SeeSAR

BioSolveIT
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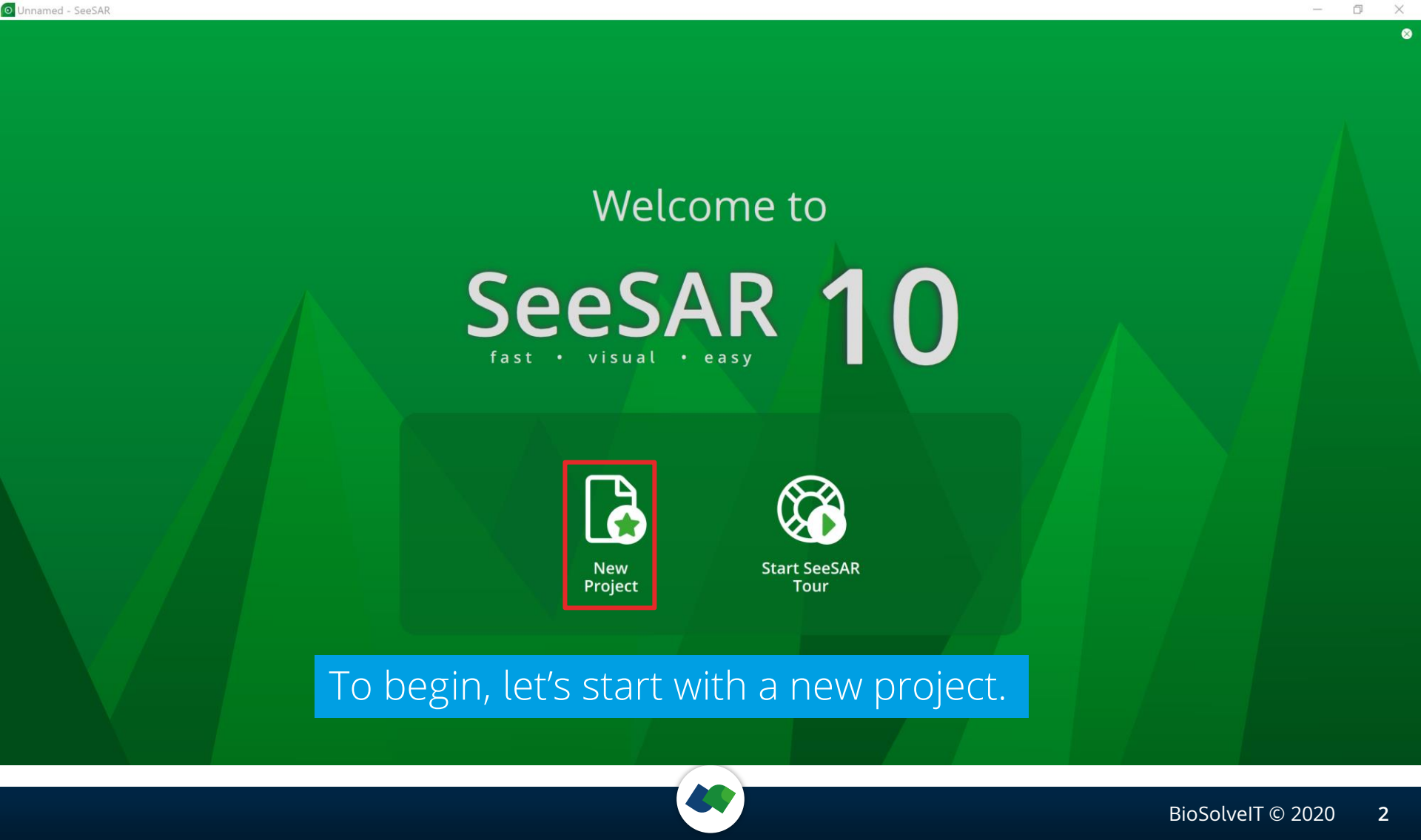
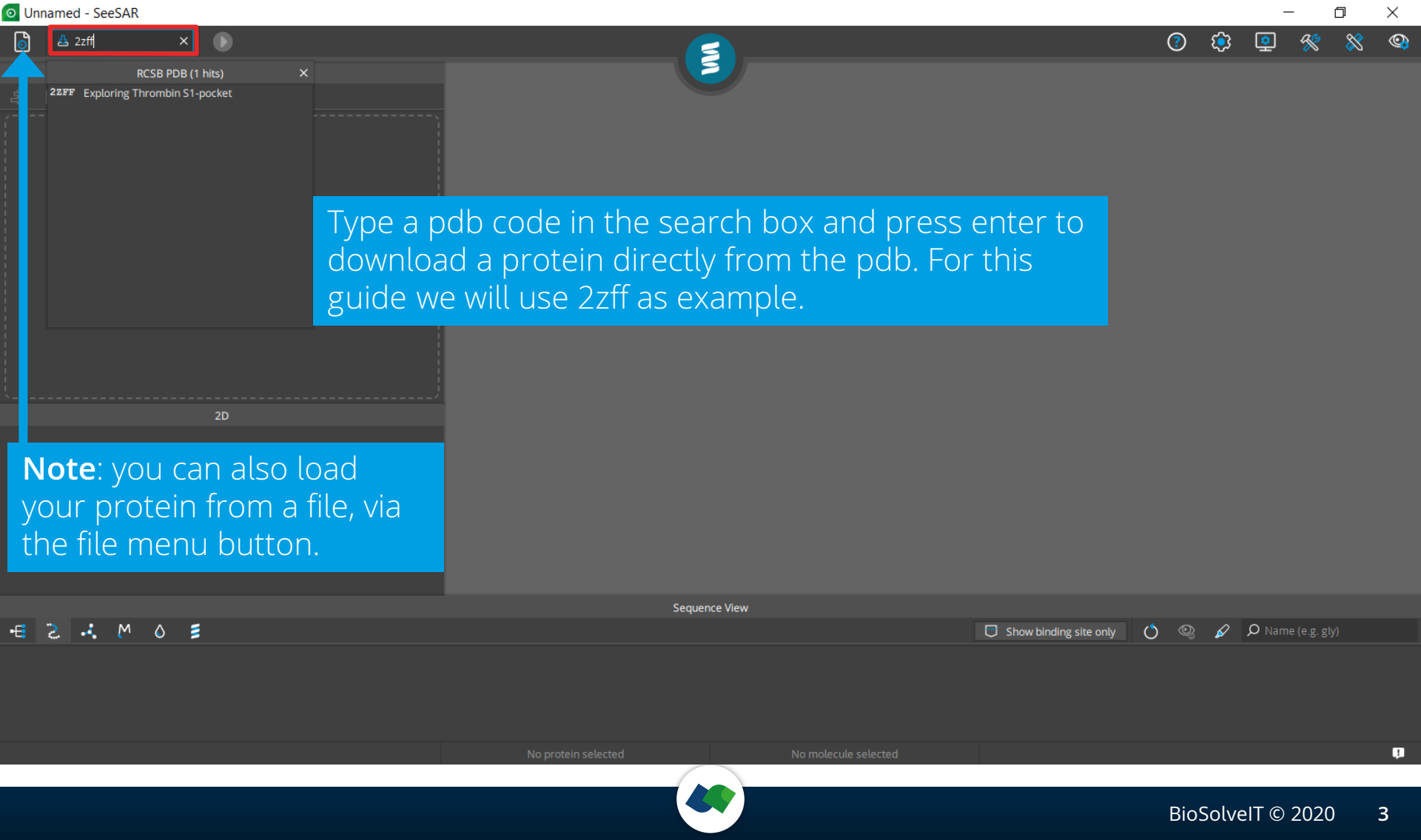
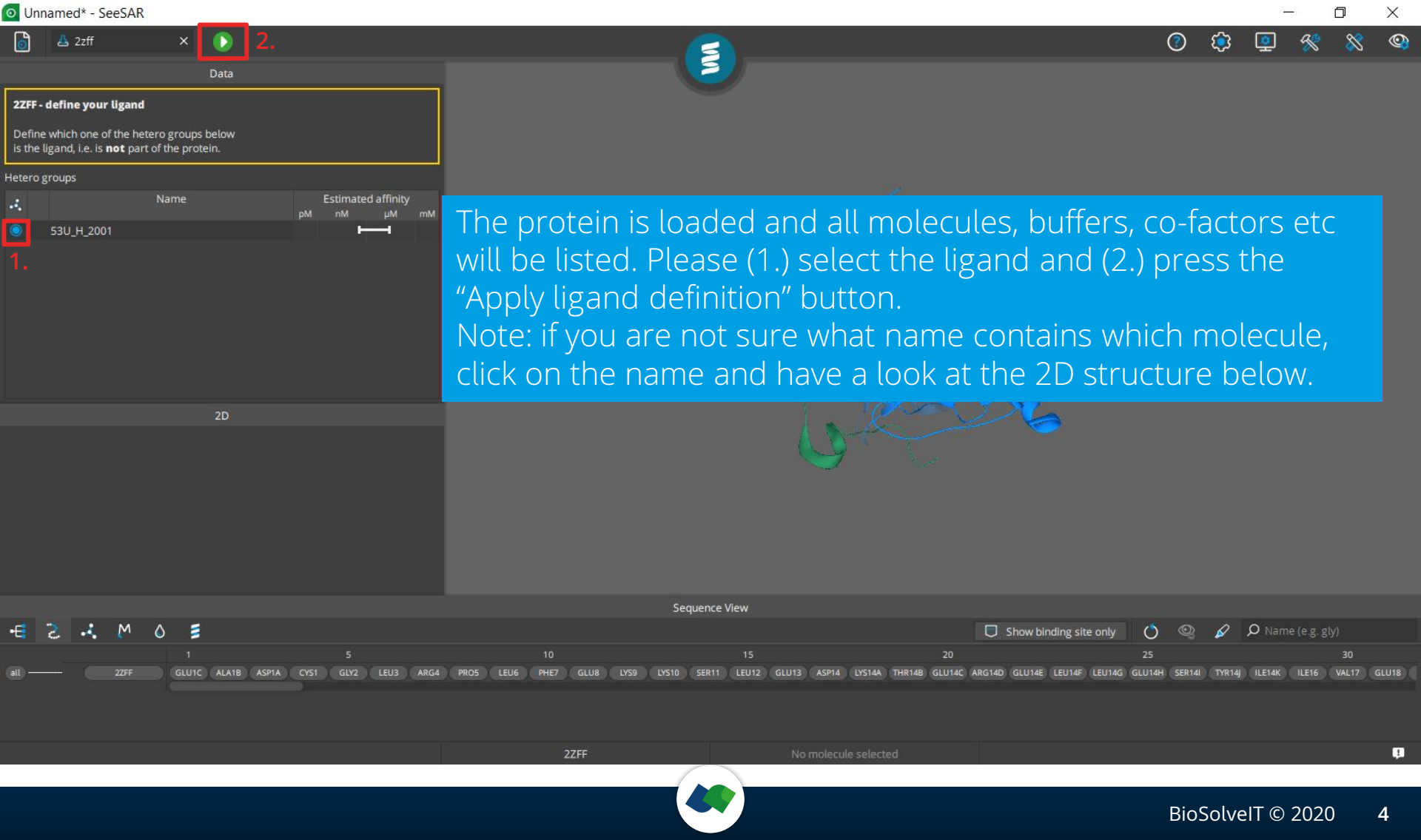
SeeSAR 10 beginner‘s guide

