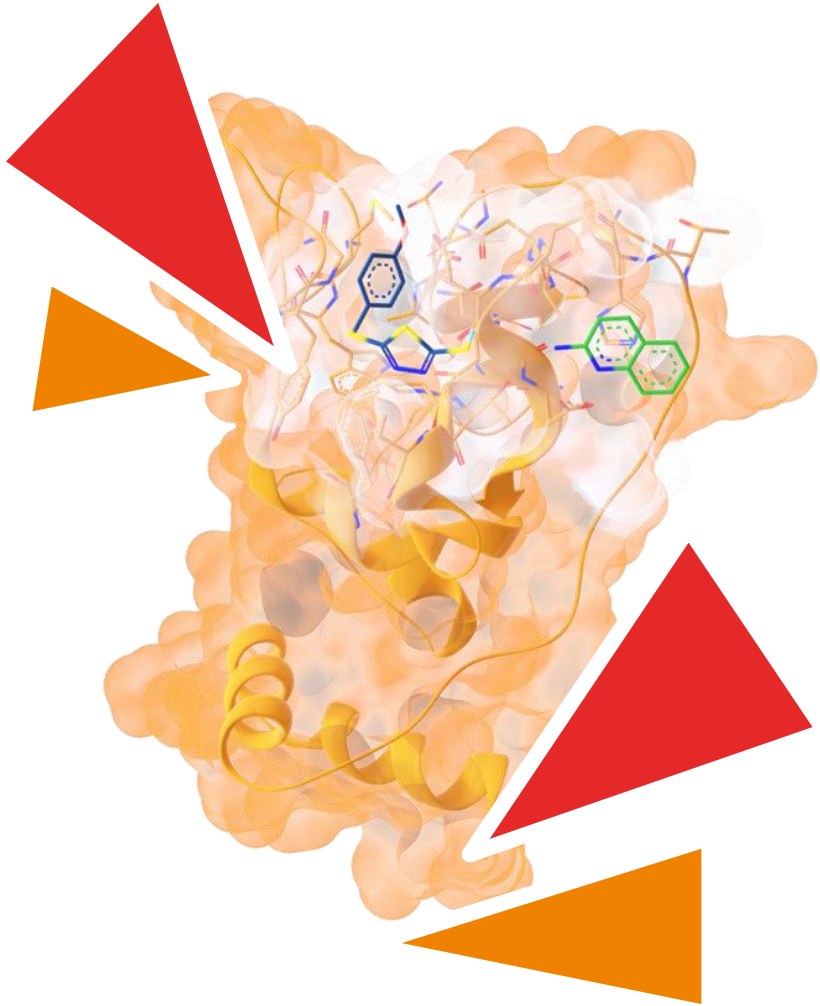
BioSolveIT
expect actives!

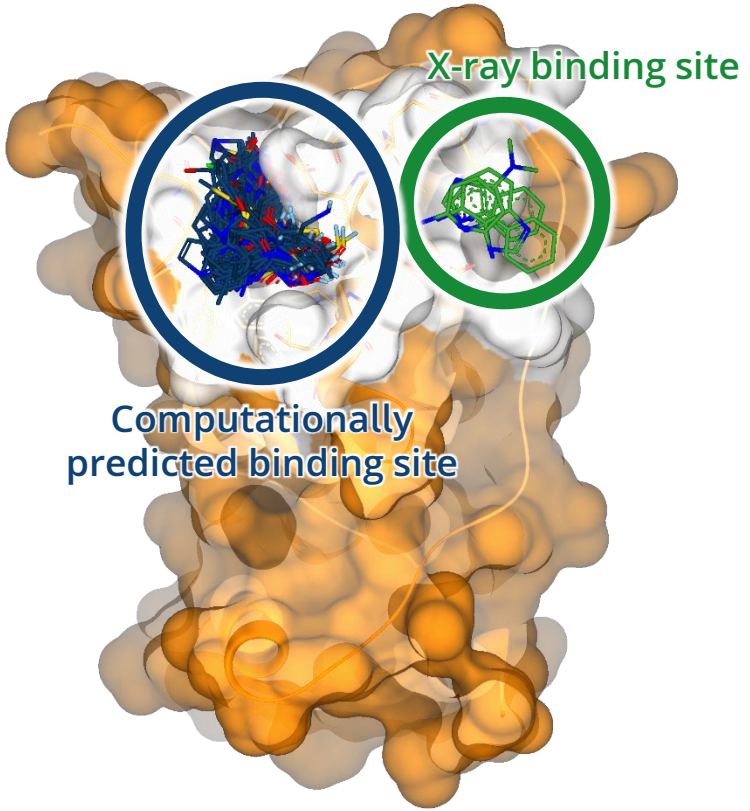
Drugathon 2023
Introduction

Targeting Nsp10 via two different fragment binding sites



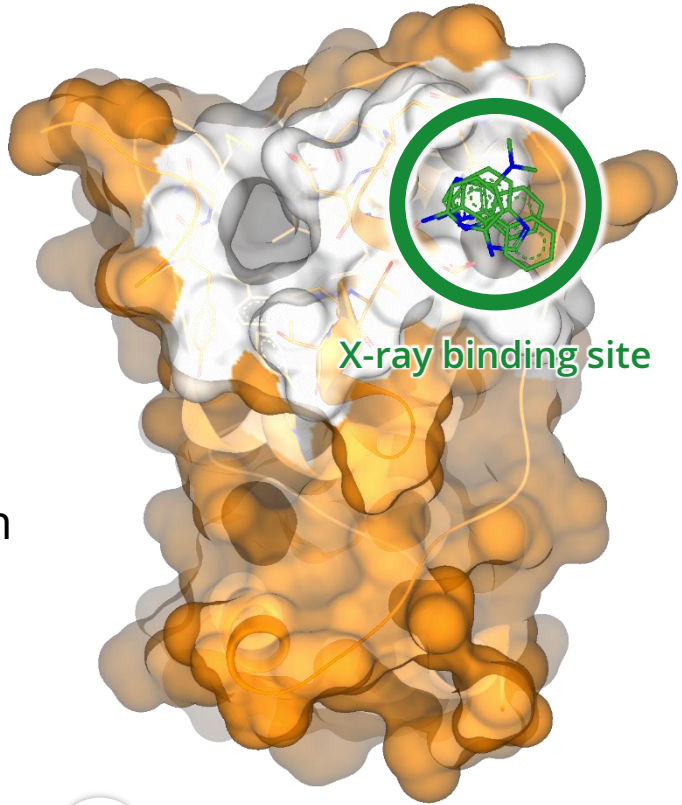
Target: Nsp10

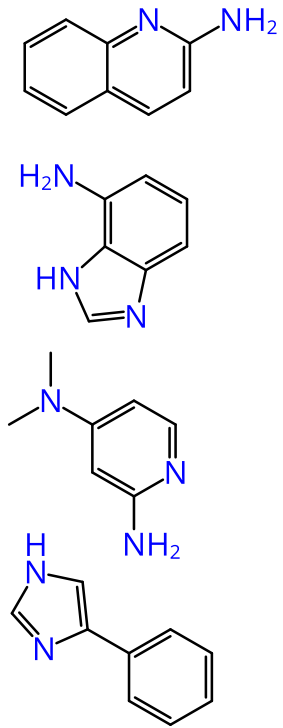
- Target: Non-structural protein 10 (Nsp10) from SARS CoV-2
- 2 binding sites (1x with fragment-like ligands, 1x computationally predicted starting points)
- Goal: Grow, design, combine fragments to improve binding affinity
- Tools:
  - **SeeSAR** for design
  - **infiniSee** to mine related compounds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



