Novel Bis- and Tris-1,2,4-trioxanes: Synthesis and Antimalarial Activity against Multidrug-Resistant *Plasmodium yoelii* in Swiss Mice[1]

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A new series of bis-1,2,4-trioxanes **12a**−**h**, **13a**−**h**, and **14a**−**h** and tris-1,2,4-trioxanes **12i**−**14i** were prepared and evaluated against multidrug-resistant *Plasmodium yoelii* in Swiss mice by oral route. Cyclopentane-based bis-trioxanes **12a**, **12b**, **12f**−**h** and cyclohexane-based bis-trioxanes **13a**, **13f**, and **13g** showed promising activity. All the tris-1,2,4-trioxanes were found to be inactive. Bis-trioxane **12a**, the most active compound of the series, provided 100% and 80% protection to infected mice at 48 and 24 mg/kg × 4 days, respectively. Clinically useful drug β-arteether provided 100% and 20% protection at similar doses.

Introduction

Despite comprehensive global efforts for eradication of malaria, about 40% of world population still is at risk of the disease. Of these 2.5 billion people at risk, more than 500 million become ill and more than 1 million, mostly children, die of malaria every year.[2] The rapid emergence of multidrug-resistant *P. falciparum* has further complicated the problem. Against this background, the isolation of artemisinin **1** as the active principle of the Chinese traditional drug against malaria, *Artemisia annua*, is a major breakthrough in malaria chemotherapy. Artemisinin and its derivatives, e.g., artemether **2**, arteether **3**, and artesunic acid **4** (Figure 1), are effective against both chloroquine-sensitive and chloroquine-resistant malaria.[3] The peroxide group present in the form of 1,2,4-trioxane is essential for the antimalarial activity of these compounds, and currently the focus is on structurally simple synthetic 1,2,4-trioxanes. We had earlier reported a photooxygenation route for the preparation of 1,2,4-trioxanes. The key steps of this method are (i) preparation of β-hydroxyhydroperoxides by photooxygenation of allylic alcohols and (ii) elaboration of these hydroperoxides into 1,2,4-trioxanes (Scheme 1).[4,5] Several trioxanes prepared by this method in our laboratory have shown promising antimalarial activity.[6] Inspired by the work of Posner et al. on artemisinin derived dimers, e.g., **5** and **6** (Figure 2), which have shown excellent antimalarial activitry,[7] we have extended our photooxygenation method for the preparation of bis-and tris-1,2,4-trioxanes. In this communication we report the synthesis and antimalarial assessment of **24** bis-trioxanes and **3** tris-trioxanes. To the best of our knowledge, this is the first report on antimalarial bis- and tris-trioxanes.

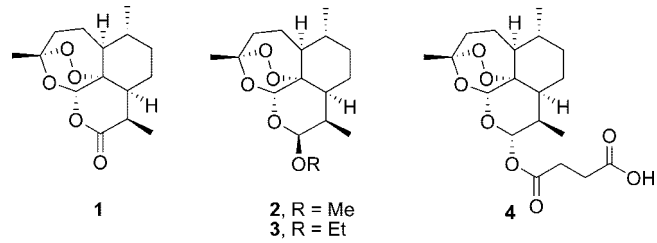
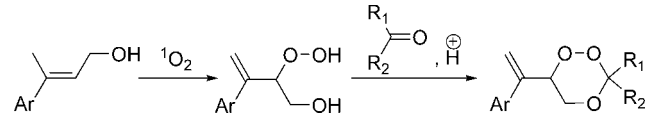


Figure 1. Artemisinin and its derivatives.

Scheme 1



Chemistry

Bis-1,2,4-trioxanes **12a**−**e**, **13a**−**e**, and **14a**−**e** were prepared by the procedure given in Scheme 2. Thus, the reaction of *p*-fluoroacetophenone with *p*-hydroxyacetophenone **7a** in refluxing in dimethyl sulfoxide furnished diketone **8a** (75% yield). A similar reaction of *p*-fluoroacetophenone with *m*-hydroxyacetophenone **7b**, quinol **7c**, 2,7-dihydroxynaphthalene **7d**, and 1,5-dihydroxynaphthalene **7e** furnished diketones **8b**−**e** in 62−78% yields, respectively (Table 1). Wittig reaction of diketone **8a** with triethylphosphonoacetate/sodium hydride furnished α,β-unsaturated diester **9a** (61% yield). A similar reaction of diketones **8b**−**e** furnished α,β-unsaturated diesters **9b**−**e** in 40−94% yields, respectively (Table 2). Reduction of α,β-unsaturated diester **9a** with $LiAlH_4$ furnished allylic alcohol **10a** (83% yield). A similar reduction of α,β-unsaturated diesters **9b**−**e** furnished allylic alcohols **10b**−**e** in 67−80% yields, respectively (Table 3). Photooxygenation of allylic alcohol **10a** furnished β-hydroxyhydroperoxide **11a**. Similar photooxygenation of allylic alcohols **10b**−**e** furnished β-hydroxyhydroperoxides **11b**−**e**. In situ acid-catalyzed condensation of β-hydroxyhydroperoxides **11a**−**e** with cyclopentanone furnished bis-1,2,4-trioxanes **12a**−**e** in 20−31% yields. A similar acid-catalyzed condensation of **11a**−**e** with cyclohexanone and

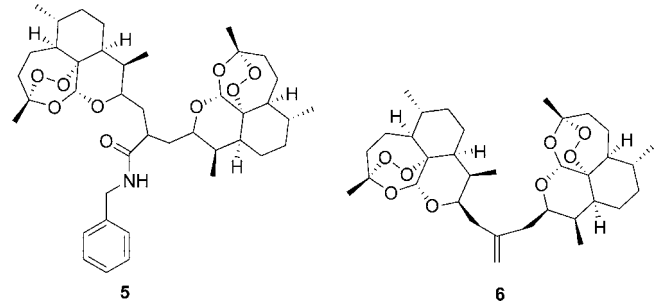


Figure 2. Artemisinin derived dimers.

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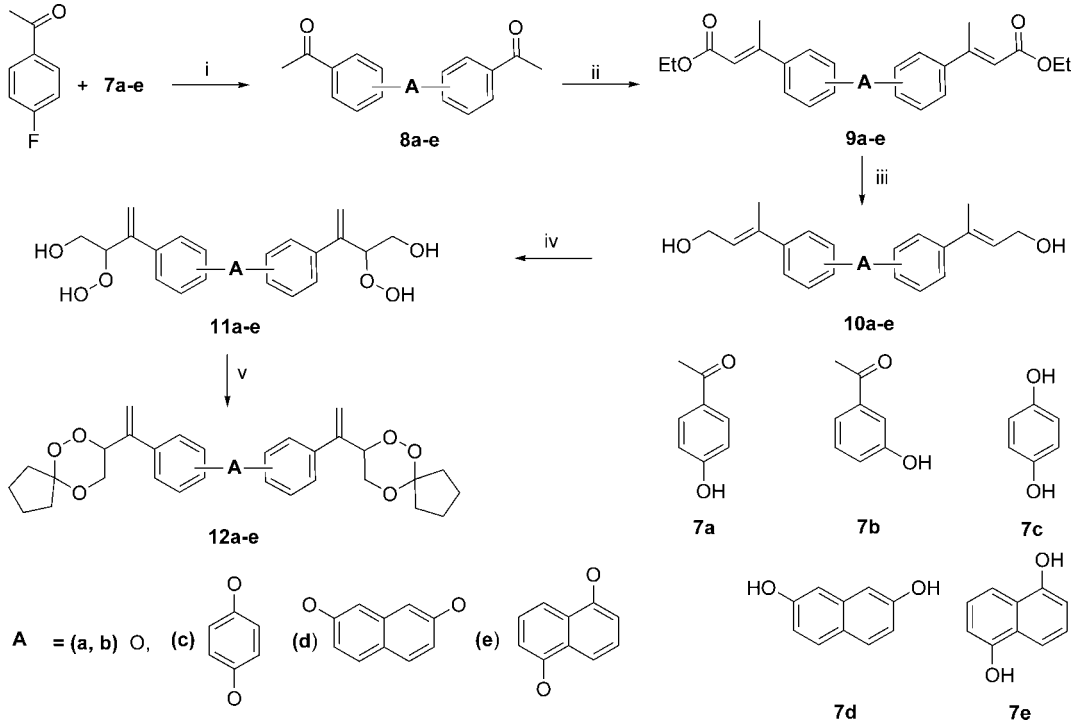
Scheme 2[a]



[a] Reagents and conditions: (i) K_2CO_3, dimethyl sulfoxide, reflux, 2 h; (ii) $(OEt)_2P(O)CH_2CO_2Et$, sodium hydride, THF, room temp, 6−21 h; (iii) $LiAlH_4$, THF, 0 °C, 1 h; (iv) $^1O_2$, organic solvent, −10 to 0 °C, 11−13 h; (v) cyclopentanone, CH_3CN, HCl, room temp, 1 h.

2-adamantanone furnished bis-1,2,4-trioxanes **13a**−**e** and **14a**−**e**, respectively, in 19−42% yields (Table 4).

Bis-1,2,4-trioxanes **12f**−**h**, **13f**−**h**, and **14f**−**h** were prepared by the procedure given in Scheme 3. Thus, the reaction of *p*-hydroxyacetophenone with epichlorohydrin **7f** at 115−130 °C furnished diketone **8f** (91% yield). A similar reaction of *p*-hydroxyacetophenone with 1,3-dibromopropane **7g** and 1,2-dibromoethane **7h** furnished diketones **8g** (98% yield) and **8h** (71% yield) (Table 1). Wittig reaction of diketone **8f** with triethylphosphonoacetate/sodium hydride furnished α,β-unsaturated diester **9f** (46% yield). A similar reaction of diketones **8g** and **8h** furnished α,β-unsaturated diesters **9g** (70% yield) and **9h** (46% yield) (Table 2). Reduction of α,β-unsaturated diester **9f** with $LiAlH_4$ furnished allylic alcohol **10f** (82% yield). A similar reduction of α,β-unsaturated diesters **9g** and **9h** furnished allylic alcohols **10g** (81% yield) and **10h** (73% yield), respectively (Table 3). Photooxygenation of allylic alcohol **10f** furnished β-hydroxyhydroperoxide **11f**. Similar photooxygenation of allylic alcohols **10g** and **10h** furnished β-hydroxyhydroperoxides **11g** and **11h**, respectively. In situ acid-catalyzed condensation of β-hydroxyhydroperoxides **11f**−**h** with cyclopentanone furnished bis-1,2,4-trioxanes **12f**−**h** in 16−40% yields. A similar acid-catalyzed condensation of **11f**−**h** with cyclohexanone and 2-adamantanone provided bis-1,2,4-trioxanes **13f**−**h** and **14f**−**h**, respectively, in 19−32% yields (Table 4).

Tris-1,2,4-trioxanes **12i**−**14i** were prepared by the procedure given in Scheme 4. Thus, the reaction of *p*-fluoroacetophenone with phluroglucinol **7i** in refluxing in dimethyl sulfoxide furnished triketone **8i** (27% yield). Wittig reaction of triketone **8i** with triethylphosphonoacetate/sodium hydride furnished α,β-unsaturated triester **9i** (61% yield). Reduction of α,β-unsaturated triester **9i** with $LiAlH_4$ furnished allylic alcohol **10i** (61% yield). Photooxygenation of allylic alcohol **10i** furnished β-hydroxyhydroperoxide **11i**, which on in situ acid-catalyzed condensation with cyclopentanone furnished tris-1,2,4-trioxane **12i** in 12% yield. Similar acid-catalyzed condensation of **11i** with cyclohexanone and 2-admantanone furnished tris-1,2,4-trioxanes **13i** and **14i** in 15% and 11% yields, respectively (Table 4).

