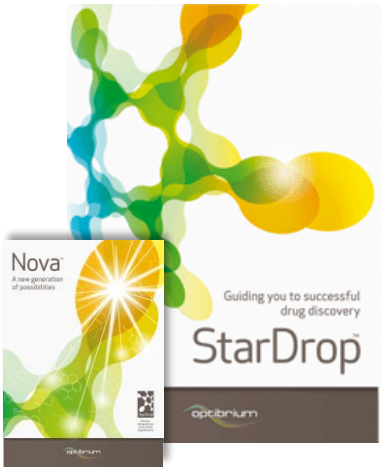
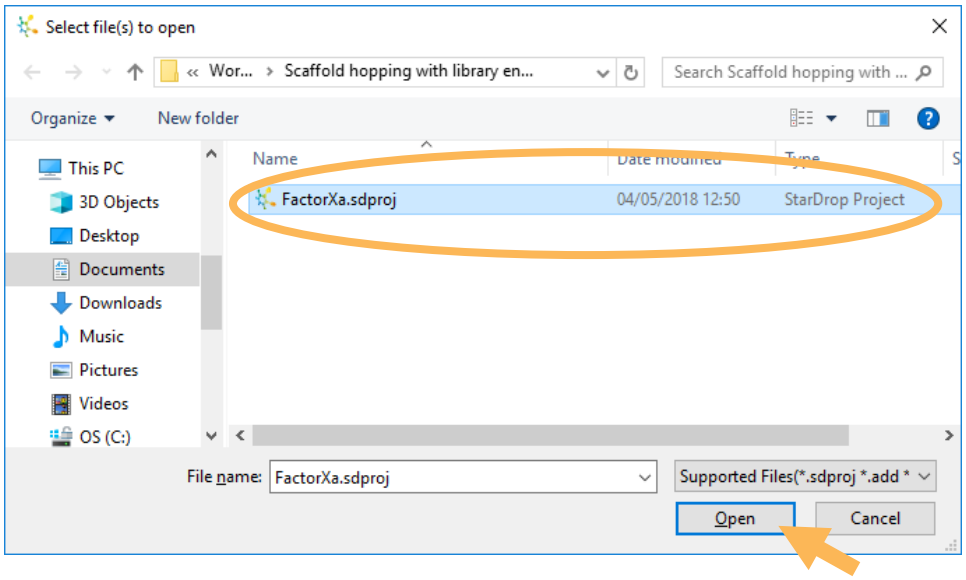


Worked Example:

Scaffold Hopping Using Virtual Library Enumeration

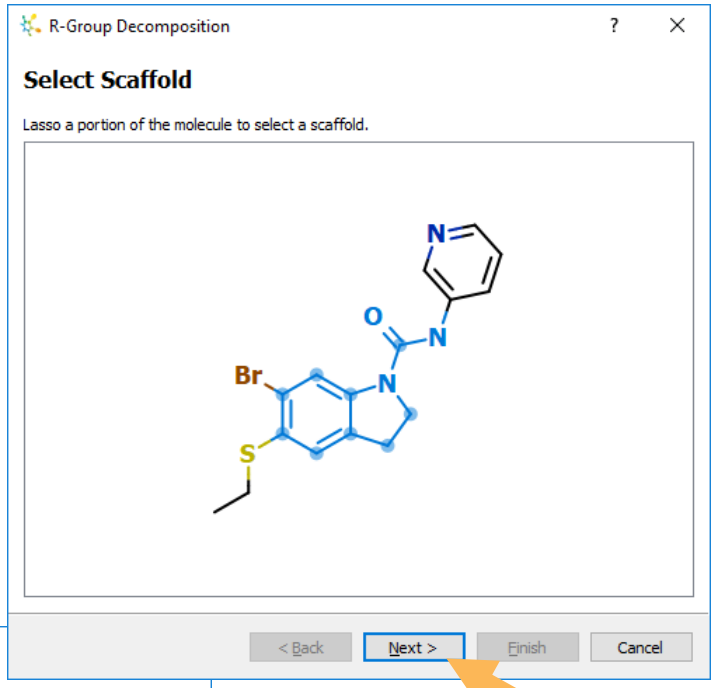
In this example we are going use the library enumeration feature in StarDrop's Nova module, in combination with R-group analysis, to generate a virtual library representing a potential new lead series. This will be based on a previous series and explore the impact of a change of scaffold and variations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

