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Orally active antimalarials: Synthesis and bioevaluation of a new series of steroid-based 1,2,4-trioxanes against multi-drug resistant malaria in mice☆

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Abstract—A new series of steroid-based 1,2,4-trioxanes **7a**–**f**, **8a**–**f** and **9b**–**e** have been synthesized and evaluated for their antimalarial activity against multi-drug resistant *Plasmodium yoelii* in Swiss mice by oral route. The biological activity shows a strong dependence on the size and the nature of the steroidal side chain. Pregnane-based trioxanes **8a**–**f** show better activity profile than trioxanes **7a**–**f** and **9b**–**e**, derived from cholesterol and tigogenine, respectively.
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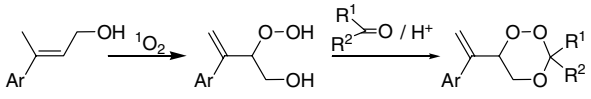
Malaria is a major parasitic disease prevalent in many countries in Africa, Asia and South America.[1] Out of the four species of *Plasmodium* that affect humans, *Plasmodium falciparum* is the most dangerous and its resistance to contemporary antimalarial drugs has further compounded the problem. Against this background, artemisinin **1**, the active principle of *Artemisia annua*, and its semisynthetic derivatives, e.g., artemether **2**, arteether **3** and artesunic acid **4**, are the only class of antimalarials which are effective against multi-drug resistant malaria[2,3] (Fig. 1). The peroxide bond in the form of 1,2,4-trioxane is essential for the antimalarial activity of this class of drugs. Several 1,2,4-trioxanes originating from different laboratories have shown promising antimalarial activity both in vitro and in vivo.[4] But the search for structurally simpler, cheaper and more effective synthetic trioxanes remains an area of hot pursuit.

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



From this detailed SAR studies, adamantane-based trioxanes were found to be more active than the other spiro-1,2,4-trioxanes. Considering the high cost of adamantane derivatives, currently we are focusing on the easily accessible steroidal ketones as substitute for 2-adamantanone. In the present communication, we report on the synthesis of steroid-based spiro-1,2,4-trioxanes and their bioevaluation against multi-drug resistant *Plasmodium yoelii* in mice by oral route. While synthesis of several steroid-based tetraoxanes with

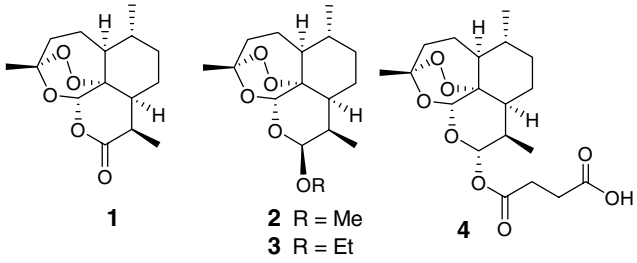


Figure 1.

Keywords: Malaria; Artemisinin; 1,2,4-Trioxanes; Steroid-based.
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modest antimalarial activity has been reported,[7] to our knowledge this is the first report on steroid-based 1,2,4-trioxanes.[8]

