BioSolveIT
expect actives!

SeeSAR

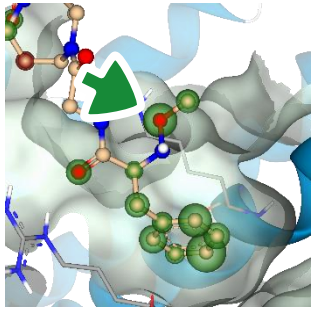
Beginner's Guide

Version 15 - Apollo

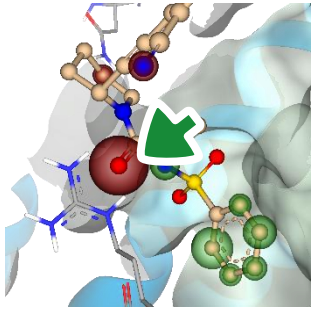
Time to start an interactive dialog with your compound!

SeeSAR's Visual Elements

HYDE Spheres

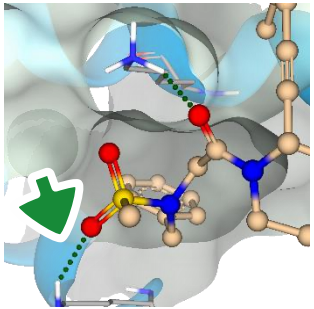


Green sphere: beneficial contribution to the binding affinity. Happy atom.

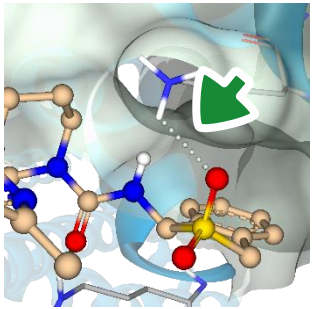


Red sphere: negative contribution to the binding affinity. Unhappy atom.

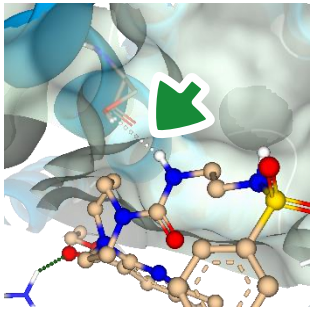
H-Bond Geometry



Dark green: Good geometry for H-bond interactions.

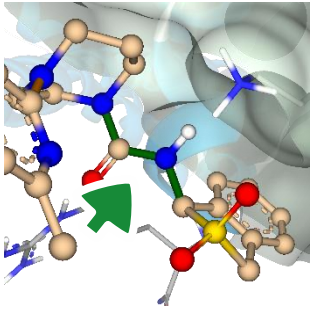


Light green: Moderate geometry for H-bond interactions.

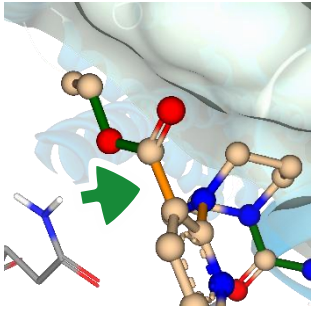


White: Poor geometry for H-bond interactions.

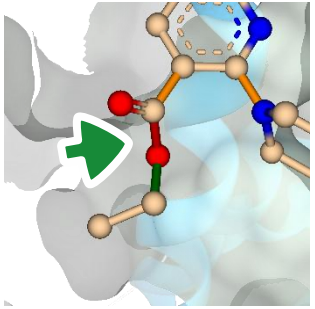
Torsions



Green: Frequent occurrence in PDB structures.



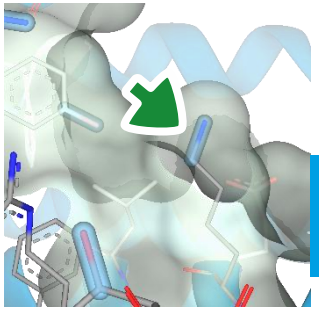
Orange: Occasional occurrence in PDB structures.



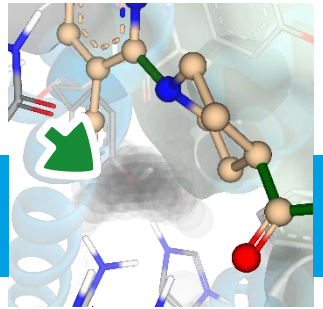
Red: Rare/no occurrence in PDB structures.

SeeSAR's Visual Elements

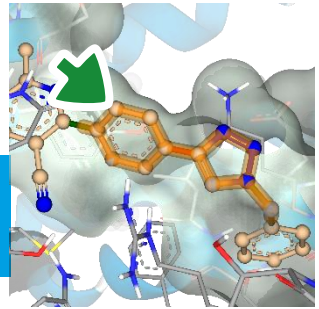
Visual Indicators



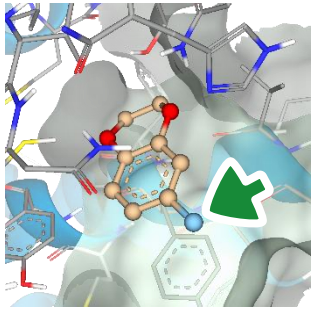
Blue tube: Potential target residue for covalent docking.



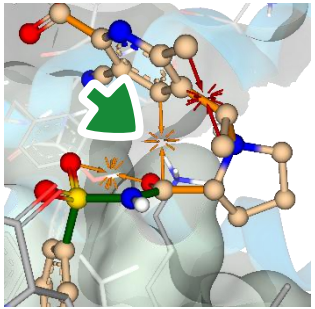
Unoccupied Space: Each sphere can host a fluorine atom.



Orange: Area replaced/added in the Inspirator Mode.



Blue atom: Linker atom. Extension point in Chemical Space Docking®.



Clashes: Intra- and intermolecular clashes of the ligand.

Table View

LLE	Tor.	Intra-clash	Inter-clash	MPO [Radar]
👎	●	●	●	●
🤏	●	●	●	●
🤏	●	●	●	●
👉	●	●	●	●
👎	●	●	●	●
👍	●	●	●	●
👉	●	●	●	●

Lipophilic Ligand Efficiency (LLE):

👍 ≥ 6.5 | 👌 ≥ 5.0 | 👉 ≥ 3.5

🤏 ≥ 2.0 | 👎 < 2.0

Torsions: green: At most two tolerable bonds, orange: More than two tolerable bonds or one strained bond and at most 2 tolerable bonds, red: Anything else.
Clashes: green: Distance of all evaluated atom pairs > 0.89 Å than the sum of their van der Waals radii, orange: Distance > 0.85 Å, red: At least one atom pair has a distance < 0.85 Å or less of the sum of their van der Waals radii, or three orange clashes.
Multi-parameter Optimization (MPO): Gradient from no violations (green), half of the parameters violated (yellow), all parameters violated (red).

Hot Keys

General Viewing

right-click	rotate*
left-click	select
[Ctrl]+right-click middle-click	translate
[Shift]+right-click	z-rotation
[Ctrl]+[Shift]+ right-click mouse-wheel	zoom
[Del]	delete table entries
[Up] and [Down] arrows	move to the respective next table entry
[Space]	center view on selected pose

*If you click on an object, this is taken as the center of rotation. Otherwise, the rotation is – depending on the viewing mode – either around the center of the entire protein or around the center of the binding site. So don't just click anywhere but close to a ligand atom of interest to rotate around it.

3D Actions

[D]+left-clicks	measure distances
[L]+left-click	label items
[A]+left-clicks	measure angle
[T]+left-clicks	measure torsion

Molecule Table

[Alt+C]	check molecule
[Alt+V]	toggle visibility
[Alt+F]	favorite
[Alt+A]	set activity (twice for 'inactive')

Editing

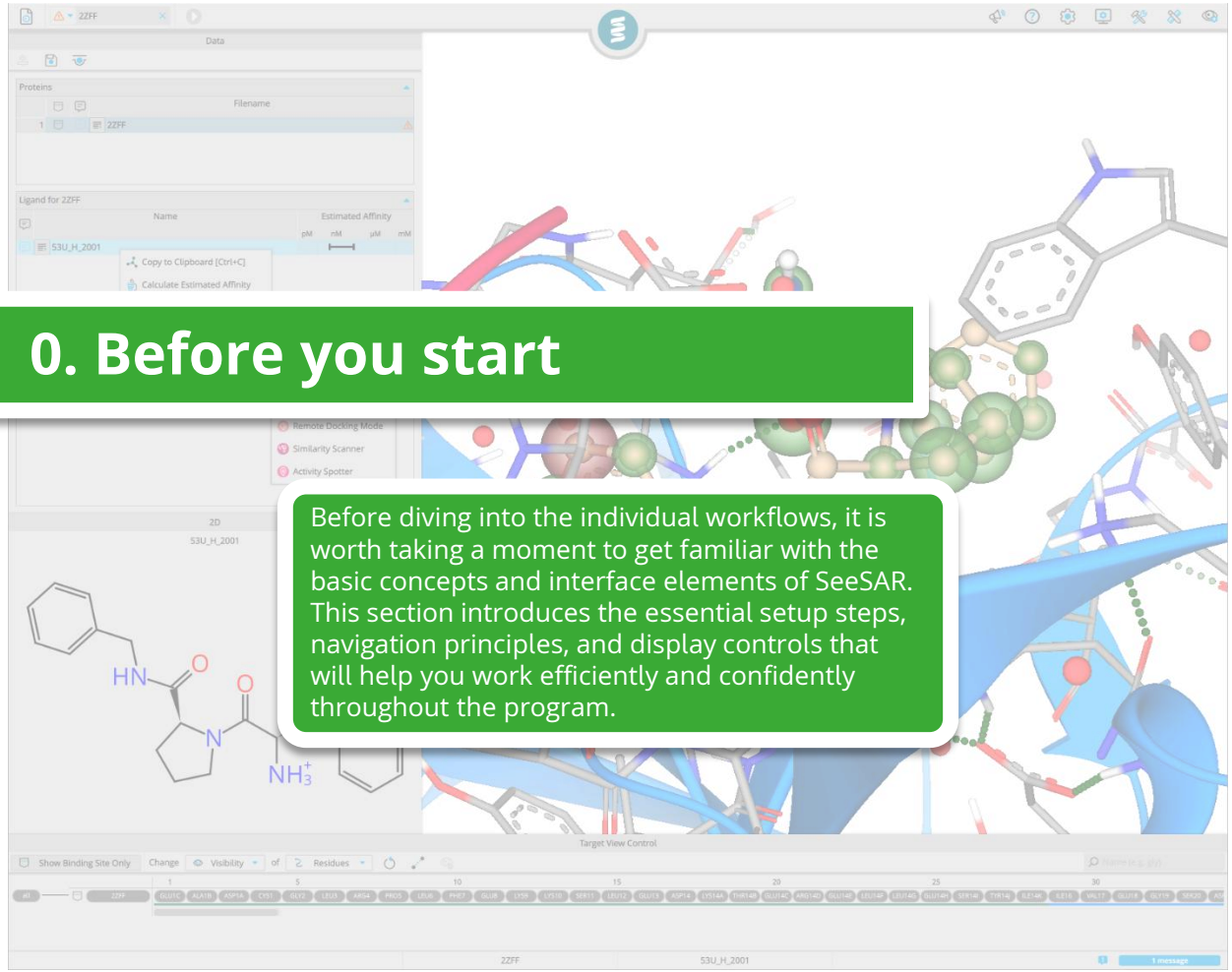
[Esc]	exit the editor
[Ctrl+S]	save the current project
[Ctrl+E]	save the current molecule in the Molecule Editor Mode
left-click: hold & drag	select all atoms and bonds in a box
[Del]	delete the current selection
[Ctrl+Z]	undo
[Ctrl+Shift+Z]	redo
right-click	context menu to add atom, resp. change bond type
left-click+ [C,B,O,S,P,F,I,1,2,3]	change element, resp. change bond type

Some keyboards will have [Strg] instead of a [Ctrl] button.
For the Mac, replace [Ctrl] by the Apple key. Also [fn]+[back] equals [del] on the Mac keyboard.

Content

Click on the section you are interested in

0. Before you start



Before diving into the individual workflows, it is worth taking a moment to get familiar with the basic concepts and interface elements of SeeSAR. This section introduces the essential setup steps, navigation principles, and display controls that will help you work efficiently and confidently throughout the program.

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Mode Overview

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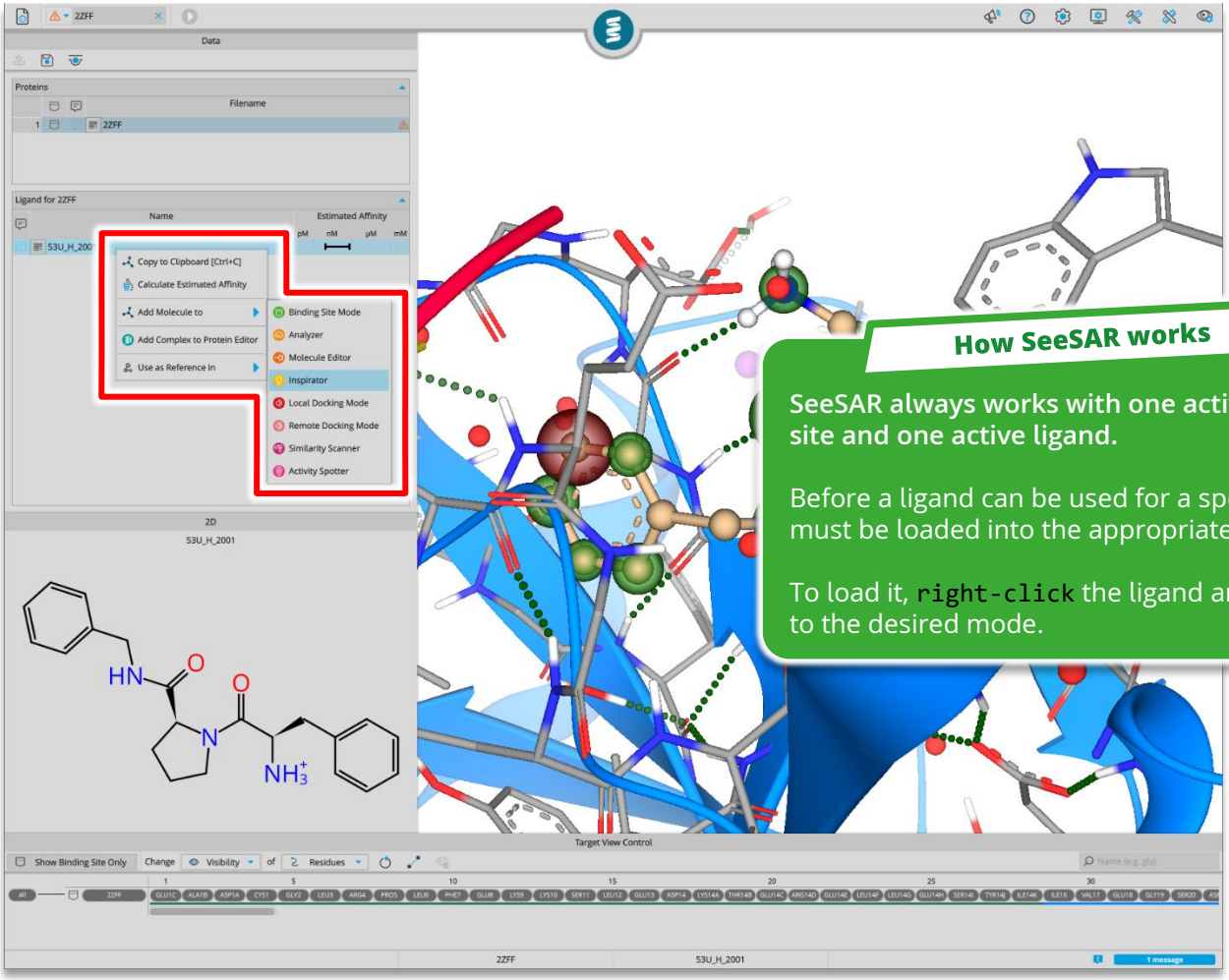
Mode Overview



How SeeSAR works

SeeSAR always works with one active binding site and one active ligand.

Before a ligand can be used for a specific task, it must be loaded into the appropriate **Mode**.

To load it, `right-click` the ligand and send it to the desired mode.

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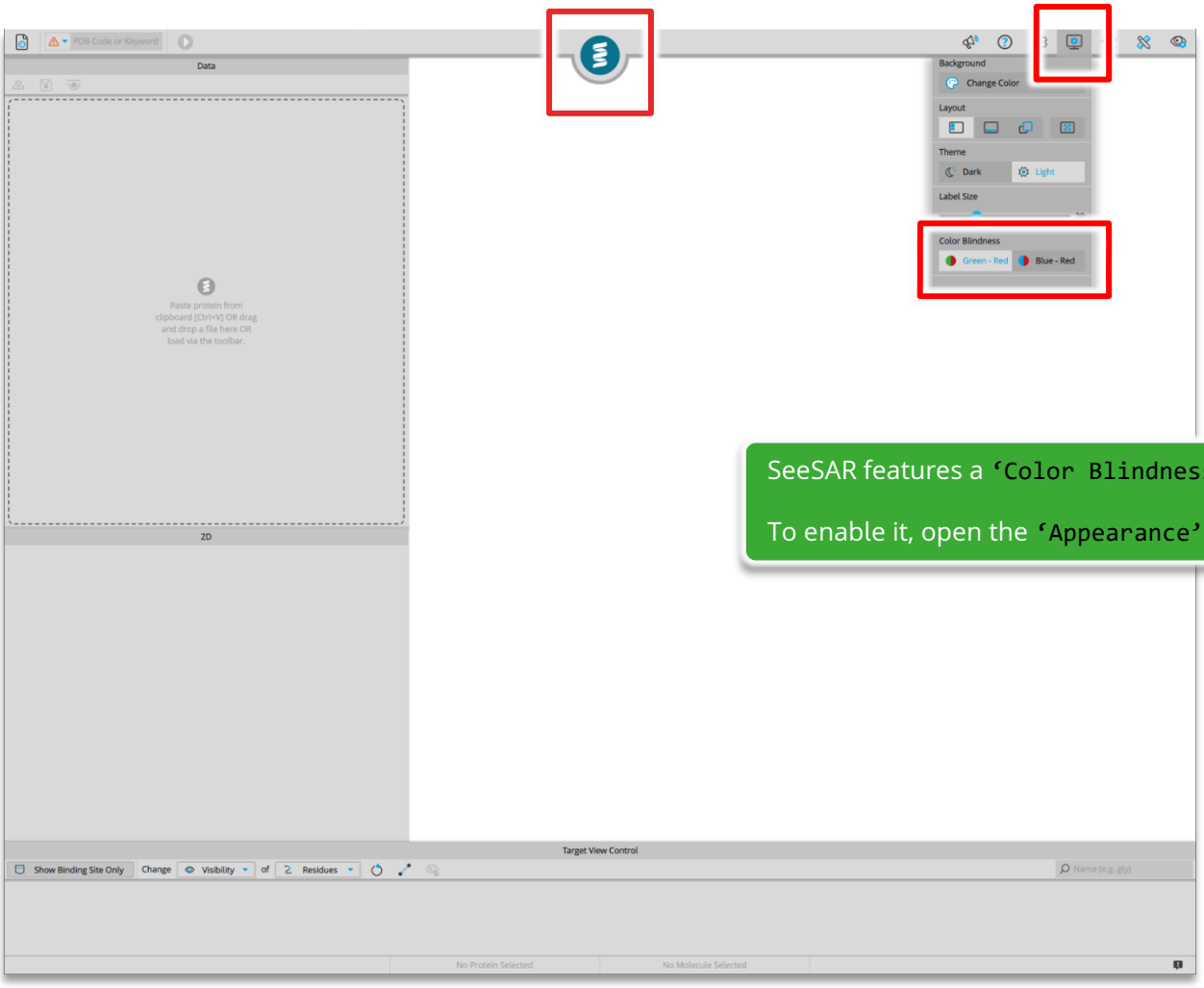
Mode Overview



SeeSAR features a ‘Color Blindness’ support.

To enable it, open the ‘Appearance’ menu.

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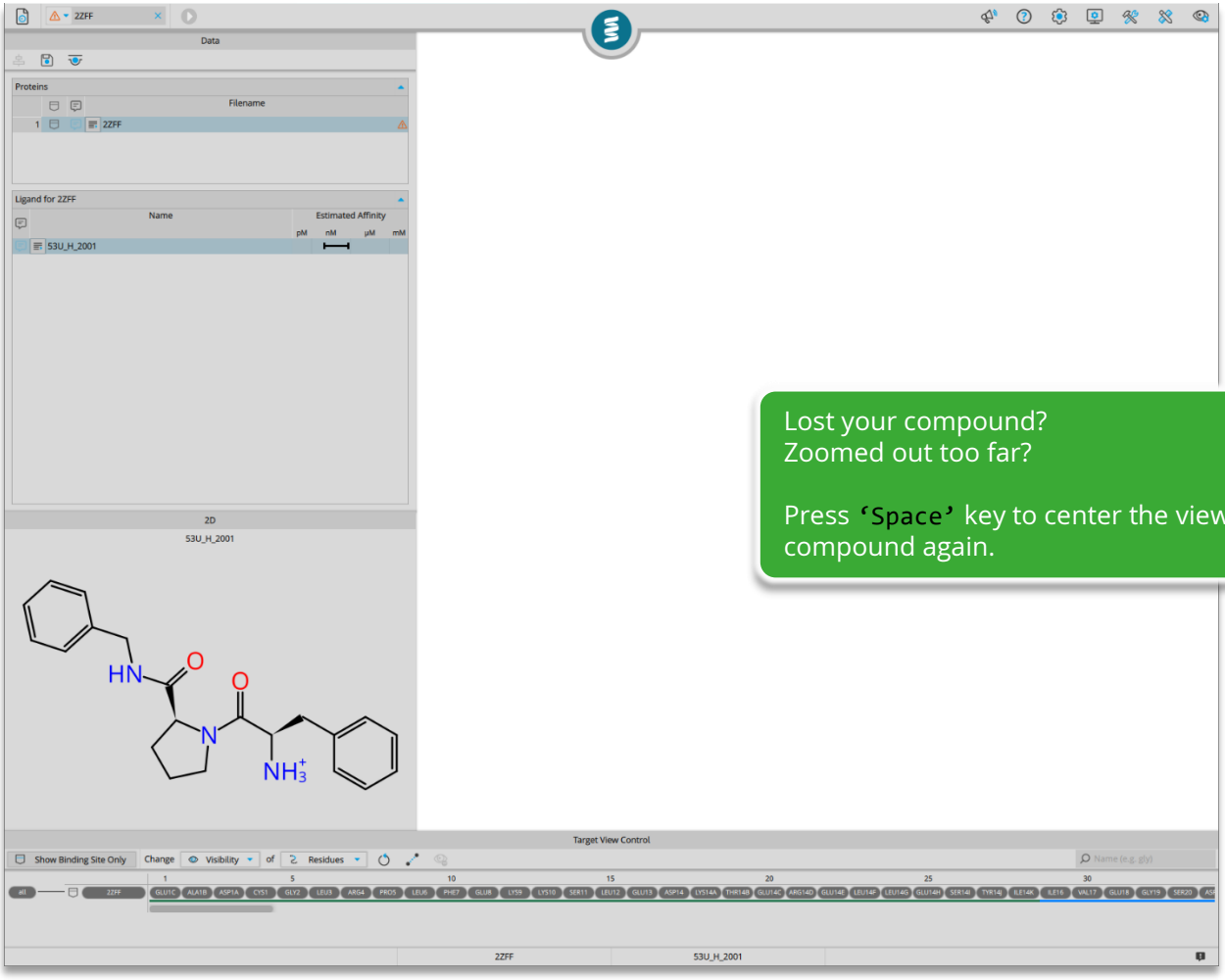
Mode Overview



Lost your compound?
Zoomed out too far?

Press ‘Space’ key to center the view on the compound again.

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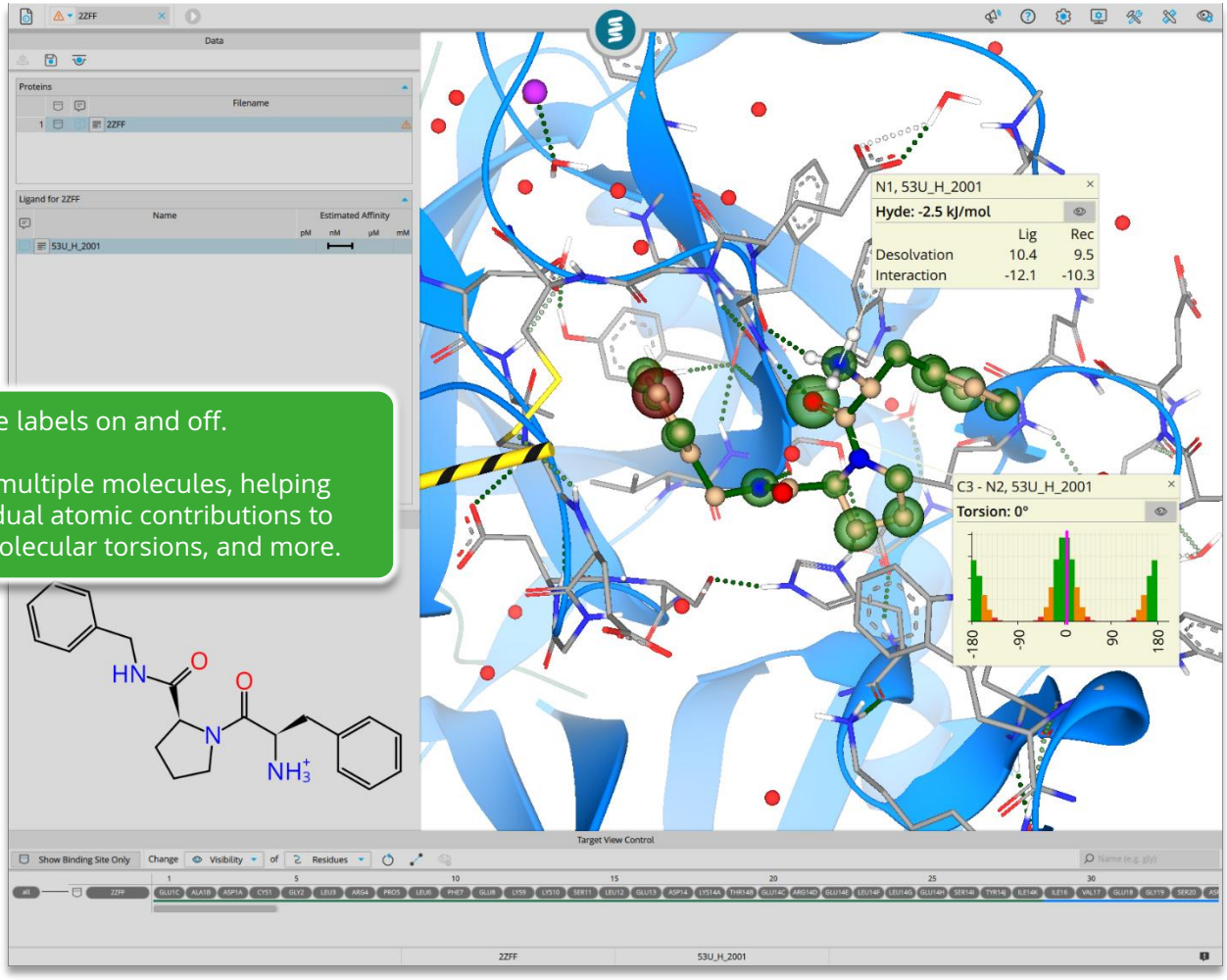
Mode Overview

Press ‘L’ to toggle labels on and off.

SeeSAR can label multiple molecules, helping you inspect individual atomic contributions to binding affinity, molecular torsions, and more.



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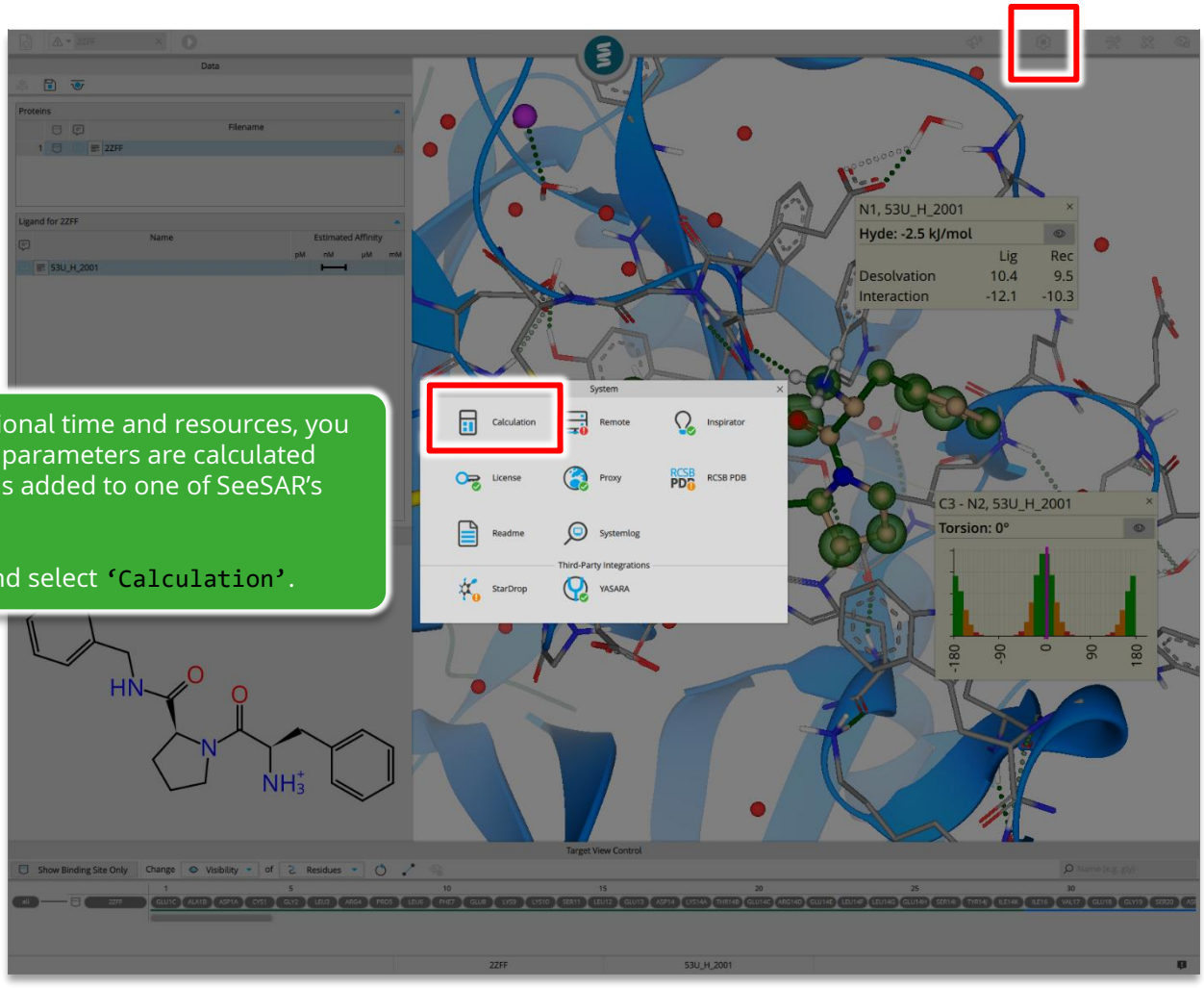
Mode Overview

To save computational time and resources, you can choose which parameters are calculated when a molecule is added to one of SeeSAR's Modes.

Go to **'System'** and select **'Calculation'**.



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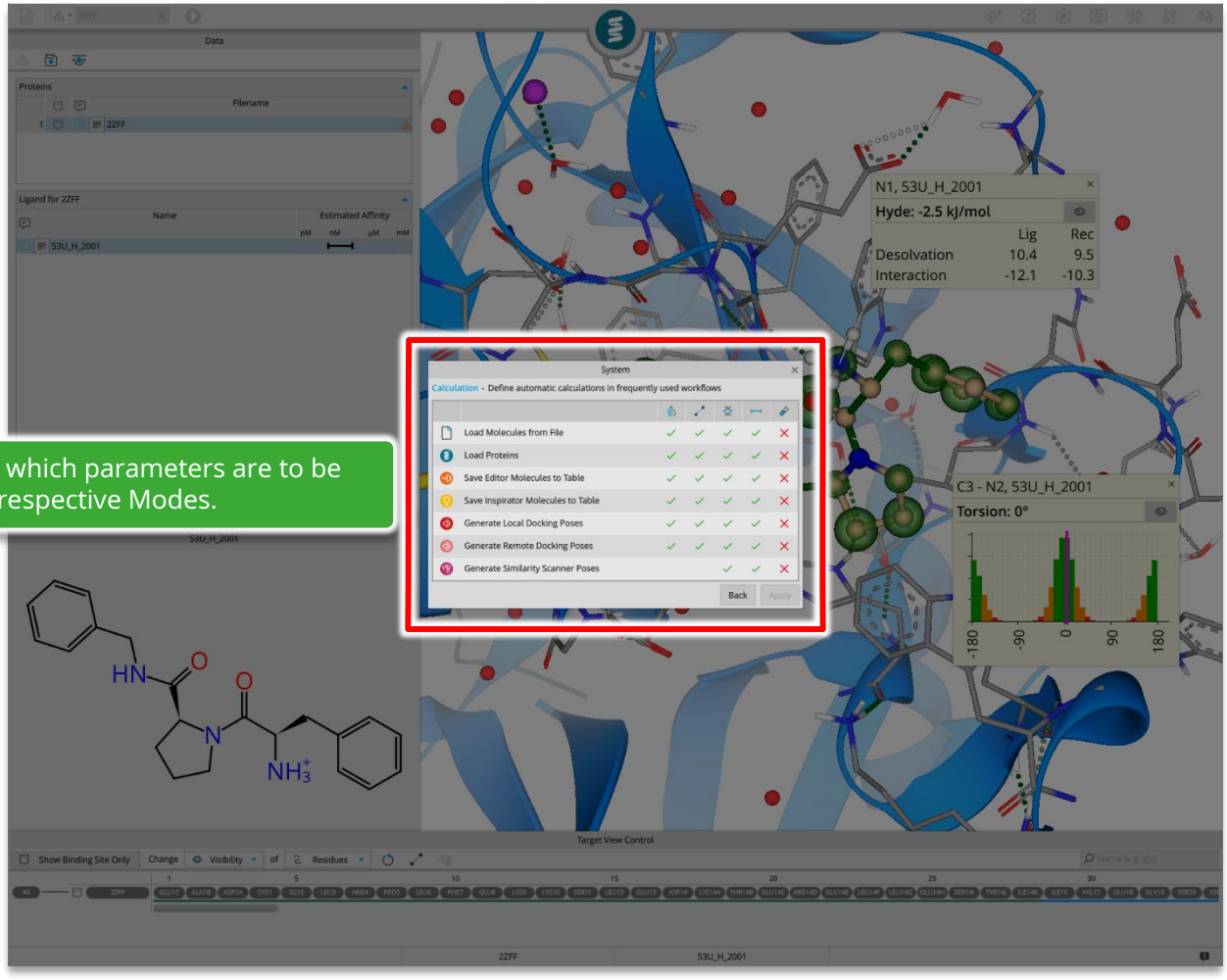
Mode Overview

In the table, select which parameters are to be calculated for the respective Modes.



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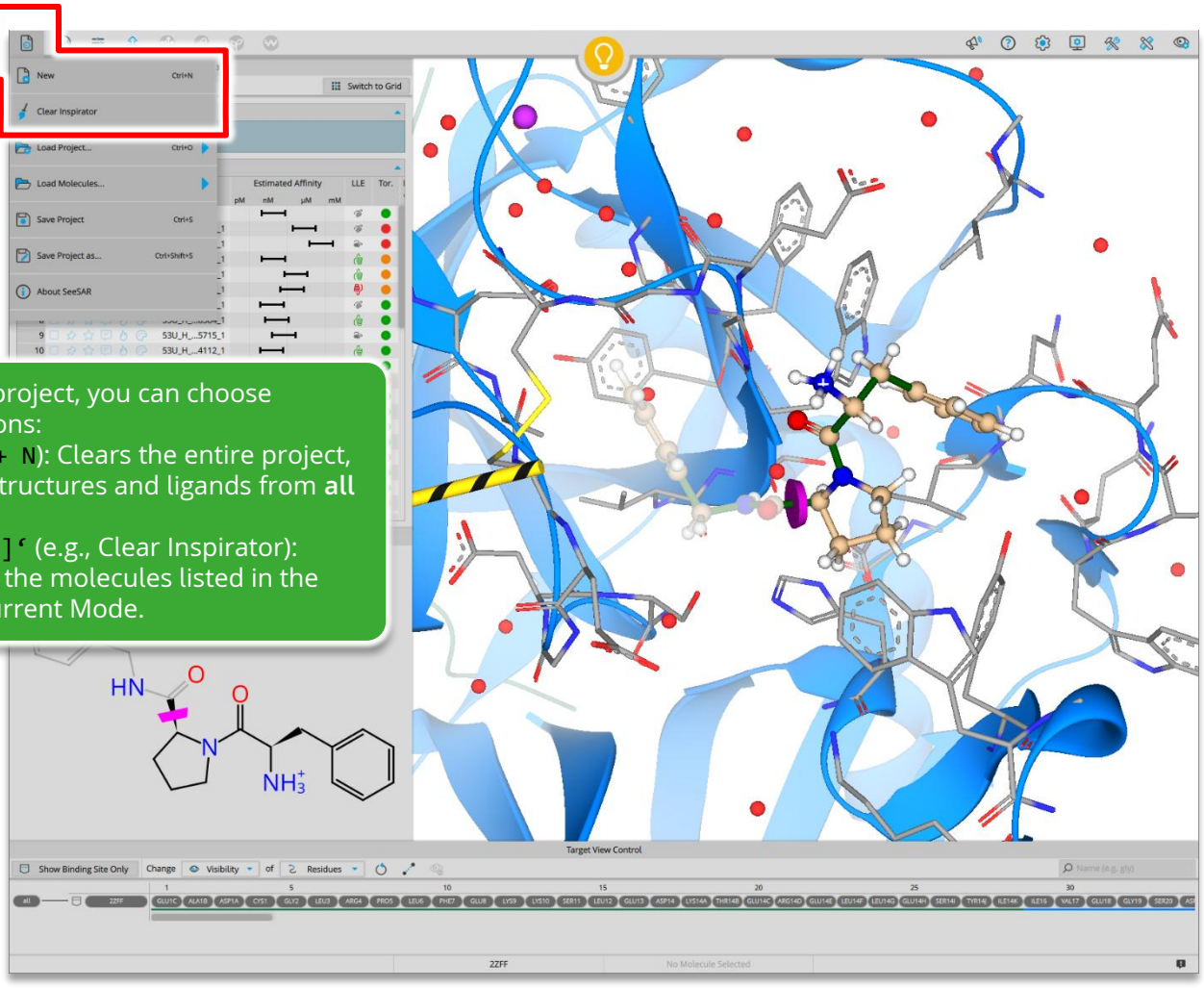
Mode Overview



To clean up your project, you can choose between two options:

- ‘New’ (`Ctrl + N`): Clears the entire project, removing all structures and ligands from **all Modes**.
- ‘`Clear [Mode]`‘ (e.g., Clear Inspirator): Removes only the molecules listed in the table of the current Mode.

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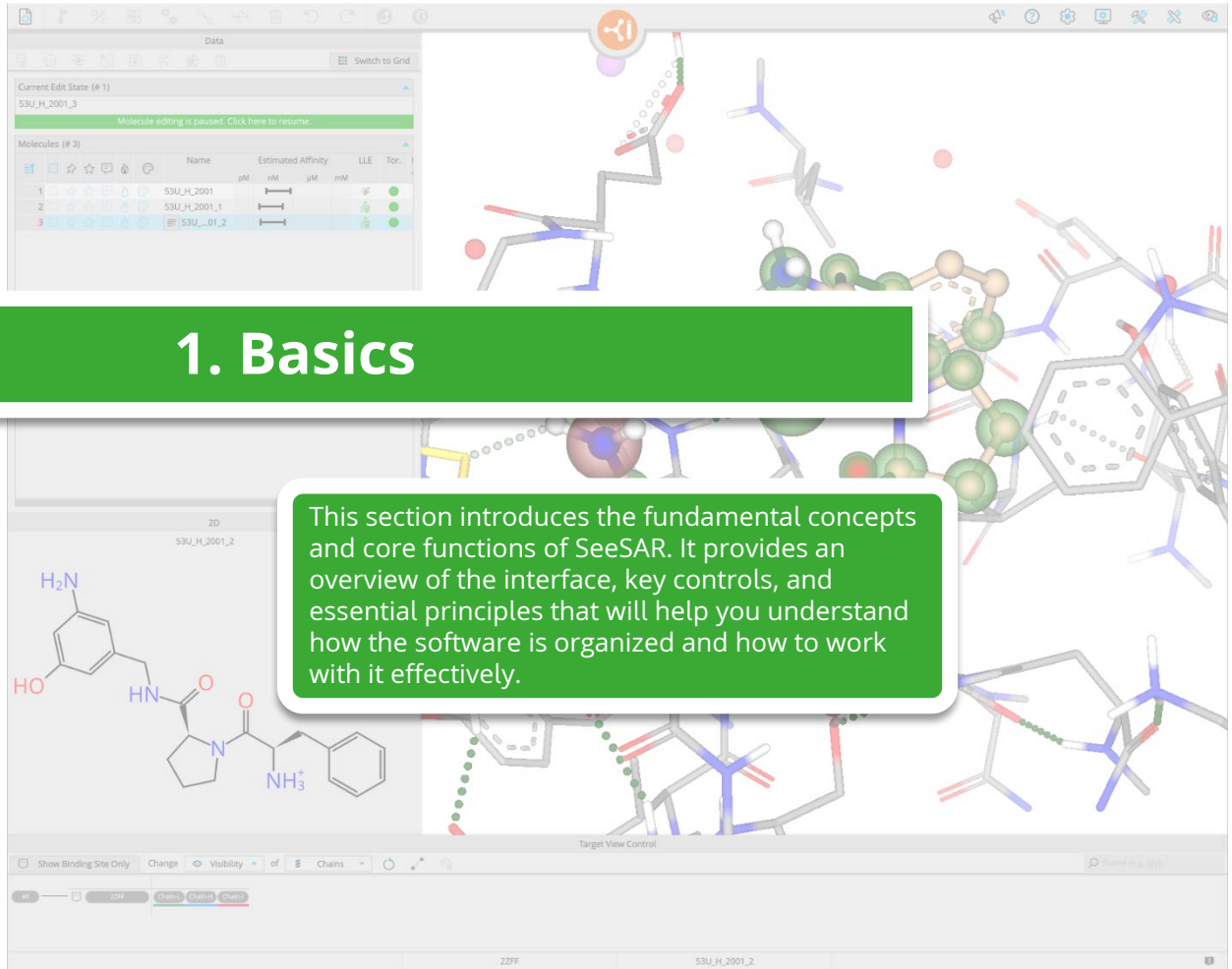
Mode Overview



1. Basics

This section introduces the fundamental concepts and core functions of SeeSAR. It provides an overview of the interface, key controls, and essential principles that will help you understand how the software is organized and how to work with it effectively.

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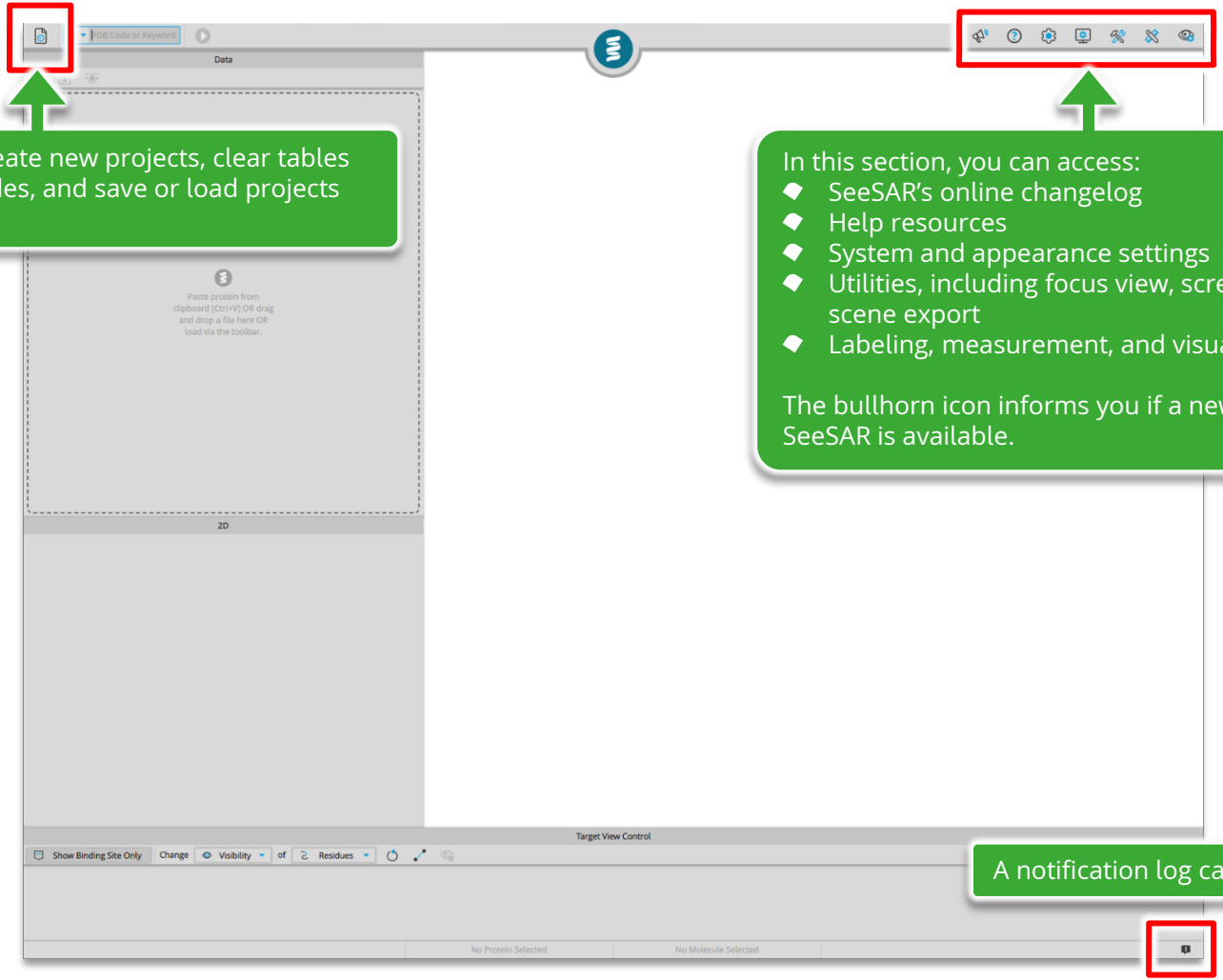
Mode Overview



Here, you can create new projects, clear tables in individual Modes, and save or load projects and molecules.

In this section, you can access:

- SeeSAR's online changelog
- Help resources
- System and appearance settings
- Utilities, including focus view, screenshots, and 3D scene export
- Labeling, measurement, and visualization tools

The bullhorn icon informs you if a new version of SeeSAR is available.

A notification log can be found here.

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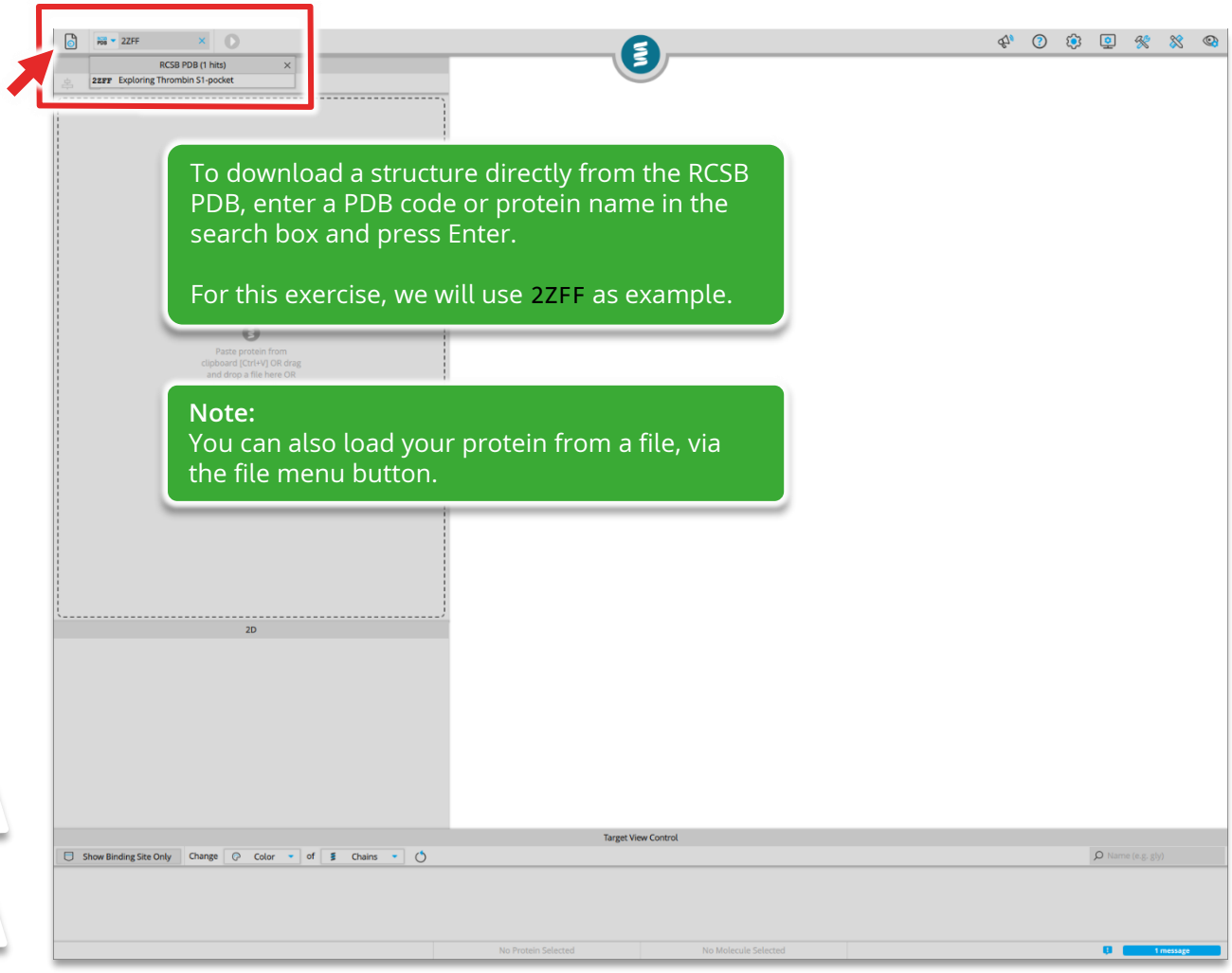
Mode Overview



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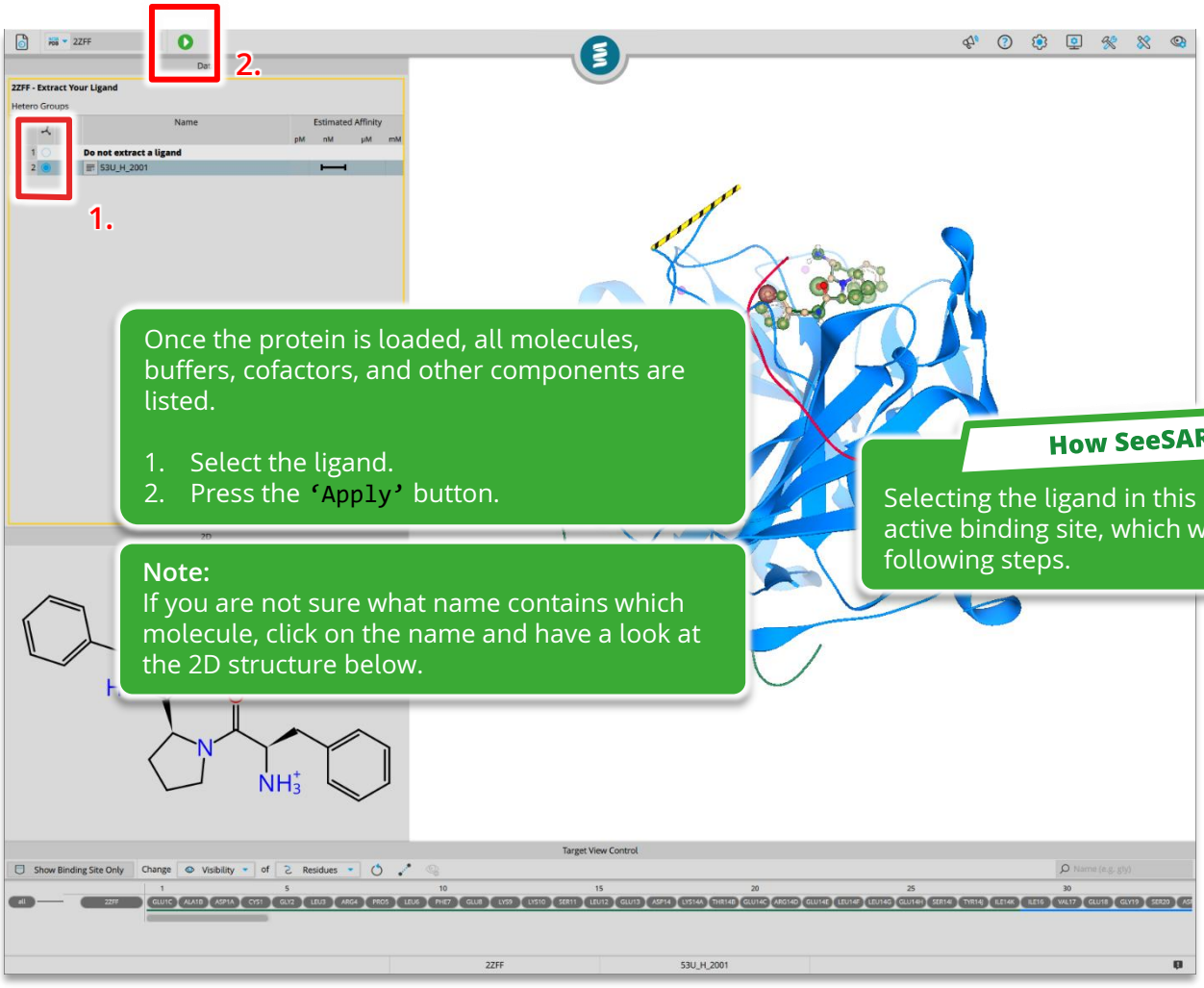
Mode Overview



Once the protein is loaded, all molecules, buffers, cofactors, and other components are listed.

1. Select the ligand.
2. Press the `'Apply'` button.

Note:
If you are not sure what name contains which molecule, click on the name and have a look at the 2D structure below.

How SeeSAR works

Selecting the ligand in this step defines the active binding site, which will be used in the following steps.

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Mode Overview

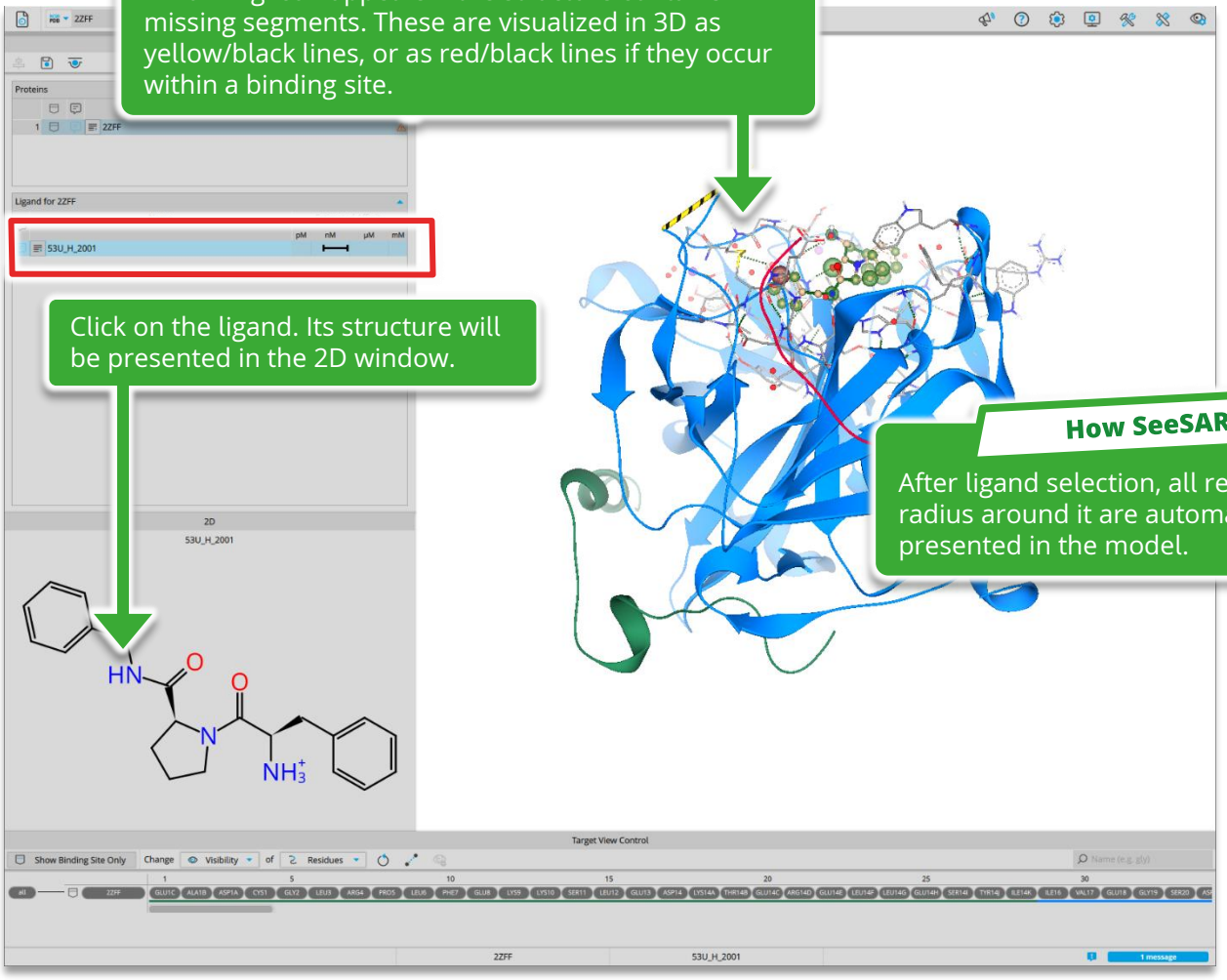
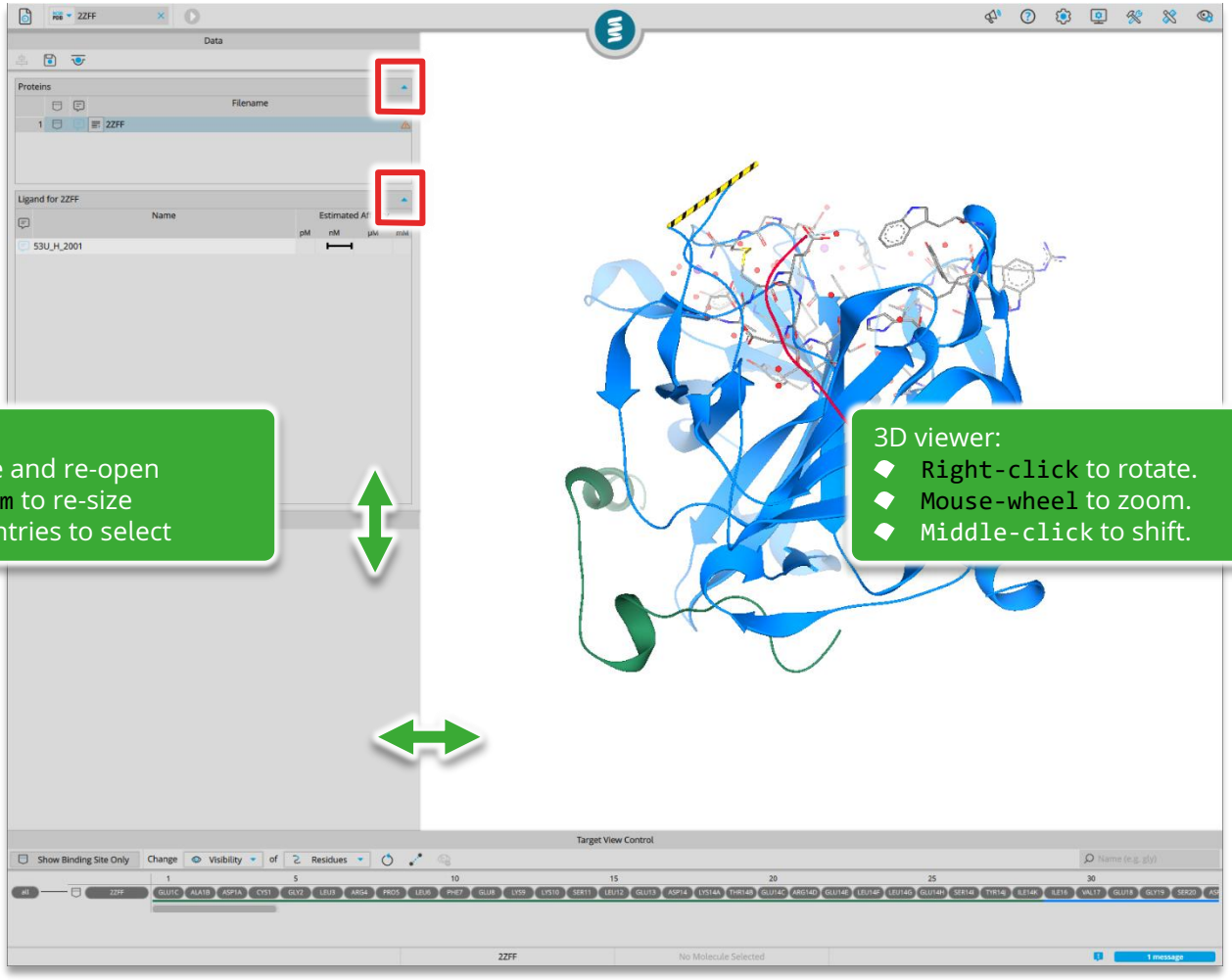


Table of Content
Mode Overview



Tables:

- Collapse and re-open
- `Drag rim` to re-size
- `Click` entries to select

3D viewer:

- `Right-click` to rotate.
- `Mouse-wheel` to zoom.
- `Middle-click` to shift.

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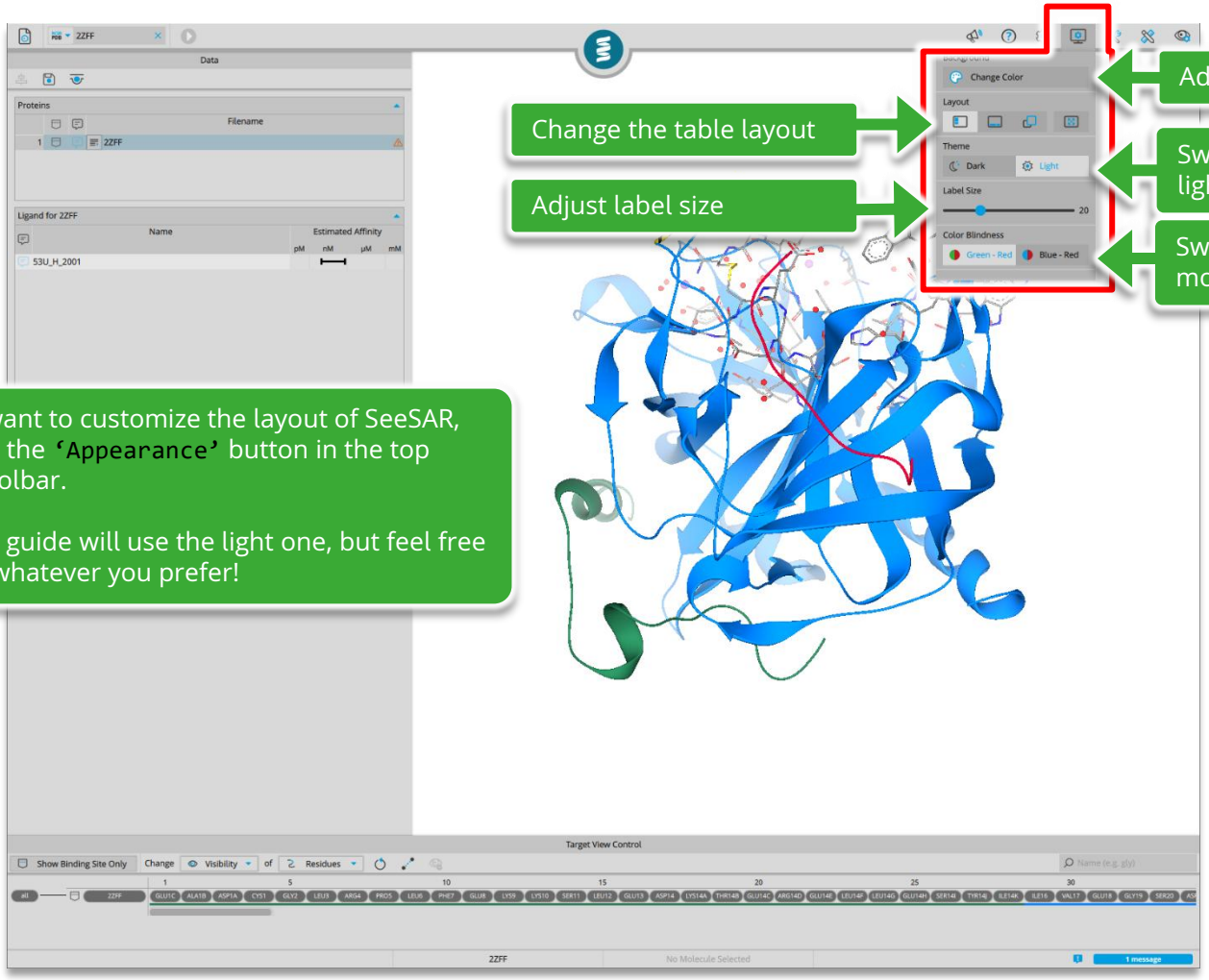
Mode Overview



If you want to customize the layout of SeeSAR, click on the `'Appearance'` button in the top right toolbar.

For this guide will use the light one, but feel free to use whatever you prefer!

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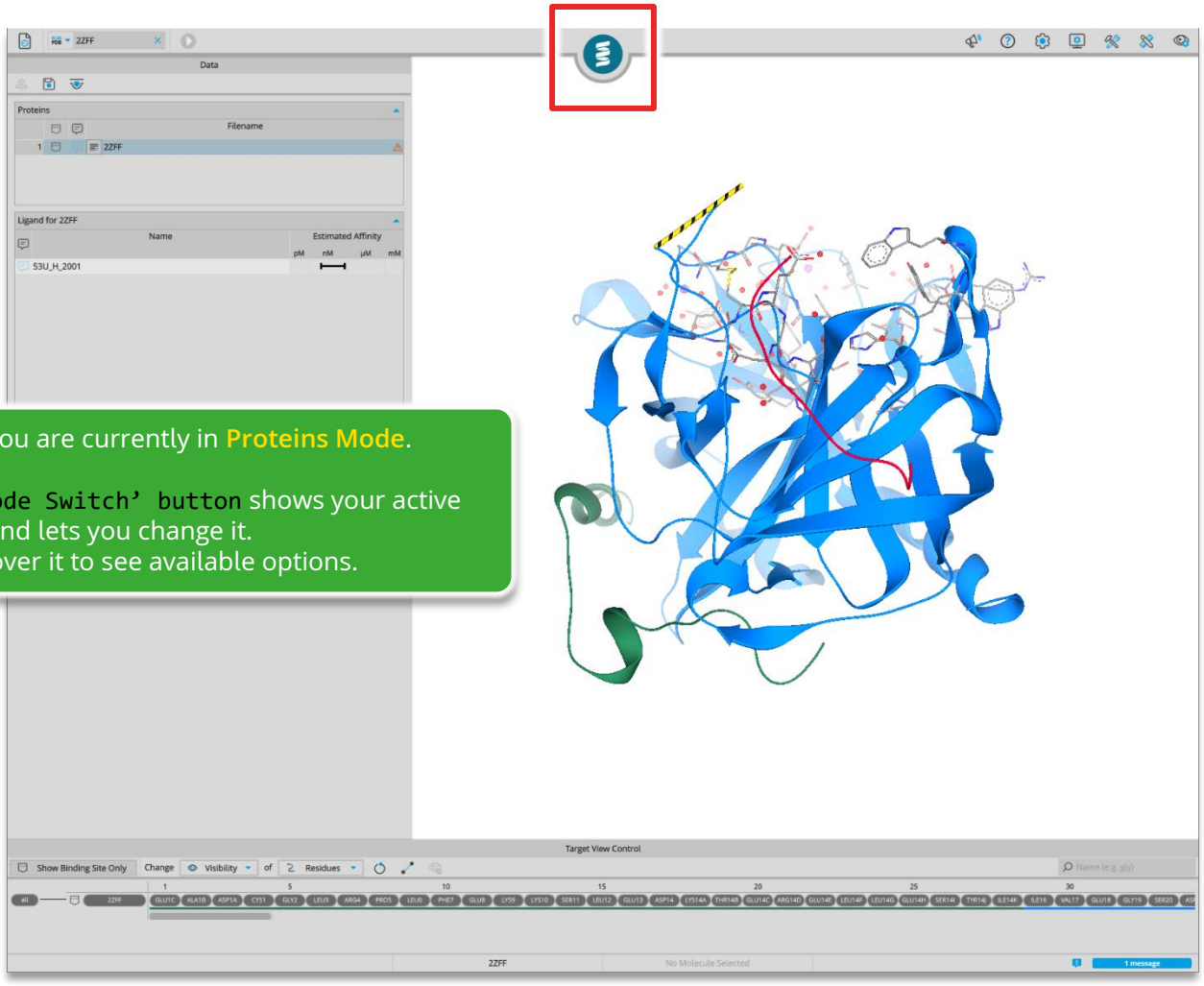
Mode Overview



Note: You are currently in **Proteins Mode**.

The **‘Mode Switch’ button** shows your active mode and lets you change it.
Hover over it to see available options.

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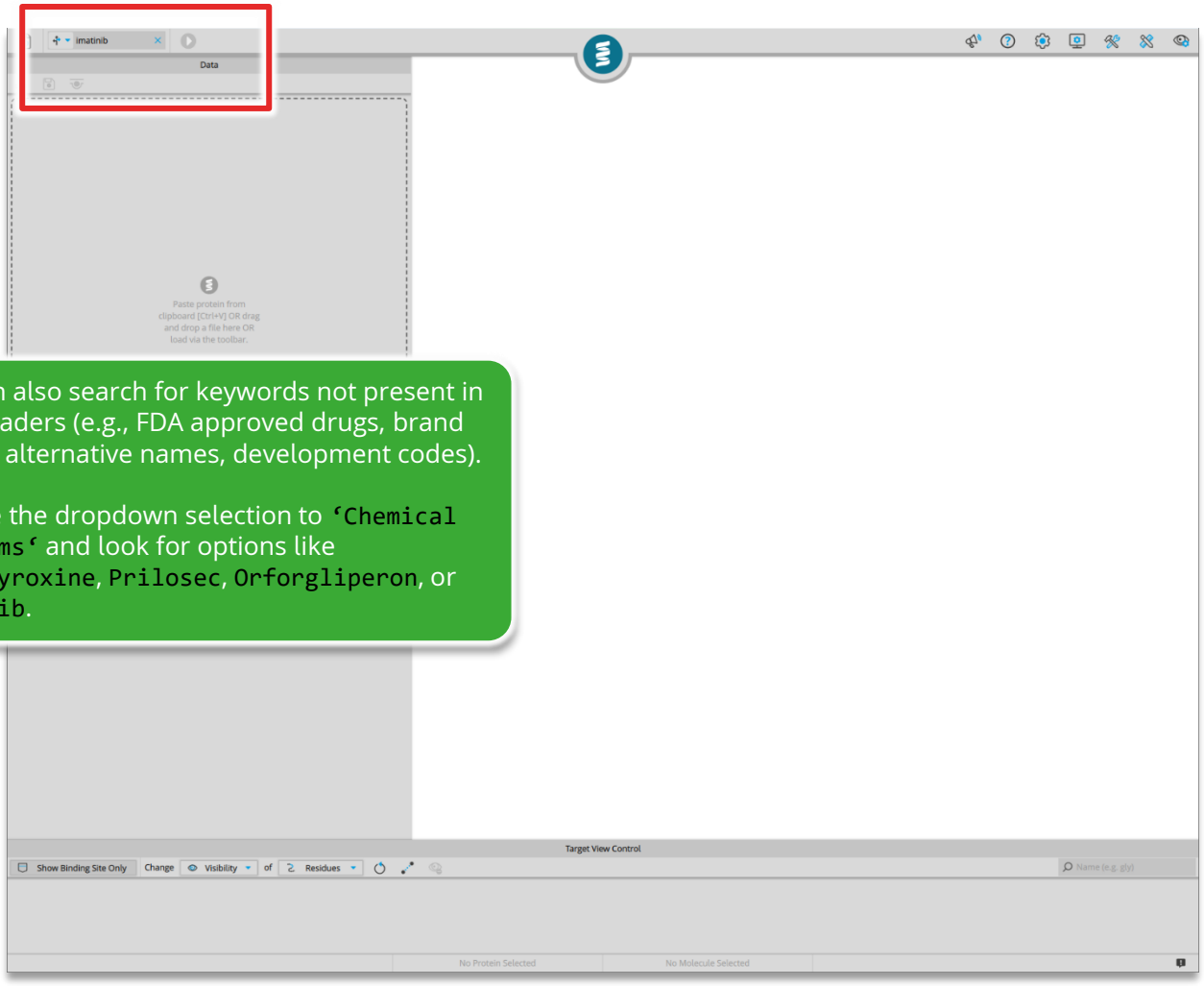
Mode Overview



You can also search for keywords not present in PDB headers (e.g., FDA approved drugs, brand names, alternative names, development codes).

Change the dropdown selection to `‘Chemical Synonyms‘` and look for options like `Levothyroxine`, `Prilosec`, `Orforgliperon`, or `Imatinib`.

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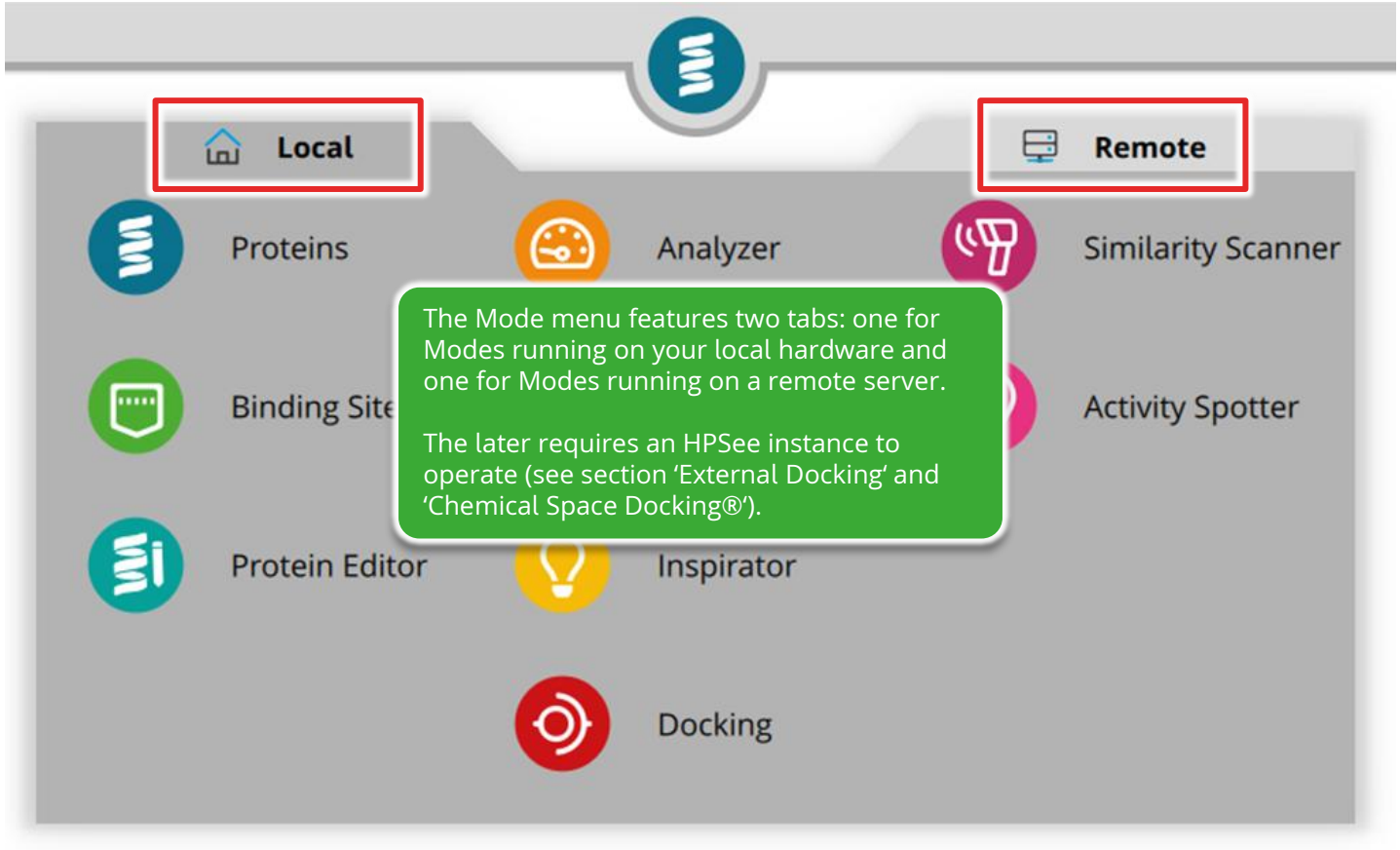
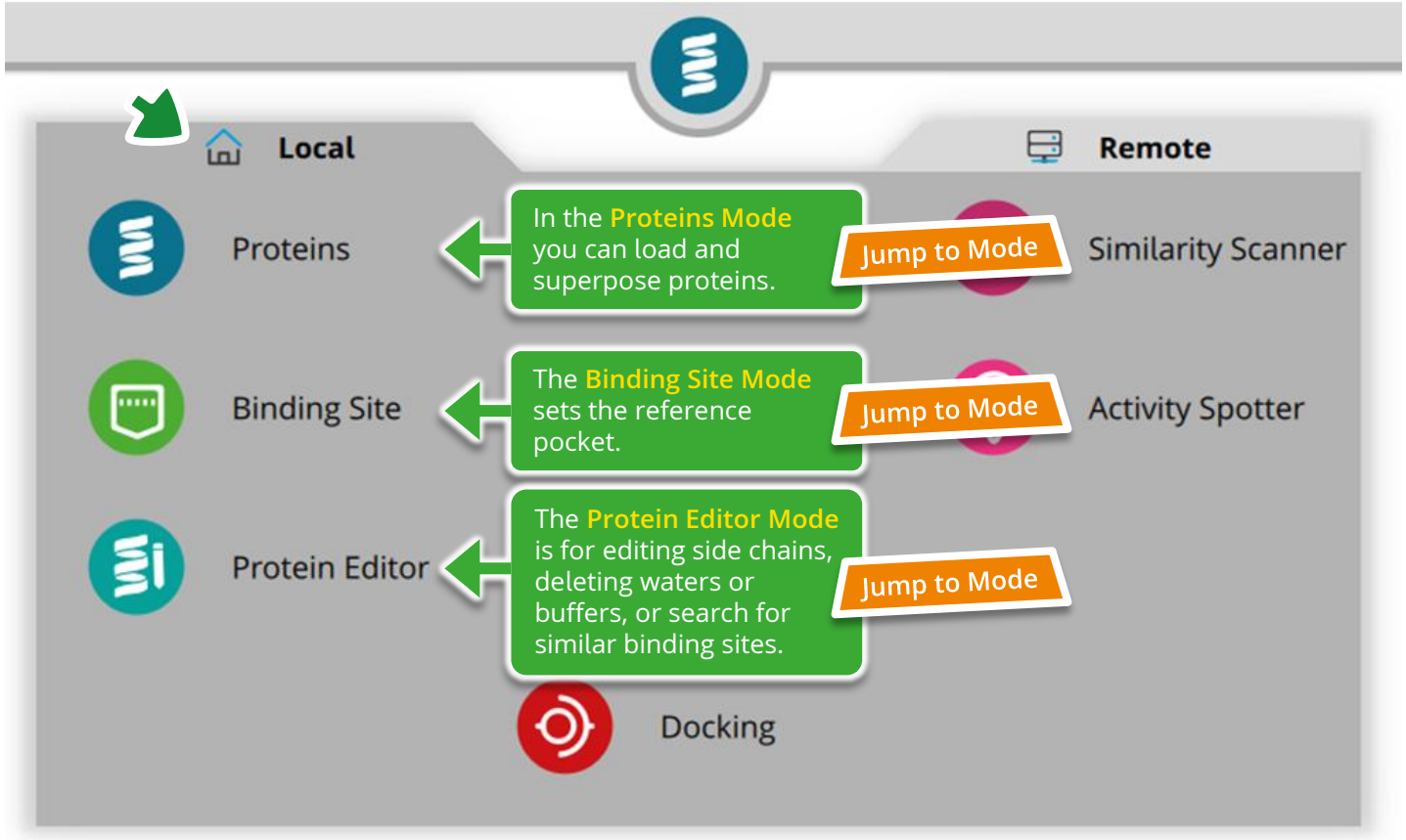
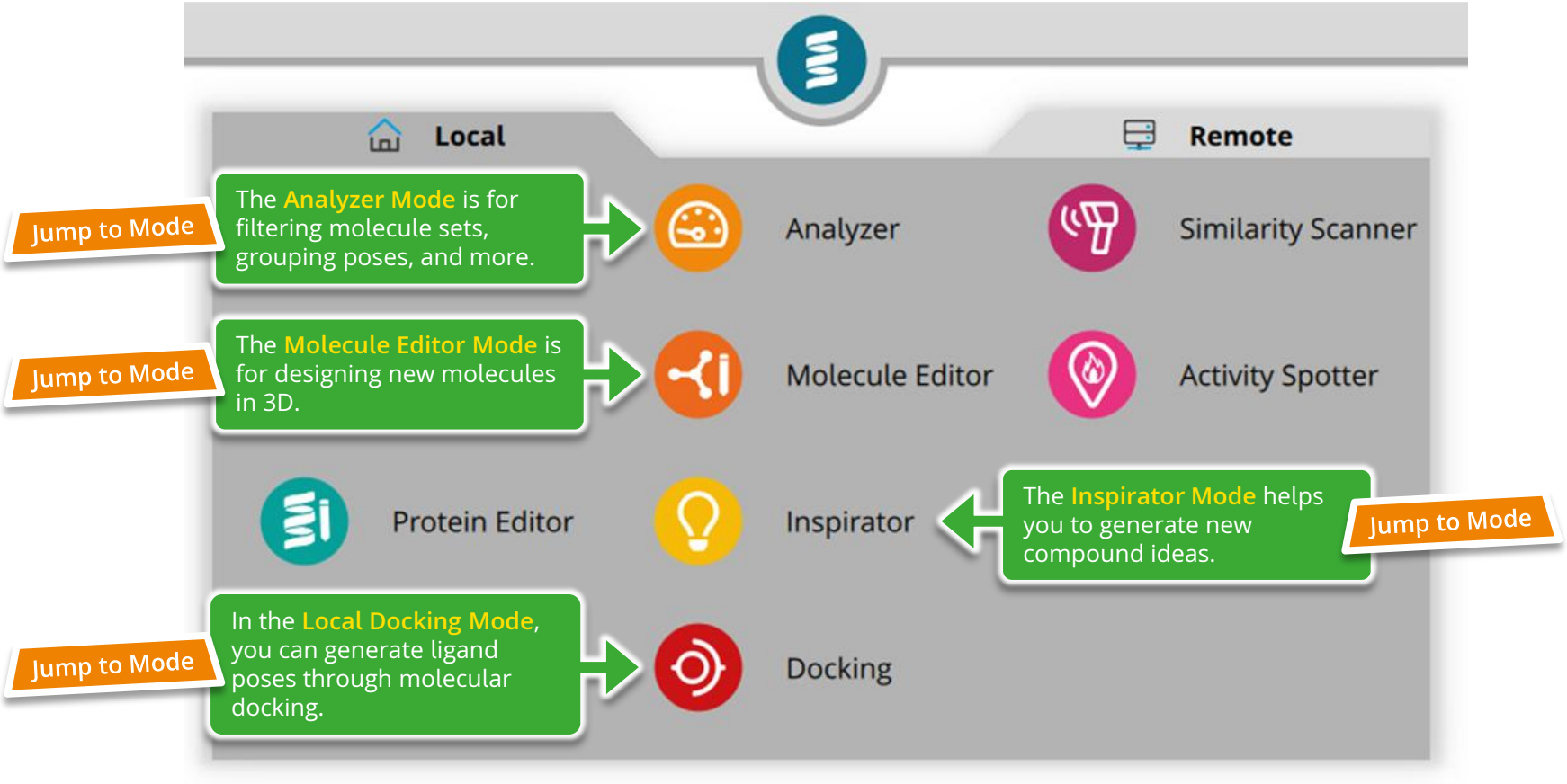
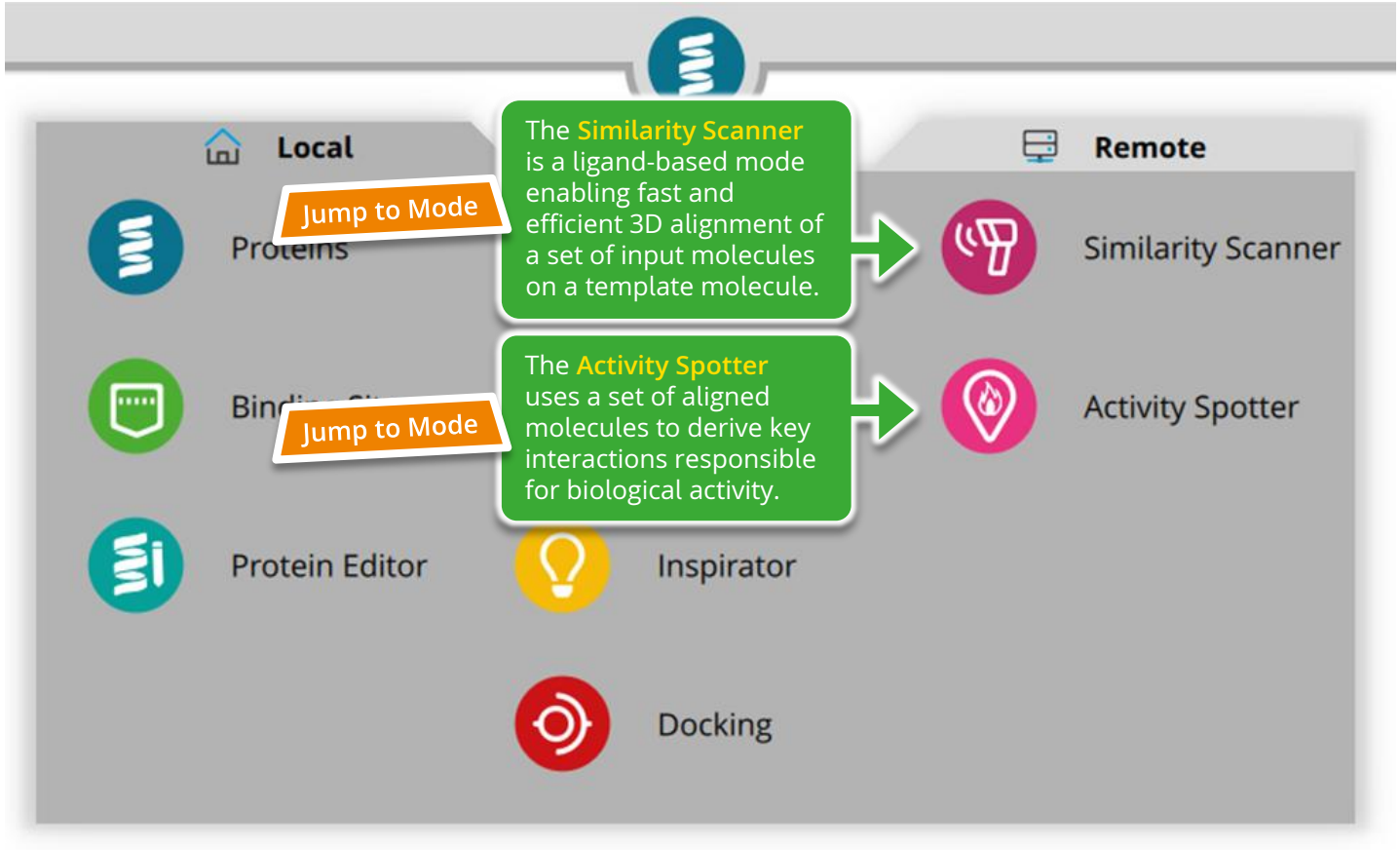
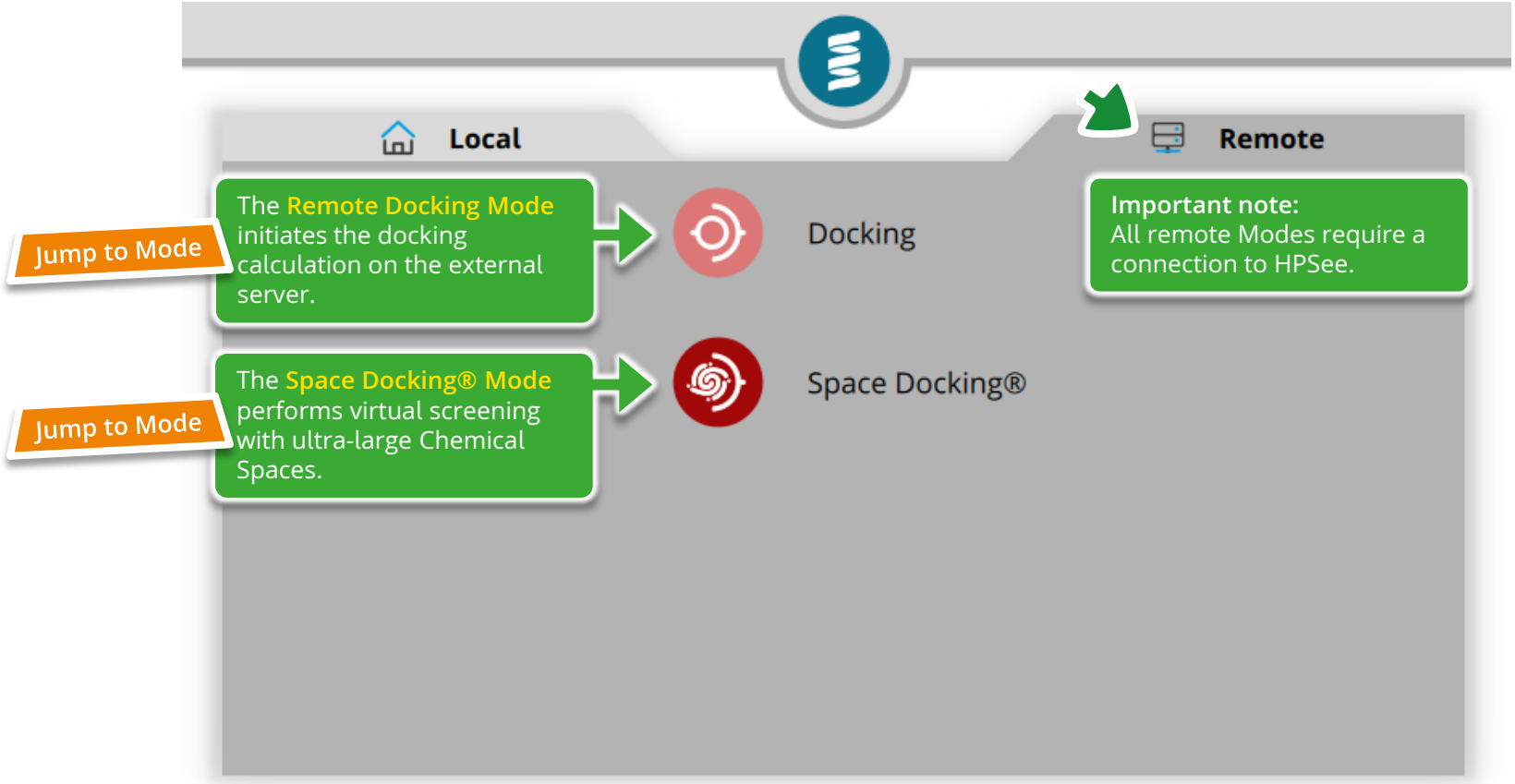
Mode Overview

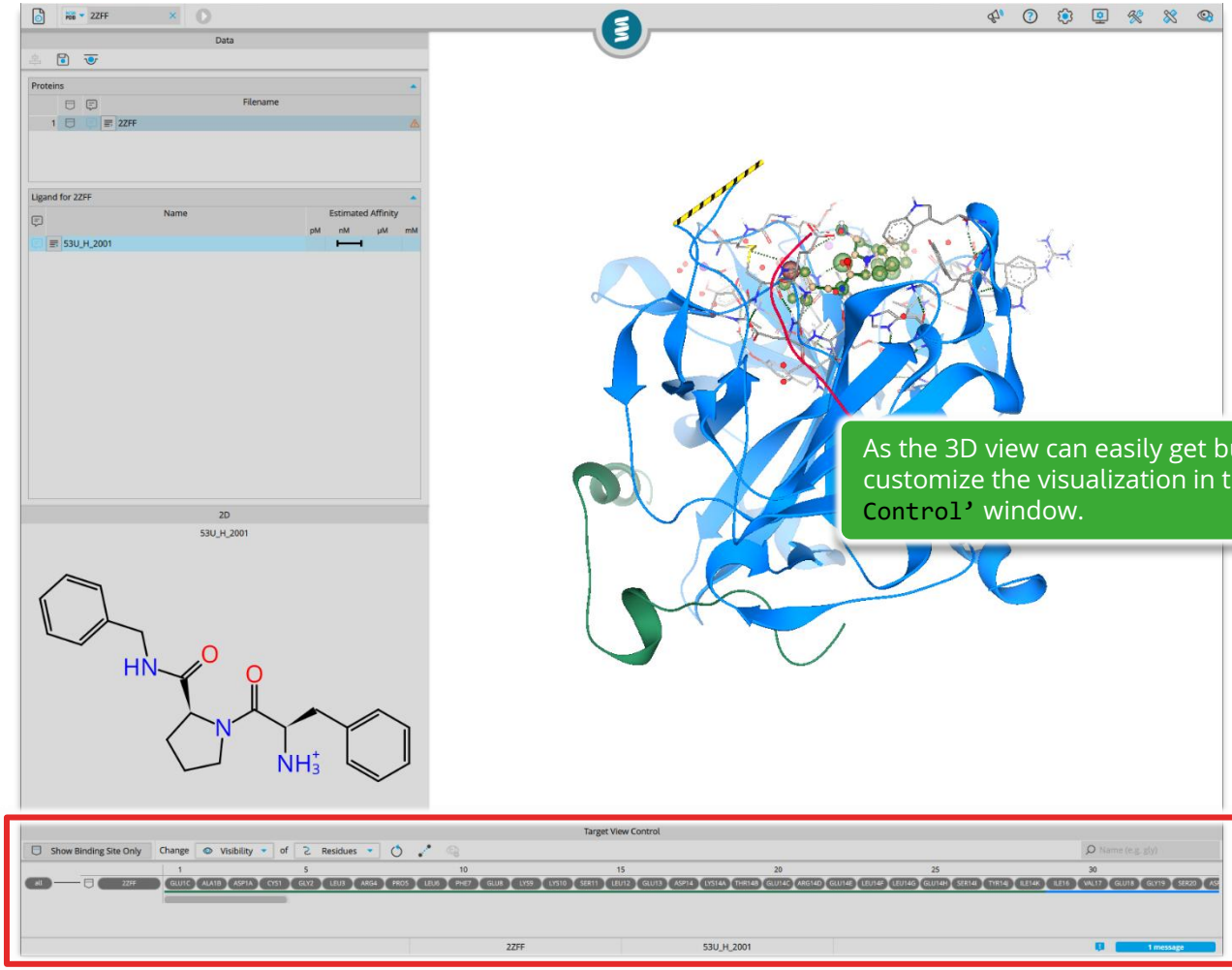

Local
Remote
Proteins
Analyzer
Similarity Scanner
Binding Site
Activity Spotter
Protein Editor
Inspirator
Docking
The Mode menu features two tabs: one for Modes running on your local hardware and one for Modes running on a remote server.
The later requires an HPSee instance to operate (see section 'External Docking' and 'Chemical Space Docking®').


Local
Remote
Proteins
In the Proteins Mode you can load and superpose proteins.
Jump to Mode
Similarity Scanner
Binding Site
The Binding Site Mode sets the reference pocket.
Jump to Mode
Activity Spotter
Protein Editor
The Protein Editor Mode is for editing side chains, deleting waters or buffers, or search for similar binding sites.
Jump to Mode
Docking


Local
Remote
Jump to Mode
The Analyzer Mode is for filtering molecule sets, grouping poses, and more.
Analyzer
Similarity Scanner
Jump to Mode
The Molecule Editor Mode is for designing new molecules in 3D.
Molecule Editor
Activity Spotter
Protein Editor
Inspirator
The Inspirator Mode helps you to generate new compound ideas.
Jump to Mode
Jump to Mode
In the Local Docking Mode, you can generate ligand poses through molecular docking.
Docking


Local
Remote
Jump to Mode
The Similarity Scanner is a ligand-based mode enabling fast and efficient 3D alignment of a set of input molecules on a template molecule.
Similarity Scanner
Jump to Mode
The Activity Spotter uses a set of aligned molecules to derive key interactions responsible for biological activity.
Activity Spotter
Protein Editor
Inspirator
Docking


Local
Remote
Jump to Mode
The Remote Docking Mode initiates the docking calculation on the external server.
Docking
Important note:
All remote Modes require a connection to HPSee.
Jump to Mode
The Space Docking® Mode performs virtual screening with ultra-large Chemical Spaces.
Space Docking®



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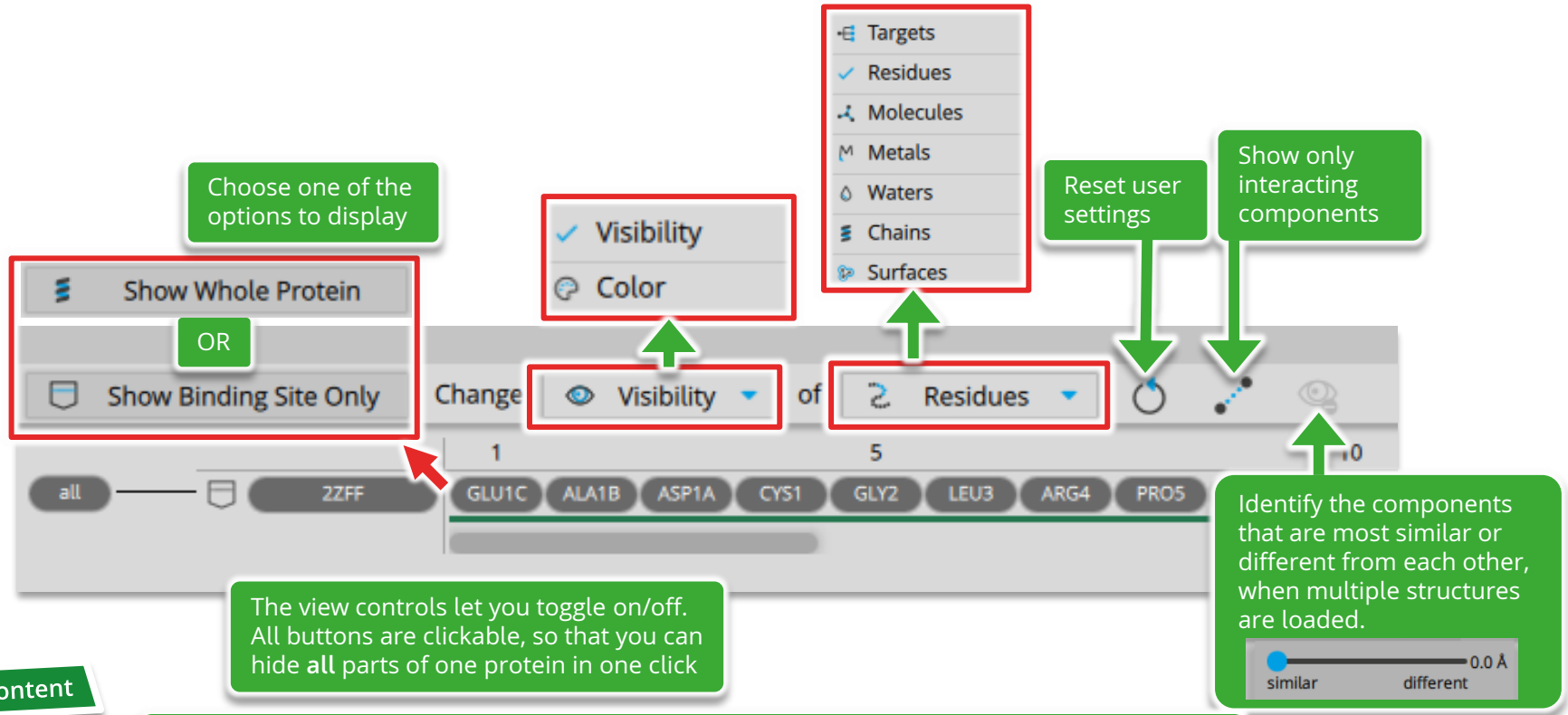

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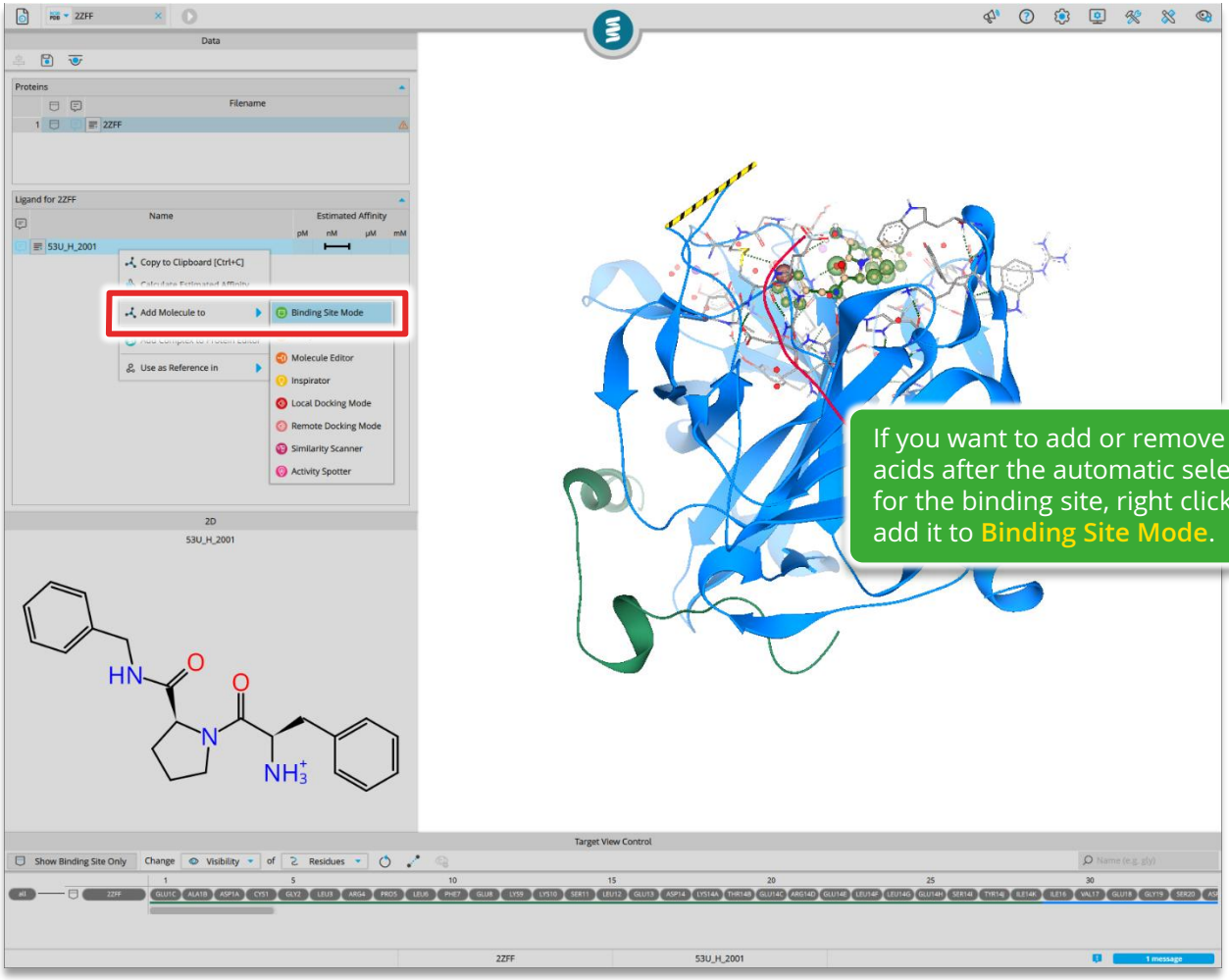
Mode Overview

Example:
To visualize surface, select `Change 'Visibility'` of `'Surfaces'` and toggle on the PDB code. To adjust this surface visibility, set Change `'Color'` of `'Surfaces'` and `right-click` on PDB code to explore the options.



If you want to add or remove individual amino acids after the automatic selection of residues for the binding site, right click your ligand and add it to **Binding Site Mode**.

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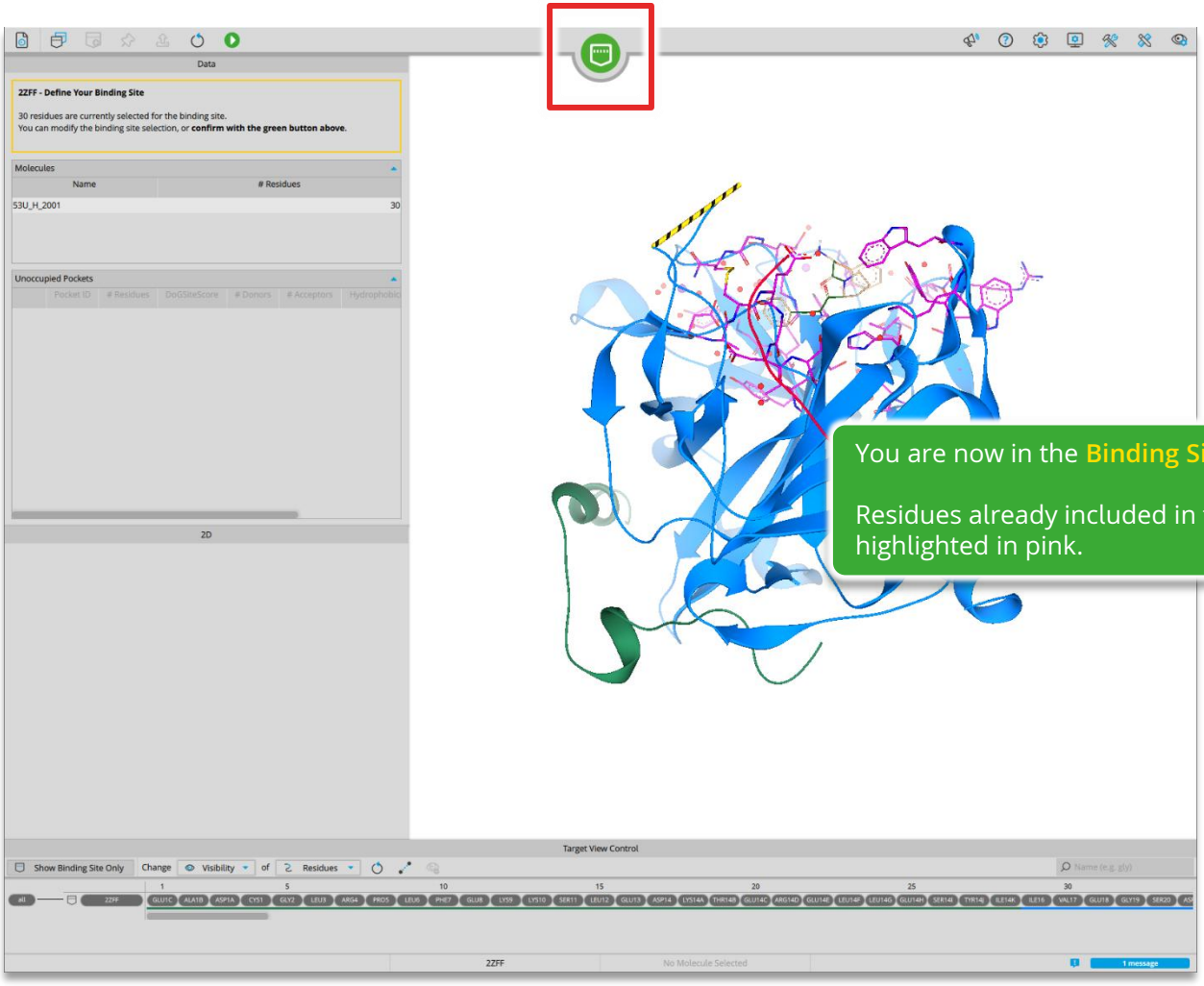
Mode Overview



You are now in the **Binding Site Mode**.

Residues already included in the binding site are highlighted in pink.

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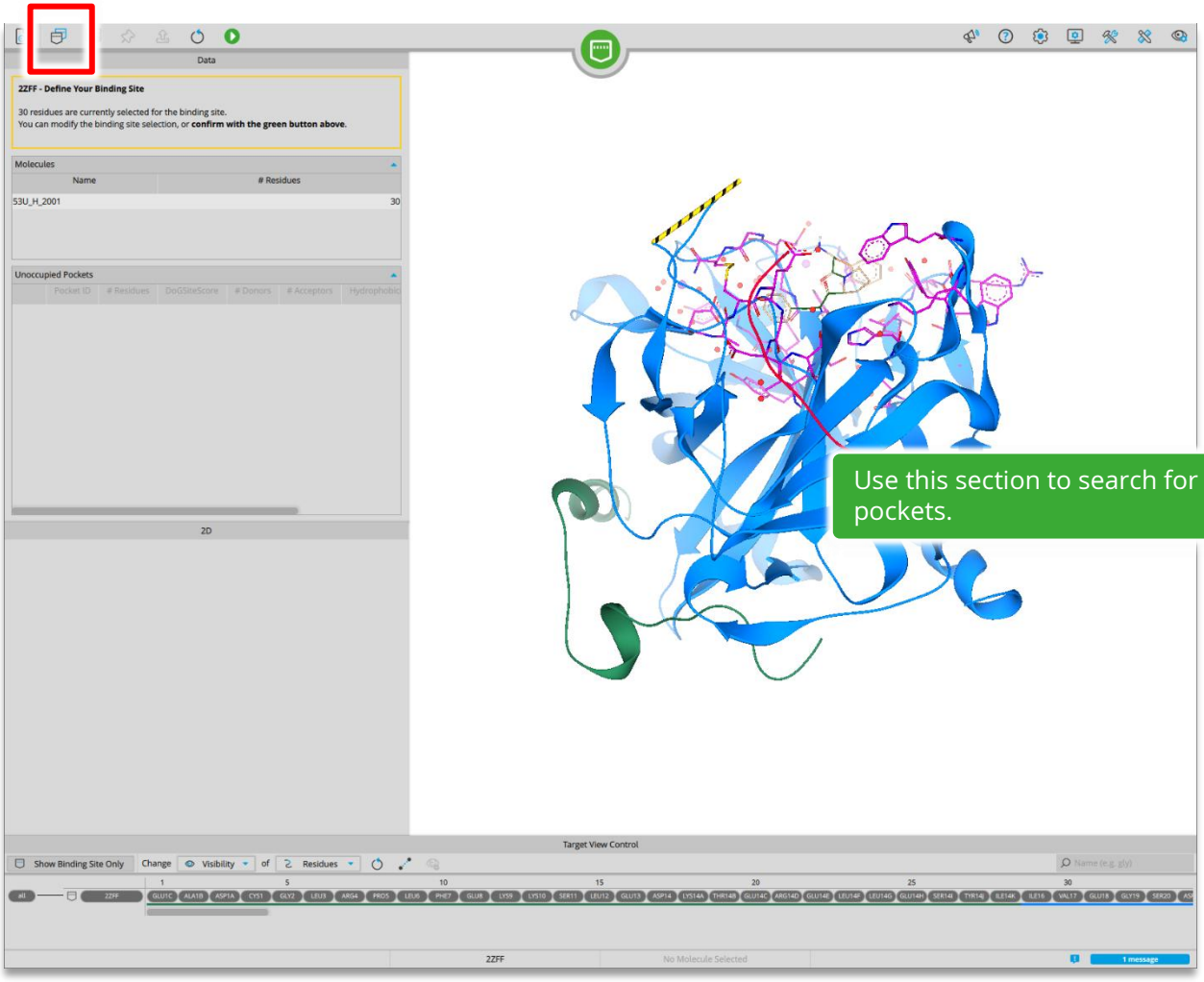
Mode Overview



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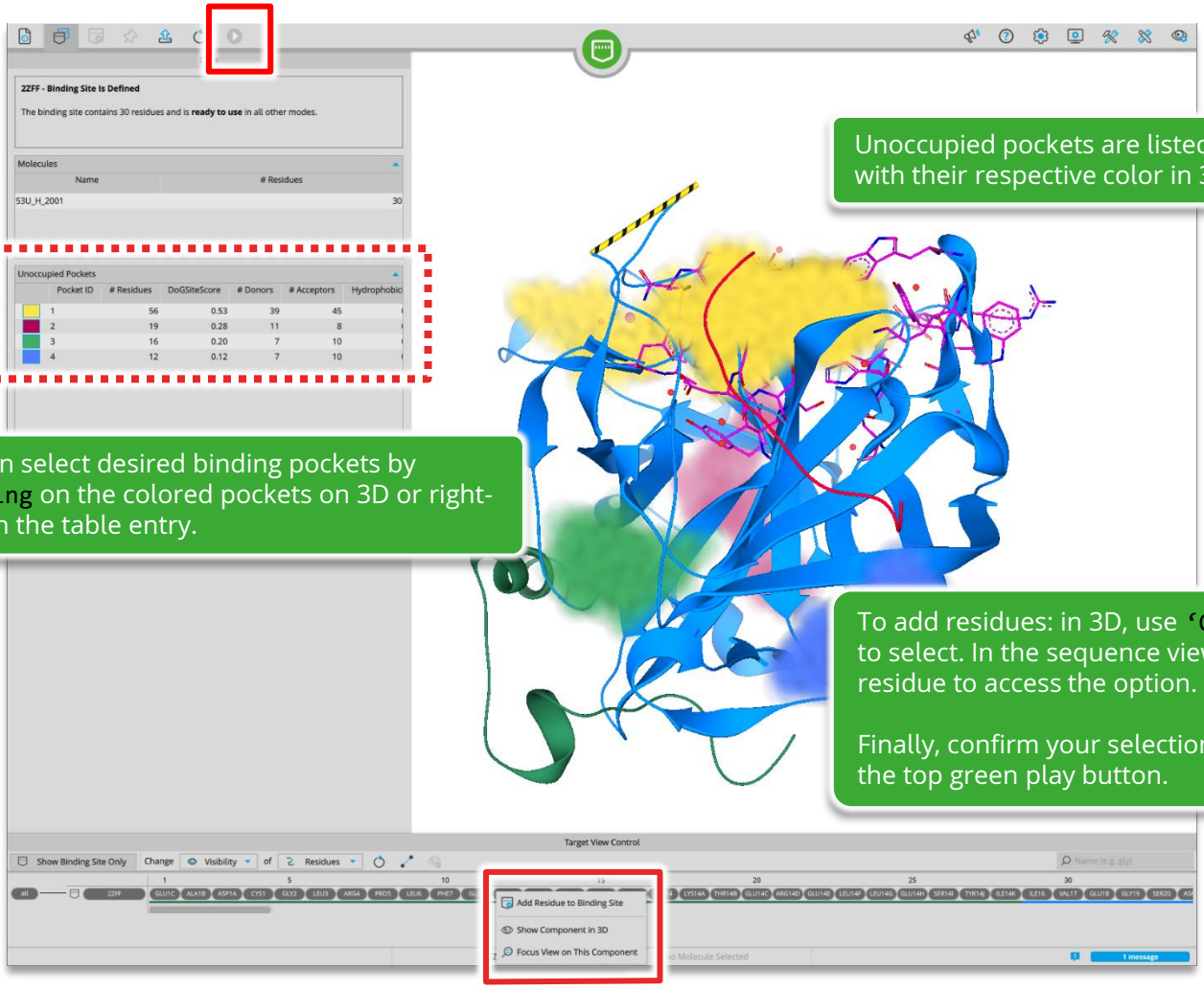
Mode Overview



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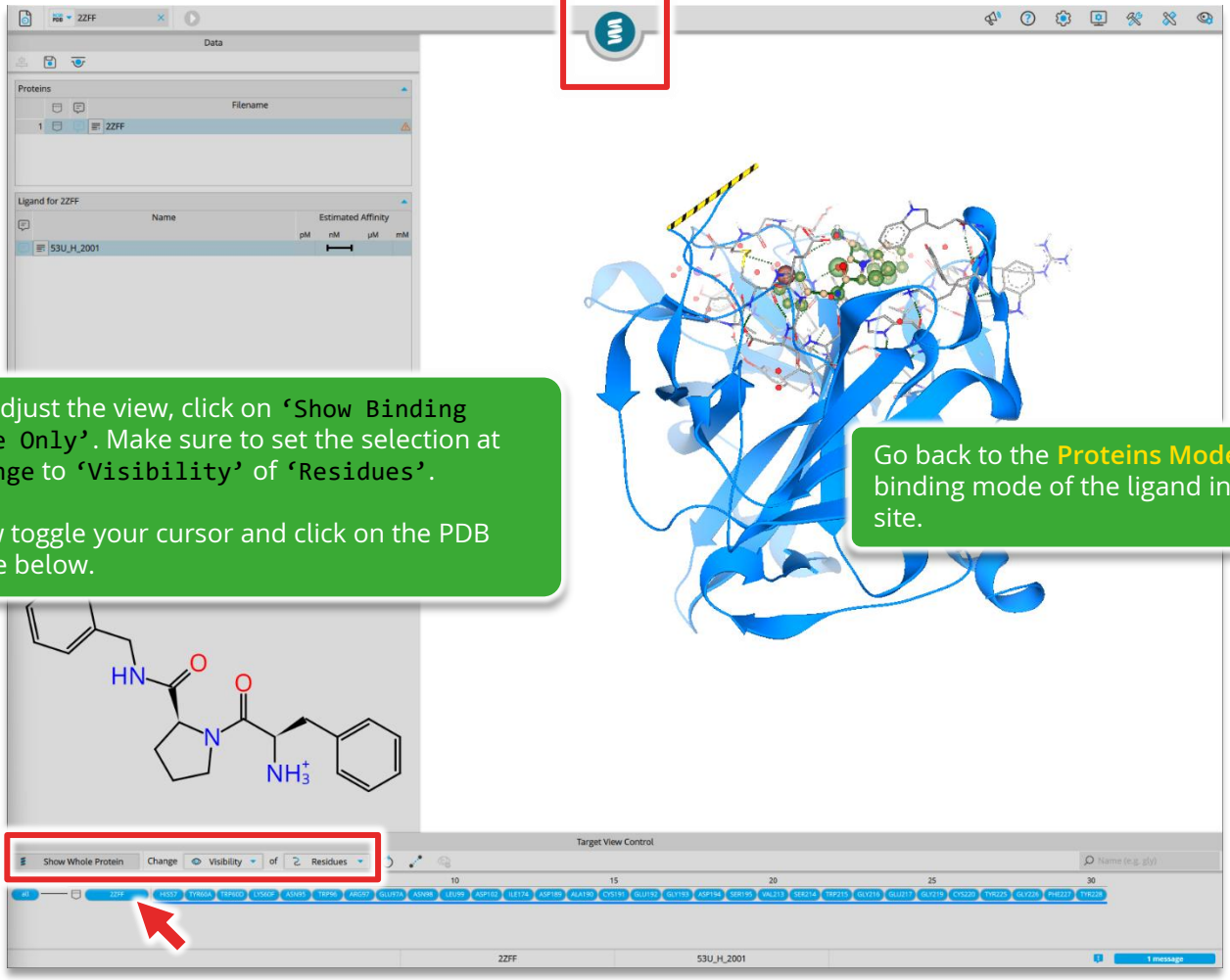
Mode Overview



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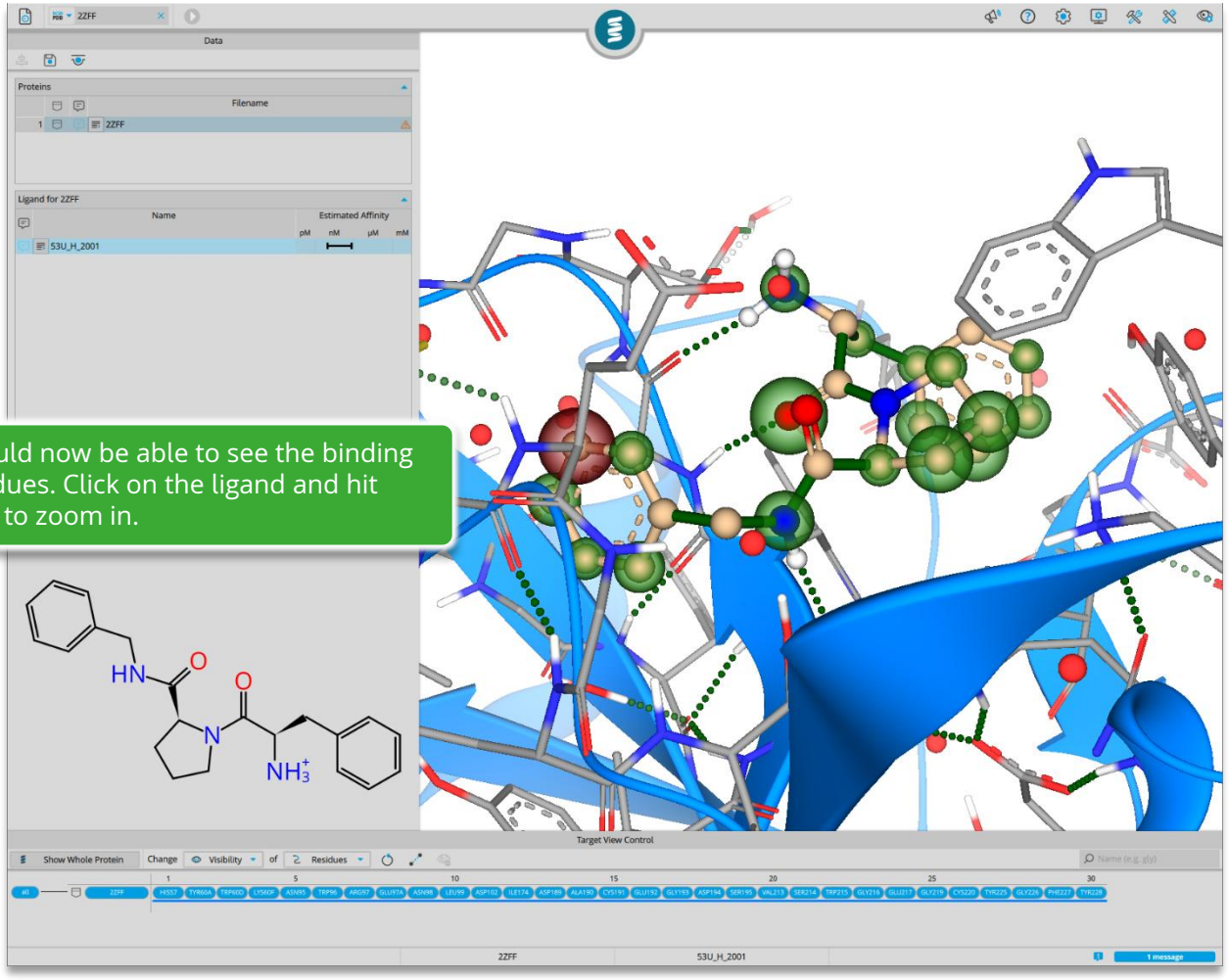
Mode Overview



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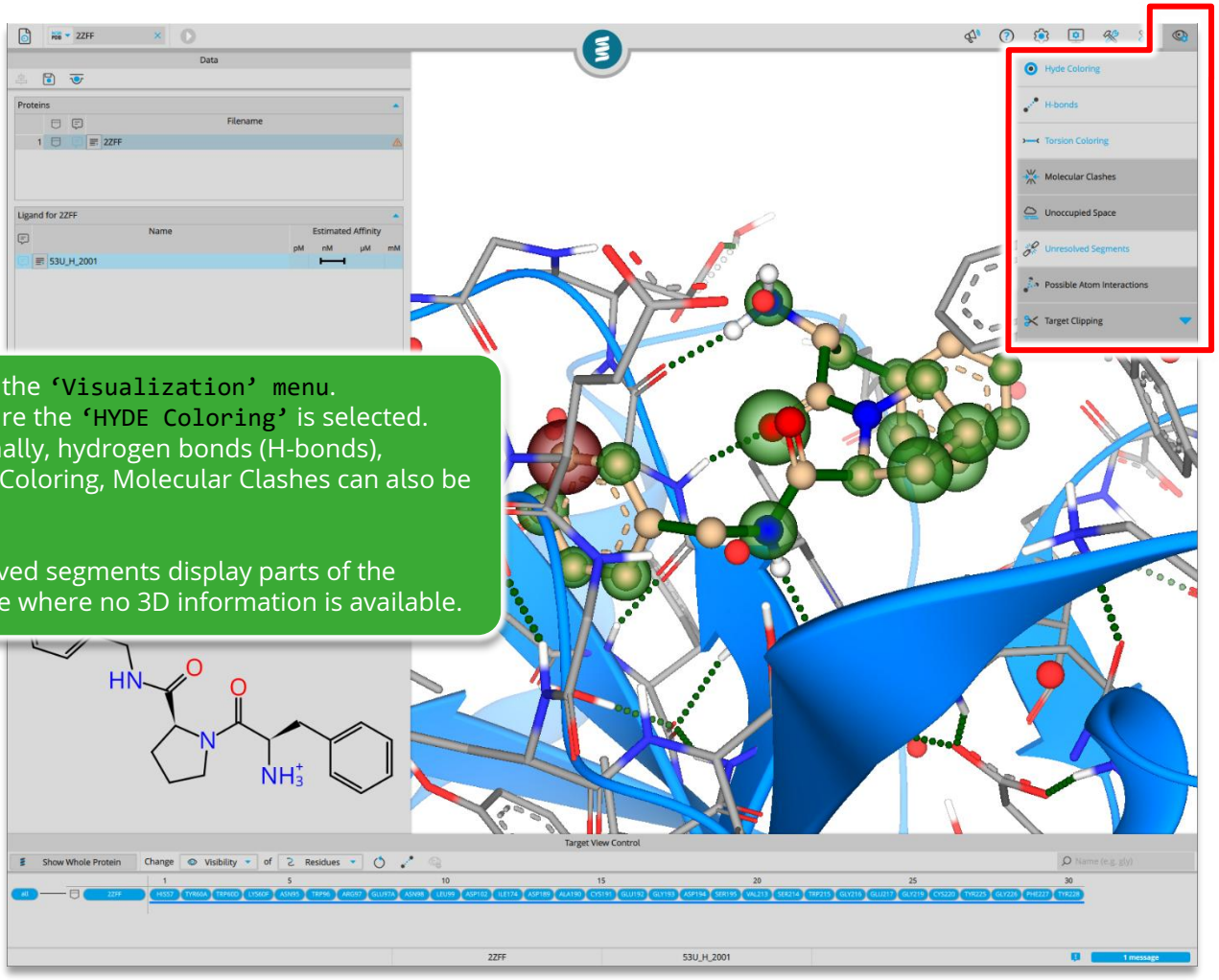
Mode Overview



Click on the **‘Visualization’ menu**.
Make sure the **‘HYDE Coloring’** is selected.
Additionally, hydrogen bonds (H-bonds), Torsion Coloring, Molecular Clashes can also be kept on.

