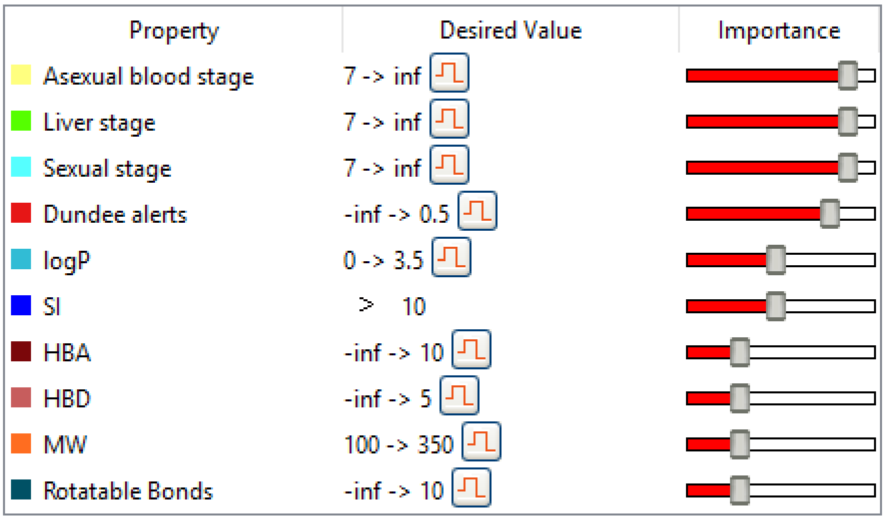
MMV Scoring Profile Notes

The property criteria below and in the accompanying scoring profile were developed in collaboration with Medicines for Malaria Ventures (MMV) to prioritise antimalarial ‘screening actives’. The following notes give further information on the parameters and criteria.



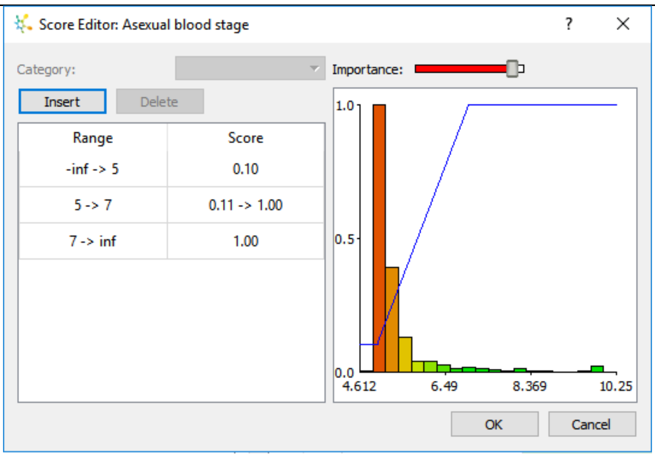
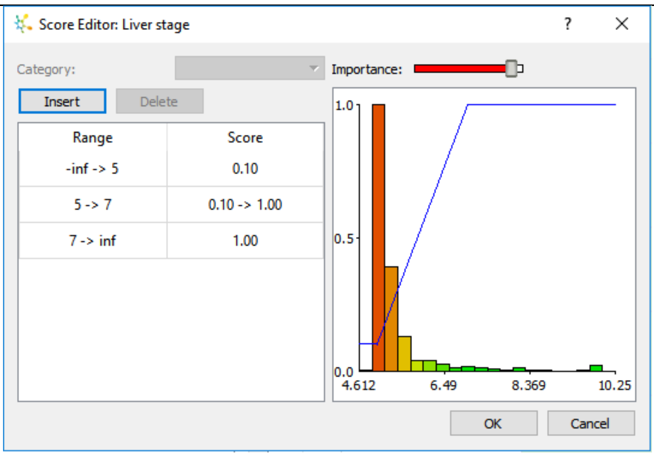
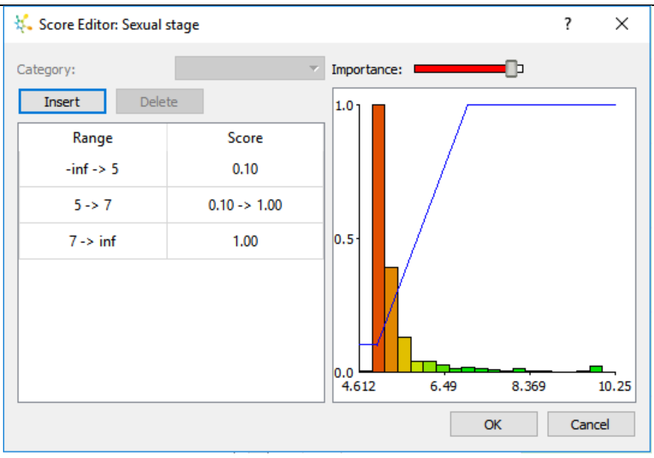
Property	Desired Value	Importance
Asexual blood stage	7 -> inf	
Liver stage	7 -> inf	
Sexual stage	7 -> inf	
Dundee alerts	-inf -> 0.5	
logP	0 -> 3.5	
SI	> 10	
HBA	-inf -> 10	
HBD	-inf -> 5	
MW	100 -> 350	
Rotatable Bonds	-inf -> 10	

