Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 16 (2008) 1816–1821
Bioorganic & Medicinal Chemistry

Orally active 1,2,4-trioxepanes: Synthesis and antimalarial activity of a series of 7-arylvinyl-1,2,4-trioxepanes against multidrug-resistant *Plasmodium yoelii* in Swiss mice☆

Chandan Singh,[a,*] Shilpi Pandey,[a] Malvika Sharma[a] and Sunil K. Puri[b]

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

Received 4 October 2007; revised 1 November 2007; accepted 2 November 2007
Available online 6 November 2007

Abstract—7-Arylvinyl-1,2,4-trioxepanes **7a–d**, **8a–d**, **9a–d**, **10a–d**, **11a–c**, and **12a–c**, prepared by photooxygenation of homoallylic alcohols **5a–d**, were evaluated against multi-drug resistant *Plasmodium yoelii nigeriensis* in Swiss mice by oral and intramuscular routes. Trioxepane **11c**, the most active compound of the series, showed more than 98% suppression of parsitaemia at 96 mg/kg by both oral and intramuscular routes. This is the first report on in vivo active 1,2,4-trioxepanes.

1. Introduction

Malaria is a major threat to the health and economic prosperity to the people living in tropical and subtropical areas. Approximately 40% of the world population lives in areas with the risk of malaria and more than a million die from this disease.[1] The increasing resistance of causal parasite, *Plasmodium* to the contemporary antimalarial drugs, including chloroquine, has further complicated the malaria problem. Against this scenario, isolation of artemisinin **1** as the antimalarial principle of Chinese traditional herb, *Artemisia annua*, is a major milestone in the history of malaria chemotherapy. Ever since its isolation, artemisinin has been a subject of intense structure activity relationship studies.[2]

The antimalarial activity of artemesinin and its clinically useful derivatives such as artemether **2**, arteether **3**, and artesunic acid **4** (Fig. 1) is due to the presence of 1,2,4-trioxane moiety in their molecular structure. Because of the limited availability of artemisinin, currently the focus is on the synthesis and antimalarial assessment of structurally simplified 1,2,4-trioxanes and a variety of methods of their synthesis have been reported in recent years.[3,4]

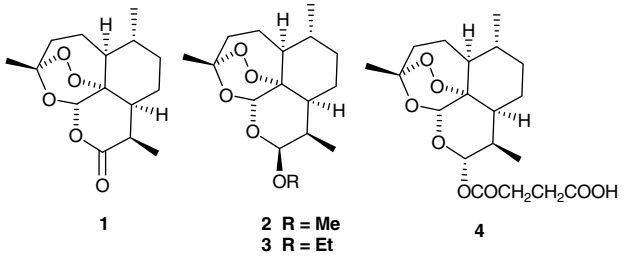


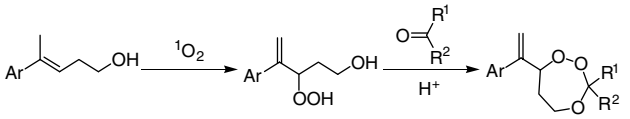
Figure 1.

In contrast, 1,2,4-trioxepanes, the next higher homologs of 1,2,4-trioxanes and the next obvious candidates for structure activity relationship (SAR) studies in this area, have received only limited attention. Only a few methods of their synthesis have been reported,[5–8] the number of compounds synthesized is small and there is only one report on their antimalarial activity.[8]

Earlier, we have reported a photooxygenation route for the preparation of 1,2,4-trioxepanes. The key steps of this method are (i) preparation of γ-hydroxyhydroperoxides by photooxygenation of homoallylic alcohols and (ii) acid catalyzed condensation of these hydroxyhydroperoxides with various ketones to furnish 1,2,4-trioxepanes (Scheme 1).[9]

Keywords: Malaria chemotherapy; 1,2,4-Trioxane; 1,2,4-Trioxepane; Multidrug resistant *Plasmodium yoelii*; Orally active.
☆ CDRI communication number: 7188.
* Corresponding author. Tel.: +91 522 2624273; fax: +91 522 2623405; e-mail: chandancdri@yahoo.com

0968-0896/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2007.11.012



Scheme 1.

