Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 18 (2008) 1436–1441
Bioorganic & Medicinal Chemistry Letters

Orally active esters of dihydroartemisinin: Synthesis and antimalarial activity against multidrug-resistant *Plasmodium yoelii* in mice☆

Chandan Singh,[a,*] Sandeep Chaudhary[a] and Sunil K. Puri[b]

[a]*Division of Medicinal and Process Chemistry, Central Drug Research Institute, Lucknow 226001, India*
[b]*Division of Parasitology, Central Drug Research Institute, Lucknow 226001, India*

Received 27 November 2007; revised 25 December 2007; accepted 29 December 2007
Available online 5 January 2008

Abstract—A series of artemisinin derived esters **7a**–**j**, incorporating pharmacologically privileged substructure, such as biphenyl, adamantane and fluorene, have been prepared and evaluated for antimalarial activity against multidrug-resistant (MDR) *Plasmodium yoelii nigeriensis* by oral route. Several of these compounds were found to be more active than the antimalarial drugs β-arteether **4** and artesunic acid **5**. Ester **7i**, the most active compound of the series, provided 100% and 80% protection to the infected mice at 24 mg/kg × 4 days and 12 mg/kg × 4 days, respectively. In this model β-arteether provided 100% and 20% protection at 48 mg/kg × 4 days and 24 mg/kg × 4 days, respectively.

The discovery of artemisinin **1**, as the active principle of the Chinese traditional drug against malaria, *Artemisia annua*, is a major breakthrough in malaria chemotherapy. The derivatives of artemisinin, for example, dihydroartemisinin **2**, artemether **3**, arteether **4** and artesunic acid **5** (Fig. 1), are more active than the parent compound, and are currently the drugs of choice for the treatment of malaria caused by multidrug-resistant *P. falciparum*.[2,3]

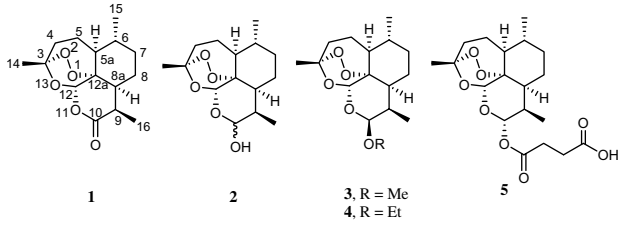


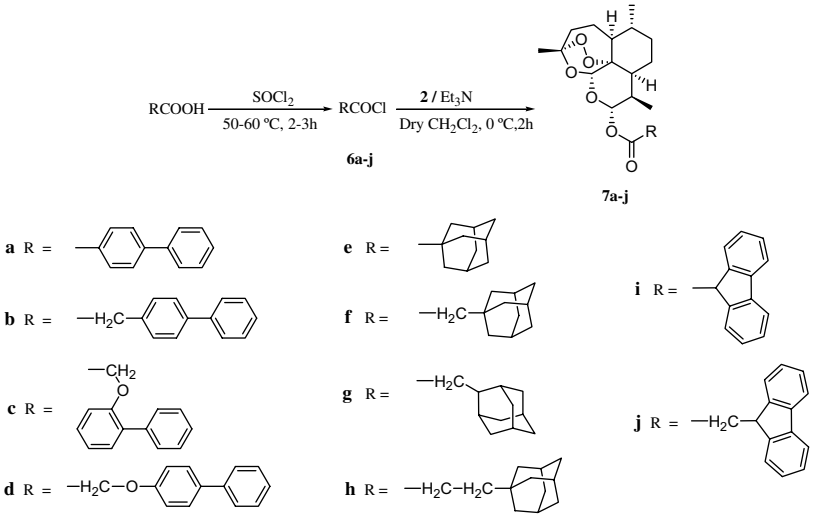
Figure 1. Artemisinin and its clinically useful derivatives.

While these compounds show high efficacy when administered by systemic routes, they are comparatively less active when given by oral route. We have recently reported the synthesis of a series of lipophilic ether derivatives of dihydroartemisinin, incorporating pharmacologically privileged substructures such as biphenyl, adamantane and fluorene, some of which showed high order of antimalarial activity against multidrug-resistant *P. yoelii* in mice by oral route.[4] A noticeable feature of these derivatives was that α-isomers, the minor products of acid catalysed etherification of dihydroartemisinin, were significantly more active than the corresponding β-isomers. Since base-catalysed esterification of dihydroartemisinin with acid chlorides/anhydrides furnishes exclusively α-isomers,[5] it made commercial sense to us to prepare and evaluate for activity the corresponding ester derivatives, incorporating these pharmacologically privileged substructures. In the event, several of these derivatives, showed very promising antimalarial activity against multidrug-resistant malaria in mice by oral route. Herein, we report the details of this study.[6]