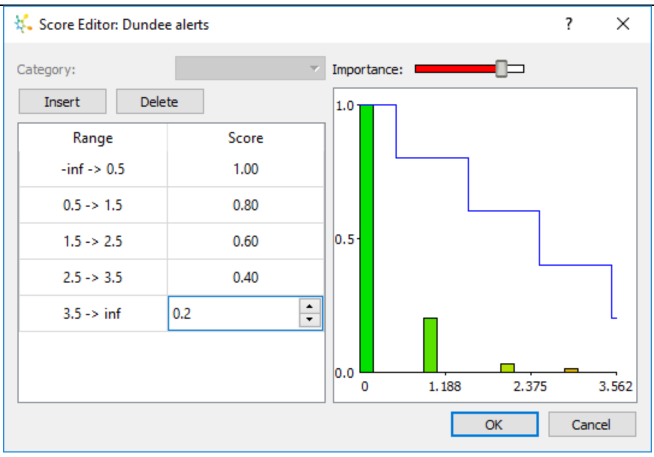
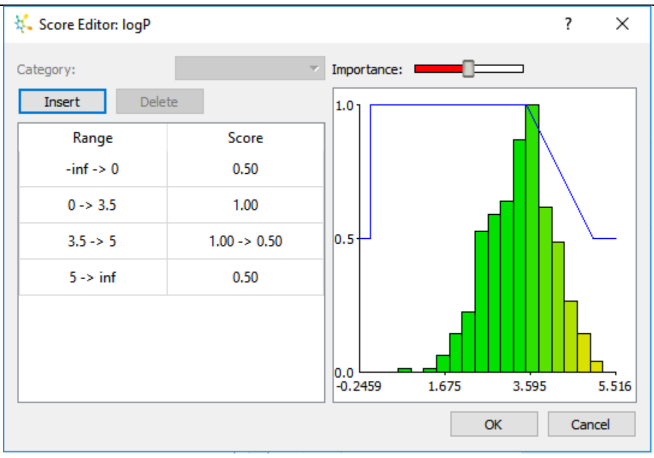
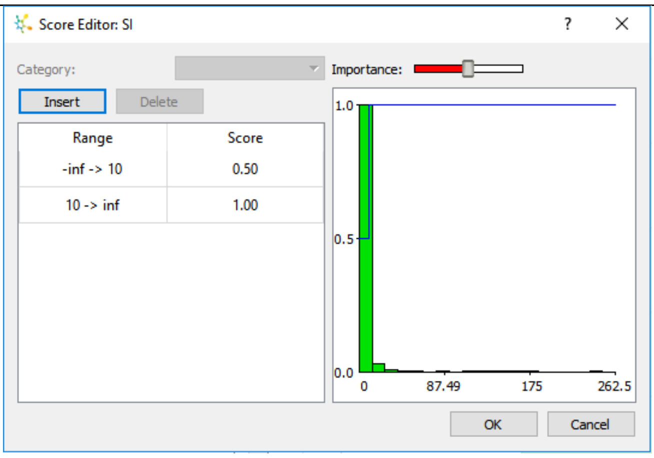
The Asexual blood stage, Liver stage and Sexual stage properties represent experimental activity data that should be imported into StarDrop. MW, logP, HBD, HBA and Rotatable bonds can be estimated or calculated using StarDrop’s Models tab. Dundee alerts are provided by a model that accompanies the scoring profile and SI can be calculated from experimental data on activity and cytotoxicity. More details are provided for each property in the scoring profile in the Scoring Criteria section below.