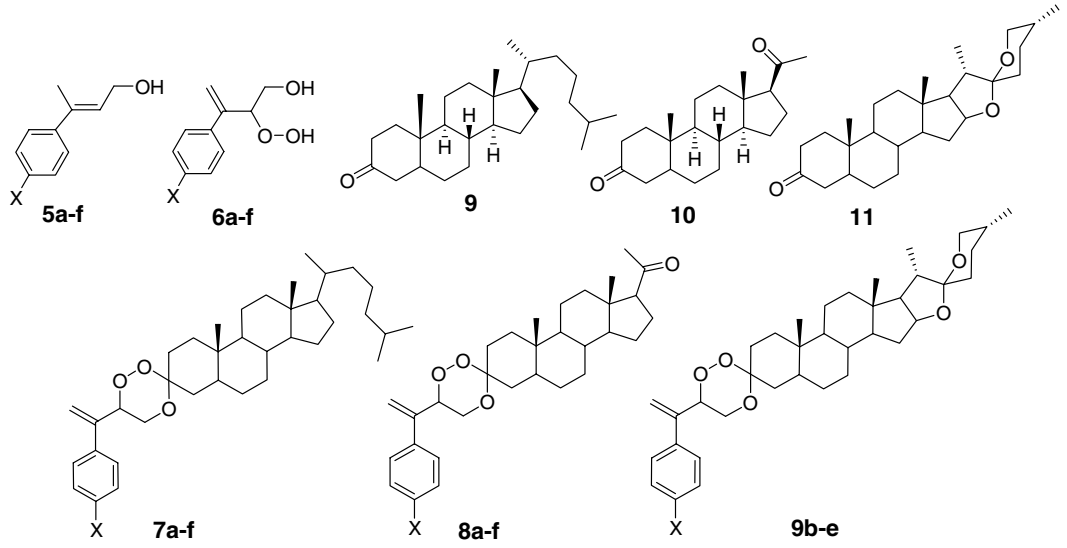
β-Hydroxyhydroperoxides **6a–f** were prepared by the photooxygenation of allylic alcohols **5a–f** according to our reported procedure and were reacted in situ with cholestanone **9** to furnish trioxanes **7a–f** in 23–69% overall yields.[6,10] A similar condensation of **6a–f** with 3,20-pregnanedione **10** furnished trioxanes **8a–f** in 40–87% overall yields. β-Hydroxyhydroperoxides **6b–e** were also reacted under similar conditions with tigogenine derived ketone **11** to furnish trioxanes **9b–e** in 35–55% overall yields[9,10] (Fig. 2). Cholestanone **9**, 3,20-pregnanedione **10** and ketone **11** were prepared from cholesterol, 16-dehydro-pregnanolone-3-acetate and diosgenin using standard procedures, respectively. All these trioxanes were obtained as inseparable mixture of diastereomers. Compounds **7a–f**, **8a–f** and **9b–e** were initially screened against multi-drug resistant *P. yoelii* in Swiss mice at 96 mg/kg × 4 days by oral route.[11–14] Trioxanes **8a–f**, which showed significant activity at 96 mg/kg, were further screened at 48 mg/kg × 4 days. Arteether which showed 100% protection at 48 mg/kg × 4 days was used as positive control. Results are summarized in Table 1.

As can be seen from Table 1, cholestane-based trioxanes **7a–f** and tigogenine-based trioxanes **9b–e** were less active than pregnane-based trioxanes **8a–f**. All the pregnane-based trioxanes **8a–f** showed 100% suppression on day 4 with 40–100% protection to the treated mice when administered at 96 mg/kg × 4 days (twice the effective dose of arteether) by oral route. Among pregnane-based trioxanes, **8b** and **8f** were the most active compounds of the series. Both these trioxanes showed 100% clearance of parasitaemia on day 4 at 96 mg/kg × 4 days and all the treated mice survived beyond day 28. Even at 48 mg/kg × 4 days, both these compounds showed 100% clearance of parasitaemia on day 4 and 40% of the treated mice survived beyond day 28. Trioxane **8c** was the next best compound of the series. It showed 60% protection at 96 mg/kg × 4 days and 20% protection at 48 mg/kg × 4 days. Trioxanes **8a** and **8d** showed 40% protection at 96 mg/kg × 4 days and 20% protection at 48 mg/kg × 4 days. Trioxane **8e** showed 20% protection at 96 mg/kg × 4 days. At 48 mg/kg, it showed 100% suppression on day 4 and none of the treated mice survived until day 28.

Trioxanes **7a–f** and **9b–e** showed weak activity. Compounds **7a–f** showed 15–73% suppression of parasitaemia on day 4 at 96 mg/kg × 4 days and none of the treated mice survived until day 28. Similarly, compounds **9b–e** showed only 36–71% suppression on day 4 at 96 mg/kg and none of the mice survived until 28.

