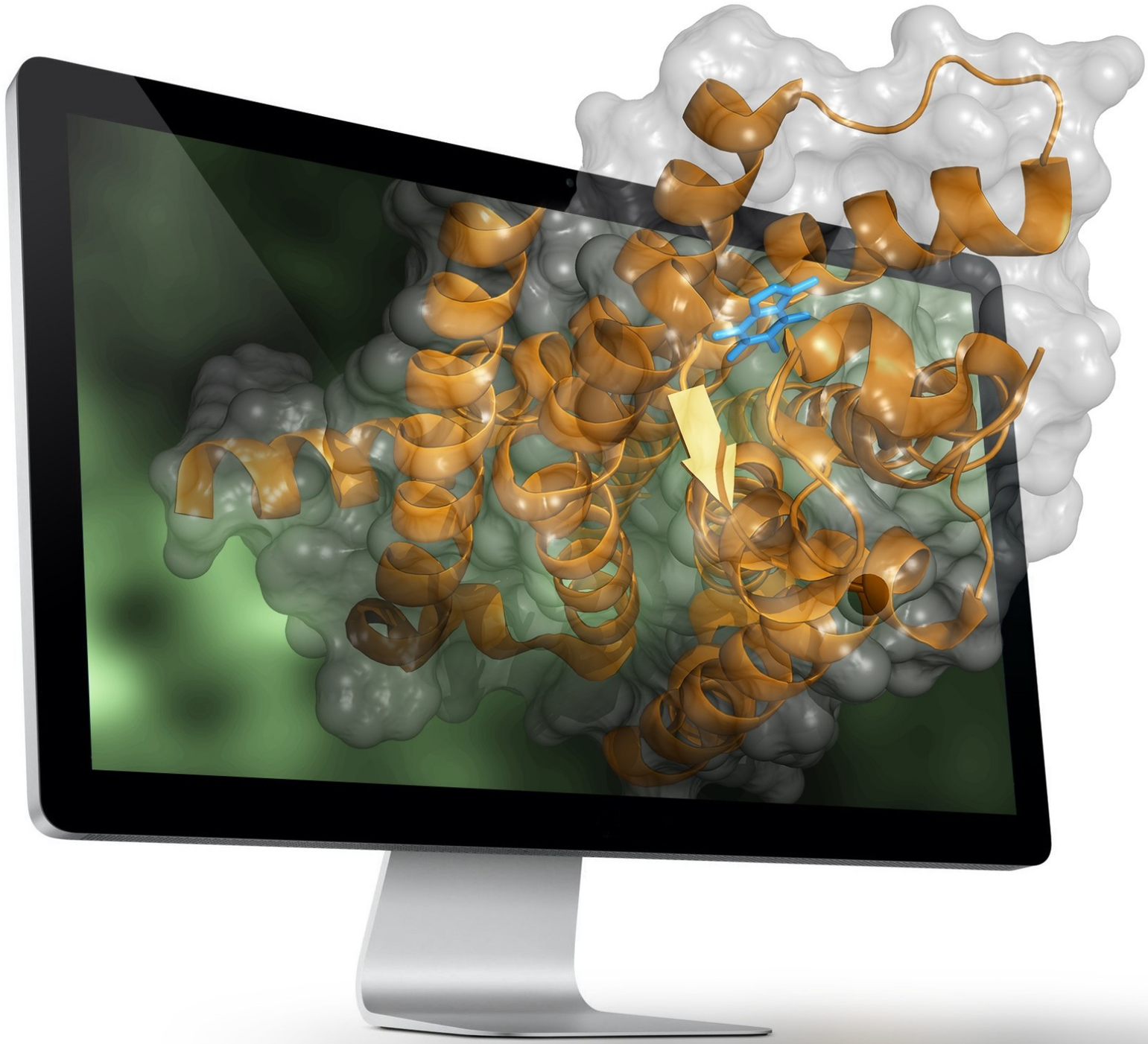


Pokročilá chemoinformatika

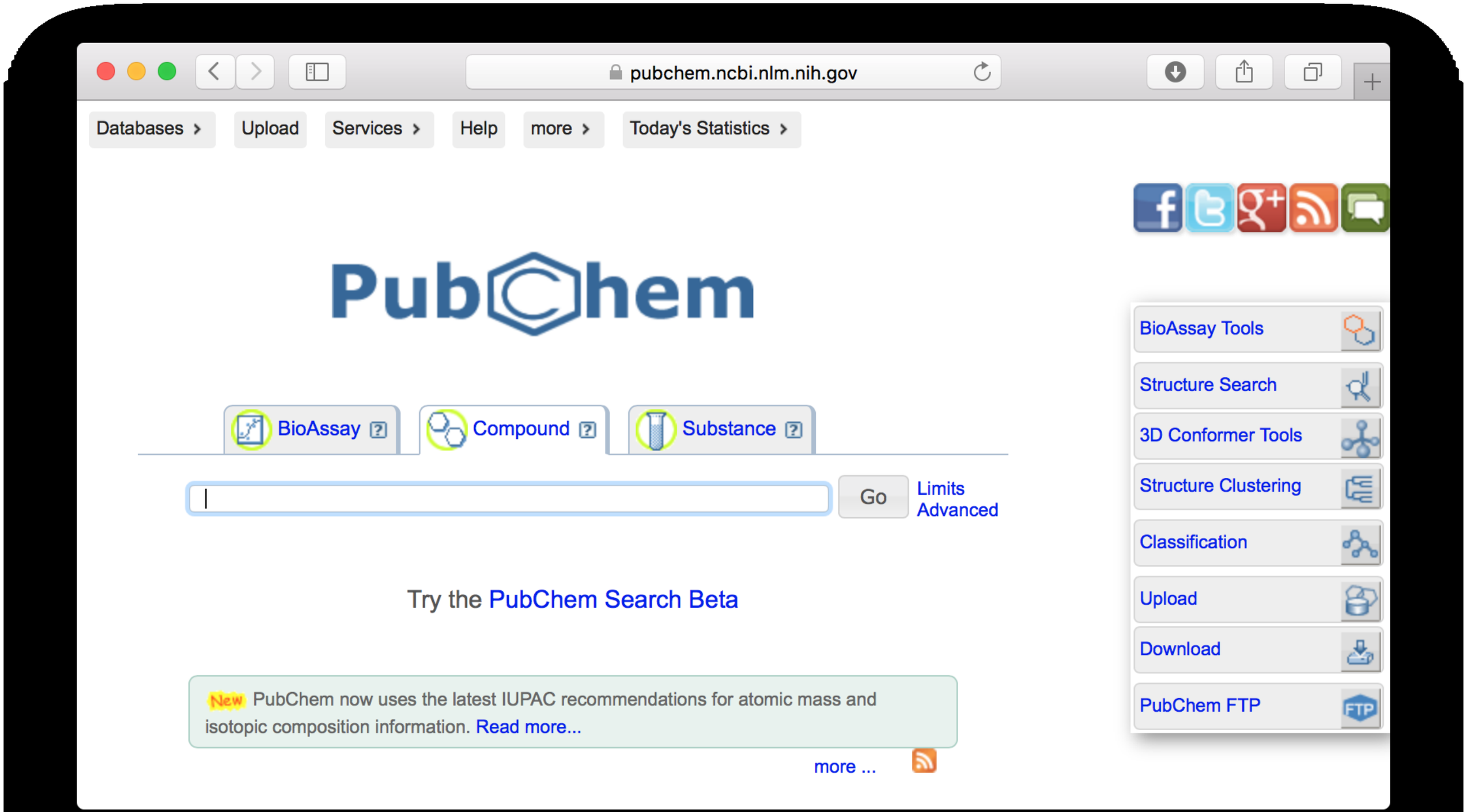
Databáze, chemický prostor
únor 2017

Chemické databáze

Chemické databáze

- Informace o molekulách, struktury molekul, vlastnosti, aktivity, …
- **PubChem**
- **DrugBank**
- **ZINC**
- **ChEMBL**
- **ChemSpider**
- **PHYSPROP**
  http://esc.syrres.com/fatepointer/search.asp

