



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.

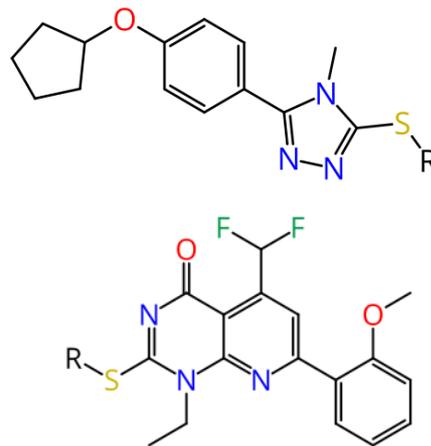
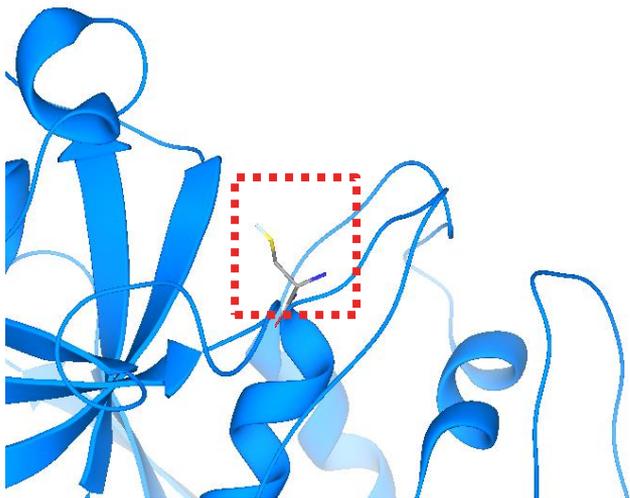
Translated supplier sets

Require prefiltering before covalent docking.



Covalent docking

To perform covalent docking you need two things prepared:

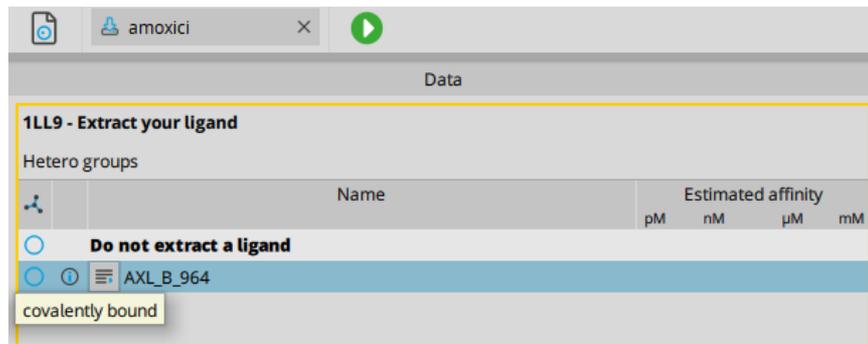


A covalent target
see → 2. Attachment Site

Covalent molecules
see → 3. Covalent libraries



2. Attachment Site



1LL9 - Extract your ligand

Hetero groups

	Name	Estimated affinity			
		pM	nM	μM	mM
<input type="radio"/>	Do not extract a ligand				
<input checked="" type="radio"/>	AXL_B_964				

covalently bound

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 attachment 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 attachment site.



Defining a covalent attachment site

Data

Filename	Description
Target	THE 2.1 ANGSTROM STRUCTURE OF A CYSTEINE PROTEASE WIT...

