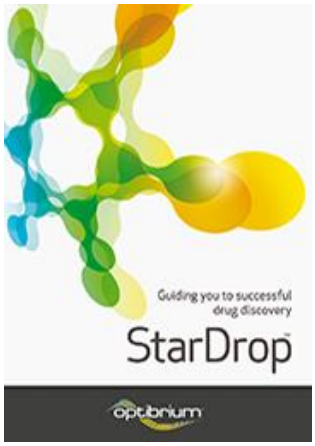
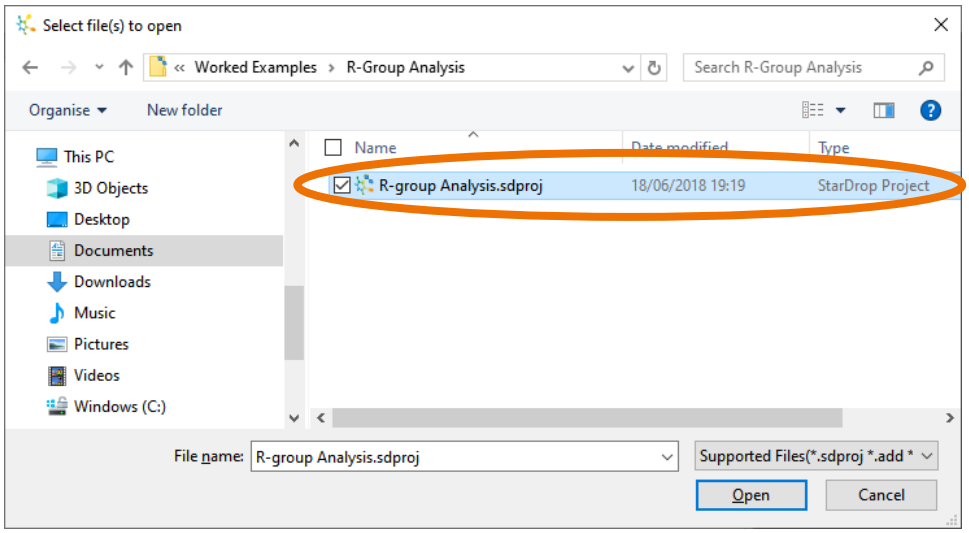


Worked Example:

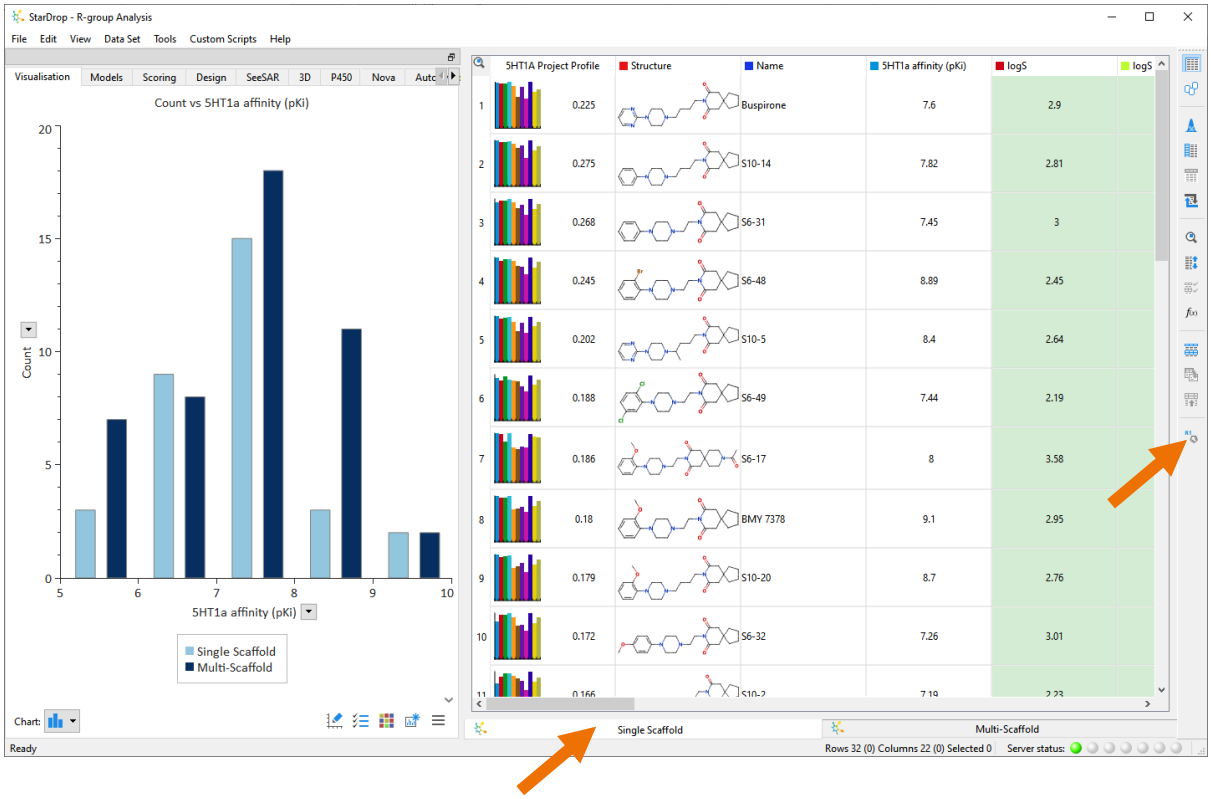
R-group Analysis

In this example, we are going to take a look at an R-group analysis of two data sets to identify functionalities influencing potency. The first data set contains Buspirone and some close analogues based on a common scaffold. In the second data set, there are different series based around multiple scaffolds, where the substitution points are equivalent because they share a similar binding pose.

- In StarDrop™, open the file **R-Group Analysis.sdproj** by selecting **Open** from the **File** menu.

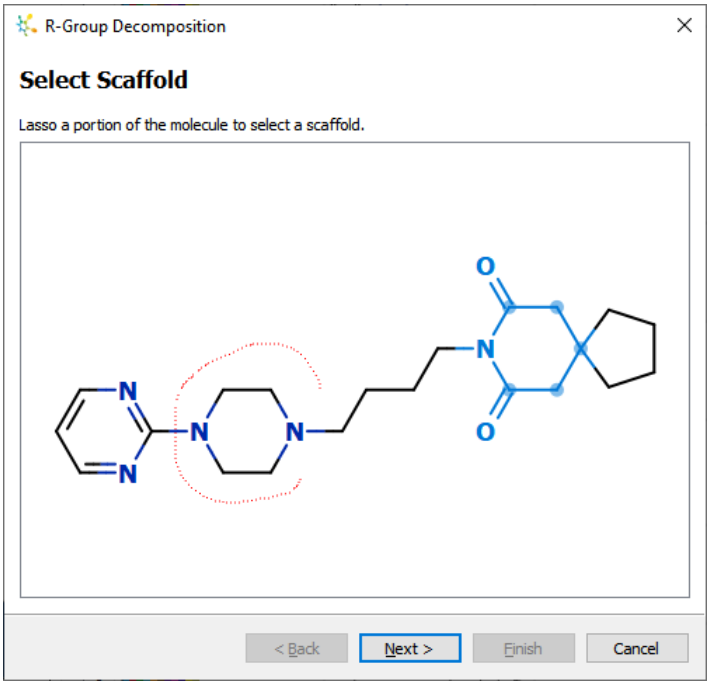


The project contains two data sets, each of which you can view by clicking on the tabs at the bottom. It also shows a histogram giving a quick overview of the distribution of potency data in each set.