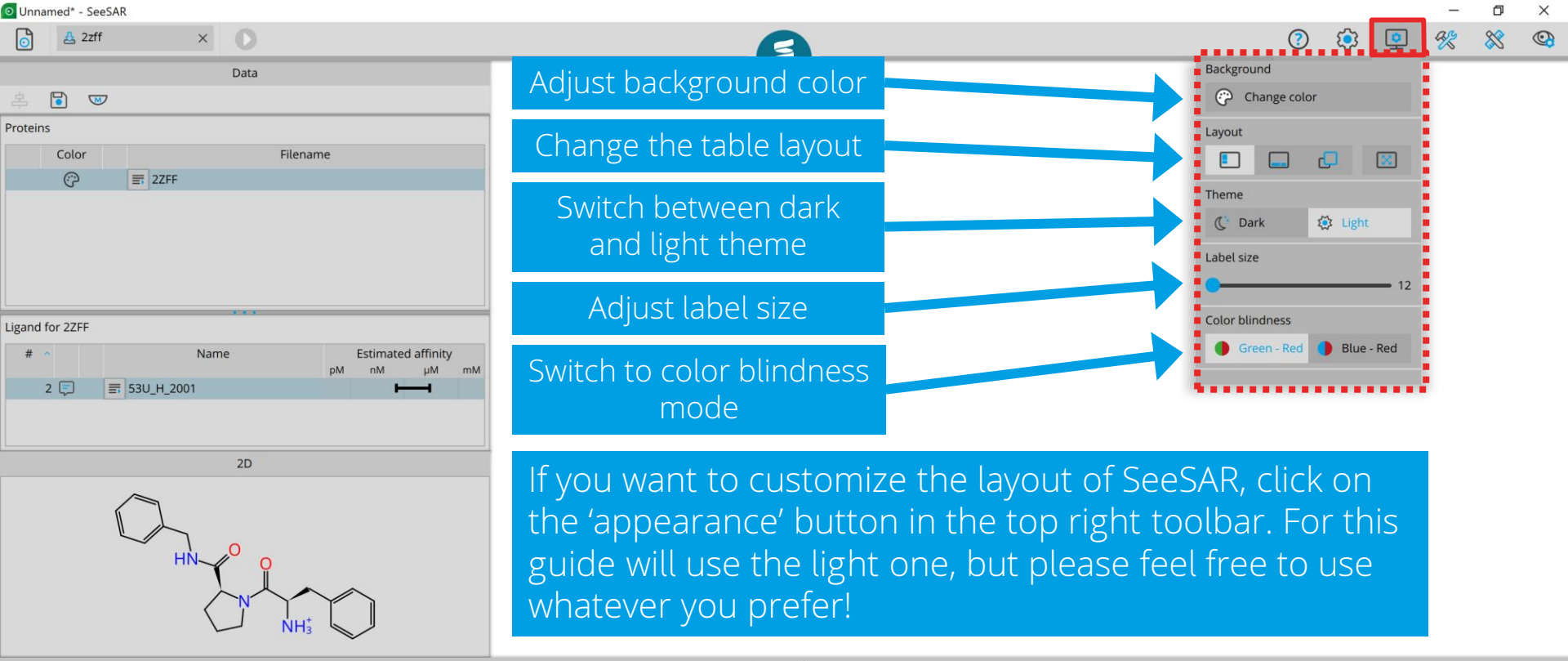
1 Basics


Unnamed - SeeSAR
Welcome to
SeeSAR 10
fast • visual • easy
New Project
Start SeeSAR Tour
To begin, let's start with a new project.

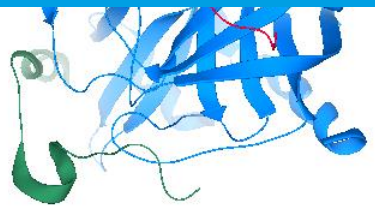

Unnamed - SeeSAR
2zff
RCSB PDB (1 hits)
2ZFF Exploring Thrombin S1-pocket
2D
Type a pdb code in the search box and press enter to download a protein directly from the pdb. For this guide we will use 2zff as example.
Note: you can also load your protein from a file, via the file menu button.
Sequence View
Show binding site only
Name (e.g. gly)
No protein selected
No molecule selected

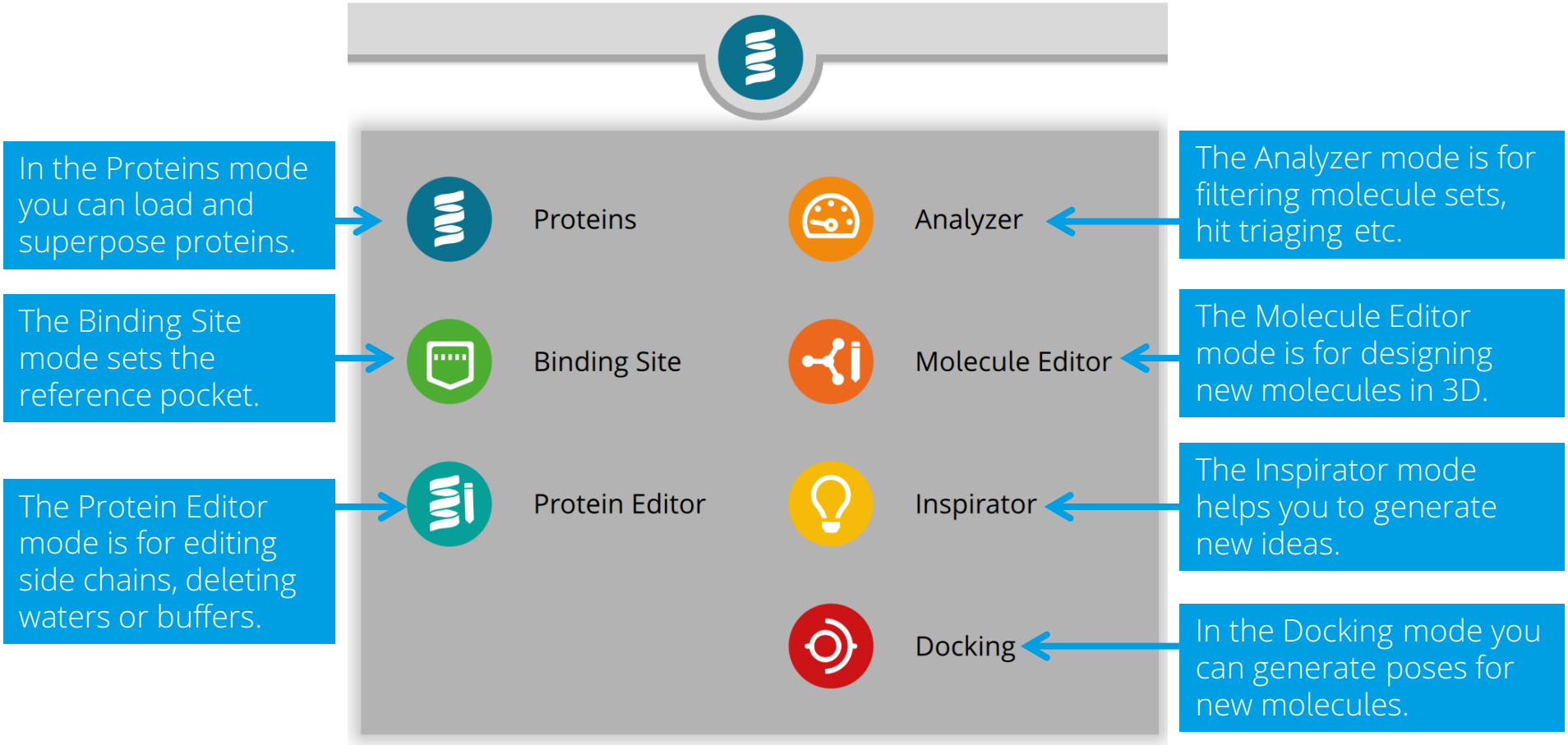

Unnamed* - SeeSAR
2zff
2.
Data
2ZFF - define your ligand
Define which one of the hetero groups below
is the ligand, i.e. is not part of the protein.
Hetero groups
Name
Estimated affinity
pM nM µM mM
53U_H_2001
1.
2D
The protein is loaded and all molecules, buffers, co-factors etc will be listed. Please (1.) select the ligand and (2.) press the "Apply ligand definition" 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
Name (e.g. gly)
2ZFF
No molecule selected

