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Malaria-Infected Mice Are Completely Cured by One 6 mg/kg Oral Dose of a New Monomeric Trioxane Sulfide Combined with Mefloquine

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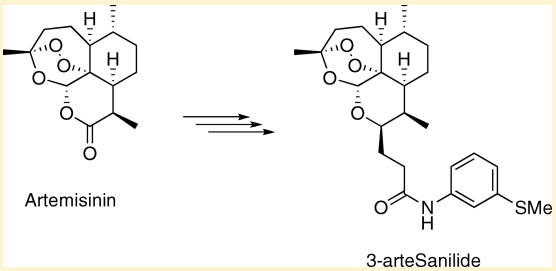
Supporting Information

ABSTRACT: Sixteen new anilide derivatives of the natural trioxane artemisinin were prepared and evaluated for antimalarial efficacy in *Plasmodium berghei* infected mice. Of these 16 new anilides administered orally as one 6 mg/kg dose combined with 18 mg/kg mefloquine hydrochloride, only sulfide 3-arteSanilide **12d** was completely curative: on day 30 after infection, all mice in this group had no detectable parasitemia, gained as much weight as the uninfected control mice, and behaved normally.



INTRODUCTION

Malaria parasites have developed widespread resistance to standard antimalarial drugs such as chloroquine.[1] Therefore, use of nonalkaloidal 1,2,4-trioxanes such as the natural product artemisinin (qinghaosu, **1**, Figure 1), combined with a standard

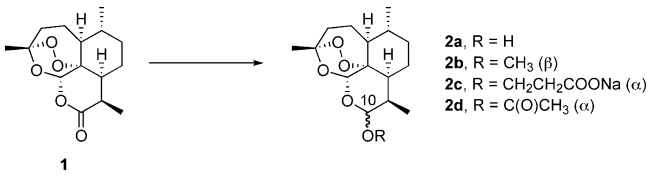


Figure 1.

alkaloidal antimalarial drug, is now recommended by the World Health Organization (WHO).[2] This type of artemisinin combination therapy (ACT) features very rapid parasite clearance by the trioxane as well as prolonged antimalarial activity by the alkaloid, each with a different mechanism of action.[3−7] One current ACT drug features a 3-day, 6-dose adult regimen totaling approximately 480 mg of artemether (**2b**) and 2880 mg of the amino alcohol lumefantrine.[8] Another current ACT drug features a 3-day, 3-dose adult regimen totaling approximately 600 mg of sodium artesunate (**2c**) and 750 mg of the quinoline mefloquine.[9] However, patient compliance with adhering to a repeated dose regimen is often problematic. A recent study reports a 2-day treatment of dihydroartemisinin−piperaquine phosphate−trimethoprim, which reported better patient compliance than the artemether−lumefantrine combination.[10] Therefore, a single dose oral cure is highly desirable. A recent report features a single dose oral cure of *P. berghei* malaria-infected mice using synthetic 1,2,4-trioxolane ozonide OZ439 (**3**, Figure 2).[11] We have recently reported single dose oral cures of *P. berghei*-infected mice using trioxane dimer sulfone carbamate **5** (Figure 2),[12] using dimer orthoester sulfone **6**,[13] and using trioxane monomer 4-fluoroanilide **12a**.[14] We report here a new series of trioxane monomer anilides carrying one or two sulfide, sulfoxide, or sulfone substituents on the anilide aromatic ring; one of these new trioxane sulfides (**12d**) fully cured malaria-infected mice using only one 6 mg/kg oral dose combined with 18 mg/kg mefloquine hydrochloride. Strikingly, this is the first example of an antimalarial trioxane sulfide being more efficacious than its corresponding sulfone.