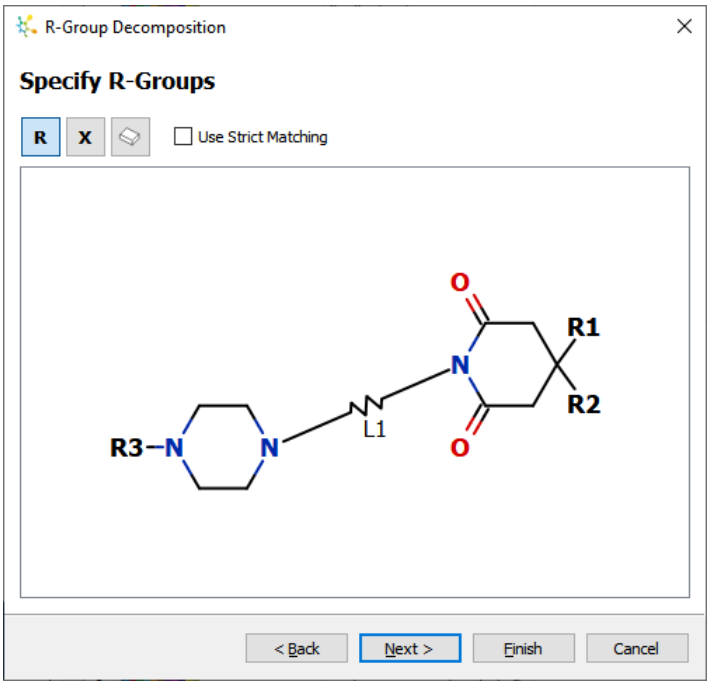
- Select the first row (Buspirone) in the first dataset (Single Scaffold) and start the R-group decomposition wizard by clicking the **R-group Decomposition** button  on the right-hand toolbar (it is also available from the **Tools** menu).

The selected molecule is displayed in the wizard so that you can now choose which regions of the molecule make up the scaffold.



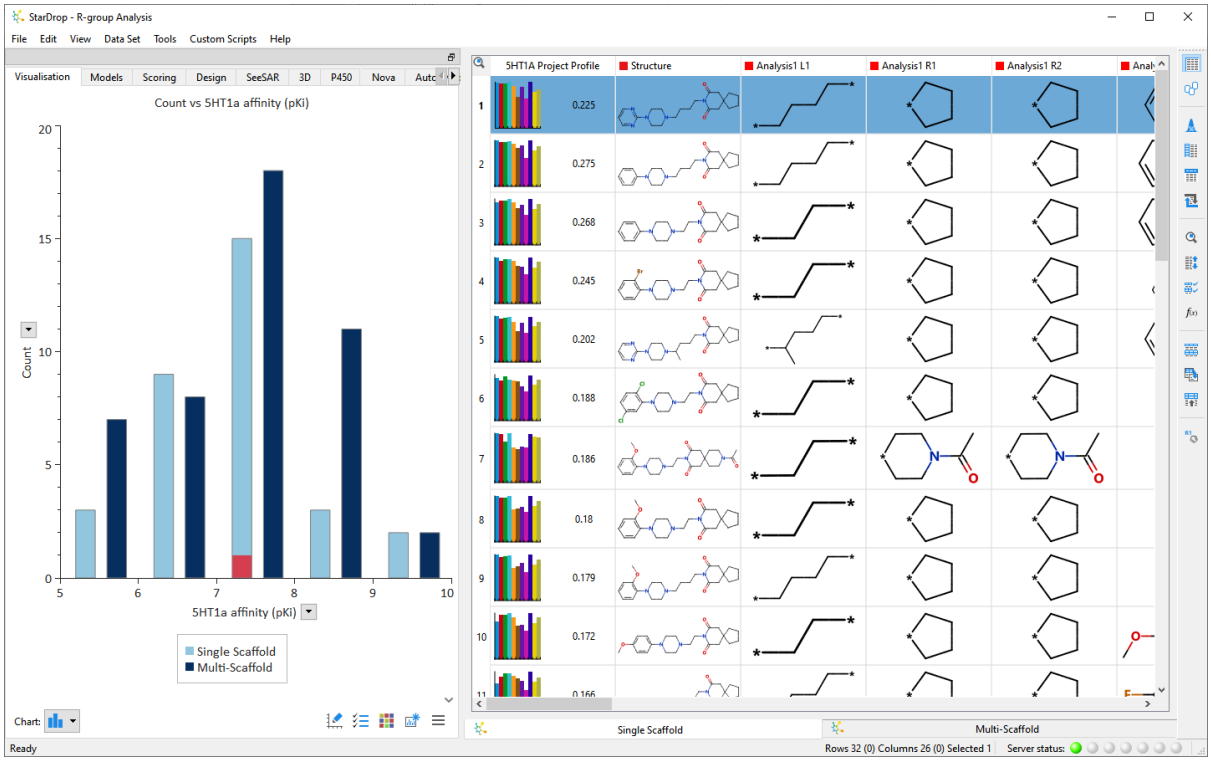
- Select the piperazine and piperidinedione rings (as shown in the screenshot to the right) by drawing around them with the mouse, holding down the **Ctrl** key in Windows or **Command** key on macOS to select a second region.

- Click the **Next** button to confirm the R-groups that will be analysed. In this example, because we selected two separate regions, the connecting functionalities will be considered as variations in linkers.



Note that you can add R-groups by clicking the **R-group** button R and then clicking at the point on the scaffold where they should be analysed. If you wish to specify variable atoms or fragments, click the **Variable Atom** button X and then select atoms on the scaffold, which may vary between the compounds being analysed. In this case, no additional R-groups, variable atoms or fragments are required.

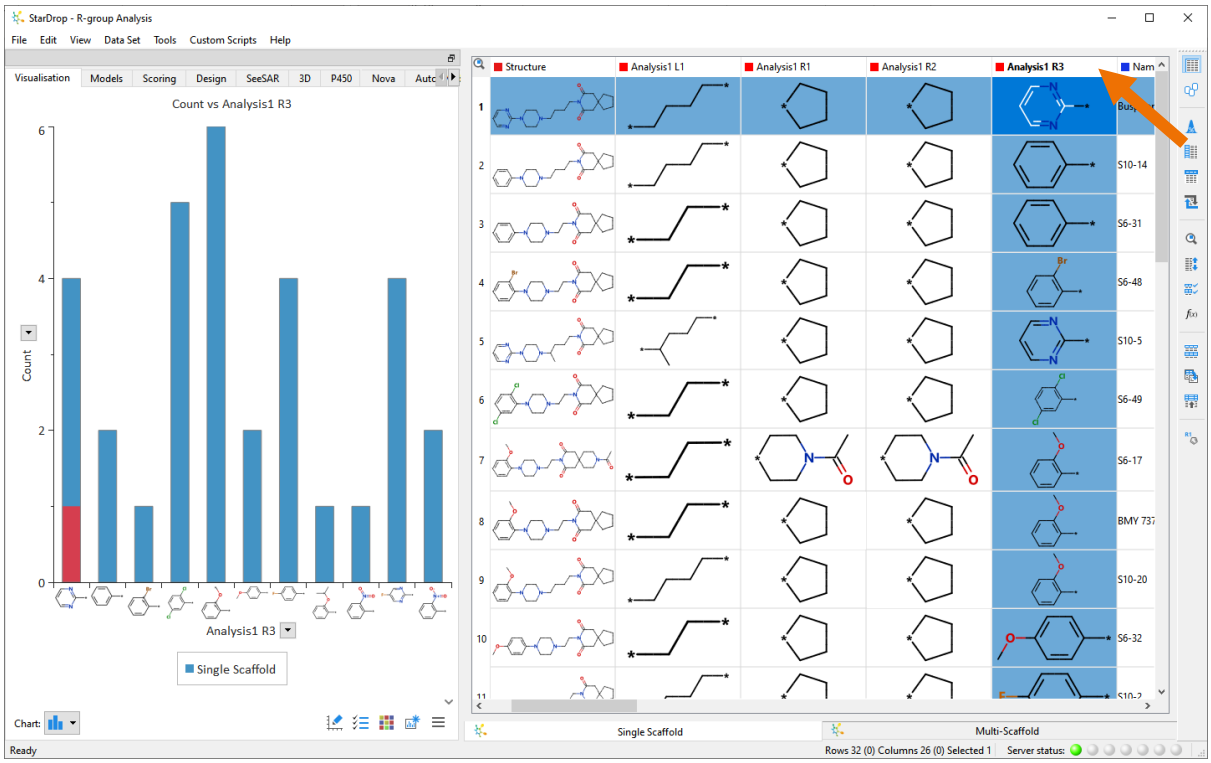
- Click the **Finish** button, and new columns will be added to the data set indicating the R-groups and linkers that have been found for each compound.



