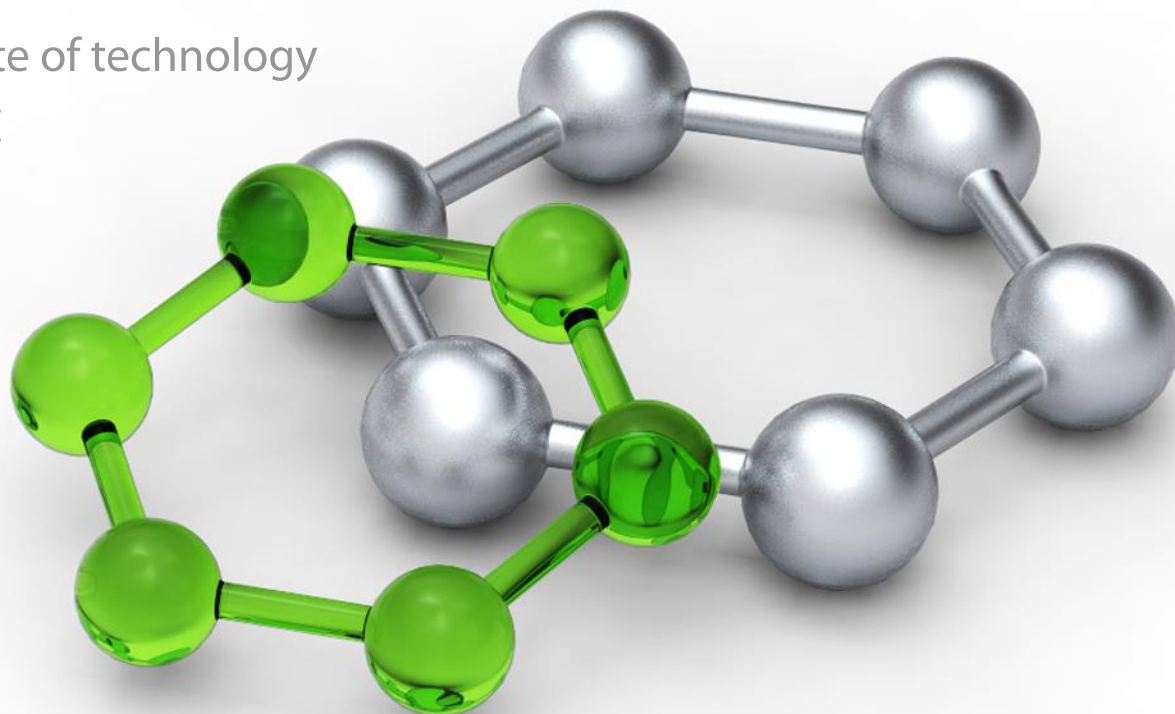




CEITEC

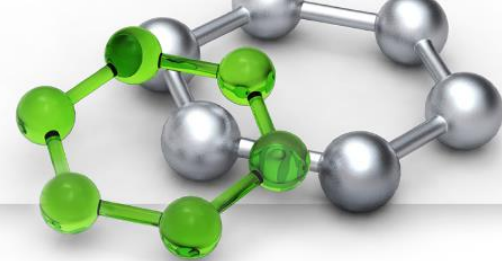
central european institute of technology
BRNO | CZECH REPUBLIC



Úvod do chemoinformatiky

Radka Svobodová

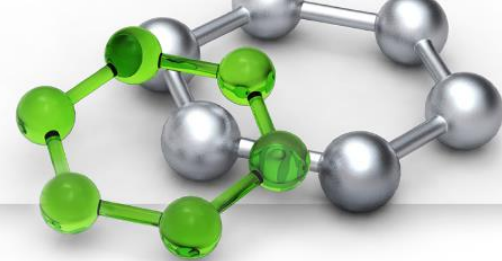
Proč nahrazovat nebo doplňovat experiment výpočtem?



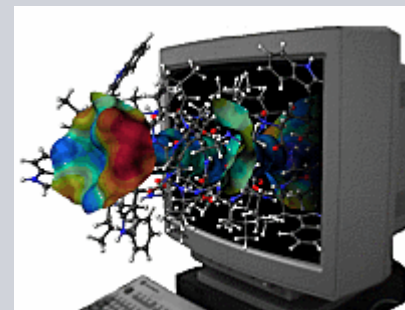
- Vyhneme se práci s toxickými, výbušnými a radioaktivními látkami
- Můžeme pracovat i s nestabilními látkami
- Ušetříme náklady za chemikálie a za realizaci experimentu
- Ušetříme čas experimentálním chemikům :-)
- ...



Chemoinformatika

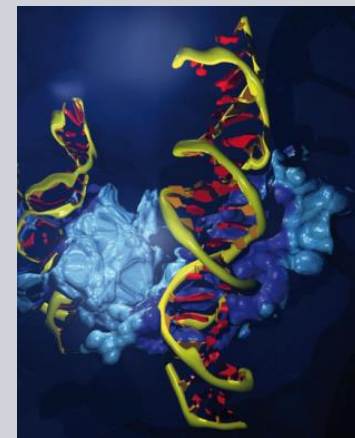


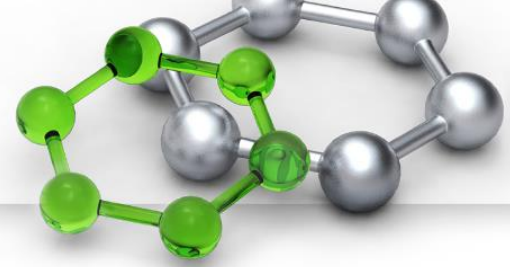
„Chemoinformatika využívá infromatických a algoritmických přístupů pro řešení chemických problémů. Převážně se zaměřuje na získání informací z databází malých nebo středně velkých molekul (léků, organických látek, ...).“



Vzniká v devadesátých létech dvacátého století.

Rozvoj spojen s dostupností velkého množství dat o molekulách léků apod. a s potřebami farmaceutického průmyslu





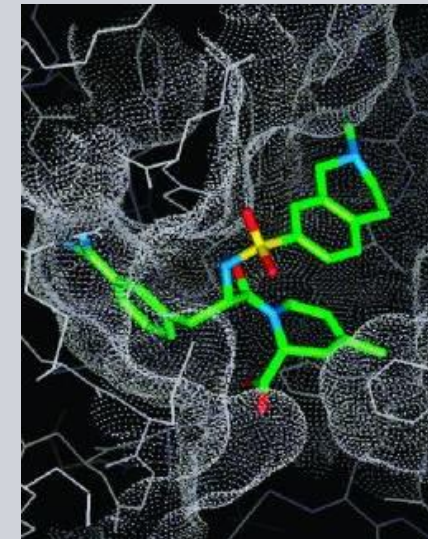
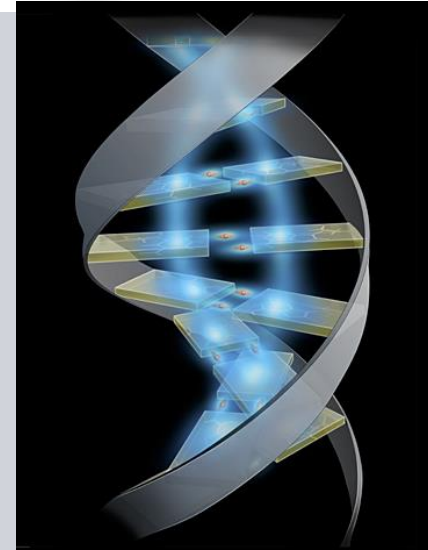
„Bioinformatika je aplikací statistických a výpočetních metod v oblasti molekulové biologie a genetiky. Převážně se specializuje na zpracování dat z databází biomolekul (sekvence DNA, RNA a proteinů).“

Vzniká v osmdesátých letech dvacátého století.

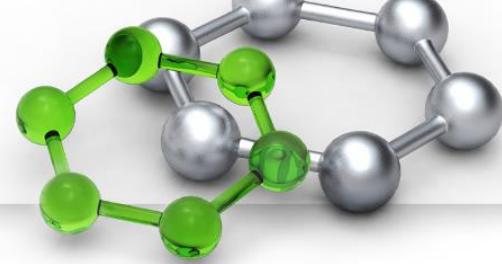
Rozvoj spojen s dostupností nadkritického množství dat o biomolekulách.

Specializace:

- Strukturní bioinformatika
- Sekvenční bioinformatika, NGS



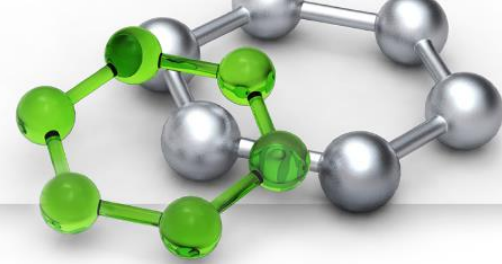
Jak zapsat molekulu v počítači?



- Zjistit, které informace molekulu popisují
- Zapsat je do počítače

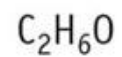


Které informace popisují molekulu?

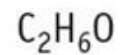


Počty atomů?

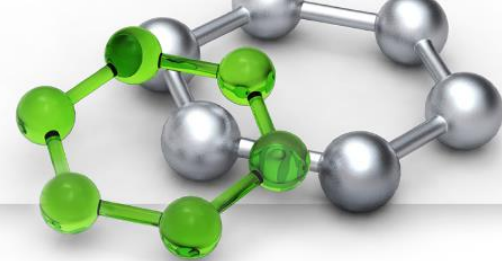
Ethanol



Dimethyl
ether



Které informace popisují molekulu?

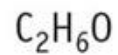


Počty atomů?

