



SeeSAR Covalent Docking Guide

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.

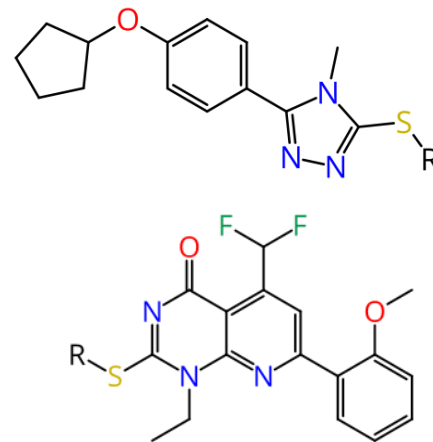
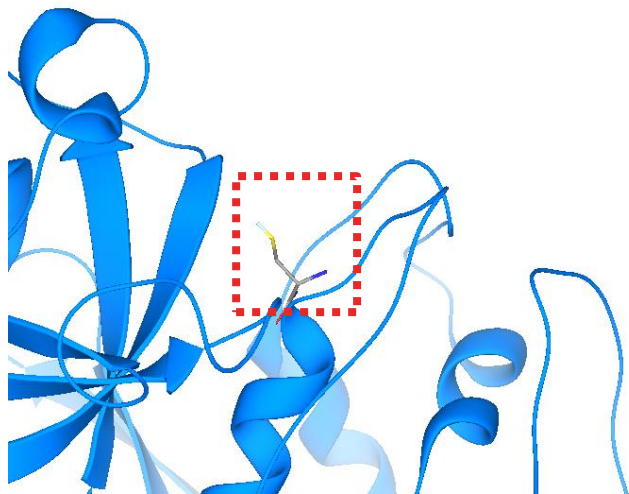
Translated supplier sets

Require prefiltering before covalent docking.



Covalent docking

To perform covalent docking you need two things prepared:

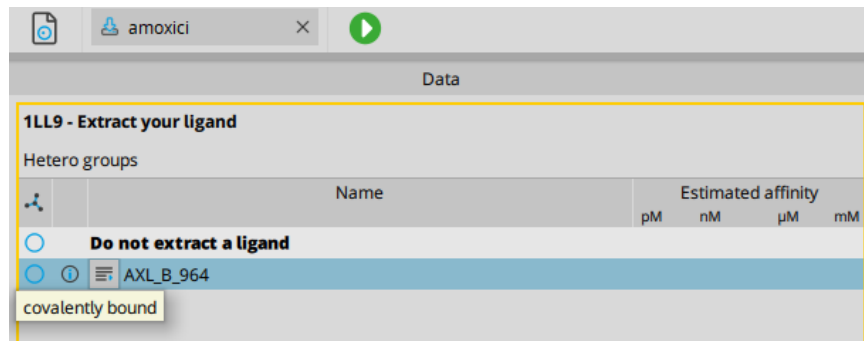


A covalent target
see → 2. Attachment Site

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.



