

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.

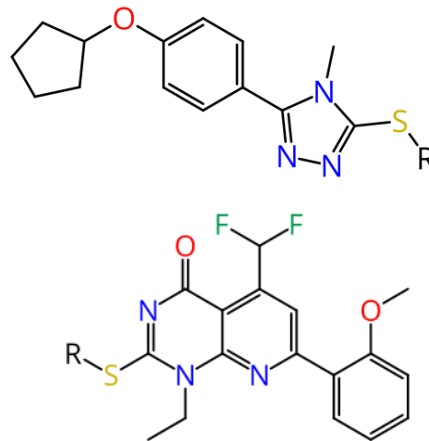
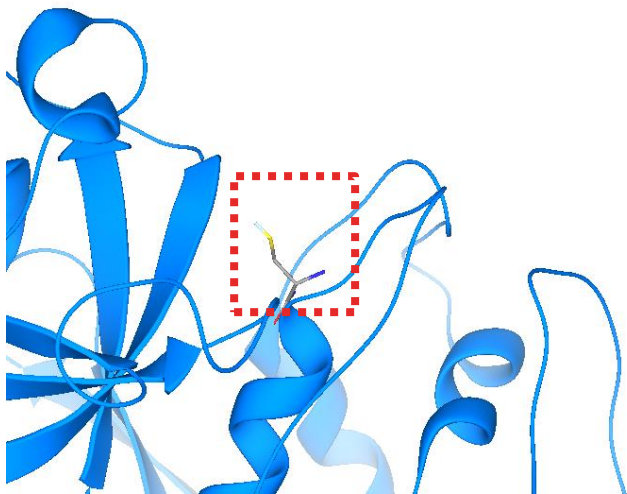
Translated supplier sets

Require prefiltering before covalent docking.



Covalent docking

To perform covalent docking you need two things prepared:

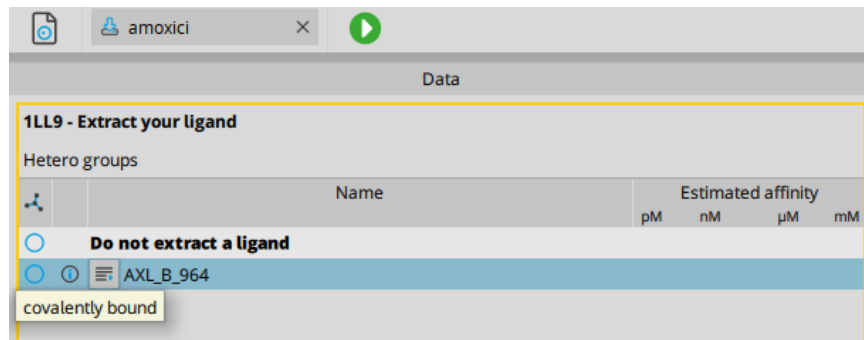


A **covalent target**
see → 2. Attachment Site

Covalent molecules
see → 3. Covalent libraries



2. Attachment Site

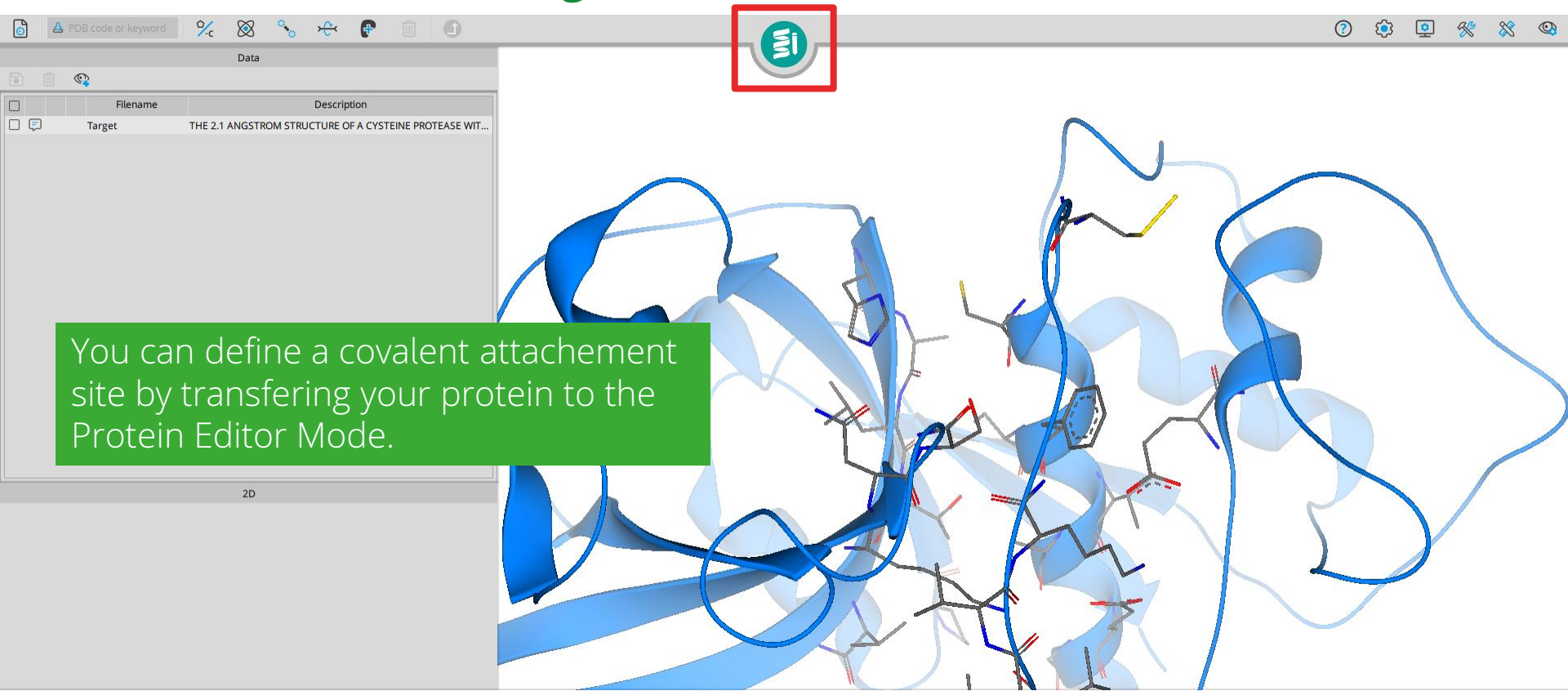


Upon loading your protein structure and defining your ligand, SeeSAR will inform you if a ligand is covalently binding at your structure. In this case the attachment point will be recognized and kept with the binding site definition by selecting the covalent ligand.

