# StarDrop™ Worked Example:

## Scaffold Hopping Using Virtual Library Enumeration

In this example, we are going to use the scaffold-based library enumeration feature in the Nova™ module in StarDrop™, in combination with R-group analysis, to generate a virtual library representing a potential new lead series. This will be based on a previous series and explore the impact of a change of scaffold and variations in a side chain while retaining the substituents at two key positions.

### Exercise

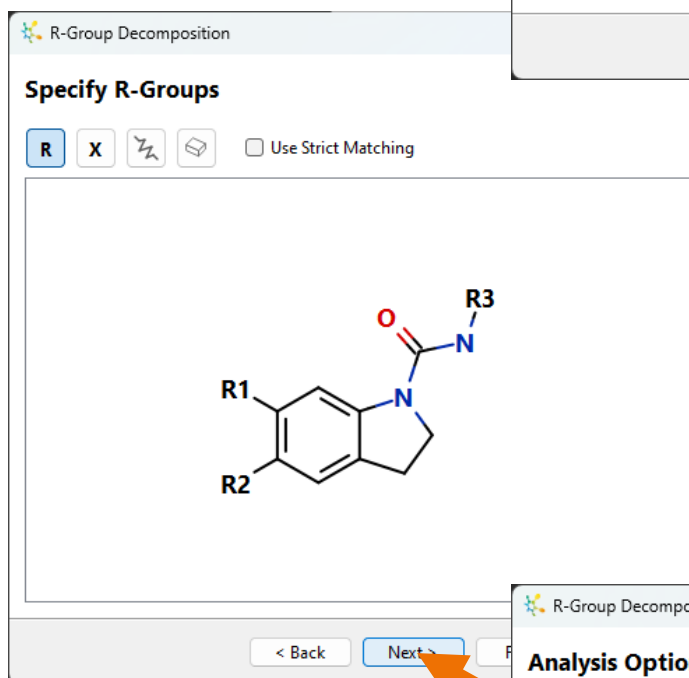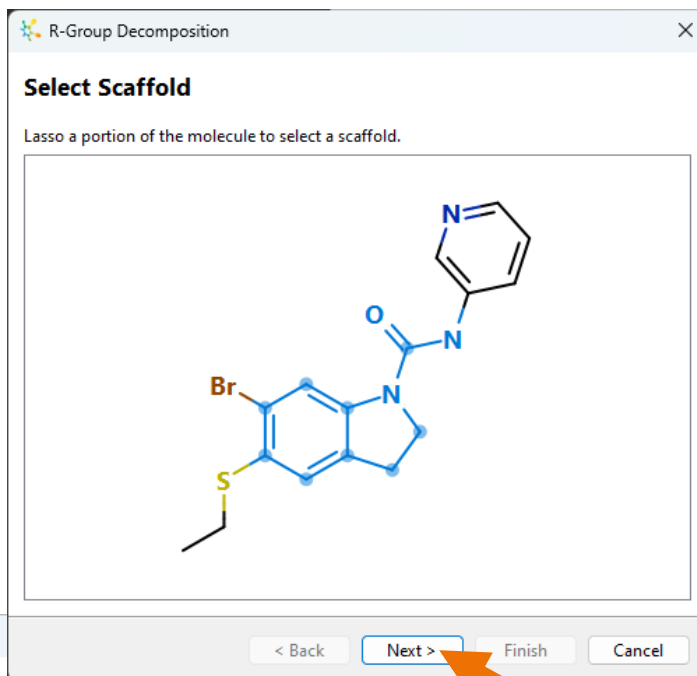- In StarDrop, open the project **FactorXa.sdproj** by selecting **Open** from the **File** menu.
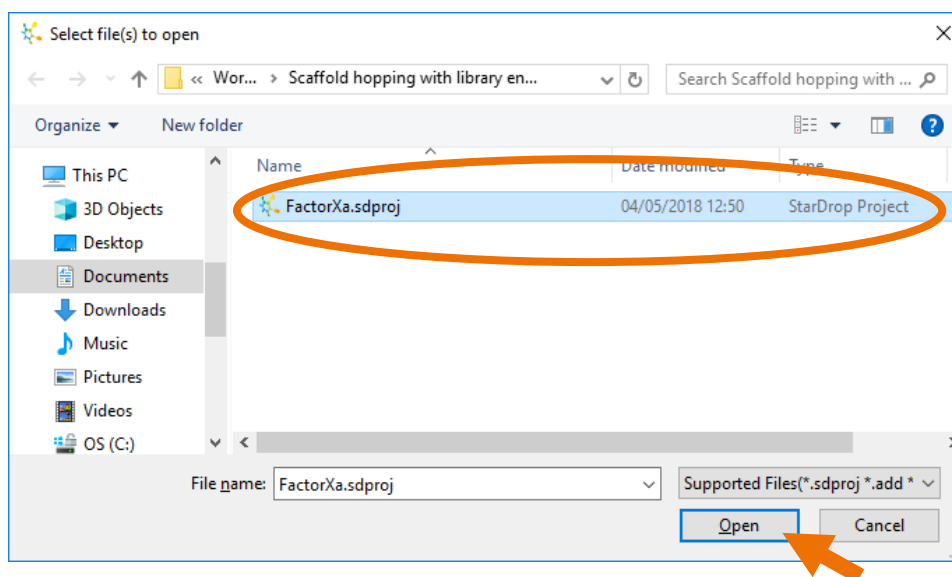


The project contains a series of 78 FactorXa inhibitors for which we have measured pK$_i$ values. First, we'll perform an R-group decomposition of this series to generate some R-groups to substitute on a new scaffold.

