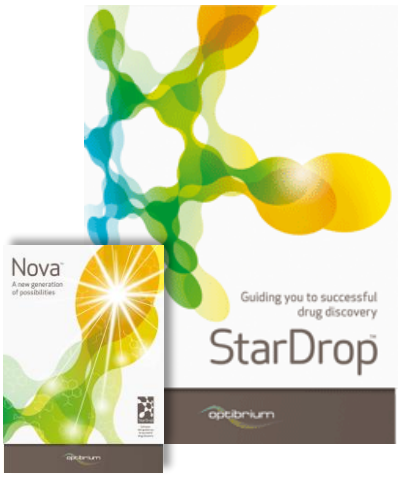


Worked Example:

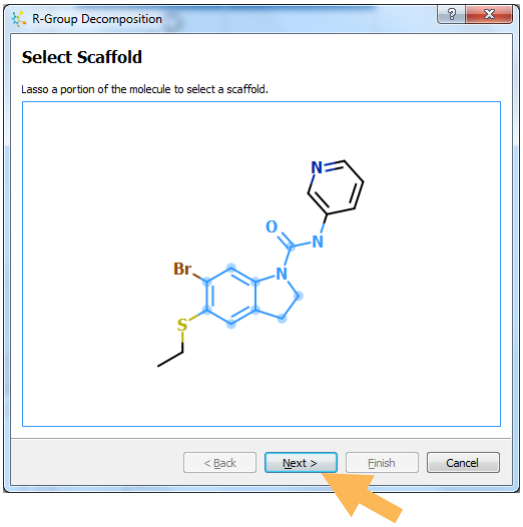
Scaffold Hopping Using Virtual Library Enumeration

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.

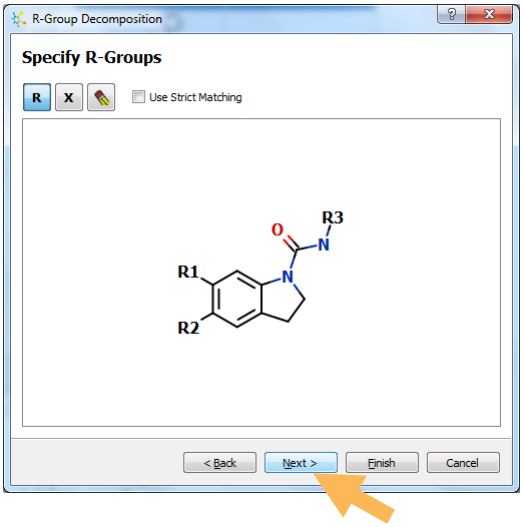
- Start StarDrop and go to the **Nova** tab.
- Load the accompanying file **FactorXa_inhibitors.add**

First, we'll perform an R-group decomposition of this series to generate some groups to substitute on a new scaffold.

- Select the first row in the data set and click the **R-group analysis tool** on the toolbar ().
- On the **Select Scaffold** page, draw around the fixed scaffold for this series, as highlighted in blue in the screenshot to the right:

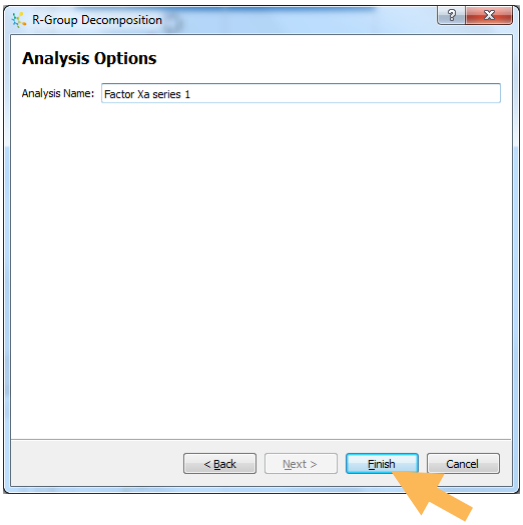


- Click **Next** to confirm that the correct substitution points for R-groups have been identified as shown in the screenshot to the right:

