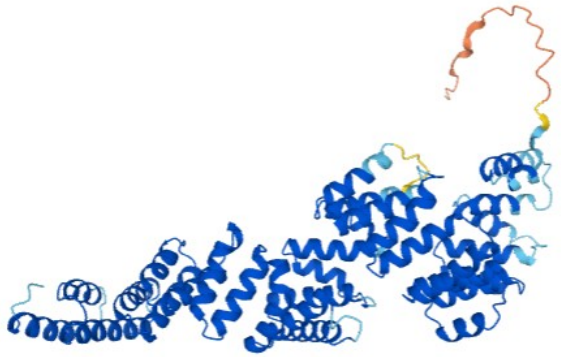
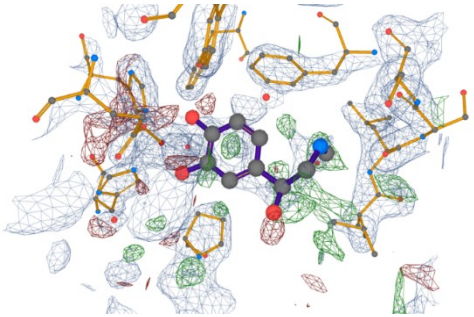
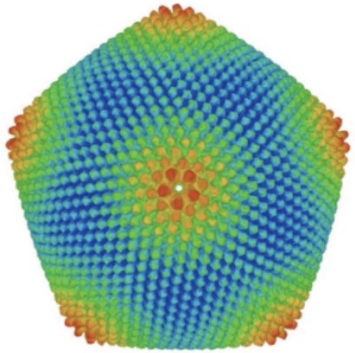
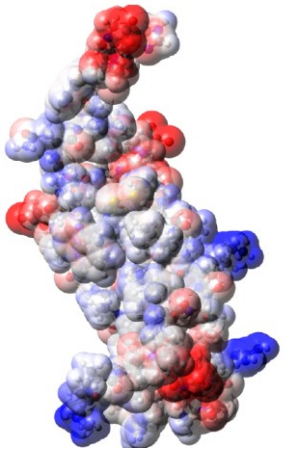
Computer model of a molecule



Radka Svobodová

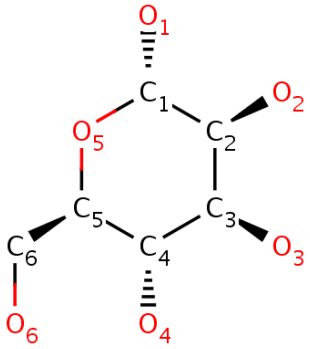


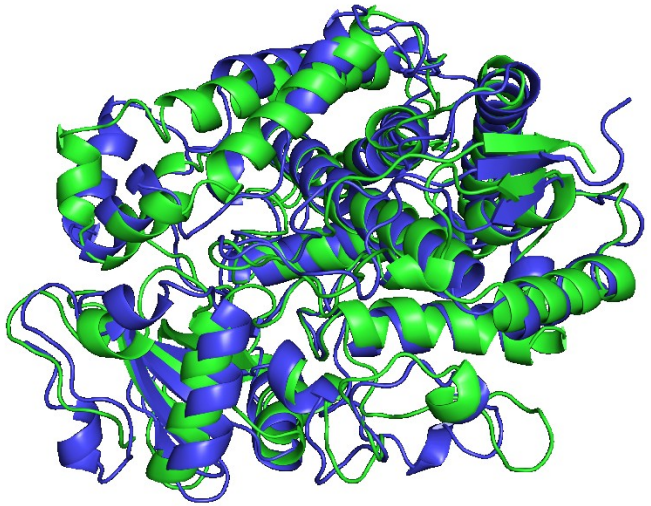




Content

- **Introduction:** concept of chemoinformatics, content of the subject, history of the field
- **Computer model of a molecule:** 1D, 2D and 3D structure, molecule representation using graph and matrix
- **2D structure (topology) of a molecule:**
  - writing a molecule using a string (SMILES, InChi, InChiKey)
  - **Molecular graphs:** Isomorphism and canonical indexing
  - **Cycle search, fingerprints**
- **3D structure (geometry) of the molecule:**
  - representation using Cartesian and internal coordinates, data formats, geometry comparison

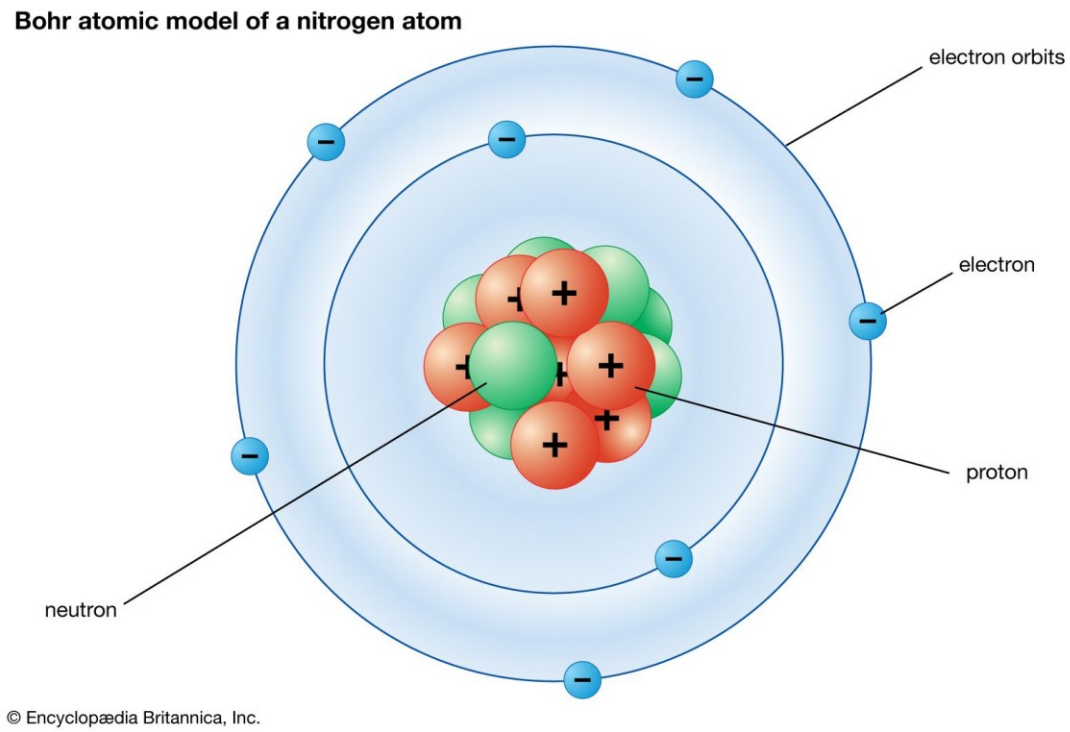




Basic chemical terms I

- Atom: basic building block from which substances are formed

- Structure of an atom:
  - Atom core: protons (positive charge), neutrons (no charge)
  - Electron shell: electrons (negative charge)

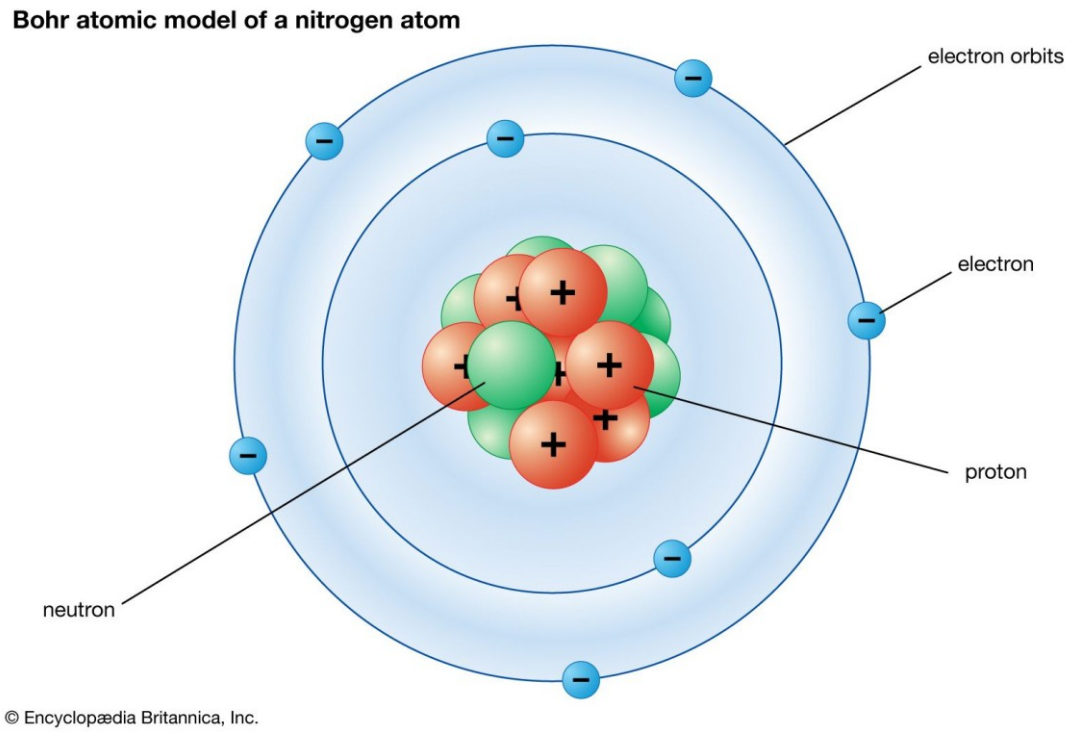


Basic chemical terms II

- All systems tend to occupy the state with the lowest possible total energy.

Basic chemical terms III

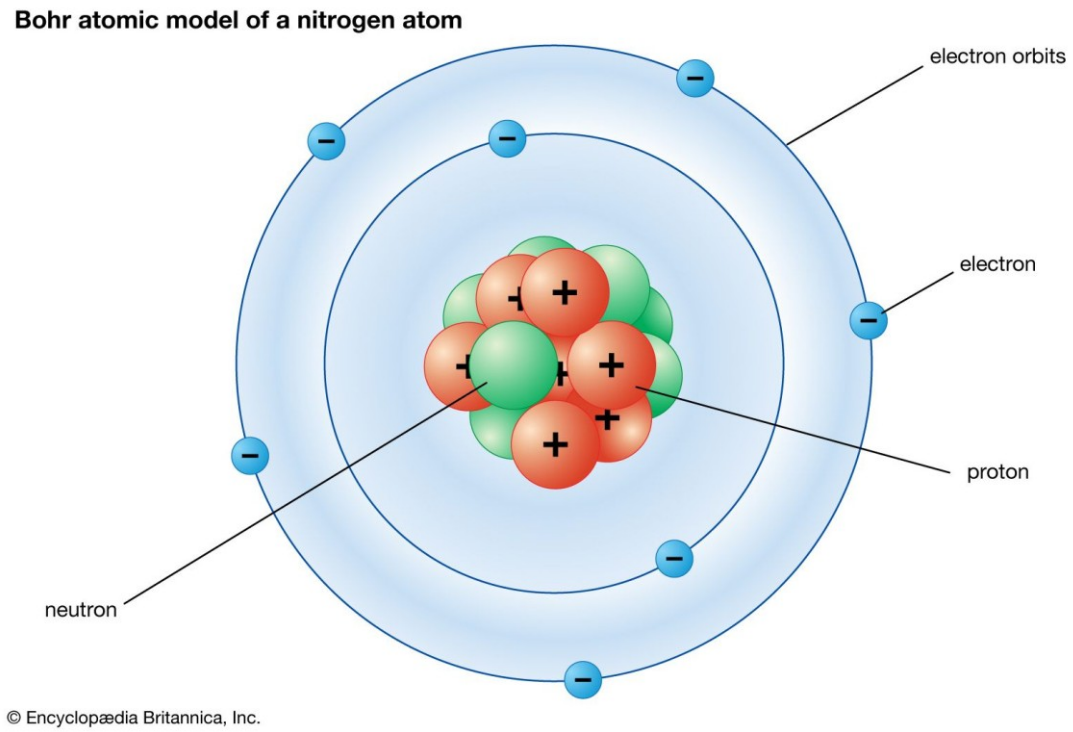
- The space of the electron shell can be divided into so-called **layers**.
- All electrons in a layer have the same energy value (this energy is characteristic of that layer).
- The further the layer is from the nucleus, the higher the energy of the electrons in it.
- The electrons in the electron shell therefore fill first the layer closest to the nucleus (the most energetically favorable), then the second closest, and so on.