Dihydroartemisinin **2** was prepared from artemisinin **1** using the known procedure.[7] The acid chlorides RCOCl **6a**–**j** were prepared from the corresponding carboxylic acids by heating with thionyl chloride at 50–60 °C for 2–3 h and reacted with dihydroartemisinin **2** in the presence of triethylamine in dry dichloromethane at 0 °C for

Keywords: Dihydroartemisinin; Arteether; Antimalarial; Multidrug-resistant; 1,2,4-Trioxanes.
☆ Ref. 1.
* Corresponding author. Tel.: +91 0522 2612411 18x4220; fax: +91 522 2623405; e-mail: chandancdri@yahoo.com

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.12.074



Scheme 1. Synthesis of ester derivatives **7a**–**j**.

2 h to furnish ester derivatives **7a**–**j** in 49–58% yields (Scheme 1, Table 1).[8]

Antimalarial drugs β-arteether and artesunic acid, when given orally at 48 mg/kg × 4 days, provide 100% protection to the mice infected with multidrug-resistant *P. yoelii nigeriensis*. At 24 mg/kg × 4 days, while artesunic acid does not provide any protection, β-arteether provides only 20% protection. Since the objective of the present study was to select compounds having activity profile better than that of β-arteether and artesunic acid, all the newly prepared ester derivatives **7a**–**j** were initially screened against multidrug-resistant *P. yoelii nigeriensis* in Swiss mice at 48 mg/kg × 4 days by oral route.[9] All these ester derivatives provided 100% protection at this dose and therefore all these active compounds were further screened at 24 mg/kg × 4 days. Compounds **7f**, **7i** and **7j** which showed 100% protection at 24 mg/kg × 4 days were further tested at 12 mg/kg × 4 days. The results are summarized in Table 2.

The semi-synthetic derivatives of artemisinin such as artemether **3**, arteether **4** and artesunic acid **5** are highly effective against both chloroquine-sensitive and resistant malaria. They are fast acting and are currently the drugs of choice for the treatment of complicated cases of malaria caused by multidrug-resistant *P. falciparum*. While these drugs show high efficacy when administered by systemic routes, they are comparatively less active when given orally. In our search for artemisinin derivatives with high efficacy by oral route, we had recently reported a series of ether derivatives of dihydroartemisinin, incorporating adamantane, biphenyl and fluorene moieties. Several of these lipophilic derivatives were found to be 2–4 times more active than arteether by oral route.[5,10,11] We also observed that the α-isomers, that is, **8a**–**d** of these ether derivatives were significantly more active than the corresponding β-isomers **9a**–**d** (Fig. 2).

This was a serious limitation because the α-isomers were the minor products (20–25% of the α- and β-mixture) and the isolation of the pure isomers required extensive chromatographic separation. The observation, however, suggested that a bulkier group on the α-face of the molecule has beneficial effect on antimalarial activity and

Table 1. Ester derivatives **7a**–**j**

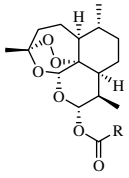
Compound	 R =	Mp	% Yield
7a		59–61 °C	57
7b		63–65 °C	57
7c		57–59 °C	56
7d		86–88 °C	53
7e		85–87 °C	49
7f		115–117 °C	58
7g		73–75 °C	57
7h		115–116 °C	55
7i		75–77 °C	52
7j		73–75 °C	57

Table 2. Blood schizontocidal activity of esters **7a**–**j** against multidrug-resistant (MDR) strain *P. yoelii nigeriensis* in Swiss mice via oral route[9]

Compound	Log *P*	Dose (mg/kg × 4 days)[a]	% Suppression of parasitaemia on day 4[b,c]	Cured/ Treated
7a	6.95	48	100	5/5
		24	100	3/5
7b	6.89	48	100	5/5
		24	100	3/5
7c	6.53	48	100	5/5
		24	100	2/5
		12	100	0/5
7d	6.53	48	100	5/5
		24	100	1/5
7e	6.05	48	100	5/5
		24	100	0/5
7f	5.99	48	100	5/5
		24	100	5/5
		12	100	1/5
7g	5.85	48	100	5/5
		24	100	4/5
		12	100	0/5
7h	6.41	48	100	5/5
		24	100	3/5
		12	100	0/5
7i	6.61	48	100	5/5
		24	100	5/5
		12	100	4/5
7j	6.79	48	100	5/5
		24	100	5/5
		12	100	0/5
4	3.84	48	100	5/5
		24	100	1/5
5	3.04	48	100	5/5
		24	100	0/5