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

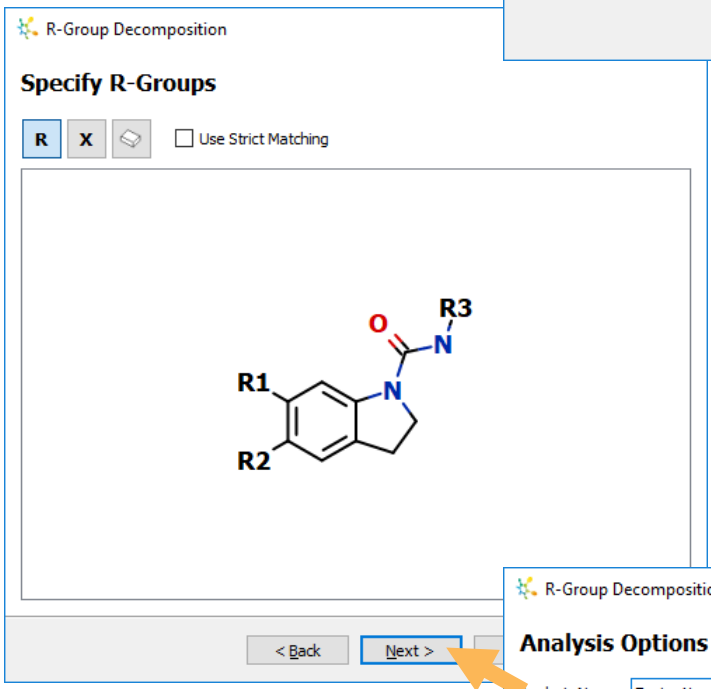


The project contains a series of 78 FactorXa inhibitors for which we have measured pK_i values. First, we'll perform an R-group decomposition of this series to generate some R-groups to substitute on a new scaffold.

- Select the first row in the data set and click the **R-group analysis button**  on the right-hand toolbar.

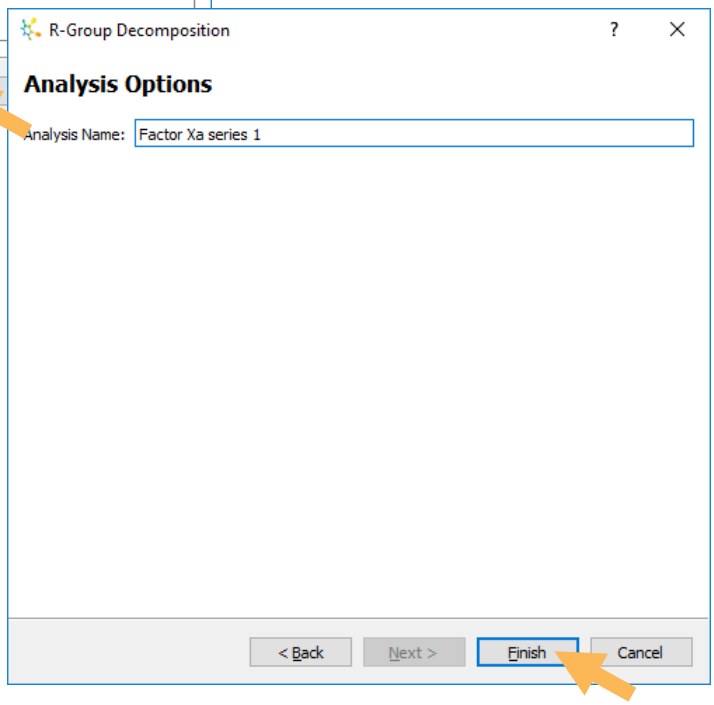


- On the **Select Scaffold** page of the **R-group Decomposition wizard** that appears, draw around the fixed scaffold for this series, as highlighted in blue in the screenshot to the right.