Unresolved segments display parts of the structure where no 3D information is available.

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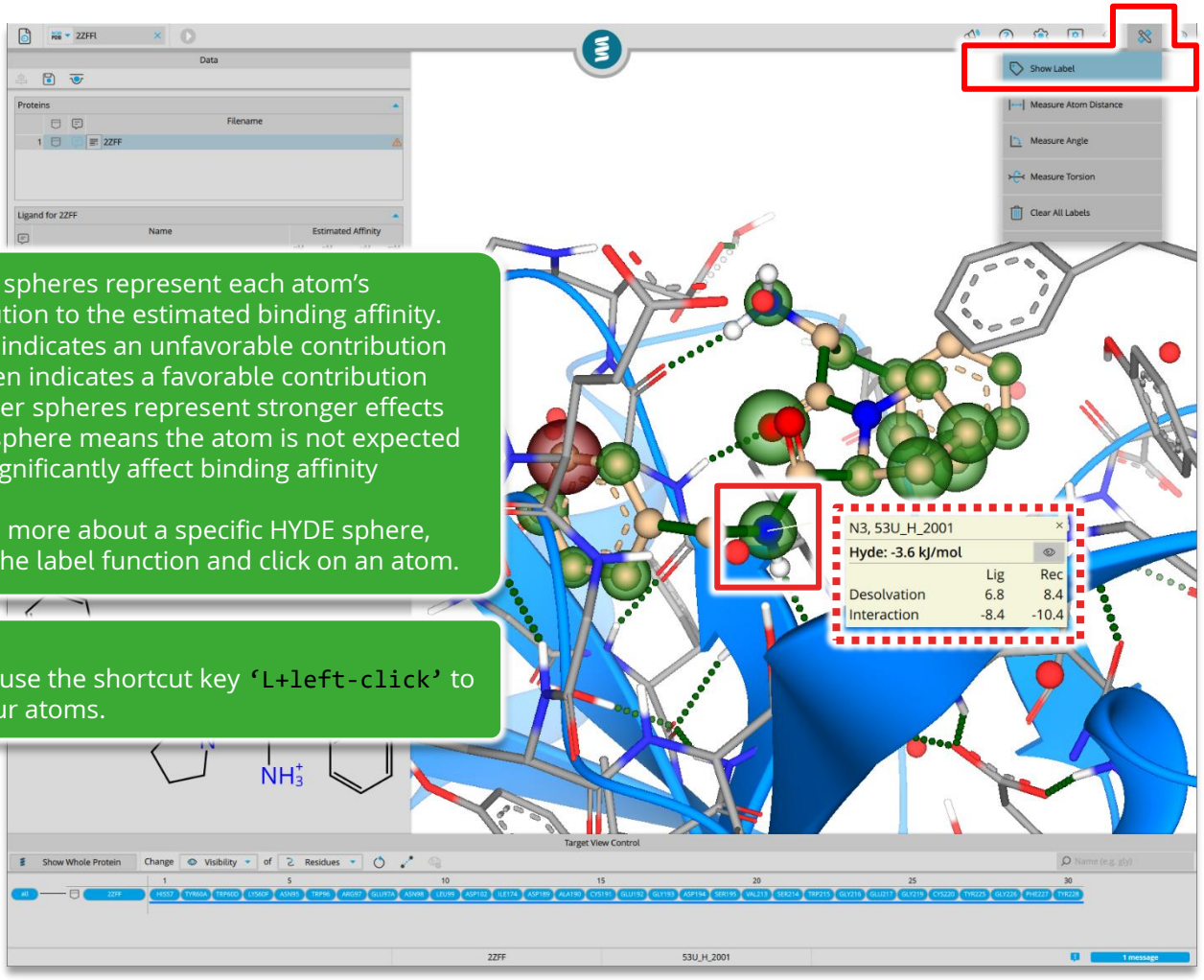
Mode Overview



Colored spheres represent each atom's contribution to the estimated binding affinity.

- Red indicates an unfavorable contribution
- Green indicates a favorable contribution
- Larger spheres represent stronger effects
- No sphere means the atom is not expected to significantly affect binding affinity

To learn more about a specific HYDE sphere, enable the label function and click on an atom.

Note:
You can use the shortcut key '`L+left-click`' to label your atoms.

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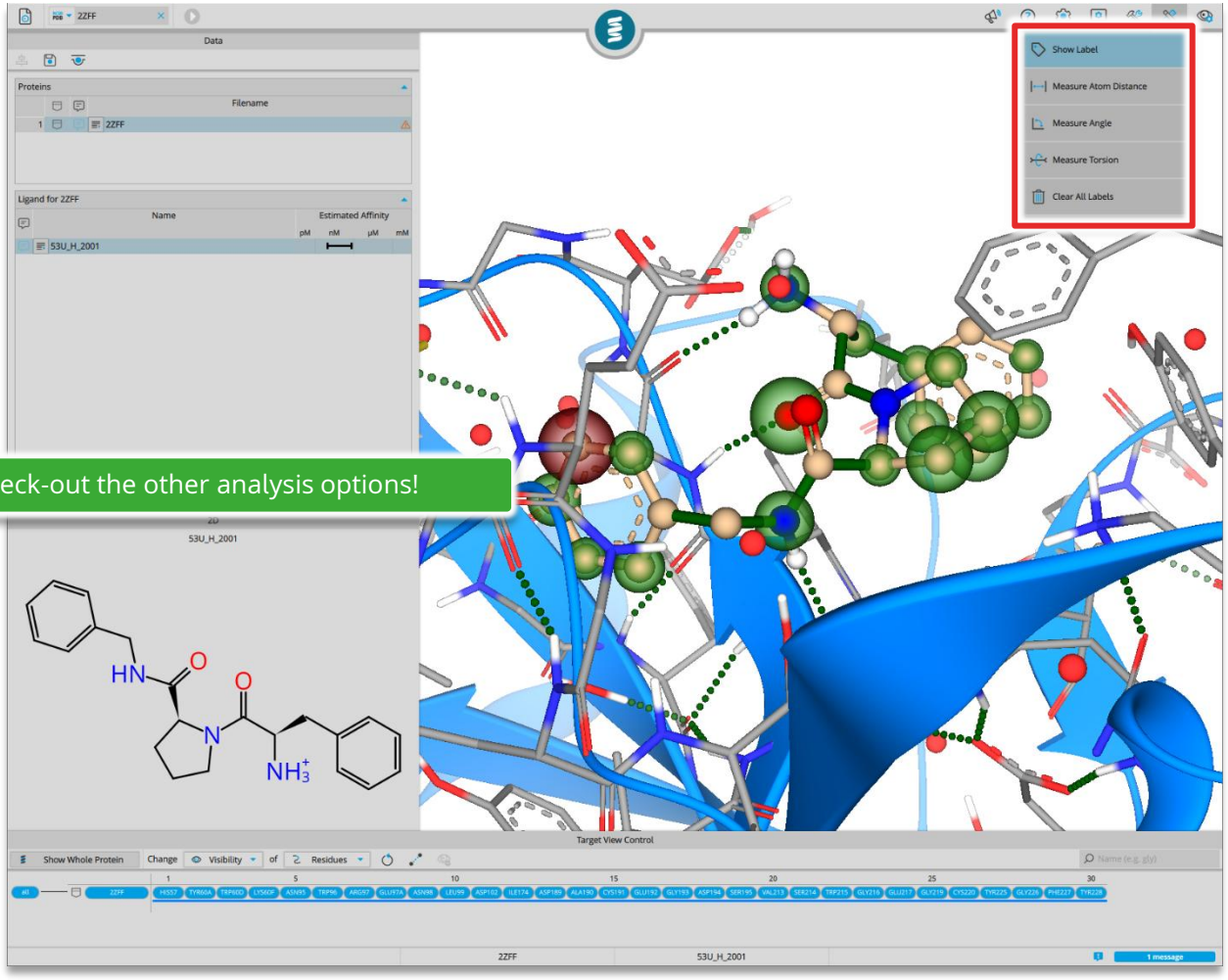
Mode Overview



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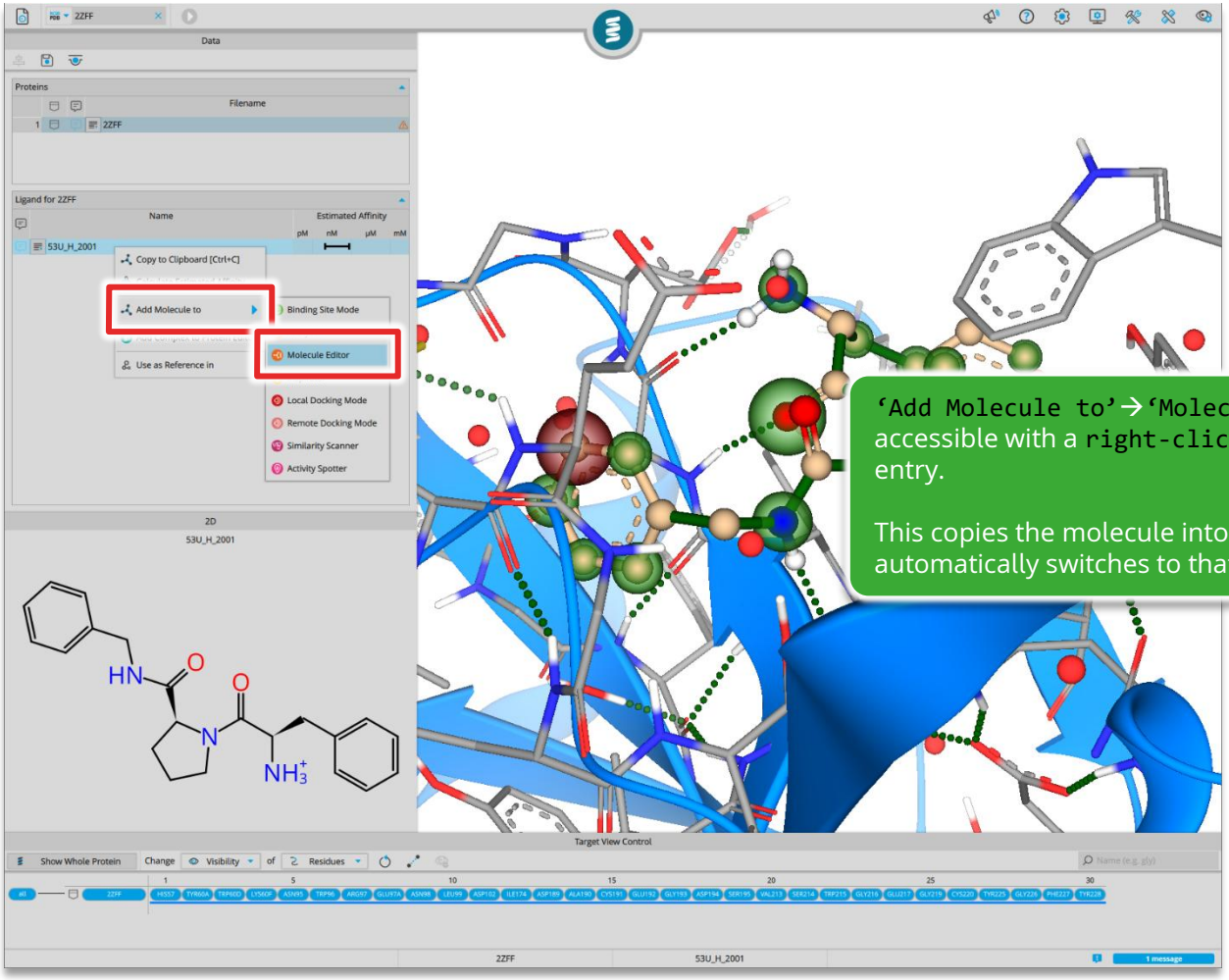
Mode Overview



'Add Molecule to'→'Molecule Editor' is accessible with a right-click on the table entry.

This copies the molecule into the mode **and** automatically switches to that Mode.

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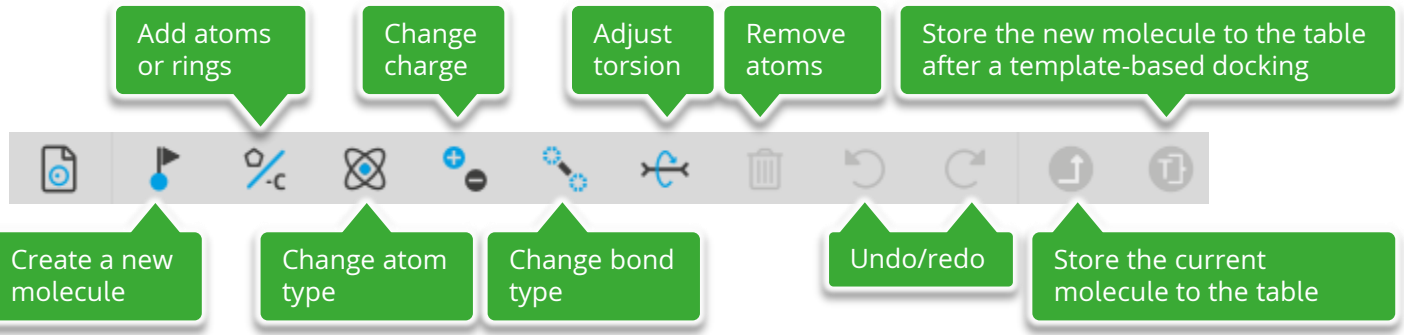
Mode Overview

The editor-menu will appear on the top left.
There you can:



To edit a molecule ALWAYS:
1. **Select** (atoms or bonds)
2. **Modify** (using the function of choice from above)

Note that many editor functions have shortcut-keys. E.g. select a bond and type `'1'`, `'2'` or, `'3'` on the keyboard, or select an atom and type the element (`'C'`, `'N'`, `'O'`, ...).

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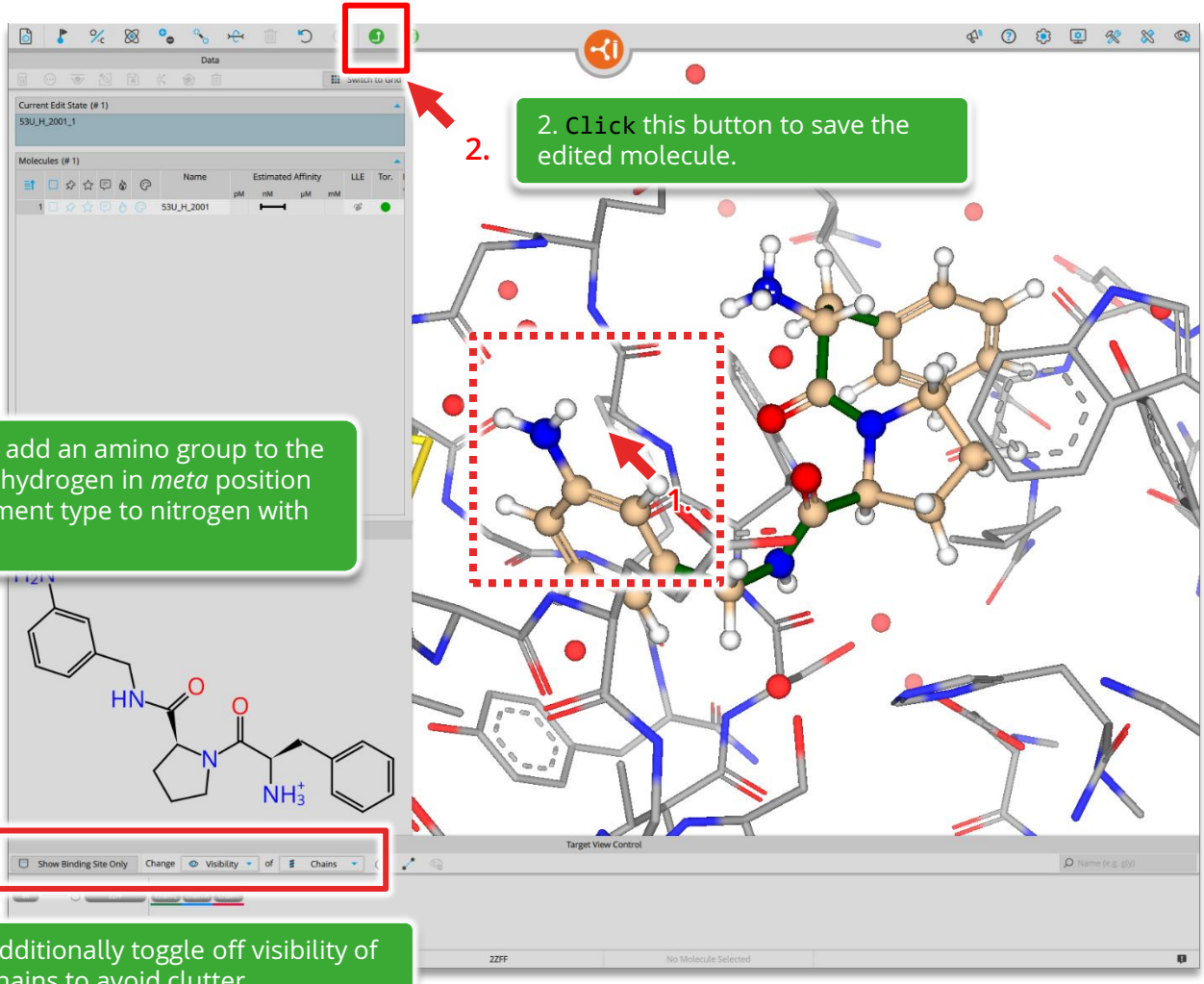
Mode Overview



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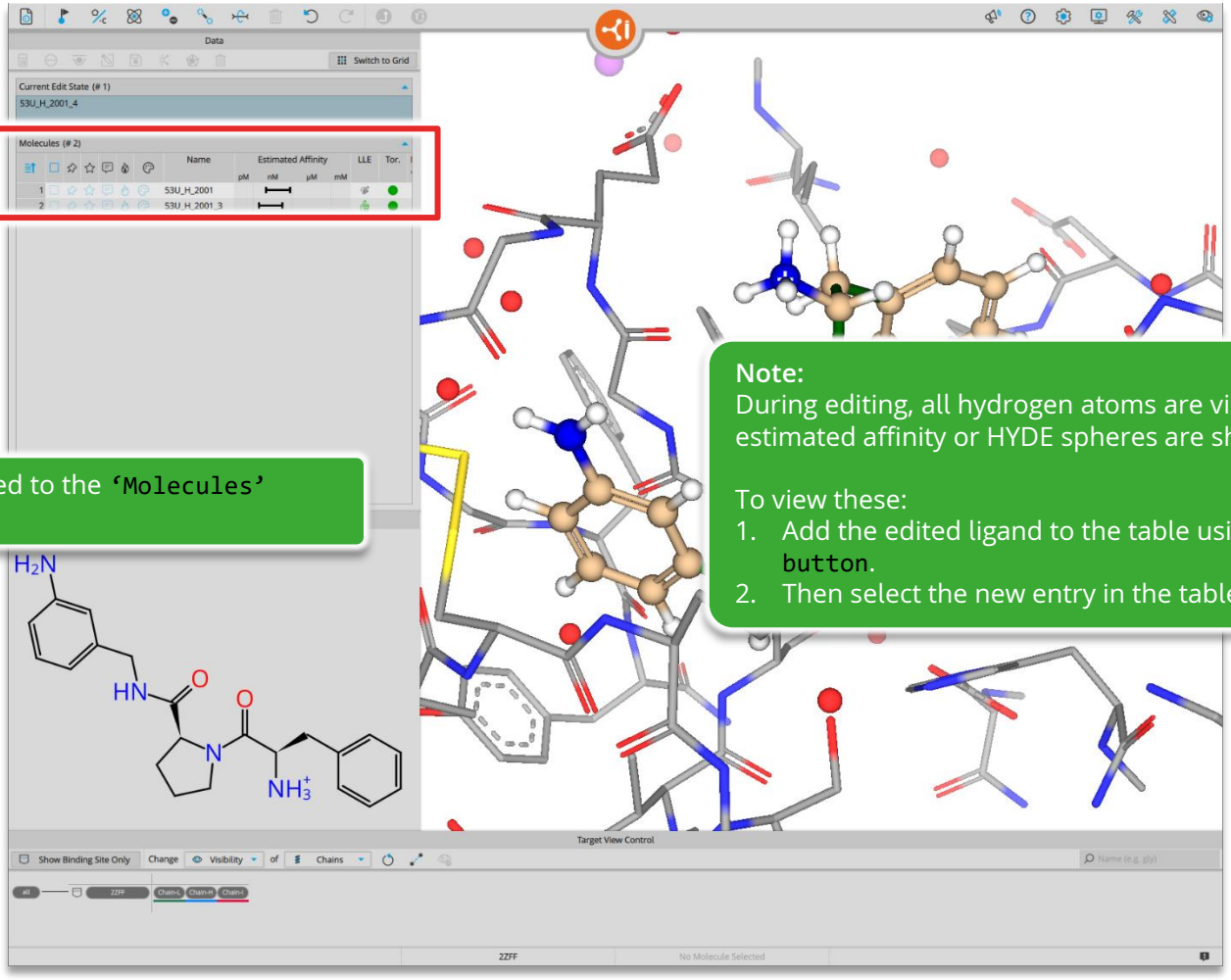
Mode Overview



New entries are added to the ‘Molecules’ table.

Note:
During editing, all hydrogen atoms are visible, but no estimated affinity or HYDE spheres are shown.

To view these:
1. Add the edited ligand to the table using the green button.
2. Then select the new entry in the table.

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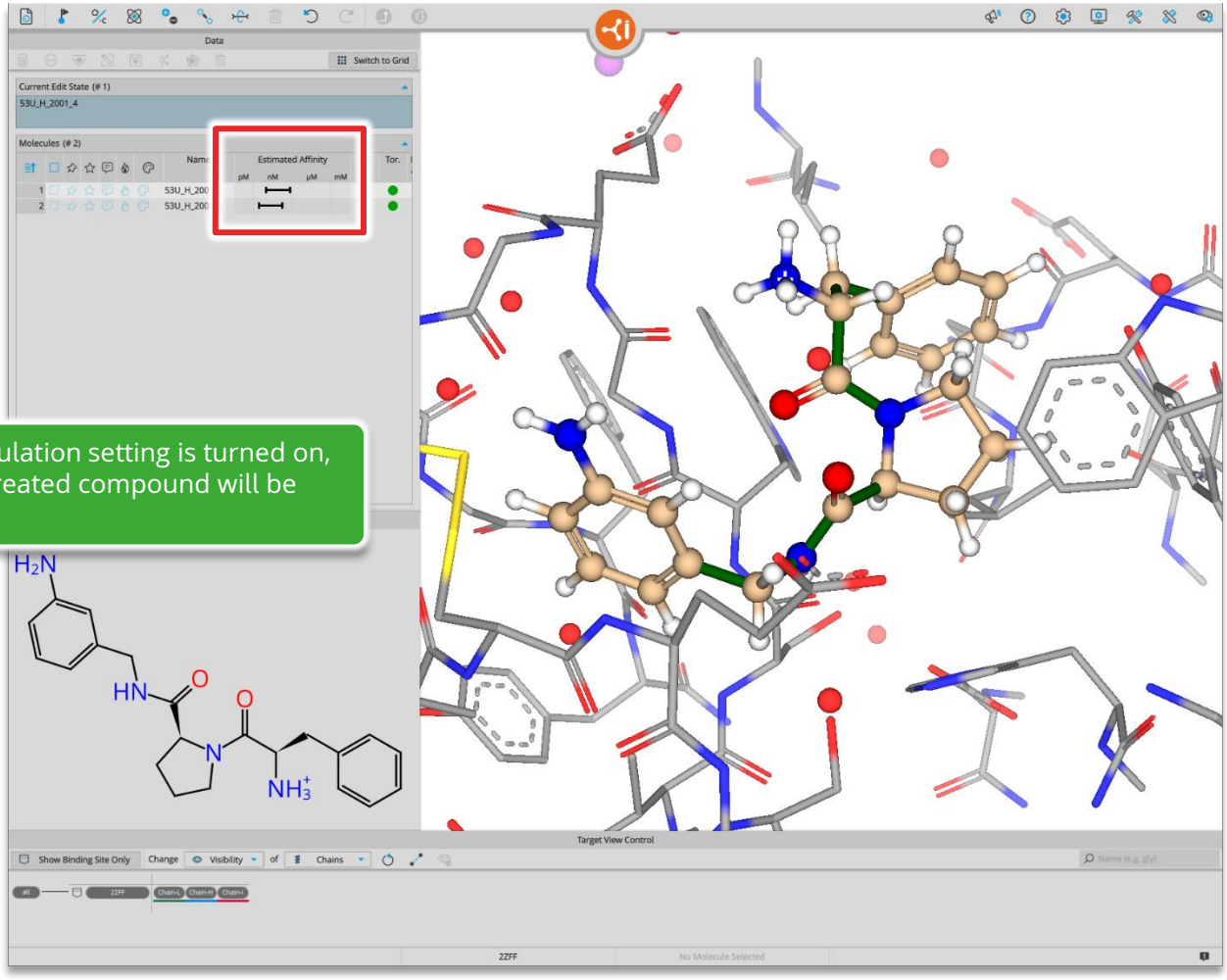
Mode Overview



If the respective calculation setting is turned on, the affinity of your created compound will be displayed.

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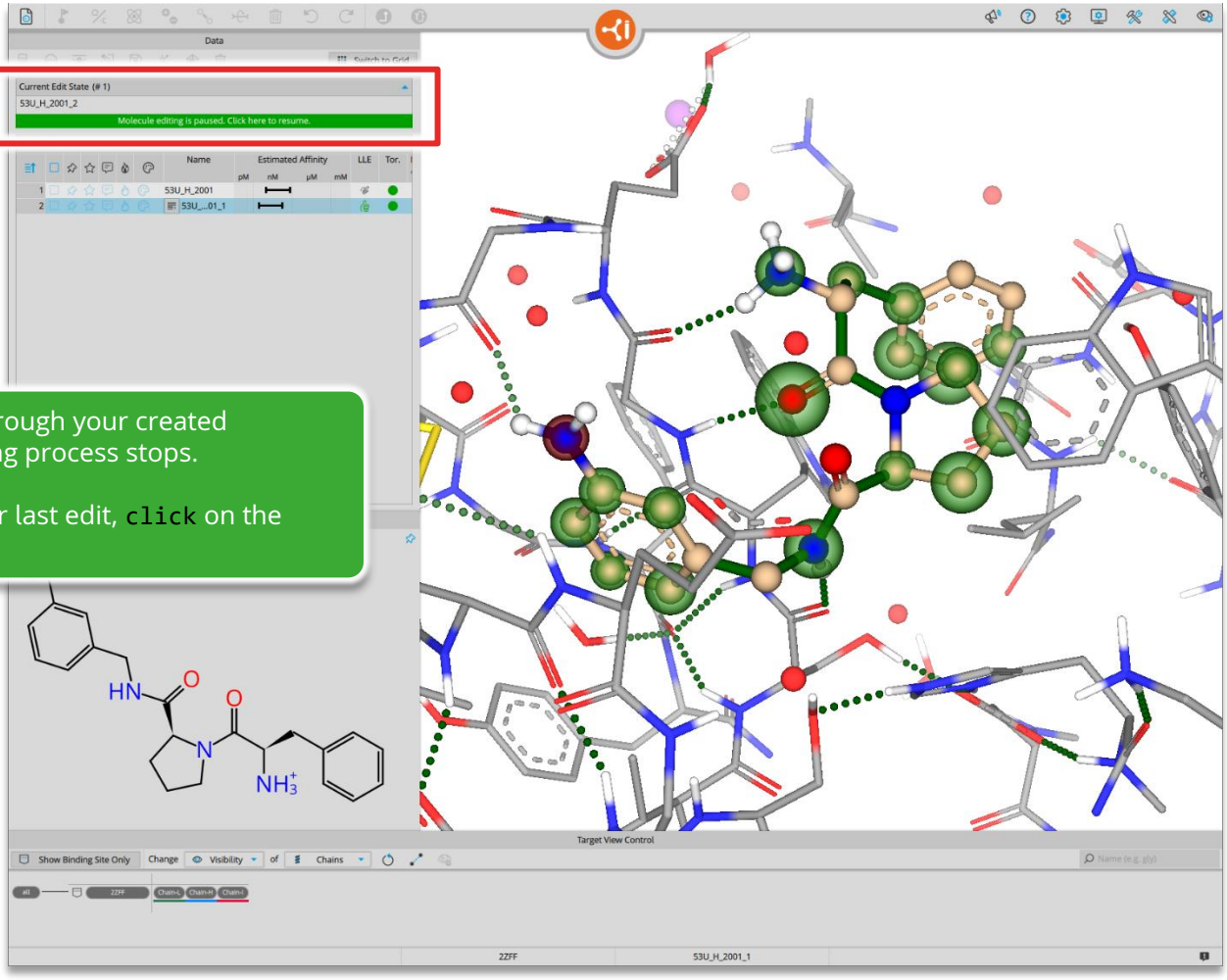
Mode Overview



Once you browse through your created molecules, the editing process stops.

To resume from your last edit, `click` on the highlighted button.

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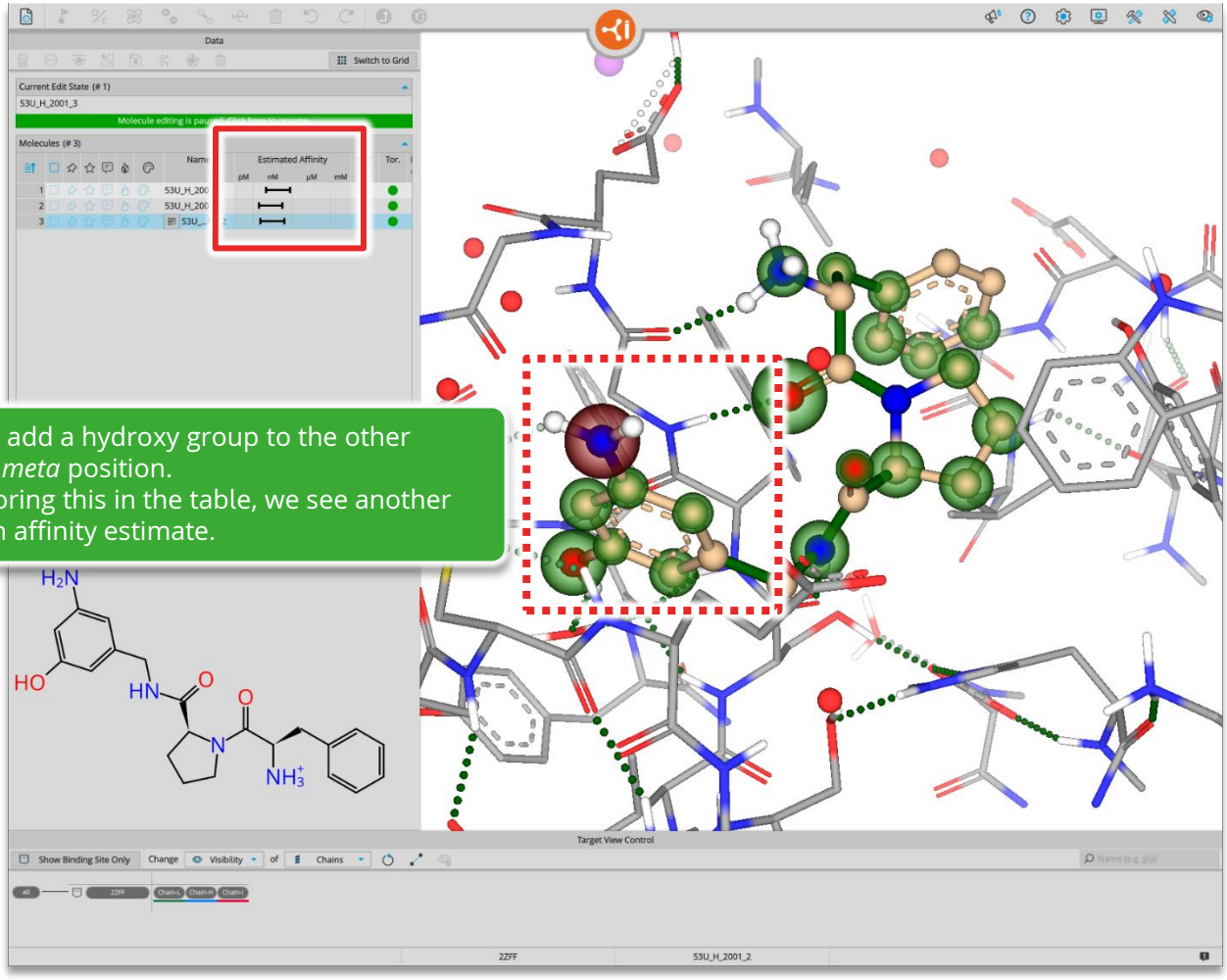
Mode Overview



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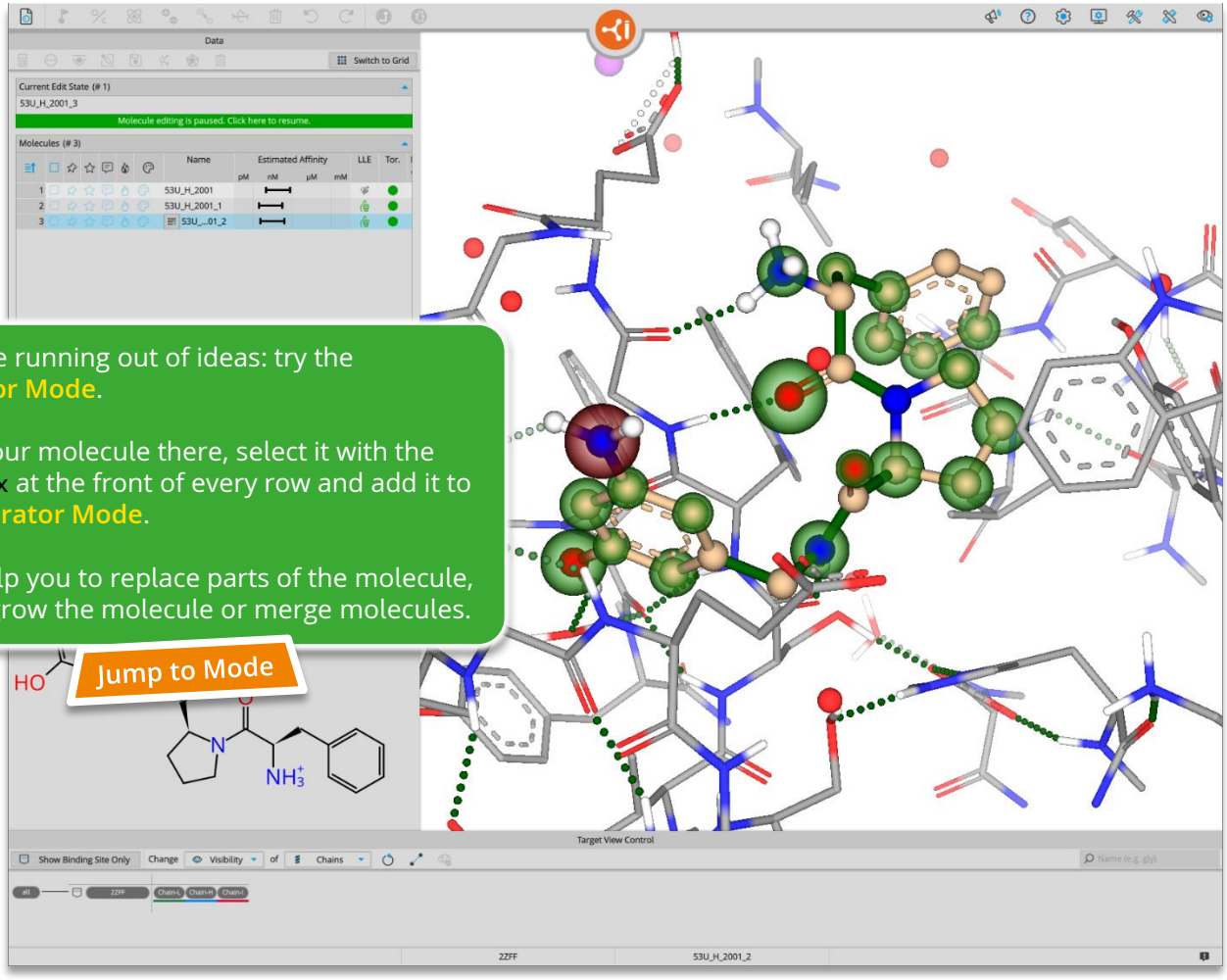
Mode Overview



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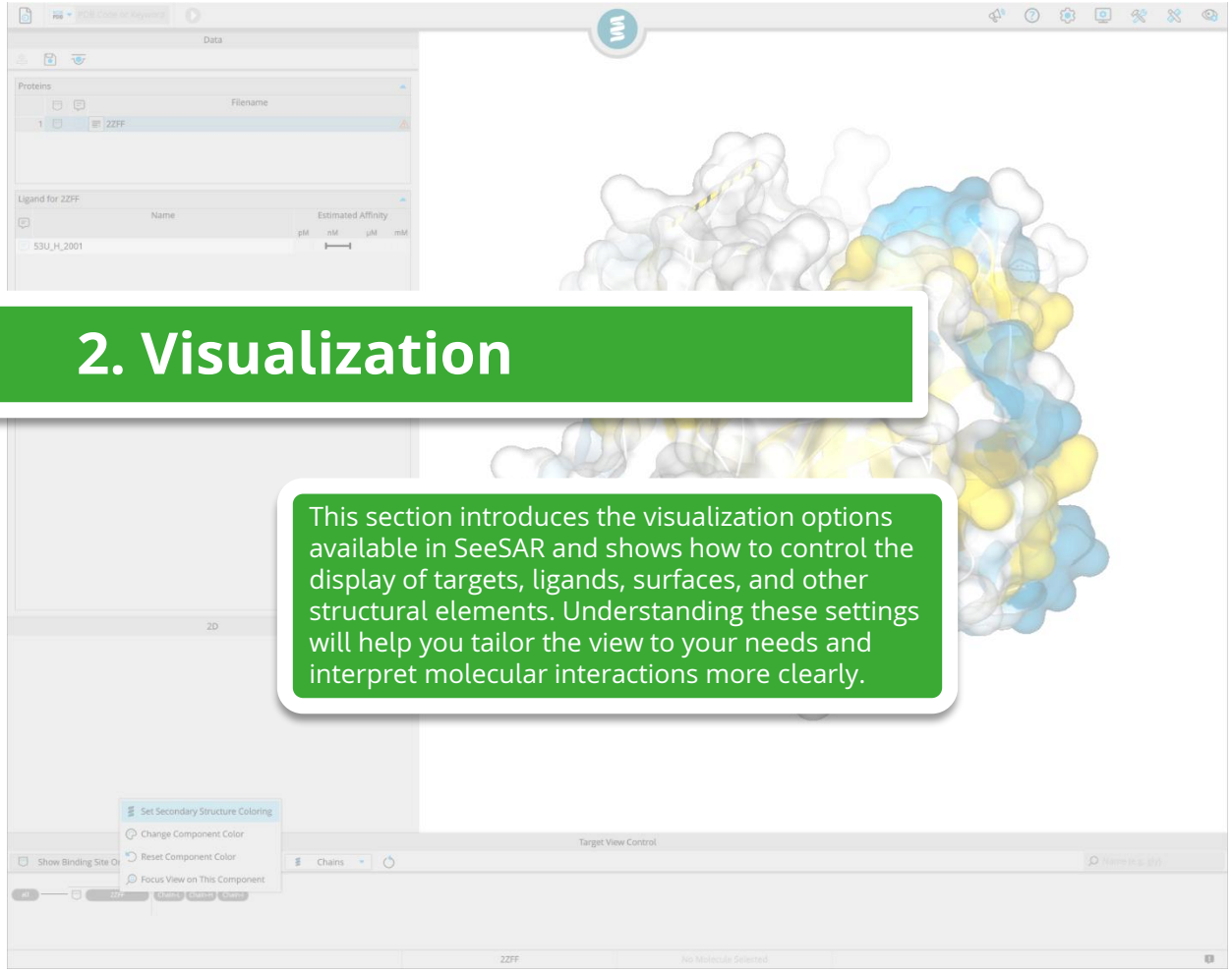
Mode Overview



2. Visualization

This section introduces the visualization options available in SeeSAR and shows how to control the display of targets, ligands, surfaces, and other structural elements. Understanding these settings will help you tailor the view to your needs and interpret molecular interactions more clearly.

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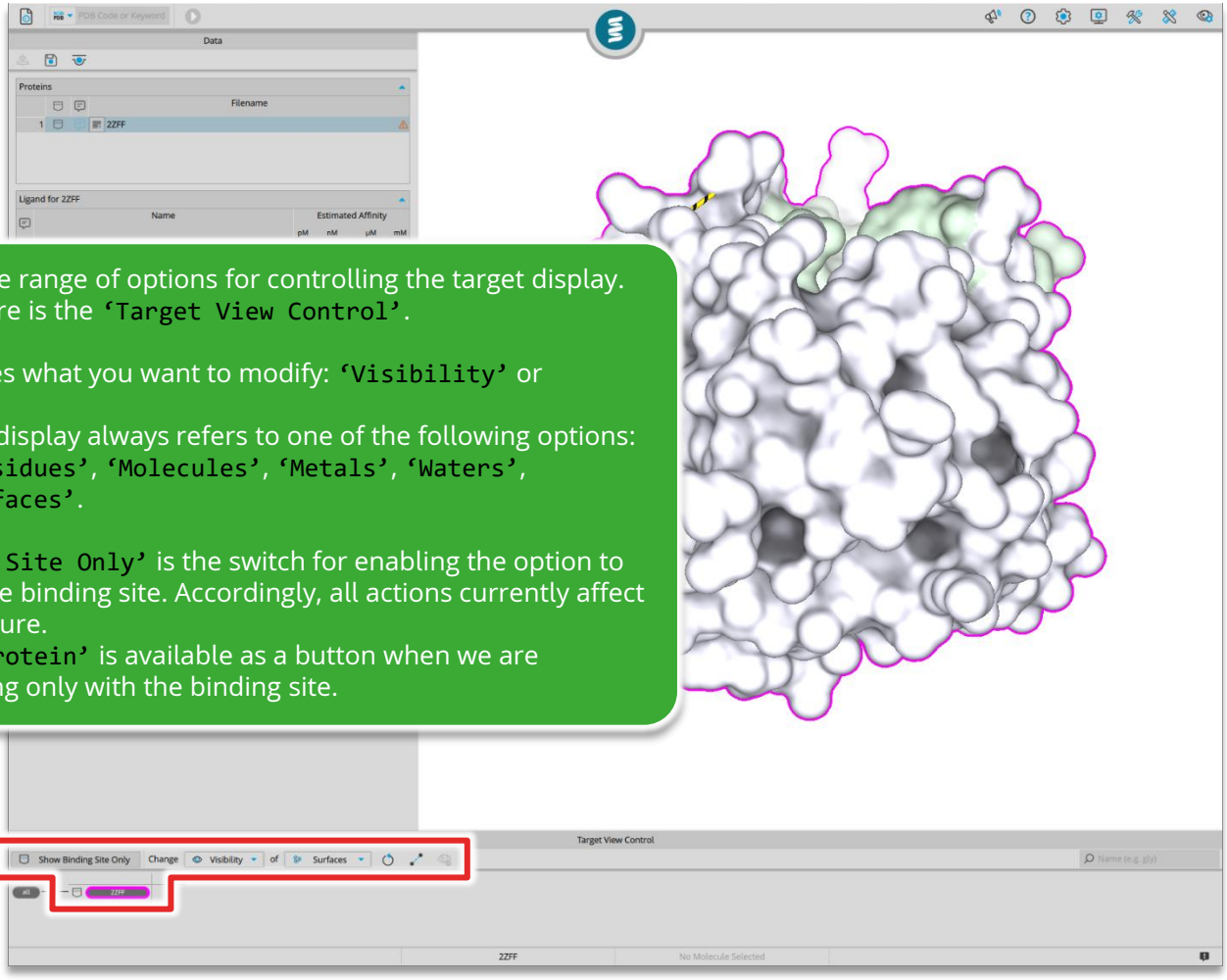
Mode Overview



SeeSAR offers a wide range of options for controlling the target display. The key element here is the **'Target View Control'**.

- **'Change'** defines what you want to modify: **'Visibility'** or **'Color'**.
- In addition, the display always refers to one of the following options: **'Targets'**, **'Residues'**, **'Molecules'**, **'Metals'**, **'Waters'**, **'Chains'**, **'Surfaces'**.

- **'Show Binding Site Only'** is the switch for enabling the option to visualize only the binding site. Accordingly, all actions currently affect the entire structure.
- **'Show Whole Protein'** is available as a button when we are currently working only with the binding site.

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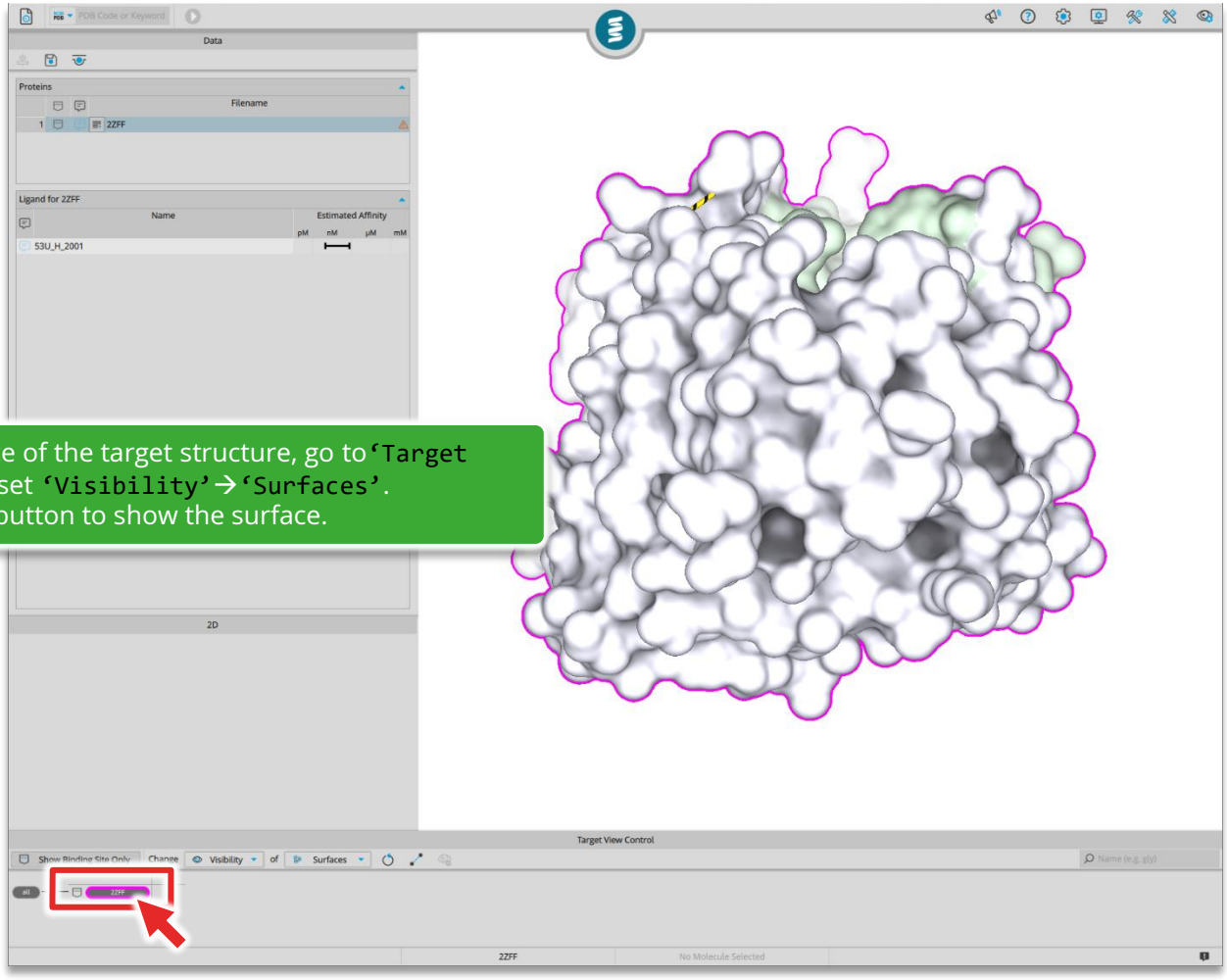
Mode Overview

To display the surface of the target structure, go to ‘Target View Control’ and set ‘Visibility’→‘Surfaces’. Click on the target button to show the surface.



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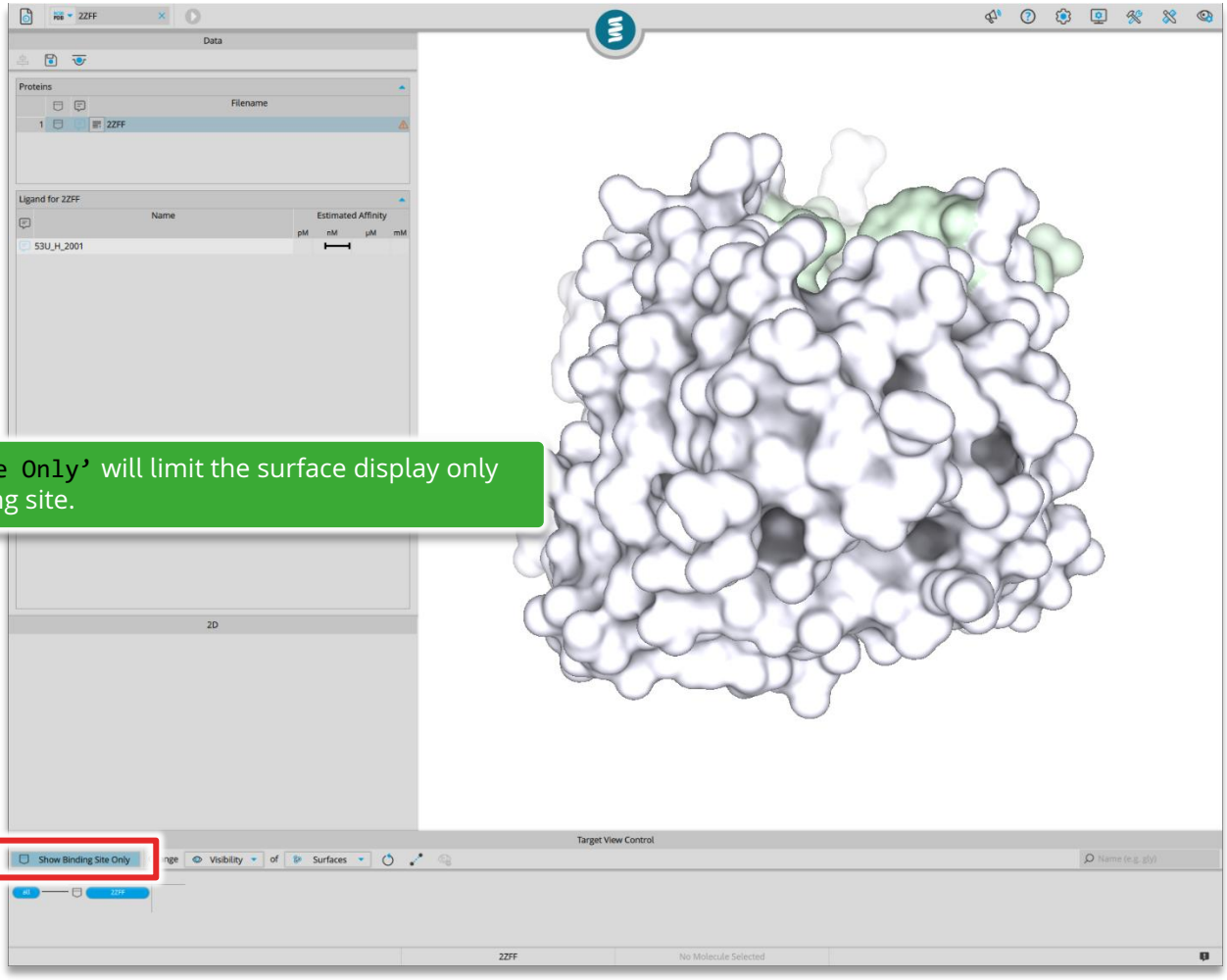
Mode Overview



'Show Binding Site Only' will limit the surface display only to the defined binding site.

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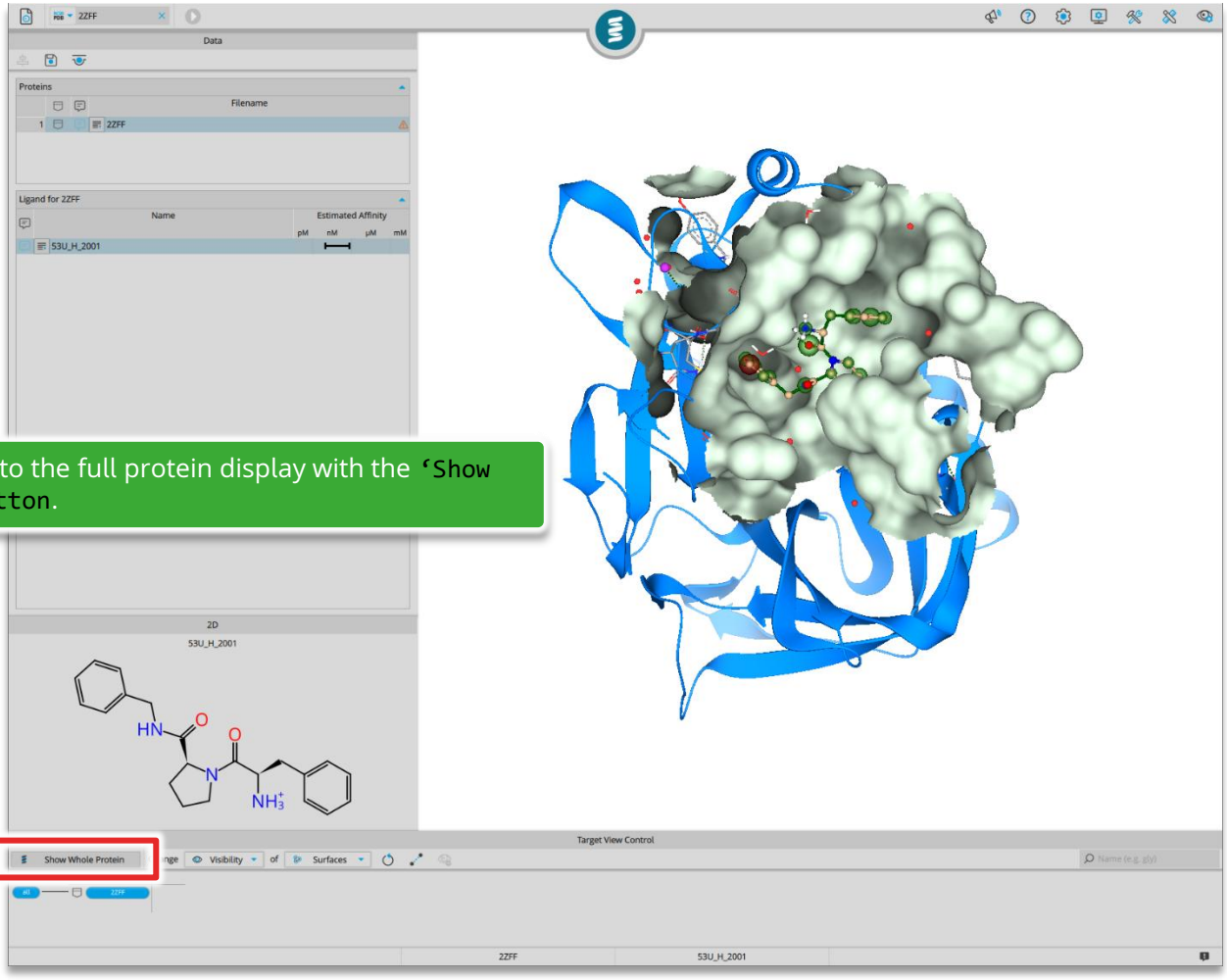
Mode Overview



You can switch back to the full protein display with the ‘Show Whole Protein’ button.

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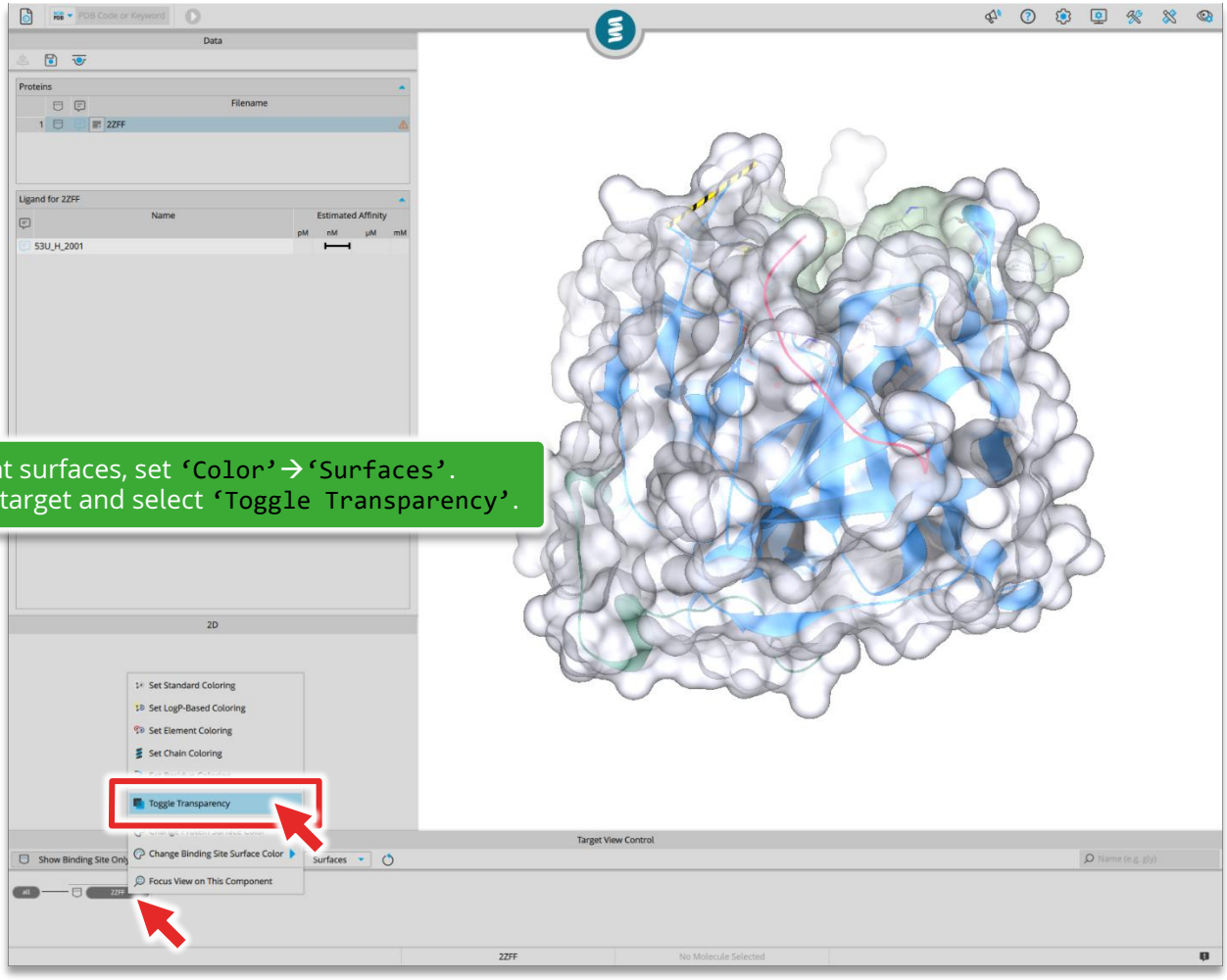
Mode Overview

To create transparent surfaces, set ‘Color’→‘Surfaces’.
Right-click on the target and select ‘Toggle Transparency’.



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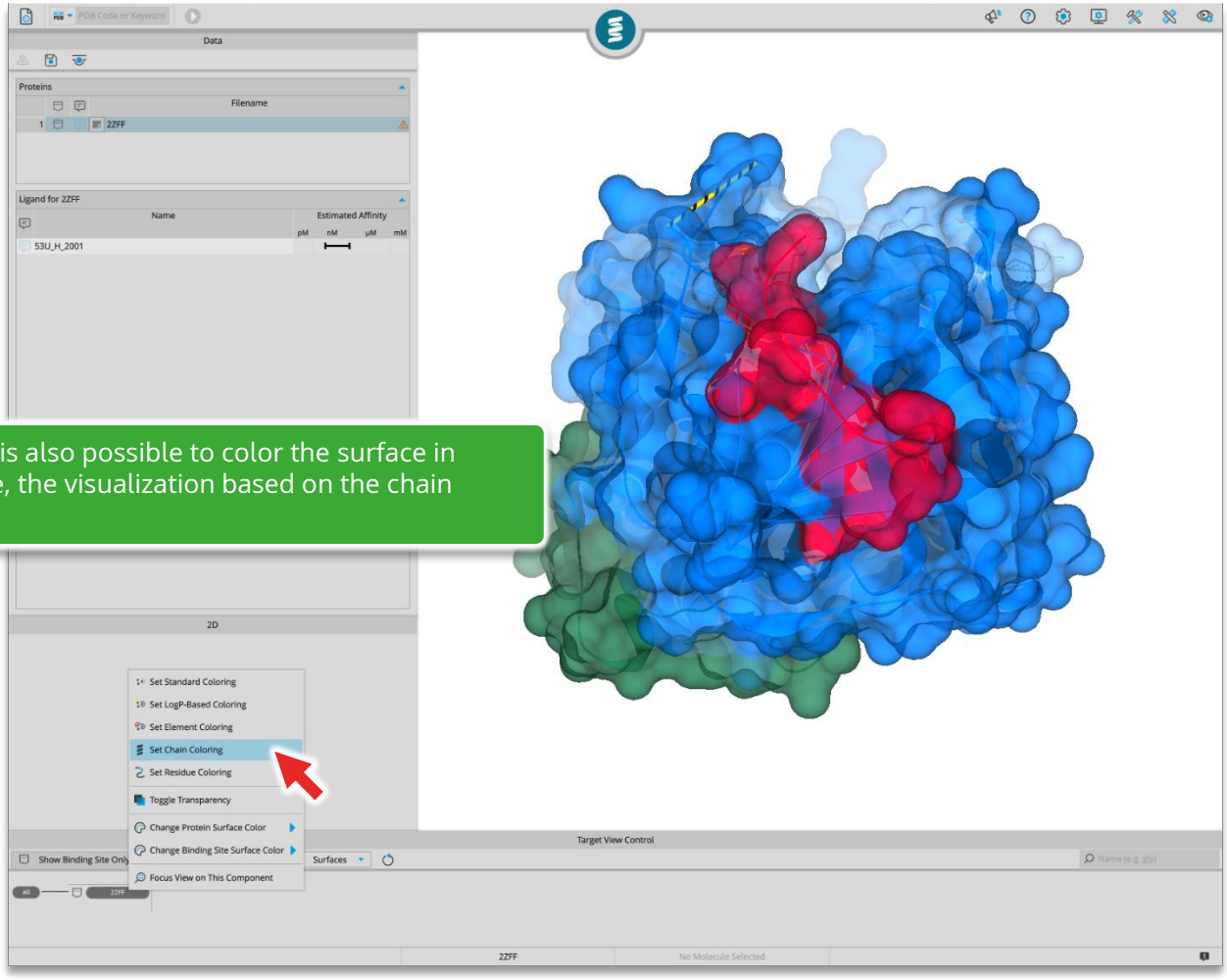
Mode Overview

In the same menu it is also possible to color the surface in different styles. Here, the visualization based on the chain colors is presented.



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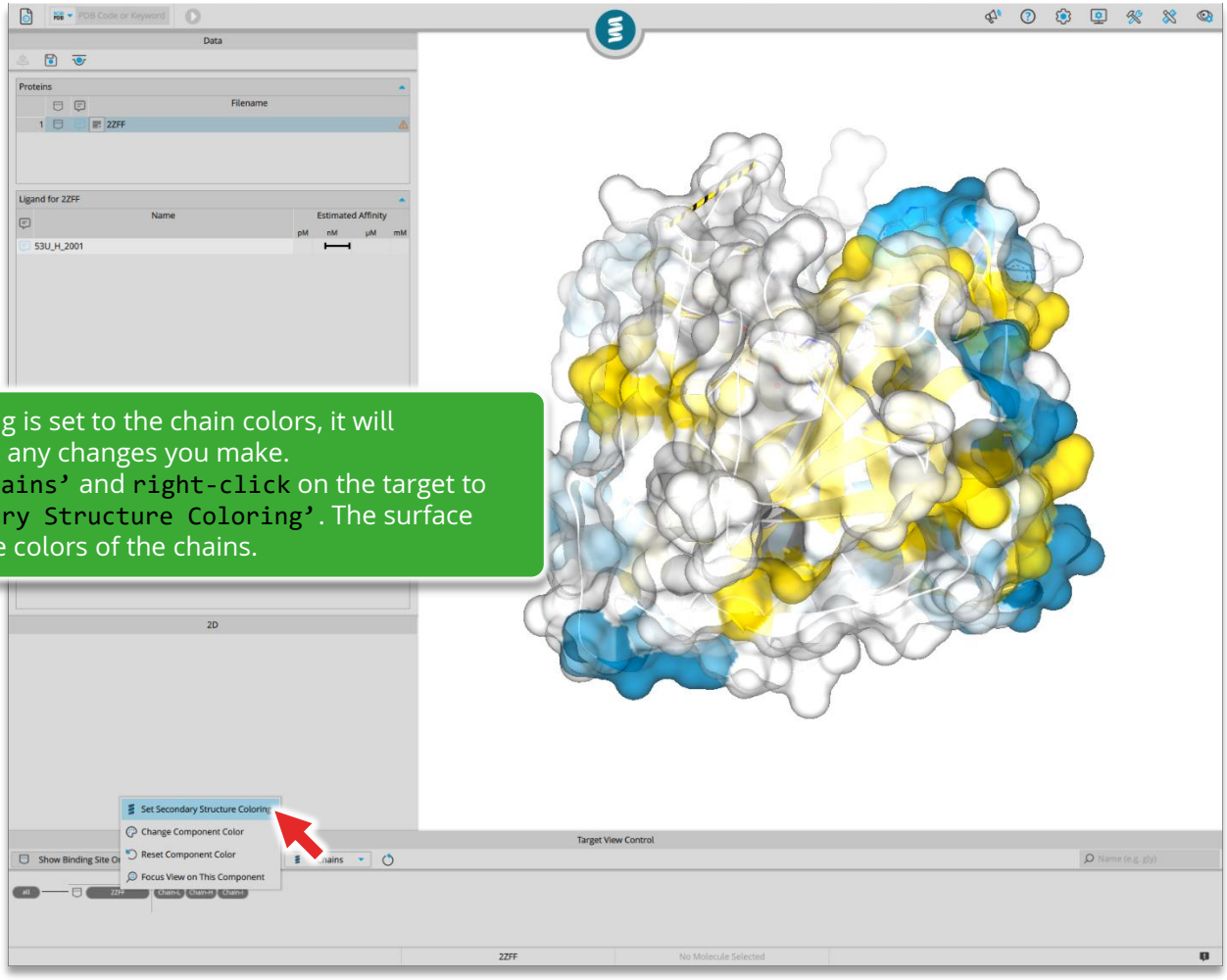
Mode Overview



If the surface coloring is set to the chain colors, it will automatically reflect any changes you make.
Select **'Color'→'Chains'** and **right-click** on the target to select **'Set Secondary Structure Coloring'**. The surface will now adapt to the colors of the chains.

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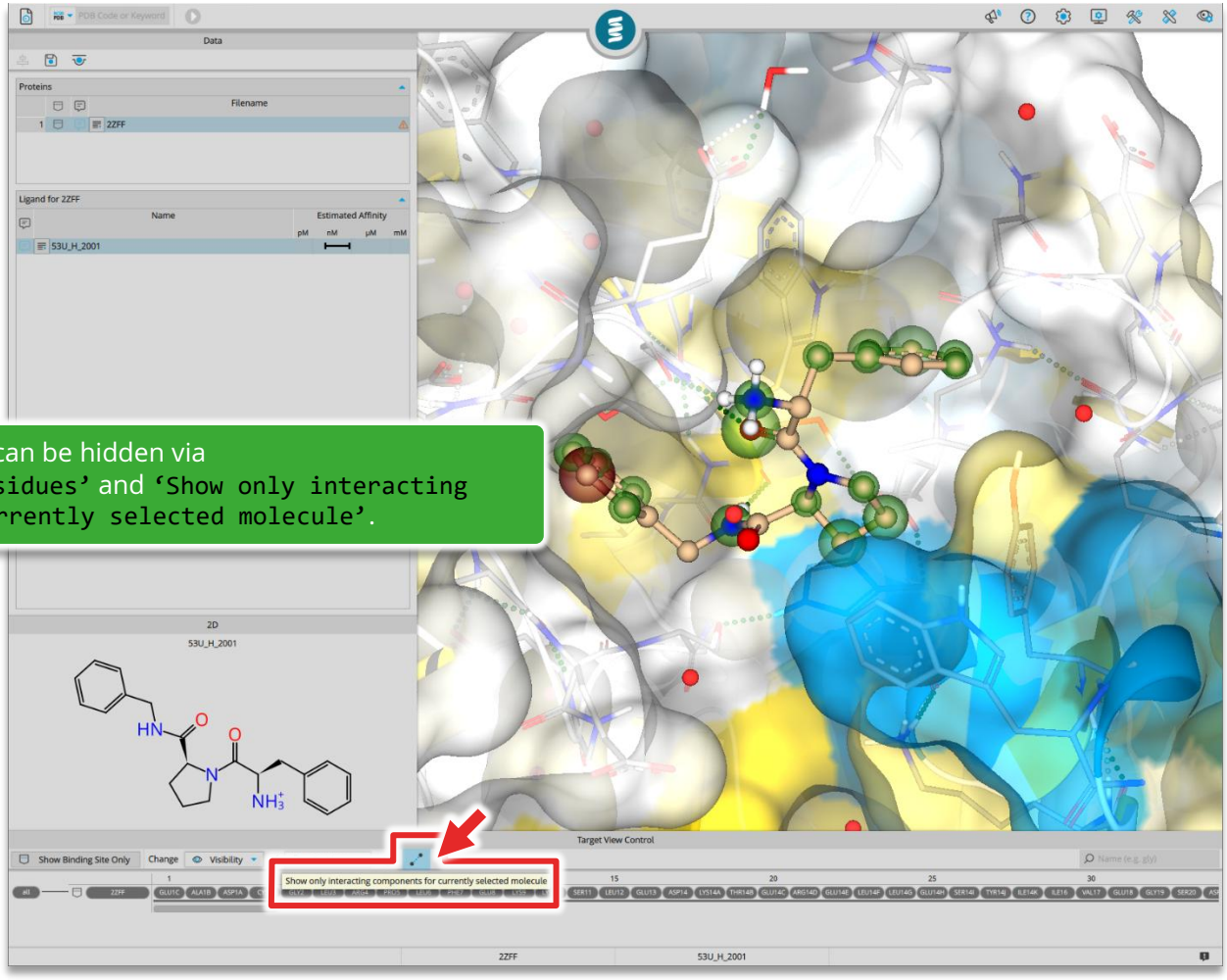
Mode Overview

Unwanted residues can be hidden via ‘Visibility’→‘Residues’ and ‘Show only interacting components for currently selected molecule’.



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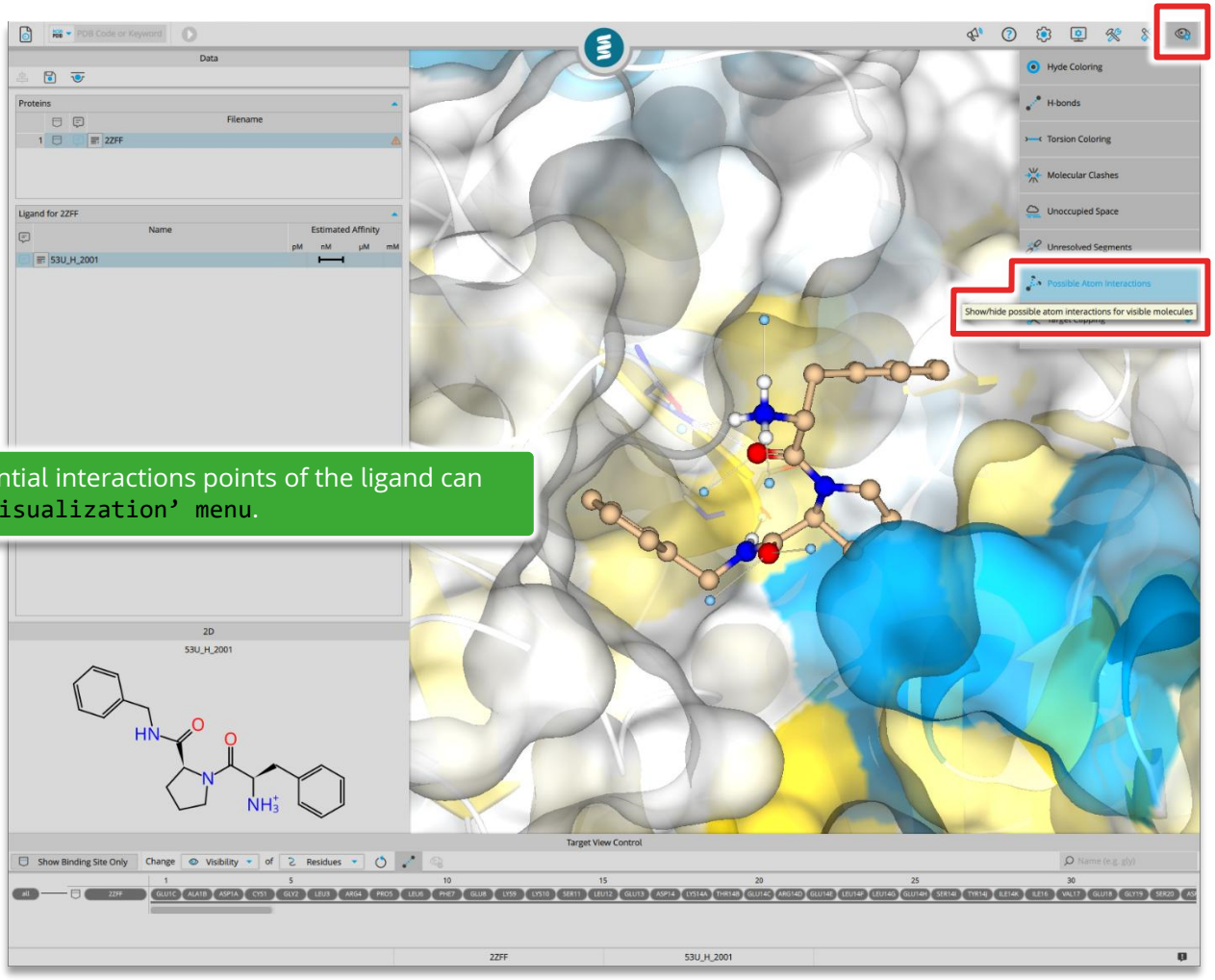
Mode Overview



Visualization of potential interactions points of the ligand can be enabled in the **'Visualization' menu**.

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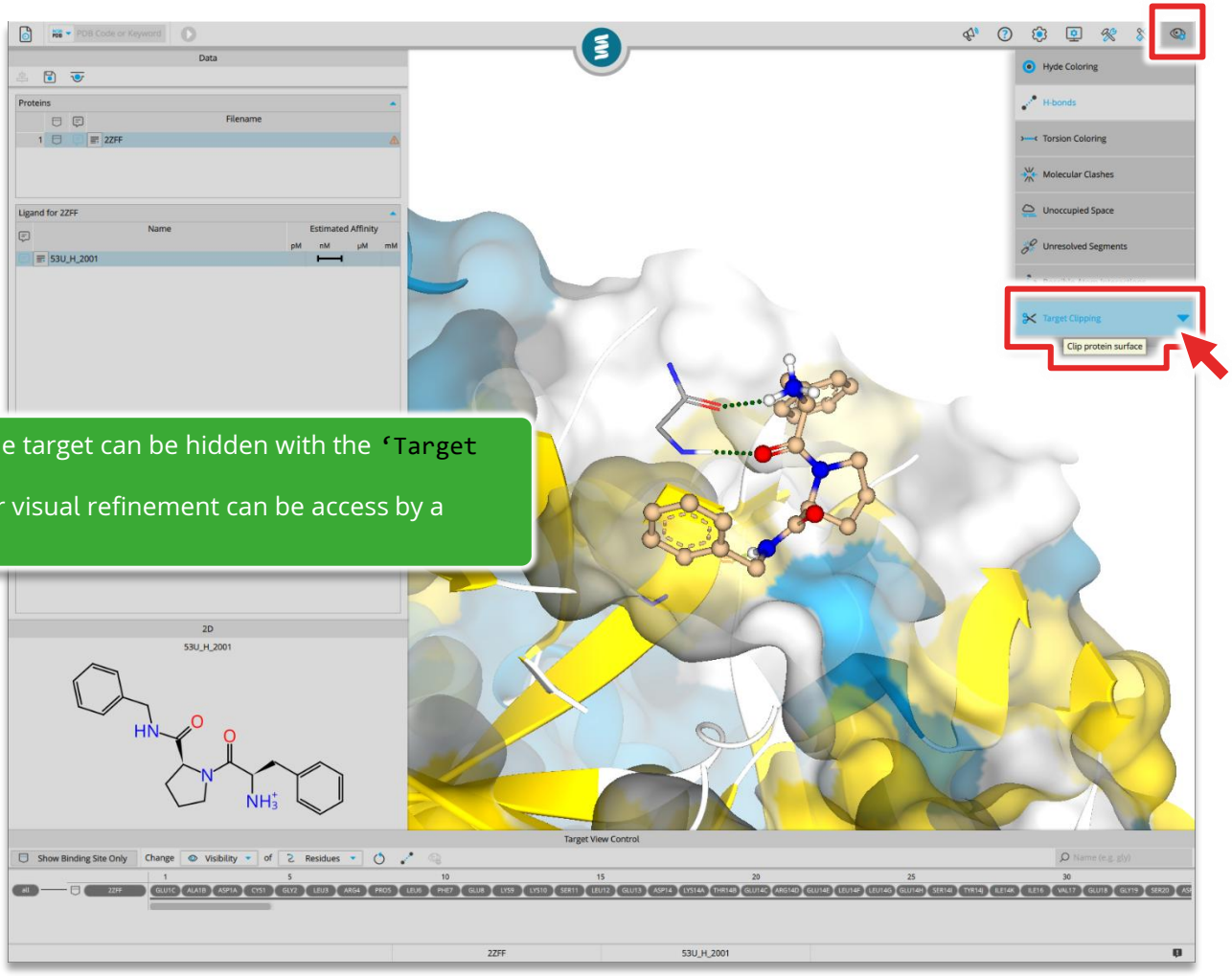
Mode Overview

Complete parts of the target can be hidden with the `'Target Clipping' option`.
Extended options for visual refinement can be access by a `click`.



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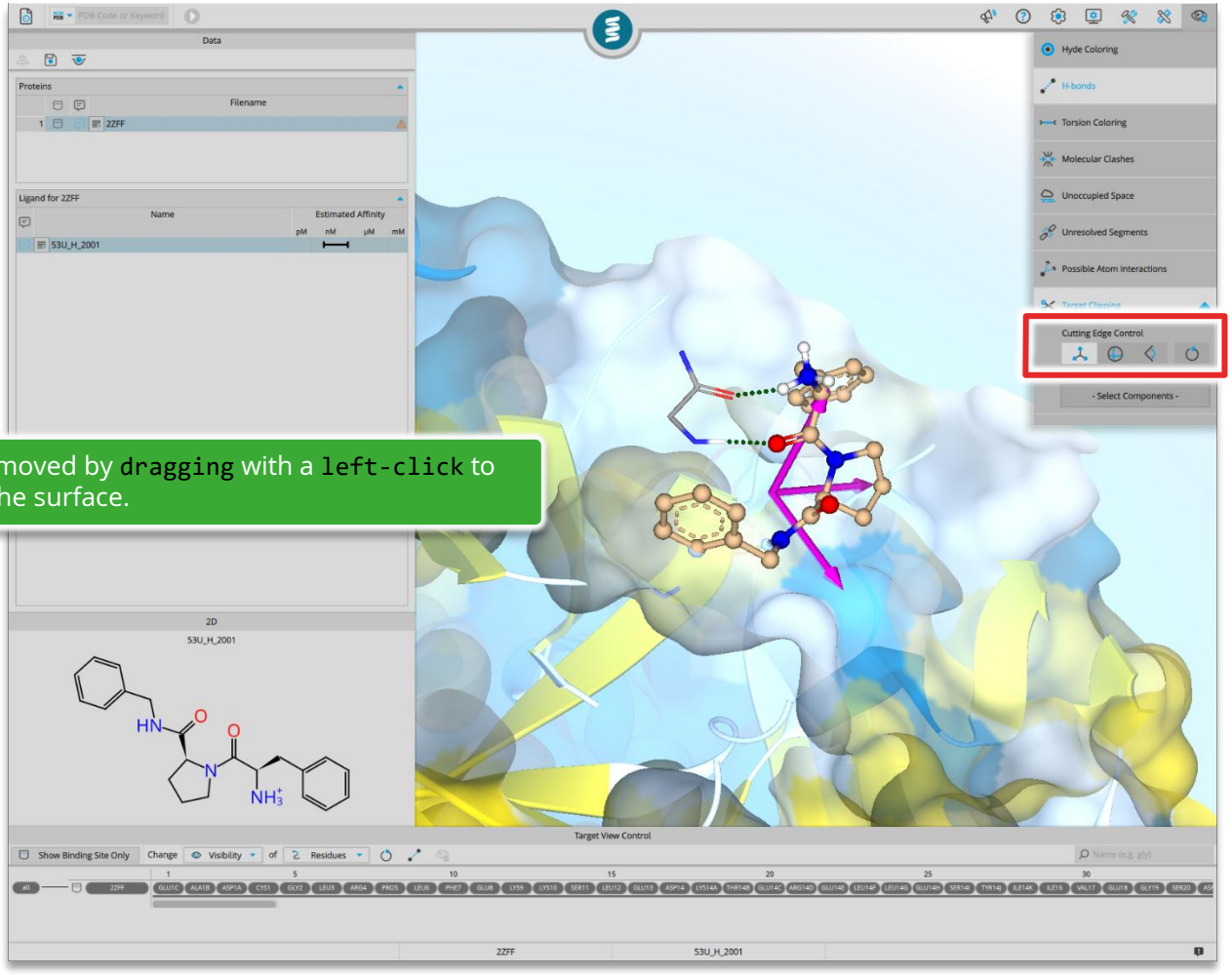
Mode Overview



Cut-off layer can be moved by `dragging` with a `left-click` to adjust the depth of the surface.

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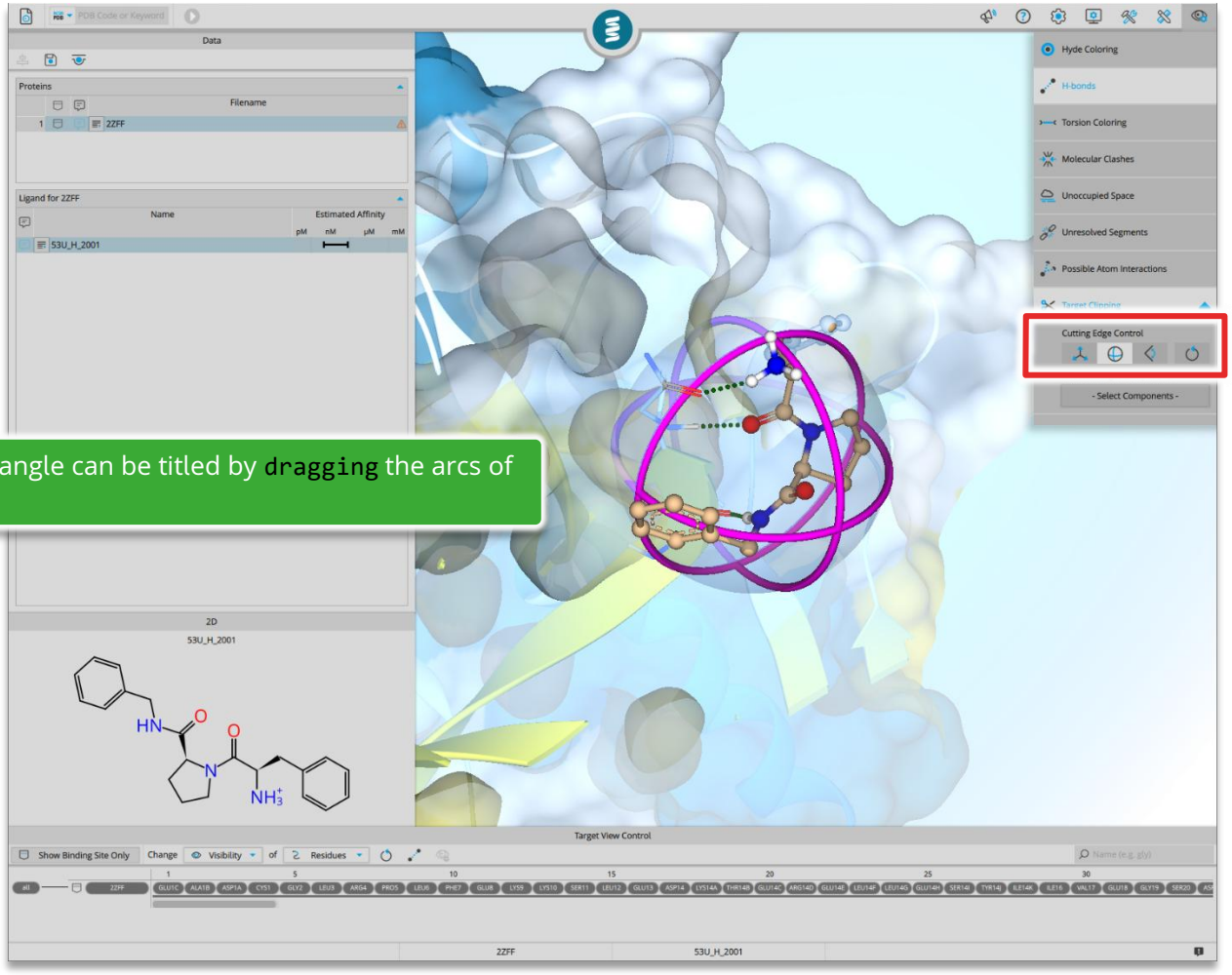
Mode Overview

Likewise, the cut-off angle can be titled by `dragging` the arcs of the sphere.



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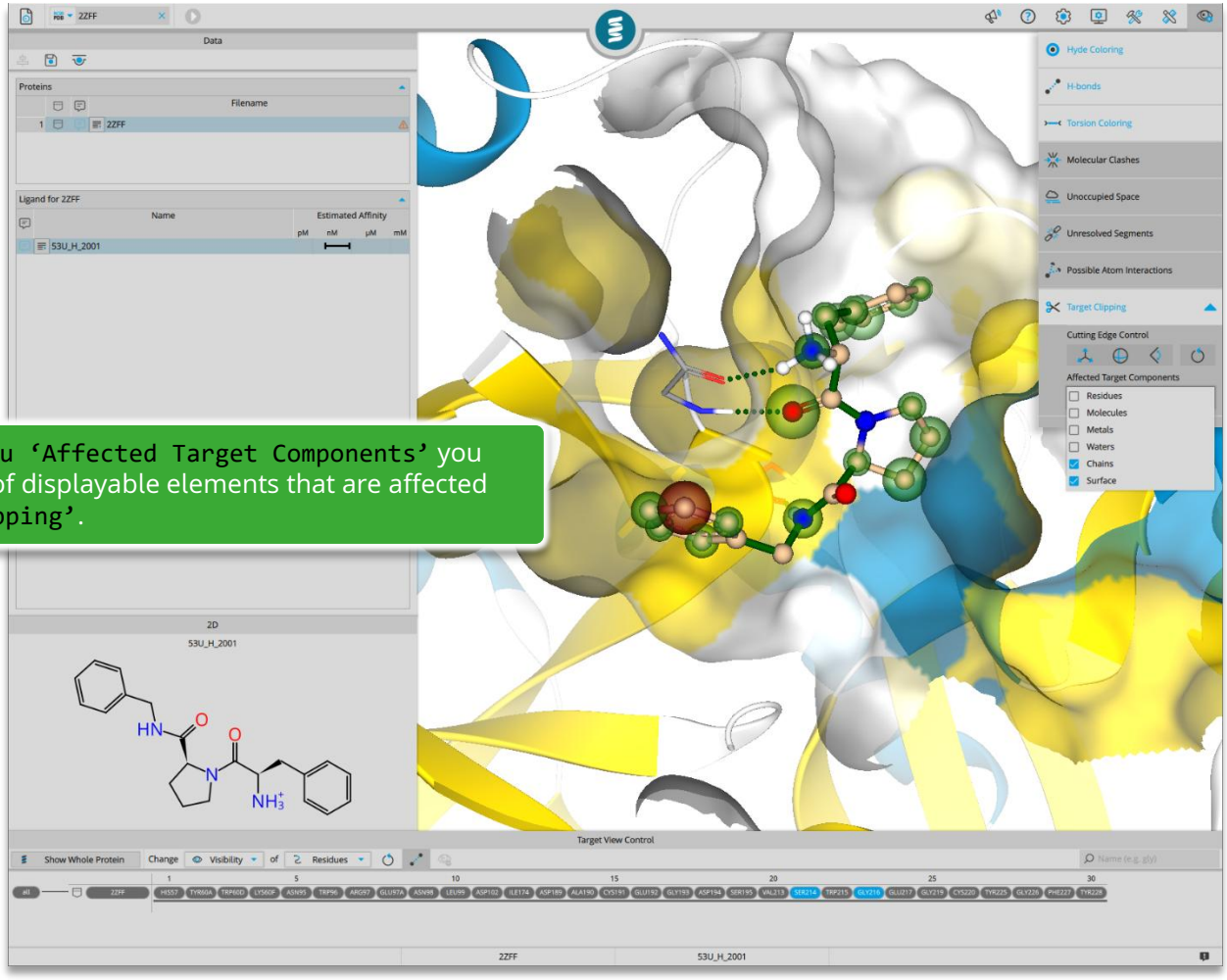
Mode Overview



In the dropdown menu ‘Affected Target Components’ you will find a selection of displayable elements that are affected by the ‘Target Clipping’.

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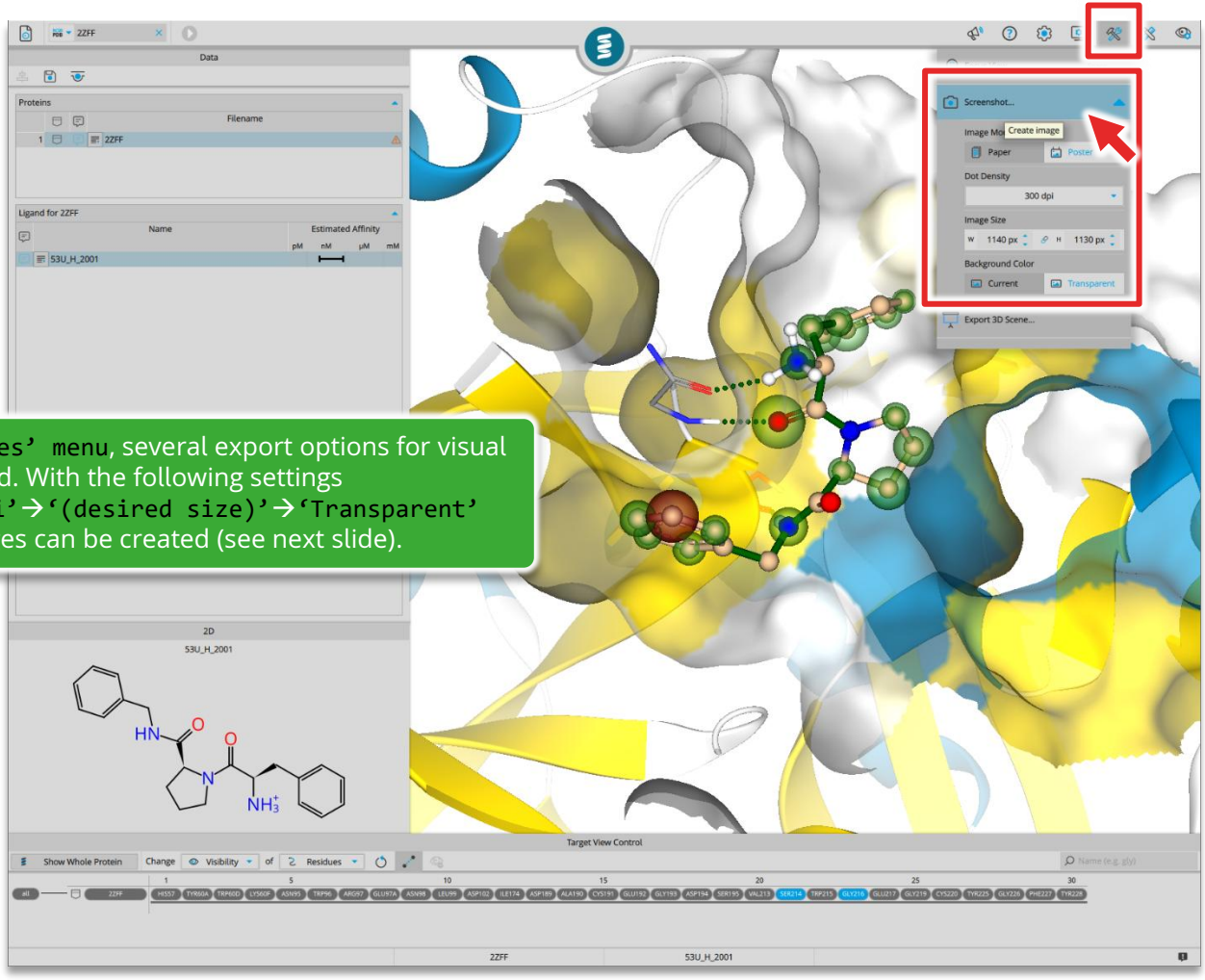
Mode Overview

Under the `'Utilities' menu`, several export options for visual formats can be found. With the following settings `'Poster'→'300 dpi'→'(desired size)'→'Transparent'` publish-worthy images can be created (see next slide).



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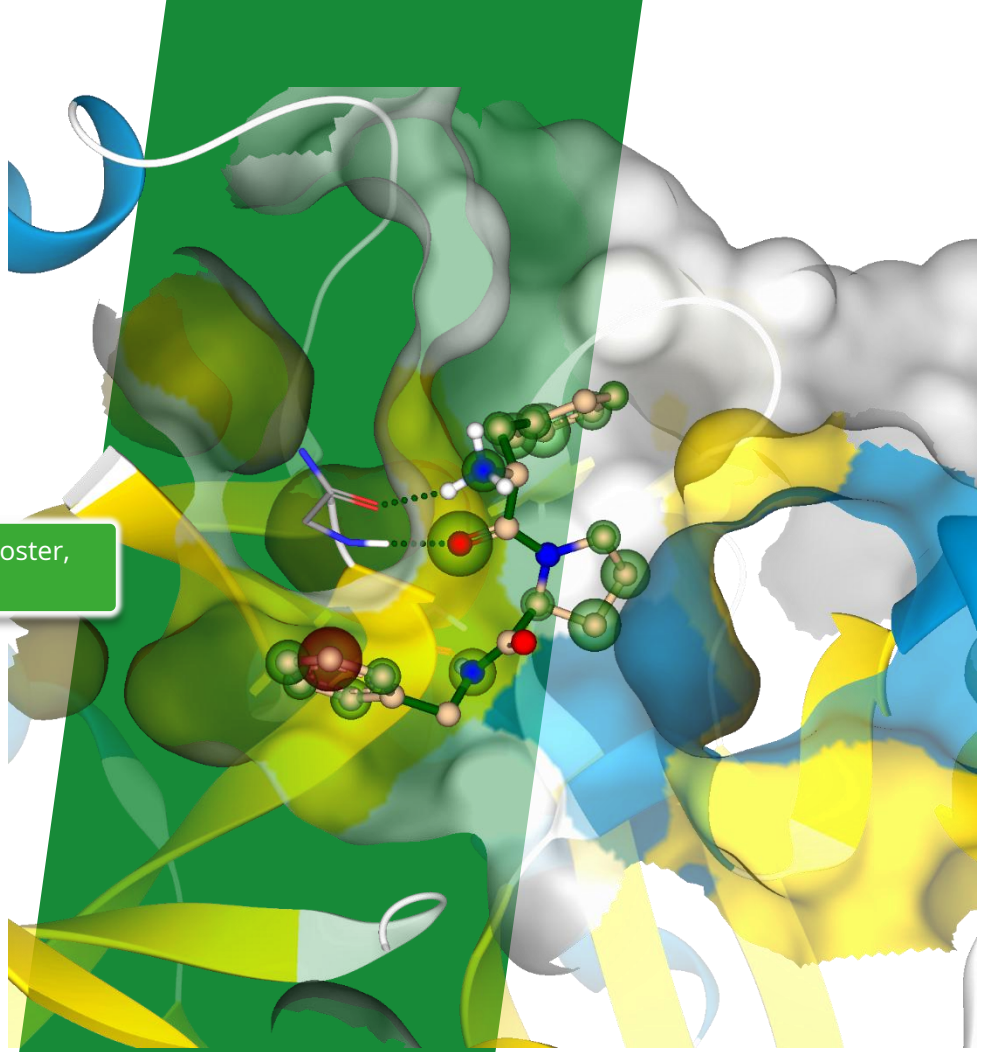
Mode Overview

Transparency support helps to create great visuals for poster, presentations, reports, and more.



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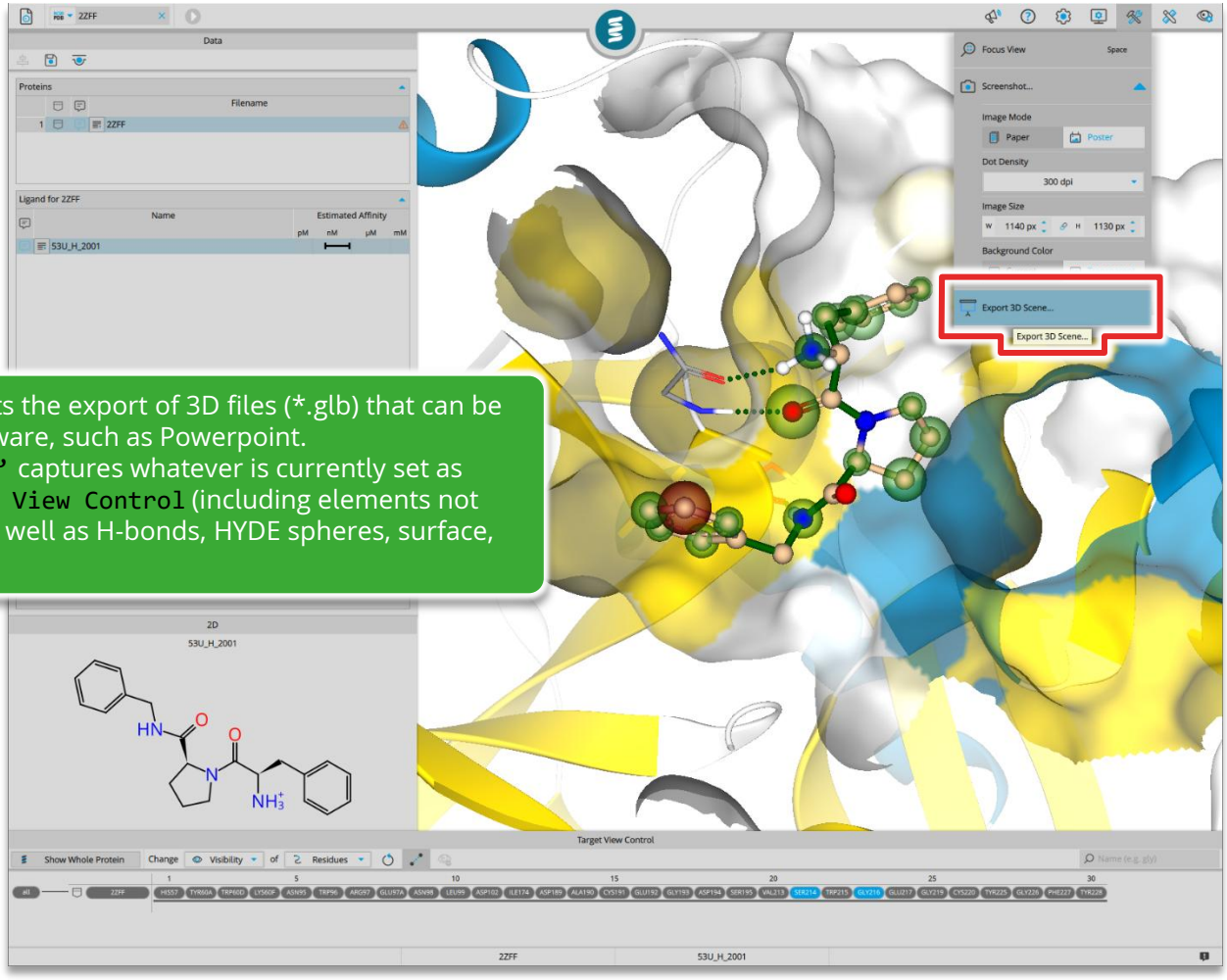
Mode Overview

SeeSAR also supports the export of 3D files (*.glb) that can be used in various software, such as Powerpoint.
`'Export 3D Scene…'` captures whatever is currently set as visible in the `Target View Control` (including elements not shown on screen, as well as H-bonds, HYDE spheres, surface, and more.)



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Mode Overview


The 3D format is great for impactful visualizations and can be used for smooth transitions. It supports motion on slides and be helpful to augment the understanding of the binding mode for the audience.
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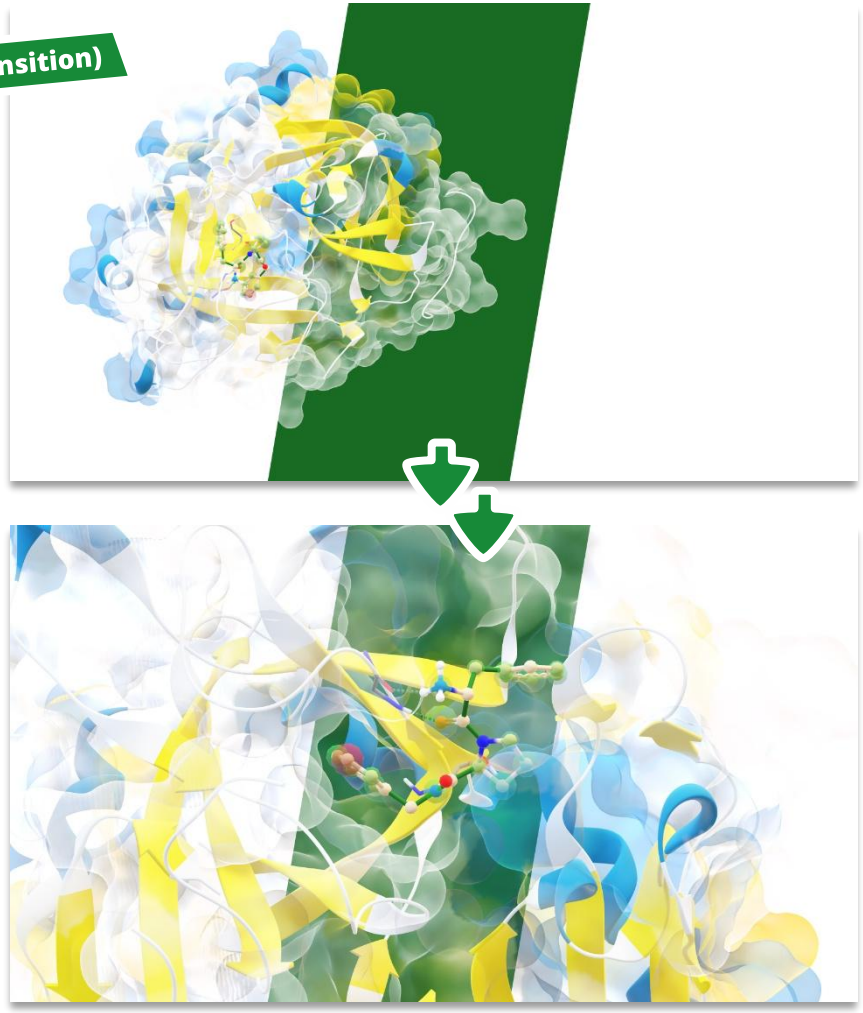
Mode Overview
BioSolveIT

PowerPoint (Morph Transition)



It works also amazingly well with transitions from one slide to the next.

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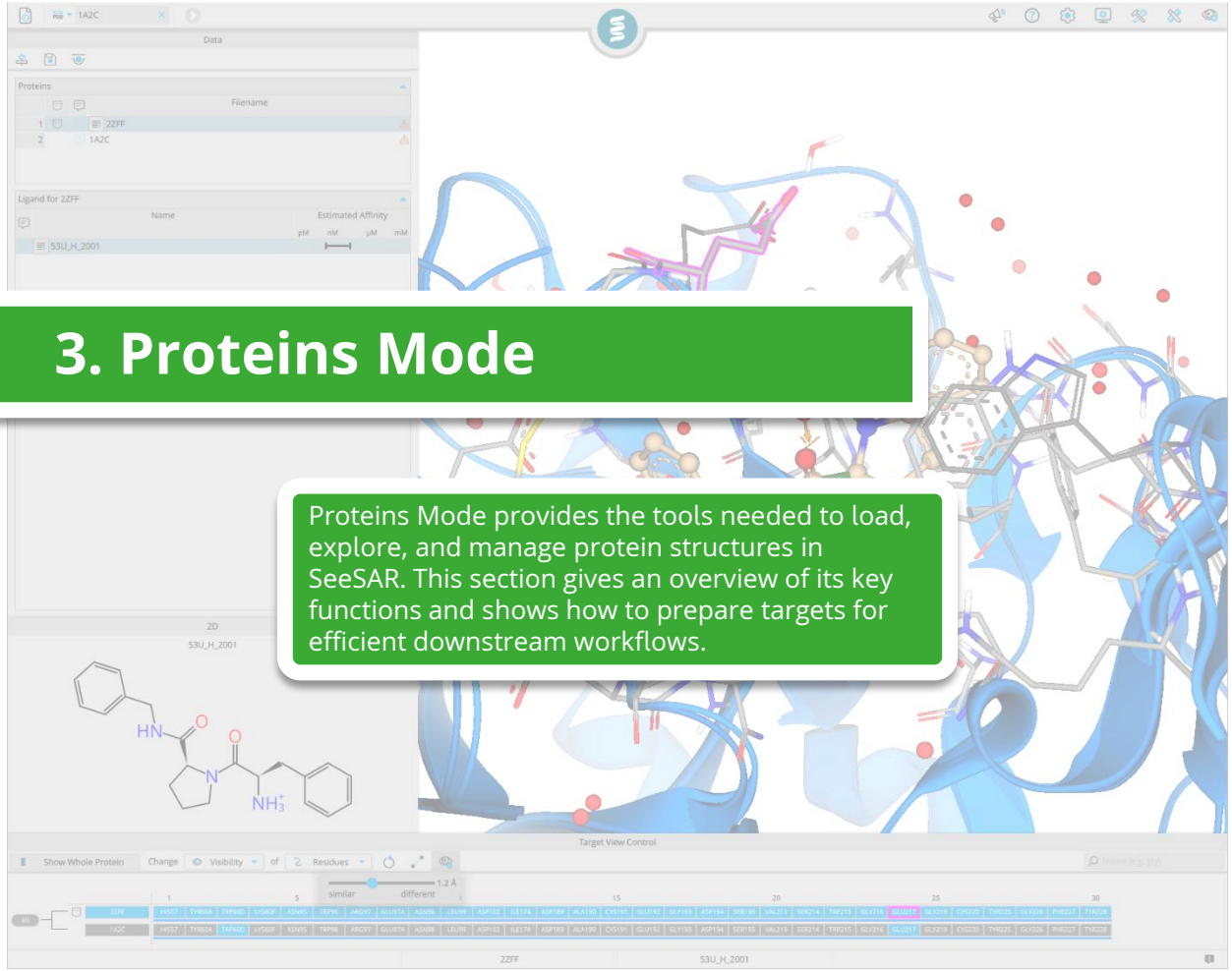
Mode Overview



3. Proteins Mode

Proteins Mode provides the tools needed to load, explore, and manage protein structures in SeeSAR. This section gives an overview of its key functions and shows how to prepare targets for efficient downstream workflows.

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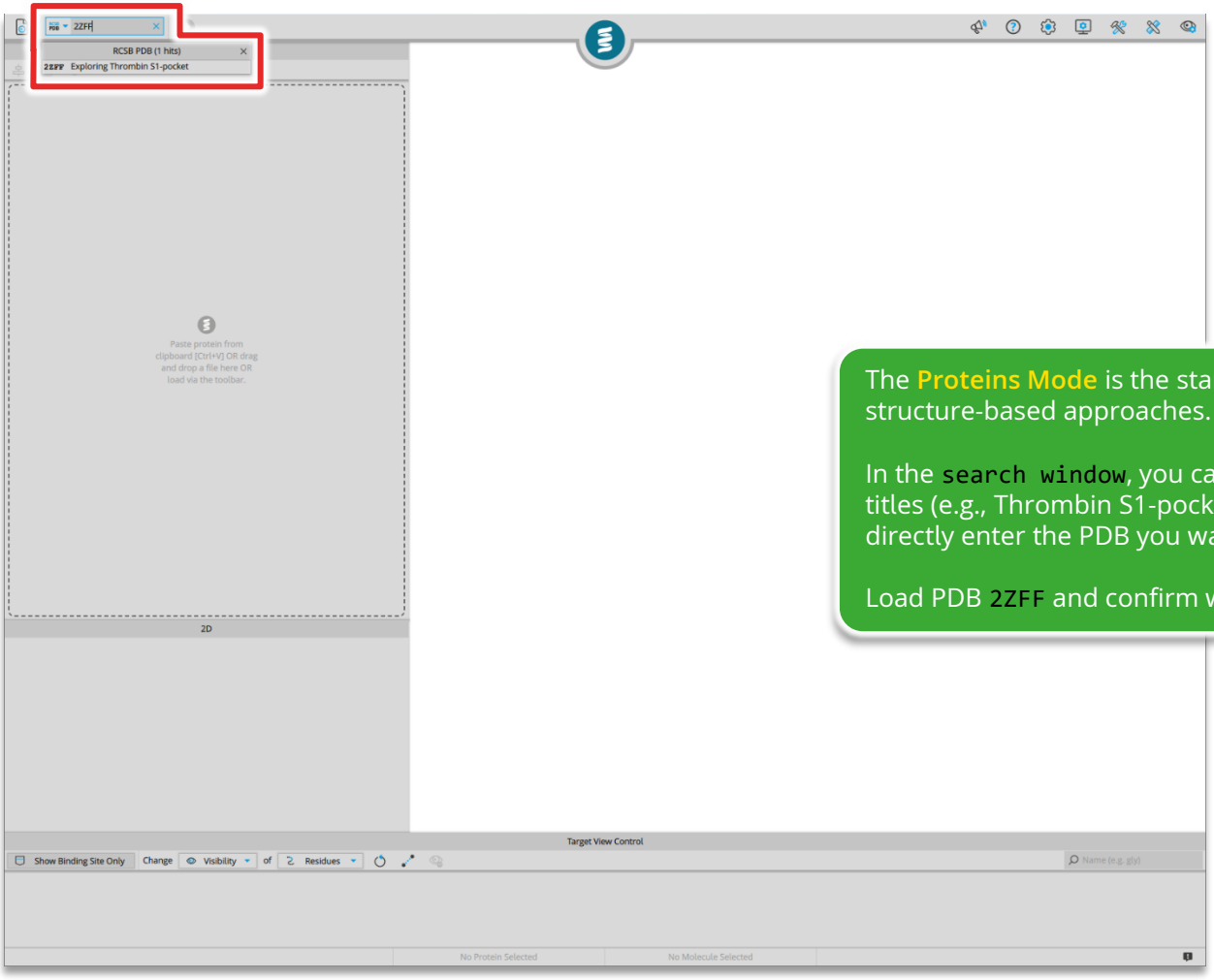
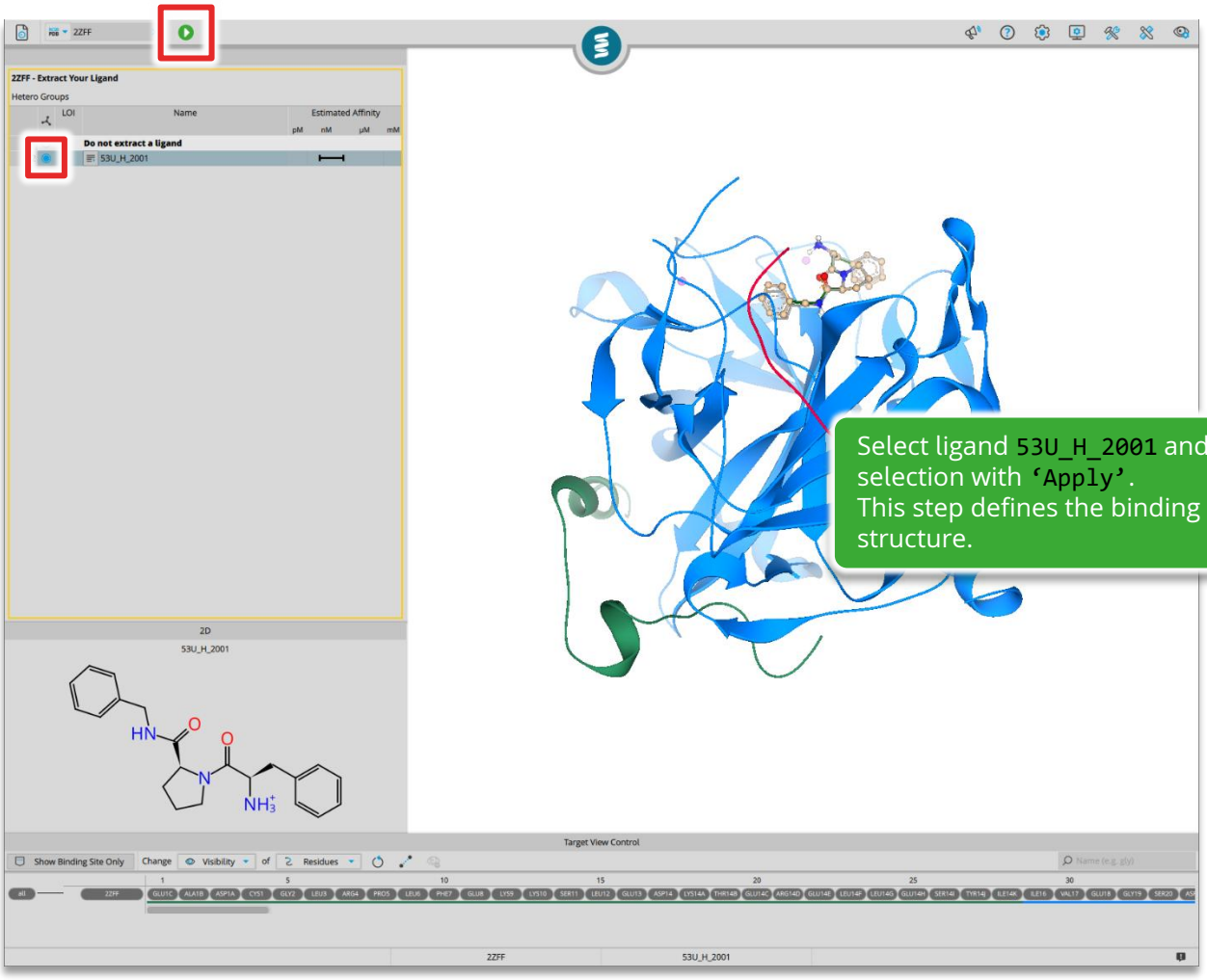
Mode Overview



The **Proteins Mode** is the starting point for structure-based approaches.

In the `search window`, you can look up PDB titles (e.g., Thrombin S1-pocket, ROCK1) or directly enter the PDB you want to access.

Load PDB `2ZFF` and confirm with `'Enter' key`.



Select ligand `53U_H_2001` and confirm your selection with `'Apply'`.
This step defines the binding site at your target structure.

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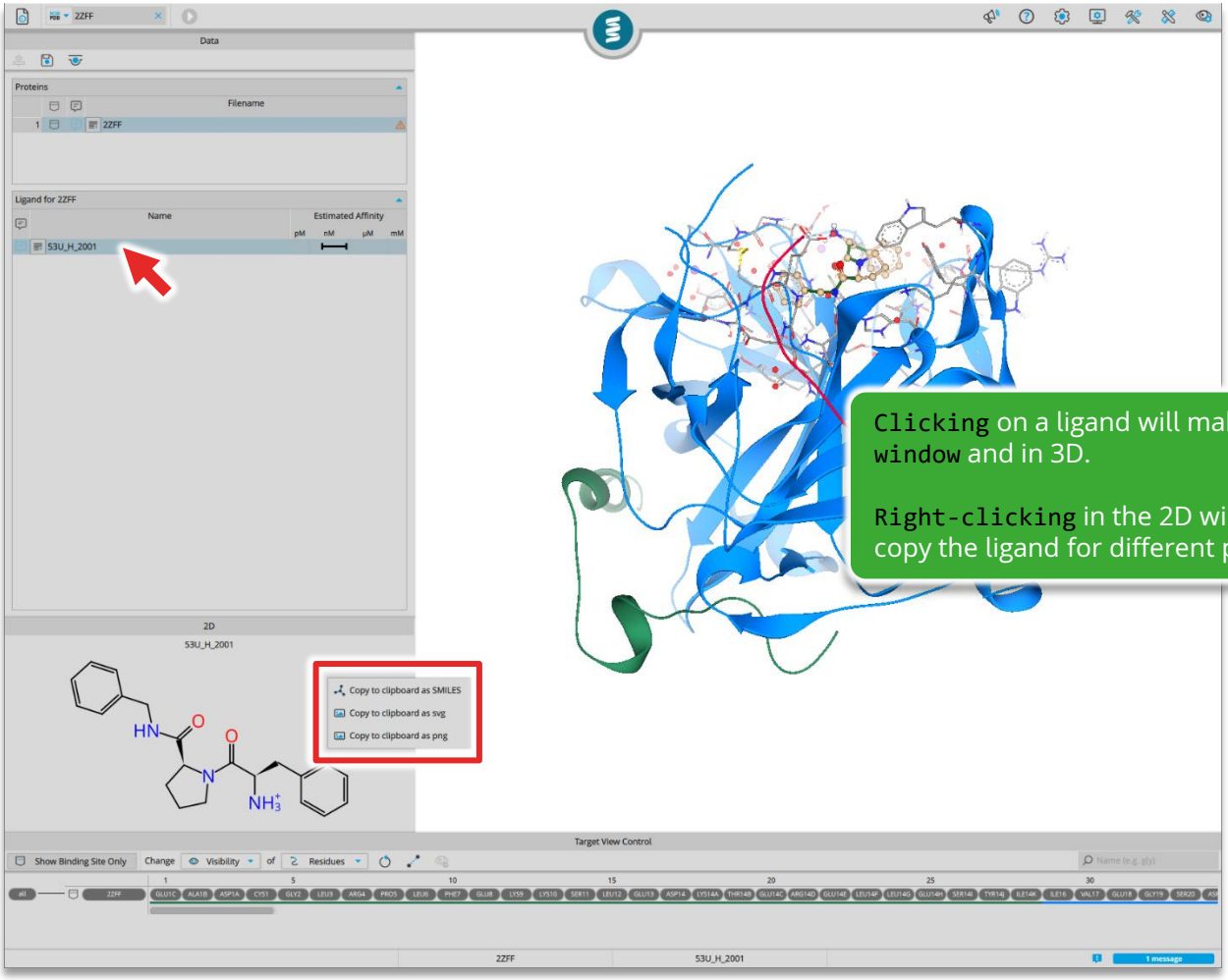
Mode Overview



`Clicking` on a ligand will make appear in the `2D window` and in 3D.