- Select the first row in the data set and click the **R-group analysis** button ⬡ on the right-hand toolbar.
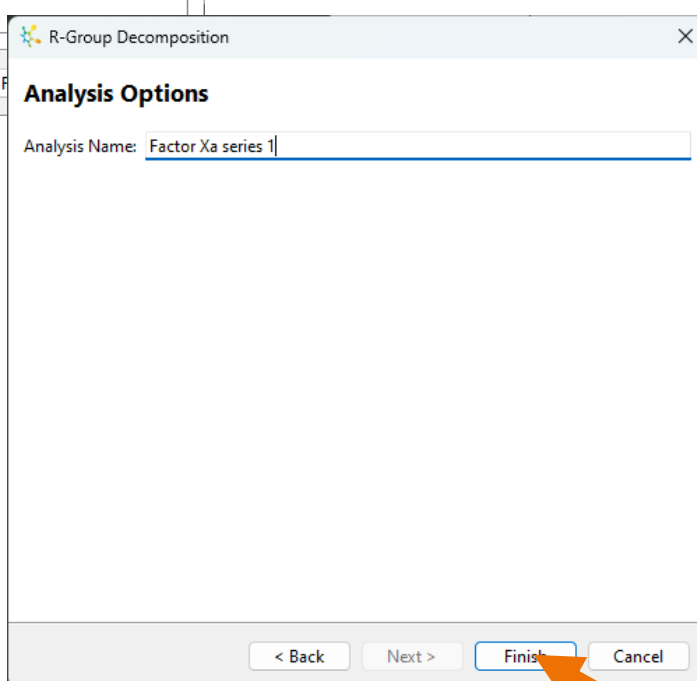
- On the **Select Scaffold** page of the **R-group Decomposition** wizard that appears, draw around the fixed scaffold for this series, as highlighted in blue in the screenshot to the right.

**R-Group Decomposition**

**Select Scaffold**

Lasso a portion of the molecule to select a scaffold.

< Back    Next >    Finish    Cancel

- Click the **Next** button to confirm that the correct substitution points for R-groups have been identified, as shown in the screenshot to the left.

- We do not want to specify any further substitution points or variable atoms, so click the **Next** button.

**R-Group Decomposition**

**Specify R-Groups**

R    X    ☐ Use Strict Matching

< Back    Next >

- On the **Analysis Options** page, give the analysis a name for future reference, for example, "Factor Xa series 1", and click the **Finish** button to complete the wizard.

**R-Group Decomposition**

**Analysis Options**

Analysis Name: Factor Xa series 1

< Back    Next >    Finish    Cancel

The resulting R-group decomposition will be shown in the data set, as shown below.
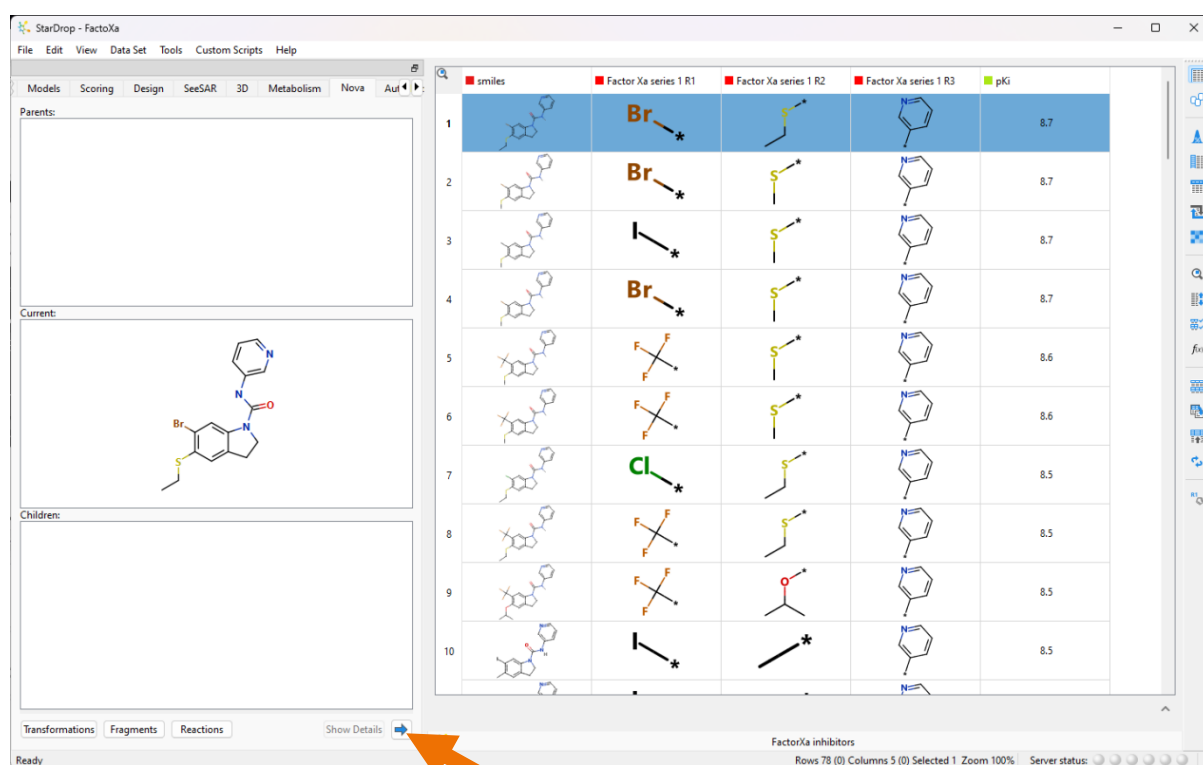


