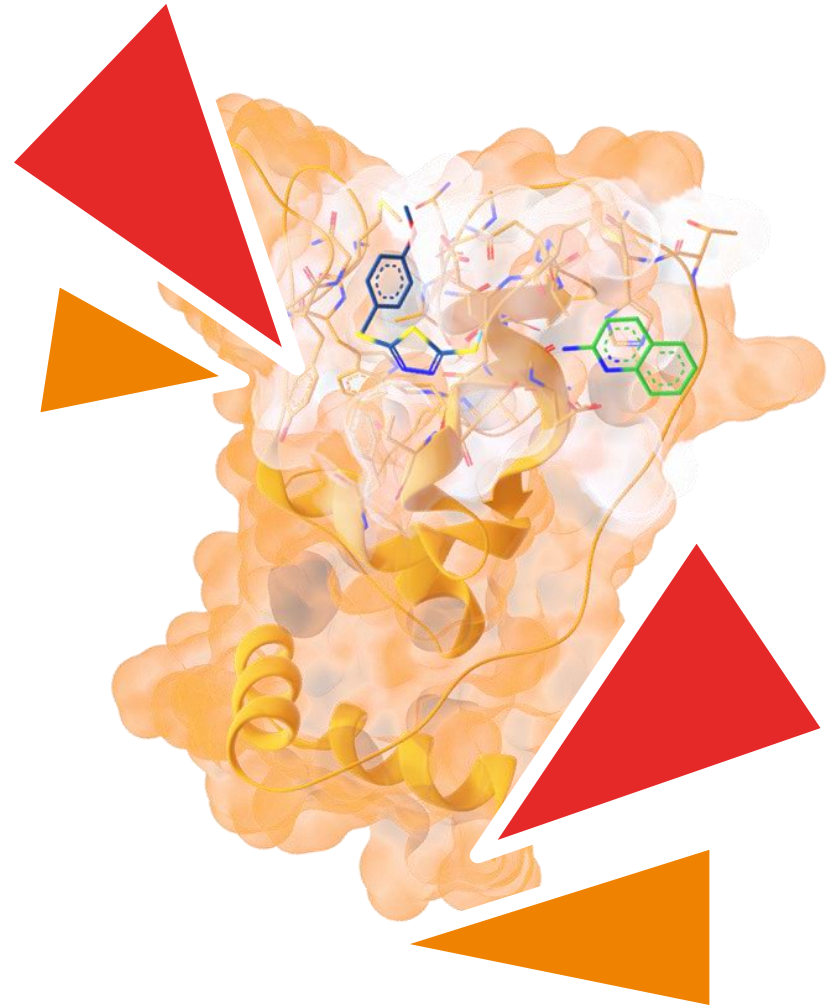




BioSolveIT
expect actives!