Using this methodology we had earlier reported the preparation of trioxepanes **7a–d**, **8a–d** and **9a–d** (Fig. 2).[9] In this article, we report the preparation of related 1,2,4-trioxepanes **10a–d**, **11a–c**, **12a–c** and antimalarial assessment of all these trioxepanes against multidrug resistant *Plasmodium yoelii nigeriensis* in Swiss mice by oral and intramuscular routes. While the activity of a few 1,2,4-trioxepanes against *P. falciparum* in vitro has been reported,[8] to the best of our knowledge this is the first report on in vivo antimalarial assessment of 1,2,4-trioxepanes.

2. Chemistry

Trioxepanes **7a–d**, **8a–d**, and **9a–d** were prepared using the procedure reported earlier.[9] γ-Hydroxyhydroperoxides **6a–d** prepared by photooxygenation of homoallylic alcohols **5a–d** according to the published procedure[9] were condensed with 2-adamantanone to furnish trioxepanes **10a–d** in 7–47% yield. A similar reaction of γ-hydroxyhydroperoxide **6a–c** with 1,4-cyclohexanedione furnished keto trioxepanes **11a–c** in 40–43% yield (Table 1). $LiAlH_4$ reduction of trioxepanes **11a–c** furnished hydroxy functionalized trioxepanes **12a–c** as inseparable mixture of diastereomers in 76–79% yields (Fig. 3).

3. Biological activity

Trioxepanes **7a–d**, **8a–d**, **9a–d**, **10a–d**, **11a–c**, and **12a–c** were evaluated for antimalarial activity against multidrug resistant *P. yoelii nigeriensis* in Swiss mice using the published protocol.[10] All of these compounds were screened at a dose of 96 mg/kg by both oral and intramuscular routes. β-Arteether was used as positive control. The results are summarized in Table 2.

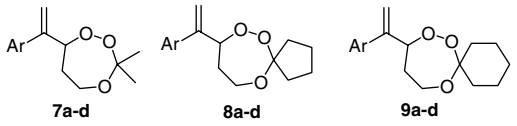


Figure 2. **a**, Ar = phenyl; **b**, Ar = 4-Cl-phenyl; **c**, Ar = 4-biphenyl; **d**, Ar = 1-naphthyl.

Table 1. 1,2,4-Trioxepanes

Compound	Ar	Yield[a] %
10a	Phenyl	46
10b	4-Cl-Phenyl	47
10c	4-Biphenyl	39
10d	1-Naphthyl	7
11a	Phenyl	41
11b	4-Cl-Phenyl	43
11c	4-Biphenyl	40

[a] Yields based on γ-hydroxyhydroperoxides.

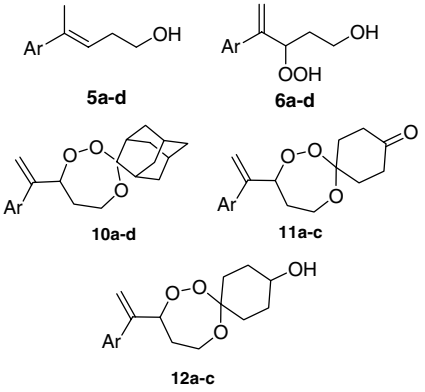


Figure 3. **a**, Ar = phenyl; **b**, Ar = 4-Cl-phenyl; **c**, Ar = 4-biphenyl; **d**, Ar = 1-naphthyl.