Now, we are going to enumerate a new virtual library for a similar series based on an indole core.

- With the first row of the data set still selected, click the ➡️ button at the bottom of the **Nova** area to start the enumeration. In the wizard that appears, select the **Scaffold-Based Library Enumeration** option and click the **Next** button.

The **Sketch Scaffold** page will be shown containing the selected member of the series. You can, of course, sketch a new scaffold by clicking the **Reset** button, but in this case, we'll edit the displayed compound to create the scaffold for our new library.
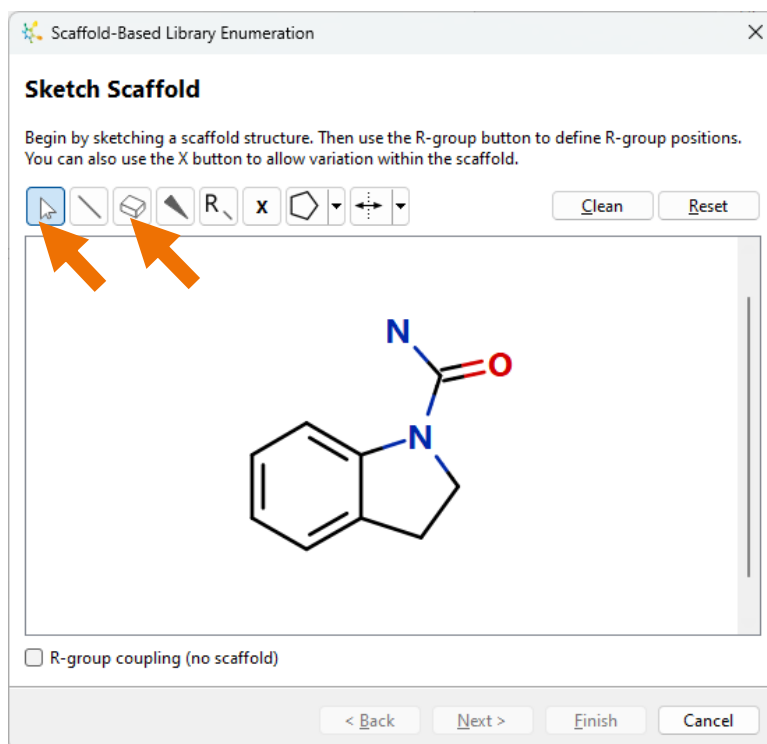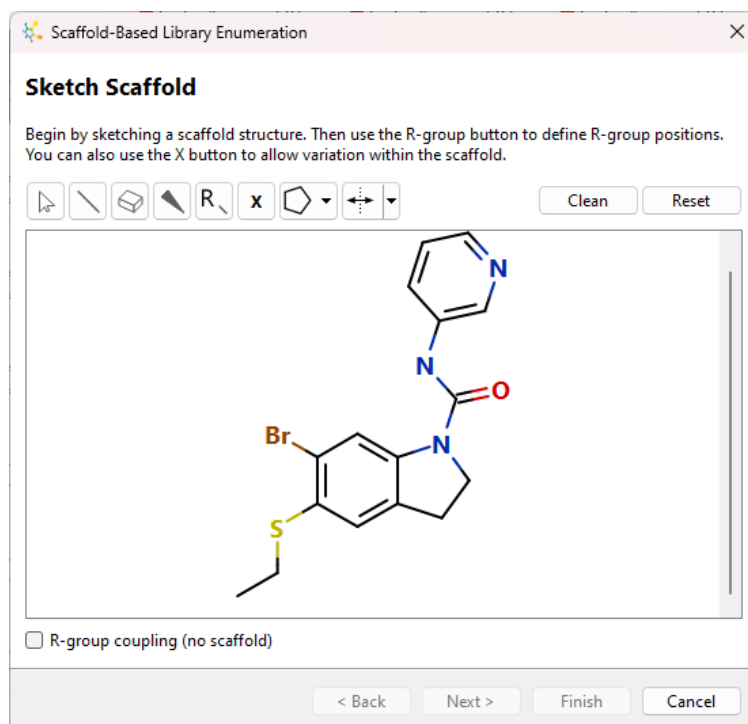
- Erase the groups at the substitution points to leave the scaffold shown to the right.
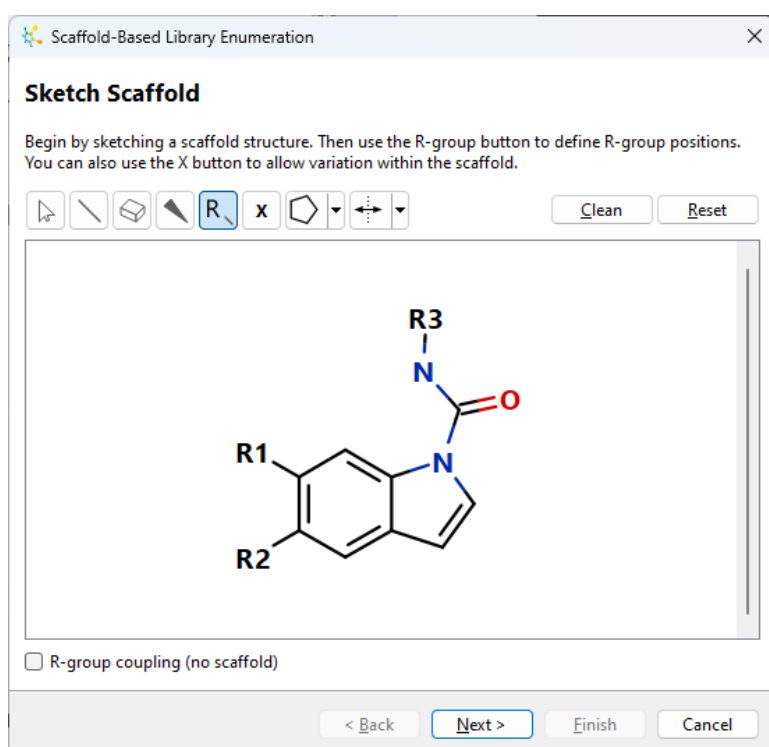
  **Hint:** you can use the

