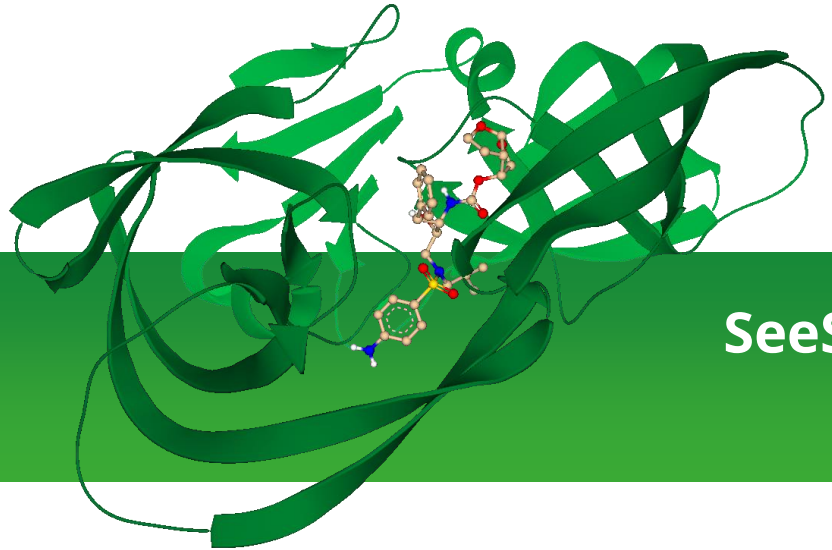
SeeSAR

BioSolveIT
expect actives!



SeeSAR Covalent Docking First Aid

Important Note

So far SeeSAR is limited to handling 50,000 (50k) molecules and respective docking poses to ensure a sophisticated user experience. Translated covalent compound libraries may exceed this limit and thus require a prefiltering to be handled satisfactorily.
The procedures are explained in this guide.

If you need any help or support please do not hesitate to contact us:

support@biosolveit.de

1. Basics

Welcome to the exciting world of covalent docking in SeeSAR!

BioSolveIT has translated supplier libraries featuring a broad range of covalent warheads into a convenient ready-to-dock format for SeeSAR.

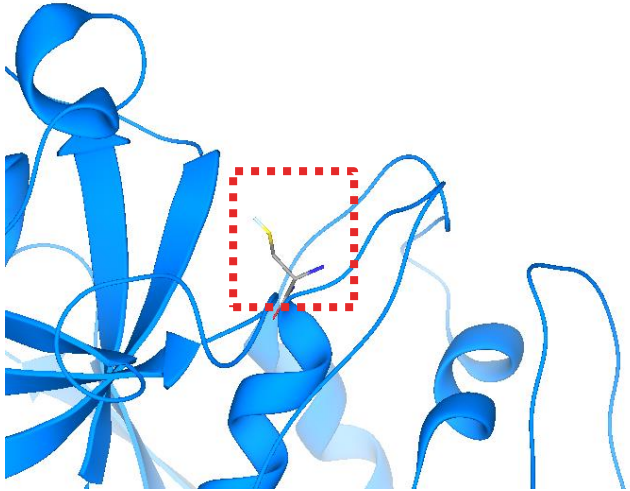
We offer two kinds of covalent libraries:

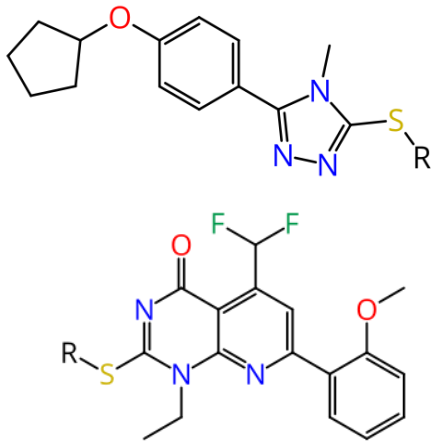
Teaser set (10k molecules)
Ready to be used in SeeSAR to evaluate covalent docking at your target.

Translated supplier sets
Require prefiltering before covalent docking.

Covalent docking

To perform covalent docking you need two things prepared:

