Protein-ligand docking 101 - running a simulation in GOLD

The following slides report all the steps that are shown in the tutorial video for this CSDU module, so you can follow each step in the format you prefer.

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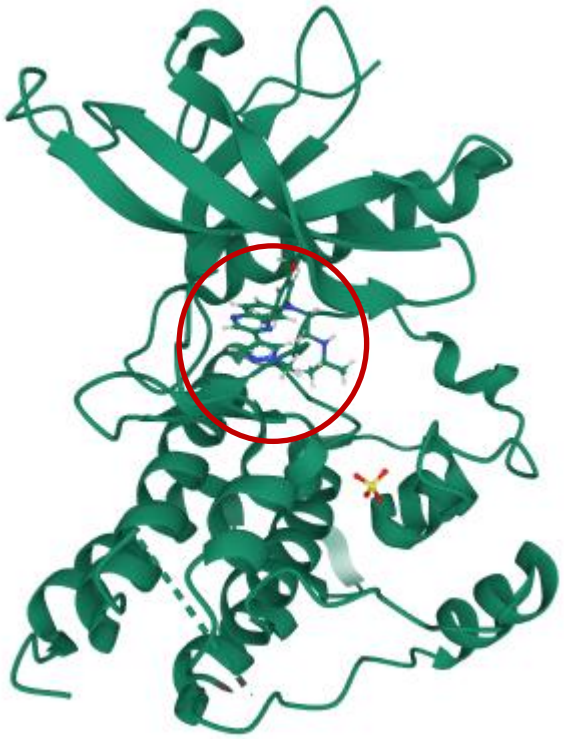
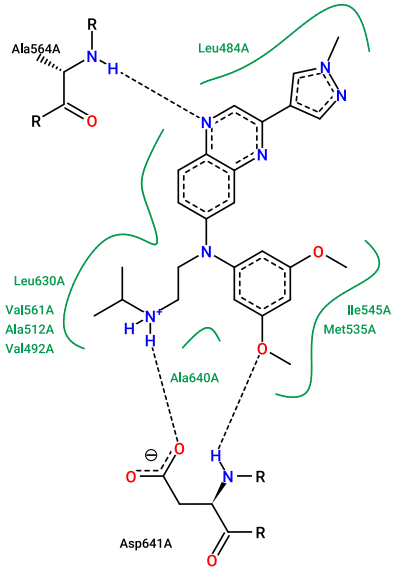
advancing structural science

Docking with GOLD: Case Study

PDB: 5EW8





- Fibroblast growth factor receptors (FGFRs) are a family of receptor **tyrosine kinases** expressed on the cell membrane that play crucial roles in both developmental and adult cells.
- Our **ligand** is (3,5-dimethoxyphenyl)-~{N}'-[3-(1-methylpyrazol-4-yl)quinoxalin-6-yl]-~{N}-propan-2-yl-ethane-1,2-diamine), aka Erdafitinib.
- It is the first-ever fibroblast growth factor receptor (FGFR) kinase inhibitor indicated for patients with locally advanced or metastatic urothelial carcinoma.

Patani H., et al., Landscape of activating cancer mutations in FGFR kinases and their differential responses to inhibitors in clinical use. Oncotarget. 2016; 7: 24252-24268.

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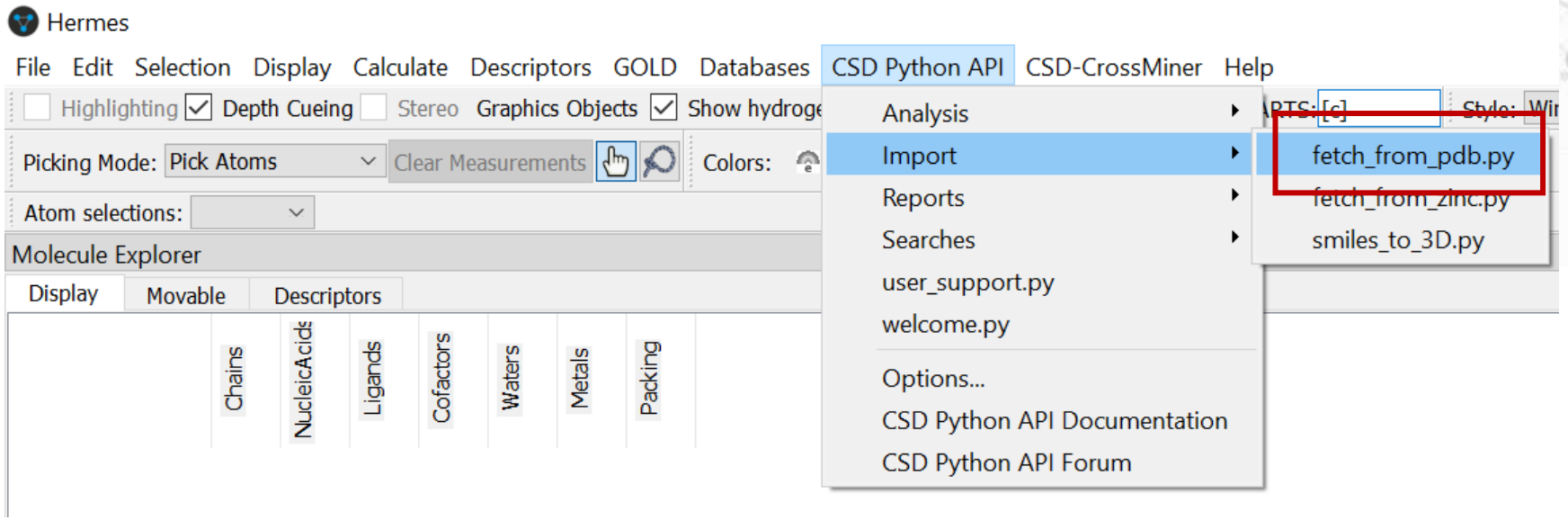
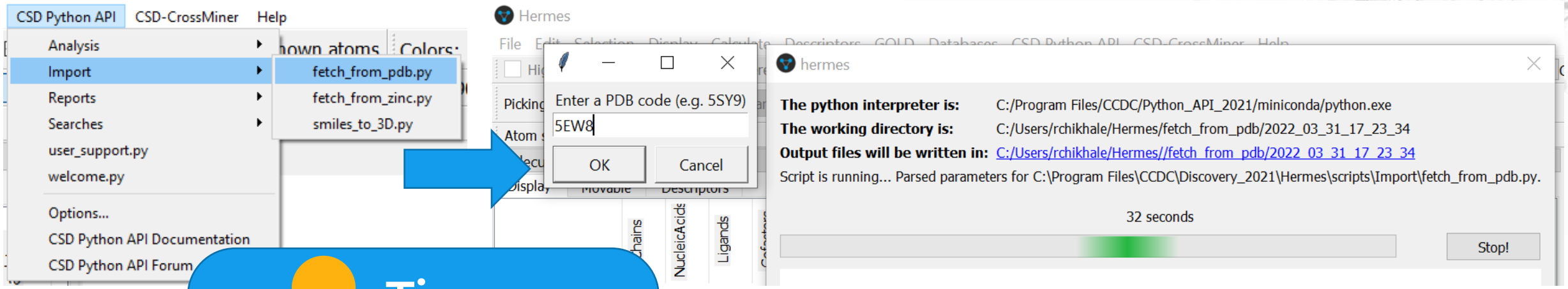
Docking with GOLD: Importing Protein

- Open the Hermes Interface and import the protein crystal structure from the PDB using the ‘fetch_from_pdb.py’ function.



Docking with GOLD: Importing Protein

- Provide with a PDB code in the '**fetch_from_pdb.py**' function search dialogue box.

