Lysyl-tRNA synthetase as a drug target in malaria and cryptosporidiosis.

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Malaria and cryptosporidiosis, caused by apicomplexan parasites, remain major drivers of global child mortality. New drugs for the treatment of malaria and cryptosporidiosis, in particular, are of high priority; however, there are few chemically validated targets. The natural product cladosporin is active against blood- and liver-stage *Plasmodium falciparum* and *Cryptosporidium parvum* in cell-culture studies. Target deconvolution in *P. falciparum* has shown that cladosporin inhibits lysyl-tRNA synthetase (*Pf*KRS1). Here, we report the identification of a series of selective inhibitors of apicomplexan KRSs. Following a biochemical screen, a small-molecule hit was identified and then optimized by using a structure-based approach, supported by structures of both *Pf*KRS1 and *C. parvum* KRS (*Cp*KRS). In vivo proof of concept was established in an SCID mouse model of malaria, after oral administration (ED_{90} = 1.5 mg/kg, once a day for 4 d). Furthermore, we successfully identified an opportunity for pathogen hopping based on the structural homology between *Pf*KRS1 and *Cp*KRS. This series of compounds inhibit *Cp*KRS and *C. parvum* and *Cryptosporidium hominis* in culture, and our lead compound shows oral efficacy in two cryptosporidiosis mouse models. X-ray crystallography and molecular dynamics simulations have provided a model to rationalize the selectivity of our compounds for *Pf*KRS1 and *Cp*KRS vs. (human) *Hs*KRS. Our work validates apicomplexan KRSs as promising targets for the development of drugs for malaria and cryptosporidiosis.