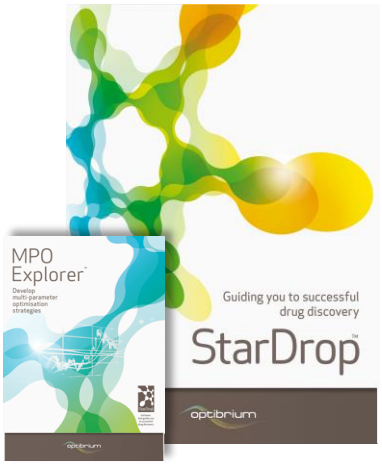


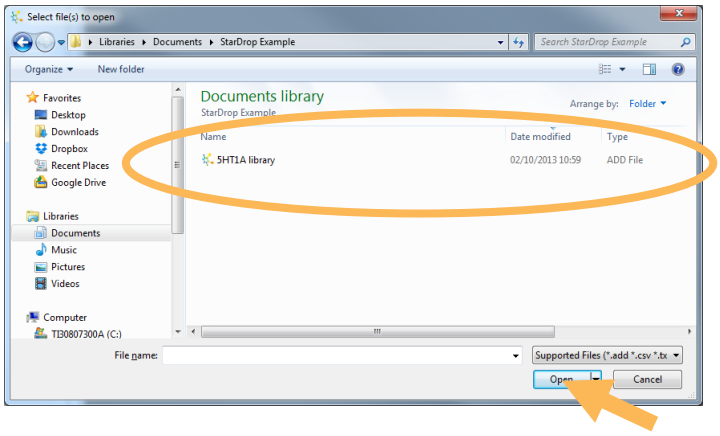
Worked Example:

MPO Explorer™: Sensitivity Analysis

In this example, we will use the Sensitivity Analysis tool in StarDrop's MPO Explorer module to check if the ranking of compounds in a data set is sensitive to any of the criteria or importance values in a scoring profile. This is important to consider because, if the compounds we would choose are very sensitive to a property criterion, we should carefully consider if this criterion is appropriate to avoid missing potentially valuable opportunities. This analysis can also help to determine if different values for a criterion would have an impact on the strategy for a project, for example if there is a disagreement regarding the most appropriate criterion to use. If the ranking of compounds is essentially unchanged within a reasonable range of values, this means that the scoring profile can be used with confidence that the ultimate selection will be robust to the chosen criteria.

Exercise

- Start StarDrop
- From the **File->Open** menu item, open the file **5HT1A library**.



The data set contains 285 compounds for which the potency (pK_i) against the intended target, $5HT_{1A}$, has been experimentally measured and a number of other absorption, distribution, metabolism and excretion (ADME) properties have been predicted. Scores against the required profile of these properties have been calculated for each compound with Probabilistic Scoring.

