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CASE STUDY with Optibrium and the Open Source Malaria Consortium

Machine learning identifies novel antimalarial compound in global challenge

Executive summary

Malaria is a tropical disease transmitted by mosquitoes that infects millions every year. Intellegens participated with drug discovery software partner Optibrium, in a global challenge organised by the Open Source Malaria consortium to design new antimalarial compounds with a novel mechanism of action despite the sparsity of available experimental bioactivity data. Applying the Alchemite™ deep learning methodology, Intellegens and Optibrium achieved joint success, and the results have now been published in the *Journal of Medicinal Chemistry*.

- Alchemite™ predicted a new antimalarial compound which showed good potency when synthesised and tested.
- The study outperformed alternative approaches, succeeding despite the sparsity of available experimental bioactivity data.
- Alchemite™ opened up new possibilities - the compound identified would have been dismissed as a candidate by the chemists assessing the project.

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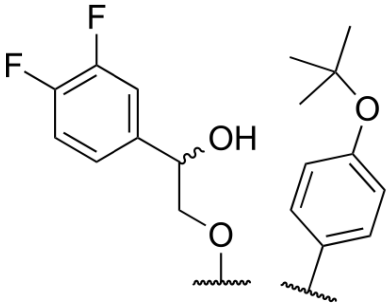
Challenge

Malaria is a parasitic infection transmitted by mosquitoes in tropical countries. A single bite from a mosquito carrying the disease is enough to become infected and, if not diagnosed and treated promptly, it can be fatal. There are approximately half a million deaths every year worldwide.

The goal of this project was to identify new antimalarial compounds using a novel mechanism of action. Over six years, the Open Source Malaria (OSM) consortium has brought together an international team of researchers who design, synthesise, and test new antimalarial candidates with the hope that they will demonstrate potent activity against *Plasmodium falciparum*, the deadliest species of the malaria-causing parasite. However, the available experimental bioactivity data is sparse; for all of the different types of experiments that are available, only a very small proportion of the compounds have actually been measured.

Outcome

Alchemite™ was applied to novel compounds generated automatically by Optibrium's drug discovery software to predict the activity of these compounds based on the very sparse available bioactivity data. A compound (*right*) that was confidently predicted to be active was proposed for synthesis and testing. The experimental validation showed good potency. Moreover, the measured activity was in strong agreement with the predicted values. This work has now been published as a peer-reviewed paper in the *Journal of Medicinal Chemistry*.



Optibrium/Intellegens
Pfal: 0.46 µM
*Pf*ATP4: Yes

The predictive accuracy of Alchemite™ earned Intellegens and Optibrium a prize in the competition, as the model presented was shown to outperform conventional quantitative

structure-activity relationship (QSAR) and other AI models in a blind test conducted by OMS.

In the J. Med Chem. publication, the project team comment that: “the Optibrium/Intellegens suggestion that included the tert-butyl pendant was thought by the human team to be a certain inactive, given what was known of variation in that part of the molecule (where related substituents such as -OMe have been observed to perform poorly, and much time had been spent in the production of inactive variants); yet, this compound displayed good potency and is a particularly useful outcome.” Indeed, the Chemists involved in assessing the challenge said that they would have dismissed the candidate as “ill advised”. This demonstrates the potential of Alchemite™ to open up productive new pathways in the drug discovery process.

“Congratulations to the Optibrium/Intellegens team for contributing one of the best models, using Alchemite. We’re excited by the new molecules that were suggested because they are not ones that we would necessarily have thought of ourselves.”

Dr Matthew Todd
Professor of Drug Discovery, UCL School of Pharmacy
Founder of the OSM.

Publications

T. M. Whitehead, B. W. J. Irwin, P. Hunt, M. D. Segall, and G. J. Conduit (2019). Imputation of Assay Bioactivity Data Using Deep Learning. Journal of Chemical Information and Modeling, 59(3), 1197-1204. DOI: 10.1021/acs.jcim.8b00768

E. G. Tse, L. Aithani, M. Anderson, J. Cardoso-Silva, G. Cincilla, G. J. Conduit, M. Galushka, D. Guan, I. Hallyburton, B. W. J. Irwin, K. Kirk, A. M. Lehane, J. C. R. Lindblom, R. Lui, S. Matthews, J. McCulloch, A. Motion, H. L. Ng, M. Öeren, M. N. Robertson, V. Spadavecchio, V. A. Tatsis, W. P. van Hoorn, A. D. Wade, T. M. Whitehead, P. Willis, and M. H. Todd (2021). An Open Drug Discovery Competition: Experimental Validation of Predictive Models in a Series of Novel Antimalarials, Journal of Medicinal Chemistry.DOI: 10.1021/acs.jmedchem.1c00313

Future opportunities

Three key opportunities offered by machine learning are:

- The predictive accuracy of Alchemite™'s models allows for the prioritisation of high-quality active compounds.
- The underlying model can be continually improved by including more historical data and/or new experimental results.
- Alchemite™ predictions can be used in a Design of Experiments campaign, to suggest which experimental measurements to take next in order to optimise the model's predictions.

About the featured organisations

The Open Source Malaria consortium, founded in 2012, aims to find new treatments for malaria. The OSM brings together an international team of researchers who design, synthesise, and test new antimalarial candidates, guided by open-source principles, everything is open and anyone can contribute.

Optibrium provides elegant software solutions for small molecule design, optimisation, and data analysis. Founded in 2009, Optibrium develops new products and technologies to improve the efficiency of the drug discovery process. They work closely with a broad range of customers and collaborations that include leading global pharmaceutical, agrochemical, and flavouring companies, biotech, and academic groups.

Intellegens provides a unique machine learning solution for real-world experimental and process data problems in industrial R&D and manufacturing. The Alchemite™ deep learning software, which originated in the University of Cambridge, can train deep neural networks from sparse or noisy data, where other machine learning approaches fail. This has enabled it to accelerate innovation for applications including design of aerospace alloys and components, development of formulated products, drug discovery, additive manufacturing, and optimisation of chemical processes.

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