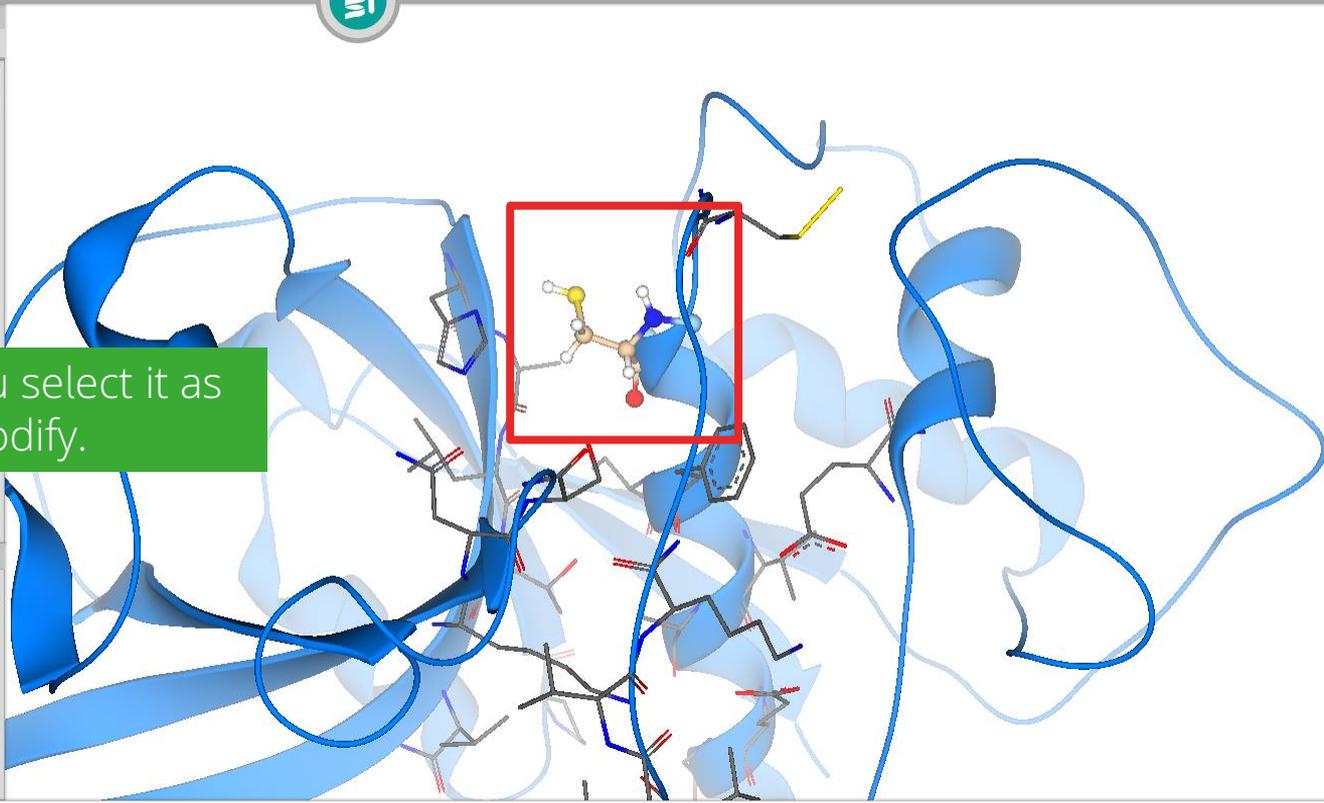
2D

You can define a covalent attachment site by transferring your protein to the Protein Editor Mode.

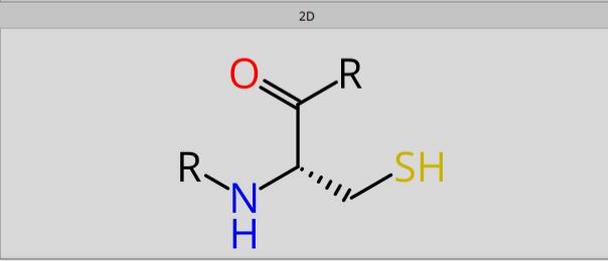


Data

Delete checked proteins	Idename	Description
<input type="checkbox"/>	Target	THE 2.1 ANGSTROM STRUCTURE OF A CYSTEINE PROTEASE WIT...



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

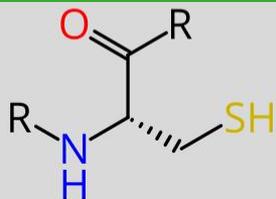


Select your attachment point (hydrogen) which will be the linker atom to your ligand. It will be highlighted in purple.