[a] The drug dilutions of compounds were prepared in groundnut oil and administered to a group of mice at each dose, from day 0 to 3, once daily.
[b] Percent suppression = $[(C–T)/C] \times 100$; where C = parasitaemia in control group and T = parasitaemia in treated group.
[c] 100% suppression of parasitaemia means no parasites were detected in 50 oil immersion fields during microscopic observation.[12]

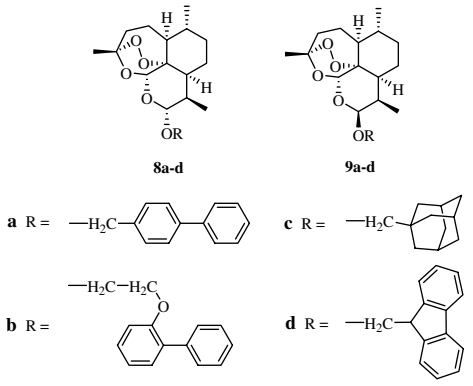


Figure 2. Structure of active ether derivatives of dihydroartemisinin **8a**–**d**.

prompted us to prepare ester derivatives of dihydroartemisinin incorporating similar substructure. The ester derivatives of dihydroartemisinin have the advantage over the ether derivatives as they are obtained exclusively as α-isomers and therefore their purification does not require elaborate chromatographic separation. In the event we prepared and screened against multidrug-resistant *P. yoelii* 10 ester derivatives **7a**–**j** incorporating adamantane, biphenyl and fluorene moieties. The lipophilicity of these derivatives (Log *P* 5.85–6.95) is comparable with that of the active ether derivatives **8a**–**d** (Log *P* 5.51–6.91) earlier reported by us.

As can be seen from Table 2, all these compounds provided 100% protection at 48 mg/kg × 4 days and therefore all these derivatives are at least as effective as β-arteether which provided 100% and 20% protection at 48 mg/kg × 4 days and 24 mg/kg × 4 days; respectively. Among the biphenyl derivatives only **7a** and **7b** provided significant protection (60% protection) at 24 mg/kg × 4 days. The adamantane-based esters showed better activity profile; while compound **7f** provided 100% protection at 24 mg/kg, compounds **7g** and **7h** provided 80% and 60% protection, respectively, at this dose. Even at 12 mg/kg × 4 days compound **7f** showed 100% clearance of parasitaemia[12] on day 4 and 20% of the treated mice survived beyond day 28. In this series adamantane moiety linked through C-1 and separated by one CH_2 from the ester group proved to be the optimum for activity; absence of CH_2 or replacement of CH_2 with CH_2CH_2 proved detrimental to biological activity. The fluorene derivative **7i**, the most active compound of the series, provided 100% protection at 24 mg/kg × 4 days. At 12 mg/kg × 4 days, it provided 80% protection. Its homologue **7j** showed 100% protection at 24 mg/kg. At 12 mg/kg × 4 days, it showed 100% clearance of parasitaemia on day 4 but none of the treated mice survived beyond day 28.

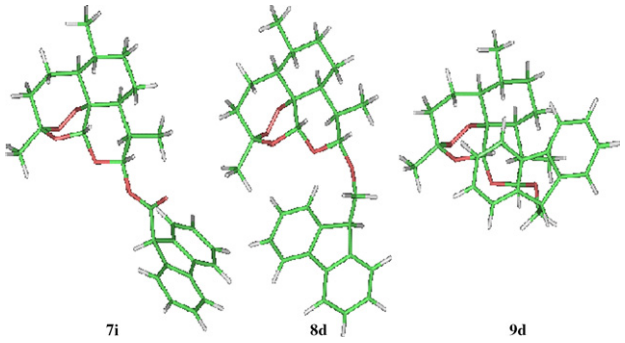


Figure 3. Three-dimensional structure of compounds **7i**, **8d** and **9d**.

Since the present work on ester derivatives was inspired by the excellent results shown by the structurally similar ether derivatives,[4] it is worthwhile to compare the biological activity of these two series. The ester derivatives incorporating the biphenyl moiety on the whole are much less active than their ether counterparts, two of which (**8a** and **8b**) had shown 100% protection at 12 mg/kg × 4 days. In the ether series, in fact, biphenyl-based compounds were more active than the adamantane- and fluorene-based derivatives. In the adamantane-based compounds, both the series have similar level of activity; in both these series the most active compounds are twice as active as β-arteether. In the fluorene-based series, the esters are marginally more active than the ethers.