  **Erase** tool ⬭ to erase atoms or bonds or click

  the **Select** tool ▷ and draw around the regions you wish to delete, clicking the **Delete** key to delete them from the structure.



- Modify the core of the original series to change it into an indole, as shown to the right.

  **Hint:** Select the **Bond** tool ╲ and click on the bond highlighted on the right to change from single to double.
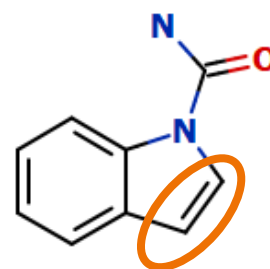




- Use the **R-group** tool ℝ to add R-groups in the R1, R2 and R3 positions, as shown to the left, by clicking on the atom to which they should be connected.

We will also define some variations in the scaffold, in this case, to the linker between the core and R3.

- Using the **Variable atom** tool [X] click on all the atoms which comprise a contiguous region defining a variable fragment (X1), as shown to the right. This will enable us to vary the linker.
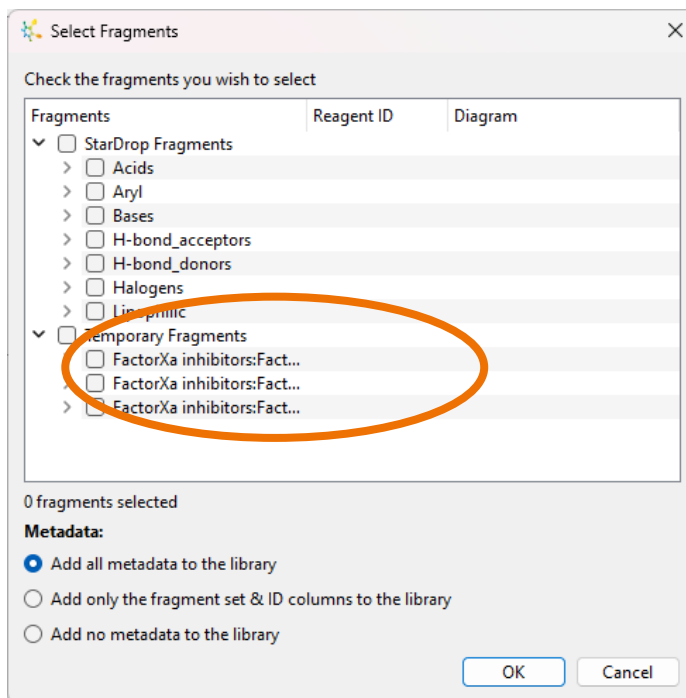
- Click the **Next** button.
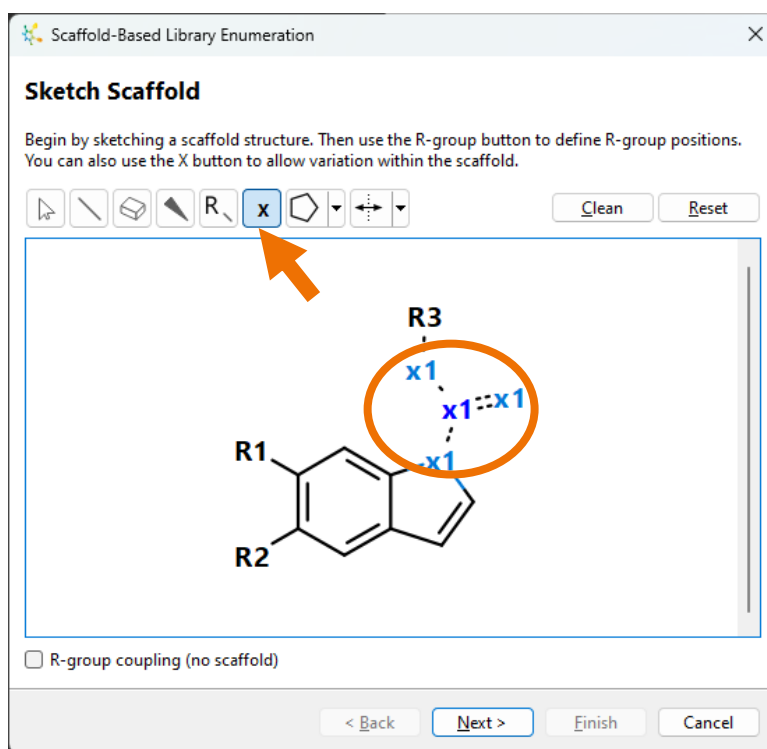


On the **Define R-Groups** page, we can list the groups to substitute at each point.

- Click the **Add** button [+▾] next to **R1** and choose **Select** to open the library of pre-defined substituent groups.
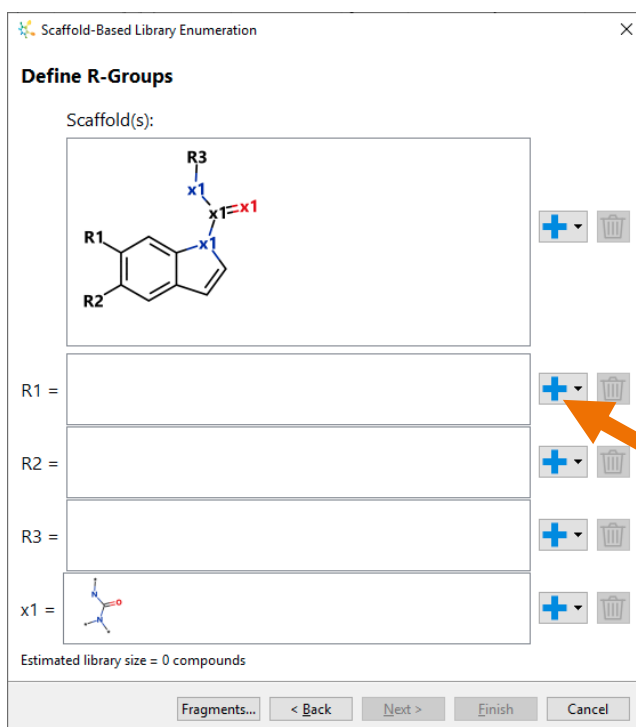
In the fragment library, you will see that the groups derived from the R-group analysis of the original series are available at the bottom of the list. Clicking the arrow next to an entry will expand the list to show the individual substituent groups in that list.

The **Metadata** options below enable you to specify which, if any, data from the fragment library are added to the new series data set. This can be valuable if you have created the fragments using StarDrop's R-group clipping tool and have associated reagent IDs with each fragment.