Antimalarial Activity

All the new bis-and tris-trioxanes were evaluated for antimalarial activity against multidrug-resistant *P. yoelii* in Swiss mice by oral route.[8] In this model β-arteether provides 100% protection at 48 mg/kg × 4 days. Therefore, all the trioxanes were initially screened at 96 mg/kg × 4 days, twice the effective dose of β-arteether. Trioxanes **12a**, **12b**, **12f**−**h**, **13a**, **13f**, and **13g**, which provided 100% protection at this dose, were further screened at 48 mg/kg × 4 days. Trioxane **12a**, which showed 100% protection at 48 mg/kg × 4 days, was further tested at 24 mg/kg × 4 days. The results are summarized in Table 5.

Results and Discussion

Artemisinin derivatives artemether **2**, arteether **3**, and artesunic acid **4** are currently the drugs of choice for the treatment of malaria caused by multidrug-resistant *P. falciparum*. These drugs, however, have short half-lives and poor bioavailability when given by oral route. We have recently reported a series of lipophilic derivatives of dihydroartemisinin with excellent antimalarial activity by oral route.[10] More recently, Posner et al. have reported orally active artemisinin dimers with high order of activity.[7] Inspired by this work, we have prepared a series of bis-1,2,4-trioxanes and evaluated them against multidrug-resistant *P. yoelii* in mice by oral route. These bis-trioxanes have been prepared by a minor modification of our photooxygenation method, which we have used in the past for the synthesis of a large number of 6-arylvinyl substituted-1,2,4-trioxanes. In fact, structurally these bis-trioxanes are two 6-aryvinyl-1,2,4-trioxane moieties joined by a variety of linkers and their antimalarial activity shows a strong dependence on the nature of the linker.

As can be seen from Table 5, bis-trioxane **12a**, which has two 6-arylvinyl-1,2,4-trioxane moieties joined by an oxygen

Table 1. Diketones **8a**−**h** and Triketone **8i**

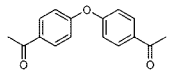
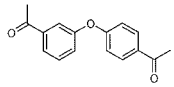
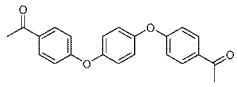
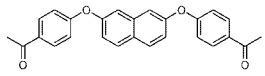
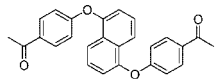
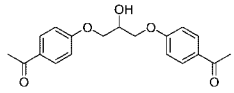
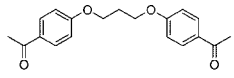
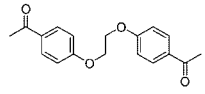
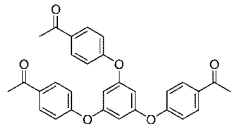
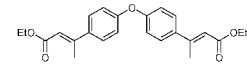
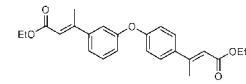
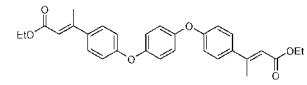
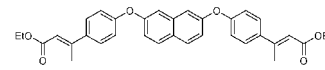
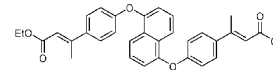
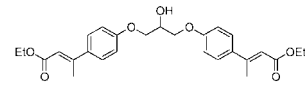
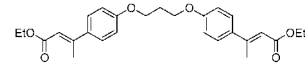
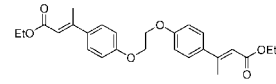
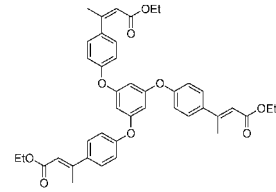
Compound no	Structure	mp (°C)	Yield (%)
8a		98-100	75
8b		65-67	78
8c		157-159	60
8d		135-137	77
8e		180-183	62
8f		102-104	91
8g		124-126	98
8h		161-162	71
8i		145-147	27

Table 2. α,β-Unsaturated Diesters **9a–h** and Triester **9i**

Compound no	Structure	mp (°C)	Yield (%)
9a		52-56	61
9b		Oil	60
9c		100-102	94
9d		58-59	71
9e		158-160	40
9f		Oil	46
9g		58-60	70
9h		115-117	46
9i		Oil	61

atom, is the most active compound of the series. It provided 100% and 80% protection at 48 and 24 mg/kg × 4 days, respectively, and therefore is slightly more active than arteether which provided only 20% protection at 24 mg/kg × 4 days. Bis-trioxanes **12b** and **12f**−**h**, which are structurally very close to trioxane **12a**, provided 100% protection only at 96 mg/kg × 4 days. Thus, not only the nature of the linker but also the point of linkage is all important for antimalarial activity. Cyclohexane-based bis-trioxanes **13a**, **13f**, and **13g** are other compounds that provided 100% protection at 96 mg/kg × 4 days. Surprisingly, all the admantane-based bis-trioxanes **14a**−**h** showed very poor activity. This is in sharp contrast with our earlier observation on 6-arylvinyl-1,2,4-trioxanes where only admantane-based trioxanes have shown antimalarial activity comparable with that of arteether;[11] the corresponding cyclopentane-and cyclohexane-based spiro trioxanes were comparatively less active.[12] The very high lipophilicity of admantane-based bis-trioxanes appears to be the main reason for their poor antimalarial activity. Similarly, the poor activity shown by cyclopentane-based bis-trioxanes **12c**−**e** could be due to their high lipophilicity.

Encouraged by the high order of activity shown by bis-trioxanes, we also prepared tris-trioxanes **12i**−**14i**. But none of these tris-trioxanes showed significant activity, the reason again could be their high lipophilicity.

Conclusion

We have successfully extended our photooxygenation method for the preparation of 1,2,4-trioxanes to the corresponding bis- and tris-trioxanes. While none of the tris-trioxanes showed significant activity, several bis-trioxanes showed promising activity. Bis-trioxane **12a**, the most active compound of the present series, showed 100% and 80% protection at 48 and 24 mg/kg × 4 days, respectively. Clinically used drug arteether showed only 20% protection at 24 mg/kg × 4 days.

Experimental Section

General. All glass apparatus were oven-dried prior to use. Melting points were taken in open capillaries on a Complab melting point apparatus and are presented uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR RXI spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Supercon Magnet DPX-200 or DRX-300 spectrometer (operating at 200 and 300 MHz, respectively, for ^{1}H and at 50 and 75 MHz, respectively, for ^{13}C) using $CDCl_3$ as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR, and $CDCl_3$ (δ 77.0 ppm) served as an internal standard in ^{13}C NMR. Chemical shifts are reported in parts per million. Splitting patterns are described as singlet (s), doublet (d), triplet (t), and multiplet (m). In NMR, numbering of atoms is presented according to the usual numbering in artemisinin as indicated in the text. Fast atom bombardment mass

Table 3. Allylic Alcohols **10a−i**

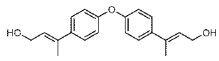
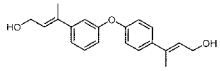
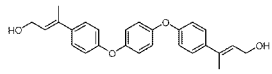
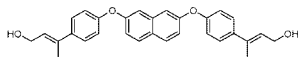
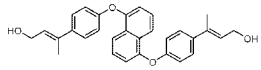
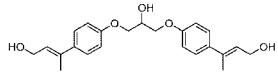
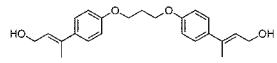
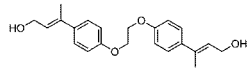
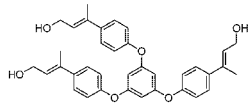
Compound no	Structure	mp (°C)	Yield (%)
10a		126-129	83
10b		Oil	80
10c		140-143	67
10d		120-122	77
10e		98-100	79
10f		Oil	82
10g		110-112	81
10h		156-160	73
10i		Oil	61

Table 4. Trioxanes **12a−i**, **13a−i**, and **14a−i**

compd	mp (°C)	yield (%)
12a	78−80	31
12b	oil	28
12c	115−120	20
12d	oil	23
12e	148−150	30
12f	100−103	21
12g	120−122	40
12h	158−160	16
13a	98−100	39
13b	oil	29
13c	135−138	20
13d	oil	32
13e	158−160	42
13f	oil	23
13g	118−120	32
13h	145−147	22
14a	60−63	19
14b	45−50	20
14c	55−60	26
14d	oil	38
14e	155−157	34
14f	oil	19
14g	114−116	19
14h	156−158	19
12i	oil	12
13i	oil	15
14i	oil	11

spectra (FAB-MS) were obtained on JEOL SX-102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Electrospray mass spectrometry (ES-MS) were recorded on a MICROMASS QUATTRO II triple quadruple mass spectrometer. High resolution electron impact mass spectra (HR-EIMS) were obtained on JEOL MS route 600H instrument. Elemental analyses were performed on Vario EL-III CHNS analyzer (Germany), and values were within ±0.4% of the calculated values except where noted. Column chromatography was performed over Merck silica gel (particle size, 60−120 mesh), procured from Qualigens (India), and flash silica gel (particle size, 230−400 mesh). All chemicals and reagents were obtained from Aldrich, Lancaster (England), or Spectrochem (India) and were used without further purification. The log *P* values of the compounds were calculated using Chem Draw Ultra 7.0 software.

General Procedure for Synthesis of Diketones 8a−e and Triketone 8i. Preparation of 8a. To a stirred mixture of *p*-hydroxyacetophenone **7a** (15 g, 110 mmol) in dimethyl sulfoxide (50 mL) were added *p*-fluoroacetophenone (15.22 g, 110 mmol, 1 equiv) and anhydrous K_2CO_3 (22.5 g, 160 mmol, 1.5 equiv), and the reaction mixture was refluxed for 2 h with continuous stirring. The reaction mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ether (3 × 200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to furnish a crude product, which on crystallization in a mixture of benzene and hexane (3:7) furnished diketone **8a** (21 g, 75% yield) as a white solid, mp 98−100 °C.

Compounds **8b−e** were prepared by the above procedure by condensing *p*-fluoroacetophenone with *m*-hydroxyacetophenone **7b**, quinol **7c**, 2,7-dihydroxynaphthalene **7d**, and 1,5-dihydroxynaphthalene **7e**, respectively. Compound **8i** was prepared by condensing *p*-fluoroacetophenone with phluroglucinol **7i.**

1-[4-(4-Acetylphenoxy)phenyl]ethanone (8a). Yield 75%, white solid, mp 98−100 °C; IR (KBr, cm^{-1}) 1678; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 6H), 7.06 (d, 4H, Ar, J = 8.8 Hz), 7.97 (d, 4H, Ar, J = 8.8 Hz); FAB-MS (*m*/*z*) 255 $[M + H]^+$.

1-[4-(3-Acetylphenoxy)phenyl]ethanone (8b). Yield 78%, white solid, mp 65−67 °C; IR (KBr, cm^{-1}) 1675; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 3H), 2.59 (s, 3H), 7.01 (d, 2H, Ar, J = 8.9 Hz), 7.25−7.29 (m, 1H, Ar), 7.50 (t, 1H, Ar, J = 8 Hz), 7.64 (t, 1H, Ar, J = 1.9 Hz), 7.77 (dd, 1H, Ar, J = 6.6 and 1.2 Hz), 7.96 (d, 2H, Ar, J = 8.9 Hz); FAB-MS (*m*/*z*) 255 $[M + H]^+$.

