Small molecule inhibition of apicomplexan FtsH1 disrupts plastid biogenesis in human pathogens

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The malaria parasite *Plasmodium falciparum* and related apicomplexan pathogens contain an essential plastid organelle, the apicoplast, which is a key anti-parasitic target. Derived from secondary endosymbiosis, the apicoplast depends on novel, but largely cryptic, mechanisms for protein/lipid import and organelle inheritance during parasite replication. These critical biogenesis pathways present untapped opportunities to discover new parasite-specific drug targets. We used an innovative screen to identify actinonin as having a novel mechanism-of action inhibiting apicoplast biogenesis. Resistant mutation, chemical-genetic interaction, and biochemical inhibition demonstrate that the unexpected target of actinonin in *P. falciparum* and *Toxoplasma gondii* is FtsH1, a homolog of a bacterial membrane AAA+ metalloprotease. P*f*FtsH1 is the first novel factor required for apicoplast biogenesis identified in a phenotypic screen. Our findings demonstrate that FtsH1 is a novel and, importantly, druggable antimalarial target. Development of FtsH1 inhibitors will have significant advantages with improved drug kinetics and multistage efficacy against multiple human parasites.

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