We also compared the three-dimensional structures of ester **7i**, the most active compound of the series, with the corresponding ethers **8d** (α-isomers) and **9d** (β-isomers) (Fig. 3).[13] Clearly, there is a similarity in the three-dimensional structures of **7i** and **8d**. In both these compounds the C_{10}–O moieties are placed away from the trioxane group while in **9d** it is very close. This probably accounts for the better activity profiles shown by α-isomers of ethers and esters.[14]

In conclusion, we have prepared a series of lipophilic ester derivatives of dihydroartemisinin, several of which show better activity profile than β-arteether and artesunic acid. Compound **7i**, the most active compound of the series, is more than twice as active as β-arteether and artesunic acid.

Acknowledgments

Sandeep Chaudhary is thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi, for the award of Senior Research Fellowship. We are thankful to Mr. G.P. Yadav for his help in generating 3D structures.

References and notes

1. CDRI Communication No.: 6926.
2. For reviews on artemisinin and its analogues, see: (a) Klayman, D. L. *Science* **1985**, *228*, 1049; (b) Luo, X. D.; Shen, C. C. *Med. Res. Rev.* **1987**, *7*, 29–52; (c) Cumming, J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1997**, *37*, 253; (d) Bhattacharya, A. K.; Sharma, R. P. *Heterocycles* **1999**, *51*, 1681–1745; (e) Borstnik, K.; Paik, I.; Shapiro, T. A.; Posner, G. H. *Int. J. Parasitol.* **2002**, *32*, 1661; (f) Ploypradith, P. *Acta Trop.* **2004**, *89*, 329; (g) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945; (h) Tang, Y.; Dong, Y.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425; (i) Jefford, C. W. *Curr. Opin. Invest. Drugs* **2004**, *5*, 866; (j) Jefford, C. W. *Drug Discov. Today* **2007**, *12*, 487–494.
3. (a) Asthana, O. P.; Srivastava, J. S.; Valecha, N. *J. Parasitic Diseases* **1997**, *211*, 1–12; (b) Jambou, R.; Legrand, E.; Niang, M.; Khim, N.; Lim, P.; Volney, B.; Therese Ekala, M.; Bouchier, C.; Esterre, P.; Fandeur, T.; Mercereau-Puijalon, O. *Res. Lett.* **2005**, *366*, 1960–1963.
4. Singh, C.; Chaudhary, S.; Puri, S. K. *J. Med. Chem.* **2006**, *49*(24), 7227–7233.
5. Haynes, R. K.; Chan, H.-W.; Cheung, M.-K.; Lam, W.-L.; Soo, M.-K.; Tsang, H.-W.; Voerste, A.; Williams, I. D. *Eur. J. Org. Chem.* **2002**, 113.
6. This work has been covered in an Indian patent: Singh, C.; Chaudhary, S.; Puri, S. K. Indian Patent Appl. No. 0391 DEL 2006, Filing Date 13-02-2006.
7. Brossi, A.; Venugopalan, B.; Dominquez, G. L.; Yeh, H. J. C.; Flippen, A. J. L.; Buchs, P.; Wo, X. D.; Milhous, W.; Peters, W. *J. Med. Chem.* **1988**, *31*, 645.
8. The preparation and antimalarial activity of esters **7a** and **7d** have been reported earlier: (a) Li, Y.; Yu, P.-L.; Chen, I.-H.; Chi, J.-Y. *Yao Hsueh Tung Pao* **1980**, *15*, 38, *Chem. Abstr.* **1980**, *96*, 6883u; (b) Li, Y.; Yu, P.; Chen, Y.; Ji, R. *HuaXue XueBao* **1982**, *40*, 557–561; *Chem. Abstr.* **1982**, *98*, 4420h. (b) *General procedure for esterification of dihydroartemisinin (compound* **7a** *as representative)*. To a solution of dihydroartemisinin (0.50 g, 1.75 mmol) and biphenyl-4-carbonyl chloride (1.14 g, 3 equiv, 5.25 mmol) dissolved in dry dichloromethane (30 mL) was added triethylamine (0.73 ml, 3 equiv, 5.29 mmol) dropwise at 0 °C. The mixture was stirred at the same temperature for 2 h. The reaction mixture was then quenched with saturated sodium bicarbonate solution (25 mL) and extracted with dichloromethane (3× 25 mL). The organic layer was washed with 10% aqueous HCl solution (2× 20 mL), then with water, dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The crude product on column chromatography over silica gel using ethyl acetate/hexane (1:25) as eluant gave pure **7a** (465 mg, 57%) as a white solid. (c) *Selected spectral data*. Compound **7a**: White solid; FT-IR (KBr, cm^{-1}): 2932.3, 2876.9, 1729.0, 1608.1, 1452.4, 1378.2, 1269.4, 1201.8, 1130.6, 1087.8, 1016.9, 754.2; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, 3H, J = 7.1 Hz, CH_3), 0.98 (d, 3 H, J = 5.8 Hz, CH_3), 1.25–2.10 (m, 10H), 1.43 (s, 3H, CH_3), 2.32–2.46 (m, 1H), 2.74–2.80 (m, 1H), 5.54 (s, 1H, C_{12}–H), 6.03 (d, 1H, J = 9.8 Hz, C_{10}–H), 7.38–7.51 (m, 3H), 7.60–7.68 (m, 4H), 8.18 (d, 2H, J = 8.4 Hz); FABMS (*m/z*): 465 $[M+H]^+$; ESMS (*m/z*): 482 $[M+NH_4]^+$, 487 $[M+Na]^+$; Anal. Calcd for ($C_{28}H_{32}O_6$·0.1-H_2O): C 72.38 H 6.94; Found C 72.11 H 6.96. Compound **7b**: White solid; FT-IR (KBr, cm^{-1}): 2931.5, 2875.8, 1748.8, 1487.4, 1452.0, 1379.1, 1243.1, 1141.1, 1099.7, 1019.8, 756.3; ^1H NMR (200 MHz, $CDCl_3$) δ 0.74 (d, 3H, J = 7.0 Hz, CH_3), 0.95 (d, 3H, J = 5.1 Hz, CH_3), 1.17–2.07 (m, 10H), 1.45 (s, 3H, CH_3), 2.30–2.44 (m, 1H), 2.52–2.63 (m, 1H), 3.75 (s, 2H), 5.44 (s, 1H, C_{12}–H), 5.80 (d, 1H, J = 9.8 Hz, C_{10}–H), 7.29–7.59 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.37 (CH_3), 20.60 (CH_3), 22.38 (CH_2), 24.99 (CH_2), 26.39 (CH_3), 32.30 (CH), 34.49 (CH_2), 36.64 (CH_2), 37.66 (CH), 41.31(CH_2), 45.68 (CH), 51.98 (CH), 80.55 (C), 91.97 (CH), 92.71 (CH),

