Supporting Compound Optimisation in Not-for-Profit and Academic Research

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Introduction

The not-for-profit and academic sectors have become important sources of novel drug candidates, particularly for neglected and developing world diseases or niche indications. Discovering new drugs in these sectors is even more challenging than in pharma for a number of reasons: challenging diseases, often affecting the developing word and with emerging resistance to current therapies; limited resources; and the need to manage complex data, often generated across large multi-centre collaborations.

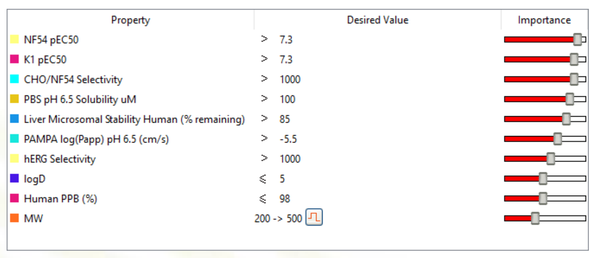
In this context, the need to make good decisions regarding which compounds to synthesise and assays to perform is critical. In this poster, we will describe an anti-malarial project and how integrated cheminformatics and computational chemistry software helped to guide the design of new compounds with a better chance of downstream success.

Project Background

Malaria is caused by plasmodium parasites transmitted through the Anopheles mosquito, most prevalent in tropical regions. Approximately 212 million cases of malaria occurred worldwide in 2015, resulting in 429,000 mortalities [1]. A major international effort aims to reduce the incidence of malaria by 90% by 2030, a big challenge given the emergence of resistance to the gold-standard artemisinin-based combination therapy in South-East Asia.

The project described here is targeting a novel anti-malarial drug and is one of several that emerged from a screen of approximately 36,000 compounds from a large commercial library. The lead compound property criteria are shown in Figure 1.

Figure 1. Profile of property criteria for an ideal lead, including potency against both the drug-sensitive NF54 and multi-drug resistant K1 strains of parasite, selectivity against cytotoxicity and a broad range of ADMET properties.



Challenges

The project team faced optimisation challenges in this series, including:

- Achieving sufficient potency against both the NF54 and K1 strains.
- Improving solubility.
- Overcoming an undesirable 'bi-phasic' dose response observed for some compounds in the K1 strain, as illustrated in Figure 2, possibly indicating polypharmacology.

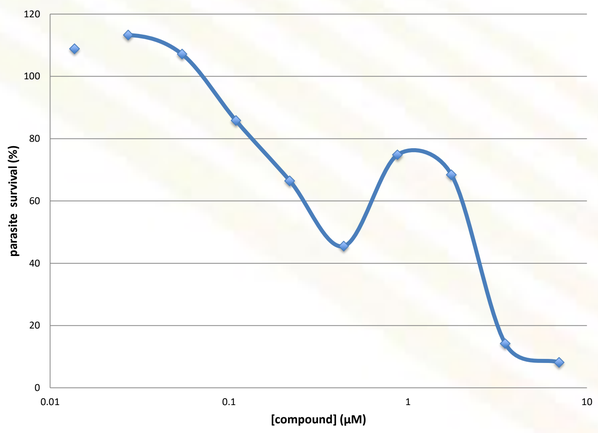


Figure 2. Example of an undesirable 'bi-phasic' dose response

Chemistry

The chemical series is characterised by a common core, which cannot be revealed for confidentiality. Optimisation focused on substitutions at positions R1 and R2, as shown in Figure 3.

Figure 3. Schematic indicating the substitution positions R1 and R2.

Matched Molecular Pair Analysis of Potency

Matched molecular pair analysis (MMPA) of multiple chemical series from the initial screen indicates that piperazine and morpholino substitutions tend to increase inhibition, as shown in Figure 4.

A 3D alignment between compounds from the current series and those from the screen suggests that this SAR will be transferable at position R2, as shown in Figure 5.

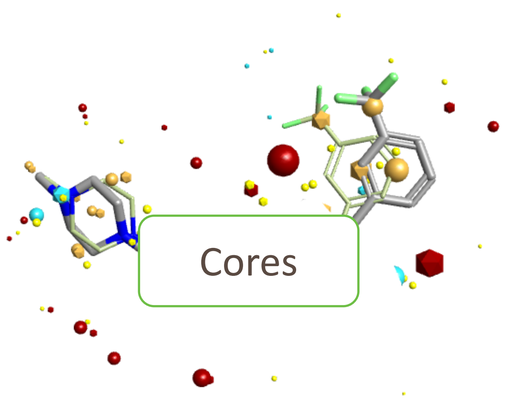


Figure 5. Example alignment between a compound from the current series and another from the initial screen, performed in the torch3D™ module of StarDrop [1] and based on Cresset's field-based technology [2].