From the limited SAR data, it appears that the steroidal side chain has a strong bearing on the biological activity. Trioxanes **8a–f** which have shorter side chain as compared with that of **7a–f** and **9b–e** are significantly more active. The data can also be rationalized in terms of lipophilicity of these compounds. The active compounds (**8a–f**), all pregnane-based, are comparatively less hydrophobic (log *P* = 7.07–8.03) than the weakly active trioxanes **7a–f** and **9b–e** (log *P* = 10.61–11.43 and 8.26–8.95). In this context, it is worth noting that pregnane moiety has earlier been identified as a biologically privileged substructure (supporting moiety) for a series of antiviral compounds.[15] More SAR data is needed to resolve the question whether the side chain per se is important or overall lipophilicity of the compound. Our current efforts are directed to answer this question.

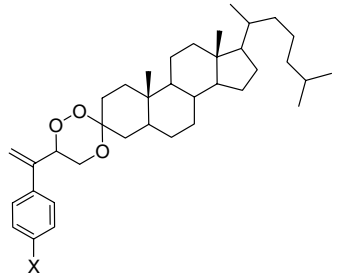
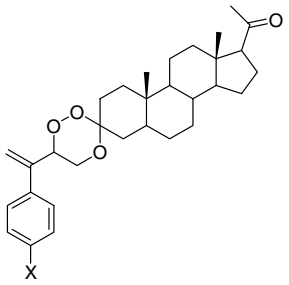
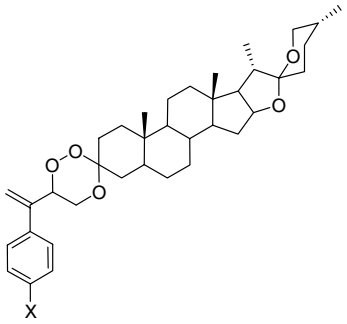
In conclusion, we have prepared a new series of steroid-based 1,2,4-trioxanes some of which show very significant activity against multi-drug resistant *P. yoelii* in Swiss mice by oral route.



X: [a] H; [b] OMe; [c] Me; [d] F; [e] Cl; [f] Br

Figure 2.

Table 1. In vivo antimalarial activity of compounds **7a–f**, **8a–f** and **9b–e** against multi-drug resistant *P. yoelii* in Swiss mice by oral route

General Structure	X	Compound	log *P*[b]	Dose (mg/kg/day)	% Suppression on day-4[a]	Mice alive on day-28
	H	**7a**	10.61	96	73.0	0/5
	OMe	**7b**	—	96	53.5	0/5
	Me	**7c**	11.09	96	27.4	0/5
	F	**7d**	10.76	96	14.8	0/5
	Cl	**7e**	11.16	96	43.4	0/5
	Br	**7f**	11.43	96	26.1	0/5
	H	**8a**	7.20	96	100.0	2/5
				48	100.0	1/5
	OMe	**8b**	7.07	96	100.0	5/5
				48	100.0	2/5
	Me	**8c**	7.69	96	100.0	3/5
				48	100.0	2/5
	F	**8d**	7.36	96	100.0	2/5
				48	100.0	1/5
	Cl	**8e**	7.76	96	100.0	1/5
				48	100.0	0/5
	Br	**8f**	8.03	96	100.0	5/5
				48	100.0	2/5
	OMe	**9b**	8.26	96	36.1	0/5
	Me	**9c**	8.87	96	50.7	0/5
	F	**9d**	8.55	96	45.1	0/5
	Cl	**9e**	8.95	96	71.7	0/5
Arteether	—	—	3.84	48	100.0	5/5
				24	100.0	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. log *P* value of compound **7b** could not be calculated by Chemdraw ultra 7.0.