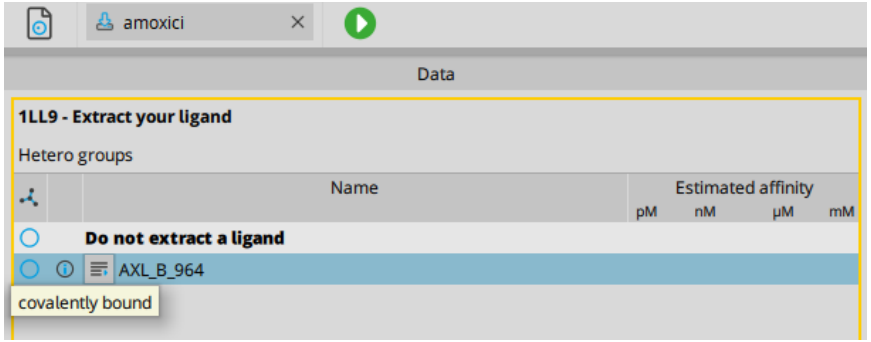




A **covalent target**
see → 2. Attachement Site

Covalent molecules
see → 3. Covalent libraries

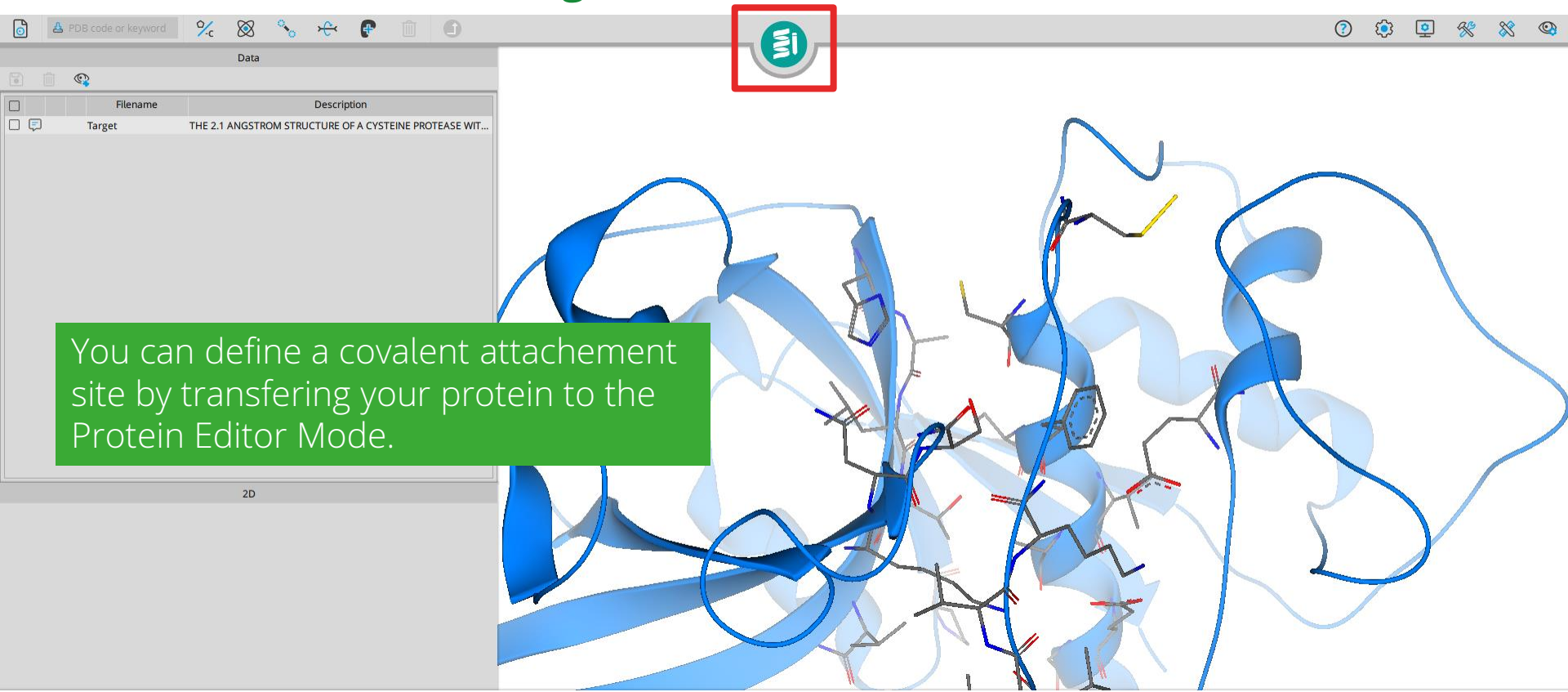
2. Attachment Site



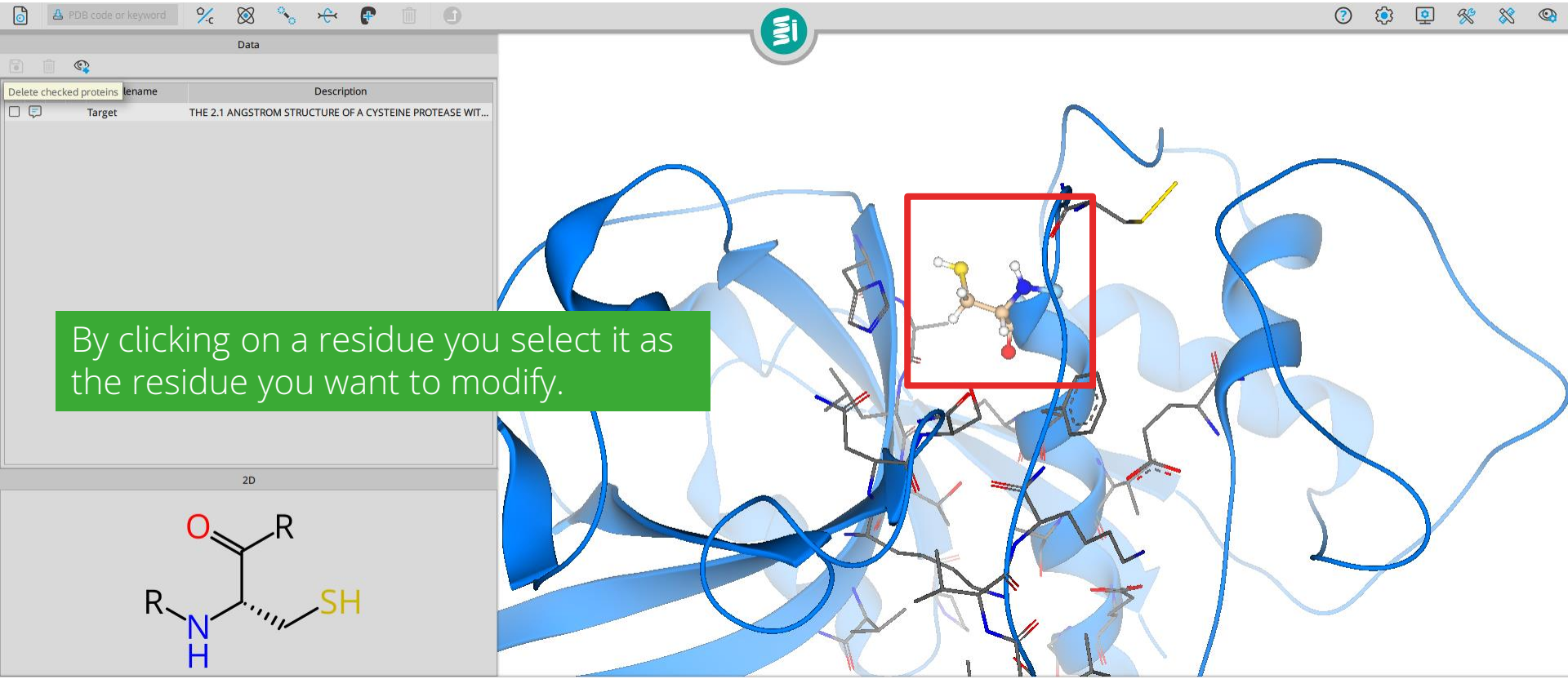
Upon loading your protein structure and defining your ligand, SeeSAR will inform you if a ligand is covalently binding at your structure.
In this case the attachement point will be recognized and kept with the binding site definition by selecting the covalent ligand.

If your structure lacks a covalently-bound ligand you need to prepare the attachement site.

