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Straightforward conversion of decoquinate into inexpensive tractable new derivatives with significant antimalarial activities

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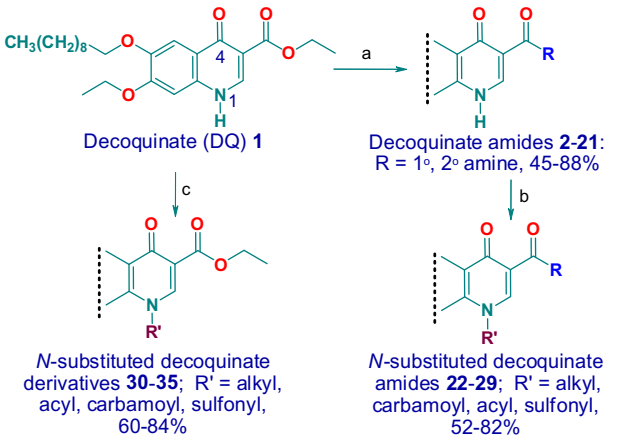
ABSTRACT

As part of a programme aimed at identifying rational new triple drug combinations for treatment of malaria, tuberculosis and toxoplasmosis, we have selected quinolones as one component, given that selected examples exhibit exceptionally good activities against the causative pathogens of the foregoing diseases. The quinolone decoquinate (DQ), an old and inexpensive coccidiostat, displays anti-malarial activity in vitro against *Plasmodium falciparum* (*Pf*). However, because of its exceedingly poor solubility in water or organic solvents, development of DQ as a drug is problematical. We have therefore converted DQ in straightforward fashion into tractable new derivatives that display good activities in vitro against chloroquine-sensitive NF54 and multidrug-resistant K1 and W2 *Pf*, and relatively low toxicities against human fibroblast cells. The most active compound, the *N*-acetyl derivative **30**, is 5-fold more active than DQ against NF54 and K1 and equipotent with DQ against W2. It possesses an activity profile against all strains comparable with that of the artemisinin derivative artesunate. Overall, this compound and the other accessible and active derivatives serve as an attractive template for development of new and economic lead quinolones.

Under a programme designed to develop new triple drug combinations for the treatment of malaria, tuberculosis, and toxoplasmosis,[1] we are preparing and evaluating efficacies of compound sets based on combinations of oxidant and redox drugs[2] coupled with a third partner with a different mode of action. In the case of malaria, the need to develop new drug combinations is particularly pressing.[3] Chemotherapy coupled with vector control and inculcation of public awareness has reduced mortality due to malaria by over 66% since 2000.[4] However, the emergence of malaria parasites resistant to the current clinically-used artemisinin derivatives[5] mandates the urgent development of newer artemisinin derivatives. Such derivatives must be incapable of providing the active metabolite dihydroartemisinin (DHA) common to the current clinical artemisinins, and should be rationally combined with the redox drug and a third combination partner to counter resistance and inhibit spread of resistant phenotypes by blocking transmission.[6] The third partner is logically



Scheme 1. Conversion of decoquinate (DQ) into DQ amide derivatives. Reagents and conditions: (a) 1° or 2° amine (5 equiv), DBU (0.9 equiv), $CHCl_3$, reflux 24–72 h; (b) DQ amide, alkyl, acyl or sulfonyl halide (5 equiv), DBU (0.6 equiv), $CHCl_3$, reflux, 15 h; (c) DQ, as for (b).

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constructed about the 4(1*H*)-quinolone scaffold. In addition to being used clinically against a variety of infectious diseases including tuberculosis,[7] certain quinolones have acquired lead status for development of drugs for treatment of toxoplasmosis[8,9] and malaria[10–12] respectively.

Our attention is drawn to decoquinate (DQ, **1**) that has been used for many years in veterinary medicine largely co-administered with poultry feed for treatment of coccidiosis wherein it displays negligible toxicity.[13,14] It is also used against other apicomplexan infections in animals[15] and is highly active in a murine model against *Toxoplasma gondii*.[16] Activity of DQ against malaria including *Plasmodium berghei*[17] in mice and *Plasmodium cynomolgi*[18] in monkeys has been known for some time. DQ is active in vitro against the liver, blood and gametocyte parasite stages of *Plasmodium falciparum* (*Pf*).[19,20] Although such multistage activity matches the profile required for blocking transmission of the malaria parasite, 6 DQ like other 4(1*H*)-quinolones including the advanced lead compound ELQ 300,[10,12] is highly lipophilic with a Log *P* of 8.19,[21] has exceedingly low solubility in water (0.06 mg L^{-1})[14] and other solvents,[12] and has low bioavailability.[19,22] The decisive benefit of DQ is its low cost, ⩽$10 per kg,[23] which renders it substantially cheaper than the other 4(1*H*)-quinolones proposed for further development as antimalarial drugs. However, the poor solubility markedly complicates screening both in vitro and in vivo and hampers evaluation of pharmacokinetic parameters, thereby restricting its further development as a drug. Because of this, resort has been made to preparation of nanoparticle formulations that appear to enhance efficacy against malaria in an animal model.[22] Our approach consistent with the overall aims of our work is to convert DQ into accessible and more tractable derivatives that in the first instance are amenable to screening in vitro. We report here the preparation and preliminary in vitro antimalarial activity and cytotoxicity of such derivatives.