RESULTS AND DISCUSSION

Chemistry. As shown in Scheme 1, artemisinin-derived dihydroartemisinin acetate (**2d**) reacted with allyl trimethylsilane in the presence of tin tetrachloride to form allyldeoxoartemisinin **10**. Hydroboration−oxidation followed by oxidation of the resulting primary alcohol produced C-10 carboxylic

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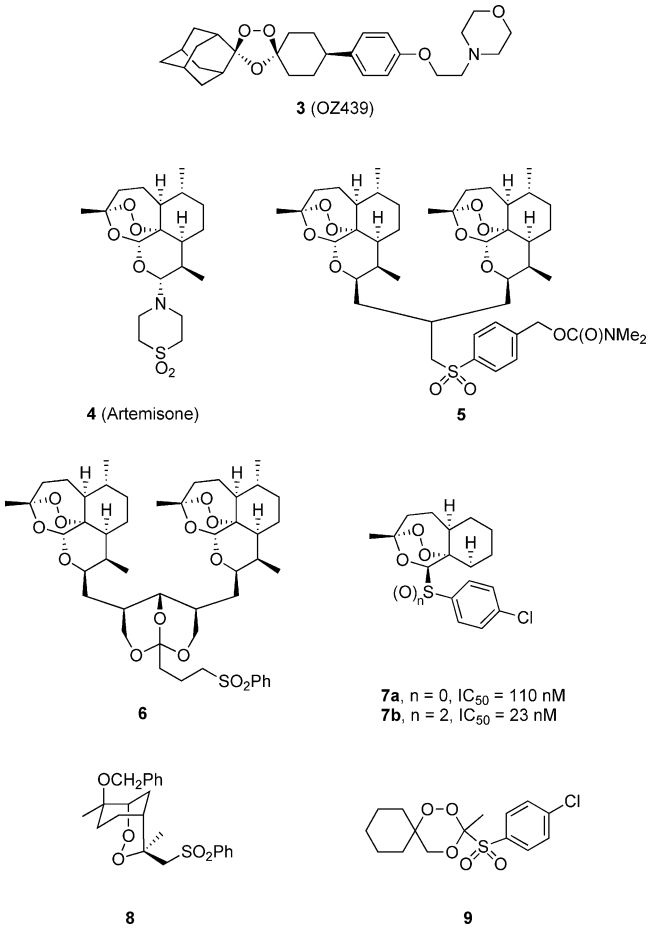
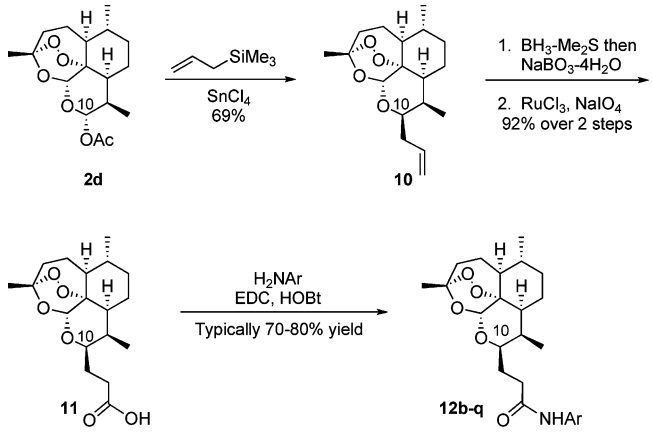


Figure 2.

acid **11**.[15] Condensation of carboxylic acid **11** with various anilines yielded a library of trioxane anilides **12b–h**, **12l**, **12o–q** (Scheme 1). Scale up synthesis is expected to be straightforward. New anilides **12b–q** are C-10 non-acetal derivatives; therefore, they are more hydrolytically stabile than the C-10 acetal first generation artemisinin derivatives such as artemether (**2b**) and artesunate (**2c**). Neat 3-arteSanilide **12d** is stable for at least 7 days at 60 °C.

To expand on our SAR, we wanted to probe the oxidation state of the sulfur-containing analogues. Initially, a mixture of sulfoxide diastereomers **12g** and **12h** was prepared by coupling artemisinin carboxylic acid **11** with racemic amino sulfoxide **15**. This diastereomeric mixture was separated by chiral HPLC. Determination of the sulfoxide absolute stereochemistry in anilides **12g** and **12h** was achieved using enantiomerically pure amino sulfoxide (+)-(*R*)-**15** as follows. Racemic 3-methylsulfinylnitrobenzene (**14**), prepared by oxidation of the commercially available sulfide **13**, was resolved by chiral HPLC; the stereochemistries of the enantiomers were assigned using the specific rotations reported in the literature.[16] Reduction of (+)-(*R*)-3-methylsulfinylnitrobenzene [(+)-(*R*)-**14**] with Raney nickel and hydrazine yielded the enantiomerically pure amino sulfoxide (+)-(*R*)-**15**, which was coupled to carboxylic acid **11** to give (*R*)-sulfoxide diastereomer **12h** (Scheme 2). HPLC comparison of the unassigned mixture of sulfoxide diastereomers with the (*R*)-sulfoxide **12h** allowed for the stereochemical sulfoxide assignment to be (*S*)-**12g** and (*R*)-**12h**. Sulfone anilides **12i–k**, **12m**, **12n** were obtained by oxidation of their corresponding sulfides using *m*-chloroperbenzoic acid.