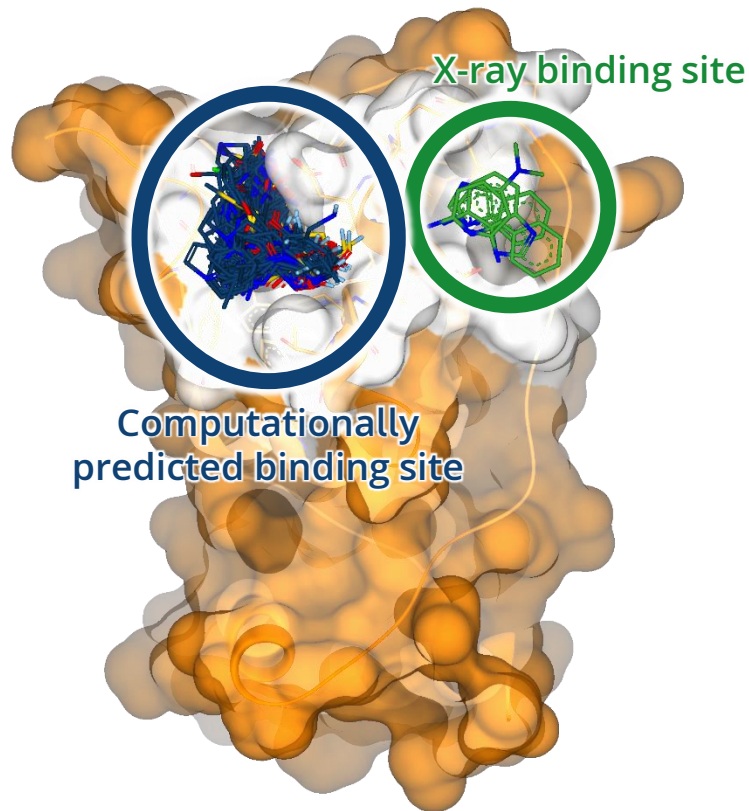
Drugathon 2023 Introduction

Targeting Nsp10 via two
different fragment binding
sites



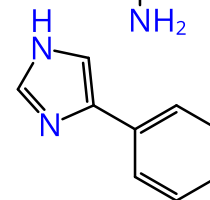
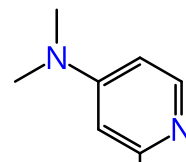
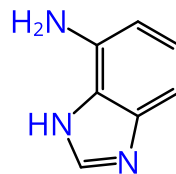
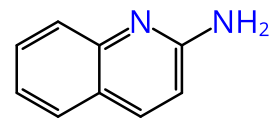
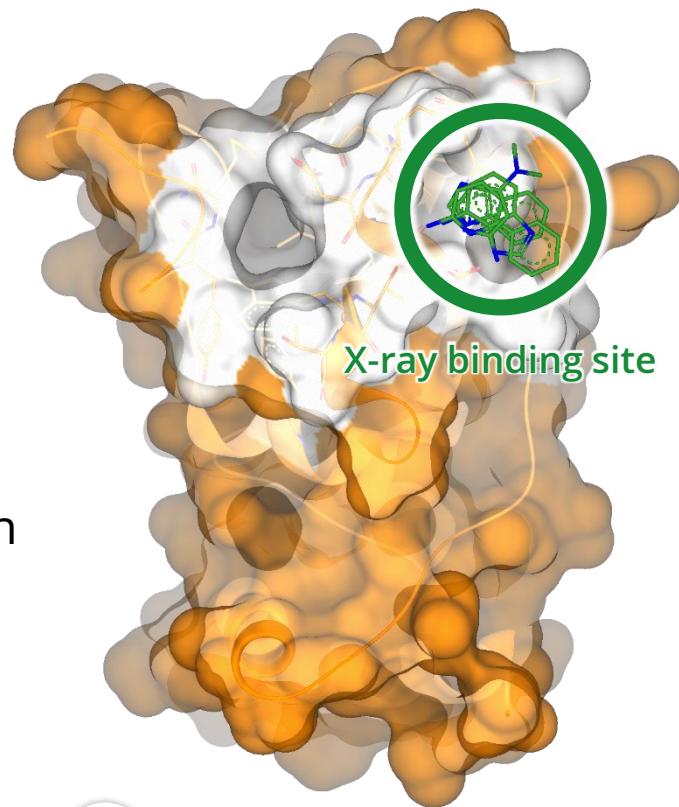
Target: Nsp10

- ◆ Target: Non-structural protein 10 (Nsp10) from SARS CoV-2
- ◆ 2 binding sites (1x with fragment-like ligands, 1x computationally predicted starting points)
- ◆ Goal: Grow, design, combine fragments to improve binding affinity
- ◆ Tools:
 - ◆ **SeeSAR** for design
 - ◆ **infiniSee** to mine related compounds from Chemical Spaces