PubChem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Try the PubChem Search Beta
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more ...
BioAssay Tools
Structure Search
3D Conformer Tools
Structure Clustering
Classification
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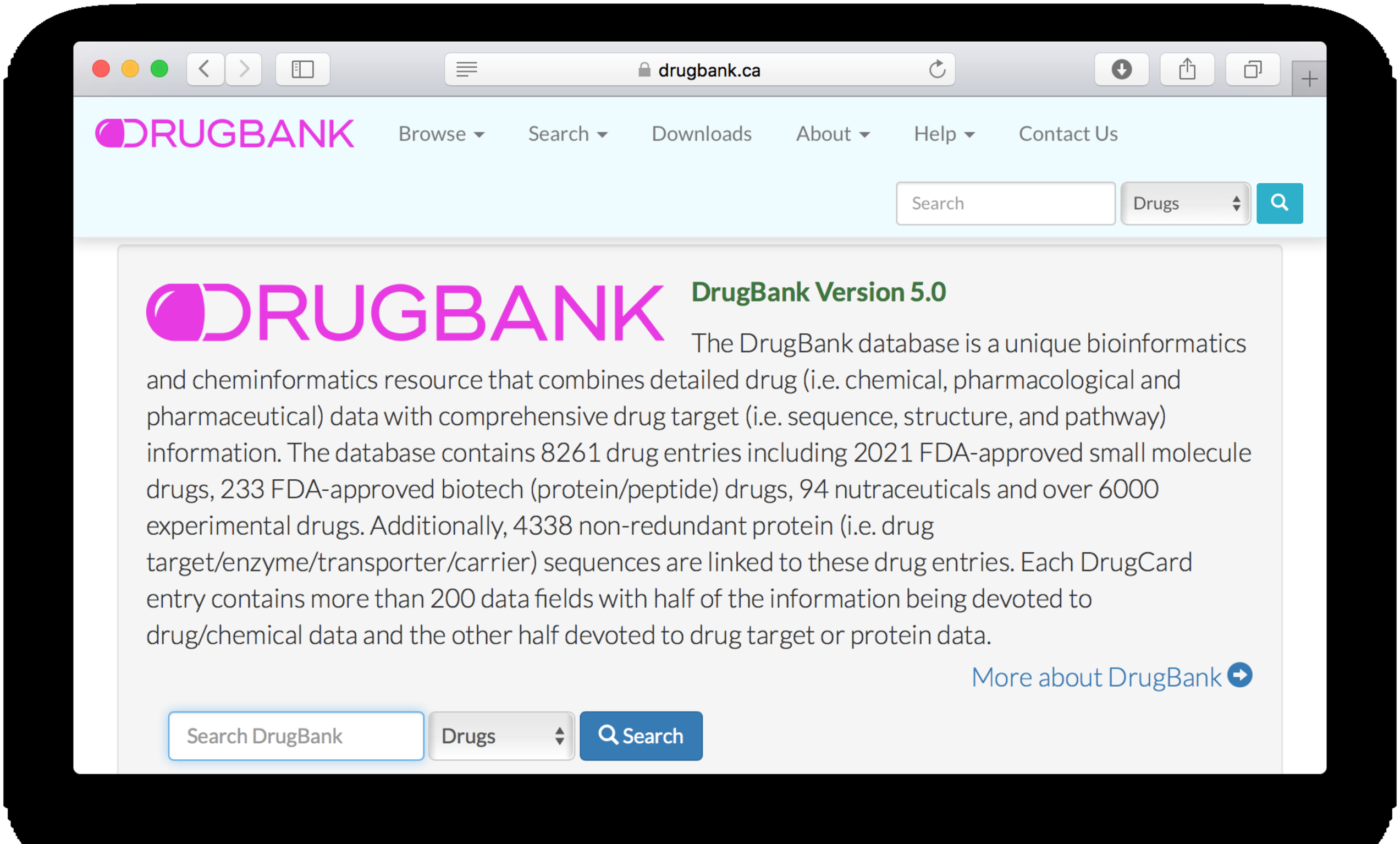
DrugBank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DrugBank Version 5.0
The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information. The database contains 8261 drug entries including 2021 FDA-approved small molecule drugs, 233 FDA-approved biotech (protein/peptide) drugs, 94 nutraceuticals and over 6000 experimental drugs. Additionally, 4338 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.
More about DrugBank
Search DrugBank
Drugs
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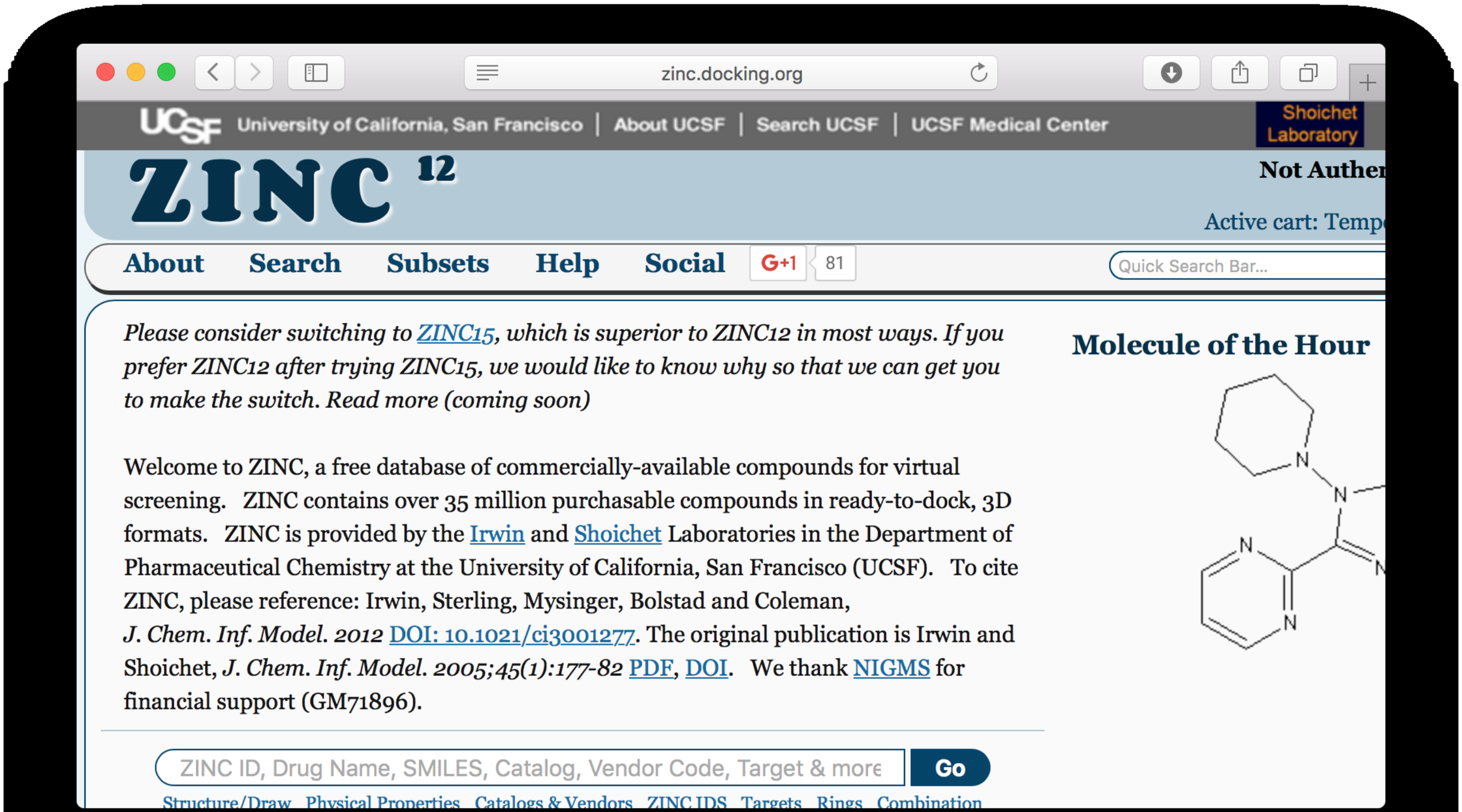
ZINC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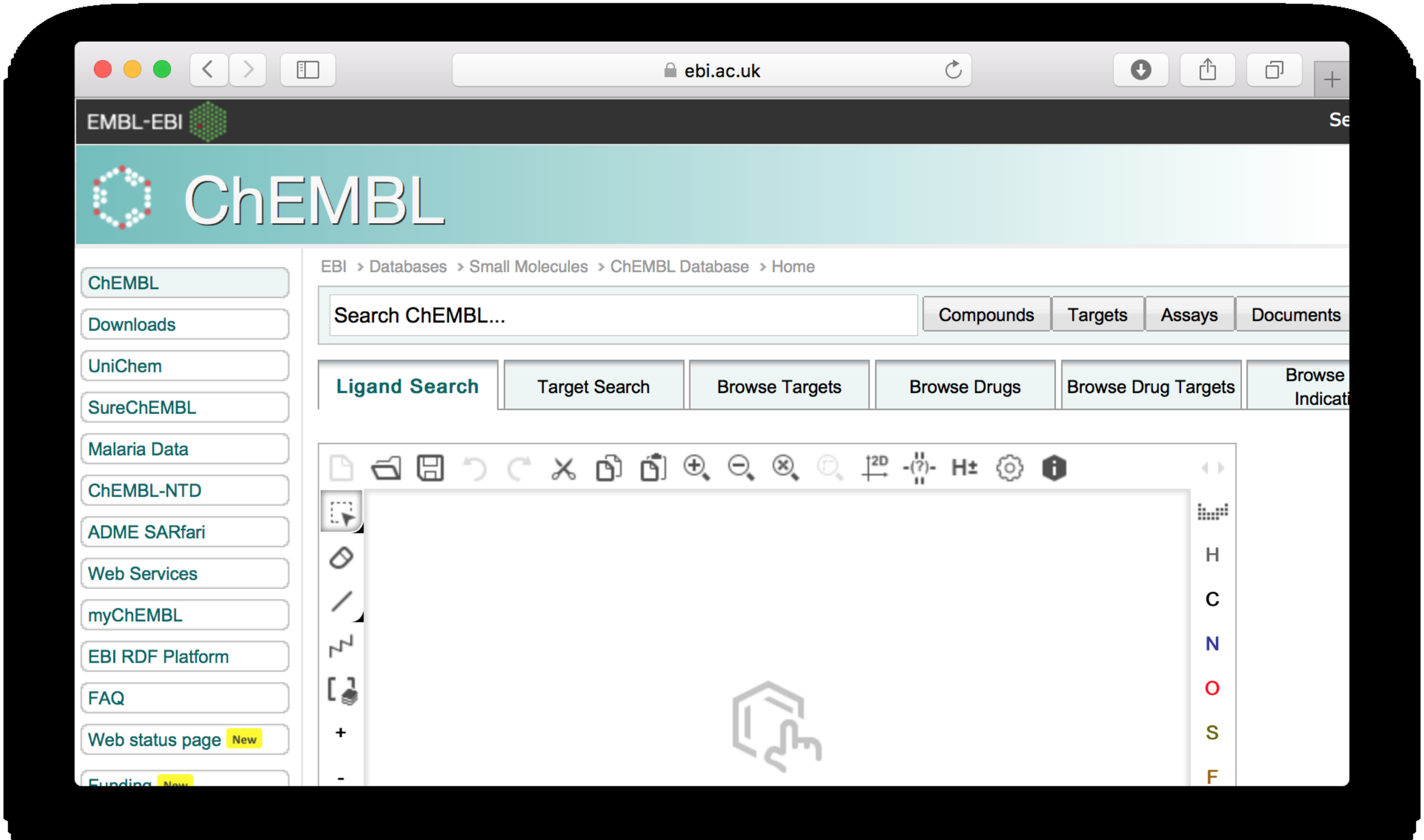
Molecule of the Hour
Welcome to ZINC, a free database of commercially-available compounds for virtual screening. ZINC contains over 35 million purchasable compounds in ready-to-dock, 3D formats. ZINC is provided by the Irwin and Shoichet Laboratories in the Department of Pharmaceutical Chemistry at the University of California, San Francisco (UCSF). To cite ZINC, please reference: Irwin, Sterling, Mysinger, Bolstad and Coleman, J. Chem. Inf. Model. 2012 DOI: 10.1021/ci3001277. The original publication is Irwin and Shoichet, J. Chem. Inf. Model. 2005;45(1):177-82 PDF, DOI. We thank NIGMS for financial support (GM71896).
ZINC ID, Drug Name, SMILES, Catalog, Vendor Code, Target & more
Go
Structure/Draw Physical Properties Catalogs & Vendors ZINC IDS Targets Rings Combination

