Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

Malaria-Infected Mice Live Until at Least Day 30 after a New Artemisinin-Derived Thioacetal Thiocarbonate Combined with Mefloquine Are Administered Together in a Single, Low, Oral Dose

Alexander M. Jacobine,[†] Jennifer R. Mazzone,[†] Rachel D. Slack,[†] Abhai K. Tripathi,[‡,§] David J. Sullivan,[‡,§] and Gary H. Posner*[,†,§]

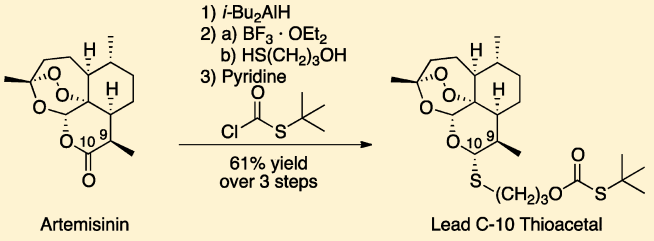
[†]Department of Chemistry, School of Arts and Sciences, The Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218, United States

[‡]W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205, United States

[§]The Johns Hopkins Malaria Research Institute, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205, United States

Supporting Information

ABSTRACT: In only three steps and in 21−67% overall yields from the natural trioxane artemisinin, a series of 21 new trioxane C-10 thioacetals was prepared. Upon receiving a single oral dose of only 6 mg/kg of the monomeric trioxane **12c** combined with 18 mg/kg of mefloquine hydrochloride, *Plasmodium berghei*-infected mice survived on average 29.8 days after infection. Two of the four mice in this group had no parasites detectable in their blood on day 30 after infection, and they behaved normally and appeared healthy. One of the mice had 11% blood parasitemia on day 30, and one mouse in this group died on day 29. Of high medicinal importance, the efficacy of this ACT chemotherapy is much better than (almost double) the efficacy under the same conditions using as a positive control the popular trioxane drug artemether plus mefloquine hydrochloride (average survival time of only 16.5 days).



INTRODUCTION

Malaria kills approximately one million people, mostly children, each year.[1−4] No vaccine is yet a fully effective prophylactic against malaria.[5,6] Widespread resistance of *Plasmodium falciparum* malaria parasites to chloroquine,[7,8] until recently the most popular malaria chemotherapeutic agent, catapulted rapidly acting artemisinin (**1**) trioxanes like artemether (**2**) and sodium artesunate (**3**) into use. Typically, the trioxane is combined with slower-acting nitrogen-aromatics like mefloquine (**4**), lumefantrine (**5**), and pyronaridine (**6**, Figure 1). Indeed, the World Health Organization (WHO) urges worldwide use of such Artemisinin Combination Therapy (ACT) as the best chemotherapy for malaria patients.[9] Much research has been focused on increasing the efficacy of artemisinin-derived antimalarial drugs through synthetic chemistry.[10−13]

One of the most promising synthetic (not derived from artemisinin) peroxides is trioxolane OZ439 (**7**), which is now in advanced human clinical trials.[14] Some semisynthetic artemisinin derivatives also are in clinical trials.[15] Antimalarial drugs now on the market include the following: a fixed combination of **2** and **5**;[16] a fixed combination of **3** and **4**;[17,18] and a fixed combination of **3** and **6**.[19,20] Each of these three combinations requires patients to take pills daily for several days.[16−21] Adherence to such a schedule of ACT multiple dosing often is not followed faithfully, leading to ineffective chemotherapy and to increased likelihood of resistance developing.[22−24] To overcome such nonadherence to a repeated dosing regimen, curing malaria patients with a single oral dose of drug is a very important goal.[25−29] Toward that goal, we have reported that malaria-infected mice are cured by a single, oral, 6 mg/kg dose of several new artemisinin derivatives combined with 18 mg/kg of mefloquine hydrochloride.[30,31]

Some thioacetal glycosides[32] and thiosugar hemithioacetals[33] have potent biological activities, and a thioacetal has been developed as a thiol protecting group.[34] Here, we disclose a new series of artemisinin-derived monomeric C-10 thioacetal carbonates, thiocarbonates, nitrogen-heterocycles, and a dimeric trioxane C-10 thioacetal amide. A trioxane monomer carbonate[35] as well as a dimer carbonate have been reported,[36] as well as some C-10 thioacetal derivatives of artemisinin.[37−41]

RESULTS AND DISCUSSION

Chemistry. Thioacetals are known to be more hydrolytically stable than the corresponding acetals.[42,43] Since some trioxane acetals are efficacious antimalarial drugs, like **2** and **3**, trioxane thioacetals were expected to be of potential value as new

Received: July 10, 2012
Published: August 14, 2012

dx.doi.org/10.1021/jm3009986 | J. Med. Chem. 2012, 55, 7892−7899

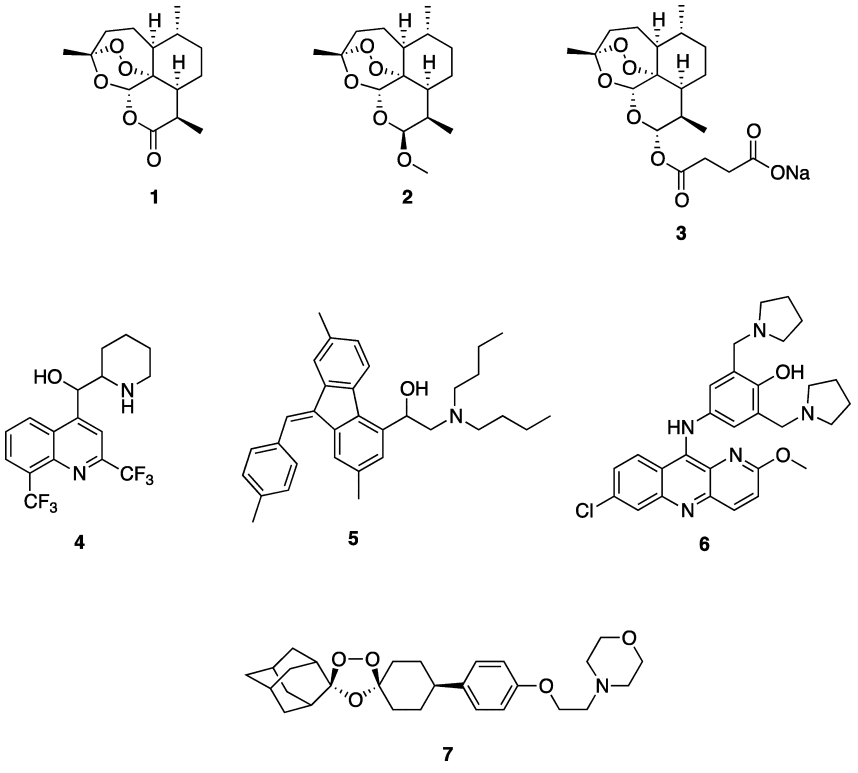
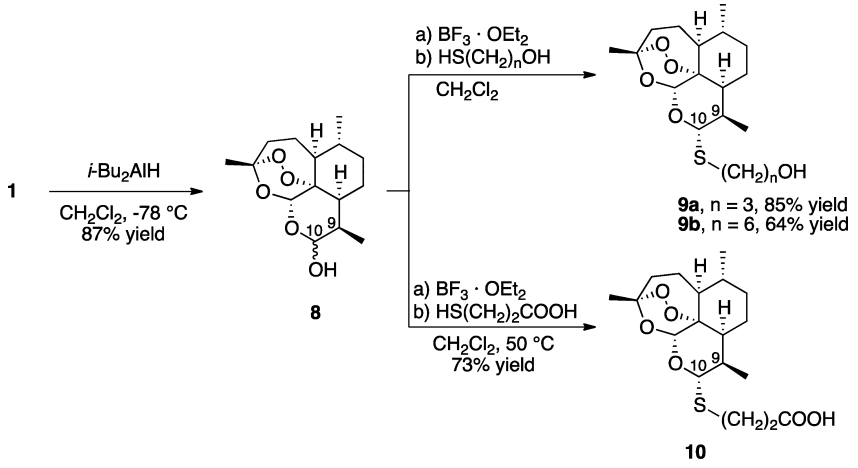


