IDENTIFICATION OF AN EARLY LEAD AND OPTIMIZATION STRATEGIES FOR THE DEVELOPMENT OF AN ORALLY BIOAVAILABLE LATE LEAD 4(1*H*)-QUINOLONE WITH ANTIMALARIAL ACTIVITY

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Previously, 6-chloro-7-methoxy-3-phenyl-4(1*H*)-quinolone was identified to be a promising candidate for in vivo antimalarial efficacy studies. Although it has potent antimalarial activity (EC50 < 10 nM against resistant strains) and acceptable aqueous solubility (6 µM at pH 7.4), the compound failed to reduce the parasitemia levels in *P. berghei* infected mice. Herein, we report our efforts to identify an orally bioavailable 4(1*H*)-quinolone with potent antimalarial activity. Degradation studies revealed that microsomal stability of the 4(1*H*)-quinolone series was as equally important as solubility when a 3-fluoroaryl analog was identified to have greater in vivo activity than the initial 6-chloro-7-methoxy-3-phenyl-4(1*H*)-quinolone. Follow-up SAR and SPR studies identified several compounds with increased microsomal stability and improved in vivo antimalarial activity (99% parasitemia suppression on day six PE at 50 mg/kg doses). The best compounds were found to be curative with all the mice surviving the infection of *P. berghei* after 30 days.