New Adamantane-Based Spiro 1,2,4-Trioxanes Orally Effective against Rodent and Simian Malaria†

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New 6-arylvinyl- and 6-adamantylvinyl-substituted 1,2,4-trioxanes (**13a**−**g** and **14a**,**b)** have been prepared and evaluated for antimalarial activity against multidrug resistant *Plasmodium yoelii nigeriensis* in mice by both oral and intramuscular routes. While all the 6-arylvinyl-substituted trioxanes, **13a**−**f**, showed promising activity, none of the 6-adamantylvinyl-substituted trioxanes, **13g** and **14a**,**b**, exhibited significant activity. Trioxane, **13f**, the most active compound of the series, provided 100% and 80% protection to malaria-infected mice at 48 mg/kg × 4 days and 24 mg/kg × 4 days, respectively, by oral route. In this model, β-arteether (**3**) provided 100% protection at 48 mg/kg × 4 days and only 20% protection at 24 mg/kg × 4 days. Trioxane **13f** also showed complete suppression of parasitaemia at 10 mg/kg × 4 days by oral route in rhesus monkeys infected with *P. cynomolgi*. None of these trioxanes, except **13f**, showed significant activity by the intramuscular route.

Introduction

Malaria is a major parasitic disease affecting around 300−500 million people of which more than one million die every year.[2] The increasing resistance of the malarial parasite against the contemporary drugs has further compounded the malaria problem. Against this background, isolation of artemisinin **1** as the active principle of *Artemisia annua*, is a major breakthrough in malaria chemotherapy.[3] Artemisinin and its semisynthetic derivatives such as artemether **2**, arteether **3**, and artesunic acid **4** (Figure 1) are effective against both the chloroquine-sensitive and chloroquine-resistant malaria, and because of their rapid action are finding increasing use for the treatment of malaria caused by multidrug resistant *P. falciparum*.[4] The peroxide group, present in the form of 1,2,4-trioxane, is essential for the antimalarial activity of these compounds. Several synthetic trioxanes have shown promising antimalarial activity both *in vitro* and *in vivo*.[5]

As part of our efforts to develop synthetic substitutes for artemisinin derivatives, we have earlier reported a photooxygenation route for the synthesis of 1,2,4-trioxanes. The preparation of β-hydroxyhydroperoxides by photooxygenation of allyl alcohols and their acid-catalyzed reaction with aldehydes/ketones are the key steps of this method (Scheme 1).[6] Several of the 1,2,4-trioxanes prepared by this method had shown significant antimalarial activity in vivo.[7] From these early studies we also discovered that 1,2,4-trioxanes spiroanellated with adamantane moiety at C-3 position, for example, **5**, **6**, and **7** (Figure 2), were more active than the other structurally related spiro 1,2,4-trioxanes. A similar beneficial effect of adamantane moiety on the antimalarial activity of the synthetic peroxides have been reported by Vennerstrom et al.[8] and Griesbeck et al.[9] Building on these lead compounds, we have done further SAR studies in this area and report, herein, synthesis and antimalarial assessment of a series of new adamantane-based 1,2,4-trioxanes **13a**−**g** and **14a**,**b**, some of which have shown promising activity against multidrug resistant *P. yoelii nigeriensis* by oral route. We also report the antimalarial activity of trioxane **13f**, the most active compound of the series, against *P. cynomolgi* in rhesus monkeys.

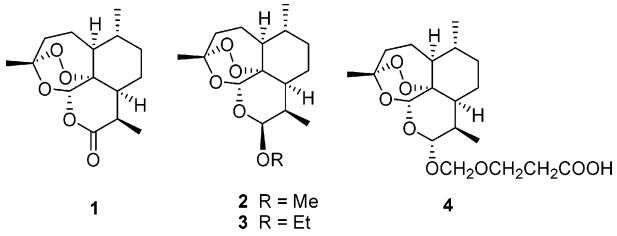


Figure 1. Artemisinin and its clinically useful derivatives.

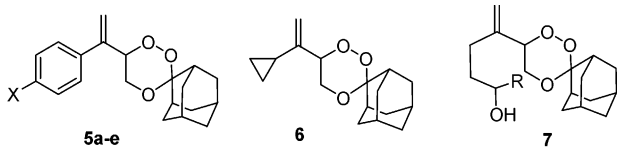
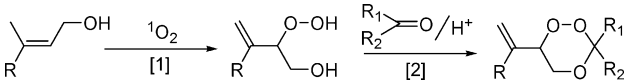


Figure 2. Prototypes **5a**−**e**, **6**, and **7** reported earlier.[7a,f,e]

Scheme 1[a,6]



[a] Reagents and conditions: [1] O_2, methylene blue, *hν*, −10−0 °C, 4−6 h; [2] ketone/aldehyde, HCl, rt.

