PSF Project 2017-2018

MMS VirtualLAB

UNIVERSITÀ DEGLI STUDI DI PADOVA

Molecular Modeling Section (MMS) – Dip. Scienze del Farmaco

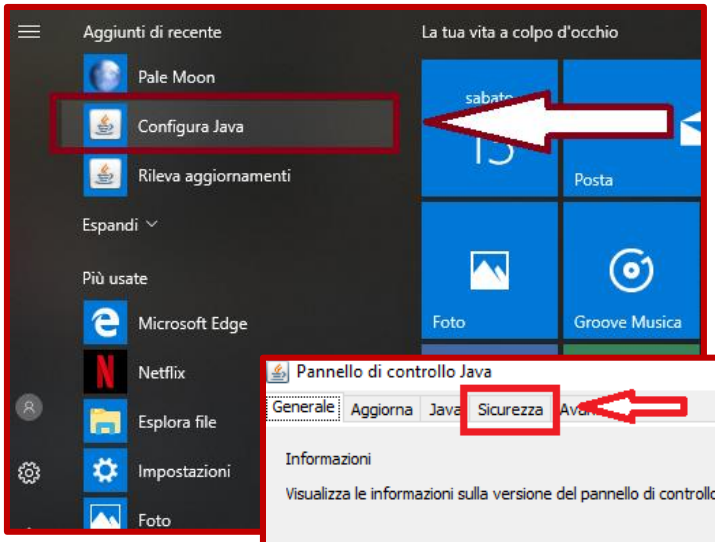
Some tricks for a better work experience:

1. Make sure you have installed **JAVA** on your laptop, otherwise download it from

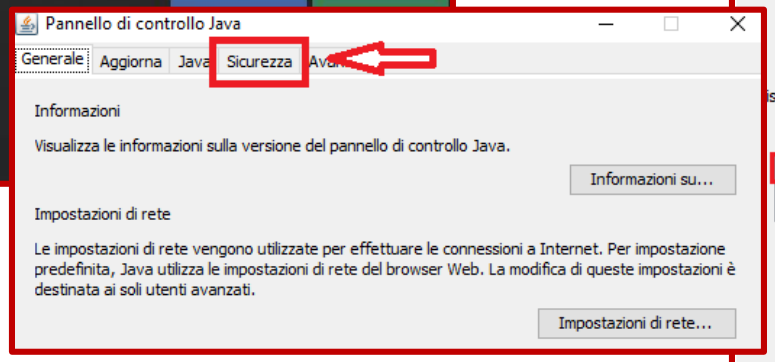
https://java.com/it/download/

Enter on Java control panel and add MMS webpage (http://147.162.61.130/) to the exception site list.