- Hover the mouse over an R-group to see a pop-up of the scaffold. To keep a scaffold window open, right-click on the R-group column header and choose **View Scaffold**. This window can be docked above the main StarDrop tabs.

In the **Visualisation** area, you can create charts to analyse the SAR in the series.

- Click on the header of the column **Analysis1 R3** in the data set to select it.

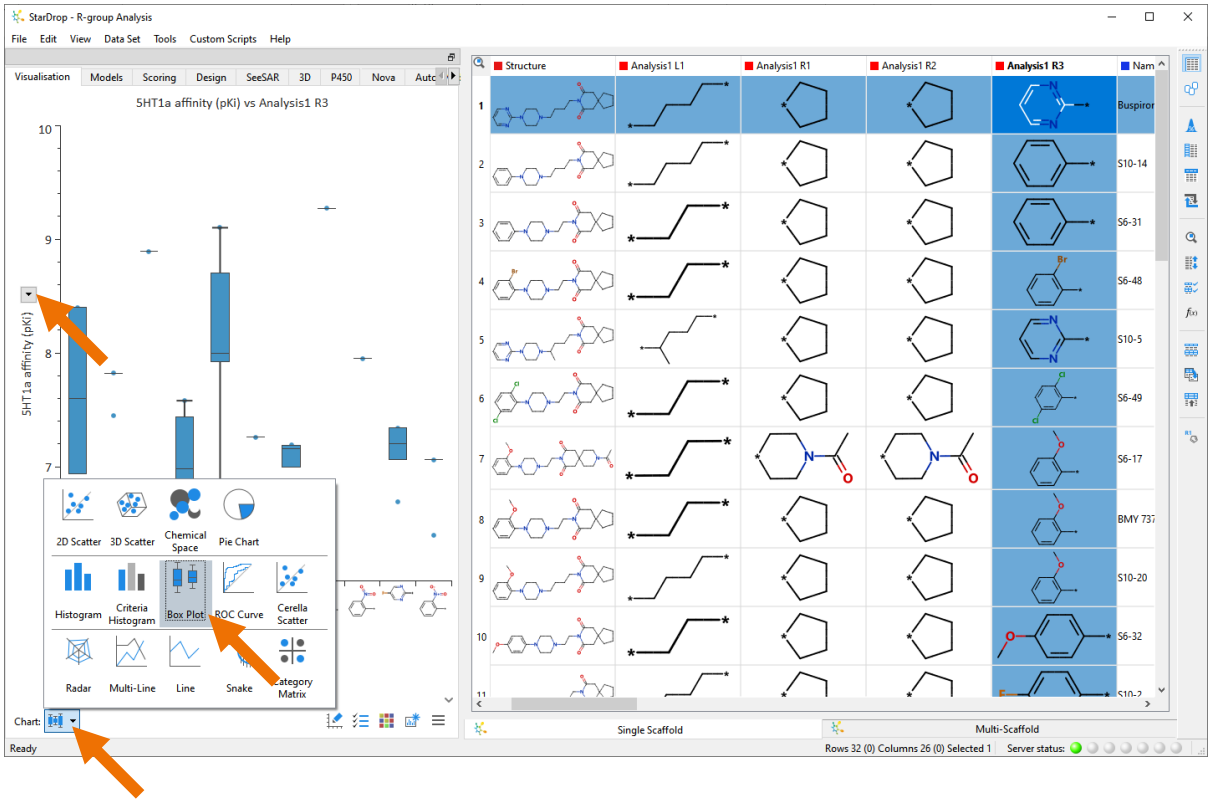


A histogram will be displayed showing the number of compounds with each group at position R3. Pointing at the picture of an R-group on the axis will pop up a larger version.

Other data can be plotted on the y-axis, and other chart types can be used to see more detailed information.

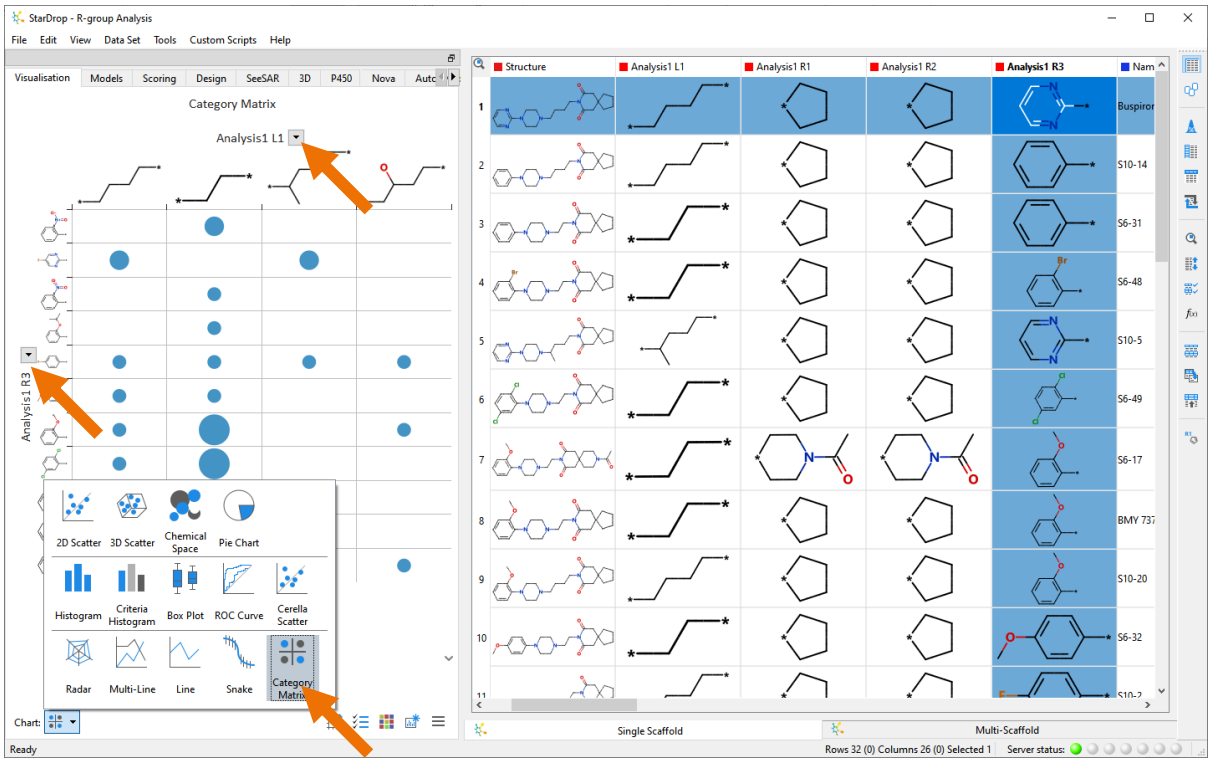
- From the **Chart** menu at the bottom of the Visualisation area, select **Box Plot**.
- On the y-axis, use the drop-down menu to change the property to **5HT affinity (pKi)**.