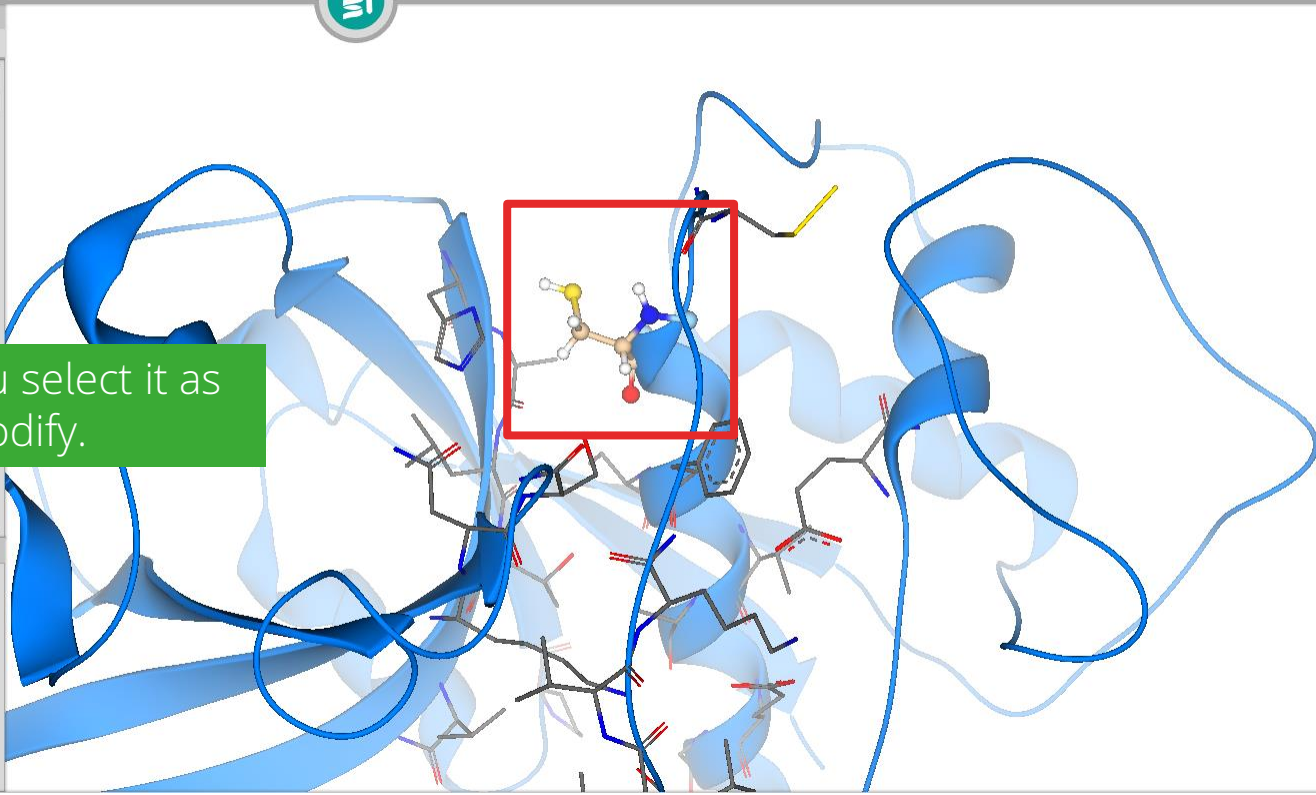
Defining a covalent attachment site

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

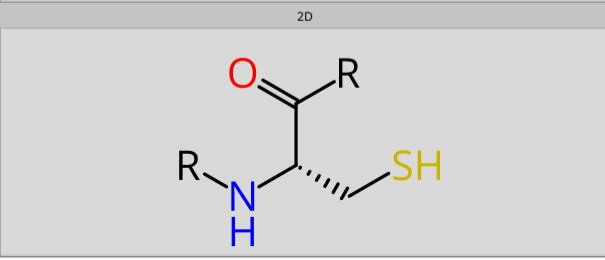


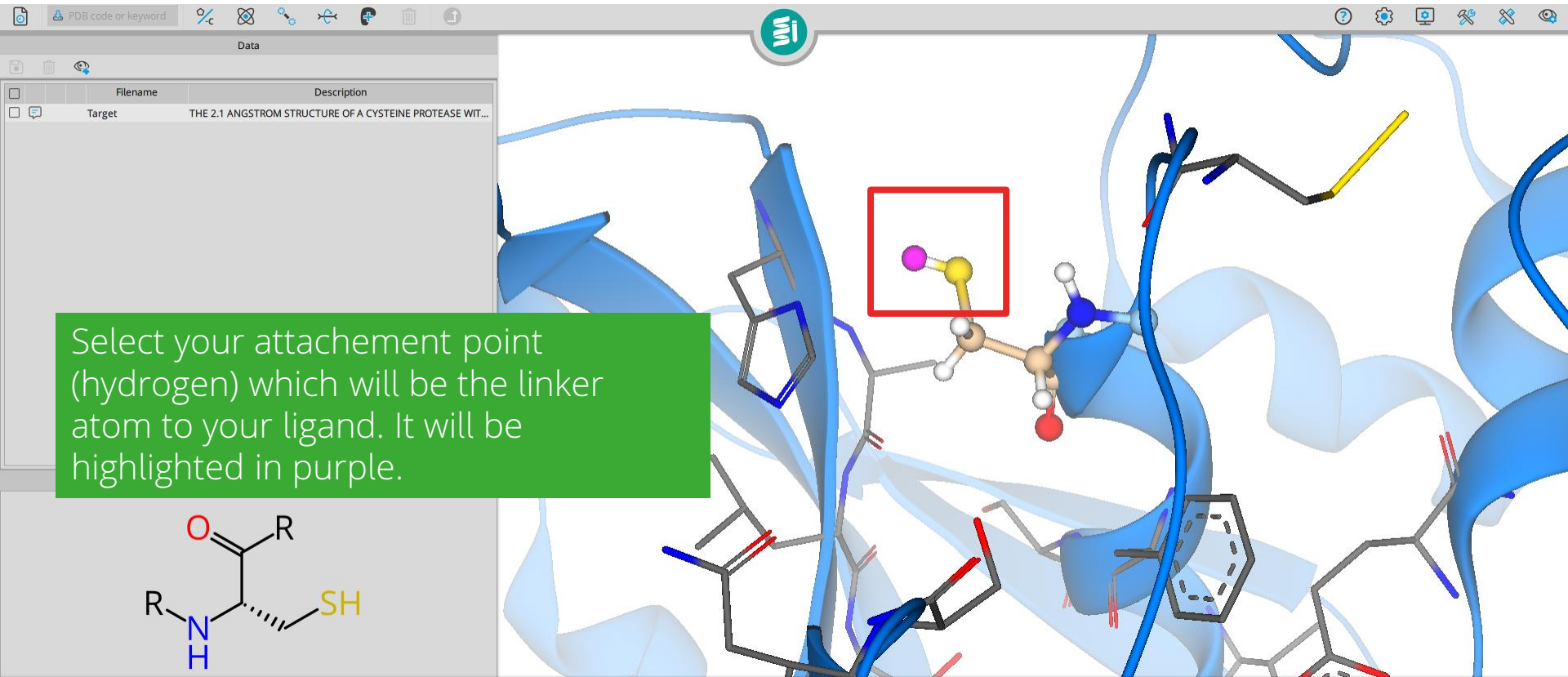
Data

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



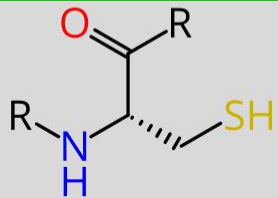
By clicking on a residue you select it as the residue you want to modify.