Binding Site 1: X-ray binding site

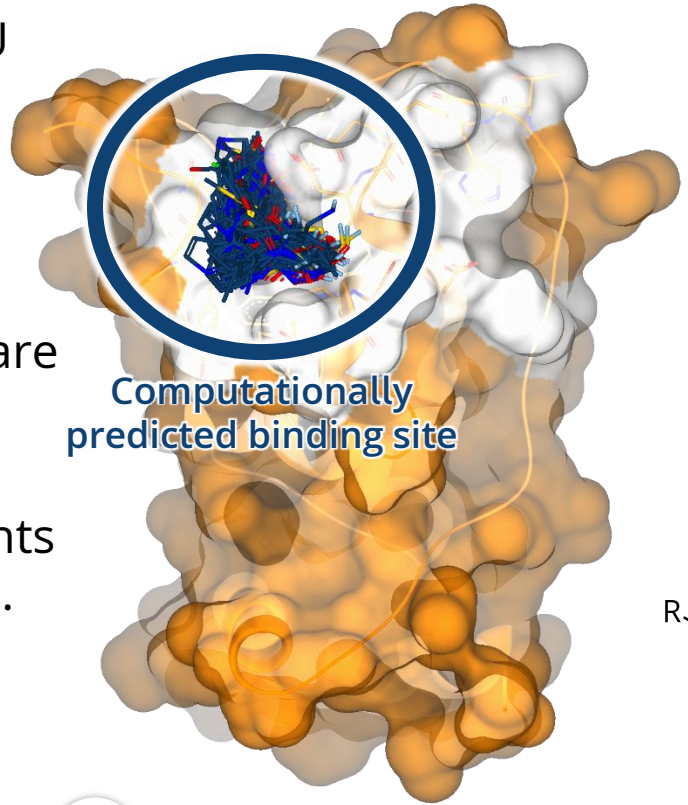
- Four PDBs with co-complexed fragments available:
  - **7ORU** (target structure for the Drugathon 2023)
  - 7ORR
  - 7ORV
  - 7ORW
- The co-complexed fragments are colored in green in the Drugathon SeeSAR project.

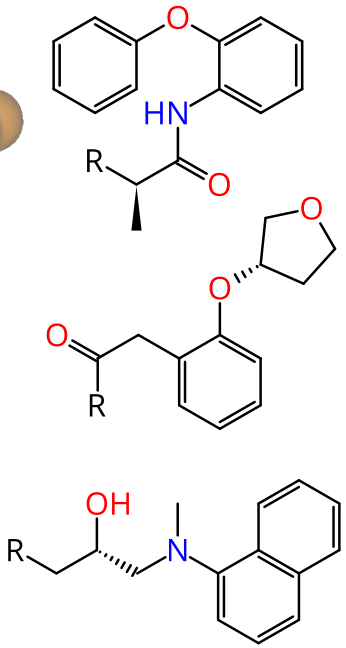


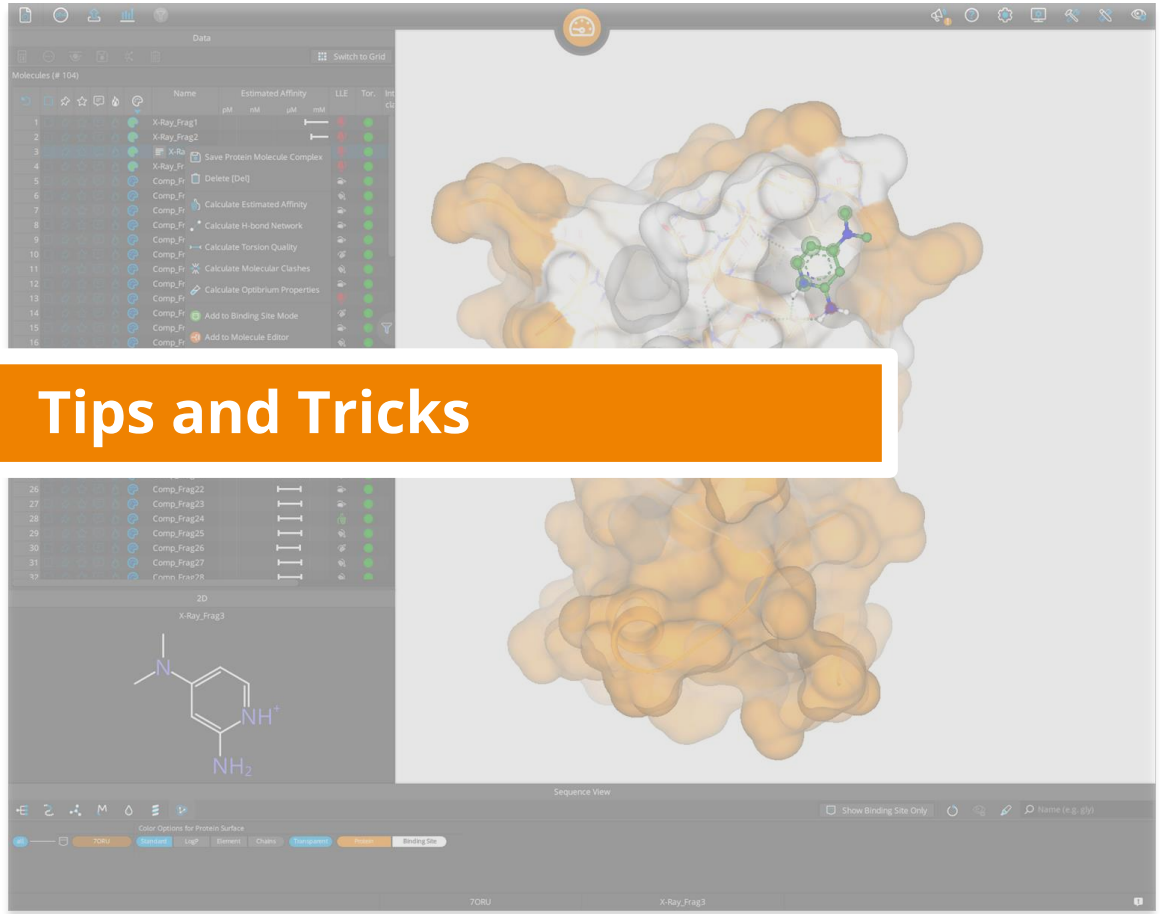


Binding site 2: Predicted binding site

- 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.