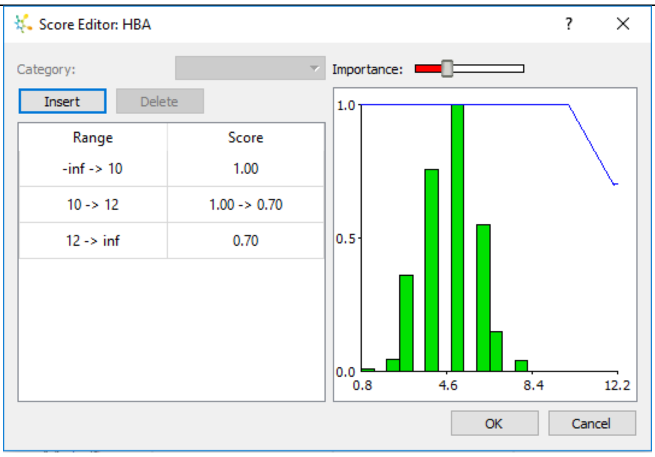
The Probabilistic Scoring algorithm [1] enables prioritisation of compounds with an appropriate balance of properties to meet a project's objective. The output is a score on a scale of 0 to 1 indicating the likelihood of achieving an ideal outcome for each property, as defined in the profile. As this assessment is based on the combination of multiple predictions and measurements, each with an associated experimental or statistical uncertainty, it is important to include the impact of this uncertainty when calculating the score. This ensures that opportunities are not missed by inappropriately discarding potentially good compounds due to an inaccurate measurement or prediction. Therefore, an estimate of the uncertainty in each score is also calculated. A histogram is also created for each compound, which shows the contributions of the properties to the overall score, as illustrated below.

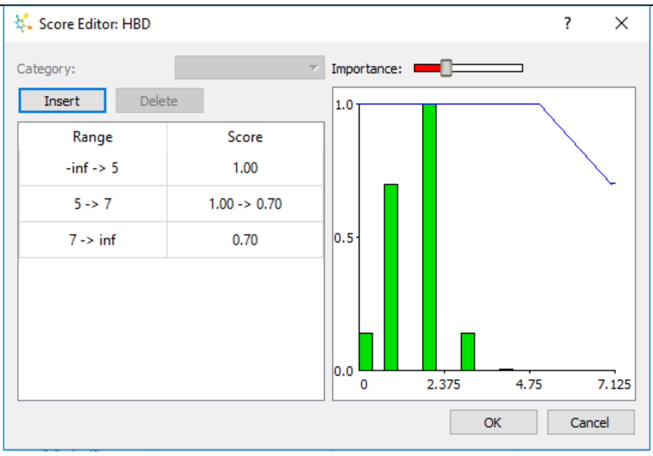
You can find more information on probabilistic scoring in Chapter 2 of the StarDrop Reference Guide from the **Help->Reference Guide** menu option in StarDrop or a short video on our community website at https://www.optibrium.com/community/videos/stardrop-hints-and-tips/202-probabilistic-scoring.