Basic chemical terms IV

- The non-empty layer that is farthest from the core is called the **valence layer**.
- In this layer are the so-called **valence electrons**.

These **valence electrons** are the subject of the study of chemistry because they can participate in chemical bonding.



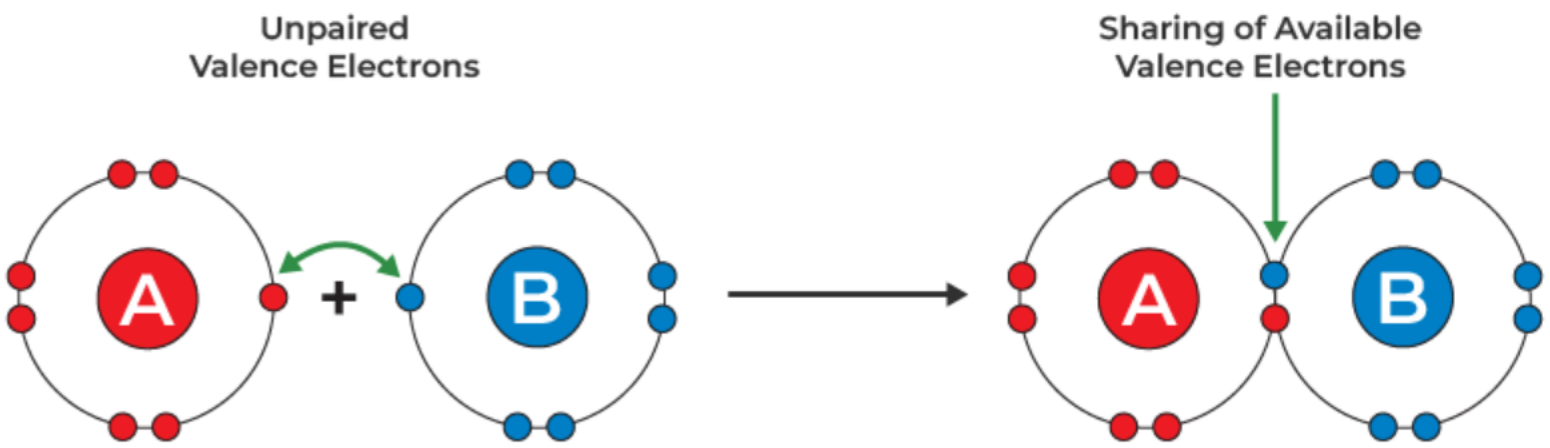
Basic chemical terms V

Chemical bond:

Two atoms come together at a sufficiently small distance (bonding distance) => overlapping of their electron shells.

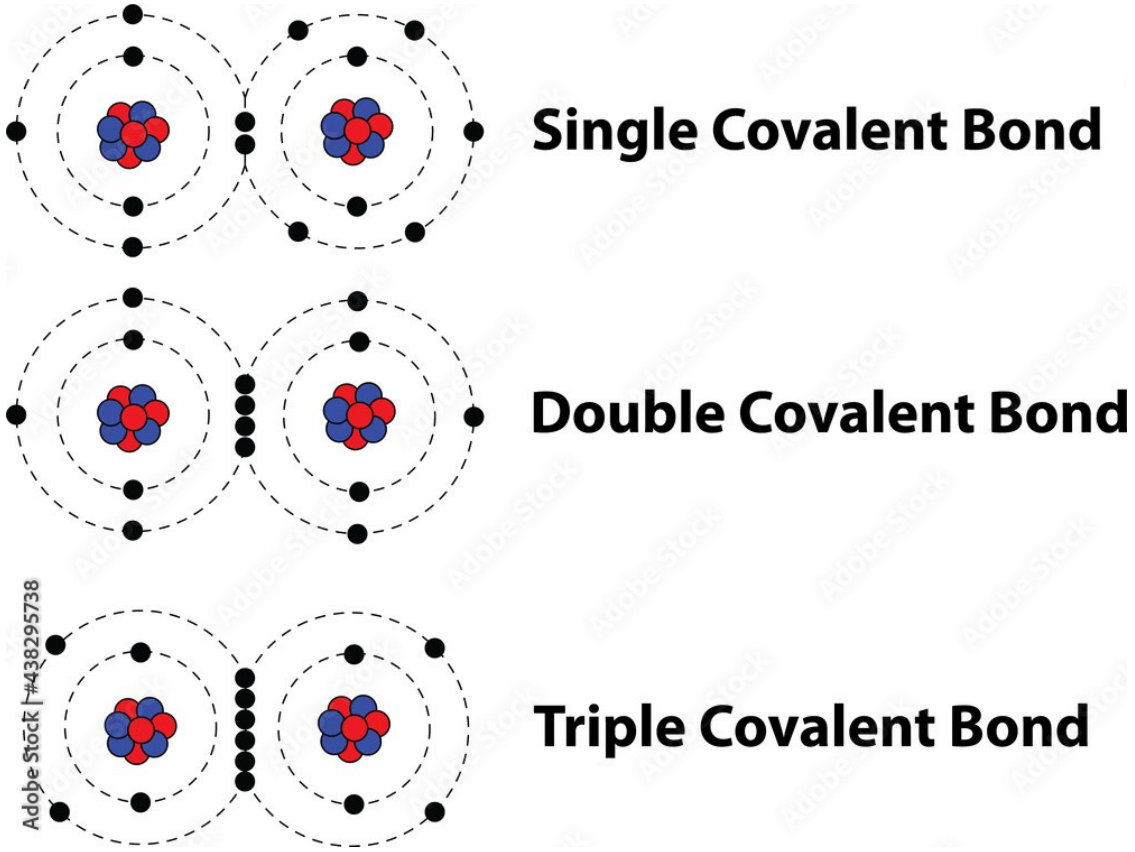
The valence electrons of both atoms change their trajectories.

If the resulting system has a lower energy than the original, the atoms remain at bonding distance => chemical bonding is formed.



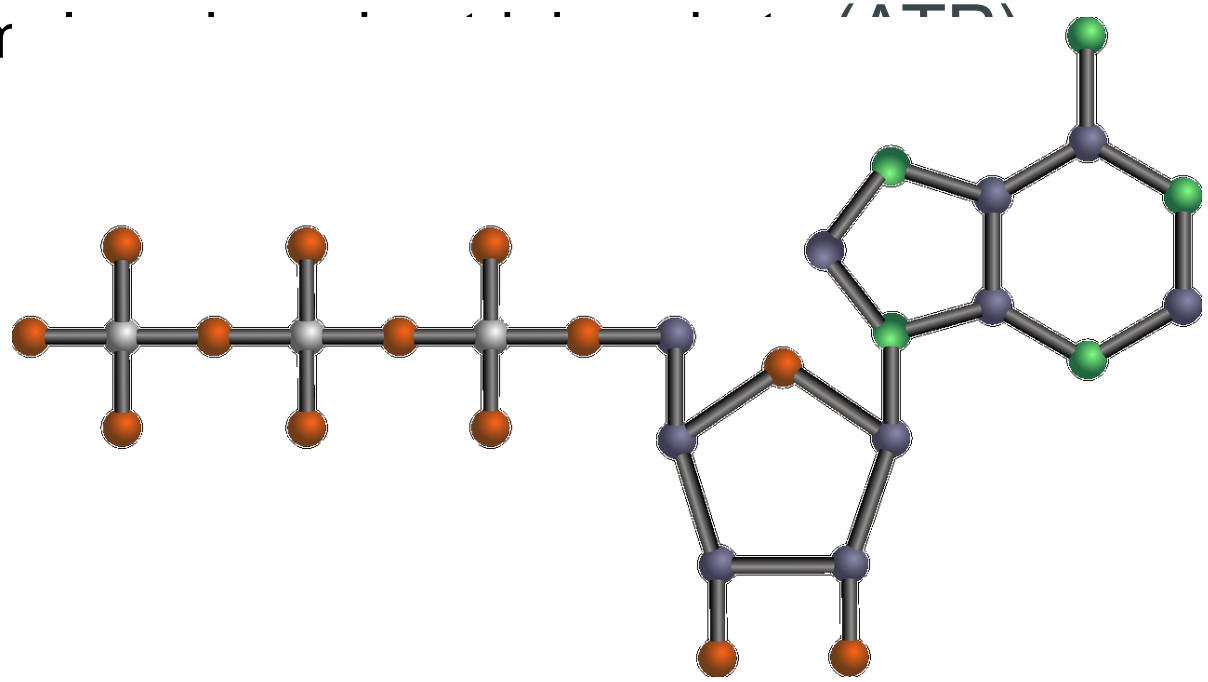
Basic chemical terms VI

- Bond order:
  - single bond: two valence electrons are involved (binding electron pair)
  - double bond: two bonding electron pairs are involved
  - Triple bond: analogous
  - higher multiplicities do not occur in real chemical environments
  - Aromatic bond: when single and double bonds alternate, the electrons are delocalised among them. These bonds have properties between single and double bonds.