4. Results and discussion

As can be seen from Table 2, several of these trioxepanes exhibited significant suppression of parasitaemia on day 4. Keto trioxepane **11c** is the most active compound of the series. It showed 100% and 98% suppression of parasitaemia by intramuscular and oral routes, respectively, but none of the treated mice survived beyond day 14. Structurally related keto trioxepanes **11a** and **11b** are relatively less active. While **11b** showed 100% suppression of parasitaemia by intramuscular route, it exhibited poor activity by oral route; keto trioxepane **11a** showed only moderate suppression of parasitaemia by oral route. Trioxepanes **7a**, **7c** and **9c** also exhibited significant activity; while all these compounds showed more than 90% suppression of parasitaemia by oral route, only **7a** showed significant suppression of parasitaemia by i.m. route. Next in order of activity are trioxepanes **7d**, **11a** and **12c**; all these compounds showed more than 70% suppression of parasitaemia by oral route. The remainder of the trioxepanes exhibited poor activity. A comparison of the activity data of these trioxepanes with our published data[4b,c–1] on structurally related trioxanes shows that trioxepanes as a class are less active than the trioxanes.

As part of our efforts to understand the mechanism of action of 1,2,4-trioxanes, we had earlier reported the Fe (II) catalyzed chemistry of several 1,2,4-trioxanes structurally related to the present 1,2,4-trioxepanes.[11] Trioxepane **8a** when reacted with $FeBr_2$ in similar reaction conditions, behaved similarly and furnished diol **13** and bromo derivative **14** in 29% and 27% yields, respectively (Scheme 2). Structure of bromo derivative **14** was further confirmed through its acetyl derivative **15**. These observations show that the difference in the order of antimalarial activity of these trioxepanes and the related 1,2,4-trioxanes is not due to their sensitivity towards Fe (II) reagents.

5. Conclusion

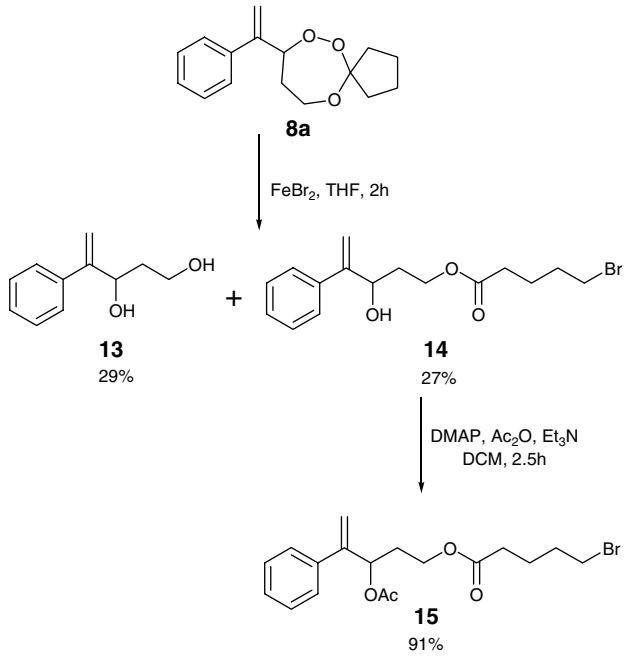
We have evaluated a series of 1,2,4-trioxepanes for antimalarial activity, several of which exhibited significant

Table 2. Antimalarial activity of 1,2,4-trioxepanes against *P. yoelii* in Swiss mice