Scheme 1[a]



Trioxane	Ar	Calculated log P
12a	4-FPh (4-artefanilide)[14]	4.96
12b	3-FPh (3-artefanilide)	4.96
12c	4-MeSPh (4-arteSanilide)	5.44
12d	3-MeSPh (3-arteSanilide)	5.44
12e	2-MeSPh (2-arteSanilide)	5.44
12f	3,5-$(MeS)_2$Ph [3,5-arteSSanilide]	6.07
12g	3-(*S*)-MeS(O)Ph	3.55
12h	3-(*R*)-MeS(O)Ph	3.55
12i	4-$MeS(O)_2$Ph[a]	3.65
12j	3-$MeS(O)_2$Ph[a]	3.65
12k	2-$MeS(O)_2$Ph[a]	3.65
12l	3-*n*-PrSPh	6.22
12m	3-*n*-$PrS(O)_2$Ph[a]	5.32
12n	2-*n*-$PrS(O)_2$Ph[a]	5.34
12o	2-Cl-4-$MeS(O)_2$Ph	3.61
12p	3-MeOPh	4.66
12q	4-*n*-HexOPh	6.82

[a]Oxidized with *m*CPBA after EDC coupling of the corresponding aniline sulfide to the carboxylic acid **11**.

Biology: In Vivo Efficacies. Each trioxane (0.64 mg) was combined with mefloquine and dissolved in 0.10 mL of 7:3 Tween 80/ethanol and then diluted with 0.97 mL of deionized water for oral administration to 5-week old, approximately 20 g C57BL/6J male mice (from the Jackson Laboratory) that were infected intraperitoneally on day 0 with the *Plasmodium berghei*, ANKA malaria strain (5×10^7 parasitized erythrocytes).[12] Each of four mice in a group was treated orally 24 h after infection with a single dose of 0.20 mL [(0.20 mL/1.07 mL) × 0.64 mg = 0.12 mg] of diluted trioxane solution, corresponding to a dose of 6 mg/kg trioxane, combined with 18 mg/kg mefloquine hydrochloride. Alternatively, a single dose of 7.5 mg/kg trioxane plus 15.0 mg/kg mefloquine hydrochloride was used. The malariometrics used involved determining blood parasitemia

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Scheme 2

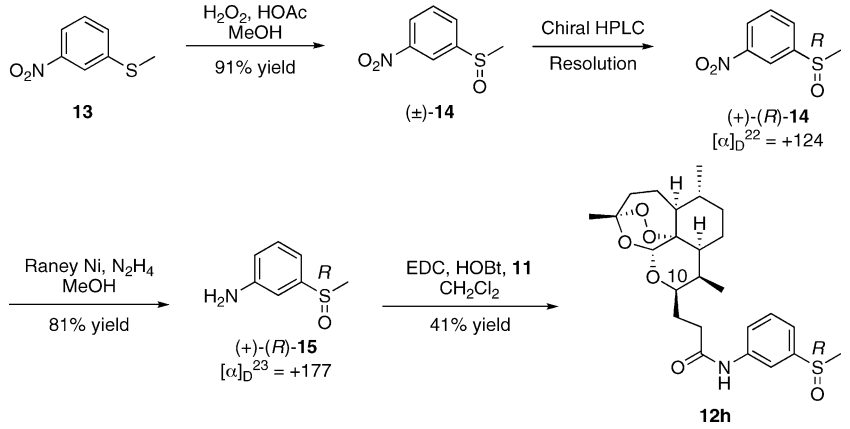

Table 1. In Vivo Antimalarial Efficacy Using a Single Oral Dose of Trioxane Combined with Mefloquine Hydrochloride in *P. berghei* Infected Mice

