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Development of a novel drug for uncomplicated malaria targeting the mitochondrial NADH: quinone oxidoreductase

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NADH:quinone oxidoreductase (PfNDH2) represents a metabolic choke point in the respiratory chain of *Plasmodium falciparum* mitochondria and is the focus of a drug discovery programme. A miniaturised assay for recombinant PfNDH2 with robust assay performance measures was generated for the high throughput screening (HTS) of a focused library of 17,000 drug-like compounds. A quantitative structure-activity relationship has been developed around one of the chemical templates derived from the HTS hits. Lead molecules developed to date show selective inhibitory activity against PfNDH2 versus *P. falciparum* bc_1 or dihydroorotate dehydrogenase (DHODH). Potent enzyme inhibition is accompanied by *in vitro* parasite kill of multidrug-resistant strains in the low nM range and clearance of parasites from *in vivo P. berghei* models. Lead molecules also display excellent *in vitro* therapeutic indices against human cell lines and bovine *bc1.* Initial metabolic studies in human liver microsomes and hepatocytes indicate favourable pharmacology. These data support the further development of this new candidate drug targeting a novel parasite component.

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