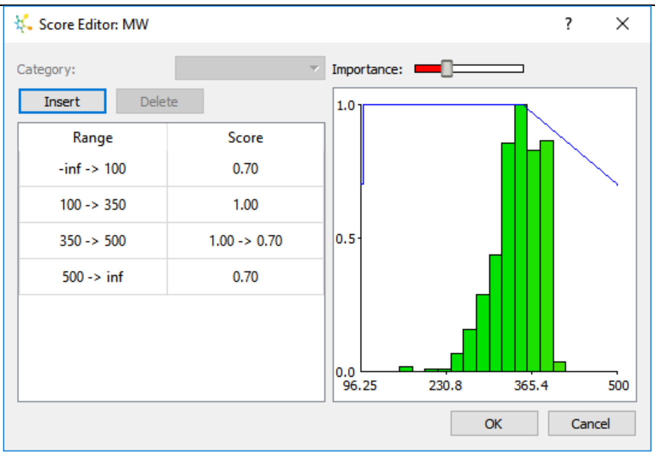
Scoring Criteria

<table>
<tr><th>Property</th><th>Column name</th><th>Criterion</th></tr>
<tr><td>Efficacy of the compound against plasmodia at the asexual blood stage of their lifecycle.*</td><td>Asexual blood stage</td><td>
 <table><tr><th>Range</th><th>Score</th></tr><tr><td>-inf -> 5</td><td>0.10</td></tr><tr><td>5 -> 7</td><td>0.11 -> 1.00</td></tr><tr><td>7 -> inf</td><td>1.00</td></tr></table></td></tr>
<tr><td>Efficacy of the compound against plasmodia at the liver stage of their lifecycle. *</td><td>Liver stage</td><td>
 <table><tr><th>Range</th><th>Score</th></tr><tr><td>-inf -> 5</td><td>0.10</td></tr><tr><td>5 -> 7</td><td>0.10 -> 1.00</td></tr><tr><td>7 -> inf</td><td>1.00</td></tr></table></td></tr>
<tr><td>Efficacy of the compound against plasmodia at the sexual stage of their lifecycle. *</td><td>Sexual stage</td><td>
 <table><tr><th>Range</th><th>Score</th></tr><tr><td>-inf -> 5</td><td>0.10</td></tr><tr><td>5 -> 7</td><td>0.10 -> 1.00</td></tr><tr><td>7 -> inf</td><td>1.00</td></tr></table></td></tr>
</table>

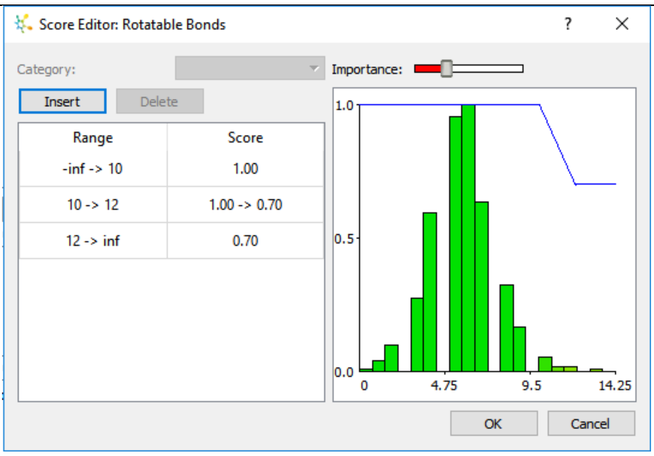
Structural alerts from Brenk, et al [2]. This flags up any compounds or substructures that are undesirable in some way. This uses the ‘Dundee alerts’ model accompanying this scoring profile. See below for details on how to load this model into StarDrop.	Dundee alerts	 Score Editor: Dundee alerts Category: Importance: Insert Delete Range Score -inf -> 0.5 1.00 0.5 -> 1.5 0.80 1.5 -> 2.5 0.60 2.5 -> 3.5 0.40 3.5 -> inf 0.2 OK Cancel
Octanol/water partition coefficient	logP	 Score Editor: logP Category: Importance: Insert Delete Range Score -inf -> 0 0.50 0 -> 3.5 1.00 3.5 -> 5 1.00 -> 0.50 5 -> inf 0.50 OK Cancel
Selectivity index of a compound for its plasmodium target. A SI column can be created using the mathematical function tool in StarDrop by selecting the *f*(x) icon (see ‘How to create functions’ and ‘How to calculate SI’ sections).	SI	 Score Editor: SI Category: Importance: Insert Delete Range Score -inf -> 10 0.50 10 -> inf 1.00 OK Cancel

<table>
<tr><td>Number of hydrogen bond acceptors</td><td>HBA</td><td>

<table>
<tr><th>Range</th><th>Score</th></tr>
<tr><td>-inf -> 10</td><td>1.00</td></tr>
<tr><td>10 -> 12</td><td>1.00 -> 0.70</td></tr>
<tr><td>12 -> inf</td><td>0.70</td></tr>
</table></td></tr>
<tr><td>Number of hydrogen bond donors</td><td>HBD</td><td>