	single oral dose			
trioxane	trioxane (mg/kg)	mefloquine hydrochloride (mg/kg)	average survival (days) after infection	% suppression of parasitemia (on day 3 after infection)
12b	6	18	24.8 (16, 20, 30, 30)[a]	>99.9
12c	7.5	15	16.3 (15, 15, 16, 19)	>99.9
12d	6	18	30 (30, 30, 30, 30)[b]	>99.9
12d	7.5	15	30 (30, 30, 30, 30)[c]	>99.9
12d	100	0	15.0 (7, 7, 16, 30)	97.2
12e	6	18	27.0 (18, 30, 30, 30)	>99.9
12f	6	18	30 (30, 30, 30, 30)[d]	>99.9
12f	100	0	7.5 (7, 7, 8, 8)	97.9
12g	6	18	23.0 (16, 19, 28, 29)	>99.9
12h	6	18	30 (30, 30, 30, 30)[e]	>99.9
12i	7.5	15	22.5(15, 16, 29, 30)	>99.9
12j	7.5	15	15.5 (15, 15, 16, 16)	99.9
12k	7.5	15	22.8 (15, 16, 30, 30)	>99.9
12l	6	18	23.0 (15, 18, 29, 30)	>99.9
12m	6	18	11.0 (9, 11, 12, 12)	>99.9
12n	6	18	21.8 (18, 18, 21, 30)	>99.9
12o	7.5	15	24.5 (16, 21, 21, 30)	>99.9
12p	6	18	21.8 (18, 18, 21, 30)	>99.9
12q	7.5	15	15.0 (14, 15, 15, 16)	>99.9
controls:				
vehicle (no drug)	0	0	6.8 (6, 7, 7, 7)	0
artemether (**2b**)	6	18	18.8 (13, 16, 20, 26)	>99.9
artemether (**2b**)	7.5	15	19.8 (15, 21, 21, 22)	>99.9
artemether (**2b**)	6	18 (lumefantrine)	12.5 (12, 12, 13, 13)	>99.9
mefloquine	0	15	15.5 (14, 15, 15, 18)	>99.9
mefloquine	0	18	19.8 (16, 16, 20, 27)	>99.9
lumefantrine	0	18	21.5 (12, 22, 25, 27)	>99.9

[a]One of the two surviving mice on day 30 after infection had 2% parasitemia. [b]No parasitemia detected on day 30 after infection. [c]The four surviving mice had 25−50% parasitemia on day 30 after infection. [d]Three mice were parasite-free on day 30, but one mouse had 5% parasitemia on day 30 after infection. [e]One mouse had 1.8% parasitemia on day 30 after infection.

levels as well as monitoring the duration of animal survival compared to survival time of infected animals receiving no drug.

Three days after infection, an average of 10% blood parasitemia (Giemsa microscopy) was observed in the group of control mice that received no drug, with an average survival time of 6.8 days after infection. The infected mice in this study receiving the trioxane drug artemether (**2b**) plus mefloquine died an average of 18.8 days after infection (Table 1, controls). In addition, a single oral dose of artemether (6 mg/kg) plus lumefantrine (18 mg/kg) was not curative, with the mice dying an average of 12.5 days after infection. Monotherapy of mefloquine hydrochloride (18 mg/kg single oral dose) prolonged the average survival time of the infected mice to 19.8 days. In comparison, a single oral dose at 18 mg/kg lumefantrine prolonged mouse survival time to 21.5 days.

A widely accepted indication of a complete cure (i.e., 100% efficacy) is survival of the mice to day 30 after infection with no detectable malaria parasites in the animals' blood at that time. It is important to note that the combination of the standard trioxane drug artemether (**2b**), with either mefloquine