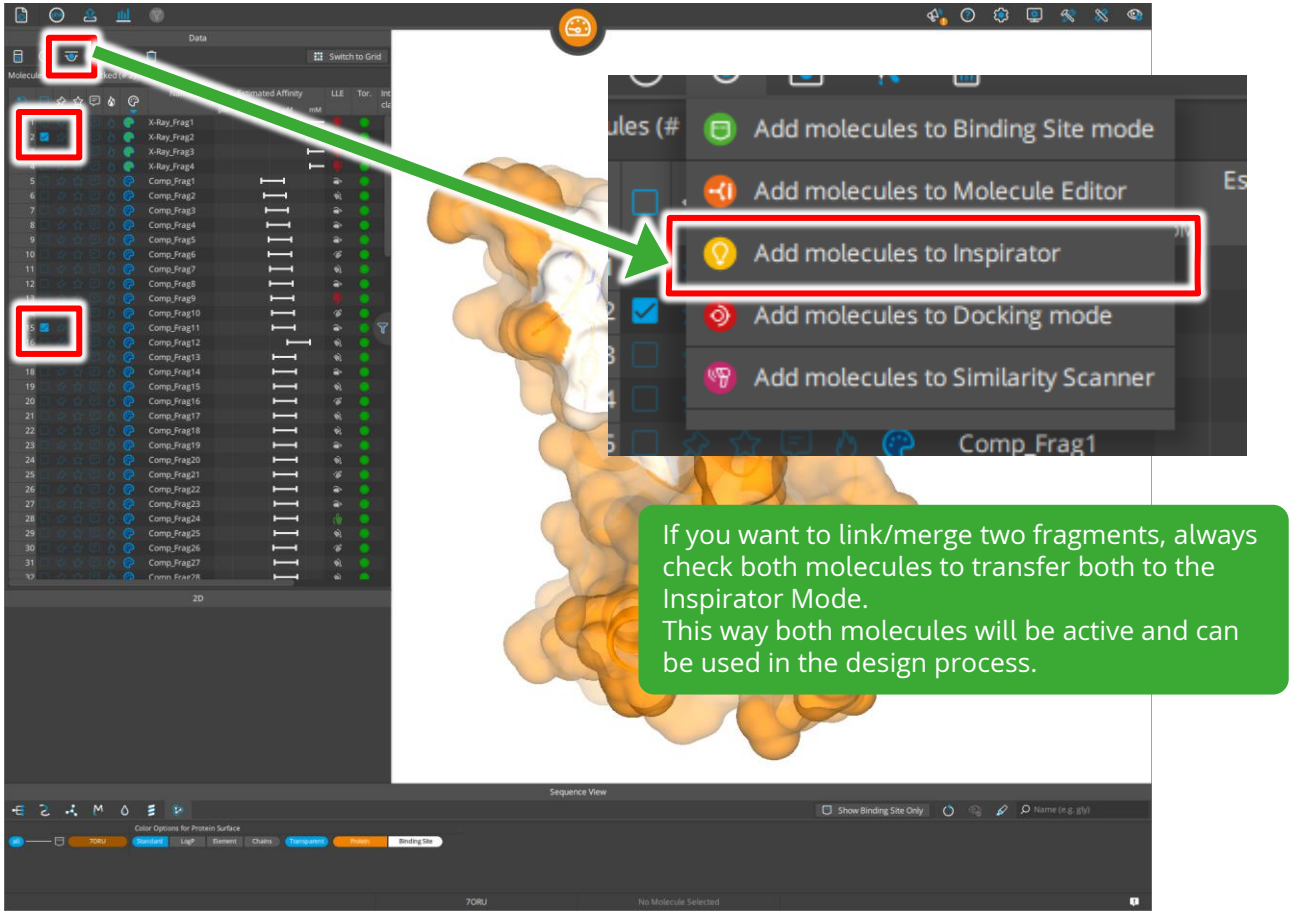




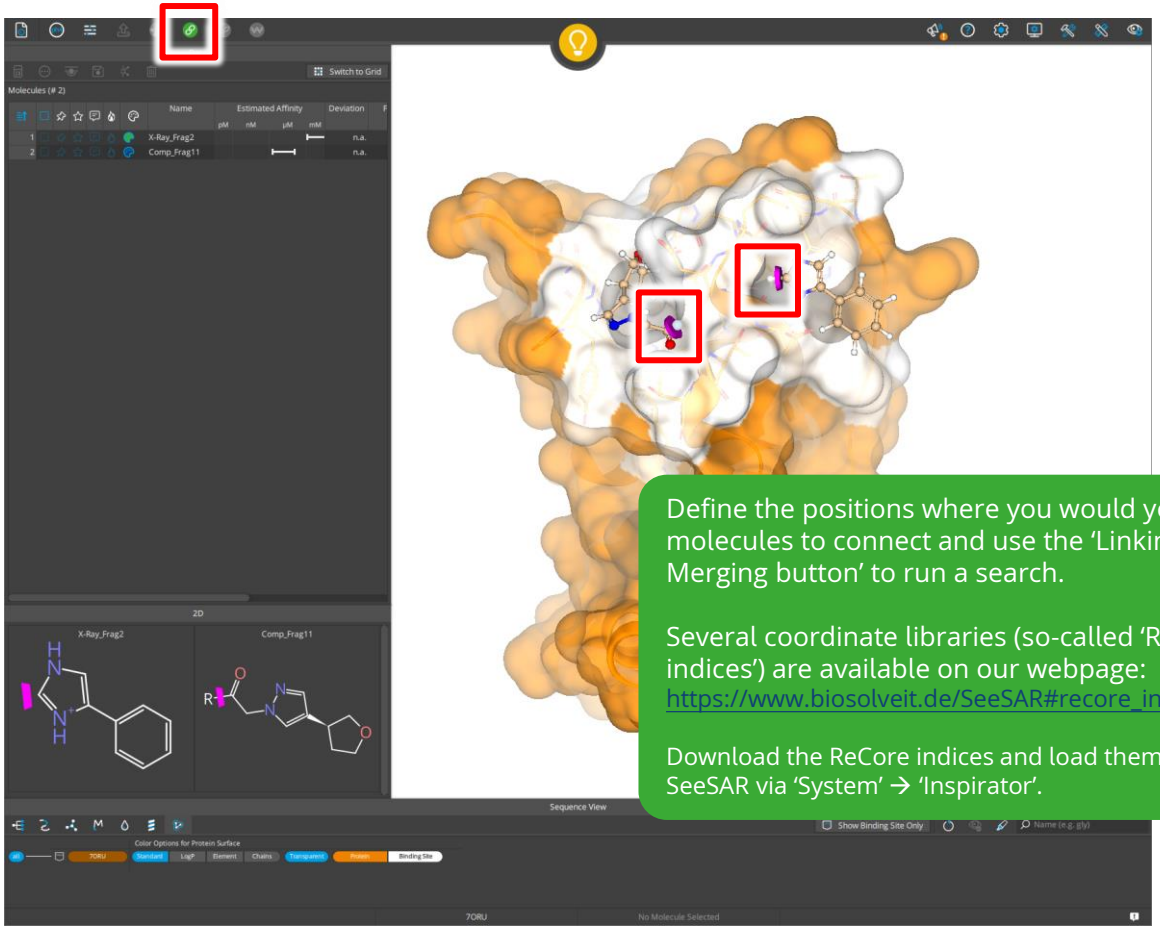


Tips and Tricks

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.