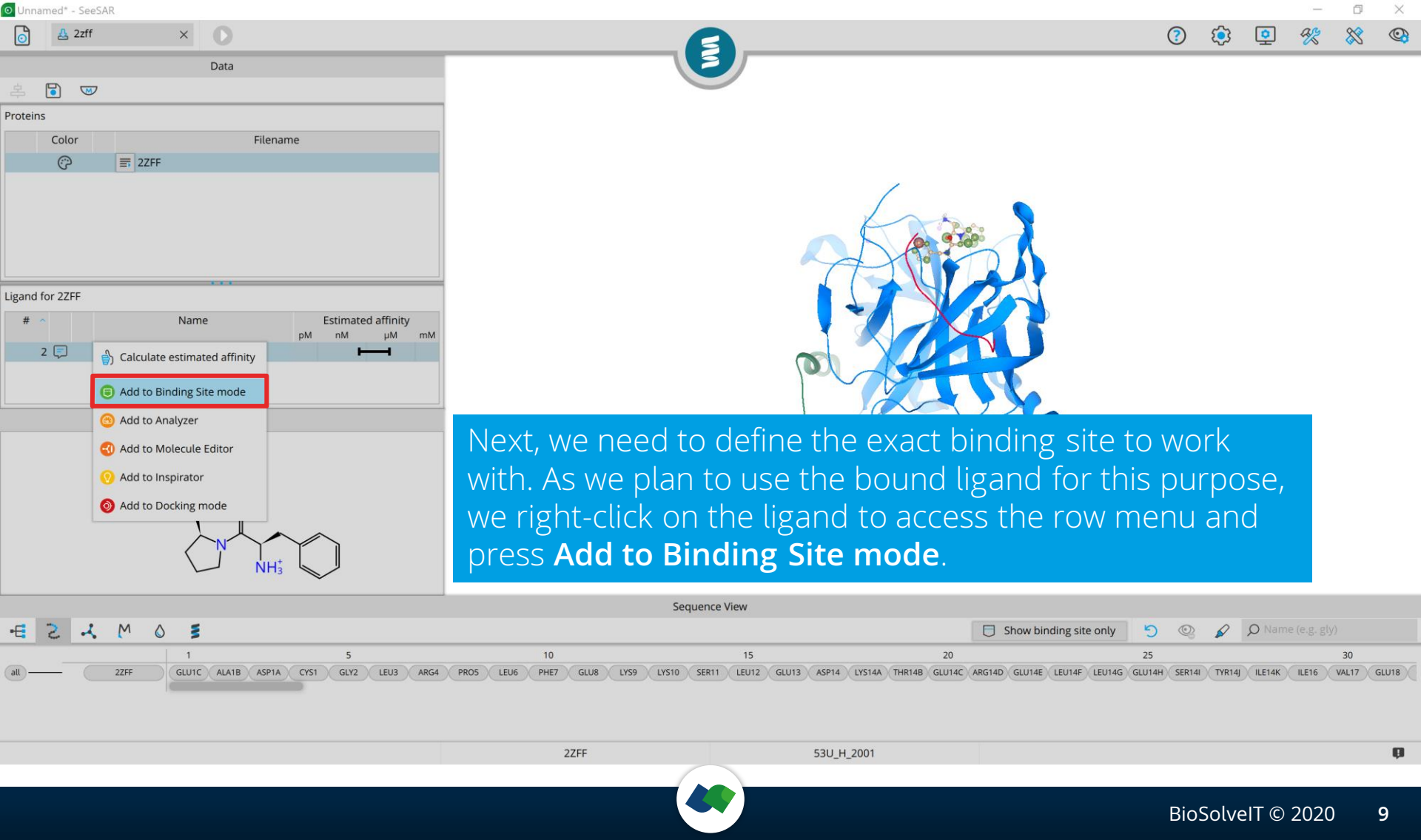

Unnamed* - SeeSAR
2zff
Data
Proteins
Color
Filename
2ZFF
Ligand for 2ZFF
#
Name
Estimated affinity
pM
nM
µM
mM
2
53U_H_2001
2D
Tables
- drag rim to re-size
- click entries to select
3D-viewer:
- right-click to rotate
- mouse-wheel to zoom
- middle-click to shift
Sequence View
Show binding site only
Name (e.g. gly)
all
2ZFF
GLU1C ALA1B ASP1A CYS1 GLY2 LEU3 ARG4 PRO5 LEU6 PHE7 GLU8 LYS9 LYS10 SER11 LEU12 GLU13 ASP14 LYS14A THR14B GLU14C ARG14D GLU14E LEU14F LEU14G GLU14H SER14I TYR14J ILE14K ILE16 VAL17 GLU18
2ZFF
No molecule selected


Unnamed* - SeeSAR
2zff
Data
Proteins
Color
Filename
2ZFF
Ligand for 2ZFF
#
Name
Estimated affinity
pM
nM
µM
mM
2
53U_H_2001
2D
HN
O
O
N
NH3+
Adjust background color
Change the table layout
Switch between dark and light theme
Adjust label size
Switch to color blindness mode
Background
Change color
Layout
Theme
Dark
Light
Label size
12
Color blindness
Green - Red
Blue - Red
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!
Sequence View
Show binding site only
Name (e.g. gly)
all
2ZFF
GLU1C
ALA1B
ASP1A
CYS1
GLY2
LEU3
ARG4
PRO5
LEU6
PHE7
GLU8
LYS9
LYS10
SER11
LEU12
GLU13
ASP14
LYS14A
THR14B
GLU14C
ARG14D
GLU14E
LEU14F
LEU14G
GLU14H
SER14I
TYR14J
ILE14K
ILE16
VAL17
GLU18
2ZFF
53U_H_2001

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.




In the Proteins mode you can load and superpose proteins.
The Binding Site mode sets the reference pocket.
The Protein Editor mode is for editing side chains, deleting waters or buffers.
Proteins
Binding Site
Protein Editor
Analyzer
Molecule Editor
Inspirator
Docking
The Analyzer mode is for filtering molecule sets, hit triaging etc.
The Molecule Editor mode is for designing new molecules in 3D.
The Inspirator mode helps you to generate new ideas.
In the Docking mode you can generate poses for new molecules.


Unnamed* - SeeSAR
2zff
Data
Proteins
Color
Filename
2ZFF
Ligand for 2ZFF
#
Name
Estimated affinity
pM
nM
µM
mM
2
Calculate estimated affinity
Add to Binding Site mode
Add to Analyzer
Add to Molecule Editor
Add to Inspirator
Add to Docking mode
N
NH3+
Next, we need to define the exact binding site to work with. As we plan to use the bound ligand for this purpose, we right-click on the ligand to access the row menu and press **Add to Binding Site mode**.
Sequence View
Show binding site only
Name (e.g. gly)
all
2ZFF
GLU1C ALA1B ASP1A CYS1 GLY2 LEU3 ARG4 PRO5 LEU6 PHE7 GLU8 LYS9 LYS10 SER11 LEU12 GLU13 ASP14 LYS14A THR14B GLU14C ARG14D GLU14E LEU14F LEU14G GLU14H SER14I TYR14J ILE14K ILE16 VAL17 GLU18
2ZFF
53U_H_2001

Unnamed* - SeeSAR

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**

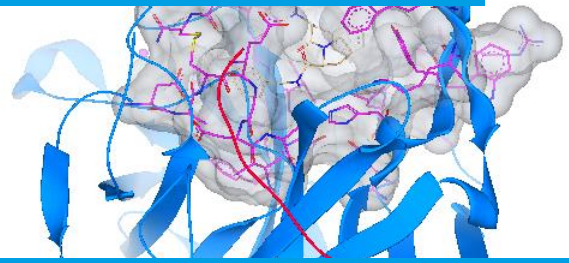
Molecules

Name	Number of residues
53U_H_2001	30

Unoccupied pockets

	Pocket ID	Number of residues

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



With the loaded ligand, all residues within a 6.5 Angstrom radius around it are automatically selected (and highlighted in pink). So all you have to do is to confirm your selection with the green arrow button.

Note: if you want to modify the automatic selection, add or remove individual amino acids in the 3D view by clicking on them in the 3D view or the sequence view.