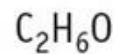
Málo

Počty atomů a umístění vazeb?

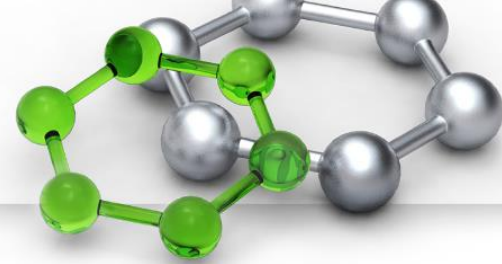
Ethanol



Dimethyl
ether



Které informace popisují molekulu?



Počty atomů?

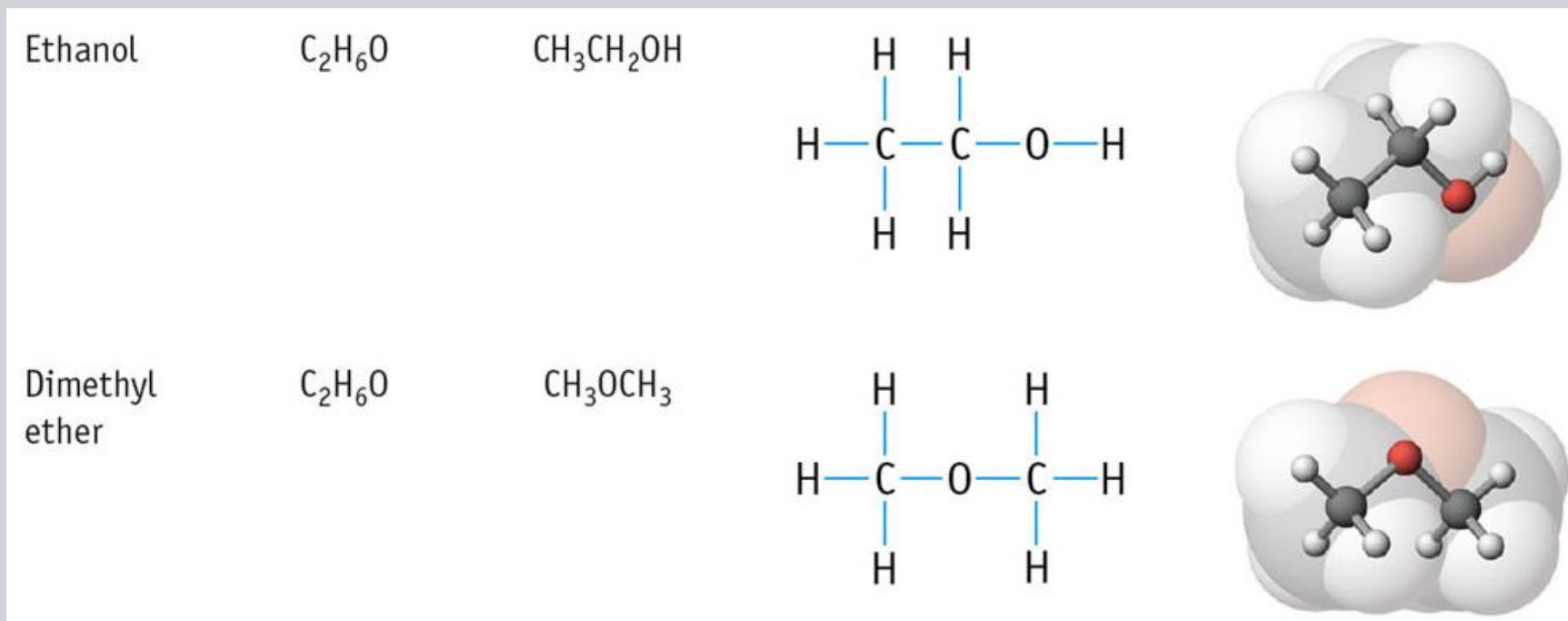
Málo

Počty atomů a umístění vazeb?

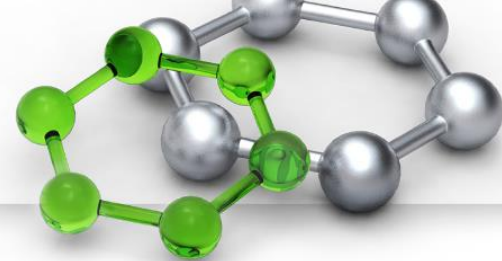
Lepší

Počty atomů, umístění vazeb a poloha atomů v prostoru?

Ano



Model molekuly pro počítačové zpracování



Atomy:

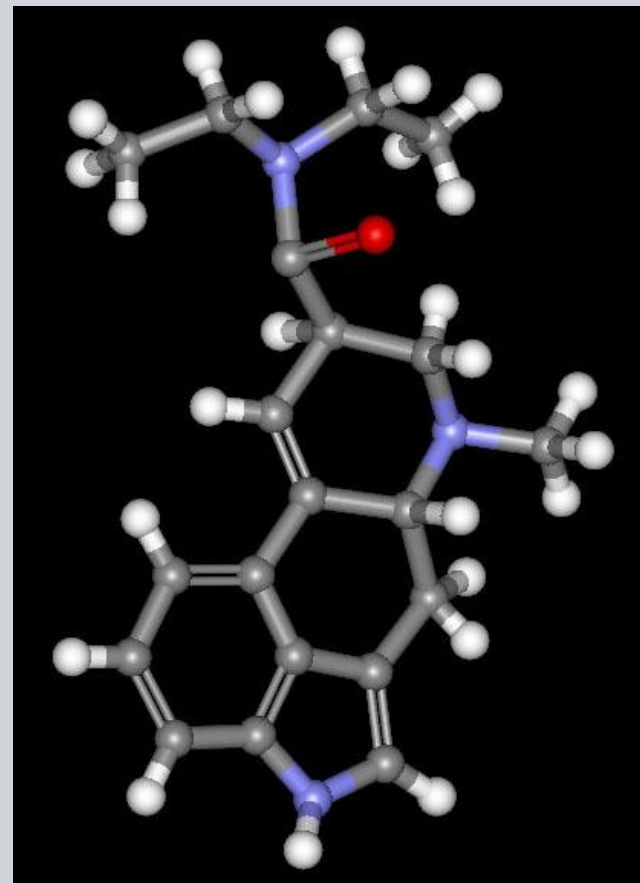
Body v prostoru

U každého uveden chemický symbol prvku

Vazby:

Dvojice atomů, které jsou vázány

Násobnost vazby



Zápis molekuly v počítači

Počet atomů

Počet vazeb

První atom je uhlík

```
-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 0 0 0 0
-3.4651 -2.3648 0.0000 C 0 0 0 0 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 0 0 0 0
-2.0338 -2.3644 0.0000 C 0 0 0 0 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 0 0 0 0
-2.7521 -1.1247 0.0000 C 0 0 0 0 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 0 0 0 0
-2.0413 0.1149 0.0000 O 0 0 0 0 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 0 0 0 0
-1.3238 -1.1186 0.0000 O 0 0 0 0 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 0 0 0
-0.6167 -2.3542 0.0000 O 0 0 0 0 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 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
```

První tři čísla jsou x, y a z souřadnice atomů

První vazba je mezi atomy 1 a 2 a jde o dvojnou vazbu

CC(=O)Oc1ccc(cc1)C(=O)O

```

21 21 0 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 0 0 0
 18.7571 -16.6359 -0.1252 C 0 0 0 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 0 0 0
 17.5465 -17.3106 -0.1545 C 0 0 0 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 0 0 0
 16.3559 -16.6013 -0.1633 C 0 0 0 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 0 0 0
 20.0592 -14.5322 -0.0715 N 0 0 0 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 0 0 0
 15.1150 -14.4620 -0.1527 N 0 0 0 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 0 0 0
 21.1073 -15.1564 -0.0523 O 0 0 0 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 0 0 0
 18.5697 -19.4030 -0.2650 O 0 0 0 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 0 0 0
 15.1330 -13.2425 -0.1568 O 0 0 0 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 0 0 0
 15.3860 -17.1427 -0.1873 H 0 0 0 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 0 0 0
 16.7057 -12.6567 0.4410 H 0 0 0 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 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

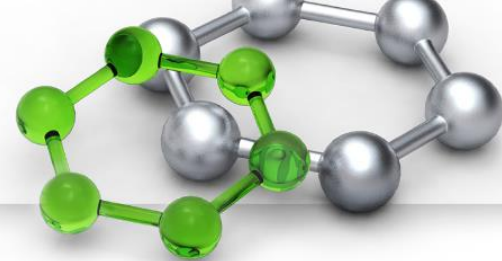
```

M END

Kvízová otázka:

**Nakresli tuto
molekulu.
Jak se daná
molekula
jmenuje?**

Současné databáze molekul



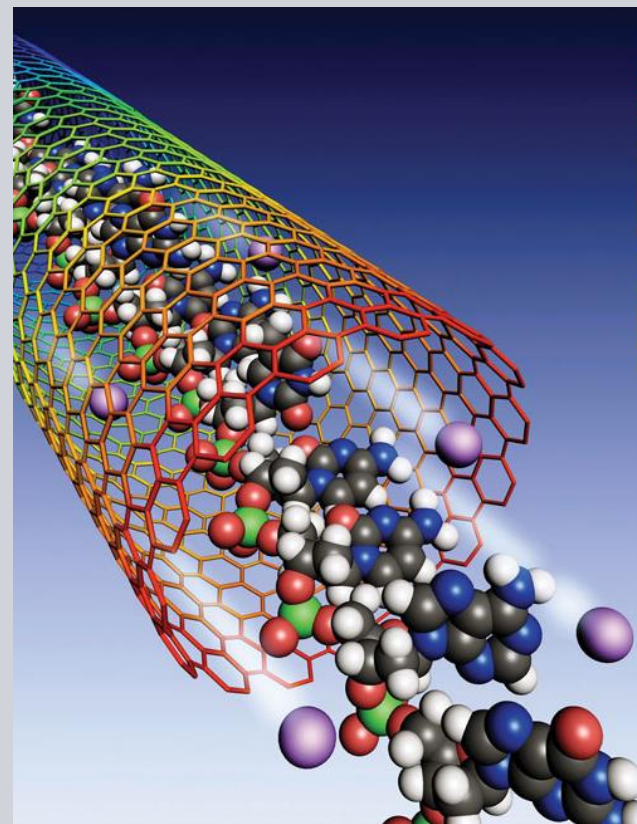
Prožíváme „**informační boom**“ v oblasti dat o molekulách