104.89 (C), 127.46 (CH), 127.66 (CH), 129.15 (CH), 130.23 (CH), 133.03 (C), 140.49 (C), 141.20 (C), 170.76 (C); ESMS (*m/z*): 501 $[M+Na]^+$; Anal. Calcd for ($C_{29}H_{34}O_6$): C 72.77 H 7.16; Found C 72.47 H 7.53. Compound **7c**: White solid; FT-IR (KBr, cm^{-1}): 1774.7, 1637.8, 1480.8, 1438.5, 1379.1, 1218.0, 1131.9, 1103.4, 1013.8, 770.4; ^1H NMR (200 MHz, $CDCl_3$) δ 0.77 (d, 3H, $J = 7.1$ Hz, CH_3), 0.96 (d, 3H, $J = 5.3$ Hz, CH_3), 1.25–2.07 (m, 10H), 1.44 (s, 3H, CH_3), 2.30–2.44 (m, 1H), 2.50–2.57 (m, 1H), 4.67 (s, 2H), 5.44 (s, 1H, C_{12}–H), 5.80 (d, 1H, $J = 9.8$ Hz, C_{10}–H), 6.87–7.62 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.38 (CH_3), 20.60 (CH_3), 22.37 (CH_2), 24.98 (CH_2), 26.32 (CH_3), 32.18 (CH), 34.47 (CH_2), 36.61 (CH_2), 37.68 (CH), 45.64 (CH), 51.93 (CH), 66.08 (CH_2), 80.49 (C), 91.99 (CH), 93.07 (CH), 104.96 (C), 113.22 (CH), 122.59 (CH), 127.50 (CH), 128.45 (CH), 128.93 (CH), 130.04 (CH), 131.67 (CH), 138.43 (C), 155.08 (C), 168.32 (C); ESMS (*m/z*): 512 $[M+Na]^+$; Anal. Calcd for ($C_{29}H_{34}O_7$): C 70.43 H 6.93; Found C 70.28 H 7.15. Compound **7d**: White solid; FT-IR (KBr, cm^{-1}): 2928.9, 2874.4, 1774.3, 1607.4, 1519.4, 1488.0, 1452.0, 1379.4, 1354.4, 1273.2, 1178.5, 1133.1, 1103.1, 1081.8, 1013.2, 764.3; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83 (d, 3H, $J = 7.0$ Hz, CH_3), 0.96 (d, 3H, $J = 5.1$ Hz, CH_3), 1.17–2.07 (m, 10H), 1.43 (s, 3H, CH_3), 2.31–2.44 (m, 1H), 2.55–2.62 (m, 1H), 4.70 and 4.80 (2 × d, 2H, $J = 16.1$ Hz, $CO\mathit{CH}_2O$), 5.46 (s, 1H, C_{12}–H), 5.91 (d, 1H, $J = 9.8$ Hz, C_{10}–H), 6.96–7.55 (m, 9H); ESMS (*m/z*): 517 $[M+Na]^+$; HR-EIMS for ($C_{29}H_{34}O_7$): Measured 494.2326, Calculated 494.2305; Anal. Calcd for ($C_{29}H_{34}O_7 \cdot 0.1H_2O$): C 70.43 H 6.93; Found C 70.21 H 6.94. Compound **7e**: White solid; mp 85–87 °C; FT-IR (KBr, cm^{-1}): 3020.4, 2910.3, 1742.5, 1451.9, 1368.5, 1219.4, 1133.5, 1098.3, 1022.0, 769.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (d, 3H, $J = 7.1$ Hz, CH_3), 0.96 (d, 3H, $J = 5.6$ Hz, CH_3), 1.25–2.01 (m, 25H), 1.42 (s, 3H, CH_3), 2.29–2.43 (m, 1H), 2.53–2.59 (m, 1H), 5.42 (s, 1H, C_{12}–H), 5.75 (d, 1H, $J = 9.7$ Hz, C_{10}–H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.58 (CH_3), 20.63 (CH_3), 22.42 (CH_2), 24.97 (CH_2), 26.29 (CH_3), 28.28 (3 × CH), 32.37 (CH_2), 34.53(CH_2), 36.87 (3 × CH_2), 37.64 (CH), 38.98 (3 × CH_2), 41.20 (CH), 45.73 (CH), 