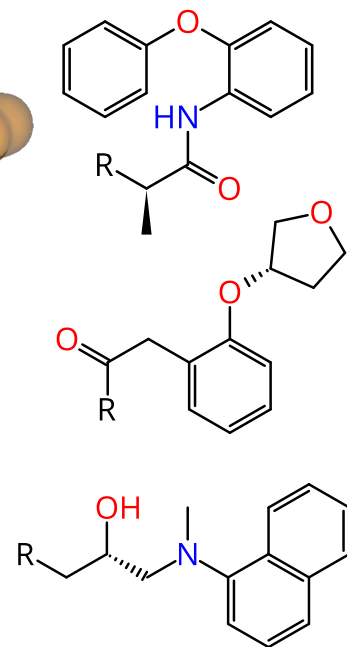
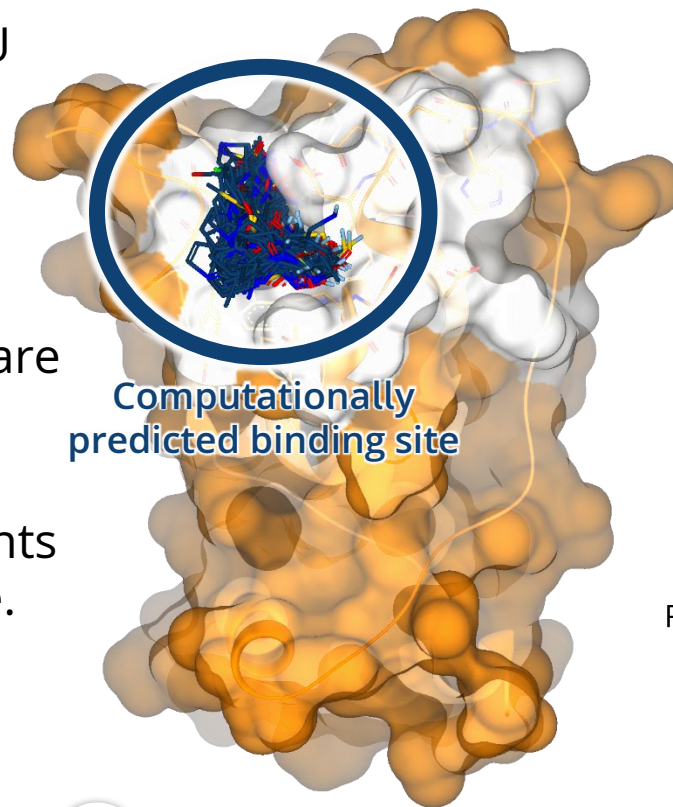
Binding Site 1: X-ray binding site

- ◆ Four PDBs with co-complexed fragments available:
 - ◆ 7ORU (target structure for the Drugathon 2023)
 - ◆ 7ORR
 - ◆ 7ORV
 - ◆ 7ORW
- ◆ The co-complexed fragments are colored in green in the Drugathon SeeSAR project.



Binding site 2: Predicted binding site

- ◆ 2nd binding site identified at 7ORU with SeeSAR (via DogSiteScorer)
- ◆ 200k building blocks docked into predicted binding site.
- ◆ 100 fragments cherry-picked as starting points. Those fragments are colored in blue in the Drugathon SeeSAR project.
- ◆ Growing vector (light blue/'R') points into direction of X-ray binding site.



The screenshot shows a software interface with a 'Data' panel on the left containing a table of molecules and their estimated affinities. The main view displays a 3D protein surface model with a ligand (green and blue spheres) docked in the binding site.

Molecules (# 104)	Name	Estimated Affinity				LLE	Tor	Ph	CS
		µM	nM	µM	nM				
1	X-Ray_Frag1								
2	X-Ray_Frag2								
3	X-Ray_Fr								
4	X-Ray_Fr								
5	Comp_Fr								
6	Comp_Fr								
7	Comp_Fr								
8	Comp_Fr								
9	Comp_Fr								
10	Comp_Fr								
11	Comp_Fr								
12	Comp_Fr								
13	Comp_Fr								
14	Comp_Fr								
15	Comp_Fr								
16	Comp_Fr								

Tips and Tricks

The screenshot shows a software interface with a 'Data' panel on the left containing a list of molecules. The main view displays a 3D protein surface model. Below the surface model, a 2D chemical structure of a ligand is shown, labeled 'X-Ray_Frag3'. The structure is a pyridine ring with a methyl group on the nitrogen, an amino group at the 3-position, and a protonated nitrogen at the 4-position.

2D
X-Ray_Frag3

CN1C=CC(=N1)N

Sequence View

Show Binding Site Only

Color Options for Protein Surface

70RU Standard Ligand Elements Chains Residues Binding Site

70RU X-Ray_Frag3



The screenshot displays the Drugathon software interface. On the left, a table lists molecules with columns for Name, Estimated Affinity (pM, nM, μM, mM), LLE, Tor, and In. A red box highlights a context menu for a selected molecule, with a green arrow pointing to the 'Add to Inspirator' option. The main view shows a 3D model of a protein (orange surface) with a ligand (green and blue ball-and-stick) bound in its pocket. A green text box on the right contains the following text:

The greatest helper during the Drugathon will be the Inspirator Mode. To gather ideas how to improve a compound, right click on it and transfer it to the Inspirator Mode.

At the bottom left, a 2D chemical structure of the ligand is shown: CN1C=CC(=N1)N. The bottom of the interface includes a 'Sequence View' section with 'Color Options for Protein Surface' (70RU, Surface, Ligand, Elements, Chains, Transmembrane, Residue, Binding Site) and a 'Show Binding Site Only' checkbox.