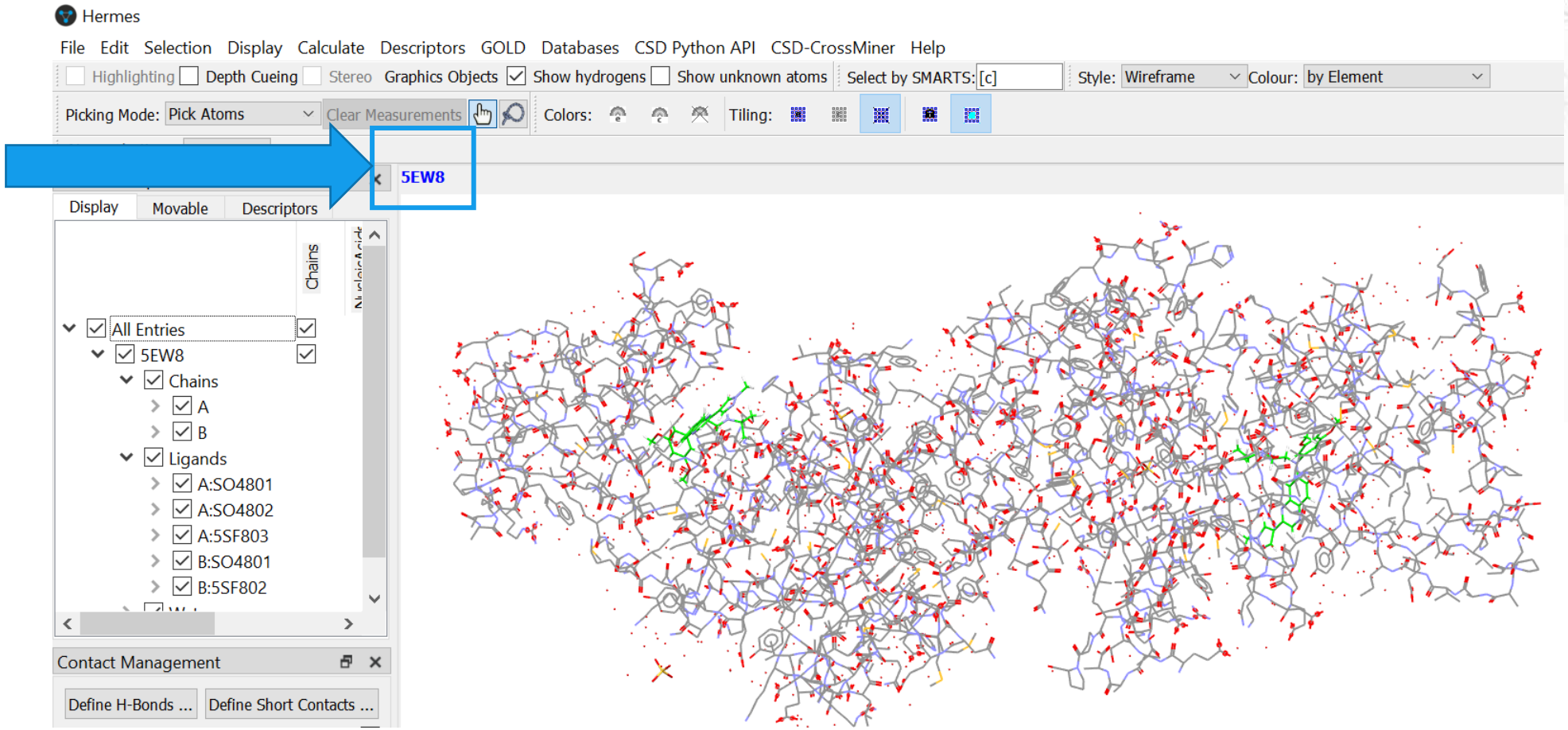


Tip

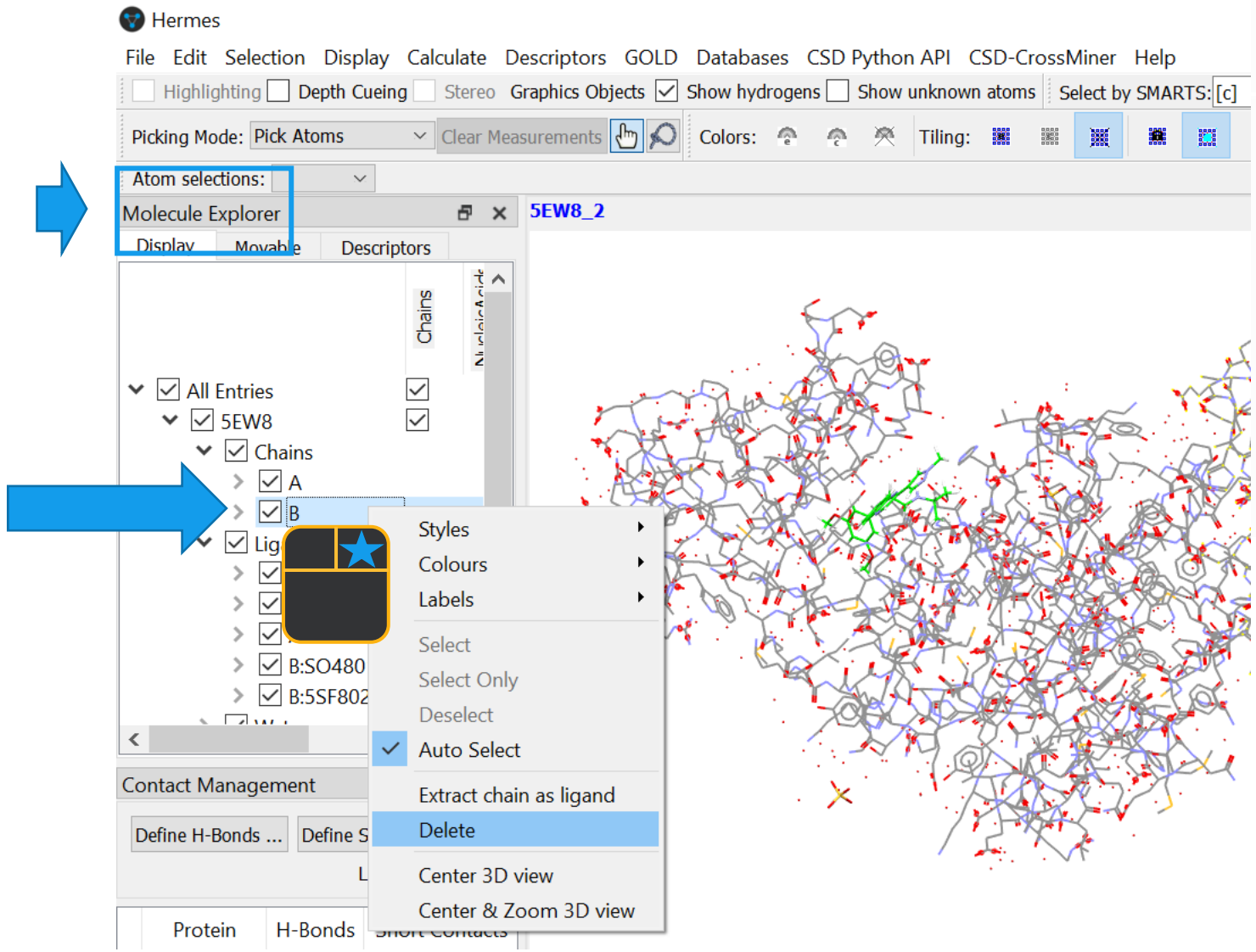
Be aware that the window for entering the PDB code might pop up in a corner of your screen.

Docking with GOLD: Importing Protein

- Once imported, the crystal structure will look like this in Hermes.



Docking with GOLD: Protein preparation



- In the *Molecule Explorer* window selected chain of the protein can be removed.
- Other components like cofactors, water molecules can be removed as per requirement.

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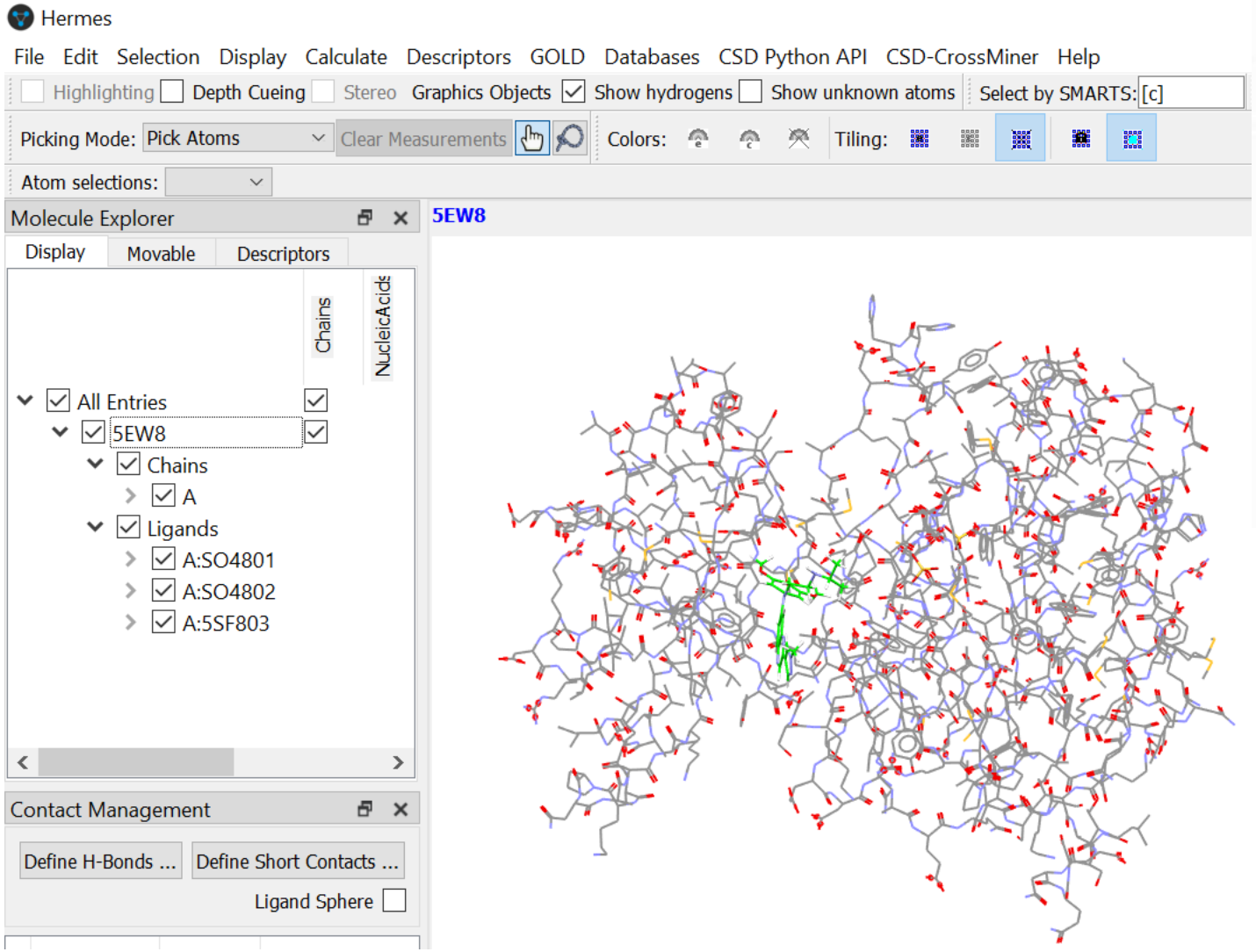
Docking with GOLD: Protein preparation



- Now we are ready for the next stage.