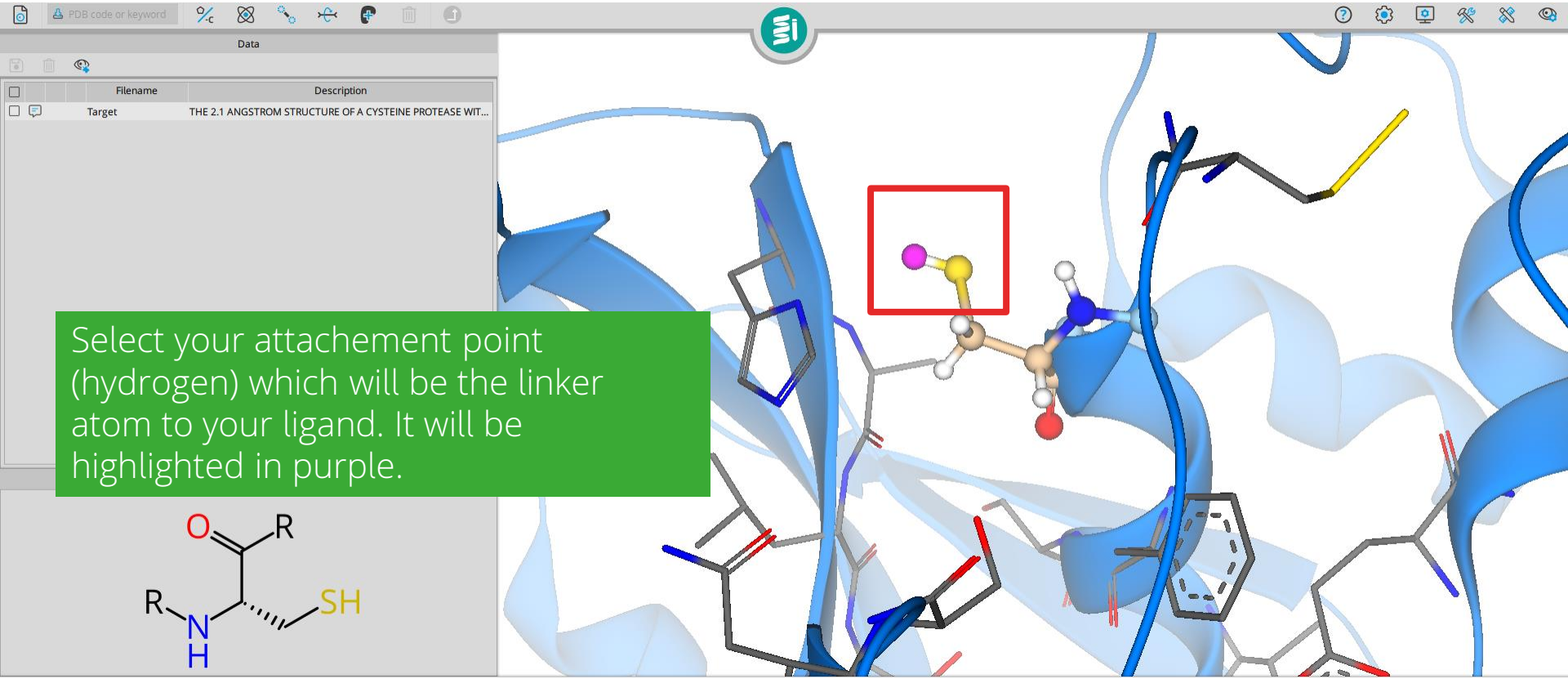
Defining a covalent attachment site

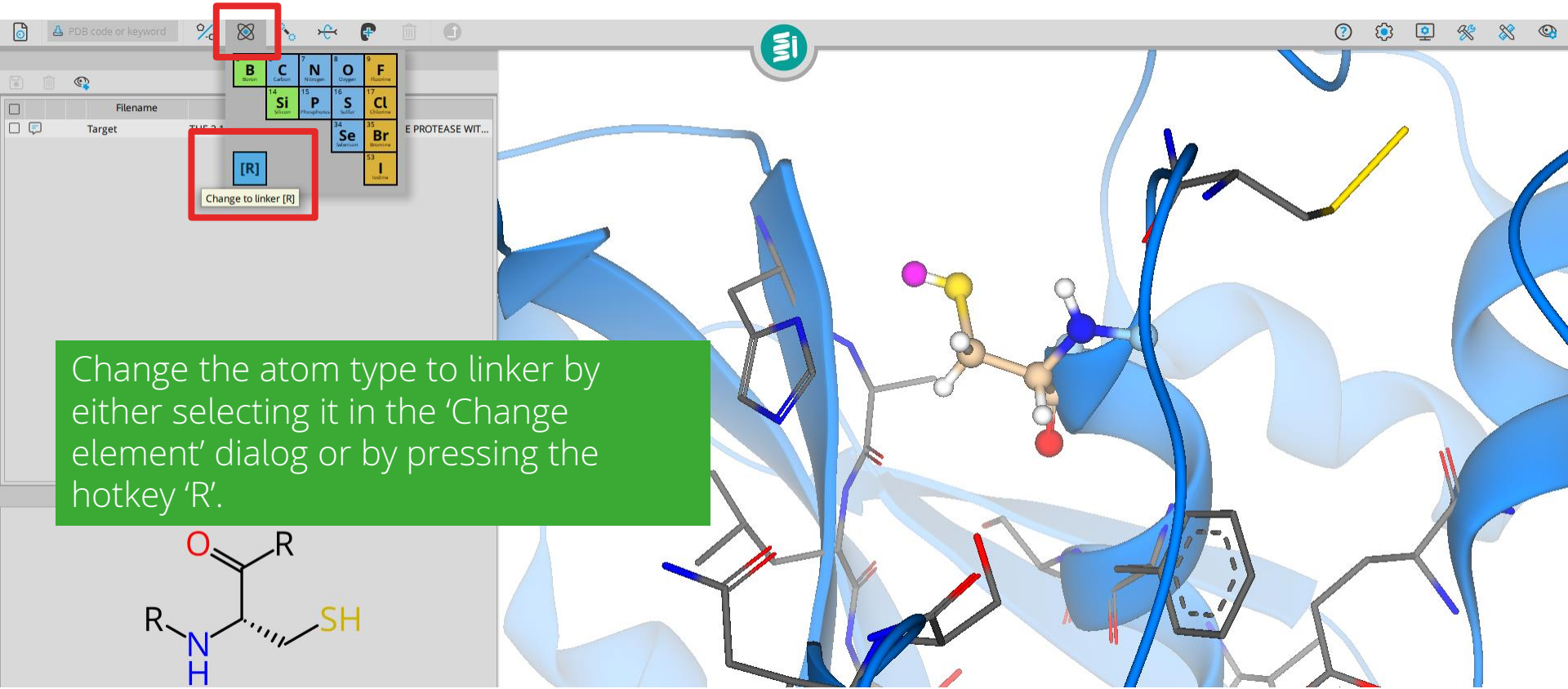


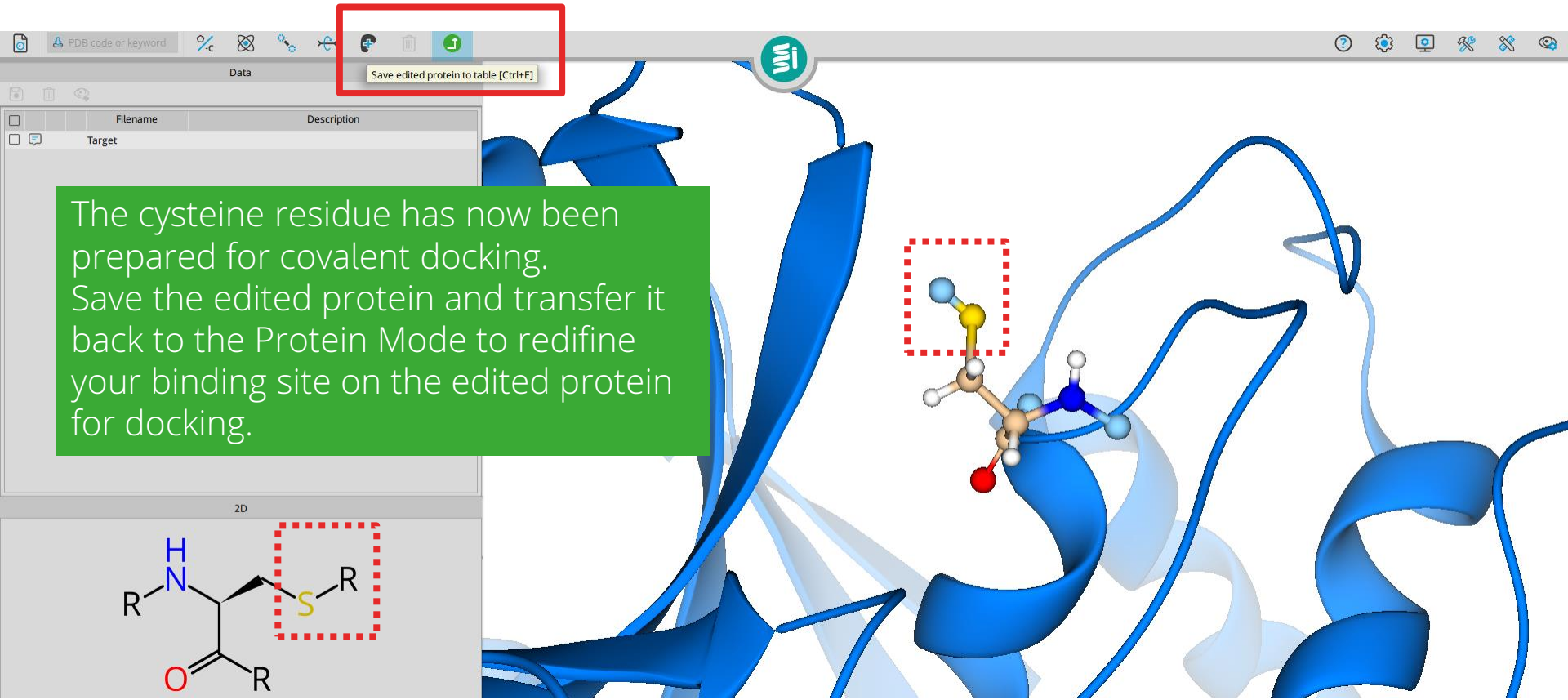
You can define a covalent attachement site by transfering your protein to the Protein Editor Mode.



By clicking on a residue you select it as the residue you want to modify.

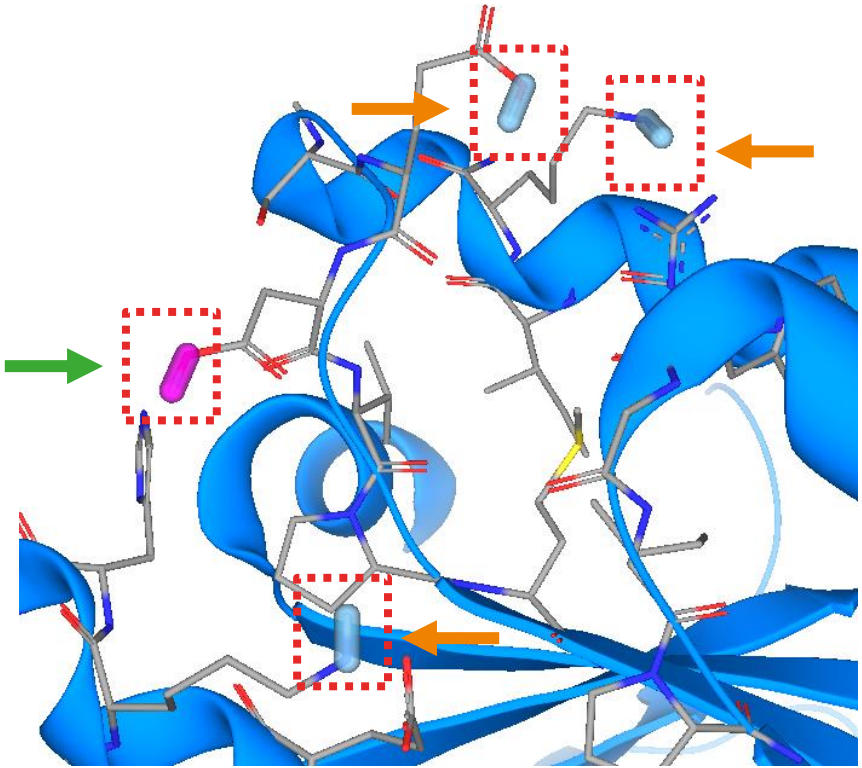

PDB code or keyword
Data
Filename
Description
Target
THE 2.1 ANGSTROM STRUCTURE OF A CYSTEINE PROTEASE WIT...
Select your attachement point (hydrogen) which will be the linker atom to your ligand. It will be highlighted in purple.
O
R
R
N
H
SH


PDB code or keyword
B
C
N
O
F
Si
P
S
Cl
Se
Br
I
[R]
Change to linker [R]
Filename
Target
Change the atom type to linker by either selecting it in the ‘Change element’ dialog or by pressing the hotkey ‘R’.
O
R
R
N
H
SH



The cysteine residue has now been prepared for covalent docking.
Save the edited protein and transfer it back to the Protein Mode to redifine your binding site on the edited protein for docking.