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hydrochloride or lumefantrine, was not curative (Table 1, controls). The average survival times of *P. berghei*-infected mice receiving a single, oral trioxane dose are shown in Table 1. Important conclusions emerge from these data. While 3-fluoroanilide **12b** was not curative, administration of 3-methylthioether 3-arteSanilide **12d** at a dose of 7.5 mg/kg plus 15 mg/kg mefloquine hydrochloride achieved mouse survival through day 30 after infection; however, all four of the surviving mice appeared sick and had considerable parasitemia levels (25−50%). Modification of the dose to 6 mg/kg 3-arteSanilide **12d** and 18 mg/kg mefloquine resulted in a complete cure, with all mice in this group having gained as much weight by day 30 after infection (data not shown) as the uninfected control mice. In addition, 3-arteSanilide **12d** is more efficacious than 4-arteSanilide **12c**. From these data, the significance of thioether substitution at the 3-position of the phenyl ring emerged. Bis-sulfide 3,5-arteSSanilide **12f** is partially curative at a single oral dose with all four mice alive on day 30 after infection but with one of the four mice possessing 5% parasitemia. Administration of 3-arteSanilide **12d** and 3,5-arteSSanilide **12f** at nontoxic single oral doses of 100 mg/kg (no mefloquine) resulted in prolonged mouse survival of the 3-arteSanilide **12d** dosed mice, compared to essentially no increase in mouse longevity of bis-sulfide 3,5-arteSSanilide **12f** treated mice. Replacing the sulfur atom in **12d** with an oxygen atom afforded methyl ether **12p**, which prolonged survival time to only 21.8 days after infection. This proved the critical nature of the sulfur atom. In addition, the lipophilicity of 3-arteSanilide **12d** was increased by lengthening the alkyl sulfide chain from methyl to *n*-propyl. 3-*n*-Propyl sulfide **12l**, however, is much less efficacious than the curative methyl sulfide 3-arteSanilide **12d**.

We also proved the effect of oxidation states of the sulfur atom on antimalarial efficacy. Several sulfide- and sulfone-containing antimalarial trioxanes have been reported in recent literature. For example, artemisone (**4**, Figure 2), a semisynthetic trioxane monomer sulfone, is currently in antimalarial clinical trials.[17] Trioxane dimer sulfone **5**[12] and trioxane dimer orthoester sulfone **6**[13] cure *P. berghei*-infected mice, while synthetic trioxane monomer sulfone **7b** is at least 4 times more antimalarially potent in vitro than the corresponding sulfide **7a**.[18] Synthetic sulfonyl endoperoxide **8** is strongly efficacious via oral administration in curing *P. berghei* infected mice,[19] and synthetic 1,2,4-trioxane sulfone **9** is more active in mice via oral administration than the corresponding sulfide.[20,21] Therefore, it was surprising to find that trioxane sulfide 3-arteSanilide **12d**, combined with mefloquine, cures malaria-infected mice but that the corresponding sulfone **12j** does not (Table 1). In addition, 3-sulfoxide anilide trioxane diastereomers **12g** and **12h** have different antimalarial activities. 3-(*R*)-Sulfoxide **12h** is partially curative and possesses antimalarial efficacy similar to that of 3-arteSanilide **12d**. In contrast, the diastereomeric 3-(*S*)-sulfoxide **12g** prolongs the average animal life span to only 23.0 days.

As further evidence of the complete cure of malaria-infected mice achieved by a single 6 mg/kg dose oral dose of 3-arteSanilide **12d** plus 18 mg/kg mefloquine, blood from the cured mice in this group was inoculated into uninfected mice; no parasitemia was detected in the inoculated mice after 30 days.[22]

Biology: In Vitro Potencies. Prompted by the unexpected in vivo efficacy of 3-arteSanilide **12d**, we assayed in vitro the intrinsic antimalarial activity, free of host-mediated factors, of compounds that differ in the oxidative state of the sulfur atom (Table 2). In keeping with the rodent study, sulfide **12d** is more potent than (*S*)-sulfoxide **12g** or sulfone **12j**.

Table 2. *In Vitro* Antimalarial Potencies of Trioxanes against *P. falciparum* (NF54) Parasites

Trioxane	Antimalarial Activity[a] EC_{50}, nM
12d	9.1 ± 0.57
12f	6.5 ± 0.28
12g	23 ± 1.3
12h	29 ± 0.43
12j	21 ± 1.1
Control	
Artemisinin (**1**)	10 ± 1.1

[a]Values are M ± SD of at least four determinations; artemisinin activity is for concurrent controls.

CONCLUSION

P. berghei infected mice receiving 3-arteSanilide **12d** not only were completely cured but also gained as much weight as the uninfected control mice. Furthermore, neither overt toxicity nor behavioral change attributable to trioxane administration was observed in any of the malaria-infected mice cured by 3-arteSanilide **12d** combined with mefloquine hydrochloride.