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

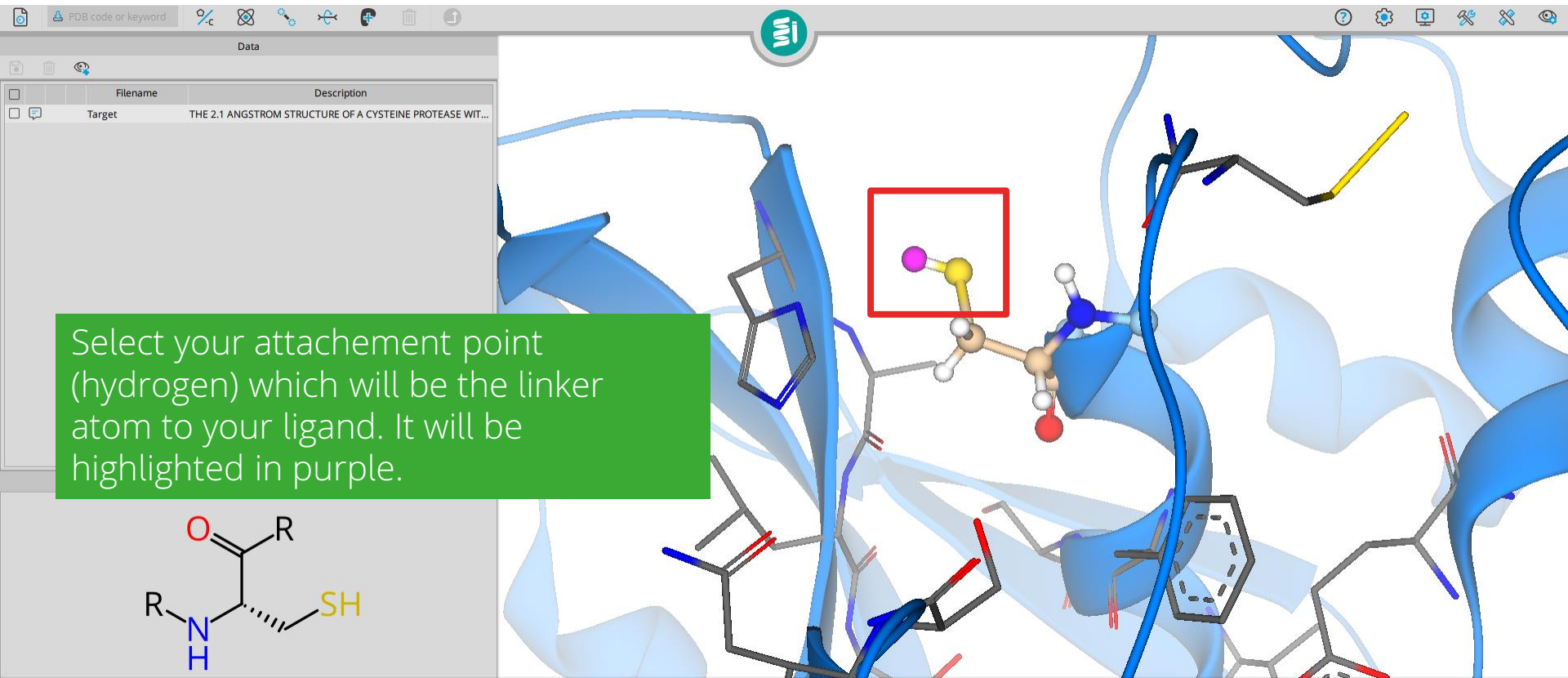


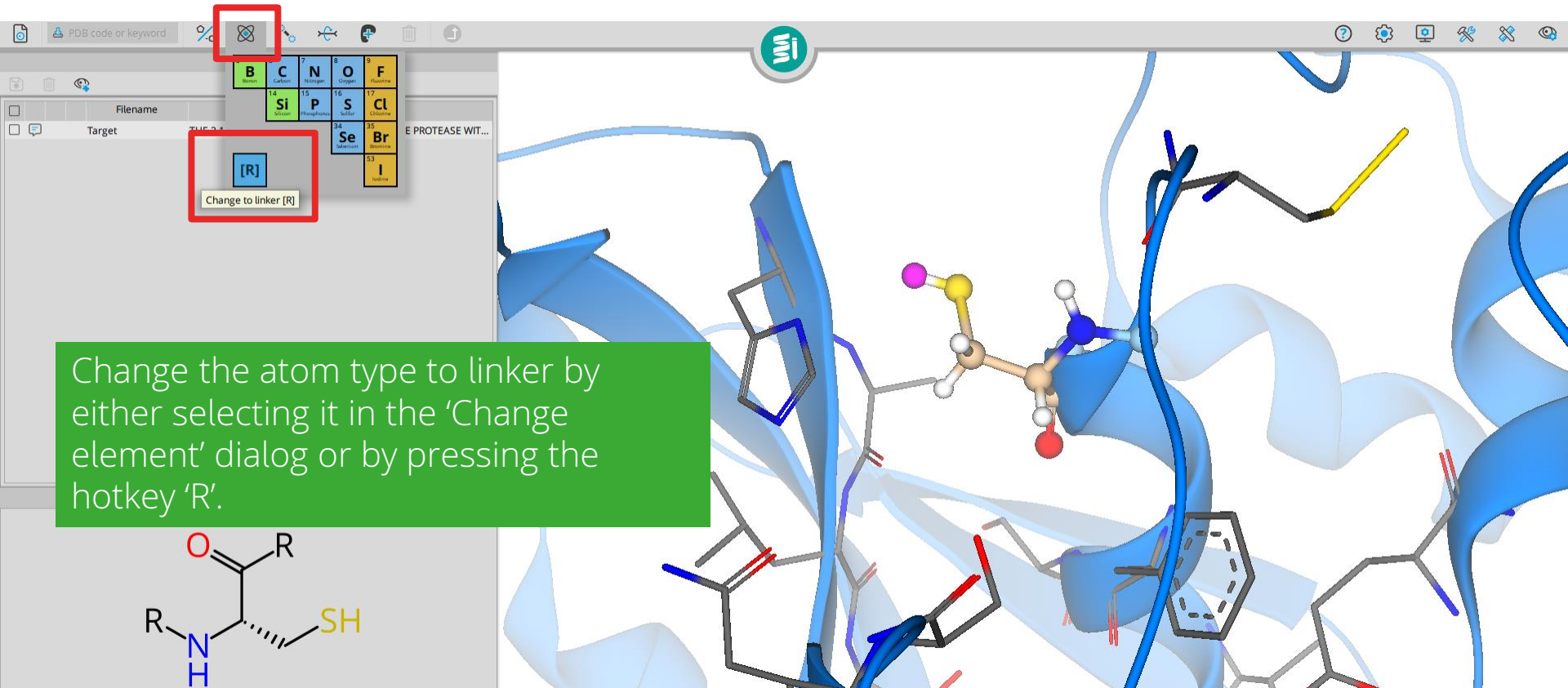
Defining a covalent attachment site



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

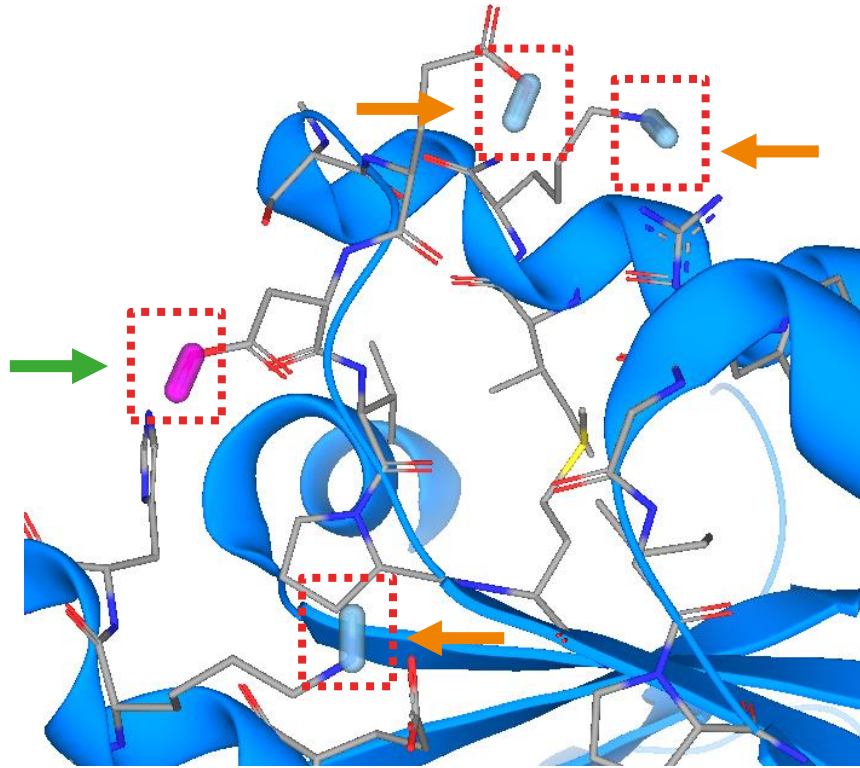
The screenshot displays the BioSolveIT software interface. On the left, a sidebar contains a 'Data' panel with a table listing protein targets. The table has columns for 'Delete checked proteins', 'PDB code or keyword', 'Name', and 'Description'. The first entry is 'THE 2.1 ANGSTROM STRUCTURE OF A CYSTEINE PROTEASE WIT...'