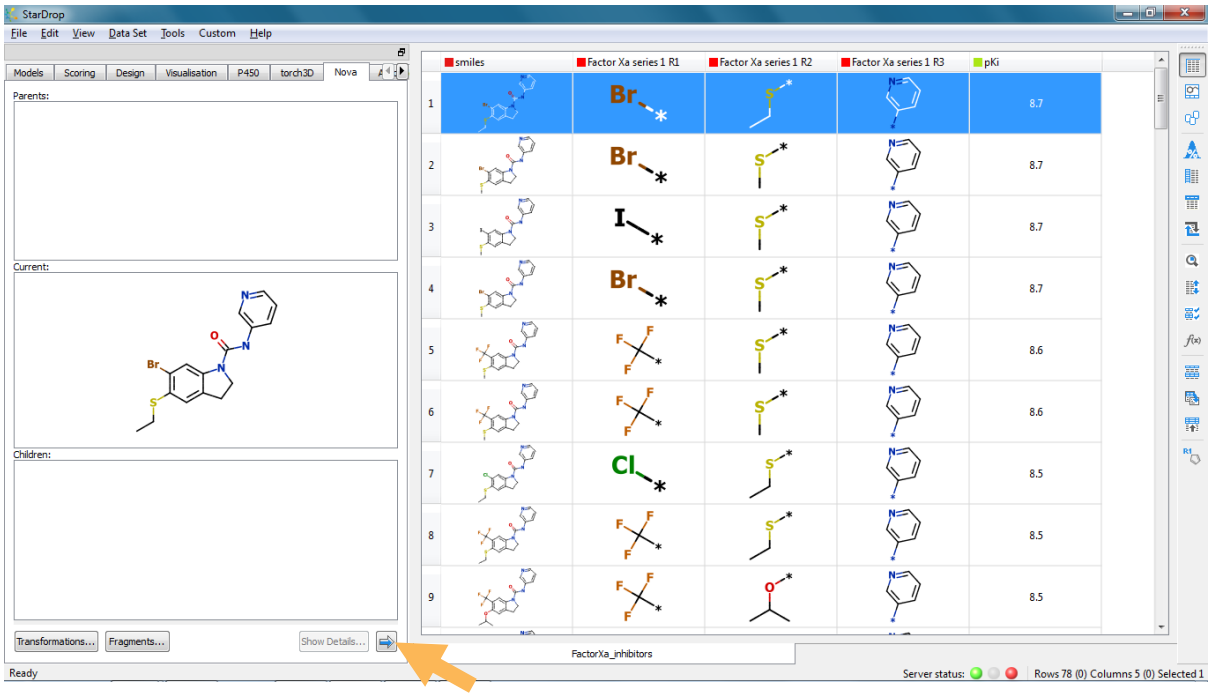


- We do not want to specify any further substitution points or variable atoms, so click **Next**

- 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 analysis.



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



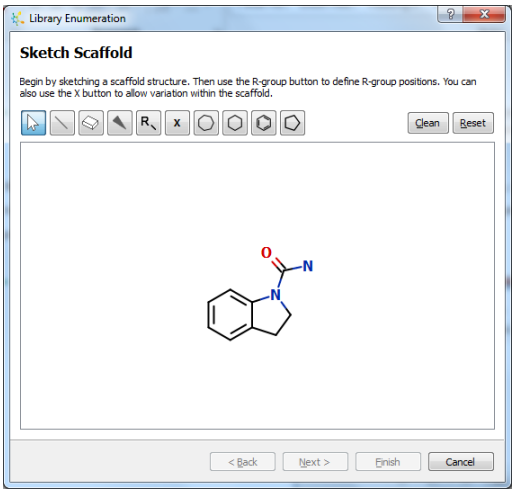
Now, we are going to enumerate a new virtual library for a similar series based on an indole core.

- Select the first row in the data set and click the  button on the **Nova** tab to start the enumeration. In the wizard window 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.

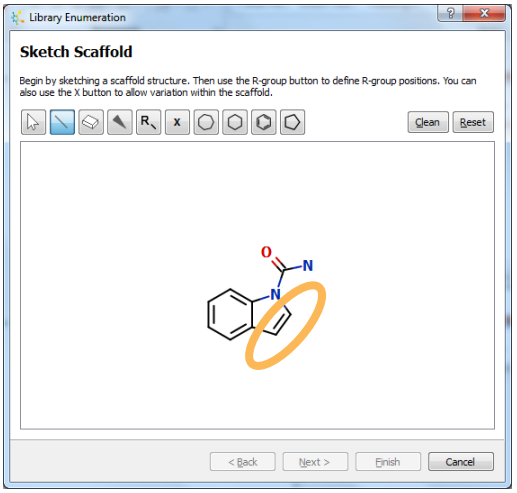
- Erase the groups at the substitution points to leave the scaffold shown to the right.