`Right-clicking` in the 2D window allows you to copy the ligand for different purposes.

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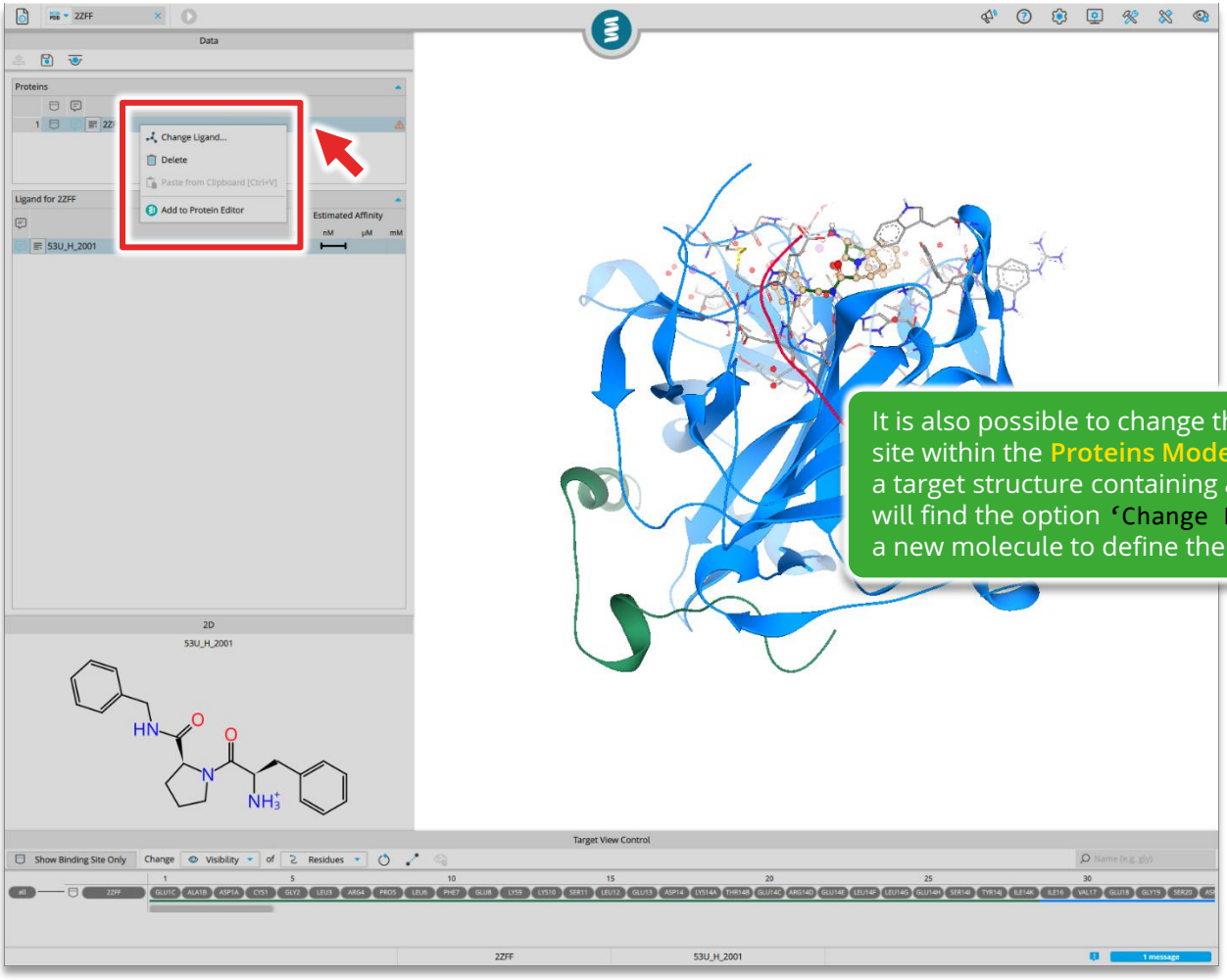
Mode Overview



It is also possible to change the active binding site within the **Proteins Mode**. `Right-click` on a target structure containing a ligand. Here, you will find the option **'`Change Ligand...`'** to select a new molecule to define the binding site.

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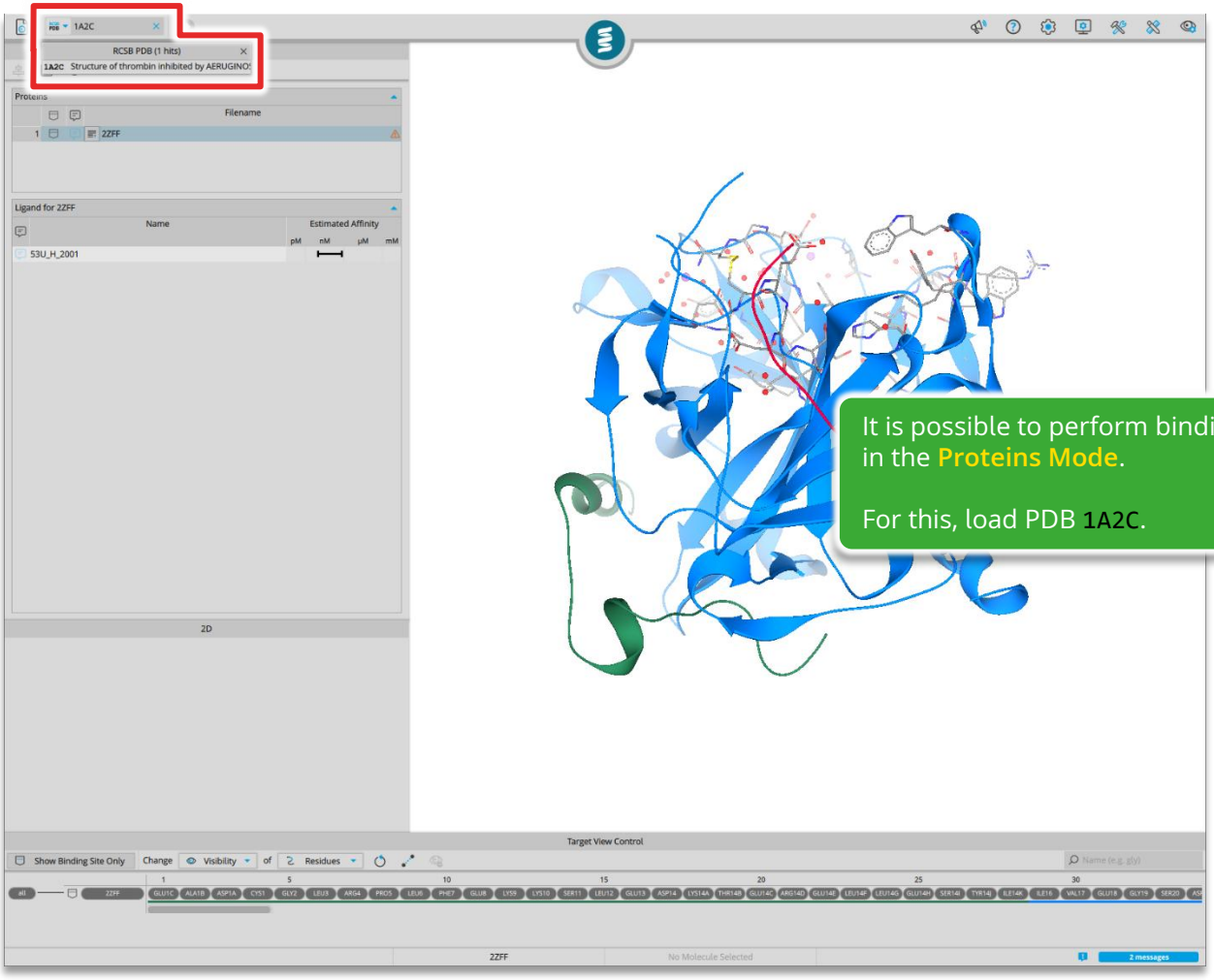
Mode Overview



It is possible to perform binding site alignment in the **Proteins Mode**.

For this, load PDB **1A2C**.

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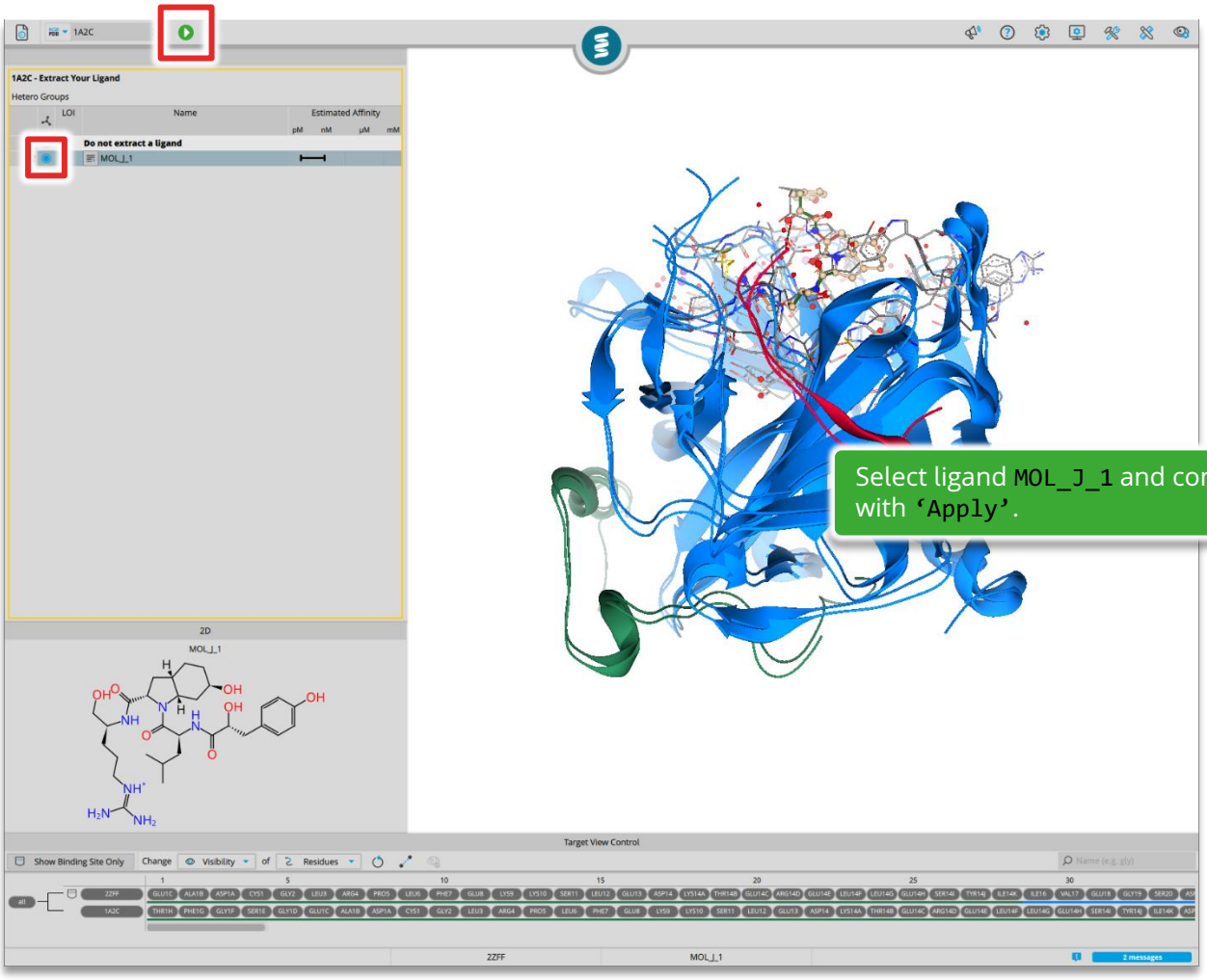
Mode Overview



Select ligand `MOL_J_1` and confirm your selection with `'Apply'`.

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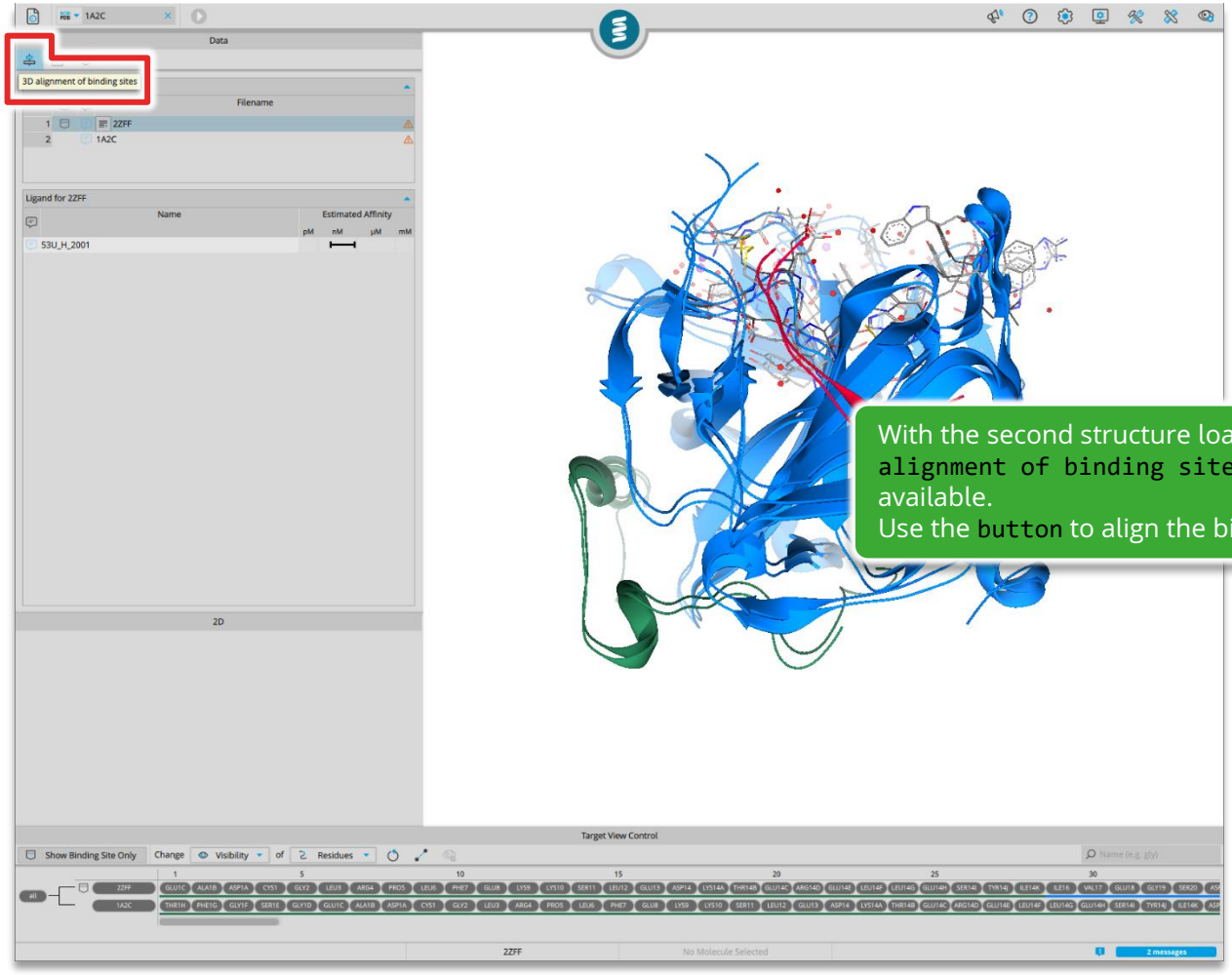
Mode Overview



With the second structure loaded, ‘3D alignment of binding sites’ becomes available.
Use the button to align the binding sites.

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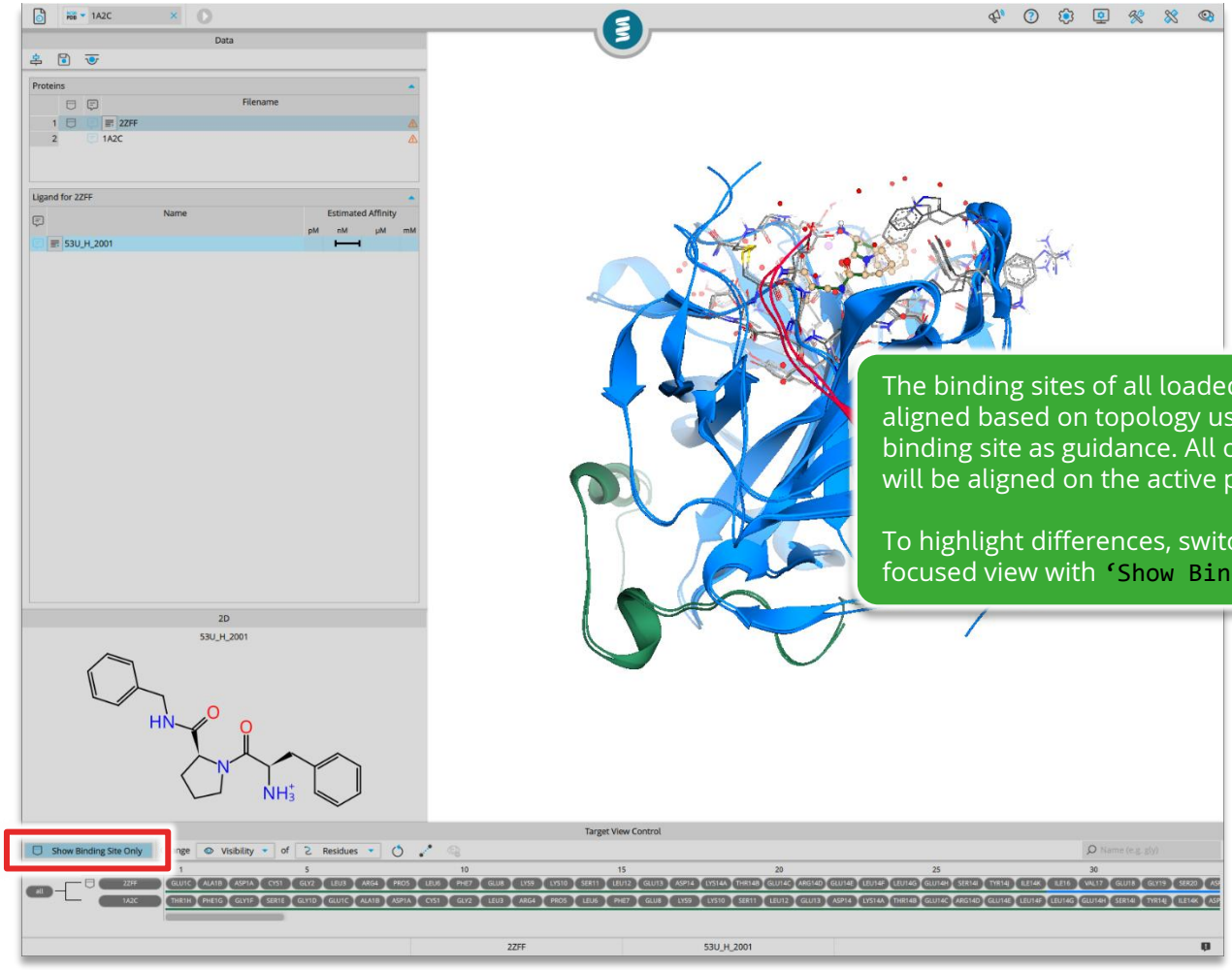
Mode Overview



The binding sites of all loaded structures will be aligned based on topology using the active binding site as guidance. All other binding sites will be aligned on the active pocket.

To highlight differences, switch to a binding site-focused view with **'Show Binding Site Only'**.

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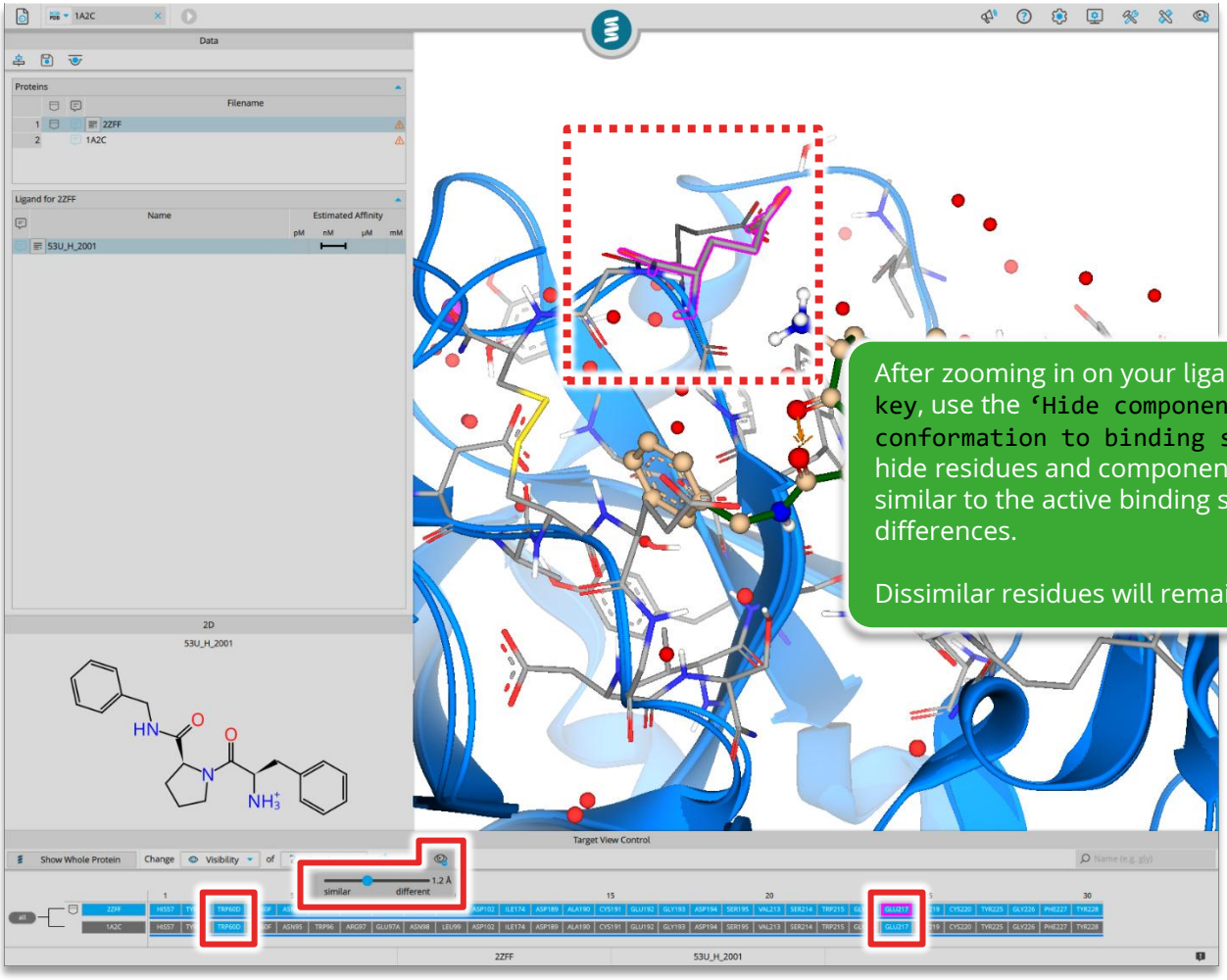
Mode Overview



After zooming in on your ligand with ‘Space’ key, use the ‘Hide components with similar conformation to binding site protein’ to hide residues and components, that are too similar to the active binding site to spot differences.

Dissimilar residues will remain visible.

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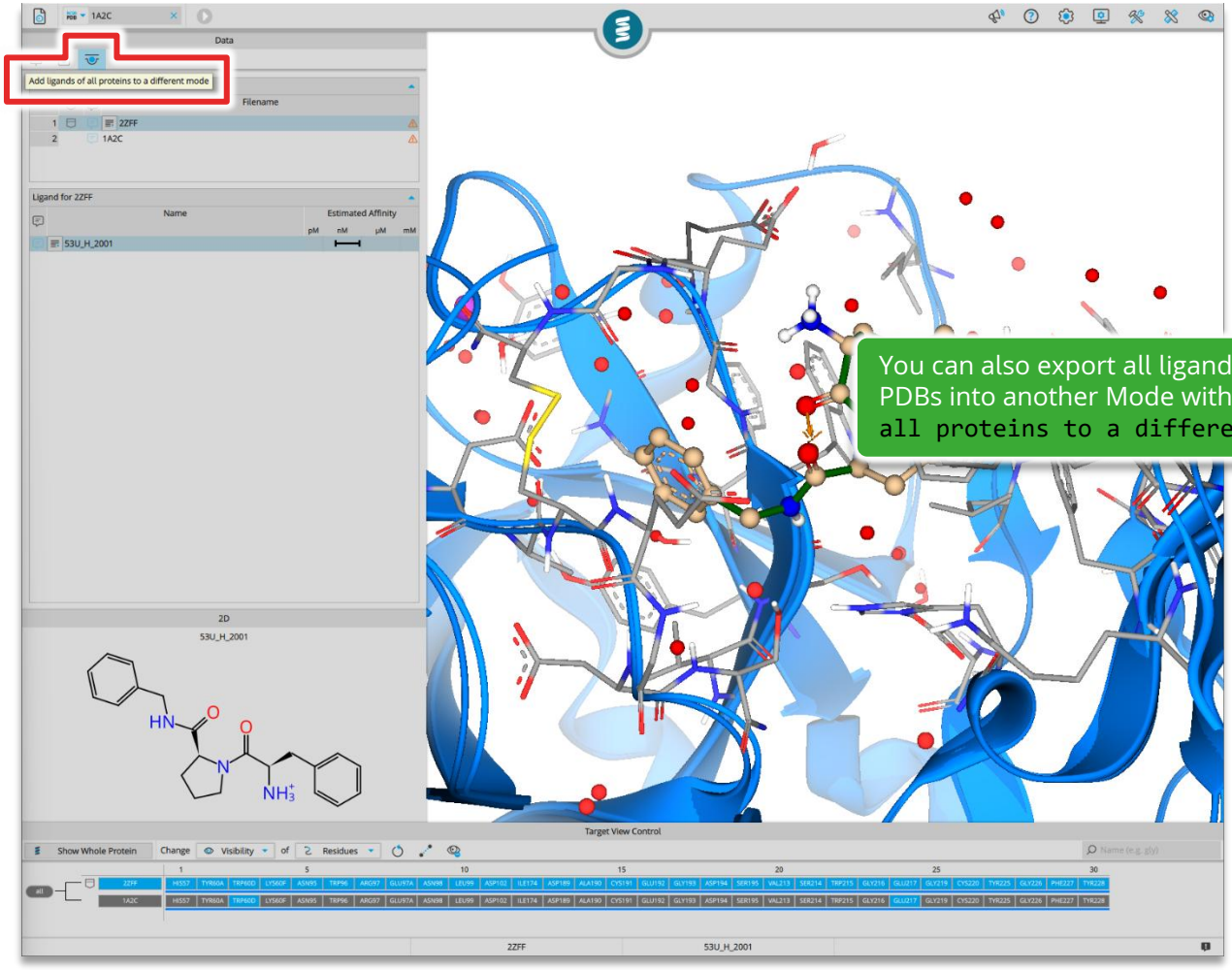
Mode Overview



You can also export all ligands from the loaded PDBs into another Mode with ‘`Add ligands of all proteins to a different mode`’.

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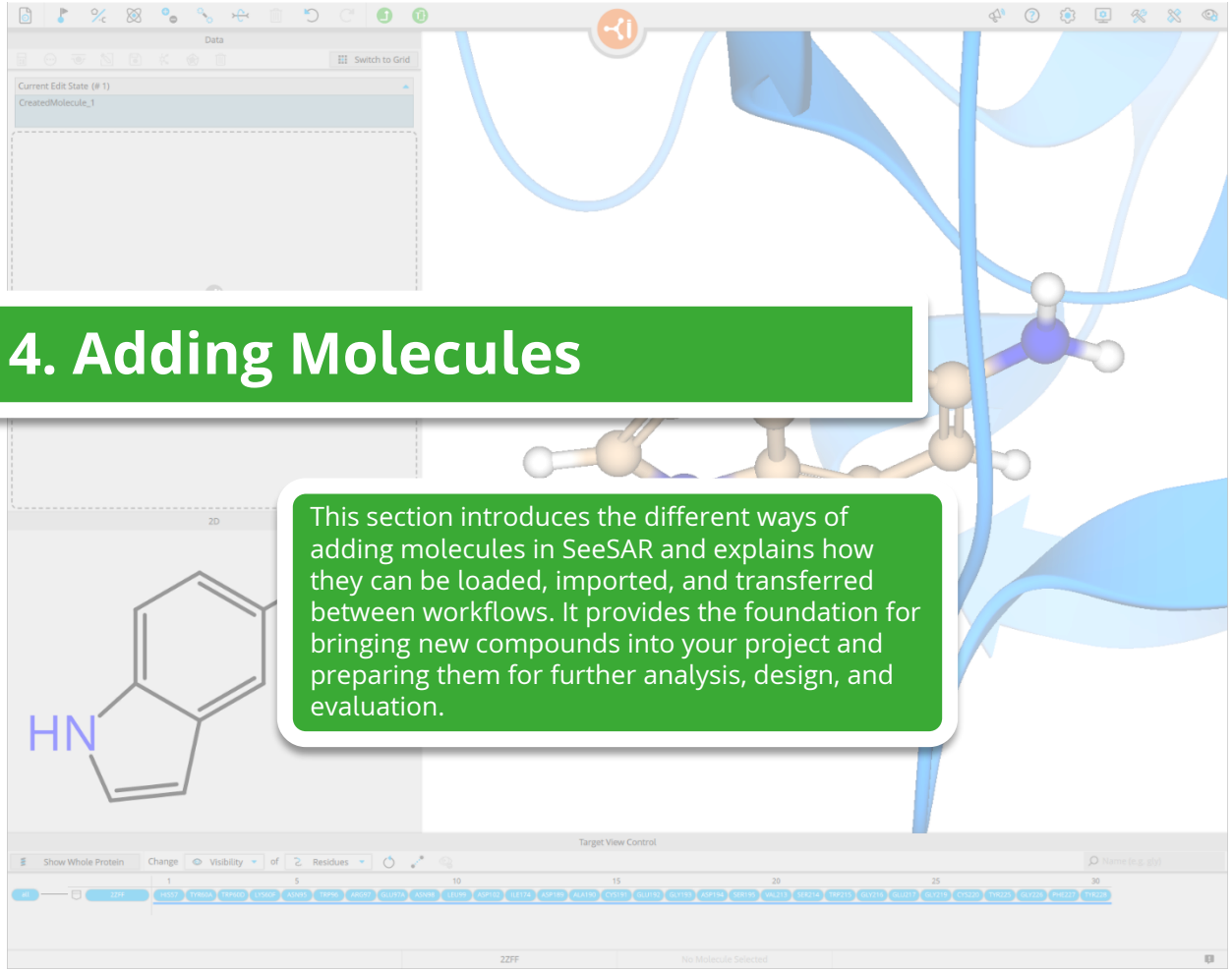
Mode Overview



4. Adding Molecules

This section introduces the different ways of adding molecules in SeeSAR and explains how they can be loaded, imported, and transferred between workflows. It provides the foundation for bringing new compounds into your project and preparing them for further analysis, design, and evaluation.

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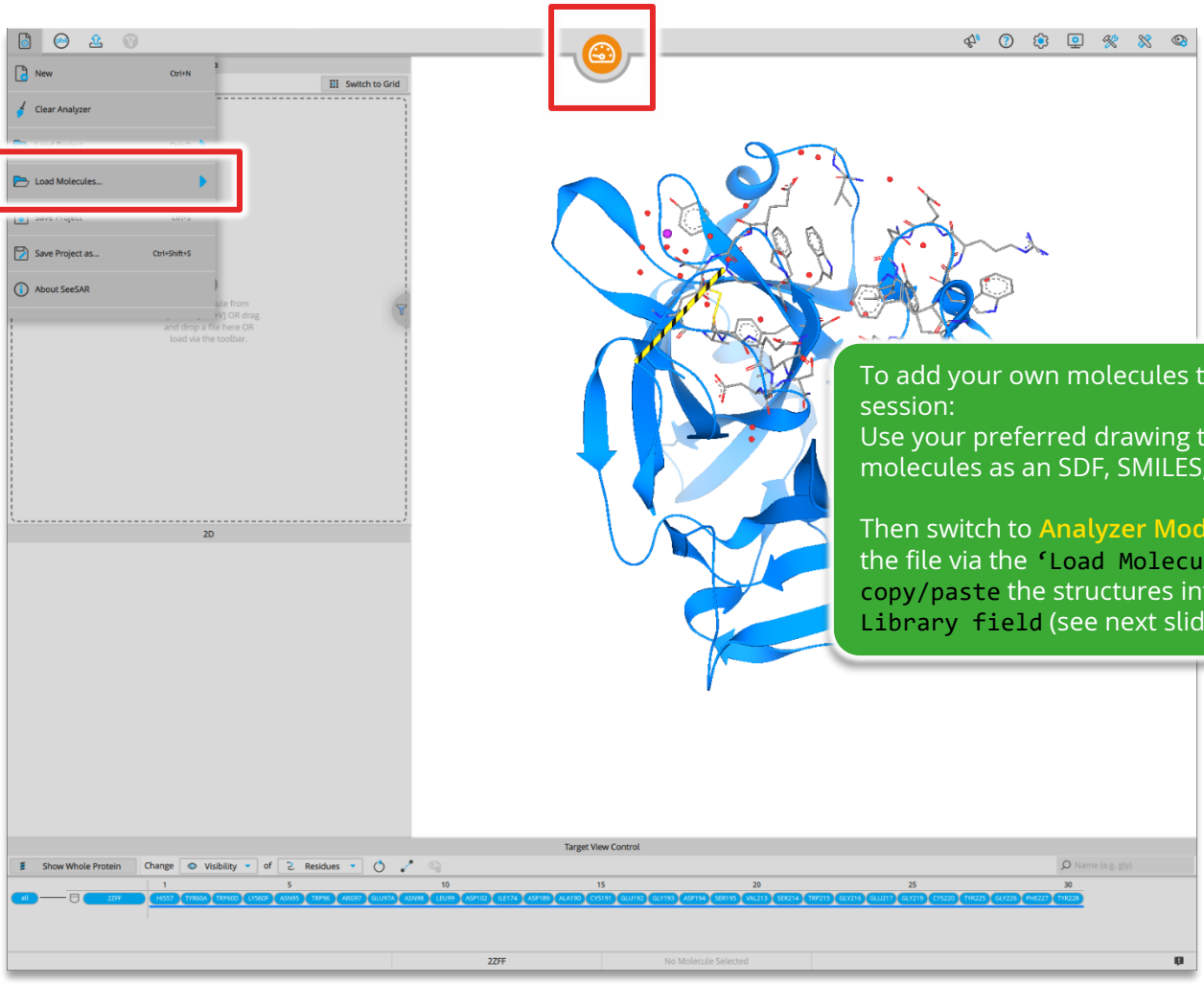
Mode Overview



To add your own molecules to a SeeSAR session:
Use your preferred drawing tool and save the molecules as an SDF, SMILES, or MOL2 file.

Then switch to Analyzer Mode and either load the file via the `'Load Molecules…' option` or `copy/paste` the structures into the `Input Library field` (see next slide).

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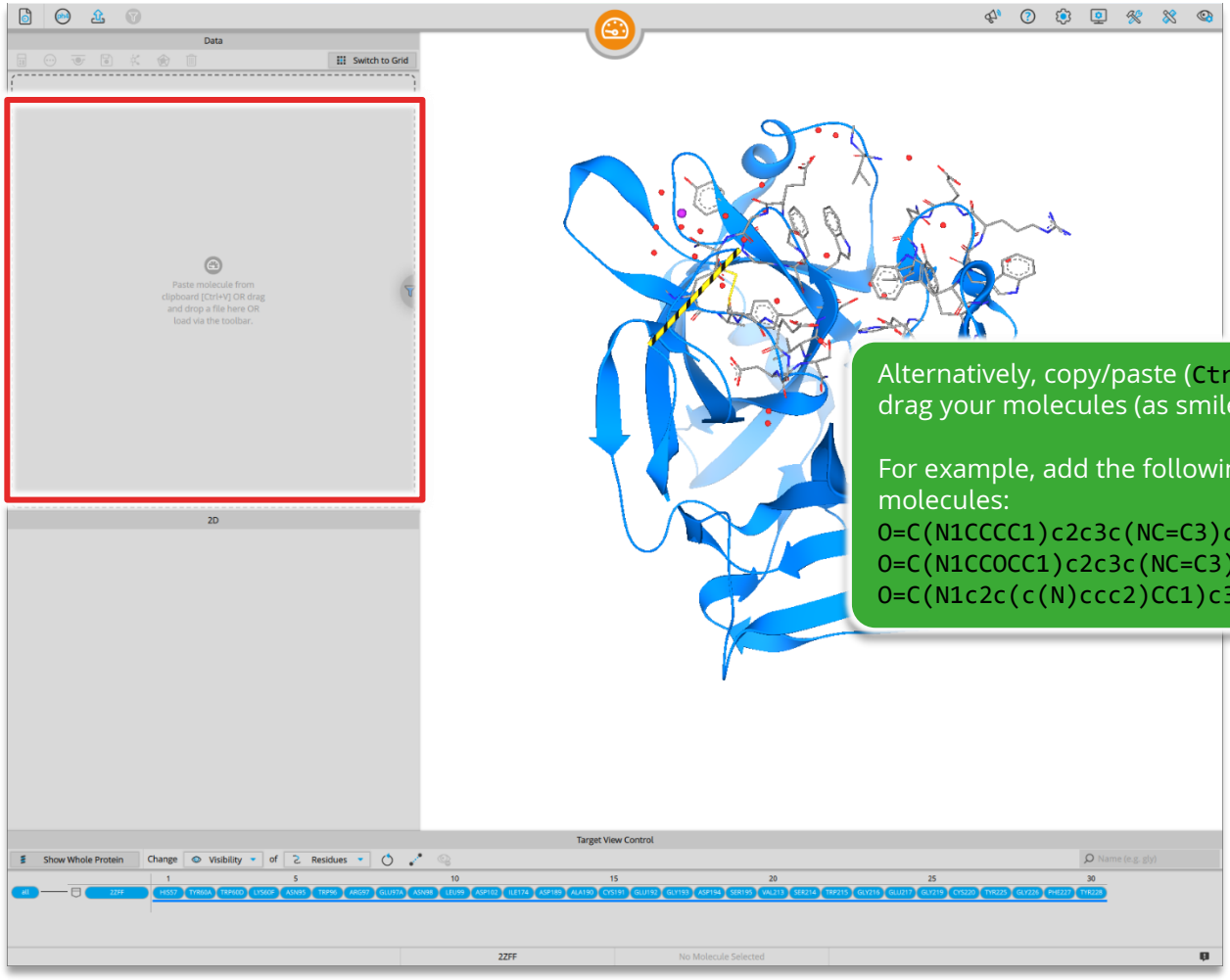
Mode Overview



Alternatively, copy/paste (`Ctrl+c/Ctrl+v`) or drag your molecules (as smiles or sdf) here.

For example, add the following three molecules:

```
O=C(N1CCCC1)c2c3c(NC=C3)ccc2
O=C(N1CCOCC1)c2c3c(NC=C3)ccc2
O=C(N1c2c(c(N)ccc2)CC1)c3c4c(NC=C4)ccc3
```

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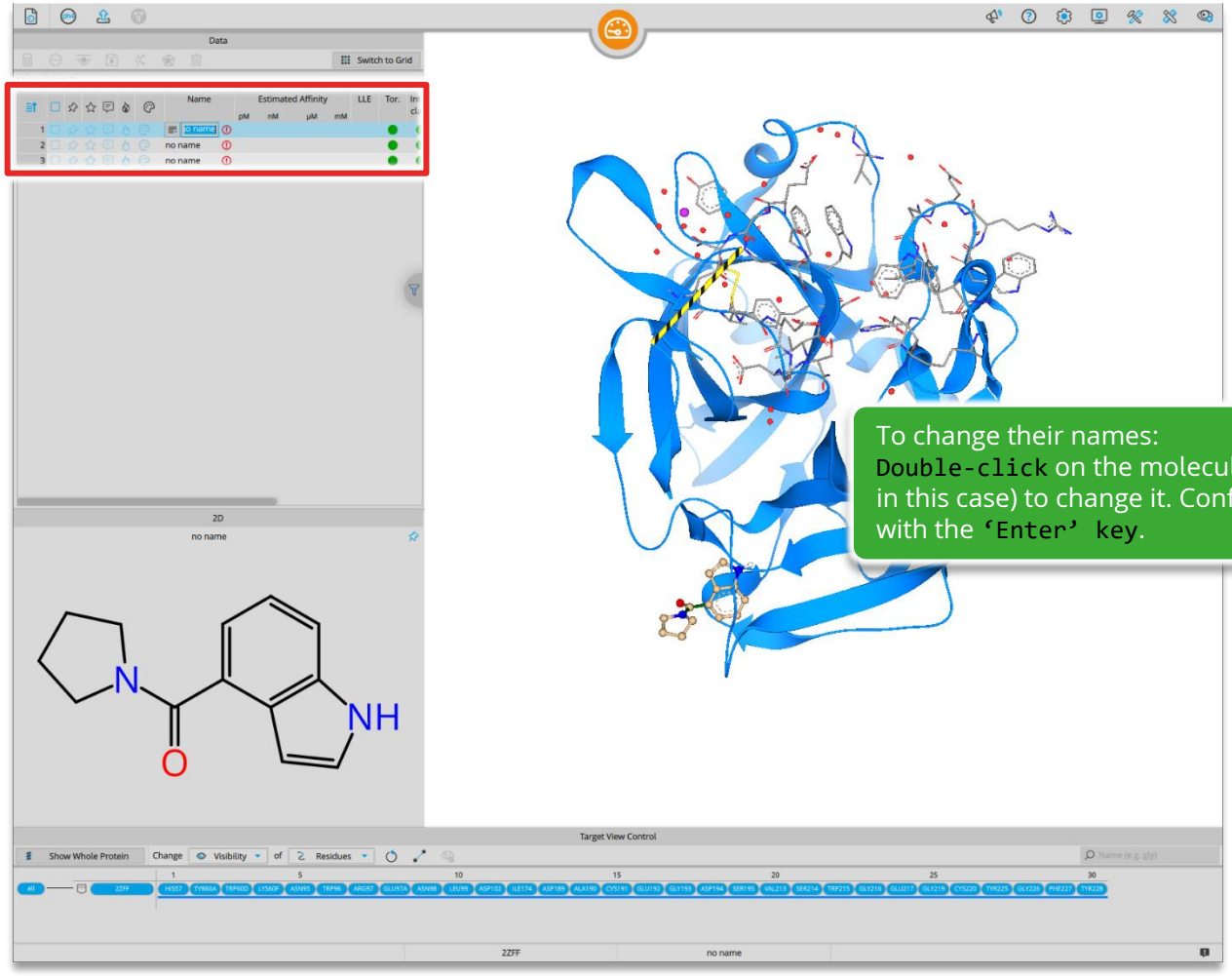
Mode Overview



To change their names:
`Double-click` on the molecule name ('no name' in this case) to change it. Confirm the change with the `'Enter' key`.

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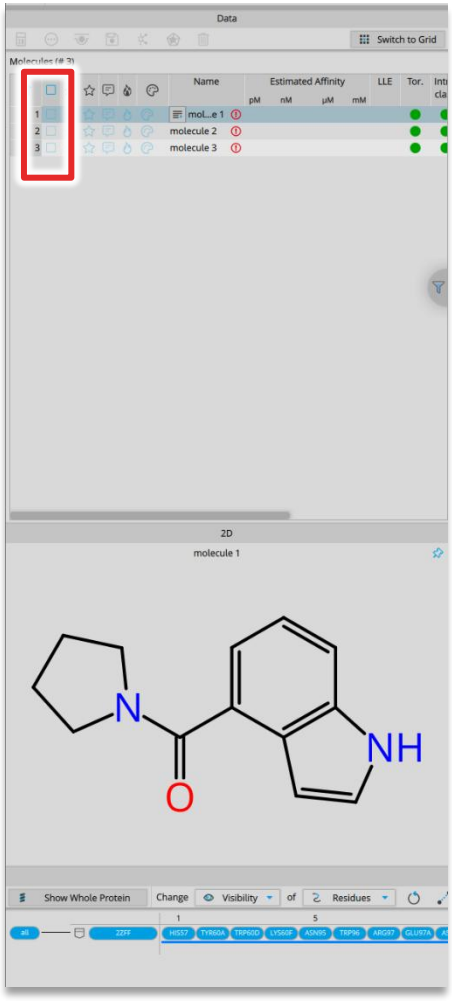
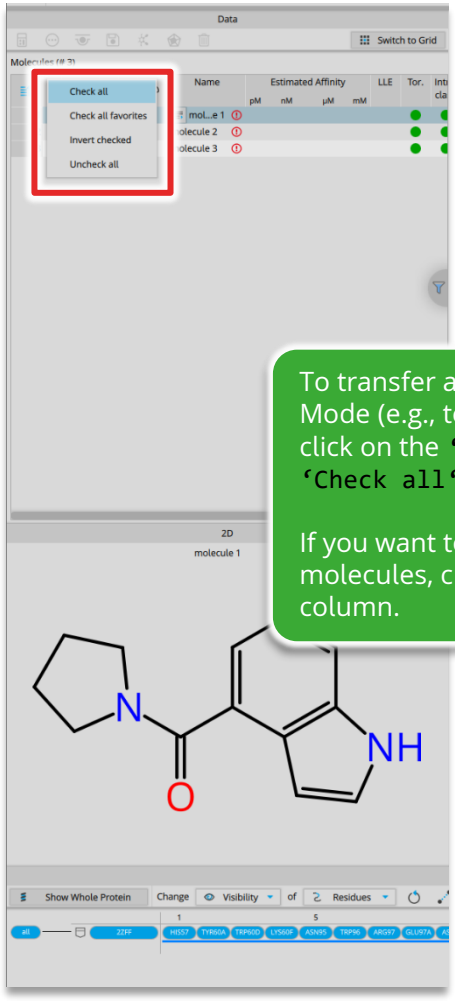
Mode Overview





To transfer all your compounds to another Mode (e.g., to dock them in the Docking mode), click on the `'Checked' column` and select `'Check all'` to mark all molecules in the list.

If you want to transfer only some of the molecules, check them individually in the column.

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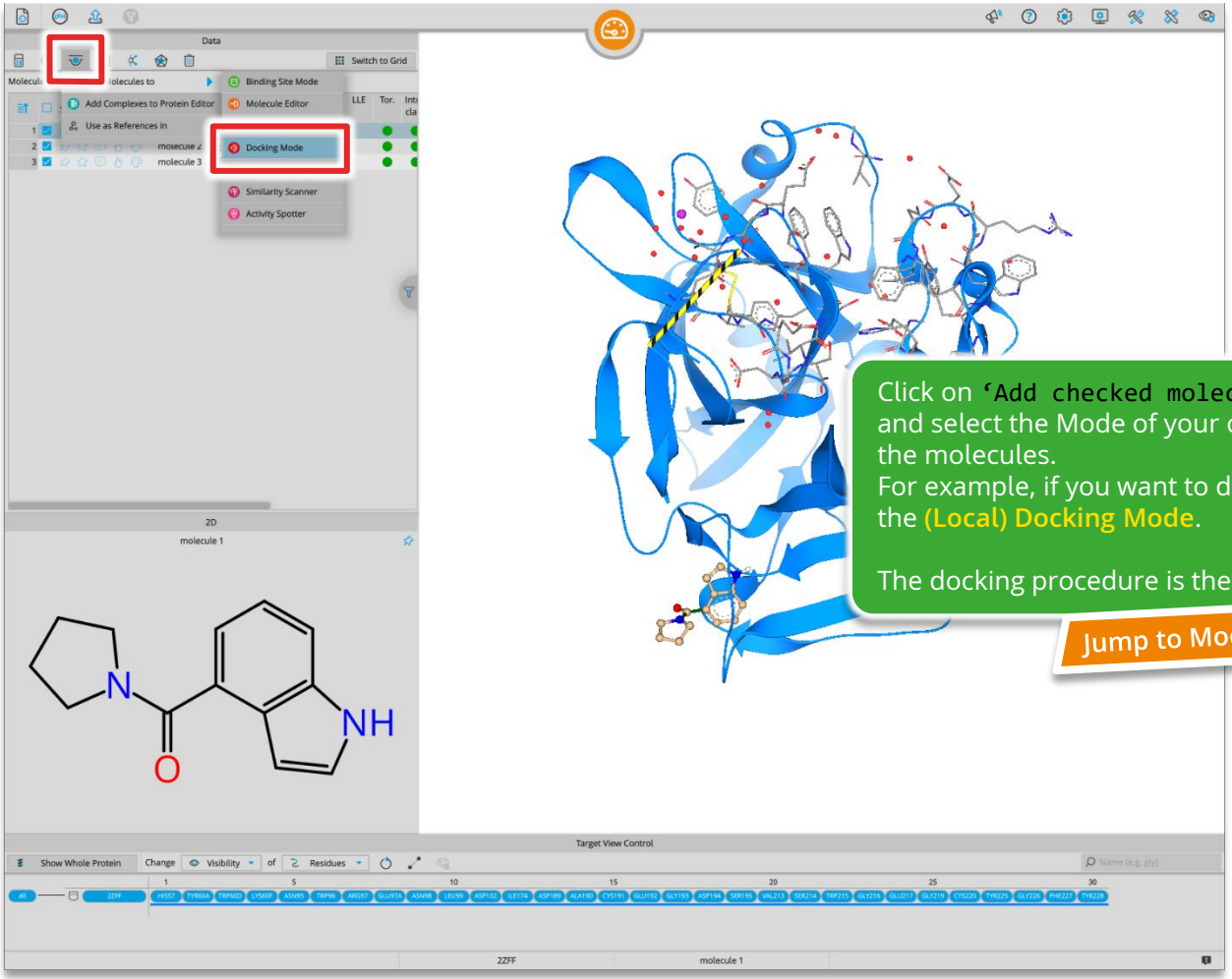
Mode Overview



Click on ‘Add checked molecules to mode’ and select the Mode of your choice to work with the molecules.
For example, if you want to dock them, select the (Local) Docking Mode.

The docking procedure is the dedicated section.

Jump to Mode

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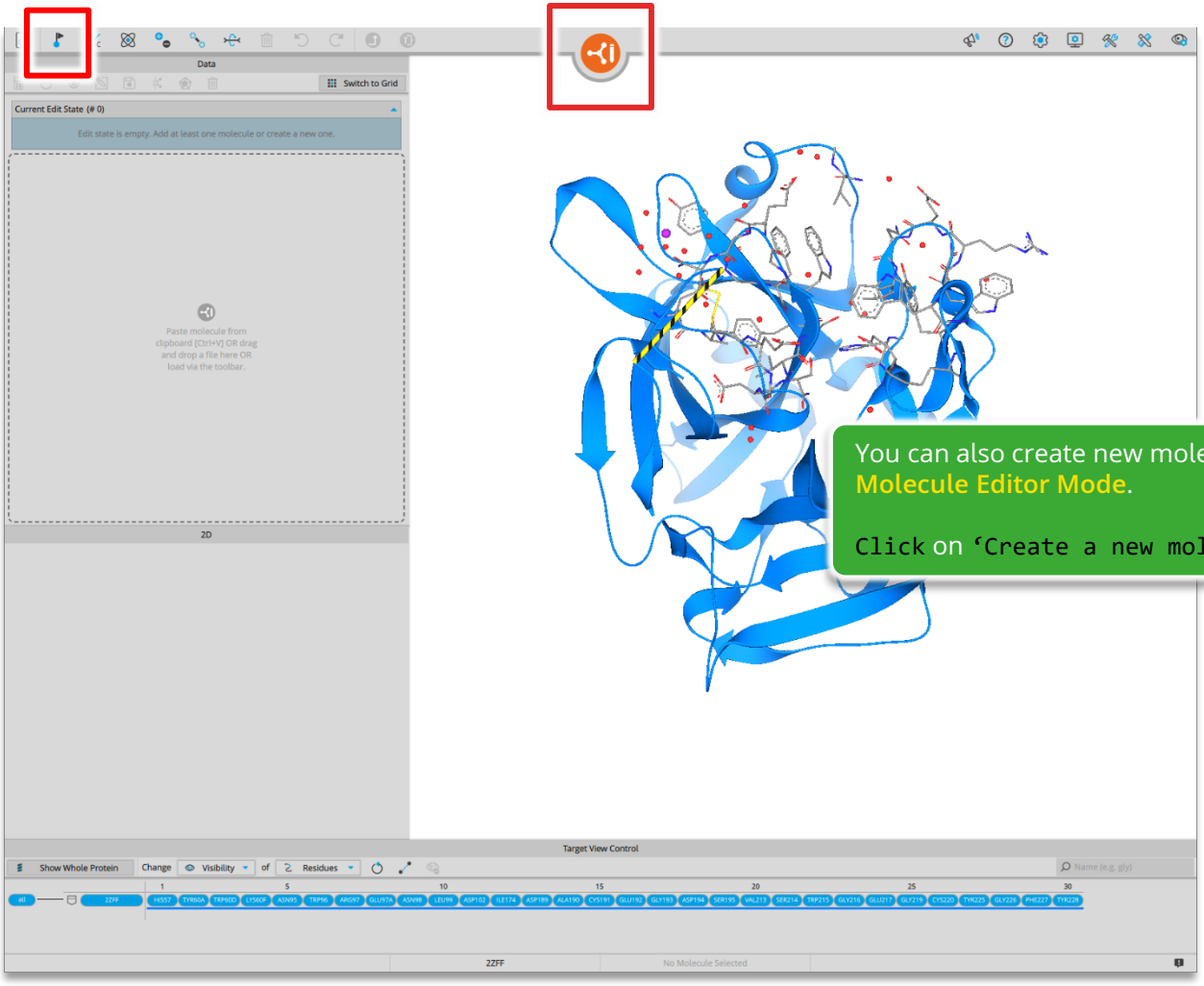
Mode Overview



You can also create new molecules in the **Molecule Editor Mode**.

Click on ‘Create a new molecule’.

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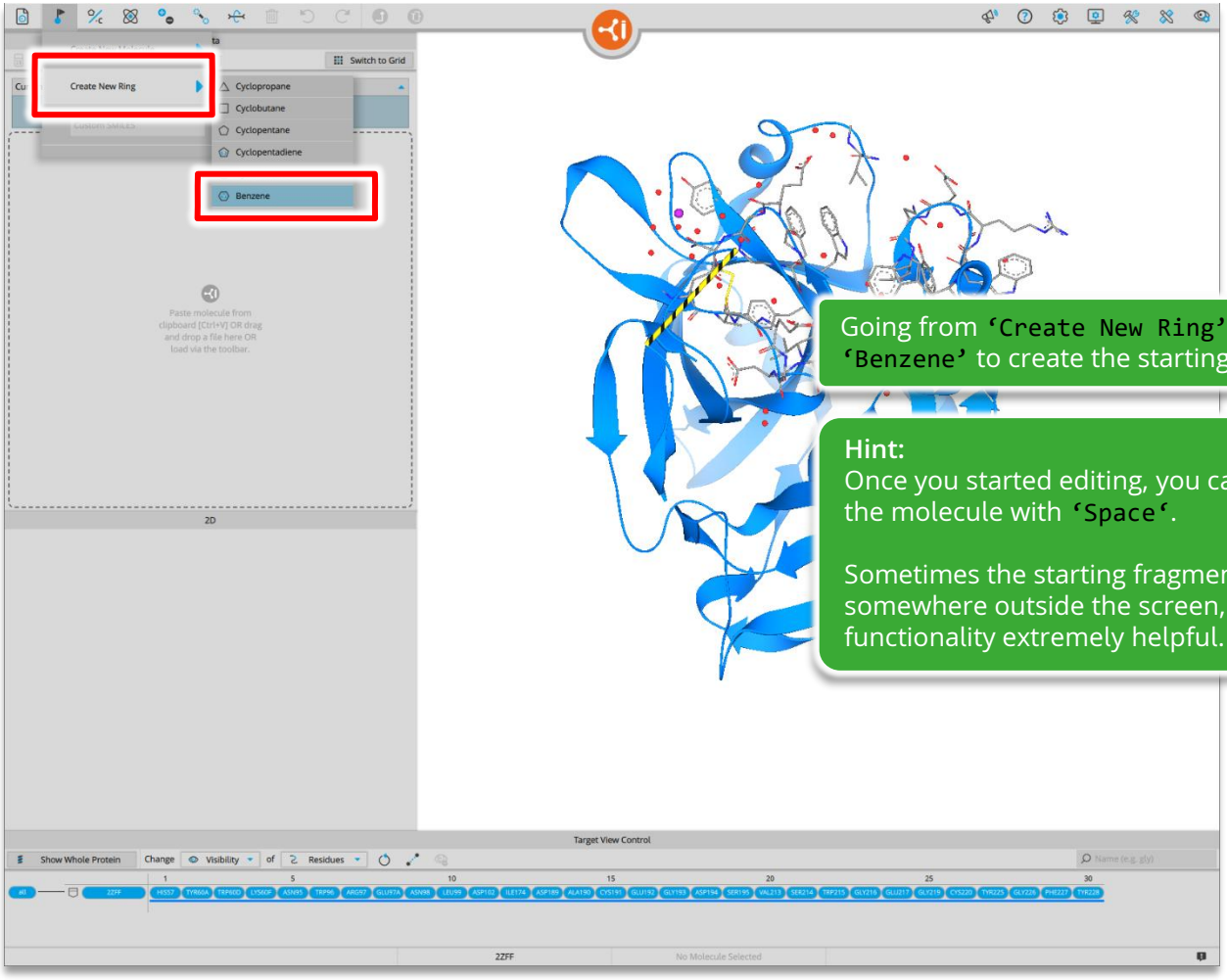
Mode Overview



Going from `'Create New Ring'`, `click` on `'Benzene'` to create the starting point.

Hint:
Once you started editing, you can always focus on the molecule with `'Space'`.

Sometimes the starting fragment is created somewhere outside the screen, which makes this functionality extremely helpful.

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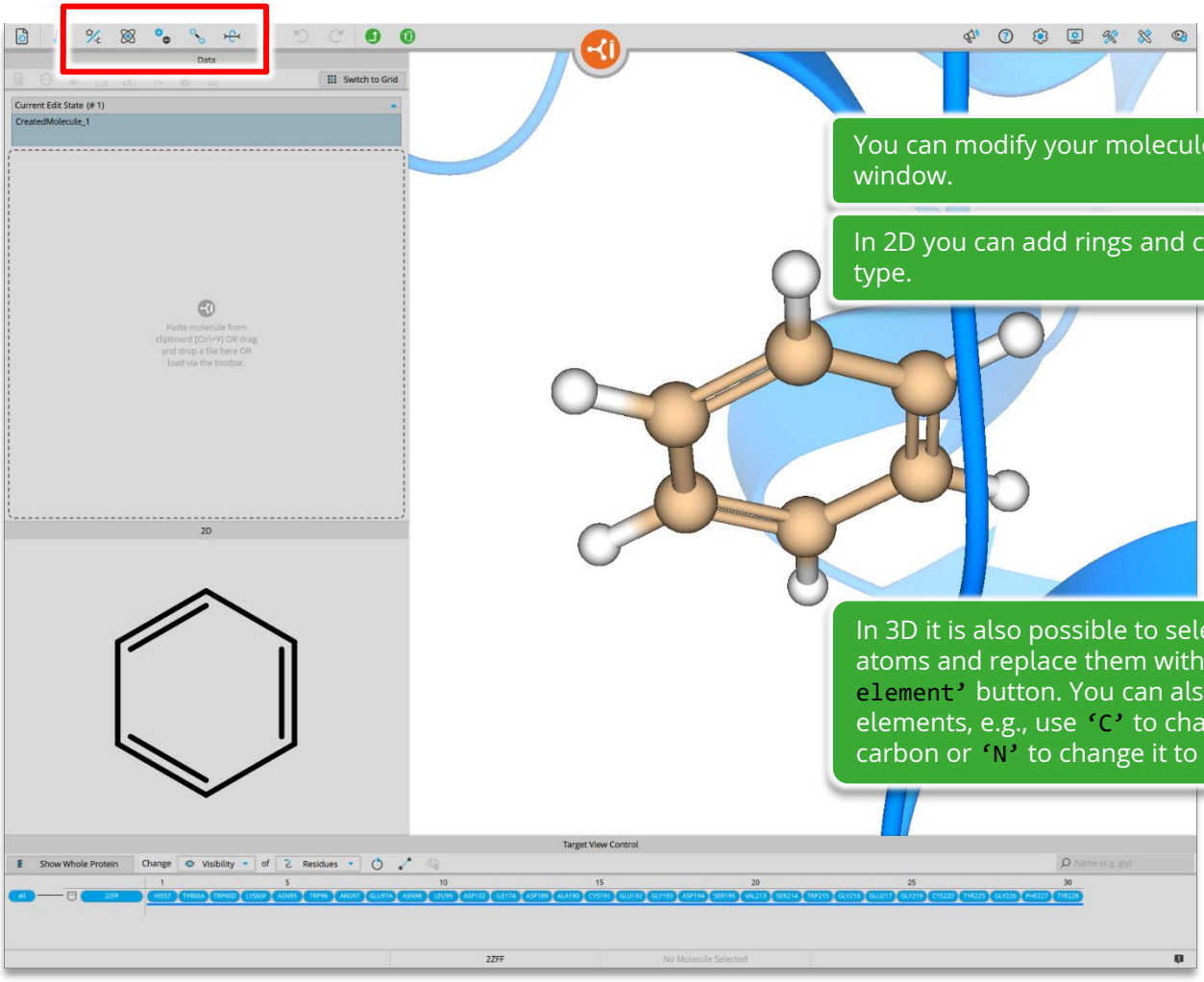
Mode Overview



You can modify your molecule in the 2D, and 3D window.

In 2D you can add rings and change the bond type.

In 3D it is also possible to select the hydrogen atoms and replace them with `'Change element'` button. You can also use hot keys for elements, e.g., use `'C'` to change an atom to a carbon or `'N'` to change it to a nitrogen.

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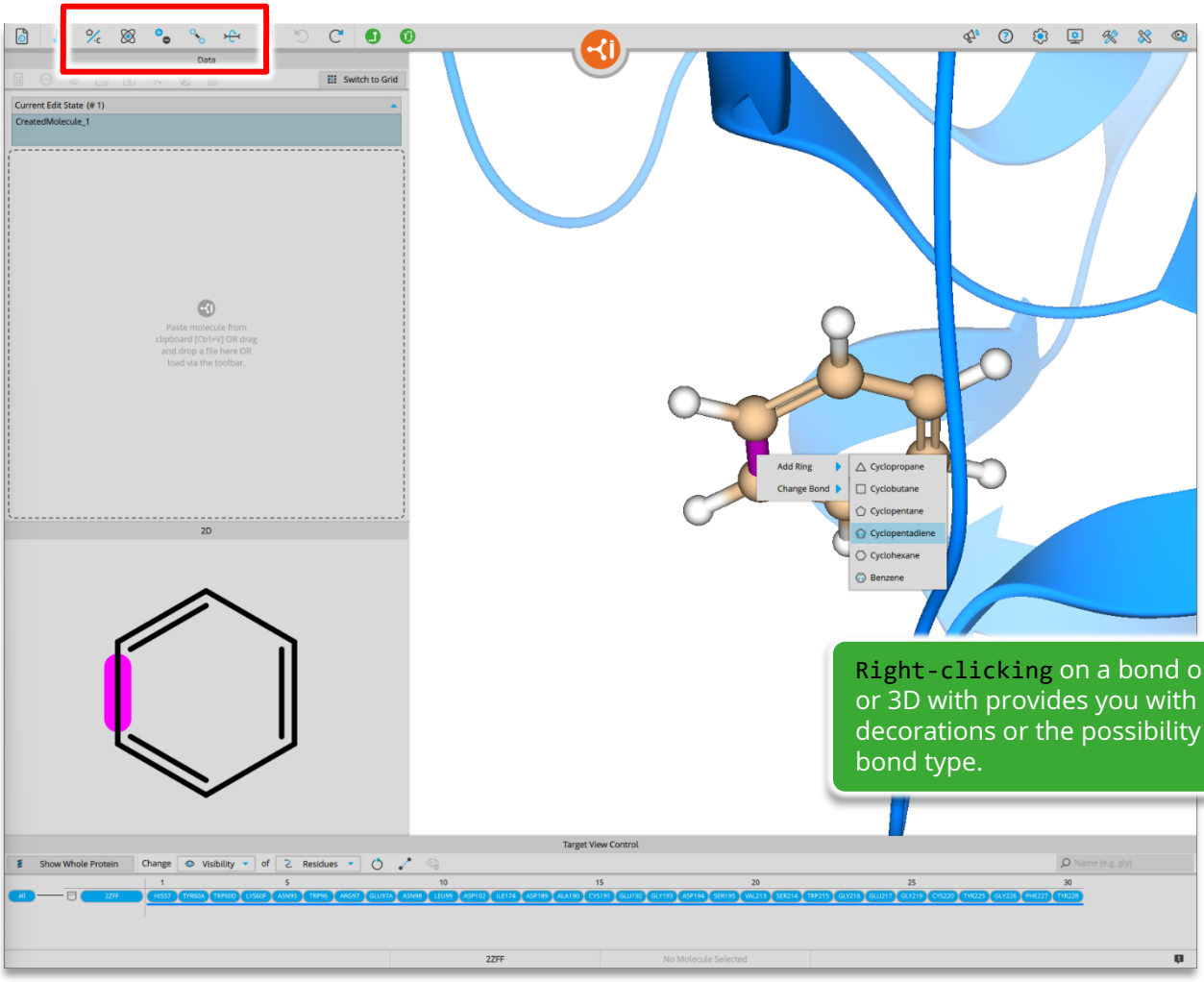
Mode Overview



`Right-clicking` on a bond or heavy atom in 2D or 3D with provides you with option on common decorations or the possibility to change the bond type.

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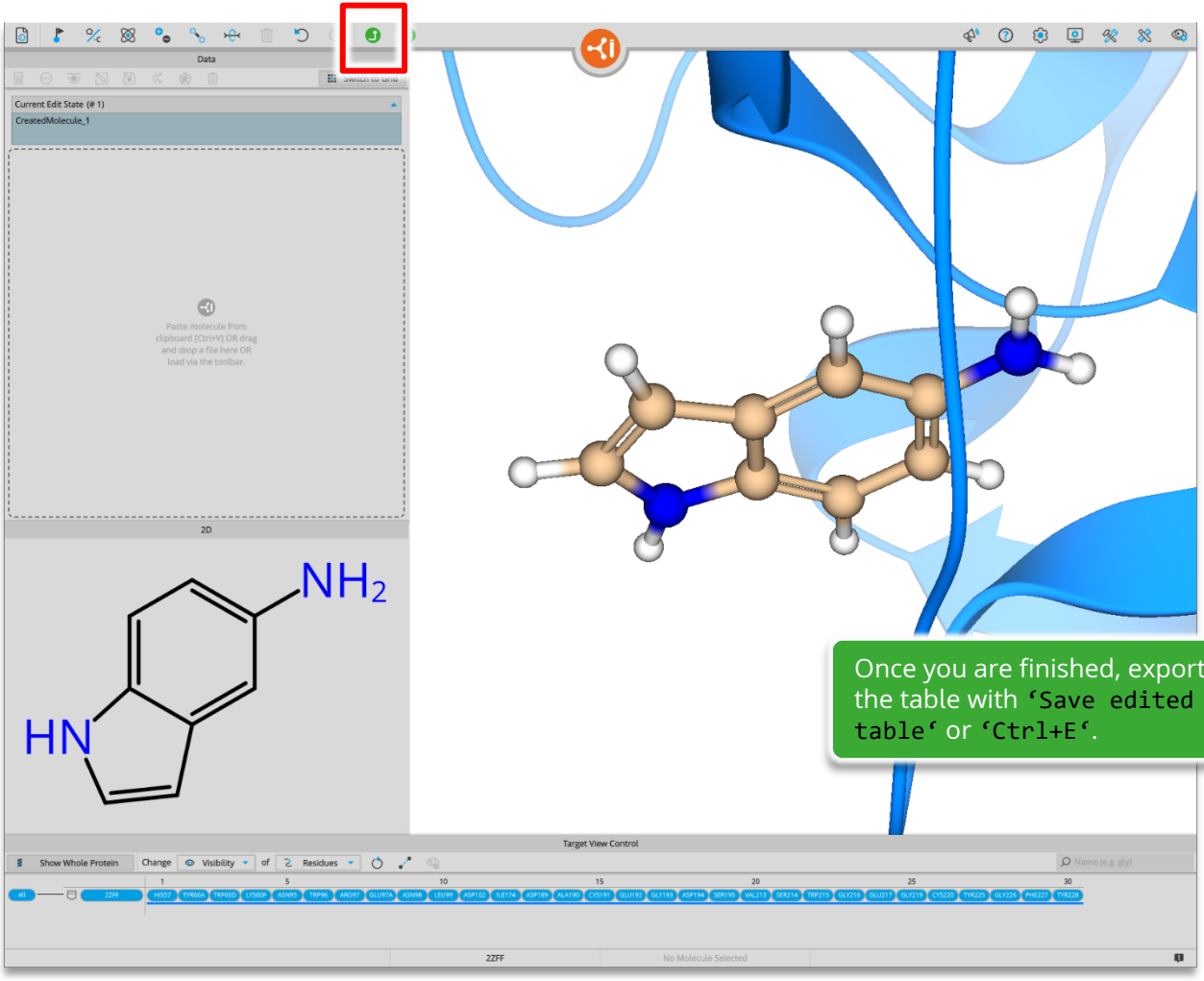
Mode Overview



Once you are finished, export the molecule to the table with ‘`Save edited molecules to table`‘ or ‘`Ctrl+E`‘.

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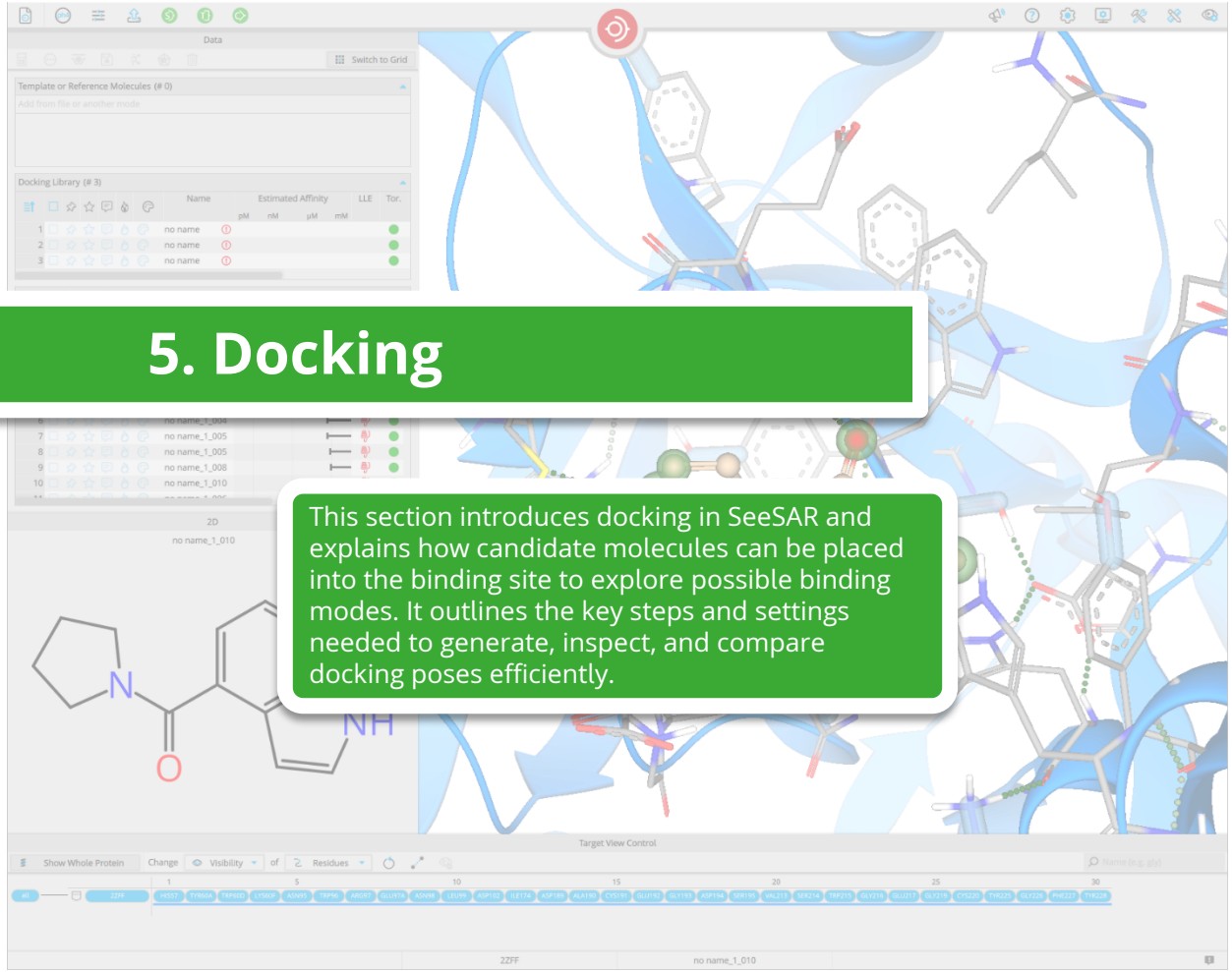
Mode Overview

5. Docking



This section introduces docking in SeeSAR and explains how candidate molecules can be placed into the binding site to explore possible binding modes. It outlines the key steps and settings needed to generate, inspect, and compare docking poses efficiently.

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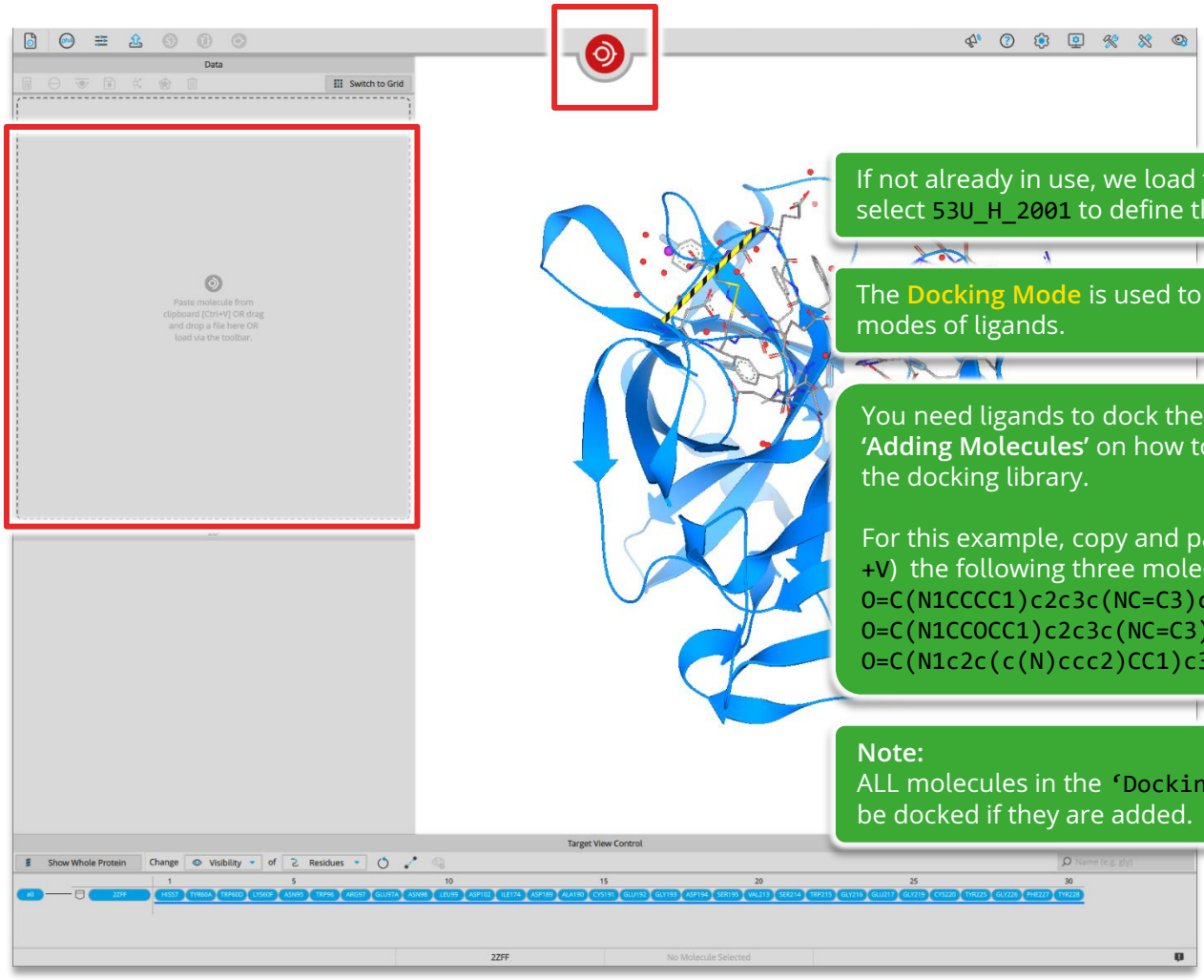
Mode Overview



If not already in use, we load the PDB `2ZFF` and select `53U_H_2001` to define the binding site.

The **Docking Mode** is used to predict the binding modes of ligands.

You need ligands to dock them. See **Section 'Adding Molecules'** on how to add molecules to the docking library.

For this example, copy and paste (`Ctrl+C/Ctrl +V`) the following three molecules into SeeSAR:

```
O=C(N1CCCC1)c2c3c(NC=C3)ccc2
O=C(N1CCOCC1)c2c3c(NC=C3)ccc2
O=C(N1c2c(c(N)ccc2)CC1)c3c4c(NC=C4)ccc3
```

Note:
ALL molecules in the `'Docking Library'` will be docked if they are added.

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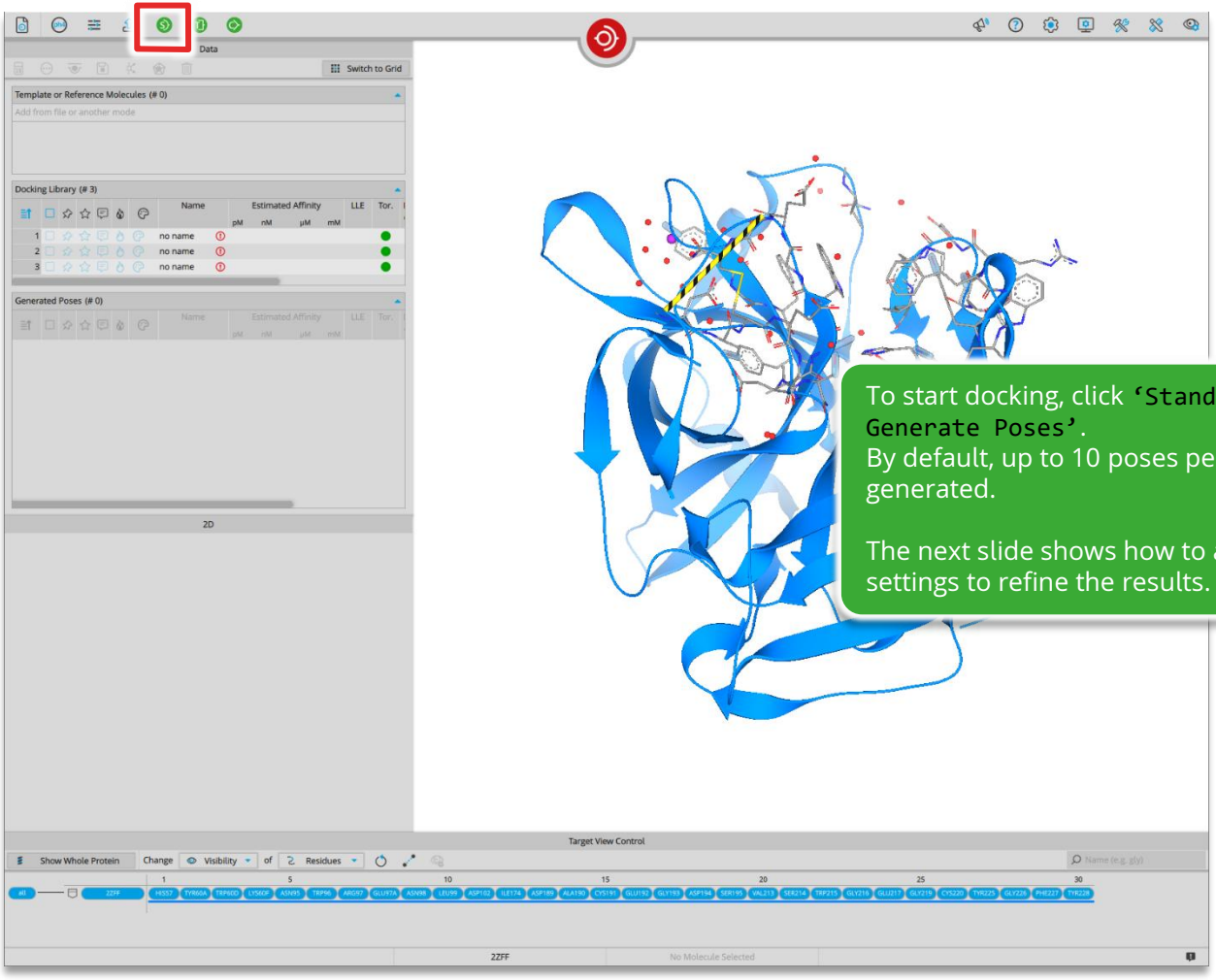
Mode Overview



To start docking, click ‘`Standard Docking: Generate Poses`’.
By default, up to 10 poses per molecule are generated.

The next slide shows how to adjust the docking settings to refine the results.

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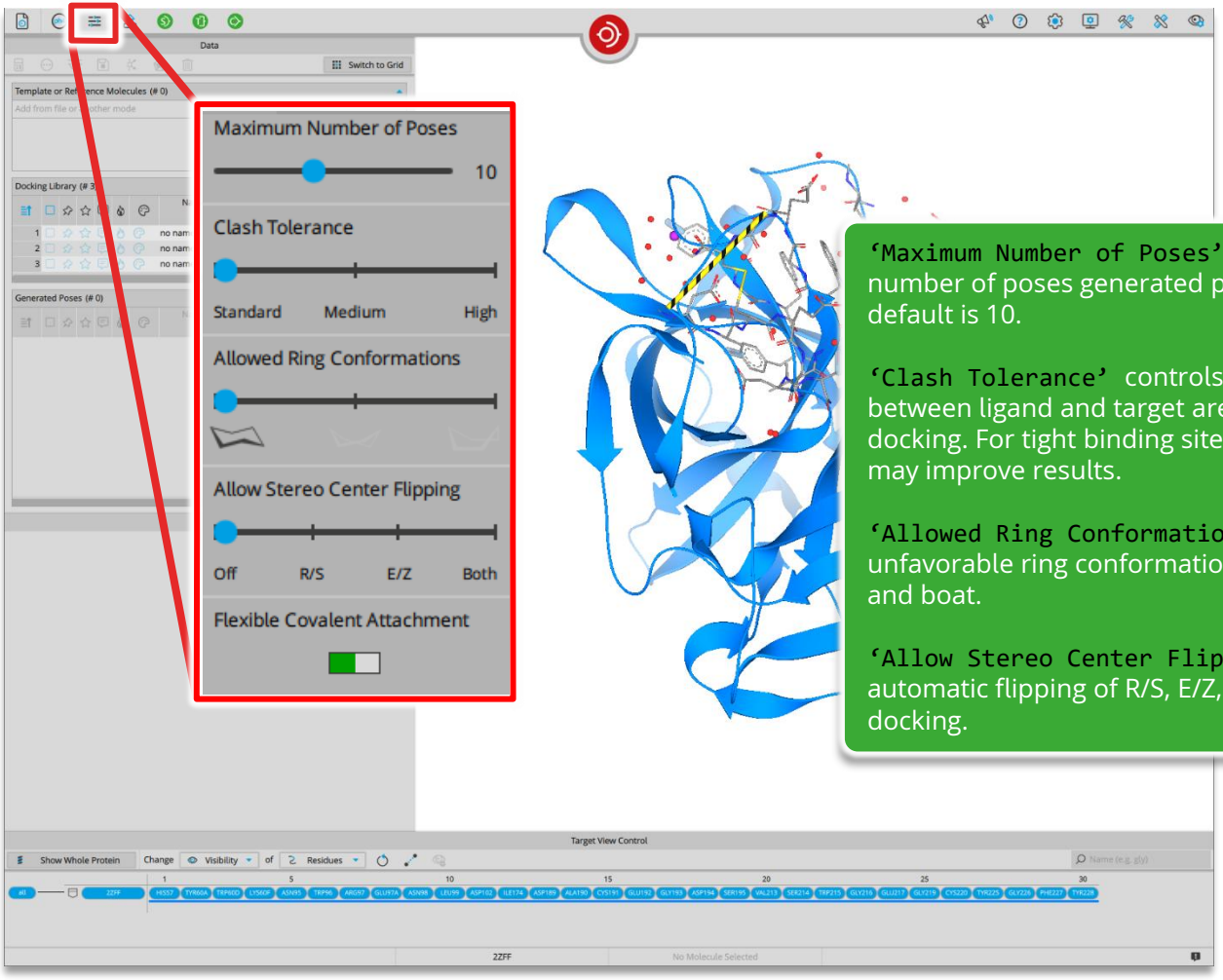
Mode Overview



'Maximum Number of Poses' sets the maximum number of poses generated per molecule. The default is 10.

'Clash Tolerance' controls how clashes between ligand and target are handled during docking. For tight binding sites, Medium or High may improve results.

'Allowed Ring Conformations' allows unfavorable ring conformations, such as twist and boat.

'Allow Stereo Center Flipping' allows automatic flipping of R/S, E/Z, or both during docking.

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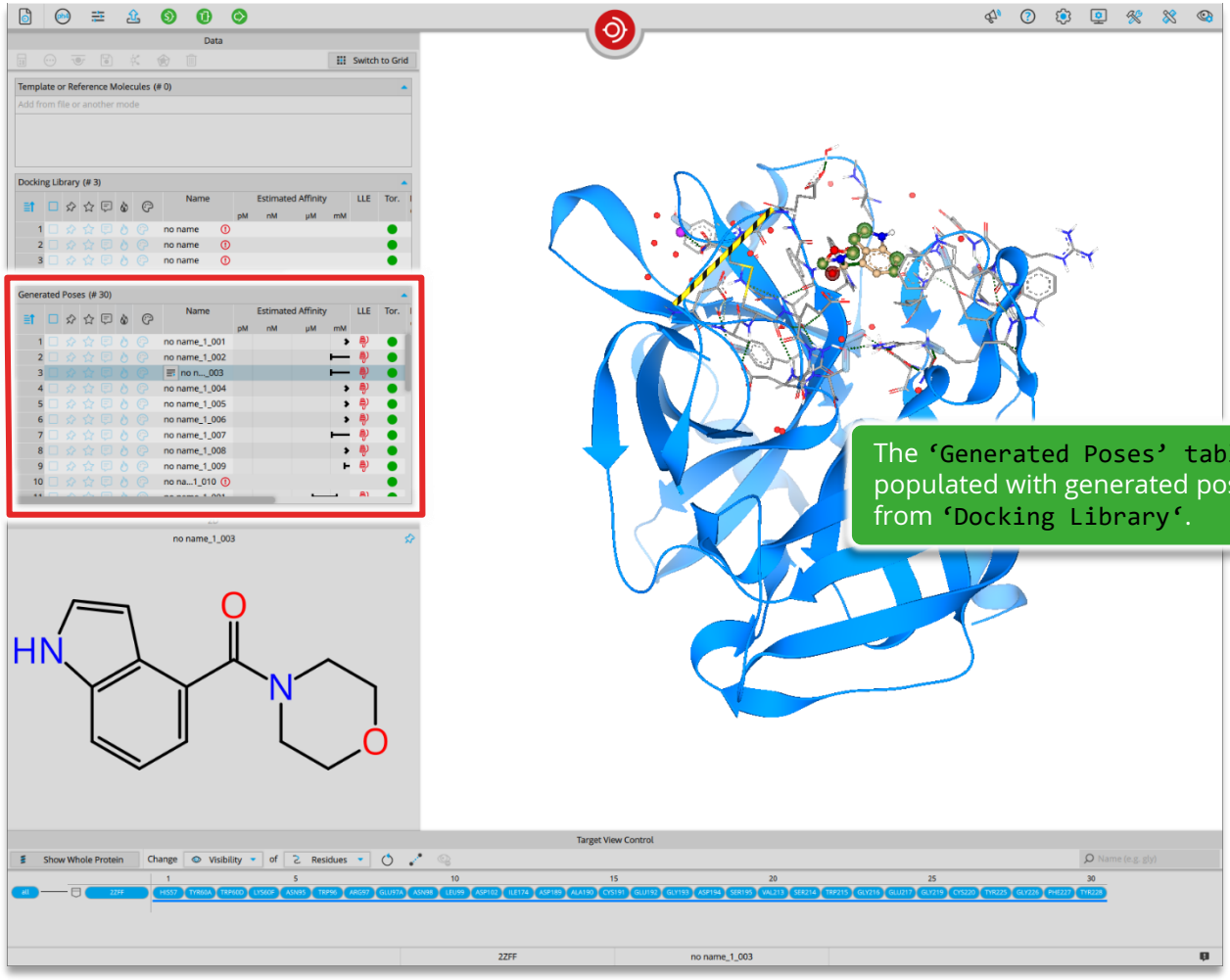
Mode Overview



The ‘Generated Poses’ table will be populated with generated poses of the ligands from ‘Docking Library‘.

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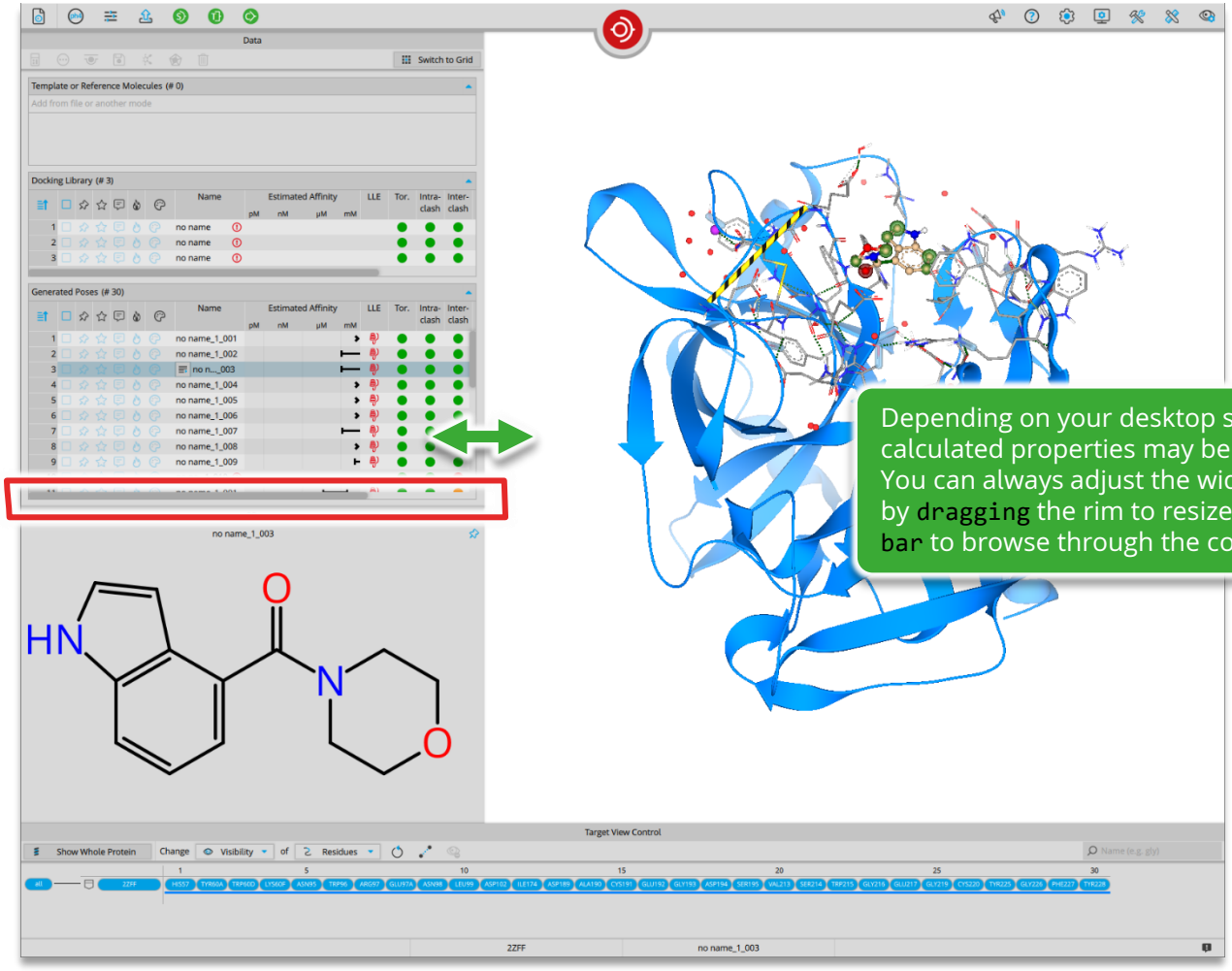
Mode Overview



Depending on your desktop setup, not all calculated properties may be displayed.
You can always adjust the width of the windows by `dragging` the rim to resize or use the `scroll bar` to browse through the columns.

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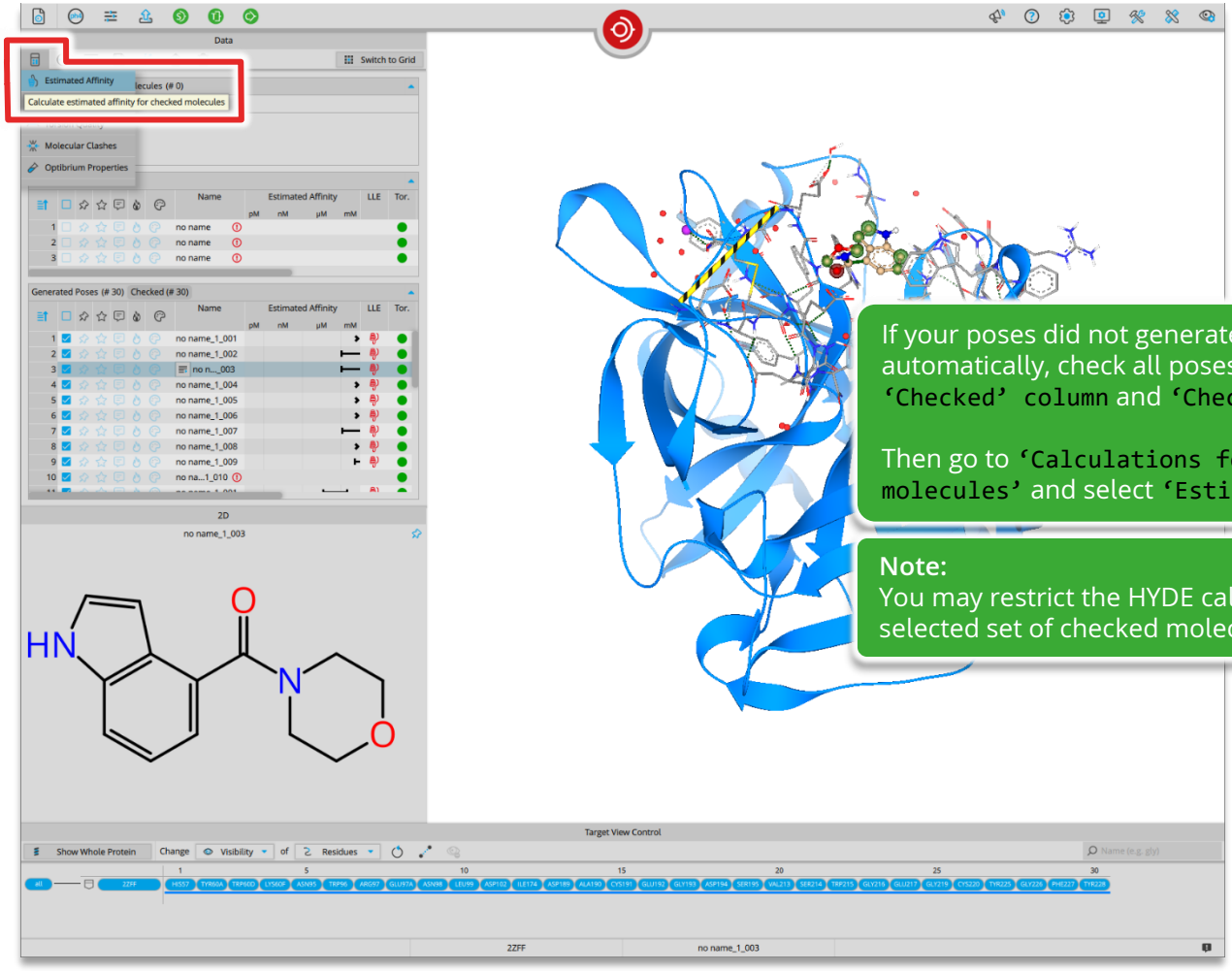
Mode Overview



If your poses did not generate affinity automatically, check all poses with the ‘Checked’ column and ‘Check all‘.

Then go to ‘Calculations for checked molecules’ and select ‘Estimated Affinity’.

Note:
You may restrict the HYDE calculation to a pre-selected set of checked molecules.

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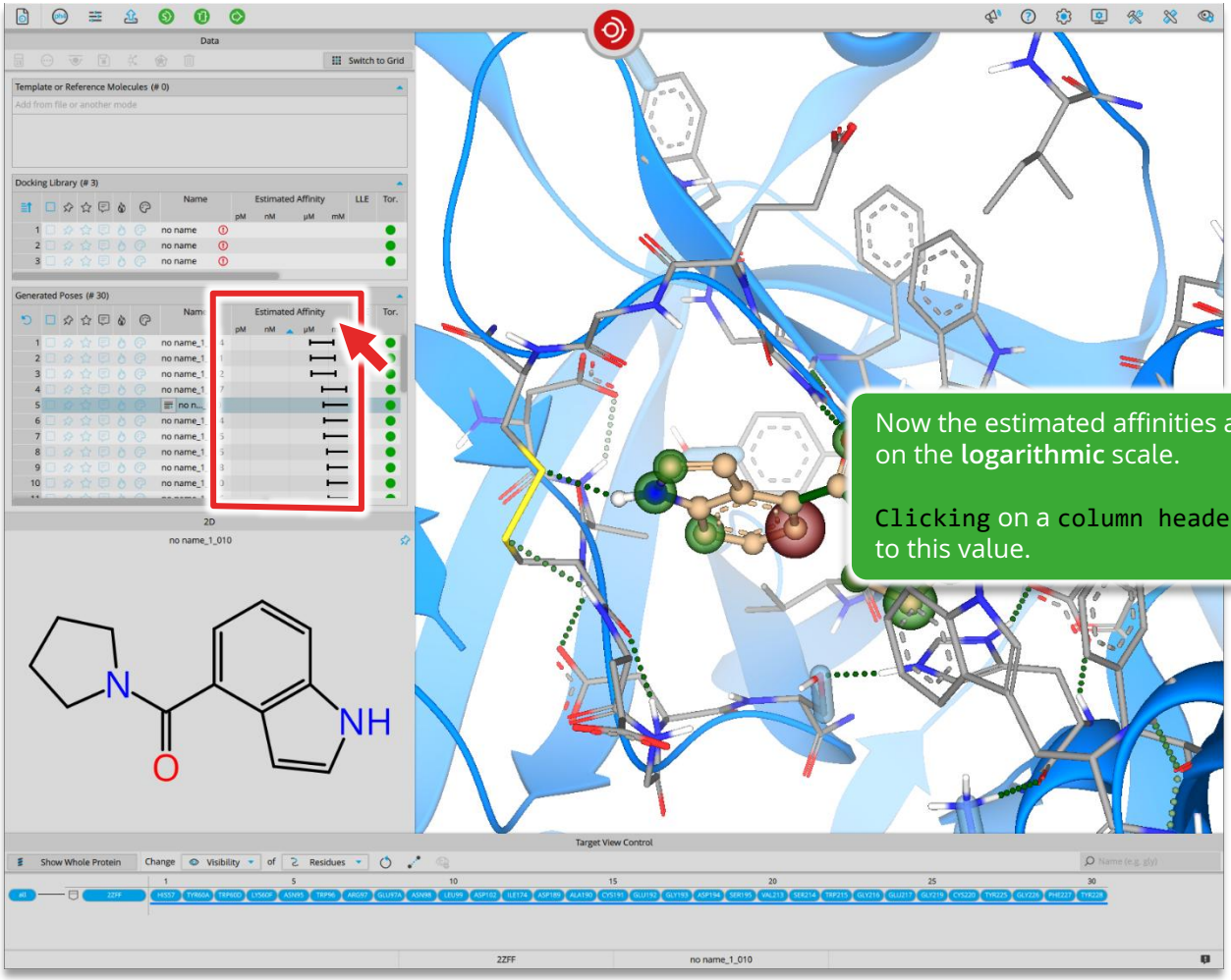
Mode Overview



Now the estimated affinities appear as a range on the **logarithmic** scale.

`Clicking` on a `column header` sorts according to this value.

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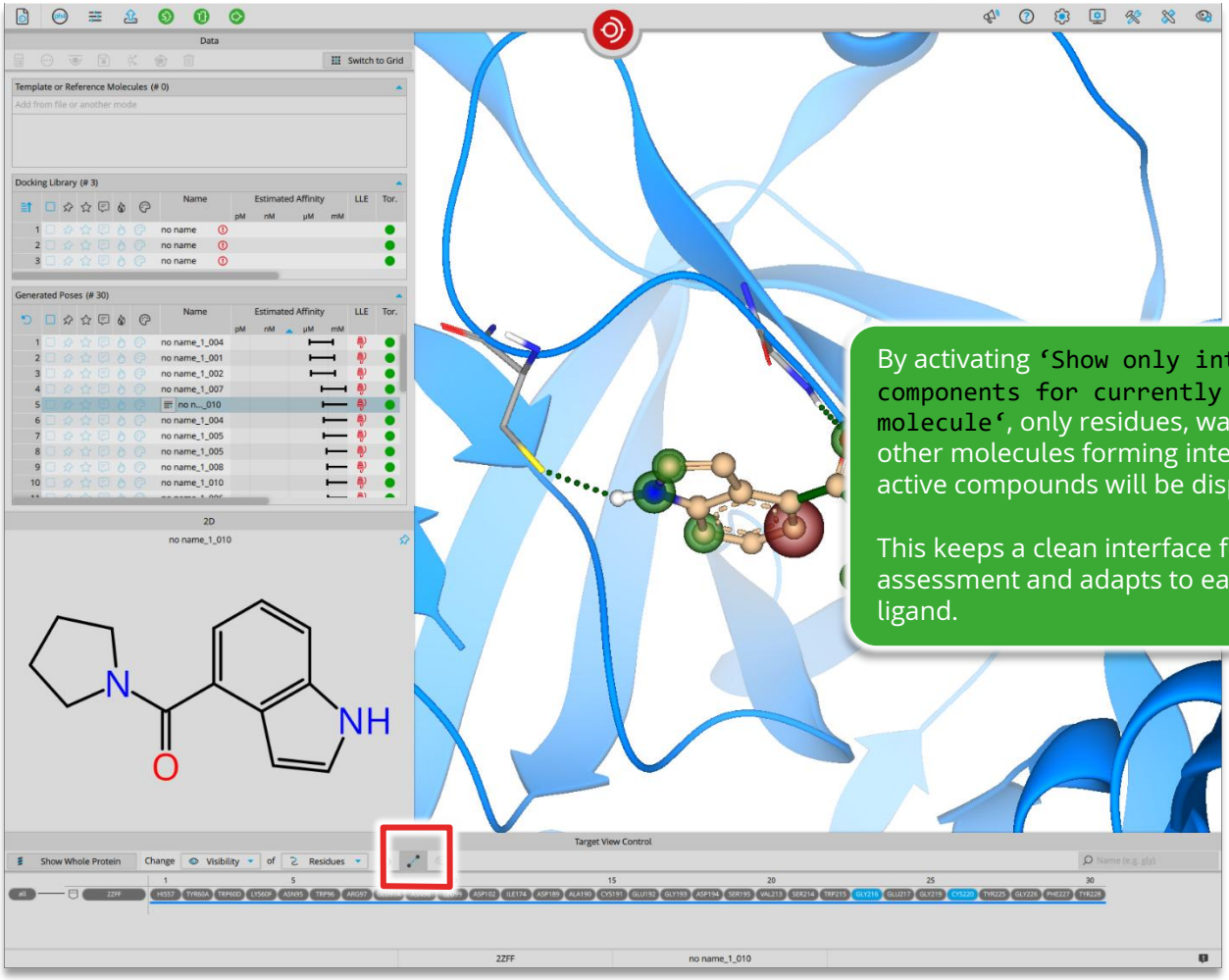
Mode Overview



By activating ‘`Show only interacting components for currently selected molecule`‘, only residues, waters, ions and other molecules forming interactions with the active compounds will be displayed.

This keeps a clean interface for easy visual assessment and adapts to each new active ligand.

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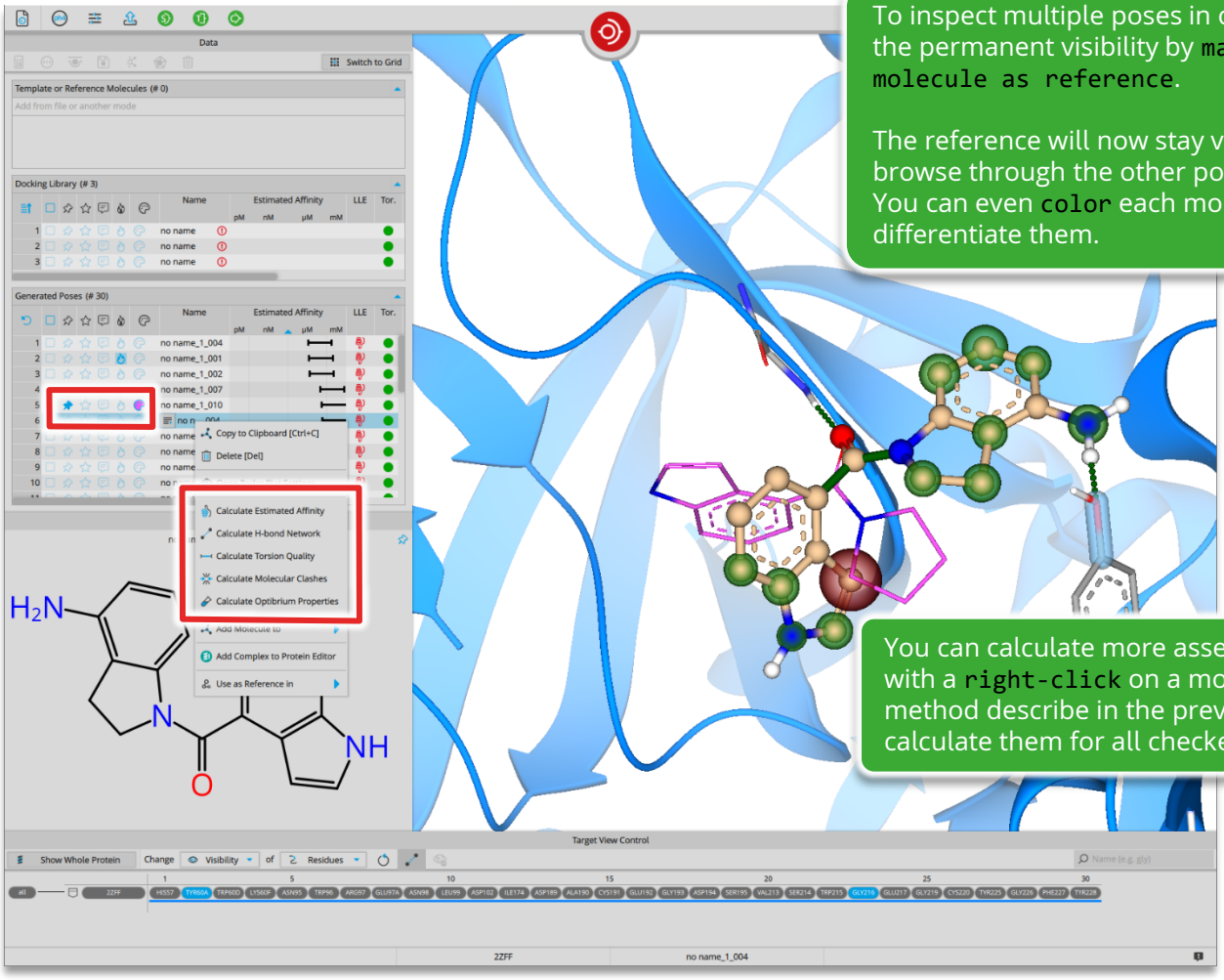
Mode Overview



To inspect multiple poses in comparison, toggle the permanent visibility by `marking a molecule as reference`.

The reference will now stay visible while you browse through the other poses.
You can even `color` each molecule to differentiate them.

You can calculate more assessment parameters with a `right-click` on a molecule, or using the method describe in the previous slides to calculate them for all checked molecules.

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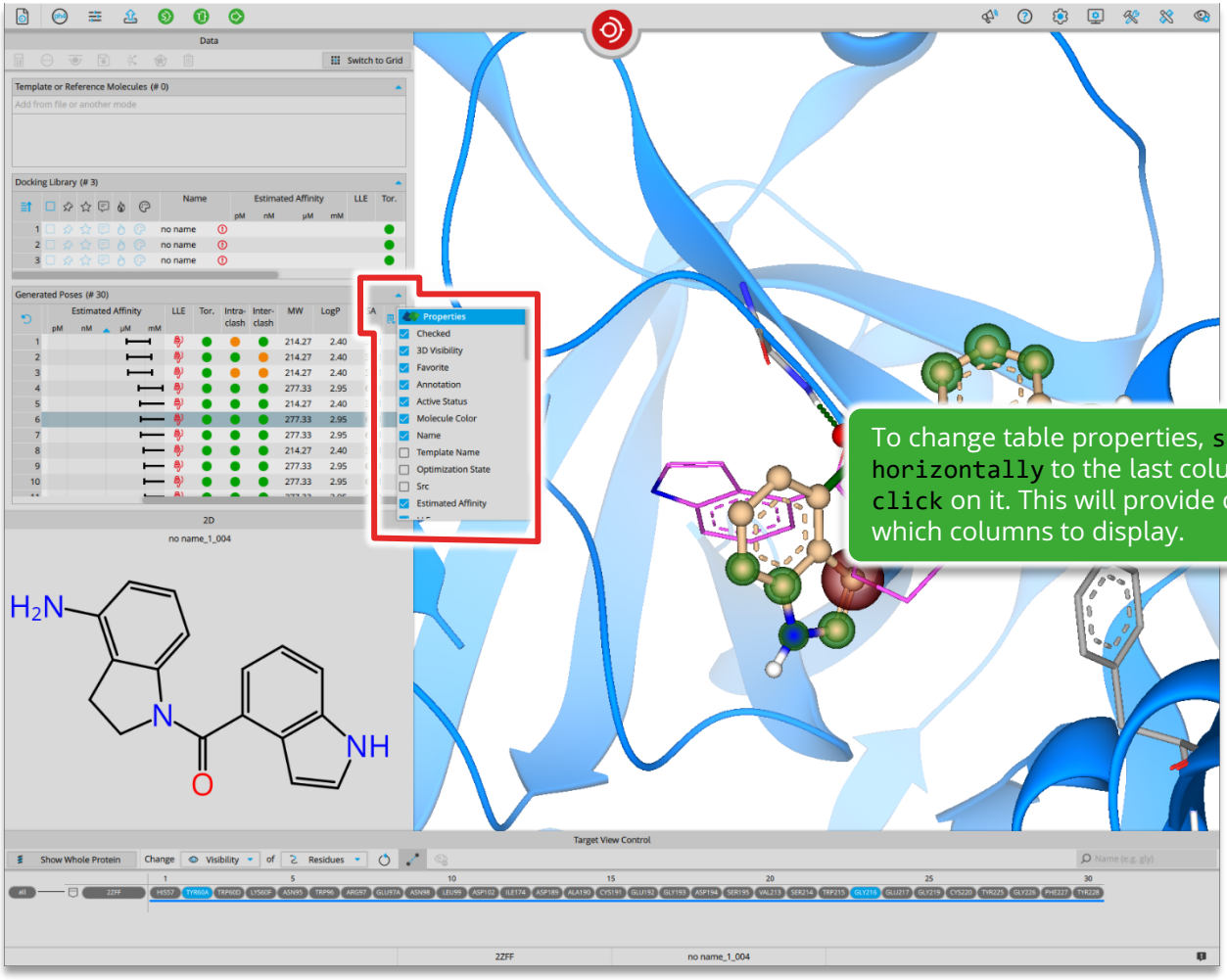
Mode Overview



To change table properties, `scroll horizontally` to the last column header and `click` on it. This will provide options to choose which columns to display.

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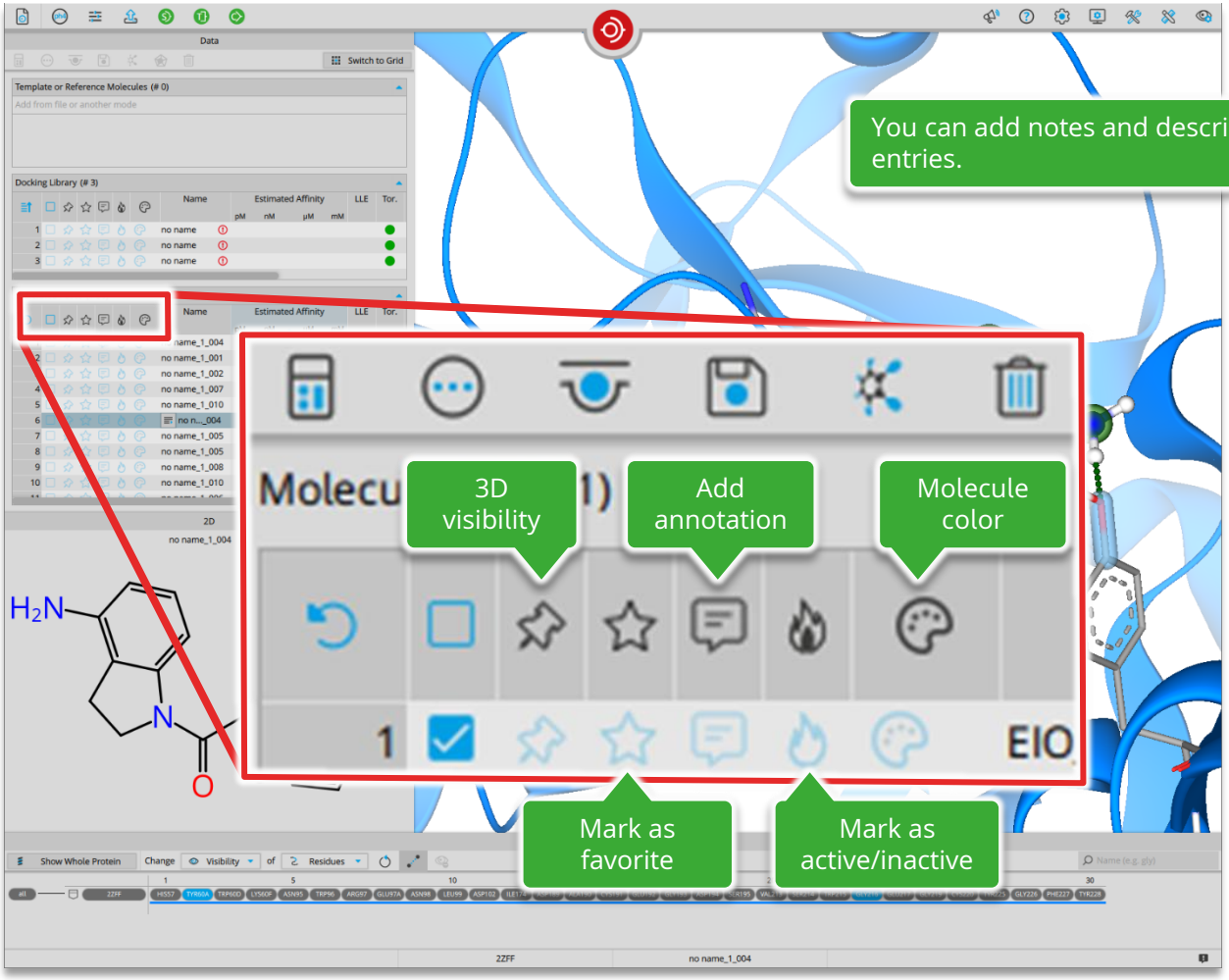
Mode Overview



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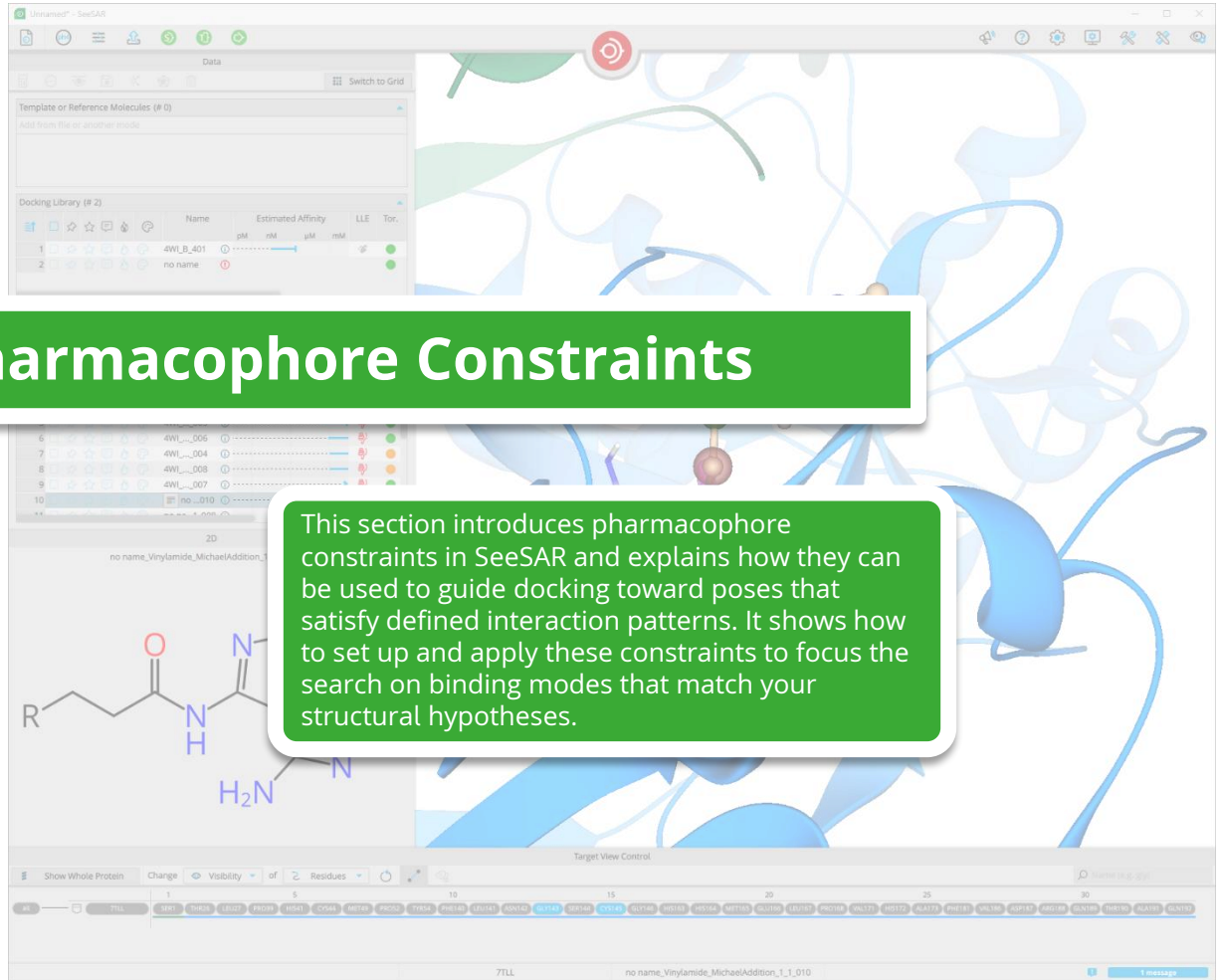
Mode Overview

5.1. Pharmacophore Constraints



This section introduces pharmacophore constraints in SeeSAR and explains how they can be used to guide docking toward poses that satisfy defined interaction patterns. It shows how to set up and apply these constraints to focus the search on binding modes that match your structural hypotheses.

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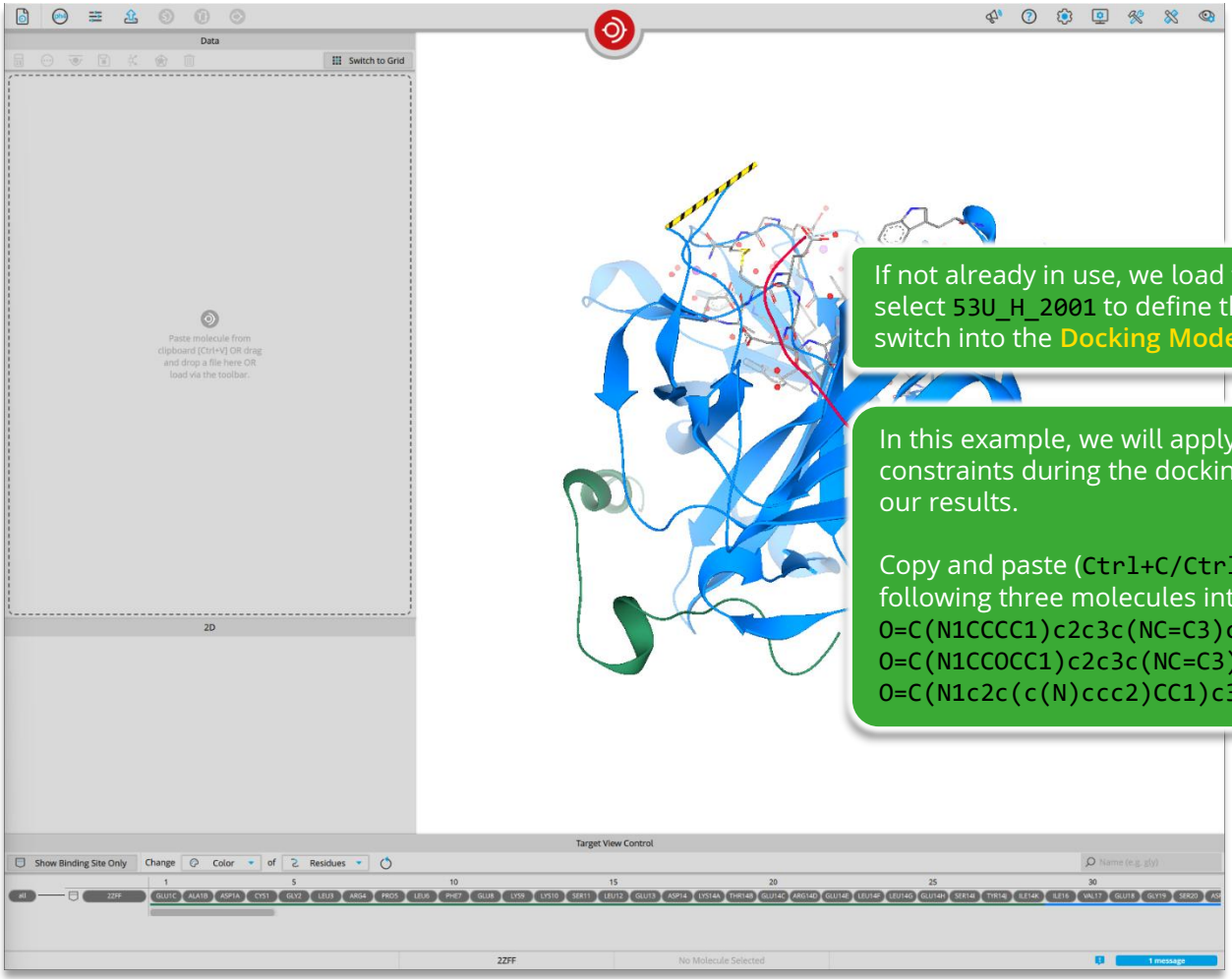
Mode Overview



If not already in use, we load the PDB `2ZFF` and select `53U_H_2001` to define the binding site and switch into the **Docking Mode**.