. Below this is a '2D' panel showing a chemical structure of a cysteine residue: R-CH(NH2)-C(=O)R-SH. The main window shows a 3D ribbon representation of a protein structure in blue. A red rectangular box highlights a specific residue, which is shown in stick representation with orange, yellow, and red atoms. The interface includes a top toolbar with various icons for file operations, editing, and viewing, and a bottom toolbar with a logo.







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.

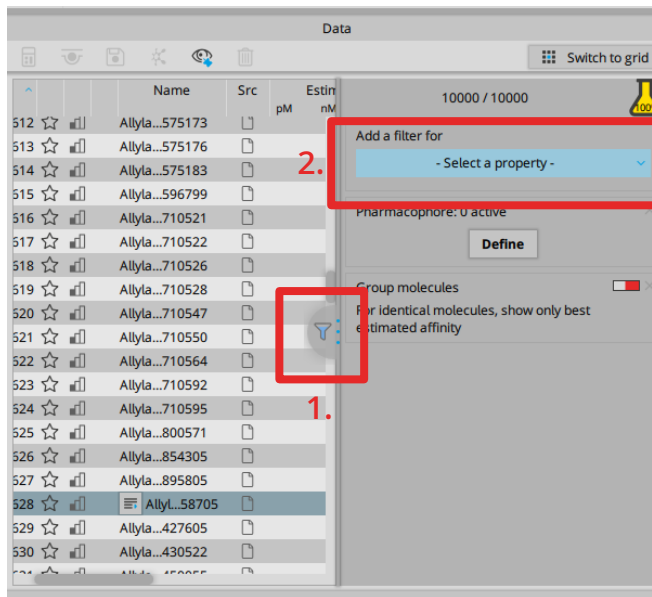
Every translated covalent library sd-file contains information on:

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

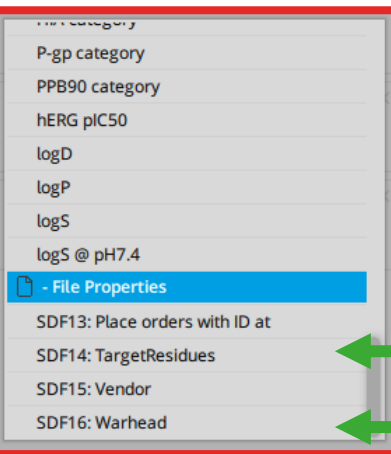
You can use this information to filter for covalent functionalities you are interested in or for compounds likely to target a specific residue.



Prefilter your library in SeeSAR



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

The screenshot shows the BioSolveIT software interface. On the left, a table lists molecules with columns for Name, Src, and Estimated affinity (pM, nM, μM). The right panel shows filter settings. The 'SDF14: Target...ues contains' filter is active (green button) and has 'Cys' entered in the search box. The 'SDF16: Warhead contains' filter is also active (green button) and has 'allylamide' entered. The 'Apply filters' button is green and located at the top of the filter panel.

	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 list of molecules on the left and a filter panel on the right. The filter panel has a section 'SDF16: Warhead contains' with a dropdown menu showing 'allylamide'. A green arrow points from a text box to this dropdown.

Name	Src	Estimated affinity
		pM nM μ M
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	


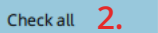
Likewise you can filter for a warhead of your choice.


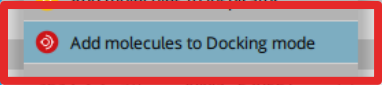
possible warheads


Aldehyde	Carbamate	Maleimide
Alkynyl	Cyanamide	Nitrile
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

1.  2. 

3.  4. 



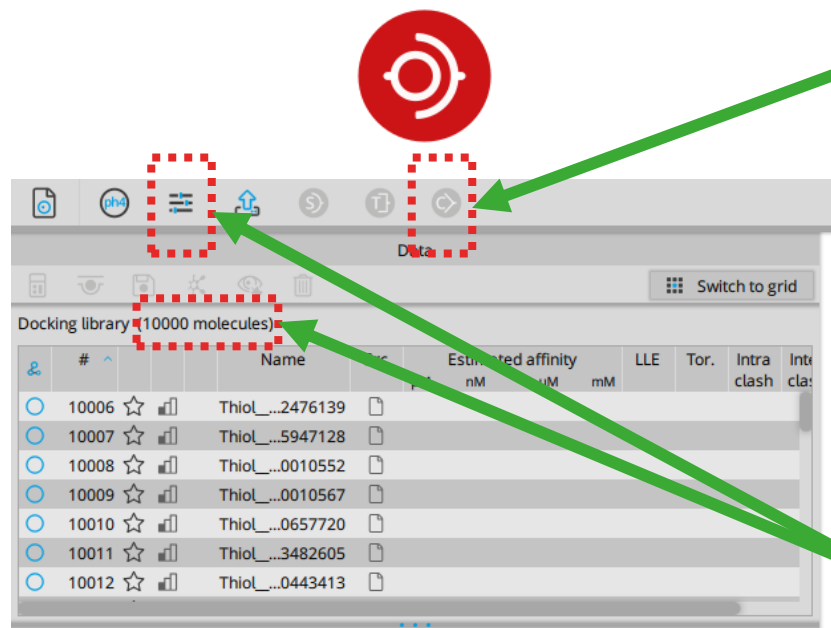
The image shows two screenshots of a software interface. The first screenshot shows a table with columns '#', 'Name', 'Src', and 'Estimate'. A red box highlights the selection icon in the toolbar, and another red box highlights the 'Check all' menu item. The second screenshot shows the same table, but with the 'Add molecules to Docking mode' button highlighted. A green arrow points from the first screenshot to the second.