Figure 1.

Scheme 1



antimalarials. Thus, our interest was to synthesize easily and to test some trioxane thioacetals for antimalarial activity in *Plasmodium berghei*-infected mice.

We prepared a series of C-10α thioacetals in the yields shown in Scheme 1 in three facile steps from **1**. The first step is reduction of **1** into dihydroartemisinin (**8**)[44] without destroying the crucial trioxane peroxide pharmacophore.[45] Introduction of the Lewis acid boron trifluoride diethyl etherate to **8** generates an intermediate oxocarbenium ion. A variety of nucleophiles are known to react with oxocarbenium ions, and, as predicted, the reaction with thiols proceeds smoothly to produce the desired C-10 thioacetals. The thiols used are commercially available bifunctional mercaptoalcohols and a mercaptocarboxylic acid, which leaves a synthetic handle, the hydroxyl or carboxylic acid group, for further manipulation and SAR studies.

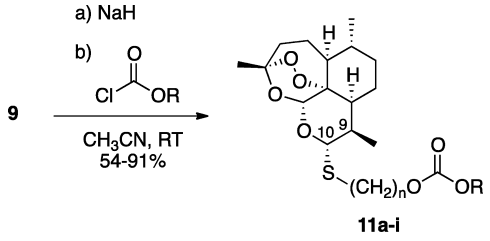
The stereochemistry at the C-10 position in thioacetals **9** and **10** was determined to establish the diastereoselectivity of the thioacetalization reaction. Since the reactive C-10 site of the intermediate oxocarbenium ion is planar, the nucleophile could attack from either face of the molecule. Consequently, each synthesized thioacetal could be a mixture of both C-10α and C-10β diastereomers. Determination of the stereochemistry of the major diastereomer formed was achieved by comparing ^{1}H NMR coupling constants between the C-10 proton and the adjacent C-9 proton in the crude thioacetals (4−9:1 ratio of diastereomers). After column chromatography purification, the major diastereomers **9a**, **9b**, and **10** were isolated in the yields shown. In each case, the major diastereomer formed was the C-10α thioacetal based on its C-10 to C-9 coupling constant of 9−11 Hz. These values were characteristic of C-10α thioacetals in previous reports.[37−41] Several C-10α and C-10β phenyl-

dx.doi.org/10.1021/jm3009986 | J. Med. Chem. 2012, 55, 7892−7899

thioacetals have been shown to be antimalarially efficacious in mice, with the C-10α thioacetals being more potent than the C-10β thioacetals.[37−41]

Carbonates are more stable than esters,[46,47] and the carbonate functional group has been used effectively before as a prodrug, subsequent hydrolysis of which releases the parent alcohol.[46,47] The steps in Scheme 2 are high-yielding and

Scheme 2



provide access to a small library of thioacetal carbonates. Thioacetal carbonates **11** (Table 1) were synthesized from the

Table 1. C-10 Thioacetal Carbonates 11

compd	n	R	log P^a	yield
11a	3	Me	4.6	91%
11b	3	*n*-Bu	5.9	81%
11c	3	*t*-Bu	5.5	85%
11d	3	PhF-4	6.4	77%
11e	3	$CH_2C{\equiv}CH$	4.9	54%
11f	6	Me	5.9	82%
11g	6	Et	6.3	88%
11h	6	$CH_2C{\equiv}CH$	6.1	64%
11i	6	$O(CH_2)_2S(O)_2Ph$	6.6	63%[b]

[a]The log *P* values were calculated using ChemOffice Ultra 11.0. [b]This reaction was run in dichloromethane with pyridine as the base.

parent alcohol **9** by reaction with base and a chloroformate (Scheme 2). Besides aliphatic and aromatic carbonates **11a**−**11h**, sulfone carbonate **11i** was of interest because of a report demonstrating the usefulness of this particular functionality in a prodrug.[48]

With the intention to test some compounds that were similar in structure to the thioacetal carbonates, we synthesized the series C-10α thioacetal thiocarbonates **12a**−**c** (Table 2) as well

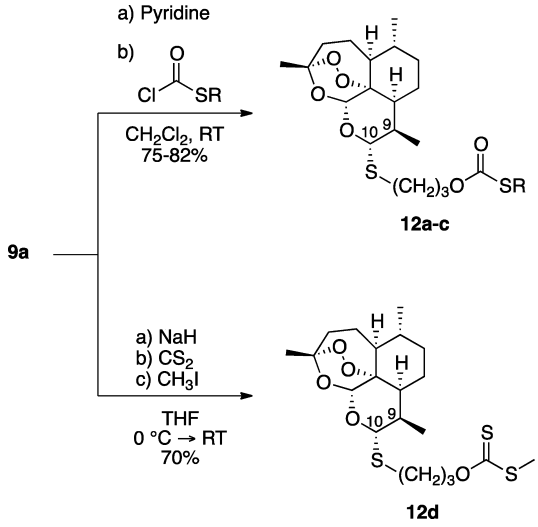
Table 2. C-10 Thioacetal Thiocarbonates 12

compd	X	R	log P^a	yield
12a	O	Me	5.2	81%
12b	O	*n*-Pr	6.0	77%
12c	O	*t*-Bu	6.1	82%
12d	S	Me	5.6	70%

[a]The log *P* values were calculated using ChemOffice Ultra 11.0.

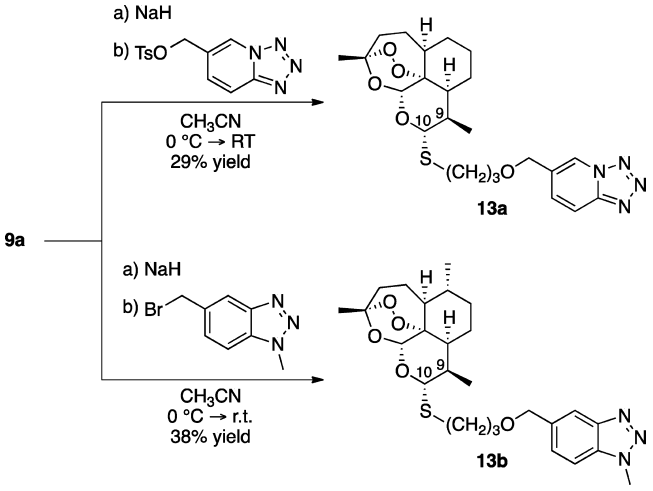
as C-10α thioacetal xanthate ester **12d** from diastereomerically pure thioacetal alcohol **9a**. Preparation of **12a**−**c** involved chemistry similar to that for the thioacetal carbonates, although change of solvent as well as base was necessary to optimize reaction conditions. In the case of **12d**, **9a** was treated with base, carbon disulfide, and methyl iodide in tetrahydrofuran (Scheme 3).