Ar	Compound	Dose (mg/kg/day)	Route[a]	% Suppression[b] on day 4
Phenyl	**7a**	96	Oral	92.38
		96	i.m.	87.31
4-Cl-phenyl	**7b**	96	Oral	48.77
		96	i.m.	57.64
4-Biphenyl	**7c**	96	Oral	98.22
		96	i.m.	42. 13
1-Naphthyl	**7d**	96	Oral	70.37
		96	i.m.	32.10
Phenyl	**8a**	96	Oral	18.21
		96	i.m.	58.71
4-Cl-phenyl	**8b**	96	Oral	27.16
		96	i.m.	6. 17
4-Biphenyl	**8c**	96	Oral	64.38
		96	i.m.	42.36
1-Naphthyl	**8d**	96	Oral	49.75
		96	i.m.	19.80
Phenyl	**9a**	96	Oral	35.80
		96	i.m.	9.38
4-Cl-phenyl	**9b**	96	Oral	24.69
		96	i.m.	46. 91
4-Biphenyl	**9c**	96	Oral	91.36
		96	i.m.	24.69
1-Naphthyl	**9d**	96	Oral	17.16
		96	i.m.	22.25
Phenyl	**10a**	96	Oral	57.36
		96	i.m.	27.41
4-Cl-phenyl	**10b**	96	Oral	58.38
		96	i.m.	12.18
4-Biphenyl	**10c**	96	Oral	44.78
		96	i.m.	31.98
1-Naphthyl	**10d**	96	Oral	38.27
		96	i.m.	11.11
Phenyl	**11a**	96	Oral	72.02
		96	i.m.	36.60
4-Cl-phenyl	**11b**	96	Oral	23.36
		96	i.m.	100.00
4-Biphenyl	**11c**	96	Oral	98.49
		96	i.m.	100.00
Phenyl	**12a**	96	Oral	53.59
		96	i.m.	21.39
4-Cl-phenyl	**12b**	96	Oral	54.59
		96	i.m.	11.47
4-Biphenyl	**12c**	96	Oral	84.13
		96	i.m.	75.47
β-Arteether	**3**	48	Oral	100

[a] The drug dilution of compounds were prepared in ground nut oil and were administered to a group of 5 mice at each dose from day 0–3 in two divided dose daily.

[b] Percent suppression = $[(C - T)/C] \times 100$, where C = parasitaemia in control group and T = parasitaemia in treated group.



Scheme 2.

activity by oral and intramuscular route. Trioxepane **11c**, the most active compound of the series, showed more than 98% suppression of parasitaemia on day 4 both by oral and intramuscular routes. To the best of our knowledge, this is the first report on in vivo active 1,2,4-trioxepanes.

6. Experimental

6.1. General section

All glass apparatus were oven dried prior to use. Melting points were determined on complab melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR RX-1 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-200 or Brucker DRX-300 (operating at 200 or 300 MHz) 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) in ^{13}C NMR. Fast Atom Bombardment Mass Spectra (FAB-MS) were obtained on JEOL SX 102 spectrometer using argon/xenon (6 kv, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Elemental analyses were done on Perkin-Elmer 2400 C, H, and N analyzer. Reactions were monitored on silica gel TLC plates (coated with TLC grade silica gel, obtained from Merck). Detecting agents used (for TLC) were: iodine vapours and/or spraying with an aq solution of vanillin in 10% sulfuric acid followed by heating at 150 °C. Column chromatograpy was performed over silica gel (60–120 mesh) procured from Qualigens^{TM} (India). All chemicals and reagents were obtained from Aldrich (USA), or Spectrochem (India) and were used without further purification. Anhydrous diethyl ether (ether) used in Grignard reac-

tions was obtained from Spectrochem and was kept over sodium overnight prior to use. γ-Hydroxyhydroperoxides **6a**–**d** were prepared by published procedure.[9]

6.2. General procedure and characterization data

6.2.1. General procedure for the preparation of 1,2,4-trioxepanes from γ-hydroxyhydroperoxides (preparation of 10a as representative). A solution of γ-hydroxyhydroperoxide **6a** (2.0 g), 2-adamantanone (3.1 g, 2 equiv) and conc HCl (0.5 mL) in dichloromethane (50 mL) was stirred for 0.5 h at rt. The reaction mixture was concentrated on a rotatory evaporator at rt and the crude product was purified by column chromatography over silica gel using 0.5% ethyl acetate-hexane as eluent to furnish 1.56 g (46% yield) of **10a** as colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.60–2.14 (m, 15H), 2.31 (brs, 1H), 3.76 (td, 1H, J = 12.3, 3.3 Hz), 4.02 (t, 1H, J = 12.1 Hz), 5.05 (dd, 1H, J = 11.2, 3.4 Hz), 5.35 & 5.40 (2× s, 2H), 7.27–7.44 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.5 (2× CH), 33.47 (CH), 34.03 (CH_2), 34.21 (CH_2), 34.33 (CH_2), 34.43 (CH_2), 35.04 (CH_2), 35.47 (CH), 37.95 (CH_2), 60.30 (CH_2), 85.77 (CH), 108.87 (C), 116.05 (CH_2), 127.15 (2× CH), 128.10 (CH), 128.74 (2× CH), 140.14 (C), 146.99 (C); MS (*m*/*z*) 327(M+H)$^+$.

