2-Hexadecynoic acid inhibits plasmodial FAS-II enzymes and arrests erythrocytic and liver stage Plasmodium infections

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Acetylenic fatty acids are known to display several biological activities, but their antimalarial activity has remained unexplored. In this study, we synthesized the 2-, 5-, 6-, and 9-hexadecynoic acids (HDAs) and evaluated their in vitro activity against erythrocytic (blood) stages of Plasmodium falciparum and liver stages of Plasmodium yoelii infections. Since the type II fatty acid biosynthesis pathway (PfFAS-II) has recently been shown to be indispensable for liver stage malaria parasites, the inhibitory potential of the HDAs against multiple P. falciparum FAS-II (PfFAS-II) elongation enzymes was also evaluated. The highest antiplasmodial activity against blood stages of P. falciparum was displayed by 5-HDA (IC(50) value 6.6 mug/ml), whereas the 2-HDA was the only acid arresting the growth of liver stage P. yoelii infection, in both flow cytometric assay (IC(50) value 2-HDA 15.3 mug/ml, control drug atovaquone 2.5 ng/ml) and immunofluorescence analysis (IC(50) 2-HDA 4.88 mug/ml, control drug atovaquone 0.37 ng/ml). 2-HDA showed the best inhibitory activity against the PfFAS-II enzymes PfFabI and PfFabZ with IC(50) values of 0.38 and 0.58 mug/ml (IC(50) control drugs 14 and 30 ng/ml), respectively. Enzyme kinetics and molecular modeling studies revealed valuable insights into the binding mechanism of 2-HDA on the target enzymes. All HDAs showed in vitro activity against Trypanosoma brucei rhodesiense (IC(50) values 3.7-31.7 mug/ml), Trypanosoma cruzi (only 2-HDA, IC(50) 20.2 mug/ml), and Leishmania donovani (IC(50) values 4.1-13.4 mug/ml) with generally low or no significant toxicity on mammalian cells. This is the first study to indicate therapeutic potential of HDAs against various parasitic protozoa. It also points out that the malarial liver stage growth inhibitory effect of the 2-HDA may be promoted via PfFAS-II enzymes. The lack of cytotoxicity, lipophilic nature, and calculated pharmacokinetic properties suggests that 2-HDA could be a useful compoun to study the interaction of fatty acids with these key P. falciparum enzymes
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