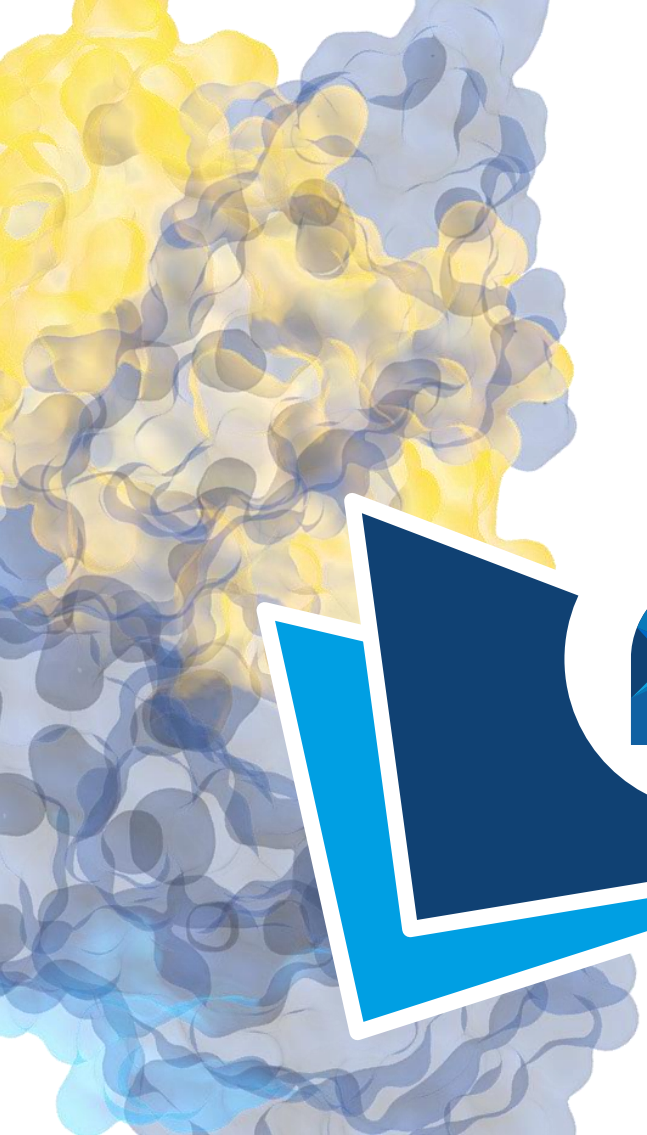


BioSolveIT
expect actives!

infiniSee xREAL

Beginner's Guide

Version 6.2 – Echo Prime

Trillions of drug-like compounds, accessible from your own hardware.

Important note

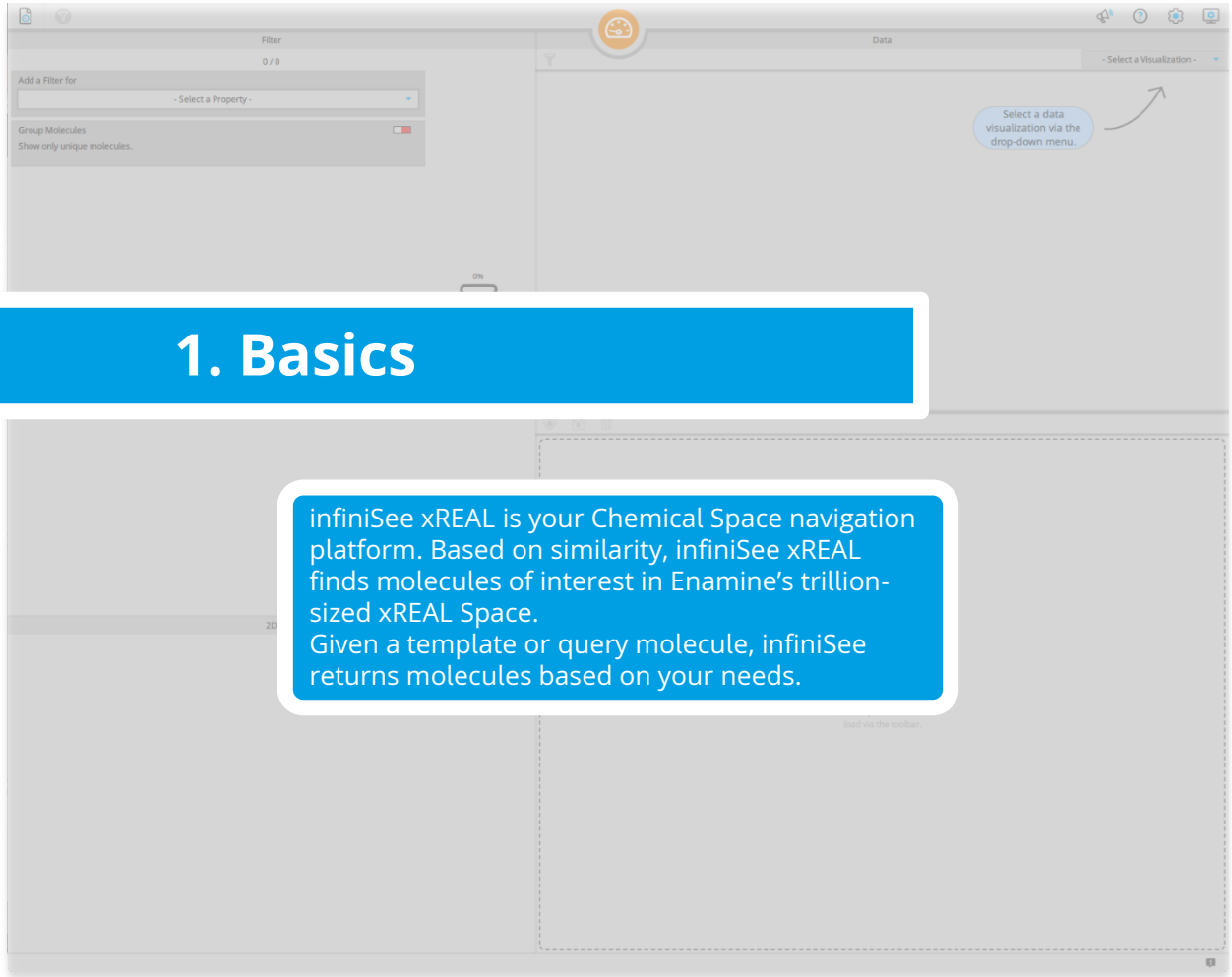
With greater numbers come increased resource requirements.
It's trillions after all.
Therefore, your hardware needs at least 32 GB of RAM and four cores to operate within the xREAL Space. But honestly, it's a small obstacle to overcome for accessing such vast chemical horizons.

Content

Click on the section you are interested in

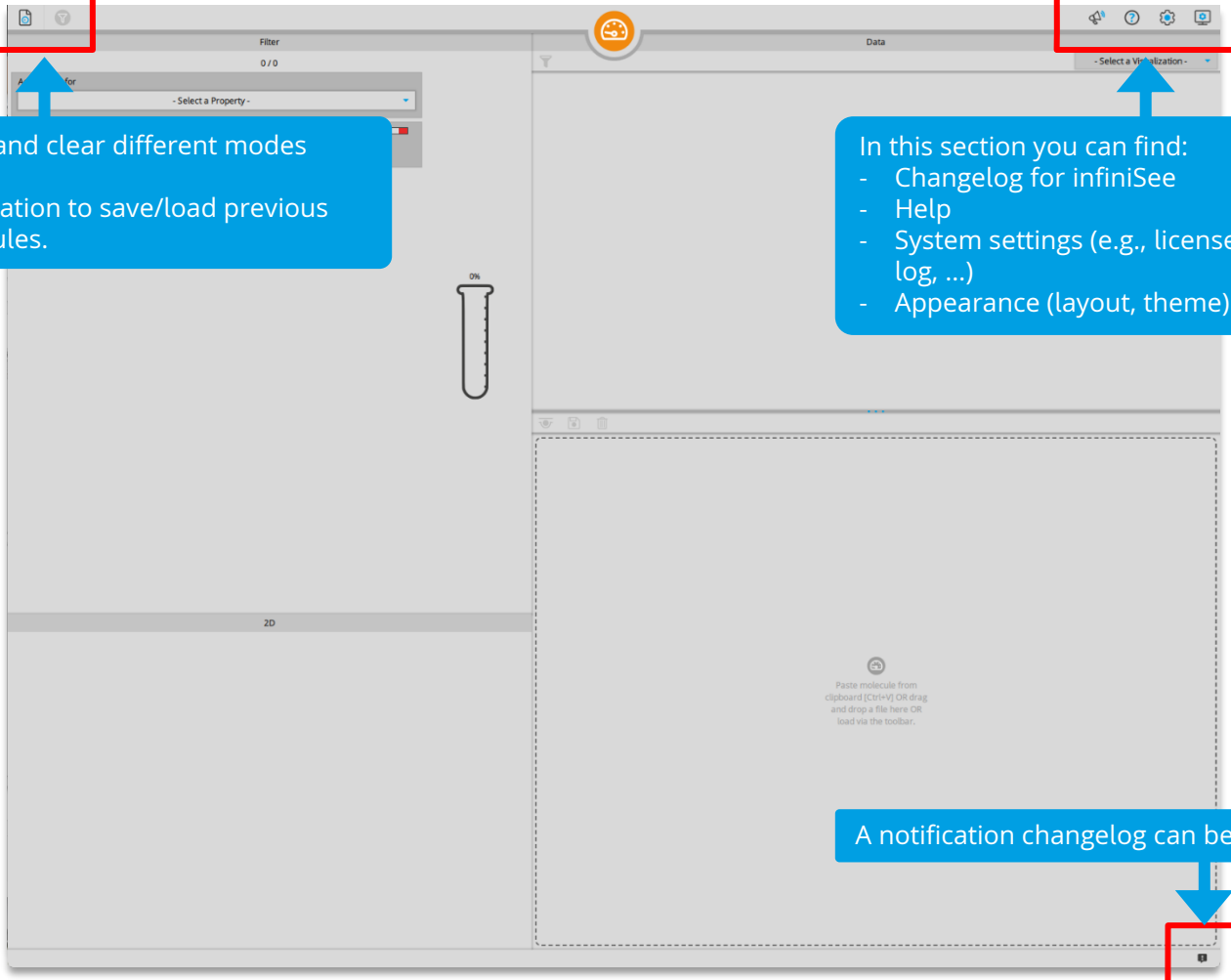

Version 6.2.0 (Echo Prime)
Welcome to
infiniSee xREAL 6.2
unlimited accessibles
Echo Prime
Enamine
Continue "last project"
New Project
Start infiniSee Tour
Continue with your last project.
Start your Chemical Space exploration here.
Find an introduction to infiniSee's interface.

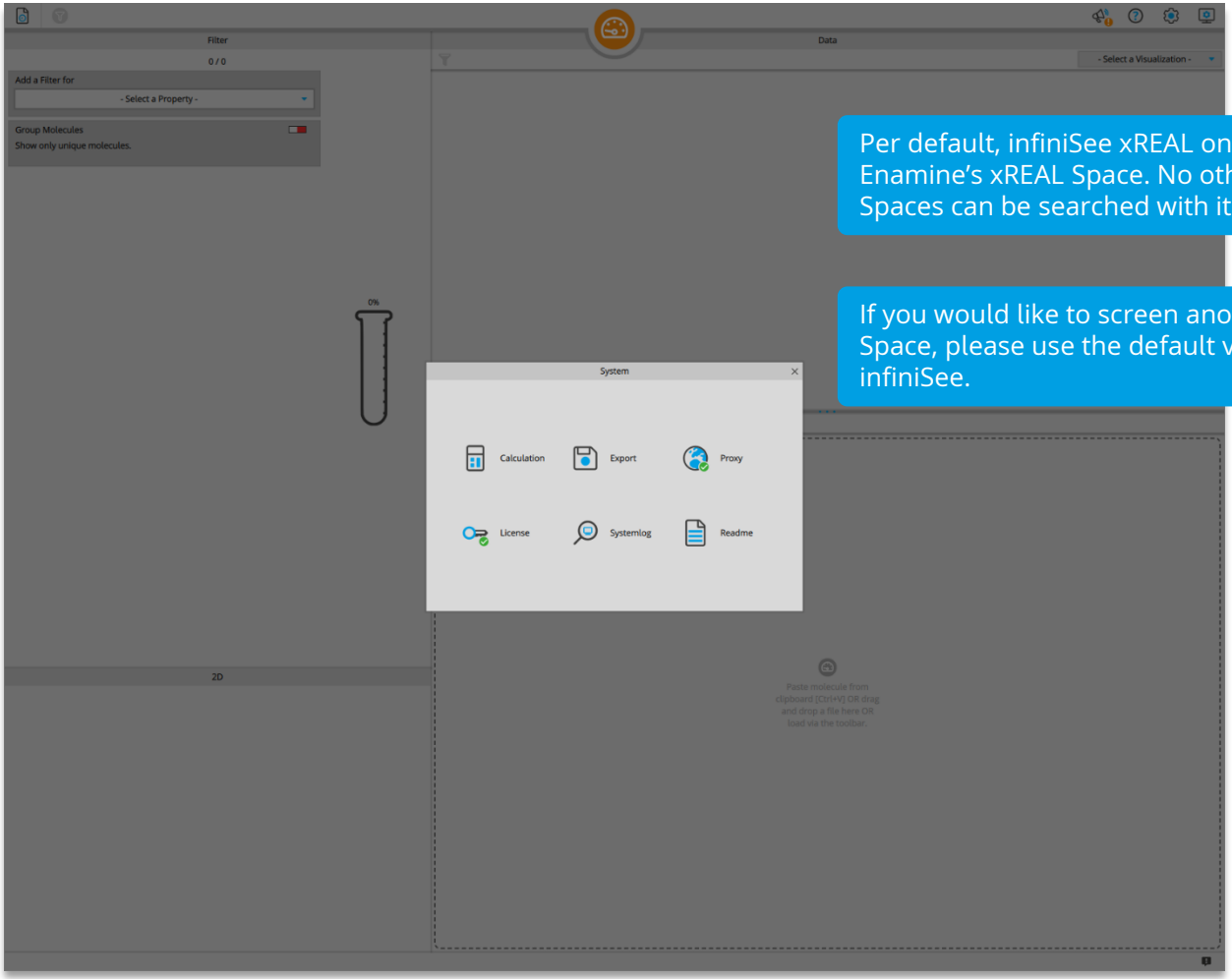

Version 6.2.0 (Echo Prime)
Welcome to
infiniSee xREAL 6.2
unlimited accessibles
Echo Prime
What are you trying to achieve?
Select to start a mode!
Find scaffold hops and pharmacophore matches
Retrieve structurally similar analogs
Seek for substructure motifs in hits
Load molecules for analysis
Enamine
After starting a new project, infiniSee assists you in choosing the appropriate mode to accomplish your project objectives.



1. Basics

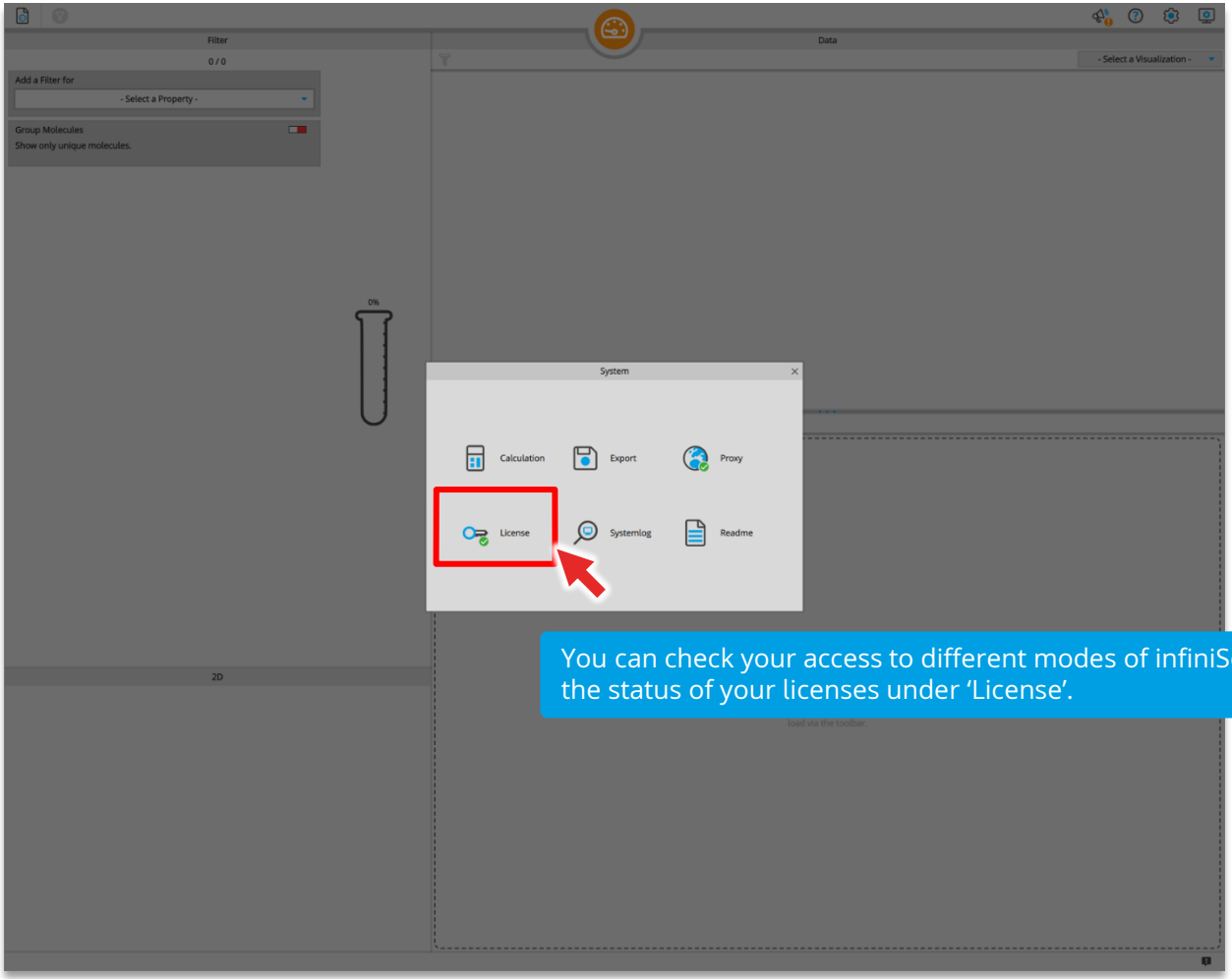
infiniSee xREAL is your Chemical Space navigation platform. Based on similarity, infiniSee xREAL finds molecules of interest in Enamine's trillion-sized xREAL Space.
Given a template or query molecule, infiniSee returns molecules based on your needs.

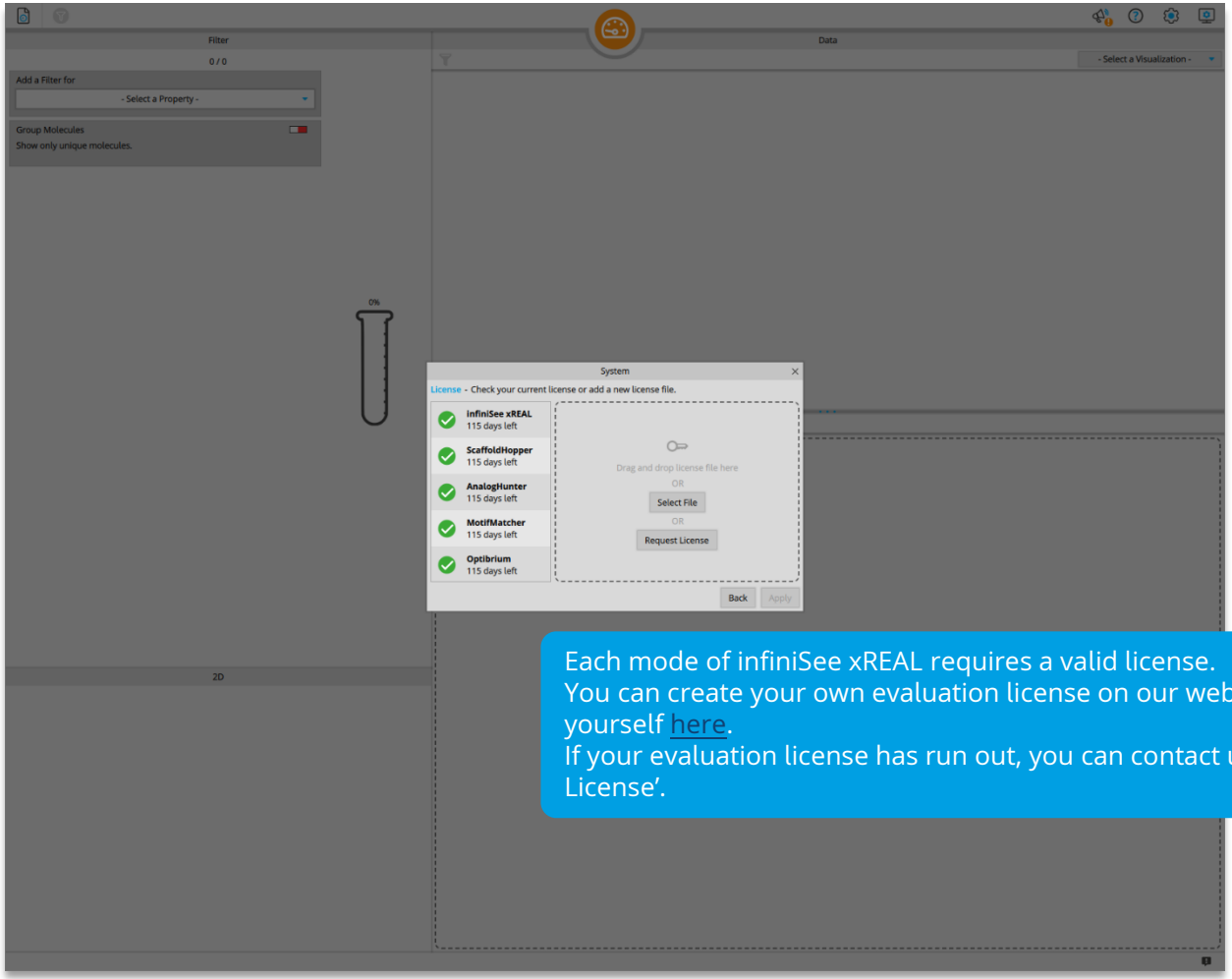

Start new project and clear different modes here.
This is also the location to save/load previous projects or molecules.
In this section you can find:
- Changelog for infiniSee
- Help
- System settings (e.g., license settings, system log, ...)
- Appearance (layout, theme)
A notification changelog can be found here.
Filter
Data
2D



Per default, infiniSee xREAL only features Enamine's xREAL Space. No other Chemical Spaces can be searched with it.

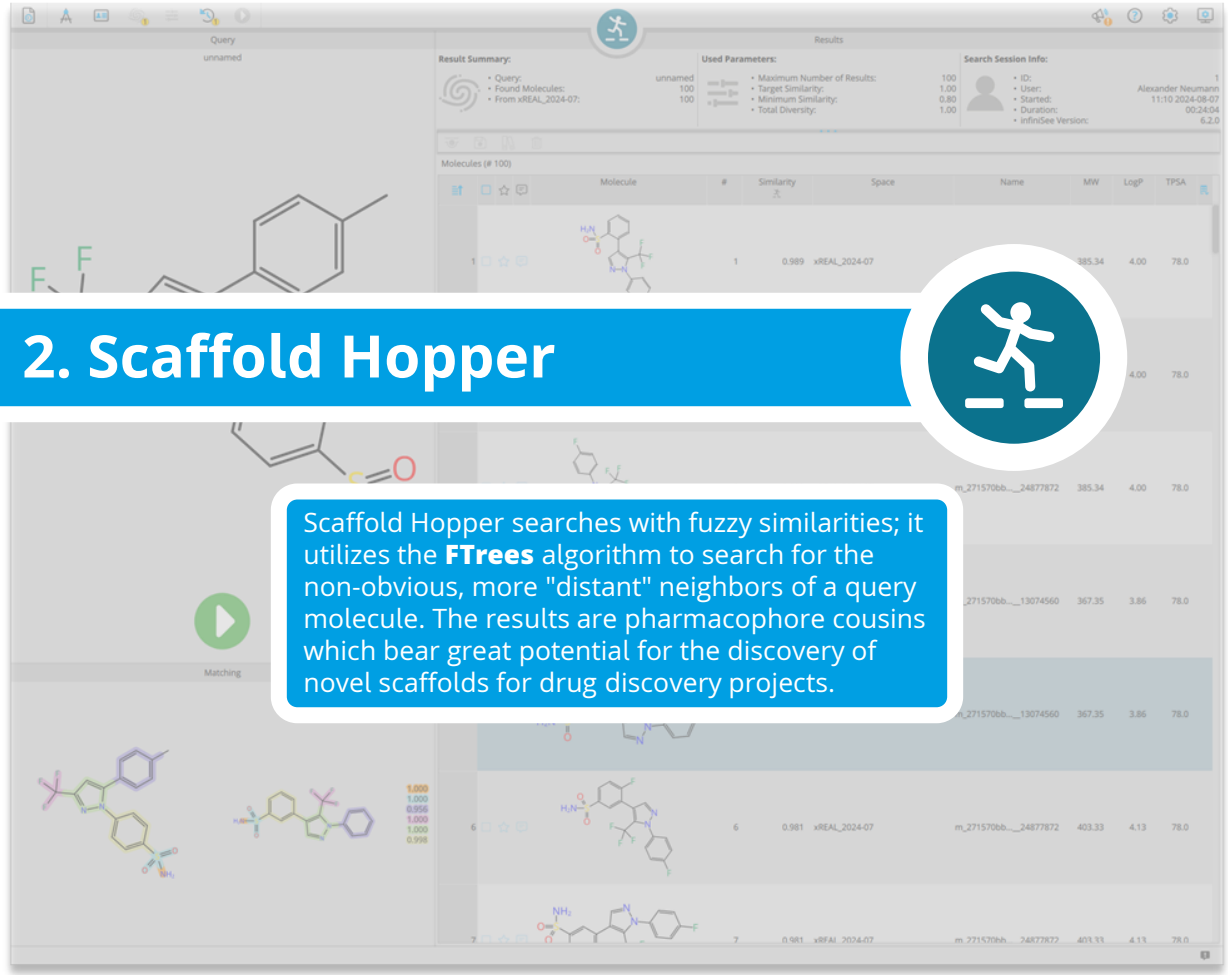
If you would like to screen another Chemical Space, please use the default version of infiniSee.


Filter
0 / 0
Add a Filter for
- Select a Property -
Group Molecules
Show only unique molecules.
Data
- Select a Visualization -
0%
System
Calculation
Export
Proxy
License
Systemlog
Readme
2D
You can check your access to different modes of infiniSee as well as the status of your licenses under ‘License’.