ChEMBL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Browse Drugs
Browse Drug Targets
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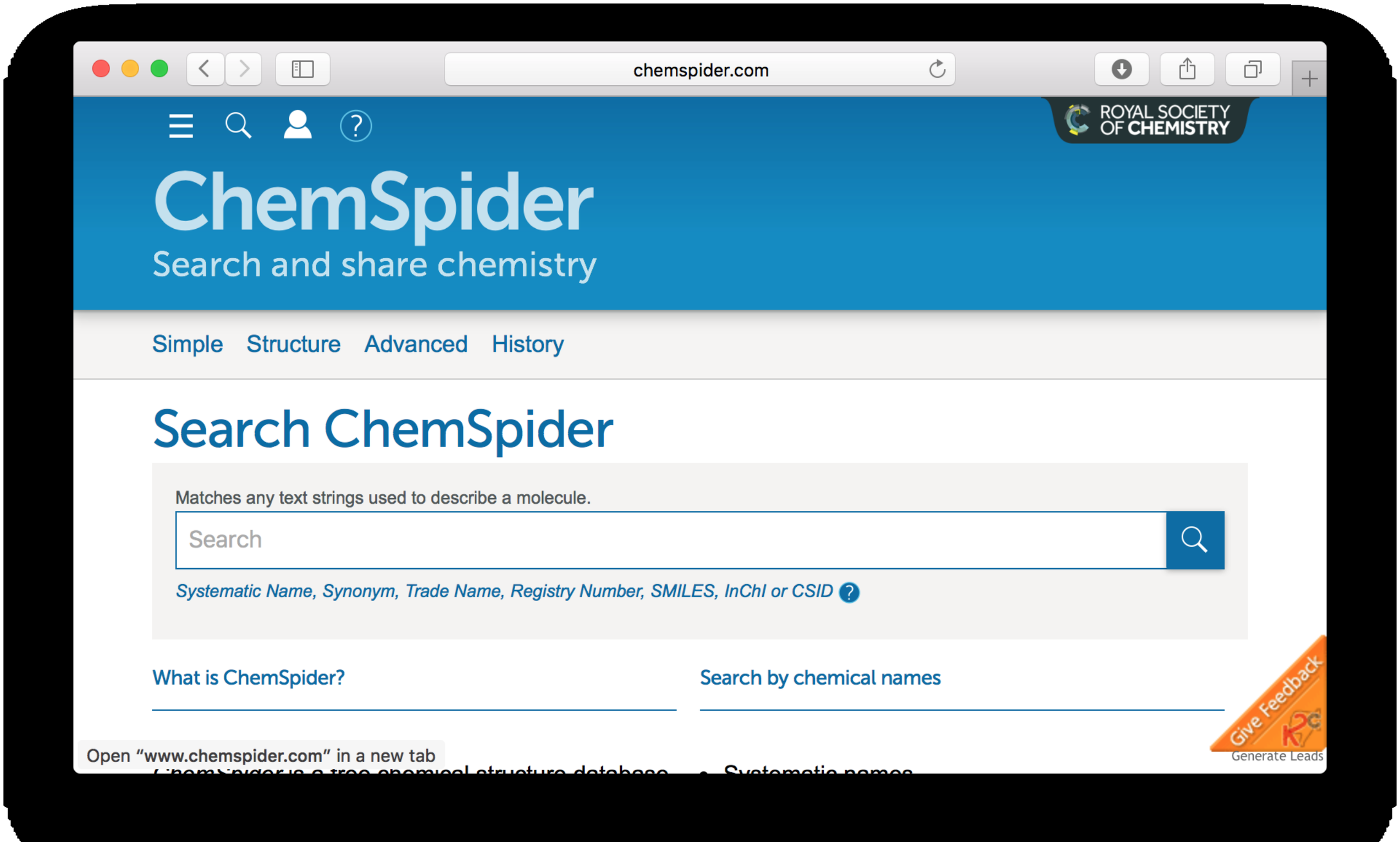
ChemSpider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What is ChemSpider?
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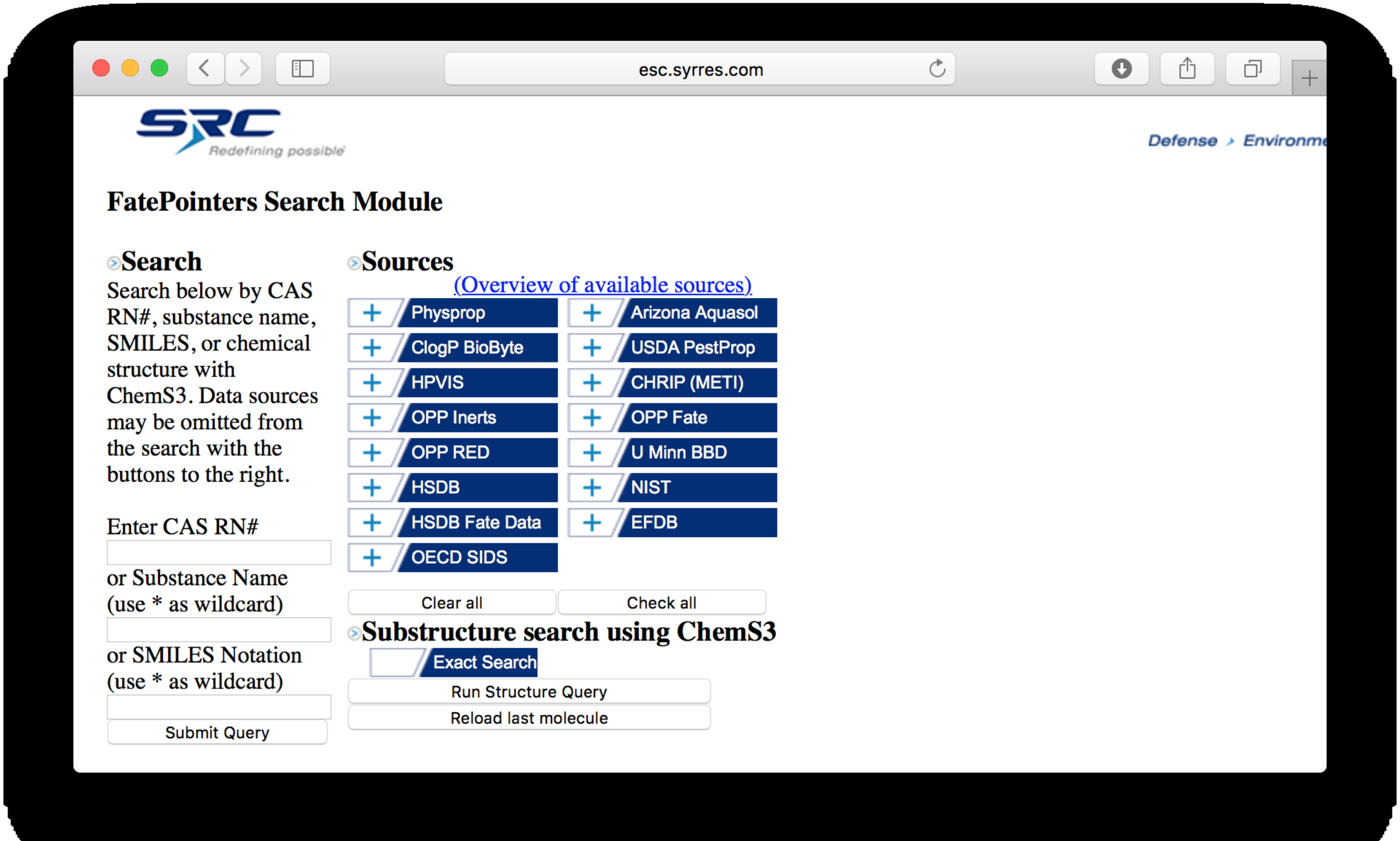
