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4-Aminoquinoline Antimalarials Containing a Benzylmethylpyridylmethylamine Group Are Active against Drug Resistant *Plasmodium falciparum* and Exhibit Oral Activity in Mice

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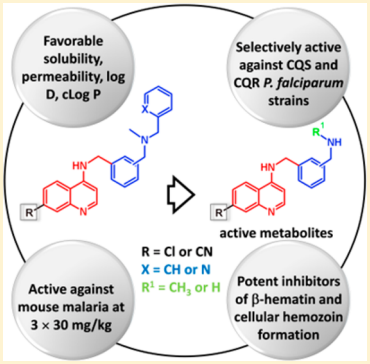
Supporting Information

ABSTRACT: Emergence of drug resistant *Plasmodium falciparum* including artemisinin-tolerant parasites highlights the need for new antimalarials. We have previously shown that dibemequines, 4-amino-7-chloroquinolines with dibenzylmethylamine (dibemethin) side chains, are efficacious. In this study, analogues in which the terminal phenyl group of the dibemethin was replaced with a 2-pyridyl group and in which the 4-amino-7-chloroquinoline was either maintained or replaced with a 4-aminoquinoline-7-carbonitrile were synthesized in an effort to improve druglikeness. These compounds exhibited significantly improved solubility and decreased lipophilicity and were potent against chloroquine-sensitive (NF54) and -resistant (Dd2 and 7G8) *P. falciparum* strains with 5/6 having IC_{50} < 100 nM against the NF54 strain. All inhibited both β-hematin (synthetic hemozoin) formation and hemozoin formation in the parasite. Parasitemia was reduced by over 90% in *P. berghei* infected mice in 3/6 derivatives following oral dosing at 4 × 30 mg/kg, with microsomal metabolic stability data suggesting that this could be attributed to highly active metabolites.



INTRODUCTION

Inhibition of the heme detoxification pathway in *Plasmodium falciparum* is an ideal target for antimalarial drugs owing to its critical role in parasite survival, absence of a human equivalent, and nongenomic derivation (hence immutability). Chloroquine (CQ) and a number of related aminoquinolines are proposed to target this pathway, inhibiting the formation of inert crystalline hemozoin.[1−3] However, the efficacy of many of these quinolines has been compromised to a greater or lesser extent by the spread of CQ-resistant (CQR) parasites that harbor mutations in the chloroquine resistance transporter gene (*Pfcrt*) whose cognate protein (alongside other transporters) mediates drug extrusion from the parasite digestive vacuole (DV).[4,5] At present, artemisinin combination therapy (ACT) constitutes the recommended treatment option against malaria, and though still largely effective, there is a growing body of evidence that artemisinin-tolerant *P. falciparum* parasite strains are emerging and consequently threatening the therapeutic utility of the ACT regimen.[6,7] Therefore, novel strategies to address the challenge of antimalarial resistance and develop cheap new drugs with good safety profiles are urgently needed.

One approach to discovery of novel and potent antimalarial agents involves structural re-engineering of existing CQ-like drugs by, for instance, coupling them to resistance reversers. Seminal work on this strategy has been reported by Peyton and co-workers, in which they proposed preservation of the fundamental pharmacophore for heme-binding (4-aminoquinoline), inhibition of hemozoin formation (4-amino-7-chloroquinoline), and drug accumulation (a tertiary amino group in the side chain) in covalent linkage with the pharmacophore for a chloroquine chemosensitizing or resistance reversal agent (RA), namely, two suitably positioned aromatic groups with an amino group separated by a short chain.[8−10] The rationale behind the potency of these molecules is that the cellular transport machinery would fail to recognize the hybrid leading to vacuolar accumulation or the molecule would directly target the function of the efflux protein(s) thus blocking its extrusion. Indeed, the feasibility of this approach has since been interrogated by other groups who have generated various modifications of such compounds. For instance, conjugates based on pentacycloundecylamine, dihydropyrimidinone, astemizole, and acridines with potent activity against CQR parasite strains have been reported.[11−14] Recently, our group also synthesized and evaluated dibemequine analogues containing a 4-amino-7-chloroquinoline nucleus with a dibenzylmethylamine side chain. These compounds exhibited strong in vitro antiplasmodial and in vivo antimalarial efficacy and notably

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