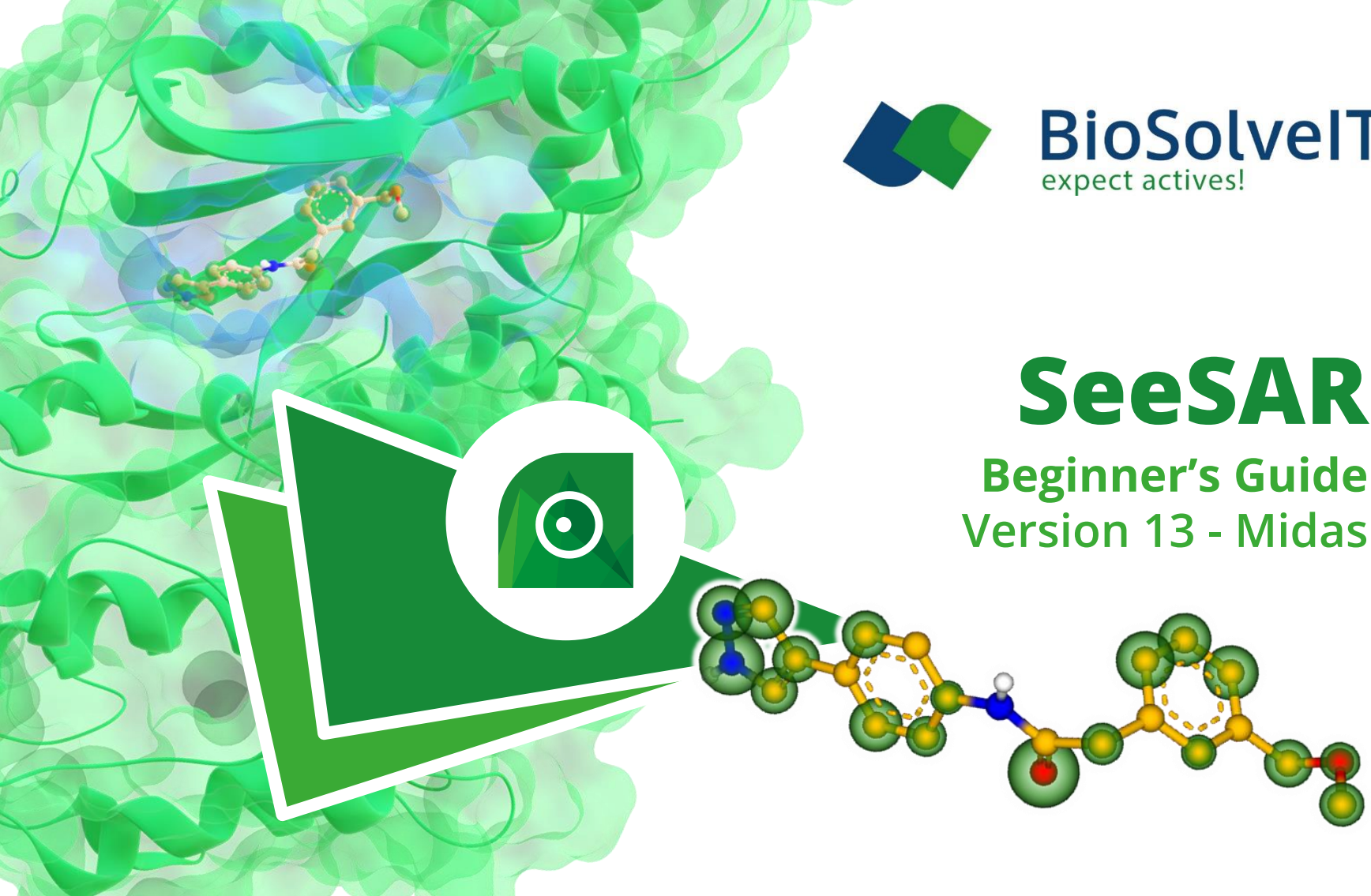


BioSolveIT
expect actives!

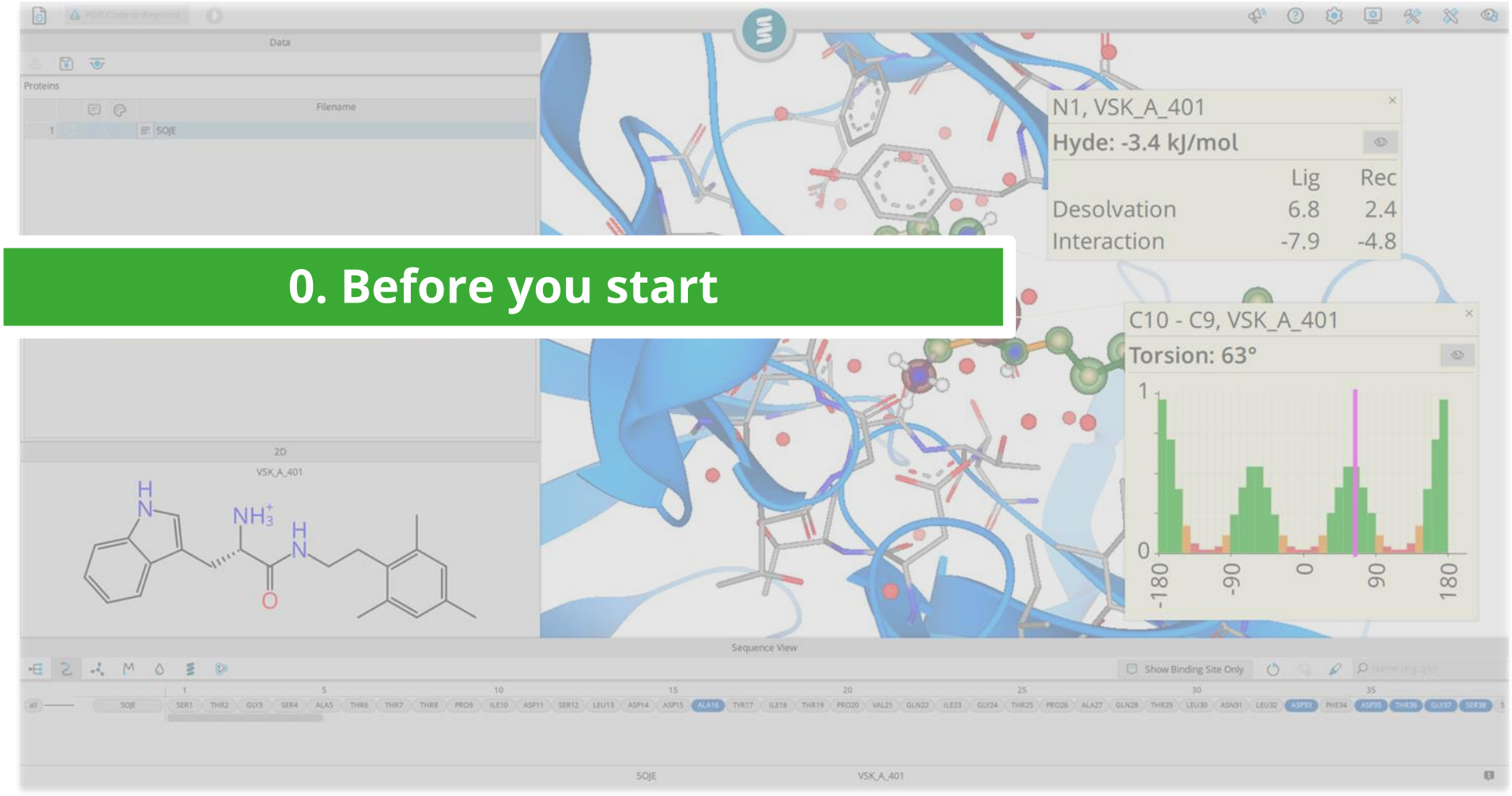
SeeSAR

Beginner's Guide
Version 13 - Midas

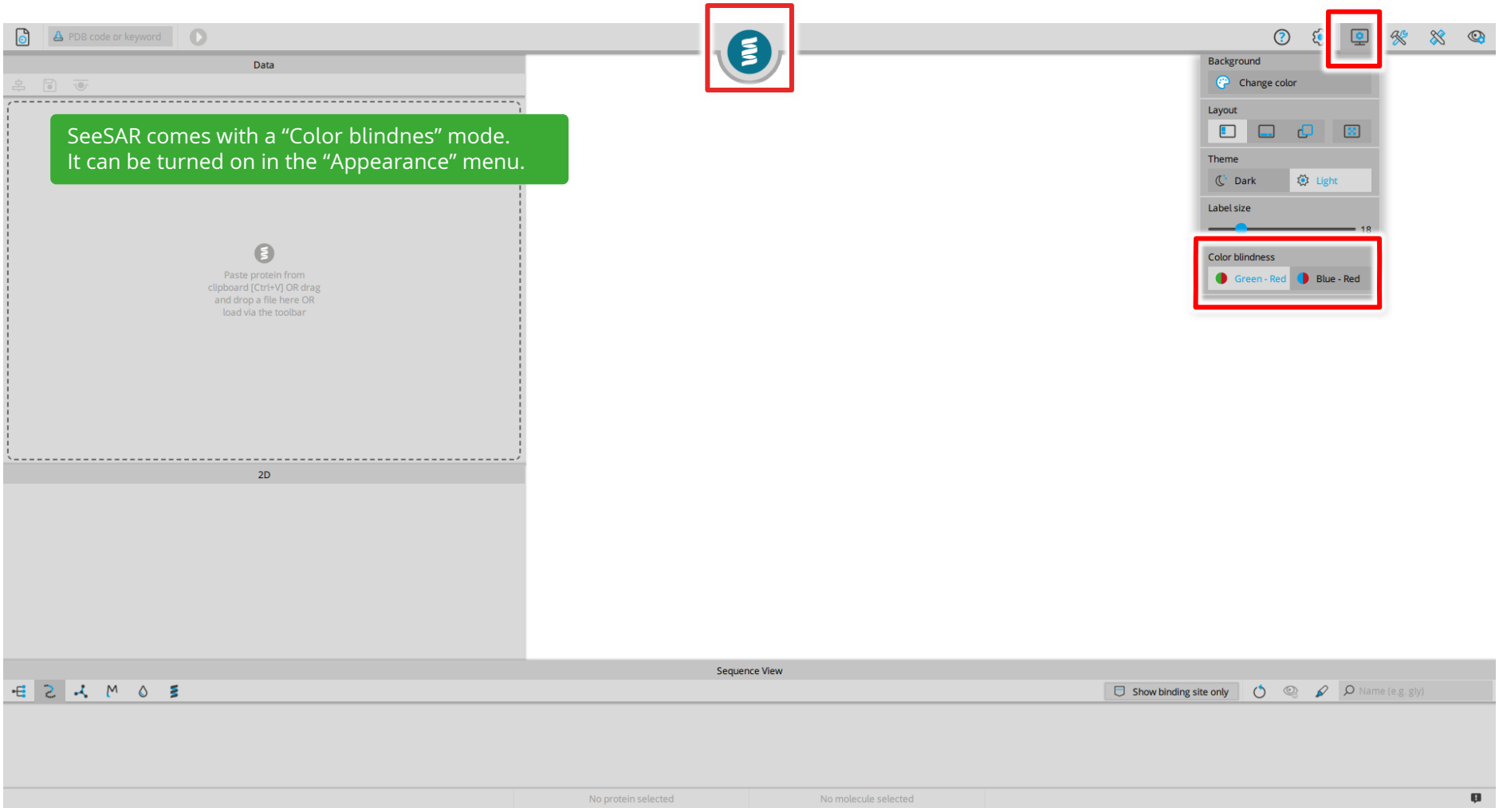
Time to start an interactive dialog with your compound!

Content

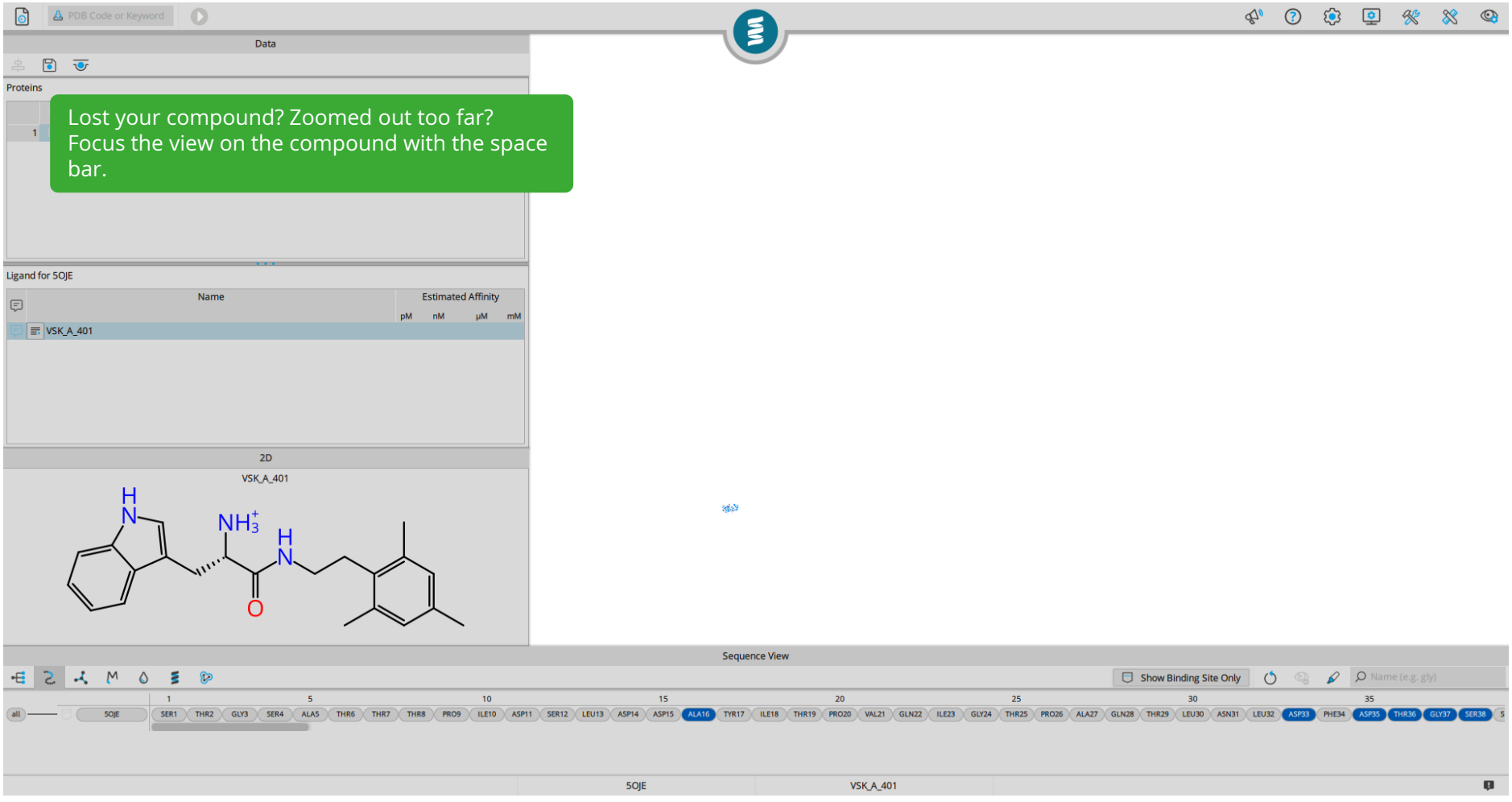
0. Before you start

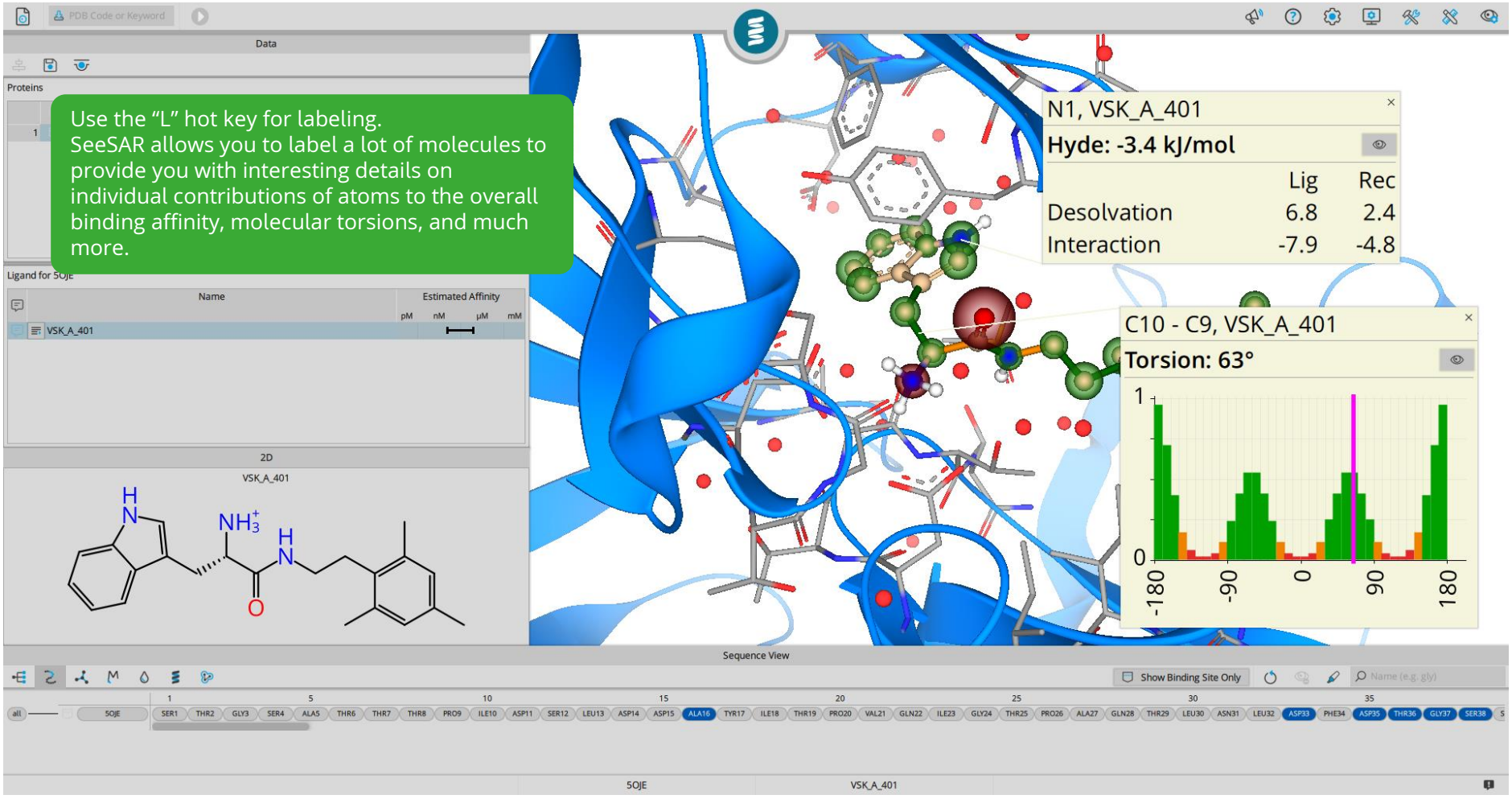


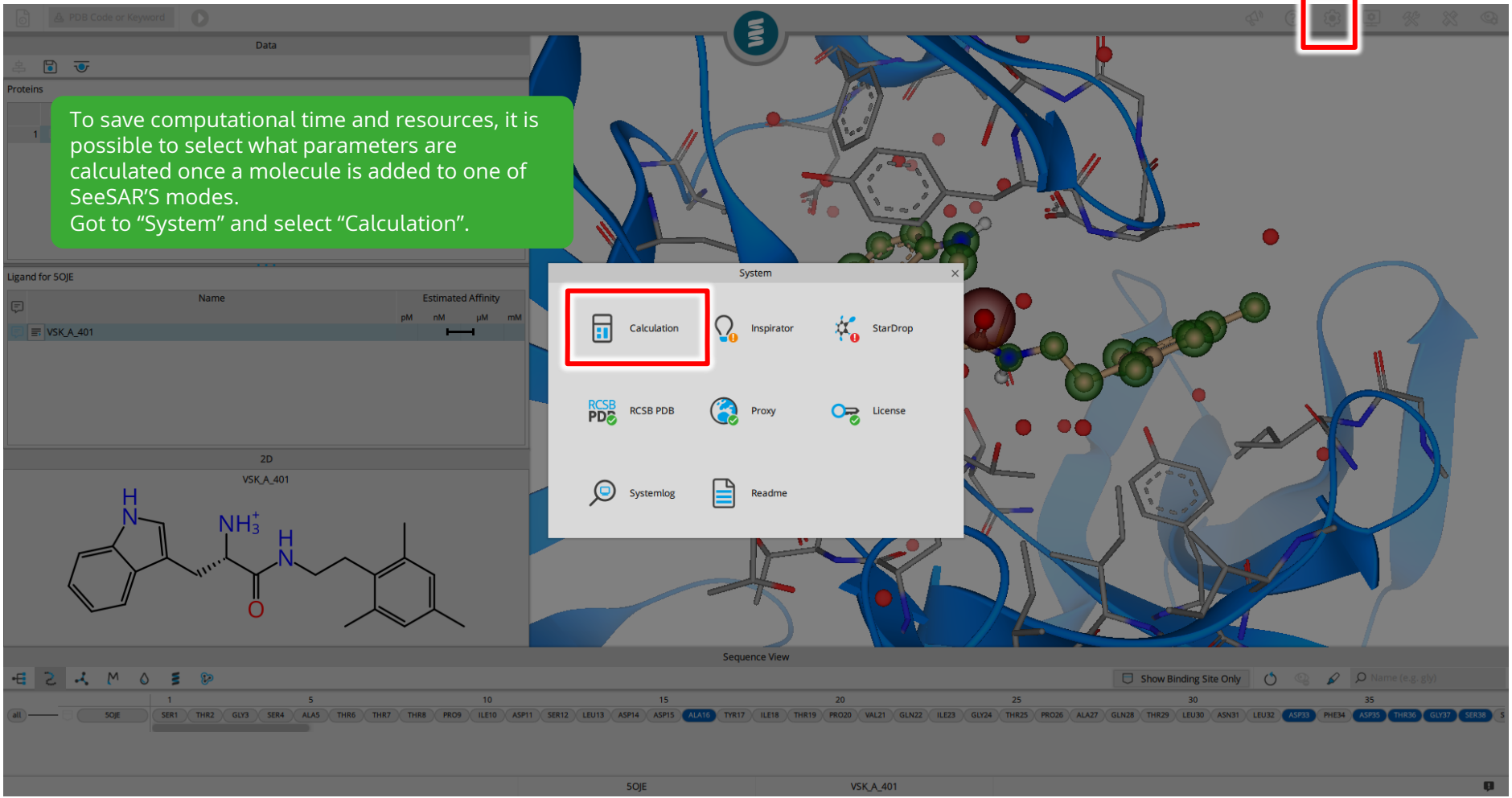

Version 13.0.0 (Midas)
Welcome to
SeeSAR 13.0
fast • visual • easy
Midas
Continue Previous Project
New Project
Start SeeSAR Tour
Continue with your last project.
Start your drug discovery project here.
Find an introduction to SeeSAR's interface.

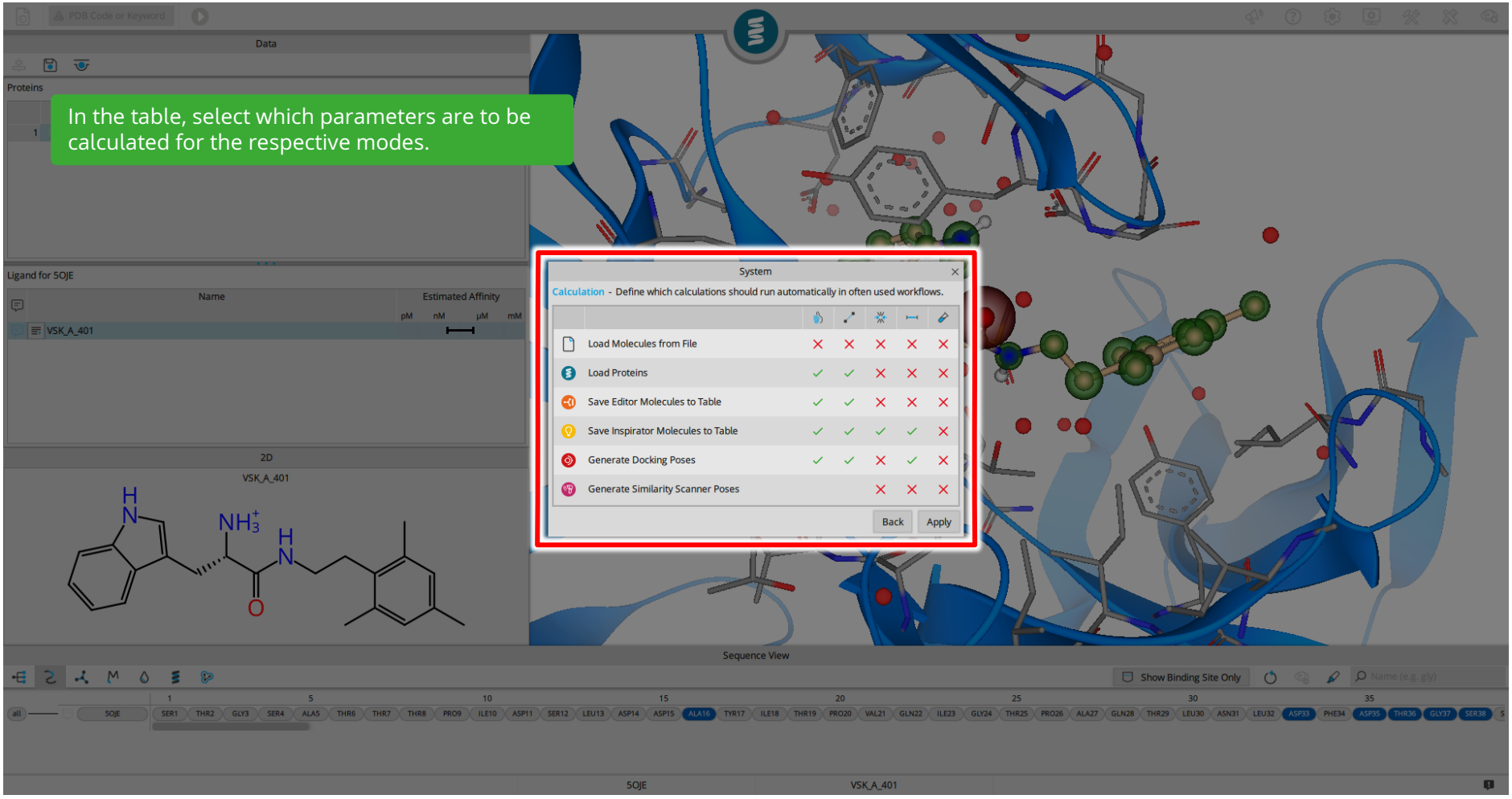

SeeSAR comes with a “Color blindnes” mode.
It can be turned on in the “Appearance” menu.
PDB code or keyword
Data
Paste protein from clipboard [Ctrl+V] OR drag and drop a file here OR load via the toolbar
2D
Background
Change color
Layout
Theme
Dark
Light
Label size
18
Color blindness
Green - Red
Blue - Red
Sequence View
Show binding site only
Name (e.g. gly)
No protein selected
No molecule selected

Lost your compound? Zoomed out too far? Focus the view on the compound with the space bar.

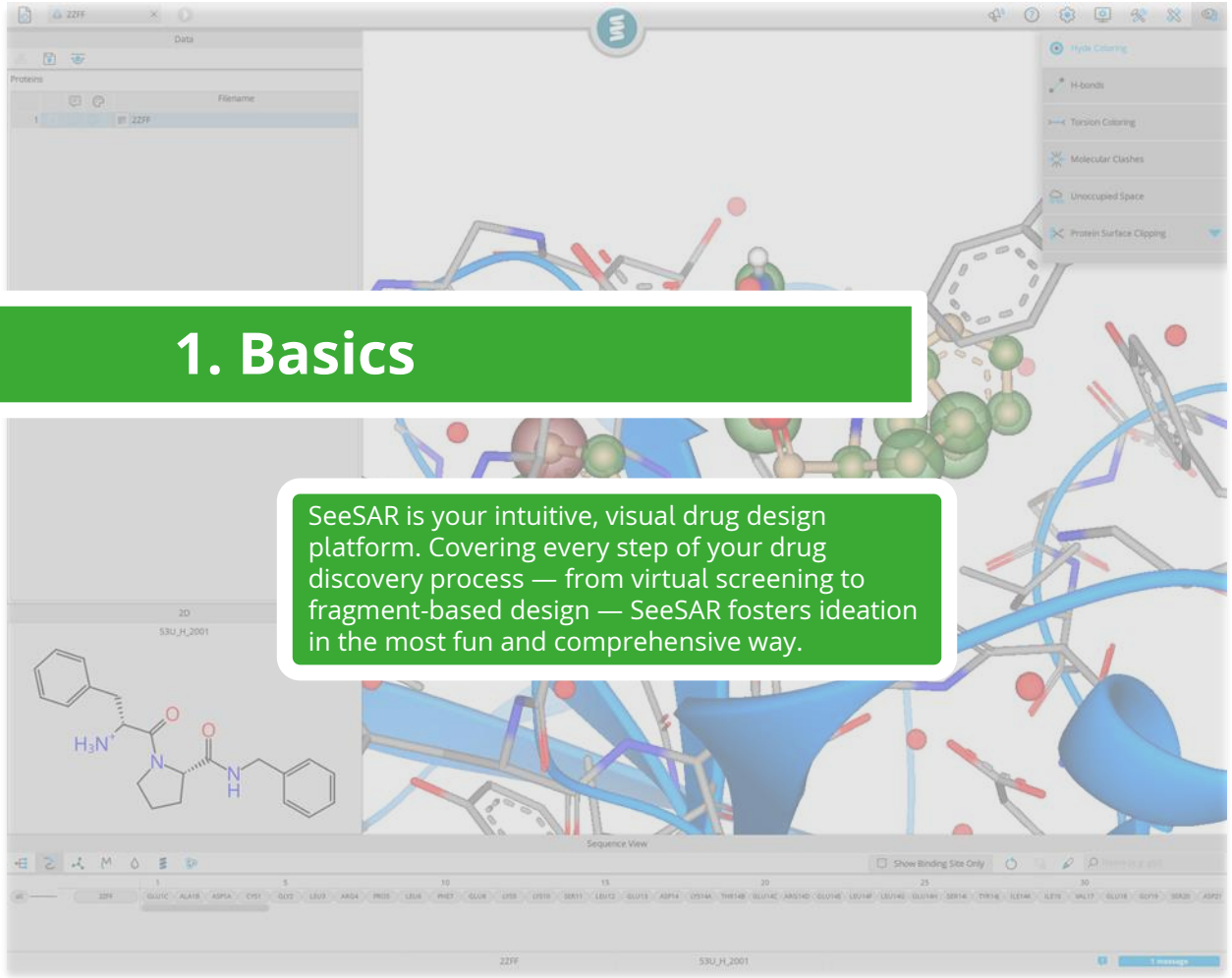



Use the “L” hot key for labeling.
SeeSAR allows you to label a lot of molecules to provide you with interesting details on individual contributions of atoms to the overall binding affinity, molecular torsions, and much more.
Data
Proteins
Ligand for 5OJE
Name
Estimated Affinity
VSK_A_401
2D
VSK_A_401
N1, VSK_A_401
Hyde: -3.4 kJ/mol
Lig
Rec
Desolvation
6.8
2.4
Interaction
-7.9
-4.8
C10 - C9, VSK_A_401
Torsion: 63°
1
0
-180
-90
0
90
180
Sequence View
Show Binding Site Only
5OJE
VSK_A_401

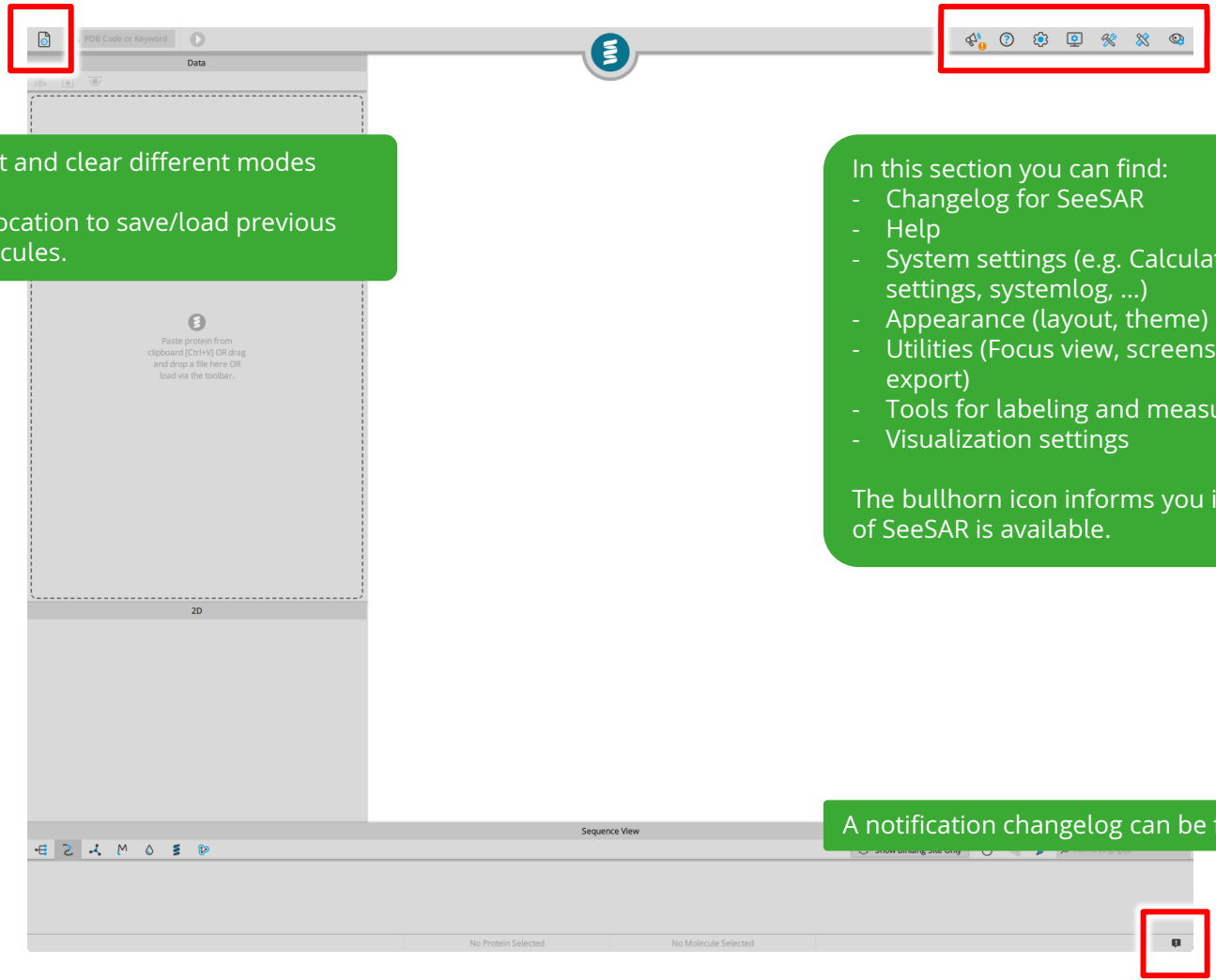

To save computational time and resources, it is possible to select what parameters are calculated once a molecule is added to one of SeeSAR'S modes.
Got to "System" and select "Calculation".
Data
Proteins
Ligand for 5OJE
Name
Estimated Affinity
VSK_A_401
2D
VSK_A_401
System
Calculation
Inspirator
StarDrop
RCSB PDB
Proxy
License
Systemlog
Readme
Sequence View
Show Binding Site Only
5OJE
VSK_A_401


In the table, select which parameters are to be calculated for the respective modes.
Data
Proteins
Ligand for 5OJE
Name
Estimated Affinity
VSK_A_401
2D
VSK_A_401
System
Calculation - Define which calculations should run automatically in often used workflows.
Load Molecules from File
Load Proteins
Save Editor Molecules to Table
Save Inspirator Molecules to Table
Generate Docking Poses
Generate Similarity Scanner Poses
Back
Apply
Sequence View
Show Binding Site Only
5OJE
VSK_A_401

1. Basics



SeeSAR is your intuitive, visual drug design platform. Covering every step of your drug discovery process — from virtual screening to fragment-based design — SeeSAR fosters ideation in the most fun and comprehensive way.

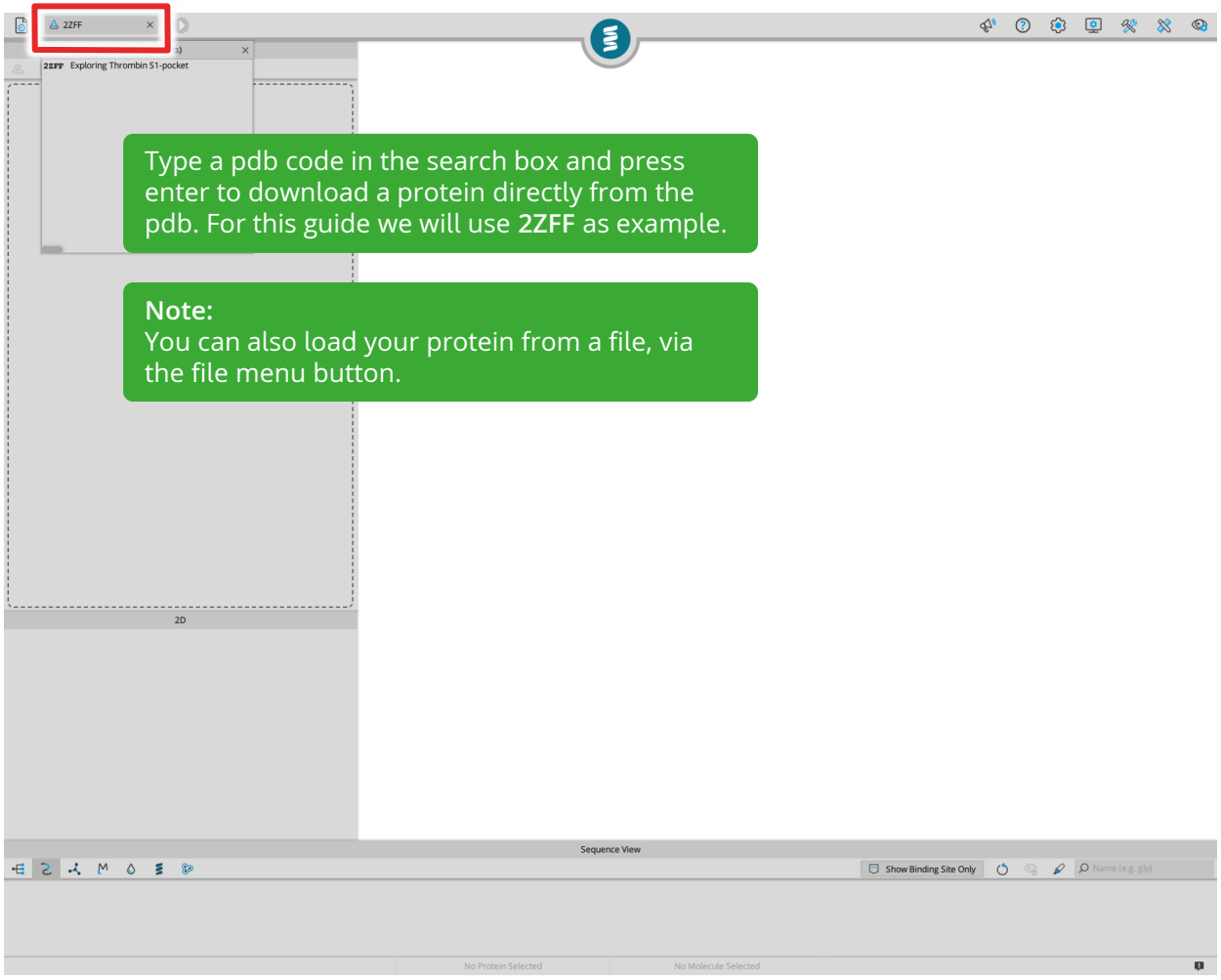


Start new project and clear different modes here.
This is also the location to save/load previous projects or molecules.