This enables us to see the distribution of potency data associated with each R-group.



To analyse the properties associated with combinations of R-groups, we can create an SAR table.

- From the **Chart** menu again, select **Category Matrix** and choose **Analysis1 R3** for the y-axis and **Analysis1 L1** for the x-axis.

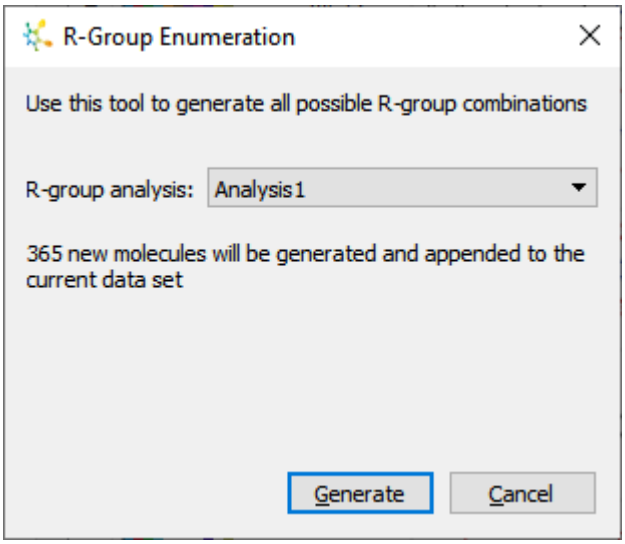


By default, this will show pie charts where the size indicates the number of compounds represented.

- Change the display to show a heatmap using the menu below the chart.
- Click the **Format** button at the bottom of the Visualisation area and choose to **Colour by** the property **5HT1a Affinity (pKi)**.

If you use the default colours, the cells with the highest average pKis will be highlighted yellow and the lowest red. The different types of charts that you show in each cell enable additional formatting options such as using size, symbols or borders to represent other properties.

Finally, StarDrop can 'fill in' the missing combinations of R-groups and linkers not present in the series, helping to explore other, potentially interesting, compounds.

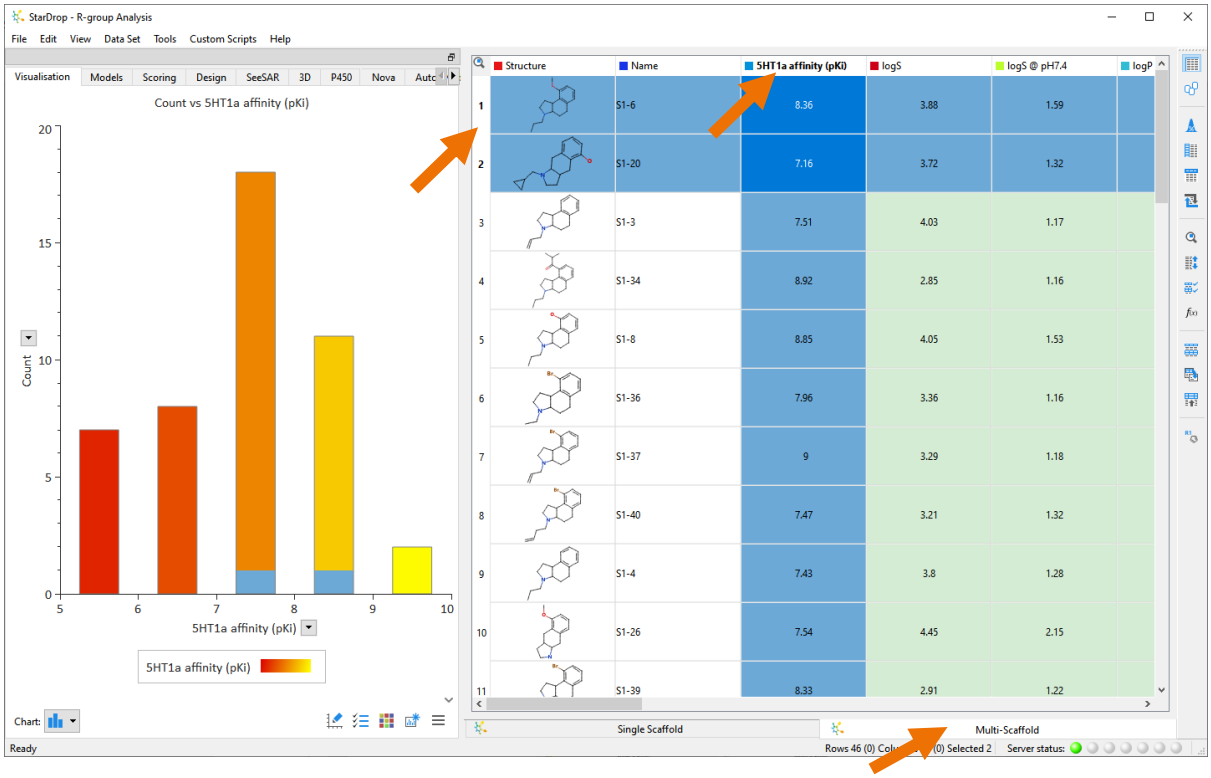


- Right-click on one of the R-group column headers and choose **R-Group Enumeration** from the menu.
- Click the **Generate** button, and the new compounds will be added to the data set and any visualisations you have created, with their predicted properties automatically calculated.

Multi-scaffold R-group Analysis

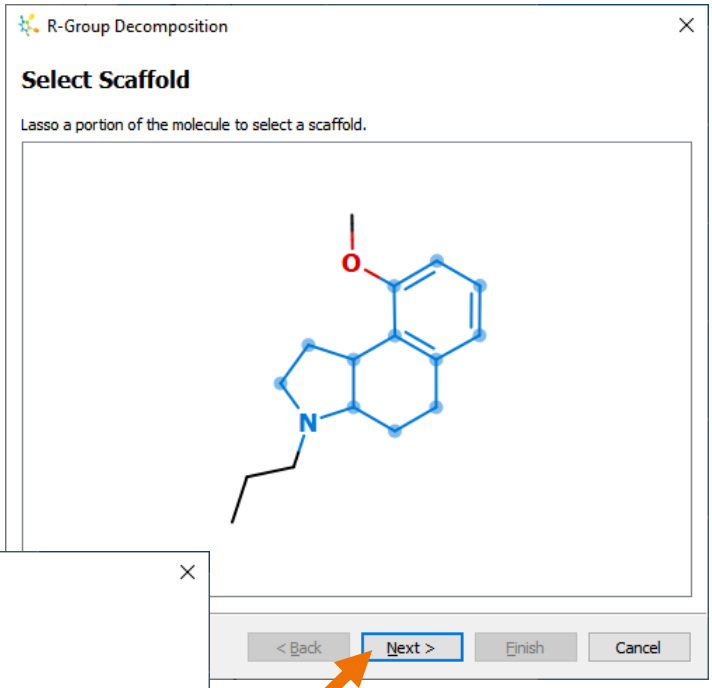
In the second data set in this project, called **Multi-Scaffold**, we have different series based around multiple scaffolds, where the substitution points are equivalent because they share a similar binding pose. We would like to identify common patterns for substitutions at equivalent positions or look for the effect of the core replacements on compound properties. This example will show how multi-scaffold R-group analysis can be performed in StarDrop.