  Hint: you can use the  button to erase atoms or bonds, or select the  tool, draw around the regions you wish to delete and click **DEL** to delete them from the structure.

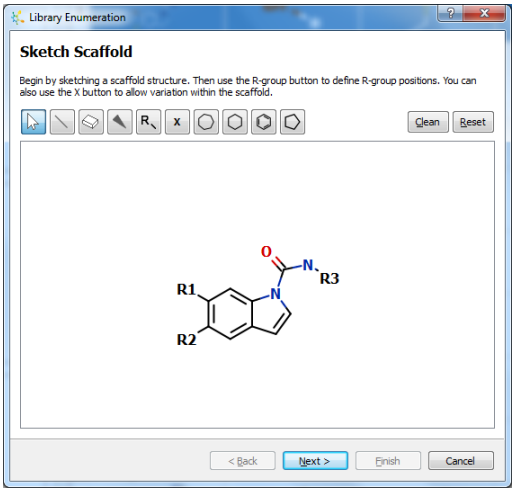


- Modify the core of the original series to change it into an indole, as shown to the right.

  Hint: Select the bond tool () and click on the bond highlighted on the right to change from single to double.

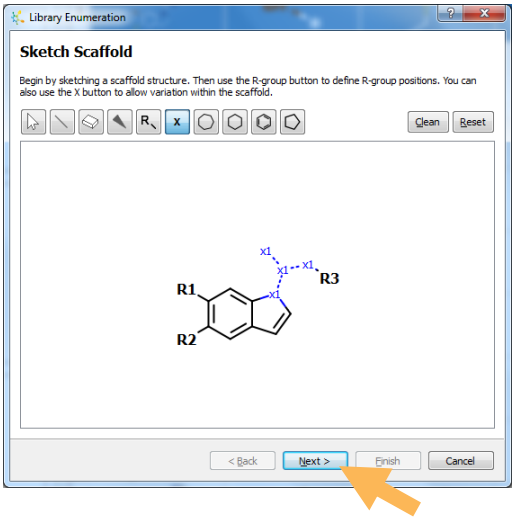


- Use the  button to add R-groups in the R1, R2 and R3 positions, as shown to the right, by clicking on the atom to which they should be connected:



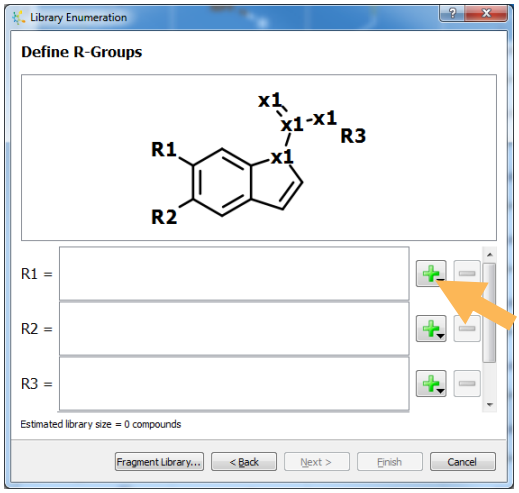
We will also define some variations in the scaffold, in this case to the linker between the core and R3.

- Using the  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**.

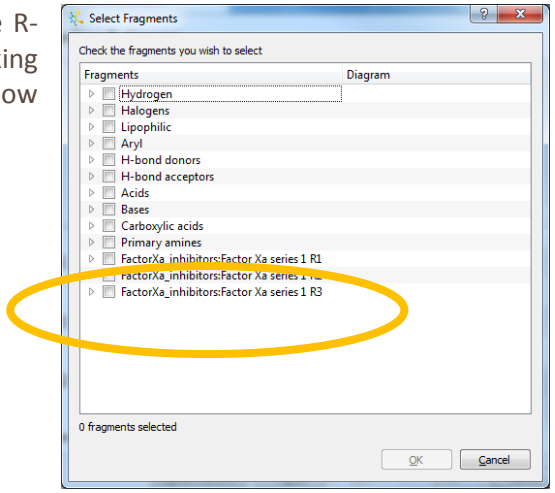


On the **Define R-Groups** page (shown right) we can list the groups to substitute at each point.

