Bioorganic & Medicinal Chemistry Letters 20 (2010) 4459–4463

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

6-(4′-Aryloxy-phenyl)vinyl-1,2,4-trioxanes: A new series of orally active peroxides effective against multidrug-resistant *Plasmodium yoelii* in Swiss mice ☆

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ARTICLE INFO

Article history:
Received 28 January 2010
Revised 26 May 2010
Accepted 8 June 2010
Available online 12 June 2010

Keywords:
Malaria
Multidrug-resistant
Arteether
1,2,4-Trioxanes

ABSTRACT

A new series of 6-(4′-aryloxy-phenyl)vinyl-1,2,4-trioxanes **10a–d**, **11a–d**, and **12a–d** have been synthesized and evaluated for their antimalarial activity against multidrug-resistant *Plasmodium yoelii* in Swiss mice by oral route. Trioxanes **10b** and **10c**, the two most active compounds of the series, provided 100% protection to the infected mice at 48 mg/kg × 4 days. Clinically useful drug β-arteether provided 100% and 20% protection at 48 mg/kg × 4 days and 24 mg/kg × 4 days, respectively, in this model.

Artemisinin **1**, the active principle of *Artemisia annua* and its semi-synthetic derivatives, for example, artemether **2**, arteether **3** and artesunic acid **4** are the only class of antimalarials which are effective against multidrug-resistant malaria[2,3] (Fig. 1).

Ever since the establishment of the peroxide group present in the form of 1,2,4-trioxane in artemisinin as the active pharmacophore, considerable efforts have been diverted towards synthesis of structurally simple synthetic trioxanes. Several synthetic 1,2,4-trioxanes originating from different laboratories, have shown promising antimalarial activity both in vitro and in vivo.[4] In spite of this, the search for structurally simpler, cheaper and more effective synthetic trioxanes remains an area of hot pursuit.

Earlier we had reported a photooxygenation route for the preparation of 1,2,4-trioxanes (Scheme 1).[5] Several of the trioxanes prepared by this method had shown promising antimalarial activity.[6]

Very recently we have extended this methodology for the synthesis of bis- and tris-trioxanes.[7] In continuation with these efforts, herein we report, the synthesis and antimalarial assessment of a new series of 6-(4′-aryloxy-phenyl)vinyl-1,2,4-trioxanes **10a–d**, **11a–d**, and **12a–d**, two of which (**10b** and **10c**) have shown antimalarial activity comparable to that of β-arteether by oral route.

Allylic alcohols **8a–d**, prepared from *p*-fluoroacetophenone in three steps, were photooxygenated to give β-hydroxyhydroperoxides **9a–d**. In situ acid-catalyzed condensation of β-hydroxyhydroperoxides **9a–d** with cyclopentanone furnished 1,2,4-trioxanes **10a–d** in 48–59% yields (Scheme 2). Similar acid-catalyzed con-

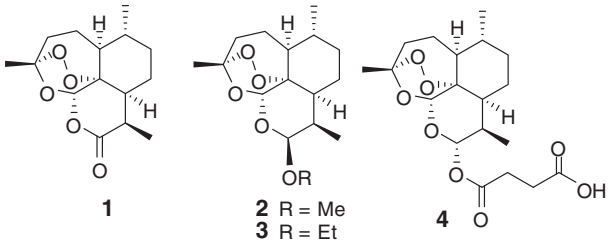
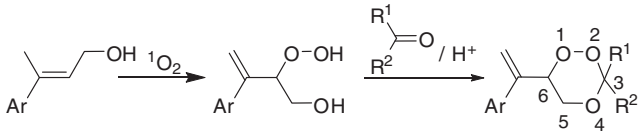


Figure 1. Artemisinin and its derivatives.



Scheme 1.

☆ See Ref. 1.