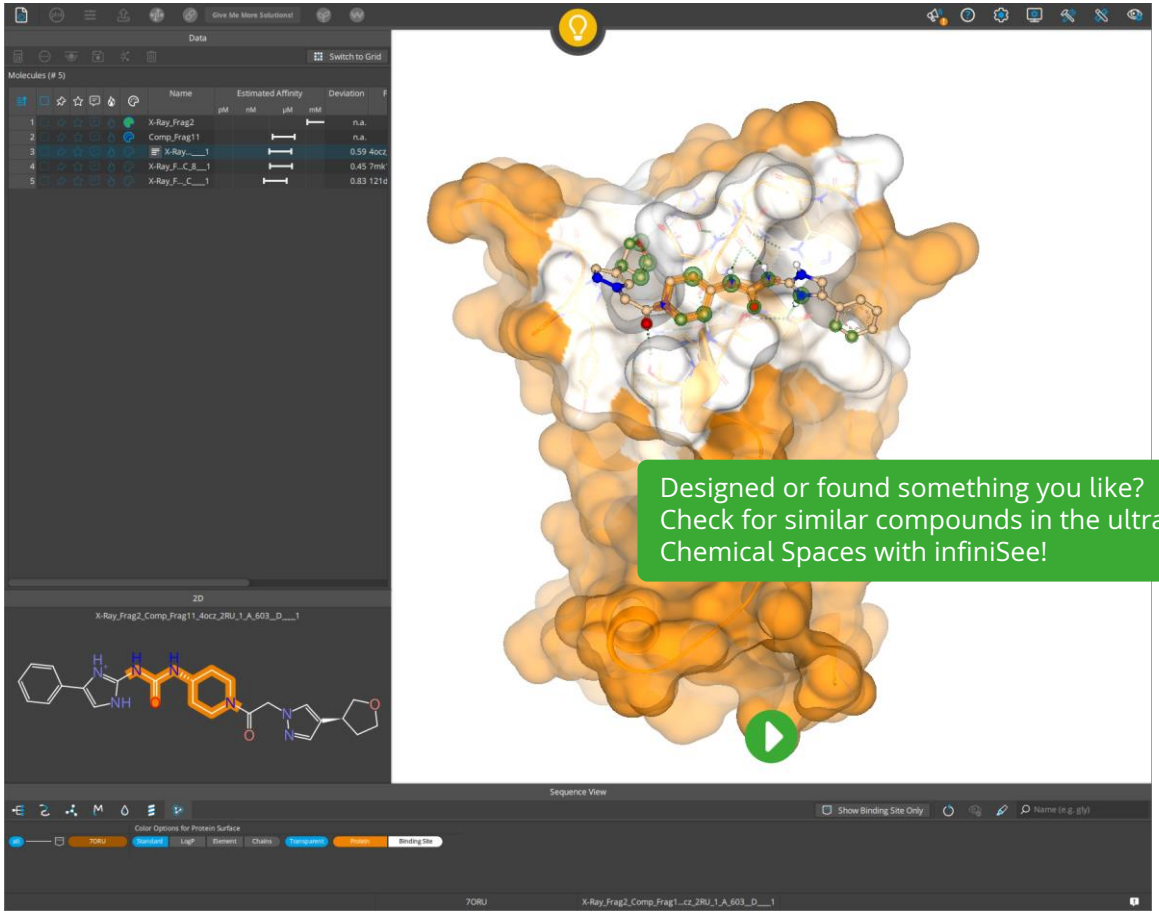
If you want to link/merge two fragments, always check both molecules to transfer both to the Inspirator Mode.
This way both molecules will be active and can be used in the design process.



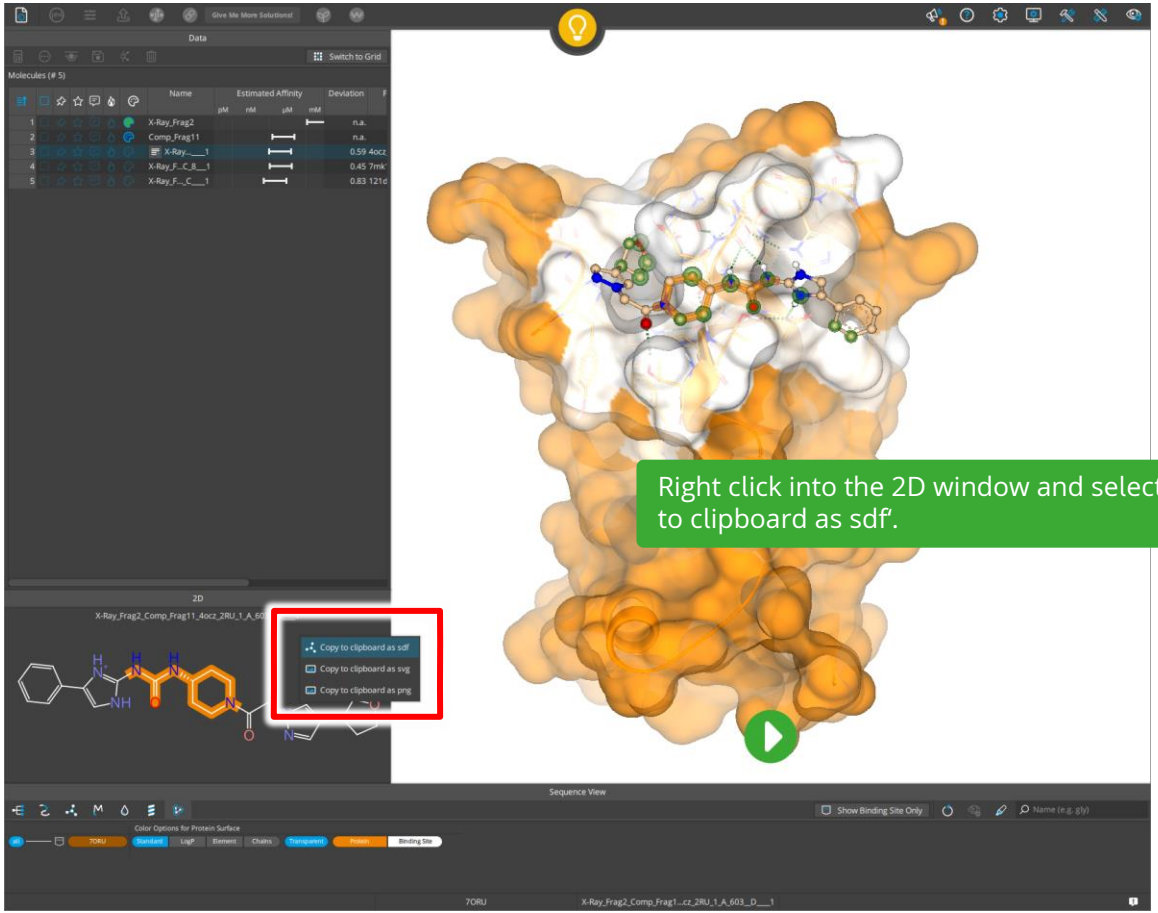
Define the positions where you would your molecules to connect and use the 'Linking & Merging button' to run a search.

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

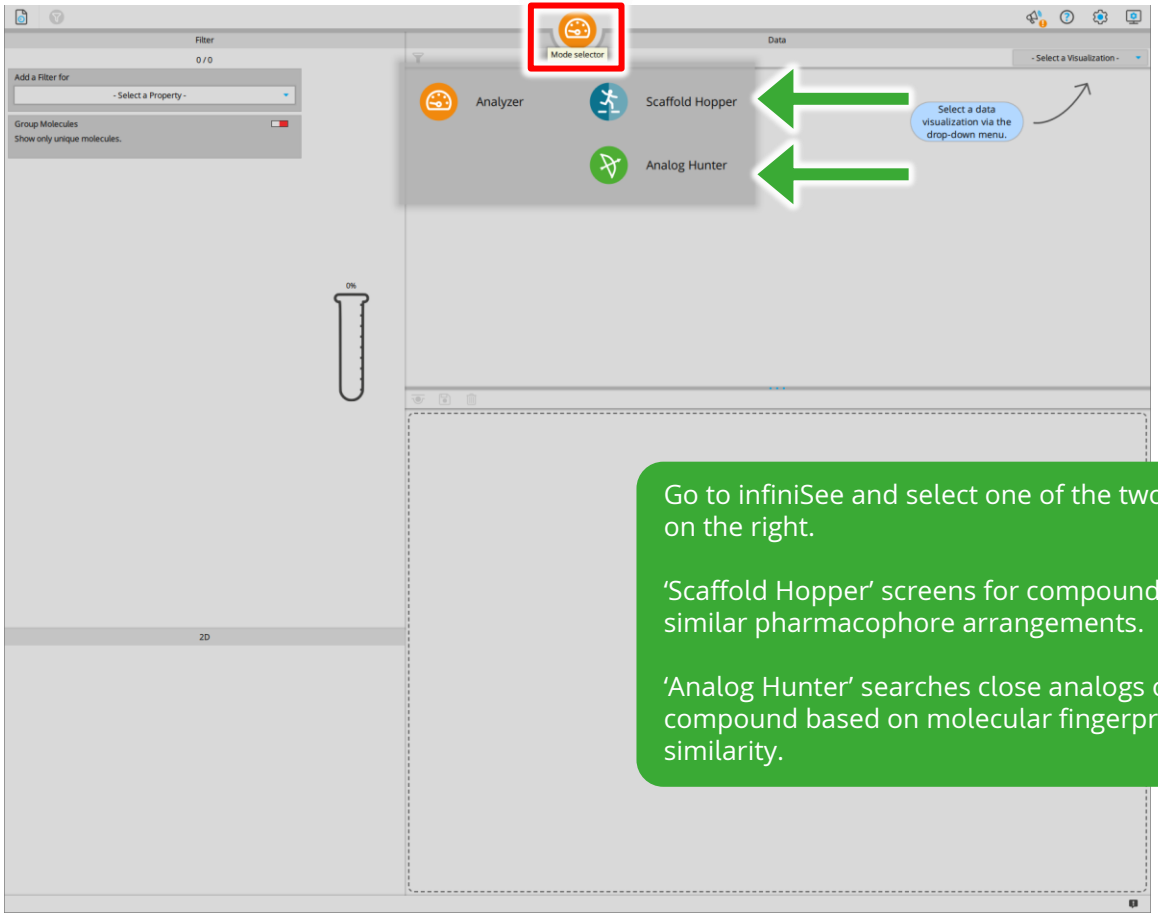
Download the ReCore indices and load them into SeeSAR via 'System' → 'Inspirator'.



