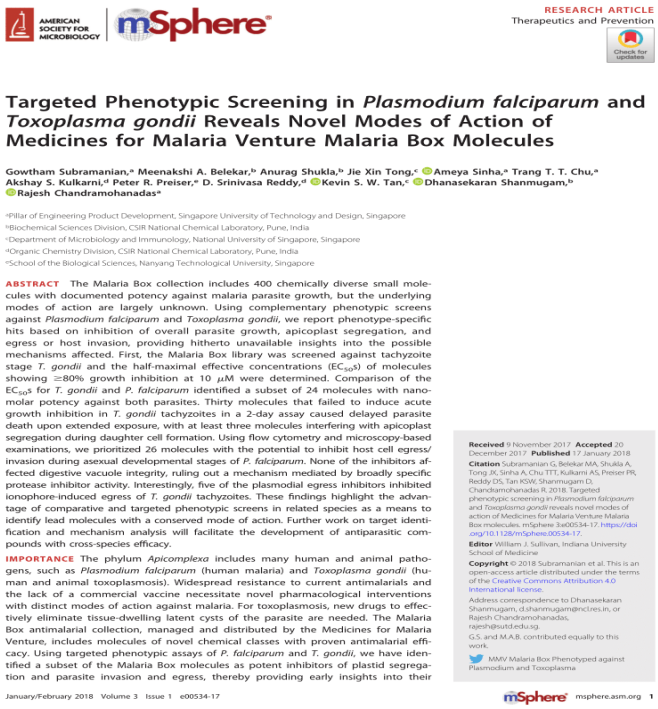
Apicomplexan Parasites: Molecular Approaches toward Targeted Drug Development (Drug Discovery in Inf



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Targeted Phenotypic Screening in *Plasmodium falciparum* and *Toxoplasma gondii* Reveals Novel Modes of Action of Medicines for Malaria Venture Malaria Box Molecules

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ABSTRACT The Malaria Box collection includes 400 chemically diverse small molecules with documented potency against malaria parasite growth, but the underlying modes of action are largely unknown. Using complementary phenotypic screens against *Plasmodium falciparum* and *Toxoplasma gondii*, we report phenotype-specific hits based on inhibition of overall parasite growth, apicoplast segregation, and egress or host invasion, providing hitherto unavailable insights into the possible mechanisms affected. First, the Malaria Box library was screened against tachyzoite stage *T. gondii* and the half-maximal effective concentrations (EC_{50}s) of molecules showing ≥80% growth inhibition at 10 μM were determined. Comparison of the EC_{50}s for *T. gondii* and *P. falciparum* identified a subset of 24 molecules with nanomolar potency against both parasites. Thirty molecules that failed to induce acute growth inhibition in *T. gondii* tachyzoites in a 2-day assay caused delayed parasite death upon extended exposure, with at least three molecules interfering with apicoplast segregation during daughter cell formation. Using flow cytometry and microscopy-based examinations, we prioritized 26 molecules with the potential to inhibit host cell egress/invasion during asexual developmental stages of *P. falciparum*. None of the inhibitors affected digestive vacuole integrity, ruling out a mechanism mediated by broadly specific protease inhibitor activity. Interestingly, five of the plasmodial egress inhibitors inhibited ionophore-induced egress of *T. gondii* tachyzoites. These findings highlight the advantage of comparative and targeted phenotypic screens in related species as a means to identify lead molecules with a conserved mode of action. Further work on target identification and mechanism analysis will facilitate the development of antiparasitic compounds with cross-species efficacy.

IMPORTANCE The phylum *Apicomplexa* includes many human and animal pathogens, such as *Plasmodium falciparum* (human malaria) and *Toxoplasma gondii* (human and animal toxoplasmosis). Widespread resistance to current antimalarials and the lack of a commercial vaccine necessitate novel pharmacological interventions with distinct modes of action against malaria. For toxoplasmosis, new drugs to effectively eliminate tissue-dwelling latent cysts of the parasite are needed. The Malaria Box antimalarial collection, managed and distributed by the Medicines for Malaria Venture, includes molecules of novel chemical classes with proven antimalarial efficacy. Using targeted phenotypic assays of *P. falciparum* and *T. gondii*, we have identified a subset of the Malaria Box molecules as potent inhibitors of plastid segregation and parasite invasion and egress, thereby providing early insights into their

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MMV Malaria Box Phenotyped against Plasmodium and Toxoplasma

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(Drug Discovery in Infectious Diseases). Code: Price: The need for new approaches to tropical disease drug discovery Drug development and registration for parasitic .. target molecules are crucial for the pathogenic agent or the pathological In countries like China, India, Cote d' Ivoire and Mali, to A plastid of probable green algal origin in Apicomplexan parasites.Table 1. Approaches to antimalarial drug discovery and development .. A plastid organelle as a drug target in apicomplexan parasites. Nature , - This review will focus on the molecular target approach to drug discovery and how the use Effective against drug-resistant parasites (e.g. those that have developed resistance to chloroquine or Fansidar) . although genetic manipulation of the related apicomplexan parasite, Toxoplasma gondii [36], .. J Chem Inf Model.Thus, virtual screening approach complemented by mathematical of interest for drug development against these parasites [1114]. To understand the mechanism of drug-target recognition, the Six FabD receptors were used in molecular docking calculations with the above filtered ligand dataset.