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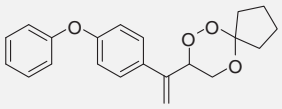
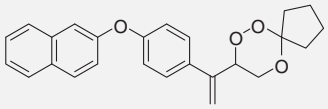
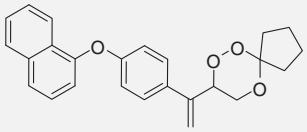
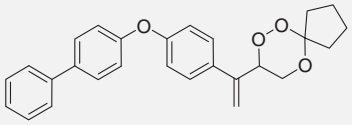
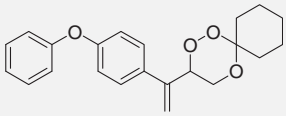
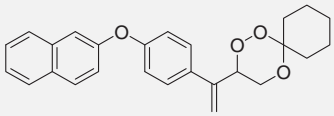
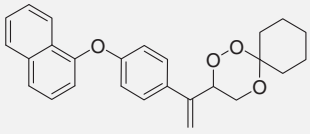
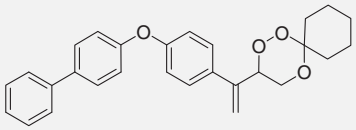
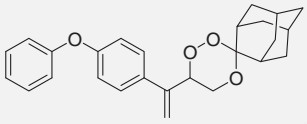
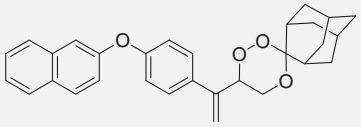
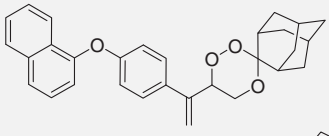
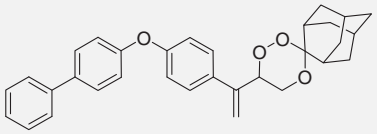
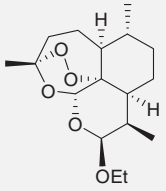
doi:10.1016/j.bmcl.2010.06.045

Table 1
In vivo antimalarial activity of trioxanes **10a–d**, **11a–d** and **12a–d** against multidrug-resistant *P. yoelii* in Swiss mice by oral route

Compound	Structure	Log *P*[b]	Dose (mg/kg × 4 days)	% Suppression of parasitaemia on day 4[a]	Cured/treated
10a		5.14	96	100	3/5
10b		6.13	96 48 24	100 100 100	5/5 5/5 0/5
10c		6.13	96 48 24	100 100 100	5/5 5/5 0/5
10d		6.81	96 48	100 100	5/5 0/5
11a		5.55	96	100	3/5
11b		6.55	96	100	2/5
11c		6.55	96	92.81	0/5
11d		7.23	96	84.39	0/5
12a		6.19	96	100	4/5
12b		7.19	96	100	3/5
12c		7.19	96	93.15	0/5
12d		7.86	96	100	4/5
3		3.84	48 24	100 100	5/5 1/5

[a] Percent suppression = $[(C-T)/C] \times 100$, where C is parasitaemia in control group and T is parasitaemia in treated group.
[b] Log *P* values have been calculated from Chemdraw ultra 7.0.