52.07 (CH), 80.58 (C), 91.94 (CH), 104.71 (C), 176.63 (C); ESMS (*m/z*): 469 $[M+Na]^+$; Anal. Calcd for ($C_{26}H_{38}O_6$): C 69.92 H 8.57; Found: C 69.48 H 8.46. Compound **7f**: White solid; mp 115–117 °C; FT-IR (KBr, cm^{-1}): 2914.3, 1751.0, 1452.2, 1401.9, 1375.0, 1267.5, 1161.1, 1096.0, 1020.3; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, 3H, $J = 7.0$ Hz, CH_3), 0.96 (d, 3H, $J = 5.6$ Hz, CH_3), 1.25–2.08 (m, 25H), 1.42 (s, 3H, CH_3), 2.15–2.23 (m, 2H), 2.29–2.45 (m, 1H), 2.50–2.61 (m, 1H), 5.43 (s, 1H, C_{12}–H), 5.77 (d, 1H, $J = 9.8$ Hz, C_{10}–H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.84 (CH_3), 20.62 (CH_3), 22.38 (CH_2), 25.01 (CH_2), 26.34 (CH_3), 29.00 (3 × CH), 31.98 (CH), 33.21 (C), 34.54 (CH_2), 36.63 (CH_2), 37.12 (3 × CH_2), 37.68 (CH), 42.73 (3 × CH_2), 45.77 (CH), 49.18 (CH_2), 51.99 (CH), 80.51 (C), 91.76 (CH), 91.96 (CH), 104.75 (C), 170.92 (C); FABMS (*m/z*): 461 $[M+H]^+$; ESMS (*m/z*): 483 $[M+Na]^+$; Anal. Calcd for ($C_{27}H_{40}O_6$): C 70.40 H 8.75; Found C 70.87 H 9.09. Compound **7g**: White solid; mp 73–75 °C; FT-IR (KBr, cm^{-1}) 2909.7, 2855.5, 1742.2, 1452.4, 1411.7, 1377.5, 1251.0, 1150.0, 1099.7, 1021.8, 757.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83 (d, 3H, $J = 6.9$ Hz, CH_3), 0.96 (d, 3H, $J = 5.0$ Hz, CH_3), 1.25–2.06 (m, 25H), 1.43 (s, 3H, CH_3), 2.24–2.37 (m, 1H), 2.46–2.57 (m, 3H), 5.44 (s, 1H, C_{12}–H), 5.78 (d, 1H, $J = 9.8$ Hz, C_{10}–H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.46 (CH_3), 20.60 (CH_3), 22.37 (CH_2), 24.99 (CH_2), 26.33 (CH_3), 28.24 (2 × CH), 31.90 (2 × CH_2), 32.17 (3 × CH), 34.51 (CH_2), 36.62 (CH_2), 37.64 (CH), 38.56 (2 × CH_2), 39.24 (2 × CH_2), 41.36 (CH), 45.70 (CH), 51.97 (CH), 80.50 (C), 91.84 (CH), 92.00 (CH), 104.78 (C), 172.58 (C); FABMS (*m/z*): 461 $[M+H]^+$; ESMS (*m/z*): 478 $[M+NH_4]^+$, 483 $[M+Na]^+$; Anal. Calcd for ($C_{27}H_{40}O_6$): C 70.40 H 8.75; Found C 70.12 H 9.10. Compound **7h**: White solid; FT-IR (KBr, cm^{-1}): 2920.0, 2853.7, 1751.5, 1591.3, 1457.0, 1378.5, 1352.1, 1161.9, 1096.4, 1022.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (d, 3H, $J = 7.0$ Hz, CH_3), 0.95 (d, 3H, $J = 5.6$ Hz, CH_3), 1.25–2.10 (m, 27H), 1.43 (s, 3H, CH_3), 2.15–2.24 (m, 2H), 2.36–2.45 (m, 1H), 2.53–2.59 (m, 1H), 5.43 (s, 1H, C_{12}–H), 5.77 (d, 1H, $J = 9.8$ Hz, C_{10}–H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.85 (CH_3), 20.63 (CH_3), 22.39 (CH_2), 24.99 (CH_2), 26.35 (CH_3), 29.01 (3 × CH), 31.99 (CH), 33.22 (C), 34.53 (CH_2), 35.15 (CH_2), 36.64 (CH_2), 37.13 (3 × CH_2), 37.69 (CH), 42.74 (3 × CH_2), 45.78 (CH), 49.19 (CH_2), 52.00 (CH), 80.52 (C), 91.77 (CH), 91.97 (CH), 104.76 (C), 170.93 (C); FABMS (*m/z*): 475 $[M+H]^+$; ESMS (*m/z*): 497 $[M+Na]^+$; Anal. for ($C_{28}H_{42}O_6$): Calcd C 70.86 H 8.92; Found C 70.57 H 8.99. Compound **7i**: White solid; FT-IR (KBr, cm^{-1}) 2943.8, 1750.1, 1596.9, 1451.5, 1353.0, 1276.0, 1190.4, 1139.1, 1100.8, 1015.9, 744.8; ^1H NMR (200 MHz, $CDCl_3$) δ 0.80 (d, 3H, $J = 7.1$ Hz, CH_3), 0.96 (d, 3H, $J = 5.6$ Hz, CH_3), 1.25–2.09 (m, 10H), 1.47 (s, 3H, CH_3), 2.27–2.48 (m, 1H), 2.68–2.74 (m, 1H), 4.99 (s, 1H, benzylic H), 5.46 (s, 1H, C_{12}–H), 5.87 (d, 1H, $J = 9.8$ Hz, C_{10}–H), 7.32–7.45 (m, 4H), 7.65–7.82 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.69 (CH_3), 20.61 (CH_3), 22.34 (CH_2), 25.01 (CH_2), 26.39 (CH_3), 32.35 (CH), 34.48 (CH_2), 36.67 (CH_2), 37.63 (CH), 45.78 (CH), 51.96 (CH), 53.61 (CH), 80.52 (C), 91.99 (CH), 93.31 (CH), 104.87 (C), 120.33 (CH), 120.48 (CH) 126.21 (CH), 126.79 (CH), 127.66 (CH), 127.82 (CH), 128.60 (CH), 140.49 (C), 140.78 (C), 141.90 (C), 169.87 (C); FABMS (*m/z*): 476 $[M]^+$, 477$[M+H]^+$; ESMS (*m/z*): 499 $[M+Na]^+$; Anal. Calcd for ($C_{29}H_{32}O_6$): C 73.09 H 6.77; Found C 73.38 H 6.73. Compound **7j**: White solid; FT-IR (KBr, cm^{-1}) 2929.9, 2877.2, 1747.2, 1653.9, 1529.6, 1450.4, 1350.9, 1275.6, 1216.2, 1145.2, 1097.4, 1014.1, 755.9; ^1H NMR (200 MHz, $CDCl_3$) δ 0.84 (d, 3H, $J = 7.1$ Hz, CH_3), 0.98 (d, 3H, $J = 5.3$ Hz, CH_3), 1.25–2.08 (m, 10H), 1.45 (s, 3H, CH_3), 2.31–2.38 (m, 1H), 2.53–2.63 (m, 1H), 2.79 (dd, 1H, $J = 16.12$ Hz, 6.55 Hz), 2.96 (dd, 1H, $J = 16.4$ Hz, 7.56 Hz), 4.44 (br t, 1H, benzylic H), 5.50 (s, 1H, C_{12}–H), 5.92 (d, 1H, $J = 9.8$ Hz, C_{10}–H), 7.28–7.41 (m, 4H), 7.51–7.58 (m, 2H), 7.75 (d, 2H, $J = 7.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.61 (CH_3), 20.65 (CH_3), 22.46 (CH_2), 25.03 (CH_2), 26.38 (CH_3), 32.11 (CH), 34.53 (CH_2), 36.63 (CH_2), 37.72 (CH), 39.10 (CH_2), 43.77 (CH), 45.68 (CH), 51.98 (CH), 80.55 (C), 91.90 (CH), 92.77 (CH), 104.90 (C), 120.30 (CH), 120.42 (CH), 124.77 (CH), 124.94 (CH), 127.68 (CH), 127.88 (CH), 128.01 (CH), 141.20 (C), 146.41 (C), 146.66 (C), 171.88 (C); ESMS (*m/z*): 508 $[M+NH_4]^+$, 513 $[M+Na]^+$; Anal. Calcd for ($C_{30}H_{34}O_6$): C 73.45 H 6.99; Found C 73.30 H 6.95.