Důvod: Vysoce výkonné techniky strukturní analýzy

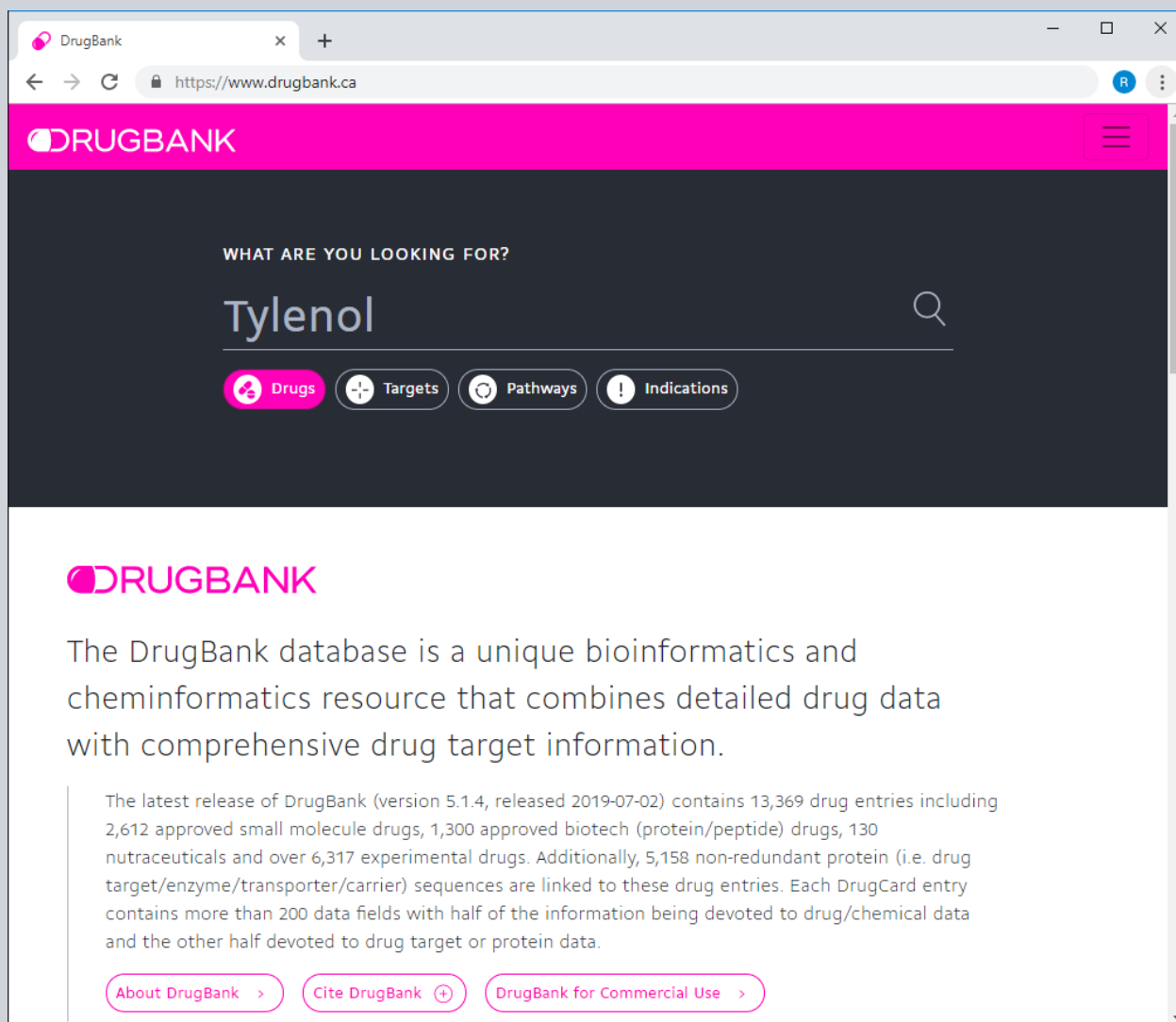
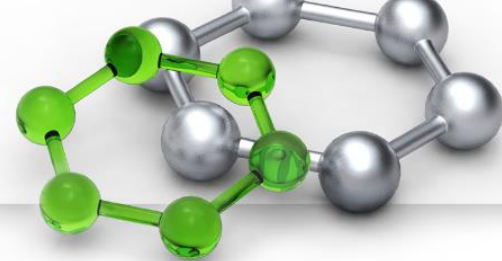
Důsledky:

- Máme k dispozici miliony struktur malých molekul (organické molekuly, léky, ...)
- Známe struktury více než 190 000 proteinů a více než 100 000 000 organických molekul
- Jsme schopni zjistit informaci o genomu jednoho člověka za pár dnů

Většina těchto informací je veřejně přístupná :-)



DrugBank – ukázka databáze léků



The screenshot shows a web browser window with the DrugBank website. The browser's address bar displays <https://www.drugbank.ca>. The website's header features the DrugBank logo in a pink bar. Below the header, a search bar contains the text "Tylenol" and a magnifying glass icon. Underneath the search bar are four buttons: "Drugs" (highlighted in pink), "Targets", "Pathways", and "Indications".

DRUGBANK

WHAT ARE YOU LOOKING FOR?

Tylenol

Drugs Targets Pathways Indications

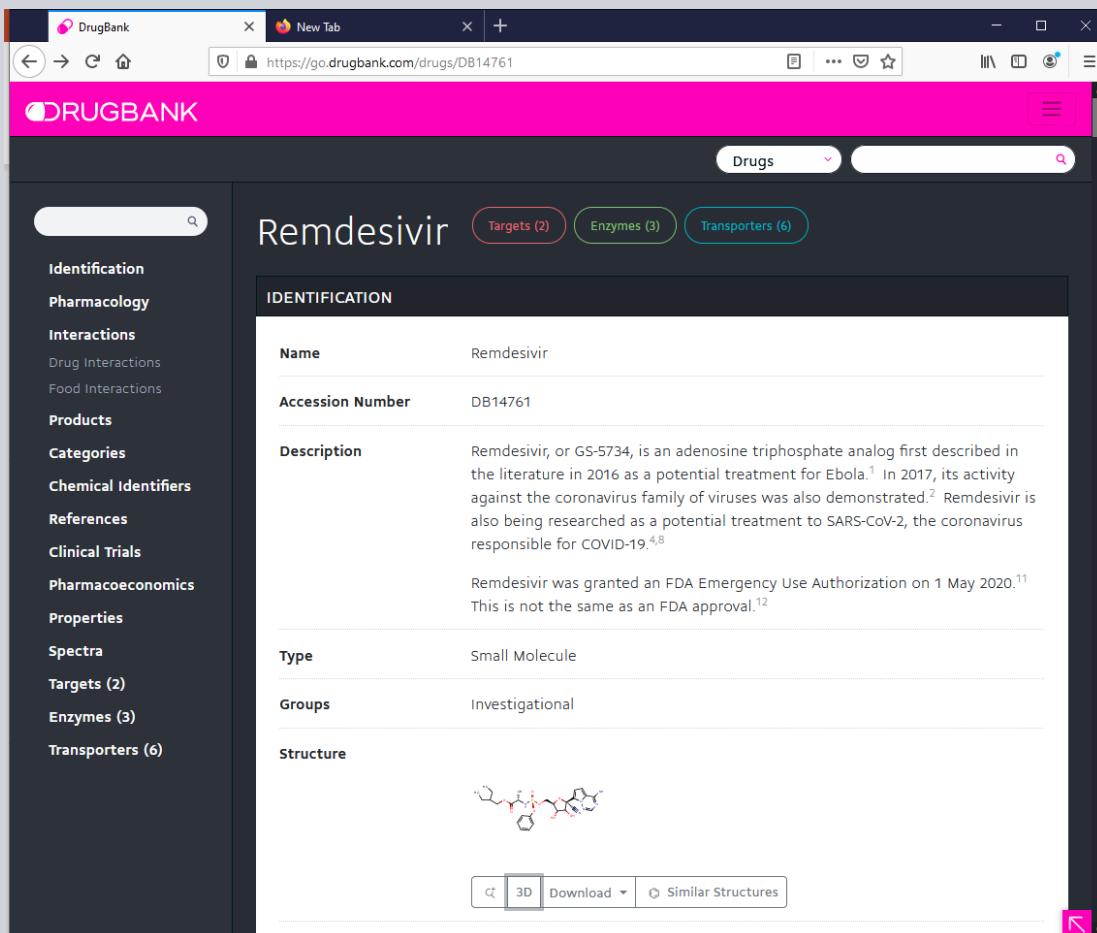
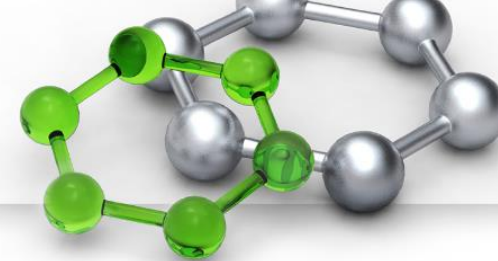
DRUGBANK

The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug data with comprehensive drug target information.