Acknowledgments

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9. General procedure for the preparation of steroid-based 1,2,4-trioxanes **7a**–**f**, **8a**–**f** and **9b**–**e**: (compound **8a** is taken as representative example). A solution of 3-phenyl-but-2-en-1-ol **5a** (1 g, 6.75 mmol) and methylene blue (10 mg) in CH_3CN (75 mL) was irradiated with 500 W tungsten-halogen lamp at −10 to 0 °C while oxygen gas was bubbled slowly into the reaction mixture for 5 h. Compound 3,20-Pregnanedione **10** (3.2 g, 1.5 equiv, 10.1 mmol) and HCl (0.1 mL) were added and the reaction mixture was stirred at room temperature for 3 h. Usual workup followed by column chromatography over silica gel furnished trioxane **8a** (1.3 g, 45% yield) as an inseparable mixture of diastereomers. Mp 124–126 °C; FT-IR (KBr, cm^{-1}): 1715; ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.59 (s, 3H), 0.82 (s, 3H), 0.89–1.97 (m, 21H), 2.10 (s, 3H), 2.20–2.52 (m, 2H), 3.73 (dd, 1 H, J = 11.7 and 2.1 MHz), 3.89 and 4.02 (2× dd, 1 H, J = 11.7 and 10.6 MHz), 5.23 (dd, 1H, J = 10.6 and 2.1), 5.32 and 5.49 (2× s, 2H), 7.30–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.86 (CH_3), 13.88 (CH_3), 21.66 (CH_2), 23.18 (CH_2), 24.81 (CH_2), 28.40 (CH_2), 28.79 (CH_2), 31.96 (CH_3), 32.18 (CH_2), 34.98 (CH_2), 35.84 (CH), 36.46 (CH_2), 39.44 (CH_2), 42.11 (CH), 42.65 (C × 2), 54.09 (CH), 57.02 (CH), 63.22 (CH_2), 64.19 (CH), 80.71 (CH), 103.22 (C), 116.75 (CH_2), 126.78 (CH × 2), 128.58 (CH), 128.98 (CH × 2), 139.09 (C), 146.23 (C), 210.08 (C); ES-MS (*m*/*z*): 501 $[M + Na]^+$; Anal. Calcd for $C_{31}H_{42}O_4$: C 77.79%, H 8.84%; found C 77.47, H 9.21%.
10. *Selected spectral data:*
Compound **7a**. ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.64 (s, 3H), 0.83 (d, 3H, J = 6.6 MHz), 0.85 (s, 3H), 0.90–1.98 (m, 37H), 3.71–3.74 (m, 1H), 3.88 and 4.02 (2× dd, 1H, J = 12.1 and 10.1 MHz), 5.21–5.23 (m, 1H), 5.32 and 5.49 (2× s, 2H), 7.27–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 11.45 (CH_3), 12.01 (CH_3), 18.68 (CH_3), 21.27 (CH_2), 22.56 (CH_3), 22.81 (CH_3), 23.84 (CH_2), 24.21 (CH_2), 24.67 (CH_2), 28.01 (CH), 28.23 (CH_2), 28.54 (CH_2), 31.88 (CH_2), 34.60 (CH_2), 35.49 (CH), 35.79 (CH), 36.19 (CH_2), 36.23 (CH_2), 39.53 (CH_2), 40.03 (CH_2), 41.77 (CH), 42.60 (C × 2), 53.98 (CH), 56.29 (CH), 56.42 (CH), 62.80 (CH_2), 80.34 and 80.36 (CH), 102.91 and 103.15 (C), 116.26 (CH_2), 126.40 (2× CH), 128.12 (CH), 128.53 (2× CH), 138.70 (C), 143.61 (CH); FAB-MS (*m*/*z*): 549 $[M+H]^+$; Anal. Calcd for $C_{37}H_{56}O_3$: C 80.97%, H 10.28%; Found C 80.61%, H 9.76%.
