

THE MALARIA BOX: A Catalyst for Drug Discovery

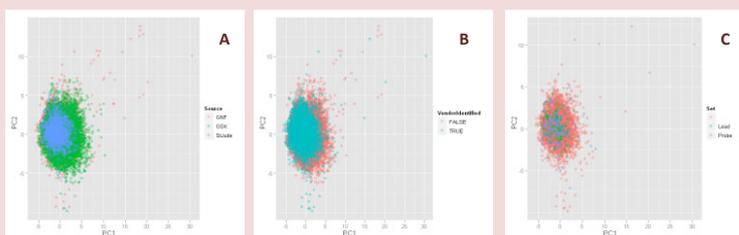
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Introduction

The Open Access Malaria Box is a treasure trove of 400 diverse compounds with antimalarial activity, assembled by MMV and SCYNEXIS in a bid to catalyse malaria and neglected disease drug discovery and research.

Making the selection

The 400 compounds were distilled from ~20,000 antimalarial hits generated by phenotypic screening of ~4,000,000 compounds from the research libraries of St. Jude Children's Research Hospital, Novartis and GSK.^[1,2,3] The first criteria for Malaria Box compounds was that they be commercially available. From the ~5000 compounds that were, the selection was then made to maximize the chemical diversity in the box, as assessed by Principal Component Analysis. The compounds (600) were then retested in a confirmatory assay for blood-stage activity against *P. falciparum* and finally reviewed by expert medicinal chemists to provide 200 diverse "drug-like" compounds as starting point for oral drug discovery and development along with 200 diverse "probe-like" compounds for use as biological tools.^[4]



Principal Component Analysis. Panel A: Chemical diversity of the 20,000 antimalarial hits Panel B: Chemical diversity of the 20,000 antimalarial hits (in red) overlaid with the commercially available selection (in blue, 5000) Panel C: Chemical diversity of the "drug-like" set (in green) and "probe-like" set (in blue). The commercially available selection from panel B is displayed in red.

Requesting and shipping

Available for free on request at www.mmv.org/malariabox, the Malaria Box can be delivered to researchers across the world. To date, more than 100 shipments have been made to more than 20 countries. In exchange, recipients agree to share their resulting data with the scientific community within 2 years.

Testing

A plethora of malaria screening activities (>100 whole-cell and target-based) are currently being conducted to identify chemotypes of interest and to understand their mode of action. Additionally, the Malaria Box is being screened for activity against numerous additional neglected tropical diseases as well as HIV and cancer. Scientists joining forces across the world to annotate a specific set of compounds in this manner is unprecedented: *The same tool box for a diverse range of therapeutic areas.*

To further catalyse the drug discovery process, MMV has sponsored *in vitro* DMPK and Pharmacokinetic studies (oral exposure in mouse) for all 400 compounds.



1) Gamo F-J, Sanz LM, Vidal J, de Cozar C, Alvarez E, et al. (2010) Thousands of chemical starting points for antimalarial lead identification. *Nature* 465: 305–310.

2) Guiguemde WA, Shelat AA, Bouck D, Duffy S, Crowther GJ, et al. (2010) Chemical genetics of *Plasmodium falciparum*. *Nature* 465: 311–315.

3) Meister S, Plouffe DM, Kuhlen KL, Bonamy GMC, Wu T, et al. (2011) Imaging of *Plasmodium* Liver Stages to Drive Next-Generation Antimalarial Drug Discovery, *Science* 334: 1373-1377

4) Burrows JN, Kowalczyk P, McDonald S, Spangenberg T, Wells TNC and Willis P. The Open Access Malaria Box: A Drug Discovery Catalyst for Neglected Diseases, (article in preparation)

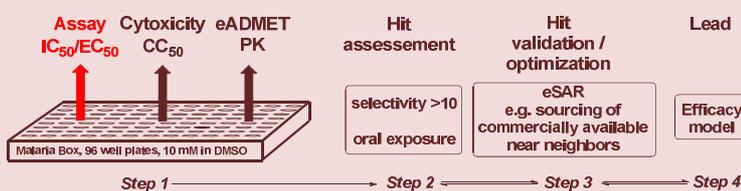
5) For more details about Target Compound Profiles and early/late lead qualification criteria, please visit our website : www.mmv.org

Sharing the data

Recently launched on the European Bioinformatic Institute portal, the ChEMBL malaria database, www.ebi.ac.uk/chembl/malaria, provides a one-stop shop for malaria drug data including data related to targets, assays and compounds. The database contains all public compounds for which there is bioactivity data from a malaria-related screen. The Malaria Box compounds are included in the database along with data resulting from other research. This tool therefore offers a global overview of compound bioactivities helping to catalyze the development of new drugs for neglected diseases.

Following up

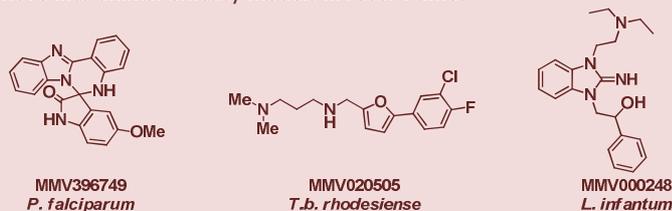
Should chemistry resources be limited, sourcing commercially available 'near neighbors' of a hit enables you to have an initial insight into the Structure-Activity-Relationship (eSAR) and therefore may allow rapid progress of the compound into *in vivo* efficacy models.



Preliminary results

Malaria. MMV396749 has been identified via mice PK to have very good exposure and long half-life (>5 h), placing the compound in an optimal position for further study/optimisation. The compound is currently being tested in an *Plasmodium* efficacy model.^[5]

Human African Trypanosomiasis and Leishmaniasis. In close collaboration with DNDi and University of Antwerp, MMV020505 and MMV000248 showed both *in vitro* potency and oral exposure in mice PK allowing them to move into animal efficacy models in record time!



Perspectives

The Malaria Box is a unique set of confirmed antimalarials that will catalyse new medicinal chemistry programmes in malaria and neglected tropical disease research. Moreover, by making the Malaria Box open access we aim to trigger a virtuous circle of open source drug discovery initiatives. Overtime, we hope that this tool will help the research community to better understand the similarities and differences between diseases.

Acknowledgements

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