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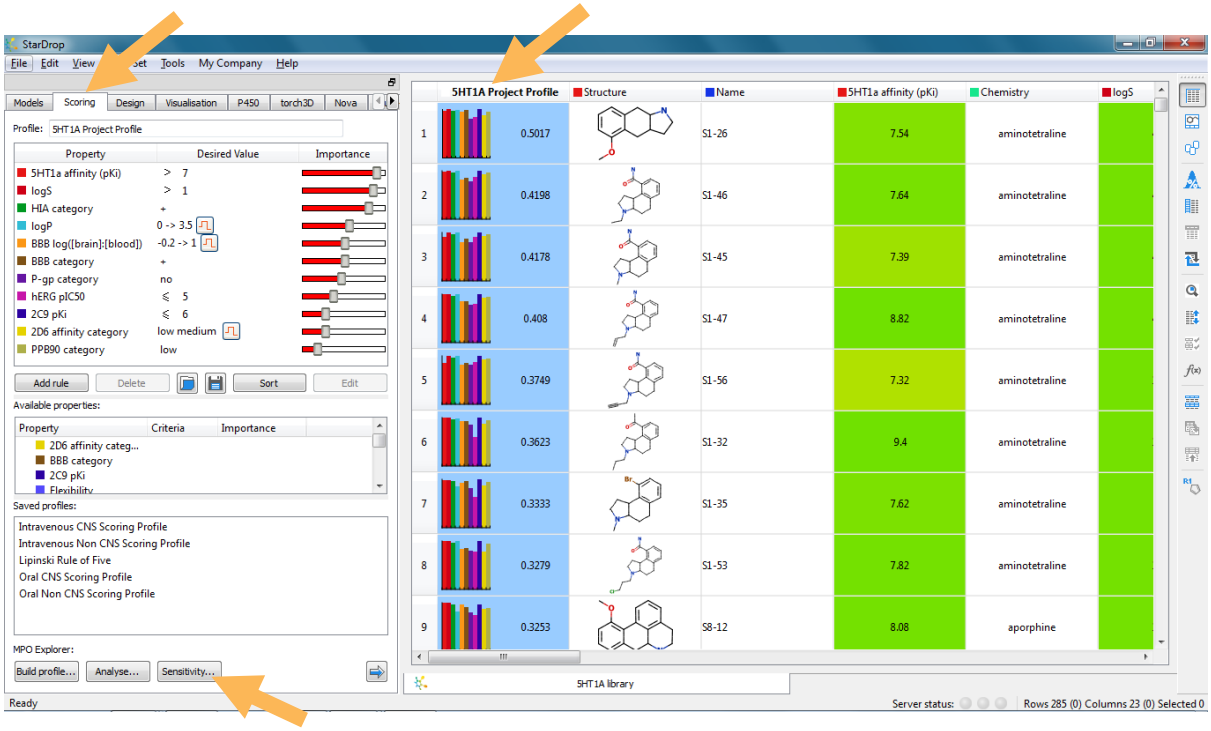
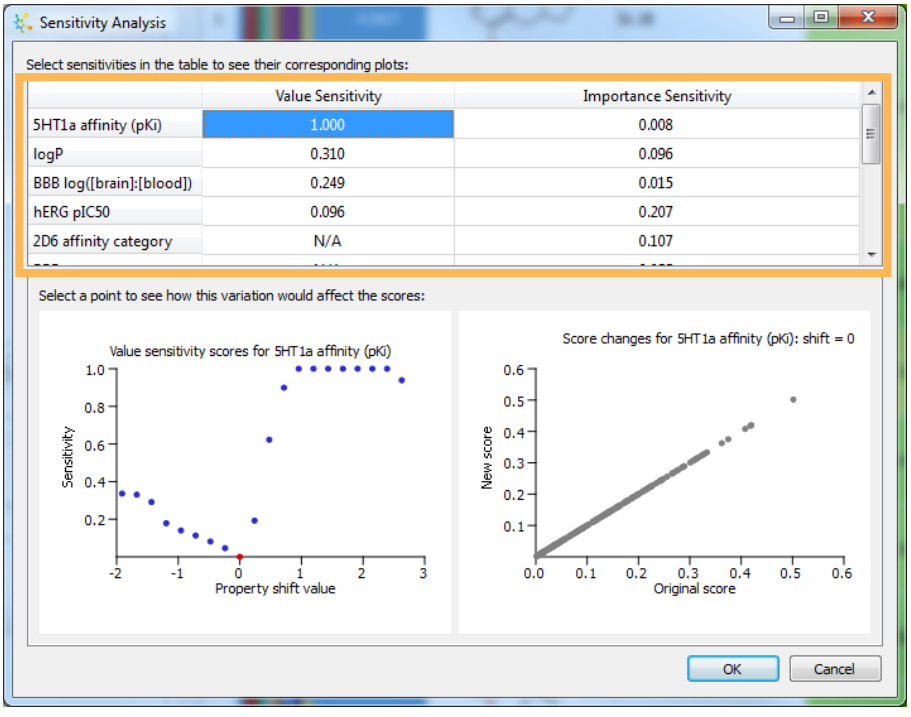
- To see the scoring profile that has been used, select the **Scoring** tab in StarDrop and click on the header of the column entitled **5HT1A Project Profile**.



We will use the **Sensitivity Analysis** tool in **MPO Explorer** to check how sensitive the ranking of the top-scoring compounds is to the criteria and importance values defined in this scoring profile.

- Click on the **Sensitivity...** button at the bottom of the scoring tab (see above). This will perform a sensitivity analysis and display the results as shown below.

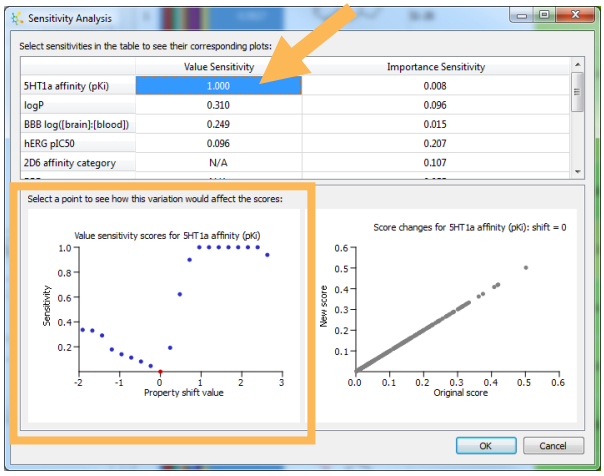


The table at the top shows the sensitivity of the ranking of the top-scoring compounds to changes in the value and importance of each property criterion, on the scale of 0 to 1. A high value, indicates that

the top-ranked compounds will change significantly for only a small change in the criterion value or importance.