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Enter CAS RN#
or Substance Name (use * as wildcard)
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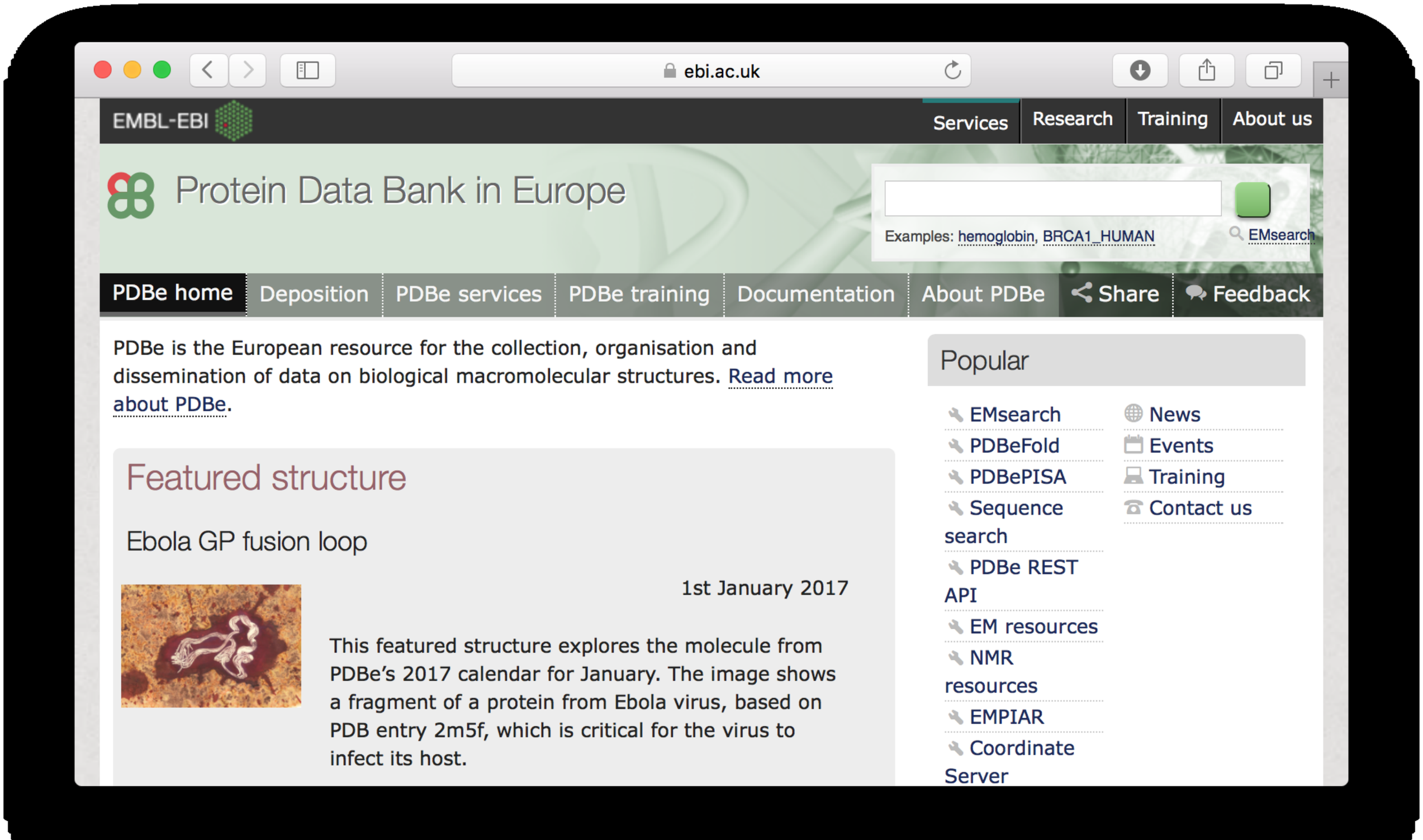
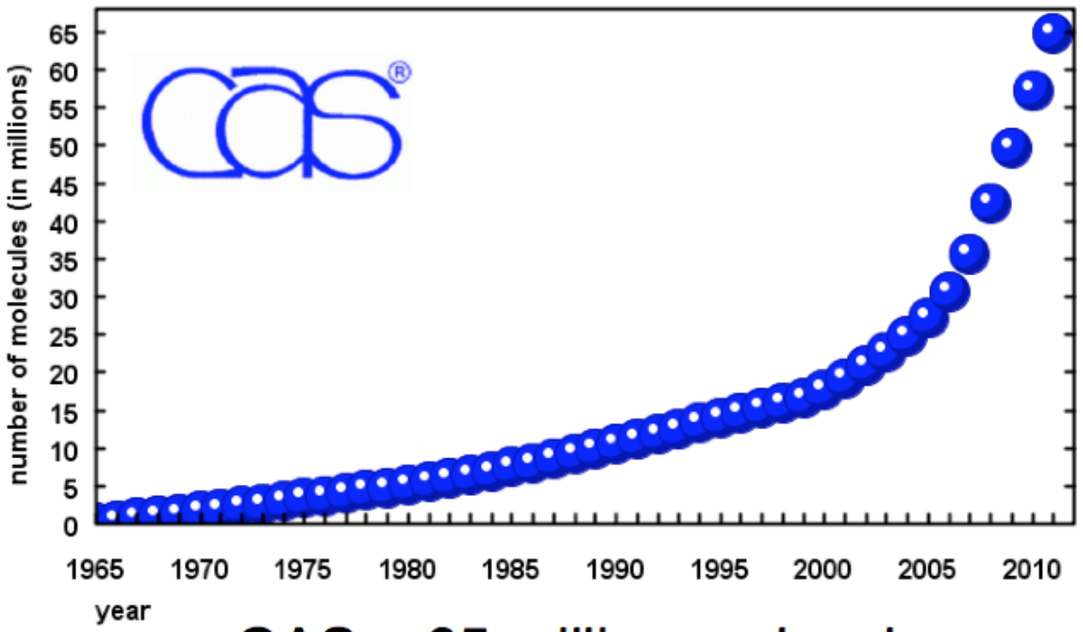
OPP RED
U Minn BBD
HSDB
NIST
HSDB Fate Data
EFDB
OECD SIDS
Clear all
Check all
Substructure search using ChemS3
Exact Search
Run Structure Query
Reload last molecule