Chemistry

3-Arylbut-2-enols **8a**,**b** and **8d**−**f** were prepared and photooxygenated according to our published procedure to give β-hydroxyhydroperoxides **9a**,**b** and **9d**−**f** (Figure 3).[7i] Allylic alcohols **8c** and **8g** were prepared from the corresponding ketones **10c** and **10g** according to Scheme 2 and were photooxygenated to give β-hydroxyhydroperoxides **9c** and **9g**, respectively.[10] β-Hydroxyhydroperoxides **9a** and **9b** were reacted with 2-adamantanone in the presence of catalytic amount of HCl to furnish trioxanes **13a** and **13b** in 42 and 45% yields,

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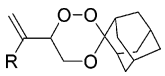
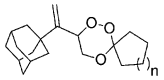
a: R = 1-naphthyl; **b**: R = 2-naphthyl; **c**: R = 2-tetrahydronaphthyl;
d: R = 2-phenanthrenyl; **e**: R = 3-phenanthrenyl; **f**: R = 2-fluorenyl

Figure 3. Allylic alcohols **8a**−**f** and their photooxygenation products **9a**−**f**.

a: R = 1-naphthyl; **b**: R = 2-naphthyl; **c**: R = 2-tetrahydronaphthyl;
d: R = 2-phenanthrenyl; **e**: R = 3-phenanthrenyl; **f**: R = 2-fluorenyl;
g: R = 1-adamantyl

Figure 4. Adamantane-based trioxanes.

Table 1. Yields of the Trioxanes **13a**−**g** and **14a**,**b**

general structure	cmpd	substituent	% yield[a,b]
	**13a**	R = 1-naphthyl	42[a]
	13b	R = 2-naphthyl	45[a]
	13c	R = 2-tetrahydronaphthyl	46[b]
	13d	R = 2-phenanthrenyl	57[b]
	13e	R = 3-phenanthrenyl	50[b]
	13f	R = 2-fluorenyl	59[b]
	13g	R = 1-adamantyl	50[b]
	**14a**	*n* = 1	38[b]
	14b	*n* = 2	54[b]

[a] Yield based on hydroperoxide. [b] Yield based on allyl alcohol.

respectively. For the preparation of trioxanes **13c**−**g**, β-hydroxyhydroperoxides **9c**−**g**, the photooxygenation products of alcohols **8c**−**g**, were not isolated and were condensed in situ with 2-adamantanone in the presence of a catalytic amount of HCl to furnish these trioxanes in 46−59% overall yields. A similar reaction of photooxygenation product of allylic alcohol **8g** with cyclopentanone and cyclohexanone furnished spiro trioxanes **14a** and **14b** in 38% and 54% yields, respectively (Figure 4, Table 1).

Antimalarial Activity

Trioxanes **13a**−**g** and **14a**,**b** were assessed for antimalarial activity against multidrug resistant *P. yoelii nigeriensis* in Swiss mice both by oral and by intramuscular routes using Peter's procedure.[11] In this model, arteether shows 100% clearance of parasitaemia at 48 mg/kg × 4 days, and all the treated mice survive beyond day 28. At 24 mg/kg × 4 days arteether provides only 20% protection. Therefore, all the trioxanes were initially evaluated at 96 mg/kg × 4 days, twice the effective dose of arteether. Trioxanes **13a**−**f**, which provided 100% protection at this dose by oral route, were further tested at 48 mg/kg × 4 days and 24 mg/kg × 4 days.[12] Results are summarized in Table 2. Trioxane **13f**, the most active compound of the series, was also tested against *P. cynomolgi* in rhesus monkeys at 10 mg/kg × 4 days and 20 mg/kg × 4 days by oral route.[13] Both these doses were effective in complete clearance of parasitaemia between 72 and 120 h. Trioxane **13f**, when given intramuscularly at 10 mg/kg × 4 days, did not show any activity. Results are summarized in Table 3.