- Change to the **Multi-Scaffold** data set by clicking on the tab at the bottom of the data sets and select the column called **5HT1a affinity (pKi)**.
- Select the first two rows (holding down the **Ctrl** key on Windows or Command key on macOS to select the second) and note that they are based on similar scaffolds with equivalent substitution points.

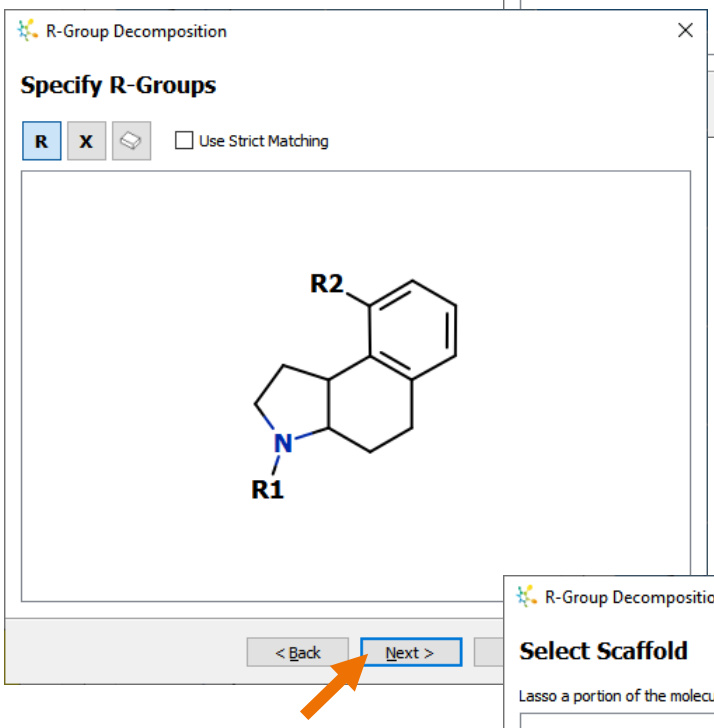


- As before, click the clicking the **R-group Decomposition** button  on the right-hand toolbar to start the **R-Group Decomposition** wizard.

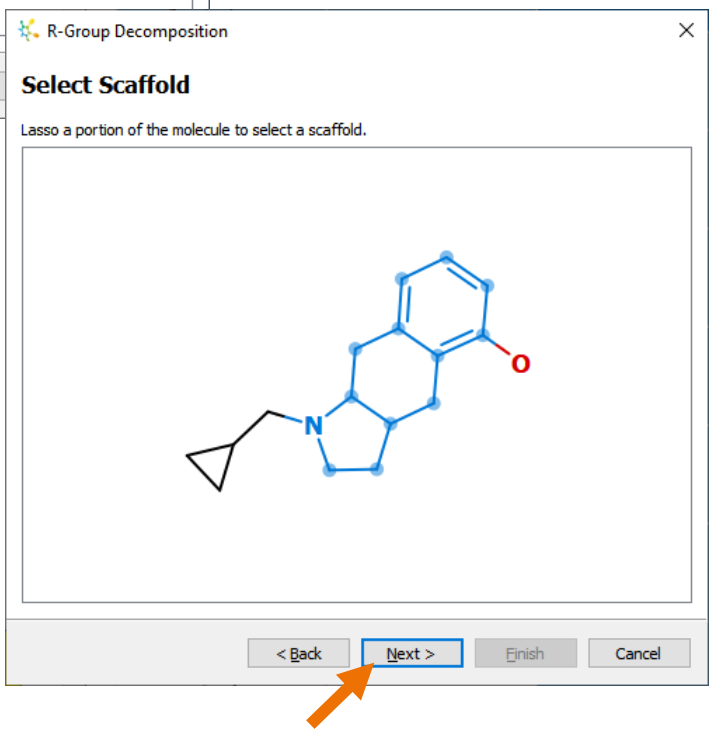
- The first compound will be shown on the **Select Scaffold** page of the wizard. Draw around the fused ring system to define this as the first scaffold (which will be highlighted in blue, as shown right) and click the **Next** button.



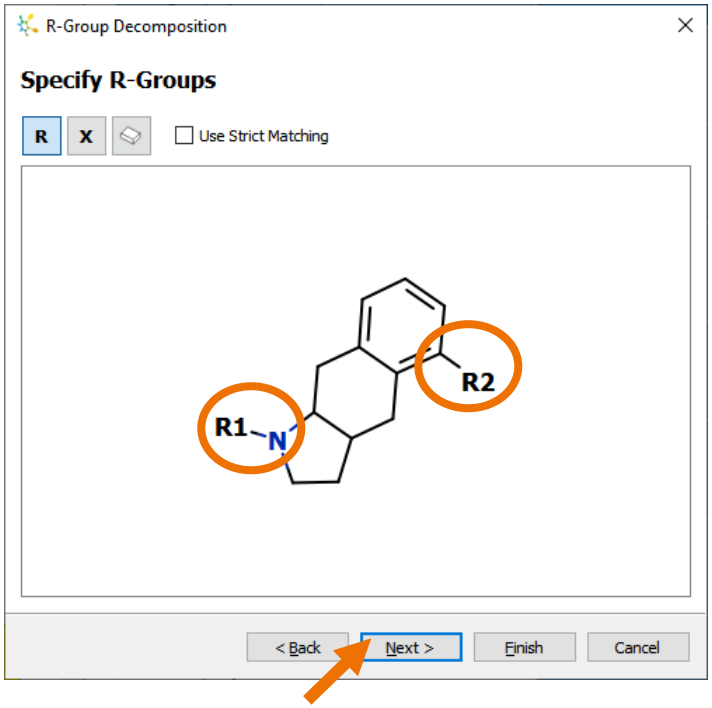
- The **Specify R-Groups** page will automatically show groups R1 and R2 at the substitution points for the selected compounds, as shown right. We do not need to add any other points of variation, so click the **Next** button again.



- The **Select Scaffold** page will now be shown again, this time displaying the second compound. Again, draw around the fused ring system to define the second scaffold as highlighted in blue to the right. Click the **Next** button to define the R-groups for this scaffold.

