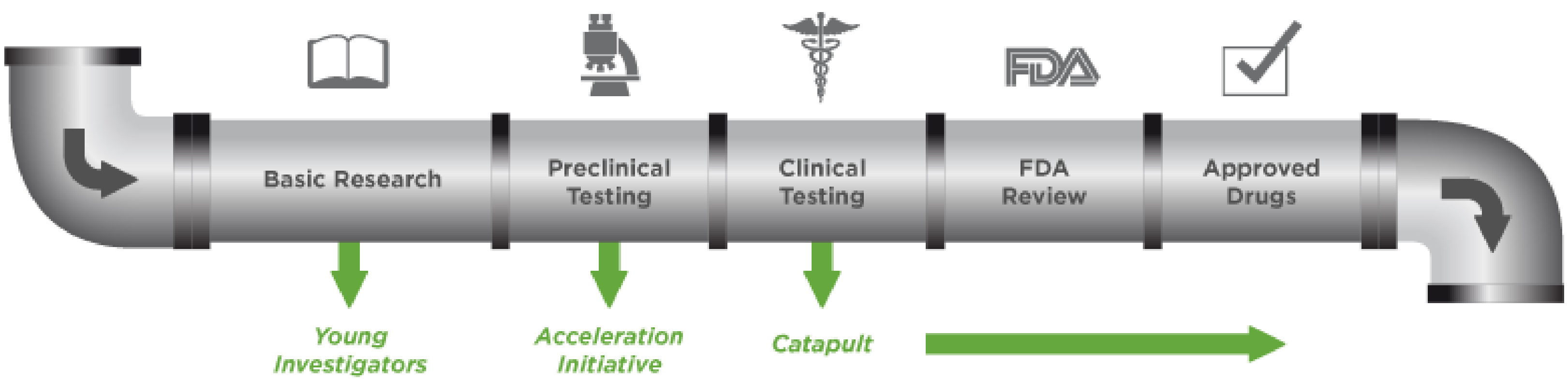
Modern Methods in Drug Discovery

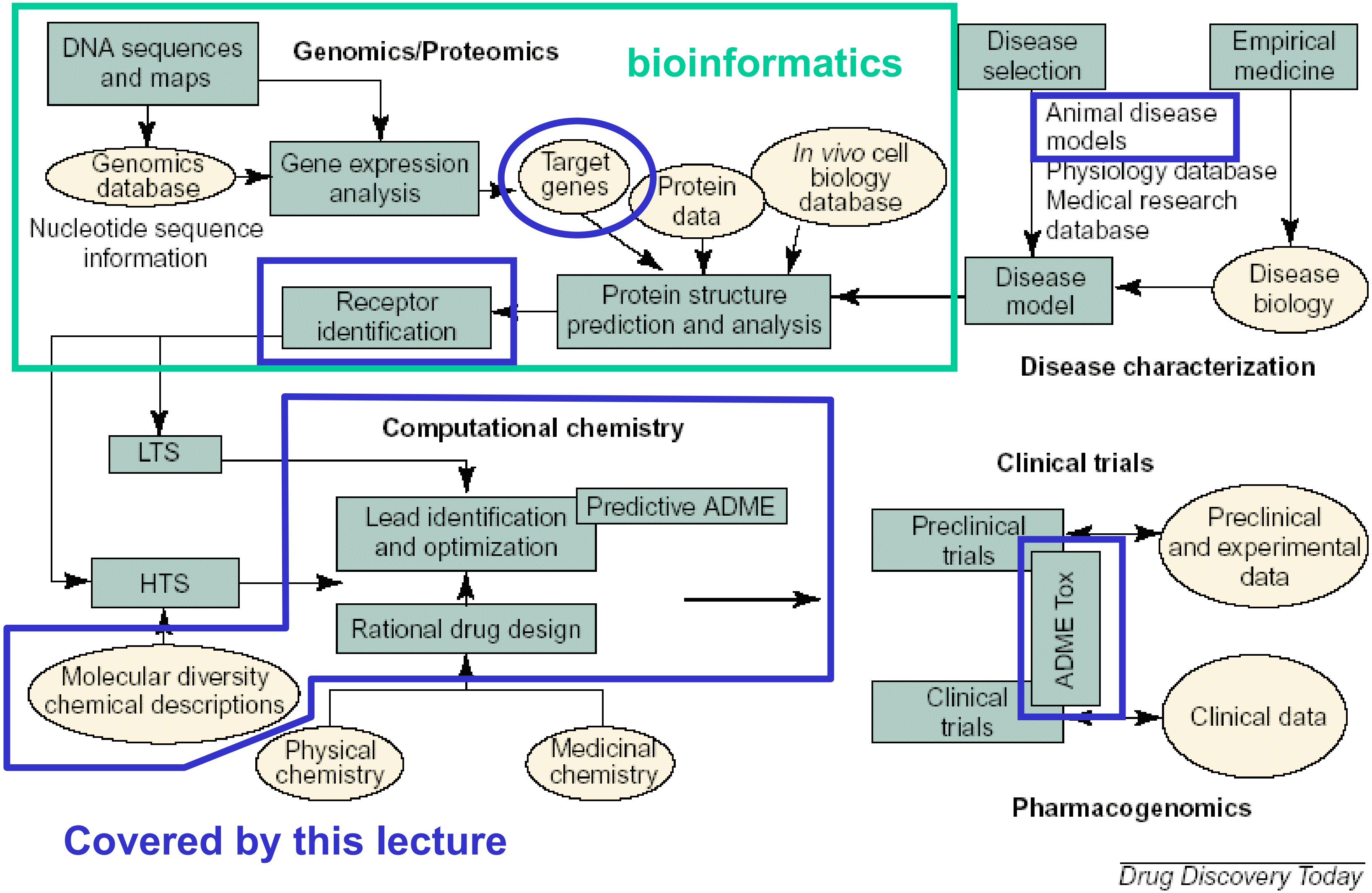
Aims of this course:

- 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, targetome,...
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, Chimera, Pymol, VMD, SPDBV

recommended prior courses:

Softwarewerkzeuge der Bioinformatik Computational Chemistry Bioinformatics I & II	Bachelor program
Structural Bioinformatics	Master program

Actual applications during the excercices and homework:

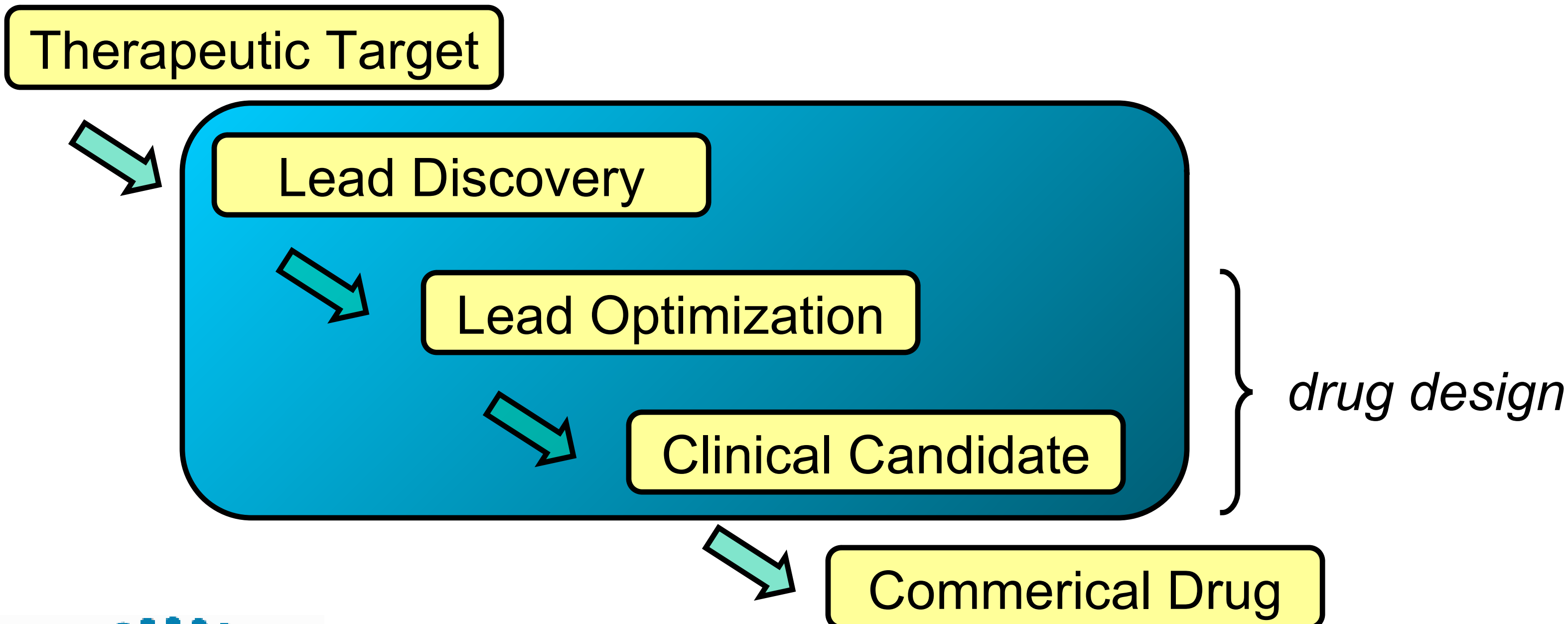
multiple sequence alignment, homology in sequences
analyzing protein-ligand interactions

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

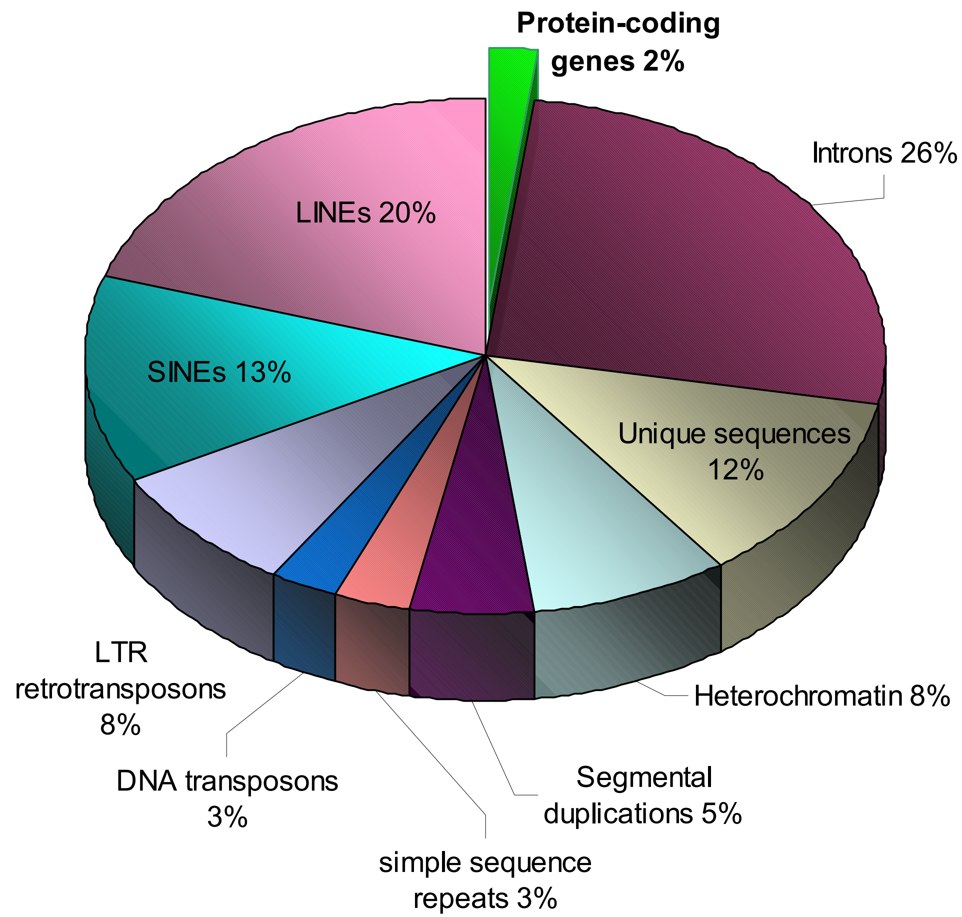
Database queries (PubChem, ChEMBL, DrugBank, ZINC, UniProt,...)