In this example, we will apply pharmacophore constraints during the docking process to guide our results.

Copy and paste (`Ctrl+C/Ctrl +V`) the following three molecules into SeeSAR:

```
O=C(N1CCCC1)c2c3c(NC=C3)ccc2
O=C(N1CCOCC1)c2c3c(NC=C3)ccc2
O=C(N1c2c(c(N)ccc2)CC1)c3c4c(NC=C4)ccc3
```

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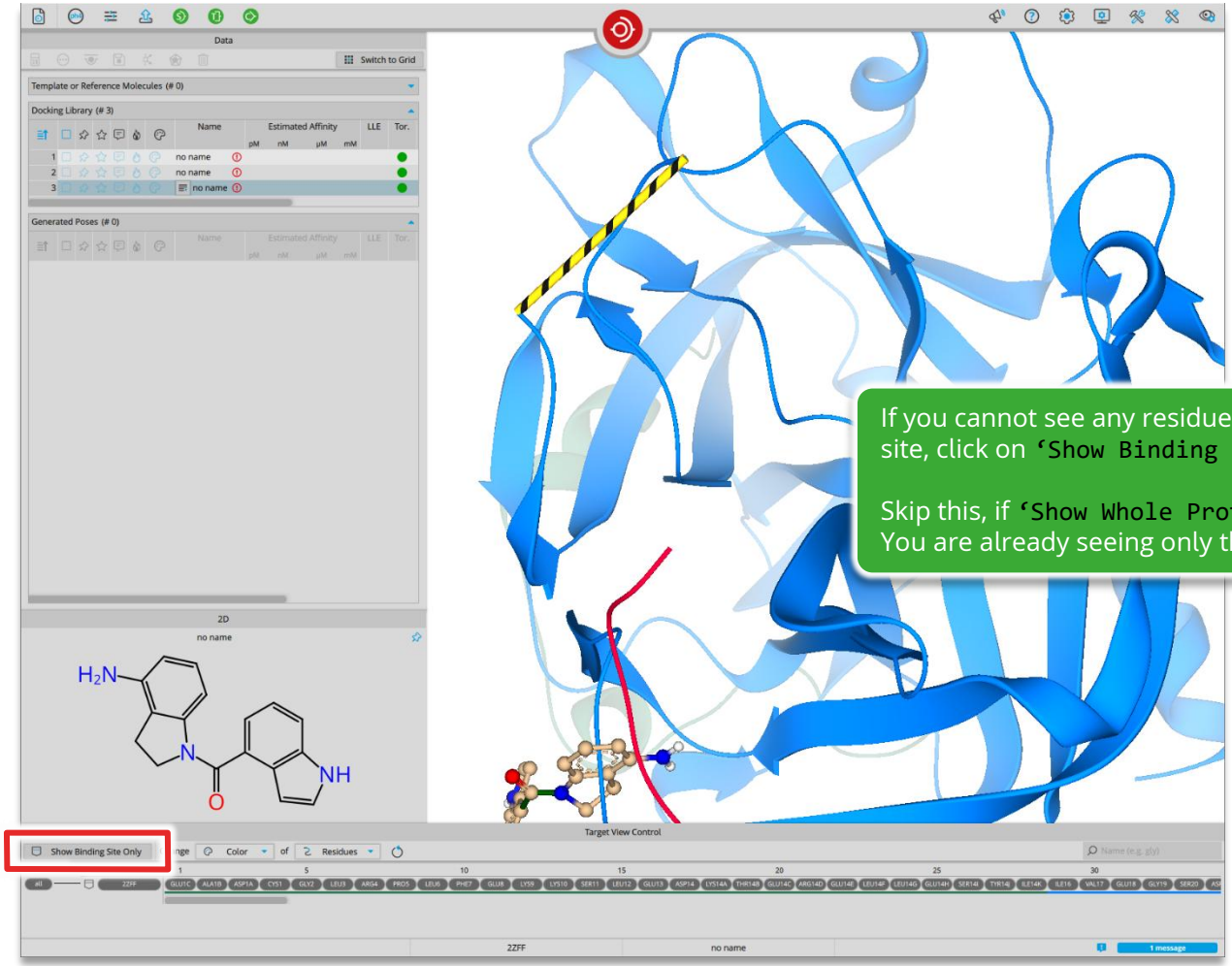
Mode Overview



If you cannot see any residues in the binding site, click on **'Show Binding Site Only'**.

Skip this, if **'Show Whole Protein'** is displayed; You are already seeing only the binding site.

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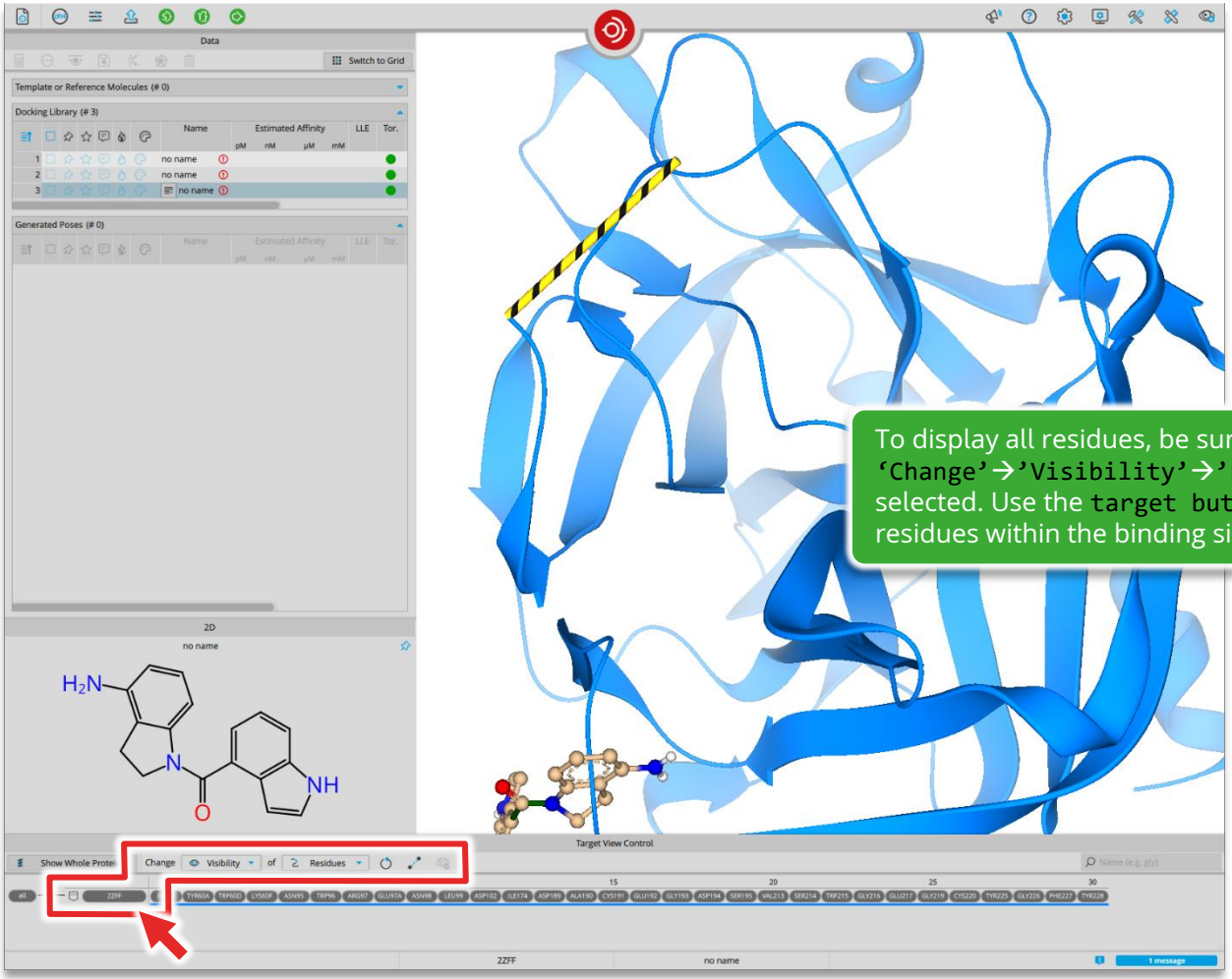
Mode Overview



To display all residues, be sure that ‘Change’→’Visibility’→’Residues’ is selected. Use the target button to show all residues within the binding site.

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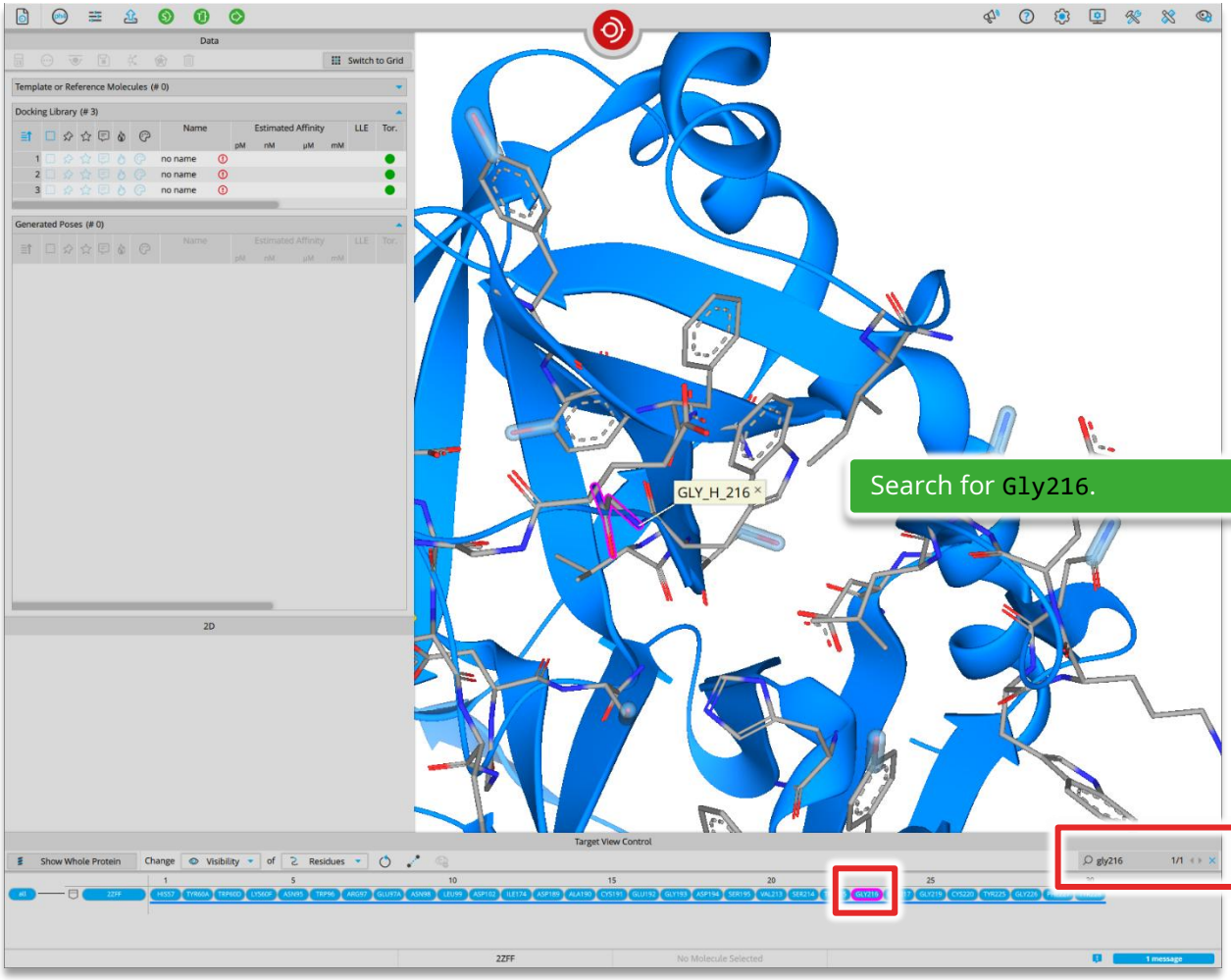
Mode Overview



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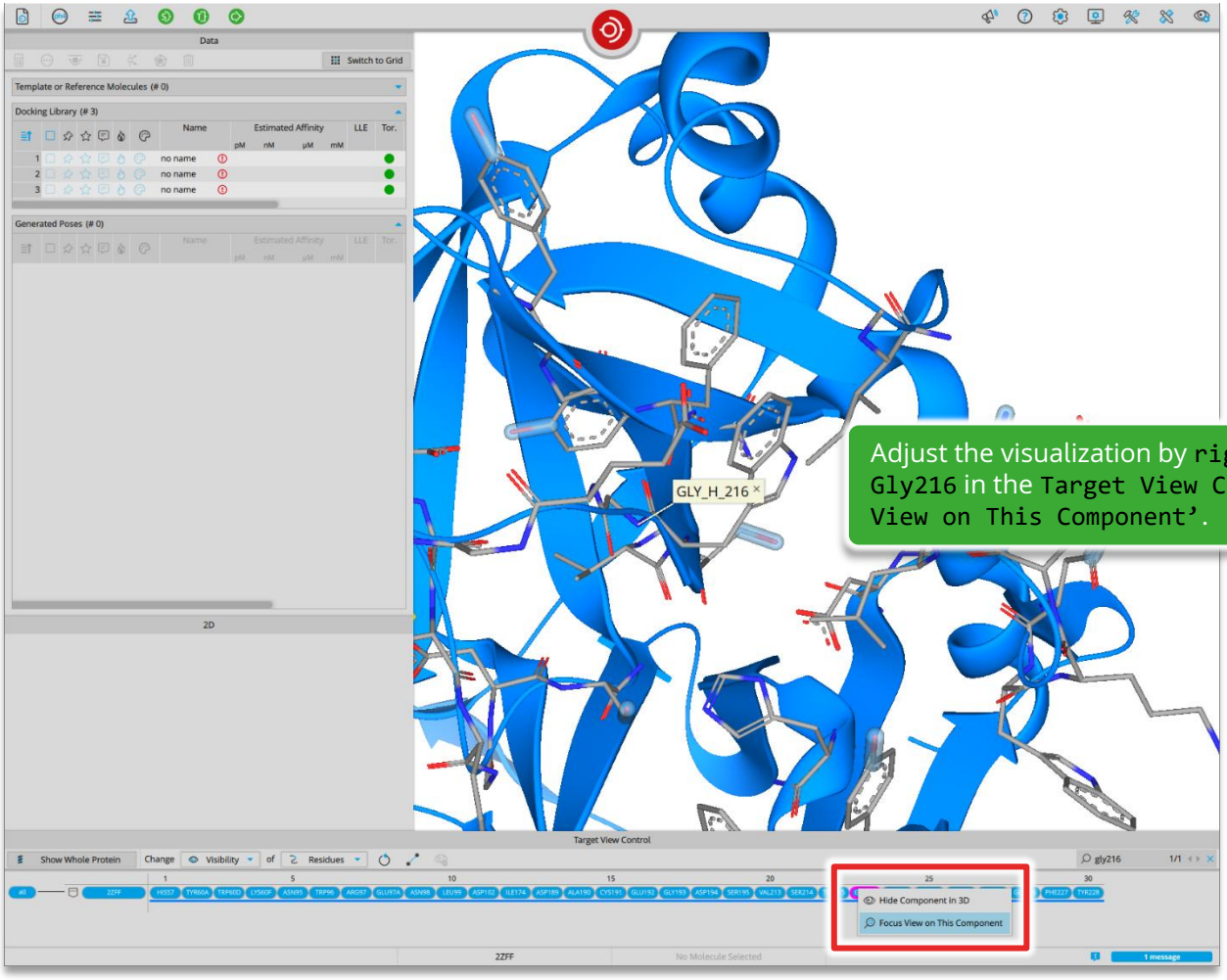
Mode Overview



Adjust the visualization by `right-clicking` on `Gly216` in the `Target View Control` and `'Focus View on This Component'`.

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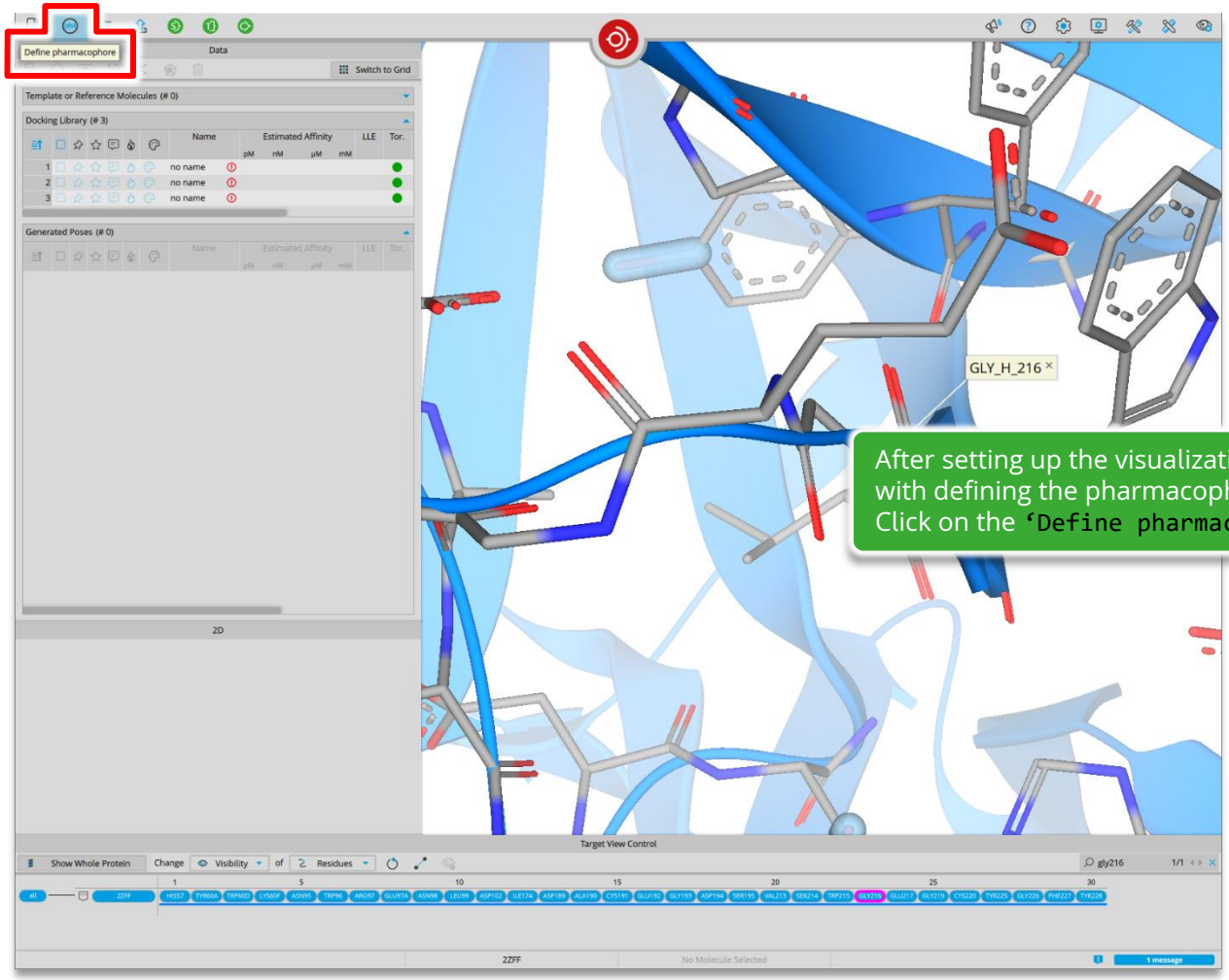
Mode Overview



After setting up the visualization, we can start with defining the pharmacophore constraints. Click on the **'Define pharmacophore' button**.

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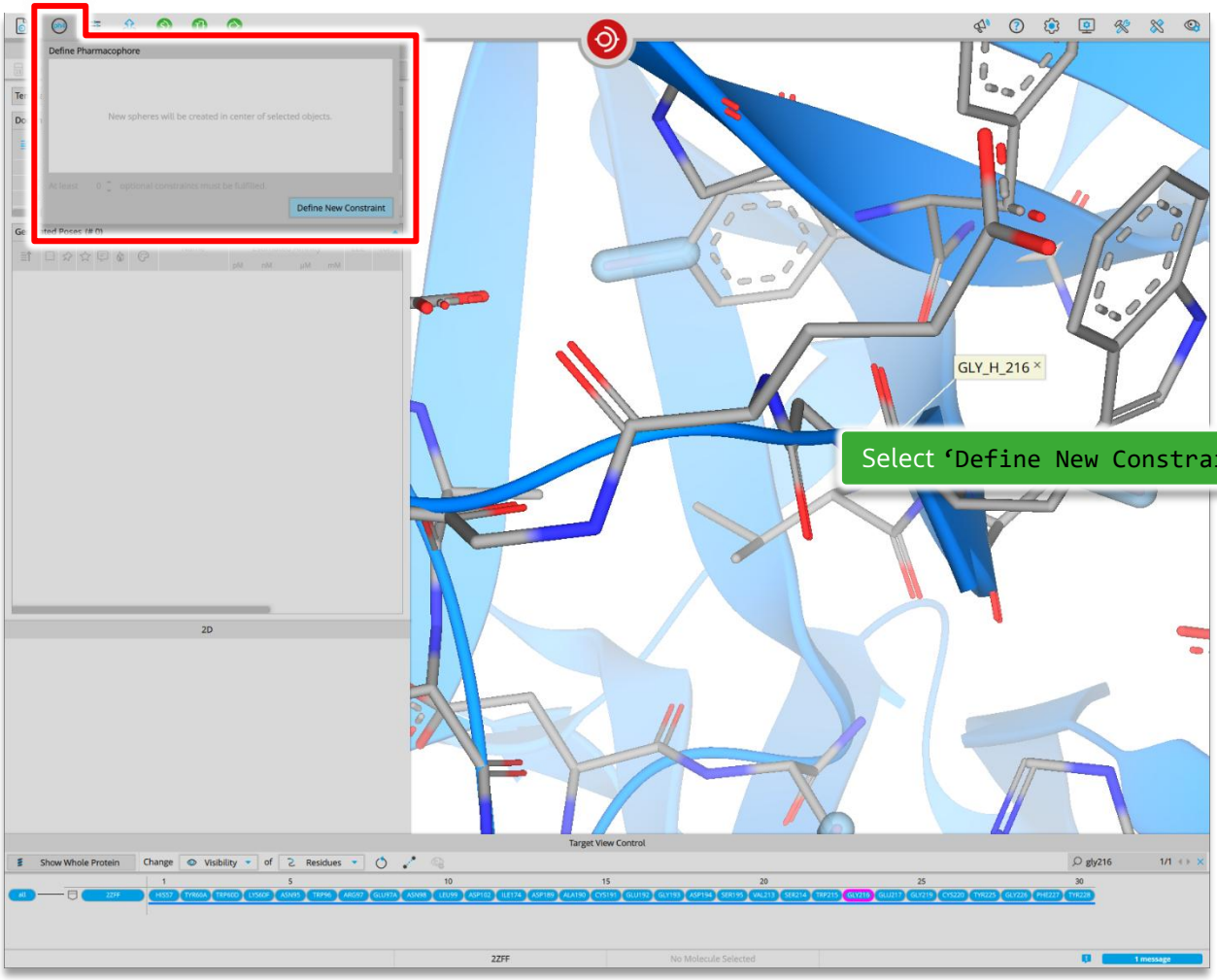
Mode Overview



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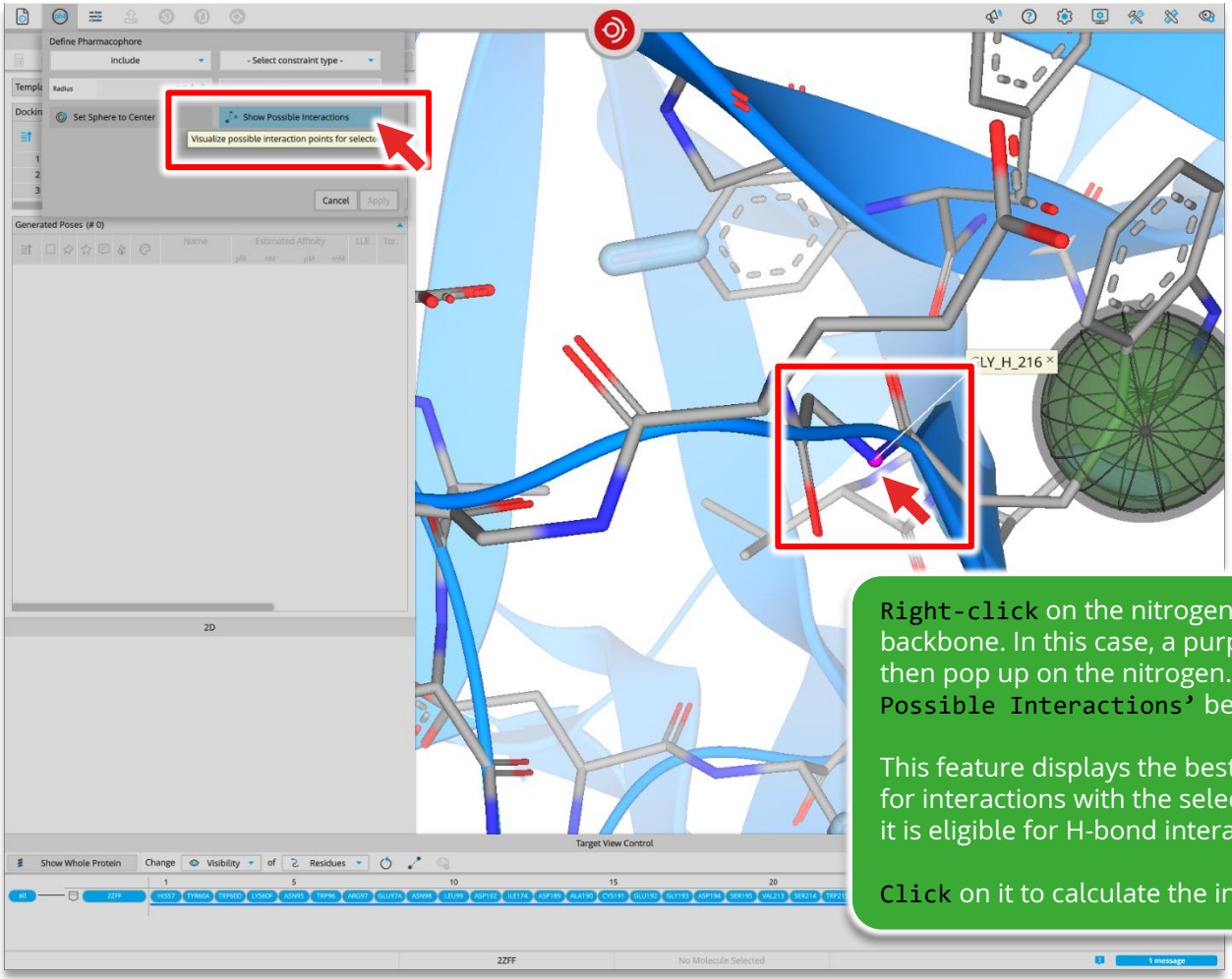
Mode Overview



`Right-click` on the nitrogen of the Gly216 backbone. In this case, a purple sphere will then pop up on the nitrogen. The option `'Show Possible Interactions'` becomes available.

This feature displays the best geometry point for interactions with the selected heavy atom if it is eligible for H-bond interactions.

`Click` on it to calculate the interaction points.

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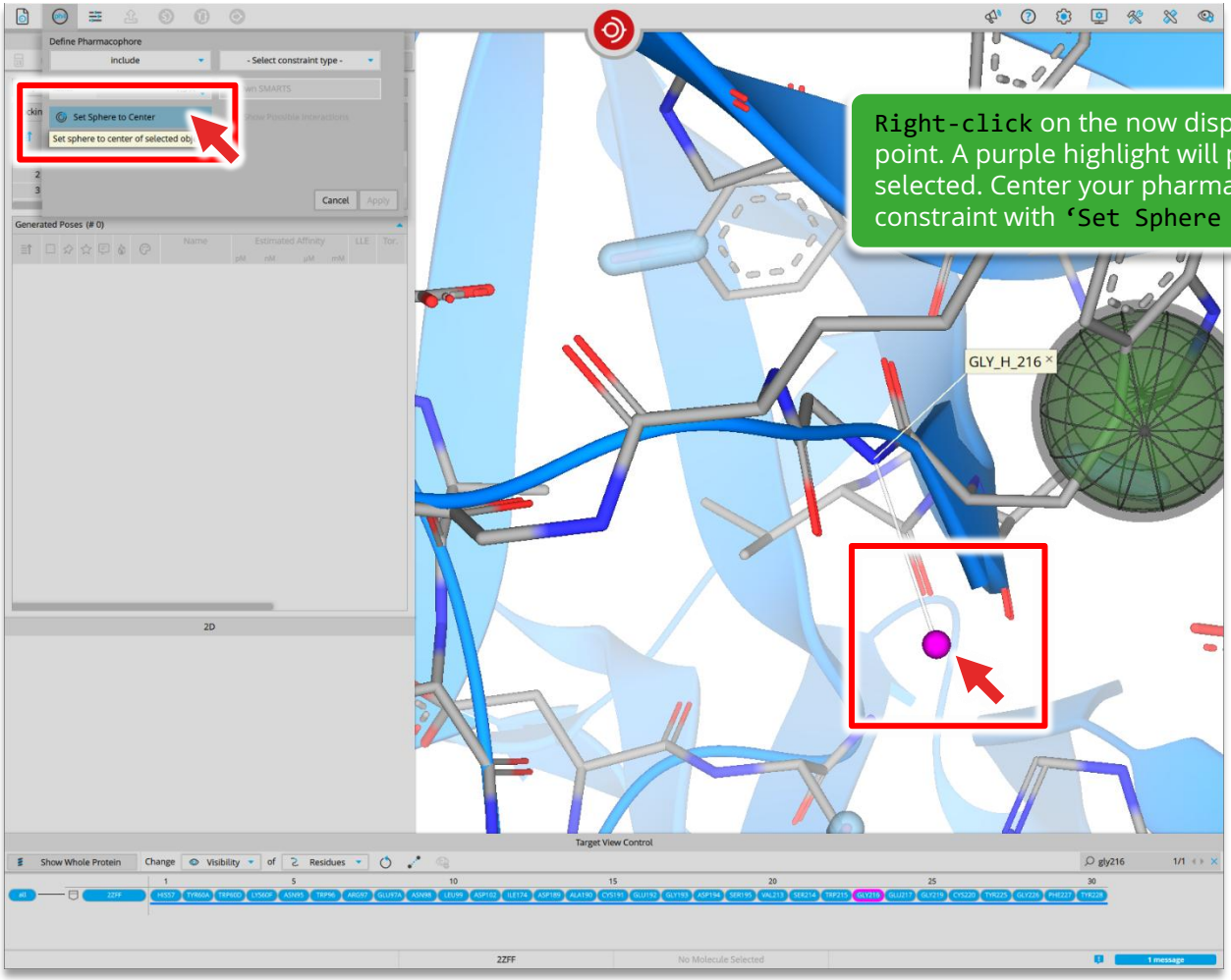
Mode Overview



`Right-click` on the now displayed interaction point. A purple highlight will pop up if it is selected. Center your pharmacophore constraint with `'Set Sphere to Center'`.

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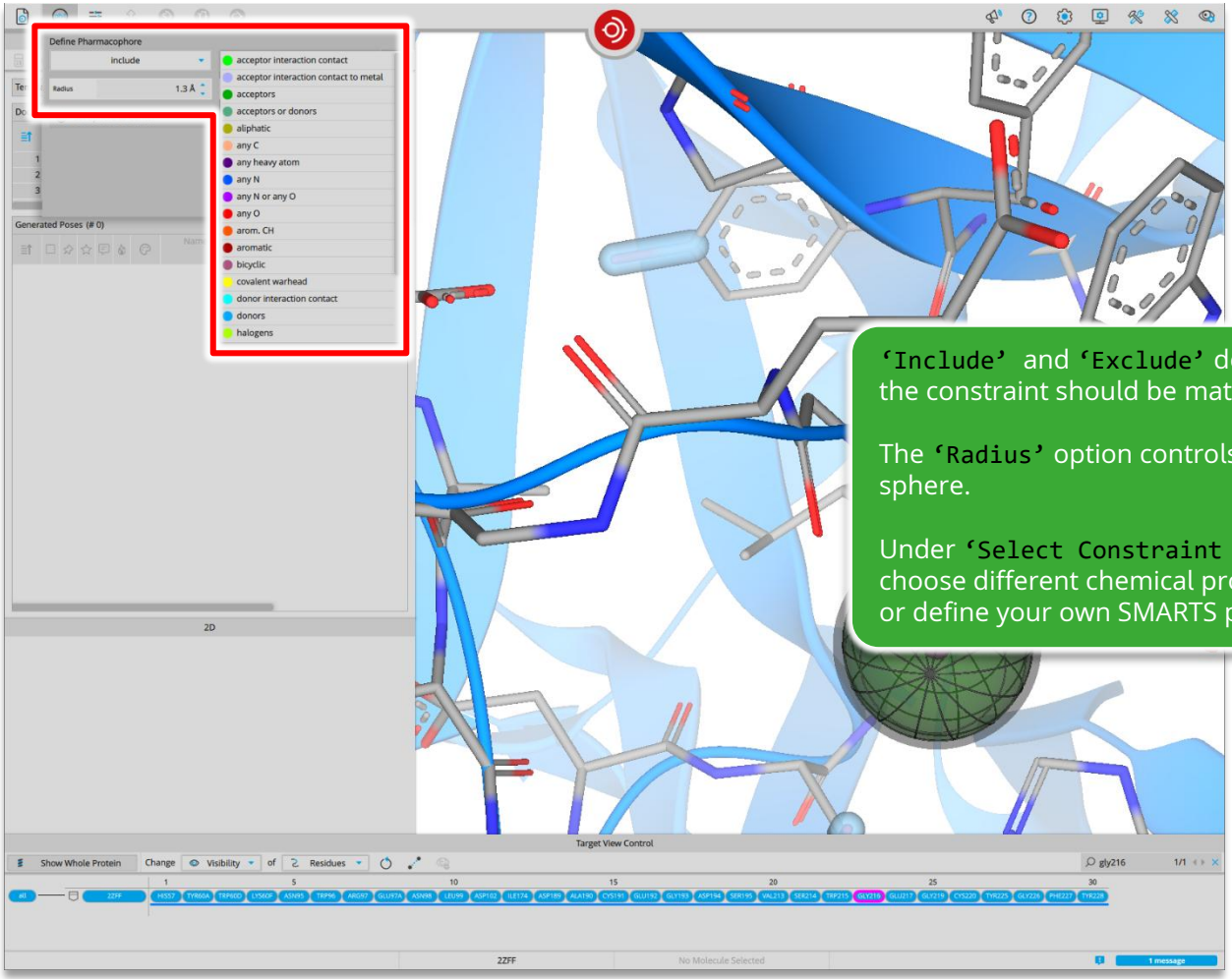
Mode Overview



‘Include’ and **‘Exclude’** determine whether the constraint should be matched or avoided.

The **‘Radius’** option controls the size of the sphere.

Under **‘Select Constraint Type’**, you can choose different chemical properties to match, or define your own SMARTS pattern.

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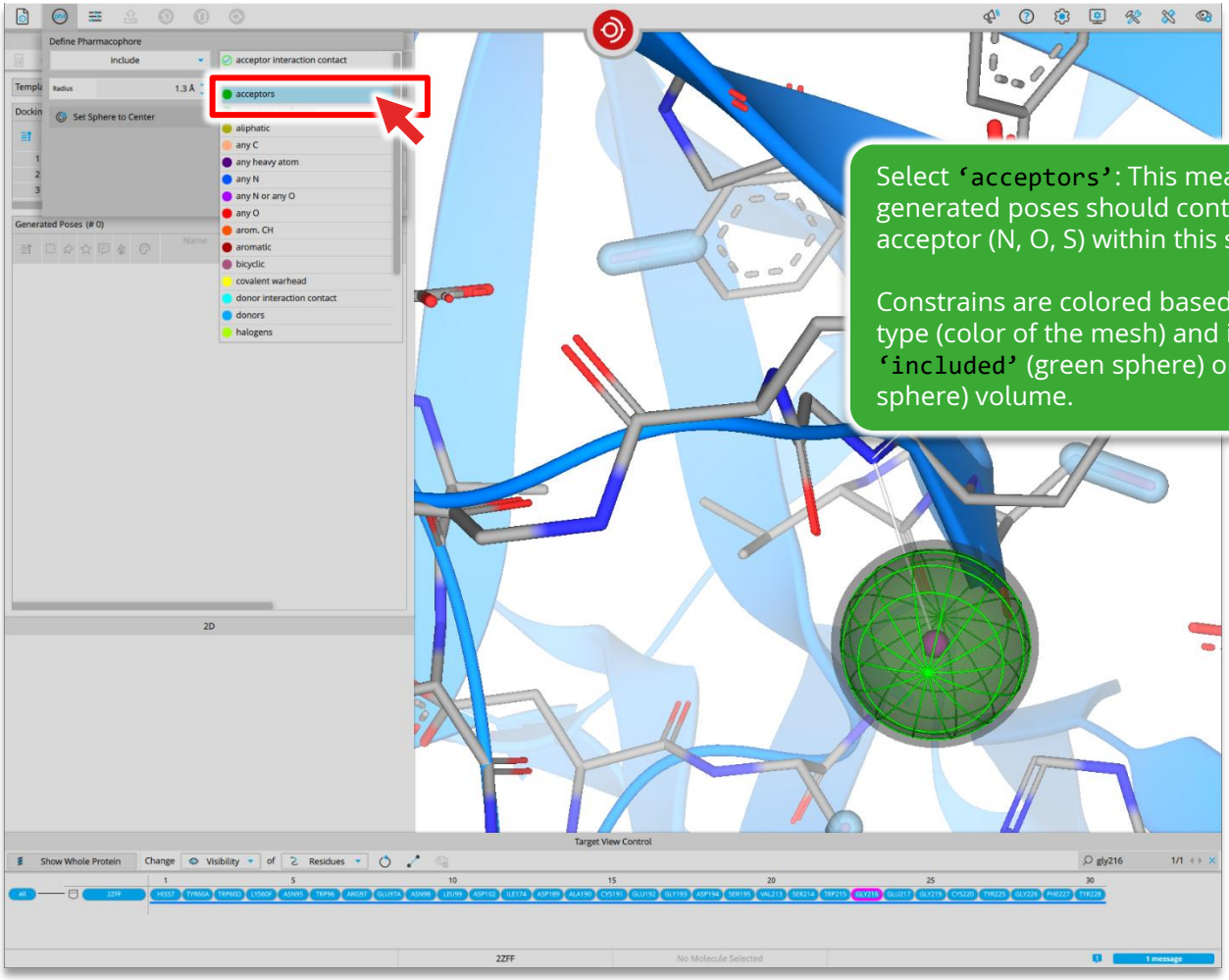
Mode Overview



Select **‘acceptors’**: This means that all generated poses should contain an H-bond acceptor (N, O, S) within this sphere constraint.

Constrains are colored based on their chemical type (color of the mesh) and if they featured an **‘included’** (green sphere) or **‘excluded’** (red sphere) volume.

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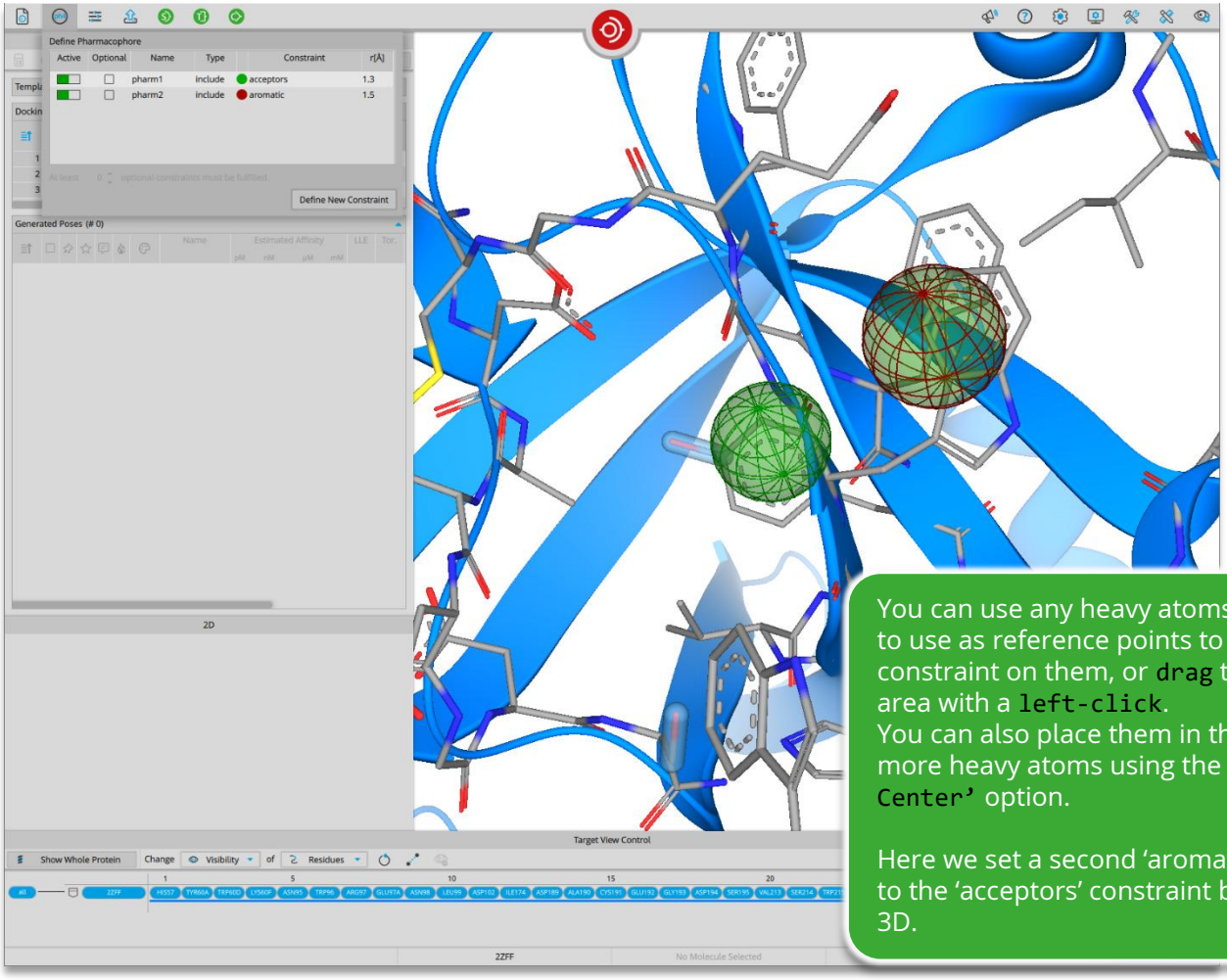
Mode Overview



You can use any heavy atoms (target or ligand) to use as reference points to center a constraint on them, or `drag` them into a desired area with a `left-click`.
You can also place them in the middle of two or more heavy atoms using the `'Set Sphere to Center'` option.

Here we set a second 'aromatic' constraint next to the 'acceptors' constraint by dragging it in 3D.

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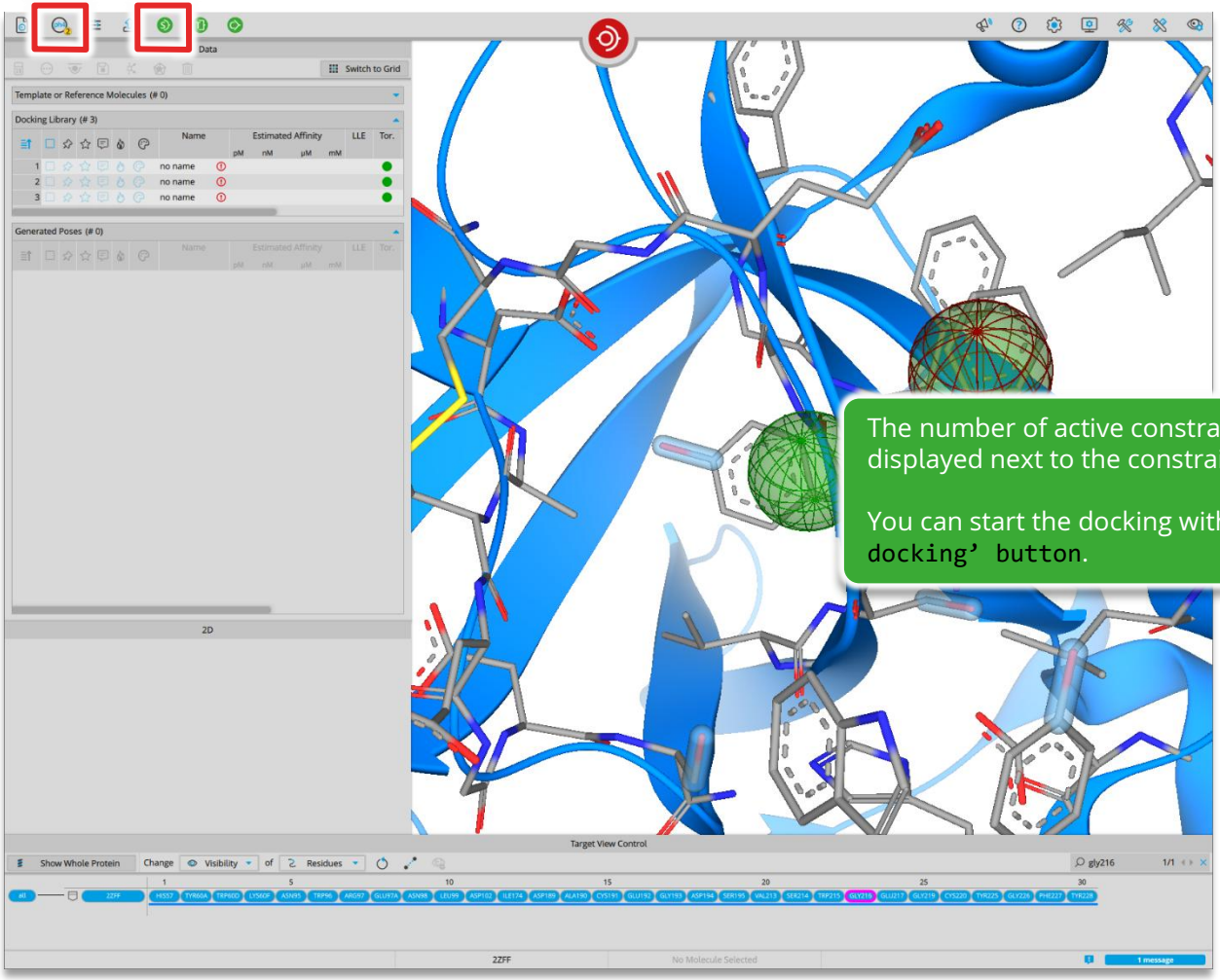
Mode Overview



The number of active constraints is always displayed next to the constraint button.

You can start the docking with the `'Standard docking' button`.

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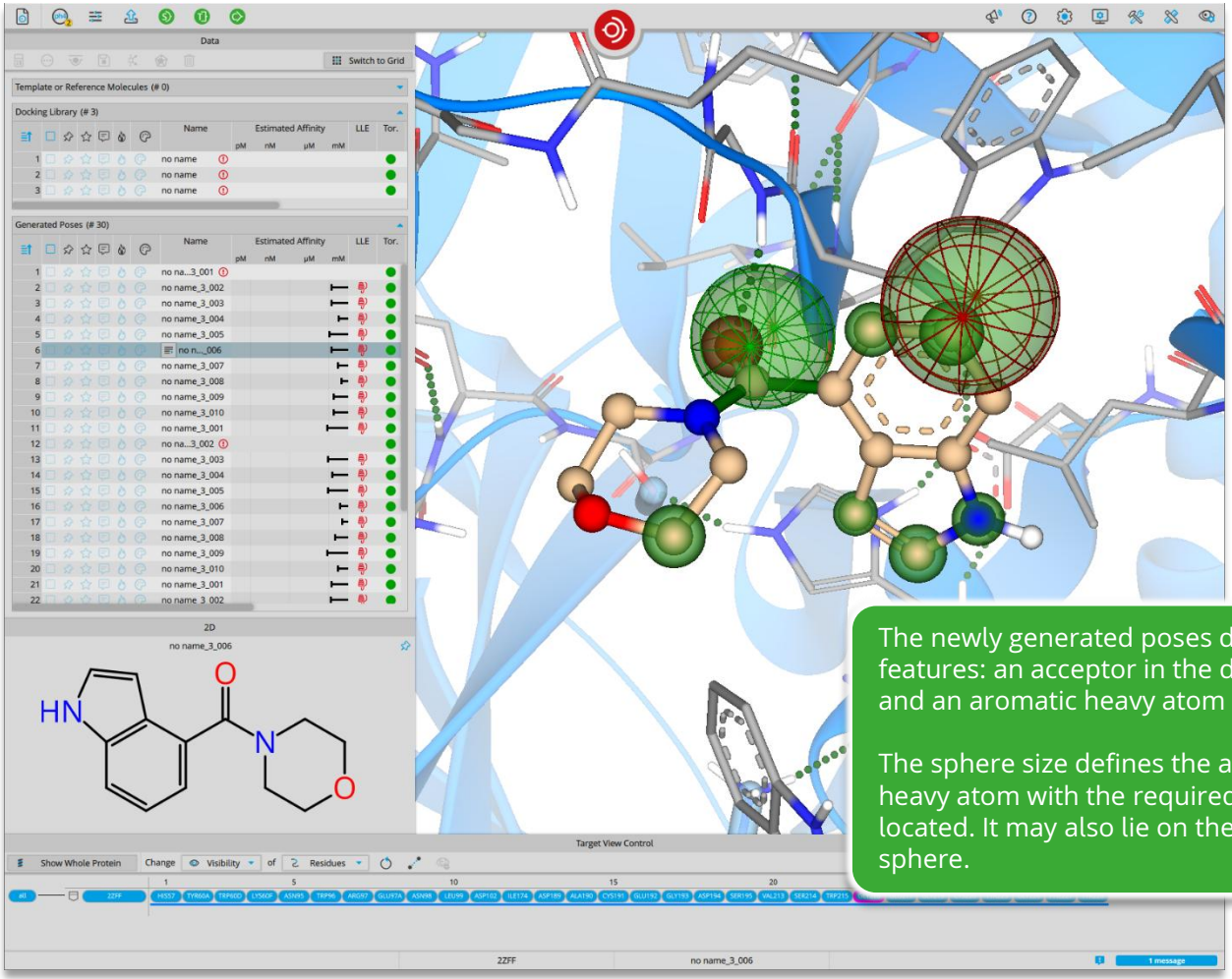
Mode Overview

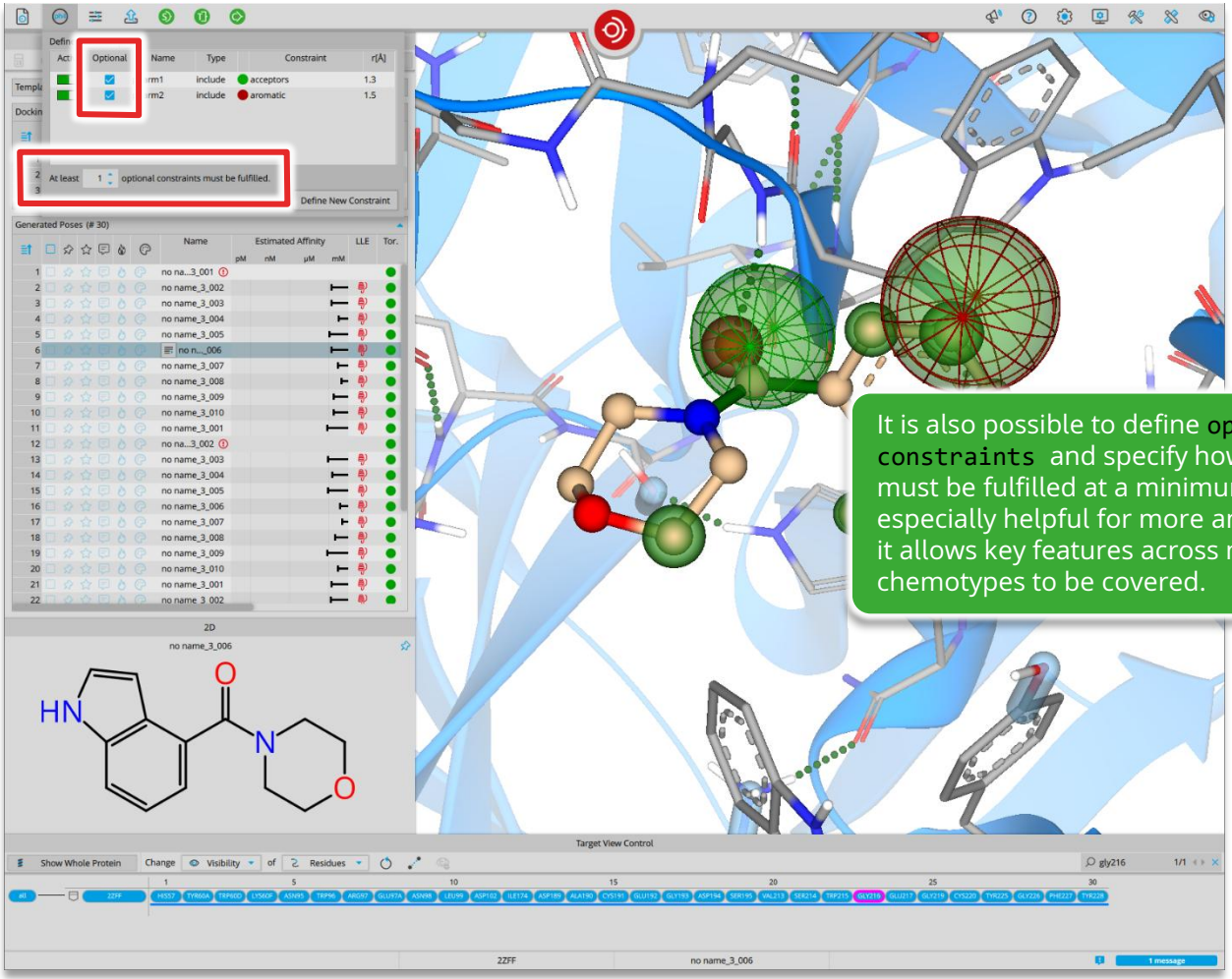


The newly generated poses display the required features: an acceptor in the dark green sphere and an aromatic heavy atom in the red sphere.

The sphere size defines the area in which the heavy atom with the required feature may be located. It may also lie on the surface of the sphere.

Table of Content

Mode Overview



It is also possible to define `optional constraints` and specify how many of them must be fulfilled at a minimum. This can be especially helpful for more ambiguous SARs, as it allows key features across multiple chemotypes to be covered.

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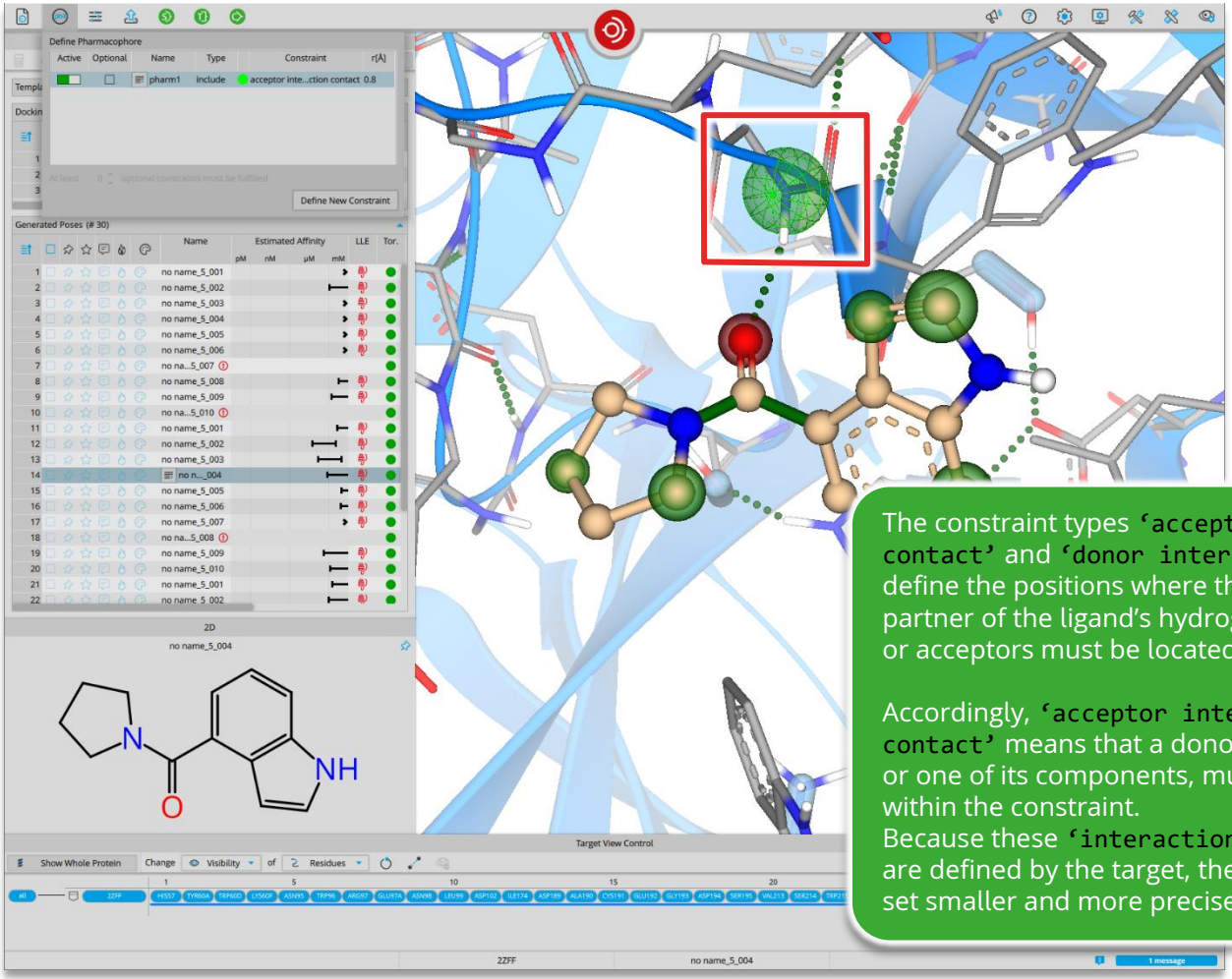
Mode Overview



The constraint types ‘`acceptor interaction contact`’ and ‘`donor interaction contact`’ define the positions where the interaction partner of the ligand’s hydrogen-bond donors or acceptors must be located.

Accordingly, ‘`acceptor interaction contact`’ means that a donor from the target, or one of its components, must be located within the constraint.
Because these ‘`interaction contact`’ types are defined by the target, they can usually be set smaller and more precisely.

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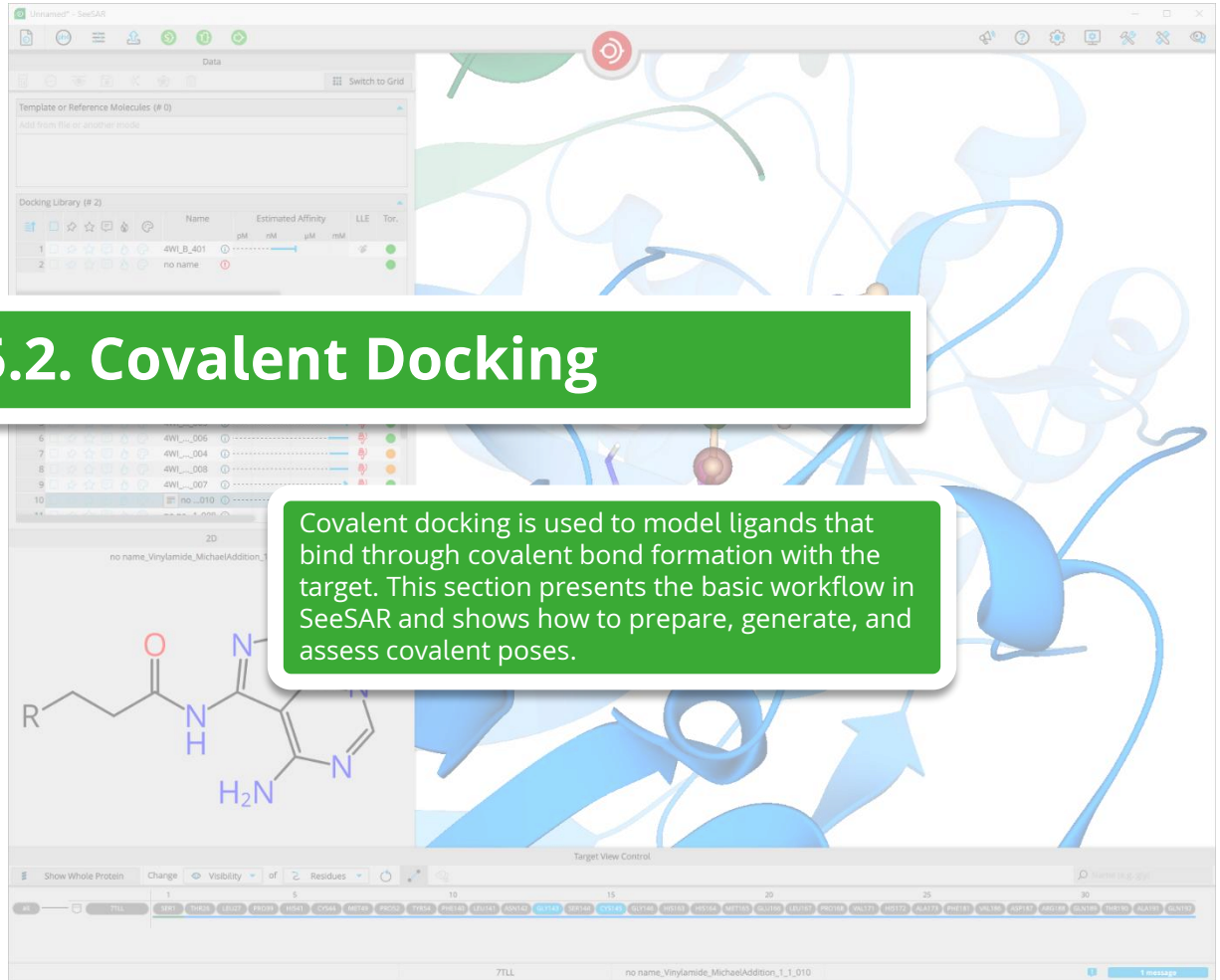
Mode Overview

5.2. Covalent Docking



Covalent docking is used to model ligands that bind through covalent bond formation with the target. This section presents the basic workflow in SeeSAR and shows how to prepare, generate, and assess covalent poses.

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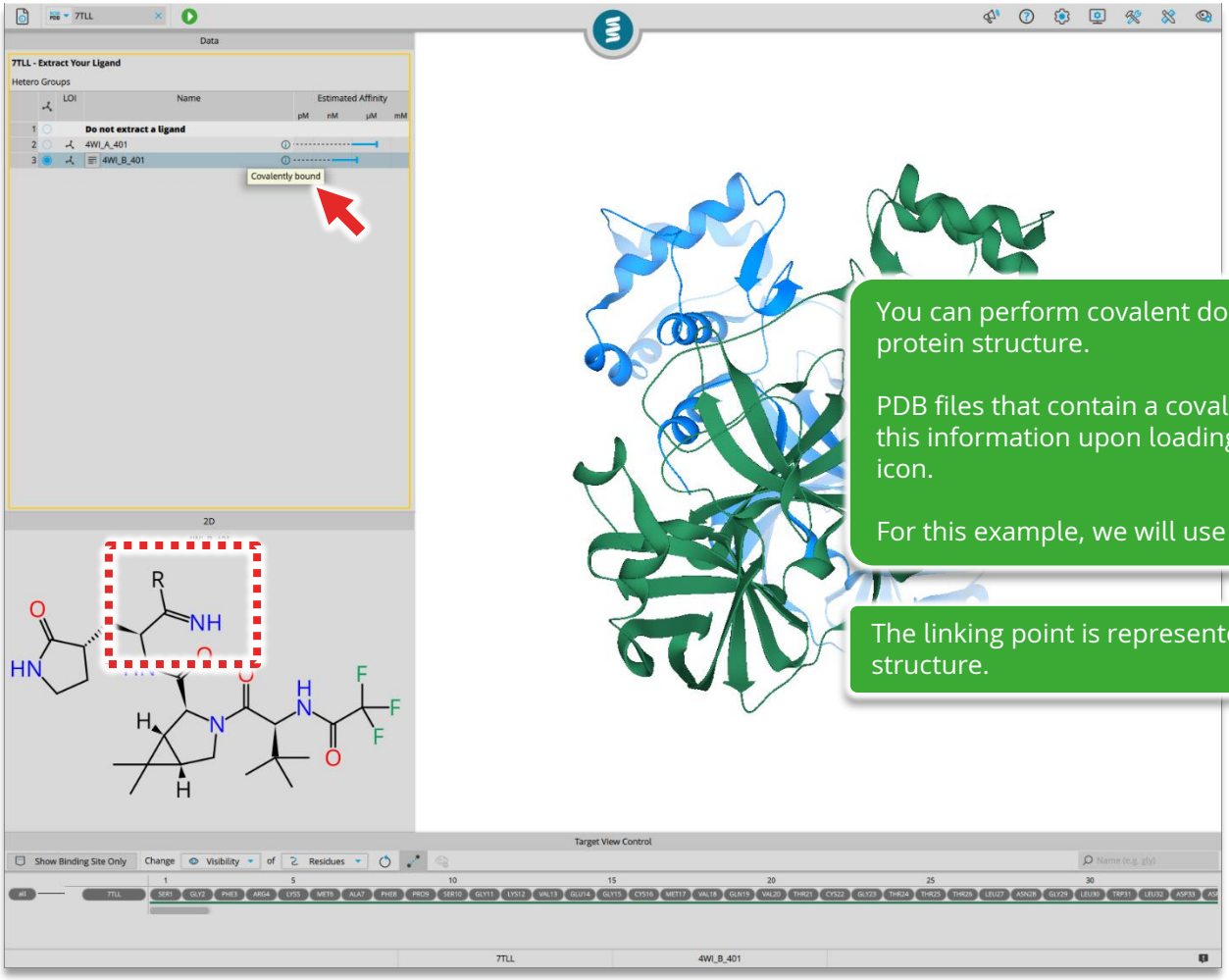
Mode Overview



You can perform covalent docking at any PDB protein structure.

PDB files that contain a covalent ligand provide this information upon loading within the info icon.

For this example, we will use the PDB 7TLL.

The linking point is represented as **R** in the 2D structure.

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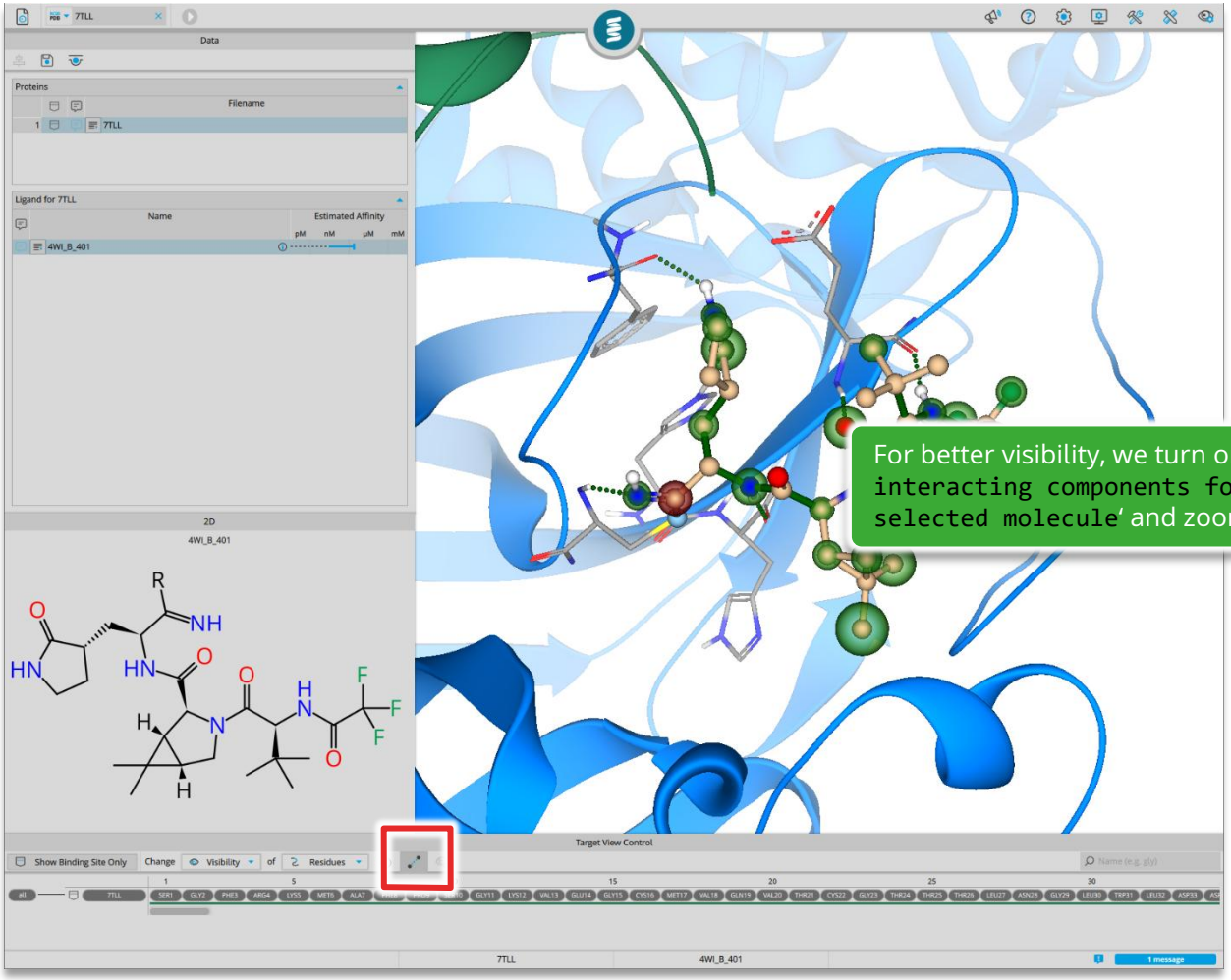
Mode Overview



For better visibility, we turn on '`Show only interacting components for currently selected molecule`' and zoom in using `Space`.

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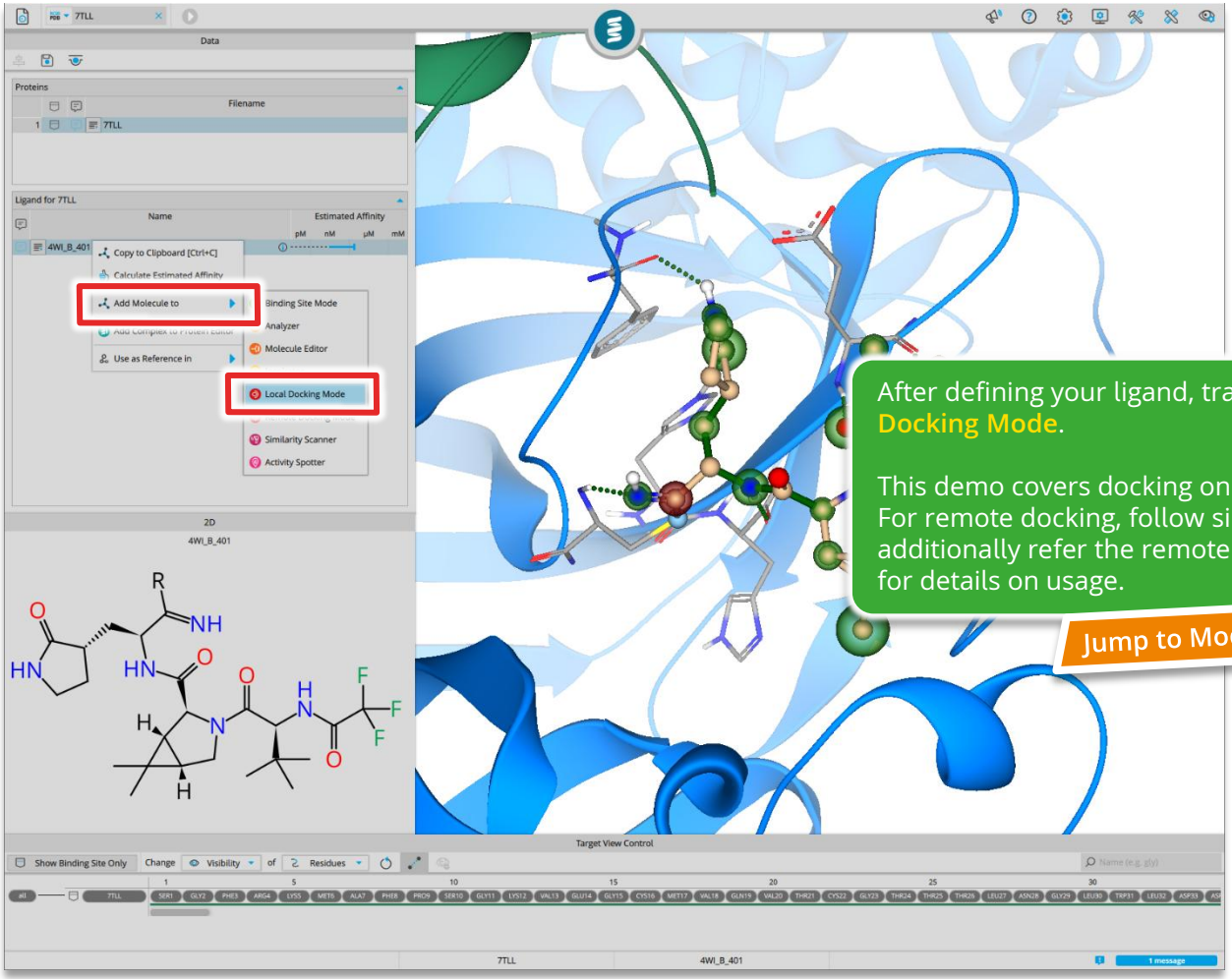
Mode Overview



After defining your ligand, transfer it to the **Docking Mode**.

This demo covers docking on a local machine. For remote docking, follow similar steps and additionally refer the remote docking section for details on usage.

Jump to Mode

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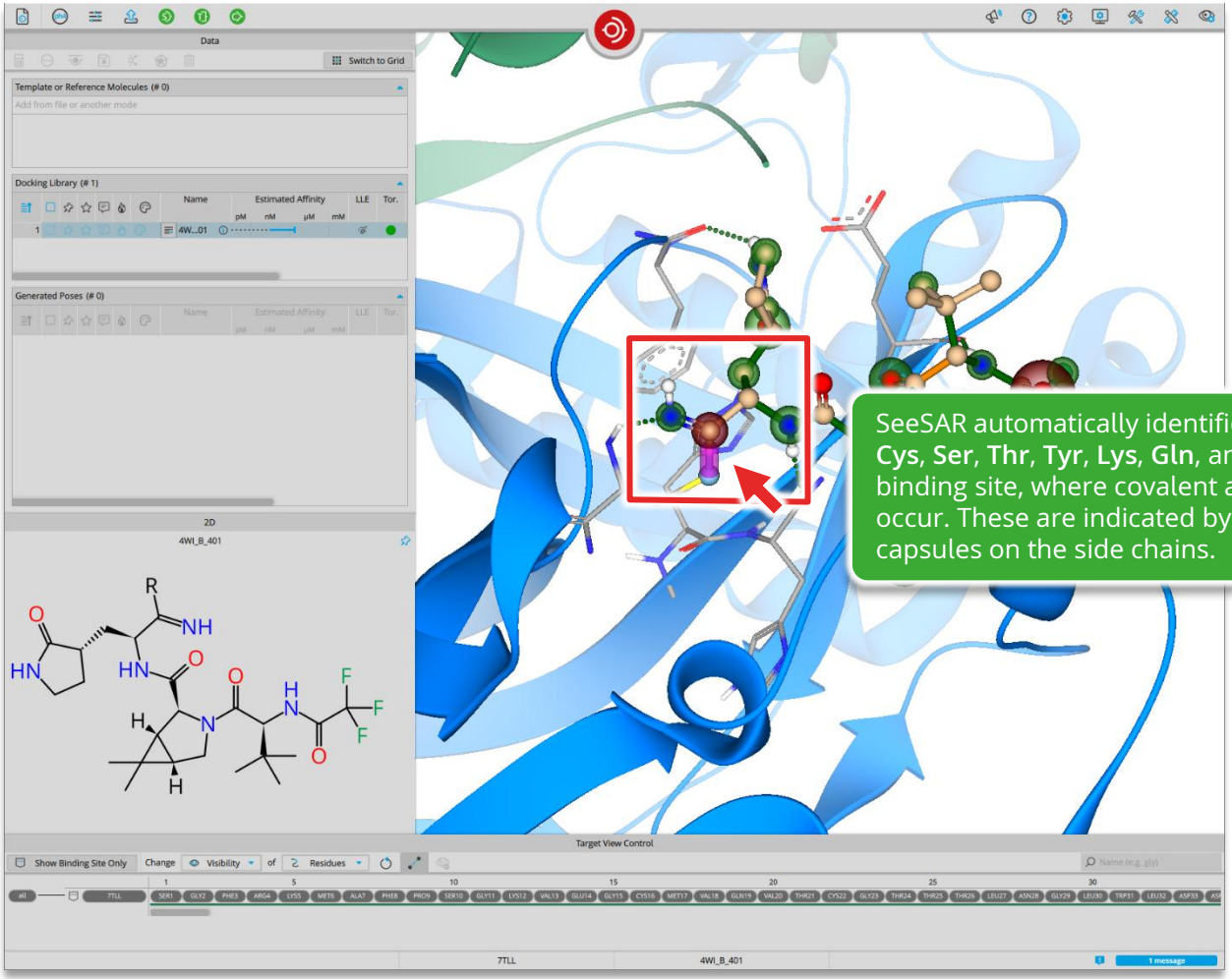
Mode Overview



SeeSAR automatically identifies the residues **Cys**, **Ser**, **Thr**, **Tyr**, **Lys**, **Gln**, and **Asn** within the binding site, where covalent attachment may occur. These are indicated by blue translucent capsules on the side chains.

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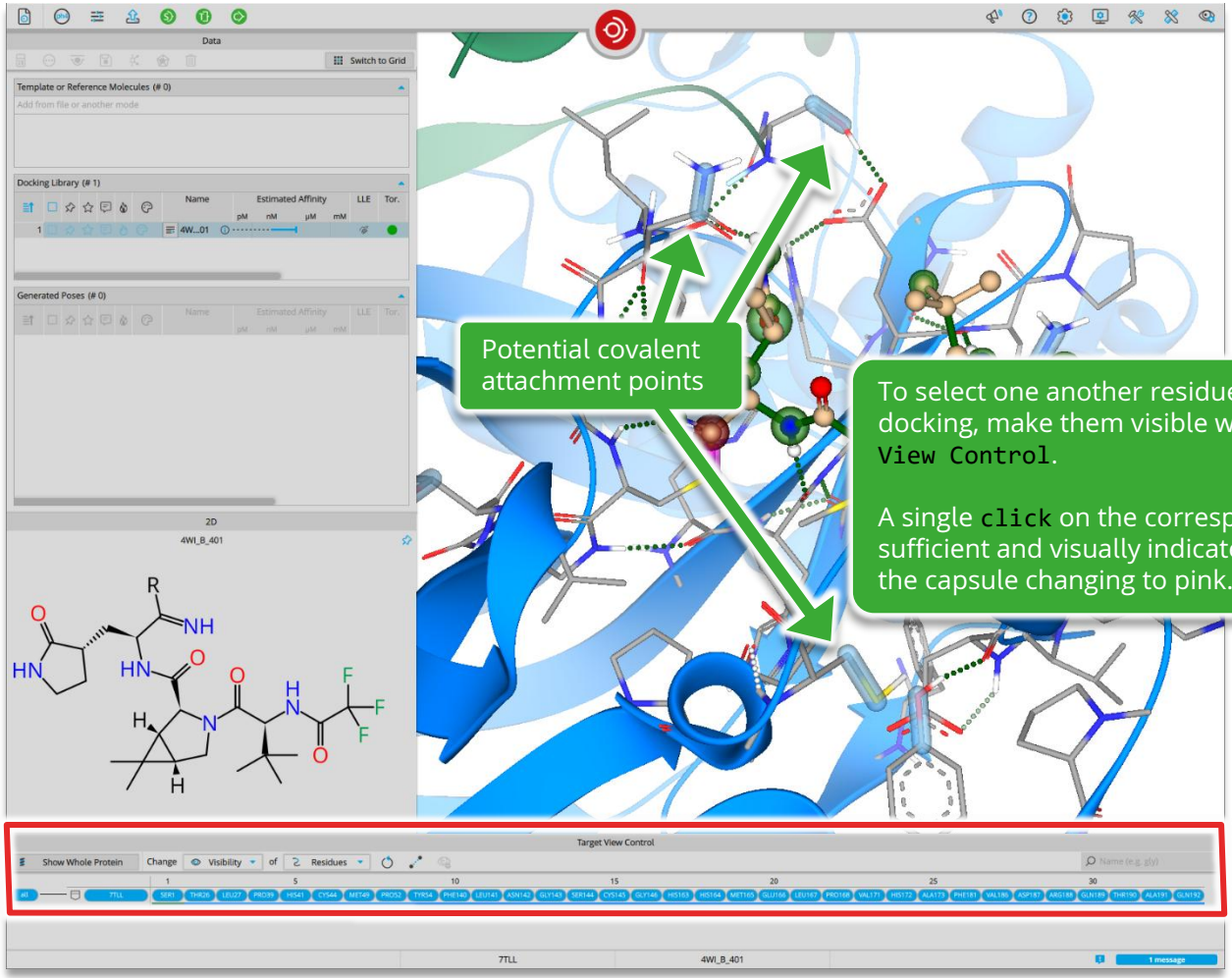
Mode Overview



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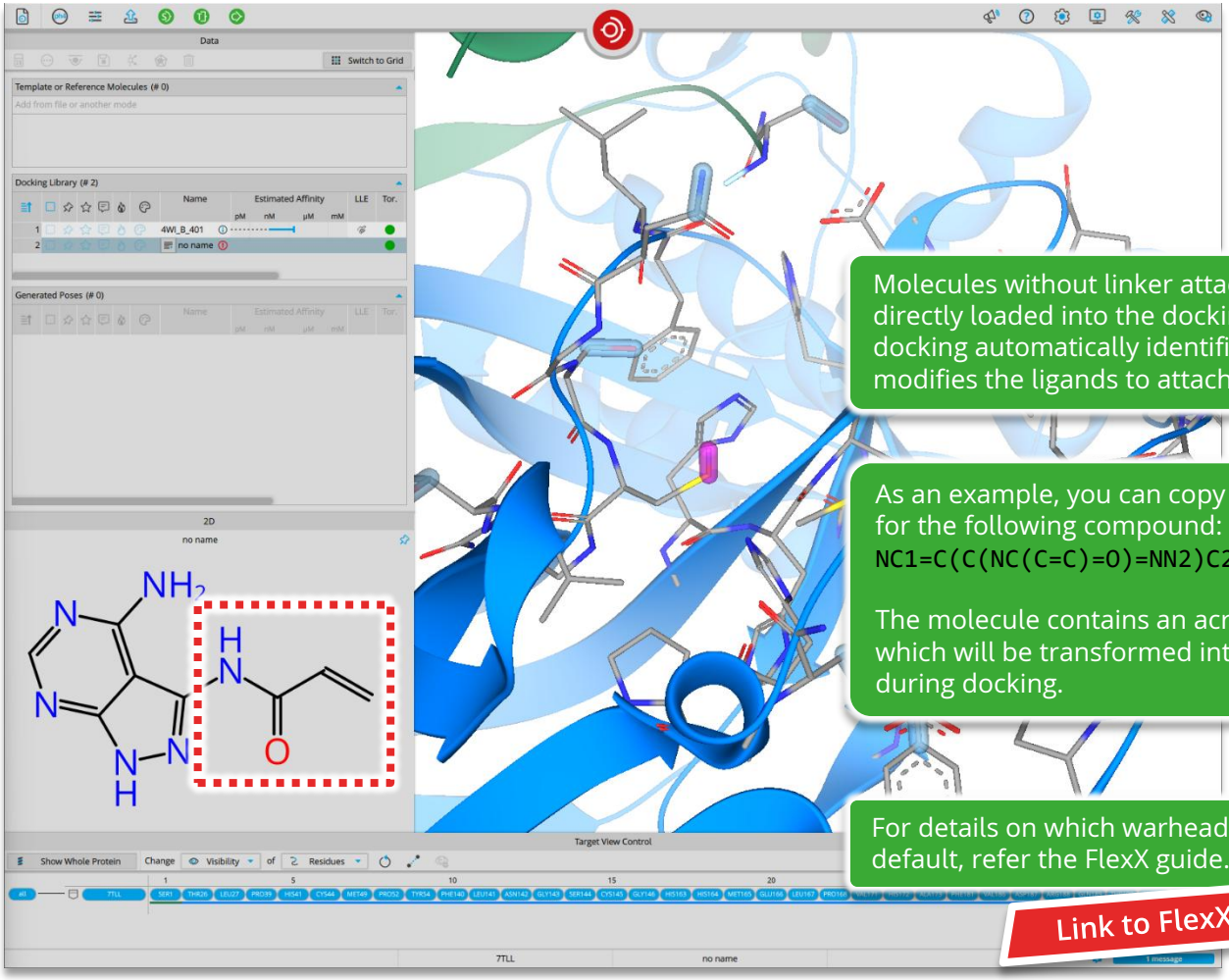
Mode Overview



Molecules without linker attachments can still be directly loaded into the docking library. Covalent docking automatically identifies warheads and modifies the ligands to attach a covalent linker.

As an example, you can copy and paste SMILES for the following compound:
`NC1=C(C(NC(C=C)=O)=NN2)C2=NC=N1`

The molecule contains an acrylamide warhead which will be transformed into its bound form during docking.

For details on which warheads are detected per default, refer the FlexX guide.

Link to FlexX Guide

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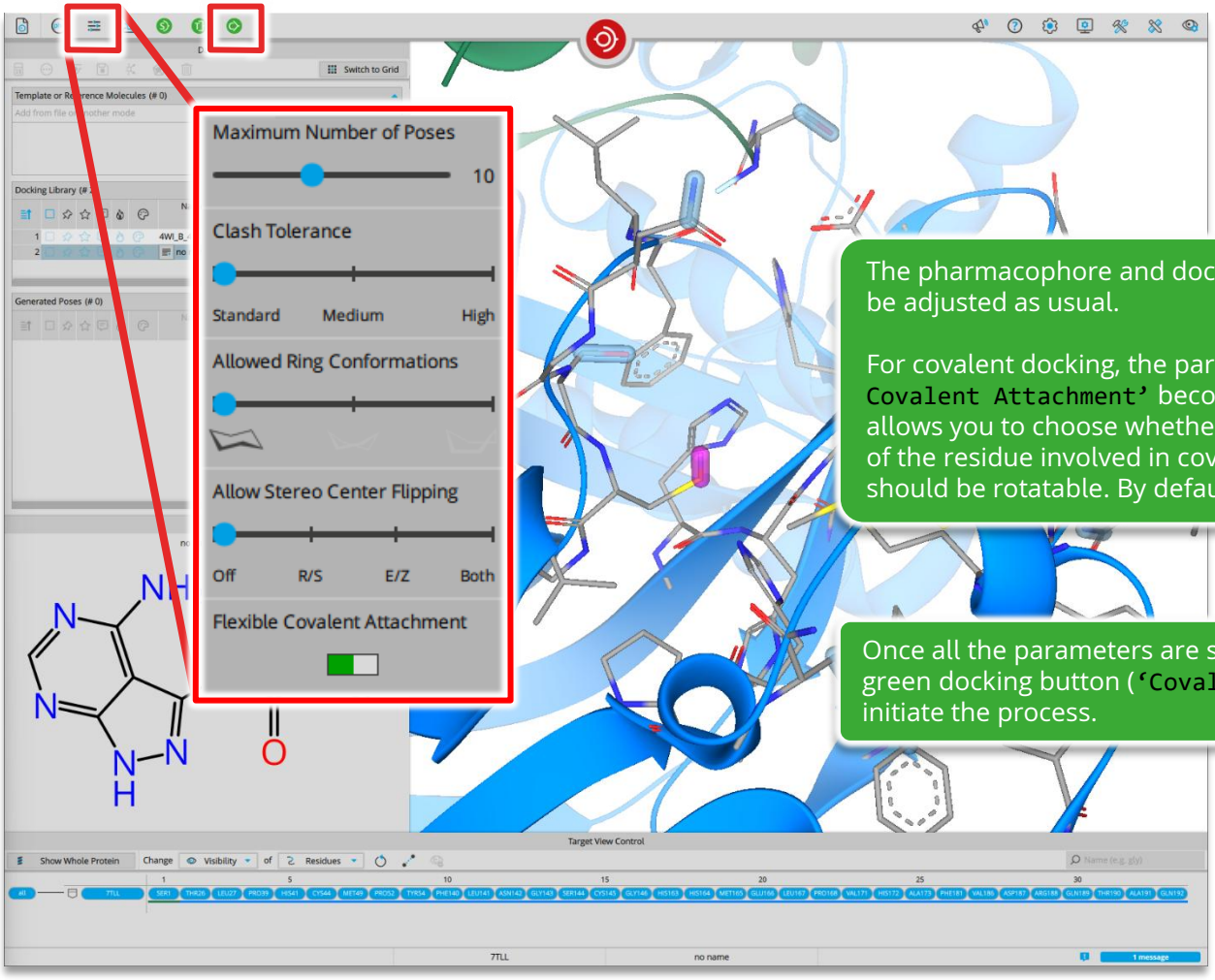
Mode Overview



The pharmacophore and docking parameters can be adjusted as usual.

For covalent docking, the parameter **‘Flexible Covalent Attachment’** becomes relevant. This allows you to choose whether the terminal bond of the residue involved in covalent attachment should be rotatable. By default, it is set to flexible.

Once all the parameters are set, click the third green docking button (**‘Covalent docking’**) to initiate the process.

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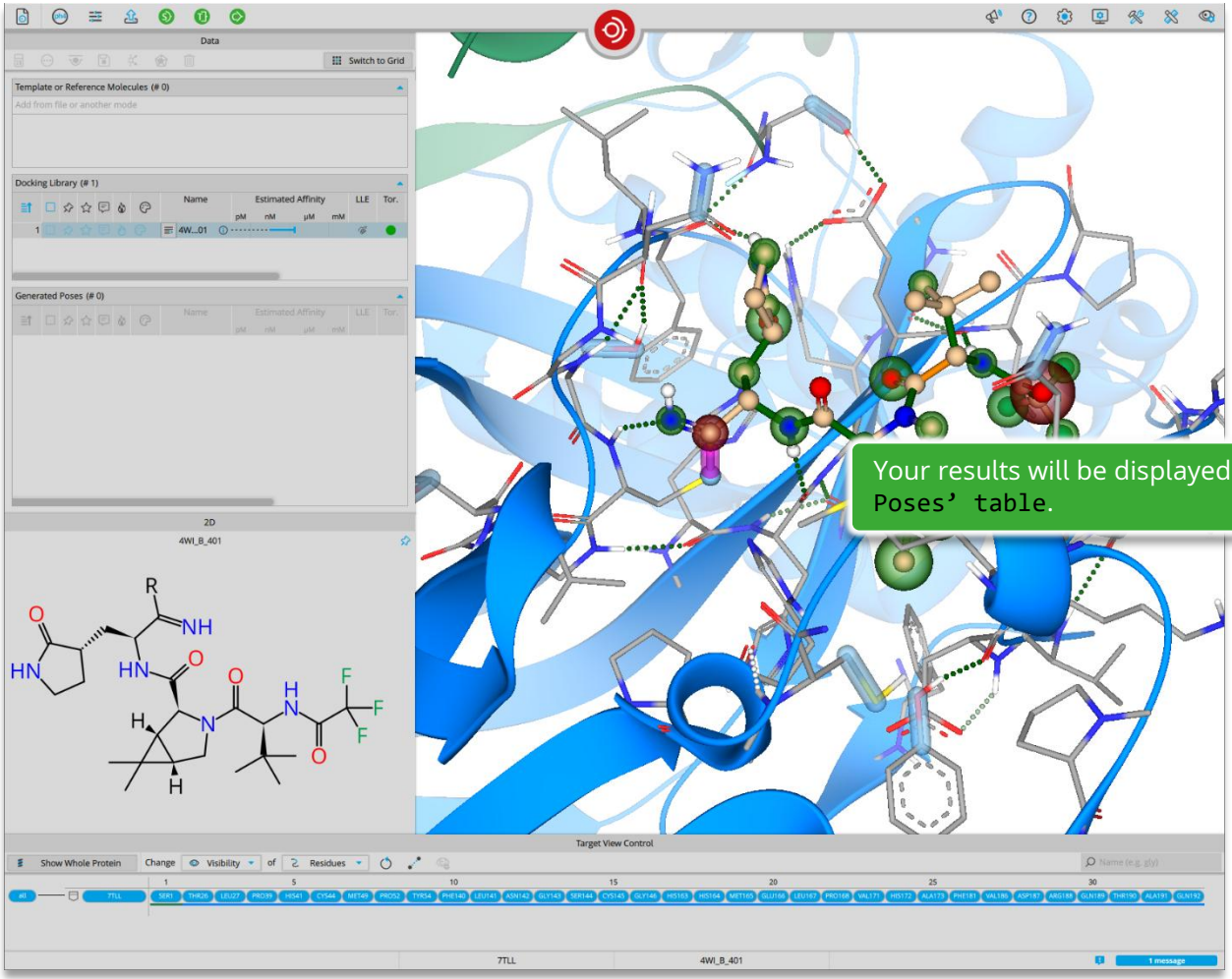
Mode Overview



Your results will be displayed in the ‘Generated Poses’ table.

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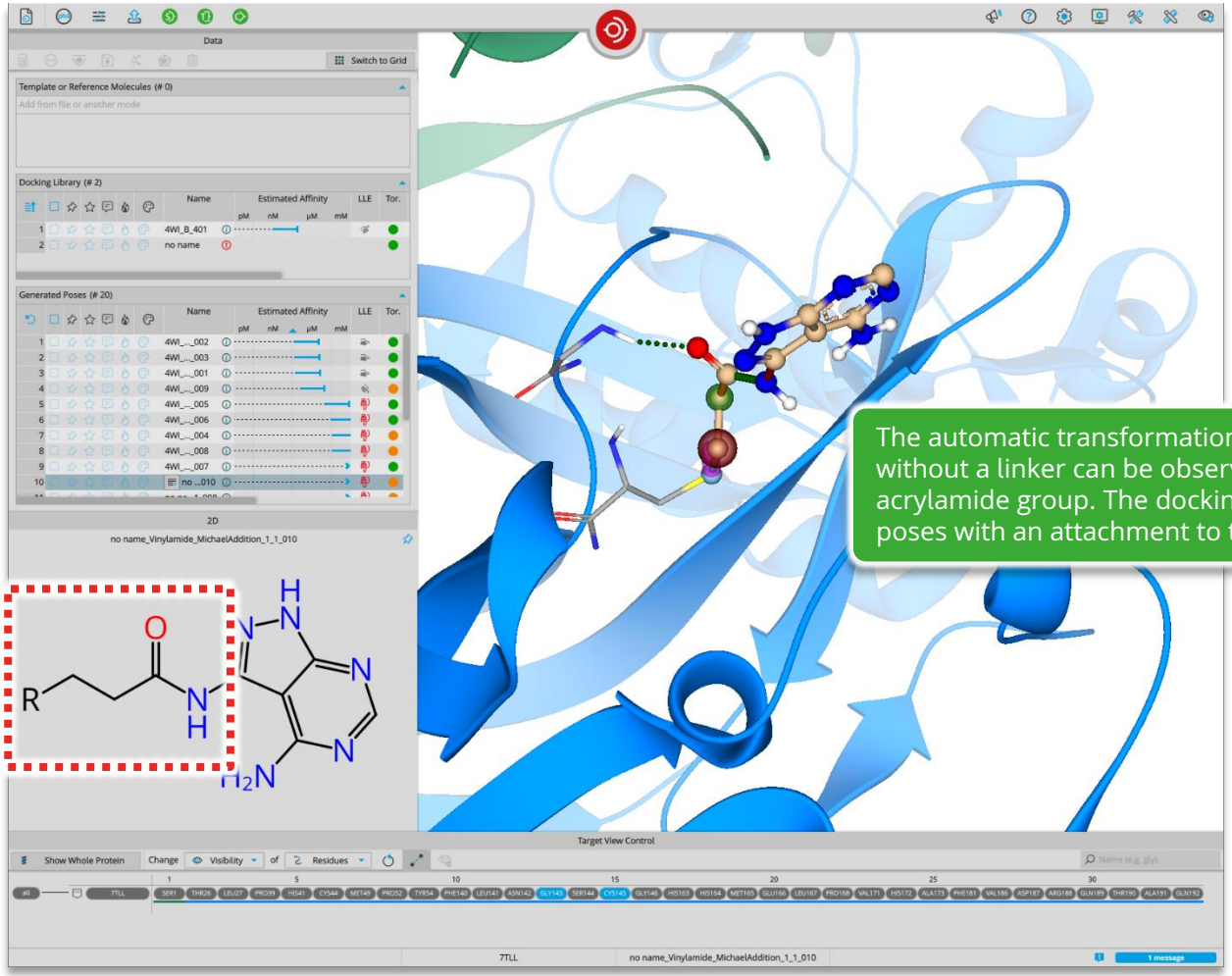
Mode Overview



The automatic transformation of the ligand without a linker can be observed for the acrylamide group. The docking has generated poses with an attachment to this linker.

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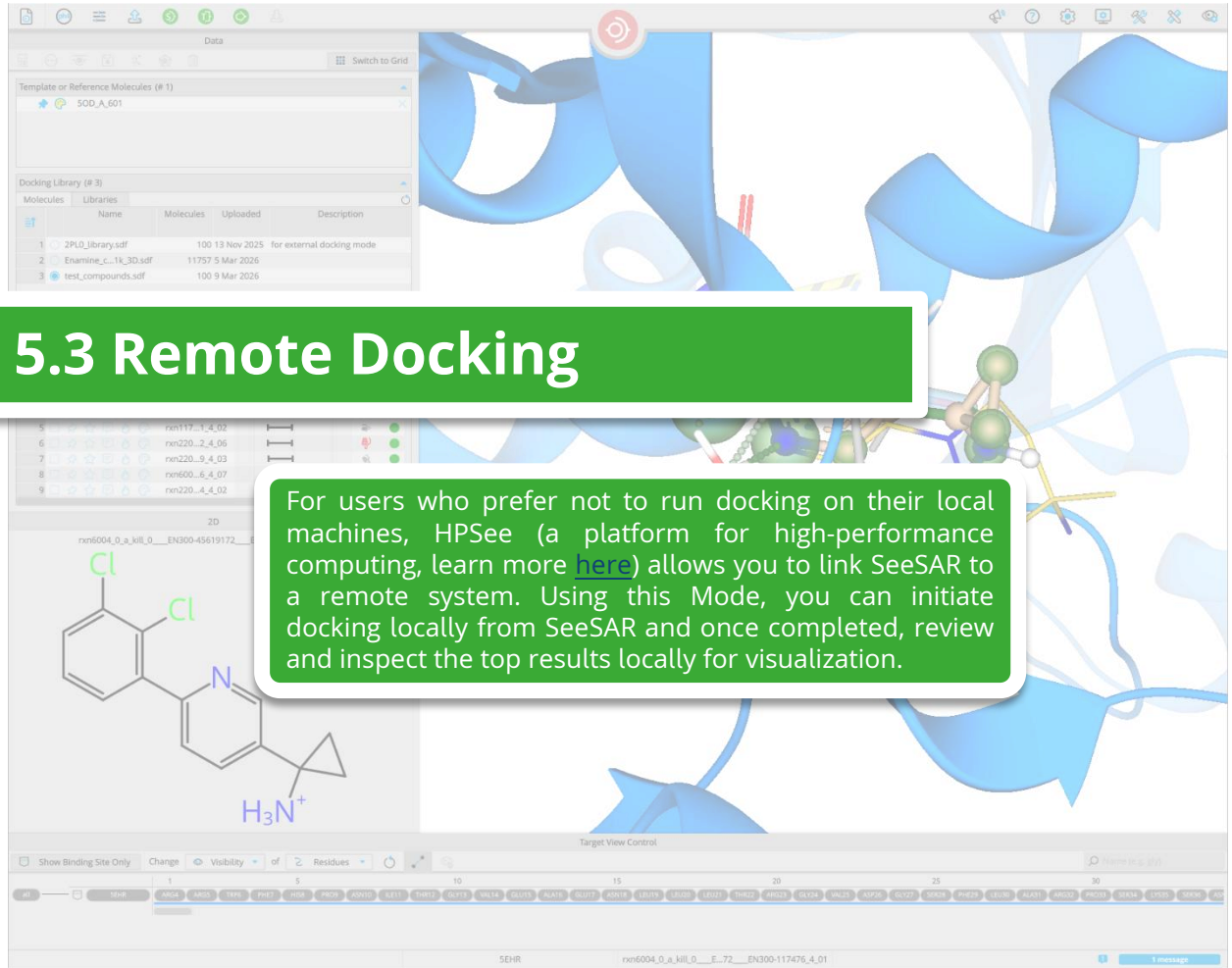
Mode Overview

5.3 Remote Docking



For users who prefer not to run docking on their local machines, HPSee (a platform for high-performance computing, learn more here) allows you to link SeeSAR to a remote system. Using this Mode, you can initiate docking locally from SeeSAR and once completed, review and inspect the top results locally for visualization.

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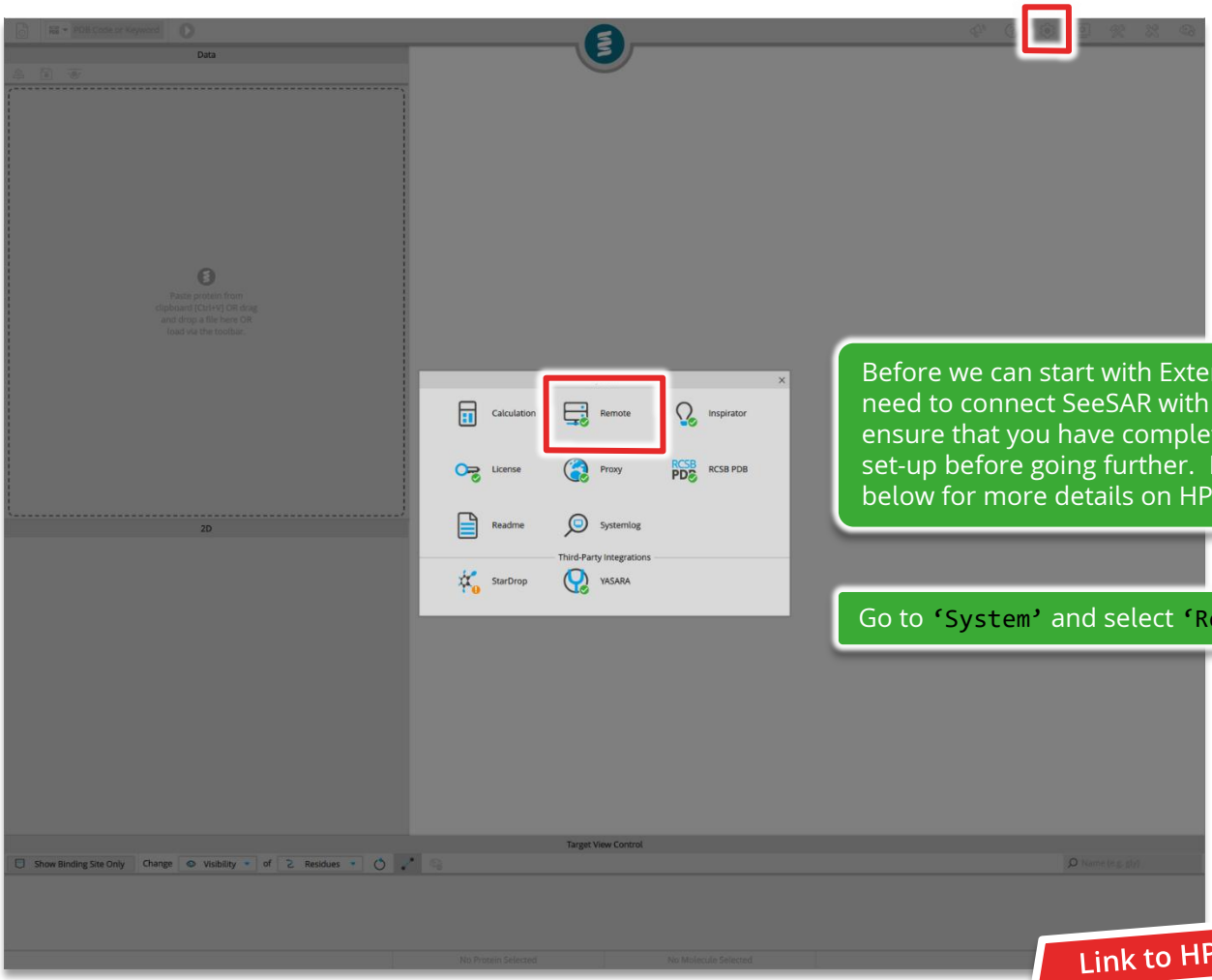
Mode Overview



Before we can start with External Docking, we need to connect SeeSAR with HPSee. Please ensure that you have completed your HPSee set-up before going further. Refer to the guide below for more details on HPSee.

Go to ‘System’ and select ‘Remote’.

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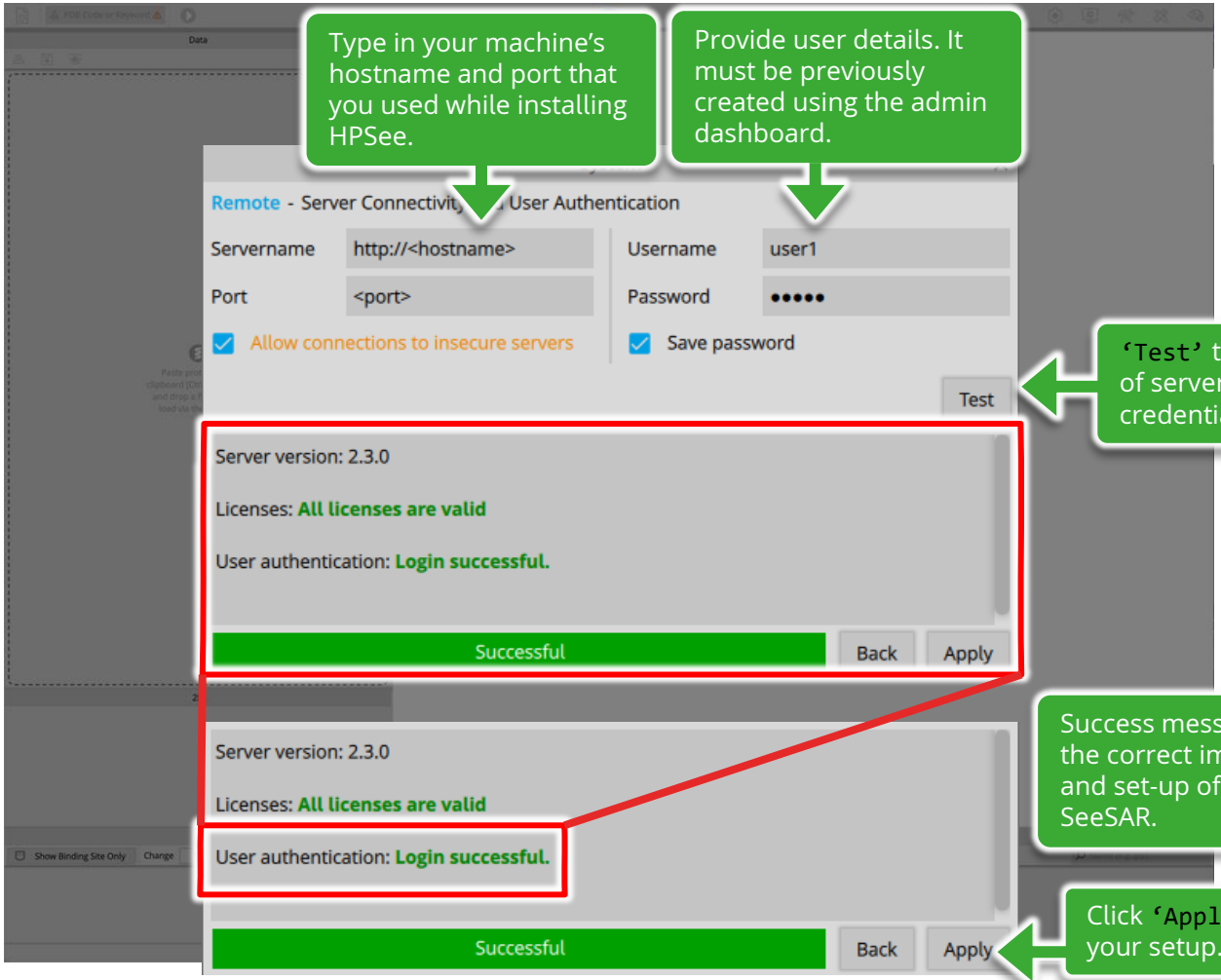
Mode Overview

Link to HPSee Guide



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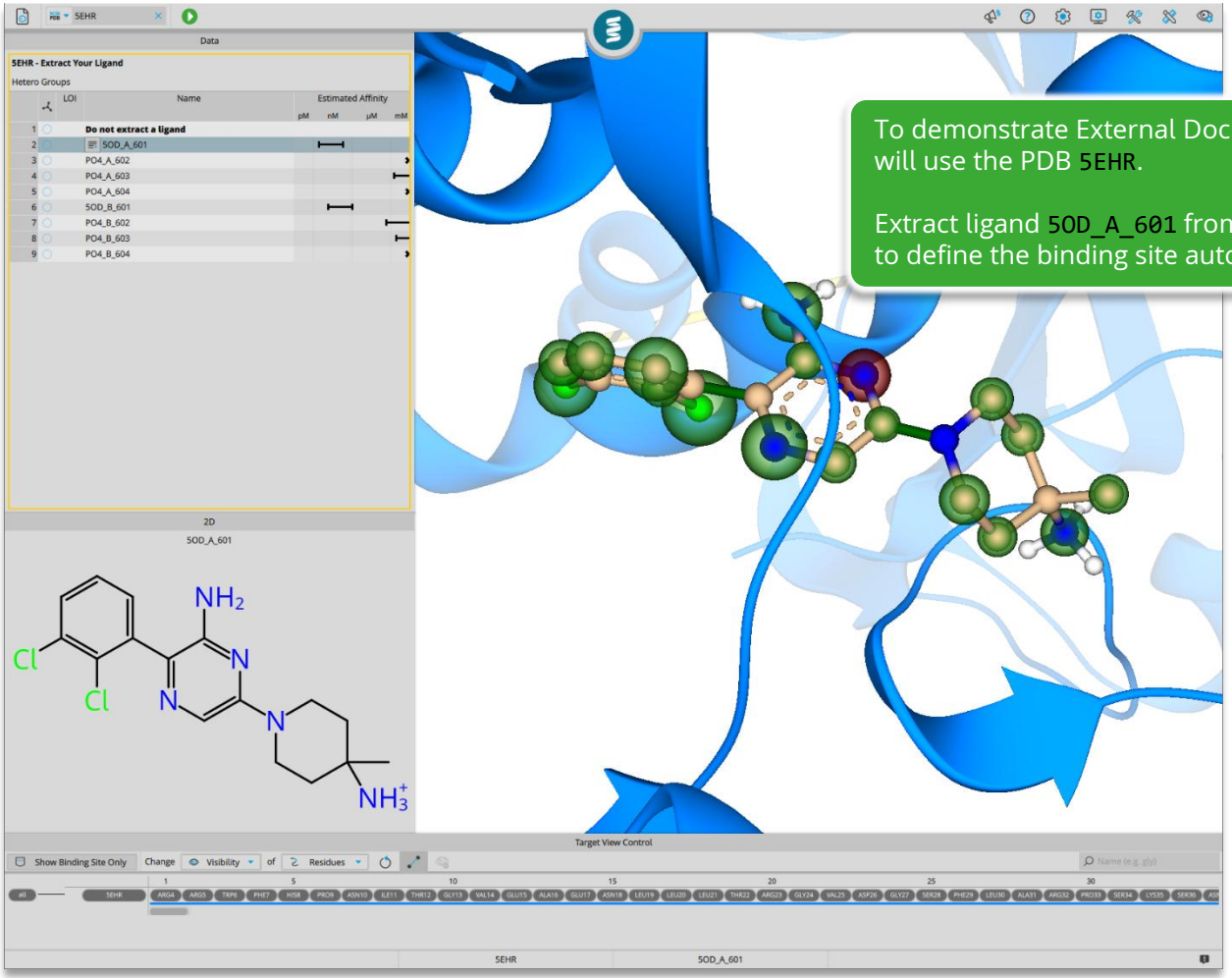
Mode Overview



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Mode Overview

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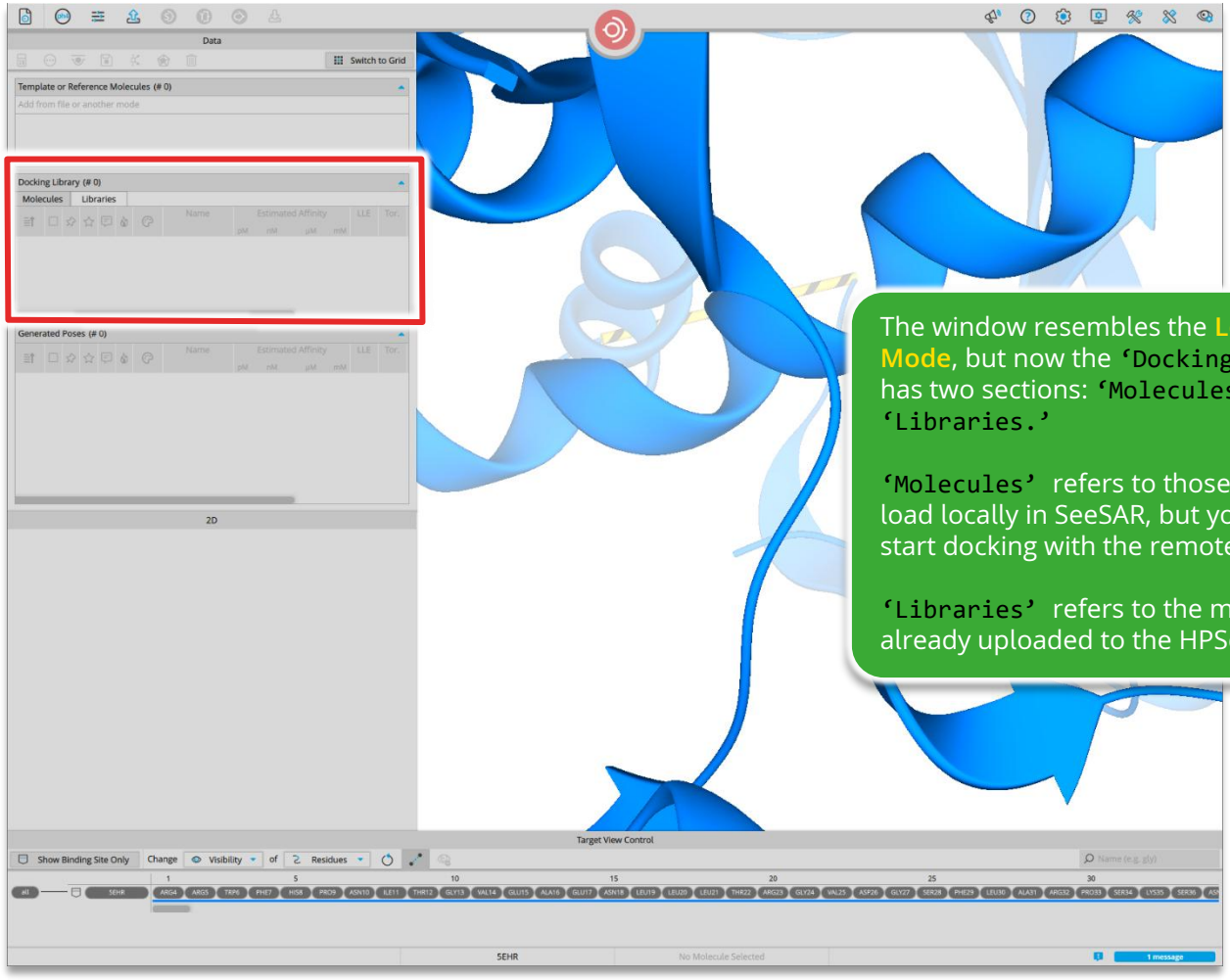
Mode Overview



The window resembles the **Local Docking Mode**, but now the `'Docking Library'` has two sections: `'Molecules'` and `'Libraries.'`

`'Molecules'` refers to those molecules you load locally in SeeSAR, but you intend to start docking with the remote machine.

`'Libraries'` refers to the molecule library already uploaded to the HPSee server.

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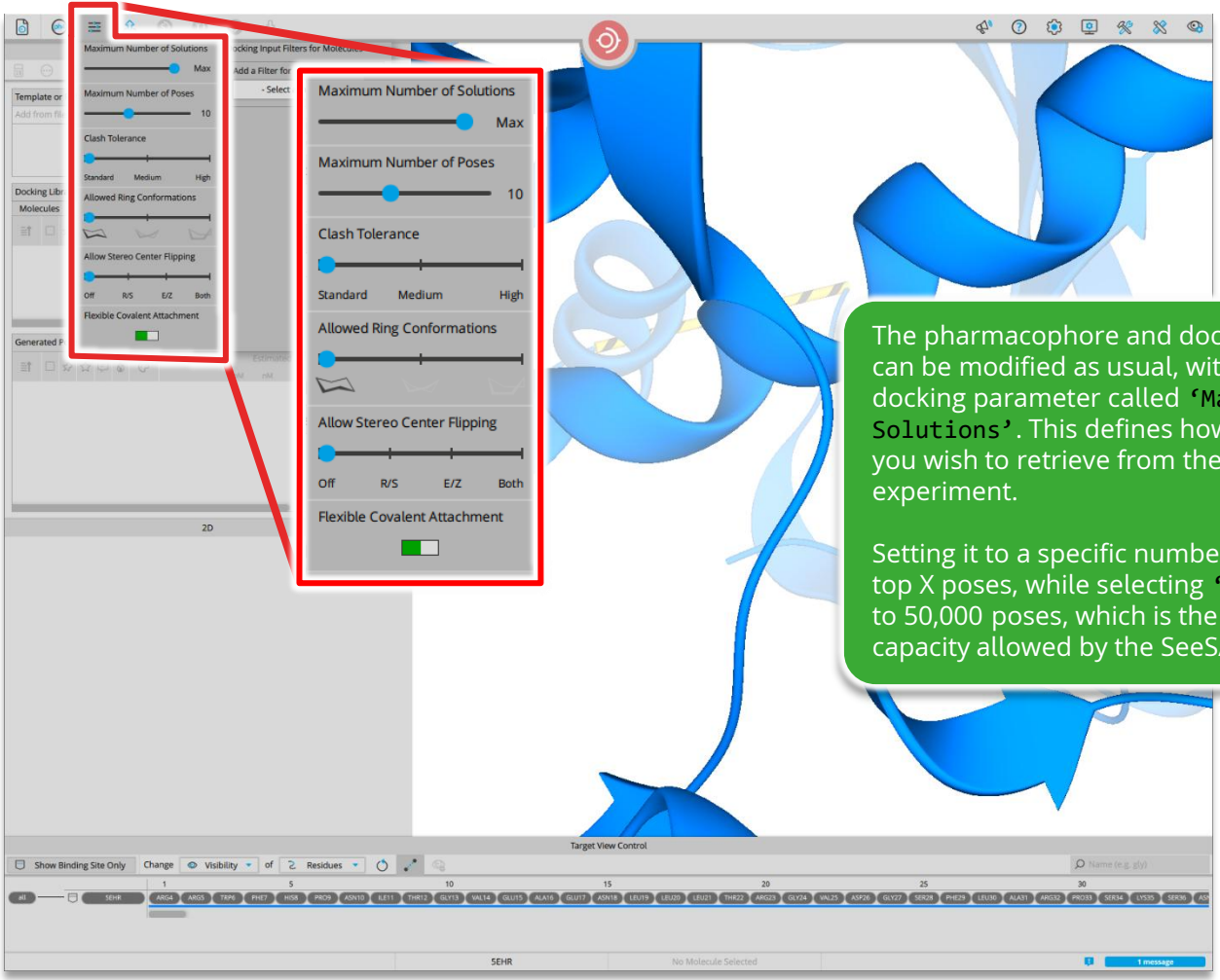
Mode Overview



The pharmacophore and docking parameters can be modified as usual, with an additional docking parameter called **‘Maximum Number of Solutions’**. This defines how many top poses you wish to retrieve from the docking experiment.

Setting it to a specific number X will return the top X poses, while selecting **‘Max’** retrieves up to 50,000 poses, which is the maximum capacity allowed by the SeeSAR table.

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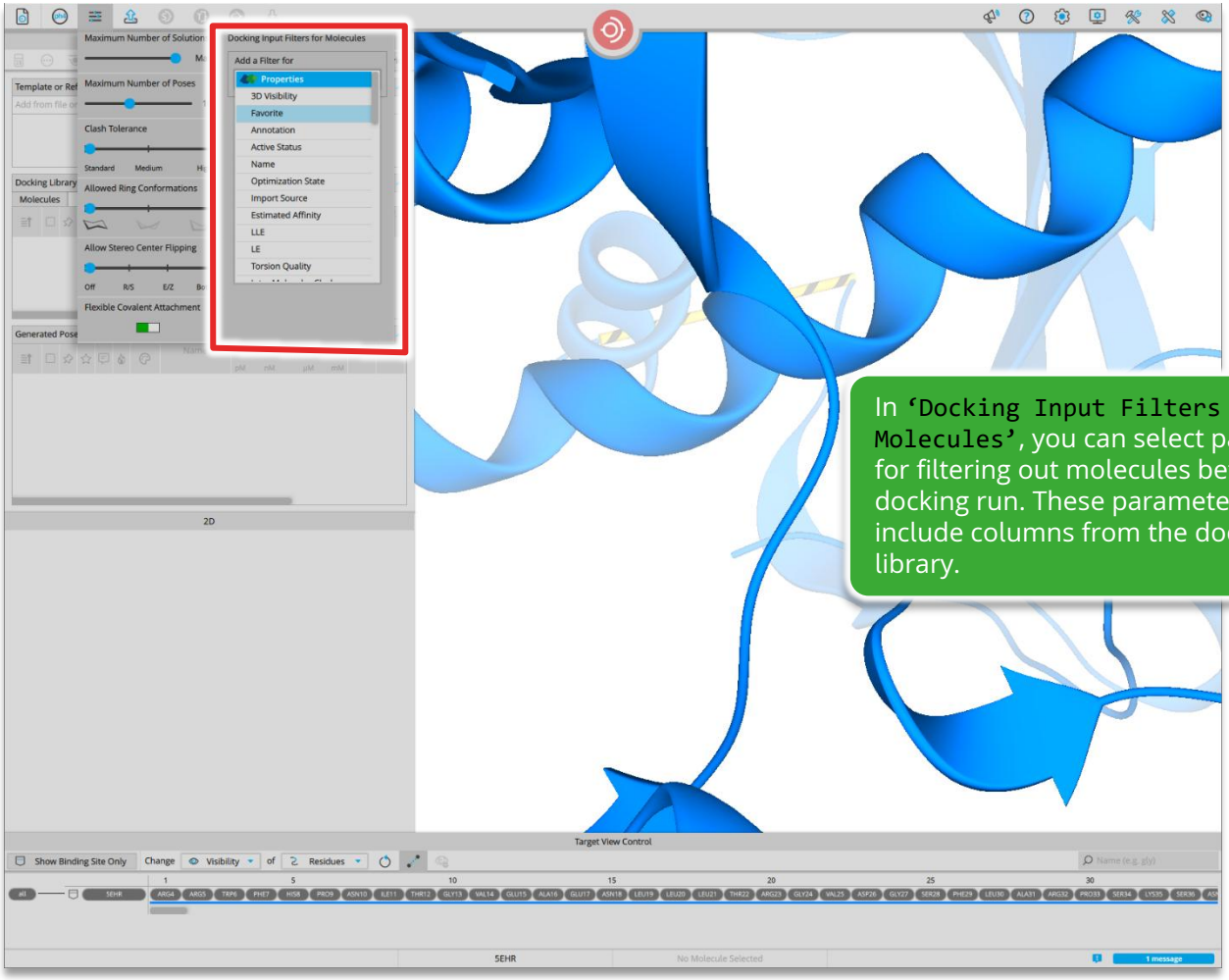
Mode Overview



In ‘Docking Input Filters for Molecules’, you can select parameters for filtering out molecules before the docking run. These parameters can also include columns from the docking library.