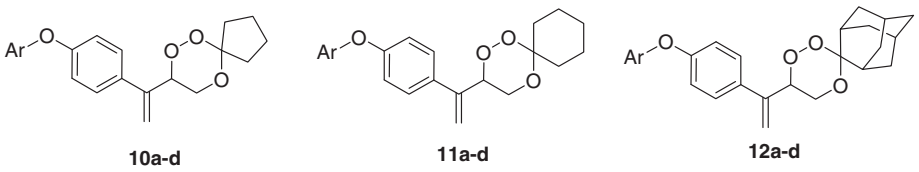
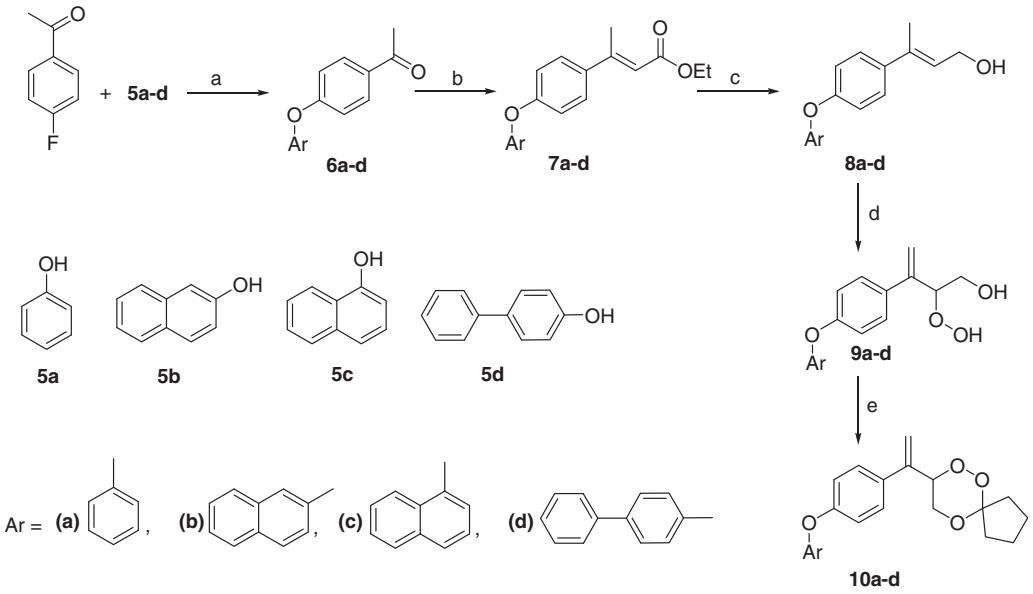


Figure 2. Trioxanes **10a–d**, **11a–d**, and **12a–d**.



Scheme 2. Reagents and conditions: (a) K_2CO_3/DMSO, reflux, 2–4 h; (b) $(OEt)_2P(O)CH_2CO_2Et$/NaH, THF, rt, 6–18 h; (c) $LiAlH_4$/THF, 0 °C, 1 h; (d) $^1O_2/CH_3CN$, −10 to 0 °C, 4–12 h; (e) cyclopentanone/CH_3CN, concd HCl, rt, 1 h.

densation of the hydroperoxides **9a–d** with cyclohexanone and 2-adamantanone at room temperature furnished 1,2,4-trioxanes **11a–d**, and **12a–d** (Fig. 2) in 45–64% and 49–70% yields, respectively.[8]

Trioxanes **10a–d**, **11a–d**, and **12a–d** were evaluated for their antimalarial activity at 96 mg/kg × 4 days against multidrug-resistant *Plasmodium yoelii* in mice by oral route.[9,10] Trioxanes **10b**, **10c**, and **10d** which showed 100% protection at this dose were further screened at 48 mg/kg × 4 days. Trioxanes **10b** and **10c** which showed 100% protection at 48 mg/kg × 4 days, were further tested at 24 mg/kg × 4 days. β-Arteether was used as a positive control. The results are summarized in Table 1.

As can be seen from Table 1, all the cyclopentane-based trioxanes **10a–d** showed promising activity. Trioxanes **10b** and **10c**, the two most active compounds of the series, provided 100% protection at 48 mg/kg × 4 days by oral route. Even at 24 mg/kg × 4 days both these compounds showed 100% suppression of parasitaemia on day 4, though none of the treated mice survived till day 28. Thus, the activity profile of both these compounds is comparable with that of arteether. Cyclohexane-based trioxanes **11a–d** showed moderate activity; only **11a** and **11b** provided significant protection at 96 mg/kg × 4 days. Among the adamantane-based compounds, trioxanes **12a** and **12d** were the most active compounds. Both of these provided 80% protection at 96 mg/kg × 4 days by oral route.

In conclusion we have prepared a new series of 1,2,4-trioxanes. Cyclopentane-based trioxanes **10b** and **10c**, the two most active compounds of the series, showed activity profile comparable to that of β-arteether.