Scheme 3



Since the development of chloroquine in the 1940s, nitrogen-containing heterocycles have been a cornerstone of antimalarial drug research.[49−51] These moieties possess unique acid/base properties and mimic many important biological molecules. With these characteristics in mind, we prepared nitrogen-heterocycle-containing C-10 thioacetal ethers **13** (Scheme 4) and benzimidazole-containing C-10 thioacetal amides **14** (Scheme 5).

Scheme 4

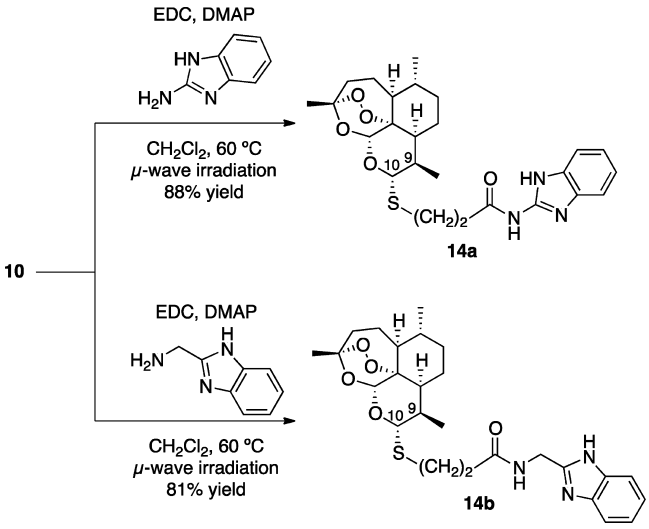


Making dimers of drug molecules is a common practice in medicinal chemistry; for every one molecule of drug, two pharmacophore moieties reach the active site within the body.[52,53] Therefore, dimer drug compounds are sometimes considerably more efficacious than their monomer counterparts.[52,53] Because of recent success with amide-containing monomeric trioxanes as antimalarials,[30,54] we synthesized bis-amide bisthioacetal dimer **15** (Scheme 6).

On the basis of our previous *in vivo* results, we have observed some trends between log *P* values and antimalarial efficacy.[30,31] Typically, monomeric trioxanes are most efficacious when the log *P* value is between 4 and 6 (Table 3). Dimeric trioxanes have displayed optimal results when the log *P* value is between 7 and 9.

dx.doi.org/10.1021/jm3009986 | J. Med. Chem. 2012, 55, 7892−7899

Scheme 5



Scheme 6

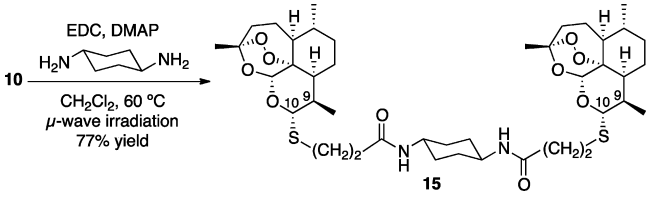


Table 3. Calculated log *P* Values for C-10 Thioacetals 13−15

compd	log P^a
13a	4.7
13b	5.3
14a	4.8
14b	4.5
15	7.4

[a]The log *P* values were calculated using MarvinSketch and a calculator plug-in by ChemAxon Kft.

Although the literature suggested that our new C-10 thioacetals **9**−**15** would be much more stable to acid than the analogous acetals,[42,43] we subjected lead trioxane **12c** to a series of stability tests since it was the most efficacious of our antimalarial thioacetals. First, hydrolytic stability was tested based on a published protocol that simulated stomach acidic conditions, which is important for a drug that is administered orally.[55] Trioxane **12c** was dissolved in a solution of aqueous hydrochloric acid and acetonitrile (pH 2) and heated in a temperature-controlled oil bath set to 37 °C. This solution was allowed to stir for 24 h and was periodically analyzed by TLC. Additionally, the solution was analyzed by ^{1}H NMR after completion of the 24 h. Since we knew that the product formed through hydrolysis of the C-10 thioacetal functionality would be **8**, we compared the ^{1}H NMR spectrum of **12c** after 24 h to that of **8** and to that of parent alcohol **9a**. Less than 2% hydrolysis of **12c** had occurred. Similarly, **9a** and **9b** were stable to hydrolysis under the same conditions. Full experimental details of the hydrolysis study are included in the Supporting Information.

Because ACT is used predominantly in tropical areas where malaria is endemic, it was important to determine the thermal stability of lead trioxane **12c** at 60 °C, neat, for 7 days; TLC as well as ^{1}H NMR showed no decomposition.

Biology. To each thioacetal trioxane (0.64 mg), 100 μL of 7:3 Tween 80/ethanol with mefloquine hydrochloride (1.92 mg) was added. This mixture was then diluted with 965 μL of water for oral administration to 5-week old C57BL/6J male mice (from the Jackson Laboratory) weighing about 20 g that were infected with *P. 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 6 mg/kg trioxane combined with 18 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 8.8% blood parasitemia was observed in the control (no drug) group on day 3 post-infection. Infected animals receiving no drug died on an average of 8 days post-infection. The antimalarial efficacy results of our C-10 thioacetals as well as controls are summarized in Table 4, which includes the parasitemia levels for mice on day 3 post-infection.

Table 4. *In Vivo* Antimalarial Efficacy Using a Single Oral Dose of 6 mg/kg Trioxane and 18 mg/kg Mefloquine Hydrochloride in *P. berghei*-Infected Mice

trioxane	average survival (days) after infection	% suppression of parasitemia (on day 3 post infection)
11a	12.8 (13, 13, 13, 12)	>99.9%
11b	18.5 (30, 16, 15, 13)	>99.9%
11c	17.8 (28, 17, 13, 13)	>99.9%
11d	19.3 (29, 17, 17, 14)	>99.9%
11e	18.8 (30, 17, 15, 13)	99.9%
11f	21.8 (30, 30, 15, 12)	>99.9%
11g	16.5 (28, 14, 12, 12)	>99.9%
11h	**25.3** (30, 29, 27, 15)	>99.9%
11i	14.5 (17, 15, 13, 13)	99.9%
12a	**24.5** (30, 30, 21, 17)	>99.9%
12b	19.3 (30, 17, 15, 15)	>99.9%
12c	**29.8** (30, 30, 30, 29)	99.9%
12d	22.0 (30, 28, 17, 13)	99.9%
13a	23.0 (30, 29, 17, 16)	>99.9%
13b	22.3 (30, 29, 17, 13)	>99.9%
14a	**26.3** (29, 28, 27, 21)	>99.9%
14b	19.5 (29, 20, 15, 14)	>99.9%
15	19.8 (30, 17, 17, 15)	99.9%
	Controls	
infected (no drug)	8.0 (10, 8, 7, 7)	0%
artemether + mefloquine-HCl	16.5 (28, 13, 13, 12)	>99.9%
mefloquine-HCl only	14.0 (17, 13, 13, 13)	>99.9%

On the basis of these data and as expected for artemisinin-derived trioxanes,[10−13] all of our new C-10α thioacetals acted rapidly to suppress parasitemia, with almost complete suppression of parasitemia as determined on day 3 post-infection. However, not all of the parasites were killed after 3 days which leads to a difference, sometimes substantial, in efficacy for each individual analogue over the full 30 day experiment.