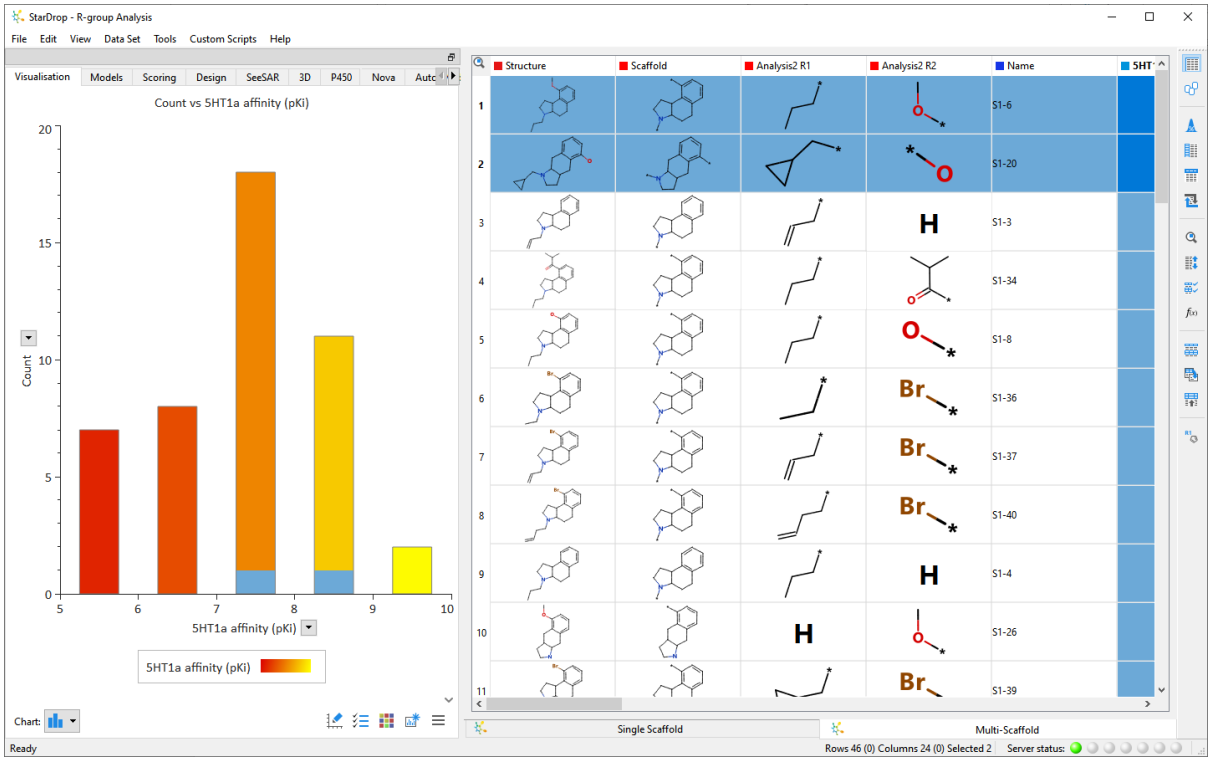


- The **Specify R-groups** page will be shown again for this scaffold. In this case, it is important to ensure that the groups at equivalent positions in each scaffold have the same label (R1 and R2). If it is necessary to change the defaults, you can edit them simply by clicking on the label (using the R button). Please ensure that the R1 and R2 labels are in the positions shown to the right. Again, click the **Next** button.



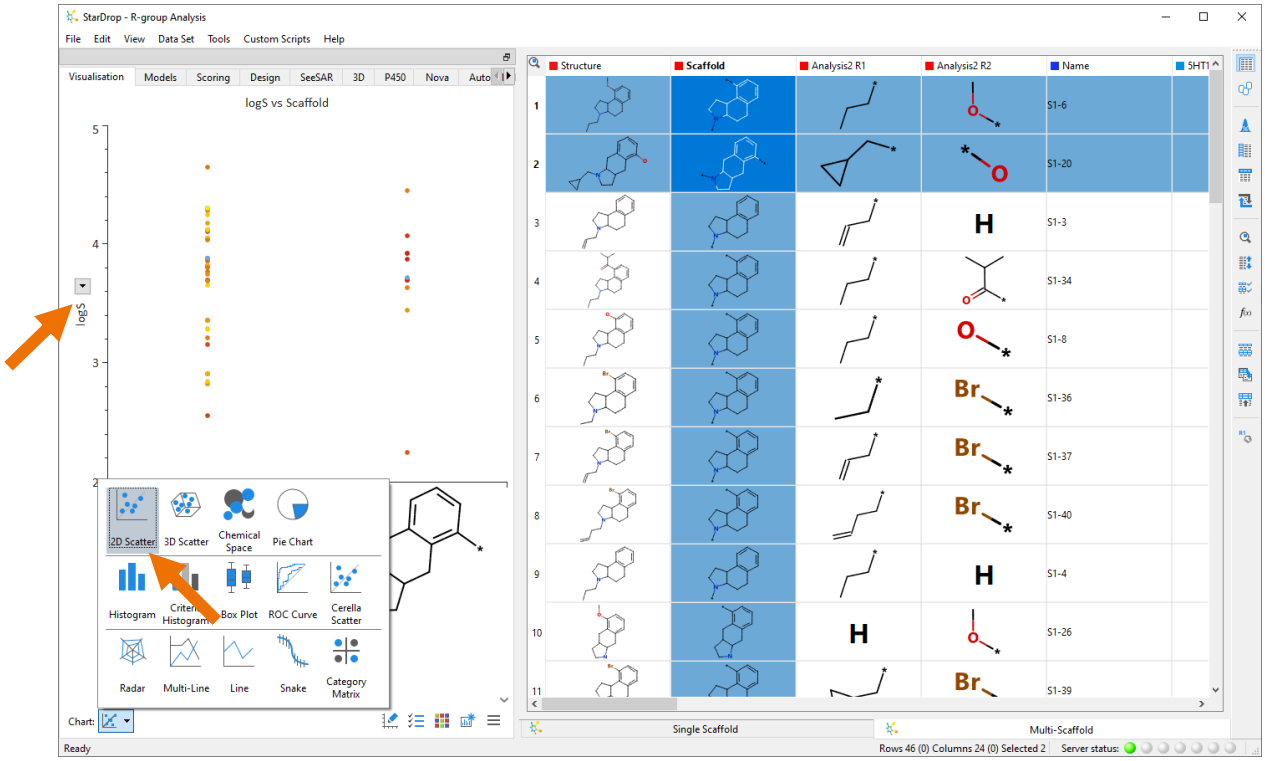
- If you wish to give the analysis a name, click the **Next** button, otherwise click the **Finish** button to run the R-group decomposition.

Three new columns will be added to the data set, showing the scaffold, R1 and R2 groups for each compound.

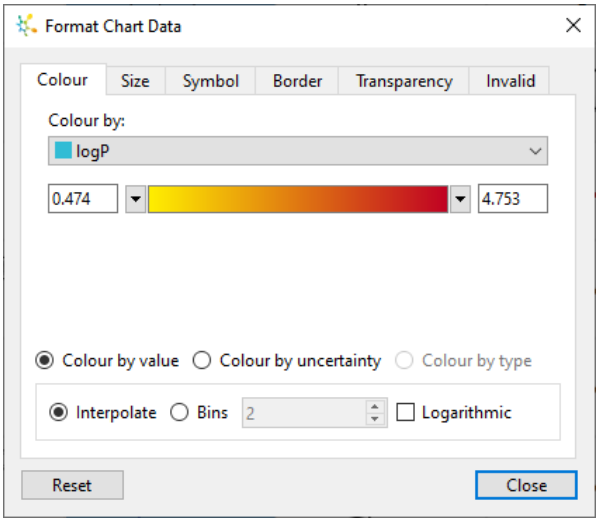


As with R-groups, the scaffold can be used in visualisations by selecting the corresponding column or choosing the scaffold from the axis drop-downs in the **Visualisation** area.