The latest release of DrugBank (version 5.1.4, released 2019-07-02) contains 13,369 drug entries including 2,612 approved small molecule drugs, 1,300 approved biotech (protein/peptide) drugs, 130 nutraceuticals and over 6,317 experimental drugs. Additionally, 5,158 non-redundant protein (i.e. drug target/enzyme/transporter/carrier) sequences are linked to these drug entries. Each DrugCard entry contains more than 200 data fields with half of the information being devoted to drug/chemical data and the other half devoted to drug target or protein data.

[About DrugBank](#) [Cite DrugBank](#) [DrugBank for Commercial Use](#)

DrugBank – ukázka databáze léků

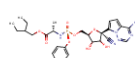


DRUGBANK

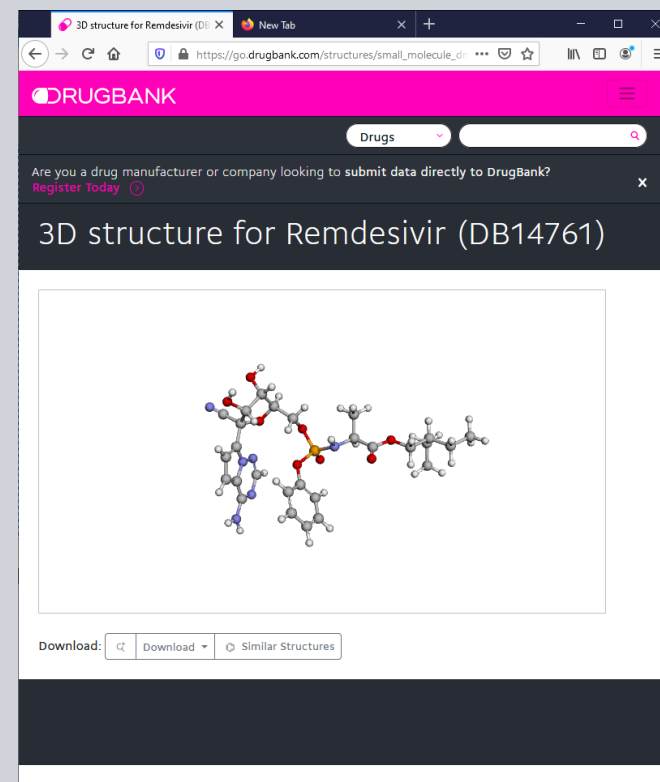
Drugs

Remdesivir Targets (2) Enzymes (3) Transporters (6)

IDENTIFICATION

Name	Remdesivir
Accession Number	DB14761
Description	Remdesivir, or GS-5734, is an adenosine triphosphate analog first described in the literature in 2016 as a potential treatment for Ebola. ¹ In 2017, its activity against the coronavirus family of viruses was also demonstrated. ² Remdesivir is also being researched as a potential treatment to SARS-CoV-2, the coronavirus responsible for COVID-19. ^{4,8}
	Remdesivir was granted an FDA Emergency Use Authorization on 1 May 2020. ¹¹ This is not the same as an FDA approval. ¹²
Type	Small Molecule
Groups	Investigational
Structure	

3D Download Similar Structures

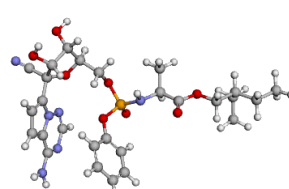


DRUGBANK

Drugs

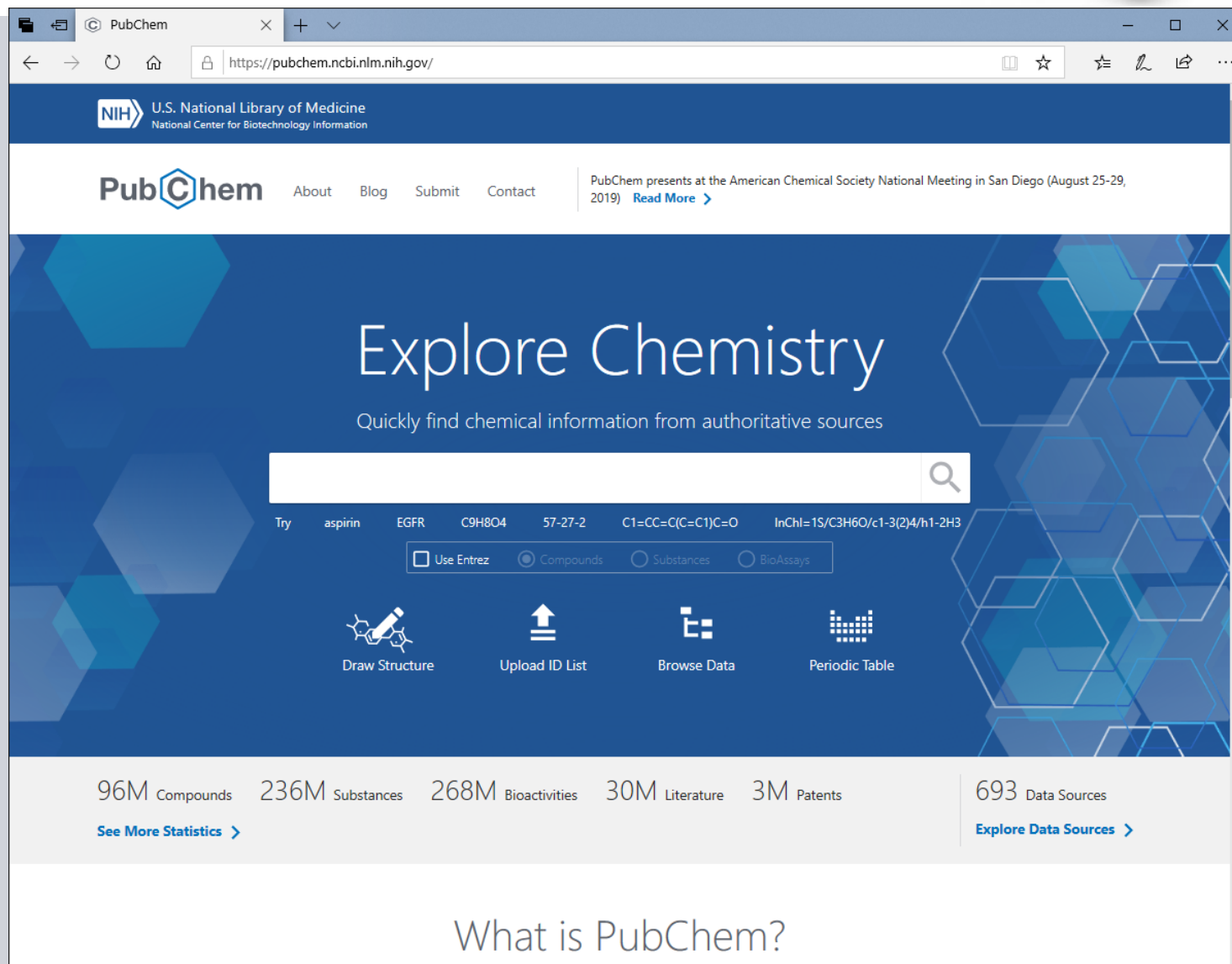
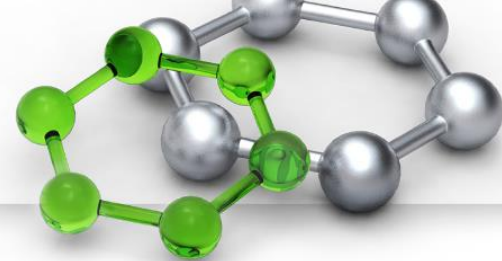
Are you a drug manufacturer or company looking to submit data directly to DrugBank?
[Register Today](#)

3D structure for Remdesivir (DB14761)



Download: Download

PubChem – ukázka databáze organických molekul



PubChem

U.S. National Library of Medicine
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PubChem presents at the American Chemical Society National Meeting in San Diego (August 25-29, 2019) [Read More >](#)

Explore Chemistry

Quickly find chemical information from authoritative sources

Try aspirin EGFR C9H8O4 57-27-2 C1=CC=C(C=C1)C=O InChI=1S/C3H6O/c1-3(2)4/h1-2H3

Use Entrez Compounds Substances BioAssays

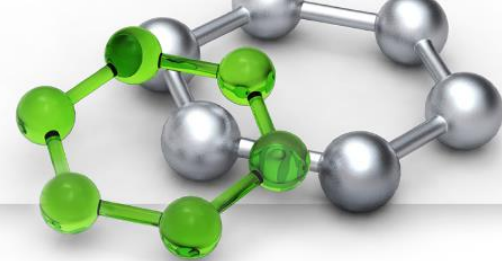
 Draw Structure  Upload ID List  Browse Data  Periodic Table

96M Compounds 236M Substances 268M Bioactivities 30M Literature 3M Patents 693 Data Sources

[See More Statistics >](#) [Explore Data Sources >](#)

What is PubChem?

PubChem – ukázka databáze organických molekul



Browser tabs: Ligand, Morj X, Ligand, Ligand, Ligand, Ligand, Ligand, Ligand, SUC_D3, SUC_D3, New Tal

Address bar: <https://pubchem.ncbi.nlm.nih.gov/compound/5288826>

COVID-19 is an emerging, rapidly evolving situation. Get the latest public health information from CDC: <https://www.coronavirus.gov>. Get the latest research from NIH: <https://www.nih.gov/coronavirus>.