EXPERIMENTAL SECTION

^{1}H NMR (400 or 300 MHz), ^{13}C NMR (100 or 75 MHz), and ^{19}F NMR (282 MHz) spectra were recorded on Bruker spectrometer using the residual solvent peak or trichlorofluoromethane as an internal standard. High resolution mass spectra from fast atom bombardment (HRMSFAB) were obtained using a VG70SE double focusing magnetic sector mass spectrometer (VG Analytical, Manchester, U.K., nowMicromass/Waters) equipped with a Cs^+ ion gun (28 kV at 2 μA), an off-axis multiplier, and a MSS data system (MasCom, Bremen,Germany). The resolution of the instrument was set at 10 000 (100 ppm peak width). Samples were mixed with *m*-nitrobenzyl alcohol matrix deposited on the target of a direct insertion probe for introduction into the source. For accurate mass measurements, a mass scan range was employed with the matrix containing 10% polyethylene glycol (PEG) or polyethylene glycol, monomethyl ether (PEGMME) mass calibrant. Low resolution mass spectra (electrospray ionization) were acquired on an Agilent Technologies 6130 quadrupole spectrometer coupled to an Agilent Technologies 1200 series HPLC instrument. High resolution mass spectra from electrospray ionization (HRMS-ESI) were obtained on an Agilent Technologies 1200 series dual absorbance detector HPLC system equipped with a Phenomenex Luna 75 mm × 3 mm, C18, 3 μm column at 45 °C (UV detection at 220 nm, BW 8 nm, and 254 nm BW 8 nm, flow rate of 0.8 mL/min (increasing), injection volume of 1.0 μL, sample solvent of 100% methanol, sample concentration of ∼0.01 mg/mL, mobile phase A consisting of water with 0.1% acetic acid, mobile phase B consisting of acetonitrile with 0.1% acetic acid) coupled to a Agilent 6210 time-of-flight mass spectrometer (ion source, Duel ESI; min range, 115 *m*/*z*; max range, 1400 *m*/*z*; scan rate, 0.9 s; gas temp, 340 °C; gas flow, 10 L/min; nebulizer, 50 PSI; ion polarity, positive; VCap, 3500 V; fragmentor, 175 V; skimmer1, 65 V; OctopoleRFPeak, 250 V; ref mass, enabled (Agilent P/N G1969-85001). Data were analyzed using Agilent Masshunter Workstation Data Acquisition (version B.02.00, patch 1,2,3) and Agilent Masshunter Qualitative Analysis (version B.02.00, build 2.0.197.7, patch 3). Fourier transform-infrared (FT-IR) experiments were performed on a Bruker Vector 22 instrument. Optical rotation values were obtained using a 100 mm quartz cell on a JASCO P-1010 polarimeter with a 589 nm source. The purity of analogues **12b−q** was determined to be >95% by HPLC. HPLC data were acquired using a Varian ProStar 210 two-pump system with a ProStar 325 dual wavelength detector set at 215 and 254 nm. Chiral Columns ((*S,S*)-Whelk-0 5/100 Kromasil 25 cm × 4.6 cm i.d. and RegisCell 25 cm × 4.6 cm i.d.) were purchased from Regis Technologies. The log *P* values

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were calculated by using MarvinSketch and a calculator plug-in by ChemAxon Kft.

Synthesis of 3-ArteSanilide 12d. To an oven-dried 10 mL round-bottom flask were added carboxylic acid monomer **11** (15 mg, 0.044 mmol), EDC (9.3 mg, 0.048 mmol), HOBt (6.5 mg, 0.048 mmol), and CH_2Cl_2 (1 mL). The mixture was stirred for 1 h before commercially available 3-aminothioanisole (6.5 μL, 0.053 mmol) was added dropwise and stirred for an additional 18 h at room temperature until TLC analysis indicated consumption of starting material. The reaction was quenched with brine (3 mL) and the appropriate layer extracted with CH_2Cl_2 (3 × 3 mL). The resulting organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by preparative thin layer chromatography (silica gel, 40% ethyl acetate/hexanes) to afford **12d** as a colorless, amorphous solid (88% yield, 18.0 mg, 0.039 mmol). FT-IR (thin film, cm^{-1}) 3331, 2941, 1670, 1550, 1466, 1384, 1301, 1299, 1106, 1053. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (bs, 1H), 7.57 (s, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 5.35 (s, 1H), 4.17 (m, 1H), 2.77−2.59 (m, 2H), 2.48 (m, 1H), 2.47 (s, 3H), 2.33 (m, 1H) 2.05−1.76 (m, 5H), 1.62 (m, 2H), 1.49−1.22 (m, 5H), 1.39 (s, 3H), 0.95 (d, J = 5.6 Hz, 3H), 0.89 (d, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 171.4, 139.3, 138.7, 129.0, 122.0, 117.3, 116.3, 103.4, 88.9, 81.1, 76.0, 52.3, 44.4, 37.4, 36.5, 36.0, 34.4, 30.2, 26.1, 26.1, 24.9, 24.6, 20.2, 15.6, 13.1. $[\alpha]_D^{26}$ +51.3 (c 0.72, $CHCl_3$). HRMS m/z for $C_{25}H_{36}NO_6$ $(M + H)^+$ calculated 463.2392, found 463.2390.