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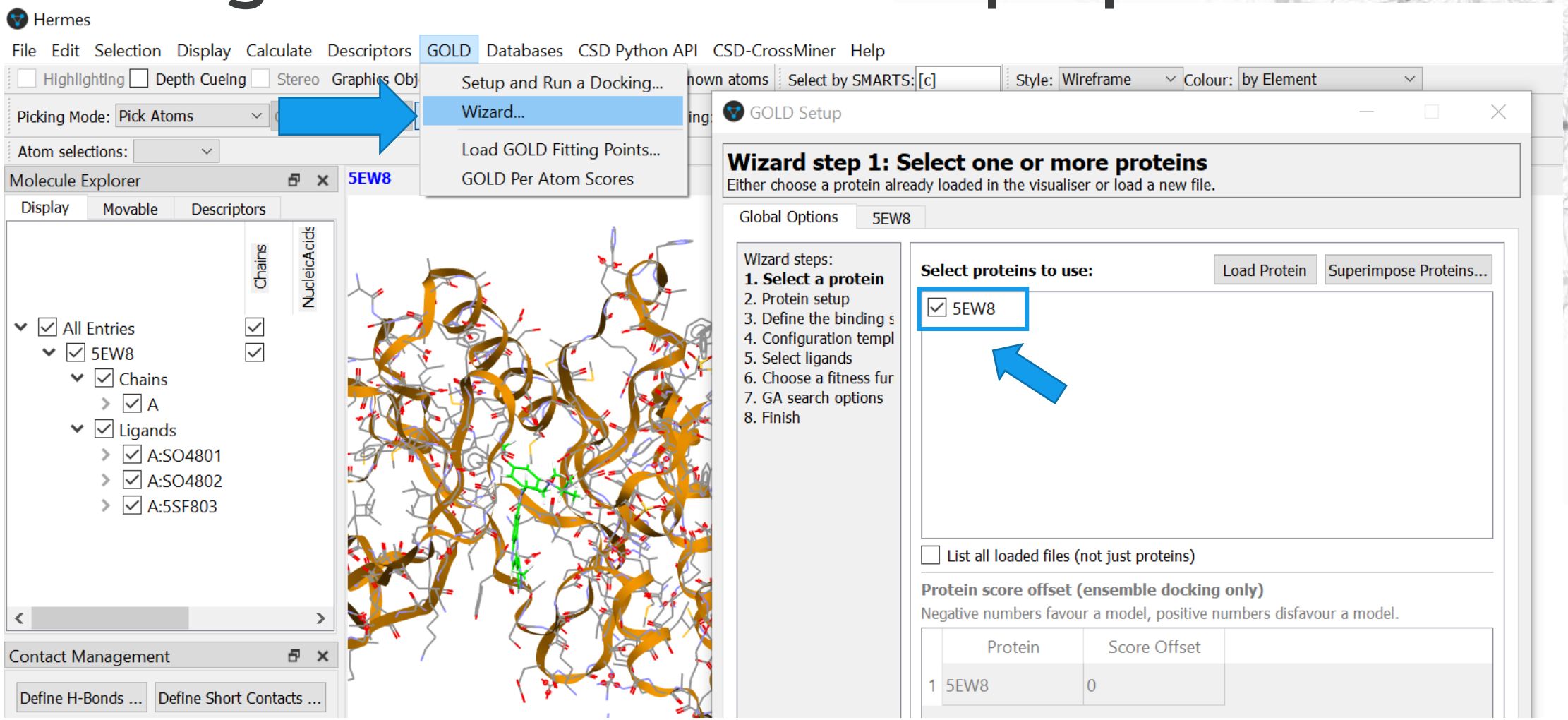
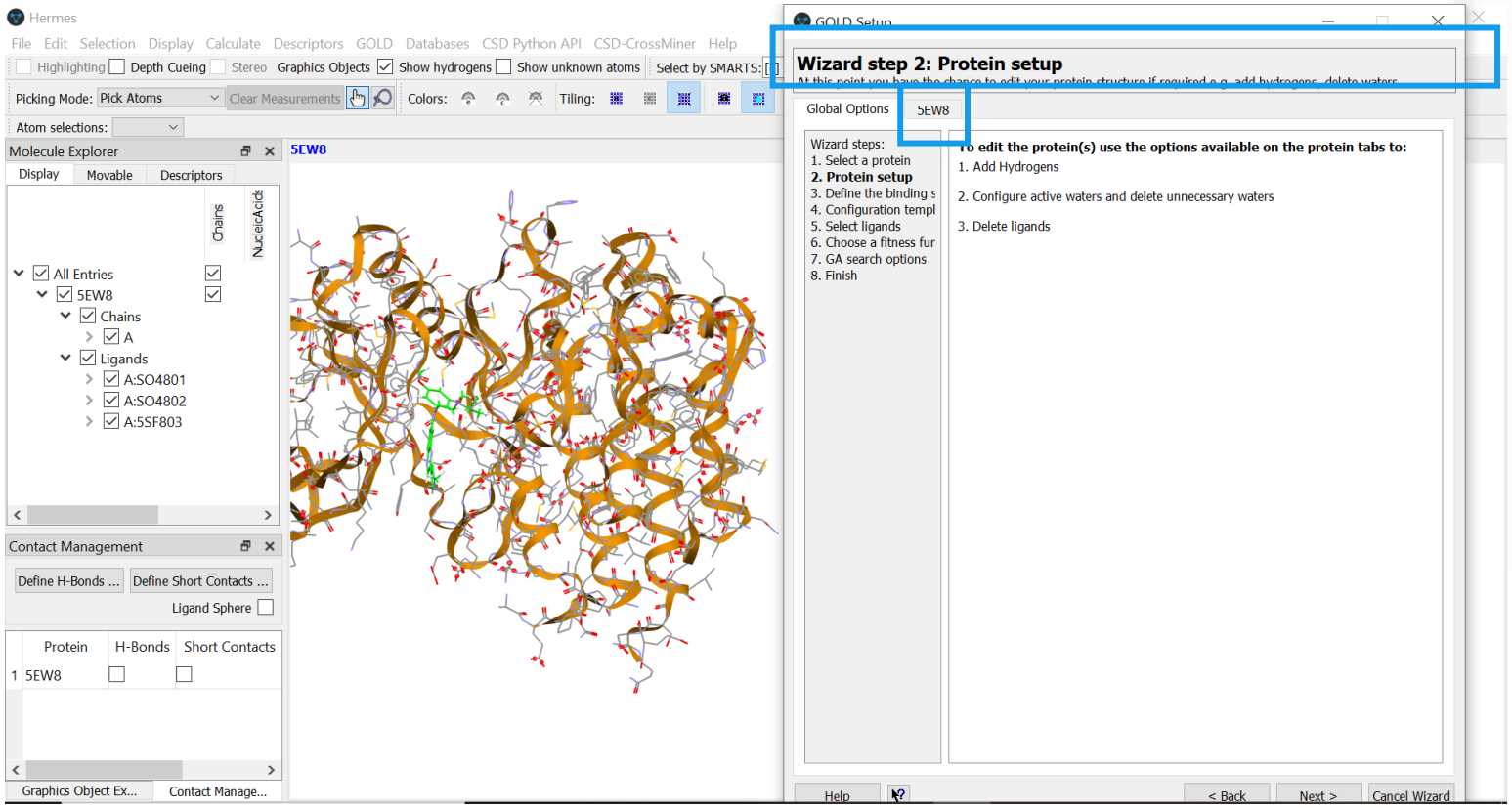
Docking with GOLD: Protein preparation

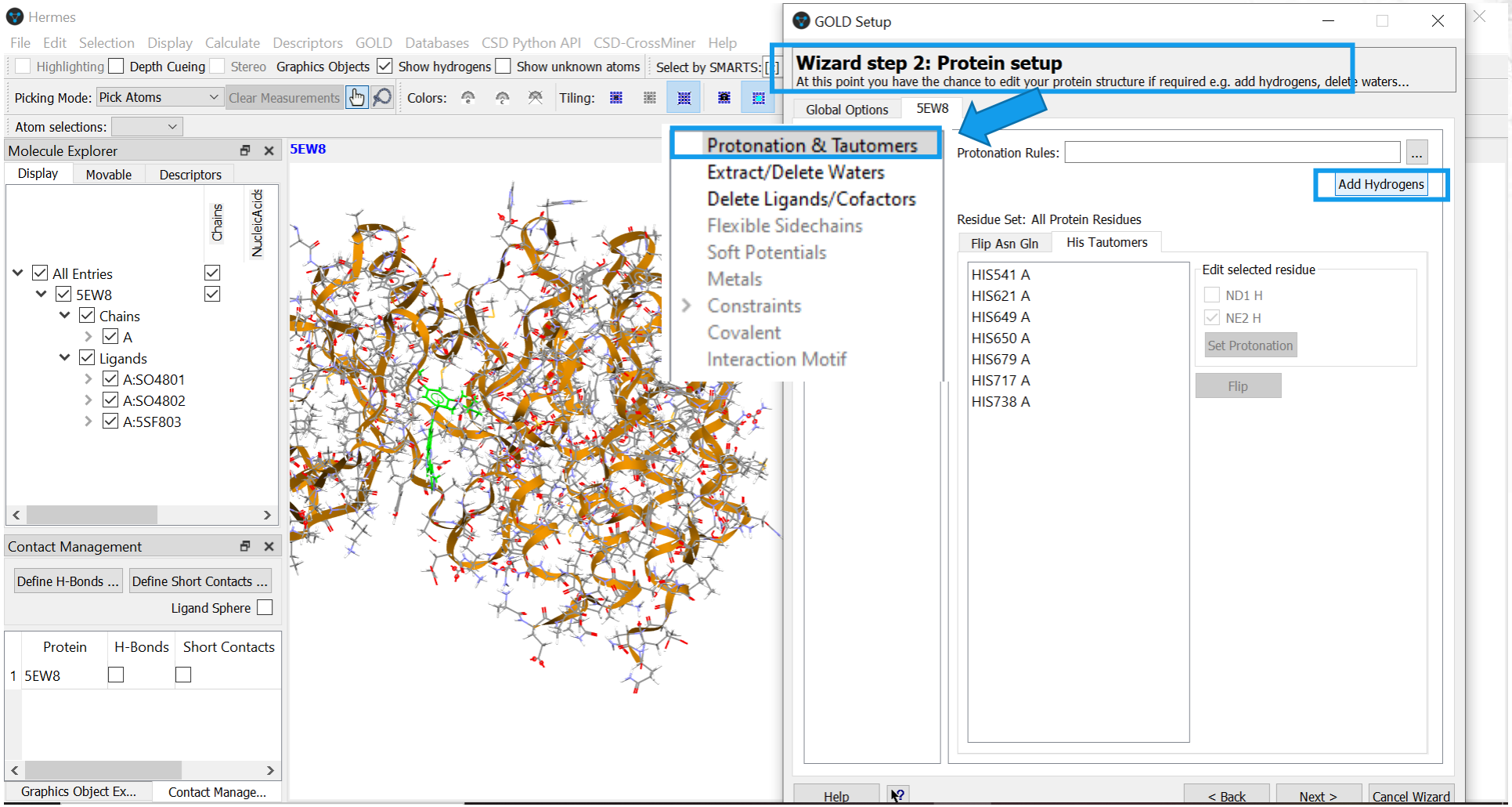


- Launch the GOLD wizard as shown above.
- Then, select the protein to investigate.