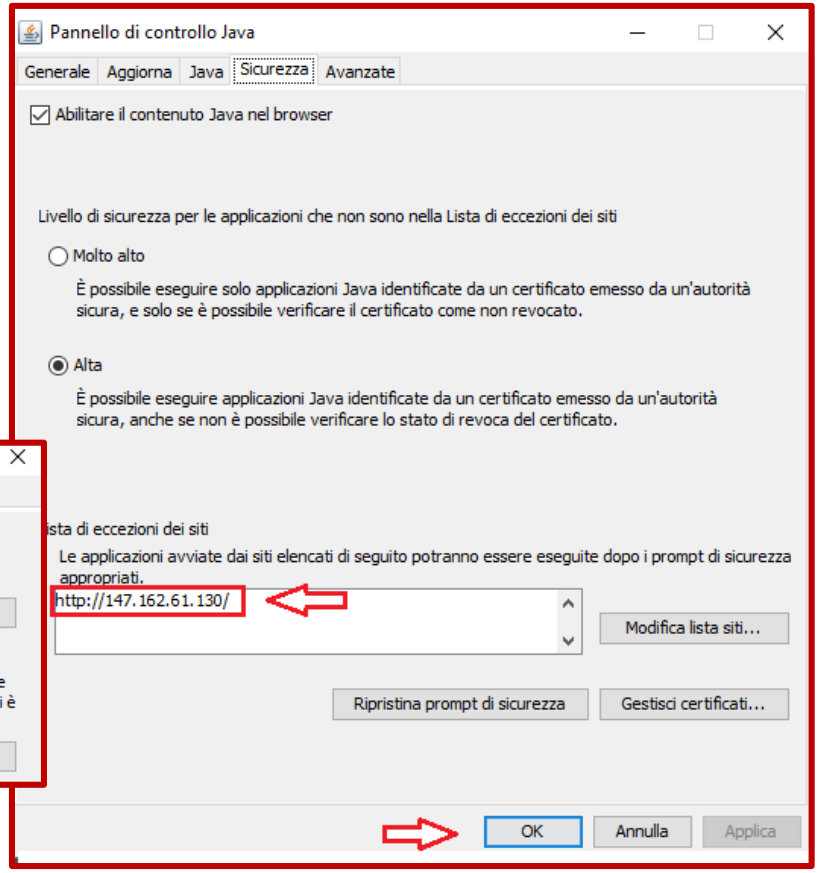
1



2



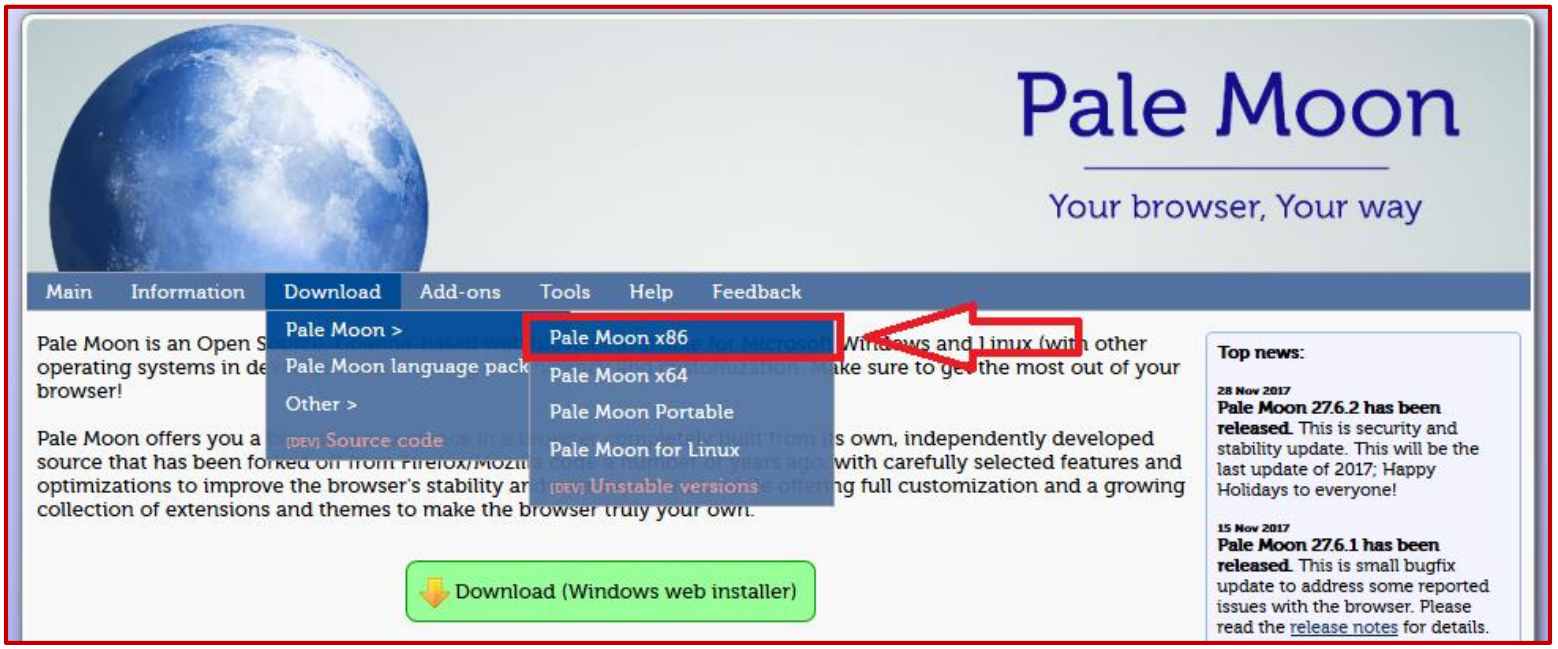
3



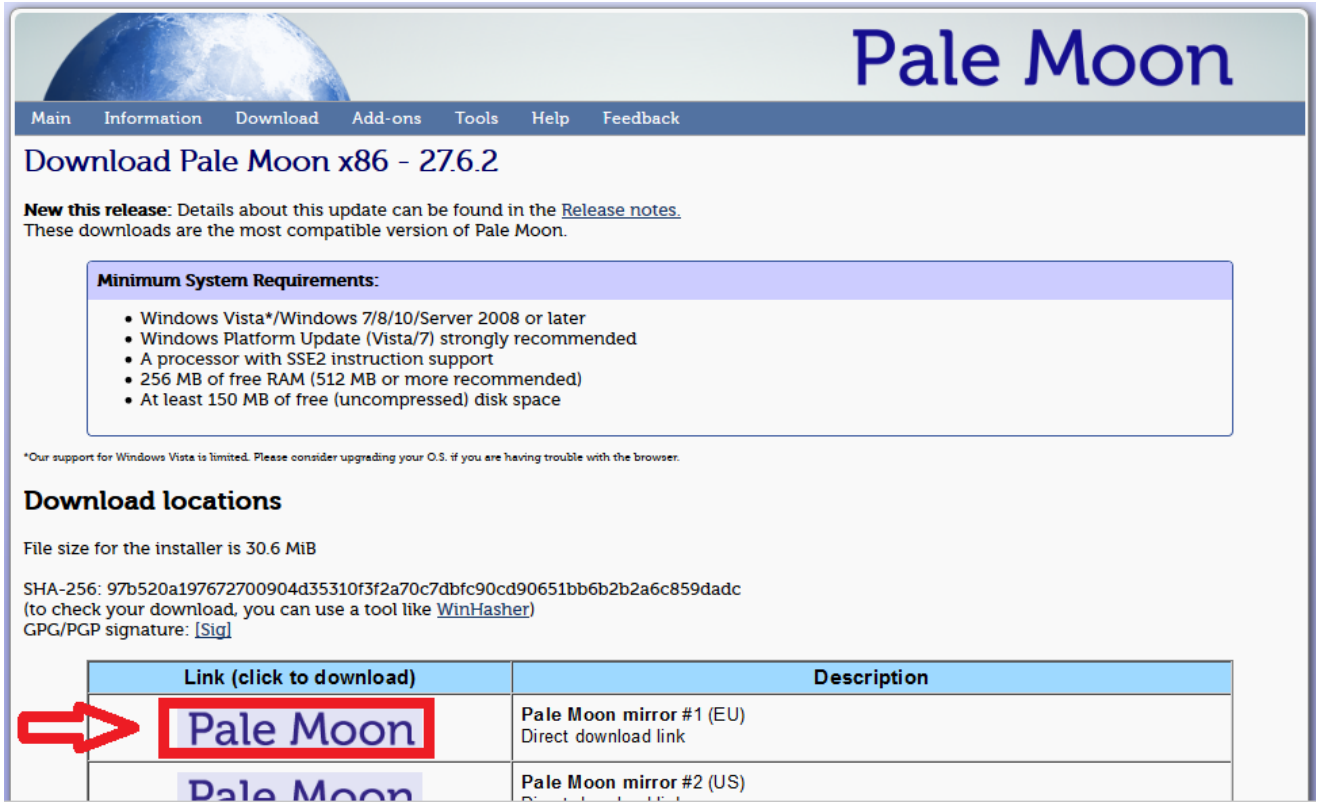
Some tricks for a better work experience:

2. Install a new browser that supports java plugin, tool to be used only for this project

https://www.palemoon.org/



To ensure the highest compatibility with JAVA pluings pay attention to install 32bit (x86) version of Pale Moon browser



Support

- For more detail, look both the “Project Aims” and the “Tutorials” sections in

  http://mms.dsfarm.unipd.it/psfetutorials.html

- For any further doubts, please contact us:

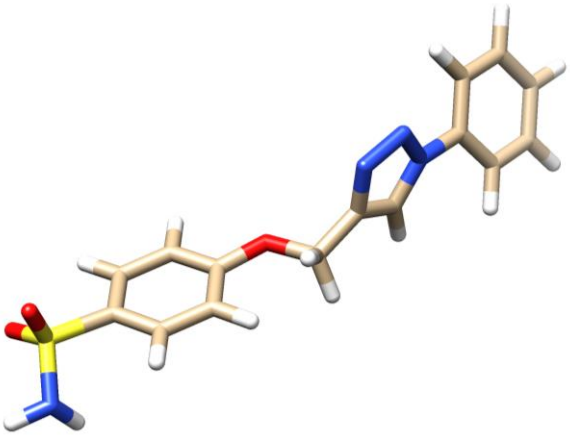
  - maicol.bissaro@phd.unipd.it
  - enrico.margiotta@phd.unipd.it
  - veronica.salmaso@studenti.unipd.it

or **visit** us in our lab . . .

Enjoy your MMSeLAB!

Target

A preview of our PSF 2016/2017 running project: CARBONIC ANHYDRASE II



SMILES

S(=O)(=O)(N)c1ccc(OCc2nnn(c2)-c2ccccc2)cc1

PDB ID: 5LJT

Benzenesulfonamides Incorporating Flexible Triazole Moieties Are Highly Effective Carbonic Anhydrase Inhibitors: Synthesis and Kinetic, Crystallographic, Computational, and Intraocular Pressure Lowering Investigations

***J. Med. Chem.*, 2016, *59* (23), pp 10692–10704**

Aim of the Project

1. **Characterize** the reference benzenesulfonamide inhibitor in complex with Carbonic Anhydrase II

2. Browsing a small chemical **database** (around 50 molecules);

3. Exploring **molecular similarity** between the reference compound and database compounds

4. Selecting **4/5** alternative **candidates**

5. Analysis the **crystallographic structure** of our drug target in complex

6. Performing a **molecular docking** study of the selected compounds (step 4)

7. Use LigBuilder to free your imagination... think, draw and dock!

8. Merging all information collected, suggest and defend your favourite candidate within a technical report that you have to send as pdf file (**lastname_PSF_2017.pdf**) at the following address: **stefano.moro@unipd.it**

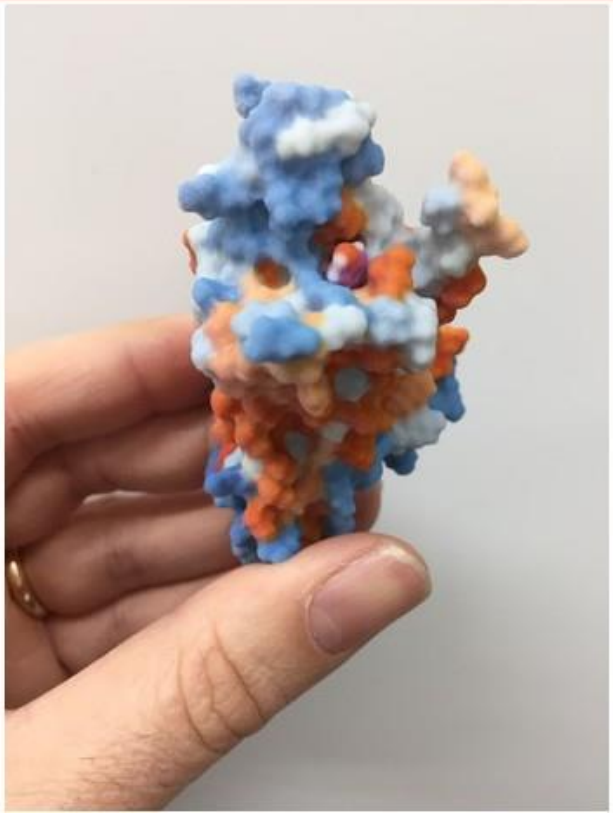
How to find the Virtual Lab

UNIVERSITÀ DEGLI STUDI DI PADOVA

MMS Molecular Modeling Section

Department of Pharmaceutical and Pharmacological Sciences, University of Padova
Via Marzolo 5, 35131 Padova (Italy) - phone: +39 049 8275704, fax: +39 049 8275366