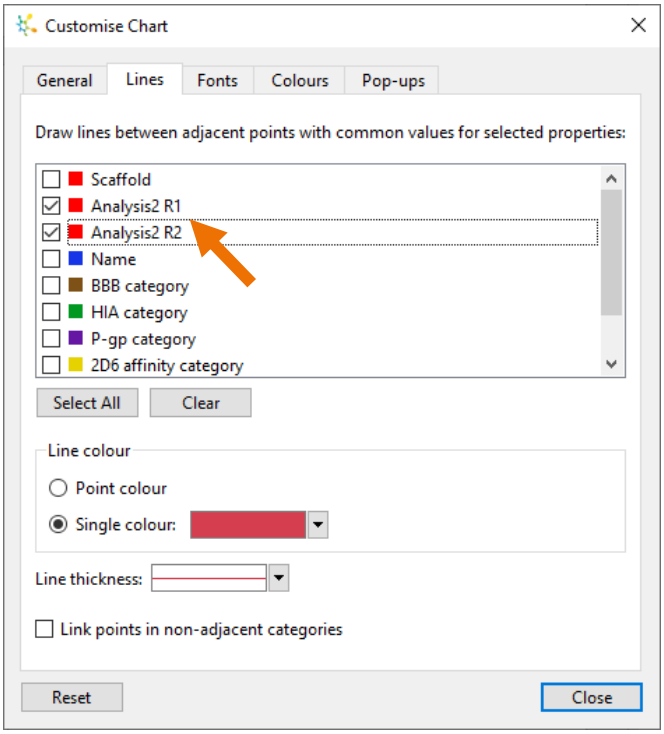
- Select the **Scaffold** column.
- From the **Chart** menu, select **Scatter Plot** and choose **logS** for the y-axis.



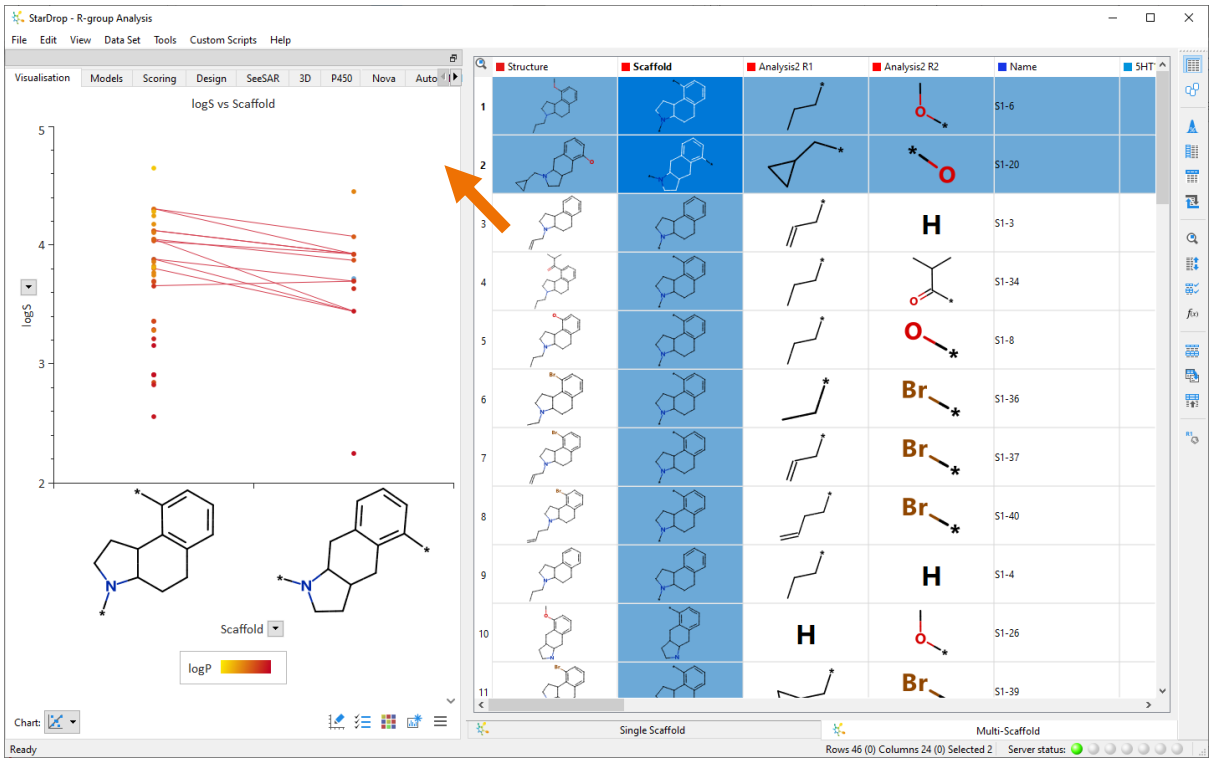
- Click the **Format** button and choose to **Colour by** the property **logP**.
- Change the default colour scale to go from yellow (low) to red (high) by clicking on the drop-downs at each end of the colour range and click the **OK** button.
- Click the **More options** button and choose **Customise**.



- In the **Lines** section, tick **Analysis2 R1** and **Analysis2 R2**.