Selection of covalent binding residue



If several covalent attachement dummies are present in your structure you can freely decide which one of them shall be docked at by clicking on the dummy tubus.
The active residue is highlighted in purple.

3. Covalent libraries

SDF14	SDF15	SDF16	
Cys, Lys, Ser	Chemspace	Allylamide	
Cys, Lys, Ser	Chemspace	Allylamide	
Cys, Lys, Ser	Chemspace	Allylamide	

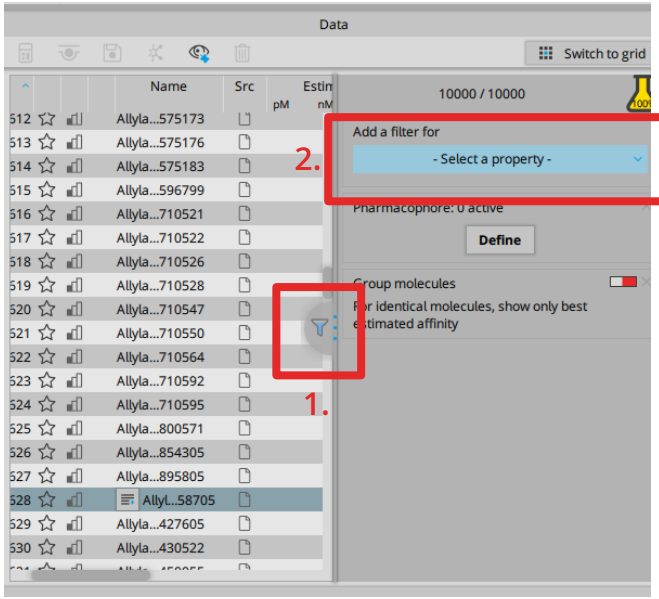
We recommend to use KNIME to assess and filter compound libraries containing more than 50k members.

Every translated covalent library sd-file contains information on:

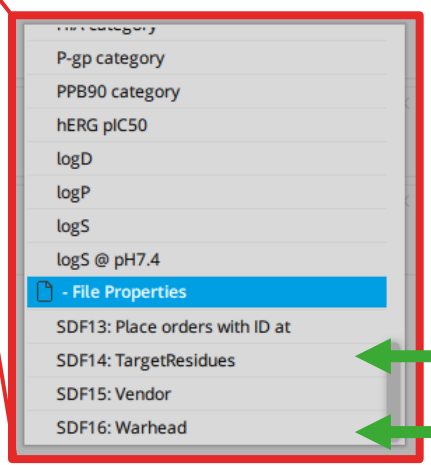
- vendor
- warhead functionality
- target residue
- (sublibrary)

You can use this information to filter for covalent functionalities you are interested in or for compounds likely to target a specific residue.

Prefilter your library in SeeSAR

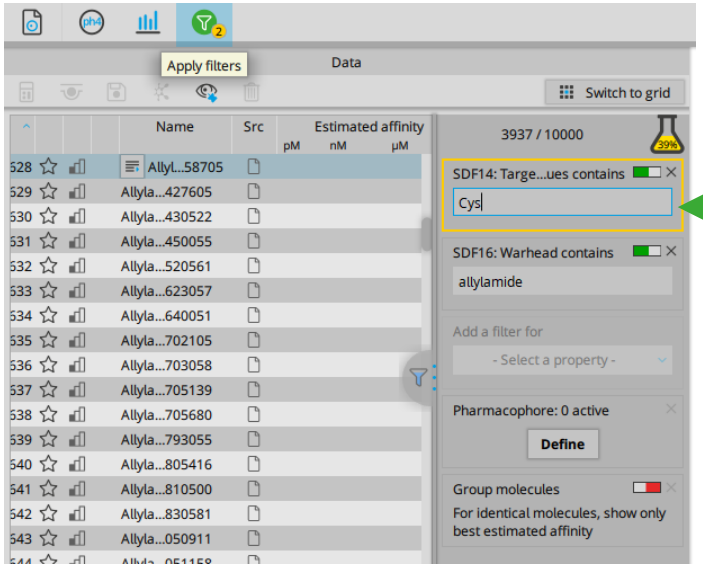


Go to the **Analyzer Mode** to filter your compounds for a specific residue or warhead.
Click on the funnel icon to open the filter window.



Scroll down to select a property of interest to filter for.

