# Guiding the Decision-Making Process to Identify High Quality Compounds

M.D. Segall, E. Champness, O. Obrezanova, C. Leeding

Optibrium Ltd. 7226 IQ Cambridge, Beach Drive, Cambridge, CB25 9TL, UK

## Introduction

Success in drug discovery projects is dependent on making key decisions about the design and selection of compounds with an appropriate balance of many properties and hence a high chance of achieving the therapeutic goals. In early drug discovery, data on a large number of compounds and properties from a wide variety of sources, *in silico* and *in vitro*, must be integrated and assessed against a project's requirements.

We have previously described an approach for scoring compounds, based on their likelihood of success against a profile defining the property requirements and their relative importance to a project's objectives [1,2]. Within this assessment, uncertainty in the data is explicitly considered; most sources of drug discovery data have significant statistical or experimental uncertainties and this information enables us to determine the degree of confidence with which we can distinguish between compounds.

Defining a property profile is subjective and often leads to lengthy, interdisciplinary discussions about the criteria and their relevance. For example, is it worth sacrificing some potency to gain additional metabolic stability or solubility? However, a question that is rarely asked is, "What impact would that trade-off have on the final outcome?", particularly given the underlying uncertainty.

In this poster, we will discuss how a rigorous scoring approach allows this question to be addressed directly. By assessing the sensitivity of the final compound selection to the property profile, criteria that have a significant effect on the ultimate decision can be identified. This, in turn, can focus attention on critical experiments, e.g. *in vivo* studies, that will help to identify the most appropriate profile to select high quality compounds with greater accuracy.

## Methods

A rigorous approach to scoring, such as the probabilistic scoring scheme implemented in StarDrop, can be used to generate a score for each compound that reflects the overall quality of a compound based on the available data, the criteria for success and their relative importance to the overall objectives of the project [1,2]. When combining data on multiple properties, it is important to consider the uncertainty in each data point, as the overall uncertainty in the scores may be high, reducing our ability to confidently distinguish high and low quality compounds. This is illustrated in Figure 1.

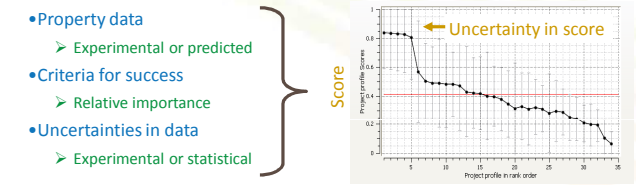


**Figure 1**. In this graph, compounds are plotted along the *x*-axis ranked from highest to lowest score. The score is plotted on the *y*-axis, with error bars indicating the overall uncertainty in the score. Here, the top 5 compounds cannot be confidently distinguished; more data or criteria are required to choose between these. However, ~50% of compounds are significantly less likely to meet the project criteria than the top 5.

The success criteria and their relative importance may be defined for any property for which data is available, whether predicted or experimental. In addition to simple pass/fail thresholds, ranges and trends may be defined in order to more subtly reflect the influence of a property value on the compound's likelihood of success, as illustrated in Figure 2.

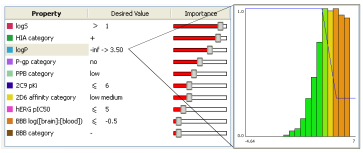


**Figure 2**. The 'scoring profile' for the project, indicating the ideal range for each property value ('Desired Value'), and relative importance (slider bars). More complex relationships between properties and scores can be defined, as illustrated here for logP; logP would ideally be <3.5, but the largest penalty is given to compounds with logP>5.

This method allows a set of compounds to be objectively prioritised against specific, project-defined criteria. In addition, it provides a rigorous basis for comparing the changes in priority order of a set of compounds if **alternative** criteria are considered and hence to assess the impact of different compound selection strategies.

## Results and Discussion

To illustrate the concepts, we will first consider the simple case of a single property for which the criterion is a threshold that we would ideally like to exceed, as illustrated in Figure 3. Here we can see that changing the criterion will not change the order of priority for the set of compounds, but will affect the confidence with which we can accept or reject compounds and select between them, as illustrated in Figure 4.

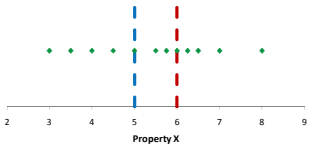


**Figure 3.** Example data for property X to illustrate the effect of changing a selection criterion. Each compound is represented by a green point indicating its property value. Two threshold criteria are shown as dashed lines, X>5 (blue) and X>6 (red). The resulting scores are shown in Figure 4. It is assumed that the uncertainty (standard deviation) for each data point Is +/- 0.5.

When scoring compounds with a profile including multiple properties, it is harder to predict the effect of modifying a criterion, because the change in priorities will also depend on the other properties of the molecules being scored. However, one would only expect the priority of compounds to change significantly if the criterion being changed corresponds to one of the properties with high importance and if the change to the criterion, e.g. a threshold, is large compared to the uncertainty in the corresponding property.