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



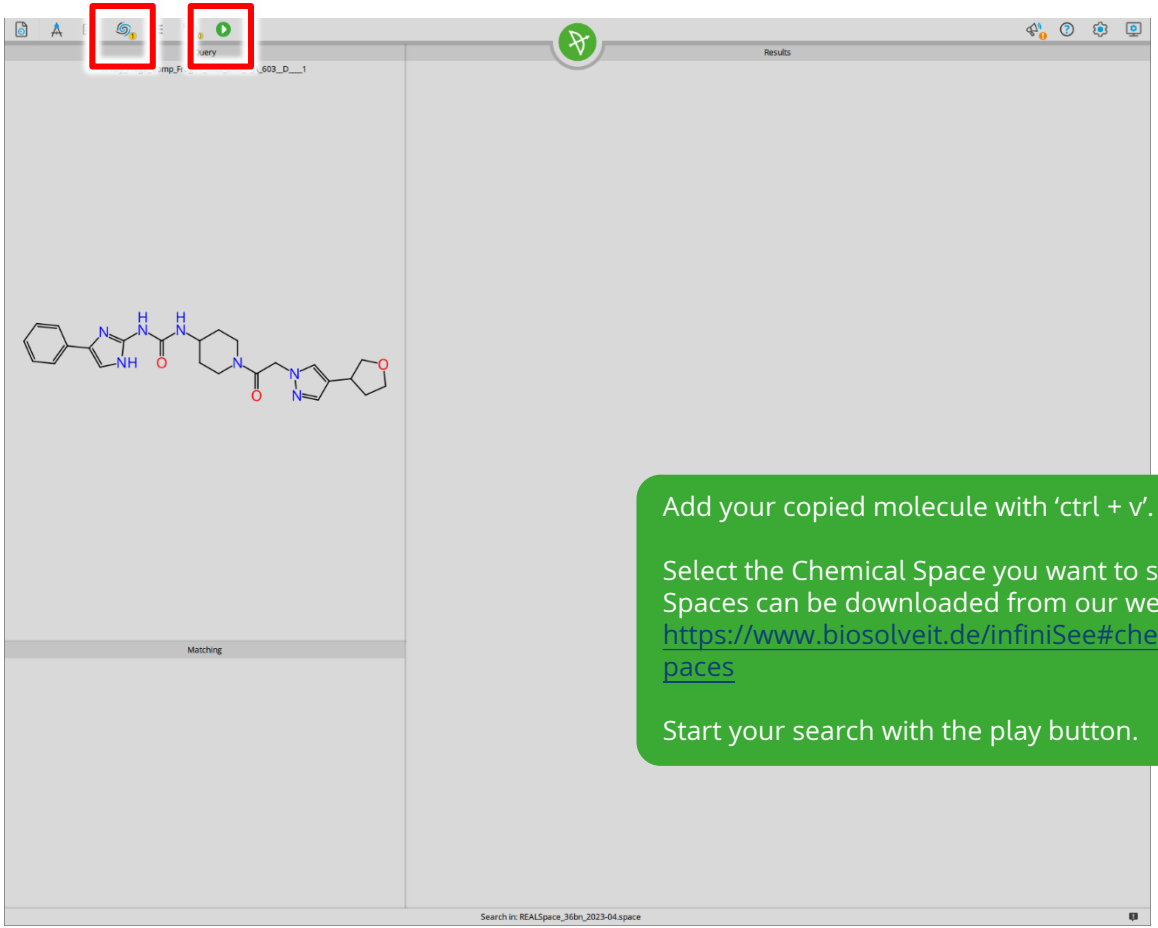
Right click into the 2D window and select ‚Copy to clipboard as sdf'.



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

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

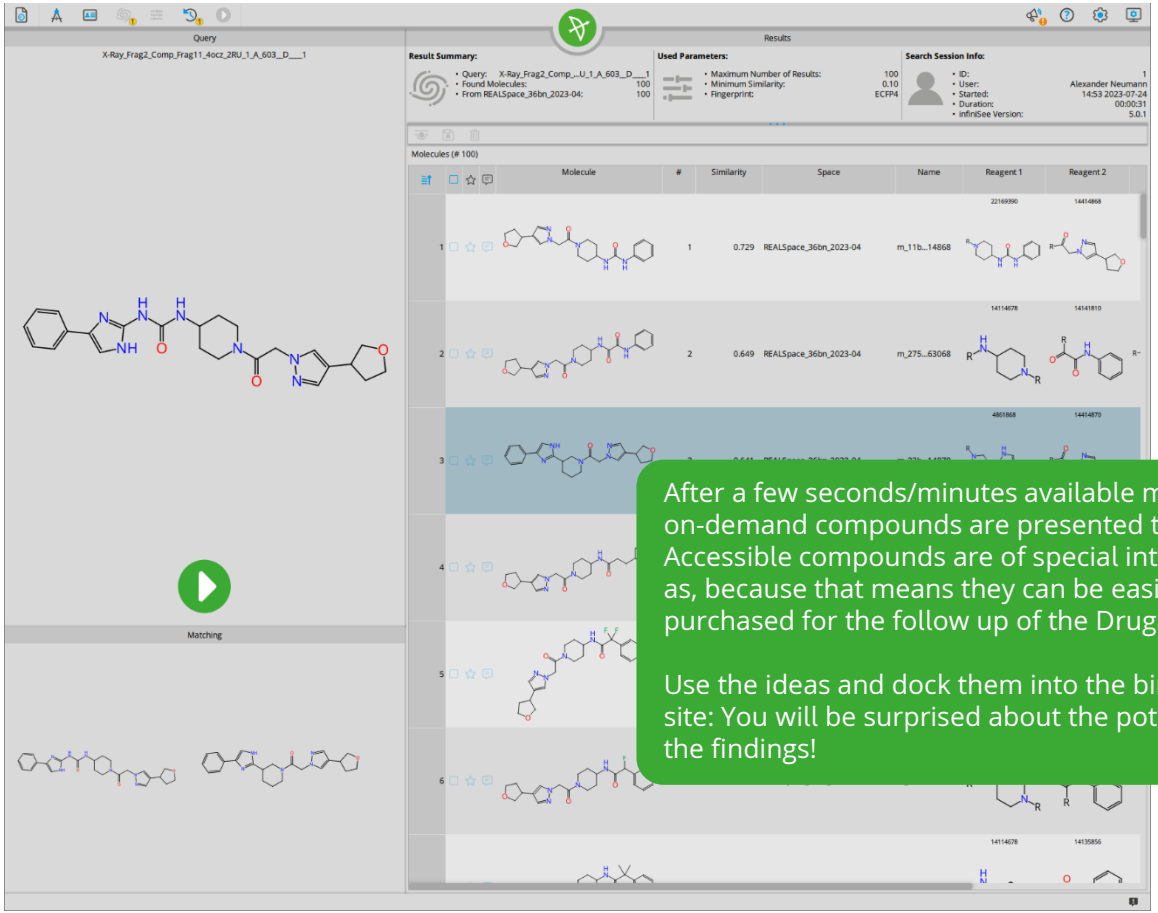
'Analog Hunter' searches close analogs of a compound based on molecular fingerprint similarity.



