3,5-Diaryl-2-aminopyridines as a novel class of orally active antimalarials demonstrating single dose cure in mice and clinical candidate potential

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A novel class of orally active antimalarial 3,5-diaryl-2-aminopyridines has been identified from phenotypic whole cell high-throughput screening of a commercially available SoftFocus kinase library. The compounds were evaluated in vitro for their antiplasmodial activity against K1 (chloroquine and drug-resistant strain) and NF54 (chloroquine-susceptible strain) as well as for their cytotoxicity. Synthesis and structure-activity studies identified a number of promising compounds with selective antiplasmodial activity. One of these frontrunner compounds, 15, was equipotent across the two strains (K1 = 25.0 nM, NF54 = 28.0 nM) and superior to chloroquine in the K1 strain (chloroquine IC(50) K1 = 194.0 nM). Compound 15 completely cured Plasmodium berghei-infected mice with a single oral dose of 30 mg/kg. Dose-response studies generated ED(50) and ED(90) values of 0.83 and 1.74 mg/kg for 15 in the standard four-dose Peters test. Pharmacokinetic studies in the rat indicated that this compound has good oral bioavailability (51% at 20 mg/kg) and a reasonable half-life (t(1/2) approximately 7-8 h)
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