Docking with GOLD: Protein preparation



Docking with GOLD: Protein preparation



- Add missing hydrogens.

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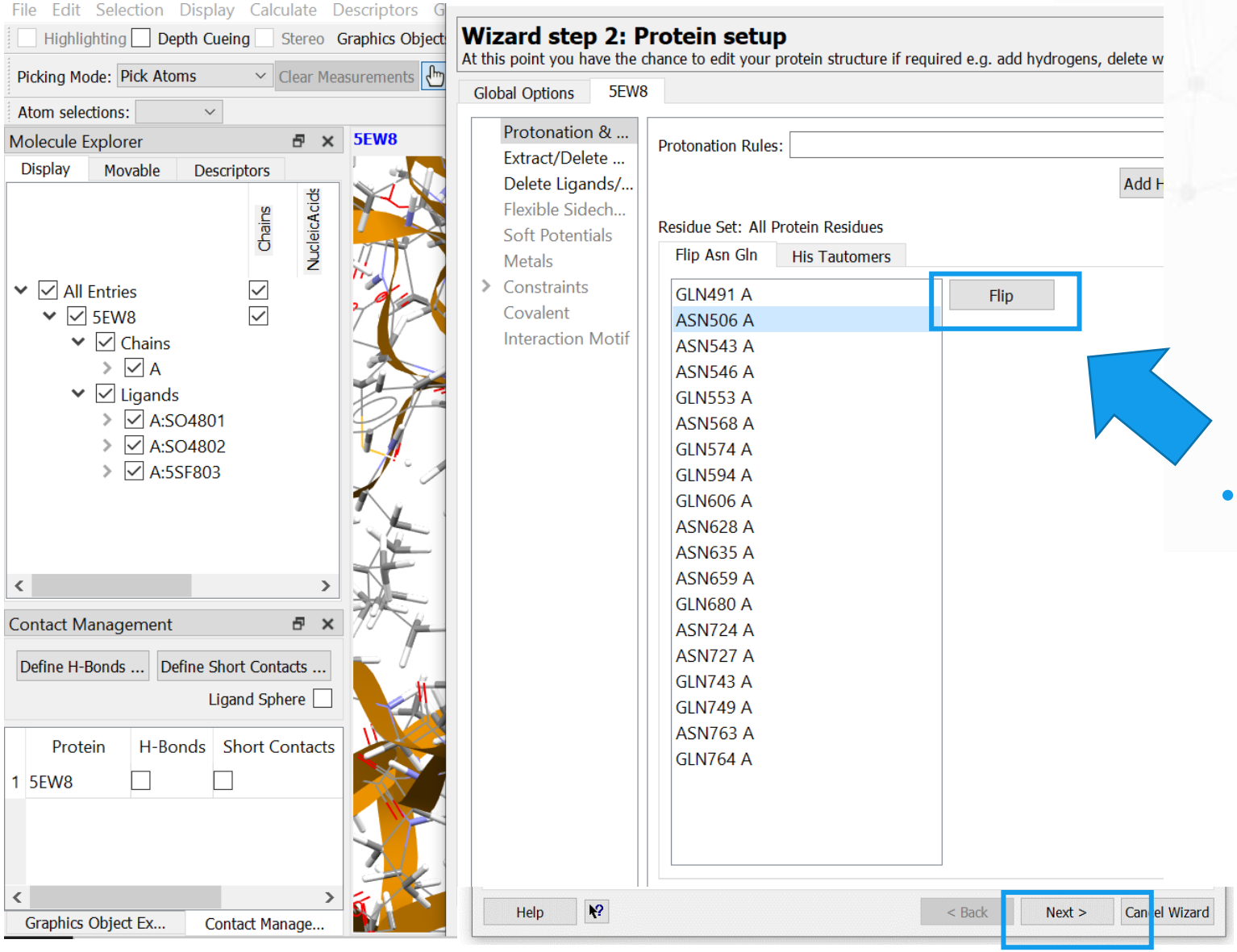
Docking with GOLD: Protein preparation



Tip

Always check the protonation around the binding site.

- You can flip the GLN and ASN based on the observation of these residues.

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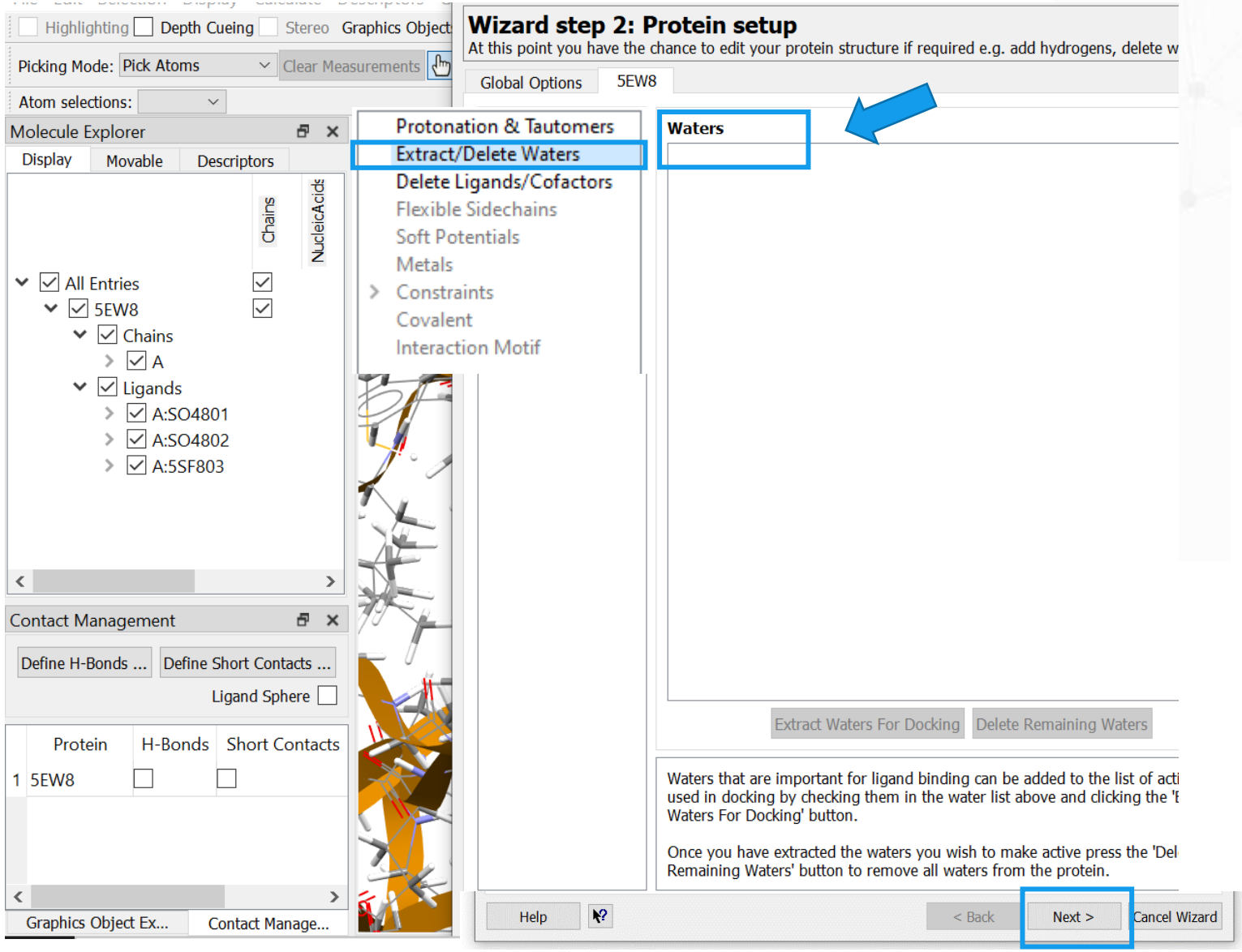
Docking with GOLD: Protein preparation



- You can extract and delete water molecules.
- In the example shown there are no water molecules to remove as we deleted them after loading the protein (before opening the GOLD Wizard).