Basic chemical terms VII

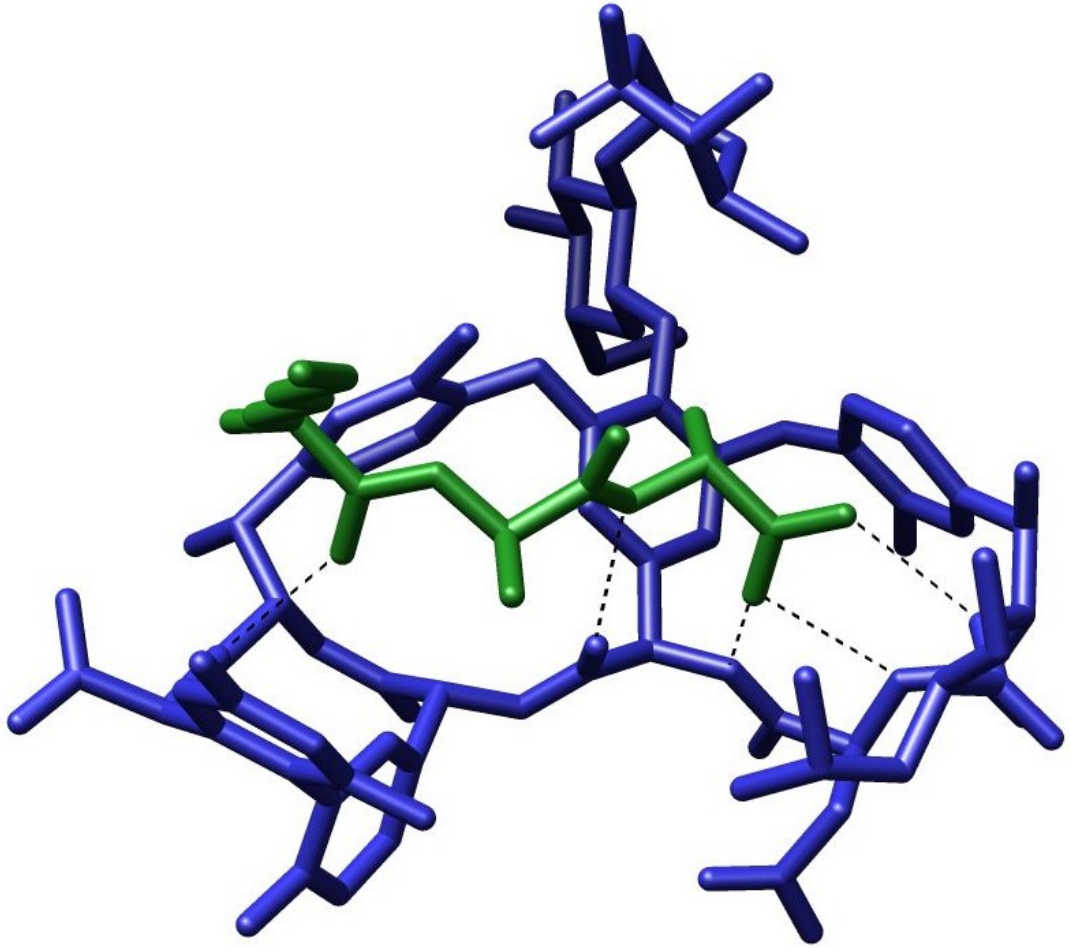
- Molecule: A system of atoms joined together by bonds to form a single unit. The basic structural unit of a substance. The carrier of the chemical properties of a substance.
- Exam



Basic chemical terms VIII

- Molecular system: A system containing one or more molecules.

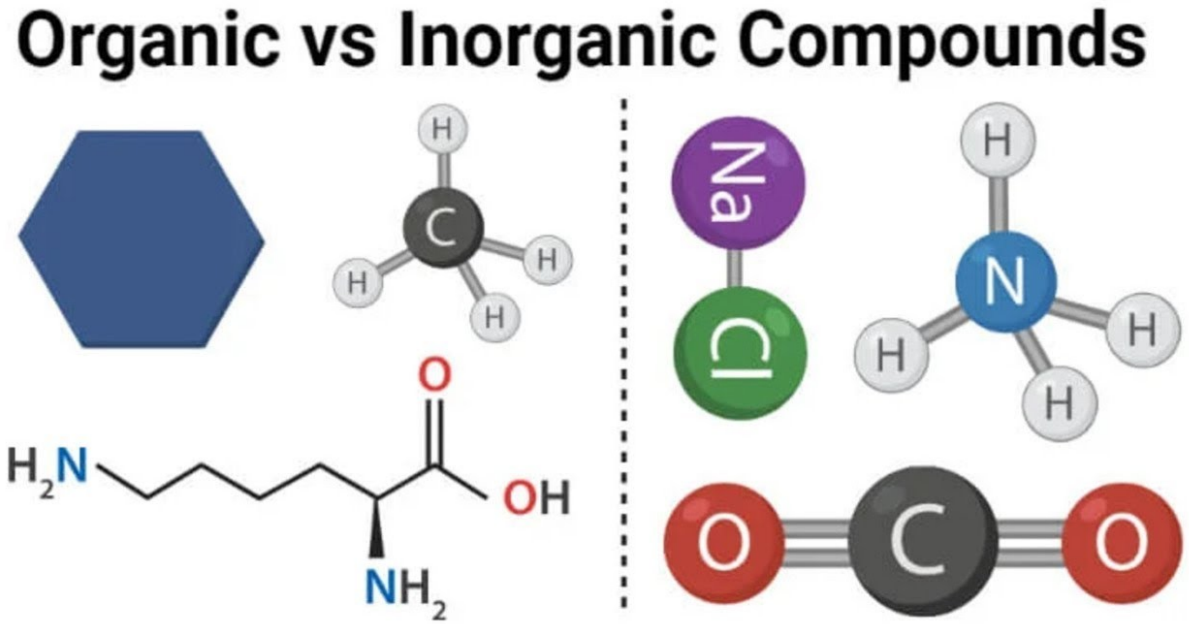
Example:



Basic chemical terms IX

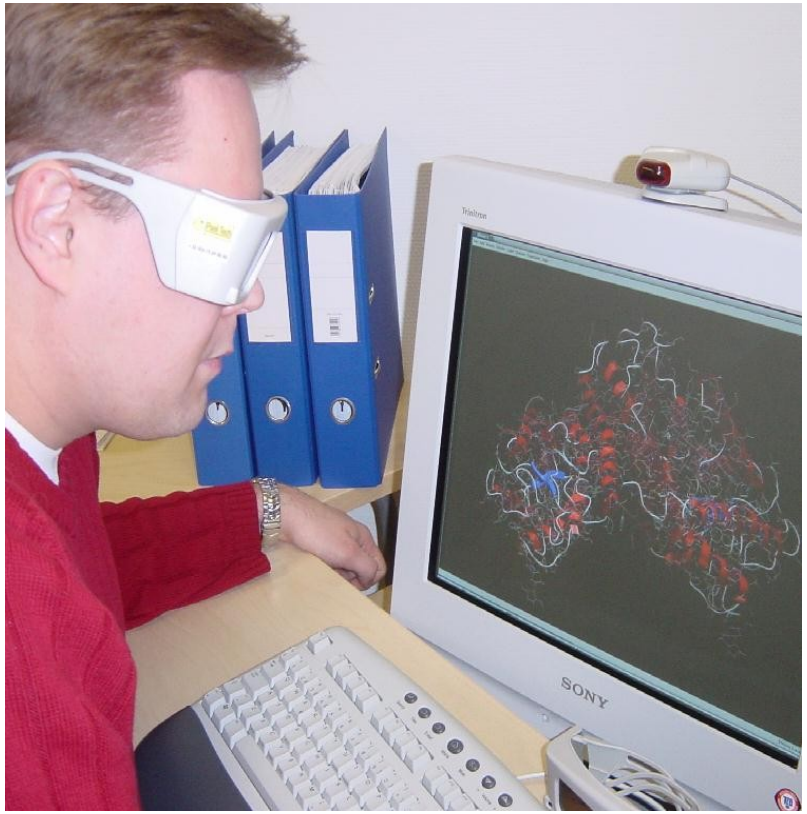
- Organic molecules:
  - Their main component is carbon, the only element that is able to form longer chains of the (-C-)n type, n > 10.
  - This property of carbon allows the formation of complex molecules - the building blocks of living systems.
  - Organic molecules also contain elements: H, O, S, N, F, Cl, Br, I

- Inorganic molecules:
  - All molecules, that are not organic.



How to describe a molecule in a computer?

- **Find out which information describes the molecule**
- **Write them into the computer**



Which information describes the molecule?

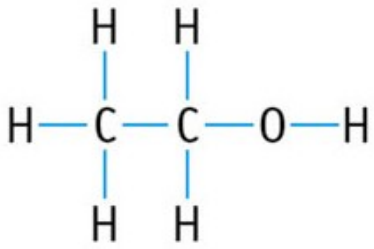
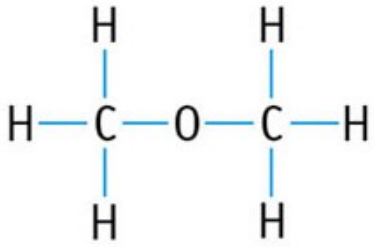
Number of atoms?

Ethanol	C_2H_6O
Dimethyl ether	C_2H_6O

Which information describes the molecule?

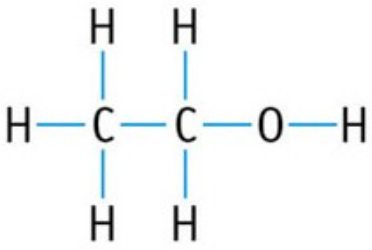
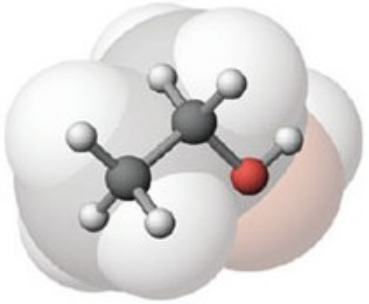
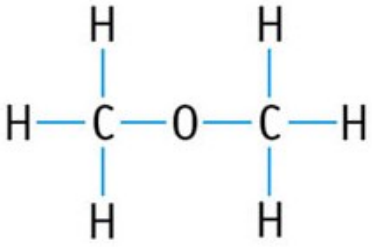
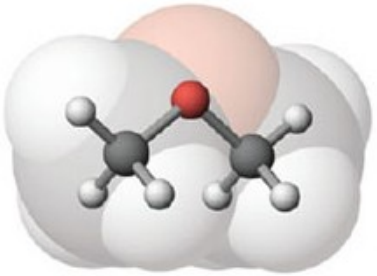
Number of atoms? **Not enough**

Number of atoms and positions of bonds?

Ethanol	C_2H_6O	CH_3CH_2OH	
Dimethyl ether	C_2H_6O	CH_3OCH_3	

Which information describes the molecule?