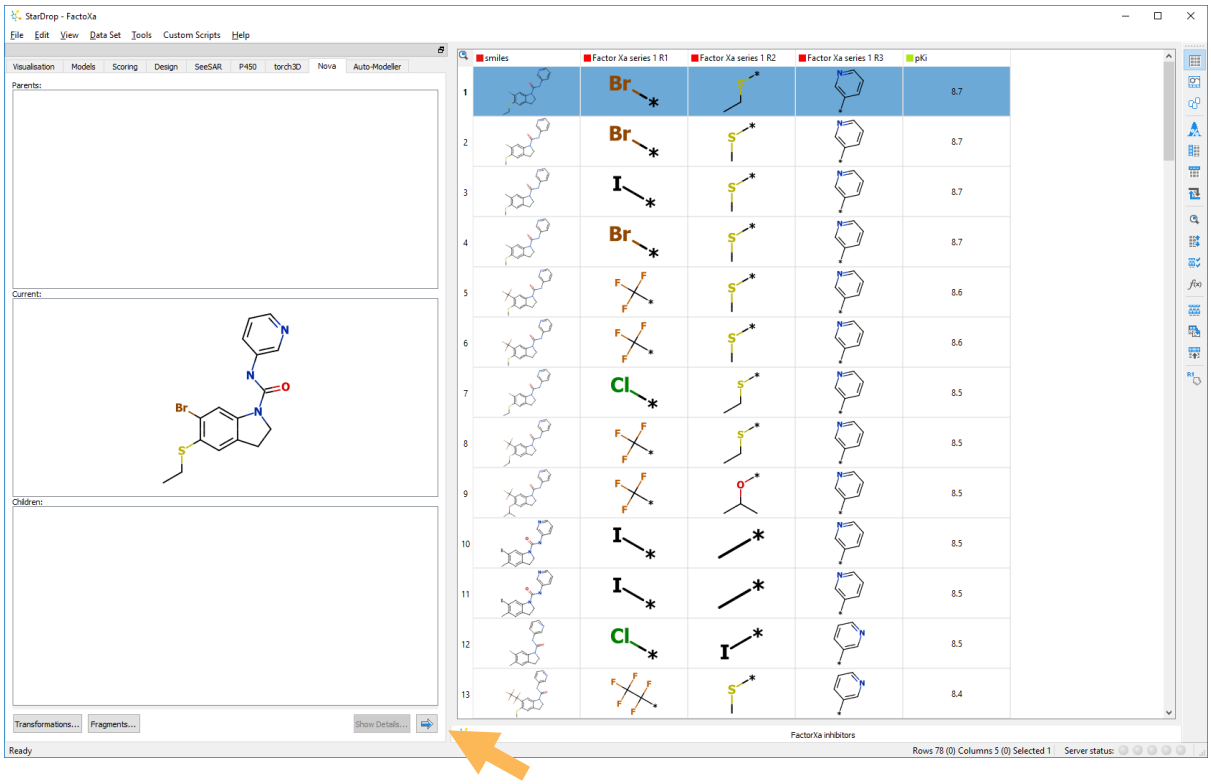
- Click **Next** to confirm that the correct substitution points for R-groups have been identified as shown in the screenshot to the left.

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



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

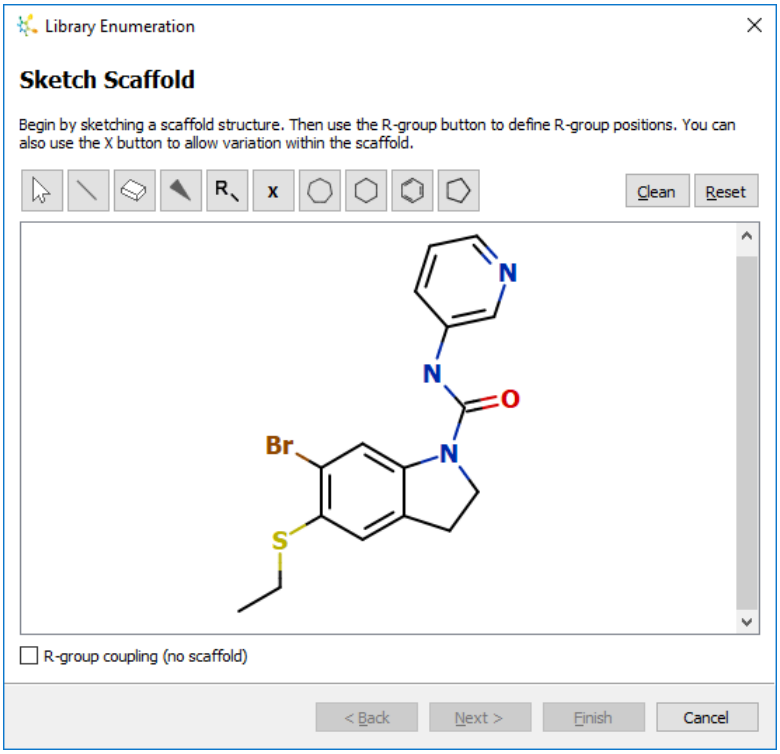
The resulting R-group decomposition will be shown in the data set as shown below.