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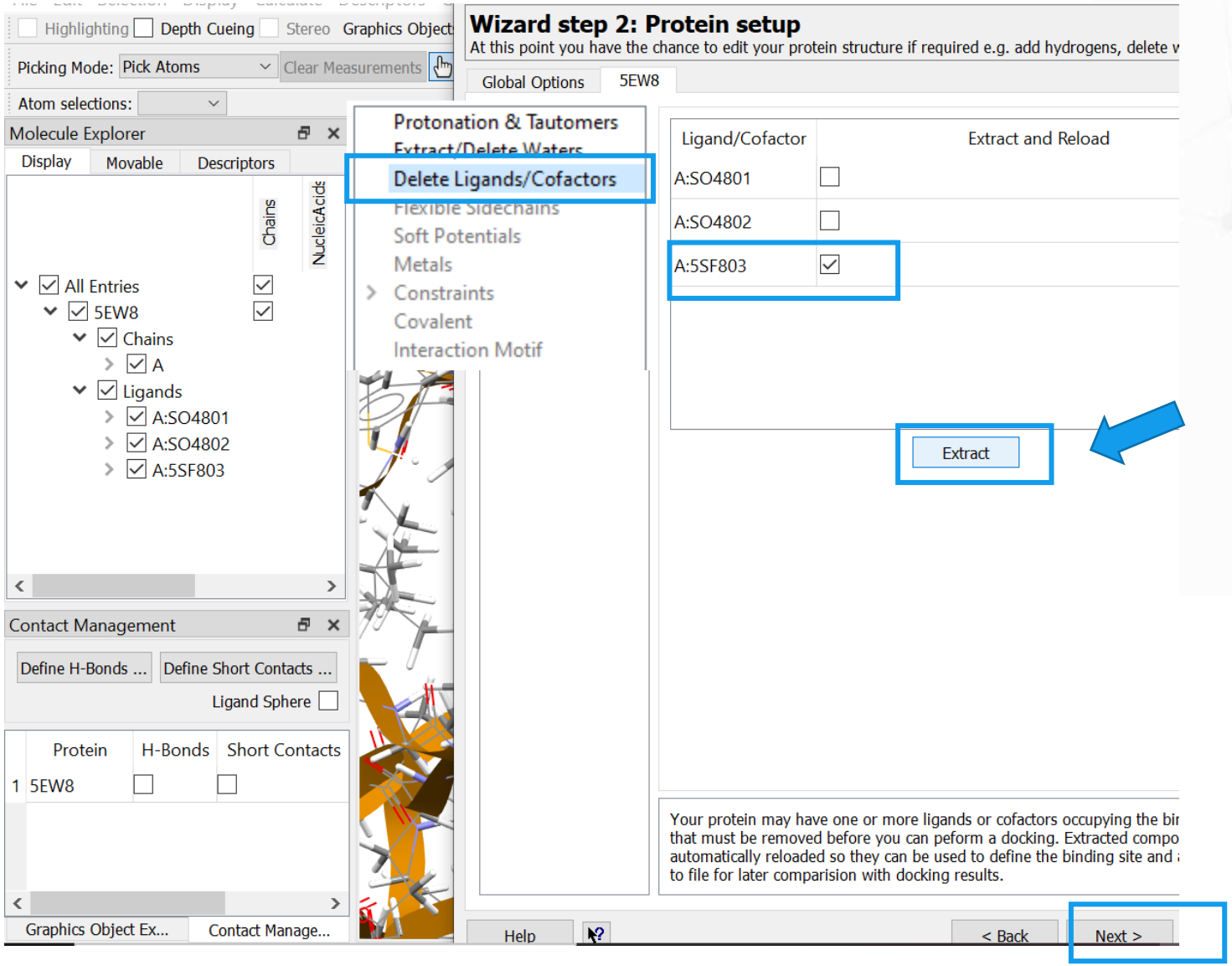
Docking with GOLD: Protein preparation



- You can extract and save the bound ligands.

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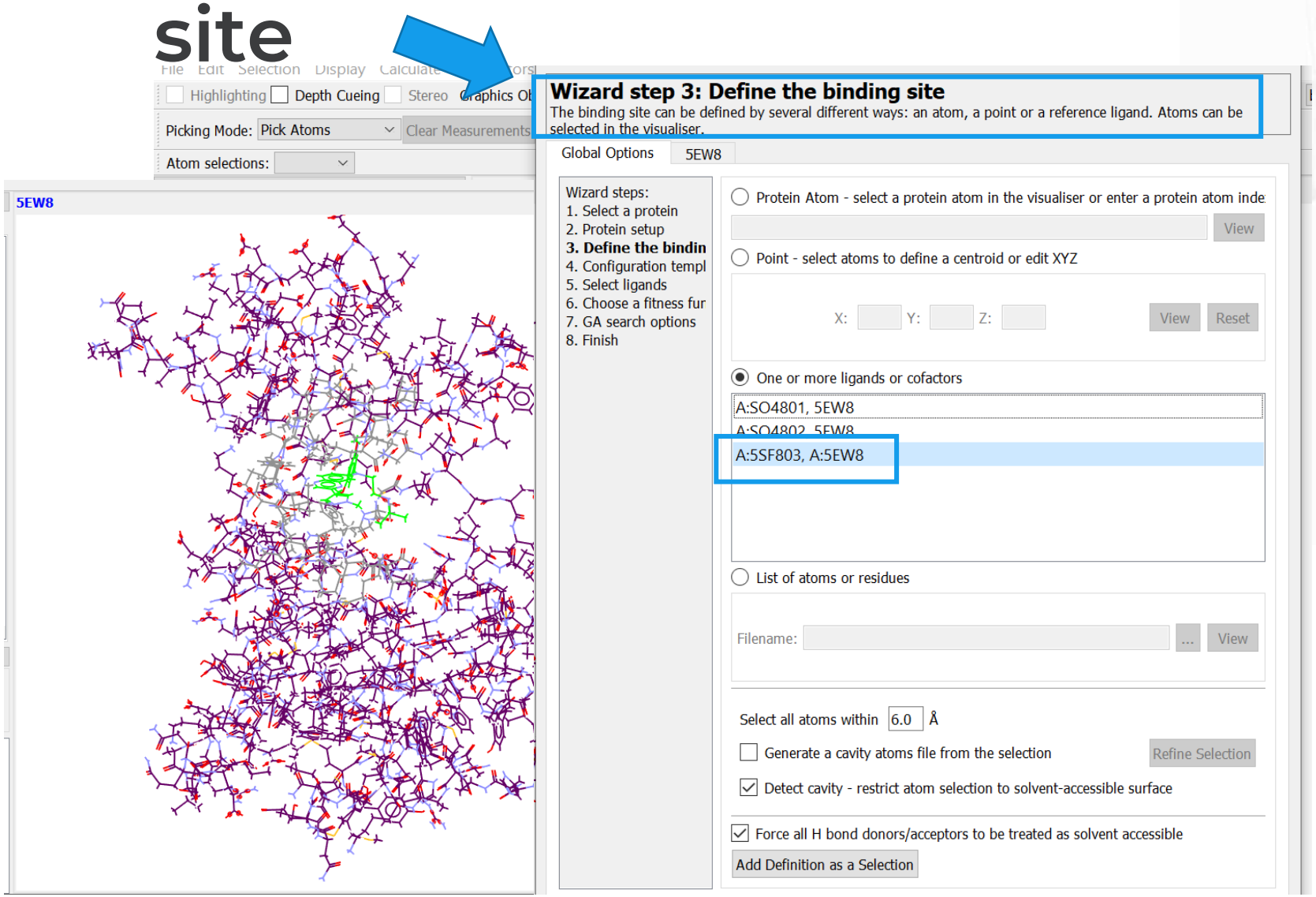
Docking with GOLD: Defining the binding site



- There are various ways in which you can define the binding site.
- Decide and select the one depending on the target protein or specific needs.
- You will see the binding site highlighted in the 3D visualizer.