Synthesis of 3,5-ArteSanilide 12f. To an oven-dried 10 mL round-bottom flask was added carboxylic acid monomer **11** (15 mg, 0.044 mmol), EDC (9.3 mg, 0.048 mmol), HOBt (6.5 mg, 0.048 mmol), and 3,5-bis(methylsulfanyl)aniline (9.8 mg, 0.053 mmol). The contents were dissolved in CH_2Cl_2 (1 mL) and stirred for 18 h at room temperature until TLC analysis indicated consumption of starting material. The reaction was quenched with brine (3 mL), and the appropriate layer was extracted with CH_2Cl_2 (3 × 3 mL). The resulting organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by preparative thin layer chromatography (silica gel, 40% ethyl acetate/hexanes) to afford **12d** as a colorless, amorphous solid (61% yield, 13.6 mg, 0.027 mmol). FT-IR (thin film, cm^{-1}) 3333, 2989, 1661, 1541, 1451, 1368, 1289, 1204, 1045, 1008. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.60 (s, 2H), 7.43 (s, 1H), 5.32 (s, 1H), 4.20 (m, 1H), 2.79−2.49 (m, 2H), 2.44 (m, 1H), 2.40 (s, 6H), 2.32 (m, 1H) 2.21−1.70 (m, 4H), 1.59 (m, 3H), 1.42−1.22 (m, 5H), 1.42 (s, 3H), 0.94 (d, J = 6.0 Hz, 3H), 0.90 (d, J = 7.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 171.0, 138.8, 138.3, 128.0, 121.0, 116.4, 116.1, 100.8, 87.5, 80.2, 75.5, 52.1, 50.4, 47.2, 38.1, 36.6, 365.7, 34.2, 30.7, 26.2, 25.8, 23.1, 22.2, 20.1, 16.0, 12.9. $[\alpha]_D^{23}$ +43 (c 0.40, $CHCl_3$). HRMS m/z calculated for $C_{28}H_{36}S_2NO_5$ $(M + H)^+$ 508.7136, found 508.7139.

Synthesis of 3-Methyl Sulfoxides 12g and 12h. Carboxylic acid **11** (15 mg, 0.044 mmol), EDC (9.3 mg, 0.048 mmol), and HOBt (6.5 mg, 0.048 mmol) were dissolved in CH_2Cl_2 (2 mL) in a 10 mL round-bottom flask. The solution was stirred for 1 h at room temperature before (±)-**15** (8.1 mg, 0.053 mmol) was added. The mixture was allowed to stir for 48 h before it was quenched with brine (3 mL) and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The resulting crude oil was purified by preparative thin layer chromatography (silica gel, 100% EtOAc) to afford a 1:1 diastereomeric mixture of **12g** and **12h** (51% yield, mg, 10.5 mg, 0.022 mmol). This mixture was separated by HPLC (Regis Whelk-01 (S,S); 10−50% IPA in hexanes; detection wavelength 254 nm; flow rate of 2.5 mL/min); t_r = 115.1 min (*S*)-sulfoxide **12g** and 128.1 min (*R*)-sulfoxide **12h**. Spectral data are shown below.