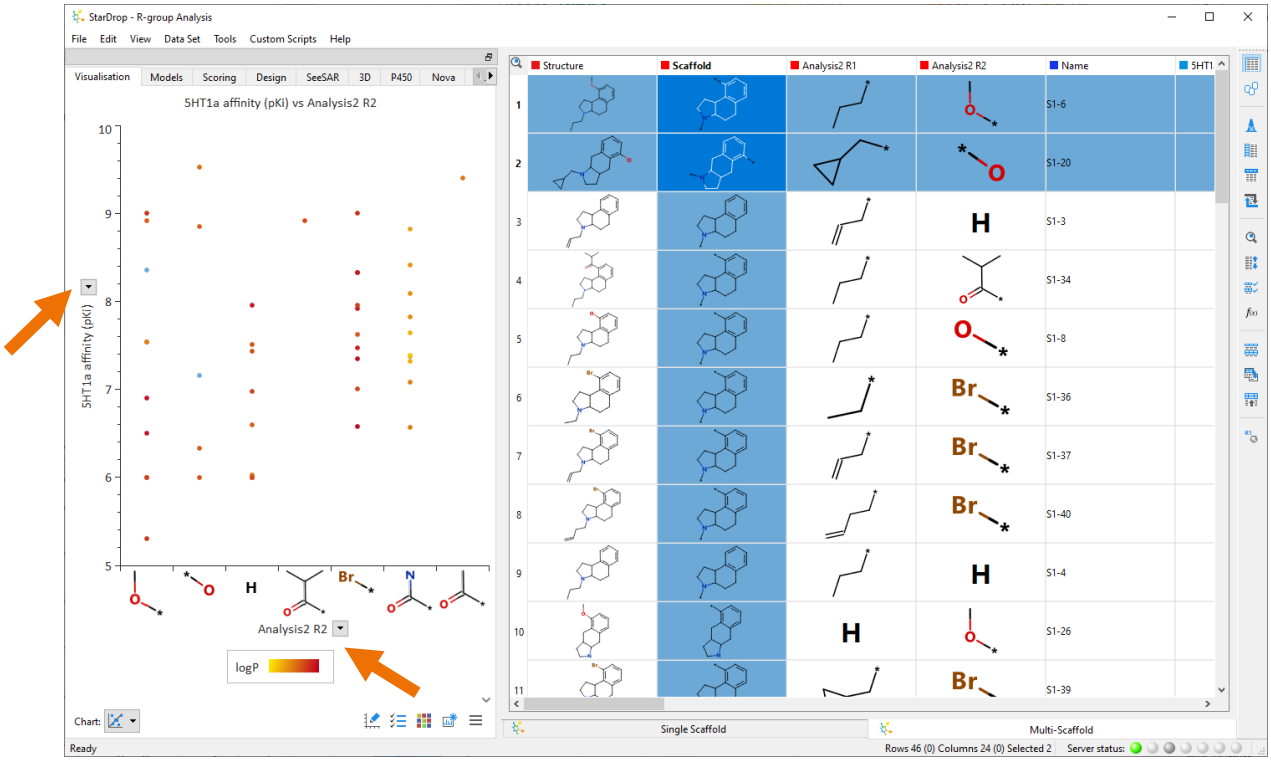


The lines link compounds where R1 and R2 are the same and enable us to visualise how changing the scaffold affects a property (or a score). In this case, we can see that the linear scaffold is slightly less soluble. The difference in solubility is only due to the difference in scaffold since we don't have additional R-groups.

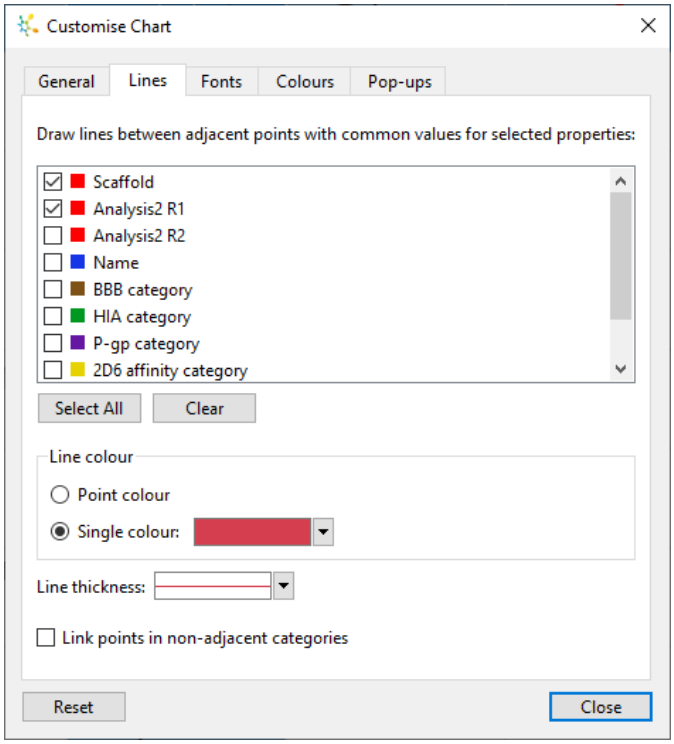


We can create another chart to explore whether changes in R-groups are transferrable between series.

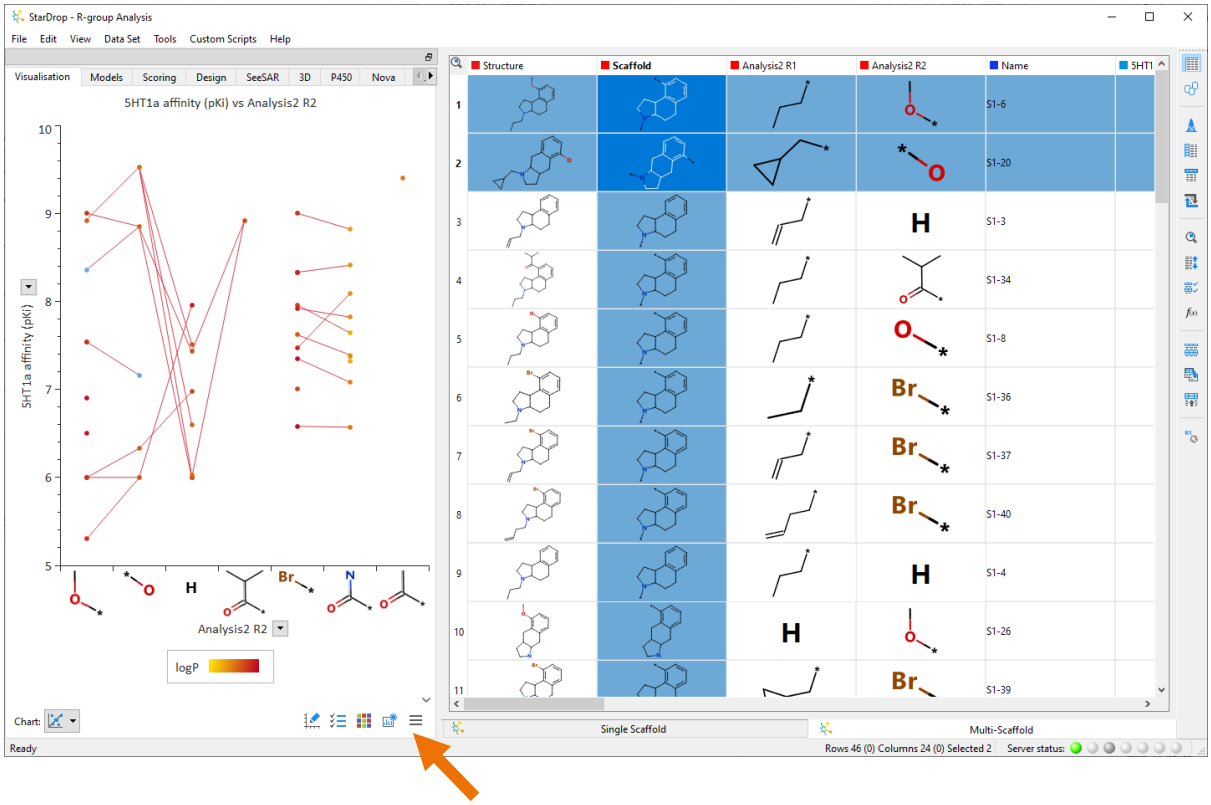
- In the **Scatter Plot** in the **Visualisation** area, choose **5HT1a Affinity (pKi)** for the y-axis and **Analysis2 R2** for the x-axis.



- Click the **More options** button and choose **Customise**.
- In the **Lines** section, untick **Analysis2 R2** and tick **Scaffold**.



The plot in the **Visualisation** area now clearly shows that there is a significant drop in potency, 5HT1a Affinity (pKi), when the hydroxy group is removed. Furthermore, we observe that when Br is replaced with an amide group, logP increases (yellow points indicate lower logP than red ones), while the potency remains fairly consistent.


StarDrop - R-group Analysis
File Edit View Data Set Tools Custom Scripts Help
Visualisation Models Scoring Design SeeSAR 3D P450 Nova
5HT1a affinity (pKi) vs Analysis2 R2
5HT1a affinity (pKi)
Analysis2 R2
logP
Chart:
Structure Scaffold Analysis2 R1 Analysis2 R2 Name 5HT1
S1-6
S1-20
S1-3
S1-34
S1-8
S1-36
S1-37
S1-40
S1-4
S1-26
S1-39
Single Scaffold
Multi-Scaffold
Ready
Rows 46 (0) Columns 24 (0) Selected 2
Server status: