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Synthesis and antimalarial activity of 6-cycloalkylvinyl substituted 1,2,4-trioxanes☆

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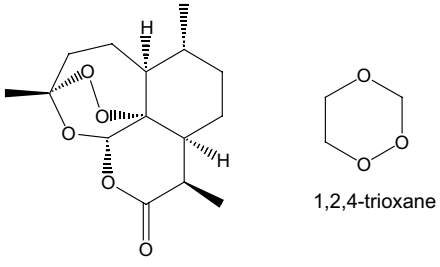
Abstract—6-Cycloalkylvinyl substituted 1,2,4-trioxanes **6**–**15** have been prepared and tested against multi-drug resistant *Plasmodium yoelii* in mice. The most active trioxane **11** provides 80% protection to the treated mice. Further derivatization of **11** leads to decrease in antimalarial activity.

1. Introduction

Malaria is a major parasitic disease of the tropics, affecting around 300–500 million people of which more than one million die each year.[1] The emergence of malarial parasites resistant to contemporary drugs has added a new dimension to malaria problem. Currently, artemisinin **1** and its derivatives are the drugs of choice to treat multi-drug resistant malaria.[2] Peroxide group, present in the form of 1,2,4-trioxane, is essential for the antimalarial activity of artemisinin-based compounds. In recent years synthesis of a large number of structurally simple trioxanes have been reported.[3] Earlier we have reported a new photooxygenation route for the synthesis of 1,2,4-trioxanes. Preparation of β-hydroxyhydroperoxide by photooxygenation of allylic alcohols is the key step of this method. Several 6-arylvinyl substituted trioxanes prepared by this method have shown significant in vivo activity against chloroquine-sensitive *P. berghei* in mice[4] by i.p. route but are weakly active against multi-drug resistant *Plasmodium yoelii* by i.m. route. Replacement of aryl group by alkyl and arylalkyl groups leads to improvement in activity.[5,6] In the present study we have prepared cyclopropyl and cyclohexyl substituted allylic alcohols **4a**–**c** and investigated their potential for the synthesis of a new series of 1,2,4-trioxanes by photooxygenation route. The twin objective of this study is to study the behavior of these alcohols, particularly the cyclopropyl substituted alcohols **4a** and **4c**, under photooxygenation condition and the effect of cycloalkyl groups on antimalarial activity. We have also prepared several derivatives of the most active trioxane (**11**) of the series.



2. Chemistry

3-Cyclopropyl and 3-cyclohexyl substituted butenoates **3a** and **3b** were prepared as inseparable mixtures of *cis* and *trans* isomers. Reduction of **3a** and **3b** with $LiAlH_4$ furnished allylic alcohols **4a** and **4b** in 89% and 85% yields, respectively. Compounds **4a** and **4b** are mixture of *cis* and *trans* isomers in the ratio of 1:3. Photooxygenation of **4a** furnished β-hydroxyhydroperoxide **5a** in 50% yield. A similar photooxygenation of **4b** furnished

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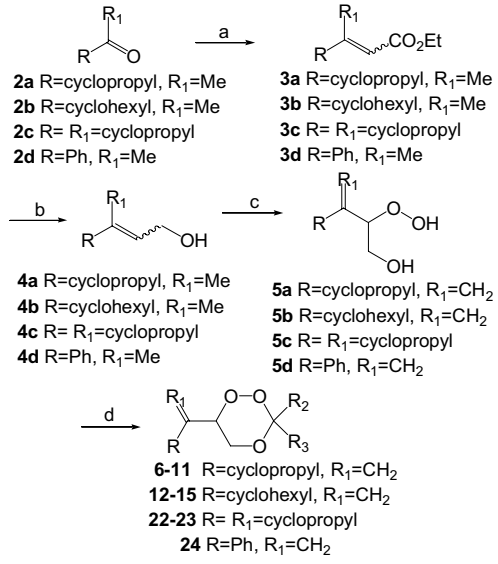
β-hydroxyhydroperoxide **5b** in 35% yield. Interestingly both these reactions were highly regiospecific. Acid catalyzed condensation of **5a** with benzaldehyde, acetone, cyclopentanone, cyclohexanone, cycloheptanone, and 2-adamantanone furnished trioxanes **6**, **7**, **8**, **9**, **10**, and **11** in 31%, 67%, 61%, 75%, 37%, and 75% yields, respectively. β-Hydroxyhydroperoxide **5b** on condensation with acetone, cyclopentanone, cyclohexanone, and 2-adamantanone gave trioxanes **12**, **13**, **14**, and **15** in 57%, 78%, 80%, and 83% yields, respectively (Scheme 1). Trioxanes **6**–**15** gave satisfactory ^{1}H NMR, ^{13}C NMR, and MS data and all these compounds except trioxanes **7**, **8**, **9**, **12**, and **13**, which are volatile oils, gave satisfactory elemental analysis.

Trioxane **11** the most active trioxane of the series (see activity section) on reaction with 3-chloroperbenzoic acid (*m*CPBA) furnished epoxide **16** as mixture of diastereomers, which on hydrolysis furnished diol **17** also as a mixture of diastereomers. Reaction of diol **17** with succinic anhydride in the presence of Et_3N furnished hemisuccinate **18** as mixture of diastereomers. The diols **17** were also separated by column chromatography to pure diastereomers **17a** and **17b** (stereochemistry not assigned). Reaction of diol **17a** with succinic anhydride in the presence of Et_3N furnished hemisuccinate derivative **18a.** Similar treatment of diol **17b** gave hemisuccinate derivative **18b**. Acid catalyzed condensation of **17** with cyclopentanone furnished spiro derivative **19**, which was separated into diastereomers **19a** (higher R_f) and **19b** (lower R_f) by column chromatography. Spiro derivatives **20** and **21** were prepared similarly and separated into diastereomers **20a**,**b** and **21a**,**b**. All these trioxanes **16**–**21** were fully characterized by ^{1}H NMR and MS spectra. These compounds also gave correct elemental analysis. Compounds **18a** and **18b** on treatment with diazomethane furnished methyl ester derivatives **25a** and **25b**, respectively, which were characterized by ^{1}H NMR, ^{13}C NMR, and MS spectra.



Scheme 1. Reagents and conditions: (a) triethylphosphonoacetate, NaH, DME, reflux, 4–30 h; (b) $LiAlH_4$, Et_2O, 0 °C, 2 h; (c) hν, O_2, methylene blue, MeCN, 0 °C, 6 h; (d) aldehyde/ketone, PTSA, CH_2Cl_2, rt, 2 h.

Table 1. In vivo antimalarial activity of trioxanes **6**–**15**, **17**–**21** and **24** against *P. yoelii* in Swiss mice by intramuscular route

Compound	Dose (mg/kg/day)	%Suppression on day 4[a]	No of mice survived on day 28
6	96	70.0	0/5
	48	57.0	0/5
7	96	89.0	0/5
	48	83.0	0/5
8	96	82.0	0/5
	48	68.0	0/5
9	96	90.0	0/5
	48	79.0	0/5
10	96	84.0	0/5
	48	61.0	0/5
11	96	91.0	4/5
	48	65.0	0/5
12	96	23.0	0/5
13	96	96.0	0/5
14	96	28.0	0/5
15	96	36.0	0/5
17	96	72.0	0/5
	48	53.0	0/5
18	96	56.0	0/5
	48	22.0	0/5
19a	96	18.0	0/5
19b	96	53.0	0/5
20a	96	16.0	0/5
20b	96	19.0	0/5
21a	96	Nil	0/5
21b	96	53.0	0/5
24	96	97.0	0/5
Artemisinin	48	100.0	5/5
	24	100.0	4/5
Vehicle control	—	—	0/15

[a] Percent suppression = $[(C-T)/C] \times 100$; where C = parasitemia in control group, and T = parasitemia in treated group.

Dicyclopropyl substituted allylic alcohol **4c** prepared from dicyclopropyl ketone in two steps on photooxygenation furnished β-hydroxyhydroperoxide **5c** in 28% yield. Condensation of **5c** with acetone and cyclohexanone furnished trioxanes **22** and **23** in very poor yields and therefore were not tested for antimalarial activity. 6-Phenylvinyl substituted trioxane **24** was prepared according to the published procedure.[4]

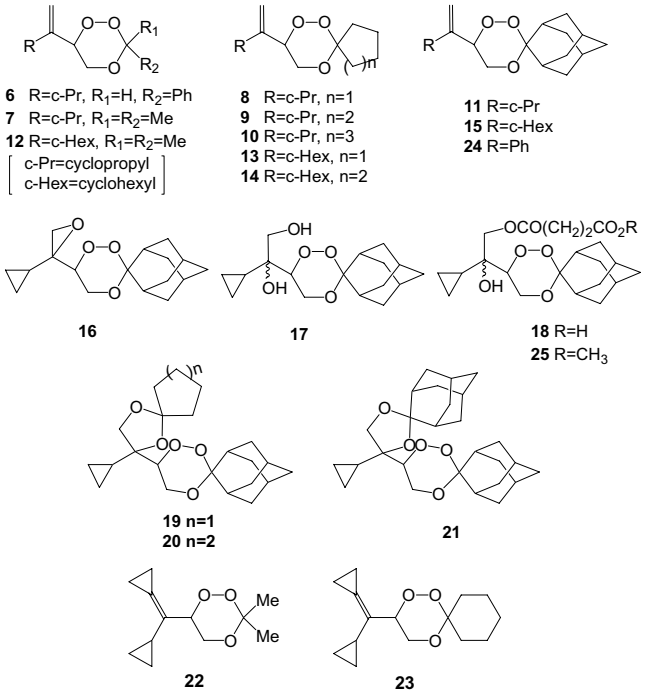
3. Antimalarial activity

Trioxanes **6**–**15**, **17**–**21**, and **24** were tested against multidrug resistant *P. yoelii* in swiss mice at 96 and 48 mg/kg by intramuscular route.[7] The results are summarized in Table 1.

4. Results and discussion

As can be seen from Table 1, trioxane **11** is the most active compound of the series. It shows more than 90%

clearance of parasitemia on day 4 at 96 mg/kg and 80% of treated mice survive beyond day 28. It is more active than the corresponding phenyl vinyl substituted trioxane **24**. All other cyclopropylvinyl substituted trioxanes (**7**–**10**) except trioxane **6** show more than 80% suppression of parasitemia on day 4 but none of the treated mice survive up to day 28. Cyclohexylvinyl substituted trioxanes **12**–**15**, on the other hand, are poorly active at 96 mg/kg. Trioxane **13** though shows 96% suppression on day 4 at 96 mg/kg but none of the treated mice survive up to day 28. Derivatization of the most active trioxane **11** leads to decrease in activity as all the derivatives (**17**–**21**) show less than 80% suppression of parasitemia on day 4 and none of the treated mice survive up to day 28.



5. Conclusion

We have investigated the potential of cyclopropyl, cyclohexyl, and dicyclopropyl substituted allylic alcohols **4a**–**c** for the preparation of 1,2,4-trioxanes by photooxygenation route. Both **4a** and **4b** undergo regiospecific photooxygenation to furnish β-hydroxyhydroperoxides in reasonable yields and both these hydroxyhydroperoxides undergo facile acid catalyzed condensation with various ketones to provide 1,2,4-trioxanes. On the other hand while photooxygenation of dicyclopropyl substituted allylic alcohol **4c** provides β-hydroxyhydroperoxide **5c** in acceptable yield, the subsequent condensation of this hydroperoxide furnished trioxanes in extremely poor yields. Trioxane **11**, the best compound of the series has shown 80% protection against multi-drug resistant *P. yoelii* in mice and is more active than the corresponding cyclohexylvinyl and phenylvinyl substituted trioxanes **15** and **24** and its own derivatives **16**–**21**.

6. Experimental

Melting points were taken in open capillaries on COMPLAB melting point apparatus and are uncorrected. Infrared spectra (cm^{-1}) were recorded on Perkin–Elmer RXI FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR were recorded on Bruker Supercon Magnet DPX-200/DRX-300 MHz using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) was used as an internal standard in ^1H NMR and $CDCl_3$ (δ 77.0 ppm) was used in ^{13}C NMR. Fast atom bombardment mass spectra (FABMS) were obtained on JEOL SX-102 spectrometer using glycerol or *m*-nitro benzyl alcohol as matrix. Electron ionization mass spectra (EIMS) were obtained on JEOL-JMS-600H spectrometer. Elemental analysis was performed on Elementar Vario EL III analyzer. The progress of the reaction was monitored by silica gel thin layer chromatography with detecting agents: iodine vapors and/or spraying with an aq solution of vanillin in 10% sulfuric acid followed by heating at 150 °C. Chromatographic purification was performed over silica gel (60–120 mesh) obtained from Qualigens (India). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (UK) or Spectrochem Pvt. Ltd (India) and were used without further purification. Esters **3a**,**b**, and **3c** were prepared by known procedures.[8,9]

6.1. 3-Cyclopropyl-but-2-en-1-ol (4a)

To an ice cooled slurry of lithium aluminum hydride (4.92 g, 129.47 mmol) in dry ether (100 mL), in a three-necked round bottomed flask, was added ethyl 3-cyclopropyl-2-butenoate **3a** (10.00 g, 64.94 mmol) in dry ether (50 mL) under nitrogen atmosphere and stirred for 2 h. Excess lithium aluminum hydride was quenched first by adding ordinary ether (25 mL) followed by water (10 mL) and then 10% aq NaOH (5 mL). Ether layer was decanted, dried over anhyd Na_2SO_4, and concentrated to give the crude product, which on column chromatography over silica gel using EtOAc–hexane (1:9) as eluant furnished **4a** (6.50 g, 89% yield) as oil: FT-IR (neat, cm^{-1}) 1658.9, 3349.3; ^1H NMR (200 MHz, $CDCl_3$): δ 0.47–0.65 (m, 4H), 1.20 (br s, 1H, OH), 1.33–1.43 (m, 1H), 1.46 and 1.56 (2 × s, 3H), 4.15 and 4.28 (2 × d, 2H, J = 7.0 Hz each), 5.46 (t, 1H, J = 7.0 Hz); FABMS (*m*/*z*) 113 $(M+H)^+$.

Compounds **4b** and **4c** were also prepared by the procedure described for **4a**.

6.2. 3-Cyclohexyl-but-2-en-1-ol (4b)

Yield 85%, oil: FT-IR (neat, cm^{-1}) 1610.5, 3390.6; ^1H NMR (200 MHz, $CDCl_3$): δ 1.06–1.37 (m, 5H), 1.64 and 1.65 (2 × s, 3H), 1.66–1.85 (m, 6H), 4.16 (d, 2H, J = 6.8 Hz), 5.39 (2 × t, 1H, J = 6.8 Hz each); FABMS (*m*/*z*) 155 $(M+H)^+$.

6.3. 3,3-Dicyclopropyl-prop-2-en-1-ol (4c)

Yield 84%, oil: FT-IR (neat, cm^{-1}) 1649.0, 3344.7; ^1H NMR (200 MHz, $CDCl_3$): δ 0.36–0.39 (m, 2H), 0.54–0.57 (m, 2H), 0.65–0.76 (m, 4H), 0.92–0.96 (m, 1H),

1.62–1.69 (m, 2H), 4.30 (d, 2H, $J = 6.8$ Hz), 5.32 (t, 1H, $J = 6.8$ Hz); FABMS (*m*/*z*) 139 $(M+H)^+$.

6.4. 3-Cyclopropyl-2-hydroperoxy-but-3-en-1-ol (5a)

A solution of allylic alcohol **4a** (1.00 g, 8.92 mmol) and methylene blue (5 mg) in acetonitrile (75 mL) was irradiated with a 500 W tungsten–halogen lamp maintained at 0 °C, while oxygen was bubbled slowly into the reaction mixture for 6 h. Solvent was evaporated under vacuum at rt to furnish crude product, which on column chromatography over deactivated silica gel (12% v/w of water) using EtOAc–hexane (2:8) as eluant furnished **5a** (0.64 g, 50% yield) as oil: FT-IR (neat, cm^{-1}) 1644.5, 3350.0; ^1H NMR (200 MHz, $CDCl_3$) 0.45–0.54 (m, 2H), 0.68–0.75 (m, 2H), 1.18–1.41 (m, 1H), 2.31 (br s, 1H, OH), 3.81 (d, 2H, $J = 5.6$ Hz), 4.61 (t, 1H, $J = 5.6$ Hz), 4.87 and 5.00 (2 × s, 2H), 9.02 (br s, 1H, OOH); FABMS (*m*/*z*) 145 $(M+H)^+$.

6.5. 3-Cyclohexyl 2-hydroperoxy-but-3-en-1-ol (5b)

A solution of allylic alcohol **4b** (1.00 g, 6.49 mmol) and methylene blue (5 mg) in acetonitrile (75 mL) was irradiated with a 500 W tungsten–halogen lamp maintained at 0 °C, while oxygen was bubbled slowly into the reaction mixture for 6 h. Solvent was evaporated under vacuum at rt to furnish crude product, which on column chromatography over deactivated silica gel (12% v/w of water) using EtOAc–hexane (2:8) as eluant furnished pure **5b** (0.42 g, 35% yield) as a white solid: mp 84–86 °C; FT-IR (KBr, cm^{-1}) 1645.0, 3394.3; ^1H NMR (200 MHz, $CDCl_3$): δ 1.01–1.23 (m, 5H), 1.60–1.84 (m, 6H), 2.20 (br s, 1H, OH), 3.60–3.66 (m, 2H), 4.48 (dd, 1H, $J = 6.6$, 4.2 Hz), 4.99 and 5.03 (2 × s, 2H), 8.43 (br s, 1H, OOH); FABMS (*m*/*z*) 187 $(M+H)^+$.

6.6. 3-Cyclopropyl-3-cyclopropylidene-2-hydroperoxy-propan-1-ol (5c)

A solution of allylic alcohol **4c** (1.00 g, 7.24 mmol) and methylene blue (5 mg) in acetonitrile (75 mL) was irradiated with a 500 W tungsten–halogen lamp maintained at 0 °C, while oxygen was bubbled slowly into the reaction mixture for 6 h. Solvent was evaporated under vacuum at rt to furnish crude product, which on column chromatography over deactivated silica gel (12% v/w of water) using EtOAc–hexane (2:8) as eluant furnished **5c** (0.35 g, 28% yield) as oil: FT-IR (neat, cm^{-1}) 1407.5, 3381.1; ^1H NMR (300 MHz, $CDCl_3$): δ 0.40–0.74 (m, 4H), 0.99–1.15 (m, 4H), 1.47–1.52 (m, 1H), 2.88 (br s, 1H, OH), 3.81 (dd, 1H, $J = 12.0$, 3.3 Hz), 4.04 (dd, 1H, $J = 12.0$, 8.4 Hz), 4.74 (dd, 1H, $J = 8.4$, 3.3 Hz), 9.02 (br s, 1H, OOH); FABMS (*m*/*z*) 171 $(M+H)^+$.

6.7. 6-(1-Cyclopropyl-vinyl)-3-phenyl-[1,2,4]trioxane (6)

To a solution of hydroperoxide **5a** (0.64 g, 4.44 mmol) in dichloromethane (15 mL) was added benzaldehyde (1.20 g, 11.3 mmol) and *p*-toluenesulfonic acid monohydrate (0.05 g, 0.26 mmol). Reaction mixture was stirred at rt for 2h and poured into saturated aq. $NaHCO_3$ solution (50 mL). Organic layer was separated, aqueous layer was extracted with dichloromethane (3 × 25 mL), dried over anhyd Na_2SO_4 and evaporated under vacuum at rt to furnish the crude trioxane, which on column chromatography over silica gel using EtOAc–hexane (0.5:99.5) as eluant furnished **6** (0.32 g, 31% yield) as oil: FT-IR (neat, cm^{-1}) 1451.7, 1641.8; ^1H NMR (200 MHz, $CDCl_3$): δ 0.45–0.53 (m, 2H), 0.68–0.77 (m, 2H), 1.29–1.41 (m, 1H), 3.99 (dd, 1H, $J = 11.5$, 10.5 Hz), 4.25 (dd, 1H, $J = 11.5$, 2.5 Hz), 4.92 and 4.99 (2 × s, 2H), 4.98 (dd, 1H, $J = 10.5$, 2.5 Hz), 6.16 (s, 1H), 7.45 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 6.50, 6.86, 14.28, 70.04, 82.25, 104.42, 111.99, 127.40, 128.82, 130.34, 134.65, 145.06; FABMS (*m*/*z*) 233 $(M+H)^+$. Anal. Calcd for $C_{14}H_{16}O_3$: C 72.38; H 6.94. Found: C 72.20; H 7.44.

Compounds **7**–**15** and **22**–**23** were also prepared by the procedure described for **6**.

6.8. 6-(1-Cyclopropyl-vinyl)-3,3-dimethyl-[1,2,4]trioxane (7)

Yield 67%, oil: FT-IR (neat, cm^{-1}) 1642.4; ^1H NMR (200 MHz, $CDCl_3$): δ 0.45–0.47 (m, 2H), 0.67–0.72 (m, 2H), 1.26–1.33 (m, 1H), 1.38 (s, 3H), 1.65 (s, 3H), 3.80 (dd, 1H, $J = 11.8$, 2.6 Hz), 4.00 (dd, 1H, $J = 11.8$, 10.1 Hz), 4.74 (dd, 1H, $J = 10.1$, 2.6 Hz), 4.87 and 4.94 (2 × s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 6.39, 6.75, 14.10, 20.43, 25.84, 63.67, 81.83, 102.66, 111.33, 145.66; FABMS (*m*/*z*) 185 $(M+H)^+$.

6.9. 8-(1-Cyclopropyl-vinyl)-6,7,10-trioxa-spiro[4,5]decane (8)

Yield 61%, oil: FT-IR (neat, cm^{-1}) 1642.4; ^1H NMR (200 MHz, $CDCl_3$): δ 0.42–0.47 (m, 2H), 0.65–0.74 (m, 2H), 1.28–1.39 (m, 1H), 1.68–1.96 (m, 7H), 2.43–2.55 (m, 1H), 3.83–3.90 (m, 2H), 4.80 (dd, 1H, $J = 7.8$, 5.3 Hz), 4.86 and 4.92 (2 × s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 6.41, 6.78, 14.13, 23.70, 25.10, 33.02, 37.44, 65.34, 81.89, 111.36, 114.81, 145.56; FABMS (*m*/*z*) 211 $(M+H)^+$.

6.10. 3-(1-Cyclopropyl-vinyl)-1,2,5-trioxa-spiro[5,5]undecane (9)

Yield 75%, oil: FT-IR (neat, cm^{-1}) 1640.6; ^1H NMR (200 MHz, $CDCl_3$): δ 0.42–0.49 (m, 2H), 0.65–0.74 (m, 2H), 1.26–1.37 (m, 1H), 1.43–1.61 (m, 8H), 1.92–2.05 (m, 1H), 2.14–2.24 (m, 1H), 3.77 (dd, 1H, $J = 11.7$, 3.1 Hz), 4.02 (dd, 1H, $J = 11.7$, 10.2 Hz), 4.74 (dd, 1H, $J = 10.2$, 3.1 Hz), 4.87 and 4.93 (2 × s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 6.40, 6.75, 14.15, 22.66, 22.71, 25.95, 29.32, 35.07, 62.92, 81.89, 102.78, 111.27, 145.78; FABMS (*m*/*z*) 225 $(M+H)^+$.

6.11. 3-(1-Cyclopropyl-vinyl)-1,2,5-trioxa-spiro[5,6]dodecane (10)

Yield 37%, oil: FT-IR (neat, cm^{-1}) 1642.5; ^1H NMR (200 MHz, $CDCl_3$): δ 0.42–0.49 (m, 2H), 0.64–0.73 (m, 2H), 1.28–1.39 (m, 1H), 1.47–1.77 (m, 10H), 2.14–2.27

(m, 2H), 3.76 (dd, 1H, $J = 11.8$, 3.2 Hz), 3.96 (dd, 1H, $J = 11.8$, 10.3 Hz), 4.73 (dd, 1H, $J = 10.3$, 3.2 Hz), 4.86 and 4.92 (2 × s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 6.35, 6.75, 14.07, 22.48, 22.61, 29.73, 30.16, 31.35, 38.67, 63.10, 81.71, 107.27, 111.06, 145.81; FABMS (*m*/*z*) 239 $(M+H)^+$. Anal. Calcd for $C_{14}H_{22}O_3 \cdot 0.3H_2O$: C 68.98; H 9.34. Found: C 68.63; H 9.36.

6.12. Trioxane 11

Yield 75%, white solid: mp 82–84 °C; FT-IR (KBr, cm^{-1}) 1641.9; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.42–0.49 (m, 2H), 0.67–0.74 (m, 2H), 1.26–1.40 (m, 1H), 1.61–2.09 (m, 13H), 2.93 (br s, 1H), 3.77 (dd, 1H, $J = 11.7$, 3.1 Hz), 3.99 (dd, 1H, $J = 11.7$, 10.4 Hz), 4.75 (dd, 1H, $J = 10.4$, 3.1 Hz), 4.87 and 4.93 (2 × s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 6.43, 6.79, 14.25, 27.58, 29.71, 33.39, 33.66, 33.86, 33.95, 36.65, 37.63, 62.45, 81.74, 104.87, 111.31, 145.86; FABMS (*m*/*z*) 277 $(M+H)^+$. Anal. Calcd for $C_{17}H_{24}O_3 \cdot 0.1H_2O$: C 73.39; H 8.77. Found: C 73.38; H 9.10.

6.13. 6-(1-Cyclohexyl-vinyl)-3,3-dimethyl-[1,2,4]trioxane (12)

Yield 57%, oil: FT-IR (neat, cm^{-1}) 1639.4; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10–1.31 (m, 5H), 1.37 (s, 3H), 1.45–1.93 (m, 6H), 1.65 (s, 3H), 3.70 (dd, 1H, $J = 11.9$, 2.9 Hz), 3.91 (dd, 1H, $J = 11.9$, 10.3 Hz), 4.69 (dd, 1H, $J = 10.3$, 2.9 Hz), 5.03 (s, 2H); FABMS (*m*/*z*) 227 $(M+H)^+$.

6.14. 8-(1-Cyclohexyl-vinyl)-6,7,10-trioxa-spiro[4,5]decane (13)

Yield 78%, oil: FT-IR (neat, cm^{-1}) 1641.6; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10–1.31 (m, 5H), 1.60–1.92 (m, 13H), 2.45–2.52 (m, 1H), 3.77–3.81 (m, 2H), 4.76 (dd, 1H, $J = 8.5$, 4.5 Hz), 5.00 and 5.03 (2 × s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.65, 25.10, 26.47, 26.90, 32.65, 33.01, 37.44, 43.28, 65.72, 80.79, 112.89, 114.64, 149.75; FABMS (*m*/*z*) 253 $(M+H)^+$.

6.15. 3-(1-Cyclohexyl-vinyl)-1,2,5-trioxa-spiro[5,5]undecane (14)

Yield 80%, oil: FT-IR (neat, cm^{-1}) 1640.6; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10–1.31 (m, 5H), 1.46–2.01 (m, 15H), 2.15–2.29 (m, 1H), 3.67 (dd, 1H, $J = 11.8$, 2.96 Hz), 3.94 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.70 (dd, 1H, $J = 10.4$, 2.96 Hz), 5.02 and 5.04 (2 × s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.67, 22.71, 25.95, 26.47, 26.89, 29.34, 32.61, 35.17, 43.39, 63.36, 80.76, 102.65, 112.87, 149.98; FABMS (*m*/*z*) 267 $(M+H)^+$. Anal. Calcd for $C_{16}H_{26}O_3 \cdot 0.8H_2O$: C 68.43; H 9.90. Found: C 68.77; H 10.20.

6.16. Trioxane 15

Yield 83%, oil: FT-IR (neat, cm^{-1}) 1640.0; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11–1.32 (m, 5H), 1.55–2.09 (m, 19H), 2.94 (br s, 1H), 3.67 (dd, 1H, $J = 11.8$, 2.92 Hz), 3.91 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.72 (dd, 1H, $J = 10.4$, 2.92 Hz), 5.01 and 5.04 (2 × s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.49, 26.89, 27.59, 29.72, 32.59, 33.39, 33.65, 33.86, 33.97, 36.76, 37.63, 43.54, 62.92, 80.59, 104.74, 112.90, 150.05; FABMS (*m*/*z*) 319 $(M+H)^+$. Anal. Calcd for $C_{20}H_{30}O_3 \cdot H_2O$: C 71.39; H 9.58. Found: C 71.70; H 9.29.

6.17. 6-(Cyclopropyl-cyclopropylidene-methyl)-3,3-dimethyl-[1,2,4]trioxane (22)

Yield 8%, oil: FT-IR (neat, cm^{-1}) 1452.0; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.52–0.70 (m, 5H), 1.09 (s, 4H), 1.38 (s, 3H), 1.67 (s, 3H), 3.70 (dd, 1H, $J = 11.8$, 2.8 Hz), 4.30 (dd, 1H, $J = 11.8$, 10.9 Hz), 4.84 (dd, 1H, $J = 10.9$, 2.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 1.67, 2.1, 5.7, 6.1, 13.7, 20.4, 25.9, 62.4, 82.0, 102.4, 122.2, 124.5; FABMS (*m*/*z*) 211 $(M+H)^+$.