The screenshot displays a software interface for molecular design. On the left, a table lists various fragments, including X-Ray_Frag1 through X-Ray_Frag4 and Comp_Frag1 through Comp_Frag28. A green arrow points from the 'Add' icons in the first three rows of this table to a context menu on the right. The context menu contains several options: 'Add molecules to Binding Site mode', 'Add molecules to Molecule Editor', 'Add molecules to Inspirator' (highlighted with a red box), 'Add molecules to Docking mode', and 'Add molecules to Similarity Scanner'. Below the menu, the text 'Comp Frag1' is visible. At the bottom of the interface, there are controls for 'Color Options for Protein Surface' and 'Show Binding Site Only'.

If you want to link/merge two fragments, always check both molecules to transfer both to the Inspirator Mode. This way both molecules will be active and can be used in the design process.



The screenshot displays the SeeSAR software interface. At the top left, a green checkmark icon is highlighted with a red box. The main window shows a 3D model of a protein binding site with two molecules, X-Ray_Frag2 and Comp_Frag11, highlighted by red boxes. A green callout box contains the following text:

Define the positions where you would your molecules to connect and use the 'Linking & Merging' button to run a search.

Several coordinate libraries (so-called 'ReCore indices') are available on our webpage: https://www.biosolveit.de/SeeSAR#recore_indices

Download the ReCore indices and load them into SeeSAR via 'System' → 'Inspirator'.

The interface also shows a table of molecules and their estimated affinities:

Molecules (# 2)	Name	Estimated Affinity	Deviation
1	X-Ray_Frag2	µM	n.a.
2	Comp_Frag11	µM	n.a.

At the bottom, there are 2D chemical structures for X-Ray_Frag2 and Comp_Frag11, and a 'Color Options for Protein Surface' menu.



The screenshot displays a molecular docking software interface. On the left, a table lists five molecules with their names, estimated affinities, and deviations. The main window shows a 3D model of a protein binding site (orange and white surface) with a ligand (stick representation) docked inside. A green play button is visible at the bottom right of the 3D view. A green text box is overlaid on the right side of the interface.

Molecules (# 5)	Name	Estimated Affinity		Deviation
		μM	mM	
1	X-Ray_Frag2			n.a.
2	Comp_Frag11			n.a.
3	X-Ray_...			0.59 40c2
4	X-Ray_F_C_B_1			0.45 7mk4
5	X-Ray_F_C_1			0.83 1214

70RU X-Ray_Frag2_Comp_Frag11_40c2_2RU_1_A_603_D_1

Color Options for Protein Surface: 70RU (Surface), Ligand, Element, Chains, Transparenc, Water, Binding Site

Designed or found something you like?
Check for similar compounds in the ultra-large
Chemical Spaces with infiniSee!