Results and Discussion

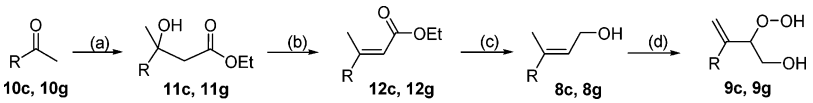
In our ongoing program on synthetic antimalarial peroxides, we had earlier synthesized and evaluated for activity a large number of 1,2,4-trioxanes.[7] From this extensive SAR studies, we had discovered that 1,2,4-trioxanes spiroanellated at C-3 with adamantane moiety, for example, **5a**−**e**,[7a] **6**,[7f] and **7**[7e] (Figure 2), showed promising antimalarial activity. Particularly relevant to the present study are the trioxanes **5a**−**e**, which had shown promising activity against chloroquine-sensitive *P. berghei* in mice by intraperitoneal route. However, these compounds showed poor activity when tested against multidrug resistant *P. yoelii nigeriensis* by oral and intramuscular routes (activity data of compound **5a** is included in Table 2). Building on these lead compounds **5a**−**e** and our own observation that lipophilic compounds show better absorption when given by oral route,[15] we initially prepared and evaluated 6-naphthylvinyl-substituted 1,2,4-trioxanes **13a**,**b**, both of which are considerably more lipophilic than **5a**−**e**. As can be seen from Table 2, both these trioxanes showed 100% clearance of parasitaemia on day 4 at 96 mg/kg × 4 days and all the treated mice survived beyond day 28. Even at 48 mg/kg × 4 days, both these compounds showed 100% clearance of parasitaemia on day 4 and 50% of the treated mice survived beyond day 28. Thus, both these compounds are significantly more active than **5a**, which showed only low-order activity at 96 mg/kg × 4 days. Replacement of 2-naphthyl moiety with 2-tetrahydronaphthyl moiety (trioxane **13c**) had only marginal effect on the activity. Trioxane **13c**, which showed 100% protection at 96 mg/kg × 4 days, provided only 20% protection at 48 mg/kg × 4 days. The 6-phenanthrenylvinyl-substituted trioxanes **13d**,**e**, though considerably more lipophilic than **13a**−**c**, showed a similar level of activity. While at 96 mg/kg × 4 days, both these compounds showed 100% protection, at 48 mg/kg × 4 days, the protection level varied from 50 to 67%, indicating that the further increase in lipophilicity was not improving the biological activity. The 6-fluorenylvinyl-substituted trioxane **13f**, which is more lipophilic than **13a**−**c** but less lipophilic than **13d**,**e**, was found to be considerably more active than the rest of the trioxanes of the series. Trioxane **13f** showed 100% suppression of parasitaemia at 48 mg/kg × 4 days, and all the treated mice survived beyond day 28. Even at 24 mg/kg × 4 days, half the effective dose of arteether, it showed 100% suppression of the parasitaemia, and 80% of the treated mice survived beyond day 28. It also showed more than 80% protection at 96 mg/kg × 4 days by intramuscular route. None of the trioxanes **13a**−**e** showed significant activity at 96 mg/kg × 4 days by intramuscular route.

Trioxane **13f** was also tested in rhesus monkeys infected with *P. cynomolgi* (Table 3). It showed 100% clearance of parasitaemia when given at 10 mg/kg × 4 days and 20 mg/kg × 4 days, by oral route, though none of these doses provided long-term protection. As expected, trioxane **13f** exhibited poor activity at 10 mg/kg × 4 days when given by intramuscular route.

Trioxane **13g** and **14a**,**b** were prepared to assess the effect of adamantyl group when it is appended to the trioxane structure at position C-6. Trioxane **13g**, though it has two adamantane moieties, showed only 70% suppression of parasitaemia on day 4 at 96 mg/kg × 4 days, and none of the treated mice survived to day 28. The 6-adamantylvinyl trioxanes **14a** and **14b**, spiroanellated with cyclopentane and cyclohexane moieties at C-3 of the trioxane structure, were totally inactive in this model. Thus, adamantane moiety, though a well-accepted fragment for bioactive molecules,[16] has an adverse effect on activity when it is placed as the adamantylvinyl group at position C-6 of the trioxane structure.

The notable feature of this series of trioxanes is that, while several of them showed very good antimalarial activity by oral route, none of them, except **13f**, showed significant activity by intramuscular route. These compounds are highly hydrophobic, and the compounds with high hydrophobicity are known to show

Scheme 2[a]



[a] Reagents and conditions: (a) $BrCH_2COOC_2H_5$, Zn, I_2, C_6H_6, reflux, 3 h; (b) *p*-TSA, C_6H_6, reflux, 5−6 h; (c) $LiAlH_4$, diethyl ether, −10−0 °C, 1 h; (d) O_2, methylene blue, *hν*, CH_3CN, −10−0 °C, 4−5 h.

good bioavailability by the oral route and poor absorption by the intramuscular route. Janssen et al.[17] have proposed a model to explain the oral absorption of lipophilic compounds. According to this model, hydrophobic compounds form aggregates of appropriate sizes in an aqueous environment of the gastrointestinal tract where they are taken up by M cells and then drained into the lymphatic circulation and emptied into systemic compartments. We had earlier observed a similar type of effect in artemisinin derivatives.[15] The poor activity of these compounds by the intramuscular route is due to their poor solubility in an aqueous system, which makes their absorption slow from the site of injection (muscle).[18]

Conclusion

We have prepared a new series of orally active adamantane-based 1,2,4-trioxanes, several of which showed significant activity against multidrug resistant *P. yoelii nigeriensis* in mice. Trioxane **13f**, the most active compound of the series, showed antimalarial activity better than that of arteether and artesunic acid by the oral route. Trioxane **13f** also showed complete clearance of parasitaemia in rhesus monkeys infected with *P. cynomolgi*. We have also shown that the adamantane moiety, a well-known scaffold associated with various types of biological activity, has a beneficial effect on antimalarial activity only when it is spiroanellated at position C-3 of the trioxane skeleton.