6.18. 3-(Cyclopropyl-cyclopropylidene-methyl)-1,2,5-trioxa-spiro[5.5]undecane (23)

Yield 8%, oil: FT-IR (neat, cm^{-1}) 1448.9; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.53–0.69 (m, 5H), 0.96–1.08 (m, 4H), 1.48–1.59 (m, 8H), 1.93–2.06 (m, 1H), 2.19–2.29 (m, 1H), 3.67 (dd, 1H, $J = 11.7$, 2.9 Hz), 4.33 (dd, 1H, $J = 11.7$, 10.8 Hz), 4.85 (dd, 1H, $J = 10.8$, 2.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 1.72, 2.15, 5.73, 6.22, 13.81, 22.70, 22.77, 26.00, 29.34, 35.26, 61.70, 82.15, 102.67, 122.27, 124.68; FABMS (*m*/*z*) 251 $(M+H)^+$.

6.19. Trioxane 16

To a magnetically stirred mixture of trioxane **11** (2.00 g, 7.24 mmol) and $NaHCO_3$ (2.20 g, 26.19 mmol) in dichloromethane (100 mL) was added *m*CPBA (2.18 g, 26.03 mmol) portion wise over 30 min and stirred at rt for 24 h. Reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (3 × 75 mL). Combined organic layer was washed first with 10% aq NaOH solution (50 mL), then with water (2 × 25 mL) and dried over anhyd Na_2SO_4. Solvent was removed under vacuum at rt to furnish the crude product, which on column chromatography over silica gel using EtOAc–hexane (0.5:99.5) as eluant furnished **16** (1.40 g, 66% yield) as mixtures of diastereomers as viscous oil: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.16–0.55 (m, 4H), 1.16–1.42 (m, 1H), 1.55–2.03 (m, 13H), 2.53 (d, 1H, $J = 5.0$ Hz), 2.71, and 2.91 (2 × d, 1H, $J = 5.0$ Hz each), 2.59 and 2.86 (2 × br m, 1H), 3.75–4.53 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 0.11, 0.27, 2.29, 2.76, 10.65, 12.28, 27.51, 30.04, 31.21, 33.39, 33.63, 33.79, 34.90, 36.14, 37.55, 49.33, 50.34, 57.08, 57.36, 58.22, 58.91, 76.82, 77.45, 78.09, 80.03, 81.86, 105.22; FABMS (*m*/*z*) 293 $(M+H)^+$. Anal. Calcd for $C_{17}H_{24}O_4 \cdot 0.3H_2O$: C 68.56, H 8.33. Found: C 68.48, H 8.56.

6.20. Trioxane 17

To an ice cooled magnetically stirred solution of **16** (1.0 g, 3.42 mmol) in 1,4-dioxane (15 mL) was added 25% aq $HClO_4$ (7.2 mL) and stirred at 0 °C for 2 h. Reaction mixture was diluted with water (50 mL) and

extracted with ether (3 × 50 mL). Combined organic layer was washed with satd $NaHCO_3$ solution (25 mL), water (2 × 25 mL) and dried over anhyd Na_2SO_4. Solvent was removed under vacuum at rt to furnish the crude product, which on column chromatography over silica gel using acetone–dichloromethane (2:98) as eluant furnished **17a** (350 mg, 33.01% yield) eluting first and **17b** (230 mg, 21.69% yield) eluting next.

Compound **17a**: mp 129–130 °C; FT-IR (KBr, cm^{-1}) 3407.6; ^1H NMR (200 MHz, $CDCl_3$): δ 0.34–0.56 (m, 4H), 0.72–0.85 (m, 1H), 1.64–2.05 (m, 14H), 2.67 (br s, 1H), 3.51 (d, 1H, J = 11.6 Hz), 3.94 (d, 1H, J = 11.6 Hz), 3.94–4.00 (m, 1H), 4.19 (dd, 1H, J = 11.7, 8.3 Hz), 4.34 (dd, 1H, J = 8.3, 3.1 Hz); EI-MS (*m*/*z*) 310 $(M)^+$. Anal. Calcd for $C_{17}H_{26}O_5 \cdot 0.2H_2O$: C 65.02; H 8.47. Found: C 65.16; H 8.60.

Compound **17b**: mp 123–124 °C; FT-IR (KBr, cm^{-1}) 3415.2; ^1H NMR (200 MHz, $CDCl_3$): δ 0.35–0.52 (m, 4H), 0.71–0.88 (m, 1H), 1.64–2.07 (m, 14H), 2.31 (br s, 1H), 2.48 (s, 1H), 2.73 (br s, 1H), 3.48 (d, 1H, J = 11.5 Hz), 3.82 (d, 1H, J = 11.5 Hz), 3.90 (dd, 1H, J = 11.6, 3.0 Hz), 4.23 (dd, 1H, J = 11.6, 9.4 Hz), 4.37 (dd, 1H, J = 9.4, 3.0 Hz); FABMS (*m*/*z*) 311 $(M+H)^+$. Anal. Calcd for $C_{17}H_{26}O_5 \cdot 0.2H_2O$: C 65.02; H 8.47. Found: C 64.91; H 8.54.

6.21. Trioxane 18a

To a solution of **17a** (200 mg, 0.65 mmol) in dichloromethane (5 mL), were added succinic anhydride (120 mg, 1.2 mmol), triethylamine (0.5 mL), and DMAP (5 mg) and stirred for 1 h at rt. Reaction mixture was poured into 10% HCl (20 mL). Organic layer was separated, aqueous layer extracted with dichloromethane (2 × 25 mL) and combined organic layer dried over anhyd Na_2SO_4. Solvent was removed under vacuum at rt to furnish the crude product, which on column chromatography over silica gel using MeOH–$CHCl_3$ (2:98) as eluant furnished **18a** (250 mg, 94.69% yield) as oil: FT-IR (neat, cm^{-1}) 1726.1, 3477.8; ^1H NMR (200 MHz, $CDCl_3$): δ 0.36–0.55 (m, 4H), 0.79–0.86 (m, 1H), 1.62–2.04 (m, 14H), 2.68 (s, 4H), 3.94 (dd, 1H, J = 11.7, 3.4 Hz), 4.16 (dd, 1H, J = 11.7, 9.0 Hz), 4.23 (s, 2H), 4.36 (dd, 1H, J = 9.0, 3.4 Hz); FABMS (*m*/*z*) 411 $(M+H)^+$. Anal. Calcd for $C_{21}H_{30}O_8 \cdot 0.7H_2O$: C 59.61; H 7.48. Found: C 59.40; H 7.57.

6.22. Trioxane 18b

To a solution of **17b** (160 mg, 0.52 mmol) in dichloromethane (5 mL), were added succinic anhydride (100 mg, 1.0 mmol), triethylamine (0.5 mL), and DMAP (5 mg) and stirred for 1 h at rt. Reaction mixture was poured into 10% HCl (20 mL). Organic layer was separated, aqueous layer extracted with dichloromethane (2 × 25 mL) and combined organic layer dried over anhyd Na_2SO_4. Solvent was removed under vacuum at rt to furnish the crude product, which on column chromatography over silica gel using MeOH–$CHCl_3$ (2:98) as eluant furnished **18b** (150 mg, 71.42% yield) as white solid. Mp 82–84 °C; FT-IR (KBr, cm^{-1}) 1724.0, 3471.4; ^1H NMR (200 MHz, $CDCl_3$) 0.33–0.54 (m, 4H), 0.77–0.81 (m, 1H), 1.65–2.07 (m, 13H), 2.69 (s, 4H), 2.80 (br s, 1H), 3.82 (dd, 1H, J = 11.6, 2.6 Hz), 4.14–4.30 (m, 3H), 4.44 (dd, 1H, J = 10.2, 2.6 Hz); FABMS (*m*/*z*) 411 $(M+H)^+$. Anal. Calcd for $C_{21}H_{30}O_8 \cdot 0.7H_2O$: C 59.61; H 7.48. Found: C 59.76; H 7.40.

6.23. Trioxanes 19a and 19b

To a magnetically stirred solution of diol **17** (0.60 g, 1.93 mmol, a mixture of **17a** and **17b**) and cyclopentanone (1.10 g, 13.09 mmol) in dichloromethane (15 mL) was added concd HCl (five drops) and stirred at rt for 3 h. Reaction mixture was poured into saturated aq $NaHCO_3$ solution (25 mL) and organic layer was separated. Aqueous layer was extracted with dichloromethane (2 × 25 mL). Combined organic layer was dried over anhyd Na_2SO_4. Solvent was removed under vacuum at rt to furnish the crude product, which on column chromatography over silica gel using EtOAc–hexane (0.5:99.5) as eluant furnished **19a** (0.15 g, 21% yield) eluting first and **19b** (0.17 g, 23% yield) eluting next.

Compound **19a**: viscous oil, ^1H NMR (200 MHz, $CDCl_3$): δ 0.32–0.51 (m, 4H), 0.87–0.97 (m, 1H), 1.56–2.1 (m, 21H), 2.89 (br s, 1H), 3.68 (d, 1H, J = 8.6 Hz), 3.75 (dd, 1H, J = 11.2, 2.4 Hz), 4.11 (d, 1H, J = 8.6 Hz), 4.26 (dd, 1H, J = 11.2. 10.8 Hz), 4.41 (dd, 1H, J = 10.8, 2.4 Hz); FABMS (*m*/*z*) 377 $(M+H)^+$. Anal. Calcd for $C_{22}H_{32}O_5 \cdot 0.5H_2O$: C 68.54; H 8.63. Found: C 68.19; H 8.80.

Compound **19b:** viscous oil, ^1H NMR (200 MHz, $CDCl_3$): δ 0.39–0.46 (m, 4H), 0.85–0.98 (m, 1H), 1.55–2.08 (m, 21H), 2.85 (br s, 1H), 3.67 (d, 1H, J = 8.6 Hz), 3.84 (dd, 1H, J = 11.7, 3.0 Hz), 4.09 (dd, 1H, J = 11.7, 10.4 Hz), 4.22 (d, 1H, J = 8.6 Hz), 4.36 (dd, 1H, J = 10.4, 3.0 Hz); FABMS (*m*/*z*) 377 $(M+H)^+$. Anal. Calcd for $C_{22}H_{32}O_5 \cdot 0.5H_2O$: C 68.54; H 8.63. Found: C 68.24; H 8.93.

Trioxanes **20a**,**b** and **21a**,**b** were prepared by the same procedure as described for **19a**,**b**.

6.24. Trioxanes 20a and 20b

Compound **20a**: yield 19%, white solid: mp 110–112 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 0.32–0.55 (m, 4H), 0.87–0.97 (m, 1H), 1.35–2.10 (m, 23H), 2.90 (br s, 1H), 3.70 (d, 1H, J = 8.7 Hz), 3.77 (dd, 1H, J = 11.4, 2.4 Hz), 4.20 (d, 1H, J = 8.7 Hz), 4.29 (dd, 1H, J = 11.4, 10.8 Hz), 4.45 (dd, 1H, J = 10.8, 2.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ –0.30, 2.25, 12.05, 24.08, 24.32, 25.43, 27.56, 29.82, 33.42, 33.69, 33.84, 33.93, 35.92, 36.72, 37.39, 37.62, 58.72, 72.44, 80.22, 83.27, 105.16, 110.56; FABMS (*m*/*z*) 391 $(M+H)^+$. Anal. Calcd for $C_{23}H_{34}O_5 \cdot 0.4H_2O$: C 69.45; H 8.82. Found: C 69.59; H 9.12.

