

A drug repositioning approach was leveraged to derivatize astemizole (AST), an antihistamine drug whose antimalarial activity was previously identified in a high-throughput screen. The multistage activity potential against the *Plasmodium* parasite's life cycle of the subsequent analogues was examined by evaluating against the parasite asexual blood, liver, and sexual gametocytic stages. In addition, the previously reported contribution of heme detoxification to the compound's mode of action was interrogated. Ten of the 17 derivatives showed half-maximal inhibitory concentrations (IC₅₀s) of <0.1 µM against the chloroquine (CQ)-sensitive *Plasmodium falciparum* NF54 (*Pf*NF54) strain while maintaining submicromolar potency against the multidrug-resistant strain, *Pf*K1, with most showing low likelihood of cross-resistance with CQ. Selected analogues (*Pf*NF54-IC₅₀ < 0.1 µM) were tested for cytotoxicity on Chinese hamster ovarian (CHO) cells and found to be highly selective (selectivity index > 100). Screening of AST and its analogues against gametocytes revealed their moderate activity (IC₅₀: 1–5 µM) against late stage *P. falciparum* gametocytes, while the evaluation of activity against *P. berghei* liver stages identified one compound (**3**) with 3-fold greater activity than the parent AST compound. Mechanistic studies showed a strong correlation between *in vitro* inhibition of β-hematin formation by the AST derivatives and their antiplasmodium IC₅₀s. Analyses of intracellular inhibition of hemozoin formation within the parasite further yielded signatures attributable to a possible perturbation of the heme detoxification machinery.