Multi-Parameter Optimisation from Hit to Candidate

The objective of this project was to identify an orally dosed compound for a cardiovascular target.

A plot of the 'chemical space' explored by the initial screening library of 500 compounds is shown in 1(a). The experimentally measured activity is indicated by the colour, showing that good activity was identified for a wide diversity of chemistry.

This experimental data was combined with *in silico* predictions for a range of ADME properties and assessed using Probabilistic Scoring against the scoring profile shown in 2(a). The resulting scores were analysed using the scoring and chemical space plots shown in 1(b), which show that only a small number of compounds in restricted areas of the chemical space are likely to exhibit both good activity and appropriate ADME properties.

To confirm this finding, approximately 40 compounds were selected for primary *in vitro* ADME assays to measure their solubility and human liver microsomal stability. The selected compounds focused on those predicted to have the best balance or properties, but a wider range of diversity was explored to confirm the predicted hypothesis. The compounds studied experimentally were, in turn, scored based only on the *in vitro* data using the profile shown in 2(b); the results are indicated by the colours of the points and the scoring plot shown in 1(c). This *in vitro* analysis reinforced the high quality chemistry identified by the *in silico* analysis.

Further chemistry expansion was undertaken in lead optimisation, along with detailed *in vitro* and *in vivo* studies. The eventual development candidate was one of the compounds identified early in the project, indicated by the blue point highlighted in 1(b) and (c).

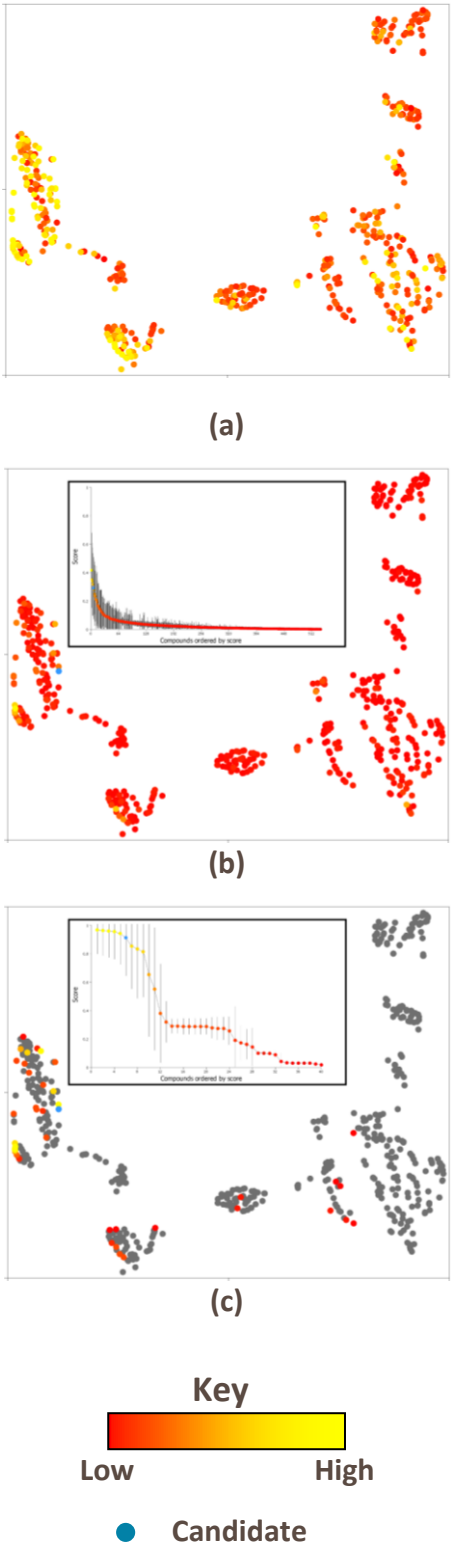
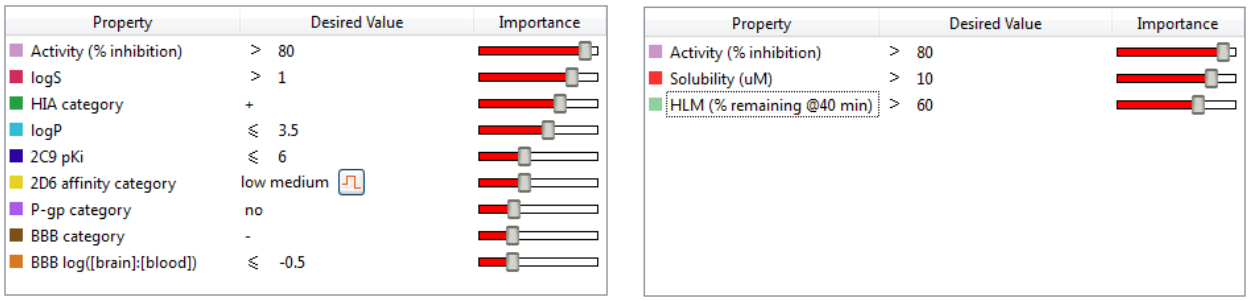


Figure 1 Chemical space plots illustrating the diversity of the library compounds screened for activity. The points in (a) are coloured by activity (% inhibition) of each compound against the target. The colours in (b) show the score of each compound against the profile shown in Figure 2(a) chosen to identify compounds with a good balance of experimental potency and predicted ADME properties. The colours of the points indicate the compound scores and a plot of the scores is shown inset. Finally, (c) shows the compounds selected for initial *in vitro* ADME studies, focussing on the chemistries most likely to have a good balance of properties. The compound scores, based on the *in vitro* data, against the profile shown in Figure 2(b), are indicated by the colours and plotted in the inset graph. The compound ultimately selected as the development candidate is highlighted in blue in plots (b) and (c).



(a) **(b)**

Figure 2 Scoring profiles used for prioritisation of compounds intended for oral dosing against a cardiovascular target. The profile shown in (a) combines the experimentally measured target activity (as a percentage inhibition) with *in silico* predictions of solubility (log µM), human intestinal absorption (HIA), logP, inhibition of cytochrome P450s CYP2D6 and CYP2C9, active transport by P-gp, and blood-brain-barrier penetration (BBB). The profile shown in (b) combines the experimental activity with the primary *in vitro* ADME assay results for solubility in µM and human liver microsomal (HLM) stability measured as percentage remaining after a 40 minute incubation.