In this section you can find:
- Changelog for SeeSAR
- Help
- System settings (e.g. Calculations, licence settings, systemlog, ...)
- Appearance (layout, theme)
- Utilities (Focus view, screenshots, 3D scene export)
- Tools for labeling and measurement
- Visualization settings

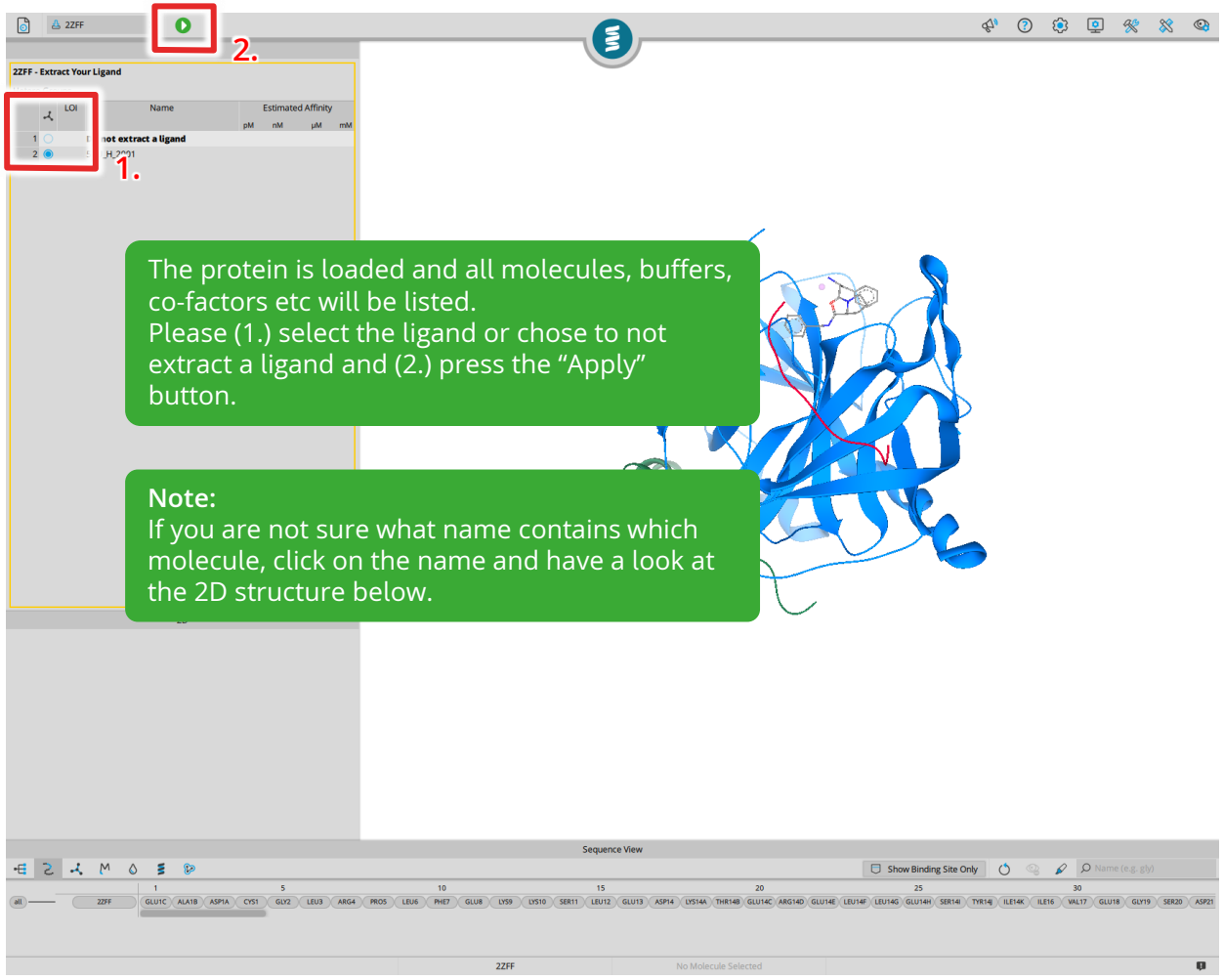
The bullhorn icon informs you if a new version of SeeSAR is available.

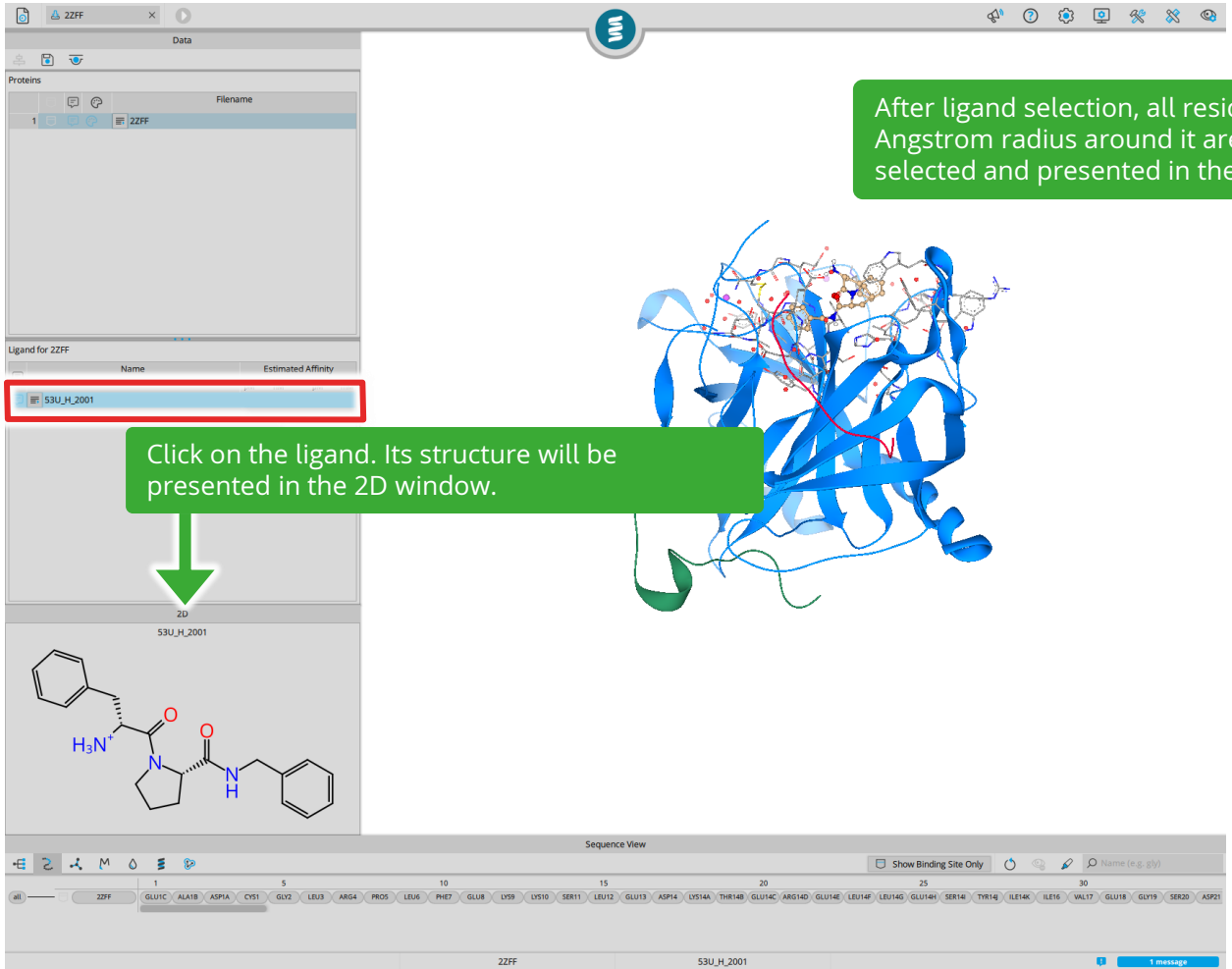
A notification changelog can be found here.



Type a pdb code in the search box and press enter to download a protein directly from the pdb. For this guide we will use **2ZFF** as example.

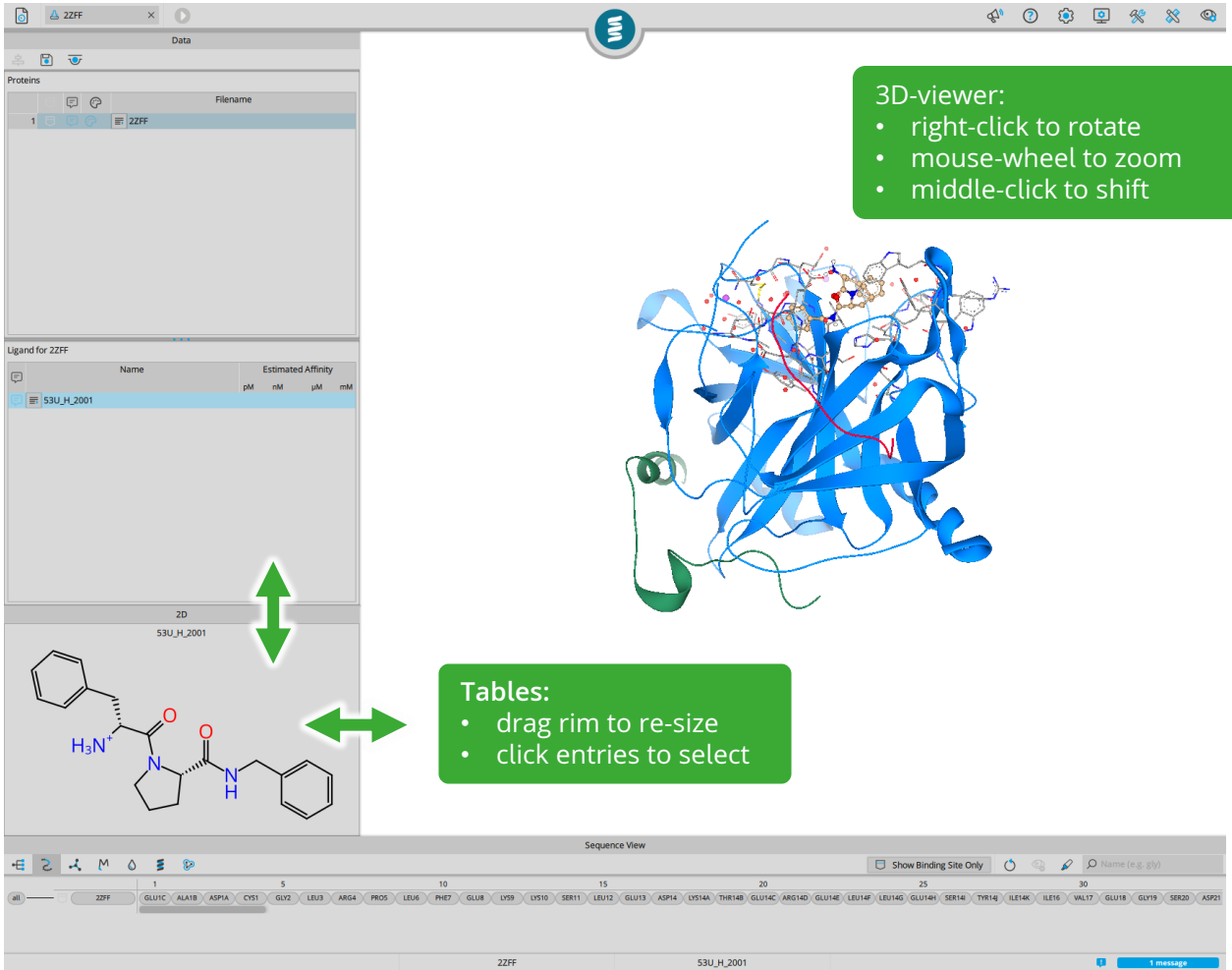
Note:
You can also load your protein from a file, via the file menu button.


2ZFF
2.
2ZFF - Extract Your Ligand
LOI
Name
Estimated Affinity
pM nM µM mM
1.
The protein is loaded and all molecules, buffers, co-factors etc will be listed.
Please (1.) select the ligand or chose to not extract a ligand and (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.
Sequence View
Show Binding Site Only
2ZFF
No Molecule Selected



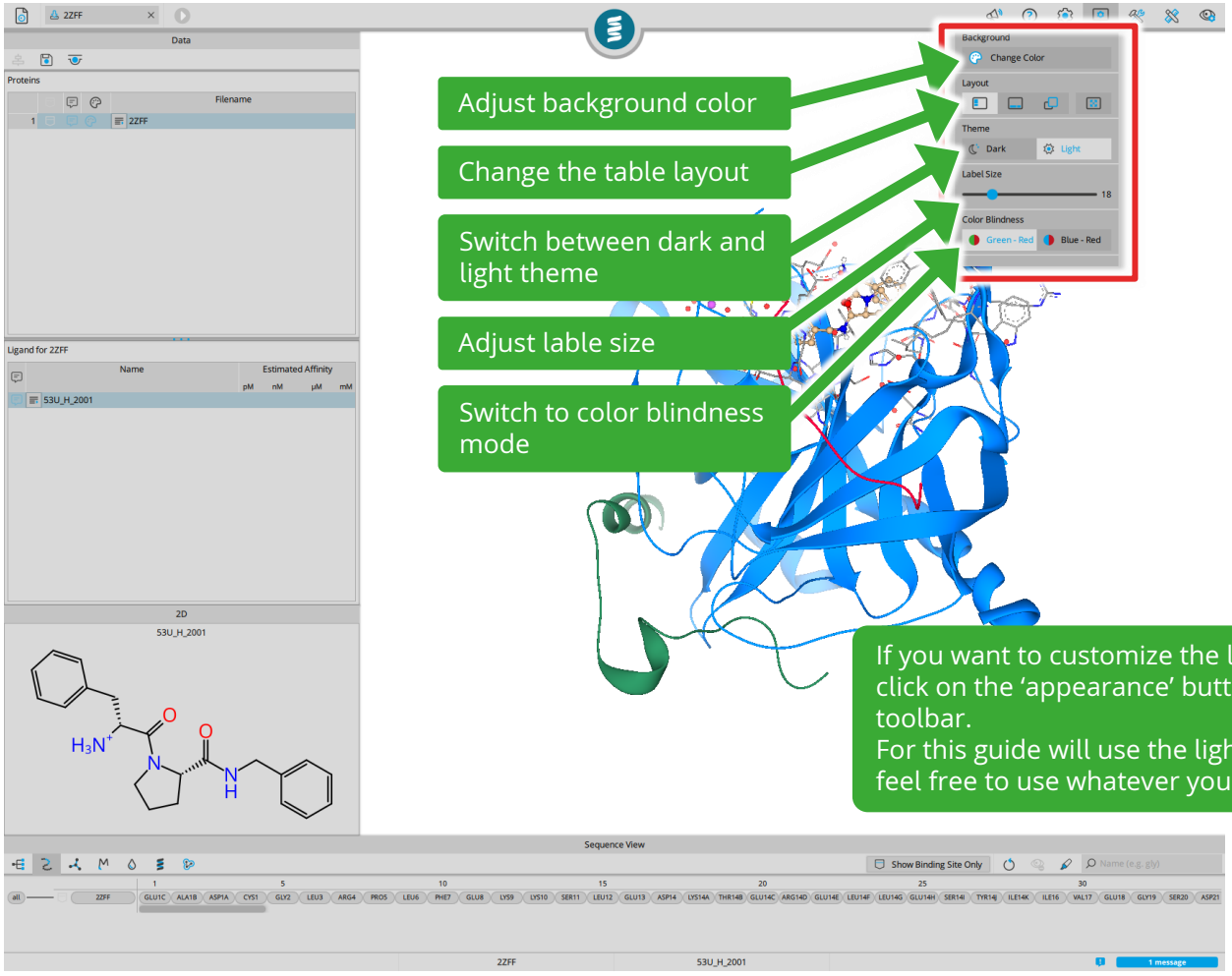
After ligand selection, all residues within a 6.5 Angstrom radius around it are automatically selected and presented in the model.

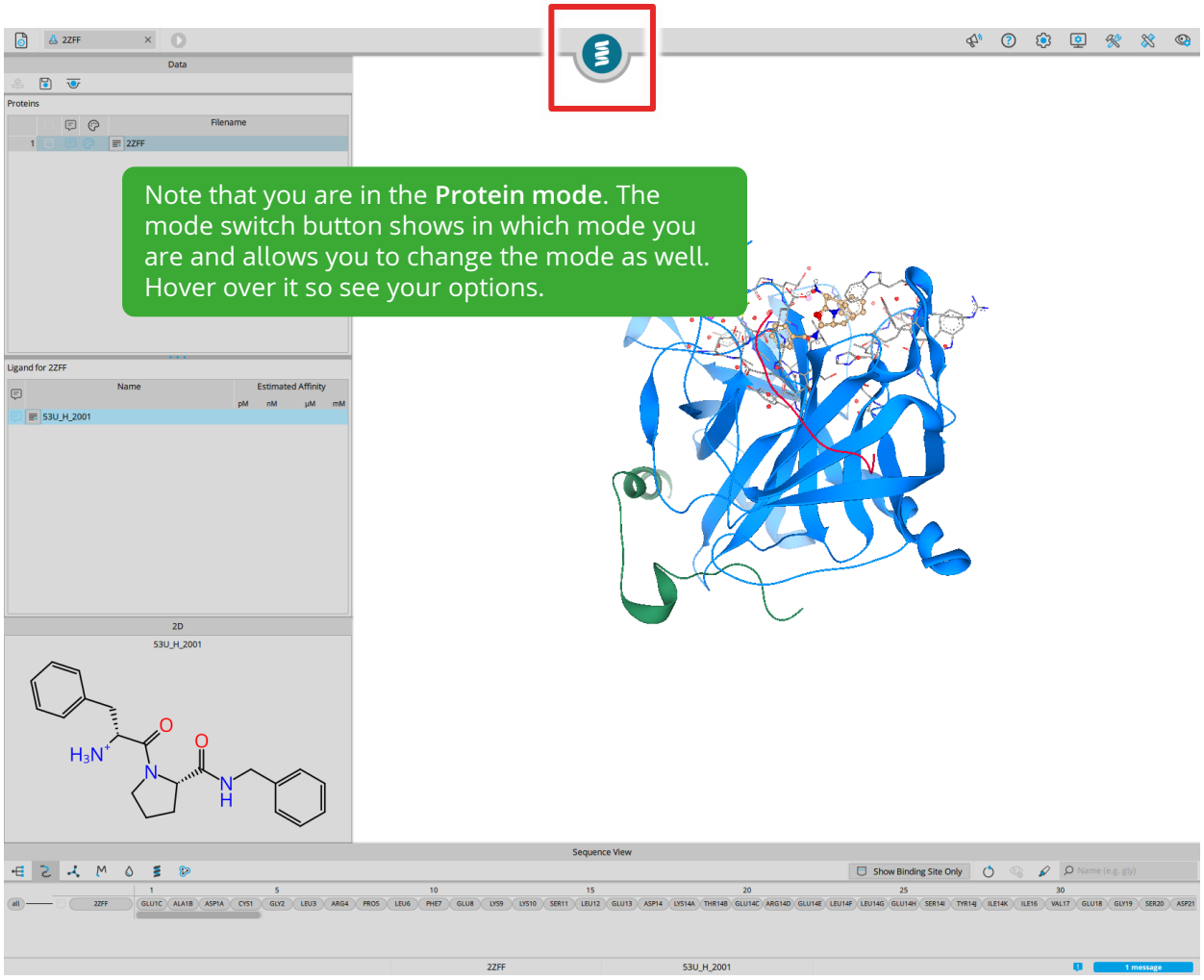
Click on the ligand. Its structure will be presented in the 2D window.

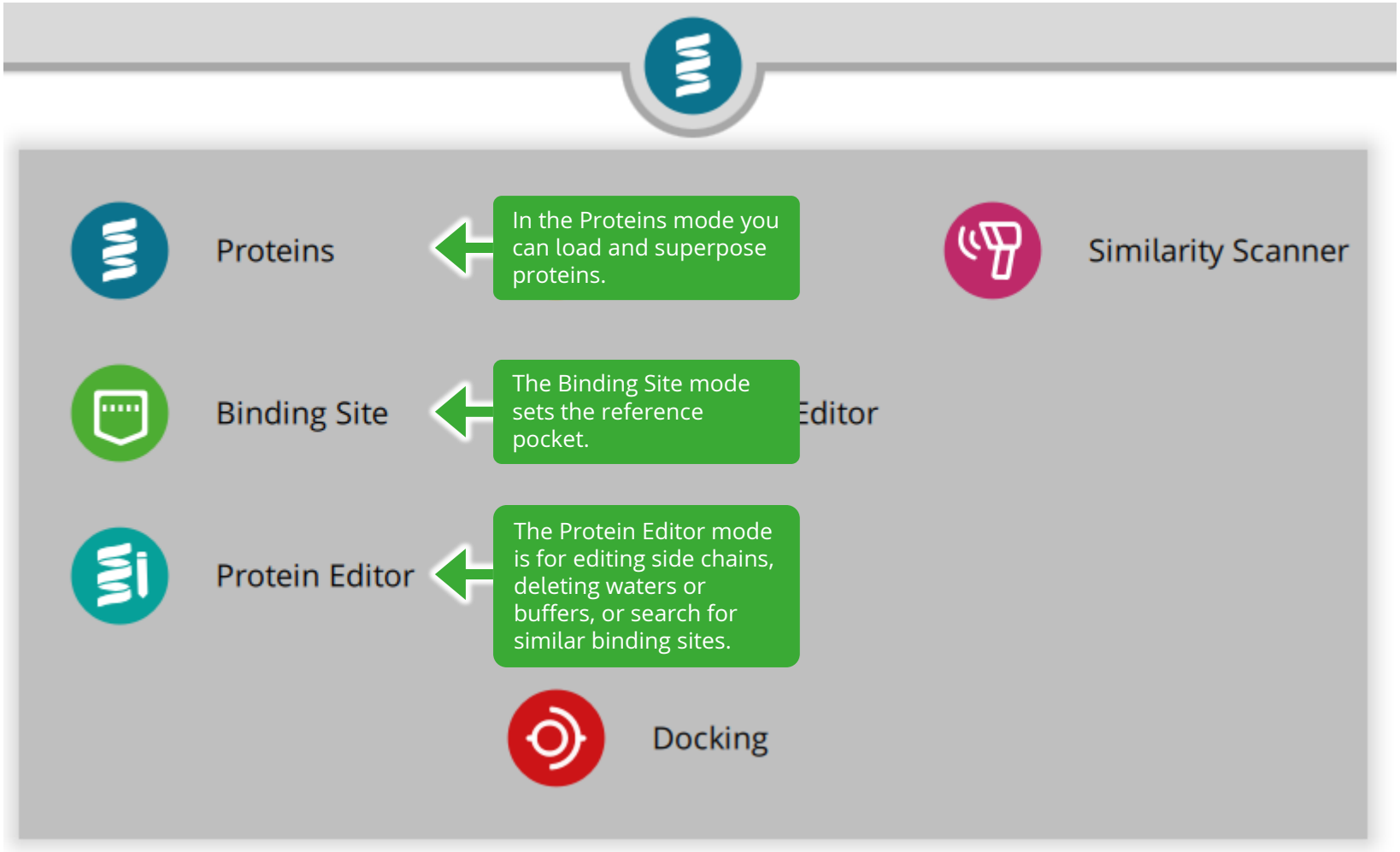


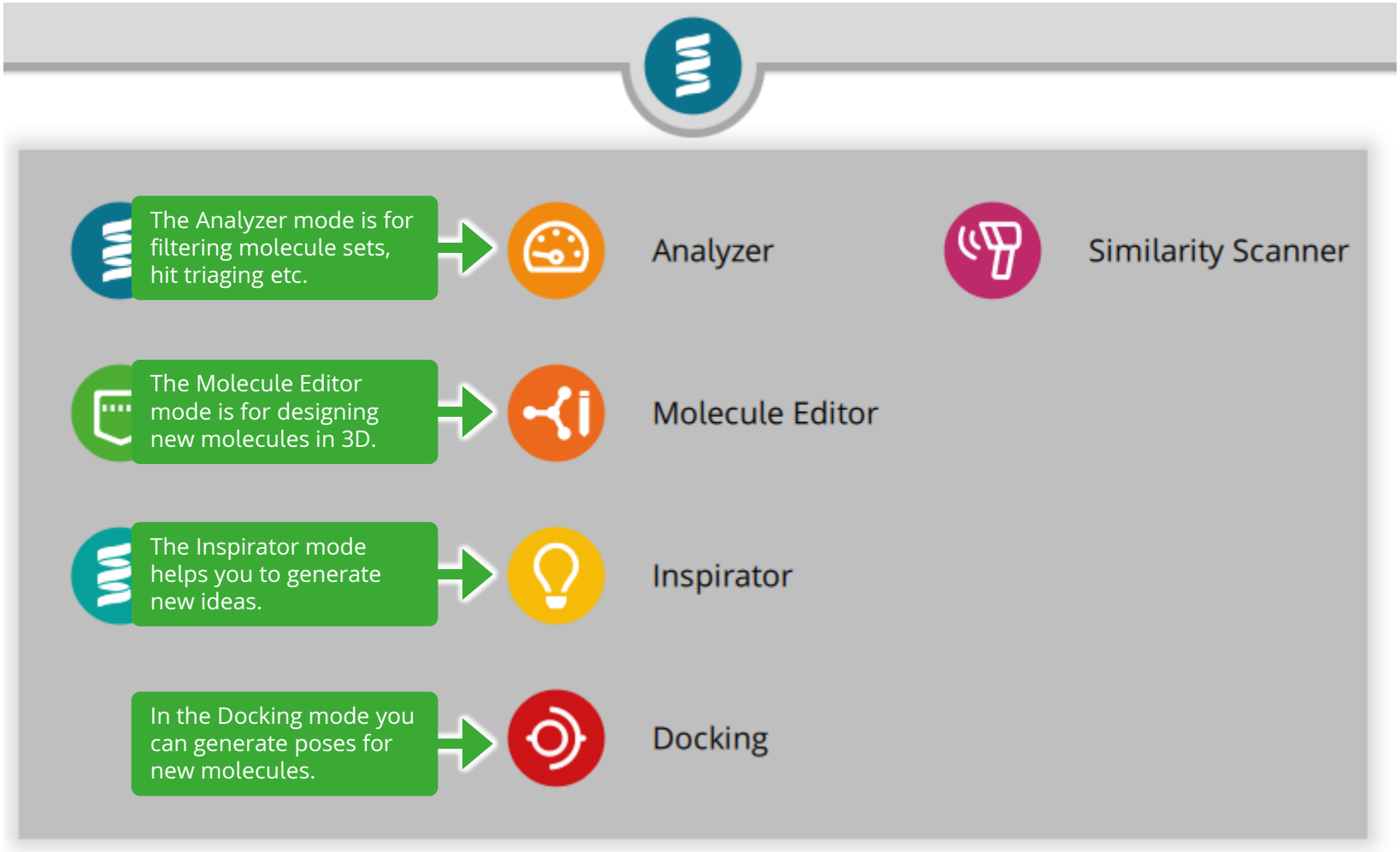
3D-viewer:
- right-click to rotate
- mouse-wheel to zoom
- middle-click to shift

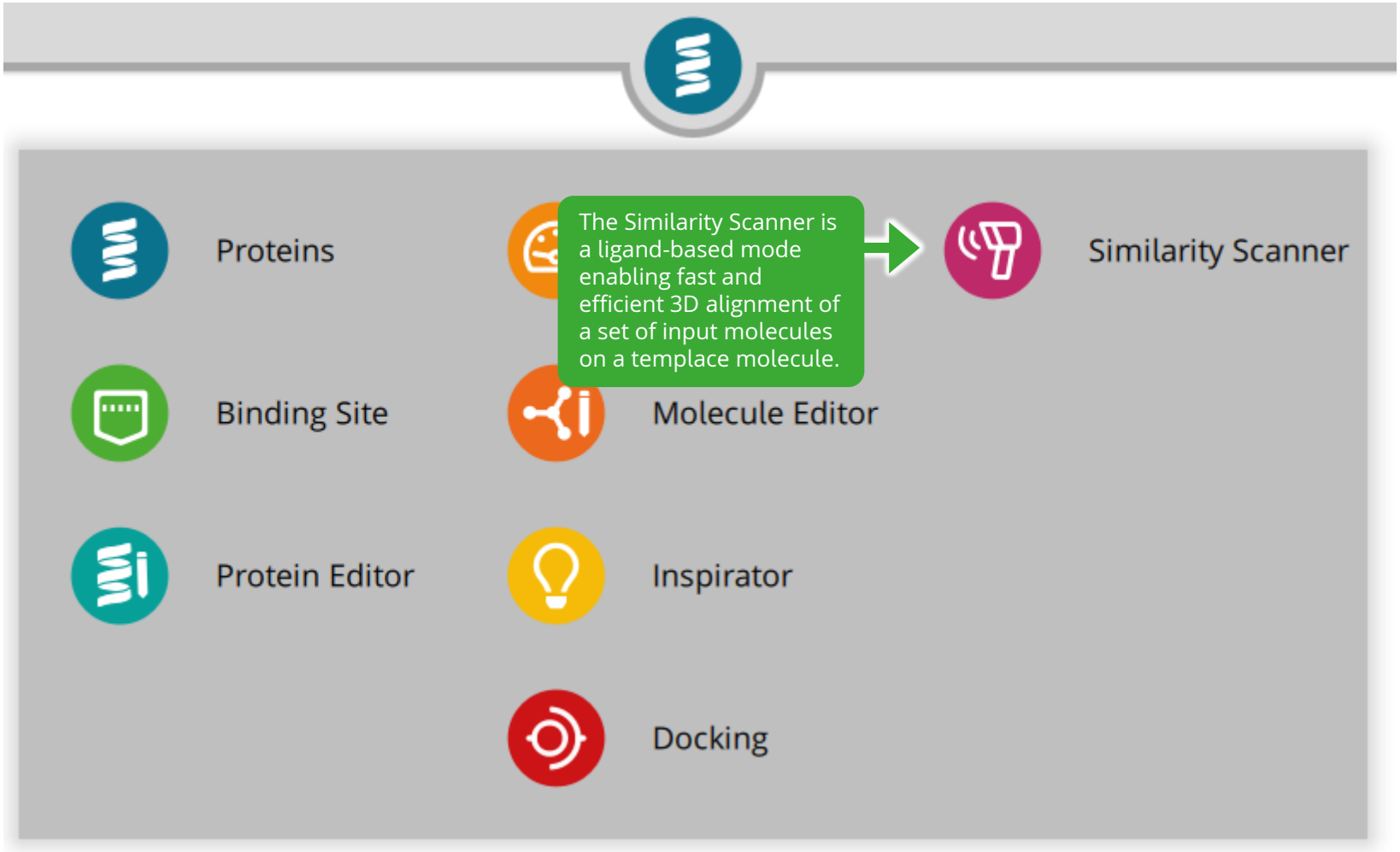
Tables:
- drag rim to re-size
- click entries to select

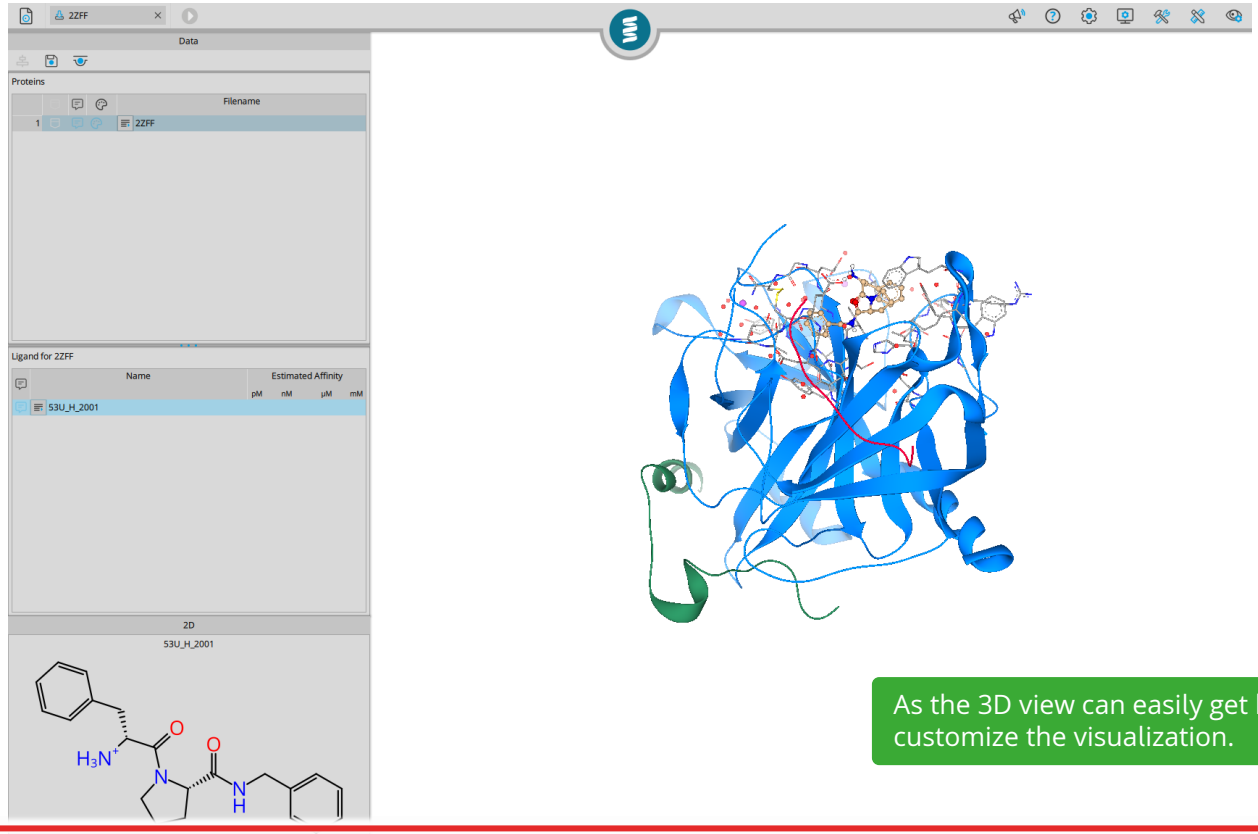

Adjust background color
Change the table layout
Switch between dark and light theme
Adjust lable size
Switch to color blindness mode
If you want to customize the layout of SeeSAR, click on the 'appearance' button in the top right toolbar.
For this guide will use the light one, but please feel free to use whatever you prefer!