Sequence View

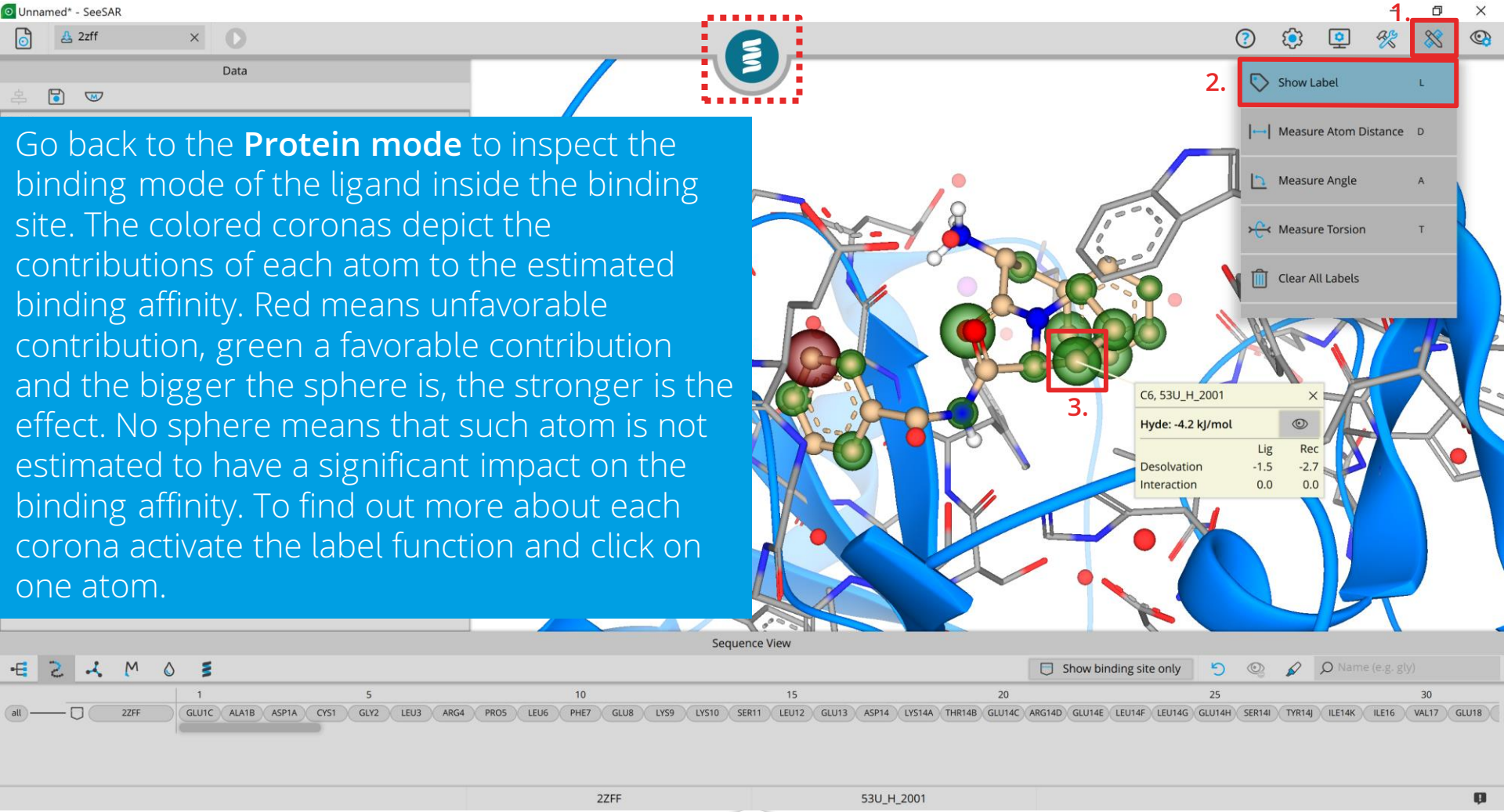
Show binding site only

Name (e.g. gly)

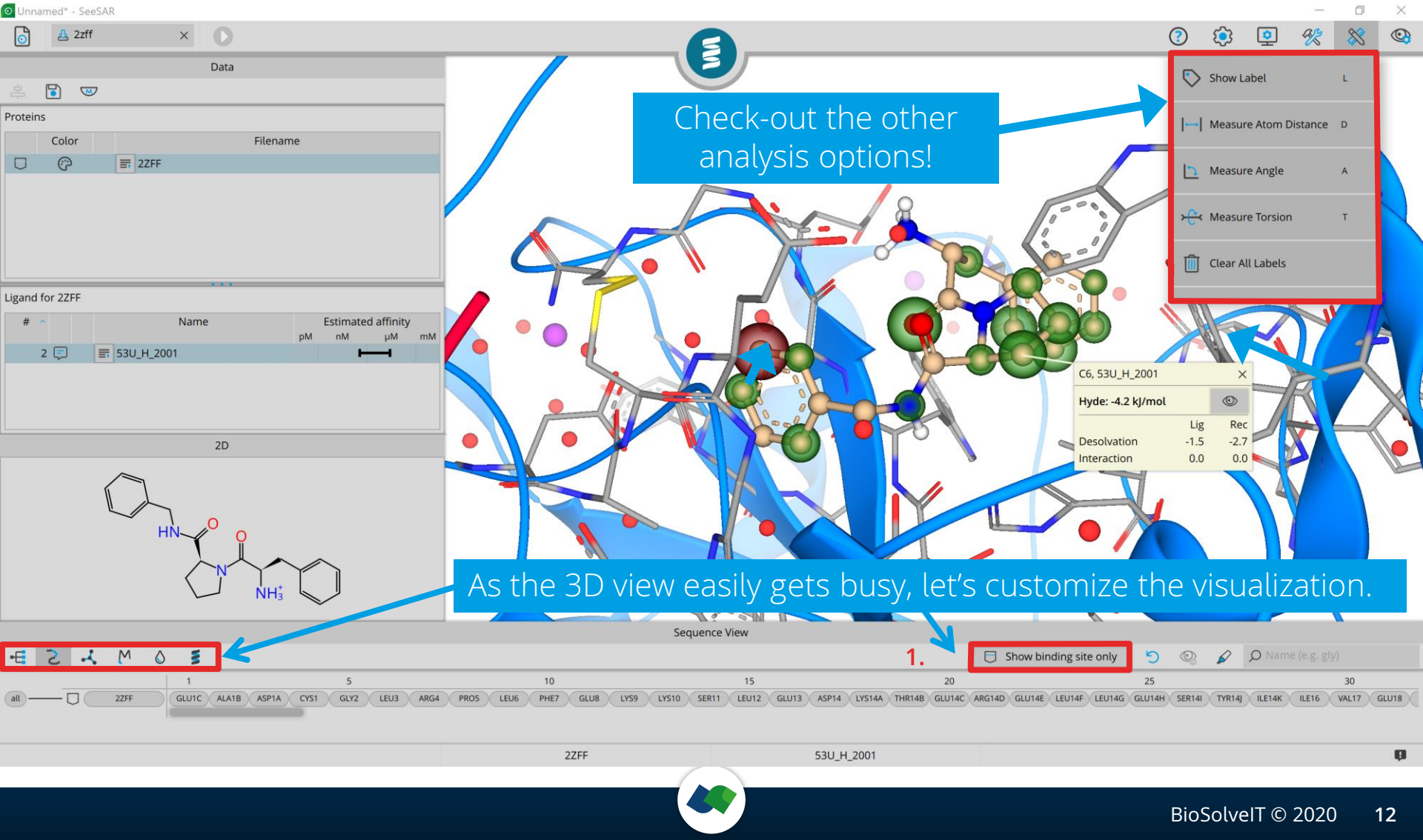
1 5 10 15 20 25 30

all 2ZFF GLU1C ALA1B ASP1A CYS1 GLY2 LEU3 ARG4 PRO5 LEU6 PHE7 GLU8 LYS9 LYS10 SER11 LEU12 GLU13 ASP14 LYS14A THR14B GLU14C ARG14D GLU14E LEU14F LEU14G GLU14H SER14I TYR14J ILE14K ILE16 VAL17 GLU18