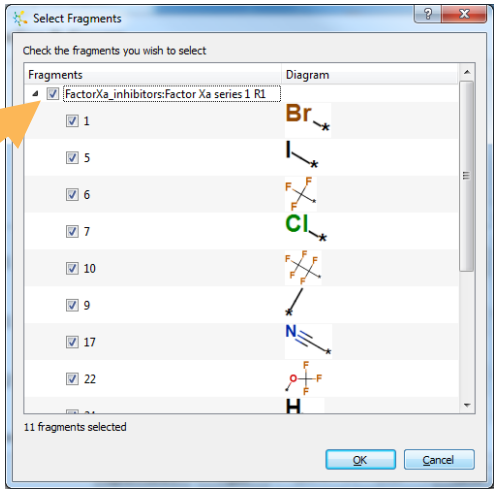
- Click the  button next to **R1** and choose the **Select…** option to open the library of pre-defined substituent groups.



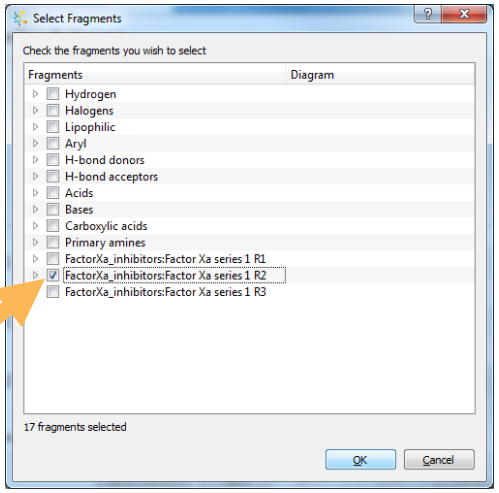
In this, you will see that the groups derived from the R-group analysis of the original series are available. Clicking the arrow next to an entry will expand the list to show the individual substituent groups in that list.



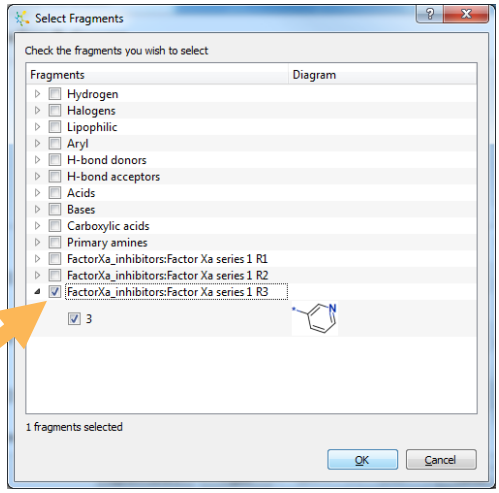
- Tick the box next to the list of R1 groups from the original series to select all of the same groups for this position and click **OK**.



- Click the  button next to **R2**, choose **Select…** and select the list of R2 groups from the original series. Click **OK** to return to the **Define R-Group** page.

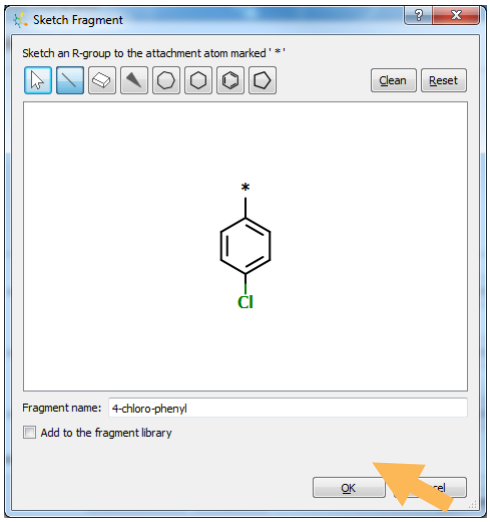


- Click the  button next to **R3**, choose **Select…** and select the one group at this position from the original series. Click **OK** to return to the **Define R-Groups** page.