Also based on these data, it is clear that each of the four C-10 thioacetals **11h** (25.3 days), **12a** (24.5 days), **12c** (29.8 days),

dx.doi.org/10.1021/jm3009986 | *J. Med. Chem.* 2012, 55, 7892−7899

and **14a** (26.3 days) in combination with mefloquine hydrochloride prolonged the mouse average survival time by more than one week (>23.5 days) compared to the survival time of the artemether plus mefloquine hydrochloride control (16.5 days). Mefloquine hydrochloride alone at 18 mg/kg gave an average survival time of only 14 days.

Most impressively, trioxane **12c** produced a partial cure with an average survival time of 29.8 days. Two of the four mice in this group showed no signs of parasitemia in their blood on day 30 post-infection and behaved normally. One mouse in this group had 11% parasitemia on day 30, and one mouse died on day 29.

CONCLUSIONS

In conclusion, several artemisinin-derived C-10α thioacetals were found to be more efficacious as antimalarials than artemether. Four of the new thioacetals (**11h**, **12a**, **12c**, and **14a**) combined with mefloquine hydrochloride prolonged the life of *P. berghei*-infected mice by at least one week longer than the artemether plus mefloquine hydrochloride control. Remarkably, when administered only once as a single, oral dose of 6 mg/kg plus 18 mg/kg of mefloquine hydrochloride, trioxane **12c** was highly efficacious with an average survival time of 29.8 days, almost double the average survival time (16.5 days) achieved by the popular antimalarial drug artemether plus the mefloquine positive control using the same protocol.

EXPERIMENTAL SECTION

The purity of compounds **11h**, **12a**, **12c**, and **14a** was determined to be >98% by HPLC. HPLC data were acquired using a Varian ProStar 210 two-pump system with a Sedex Model 75 Evaporative Light Scattering Detector (ELSD). A Varian 250 × 4.6 mm × 1/4″ Microsorb-MV 100-5 Si column was used. All other instrumentation details are included in the Supporting Information.

Thioacetal Alcohol 9a. An oven-dried, 5 dram vial, equipped with a magnetic stir bar, under argon was charged with **8**[44] (250 mg, 0.88 mmol, 1.0 equiv) and anhydrous dichloromethane (10 mL). 3-Mercaptopropanol (89 mg, 0.97 mmol, 1.1 equiv) was added and allowed to stir for 10 min at 50 °C, under argon. Boron trifluoride diethyl etherate (0.125 mL, 0.88 mmol, and 1.0 equiv) was added dropwise, and the reaction was allowed to stir under argon at 50 °C for 30 min. After 30 min, the reaction was quenched with water (5 mL) and extracted with dichloromethane (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated on a rotary evaporator at room temperature. The ^{1}H NMR of the crude reaction mixture indicated a mixture of 10-α and 10-β diastereomers in a ratio of 9:1 (α:β). The crude amorphous solid was purified via column chromatography (5−10% ethyl acetate in hexanes) to afford **9a** as a white solid (268 mg, 85% yield). Mp = 108.6−110.0 °C; $[\alpha]_D^{23.3}$ +31.49 (c. 0.58, $CHCl_3$); IR (thin film) ν 3445, 2926, 2871, 2363, 1716, 1586, 1446, 1378, 1279, 1195, 1126, 1035, 928, 900, 878 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (s, 1H), 4.52 (d, J = 10.7 Hz, 1H), 3.87−3.76 (m, 2H), 2.94 (ddd, J = 13.5, 7.7, 5.8 Hz, 1H), 2.80 (s, 1H), 2.70 (ddd, J = 13.3, 7.1, 5.9 Hz, 1H), 2.59 (ddd, J = 11.1, 7.3, 4.3 Hz, 1H), 2.33 (ddd, J = 14.6, 13.4, 4.0 Hz, 1H), 1.98 (ddd, J = 14.6, 4.8, 2.8 Hz, 1H), 1.92−1.63 (m, 4H), 1.57 (dt, J = 13.5, 4.3 Hz, 1H), 1.50−1.15 (m, 7H), 1.10−0.95 (m, 1H), 0.91 (dd, J = 12.2, 6.7 Hz, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.7, 92.6, 80.8, 80.7, 59.8, 51.9, 46.1, 37.6, 36.4, 34.2, 32.2, 31.9, 25.9, 24.9, 24.1, 21.5, 20.4, 15.2; HRMS (FAB) m/z calcd for $C_{18}H_{30}O_5S$ $[M + H]^+$ 359.1892; found, 359.1888.

Thioacetal Alcohol 9b. A 2-dram vial, equipped with magnetic stir bar and argon inlet adaptor, was charged with **8** (0.18 mmol, 50 mg) in anhydrous dichloromethane (2 mL). 6-Mercaptohexanol (0.19 mmol, 26 mg) was added in one portion neat directly to the stirring solution. Boron trifluoride diethyl etherate (0.18 mmol, 25 mg) was added dropwise via a needle and plastic syringe, and the reaction was stirred for 20 min. The reaction was quenched with water (2 mL) and extracted with dichloromethane (3 × 2 mL). The organic layers were pooled, dried with magnesium sulfate, vacuum filtered, and concentrated via rotary evaporation at room temperature. The crude residue was purified by flash column chromatography on silica, eluting with a gradient mobile phase (5−10% ethyl acetate in hexane) to yield **9b** as a clear amorphous solid (45 mg, 64%). $[\alpha]_D^{24.0}$ +14.6 (c. 0.65, $CHCl_3$); IR (thin film) ν 3458, 2927, 2871, 1455, 1377, 1128, 1037, 928, 879, 829, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (s, 1H), 4.51 (d, J = 10.7 Hz, 1H), 3.63 (br t, J = 6.6 Hz, 2 H), 2.78 (ddd, J = 12.5, 8.3, 6.3 Hz, 1H), 2.72−2.51 (m, 2H), 2.36 (ddd, J = 14.6, 13.3, 4.0 Hz, 1H), 2.01 (ddd, J = 14.5, 4.9, 2.9 Hz, 1H), 1.90−1.83 (m, 1H), 1.77−1.15 (m, including a singlet at 1.41, 19 H), 1.07−0.99 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ104.4, 92.4, 80.7, 80.6, 63.0, 52.0, 46.2, 37.5, 36.4, 34.2, 32.7, 31.9, 29.9, 28.8, 28.3, 26.1, 25.4, 24.9, 21.4, 20.4, 15.2; HRMS (FAB) m/z calcd for $C_{21}H_{36}O_5S$ (M + H)+ 401.2362; found, 401.2355.