Experimental Section

All glass apparatus were properly cleaned and oven dried prior to use. Yields refer to purified products and are not optimized. Commercially available anhydrous diethyl ether was kept over Na-wires overnight prior to use. HPLC grade CH_3CN was used. Melting points were determined in open capillaries on a COMPLAB melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer RXI FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR were recorded on a Bruker Supercon Magnet DPX-200 (operating at 200 MHz for ^1H and 50 MHz for ^{13}C) spectrometer using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^1H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. Multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), bs (broad singlet), and m (multiplet). Fast atom bombardment mass spectra (FAB-MS) were obtained on a JEOL SX 120 spectrometer using glycerol/*m*-nitrobenzyl alcohol as matrix. High-resolution electron impact mass spectra (HR-EIMS) were obtained on a JEOL JMS-600H instrument. Elemental analyses were done on an Elementar Vario EL-III analyzer. Reactions were monitored on silica gel TLC plates. Column chromatography was performed over silica gel (60−120 mesh) procured from Qualigens (India) using freshly distilled solvents. All the chemicals and reagents were obtained from Aldrich (USA), Lancaster (England), or Spectrochem (India) and were used without purification. Log *p* values of the compounds were calculated using Chem Draw Ultra 7.0 software.

3-(5,6,7,8-Tetrahydro-naphthalen-2-yl)-but-2-enoic Acid Ethyl Ester (12c). To a refluxing mixture of 2-acetyl-5,6,7,8-tetrahydronaphthalene **10c** (10 g, 57.5 mmol), Zn dust (7.47 g, 114.9 mmol), and I_2 (15 mg) in benzene (100 mL) was added a solution of ethyl bromoacetate (11.5 g, 68.96 mmol) in benzene (50 mL) over 45 min, and the reaction mixture was stirred at the same temperature for 2 h. It was cooled to 0 °C, quenched with 10% aqueous HCl solution (120 mL), the organic layer was separated, washed successively with 5% aqueous $NaHCO_3$ (2 × 50 mL) followed by brine solution (70 mL), dried over anhydrous Na_2SO_4, and concentrated, and the crude product (**11c**) was reacted in situ with *p*-TSA (500 mg) in refluxing benzene (150 mL) for 5 h. The reaction mixture was cooled to room temperature, neutralized with saturated $NaHCO_3$ solution (100 mL), extracted with benzene (4 × 75 mL), and concentrated, and the crude product was purified by column chromatography over silica gel to furnish **12c** (oil, 10 g, yield 71%, based on **10c**). FT-IR (neat, cm^{-1}) 1731, 1670; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.0 Hz), 1.79 (bs, 4H), 2.55 (s, 3H), 2.77 (bs, 4H), 4.20 (q, 2H, J = 7.0 Hz), 6.12 (s, 1H), 7.03−7.23 (m, 3H). FAB-MS (*m/z*): 245 $[M + H]^+$. HR-EIMS calcd for $C_{16}H_{20}O_2$, 244.1463; found, 244.1475.

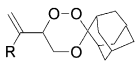
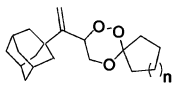
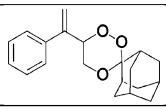
3-Adamantan-1-yl-but-2-enoic Acid Ethyl Ester (12g). To a refluxing mixture of 1-acetyladamantane **10g** (5 g, 28.1 mmol), Zn dust (3.7 g, 56.2 mmol), and I_2 (10 mg) in benzene (75 mL) was added a solution of ethyl bromoacetate (5.6 g, 33.7 mmol) in benzene (40 mL) dropwise over 30 min, and the reaction mixture was stirred at the same temperature for 2 h. It was cooled to 0 °C and quenched with 10% aqueous HCl solution (60 mL), the organic layer was separated, washed successively with 5% aqueous $NaHCO_3$ (2 × 30 mL) and brine solution (40 mL), dried over anhydrous Na_2SO_4, concentrated, and the crude product (**11g**) was reacted in situ with *p*-TSA (200 mg) in refluxing benzene (100 mL) for 5 h. The reaction mixture was cooled at room temperature, neutralized with saturated $NaHCO_3$ solution (75 mL), extracted with benzene (4 × 50 mL), and the solvent was distilled off, and the crude product was purified by column chromatography over silica gel to furnish **12g** (oil, 4.5 g, yield 65%, based on **10g**). FT-IR (neat, cm^{-1}) 1712, 1625; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.1 Hz), 1.62−2.03 (m, 15H), 2.13 (s, 3H), 4.13 (q, 2H, J = 7.1 Hz), 5.66 (s, 1H). FAB-MS (*m/z*): 249 $[M + H]^+$. HR-EIMS calcd for $C_{16}H_{24}O_2$, 248.1776; found, 248.1776.