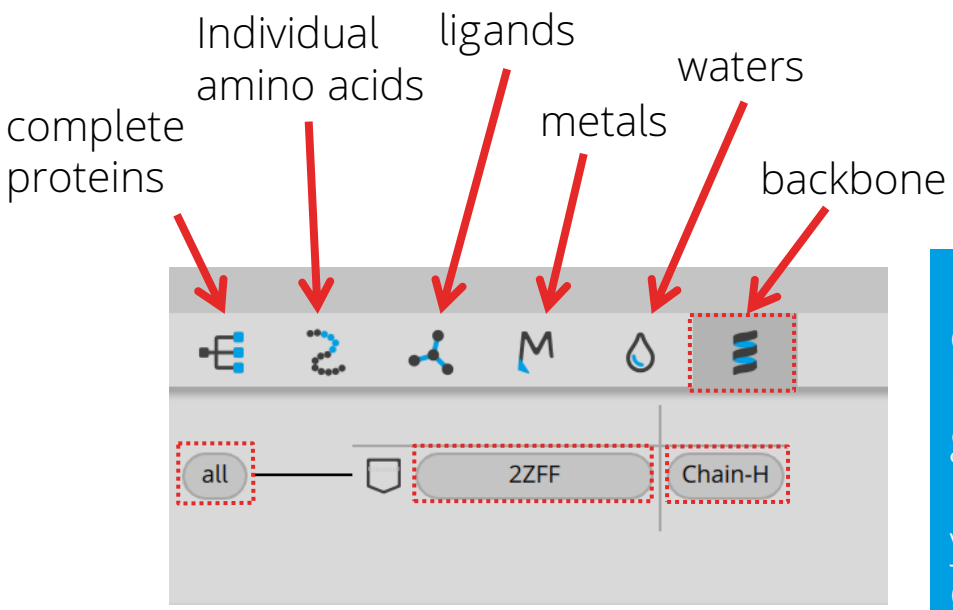
2ZFF No molecule selected



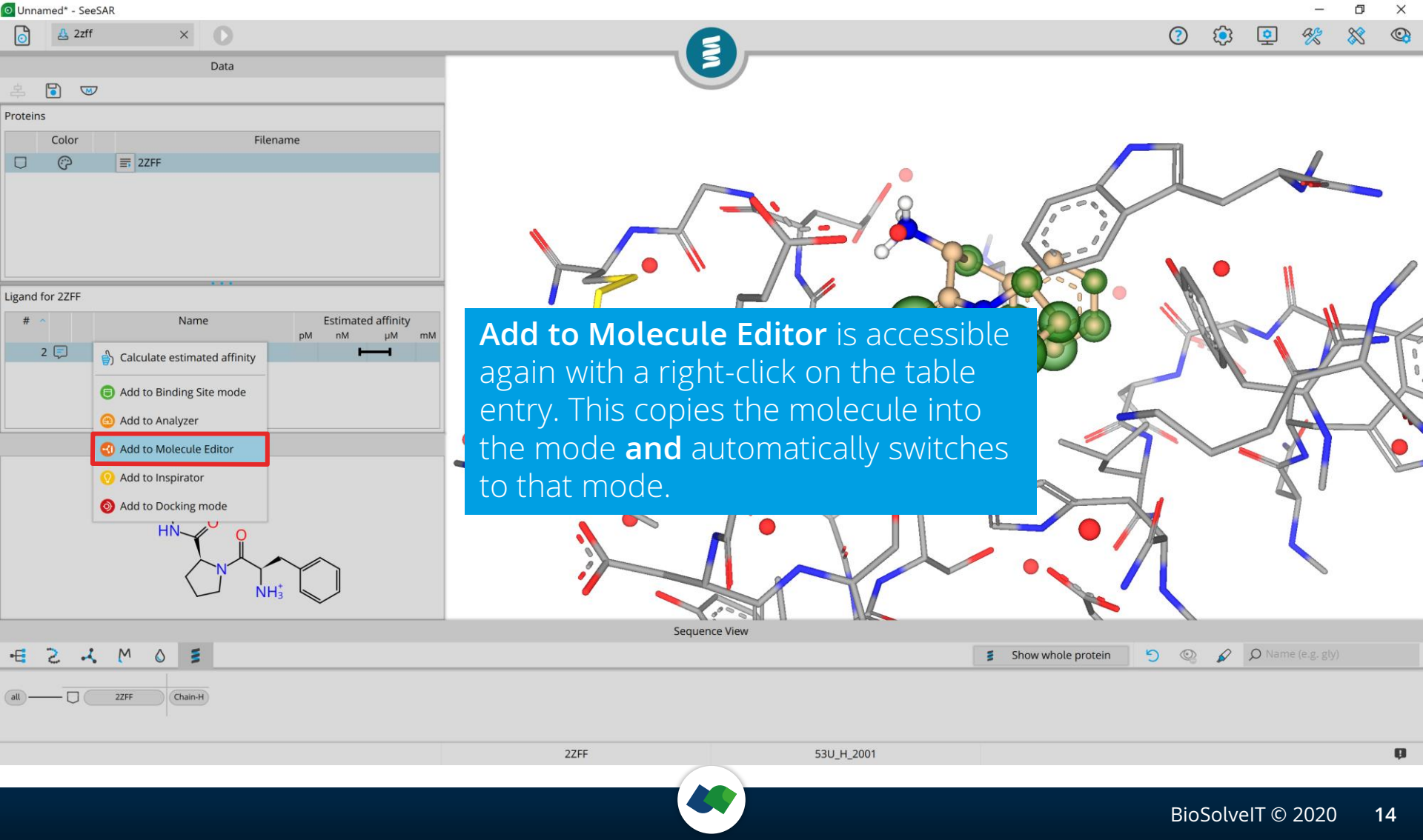
Go back to the **Protein mode** to inspect the binding mode of the ligand inside the binding site. The colored coronas depict the contributions of each atom to the estimated binding affinity. Red means unfavorable contribution, green a favorable contribution and the bigger the sphere is, the stronger 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 corona activate the label function and click on one atom.


Unnamed* - SeeSAR
2zff
Data
Proteins
Color
Filename
2ZFF
Ligand for 2ZFF
#
Name
Estimated affinity
pM
nM
µM
mM
2
53U_H_2001
2D
Check-out the other analysis options!
Show Label L
Measure Atom Distance D
Measure Angle A
Measure Torsion T
Clear All Labels
C6, 53U_H_2001
Hyde: -4.2 kJ/mol
Lig
Rec
Desolvation -1.5 -2.7
Interaction 0.0 0.0
As the 3D view easily gets busy, let's customize the visualization.
Sequence View
1.
Show binding site only
Name (e.g. gly)
all
2ZFF
GLU1C ALA1B ASP1A CYS1 GLY2 LEU3 ARG4 PRO5 LEU6 PHE7 GLU8 LYS9 LYS10 SER11 LEU12 GLU13 ASP14 LYS14A THR14B GLU14C ARG14D GLU14E LEU14F LEU14G GLU14H SER14I TYR14J ILE14K ILE16 VAL17 GLU18
2ZFF
53U_H_2001

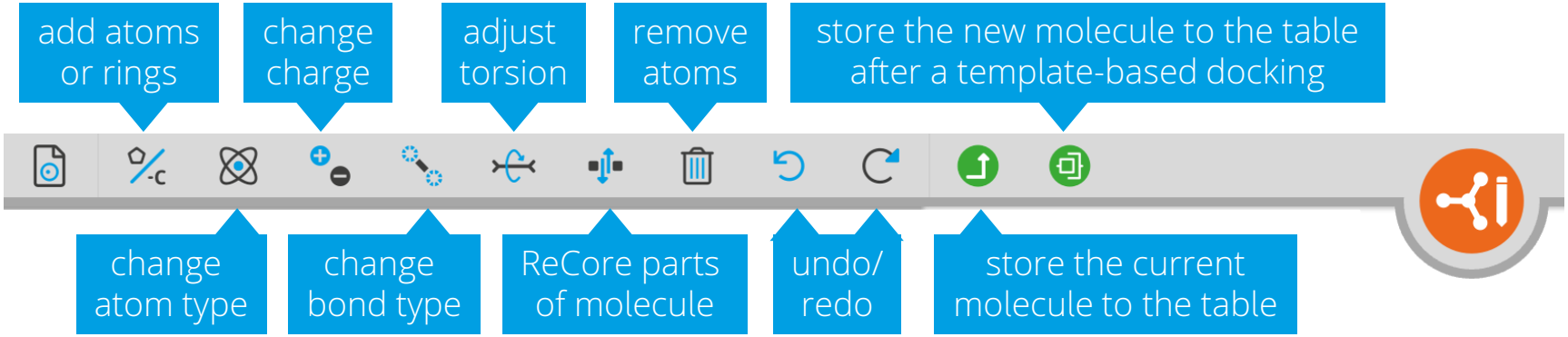
The view controls let you toggle on/off:



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).


Unnamed* - SeeSAR
2zff
Data
Proteins
Color
Filename
2ZFF
Ligand for 2ZFF
#
Name
Estimated affinity
pM
nM
µM
mM
2
Calculate estimated affinity
Add to Binding Site mode
Add to Analyzer
Add to Molecule Editor
Add to Inspirator
Add to Docking mode
HN
O
N
NH3+
Add to Molecule Editor is accessible again with a right-click on the table entry. This copies the molecule into the mode and automatically switches to that mode.
Sequence View
Show whole protein
Name (e.g. gly)
all
2ZFF
Chain-H
2ZFF
53U_H_2001

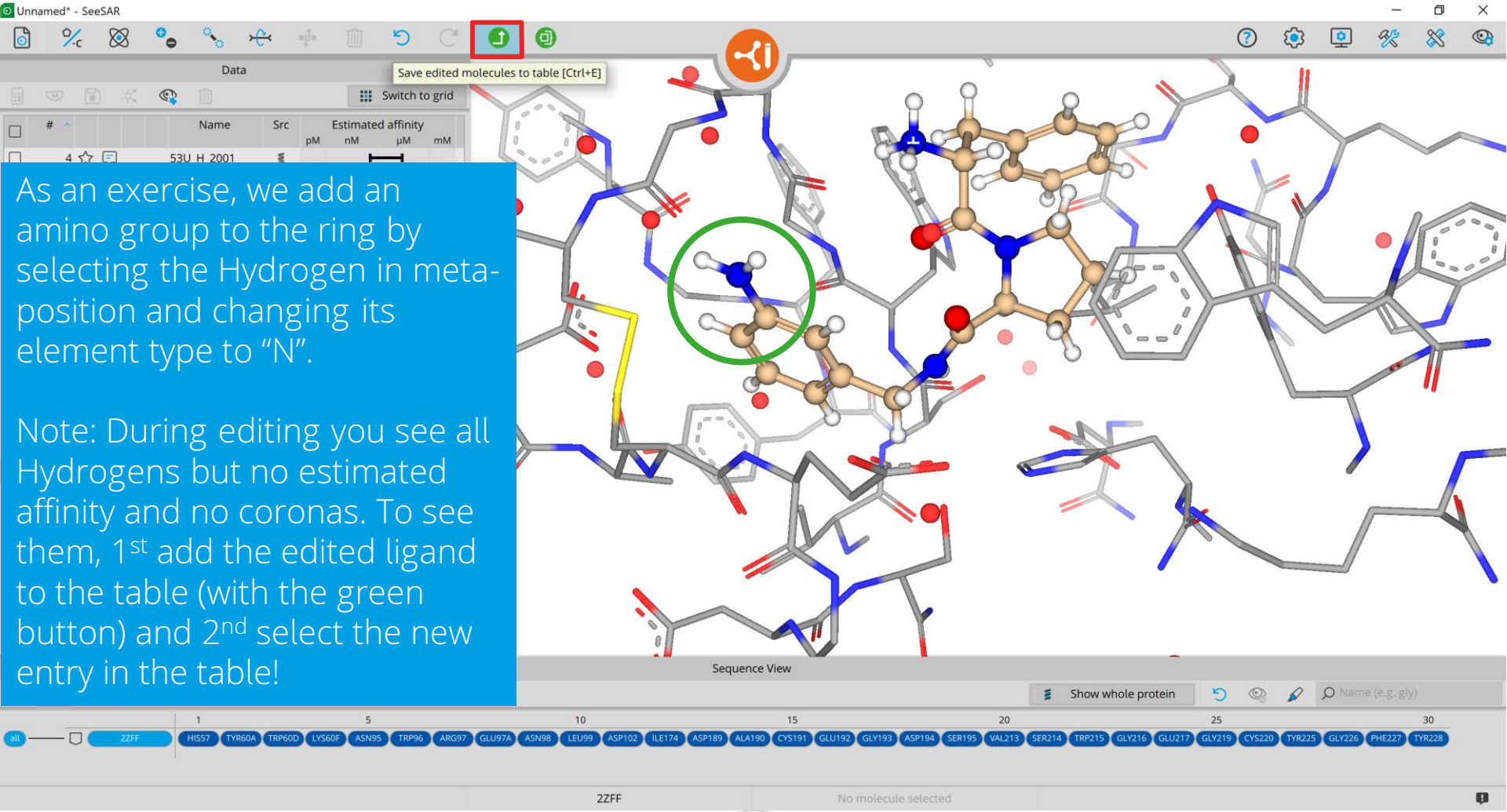
The editor-menu will appear on the top left. There you can:

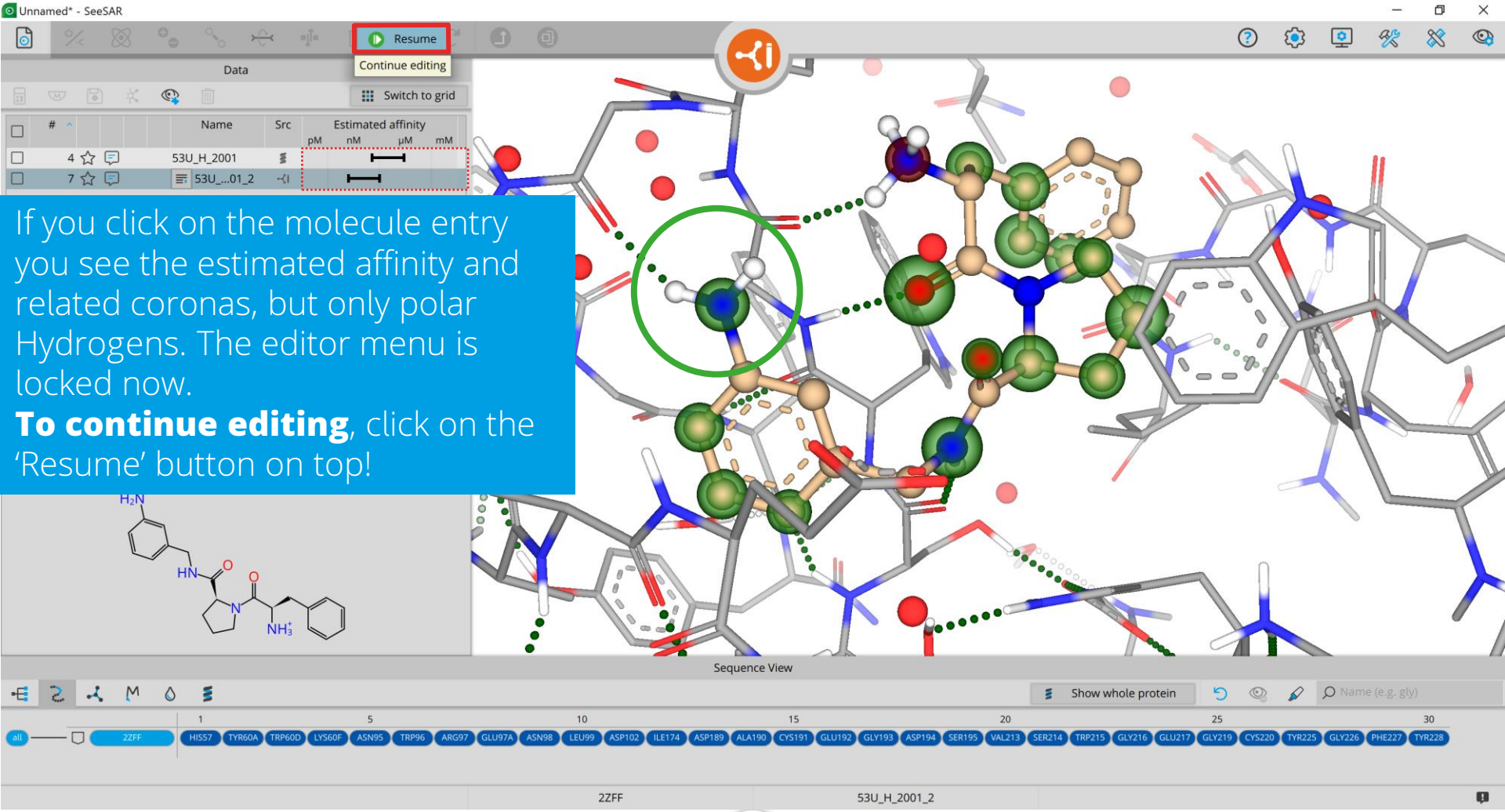


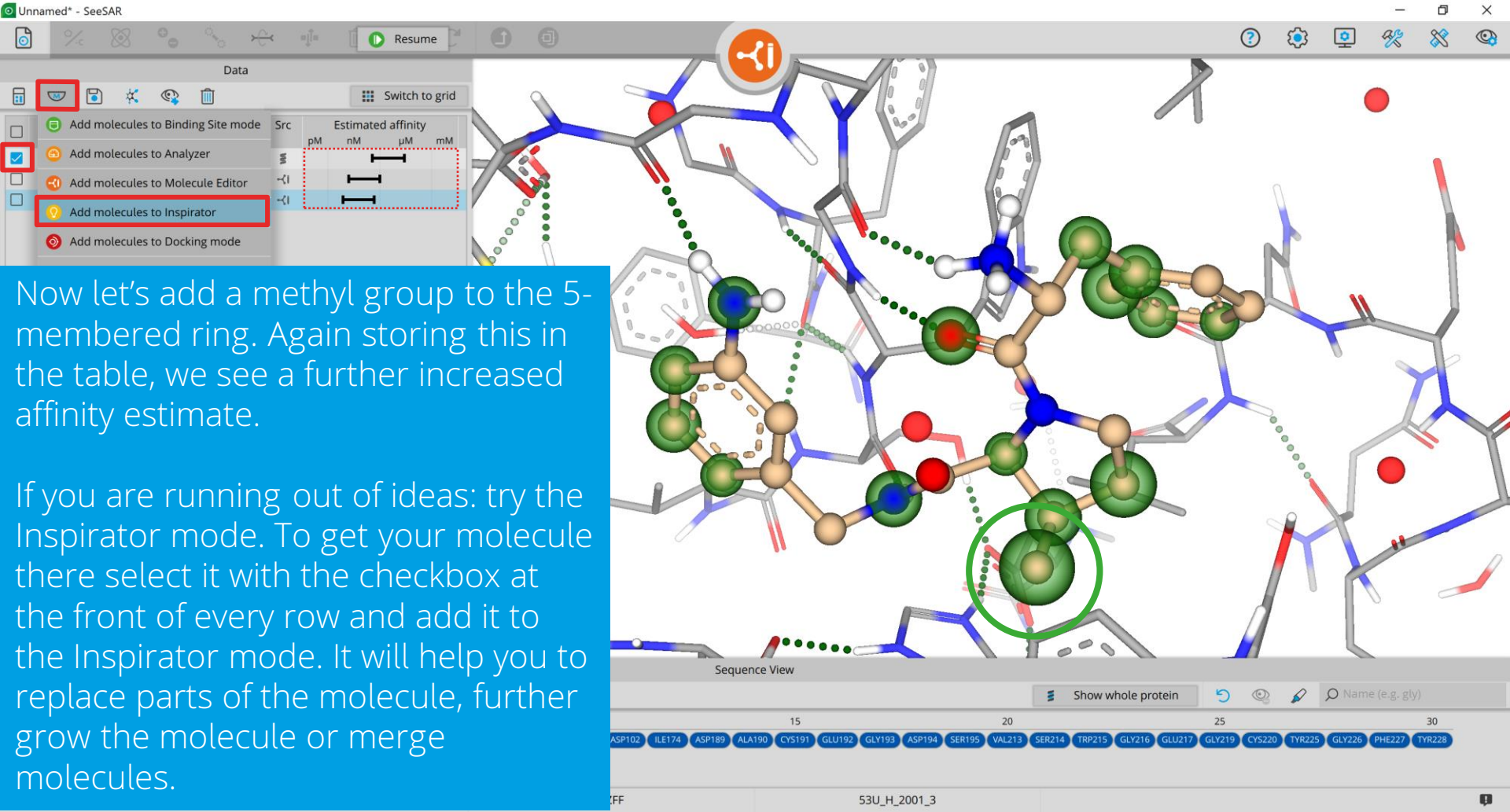
To edit a molecule ALWAYS:

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, ...).