1-{4-[4-(4-Acetylphenoxy)phenoxy]phenyl}ethanone (8c). Yield 60%, white solid, mp 157−159 °C; IR (KBr, cm^{-1}) 1671; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 6H), 7.03 (d, 4H, Ar, J = 8.8 Hz), 7.11 (s, 4H, Ar), 7.97 (d, 4H, Ar, J = 8.8 Hz); FAB-MS (*m*/*z*) 347 $[M + H]^+$.

1-{4-[7-(4-Acetylphenoxy)naphthalen-2-yloxy]phenyl}ethanone (8d). Yield 77%, white solid, mp 135−137 °C; IR (KBr, cm^{-1}) 1673; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 6H,), 7.08 (d, 4H, Ar, J = 8.8 Hz), 7.23 (dd, 2H, J = 8.9 and 2.3 Hz), 7.33 (d, 2H, Ar, J = 2.1 Hz), 7.89 (d, 2H, Ar, J = 8.9 Hz), 7.97 (d, 4H, Ar, J = 8.8 Hz); FAB-MS (*m*/*z*) 397 $[M + H]^+$.

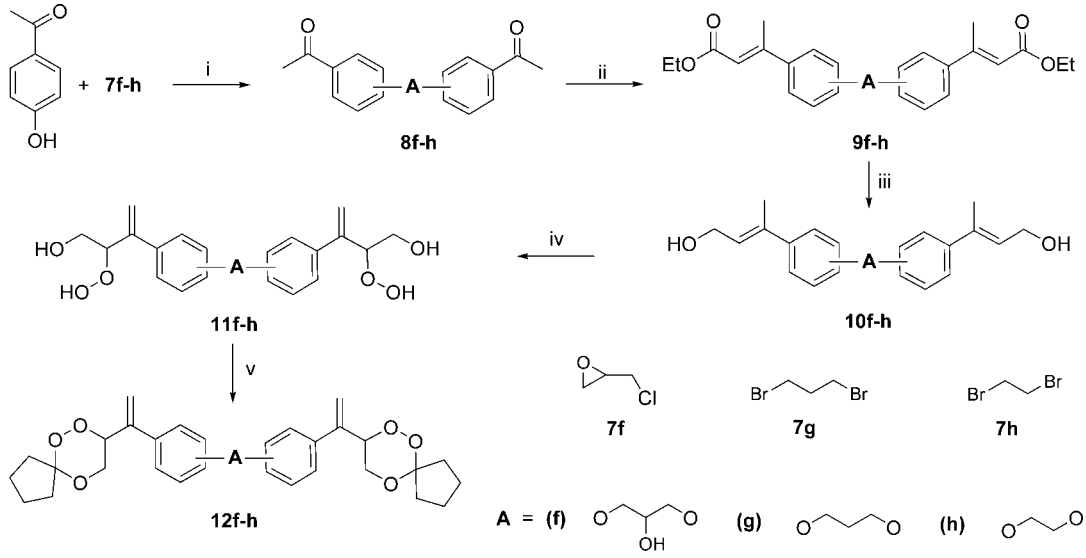
1-{4-[5-(4-Acetylphenoxy)naphthalen-1-yloxy]phenyl}ethanone (8e). Yield 62%, yellow solid, mp 180−183 °C; IR (KBr, cm^{-1}) 1680; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 6H), 7.07 (d, 4H, Ar, J = 8.6 Hz), 7.16 (d, 2H, Ar, J = 7.5 Hz), 7.44−7.49 (m, 2H, Ar), 7.95 (d, 2H, Ar, J = 8.8 Hz), 7.98 (d, 4H, Ar, J = 8.7 Hz); FAB-MS (*m*/*z*) 397 $[M + H]^+$.

1-{4-[3,5-Bis(4-acetylphenoxy)phenoxy]phenyl}ethanone (8i). Yield 27%, white solid, mp 145−147 °C; IR (KBr, cm^{-1}) 1674; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.57 (s, 9H), 6.54 (s, 3H, Ar), 7.07 (d, 6H, Ar, J = 8.6 Hz), 7.96 (d, 6H, Ar, J = 8.6 Hz); FAB-MS (*m*/*z*) 481 $[M + H]^+$.

General Procedure for Preparation of Diketones 8f−h. Preparation of 8f. To a stirred mixture of epichlorohydrin (15 g, 160 mmol) and *p*-hydroxyacetophenone (48.5 g, 360 mmol, 2.2 equiv) was added anhydrous K_2CO_3 (49.21 g, 360 mmol, 2.2 equiv), and the reaction mixture was heated at 115−130 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ether (3 × 200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to furnish a crude product, which on column chromatography over silica gel (60−120 mesh) using EtOAc/hexane (10:90) as eluant furnished diketone **8f** (48.40 g, 91% yield) as a white solid, mp 102−104 °C.

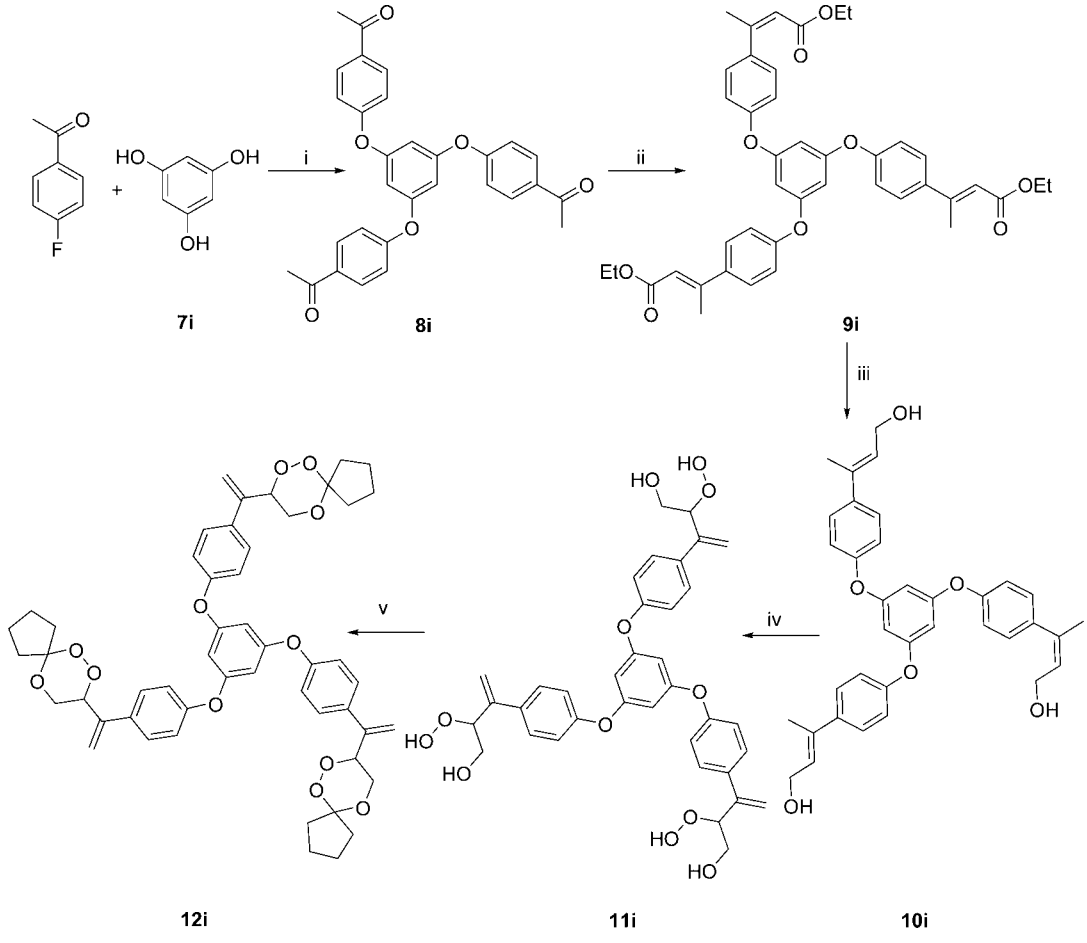
Compounds **8g** and **8h** were prepared by the above procedure by replacing epichlorohydrin **7f** with 1,3-dibromopropane **7g** and 1,2-dibromoethane **7h**, respectively.

Scheme 3[a]



[a] Reagents and conditions: (i) K_2CO_3, 115−130 °C, 2 h; (ii) $(OEt)_2P(O)CH_2CO_2Et$, sodium hydride, THF, room temp, 21−24 h; (iii) $LiAlH_4$, THF, 0 °C, 1 h; (iv) $^1O_2$, organic solvent, −10 to 0 °C, 10−11 h; (v) cyclopentanone, CH_3CN, HCl, room temp, 1 h.

Scheme 4[a]



[a] Reagents and conditions: (i) K_2CO_3, dimethyl sulfoxide, reflux, 6 h; (ii) $(OEt)_2P(O)CH_2CO_2Et$, sodium hydride, THF, room temp, 26 h; (iii) $LiAlH_4$, THF, 0 °C, 1 h; (iv) $^1O_2$, organic solvent, −10 to 0 °C, 13 h; (v) cyclopentanone, CH_3CN, HCl, room temp, 1 h.

1-{4-[3-(4-Acetylphenoxy)-2-hydroxypropoxy]phenyl}ethanone (8f). Yield 91%, white solid, mp 102−104 °C; IR (KBr, cm^{-1}) 1666, 3389; ^1H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 6H), 2.96 (bs, 1H), 4.20−4.29 (m, 4H), 4.43−4.48 (m, 1H), 6.97 (d, 4H, Ar, J = 9 Hz), 7.93 (d, 4H, Ar, J = 8.9 Hz); ESI 329 $[M + H]^+$.

1-{4-[3-(4-Acetylphenoxy)propoxy]phenyl}ethanone (8g). Yield 98%, white solid, mp 124−126 °C; IR (KBr, cm^{-1}) 1667; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25−2.33 (m, 2H), 2.51 (s, 6H), 4.21 (t, 4H, J = 6 Hz), 6.92 (d, 4H, Ar, J = 8.8 Hz), 7.89 (d, 4H, Ar, J = 8.8 Hz); ESI 313 $[M + H]^+$.

