

# Protein-ligand interaction

In this tutorial we use the Discovery Studio Visualizer for analyzing the interactions between a macromolecular target (a protein) and a ligand.

There are various kinds of interactions which bind a ligand to its target, namely:

Electrostatic interactions, when a charged group of the ligand binds an opposite charged group of the protein. Here you have a positive charged group interacting with a negative charged group. The interaction energy depends on the charges and the distance between them.

Hydrogen bonds, these are the most important and strong dipole-dipole interactions. Here you have a proton donor group interacting with a proton acceptor group. The interaction energy depends on the X-H bond polarity and therefore on the electronegativity of X, on the distance H...Y and therefore on the dimension of Y and finally on the angle X-H...Y.

Hydrophobic interactions, they are due to van der Waals forces, but really they are due to a solvent effect which drives apolar moieties not to be exposed to the aqueous surrounding. Here you have hydrophobic groups of the ligand occupying hydrophobic pockets of the target. The interaction energy depends on the amount of exposed surfaces, therefore depends on the ability of the hydrophobic groups of the ligand to optimally occupy the hydrophobic pockets of the protein.

There are also other interaction: a H-bond can be accepted by a negative charged group or a positive charged protonated nitrogen can act as H-bond donor. You can also find dipole-dipole, dipole-charge interaction.

Moreover there are very strong interactions with metallic cations as for example in the metalloproteinases where a zinc atom is a fundamental part of the binding site.

## MMP13 complexed with an inhibitor (PDB = 1YOU)

MMP13 is a zinc metalloproteinases involved in the break ground of extracellular matrix.

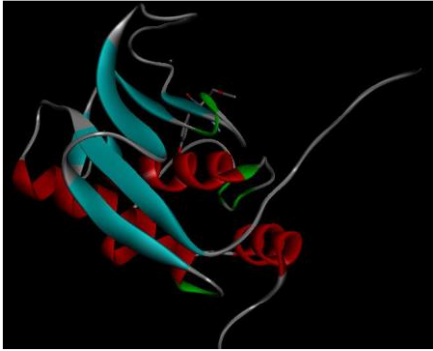
Load the X-ray structure (**File** | **Open URL...** **Site** = [pdbs-PDB](http://pdbs-PDB) **structures (ftp)** **ID=1you**)



The X-ray structure is a dimer, delete chain B, water molecules, Ca cation and sulfate anions (use Hierarchical window).

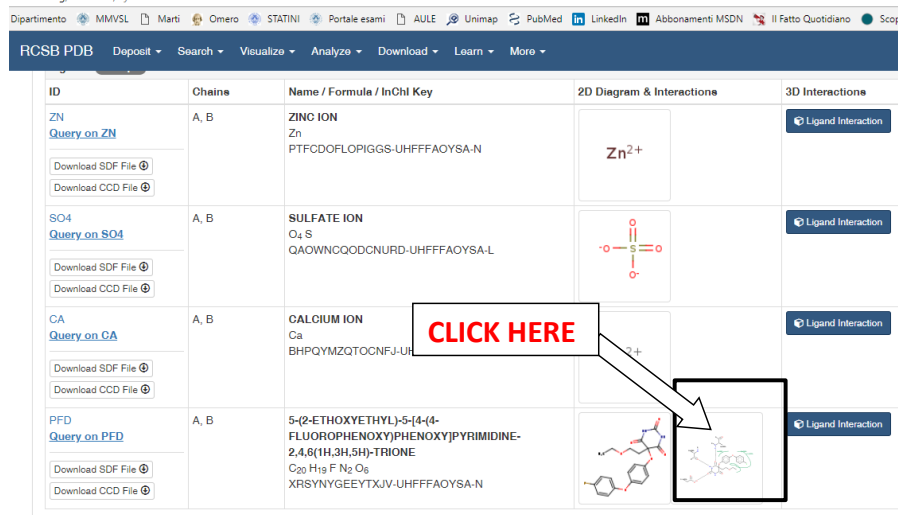
Formattato: Tipo di carattere: Grassetto