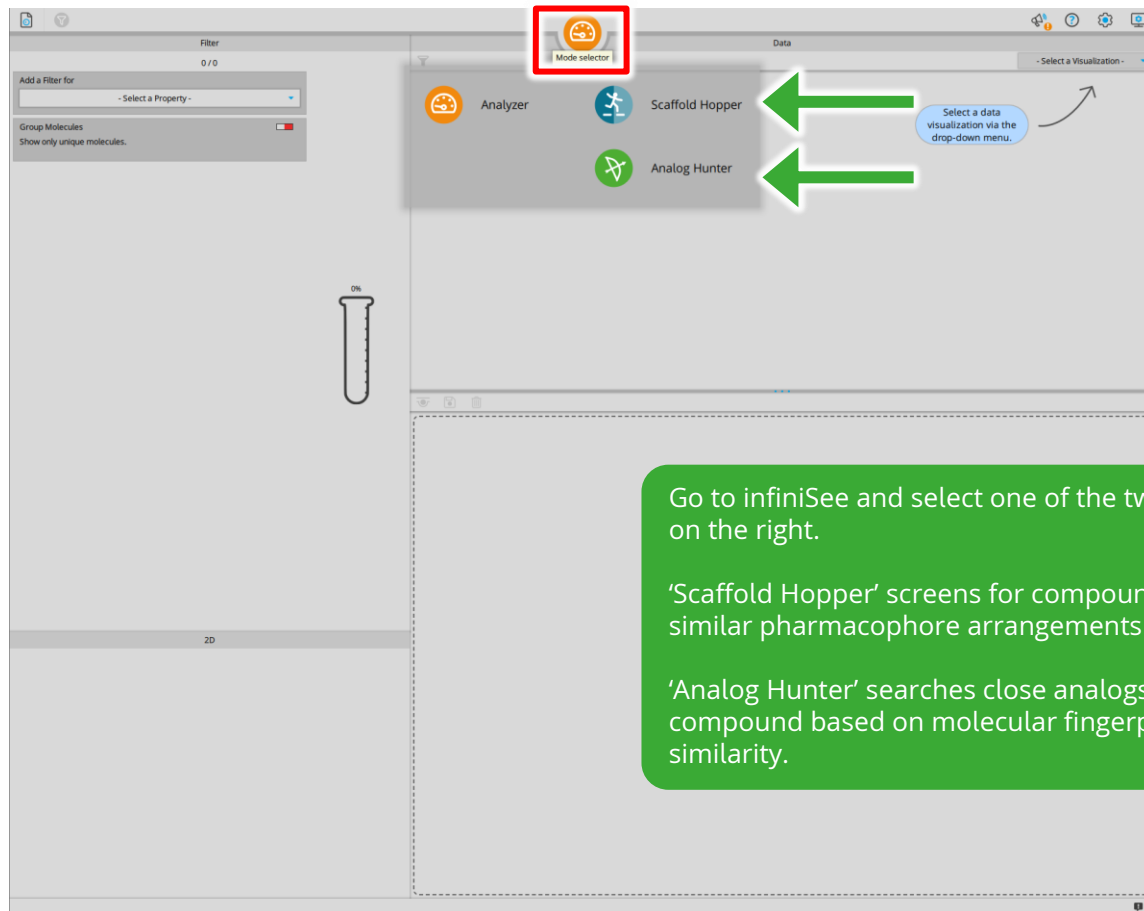


The screenshot displays a molecular docking software interface. On the left, a 'Data' panel shows a table of molecules and their estimated affinities. The main window shows a 3D model of a protein (orange surface) with a ligand (stick representation) docked in its binding site. A 2D window at the bottom left shows the chemical structure of the ligand, with a red box highlighting a context menu that includes 'Copy to clipboard as sdf'. A green callout box points to this menu with the text: 'Right click into the 2D window and select ,Copy to clipboard as sdf.'. A green play button is visible at the bottom center of the 3D view.

Molecules (# 5)	Name	Estimated Affinity			Deviation
		μM	nM	μM	
1	X-Ray_Frag2				n.a.
2	Comp_Frag11				n.a.
3	X-Ray_..._1				0.59 40c2
4	X-Ray_F_..._1				0.45 7m4
5	X-Ray_F_..._1				0.83 121d

Right click into the 2D window and select ,Copy to clipboard as sdf.





Go to infiniSee and select one of the two modes on the right.

'Scaffold Hopper' screens for compounds with similar pharmacophore arrangements.

'Analog Hunter' searches close analogs of a compound based on molecular fingerprint similarity.



The screenshot displays the BioSolveIT web interface. At the top, there are two buttons: a blue 'S' icon and a green play button icon, both highlighted with red boxes. The main area shows a chemical structure of a complex molecule. Below the structure, there is a 'Matching' section. The bottom status bar indicates the search space: 'Search in: REALSpace_36bn_2023-04.space'.

mp_fr
_603_D__1

Results

O=C1Nc2ccccc2N1C(=O)Nc3ccccc3

Matching

Search in: REALSpace_36bn_2023-04.space

Add your copied molecule with 'ctrl + v'.

Select the Chemical Space you want to search.
Spaces can be downloaded from our website:
https://www.biosolveit.de/infiniSee#chemical_spaces

Start your search with the play button.



Query: X-Ray_Frag2_Comp_Frag11_4oc2_2R2_1_A_603_D__1

Result Summary:

- Query: X-Ray_Frag2_Comp_U_1_A_603_D__1 100
- Found Molecules: 100
- From REALSpace_36bn_2023-04: 100

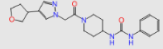


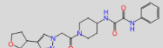


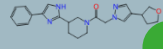
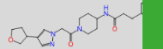
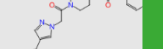
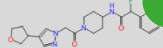
Used Parameters:

- Maximum Number of Results: 100
- Minimum Similarity: 0.10
- Fingerprint: ECFP4

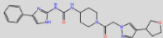
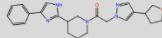
Search Session Info:

- ID: Alexander Neumann
- User: 1453 2023-07-24
- Started: 00:00:31
- Duration: 5.0.1
- infrSee Version: 5.0.1