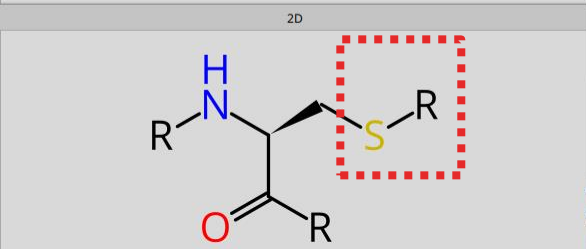
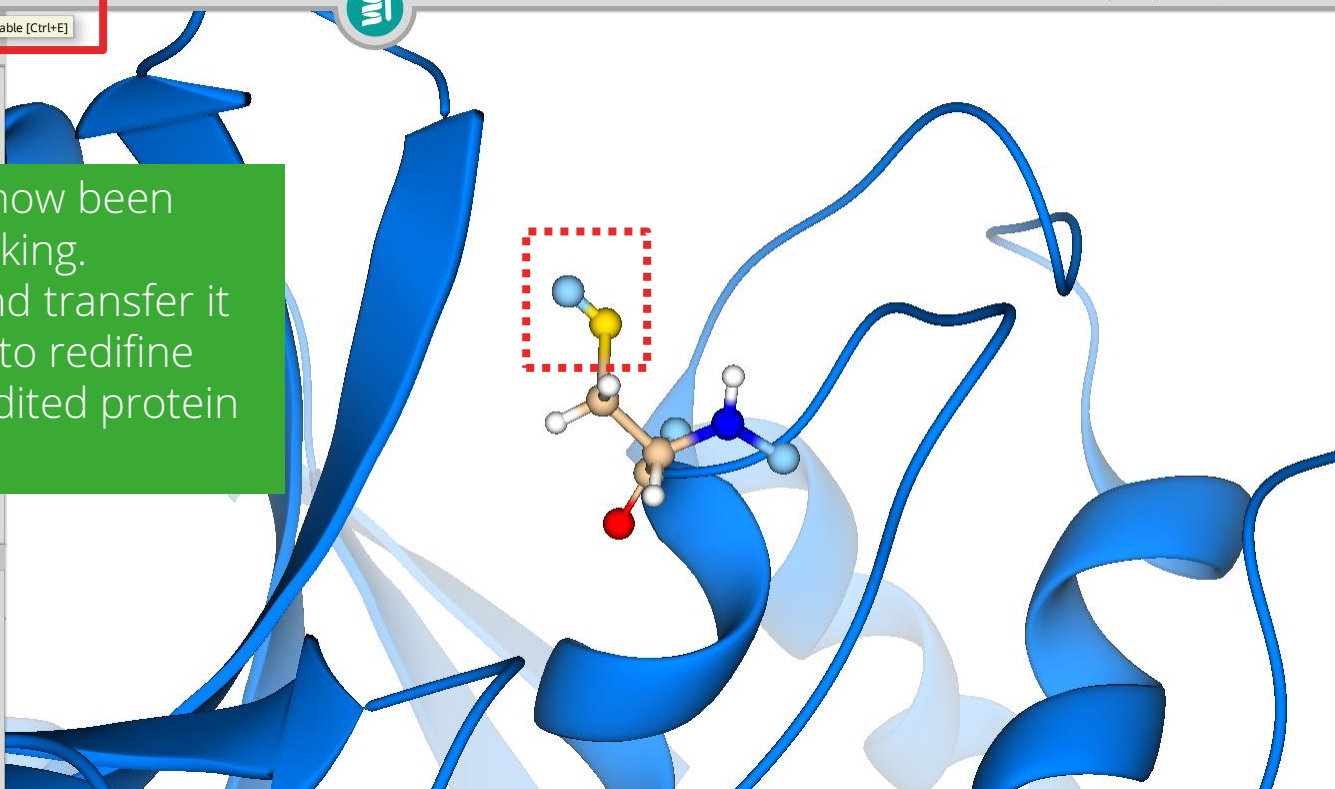
The screenshot displays a molecular modeling software interface. On the left, a 'Change element' dialog box is open, showing a periodic table with the element [R] highlighted. A red box highlights the 'Change to linker [R]' button. The main window shows a 3D ribbon representation of a protein structure in blue, with a yellow stick model of a ligand bound to it. The interface includes a top toolbar with various tools and a bottom toolbar with a logo.