Number of atoms?	**Not enough**
Number of atoms and positions of bonds?	**Better**
Number of atoms, positions of bonds and positions of atoms in 3D space?	**Yes**

Ethanol	C_2H_6O	CH_3CH_2OH		
Dimethyl ether	C_2H_6O	CH_3OCH_3		

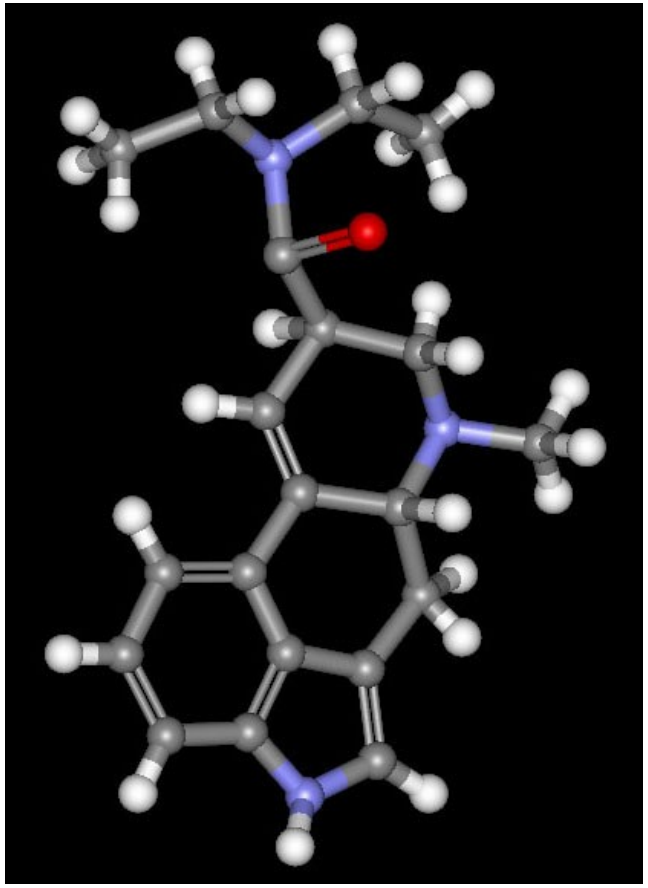
Model of molecule for computer processing

Atoms:

- Points in space
- Chemical symbol of the element listed for each

Bonds:

- Pairs of atoms that are bonded
- Bond order



Description of a molecule in a computer

number of atoms

number of bonds

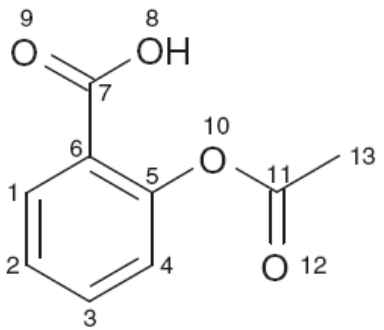
the first atom is a carbon

```
-ISIS-  09270222202D

13 13  0  0  0  0  0  0  0  0999 V2000
  -3.4639   -1.5375    0.0000 C  0  0  0  0  0  0  0  0  0  0  0  0
  -3.4651   -2.3648    0.0000 C  0  0  0  0  0  0  0  0  0  0  0  0
  -2.7503   -2.7777    0.0000 C  0  0  0  0  0  0  0  0  0  0  0  0
  -2.0338   -2.3644    0.0000 C  0  0  0  0  0  0  0  0  0  0  0  0
  -2.0367   -1.5338    0.0000 C  0  0  0  0  0  0  0  0  0  0  0  0
  -2.7521   -1.1247    0.0000 C  0  0  0  0  0  0  0  0  0  0  0  0
  -2.7545   -0.2997    0.0000 C  0  0  0  0  0  0  0  0  0  0  0  0
  -2.0413    0.1149    0.0000 O  0  0  0  0  0  0  0  0  0  0  0  0
  -3.4702    0.1107    0.0000 O  0  0  0  0  0  0  0  0  0  0  0  0
  -1.3238   -1.1186    0.0000 O  0  0  0  0  0  0  0  0  0  0  0  0
  -0.6125   -1.5292    0.0000 C  0  0  0  0  0  0  0  0  0  0  0  0
  -0.6167   -2.3542    0.0000 O  0  0  0  0  0  0  0  0  0  0  0  0
   0.1000   -1.1125    0.0000 C  0  0  0  0  0  0  0  0  0  0  0  0
 1  2  2  0  0  0  0
 6  7  1  0  0  0  0
 3  4  2  0  0  0  0
 7  8  1  0  0  0  0
 7  9  2  0  0  0  0
 4  5  1  0  0  0  0
 5 10  1  0  0  0  0
 2  3  1  0  0  0  0
10 11  1  0  0  0  0
 5  6  2  0  0  0  0
11 12  2  0  0  0  0
 6  1  1  0  0  0  0
11 13  1  0  0  0  0
M END
```

the first three numbers are the *x*, *y* and *z* coordinates of the atom

the first bond is between atoms 1 and 2 and has order 2



```
 ACD/Labs08061122363D

 21 21  0  0  0  0  0  0  0  0  1 V2000
   18.7769  -15.2504   -0.1032 C   0  0  0  0  0  0  0  0  0  0  0  0
   18.7571  -16.6359   -0.1252 C   0  0  0  0  0  0  0  0  0  0  0  0
   17.5868  -14.5409   -0.1114 C   0  0  0  0  0  0  0  0  0  0  0  0
   17.5465  -17.3106   -0.1545 C   0  0  0  0  0  0  0  0  0  0  0  0
   16.3767  -15.2158   -0.1421 C   0  0  0  0  0  0  0  0  0  0  0  0
   16.3559  -16.6013   -0.1633 C   0  0  0  0  0  0  0  0  0  0  0  0
   17.6081  -13.0313   -0.0880 C   0  0  0  0  0  0  0  0  0  0  0  0
   20.0592  -14.5322   -0.0715 N   0  0  0  0  0  0  0  0  0  0  0  0
   17.5247  -18.7799   -0.1764 N   0  0  0  0  0  0  0  0  0  0  0  0
   15.1150  -14.4620   -0.1527 N   0  0  0  0  0  0  0  0  0  0  0  0
   20.0742  -13.3140   -0.0089 O   0  0  0  0  0  0  0  0  0  0  0  0
   21.1073  -15.1564   -0.0523 O   0  0  0  0  0  0  0  0  0  0  0  0
   16.4750  -19.3759    0.0000 O   0  0  0  0  0  0  0  0  0  0  0  0
   18.5697  -19.4030   -0.2650 O   0  0  0  0  0  0  0  0  0  0  0  0
   14.0496  -15.0560   -0.1515 O   0  0  0  0  0  0  0  0  0  0  0  0
   15.1330  -13.2425   -0.1568 O   0  0  0  0  0  0  0  0  0  0  0  0
   19.7111  -17.2054   -0.1194 H   0  0  0  0  0  0  0  0  0  0  0  0
   15.3860  -17.1427   -0.1873 H   0  0  0  0  0  0  0  0  0  0  0  0
   17.6136  -12.6451   -1.1298 H   0  0  0  0  0  0  0  0  0  0  0  0
   16.7057  -12.6567    0.4410 H   0  0  0  0  0  0  0  0  0  0  0  0
   18.5209  -12.6823    0.4410 H   0  0  0  0  0  0  0  0  0  0  0  0
  2  1  1  0  0  0  0
  3  1  2  0  0  0  0
  4  2  2  0  0  0  0
  5  3  1  0  0  0  0
  6  4  1  0  0  0  0
  6  5  2  0  0  0  0
  3  7  1  0  0  0  0
  1  8  1  0  0  0  0
  4  9  1  0  0  0  0
  5 10  1  0  0  0  0
  8 11  2  0  0  0  0
  8 12  2  0  0  0  0
  9 13  2  0  0  0  0
  9 14  2  0  0  0  0
 10 15  2  0  0  0  0
 10 16  2  0  0  0  0
 17  2  1  0  0  0  0
 18  6  1  0  0  0  0
 19  7  1  0  0  0  0
 20  7  1  0  0  0  0
 21  7  1  0  0  0  0
M  END
```

Challenge:

Draw this molecule. What is the name of the molecule?

Databases of small organic molecules

> 1 M structures of small molecules

- Small molecule: < 100 atoms
- Small molecules = “drug-like” molecules
- Experimental structures
- Predicted (computed) structures