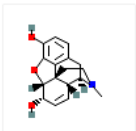
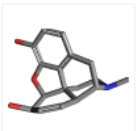
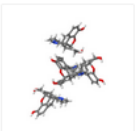
NIH National Library of Medicine National Center for Biotechnology Information

PubChem About Blog Submit Contact Search PubChem


COMPOUND SUMMARY

Morphine

PubChem CID: 5288826

Structure:  2D  3D  Crystal

[Find Similar Structures](#)

Chemical Safety:  Irritant

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CONTENTS

- Title and Summary
- 1 Structures
- 2 Names and Identifiers
- 3 Chemical and Physical Properties
- 4 Spectral Information
- 5 Related Records
- 6 Chemical Vendors
- 7 Drug and Medication Information
- 8 Pharmacology and Biochemistry
- 9 Used Manufacturing

Ligand Expo – ukázka databáze ligandů



Browser tabs: Ligand E X, Ligand Dep, Ligand Dep, Ligand Dep, Ligand Dep, Ligand Dep, SUC_D3L1, SUC_D3L1, New Tab

URL: ligand-expo.rcsb.org/ld-search.html

RCSB PDB PROTEIN DATA BANK
RCSB PDB | [Contact Us](#)

Ligand Expo

Home Search Browse Download Ligand Expo Help

Chemical Component Search Tools

Use the forms below to search for chemical components within the PDB Component Dictionary.

- Search for chemical components by 3-letter component identifier code, molecular name, molecular formula, SMILES description, or InChI/InChIKey chemical description.
You can also check to see if a 3-letter code is being held by a deposition in progress.
- Chemical substructure searches can also be conducted by starting from a chemical drawing created within the [MarvinSketch](#) tool.
Either start with a SMILES description or chemical data file (see drop-menu for acceptable formats), or draw a 2D chemical structure from scratch (**Launch** without input). It can also generate chemical component definitions from your 2D structure.
- Search for instances of a chemical component throughout the PDB. The **Display** option allows you to simply see a list of PDB codes, or to download these coordinates in PDB, MOL/SDF and mmCIF formats.
- You can also search for analogs to the standard amino acids, nucleotides, popular drugs, and common aromatic ring systems by using the *Browse* feature in the top menu bar.

Your query results are also searchable! Each hit from your initial query will contain links to continue searching by similar name, chemical formula, or structure (SMILES).

MOLECULAR NAME, FORMULA, AND DESCRIPTOR SEARCH OPTIONS ?

Search term Search type

SKETCH INPUT AND/OR STRUCTURE SEARCH OPTIONS ?

File name File format

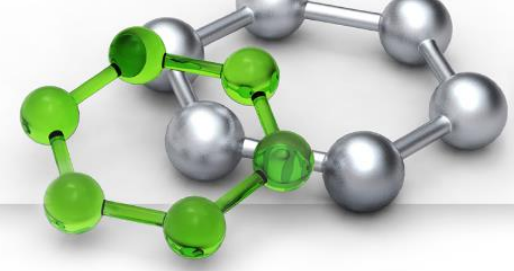
-- OR --

SMILES string Display size

SEARCH FOR INSTANCES OF CHEMICAL COMPONENTS BY 3-LETTER ID CODE ?

Component ID code Display

Ligand Expo – ukázka databáze ligandů



ligand-expo.rcsb.org/reports/B/BCL/index.html

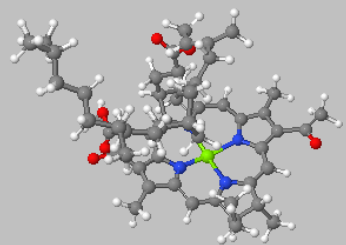
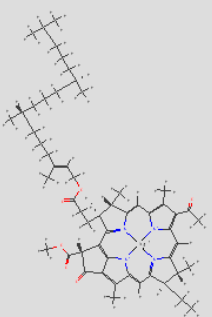
RCSB PDB
PROTEIN DATA BANK
RCSB PDB | [Contact Us](#)

Ligand Expo

Home Search Browse Download Ligand Expo Help

Chemical Details **Geometry** Atom Nomenclature Downloads Related Resources

PDB Chemical Component BCL



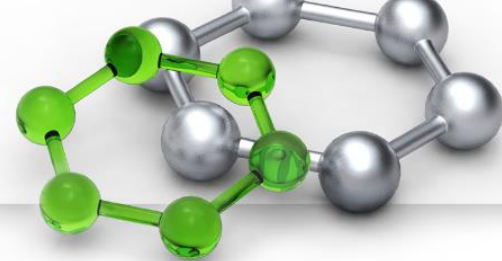
Ideal Model JSmol

Chemical Description

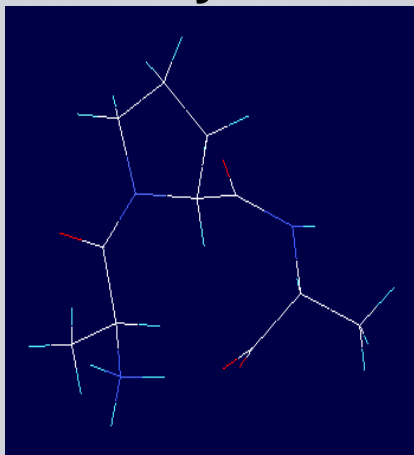
Name	BACTERIO CHLOROPHYLL A
Formula	C55 H74 Mg N4 O6
Formal charge	0
Molecular weight	911.504 g/mol
Component type	NON-POLYMER

Ambiguous Chemistry Warning The chemical description of this component is not well described in this definition. Descriptors and chemical names should be used with caution.

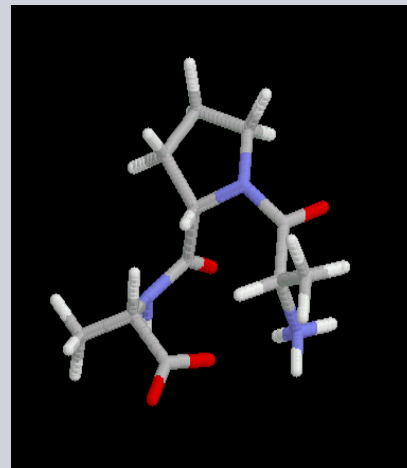
Vizualizace malé molekuly v počítači



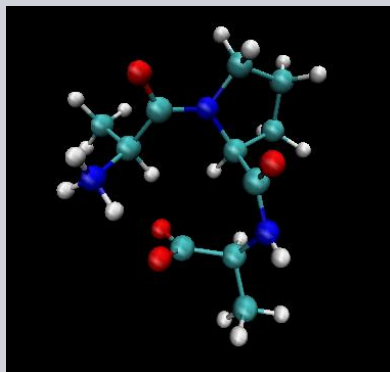
Drátový model:



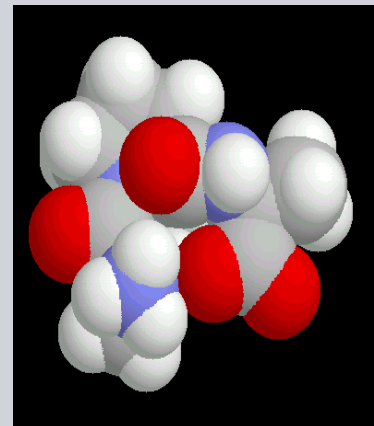
Tyčinkový model:



Tyčinky a kuličky:



Kalotový model (CPK):



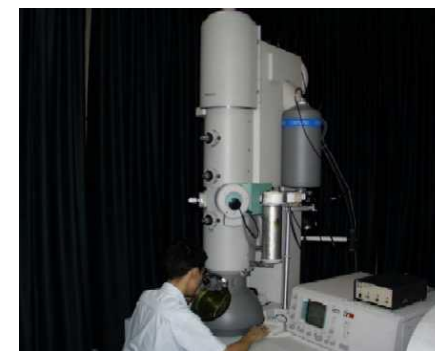
Protein Data Bank – zdroje dat



89% Rentgenová
krystalografie



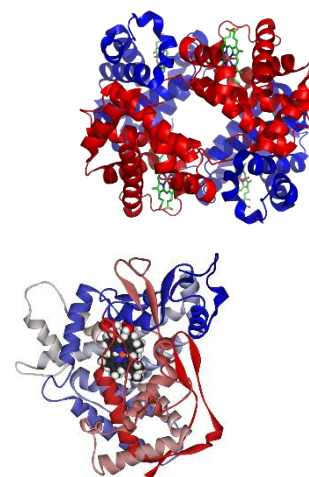
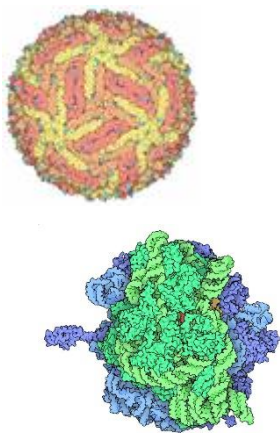
10% NMR
spektroskopie