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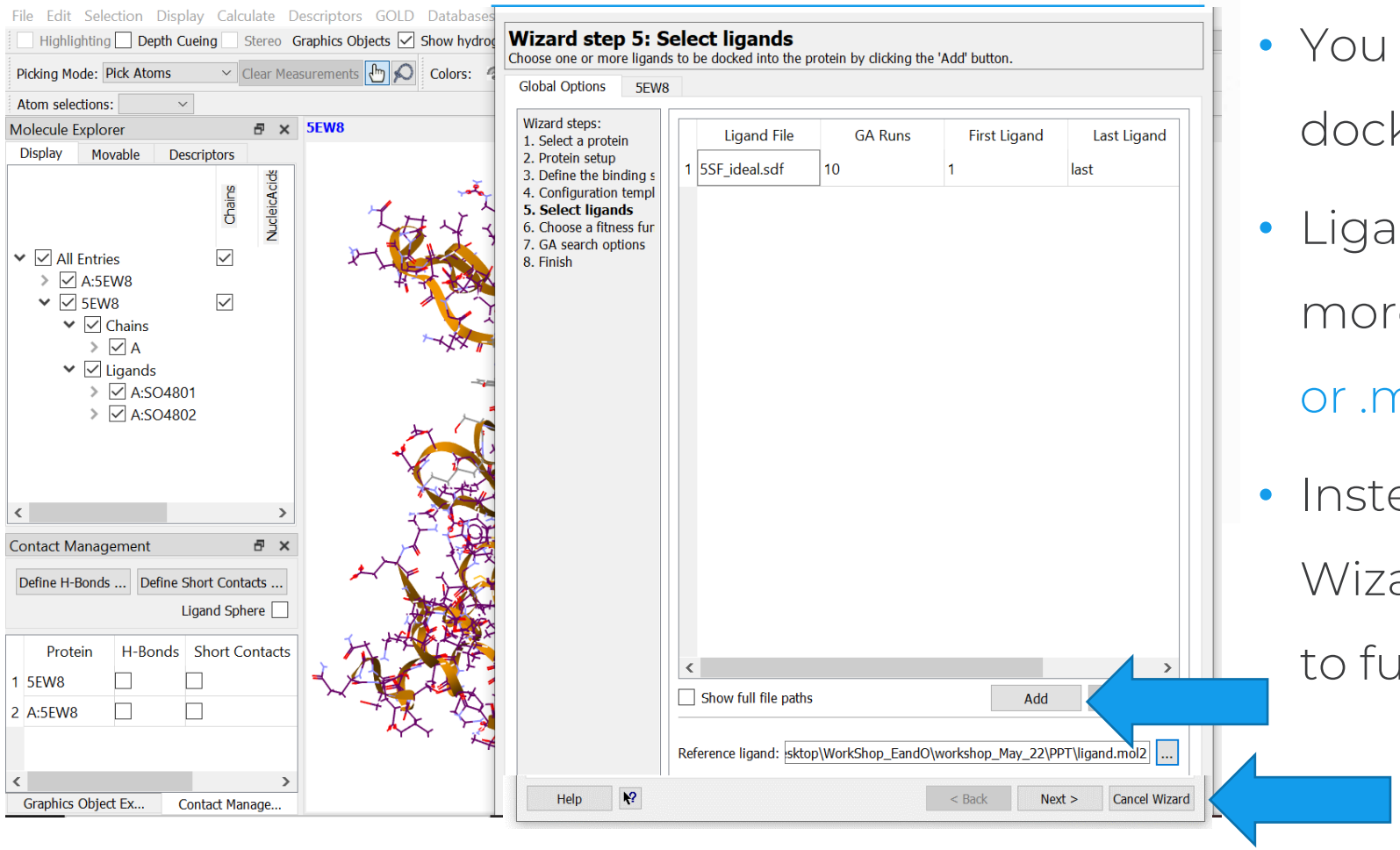
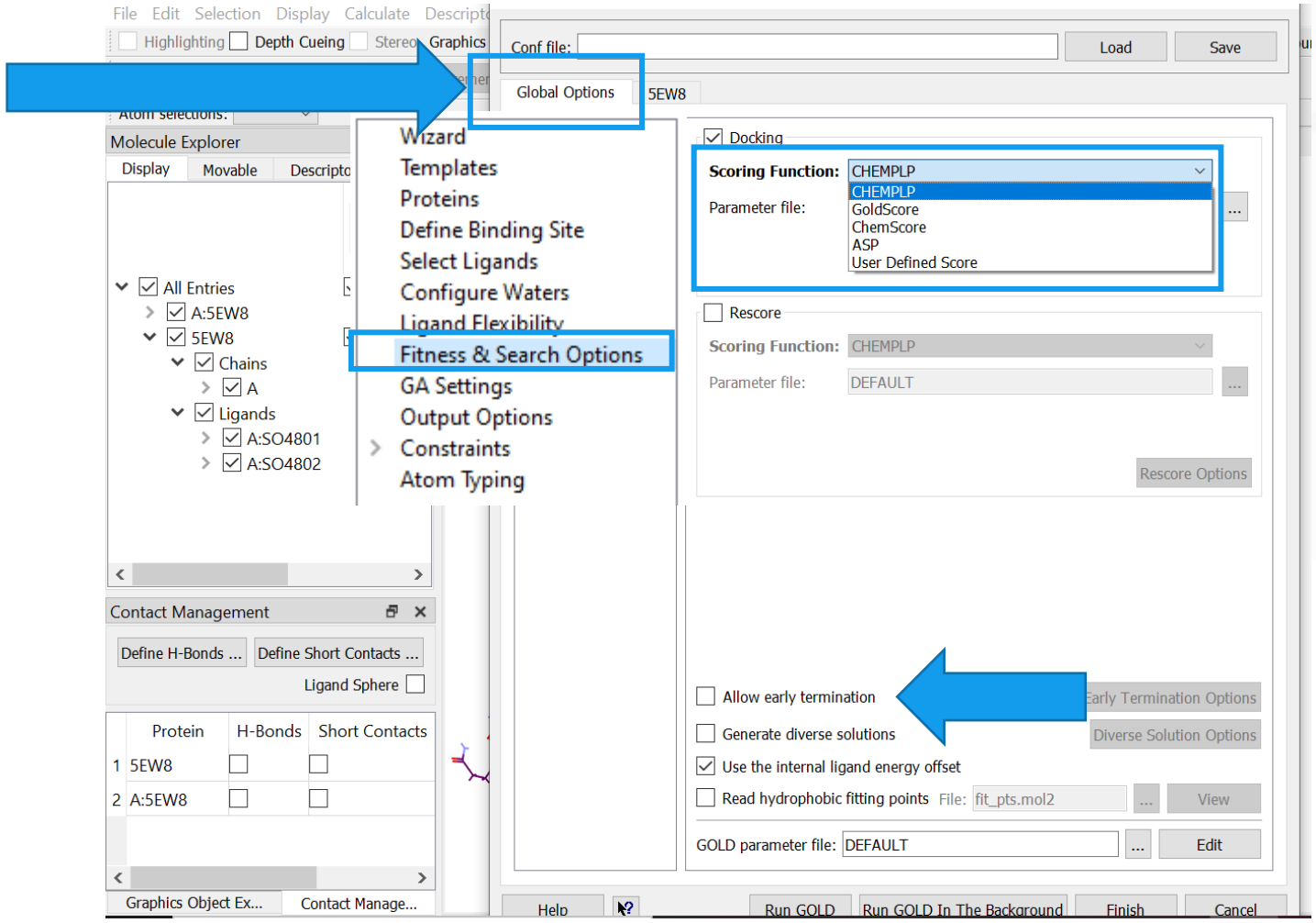
Docking with GOLD: Select ligand/s



- You can select the ligands to be docked.
- Ligand file could contain one or more than one molecule in .sdf or .mol format.
- Instead of continuing with the Wizard, cancel the wizard now to further configure.

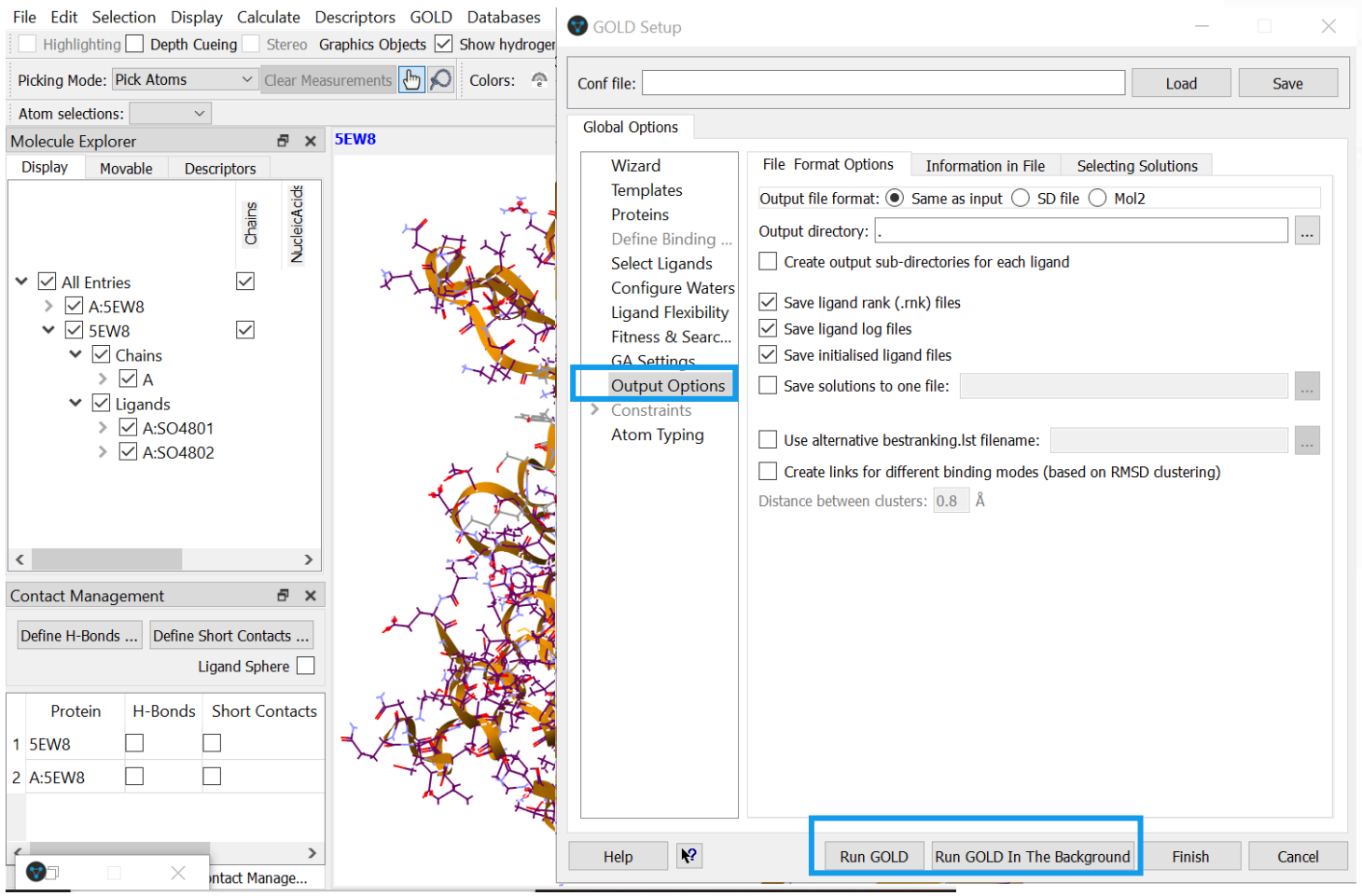
Docking with GOLD: Scoring function



- Under the Global Options, Fitness and Search Options you can select the Scoring Function.
- Here rescoring function is available for generating consensus.

- Untick *Allow early termination*

Docking with GOLD: Run the setup



In Output Options

- Select output destination/directory.
- Format of output you require.

