 13	
N=N	1.25	418	
N–O	1.40	201	
N=O	1.21	607	
P–O	1.63	≈335	
P=O	≈1.50	≈544	

reason:
N, O, and S are more electronegative than C;

heterolytic cleavage that leads to ions
e.g. O^- H^+

Bond angles (I)

Strongly dependend on the hybridization



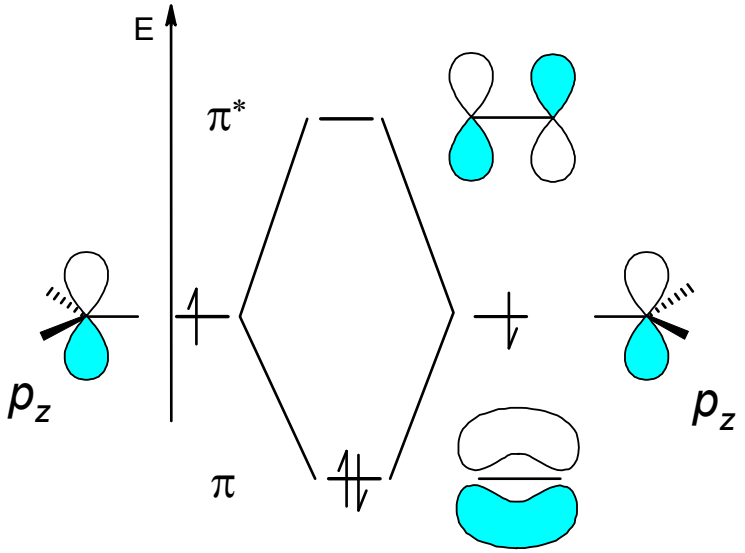
The C–C σ-bond is formed by overlap of the 1s orbitals

These are hybrizided atomic orbitals. Do not confuse with molecular orbitals (=linear combination of atomic orbitals)

Molecular Orbitals

MO = linear combination of atomic orbitals (LCAO)

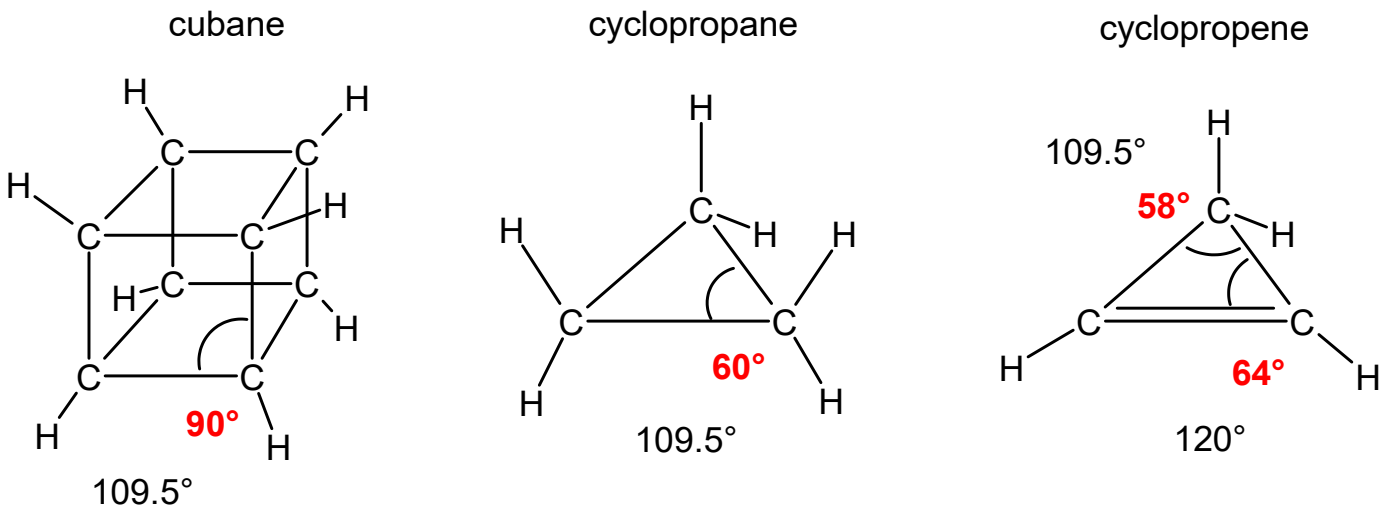
π-bond of ethylene $H_2C=CH_2$



The two combinations usually result in one bonding and one anti-bonding MO

Bond angles (II)