Filter for target residues

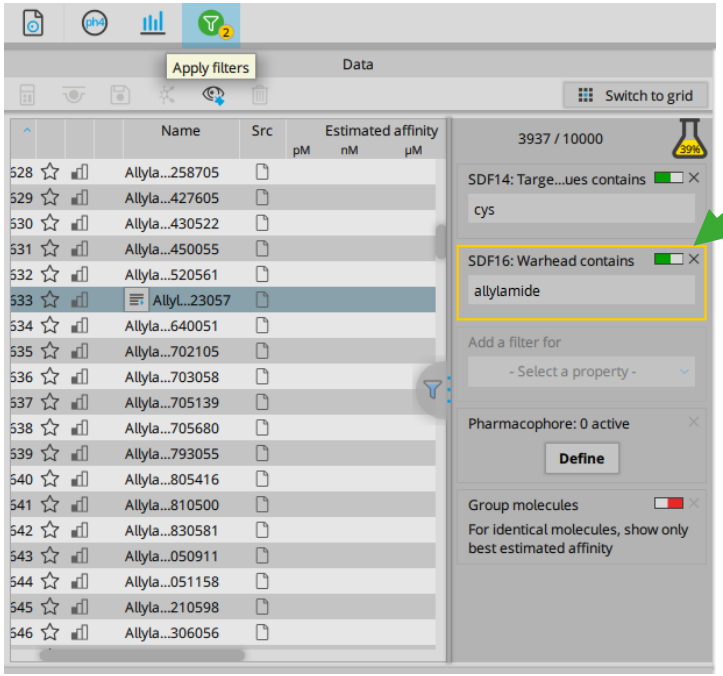


Type the 3-letter-code of your target residue (and press the 'Apply filters' button if it is green to activate your selection).

Residues you can filter for:

Cys – cysteine
Glu – glutamic acid
Lys – lysine
Ser – serine
Thr – threonine
Tyr – tyrosine

Filter for warheads

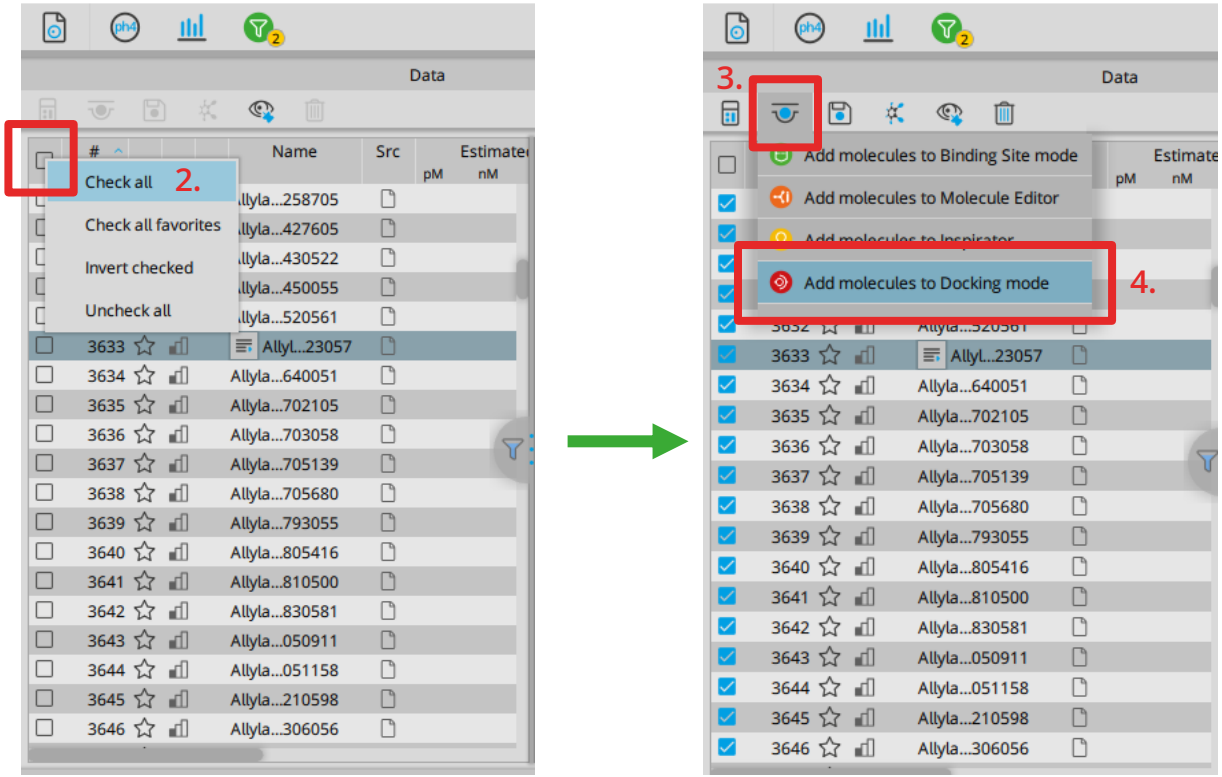


Likewise you can filter for a warhead of your choice.