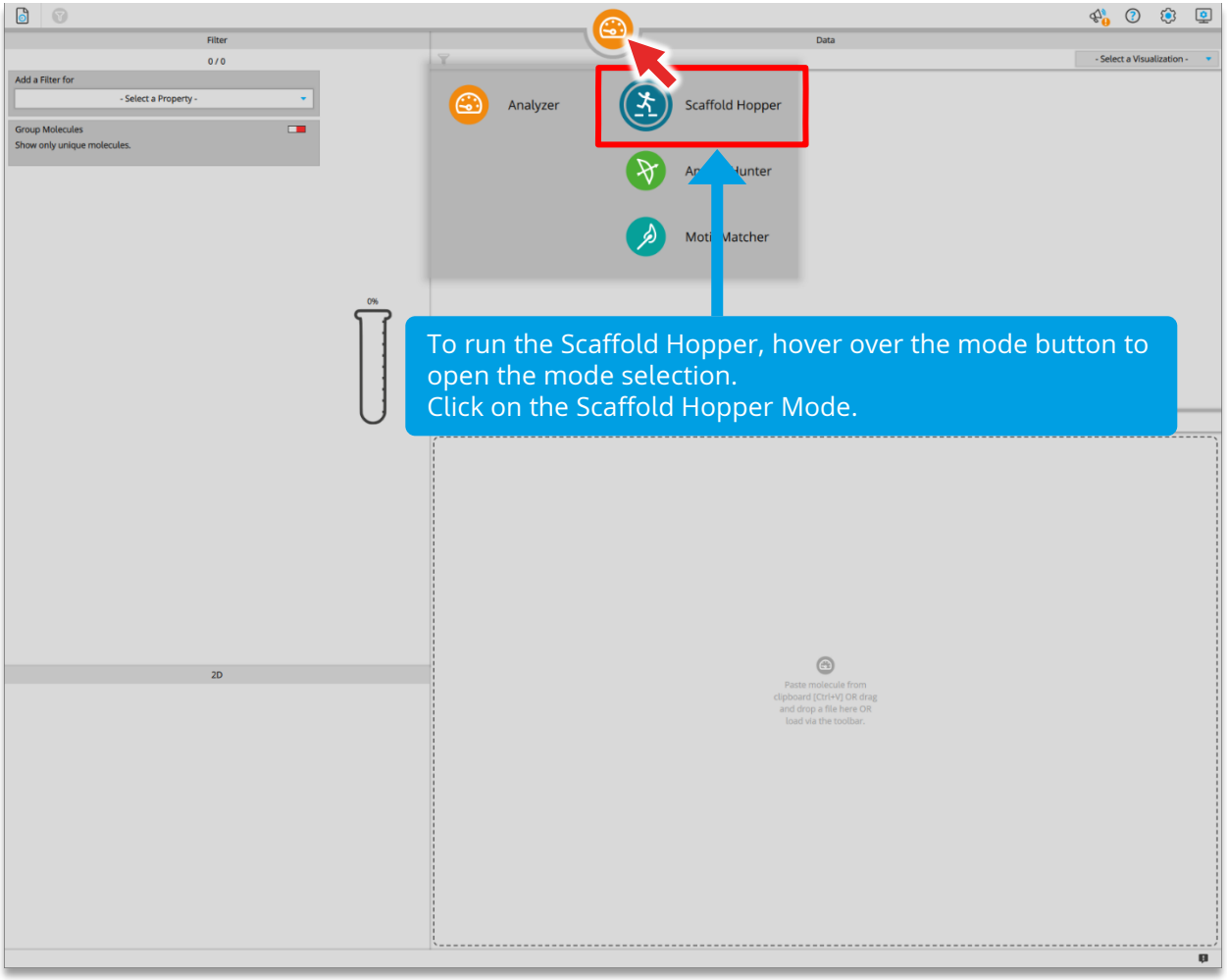


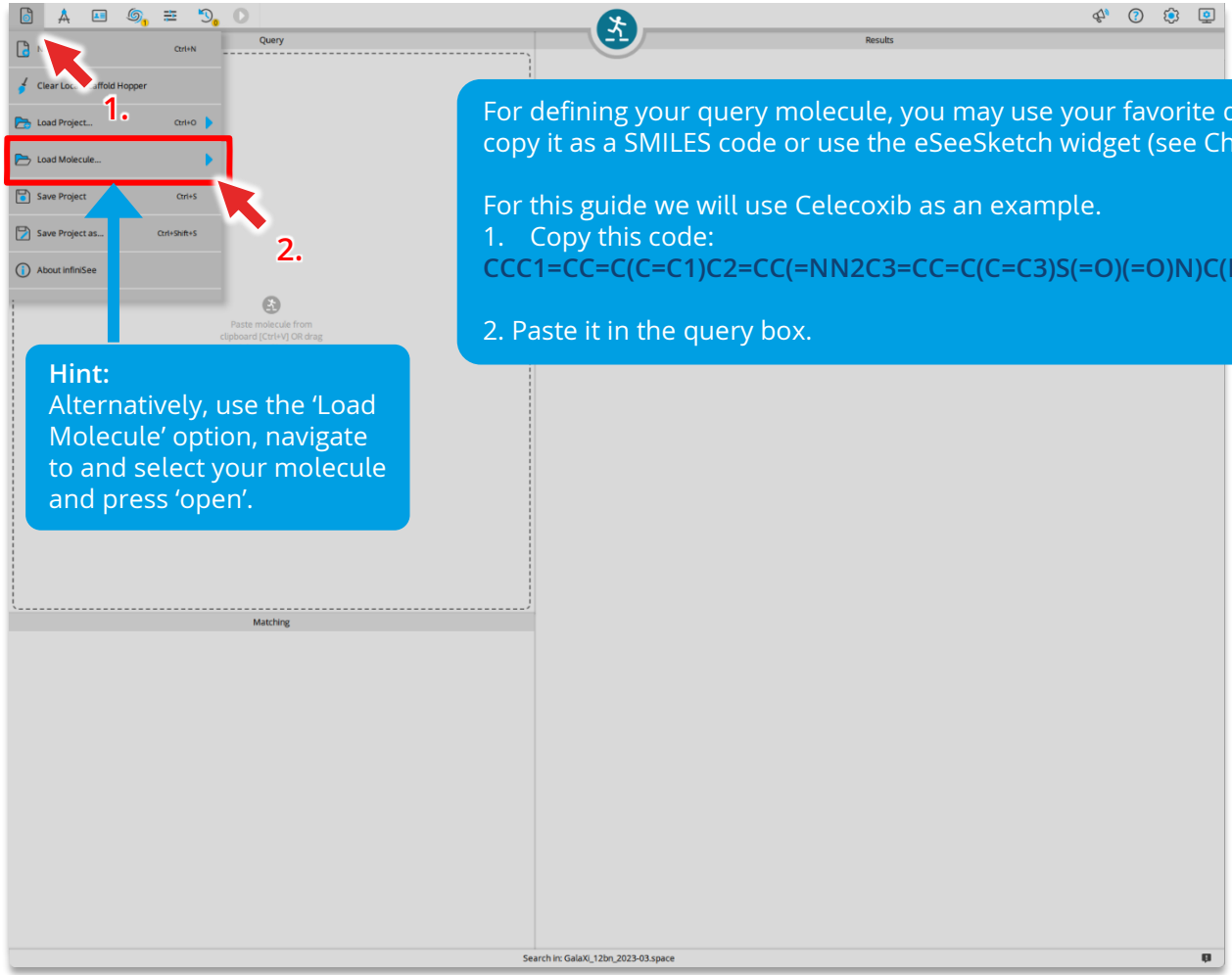
Each mode of infiniSee xREAL requires a valid license.
You can create your own evaluation license on our website by yourself here.
If your evaluation license has run out, you can contact us via 'Request License'.

2. Scaffold Hopper



Scaffold Hopper searches with fuzzy similarities; it utilizes the **FTrees** algorithm to search for the non-obvious, more "distant" neighbors of a query molecule. The results are pharmacophore cousins which bear great potential for the discovery of novel scaffolds for drug discovery projects.


Filter
0 / 0
Add a Filter for
- Select a Property -
Group Molecules
Show only unique molecules.
2D
Data
- Select a Visualization -
Analyzer
Scaffold Hopper
Hunter
Matcher
0%
To run the Scaffold Hopper, hover over the mode button to open the mode selection.
Click on the Scaffold Hopper Mode.
Paste molecule from clipboard (Ctrl+V) OR drag and drop a file here OR load via the toolbar.



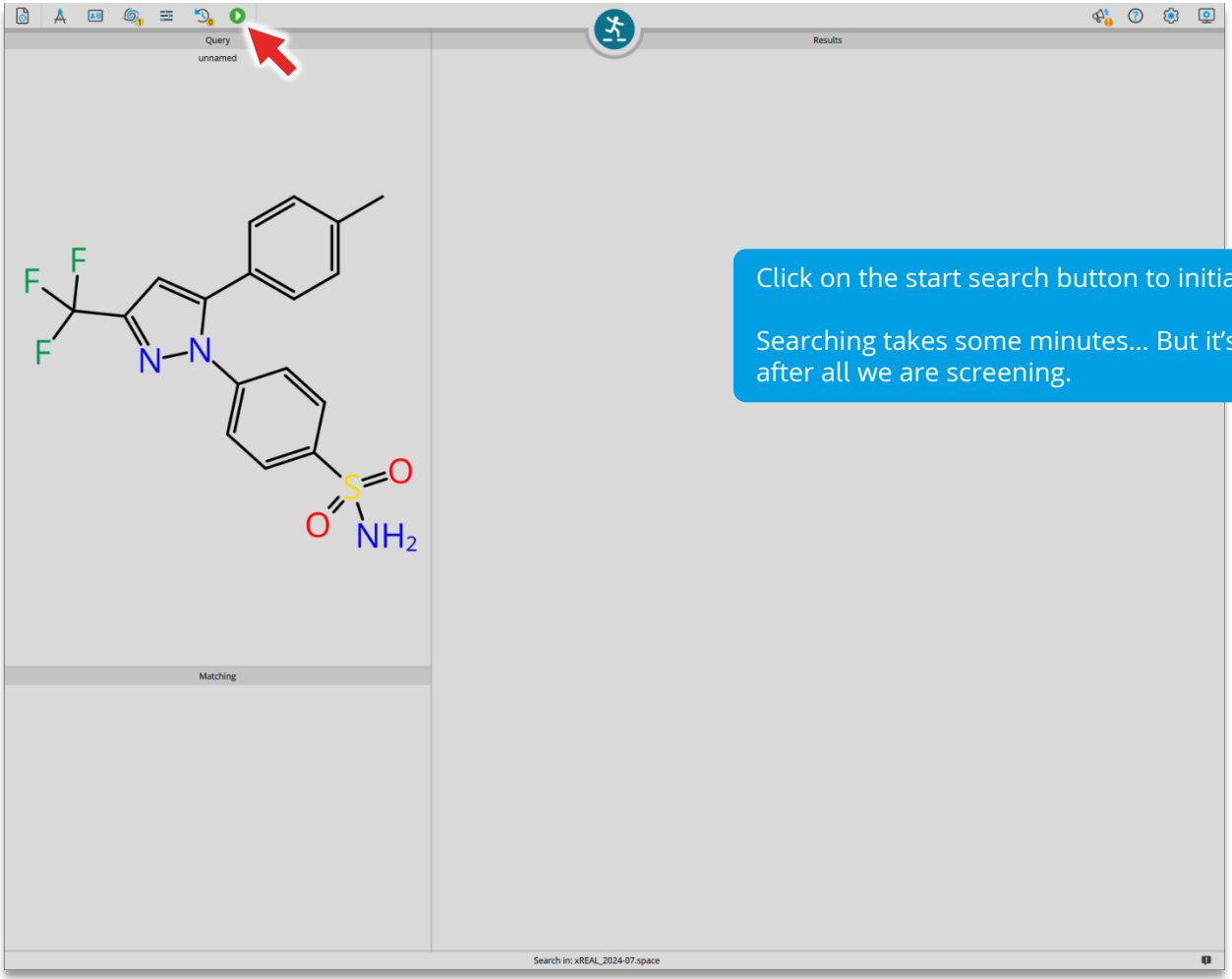
Hint:
Alternatively, use the 'Load Molecule' option, navigate to and select your molecule and press 'open'.

For defining your query molecule, you may use your favorite drawing tool and copy it as a SMILES code or use the eSeeSketch widget (see Chapter 6).

For this guide we will use Celecoxib as an example.

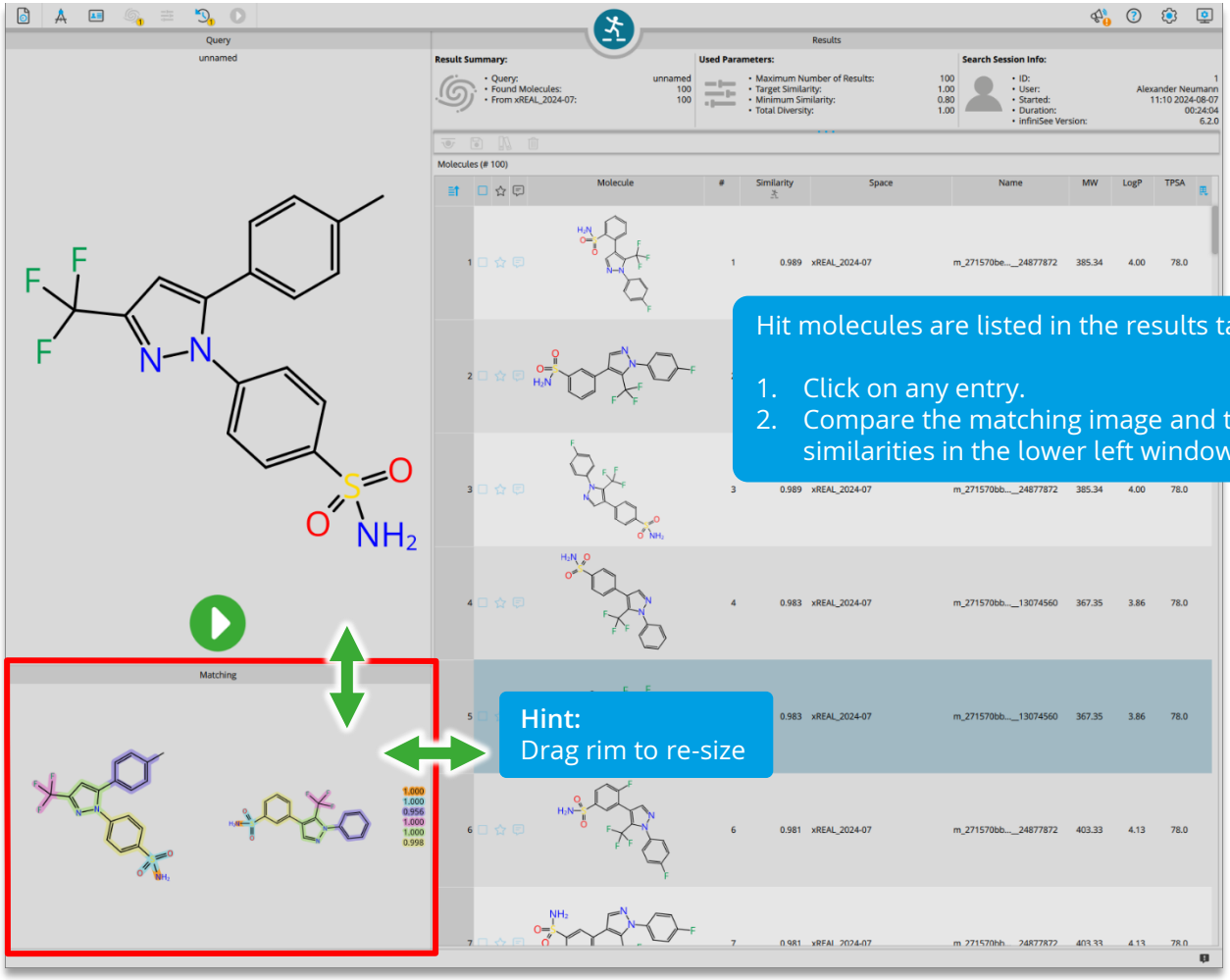
1. Copy this code:
CCC1=CC=C(C=C1)C2=CC(=NN2C3=CC=C(C=C3)S(=O)(=O)N)C(F)(F)F

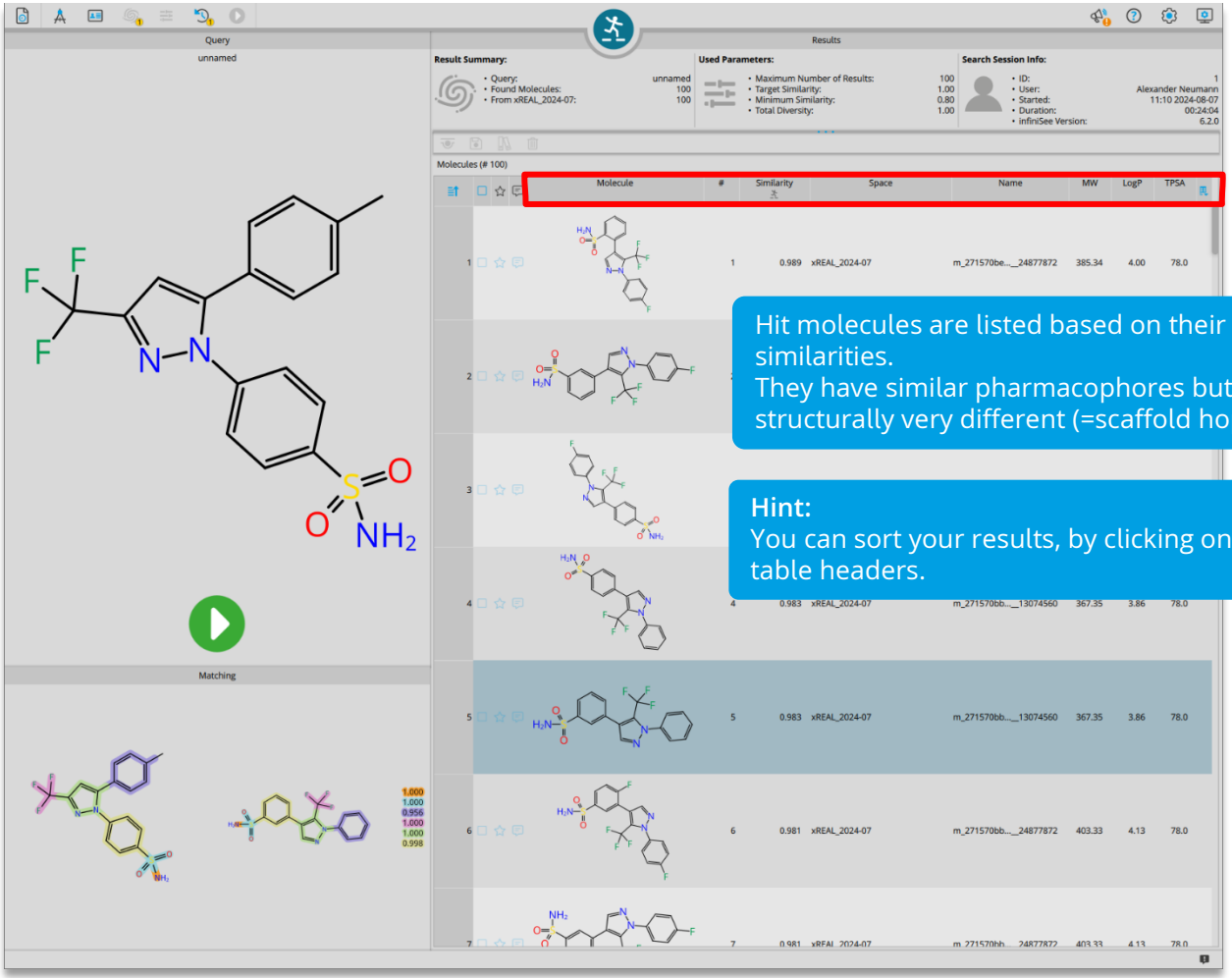
2. Paste it in the query box.



Click on the start search button to initiate the run.

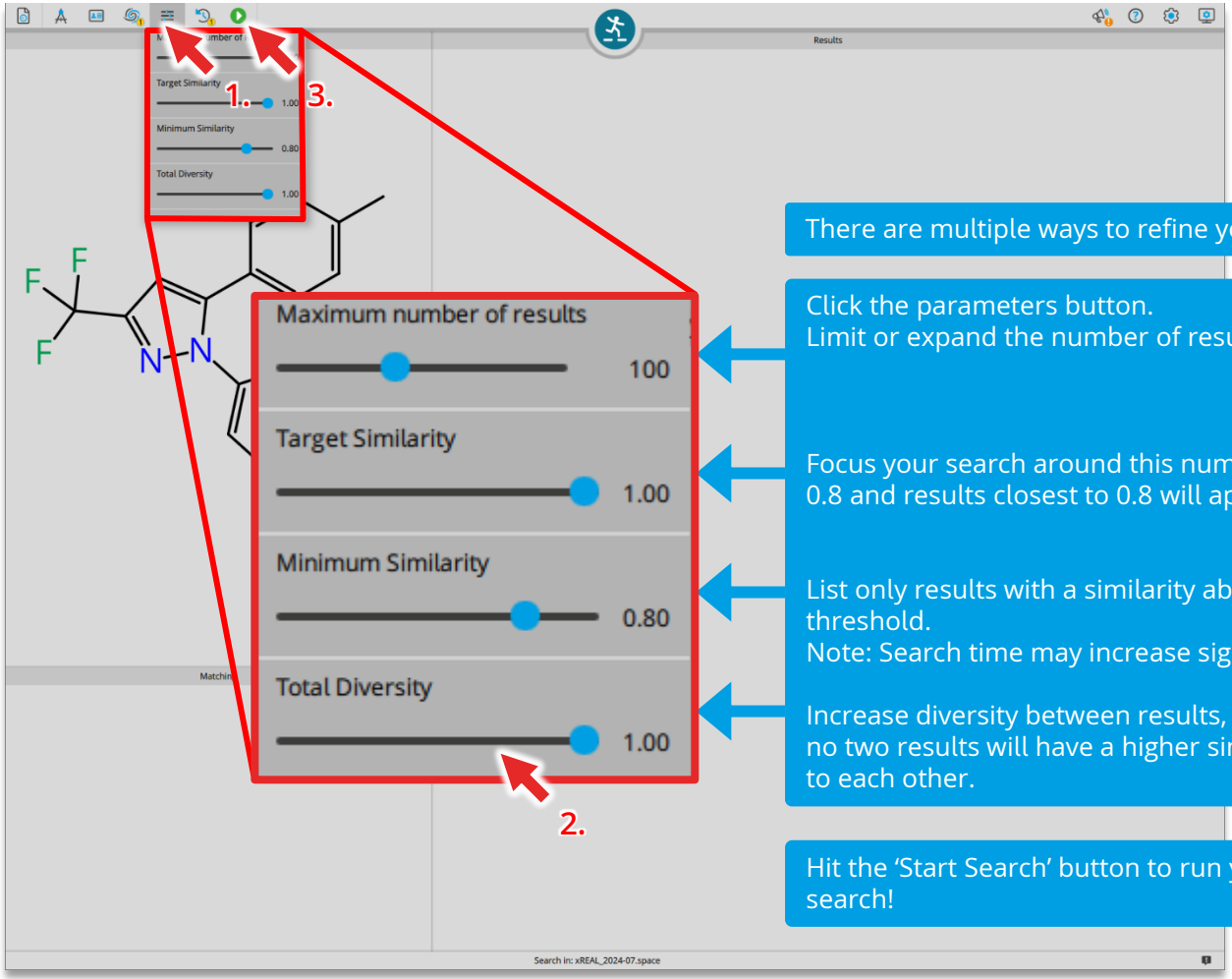
Searching takes some minutes... But it's trillions after all we are screening.


Query
unnamed
Results
Result Summary:
Query: unnamed
Found Molecules: 100
From xREAL_2024-07: 100
Used Parameters:
Maximum Number of Results: 100
Target Similarity: 1.00
Minimum Similarity: 0.80
Total Diversity: 1.00
Search Session Info:
ID: 1
User: Alexander Neumann
Started: 11:10 2024-08-07
Duration: 00:24:04
InfiniSee Version: 6.2.0
Molecules (# 100)
Molecule
#
Similarity
Space
Name
MW
LogP
TPSA
Matching
Hit molecules are listed in the results table.
1. Click on any entry.
2. Compare the matching image and the local similarities in the lower left window.
Hint:
Drag rim to re-size



Hit molecules are listed based on their FTrees-similarities.
They have similar pharmacophores but can be structurally very different (=scaffold hopping).

Hint:
You can sort your results, by clicking on any of the table headers.



There are multiple ways to refine your searches.

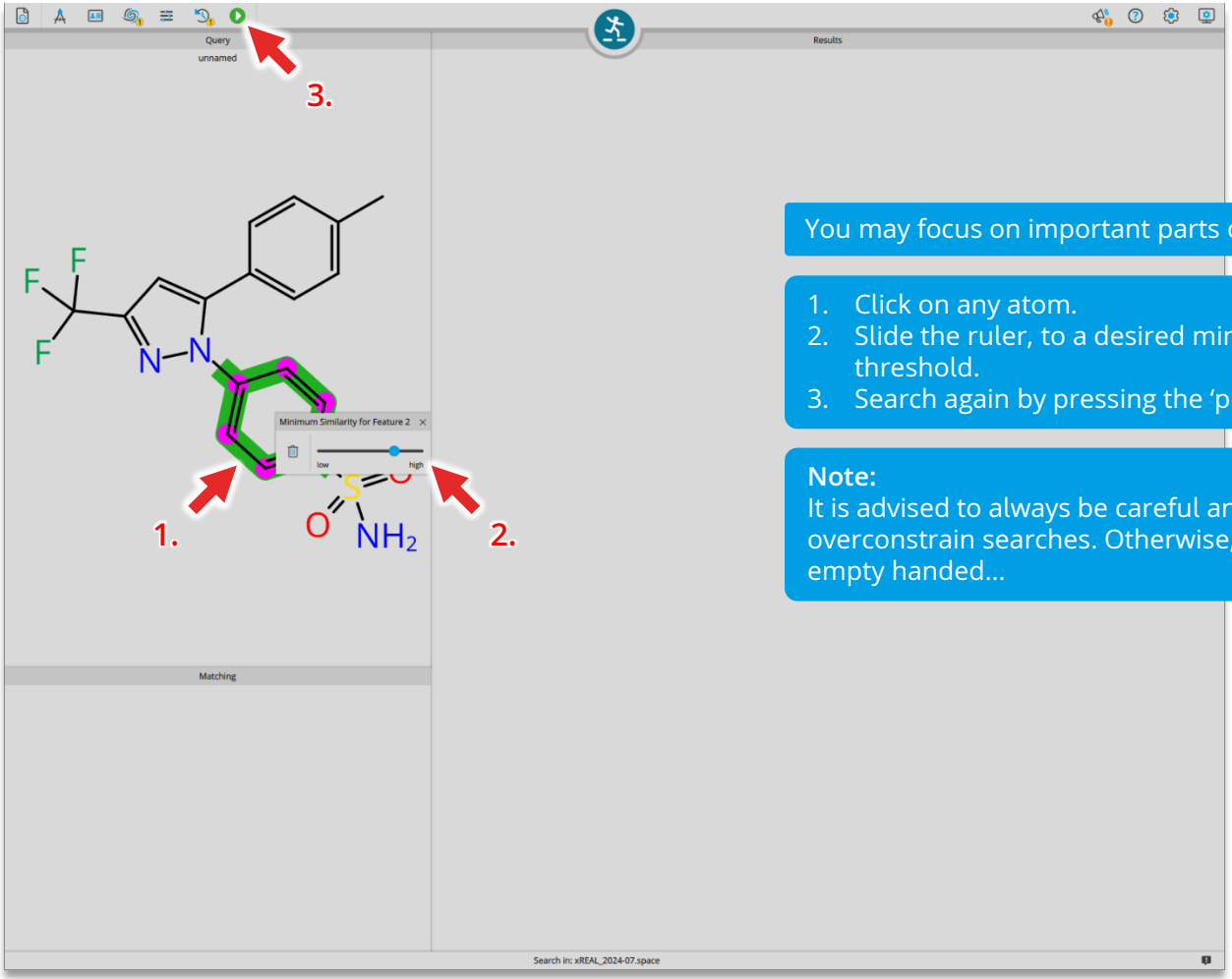
Click the parameters button.
Limit or expand the number of results.

