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Synthesis and antiplasmodial evaluation of novel (4-aminobutyloxy)quinolines

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ABSTRACT

A variety of 5-, 6- and 8-(4-aminobutyloxy)quinolines as novel oxygen analogues of known 4- and 8-(4-aminobutylamino)quinoline antimalarial drugs was generated from hydroxyquinolines through a three-step approach with a rhodium-catalyzed hydroformylation as the key step. Antiplasmodial assays of these new quinolines revealed micromolar potency for all representatives against a chloroquine-sensitive strain of *Plasmodium falciparum*, and three compounds showed submicromolar activity against a chloroquine-resistant strain of *P. falciparum* with IC_{50}-values ranging between 150 and 680 nM.

Malaria remains a major issue in health control, mostly among African children and pregnant women, with 216 million clinical cases and roughly 655,000 deaths worldwide in 2010.[1] Quinoline compounds, and especially the potent, inexpensive chloroquine **1** (Fig. 1), have a long history in the treatment of malaria.[2,3] However, the spread of chloroquine resistance within *Plasmodium falciparum* strains has complicated medicinal treatment of malaria in the affected areas. Despite the promising progress regarding the development of live sporozoite-based vaccines[4,5] and new compounds with antimalarial activity,[6] there is still an urgent need for new antimalarial agents active against drug-resistant malaria strains. Many important antimalarial drugs comprise a quinoline system as the core unit, and systematic synthetic modifications of these structures have led to a variety of antimalarial drugs and lead candidates with diverse substitutions around the quinoline ring.[7–10] Literature reports on chloroquine analogues reveal that replacement of the nitrogen atom at the 4-position of the quinoline ring by oxygen or sulfur results in compounds with lower antimalarial potency.[9] This introduction of oxygen or sulfur was suggested to cause a significant reduction of the quinolyl nitrogen's basicity, inflicting the 4-*O* and 4-*S* analogues to be monoprotic weak bases compared to the diprotic weak basic 4-aminoquinoline derivatives. In spite of the lower antimalarial potency of these compounds, an improved resistance index (RI) was observed.[8,9] Since the rise of chloroquine resistance, novel drug design has been focused on diverse substitutions around the quinoline ring, but especially the potency of 4-substituted (amino)quinolines has been unraveled extensively.[8–13] Other, but far less thorough studies have been performed concerning the synthesis and antimalarial evaluation of 8-substituted quinolines,[6,14,15] although the elaboration of this class has mainly been focused on the derivatization of known 8-aminoquinoline antimalarial drugs such as pamaquine **2** and primaquine **3** (Fig. 1).[14–17]

In both cases the modification of the quinoline side chain has been well examined,[10,12,13,18–22] however, substitution of the amino group by oxygen or sulfur equivalents has only been described for 4-substituted quinolines so far.[8,9] Given the fact that 4-*O* (and 4-*S*) analogues showed improved RI's and toxicological advantages compared to 4-amino derivatives,[9] and knowing that the decrease in antimalarial activity of 4-*O* and 4-*S* chloroquine derivatives correlates to the decrease in basicity of the quinolyl nitrogen atom as a result of this particular substitution pattern (i.e., *para*-positioning),[9] the introduction of a functionalized alkoxy side chain at a more remote position with respect to the quinoline nitrogen atom might result in an overall beneficial effect with regard to the antiplasmodial activity of these novel structures. Thus, in the present paper, the preparation of new 8-(4-aminobutyloxy)quinolines is described as well as the assessment of their antiplasmodial