Note that you are in the **Protein mode**. The mode switch button shows in which mode you are and allows you to change the mode as well. Hover over it so see your options.
Data
Proteins
Filename
2ZFF
Ligand for 2ZFF
Name
Estimated Affinity
53U_H_2001
2D
Sequence View
Show Binding Site Only
1 message


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

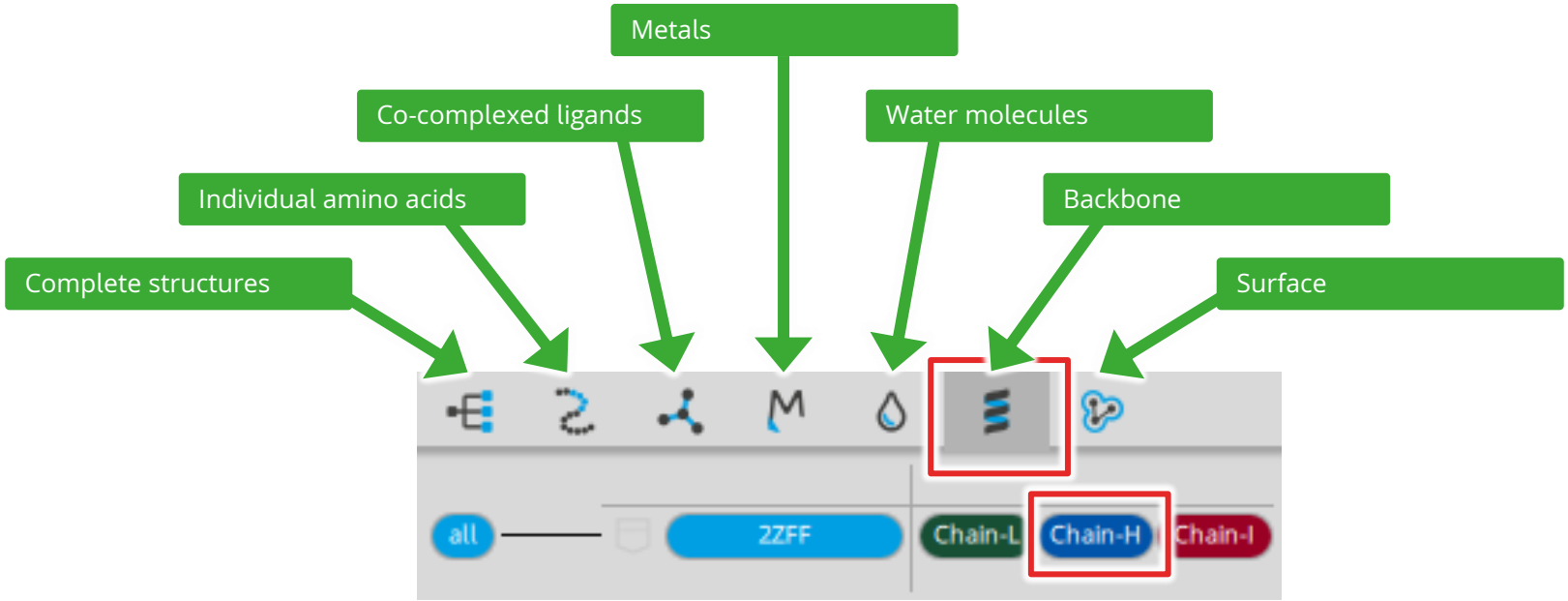

The Analyzer mode is for filtering molecule sets, hit triaging etc.
Analyzer
Similarity Scanner
The Molecule Editor mode is for designing new molecules in 3D.
Molecule Editor
The Inspirator mode helps you to generate new ideas.
Inspirator
In the Docking mode you can generate poses for new molecules.
Docking


Proteins
Binding Site
Protein Editor
The Similarity Scanner is a ligand-based mode enabling fast and efficient 3D alignment of a set of input molecules on a templace molecule.
Molecule Editor
Inspirator
Docking
Similarity Scanner



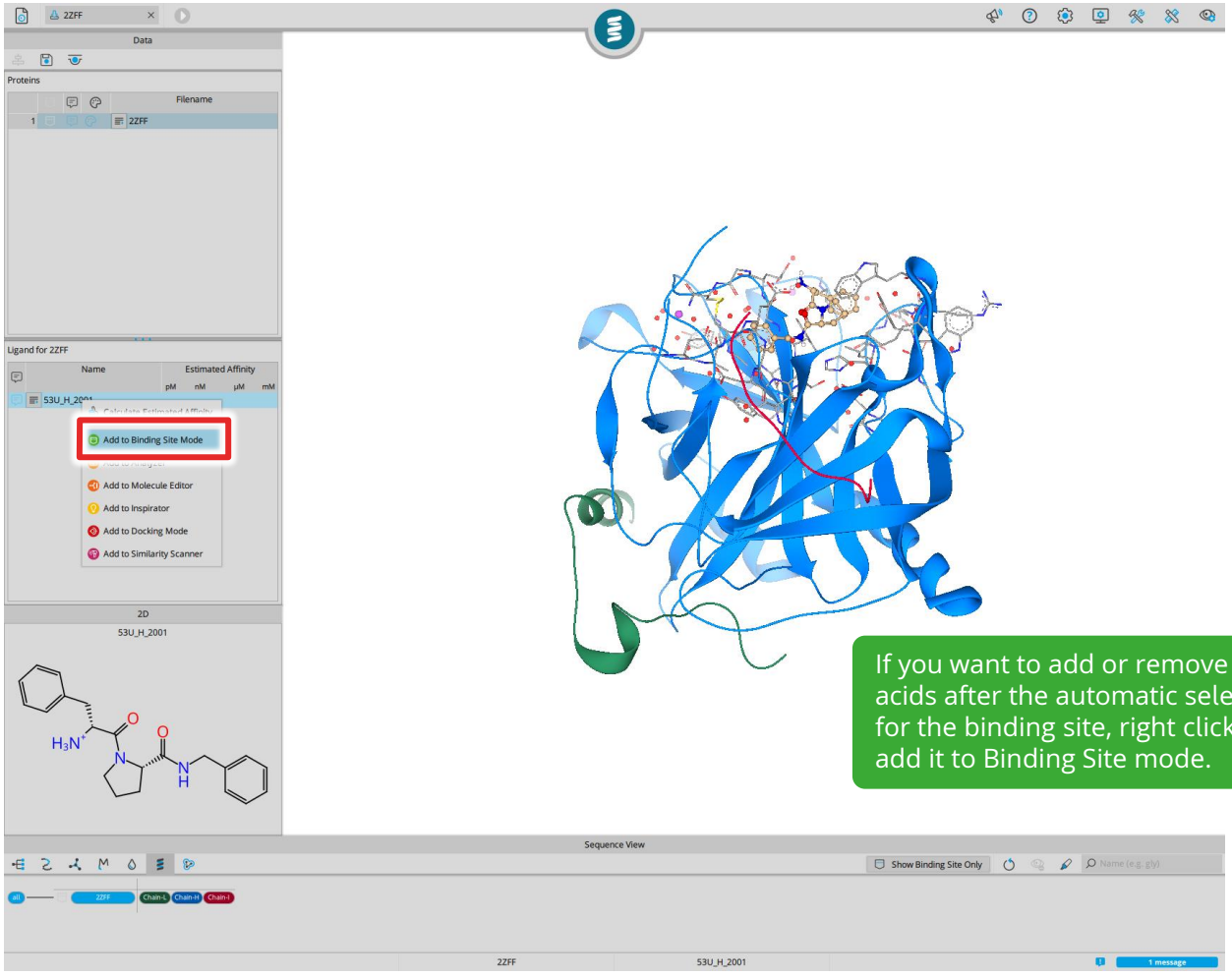
As the 3D view can easily get busy, let's customize the visualization.

The view controls let you toggle on/off:

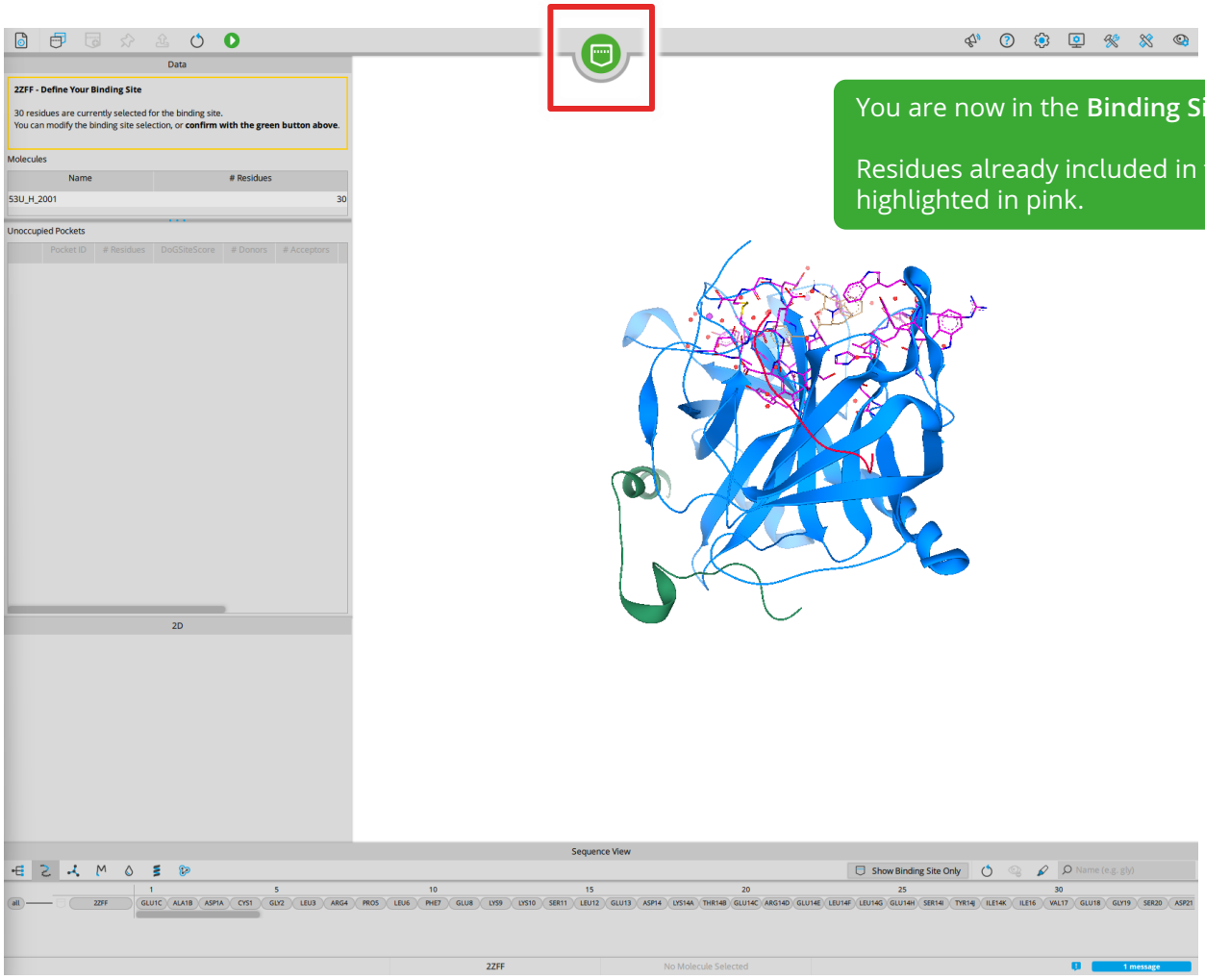


Let's hide the secondary structure, by clicking on the "Chain-H" button in the backbone tab. Upon clicking it turns grey (deactivated)

Note:
All buttons are clickable, so that you can hide **all** parts of one protein in one click (useful with several proteins).

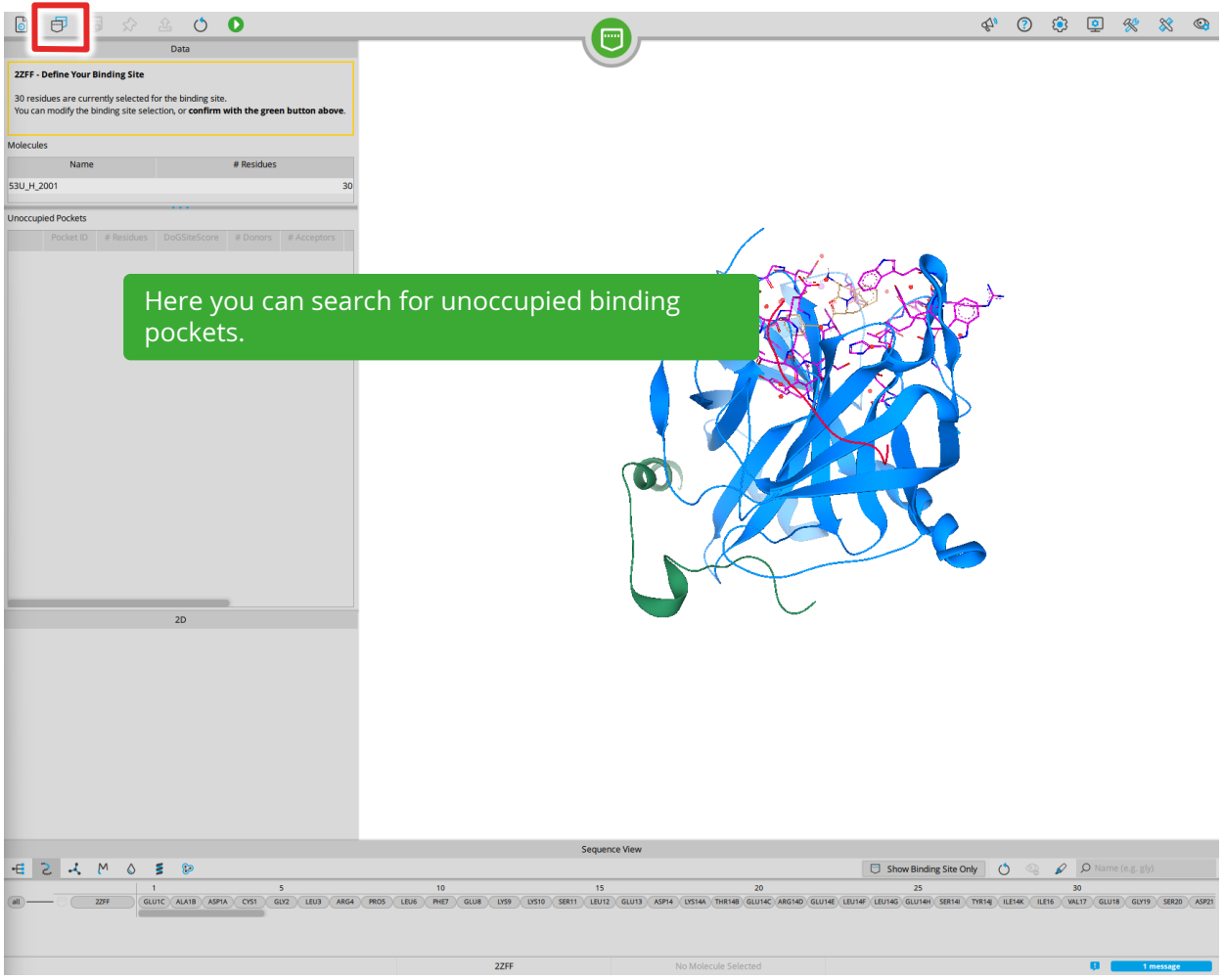


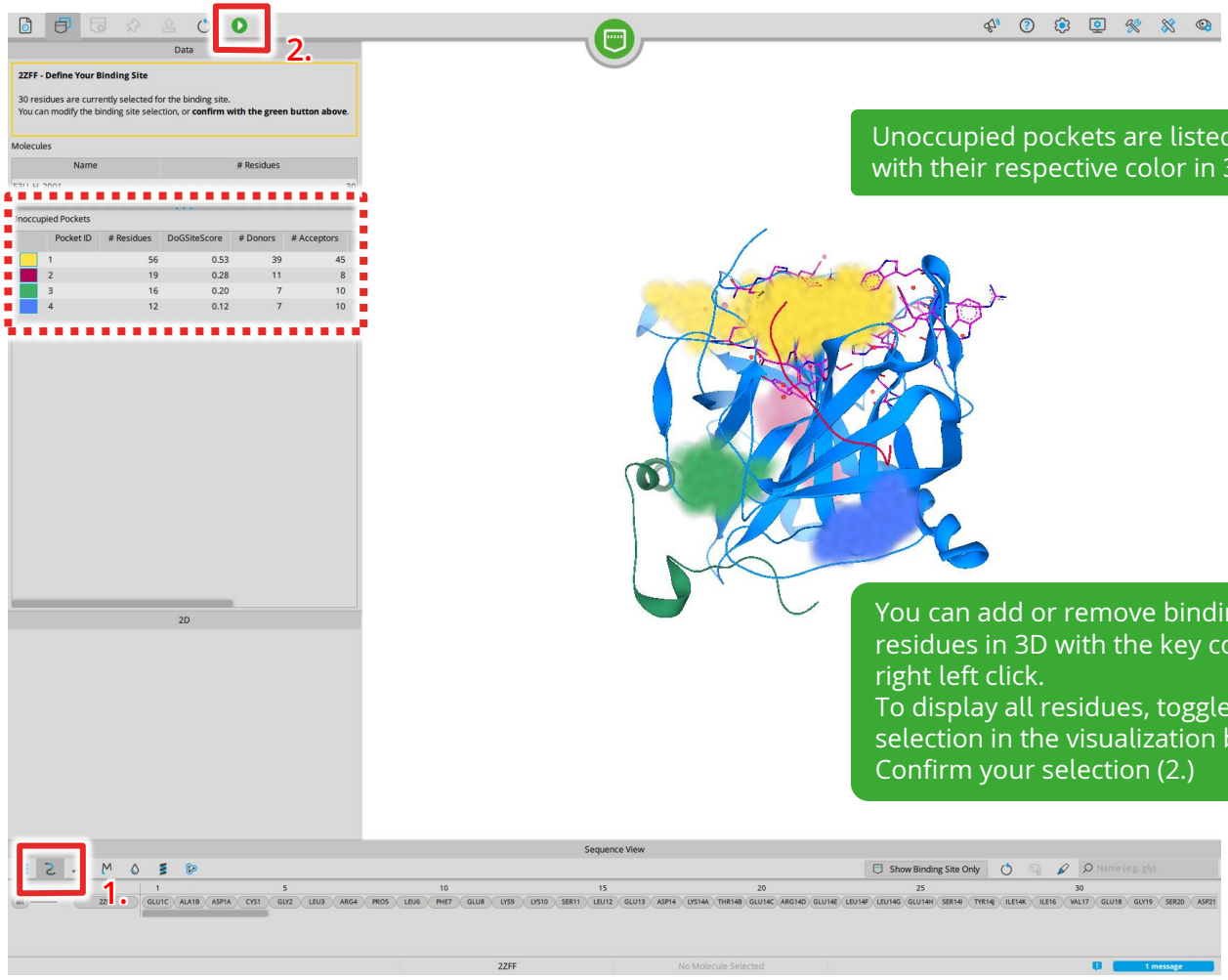
If you want to add or remove individual amino acids after the automatic selection of residues for the binding site, right click your ligand and add it to Binding Site mode.



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

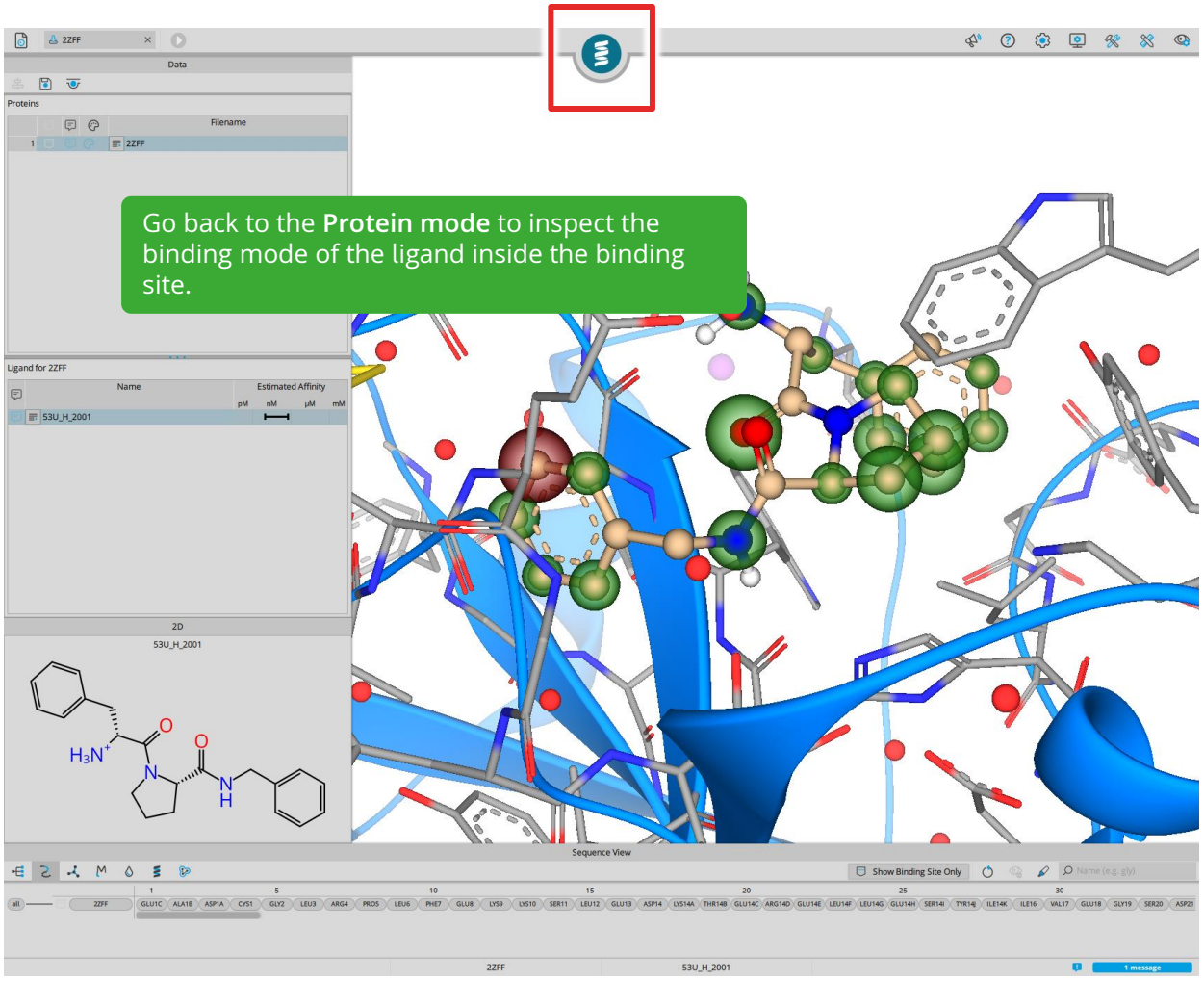
Residues already included in the binding site are highlighted in pink.

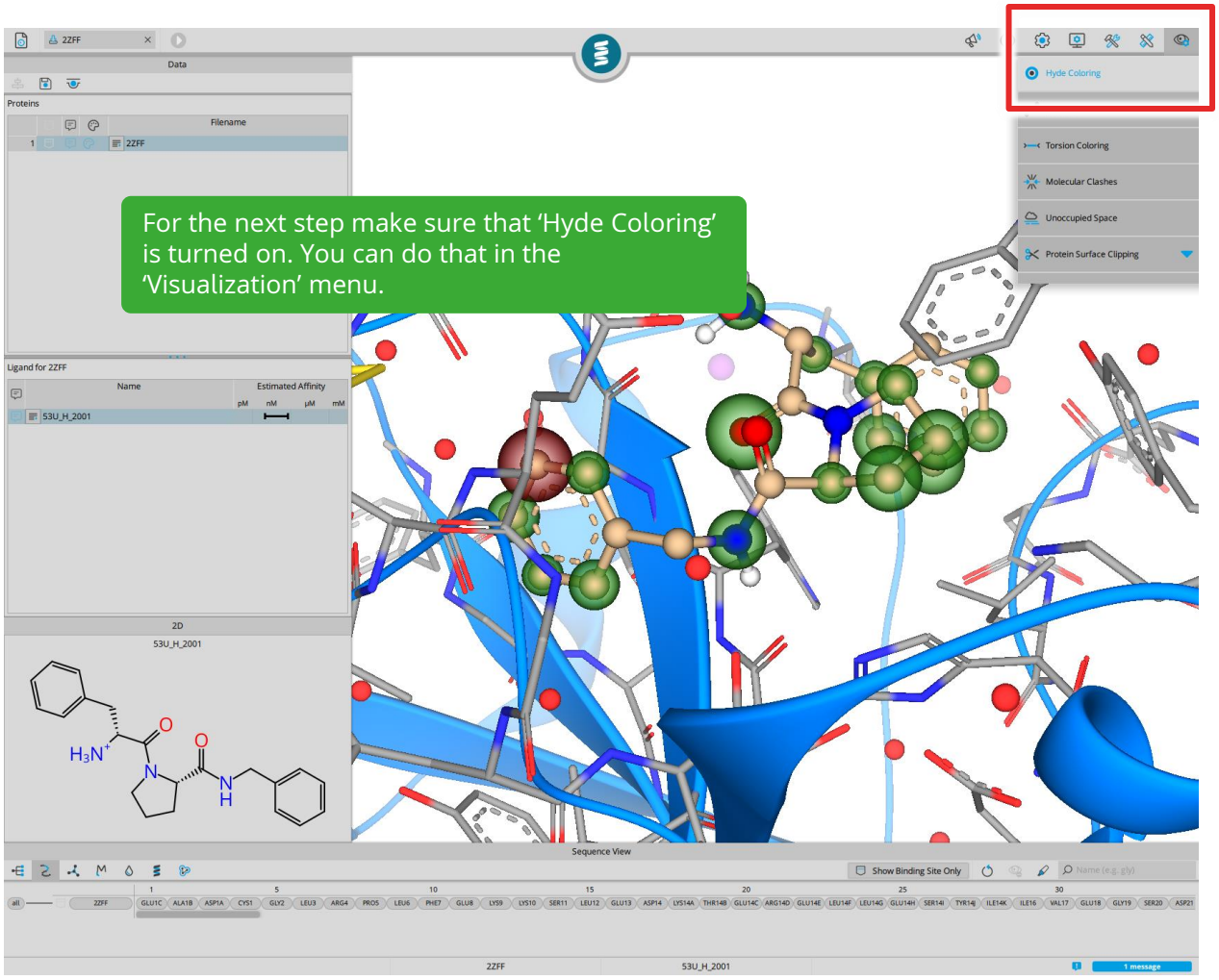

Data
2ZFF - Define Your Binding Site
30 residues are currently selected for the binding site.
You can modify the binding site selection, or confirm with the green button above.
Molecules
Name
Residues
53U_H_2001
30
Unoccupied Pockets
Pocket ID
Residues
DoGSiteScore
Donors
Acceptors
2D
Here you can search for unoccupied binding pockets.
Sequence View
Show Binding Site Only
2ZFF
No Molecule Selected
1 message

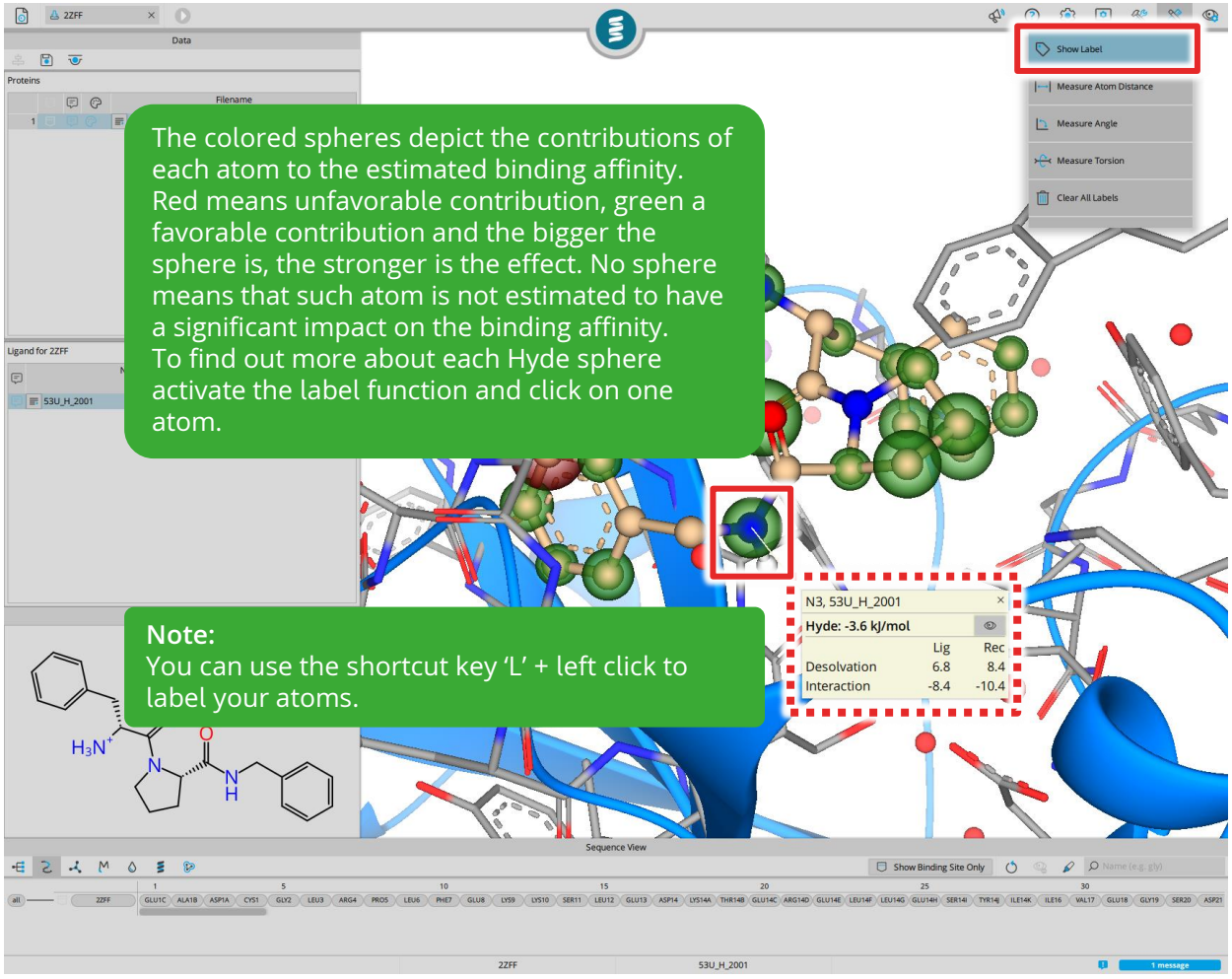


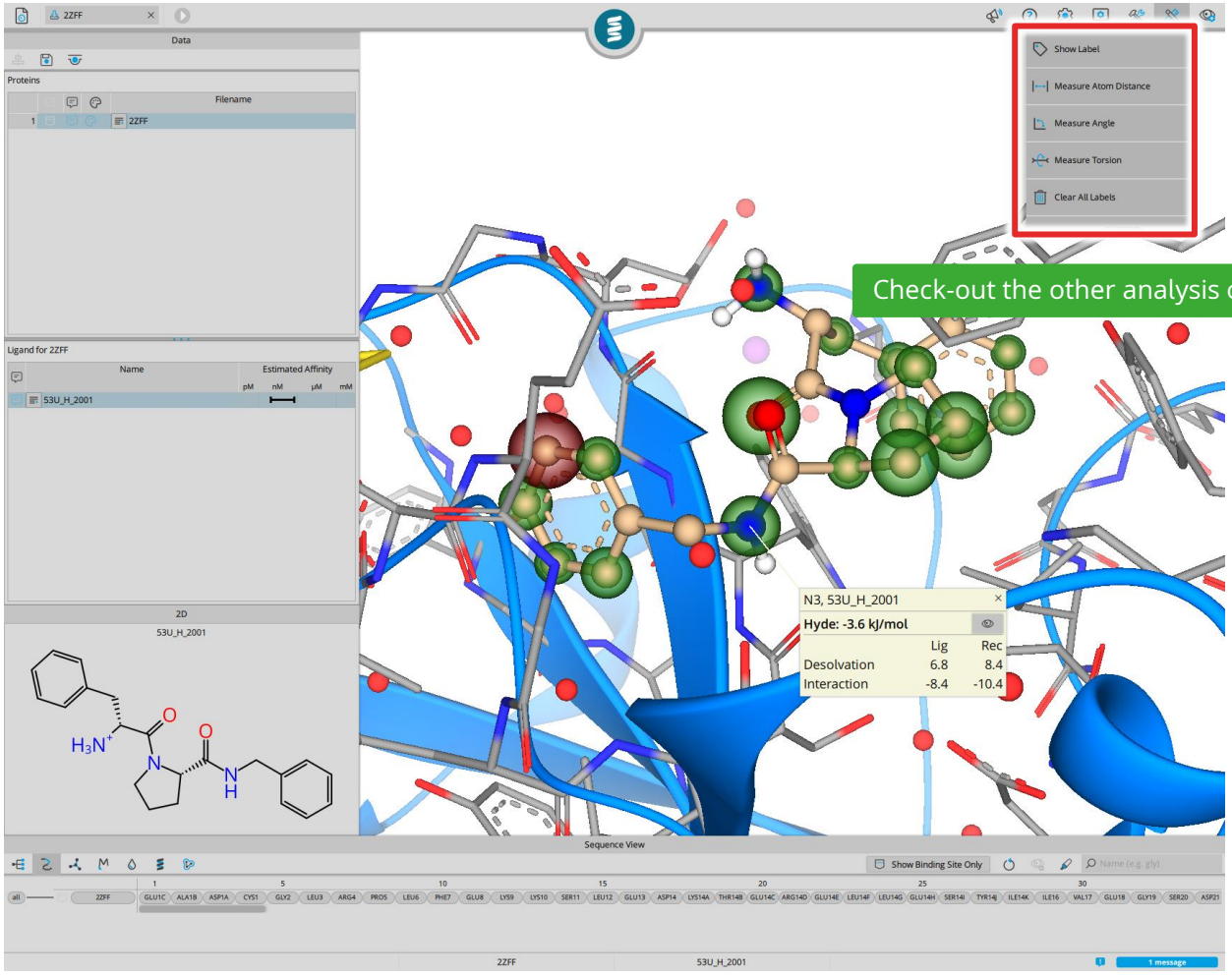
Unoccupied pockets are listed and presented with their respective color in 3D.

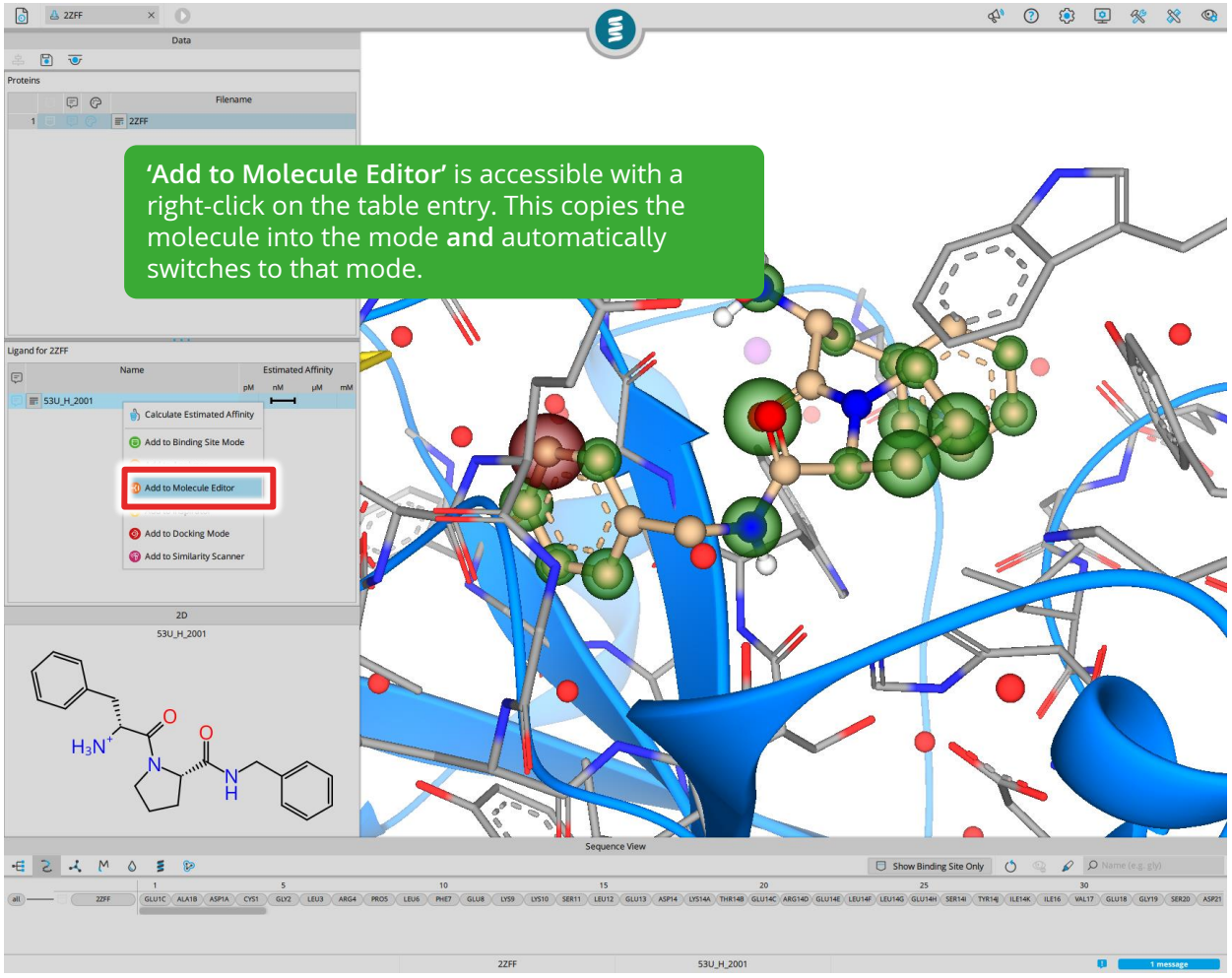
You can add or remove binding pockets and residues in 3D with the key combination ctrl + right left click.
To display all residues, toggle the residue selection in the visualization bar (1.)
Confirm your selection (2.)


Go back to the **Protein mode** to inspect the binding mode of the ligand inside the binding site.
2ZFF
Data
Proteins
Filename
2ZFF
Ligand for 2ZFF
Name
Estimated Affinity
53U_H_2001
2D
53U_H_2001
Sequence View
Show Binding Site Only
2ZFF
53U_H_2001


For the next step make sure that ‘Hyde Coloring’ is turned on. You can do that in the ‘Visualization’ menu.
Hyde Coloring
Torsion Coloring
Molecular Clashes
Unoccupied Space
Protein Surface Clipping
Data
Proteins
Filename
2ZFF
Ligand for 2ZFF
Name
Estimated Affinity
53U_H_2001
2D
Sequence View
Show Binding Site Only

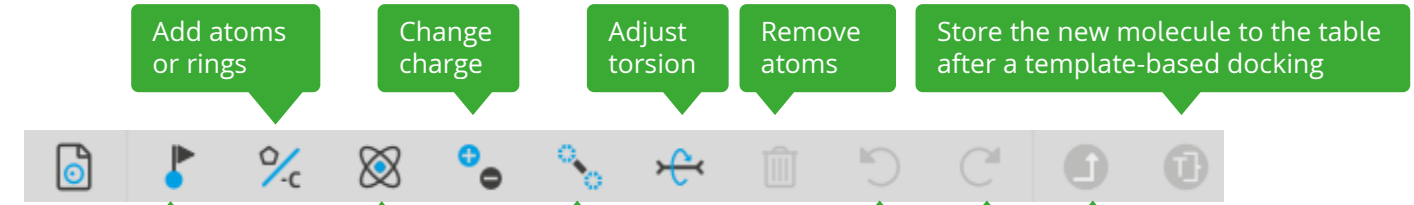

The colored spheres depict the contributions of each atom to the estimated binding affinity. Red means unfavorable contribution, green a favorable contribution and the bigger the sphere is, the stronger is the effect. No sphere means that such atom is not estimated to have a significant impact on the binding affinity.
To find out more about each Hyde sphere activate the label function and click on one atom.
Note:
You can use the shortcut key 'L' + left click to label your atoms.
Show Label
Measure Atom Distance
Measure Angle
Measure Torsion
Clear All Labels
N3, 53U_H_2001
Hyde: -3.6 kJ/mol
Lig
Rec
Desolvation
6.8
8.4
Interaction
-8.4
-10.4
Sequence View
Show Binding Site Only


2ZFF
Data
Proteins
Filename
2ZFF
Ligand for 2ZFF
Name
Estimated Affinity
53U_H_2001
2D
53U_H_2001
Show Label
Measure Atom Distance
Measure Angle
Measure Torsion
Clear All Labels
Check-out the other analysis options!
N3, 53U_H_2001
Hyde: -3.6 kJ/mol
Lig
Rec
Desolvation
6.8
8.4
Interaction
-8.4
-10.4
Sequence View
Show Binding Site Only
2ZFF
53U_H_2001



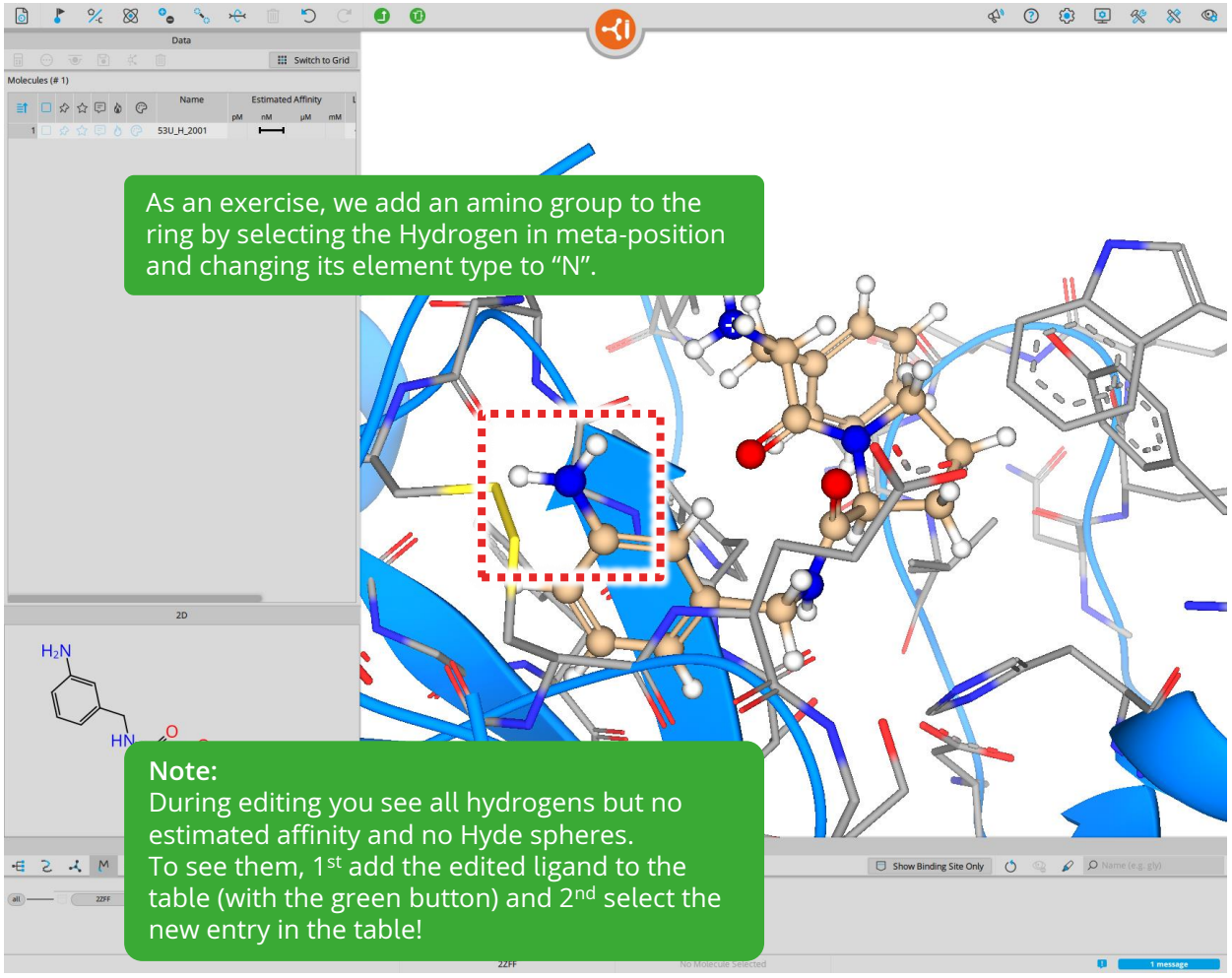
'Add to Molecule Editor' is accessible with a right-click on the table entry. This copies the molecule into the mode **and** automatically switches to that mode.