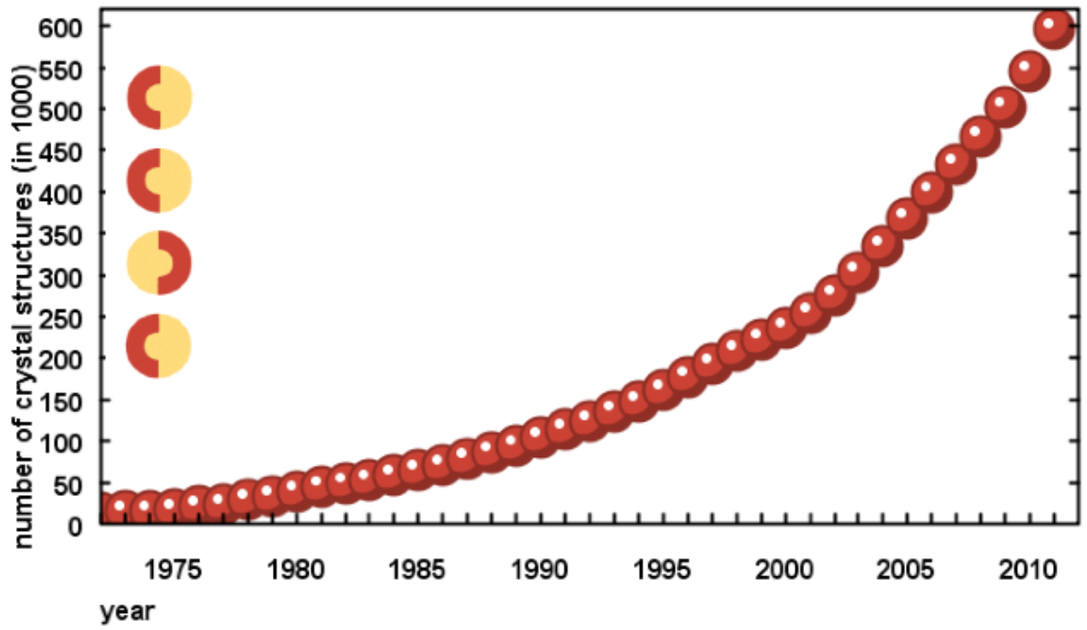
PDB databáze



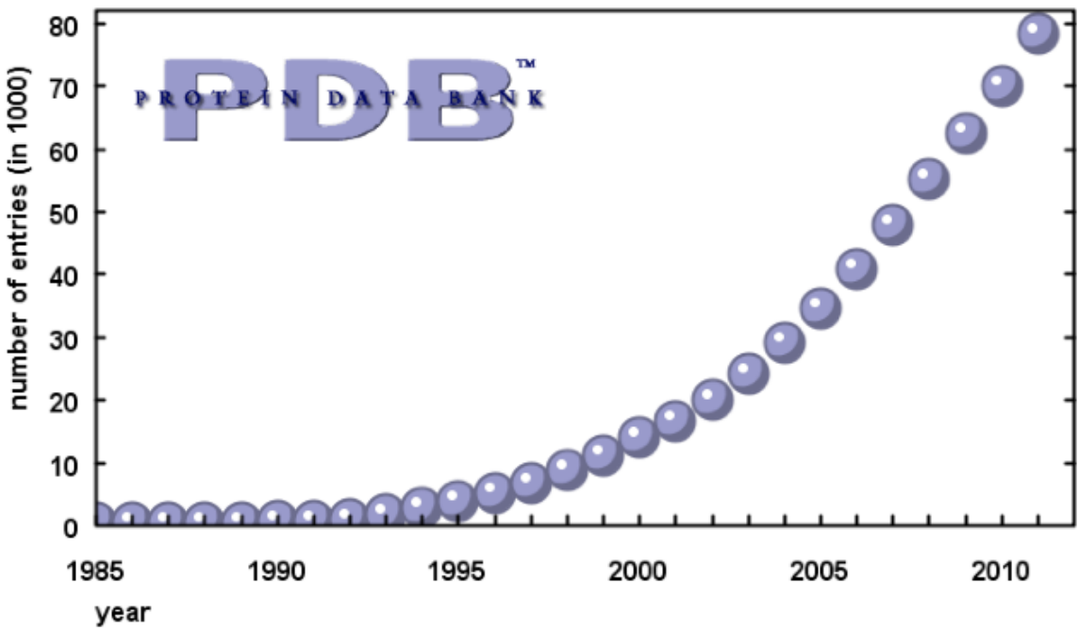
Velikost základních chemických databází



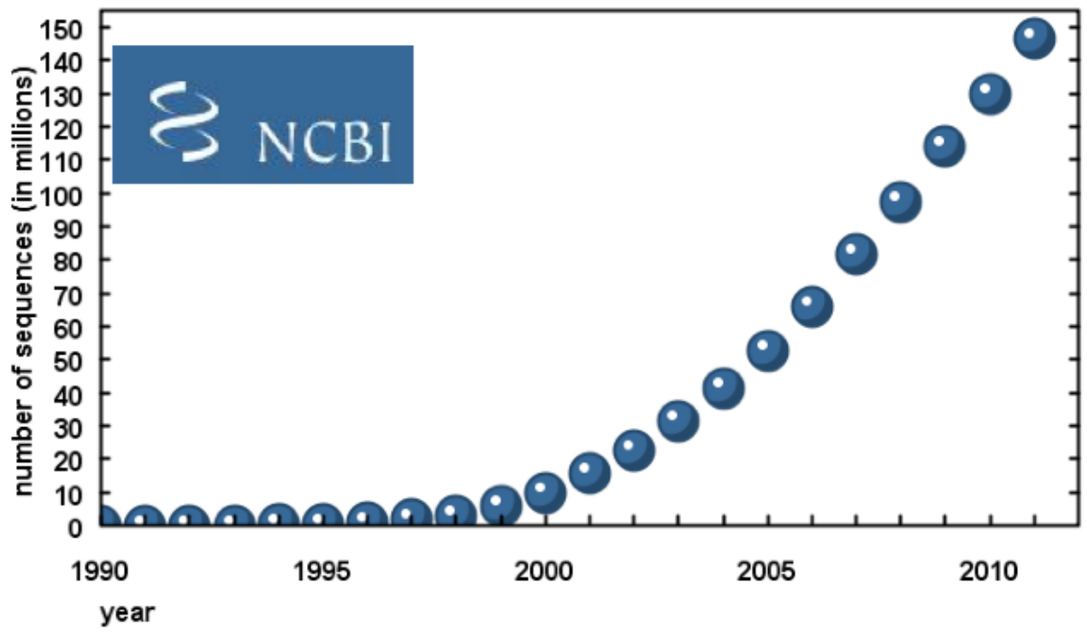
CAS – 65 million molecules



CCDC – 600’000 structures



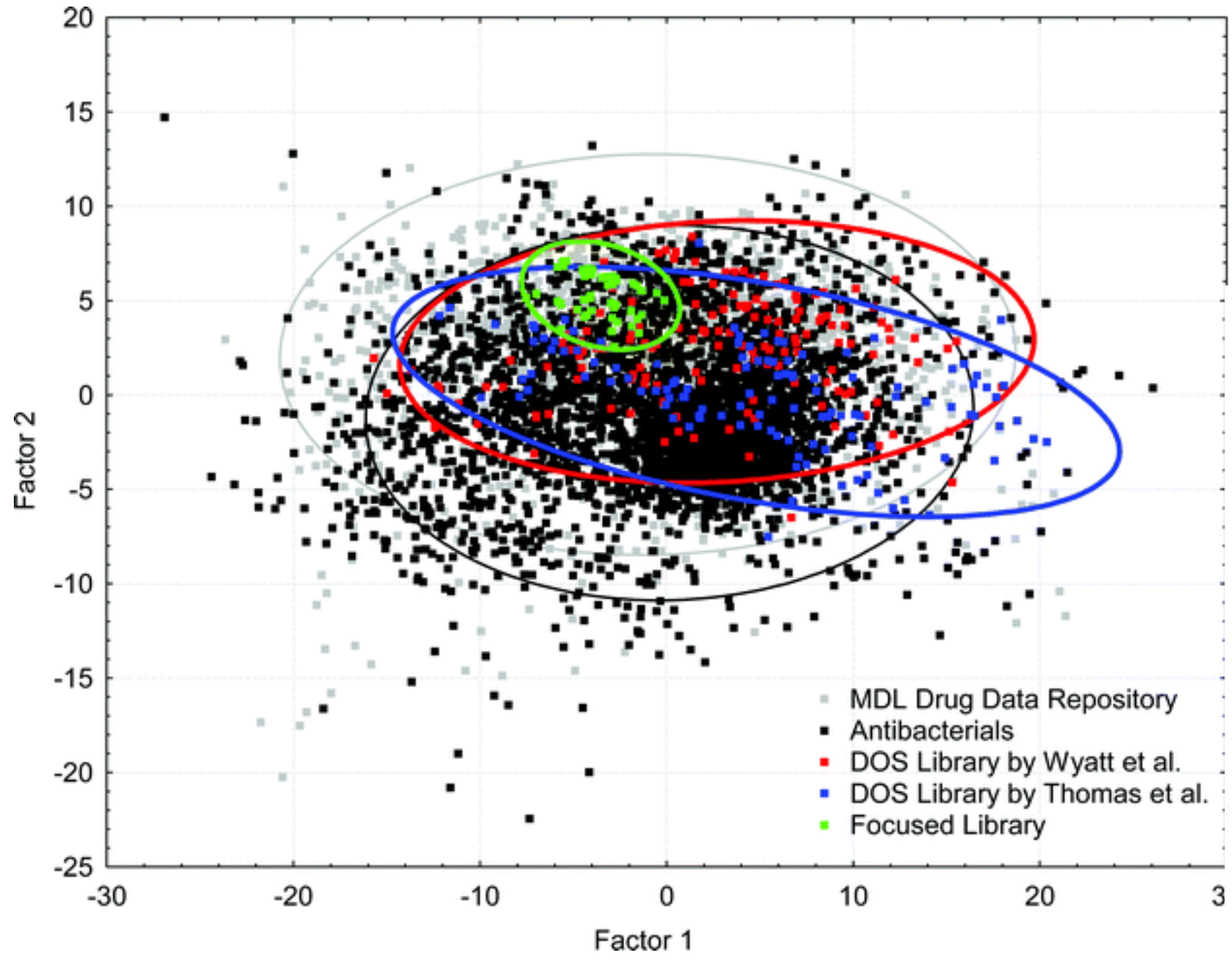
PDB – 78’000 proteins

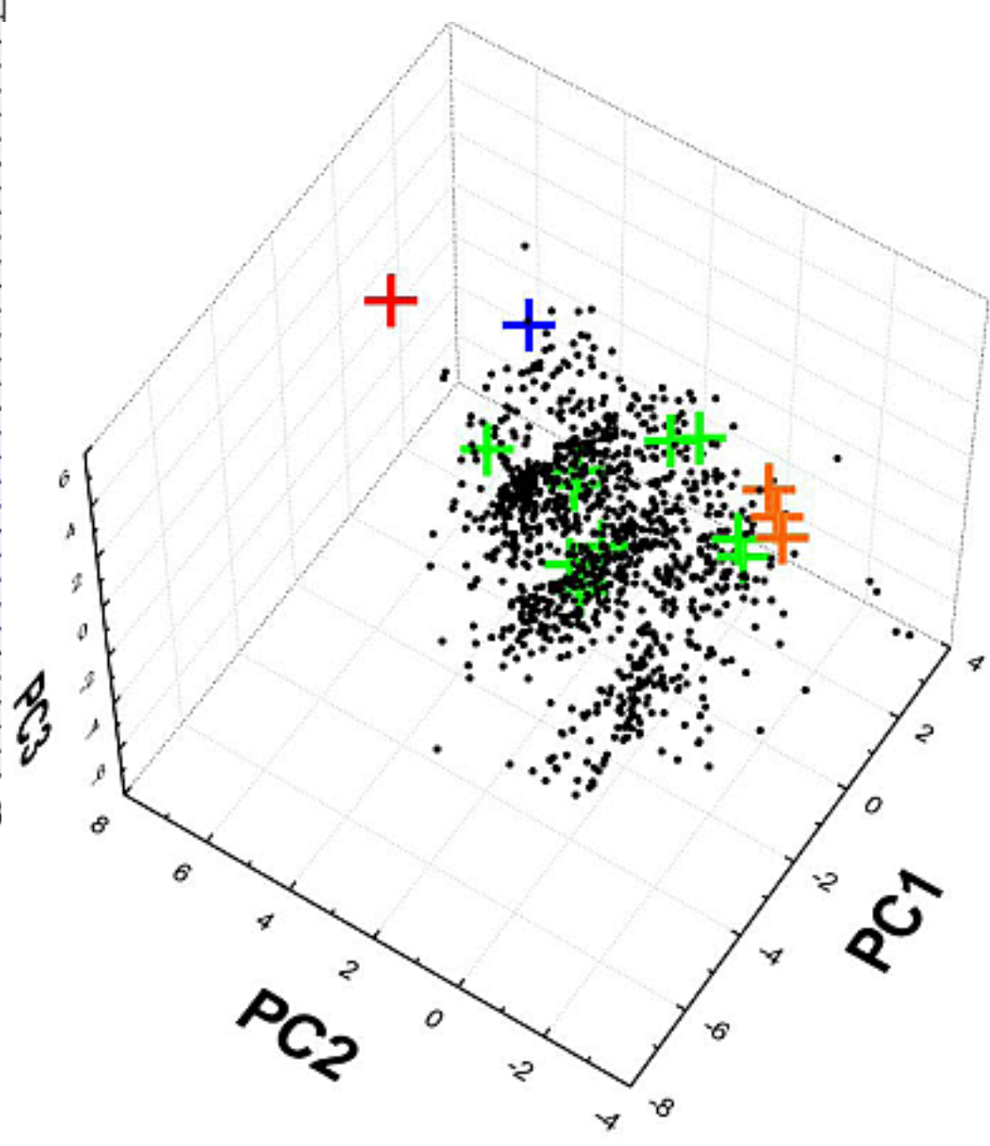


GenBank – 145 million sequences

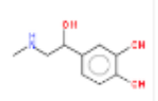
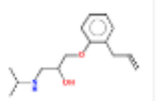
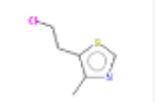
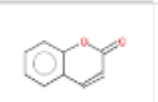
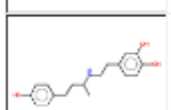
NOVARTIS

Chemický prostor (chemical space)





Práce s chemickým prostorem

Molecule	logP	PSA	natoms	MW	…
	-0.06	72.7	13	183.2	…
	2.58	41.5	18	249.3	…
	2.11	12.9	9	161.6	…
	2.01	20.2	11	146.1	…
	3.31	78.8	30	425.9	…
..					