Table 5. Blood Schizontocidal Activity of Trioxanes **12a−i**, **13a−i**, and **14a−i** against Multidrug-Resistant *P.yoelii* in Swiss Mice via Oral Route[c]

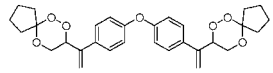
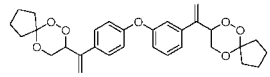
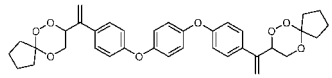
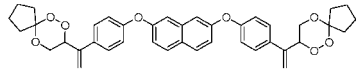
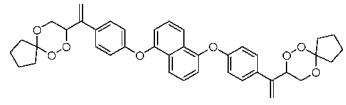
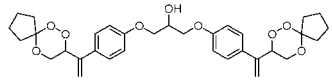
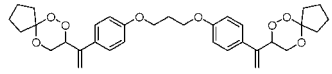
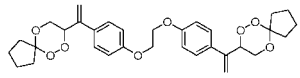
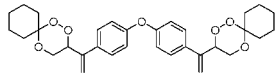
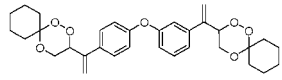
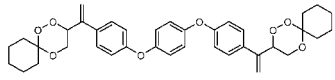
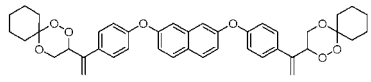
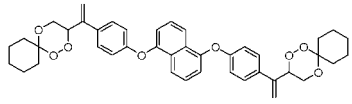
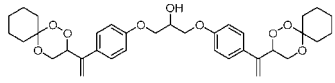
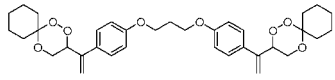
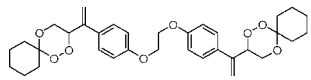
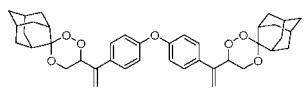
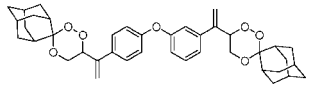
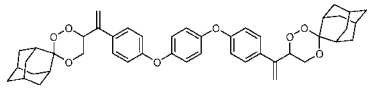
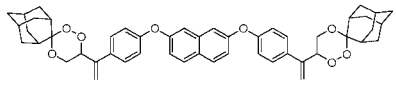
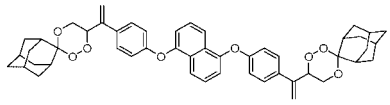
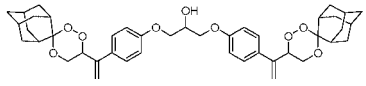
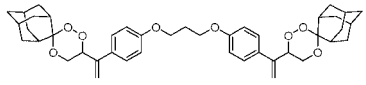
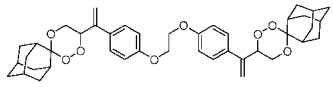
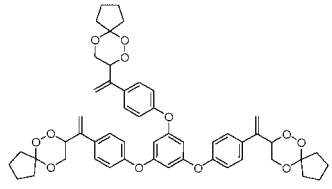
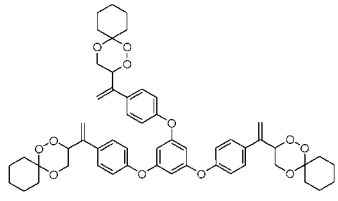
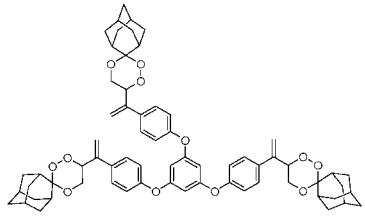
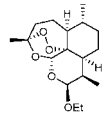
Comp. No.	Structure	*Log P*	Dose mg/kg x 4 days	% supp. on day-4[a,b]	Mean survival Time	Cured**/ Treated
12a		6.70	96	100	>28*	5/5
			48	100	>28	5/5
			24	100	>21.2 ± 5.2	4/5
12b		6.70	96	100	>28	5/5
			48	100	12.2 ± 3.5	0/5
12c		8.24	96	50.83	7.6 ± 0.74	0/5
12d		9.24	96	42.29	7.8 ± 0.37	0/5
12e		9.24	96	40.05	8.4 ± 0.98	0/5
12f		6.17	96	100	>28	5/5
			48	74.32	9.60 ± 0.98	0/5
12g		6.81	96	100	>28	5/5
			48	100	12.8 ± 1.02	0/5
12h		6.70	96	100	>28	5/5
			48	87.76	12.2 ± 1.53	0/5
13a		7.54	96	100	>28	5/5
			48	100	11.8 ± 1.24	0/5
13b		7.54	96	76.79	10.0 ± 0.95	0/5
13c		9.07	96	47.33	8.6 ± 0.68	0/5
13d		10.07	Insoluble in vehicle oil			
13e		10.07	96	16.36	8.2 ± 0.37	0/5
13f		7.0	96	100	>28	5/5
			48	75.86	8.0 ± 0.77	0/5
13g		7.64	96	100	>28	5/5
			48	87.47	10.8 ± 1.96	0/5
13h		7.54	96	86.29	10.6 ± 1.83	0/5
14a		8.81	96	36.74	7.2 ± 0.20	0/5

Table 5. Continued

Comp. No.	Structure	*Log P*	Dose mg/kg x 4 days	% supp. on day-4[a,b]	Mean survival Time	Cured**/ Treated
14b		8.81	96	07.16	7.6 ± 0.24	0/5
14c		-	96	38.46	9.0 ± 0.84	0/5
14d		-	96	36.07	7.4 ± 0.24	0/5
14e		-	96	12.27	7.4 ± 0.24	0/5
14f		-	96	26.76	8.6 ± 0.68	0/5
14g		-	96	32.54	7.4 ± 0.24	0/5
14h		-	96	66.39	7.6 ± 0.40	0/5
12i		-	96	3.22	7.2 ± 0.37	0/5
13i		-	96	26.37	8.4 ± 0.93	0/5
14i		-	96	5.47	7.4 ± 0.24	0/5
3		3.84	48	100	>28	5/5
			24	100	-	1/5
	Vehicle control	-	-	-	7.3 ± 0.18	0/20

[a] Percent suppression = $[(C - T)/C] \times 100$, where C is parasitaemia in control group and T is parasitaemia in treated group. [b] 100% suppression of parasitaemia means no parasites were detected in 50 oil immersion fields during microscopic observation.[9] [c] Asterisk symbols represent the following: (∗) observation was discontinued after day 28; (∗∗) mice that did not develop patent infection till day 28 were recorded as cured.

1-{4-[2-(4-Acetylphenoxy)ethoxy]phenyl}ethanone (8h). Yield 71%, white solid, mp 161−162 °C; IR (KBr, cm^{-1}) 1673; ^1H NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 6H), 4.41 (s, 4H), 6.98 (d, 4H, Ar, J = 8.9 Hz), 7.94 (d, 4H, Ar, J = 8.9 Hz); ESI 299 $[M + H]^+$.

General Procedure for Preparation of Esters 9a−i. Preparation of 9a. To a stirred slurry of sodium hydride (60% dispersion in mineral oil, 6.08 g, 250 mmol, 4 equiv), in dry THF (20 mL) at 0 °C under nitrogen atmosphere was added a solution of triethylphosphonoacetate (34.07 g, 152 mmol, 4 equiv) in dry THF (50 mL). The reaction mixture was stirred at room temperature for 1 h. The diketone **8a** (15 g, 3.81 mmol), dissolved in dry THF (100 mL), was added to the reaction mixture dropwise, and the reaction mixture was further stirred at room temperature for 6 h. The reaction mixture was diluted with water (100 mL) and extracted with ether (3 × 200 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography over silica gel (60−120 mesh) using EtOAc/hexane (1:99) as eluant to furnish diester **9a** (14 g, 61% yield) as a white solid, mp 52−56 °C.

Compounds **9b−h** were prepared by the above procedure from diketones **8b−h**, and **9i** was prepared from triketone **8i.**

3-{4-[4-(2-Ethoxycarbonyl-1-methylvinyl)phenoxy]phenyl}but-2-enoic Acid Ethyl Ester (9a). Yield 61%, white solid, mp 52−56 °C; IR (KBr, cm^{-1}) 1711; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, 6H, J = 7.2 Hz), 2.58 (d, 6H, J = 1 Hz), 4.23(q, 4H, J = 7.1 Hz), 6.14 (d, 2H, J = 1.2 Hz), 7.02 (d, 4H, Ar, J = 8.7 Hz), 7.49 (d, 4H, Ar, J = 8.7 Hz); FAB-MS (m/z) 395 $[M + H]^+$.

3-{4-[3-(2-Ethoxycarbonyl-1-methylvinyl)phenoxy]phenyl}-but-2-enoic Acid Ethyl Ester (9b). Yield 60%, oil; IR (neat, cm^{-1}) 1718; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28−1.33 (m, 6H), 2.54 (s, 3H), 2.57 (s, 3H), 4.17−4.24 (m, 4H), 6.12 (s, 1H), 6.13 (s, 1H), 6.98 (d, 2H, Ar, J = 8.7 Hz), 7.02 (d, 1H, Ar, J = 1.5 Hz), 7.16 (s, 1H, Ar), 7.25 (d, 1H, Ar, J = 7.8 Hz), 7.34 (dd, 1H, Ar, J = 7.8 and 1.5 Hz), 7.47 (d, 2H, Ar, J = 8.7 Hz); FAB-MS (m/z) 395 $[M + H]^+$.

3-(4-{4-[4-(2-Ethoxycarbonyl-1-methylvinyl)phenoxy]phenoxy}-phenyl)but-2-enoic Acid Ethyl Ester (9c). Yield 94%, white solid, mp 100−102 °C; IR (KBr, cm^{-1}) 1704; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, 6H, J = 7.1 Hz), 2.58 (d, 6H, J = 1 Hz), 4.23 (q, 4H, J = 7.1 Hz), 6.13 (d, 2H, J = 1.1 Hz), 7.0 (d, 4H, Ar, J = 8.8 Hz), 7.06 (s, 4H, Ar), 7.48 (d, 4H, Ar, J = 8.8 Hz); FAB-MS (m/z) 487 $[M + H]^+$.

3-(4-{7-[4-(2-Ethoxycarbonyl-1-methylvinyl)phenoxy]naphthalen-2-yloxy}phenyl)but-2-enoic Acid Ethyl Ester (9d). Yield 71%, white solid, mp 58−59 °C; IR (KBr, cm^{-1}) 1704; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 6H, J = 7.1 Hz), 6.12 (d, 6H, J = 1.1 Hz), 4.21 (q, 4H, J = 7.1 Hz), 6.12 (d, 2H, J = 1.2 Hz), 7.04 (dd, 4H, Ar, J = 6.8 and 2 Hz), 7.17−7.24 (m, 4H, Ar), 7.48 (dd, 4H, Ar, J = 6.9 and 1.9 Hz), 7.83 (d, 2H, Ar, J = 8.9 Hz); FAB-MS (m/z) 537 $[M + H]^+$.

3-(4-{7-[4-(2-Ethoxycarbonyl-1-methylvinyl)phenoxy]naphthalen-2-yloxy}phenyl)but-2-enoic Acid Ethyl Ester (9e). Yield 40%, yellow solid, mp 158−160 °C; IR (KBr, cm^{-1}) 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 6H, J = 7.1 Hz), 2.60 (d, 6H, J = 1 Hz), 4.24 (q, 4H, J = 7.1 Hz), 6.15 (d, 2H, J = 1 Hz), 7.04−7.09 (m, 6H, Ar), 7.41−7.52 (m, 6H, Ar), 7.98 (d, 2H, Ar, J = 8.4 Hz); FAB-MS (m/z) 537 $[M + H]^+$

3-(4-{3-[4-(2-Ethoxycarbonyl-1-methylvinyl)phenoxy]-2-hydroxypropoxy}phenyl)but-2-enoic Acid Ethyl Ester (9f). Yield 46%, oil; IR (neat, cm^{-1}) 1704, 3435; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 6H, J = 7.1 Hz), 2.57 (d, 6H, J = 1 Hz), 2.71 (bs, 1H), 4.18−4.26 (m, 8H), 4.41−4.47 (m, 1H), 6.12 (d, 2H, J = 1.1 Hz), 6.94 (d, 4H, Ar, J = 8.8 Hz), 7.46 (d, 4H, Ar, J = 8.9 Hz); ESI 486 $[M + NH_4]^+$.

3-(4-{3-[4-(2-Ethoxycarbonyl-1-methylvinyl)phenoxy]propoxy}-phenyl)but-2-enoic Acid Ethyl Ester (9g). Yield 70%, white solid, mp 58−60 °C; IR (KBr, cm^{-1}) 1719; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 6H, J = 7.1 Hz), 2.24−2.32 (m, 2H), 2.57 (d, 6H, J = 1.2 Hz), 4.17−4.25 (m, 8H), 6.12 (d, 2H J = 1 Hz), 6.91 (d, 4H, Ar, J = 8.8 Hz), 7.45 (d, 4H, Ar, J = 8.8 Hz); ESI 475 $[M + Na]^+$.