Focus your search around this number, e.g. set it at 0.8 and results closest to 0.8 will appear first.

List only results with a similarity above this threshold.
Note: Search time may increase significantly!!

Increase diversity between results, e.g. if set at 0.9, no two results will have a higher similarity than 0.9 to each other.

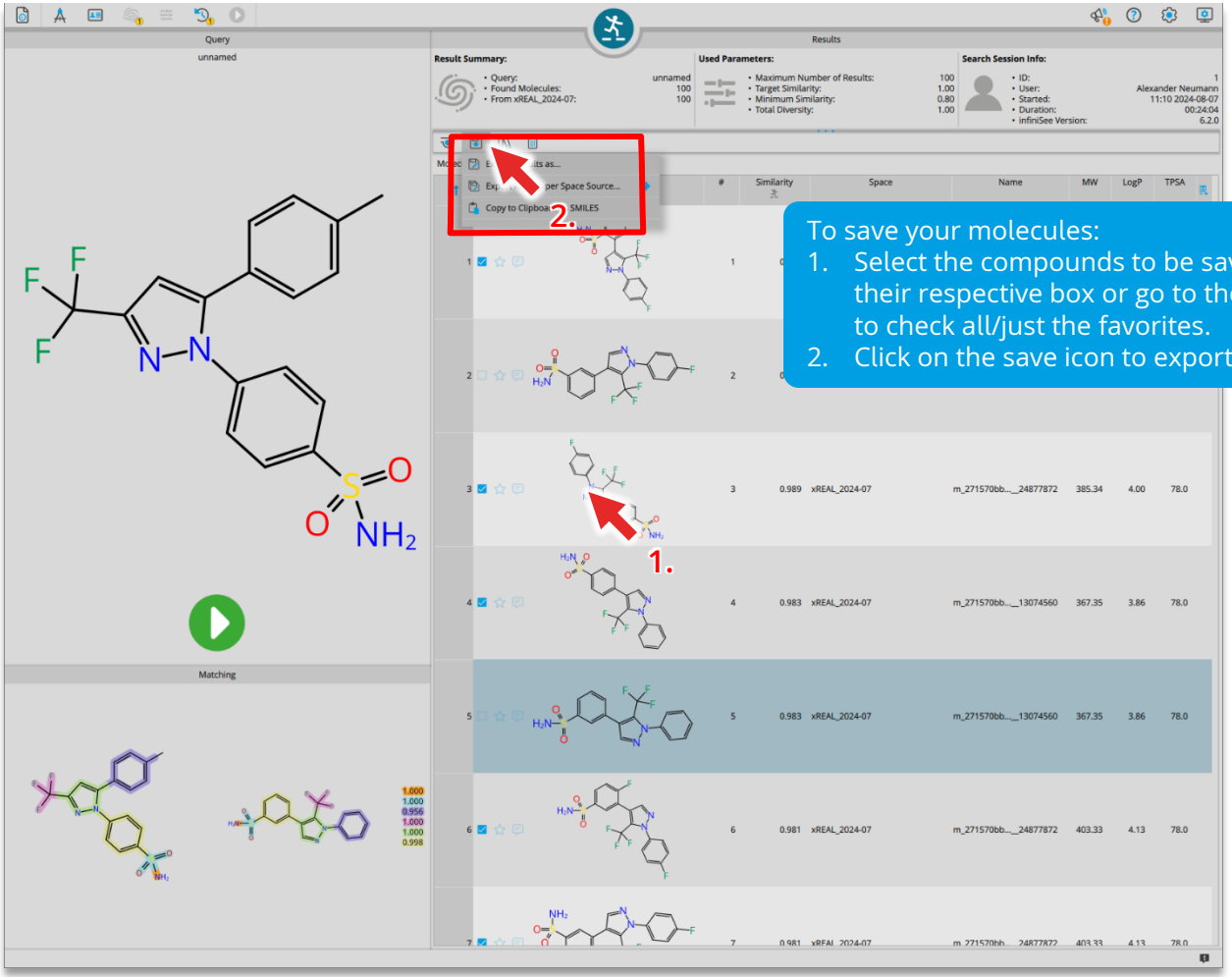
Hit the 'Start Search' button to run your refined search!



You may focus on important parts of your query.

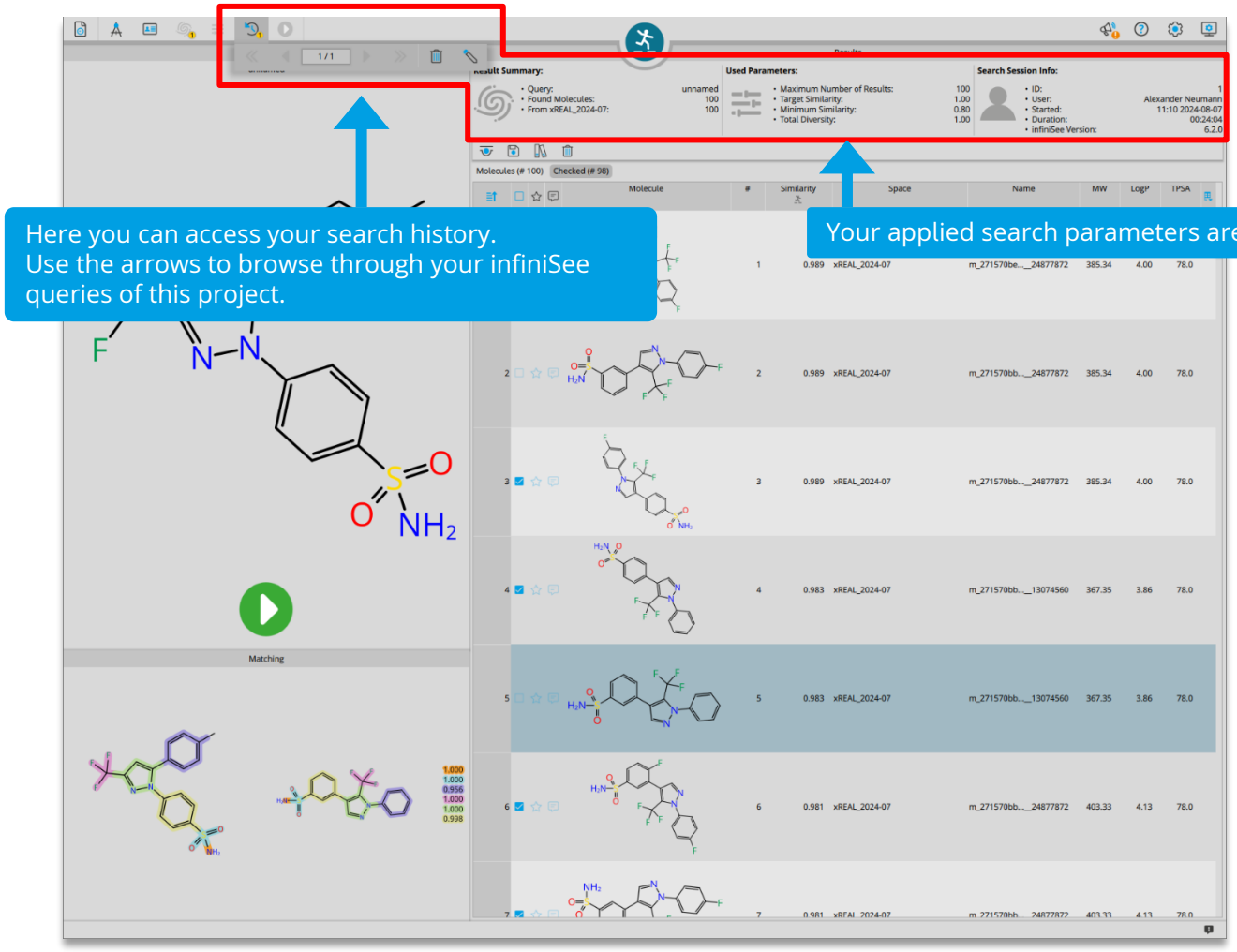
1. Click on any atom.
2. Slide the ruler, to a desired minimum similarity threshold.
3. Search again by pressing the ‘play’ button.

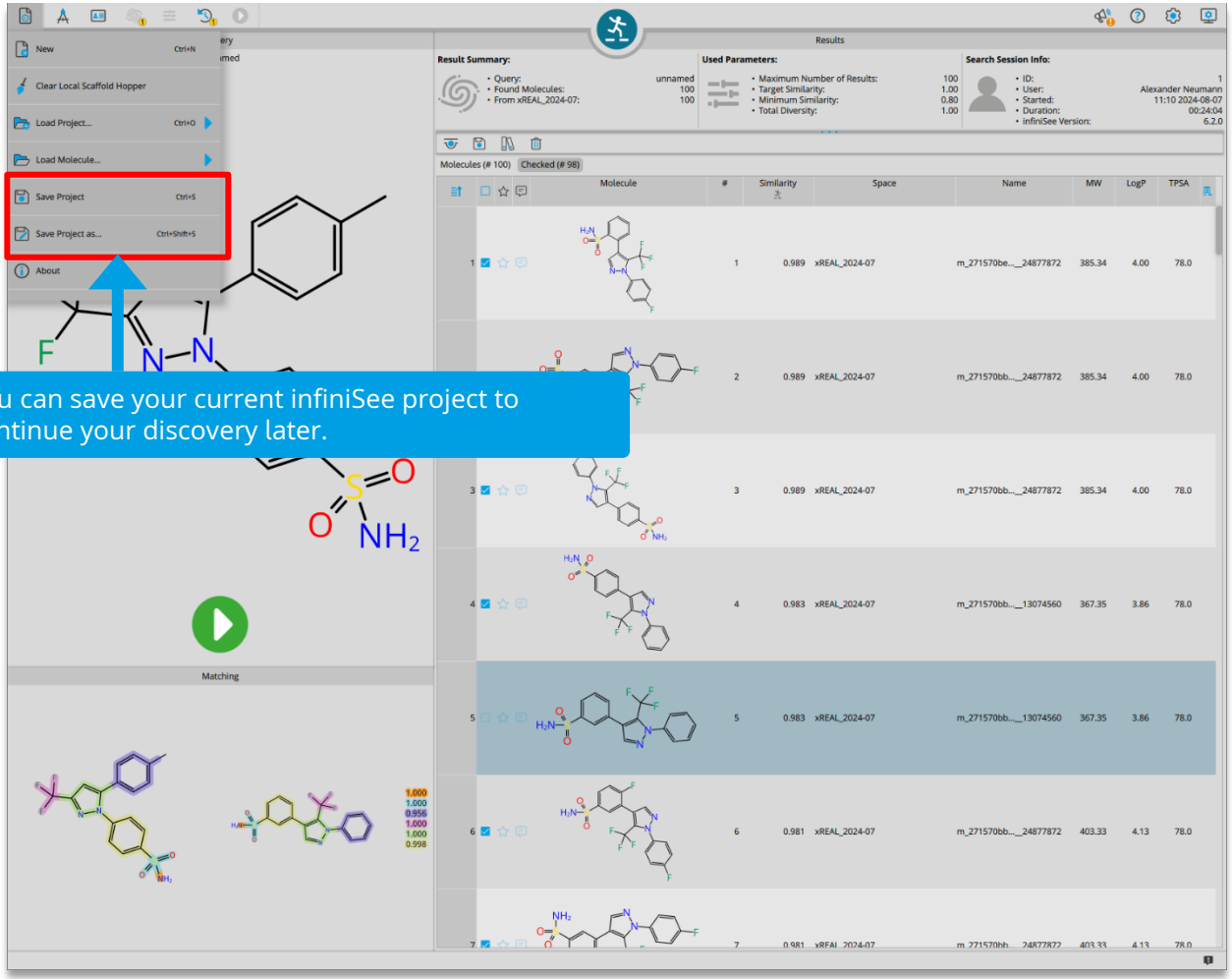
Note:
It is advised to always be careful and not to overconstrain searches. Otherwise, you may end up empty handed…

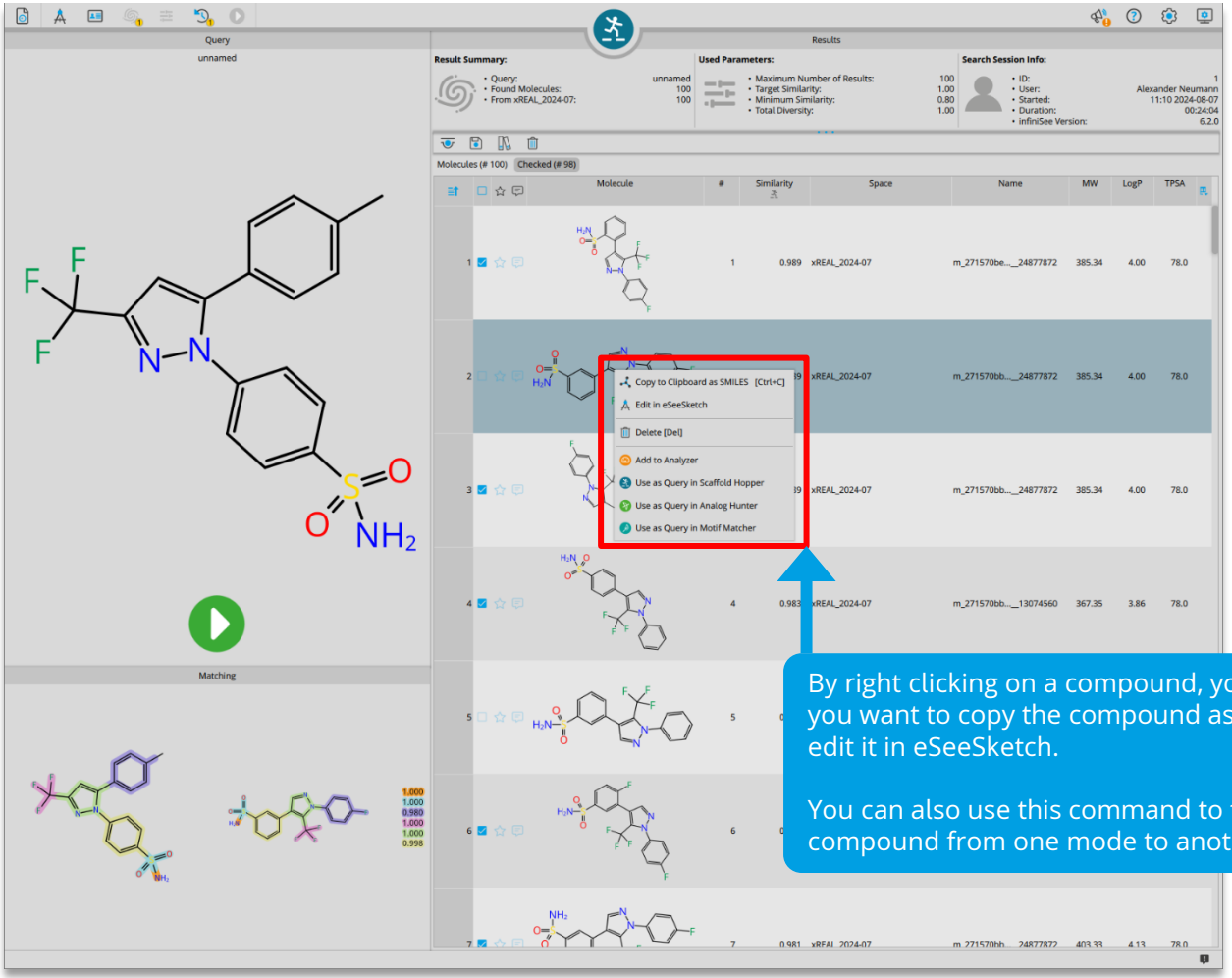


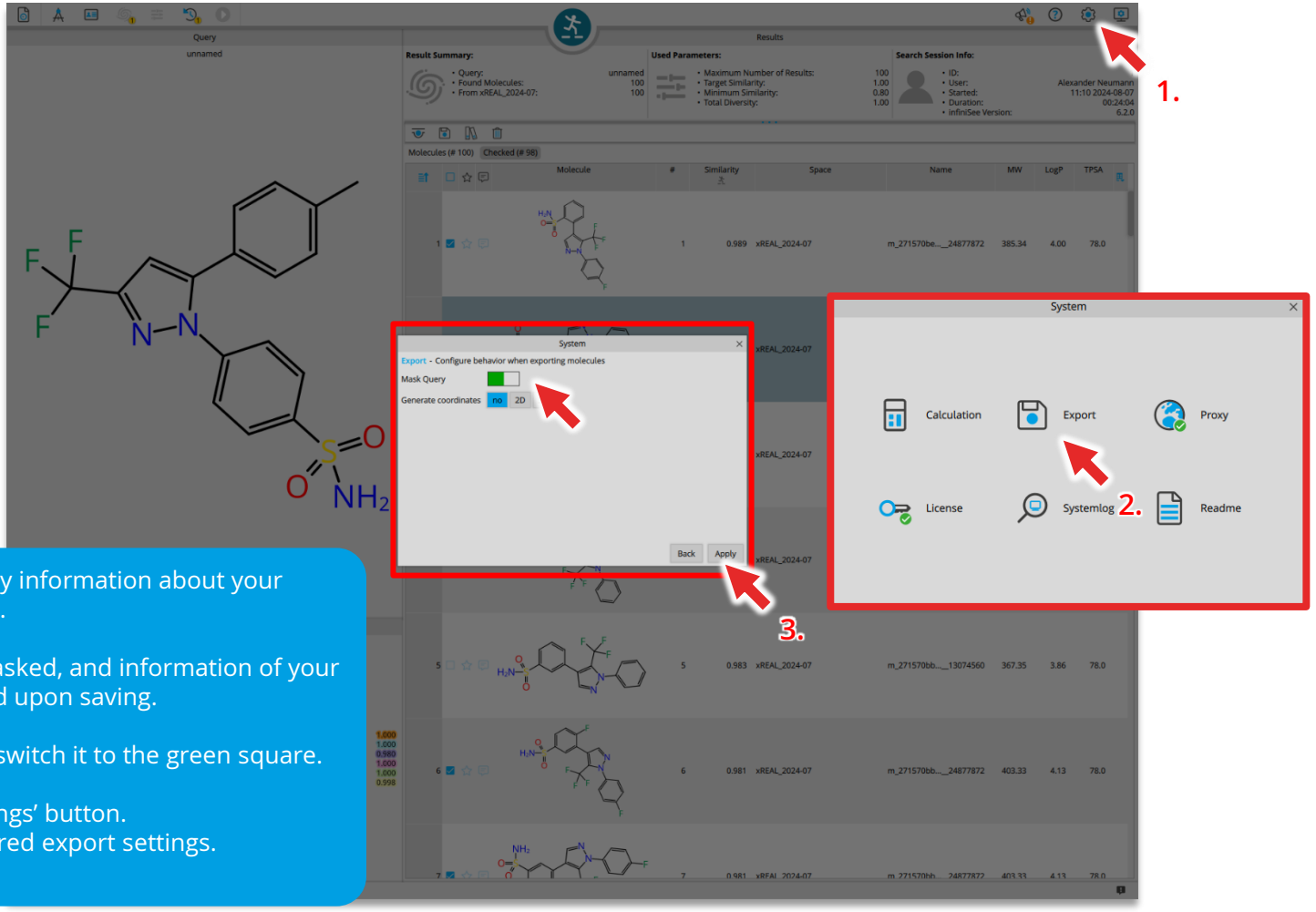
To save your molecules:

1. Select the compounds to be saved by checking their respective box or go to the top check box to check all/just the favorites.
2. Click on the save icon to export your results.


Here you can access your search history.
Use the arrows to browse through your infiniSee queries of this project.
Your applied search parameters are presented here.
Result Summary:
Used Parameters:
Search Session Info:
Molecules (# 100)
Checked (# 98)
Molecule
Similarity
Space
Name
MW
LogP
TPSA
Matching


New Ctrl+N
Clear Local Scaffold Hopper
Load Project... Ctrl+O
Load Molecule...
Save Project Ctrl+S
Save Project as... Ctrl+Shift+S
About
You can save your current infiniSee project to continue your discovery later.
Matching
Results
Result Summary:
Query: unnamed
Found Molecules: 100
From xREAL_2024-07: 100
Used Parameters:
Maximum Number of Results: 100
Target Similarity: 1.00
Minimum Similarity: 0.80
Total Diversity: 1.00
Search Session Info:
ID: 1
User: Alexander Neumann
Started: 11:10 2024-08-07
Duration: 00:24:04
infiniSee Version: 6.2.0
Molecules (# 100)
Checked (# 98)
Molecule
#
Similarity
Space
Name
MW
LogP
TPSA
1 0.989 xREAL_2024-07 m_271570be..._24877872 385.34 4.00 78.0
2 0.989 xREAL_2024-07 m_271570bb..._24877872 385.34 4.00 78.0
3 0.989 xREAL_2024-07 m_271570bb..._24877872 385.34 4.00 78.0
4 0.983 xREAL_2024-07 m_271570bb..._13074560 367.35 3.86 78.0
5 0.983 xREAL_2024-07 m_271570bb..._13074560 367.35 3.86 78.0
6 0.981 xREAL_2024-07 m_271570bb..._24877872 403.33 4.13 78.0


Query
unnamed
Matching
Results
Result Summary:
Query: unnamed
Found Molecules: 100
From xREAL_2024-07: 100
Used Parameters:
Maximum Number of Results: 100
Target Similarity: 1.00
Minimum Similarity: 0.80
Total Diversity: 1.00
Search Session Info:
ID: 1
User: Alexander Neumann
Started: 11:10 2024-08-07
Duration: 00:24:04
InfiniSee Version: 6.2.0
Molecules (# 100)
Checked (# 98)
Molecule
#
Similarity
Space
Name
MW
LogP
TPSA
Copy to Clipboard as SMILES [Ctrl+C]
Edit in eSeeSketch
Delete [Del]
Add to Analyzer
Use as Query in Scaffold Hopper
Use as Query in Analog Hunter
Use as Query in Motif Matcher
By right clicking on a compound, you can select if you want to copy the compound as SMILES or to edit it in eSeeSketch.
You can also use this command to transfer a compound from one mode to another.

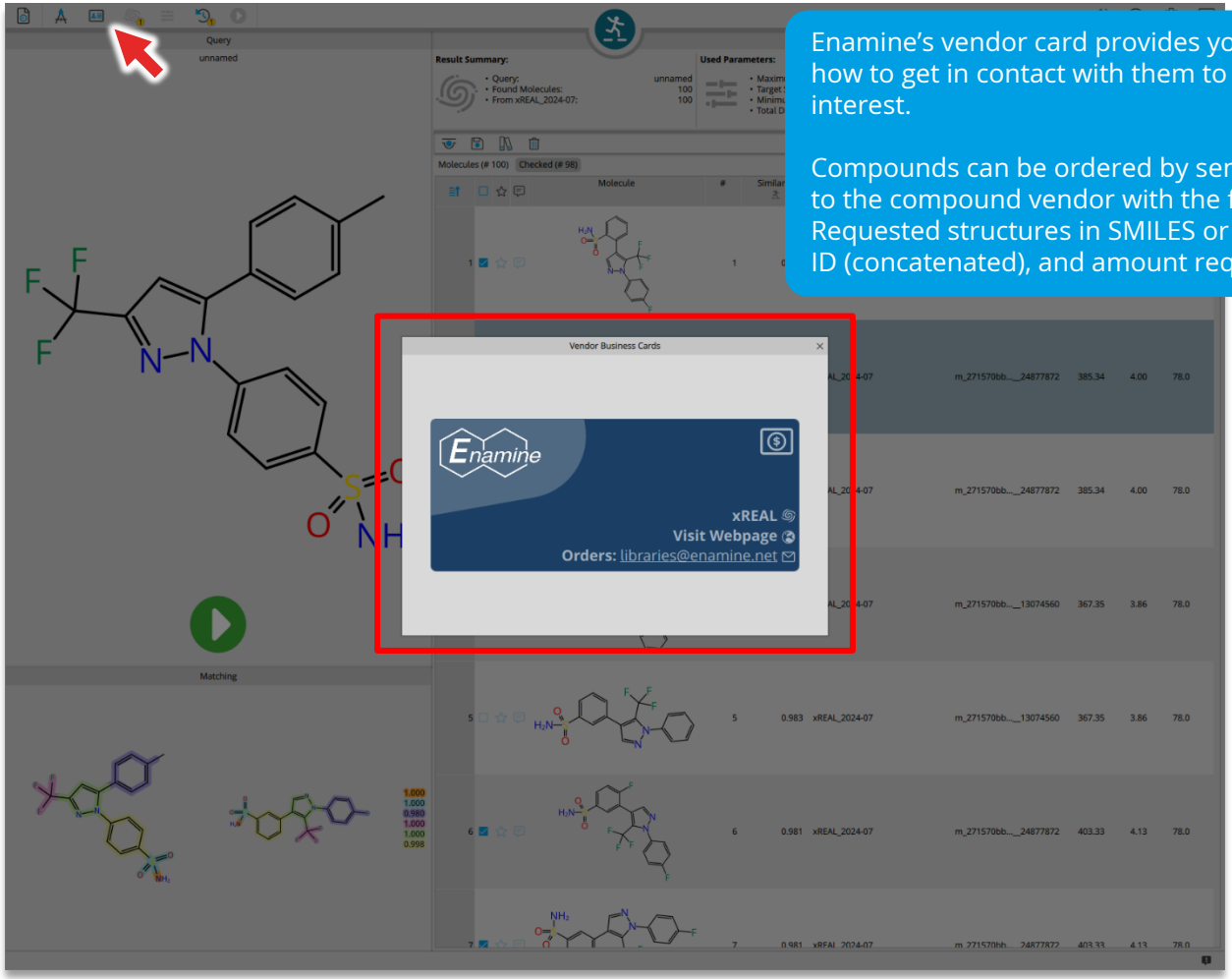


To protect your IP, any information about your query can be masked.

By default it is not masked, and information of your query will be included upon saving.

To mask your query, switch it to the green square.