#	Name	Src	Estimate
	Allyla...258705		pM nM
	Allyla...427605		
	Allyla...430522		
	Allyla...450055		
	Allyla...520561		
3633	Allyl...23057		
3634	Allyla...640051		
3635	Allyla...702105		
3636	Allyla...703058		
3637	Allyla...705139		
3638	Allyla...705680		
3639	Allyla...793055		
3640	Allyla...805416		
3641	Allyla...810500		
3642	Allyla...830581		
3643	Allyla...050911		
3644	Allyla...051158		
3645	Allyla...210598		
3646	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:

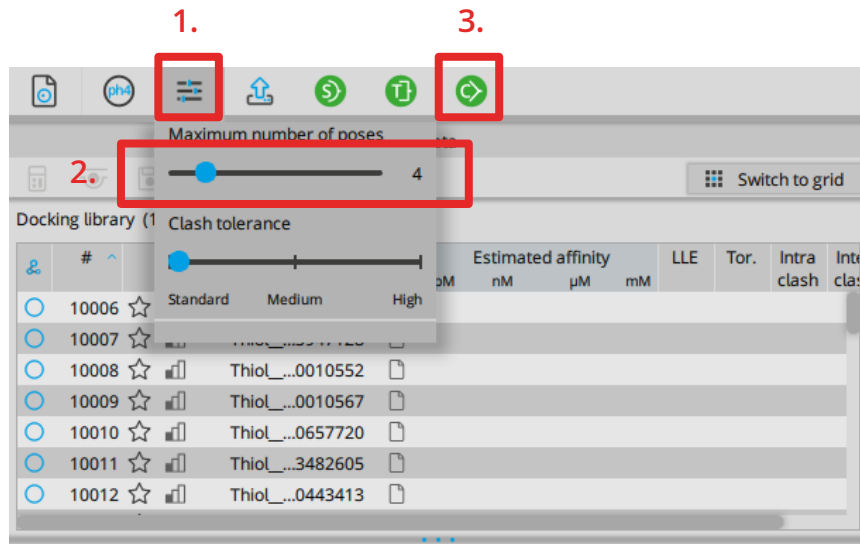
1. No covalent binding residue has been defined

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.



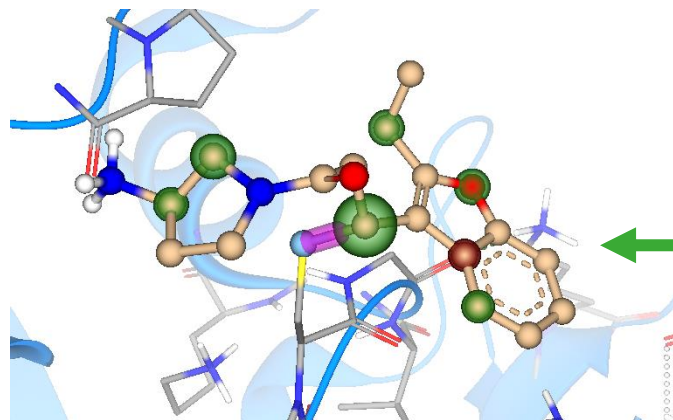
Data

Switch to grid

	#		Name	Src	Estimated affinity
					pM nM μ M mM
<input type="checkbox"/>	10	☆	21F_A_202_6	-<	
<input type="checkbox"/>	16	☆	21F_A_202_6_12	-<	
<input type="checkbox"/>	15	☆	21F_A_202_6_11	-<	
<input type="checkbox"/>	11	☆	21F_A_202_7	-<	
<input type="checkbox"/>	4	☆	21F_A_202	≡	
<input type="checkbox"/>	5	☆	21F_A_202_1	-<	
<input type="checkbox"/>	6	☆	21F_A_202_2	-<	
<input type="checkbox"/>	13	☆	21F_A_202_9	-<	
<input type="checkbox"/>	12	☆	21F_A_202_8	-<	
<input type="checkbox"/>	9	☆	21F_A_202_5	-<	
<input type="checkbox"/>	8	☆	21F_A_202_4	-<	
<input type="checkbox"/>	7	☆	21F_A_202_3	-<	

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.



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