Add your copied molecule with ‘ctrl + v’.

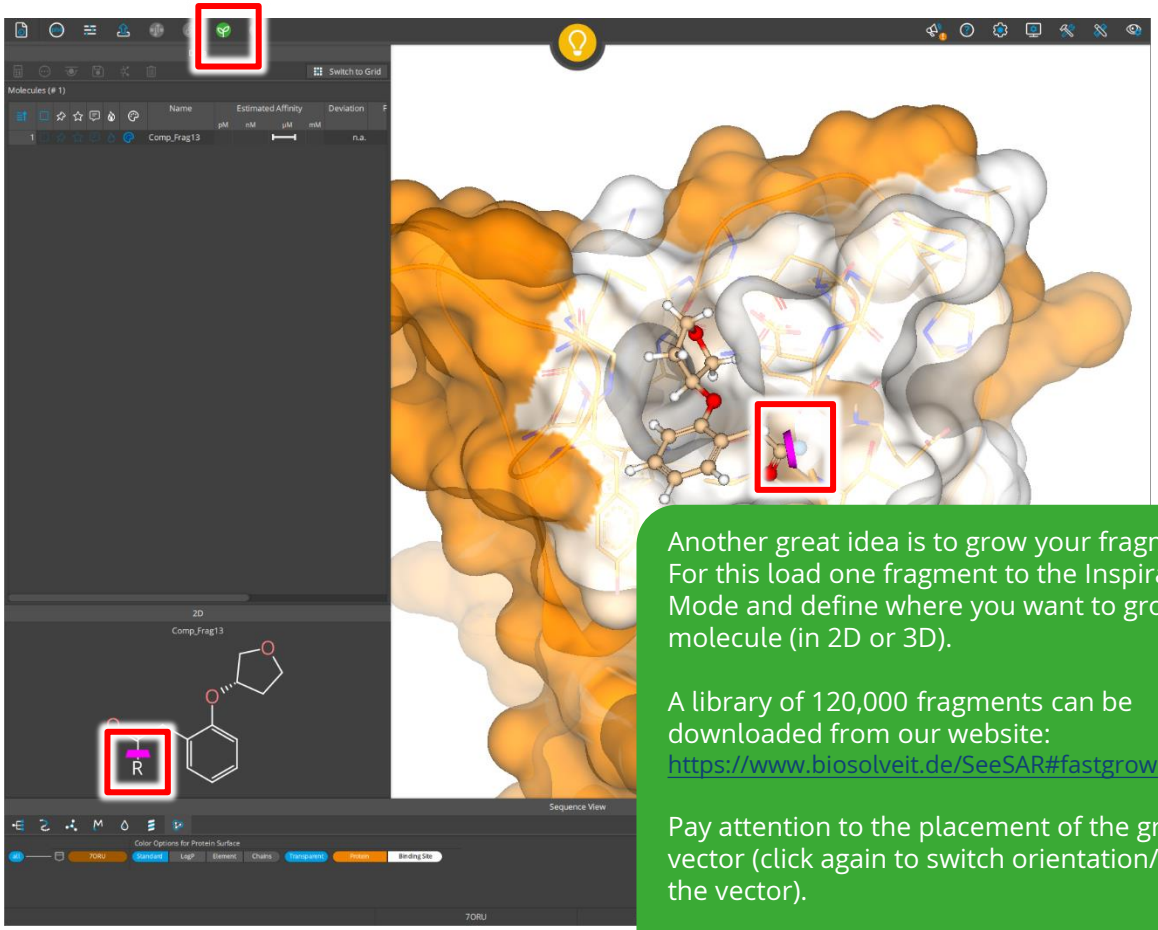
Select the Chemical Space you want to search. Spaces can be downloaded from our website: https://www.biosolveit.de/infiniSee#chemical_spaces

Start your search with the play button.



After a few seconds/minutes available make-on-demand compounds are presented to you. Accessible compounds are of special interest to as, 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!