Molecules (# 100)

	Molecule	#	Similarity	Space	Name	Reagent 1	Reagent 2
1		1	0.729	REALSpace_36bn_2023-04	m_11b_14868		
2		2	0.649	REALSpace_36bn_2023-04	m_275_63068		
3							
4							
5							
6							

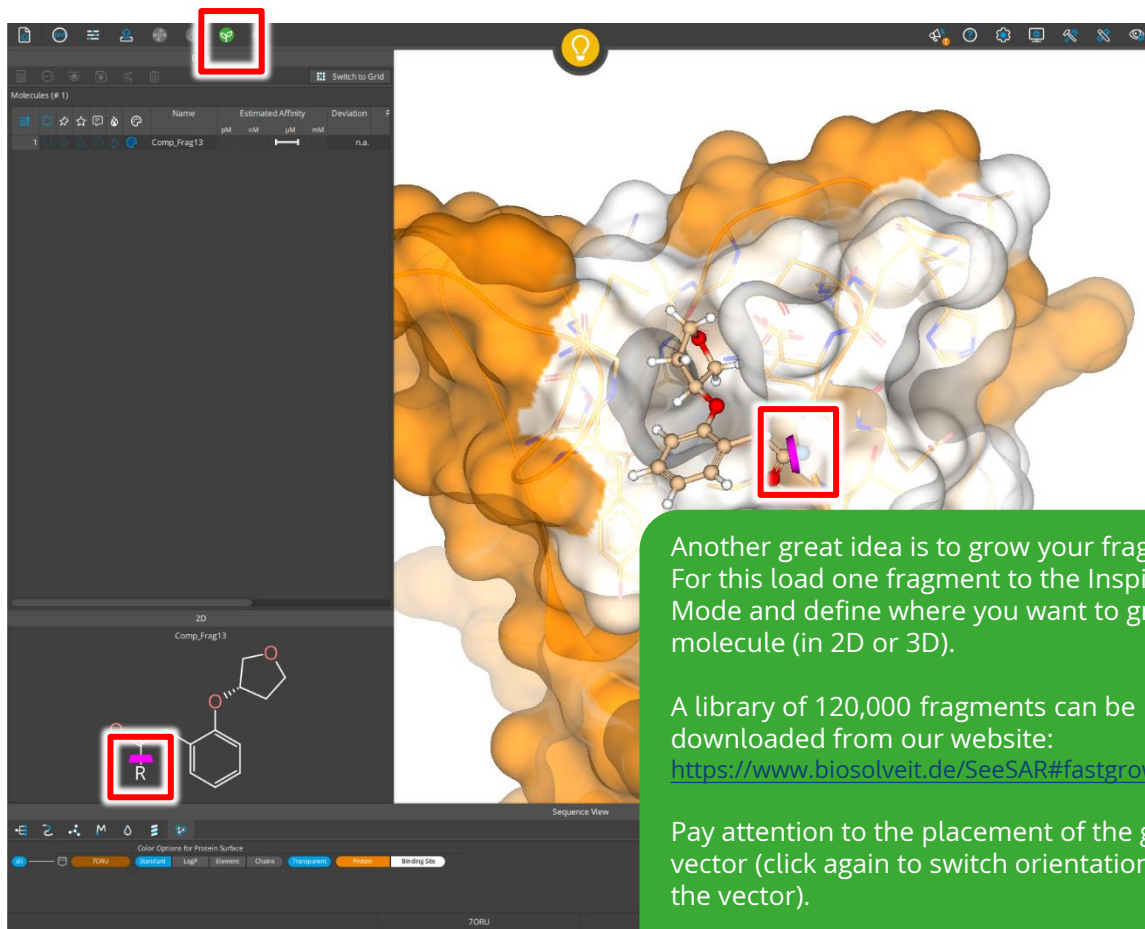
Matching

After a few seconds/minutes available make-on-demand compounds are presented to you. Accessible compounds are of special interest to us, because that means they can be easily purchased for the follow up of the Drugathon.

Use the ideas and dock them into the binding site: You will be surprised about the potential of the findings!





Another great idea is to grow your fragment. For this load one fragment to the Inspirator Mode and define where you want to grow your molecule (in 2D or 3D).

A library of 120,000 fragments can be downloaded from our website:
<https://www.biosolveit.de/SeeSAR#fastgrowdblib>

Pay attention to the placement of the growing vector (click again to switch orientation/remove the vector).

