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8-(1-Naphthalen-2-yl-vinyl)-6,7,10-trioxaspiro (4.5) decane, a new 1,2,4-trioxane effective against rodent and simian malaria ☆

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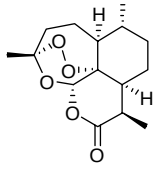
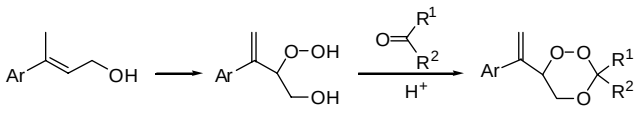
Abstract—A new series of 8-(1-aryl-vinyl)-6,7,10-trioxaspiro [4.5] decanes **7a–e** and 3-(1-aryl-vinyl)-l,2,5-trioxaspiro [5.5] undecanes **8a–e** have been prepared and screened against multi-drug resistant *Plasmodium yoelii* in mice. 8-(1-Naphthalen-2-yl-vinyl)-6,7,10-trioxaspiro [4.5] decane **7b**, the most active trioxane of the series, has also shown promising activity against *Plasmodium cynomolgi* in rhesus monkeys.

Artemisinin **1**, the active principle of the Chinese traditional drug against malaria, *Artemisia annua* and its derivatives are currently the drugs of choice for the treatment of malaria caused by multi-drug resistant *Plasmodium falciparum*.[1] The peroxide group, present in the form of a 1,2,4-trioxane, is essential for the antimalarial activity of these compounds.



1

As part of our endeavour to develop synthetic substitutes for artimisinin derivatives, we had earlier reported a novel photooxygenation route for the preparation of 1,2,4-trioxanes. Preparation of β-hydroxyhydroperoxides by photooxygenation of suitably substituted allylic alcohols and their acid-catalysed reaction with ketones are the key steps of this method.[2,3]



Keywords: Artemisinin; 1,2,4-Trioxanes; Rodent malaria; Simian malaria.

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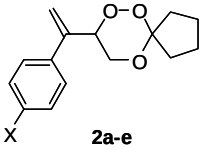
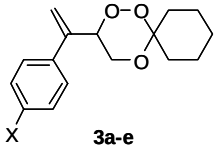
Several 8-(l -aryl-vinyl)-6,7,10-trioxaspiro (4.5) decanes **2a–e** and 3-(1-aryl-vinyl)-1,2,5-trioxaspiro [5.5] undecanes **3a–e**, prepared by this method, had shown significant activity against chloroquine-sensitive *Plasmodium berghei* by intraperitoneal route in mice but showed poor activity against multi-drug resistant *Plasmodium yoelii* in mice by im and oral routes.[4,5] We have conducted further structure–activity relationship in this series and report herein synthesis and antimalarial assessment of series of new 1,2,4-trioxanes, one of which shows promising antimalarial activity against both rodent and simian malaria.



2a-e

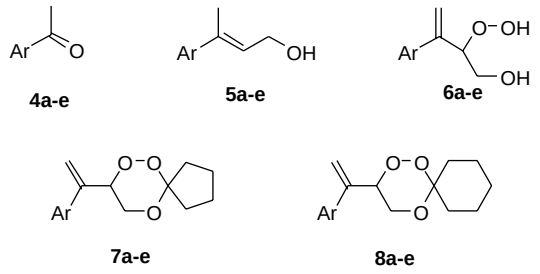


3a-e

a, X = H; **b**, X = F; **c**, X = Cl; **d** = Me; **e** = OMe

Allylic alcohols **5a–e** were prepared from aryl methyl ketones **4a–e** in two steps. Photooxygenation of allylic alcohol **5a** in CH_3CN with methylene blue as sensitizer, furnished β-hydroxyhydroperoxide **6a** in 59% yield. A similar reaction of allylic alcohol **5b** furnished β-hydroxyhydroperoxide **6b** in 61% yield. Both these hydroperoxides were crystalline solids and gave satisfactory ^1H NMR and mass spectral data.[6] Acid-catalysed condensation of **5a** with cyclopentanone and cyclohexanone at room temperature in CH_3CN furnished trioxanes **7a** and **8a** in 50% and 45% yields, respectively. A similar reaction of hydroperoxide **5b** with cyclopentanone and cyclohexanone furnished trioxanes **7b** and **8b** in 76% and 86% yields,

respectively. For the preparation of the rest of the trioxanes, β-hydroxyhydroperoxides **6c**–**e**, the products of photooxygenation of allylic alcohols **5c**–**e**, were not isolated and were condensed with appropriate ketones in situ. Thus, photooxygenation of allylic alcohol **6c** in CH_3CN, followed by condensation of the reaction product in situ with cyclopentanone and cyclohexanone, furnished trioxanes **7c** and **8c** in 25% and 31% yields, respectively. Trioxanes **7d**,**e** and **8d**,**e** were prepared similarly from allylic alcohols **5d**,**e** in 22–48% overall yields.[6]



a, Ar = 1-naphthyl; **b**, Ar = 2-naphthyl; **c**, Ar = 2-phenanthrenyl
d, Ar = 3-phenanthrenyl; **e**, Ar = 2-fluorenyl

Table 1. In vivo antimalarial activity against *Plasmodium yoelii* in Swiss mice

Compound	Dose	Route[a]	% Suppression on day-4[b]	Mice alive on day-28
2a	96	im	100	0/5
	96	Oral	15	0/5
3b	96	im	89	0/5
	96	Oral	14	0/5
7a	96	im	91	1/2
	96	Oral	78	0/5
7b	96	im	100	12/12
	72	im	96	6/6
	48	im	97	1/5
	96	Oral	90	0/5
	192	Oral	100	0/6
7c	96	im	100	3/5
	96	Oral	100	1/5
7d	96	im	99	0/6
	96	Oral	64	0/6
7e	96	im	100	1/6
	96	Oral	100	1/6
8a	96	im	87	0/5
	96	Oral	83	0/5
8b	96	im	97	0/6
	48	im	60	0/6
	96	Oral	ND	—
8c	96	im	81	0/6
	96	Oral	100	2/6
8d	96	im	13	0/6
	96	Oral	99	0/6
8e	96	im	83	0/6
	96	Oral	100	0/6
Artimisinin	48	im	100	5/5
	24	im.	100	3/5
Chloroquine	96	Oral	100	4/5
	48	Oral	100	2/5

[a] The drug dilutions of compounds were prepared in groundnut oil and were administered to a group of five mice at each dose, from day 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.

Trioxanes **2a**, **3a**, **7a**–**e** and **8a**–**e** were tested against multi-drug resistant *P. yoelii* in Swiss mice initially at 96 mg/kg both by intramuscular and oral routes.[7] Trioxane **7b**, which showed 100% protection to the treated mice at 96 mg/kg by im route only was further tested at 72 and 48 mg/kg by im route and at 192 mg/kg by oral route. Trioxane **7b** was also tested against *Plasmodium cynomolgi* in rhesus monkeys at 20 mg/kg by im route and 40 mg/kg by oral route. Results are shown in Tables 1 and 2.

As can be seen from Table 1, cyclopentane-based spirotrioxanes **7a**–**e** as a class are more active than the corresponding cyclohexane-based spirotrioxanes **8a**–**e**. Among the cyclopentane-based trioxanes, **7b** is the most active compound. It shows 100% suppression of parasitaemia at 96 mg/kg by im route and all the treated mice survive beyond 28 days. Even at 72 and 48 mg/kg by im route it shows more than 95% suppression of parasitaemia on day-4 and significant protection to the treated mice. This compound also shows more than 90% suppression of parasitaemia at 96 mg/kg by oral route also, though none of the treated mice survive beyond 28 days. Trioxane **7b** also shows 100% clearance of parasitaemia at 20 mg/kg × 4 days by intramuscular route and 40 mg/kg × 5 day by oral route in monkeys infected with *P. cynomolgi* though all the treated monkeys show recrudescence. Trioxane **7c**, the next best compound of the series, shows 100% suppression of parasitaemia at 96 mg/kg by both the routes but provides significant protection (60%) to the treated mice only by im route. Trioxane **7e** also shows 100% suppression of the parasitaemia at 96 mg/kg and partial protection to the treated mice by both routes. Among the cyclohexane-based spirotrioxanes, while several of them show significant suppression of parasitaemia at 96 mg/kg, only **8c** shows significant protection to the treated mice. It is also significant to note that the compound is more active by oral route as compared with the im route. Also in both the cyclopentane-based trioxanes **7a**–**e** and cyclohexane-based trioxanes **8a**–**e**, the activity by oral route increases as the aryl group is changed from naphthyl to phenanthrenyl and fluorenyl groups. This could be due to the increase in lipophilicity of the trioxanes which would favour the absorption of these trioxanes by oral route.

In conclusion, we have prepared a series of new structurally simple spirotrioxanes, one of which (**7b**) shows promising antimalarial activity both against rodent

Table 2. Antimalarial activity of **7b** against *Plasmodium cyanomolgi* in rhesus monkeys

Dose	Route[a]	Initial parasitaemia	Parasite clearance time (h)	Day of recurrence of parasitaemia
20	im	35,360	96	12
20	im	33,288	96	11
40	Oral	8691	48	14
40	Oral	7828	120	9

[a] Trioxane **7b** was dissolved in groundnut oil and administered 20 mg/kg × 4 days by intramuscular route or 40 mg/kg × 4 days by oral route, in two divided doses daily.

and simian malaria. The activity of **7b** is very close to that of artemisinin, the active principle of *Artemisia annua*.

Acknowledgment

Rani Kanchan thanks CSIR, New Delhi for senior research fellowship.

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5. The activity data of **2a** and **3a**, two representative compounds, against *Plasmodium yoelii* by oral and im route are given in Table 1.
6. Selected spectral data: compound **6a** mp 118–120 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.66 (dd, 1H, J = 12.0, 7.0 Hz), 3.79 (dd, 1H, J = 12.0, 3.0 Hz), 5.0 (dd, 1H, J = 7.0, 3.0 Hz), 5.43 and 5.78 (2 × s, 2H), 7.2–8.1 (m, 7H); MS (*m*/*z*) 230 (M^+), 212 (M^+-H_2O).
Compound **6b** mp 124–125 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.71 (br s, 1H, OH), 3.79 (m, 2H), 5.2 (m, 1H), 5.51 and 5.67 (2 × s, 2H), 7.35–7.86 (m, 7H); MS (*m*/*z*) 230 (M^+), 212 (M^+-H_2O).
Compound **7a** colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65–2.60 (m, 8H), 3.73 (dd, 1H, J = 11.7, 3.5 Hz), 3.83 (dd, 1H, J = 11.7, 9.3 Hz), 5.17 (dd, 1H, J = 9.3, 3.5 Hz), 5.39 and 5.69 (2 × s, 2H), 7.2–8.0 (m, 7H); MS (*m*/*z*) 296 (M^+); Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.33; H, 6.88.
Compound **7b** mp 52 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46–2.61 (m, 8H), 3.89 (d, 2H, J = 6.0 Hz), 5.46 (t, 1H, J = 6.0 Hz), 5.44 and 5.63 (2 × s, 2H), 7.40–7.84 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.35 (CH_2), 25.01 (CH_2), 32.76 (CH_2), 36.99 (CH_2), 65.71 (CH_2), 80.04 (CH), 114.8 (C), 117.0 (CH_2), 124.6 (CH), 125.4 (CH), 126.4 (CH), 126.8 (CH), 127.2 (CH), 128.6 (2 × CH), 133.2 (C), 133.6 (C), 135.8 (C), 143.7 (C); MS (*m*/*z*) 296 (M^+); HR-EIMS calcd for $C_{19}H_{20}O_3$: 296.1419. Found: 296.1413.
Compound **7c** mp 94–96 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65–1.96 (m, 8H), 3.82 (d, 2H, J = 6.0 Hz), 5.44 and 5.74 (2 × s, 2H), 5.48 (t, 1H J = 6.0 Hz), 7.57–8.67 (m, 9H), MS (*m*/*z*) 346 (M^+); Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.93; H, 6.53.
Compound **7d** mp 70–72 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.68–2.5 (m, 8H), 3.92 (d, 2H, J = 6.5 Hz), 5.47 and 5.68 (2 × s, 2H), 5.49 (t, 1H, J = 6.5 Hz), 7.57–8.73 (m, 9H), MS (*m*/*z*) 346 (M^+); Anal. Calcd for $C_{23}H_{22}O_3$: C,79.74; H, 6.40. Found: C, 80.19; H, 6.63.
Compound **7e** mp 86–88 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.66–2.60 (m, 8H), 3.88 (d, 2H, J = 6.0 Hz), 3.89 (s, 2H), 5.37 and 5.55 (2 × s, 2H), 5.40 (t, 1H, J = 6.0 Hz), 7.25–7.84 (m, 7H); MS (*m*/*z*) 334 (M^+); HR-EIMS calcd for $C_{22}H_{22}O_3$: 334.1568. Found: 334.1569.
Compound **8a** oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56–2.23 (m 10H), 3.67 (dd, 1H, J = 12.0, 3.0 Hz), 3.97 (dd, 1H, J = 12.0, 10.5 Hz), 5.1 (dd, 1H, J = 10.5, 3.0 Hz), 5.41 and 5.71 (2 × s, 2H), 7.26–7.90 (m, 7H); MS (*m*/*z*) 320 (M^+); Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.80; H, 7.50.
Compound **8b** mp 95 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48–2.45 (m, 10H), 3.7 (dd, 1H, J = 12.22, 3.04 Hz), 4.02 (dd, 1H, J = 12.22, 10.27 Hz), 5.39 (dd, 1H, J = 10.27, 3.04 Hz), 5.43 and 5.67 (2 × s, 2H), 7.45–7.84 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.25 (2 × CH_2), 25.56 (CH_2), 29.61 (CH_2), 34.66 (CH_2), 62.76 (CH_2), 80.26 (CH), 102.54 (C), 116.60 (CH_2), 124.35 (CH), 125.22 (CH), 126.17 (CH), 126.27 (CH), 127.47 (CH), 128.13 (2 × CH), 132.97 (C), 133.27 (C), 135.29 (C), 143.42 (C); MS (*m*/*z*) 310 (M^+); Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.25; H, 6.89.
Compound **8c** mp 102–104 °C; ^{1}H NMR (200 MHz, $CDCl_3$): 1.56–2.20 (m, 10H), 3.83 (dd, 1H, J = 11.5, 3.2 Hz), 4.06 (dd, 1H, J = 11.5, 9.7 Hz), 5.44 (dd, 1H, J = 9.7, 3.2 Hz), 5.45 and 5.69 (2 × s, 2H), 7.59–8.67 (m, 9H); MS (*m*/*z*) 360 (M^+); Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 78.84; H, 6.53.
Compound **8d** mp 84–85 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48–2.3 (m, 10H), 3.82 (dd, 1H, J = 11.8, 2.8 Hz), 4.0 (dd, 1H, J = 11.8, 10.2 Hz), 5.45 (dd, 1H, J = 10.2, 2.8 Hz), 5.49 and 5.69 (2 × s, 2H), 7.6–8.8 (m, 9H); MS (*m*/*z*) 360 (M^+); Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.47; H, 6.35.
Compound **8e** mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.56–2.28 (m, 10H), 3.79 (dd, 1H, J = 11.11, 2.46 Hz), 3.90 (s, 2H), 4.0 (dd, 1H, J = 11.11, 9.87 Hz), 5.32 (dd, 1H, J = 9.87, 2.46 Hz), 5.34 and 5.56 (2 × s, 2H), 7.25–7.91 (m, 7H); MS (*m*/*z*) 348 (M^+); HR-EIMS calcd for $C_{23}H_{24}O_3$: 348.1731. Found: 348.1725.
7. The in vivo efficacy of compounds was evaluated against *Plasmodium yoelii* (MDR) in Swiss mice model. The colony bred Swiss mice (25 ± lg) were inoculated with 1×10^6 parasitised RBC on day zero and treatment was administered to a group of five mice at each dose, from day 0–3, in two divided doses daily. The drug dilutions of compounds 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 and 0.6 mg for a dose of 48 mg/kg) in 0.1 ml and administered either intramuscularly or orally for each dose. Parasitaemia level were recorded from thinblood smears between days 4 and 28.[8] Mice treated with artemisinin and chloroquine served as positive controls. For activity against *Plasmodium cyanomolgi*, rhesus monkeys were inoculated intravenously with 1×10^5 parasitised RBC and treatment was initiated when the parasitaemia level reached above 0.5%. Trioxane **7b** was dissolved in groundnut oil and administered 20 mg/kg × 4 days by intramuscular route or 40 mg/kg × 4 days by oral route, in two divided doses daily. The blood smears from the treated monkeys were examined once daily to record parasitaemia clearance time and subsequent recurrence of parasitaemia.
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