9. (a) Peters, W. In *Chemotherapy and Drug Resistance in Malaria*; Academic Press: London, 1970; pp 64–136; (b) *In vivo antimalarial efficacy test.* The blood schizontocidal activity of the test compounds was evaluated in rodent model using multidrug-resistant strain of *Plasmodium yoelii nigeriensis*. Multidrug-resistant *Plasmodium yoelii nigeriensis* used in this study is resistant to chloroquine, mefloquine and halofantrine. The colony bred Swiss mice of either sex (20 ± 2 g) were inoculated intraperitoneally with 1×10^5 *P. yoelii* (MDR) parasites on day zero, and treatment was administered to group of five mice at each dose, from day 0 to 3, once daily. The drug dilutions of all compounds were prepared in groundnut oil so as to contain the required amount of the drug (0.6 mg/kg for a dose of 48 mg/kg, 0.3 mg for a dose of 24 mg/kg, 0.15 mg

for a dose of 12 mg/kg) in 0.1 mL and administered orally for each dose. Parasitaemia level was recorded from thin blood smears on day 4 and subsequently twice a week until day 28. The animals which did not develop patent infection until day 28 were recorded as cured.[15] Mice treated with β-arteether served as positive control.

10. (a) Also in our programme on synthetic 1,2,4-trioxanes, we had observed that trioxane built around these moieties showed promising antimalarial activity: Singh, C.; Kanchan, R.; Puri, S. K. Indian Patent Appl. No. 1554 DEL 99, **1999**; (b) Singh, C.; Tiwari, P.; Puri, S. K. U.S. Patent 6,737,438 B2, **2004**; (c) Singh, C.; Kanchan, R.; Sharma, U.; Puri, S. K. *J. Med. Chem.* **2007**, *50*(3), 521–527.
11. (a) Hindley, S.; Ward, S. A.; Storr, R. C.; Searle, N. L.; Bray, P. G.; Park, B. K.; Davies, J.; O'Neill, P. M. *J. Med. Chem.* **2002**, *45*, 1052–1063; (b) Avery, M. A.; Alvim-Gaston, M.; Vroman, J. A.; Wu, B.; Ager, A.; Peters, W.; Robinson, B. L.; Charman, W. *J. Med. Chem.* **2002**, *45*, 4321–4335; (c) Posner, G. H.; Paik, I.-H.; Sur, S.; McRiner, A. J.; Borstnik, K.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **2003**, *46*, 1060–1065; (d) Grellepois, F.; Chorki, F.; Ourevitch, M.; Charneau, S.; Grellier, P.; McIntosh, K. A.; Charman, W. N.; Pradines, B.; Crousse, B.; Bonnet-delpon, D.; Begue, J. P. *J. Med. Chem.* **2004**, *47*, 1423–1433; (e) Paik, I.-H.; Xie, S.; Shapiro, T. A.; Labonte, T.; Narducci Sarjeant, A. A.; Baege, A. C.; Posner, G. H. *J. Med. Chem.* **2006**, *49*(9), 2731–2734; (f) Posner, G. H.; Paik, I.-H.; Chang, W.; Borstnik, K.; Sinishtaj, S.; Rosenthal, A. S.; Shapiro, T. A. *J. Med. Chem.* **2007**, *50*(10), 2516–2519.
12. (a) 100% suppression of parasitamia means no parasites were detected in 50 oil immersion microscopic fields (parasites if at all present were 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; (b) 100% protection means none of the treated mice developed patent infection during the 28 days observation period and hence were recorded as cured. Similarly 60% protection means only 3 out of 5 mice were cured.
13. Energy minimized three-dimensional structures were generated using Builder (Insight II) module.
14. Following a suggestion from one of the reviewers, we compared the stabilities of artemether **3** and ester **7i** under acidic conditions (1:1 mixture of THF and 10% aqueous HCl). While artemether was completely degraded within 96 h, 80% of the ester **7i** was recovered unchanged under the same conditions.
15. Puri, S. K.; Singh, N. *Expl. Parasitol.* **2000**, *94*, 8–14.