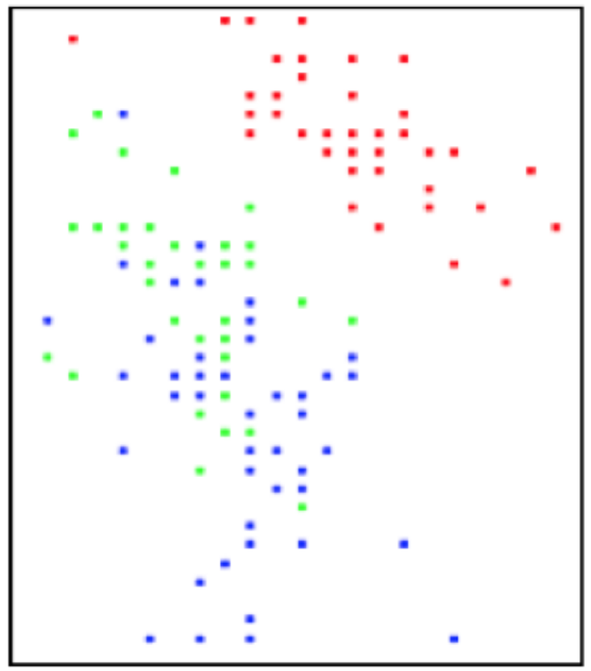


table with properties or fragments

dimensionality reduction

visualization

Formáty pro ukládání chemických, chemoinformatických a bioinformatických dat

Alchemy, Boogie, Cambridge CADPAC, Chem3D Cartesian 1, CSD CSSR, CSD GSTAT, Free Form Fractional, Gaussian Z-Matrix, Hyperchem HIN, Mac Molecule, Micro World, MM2 Ouput, MMADS, MOLIN, Mopac Internal, PC Model, Quanta, Spartan, Spartan Mol, Sybyl Mol2, Maccs 2d, UniChem XYZ, XED, AMBER PREP, Biosym , Cacao Cartesian, CHARMm, Chem3D Cartesian 2, CSD FDAT, Feature, GAMESS Output, Gaussian Output, MDL Isis, Macromodel, MM2 Input, MM3, MDL MOLfile, Mopac Cartesian, Mopac Output, PDB, ShelX, Spartan Semi-Empirical, Sybyl Mol, Conjure, Maccs 3d, XYZ

Formáty pro ukládaní struktury mokul

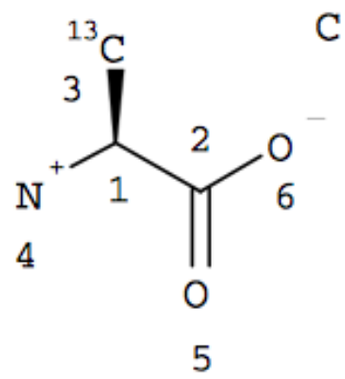
- MOL (V2000, V3000), SDF
  http://c4.cabrillo.edu/404/ctfile.pdf
- MOL2
- PDB, mmCIF
- XYZ
- Smiles a InChI, InChIKey
- ASN.1 (textový a binární formát pro molekuly v PubChemu)

Formáty pro ukládaní informací

- SDF
- csv
- XML

MOL (V2000)

L-Alanine



Chiral

```
  6  5  0  0  1  0              3 V2000
   -0.6622    0.5342    0.0000 C   0  0  2  0  0  0
    0.6622   -0.3000    0.0000 C   0  0  0  0  0  0
   -0.7207    2.0817    0.0000 C   1  0  0  0  0  0
   -1.8622   -0.3695    0.0000 N   0  3  0  0  0  0
    0.6220   -1.8037    0.0000 O   0  0  0  0  0  0
    1.9464    0.4244    0.0000 O   0  5  0  0  0  0
  1  2  1  0  0  0
  1  3  1  1  0  0
  1  4  1  0  0  0
  2  5  2  0  0  0
  2  6  1  0  0  0
M  CHG  2   4   1   6  -1
M  ISO  1   3  13
M  END
```

Blocks not used in this Ctab: Atom List, Stext

Counts Line

Atom Block

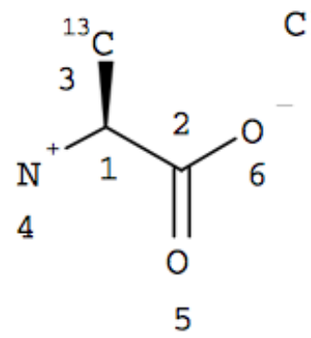
Bond Block

Properties Block

Connection Table (Ctab)

MOL (V3000)

L-Alanine



Chiral

```
L-Alanine
GSMACCS-II07189510252D 1   0.00366     0.00000     0
Figure 1, J. Chem. Inf. Comput. Sci., Vol 32, No. 3., 1992
  0  0  0     0  0            999 V3000
M  V30 BEGIN CTAB
M  V30 COUNTS 6 5 0 0 1
M  V30 BEGIN ATOM
M  V30 1 C -0.6622 0.5342 0 0 CFG=2
M  V30 2 C 0.6622 -0.3 0 0
M  V30 3 C -0.7207 2.0817 0 0 MASS=13
M  V30 4 N -1.8622 -0.3695 0 0 CHG=1
M  V30 5 O 0.622 -1.8037 0 0
M  V30 6 O 1.9464 0.4244 0 0 CHG=-1
M  V30 END ATOM
M  V30 BEGIN BOND
M  V30 1 1 1 2
M  V30 2 1 1 3 CFG=1
M  V30 3 1 1 4
M  V30 4 2 2 5
M  V30 5 1 2 6
M  V30 END BOND
M  V30 END CTAB
M  END
```

Header Block

Comment Line

Counts Line

Atom Block

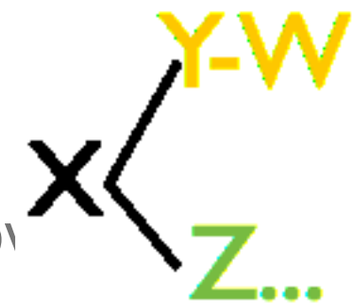
Bond Block

Connection Table (Ctab)

Blocks not used in this Ctab:
Sgroup block, Rgroup block, 3D block

Simplified molecular-input line-entry system SMILES

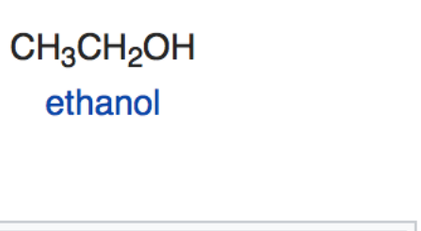
- vodíky (které mohou být snadno dopočítány, například v alkanech) se v notaci vynechávájí a dopočítávají se
- atomy jdoucí za sebou jsou spojeny jednoduchou vazbou
  příklady: C (metan), CC (ethan), ..., CO (H_3COH, methanol)
- dvojná vazba je znázorněna “=” a trojná “#”
  příklady: C=C (ethen), C=O (formaldehyd), C#C (ethyn), C#N (kyano



- pomocí závorek “()” znázorňujeme větvení
  X(YW)Z... - na X je jednoduchou vazbou navázano Y a Z, Y a W jsou spojeny jednoduchou vabou, mezi Y nebo W a Z není žádná vazba
  příklady: CC(CC)CCC (2-ethylpentan), CC(Cl)C (2-chloropropan), CC(=O)C (aceton)
- pomocí čísel jsou označovány kruhy: C1 .... C1 (začátek a konec kruhu)
  příklady: C1CCCCC1 (cyklohexan), C1OC1 (oxiran)
- malými písmeny označujeme aromatické atomy
  příklady: c1ccccc1 (benzen), n1ccccc1 (pyridin)
- [NH] explicitně vyjadřený vodík, [O-] vyjádřený ion, [C@@H] vyznačená chiralita, ...
- tutoriál v angličtině:

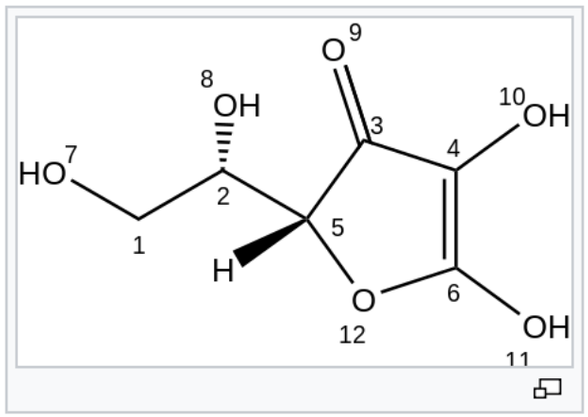
International Chemical Identifier
InChI & InChIKey

- Podobně jako SMILES se jedná o textový zápis molekuly, který se skládá z několika vrstev, které nemusí být vždy všechny zastoupeny



`InChI=1/C2H6O/c1-2-3/h3H,2H2,1H3`

`InChI=1S/C2H6O/c1-2-3/h3H,2H2,1H3` (standard InChI)



L-ascorbic acid

`InChI=1/C6H8O6/c7-1-2(8)5-3(9)4(10)6(11)12-5/h2,5,7-10H,1H2/t2-,5+/m0/s1`

`InChI=1S/C6H8O6/c7-1-2(8)5-3(9)4(10)6(11)12-5/h2,5,7-8,10-11H,1H2/t2-,5+/m0/s1` (standard InChI)

- INCHIkey je pak hash INChI
  z InChIKey nelze zpětně vytvořit InChI!