<table>
<tr><th>Range</th><th>Score</th></tr>
<tr><td>-inf -> 5</td><td>1.00</td></tr>
<tr><td>5 -> 7</td><td>1.00 -> 0.70</td></tr>
<tr><td>7 -> inf</td><td>0.70</td></tr>
</table></td></tr>
<tr><td>Molecular Weight</td><td>MW</td><td>

<table>
<tr><th>Range</th><th>Score</th></tr>
<tr><td>-inf -> 100</td><td>0.70</td></tr>
<tr><td>100 -> 350</td><td>1.00</td></tr>
<tr><td>350 -> 500</td><td>1.00 -> 0.70</td></tr>
<tr><td>500 -> inf</td><td>0.70</td></tr>
</table></td></tr>
</table>

Number of bonds that are rotatable	Rotatable bonds	

Score Editor: Rotatable Bonds

Category:

Importance:

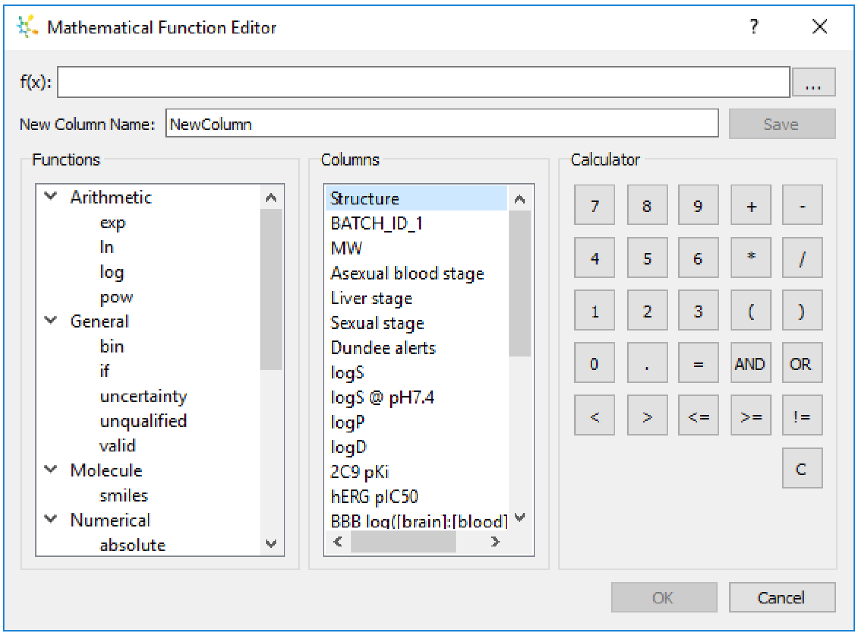
Range	Score
-inf -> 10	1.00
10 -> 12	1.00 -> 0.70
12 -> inf	0.70

*These columns should be in log units, for which the scoring function has been defined. To convert to logarithmic units (e.g. pK_i, pIC_{50}, pEC_{50}) from unlogged units (e.g. K_i, IC_{50}, EC_{50}), StarDrop's mathematical function tool can be used to create a new log unit column (see 'How to create functions' section). Give the new column a name that exactly matches the property name in the scoring profile.

How to Create Functions

StarDrop's mathematical function editor can be used to create new columns that are calculated from the values in other columns.

Click the ƒ(x) button on the toolbar to the right (or select it from the **Tools->Function Editor** menu item) to open the **Mathematical Function Editor**.



Mathematical Function Editor

f(x):

