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Design, synthesis and evaluation of novel leads for drug-resistant malaria

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Malaria is caused by parasite infection of the genus *Plasmodium*. Human infection is caused by one of five *Plasmodium* species including *falciparum, malariae, knowlesi, vivax* and *ovale. P. falciparum* is associated with the most severe form of malaria and responsible for approximately 400,000 deaths per year. A number of antimalarial drugs are currently used to treat malaria. However, *P. falciparum*, which is responsible for mortality especially in Eastern and Southern Africa, has developed resistance to all currently used drugs. Hence, there is a great need for the development of new drugs for malaria. Here, we report non-symmetrical furan-amidines as novel antimalarial leads. The non-symmetrical furan-amidines were originally designed and shown to be inhibitors of NRH:quinone oxidoreductase 2 (NQO2), a potential therapeutic target in cancer chemotherapy. The malaria parasite *P. falciparum* contains an enzyme that has similar activity to NQO2 called PfNDH2, therefore the non-symmetrical furan-amidines were tested against *Plasmodium*. The most active furan-amidines showed IC50 values in the nanomolar range for the inhibition of *P. falciparum* erythrocyte development. Interestingly, upon screening, the most active non-symmetrical furan-amidines showed poor inhibition of Pf*N*DH2. In addition, the non-symmetrical furan-amidines showed very low binding affinities towards DNA in comparison to the known symmetrical furan-amidine (DB75), which is a known DNA intercalator. This confirmed that the non-symmetrical furan-amidines are not DNA intercalators and do not target the Pf*N*DH2 enzyme. Synthesis of further novel non-symmetrical furan-amidines and their target identification is ongoing.

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