RNC(R)C(S)R

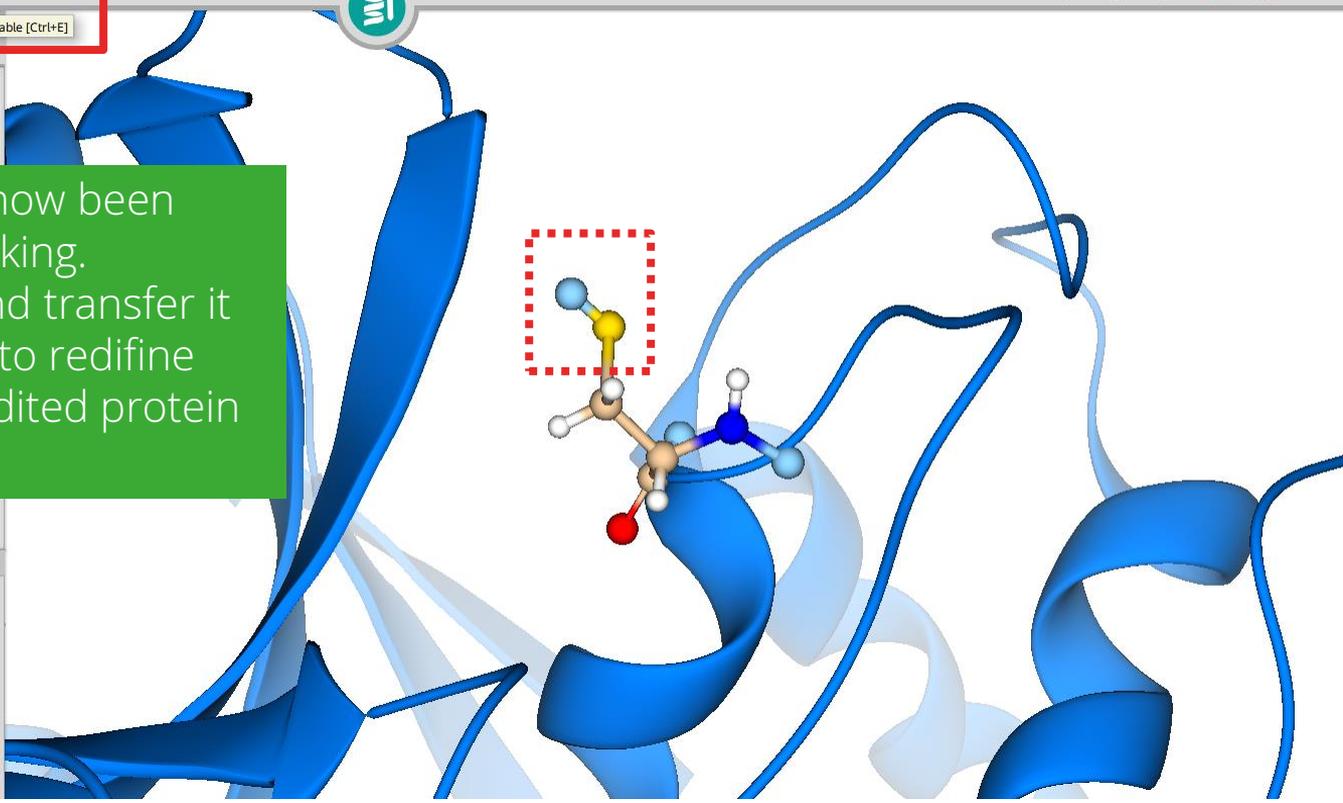
The screenshot shows a molecular modeling software interface. On the left, a 'Change element' dialog box is open, displaying a periodic table of elements. The element [R] is highlighted, and a tooltip below it reads 'Change to linker [R]'. A red box highlights the 'Change element' icon in the top toolbar. The main window displays a 3D ribbon representation of a protein structure in light blue, with a ligand molecule shown in stick representation. The ligand consists of a central carbon atom bonded to a nitrogen atom (blue), a sulfur atom (yellow), and two oxygen atoms (red). The protein structure is shown in a light blue ribbon representation, with various side chains visible. The interface includes a top toolbar with various icons, a left sidebar with a file browser, and a bottom status bar with a logo and page number.

Change the atom type to linker by either selecting it in the 'Change element' dialog or by pressing the hotkey 'R'.