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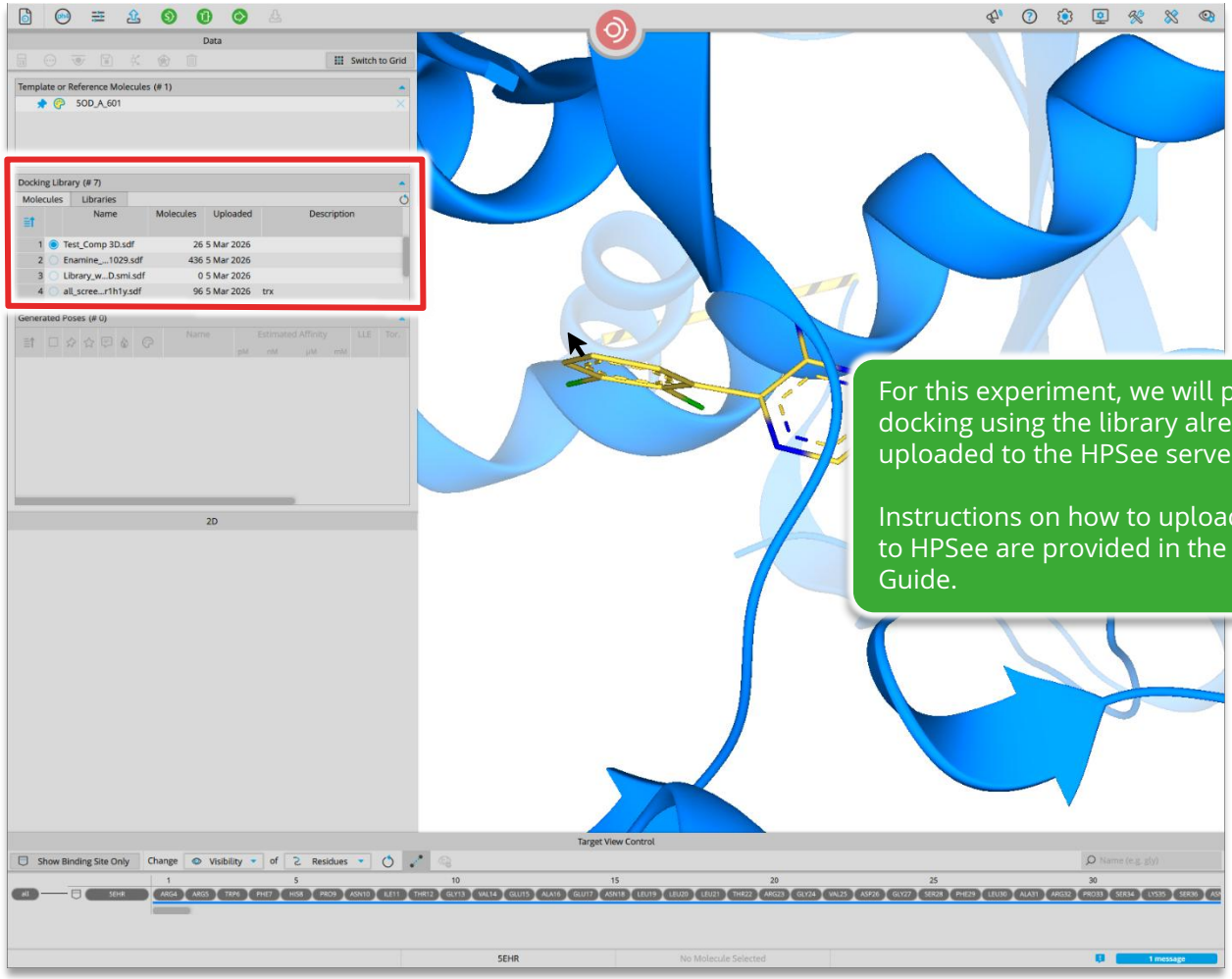
Mode Overview



For this experiment, we will perform docking using the library already uploaded to the HPSee server.

Instructions on how to upload a library to HPSee are provided in the HPSee Guide.

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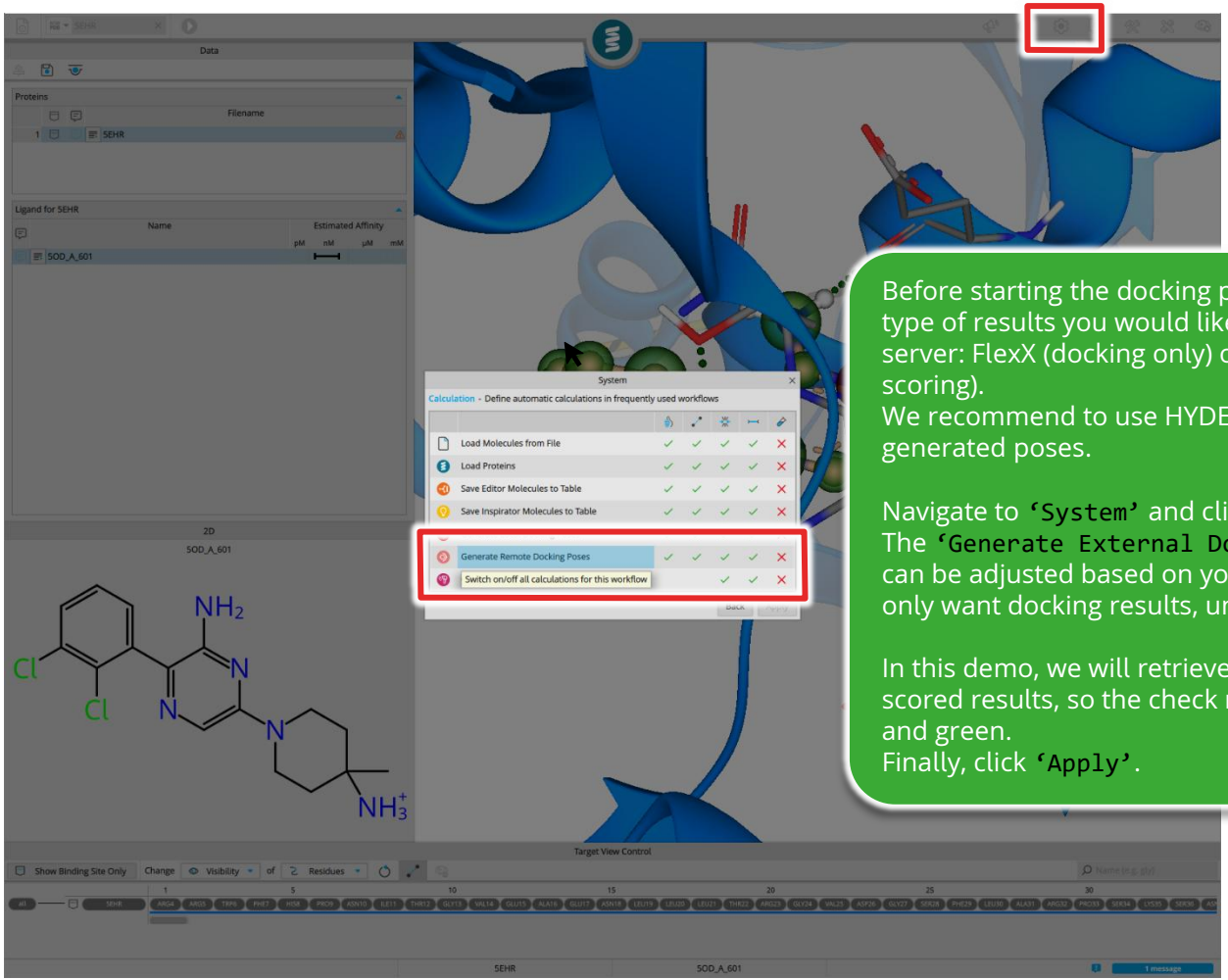
Mode Overview



Before starting the docking process, decide what type of results you would like to retrieve from the server: FlexX (docking only) or HYDE (docking and scoring).
We recommend to use HYDE for rescoring of FlexX generated poses.

Navigate to **'System'** and click on **'Calculation'**. The **'Generate External Docking Poses'** option can be adjusted based on your preference. If you only want docking results, uncheck the boxes.

In this demo, we will retrieve both docked and scored results, so the check marks are enabled and green.
Finally, click **'Apply'**.

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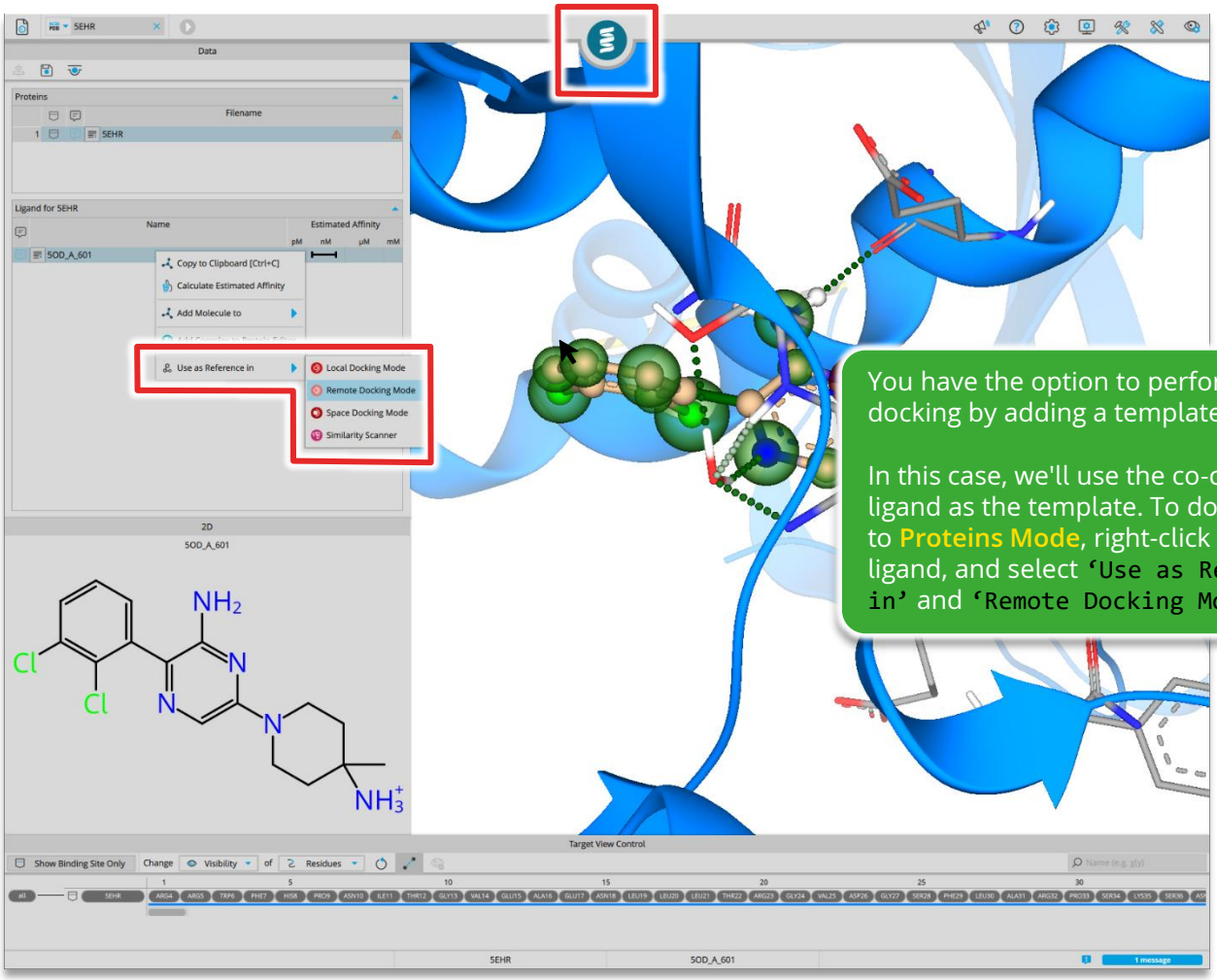
Mode Overview



You have the option to perform template docking by adding a template molecule.

In this case, we'll use the co-crystallized ligand as the template. To do this, return to **Proteins Mode**, right-click on the ligand, and select ‘Use as Reference in’ and ‘Remote Docking Mode’.

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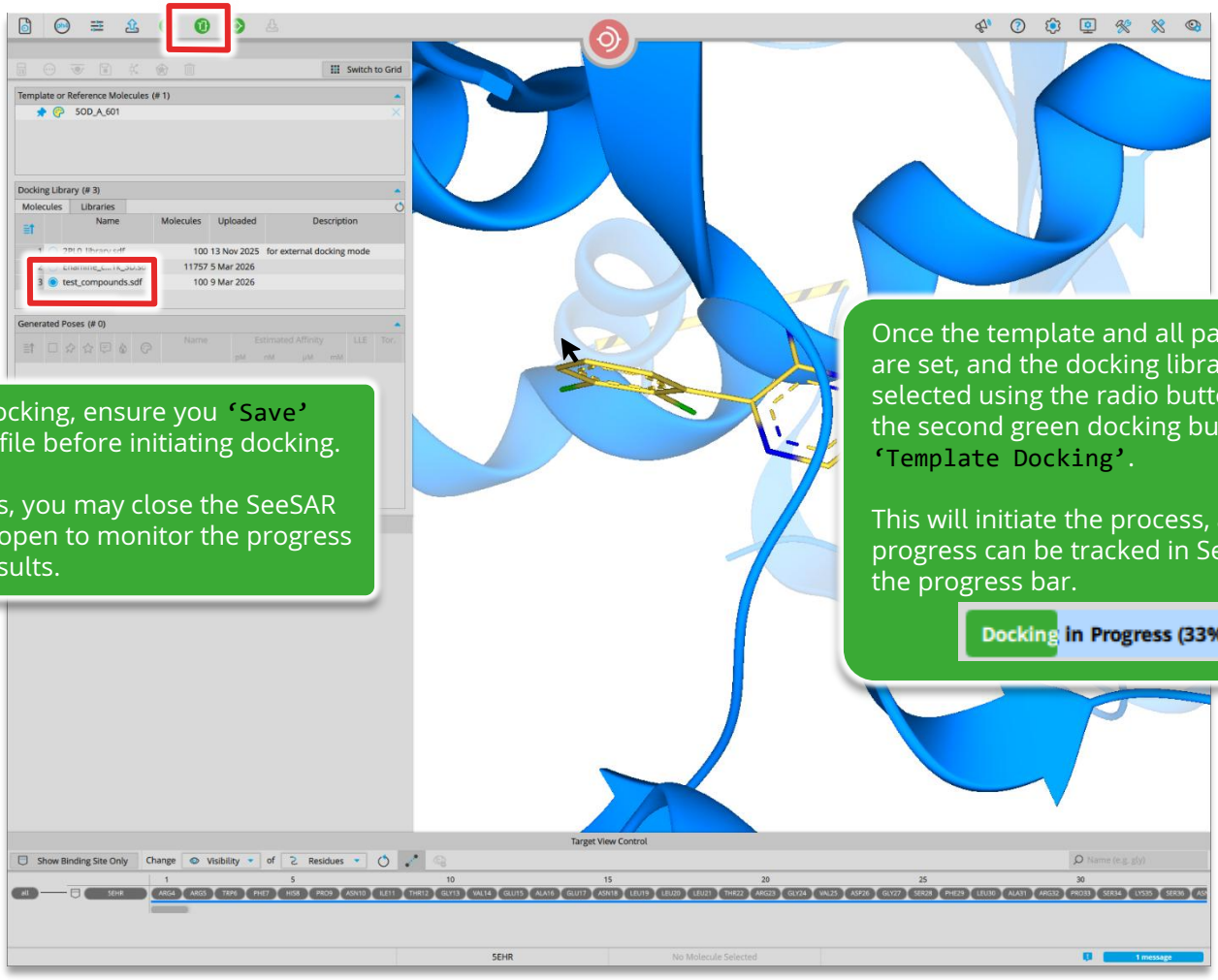
Mode Overview



After starting the docking, ensure you **'Save'** the SeeSAR project file before initiating docking.

Once the run begins, you may close the SeeSAR project and later reopen to monitor the progress or download the results.

Once the template and all parameters are set, and the docking library is selected using the radio button, **click** the second green docking button: **'Template Docking'**.

This will initiate the process, and the progress can be tracked in SeeSAR via the progress bar.

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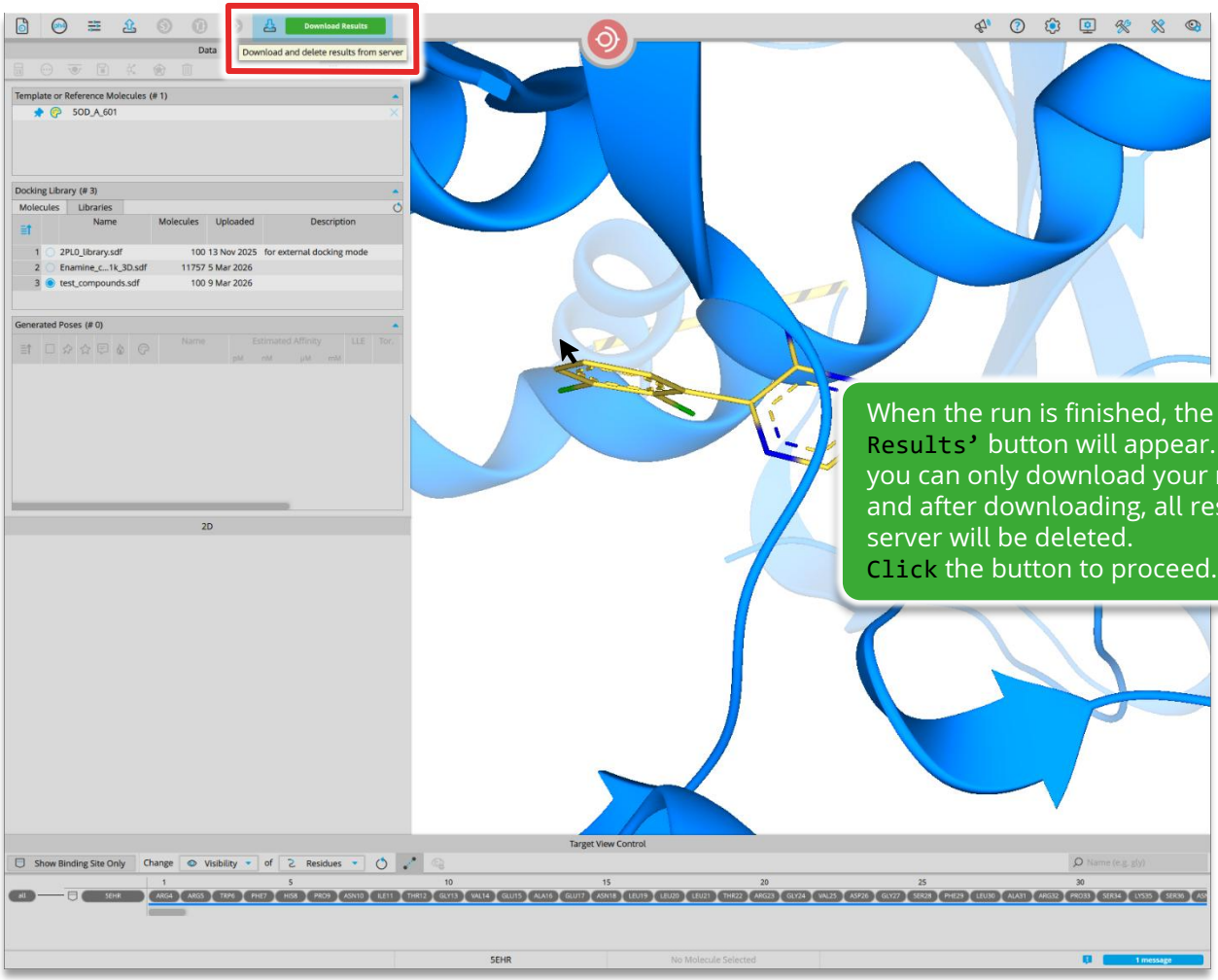
Mode Overview



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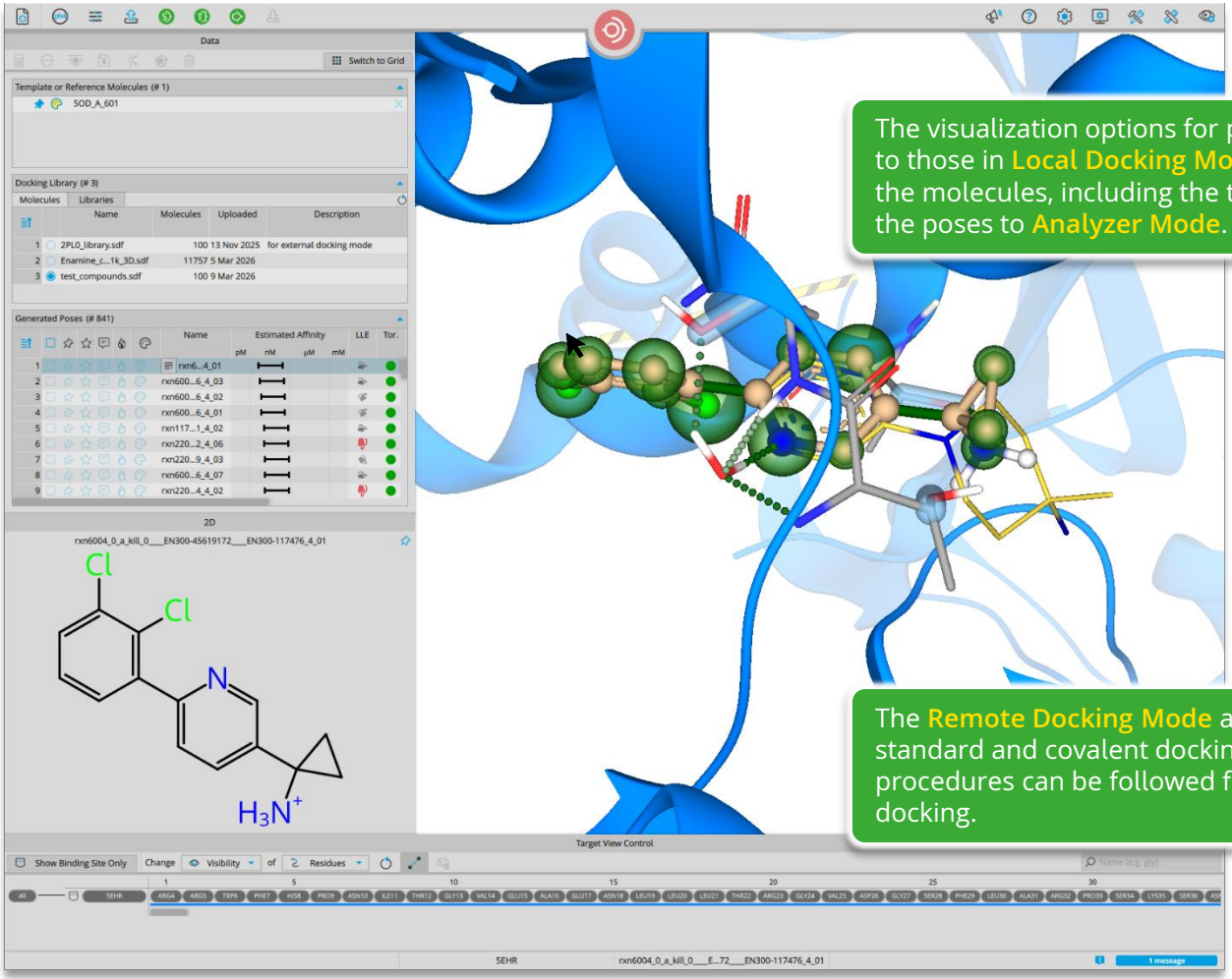
Mode Overview



The visualization options for poses are similar to those in **Local Docking Mode**. You can color the molecules, including the template, or move the poses to **Analyzer Mode**.

The **Remote Docking Mode** also supports standard and covalent docking. Similar procedures can be followed for these types of docking.

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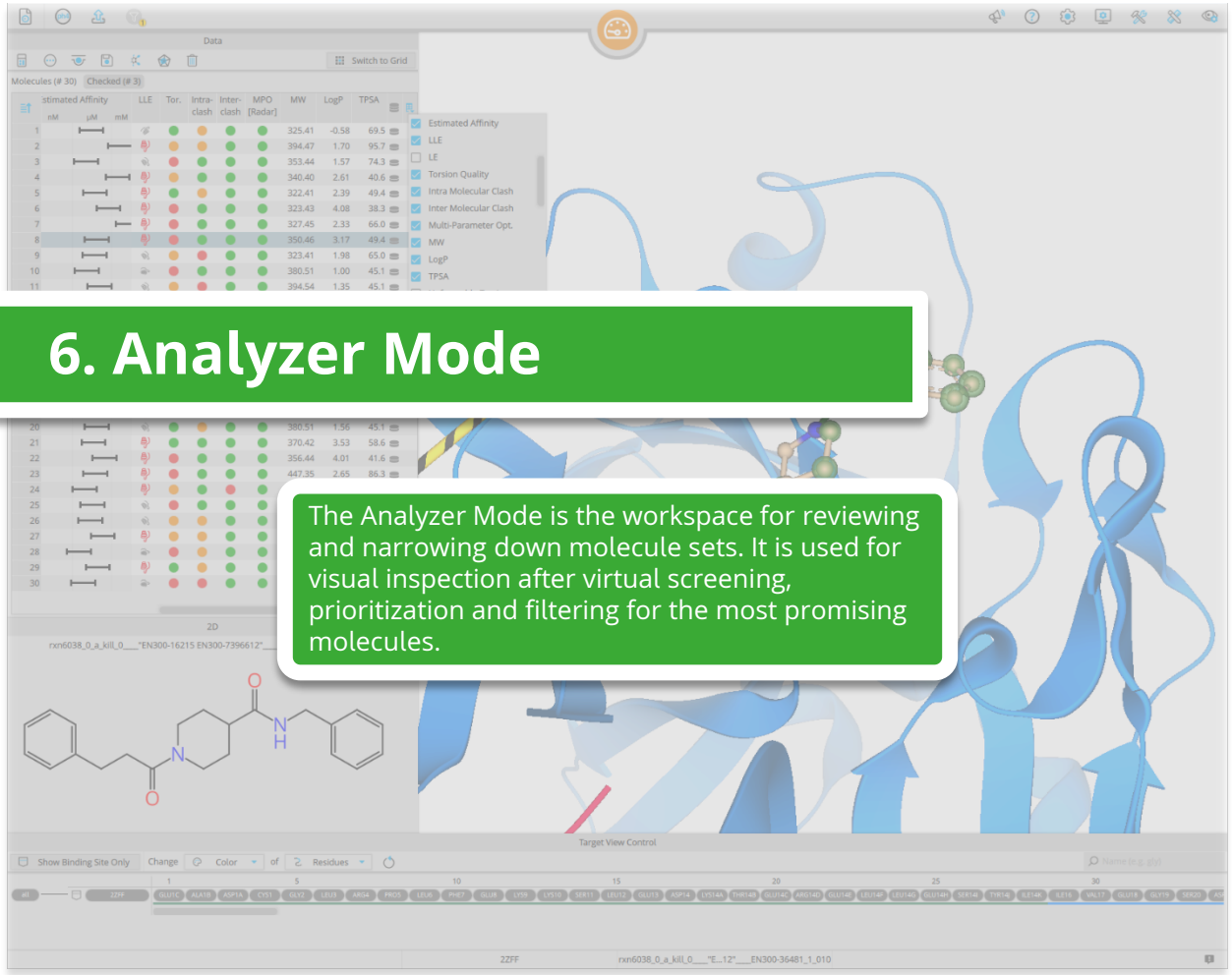
Mode Overview

6. Analyzer Mode



The Analyzer Mode is the workspace for reviewing and narrowing down molecule sets. It is used for visual inspection after virtual screening, prioritization and filtering for the most promising molecules.

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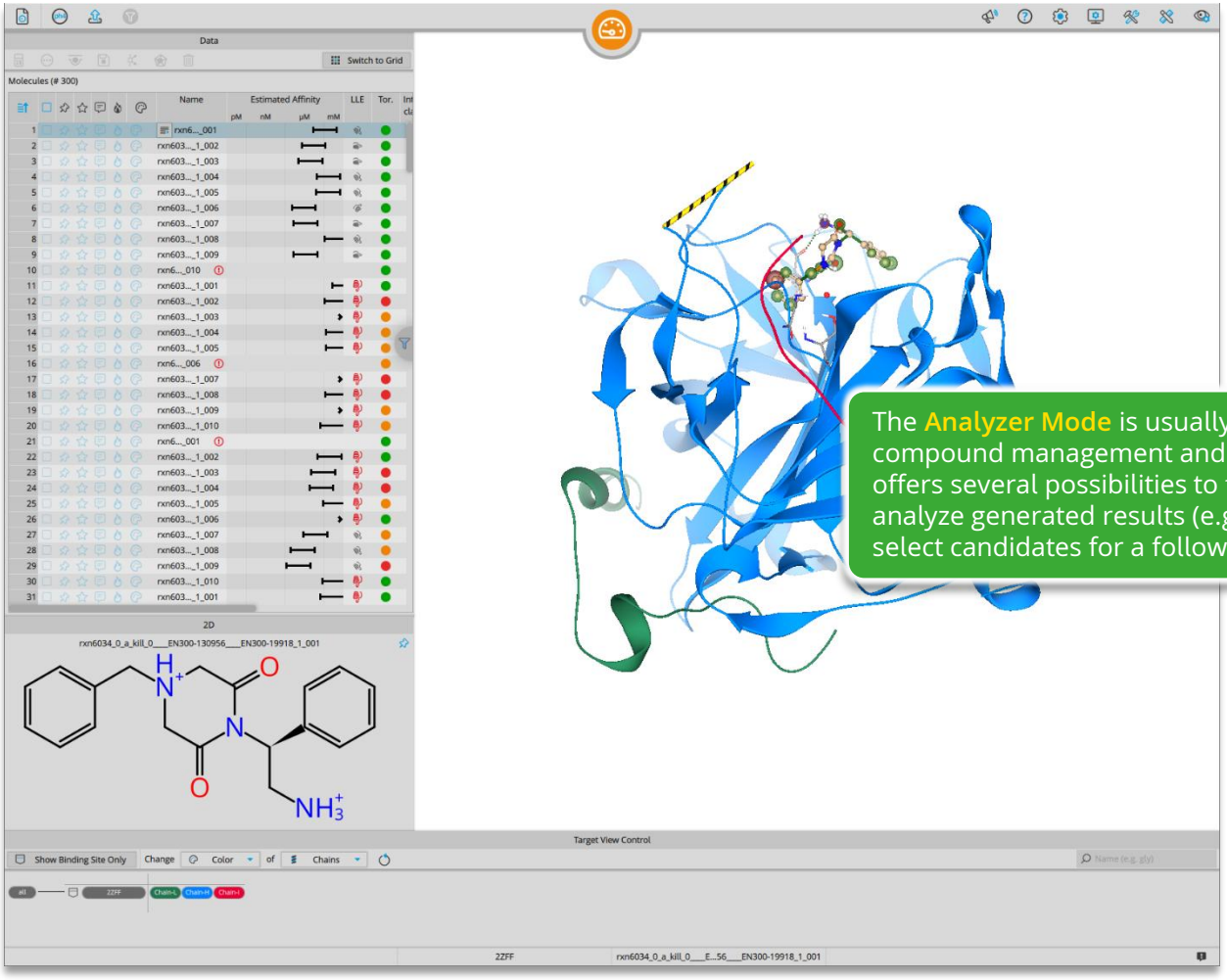
Mode Overview



The **Analyzer Mode** is usually used for compound management and orchestration. It offers several possibilities to filter sets and analyze generated results (e.g. from docking to select candidates for a follow up).

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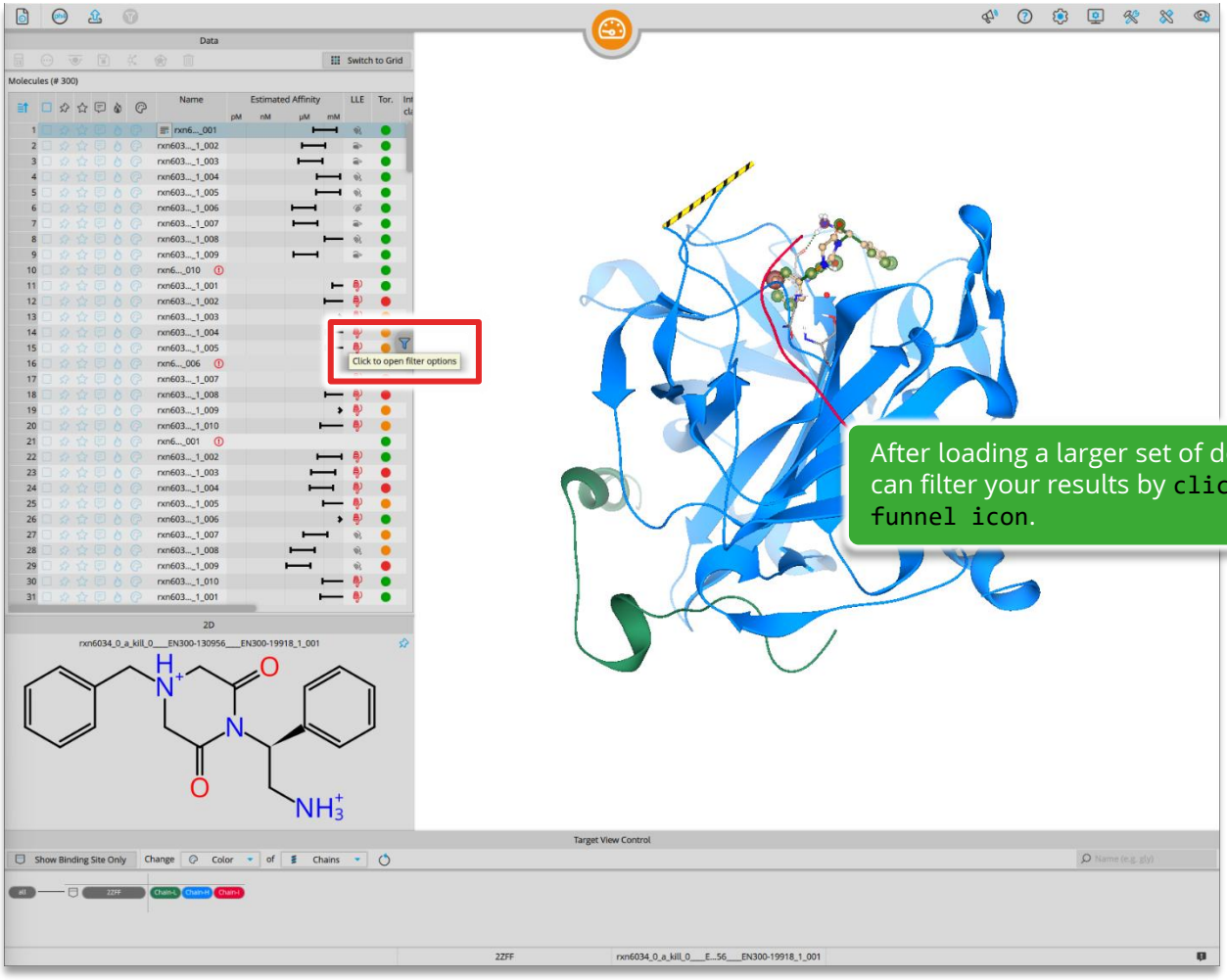
Mode Overview



After loading a larger set of docking results, you can filter your results by `clicking` on the `funnel icon`.

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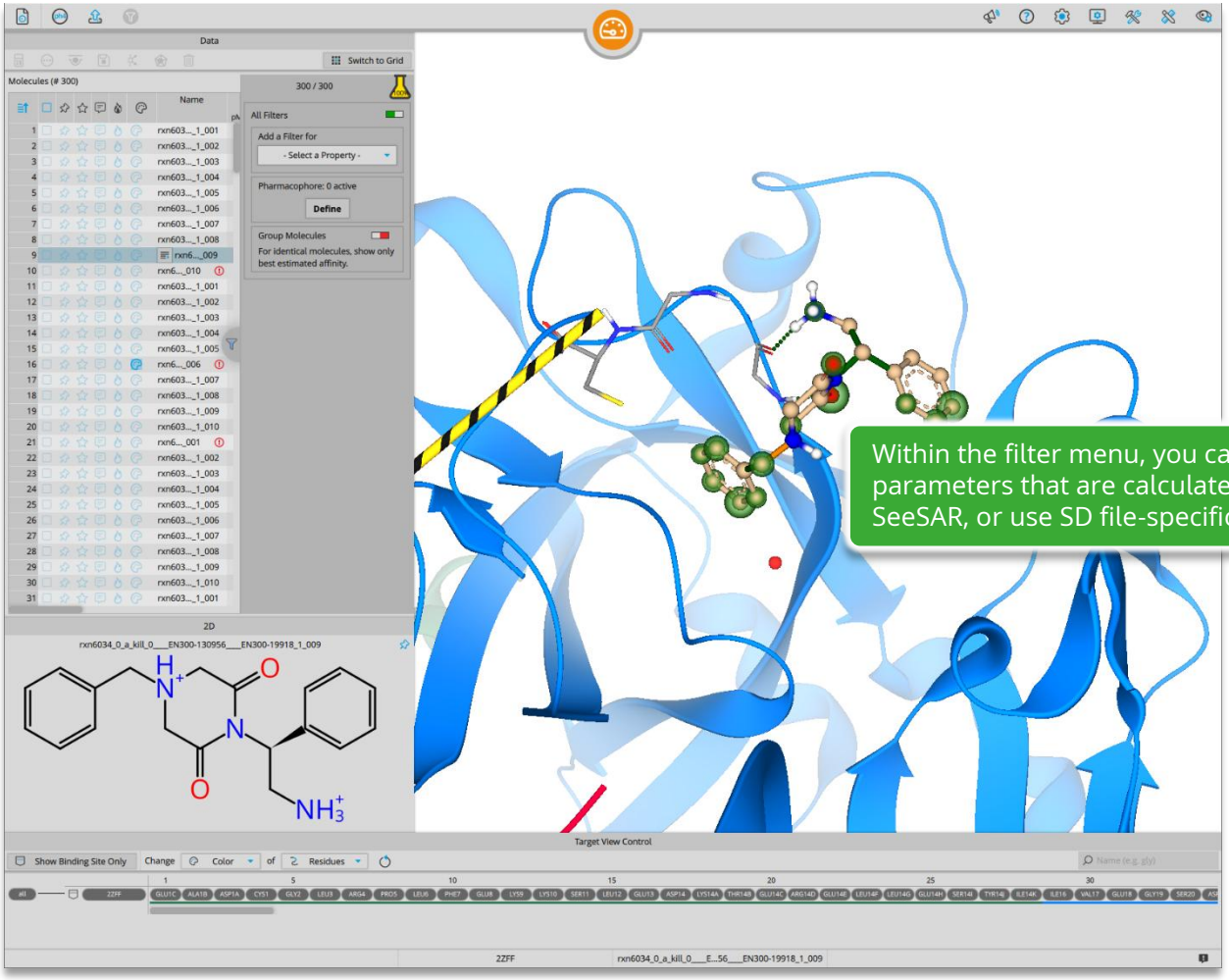
Mode Overview



Within the filter menu, you can select various parameters that are calculated automatically by SeeSAR, or use SD file-specific column entries.

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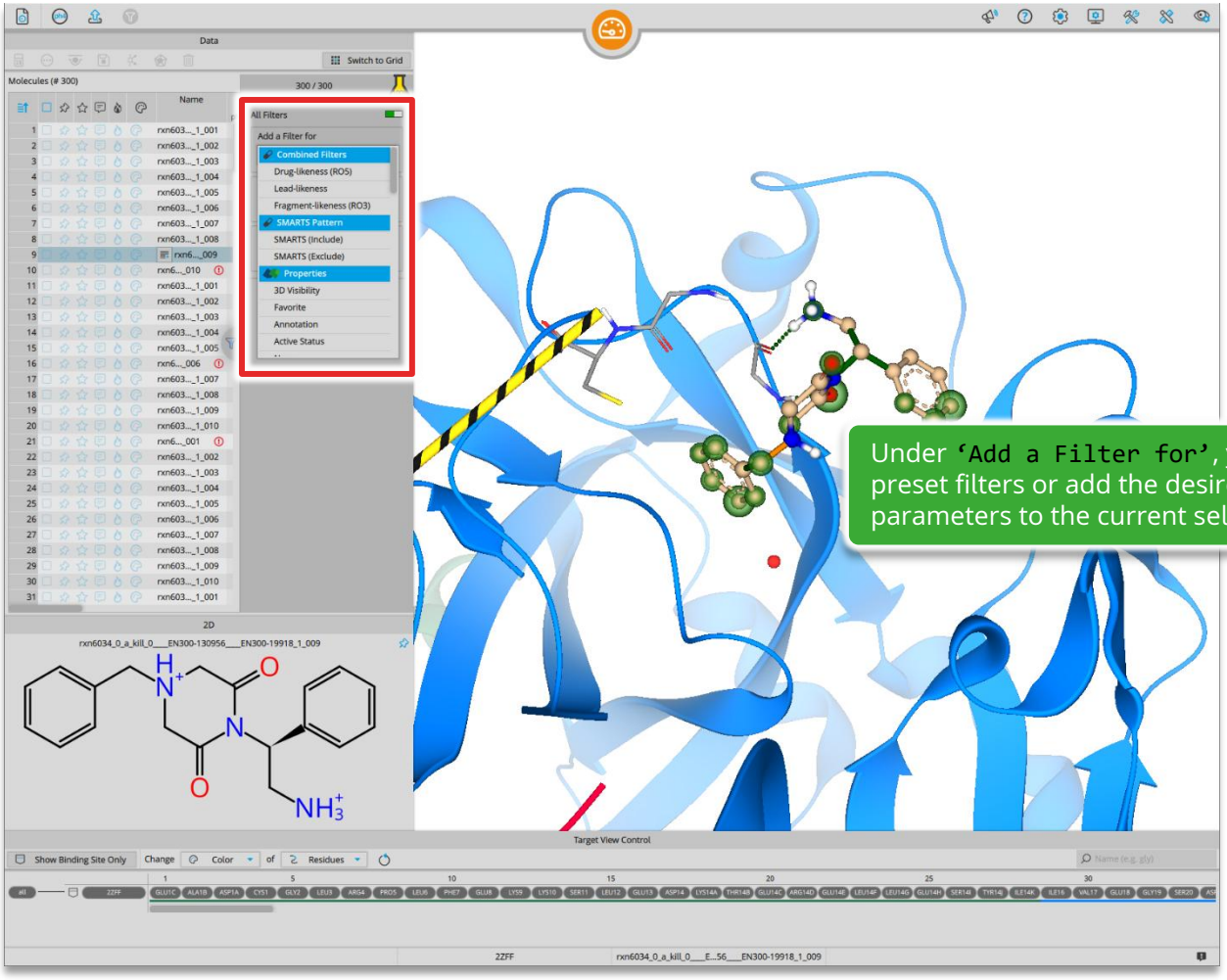
Mode Overview



Under ‘Add a Filter for’, you can select preset filters or add the desired filter parameters to the current selection.

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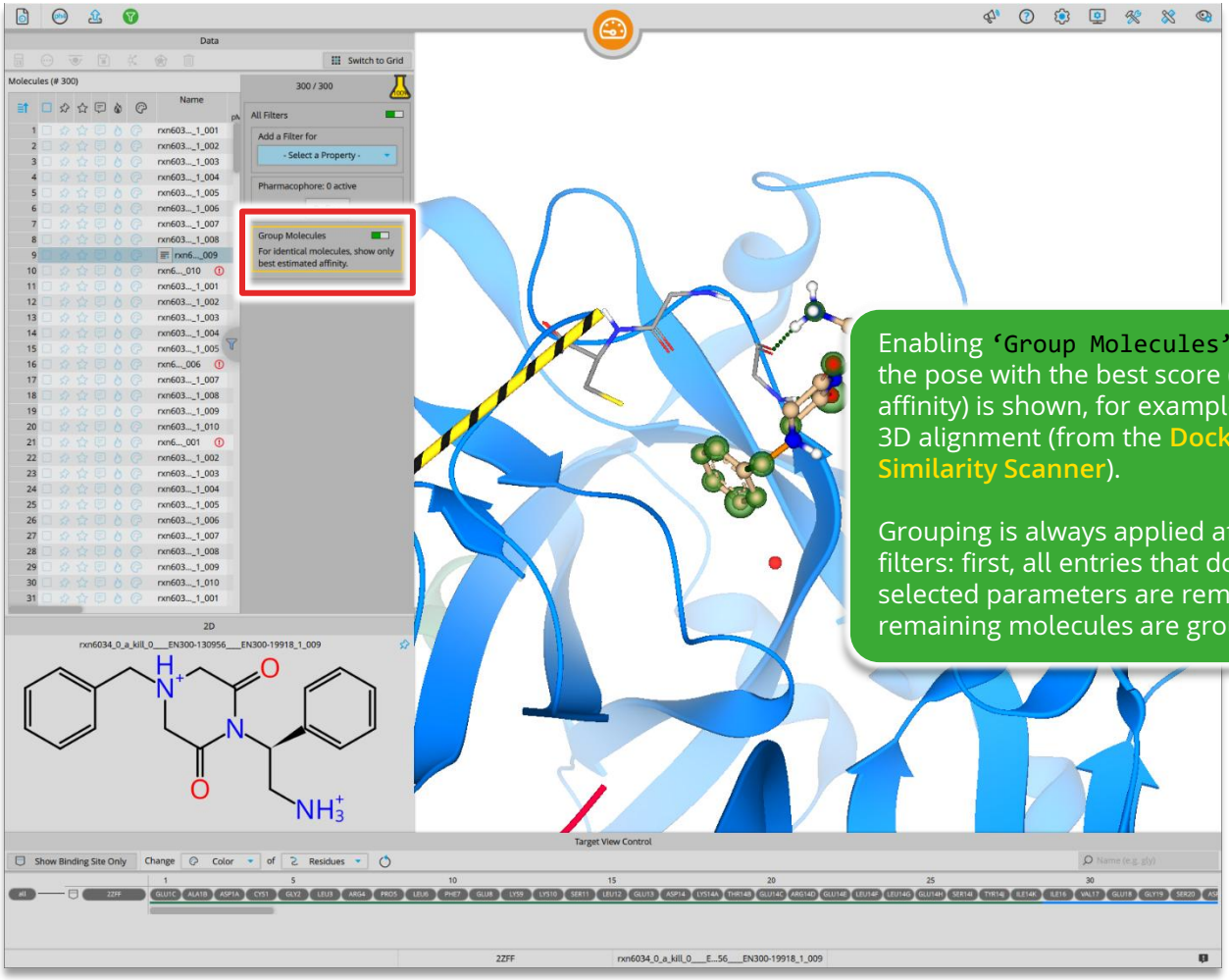
Mode Overview



Enabling **'Group Molecules'** ensures that only the pose with the best score (HYDE, estimated affinity) is shown, for example from docking or 3D alignment (from the **Docking Mode(s)** and **Similarity Scanner**).

Grouping is always applied after the preset filters: first, all entries that do not match the selected parameters are removed, and then the remaining molecules are grouped.

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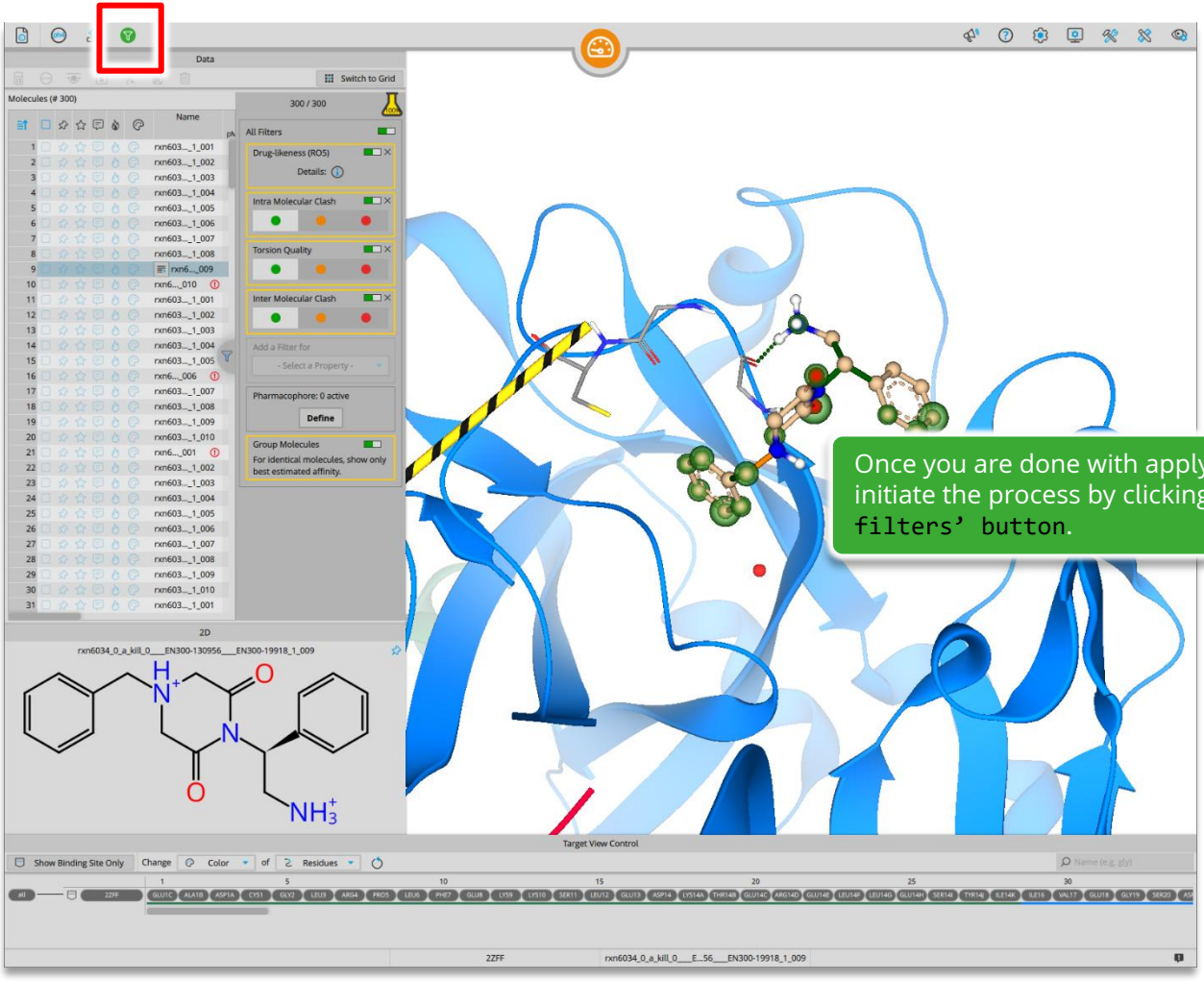
Mode Overview



Once you are done with applying your filters, initiate the process by clicking on **'Apply filters' button**.

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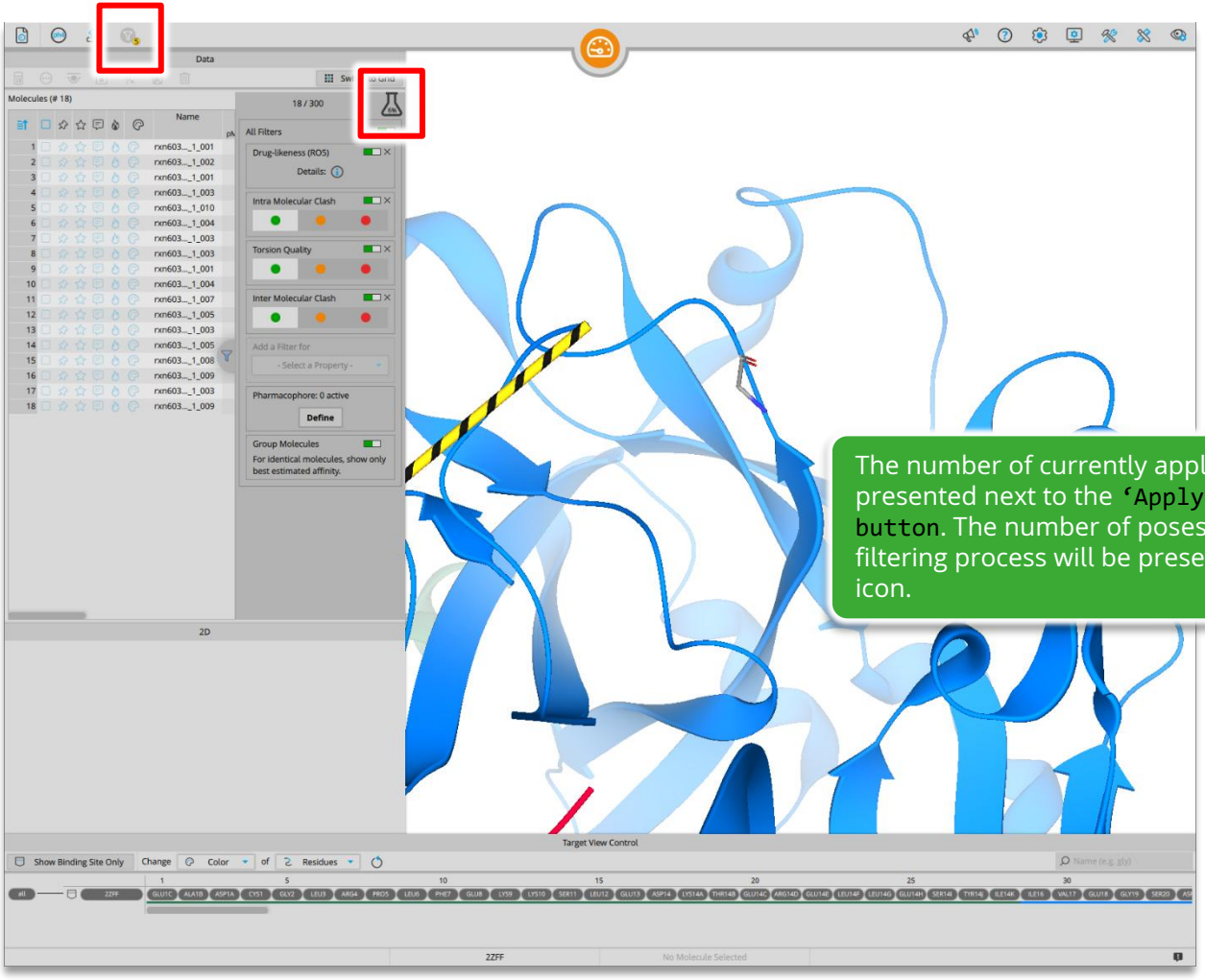
Mode Overview



The number of currently applied filters will be presented next to the **'Apply filters' button**. The number of poses that survived the filtering process will be presented in the flask icon.

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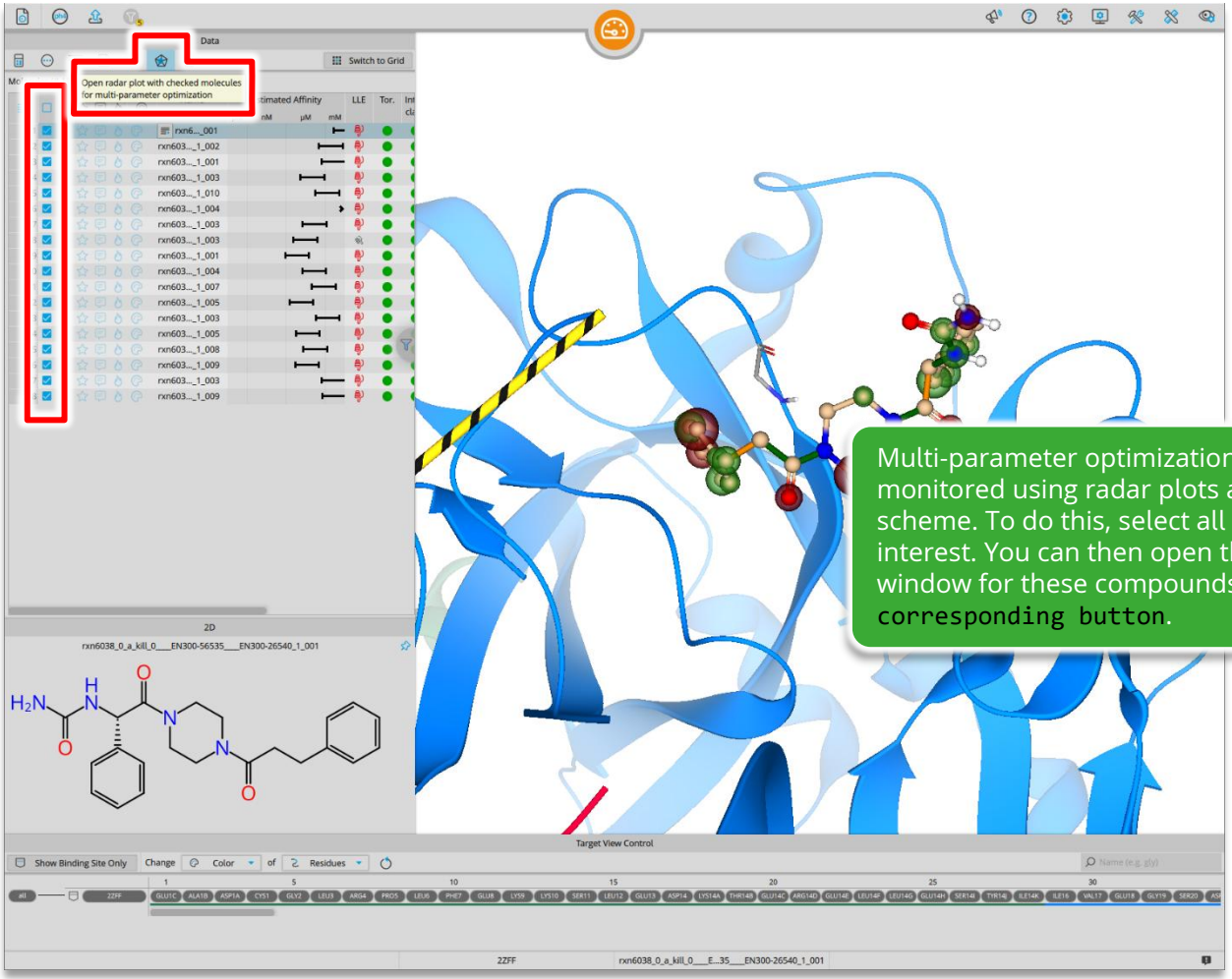
Mode Overview



Multi-parameter optimization (MPO) can be monitored using radar plots and a traffic light scheme. To do this, select all compounds of interest. You can then open the radar plot window for these compounds using the `corresponding button`.

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Mode Overview

In this window, you can define the desired parameter ranges and `add new properties`. Use the `arrow keys` to browse through the radar plots of the selected molecules.

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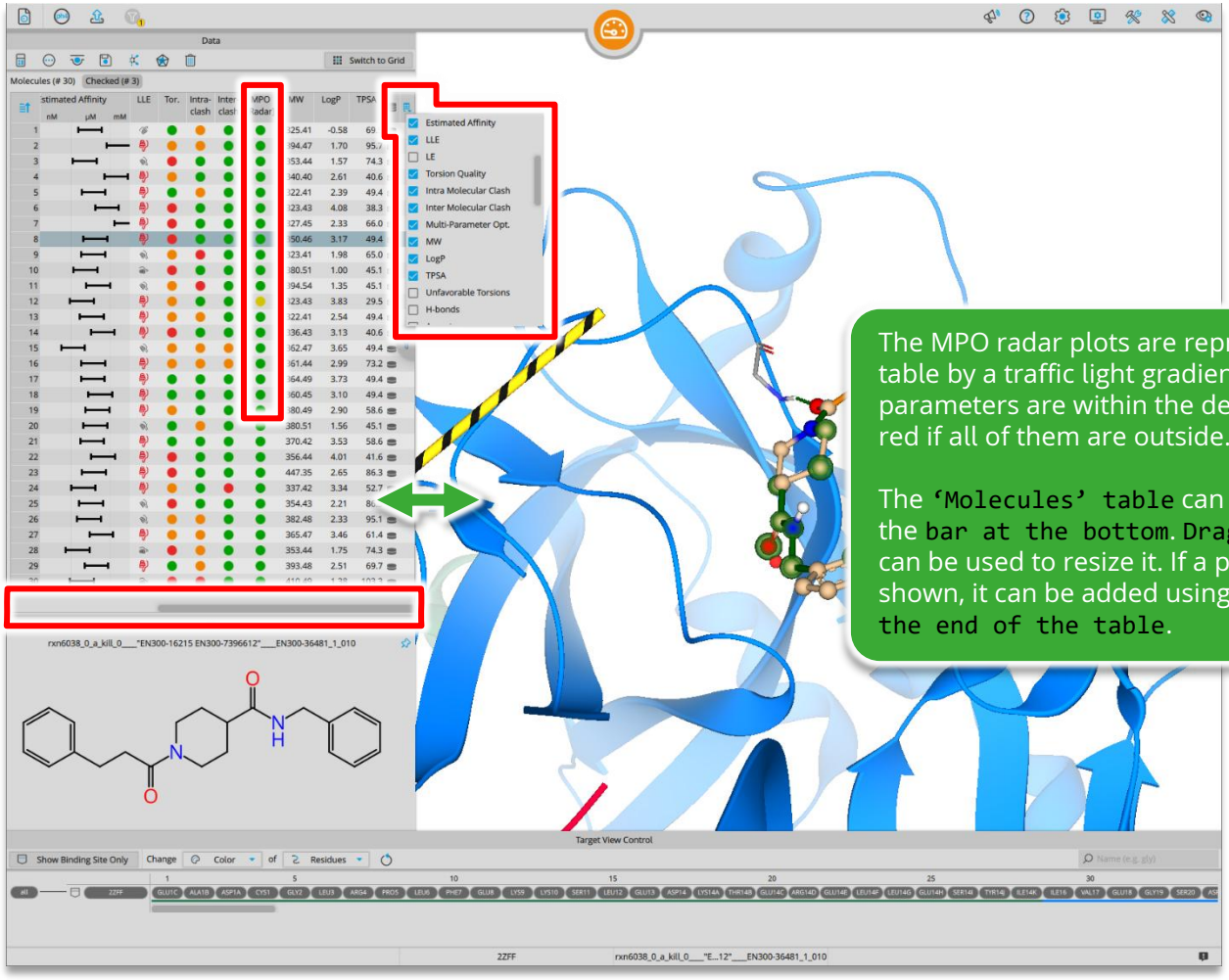
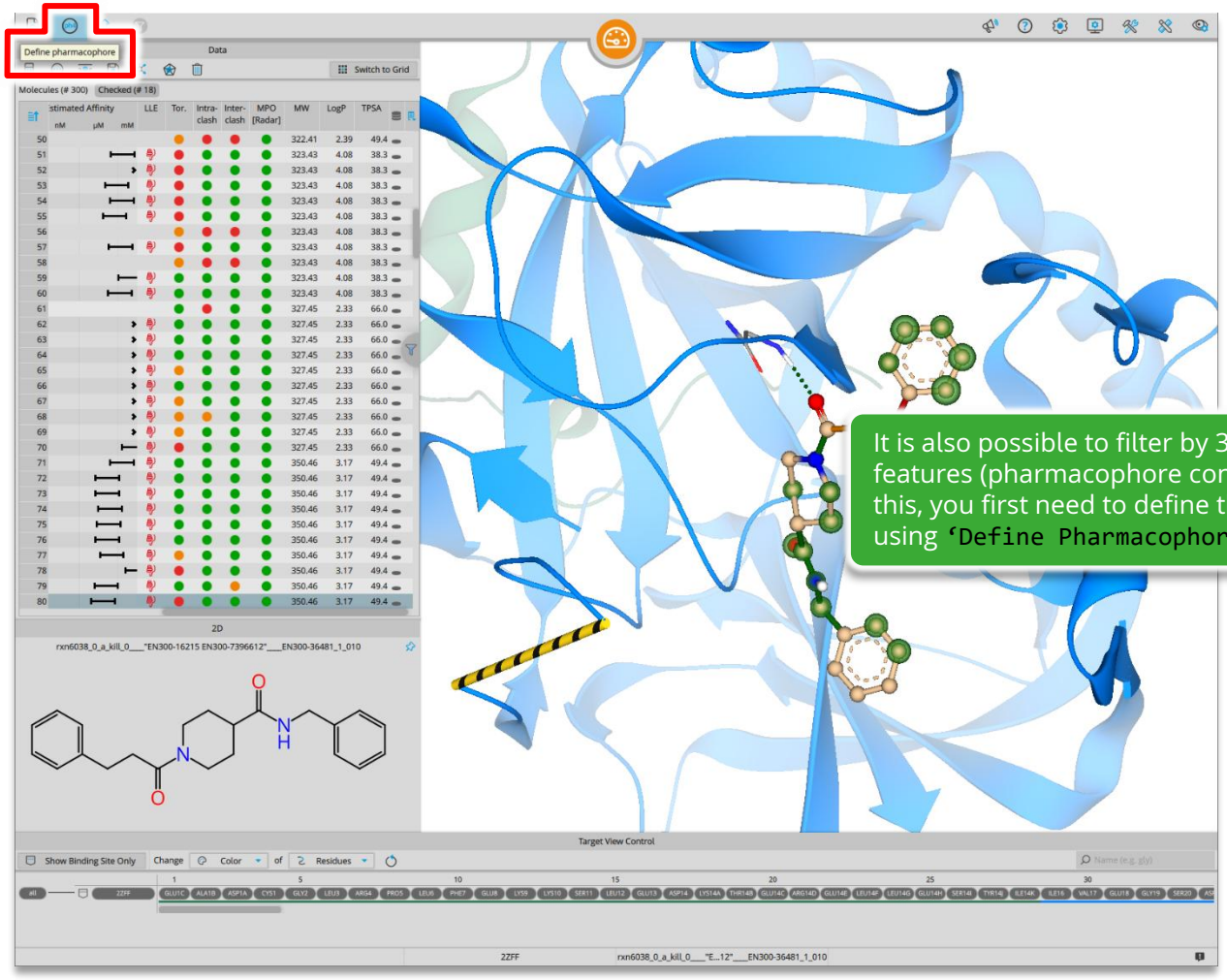
Mode Overview



The MPO radar plots are represented in the table by a traffic light gradient: green if all parameters are within the defined ranges, and red if all of them are outside.

The `'Molecules' table` can be `scrolled` using the `bar at the bottom`. `Dragging the edge` can be used to resize it. If a parameter is not shown, it can be added using the `blue icon at the end of the table`.

Table of Content
Mode Overview



It is also possible to filter by 3D molecular features (pharmacophore constraints). To do this, you first need to define the 3D features using **'Define Pharmacophore'**.

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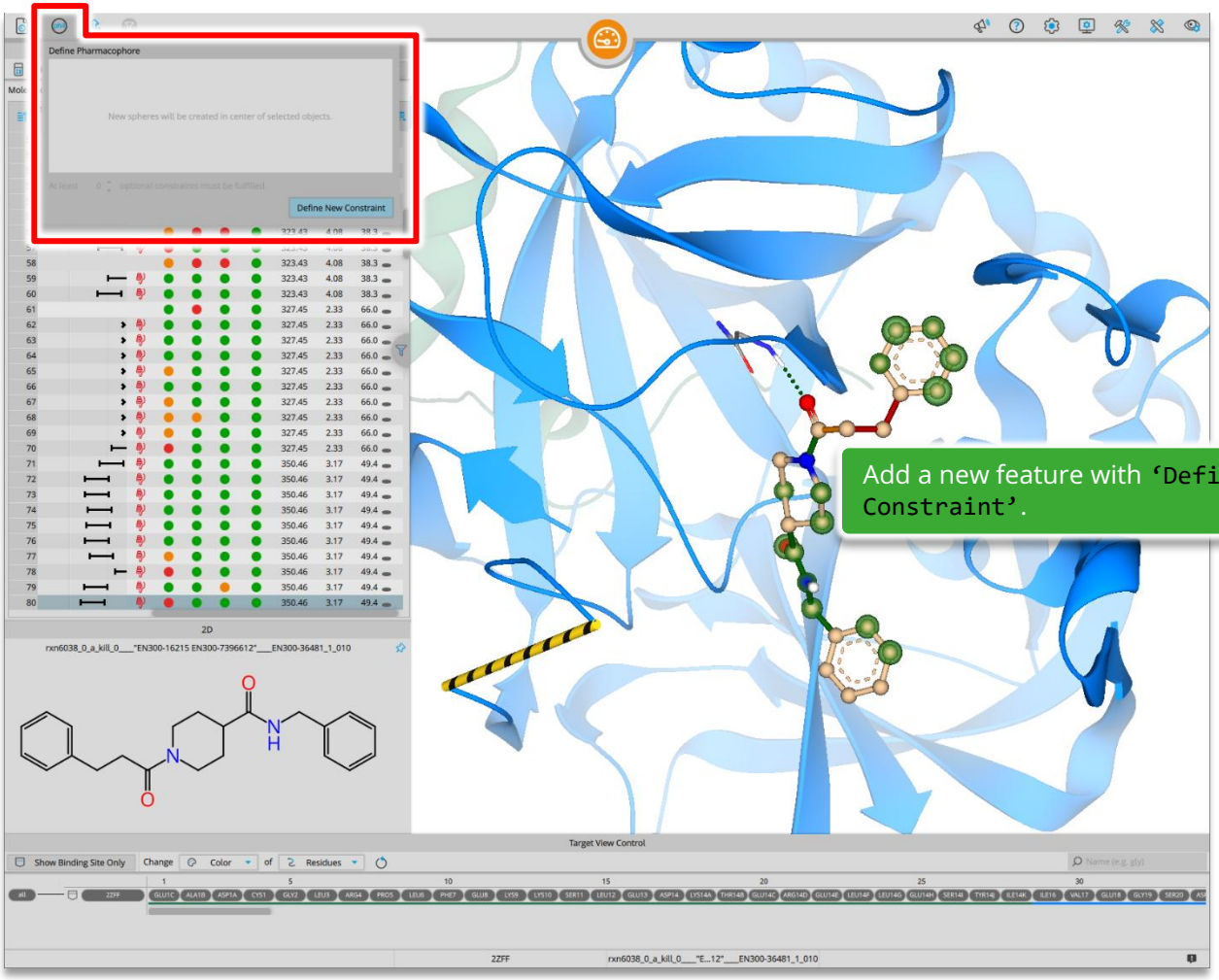
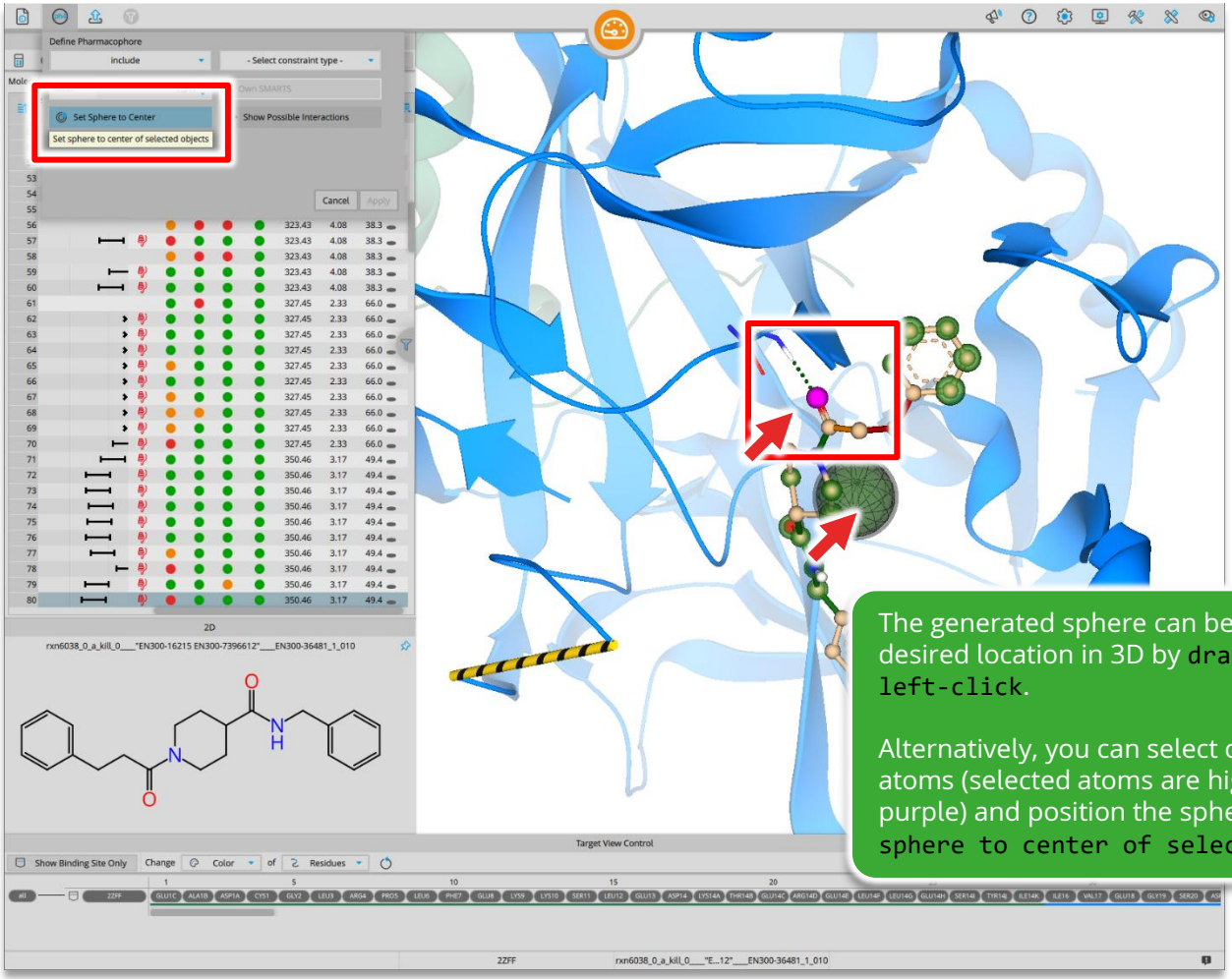
Mode Overview



Add a new feature with ‘Define New Constraint’.

Table of Content

Mode Overview



The generated sphere can be positioned at the desired location in 3D by `dragging` them with a `left-click`.

Alternatively, you can select one or more heavy atoms (selected atoms are highlighted in purple) and position the sphere using `'Set sphere to center of selected objects'`.

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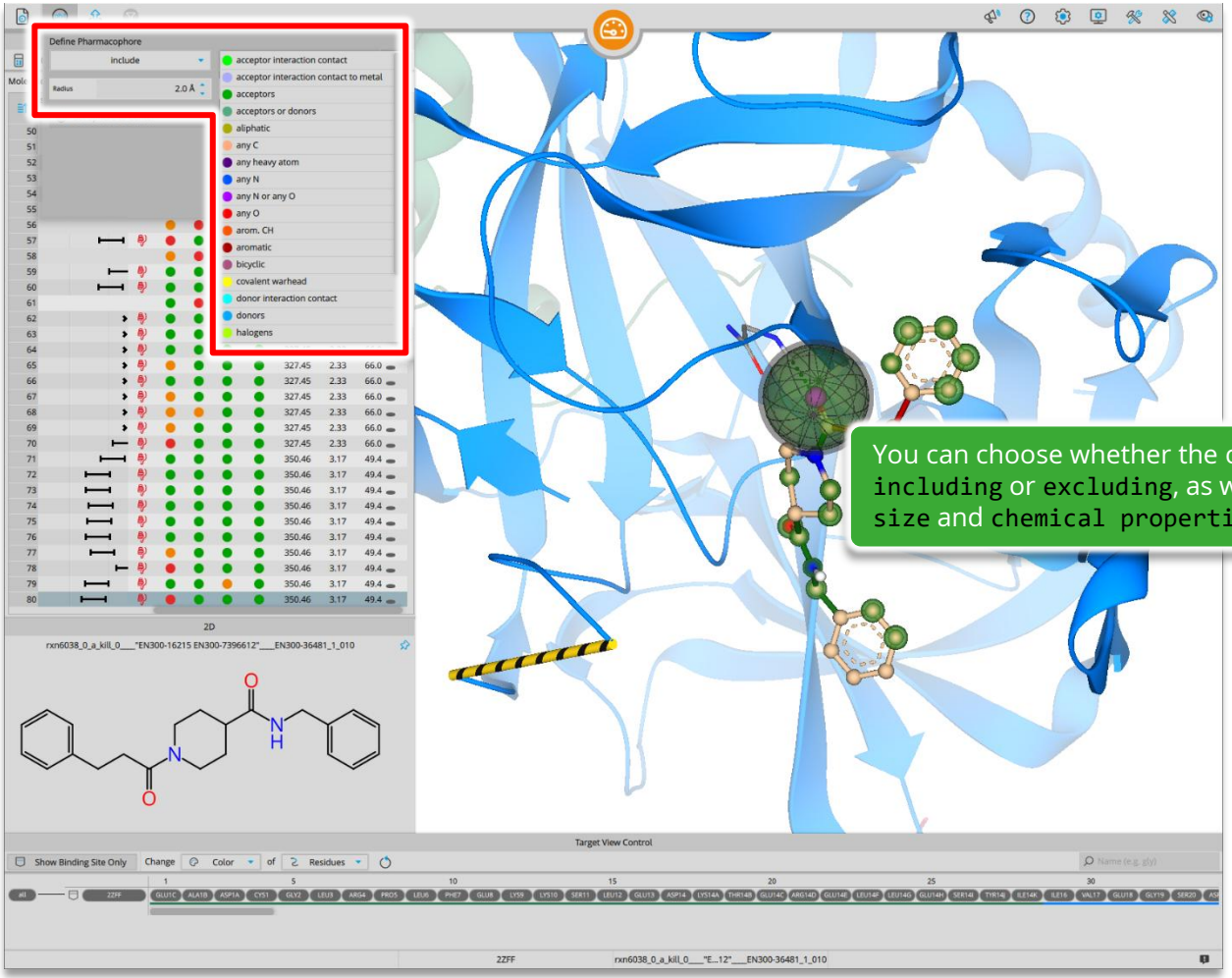
Mode Overview



You can choose whether the constraint is `including` or `excluding`, as well as define its `size` and `chemical properties`.

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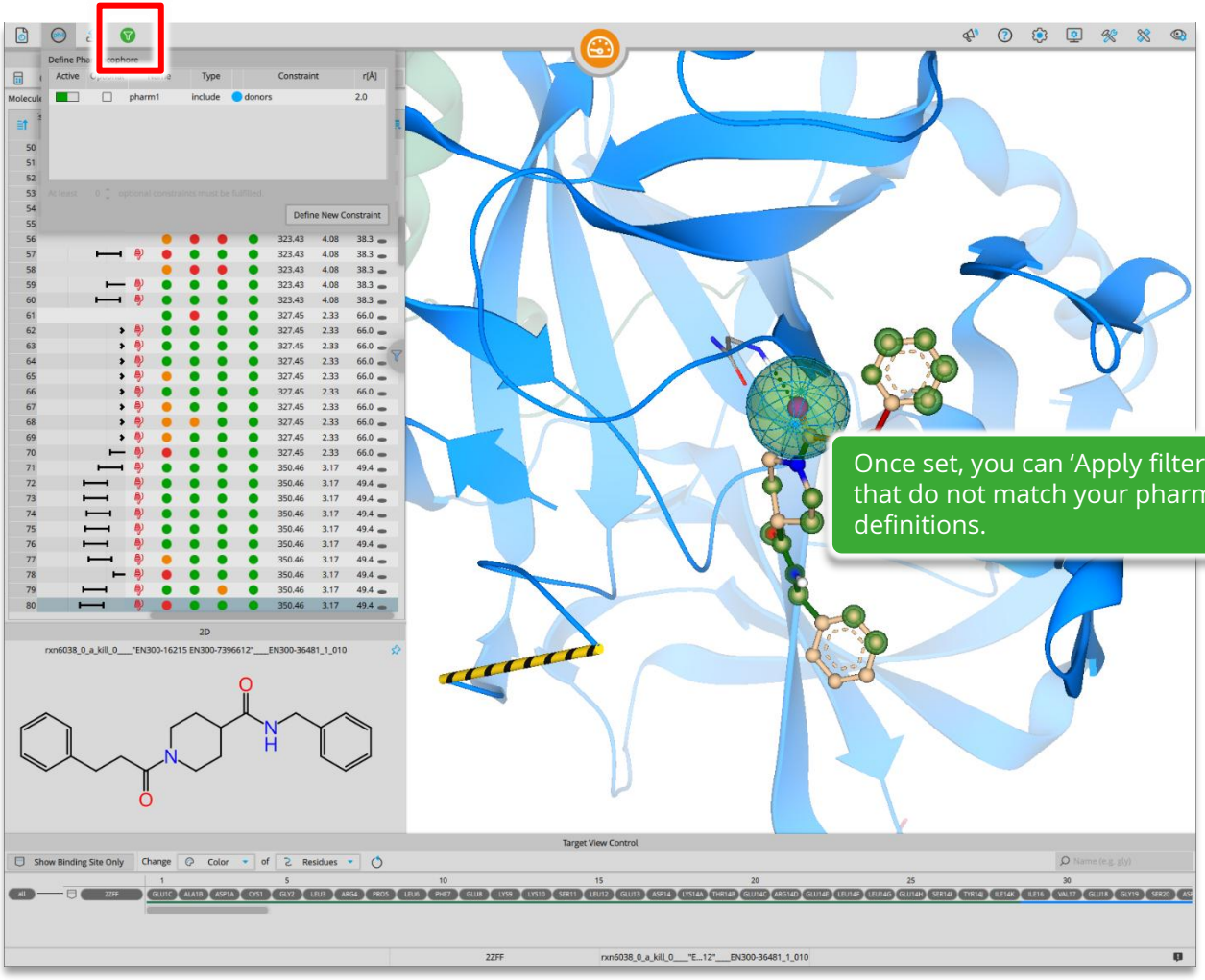
Mode Overview



Once set, you can 'Apply filters' to remove poses that do not match your pharmacophore definitions.

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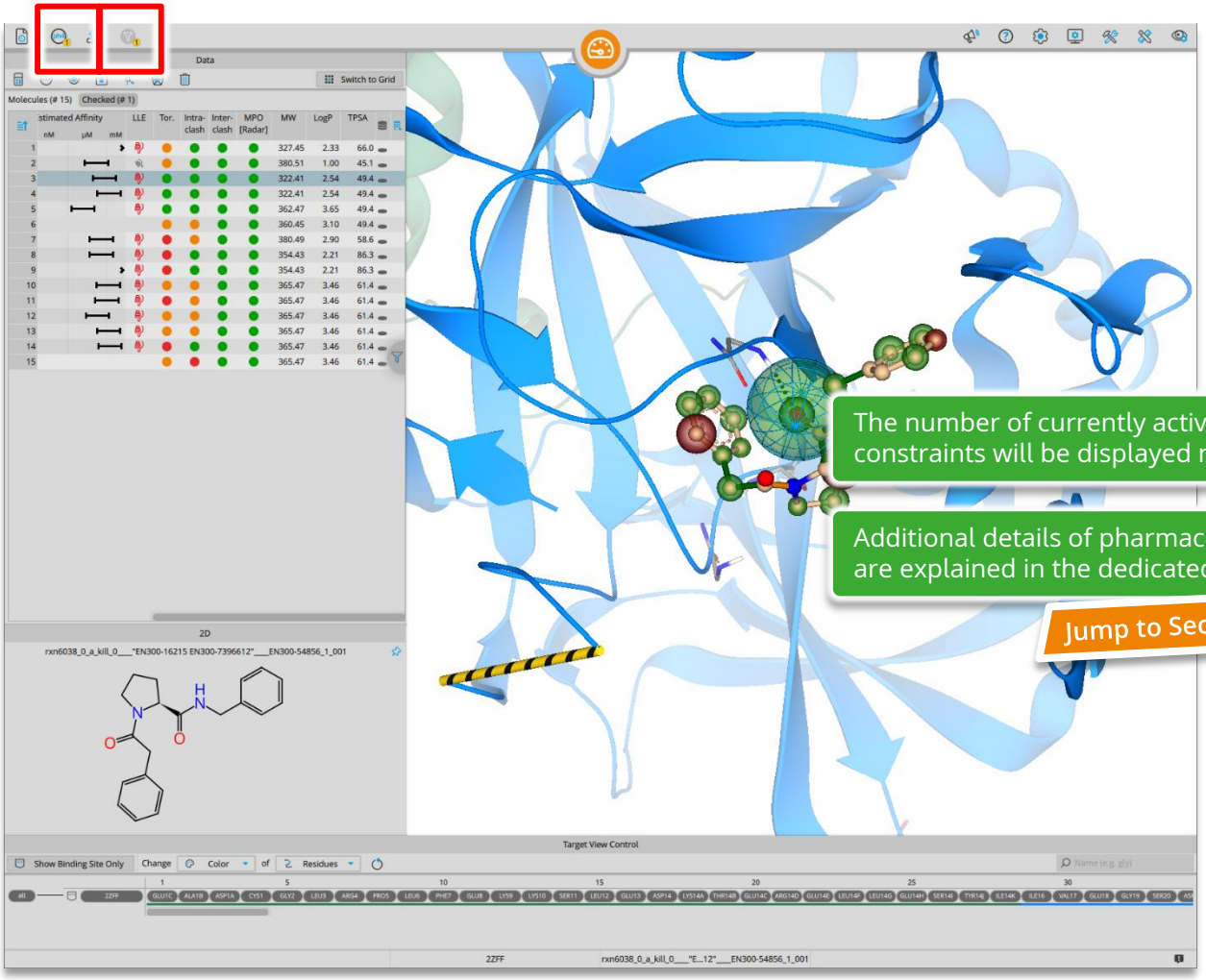
Mode Overview



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Mode Overview

7. Inspirator

Inspirator Mode helps you explore ways to improve your compound. Grow into unoccupied binding sites, test small modifications, or even replace entire scaffolds.

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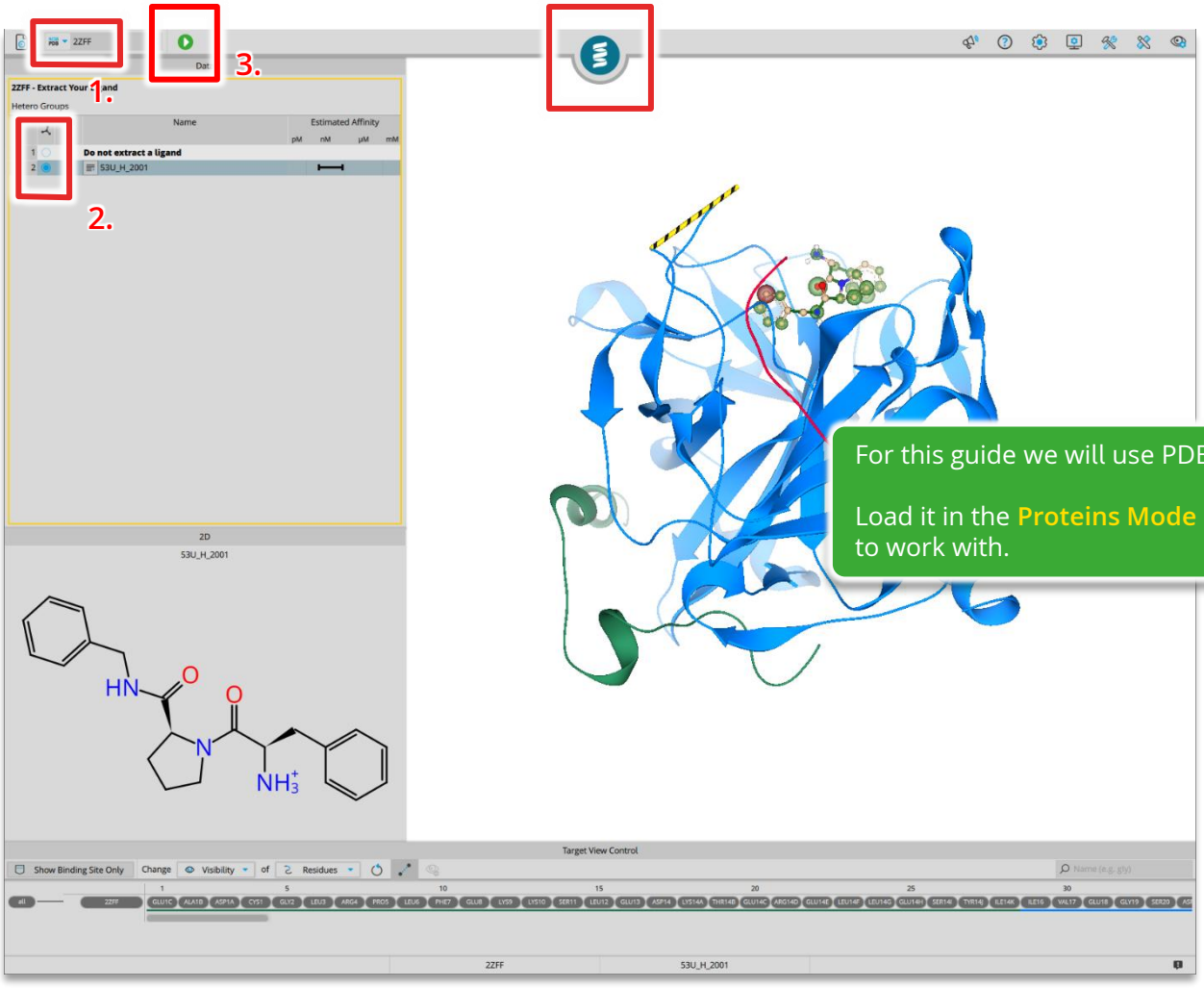
Mode Overview



For this guide we will use PDB **2ZFF** as example.

Load it in the **Proteins Mode** and select a ligand to work with.

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Mode Overview

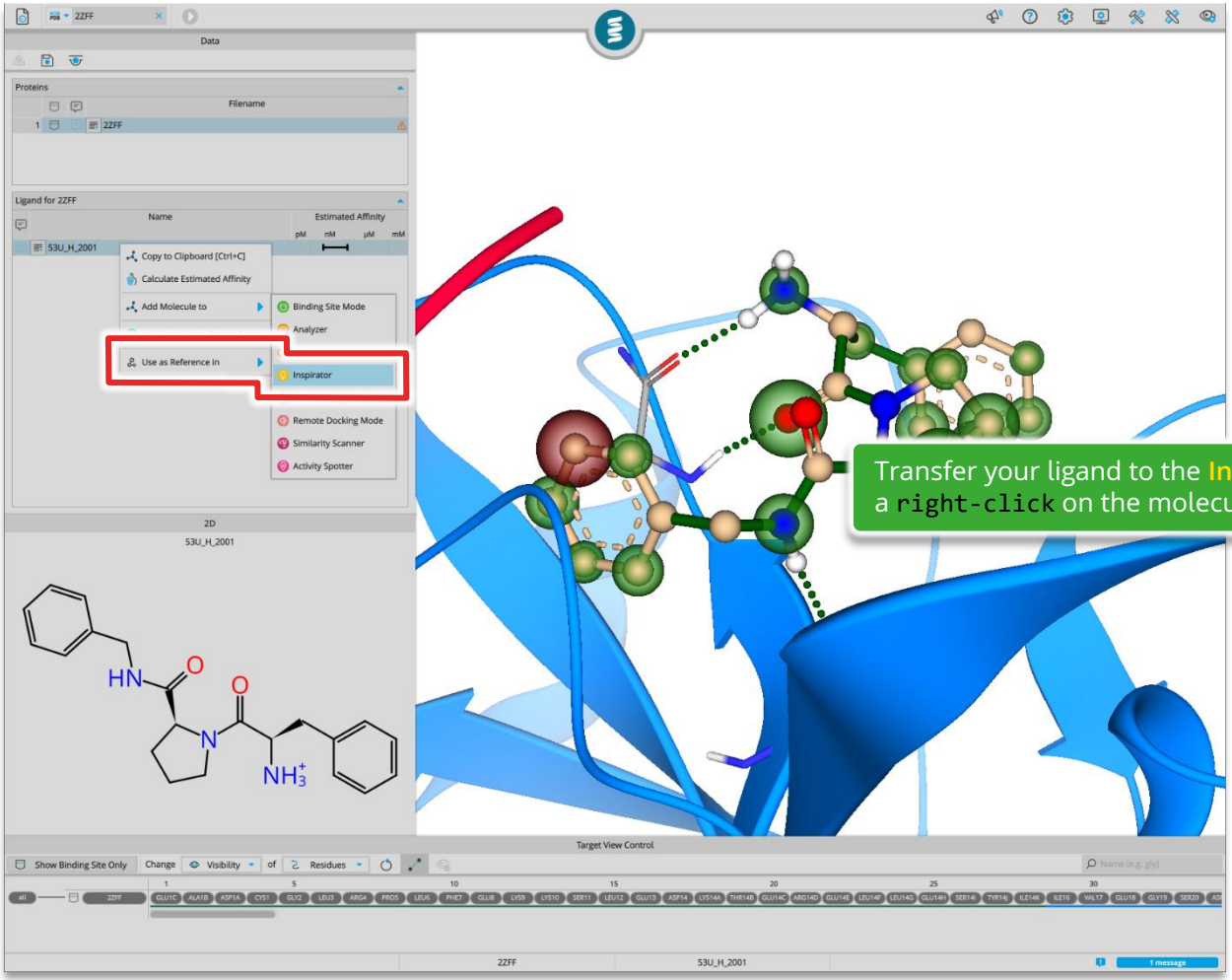


Table of Content

Mode Overview

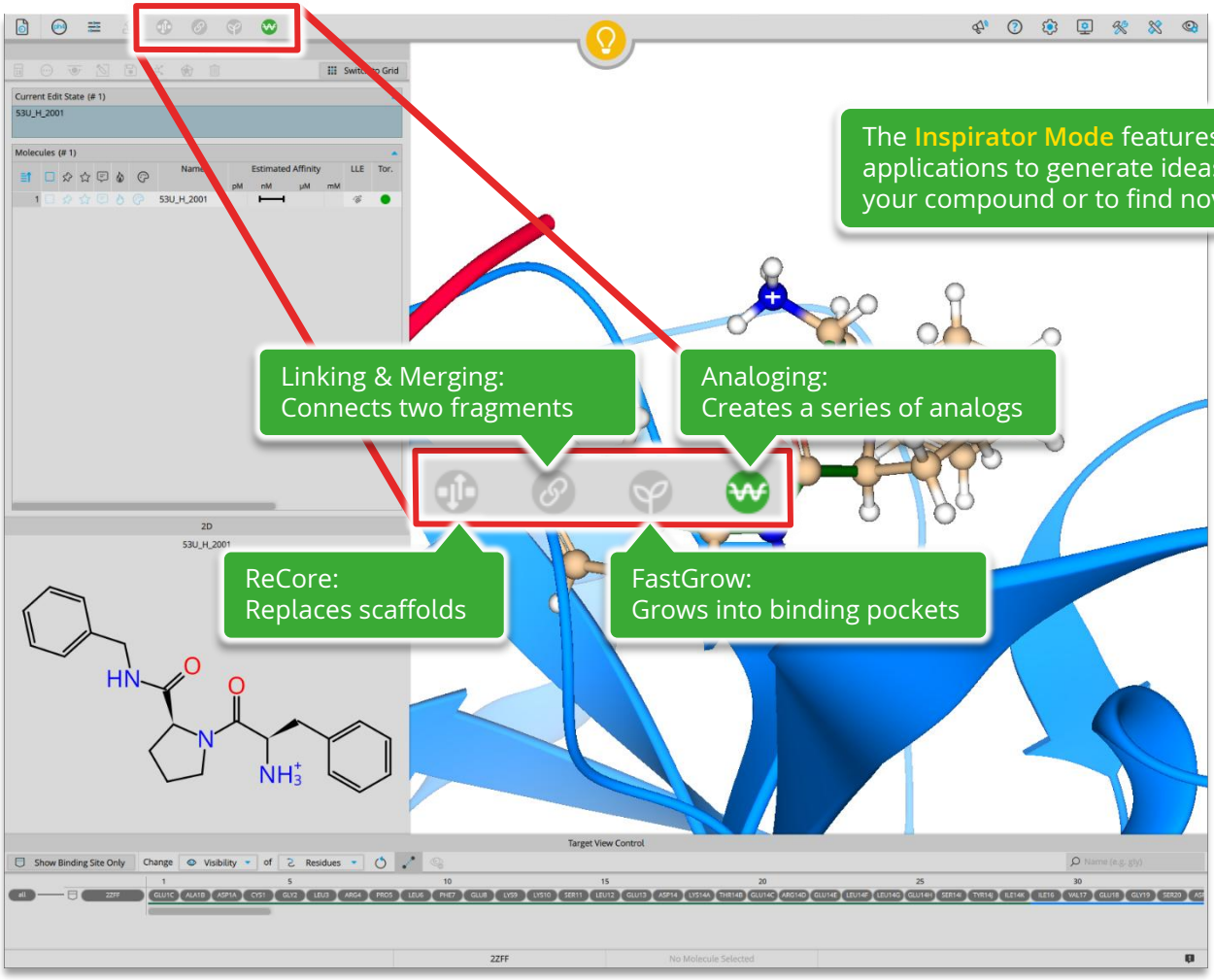
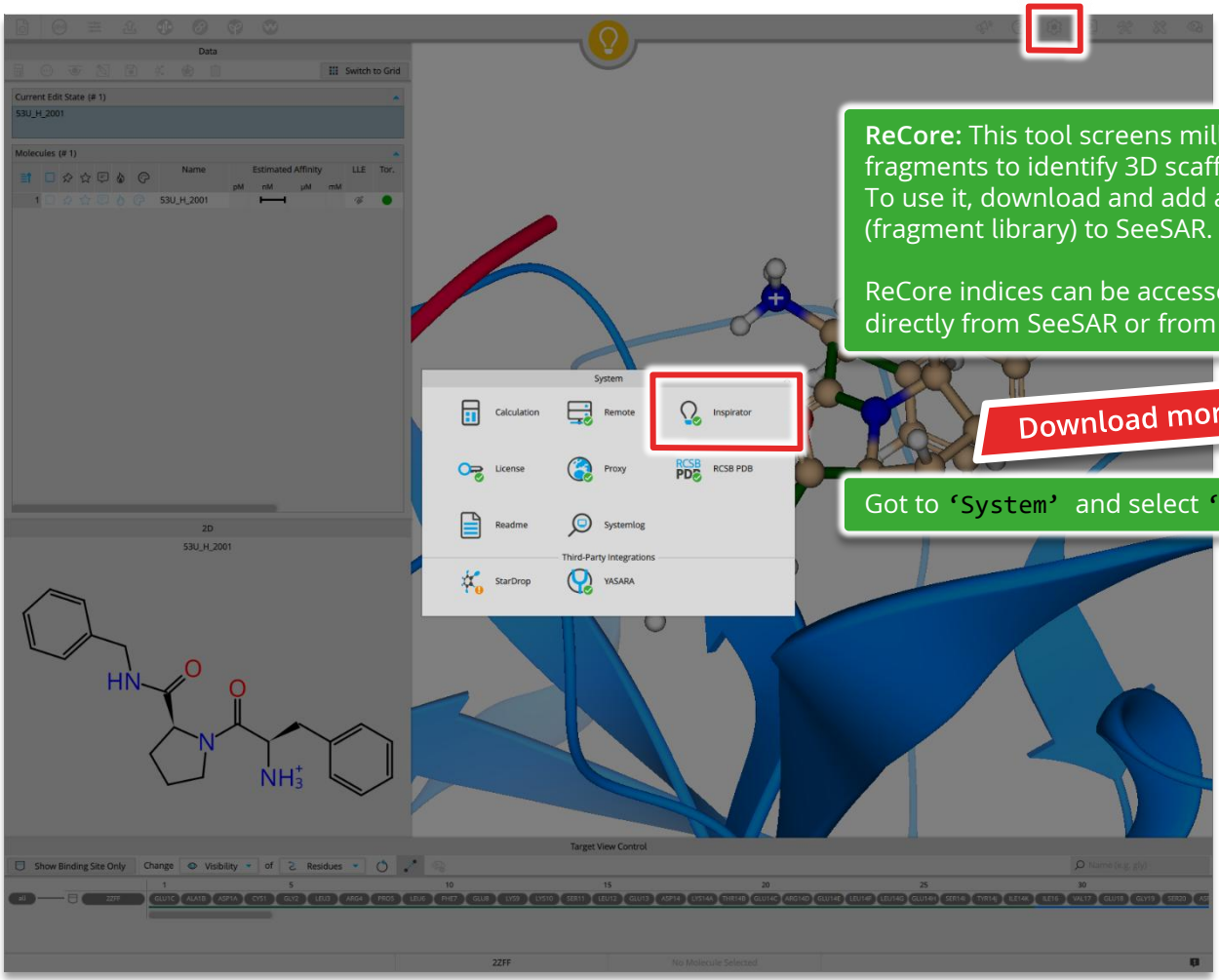


Table of Content
Mode Overview



ReCore: This tool screens millions of molecular fragments to identify 3D scaffold replacements. To use it, download and add a ReCore index (fragment library) to SeeSAR.

ReCore indices can be accessed and downloaded directly from SeeSAR or from our website:

Download more files

Got to ‘System’ and select ‘Inspirator’.

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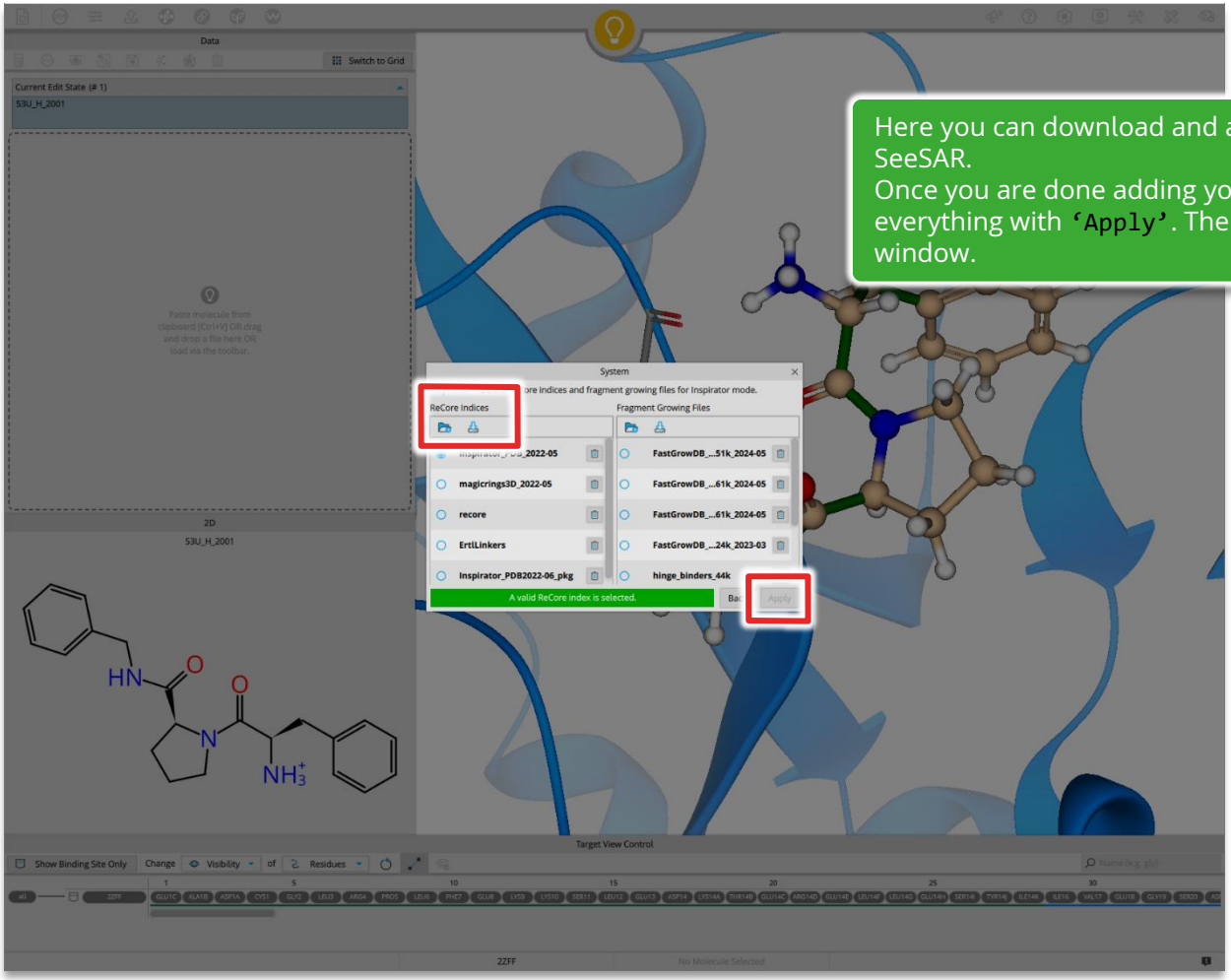
Mode Overview



Here you can download and add ReCore files to SeeSAR.
Once you are done adding your indices, confirm everything with `'Apply'`. Then you can close the window.

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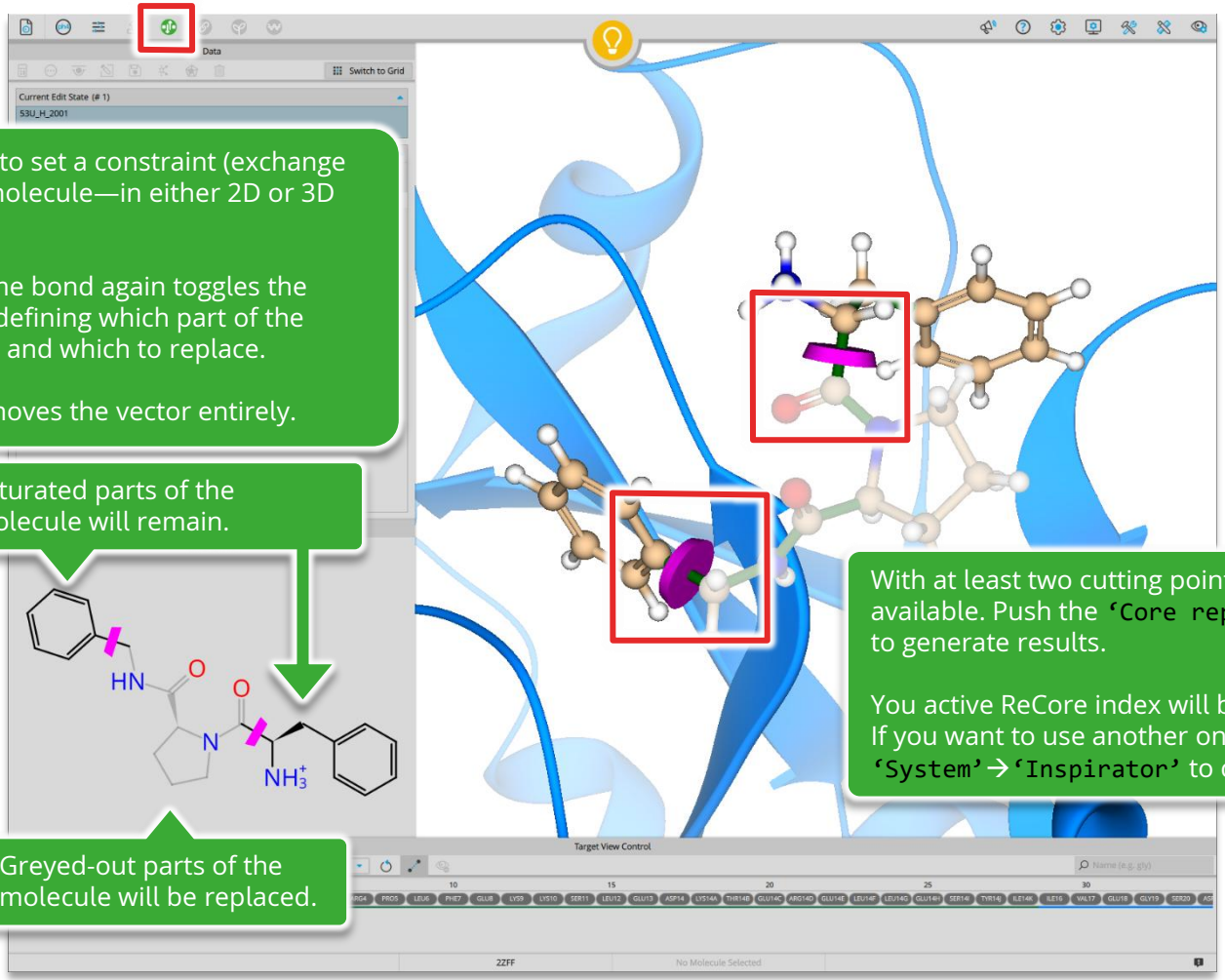
Mode Overview



`Click` on a bond to set a constraint (exchange vector) on your molecule—in either 2D or 3D view.

`Clicking` the same bond again toggles the vector direction, defining which part of the molecule to keep and which to replace.

A third `click` removes the vector entirely.

Saturated parts of the molecule will remain.

Greyed-out parts of the molecule will be replaced.

With at least two cutting points ReCore becomes available. Push the `'Core replacement'` button to generate results.

You active ReCore index will be used for this. If you want to use another one, go back to `'System'`→`'Inspirator'` to change the index.

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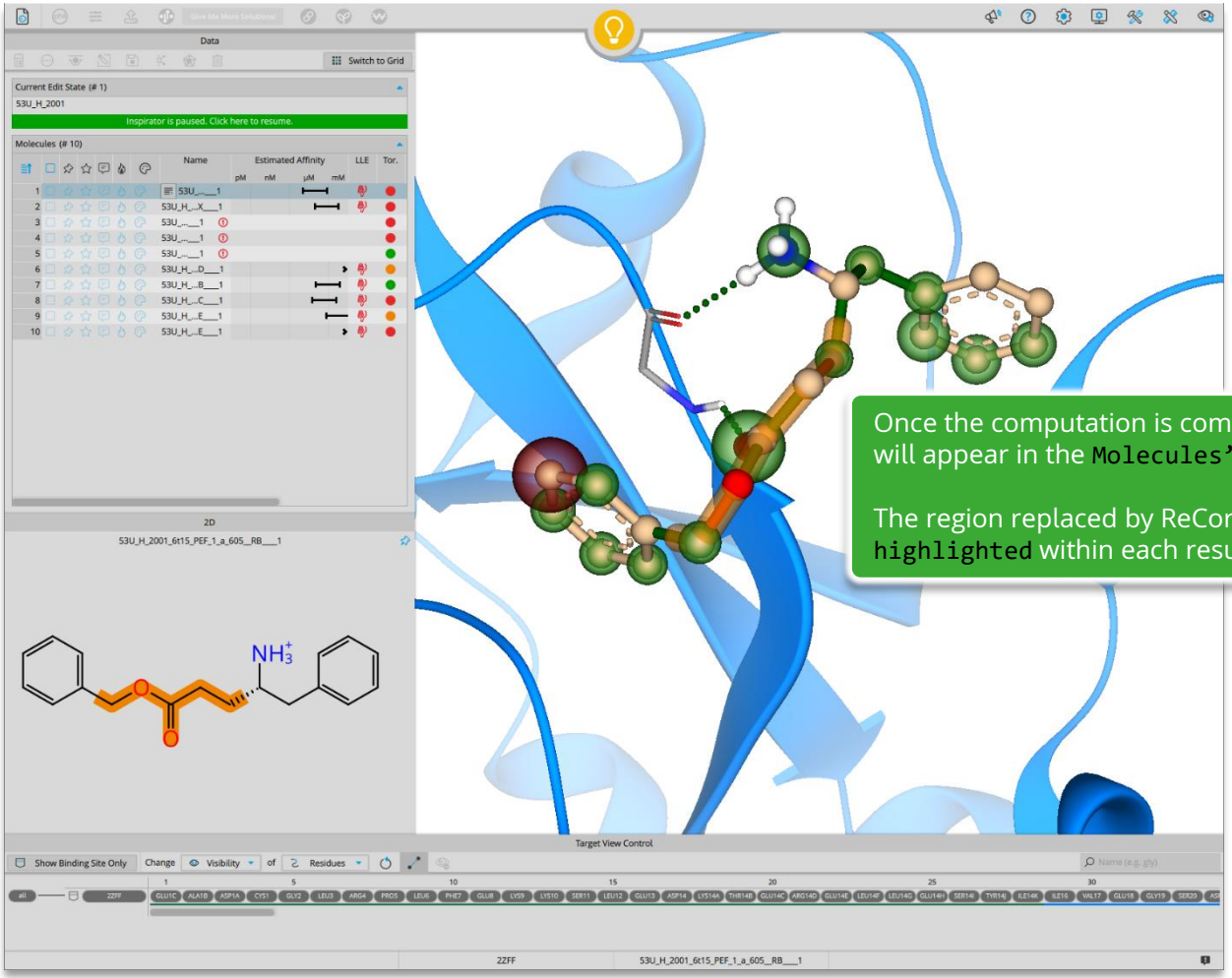
Mode Overview



Once the computation is complete, the results will appear in the `Molecules' table`.

The region replaced by ReCore will be `highlighted` within each resulting molecule.

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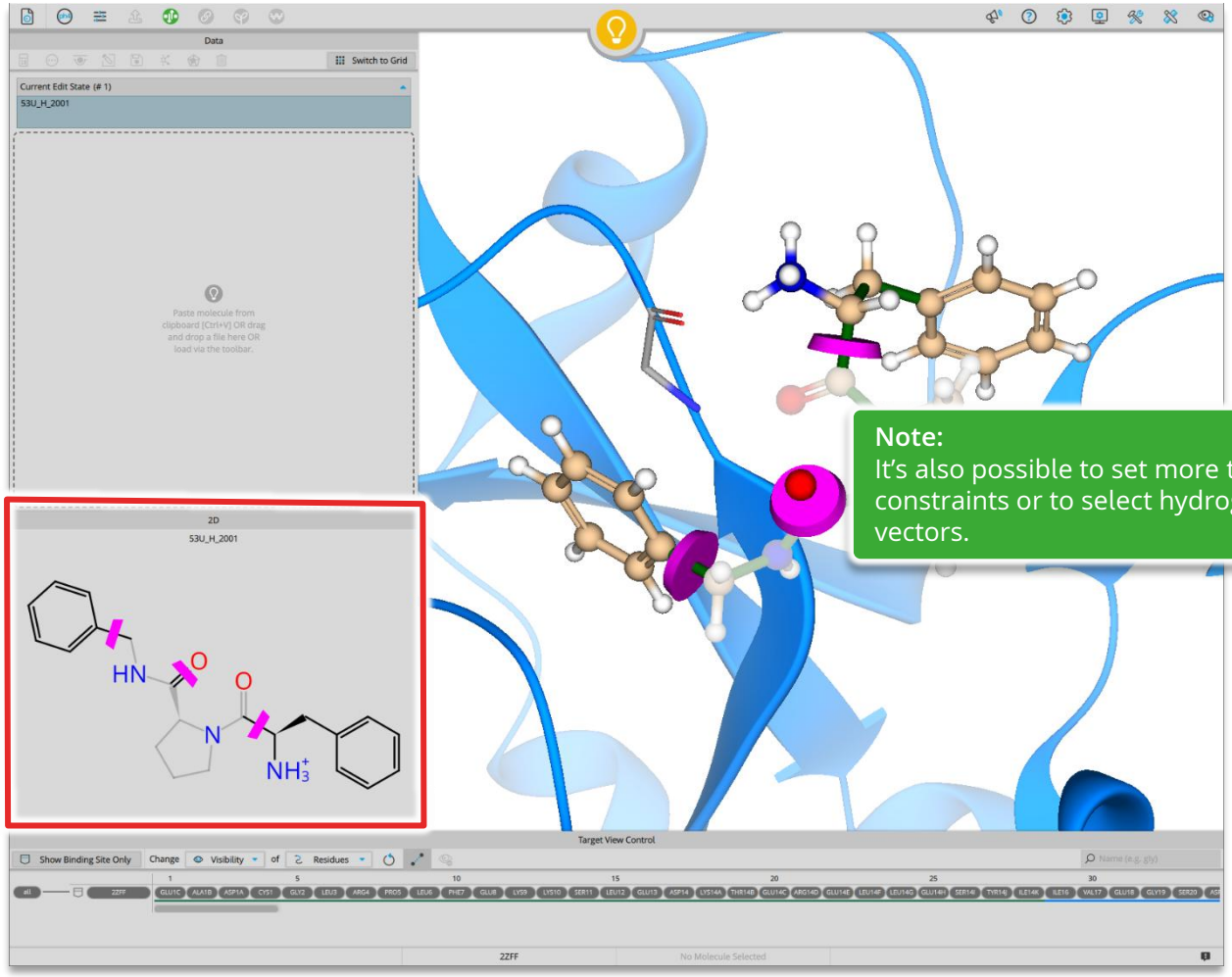
Mode Overview



Note:
It's also possible to set more than two constraints or to select hydrogen bonds as vectors.

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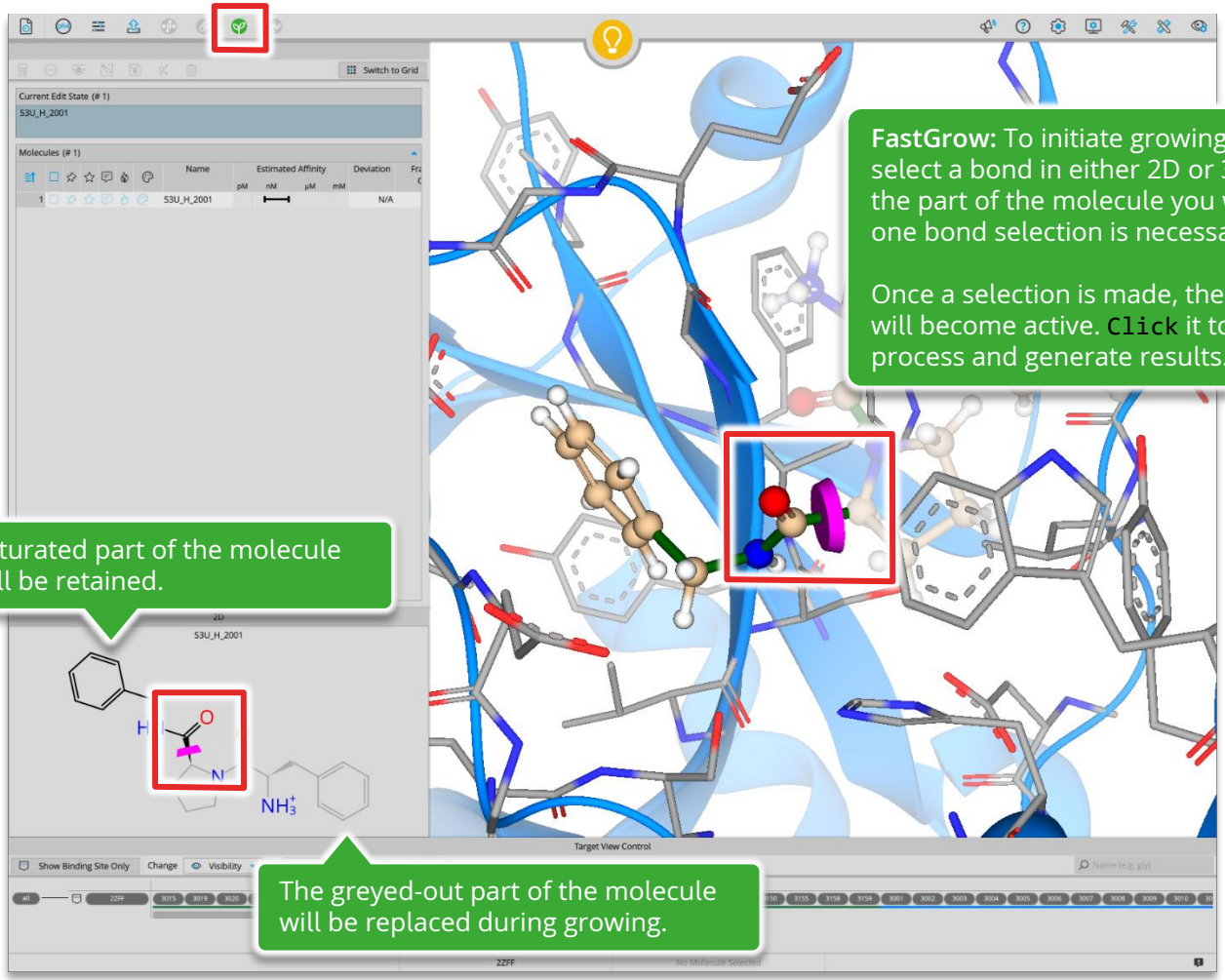
Mode Overview



FastGrow: To initiate growing into a binding site, select a bond in either 2D or 3D view to define the part of the molecule you wish to retain. Only one bond selection is necessary to proceed.

Once a selection is made, the `'Growing'` button will become active. `Click` it to start the growing process and generate results.

Saturated part of the molecule will be retained.

The greyed-out part of the molecule will be replaced during growing.