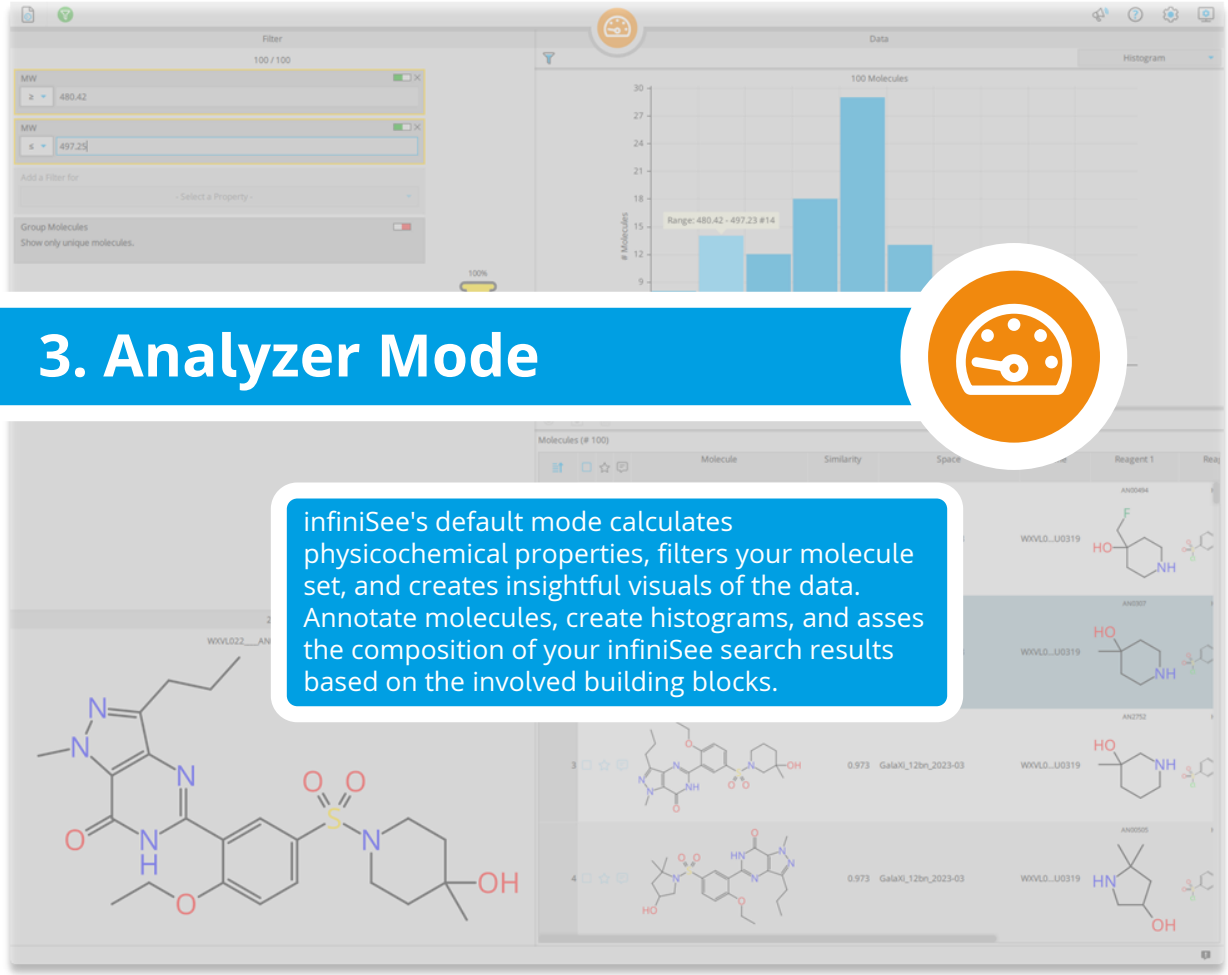
1. Click on the 'Settings' button.
2. Choose your desired export settings.
3. Press 'Apply'.



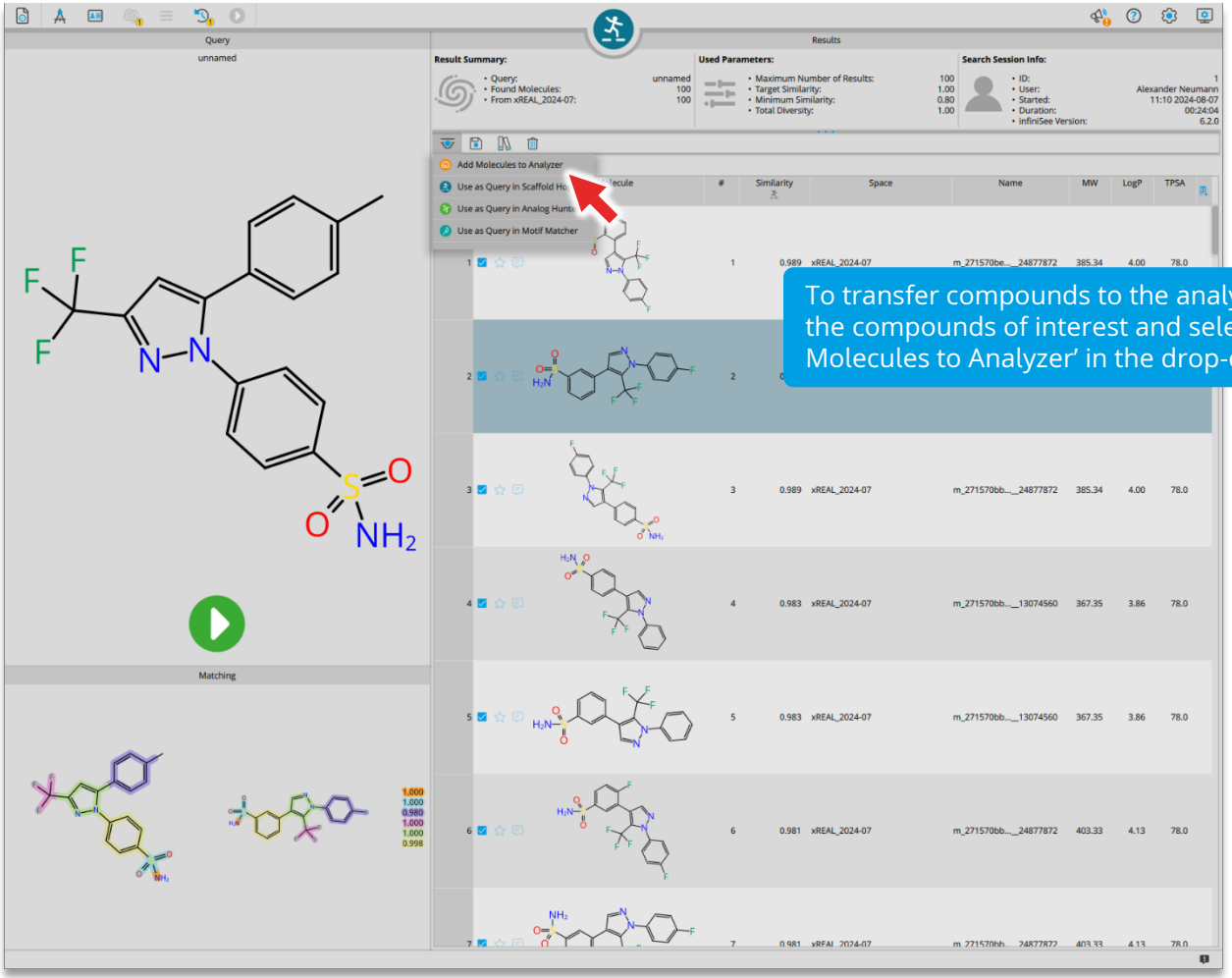
Enamine's vendor card provides you with information on how to get in contact with them to order compounds of interest.

Compounds can be ordered by sending a quote request to the compound vendor with the following information: Requested structures in SMILES or SD format, Compound ID (concatenated), and amount requested.

3. Analyzer Mode

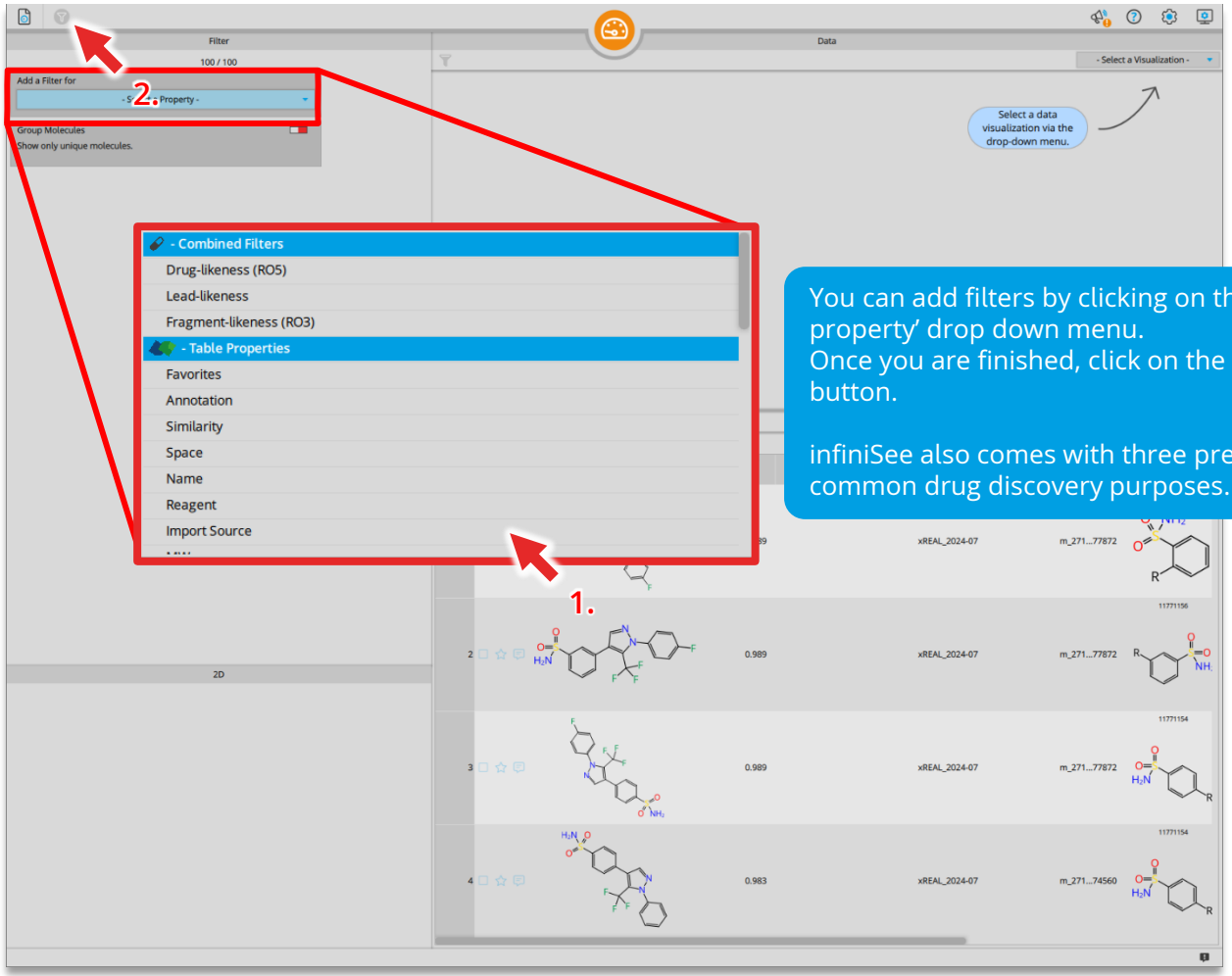


infiniSee's default mode calculates physicochemical properties, filters your molecule set, and creates insightful visuals of the data. Annotate molecules, create histograms, and asses the composition of your infiniSee search results based on the involved building blocks.



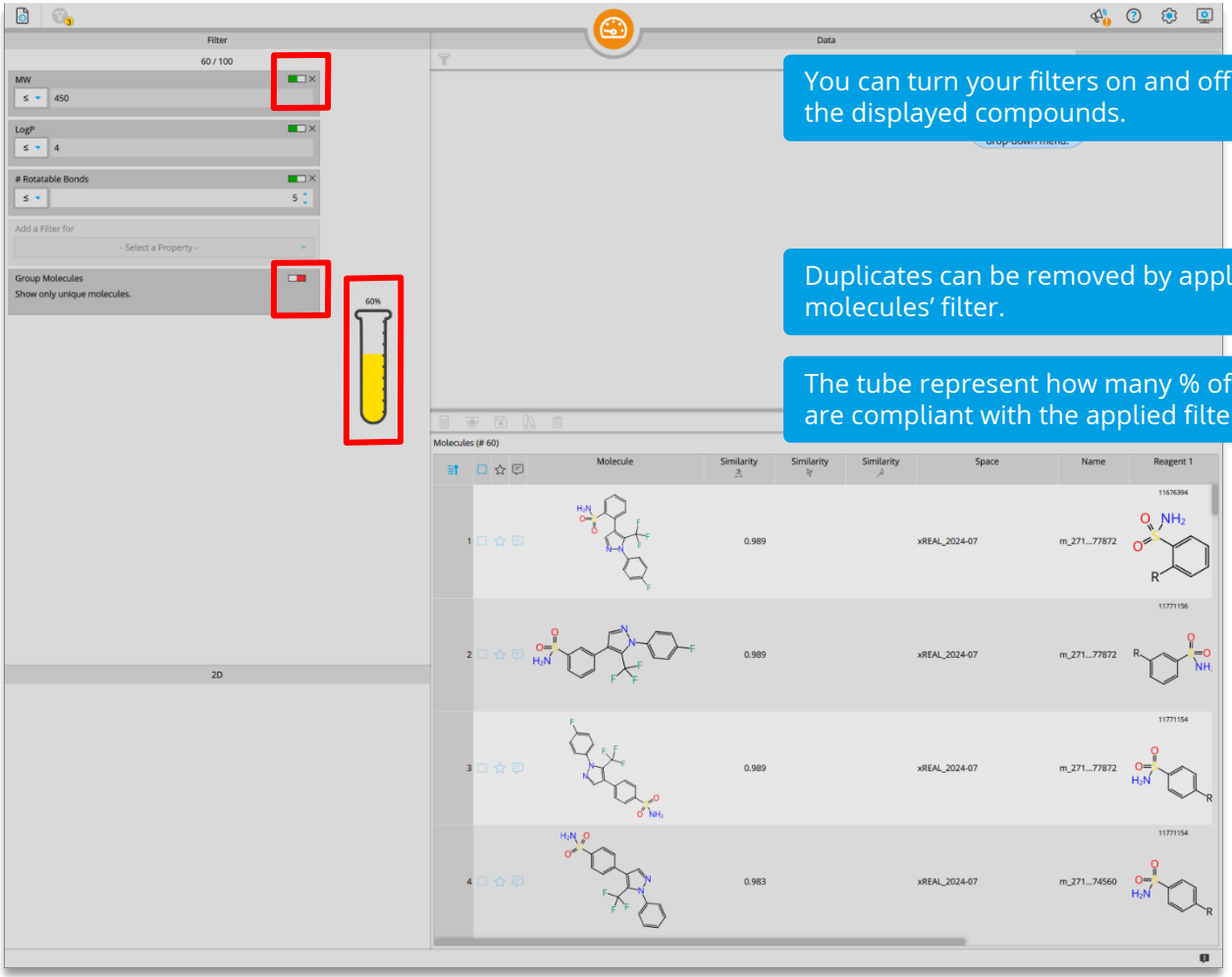
To transfer compounds to the analyzer mode, check the compounds of interest and select ‘Add Molecules to Analyzer’ in the drop-down menu.

... or hover over the mode button and select 'Analyzer'. Once in the Analyzer Mode you can load molecules (.sdf, .sd, .mol, .mol2, .smi, .smiles, .pdb formats) from a local folder directly into infiniSee.



You can add filters by clicking on the 'Select a property' drop down menu.
Once you are finished, click on the 'Apply filters' button.

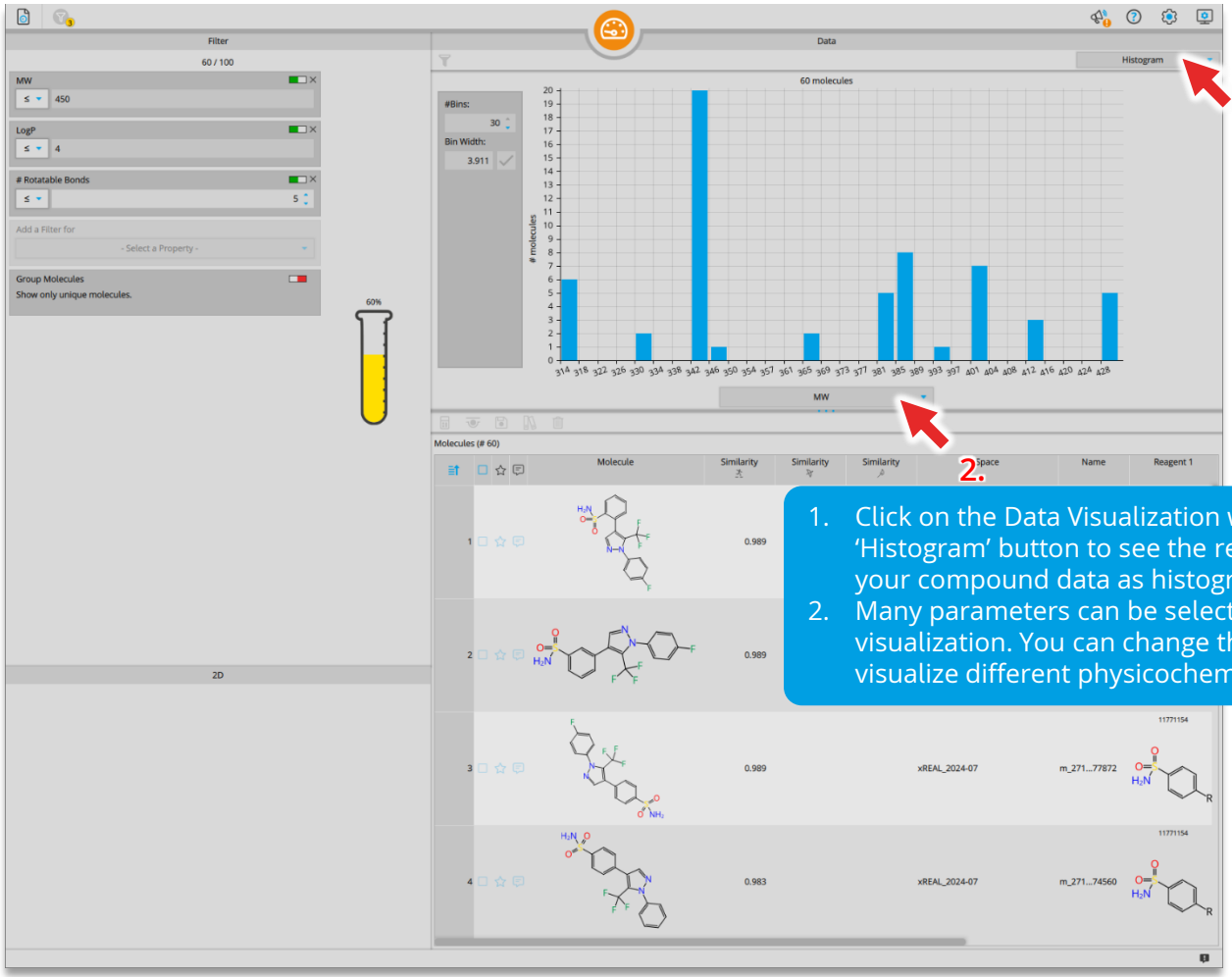
infiniSee also comes with three premade filters for common drug discovery purposes.



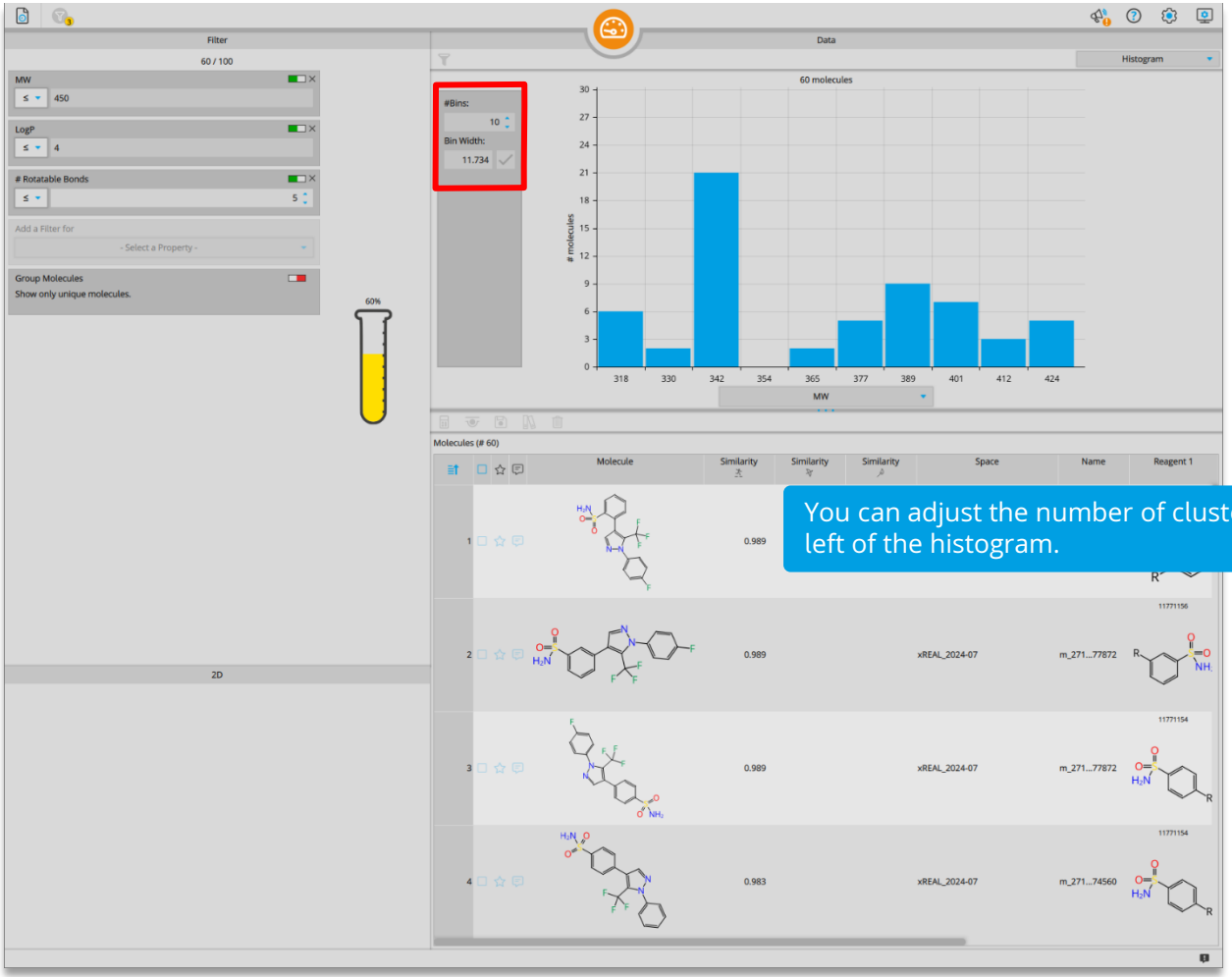
You can turn your filters on and off to manipulate the displayed compounds.

Duplicates can be removed by applying the 'Group molecules' filter.

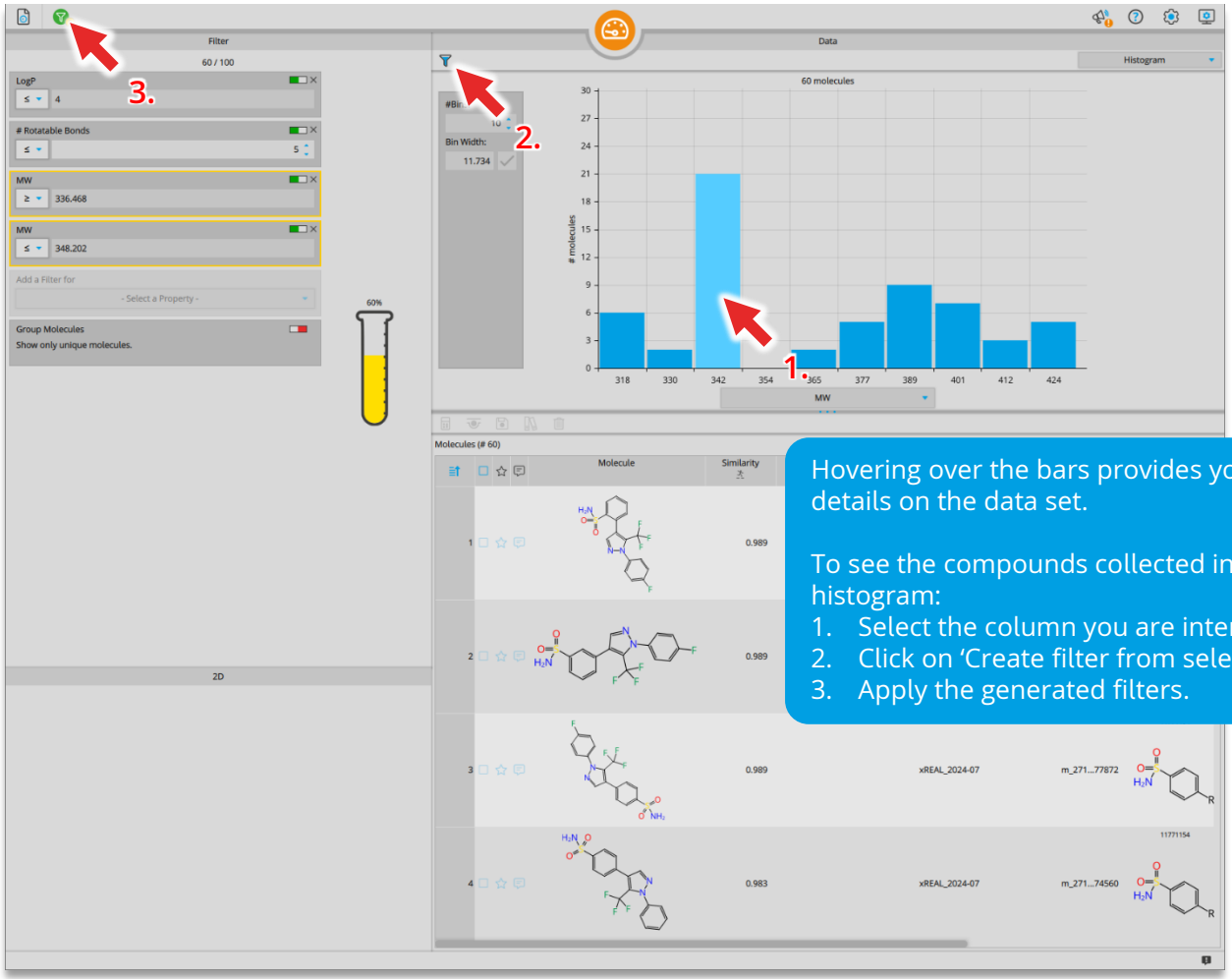
The tube represent how many % of the compounds are compliant with the applied filters.



1. Click on the Data Visualization window 'Histogram' button to see the representation of your compound data as histogram.
2. Many parameters can be selected for visualization. You can change the display to visualize different physicochemical properties.