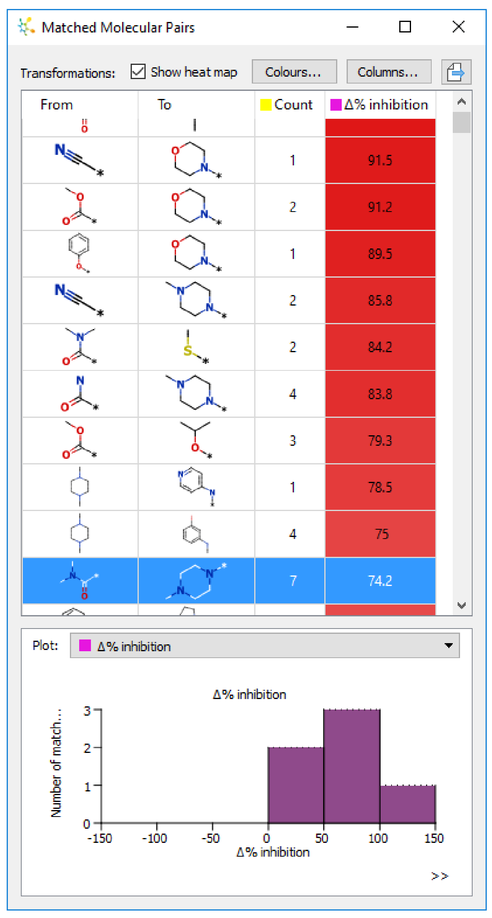


Figure 4. Illustrative results of MMPA of ~3,000 compounds, showing the change in % inhibition of the NF54 strain at 1.3 µM.

Improving Solubility

Early compounds in the project had poor solubility when measured in phosphate-buffered solution (PBS) at pH 6.5. These data are not expected to correlate directly with the quantitative structure-activity relationship model of intrinsic, aqueous solubility in StarDrop [3]; however Figure 6 shows that compounds predicted to have high aqueous solubility are significantly more likely to also achieve good solubility in PBS at pH 6.5.

This enabled selection of compounds for the next round of synthesis that predominantly met the experimental criterion of >100 µM in PBS at pH 6.5. Furthermore, these included compounds with piperazine substituents at position R2.

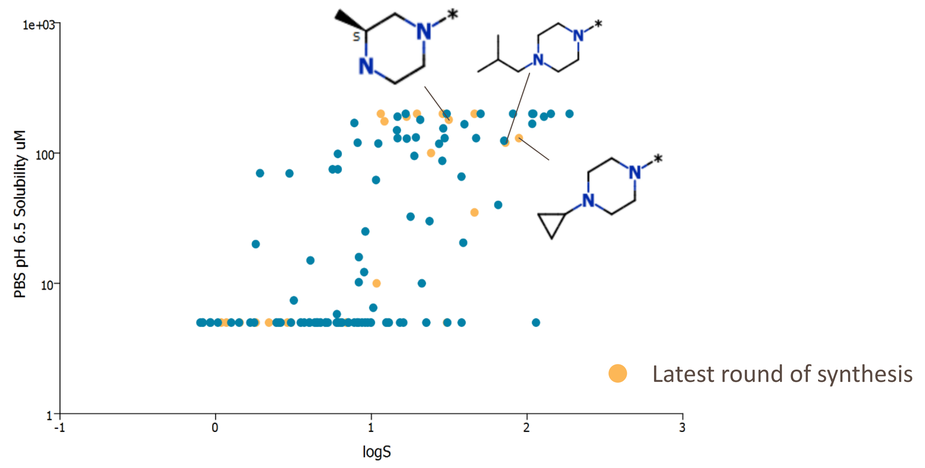


Figure 6. Plot of predicted intrinsic aqueous solubility (logS) against experimental solubility in PBS at pH 6.5. The most recently synthesised compounds predominantly achieve the experimental criteria of >100 µM.

Overcoming Bi-phasic Response

As Figure 7(a) shows, the compounds observed to exhibit a bi-phasic response against the K1 strain had a topological polar surface area (TPSA) of 66 Å, which corresponds to the TPSA of the core with non-polar substituents. The only exceptions to this contain reactive nitrile substituents. This suggested that the addition of polar substituents, such as piperazine, would reduce the risk of a bi-phasic response, which was confirmed by the compounds synthesised and tested subsequently (Figure 7(b)).