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

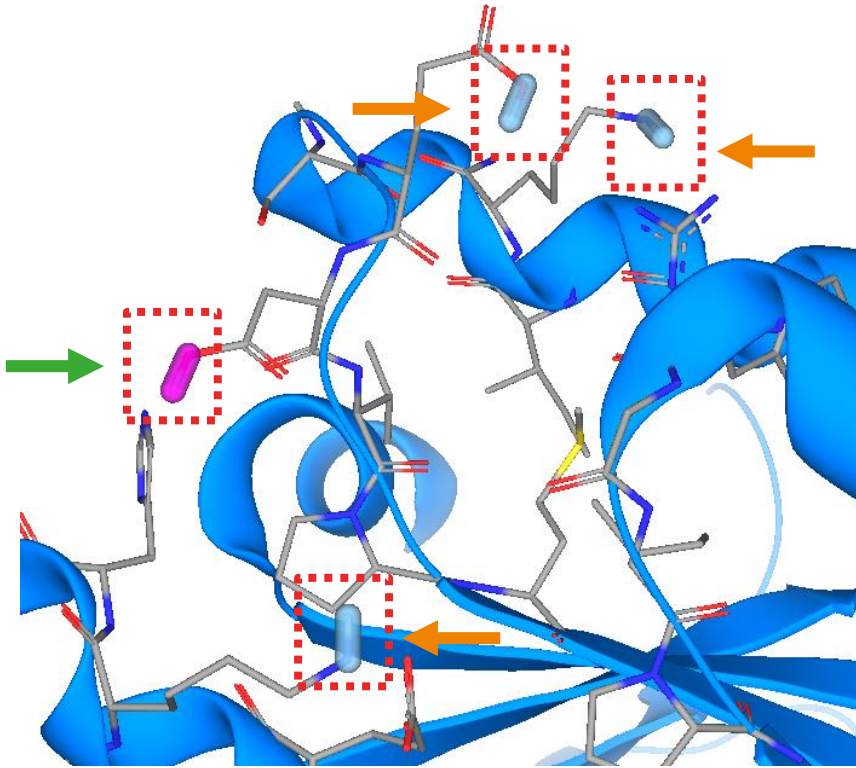




The cysteine residue has now been prepared for covalent docking. Save the edited protein and transfer it back to the Protein Mode to redefine your binding site on the edited protein for docking.



Selection of covalent binding residue



In the Docking Mode:

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 software interface. At the top, there is a 'Data' header and a 'Switch to grid' button. Below this is a table with columns: Name, Src, Estin, and nM. The table contains rows of data with IDs ranging from 512 to 530. A red box labeled '1.' highlights a funnel icon in the bottom left corner of the table. Another red box labeled '2.' highlights a dialog box titled 'Add a filter for' with a dropdown menu showing '- Select a property -'. To the right of the table, there are additional settings like 'Pharmacophore: 0 active' and a 'Define' button.

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

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. 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

The screenshot shows a software interface with a table of molecules and a filter panel. The table has columns for Name, Src, and Estimated affinity (pM, nM, μM). The filter panel on the right shows a filter for 'SDF16: Warhead contains' with 'allylamide' selected. A green arrow points from a text box to this filter.

Name	Src	Estimated affinity
		pM nM μM
528	Allyla...258705	
529	Allyla...427605	
530	Allyla...430522	
531	Allyla...450055	
532	Allyla...520561	
533	Allyla...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	

Likewise you can filter for a warhead of your choice.

possible warheads

Aldehyde	Carbamate	Maleimide
Alkynyl	Cyanamide	Nitrile
Alkynyllyl	Diazerine	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. Check all 2.

#	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. Add molecules to Binding Site mode

Add molecules to Molecule Editor

Add molecules to Inspector

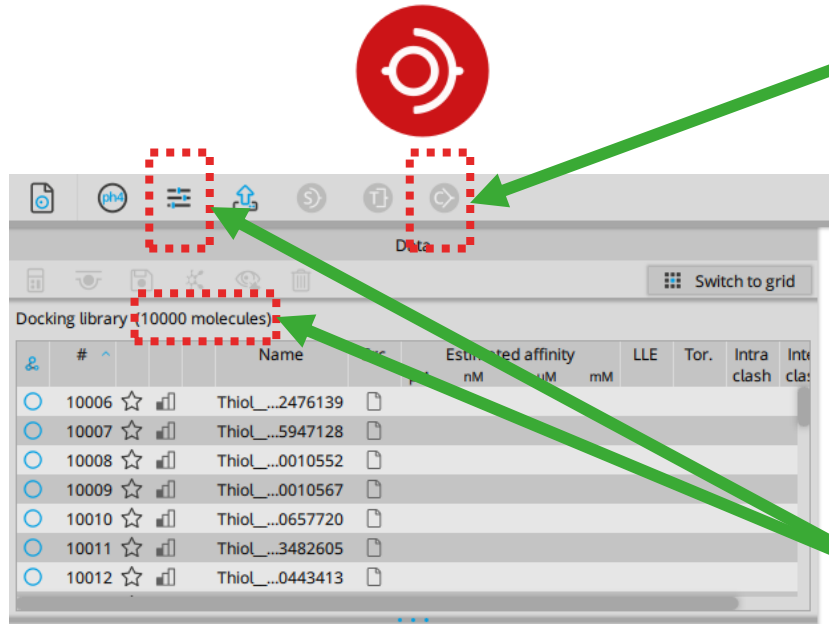
Add molecules to Docking mode 4.