- Tick the box next to the list of R1 groups from the original series to select all the same groups for the R1 position on the new indole scaffold and click the **OK** button.
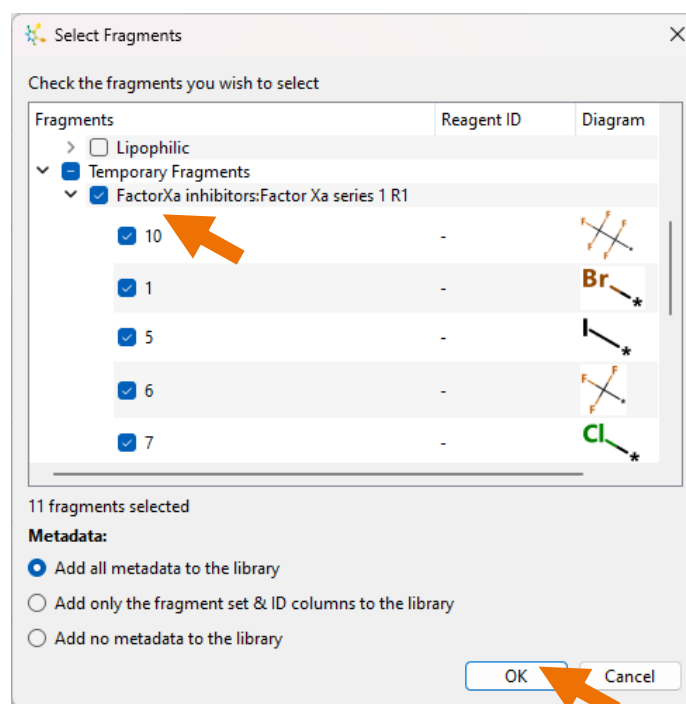


- Follow the same steps for each of R2 and R3, clicking the **Add** button  for each of them and selecting the appropriate R-groups from the library so that we can create a series based around the indole scaffold, which has equivalent R-groups at each position.

The indoline library only generated a single fragment to use at R3. We will now sketch an additional substituent for the R3 position.

- Click the **Add** button  next to **R3** and choose **Sketch**.

- Draw a 4-chloro-phenyl as shown to the right and click the **OK** button.

**Hint:** The **\*** indicates the attachment point of the R-group, so the fragment must link to this point.

**Note:** As you sketch a fragment, StarDrop will suggest other similar fragments you might be interested in adding. Use **CTRL**+click (**CMD**+click on Mac) to select any fragments of interest and add them to your fragment list.
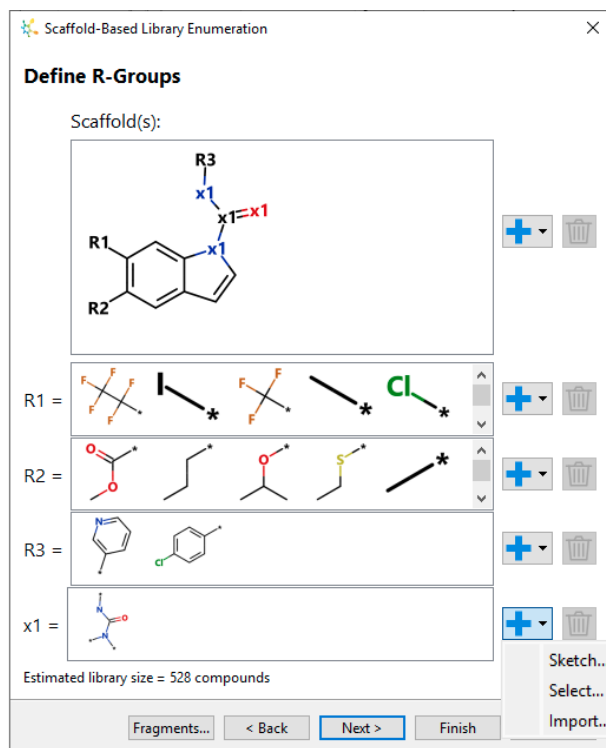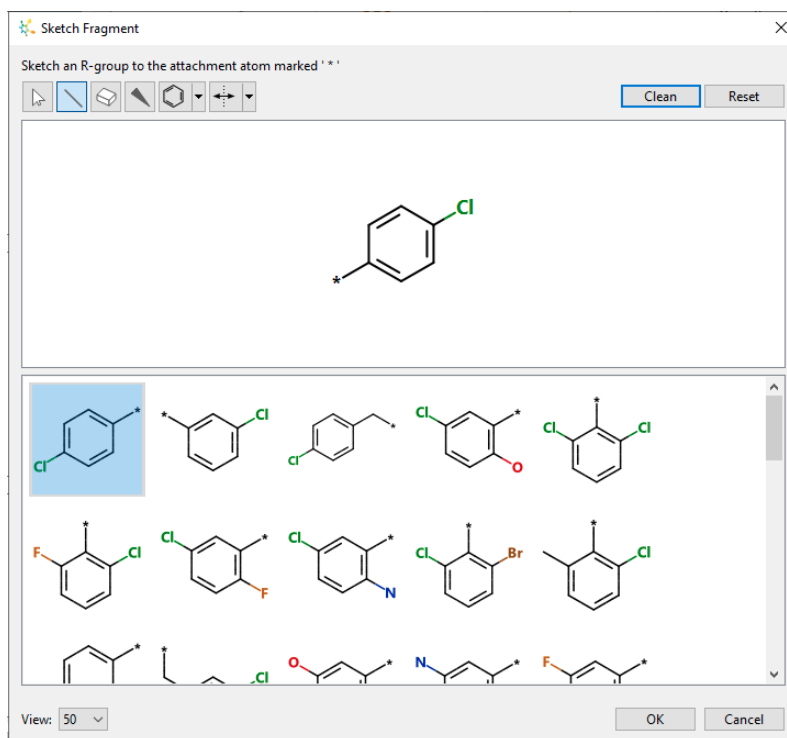


The first fragment is already defined for **X1** (you may need to scroll down through the list of points of variation). This is the linker from the original library.