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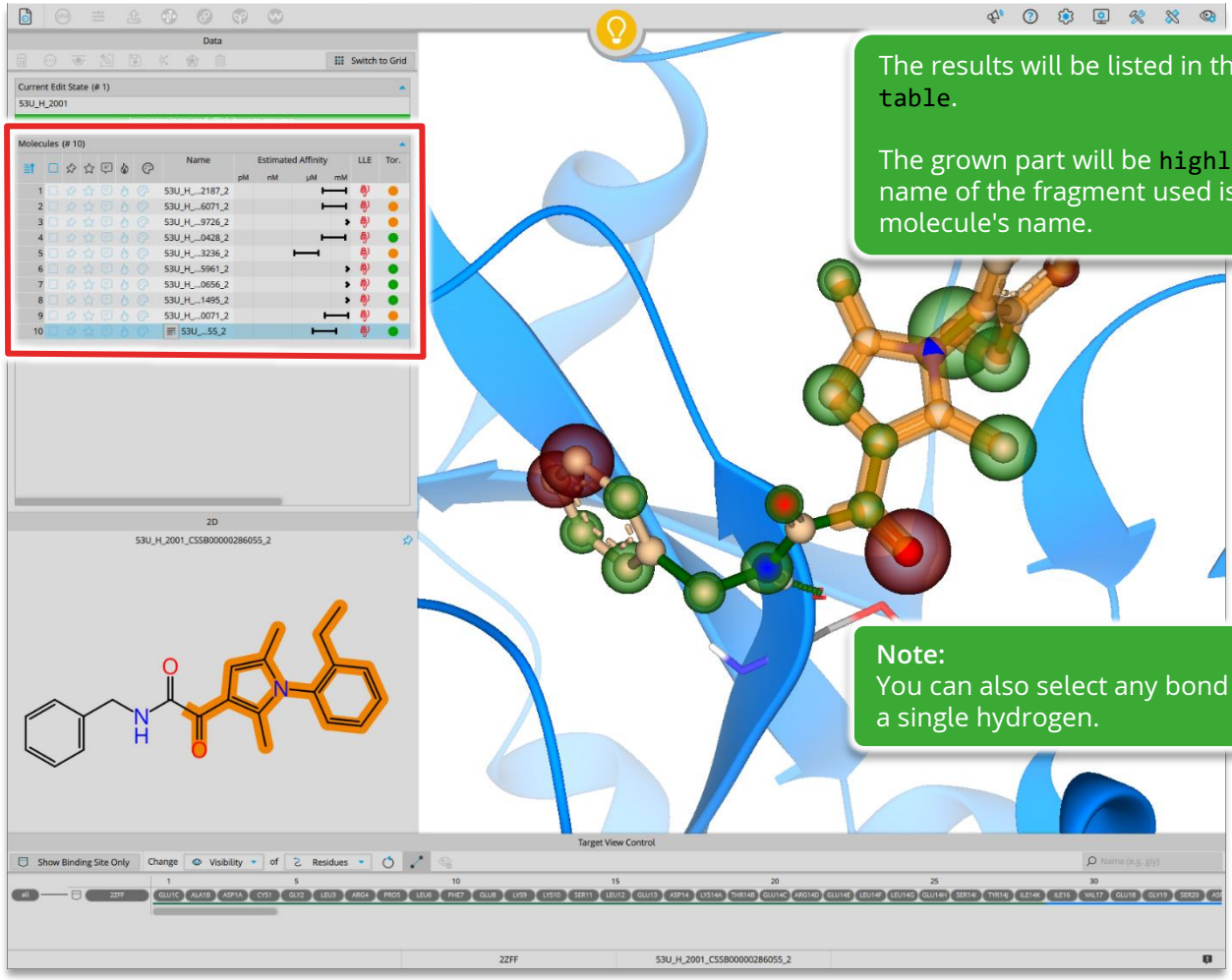
Mode Overview



The results will be listed in the **‘Molecules’ table**.

The grown part will be **highlighted**, and the name of the fragment used is appended to the molecule's name.

Note:
You can also select any bond to grow from, even a single hydrogen.

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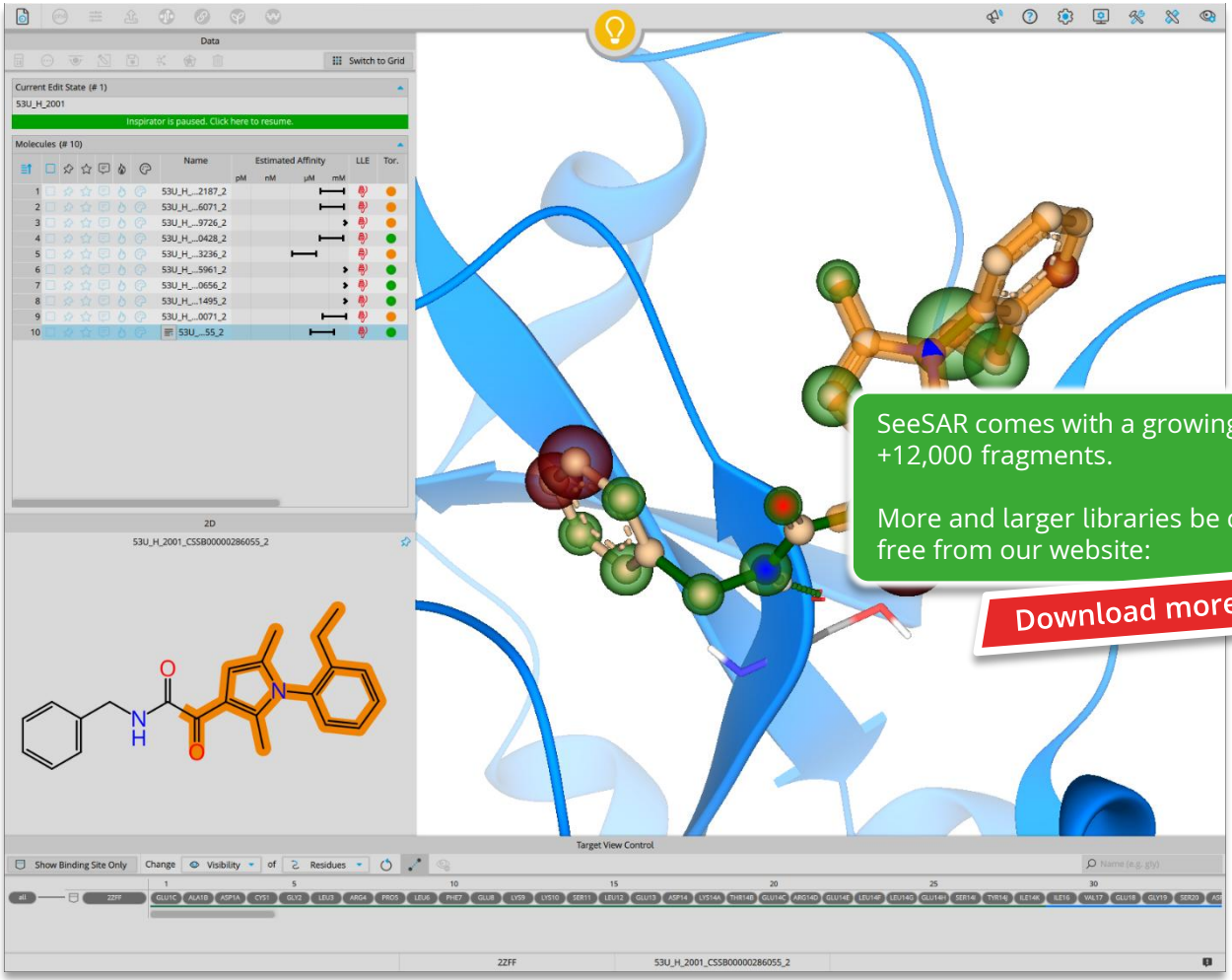
Mode Overview



SeeSAR comes with a growing library featuring +12,000 fragments.

More and larger libraries be downloaded for free from our website:

Download more libraries

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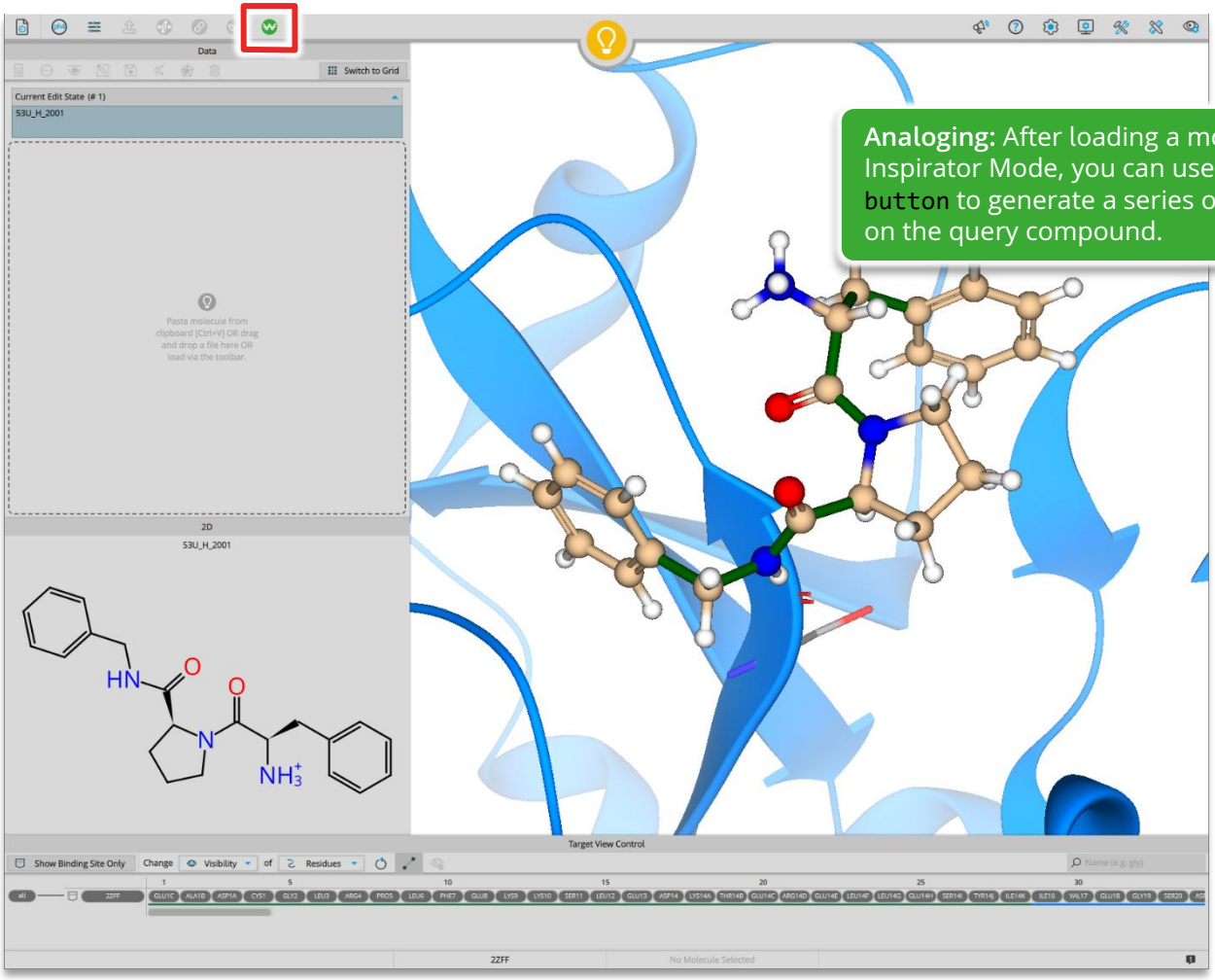
Mode Overview



Analoging: After loading a molecule into Inspirator Mode, you can use the **'Analoging' button** to generate a series of derivatives based on the query compound.

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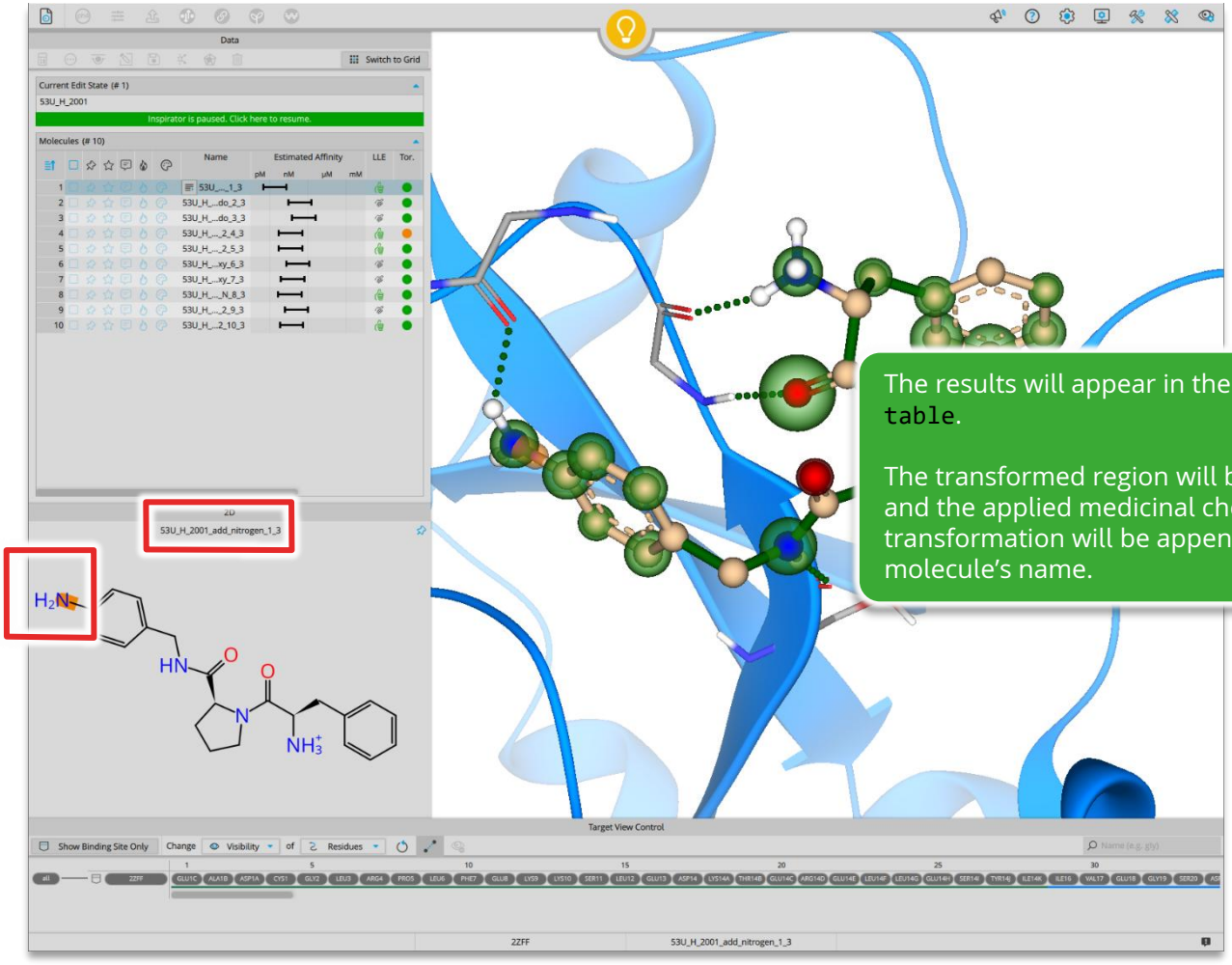
Mode Overview



The results will appear in the `'Molecules' table`.

The transformed region will be `highlighted`, and the applied medicinal chemistry transformation will be appended to the molecule's name.

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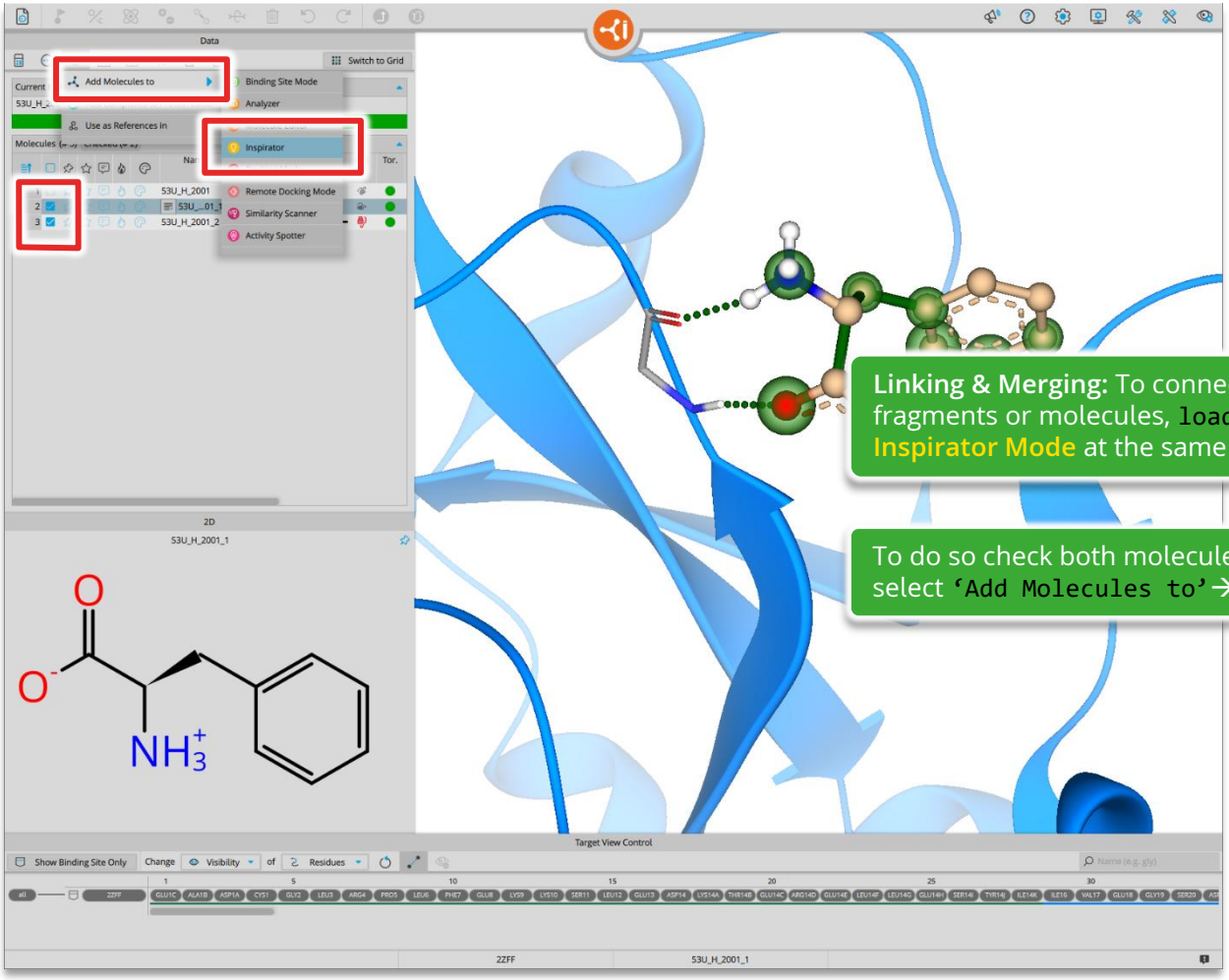
Mode Overview



Linking & Merging: To connect two different fragments or molecules, `load both` into **Inspirator Mode** at the same time.

To do so check both molecules in any Mode and select `'Add Molecules to'→'Inspirator'`.

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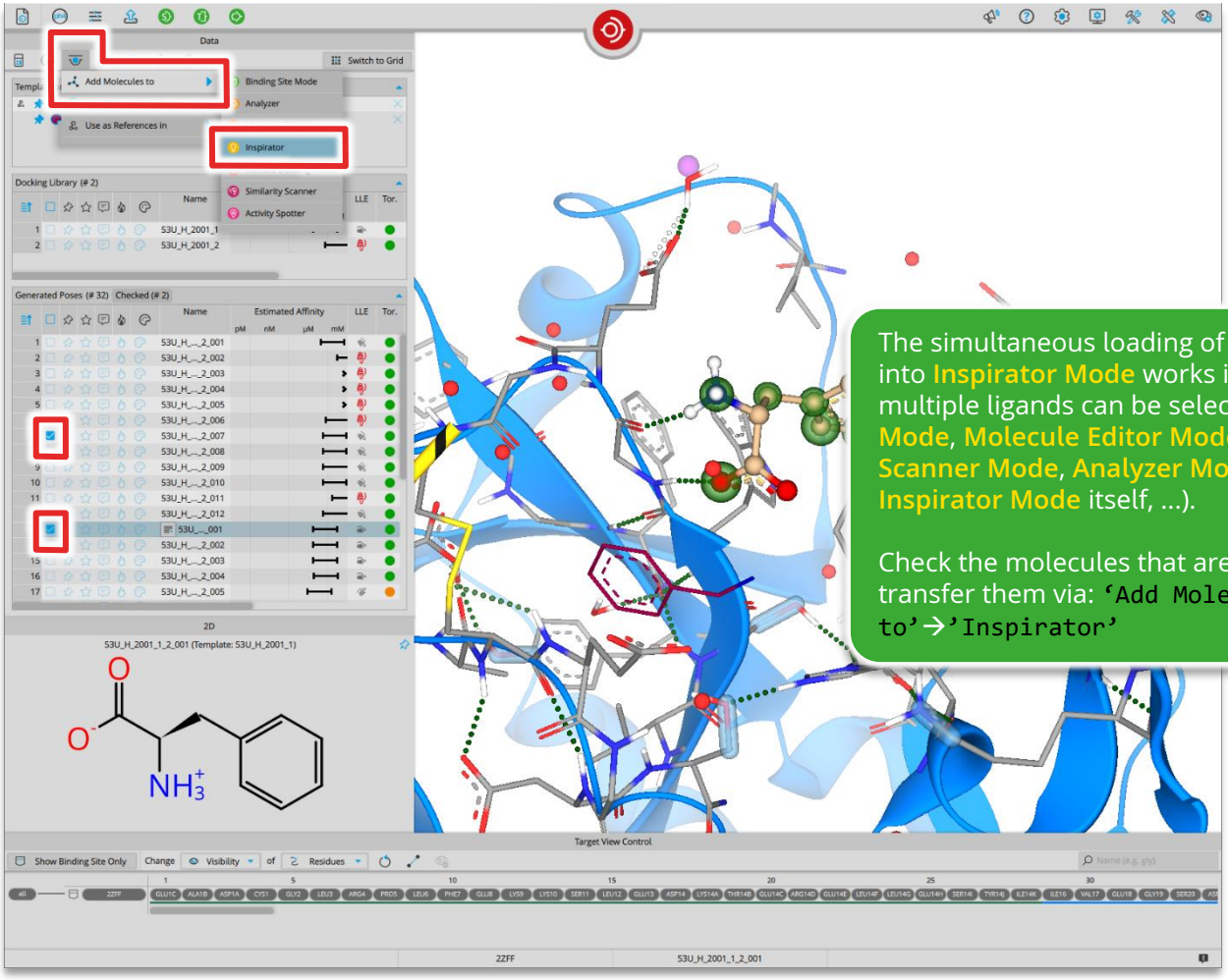
Mode Overview



The simultaneous loading of two molecules into **Inspirator Mode** works in any mode where multiple ligands can be selected (e.g., **Docking Mode**, **Molecule Editor Mode**, **Similarity Scanner Mode**, **Analyzer Mode**, even **Inspirator Mode** itself, ...).

Check the molecules that are to be merged and transfer them via: `'Add Molecules to'→'Inspirator'`

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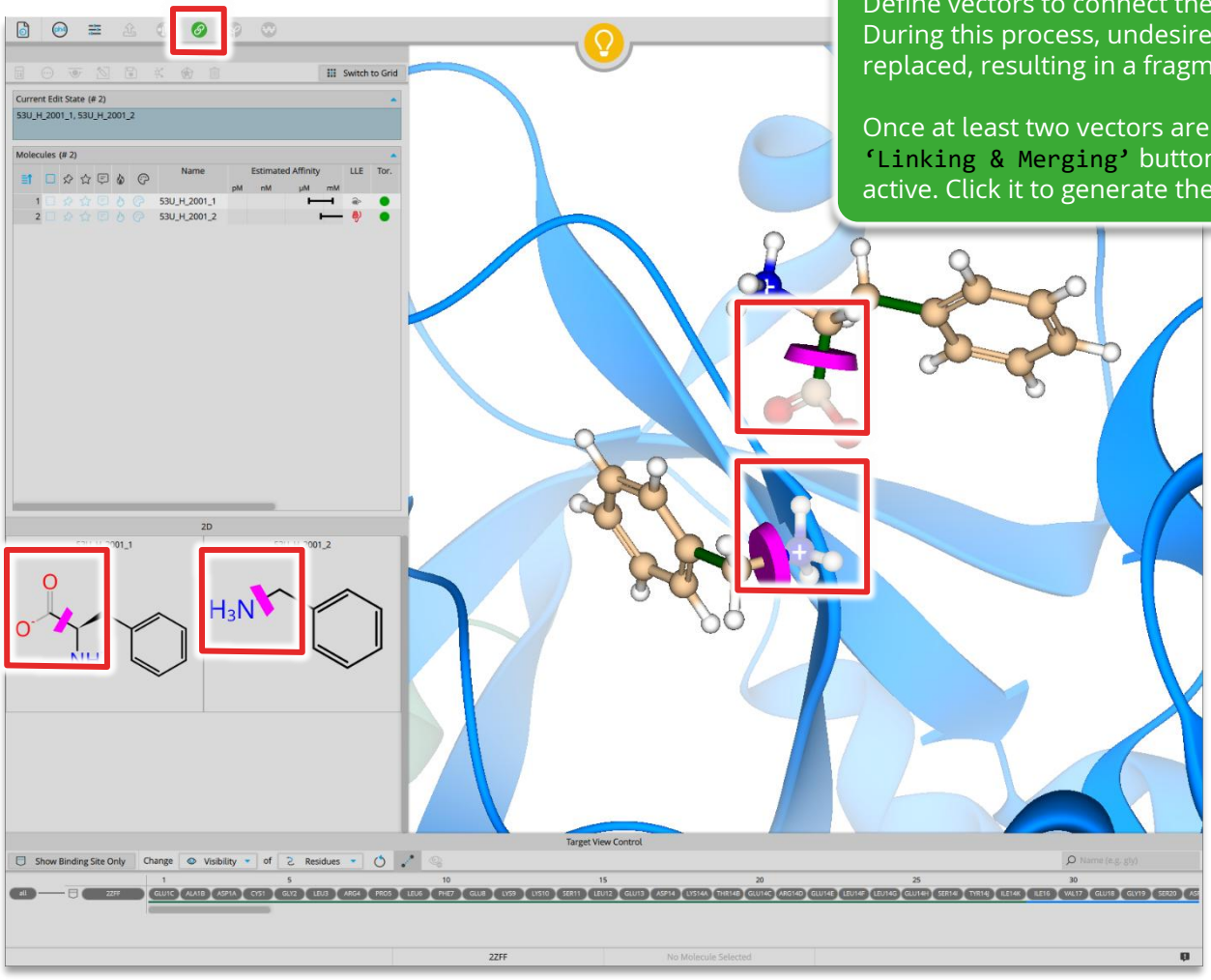
Mode Overview



Define vectors to connect the two molecules. During this process, undesired parts can be replaced, resulting in a fragment merge.

Once at least two vectors are defined, the **'Linking & Merging'** button will become active. Click it to generate the results.

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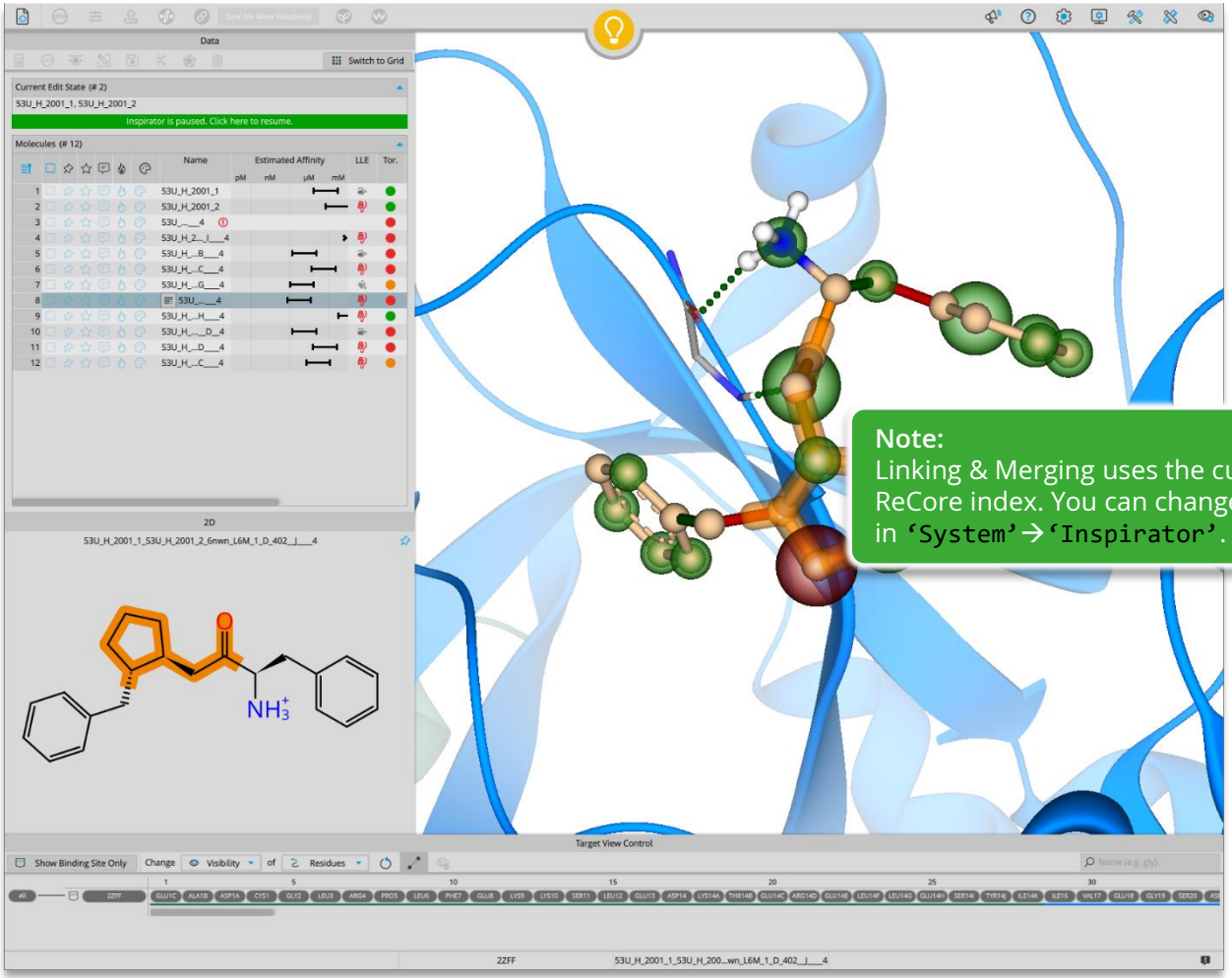
Mode Overview



Note:
Linking & Merging uses the currently active ReCore index. You can change the fragment set in `'System'→'Inspirator'`.

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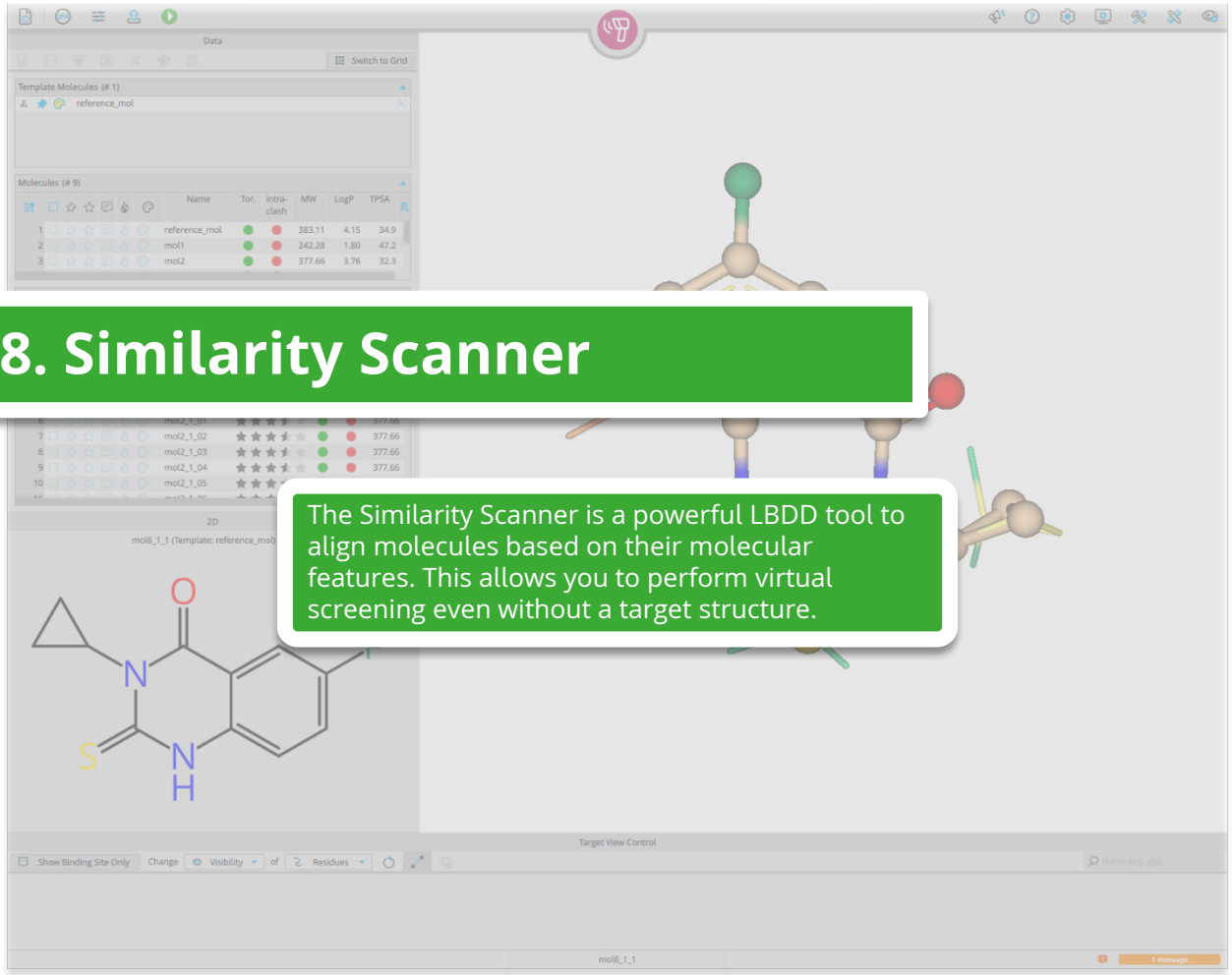
Mode Overview

8. Similarity Scanner



The Similarity Scanner is a powerful LBDD tool to align molecules based on their molecular features. This allows you to perform virtual screening even without a target structure.

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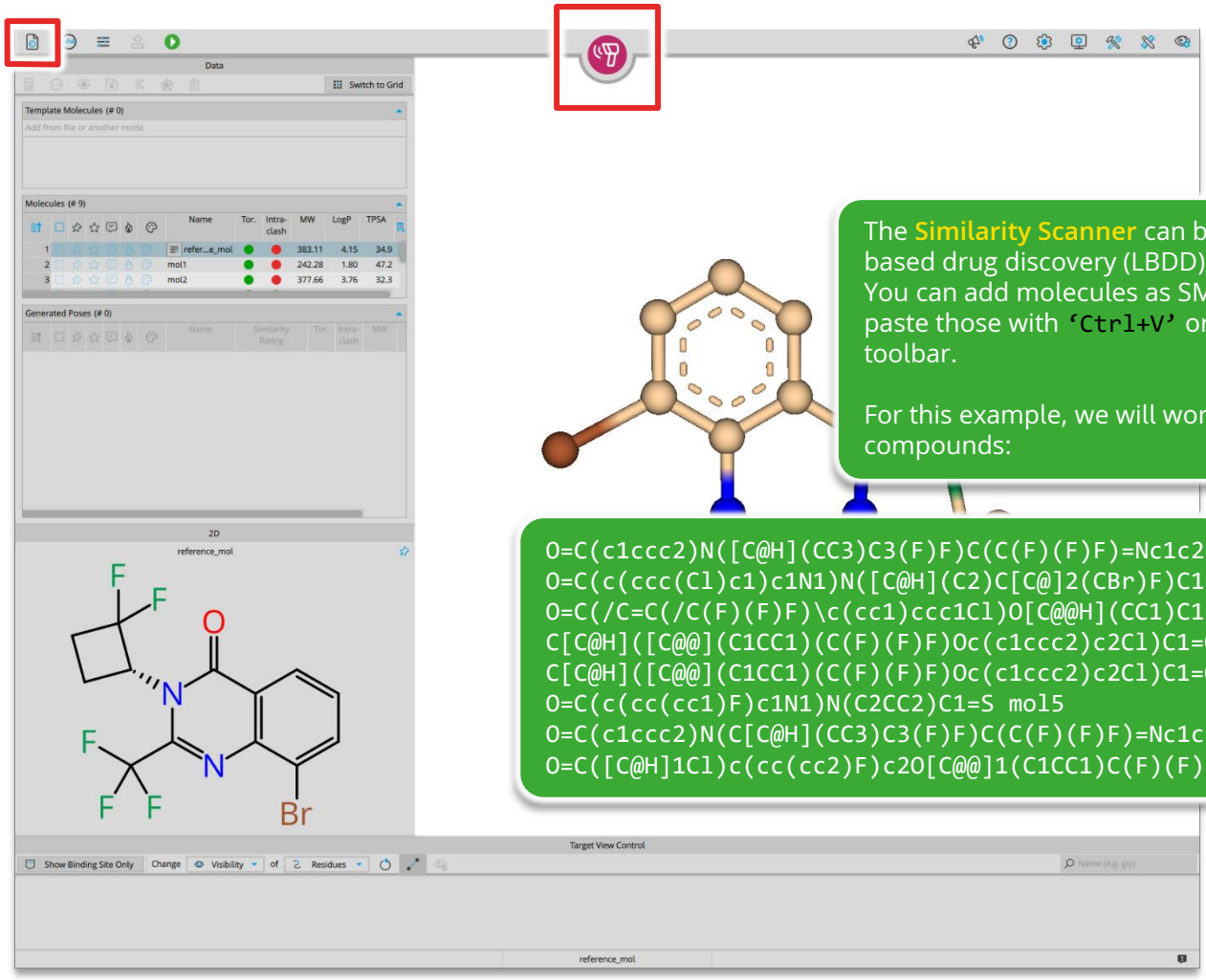
Mode Overview



The **Similarity Scanner** can be used for ligand-based drug discovery (LBDD).
You can add molecules as SMILES by copy-and-paste those with **'Ctrl+V'** or load those via the toolbar.

For this example, we will work with a set of compounds:

```
O=C(c1ccc2)N([C@H](CC3)C3(F)F)C(C(F)(F)F)=Nc1c2Br reference_mol
O=C(c(ccc(Cl)c1)c1N1)N([C@H](C2)C[C@]2(CBr)F)C1=S mol1
O=C(/C=C(/C(F)(F)F)\c(cc1)ccc1Cl)O[C@@H](CC1)C1(F)F mol2
C[C@H]([C@@](C1CC1)(C(F)(F)F)Oc(c1ccc2)c2Cl)C1=O mol3
C[C@H]([C@@](C1CC1)(C(F)(F)F)Oc(c1ccc2)c2Cl)C1=O mol4
O=C(c(cc(cc1)F)c1N1)N(C2CC2)C1=S mol5
O=C(c1ccc2)N(C[C@H](CC3)C3(F)F)C(C(F)(F)F)=Nc1c2Br mol6
O=C([C@H]1Cl)c(cc(cc2)F)c2O[C@@]1(C1CC1)C(F)(F)F mol7
```

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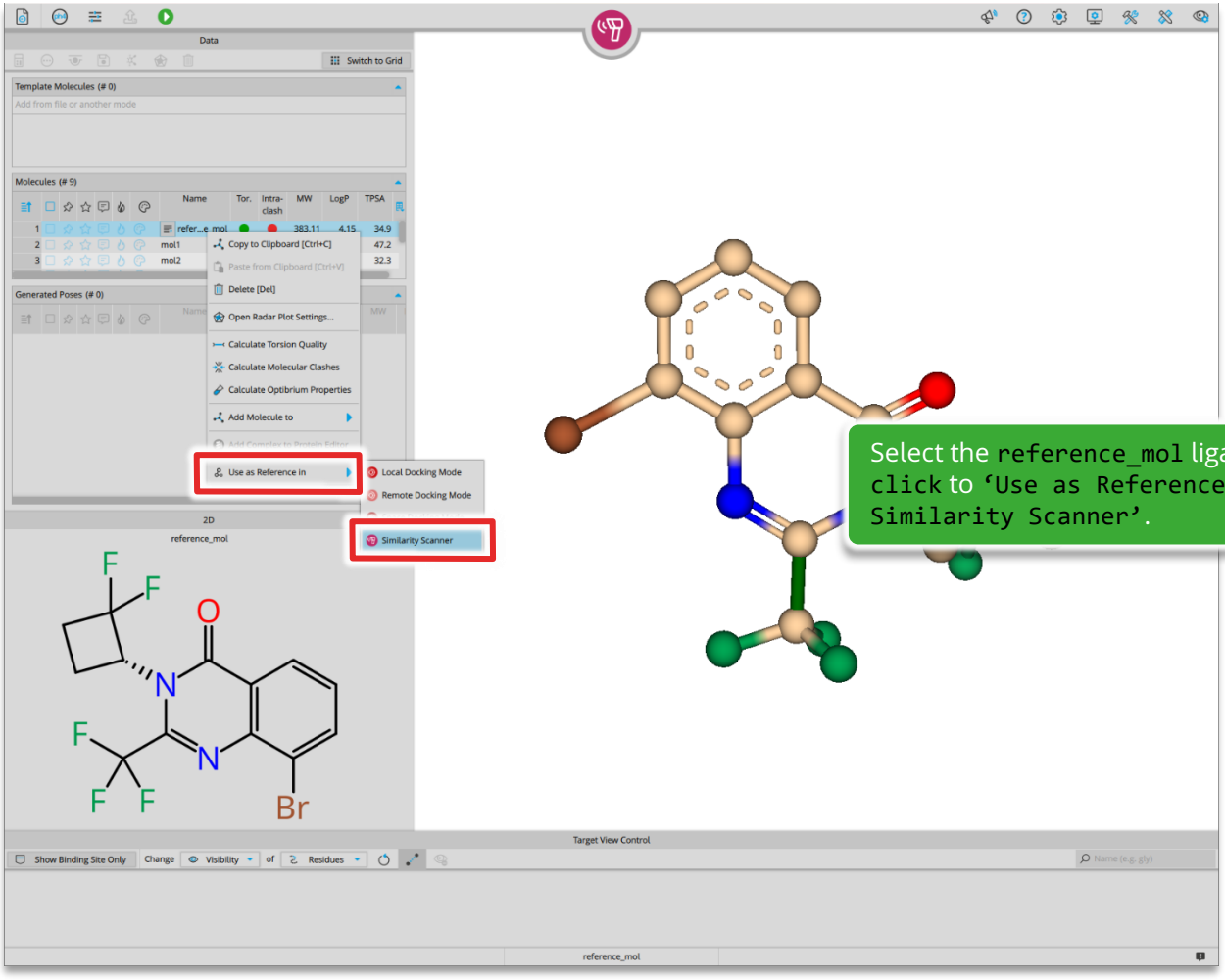
Mode Overview



Select the `reference_mol` ligand with `right-click` to `'Use as Reference'`→`'In Similarity Scanner'`.

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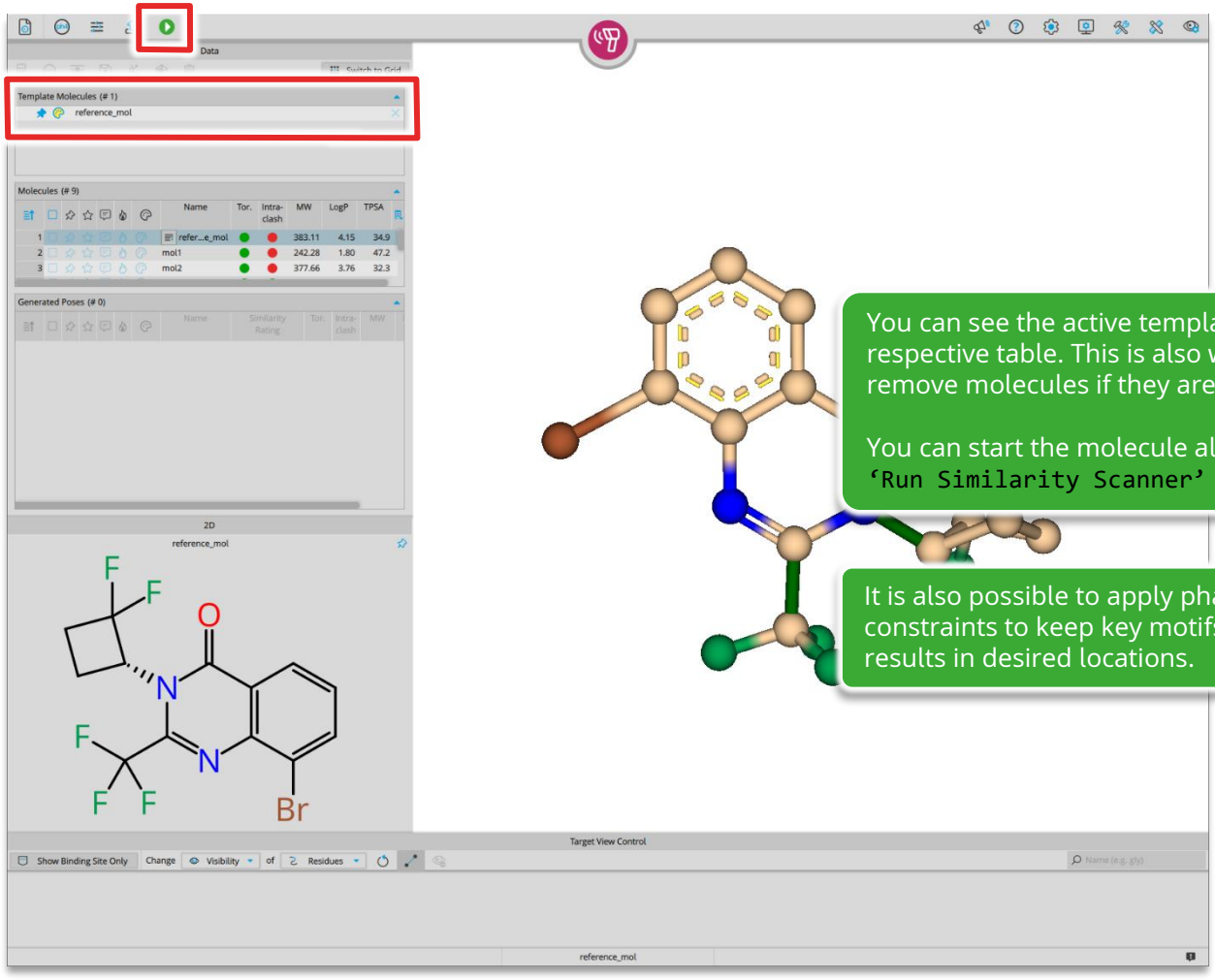
Mode Overview



You can see the active template in the respective table. This is also where you can remove molecules if they are no longer needed.

You can start the molecule alignment with the `'Run Similarity Scanner'` button.

It is also possible to apply pharmacophore constraints to keep key motifs in the generated results in desired locations.

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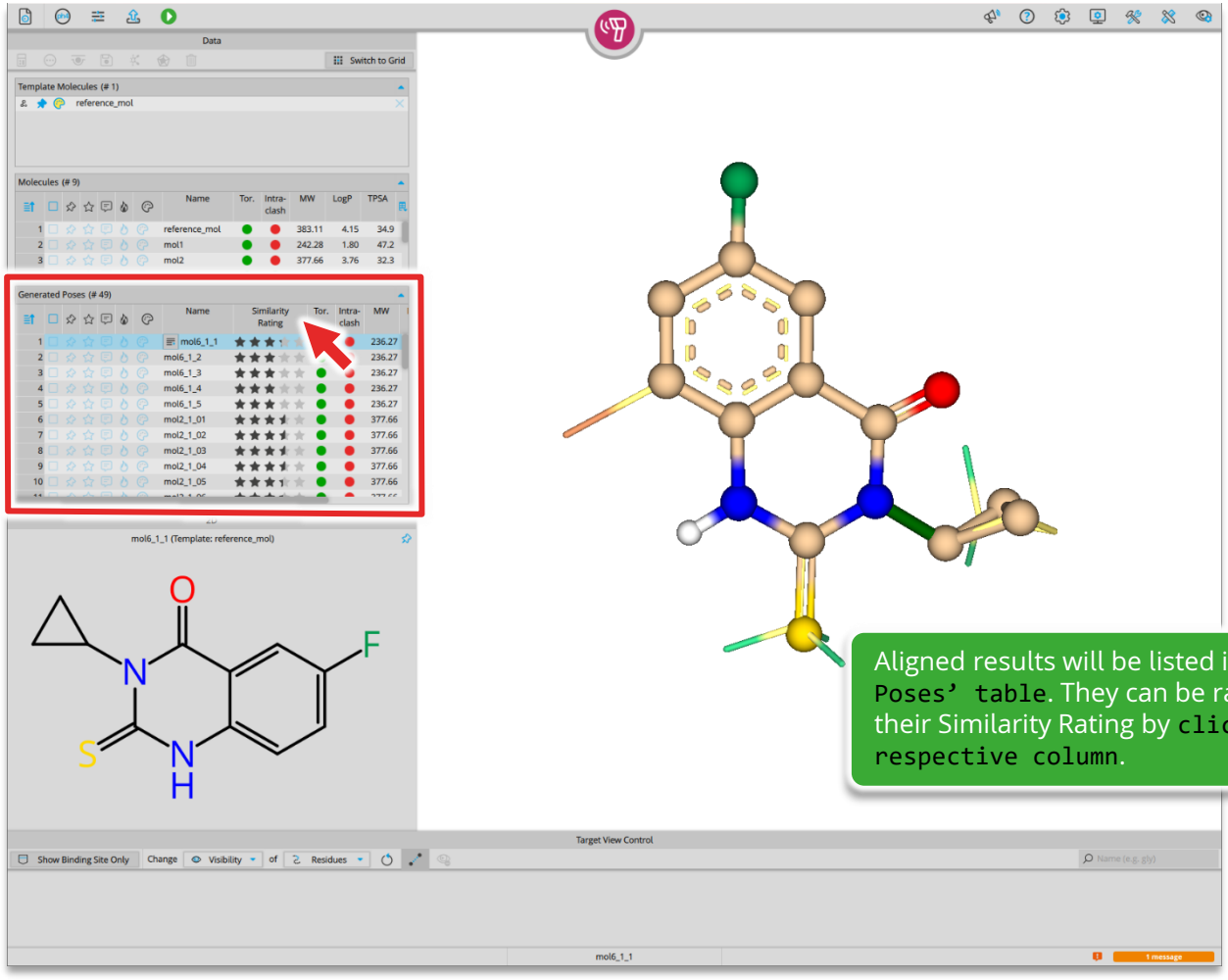
Mode Overview



Aligned results will be listed in the ‘Generated Poses’ table. They can be ranked based on their Similarity Rating by clicking on the respective column.

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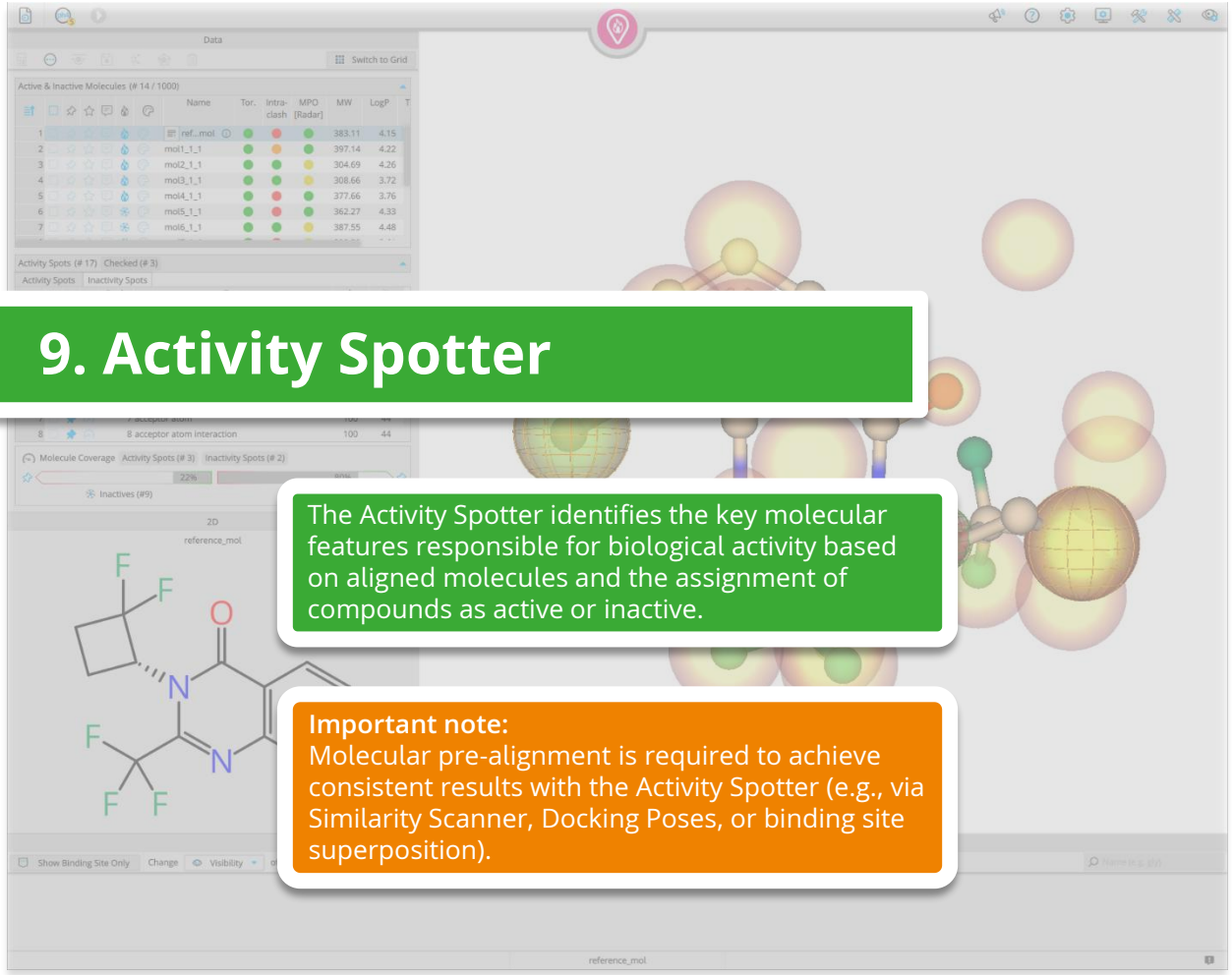
Mode Overview

9. Activity Spotter



The Activity Spotter identifies the key molecular features responsible for biological activity based on aligned molecules and the assignment of compounds as active or inactive.

Important note:
Molecular pre-alignment is required to achieve consistent results with the Activity Spotter (e.g., via Similarity Scanner, Docking Poses, or binding site superposition).

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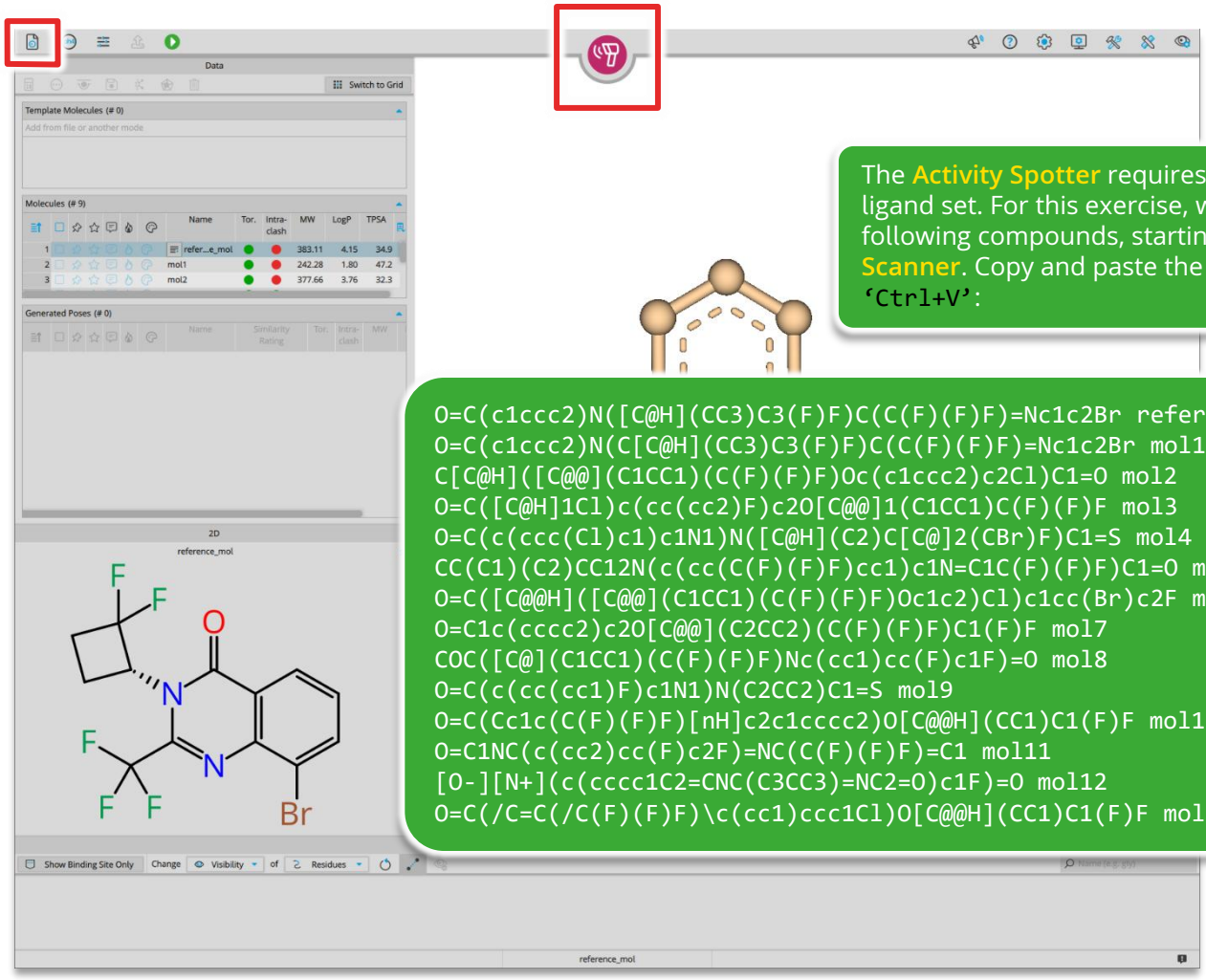
Mode Overview



The **Activity Spotter** requires a pre-aligned ligand set. For this exercise, we will use the following compounds, starting in the **Similarity Scanner**. Copy and paste the ligands using ‘Ctrl+V’:

```
O=C(c1ccc2)N([C@H](CC3)C3(F)F)C(C(F)(F)F)=Nc1c2Br reference_mol
O=C(c1ccc2)N(C[C@H](CC3)C3(F)F)C(C(F)(F)F)=Nc1c2Br mol1
C[C@H]([C@@](C1CC1)(C(F)(F)F)Oc(c1ccc2)c2Cl)C1=O mol2
O=C([C@H]1Cl)c(cc(cc2)F)c2O[C@@]1(C1CC1)C(F)(F)F mol3
O=C(c(ccc(Cl)c1)c1N1)N([C@H](C2)C[C@]2(CBr)F)C1=S mol4
CC(C1)(C2)CC12N(c(cc(C(F)(F)F)cc1)c1N=C1C(F)(F)F)C1=O mol5
O=C([C@@H]([C@@](C1CC1)(C(F)(F)F)Oc1c2)Cl)c1cc(Br)c2F mol6
O=C1c(cccc2)c2O[C@@](C2CC2)(C(F)(F)F)C1(F)F mol7
COC([C@](C1CC1)(C(F)(F)F)Nc(cc1)cc(F)c1F)=O mol8
O=C(c(cc(cc1)F)c1N1)N(C2CC2)C1=S mol9
O=C(Cc1c(C(F)(F)F)[nH]c2c1cccc2)O[C@@H](CC1)C1(F)F mol10
O=C1NC(c(cc2)cc(F)c2F)=NC(C(F)(F)F)=C1 mol11
[O-][N+](c(cccc1C2=CNC(C3CC3)=NC2=O)c1F)=O mol12
O=C(/C=C(/C(F)(F)F)\c(cc1)ccc1Cl)O[C@@H](CC1)C1(F)F mol13
```

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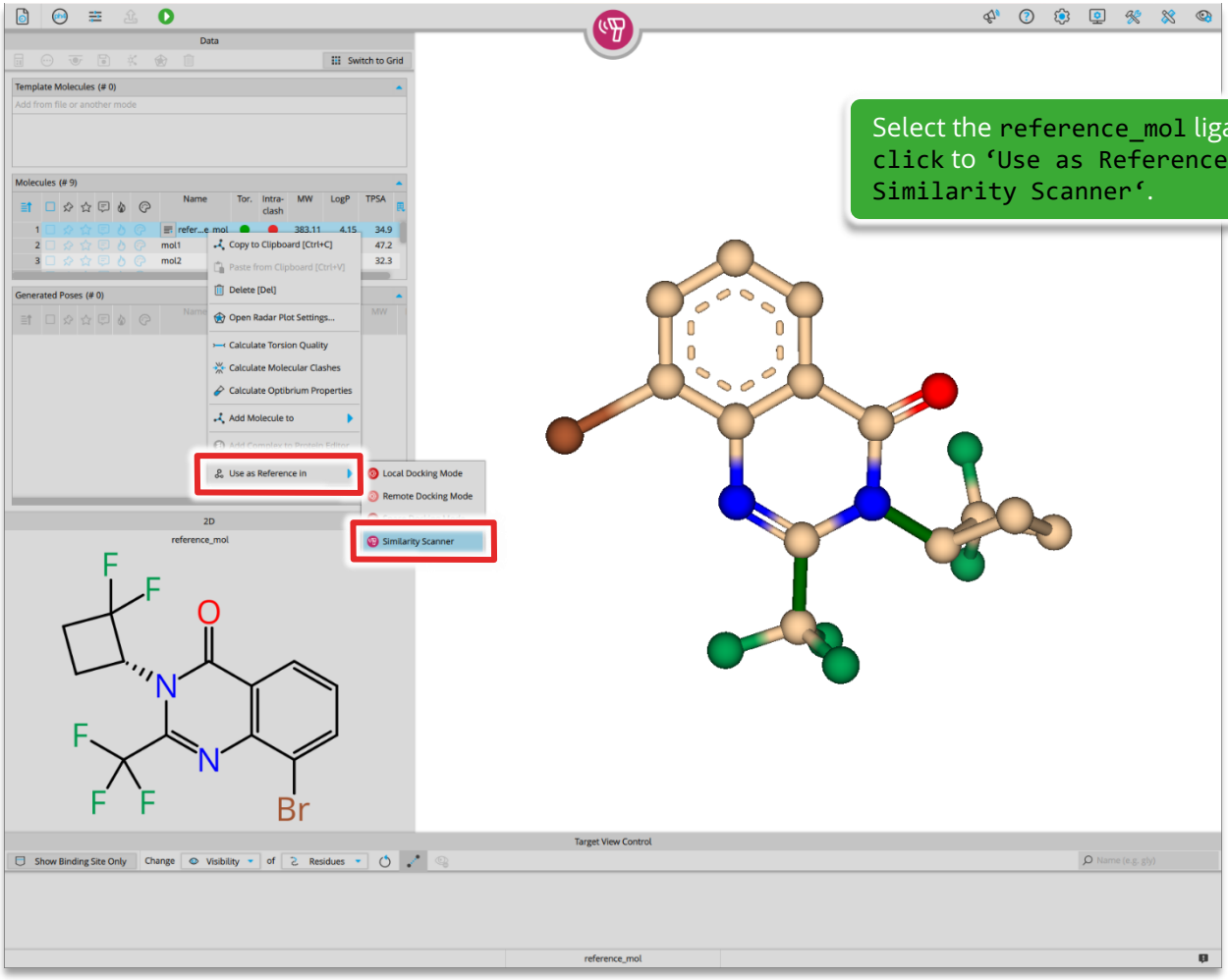
Mode Overview



Select the `reference_mol` ligand with a `right click` to '`Use as Reference`' → '`In Similarity Scanner`'.

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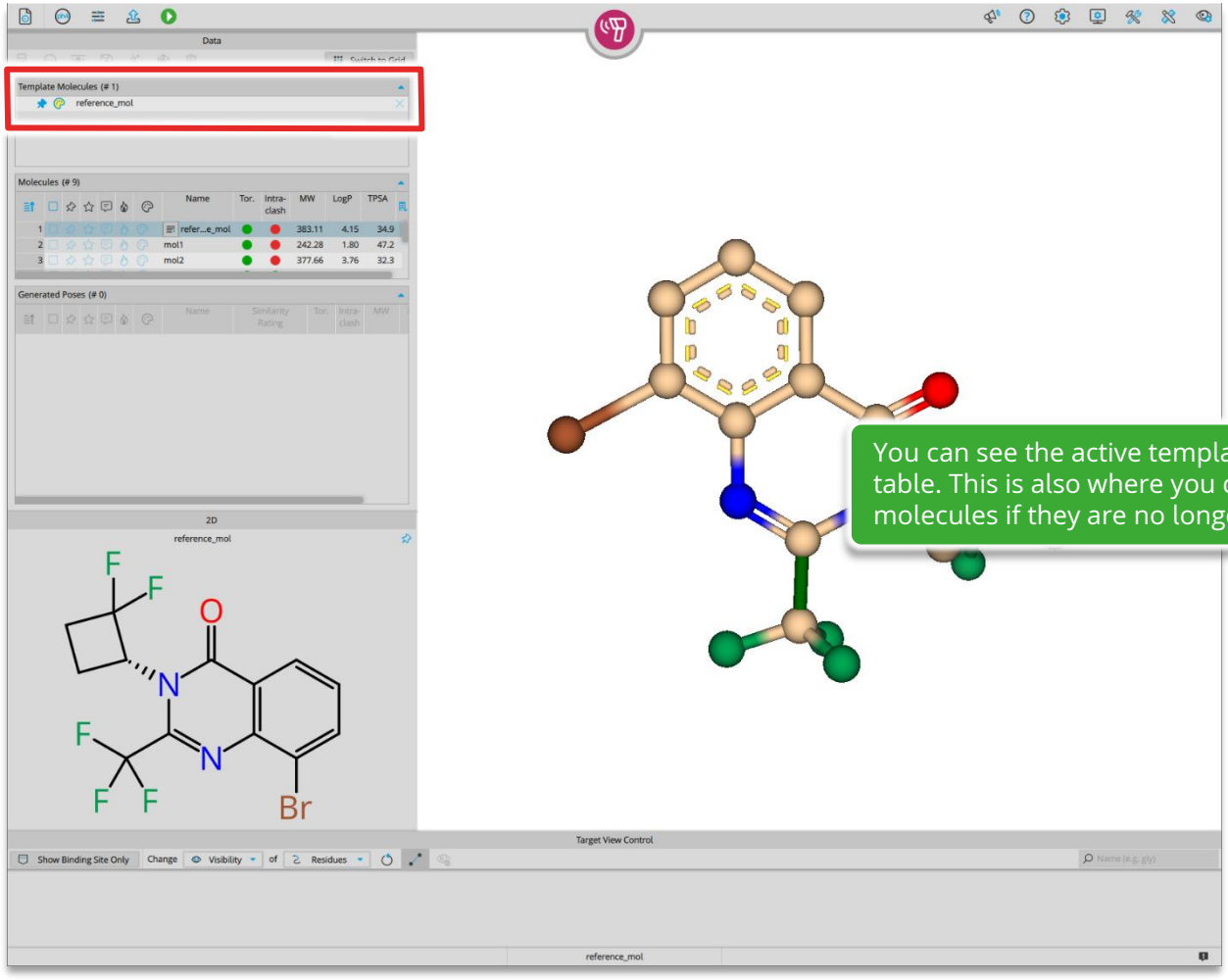
Mode Overview



You can see the active template in the respective table. This is also where you can remove molecules if they are no longer needed.

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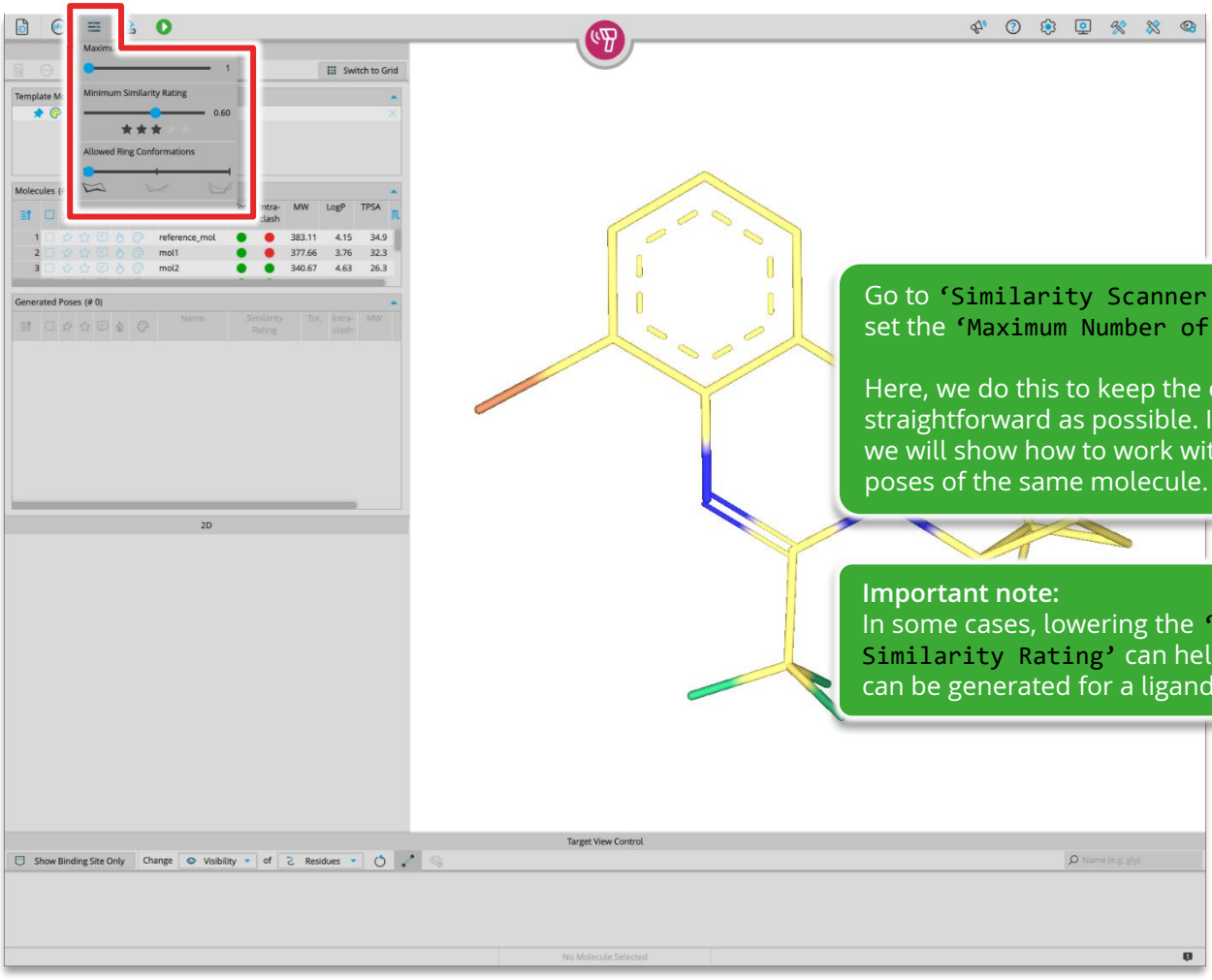
Mode Overview



Go to ‘Similarity Scanner Parameters’ and set the ‘Maximum Number of Poses’ to ‘1’.

Here, we do this to keep the exercise as straightforward as possible. In the later slides, we will show how to work with larger sets of poses of the same molecule.

Important note:
In some cases, lowering the ‘Minimum Similarity Rating’ can help when no poses can be generated for a ligand.

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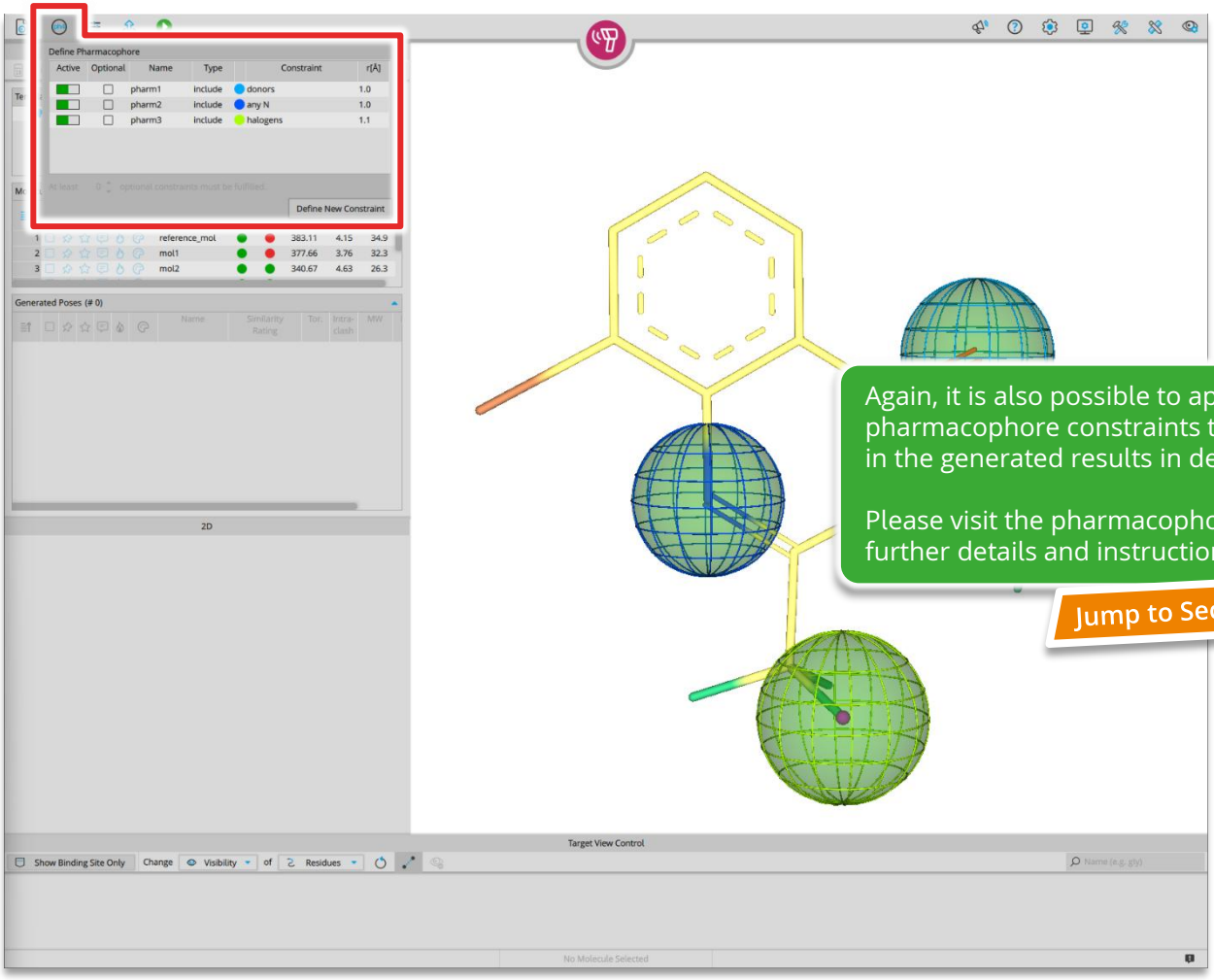
Mode Overview



Again, it is also possible to apply pharmacophore constraints to keep key motifs in the generated results in desired locations.

Please visit the pharmacophore section for further details and instructions.

Jump to Section

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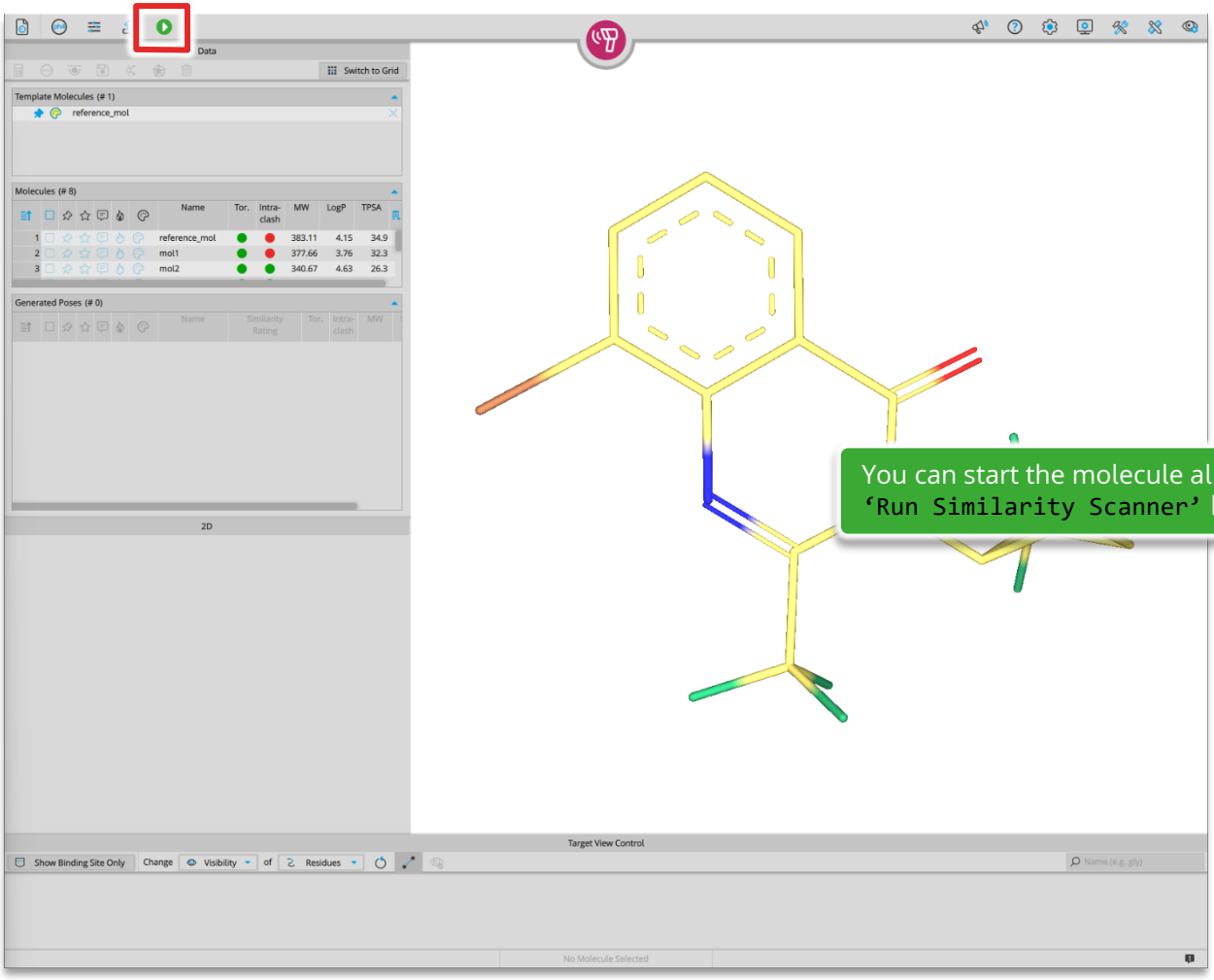
Mode Overview



You can start the molecule alignment with the ‘Run Similarity Scanner’ button.

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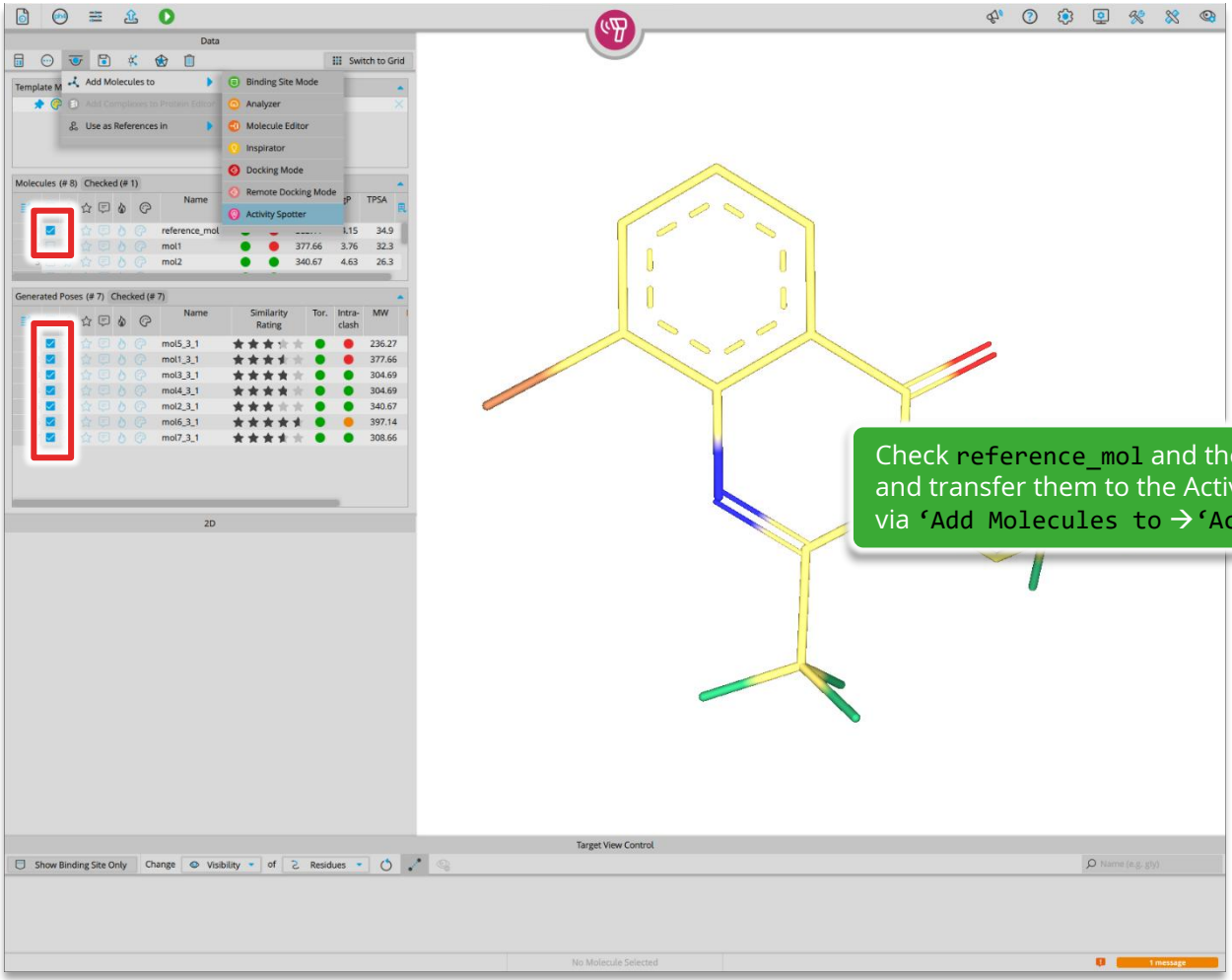
Mode Overview



Check `reference_mol` and the `generated poses` and transfer them to the Activity Spotter Mode via '`Add Molecules to` → '`Activity Spotter`'.

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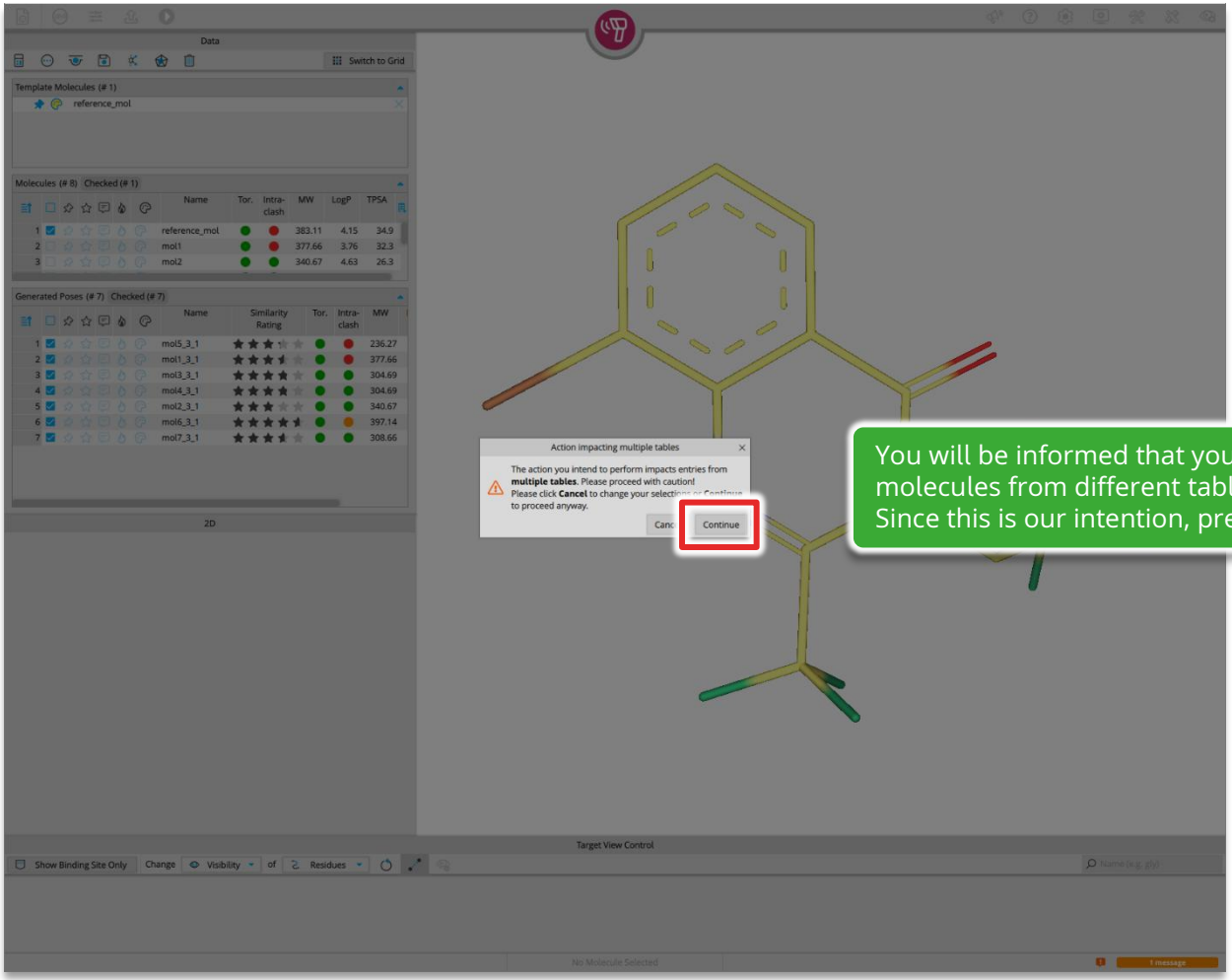
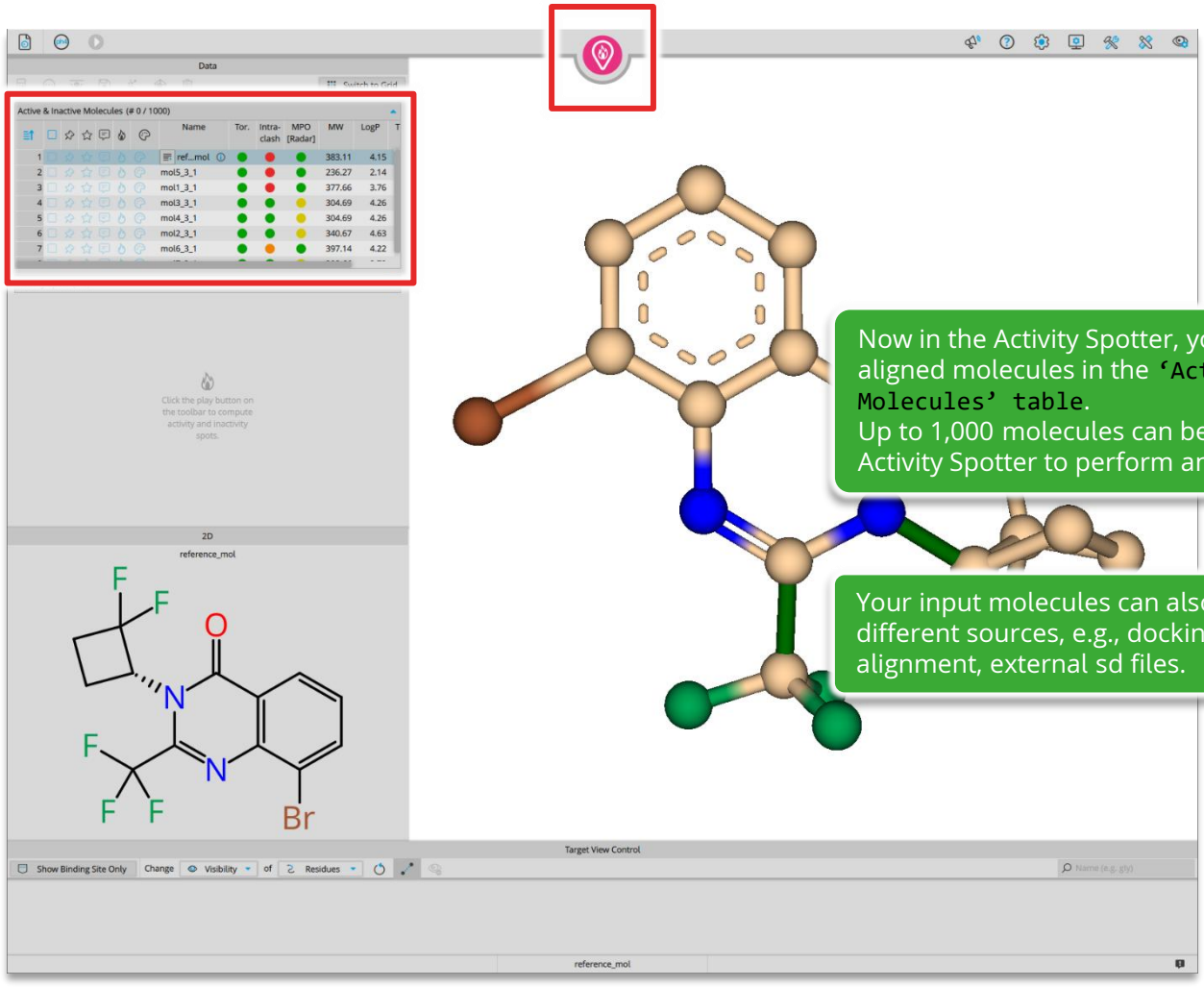
Mode Overview



You will be informed that you want to move molecules from different tables.
Since this is our intention, press **'Continue'**.

Table of Content
Mode Overview



Now in the Activity Spotter, you will find your aligned molecules in the **'Active & Inactive Molecules' table**.
Up to 1,000 molecules can be used in the Activity Spotter to perform an SAR analysis.

Your input molecules can also come from different sources, e.g., docking, binding site alignment, external sd files.

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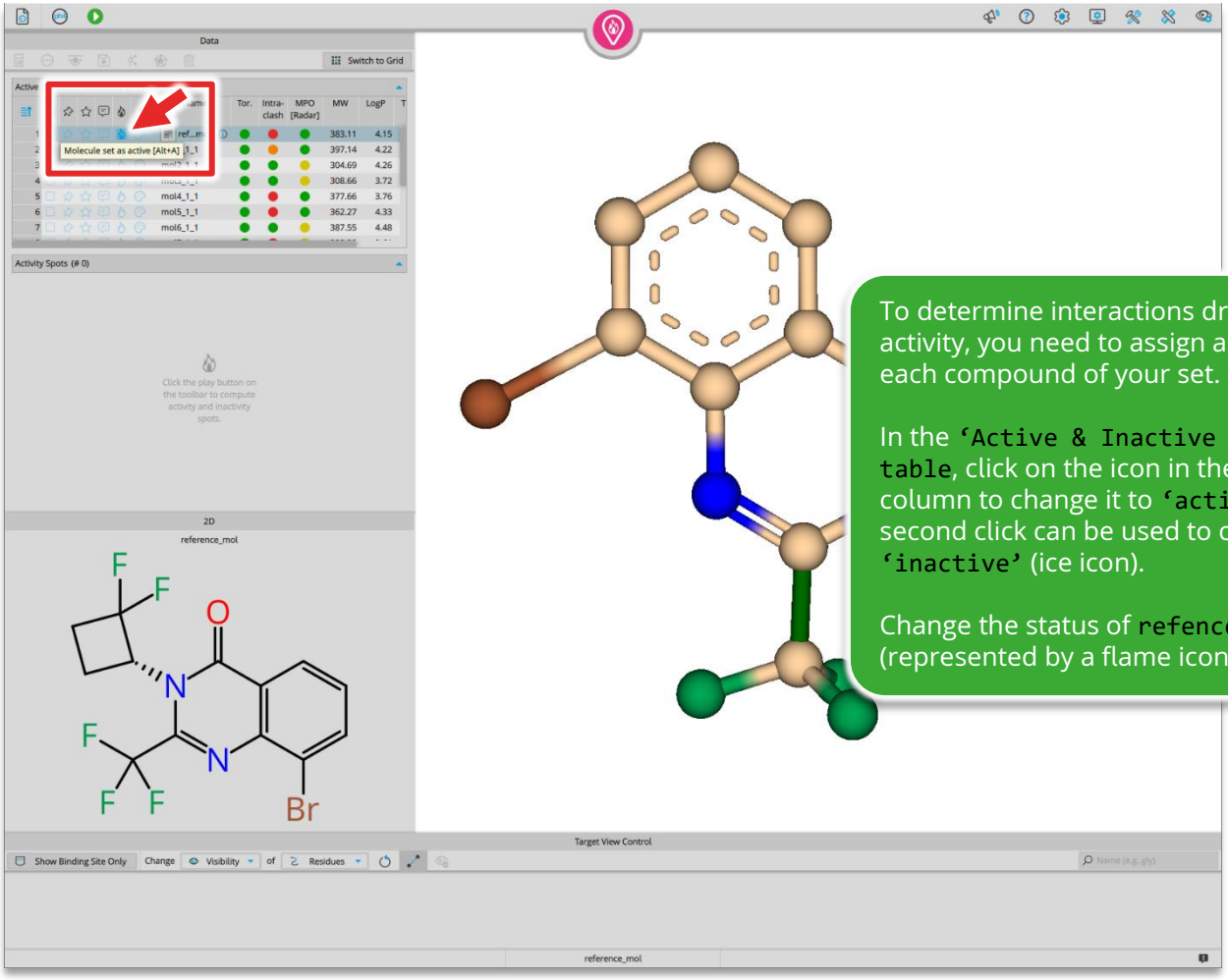
Mode Overview



To determine interactions driving the biological activity, you need to assign an activity status to each compound of your set.

In the `'Active & Inactive Molecules' table`, click on the icon in the `'Active Status'` column to change it to `'active'` (flame icon). A second click can be used to change it to `'inactive'` (ice icon).

Change the status of `refence_mol` to `'active'` (represented by a flame icon).

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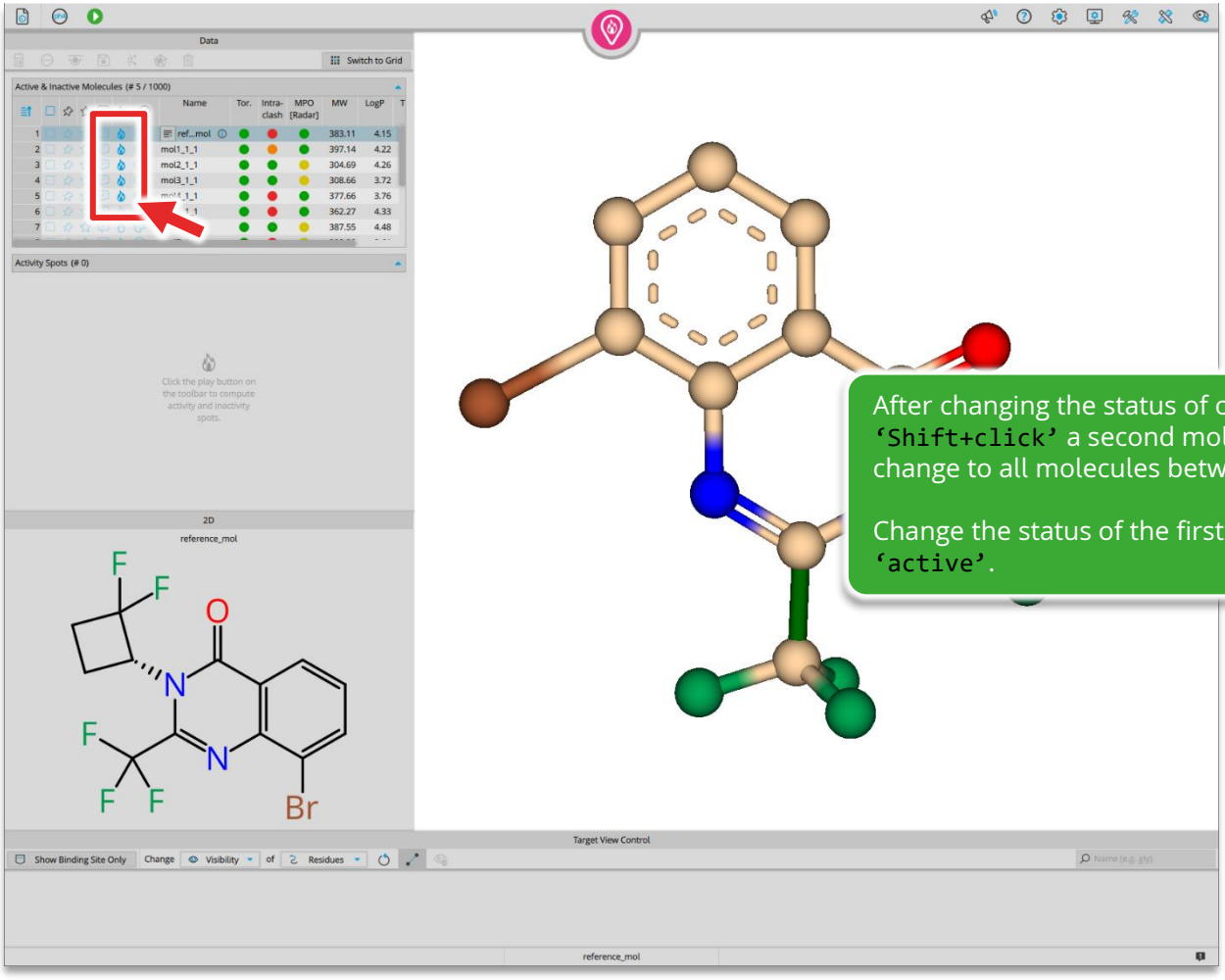
Mode Overview



After changing the status of one molecule, ‘`Shift+click`’ a second molecule applies the change to all molecules between the two.

Change the status of the first five molecules to ‘`active`’.

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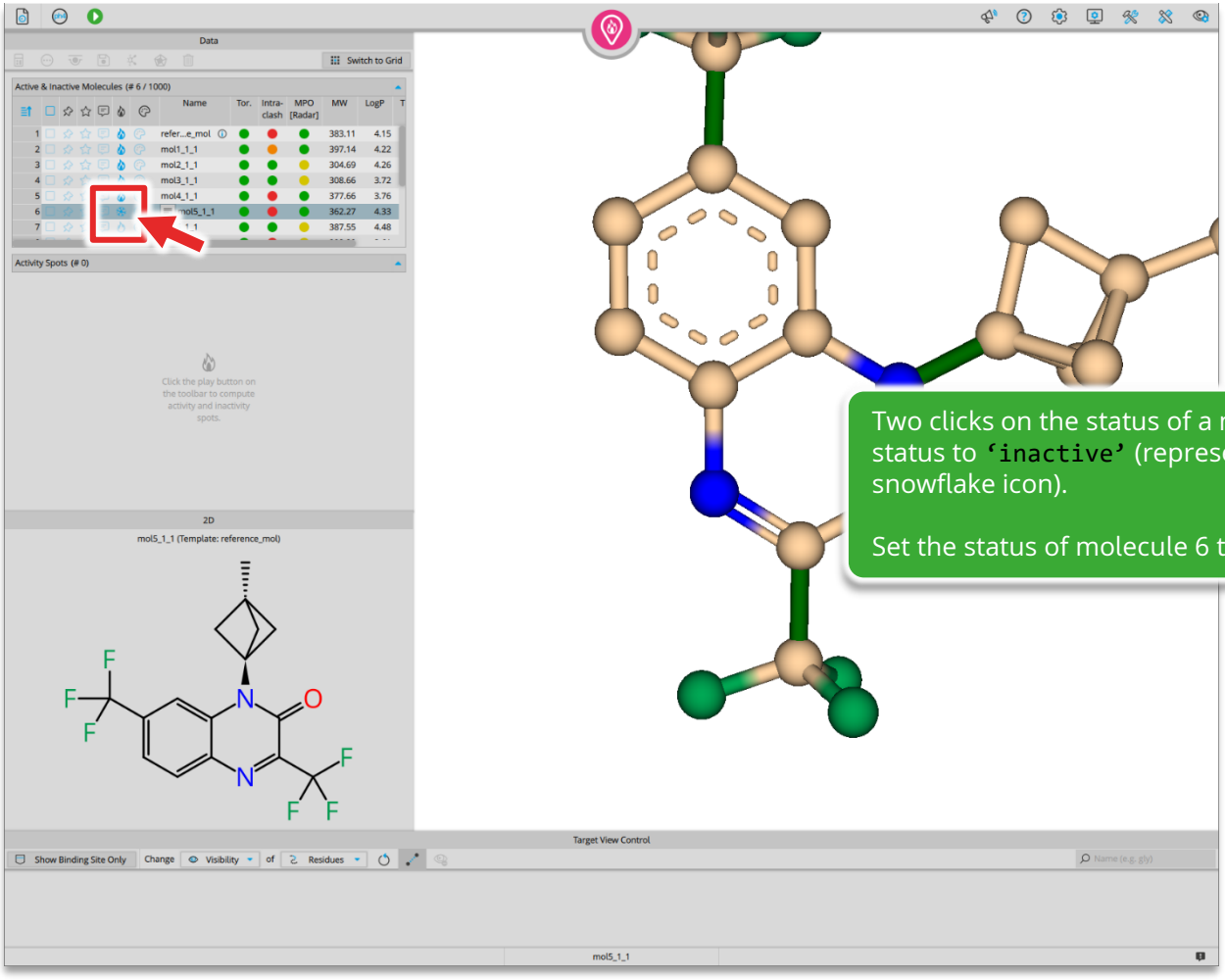
Mode Overview



Two clicks on the status of a molecule change its status to `'inactive'` (represented by a snowflake icon).

Set the status of molecule 6 to `'inactive'`.

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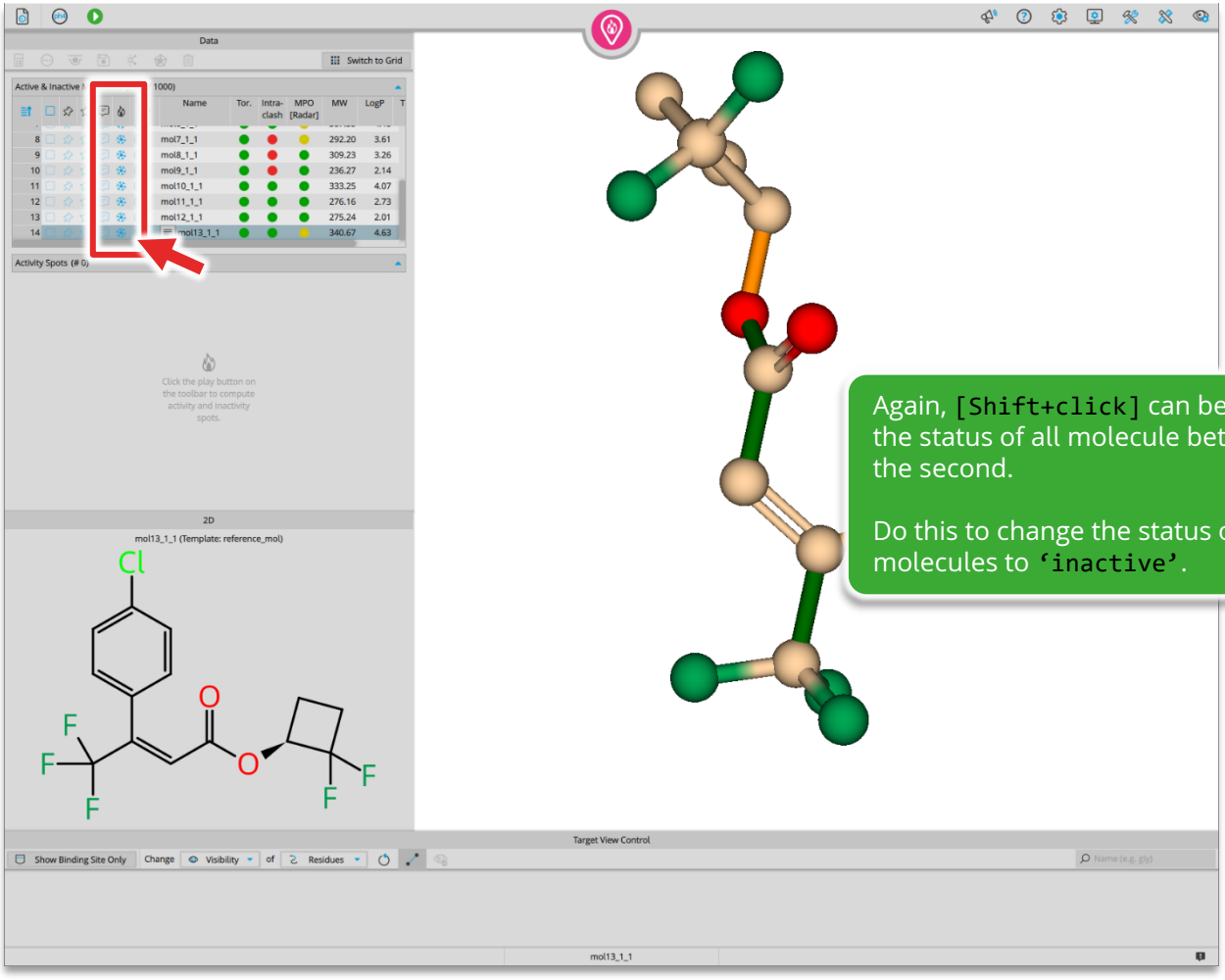
Mode Overview



Again, [Shift+click] can be used to change the status of all molecule between the first and the second.

Do this to change the status of the remaining molecules to 'inactive'.

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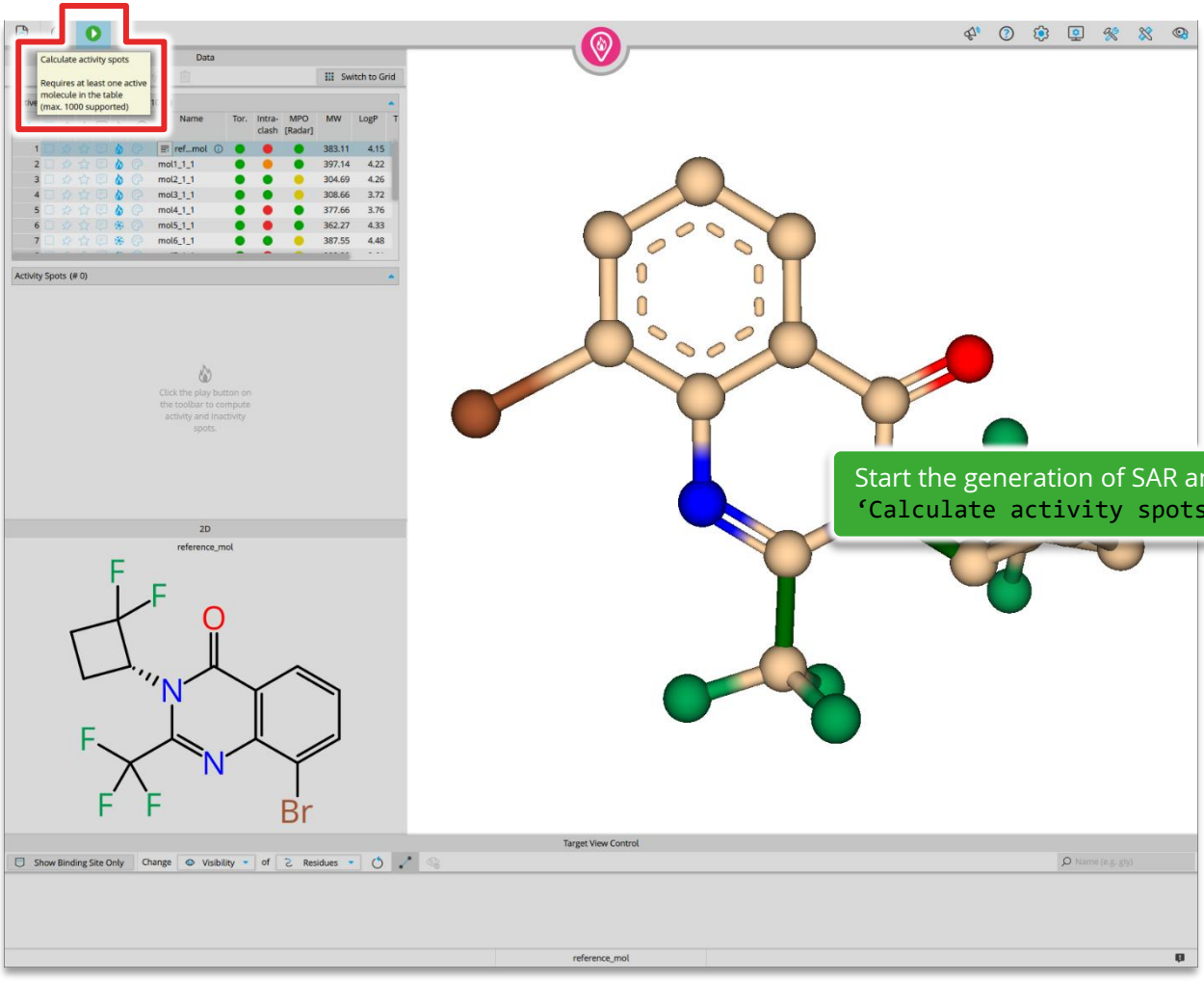
Mode Overview



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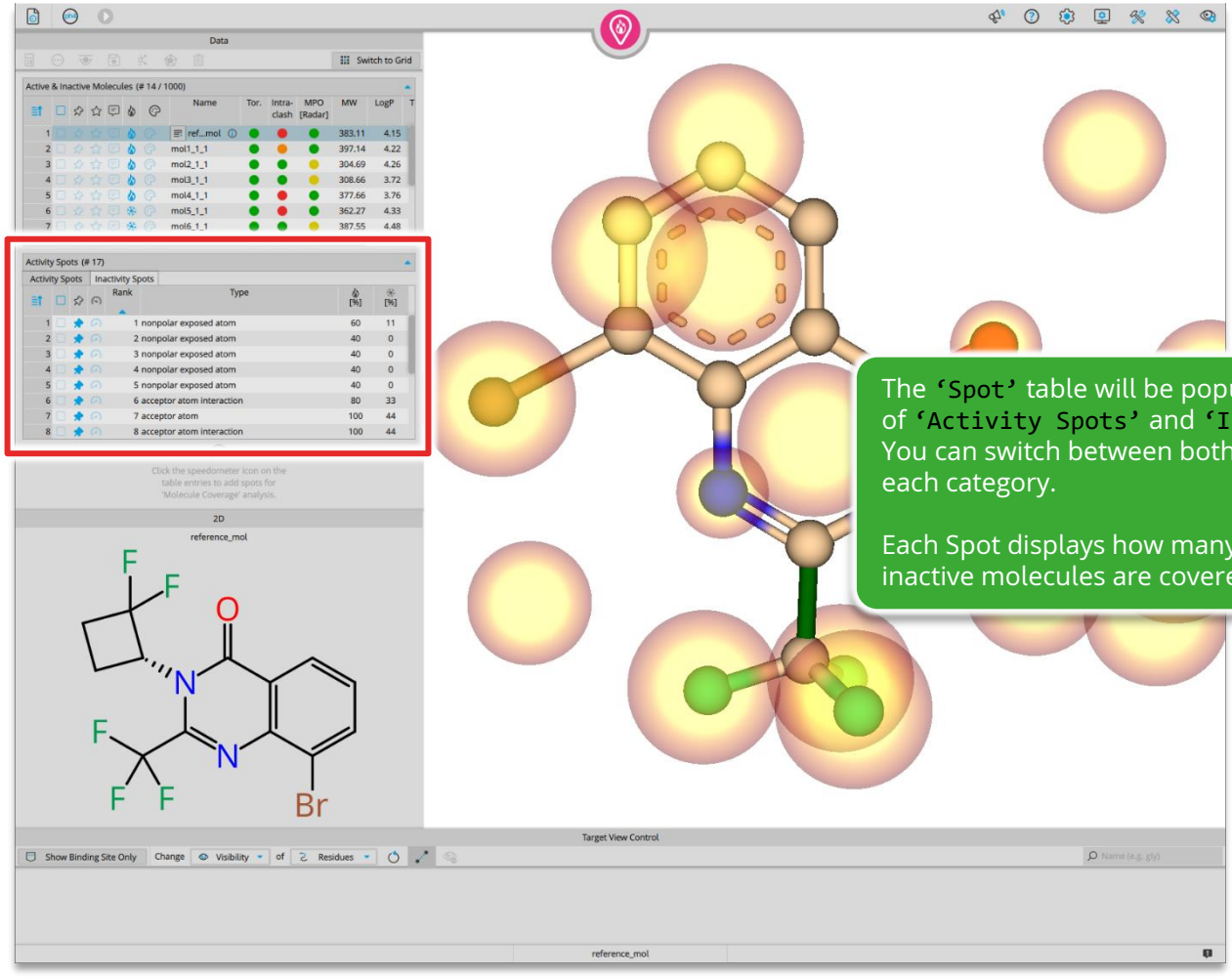
Mode Overview



The ‘Spot’ table will be populated with entries of ‘Activity Spots’ and ‘Inactivity Spots’. You can switch between both tabs to explore each category.

Each Spot displays how many of the active and inactive molecules are covered by it.

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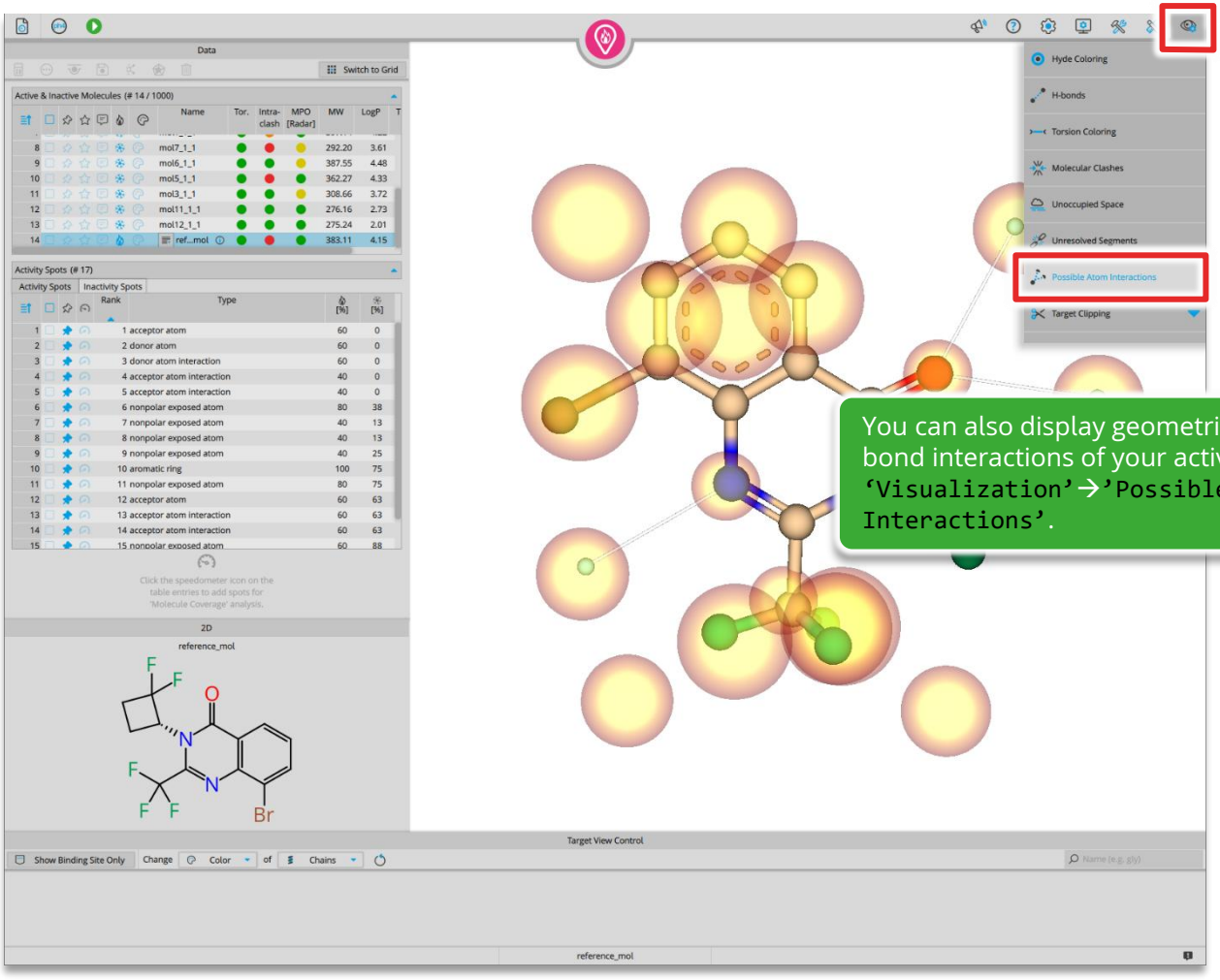
Mode Overview



You can also display geometrically potential H-bond interactions of your active molecule under ‘Visualization’→’Possible Atom Interactions’.

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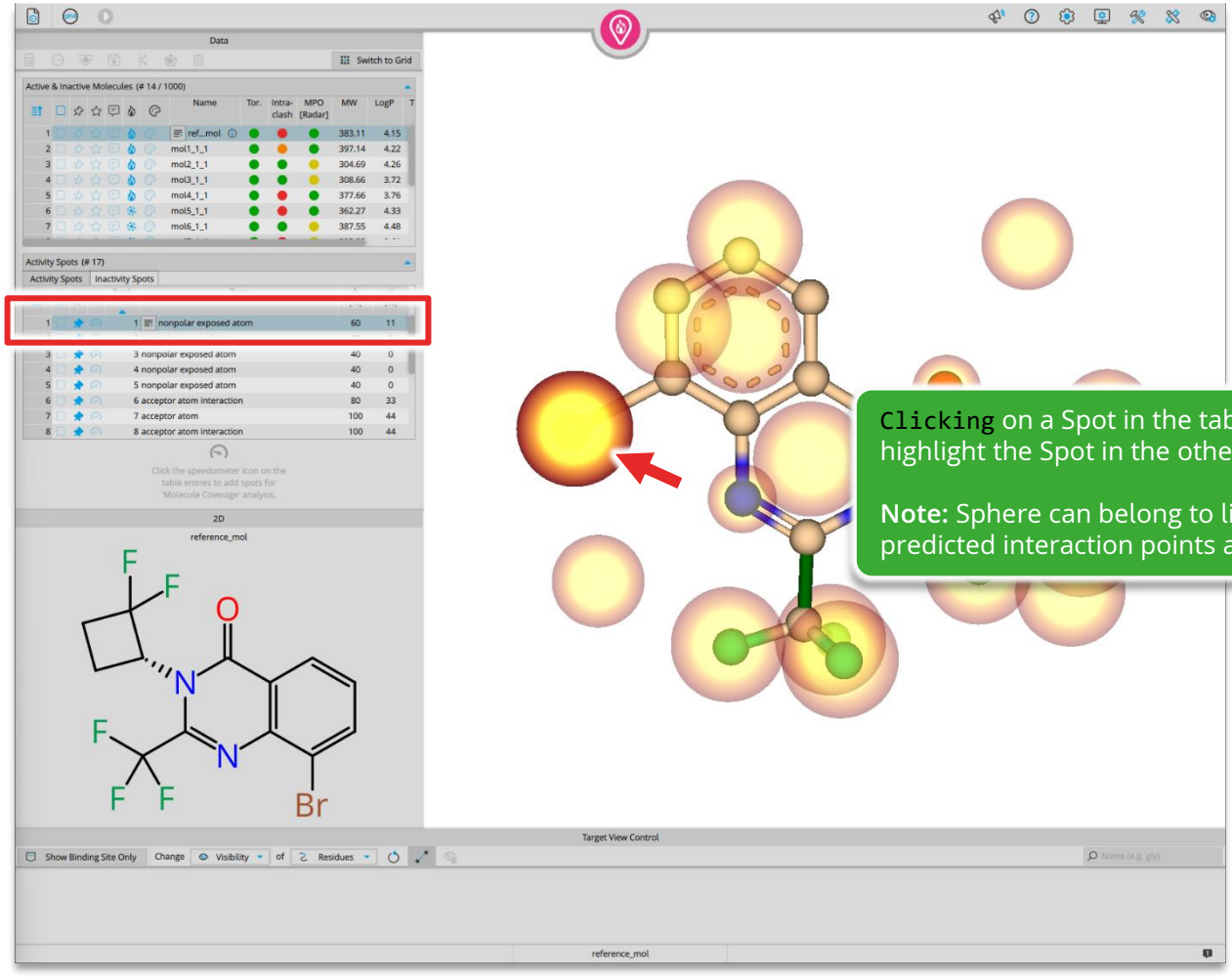
Mode Overview



Clicking on a Spot in the table or 3D will also highlight the Spot in the other section.

Note: Sphere can belong to ligands OR predicted interaction points at the target.

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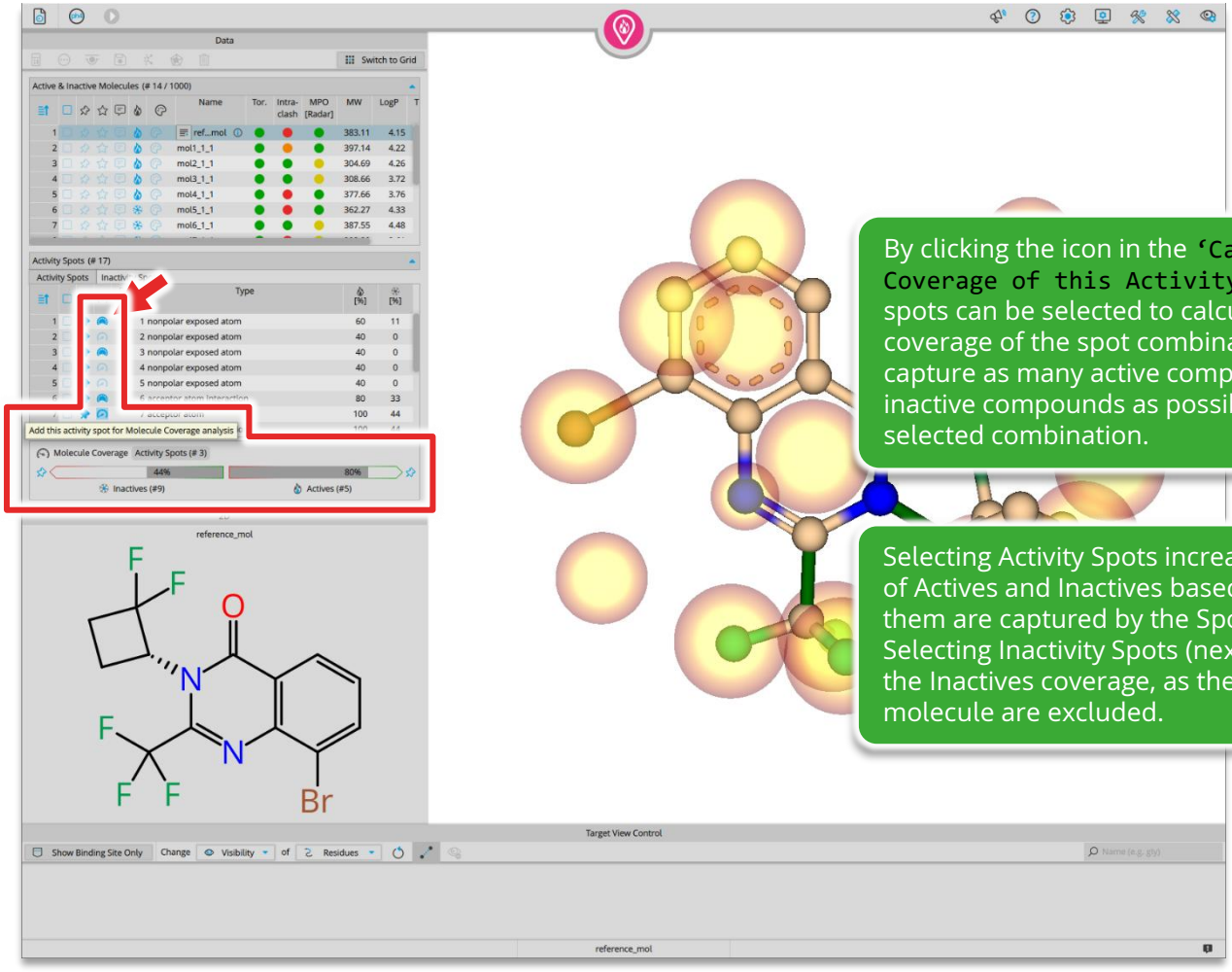
Mode Overview



By clicking the icon in the ‘`Calculate Molecule Coverage of this Activity Spot`’ column, spots can be selected to calculate the molecule coverage of the spot combination. The goal is to capture as many active compounds and as few inactive compounds as possible through the selected combination.

Selecting Activity Spots increases the coverage of Actives and Inactives based on how many of them are captured by the Spot, respectively. Selecting Inactivity Spots (next slide) decreases the Inactives coverage, as the covered inactive molecule are excluded.

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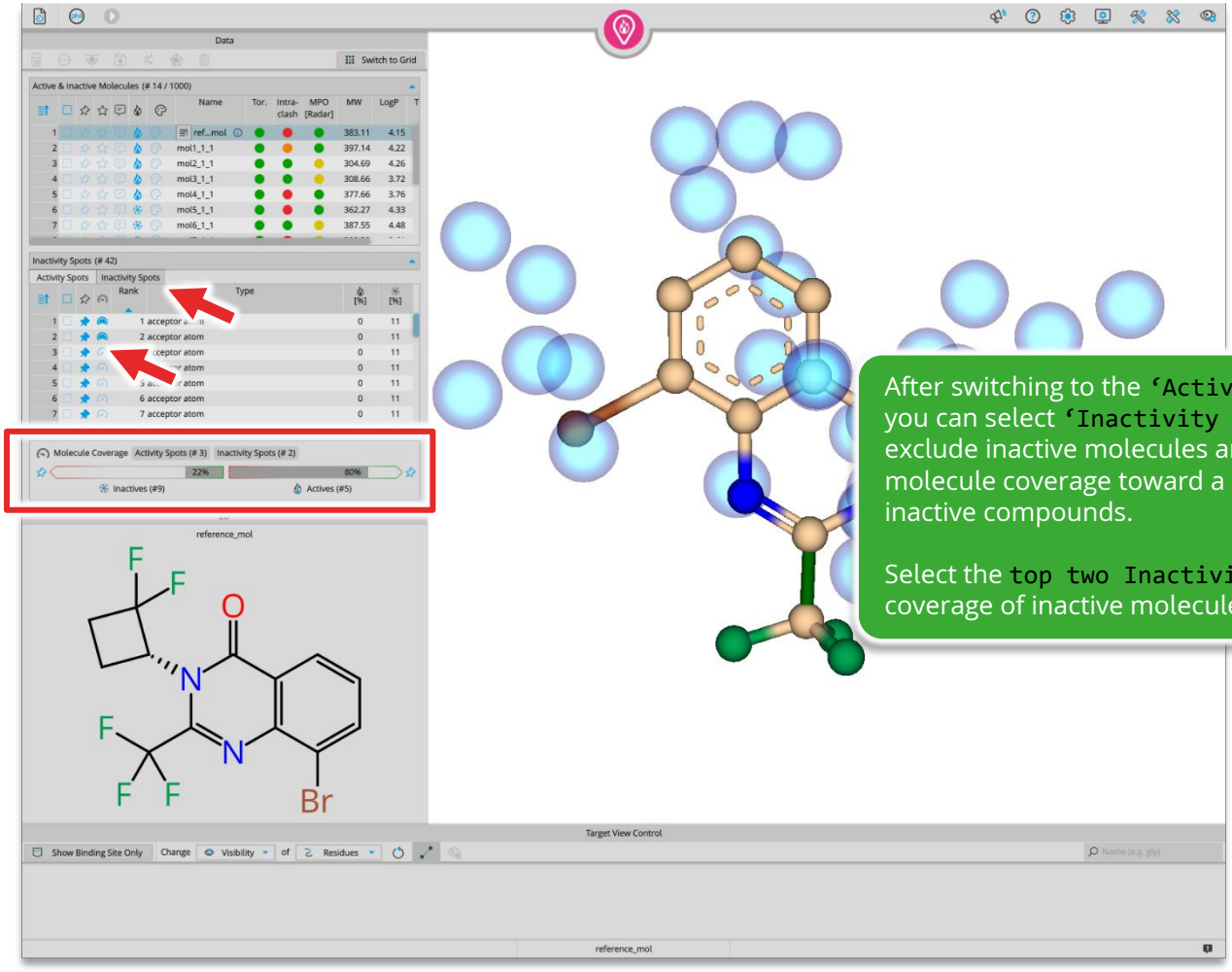
Mode Overview



After switching to the **'Activity Spots' tab**, you can select **'Inactivity Spots'**. These help exclude inactive molecules and shift the molecule coverage toward a lower number of inactive compounds.

Select the **top two Inactivity Spots**. The coverage of inactive molecules will decrease.

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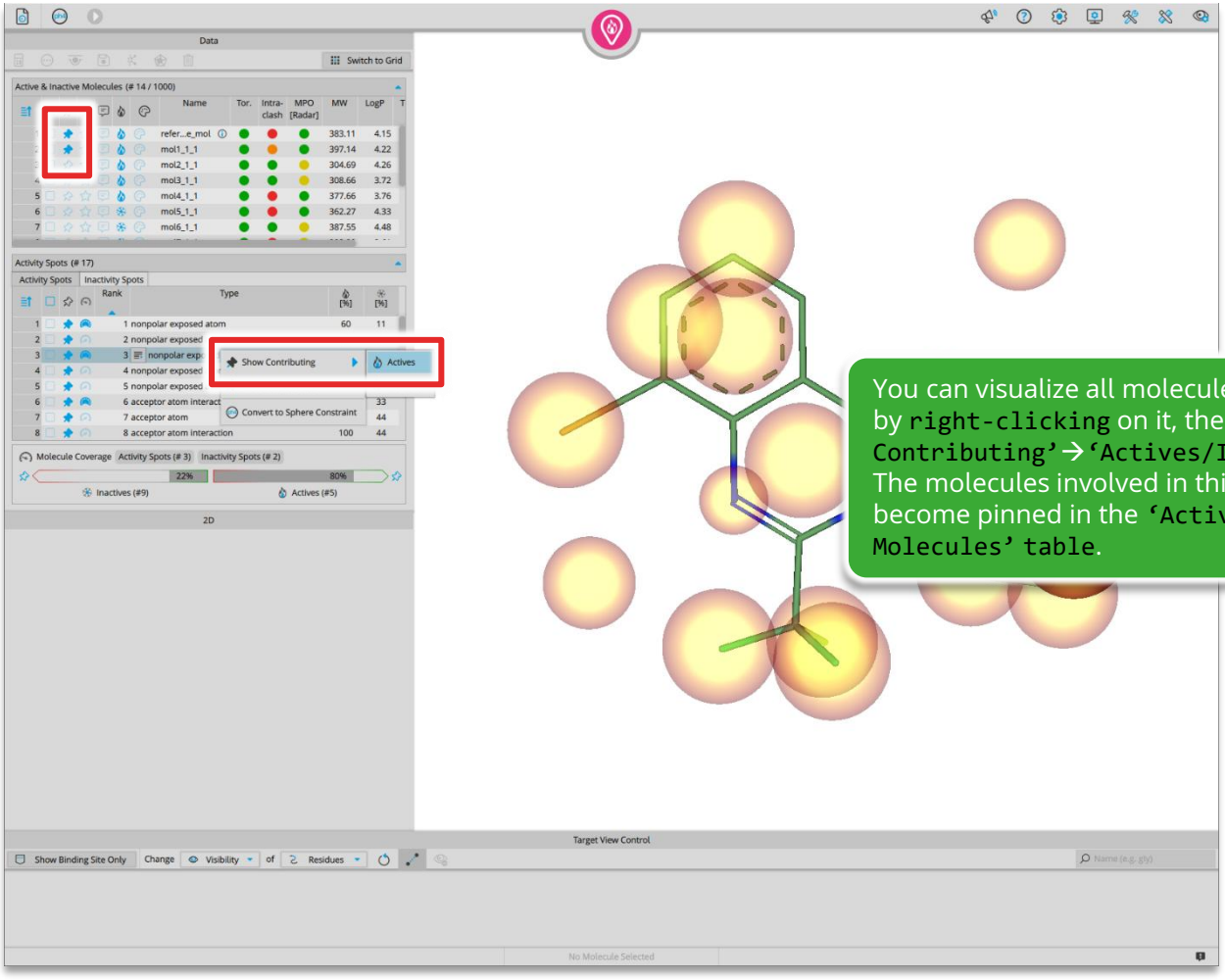
Mode Overview



You can visualize all molecule covered by a Spot by `right-clicking` on it, then `'Show Contributing'→'Actives/Inactives'`. The molecules involved in this spot will also become pinned in the `'Active & Inactive Molecules' table`.

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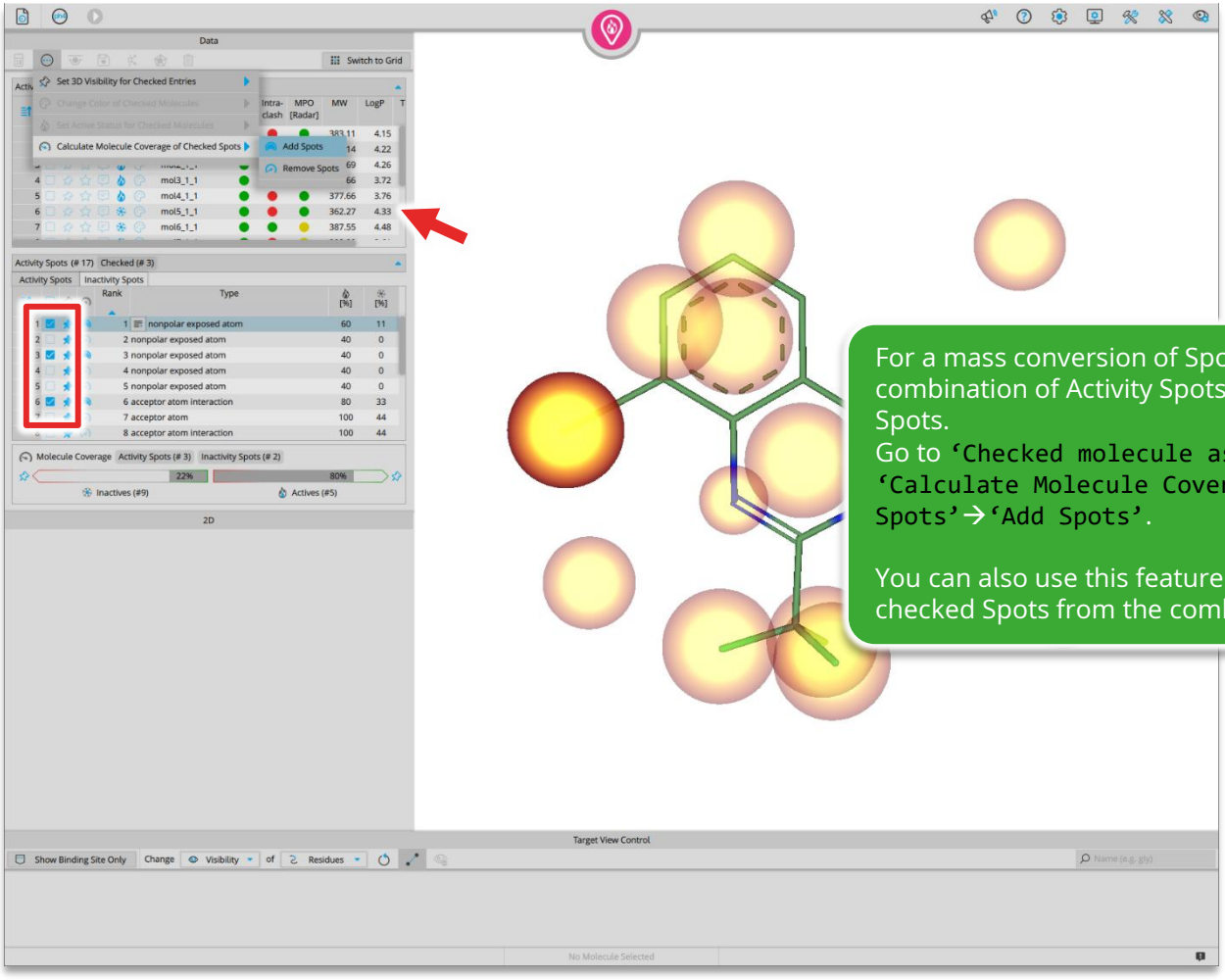
Mode Overview



For a mass conversion of Spots, select a combination of Activity Spots and Inactivity Spots.
Go to ‘Checked molecule assignments’→ ‘Calculate Molecule Coverage of Checked Spots’→‘Add Spots’.

You can also use this feature to remove checked Spots from the combination selection.

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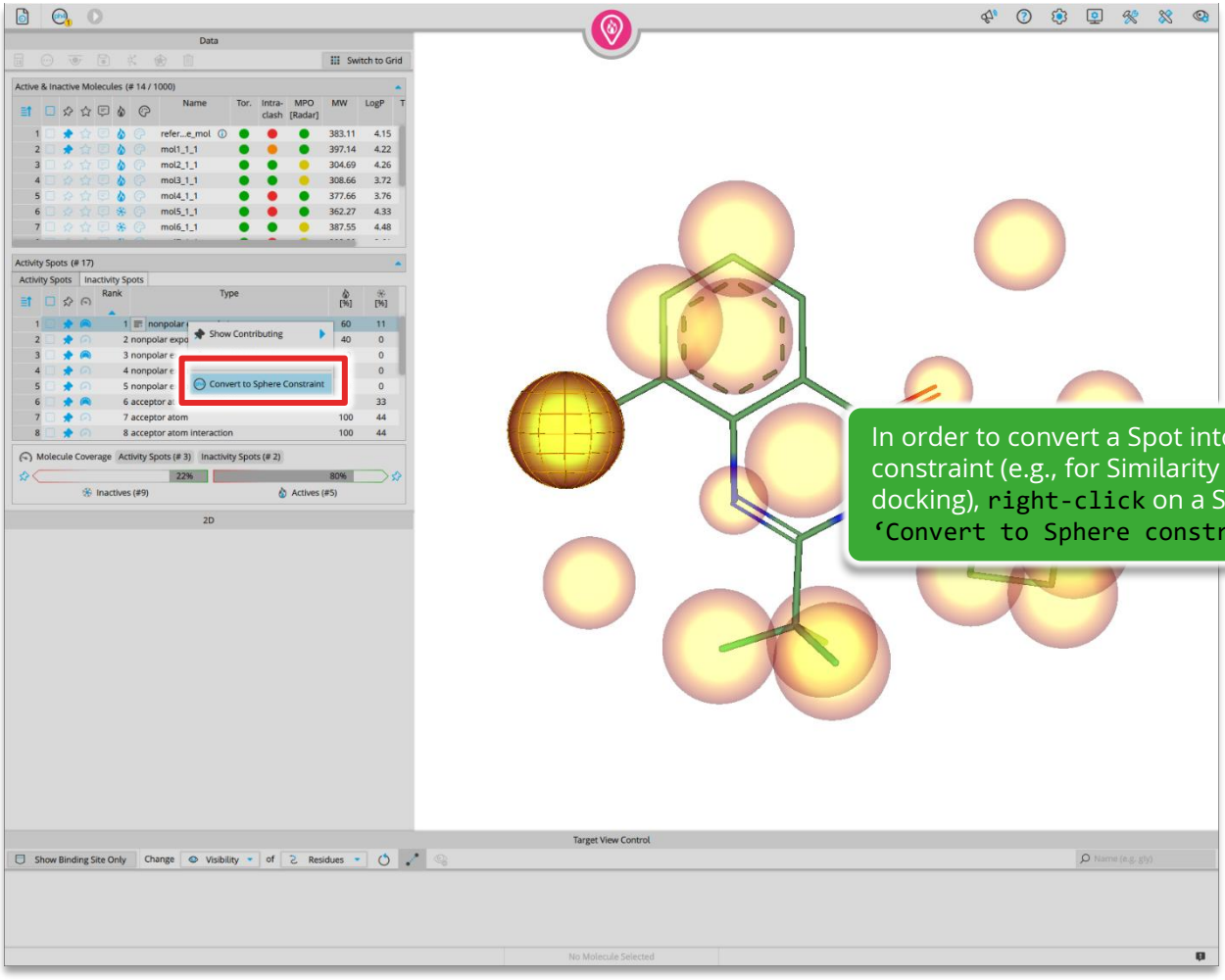
Mode Overview



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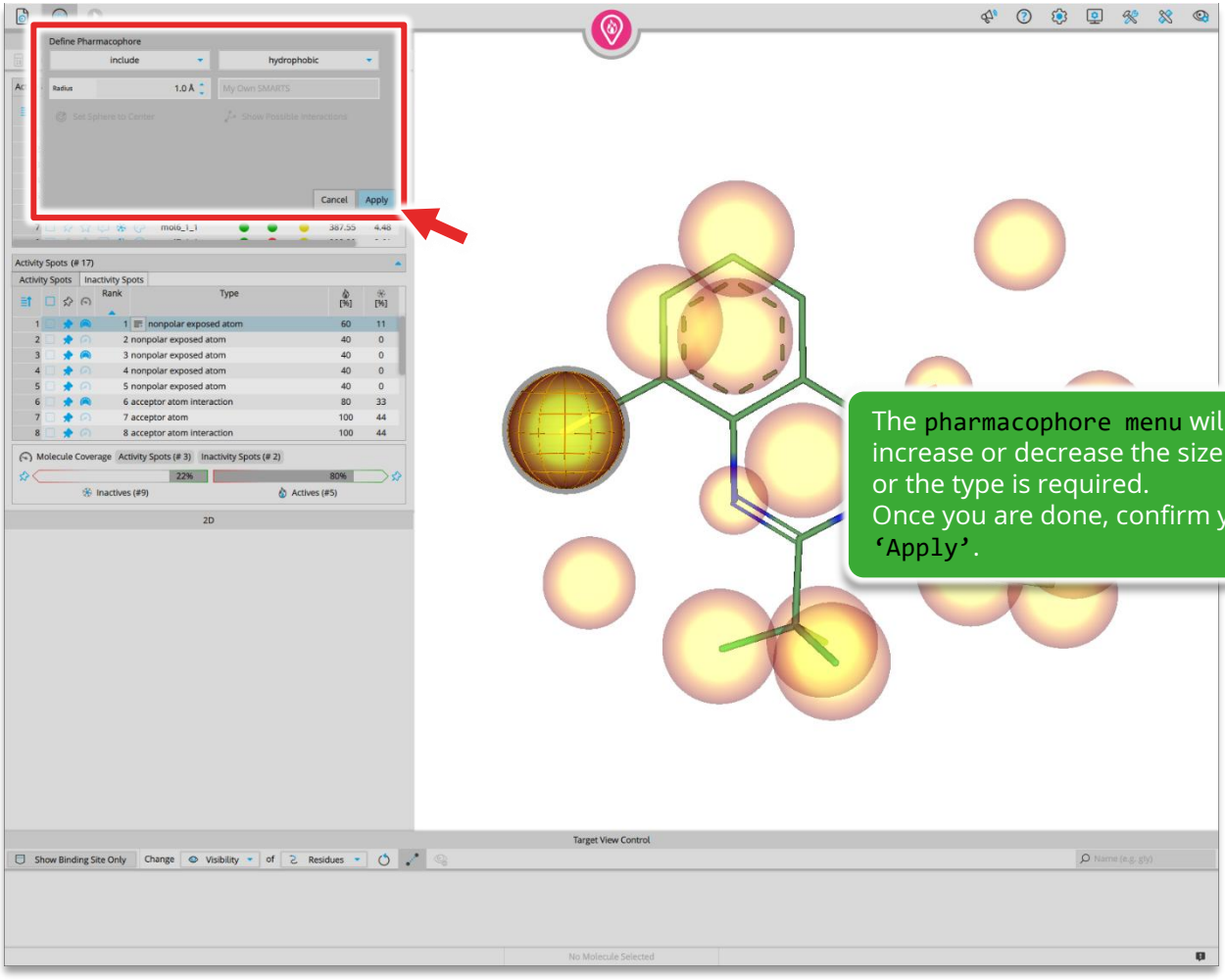
Mode Overview



The `pharmacophore menu` will open up. You can increase or decrease the size of the constraint or the type is required.
Once you are done, confirm your setup with `'Apply'`.

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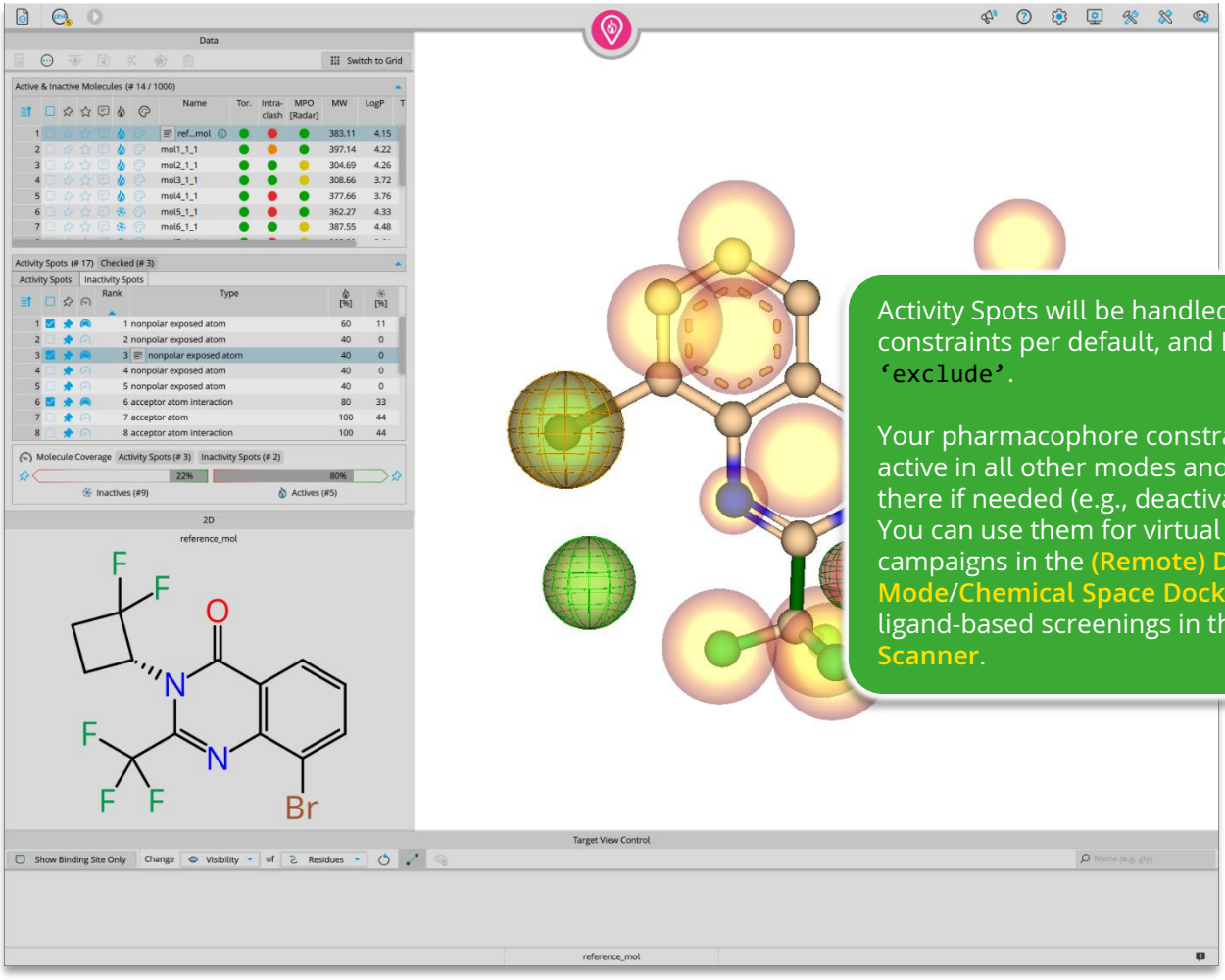
Mode Overview



Activity Spots will be handled as `'include'` constraints per default, and Inactivity Spots as `'exclude'`.

Your pharmacophore constraints will now be active in all other modes and can be adjusted there if needed (e.g., deactivated, re-sized, etc.). You can use them for virtual screening campaigns in the **(Remote) Docking Mode**/**Chemical Space Docking® Mode**, or for ligand-based screenings in the **Similarity Scanner**.

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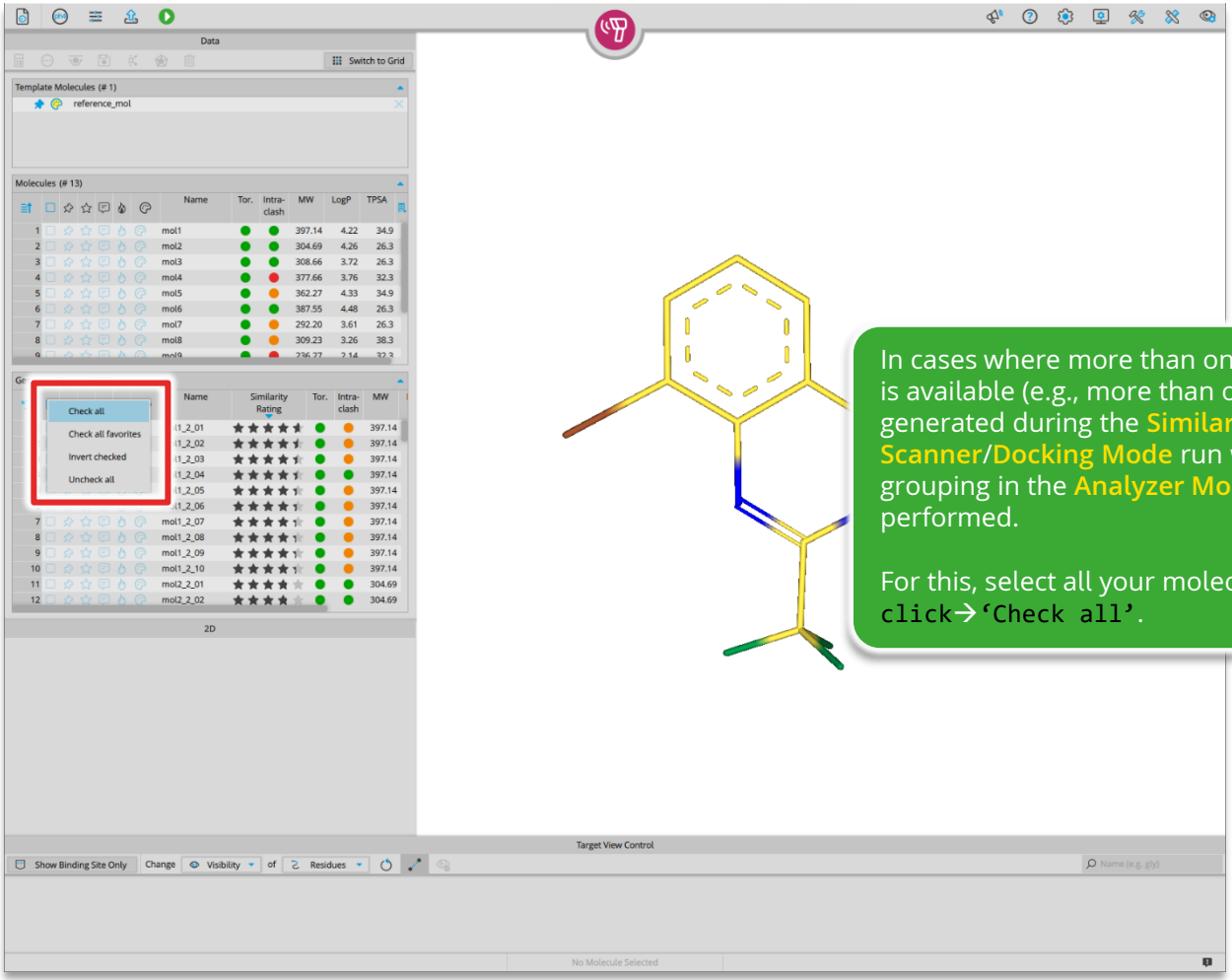
Mode Overview



In cases where more than one pose of a ligand is available (e.g., more than one pose was generated during the **Similarity Scanner**/**Docking Mode** run was generated), a grouping in the **Analyzer Mode** can be performed.

For this, select all your molecules by `right-click→'Check all'`.

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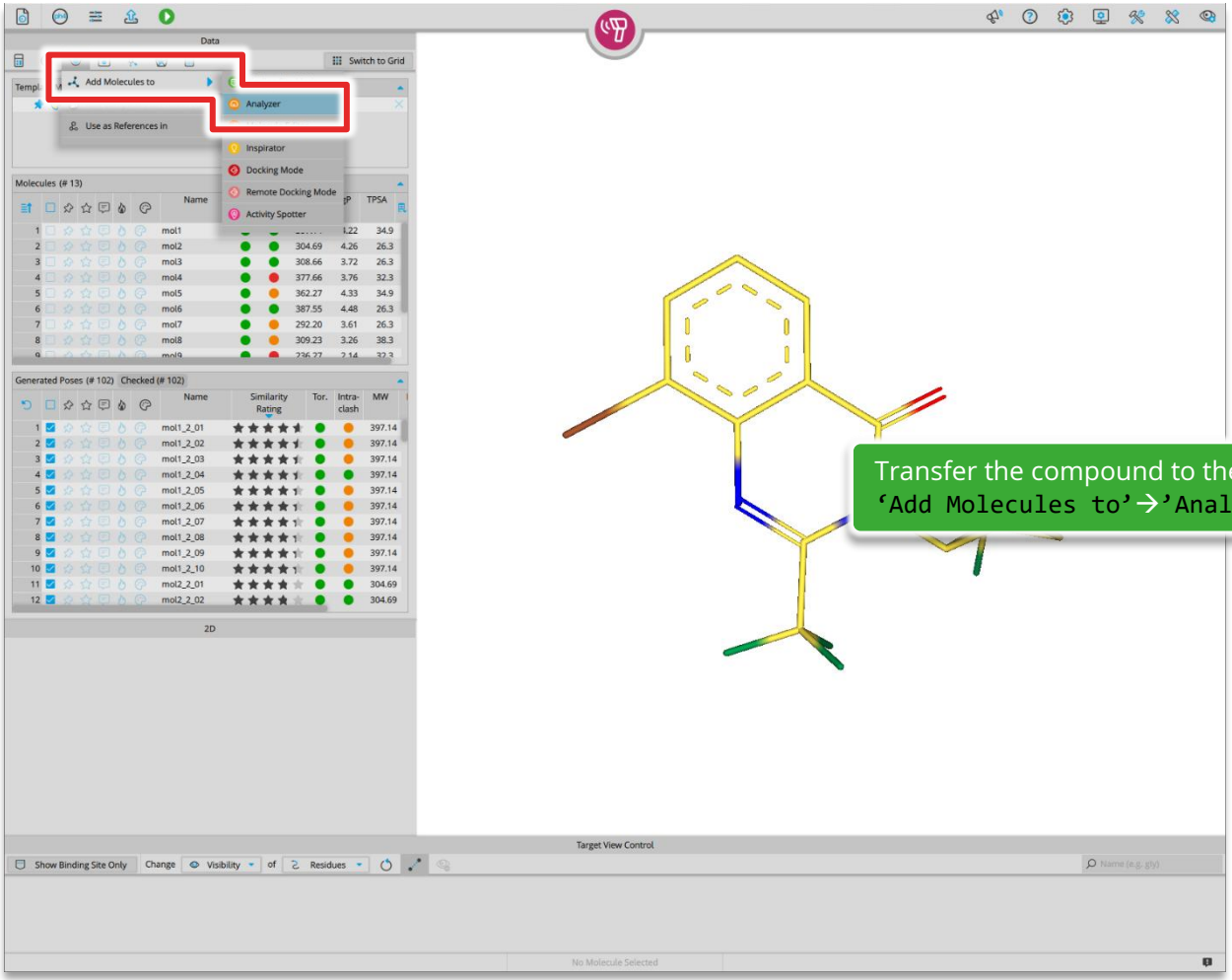
Mode Overview



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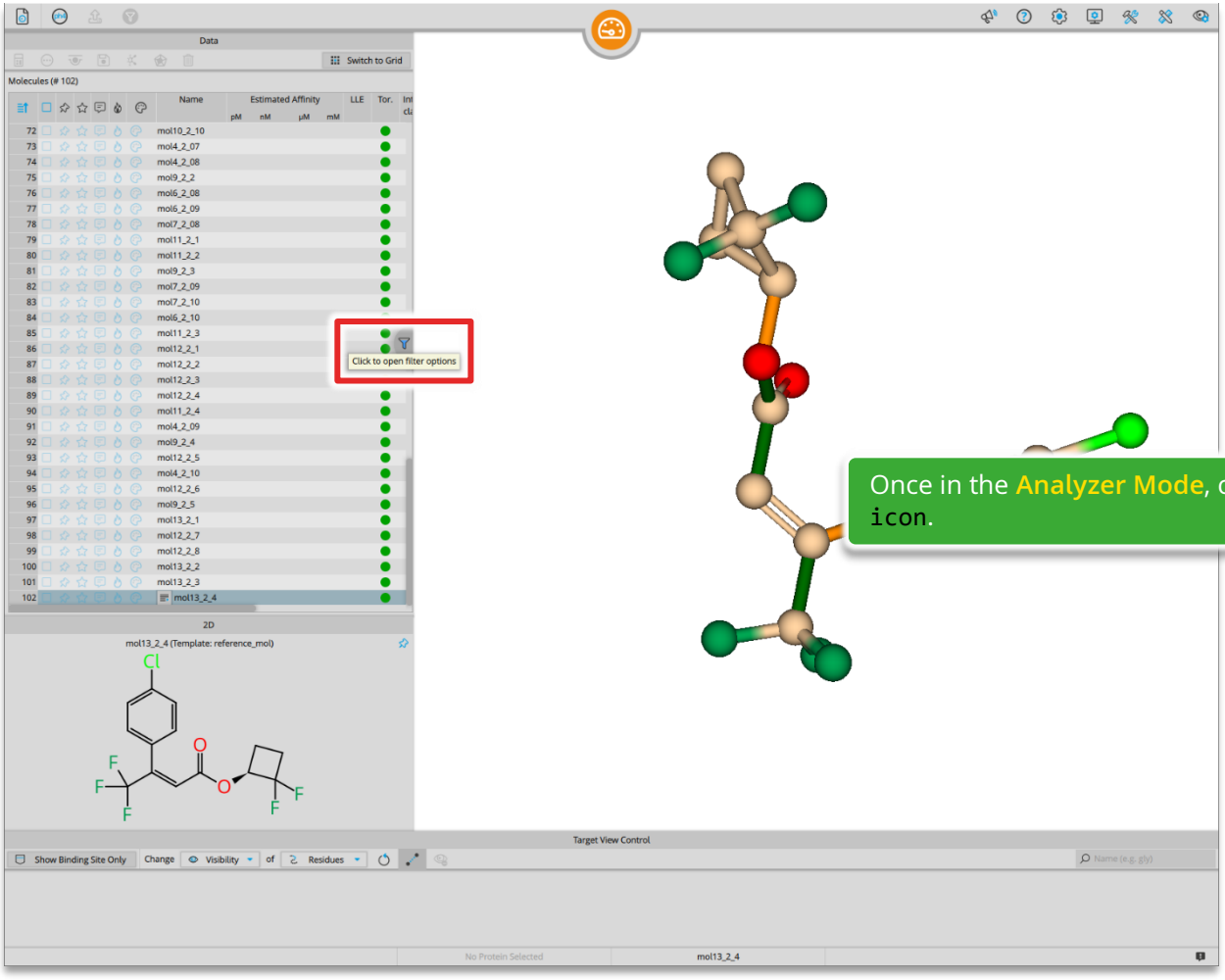
Mode Overview



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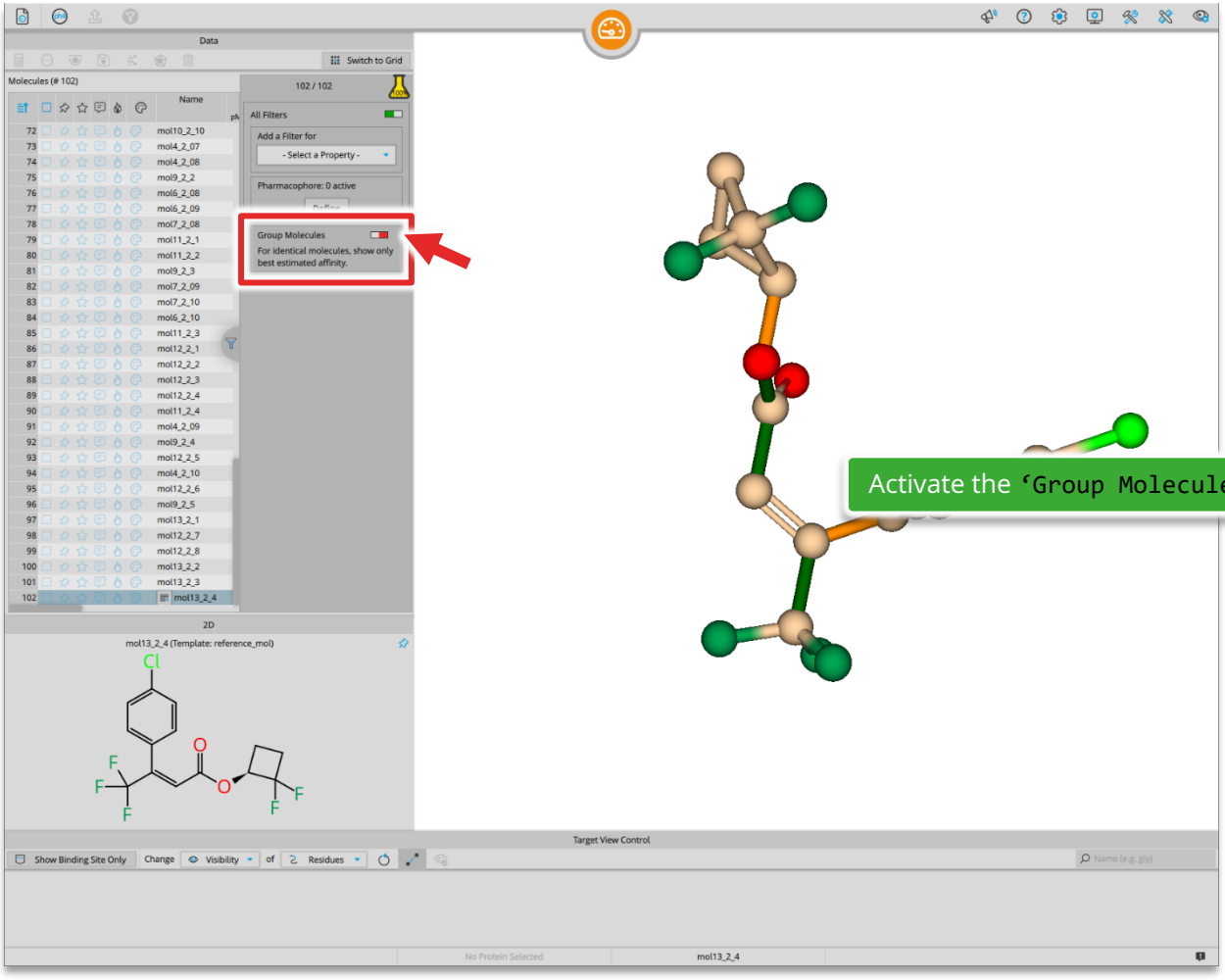
Mode Overview



Activate the ‘Group Molecules’ option.

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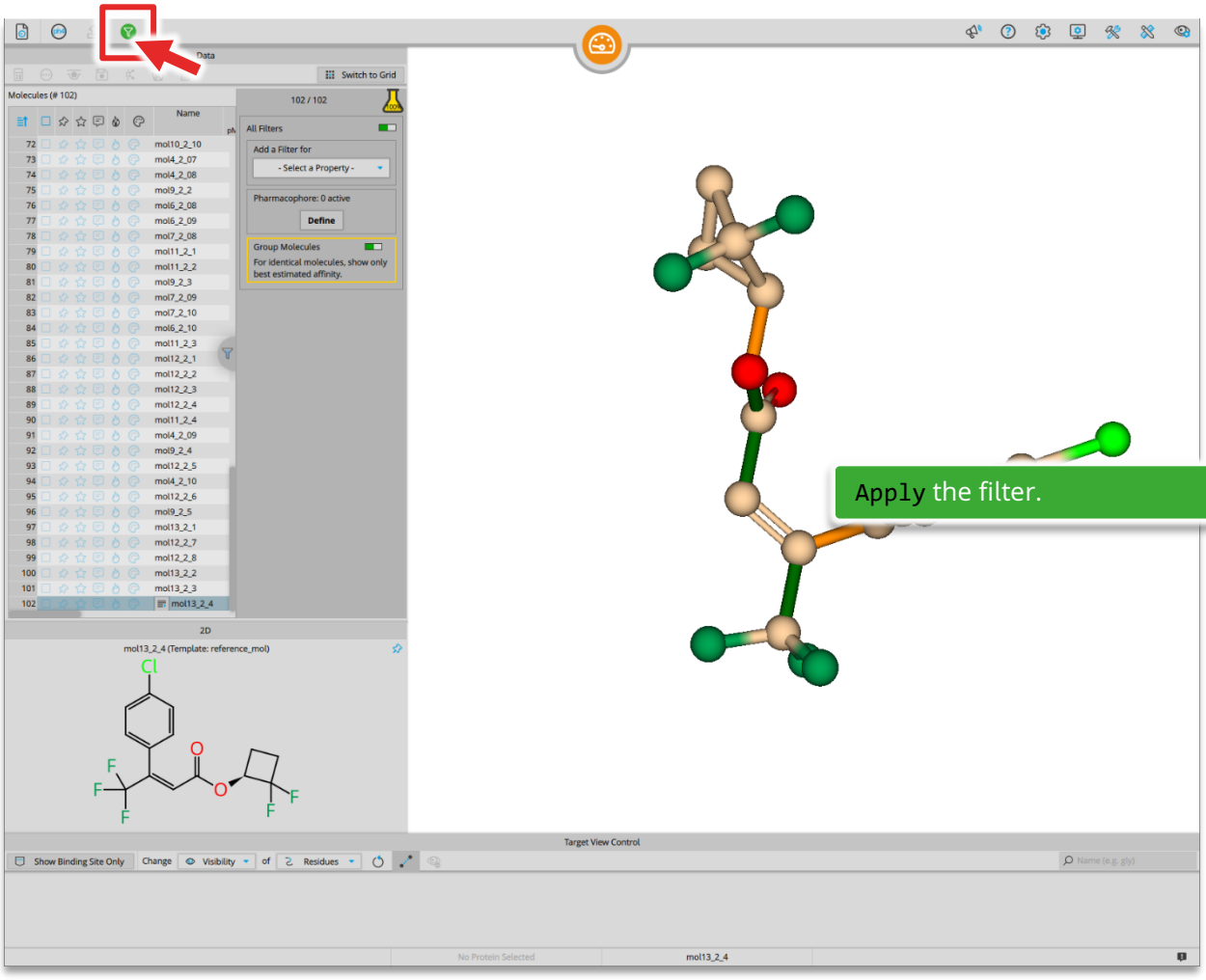
Mode Overview



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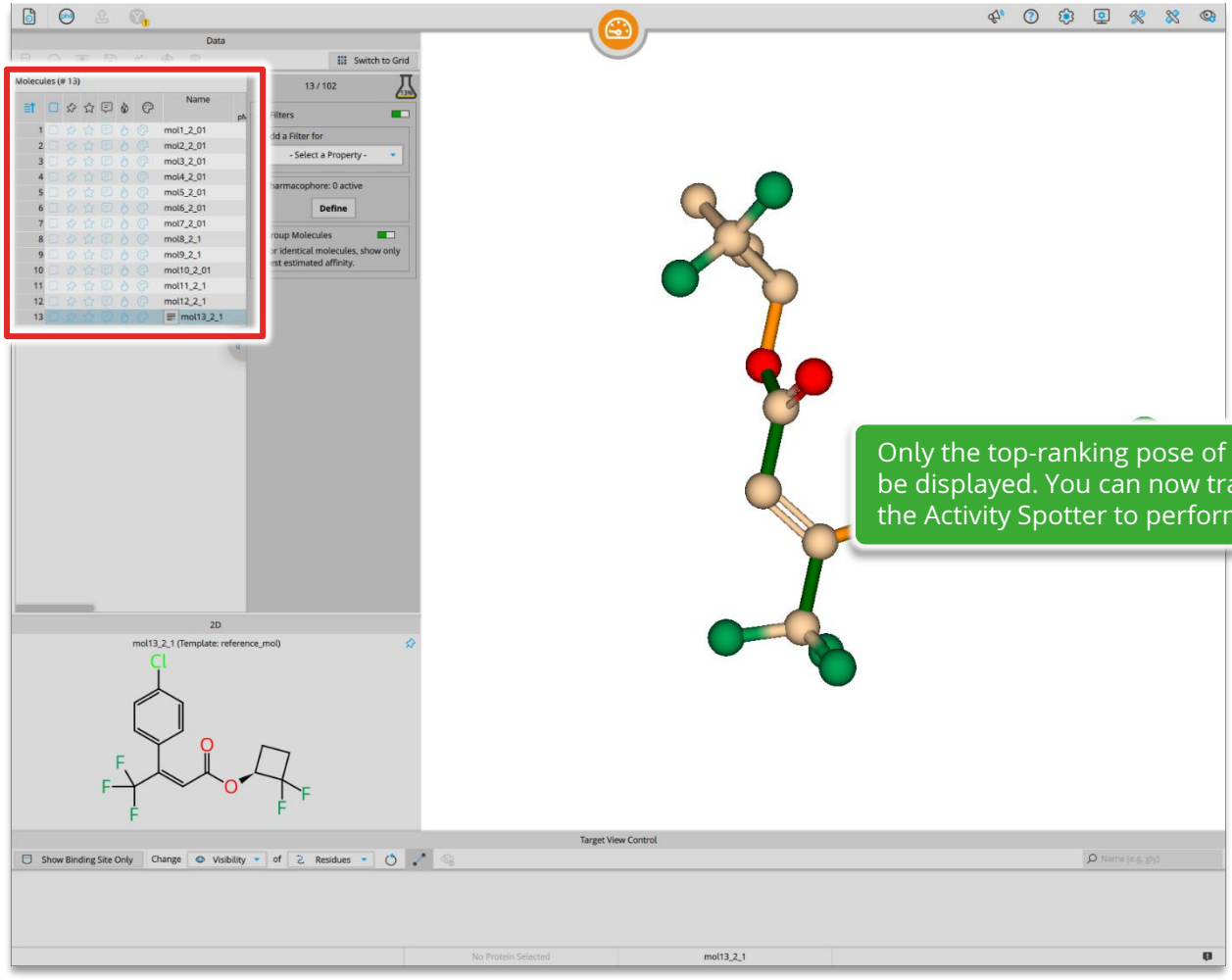
Mode Overview



Only the top-ranking pose of each molecule will be displayed. You can now transfer them into the Activity Spotter to perform an SAR analysis.

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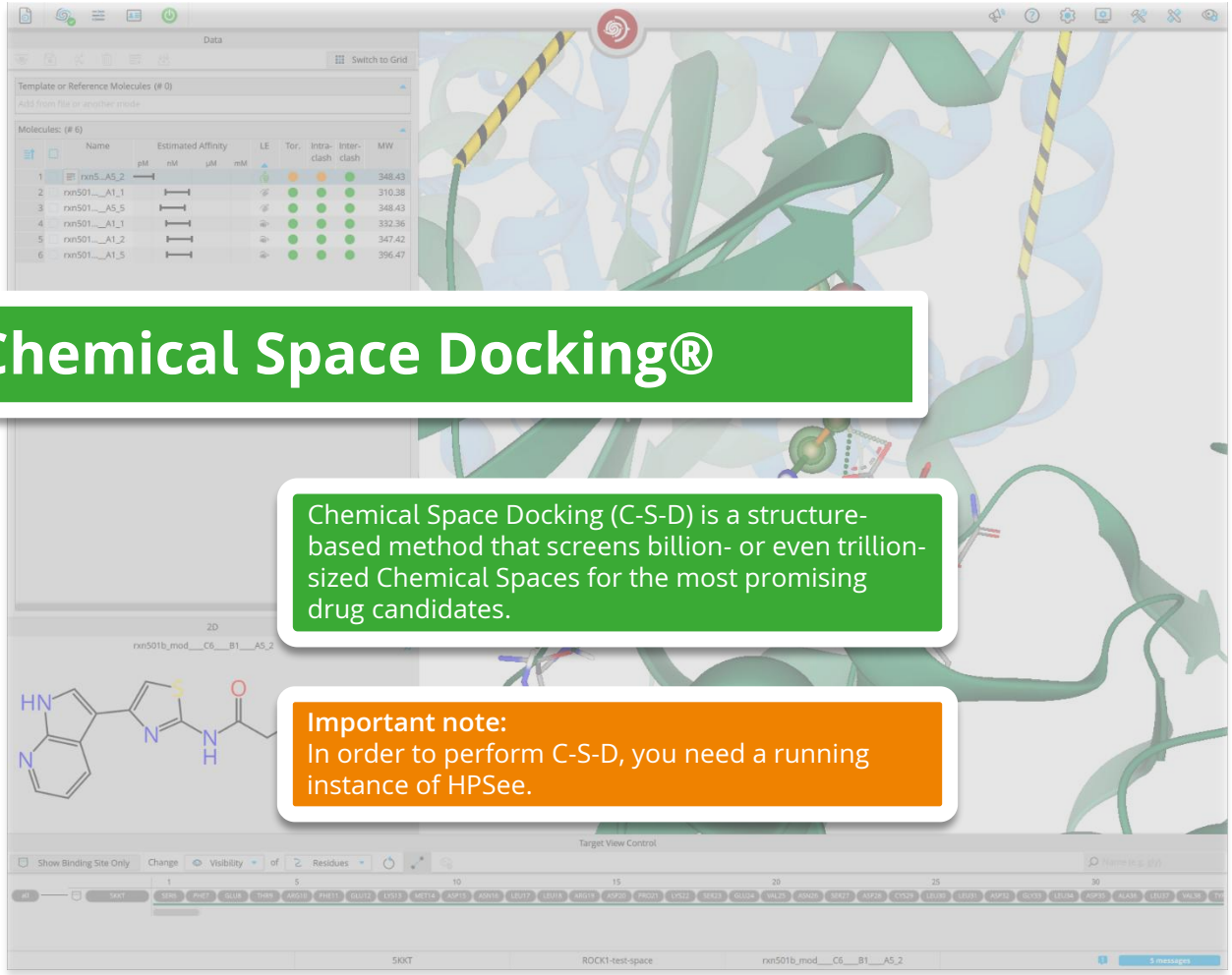
Mode Overview

10. Chemical Space Docking®



Chemical Space Docking (C-S-D) is a structure-based method that screens billion- or even trillion-sized Chemical Spaces for the most promising drug candidates.

Important note:
In order to perform C-S-D, you need a running instance of HPSee.

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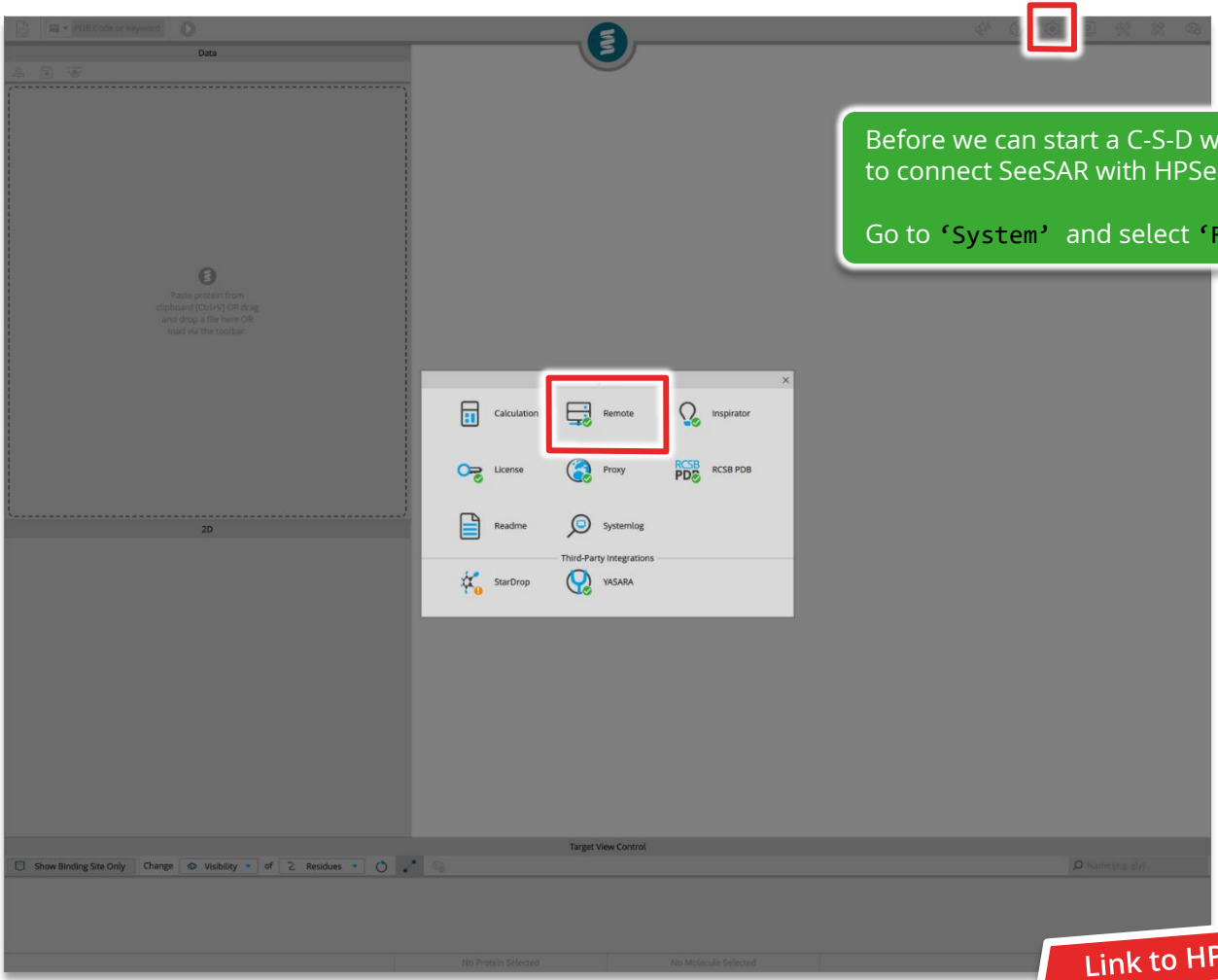
Mode Overview



Before we can start a C-S-D workflow, we need to connect SeeSAR with HPSee.

Go to ‘System’ and select ‘Remote’.

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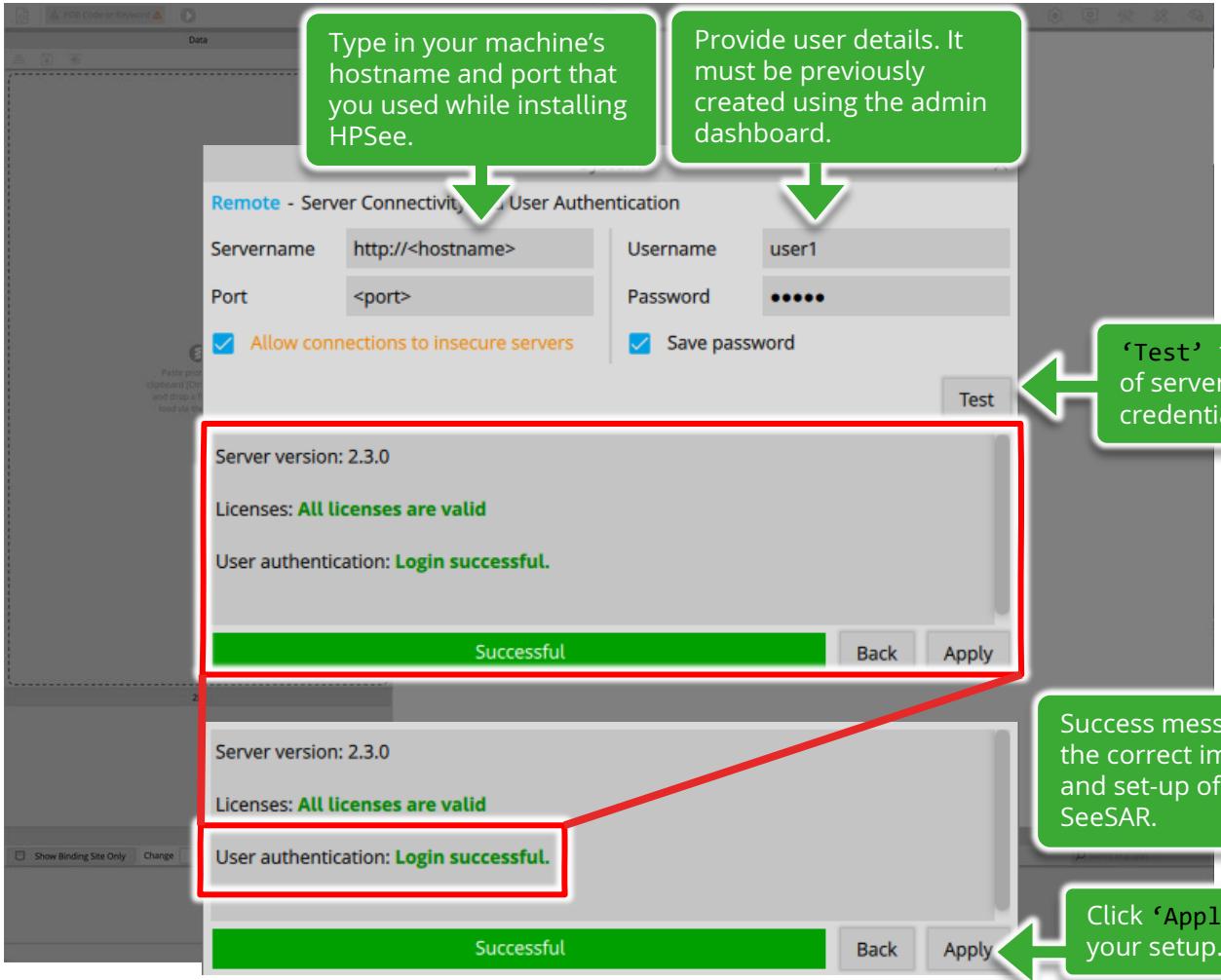
Mode Overview

Link to HPSee Guide



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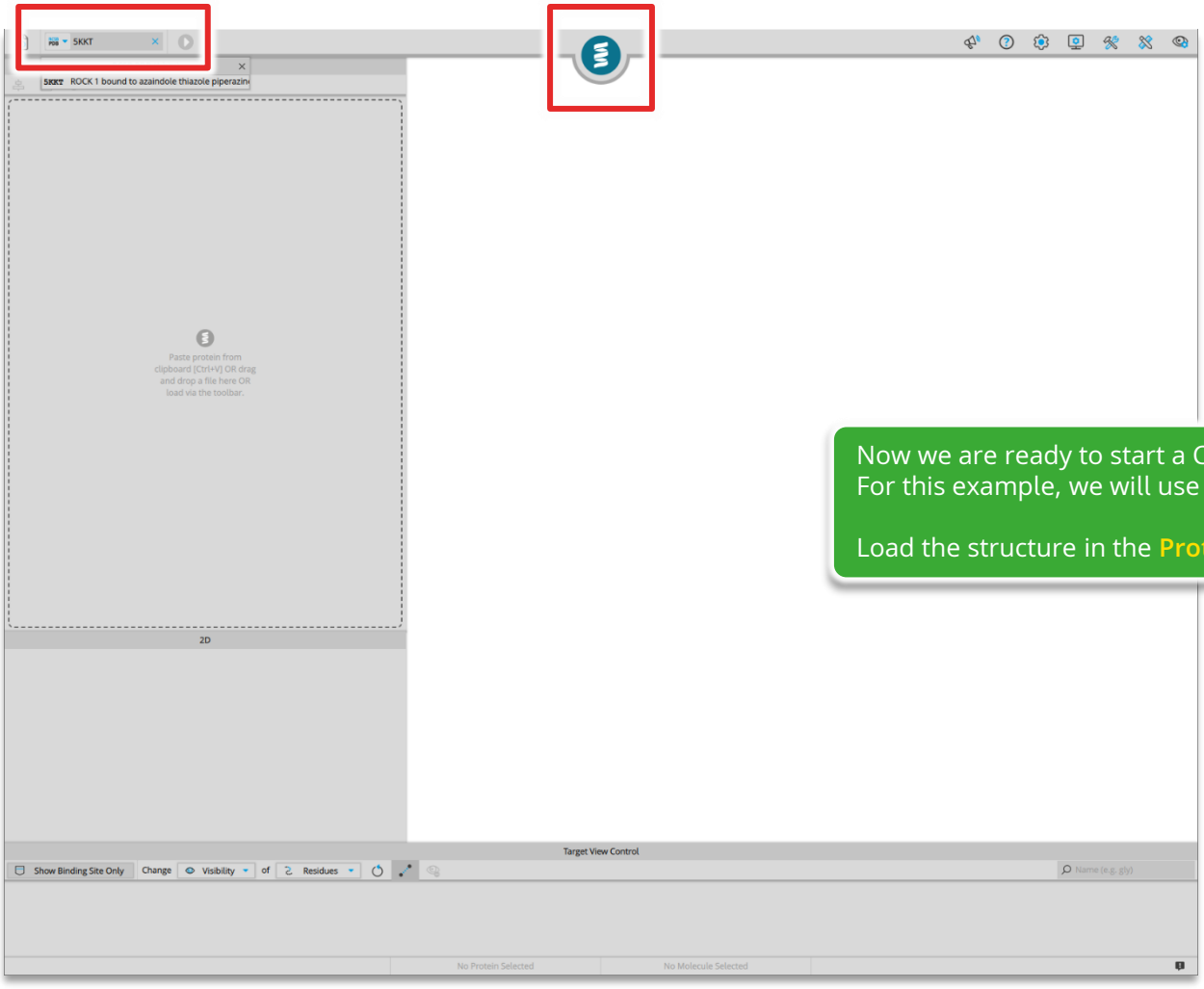
Mode Overview



Now we are ready to start a C-S-D run.
For this example, we will use 5KKT as PDB.

Load the structure in the **Proteins Mode**.

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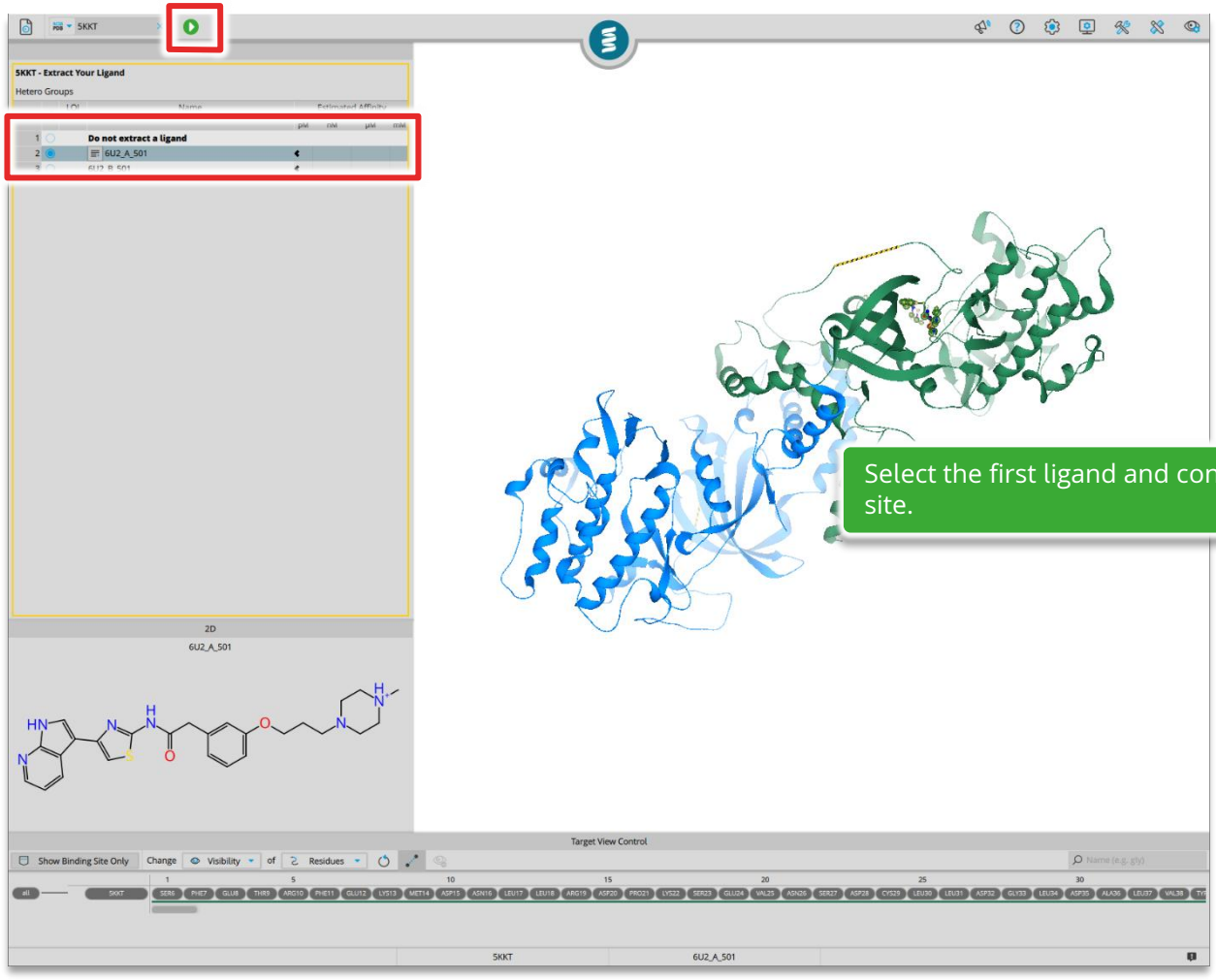
Mode Overview



Select the first ligand and confirm your binding site.

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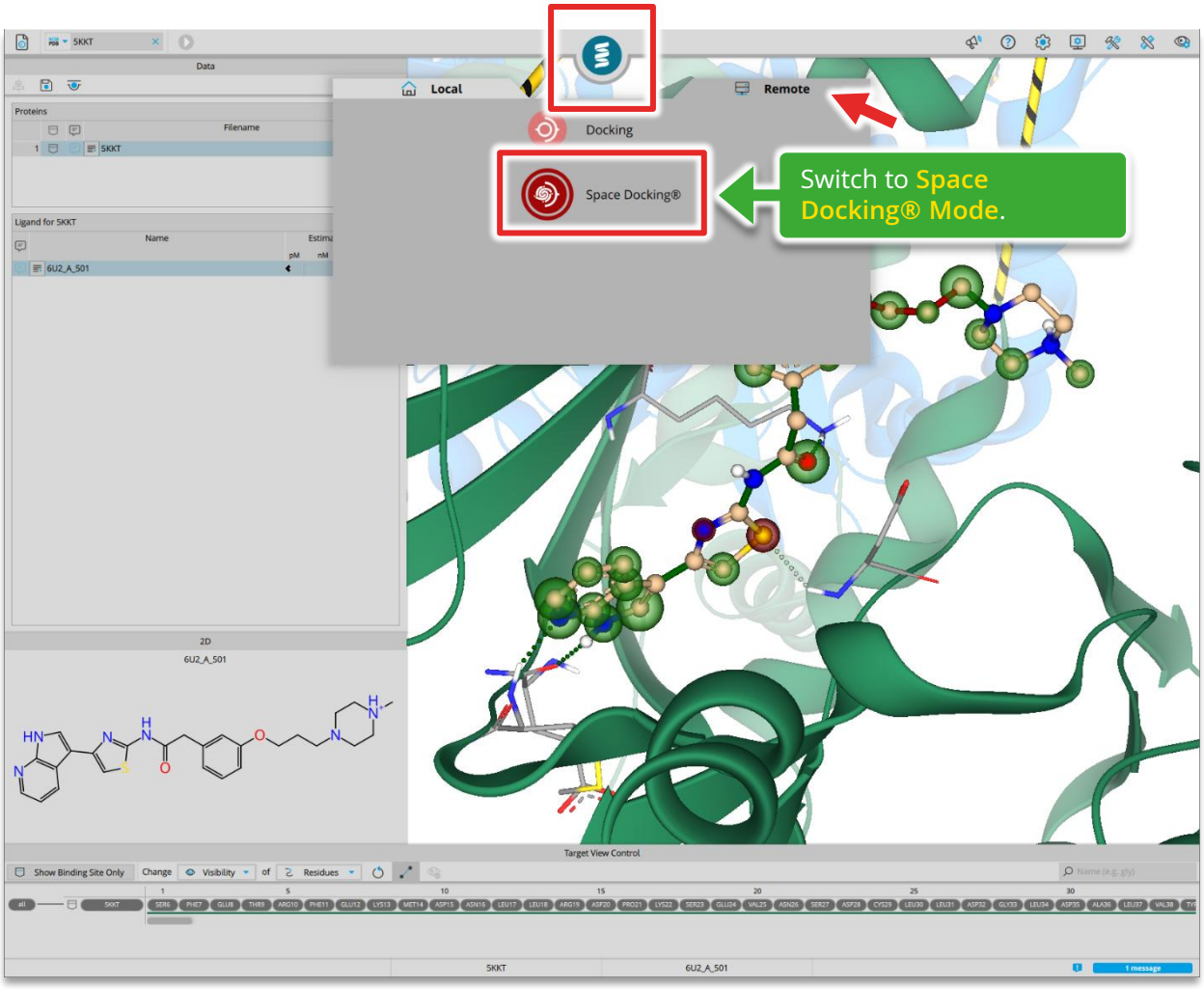
Mode Overview



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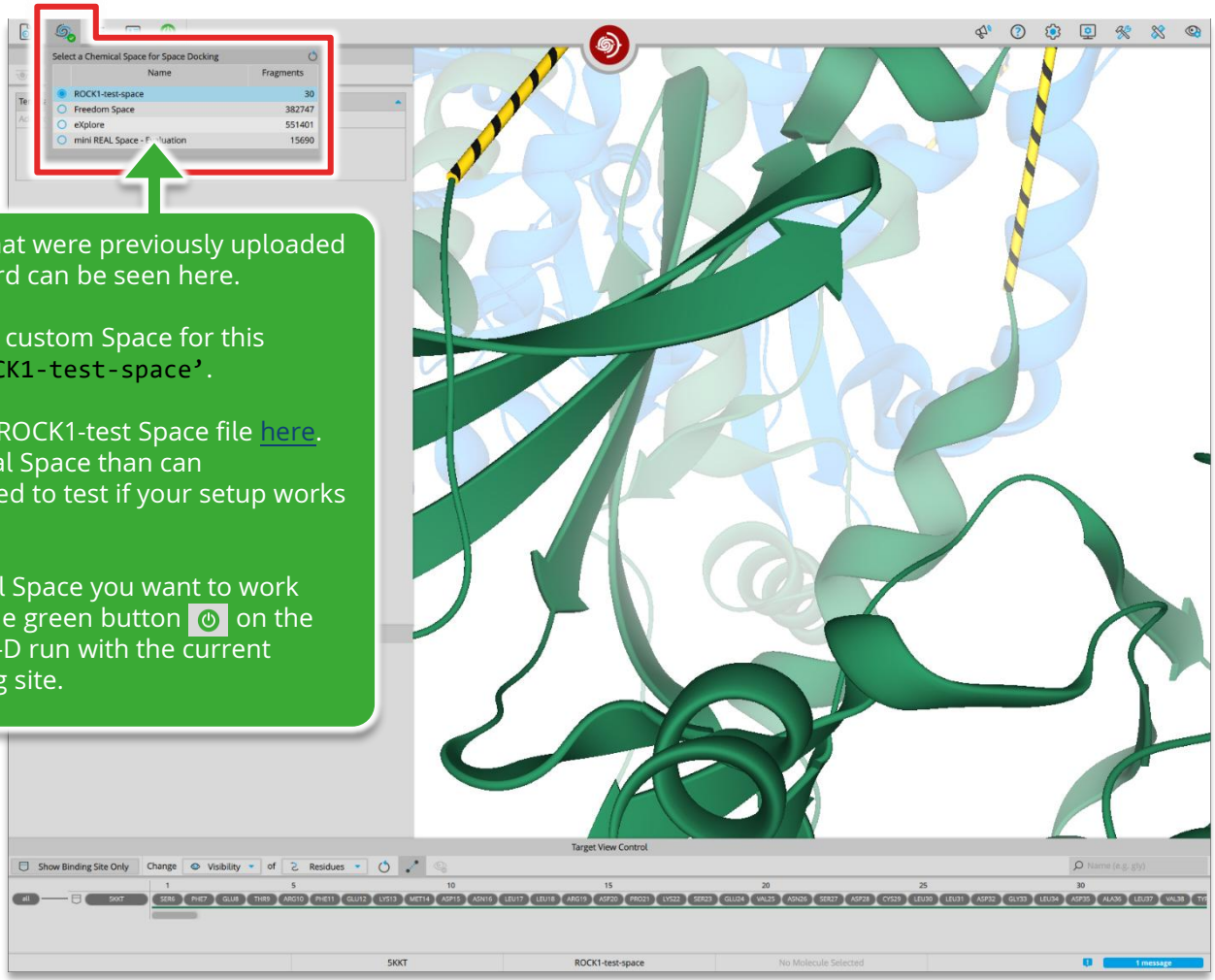
Mode Overview



Chemical Spaces that were previously uploaded using the Dashboard can be seen here.

We will use a small custom Space for this tutorial, called `'ROCK1-test-space'`.

You download the ROCK1-test Space file here. It's a small Chemical Space than can conveniently be used to test if your setup works as intended.

Select the Chemical Space you want to work with and click on the green button on the top to start the C-S-D run with the current protein and binding site.

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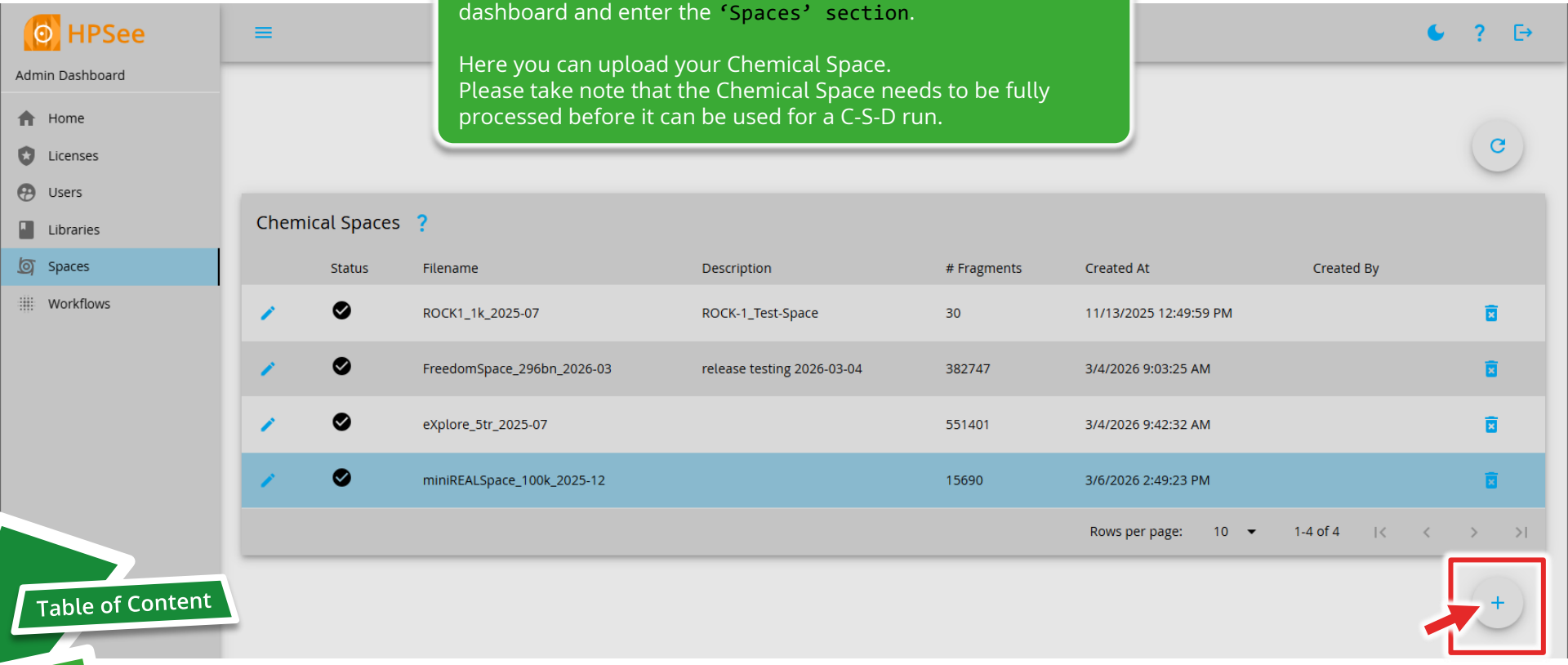
Mode Overview

In order to upload a Chemical Space, please go to your HPSee dashboard and enter the `'Spaces' section`.

Here you can upload your Chemical Space.
Please take note that the Chemical Space needs to be fully processed before it can be used for a C-S-D run.



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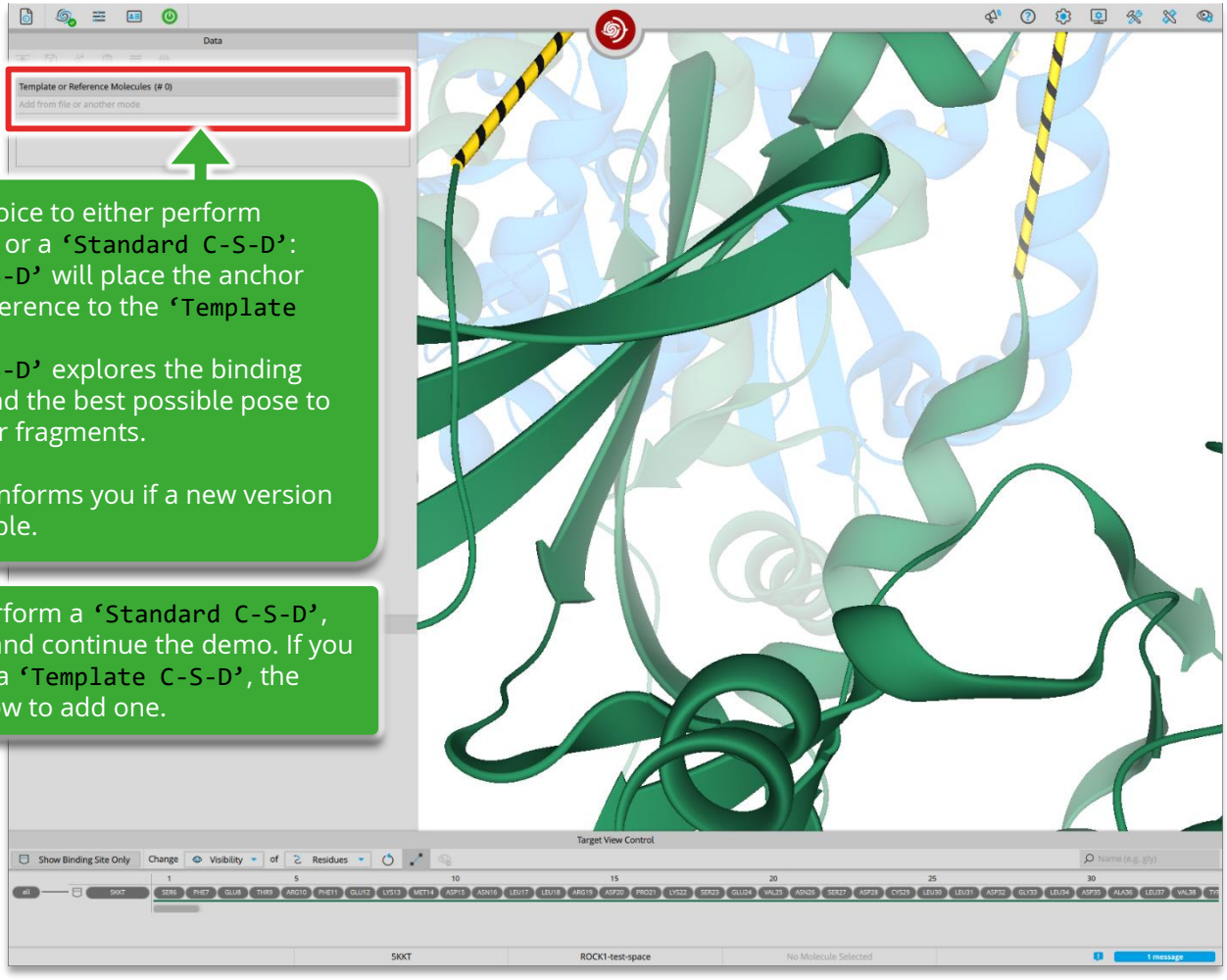
Mode Overview



You now have a choice to either perform ‘Template C-S-D’ or a ‘Standard C-S-D’:

- ‘Template C-S-D’ will place the anchor fragment in reference to the ‘Template Molecule’.
- ‘Standard C-S-D’ explores the binding site freely to find the best possible pose to bind the anchor fragments.

The bullhorn icon informs you if a new version of SeeSAR is available.

If you choose to perform a ‘Standard C-S-D’, skip the next slide and continue the demo. If you choose to perform a ‘Template C-S-D’, the next slide shows how to add one.

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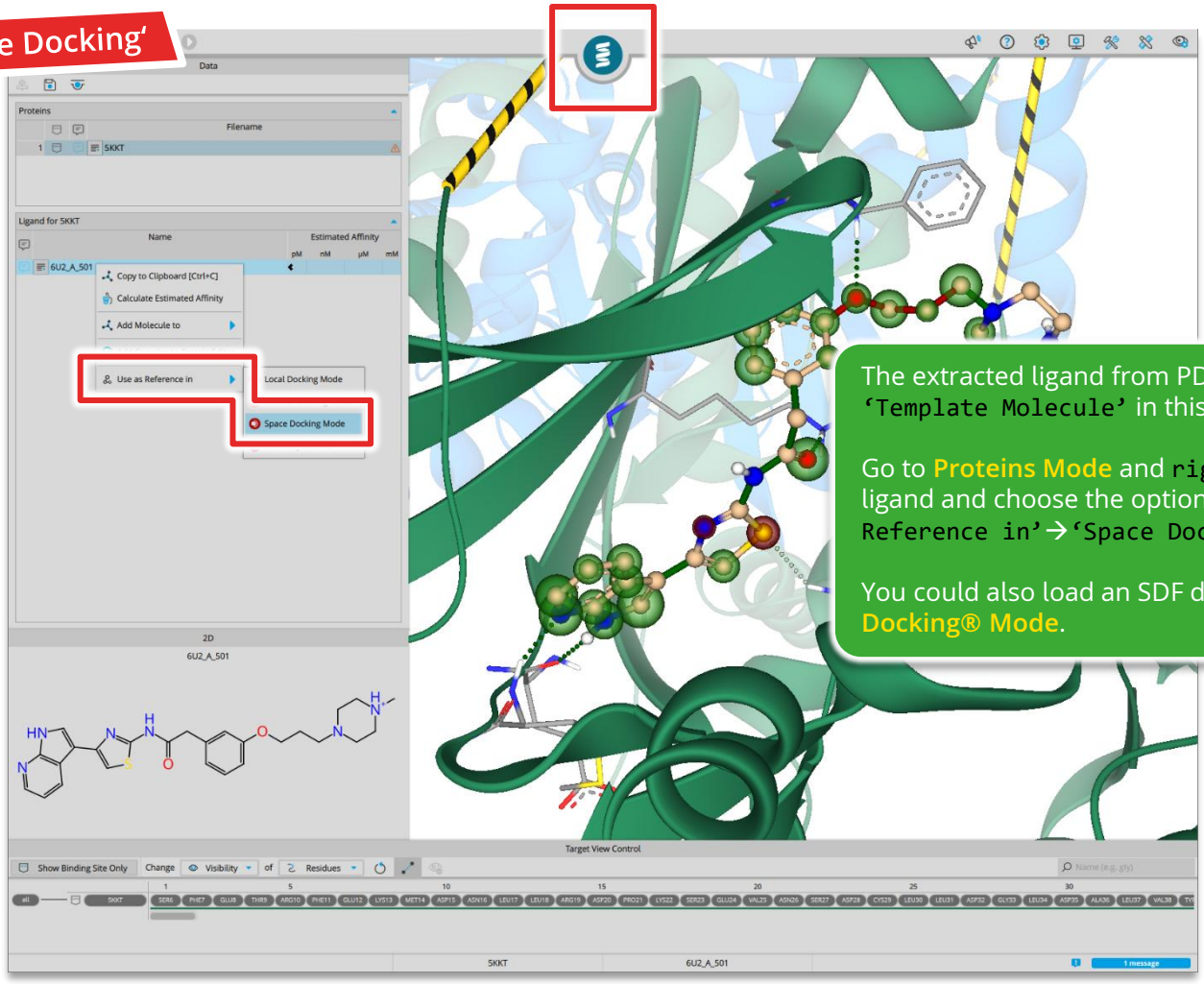
Mode Overview

‘Template Docking’



The extracted ligand from PDB can be used as a ‘Template Molecule’ in this demo.

Go to **Proteins Mode** and right-click on the ligand and choose the options ‘Use as Reference in’→‘Space Docking Mode’.

You could also load an SDF directly in **Space Docking® Mode**.

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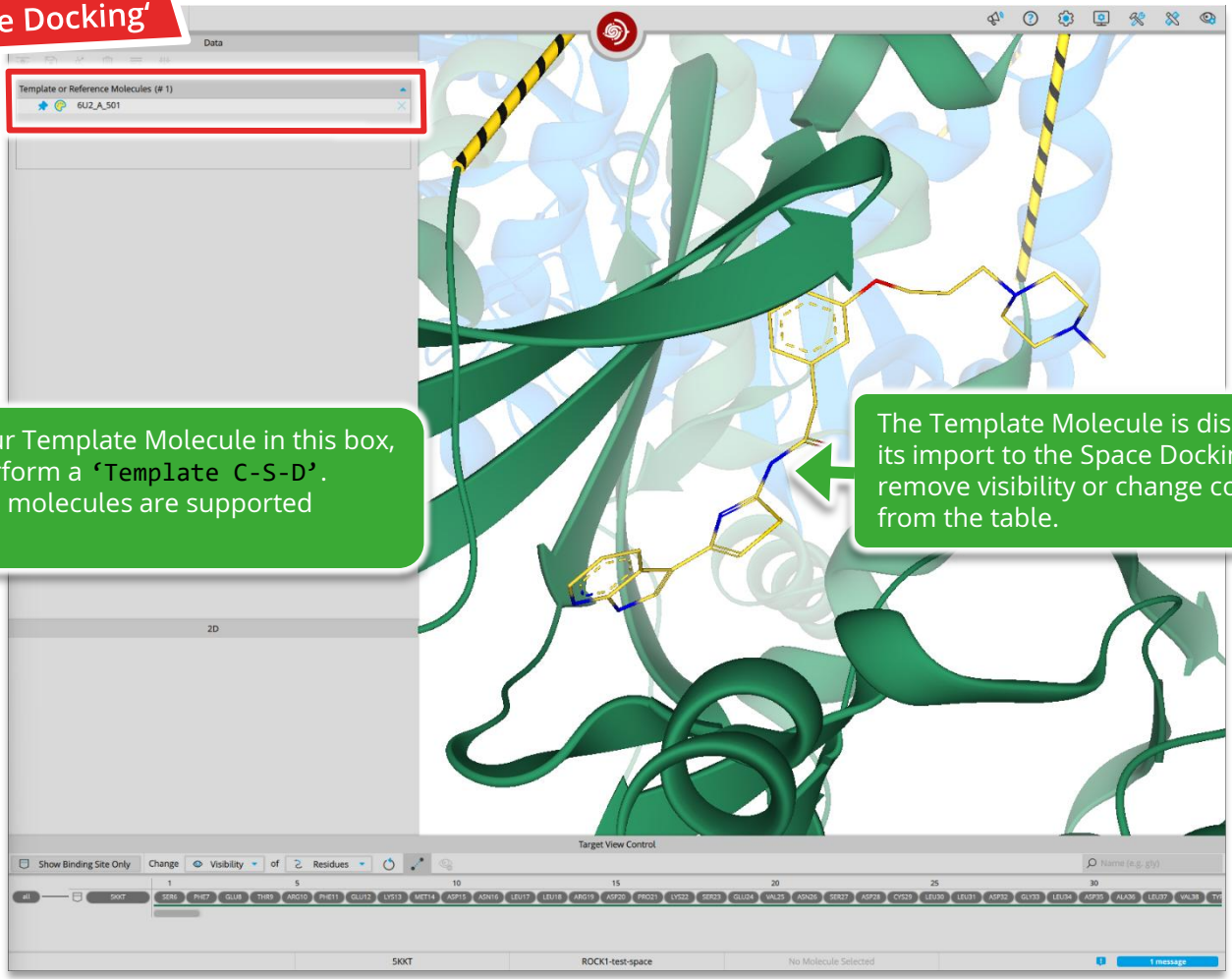
Mode Overview

‘Template Docking’



You should see your Template Molecule in this box, if you decide to perform a ‘`Template C-S-D`’. Up to five template molecules are supported during a C-S-D run.

The Template Molecule is displayed in 3D after its import to the Space Docking Mode. You can remove visibility or change color using from the table.

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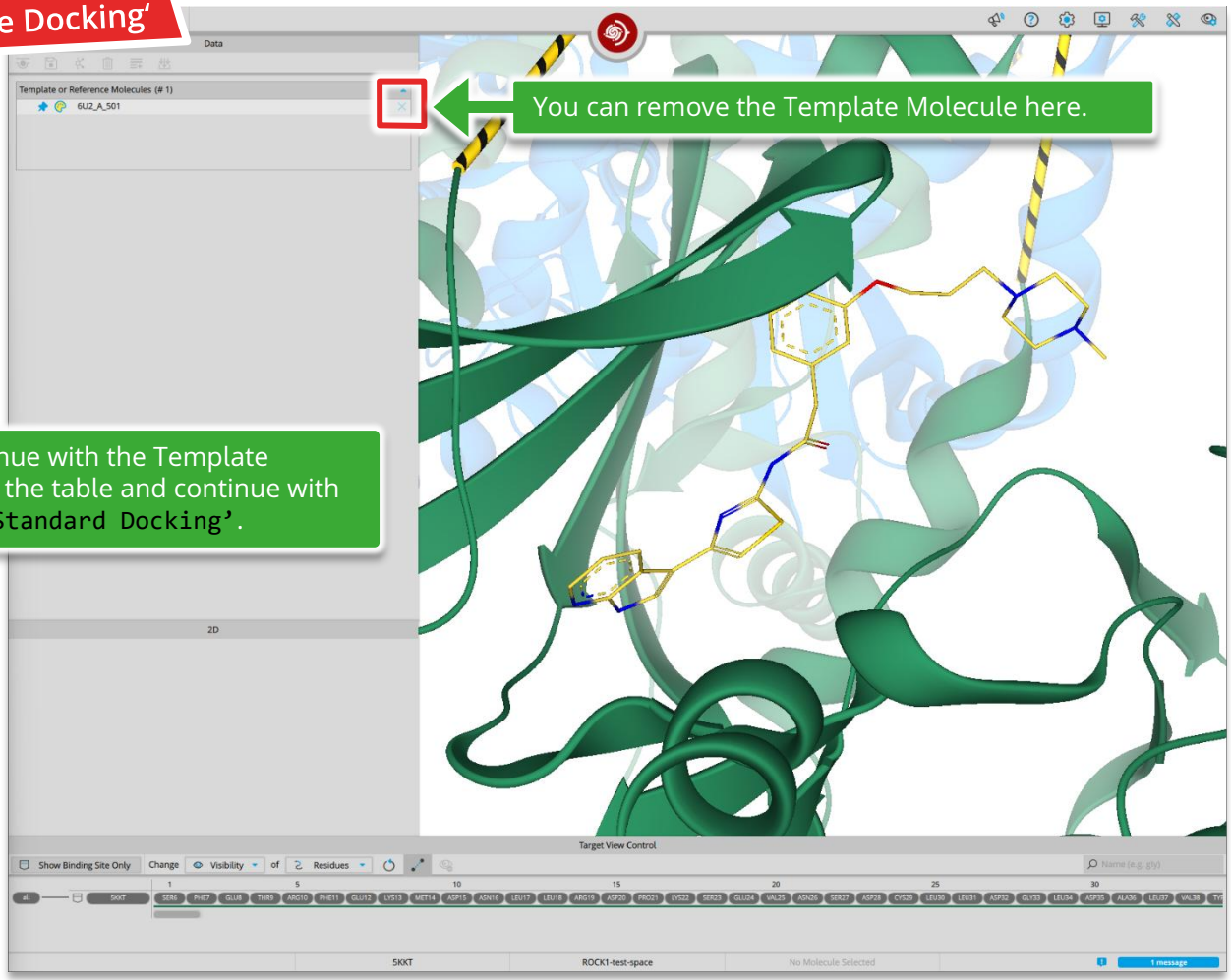
Mode Overview

‘Template Docking’



If you want to continue with the Template Molecule, keep it in the table and continue with the next slides of **‘Standard Docking’**.

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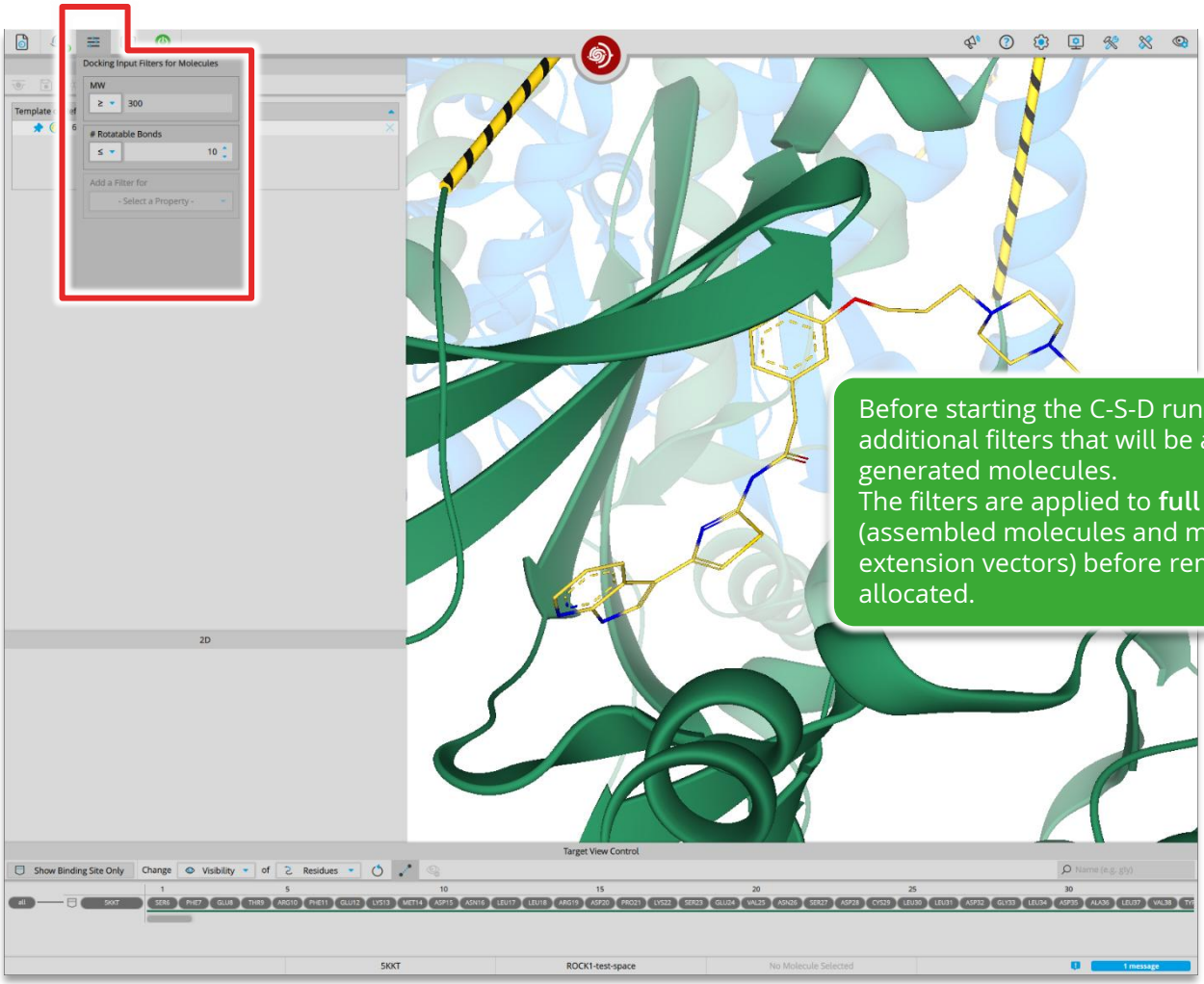
Mode Overview



Before starting the C-S-D run, you can apply additional filters that will be applied on the generated molecules.
The filters are applied to **full molecules** (assembled molecules and molecules without extension vectors) before remote compute is allocated.

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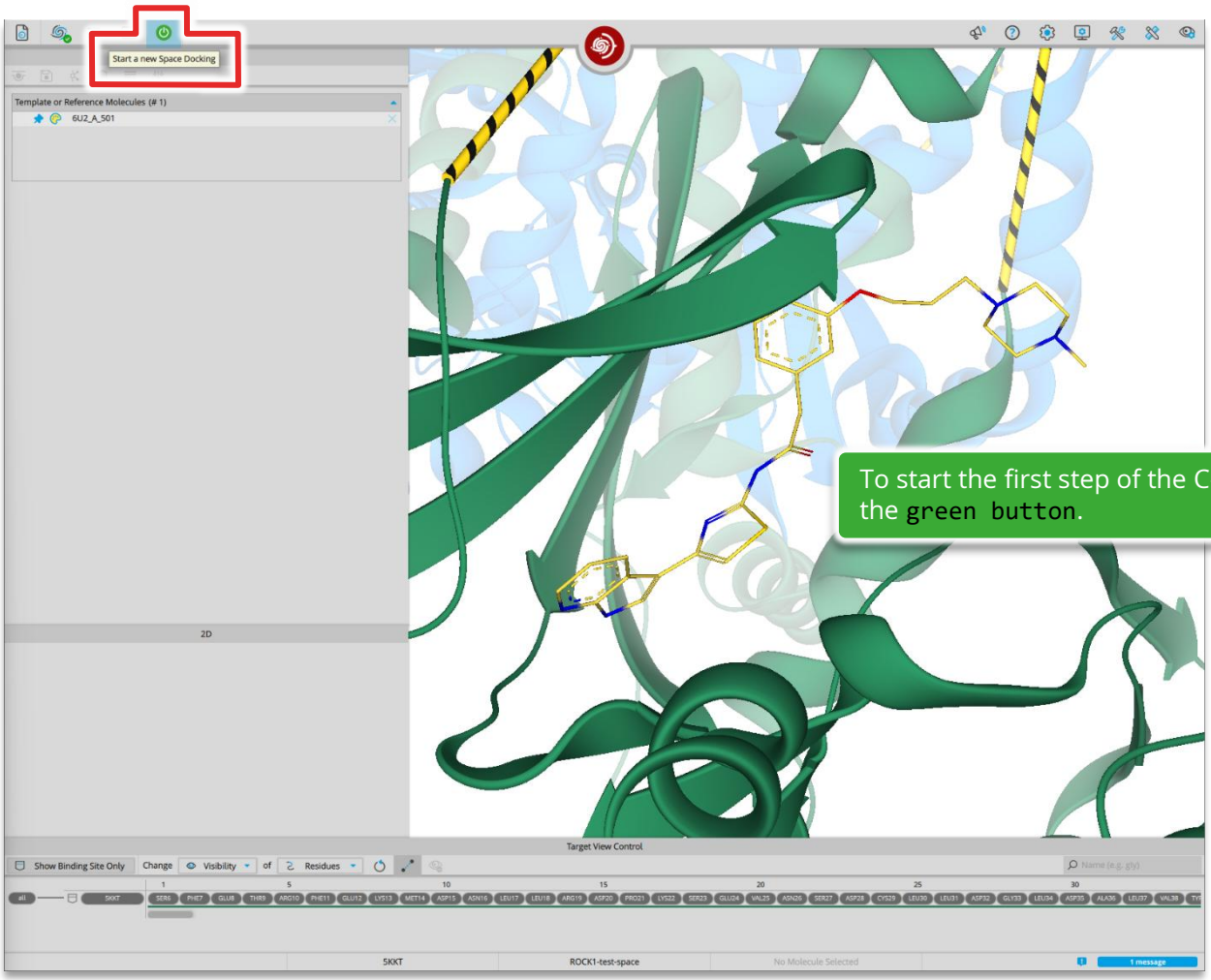
Mode Overview



To start the first step of the C-S-D workflow, use the `green button`.

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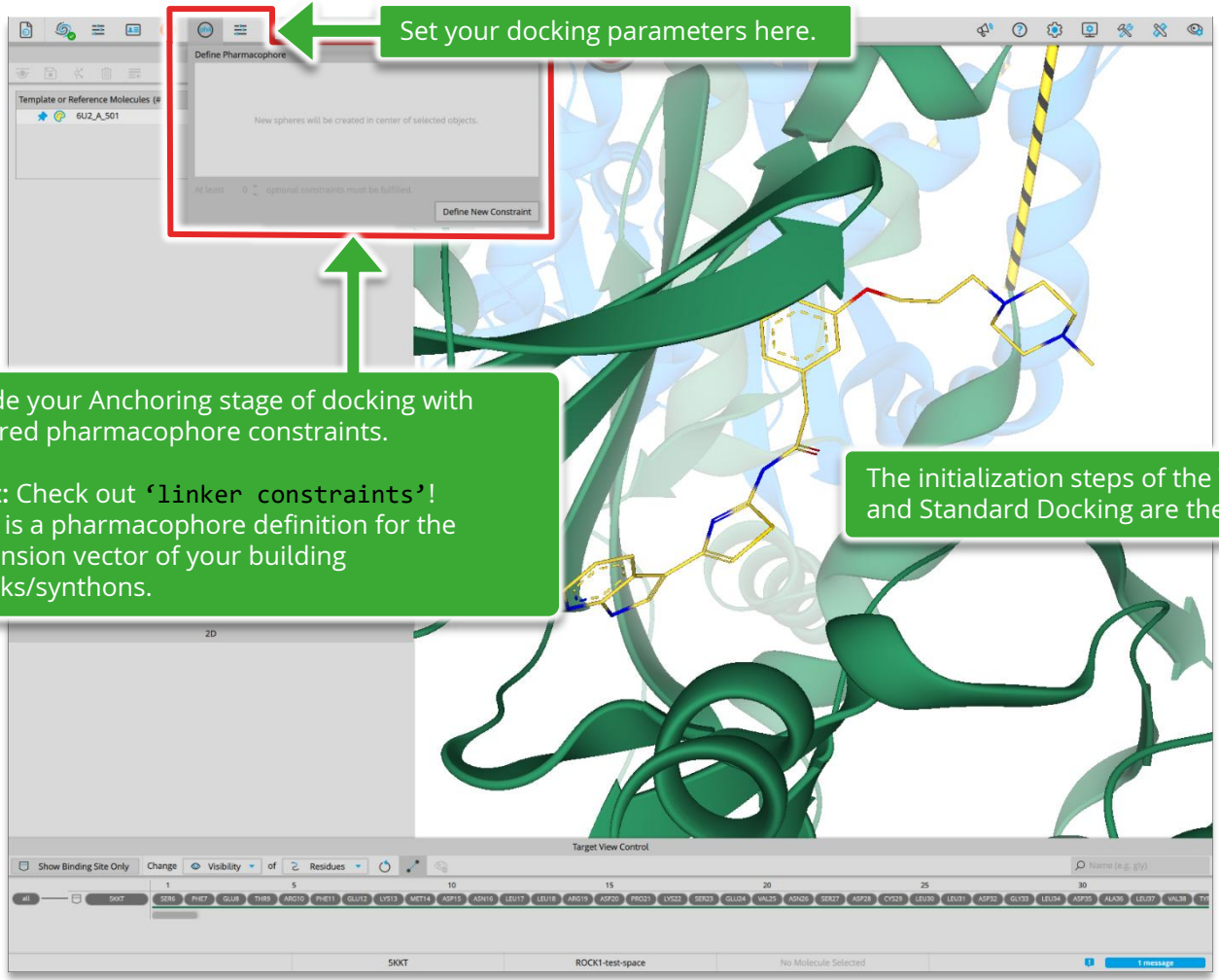
Mode Overview



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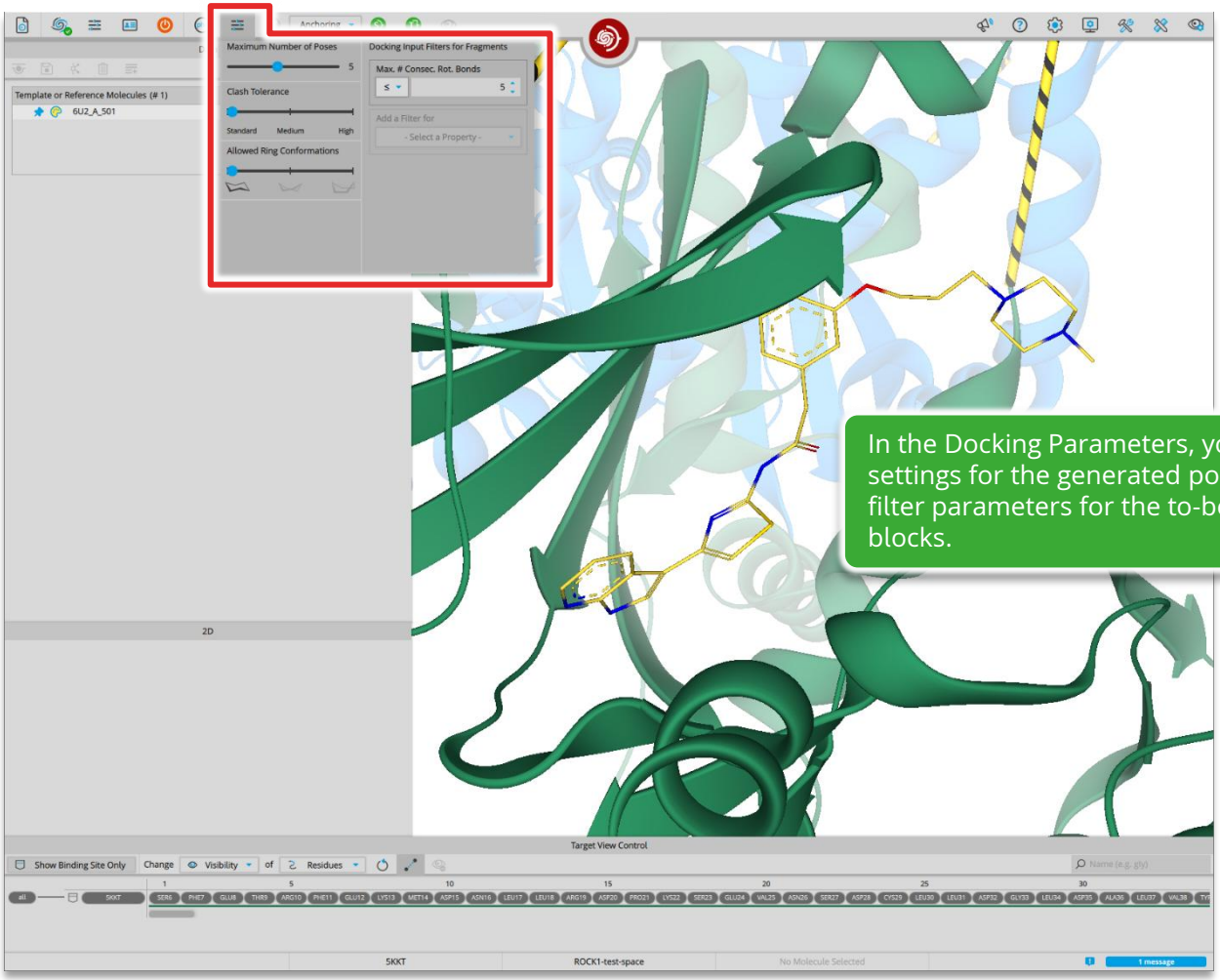
Mode Overview



In the Docking Parameters, you can adjust the settings for the generated poses or add more filter parameters for the to-be-docked anchor blocks.

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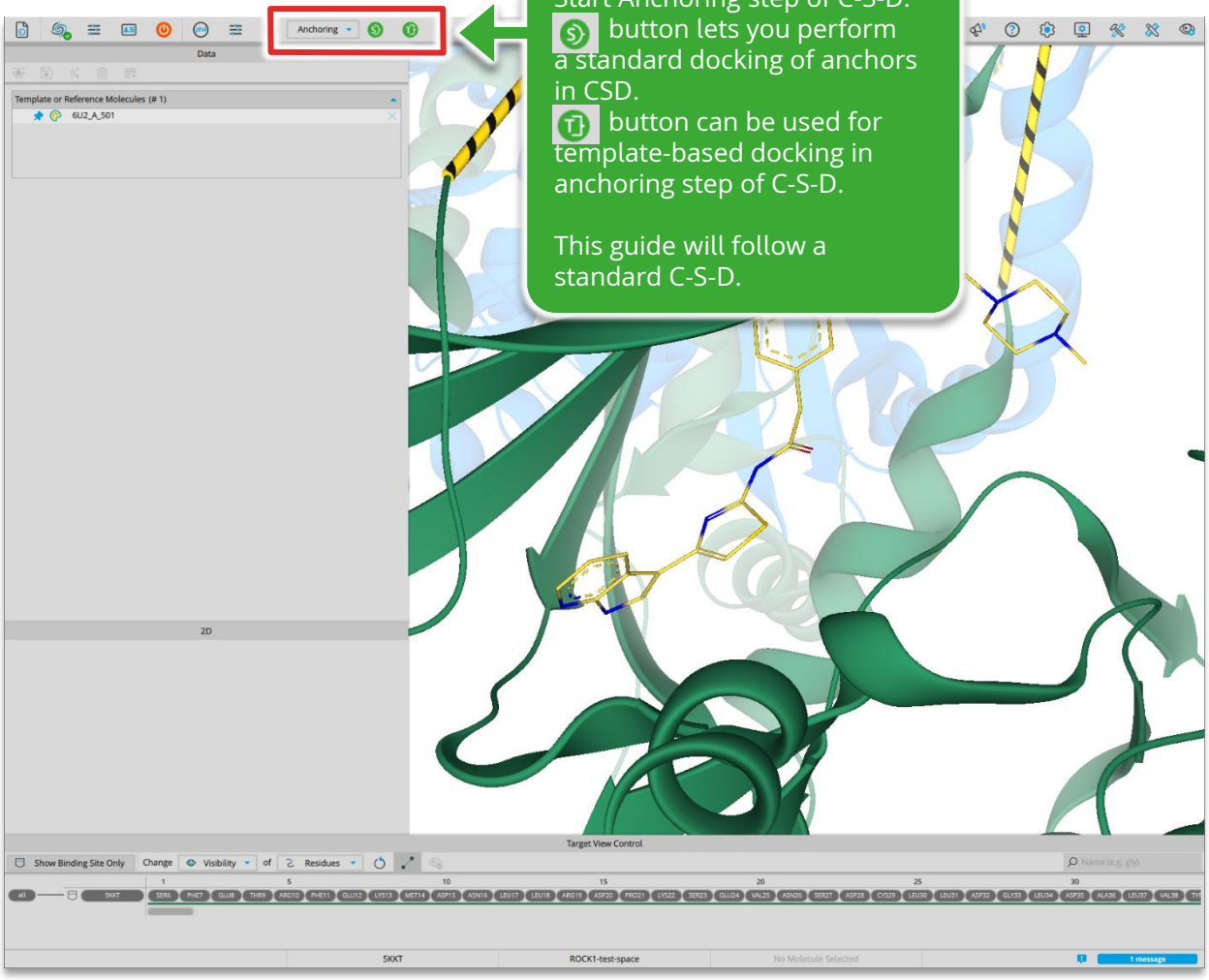
Mode Overview



Start Anchoring step of C-S-D.
button lets you perform a standard docking of anchors in CSD.
button can be used for template-based docking in anchoring step of C-S-D.

This guide will follow a standard C-S-D.

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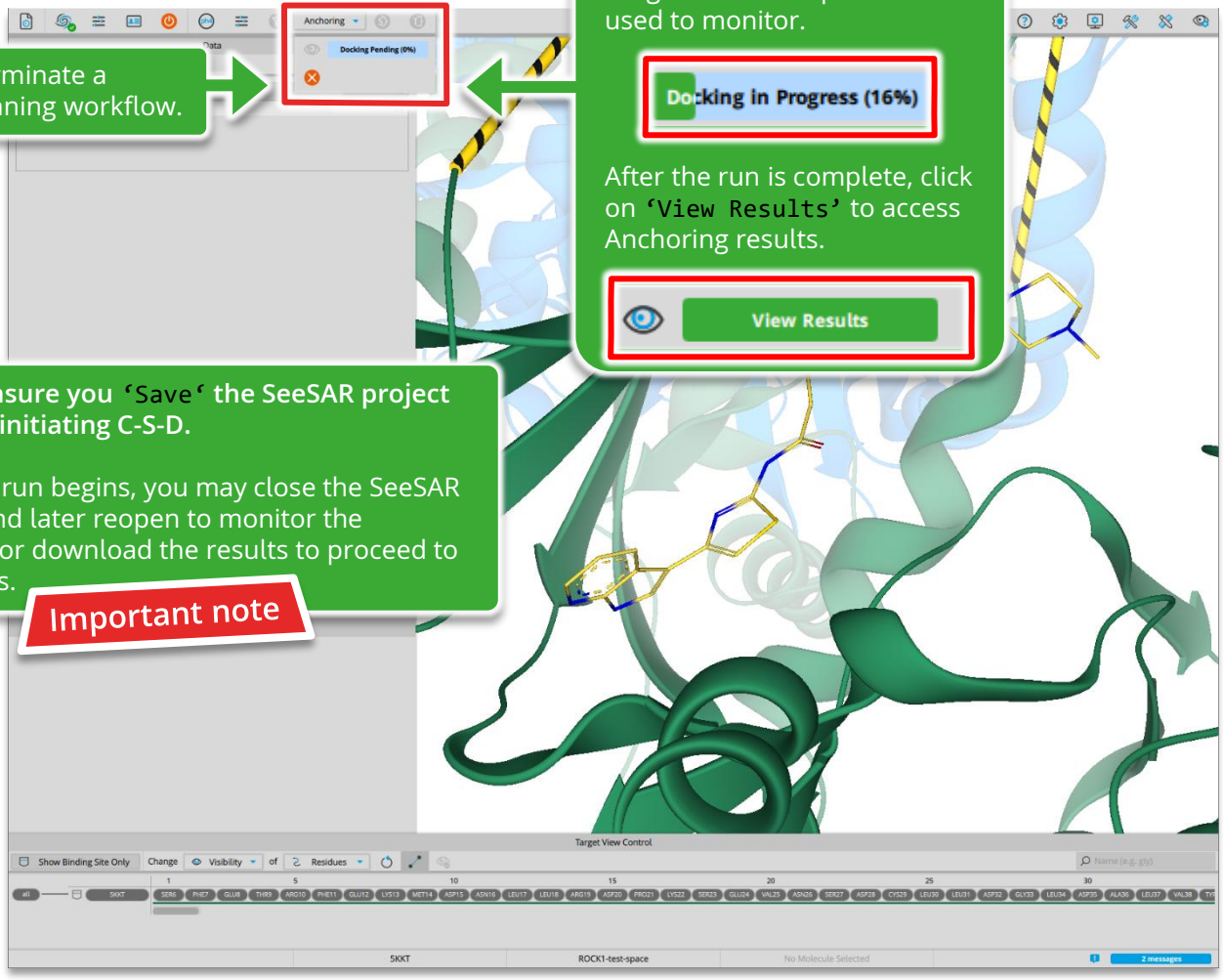
Mode Overview



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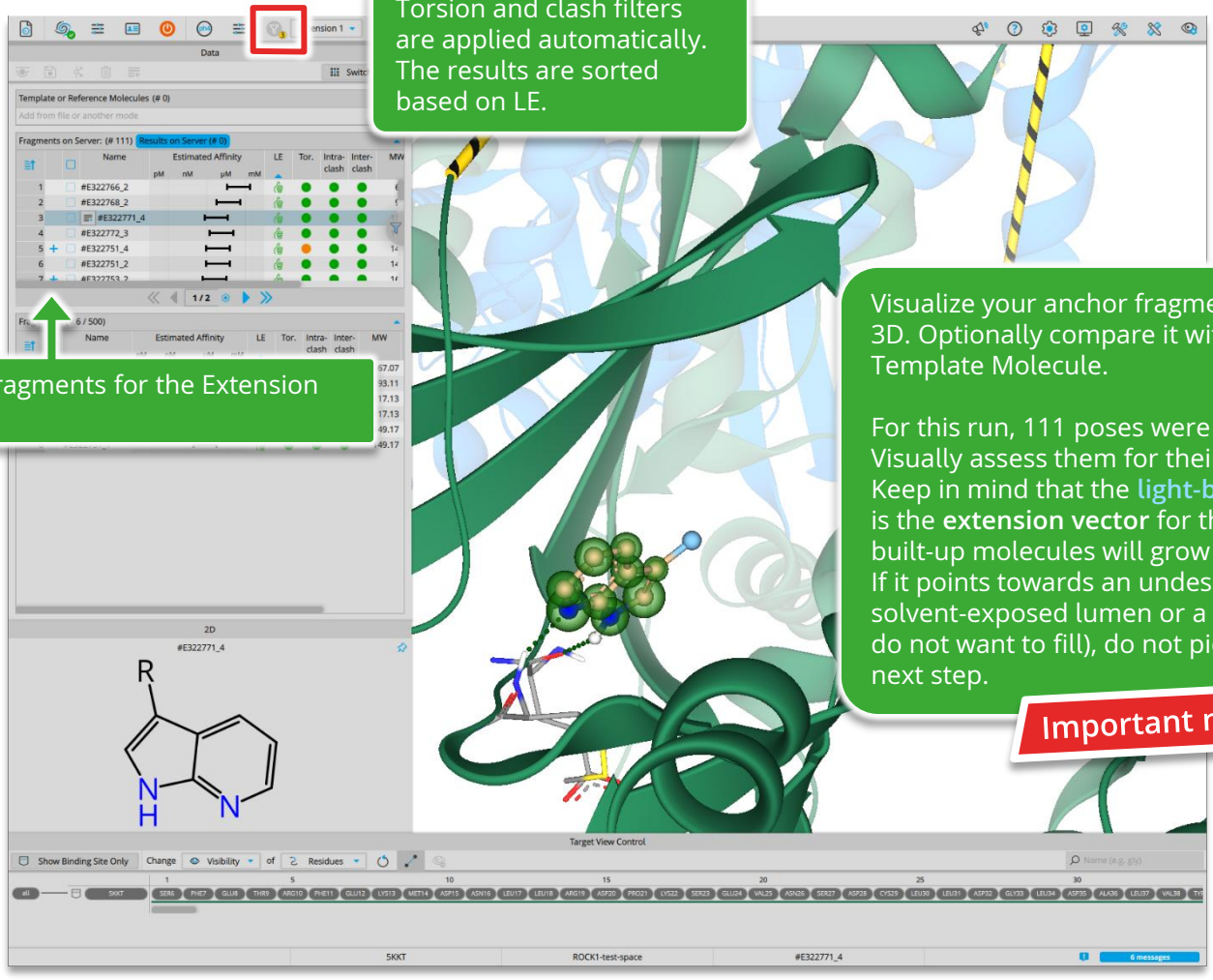
Mode Overview


Torsion and clash filters are applied automatically. The results are sorted based on LE.
Click '+' to select fragments for the Extension step.
Visualize your anchor fragment to the right in 3D. Optionally compare it with respect to your Template Molecule.
For this run, 111 poses were generated. Visually assess them for their binding modes. Keep in mind that the light-blue dummy atom is the extension vector for this synthon: All built-up molecules will grow from it.
If it points towards an undesired area (e.g., solvent-exposed lumen or a binding site you do not want to fill), do not pick this pose for the next step.
Important note
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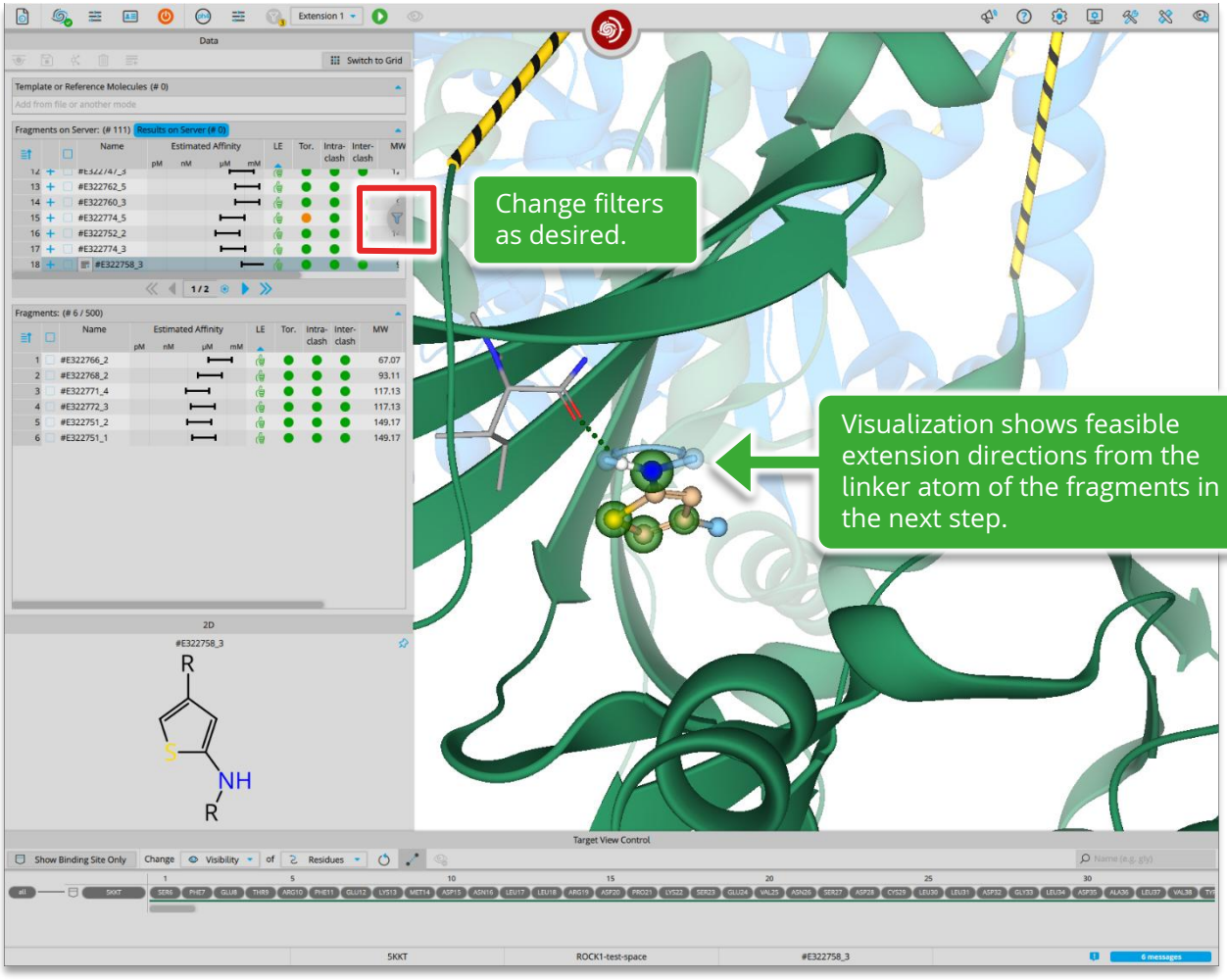
Mode Overview



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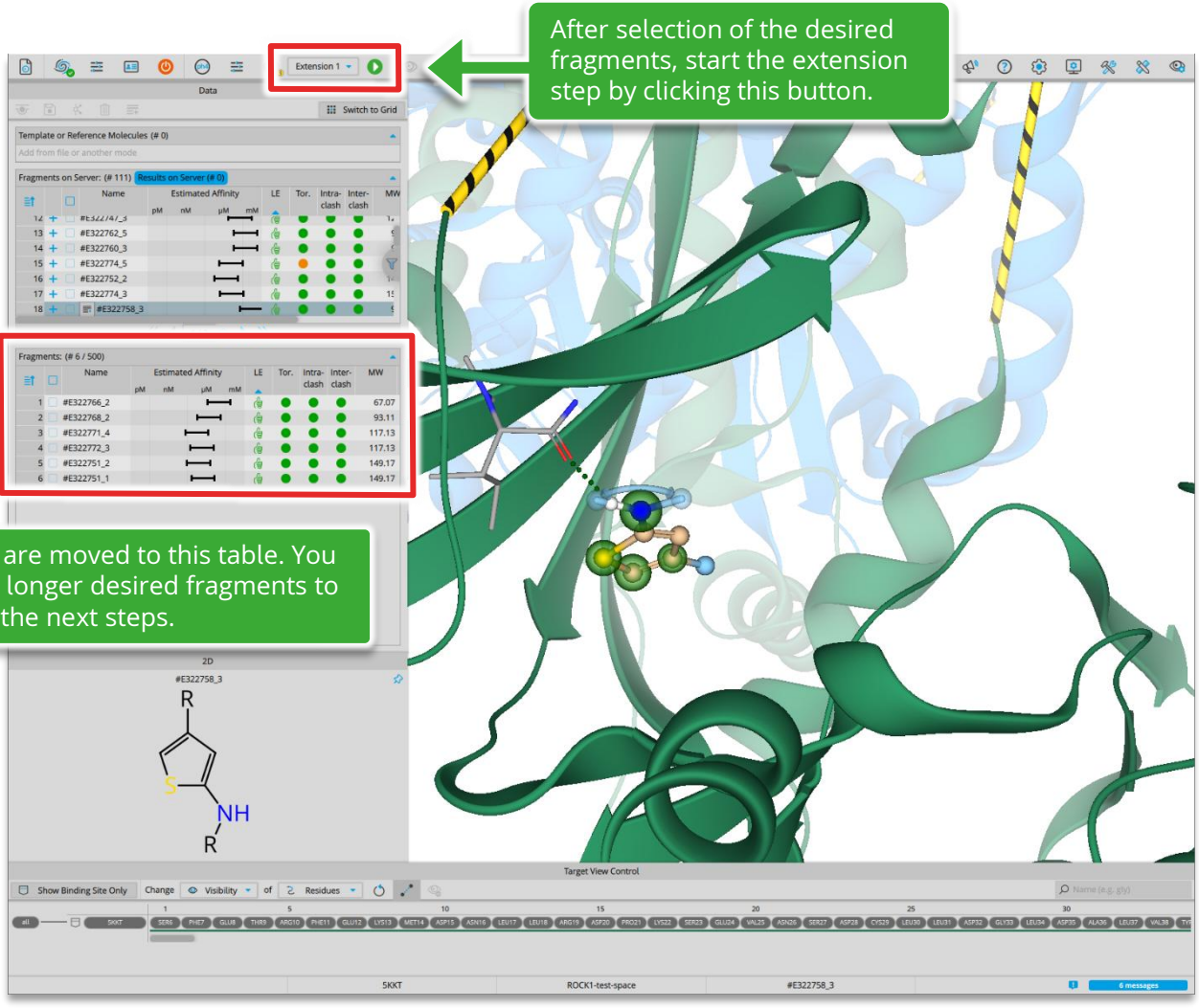
Mode Overview



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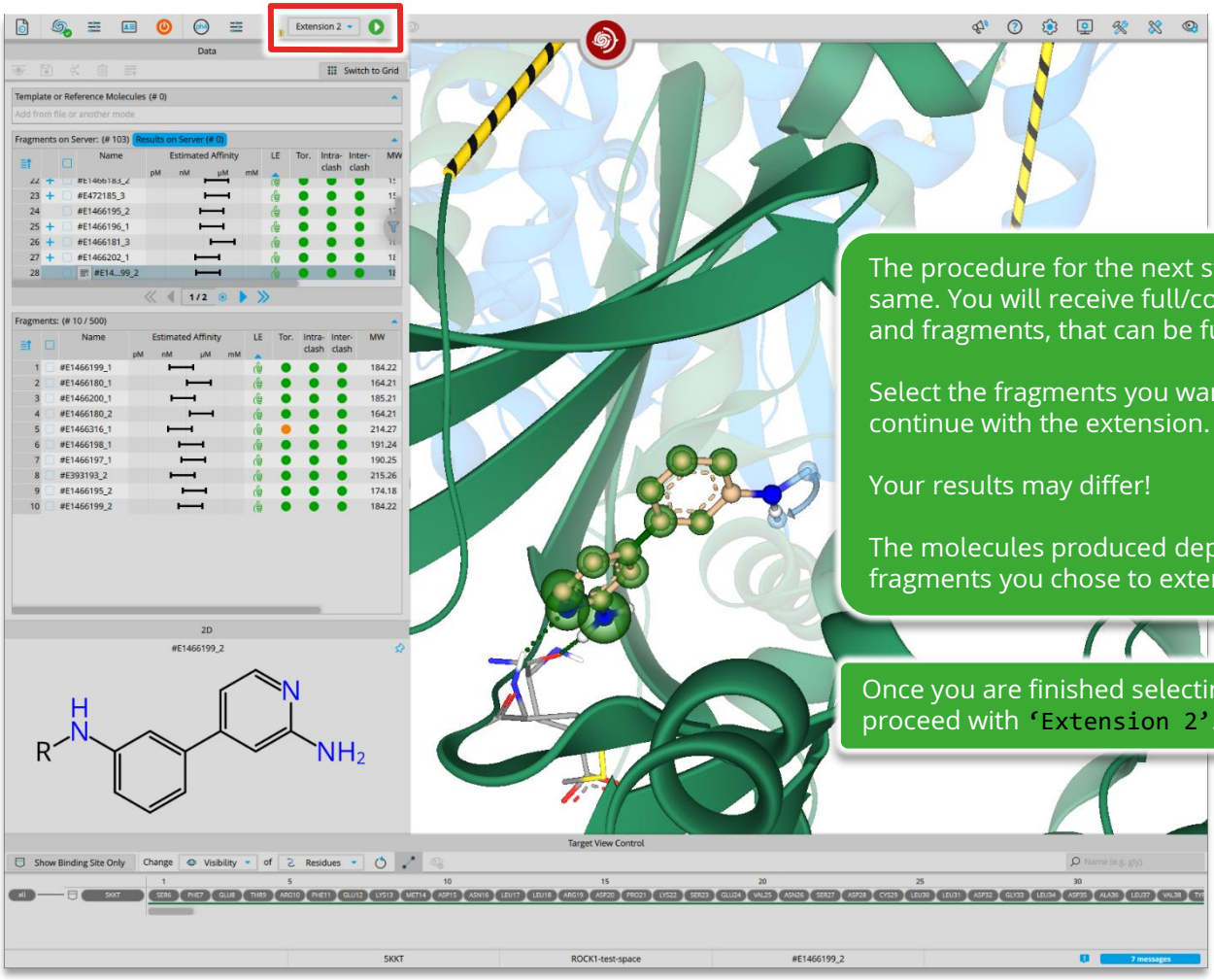
Mode Overview



The procedure for the next step remains the same. You will receive full/complete molecules and fragments, that can be further extended.

Select the fragments you want to grow and continue with the extension.

Your results may differ!

The molecules produced depend on the fragments you chose to extend.

Once you are finished selecting your compound, proceed with ‘Extension 2’.

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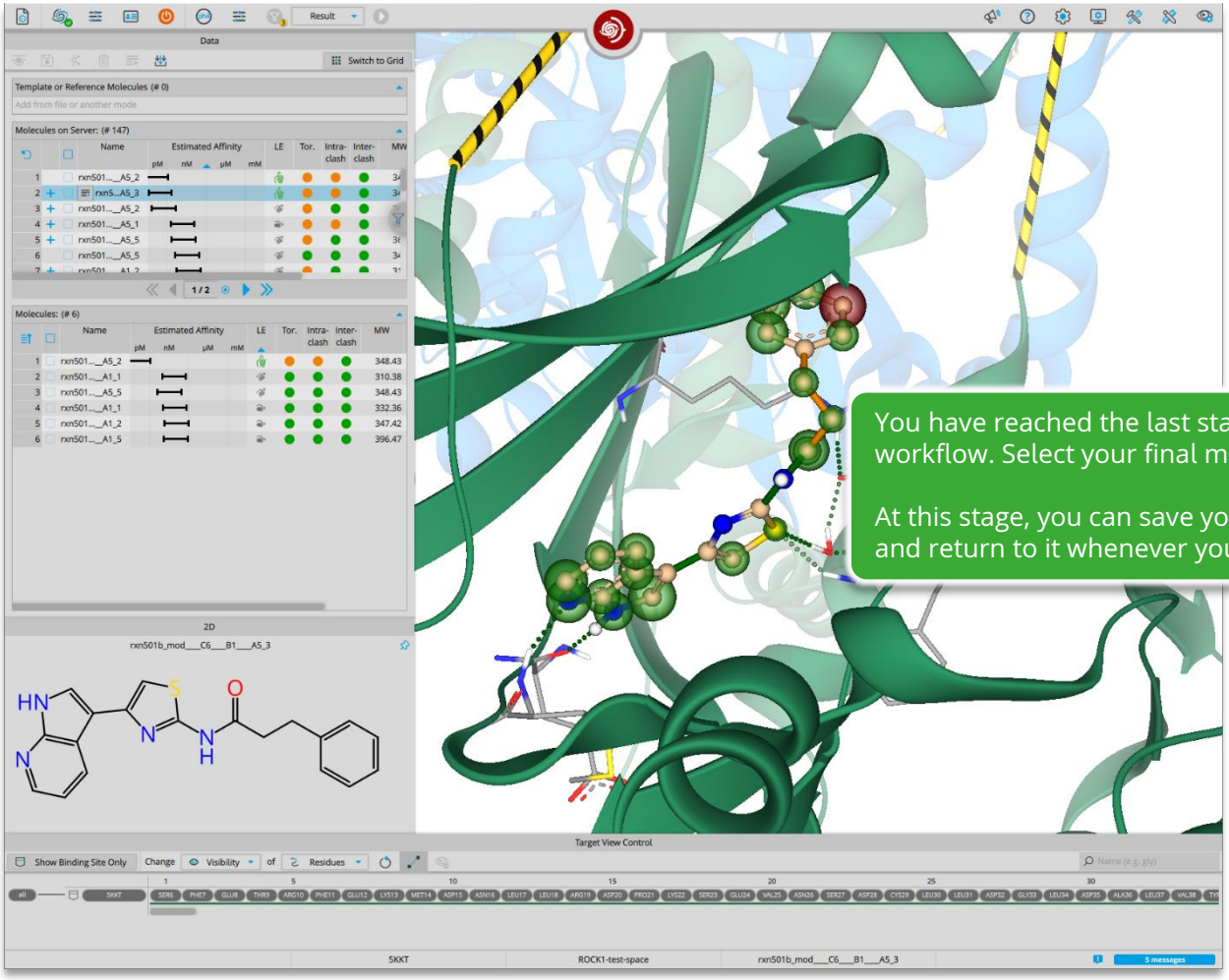
Mode Overview



You have reached the last stage of the C-S-D workflow. Select your final molecules.

At this stage, you can save your SeeSAR project and return to it whenever you wish.

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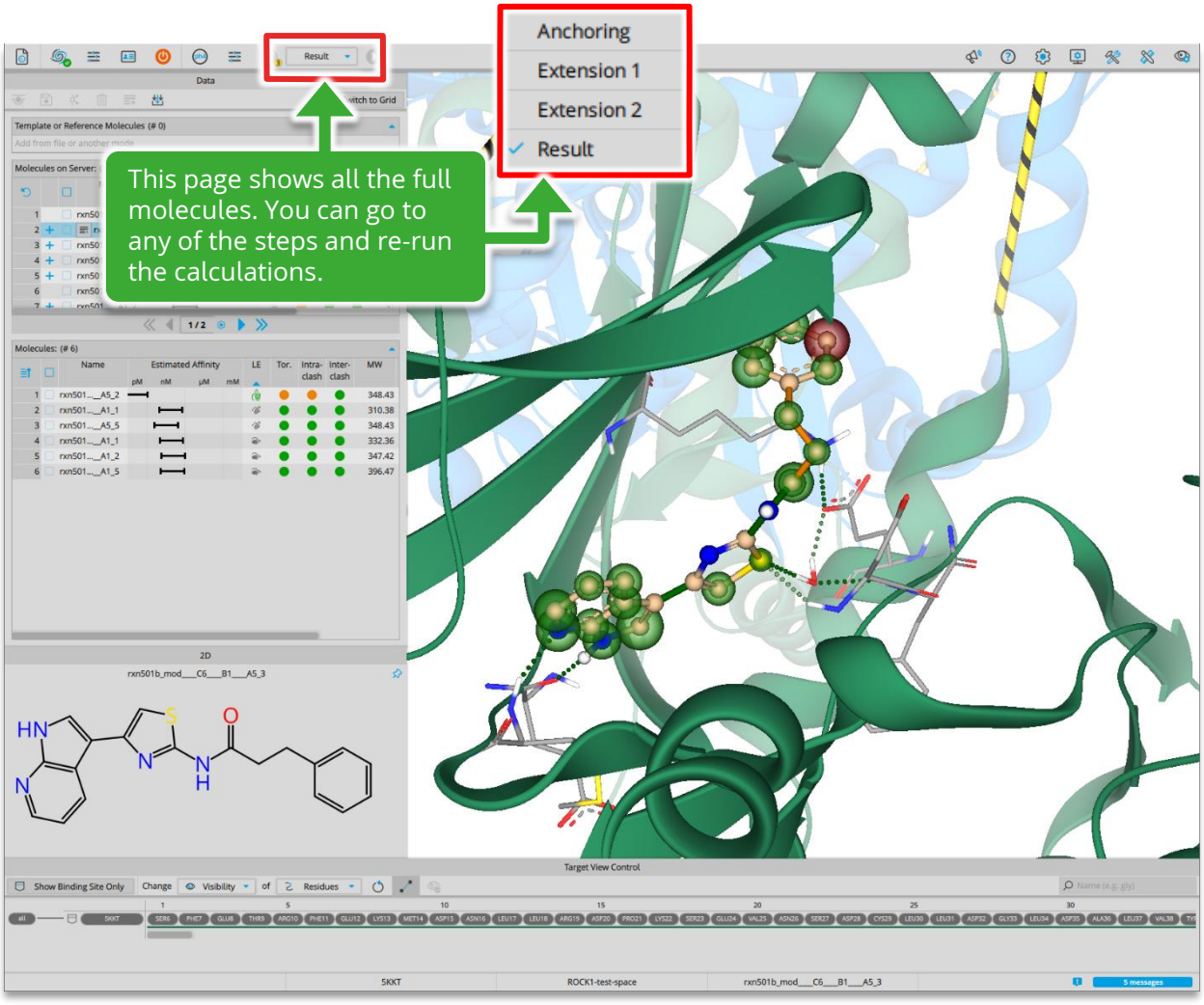
Mode Overview



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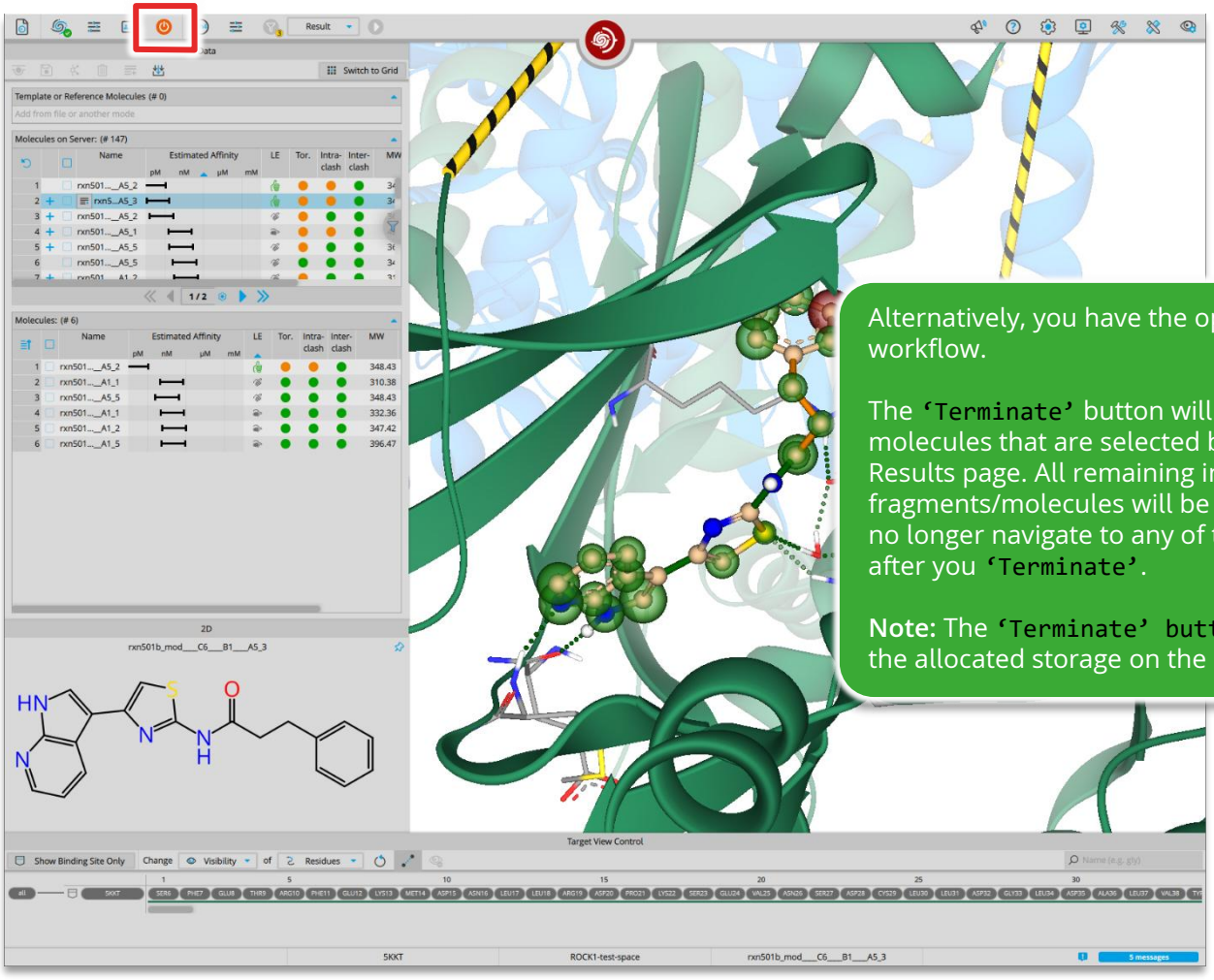
Mode Overview



Alternatively, you have the option to end the workflow.

The `'Terminate'` button will only show the full molecules that are selected below, into a Results page. All remaining intermediate fragments/molecules will be deleted. You can no longer navigate to any of the previous steps after you `'Terminate'`.

Note: The `'Terminate' button` also releases the allocated storage on the HPSee cluster.

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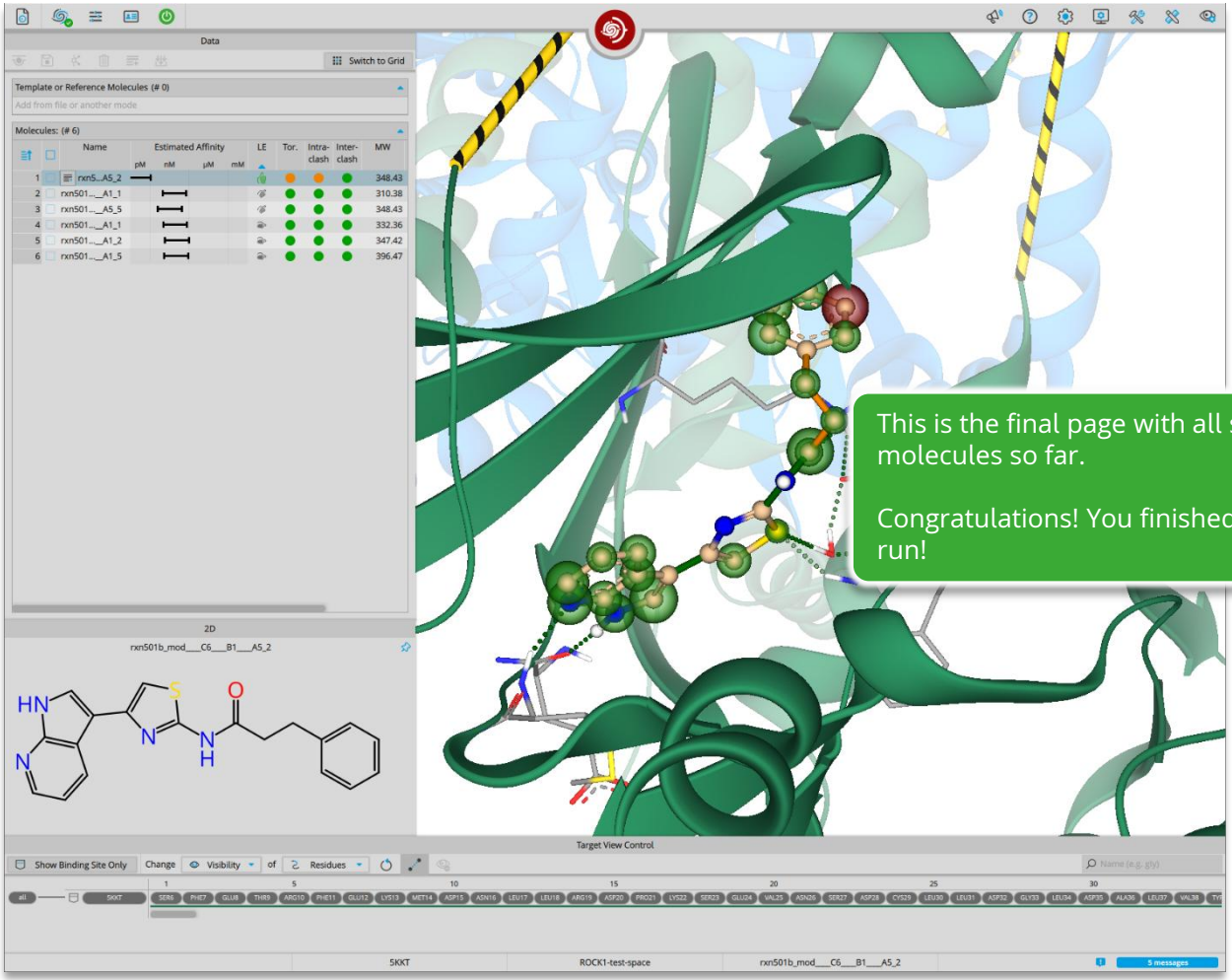
Mode Overview



This is the final page with all selected full molecules so far.

Congratulations! You finished your first C-S-D run!

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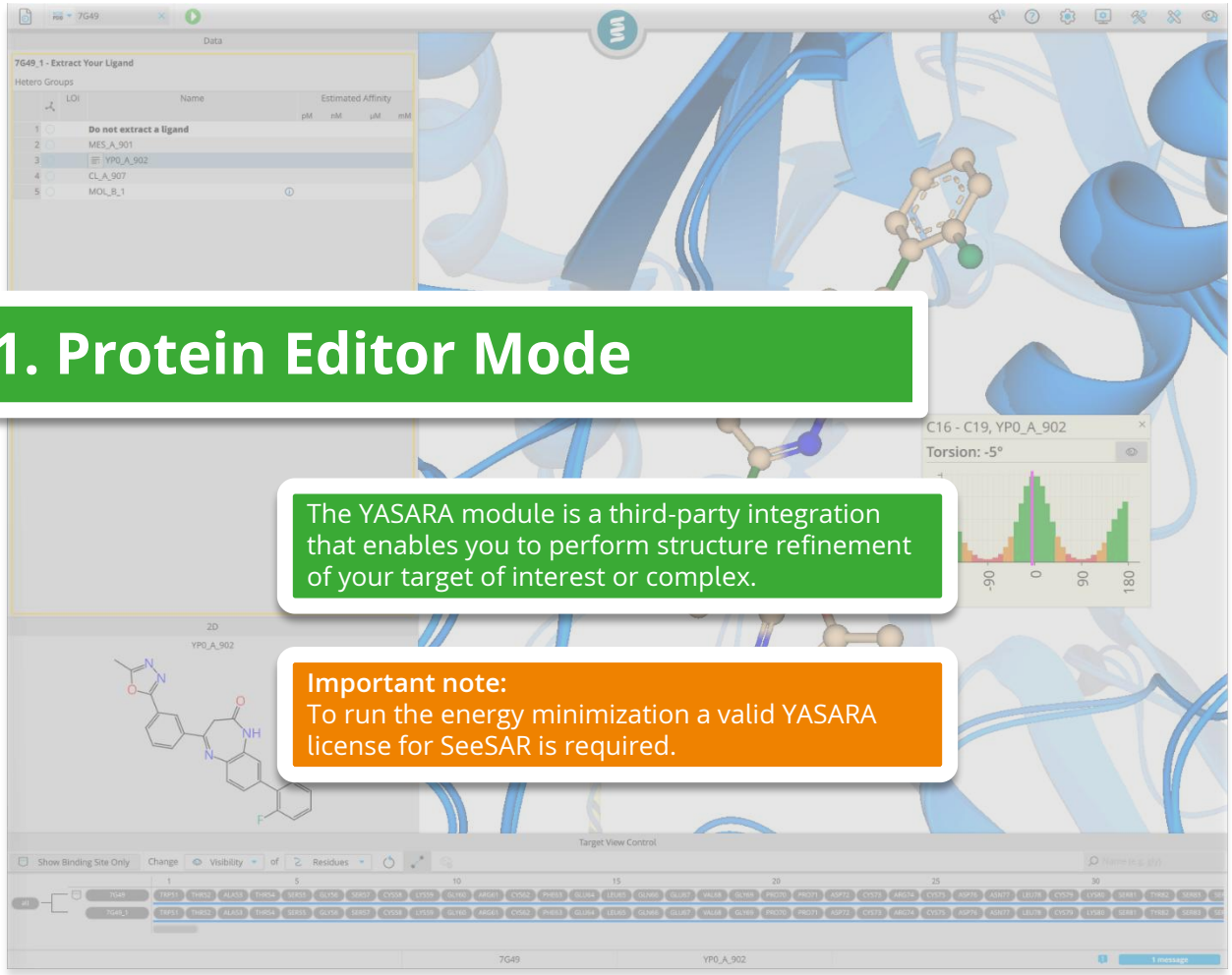
Mode Overview

11. Protein Editor Mode



The YASARA module is a third-party integration that enables you to perform structure refinement of your target of interest or complex.

Important note:
To run the energy minimization a valid YASARA license for SeeSAR is required.

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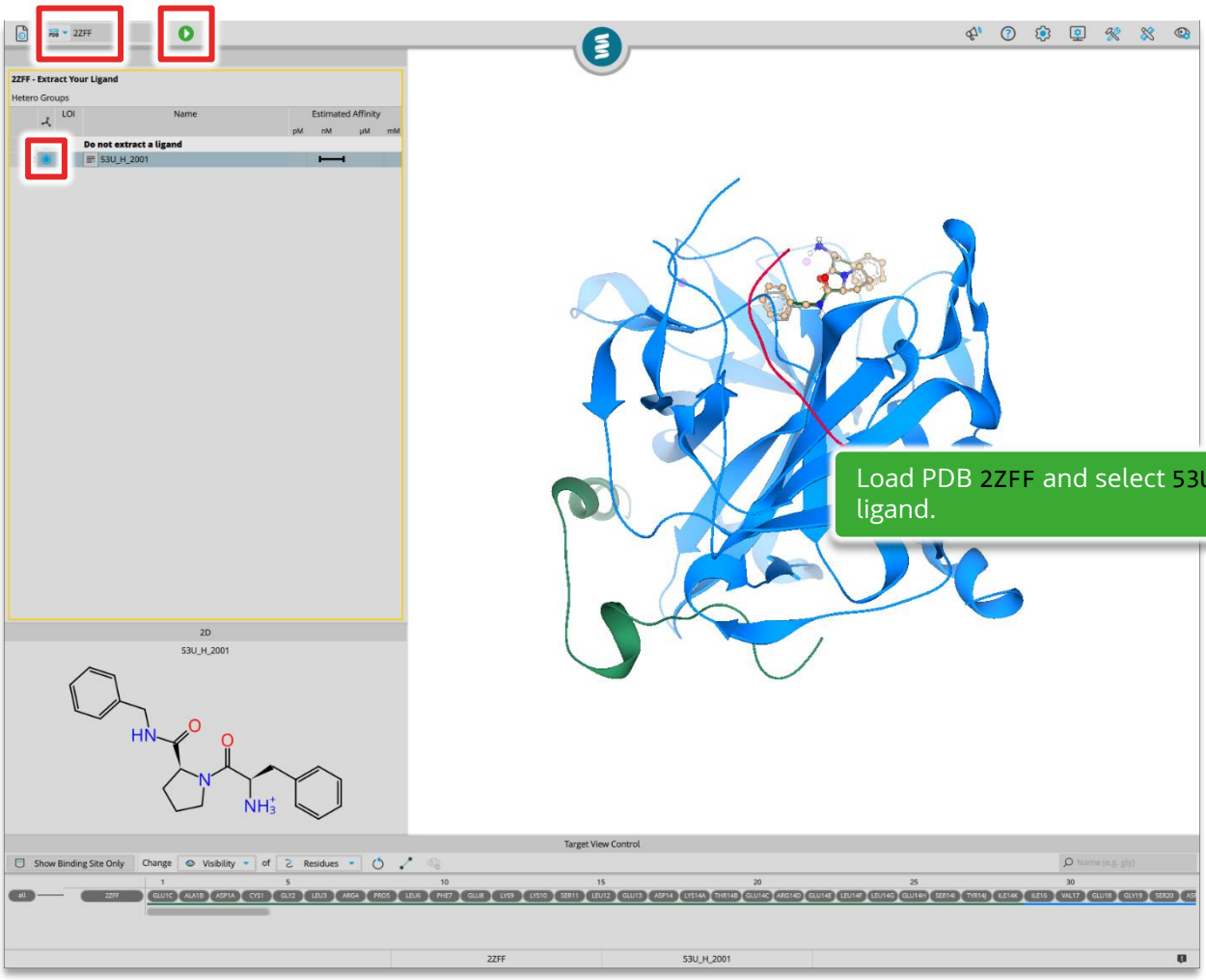
Mode Overview



Load PDB `2ZFF` and select `53U_H_2001` as the ligand.

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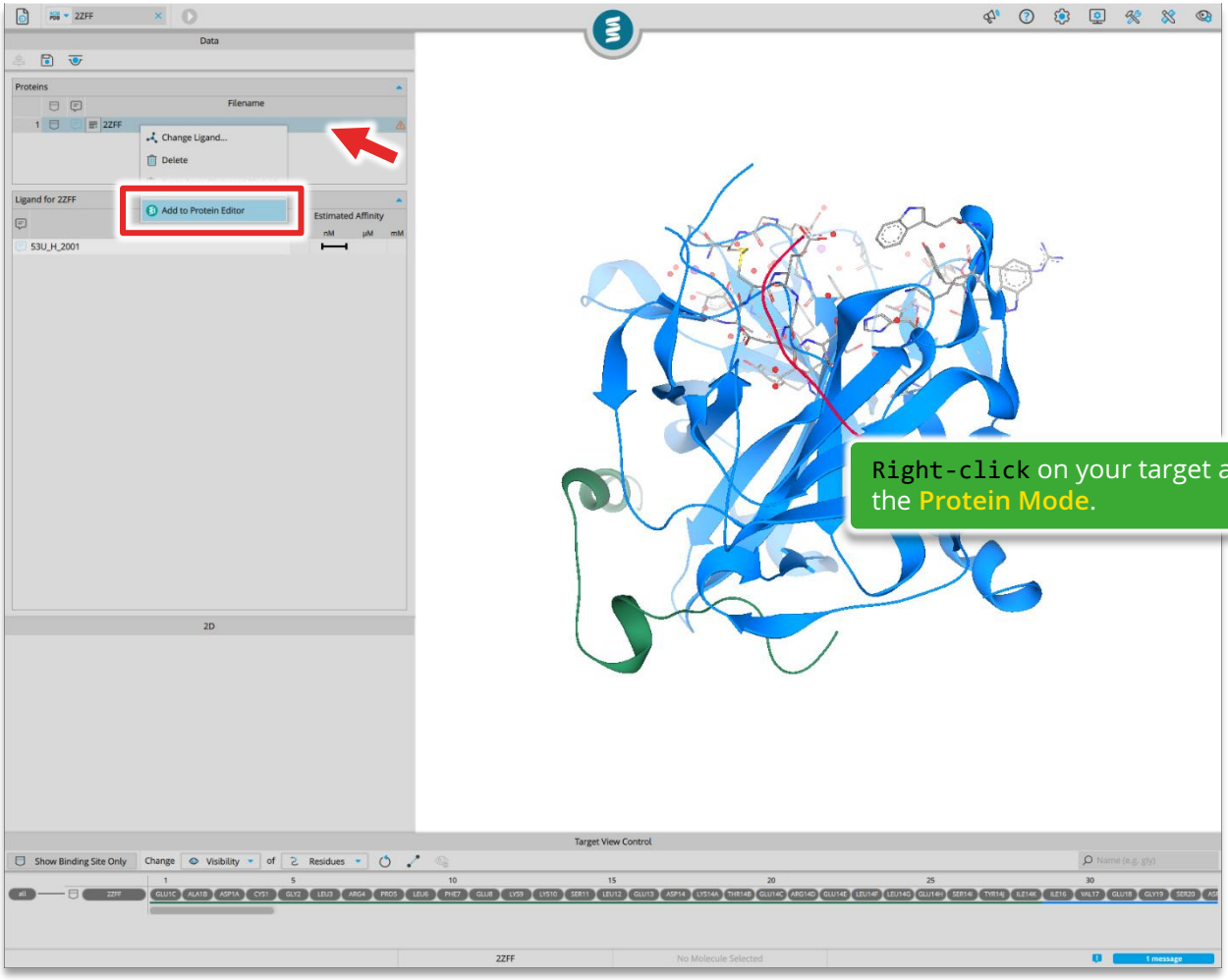
Mode Overview



`Right-click` on your target and transfer it to the **Protein Mode**.

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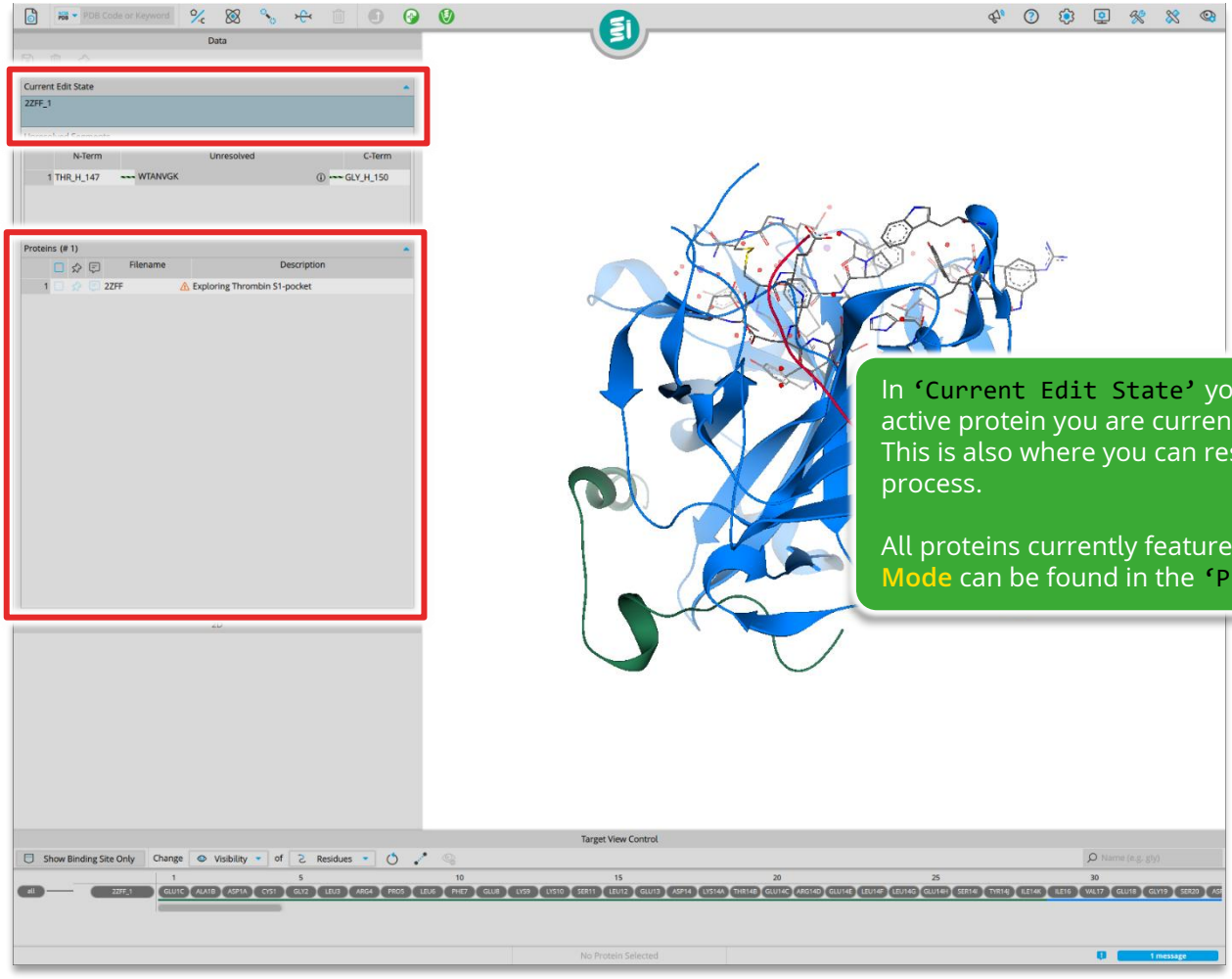
Mode Overview



In ‘Current Edit State’ you will find the active protein you are currently working with. This is also where you can resume your editing process.

All proteins currently featured in the Proteins Mode can be found in the ‘Proteins’ window.

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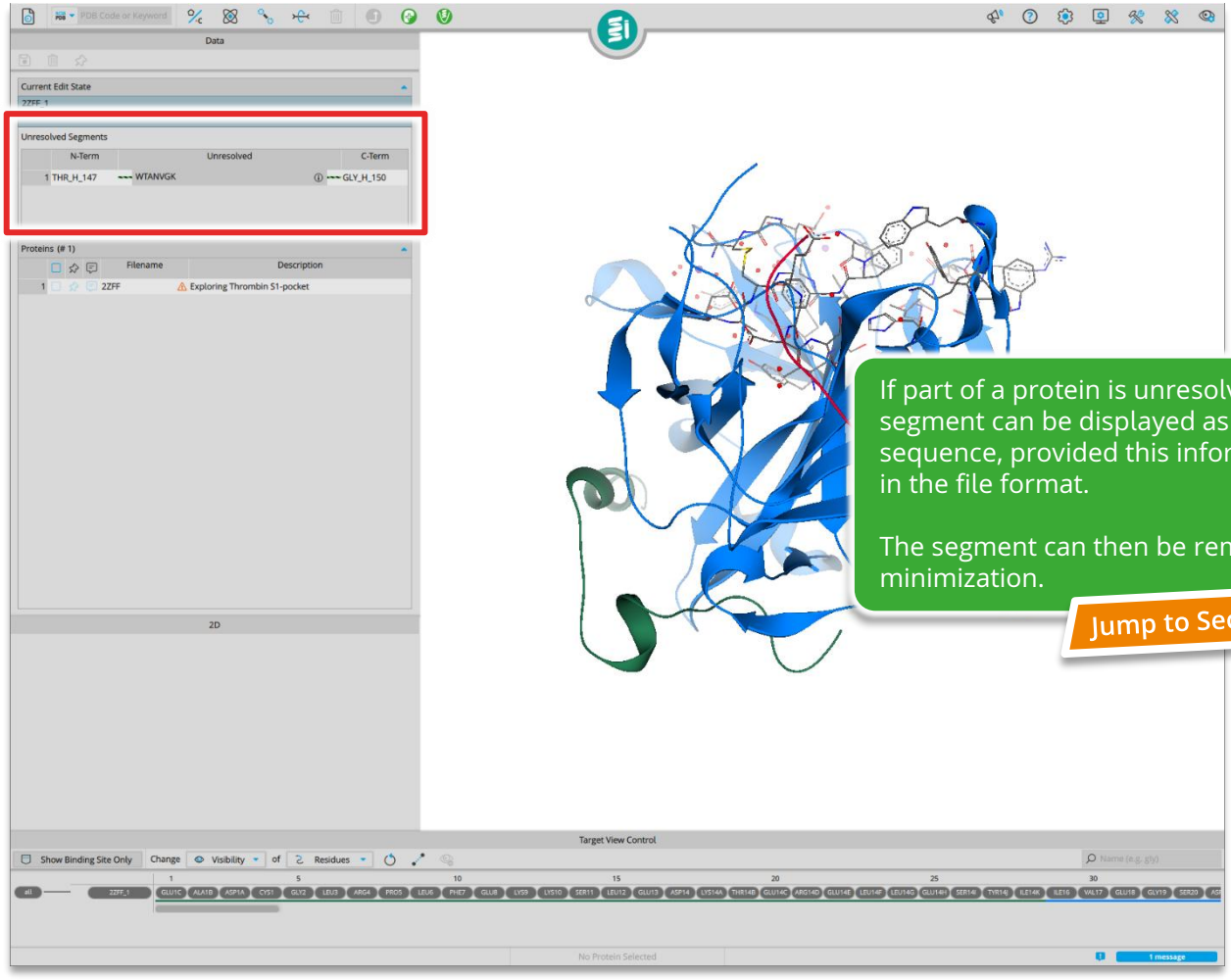
Mode Overview



If part of a protein is unresolved, the missing segment can be displayed as a suggested sequence, provided this information is available in the file format.

The segment can then be remodeled by energy minimization.

Jump to Section

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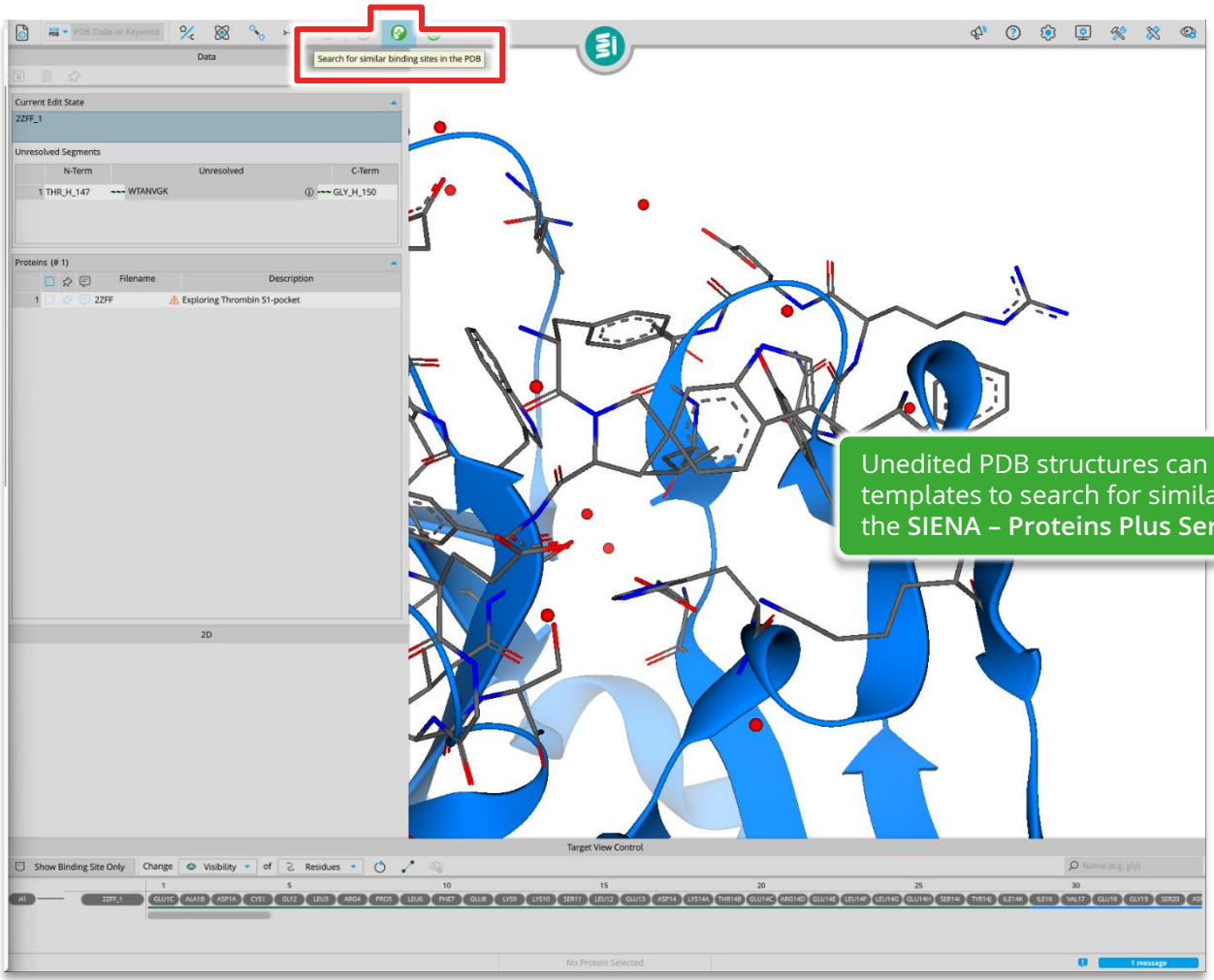
Mode Overview



Unedited PDB structures can be used as templates to search for similar binding sites via the **SIENA – Proteins Plus Server**.

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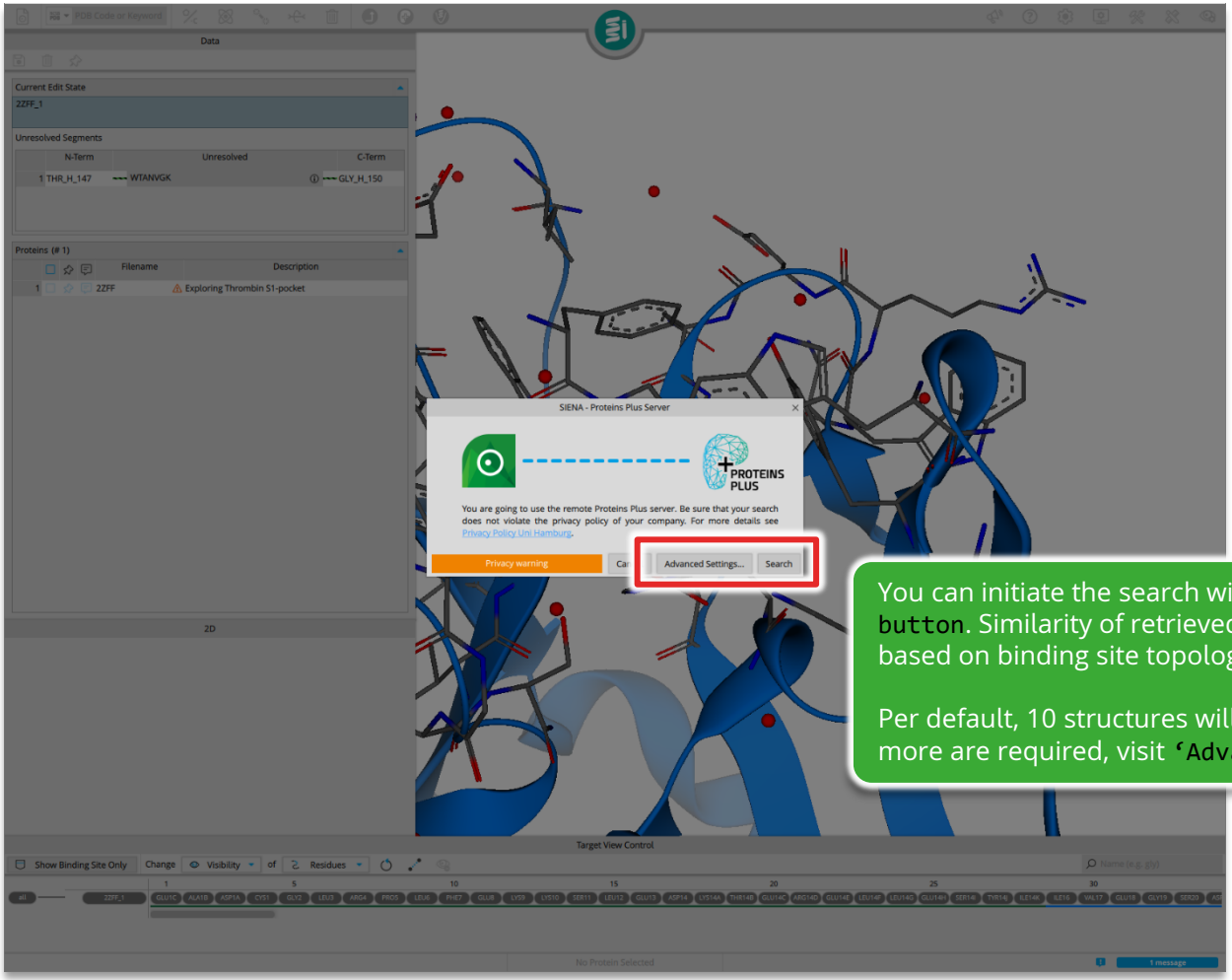
Mode Overview



You can initiate the search with the `'Search' button`. Similarity of retrieved structures is based on binding site topology (not sequence).

Per default, 10 structures will be retrieved. If more are required, visit `'Advanced Settings…'`.

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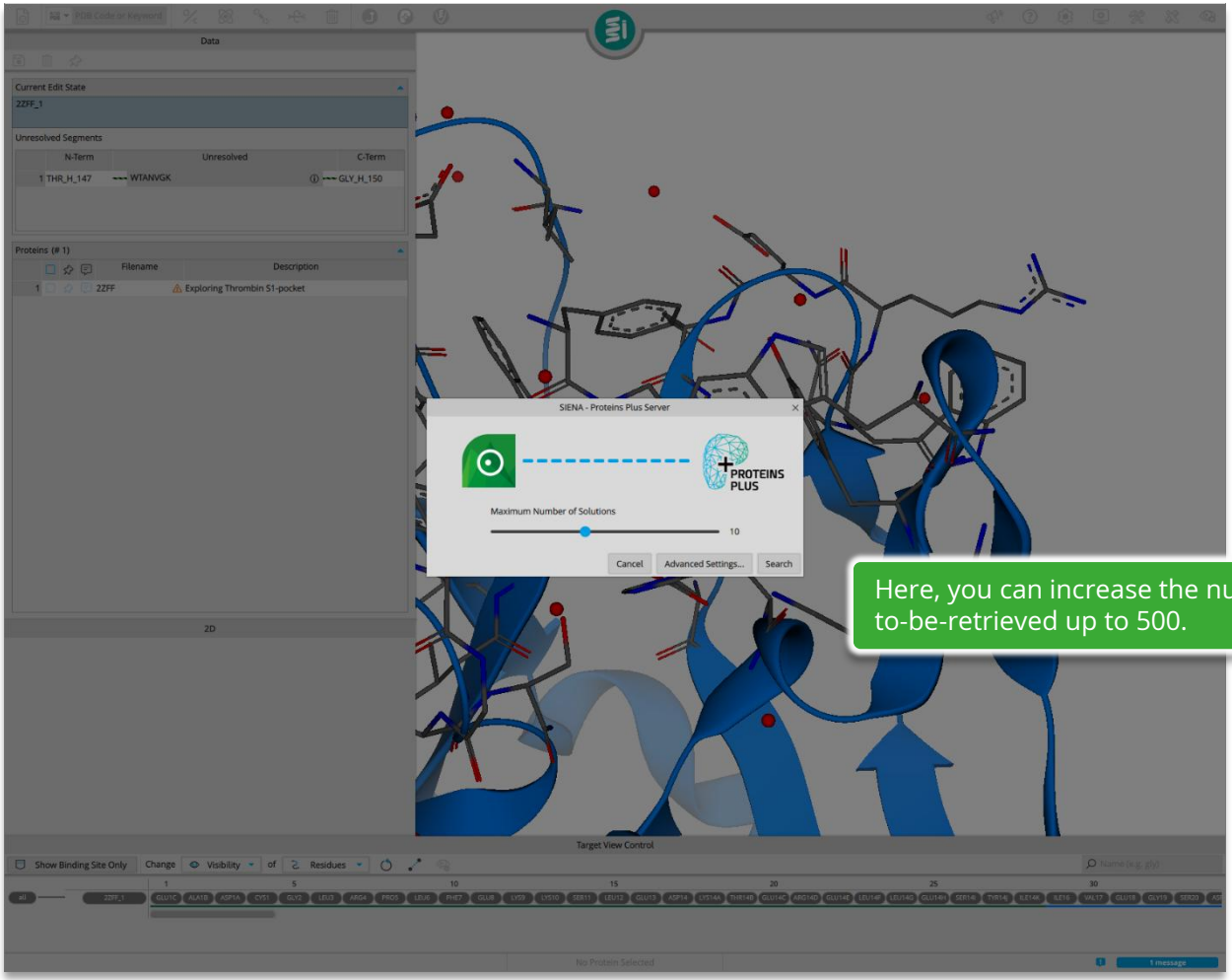
Mode Overview



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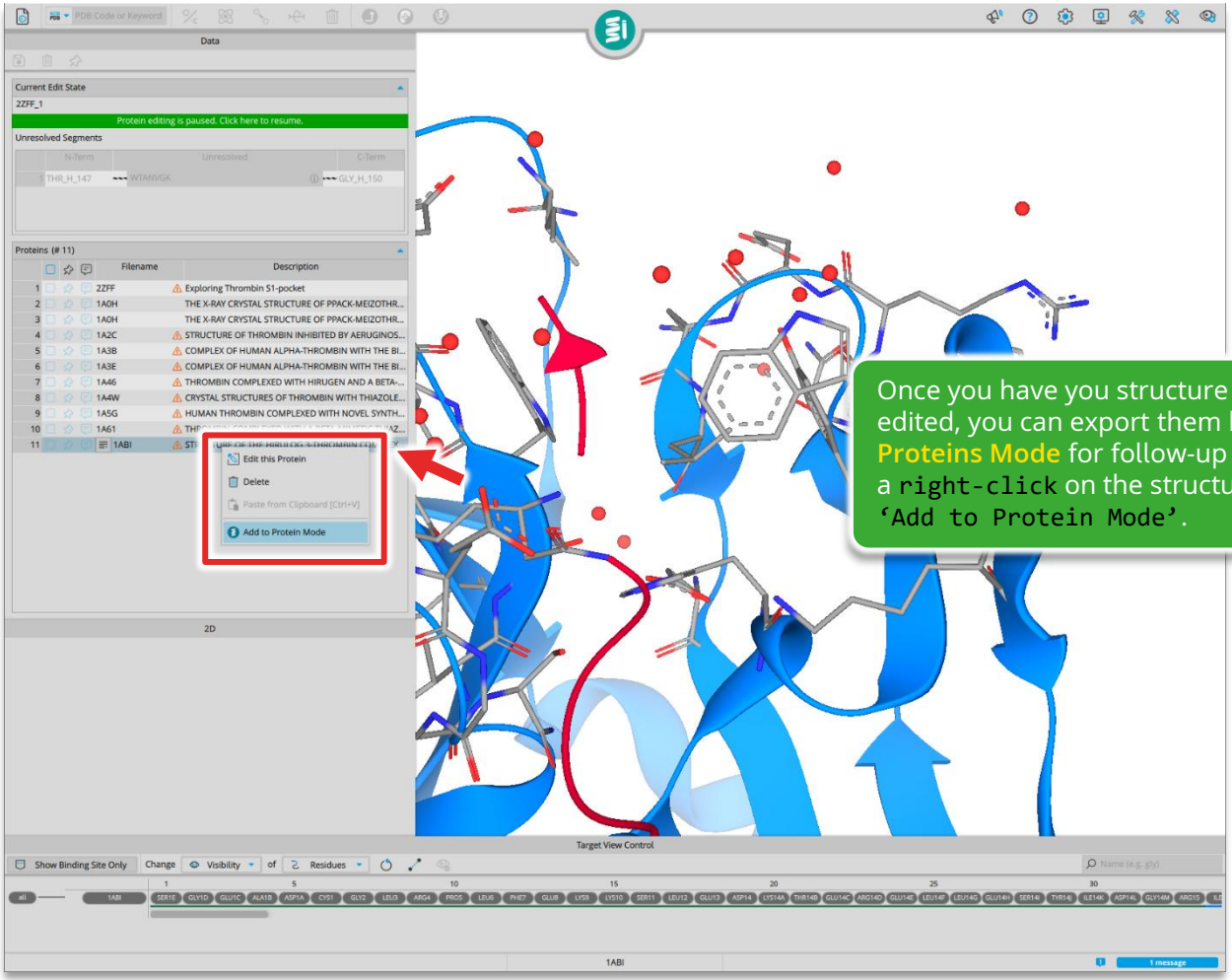
Mode Overview



Once you have you structure retrieved or edited, you can export them back to the **Proteins Mode** for follow-up investigations with a `right-click` on the structure of interest and `'Add to Protein Mode'`.

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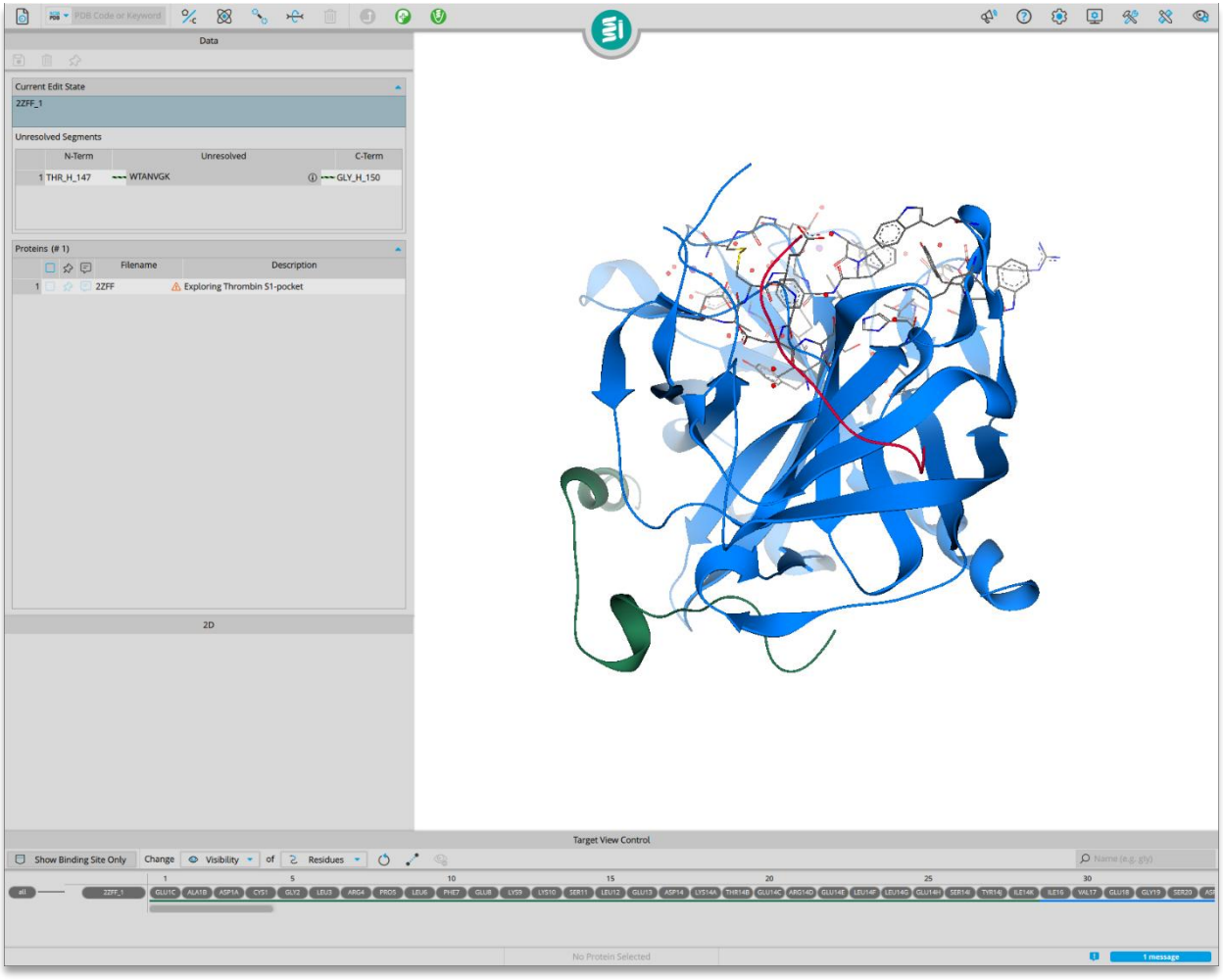
Mode Overview



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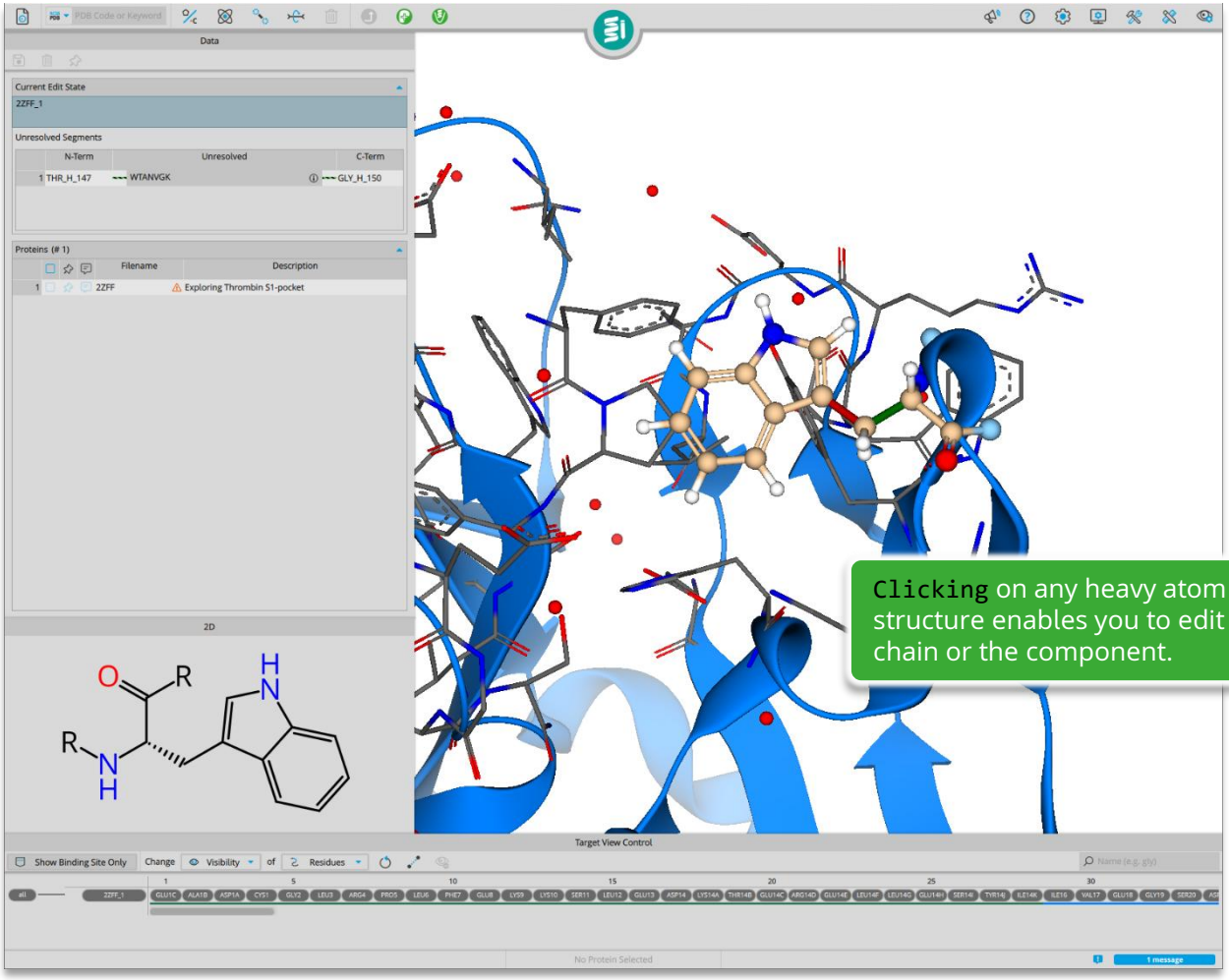
Mode Overview



Clicking on any heavy atom of the target structure enables you to edit the residue side chain or the component.

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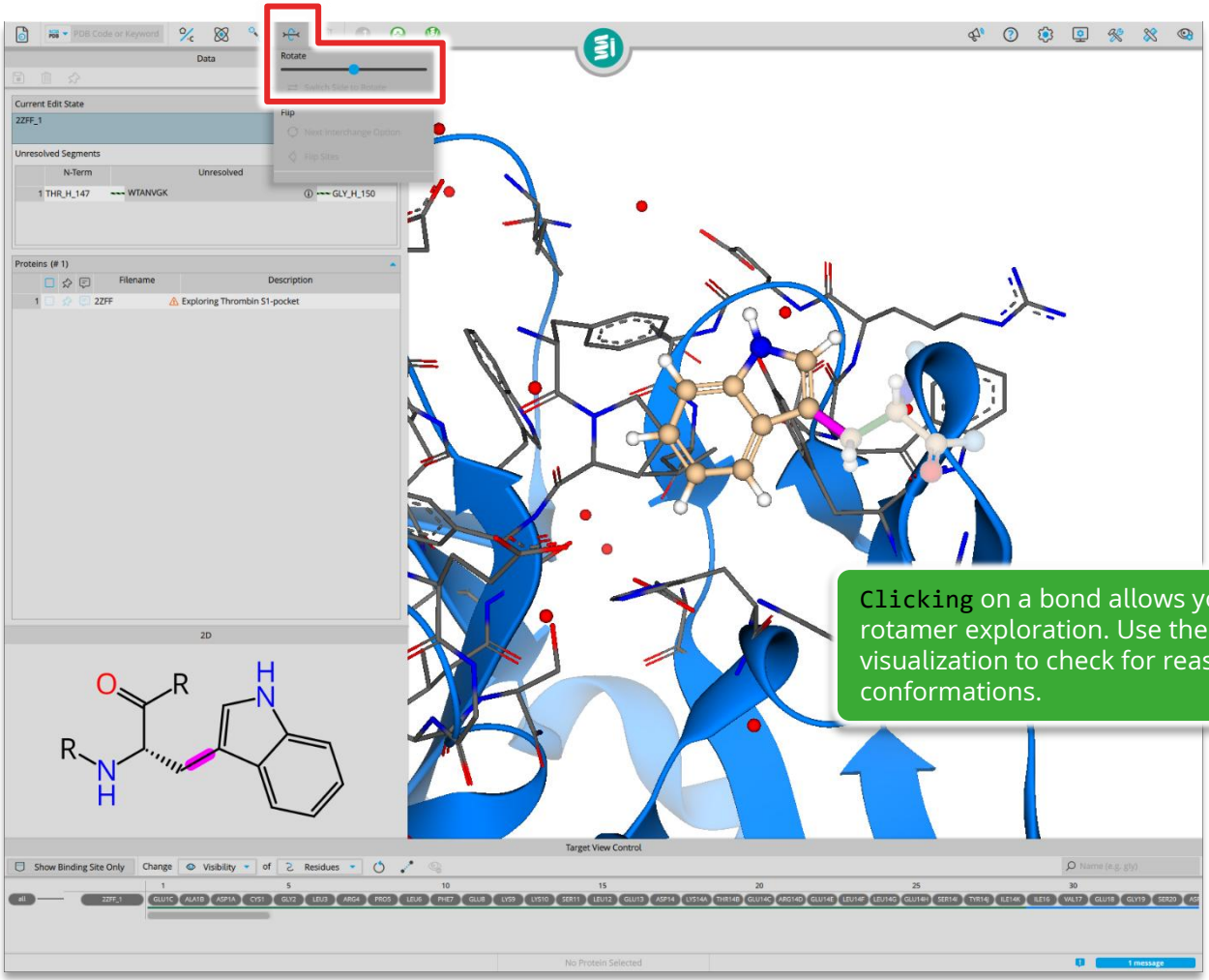
Mode Overview



`Clicking` on a bond allows you to rotate it for rotamer exploration. Use the clashes visualization to check for reasonable conformations.

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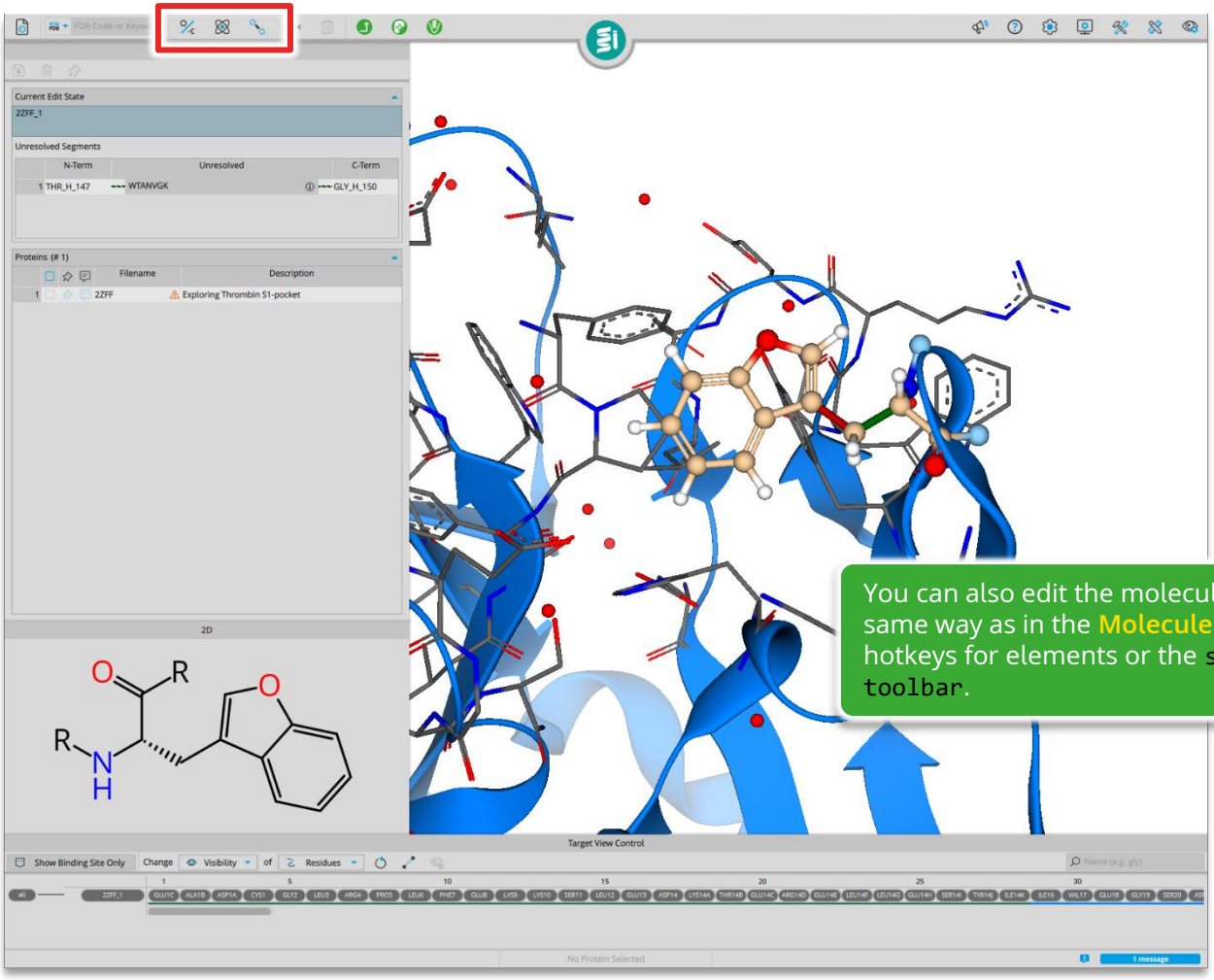
Mode Overview



You can also edit the molecular structure in the same way as in the **Molecule Editor**. Use hotkeys for elements or the `supporting toolbar`.

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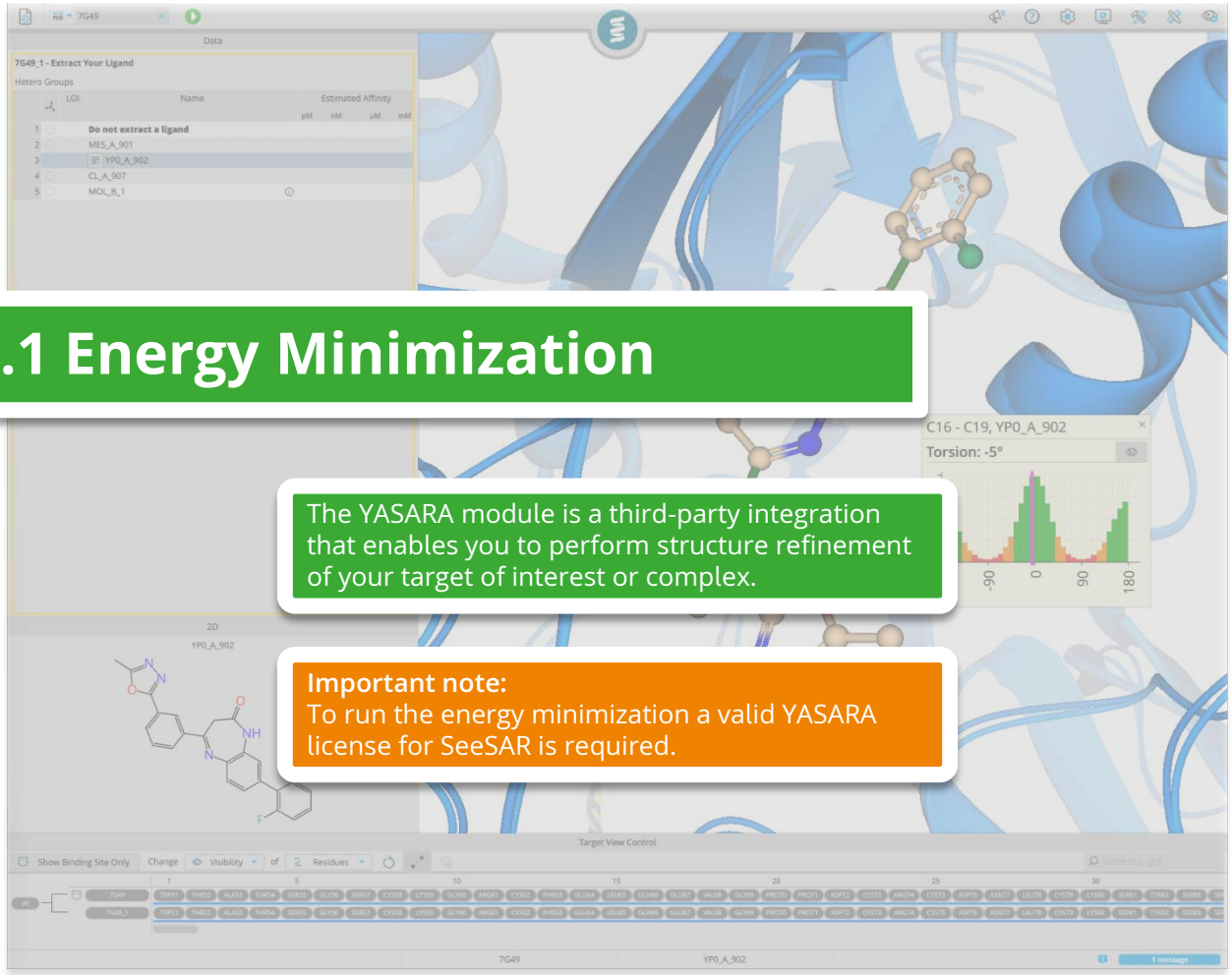
Mode Overview

11.1 Energy Minimization



The YASARA module is a third-party integration that enables you to perform structure refinement of your target of interest or complex.

Important note:
To run the energy minimization a valid YASARA license for SeeSAR is required.

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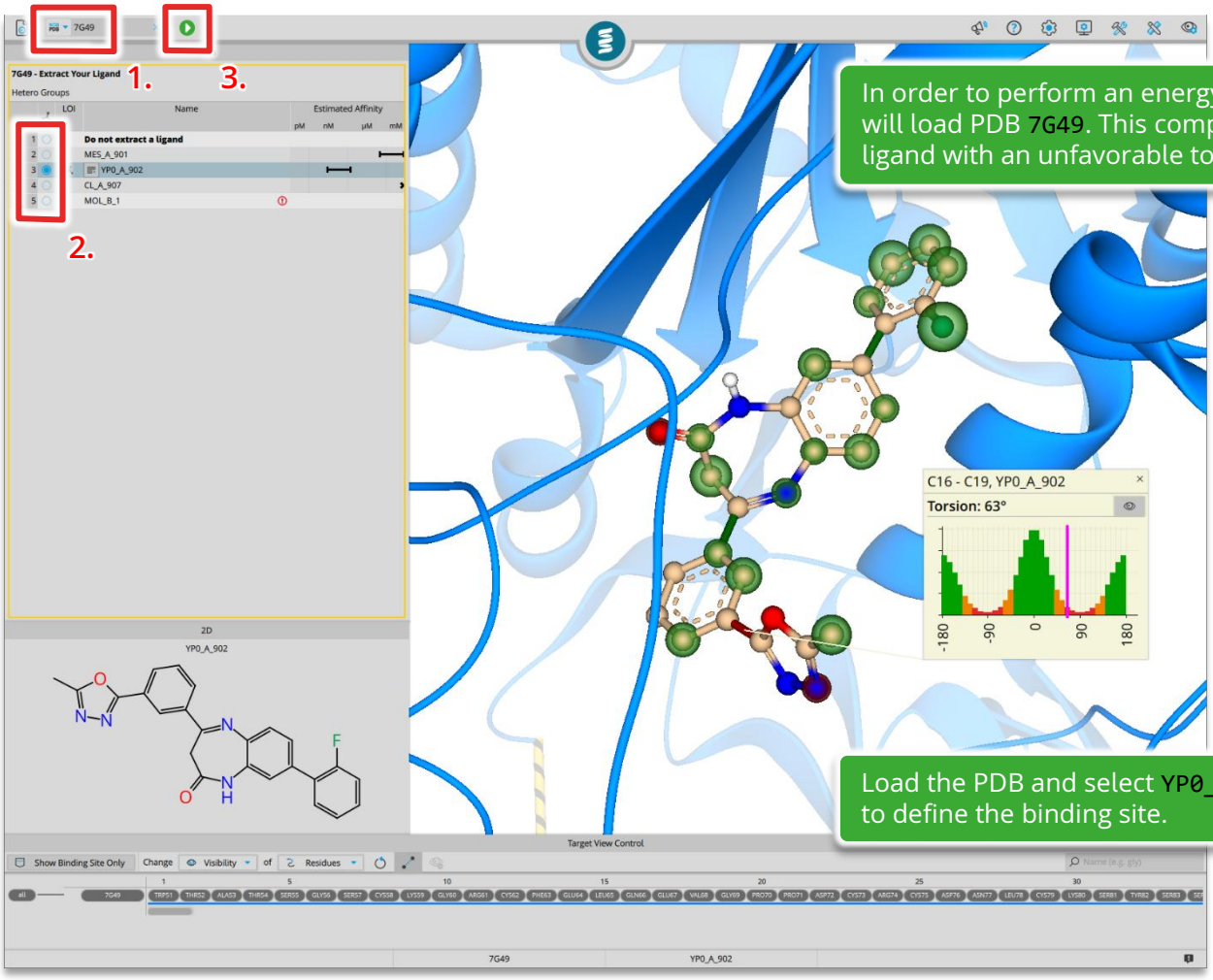
Mode Overview



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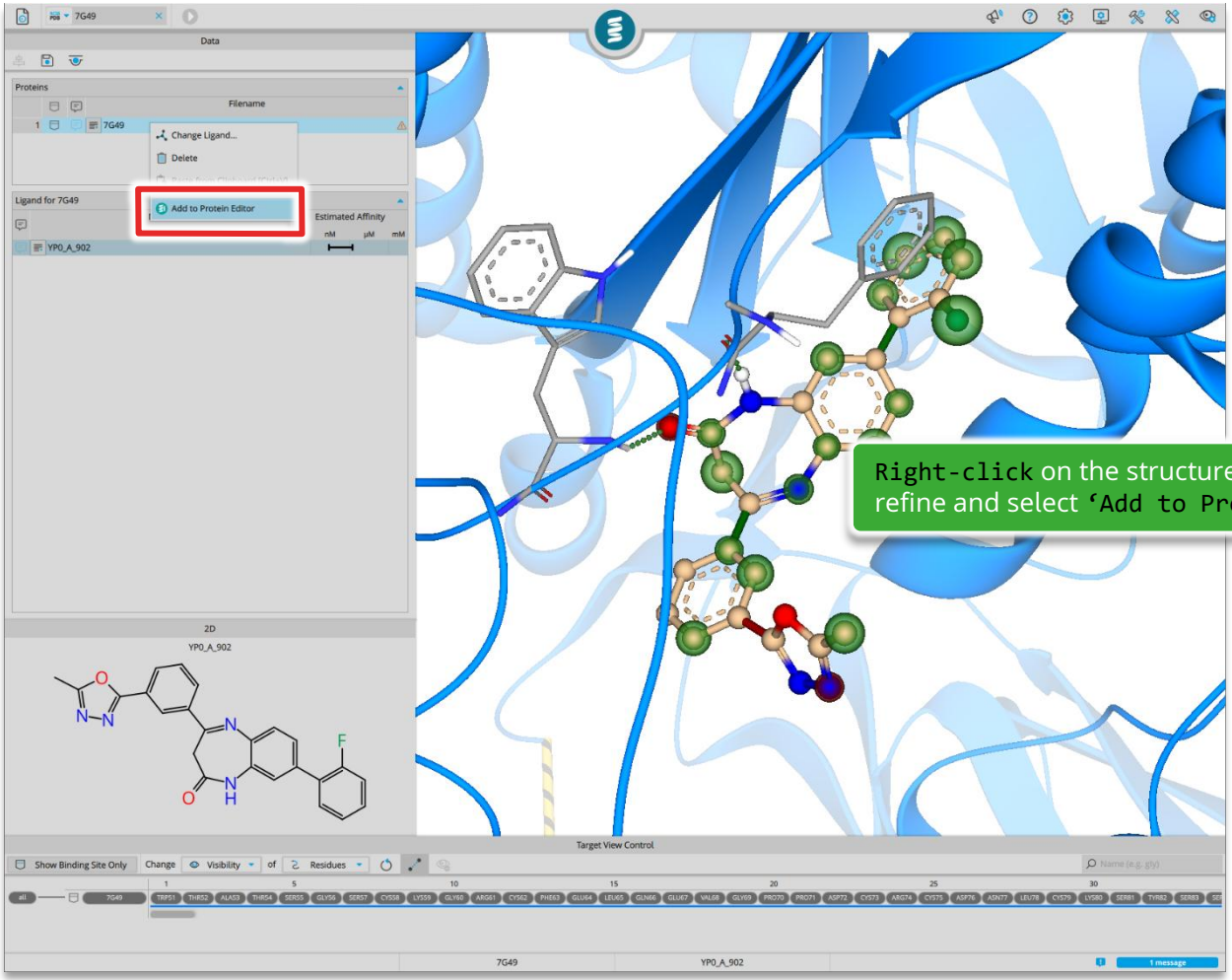
Mode Overview



`Right-click` on the structure you would like to refine and select `'Add to Protein Editor'`.

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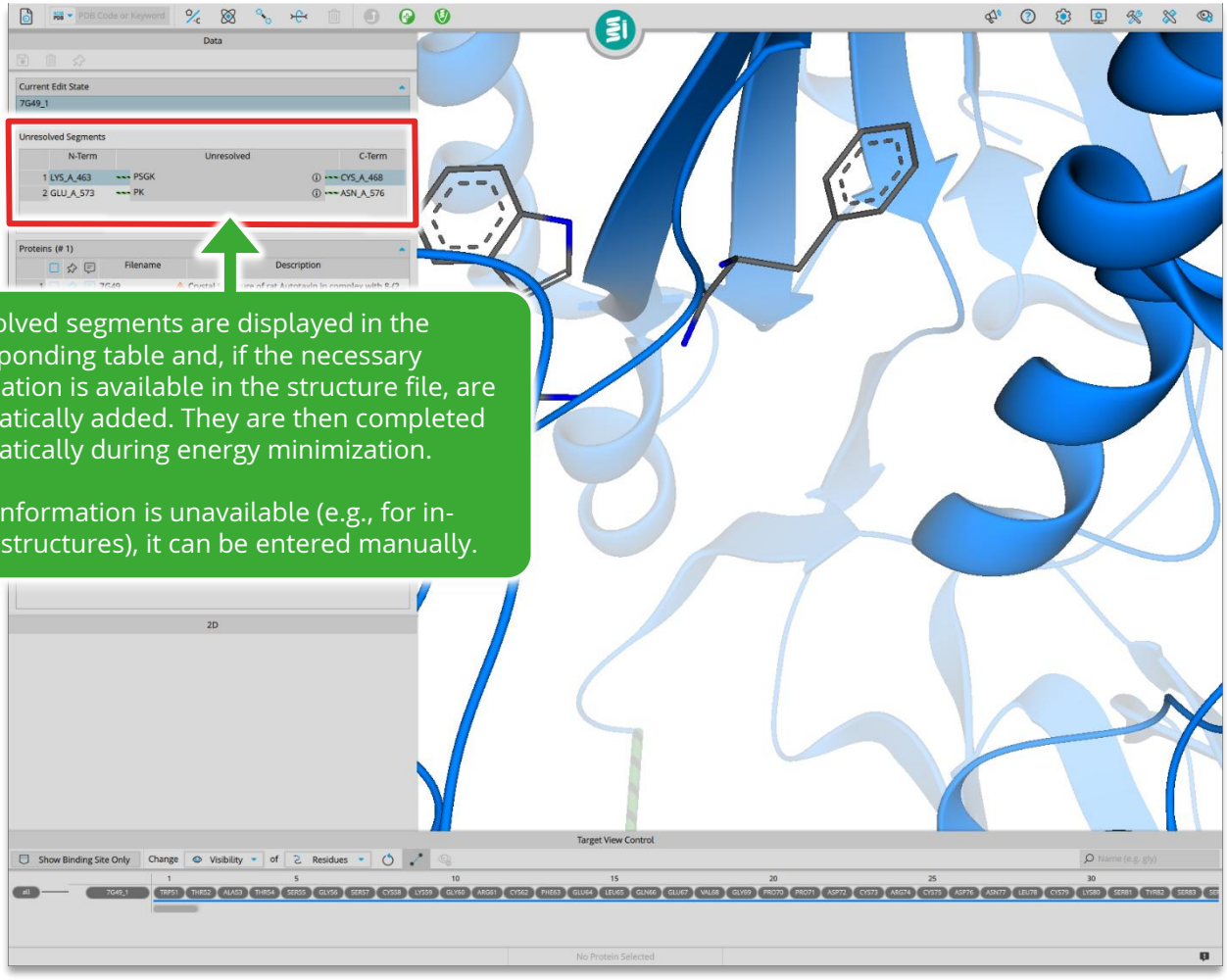
Mode Overview



Unresolved segments are displayed in the corresponding table and, if the necessary information is available in the structure file, are automatically added. They are then completed automatically during energy minimization.

If this information is unavailable (e.g., for in-house structures), it can be entered manually.

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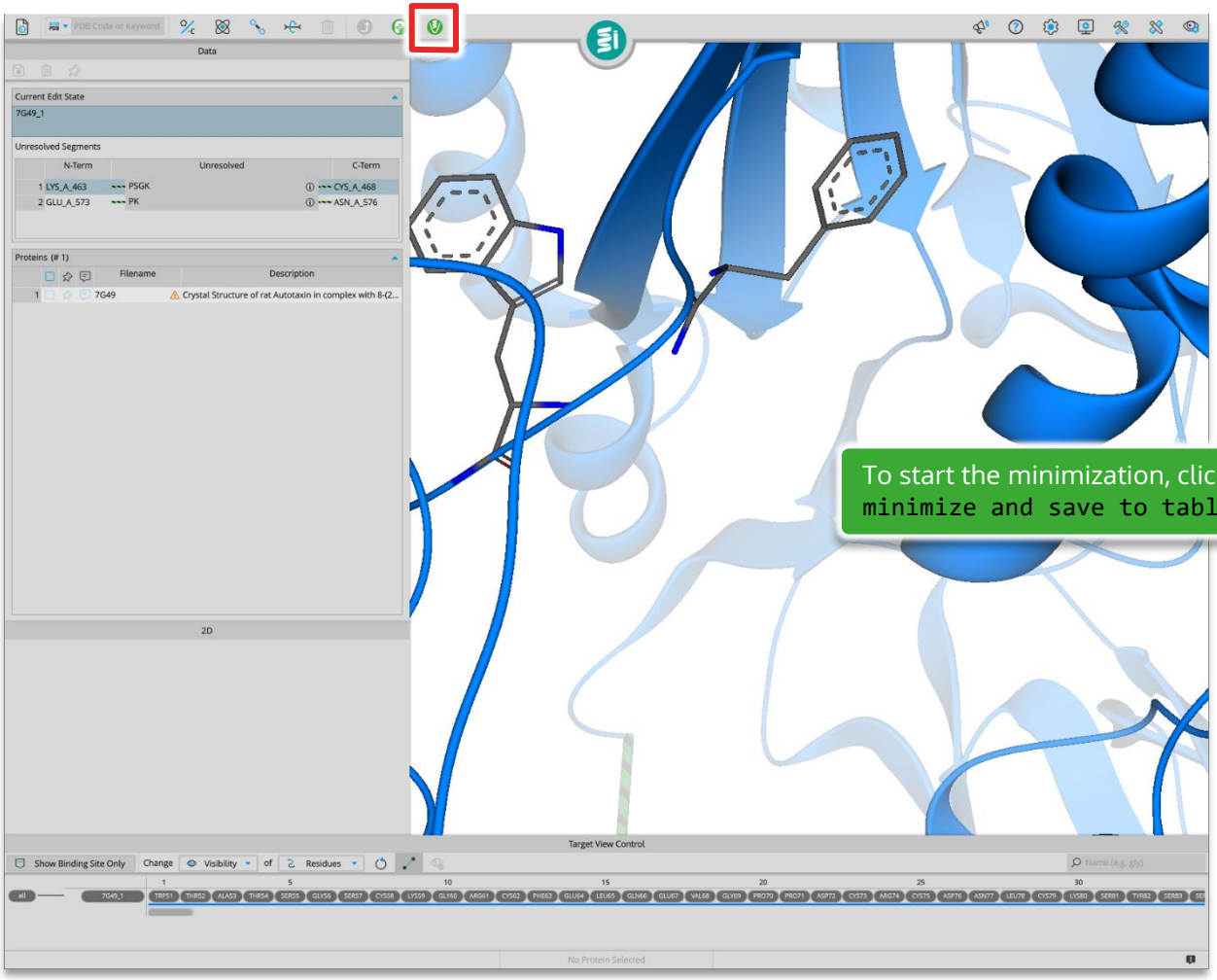
Mode Overview



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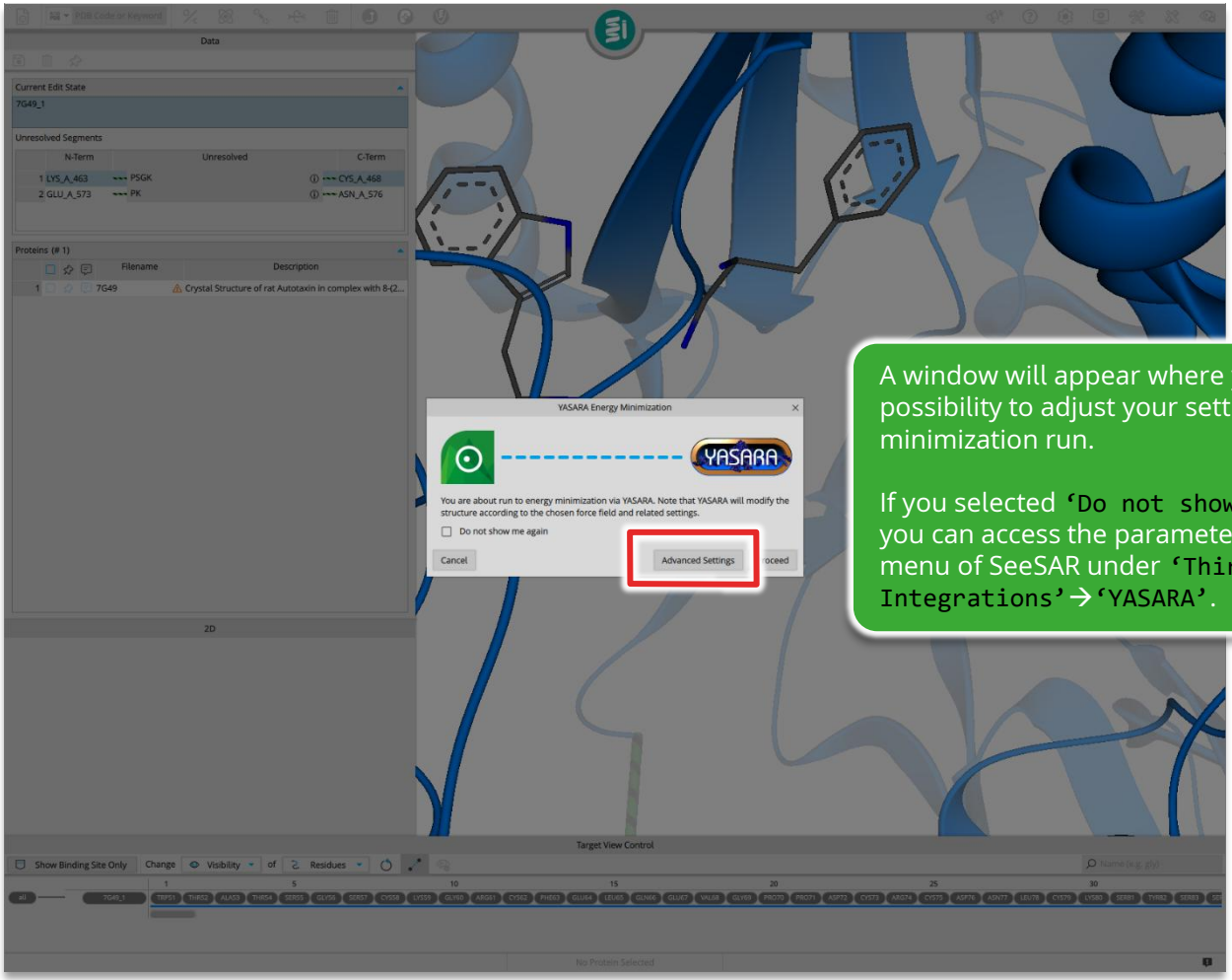
Mode Overview



A window will appear where you will have the possibility to adjust your settings or start the minimization run.

If you selected ‘Do not show me again’, then you can access the parameters in the ‘System’ menu of SeeSAR under ‘Third-Party Integrations’→‘YASARA’.

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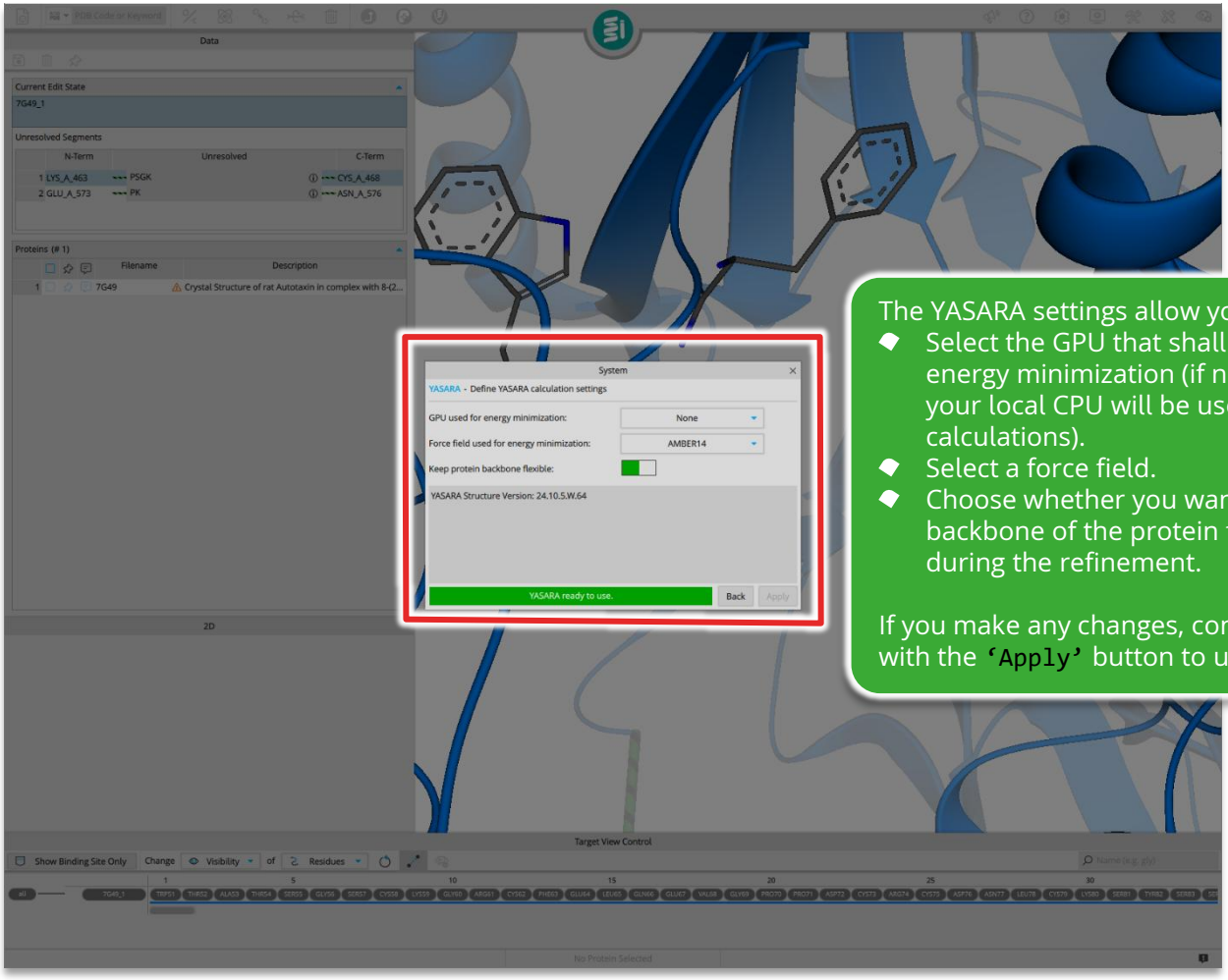
Mode Overview



The YASARA settings allow you to:

- Select the GPU that shall be used for the energy minimization (if no GPU is selected, your local CPU will be used for the calculations).
- Select a force field.
- Choose whether you want to keep the backbone of the protein flexible or rigid during the refinement.

If you make any changes, confirm the settings with the `'Apply'` button to use them.

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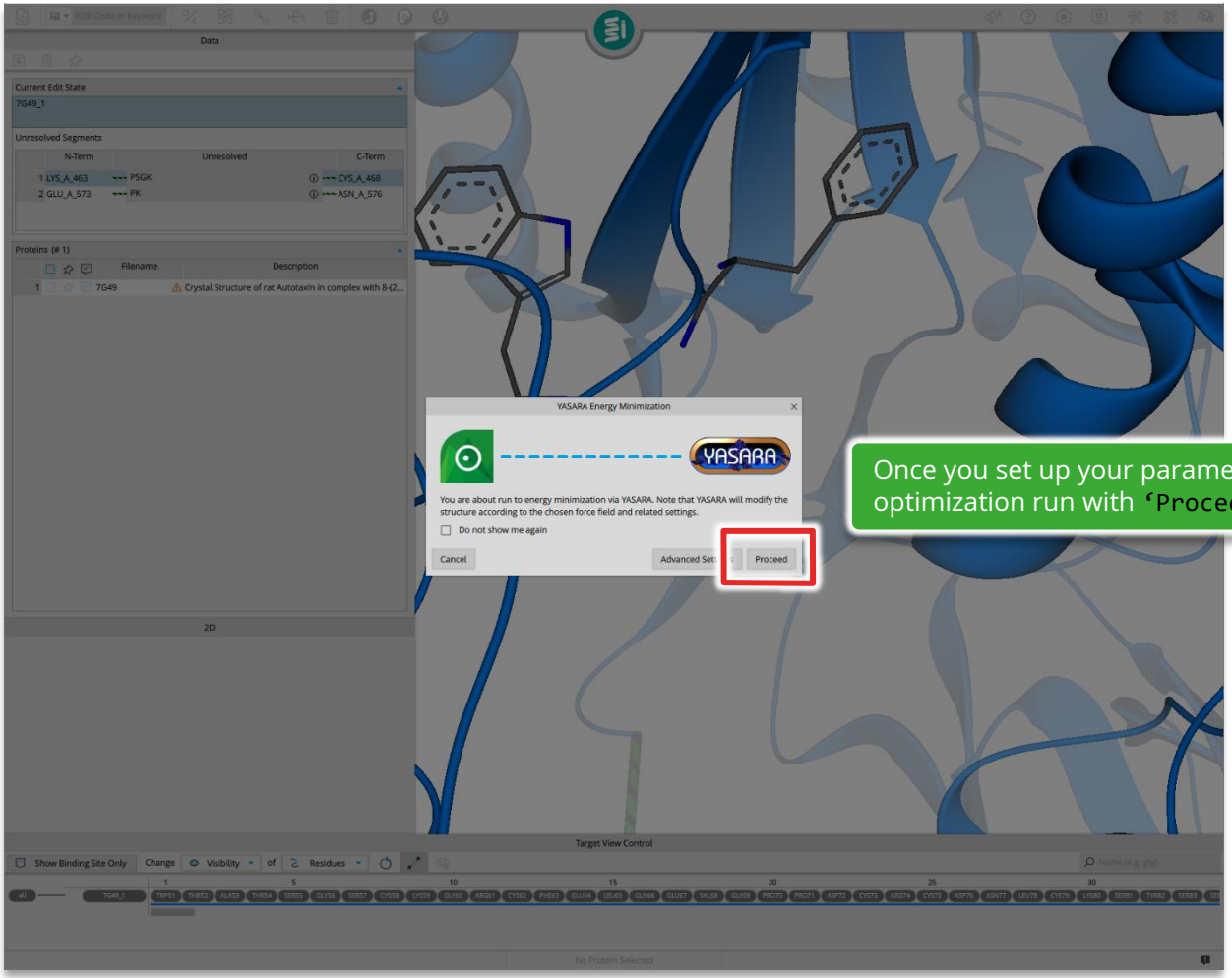
Mode Overview



Once you set up your parameters, start the optimization run with ‘Proceed’.

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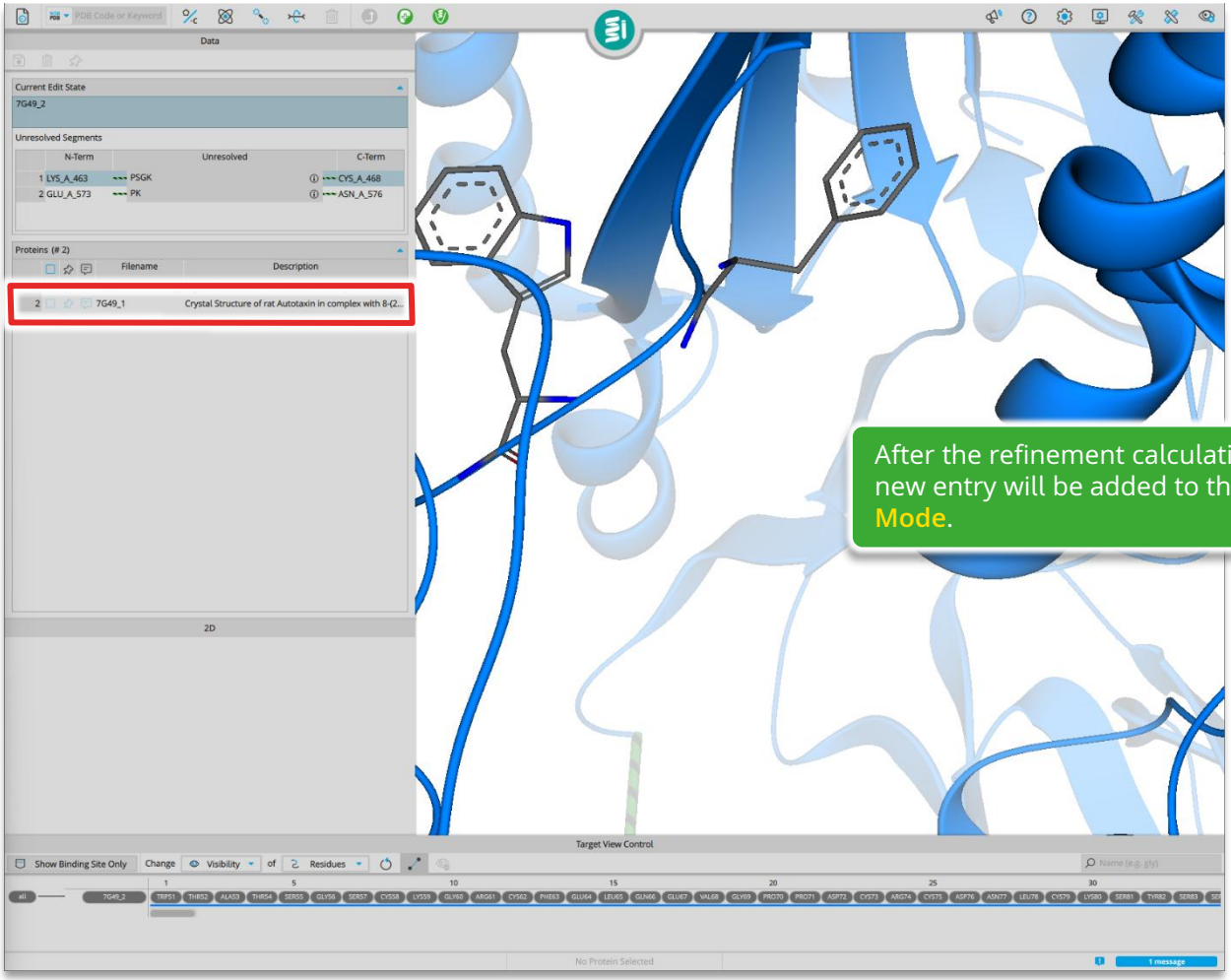
Mode Overview



After the refinement calculation has finished, a new entry will be added to the **Protein Editor Mode**.

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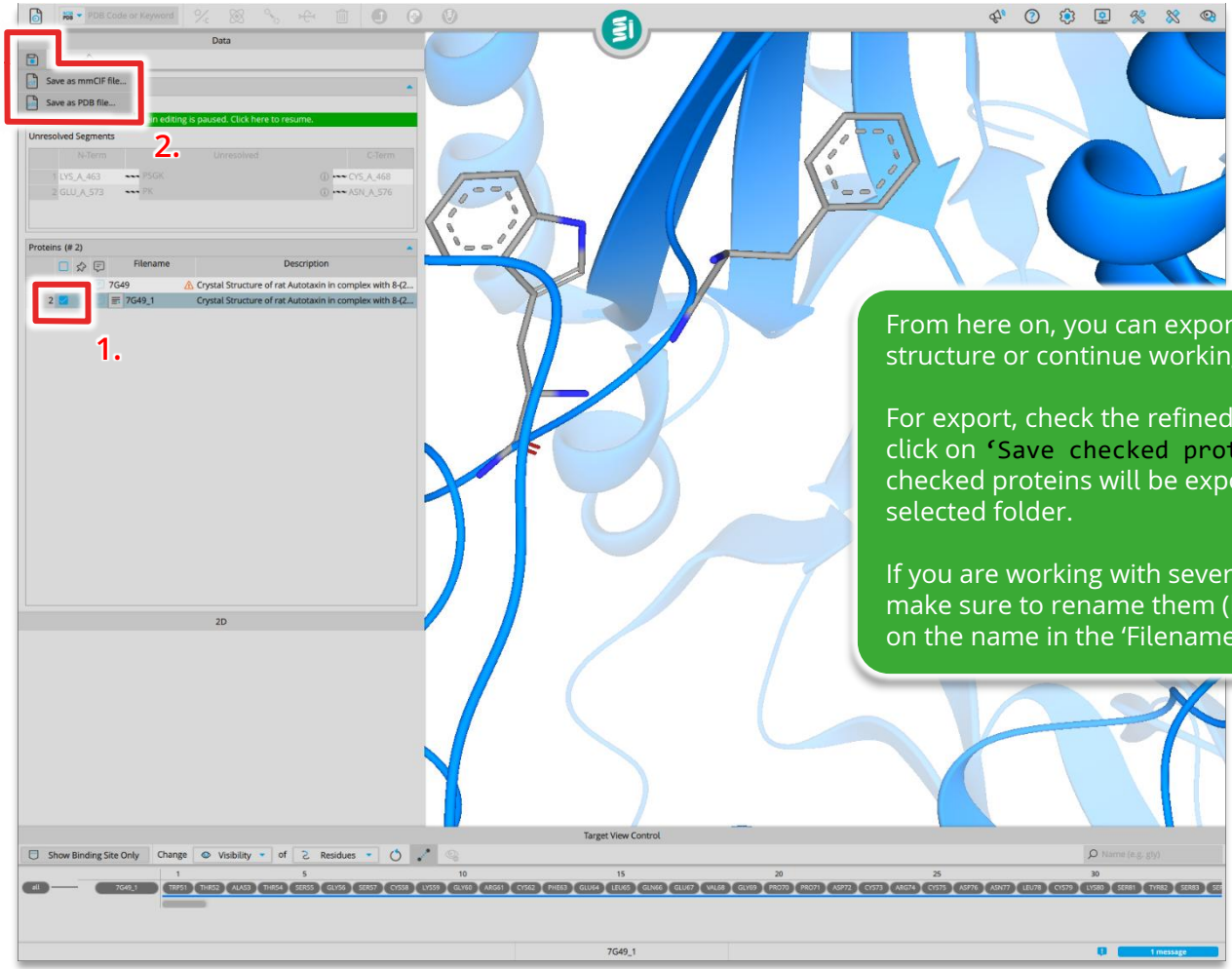
Mode Overview



From here on, you can export the refined structure or continue working with it.

For export, check the refined structure and click on **‘Save checked proteins’**. All checked proteins will be exported to your selected folder.

If you are working with several structures, make sure to rename them (by double clicking on the name in the ‘Filename‘ column).

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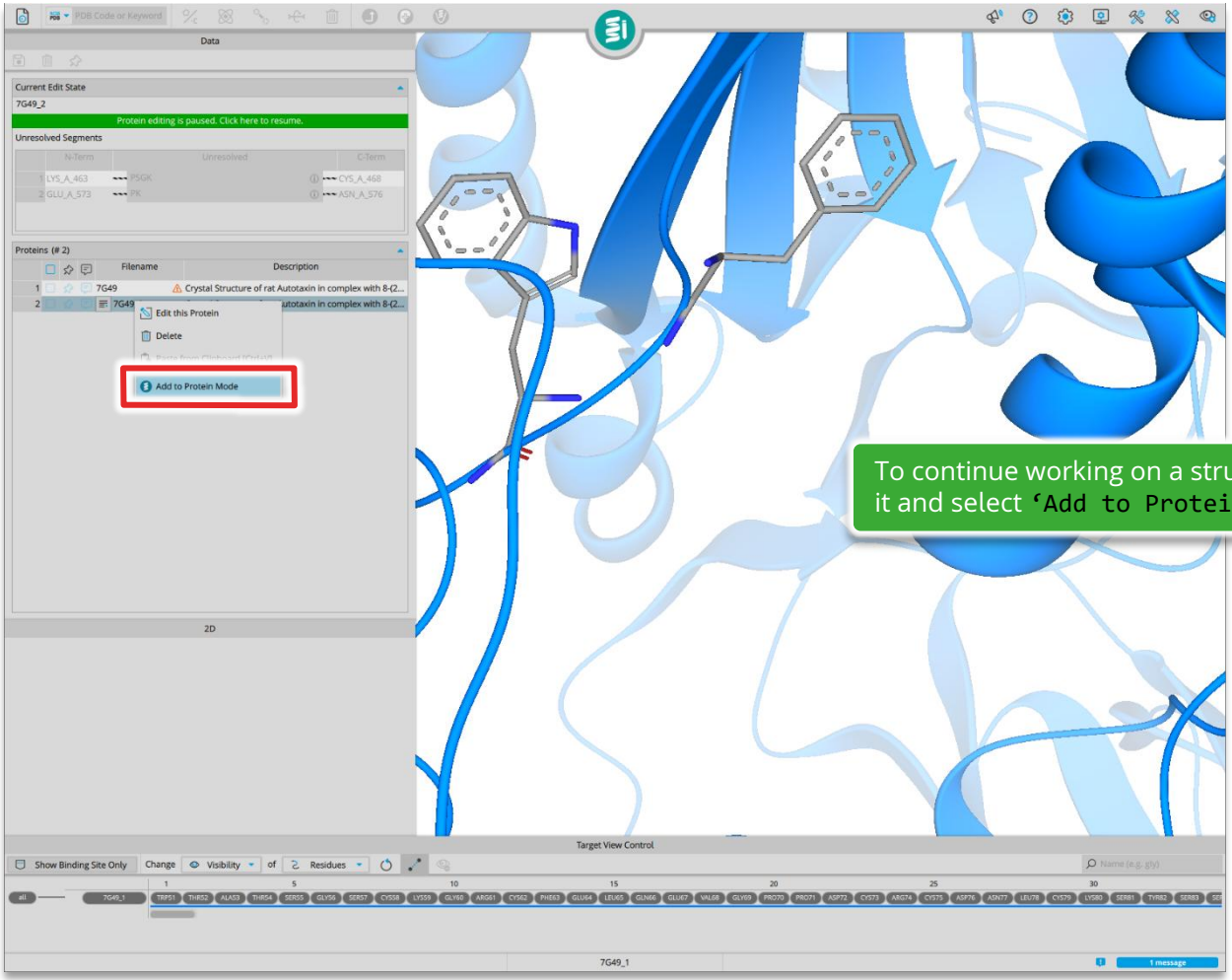
Mode Overview



To continue working on a structure, right click on it and select ‘Add to Protein Mode‘.

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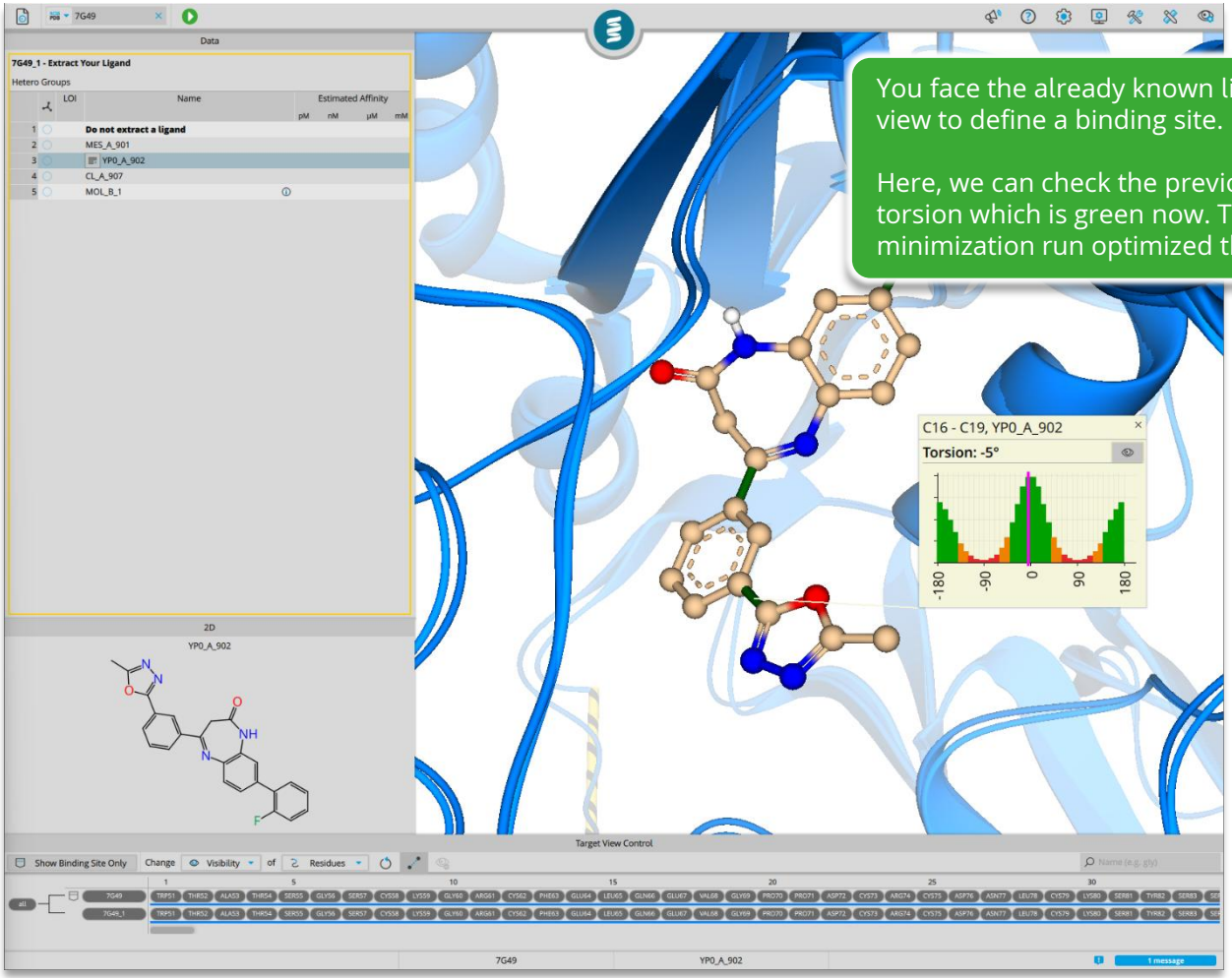
Mode Overview



You face the already known ligand selection view to define a binding site.

Here, we can check the previously red colored torsion which is green now. The energy minimization run optimized the strained torsion.

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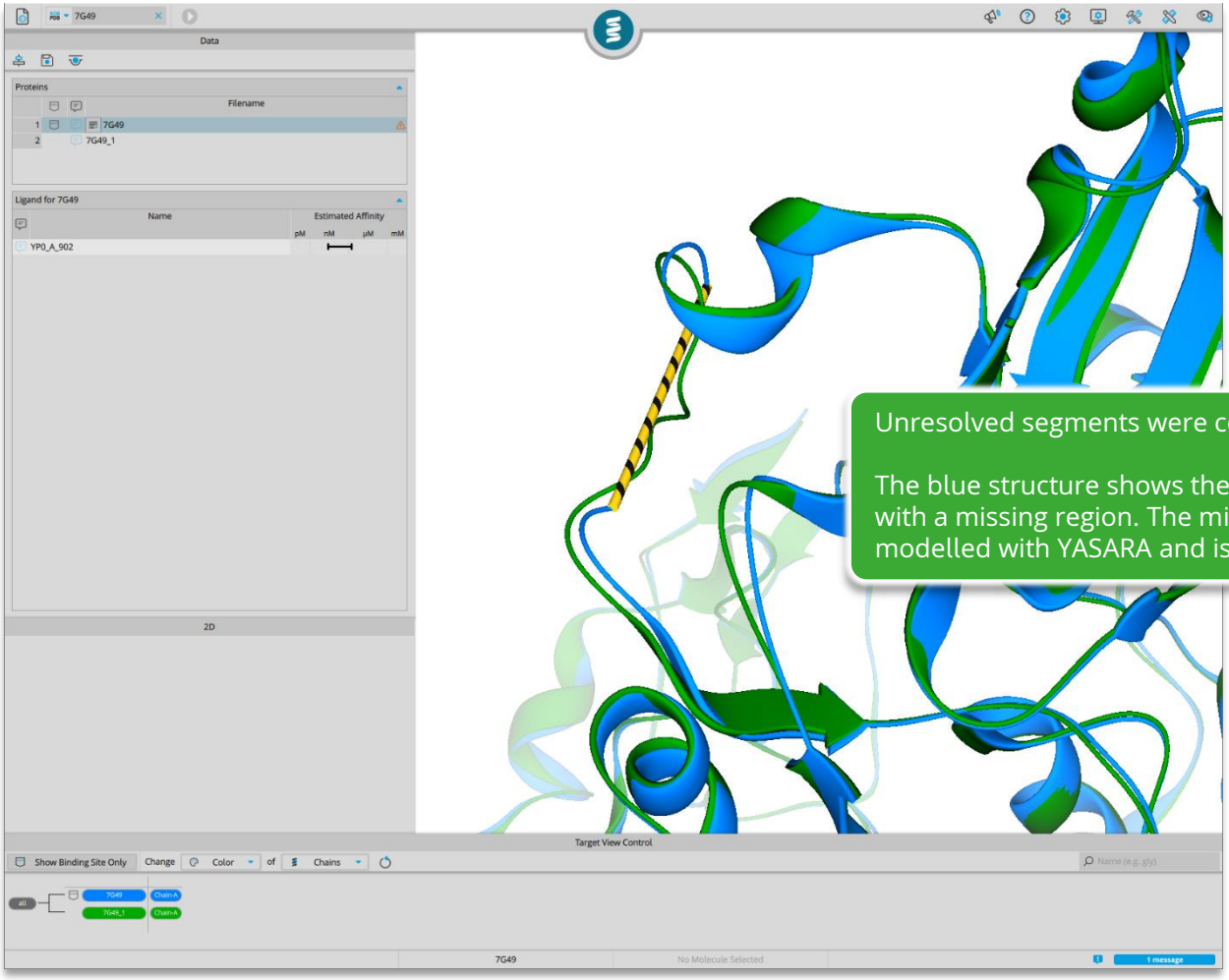
Mode Overview



Unresolved segments were completed.

The blue structure shows the original protein with a missing region. The missing part was modelled with YASARA and is shown in green.

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Mode Overview

Have fun and enjoy your interactive drug discovery journey with SeeSAR!

If you have any problems, please reach out to us:
support@biosolveit.de

Mode Overview