Thioacetal Carboxylic Acid 10. An oven-dried, 2 dram vial, equipped with a magnetic stir bar, under argon was charged with **8** (100 mg, 0.35 mmol, 1.0 equiv) and anhydrous dichloromethane (4 mL). 3-Mercaptopropionic acid (40 mg, 0.39 mmol, 1.1 equiv) was added and allowed to stir for 10 min at 50 °C, under argon. Boron trifluoride diethyl etherate (49.6 μL, 0.35 mmol, 1.0 equiv) was added dropwise, and the reaction was allowed to stir under argon at 0 °C for 30 min. After 30 min, the reaction was quenched with water (5 mL), extracted with dichloromethane (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator at room temperature. The ^{1}H NMR of the crude reaction mixture indicated a mixture of 10-α and 10-β diastereomers in a ratio of 6:1 (α:β). The crude amorphous solid was purified via column chromatography (5−10% ethyl acetate in hexanes) to afford **10** as an amorphous solid (96 mg, 73% yield). $[\alpha]_D^{22.6}$ +26.08 (c 1.1, $CHCl_3$); IR (thin film) ν 2926, 2872, 1707, 1449, 1378, 1268, 1230, 1195, 1128, 1086, 1069, 1036, 959, 928, 900, 879 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (s, 1H), 4.57 (d, J = 10.8 Hz, 1H), 3.16−2.94 (m, 1H), 2.95−2.75 (m, 3H), 2.73−2.55 (m, 1H), 2.36 (ddd, J = 14.5, 13.2, 4.0 Hz, 1H), 2.01 (ddd, J = 14.5, 4.9, 2.9 Hz, 1H), 1.95−1.80 (m, 1H), 1.80−1.54 (m, 3H), 1.54−1.15 (m, 7H), 1.13−0.98 (m, 1H), 0.94 (dd, J = 9.2, 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 104.7, 92.3, 81.1, 80.6, 51.9, 46.1, 37.5, 36.4, 35.7, 34.2, 31.4, 25.9, 24.9, 23.6, 21.4, 20.4, 15.1; HRMS (FAB) m/z calcd for $C_{18}H_{28}O_6S$ $[M + H]^+$ 373.1685; found, 373.1669.

Thioacetal Carbonate 11h. An oven-dried 2-dram vial, equipped with magnetic stir bar and argon gas inlet needle, was charged with **9b** (17.7 mg, 0.044 mmol, 1 equiv) in dry CH_3CN (1 mL). Sodium hydride (2 mg, 0.088 mmol, 2 equiv) was added as a solid in one portion and the reaction was stirred at room temperature for 30 min. Propargyl chloroformate (21 mg, 0.176 mmol, 4 equiv) was added dropwise via a syringe. The reaction was stirred for 24 h at room temperature, and then more sodium hydride (2 mg, 0.088 mmol, 2 equiv) and propargyl chloroformate (21 mg, 0.176 mmol, 2 equiv) were added. After 12 h, the reaction was quenched with water (2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The organic layers were pooled, dried with $MgSO_4$ (ca. 1 g), vacuum filtered, and concentrated via rotary evaporation at room temperature. The crude residue was purified by flash chromatography on silica gel to yield **11h** as a clear oil (13.4 mg, 64%). $[\alpha]_D^{22.7}$ +11.8 (c. 0.59, $CHCl_3$); IR (thin film) ν 3279, 2973−2851, 1751, 1377, 1279, 1259, 1229, 1128, 1051, 1037, 1017, 928, 880, 678 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (s, 1H), 4.71 (d, J = 2.4 Hz, 2H), 4.51 (d, J = 10.7 Hz, 1H), 4.16 (t, J = 6.6 Hz, 2H), 2.77 (ddd, J = 12.5, 8.2, 6.3 Hz, 1H), 2.68−2.59 (m, 2H), 2.52 (t, J = 2.4 Hz, 1H), 2.36 (ddd, J = 14.6, 13.3, 4.0 Hz, 1H), 2.00 (ddd, J = 14.4, 4.9, 2.9 Hz, 1H), 1.92−1.81 (m, 1H), 1.75−1.52 (m, 8H), 1.50−1.19 (m, 10H), 1.10−0.98 (m, 1H), 0.96−0.90 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 104.4, 92.4, 80.7, 80.6, 75.7, 75.7, 68.8, 55.2, 52.0, 46.2, 37.5, 36.4, 34.2, 31.9, 29.9, 28.7, 28.6, 28.3, 26.1, 25.4, 24.9, 21.5, 20.4, 15.2; HRMS (FAB) m/z calcd for $C_{25}H_{39}O_7S$ (M + H)+ 483.2417; found, 483.2408.

Thioacetal Thiocarbonate 12a. An oven-dried, 2 dram vial, equipped with a magnetic stir bar, under argon was charged with **9a** (10 mg, 0.028 mmol, 1.0 equiv) and dichloromethane (1.0 mL). Pyridine (3 mg, 0.42 mmol, 1.5 equiv) was added, and the mixture was allowed to stir for 15 min. After 15 min, *S*-methyl chlorothioformate (5 mg, 0.042 mmol, 1.5 equiv) was added, and the reaction was allowed to stir under argon for 24 h. After 24 h, the reaction was quenched with water (5 mL) and extracted with dichloromethane (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated on a rotary evaporator at room temperature. The crude amorphous solid was purified via column chromatography (10% ethyl acetate in hexanes) to afford **12a** as a white amorphous solid (9.8 mg, 81% yield). $[\alpha]_D^{22.1}$ −2.40 (c. 0.55, $CHCl_3$); IR (thin film) ν 2925, 2871, 1709, 1452, 1377, 1149, 1033, 926, 877, 826 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (s, 1H), 4.52 (d, J = 10.8 Hz, 1H), 4.35 (td, J = 6.3, 1.0 Hz, 2H), 2.87 (dt, J = 13.6, 6.9 Hz, 1H), 2.76−2.53 (m, 2H), 2.33 (s, 4H), 2.14−1.96 (m, 3H), 1.87 (ddt, J = 13.5, 6.7, 3.3 Hz, 1H), 1.77−1.65 (m, 2H), 1.64−1.21 (m, 8H), 1.11−0.98 (m, 1H), 0.93 (dd, J = 9.8, 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 104.4, 92.4, 80.8, 80.5, 66.4, 51.9, 46.2, 37.5, 36.4, 34.2, 31.8, 29.3, 26.1, 24.9, 21.4, 20.4, 15.2, 13.6; HRMS (FAB) m/z calcd for $C_{20}H_{32}O_6S_2$ $[M + Na]^+$ 455.1538; found, 455.1532.

