

Case Study

Balancing Properties in Early Lead Optimization

Background

Two of the major problems currently impacting productivity in drug discovery are the quality of initial hits and leads against targets, and the time taken to optimize those leads to candidates. Huge amounts of data are generated during the drug discovery process, whether *in silico*, *in vitro* or *in vivo*, and each of these data points will have a degree of error or uncertainty associated with it. Taking account of this uncertainty is essential to making balanced decisions on compound progression. Often it is ignored and compound prioritization is based on filtering out those which fail to reach a specified value in a particular screen. This approach can result in some of the best balanced compounds being discarded if they only just fail the specific criterion for one of several tests. The StarDrop proprietary scoring algorithm has been designed to accept all available experimental and predicted chemical, biological or ADME data, along with their associated uncertainties, and enable project teams to reach objective decisions on the most appropriate compounds to progress for their specific target.

Objective

In vitro potency, selectivity, solubility and microsomal stability data had been generated for a set of 150 client compounds. Compounds had previously been selected for *in vivo* study based on selectivity and potency, ignoring potential solubility and metabolic stability problems and resulting in poor bioavailability in rats. We were asked to select compounds with a balanced set of properties for progression *in vivo* using our proprietary prioritization suite.

Project Criteria		Score Weighting
Selectivity	> 8 fold	↓
Potency	< 1µM	
Solubility (2% DMSO)	> 10µM	
HLM Stability	< 60% turnover	
RLM Stability	< 60% turnover	

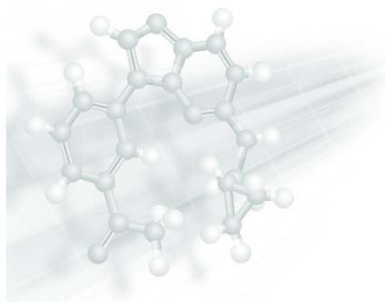
Profile 1 – Selectivity and Potency only

Historically, compounds were filtered and ranked on the basis of their selectivity and potency alone, with selectivity being the most important criterion. ***This approach did not take into account the errors and uncertainties in the experiments.*** The table on the right shows the top 16 compounds when ranked by this method. Highlighted is compound XXX572, which was neither the most selective nor the most potent compound in the set. Its relative position in the 'rankings' will be followed throughout this case study.

Name	Profile 1
XXX322	1
XXX326	2
XXX137	3
XXX292	4
XXX104	5
XXX318	6
XXX540	7
XXX313	8
XXX160	9
XXX289	10
XXX280	11
XXX502	12
XXX582	13
XXX572	14
XXX316	15

Selectivity 11 fold
Potency 0.21 uM





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Profile 2 – Factoring in Uncertainty

In consultation with the client, estimates were made of the experimental uncertainties in the assays they were using. These data were imported into StarDrop and the compounds were re-scored. In the table opposite, some compounds, now ranked according to Profile 2, shifted significantly in rank. Compound **XXX561** jumped from 28th to 12th position as it was extremely potent and, while it previously “failed” the selectivity cut-off of 8-fold, there was a relatively high probability that its true selectivity was indeed greater than 8-fold due to the uncertainties in the selectivity measurement.

Selectivity 7 fold
Potency 0.12 uM

Name	Profile 2	Profile 1
XXX326	1	2
XXX137	2	3
XXX322	3	1
XXX313	4	8
XXX540	5	7
XXX160	6	9
XXX572	7	14
XXX104	8	5
XXX292	9	4
XXX541	10	22
XXX318	11	6
XXX561	12	28
XXX280	13	11
XXX537	14	17
XXX502	15	12

Profile 3 – All Available In Vitro Data

Finally, taking into account all of the *in vitro* data along with accompanying statistics relating to experimental uncertainties, we saw a considerable change in the compound order. Compound **XXX572** was now on top because it satisfied four out of the five criteria. **XXX518** came second, as the only compound to satisfy all three of the ADME criteria with potency and selectivity data that, based on assay statistics, were not significantly below the required levels.

Selectivity 11 fold
Potency 0.21 uM
Solubility 136 uM
HLM 36%
RLM 86%

Selectivity 5 fold
Potency 1.67 uM
Solubility 138 uM
HLM 4%
RLM 38%

Name	Profile 3	Profile 2	Profile 1
XXX572	1	7	14
XXX518	2	52	36
XXX582	3	21	13
XXX295	4	16	16
XXX321	5	26	26
XXX025	6	38	35
XXX502	7	15	12
XXX274	8	35	25
XXX292	9	9	4
XXX316	10	44	15
XXX280	11	13	11
XXX278	12	18	23
XXX319	13	51	44
XXX294	14	17	24
XXX282	15	19	20

Value

Parallel optimization is essential to developing compounds with the correct balance of properties. In this study, we identified four compounds that had been overlooked by traditional compound selection based on selectivity and potency cut-off values. When tested *in vivo*, one of these compounds, **XXX518**, the only synthesized representative of a novel chemotype, was found to have a superior PK profile. Project chemists have now expanded this series, investigating ways of improving selectivity and potency in what appears to be a “Good ADME” chemotype. This new chemistry would not have been considered without the use of StarDrop.