What is *drug discovery* ?

rational and targeted search for new drugs



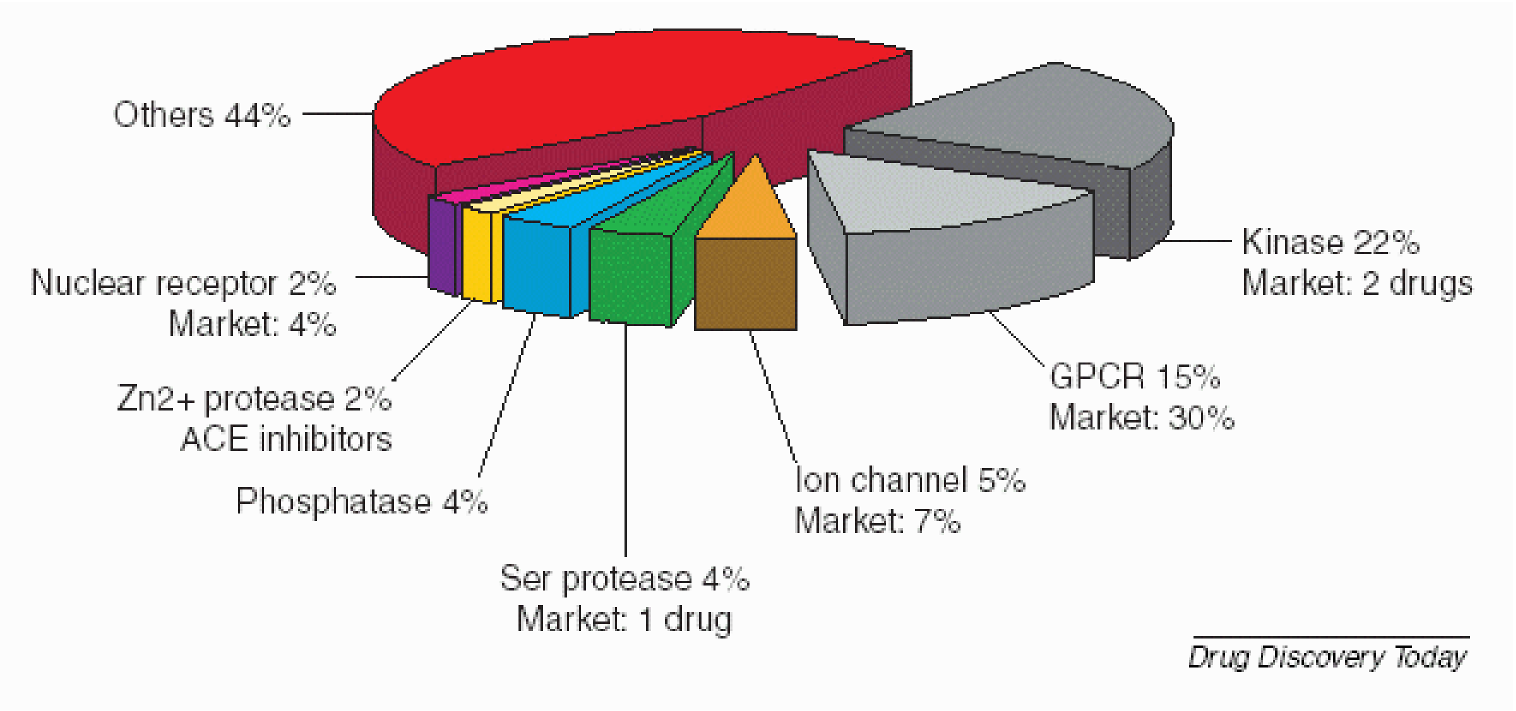
Content of the Human Genome



Fraction of protein-coding sequences

Data from the NHS National Genetics and Genomic Education Centre estimated in 2014.

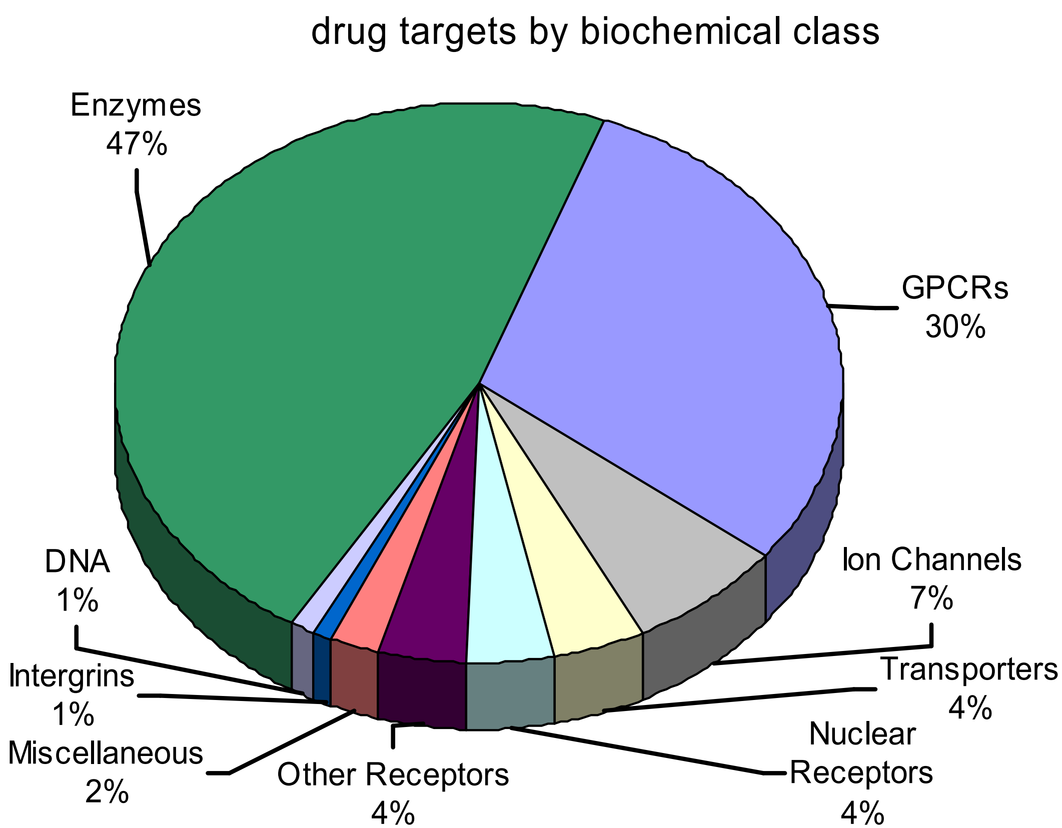
Typical targets (I)



Contribution to the human genome and marketed drugs

Estimated drug targets: >3.000

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
12. current trends

Preliminary schedule (exercises/tutorials)

Biweekly online via MS-Teams meeting

→ you will be added to the corresponding MS-Teams after registration by email (conditions and restrictions apply, see our web-site)

- discussion of the assignments
- Hands-on tutorials about:
- 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

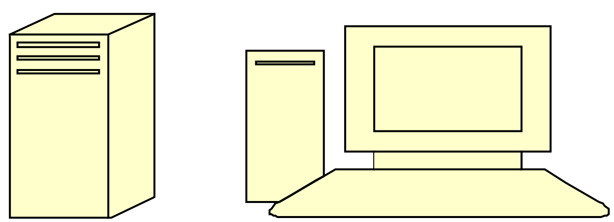
1. You will be enrolled to the course in the moodle system.
2. Passing the two online tests (will be available in the moodle system) covering the topics of the previous assignments.
   → You don‘t have to hand in the assignments!
3. 50% of all accomplishable points from the final exam taking place at 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 final exam 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

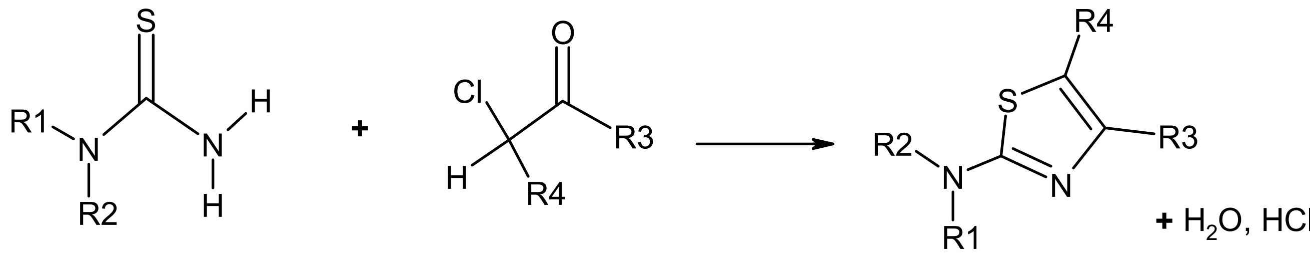
PubChem	> 112,000,000 compounds	NCBI	academic
ChEMBL	> 2,200,000 compounds	EMBL	
DrugBank	> 500,000 drugs	Uni. Alberta	
ZINC15	>750,000,000 compounds	UCSF	



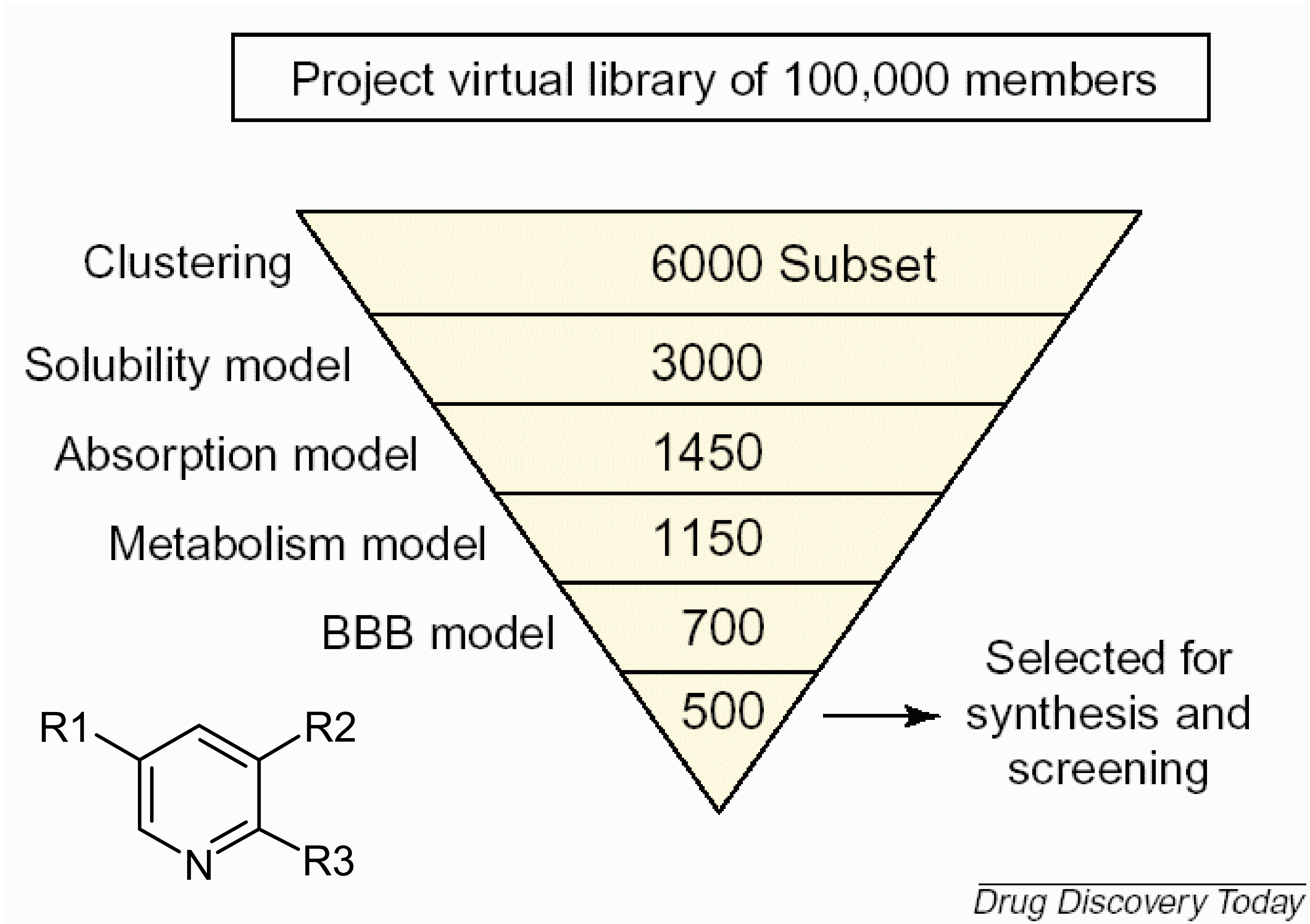
Investment per new chemical entity: >800,000 $