Thioacetal Thiocarbonate 12c. An oven-dried, 2 dram vial, equipped with a magnetic stir bar, under argon was charged with **9a** (10 mg, 0.028 mmol, 1.0 equiv) and dichloromethane (1.0 mL). Pyridine (3 mg, 0.042 mmol, 1.5 equiv) was added, and the mixture was allowed to stir for 15 min. After 15 min, *S*-*t*-butyl chlorothioformate (6 mg, 0.042 mmol, 1.5 equiv) was added, and the reaction was allowed to stir under argon for 24 h. After 24 h, the reaction was quenched with water (5 mL) and extracted with dichloromethane (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated on a rotary evaporator at room temperature. The crude amorphous solid was purified via column chromatography (10% ethyl acetate in hexanes) to afford **12c** as a white solid (10.9 mg, 82% yield). Mp = 102.4−103.9 °C; $[\alpha]_D^{22.1}$ +2.40 (c. 0.29, $CHCl_3$); IR (thin film) ν 2961, 2922, 2872, 1706, 1455, 1377, 1125, 1036, 927, 879, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (s, 1H), 4.52 (d, J = 10.8 Hz, 1H), 4.30 (td, J = 6.4, 0.9 Hz, 2H), 2.92−2.78 (m, 1H), 2.76−2.52 (m, 2H), 2.43−2.28 (m, 1H), 2.11−1.95 (m, 3H), 1.94−1.81 (m, 1H), 1.79−1.66 (m, 2H), 1.64−1.37 (m, 15H), 1.37−1.20 (m, 2H), 1.12−0.98 (m, 1H), 0.93 (dd, J = 9.9, 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 104.4, 92.4, 80.8, 80.5, 65.3, 51.9, 47.2, 46.2, 37.5, 36.4, 34.2, 31.8, 30.3, 29.3, 26.1, 25.0, 24.9, 21.4, 20.4, 15.2; HRMS (FAB) m/z calcd for $C_{23}H_{38}O_6S_2$ $[M + H]^+$ 475.2188; found, 475.2174.

Thioacetal Benzimidazole Amide 14a. To a 2.5 mL microwave vial was added **10** (15 mg, 0.040 mmol), EDC (8.5 mg, 0.044 mmol), DMAP (5.4 mg, 0.044 mmol), and commercially available 2-aminobenzimidazole (5.86 mg, 0.044 mmol) and dissolved in CH_2Cl_2 (1 mL) under an Ar blanket. The solution was heated to 60 °C for 1.5 h via microwave irradiation, at which point it was quenched with saturated $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 × 1.5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by column chromatography (0−4% MeOH/CH_2Cl_2) to provide **14a** as a colorless, amorphous solid (88% yield, 17.3 mg, 0.035 mmol). $[\alpha]_D^{23.9}$ = −69.6 (c = 1.550, $CHCl_3$); FTIR (thin film) ν 3341, 2926, 2872, 1686, 1633, 1578, 1456, 1271, 1127, 1085; ^1H NMR (300 MHz, $CDCl_3$) δ 11.27 (s, 1H), 7.52 (s, 3H), 7.25−7.16 (m, 2H), 5.19 (s, 1H), 4.51 (d, J = 10.8 Hz, 1H), 3.33−3.15 (m, 2H), 3.10−2.87 (m, 2H), 2.62 (dqd, J = 11.0, 7.2, 4.0 Hz, 1H), 2.33 (td, J = 13.3, 3.9 Hz, 1H), 2.04−1.91 (m, 1H), 1.90−1.76 (m, 1H), 1.68−1.49 (m, 3H), 1.48−1.36 (m, 1H), 1.35 (s, 3H), 1.29−1.13 (m, 3H), 1.11−0.95 (m, 1H), 0.95−0.92 (d, J = 6.0 Hz, 3H), 0.86 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 172.4, 147.6, 122.2, 104.5, 92.2, 92.1, 89.6, 80.4, 80.3, 51.6, 45.8, 37.39, 37.3, 36.22, 34.0, 31.1, 25.8, 24.6, 24.0, 21.0, 20.12, 18.4, 14.8, 6.8.; HRMS (ESI) calcd for $C_{25}H_{34}N_3O_5S$ $(M + H)^+$ 488.2219; found, 488.2217.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional experimental details, analytical data, and copies of ^1H and ^{13}C NMR spectra for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: 410-516-4670. Fax: 410-516-8420. E-mail: ghp@jhu.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NIH (AI 34885), the Johns Hopkins Malaria Research Institute, and the Bloomberg Family Foundation for financial support. We also thank Bryan T. Mott for help in obtaining some HRMS data.

■ ABBREVIATIONS USED

ACT, artemisinin combination therapy; WHO, world health organization; DHA, dihydroartemisinin; EDC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; DMAP, 4-dimethylaminopyridine

■ REFERENCES

(1) *World Malaria Report 2011*; World Health Organization: Geneva, Switzerland, 2011.

(2) Delves, M.; Plouffe, D.; Scheurer, C.; Meister, S.; Wittlin, S.; Winzeler, E. A.; Sinden, R. E.; Leroy, D. The activities of current antimalarial drugs on the life cycle stages of *Plasmodium*: a comparative study with human and rodent parasites. *PLoS Med.* **2012**, *9*, e1001169 DOI: 10.1371/journal.pmed.1001169.

(3) Murray, C. J. L.; Rosenfeld, L. C.; Lim, S. S.; Andrews, K. G.; Foreman, K. J.; Hqqaring, D.; Fullman, N.; Naghavi, M.; Lozano, R.; Lopez, A. D. Global malaria mortality between 1980 and 2010: a systematic analysis. *Lancet* **2012**, *379*, 413−431.

(4) Gulland, A. Death toll from Malaria is double the WHO estimate, study finds. *Brit. Med. J.* **2012**, *344*, 895.

(5) Thera, M. A.; Plowe, C. V. Vaccines for malaria: how close are we? *Annu. Rev. Med.* **2012**, *63*, 345−357.

(6) Nussenzweig, V.; Good, M. F.; Hill, A. V. S. Mixed results for a malaria vaccine. *Nature Med.* **2011**, *17*, 1560−1561.

(7) Olliaro, P. L.; Boland, P. B. Clinical Public Health Implications of Antimalarial Drug Resistance. In *Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery*; Rosenthal, P. J., Ed.; Humana Press: Totowa, NJ, 2001; pp 65−84.

(8) Burgess, S. J.; Selzer, A.; Kelly, J. X.; Smilkstein, M. J.; Riscoe, M. K.; Peyton, D. H. A chloroquine-like molecule designed to reverse resistance in *Plasmodium falciparum*. *J. Med. Chem.* **2006**, *49*, 5623−5625.

(9) *Guidelines for Treatment of Malaria*; World Health Organization: Geneva, Switzerland, 2006.

(10) Slack, R. D.; Jacobine, A. M.; Posner, G. H. Antimalarial peroxides: advances in drug discovery and design. *Med. Chem. Commun.* **2012**, *3*, 281−297.

(11) Tilley, L.; Charman, S. A.; Vennerstrom, J. L. Semisynthetic Artemisinin and Synthetic Peroxide Antimalarials. *RSC Drug Discovery Series*; Neglected Diseases and Drug Discovery; Royal Society of Chemistry: London, 2012; Vol. *14*, 33−64.

(12) Wells, T. N. C. Natural products as starting points for future anti-malarial therapies: going back to our roots? *Malaria J.* **2011**, *10*, 1−12.