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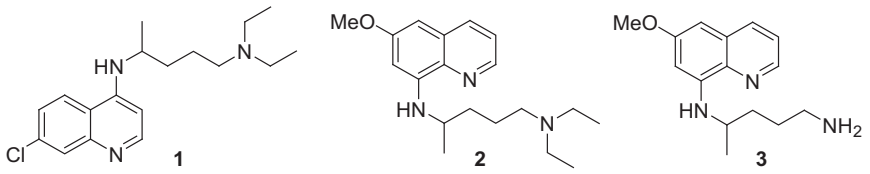
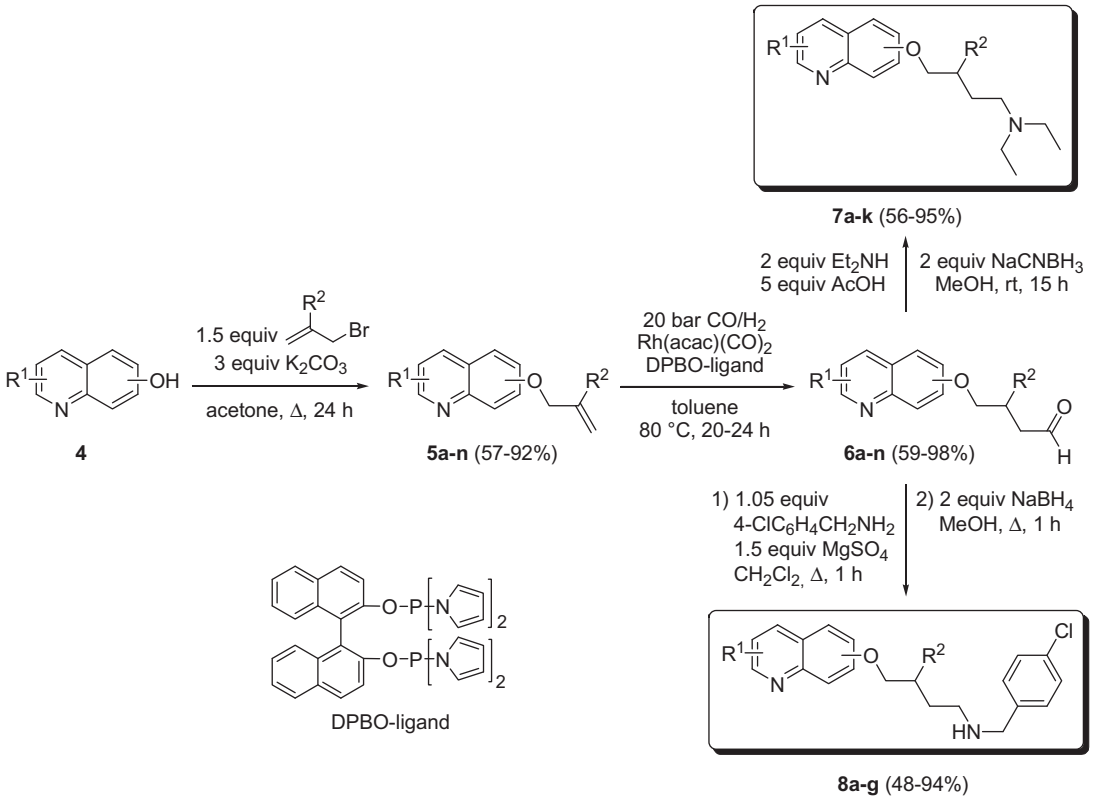


Figure 1. Structures of chloroquine, pamaquine and primaquine.

activity. In addition, the scope of this study was further extended toward the synthesis and biological evaluation of novel 5- and 6-(4-aminobutyloxy)quinolines as well. It should be mentioned that the synthesis of 4-substituted quinolines can be easily accomplished through nucleophilic aromatic substitution starting from 4-chloroquinolines.[9] Unfortunately this method is not extendable toward the preparation of the desired quinolines bearing a functionalized side chain at, for example, the 5-, 6- or 8-position, which made a novel approach of side chain introduction necessary. The implementation of a rhodium-catalyzed hydroformylation as the key step in the synthesis of functionalized quinoline systems was used and shown to be a powerful tool to accomplish this objective.

At first, a variety of allyloxyquinolines **5a–n** was prepared through O-alkylation of 5-, 6- and 8-hydroxyquinolines **4** upon treatment with 1.5 equiv of allyl bromide or 2-methylallyl bromide (in order to introduce structural diversity) in acetone under reflux for 24 h in the presence of three equiv of potassium carbonate (Scheme 1). Subsequently, the obtained quinolines **5** were evaluated as substrates for a rhodium-catalyzed hydroformylation toward the corresponding linear aldehydes. It should be noted that [(2-methyl-)2-propenyloxy]quinolines have not been studied so far as potential substrates for a catalytic hydroformylation reaction. Initially, quinolines **5** were subjected to standard hydroformylation conditions, that is, applying syngas (20 bar CO/H_2, 1:1) using (acetylacetonato)dicarbonylrhodium(I) [$Rh(acac)(CO)_2$] as a catalyst precursor (substrate/Rh = 500/1) and xantphos (ligand/Rh = 4) as a ligand in toluene at 80 °C (2 h preformation, 20 h reaction).[23] This method gave satisfying results for non-substituted (2-propenyloxy)quinolines (R^1 = H), but when substituted (2-propenyloxy)quinolines **5** (R^1 = Cl, I, Br) were used, only partial conversion was obtained (5–75%). Elevating the reaction temperature (120 °C), changing the solvent (2-Me-THF) or prolonging the reaction time (40–115 h) had no or a negative influence on the conversion. The same problem arose when (2-methyl-2-propenyloxy)quinolines **5** (R^2 = CH_3) were used as substrates, even those bearing no additional substituents on the quinoline ring (R^1 = H). It seemed that steric hindrance prevented the catalyst to reach the double bond in these cases. Subsequently, triphenylphosphine, a typical monodentate ligand which is less rigid than the bidentate xantphos, was used, but unfortunately conversion dropped even further (5–15%), also when large quantities of the ligand were utilized (20–40 equiv). The use of tris(2,4-di-*tert*-butylphenyl)phosphite,[24,25] a ligand that is typically used for hydroformylation of internal and sterically more demanding olefins,[26] gave no conversion at all. Other ligands known to be very selective toward the formation of linear aldehydes are bidentate phosphordiamidite ligands.[27] Thus, in a final attempt, the pyrrole-containing phosphordiamidite ligand DPBO (Scheme 1) was used, a ligand with a



Scheme 1. Synthesis of 4-(quinolinyloxy)butyraldehydes 6 via [(2-methyl-)2-propenyloxy]quinolines 5 and their conversion into (4-aminobutyloxy)quinolines **7** and **8**.