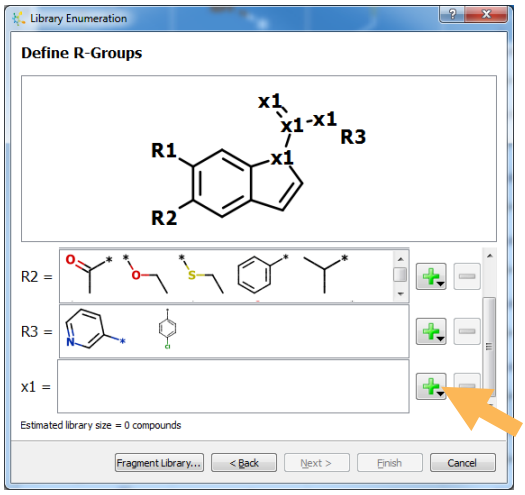


We will now sketch an additional substituent for the R3 position.

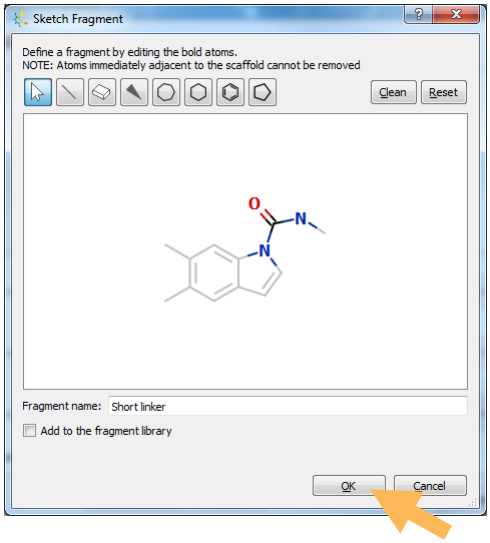
- Click the  button next to **R3**, and choose the **Sketch…** menu option.
- Draw a 4-chloro-phenyl as shown to the right and click **OK**.
  Hint: The * indicates the attachment point of the R-group, so the fragment must link to this point.



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

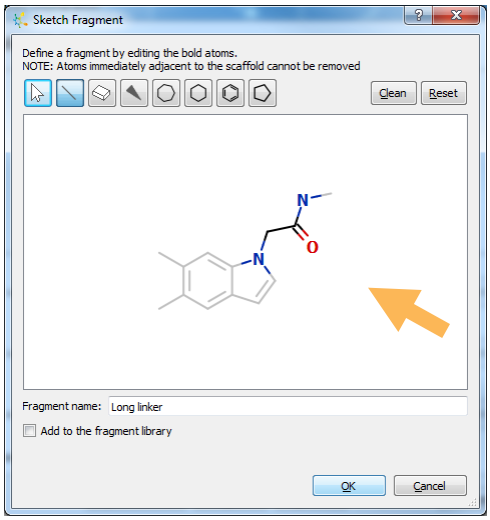


- In the fragment sketcher, click **OK** to add the same linker as in the previous series to the list (you can give the fragment a name if you wish).



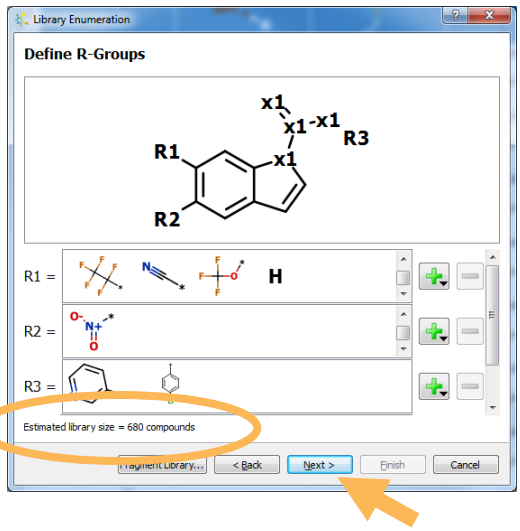
- Once again, click on the  button next to the **X1** box and select the **Sketch…** option to draw a different fragment, in this case a longer linker as shown to the right.
  Hint: Erase the bond between the N and amide carbon and insert an additional methylene. Click **Clean** to normalise the bond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

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



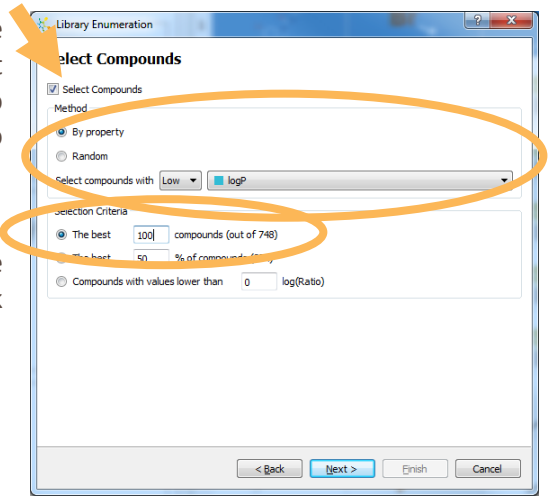
You should see that the resulting library is estimated to contain 680 compounds.