Formattato: Sottolineato



Search on the Protein Data Bank site ([www.rcsb.org](http://www.rcsb.org)) 1YOU

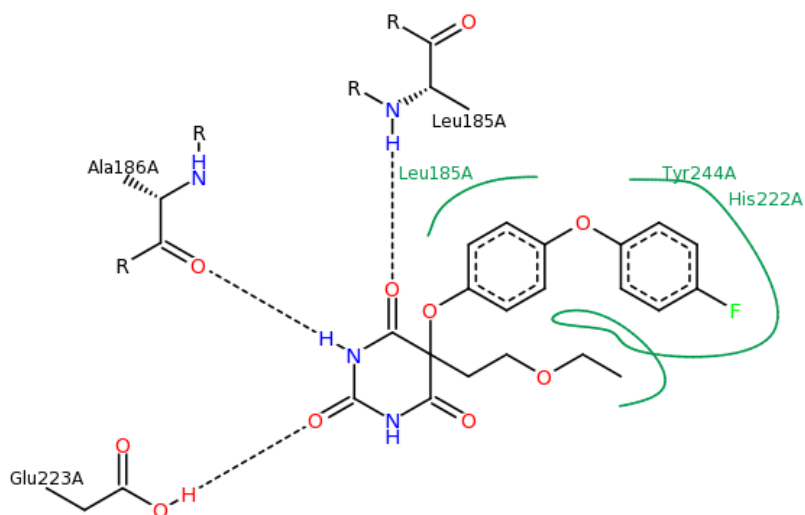
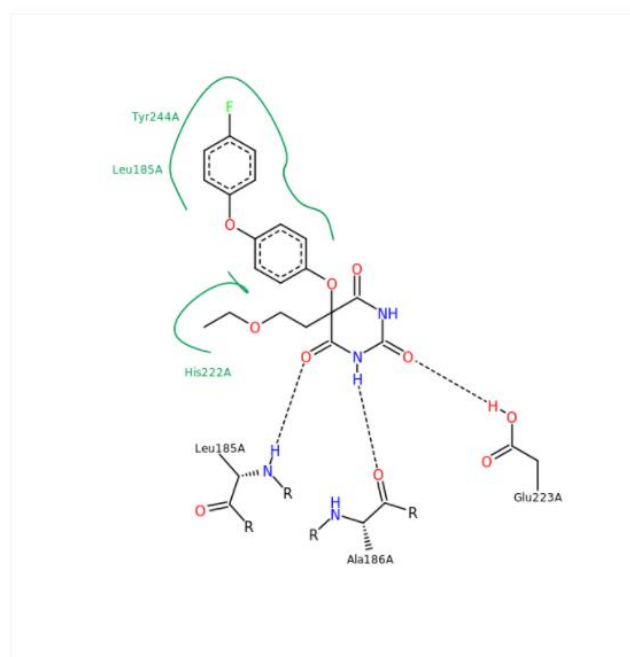
Go down in the page and find the Ligand Chemical Component and click where shown



ID	Chains	Name / Formula / InChI Key	2D Diagram & Interactions	3D Interactions
<a href="#">ZN</a> <a href="#">Query on ZN</a> Download SDF File Download CCD File	A, B	<b>ZINC ION</b> Zn PTFCDOFLOPIGGS-UHFFFAOYSA-N		<a href="#">Ligand Interaction</a>
<a href="#">SO4</a> <a href="#">Query on SO4</a> Download SDF File Download CCD File	A, B	<b>SULFATE ION</b> O <sub>4</sub> S QAOWNQOOCNURD-UHFFFAOYSA-L		<a href="#">Ligand Interaction</a>
<a href="#">CA</a> <a href="#">Query on CA</a> Download SDF File Download CCD File	A, B	<b>CALCIUM ION</b> Ca BHPQYMZQTOCNFJ-UHFFFAOYSA-N		<a href="#">Ligand Interaction</a>
<a href="#">PFD</a> <a href="#">Query on PFD</a> Download SDF File Download CCD File	A, B	<b>5-(2-ETHOXYETHYL)-5-[4-(4-FLUOROPHENOXY)PHENOXY]PYRIMIDINE-2,4,6(1H,3H,5H)-TRIONE</b> C <sub>20</sub> H <sub>19</sub> F N <sub>2</sub> O <sub>6</sub> XRSYNYGEEYTXJV-UHFFFAOYSA-N		<a href="#">Ligand Interaction</a>

You can see a scheme of the ligand-protein interactions (H-bond and hydrophobic).

Poseview Image of PFD in 1YOU

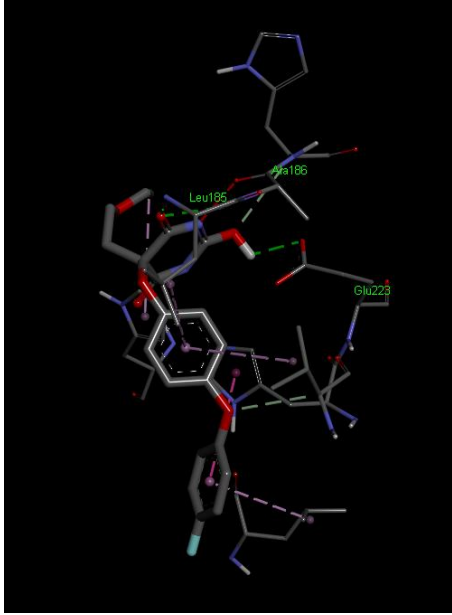


To visualize these interactions on the program:

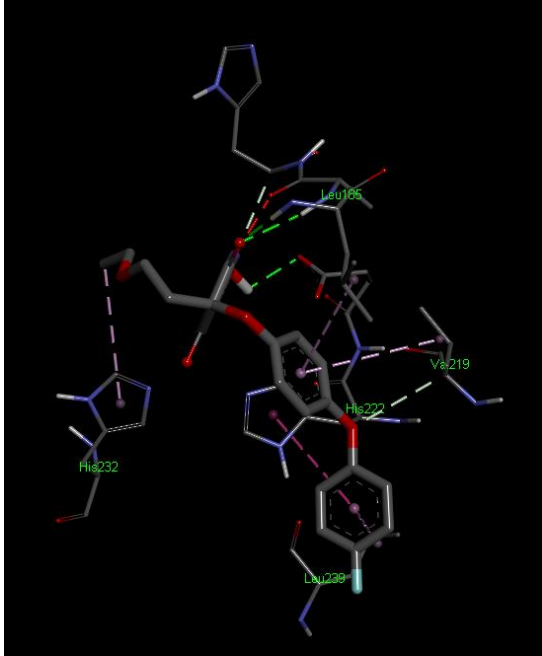
- 1) Add Polar hydrogens (**Chemistry | Hydrogens | add-Add polarPolar**)
- 2) Click on the **Receptor-Ligand Interactions panel**
- 3) Select the ligand (double click on the ligand's structure or ~~F~~-select PFD998 from the Hierarchical Windows)
- 4) Click on **Define Ligand**: <undefined> and press **OK** (Receptor-Ligand Interactions panel)
- 5) Click on **Ligand Interactions** (Receptor-Ligand Interactions panel)

The software automatically highlights all the main H-bonds and lipophilic interactions between the protein and the ligand.

Add a label showing the name and number of the residues that forms H-bonds with the ligand.

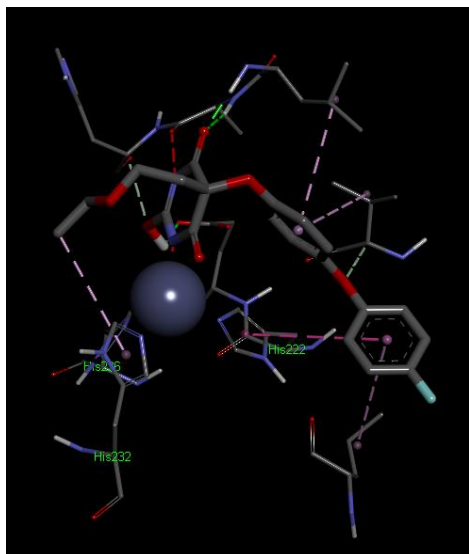


Then, remove this labels and labels to hydrophobic interactions (highlighted violet)

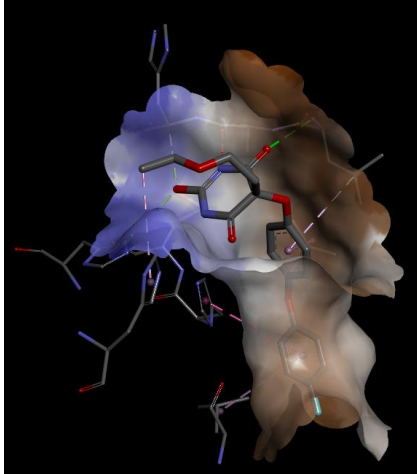


In this protein there is two zinc cations giving strong coordination interactions ~~both with the protein and the~~ ~~with both the protein and the~~ ligand. These interactions are often considered as bonds ~~and also~~ and the program does like this. The most common coordination bonds with proteins are due to side chains of histidines. In order to show these interactions, remove the current label, then tick in the hierarchy window the ZN301 square (to make it visible), select it clicking on name, the zinc cation ZN301 (from the hierarchy) and make it as CPK (Display style). Unselect the zinc ~~atom and select~~ ~~atom, select~~, and delete the three bonds showed by the Zinc atom. Select from the hierarchy HIS226, from the Display style show it as stick with a Stick size of 0,10). Label the three histidines as shown in Figure.

Commentato [s1]: È già così



A nice visualization of the ligand-receptor complex can be obtained if the binding site is visualized through its surface. In the Receptor-Ligand Interactions click on **Display receptor surfaces=Hydrophobic**. A colored surface of the binding site will be shown. Blue region are the less hydrophobic, brown are the more hydrophobic regions.



## Exercise

Do the same analysis (collecting the same pictures) for the streptavidin-biotin (PDB=3RY2) complex.