Extreme deviations from ideal bond angles

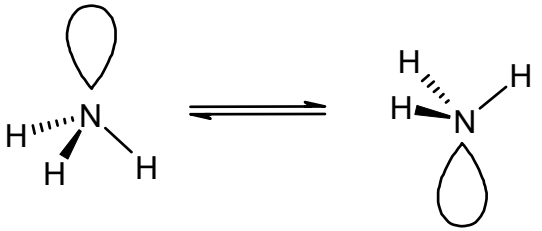


gives rise to strain energy in small rings

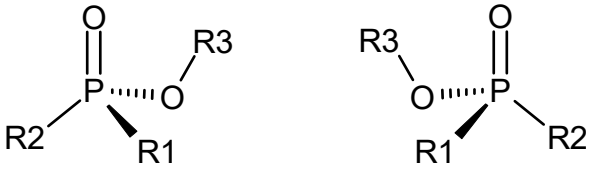
→ problems in force fields. More than one atom type for each hybridization state (e.g. Csp^3) neccessary.

Chiral atoms

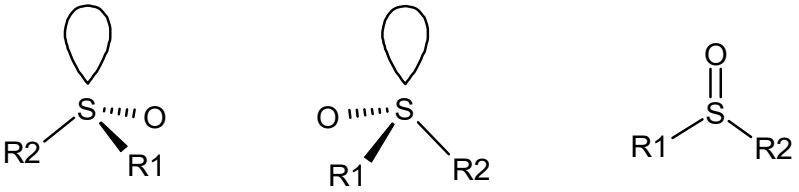
Further elements showing chirality/stereochemistry
(the lone electron pair behaves like a substituent)



