Chemogenomic Approaches to Single and Dual-Stage Antimalarial Agents

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Antimalarial drugs currently in use engage a reduced number of validated targets, and their efficacy is being undermined by the spread of parasite resistance. In addition, chemical diversity among these drugs is limited, which also contributes to the emergence of cross-resistance. Antimalarial drug discovery has traditionally focused on the optimization of known lead compounds to achieve efficacious drug exposures with the lowest possible dose. Recently, ligand- and structure-based design approaches complemented by cell-based screening have been developed to identify innovative and readily synthesizable hit and lead compounds. Here, we review how low molecular weight as well as chimeric compounds have been designed and synthesized to engage different molecular targets in malaria parasites, enabling efficient elimination of parasites both in vitro and in vivo. In addition, we will report how structure-based design and target agnostic cell-based screening led to the discovery of novel small molecules that will help to overcome our limited understanding of *Plasmodium* biology.

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