Chemistry. The proposed steps involve conversion of the ethyl ester into the less readily metabolized amide[24] and replacement of H-1 largely by acyl, carbamoyl or sulfonyl groups, operations that should improve physicochemical properties associated with enhanced polarity (Scheme 1). *N*-Alkyl derivatives are also prepared based on structure–activity considerations vis-à-vis the *N*-acyl and *N*-sulfonyl derivatives.

For the ester aminolysis (step a, Scheme 1), DQ is acidic with a pK_a of 9.81,[21] and thus a basic amine nucleophile under standard aminolysis conditions[25] is likely to undergo competitive equilibrating proton transfer with H-1 of the 4(1*H*)-quinolone (cf. Fig. 2 below). Whilst this problem may be countered by the use of Lewis acidic reagents,[26] base-catalyzed aminolysis with an amine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[27] attracts because of its economy. Although the reactions may be conducted with the neat reactants and reagents, the most expeditious involved the heating of DQ and excess of primary or secondary amine with DBU in a solvent. We use chloroform here because of lack of solubility of DQ in other solvents, although it is emphasized that our initial concern is to obtain the new derivatives in the first place and then to optimize preparation for hit compounds using industrially acceptable solvents. Amides **2**–**21** (Fig. 1) were obtained in

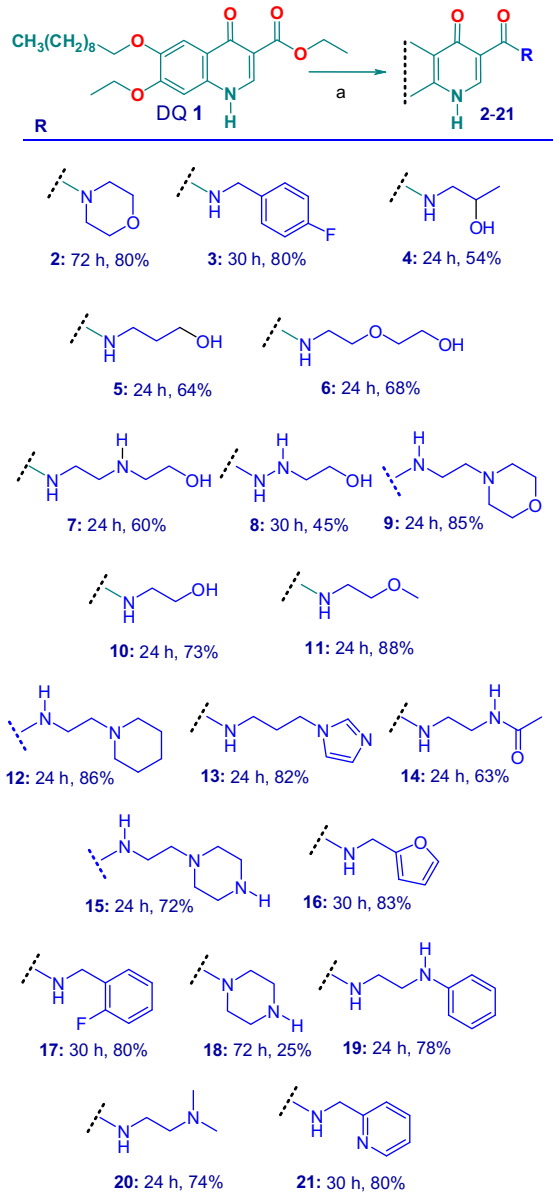

Figure 1. Amides obtained from direct aminolysis of decoquinate **1** with primary and secondary amines in chloroform according to method a, Scheme 1; reaction time (h), overall yields given.

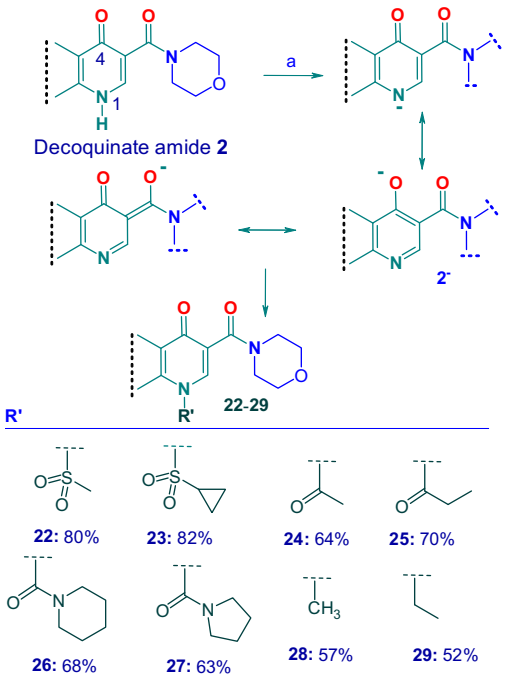

Figure 2. *N*-Substituted amide derivatives obtained from decoquinate amide **2** by treatment with DBU in the presence of sulfonyl, acyl and alkyl halides in chloroform with a reaction time of 15 h according to method b, Scheme 1; overall yields given.