A052 · Structure and Sequence Guided Drug Repurposing Framework for Antimalarial Target Discovery

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Malaria remains one of the deadliest infectious diseases, causing over 200 million cases and roughly 600,000 deaths annually. Rising drug resistance in Plasmodium falciparum makes new therapeutics increasingly urgent, but discovery is hampered by low hit rates in high-throughput screens and limited understanding of which parasite proteins are druggable. We present a computational pipeline for drug repurposing that leverages existing drug-protein interaction data to prioritize candidate antimalarial compounds. Starting from active compounds identified through growth-inhibition screening against P. falciparum, we identify known protein targets and assess sequence and structural similarity between these targets and parasite proteins. Drugs whose targets show strong homology to a parasite protein are flagged as potential binders and further validated through structural modeling and binding-energy analysis. In parallel, we apply the pipeline in reverse-search mode across a druggability-informed map of the P. falciparum proteome, generating AlphaFold 3 structural models where experimental structures are unavailable. We test the pipeline's generalizability on an independent set of 50 compounds against 541 known druggable parasite proteins. This work produces a ranked, structure-informed map of the druggable Plasmodium proteome and experimentally supported compound-target relationships, including high-confidence drug-protein pairs. Future work will scale this approach to libraries of thousands of compounds, systematically mapping interactions and binding sites across the druggable malaria proteome. A Plasmodium-tuned structural tool as an HPC-ready repository will be provided.

Structure and Sequence Guided Drug Repurposing Framework for Antimalarial Target Discovery

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Rising drug resistance in *Plasmodium falciparum* makes new antimalarial therapeutics increasingly urgent, yet discovery is hampered by low screening hit rates and limited knowledge of druggable parasite proteins. We present a computational drug-repurposing pipeline that leverages existing drug-protein interaction data to prioritize candidate antimalarial compounds. Starting from active compounds identified through growth-inhibition screening against *P. falciparum*, we identify their known protein targets and assess sequence and structural similarity between these targets and *P. falciparum* proteins. Drugs whose targets show strong homology to parasite proteins are prioritized as potential binders, with predicted interactions further evaluated through structural modeling and binding-energy analysis. This approach yields high-confidence drug–protein pairs linking known drugs to specific, previously unmapped malaria targets.

In parallel, we apply the pipeline in reverse-search mode to a curated set of ~50 drugs and a druggability-informed map of the *P. falciparum* proteome comprising 541 known druggable proteins from prior structure-based druggability mining. This identifies the parasite proteins each drug is most likely to engage. Given the limited availability of experimentally resolved *Plasmodium* structures, we generate models for relevant proteins using AlphaFold 3, enabling structural comparison and interaction analysis for previously uncharacterized targets. This provides additional validation of the pipeline and expands high-confidence drug–protein predictions across a broader, structure-informed proteome map.

Building on this framework, we plan to scale the approach to thousands of compounds, systematically mapping predicted interactions and binding sites across the druggable *Plasmodium* proteome. To date, the work has delivered a ranked, structure and function-informed map of the druggable *Plasmodium* proteome. We have also generated an experimentally supported compound-target set of relationships, with high-confidence drug-protein pairs from initial validation. A *Plasmodium*-tuned structural tool as an HPC-ready repository will be provided as our future work.

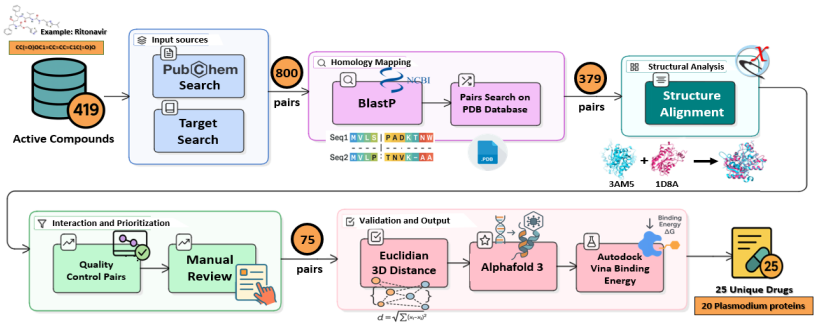

Figure 1. Computational Drug-repurposing Pipeline. Identifying known protein targets for the initial drug dataset and assessing sequence and structural similarity between these targets and *P. falciparum* proteins.