MMS Home | About us... | Lab Members | Projects | Pubblications | @learning | MMStools | MMS_Intranet



(SuMD) tool. *more...*

January 01, 2014
MMS is among the top 10 ranked groups in the GPCR Dock 2013 competition. *more...*

October 01, 2013
MMS partecipates at the GLISTEN-COST action.

MMS: Events

January 24-28, 2016
Keystone Symposia - Purinergic Signaling
Fairmont Hotel Vancouver - Vancouver, British Columbia, Canada... *more*

MMS: Latest Hot Publication

Ciancetta A. et al. "Advances in Computational Techniques to Study GPCR-Ligand Recognition." TIPS (2015) *more...*

How to find the Virtual Lab

How to find the Virtual Lab

MMSeLAB:	
PSF@podcast:	
@sertiamoci:	
Great Memories:	

1. Introduzione alla progettazione di un farmaco			
2. Ligand-based Drug Design (LBDD)			
	Rappresentazioni Molecolari e Similarità Strutturale		
	Ipotesi Farmacoforiche		
	Superfici e Descrittori Molecolari		
	QSARs : introduzione		
	QSARs: elementi di statistica		
3. Structure-based Drug Design (SBDD)			
	Analisi Conformazionale		
	Energetica Molecolare		
	Docking & Scoring Virtual Screening		
	Dinamica Molecolare		
	Elementi di Chimica Quantistica		

ro stressati abbastanza, ecco alcuni suggerimenti per procurarsi

How to find the Virtual Lab

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Great Memories:	

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How to find the Virtual Lab

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MMSeLab... broadening perspectives.

Running Project:	
Project Aims:	
eTools:	
Tutorials:	
References:	

This project was possible thanks to the irreplaceable contributions of Matteo Floris, Davide Sabbadin, , Mattia Sturlese and Andrea Cristiani.

We warmly thank Chemical Computing Group (CCG) for giving access to MOEweb, OpenEye for giving access to OMEGA, Thomas E. Exner for provinding us PLANTS docking tool, Matthias Rarey for ging access to PoseView, and Peter Ertl for its editor.

We are very grateful to the large community of Developers who make possible the use of the following free tools: Ubuntu Linux operating system, Apache web server, PHP scripting language, Jmol - the open source molecular viewer, Jquery - Javascript library, CDK - the chemistry development kit, CACTVS toolkit by Xemistry, Indigo command line utilities by GGA Software Services.

Virtual Lab Sections

UNIVERSITÀ DEGLI STUDI DI PADOVA

MMS Home | About us... | Lab Members | Projects | Pubblications | @learning | MMStools | MMS_Intranet

MMSeLab... broadening perspectives.

@lab MS

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Virtual Lab Tools

UNIVERSITÀ DEGLI STUDI DI PADOVA

...broadening perspectives.

Load your assigned SDF files MS		
	Visualize your SDF file using Ligand_Brower MS	
		Draw and characterize your ligand MS
		Exploring structural similarity MS
		Remove your PAINS MS
Search and save your PDB file MS		
	Visualize your PDB file using Protein_Brower MS	
		Dock your candidate MS

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Download your database

Pick up your assigned chemical database and... and good luck!

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31	32	33	34	35
36	37	38	39	40	41	42
43	44	45	46	47	48	49

1,4-Oxazine.sdf

1,4-Oxazine.pdb

5CLM_Fix.pdb

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1,4-Oxazine.sdf MS

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Search and save your PDB file MS		
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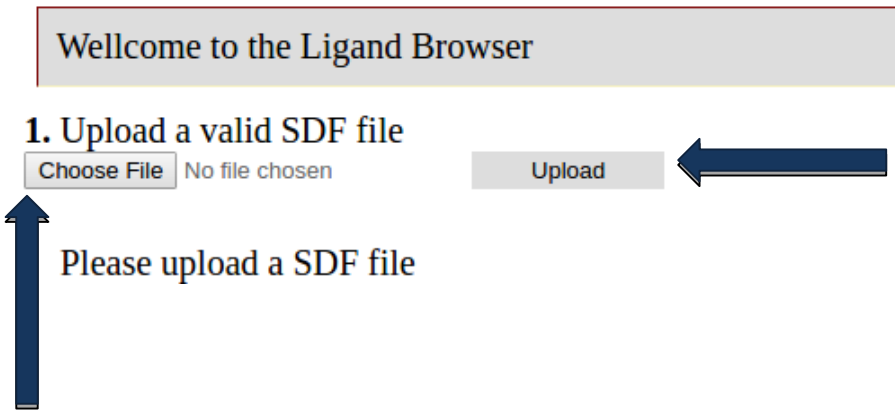
Visualize Molecules



How to use the “Visualize Molecule” tool:

- *Click* on **“Choose File”** button and select the ligand any **sdf** file
- *Click* on **“Upload”** button and wait for the results

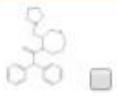
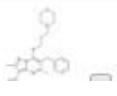
Visualize Molecules