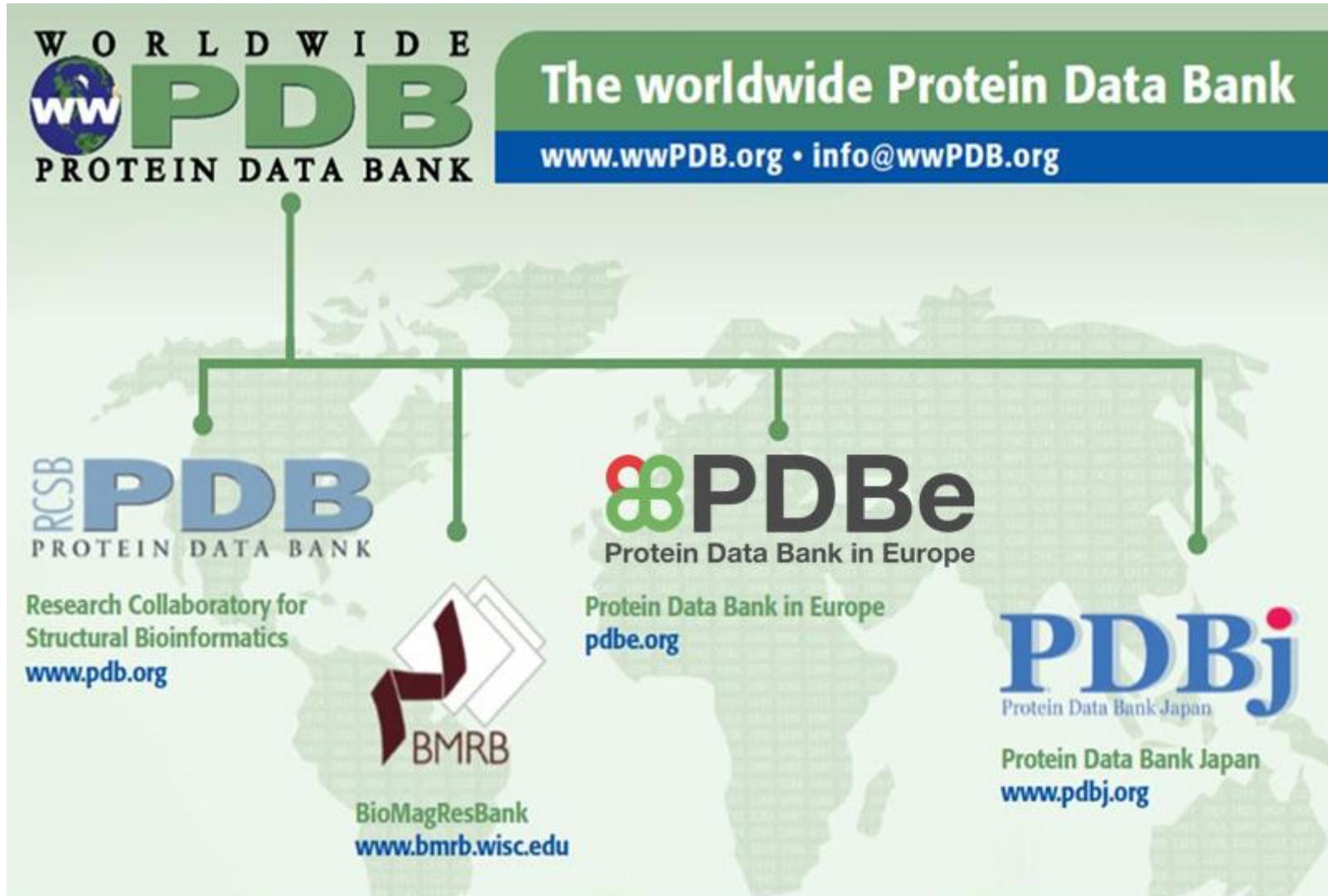
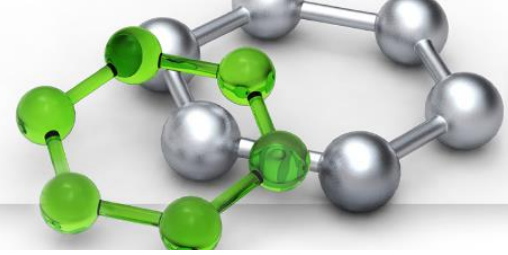
1% kryo-elektronová
mikroskopie

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
...								

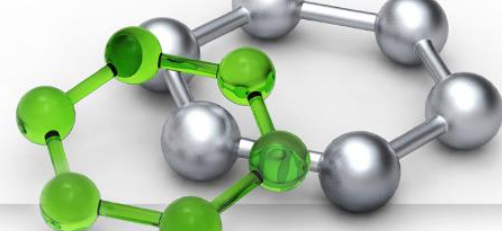


Protein Data Bank



> 190 000 biomacromolecular structures

Protein Data Bank – ukázka databáze proteinů



Screenshot of the Protein Data Bank (PDB) website interface. The browser address bar shows the URL: <https://www.ebi.ac.uk/pdbe/>. The page header includes the EMBL-EBI logo and the text "Protein Data Bank in Europe Bringing Structure to Biology". A search bar is visible with a search button and examples: hemoglobin, BRCA1_HUMAN. The main navigation menu includes: PDBe home, Deposition, PDBe services, PDBe training, Documentation, About PDBe, Share, and Feedback.

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](#)

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](#)

Popular

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

News

- News
- Events
- Training
- Contact us

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 – ukázka databáze proteinů



Search the PDB archive < PD PDB 3hyu structure surr X + v

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

EMBL-EBI Protein Data Bank in Europe Bringing Structure to Biology

Services Research Training About us

Search Examples: hemoglobin, BRCA1_HUMAN Advanced search

Feedback

PDBe > 3hyu

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.

Pairat B, Jaenicke E
PLoS ONE 5 e12389 (2010)
PMID: 20811494

X-ray diffraction
1.67Å resolution
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

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

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

Structure analysis

Details

Assembly composition: hetero tetramer (preferred)

Entry contents: 2 distinct polypeptide molecules

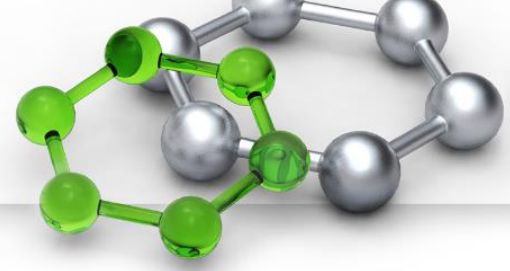
Macromolecules (2 distinct): Hemoglobin subunit alpha

Experiments and Validation

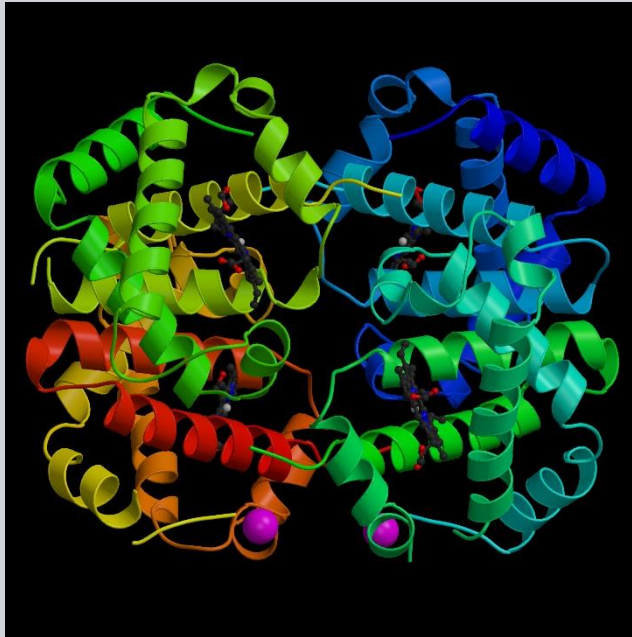
Details

Metric	Percentile Ranks	Value
Rfree		0.201
Clashscore		3
Ramachandran outliers		0
Sidechain outliers		0.4%
RSRZ outliers		3.1%

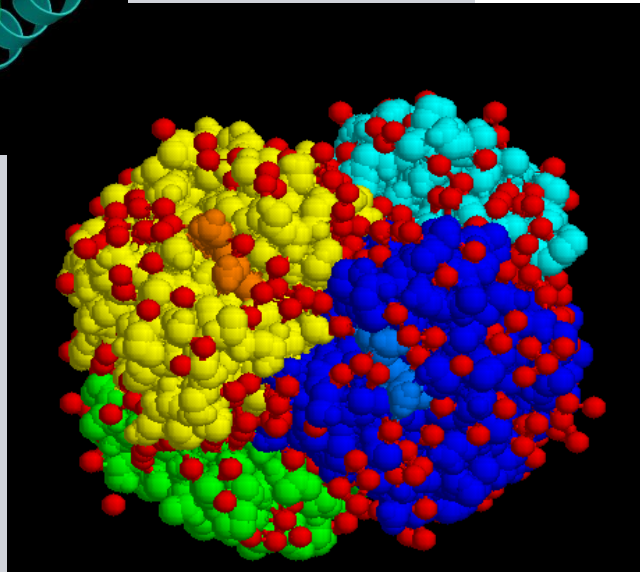
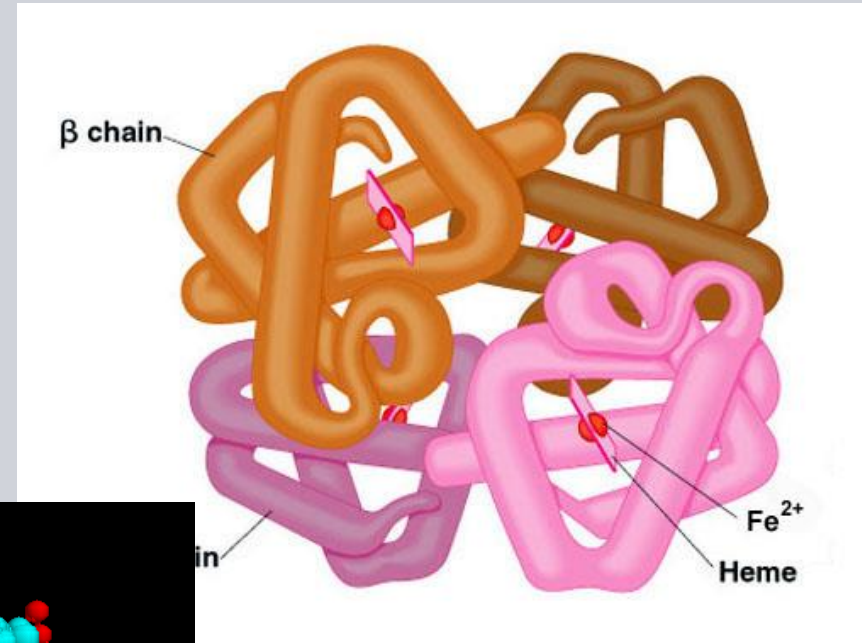
Vizualizace biomolekuly v počítači