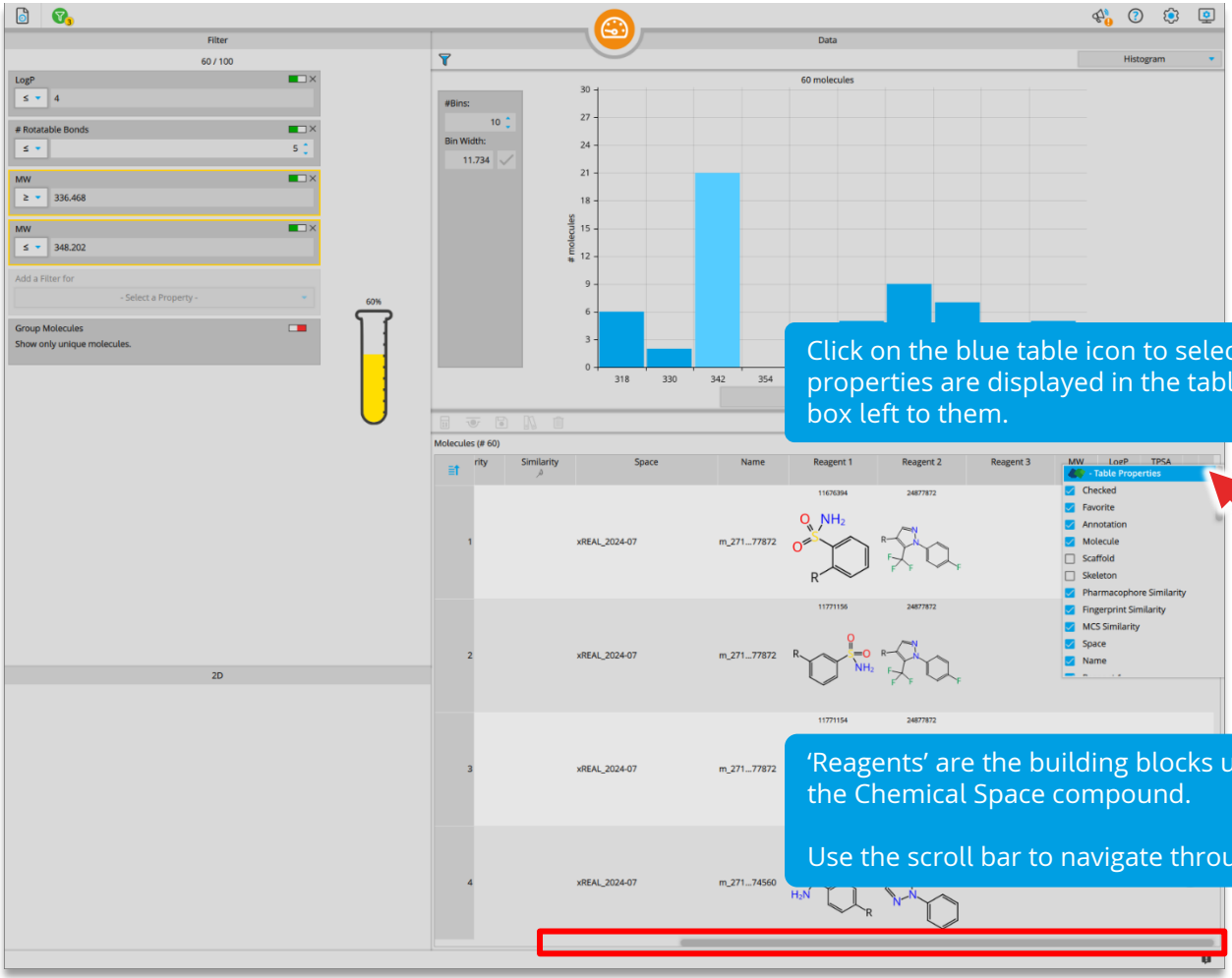
You can adjust the number of clustered bins to the left of the histogram.

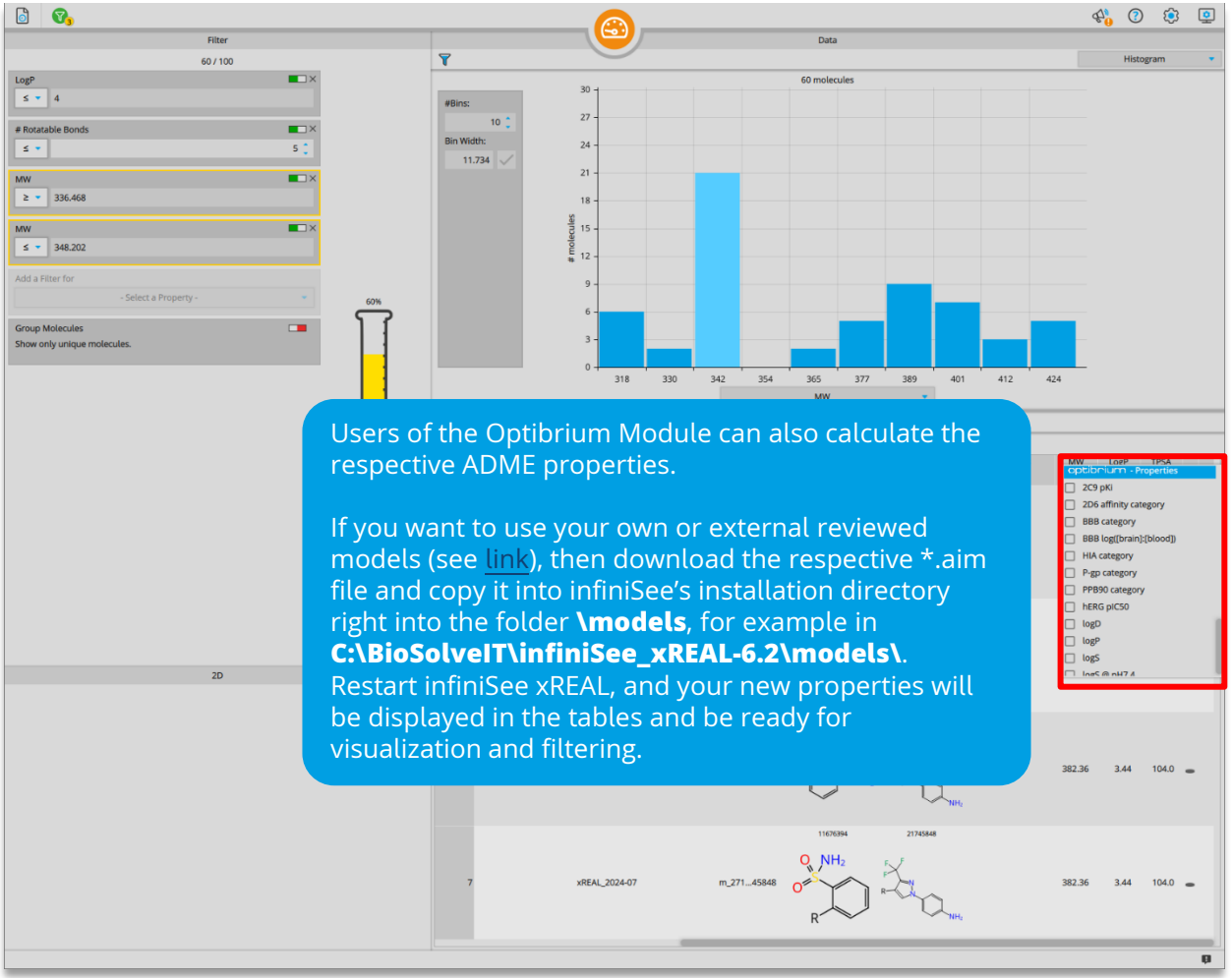


Hovering over the bars provides you with further details on the data set.

To see the compounds collected in a bar of the histogram:

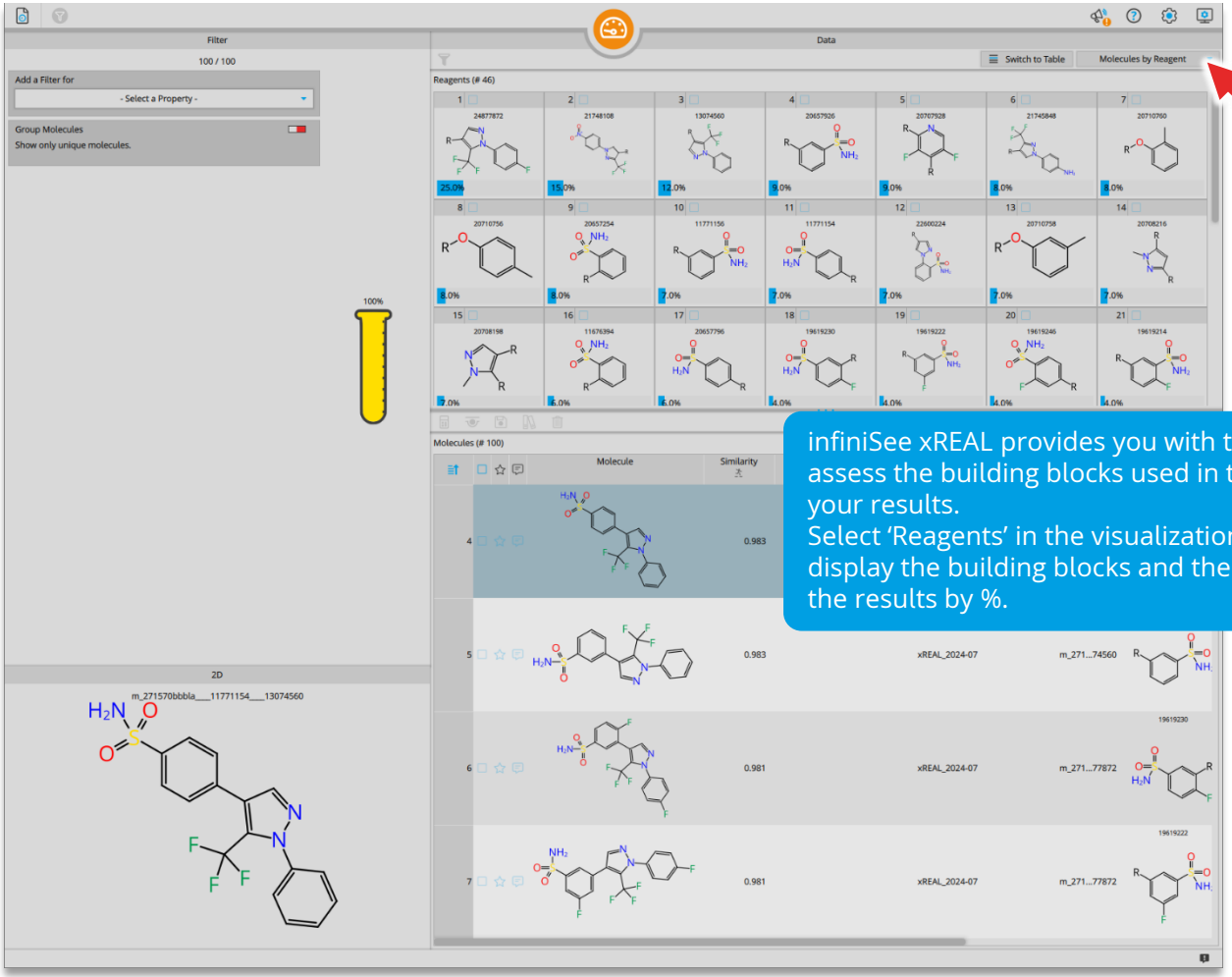
1. Select the column you are interested in.
2. Click on 'Create filter from selection'.
3. Apply the generated filters.


Filter
60 / 100
LogP
≤ 4
Rotatable Bonds
≤ 5
MW
≥ 336.468
MW
≤ 348.202
Add a Filter for
- Select a Property -
Group Molecules
Show only unique molecules.
60%
2D
Data
Histogram
60 molecules
#Bins:
10
Bin Width:
11.734
molecules
Molecules (# 60)
Similarity
Space
Name
Reagent 1
Reagent 2
Reagent 3
MW
LogP
TPSA
xREAL_2024-07
- Table Properties
Checked
Favorite
Annotation
Molecule
Scaffold
Skeleton
Pharmacophore Similarity
Fingerprint Similarity
MCS Similarity
Space
Name
Click on the blue table icon to select which properties are displayed in the table by checking the box left to them.
'Reagents' are the building blocks used to synthesize the Chemical Space compound.
Use the scroll bar to navigate through your results.

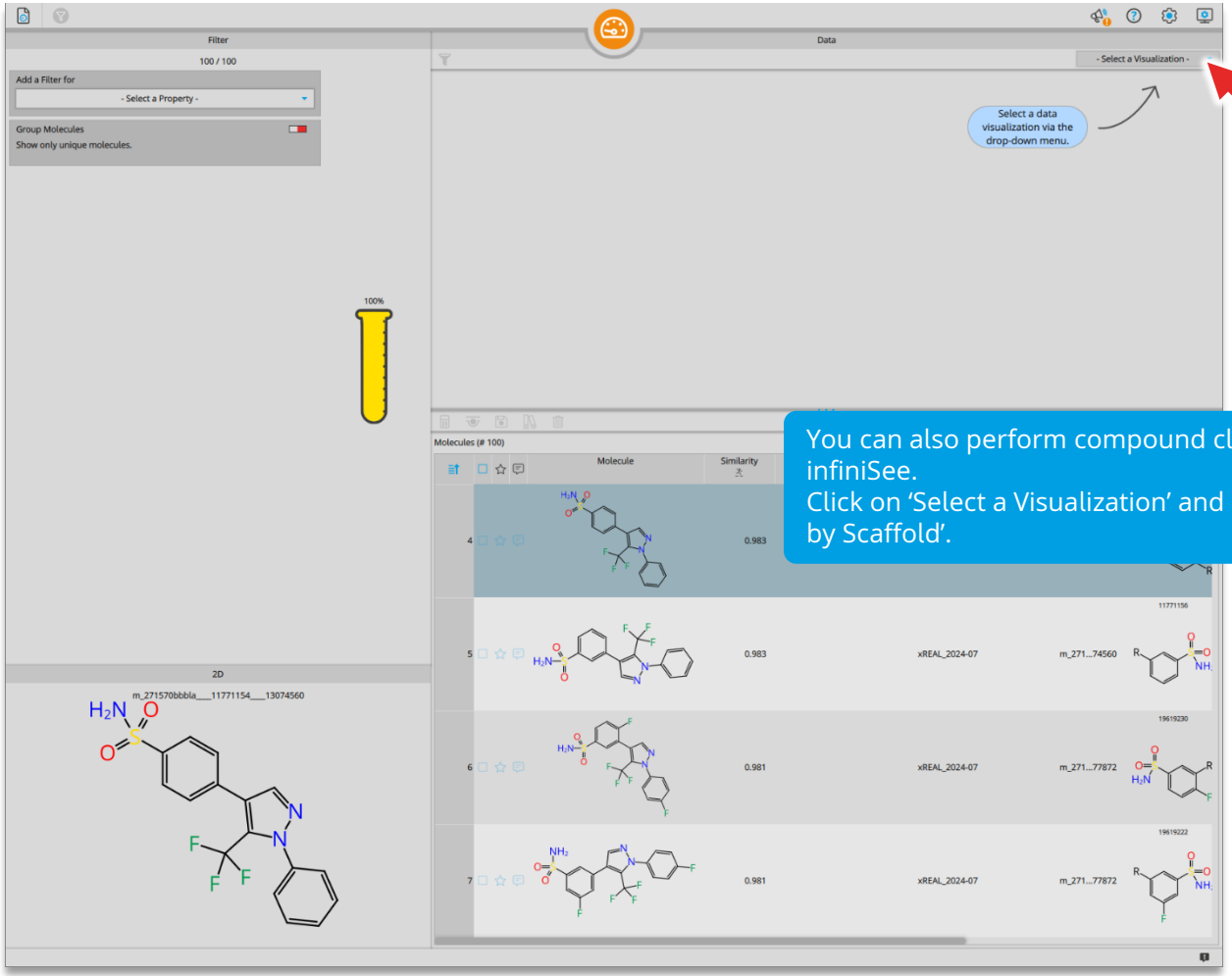


Users of the Optibrium Module can also calculate the respective ADME properties.

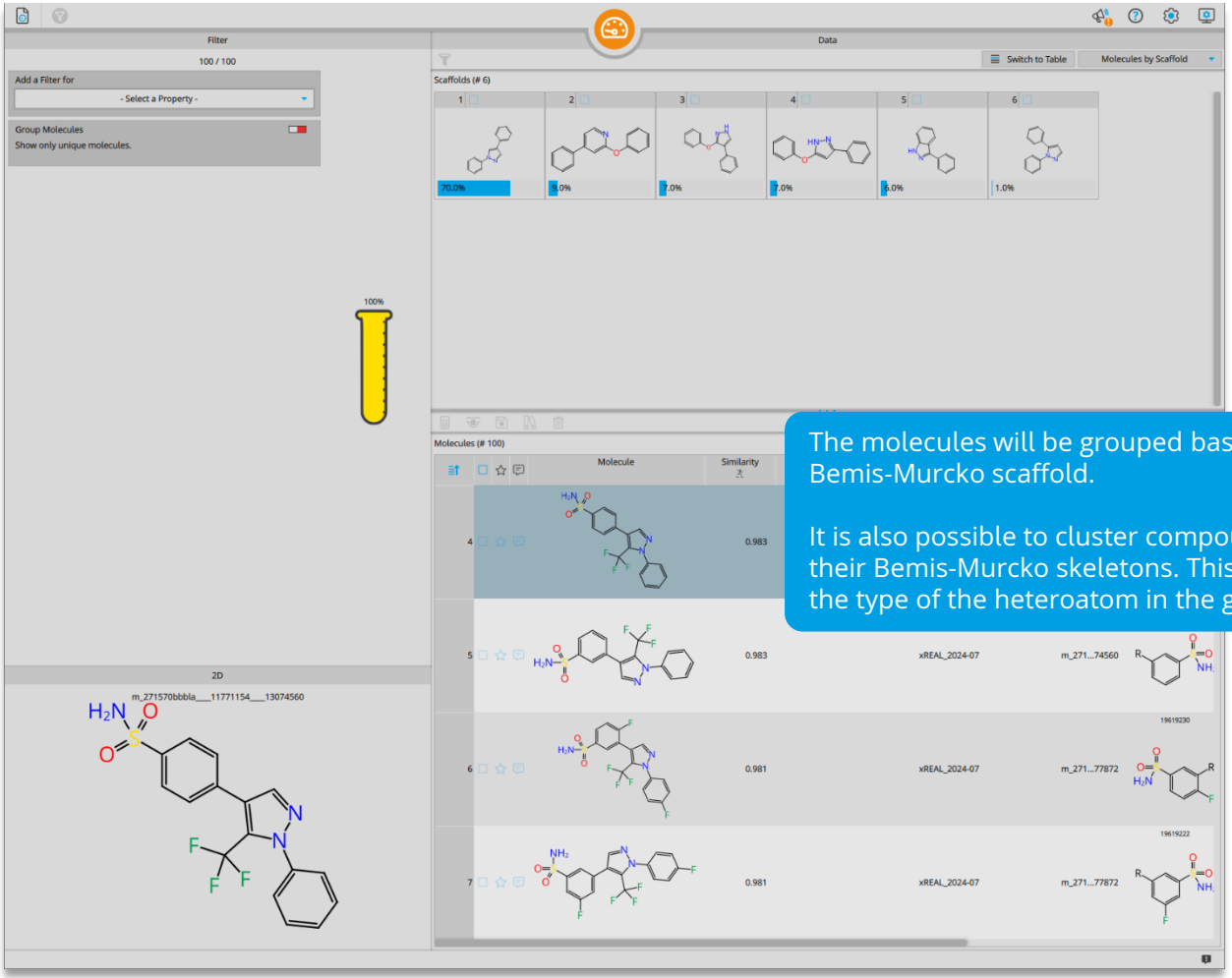
If you want to use your own or external reviewed models (see link), then download the respective *.aim file and copy it into infiniSee's installation directory right into the folder **\models**, for example in **C:\BioSolveIT\infiniSee_xREAL-6.2\models**. Restart infiniSee xREAL, and your new properties will be displayed in the tables and be ready for visualization and filtering.



infiniSee xREAL provides you with the possibility to assess the building blocks used in the generation of your results.
Select ‘Reagents’ in the visualization window to display the building blocks and their occurrence in the results by %.



You can also perform compound clustering in infiniSee.
Click on 'Select a Visualization' and select 'Molecules by Scaffold'.



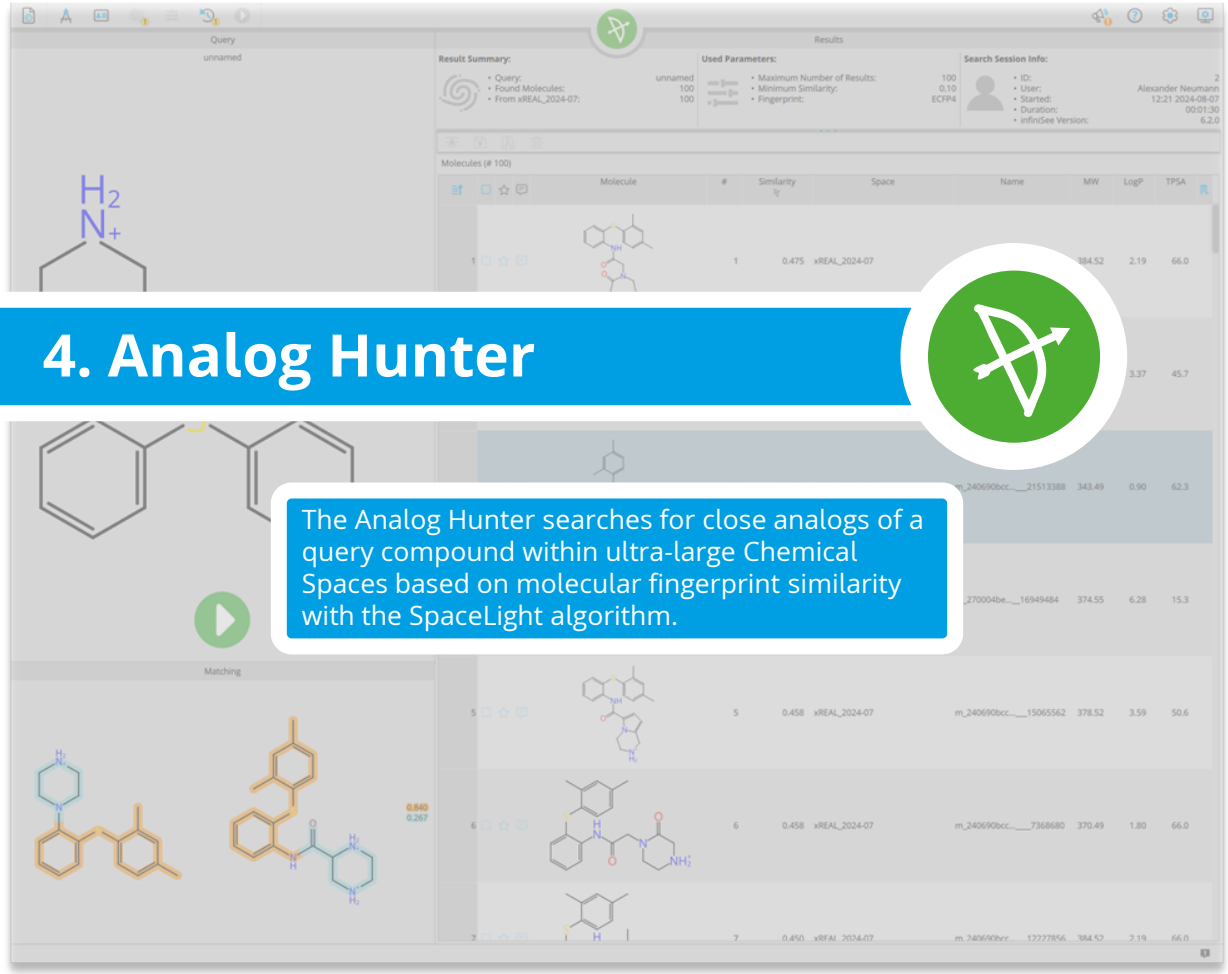
The molecules will be grouped based on their Bemis-Murcko scaffold.

It is also possible to cluster compounds based on their Bemis-Murcko skeletons. This method ignores the type of the heteroatom in the grouping process.

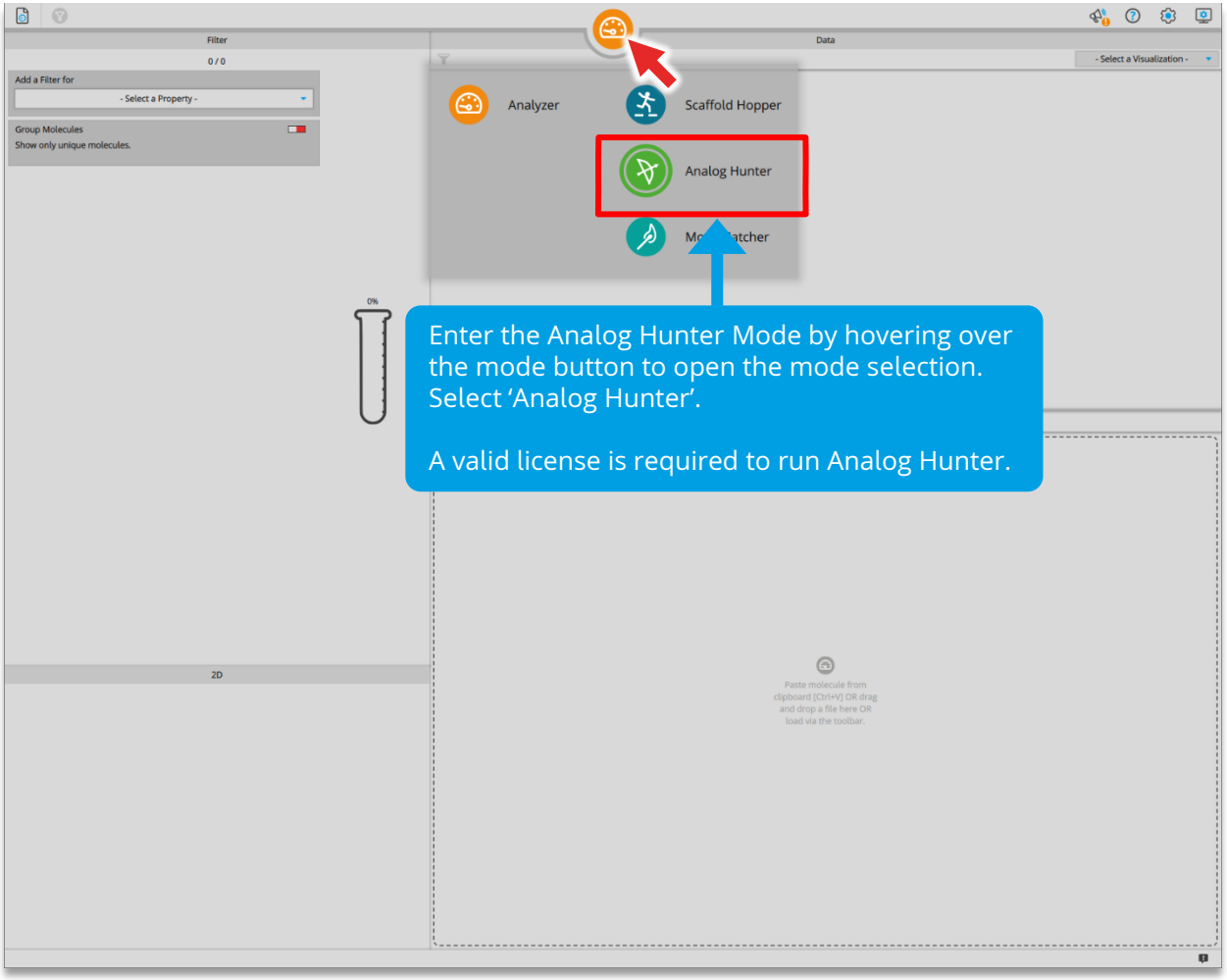
You can create custom filters by right-clicking on a scaffold and selecting ‘Create Filter’.