3-(5,6,7,8-Tetrahydro-naphthalen-2-yl)-but-2-en-1-ol (8c). To a magnetically stirred, ice-cooled mixture of $LiAlH_4$ (1.7 g, 45.1 mmol) in dry ether (75 mL) was added a solution of 3-(5,6,7,8-tetrahydro-naphthalen-2-yl)-but-2-enoic acid ethyl ester **12c** (10 g, 40.9 mmol) in dry ether (50 mL) dropwise over 20 min. The resulting mixture was stirred for an additional 1 h at 0 °C. The mixture was quenched with water (10 mL) and 5% aqueous NaOH (5 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated, and the crude product was purified by column chromatography over silica gel to furnish **8c** (oil, 6 g, 72% yield). FT-IR (neat, cm^{-1}) 3628; ^1H NMR (200 MHz, $CDCl_3$) δ 1.79 (bs, 4H), 2.05 (s, 3H), 2.75 (bs, 4H), 4.33 (d, 2H, J = 6.7 Hz), 5.93 (t, 1H, J = 6.7 Hz), 7.03−7.16 (m, 3H). FAB-MS (*m/z*): 203 $[M + H]^+$, 185 $[M + H - H_2O]^+$.

3-Adamantan-1-yl-but-2-en-1-ol (8g). To a magnetically stirred, ice-cooled mixture of $LiAlH_4$ (670 mg, 17.7 mmol) in dry ether (50 mL) was added a solution of 3-adamantan-1-yl-but-2-enoic acid ethyl ester **12g** (4.0 g, 16.1 mmol) in dry ether (50 mL) over 15 min. The resulting mixture was stirred for an additional 1 h at 0 °C. The mixture was quenched with water (10 mL) and 5% aqueous NaOH (3 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated, and the crude product was purified by column chromatography over silica gel to furnish **8g** (oil, 3 g, 91% yield). FT-IR (neat, cm^{-1}) 3436; ^1H NMR (200 MHz, $CDCl_3$) δ 1.49−2.01 (m, 18H), 4.20 (d, 2H, J = 6.3 Hz), 5.38 (t, 1H, J = 6.3 Hz). FAB-MS (*m/z*): 207 $[M + H]^+$, 189 $[M + H - H_2O]^+$.

Trioxane 13a: To a solution of 2-hydroperoxy-3-naphthalen-1-yl-but-3-en-1-ol **9a** (270 mg, 1.2 mmol) and 2-adamantanone (250

Table 2. *In Vivo* Antimalarial Activity of Trioxanes **13a**−**g** and **14a,b** against *Plasmodium yoelii* in Swiss Mice by the Oral and Intramuscular Routes[a,12]

general structure	comp.	substituent	Log *P*	route	dose (mg/kg/day)	% supp. on day 4[b]	mice alive on day 28
	**13a**	R = 1-naphthyl	5.65	Oral	96	100	6/6
				Oral	48	100	3/6
				im	96	87	0/5
	13b	R = 2-naphthyl	5.65	Oral	96	100	9/11
				Oral	48	100	3/6
				im	96	71	0/5
	13c	R = 2-tetrahydronaphthyl	5.96	Oral	96	100	5/5
				Oral	48	100	1/5
				im	96	100	1/5
	13d	R = 2-phenanthrenyl	6.65	Oral	96	100	10/11
				Oral	48	100	5/11
				im	96	100	1/5
	13e	R = 3-phenanthrenyl	6.65	Oral	96	100	6/6
				Oral	48	100	4/6
				im	96	69	0/6
	13f	R = 2-fluorenyl	6.39	Oral	96	100	5/5
				Oral	48	100	10/10
				Oral	24	100	8/10
				im	96	100	9/11
	13g	1-adamantyl	5.43	Oral	96	70	0/5
				im	96	14	0/5
	**14a**	n = 1	4.38	Oral	96	57	0/5
				im	96	38	0/5
	14b	n = 2	4.79	Oral	96	52	0/5
				im	96	Nil	0/5
	**5a**	-	4.65	Oral	96	99	0/5
				im	96	97	0/5
Arteether	-	-	3.84	Oral	48	100	5/5
				Oral	24	100	1/5
Artesunic acid	-	-	3.04	Oral	48	100	5/5
				Oral	24	100	0/5

[a] The drug dilutions of compounds were prepared in ground oil and administered to a group of mice at each dose from days 0−3 in two divided doses daily. [b] Percent suppression = $[(C - T)/C] \times 100$; where C = parasitaemia in control group and T = parasitaemia in treated group.