New chemical entities per year: ca. 15 strongly fluctuating

Methods of Combinatorial Synthesis for High Throughput Screening (HTS)



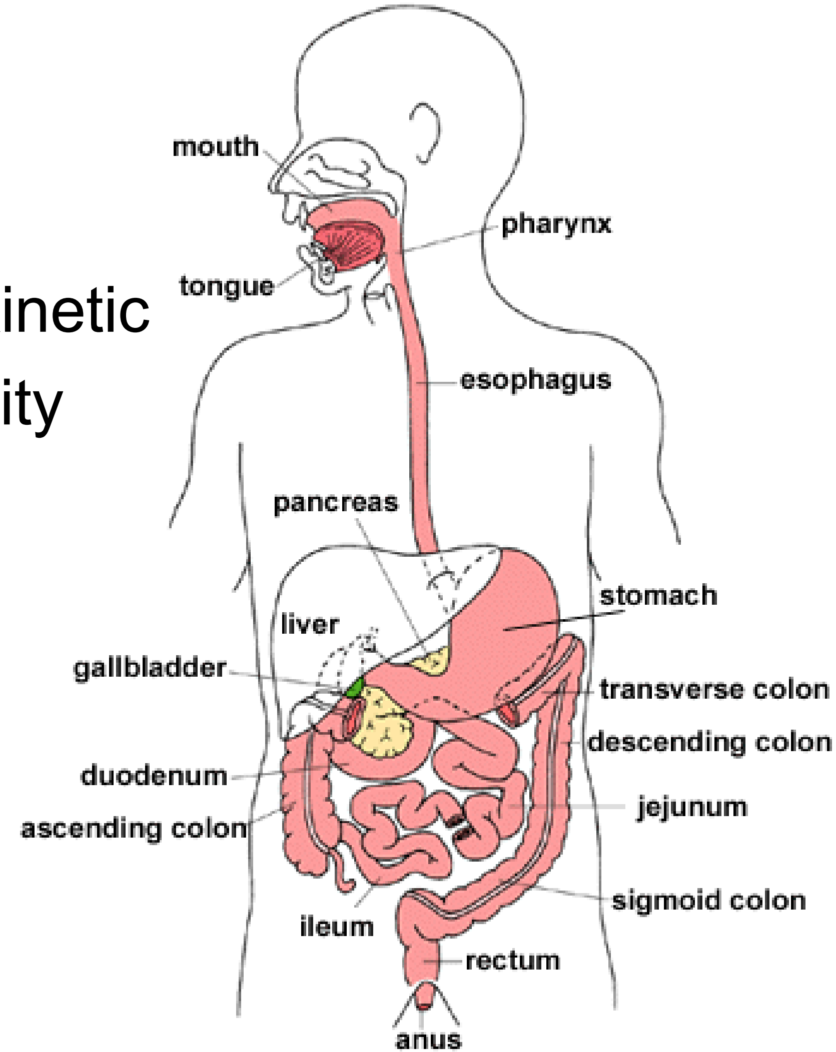
Selection of compounds for High Throughput Screening (HTS)



Predictive ADME

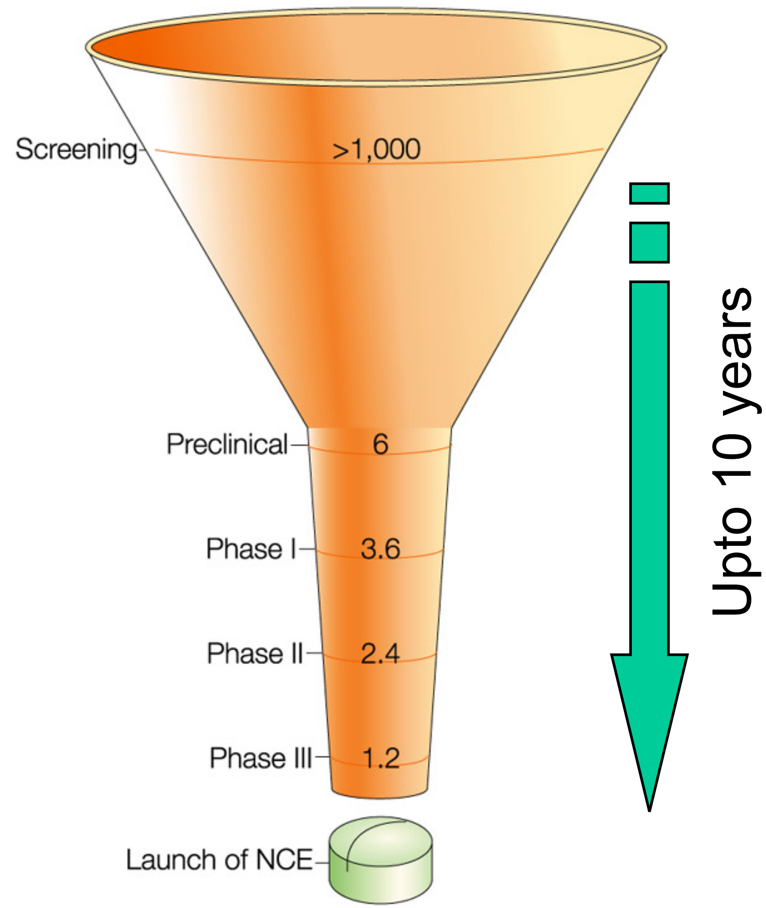
Absorption
Distribution
Metabolism
Elimination

Pharmacokinetic
Bioavailability



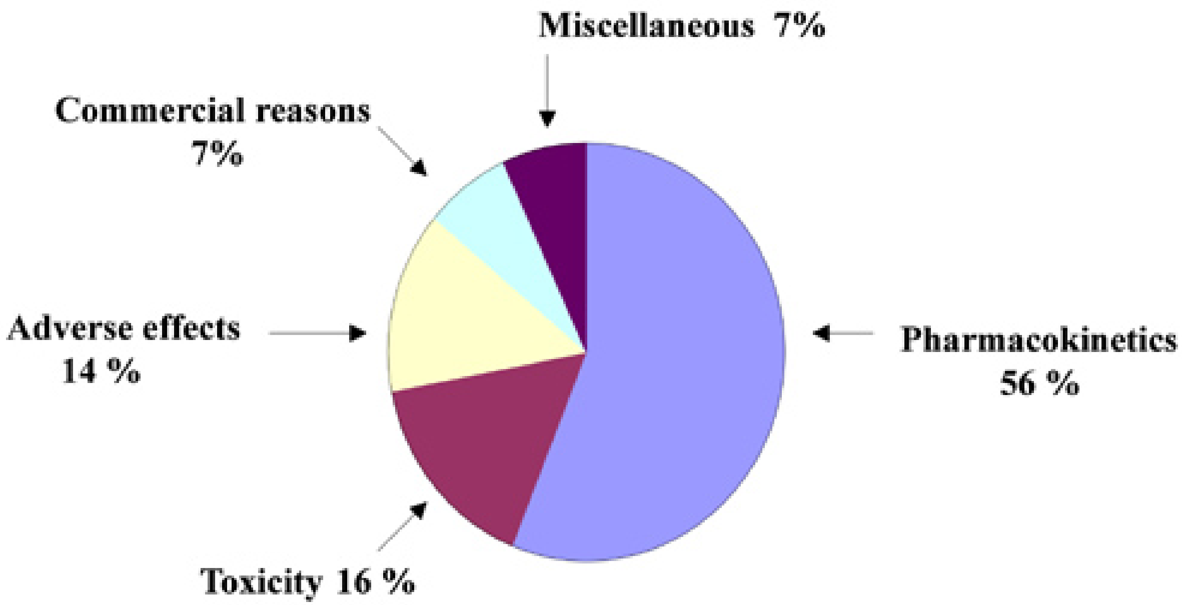
From the pipeline until the commerical launch

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.



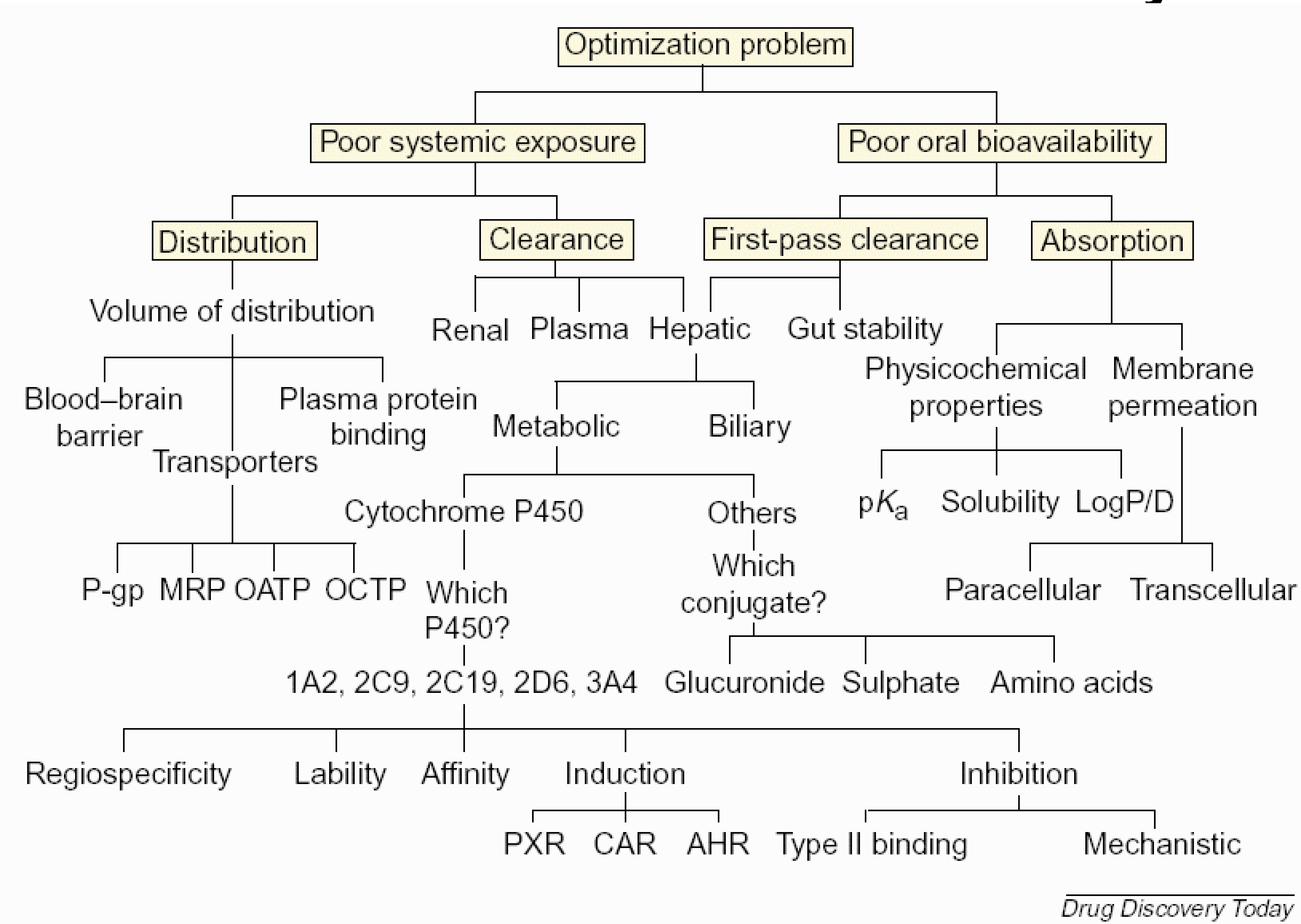
Nature Reviews | Drug Discovery

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



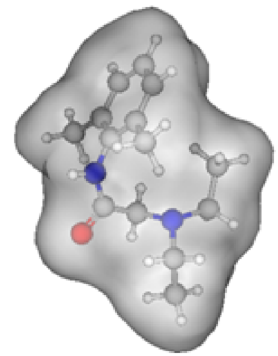
(Some) descriptors based on molecular properties used to predict ADME properties