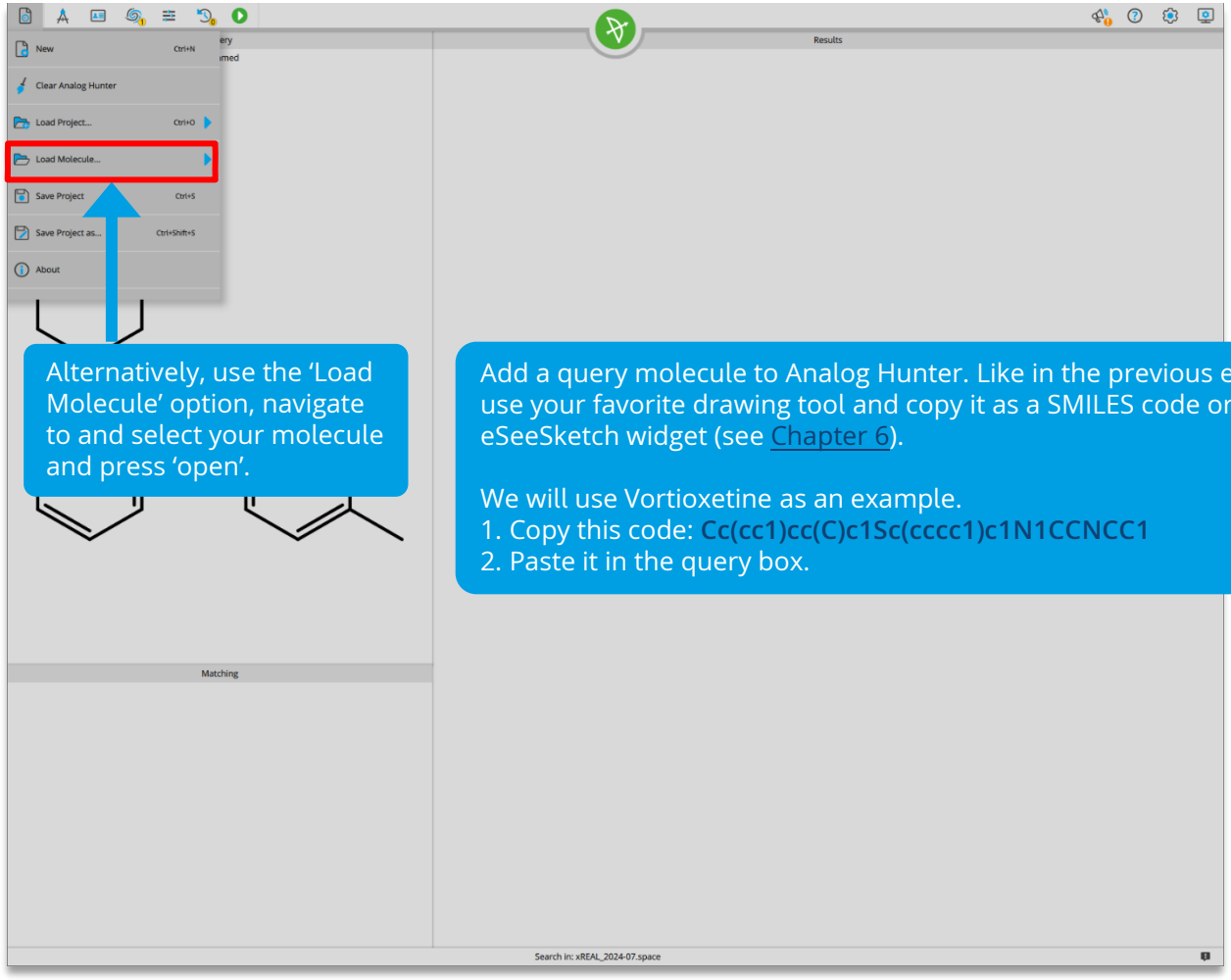
Apply the filter with ‘Apply filters’ to see only the compounds featuring a particular scaffold.

4. Analog Hunter



The Analog Hunter searches for close analogs of a query compound within ultra-large Chemical Spaces based on molecular fingerprint similarity with the SpaceLight algorithm.

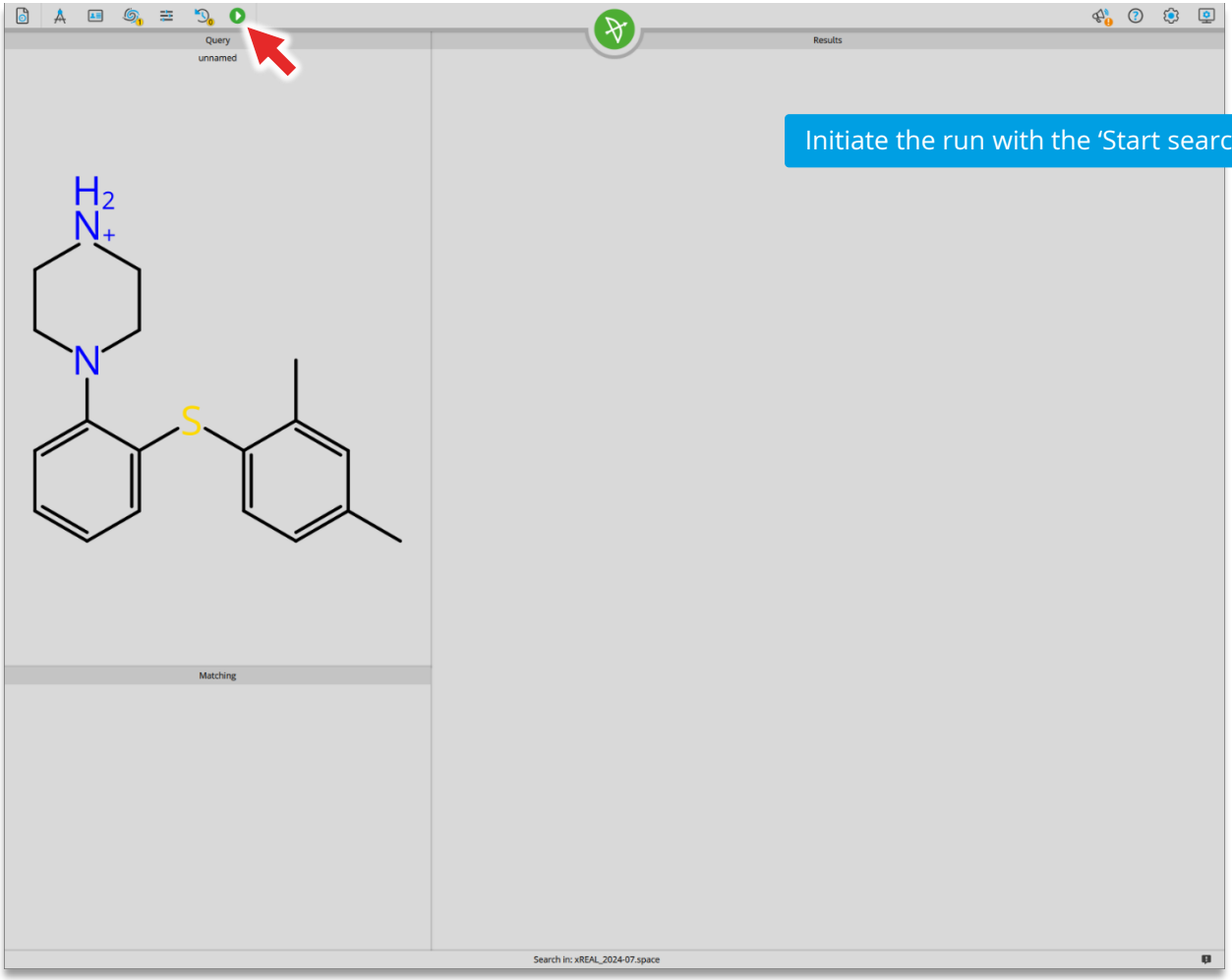

Filter
0 / 0
Add a Filter for
- Select a Property -
Group Molecules
Show only unique molecules.
2D
Data
- Select a Visualization -
Analyzer
Scaffold Hopper
Analog Hunter
0%
Enter the Analog Hunter Mode by hovering over the mode button to open the mode selection. Select 'Analog Hunter'.
A valid license is required to run Analog Hunter.



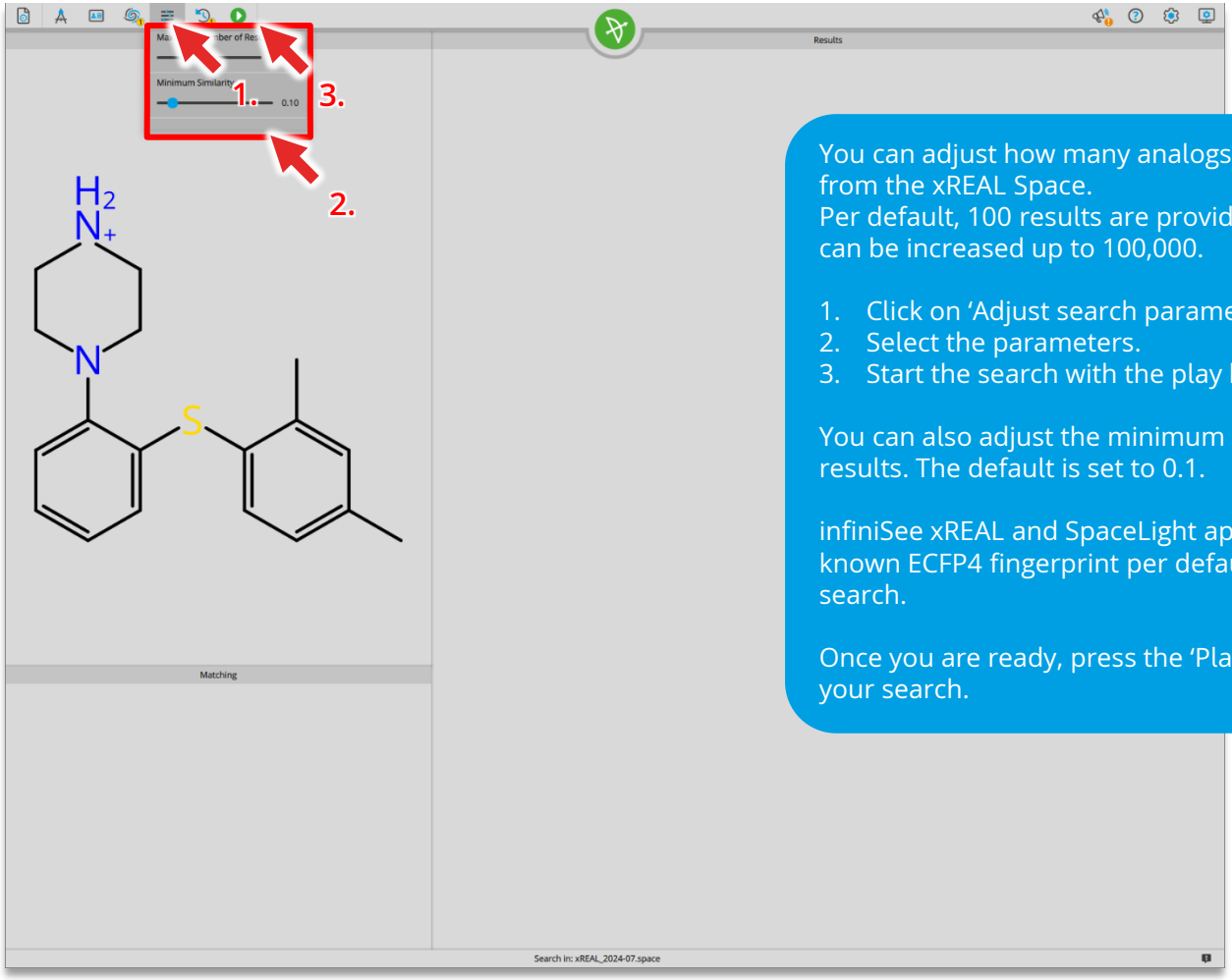
Alternatively, use the 'Load Molecule' option, navigate to and select your molecule and press 'open'.

Add a query molecule to Analog Hunter. Like in the previous example, you may use your favorite drawing tool and copy it as a SMILES code or use the eSeeSketch widget (see Chapter 6).

We will use Vortioxetine as an example.
1. Copy this code: **Cc(cc1)cc(C)c1Sc(cccc1)c1N1CCNCC1**
2. Paste it in the query box.



Initiate the run with the ‘Start search’ button.



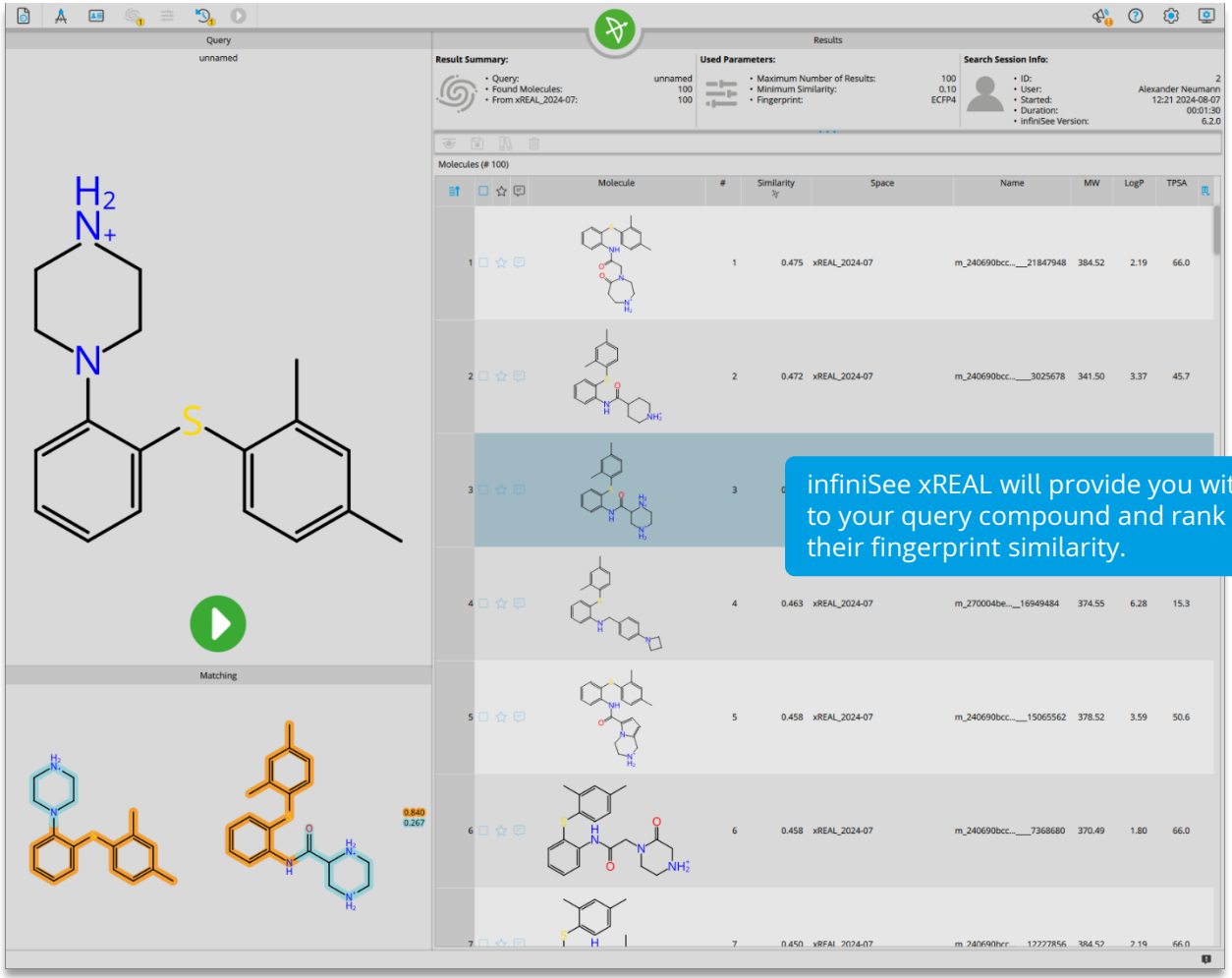
You can adjust how many analogs are retrieved from the xREAL Space.
Per default, 100 results are provided. The number can be increased up to 100,000.

1. Click on ‘Adjust search parameters’
2. Select the parameters.
3. Start the search with the play button!

You can also adjust the minimum similarity of the results. The default is set to 0.1.

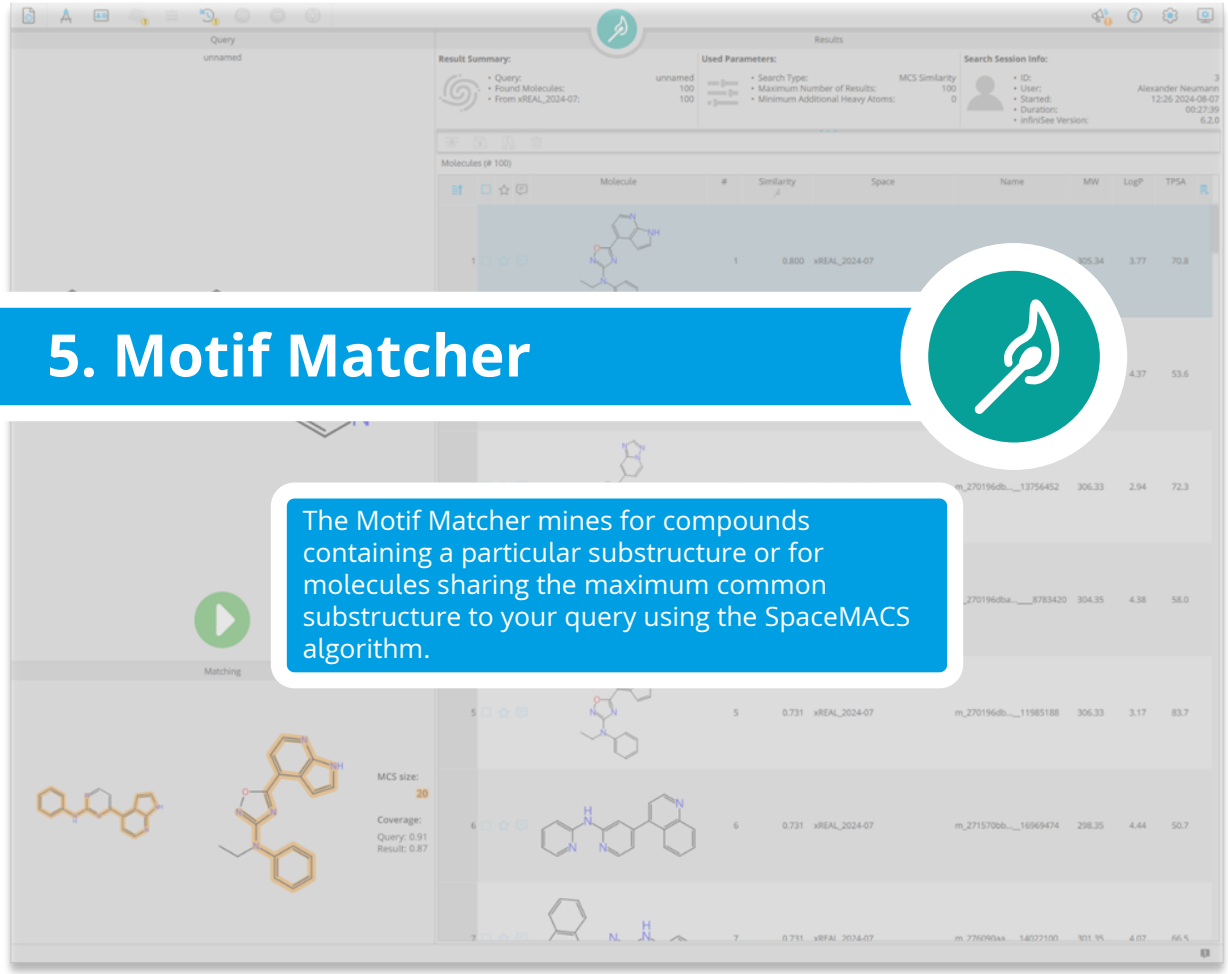
infiniSee xREAL and SpaceLight apply the well-known ECFP4 fingerprint per default for the search.

Once you are ready, press the ‘Play’ button to start your search.

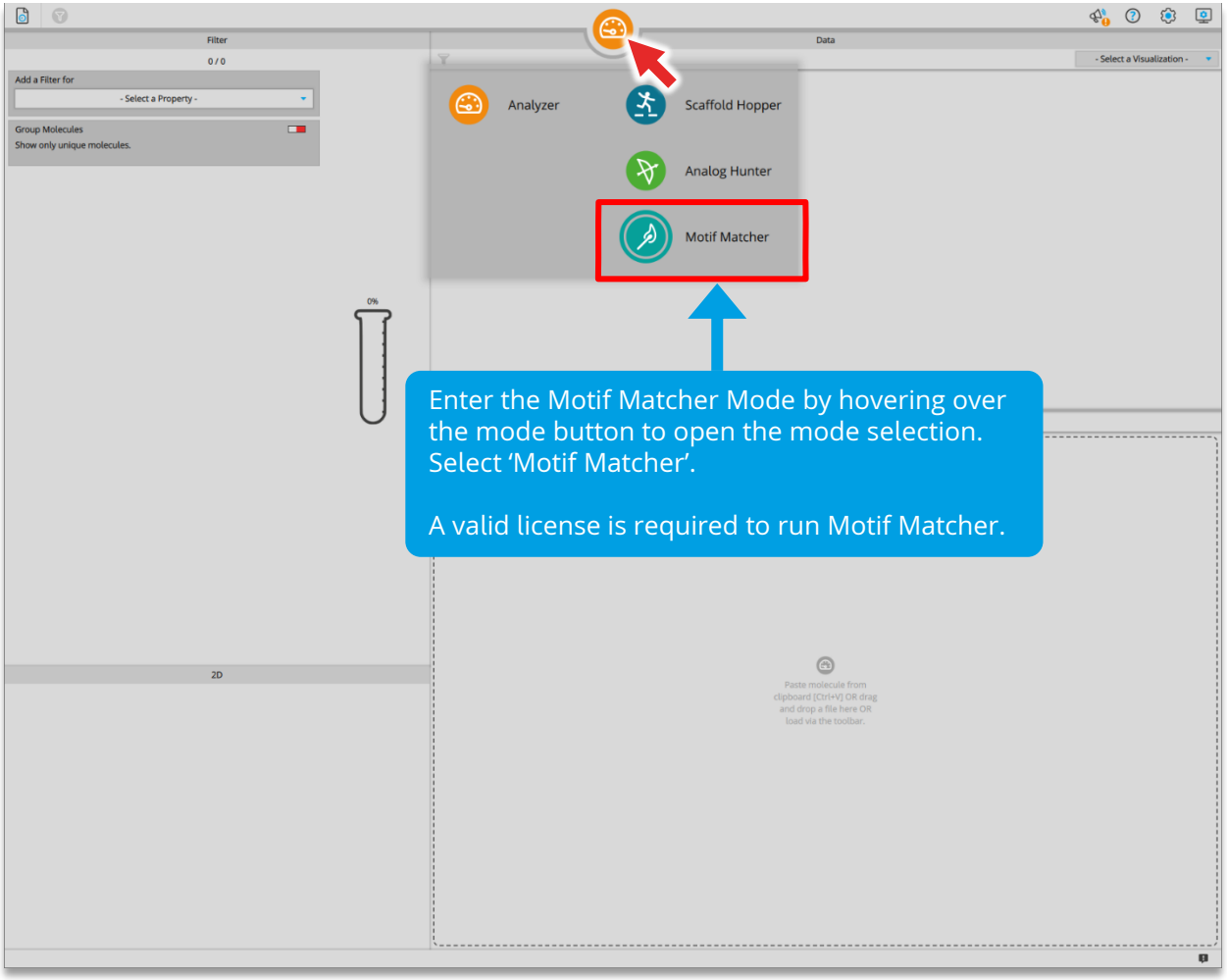


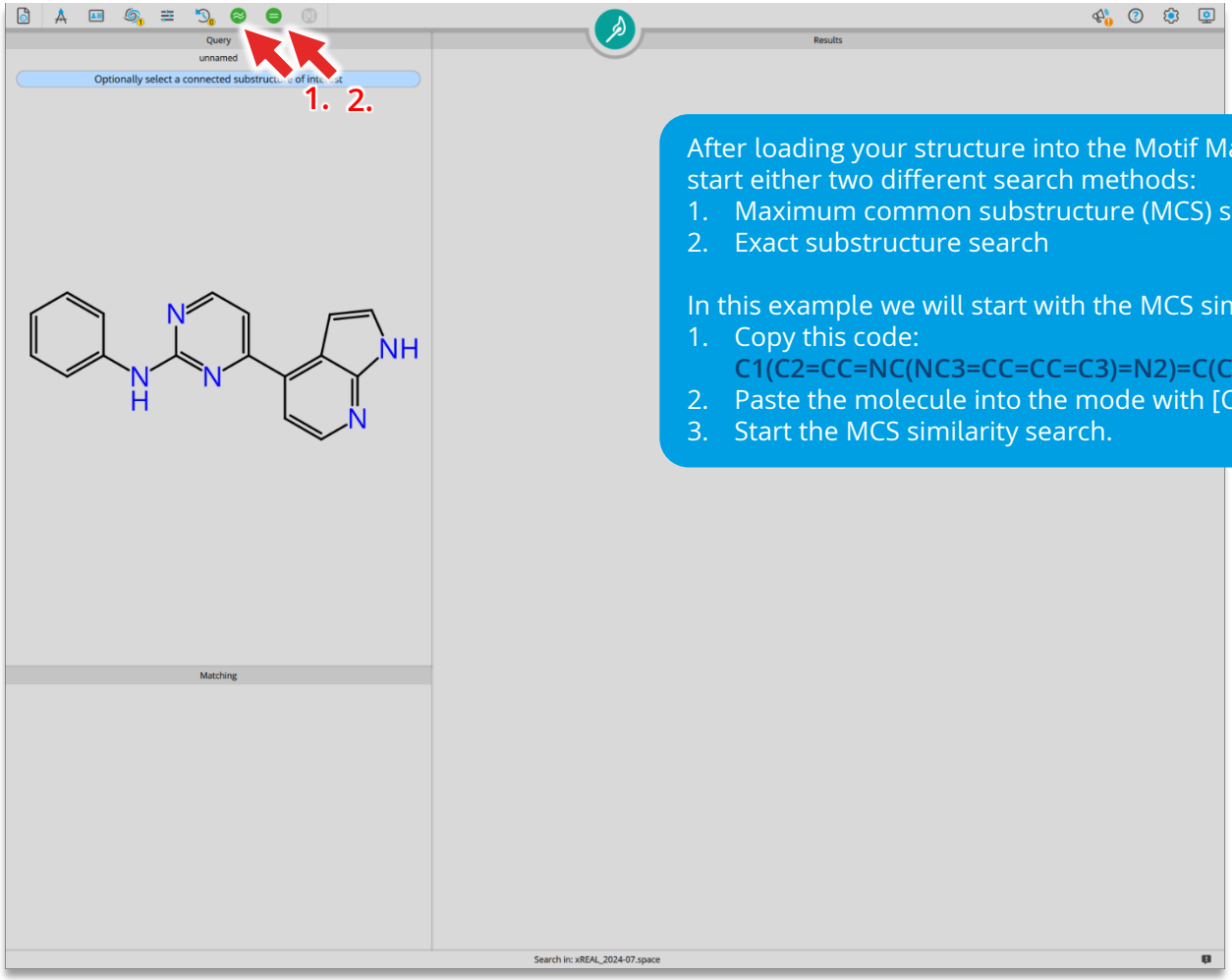
infiniSee xREAL will provide you with close analogs to your query compound and rank them based on their fingerprint similarity.

5. Motif Matcher



The Motif Matcher mines for compounds containing a particular substructure or for molecules sharing the maximum common substructure to your query using the SpaceMACS algorithm.