Compound **7b**. ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.65 (s, 3H), 0.82 (d, 3H, J = 6.4 MHz), 0.87 (s, 3H), 0.90–1.99 (m, 37H), 3.72–3.80 (m, 1H), 3.81 (s, 3H), 3.82–3.88 (m, 1H), 5.19–5.20 (m, 1H), 5.22 and 5.42 (2× s, 2H), 6.86 (d, 2H, J = 8.5 MHz), 7.32 (d, 2H, J = 8.5 MHz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 11.52 (CH_3), 12.08 (CH_3), 18.68 (CH_3), 21.26 (CH_2), 22.56 (CH_3), 22.81 (CH_3), 23.83 (CH_2), 24.20 (CH_2), 24.64 (CH_2), 28.01 (CH), 28.23 (CH_2), 28.32 (CH_2), 31.72 (CH_2), 31.91 (CH_2), 34.33 (CH_2), 35.47 (CH), 35.79 (CH), 36.17 (CH_2), 36.62 (CH_2), 39.52 (CH_2), 40.01 (CH_2), 41.76 (CH), 42.56 (C × 2), 53.95 (CH), 55.30 (CH_3), 56.27 (CH), 56.45 (CH), 62.86 (CH_2), 80.49 and 80.51 (CH), 101.60 and 101.73 (C), 113.91 (2× CH), 114.85 (CH_2), 127.57 (2× CH), 131.00 (C), 142.88 (C), 159.56 (C); FAB-MS (*m*/*z*): 579 $[M+H]^+$; Anal. Calcd for $C_{38}H_{58}O_4$: C 78.85%, H 10.10%; Found C 78.63%, H 10.36%.
Compound **7c**. ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.64 (s, 3H), 0.82 (d, 3H, J = 6.7 MHz), 0.87 (s, 3H), 0.91–1.93 (m, 37H), 2.33 (s, 3H),3.69–3.74 (m, 1H), 3.84 and 4.00 (2× dd, 1H, J = 11.8 and 10.3 MHz), 5.20–5.22 (m, 1H), 5.26 and 5.46 (2× s, 2H), 7.13 (d, 2H, J = 7.7 MHz), 7.28 (d, 2H, J = 7.7 MHz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.90 (CH_3), 12.54 (CH_3), 19.14 (CH_3), 21.58 (CH_3), 21.62 (CH_2), 23.05 (CH_3), 23.29 (CH_3), 23.84 (CH_2), 24.23 (CH_2), 24.76 (CH_2), 28.47 (CH), 28.52 (CH_2) 28.98 (CH_2), 34.68 (CH_2), 34.77 (CH_2), 35.91 (CH), 36.27 (CH), 37.21 (CH_2), 37.78 (CH_2), 38.56 (CH_2), 39.91 (CH_2), 42.10 (CH), 43.03 (C × 2), 54.37 (CH), 56.45 (CH), 56.71 (CH), 62.64 and 62.86 (CH_2), 80.70 and 80.84 (CH), 103.27 and 103.41 (C), 115.77 (CH_2), 126.65 (2× CH), 129.67 (2× CH), 136.17 (C), 138.36 (C), 143.81 (C); FAB-MS (*m*/*z*): 563 $[M]^+$; Anal. Calcd for $C_{38}H_{58}O_3$: C 81.09%, H 10.36%; Found C 80.87%, H 10.58%.
Compound **8b**. FT-IR (KBr, cm^{-1}): 1711; ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.59 (s, 3H), 0.82 (s, 3H), 0.89–2.02 (m, 21H), 2.10 (s, 3H), 2.46–2.52 (m, 2H), 3.70–3.76 (m, 1H), 3.79 (s, 3H), 3.83–3.88 (m, 1H), 5.19–5.20 (m, 1H); 5.22 and 5.42 (2× s, 2H), 6.86 (d, 2H, J = 8.6 MHz), 7.32 (d, 2H, J = 8.6Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.93 (CH_3), 13.84 (CH_3), 21.65 (CH_2), 23.18 (CH_2), 24.79 (CH_2), 28.40 (CH_2), 28.79 (CH_2), 31.88 (CH_3), 32.21 (CH_2), 34.98 (CH_2), 35.82 (CH), 36.43 (CH_2), 39.40 (CH_2), 42.27 (CH), 44.57 (C × 2), 54.08 and 54.19 (CH), 55.64 (CH_3), 56.98 (CH) 63.23 (CH_2) 64.13 (CH), 80.71 and 80.75 (CH), 103.10 and 103.22 (C), 114.31 (CH × 2), 115.01 (CH_2), 127.89 (CH × 2), 131.36 (C), 143.13 and 143.23 (C), 159.99 (C), 209.77 (C); ES-MS (*m*/*z*): 531 $[M+Na]^+$; Anal. Calcd for $C_{32}H_{44}O_5$: C 75.56%, H 8.72%; Found C 75.23%, H 9.21%.
Compound **8c**. FT-IR (KBr, cm^{-1}): 1714; ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.59 (s, 3H), 0.82 (s, 3H), 0.89–2.02 (m, 21H), 2.09 (s, 3H), 2.33 (s, 3H), 2.47–2.54 (m, 2H), 3.74 (dd, 1H, J = 11.8 and 2.7 MHz), 3.85 and 3.90 (2× dd, 1H, J = 11.8 and 10.3 MHz), 5.20 (dd, 1H, J = 10.3 and 2.7 MHz); 5.22 and 5.42 (2× s, 2H), 7.13(d,