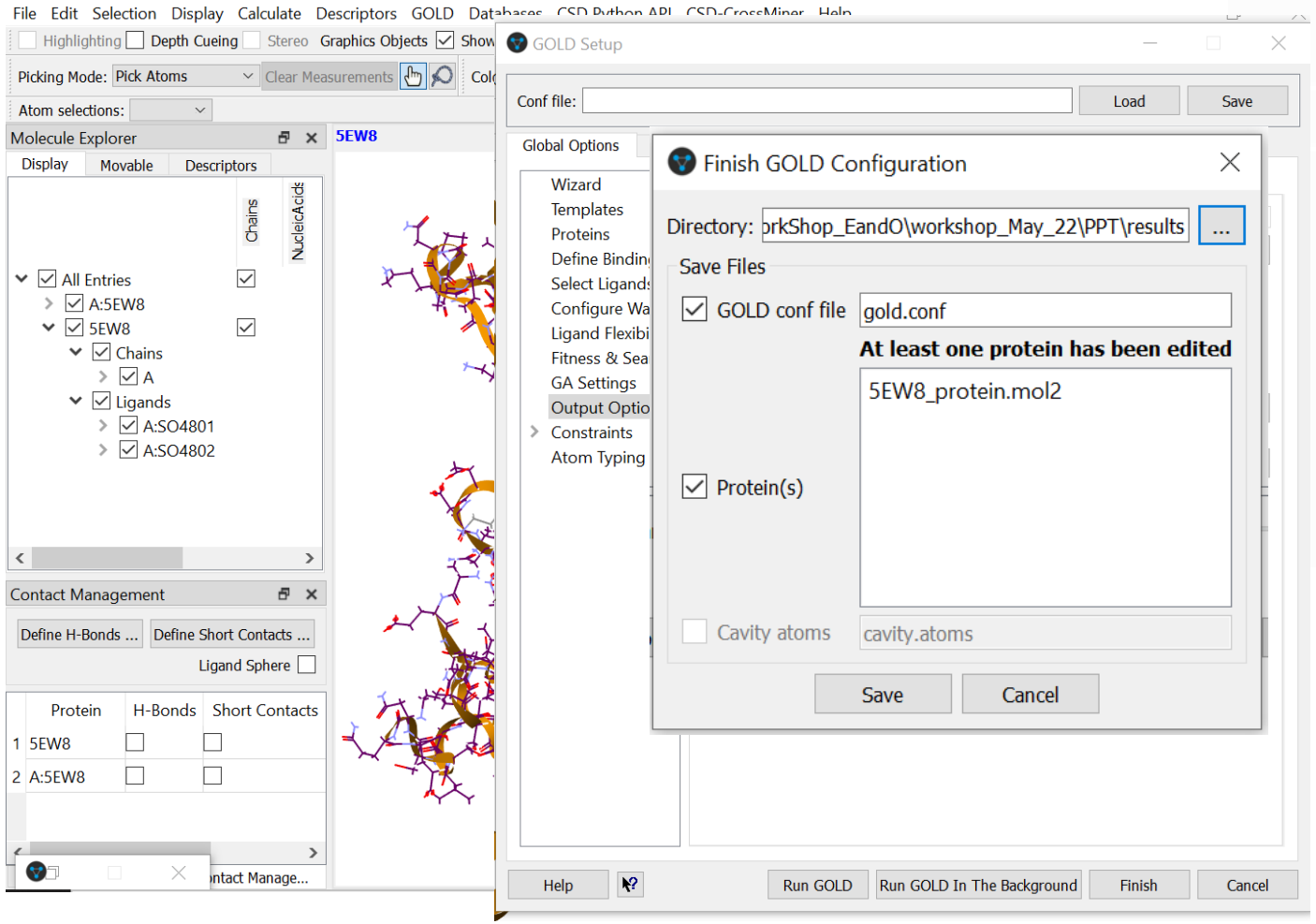
Run the GOLD calculations.

- Two options are available;

1. Run Gold: Interactive mode.

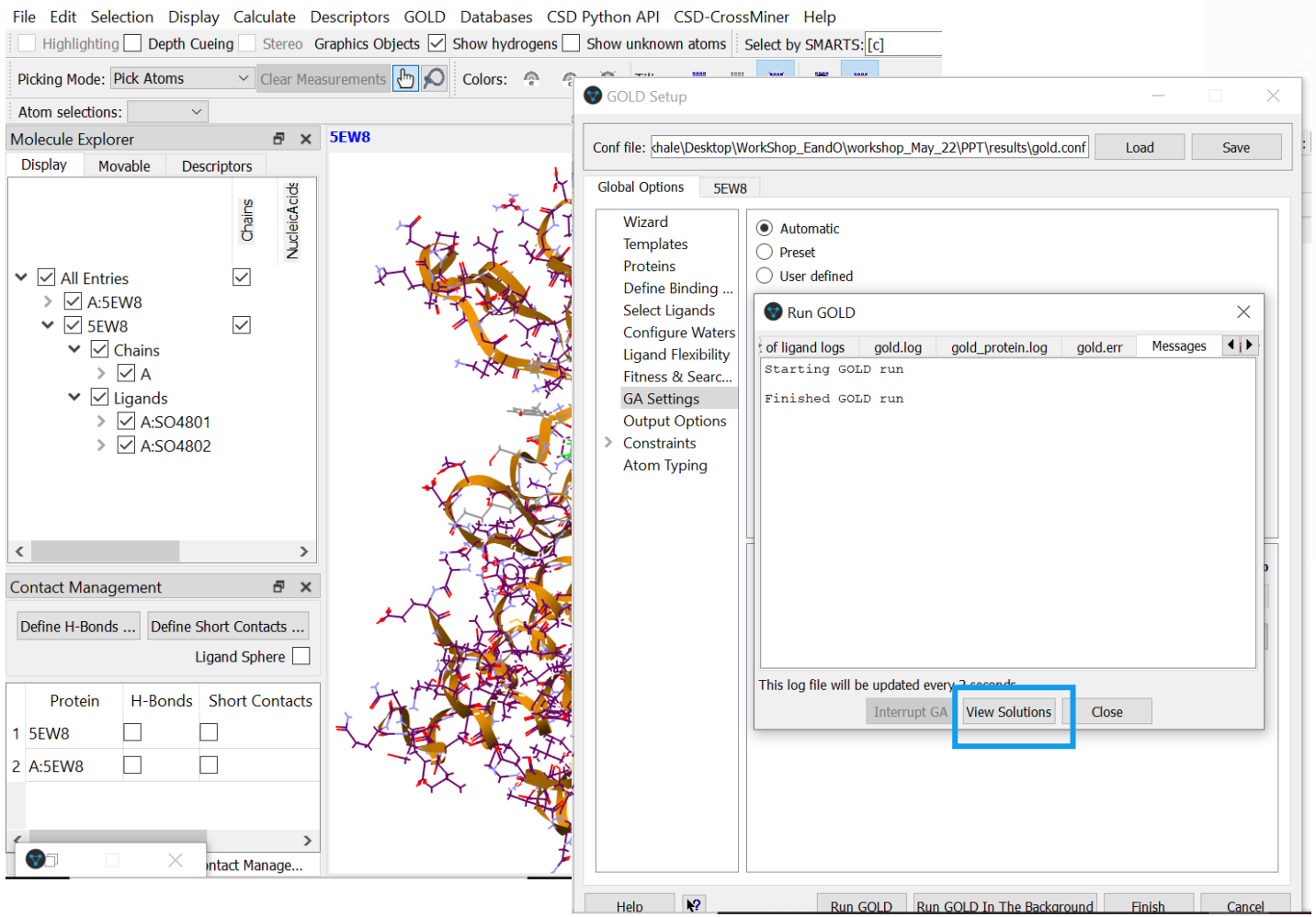
2. Run GOLD in Background: Results are seen in the output folder.

Docking with GOLD: Run the setup



- The run function asks for various options.
- The *gold.conf* file is the one with all the details. It is an editable file.

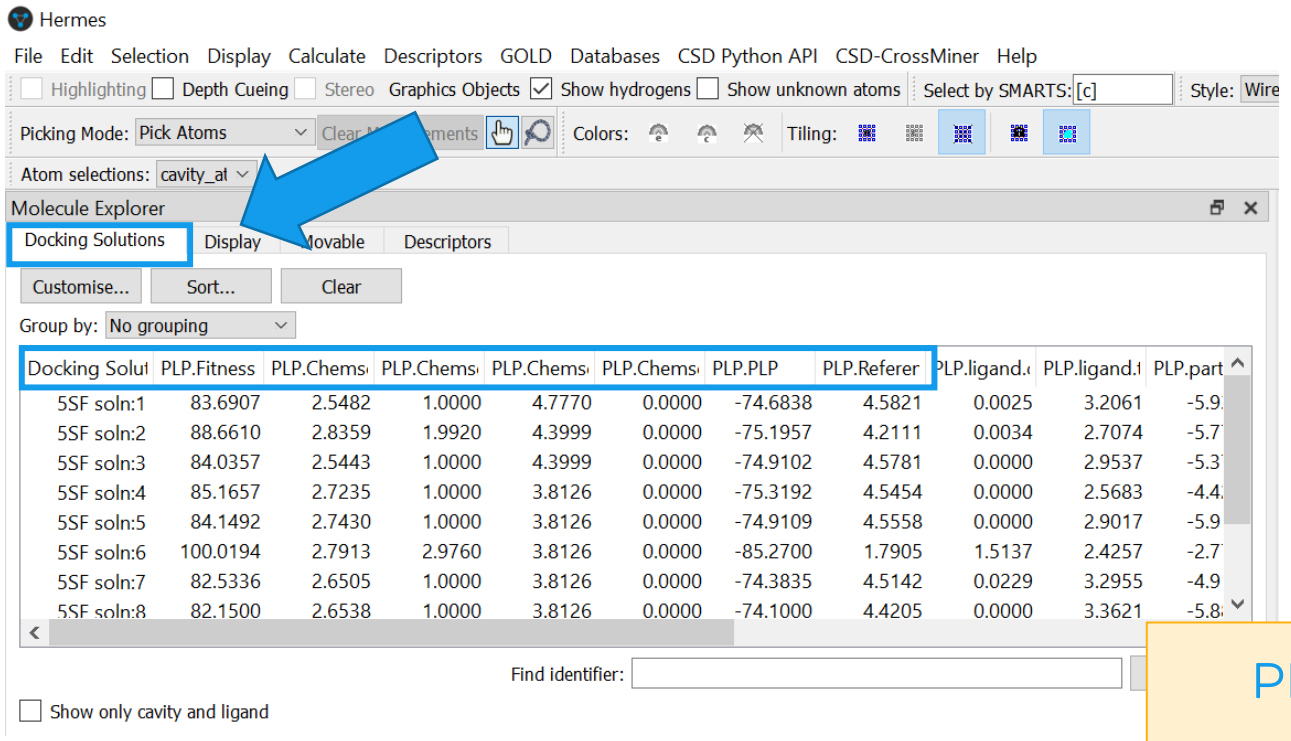
Docking with GOLD: Docking calculations



- You can check the progress of the calculation.
- The *Run GOLD* window has various tabs, which provide with on-the-fly status of your calculations.
- Once the run is complete, you can click *View Solutions*.

Docking with GOLD: Analysis of results

- Results are displayed in the *Molecular Explorer*.



- In most cases we are interested in the PLP fitness score and the RMSD.
- For PLP scoring function, higher scores and lower RMSD means better results.