3-(4-{2-[4-(2-Ethoxycarbonyl-1-methylvinyl)phenoxy]ethoxy}-phenyl)but-2-enoic Acid Ethyl Ester (9h). Yield 46%, white solid, mp 115−117 °C; IR (KBr, cm^{-1}) 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 6H, J = 7.1 Hz), 2.59 (d, 6H, J = 1 Hz), 4.23 (q, 4H, J = 7.1 Hz), 4.38 (s, 4H), 6.14 (d, 2H, J = 1.1 Hz), 6.97 (d, 4H, Ar, J = 8.9 Hz), 7.49 (d, 4H, Ar, J = 8.9 Hz); ESI 461 $[M + Na]^+$.

3-(4-{3,5-Bis[4-(2-ethoxycarbonyl-1-methylvinyl)phenoxy]phenoxy}phenyl)but-2-enoic Acid Ethyl Ester (9i). Yield 61%, oil; IR (neat, cm^{-1}) 1711; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, 9H, J = 6 Hz), 2.56 (s, 9H), 4.22(q, 6H, J = 9 Hz), 6.10 (s, 3H, Ar), 6.44 (s, 3H, Ar), 7.02 (d, 6H, Ar, J = 9 Hz), 7.49 (d, 6H, Ar, J = 9 Hz); FAB-MS (m/z) 691 $[M + H]^+$.

General Procedure for Preparation of Allylic Alcohols 10a−i. Preparation of 10a. To a stirred slurry of $LiAlH_4$ (2.9 g, 80 mmol, 2 equiv) in dry THF (100 mL) at 0 °C was added diester **9a** (15 g, 3.81 mmol) in dry THF (100 mL) dropwise. The reaction mixture was stirred for 2 h at 0 °C. The reaction was quenched with 5% aqueous NaOH (5 mL) and water (10 mL). The organic layer was decanted, dried over anhydrous Na_2SO_4, and concentrated to furnish a crude product, which on crystallization in $CHCl_3$ furnished compound **10a** (9.10 g, 83% yield) as white solid, mp 126−129 °C.

Compounds **10b−h** were prepared by the above procedure from diesters **9b−h**, and **10i** was prepared from triester **9i.**

3-{4-[4-(3-Hydroxy-1-methylpropenyl)phenoxy]phenyl}but-2-ene-1-ol (10a). Yield 83%, white solid, mp 126−129 °C; IR (KBr, cm^{-1}) 3457; ^1H NMR (200 MHz, $CDCl_3$) δ 2.05 (d, 6H, J = 1 Hz), 3.5 (bs, 2H), 4.32 (d, 4H, J = 6.6 Hz), 5.89−5.96 (m, 2H,), 6.95 (d, 4H, Ar, J = 8.8 Hz), 7.38 (d, 4H, Ar, J = 8.8 Hz); FAB-MS (m/z) 311 $[M + H]^+$.

3-{4-[3-(3-Hydroxy-1-methylpropenyl)phenoxy]phenyl}but-2-ene-1-ol (10b). Yield 80%, oil; IR (neat, cm^{-1}) 3450; ^1H NMR (300 MHz, $CDCl_3$) δ 2.0 and 2.03 (2 × s, 6H), 4.04 (bs, 2H), 4.28−4.31 (m, 4H), 5.92−5.98 (m, 2H), 6.84−6.93 (m, 3H, Ar), 7.06 (s, 1H, Ar), 7.15 (d, 1H, Ar, J = 7.8 Hz), 7.25 (d, 1H, Ar, J = 7.8 Hz), 7.36 (d, 2H, Ar, J = 8.7 Hz); FAB-MS (m/z) 311 $[M + H]^+$.

3-(4-{4-[4-(3-Hydroxy-1-methylpropenyl)phenoxy]phenoxy}-phenyl)but-2-en-1-ol (10c). Yield 67%, white solid, mp 140−143 °C; IR (KBr, cm^{-1}) 3404; ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (s, 6H), 4.15 (bs, 4H), 4.71 (bs, 2H), 5.86 (t, 2H, J = 5 Hz), 6.96 (d, 4H, Ar, J = 8.6 Hz), 7.06 (s, 4H, Ar), 7.43 (d, 4H, Ar, J = 8.6 Hz); FAB-MS (m/z) 403 $[M + H]^+$.

3-(4-{7-[4-(3-Hydroxy-1-methylpropenyl)phenoxy]naphthalen-2-yloxy}phenyl)but-2-en-1-ol (10d). Yield 77%, white solid, mp 120−122 °C; IR (KBr, cm^{-1}) 3505; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 6H), 4.38 (d, 4H, J = 6.7 Hz), 5.96−6.01 (m, 2H), 7.03 (d, 4H, Ar, J = 8.8 Hz), 7.15−7.21 (m, 4H, Ar), 7.42 (d, 4H, Ar, J = 8.7 Hz), 7.81 (d, 2H, Ar, J = 8.8 Hz); FAB-MS (m/z) 453 $[M + H]^+$.

3-(4-{5-[4-(3-Hydroxy-1-methylpropenyl)phenoxy]naphthalen-1-yloxy}phenyl)but-2-en-1-ol (10e). Yield 79%, yellow solid, mp 98−100 °C; IR (KBr, cm^{-1}) 3640; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (bs, 2H), 1.95 (s, 6H), 4.17 (d, 4H, J = 6.6 Hz), 5.78−5.83 (m, 2H), 6.86 (d, 6H, Ar, J = 8.5 Hz), 7.27−7.33 (m, 6H, Ar), 7.8 (d, 2H, Ar, J = 8.6 Hz); FAB-MS (m/z) 453 $[M + H]^+$.

3-(4-{2-Hydroxy-3-[4-(3-hydroxy-1-methylpropenyl)phenoxy]-propoxy}phenyl)but-2-en-1-ol (10f). Yield 82%, oil; IR (neat, cm^{-1}) 3406, 3435; ^1H NMR (300 MHz, MeOD) δ 2.02 (s, 6H), 4.06−4.16 (m, 5H), 4.28 (d, 4H J = 6.6 Hz), 5.86−5.91 (m, 2H), 6.91 (d, 4H, Ar, J = 8.8 Hz), 7.35 (d, 4H, Ar, J = 12.3 Hz); FAB-MS (m/z) 385 $[M + H]^+$.

3-(4-{3-[4-(3-Hydroxy-1-methylpropenyl)phenoxy]propoxy}phenyl)but-2-en-1-ol (10g). Yield 81%, white solid, mp 110−112 °C; IR (KBr, cm^{-1}) 3446; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (bs, 2H), 2.07 (d, 6H, J = 0.6 Hz), 2.23−2.31 (m, 2H), 4.18 (t, 4H, J = 6.1 Hz), 4.36 (d, 4H J = 6.8 Hz), 5.90−5.96 (m, 2H), 6.88 (d, 4H, Ar, J = 8.8 Hz), 7.35 (d, 4H, Ar, J = 8.8 Hz); ESI 369 $[M + NH_4]^+$.

3-(4-{2-[4-(3-Hydroxy-1-methylpropenyl)phenoxy]ethoxy}phenyl)but-2-en-1-ol (10h). Yield 73%, white solid, mp 156−160 °C; IR (KBr, cm^{-1}) 3337; ^1H NMR (300 MHz, DMSO) δ 1.95 (s, 6H), 4.13 (t, 4H, J = 5.8 Hz), 4.30 (s, 4H), 4.68 (t, 2H, J = 5.4

Hz), 5.80−5.85 (m, 2H), 6.94 (d, 4H, Ar, J =8.8 Hz), 7.36 (d, 4H, Ar, J = 8.8 Hz); ESI 355 $[M + H]^+$.

3-(4-{3,5-Bis[4-(3-hydroxy-1-methylpropenyl)phenoxy]phenoxy}-phenyl)but-2-en-1-ol (10i). Yield 61%, oil; IR (neat, cm^{-1}) 3440; ^1H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, 9H), 2.25 (bs, 3H), 4.34 (d, 6H, J= 6.6 Hz), 5.90−5.94 (m, 3H), 6.36 (s, 3H, Ar), 6.98 (dd, 6H, Ar, J = 8.7 and 3 Hz), 7.38 (dd, 6H, Ar, J = 8.8 and 2.3 Hz); FAB-MS (m/z) 565 $[M + H]^+$.

General Procedure for Preparation of 1,2,4-Trioxanes. Preparation of 12a. A solution of allylic alcohol **10a** (1 g, 3.22 mmol) and methylene blue (5 mg) in a mixture of acetonitrile (100 mL), THF (100 mL), and $CHCl_3$ (50 mL) was irradiated with a 500 W tungsten−halogen lamp at −10 to 0 °C, while oxygen gas was bubbled into the reaction mixture for 11 h. The reaction mixture was concentrated on a rotatory evaporator at room temperature and then dissolved in acetonitrile (100 mL). Cyclopentanone (1.62 mL, 19.3 mmol, 6 equiv) and HCl (0.5 mL) were added to the reaction mixture, and it was stirred for 1 h at room temperature. The reaction mixture was concentrated and the crude product was purified by column chromatography over silica gel (60−120 mesh) using EtOAc/hexane (1:99) as eluant to furnish compound **12a** (500 mg, 31% yield) as white solid, mp 78−80 °C.

Trioxanes **12b**−**i**, were prepared from allylic alcohols **10b**−**i** using the above procedure, and trioxanes **13a**−**i** and **14a**−**i** were prepared from allylic alcohols **10a**−**i** by replacing cyclopentanone with cyclohexanone and 2-admantanone, respectively.

Trioxane 12a. Yield 31%, white solid, mp 78−80 °C; IR (KBr, cm^{-1}) 1596; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68−1.96 (m, 14H), 2.48−2.56 (m, 2H), 3.87 (d, 4H, J = 6.5 Hz), 5.27−5.31 (m, 4H), 5.49 (s, 2H), 7.00 (d, 4H, Ar, J = 8.7 Hz), 7.39 (d, 4H, Ar, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.38 (2 × CH_2), 24.79 (2 × CH_2), 32.81 (2 × CH_2), 37.04 (2 × CH_2), 65.02 (2 × CH_2), 80.27 (2 × CH), 114.60 (2 × C), 116.02 (2 × CH_2), 118.88 (4 × CH), 127.92 (4 × CH), 133.78 (2 × C), 142.45 (2 × C), 156.96 (2 × C); FAB-MS (m/z) 507 $[M + H]^+$. Anal. Calcd for $C_{30}H_{34}O_7$: C, 71.13; H, 6.76. Found: C, 71.25; H, 6.82.

Trioxane 12b. Yield 28%, oil; IR (neat, cm^{-1}) 1505; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69−1.95 (m, 14H), 2.48−2.56 (m, 2H), 3.86−3.90 (m, 4H), 5.26−5.36 (m, 4H), 5.50 and 5.53 (2 × s, 2H), 6.97−7.01 (m, 3H, Ar), 7.11−7.12 (m, 1H, Ar), 7.17−7.20 (m,1H, Ar), 7.31−7.43 (m, 3H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.51 (2 × CH_2), 24.92 (2 × CH_2), 32.94 (2 × CH_2), 37.12 (CH_2), 37.16 (CH_2), 65.07 (CH_2), 65.14 (CH_2), 80.41 (CH), 80.44 (CH), 114.70 (2 × C), 116.03 (CH_2), 116.05 (CH_2), 117.32 (CH), 117.44 (CH), 118.75 (CH), 118.86 (CH), 121.81 (C), 128.06 (CH), 130.07 (CH), 133.78 (CH), 140.67 (C), 142.64 (C), 142.81 (C), 157.13 (C), 157.32 (C); FAB-MS (m/z) 507 $[M + H]^+$. Anal. Calcd for $C_{30}H_{34}O_7$: C, 71.13; H, 6.76. Found: C, 71.23; H, 6.93. HRMS calcd for $C_{30}H_{34}O_7$ 506.2305; found, 506.2317.