Compounds **10b**–**d** and **11a**–**c** were also prepared by the same procedure.

6.2.1.1. Compound 10b. Yield 47%, mp 81–85 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.60–2.17 (m, 15H), 2.27 (brs, 1H), 3.76 (td, 1H, J = 12.1, 3.4 Hz), 4.01 (t, 1H, J = 11.8 Hz), 4.99 (dd, 1H, J = 11.5, 3.6 Hz), 5.37 & 5.41 (2× s, 2H), 7.27–7.37 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.53 (2× CH), 33.42 (CH), 34.00 (CH_2), 34.31 (CH_2), 34.39 (CH_2), 35.02 (CH_2), 35.47 (CH), 37.61 (CH_2), 37.82 (CH_2), 60.19 (CH_2), 85.72 (CH), 108.94 (C), 116.93 (CH_2), 128.56 (2× CH), 128.91 (2× CH), 134.01 (C), 138.44 (C), 145.74 (C); MS (*m*/*z*) 361, 363 (M+H)$^+$; Anal. Calcd for $C_{21}H_{25}O_3Cl$ + 0.35 H_2O: C, 68.69; H, 7.05. Found: C, 68.40; H, 6.92.

6.2.1.2. Compound 10c. Yield 39%, mp 99–102 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.61–2.12 (m, 15H), 2.32 (brs, 1H), 3.78 (td, 1H, J = 12.3, 3.3 Hz), 4.04 (t, 1H, J = 12.4 Hz), 5.10 (dd, 1H, J = 11.16, 3.3 Hz), 5.38 & 5.48 (2× s, 2H), 7.40–7.61 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.59 (2× CH), 33.50 (CH), 34.05, (CH_2), 34.35 (CH_2), 34.45 (CH_2), 35.06 (CH_2), 35.51 (CH), 37.89 (CH_2), 60.31 (CH_2), 85.77 (CH), 108.92 (C), 116.08 (CH_2), 127.41 (CH), 127.46 (CH), 127.55 (CH), 127.74 (CH), 129.18 (CH), 138.96 (C), 140.95 (C), 141.07 (C), 146.50 (C); MS (*m*/*z*) 403 (M+H)$^+$; HRMS Calcd for $C_{27}H_{30}O_3$: 402.2195. Found: 402.2189.; Anal. Calcd for $C_{27}H_{30}O_3$ + 0.1 H_2O: C, 80.20; H, 8.02. Found: C, 80.11; H, 8.04.

6.2.1.3. Compound 10d. Yield 7%, oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48–2.01 (m, 15H), 2.31 (brs, 1H), 3.67 (td, 1H, J = 12.3, 3.4 Hz), 3.89 (t, 1H, J = 12.1 Hz), 4.96 (dd, 1H, J = 10.9, 3.5 Hz), 5.25 & 5.66 (2× s, 2H), 7.29–7.52 (m, 4H), 7.87–7.52 (m, 2H), 8.02–8.07 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.58 (2× CH), 30.10 (CH_2), 33.49 (CH), 34.34 (CH_2), 34.98 (CH_2), 35.38 (CH), 37.90 (CH_2), 38.02 (CH_2), 60.21 (CH_2), 86.36 (CH), 108.89 (C), 118.08 (CH_2), 125.56 (CH), 126.17 (2× CH), 126.36 (CH), 126.44 (CH), 128.20 (CH), 128.64 (CH), 132.01 (C), 134.08 (C), 138.97 (C), 146.58 (C); MS (*m*/*z*) 377 (M+H)$^+$; Anal. Calcd for $C_{25}H_{28}O_3$: C, 79.75; H, 7.50. Found: C, 79.29; H, 7.92.