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

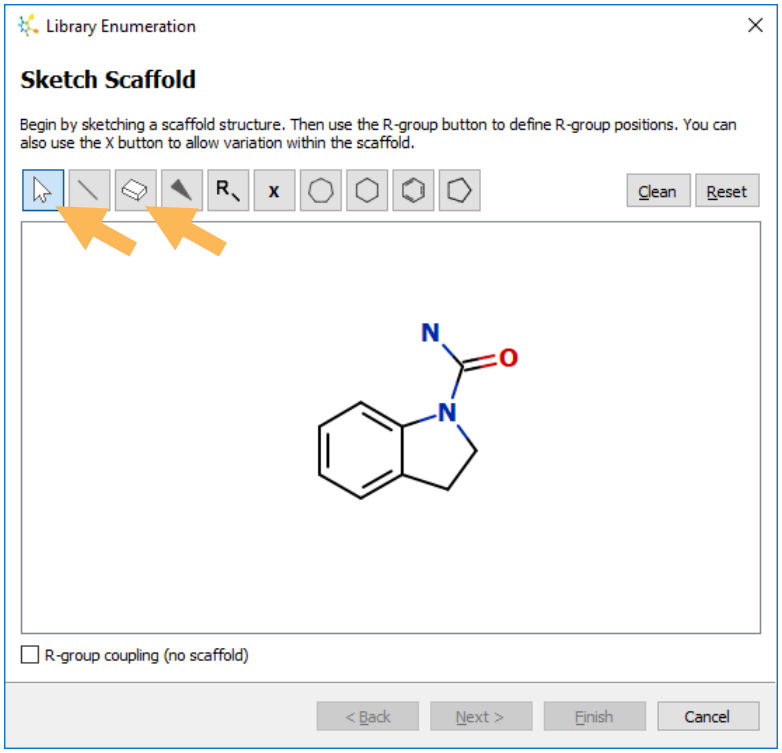
- With the first row of the data set still selected, click the  button at the bottom of the **Nova area** to start the enumeration. In the wizard that appears, select the **Library Enumeration** option and click **Next**.

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.



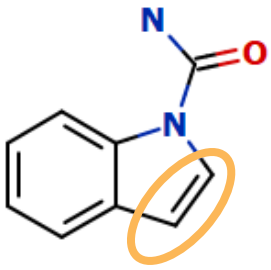
- Erase the groups at the substitution points to leave the scaffold shown to the right.

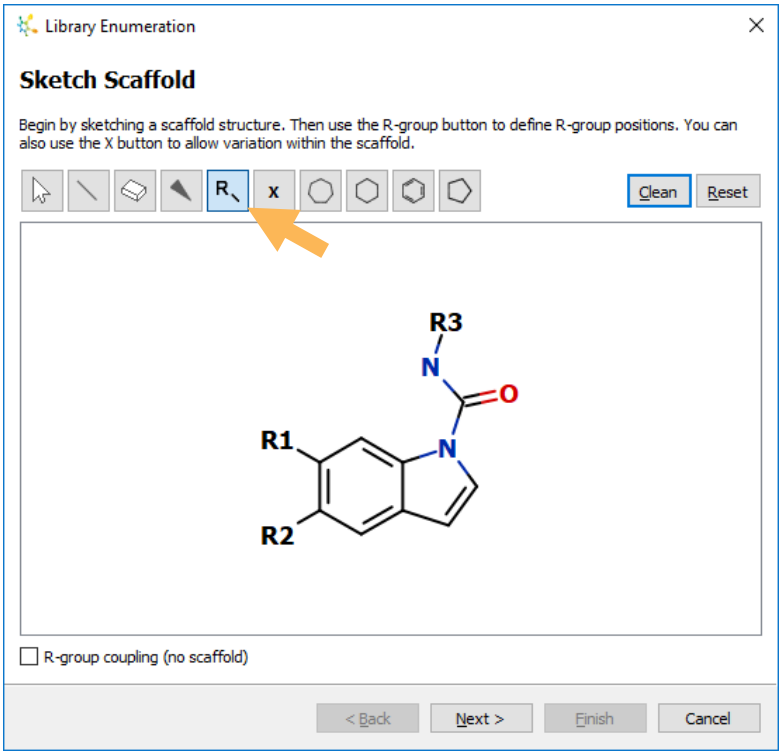
  Hint: you can use the **Erase tool**  to erase atoms or bonds or click the **Select tool**  and draw around the regions you wish to delete, clicking the **Delete key** to delete them from the structure.



- 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.