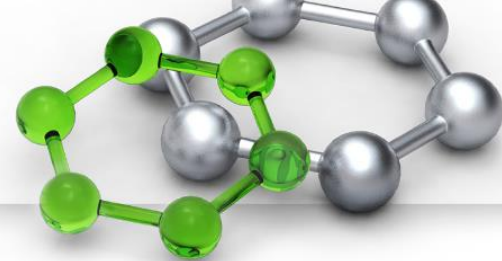
Cartoon model:



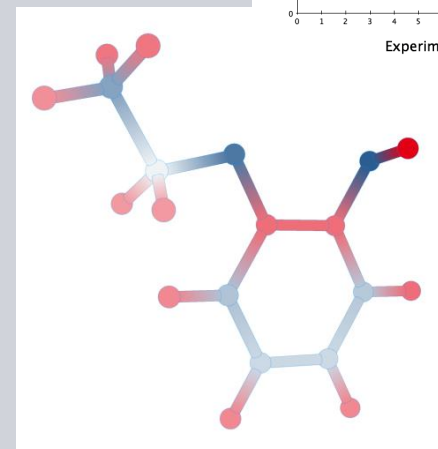
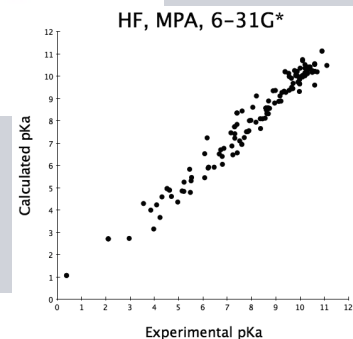
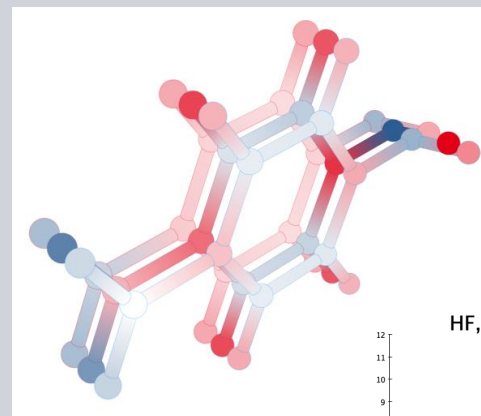
Schématický model:



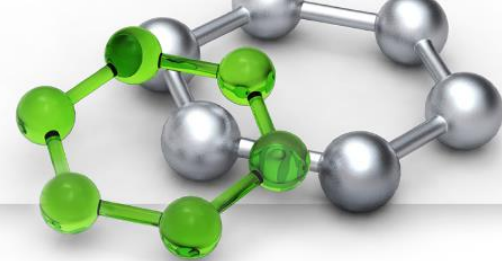
Chemoinformatika – hlavní oblasti



- Podobnostní vyhledávání v databázích
- Výpočty a aplikace deskriptorů
- QSAR / QSPR
- Vytváření a aplikace virtuálních knihoven molekul
- Virtuální screening



Proces návrhu a vývoje léku



Uvedení nového léku na trh stojí v průměru 900 milionů dolarů a trvá více než 10 let.

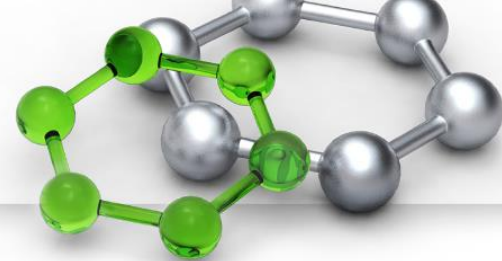
Farmaceutické společnosti často zkoumají a testují 10 000 – 30 000 rozličných látek předtím, než je jedna z nich úspěšně uvedena na trh.

Látky jsou nejdříve **navrženy v základním výzkumu.**

Poté musí projít předklinickými a klinickými zkouškami.

Většina nepostoupí dále, ale ty, které postoupí, mohou nabídnout šanci na kvalitnější život pacientů.

Proces návrhu a vývoje léků



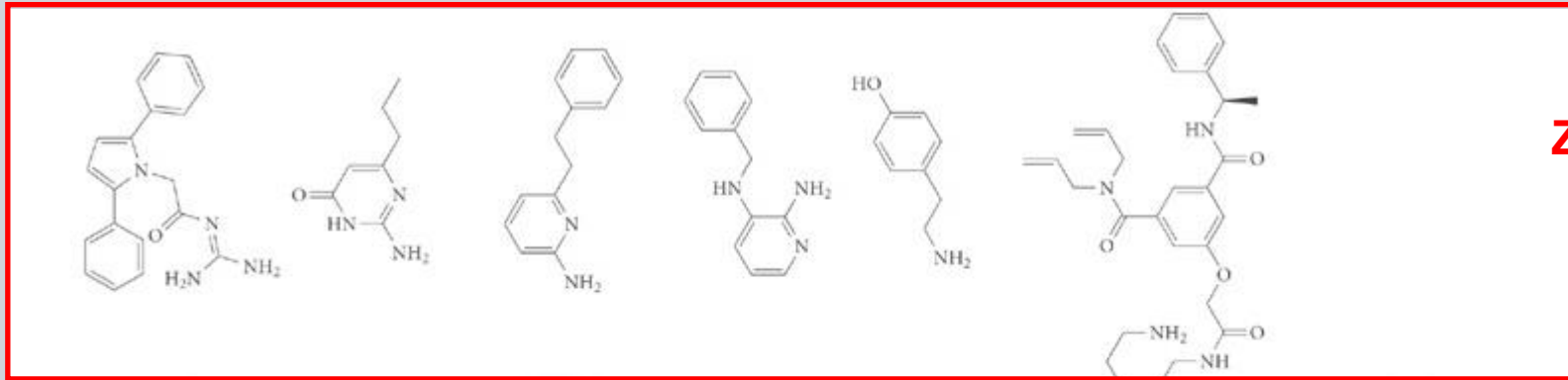
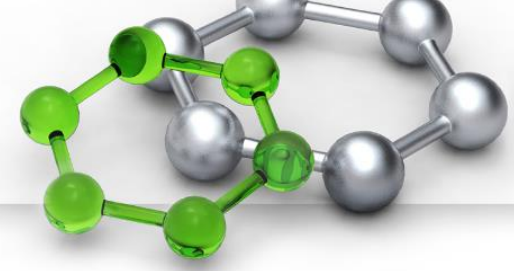
1 nový lék na trhu



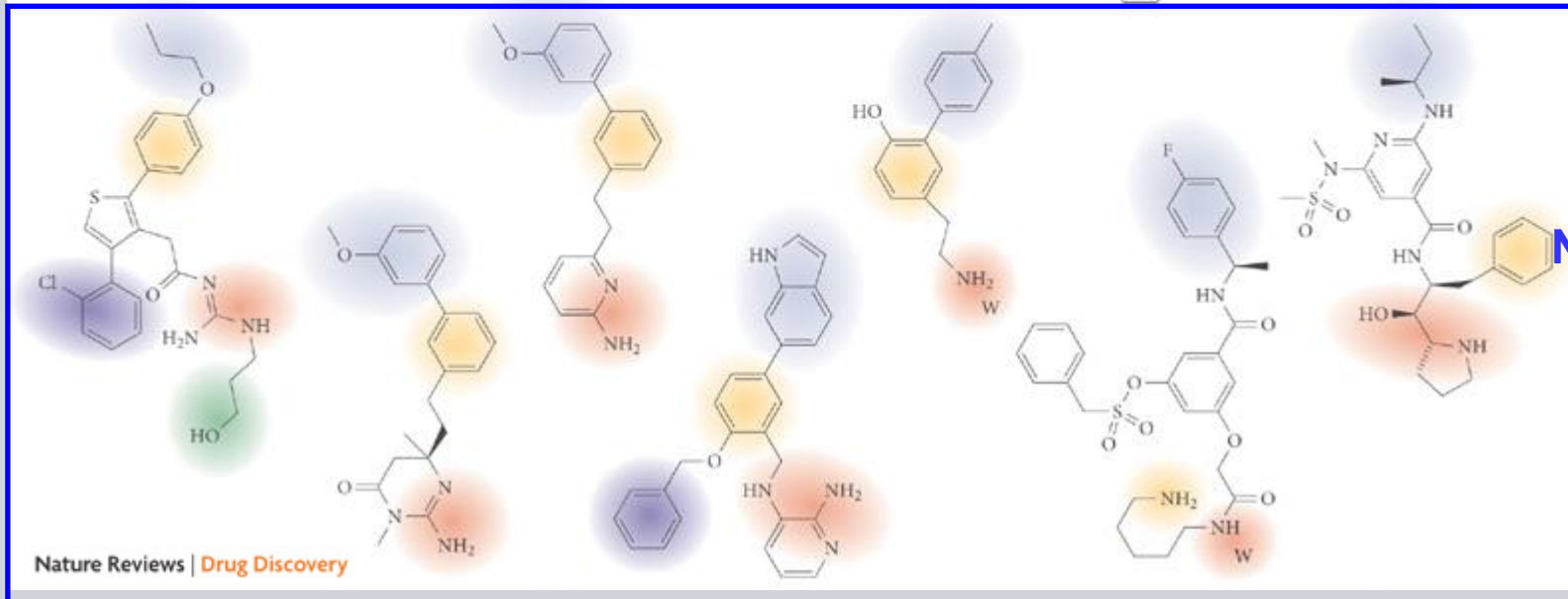
Čím sofistikovanější je výběr nejvhodnějších kandidátů, tím efektivnější a levnější je celý proces.