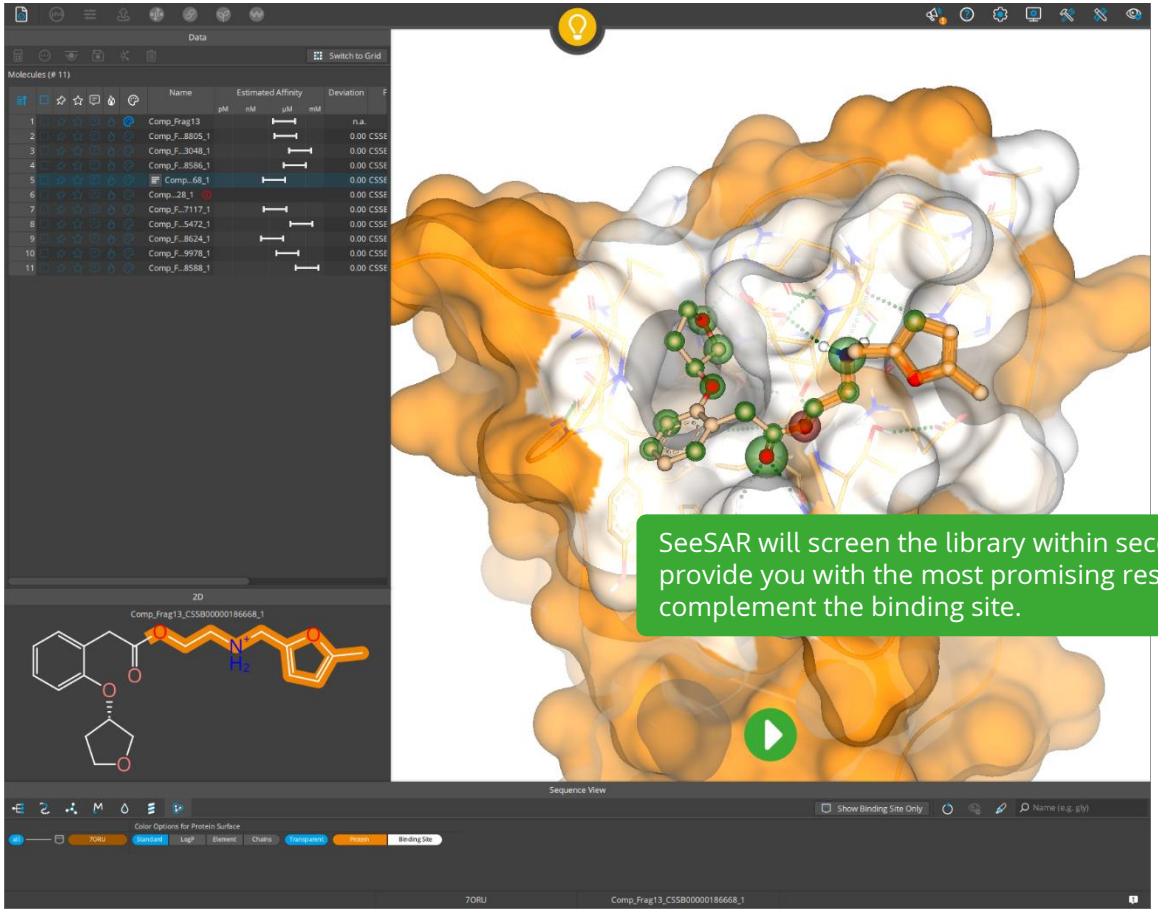


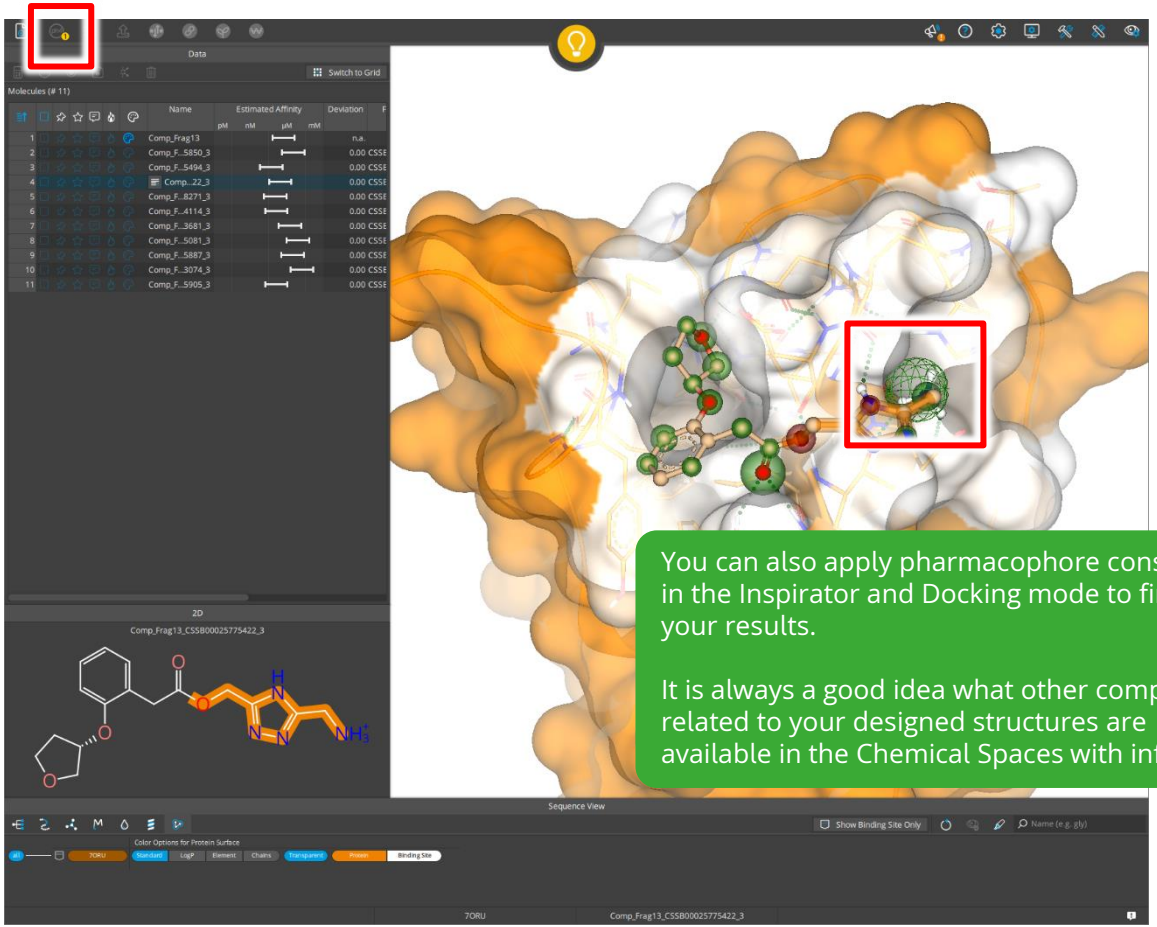
Another great idea is to grow your fragment. For this load one fragment to the Inspirator Mode and define where you want to grow your molecule (in 2D or 3D).

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).

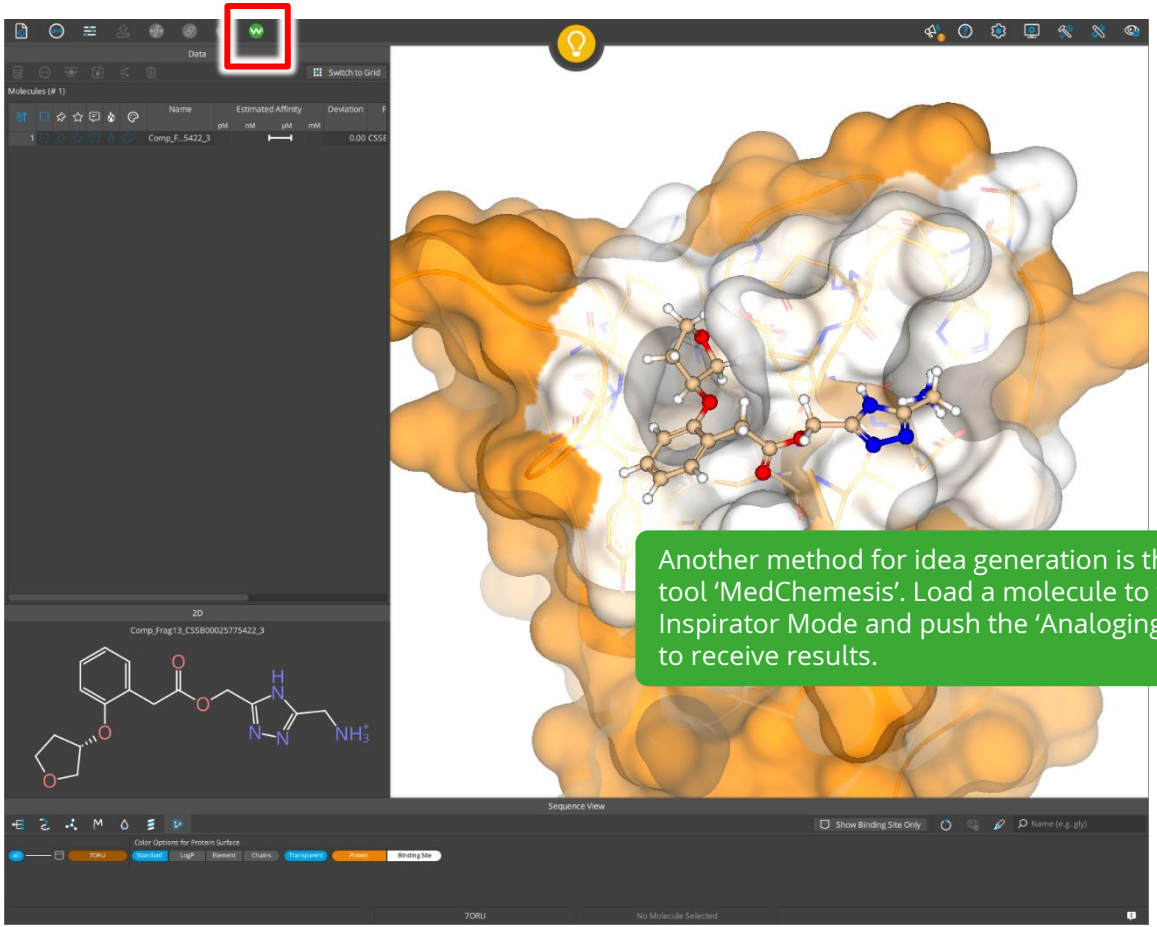
Use the 'Growing' button to generate results.