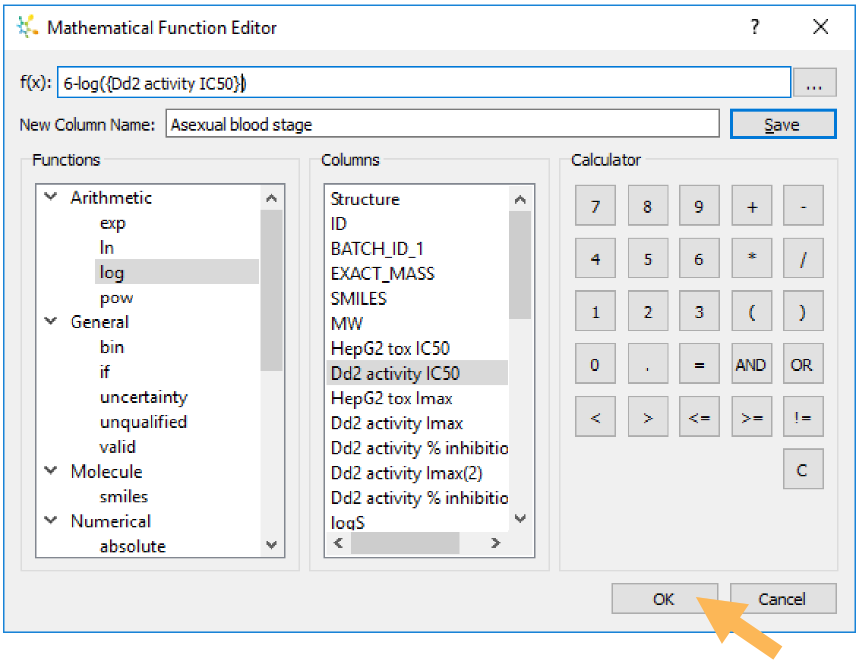
New Column Name: NewColumn

Clicking on a function in the list displays a template in the editor with the first item that needs to be filled in already selected and ready for input.

To add column names, choose them from the list or type them in. Note: Column names should be enclosed in curly brackets e.g. {logP}.

Converting IC_{50} to pIC_{50}

To convert IC_{50} values into pIC_{50} values, you can use the function shown below:



f(x): 6-log({Dd2 activity IC50})

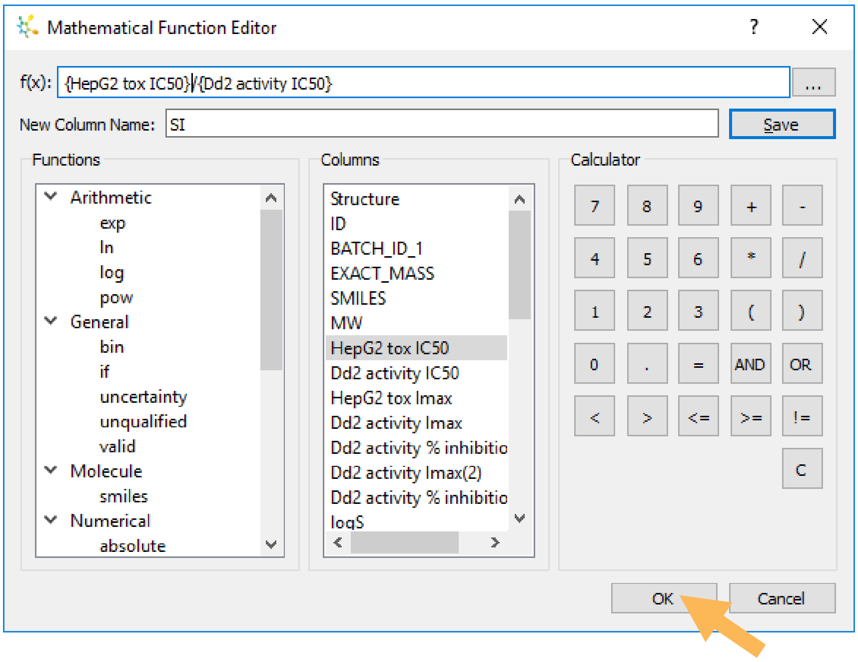
New Column Name: Asexual blood stage

In this case, the column **Dd2 activity IC50** contains the activities against the asexual blood stage of the Dd2 strain of plasmodium falciparum.

Clicking the **OK** button will close the dialogue and add a new column to the data set which has the name specified in the New Column Name field.