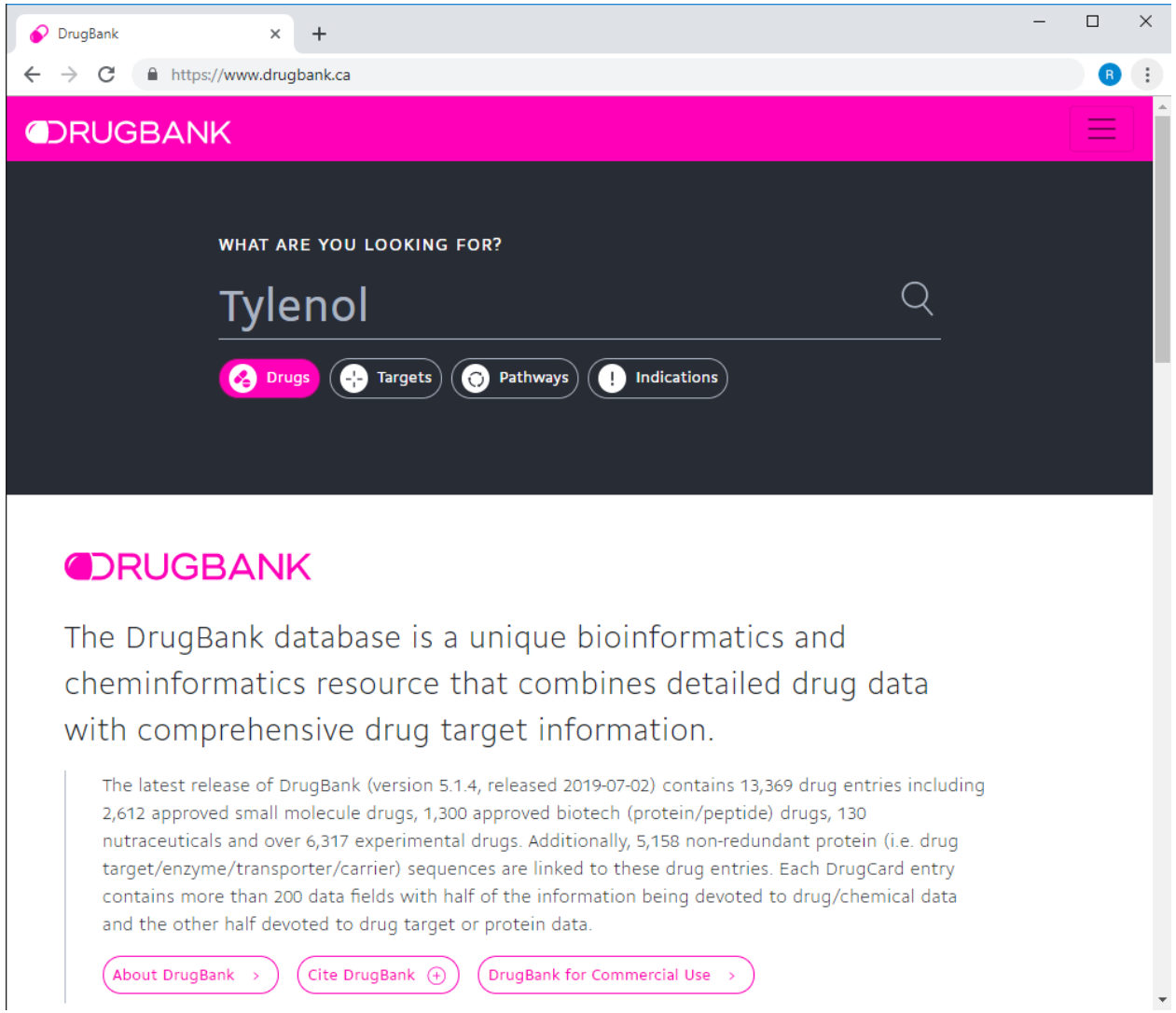
PubChem

ZINC

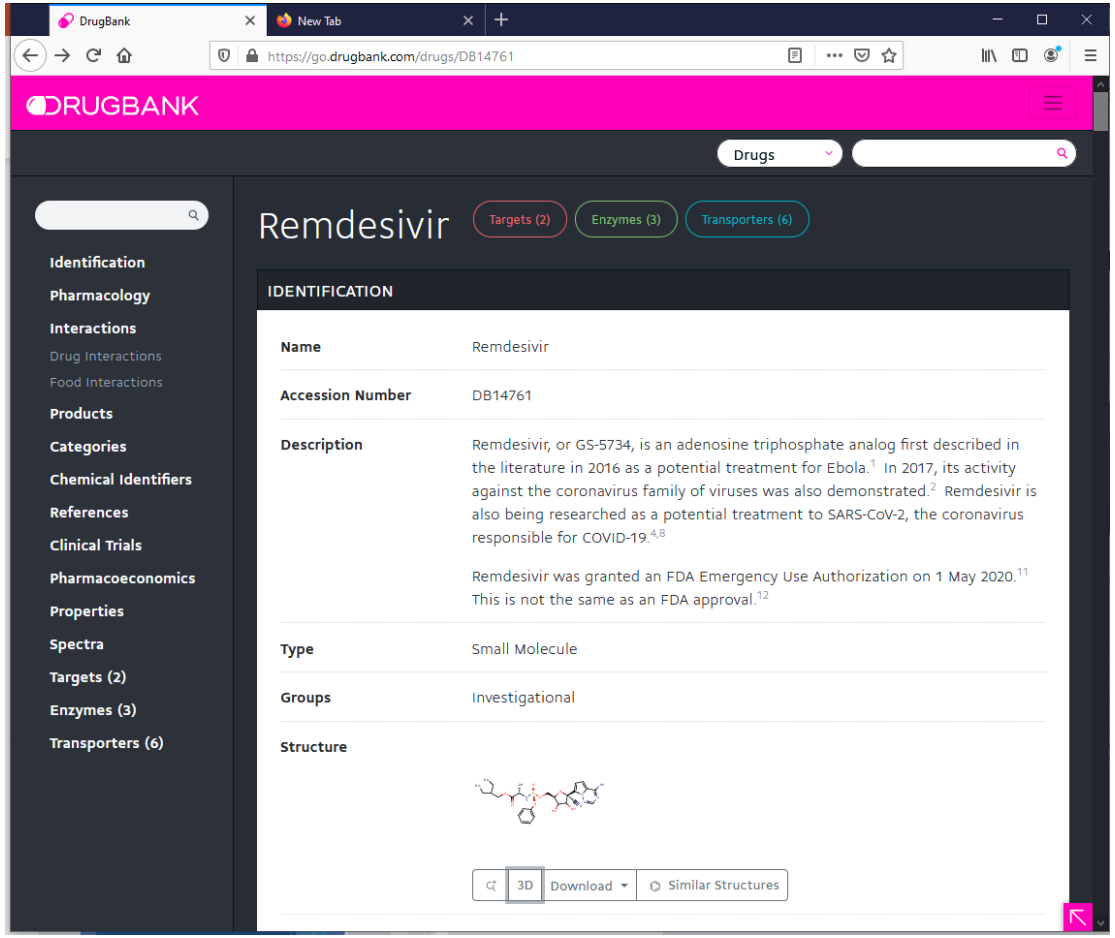
ChEMBL

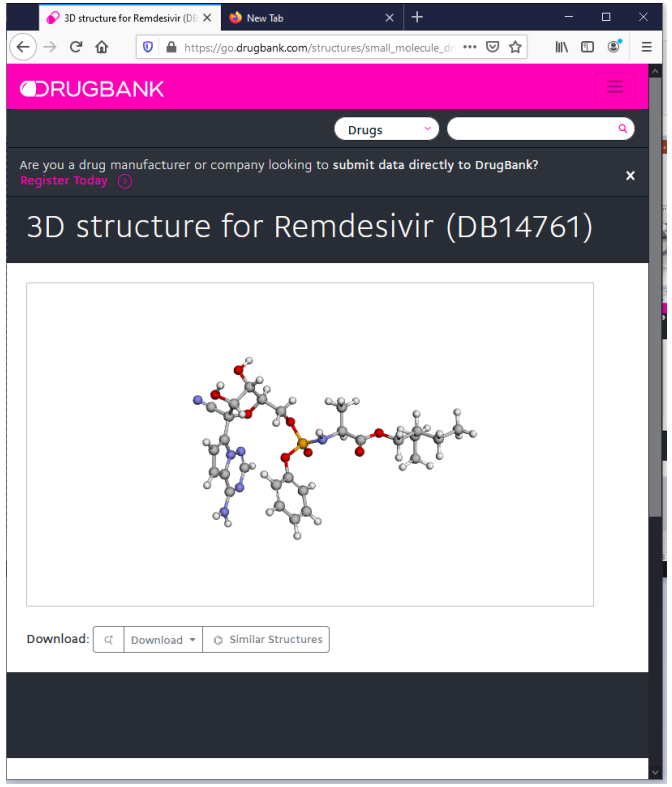
DRUGBANK

DrugBank – database of drugs

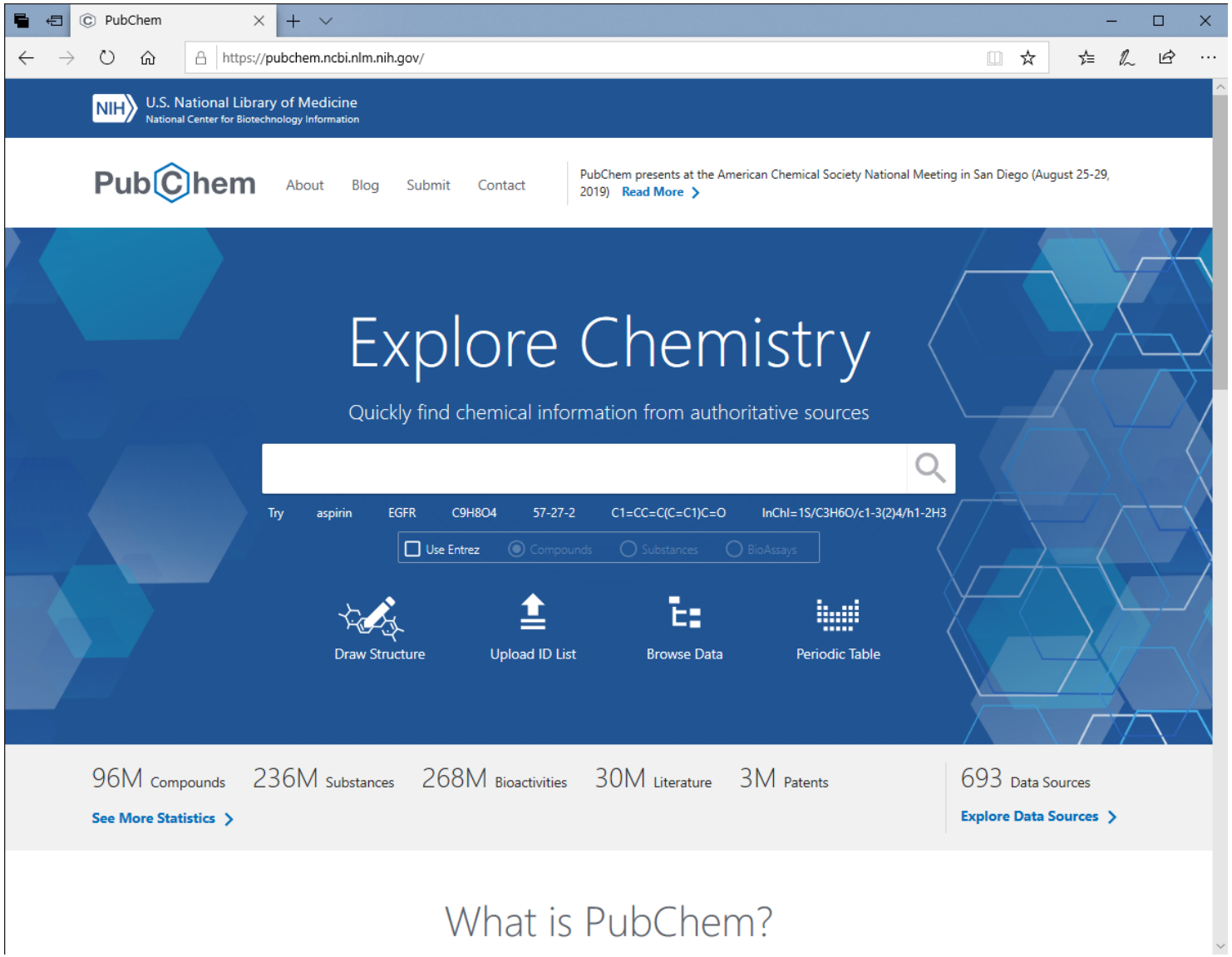


DrugBank – database of drugs

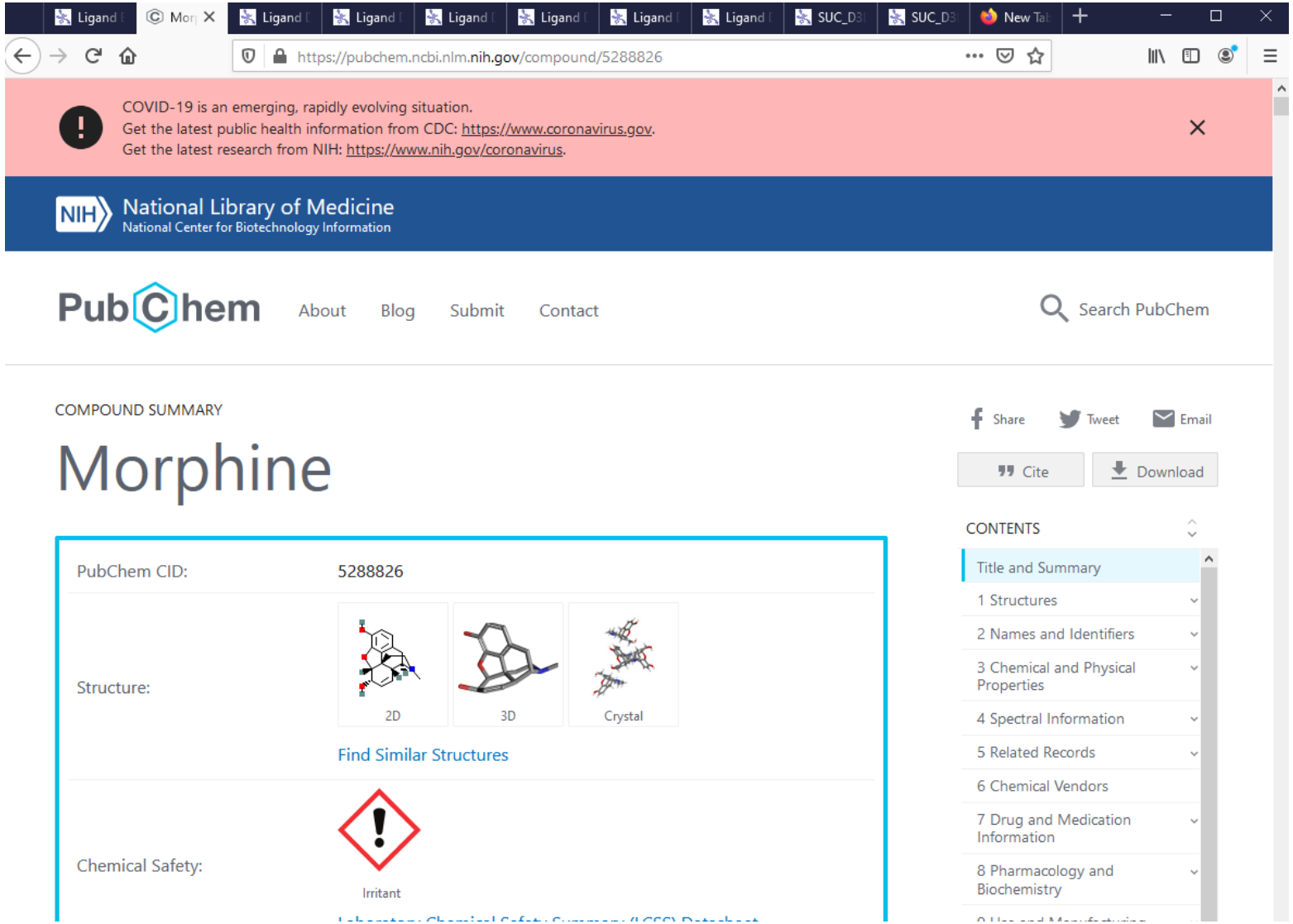




PubChem – database of organic molecules



PubChem – database of organic molecules



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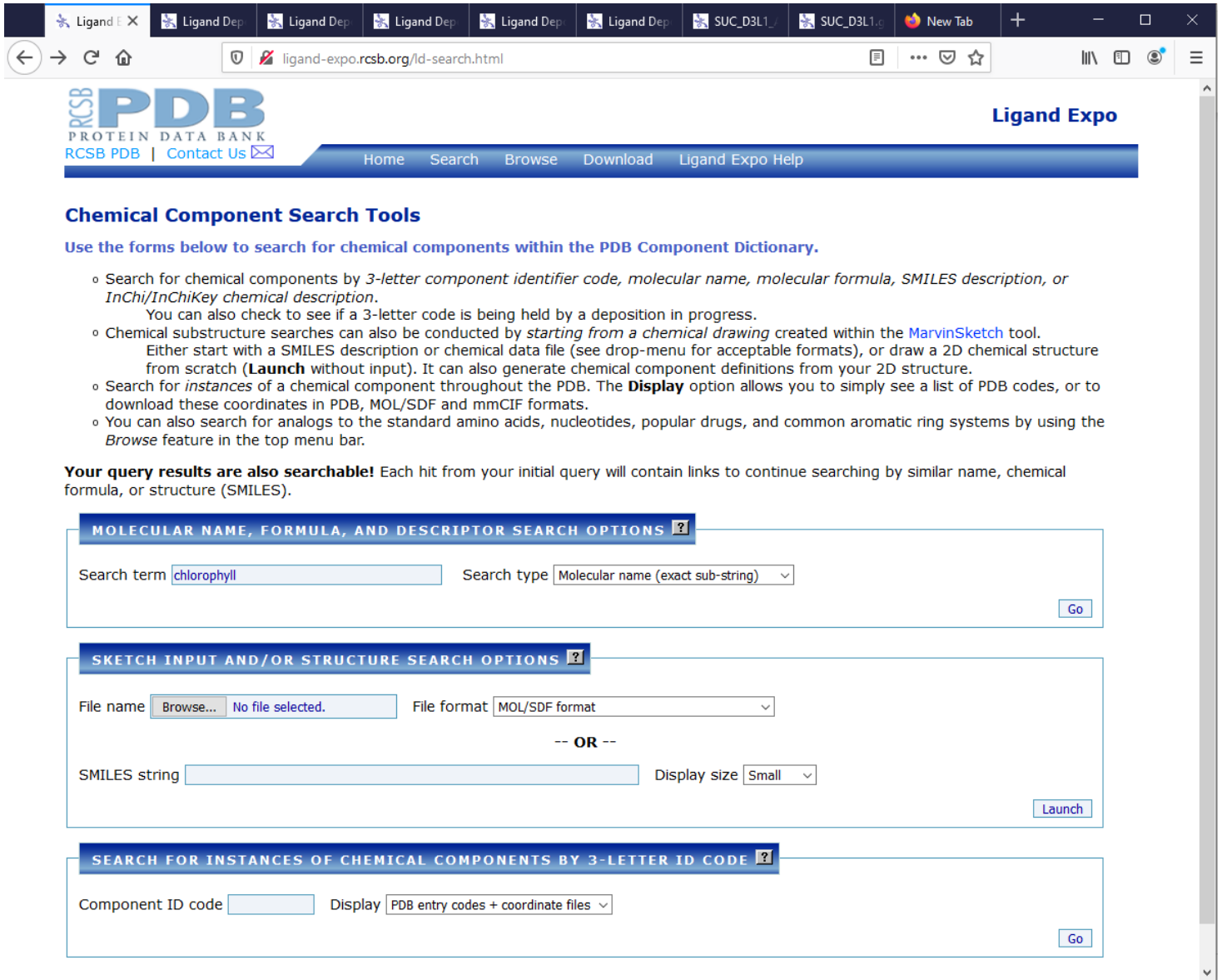
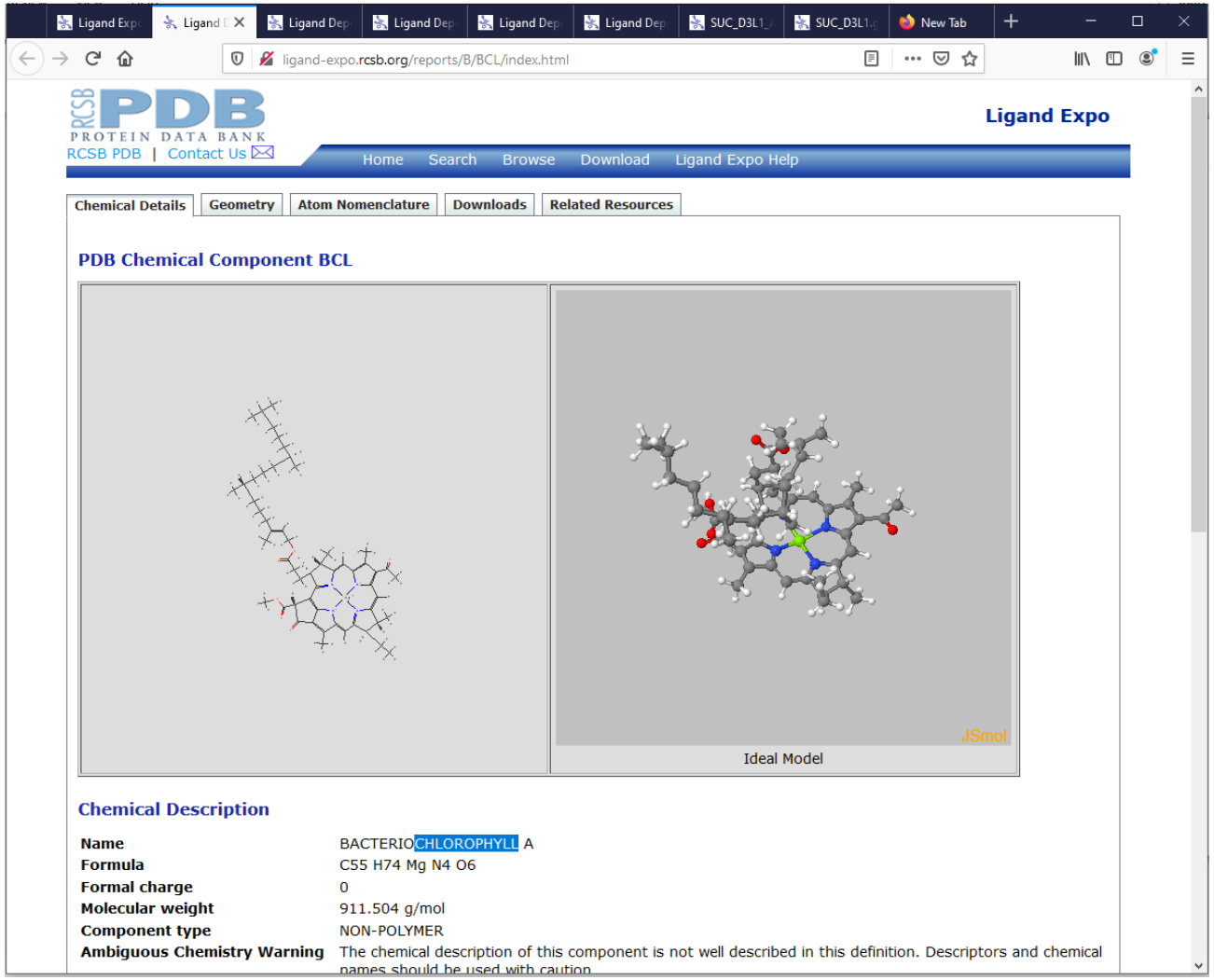
Ligand Expo – database of ligands
Ligand = molecule bound in a protein



24

Ligand Expo – database of ligands
Ligand = molecule bound in a protein



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Databases of biomacromolecules