2H, $J = 7.8$ MHz), 7.28 (d, 2H, $J = 7.8$ MHz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.95 (CH_3), 13.86 (CH_3), 21.55 (CH_2), 21.58 (CH_3), 23.17 (CH_2), 24.81 (CH_2), 28.54 (CH_2), 28.79 (CH_2), 31.89 (CH_3), 32.20 (CH_2), 34.98 (CH_2), 35.82 (CH), 36.43 (CH_2), 39.39 (CH_2), 42.32 (CH), 44.57 (C × 2), 54.11 (CH), 56.98 (CH), 63.26 (CH_2) 64.11 (CH), 80.65 (CH), 103.08 and 103.21 (C), 115.75 (CH_2), 126.57 (CH × 2), 129.66 (CH × 2), 136.06 (C), 138.33 (C), 143.68 (C), 209.76 (C); ES-MS (*m*/*z*): 515 $[M+Na]^+$; Anal. Calcd for $C_{32}H_{44}O_4$: C 78.01%, H 9.00%; Found C 77.85%, H 8.55%.

Compound **8d**. FT-IR (KBr, cm^{-1}): 1716; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.60 (s, 3H), 0.82 (s, 3H), 0.87–2.02 (m, 21H), 2.10 (s, 3H), 2.51–2.55 (m, 2H), 3.73 (dd, 1H, $J = 11.9$ and 2.9 MHz), 3.83 and 4.10 (2× dd, 1H, $J = 10.3$ and 11.9 MHz), 5.18 (dd, 1H, $J = 10.3$ and 2.9 MHz); 5.31 and 5.45 (2× s, 2H), 7.02 (t, 2H, $J = 8.6$), 7.30–7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.90 (CH_3), 13.84 (CH_3), 21.64 (CH_2), 23.18 (CH_2), 24.78 (CH_2), 28.56 (CH_2), 28.63 (CH_2), 31.88 (CH_3), 32.23 (CH_2), 34.96 (CH_2), 35.82 (CH), 36.43 (CH_2), 39.41 (CH_2), 42.07 (CH), 44.59 (C × 2), 54.20 (CH), 57.00 (CH), 62.89 (CH_2), 64.15 (CH), 80.66 and 80.79 (CH), 103.34 and 103.44 (C), 115.63 (CH), 116.05 (CH), 116.86 (CH_2), 128.51 (CH), 128.67 (CH), 135.10 (C), 142.91 (C), 160.58 (C), 209.86 (C); ES-MS (*m*/*z*): 519 $[M+Na]^+$.