Wellcome to the Ligand Browser

1. Upload a valid SDF file

Choose File | No file chosen | Upload

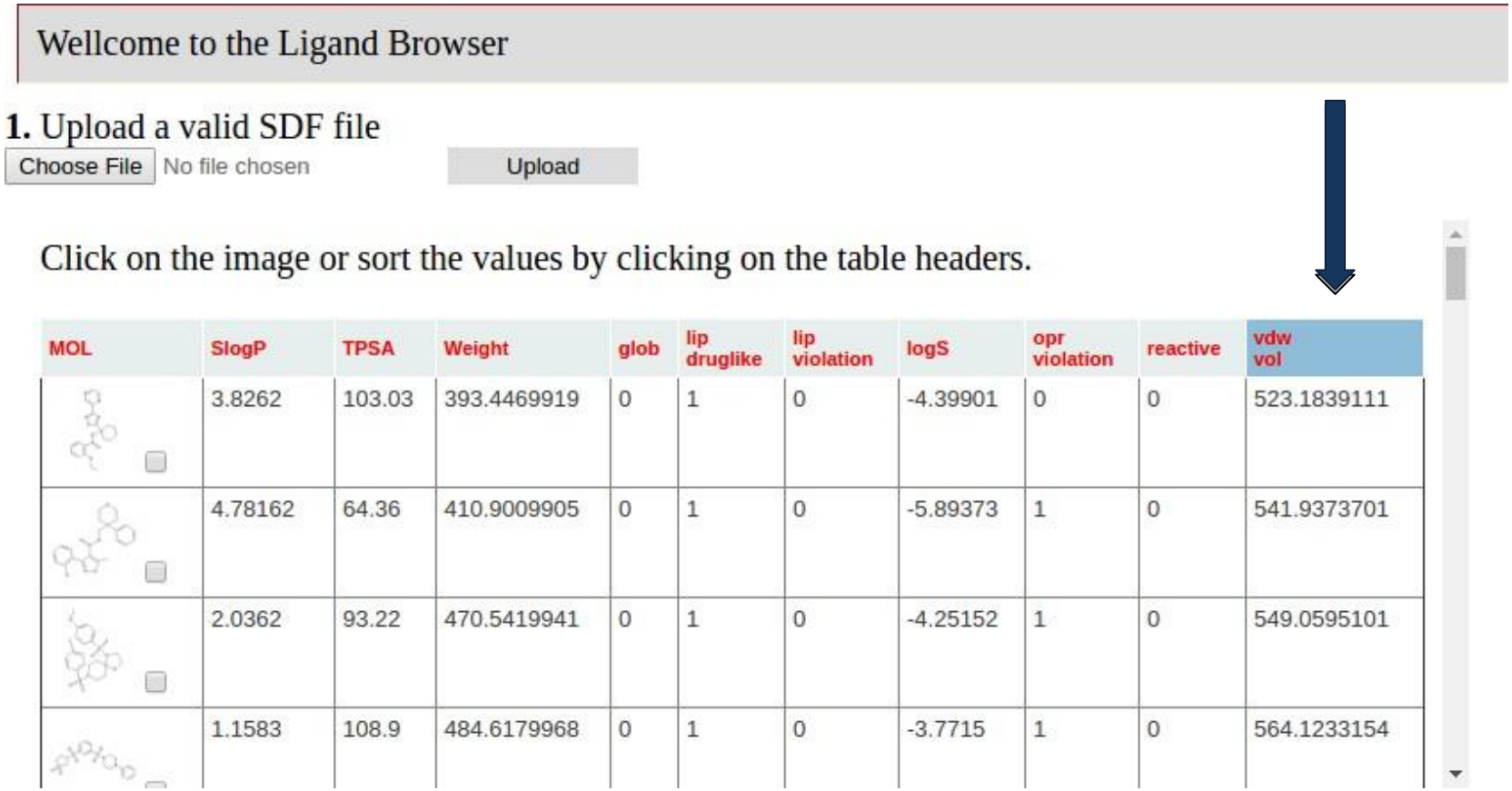
Click on the image or sort the values by clicking on the table headers.

MOL	SlogP	TPSA	Weight	glob	lip druglike	lip violation	logS	opr violation	reactive	vdw vol
	4.2484	23.55	394.5829937	0	1	0	-4.92171	0	0	568.5692962
	6.1666	42.43	438.5509924	0	1	1	-7.74628	2	0	600.66263
	5.39377	44.81	463.6459923	0	1	1	-5.89871	2	0	657.0019302
	4.68769	54.68	455.6059905	0	1	0	-6.00217	3	0	662.0650726

Results of "Visualize Molecule" tool:

- An interactive table with several parameters computed, such as SlogP, MW, Lipinsky violatons

Visualize Molecules

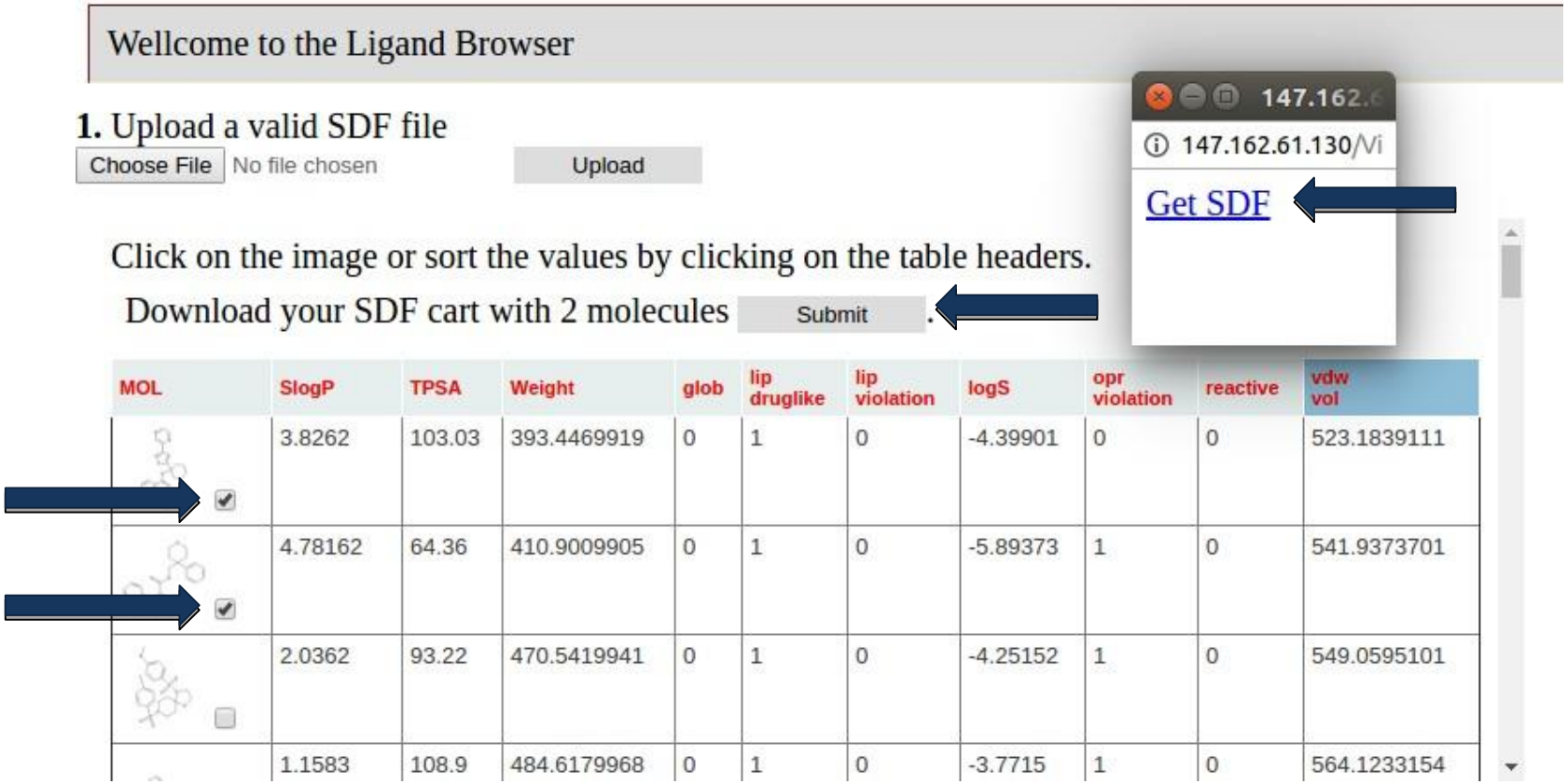


MOL	SlogP	TPSA	Weight	glob	lip druglike	lip violation	logS	opr violation	reactive	vdw vol
	3.8262	103.03	393.4469919	0	1	0	-4.39901	0	0	523.1839111
	4.78162	64.36	410.9009905	0	1	0	-5.89373	1	0	541.9373701
	2.0362	93.22	470.5419941	0	1	0	-4.25152	1	0	549.0595101
	1.1583	108.9	484.6179968	0	1	0	-3.7715	1	0	564.1233154

Features of "Visualize Molecule" tool:

- *Click* on table column header to **sort** by the specific parameter

Visualize Molecules



Features of "Visualize Molecule" tool:

- *Click* on tips in mol field **select** the compound to keep
- *Click* on **Submit** and then on **Get SDF**

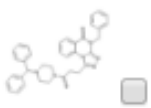
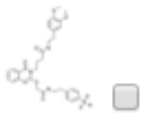
Visualize Molecules

Wellcome to the Ligand Browser

1. Upload a valid SDF file

Choose File | No file chosen | Upload

Click on the image or sort the values by clicking on the table headers.