(13) Eastman, R. T.; Fidock, D. A. Artemisinin-based combination therapies: a vital tool in efforts to eliminate malaria. *Nat. Rev. Microbiol.* **2009**, *7*, 864−874.
(14) Charman, S. A.; Arbe-Barnes, S; Bathurst, I. C.; Brun, R.; Campbell, M.; Charman, W. N.; Chiu, F. C. K.; Chollet, J.; Craft, J. C.; Creek, D. J.; Dong, Y.; Matile, H.; Maurer, M.; Morizzi, J.; Nguyen, T.; Papastogiannidis, P.; Scheurer, C.; Shackleford, D. M.; Sriraghavan, K.; Stingelin, L.; Tang, Y.; Urwyler, H.; Wang, X.; White, K. L.; Wittlin, S.; Zhou, L.; Vennerstrom, J. L. Synthetic ozonide drug candidate OZ439 offers new hope for a single-dose cure of uncomplicated malaria. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 4400−4405.
(15) O'Neill, P. M. The therapeutic potential of semi-synthetic artemisinin and synthetic endoperoxide antimalarial agents. *Expert Opin. Invest. Drugs* **2005**, *14*, 1117−1128.
(16) Yavo, W.; Faye, B.; Kuete, T.; Djohan, V.; Oga, S. A.; Kassi, R. R.; Diatta, M.; Ama, M. V.; Tine, R.; Ndiaye, J.-L.; Evi, J.-B.; Same-Ekobo, A.; Faye, O.; Koné, M. Multicentric assessment of the efficacy and tolerability of dihydroartemisinin-piperaquine compared to artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in sub-Saharan Africa. *Malaria J.* **2011**, *10*, 198−205.
(17) Macedo de Oliveira, A.; Chavez, J.; Ponce de Leon, G.; Durand, S.; Arrospide, N.; Roberts, J.; Cabezas, C.; Marquiño, W. Efficacy and effectiveness of mefloquine and artesunate combination therapy for uncomplicated *Plasmodium falciparum* malaria in the Peruvian Amazon. *Am. J. Trop. Med. Hyg.* **2011**, *85*, 573−578.
(18) Sagara, I.; Diallo, A.; Kone, M.; Coulibaly, M.; Diawara, S. I.; Guindo, O.; Maiga, H.; Niambele, M. B.; Sissoko, M.; Dicko, A.; Djimde, A.; Doumbo, O. K. A randomized trial of artesunate-mefloquine versus artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria in Mali. *Am. J. Trop. Med. Hyg.* **2008**, *79*, 655−661.
(19) Rueangweerayut, R.; Phyo, A. P.; Uthaisin, C.; Poravuth, Y.; Binh, T. Q.; Tinto, H.; Pénali, L. K.; Valecha, N.; Tien, N. T.; Abdulla, S.; Borghini-Fuhrer, I.; Duparc, S.; Shin, C.-K.; Fleckenstein, L. Pyronaridine-artesunate versus mefloquine plus artesunate for malaria. *N. Engl. J. Med.* **2012**, *366*, 1298−1309.
(20) Kurth, F.; Bélard, S.; Basra, A.; Ramharter, M. Pyronaridine-artesunate combination therapy for the treatment of malaria. *Curr. Opin. Infect. Dis.* **2011**, *24*, 564−569.
(21) Sagara, I.; Diallo, A.; Kone, M.; Coulibaly, M.; Diawara, S. I.; Guindo, O.; Maiga, H.; Diambele, M. B.; Sissoko, M.; Dicko, A.; Djimde, A.; Doumbo, O. K. A randomized trial of aresunate-mefloquine versus artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria in Mali. *Am. J. Trop. Med. Hyg.* **2008**, *79*, 655−661.
(22) Cohen, J. L.; Yavuz, E.; Morris, A.; Arkedis, J.; Sabot, O. Do malaria patients adhere to over-the-counter artemisinin combination therapy for malaria? evidence from an intervention study in Uganda. *Malaria J.* **2012**, *11*, 83−93.
(23) Lawford, H.; Zurovac, D.; O'Reilly, L.; Hoibak, S.; Cowley, A.; Munga, S.; Vulule, J.; Juma, E.; Snow, R. W; Allan, R. Adherence to prescribed artemisinin-based combination therapy in Garissa and Bunyala districts, Kenya. *Malaria J.* **2011**, *10*, 281−288.
(24) O'Brien, C.; Philipp, H. P.; Passi, N.; Fidock, D. A. Recent clinical and molecular insights into emerging artemisinin resistance in *Plasmodium falicaparum*. *Curr. Opin. Infect. Dis.* **2011**, *24*, 570−577.
(25) Ferrer, P.; Tripathi, A. K.; Clark, M. A.; Hand, C. C.; Rienhoff, H. Y., Jr.; Sullivan, D. J. Antimalarial iron chelator, FBS0701, shows asexual and gametocyte *Plasmodium falciparum* activity and single oral dose cure in murine malaria model. *PLoS One* **2012**, *7*, e37171.
(26) Tun, T.; Tint, H. S.; Lin, K.; Kyaw, T. T.; Myint, M. K.; Khaing, W.; Tun, Z W. Efficacy of oral single dose therapy with artemisinin-naphthoquine phosphate in uncomplicated *falciparum* malaria. *Acta Tropica* **2009**, *111*, 275−278.
(27) Younis, Y.; Douelle, F.; Feng, T.-S.; González Cabrera, D.; Le Manach, C.; Nchinda, A. T.; Duffy, S.; White, K. L.; Shackleford, D. M.; Morizzi, J.; Mannila, J.; Katneni, K.; Bhamidipati, R.; Zabiulla, K. M.; Joseph, J. T.; Bashyam, S.; Waterson, D.; Witty, M. J.; Hardick, D.; Wittlin, S.; Avery, V.; Charman, S. A.; Chibale, K. 3,5-Diaryl-2-aminopyridines as a novel class of orally active antimalarials demonstrating single dose cure in mice and clinical candidate potential. *J. Med. Chem.* **2012**, *55*, 3479−3487.
(28) Benjamin, J.; Morre, B.; Lee, S. T.; Senn, M.; Griffin, S.; Lautu, D.; Salman, S.; Siba, P.; Mueller, I.; Davis, T. M. E. Artemisinin-naphthoquine combination therapy for uncomplicated pediatric malaria: a tolerability, safety, and preliminary efficacy study. *Antimicrob. Agents Chemother.* **2012**, *56*, 2465−2471.
(29) Batty, K. T.; Salman, S.; Moore, B. R.; Benjamin, J.; Lee, S. T.; Page-Sharp, M.; Pitus, N.; Ilett, K. F.; Mueller, I.; Hombhanje, F. W.; Siba, P.; Davis, T. M. E. Artemisinin-napthoquine combination therapy for uncomplicated pediatric malaria: a pharmacokinetic study. *Antimicrob. Agents Chemother.* **2012**, *56*, 2472−2484.
(30) Slack, R. D.; Mott, B. T.; Woodard, L. E.; Tripathi, A.; Sullivan, D.; Nenortas, E; Girdwood, S. C. T.; Shapiro, T. A.; Posner, G. H. Malaria-infected mice are completely cured by one 6 mg/kg oral dose of new monomeric trioxane sulfide combined with mefloquine. *J. Med. Chem.* **2012**, *55*, 291−296.
(31) Moon, D. K.; Tripathi, A.; Sullivan, D.; Siegler, M. A.; Parkin, S.; Posner, G. H. A single, low, oral dose of a 5-carbon-linked trioxane dimer orthoester plus mefloquine cures malaria-infected mice. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2773−2775.
(32) García-Álvares, I.; Groult, H.; Casas, J.; Barreda-Manso, M. A.; Yanguas-Casás, N.; Nieto-Sampedro, M.; Romero-Ramírez, L.; Fernández-Mayoralas, A. Synthesis of antimitotic thioglycosides: in vitro and in vivo evaluation of their anticancer activity. *J. Med. Chem.* **2011**, *54*, 6949−6955.
(33) Fanton, J.; Camps, F; Castillo, J. A.; Guérard-Hélaine, C.; Lemaire, M.; Charmantray, F.; Hecquet, L. Enzymatic and organo-catalyzed asymmetric aldolization reactions for the synthesis of thiosugar scaffolds. *Eur. J. Org. Chem.* **2012**, 203−210.
(34) Hibino, H.; Nishiuchi, Y. 4-Methoxybenzyloxymethyl group, a racemization-resistant protecting group for cysteine in Fmoc solid phase peptide synthesis. *Org. Lett.* **2012**, *14*, 1926−1929.
(35) Posner, G. H.; Cumming, J. N.; Woo, S.-H.; Ploypradith, P.; Xie, S.; Shapiro, T. A. Orally active antimalarial 3-substituted trioxanes: new synthetic methodology and biological evaluation. *J. Med. Chem.* **1998**, *41*, 940−951.
(36) Chadwick, J.; Mercer, A. E.; Park, B. K.; Cosstick, R.; O'Neill, P. M. Synthesis and biological evaluation of extraordinarily potent C-10 carba artemisinin dimers against *P. falciparum* malaria parasites and HL-60 cancer cells. *Bioorg. Med. Chem.* **2009**, *17*, 1325−1338.
(37) Venugopalan, B.; Karnik, P. J.; Bapat, C. P.; Chatterjee, D. K.; Iver, N.; Lepcha, D. Antimalarial activity of new ether and thioethers of dihydroartemisinin. *Eur. J. Med. Chem.* **1995**, *30*, 697−706.
(38) Lee, S.; Oh, S. A simple synthesis of C-10 substituted deoxoartemisinin and 9-*epi*-deoxoartemisinin with various organozinc reagents. *Tetrahedron Lett.* **2002**, *43*, 2891−2894.
(39) Oh, S.; Jeong, I. H.; Shin, W.-S.; Lee, S. Growth inhibition activity of thioacetal artemisinin derivatives against human umbilical vein endothelial cells. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3665−3668.
(40) Lee, S.; Oh, S.; Park, G.-M.; Kim, T.-S.; Ryu, J.-S.; Choi, H.-K. Antimalarial activity of thiophenyl- and benzenesulfonyl-artemisinin. *Korean J. Parasitol.* **2005**, *43*, 123−126.
(41) Oh, S.; Jeong, I. H.; Ahn, C. M.; Shin, W.-S.; Lee, S. Synthesis and antiangiogenic activity of thioacetal artemisinin derivatives. *Bioorg. Med. Chem.* **2004**, *12*, 3783−3790.
(42) Satchell, D. P. N.; Satchell, R. S. Mechanisms of hydrolysis of thioacetals. *Chem. Soc. Rev.* **1990**, *19*, 55−81.
(43) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2007; pp 501−503.
(44) Ma, J.; Katz, E.; Kyle, D. E.; Ziffer, H. Syntheses and antimalarial activities of 10-substituted deoxoartemisinins. *J. Med. Chem.* **2000**, *43*, 4228−4232.
(45) Klayman, D. L. Qinghaosu (artemisinin): an antimalarial drug from China. *Science* **1985**, *228*, 1049−1055.