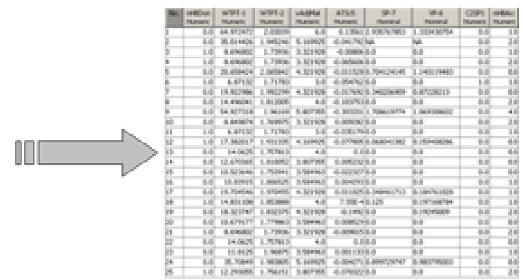
logP water/octanol partitioning coefficient

topological indices

count of hydrogen-bonds

polar surface area

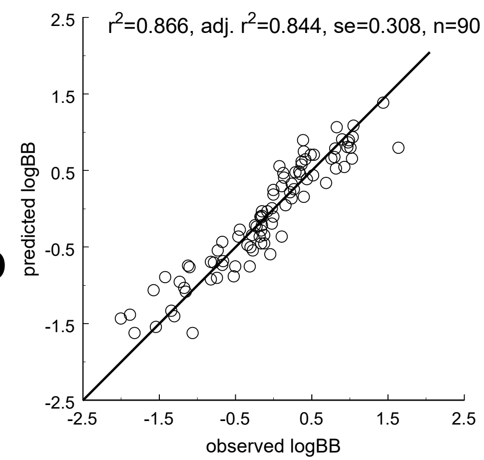




Multiple linear regression analysis

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 $\rightarrow$ esp. cytochrome P450 enzymes

Phase II:

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

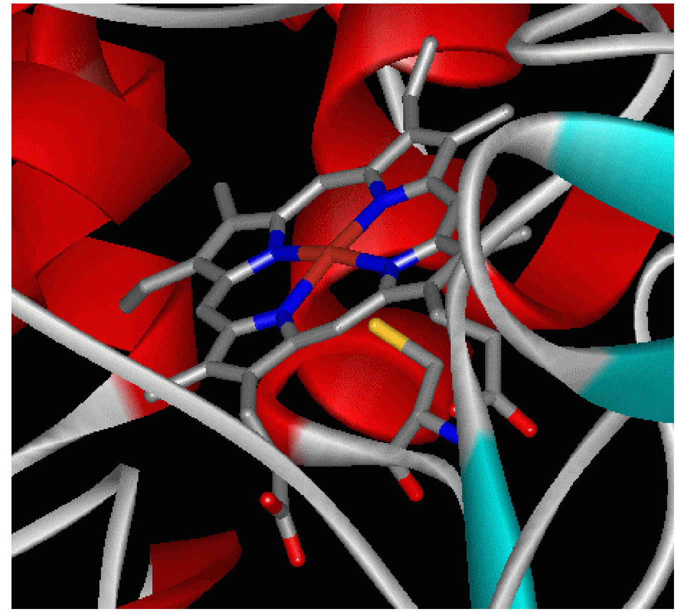
Phase III:

elimination by transporters

Cytochrome P450 Enzymes (I)

$$\text{Drug-R} + O_2 \xrightarrow{\text{CYP}} \text{Drug-OR} + H_2O$$

NADPH NADP



flavin monooxygenase isoenzyme (FMO)

monoamine dehydrogenase (MAO)

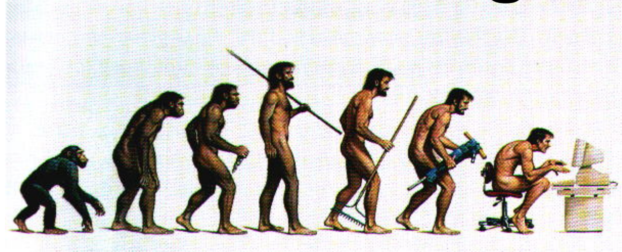
aldo-keto reductase (AKR)

alcohol dehydrogenase

aldehyde oxidase

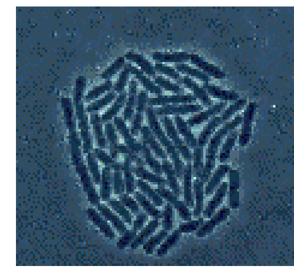
Further phase I enzymes

Cytochrome P450 gene families



Human 17+

Molluscs 1



CYP450

Plants 22

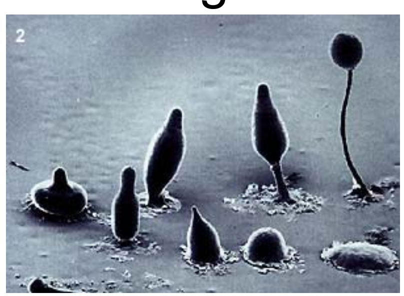
Insects 3

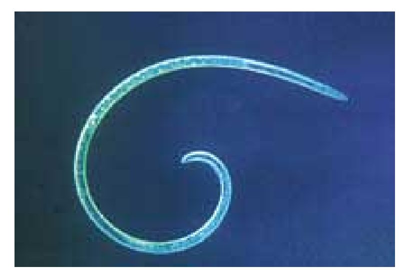
Bacteria 18

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.

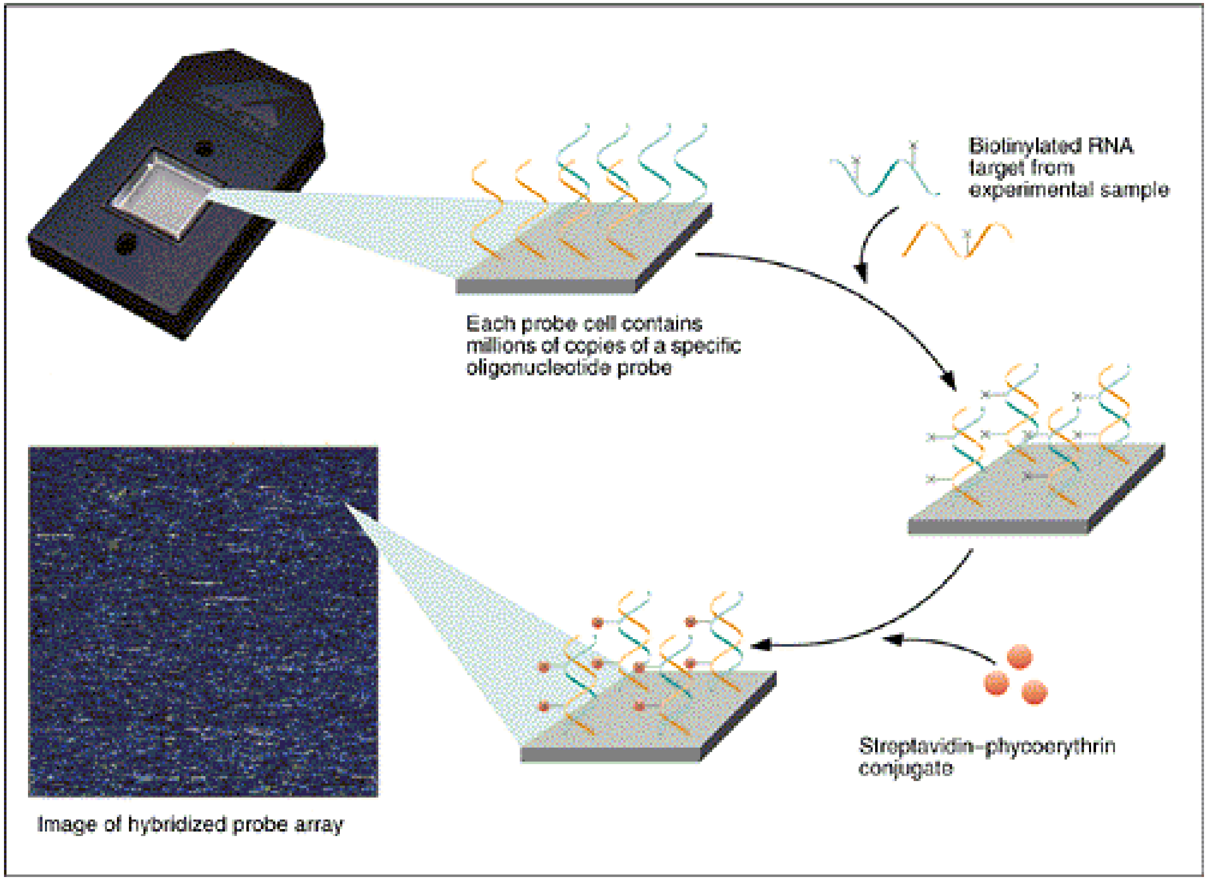
Thus, the same genotype enables several different phenotypes

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

→ other statistical methods, e.g. partial least square

→ decision trees, machine learning algorithms, e.g. support vector machines, boosting, neural networks, deep learning,...

Prediction of molecular properties (II)

What are (physical) molecular properties?

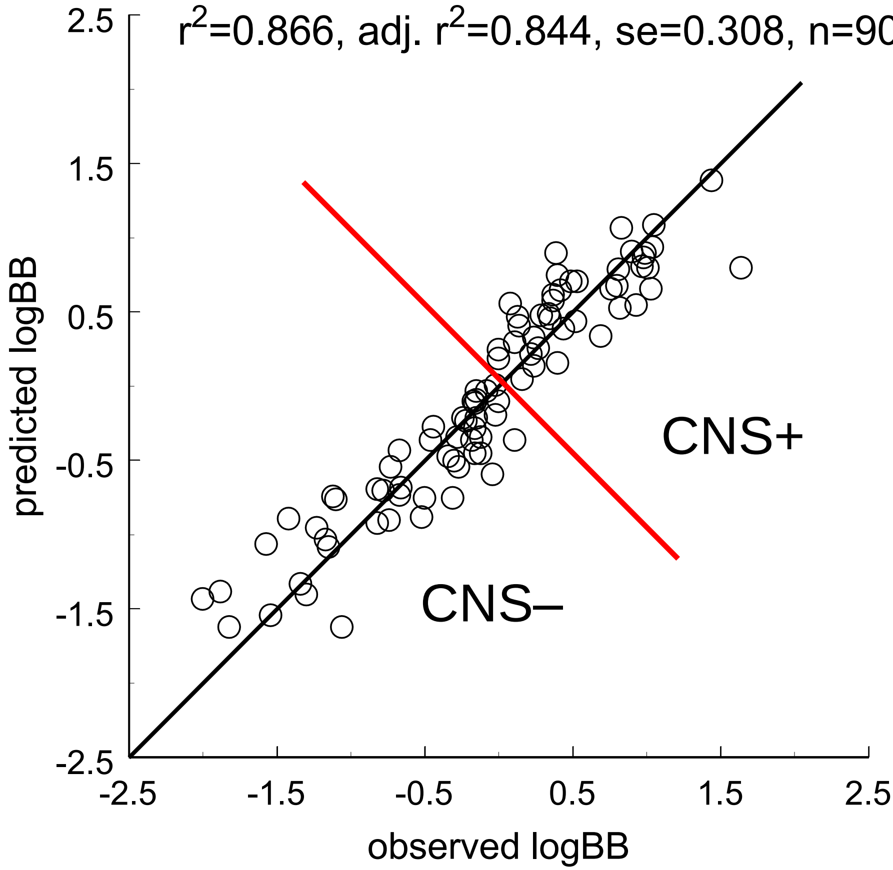
observables

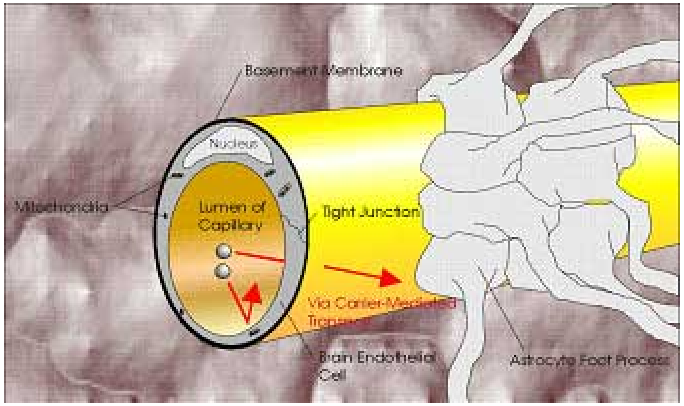
- molecular weight MW (from the sum formula $C_{12}H_{11}N_3O_2$)
- melting point
- boiling point
- vapour pressure
- solubility (in water)
- charge
- dipole moment
- polarizability
- ionization potential
- electrostatic potential