MOL	SlogP	TPSA	Weight	glob	lip druglike	lip violation	logS	opr violation	reactive	vdw vol
	5.65597	74.57	582.7079875	0	0	2	-7.68727	3	0	817.314439
	3.02564	169.49	667.8079905	0	0	2	-7.54824	3	0	847.4244333

Filtered database

Virtual Lab Tools

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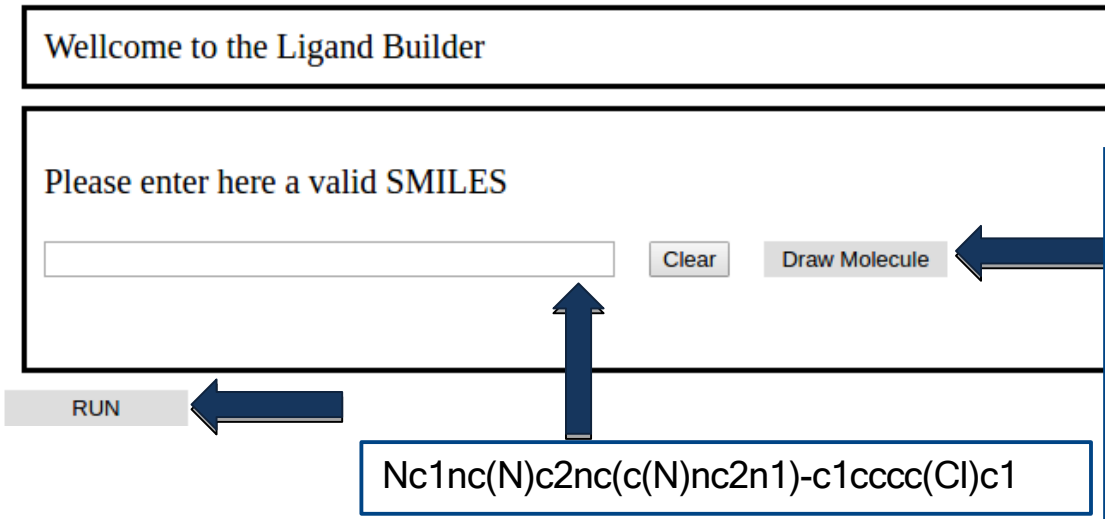
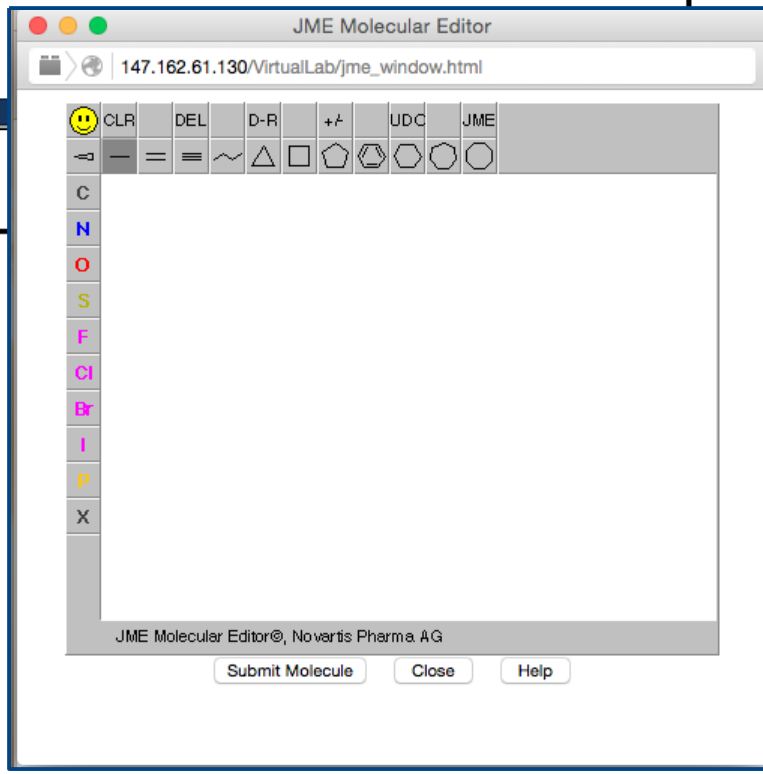
...broadening perspectives.

Load your assigned SDF files		
	Visualize your SDF file using Ligand_Brower	
		Draw and characterize your ligand
		Exploring structural similarity
		Remove your PAINS
Search and save your PDB file		
	Visualize your PDB file using Protein_Brower	
		Dock your candidate

Ligand Builder & Ligand Properties





How to use the "Ligand Builder" tool:

- *Click* on **"Draw Molecule"** button and draw your ligand. Then *click* on **"Submit Molecule"** button.
- Alternatively *click* on *insert* the **smile** in the entry.

- *Click* on **"Run"** button and wait for the results

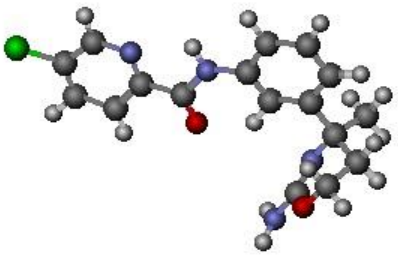
Ligand Builder & Ligand Properties

Please enter here a valid SMILES

C[C@]3(c2cccc(NC(=O)c1ccc(Cl)cn1)c2)CCC Clear Draw Molecule

RUN

PDB Download
SDF Download



Molecular Weight	344.8019927
Mass density	0.7914587778
Octanol/water log P	3.249
Water solubility log S	-4.08547
Surface Area	332.5713144
Polar Surface Area	89.6
vdW volume	435.6537608
H-bond acceptors	3
H-bond donors	2
Hydrophobes	16
Acidic atoms	0
Basic atoms	0
Aromatic atoms	12
Rotatable bonds	4
Chiral centers	1
Druglike	1
Leadlike	1
Reactive	0

Results of "Ligand Builder" tool:

- A table with several parameters computed, such as H-bond donor/acceptor, drugability propeties

Features of "Visualize Molecule" tool:

- *Click* on **"PDB Download"** or **"SDF Download"** to retrieve the structure

Virtual Lab Tools

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...broadening perspectives.

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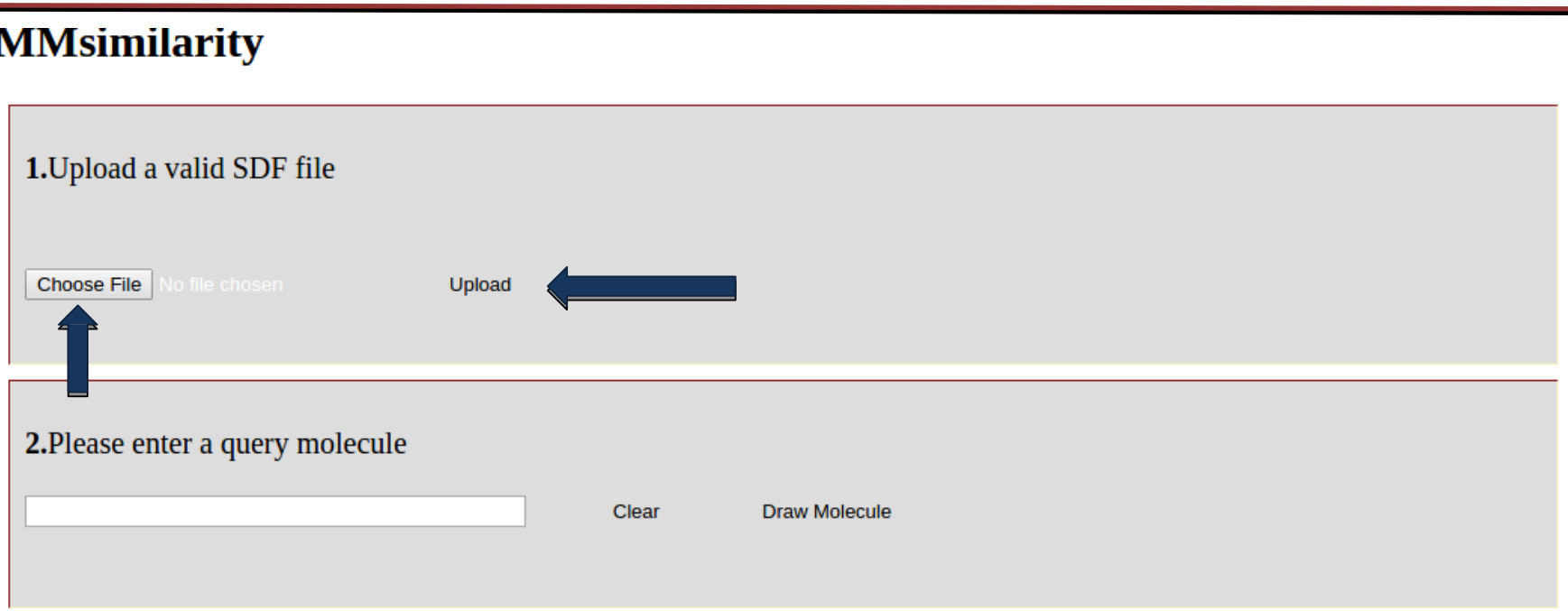
		Draw and characterize your ligand
		Exploring structural similarity
		Remove your PAINS
Search and save your PDB file		
	Visualize your PDB file using Protein_Brower	
		Dock your candidate