mg, 1.6 mmol) in CH_2Cl_2 (10 mL) was added HCl (0.1 mL), and the reaction mixture was stirred at room temperature for 1 h. Usual workup followed by column chromatography over silica gel furnished trioxane **13a** (180 mg, 42% yield); mp 108−110 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.54−2.04 (m, 13H), 2.94 (bs, 1H), 3.65 (dd, 1H, J = 11.8 and 3.0 Hz), 3.92 (dd, 1H, J = 11.8 and 10.3 Hz), 5.11 (dd, 1H, J = 10.3 and 3.0 Hz), 5.37 and 5.67 (2 × s, 2H), 7.22−7.98 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.63 (CH × 2), 29.83 (CH), 33.46 (CH_2), 33.75 (CH_2), 33.95 (CH_2), 33.99 (CH_2), 36.61 (CH), 37.66 (CH_2), 62.61 (CH_2), 81.88 (CH), 104.98 (C), 119.85 (CH_2), 125.59 (CH), 125.83 (CH), 126.32 (CH), 126.43 (CH), 126.84 (CH), 128.75 (CH), 128.82 (CH), 131.77 (C), 134.12 (C), 137.84 (C), 144.04 (C). FAB-MS (*m/z*): 363 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{26}O_3$: C, 79.52%; H, 7.23%. Found: C, 79.56%; H, 7.62%.

Compound **13b** was prepared by the above procedure.

Table 3. Antimalarial Activity of **13f** against *Plasmodium cynomolgi* in Rhesus Monkeys by the Oral and im Routes[a]

dose	route	involve parasitaemia	parasite clearance	day of recurrence
10 mg/kg × 4	im	14 490	no clearance	
		18 228	no clearance	
10 mg/kg × 4	oral	12 978	120 h	R−9
		13 392	120 h	R−9
20 mg/kg × 5	oral	8624	96 h	R−10
		15 456	72 h	R−19

[a] Trioxane **13f** was dissolved in ground oil and administered 10 mg/kg × 4 days and 20 mg/kg × 4 days by oral and intramuscular route.

Trioxane 13b: Yield 45%; mp 117−119 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.54−2.04 (m, 13H), 2.94 (bs, 1H), 3.81 (dd, 1H, J = 11.8 and 2.8 Hz), 3.99 (dd, 1H, J = 11.8 and 10.5 Hz), 5.40 (dd, 1H, J = 10.5 and 2.8 Hz), 5.41 and 5.64 (2 × s, 2H), 7.44−7.84 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.61 (CH × 2), 29.81 (CH), 33.45 (CH_2), 33.73 (CH_2), 33.93 (CH_2), 33.97 (CH_2), 36.59 (CH), 37.65 (CH_2), 62.59 (CH_2), 81.87 (CH), 104.98 (C), 119.85 (CH_2), 125.58 (CH), 125.82 (CH), 126.31 (CH), 126.41 (CH), 126.82 (CH), 128.73 (CH), 128.79 (CH), 131.75 (C), 134.10 (C), 137.82 (C), 144.01 (C). FAB-MS (*m/z*): 363 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{26}O_3$: C, 79.52%; H, 7.23%. Found: C, 79.42%; H, 7.47%.

Trioxane 13c: A solution of 3-(5,6,7,8-tetrahydro-naphthalen-2-yl)-but-2-en-1-ol (500 mg, 2.5 mmol) and methylene blue (20 mg) in CH_3CN (75 mL) was irradiated with 500 W tungsten-halogen lamp at −10 to 0 °C, while oxygen gas was bubbled slowly into the reaction mixture for 5 h. 2-Adamantanone (600 mg, 4.0 mmol) and HCl (0.2 mL) were added, and the reaction mixture was stirred at room temperature for 2.5 h. The usual workup followed by column chromatography over silica gel furnished trioxanes **13c** (420 mg, yield 46%, based on allylic alcohol **8c**); mp 117−120 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.56−2.09 (m, 17H), 2.75 (bs, 4H), 2.96 (bs, 1H), 3.76 (dd, 1H, J = 11.3 and 2.1 Hz), 3.94 (dd, 1H, J = 11.3 and 11.0 Hz), 5.24 (s, 1H), 5.25 (dd, 1H, J = 11.0 and 2.1 Hz), 5.46 (s, 1H), 7.09−7.14 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.59 (CH_2 × 2), 27.62 (CH × 2), 29.58 (CH), 29.78 (CH_2), 29.91 (CH_2), 33.43 (CH_2), 33.68 (CH_2), 33.92 (CH_2), 34.01 (CH_2), 36.72 (CH), 37.66 (CH_2), 62.85 (CH_2), 80.53 (CH), 104.99 (C), 115.55 (CH_2), 123.87 (CH), 127.30 (CH), 129.76 (CH), 136.31 (C), 137.68 (C), 137.75 (C), 143.96 (C). FAB-MS (*m/z*): 367 $[M + H]^+$. Anal. Calcd. for $C_{24}H_{30}O_3$: C, 78.65%; H, 8.25%. Found: C, 78.62%; H, 8.21%.

Compounds **13d**−**f** were prepared by the above procedure.