6.2.1.4. Compound 11a. Yield 41%, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.68–2.55 (m, 10H), 3.86 (td, 1H, J = 12.4, 3.2 Hz), 4.09 (m, 1H), 5.13 (dd, 1H, J = 11.2, 3.2 Hz), 5.38 & 5.46 (2× s, 2H), 7.22–7.49 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ; 30.07 (CH_2), 30.66 (CH_2), 32.92 (CH_2), 37.57 (CH_2), 53.85 (CH_2), 61.41 (CH_2), 86.12 (CH), 105.56 (C), 116.56 (CH_2), 127.04 (CH), 128.29 (CH), 128.44 (CH), 128.84 (CH), 139.93 (C), 146.34 (C), 210.66 (C). ESMS (*m*/*z*) (M)$^+$ 288, (M+Na)$^+$ 311, (M+K)$^+$ 327; FT-IR (cm^{-1}) 1716.9; Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 71.23; H, 7.44.

6.2.1.5. Compound 11b. Yield 43%, mp 74–80 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70–2.54 (m, 10H), 3.86 (td, 1H, J = 12.4, 3.4 Hz), 4.04–4.15 (m, 1H), 5.08 (dd, 1H, J = 11.2, 3.2 Hz), 5.40 & 5.46 (2× s, 2H), 7.28–7.38 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.60 (CH_2), 32.90 (CH_2), 37.21 (CH_2), 37.51 (CH_2), 61.31 (CH_2), 85.99 (CH), 105.62 (C), 117.62 (CH_2), 128.43 (CH), 129.43 (CH), 134.23 (C), 138.30 (C), 145.08 (C), 210.76 (C); MS (*m*/*z*) (M+H)$^+$ 323; FT-IR (cm^{-1}) 1717.4.

6.2.1.6. Compound 11c. Yield 40%, mp 80–85 °C;^{1}H NMR (200 MHz, $CDCl_3$) δ 1.91–2.57 (m, 10H), 3.87 (td, 1H, J = 12.3, 3.4 Hz), 4.07–4.18 (m, 1H), 5.18 (dd, 1H, J = 11.2, 3.2 Hz), 5.41 & 5.53 (2× s, 2H), 7.25–7.61 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.25 (CH_2) 32.52 (CH_2) 37.12 (CH_2), 61.01 (CH_2), 85.69 (CH), 105.18 (C), 116.19 (CH_2), 127.01 (CH), 127.14 (CH), $_{27}$127.41 (CH), 128.79 (CH), 138.32 (C), 140.51 (C), 140.74 (C), 210.38 (C); MS (*m*/*z*) 365.0 (M+H)$^+$, 382.1 (M+NH_4)$^+$, 387.2 (M+Na)$^+$; FT-IR (cm^{-1}) 1727.4; Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.35; H, 7.07.

6.2.2. General procedure for the $LiAlH_4$ reduction of trioxepanes 11a–c (preparation of 12a as representative). To a precooled (0 °C) magnetically stirred slurry of $LiAlH_4$ (25 mg) in anhydrous ether (10 mL) was added a solution of ester **11** (500 mg) in anhydrous ether (10 mL), under nitrogen and stirred at 0 °C for 1 h. Excess $LiAlH_4$ was quenched by careful addition of cold water followed by 10% aq NaOH, during which gray colour changed to white. The ether layer was decanted off and the white precipitate rinsed with ether (3 × 5 mL). Combined organic extract was concentrated and the crude product was purified over a silica gel column using dichloromethane as eluent to furnish 400 mg (79% yield) of **12a** as a colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52–2.16 (m, 10H), 3.77–3.83 (m, 2H), 3.96–4.03 (m, 1H), 5.06 (dd, 1H, J = 11.1, 2.2 Hz), 5.36 & 5.43 (2× s, 2H), 7.26–7.42 (m, 5H); ^{13}C