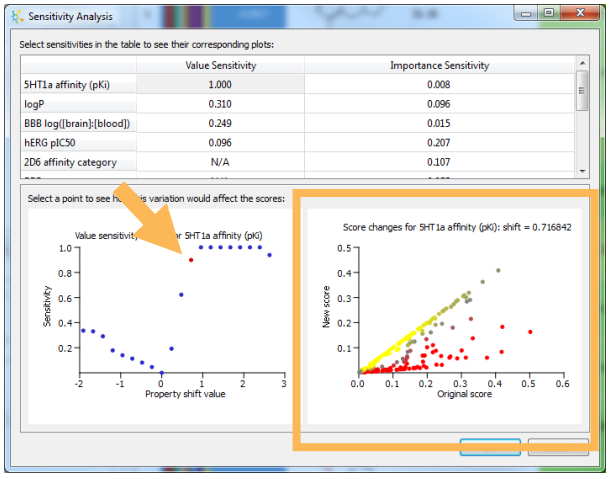
In this example, we can see that the **Value Sensitivity** of the criterion for **5HT1a affinity (pKi)** is 1, the maximum possible sensitivity.

- Click on the **Value Sensitivity** to see the impact of a shift in the value for this criterion on the ranking of the compounds in this data set, in the plot on the bottom-left.



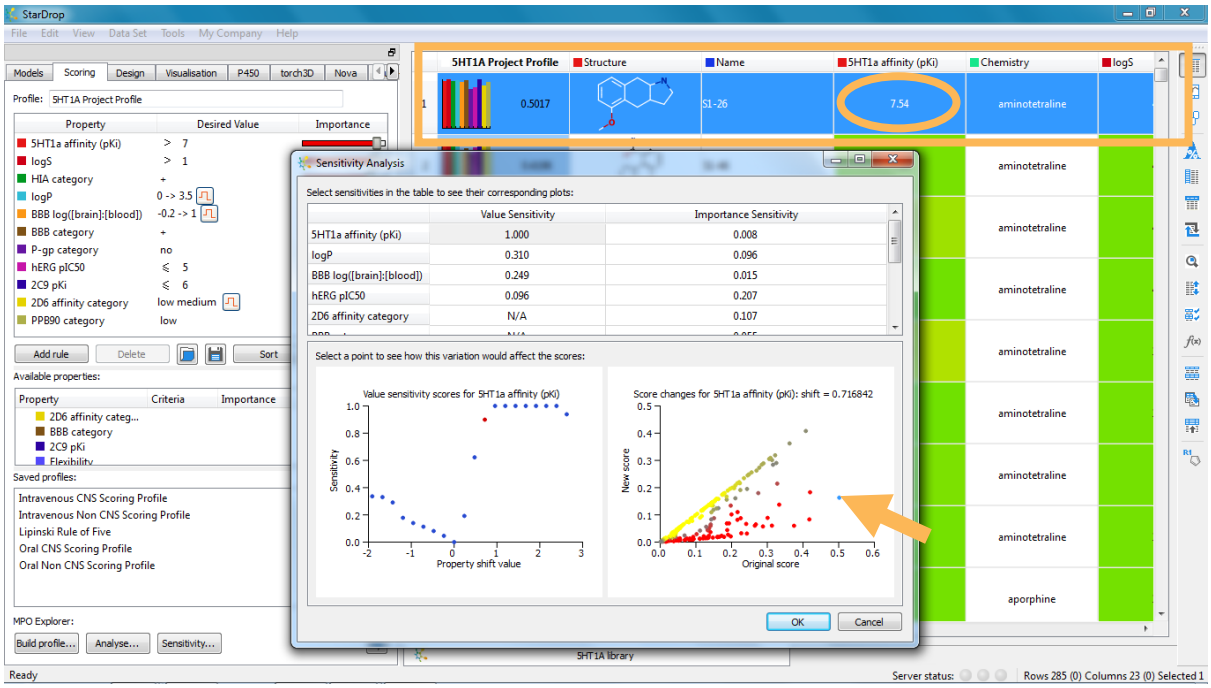
In this plot, a **Property shift value** of 0 corresponds to the value of the criterion in the current profile and hence has a **Sensitivity** of 0, i.e. the rank order is unchanged because the profile is unchanged. However, we can see that only a small increase in the value of the criterion results in a high sensitivity (i.e. the rank order will be changed significantly). Therefore, we need to explore the effect of this change on the top-ranked compounds.