Unnamed* - SeeSAR
Save edited molecules to table [Ctrl+E]
Data
Switch to grid
Name
Src
Estimated affinity
pM
nM
µM
mM
53U_H_2001
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 coronas. To see them, 1st add the edited ligand to the table (with the green button) and 2nd select the new entry in the table!
Sequence View
Show whole protein
Name (e.g. gly)
all
2ZFF
HIS57
TYR60A
TRP60D
LYS60F
ASN95
TRP96
ARG97
GLU97A
ASN98
LEU99
ASP102
ILE174
ASP189
ALA190
CYS191
GLU192
GLY193
ASP194
SER195
VAL213
SER214
TRP215
GLY216
GLU217
GLY219
CYS220
TYR225
GLY226
PHE227
TYR228
2ZFF
No molecule selected


Unnamed* - SeeSAR
Resume
Continue editing
Data
Switch to grid
Name
Src
Estimated affinity
pM nM µM mM
4 53U_H_2001
7 53U_...01_2
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 on top!
Sequence View
Show whole protein
Name (e.g. gly)
all
2ZFF
HIS57 TYR60A TRP60D LYS60F ASN95 TRP96 ARG97 GLU97A ASN98 LEU99 ASP102 ILE174 ASP189 ALA190 CYS191 GLU192 GLY193 ASP194 SER195 VAL213 SER214 TRP215 GLY216 GLU217 GLY219 CYS220 TYR225 GLY226 PHE227 TYR228
2ZFF
53U_H_2001_2



Now let's add a methyl group to the 5-membered ring. 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 own 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 docking mode in SeeSAR and add your molecules via the load button or copy/paste them to the input library field.

Loaded molecules may not yet be placed in the binding site (the information icon tells you upon mouse-over).
If your molecules were docked using another program you can load them straight into the Analyzer mode.

Alternatively, copy/paste your molecules (as smiles or sdf) here. If you like and example, copy the three molecules on the right in there, and change their names:

3-Amine-derivative:

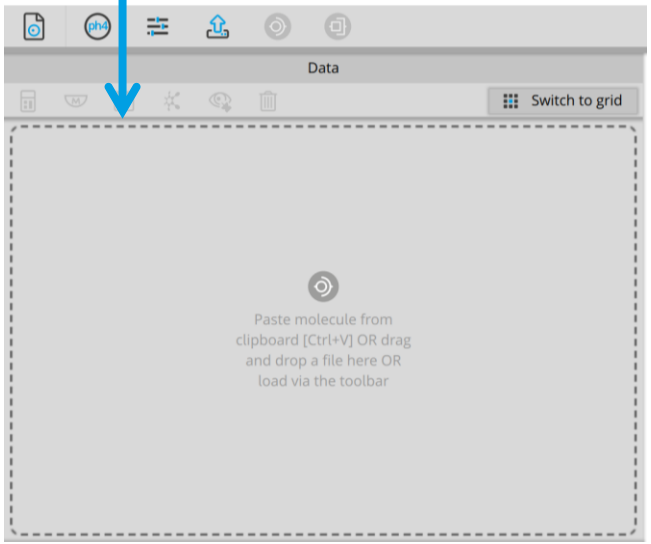
1) **N[C@H](CC1=CC=CC=C1)C(=O)N1CCC[C@H]1C(=O)NCC1=CC=CC(N)=C1**

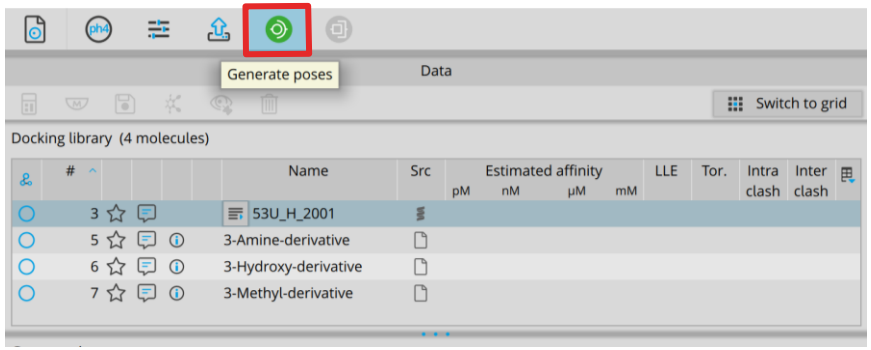
3-Hydroxy-derivative:

2) **N[C@H](CC1=CC=CC=C1)C(=O)N1CCC[C@H]1C(=O)NCC1=CC=CC(O)=C1**

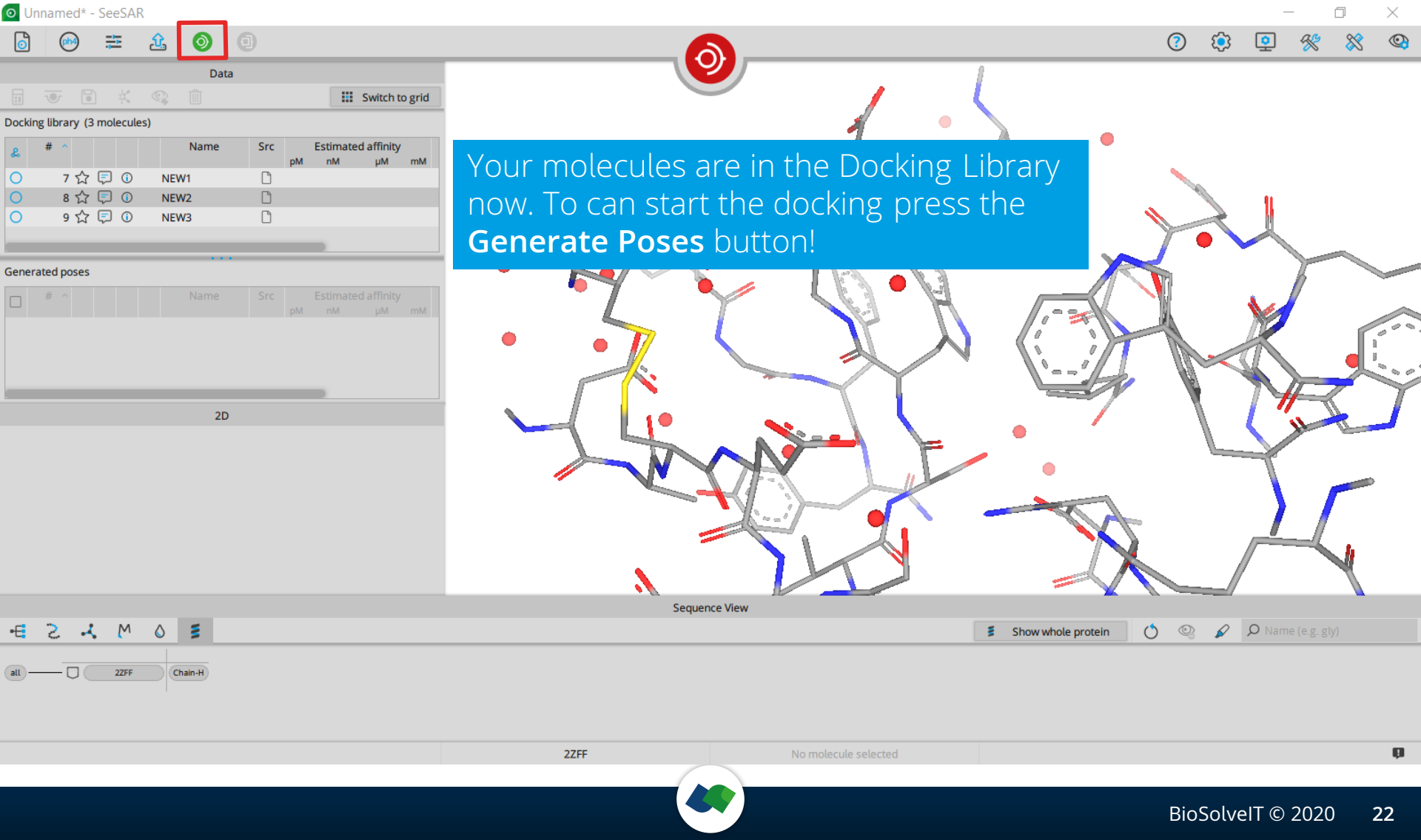
3-Methyl-derivative:

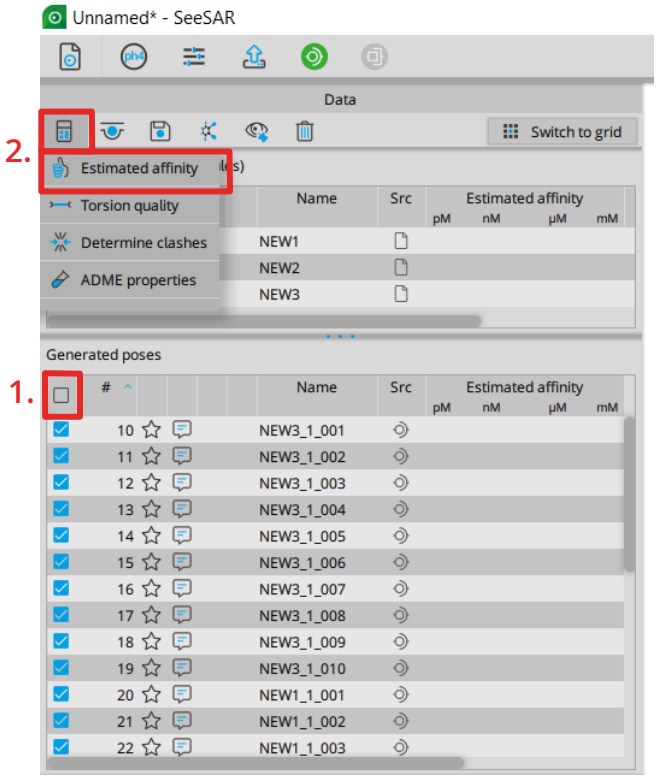
3) **CC1=CC(CNC(=O)[C@@H]2CCCN2C(=O)[C@H](N)CC2=CC=CC=C2)=CC=C1**