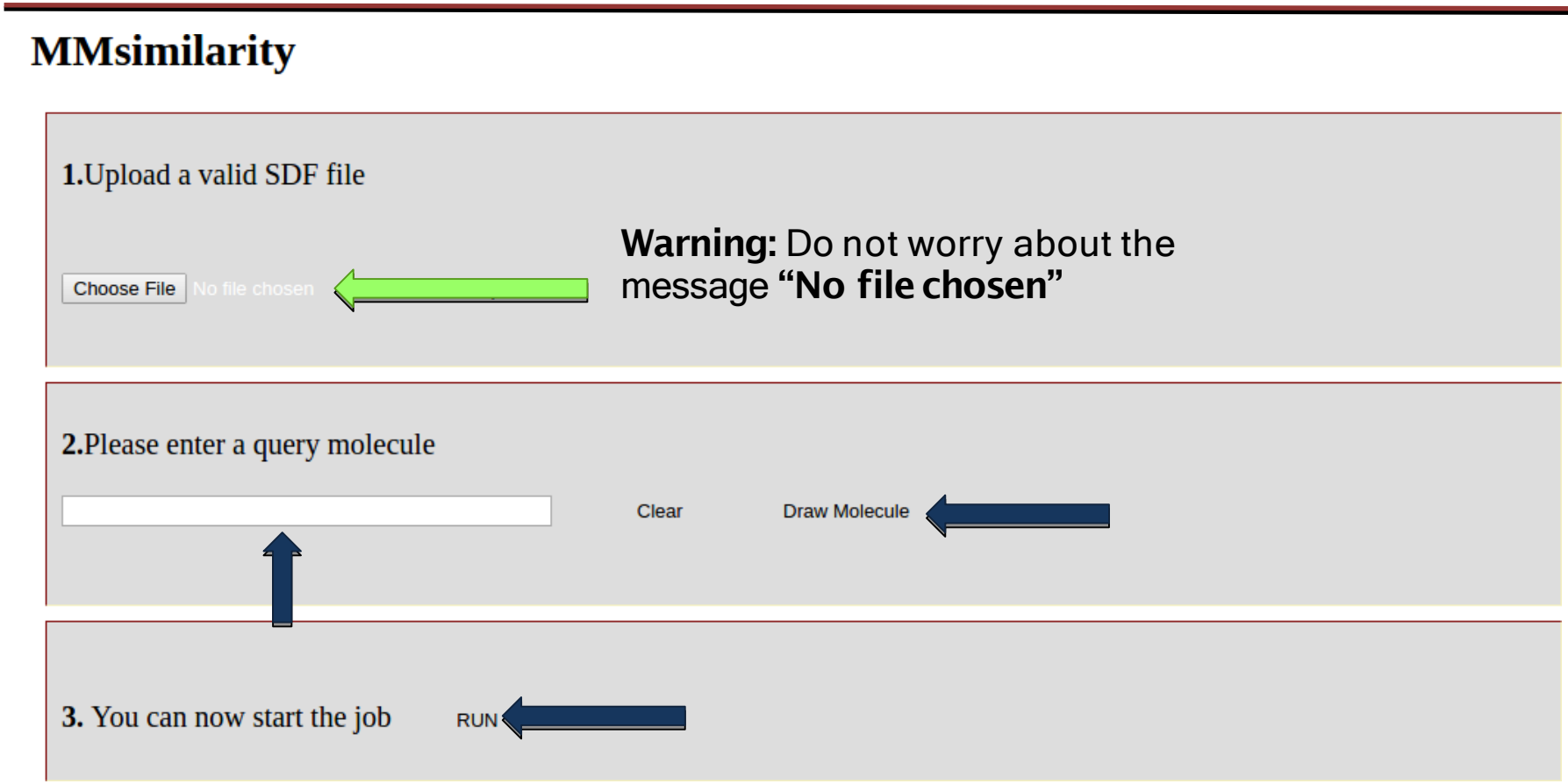
Ligands Similarity



How to use the “Ligand Similarity” tool:

- *Click* on **“Choose File”** button and select the ligand any **sdf** file
- *Click* on **“Upload”** button