Mainly proteins
> 200 k experimental structures
> 200 M computed structures

WORLDWIDE PDB
PROTEIN DATA BANK

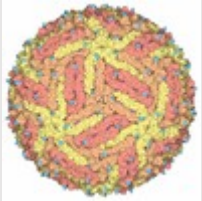
AlphaFold
Protein Structure Database
Developed by DeepMind and EMBL-EBI

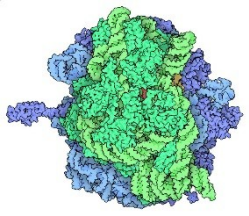
Protein Data Bank – sources of data

89% X-ray crystallography

10% NMR spectroscopy

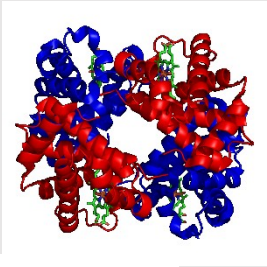
1% cryoelectron microscopy

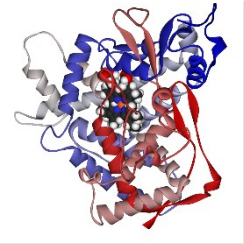




3D struktura

```
...
ATOM   46  C   GLY A  70    51.536  23.360  40.507
ATOM   47  O   GLY A  70    50.947  22.279  40.325
ATOM   48  N   ILE A  71    50.965  24.532  40.270
ATOM   49  CA  ILE A  71    49.595  24.644  39.786
...
```