- Click the **Add** button  next to **X1** and choose **Sketch** to define an additional X1 fragment.
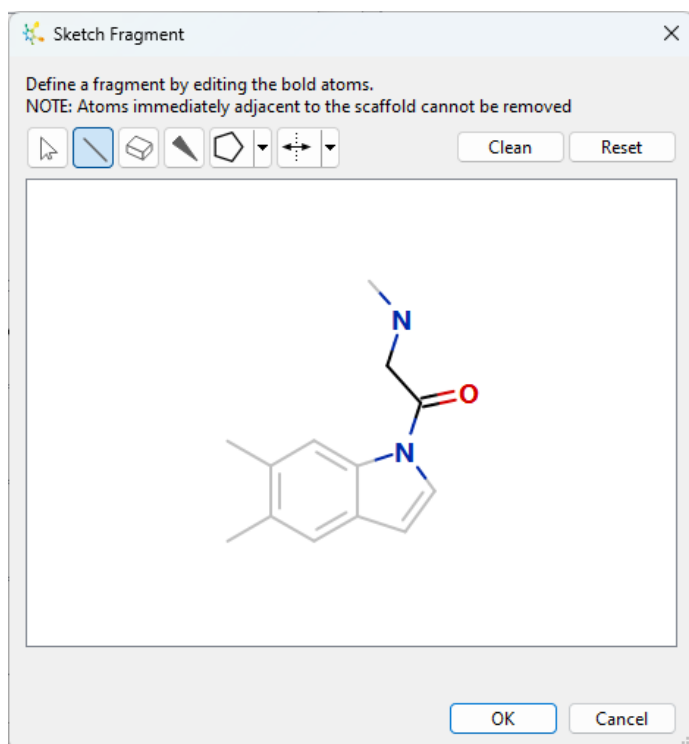
The fragment sketcher will show the original linker fragment from our starting compound. Modify the structure to draw a fragment with a longer linker, as shown to the left.

**Hint:** Erase the bond between the N and amide carbon and insert an additional methylene. Click the **Clean** button to normalise the bond angles and lengths.

- Click the **OK** button to add it to the list of X1 linkers.

You should see that the resulting library is estimated to contain over 1000 compounds.

- Click the **Next** button.
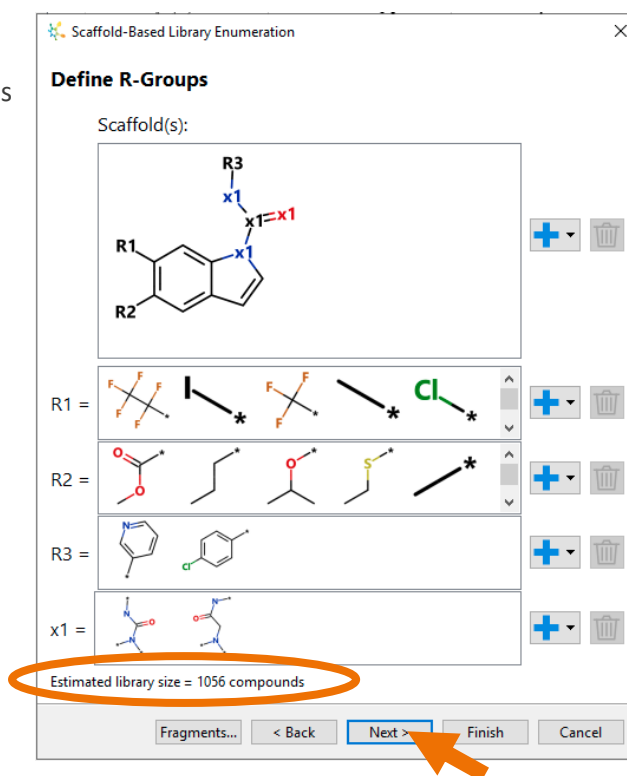


If you wish, you can automatically calculate the properties of the compounds in the resulting library and select a subset of compounds according to a given property or score.

In this case, the library will be quite small, so we could easily enumerate all the compounds, but as an example, we will select the 100 compounds with the lowest predicted logP for further analysis.

- Check the **Select Compounds** option, choose the selection method **Property**, and select compounds with **Low logP**.

- Choose to select **the best 100 compounds**, as shown to the right, and click the **Next** button.