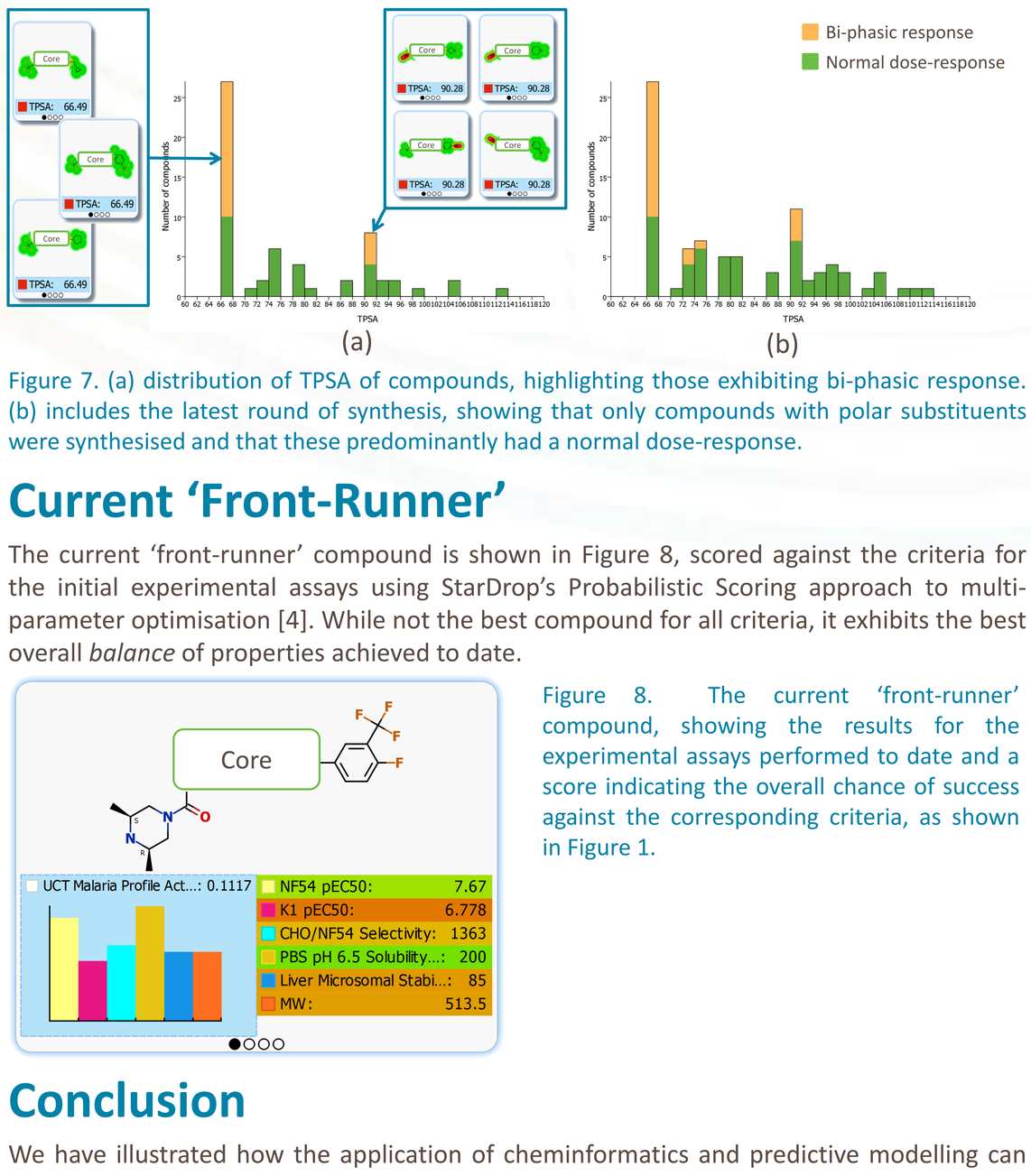


Figure 7. (a) distribution of TPSA of compounds, highlighting those exhibiting bi-phasic response. (b) includes the latest round of synthesis, showing that only compounds with polar substituents were synthesised and that these predominantly had a normal dose-response.

Current 'Front-Runner'

The current 'front-runner' compound is shown in Figure 8, scored against the criteria for the initial experimental assays using StarDrop's Probabilistic Scoring approach to multi-parameter optimisation [4]. While not the best compound for all criteria, it exhibits the best overall *balance* of properties achieved to date.

Figure 8. The current 'front-runner' compound, showing the results for the experimental assays performed to date and a score indicating the overall chance of success against the corresponding criteria, as shown in Figure 1.

Conclusion

We have illustrated how the application of cheminformatics and predictive modelling can help to guide the multi-parameter optimisation of high-quality compounds in the context of a challenging, not-for-profit drug discovery project. The seamless integration of these methods helps to improve and accelerate the decision-making process.

References

[1] World Heath Organisation 2016 World Malaria Report

[2] StarDrop. www.optibrium.com/stardrop

[3] Cresset. www.cresset-group.com/products/

[4] Obrezanova *et al.* J. Comp.-Aided Mol. Design (2008) 22(6-7) pp. 431-440

[5] M.D. Segall. Curr. Pharm. Des. (2012) 18(9) pp. 1292-1310