- Click Next.



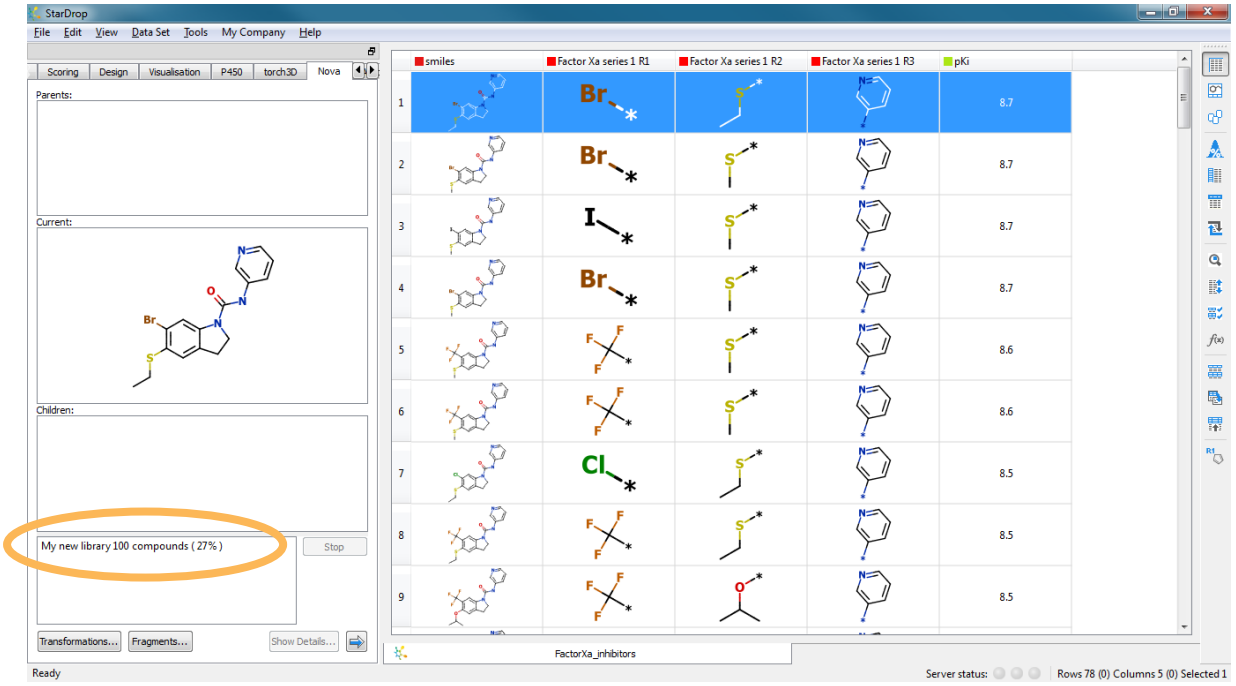
If we wish, we can automatically calculate the properties of the compounds in the resulting library and select a subset of compounds according to a given property or score. In this case the library will be quite small, so we could easily enumerate all of the compounds, but as an example we will select the 100 compounds with the lowest predicted logP for further analysis.

- Tick the **Select Compounds** box, 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**.

An indicator will show the progress as the library is enumerated, the logP is calculated and the compounds selected:



When complete, the resulting library will appear in StarDrop and all of StarDrop's capabilities can be used to select compounds or consider further improvements.


StarDrop
File Edit View Data Set Tools My Company Help
Models Scoring Design Visualisation P450 torch3D Nova Auto-Modeller
logP
Number of compounds
logP
Data Set Colour Size
My new library logP
Plot Customise Filters
X: logP
Y: <None>
Trellis: <None>
Ready
Structure logP R1 R2 R3
46 2.463 H
47 2.445 Cl
48 2.437 H
49 2.423
My new library
R1
R2
Br Cl H I F