- Finally, on the **Enter Data Set Name** page, we can give the resulting library a name and click the **Finish** button.
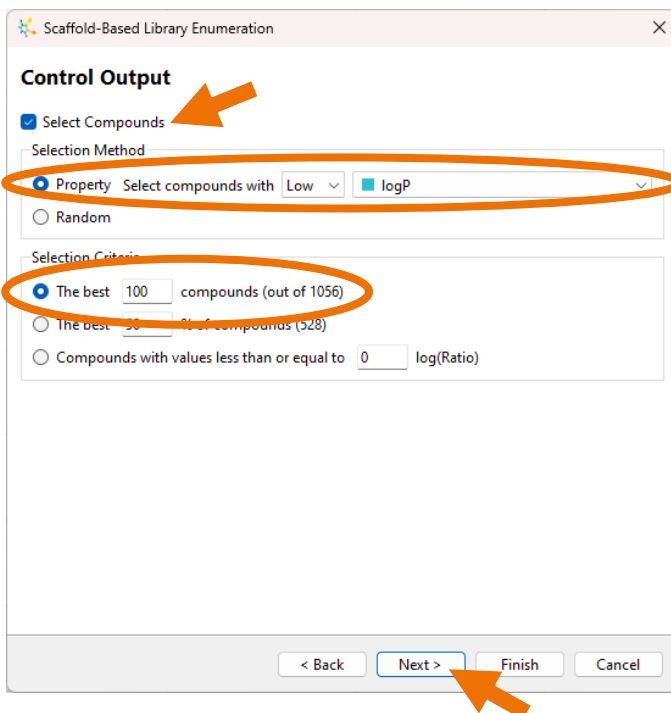


In the Nova area, an indicator will show the progress as the library is enumerated, the logP calculated, and the compounds selected. When complete, the resulting library will appear in StarDrop, and all StarDrop's capabilities can be used to select compounds or consider further improvements.
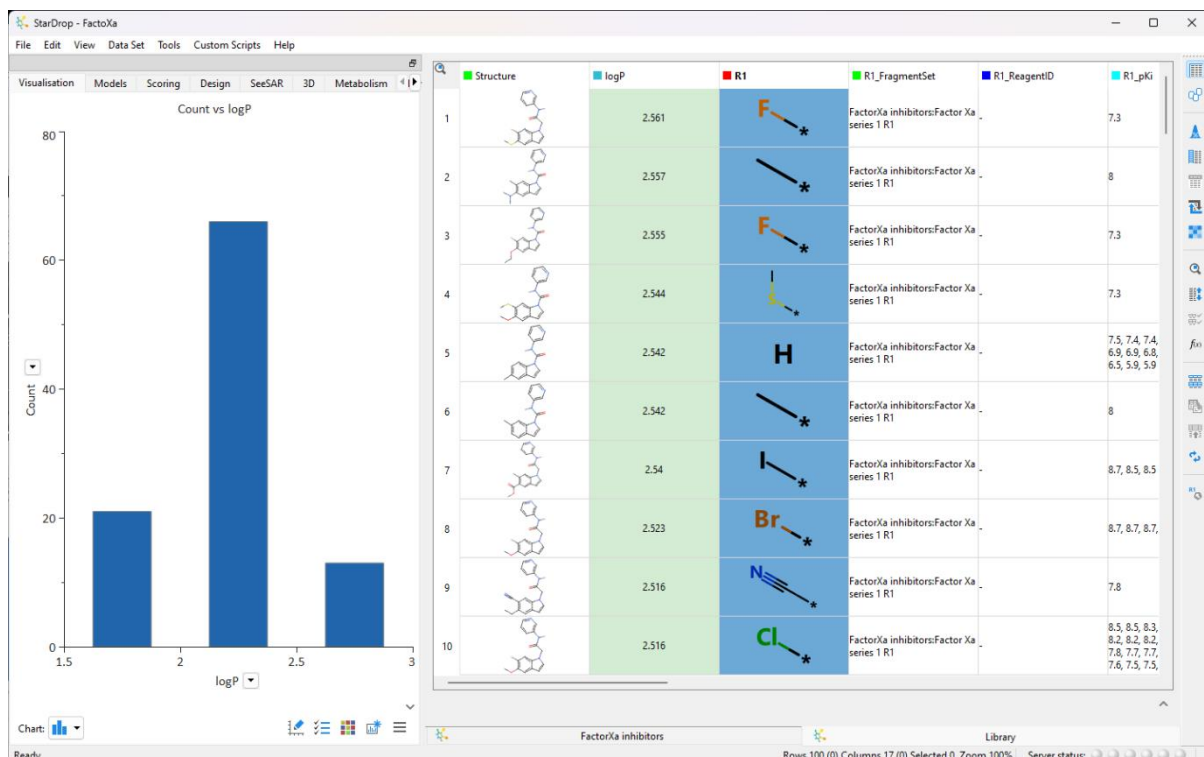
## Conclusion and Additional Resources

This example shows how we can use the scaffold-based library enumeration feature in StarDrop's Nova module, in combination with R-group analysis, to generate a virtual library representing a potential new lead series.

If you have any questions, please contact support@optibrium.com, and also feel free to explore our online community at www.optibrium.com/community for additional tutorials and videos.