Compound **8e**. FT-IR (KBr, cm^{-1}): 1719; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.59 (s, 3H), 0.82 (s, 3H), 0.84–2.02 (m, 21H), 2.10 (s, 3H), 2.51–2.55 (m, 2H), 3.73 (dd, 1H, $J = 11.9$ & 2.7 MHz), 3.88 and 4.02 (2× dd, 1H, $J = 11.9$ and 10.1 MHz), 5.15 (dd, 1H, $J = 10.1$ and 2.7 MHz), 5.34 and 5.49 (2× s, 2H), 7.29–7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.92 (CH_3), 13.84 (CH_3), 21.63 (CH_2), 23.17 (CH_2), 24.83 (CH_2), 28.76 (CH_2), 28.77 (CH_2), 31.87 (CH_3), 32.20 (CH_2), 34.95(CH_2), 35.79 (CH), 36.41 (CH_2), 39.38 (CH_2), 42.25 (CH), 44.55 (C × 2), 54.17 (CH), 56.97 (CH), 62.83 (CH_2), 64.11 (CH), 80.43 and 80.56 (CH), 103.21 and 103.33 (C), 117.36 (CH_2), 128.13 (CH × 2), 129.10 (CH × 2), 134.46 (C), 137.46 (C), 142.68 (C), 209.76 (C). ES-MS (*m*/*z*) 512 $[M+Na]^+$. Anal. Calcd for $C_{31}H_{41}ClO_4$: C 72.56%, H 8.05%; Found C 72.45%, H 8.33%.

Compound **8f**. FT-IR (KBr, cm^{-1}): 1712; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.60 (s, 3H), 0.82 (s, 3H), 1.21–2.02 (m, 21H), 2.10 (s, 3H), 2.51–2.55 (m, 2H), 3.73 (dd, 1H, $J = 11.5$ and 2.7 MHz), 3.88 and 4.02 (2× dd, 1H, $J = 10.0$ & 11.5 MHz), 5.15 (dd, 1H, $J = 10.0$ and 2.7 MHz), 5.34 and 5.50 (2× s, 2H), 7.24–7.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.84 (CH_3), 13.86 (CH_3), 21.65 (CH_2), 23.21 (CH_2), 24.80 (CH_2), 28.41 (CH_2), 28.79 (CH_2), 31.91 (CH_3), 32.20 (CH_2), 34.99 (CH_2), 35.85 (CH), 36.46 (CH_2), 39.44 (CH_2), 42.09 (CH), 44.62 (C × 2), 54.22 (CH), 57.02 (CH), 62.86 (CH_2), 64.19 (CH), 80.46 and 80.50 (CH), 103.93 and 103.31 (C), 117.48 (CH_2), 122.70 (C), 128.48 (CH × 2), 129.10 (CH × 2), 137.97 (C), 143.79 (C), 209.97 (C); ES-MS (*m*/*z*) 579 $[M+Na]^+$; Anal. Calcd for $C_{31}H_{41}BrO_4$: C 66.78%, H 7.41%; Found C 66.43%, H 7.98%. **9b.** ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.78 (s, 3H), 0.80 (d, 3H, $J = 6.3$ MHz), 0.89 (s, 3H), 0.97 (d, 3H, $J = 6.9$ MHz), 1.11–2.01 (m, 27H), 3.37 (t, 1H, $J = 12.0$ MHz), 3.48 (dd, 1H, $J = 12.0$ and 6.0 MHz), 3.75 (dd, 1H, $J = 12.0$ and 2.1 MHz), 3.83 (s, 3H), 3.86–3.90 and 3.99–4.08 (2× m, 1H), 4.37–4.45 (m, 1H), 5.24–5.26 (m, 1H), 5.28 and 5.43 (2× s, 2H), 6.88 and 6.96 (2× d, 2H, $J = 9.0$ MHz), 7.34 and 7.36 (2× d, 2H, $J = 9.0$ MHz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 11.29 (CH_3), 14.23 (CH_3), 16.91 (CH_3), 17.03 (CH_3), 21.38 (CH_2), 27.54 (CH_2), 29.02 (CH_2), 30.11 (CH_2), 31.50 (CH_2), 32.71 (CH), 34.86 (CH_2), 35.14 (CH_2), 37.15 (CH_2), 38.76 (CH_2), 40.04 (CH_2), 42.82 (CH), 43.13 (CH), 44.08 (C × 2), 54.18 (CH),55.24 (CH), 55.65 (CH_3), 62.56 (CH), 63.24 (CH_2), 65.55 (CH_2), 67.18 (CH_2), 79.94 (CH), 81.24 (CH), 101.52 and 101.59 (C), 108.65 (C), 112.65 (CH_2), 126.28 (CH × 2), 129.79 (CH × 2), 136.10 (C), 138.43 (C), 158.33 (C); ES-MS (*m*/*z*) 606 $[M+H]^+$; Anal. Calcd for $C_{38}H_{54}O_6$: C 75.28%, H 8.97%; Found C 75.01%, H 9.26%.

