Novel type II fatty acid biosynthesis (FAS II) inhibitors as multistage antimalarial agents.


Abstract

Malaria is a potentially fatal disease caused by Plasmodium parasites and poses a major medical risk in large parts of the world. The development of new, affordable antimalarial drugs is of vital importance as there are increasing reports of resistance to the currently available therapeutics. In addition, most of the current drugs used for chemoprophylaxis merely act on parasites already replicating in the blood. At this point, a patient might already be suffering from the symptoms associated with the disease and could additionally be infectious to an Anopheles mosquito. These insects act as a vector, subsequently spreading the disease to other humans. In order to cure not only malaria but prevent transmission as well, a drug must target both the blood- and pre-erythrocytic liver stages of the parasite. P. falciparum (Pf) enoyl acyl carrier protein (ACP) reductase (ENR) is a key enzyme of plasmodial type II fatty acid biosynthesis (FAS II). It has been shown to be essential for liver-stage development of Plasmodium berghei and is therefore qualified as a target for true causal chemoprophylaxis. Using virtual screening based on two crystal structures of PfENR, we identified a structurally novel class of FAS inhibitors. Subsequent chemical optimization yielded two compounds that are effective against multiple stages of the malaria parasite. These two most promising derivatives were found to inhibit blood-stage parasite growth with IC(50) values of 1.7 and 3.0 μM and lead to a more prominent developmental attenuation of liver-stage parasites than the gold-standard drug, primaquine.

Involved Units and Groups

Infection Biology

HKI-Authors