Acknowledgments

V.P.V., N.N., A.S.S., and M.H. are thankful to the Council of Scientific and Industrial Research (CSIR) and University of Grants Commission (UGC), New Delhi for the award of Senior Research Fellowship.

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8. (a) *General procedure for the preparation of 6-(4′-aryloxy-phenyl)vinyl-1,2,4-trioxanes* **10a–d, 11a–d, and 12a–d:** (compound **10a** is taken as a representative example). A solution of 3-(4-phenoxy-phenyl)-but-2-en-1-ol **8a** (1 g, 4.16 mmol) and methylene blue (10 mg) in CH_3CN (100 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 6 h. Cyclopentanone (3.15 mL, 37.5 mmol, 9 equiv) and HCl (0.1 mL) were added and the reaction mixture was stirred at room temperature for 1 h. Usual workup followed by column chromatography over silica gel furnished trioxane. *8-[1-(4-Phenoxy-phenyl)-vinyl]-6,7,10-trioxa-spiro[4.5]decane* **(10a)** (672 mg, 48% yield) as a white solid, mp 51–52 °C; IR (KBr, cm^{-1}) 1590; ^1H NMR (200 MHz, $CDCl_3$) δ 1.66–1.98 (m, 7H), 2.47–2.59 (m, 1H), 3.86 (d, 2H, J = 6.2 Hz), 5.26–5.33 (m, 2H), 5.47 (s, 1H), 6.95–7.16 (m, 5H, Ar), 7.32–7.39 (m, 4H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.80 (CH_2), 25.21 (CH_2), 33.21 (CH_2), 37.46 (CH_2), 65.47 (CH_2), 80.73 (CH), 115.01 (C), 116.21 (CH_2), 119.0 (CH), 124.03 (CH), 128.28 (CH), 130.26 (CH), 133.85 (C), 142.99 (C), 157.23 (C), 157.90 (C); FAB-MS (m/z) 339 $[M+H]^+$; HRMS calcd for $C_{21}H_{22}O_4$ 338.1518; found, 338.1529. *8-{1-[4-(Naphthalen-2-yloxy)-phenyl]-vinyl}6,7,10-trioxa-spiro[4.5]decane* **(10b)**. This was obtained in 52% yield as white solid, mp 87–90 °C; IR (KBr, cm^{-1}) 1591; ^1H NMR (200 MHz, $CDCl_3$) δ 1.67–1.99 (m, 7H), 2.48–2.60 (m, 1H), 3.88 (d, 2H, J = 6.3 Hz), 5.28–5.34 (m, 2H), 5.50 (s, 1H), 7.04 (dd, 2H, Ar, J = 6.4 and 2.2 Hz), 7.24–7.28 (m, 1H, Ar), 7.35–7.52 (m, 5H, Ar), 7.73 (dd, 1H, Ar, J = 6.9 and 2.2 Hz), 7.84 (dd, 2H, Ar, J = 9.1 and 2.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.83 (CH_2), 25.27 (CH_2), 33.26 (CH_2), 37.48 (CH_2), 65.43 (CH_2), 80.68 (CH), 114.98 (C), 116.30 (CH_2), 119.24 (CH), 120.49 (CH), 125.33 (CH), 127.05 (CH), 127.66 (CH), 128.23 (CH), 128.40 (CH), 130.40 (CH), 130.80 (C), 134.08 (C), 134.79 (C), 143.08 (C), 155.03 (C), 158.17 (C); FAB-MS (m/z) 389 $[M+H]^+$; HRMS calcd for $C_{25}H_{24}O_4$ 388.1675; found, 388.1674. *8-{1-[4-(Naphthalen-1-yloxy)-phenyl]-vinyl}-6,7,10-trioxa-spiro[4.5]decane* **(10c)**. This was obtained in 57% yield as oil; IR (neat, cm^{-1}) 1599; ^1H NMR (200 MHz, $CDCl_3$) δ 1.71–1.99 (m, 7H), 2.48–2.60 (m, 1H), 3.88 (d, 2H, J = 6.2 Hz), 5.29–5.34 (m, 2H), 5.48 (s, 1H), 6.99–7.03 (m, 3H, Ar), 7.36–7.57 (m, 5H, Ar), 7.66 (d, 1H, Ar, J = 8.3 Hz), 7.90 (dd, 1H, Ar, J = 6.4 and 2.7 Hz), 8.17 (dd, 1H, Ar, J = 6.9 and 2.