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The survival times of malaria-infected mice are prolonged more by several new two-carbon-linked artemisinin-derived dimer carbamates than by the trioxane antimalarial drug artemether

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ABSTRACT

Sixteen new artemisinin-derived 2-carbon-linked trioxane dimers were prepared to study chemical structure/antimalarial activity relationships (SAR). Administering a very low single oral dose of only 5 mg/kg of dimer secondary alcohol **6a** or **6b** plus 15 mg/kg of mefloquine hydrochloride prolonged the lives of *Plasmodium berghei*-infected mice to an average of 25 days after infection. This ACT chemotherapy result is of high medicinal significance because the antimalarial efficacy of the popular trioxane drug artemether (**2**) plus mefloquine under the same conditions was significantly lower (only 20 day average survival). NH-aryl carbamate derivatives **7e**, **7i**, and **7j** of 2-carbon-linked dimer alcohol **6b** also significantly outperformed artemether (**2**) in prolonging the survival times (25–27 days) of malaria-infected mice.

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Malaria remains a devastating infectious disease, especially in tropical and sub-tropical areas of the world. Attempts at developing vaccines to protect humans from contracting malaria have been only partially successful.[1] Therefore, safe and effective chemotherapy to cure malaria-infected patients is desperately needed. With widespread resistance of *Plasmodium falciparum* malaria parasites to such previously reliable antimalarial drugs like chloroquine,[2–4] antimalarial drugs with new mechanism(s) of action are valuable for chemotherapy of malaria patients.[5,6] In recent years, a dramatic advance has been made with the use of the trioxane artemisinin (**1**) and its derivatives artemether (**2**) and sodium artesunate (**3**, Fig. 1) as fast-acting and highly efficacious antimalarials.[7,8] Combining such fast-acting but short lived trioxanes with known slower-acting but longer-lived nitrogen-containing compounds like mefloquine or lumefantrine is now recommended as standard operating procedure by the World Health Organization (WHO).[9] Such artemisinin combination therapy (ACT) has led to several combinations that are now readily available as over-the-counter drugs. These commercial ACTs, however, typically require multiple dosing for several days in order to achieve full cures.[10–18] Compliance with such a regimen is often problematic. Therefore, a single dose cure is becoming a major goal in modern antimalarial chemotherapy.[19–24] We have recently designed, synthesized, and biologically evaluated a series of new C-10 carbon-linked trioxane dimers some of which completely cure malaria-infected mice using one single-digit oral dose of trioxane along with a non-trioxane drug.[25–29] Artemisinin-derived C-10 carbon-linked dimers having linking units of five,[26] four,[27] and three[28,29] carbon atoms as well as dimers with structurally distinct linking units[30–32] having potent antimalarial activity have been reported. Recently we described preparation of artemisinin-derived 2-carbon-linked dimer ketone **4** (36% overall yield from artemisinin) and of its corresponding curative oxime derivatives **5**.[25] We have now discovered that 2-carbon-linked dimer ketone **4** can be reduced with very high stereocontrol predominantly into secondary alcohol diastereomer **6b**. The new chemical entity alcohol **6b** was easily transformed in one step into a series of fourteen NH-aryl carbamates **7** some of which are more efficacious than the popular monomeric trioxane drug artemether (**2**) in prolonging the survival times of malaria-infected mice (Scheme 1).

It was important to explore the utility of this new 2-carbon-linked dimer scaffold by performing a number of functional group transformations. The dimer ketone **4** was reduced into a pair of diastereomeric alcohols **6a** and **6b** that were easily separable on

Abbreviations: SAR, structure–activity relationship; ACT, artemisinin combination therapy; DIBALH, diisobutylaluminum hydride.

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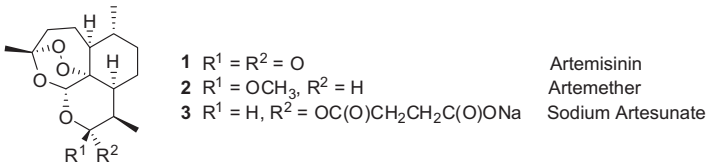


Figure 1. Artemisinin and first generation derivatives.

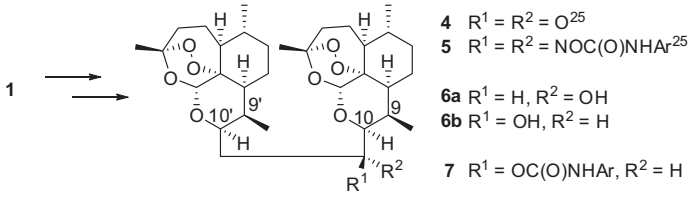
silica gel (Scheme 2). Surprisingly, even with a bulky reducing agent such as diisobutylaluminum hydride (DIBALH), the alcohols **6a** and **6b** were obtained in a 1:1 ratio. However, treatment with commercially available enantiopure (*R*)-CBS-oxazaborolidine[33] **8a** and borane in tetrahydrofuran (BH_3·THF) achieved highly stereoselective reduction of the ketone (98% diastereomeric excess, as determined by ^{1}H NMR of the crude reaction mixture), allowing direct access to diastereomer **6b**. Employing the enantiomeric (*S*)-CBS oxazaborolidine **8b** did not afford the same selectivity, forming both alcohol products **6a** and **6b** in a 62:48 ratio under these conditions.