- Click on the point corresponding to a **Property shift value** of approximately 0.7, corresponding to a criterion of 5HT1a affinity (pKi) > 7.7 (the original criterion was >7). This shows a plot in the bottom right, showing the original scores on the x-axis and the scores corresponding to the profile with the new criterion on the y-axis. This is coloured to show the most significant changes in rank. Points coloured red indicate compounds with a significantly decreased rank. Points coloured yellow indicate compounds with a significantly increased rank.



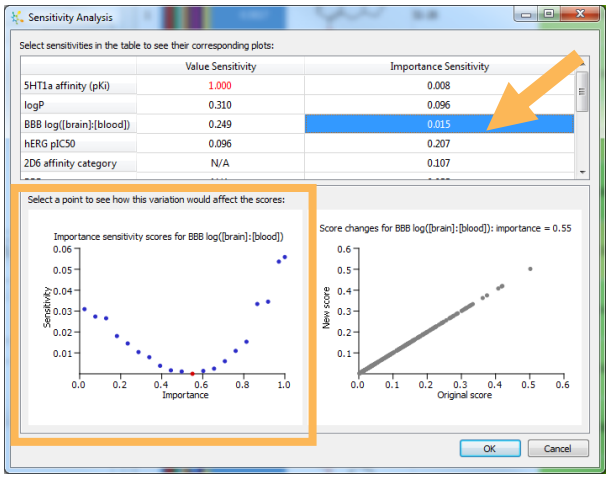
From this plot we can see that a number of the highest-ranked compounds, according to the original score are ranked significantly lower by the new, modified scoring profile. This might change our choice of compounds from this data set, so we would like to check which compounds this affects.

- Click on the right-most, red point in the plot to highlight the corresponding compound in the data set, as shown below.

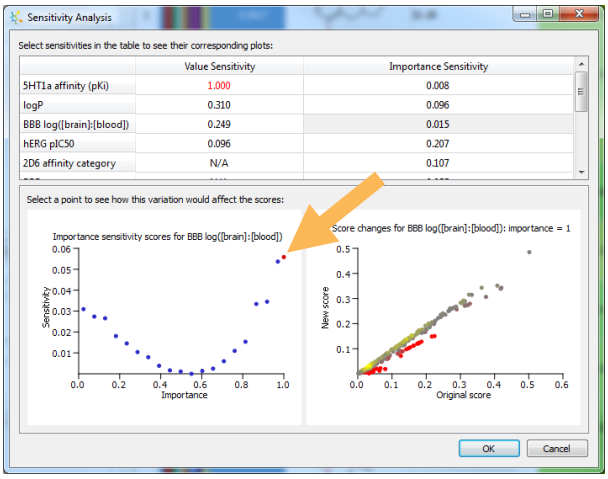


From this, we can see that this compound is the highest scoring based on the original profile. However, the measured pK_i of this compounds is 7.54, so we can understand that a small increase in the criterion from >7 to >7.7 would significantly change our view of this compound. It may be worth considering this compound (and possibly other similar compounds highlighted by the plot) in more detail before committing resources to further study.

- Returning to the **Sensitivity Analysis** dialogue box, select the **Importance Sensitivity** for **BBB log([brain]:[blood])** in the table, as shown right. The plot in the bottom left shows that even a large change in the importance of this property criterion will have only a small effect on the ranking of compounds. Note that the maximum **Sensitivity** in this case is only 0.06 for an **Importance** of 1.0.



- Confirm this by selecting the point corresponding to the Importance of 1.0, as shown right. The resulting plot in the bottom right shows that there is no significant change in the ranking of the top compounds.



From this we can conclude that the selection of compounds will not change significantly if we vary the importance of **BBB log([brain]:[blood])** within a reasonable range. We can use this importance value with confidence that it is not inappropriately biasing our decision.

Conclusion

Sensitivity analysis is an important part of validation of a scoring profile, to ensure that there are no unexpected biases introduced by our choice of criteria and their importance in the scoring profile. The Sensitivity Analysis tool automatically analyses this and highlights those scoring profile parameters or compounds that may warrant more detailed consideration before a decision is made; these may represent valuable new avenues for exploration or opportunities to save time and effort. Furthermore, because it is a quick analysis, it can easily be applied to any new data sets that are scored and prioritised for progression.