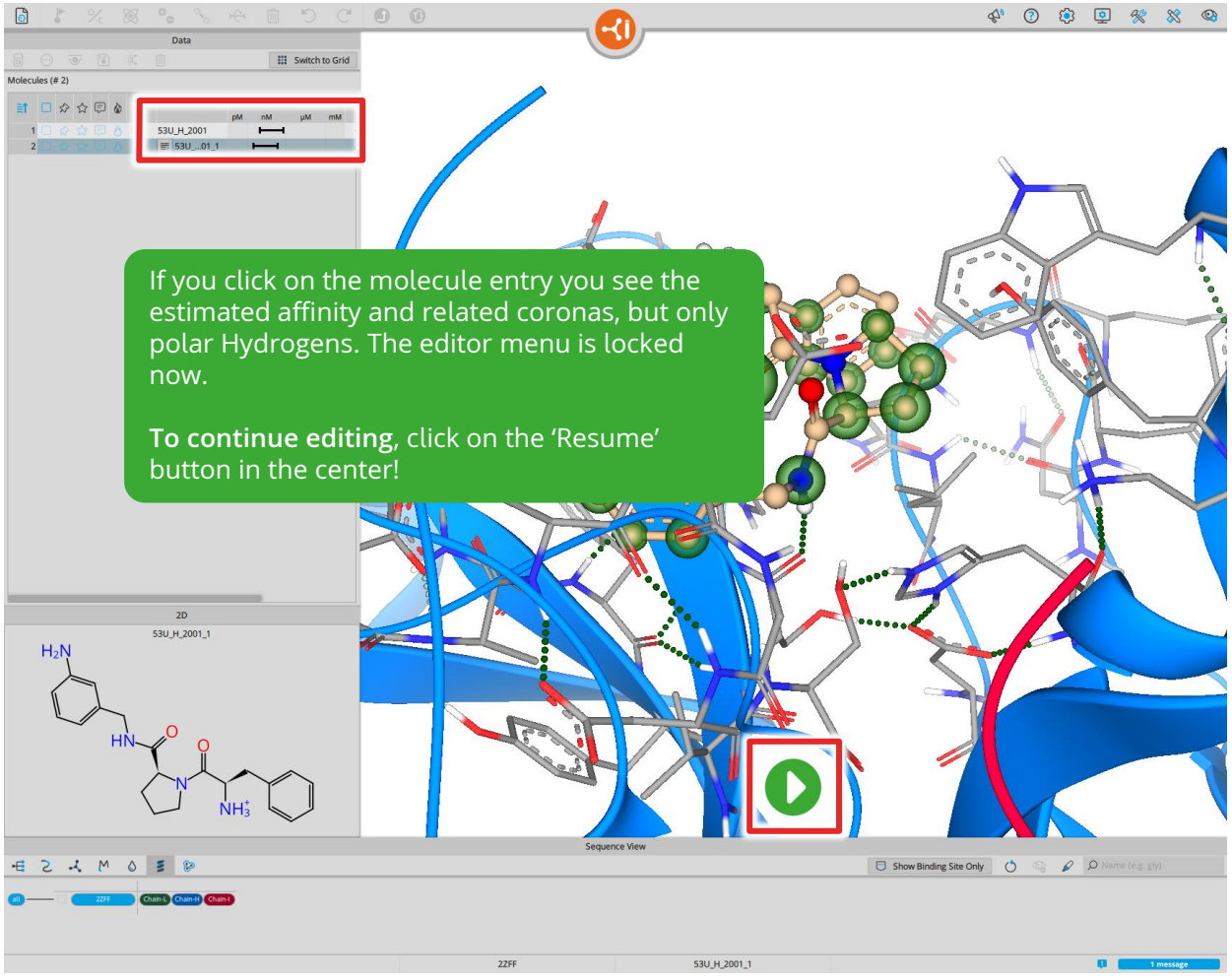
The editor-menu will appear on the top left.
There you can:

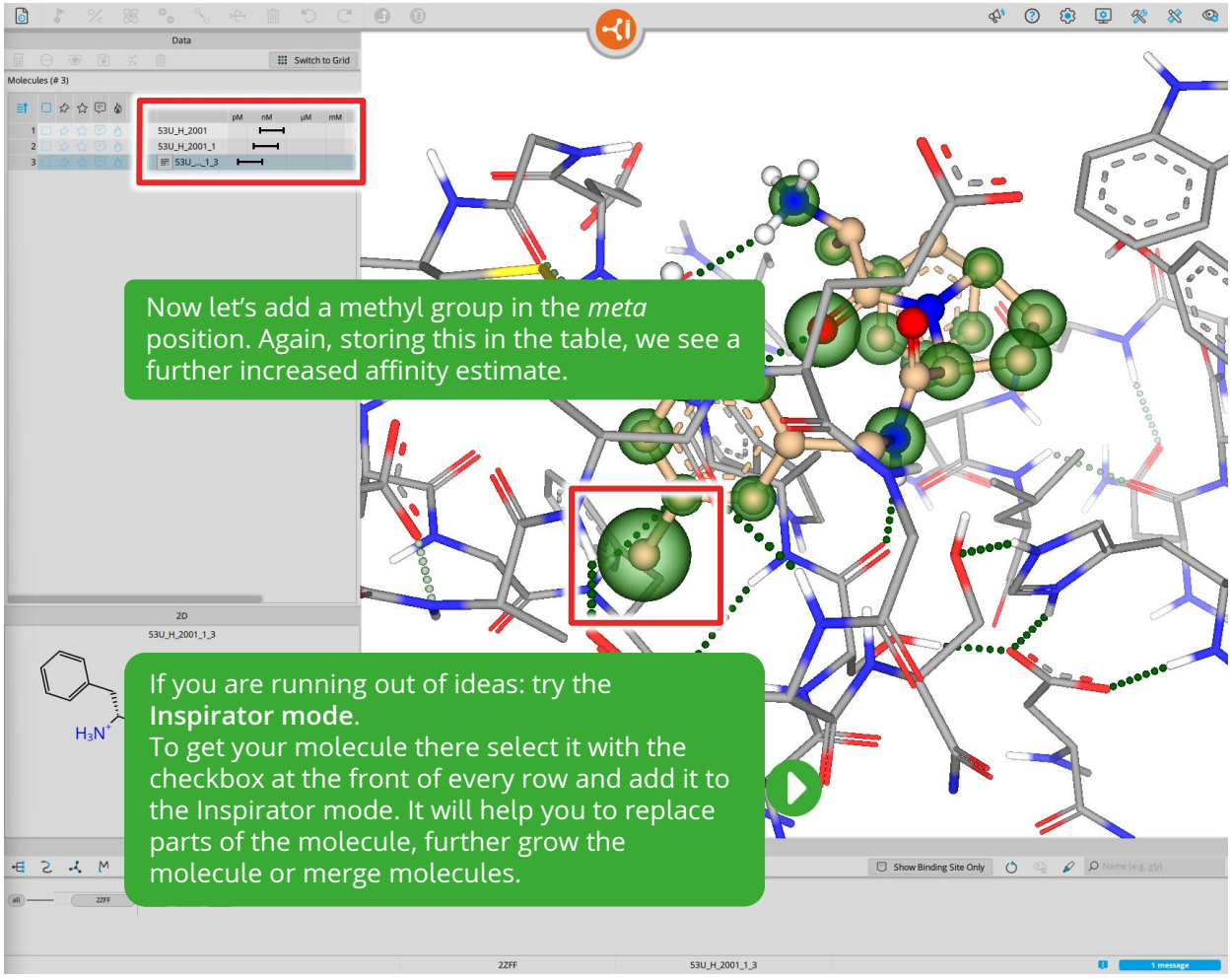


To edit a molecule ALWAYS:
1. **select** (atoms or bonds)
2. **modify** (using the function of choice from above)

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, ...).


Data
Switch to Grid
Molecules (# 1)
Name
Estimated Affinity
53U_H_2001
2D
As an exercise, we add an amino group to the ring by selecting the Hydrogen in meta-position and changing its element type to “N”.
Note:
During editing you see all hydrogens but no estimated affinity and no Hyde spheres.
To see them, 1st add the edited ligand to the table (with the green button) and 2nd select the new entry in the table!
Show Binding Site Only
1 message

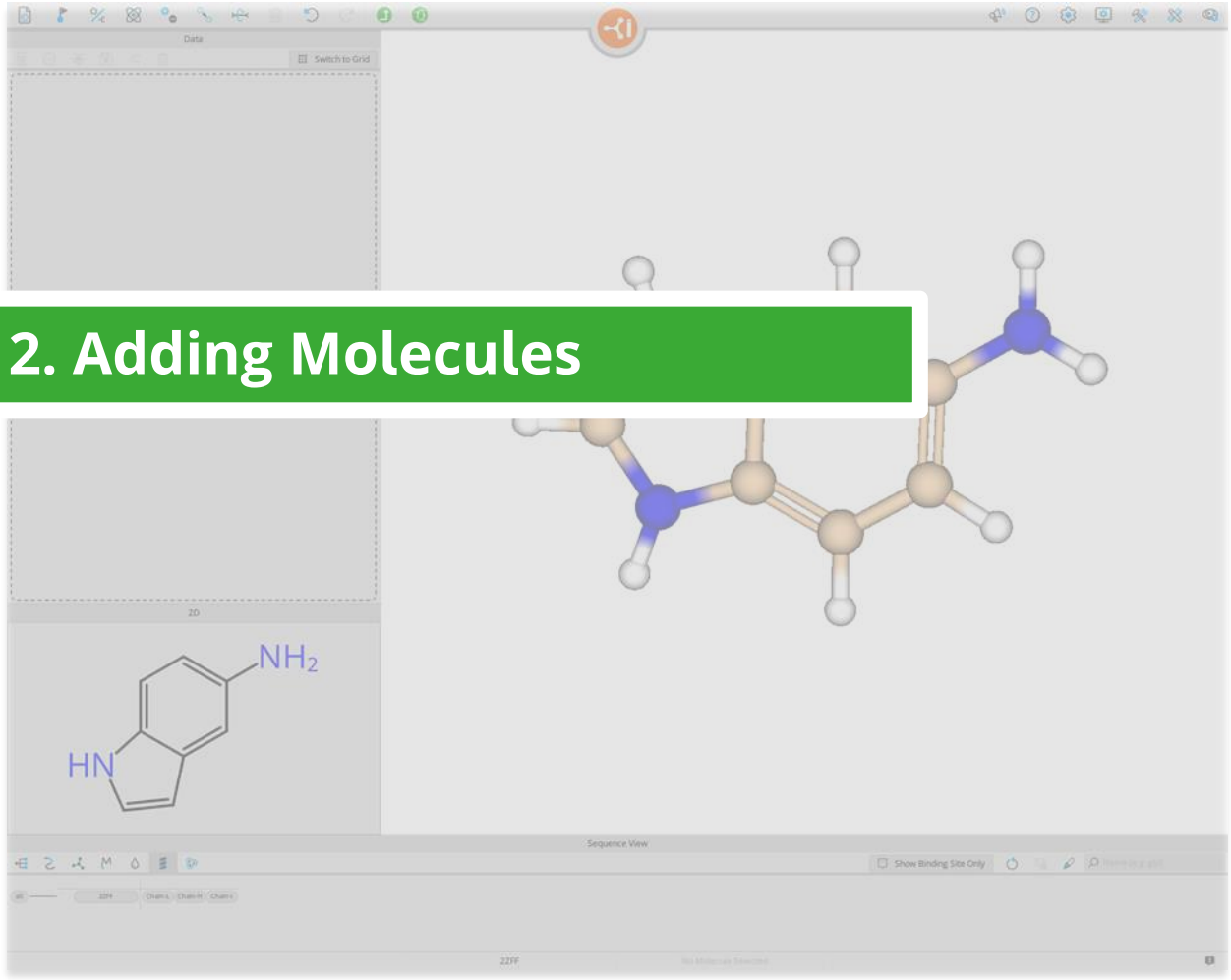

Data
Switch to Grid
Molecules (# 2)
pM
nM
µM
mM
53U_H_2001
53U_...01_1
2D
53U_H_2001_1
H_2N
HN
O
O
N
NH_3^+
If you click on the molecule entry you see the estimated affinity and related coronas, but only polar Hydrogens. The editor menu is locked now.
To continue editing, click on the 'Resume' button in the center!
Sequence View
Show Binding Site Only
2ZFF
Chain-L
Chain-H
Chain-I
2ZFF
53U_H_2001_1
1 message

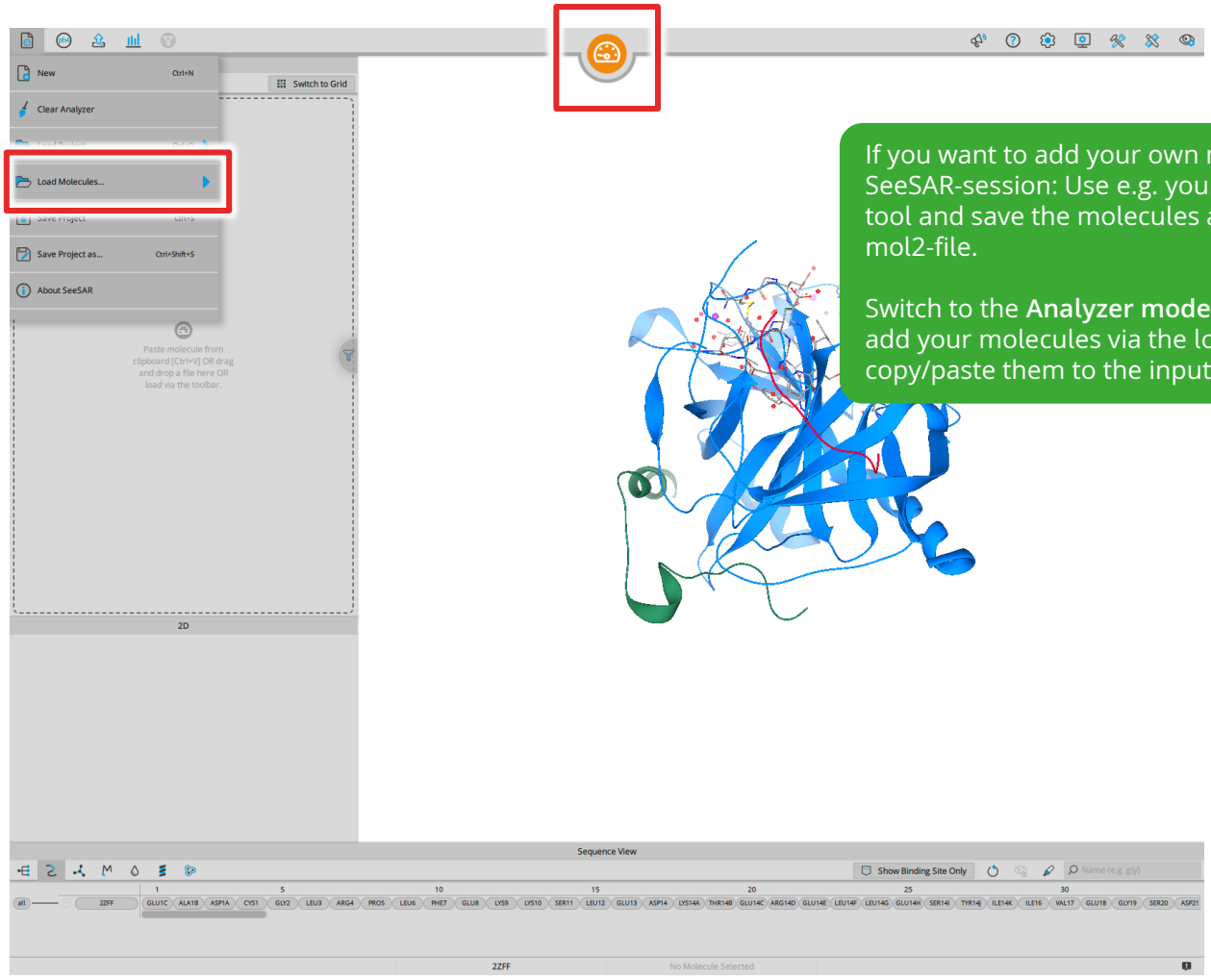


Now let's add a methyl group in the *meta* position. Again, storing this in the table, we see a further increased affinity estimate.

If you are running out of ideas: try the **Inspirator mode**.
To get your molecule there select it with the checkbox at the front of every row and add it to the Inspirator mode. It will help you to replace parts of the molecule, further grow the molecule or merge molecules.

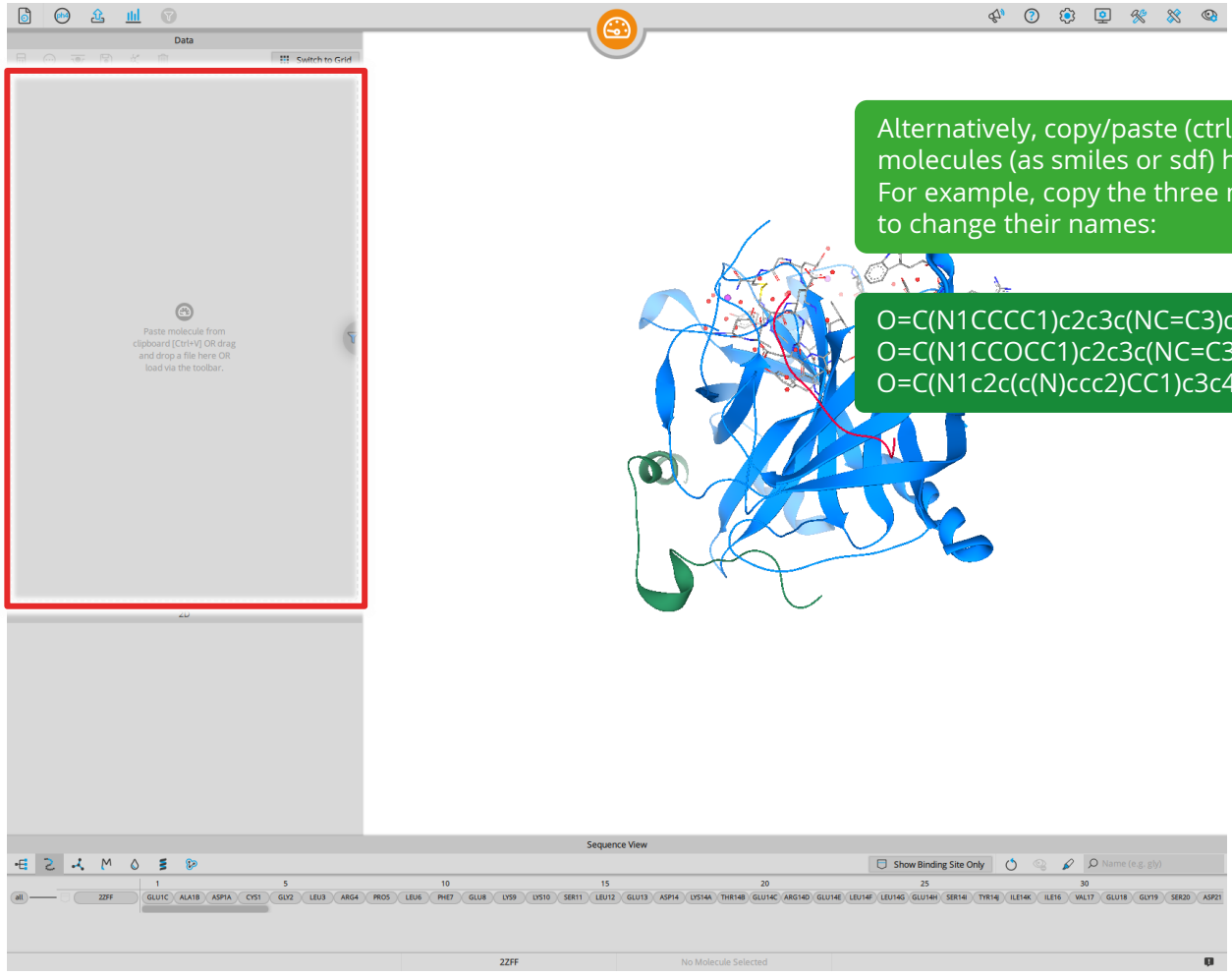
2. Adding Molecules

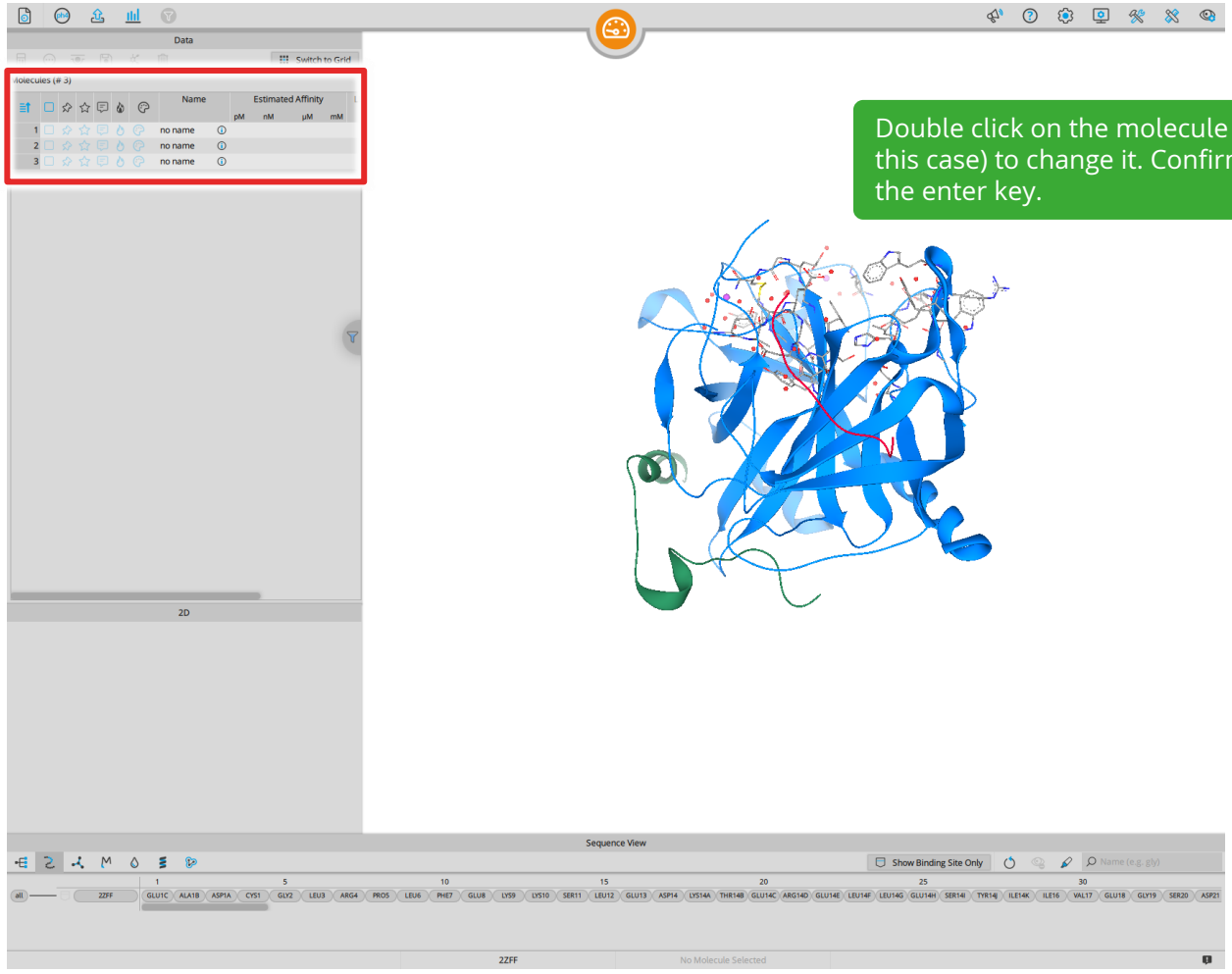




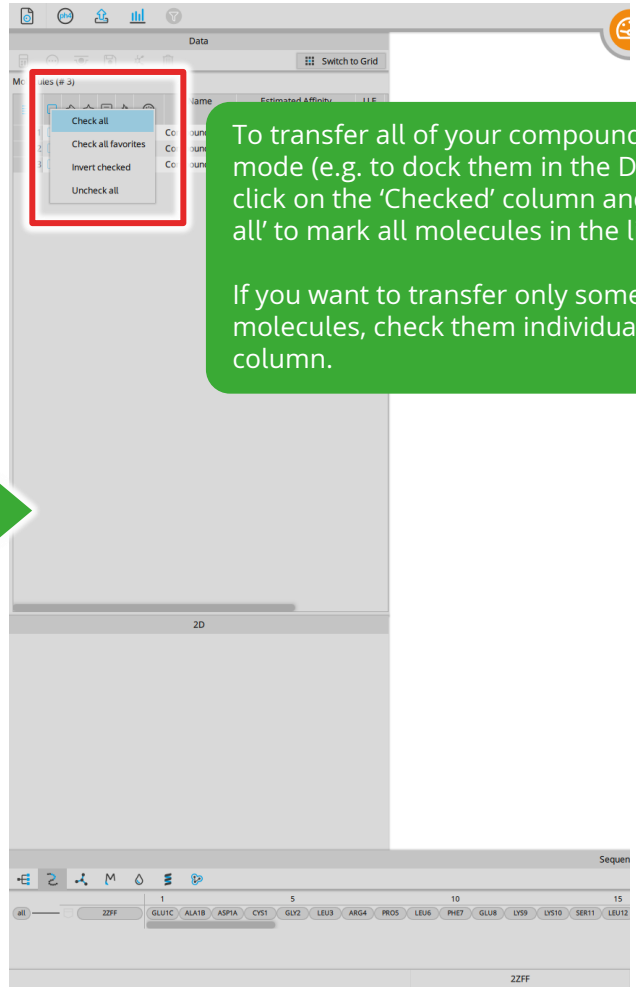
If you want to add your own molecules to a SeeSAR-session: Use e.g. your favorite drawing tool and save the molecules as sdf-, smiles-, or mol2-file.

Switch to the **Analyzer mode** in SeeSAR and add your molecules via the load button or copy/paste them to the input library field.


Data
Switch to Grid
Paste molecule from clipboard [Ctrl+V] OR drag and drop a file here OR load via the toolbar.
Alternatively, copy/paste (ctrl + c/ctrl + v) your molecules (as smiles or sdf) here.
For example, copy the three molecules below, to change their names:
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
Sequence View
Show Binding Site Only
2ZFF
No Molecule Selected

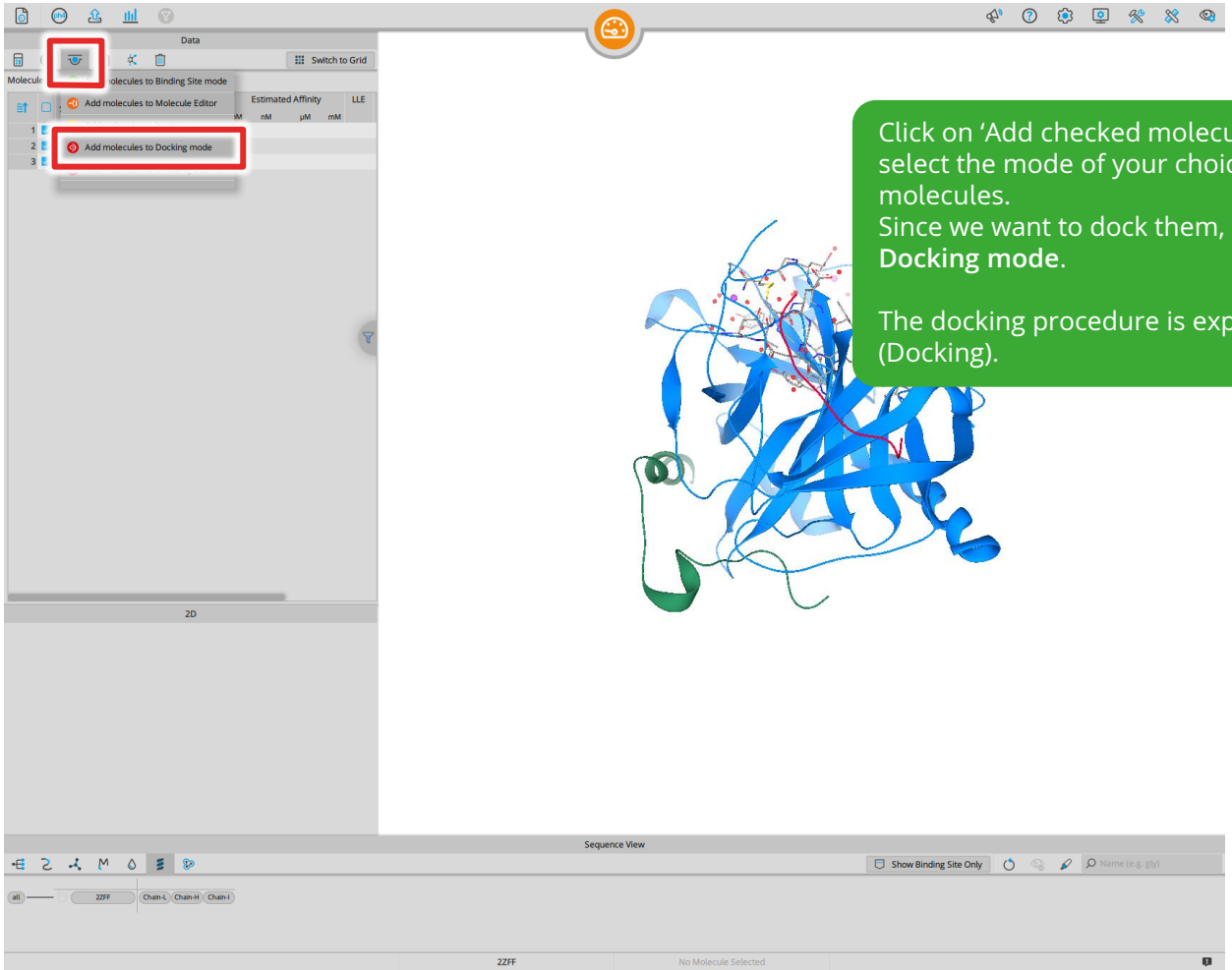


Double click on the molecule name (‘no name’ in this case) to change it. Confirm the change with the enter key.



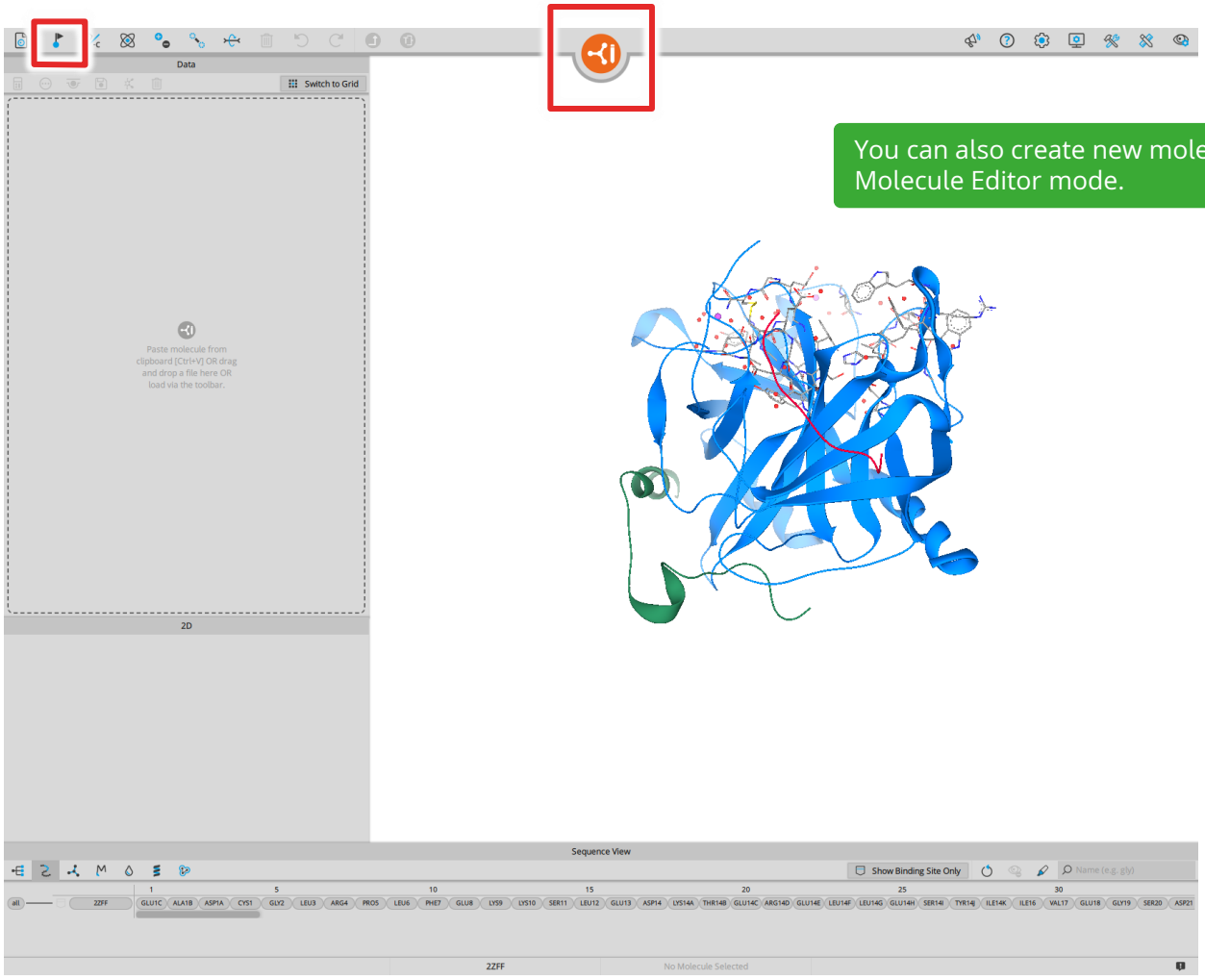
To transfer all of your compounds to another mode (e.g. to dock them in the Docking mode), click on the 'Checked' column and select 'Check all' to mark all molecules in the list.

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

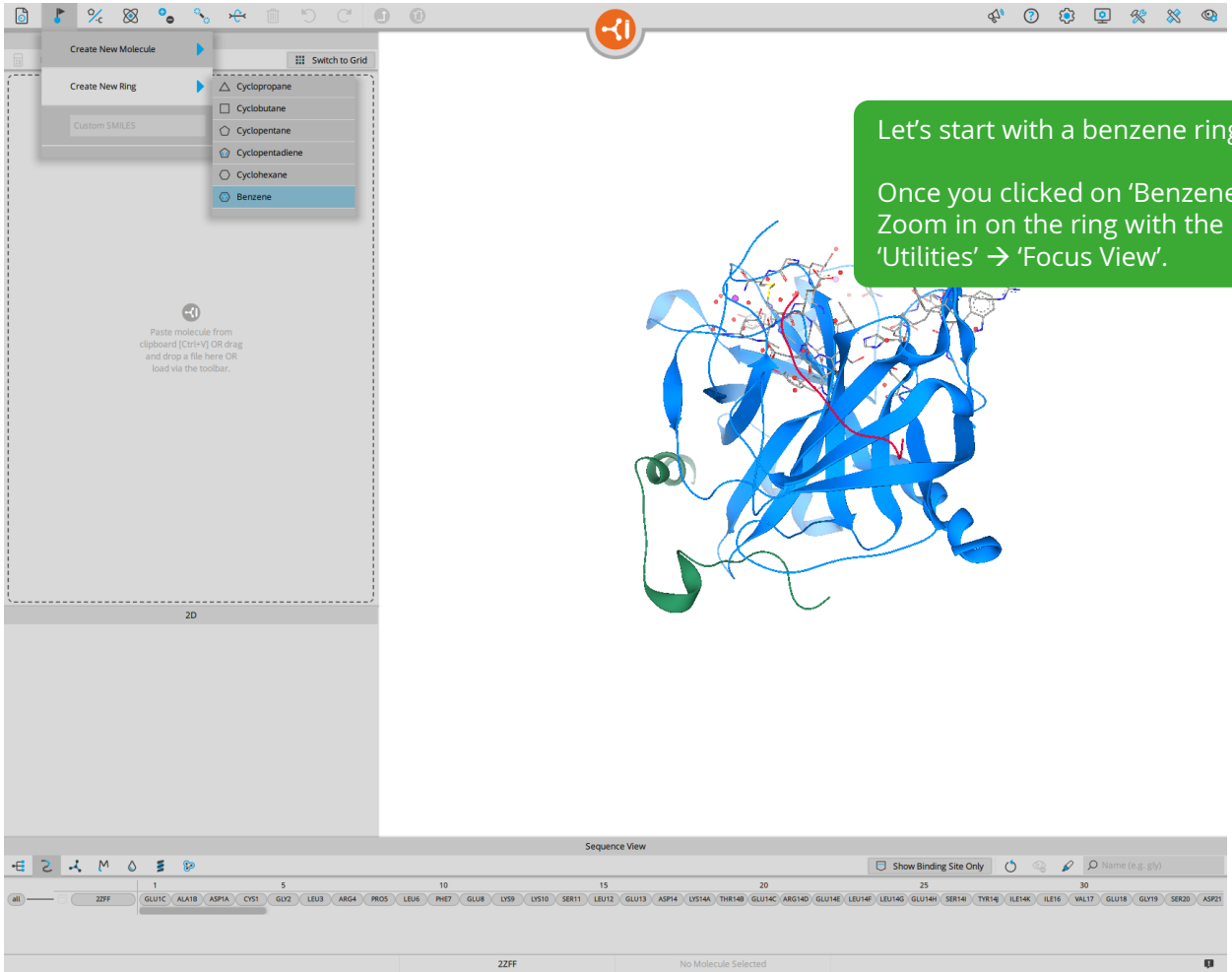


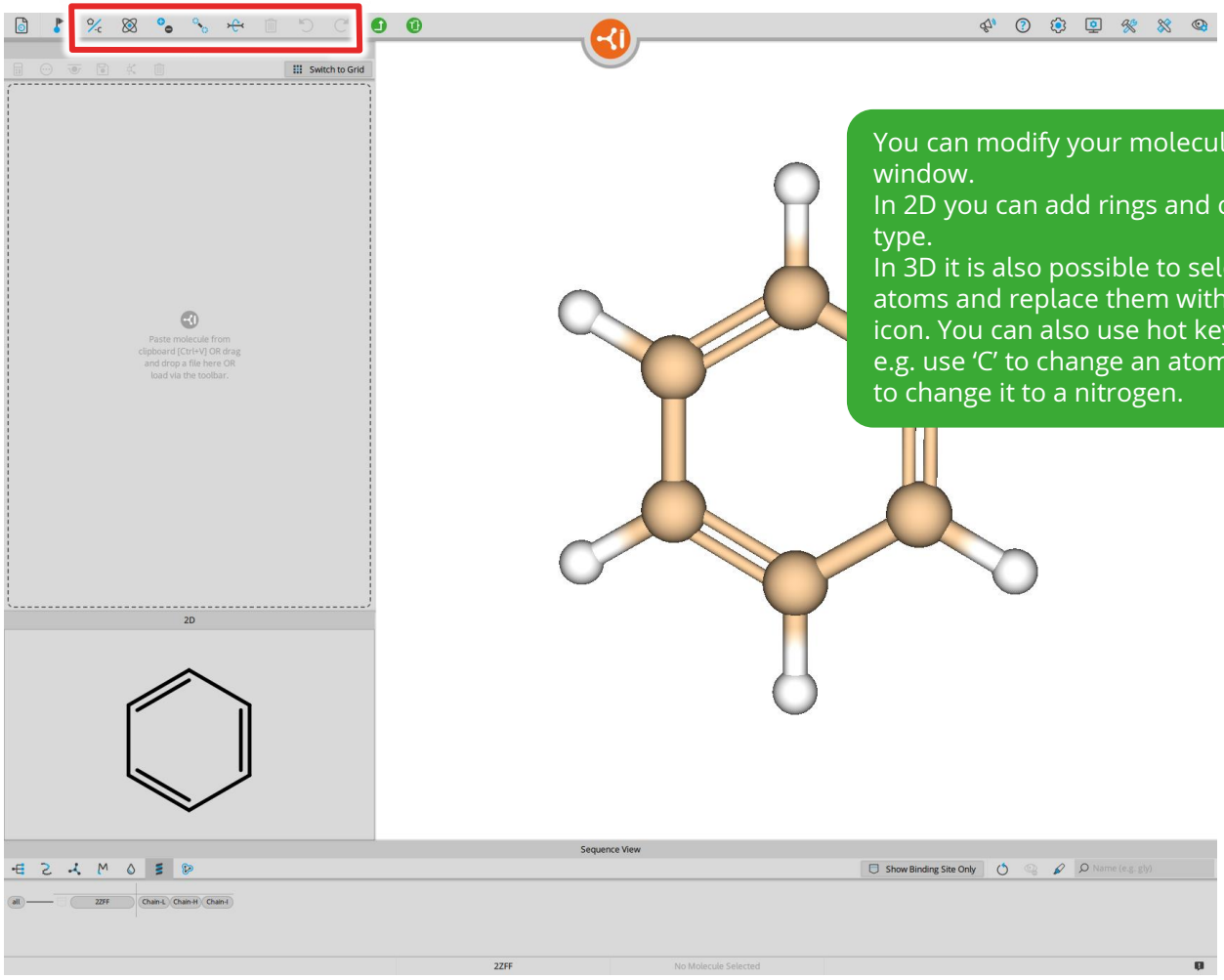
Click on 'Add checked molecules to mode' and select the mode of your choice to work with the molecules.
Since we want to dock them, we will select the **Docking mode**.

The docking procedure is explained in Section 3 (Docking).

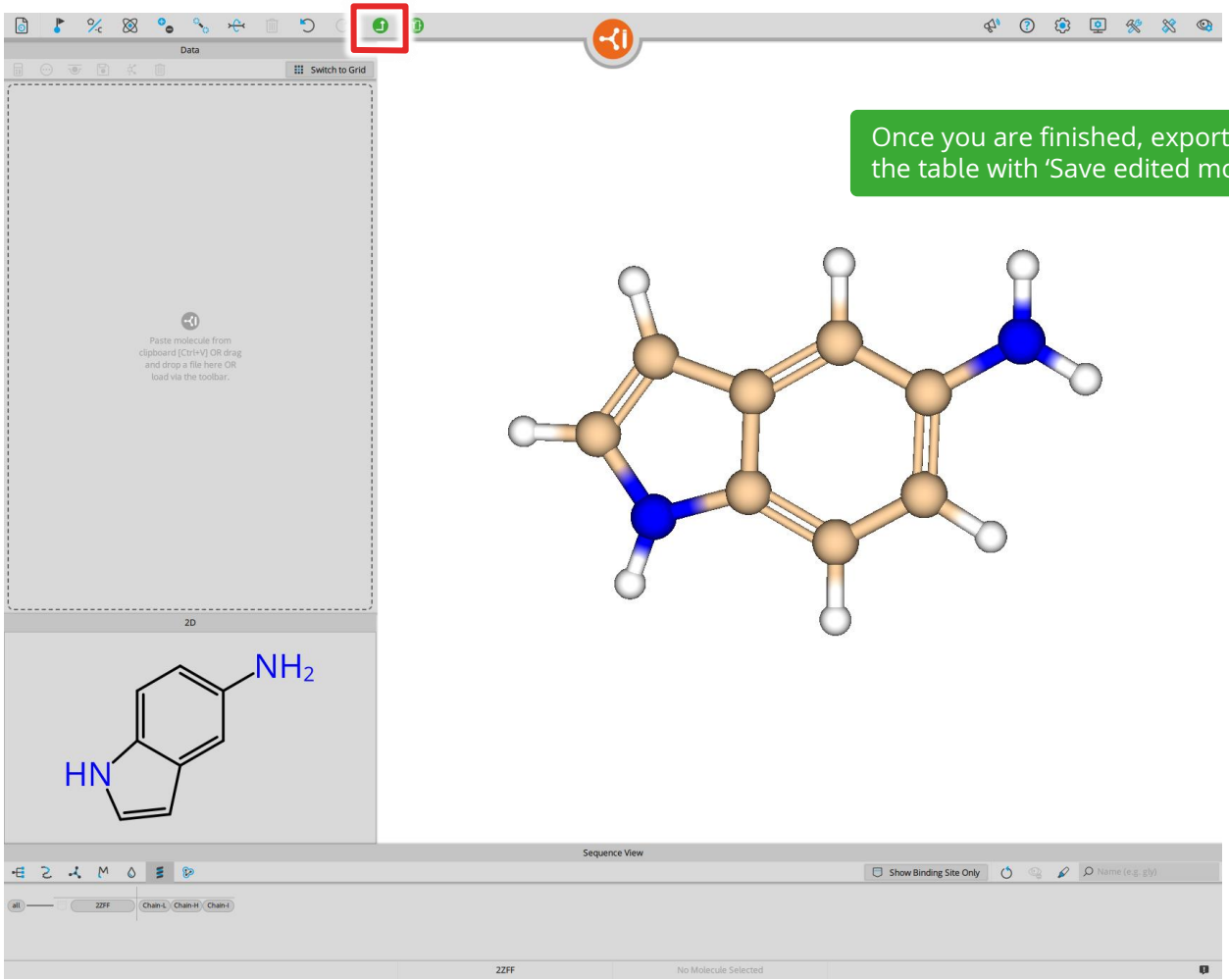


You can also create new molecules in the Molecule Editor mode.


Create New Molecule
Create New Ring
Custom SMILES
Switch to Grid
Cyclopropane
Cyclobutane
Cyclopentane
Cyclopentadiene
Cyclohexane
Benzene
Paste molecule from clipboard [Ctrl+V] OR drag and drop a file here OR load via the toolbar.
2D
Let's start with a benzene ring.
Once you clicked on 'Benzene' a ring will appear. Zoom in on the ring with the space bar or via 'Utilities' → 'Focus View'.
Sequence View
Show Binding Site Only
2ZFF
No Molecule Selected

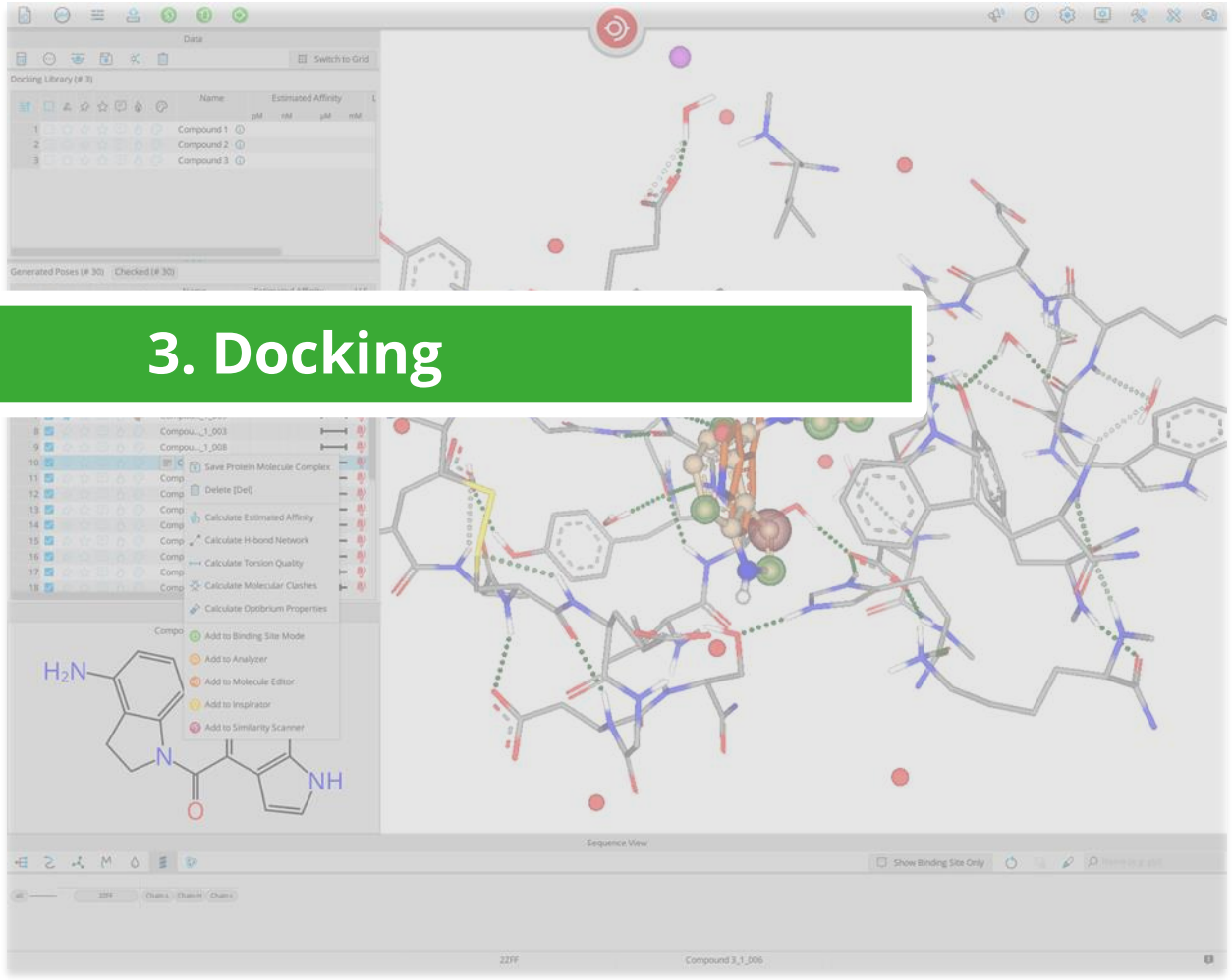


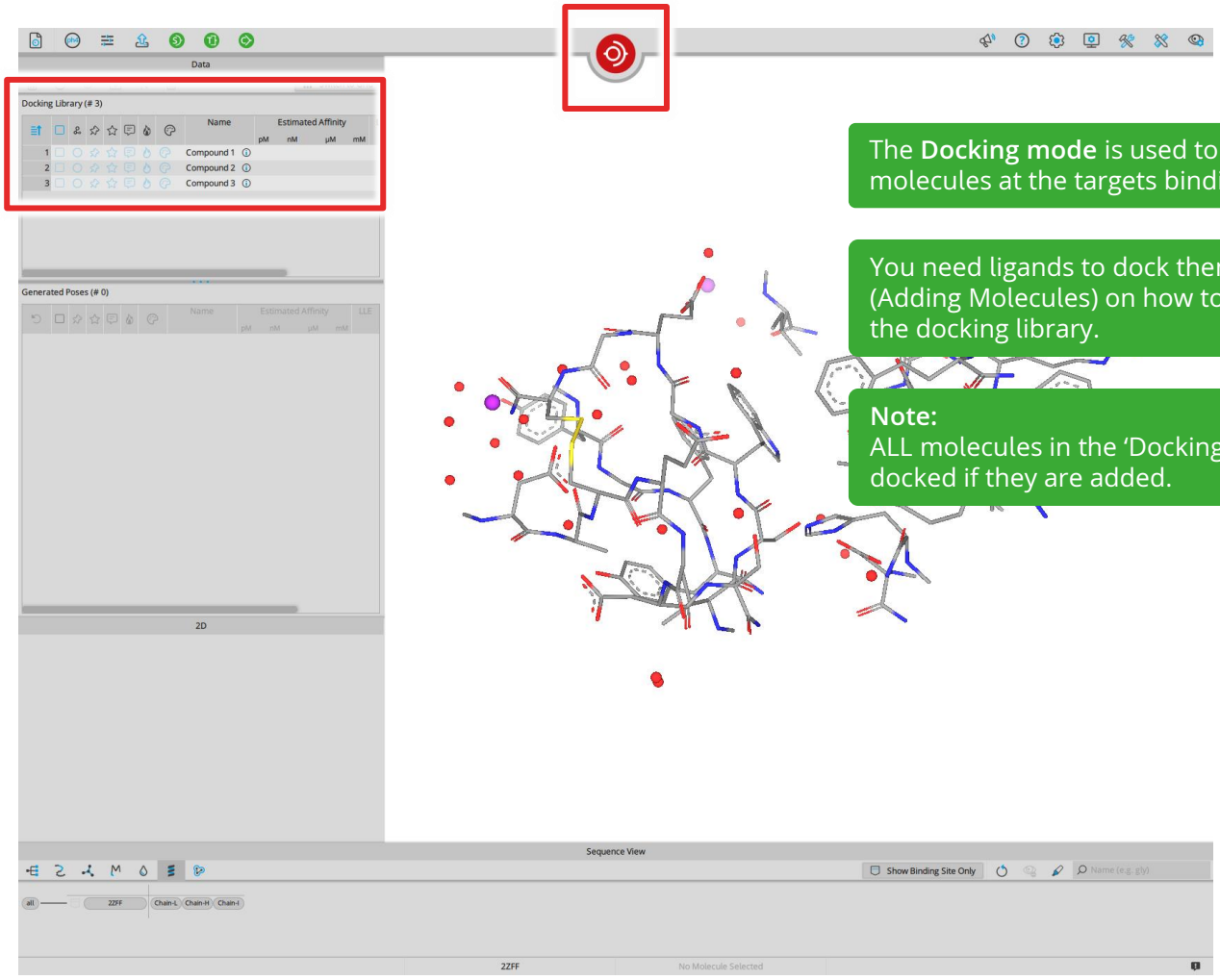
You can modify your molecule in the 2D and 3D window.
In 2D you can add rings and change the bond type.
In 3D it is also possible to select the hydrogen atoms and replace them with 'Change element' icon. You can also use hot keys for elements, e.g. use 'C' to change an atom to a carbon or 'N' to change it to a nitrogen.



Once you are finished, export the molecule to the table with ‘Save edited molecules to table’.

3. Docking

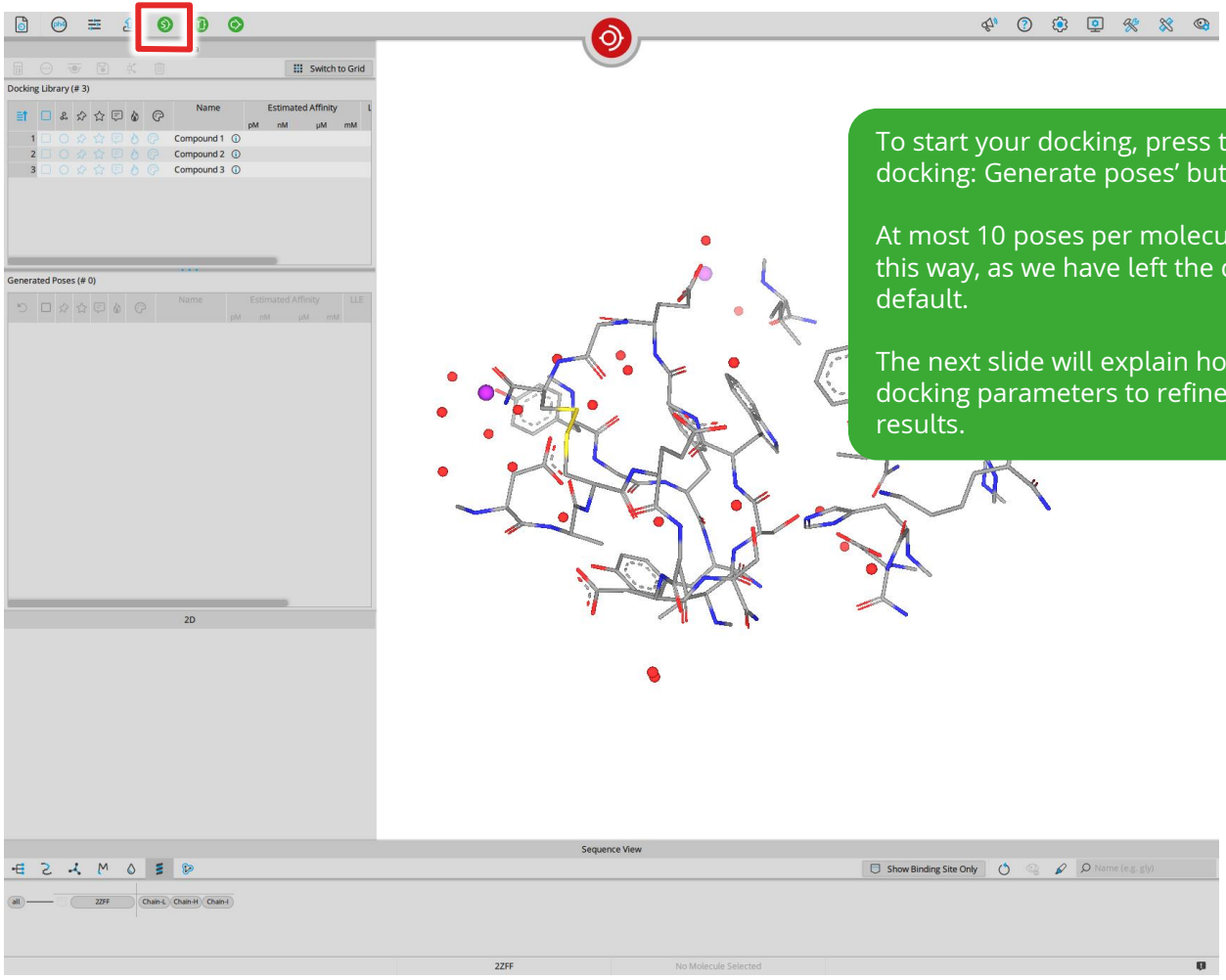

Data
Switch to Grid
Docking Library (# 3)
Name
Estimated Affinity
Compound 1
Compound 2
Compound 3
Generated Poses (# 30)
Checked (# 30)
Save Protein Molecule Complex
Delete [Del]
Calculate Estimated Affinity
Calculate H-bond Network
Calculate Torsion Quality
Calculate Molecular Clashes
Calculate Optibrium Properties
Add to Binding Site Mode
Add to Analyzer
Add to Molecule Editor
Add to Inspirator
Add to Similarity Scanner
H2N
N
NH
O
Sequence View
Show Binding Site Only
22FF
Compound 3_1_006



The **Docking mode** is used to place (= dock) molecules at the targets binding site.

You need ligands to dock them. See Section 2 (Adding Molecules) on how to add molecules to the docking library.

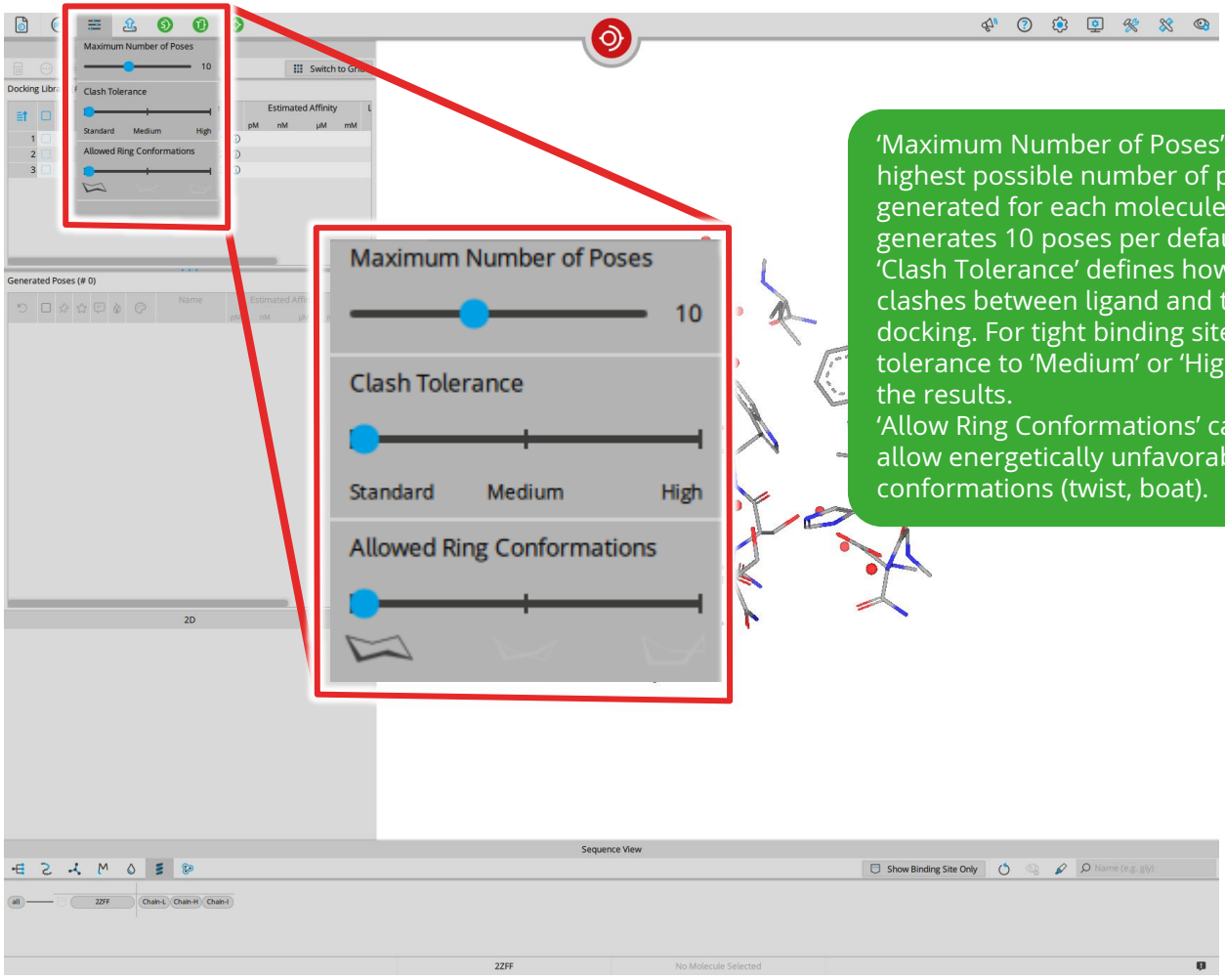
Note:
ALL molecules in the 'Docking library' will be docked if they are added.



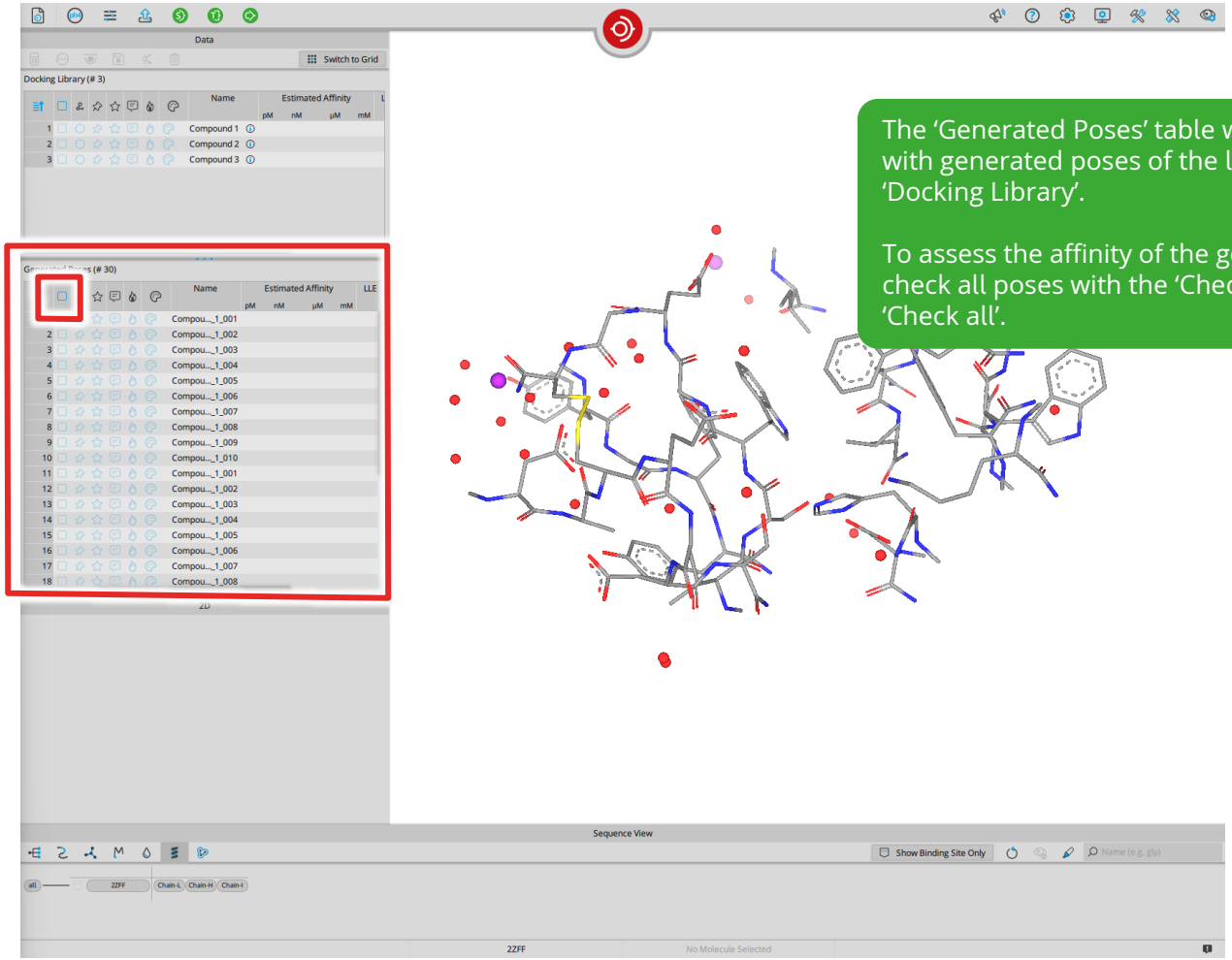
To start your docking, press the 'Standard docking: Generate poses' button.

At most 10 poses per molecule are generate this way, as we have left the docking settings on default.

The next slide will explain how to adjust docking parameters to refine your docking results.

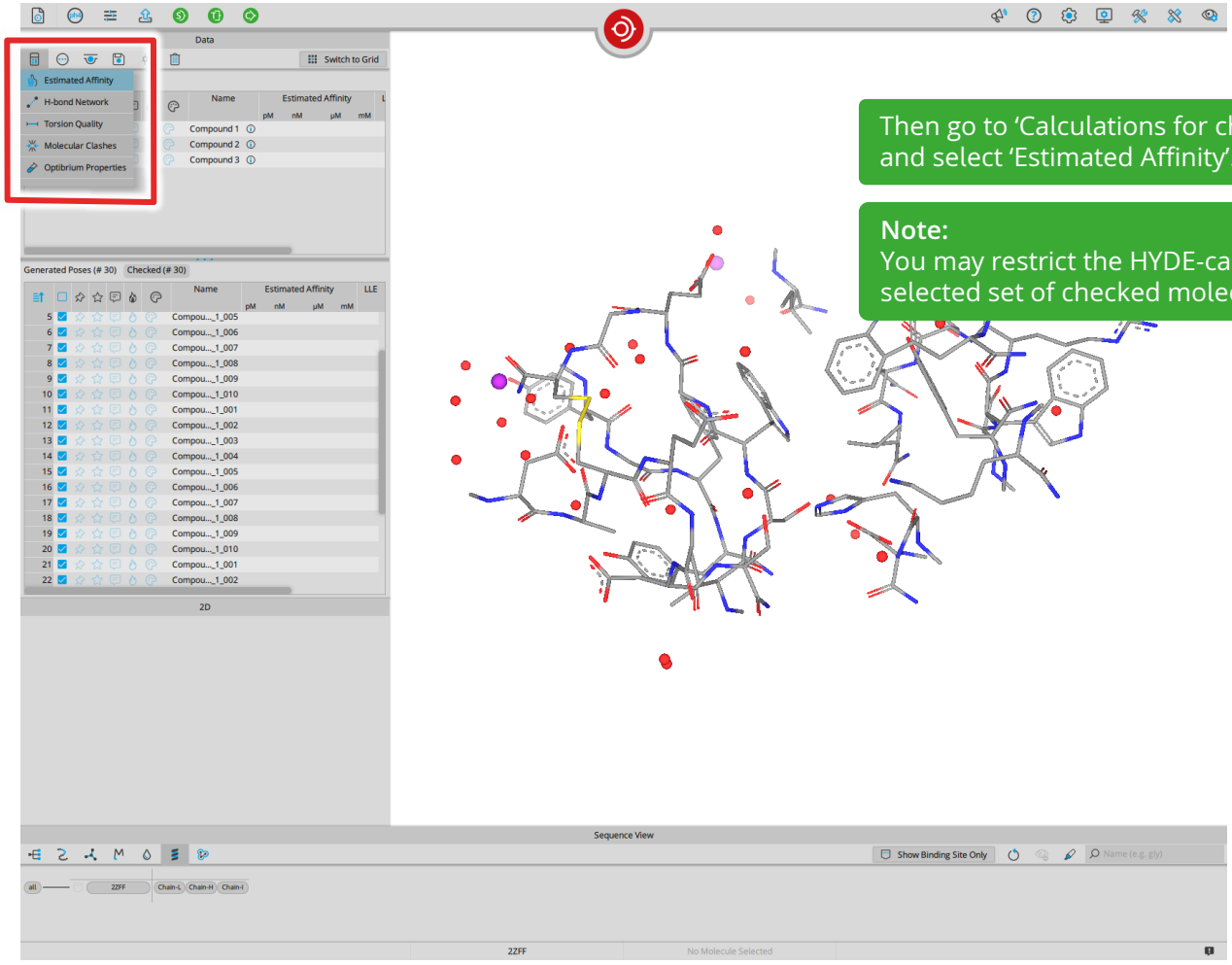


'Maximum Number of Poses' defines the highest possible number of poses that will be generated for each molecule. SeeSAR generates 10 poses per default.
'Clash Tolerance' defines how SeeSAR handles clashes between ligand and tartget during docking. For tight binding sites increase of the tolerance to 'Medium' or 'High' may improve the results.
'Allow Ring Conformations' can be used to allow energetically unfavorable ring conformations (twist, boat).



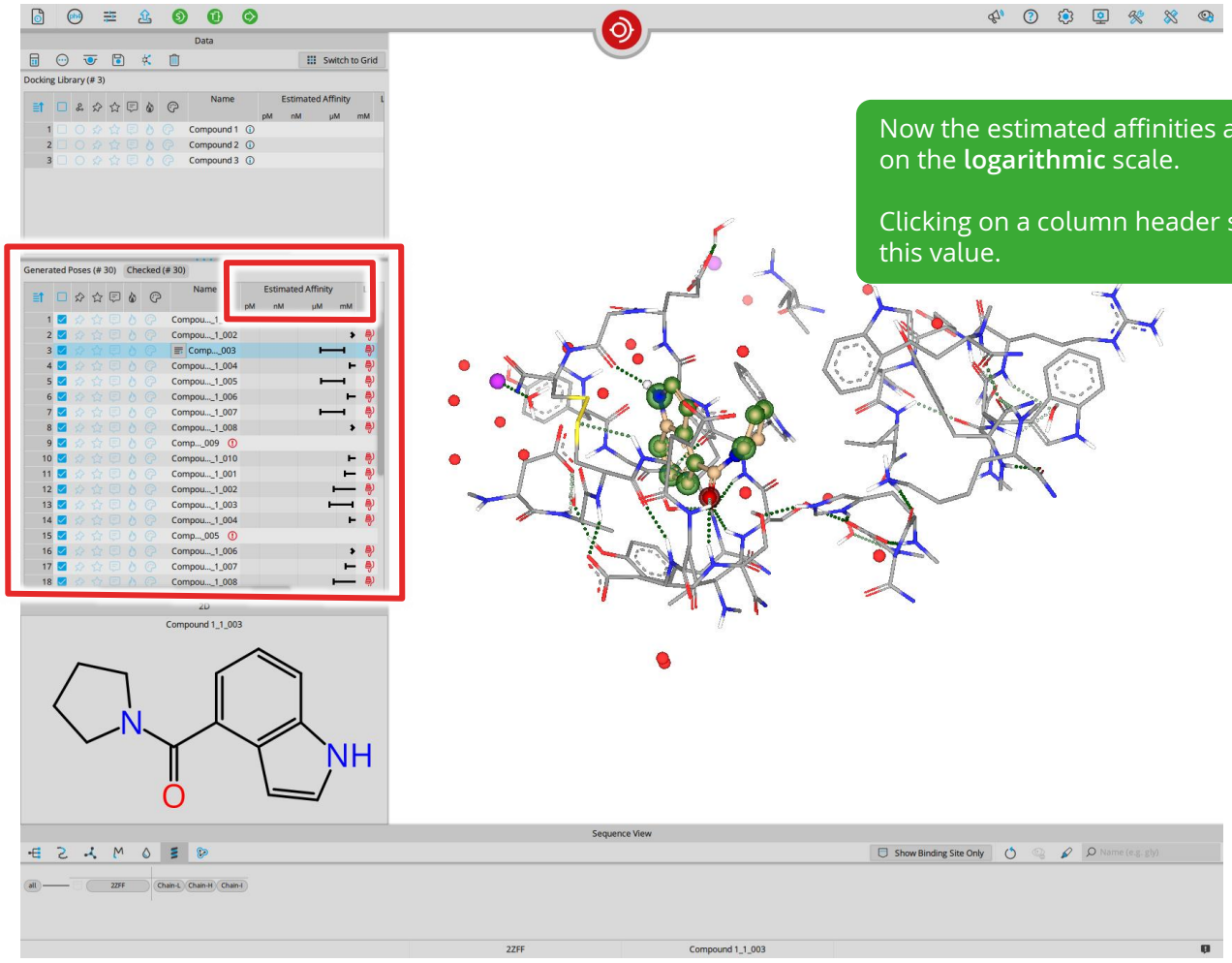
The ‘Generated Poses’ table will be populated with generated poses of the ligands from ‘Docking Library’.

To assess the affinity of the generated poses check all poses with the ‘Checked’ column and ‘Check all’.



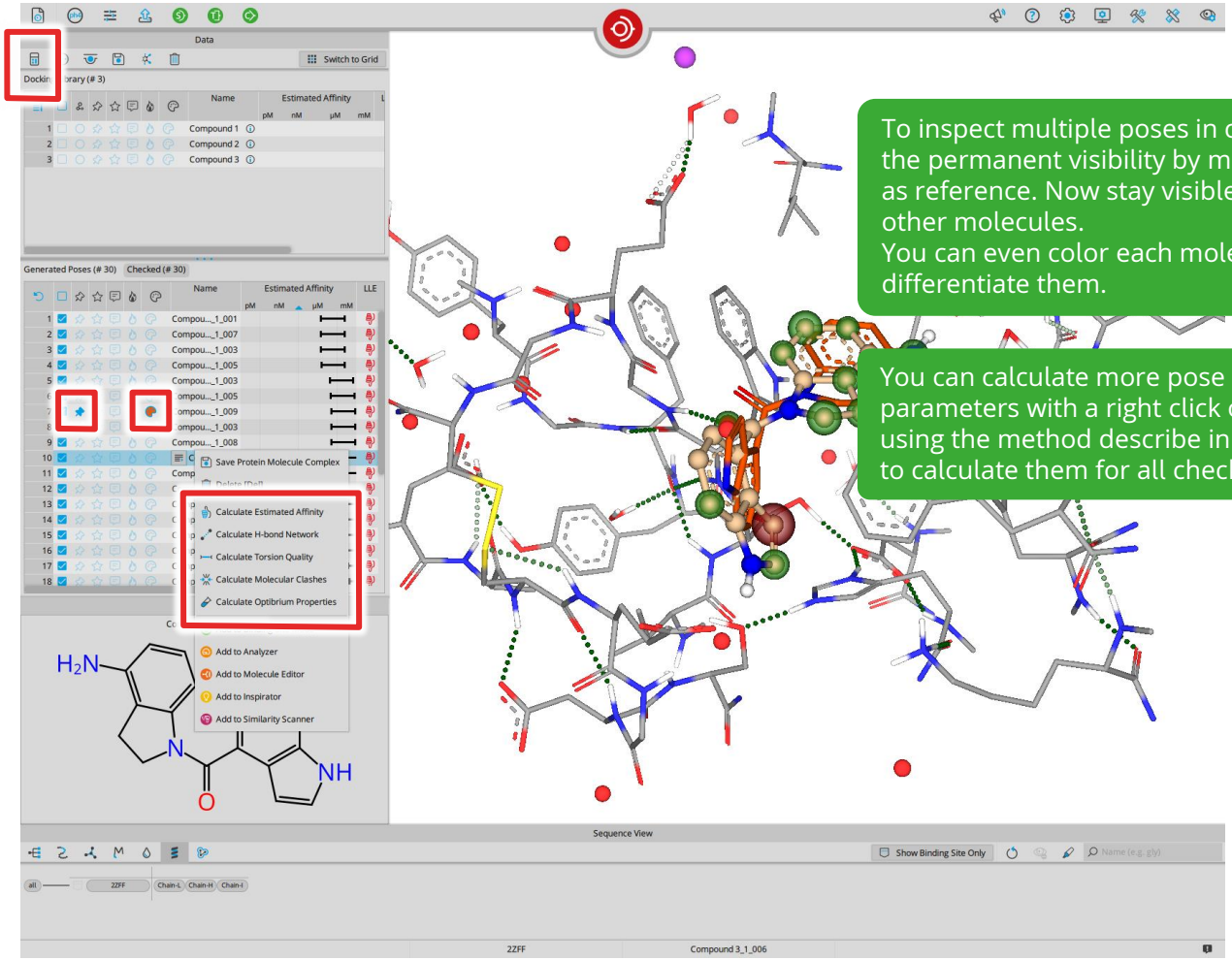
Then go to ‘Calculations for checked molecules’ and select ‘Estimated Affinity’.

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



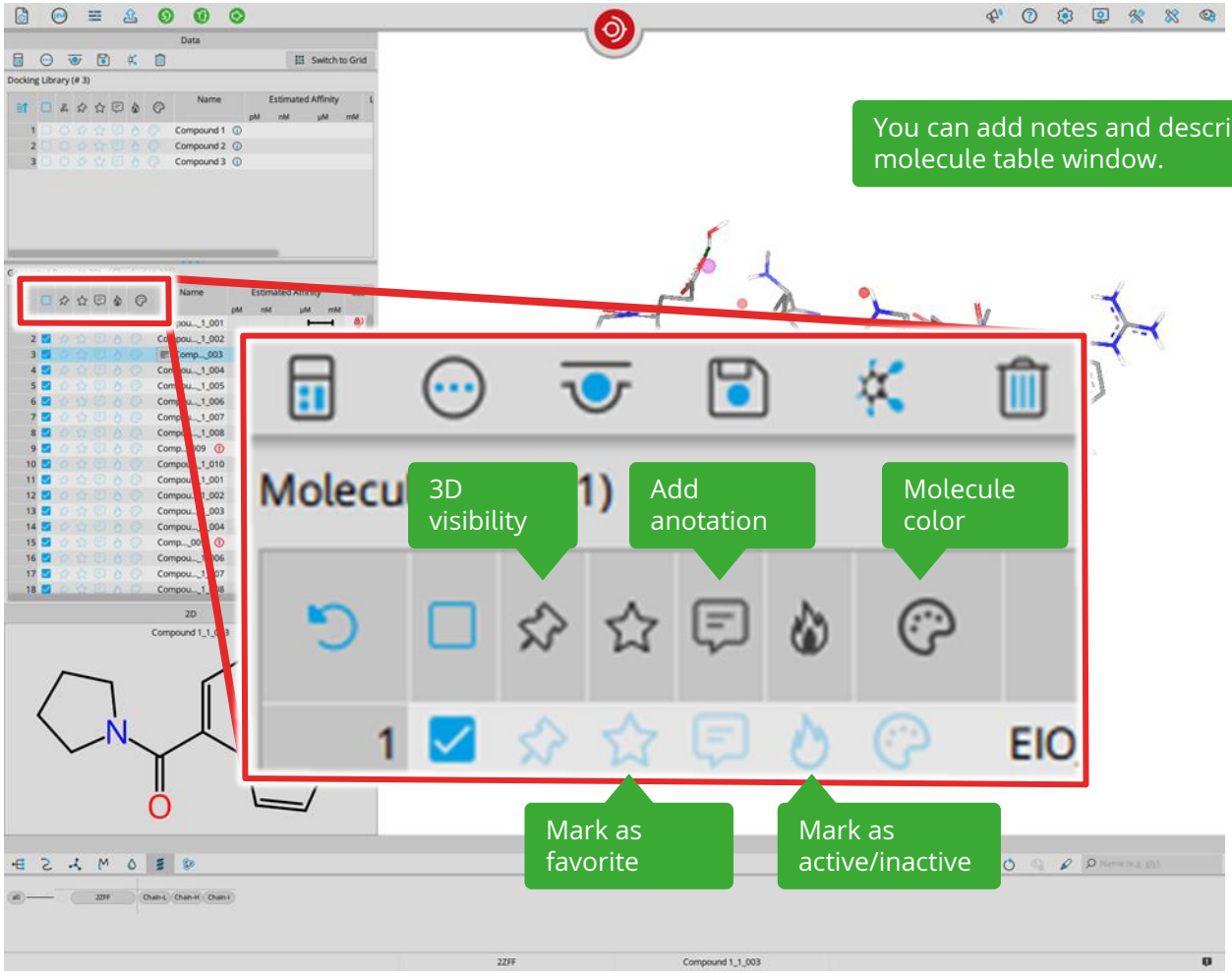
Now the estimated affinities appear as a range on the **logarithmic** scale.

Clicking on a column header sorts according to this value.

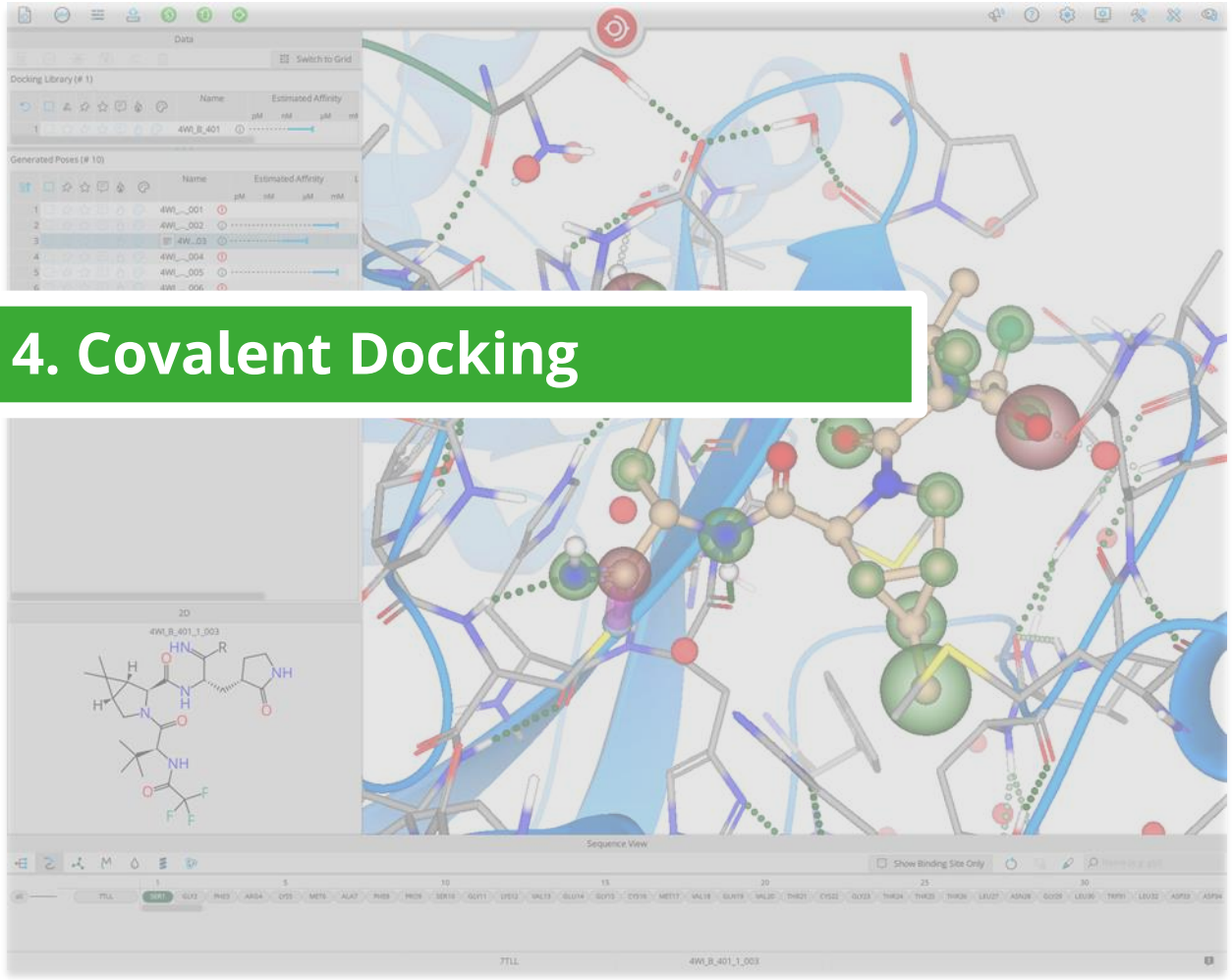


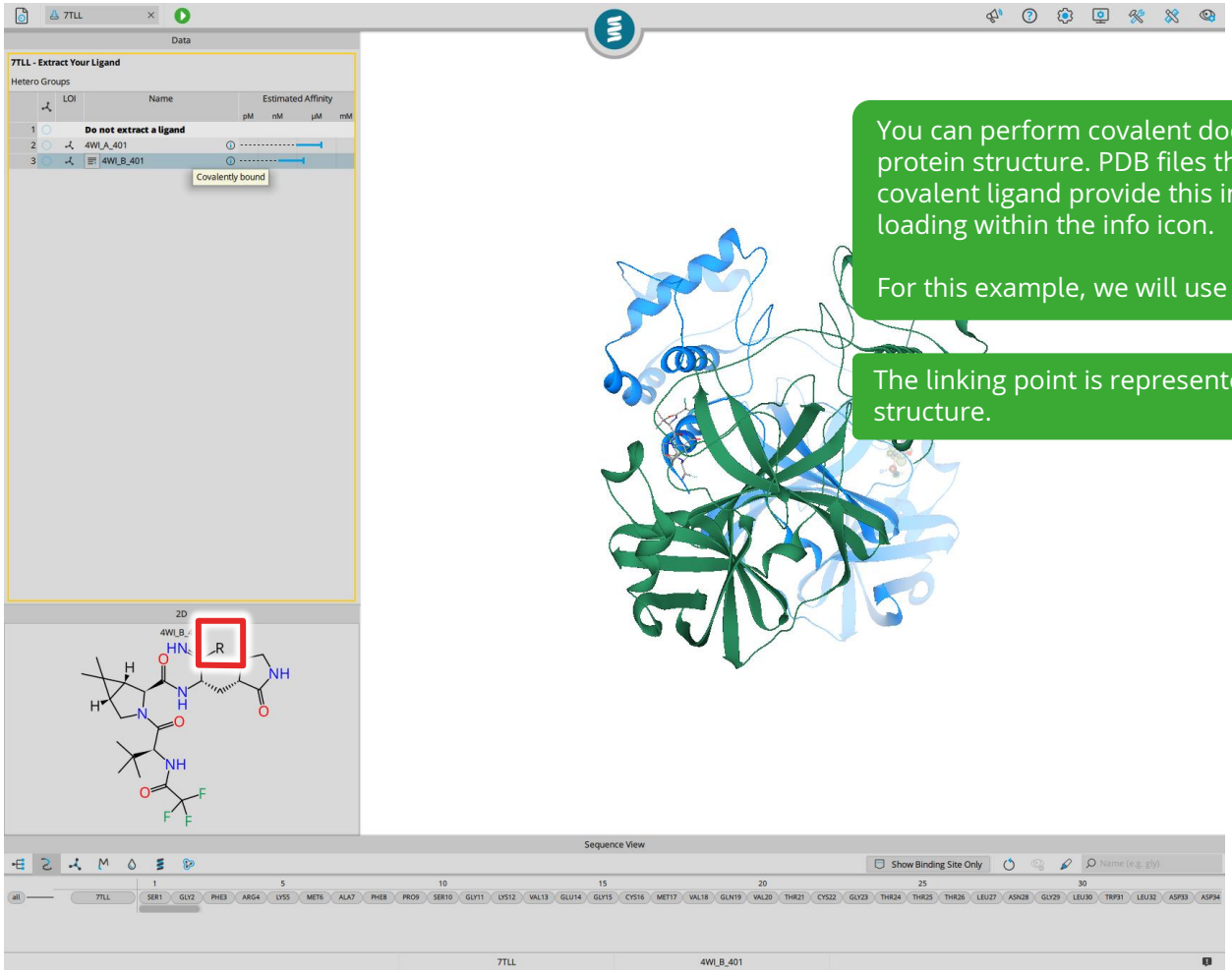
To inspect multiple poses in comparison, toggle the permanent visibility by marking a molecule as reference. Now stay visible as you select other molecules.
You can even color each molecule to differentiate them.

You can calculate more pose 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.


You can add notes and descriptors in the molecule table window.
3D visibility
Add anotation
Molecule color
Mark as favorite
Mark as active/inactive

4. Covalent Docking

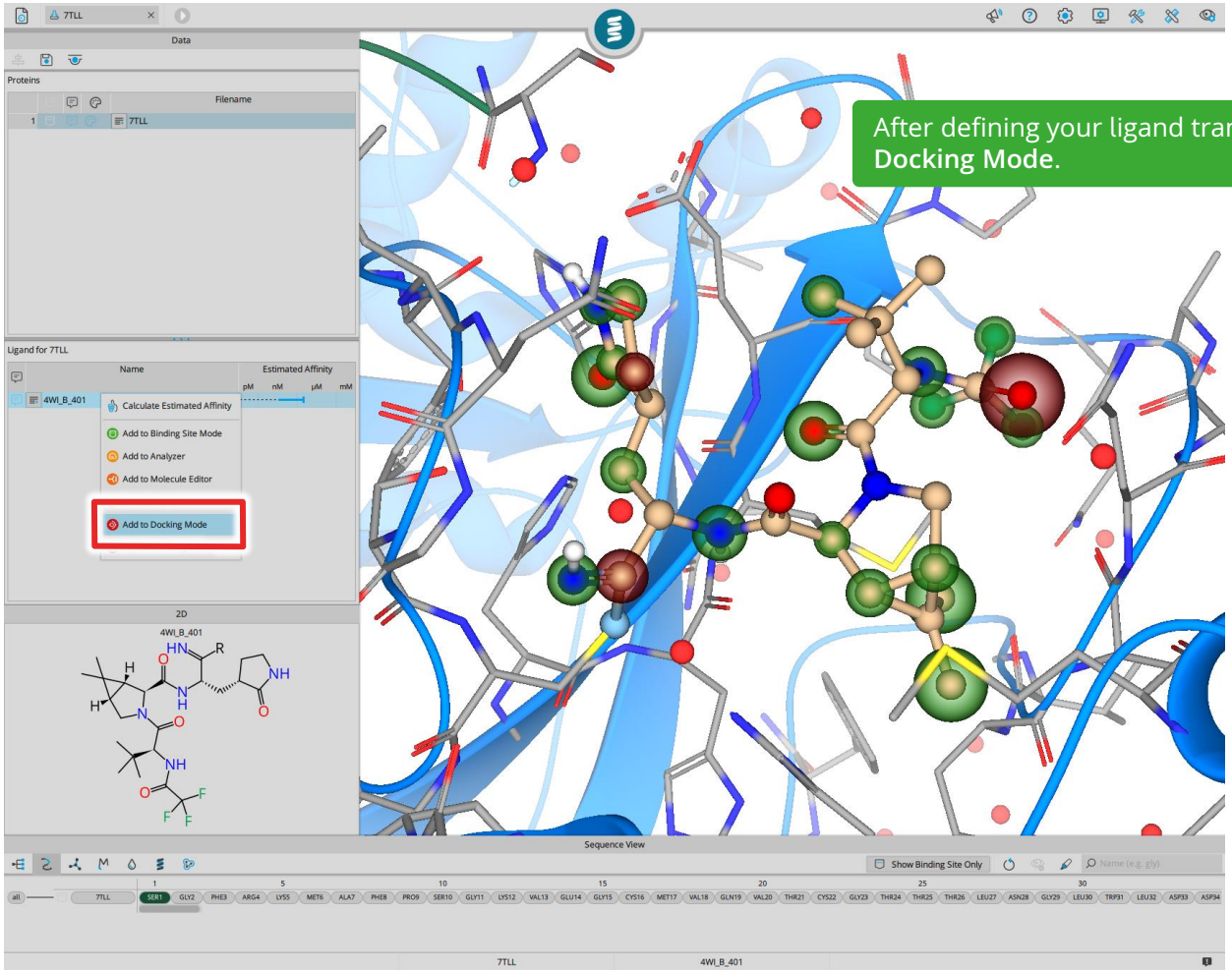




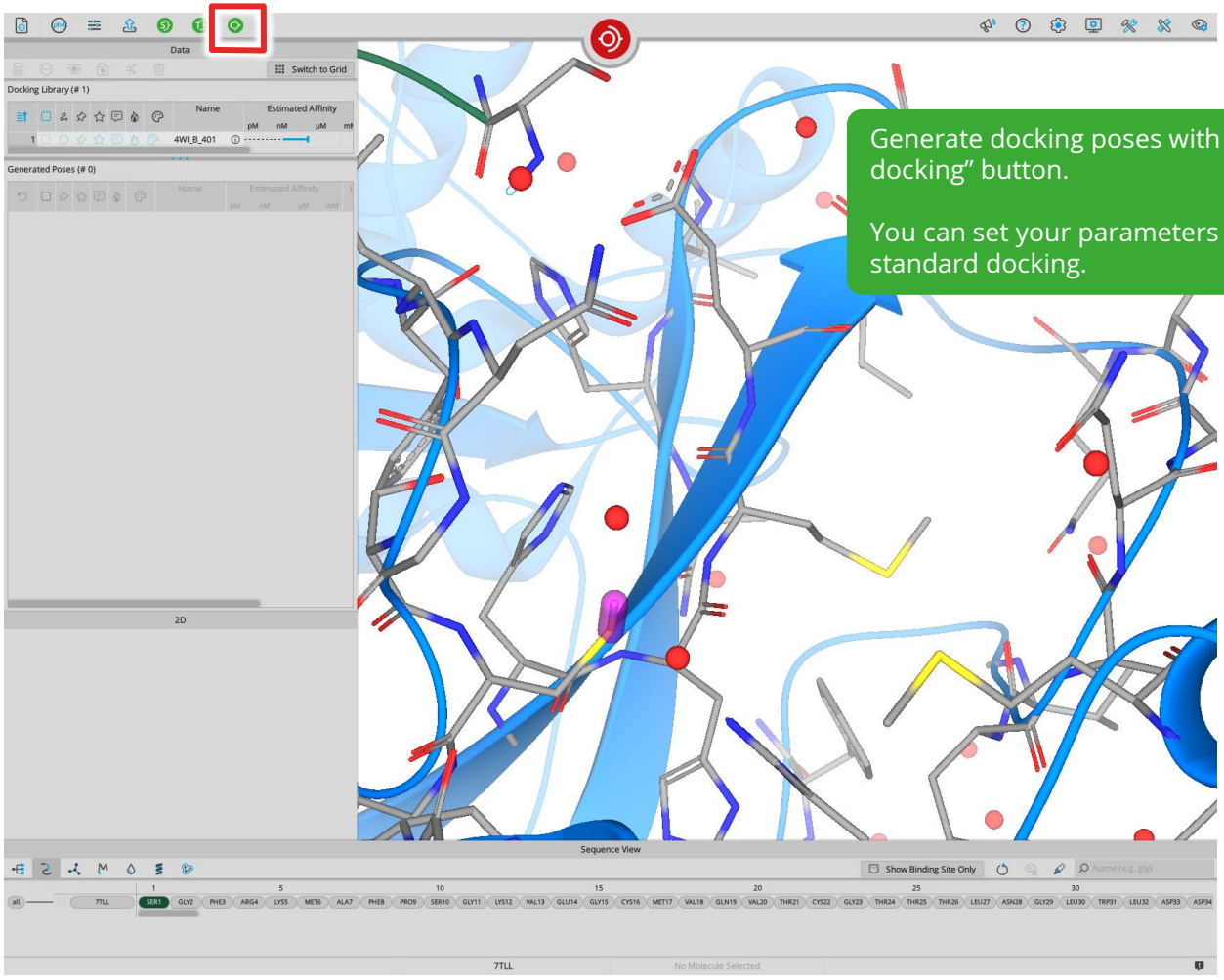
You can perform covalent docking at any PDB protein structure. PDB files that contain a covalent ligand provide this information upon loading within the info icon.

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

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

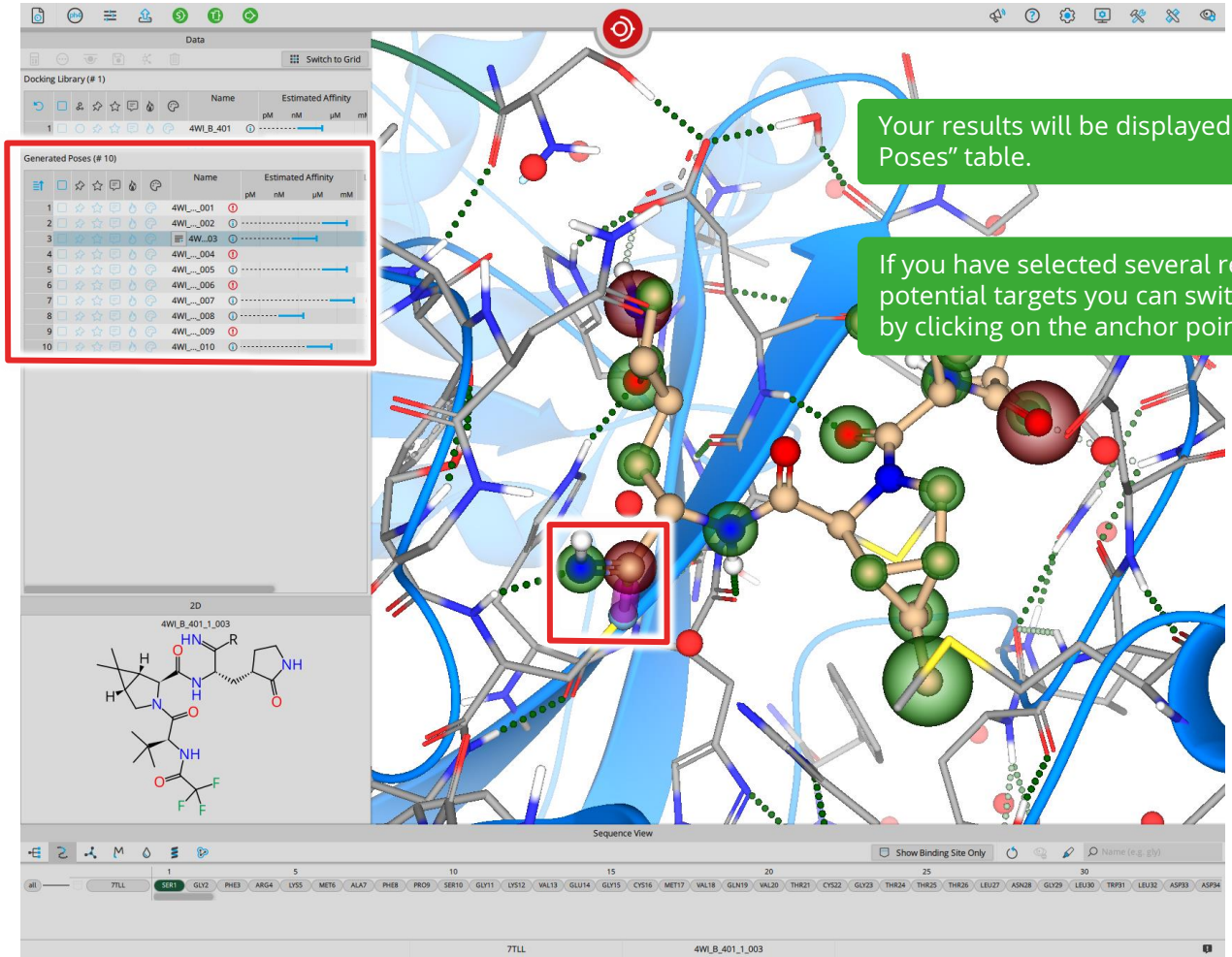


After defining your ligand transfer it to the **Docking Mode**.



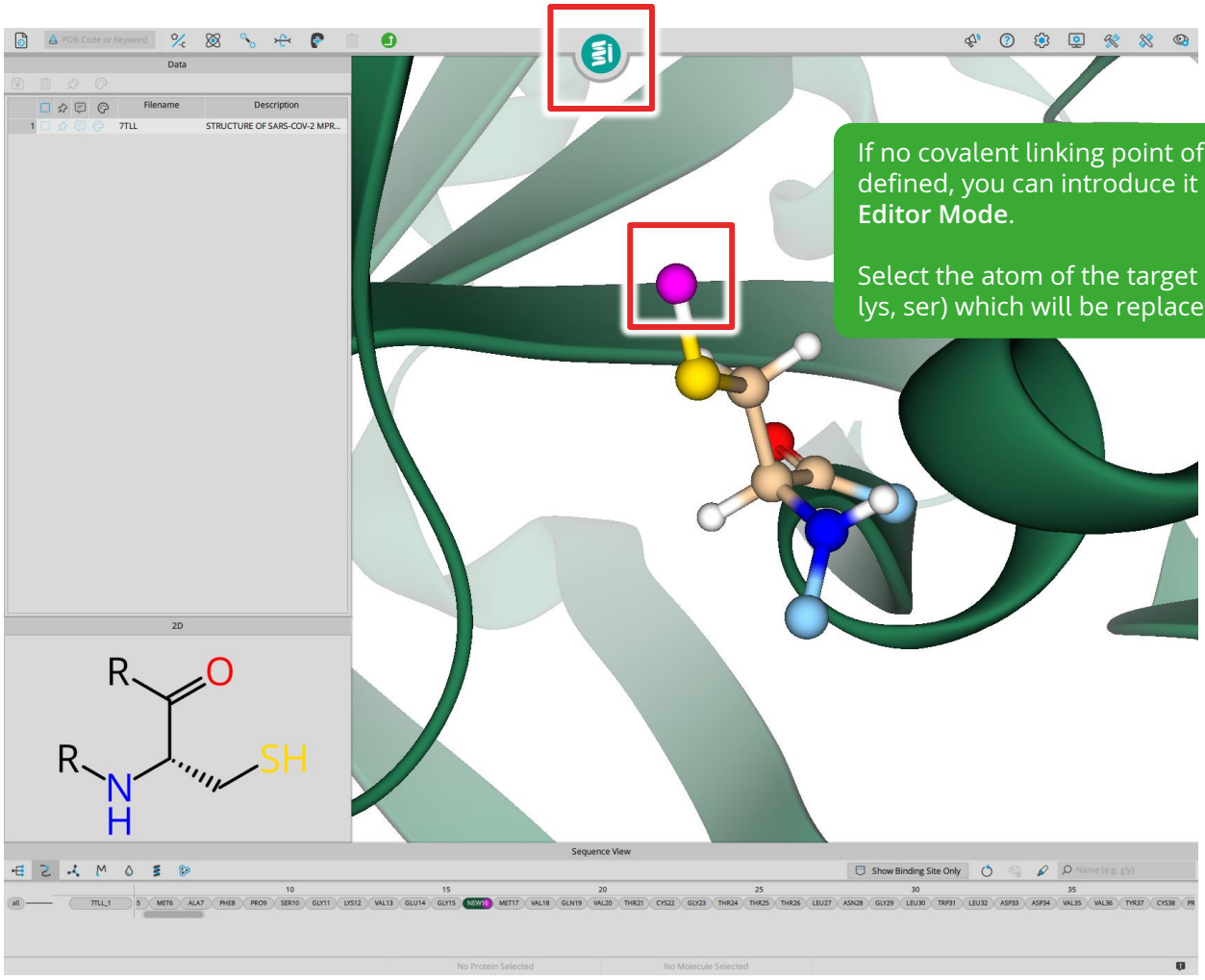
Generate docking poses with the “Covalent docking” button.

You can set your parameters the same as for standard docking.



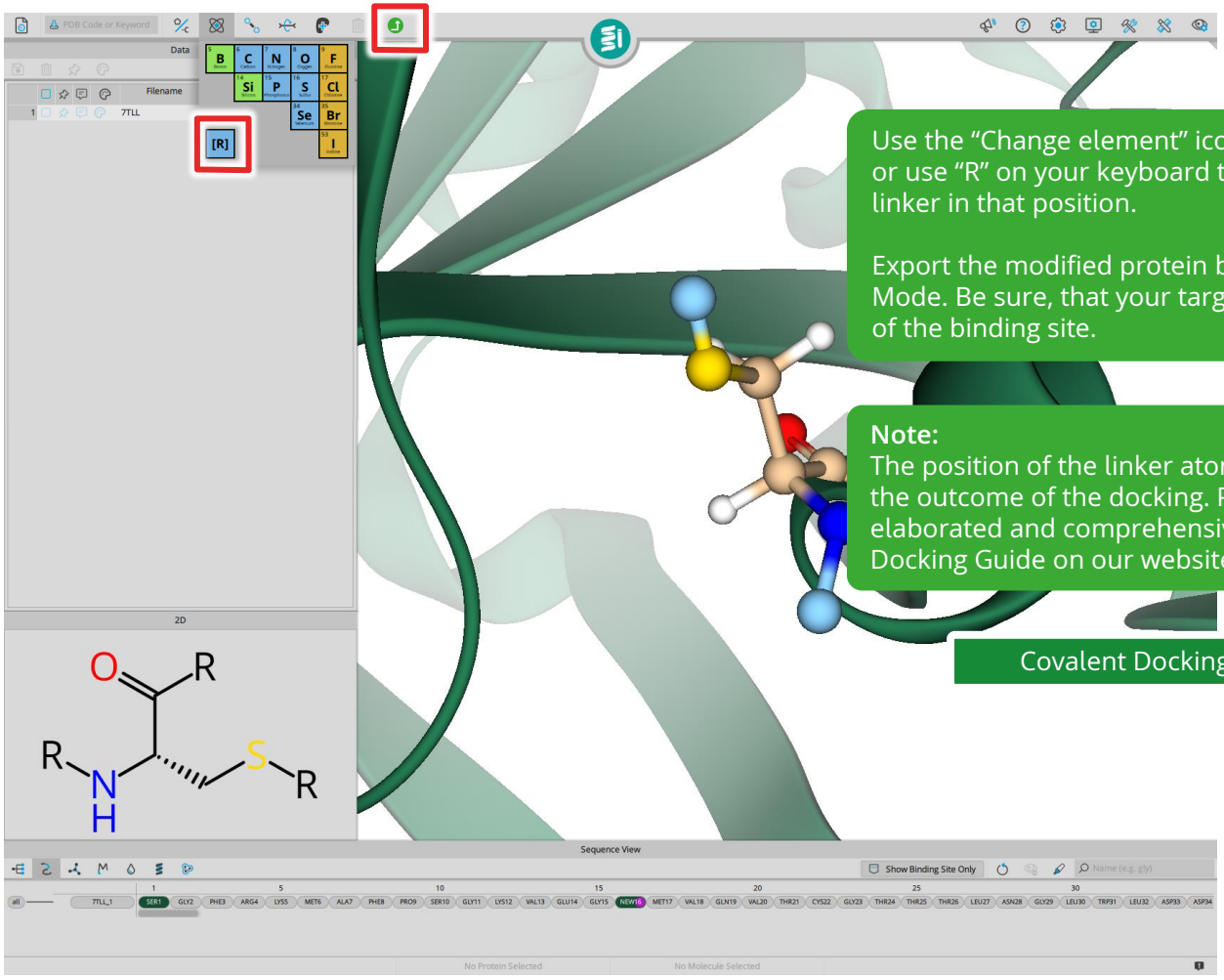
Your results will be displayed in the “Generated Poses” table.

If you have selected several residues as potential targets you can switch between them by clicking on the anchor point.



If no covalent linking point of the structure is defined, you can introduce it in the **Protein Editor Mode**.

Select the atom of the target residue (e.g. cys, lys, ser) which will be replaced with the ligand.

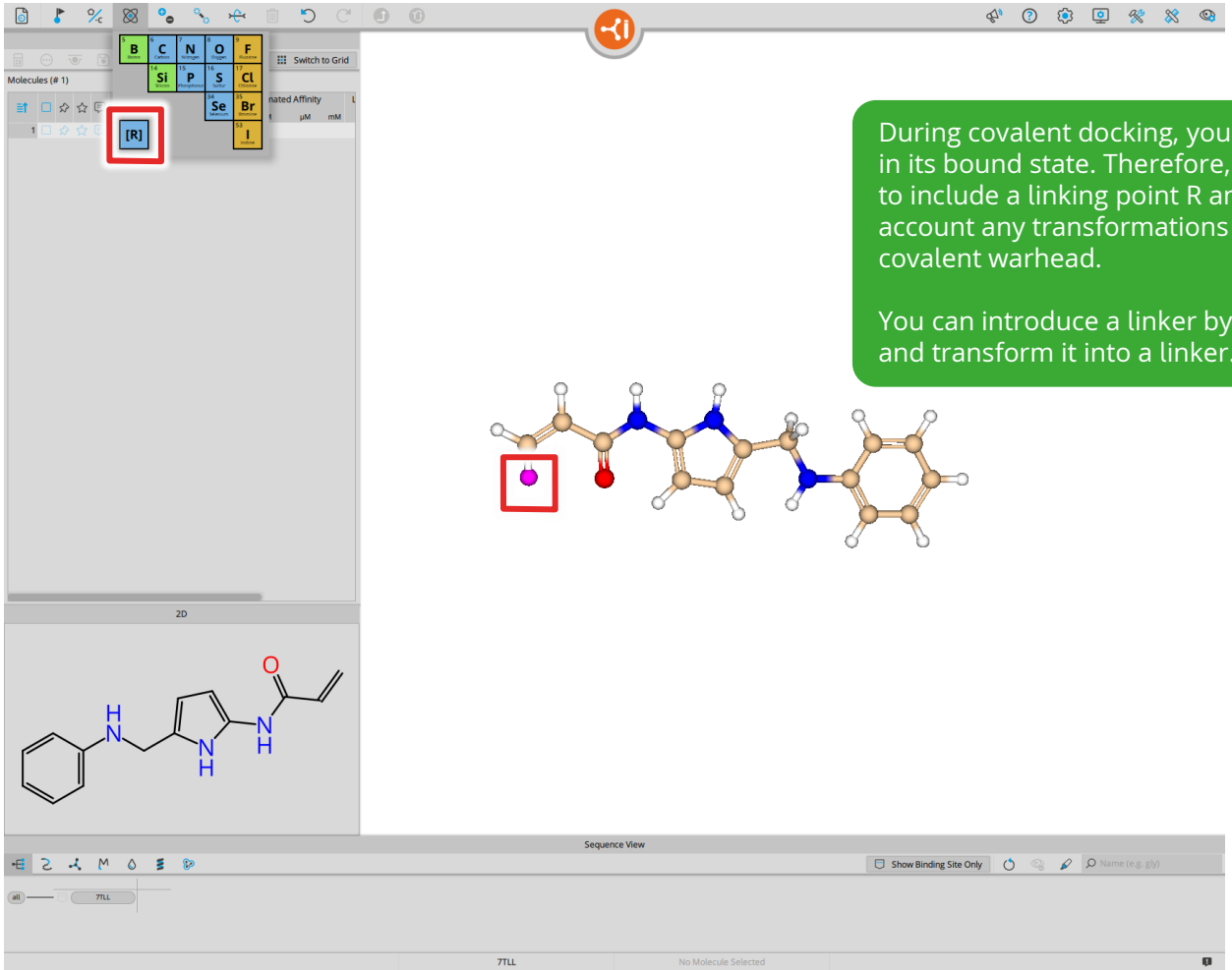


Use the “Change element” icon and select “[R]” or use “R” on your keyboard to introduce a linker in that position.

Export the modified protein back to the Protein Mode. Be sure, that your target residue is part of the binding site.

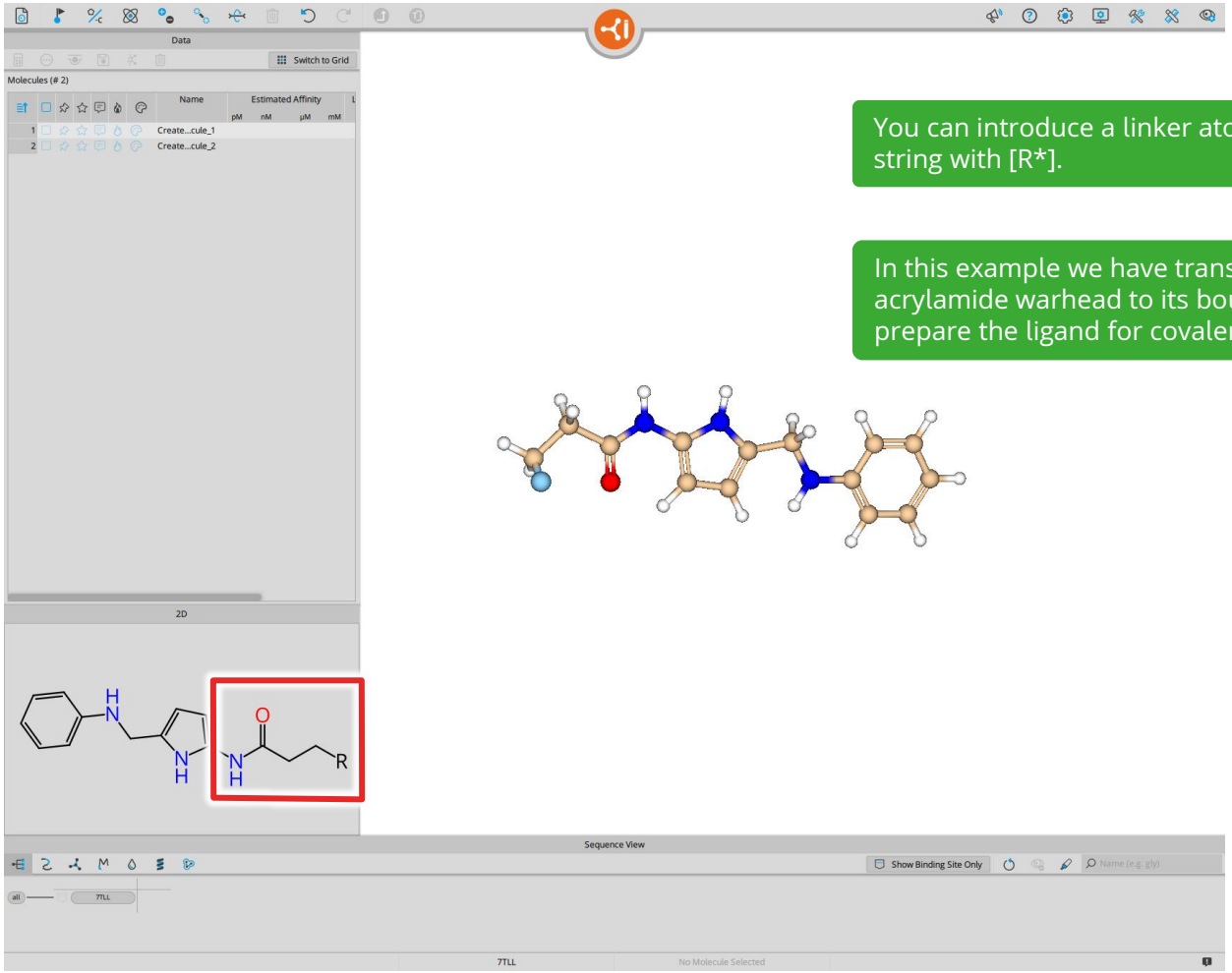
Note:
The position of the linker atom is important for the outcome of the docking. Please check the elaborated and comprehensive Covalent Docking Guide on our website for more details:

Covalent Docking Guide



During covalent docking, your ligand is docked in its bound state. Therefore, your structure has to include a linking point R and take into account any transformations that occur at the covalent warhead.

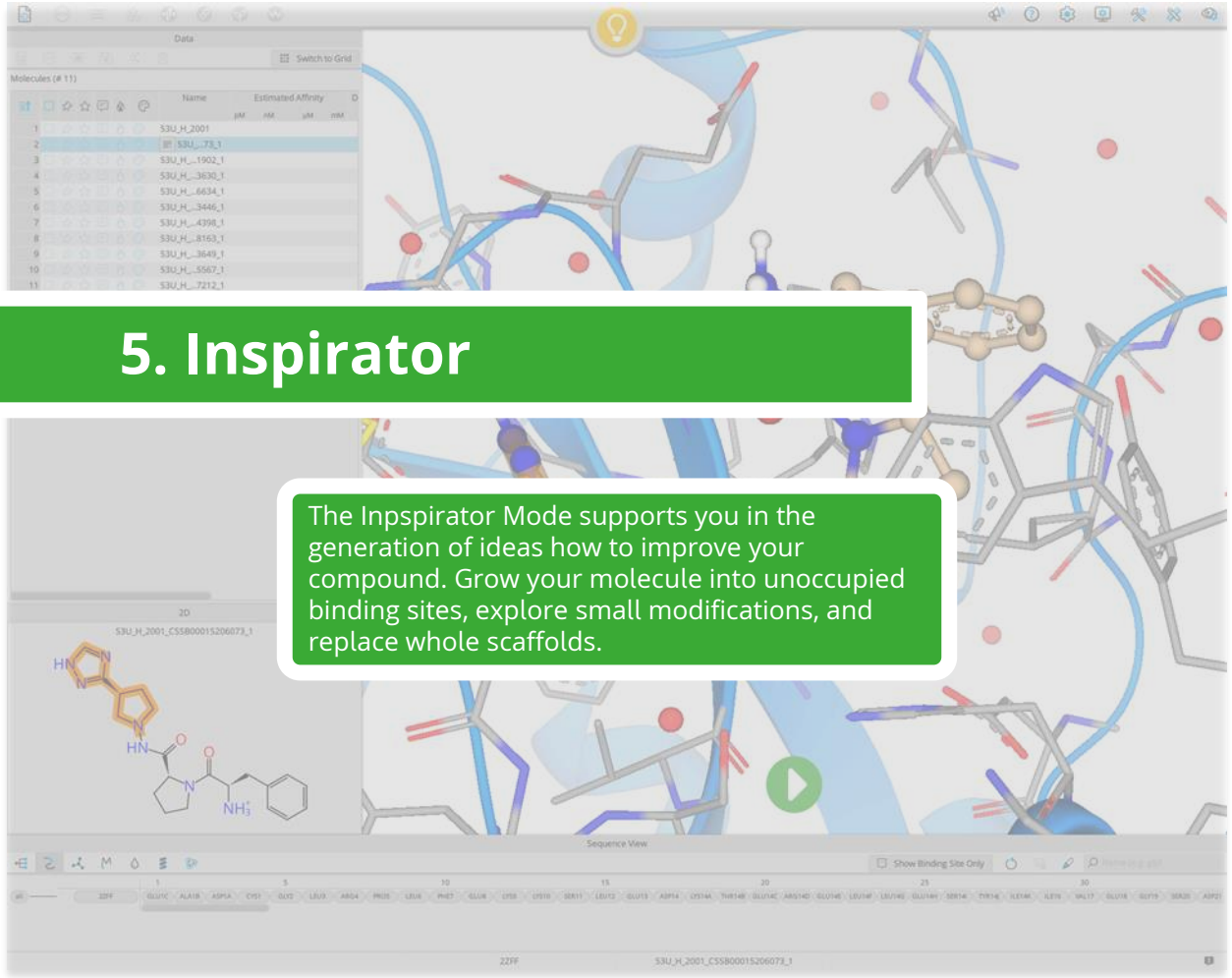
You can introduce a linker by selecting an atom and transform it into a linker.



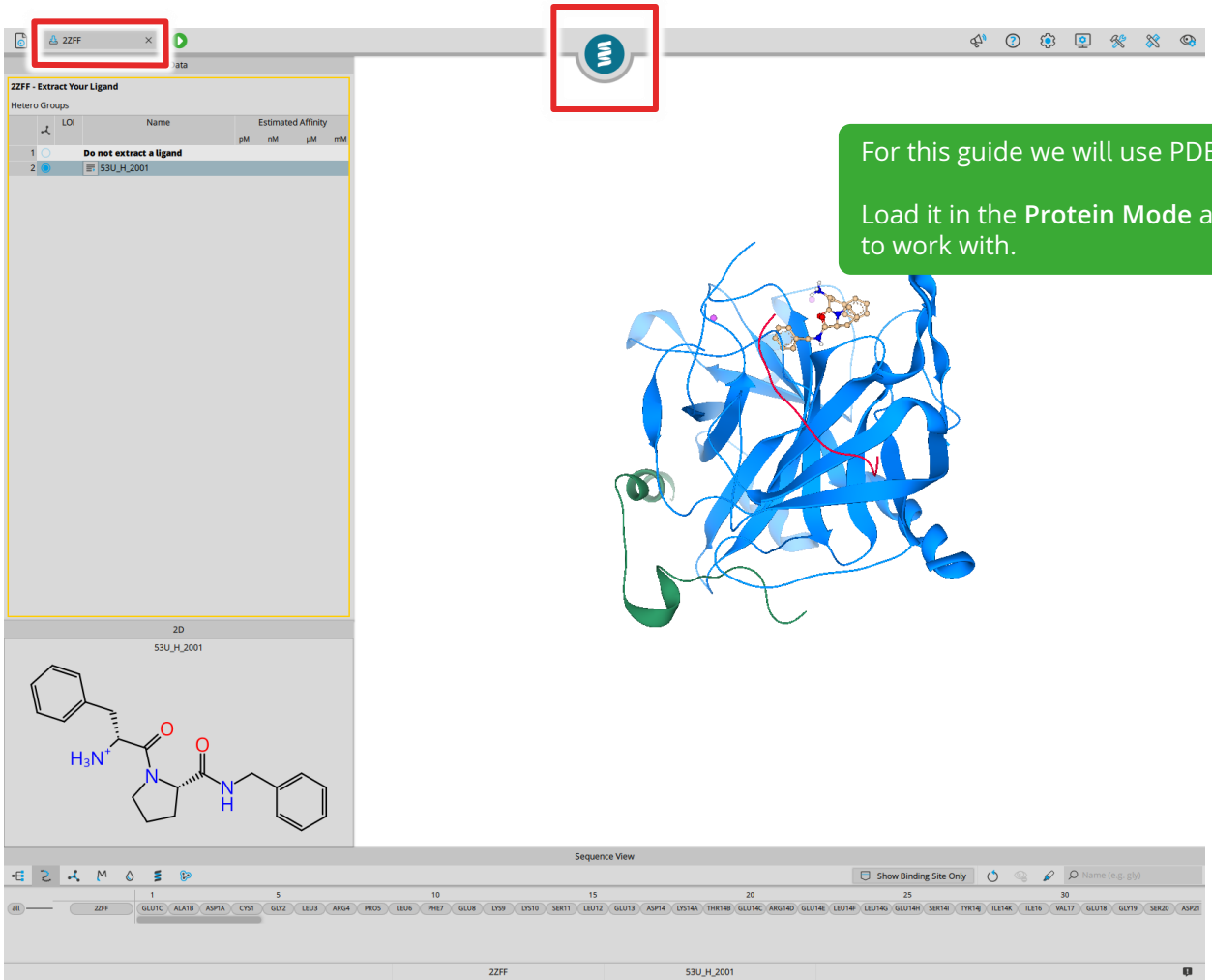
You can introduce a linker atom to your SMILES string with [R*].

In this example we have transformed an acrylamide warhead to its bound form to prepare the ligand for covalent docking.

5. Inspirator

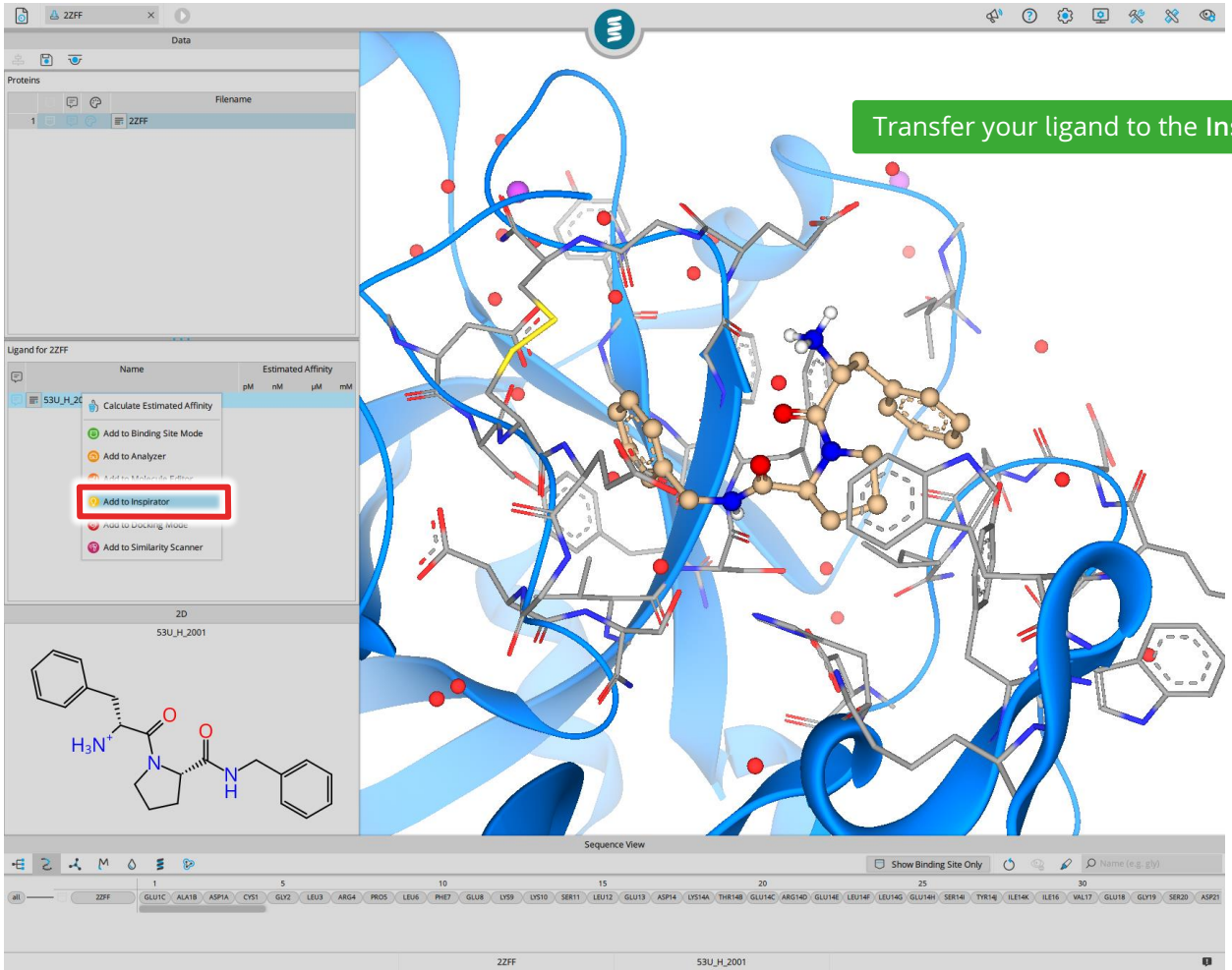


The Inpspirator Mode supports you in the generation of ideas how to improve your compound. Grow your molecule into unoccupied binding sites, explore small modifications, and replace whole scaffolds.

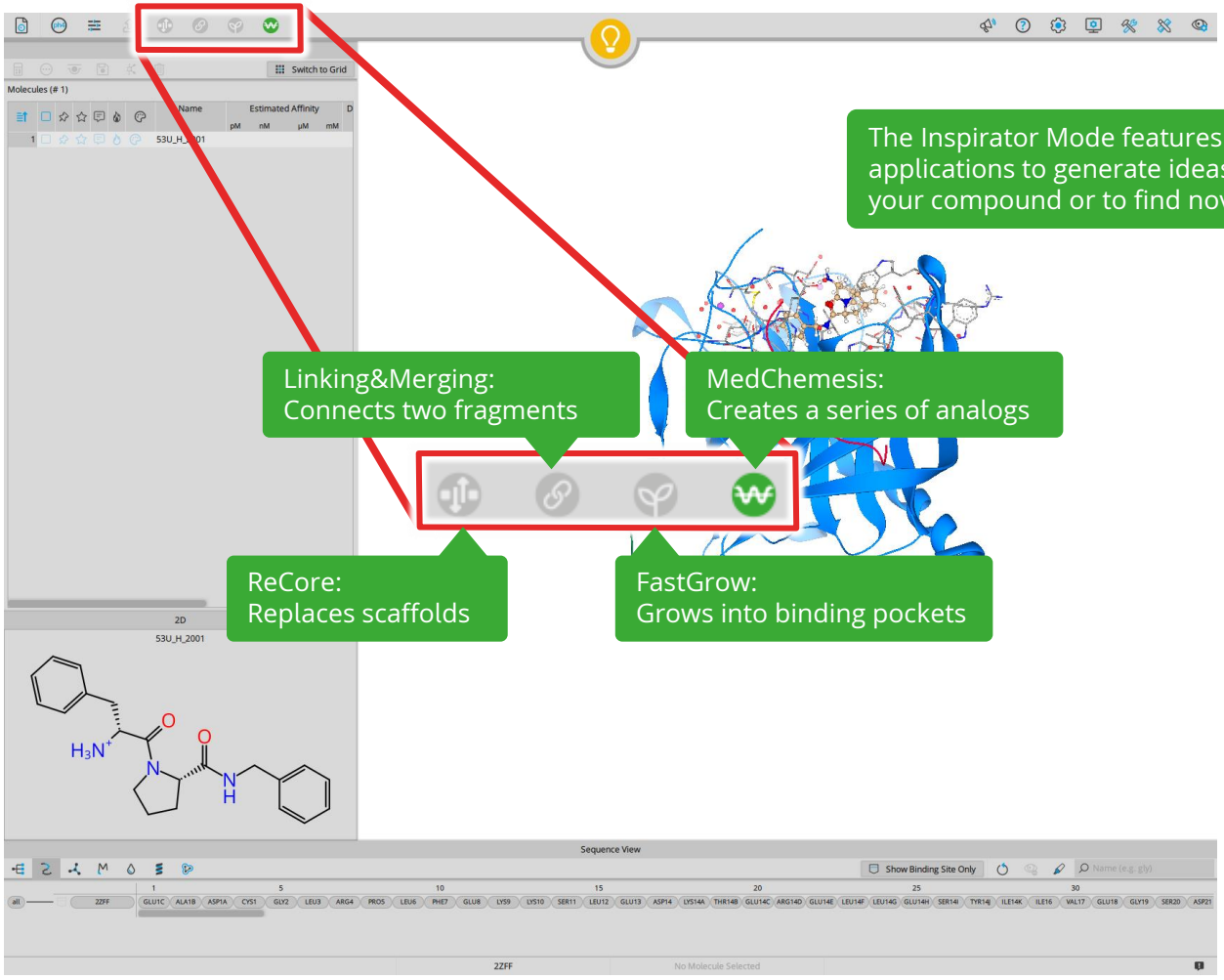


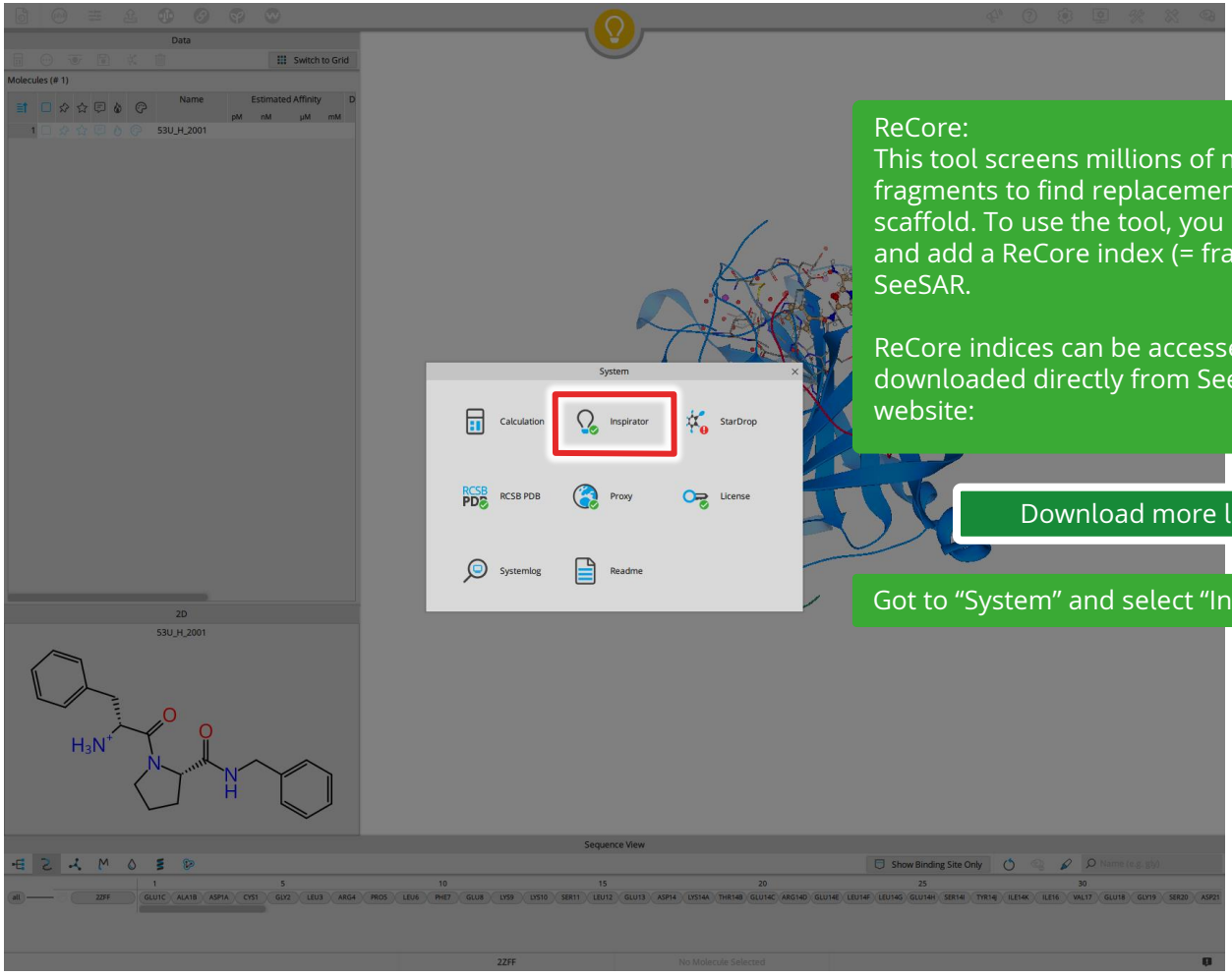
For this guide we will use PDB **2ZFF** as example.

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



Transfer your ligand to the **Inspirator Mode**.


The Inspirator Mode features several tools and applications to generate ideas how to improve your compound or to find novel scaffolds.
Linking&Merging:
Connects two fragments
MedChemesis:
Creates a series of analogs
ReCore:
Replaces scaffolds
FastGrow:
Grows into binding pockets
Switch to Grid
Molecules (# 1)
Name
Estimated Affinity
2D
53U_H_2001
Sequence View
Show Binding Site Only
2ZFF
No Molecule Selected

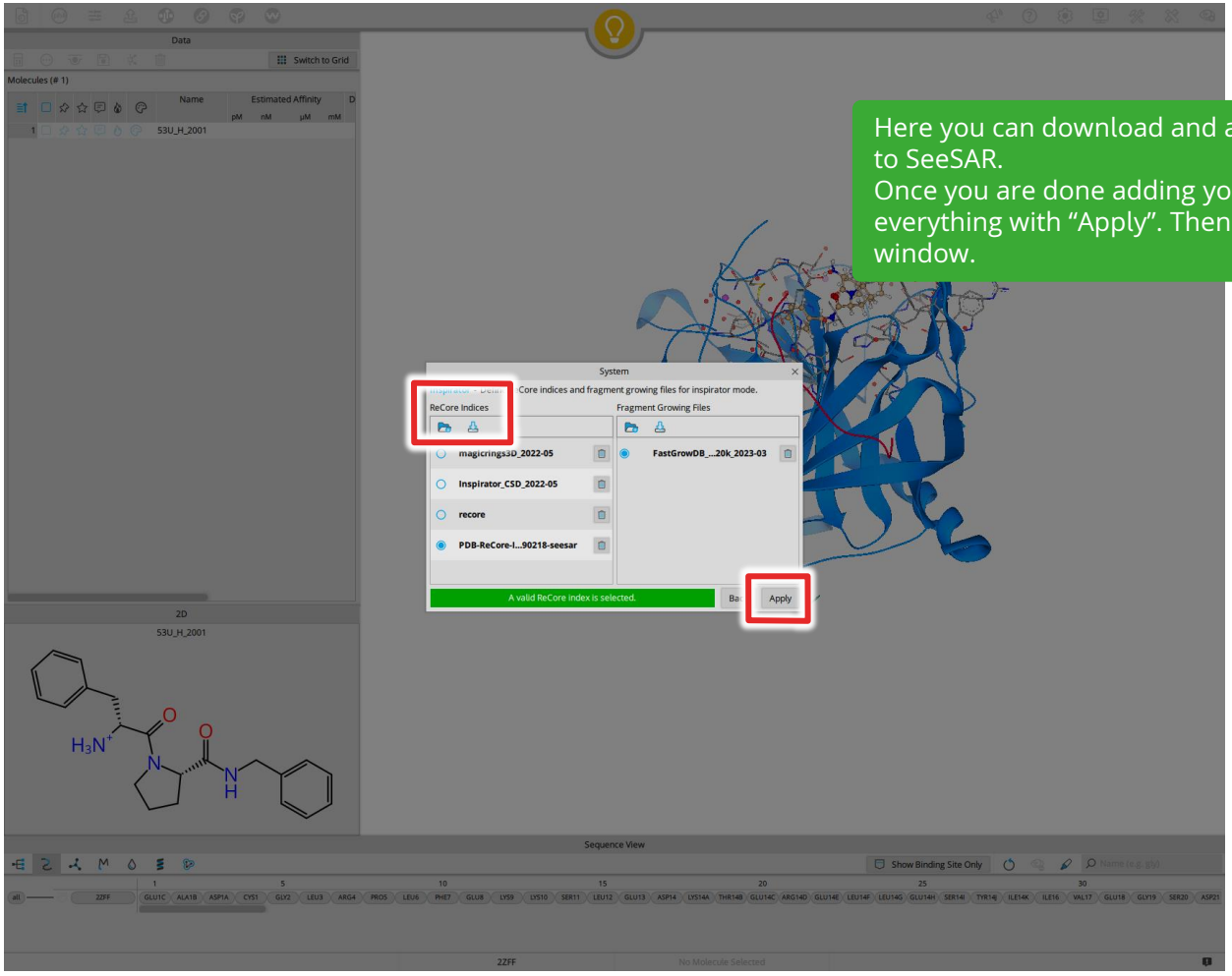


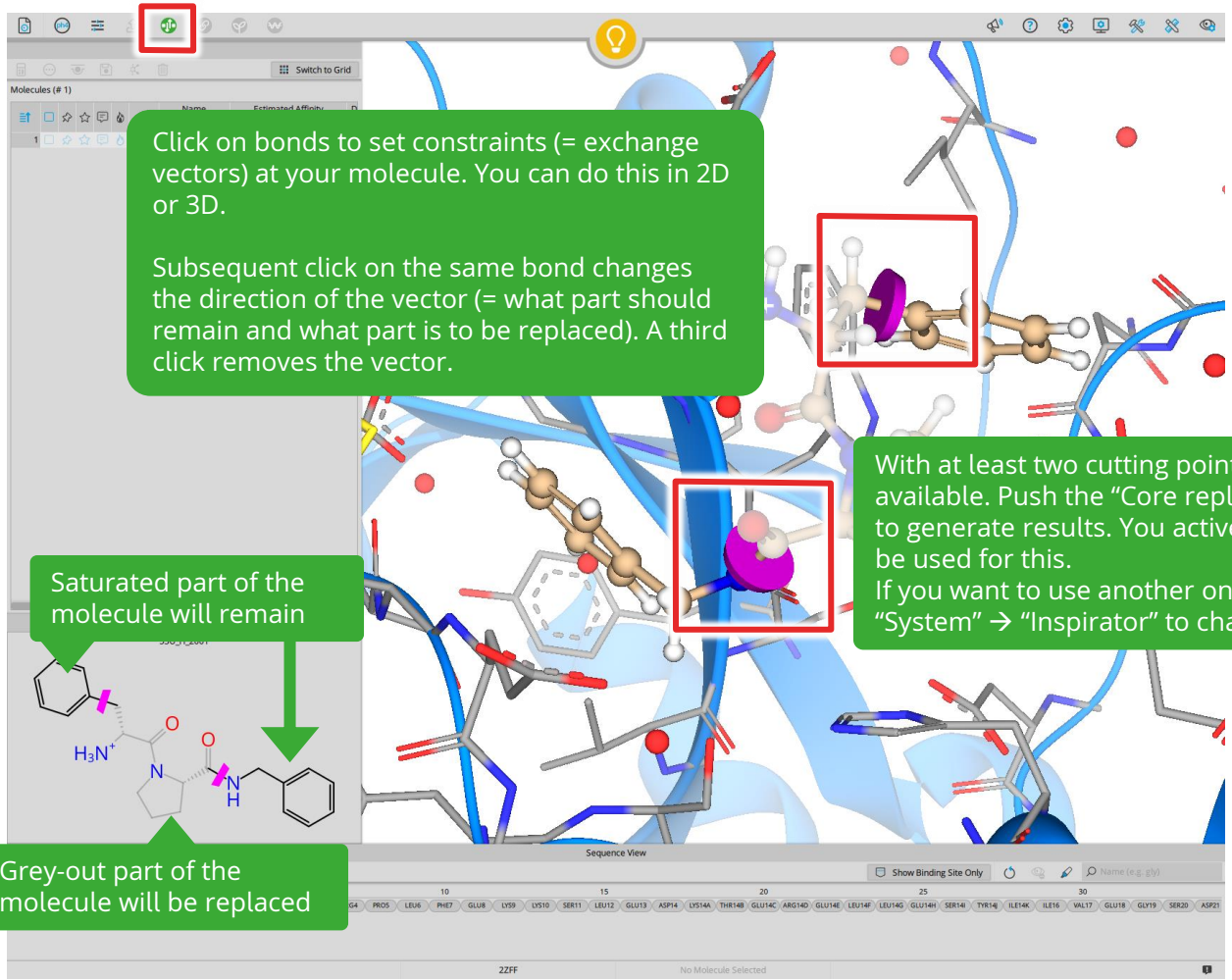
ReCore:
This tool screens millions of molecular fragments to find replacements for a 3D scaffold. To use the tool, you need to download and add a ReCore index (= fragment library) to SeeSAR.

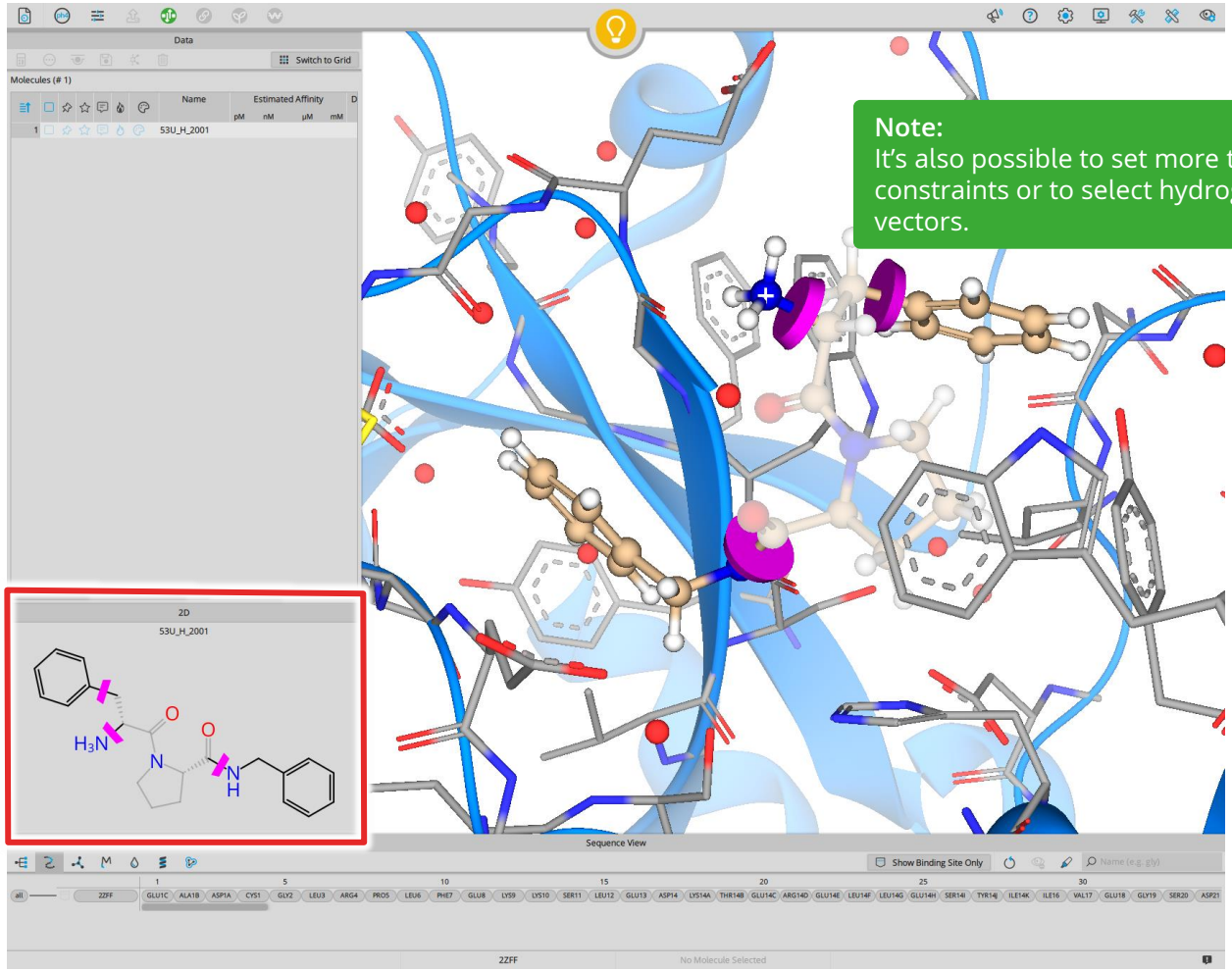
ReCore indices can be accessed and downloaded directly from SeeSAR or from our website:

Download more libraries

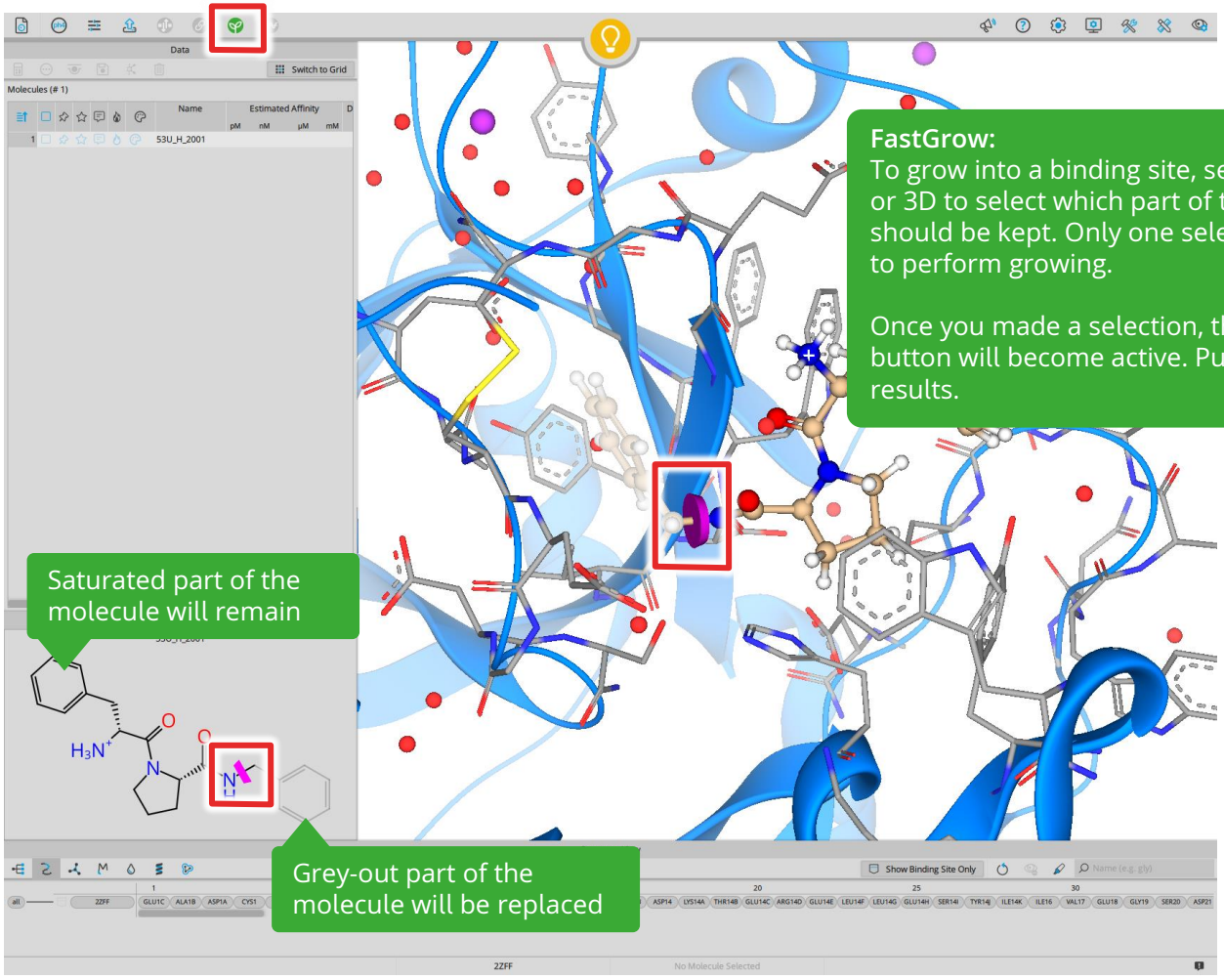
Got to “System” and select “Inspirator”.


Here you can download and add ReCore indices to SeeSAR.
Once you are done adding your indices, confirm everything with “Apply”. Then you can close the window.
System
Core indices and fragment growing files for inspirator mode.
ReCore Indices
Fragment Growing Files
magicrings3D_2022-05
Inspirator_CSD_2022-05
recore
PDB-ReCore-I...90218-seesar
FastGrowDB_...20k_2023-03
A valid ReCore index is selected.
Apply
Data
Switch to Grid
Molecules (# 1)
Name
Estimated Affinity
53U_H_2001
2D
Sequence View
Show Binding Site Only


Click on bonds to set constraints (= exchange vectors) at your molecule. You can do this in 2D or 3D.
Subsequent click on the same bond changes the direction of the vector (= what part should remain and what part is to be replaced). A third click removes the vector.
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.
Saturated part of the molecule will remain
Grey-out part of the molecule will be replaced
Switch to Grid
Molecules (# 1)
Sequence View
Show Binding Site Only
2ZFF
No Molecule Selected

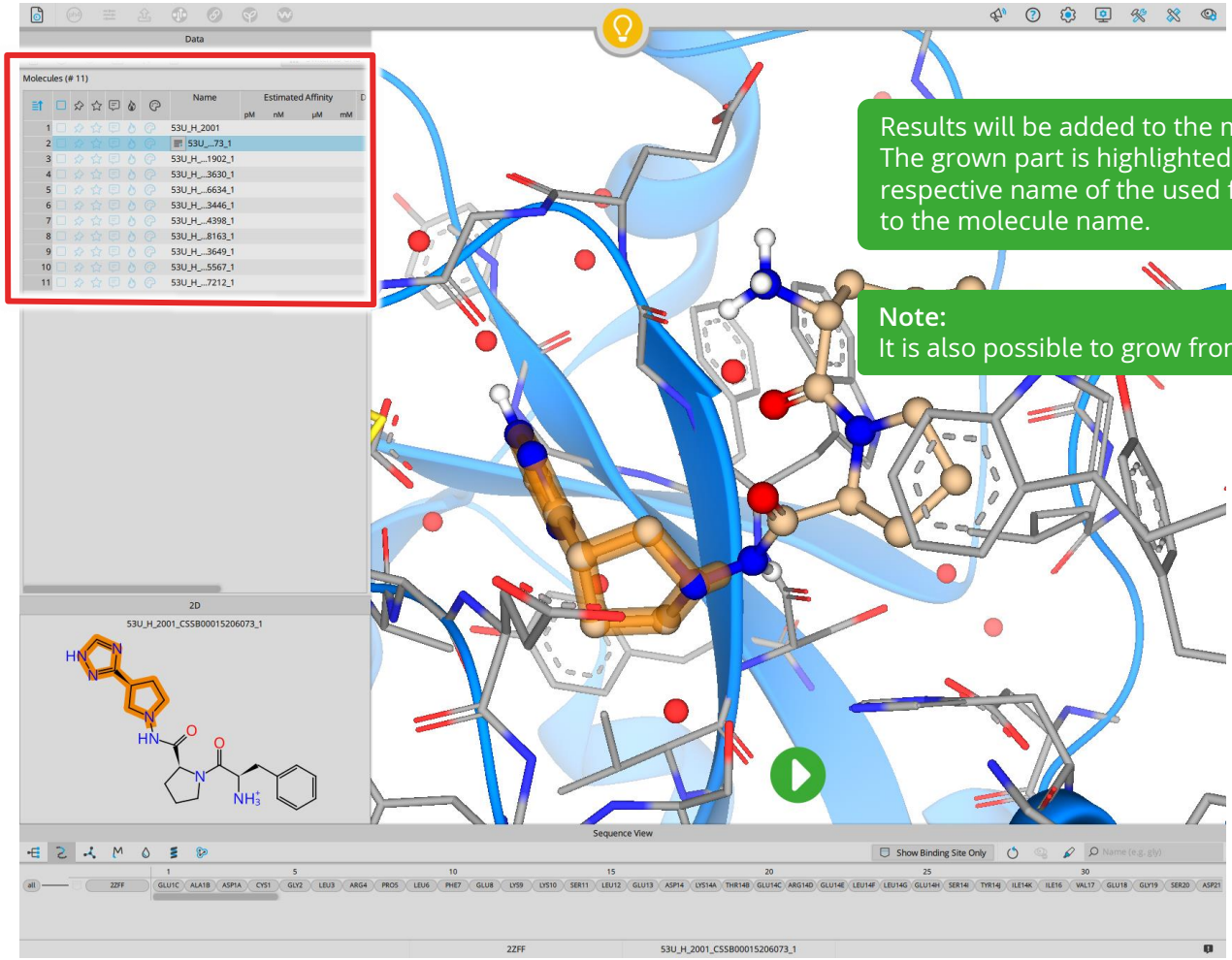


Note:
It's also possible to set more than two constraints or to select hydrogen bonds as vectors.



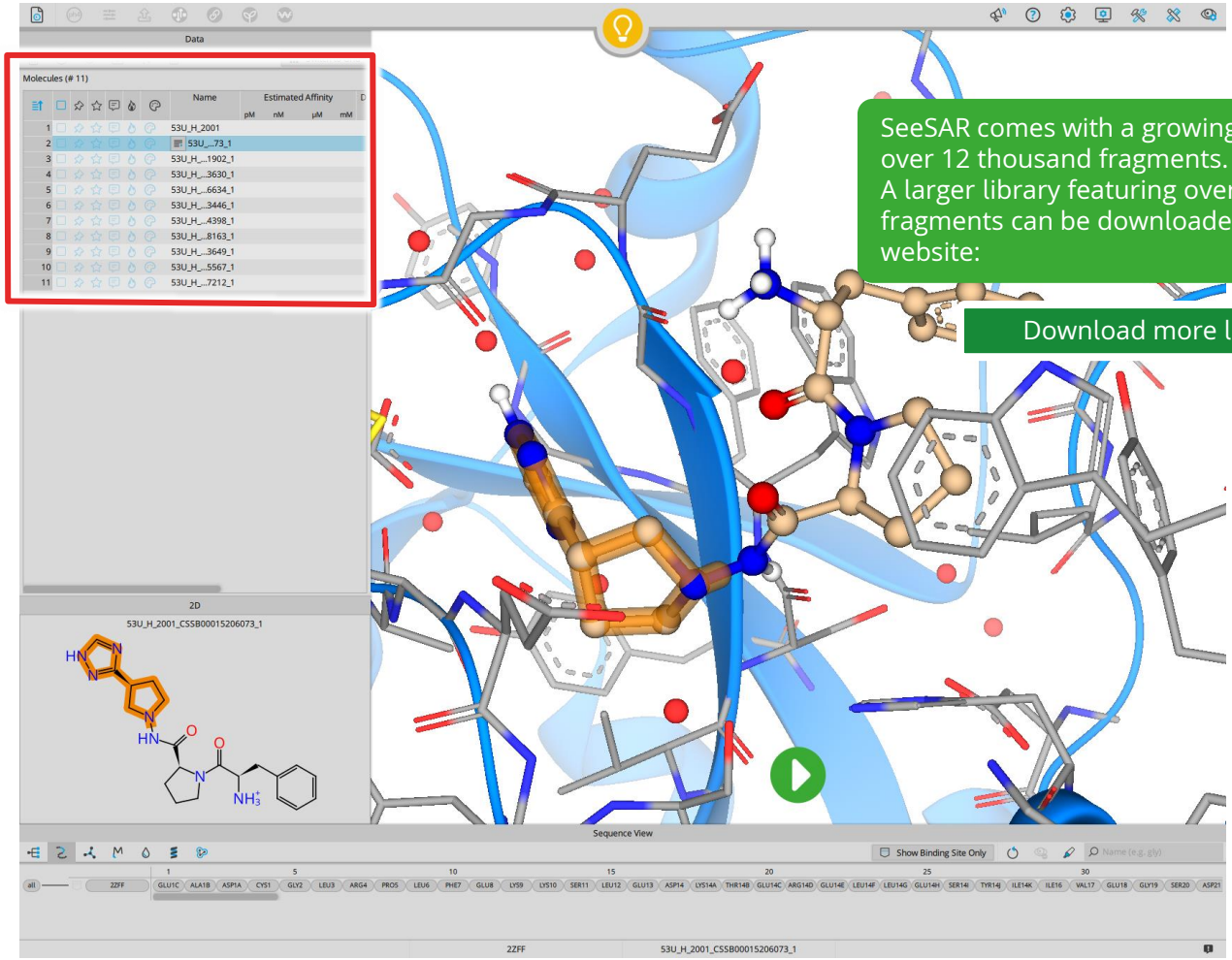
FastGrow:
To grow into a binding site, select a bond in 2D or 3D to select which part of the molecule should be kept. Only one selection is required to perform growing.

Once you made a selection, the “Growing” button will become active. Push it to generate results.



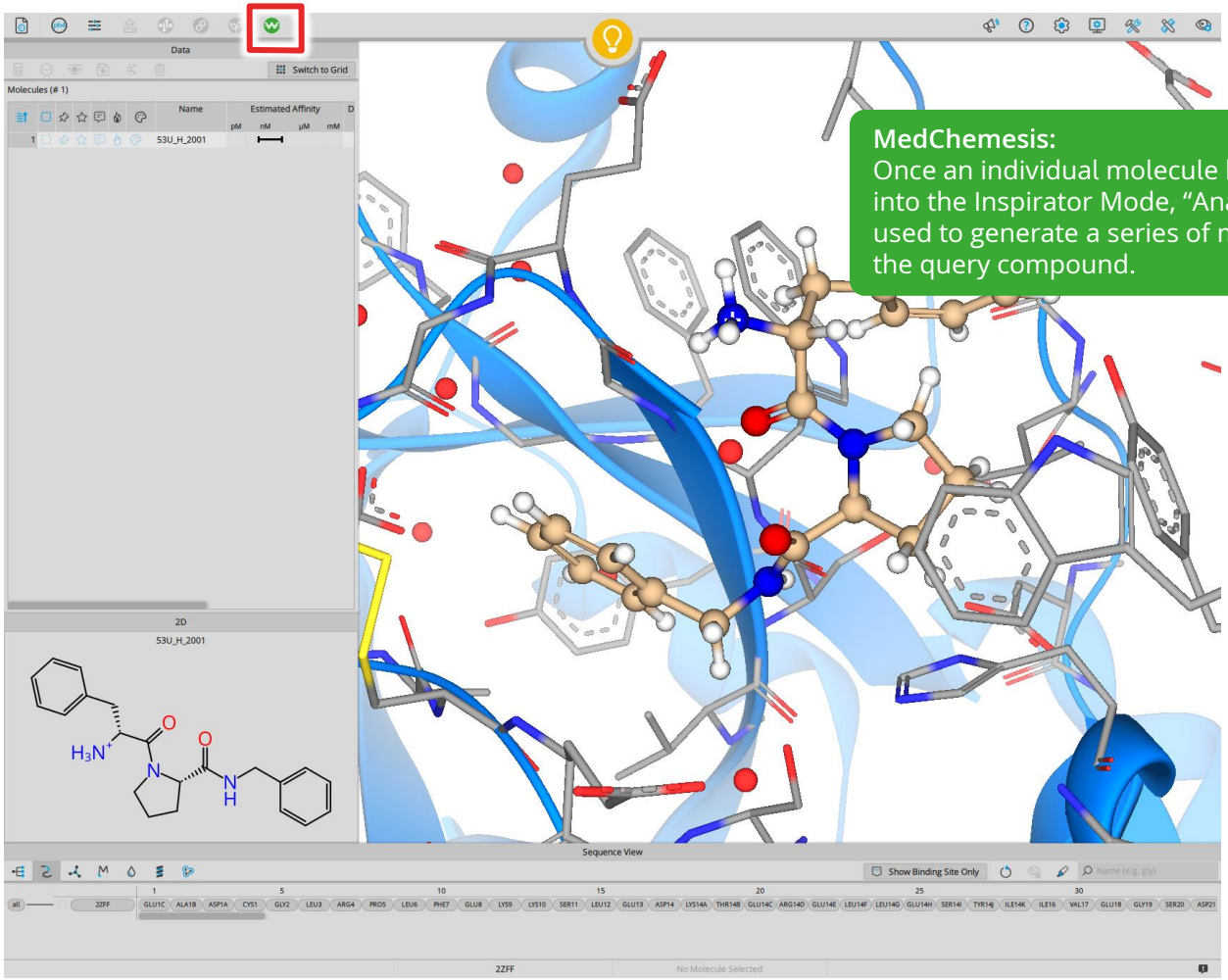
Results will be added to the molecule table. The grown part is highlighted, and the respective name of the used fragment is added to the molecule name.

Note:
It is also possible to grow from a hydrogen in 3D.

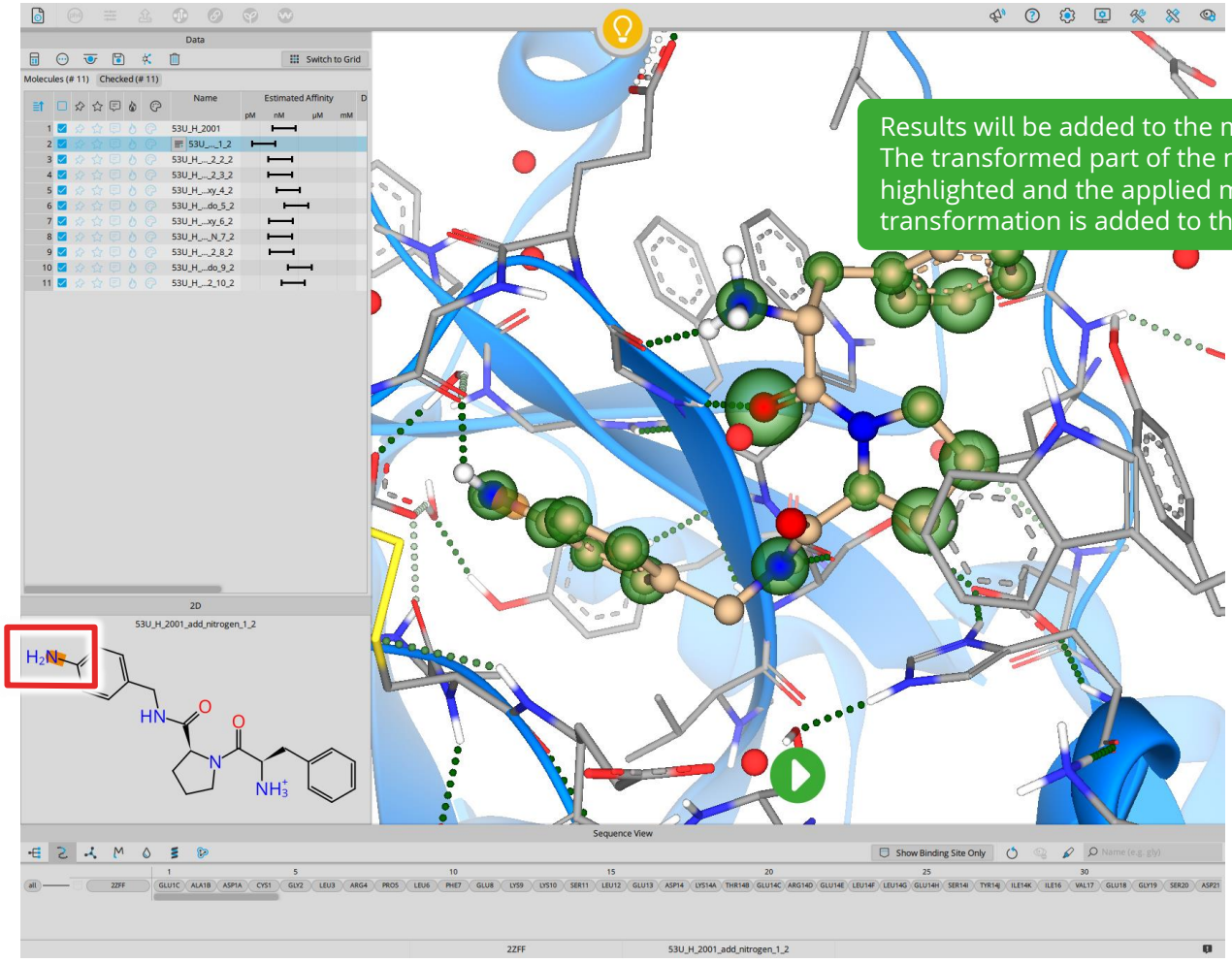


SeeSAR comes with a growing library featuring over 12 thousand fragments.
A larger library featuring over 120 thousand fragments can be downloaded for free from our website:

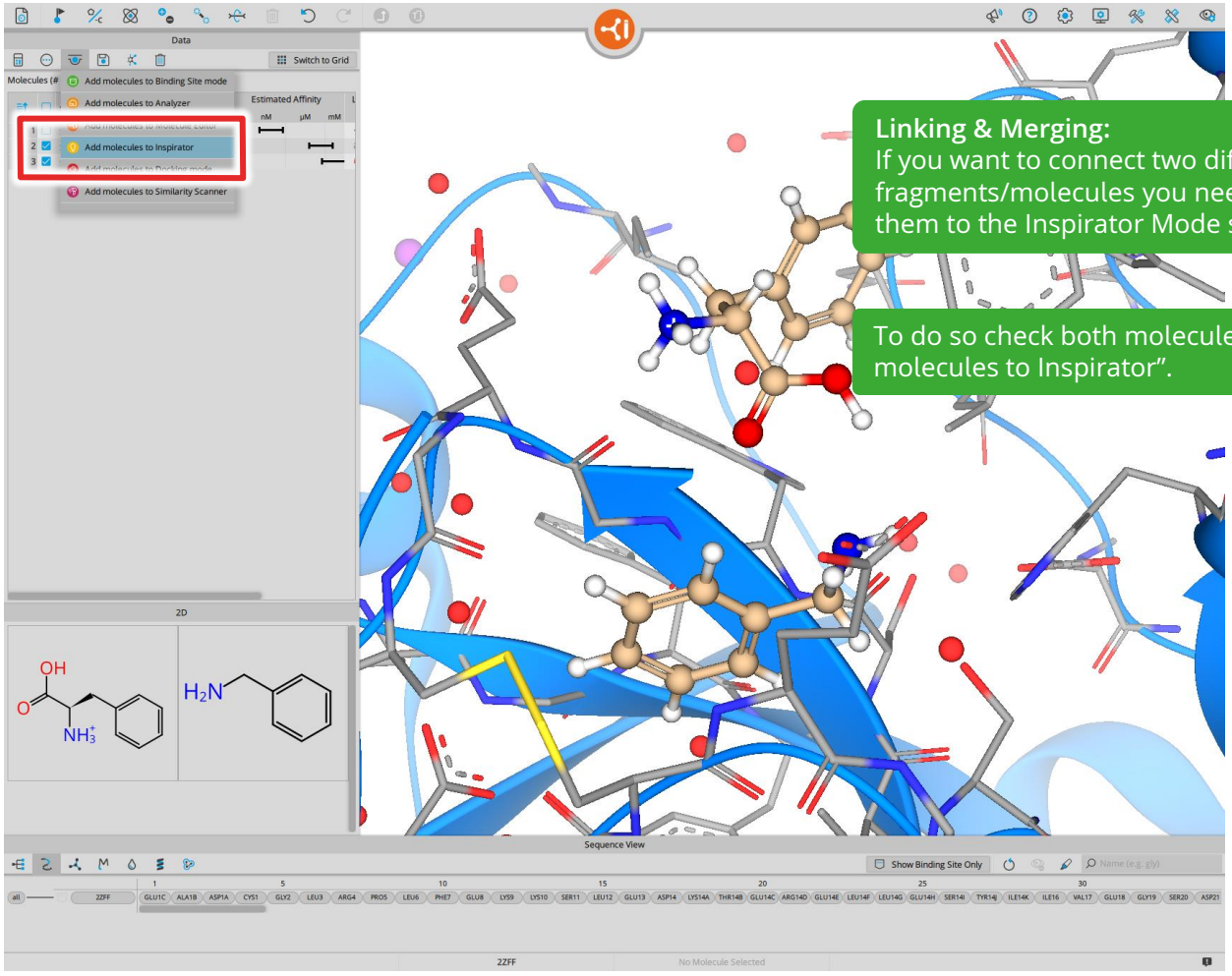
Download more libraries



MedChemesis:
Once an individual molecule has been loaded into the Inspirator Mode, “Analoging” can be used to generate a series of molecules based on the query compound.

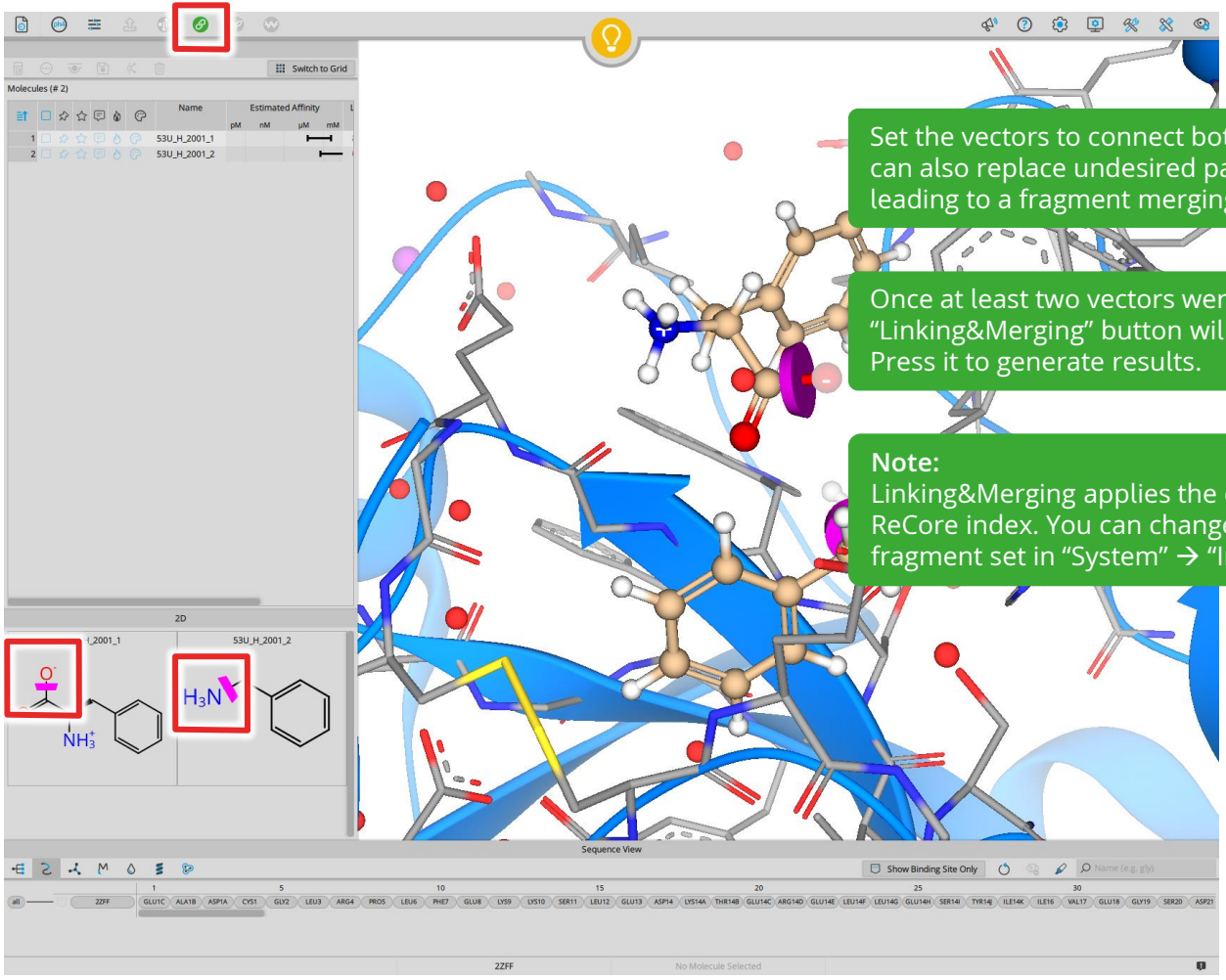


Results will be added to the molecule table. The transformed part of the molecule will be highlighted and the applied medicinal chemistry transformation is added to the molecule name.



Linking & Merging:
If you want to connect two different fragments/molecules you need to load both of them to the Inspirator Mode simultaneously.

To do so check both molecules and select “Add molecules to Inspirator”.

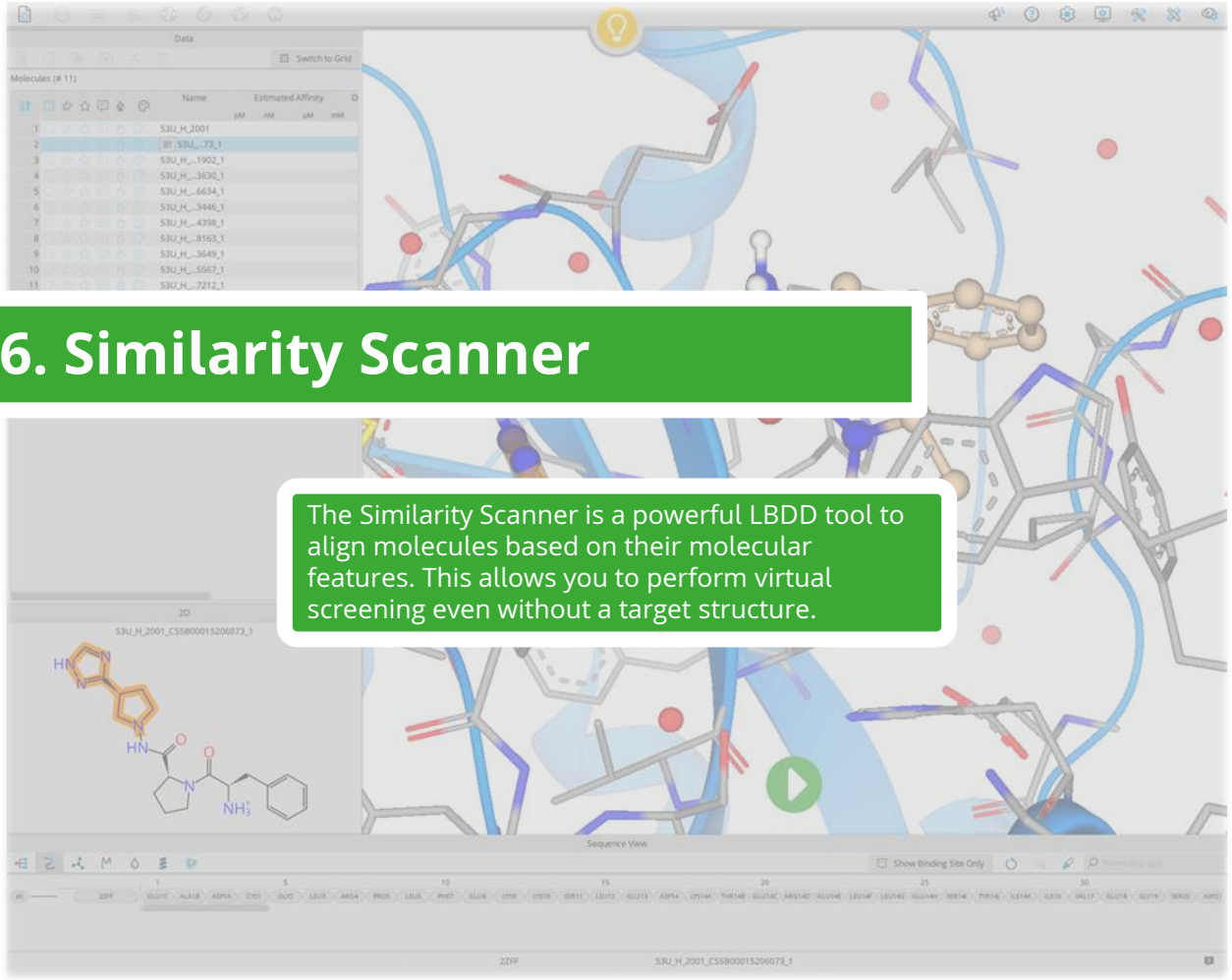


Set the vectors to connect both molecules. You can also replace undesired parts in the process leading to a fragment merging.

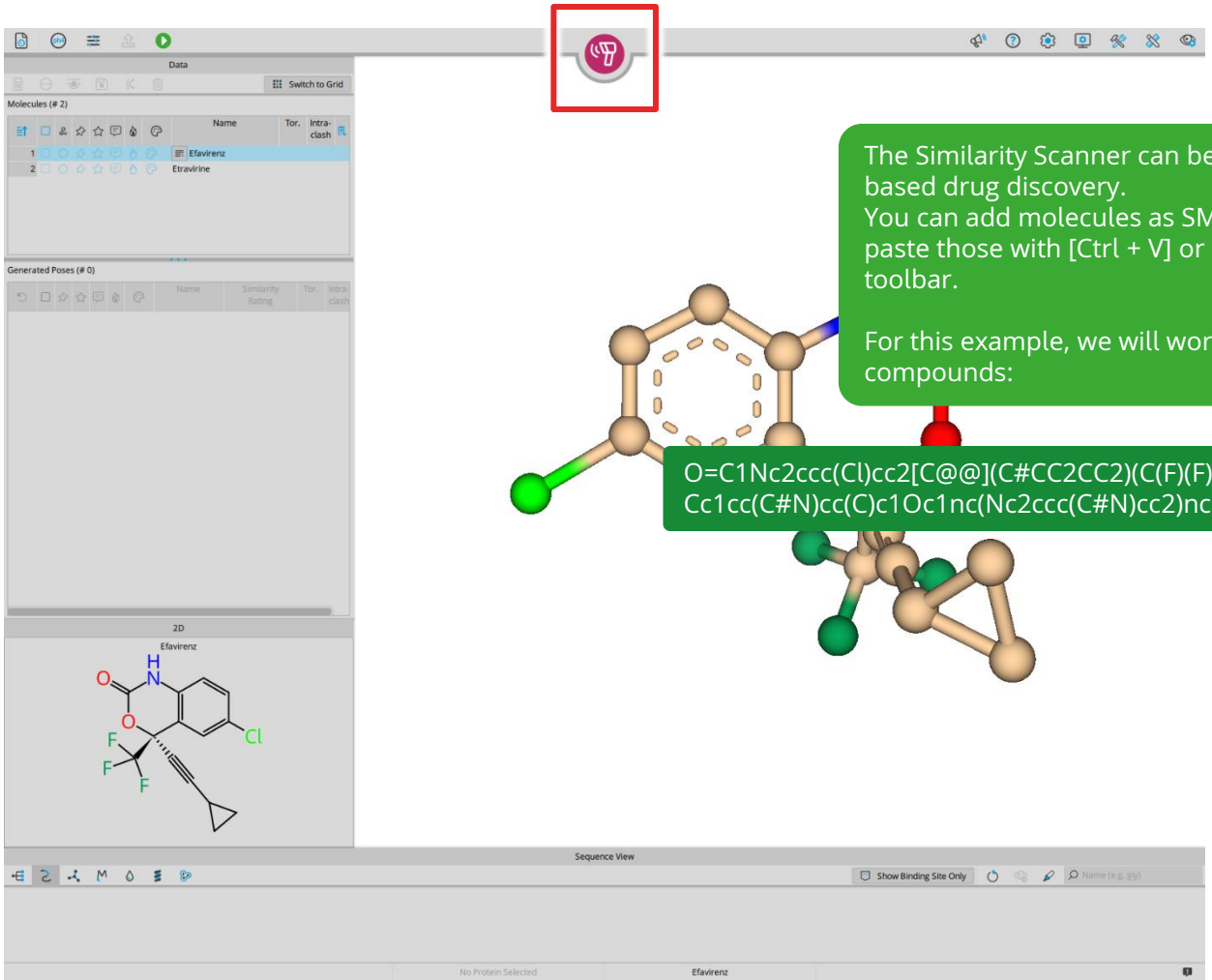
Once at least two vectors were set, the “Linking&Merging” button will become active. Press it to generate results.

Note:
Linking&Merging applies the current active ReCore index. You can change the used fragment set in “System” → “Inspirator”.

6. Similarity Scanner



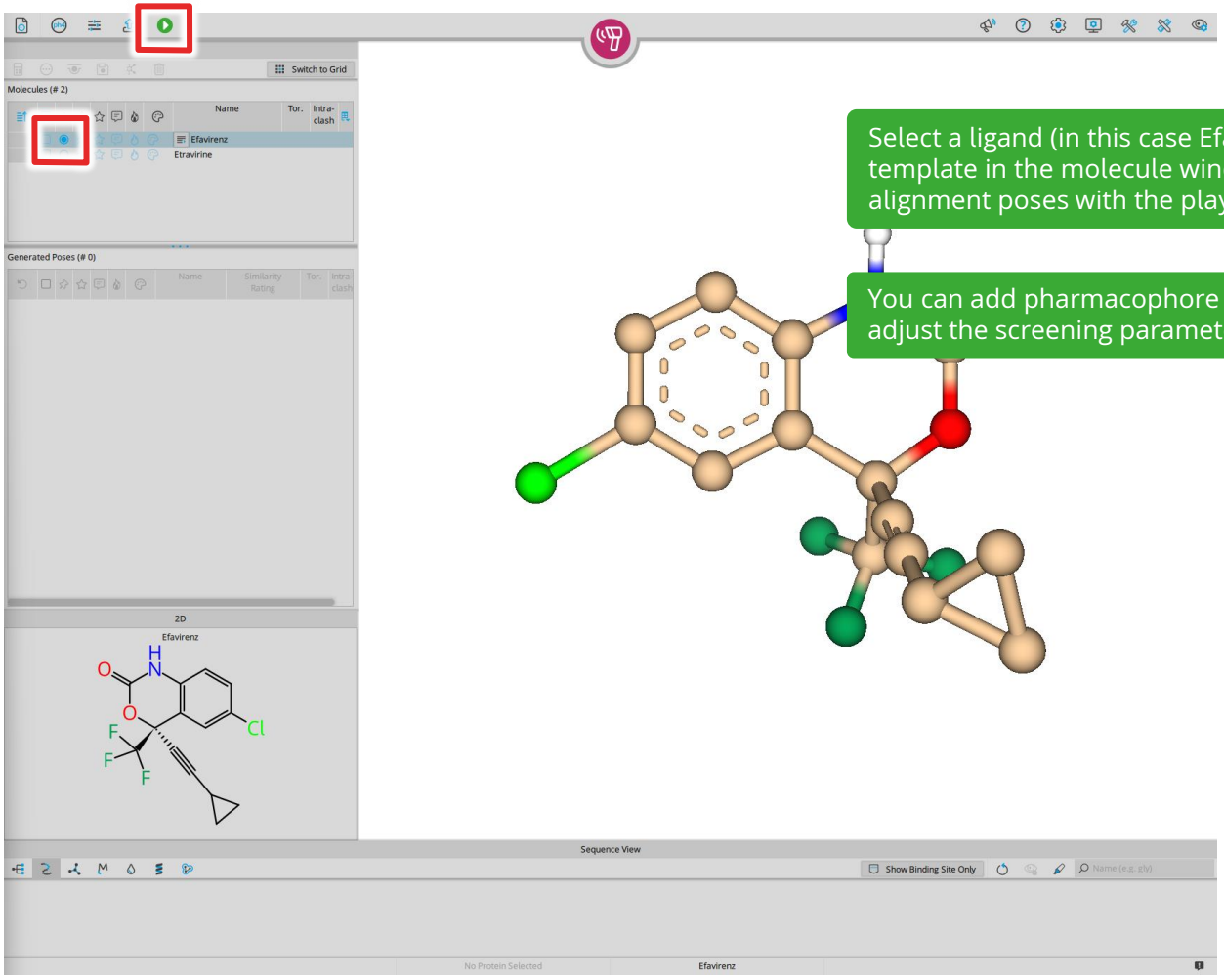
The Similarity Scanner is a powerful LBDD tool to align molecules based on their molecular features. This allows you to perform virtual screening even without a target structure.



The Similarity Scanner can be used for liband-based drug discovery.
You can add molecules as SMILES by copy-and-paste those with [Ctrl + V] or load those via the toolbar.

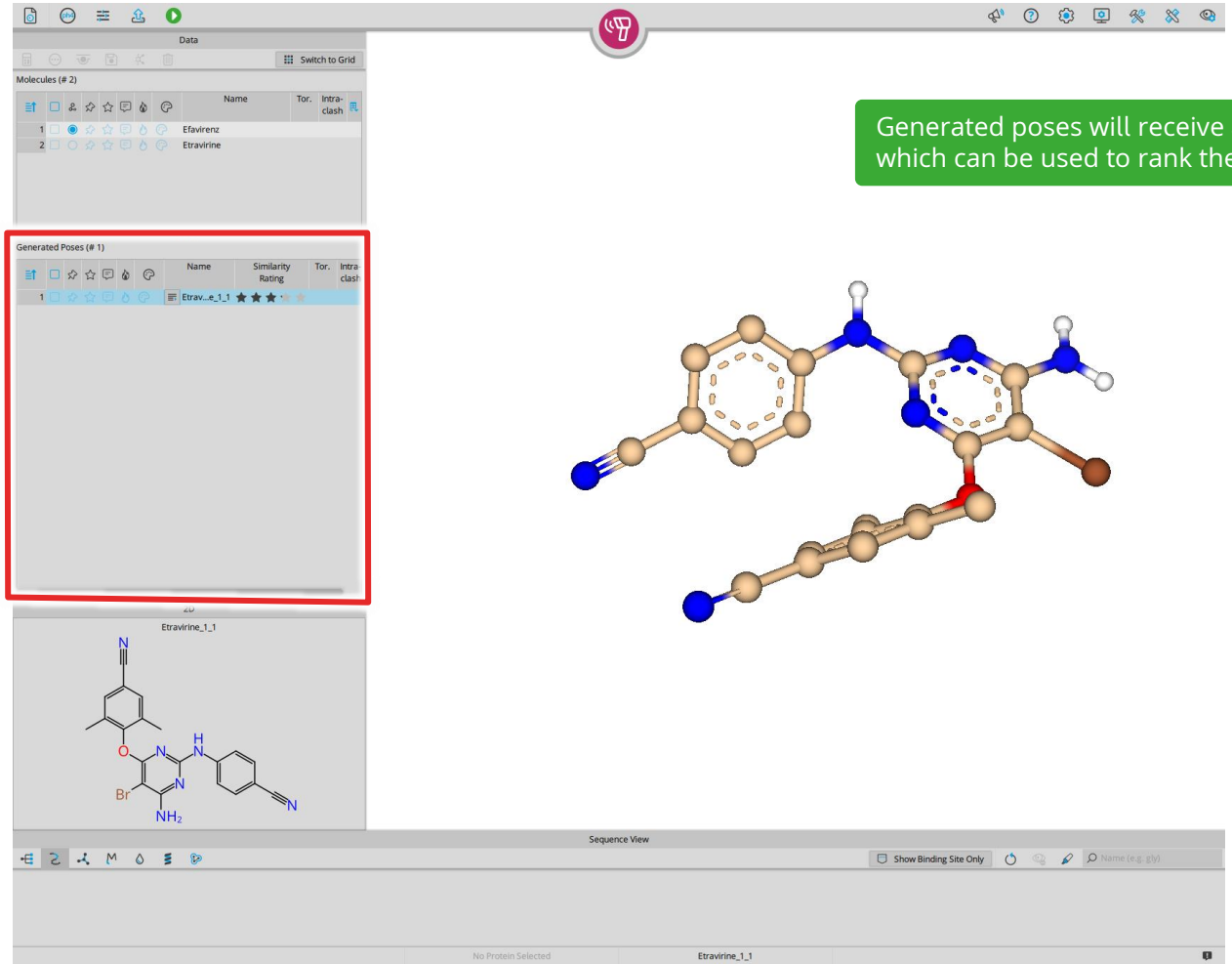
For this example, we will work with two compounds:

O=C1Nc2ccc(Cl)cc2[C@@](C#CC2CC2)(C(F)(F)F)O1 Efavirenz
Cc1cc(C#N)cc(C)c1Oc1nc(Nc2ccc(C#N)cc2)nc(N)c1Br Etravirine



Select a ligand (in this case Efavirenz) as a template in the molecule window. Generate alignment poses with the play button.

You can add pharmacophore constraints and adjust the screening parameters as well.



Generated poses will receive an alignment score which can be used to rank the compounds.

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

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