Analytical Data of 3-(*S*)-Sulfoxide 12g. Amorphous, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 8.5 Hz, 1H), 7.82 (dd, J = 7.4, 1.2 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 5.32 (s, 1H), 4.20 (dd, J = 9.1, 6.8 Hz, 1 H), 3.10 (m, 2H), 2.75 (s, 3H), 2.73 (m, 2H), 2.51 (m, 1H), 2.31 (td, J = 14.1, 3.6 1H), 2.04 (m, 2H), 1.71 (m, 4H), 1.70 (m, 4H), 1.36 (s, 3H), 0.94 (d, J = 6 Hz, 3H), 0.88 (d, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 137.3, 134.9, 129.9, 125.8, 123.6, 123.0, 103.7, 89.0, 87.1, 75.4, 57.8, 48.8, 40.0, 36.6, 36.3, 36.1, 34.4, 30.2, 26.1, 24.9, 24.7, 20.2, 16.1, 13.0. $[\alpha]_D^{24}$ +29 (c 0.12, $CHCl_3$); $[\alpha]_D^{24}$ +44 (c 0.12, $CHCl_3$). HRMS m/z calculated for $C_{25}H_{36}SNO_6$ $(M + H)^+$ 478.2263, found 478.2266.

Analytical Data of 3-(*R*)-Sulfoxide 12h. Amorphous, white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (bs, 1H), 7.88 (m, 1H), 7.75 (d, J = 6.9 Hz, 1H) 7.47 (t, J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 5.35 (s, 1H), 4.22 (m, 1H), 2.79−2.46 (m, 5H), 2.74 (s, 3H), 2.34 (td, J = 14.4, 3.9 Hz, 1H), 2.09−1.79 (m, 5H), 1.69−1.55 (m, 2H), 1.50−1.20 (m, 3H), 1.38 (s, 3H), 0.96 (d, J = 5.7 Hz, 3H), 0.91 (d, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 137.4, 134.9, 129.9, 125.6, 123.3, 122.9, 103.9, 89.3, 87.0, 75.4, 57.2, 48.6, 39.8, 36.8, 36.3, 36.0, 34.5, 30.1, 26.3, 24.8, 24.3, 20.2, 16.1, 13.0. $[\alpha]_D^{24}$ +61 (c 0.12, $CHCl_3$). HRMS m/z calculated for $C_{25}H_{36}SNO_6$ $(M + H)^+$ 478.2263, found 478.2265.

Synthesis of 3-Sulfone 12j. 3-ArteSanilide **12d** (16.1 mg, 0.035 mmol) was dissolved in CH_2Cl_2 (1.5 mL) to which *m*CPBA (≤77%, 17.1 mg, 0.077 mmol) was added and stirred for 2.5 h. The reaction was quenched with $NaHCO_3$ (aq, 2 mL) and the appropriate layer extracted with CH_2Cl_2 (3 × 3 mL). The organic layers were washed with saturated $NaHCO_3$ and saturated $NaHSO_3$, dried with $MgSO_4$, concentrated in vacuo, and purified by preparative thin layer chromatography (silica gel, 60%, ethyl acetate/hexanes) to yield **12j** as a colorless, amorphous solid (94% yield, 16.2 mg, 0.033 mmol). FT-IR (thin film, cm^{-1}) 3298, 2921, 1666, 1570, 1531, 1444, 1372, 1296, 1124, 1092, 1058, 1008. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (bs, 1H), 8.11 (s, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 7.9, 1H), 7.50 (t, J = 8.0 Hz, 1H), 5.36 (s, 1H), 4.19 (m, 1 H), 3.06 (s, 3H), 2.79−2.50 (m, 3H), 2.33 (m, 1H), 2.04−1.58 (m, 6H), 1.46−1.16 (m, 7H), 1.38 (s, 3H), 0.96 (d, J = 9.0 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 138.6, 135.3, 129.9 128.8, 126.4, 123.7, 122.9, 103.3, 89.0, 87.1, 75.4, 57.8, 54.6, 43.8, 37.4, 36.5, 36.1, 34.4, 30.2, 26.1, 24.9, 24.4, 20.2, 12.9. $[\alpha]_D^{22}$ +41 (c 0.19, $CHCl_3$). HRMS m/z calculated for $C_{25}H_{36}NO_7S$ $(M + H)^+$ 494.2212, found 494.2216.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional synthesis details and analytical data for compounds **12b**, **12c**, **12e**, **12i**, and **12k−q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

ACT, artemisinin combination therapy; EDC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; HOBT, 1-hydroxybenzotriazole; DMSO, dimethylsulfoxide; mCPBA, *m*-chloroperbenzoic acid

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