Filter
0 / 0
Add a Filter for
- Select a Property -
Group Molecules
Show only unique molecules.
Data
- Select a Visualization -
Analyzer
Scaffold Hopper
Analog Hunter
Motif Matcher
0%
2D
Paste molecule from clipboard (Ctrl+V) OR drag and drop a file here OR load via the toolbar.
Enter the Motif Matcher Mode by hovering over the mode button to open the mode selection. Select 'Motif Matcher'.
A valid license is required to run Motif Matcher.

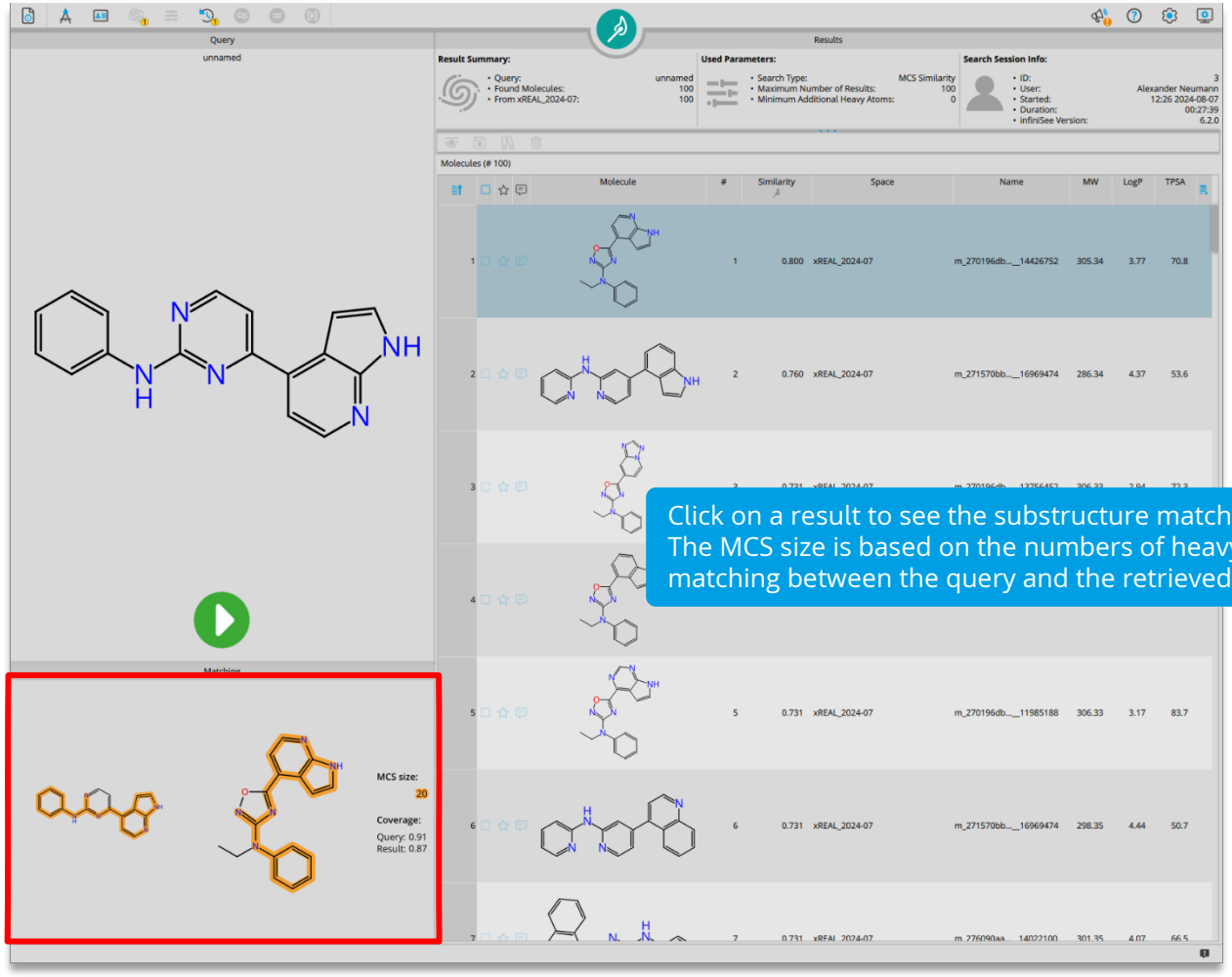


After loading your structure into the Motif Matcher, you can start either two different search methods:

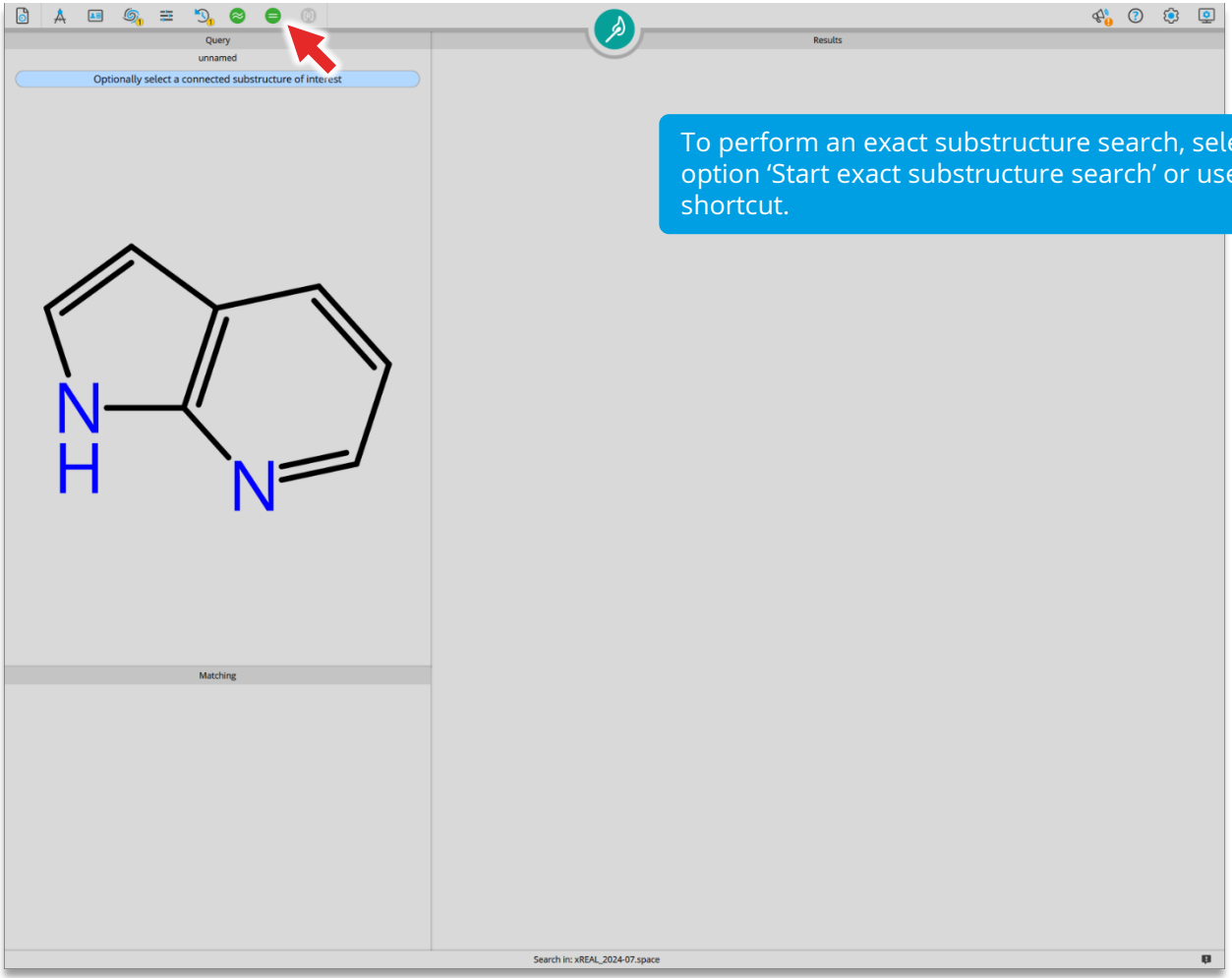
1. Maximum common substructure (MCS) similarity search
2. Exact substructure search

In this example we will start with the MCS similarity search.

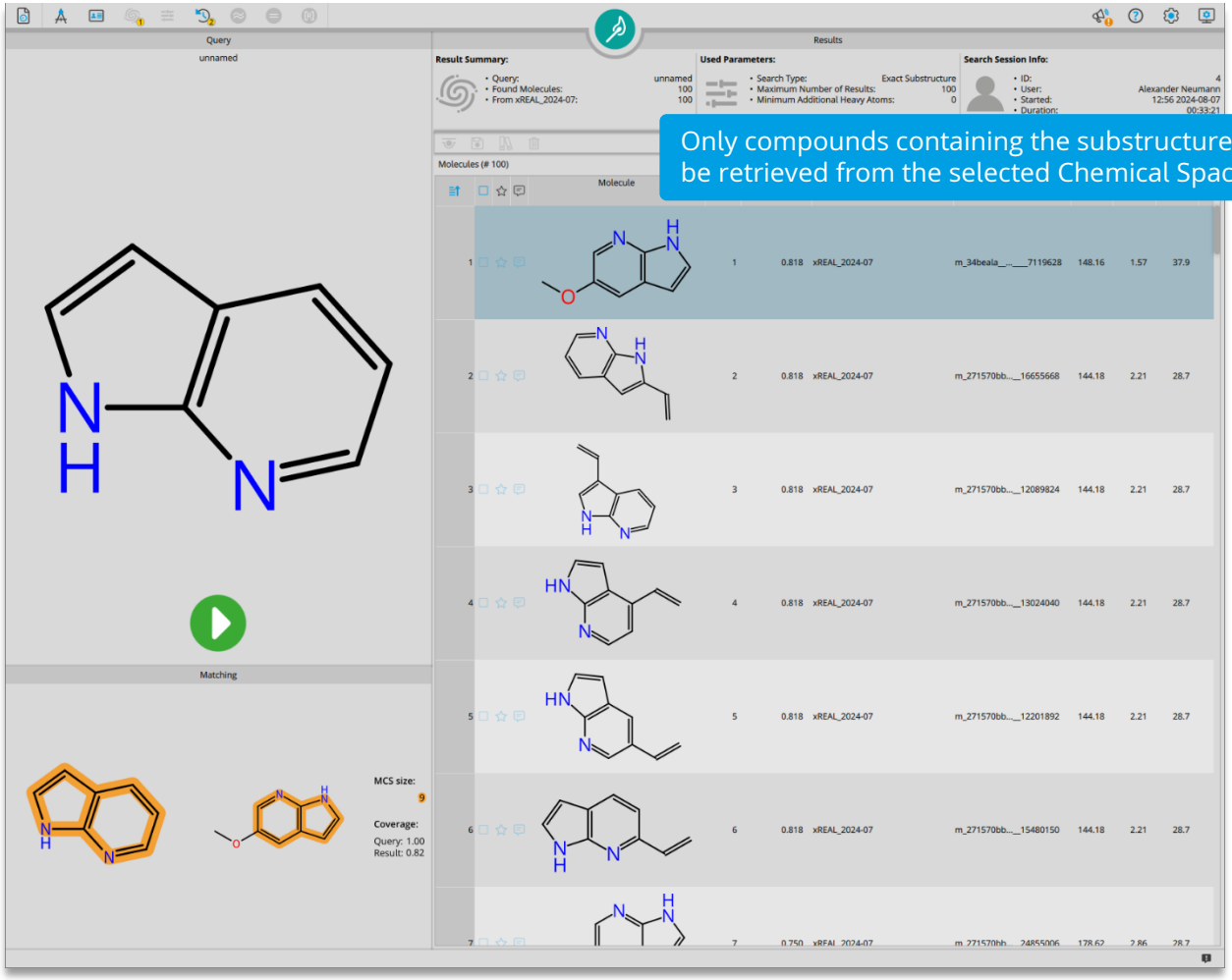
1. Copy this code:
   C1(C2=CC=NC(NC3=CC=CC=C3)=N2)=C(C=CN4)C4=NC=C1
2. Paste the molecule into the mode with [Ctrl+V]
3. Start the MCS similarity search.

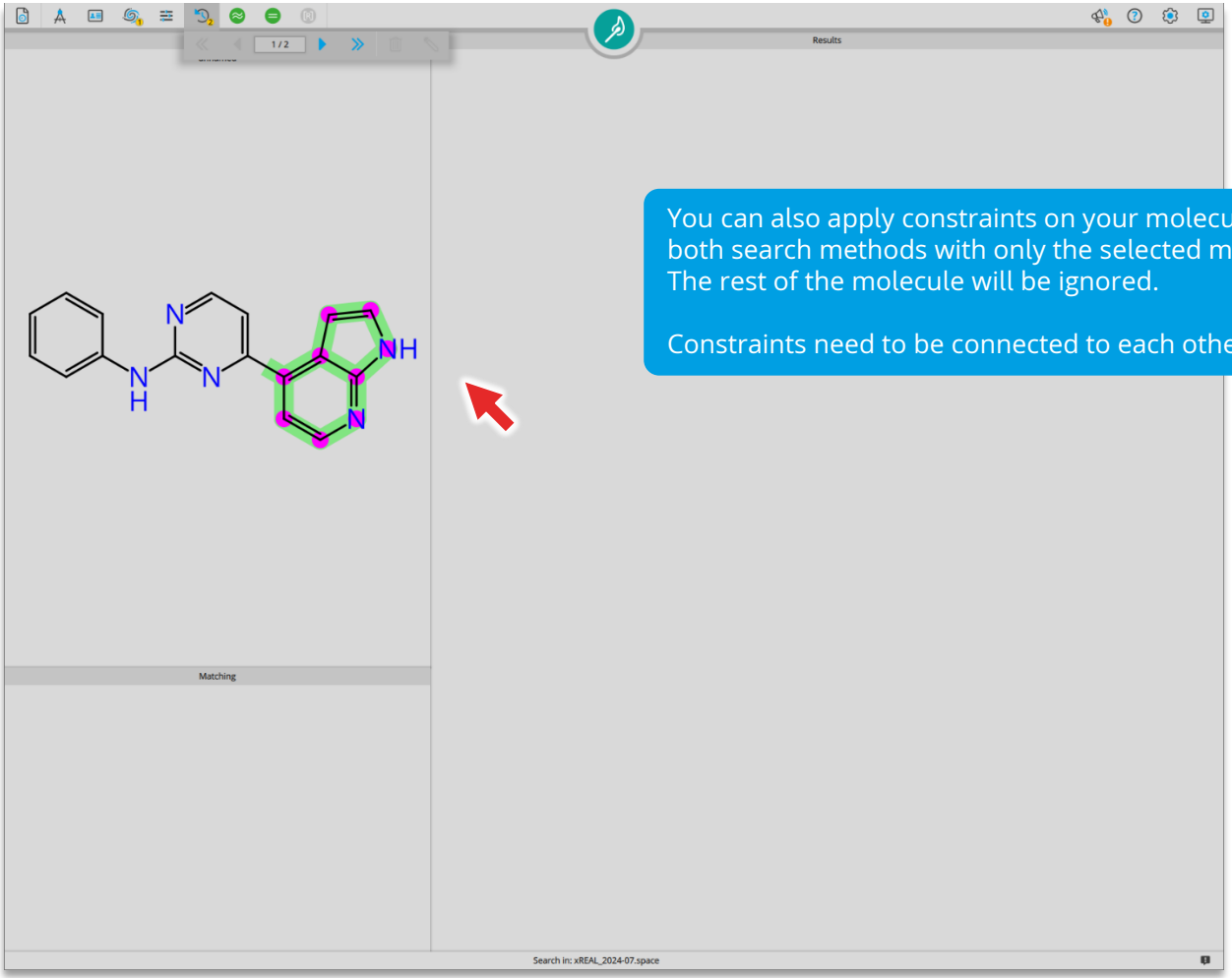


Click on a result to see the substructure matching.
The MCS size is based on the numbers of heavy atoms matching between the query and the retrieved compound.



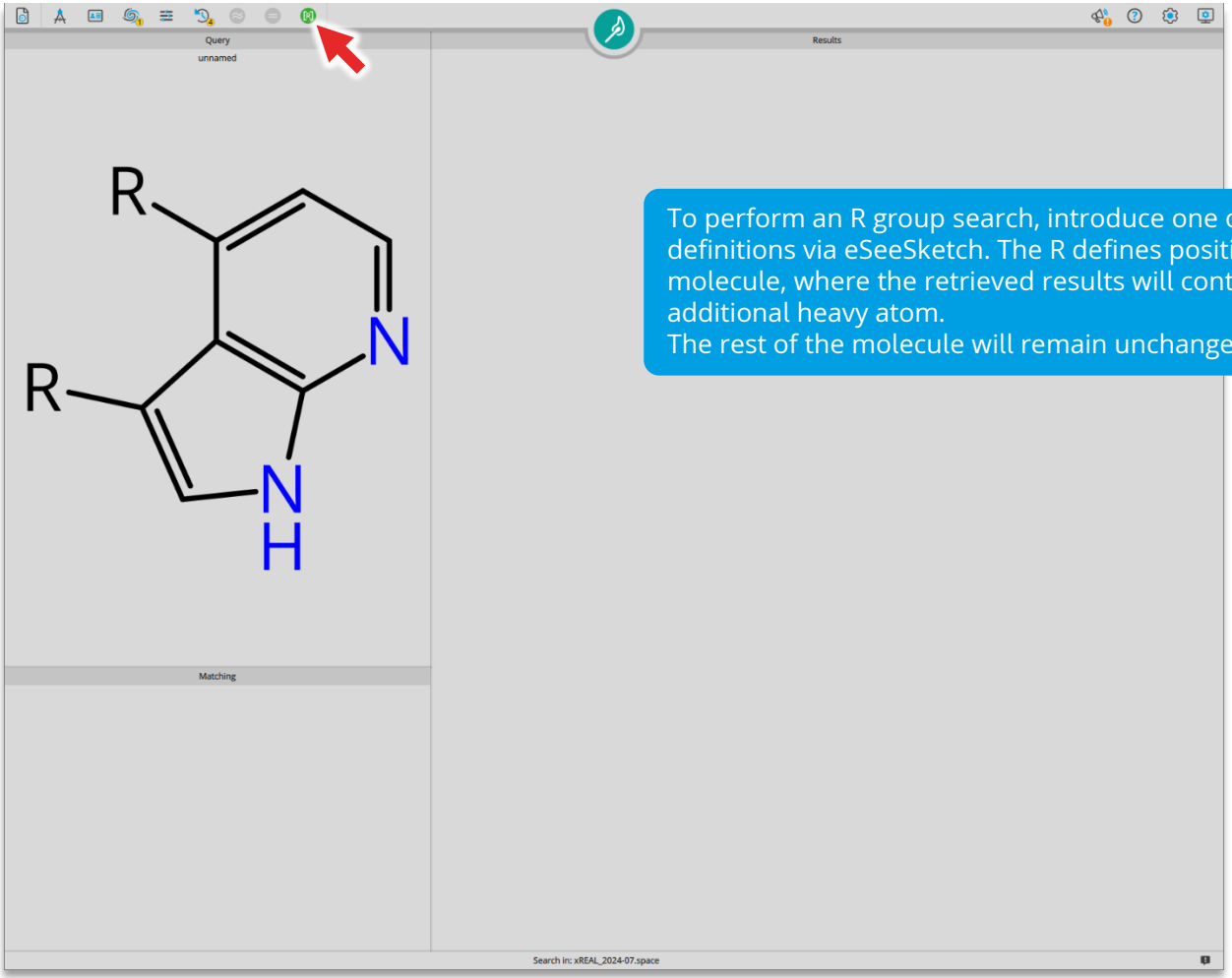
To perform an exact substructure search, select the second option ‘Start exact substructure search’ or use the [Ctrl+E] shortcut.


Query
unnamed
Results
Result Summary:
Query: unnamed
Found Molecules: 100
From xREAL_2024-07: 100
Used Parameters:
Search Type: Exact Substructure
Maximum Number of Results: 100
Minimum Additional Heavy Atoms: 0
Search Session Info:
ID: 4
User: Alexander Neumann
Started: 12:56 2024-08-07
Duration: 00:33:21
Molecules (# 100)
Molecule
Only compounds containing the substructure of interest will be retrieved from the selected Chemical Space.
Matching
MCS size:
9
Coverage:
Query: 1.00
Result: 0.82

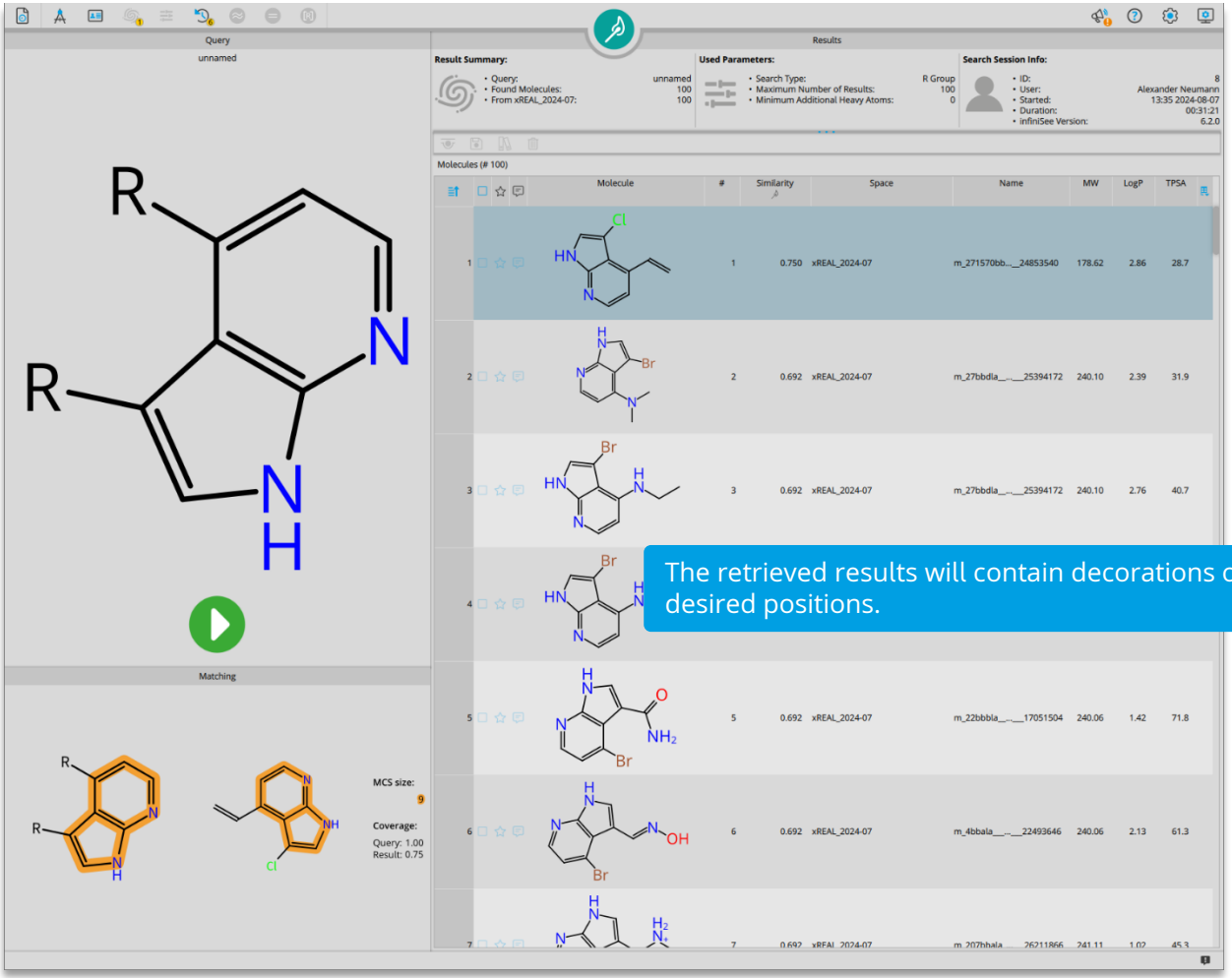


You can also apply constraints on your molecule to perform both search methods with only the selected moieties.
The rest of the molecule will be ignored.

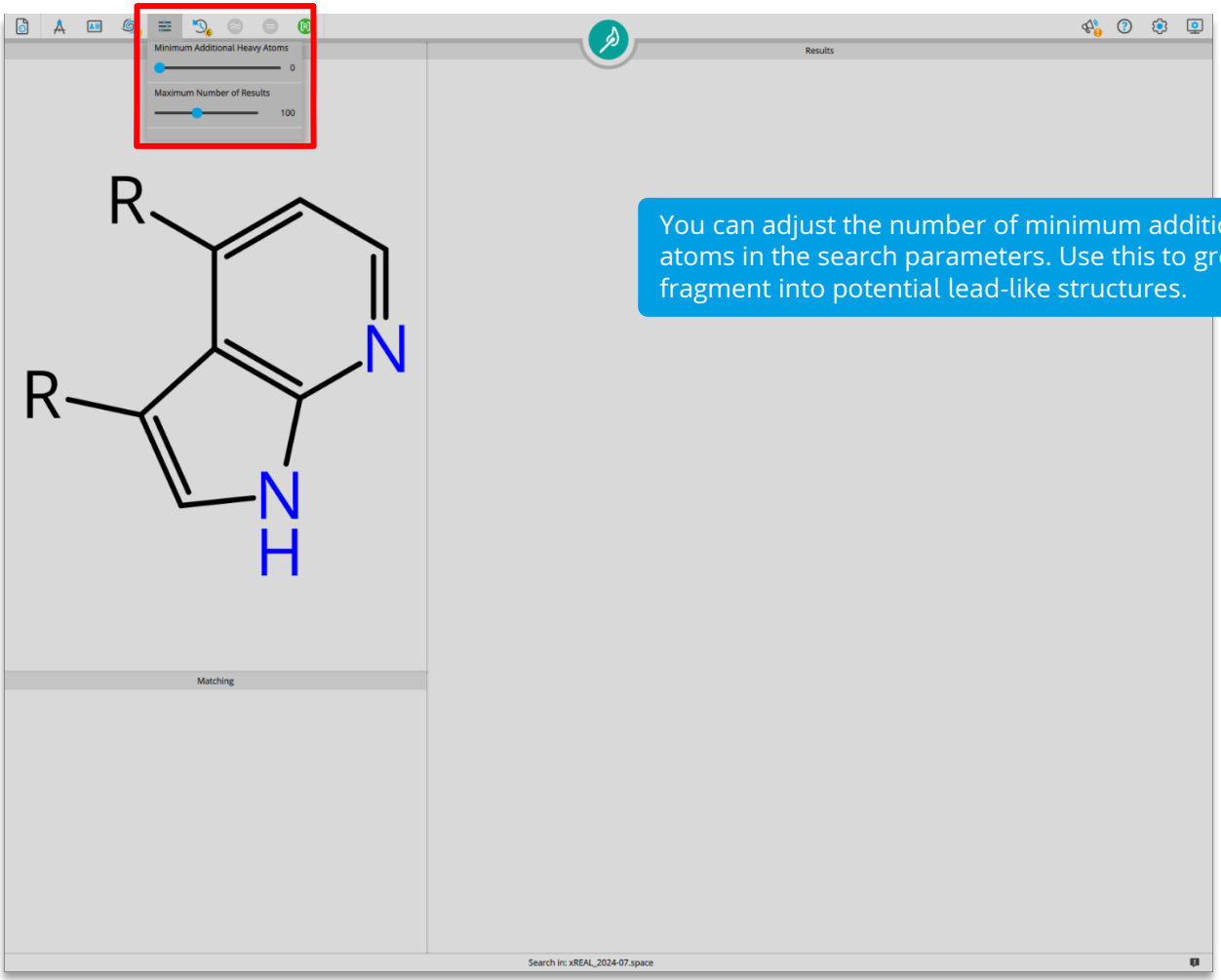
Constraints need to be connected to each other.