Directly computable from the electronic wave function of a molecule

BBB-model with 12 descriptors

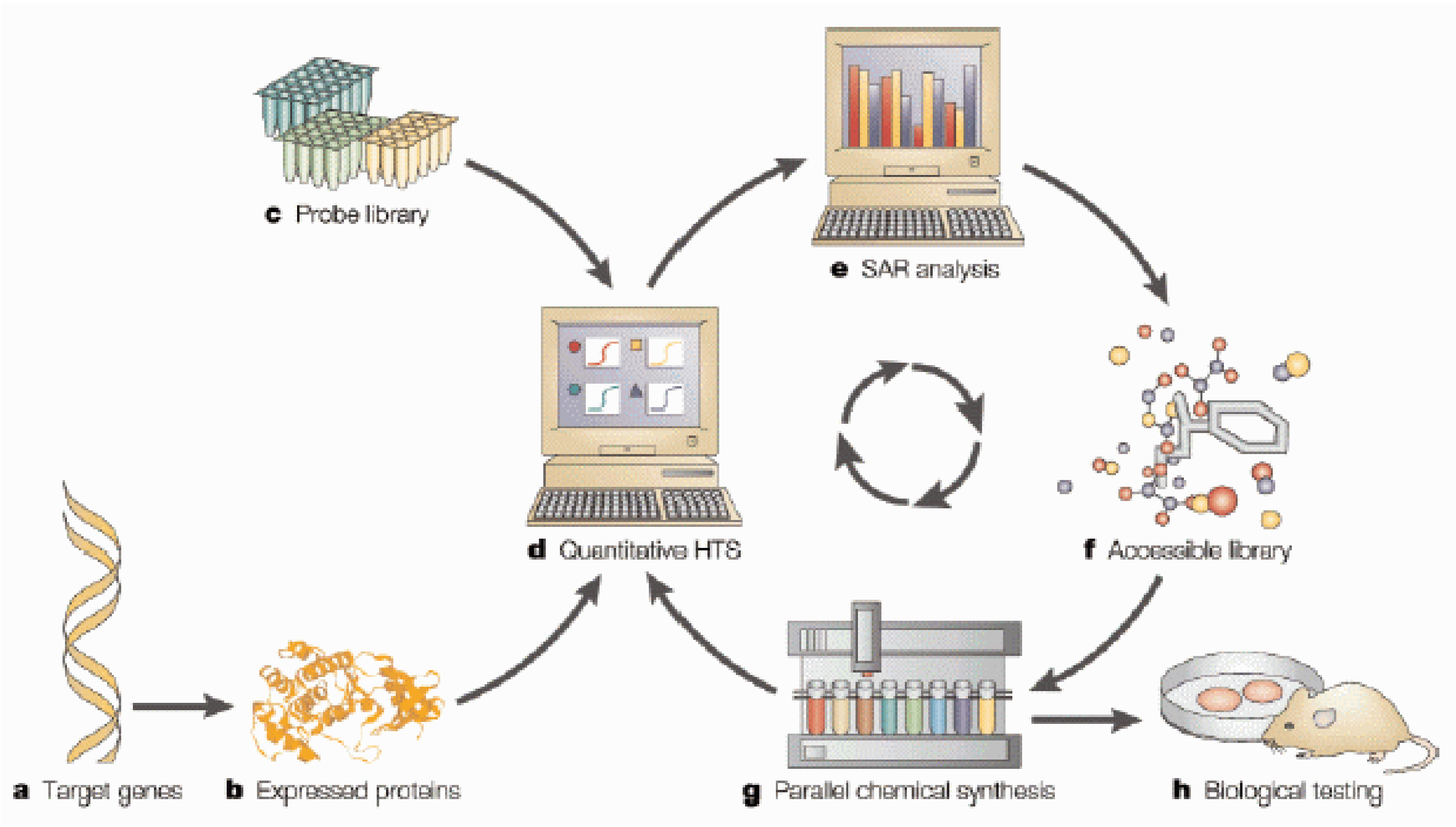
Descriptors mainly from QM calculations: electrostatic surface, principal components of molecular geometry, H-bond properties





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

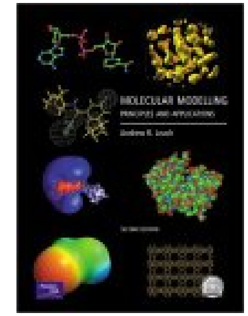
Cycle of optimization in the drug discovery pipeline



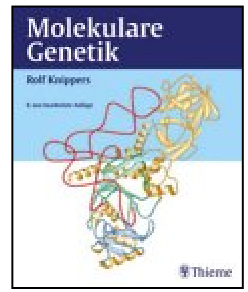
Source: D.K. Agrafiotis et al. *Nature.Rev.Drug.Discov.* **1** (2002) 337.

Accompanying books and further reading (I)

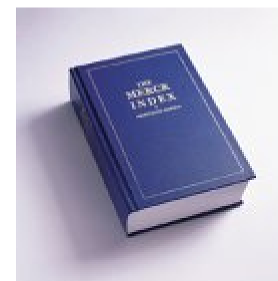
Andrew R. Leach*
Molecular Modelling. Principles and Applications
2nd edition, Prentice Hall, 2001



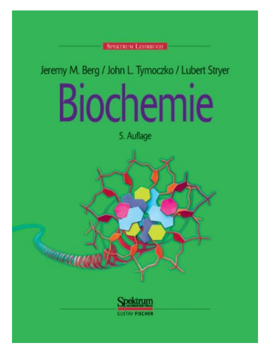
Rolf Knippers*
Molekulare Genetik
8. Auflage, Thieme, 2001



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



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

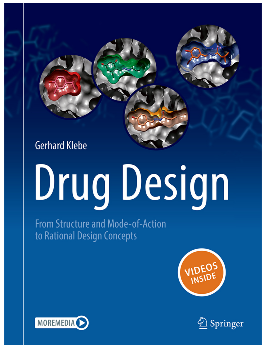


*Available in the „Semesterapparat"

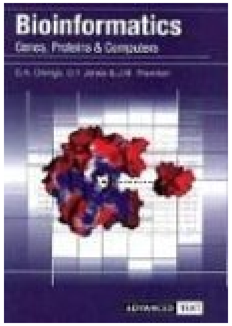
ZBI

Accompanying books and further reading (II)

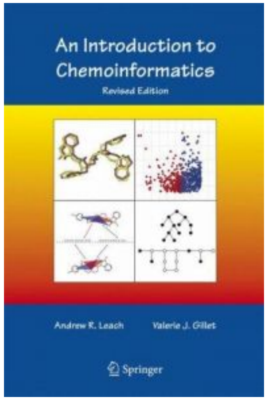
Gerhard Klebe
Drug Design, Springer, 2025
„Wirkstoffdesign" 3. Auflage 2023
online verfügbar über SULB

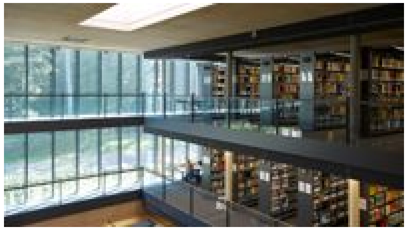


C.A. Orengo, D.T. Jones, J.M. Thornton*
Bioinformatics
Genes, Proteins & Computers
1st ed., Bios Scientific Publishers, 2003



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

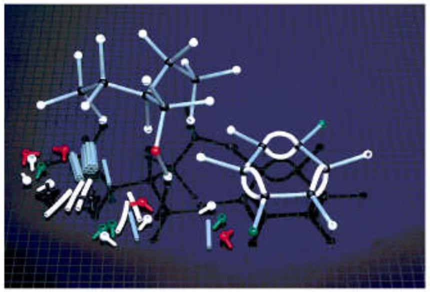


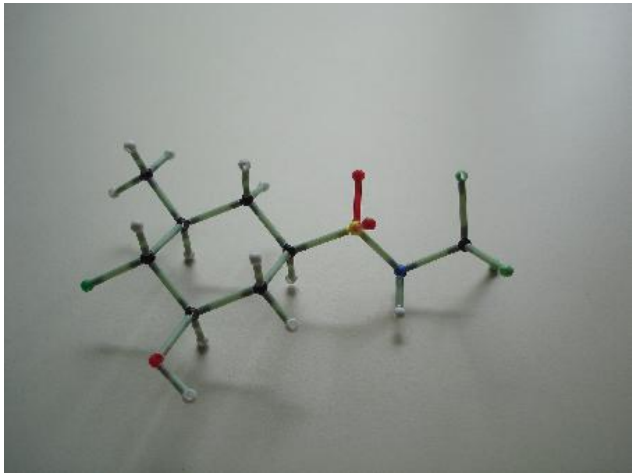


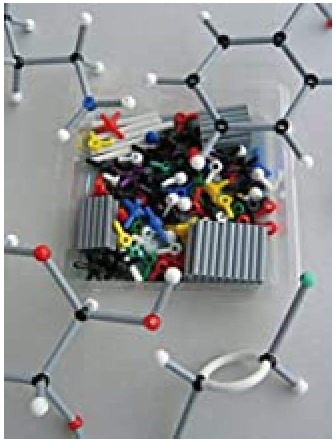
*Available in the „Semesterapparat"
located at the library in E2.3

Further hands-on tools

Molecular model sets / Molekülbaukasten







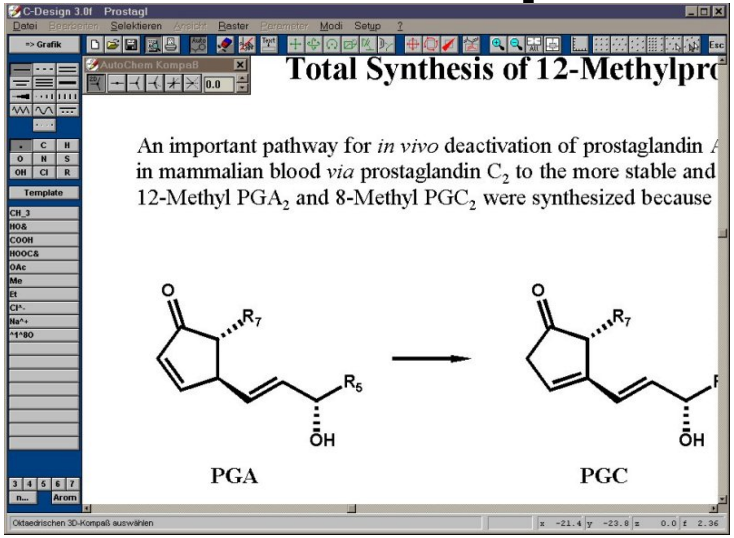
Commerically available at various price ranges

Other useful software to make nice pictures

Chemical structures
and other objects:

C-Design 3.0f

Windows-Platform

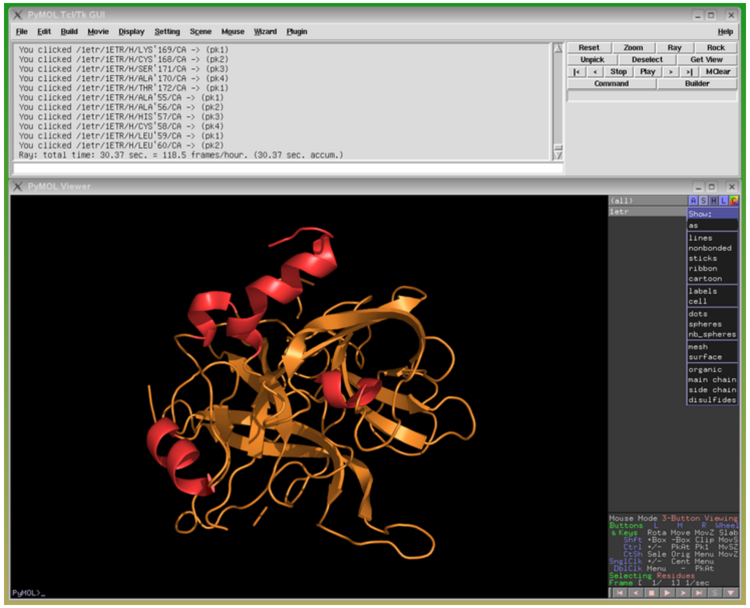


Protein structures:

PyMOL www.pymol.org

Chimera

Linux, Mac OS X, Windows



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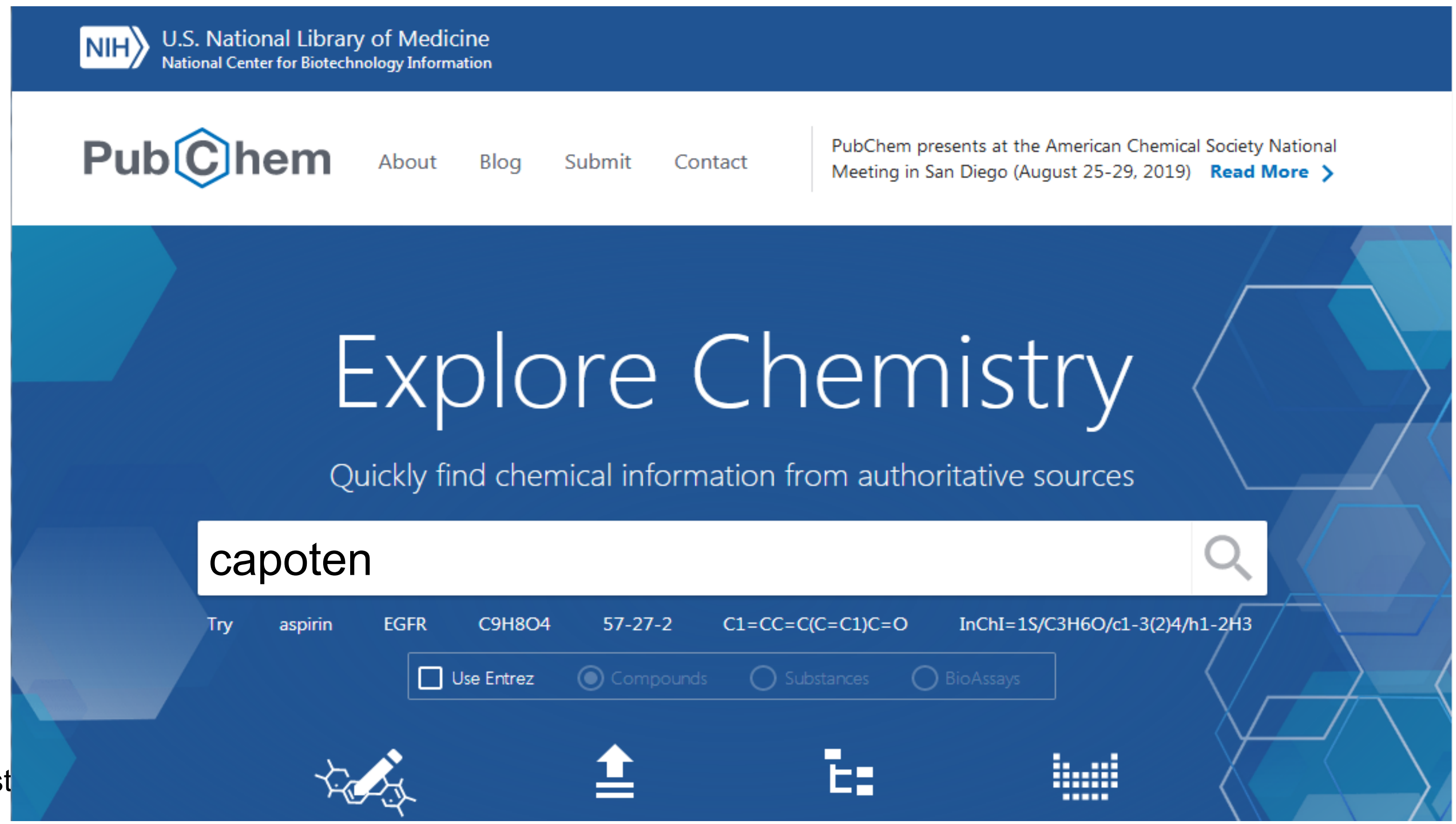
1st assignment (I)

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)

PubChem   About   Blog   Submit   Contact

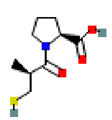
PubChem presents at the American Chemical Society National Meeting in San Diego (August 25-29, 2019) **Read More**

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

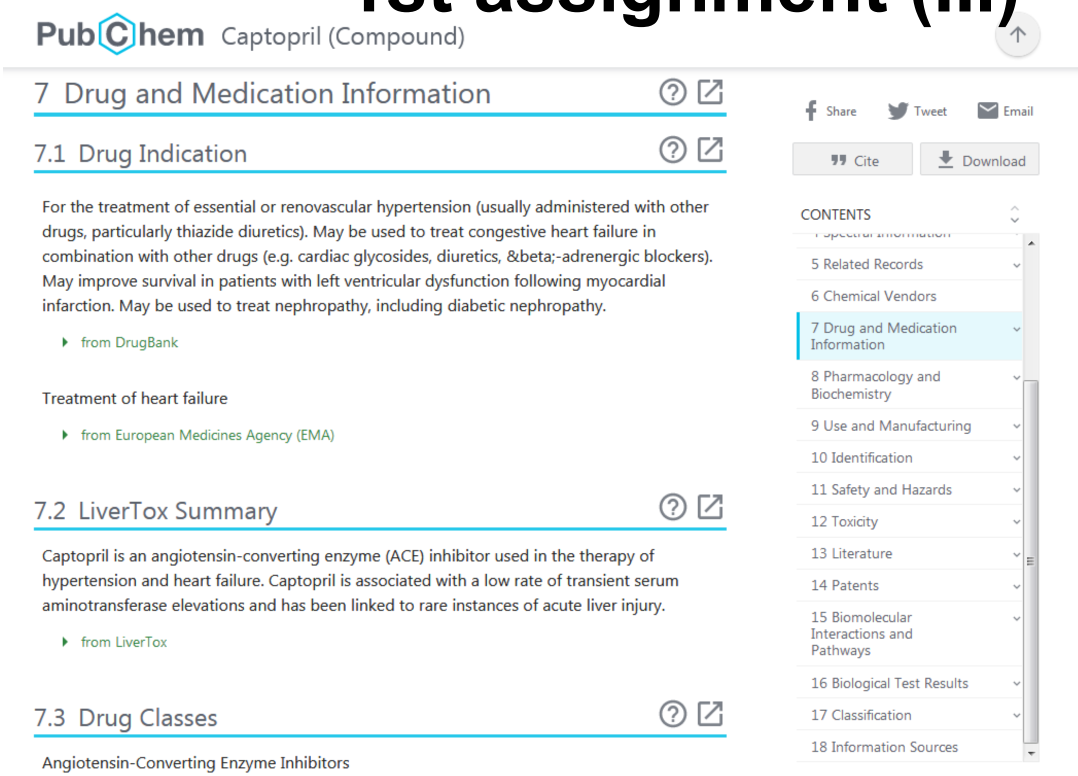
Create Date: 2005-06-24

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)



PubChem Captopril (Compound)

7 Drug and Medication Information

7.1 Drug Indication

For the treatment of essential or renovascular hypertension (usually administered with other drugs, particularly thiazide diuretics). May be used to treat congestive heart failure in combination with other drugs (e.g. cardiac glycosides, diuretics, β-adrenergic blockers). May improve survival in patients with left ventricular dysfunction following myocardial infarction. May be used to treat nephropathy, including diabetic nephropathy.

- from DrugBank

Treatment of heart failure

- from European Medicines Agency (EMA)

7.2 LiverTox Summary

Captopril is an angiotensin-converting enzyme (ACE) inhibitor used in the therapy of hypertension and heart failure. Captopril is associated with a low rate of transient serum aminotransferase elevations and has been linked to rare instances of acute liver injury.

- from LiverTox

7.3 Drug Classes

Angiotensin-Converting Enzyme Inhibitors

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Cite Download

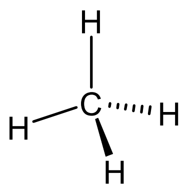
CONTENTS

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

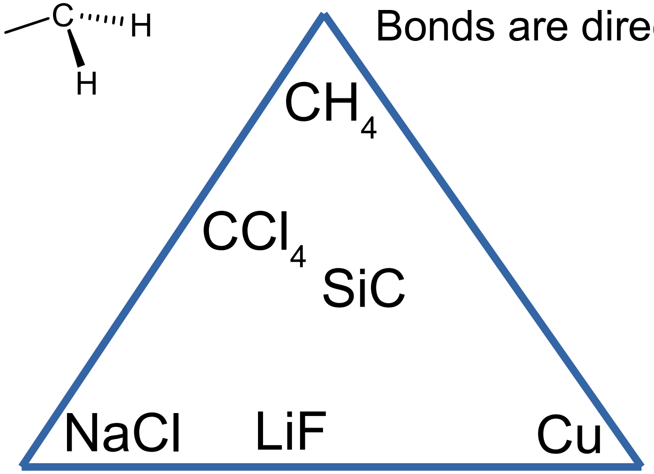
Recapitulation: The Chemical Bond

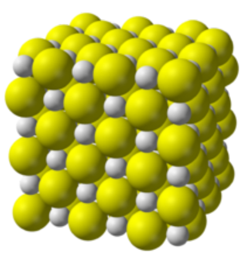
Entirely covalent, ionic, or metallic bonds between atoms are the extrem cases. More often the actual kind of bonding is somewhere in between and is subject to the difference in electronegativity of the atoms/elements involved.
→ Uneven distribution of electrons between the atoms



covalent

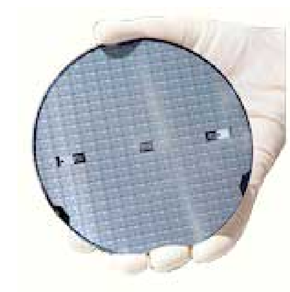
Bonds are directional





ionic

Crystal lattice

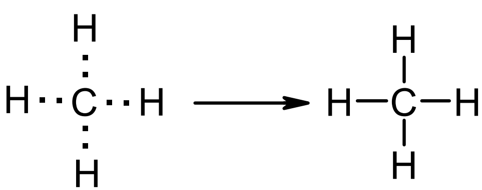


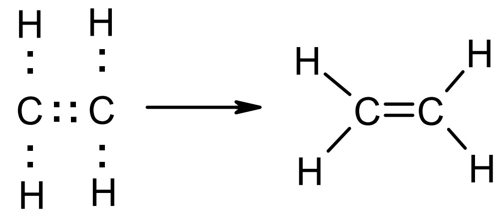
metallic

Delocalization of valence electrons

Representation of chemical structures (I)

The valence electrons of the atoms are pairwise grouped together

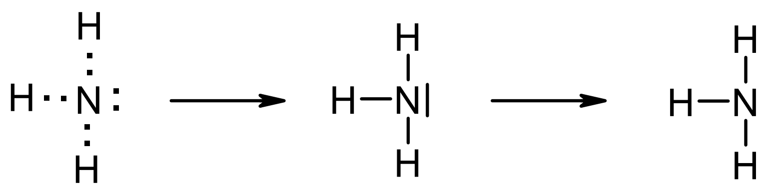




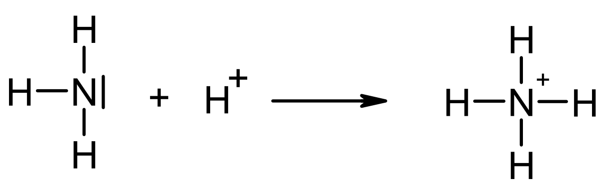
Such Lewis structures reflect covalent bonds between atoms in a molecule.
Therefore any molecule can be regarded as graph with the atoms being the nodes and the bonds as vertices.