Calculating Selectivity Index (SI)

The function below illustrates how to calculate the selectivity index from activity against the plasmodium parasite (IC_{50}) and toxicity against a mammalian cell line (in this case IC_{50} against the HepG2 cell line):



f(x): {HepG2 tox IC50}/{Dd2 activity IC50}

New Column Name: SI

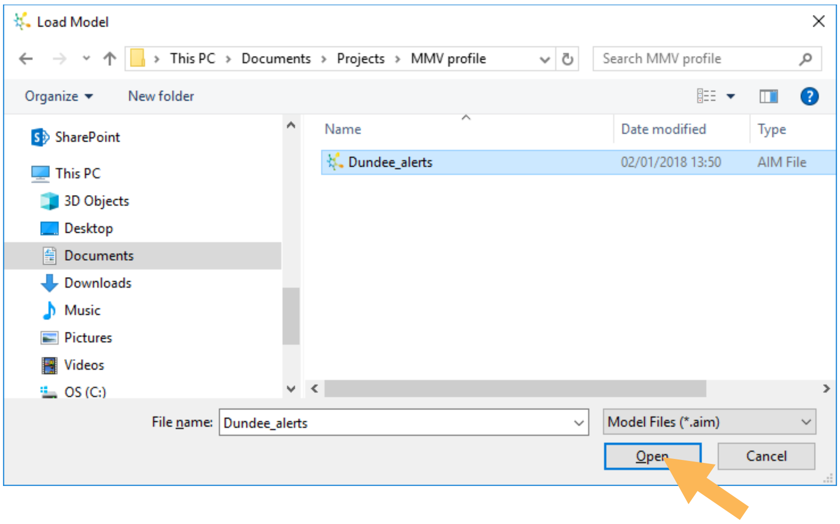
In this case the column **HepG2 tox IC50** contains the IC_{50} values against the HepG2 cell line and **Dd2 activity IC50** contains the activities against the asexual blood stage of the Dd2 strain of plasmodium falciparum.

If you would like to calculate selectivity index in logarithmic units, change the scoring profile cut-off for SI to > 1 and calculate the selectivity as the difference between the plasmodium activity and mammalian cell toxicity in logged units.

Note: **If values in columns which are used as part of the function are changed after the function column has been created, the values in the function column will update automatically to reflect the changed values.**

Loading a Model into StarDrop

The 'Dundee alerts' model can be loaded into StarDrop to calculate the number of matches to the structural alerts described in Brenk *et al.* **[2]**. To do this, change to the **Models** tab in StarDrop and select the 📂 button in the bottom-left of the tab. Navigate to the directory where you saved the model, select it and click **Open**.

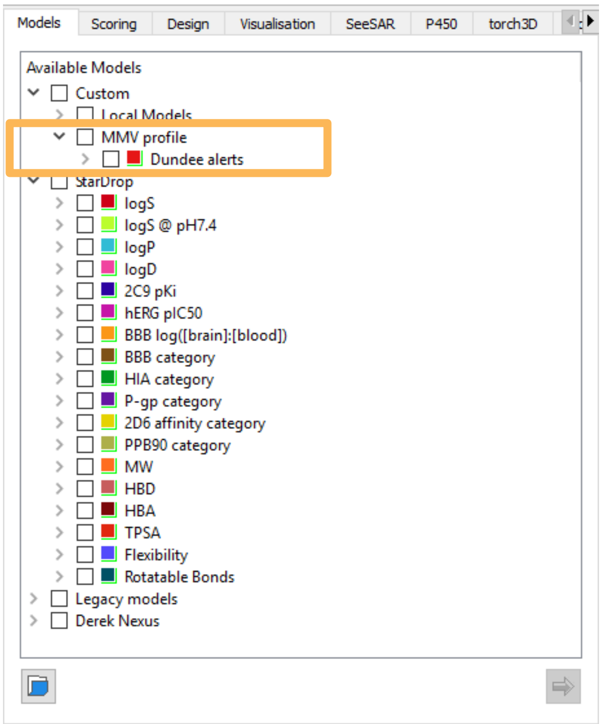


Dundee_alerts 02/01/2018 13:50 AIM File

File name: Dundee_alerts

Model Files (*.aim)

The model will appear in a branch in the **Models** tab with the name of the directory from which it was opened:



References

1 Segall, M.D. Multi-Parameter Optimization: Identifying high quality compounds with a balance of properties. *Curr. Pharm. Des.*, 18, 9 (2012), 1292-1310.

2 Brenk, R, Schipani, A, James, D, Krasowski, A, Gilbert, IH, Frearson, J, and Wyatt, PG. Lessons learnt from assembling screening libraries for drug discovery for neglected diseases. *ChemMedChem* (2008), 3(3):435-44.