one-chloroquinoline Hybrid Analogues: In Silico Guided Design, Synthesis, Antiplasmodial Activity, In Vitro Metabolism, And Mechanistic Studies

Guantai, Eric; Ncokazi ., K; Egan, T; Et Al , J.

Abstract:

Analogues of the previously reported antimalarial hybrid compounds 8b and 12 were proposed with the aim of identifying compounds with improved solubility and retained antimalarial potency. In silico characterization predicted improved solubilities of the analogues, particularly at low pH; they retained acceptable predicted permeability properties but were predicted to be susceptible to hepatic metabolism. These analogues were synthesized and found to exhibit notable in vitro antimalarial activity. Compounds 25 and 27 were the most active of the analogues. In vitro metabolism studies indicated susceptibility of the analogues to hepatic metabolism. There was also evidence of primary glucuronidation for analogues 24 -27. Presumed cis- trans isomerism of 12, 22, and 23 under in vitro metabolism assay conditions was also observed, with differences in the nature and rates of metabolism observed between isomers. Biochemical studies strongly suggested that inhibition of hemozoin formation is the primary mechanism of action of these analogues.