The more polar alcohol (by analytical TLC) was hypothesized to be the (*S*)-isomer **6b** based on analysis of the proton NMR signals (Fig. 2), on the expected product from the known mechanism of this reaction,[34] and on the structural configuration by molecular model. In the (*S*)-isomer, the alcohol points toward the C5 proton, facilitating a deshielding interaction with this proton (Fig. 2III). Furthermore, the C10 proton would be locked into a pseudo equatorial–axial conformation with the C17 proton (looking down the C10—C17 bond), resulting in a smaller coupling constant (Fig. 2IV). Conversely, the alcohol would be pointed away from the C5 proton in the (*R*)-isomer (Fig. 2I), and the C10–C17 protons would be in a pseudo trans-diaxial orientation (Fig. 2II). Indeed this trend is seen in the ^{1}H NMR. Crystals of **6b** were obtained via slow evaporation of a mixed solvent system (1:4 mixture of dichloromethane and hexanes, with several drops of benzene added). X-ray structure determination confirms the stereochemistry as described in Figure 3. The crystal structure (Fig. 3) also revealed interesting structural characteristics when compared with the ketone precursor.[25] The ketone is a rigid, cage-like structure that locked the endoperoxide pharmacophore on the outside of the molecule, and it was hypothesized that this would be beneficial for antimalarial activity. Reduction to the alcohol seems to contort the six-membered glycosidic ring of the artemisinin core into a twisted conformation. The endoperoxides are also facing in, though flexibility in solution would still be expected.

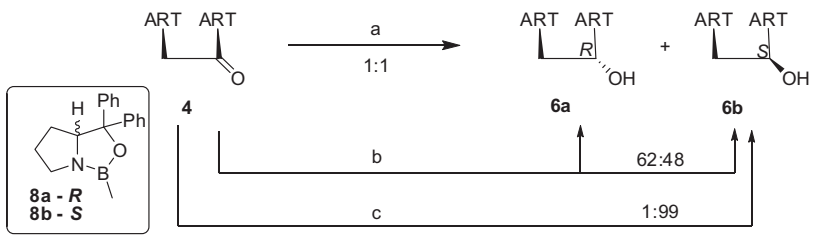
The major diastereomeric alcohol **6b** was converted easily in one step using commercial aryl isocyanates into a series of fourteen NH-aryl carbamates **7** which include phenyl, monofluoro, difluoro, trifluoro, monochloro, monobromo, cyano, and nitro derivatives (Fig. 4). Attempts at preparing NH-alkyl carbamates using commercial alkyl isocyanates were unsuccessful.

Our recent experience showed that all of the new 2-carbon-linked dimer oxime NH-aryl carbamates **5** had significant in vivo antimalarial efficacy.[25] Therefore, we proceeded directly with *in vivo* efficacy evaluation of the new series of OC(O)NH-aryl carbamates **7**. Indeed, as expected, all of these carbamates **7** had significant chemotherapeutic value, with some outperforming the trioxane antimalarial drug artemether (**2**).

To each two-carbon-linked dimer alcohols **6a** and **6b** and carbamates **7** (0.60 mg), 113 μL of 7:3 Tween 80/ethanol with mefloquine hydrochloride (1.80 mg) was added and then diluted with 1087 μL of deionized water for oral administration to 5-week old *C57BL/6J* male mice (from Jackson Laboratory) weighing about 20 g that were infected with *Plasmodium berghei* ANKA strain (2×10^7 parasitized erythrocytes). Each of four mice in a group was treated orally 24 h post-infection with a single dose of 200 μL of diluted compound solution, corresponding to a dose of 5 mg/kg trioxane combined with 15 mg/kg of mefloquine hydrochloride. Determining blood parasitemia levels and monitoring the duration of animal survival compared to survival time of animals receiving no drug are both widely accepted as measures of a drug's antimalarial efficacy. An average of 9.8% parasitemia was observed in the control (infected but no drug treatment) group



Scheme 1. Two-carbon-linked dimer derivatives.



a) DIBALH, CH_2Cl_2, -78 °C; 98% b) **8b**, BH_3·THF, 0 °C -rt, 99% overall yield for both diastereomers; c) **8a**, BH_3·THF, 0° C - rt, 92%

Scheme 2. Two-carbon-linked dimer alcohols **6**.

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