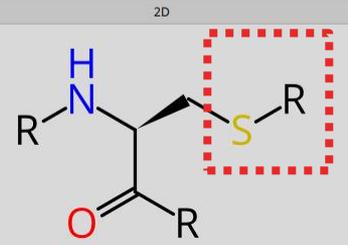




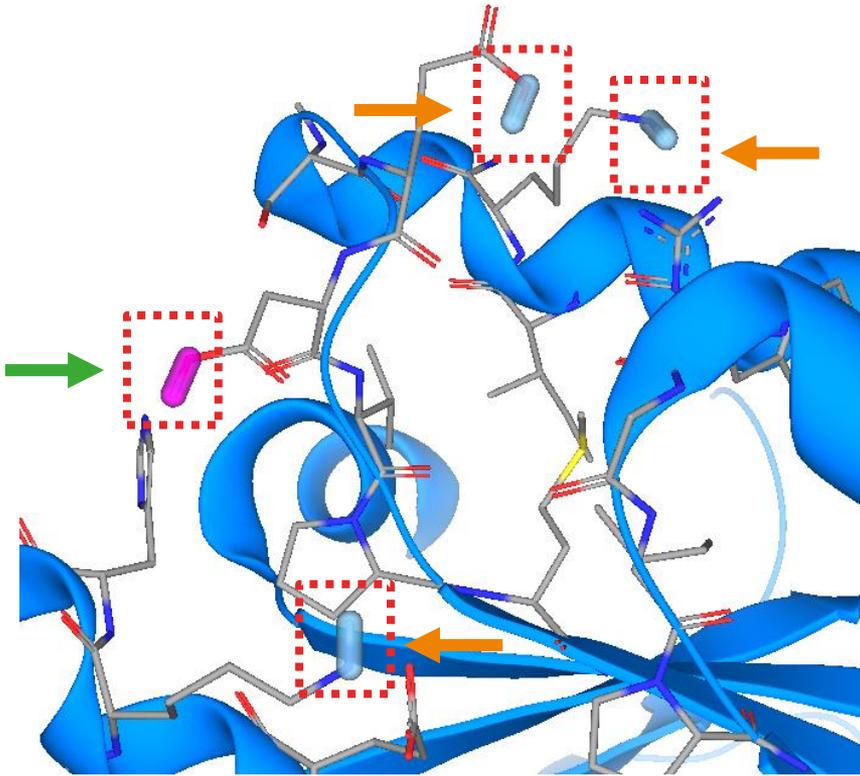
The cysteine residue has now been prepared for covalent docking. Save the edited protein and transfer it back to the Protein Mode to redefine your binding site on the edited protein for docking.



Filename	Description
Target	



Selection of covalent binding residue



If several covalent attachment 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



The screenshot shows the SeeSAR interface with a table of compounds. The table has columns for Name, Src, Estin, and nM. The 'Estin' column is set to 10000 / 10000. A red box labeled '1.' highlights a funnel icon in the top right of the table. Another red box labeled '2.' highlights a dropdown menu that says 'Add a filter for' and '- Select a property -'. Below the table, there are options for 'Pharmacophore: 0 active' and 'Group molecules'.

	Name	Src	Estin	nM
512	Allyla...575173			
513	Allyla...575176			
514	Allyla...575183			
515	Allyla...596799			
516	Allyla...710521			
517	Allyla...710522			
518	Allyla...710526			
519	Allyla...710528			
520	Allyla...710547			
521	Allyla...710550			
522	Allyla...710564			
523	Allyla...710592			
524	Allyla...710595			
525	Allyla...800571			
526	Allyla...854305			
527	Allyla...895805			
528	Allyl...58705			
529	Allyla...427605			
530	Allyla...430522			

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.

The filter window shows a list of properties to filter by. The list includes: P-gp category, PPB90 category, hERG pIC50, logD, logP, logS, logS @ pH7.4, - File Properties (highlighted), SDF13: Place orders with ID at, SDF14: TargetResidues, SDF15: Vendor, and SDF16: Warhead. Green arrows point to 'SDF14: TargetResidues' and 'SDF16: Warhead'.

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



Filter for target residues

The screenshot shows a software interface with a data table and a filter panel. The data table has columns for Name, Src, and Estimated affinity (pM, nM, μM). The filter panel on the right has a text input field containing 'Cys' and a green arrow pointing to it from the right. The filter panel also shows other filters like 'SDF14: Target...ues contains' and 'SDF16: Warhead contains'.