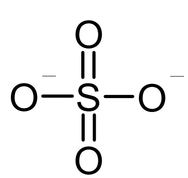
Representation of chemical structures (II)

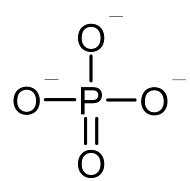
(electron) lone pairs are often not shown for visual clarity



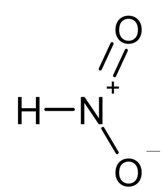
octet rule and hypervalent atoms

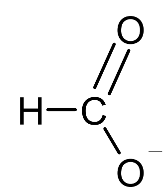






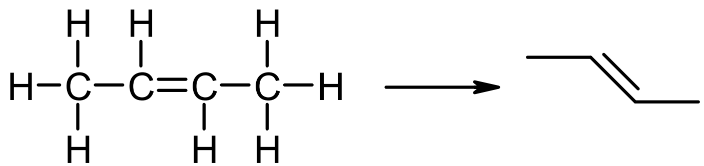
Equal bond lengths!

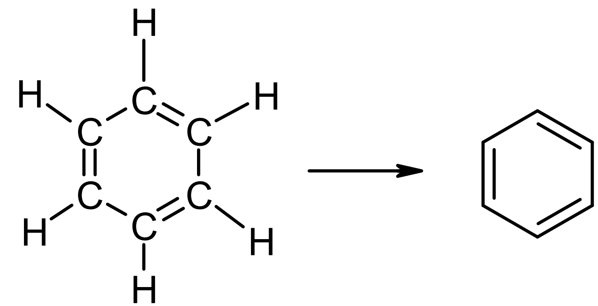


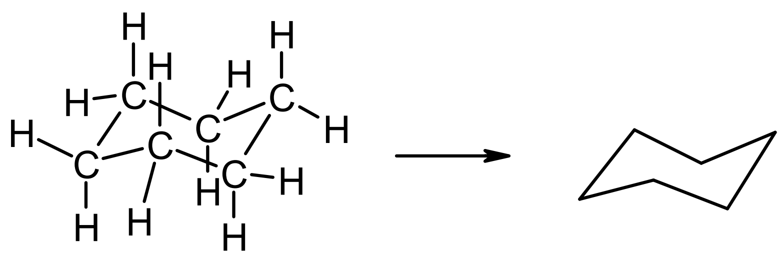


Representation of chemical structures (III)

Also carbon atoms are often omitted



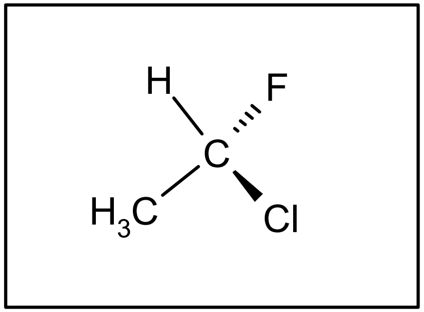




Corners and end of lines denote carbon atoms saturated with the appropriate number of hydrogen atoms

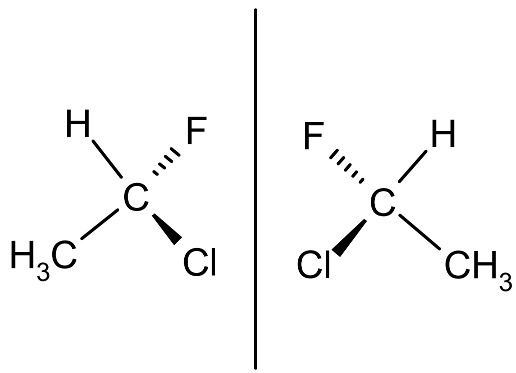
Representation of chemical structures (IV)

Stereochemistry



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

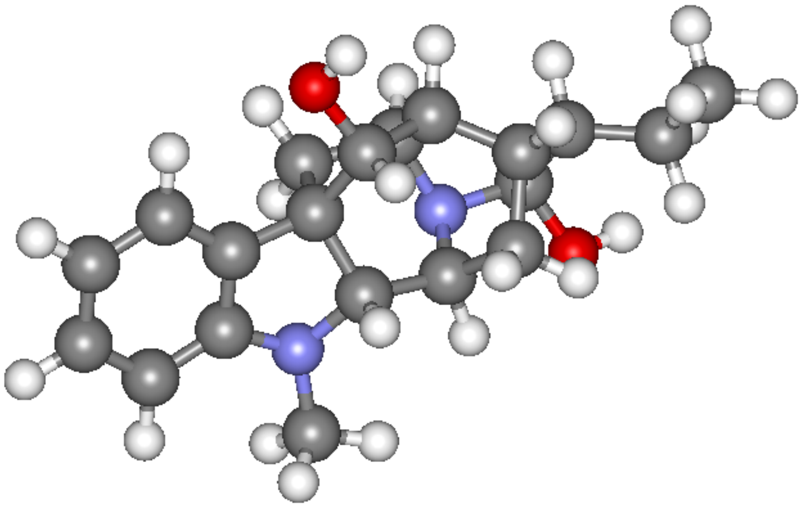
Four different substituents at a carbon atom cause chirality. Similar: silicon, sulfur, phosphorus,...

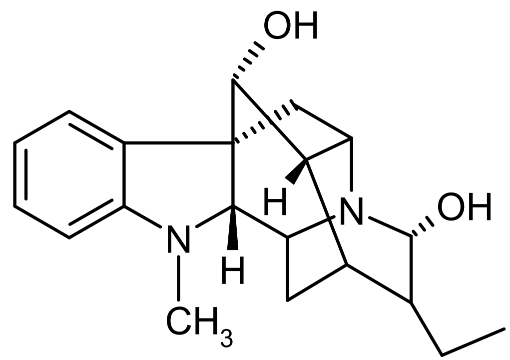


Examples: Most amino acids, sugars, many natural compounds,...

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.

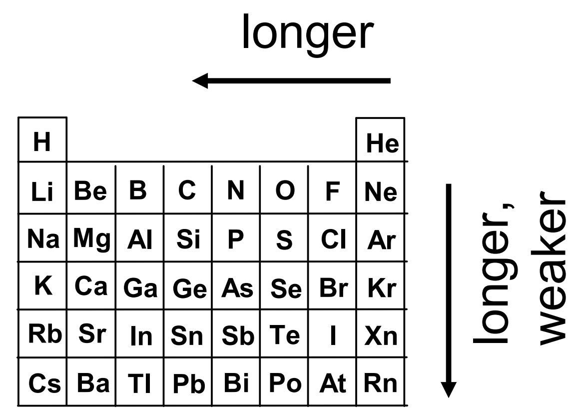




Exercise: Construct this molecule using a molecular model set. Specify the chiral carbon atoms.

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
O–H	0.96	459
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

non-polar hydrogen

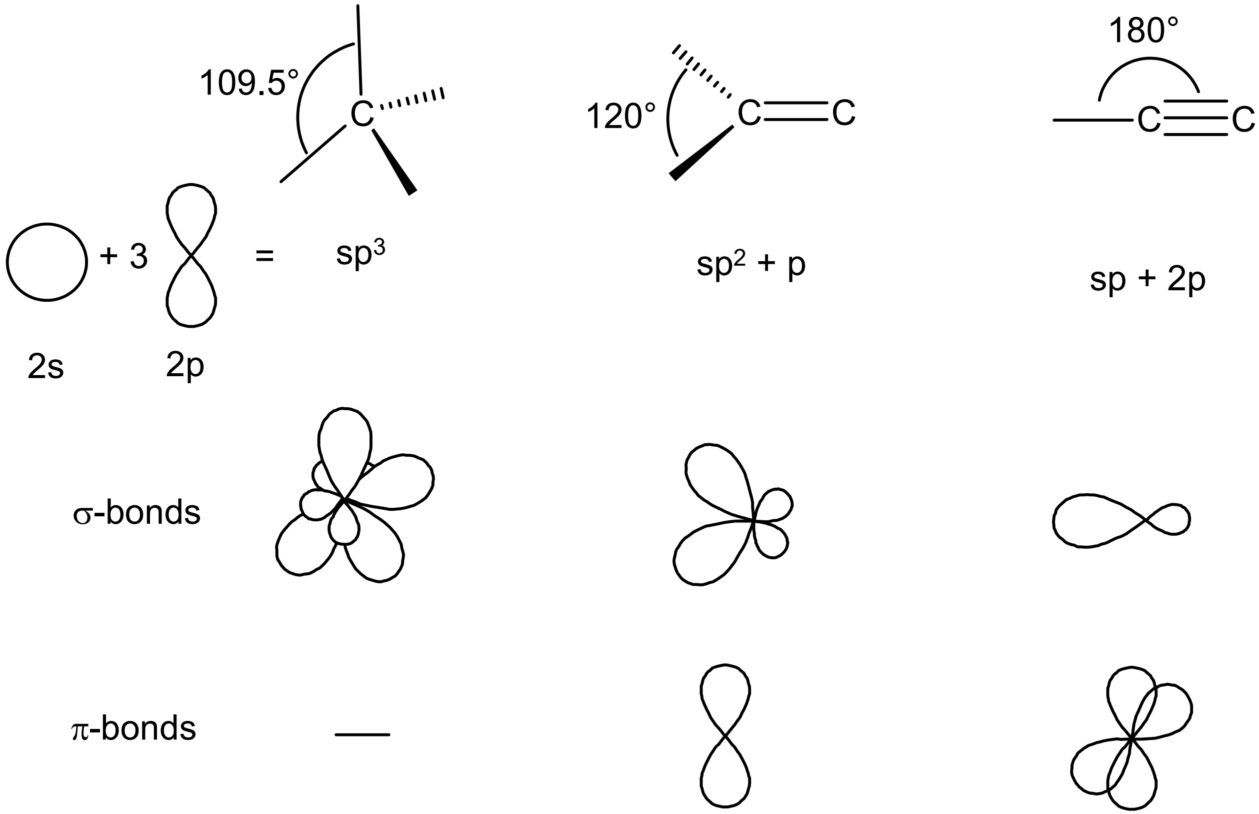
polar hydrogens, exchangable in polar solvents, e.g. water

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



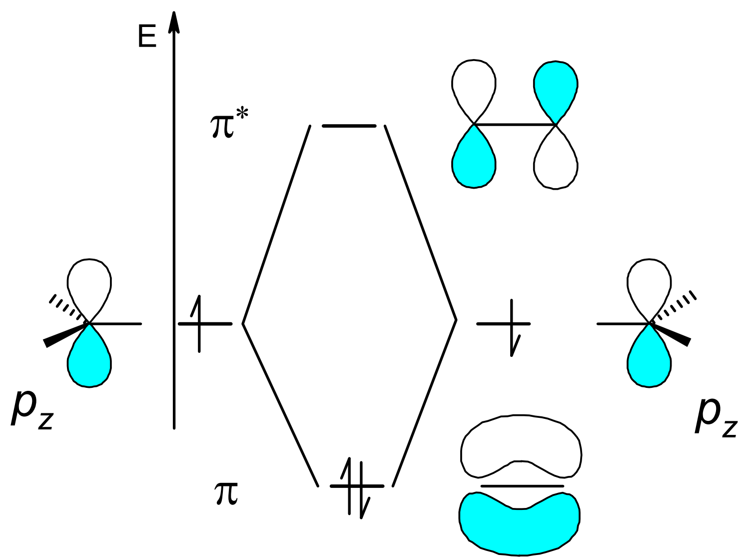
The C–C σ-bond is formed by overlap of the 1s orbitals

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 $H_2C{=}CH_2$

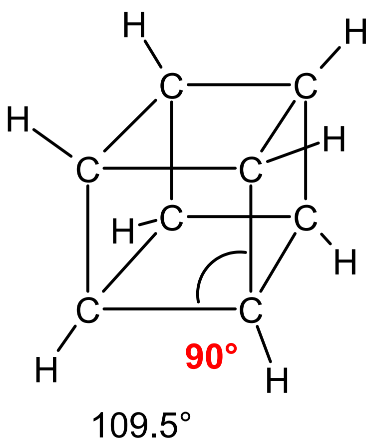


The two combinations usually result in one bonding and one anti-bonding MO

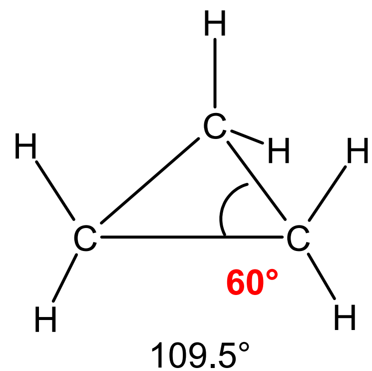
Bond angles (II)

Extreme deviations from ideal bond angles

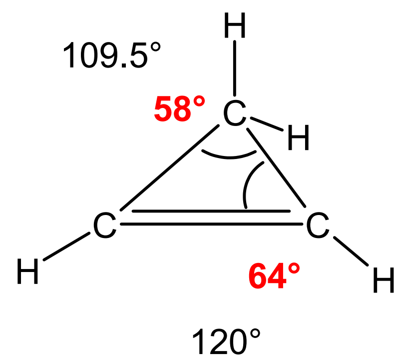
cubane



cyclopropane



cyclopropene

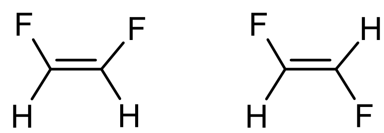


gives rise to strain energy in small rings

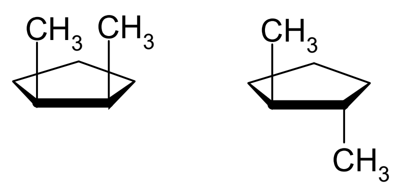
→ problems in force fields. More than one atom type for each hybridization state (e.g. C*sp*^{3}) neccessary.