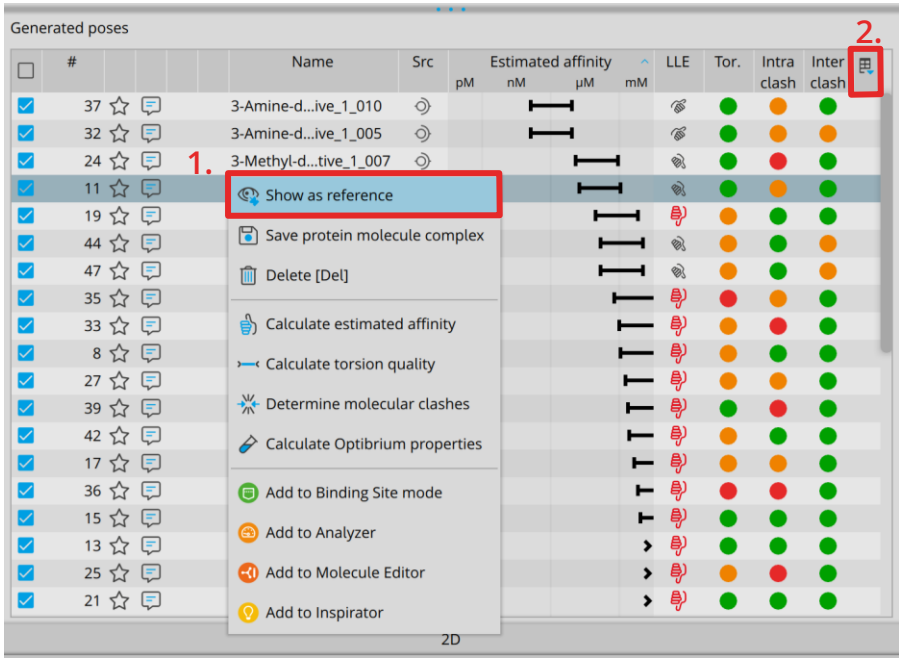
Now you can start the docking by pressing the **Generate Poses** button!


Unnamed* - SeeSAR
Data
Switch to grid
Docking library (3 molecules)
Name
Src
Estimated affinity
pM
nM
µM
mM
7 NEW1
8 NEW2
9 NEW3
Generated poses
2D
Your molecules are in the Docking Library now. To can start the docking press the **Generate Poses** button!
Sequence View
Show whole protein
Name (e.g. gly)
all
2ZFF
Chain-H
2ZFF
No molecule selected



At most 10 poses per molecule are generate this way, as we have left the docking settings on default. To get the estimated affinities, (1.) select all docking solutions with the checkmark in the first column and (2.) press the thumbs-up button under the calculator at the top of the table!

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.

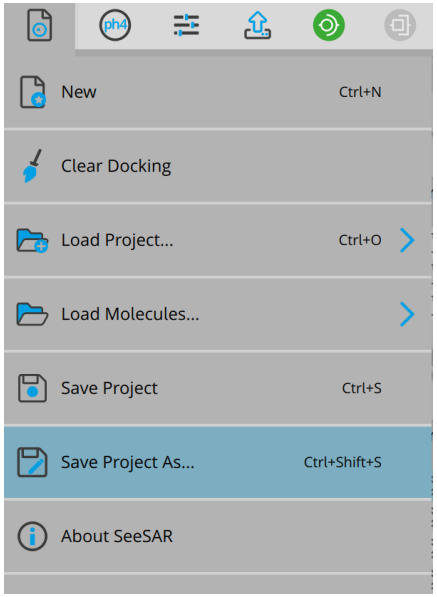
Clicking on a column header sorts according to this value.

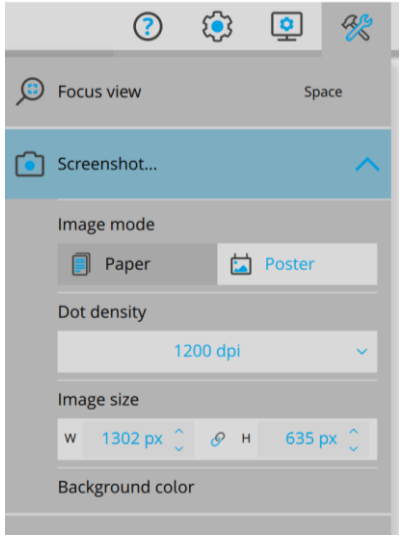
To inspect multiple poses in comparison, (1.) toggle the permanent visibility by marking a molecule as reference. Now it will appear in purple color and stay visible as you select other molecules.

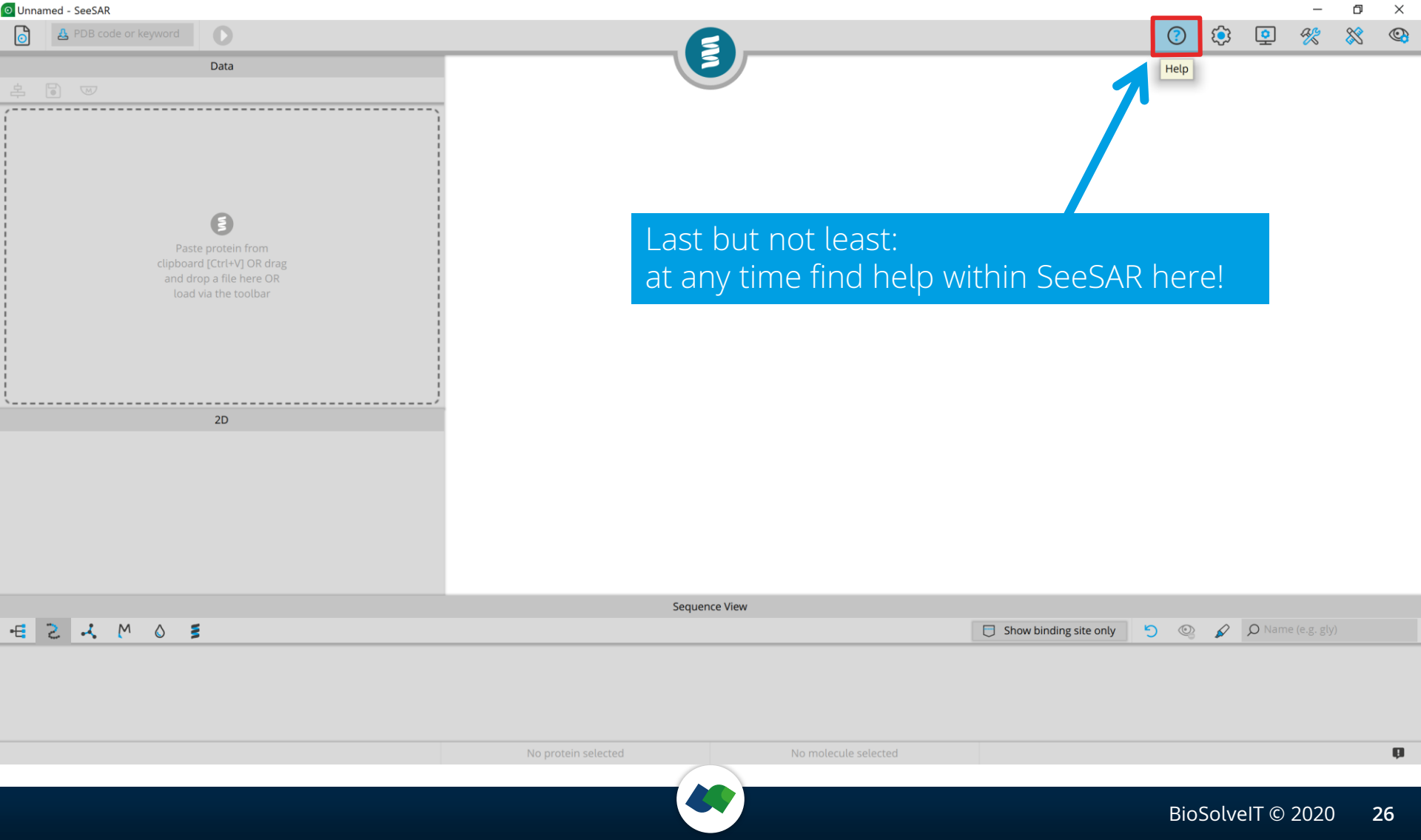
You can add more physico-chemical and ADME-properties as well as pharmacological parameters to your table with a click on the table button (2.).

By now you have a lot of interesting values and possibly many molecules. You may want to:

- apply some (pharmacophore) filters? Copy the molecules of interest to the Analyzer mode and use the filter panel on the right side of the table.
- grow your molecule? Add it to the Inspirator and use the growing functionality.
- generate pictures for a report or publication? You can do this under the 'utilities' button in the upper right toolbar.
- save your session, to continue working a different time, by clicking **Save Project As...**






Unnamed - SeeSAR
PDB code or keyword
Help
Data
Paste protein from clipboard [Ctrl+V] OR drag and drop a file here OR load via the toolbar
2D
Last but not least:
at any time find help within SeeSAR here!
Sequence View
Show binding site only
Name (e.g. gly)
No protein selected
No molecule selected

Now we wish you happy SeeSAR-ing!