	Name	Src	Estimated affinity
			pM nM μM
528	Allyl...58705		
529	Allyl...427605		
530	Allyl...430522		
531	Allyl...450055		
532	Allyl...520561		
533	Allyl...623057		
534	Allyl...640051		
535	Allyl...702105		
536	Allyl...703058		
537	Allyl...705139		
538	Allyl...705680		
539	Allyl...793055		
540	Allyl...805416		
541	Allyl...810500		
542	Allyl...830581		
543	Allyl...050911		
544	Allyl...051158		

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

Apply filters Data

Name	Src	Estimated affinity
		pM nM μ M
528 ☆	Allyla...258705	
529 ☆	Allyla...427605	
530 ☆	Allyla...430522	
531 ☆	Allyla...450055	
532 ☆	Allyla...520561	
533 ☆	Allyl...23057	
534 ☆	Allyla...640051	
535 ☆	Allyla...702105	
536 ☆	Allyla...703058	
537 ☆	Allyla...705139	
538 ☆	Allyla...705680	
539 ☆	Allyla...793055	
540 ☆	Allyla...805416	
541 ☆	Allyla...810500	
542 ☆	Allyla...830581	
543 ☆	Allyla...050911	
544 ☆	Allyla...051158	
545 ☆	Allyla...210598	
546 ☆	Allyla...306056	

3937 / 10000

SDF14: Target...ues contains ×

cys

SDF16: Warhead contains ×

allylamide

Add a filter for

- Select a property -

Pharmacophore: 0 active

Define

Group molecules ×

For identical molecules, show only best estimated affinity

Likewise you can filter for a warhead of your choice.

possible warheads

Aldehyde	Carbamate	Maleimide
Alkynyl	Cyanamide	Nitrile
Alkynyllyl	Diazirine	Nitroalkane
Allylamide	Disulfide	Oxetane
Allylester	Epoxide	Propargylamine
Arylator	Imidazole	Pyrazole
Azaridine	Ketoalkynyl	Sulfonylallyl
Azido	Ketoamide	Sulfonylfluoride
β -aminoketone	Ketohalogen	Thiol
Boronate	Lactam	Urea



Transfer your selection to Docking Mode

1. 2. Check all

#	Name	Src	Estimate
			pM nM
<input type="checkbox"/>	Allyla...258705		
<input type="checkbox"/>	Allyla...427605		
<input type="checkbox"/>	Allyla...430522		
<input type="checkbox"/>	Allyla...450055		
<input type="checkbox"/>	Allyla...520561		
<input type="checkbox"/>	AllyL...23057		
<input type="checkbox"/>	Allyla...640051		
<input type="checkbox"/>	Allyla...702105		
<input type="checkbox"/>	Allyla...703058		
<input type="checkbox"/>	Allyla...705139		
<input type="checkbox"/>	Allyla...705680		
<input type="checkbox"/>	Allyla...793055		
<input type="checkbox"/>	Allyla...805416		
<input type="checkbox"/>	Allyla...810500		
<input type="checkbox"/>	Allyla...830581		
<input type="checkbox"/>	Allyla...050911		
<input type="checkbox"/>	Allyla...051158		
<input type="checkbox"/>	Allyla...210598		
<input type="checkbox"/>	Allyla...306056		