NMR (50 MHz, $CDCl_3$) δ 27.92 (CH_2) 29.13 (CH_2) 30.83 (CH_2), 30.87 (CH_2), 31.08 (CH_2), 31.25 (CH_2), 31.49 (CH_2), 31.64 (CH_2), 37.63 (CH_2), 37.71 (CH_2), 60.82 (CH_2), 61.06 (CH_2), 68.35 (CH), 69.09 (CH), 85.92 (CH), 106.30 (C), 106.33 (C), 116.44 (CH_2), 127.08 (2× CH), 128.21 (CH), 128.81 (2× CH), 140.03 (C), 140.56 (C); MS (*m*/*z*) 291.2 $(M+H)^+$; FT-IR (cm^{-1}) 3427.2, Anal. Calcd for $C_{17}H_{22}O_4 + 0.1H_2O$: C, 69.88; H, 7.67. Found: C, 69.62; H, 7.88.

Compounds **12b** & **12c** were also prepared by the same procedure.

6.2.2.1. Compound 12b. Yield 77%, ^1H NMR (200 MHz, $CDCl_3$) δ 1.49–2.09 (m, 10H), 3.71–3.91 (m, 2H), 4.02 (td, 1H, J = 11.4, 2.3 Hz), 5.01 (dd, 1H, J = 11.1, 2.2 Hz), 5.38 & 5.43 and 5.40 & 5.46 (4× s, together integrating for 2H), 7.26–7.37 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.89 (CH_2) 29.00 (CH_2) 30.59 (CH_2), 30.83 (CH_2), 31.04 (CH_2), 31.23 (CH_2), 31.42 (CH_2), 31.58 (CH_2), 32.89 (CH_2), 37.08 (CH_2), 37.39 (CH_2), 60.69 (CH_2), 60.94 (CH_2), 68.30 (CH), 68.94 (CH), 85.79 (CH), 106.36 (C), 117.17 (CH_2), 129.02 (2× CH), 130.28 (CH), 134.08 (C), 134.22 (C), 138.39 (C), 145.37 (C); MS (*m*/*z*) 325.2 $(M + H)^+$; Anal. Calcd for $C_{17}H_{21}O_3Cl + 0.15\ H_2O$: C, 62.34; H, 6.56. Found: C, 62.20; H, 6.87; FT-IR (cm^{-1}) 3424.8.

6.2.2.2. Compound 12c. Yield 76%, mp 123–127 °C, 1H NMR (200 MHz, $CDCl_3$) δ 1.51–2.21 (m, 10H), 3.79–3.82 (m, 2H), 3.99–4.11 (m, 1H), 5.11 (dd, 1H, J = 10.94, 2.1 Hz), 5.39 & 5.51 (2× s, 2H), 7.25-7.61 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.51 (CH_2) 28.64 (CH_2) 30.43 (CH_2), 30.68 (CH_2), 30.85 (CH_2), 31.07 (CH_2), 31.22 (CH_2), 37.18 (CH_2), 60.38 (CH_2), 67.96 (CH), 68.62 (CH), 85.46 (CH), 105.92 (C), 115.93 (CH_2), 126.97 (CH), 127.06 (CH), 127.34 (CH), 128.76 (CH), 138.39 (C), 140.59 (C), 145.64 (C); MS (*m*/*z*) 367.2 $(M+H)^+$; Anal. Calcd for $C_{21}H_{25}O_3Cl + 0.25\ H_2O$: C, 74.47; H, 7.21. Found: C, 74.11; H, 7.65; FT-IR (cm^{-1}) 3428.8.