Trioxane 13d: Yield 50% (based on allylic alcohol **8d**); mp 85−88 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.56−2.10 (m, 13H), 3.0 (bs, 1H), 3.82 (dd, 1H, J = 11.9 and 3.1 Hz), 4.02 (dd, 1H, J = 11.9 and 10.4 Hz), 5.43 (dd, 1H, J = 10.4 and 3.1 Hz), 5.49 and 5.69 (2 × s, 2H), 7.57−8.72 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.65 (CH × 2), 29.93 (CH), 33.48 (CH_2), 33.74 (CH_2), 33.98 (CH_2), 34.05 (CH_2), 36.75 (CH), 37.67 (CH_2), 62.77 (CH_2), 80.58 (CH), 105.19 (C), 117.19 (CH_2), 123.16 (CH), 123.52 (CH), 125.26 (CH), 126.43 (CH), 127.21 (CH × 2), 127.39 (CH), 127.94 (CH), 129.06 (CH), 130.45 (C), 132.47 (C), 132.58 (C), 137.09 (C × 2), 143.66 (C). FAB-MS (*m/z*): 413 $[M + H]^+$. Anal. Calcd. for $C_{28}H_{28}O_3$: C, 81.52%; H, 6.84%. Found: C, 81.80%; H, 7.06%.

Trioxane 13e: Yield 57% (based on allylic alcohol **8e**), mp 130−135 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42−2.11 (m, 13H), 2.99 (bs, 1H), 3.84 (dd, 1H, J = 11.8 and 2.9 Hz), 4.02 (dd, 1H, J = 11.8 and 10.6 Hz), 5.42 (dd, 1H, J = 10.6 and 2.9 Hz), 5.45 and 5.69 (2 × s, 2H), 7.57−8.75 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.61 (CH × 2), 29.88 (CH), 33.44 (CH_2), 33.70 (CH_2), 33.95 (CH_2), 34.02 (CH_2), 36.71 (CH), 37.64 (CH_2), 62.75 (CH_2), 80.58 (CH), 105.17 (C), 117.21 (CH_2), 123.13 (CH), 123.49 (CH), 125.63 (CH), 126.43 (CH), 127.19 (CH × 2), 127.38 (CH), 127.92 (CH), 129.04 (CH), 130.43 (C), 132.45 (C), 132.56 (C), 137.09 (C × 2), 143.65 (C). FAB-MS (*m/z*): 413 $[M + H]^+$. Anal. Calcd. for $C_{28}H_{28}O_3$: C, 81.52%; H, 6.84%. Found: C, 81.12%; H, 6.86%.

Trioxane 13f: Yield 59% (based on allylic alcohol **8f**); mp 98−100 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.58−2.21 (m, 13H), 2.98 (bs, 1H), 3.80 (dd, 1H, J = 11.8 and 3.0 Hz), 3.89 (s, 2H), 3.98 (dd, 1H, J = 11.8 and 10.5 Hz), 5.32 (dd, 1H, J = 10.5 and 3.0 Hz), 5.36 and 5.56 (2 × s, 2H), 7.23−8.16 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.60 (CH × 2), 29.85 (CH), 33.43 (CH_2), 33.68 (CH_2), 33.92 (CH_2), 34.00 (CH_2), 36.70 (CH), 37.31 (CH_2), 37.64 (CH_2), 62.70 (CH_2), 80.69 (CH), 105.08 (C), 116.22 (CH_2), 120.26 (CH), 120.42 (CH), 123.38 (CH), 125.46 (CH), 125.60 (CH), 127.25 (CH), 127.33 (CH), 137.30 (C), 141.58 (C), 142.18 (C), 143.88 (C), 143.98 (C), 144.19 (C). FAB-MS (*m/z*): 401 $[M + H]^+$. Anal. Calcd. for $C_{27}H_{28}O_3 \cdot 0.1H_2O$: C, 80.61%; H, 7.46%. Found: C, 80.37%; H, 7.82%.

Trioxane 13g: A solution of allylic alcohol **8g** (300 mg, 1.5 mmol) and methylene blue (10 mg) in CH_3CN (50 mL) was irradiated with a 500 W tungsten-halogen lamp at −10 to 0 °C, while oxygen gas was bubbled slowly into the reaction mixture for 4 h. 2-Adamantanone (330 mg, 2.2 mmol) and HCl (0.2 mL) were added, and the reaction mixture was stirred at room temperature for 1.5 h. Usual workup followed by chromatography over silica gel furnished trioxanes **13g** (270 mg, yield 50%, based on allylic alcohol **8g**); mp 166−168 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.60−2.10 (m, 28H), 2.99 (bs, 1H), 3.57 (dd, 1H, J = 11.9 and 2.9 Hz), 3.92 (dd, 1H, J = 11.9 and 10.6 Hz), 4.90 (dd, 1H, J = 10.6 and 2.9 Hz), 5.12 (bs, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.60 (CH × 2), 28.73 (CH × 3), 29.85 (CH), 33.39 (CH_2), 33.65 (CH_2), 33.87 (CH_2), 33.99 (CH_2), 36.89 (CH), 37.05 (CH_2 × 3), 37.65 (C), 37.66 (CH_2), 40.70 (CH_2 × 3), 64.13 (CH_2), 77.72 (CH), 104.69 (C), 113.48 (CH_2), 153.61(C). FAB-MS (*m/z*): 371 $[M + H]^+$. Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80%; H, 9.25%. Found: C, 77.65%; H, 9.20%.