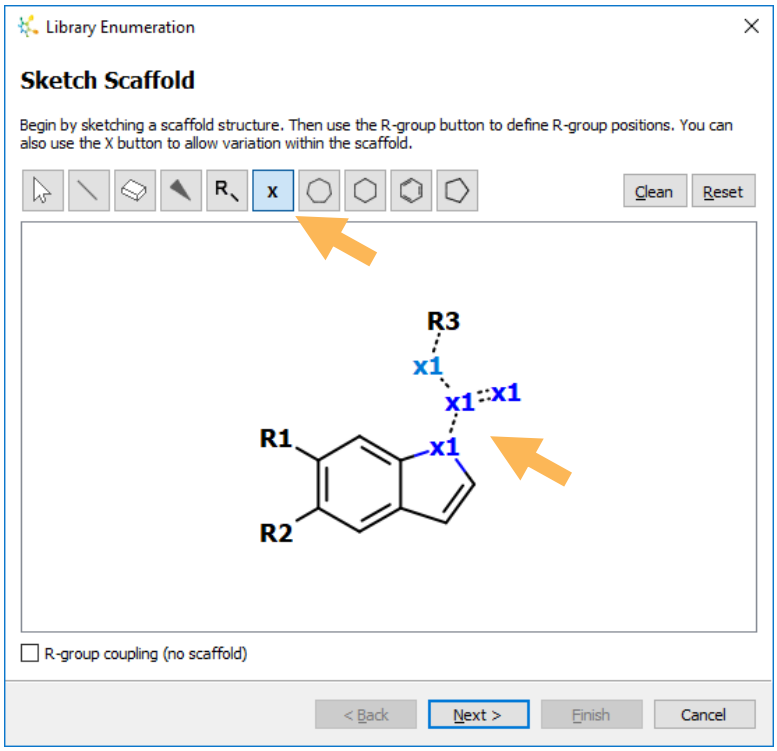




- Use the **R-group tool**  to add R-groups in the R1, R2 and R3 positions, as shown to the left, by clicking on the atom to which they should be connected.

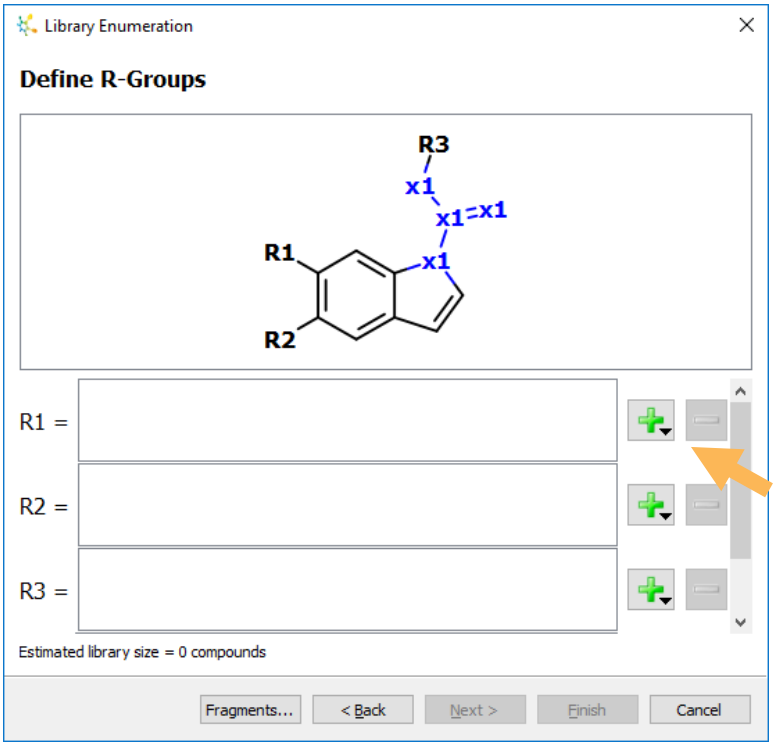
We will also define some variations in the scaffold, in this case to the linker between the core and R3.

- Using the **Variable atom tool**  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 **Next**.

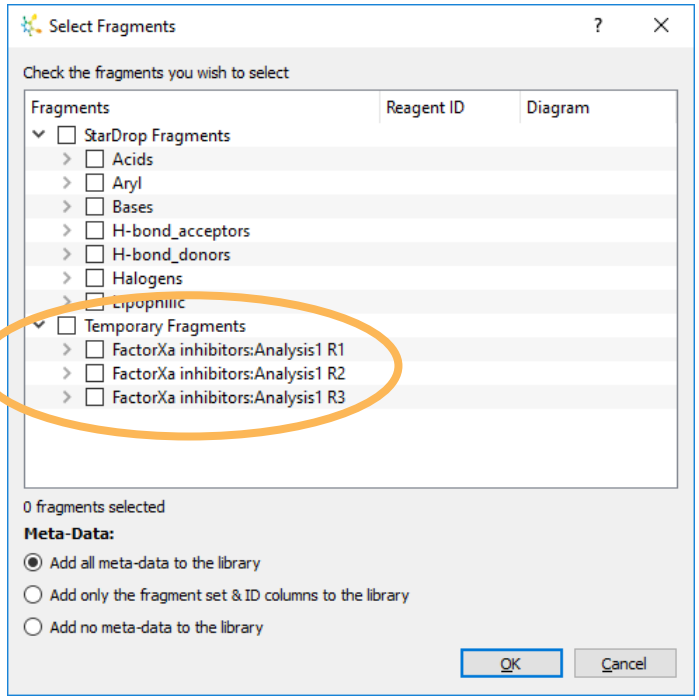


On the **Define R-Groups** page we can list the groups to substitute at each point.