Trioxane 12c. Yield 20%, white solid, mp 115−120 °C; IR (KBr, cm^{-1}) 1509; ^1H NMR (300 MHz, $CDCl_3$) δ 173−1.96 (m, 14H), 2.50−2.59 (m, 2H), 3.89 (d, 4H J = 6.3 Hz), 5.29−5.33 (m, 4H), 5.50 (s, 2H), 7.0 (d, 4H, Ar, J = 8.8 Hz), 7.06 (s, 4H, Ar), 7.41 (d, 4H, Ar, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.56 (2 × CH_2), 24.91 (2 × CH_2), 32.99 (2 × CH_2), 37.22 (2 × CH_2), 65.22 (2 × CH_2), 80.49 (2 × CH), 114.79 (2 × C), 116.01 (2 × CH_2), 118.28 (4 × CH), 120.93 (4 × CH), 128.07 (4 × CH), 133.52 (2 × C), 142.69 (2 × C), 152.71 (2 × C), 158.03 (2 × C); FAB-MS (m/z) 599 $[M + H]^+$. Anal. Calcd for $C_{36}H_{38}O_8$: C, 72.22; H, 6.40. Found: C, 72.34; H, 6.62.

Trioxane 12d. Yield 23%, oil; IR (neat, cm^{-1}) 1600; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68−1.91 (m, 14H), 2.48−2.56 (m, 2H), 3.88 (d, 4H, J = 6.5 Hz), 5.28−5.32 (m, 4H), 5.50 (s, 2H), 7.02−7.07 (m, 4H, Ar), 7.19 (dd, 4H, Ar, J = 7.1 and 2.4 Hz), 7.38−7.43 (m, 4H, Ar), 7.83 (dd, 2H, Ar, J = 7 and 2.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.58 (2 × CH_2), 24.99 (2 × CH_2), 33.02 (2 × CH_2), 37.24 (2 × CH_2), 65.24 (2 × CH_2), 80.48 (2 × CH), 113.77 (2 × CH), 114.83 (2 × C), 116.22 (2 × CH_2), 118.15 (2 × CH), 119.28 (4 × CH), 127.21 (C), 128.15 (4 × CH), 130.04 (2 × CH), 134.06 (2 × C), 135.64 (C), 142.68 (2 × C), 155.77 (2 × C), 157.27 (2 × C); FAB-MS (m/z) 649 $[M + H]^+$. Anal. Calcd for $C_{40}H_{40}O_8$: C, 74.06; H, 6.21. Found: C, 74.20; H, 6.35.

Trioxane 12e. Yield 30%, white solid, mp 148−150 °C; IR (KBr, cm^{-1}) 1596; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66−1.92 (m, 14H), 2.46−2.52 (m, 2H), 3.86 (d, 4H, J = 6.4 Hz), 5.26−5.30 (m, 4H), 7.02 (dd, 6H, Ar, J = 6.3 and 2.1 Hz), 7.36−7.42 (m, 6H), 7.96 (d, 2H, Ar, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.58 (2 × CH_2), 24.99 (2 × CH_2), 30.03 (2 × CH_2), 37.25 (2 × CH_2), 65.26 (2 × CH_2), 80.53 (2 × CH), 114.89 (2 × C), 116.09 (2 × CH_2), 118.05 (2 × CH), 118.59 (4 × CH), 126.22 (2 × CH), 128.19 (4 × CH), 133.80 (2 × C), 142.76 (2 × C), 152.95 (2 × C), 158.14 (2 × C); FAB-MS (m/z) 649 $[M + H]^+$. Anal. Calcd for $C_{40}H_{40}O_8$: C, 74.06; H, 6.21. Found: C, 74.17; H, 6.38.

Trioxane 12f. Yield 21%, white solid, mp 100−103 °C; IR (KBr, cm^{-1}) 3460; ^1H NMR (300 MHz, $CDCl_3$) δ 1.71−1.93 (m, 14H), 2.49−2.57 (m, 2H), 2.63 (d, 1H, J = 5.2 Hz), 3.85 (d, 4H, J = 6.5 Hz), 4.14−4.23 (m, 4H), 4.38−4.46 (m, 1H), 5.26−5.32 (m, 4H), 5.45 (s, 2H), 6.93 (d, 4H, Ar, J = 8.8 Hz), 7.37 (d, 4H, Ar, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.56 (2 × CH_2), 24.98 (2 × CH_2), 32.25 (2 × CH_2), 37.25 (2 × CH_2), 65.30 (2 × CH_2), 68.30 (2 × CH_2), 80.53 (2 × CH), 114.75 (4 × CH), 115.41 (2 × CH_2), 127.89 (4 × CH), 131.83 (2 × C), 142.67 (2 × C), 158.58 (2 × C); ESI 598 $[M + NH_4]^+$, 603 $[M + Na]^+$. Anal. Calcd for $C_{33}H_{40}O_9$: C, 68.26; H, 6.94. Found: C, 68.49; H, 6.99.

Trioxane 12g. Yield 40%, white sold, mp 120−122 °C; IR (KBr, cm^{-1}) 1609; ^1H NMR (300 MHz, $CDCl_3$) δ 168−1.96 (m, 14H), 2.24−2.32 (m, 2H), 2.49−2.57 (m, 2H), 3.84 (d, 4H, J = 6.4 Hz), 4.18 (t, 4H, J = 6.1 Hz), 5.23−5.31 (m, 4H), 5.43 (s, 2H), 6.89 (d, 4H, Ar, J = 8.8 Hz), 7.34 (d, 4H, Ar, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.56 (2 × CH_2), 24.98 (2 × CH_2), 29.48 (CH_2), 32.99 (2 × CH_2), 37.27 (2 × CH_2), 64.66 (2 × CH_2), 66.37 (2 × CH_2), 80.61 (2 × CH), 114.73 (2 × C), 114.75 (4 × CH), 115.08 (2 × CH_2), 127.82 (4 × CH), 131.33 (2 × C), 142.88 (2 × C), 142.88 (2 × C), 159.10 (2 × C); EI^+ 564, ESI 582 $[M + NH_4]^+$. Anal. Calcd for $C_{33}H_{40}O_8 \cdot 0.1H_2O$: C, 70.19; H, 7.14. Found: C, 69.97; H, 7.12.

Trioxane 12h. Yield 16%, white solid, mp 158−160 °C; IR (KBr, cm^{-1}) 1607; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68−1.94 (m, 14H), 2.49−2.58 (m, 2H), 3.86 (d, 4H, J = 6.4 Hz), 4.35 (s, 4H), 5.25−5.32 (m, 4H), 5.45 (s, 2H), 6.94 (d, 4H, Ar, J = 8.8 Hz), 7.37 (d, 4H, Ar, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.55 (2 × CH_2), 24.97 (2 × CH_2), 32.96 (2 × CH_2), 37.24 (2 × CH_2), 65.32 (2 × CH_2), 66.69 (2 × CH_2), 80.53 (2 × CH), 114.76 (4 × CH), 115.25 (2 × CH_2), 127.82 (4 × CH), 131.62 (2 × C), 158.79 (2 × C); ESI 568 $[M + NH_4]^+$. Anal. Calcd for $C_{32}H_{38}O_8$: C, 69.80; H, 6.96. Found: C, 69.93; H, 6.99. HRMS calcd for $C_{32}H_{38}O_8$ 550.2567; found, 550.2546.

Trioxane 13a. Yield 39%, white solid, mp 98−100 °C; IR (KBr, cm^{-1}) 1595; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46−1.66 (m, 16H), 2.01−2.07 (m, 2H), 2.19−2.26 (m, 2H), 3.79 (dd, 2H, J = 11.8 and 2.9 Hz), 4.0 (dd, 2H, J = 11.7 and 10.7 Hz), 5.23 (dd, 2H, J = 10.2 and 2.6 Hz), 5.39 and 5.49 (2 × s, 4H), 6.99 (d, 4H, Ar, J = 8.6 Hz), 7.39 (d, 4H, Ar, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.48 (2 × CH_2), 22.52 (2 × CH_2), 25.74 (2 × CH_2), 29.23 (2 × CH_2), 34.83 (2 × CH_2), 62.80 (2 × CH_2), 80.47 (2 × CH), 102.81 (2 × C), 116.07 (2 × CH_2), 119.05 (4 × CH), 128.10 (4 × CH), 134.11 (2 × C), 142.92 (2 × C), 157.17 (2 × C); FAB-MS (m/z) 535 $[M + H]^+$. Anal. Calcd for $C_{32}H_{38}O_7$: C, 71.89; H, 7.16. Found: C, 71.98; H, 7.22. HRMS calcd for $C_{32}H_{38}O_7$ 534.2618; found, 534.2614.

Trioxane 13b. Yield 29%, oil; IR (neat, cm^{-1}) 1505; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43−1.64 (m, 16H), 1.97−2.08 (m, 2H), 2.17−2.26 (m, 2H), 3.75−3.82 (m, 2H), 3.95−4.04 (m, 2H), 5.19−5.36 (m, 4H), 5.50 and 5.52 (2 × s, 2H), 6.95−7.06 (m, 3H, Ar), 7.09−7.11 (m,1H, Ar), 7.18 (d, 1H, Ar, J = 7.8 Hz), 7.30−7.41 (m, 3H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.40 (2 × CH_2), 22.44 (2 × CH_2), 25.65 (2 × CH_2), 29.13 (2 × CH_2), 34.69 (2 × CH_2), 34.74 (CH_2), 62.66 (CH_2), 66.72 (CH_2), 80.25 (CH), 80.35 (CH), 102.70 (2 × C), 115.88 (CH_2), 117.17 (CH), 117.38 (CH), 118.71 (CH), 118.76 (CH), 121.75 (CH_2), 128.01 (CH), 130.05 (CH), 140.73 (C), 142.80 (C), 142.98 (C), 157.09 (C), 157.26 (C); FAB-

MS (*m*/*z*) 535 $[M + H]^+$. Anal. Calcd for $C_{32}H_{38}O_7 \cdot 0.1H_2O$: C, 71.89; H, 7.16. Found: C, 71.65; H, 7.14. HRMS calcd for $C_{32}H_{38}O_7$ 534.2618; found, 534.2623.

Trioxane 13c. Yield 20%, white solid, mp 135−138 °C; IR (KBr, cm^{-1}) 1507; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21−1.62 (m, 16H), 1.94−2.08 (m, 2H), 2.16−2.28 (m, 2H), 3.76 (dd, 2H, J = 11.8 and 3 Hz), 3.98 (dd, 2H, J = 11.8 and 10.3 Hz), 5.22 (dd, 2H, J = 10.4 and 2.8 Hz), 5.28 and 5.46 (2 × s, 4H), 6.96 (d, 4H, Ar, J = 8.7 Hz), 7.01 (s, 4H, Ar), 7.36 (d, 4H, J = 8.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.18 (2 × CH_2), 22.70 (2 × CH_2), 24.80 (2 × CH_2), 29.43 (2 × CH_2), 35.04 (2 × CH_2), 63.03 (2 × CH_2), 80.69 (2 × CH), 103.02 (2 × C), 116.09 (2 × CH_2), 118.50 (4 × CH), 121.10 (4 × CH), 128.26 (4 × CH), 133.86 (2 × C), 143.14 (2 × C), 152.94 (2 × C), 158.22 (2 × C); FAB-MS (*m*/*z*) 627 $[M + H]^+$. Anal. Calcd for $C_{38}H_{42}O_8$: C, 72.82; H, 6.75. Found: C, 72.40; H, 6.95.