Compounds **14a** and **14b** were prepared by the above procedure.

8-(1-Adamantan-1-yl-vinyl)-6,7,10-trioxaspiro[4.5]decane (14a). Yield 38% (viscous oil, based on allylic alcohol **8g**); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.59−2.56 (m, 23H), 3.66 (dd, 1H, J = 11.9 and 3.0 Hz), 3.80 (dd, 1H, J = 11.9 and 10.2 Hz), 4.94 (dd, 1H, J = 10.2 and 3.0 Hz), 5.09 (bs, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.74 (CH_2), 25.98 (CH_2), 28.71 (CH × 3), 29.44 (CH_2), 35.32 (CH_2), 37.03 (CH_2 × 3), 37.65 (C), 40.67 (CH_2 × 3), 64.59 (CH_2), 77.79 (CH), 102.60 (C), 113.52 (CH_2), 153.49 (C). FAB-MS (*m/z*): 305 $[M + H]^+$. Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96%; H, 9.27%. Found: C, 74.37%; H, 9.74%.

3-(1-Adamantan-1-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undecane (14b). Yield 54% (based on allylic alcohol **8g**); mp 130−132 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43−2.26 (m, 25H), 3.57 (dd, 1H, J = 12.0 and 2.9 Hz), 3.95 (dd, 1H, J = 12.0 and 10.7 Hz), 4.88 (dd, 1H, J = 10.7 and 2.9 Hz), 5.11 and 5.12 (2 × s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.70 (CH_2), 22.73 (CH_2), 25.97 (CH_2), 28.70 (CH × 3), 29.45 (CH_2), 35.31 (CH_2), 37.03 (CH_2 × 3), 37.65 (C), 40.69 (CH_2 × 3), 64.59 (CH_2), 77.79 (CH), 102.61 (C), 113.49 (CH_2), 153.51(C). FAB-MS (*m/z*): 319 $[M + H]^+$. Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43%; H, 9.49%. Found: C, 75.39%; H, 9.12%.

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Supporting Information Available: Purity table showing degree of purity (elemental analyses) of compounds **13a**−**g** and **14a**,**b**. ^{1}H NMR spectra of compounds **12c**, **12g**, **8c**, **8g**, **13a**−**g**, and **14a**,**b** and ^{13}C NMR of compounds **13a**−**g** and **14a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Peters, W. Techniques for the study of drug response in experimental malaria. In *Chemotherapy and drug resistance in malaria*; Academic Press: London, 1970; pp 64−136. (b) In vivo test procedure: The colony bred Swiss mice (25 ± 1 g) were inoculated with 1×10^6 parasitized RBC on day zero and treatment was administered to a group of five mice at each dose, from day 0 to 3, in two divided doses daily. The drug dilutions of compounds **13a**−**g** and **14a**,**b** were prepared in groundnut oil so as to contain the required amount of the drug (1.2 mg for a dose of 96 mg/kg, 0.6 mg for a dose of 48 mg/kg and 0.3 mg for a dose of 24 mg/kg) in 0.1 ml and administered orally/intramuscularly for each dose. Parasitaemia level were recorded from thin blood smears between days 4−28.[14] The treated mice surviving beyond day 28 were recorded as the mice protected by the drug. Mice treated with β-Arteether served as positive controls.

(12) (a) 100% suppression of parasiteamia means that the number of parasites, if at all present, are below the detection limit. The parasites present below the detection limit can multiply and eventually can be detected. In such cases though the drug is providing near 100% suppression of the parasiteamia but will not provide full protection to the treated mice. Multidrug resistant *Plasmodium yoelii nigeriensis* used in this study is resistant to chloroquine, mefloquine and halofantrine. (b) 100% protection means all the treated mice survive till day 28. Similarly, 50% and 20% protection means only 50% and 20% of the treated mice survive to day 28.

(13) For activity against *P. cynomolgi*, rhesus monkeys were inoculated intravenously with 1×10^5 parasitized RBC, and treatment was initiated when the parasiteamia level reached above 0.5%. Trioxane **13f** was dissolved in groundnut oil and administered 10 mg/kg × 4 days by oral/intramuscular routes and 20 mg/kg × 4 days by oral route. The blood smears from the treated monkeys were examined once daily to record parasiteamia clearance time and subsequent recurrence of parasiteamia.

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