Nástroje pro práci se strukturami molekul

OpenBabel

- Chemoinformatický nástroj pro práci s různými formáty molekul a dalšími pomocnými nástroji

- https://openbabel.org

- *Pro práci na wolfech použijte:*
  module add openbabel

OpenBabel - konverze různých formatů

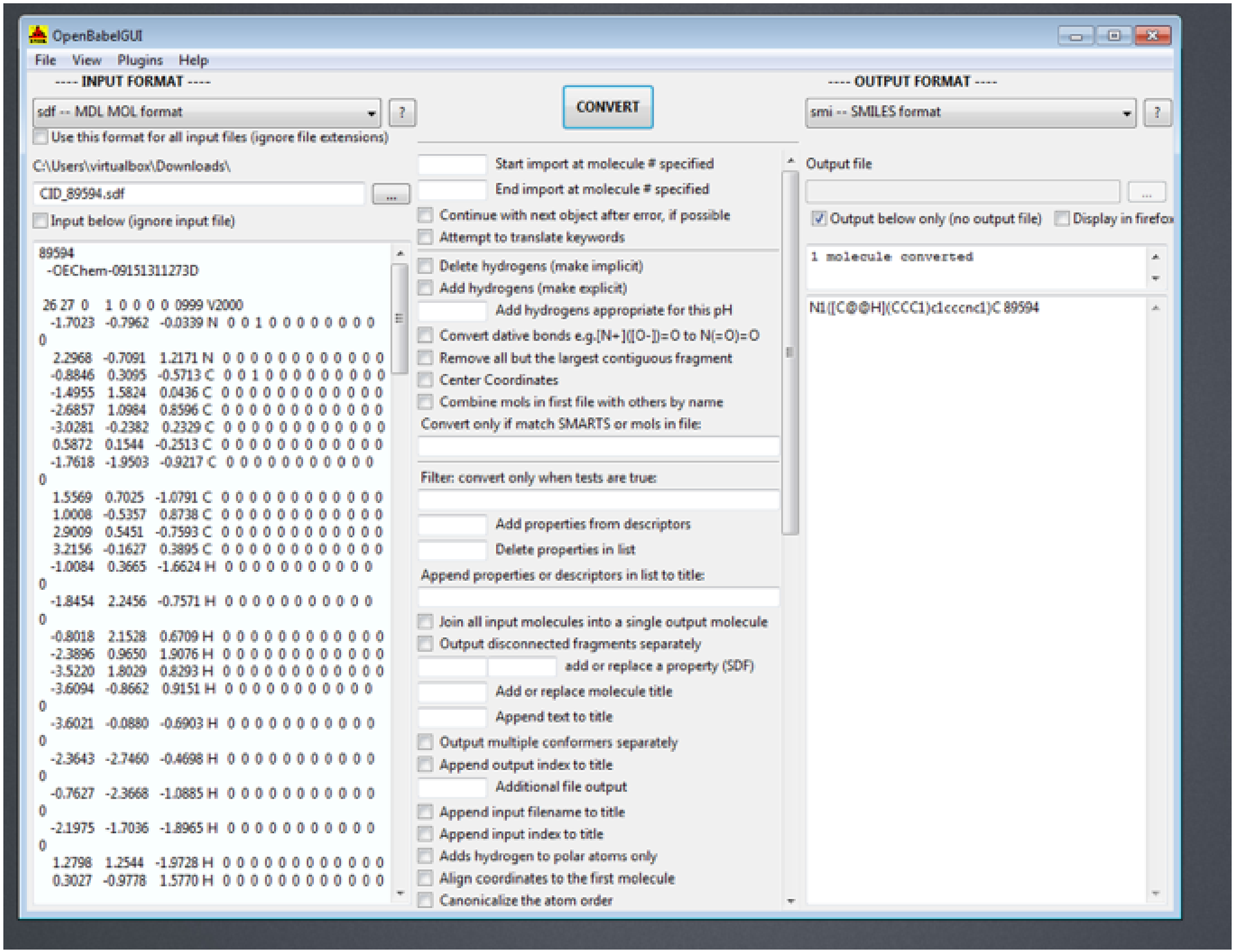
- Spouštíme v příkazové řádce pomocí
  obabel nebo babel

- Seznam podporovaných formátů
  babel –L formats

- Převod struktury mezi různými formáty (2.31)
  obabel –i**xxx** molecule.**xxx** –o**yyy** -O molecule.**yyy**
  kde **xxx** je vstupní a **yyy** je výstupní format molekuly

- Převod struktury mezi různými formáty (<2.31)
  obabel –i**xxx** molecule.**xxx** –o**yyy** molecule.**yyy**

OpenBabel - konverze různých formatů (windows)



OpenBabel – přiložení dvou struktur

- Spouštíme v příkazové řádce pomocí
  obfit

- program obfit potřebuje celkem 3 parametry, vzor, podle kterého bude přikládat (SMILES) a dvě struktury, první zafixuje a druhou se snaží hýbat

- obfit “N1([C@@H](CCC1)c1cccnc1)C” CID_89594.sdf zinc_1798.sdf

Fingerprinty a podobnost

Podobnostní hledání

Fingerprint

- Binární data informující o výskytu nějaké konkretní skupiny
- 10010001010011110101001010001 …
- Příklad z openBabelu:

```
>3rfm.pdb   256 bits set
0407002a 81807e18 60180100 47910f50 041c12c0 0200c110
0200a020 2000200c 86600b80 820f4be2 2c30800c 5007b800
1e01983e 01542801 853a00c0 001c000c 14801000 0e088001
00e02418 404e2301 e0000d40 383d8e78 238007c3 9770001c
00043801 c0a00200 68120600 10040100 0c004016 0046803b
e00c4200 23c12ea0
```

Podobnost/vzdálenost

		molekula B		
		0	1	celkem
molekula A	0	*d*	*b*	*b + d*
	1	*a*	*c*	*a + c = A*
	celkem	*a + d*	*c + b = B*	*n*

a je počet „1“, které má molekula A, ale které zároveň nemá molekula B
b je počet „1“, které má molekula B, ale které zároveň nemá molekula A
c je počet „1“, které má molekula A a které má zároveň i molekula B
d je počet „0“, které má molekula A a které má zároveň i molekula B

n je počet dvojnásobný počet fragmentů, platí n = a + b + c + d
A je celkový počet „1“ v molekule A
B je celkový počet „1“ v molekule B

Podobnostní koeficienty

Table II - Similarity coefficients studied.

Coefficients	Similarity expression	Source
1. Simple matching (SM)	$\frac{a+d}{a+b+c+d}$	Sokal and Michener, 1958
2. Rogers and Tanimoto (RT)	$\frac{a+d}{a+2b+2c+d}$	Rogers and Tanimoto, 1960
3. Anderberg (A)	$\frac{a}{a+2(b+c)}$	Anderberg, 1973
4. Russel and Rao (RR)	$\frac{a}{a+b+c+d}$	Russel and Rao, 1940
5. Jaccard (J)	$\frac{a}{a+b+c}$	Jaccard, 1901
6. Sorensen-Dice (SD)	$\frac{2a}{2a+b+c}$	Dice, 1945; Sorensen, 1948
7. Ochiai (O)	$\frac{a}{\sqrt{(a+b)(a+c)}}$	Ochiai, 1957
8. Ochiai II (OII)	$\frac{ad}{\sqrt{[(a+b)][a+c][d+b][d+c]}}$	Ochiai, 1957

Podobnostní hledání v OpenBabelu

- `babel mysmiles.smi mymols.sdf -ofpt`

```
MOL_00000067 Tanimoto from first mol = 0.0888889
MOL_00000083 Tanimoto from first mol = 0.0869565
MOL_00000105 Tanimoto from first mol = 0.0888889
MOL_00000296 Tanimoto from first mol = 0.0714286
MOL_00000320 Tanimoto from first mol = 0.0888889
MOL_00000328 Tanimoto from first mol = 0.0851064
MOL_00000338 Tanimoto from first mol = 0.0869565
MOL_00000354 Tanimoto from first mol = 0.0888889
MOL_00000378 Tanimoto from first mol = 0.0816327
MOL_00000391 Tanimoto from first mol = 0.0816327
11 molecules converted
```

Podobnostní hledání v PubChemu