Compound **9c**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.78 (s, 3H), 0.80 (d, 3H, $J = 6.3$ MHz), 0.85 (s, 3H), 0.97 (d, 3H, $J = 6.8$ MHz), 1.10–1.88 (m, 27H), 2.36 (s, 3H), 3.87 (t, 1H, $J = 10.7$ MHz), 3.47 (dd, 1H, $J = 10.4$ and 3.3 MHz), 3.73 and 3.77 (2× dd, 1H, $J = 11.9$ and 3.0 MHz), 3.89 and 4.02 (2× dd, 1H, $J = 11.9$ and 10.3 MHz), 4.36–4.44 (m, 1H), 5.22 and 5.25 (2× dd, 1H, $J = 10.3$ and 3.0 MHz), 5.28 and 5.47 (2× s, 2H), 7.15 and 7.16 (2× d, 2H, $J = 8.0$ MHz), 7.28 and 7.30 (2× d, 2H, $J = 8.0$ MHz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 11.90 (CH_3), 14.93 (CH_3), 16.91 (CH_3), 17.57 (CH_3), 21.38 (CH_2), 21.55 (CH_3), 27.12 (CH_2), 28.42 (CH_2), 31.11 (CH_2), 32.50 (CH_2), 32.71 (CH), 34.86 (CH_2), 35.14 (CH_2), 37.15 (CH_2), 39.48 (CH_2), 40.04 (CH_2), 42.82 (CH), 43.13 (CH), 44.03 (C × 2), 54.21 (CH), 56.64 (CH), 62.56 (CH), 63.24 (CH_2), 64.11 (CH_2), 67.18 (CH_2), 80.74 (CH), 81.24 (CH), 103.21 and 103.35 (C), 109.64 (C), 115.85 (CH_2), 126.65 (CH × 2), 129.65 (CH × 2), 136.10 (C), 138.43 (C), 143.56 (C); FAB-MS (*m*/*z*): 591 $[M+H]^+$; Anal. Calcd for $C_{38}H_{54}O_5$: C 77.25%, H 9.21%; Found C 76.81%, H 8.88%.

11. *In vivo test procedure*. The colony-bred Swiss mice (25 ± 1 g) were inoculated with 1×10^6 parasitized RBC on day 0 and treatment was administered to a group of five mice at each dose, from day 0 to day 3, in two divided doses daily. The drug dilutions of compounds **7a–f**, **8a–f** and **9b–e** were prepared in groundnut oil 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) in 0.1 ml and administered orally. Parasitaemia level was recorded from thin blood smears between day 4 and 28.[13] The treated mice surviving beyond day 28 were recorded as the mice protected by the drug. Mice treated with β-Arteether served as positive controls.
12. (a) One hundred percent suppression of parasitaemia means number of parasites below the detection limit; (b) One hundred percent protection means all the treated mice survive until day 28. Similarly 50% and 20% protection mean only 50% and 20% of the treated mice survive until day 28.
13. Puri, S. K.; Singh, N. *Exp. Parasitol* **2000**, *94*, 8.
14. Most researchers in this field use the *Plasmodium berghei* mouse-model for the antimalarial screening. But we find multi-drug resistant *P. yoelii* mouse-model is a more reliable model for the discovery of new compounds to combat drug-resistant malaria.
15. Cavallini, G.; Massarani, E.; Nardi, D. *J. Med. Chem.* **1964**, *7*, 673.