Compound **20b**: yield 20%, white solid: mp 94–96 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 0.40–0.49 (m, 4H), 0.85–0.93 (m, 1H), 1.36–2.00 (m, 23H), 2.87 (br s, 1H), 3.72 (d, 1H, J = 8.6 Hz), 3.89 (dd, 1H, J = 11.6, 3.0 Hz),

4.12 (dd, 1H, $J = 11.6, 10.4$ Hz), 4.24 (d, 1H, $J = 8.6$ Hz), 4.35 (dd, 1H, $J = 10.4, 3.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 0.49, 1.48, 16.09, 24.29, 25.53, 27.57, 30.02, 33.48, 33.92, 35.59, 36.26, 36.49, 37.64, 59.18, 69.92, 80.89, 82.81, 105.00, 110.93; FABMS (*m*/*z*) 391 $(M+H)^+$. Anal. Calcd for $C_{23}H_{34}O_5 \cdot 0.5H_2O$: C 69.14; H 8.83. Found: C 68.81; H 8.98.

6.25. Trioxanes 21a and 21b

Compound **21a**: yield 25%, white solid: mp 156–157 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.26–0.38 (m, 2H), 0.43–0.58 (m, 2H), 0.87–0.98 (m, 1H), 1.55–2.10 (m, 27H), 2.90 (br s, 1H), 3.70 (d, 1H, $J = 8.5$ Hz), 3.77 (dd, 1H, $J = 10.9, 2.0$ Hz), 4.21 (d, 1H, $J = 8.5$ Hz), 4.32 (dd, 1H, $J = 10.9$ Hz each), 4.44 (dd, 1H, $J = 10.9, 2.0$ Hz); FABMS (*m*/*z*) 443 $(M+H)^+$. Anal. Calcd for $C_{27}H_{38}O_5 \cdot 0.7H_2O$: C 71.23, H 8.72. Found: C 71.36, H 8.76.

Compound **21b**: yield 24%, white solid: mp 159–160 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.37–0.52 (m, 4H), 0.85–0.91 (m, 1H), 1.55–2.00 (m, 27H), 2.88 (br s, 1H), 3.74 (d, 1H, $J = 8.5$ Hz), 3.91 (dd, 1H, $J = 11.5, 2.8$ Hz), 4.13 (dd, 1H, $J = 11.5, 10.2$ Hz), 4.25 (d, 1H, $J = 8.5$ Hz), 4.36 (dd, 1H, $J = 10.2, 2.8$ Hz); FABMS (*m*/*z*) 443 $(M+H)^+$. Anal. Calcd for $C_{27}H_{38}O_5$: C 73.27, H 8.65. Found: C 73.03, H 8.83.

6.26. Trioxane 25a

To an ice-cooled solution of **18a** (150 mg, 0.36 mmol) in ether (10 mL) was added ice-cooled solution of CH_2N_2 in ether (15 mL), prepared by the reaction of *N*-nitroso *N*-methyl urea (180 mg, 1.74 mmol) with 40% aq KOH (15 mL), and stirred for 30 min. Solvent was evaporated to furnish the crude product, which on column chromatography over silica gel using EtOAc–hexane (15:85) as eluant furnished **25a** (0.15 g, 96.77% yield) as solid: mp 128–130 °C; FT-IR (KBr, cm^{-1}) 1739.2, 3492.3; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.36–0.53 (m, 4H), 0.77–0.87 (m, 1H), 1.63–1.99 (m, 14H), 2.32 (s, 1H, OH), 2.66 (s, 4H), 3.69 (s, 3H), 3.94 (dd, 1H, $J = 11.6, 3.1$ Hz), 4.12–4.29 (m, 3H), 4.36 (dd, 1H, $J = 8.9, 3.1$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −0.83, 0.0, 13.99, 27.08, 28.89, 29.17, 30.33, 33.00, 33.22, 33.36, 33.43, 35.02, 37.11, 51.89, 57.56, 67.99, 71.66, 81.88, 104.89, 172.13, 172.73; EIMS (*m*/*z*) 424 $(M)^+$. Anal. Calcd for $C_{22}H_{32}O_8$: C 62.25; H 7.60. Found: C 62.86; H 8.15.

6.27. Trioxane 25b

To an ice-cooled solution of **18b** (80 mg, 0.19 mmol) in ether (10 mL) was added ice-cooled solution of CH_2N_2 in ether (15 mL), prepared by the reaction of *N*-nitroso *N*-methyl urea (100 mg, 0.97 mmol) with 40% aq KOH (10 mL), and stirred for 30 min. Solvent was evaporated to furnish the crude product, which on column chromatography over silica gel using EtOAc–hexane (15:85) as eluant furnished **25b** (0.08 g, 97.56% yield) as oil: FT-IR (neat, cm^{-1}) 1737.9, 3490.3; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.39–0.58 (m, 4H), 0.78–0.88 (m, 1H), 1.65–2.03 (m, 13H), 2.62 (s, 1H, OH), 2.66 (s, 4H), 2.81 (br s, 1H), 3.70 (s, 3H), 3.82 (dd, 1H, $J = 11.6, 2.5$ Hz), 4.14–4.31 (m, 3H), 4.44 (dd, 1H, $J = 10.0, 2.5$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ −0.51, 0.38, 12.68, 27.51, 29.40, 29.67, 30.07, 33.38, 33.63, 33.80, 33.89, 36.27, 37.56, 52.41, 58.30, 68.71, 71.68, 82.03, 105.29, 173.09, 173.36; EIMS (*m*/*z*) 424$(M)^+$. Anal. Calcd for $C_{22}H_{32}O_8$: C 62.25; H 7.60. Found: C 61.88; H 7.92.

7. In vivo antimalarial efficacy test

The in vivo efficacy of compounds was evaluated against *P. yoelii* (MDR) in Swiss mice model. The colony bred Swiss mice (25 ± 1 g) were inoculated with 1×10^6 parasitized RBC on day 0 and treatment was administered to a group of five mice at each dose, from day 0 to day 3, in two divided doses daily. The drug dilutions were prepared so as to contain the required amount of the drug (1.2 mg for a dose of 96 mg/kg and 0.6 mg for a dose of 48 mg/kg) in 0.1 mL neutralized groundnut oil and administered intramuscularly for each dose. Parasitemia level were recorded from thin blood smears between day 4 and 28.[10] Mice treated with artemisinin served as positive controls.

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