Data
Switch to Grid
Molecules (# 11)
Name
Estimated Affinity
Deviation
pM
nM
µM
mM
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
2D
Comp_Frag13_CSSB00000186668_1
SeeSAR will screen the library within seconds to provide you with the most promising results to complement the binding site.
Sequence View
Show Binding Site Only
Color Options for Protein Surface
7ORU
Comp_Frag13_CSSB00000186668_1

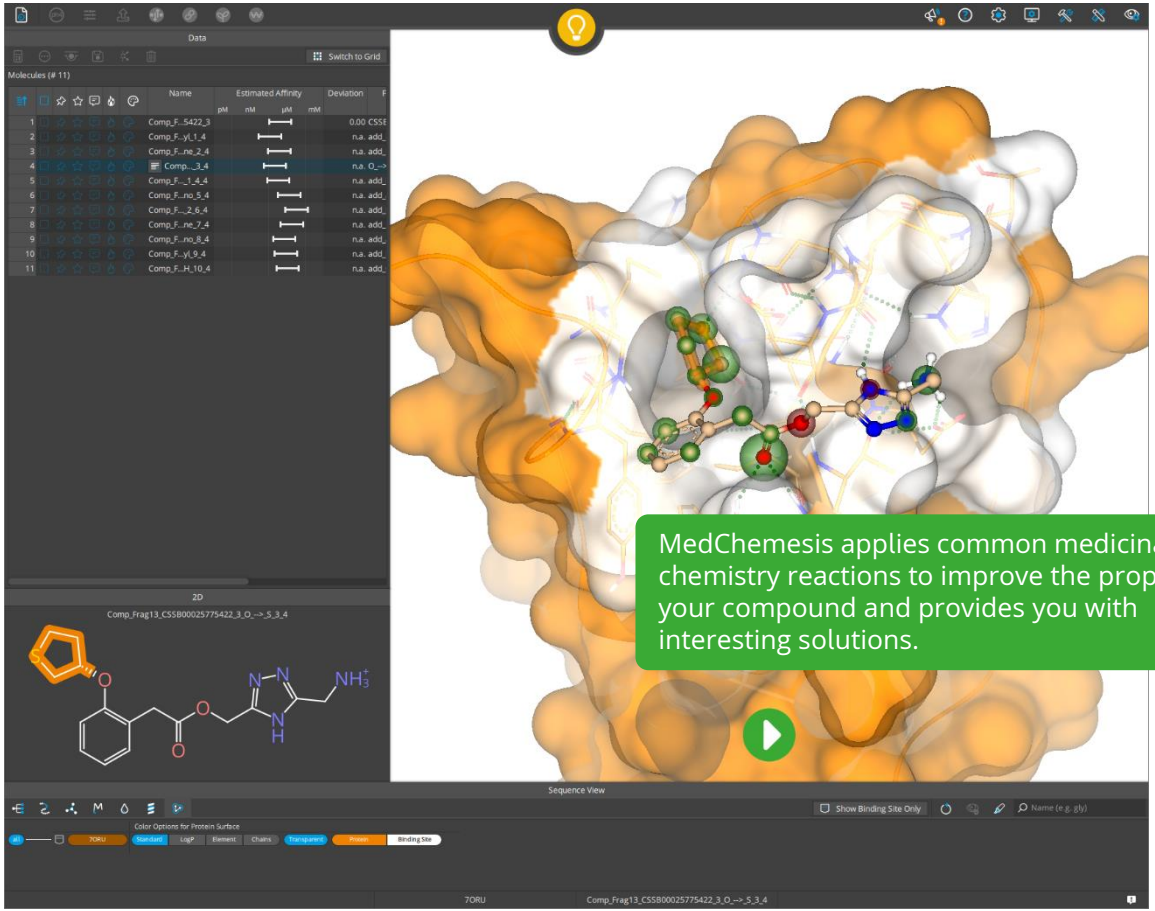


You can also apply pharmacophore constraints in the Inspirator and Docking mode to fine-tune your results.

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



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.


Data
Switch to Grid
Molecules (# 11)
Name
Estimated Affinity
Deviation
2D
Sequence View
Show Binding Site Only
Color Options for Protein Surface
7ORU
MedChemesis applies common medicinal chemistry reactions to improve the properties of your compound and provides you with interesting solutions.

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

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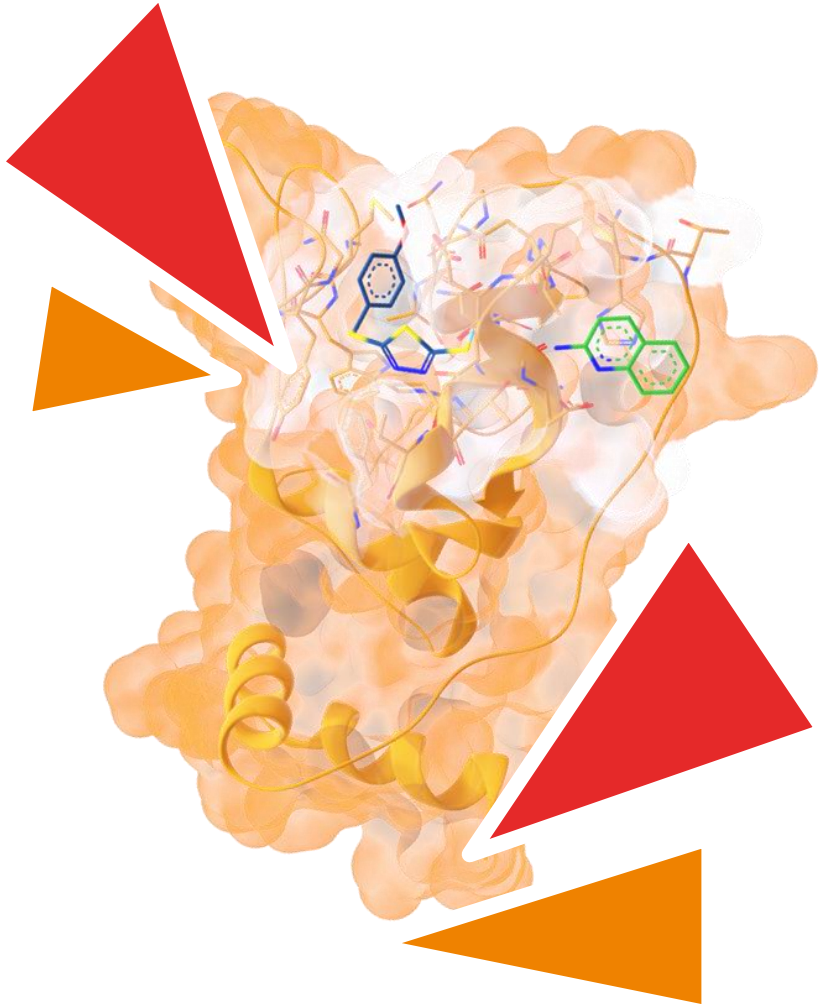

We wish you a lot of fun for the Drugathon!

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

We are happy to help!