Stereoisomers

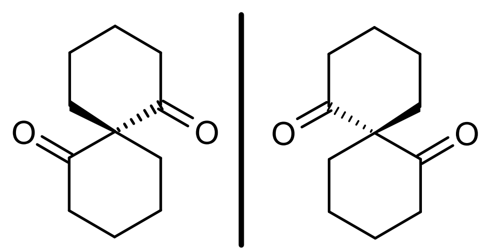
Gives rise to different orientation in 3D-space despite identical 2D-topology



cis/trans form at double bonds



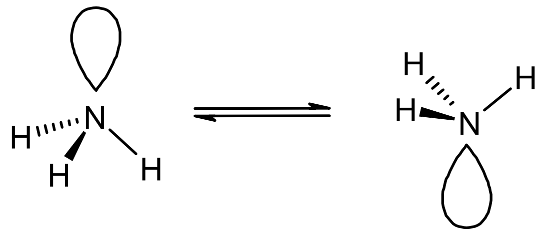
cis-trans isomers in ring systems



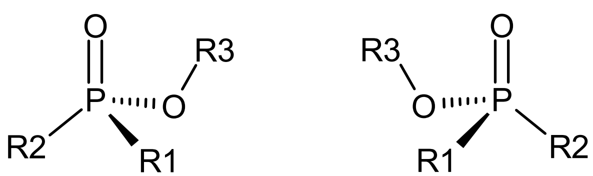
Chiral spiranes

Chiral atoms

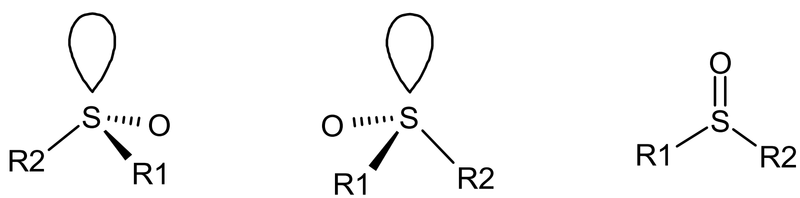
Further elements showing chirality/stereochemistry
(the lone electron pair behaves like a substituent)



Fast exchange at room temperature, but slow at 77K



phosphorus inverts even slower

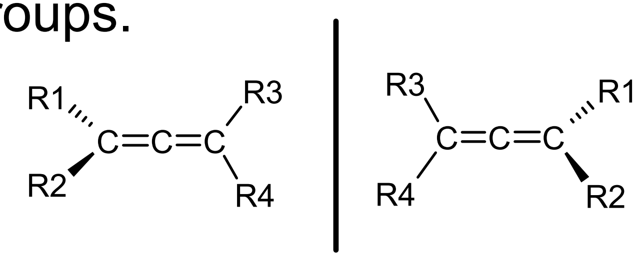


sulfoxides, sulfinic esters, etc
→ Different compounds at room temperature

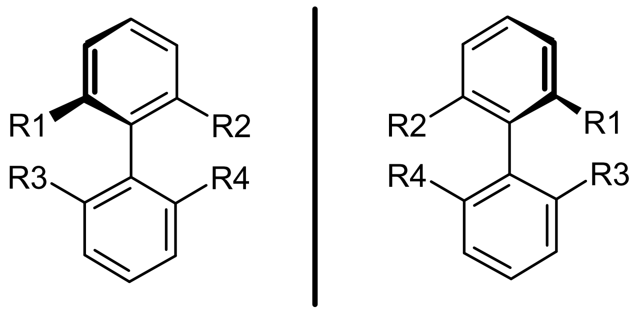
Furthermore: As, Si, ..., compounds with transition elements, esp. octahedral and square planar metal complexes e.g. Pt

Axial Chirality

Even without a chiral center, stereochemistry can occur due to aggregated double bonds or steric hindrance caused by bulky groups.



Axial chirality in allenes

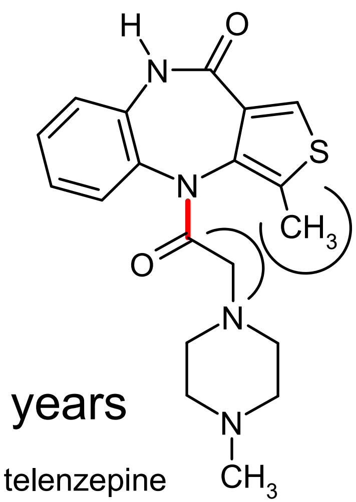


Atropisomers in ortho substituted biaryls.

Recent examples: daraxonrasib, navlimethostat, sosimerasib, zoldonrasib.

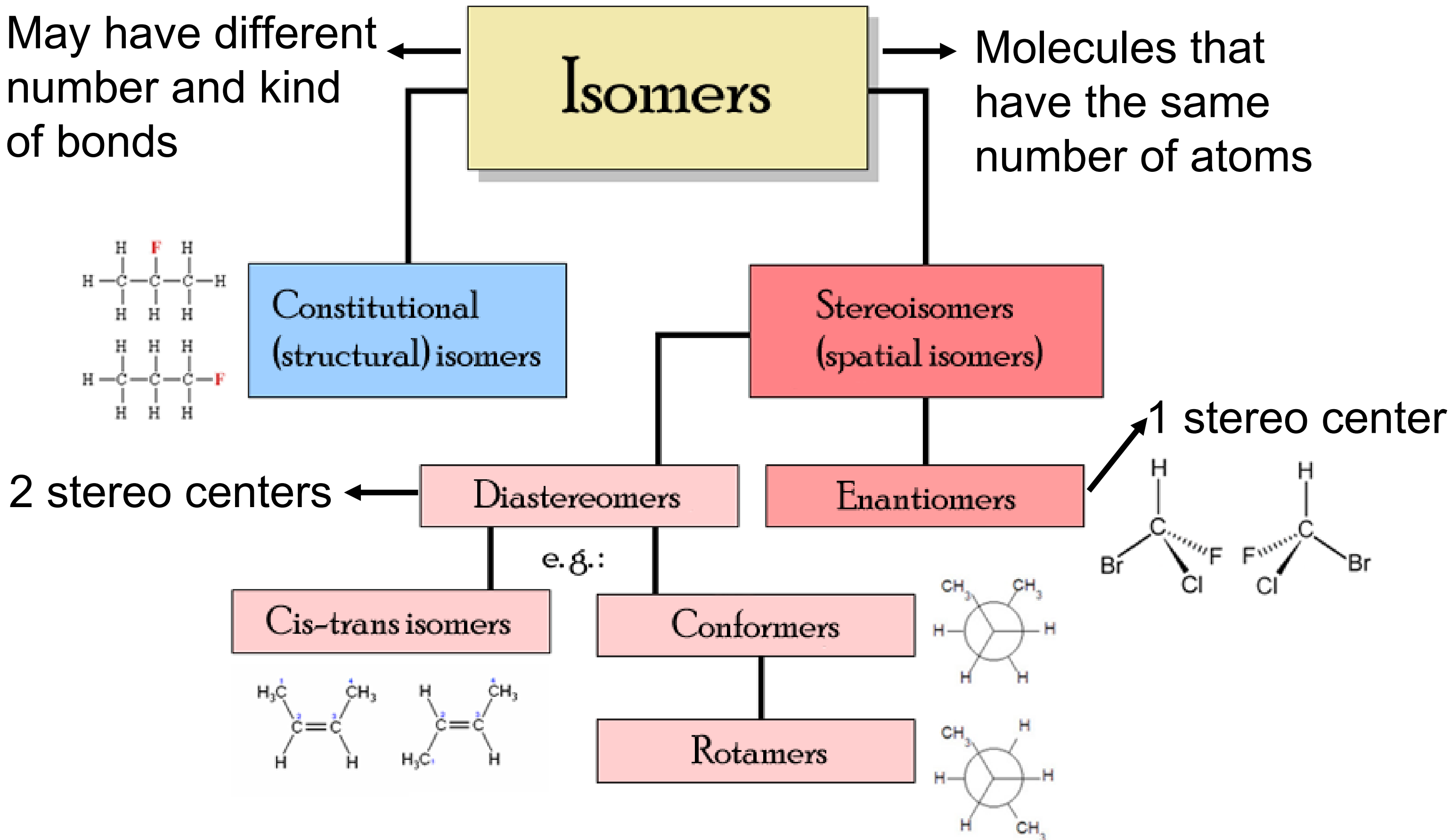
→ correct isomer needed for docking

Half-life of racemization > 1000 years



telenzepine

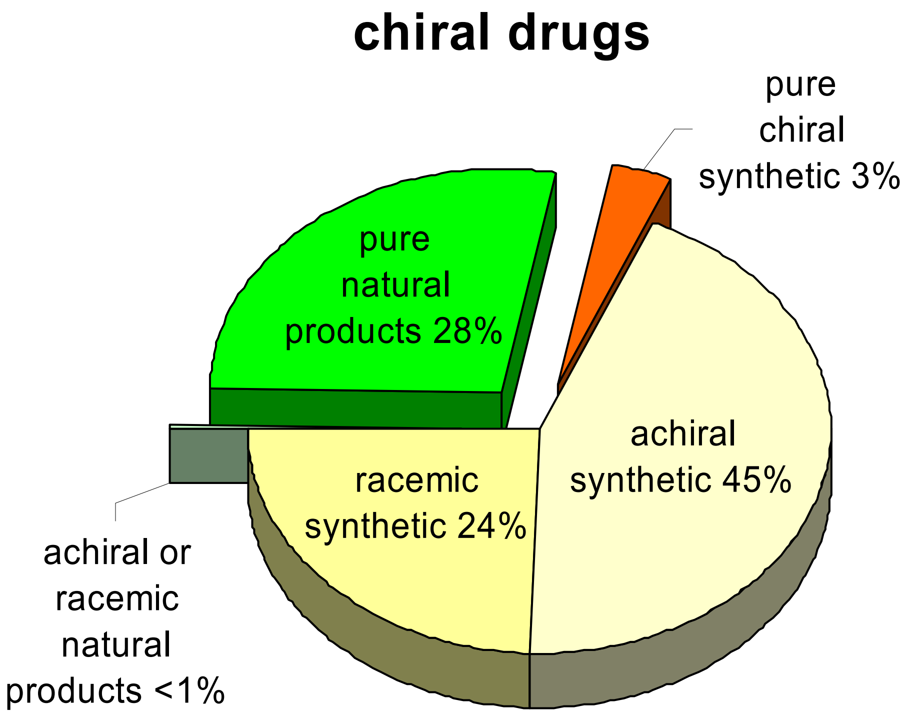
Isomers



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*