To perform an R group search, introduce one or more R definitions via eSeeSketch. The R defines positions of the molecule, where the retrieved results will contain at least one additional heavy atom.
The rest of the molecule will remain unchanged.

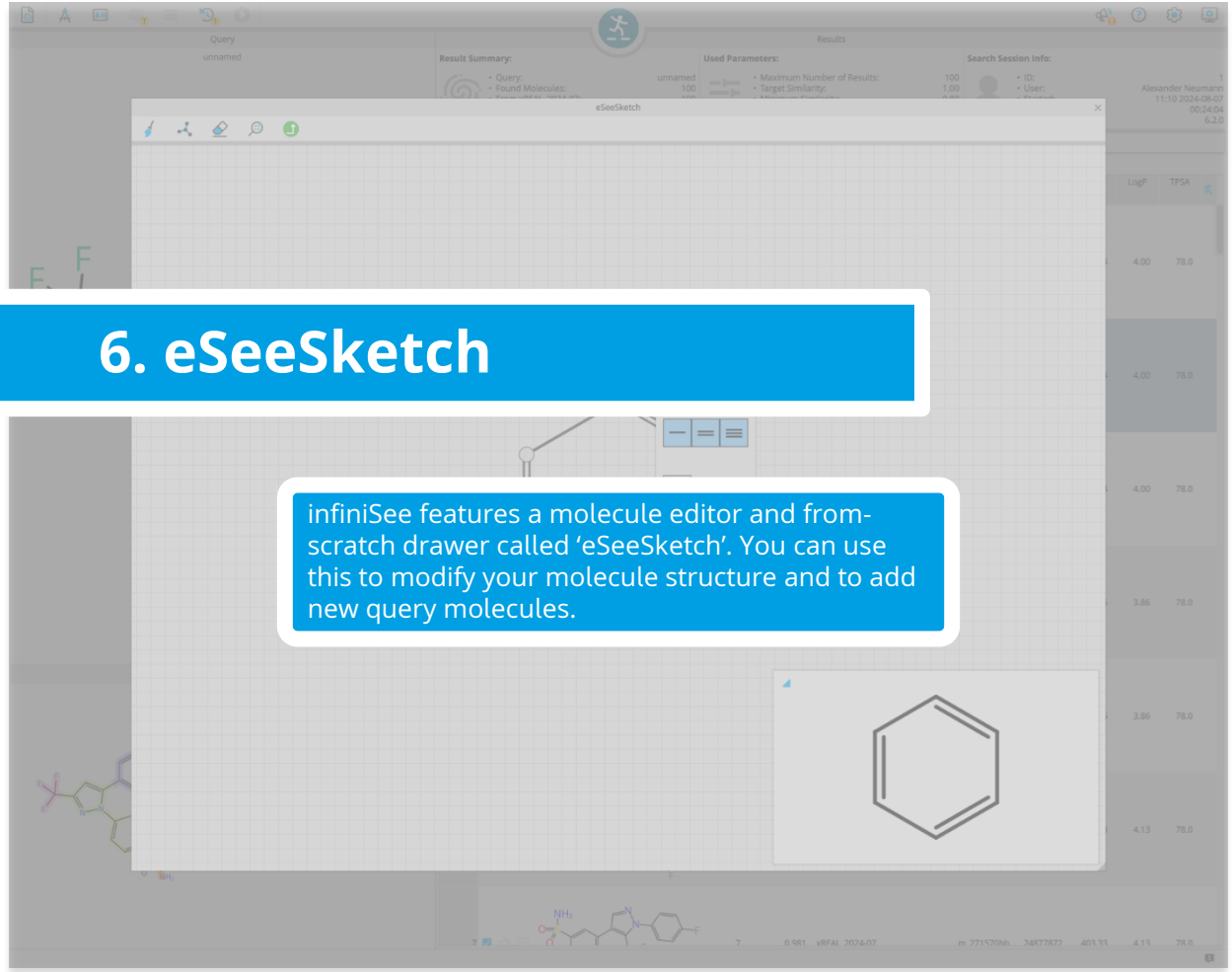


The retrieved results will contain decorations only in the desired positions.

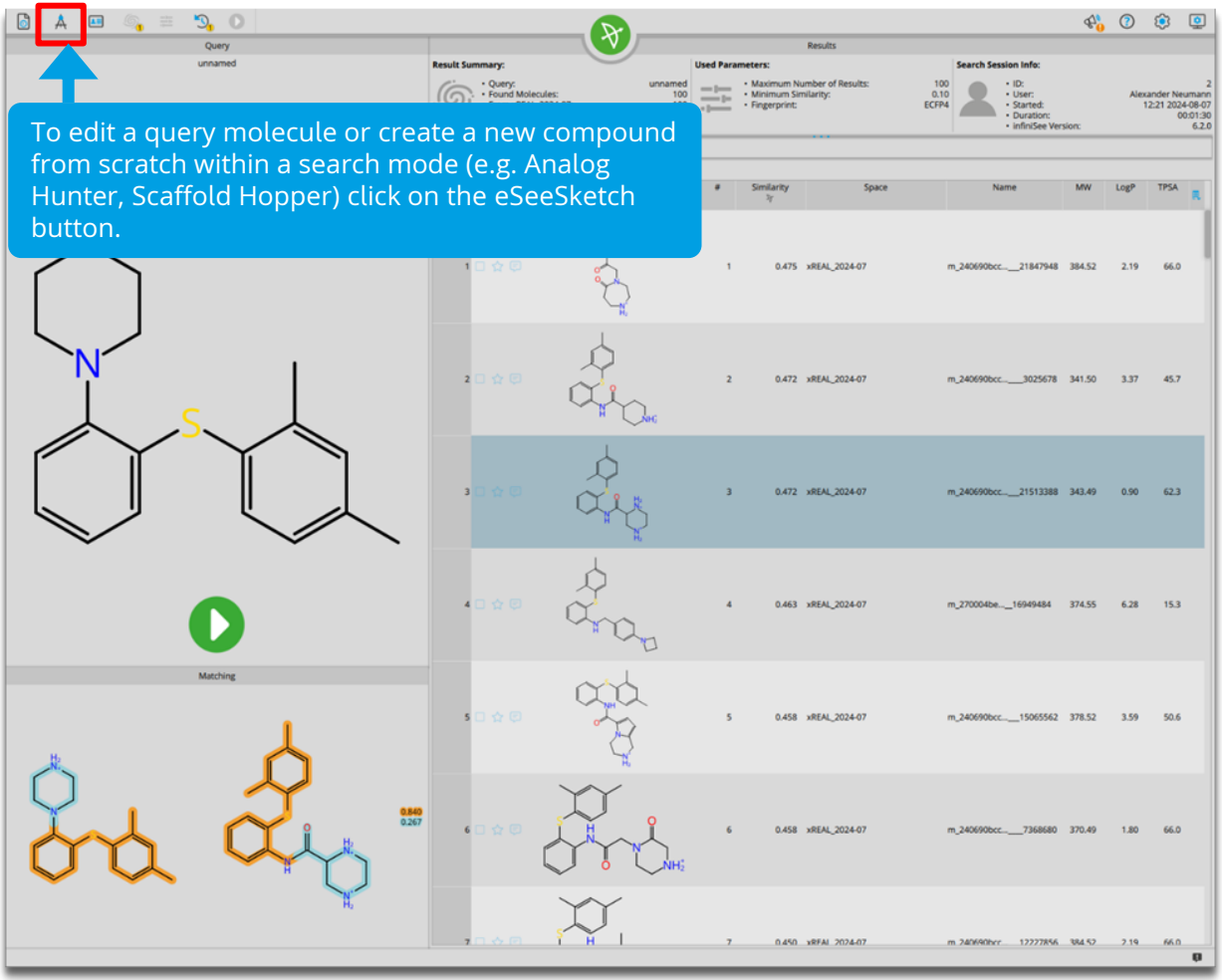


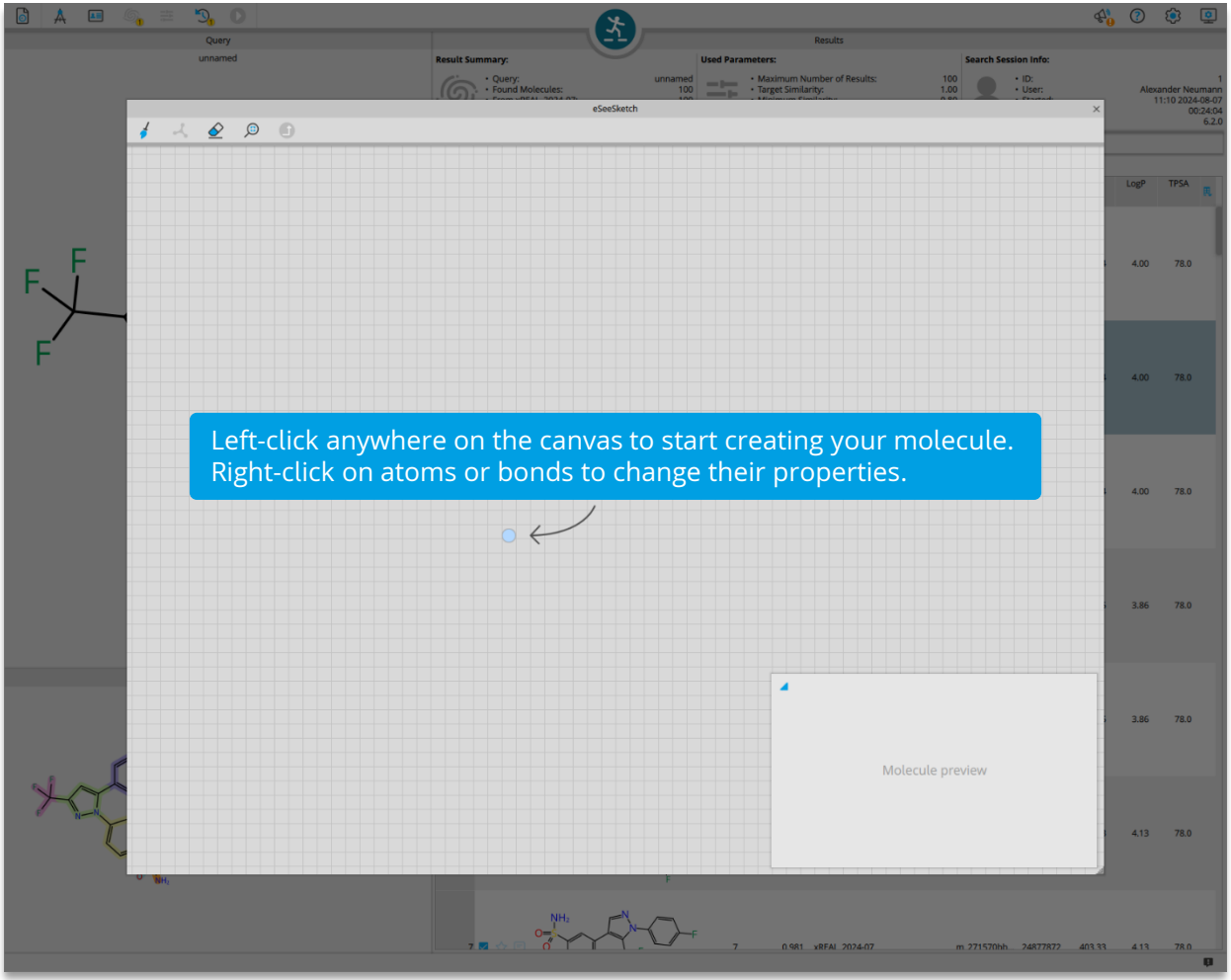
You can adjust the number of minimum additional heavy atoms in the search parameters. Use this to grow your fragment into potential lead-like structures.

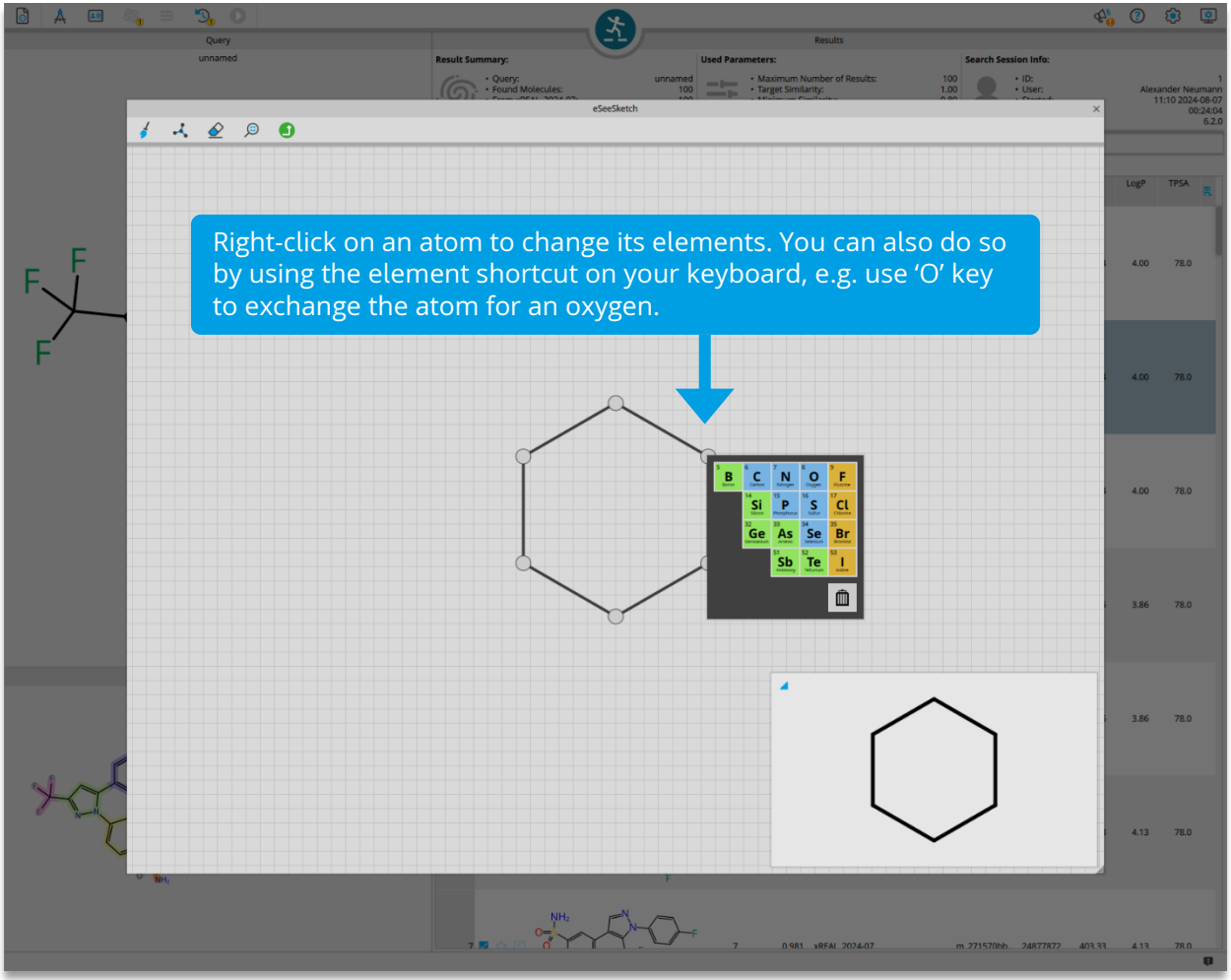
6. eSeeSketch

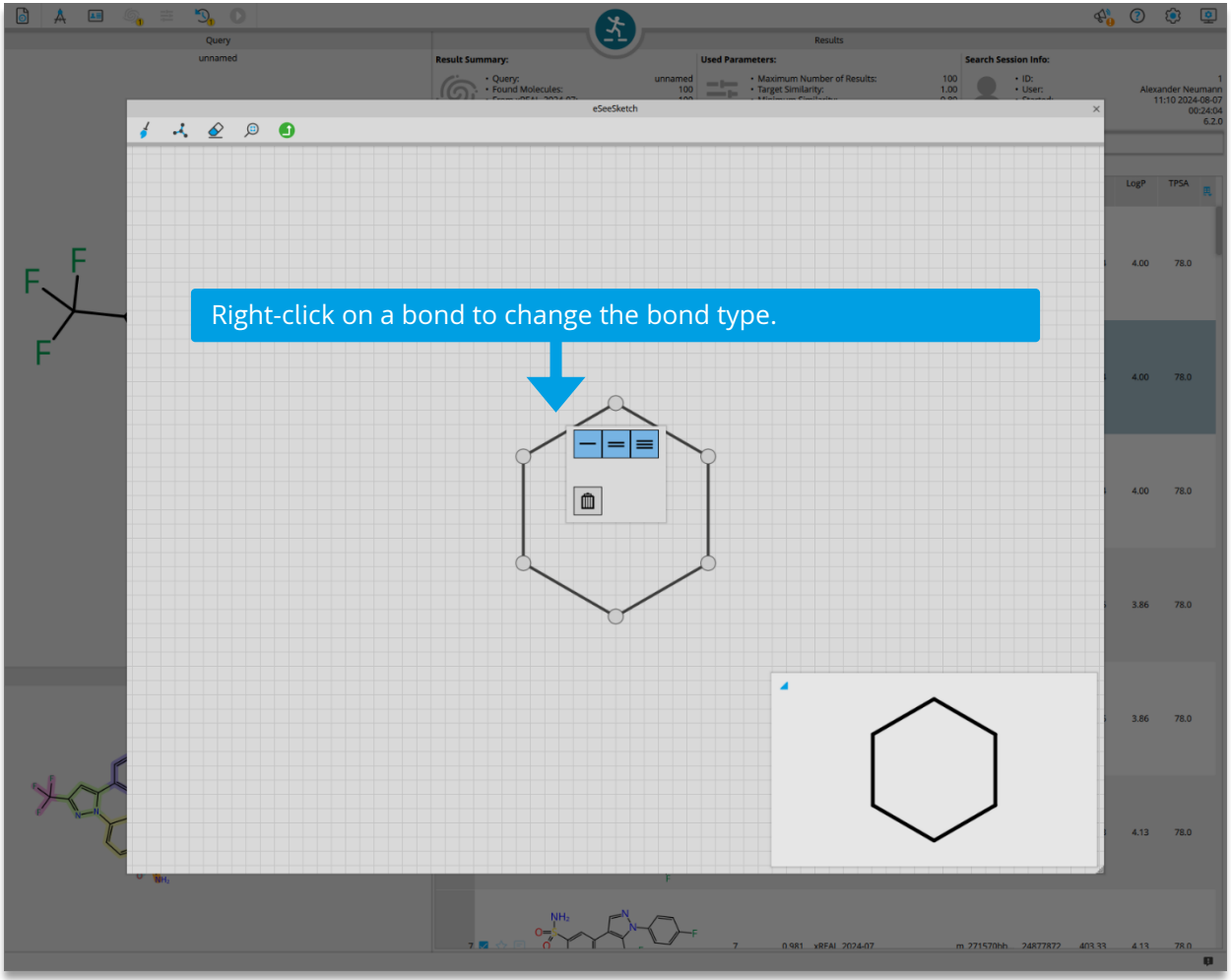


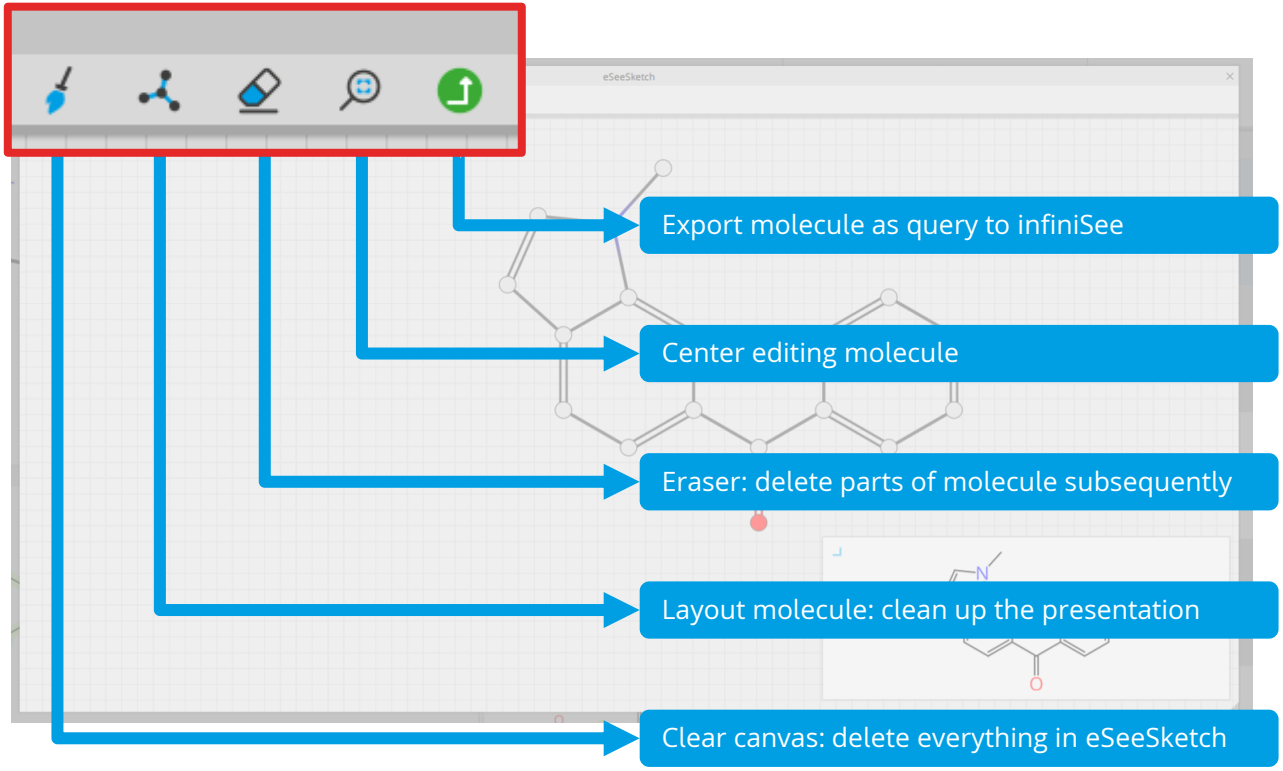
infiniSee features a molecule editor and from-scratch drawer called ‘eSeeSketch’. You can use this to modify your molecule structure and to add new query molecules.

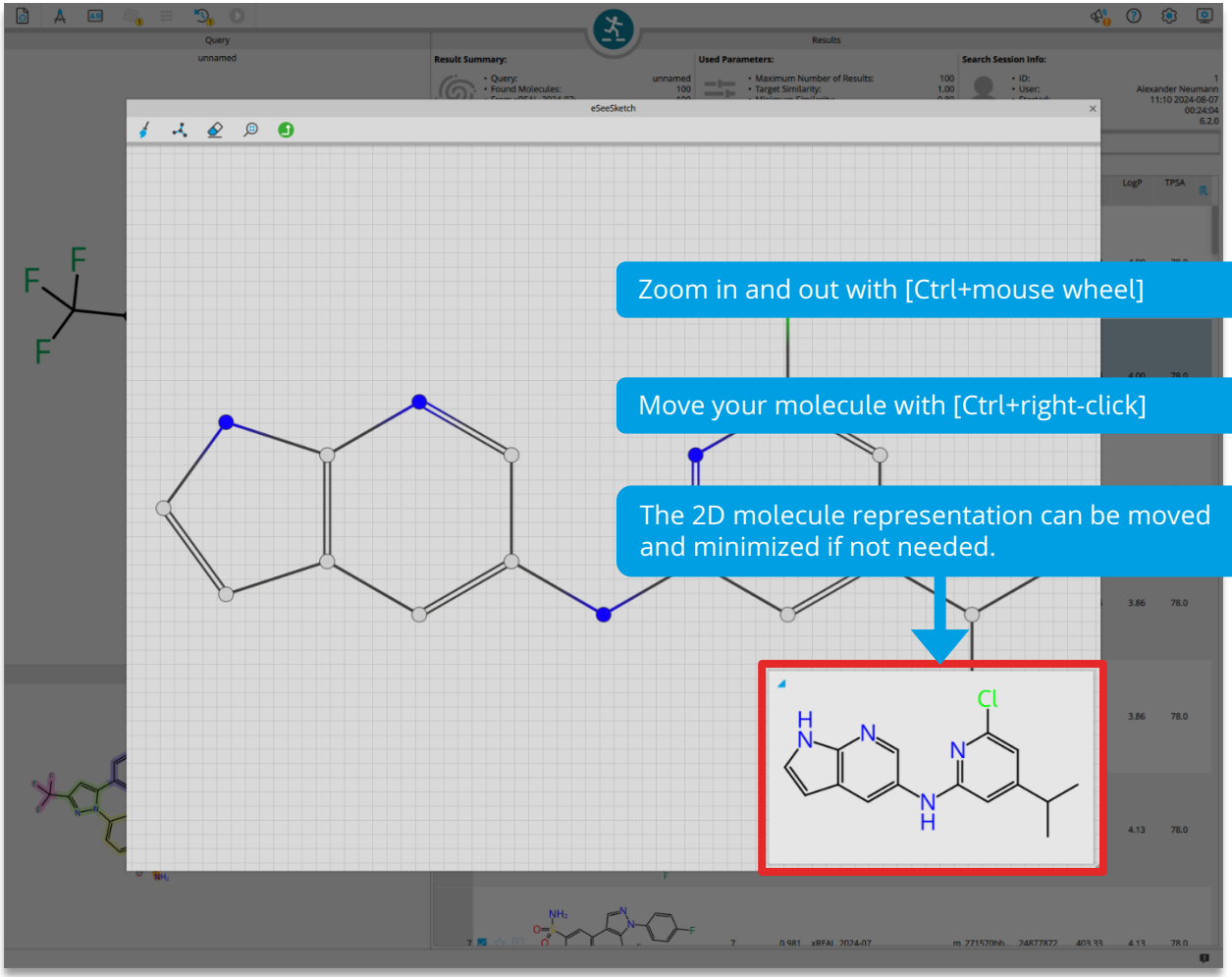

To edit a query molecule or create a new compound from scratch within a search mode (e.g. Analog Hunter, Scaffold Hopper) click on the eSeeSketch button.
Query
unnamed
Results
Result Summary:
Used Parameters:
Search Session Info:
Matching


eSeeSketch
Left-click anywhere on the canvas to start creating your molecule.
Right-click on atoms or bonds to change their properties.
Molecule preview


eSeeSketch
Right-click on an atom to change its elements. You can also do so by using the element shortcut on your keyboard, e.g. use ‘O’ key to exchange the atom for an oxygen.
B C N O F
Si P S Cl
Ge As Se Br
Sb Te I


Right-click on a bond to change the bond type.


Export molecule as query to infiniSee
Center editing molecule
Eraser: delete parts of molecule subsequently
Layout molecule: clean up the presentation
Clear canvas: delete everything in eSeeSketch


Zoom in and out with [Ctrl+mouse wheel]
Move your molecule with [Ctrl+right-click]
The 2D molecule representation can be moved and minimized if not needed.

Enter the largest hunting ground for drug-like compounds with infiniSee xREAL.

If you have any problems, please reach out to us:
support@biosolveit.de