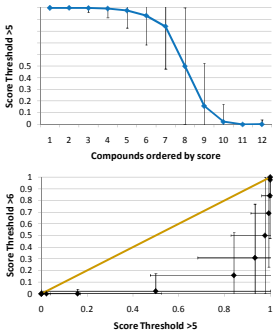


**Figure 4.** Score distributions resulting from scoring the data in Figure 3 with two scoring profiles with criteria X>5 (blue) and X>6 (red). The scores are plotted against one another in the bottom left graph. Here we can see that, while the order of compounds is not changed, the confidence with which compounds may be rejected changes significantly. In the case of X>5, only the 3 lowest scoring compounds may be rejected with confidence, (p<0.05) but with X>6 five compounds may be rejected with the same confidence.

An example of this may be seen if we consider the data from a project (Project X), scored for potency, selectivity, solubility, and turnover by human and rat liver microsomes (HLM and RLM) using the profile shown in Figure 5. The resulting top-ten ranked compounds, along with their corresponding data are also shown in Figure 5.

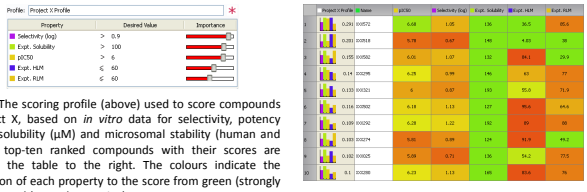


**Figure 5.** The scoring profile (above) used to score compounds for Project X, based on *in vitro* data for selectivity, potency (pIC50) , solubility (μM) and microsomal stability (human and rat). The top-ten ranked compounds with their scores are shown in the table to the right. The colours indicate the contribution of each property to the score from green (strongly positive) to red (strongly negative).

If the project team decides to change the requirements so that the required selectivity is a factor of 16 (log selectivity >1.2) rather than 8 (log selectivity >0.9), rescoring the compounds shows a very high correlation between the original scores and the new scores, as shown in Figure 6. Therefore, the choice of compound would be unaffected, although the confidence with which compounds could be rejected would change slightly. We can understand this because, even though the selectivity is the most important property, the change in the selection criterion (0.3 log units) is small with respect to the uncertainty in the underlying data (0.7 log units).

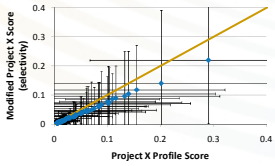


**Figure 6.** A graph of the original compound scores against the scores for a modified profile, where the criteria for selectivity has been increased to log selectivity >1.2 (factor of 16). Here we can see a strong correlation between the scores derived from the two profiles, indicating that there would be no change in the compounds selected with the two different sets of criteria. The identity line (y=x) is shown as an orange line for comparison.

However, if the project team decides that a solubility of >10 μM may be sufficient, instead of the original requirement of >100 μM, the results would change significantly. A number of compounds would achieve a significantly higher score, which would lead to a different order of priority. The correlation between the original and new scores along with the resulting new top-ten compounds is shown in Figure 7. In this case, we can see that the selection is sensitive to the choice of this criterion, so care must be taken to choose the most appropriate property requirement before proceeding. Alternatively, a larger set of compounds could be progressed, combining the top compounds from both the original and modified profiles until more data can be obtained to better define the required properties.

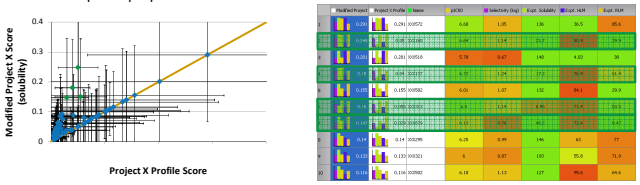


**Figure 7.** A graph of the original compound scores against the scores for a modified profile where the criterion for solubility has been reduced to >10 μM. Here we can see that the scores for four compounds, highlighted in green, change significantly and that these compounds are promoted into the top-ten. The identity line (y=x) is shown as an orange line for comparison.

The table on the right shows the scores and data for the top-ten compounds, colour coded as in Figure 5. The four promoted compounds are highlighted by a green box.

## Conclusions

The choice of property criteria for selection of compounds for progression, particularly early in a drug discovery project, is a subjective matter and often the cause of extensive debate. We have demonstrated that a rigorous approach to prioritisation of compounds according to a profile of property requirements allows the impact of different choices of criteria to be objectively assessed. Sometimes the ultimate decision, i.e. the selection of compounds, is not sensitive to changes in a criterion. In this case the selection can proceed with confidence. However, where the selection is sensitive, this suggests an opportunity to gather more detailed data, for example *in vivo* studies, to better define the properties required to achieve an appropriate pharmacokinetic/pharmacodynamic profile.

## References

[1] Segall et al. Expert Opin. Drug. Metab. Toxicol. 2006, 2, pp. 325-37 [2] Segall et al. Chemistry and Biodiversity, 2009 (in press) doi: 10.1002/cbdv.200900148