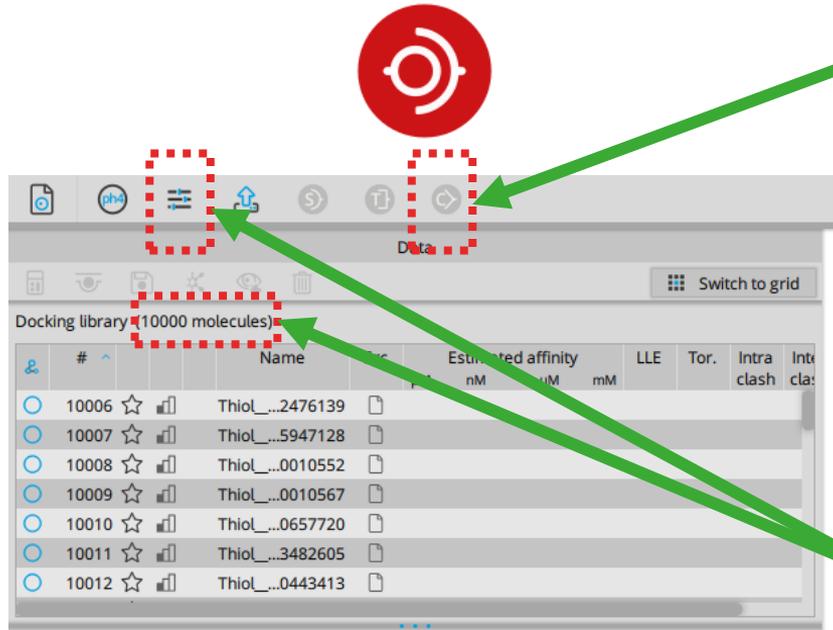
3. 4. Add molecules to Docking mode

#	Name	Src	Estimate
			pM nM
<input checked="" type="checkbox"/>	Allyla...520561		
<input checked="" type="checkbox"/>	AllyL...23057		
<input checked="" type="checkbox"/>	Allyla...640051		
<input checked="" type="checkbox"/>	Allyla...702105		
<input checked="" type="checkbox"/>	Allyla...703058		
<input checked="" type="checkbox"/>	Allyla...705139		
<input checked="" type="checkbox"/>	Allyla...705680		
<input checked="" type="checkbox"/>	Allyla...793055		
<input checked="" type="checkbox"/>	Allyla...805416		
<input checked="" type="checkbox"/>	Allyla...810500		
<input checked="" type="checkbox"/>	Allyla...830581		
<input checked="" type="checkbox"/>	Allyla...050911		
<input checked="" type="checkbox"/>	Allyla...051158		
<input checked="" type="checkbox"/>	Allyla...210598		
<input checked="" type="checkbox"/>	Allyla...306056		

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



4. Covalent Docking



A greyed out docking button can have different reasons:

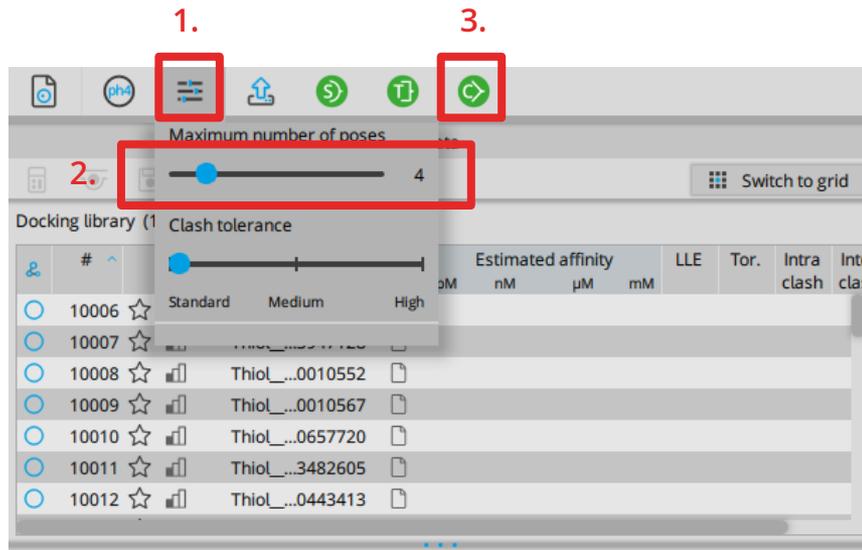
1. No covalent binding residue has been defined

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

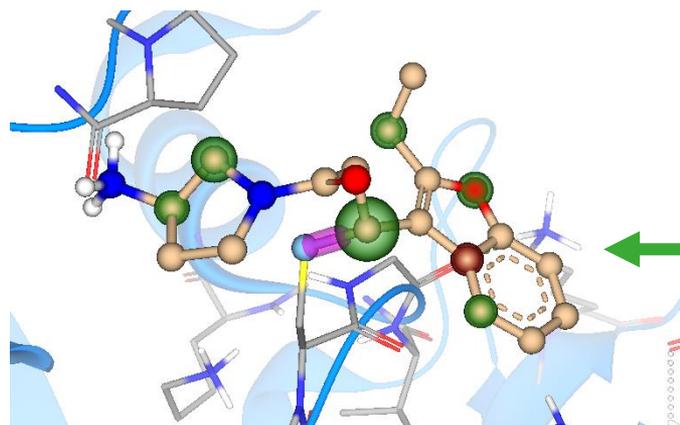


- (1) Go to the pose generator parameters
- (2) Adjust the maximum number of poses till the covalent docking button is green.
- (3) Start the covalent docking with your selected parameters.



Generated poses

#	Name	Src	Estimated affinity				LF	Tor.	Intra	Inter
			pM	nM	µM	mM				
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 your 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.