PLP: Piecewise Linear Potential, it is an empirical fitness functions optimised for pose prediction.

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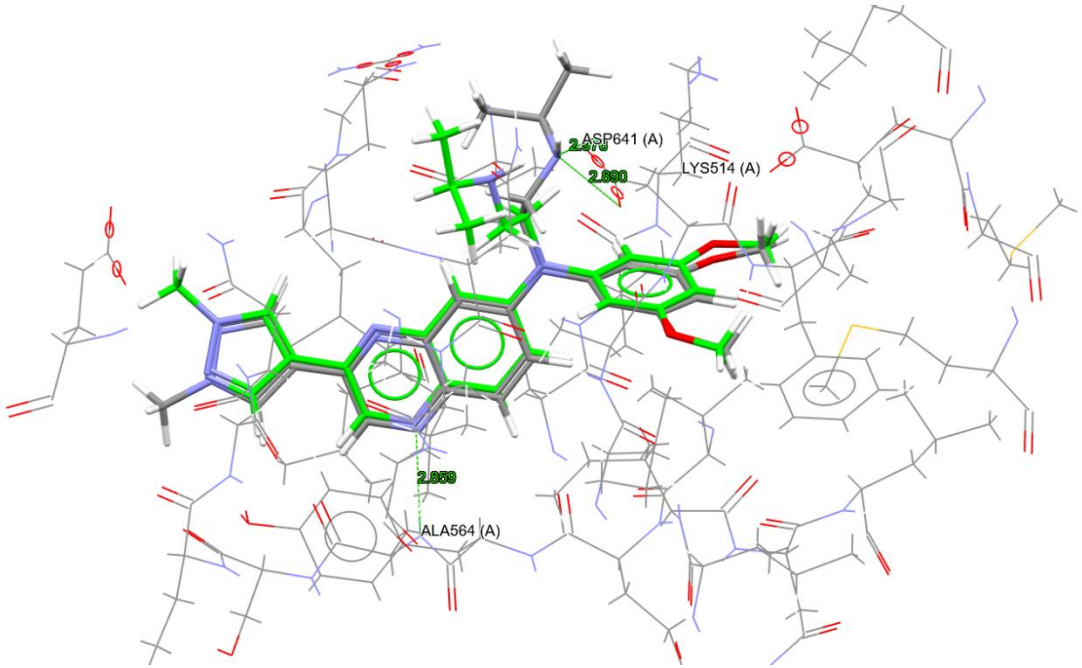
Docking with GOLD: Analysis of results



- Use the *Molecular Explorer* to display docking solutions, component of the system and the molecules.
- Manage the views and study the interactions.

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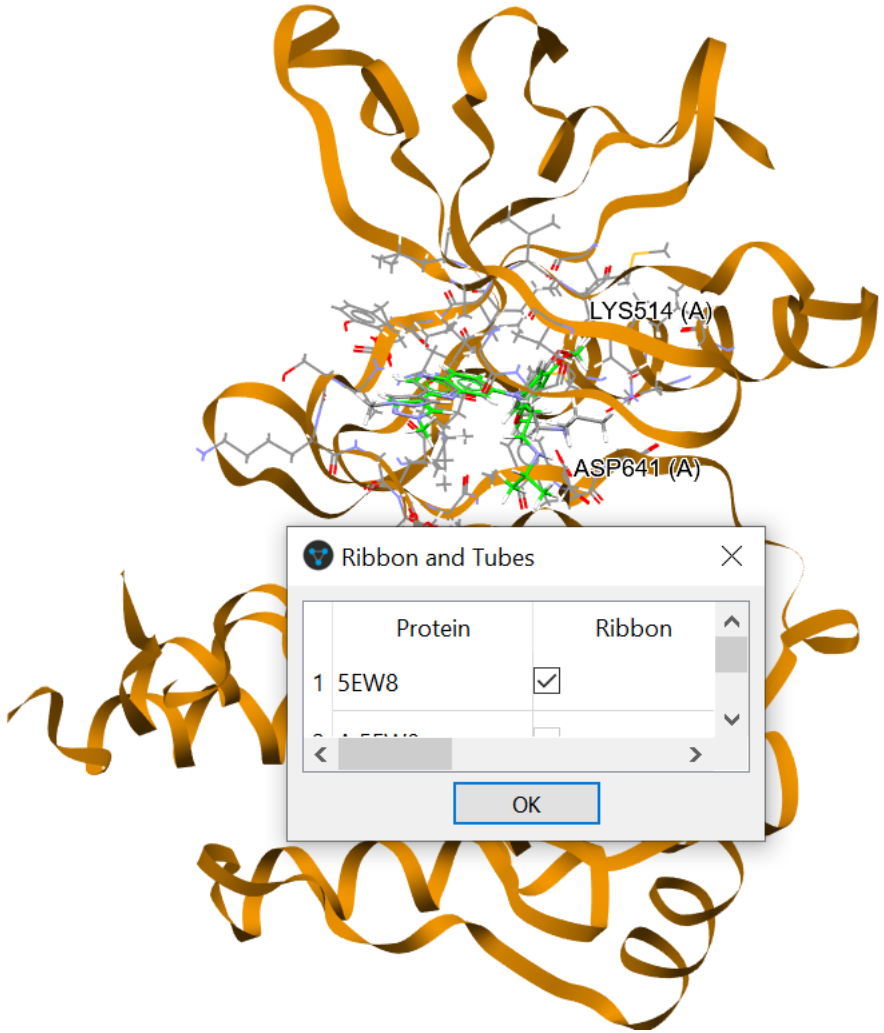
Docking with GOLD: Analysis of results



- Select Display

Ribbons and Tubes

Explore various options to create various colour combinations and displays

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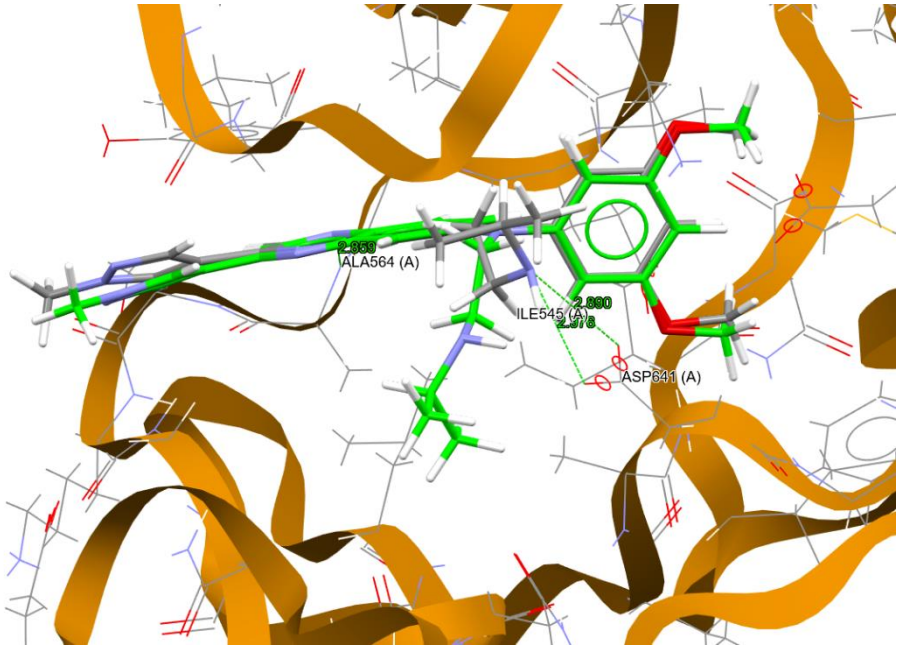
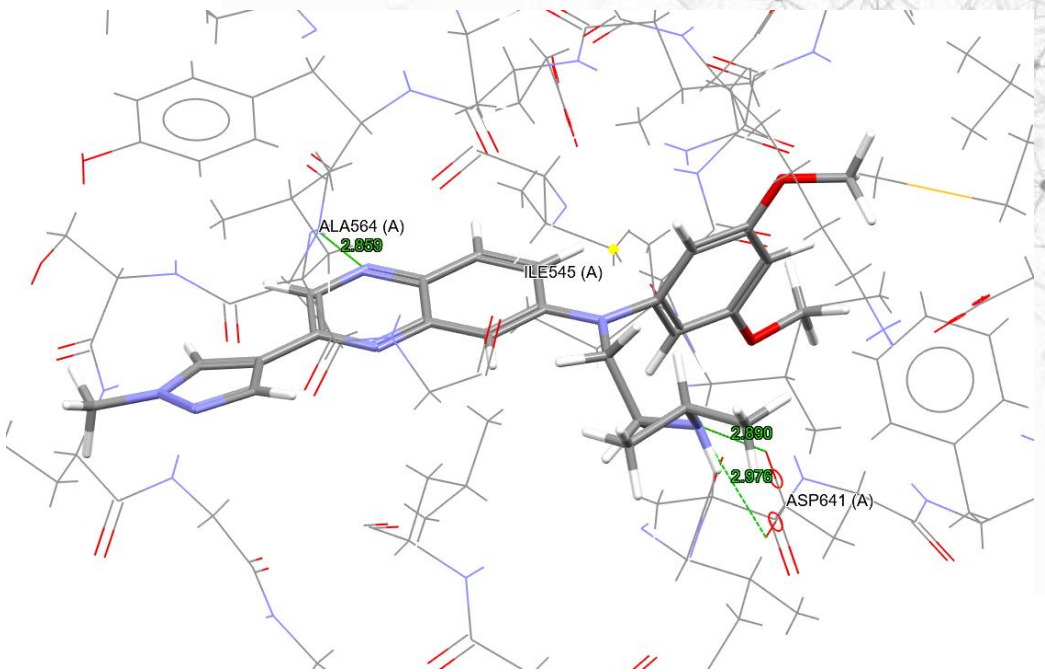
Docking with GOLD: Analysis of results





- Results can be visualised in various ways and representations.
- Can display hydrogen bonds for the docked and reference ligands.

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