- Click the **Add button**  next to **R1** and choose **Select** to open the library of pre-defined substituent groups.

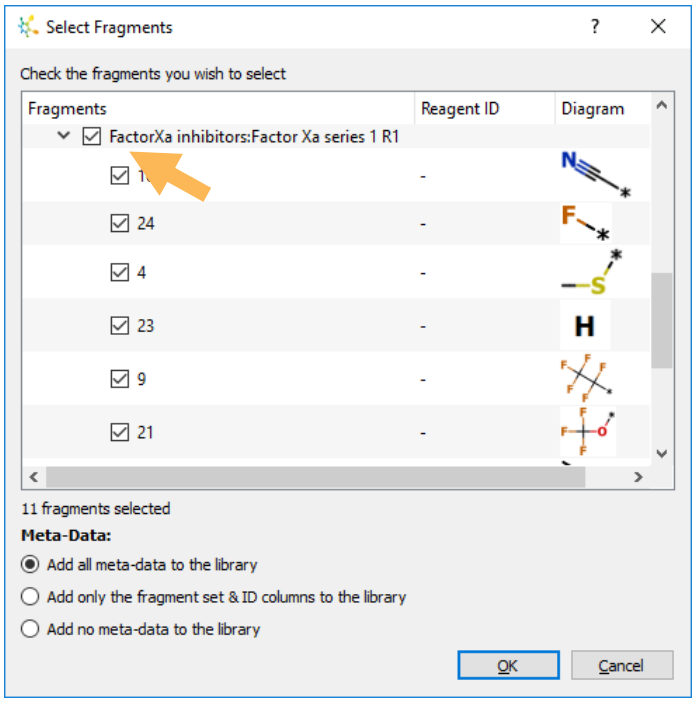


In the fragment library you will see that the groups derived from the R-group analysis of the original series are available at the bottom of the list. Clicking the arrow next to an entry will expand the list to show the individual substituent groups in that list.



The **Meta-Data** options below enable you to specify what, 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 **OK**.