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.81 (CH_2), 25.22 (CH_2), 33.24 (CH_2), 37.48 (CH_2), 65.5 (CH_2), 80.74 (CH), 114.55 (CH), 115.02 (C), 116.20 (CH_2), 118.63 (CH), 122.47 (CH), 124.24 (CH), 126.23 (CH), 126.51 (CH), 127.10 (CH), 128.28 (CH), 128.34 (CH), 133.78 (C), 135.43 (C), 142.99 (C), 152.97 (C), 158.58 (C); FAB-MS (m/z) 389 $[M+H]^+$; HRMS calcd for $C_{25}H_{24}O_4$ 388.1674; found, 388.1672. *8-{1-[4-(Biphenyl-4-yloxy)-phenyl]-vinyl}-6,7,10-trioxa-spiro[4.5]decane* **(10d)**. This was obtained in 59% yield as oil; IR (KBr, cm^{-1}) 1598; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75–2.02 (m, 7H), 2.54–2.63 (m, 1H), 3.93 (d, 2H, J = 6.4 Hz), 5.35–5.38 (m, 2H), 5.53 (s, 1H), 7.08 (d, 2H, Ar, J = 8.7 Hz), 7.15 (d, 2H, Ar, J = 8.6 Hz), 7.35–7.51 (m, 5H, Ar), 7.63 (dd, 4H, Ar, J = 8.6 and 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5 (CH_2), 24.9 (CH_2), 32.94 (CH_2), 37.15 (CH_2), 65.12 (CH_2), 80.4 (CH), 114.68 (C), 115.96 (CH_2), 118.82 (CH), 119.47 (CH), 127.02 (CH), 127.23 (CH), 128.62 (CH), 128.6 (CH), 128.93 (CH), 133.71 (C), 136.75 (C), 140.55 (C), 142.58 (C), 156.5 (C), 157.48 (C); ESI (m/z) 415 $[M+H]^+$; HRMS calcd for $C_{27}H_{26}O_4$ 414.1831; found, 414.1834. *3-[1-(4-Phenoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undecane* **(11a)**. This was obtained in 46% yield as white solid, mp 54–55 °C; IR (KBr, cm^{-1}) 1590; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38–1.63 (m, 8H), 1.95–2.08 (m, 1H), 2.17–2.29 (m, 1H), 3.78 (dd, 1H, J = 11.8 and 3.3 Hz), 3.99 (dd, 1H, J = 11.9 and 10.2 Hz), 5.23 (dd, 1H, J = 10.6 and 3.5 Hz), 5.29 and 5.48 (2 × s, 2H), 6.95–7.16 (m, 5H, Ar), 7.32–7.39 (m, 4H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.73 (CH_2), 22.76 (CH_2), 25.97 (CH_2), 29.44 (CH_2), 35.08 (CH_2), 63.09 (CH_2), 80.70 (CH), 103.04 (C), 116.12 (CH_2), 119.02 (CH), 119.58 (CH), 123.99 (CH), 128.25 (CH), 130.24 (CH), 133.96 (CH), 143.16 (C), 157.24 (C), 157.86 (C); FAB-MS (m/z) 353 $[M+H]^+$; HRMS calcd for $C_{22}H_{24}O_4$ 352.1675; found, 352.1677. *3-{1-[4-(Naphthalen-2-yloxy)-phenyl]-vinyl}-1,2,5-trioxa-spiro[5.5]undecane* **(11b)**. This was obtained in 45% yield as white solid, mp 108–110 °C; IR (KBr, cm^{-1}) 1596; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45–1.65 (m, 8H), 1.97–2.10 (m, 1H), 2.18-2.32 (m, 1H), 3.80 (dd, 1H, J = 11.9 and 3 Hz), 4.02 (dd, 1H, J = 11.9 and 10.3 Hz), 5.23–5.31 (m, 2H), 5.51 (s, 1H), 7.0–7.08 (m, 2H, Ar), 7.27 (dd, 1H, Ar, J = 8.8 and 2.4 Hz), 7.35–7.52 (m, 5H, Ar), 7.73 (dd, 1H, Ar, J = 6.6 and 2.0 Hz), 7.85 (dd, 2H, Ar, J = 9.3 and 2.