Pilot study to compare a traditional HTS approach with AI-driven compound selection for the identification of kinase inhibitors

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1 INTRODUCTION

High-throughput screening (HTS) typically involves testing thousands of compounds in a step-wise manner, progressing putative hits from the initial single point testing through to XC_{50} determination, with an array of hit confirmation and counter screen assays included in the screening cascade. Selecting compounds for screening using Artificial Intelligence (AI) is a compelling alternative to the traditional HTS, with the potential to significantly reduce the number of compounds being tested and thereby shortening the time to advance initial hits into the Hit-to-Lead and Lead Optimisation phases of drug development.

In the present study, our approach to identifying inhibitors of a kinase implicated in a wide range of inflammatory conditions involved performing a HTS alongside profiling compounds selected using AI (Fig. 1). The HTS was performed on 160,000 compounds from the Charles River Lead Like and SoftFocus Kinase Libraries, taking eighteen weeks from the initiation of assay development through to completion of IC_{50} analysis.

The AI modelling was performed at Valo Health, Charles River's strategic partner for AI-powered drug discovery, using Valo's AI-powered Opal Computational Platform. Available training data were curated, models trained, and compounds selected within 3 weeks of project initiation. Compounds were selected from proprietary libraries and commercial suppliers for screening in the same assay as the compounds from the HTS.

2 STRATEGY

- The screening assay was developed and validated using the ADP-Glo™ Kinase technology (Promega) to screen 160,000 Charles River compounds in singlicate at 12.5µM in a 1536-well format.
- Compounds were tested under conditions that would favour identification of ATP competitive inhibitors of the target kinase.
- Putative hits from the HTS were progressed directly from single point testing to full concentration-response analysis, without the intermediate hit confirmation step routinely included in screening cascades, in order to accelerate the time to IC_{50} determination.
- Using Valo Health's proprietary AI platform a ligand based model to predict actives for the target kinase was used to prioritise compounds for evaluation. Approximately 150 compounds selected using AI, including 38 from commercial sources, were screened in concentration-response format alongside the actives from the HTS.
- Compounds progressed to concentration-response testing were additionally tested in a technology counter screen assay to identify compounds displaying off-target interference, and analysed by LCMS to confirm sample purity.

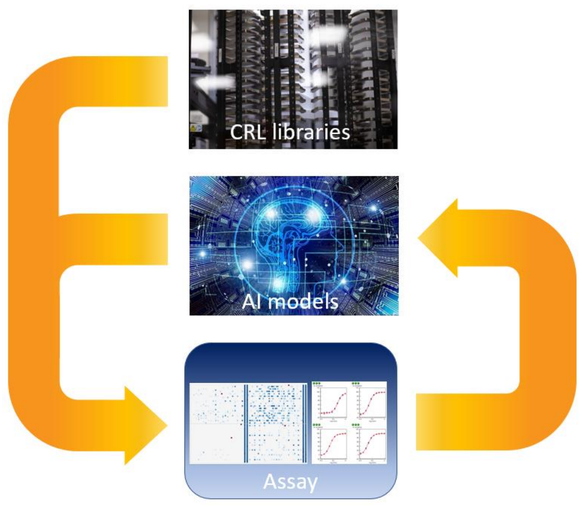

Fig. 1. Combining traditional curated libraries with AI selected novel libraries in initial HTS. Hits from that screen feed the AI model to build better predictions of improved potency (whilst optimising other properties) for Hit Expansion and continued SAR profiling rounds

3 RESULTS

- Hit compounds from the HTS were defined by a percentage inhibition threshold three standard deviations above the mean.
- 650 compounds (hit rate 0.4%) from the Lead Like and SoftFocus Kinase Libraries were selected (Fig. 2) for progression to testing in full concentration response curves to determine IC_{50} values.
- HTS hits screened in concentration-response format in parallel with AI selected compounds (Fig. 3).
- >50 compounds with IC_{50} < 1 µM.
- Traditional HTS yielded high proportion of sub-micromolar compounds, while AI approach produced several compounds with single digit nanomolar IC_{50}.
- 13 clusters of >9 compounds identified (Tanimoto score 0.6), largest cluster containing 91 compounds.
- Early SAR was identified and medicinal chemistry optimisation initiated.

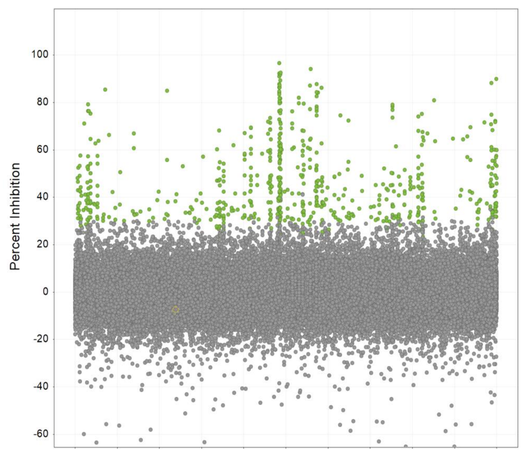

Fig. 2. Summary of Percent Inhibition data of 160,000 compounds screened at 12.5 µM against the target kinase, putative hit compounds with Percent Inhibition >3*SD above the mean (green)

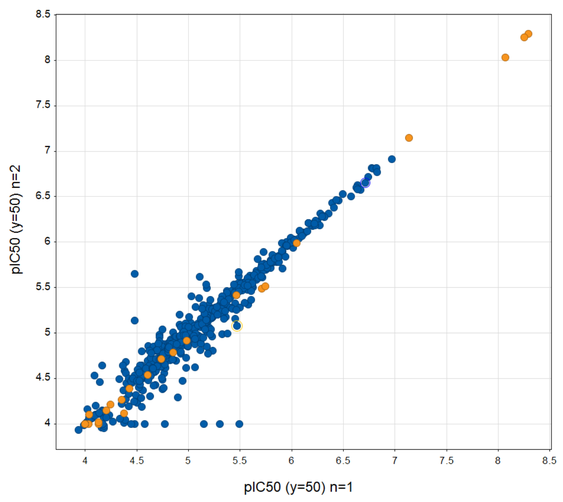

Fig. 3. pIC50 values (y=50) obtained from duplicate concentration-response testing of compounds progressed from CRL library (blue) compared to compounds selected using AI models (orange)

4 CONCLUSIONS

The study illustrates the benefits of the two approaches used here to identify inhibitors of the target kinase. The HTS identified multiple clusters of hit compounds, which due to the condensed screening cascade being employed was achieved within a reduced time frame. The confirmed hits identified in the HTS also generated preliminary SAR to enable a hit expansion and further medicinal chemistry optimisation, while from a relatively low number of compounds the AI modelling provided some highly potent inhibitors. The added value of using both strategies in parallel is in broadening the diversity of the hit series, taking the confirmed hits and feeding these compounds back into the AI to enrich the training models and then using the machine learning to plan future strategy. The two approaches form a powerful combination in drug discovery, accelerating the time to delivery of hit series for medicinal chemistry optimisation.

The integration of experimental and AI driven drug discovery can be accessed through Logica™, Charles River and Valo Health's combined offering in transformative drug design.

5 ACKNOWLEDGEMENTS

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