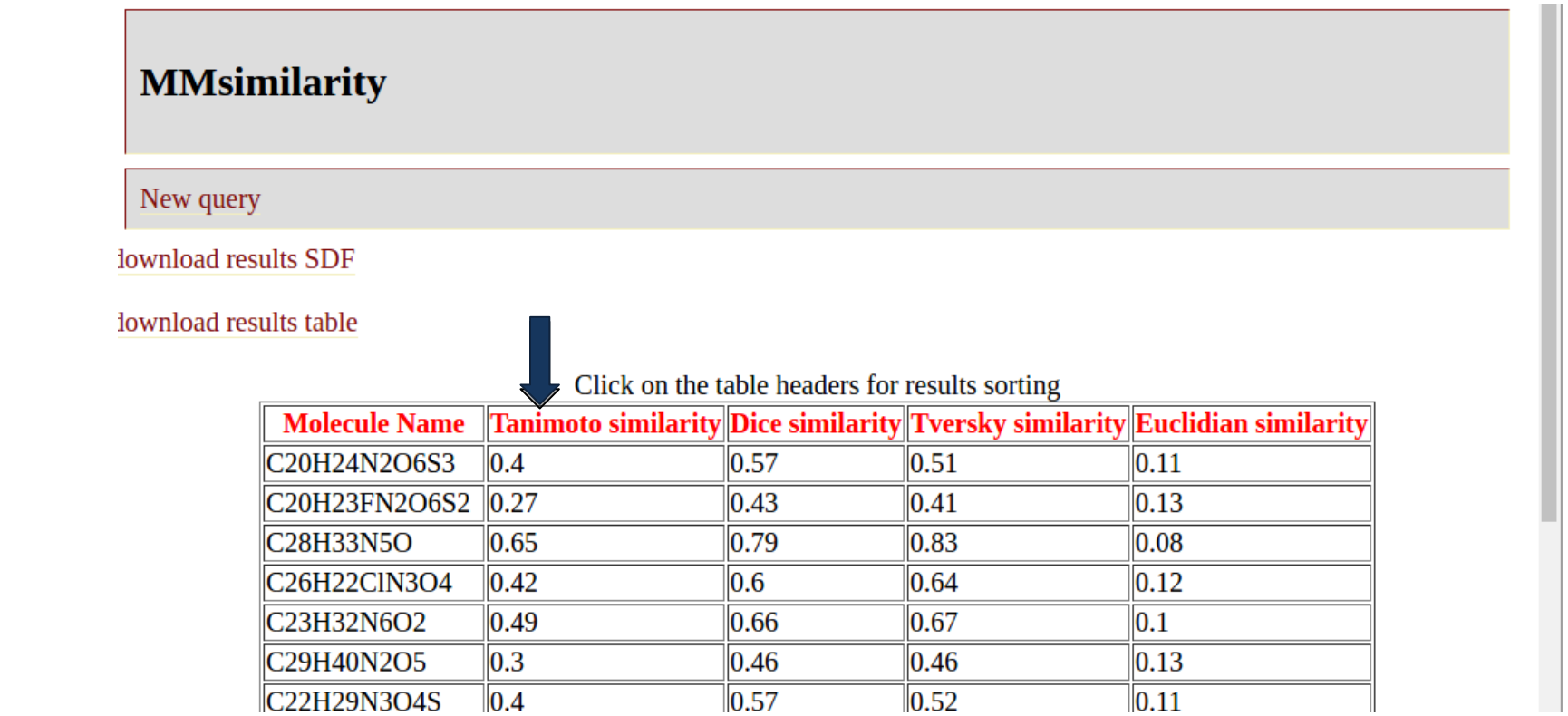
Ligands Similarity



How to use the "Ligand Similarity" tool (continue):

- *Click* on **"Draw Molecule"** button or on *insert* the **smile** in the entry.
- *Click* on **"Run"** button and wait for the results

Ligands Similarity



MMsimilarity

New query

download results SDF

download results table

Click on the table headers for results sorting

Molecule Name	Tanimoto similarity	Dice similarity	Tversky similarity	Euclidian similarity
C20H24N2O6S3	0.4	0.57	0.51	0.11
C20H23FN2O6S2	0.27	0.43	0.41	0.13
C28H33N5O	0.65	0.79	0.83	0.08
C26H22ClN3O4	0.42	0.6	0.64	0.12
C23H32N6O2	0.49	0.66	0.67	0.1
C29H40N2O5	0.3	0.46	0.46	0.13
C22H29N3O4S	0.4	0.57	0.52	0.11

Results of "Ligand Similarity" tool:

- A table with several parameters computed, such as Tanimoto, Tversky similarities

Features of "Ligand Similarity" tool:

- *Click* on table column header to **sort** by the specific parameter

Ligands Similarity

MMsimilarity

New query

download results SDF

download results table

Click on the table headers for results sorting

Molecule Name	Tanimoto similarity	Dice similarity	Tversky similarity	Euclidian similarity
C20H23FN2O6S2	0.27	0.43	0.41	0.13
C29H40N2O5	0.3	0.46	0.46	0.13
C22H28N2O7S2	0.3	0.47	0.45	0.12
C29H29N3O5S	0.3	0.46	0.49	0.13
C26H30N4O5S	0.32	0.48	0.53	0.13
C28H27N3O6	0.33	0.5	0.54	0.13
C32H37N5O7S2	0.34	0.51	0.57	0.13
C24H30N2OS	0.35	0.52	0.46	0.11
C28H35N3O3S	0.35	0.52	0.56	0.13
C27H24N2O4S	0.35	0.52	0.54	0.12
C28H21N3O4	0.36	0.53	0.62	0.13

Features of “Ligand Similarity” tool:

- *Click* on tips in mol field **select** the compound to keep
- *Click* on **Submit** and then on **Get SDF**

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Load your assigned SDF files MS		
	Visualize your SDF file using Ligand_Brower MS	
		Draw and characterize your ligand MS
		Exploring structural similarity MS
		Remove your PAINS MS 
Search and save your PDB file MS		
	Visualize your PDB file using Protein_Brower MS	
		Dock your candidate MS

PAINS

Pan Assay Interference Compounds

COMMENT

ETHOLOGY Julian Huxley's animal-behaviour classic at 100 p.484

ASTROPHYSICS Literary experiment conveys cosmology in few words p.485

MUSIC Tree-ring expert authenticates priceless violins p.486

PALAEONTOLOGY 'Hobbit' scientists urge Twitter critics to read the literature p.487

- Baell J. et al.- Nature 2014 - 513(7519)
- Baell J.et al - J. Med. Chem 2010 - 53(7), pp. 2719-2740

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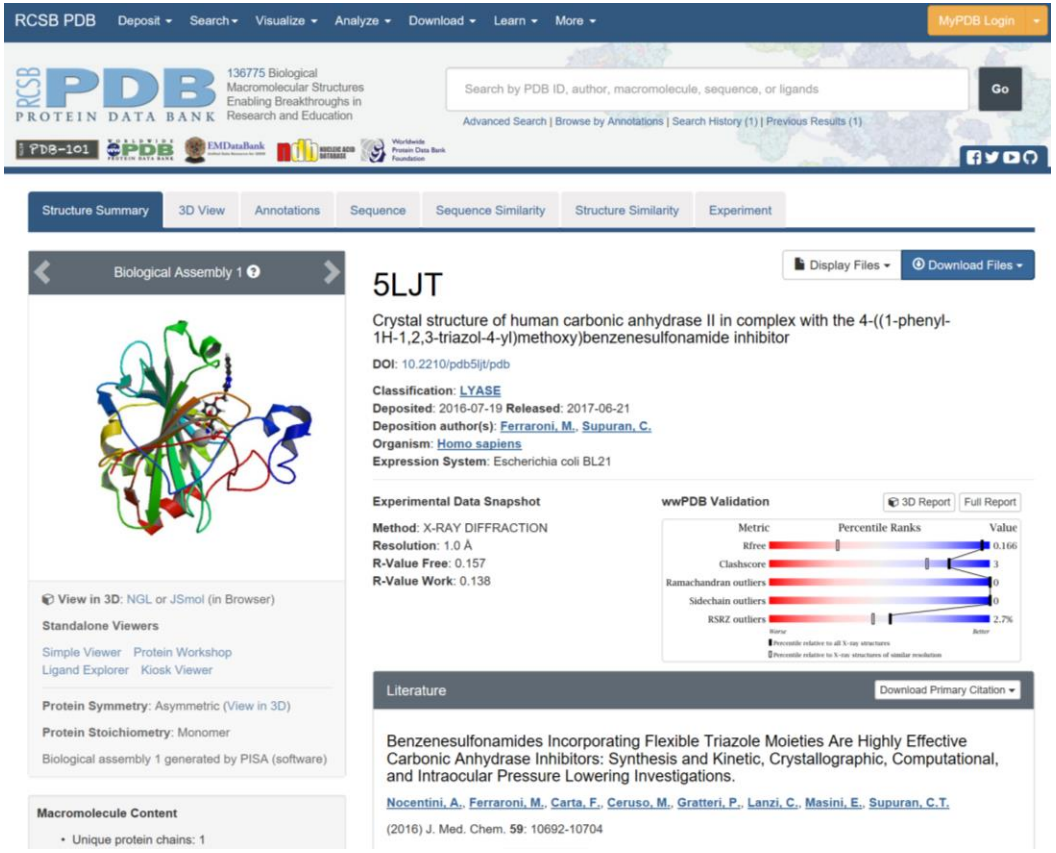
Download PDB structure



The **"Search & save PDB"** redirect you to the **PDB website.**

Insert the PDBcode (5lH5) in the entry and go the specific structure page.