possible warheads

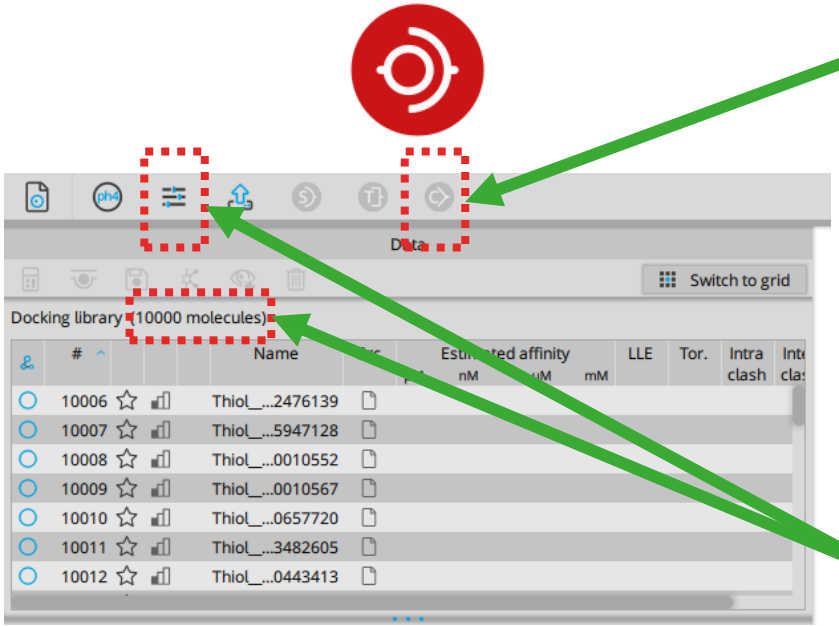
Aldehyde	Carbamate	Maleimide
Alkynyl	Cyanamide	Nitrile
Alkynylyl	Diazerine	Nitroalkane
Allylamide	Disulfide	Oxetane
Allylester	Epoxide	Propagylamine
Arylator	Imidazole	Pyrazole
Azaridine	Ketoalkynylyl	Sulfonylallyl
Azido	Ketoamide	Sulfonylfluoride
β-aminoketone	Ketohalogen	Thiol
Boronate	Lactam	Urea

Transfer your selection to Docking Mode



To proceed with covalent docking transfer the compounds to the docking mode.

4. Covalent Docking



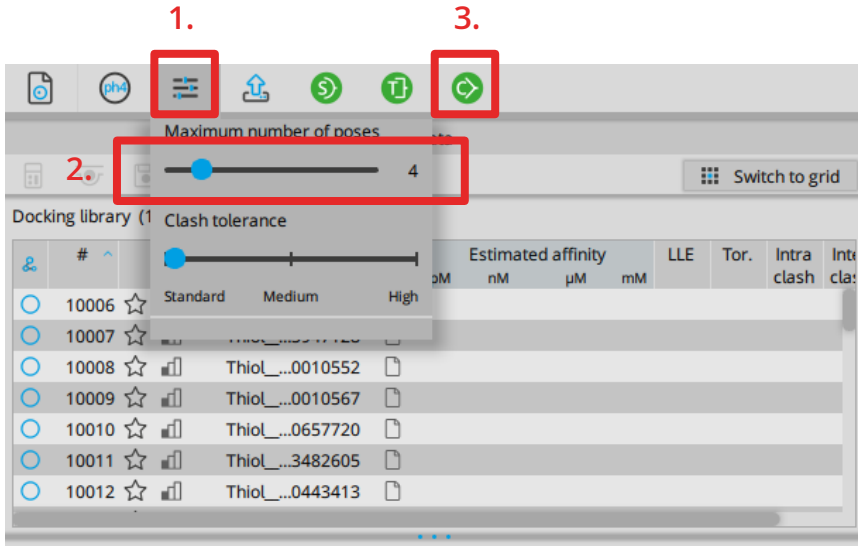
A greyed out docking button can have different reasons:

1. No covalent binding residue has been defined

2. No covalent compound is present in the docking mode

3. The resulting docking poses would exceed the limit of 50,000 entries
→ Number of molecules in the docking library x maximum number of poses during docking

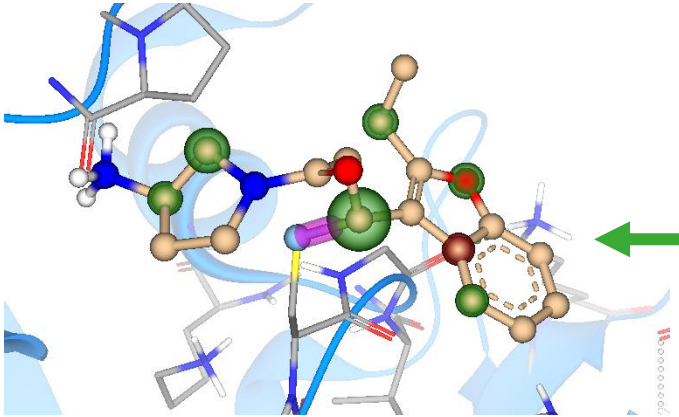
Adjust the number of poses



(1) Go to the pose generator parameters
(2) Adjust the maximum number of poses till the covalent docking button is green.
(3) Start the covalent docking with your selected parameters.

Generated poses

#	Name	Src	Estimated affinity (pM nM µM mM)	Tor.	Intra clash	Inte clas
10014	Allyl..._1_03					
10015	Allylam...05_1_04					
10012	Allylam...05_1_01					
10024	Allylam...02_1_01					
10020	Allylam...3_1_001					
10022	Allylam...3_1_003					
10031	Allylam...8_1_004					



After docking and HYDE assessment:
Rank you compounds by clicking on the 'Estimated affinity' column till the arrow points upwards (^).
The compounds are now ranked with the highest (best) score on the top and the lowest (worst) score on the bottom of the table.
→ Assistance to rank docked compounds is in the works. stay tuned.

Now it is up to you to decide which binding modes are of interest. Go through your generated poses and visually inspect the results.