#	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



The screenshot shows a software interface for docking. At the top, there is a toolbar with several icons. A red circle icon is highlighted with a red dashed box. Below the toolbar, there is a table titled "Docking library (10000 molecules)". The table has columns for "#", "Name", "Estimated affinity", "LLE", "Tor.", "Intra clash", and "Inter clash". The table contains several rows of data, including molecule IDs and names like "Thio_...2476139".

#	Name	Estimated affinity	LLE	Tor.	Intra clash	Inter clash
10006	Thio_...2476139	nM	μM	mM		
10007	Thio_...5947128					
10008	Thio_...0010552					
10009	Thio_...0010567					
10010	Thio_...0657720					
10011	Thio_...3482605					
10012	Thio_...0443413					

A greyed out docking button can have different reasons:

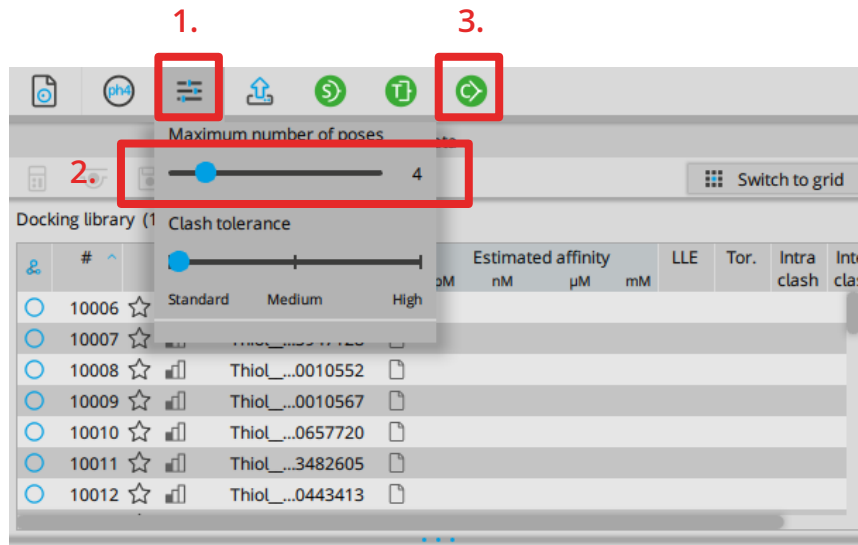
1. No covalent binding residue has been defined

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



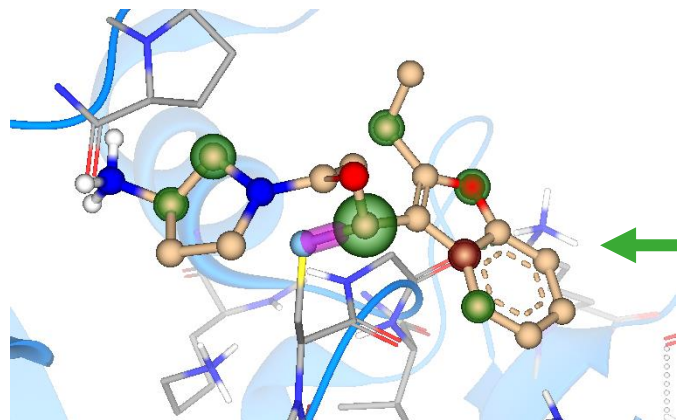
- (1) Go to the pose generator parameters
- (2) Adjust the maximum number of poses till the covalent docking button is green.
- (3) Start the covalent docking with your selected parameters.



#	Name	Src	Estimated affinity			
			pM	nM	μM	mM
10	21F_A_202_6	-				
16	21F_A_202_6_12	-				
15	21F_A_202_6_11	-				
11	21F_A_202_7	-				
4	21F_A_202					
5	21F_A_202_1	-				
6	21F_A_202_2	-				
13	21F_A_202_9	-				
12	21F_A_202_8	-				
9	21F_A_202_5	-				
8	21F_A_202_4	-				
7	21F_A_202_3	-				

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.



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