Click on the **"Download File"** button and then on **"PDB Format"**

Warning: Do not use the structure you will downloaded from this web site for the next steps.
We will provided you a structure that was optimized for your assay

→ 5LJT_fix.pfd

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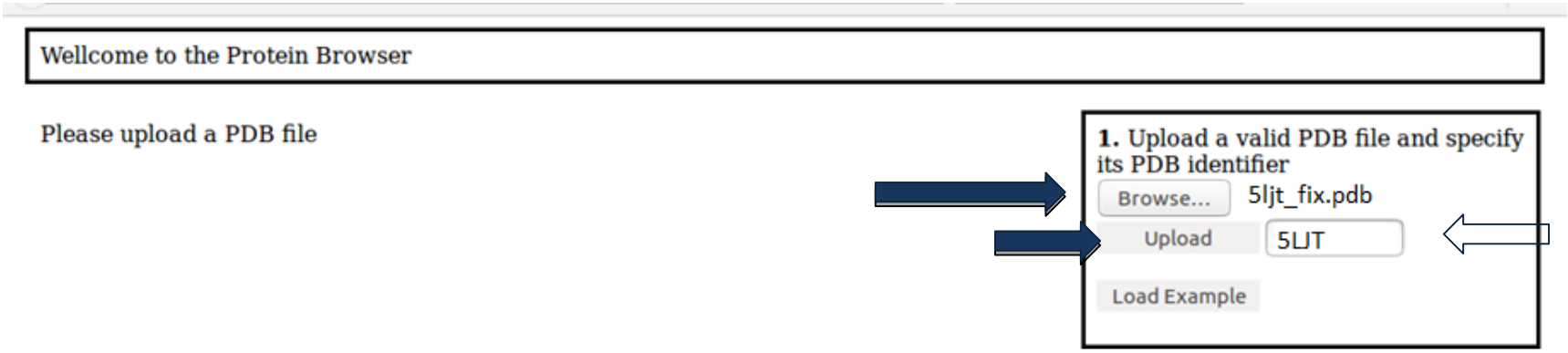
		Remove your PAINS MS
Search and save your PDB file MS		
	Visualize your PDB file using Protein_Brower MS	
		Dock your candidate MS

Visualize Protein



How to use the "Visualize your PDB" tool:

- *Click* on **"Browse…"** button and select the **"5ljt_fix.pdb"** provided
- *Insert* the PDBcode **(5LJT)** on the entry
- *Click* on **"Upload"** button and wait for the results

Visualize Protein

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Wellcome to the Protein Browser

1. Upload a valid PDB file and specify its PDB identifier

Browse... No file selected. Upload

Load Example

2. Pick any residues from the Jmol window

or select from here

Color by Secondary Structure Chain Rainbow Aminoacid Hydrophobicity

Selection Ligands and Pocket

Surface Off Solvent Accessible Solvent Excluded Cavities

Settings Black Background White Background Wireframe on Wireframe off

Reset Display

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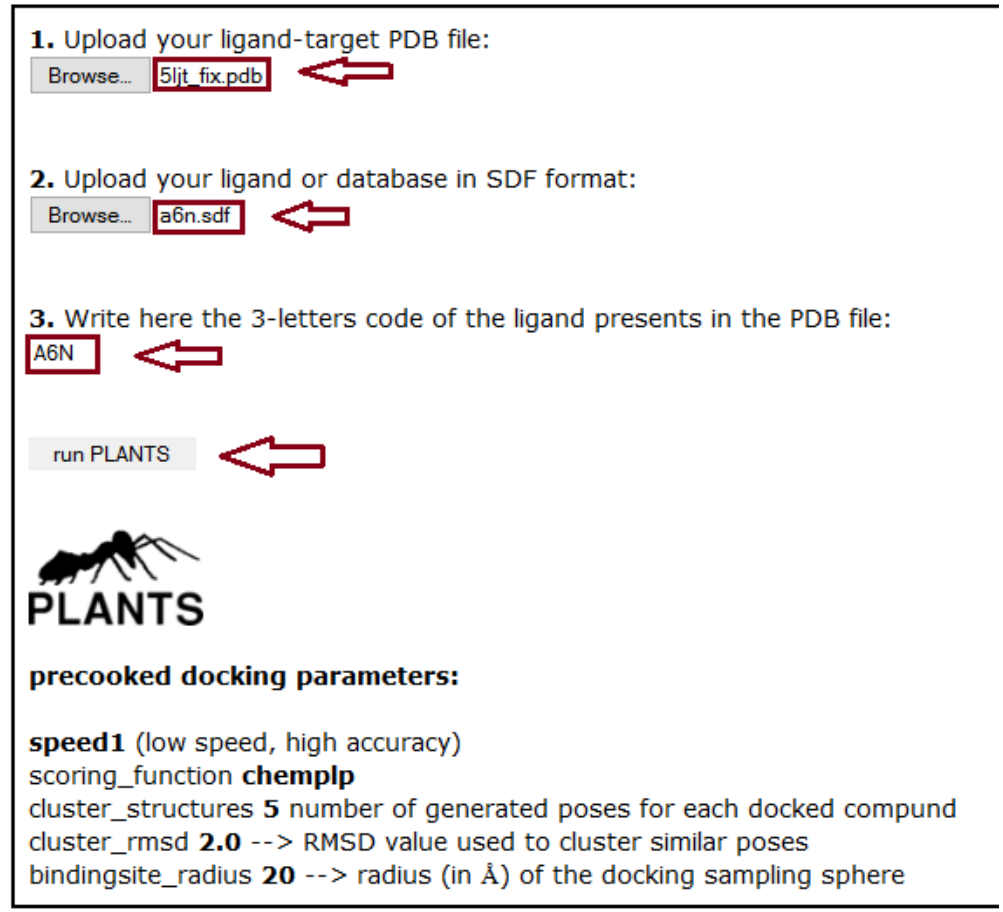
		Exploring structural similarity MS
		Remove your PAINS MS
Search and save your PDB file MS		
	Visualize your PDB file using Protein_Brower MS	
		Dock your candidate MS

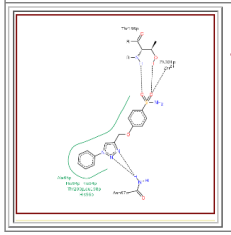
Dock your compounds

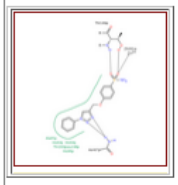
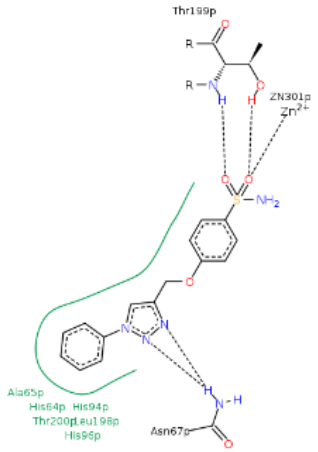


How to use "Dock your candidate" tool:

- *Click* on **"Choose File"** button and select the structure provided **(5ljt_fix.pdb)**
- *Click* on **"Choose File"** button and select the **sdf** file of the ligands you want to dock
- *Insert* the ligand name **(A6N)** in the entry
- *Click* on **"run PLANTS"** button and wait for the results
- **Warning:** Please do not dock to many compounds.

Dock your compounds

Best Ranked Poses	Scoring
	-116.431

Best Ranked Poses	Scoring	Pose interactions	3D view
	-116.431	 Download PDB Download picture	 Color by: Secondary Structure / Chain / Rainbow / Aminoacid / Hydrophobicity Surface: Off / Solvent Accessible / Solvent Excluded / Cavities Settings: Black Background / White Background / Wireframe on / Wireframe off Reset Display

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		Remove your PAINS MS
Search and save your PDB file MS		
	Visualize your PDB file using Protein_Brower MS	
		Dock your candidate MS 

Write the report

- Write your report, following the indications in the “Project Aims”.
- Try to discuss and present your observations and considerations.
- Send to **stefano.moro@unipd.it** and please format the name as follows:
  - **lastname_PSF_2017.pdf**

- For any problems or doubts, remember that we can help you:
  - maicol.bissaro@phd.unipd.it
  - enrico.margiotta@phd.unipd.it
  - veronica.salmaso@studenti.unipd.it