(46) Rautio, J.; Kumpulainen, H.; Heimbach, T.; Oliyai, R.; Oh, D.; Järvinen, T.; Savolainen, J. Prodrugs: design and clinical applications. *Nat. Rev. Drug Discovery* **2008**, *7*, 255−270.
(47) Ueda, Y.; Wong, H.; Matiskella, J. D.; Mikkilineni, A. B.; Farina, V.; Fairchild, C.; Rose, W. C.; Mamber, S. W.; Long, B. H.; Kerns, E. H.; Casazza, A. M.; Vyas, D. M. Synthesis and antitumor evaluation of 2′-oxycarbonylpaclitaxels (paclitaxel-2′-carbonates). *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1861−1864.
(48) Nicolaou, K. C.; Riemer, C.; Kerr, M. A.; Rideout, D.; Wrasidlo, W. Design, synthesis and biological activity of protaxols. *Nature* **1993**, *364*, 464−466.
(49) Skinner-Adams, T. S.; Davis, T. M.; Manning, L. S.; Johnston, W. A. The efficacy of benzimidazole drugs against *Plasmodium falciparum in vitro*. *Trans. R. Soc. Trop. Med. Hyg.* **1997**, *91*, 580−594.
(50) Berger, O.; Kaniti, A.; Tran van Ba, C.; Vial, H.; Ward, S. A.; Biagini, G. A.; Bray, P. G.; O'Neill, P. M. Synthesis and antimalarial activities of a diverse set of triazole-containing furamidine analogues. *ChemMedChem* **2011**, *6*, 2094−2108.
(51) Saify, Z. S.; Azim, M. K.; Ahmad, W.; Nisa, M.; Goldberg, D. E.; Hussain, S. A.; Akhtar, S.; Akram, A.; Arayne, A.; Oksman, A.; Khan, I. A. New benzimidazole derivatives as antiplasmodial agents and plasmepsin inhibitors: synthesis and analysis of structure−activity relationships. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1282−1286.
(52) Taudon, N.; Margout, D.; Wein, S.; Calas, M.; Vial, H. J.; Bressole, F. M. M. Quantitative analysis of a bis-thiazolium antimalarial compound, SAR97276, in mouse plasma and red blood cell samples, using liquid chromatography mass spectrometry. *J. Pharm. Biomed. Anal.* **2008**, *46*, 148−156.
(53) Ban, K.; Duffy, S.; Khakham, Y.; Avery, V. M.; Hughes, A.; Montagnat, O.; Katneni, K.; Ryan, E.; Baell, J. B. 3-Alkyl-1,2,4-triazine dimers with potent antimalarial activity. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6024−6029.
(54) Woodard, L. E.; Chang, W.; Chen, X.; Liu, J. O.; Shapiro, T. A.; Posner, G. H. Malaria-infected mice live until at least day 30 after a new monomeric trioxane combined with mefloquine are administered together in a single low oral dose. *J. Med. Chem.* **2009**, *52*, 7458−7462.
(55) Jung, M.; Lee, S. Stability of acetal and non acetal-type analogs of artemisinin in simulated stomach acid. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1003−1006.