Trioxane 13d. Yield 32%, oil; IR (neat, cm^{-1}) 1603; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46−165 (m, 16H), 2.01−2.07 (m, 2H), 2.19−2.26 (m, 2H), 3.80 (dd, 2H, J = 11.8 and 2.9 Hz), 4.01 (dd, 2H, J = 11.8 and 10.4 Hz), 5.25 (dd, 2H, J = 10.3 and 2.5 Hz), 5.32 and 5.51 (2 × s, 4H), 7.04 (dd, 4H, Ar, J = 6.8 and 1.9 Hz), 7.18−7.22 (m, 4H, Ar), 7.38−7.42 (m, 4H, Ar), 7.81−7.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.01 (3 × CH_2), 24.25 (2 × CH_2), 27.73 (2 × CH_2), 33.35 (2 × CH_2), 61.34 (2 × CH_2), 78.96 (2 × CH), 101.37 (2 × C), 112.22 (2 × CH), 114.62 (2 × CH_2), 117.47 (2 × CH), 117.81 (4 × CH), 125.69 (C), 126.64 (4 × CH), 128.53 (2 × CH), 132.67 (2 × C), 134.14 (C), 141.38 (2 × C), 154.30 (2 × C), 155.74 (2 × C); FAB-MS (*m*/*z*) 677 $[M + H]^+$. Anal. Calcd for $C_{42}H_{44}O_8$: C, 74.54; H, 6.55. Found: C, 74.66; H, 6.68.

Trioxane 13e. Yield 42%, white solid, mp 158−160 °C; IR (KBr, cm^{-1}) 1596; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42−1.63 (m, 16H), 1.97−2.05 (m, 2H), 2.17−2.26 (m, 2H), 3.78 (dd, 2H, J = 12 and 3 Hz), 3.99 (dd, 2H, J = 12 and 10.5 Hz), 5.22 (dd, 2H, J = 10.6 and 3.1 Hz), 5.29 and 5.47 (2 × s, 4H), 7.01 (dd, 6H, Ar, J = 9.3 and 7.3 Hz), 7.36−7.42 (m, 6H, Ar), 7.96 (d, 2H, Ar, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.52 (2 × CH_2), 22.56 (2 × CH_2), 25.77 (2 × CH_2), 29.27 (2 × CH_2), 34.87 (2 × CH_2), 62.87 (2 × CH_2), 80.52 (2 × CH), 102.85 (2 × C), 114.63 (2 × CH), 115.97 (2 × CH_2), 118.03 (2 × CH), 118.61 (4 × CH), 126.20 (2 × CH), 128.17 (4 × CH), 128.72 (2 × C), 133.92 (2 × C), 142.99 (2 × C), 152.97 (2 × C), 158.11 (2 × C); FAB-MS (*m*/*z*) 677 $[M + H]^+$. Anal. Calcd for $C_{42}H_{44}O_8$: C, 74.54; H, 6.55. Found: C, 74.62; H, 6.65.

Trioxane 13f. Yield 23%, oil; IR (neat, cm^{-1}) 3455; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45−1.64 (m, 16H), 1.97−2.06 (m, 2H), 2.18−2.25 (m, 2H), 3.76 (dd, 2H, J = 11.9 and 2.9 Hz), 3.97 (dd, 2H, J = 11.8 and 10.4 Hz), 4.12−4.12 (m, 5H), 4.36−4.43 (m, 1H), 5.23 (dd, 2H, J = 10.8 and 2.8 Hz), 5.26 and 5.44 (2 × s, 4H), 6.91 (d, 4H, Ar, J = 8.8 Hz), 7.34 (d, 4H, Ar, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.45 (2 × CH_2), 22.49 (2 × CH_2), 25.70 (2 × CH_2), 29.17 (2 × CH_2), 34.82 (2 × CH_2), 62.84 (2 × CH_2), 68.89 (CH), 68.98 (2 × CH_2), 80.50 (2 × CH), 102.77 (2 × C), 114.76 (4 × CH), 115.25 (2 × CH_2), 127.83 (4 × CH), 131.90 (2 × C), 142.91 (2 × C), 158.59 (2 × C); ESI 626 $[M + NH_4]^+$. Anal. Calcd for $C_{35}H_{44}O_9 \cdot 0.1H_2O$: C, 69.06; H, 7.29. Found: C, 68.86; H, 7.26.

Trioxane 13g. Yield 32%, white solid, mp 118−120 °C; IR (KBr, cm^{-1}) 1608; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46−1.65 (m, 16H), 1.98−2.07 (m, 2H), 2.19−2.32 (m, 4H), 3.76 (dd, 2H, J = 11.9 and 2.9 Hz), 3.97 (dd, 2H, J = 11.8 and 10.4 Hz), 4.18 (t, 4H, J = 6 Hz) 5.22 (d, 2H, J = 2.9 Hz), 5.25 and 5.44 (2 × s, 4H), 6.89 (d, 4H, Ar, J = 8.8 Hz), 7.34 (d, 4H, Ar, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.47 (2 × CH_2), 22.51 (2 × CH_2), 25.73 (2 × CH_2), 29.18 (2 × CH_2), 29.43 (CH_2), 34.86 (2 × CH_2), 62.94 (2 × CH_2), 64.91 (2 × CH_2), 80.54 (2 × CH), 102.74 (2 × C), 114.68 (4 × CH), 114.95 (2 × CH_2), 127.75 (4 × CH), 131.36 (2 × C), 143.03 (2 × C), 159.04 (2 × C); ESI 610 $[M + NH_4]^+$. Anal. Calcd for $C_{35}H_{44}O_8 \cdot 0.1H_2O$: C, 70.92; H, 7.48. Found: C, 70.71; H, 7.46.

Trioxane 13h. Yield 22%, white solid, mp 145−147 °C; IR (KBr, cm^{-1}) 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47−1.65 (m, 16H), 1.99−2.08 (m, 2H), 2.21−2.29 (m, 2H), 3.77 (dd, 2H, J = 11.9 and 2.9 Hz), 3.99 (dd, 2H, J = 11.8 and 10.4 Hz), 5.23 (d, 2H, J = 2.9 Hz), 5.27 and 5.46 (2 × s, 4H), 6.94 (d, 4H, Ar, J = 8.6 Hz), 7.37 (d, 4H, Ar, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.50 (2 × CH_2), 25.72 (2 × CH_2), 29.15 (2 × CH_2), 34.86 (2 × CH_2), 62.91 (2 × CH_2), 66.67 (2 × CH_2), 80.47 (2 × CH), 102.77 (2 × C), 114.83 (4 × CH), 115.15 (2 × CH_2), 127.79 (4 × CH), 131.70 (2 × C), 142.91 (2 × C), 158.76 (2 × C); ESI 596 $[M + NH_4]^+$. Anal. Calcd for $C_{34}H_{42}O_8$: C, 70.57; H, 7.32. Found: C, 70.67; H, 7.48.

Trioxane 14a. Yield 19%, white solid, mp 60−63 °C; IR (KBr, cm^{-1}) 1596; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60−2.11 (m, 26H), 2.96 (s, 2H), 3.79 (dd, 2H, J = 11.8 and 2.9 Hz), 3.99 (dd, 2H, J = 11.7 and 10.5 Hz), 5.25 (dd, 2H, J = 10.3 and 2.7 Hz), 5.31 and 5.49 (2 × s, 4H), 6.99 (d, 4H, Ar, J = 8.6 Hz), 7.4 (d, 4H, Ar, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.38 (4 × CH), 29.64 (2 × CH), 33.22 (2 × CH_2), 33.46 (2 × CH_2), 33.69 (2 × CH_2), 33.79 (2 × CH_2), 36.44 (2 × CH), 37.42 (2 × CH_2), 62.33 (2 × CH_2), 80.33 (2 × CH), 104.89 (2 × C), 116.02 (2 × CH_2), 119.07 (4 × CH), 128.09 (4 × CH), 134.20 (2 × C), 142.97 (2 × C), 157.18 (2 × C); FAB-MS (*m*/*z*) 639 $[M + H]^+$. Anal. Calcd for $C_{40}H_{46}O_7$: C, 75.21; H, 7.26. Found: C, 75.30; H, 7.30.

Trioxane 14b. Yield 20%, white solid, mp 45−50 °C; IR (KBr, cm^{-1}) 1606; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60−2.10 (m, 26H), 2.95 and 2.97 (2 × s, 2H), 3.77−3.83 (m, 2H), 3.94−4.03 (m, 2H), 5.22−5.36 (m, 4H), 5.51 and 5.53 (2 × s, 2H), 6.96−7.0 (m, 3H, Ar), 7.09−7.11 (m, 1H, Ar), 7.18 (d, 1H, Ar, J = 7.8 Hz), 7.31−7.42 (m, 3H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.36 (4 × CH), 29.62 (2 × CH), 33.20 (2 × CH_2), 33.44 (2 × CH_2), 33.68 (2 × CH_2), 37.77 (2 × CH_2), 36.38 (CH), 36.44 (CH), 37.40 (2 × CH_2), 62.30 (CH_2), 62.39 (CH_2), 80.22 (CH), 80.32 (CH), 104.87 (2 × C), 115.93 (CH_2), 117.22 (CH_2), 117.49 (CH), 118.80 (CH), 118.90 (CH), 121.84 (CH), 128.11(CH), 130.15 (CH), 134.06 (C), 140.90 (CH), 142.94 (CH), 143.14 (C), 157.19 (C), 157.37 (C); FAB-MS (*m*/*z*) 639 $[M + H]^+$. Anal. Calcd for $C_{40}H_{46}O_7 \cdot 0.1H_2O$: C, 75.21; H, 7.26. Found: C, 75.00; H, 7.08.

Trioxane 14c. Yield 26%, white solid, mp 55−60 °C; IR (KBr, cm^{-1}) 1490; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60−2.11 (m, 26H), 2.96 (s, 2H), 3.8 (dd, 2H, J = 11.9 and 2.9 Hz), 3.99 (dd, 2H, J = 11.7 and 10.5 Hz), 5.26 (dd, 2H, J = 10.7 and 2.7 HZ), 5.30 and 5.49 (2 × s, 4H), 6.99 (d, 4H, Ar, J = 8.7 Hz), 7.04 (s, 4H, Ar), 7.39 (d, 4H, Ar, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.36 (4 × CH), 29.60 (2 × CH), 33.20 (2 × CH_2), 33.45 (2 × CH_2), 33.68 (2 × CH_2), 33.78 (2 × CH_2), 36.44 (2 × CH), 37.40 (2 × CH_2), 62.34 (2 × CH_2), 80.31 (2 × CH), 104.89 (2 × C), 115.85 (2 × CH_2), 118.32 (4 × CH), 120.91 (4 × CH), 128.03 (4 × CH), 133.71 (2 × C), 142.92 (2 × C), 152.73 (2 × C), 158.01 (2 × C); FAB-MS (*m*/*z*) 731 $[M + H]^+$. Anal. Calcd for $C_{46}H_{50}O_8$: C, 75.59; H, 6.90. Found: C, 75.74; H, 6.98.