Use the 'Growing' button to generate results.



The screenshot displays a molecular docking software interface. On the left, a table lists 11 molecules with their names and estimated affinity values. The table is as follows:

Molecules (# 11)	Name	Estimated Affinity		Deviation	F
		μM	nM		
1	Comp_Frag13			n.a.	
2	Comp_F_8805_1			0.00	CSSE
3	Comp_F_3048_1			0.00	CSSE
4	Comp_F_8586_1			0.00	CSSE
5	Comp_68_1			0.00	CSSE
6	Comp_28_1			0.00	CSSE
7	Comp_F_7117_1			0.00	CSSE
8	Comp_F_5472_1			0.00	CSSE
9	Comp_F_8624_1			0.00	CSSE
10	Comp_F_9978_1			0.00	CSSE
11	Comp_F_8588_1			0.00	CSSE

Below the table, a 2D chemical structure is shown for the selected molecule, **Comp_Frag13_C5S00000186668_1**. The structure is a complex organic molecule with a benzene ring, a five-membered ring, and a long chain with a nitrogen atom and a sulfur atom.

The main part of the interface shows a 3D visualization of a protein binding site. The protein surface is colored in shades of orange and yellow. A ligand is shown in a stick representation, with atoms colored by element (carbon in green, oxygen in red, nitrogen in blue). The ligand is bound within the protein's binding pocket. A green play button is visible at the bottom center of the 3D view.

A green text box overlaid on the 3D view contains the following text:

SeeSAR will screen the library within seconds to provide you with the most promising results to complement the binding site.



The screenshot displays the Docking Explorer software interface. On the left, a table lists 11 molecules with their names and estimated affinities. The 3D model on the right shows a protein surface (orange and white) with a ligand (green and red spheres) docked in the binding site. A red box highlights a specific interaction point in the 3D model. Below the 3D model, a 2D chemical structure is shown for the selected molecule, Comp_Frag13_CSS800025775422_3.

Molecules (# 11)	Name	Estimated Affinity		Deviation	F
		pM	nM		
1	Comp_Frag13			n.a.	
2	Comp_F_5850_3			0.00	CSSE
3	Comp_F_5494_3			0.00	CSSE
4	Comp_22_3			0.00	CSSE
5	Comp_F_8271_3			0.00	CSSE
6	Comp_F_4114_3			0.00	CSSE
7	Comp_F_3681_3			0.00	CSSE
8	Comp_F_5081_3			0.00	CSSE
9	Comp_F_5887_3			0.00	CSSE
10	Comp_F_3374_3			0.00	CSSE
11	Comp_F_5905_3			0.00	CSSE