Fast exchange at room temperature,
but slow at 77K



phosphorus inverts even slower

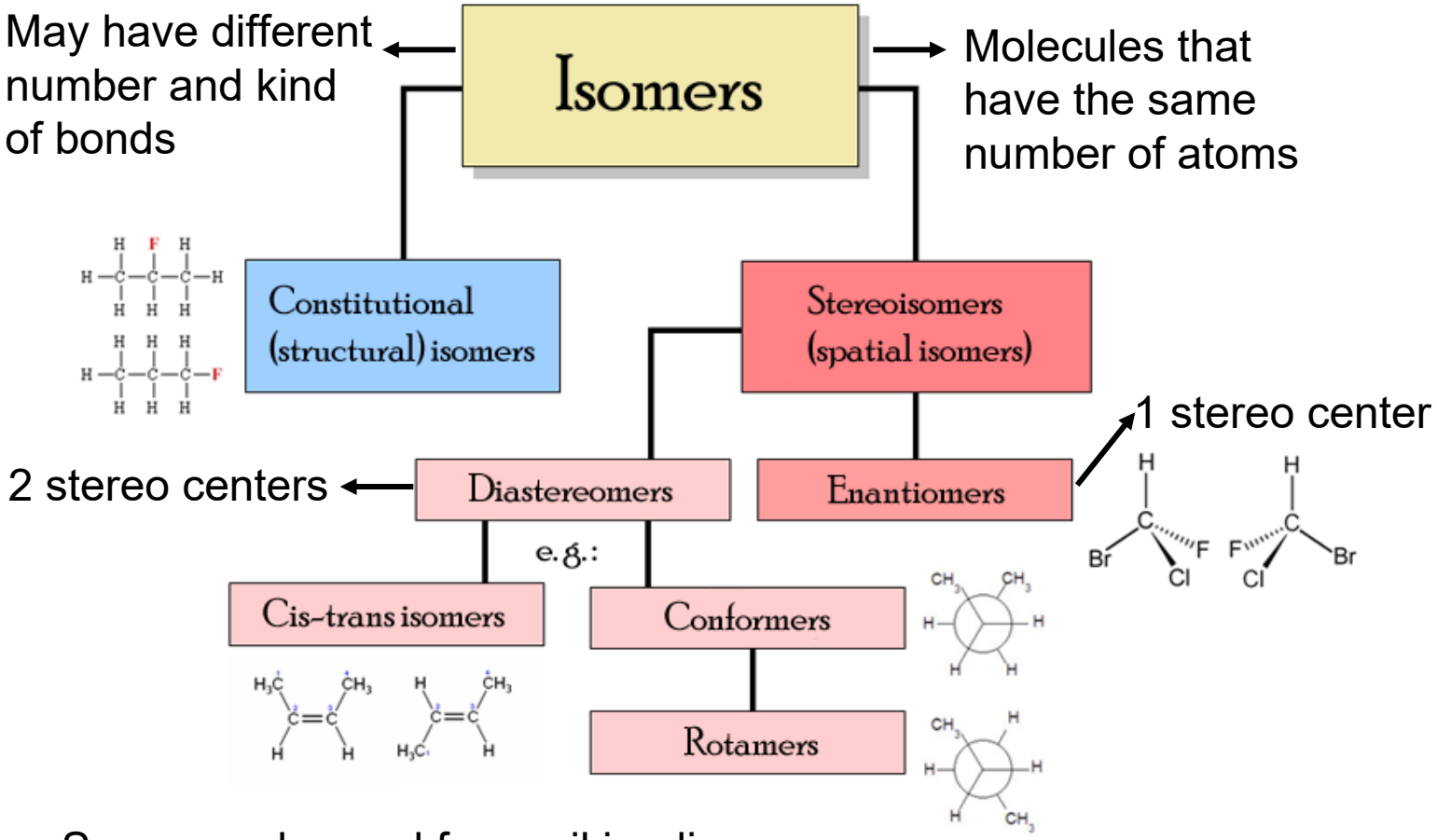


sulfoxides, sulfinic esters, etc

→ Different compounds at
room temperature

Furthermore: As, Si, ..., compounds with transition elements,
esp. octahedral and square planar metal complexes e.g. Pt

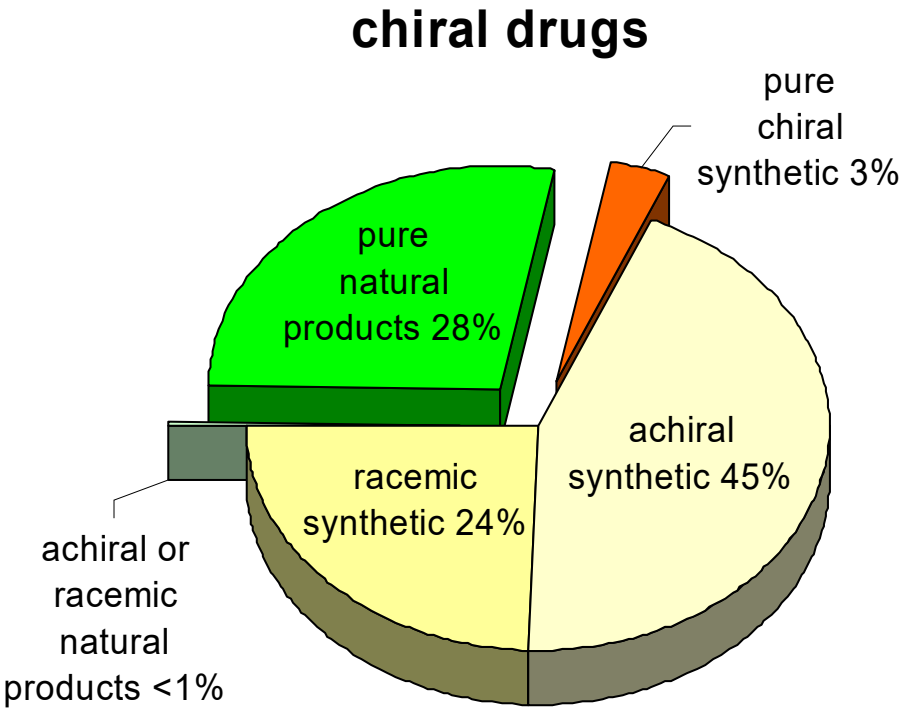
Isomers



Source: enhanced from wikipedia

Question: Which kind of computational method(s) allow(s) to calculate differences in energy between the respective isomers ?

Is stereochemistry important ?



Data from 1982: Böhm, Klebe & Kubinyi, *Wirkstoffdesign*