Trioxane 14d. Yield 38%, oil; IR (neat, cm^{-1}) 1598; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68−2.08 (m, 26 H), 2.96 (s, 2H), 3.81 (dd, 2H, J = 11.9 and 2.9 Hz), 4.0 (dd, 2H, J = 11.8 and 10.6 Hz), 5.27 (dd, 2H, J = 10.7 and 2.9 Hz), 5.31 and 5.51 (2 × s, 4H), 7.04 (dd, 4H, Ar, J = 6.8 and 1.9 Hz), 7.18−7.22 (m, 4H, Ar), 7.39−7.43 (m, 4H, Ar), 7.80−7.84 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.36 (4 × CH), 29.62 (2 × CH), 33.20 (2 × CH_2), 33.44 (2 × CH_2), 33.67 (2 × CH_2), 33.77 (2 × CH_2), 36.42 (2 × CH), 37.40 (2 × CH_2), 62.31 (2 × CH_2), 80.28 (2 × CH), 104.88 (2 × C), 113.71 (2 × CH), 115.99 (2 × CH_2), 118.93 (2 × CH), 119.29 (4 × CH), 127.18 (C), 128.09 (4 × CH), 129.99 (2 × CH), 134.24 (2 × CH), 135.63 (C), 142.93 (2 × C), 155.80 (2 × C), 157 0.21 (2 × C); FAB-MS (*m*/*z*) 781 $[M + H]^+$. Anal. Calcd for $C_{50}H_{52}O_8$: C, 76.90; H, 6.71. Found: C, 76.97; H, 6.98.

Trioxane 14e. Yield 34%, white solid, mp 155−157 °C; IR (KBr, cm^{-1}) 1598; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57−2.09 (m, 26H), 2.94 (s, 2H), 3.78 (dd, 2H, J = 11.8 and 2.9 Hz), 3.97 (dd, 2H, J = 11.8 and 10.6 Hz), 5.24 (dd, 2H, J = 10.9 and 2.9 Hz), 5.28 and 5.47 (2 × s, 4H), 7.01 (dd, 6H, Ar, J = 6.9 and 2 Hz), 7.37−7.42 (m, 6H, Ar), 7.95 (d, 2H, Ar, J = 8.4 Hz); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 27.40 (4 × CH), 29.67 (2 × CH), 33.24 (2 × CH_2), 33.48 (2 × CH_2), 33.71 (2 × CH_2), 38.81 (2 × CH_2), 36.46 (2 × CH), 37.44 (2 × CH_2), 62.37 (2 × CH_2), 80.34 (2 × CH), 104.90 (2 × C), 114.84 (2 × CH), 115.89 (2 × CH_2), 118.03 (2 × CH), 118.62 (4 × CH), 126.20 (2 × CH), 128.14 (4 × CH), 128.72 (2 × C), 134 (2 × C), 143.01 (2 × C), 152.99 (2 × C), 158.10 (2 × C); FAB-MS (*m*/*z*) 781 $[M + H]^+$. Anal. Calcd for $C_{50}H_{52}O_8$: C, 76.90; H, 6.71. Found: C, 76.87; H, 6.95.

Trioxane 14f. Yield 19%, oil; IR (neat, cm^{-1}) 3450; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60−2.10 (m, 26H), 2.62 (bs, 1H), 2.96 (s, 2H), 3.77 (dd, 2H, J = 11.9 and 2.9 Hz), 3.96 (dd, 2H, J = 11.8 and 10.62 Hz), 4.13−4.22 (m, 4H), 4.39−4.42 (m, 1H), 5.23 (d, 2H, J = 2.9 Hz), 5.26 and 5.45 (2 × s, 4H), 6.92 (d, 4H, Ar, J = 8.8 Hz), 7.35 (d, 4H, Ar, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.37 (4 × CH), 29.60 (2 × CH), 33.21 (2 × CH_2), 33.45 (2 × CH_2), 33.69 (2 × CH_2), 33.78 (2 × CH_2), 36.47 (2 × CH), 37.42 (2 × CH_2), 62.40 (2 × CH_2), 68.99 (2 × CH_2), 80.38 (2 × CH), 104.85 (2 × C), 114.80 (4 × CH), 115.26 (2 × CH_2), 127.86 (4 × CH), 132.07 (2 × C), 143.00 (2 × C), 158.61 (2 × C); ESI 730 $[M + NH_4]^+$. Anal. Calcd for $C_{43}H_{52}O_9$: C, 72.45; H, 7.35. Found: C, 72.48; H, 7.50.

Trioxane 14g. Yield 19%, white solid, mp 114−116 °C; IR (KBr, cm^{-1}) 1606; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59−2.11 (m, 26H), 2.23−2.32 (m, 2H), 2.97 (s, 2H), 3.76 (dd, 2H, J = 11.9 and 2.8 Hz), 3.95 (dd, 2H, J = 12.1 and 10.7 Hz), 4.17 (t, 4H, J = 5.8 Hz), 5.22−5.26 (m, 4H), 5.43 (s, 2H) 6.88 (d, 4H, Ar, J = 8.9 Hz), 7.33 (d, 4H, Ar, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.46 (4 × CH), 29.65 (2 × CH_2), 29.76 (2 × CH), 33.39 (2 × CH_2), 33.64 (2 × CH_2), 33.89 (2 × CH_2), 33.87 (2 × CH_2), 36.67 (2 × CH), 37.61 (2 × CH_2), 62.66 (2 × CH_2), 64.82 (2 × CH_2), 80.58 (2 × CH), 105.01 (2 × C), 114.89 (4 × CH), 115.11 (2 × CH_2), 127.94 (4 × CH), 131.63 (2 × C), 143.25 (2 × C), 159.25 (2 × C); ESI 714 $[M + NH_4]^+$. Anal. Calcd for $C_{43}H_{52}O_8$: C, 74.11; H, 7.52. Found: C, 74.32; H, 7.64.

Trioxane 14h. Yield 19%, white solid, mp 156−158 °C; IR (KBr, cm^{-1}) 1607; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61−2.09 (m, 26H), 2.98 (s, 2H), 3.78 (dd, 2H, J = 11.8 and 2.9 Hz), 3.98 (dd, 2H, J = 11.7 and 10.7 Hz), 4.35 (s, 4H), 5.25−5.29 (m, 4H), 5.46 (s, 2H), 6.94 (d, 4H, Ar, J = 8.8 Hz), 7.37 (d, 4H, Ar, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.34 (4 × CH), 29.54 (2 × CH), 33.17 (2 × CH_2), 33.43 (2 × CH_2), 33.67 (2 × CH_2), 33.76 (2 × CH_2), 36.45 (2 × CH), 37.387 (2 × CH_2), 62.41 (2 × CH_2), 66.70 (2 × CH_2), 80.35 (2 × CH), 104.83 (2 × C), 114.85 (4 × CH), 115.11 (2 × CH_2), 127.77 (4 × CH), 131.79 (2 × C), 142.95 (2 × C), 158.77 (2 × C); ESI 700 $[M + NH_4]^+$, 705 $[M + Na]^+$;. Anal. Calcd for $C_{42}H_{50}O_8$: C, 73.88; H, 7.38. Found: C, 73.96; H, 7.50.

Trioxane 12i. Yield 12%, oil; IR (neat, cm^{-1}) 1602; ^1H NMR (200 MHz, $CDCl_3$) δ 1.68−1.96 (m, 21H), 2.44−2.55 (m, 3H), 3.83 (d, 6H, J = 6.5 Hz), 5.22−5.27 (m, 6H), 5.46 (s, 3H), 6.39 (s, 3H, Ar), 6.99 (d, 6H, Ar, J = 8.8 Hz), 7.37 (d, 6H, Ar, J = 8.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.74 (3 × CH_2), 25.51 (3 × CH_2), 33.18 (3 × CH_2), 37.40 (3 × CH_2), 65.34 (3 × CH_2), 80.64 (3 × CH), 104.51 (3 × CH), 114.98 (3 × C), 116.56 (3 × CH_2), 119.55 (6 × CH), 128.37 (6 × CH), 134.67 (3 × C), 142.81 (3 × C), 156.64 (3 × C), 159.64 (3 × C); FAB-MS (*m*/*z*) 859 $[M + H]^+$. Anal. Calcd for $C_{51}H_{54}O_{12}$: C, 71.31; H, 6.34. Found: C, 71.30; H, 6.39.

Trioxane 13i. Yield 15%, oil; IR (neat, cm^{-1}) 1604; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43−1.67 (m, 24H), 1.97−2.06 (m, 3H), 2.17−2.26 (m, 3H), 3.79 (dd, 3H, J = 12 and 3.1 Hz), 3.99 (dd, 3H, J = 11.8 and 10.4 Hz), 5.22 (dd, 3H, J = 10. and 2.9 Hz), 5.39 and 5.48 (2 × s, 6H), 6.42 (s, 3H, Ar), 7.01 (d, 6H, Ar, J = 9 Hz), 7.38 (d, 6H, Ar, J = 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.46 (3 × CH_2), 22.49 (3 × CH_2), 25.71 (3 × CH_2), 29.20 (3 × CH_2), 34.78 (3 × CH_2), 62.72 (3 × CH_2), 80.38 (3 × CH), 102.79 (3 × C), 104.25 (3 × CH), 116.21 (3 × CH_2), 119.33 (6 × CH), 128.13 (6 × CH), 134.54 (3 × C), 142.78 (3 × C), 156.40 (3 × C), 159.38 (3 × C); FAB-MS (*m*/*z*) 901 $[M + H]^+$. Anal. Calcd for $C_{54}H_{60}O_{12}$: C, 71.98; H, 6.71. Found: C, 71.84; H, 6.92.

Trioxane 14i. Yield 11%, oil; IR (KBr, cm^{-1}) 1593; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60−2.10 (m, 39H), 2.94 (s, 3H), 3.77 (dd, 3H, J = 11.8 and 2.9 Hz), 3.97 (dd, 3H, J = 11.8 and 10.4 Hz), 5.26 (dd, 3H, J = 10.3 and 2.7 Hz), 5.30 and 5.48 (2 × s, 6H), 6.99 (d, 4H, Ar, J = 8.6 Hz), 7.4 (d, 4H, Ar, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.38 (6 × CH), 29.64 (3 × CH), 33.22 (3 × CH_2), 33.46 (3 × CH_2), 33.69 (3 × CH_2), 33.79 (3 × CH_2), 36.44 (3 × CH), 37.42 (3 × CH_2), 62.29 (3 × CH_2), 80.28 (3 × CH), 104.29 (3 × C), 104.91 (3 × CH), 116.22 (3 × CH_2), 119.40 (6 × CH), 128.16 (6 × CH), 134.66 (3 × C), 142.86 (3 × C), 156.44 (3 × C), 159.43 (3 × C); FAB-MS (*m*/*z*) 1058 $[M + H]^+$. Anal. Calcd for $C_{66}H_{72}O_{12}$: C, 74.98; H, 6.86. Found: C, 74.90; H, 6.96.

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Supporting Information Available: ^1H NMR spectra of compounds **8a**−**i**, **9a**−**i**, and **10a**−**i**; elemental analysis results; ^1H NMR and ^{13}C NMR spectra of compounds **12a**−**i**, **13a**−**i**, and **14a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) 100% 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, it will not provide full protection to the treated mice in the 28 day survival assay. Multi-drug resistant *Plasmodium yoelii nigeriensis* used in this study is resistant to chloroquine, mefloquine, and halofantrine. (b) 100% protection means none of the treated mice developed patent infection during the 28-day observation period and hence recorded as cured. Similarly, 20% protection means only 1 out of 5 mice was cured.

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