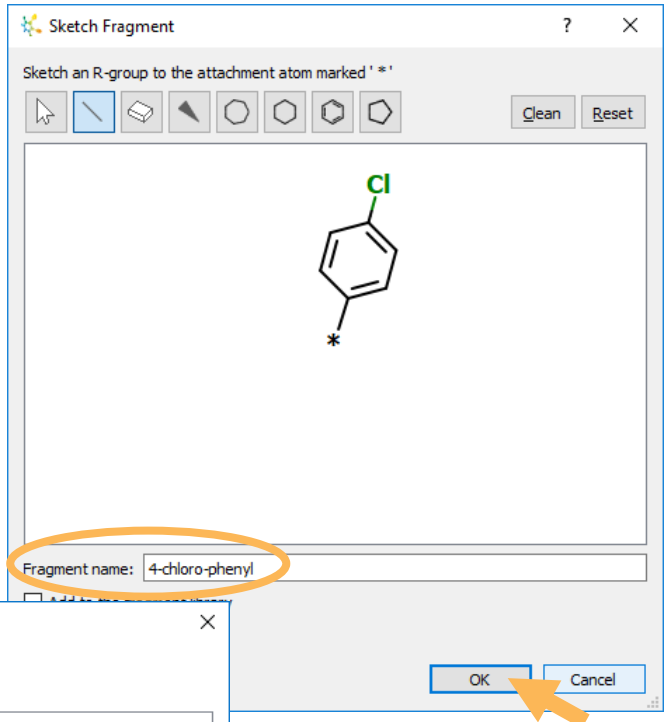


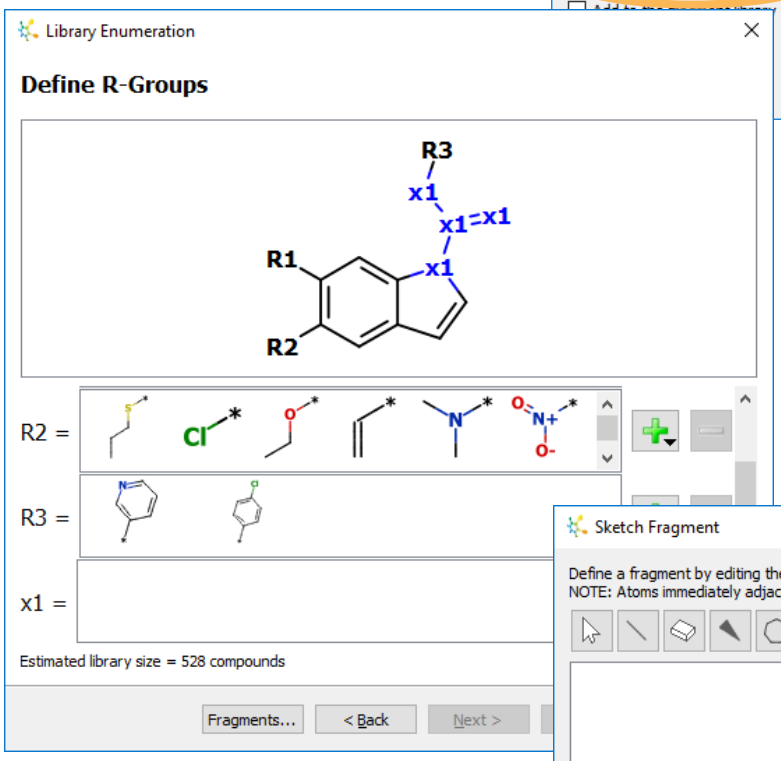
- Follow the same steps of each of R2 and R3, clicking the **Add button**  for each of them and selecting the appropriate R-groups from the library so that we can create a series based around the indole scaffold which has equivalent R-groups at each position.

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 **OK**.

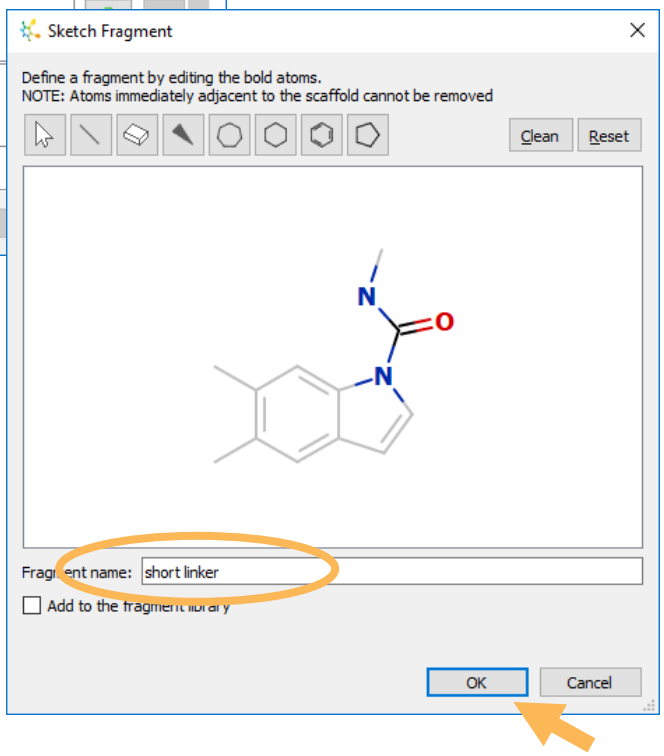
  Hint: The * indicates the attachment point of the R-group, so the fragment must link to this point.



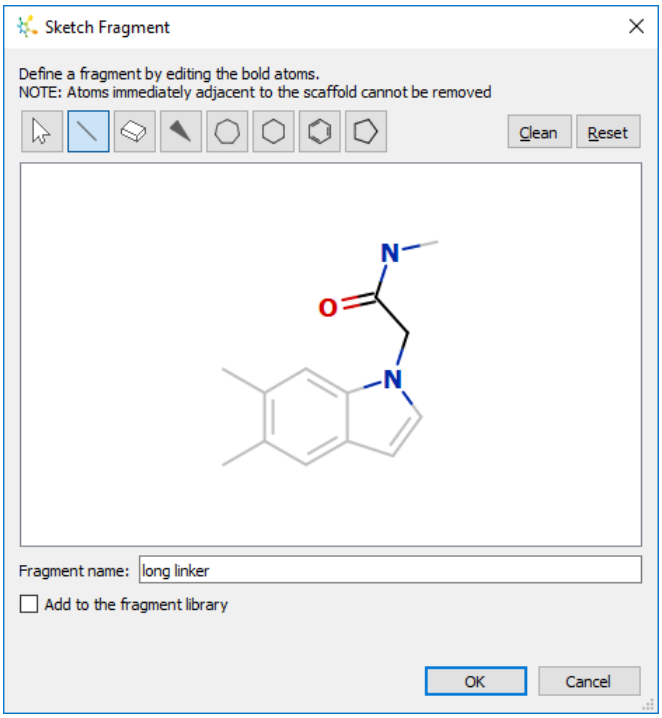


- Click the **Add button**  next to **X1** (you may need to scroll down through the list of points of variation) and choose **Sketch** to define the first X1 fragment.