Chemoinformatika je klíčová při výběru nejvhodnějších kandidátů. Umožňuje totiž predikci vlastností nově navržených molekul léků.

Návrh léku (drug design)



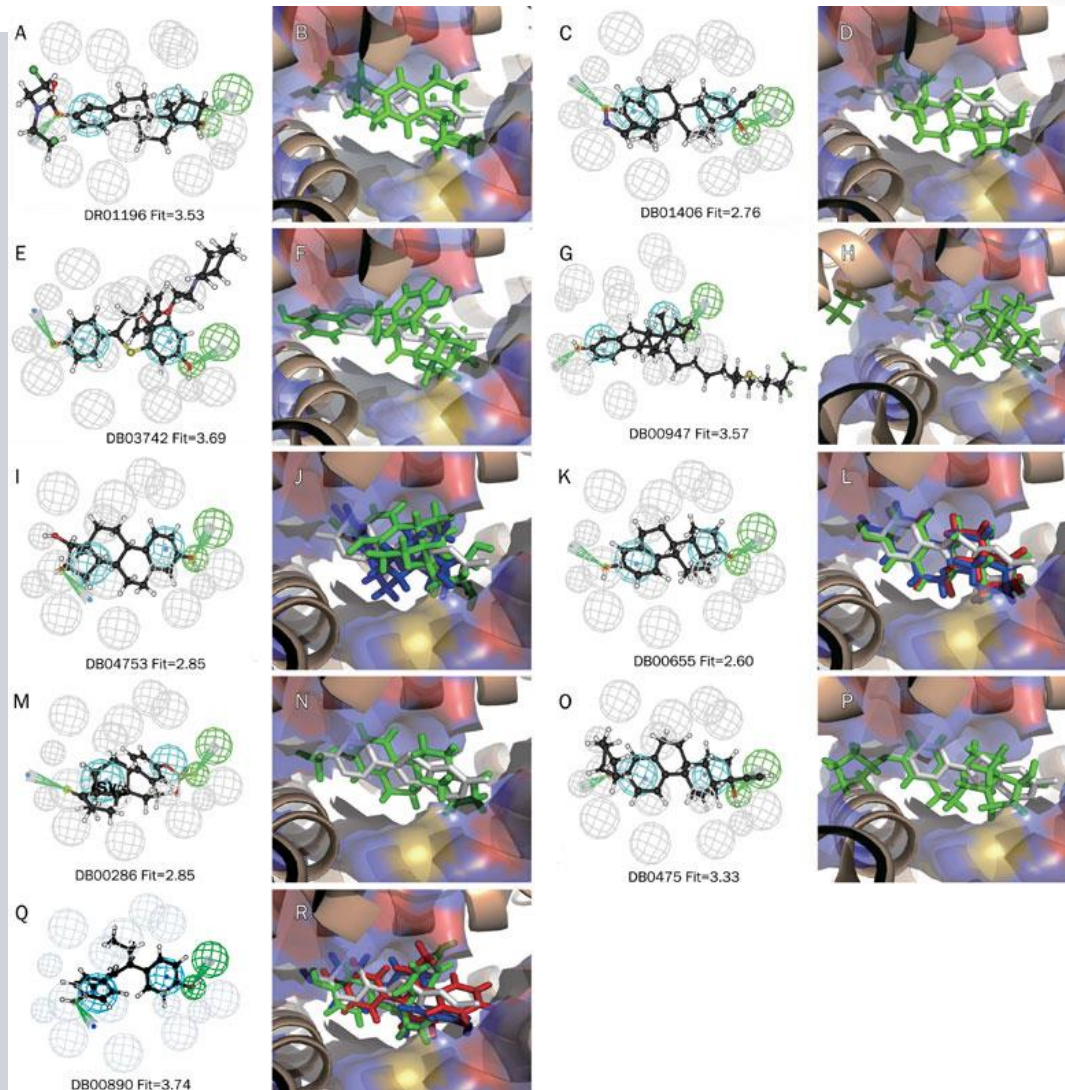
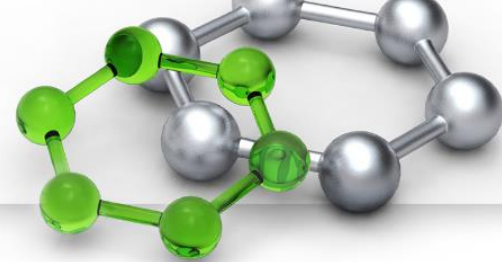
Známé
léky



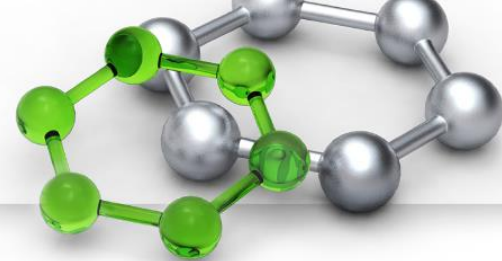
Nově
navržené
léky

Nature Reviews | Drug Discovery

Návrh léku (drug design)



Návrh léku (drug design)

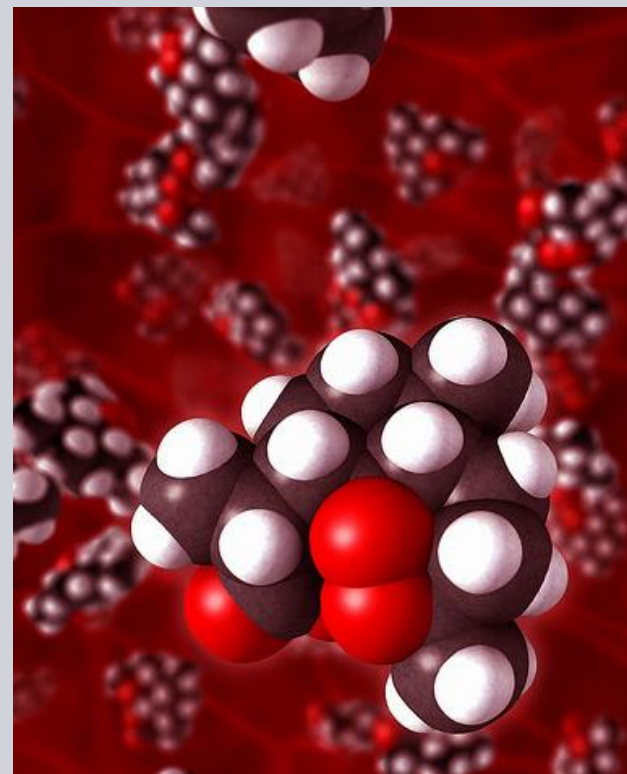


Na základě několika známých molekul léků můžeme vytvořit (ručně nebo automaticky) rozsáhlé sady molekul.

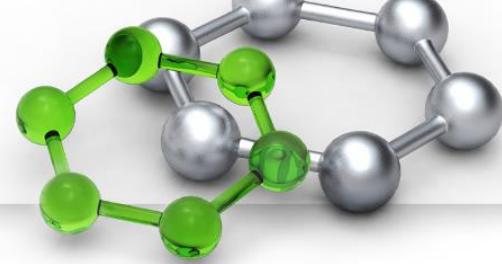
Tyto sady se nazývají virtuální knihovny a obsahují desítky, stovky i miliony molekul.

Několik z molekul ve virtuální knihovně může být velmi účinnými léky.

Ale které to jsou ???



Jak zjistit, která z navržených molekul je lékem?



Navržené molekuly existují jen na papíře nebo v počítači a nebyly zatím syntetizovány.

Nemáme tedy naměřeny jejich fyzikální a chemické vlastnosti ani nevíme nic o jejich aktivitě.

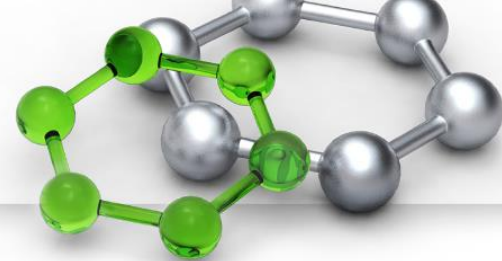
Jak tedy určit, která z nich bude vhodným lékem?

Máme dvě možnosti:

a) Molekuly syntetizovat a jejich vlastnosti i aktivitu změřit.

b) Vlastnosti i aktivitu molekul odhadnout (predikovat) na základě jejich struktury.

Chemoinformatika



Přednáška + praktická cvičení
Prosím, noste si notebooky

Občas nepovinné úkoly – možnost získat procenta navíc

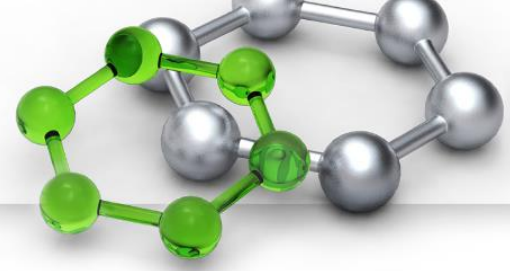
Ukončení předmětu:

Písemka

- Teoretické otázky
- Příklady a cvičení

Povoleny všechny materiály

Organizace výuky 2



Klasifikace:

<100%, 90%>: A

(90%, 80%>: B

(80%, 70%>: C

(70%, 60%>: D

(60%, 50%>: E

(50%, 0%>: F