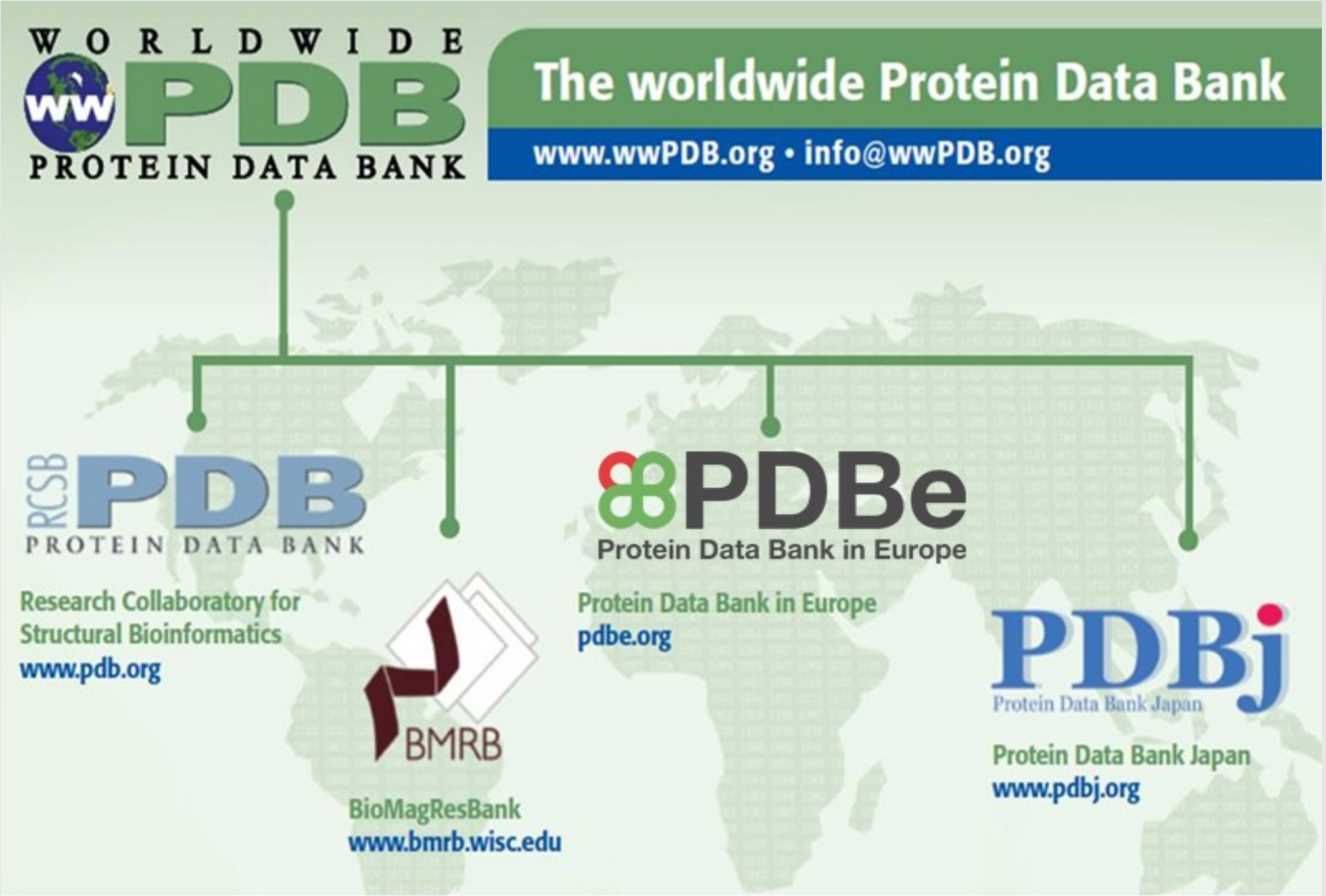




WORLDWIDE PDB PROTEIN DATA BANK

27

Protein Data Bank



> 225 000 biomacromolecular structures

Protein Data Bank

PDBe home < EMBL-EB

European Bioinformatics Institute [GB] https://www.ebi.ac.uk/pdbe/

EMBL-EBI | Services | Research | Training | About us

Protein Data Bank in Europe

Bringing Structure to Biology

Search

Examples: hemoglobin, BRCA1_HUMAN

Advanced search

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PDBe is the European resource for the collection, organisation and dissemination of data on biological macromolecular structures. Read more about PDBe.

Featured structure

Pygmalion 5x2g

1st September 2019

The September image in our 2019 calendar is inspired by a molecular system that can edit DNA and the story of a statue coming to life.

Read more...

Previous featured structures

Popular

- PDBe-KB
- EMsearch
- PDBeFold
- PDBePISA
- PDBeChem
- Sequence search
- PDBe REST API
- EM resources
- NMR resources
- EMPIAR
- Coordinate Server
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News

Links added to raw experimental data at PDBe

12 August, 2019

Improve your previously released PDB coordinates with OneDep

1 August, 2019

A celebration of the PDB Art project

26 July, 2019

Mandatory mmCIF format for crystallographic depositions to the PDB

1 July, 2019

More news

Events

Art Exhibition: Molecules of Life

Kendrew Foyer, EBI South Building Wellcome Genome Campus
10 Sep 2019 to 27 Sep 2019

EBI Structural bioinformatics course

EMBL-EBI, Cambridge, UK
16 Sep 2019 to 20 Sep 2019

EBI Exploring Biological Sequence course

EMBL-EBI, Cambridge, UK
10 Oct 2019

More events

Latest archive statistics

As of 11 September 2019 the PDB contains 155830 entries (latest PDB entries, chemistry, biology) and EMDB contains 9016 entries (latest map releases, latest header releases, latest updates).

Tweets by @PDBeurope

Protein Data Bank Retweeted

David Armstrong
@DaveASci
Really looking forward to giving this @PDBeurope training course Medellin in Colombia. Thanks to @raod85, @unubiolac and @CabanaGcrf for supporting this.
https://twitter.com/raod85/status/1173657623155154944

13h

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Protein Data Bank

Search the PDB archive ‹ PD | PDB 3hyu structure sum

European Bioinformatics Institute [GB] https://www.ebi.ac.uk/pdbe/entry/pdb/3hyu

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Protein Data Bank in Europe
Bringing Structure to Biology

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PDBe › 3hyu

X-ray diffraction
1.67Å resolution

Crystal structure of the altitude adapted hemoglobin of guinea pig.

Source organism: *Cavia porcellus*

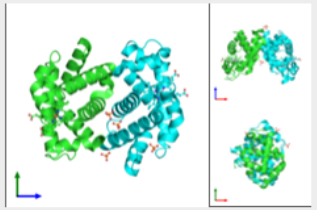
Primary publication:
Structure of the altitude adapted hemoglobin of guinea pig in the R2-state.

Pairet B, Jaenicke E

PLoS ONE **5** e12389 (2010)
PMID: 20811494

Released: 23 Jun 2010

Model geometry
Fit model/data



Quick links

- 3hyu overview
  - Citations
- Structure analysis
- Function and Biology
- Ligands and Environments
- Experiments and Validation

- View
- Downloads
- 3D Visualisation

Function and Biology

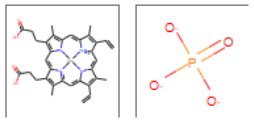
Details

Biochemical function: heme binding
Biological process: oxygen transport
Cellular component: hemoglobin complex

Sequence domains:
- Haemoglobin, alpha-type
- Haemoglobin, beta-type
- Globin
- Globin/Protoglobin
- Globin-like superfamily

Ligands and Environments

2 bound ligands:



2 x HEM 4 x PO4

No modified residues

PDB-REDO

The sliders below show the change in model quality between original PDB entry and the PDB-REDO entry

Model Geometry
Fit model/data

PDB-REDO

Structure analysis

Details

Assembly composition: hetero tetramer (preferred)

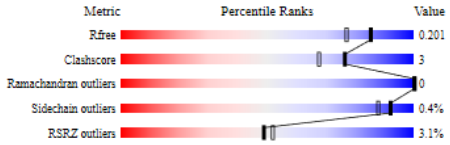
Entry contents: 2 distinct polypeptide molecules

Macromolecules (2 distinct):