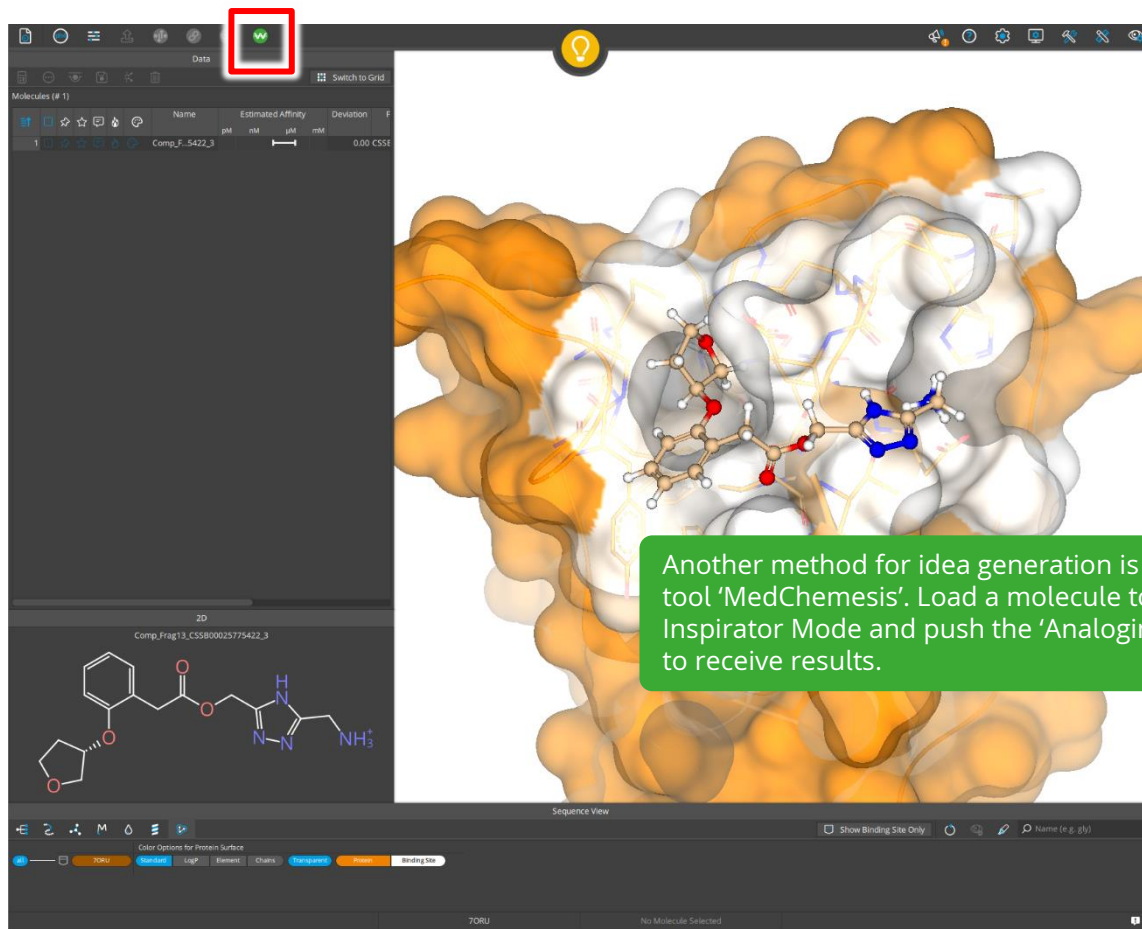
2D
Comp_Frag13_CSS800025775422_3

Sequence View
Show Binding Site Only
Color Options for Protein Surface
70RU
Comp_Frag13_CSS800025775422_3

You can also apply pharmacophore constraints in the Inspirator and Docking mode to fine-tune your results.

It is always a good idea what other compounds related to your designed structures are available in the Chemical Spaces with inifiniSee.





Another method for idea generation is the novel tool 'MedChemesis'. Load a molecule to the Inspirator Mode and push the 'Analoging' button to receive results.



The screenshot displays the MedChemesis software interface. On the left, a table lists 11 molecules with their names, estimated affinities in pM and mM, and deviations. The main view shows a 3D model of a protein binding site (orange surface) with a molecule (stick representation) docked inside. A green text box highlights the software's function: "MedChemesis applies common medicinal chemistry reactions to improve the properties of your compound and provides you with interesting solutions." Below the text box is a play button icon. At the bottom, there is a 2D chemical structure of the molecule and a "Sequence View" section.

Molecules (# 11)	Name	Estimated Affinity		Deviation	r
		pM	mM		
1	Comp_F_5422_3	0.00	0.00	0.00	CS51
2	Comp_F_y1_4	n.a.	add.	n.a.	add.
3	Comp_F_no_2_4	n.a.	add.	n.a.	add.
4	Comp_3_4	n.a.	add.	n.a.	O→
5	Comp_F_1_4_4	n.a.	add.	n.a.	add.
6	Comp_F_no_5_4	n.a.	add.	n.a.	add.
7	Comp_F_2_6_4	n.a.	add.	n.a.	add.
8	Comp_F_no_7_4	n.a.	add.	n.a.	add.
9	Comp_F_no_8_4	n.a.	add.	n.a.	add.
10	Comp_F_y1_9_4	n.a.	add.	n.a.	add.
11	Comp_F_H_10_4	n.a.	add.	n.a.	add.

2D
Comp_Frag13_CS5800025775422_3_O→_5_3_4

Sequence View

Show Binding Site Only

Color Options for Protein Surface

70RU

Comp_Frag13_CS5800025775422_3_O→_5_3_4





BioSolveIT
expect actives!

SeeSAR
Beginner's Guide
Version 13 - Midas



A detailed guide to SeeSAR can be found on our homepage:

<https://www.biosolveit.de/SeeSAR/BeginnersGuide.pdf>

A guide to infiniSee can be accessed here:

<https://www.biosolveit.de/infiniSee/BeginnersGuide.pdf>





BioSolveIT
expect actives!

We wish you a lot of fun for the Drugathon!

Approach us if you need any
help or guidance to perform a
particular task.

We are happy to help!