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.74 (CH_2), 22.79 (CH_2), 25.99 (CH_2), 29.46 (CH_2), 35.09 (CH_2), 63.09 (CH_2), 80.70 (CH), 103.07 (C), 114.97 (CH), 116.23 (CH_2), 119.27 (CH), 120.46 (CH), 125.30 (CH), 127.04 (CH), 127.60 (CH), 128.20 (CH), 128.33 (CH), 130.41 (CH), 130.76 (C), 134.19 (C), 134.75 (C), 143.16 (C), 155.05 (C), 157.79 (C); FAB-MS (m/z) 403 $[M+H]^+$; HRMS calcd for $C_{26}H_{26}O_4$ 402.1831; found, 402.1828. *3-{1-[4-(Naphthalen-1-yloxy)-phenyl]-vinyl}-1,2,5-trioxa-spiro[5.5]undecane* **(11c)**. This was obtained in 58% yield as oil; IR (neat, cm^{-1}) 1598; ^1H NMR (200 MHz, $CDCl_3$) δ 1.39–1.65 (m, 8H), 1.96–2.08 (m, 1H), 2.18–2.35 (m, 1H), 3.79 (dd, 1H, J = 11.9 and 2.9 Hz), 4.01 (dd, 1H, J = 11.9 and 10.3 Hz), 5.21–5.30 (m, 2H), 5.48 (s, 1H), 7.01 (d, 3H, Ar, J = 8.7 Hz), 7.34–7.55 (m, 5H, Ar), 7.66 (d, 1H, Ar, J = 8.1 Hz), 7.89 (dd, 1H, Ar, J = 5.4 and 1.6 Hz), 8.17 (dd, 1H, Ar, J = 6.9 and 2.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.74 (CH_2), 22.79 (CH_2), 25.99 (CH_2), 29.46 (CH_2), 35.10 (CH_2), 63.11 (CH_2), 80.72 (CH), 103.06 (C), 114.50 (CH), 116.09 (CH_2), 118.66 (CH), 122.47 (CH), 124.22 (CH), 126.23 (CH), 126.5 (CH), 127.09 (CH), 127.36 (C), 128.26 (CH), 128.32 (CH), 133.9 (C), 135.42 (C), 143.19 (C), 153.0 (C), 158.55 (C); FAB-MS (m/z) 403 $[M+H]^+$; HRMS calcd for $C_{26}H_{26}O_4$ 402.1831; found, 402.1830. *3-{1-[4-(Biphenyl-4-yloxy)-phenyl]-vinyl}-1,2,5-trioxa-spiro[5.5]undecane* **(11d)**. This was obtained in 64% yield as white solid, mp 54–56 °C; IR (KBr, cm^{-1}) 1594; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49–1.67 (m, 8H), 2.0–2.09 (m, 1H), 2.21–2.30 (m, 1H), 3.81 (dd, 1H, J = 11.9 and 2.9 Hz), 4.02 (dd, 1H, J = 11.9 and 10.5 Hz), 5.26 (dd, 1H, J = 10.4 and 2.8 Hz), 5.33 and 5.51 (2× s, 2H), 7.05 (d, 2H, Ar, J = 8.7 Hz), 7.11 (d, 2H, Ar, J = 8.7 Hz), 7.33–7.48 (m, 5H, Ar), 7.60 (dd, 4H, Ar, J = 9 and 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.51 (CH_2), 22.55 (CH_2), 25.76 (CH_2), 29.25 (CH_2), 34.86 (CH_2), 65.85 (CH_2), 80.5 (CH), 102.83 (C), 115.96 (CH_2), 118.93 (CH), 119.51 (CH), 127.12 (CH), 127.3 (CH), 128.09 (CH), 128.69 (CH), 129 (CH), 133.93 (C), 136.85 (C), 140.68 (C), 142.98 (C), 156.61 (C), 157.53 (C); ESI (m/z) 428 $[M+H]^+$; HRMS calcd for $C_{28}H_{28}O_4$ 428.1988; found, 428.1990. *Trioxane* **(12a)**. This was obtained in 49% yield as white solid, mp 53–56 °C; IR (KBr, cm^{-1}) 1591; ^1H NMR (200 MHz, $CDCl_3$) δ 1.59–2.10 (m, 13H), 2.96 (s, 1H), 3.78 (dd, 1H, J = 12 and 3.3 Hz), 3.98 (dd, 1H, J = 11.8 and 10.5 Hz), 5.22–5.28 (m, 2H), 5.48 (s, 1H), 6.95–7.16 (m, 5H, Ar), 7.31–7.39 (m, 4H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.59 (2× CH), 29.83 (CH), 33.44 (CH_2), 33.68 (CH_2), 33.91 (CH_2), 34.01 (CH_2), 36.67 (CH), 37.63 (CH_2), 62.57 (CH_2), 80.53 (CH), 105.08 (C), 116.03 (CH_2), 119.03 (CH), 119.57 (CH), 123.99 (CH), 128.23 (CH), 130.24 (CH), 13403 (C), 143.20 (C), 157.26 (C), 157.85 (C); FAB-MS (m/z) 405 $[M+H]^+$; HRMS. calcd for $C_{26}H_{28}O_4$: 404.1988, found: 404.1967. *Trioxane* **(12b)**. This was obtained in 53% yield as white solid, mp 103–105 °C; IR (KBr, cm^{-1}) 1593; ^1H NMR (200 MHz, $CDCl_3$) δ 1.61–2.11 (m, 13H), 2.9 (s, 1H), 3.80 (dd, 1H, J = 12 and 3 Hz), 4.0 (dd, 1H, J = 11.9 and 10.4 Hz), 5.24–5.30 (m, 2H), 5.50 (s, 1H), 7.03 (d, 2H, Ar, J = 8.6 Hz), 7.26 (dd, 1H, Ar, J = 8.9 and 2.6 Hz), 7.35–7.52 (m, 5H, Ar), 7.74 (dd, 1H, Ar, J = 9.6 and 1.9 Hz), 7.86 (dd, 2H, Ar, J = 9.1 and 2.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.59 (2× CH), 29.83 (CH), 33.44 (CH_2), 33.68 (CH_2), 33.91 (CH_2), 34.01 (CH_2), 36.67 (CH), 37.63 (CH_2), 62.57 (CH_2), 80.54 (CH), 105.11 (C), 114.96 (CH), 116.17 (CH_2), 119.27 (CH), 120.45 (CH), 125.29 (CH), 127.03 (CH), 127.60 (CH), 128.20 (CH), 128.30 (CH), 130.40 (CH), 130.74 (C), 134.25 (C), 134.74 (C), 143.17 (C), 155.05 (C), 157.76 (C); FAB-MS (m/z) 455 $[M+H]^+$; HRMS calcd for $C_{30}H_{30}O_4$ 454.2144; found, 454.2156. *Trioxane* **(12c)**. This was obtained in 49% yield as oil; IR (neat, cm^{-1}) 1593; ^1H NMR (200 MHz, $CDCl_3$) δ 1.58–2.11 (m, 13H), 2.97 (s, 1H), 3.81 (dd, 1H, J = 11.8 and 3 Hz), 4.0 (dd, 1H, J = 11.7 and 10.3 Hz), 5.24–5.29 (m, 2H), 5.49 (s, 1H), 7.01 (d, 3H, Ar, J = 8.6 Hz), 7.35–7.55 (m, 5H, Ar), 7.66 (d, 1H, Ar, J = 8.3 Hz), 7.90 (dd, 1H, Ar, J = 6 and 2.4 Hz), 8.15–8.20 (m, 1H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.35 (2× CH), 29.59 (CH), 33.19 (CH_2), 33.44 (CH_2), 33.67 (CH_2), 33.77 (CH_2), 36.43 (CH), 37.39 (CH_2), 62.35 (CH_2), 80.28 (CH), 104.84 (C), 114.23 (CH), 115.75 (CH_2), 118.42 (CH), 122.23 (CH), 123.95 (CH), 125.98 (CH), 126.25 (CH), 126.84 (CH), 127.10 (CH), 128.03 (CH), 133.71 (C), 135.16 (C), 142.95 (C), 152.76 (C), 158.27 (C); FAB-MS (m/z) 455 $[M+H]^+$; HRMS calcd for $C_{30}H_{30}O_4$ 454.2144; found, 454.2143. *Trioxane* **(12d)**. This was obtained in 70% yield as white solid, mp 122–125 °C; IR (KBr, cm^{-1}) 1592; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61–2.13 (m, 13H), 2.98 (s, 1H), 3.82 (dd, 1H, J = 11.9 and 3 Hz), 4.01 (dd, 1H, J = 11.8 and 10.4 Hz), 5.28 (dd, 1H, J = 10.5 and 2.9 Hz), 5.32 and 5.51 (2× s, 2H), 7.05 (d, 2H, Ar, J = 8.8 Hz), 7.11 (d, 2H, Ar, J = 8.7 Hz), 7.33–7.49 (m, 5H, Ar), 7.60 (dd, 4H, Ar, J = 9 and 2.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.39 (2× CH), 29.65 (CH), 33.23 (CH_2), 33.47 (CH_2), 33.7 (CH_2), 33.80 (CH_2), 36.46 (CH), 37.43 (CH_2), 62.36 (CH_2), 80.34 (CH), 104.89 (C), 115.91 (CH_2), 118.96 (CH), 119.51 (CH), 127.14 (CH), 127.31 (CH), 128.08 (CH), 128.7 (CH), 129.01 (CH), 134.02 (C), 136.86 (C), 140.70 (C), 143.01 (C), 156.64 (C), 157.52 (C); FAB-MS (m/z) 481 $[M+H]^+$; HRMS calcd for $C_{32}H_{32}O_4$ 480.2301; found, 480.2250. (b) The compounds reported in this communication are stable at room temperature; the stability studies at higher temperature have not been done.
9. (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 **10a–d**, **11a–d**, and **12a–d** 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 for each dose. Parasitaemia levels were recorded from thin blood smears between days 4 and 28. The animals which did not develop patent infection till day 28 were recorded as cured.[11] Mice treated with β-arteether served as positive control. Multidrug-resistant *Plasmodium yoelii nigeriensis* used in this study is resistant to chloroquine, mefloquine and halofantrine.
10. (a) One hundred percent protection means none of the treated mice developed patent infection during the 28 days observation period and hence recorded as cured. Similarly, 20% protection means only one out of five mice was cured. (b)

One hundred percent suppression of parasitaemia means no parasites were detected in 50 oil immersion microscopic fields (parasites if at all present, are below the detection limit). The parasites present below the detection limit can multiply and eventually can be detected during observation on subsequent days. In such cases though the drug is providing near 100% suppression of the parasitaemia on day 4 but will not provide full protection to the treated mice in the 28 day survival assay.

11. Puri, S. K.; Singh, N. *Expl. Parasitol.* **2000**, *94*, 8.