Hemoglobin subunit alpha

Experiments and Validation

Details



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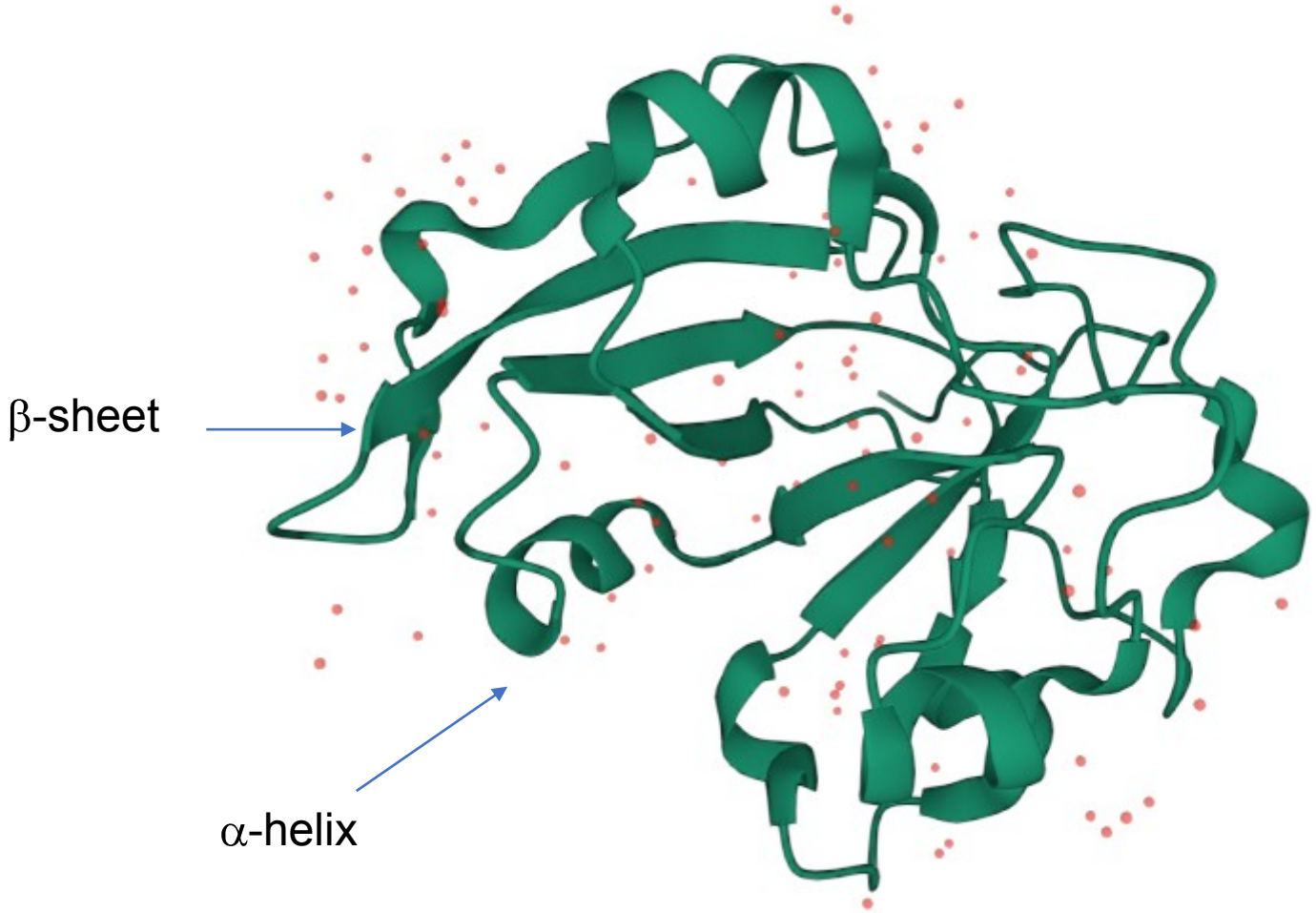
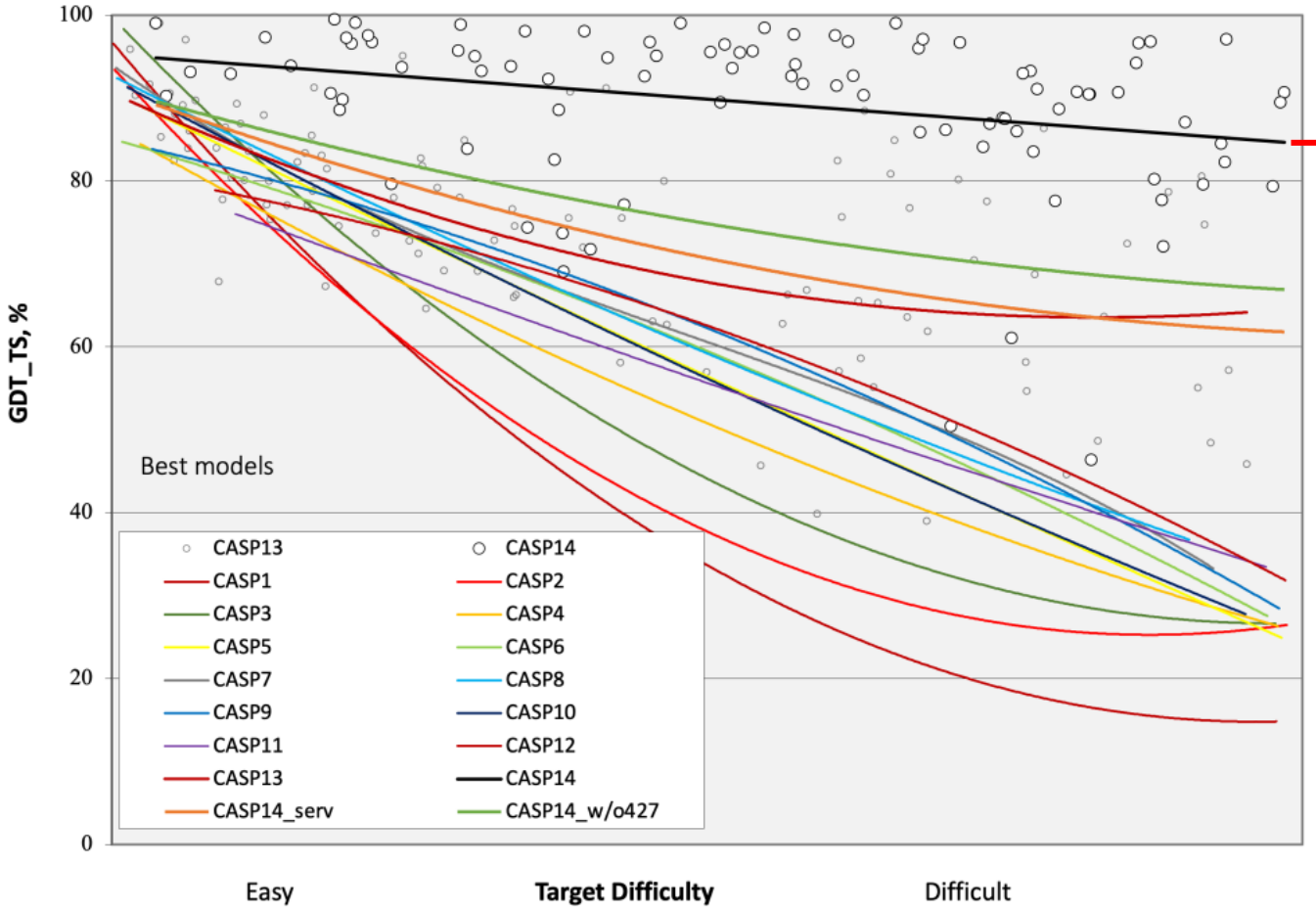
Protein Data Bank



Scabin
6vv4

Prediction of protein structures by AlphaFold

Structures generated by artificial intelligence



Structure prediction challenge 2020: AlphaFold2 wins

https://predictioncenter.org/casp14/doc/presentations/2020_11_30_CASP14_Introduction_Moult.pdf

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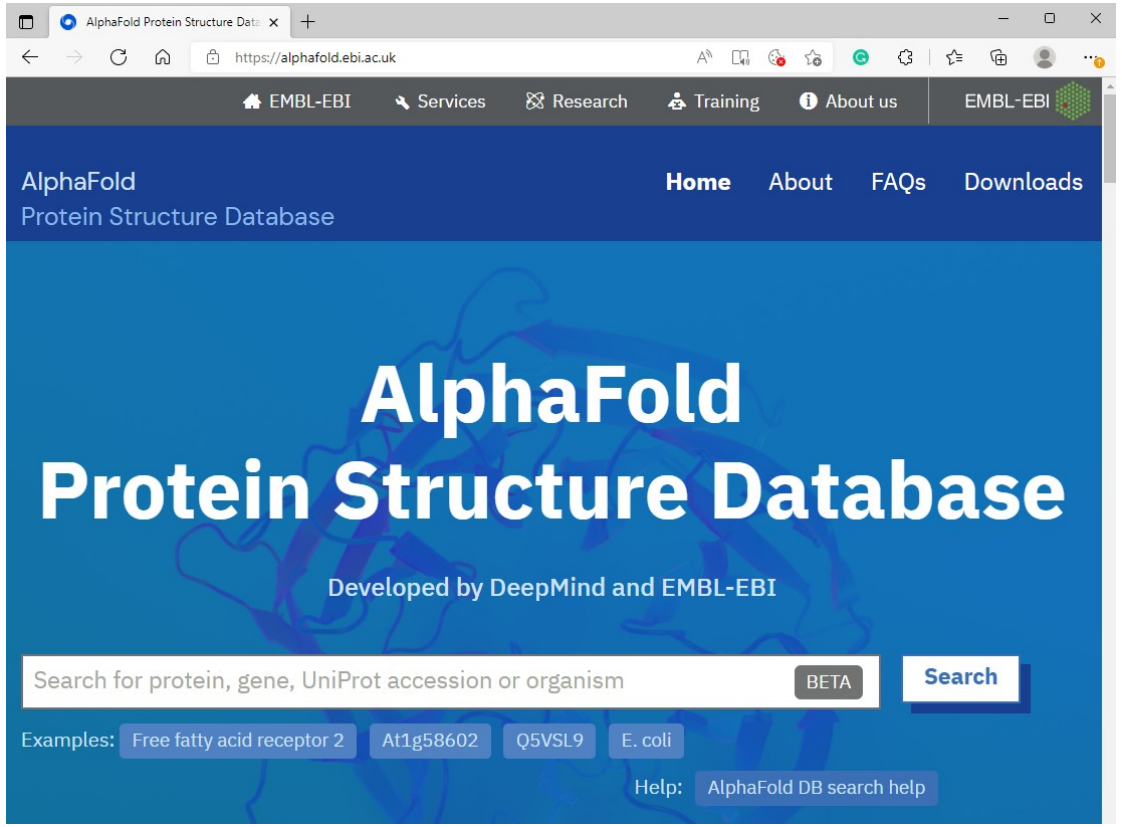
Prediction of protein structures by AlphaFold

Structures generated by artificial intelligence



> 200M protein structures

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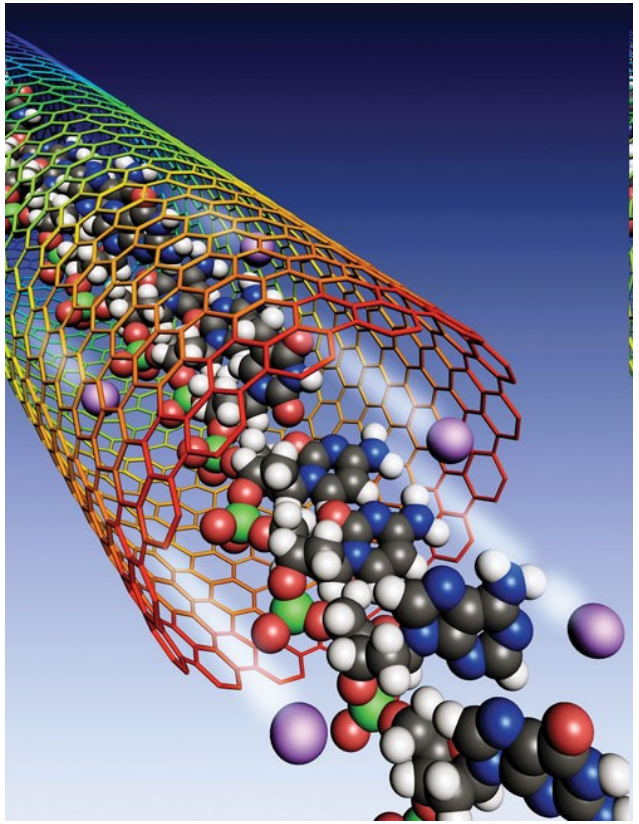
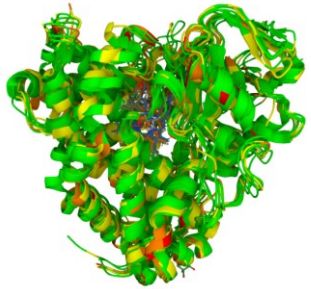
Exercises

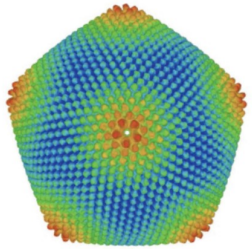
- Search the PubChem database for a testosterone molecule:
  - See its 2D structure. How many O's does it have?
  - Look at its 3D structure. Is any of its cycles planar?
  - Look at its SDF file. What are the x, y, and z coordinates of the first atom?
- Search the DrugBank database for a penicillin molecule:
  - How many S atoms does it have?
  - Are any of its cycles planar?
  - Look at its SDF file. What 2 atoms form the first bond?
- Search the LigandExpo database for a fructose molecule:
  - How many double bonds does it has?
  - How many C's are off cycle?
  - Look at its SDF file. What are the coordinates of the first hydrogen?
- Look up the green mamba venom molecule in the Protein Data Bank:
  - How many beta-sheets does it have?
  - Look at the PDB file. Which amino acid is the first?

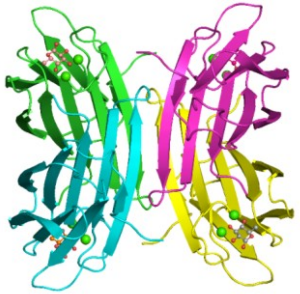


Thank you for your attention

Bioinformatics







Tools
Databases
AI

Chemoinformatics