- The fragment sketcher will show the original linker fragment from our starting compound so, to use this in our new series, click **OK** (you can give the fragment a name if you wish).



- Once again, click on the **Add button**  next to **X1** select **Sketch** to draw another fragment, in this case a longer linker as shown to the right. **Hint:** Erase the bond between the N and amide carbon and insert an additional methylene. Click **Clean** to normalise the bond angles and lengths.

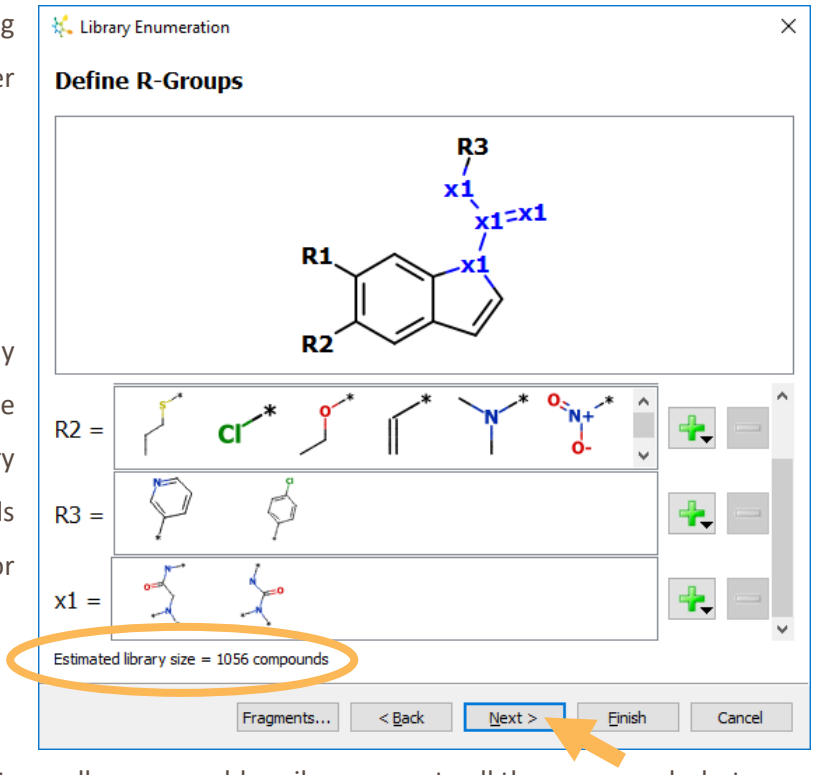


- Click **OK** to add this to the list of X1 linkers.

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

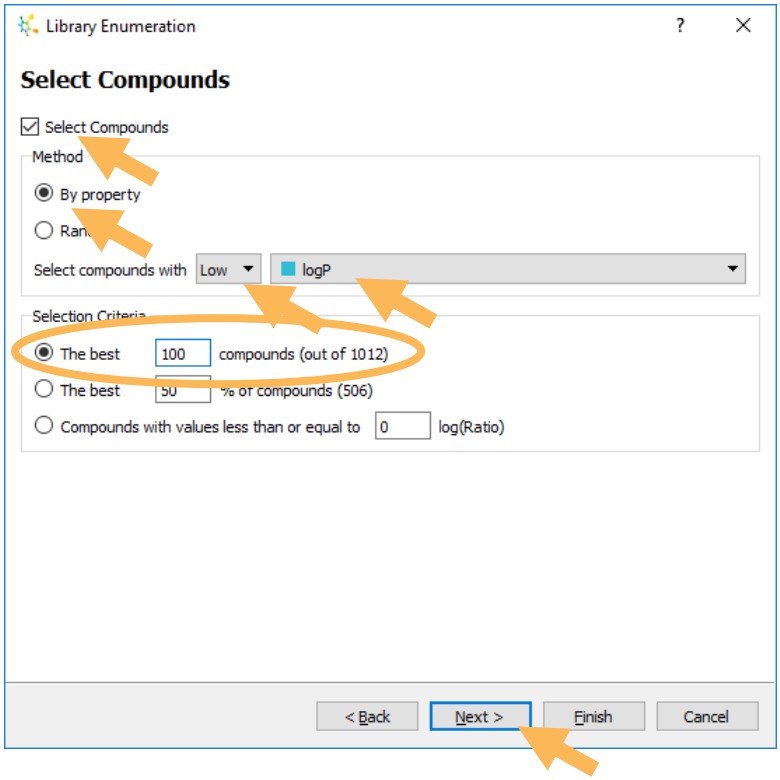
- Click **Next**.

If we wish, we 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 method **By property** and choose to select compounds with **Low logP**. Finally, choose to select **the best 100 compounds**, as shown to the right, and click **Next**.



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

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.