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Antimalarial chemotherapy: Orally curative artemisinin-derived trioxane dimer esters

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ABSTRACT

Eight new artemisinin-derived trioxane dimer esters **5** have been prepared and tested for antimalarial efficacy in malaria-infected mice. At a single oral dose of only 6 mg/kg combined with 18 mg/kg of mefloquine, each of the dimer esters **5** outperformed the antimalarial drug artemether (**2**). The most efficacious dimer, dichlorobenzoate ester **5h**, prolonged mouse survival past day 30 of infection with three of the four mice in this group having no detectable parasitemia and appearing and acting healthy on day 30.

Malaria kills more than 600,000 people, mostly children, each year.[1–3] No vaccine has been developed yet to fully prevent people from becoming infected with malaria parasites.[4–6] Antimalarial chemotherapy using nitrogen-containing heteroaromatic compounds like chloroquine and mefloquine has been used successfully for many years to cure malaria-infected people.[7–10] In recent years, however, widespread resistance of malaria parasites has developed to many of these heteroaromatic drugs.[11–13] Therefore, new classes of antimalarial drugs are desperately needed. A breakthrough occurred in the early 1970s with the discovery in China that artemisinin (**1**), a naturally occurring endoperoxide sesquiterpene lactone, is strongly efficacious as an antimalarial.[14,15] Several short-lived, artemisinin-derived 1,2,4-trioxanes have been prepared and some, especially artemether (**2**) and artesunate (**3**), are currently used combined with long-lived, nitrogen-containing antimalarials.[16–22] Such **a**rtemisinin **c**ombination **t**herapy (ACT) is recommended as standard chemotherapeutic protocol by the World Health Organization (WHO).[23] Typically, multidose regimens of ACT daily for several days are needed to achieve a complete cure of malaria-infected people.[16–20] A major problem arises, however, when infected individuals stop taking the ACT prematurely, thereby leading often to parasite recrudescence. Therefore, a major goal of modern antimalarial chemotherapy is to develop new endoperoxides capable of single oral dose ACT cures. Toward this goal, many simple endoperoxides[24–32] and artemisinin-modified trioxanes[33–43] have been synthesized and evaluated for antimalarial effectiveness (see Fig. 1).

Substituted pyridines are important structural units in various pathogen-resistant agrochemicals[44–50] and in some pharmaceutical drugs.[51–54] We converted artemisinin (**1**) into 3-carbon linked dimer primary alcohol **4** in 65% overall yield (Scheme 1).[55] Esterification of primary alcohol **4** without compromising the endoperoxide pharmacophore formed 3-carbon-linked pyridine containing dimer isonicotinate ester **5a** (Scheme 1).[55] Dimer isonicotinate **5a** had high in vitro antimalarial potency: IC_{50} = 1.7 nM versus IC_{50} = 9 nM for artemisinin (**1**).[55] Based on the structure of this potent antimalarial dimer isonicotinate ester **5a**, we performed and report here a structure–activity (SAR) study featuring artemisinin-derived 3-carbon-linked trioxane dimer esters **5** with diverse substituents on the pyridine ring and on the phenyl ring (Scheme 1).[56]

Antimalarial efficacy data in mice are more valuable and more demanding for preclinical drug development than in vitro potency data. Based on our experience with trioxanes we conclude that, within a family of antimalarial trioxanes, in vitro potency (IC-50) data do not precisely predict levels of in vivo efficacy. Thus, we chose to explore our antimalarial trioxane dimer esters **5** directly by ACT in malaria-infected mice.

Abbreviations: SAR, structure–activity relationship; ACT, artemisinin combination therapy; DMAP, 4-dimethylaminopyridine; EDC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride.

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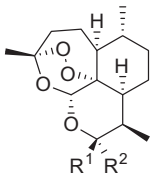
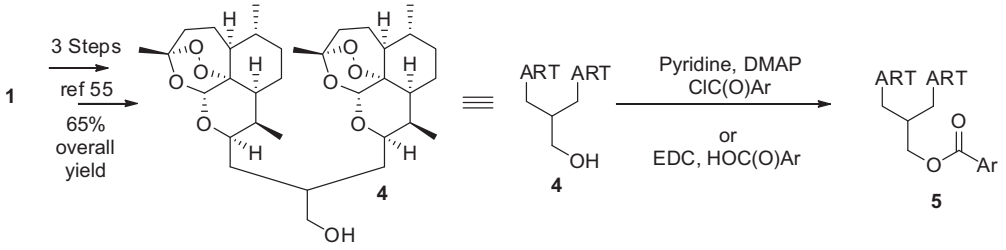
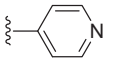
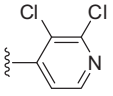
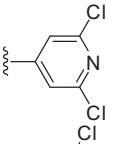
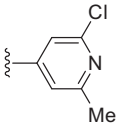
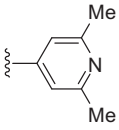
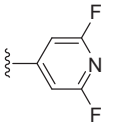
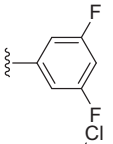
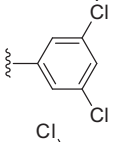
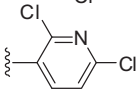


1 $R^1 = R^2 = O$ Artemisinin
2 $R^1 = OCH_3$, $R^2 = H$ Artemether
3 $R^1 = H$, $R^2 = OC(O)CH_2CH_2C(O)ONa$ Sodium Artesunate

Figure 1. Artemisinin and first generation derivatives.



	Ar	% yield	log p
5a		98	7.8
5b		98	9.2
5c		95	9.5
5d		98	9.5
5e		93	8.1
5f		91	8.9
5g		98	9.3
5h		95	10.2
5i		95	9.5

Scheme 1. Three-carbon-linked trioxane dimer esters **5**.

Stock solutions were prepared by dissolving mefloquine hydrochloride (1.8 mg) in 93.9 μL of 7:3 Tween 80:ethanol. This solution was added to 0.6 mg of dimer ester **5** in a 1 dram vial. After approximately 18 h at room temperature, 906.1 μL of deionized water was added, and then 200 μL of this stock solution was administered by oral gavage one day post infection to 5-week old C57BL/6J male mice (from Jackson Laboratory) that weighed approximately 20 g, which had been infected with *Plasmodium berghei*