6.2.3. Reaction of 1,2,4-trioxepane 8a with $FeBr_2$. A solution of compound **8a** (500 mg) and $FeBr_2$ (210 mg, 0.5 equiv) in anhydrous THF stirred at rt for 2 h. THF was evaporated, crude was taken in dichloromethane and filtered through celite-545, concentrated on a rotatory evaporator at rt. The crude product was purified by column chromatography over silica gel to furnish compound **13** (0.1 g, yield 29%), and compound **14** (0.18 g, yield 27%).

6.2.3.1. Compound 13. Oil; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72–1.90 (m, 2H), 2.23 (bs, 1H), 2.72 (bs, 1H), 3.82–3.89 (m, 2H), 4.93–4.95 (m, 1H), 5.37–5.46 (2× s, 2H), 7.31–7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 37.43 (CH_2), 61.52 (CH_2),73.60 (CH), 112.98 (CH_2), 127.21 (2× CH), 128.12 (CH), 128.86 (2× CH), 140.24 (C), 151.75 (C); FAB-MS (*m*/*z*) 179 $(M+H)^+$, 161 $(M+H\ -H_2O)^+$, 143 $(M+H\ -2\ H_2O)^+$.

6.2.3.2. Compound 14. Oil; ^1H NMR (300 MHz, $CDCl_3$): δ 1.59 (brs, OH), 1.76–2.13 (m, 6H), 2.35 (t, 2H, J = 7.2 Hz), 3.41 (t, 2H, J = 9.6 Hz), 4.16–4.31 (m, 2H), 4.74–4.77 (m, 1H), 5.35 & 5.41 (2× s, 2H), 7.27–7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.89 (CH_2), 32.35 (CH_2), 33.42 (CH_2), 33.68 (CH_2), 35.43 (CH_2), 62.08 (CH_2), 71.10 (CH), 109.95 (C), 113.36 (CH_2), 127.24 (2× CH), 125.43 (CH), 128.25 (2× CH), 139.92 (C), 151.59 (C), 173.65 (C); FT-IR: 3020.1, 2928.2, 1728.5 cm^{-1}.

6.2.4. Compound 15. To a solution of compound **14** (50 mg), triethylamine (0.2 ml) and 4-dimethylaminopyridine (0.01 g) in dichloromethane (2 ml) was added Ac_2O (0.2 ml) with constant stirring.The reaction mixture was stirred for 2.5 h, concentrated under vacuum and the crude product was purified by column chromatography over silica gel using 5% ethyl acetate-hexane as eluent to furnish 50 mg (91% yield) of **15** as a colourless oil; yield 91%; ^1H NMR (300 MHz, $CDCl_3$): δ 1.71–2.06 (m, 6H), 2.12 (s, 3H), 2.30 (t, 2H, J = 7.2 Hz), 3.92 (t, 2H, J = 6.6 Hz), 4.06–4.12 (m, 2H), 5.30 & 5.53 (2× s, 2H), 5.80 (dd, 1H, J = 7.2, 5.7 Hz) 7.26–7.43 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.56 (CH_3), 23.80 (CH_2), 30.08 (CH_2), 32.34 (CH_2), 33.37 (CH_2), 33.54 (CH_2), 61.05 (CH), 72.59 (CH), 114.49 (CH_2), 127.35 (2× CH), 128.43 (CH), 128.90 (2× CH), 139.39 (C), 148.21 (C), 170.48 (C), 173.31 (C); FAB-MS: 323, 325, $(M)^+$–CH_3COOH, EIMS: 405.1 $(M+Na)^+$; HRMS: Cald for $C_{16}H_{20}O_2Br$: 323.06466, found: 323.06458; FT-IR: 1739.0 cm^{-1}.

6.3. In vivo antimalarial activity

The in vivo efficacy of compounds was evaluated against *Plasmodium yoelii nigeriensis* (MDR) in Swiss mice model. The colony bred Swiss mice (25 ± 1 g) were inoculated with 10^6 parasitised RBC on day zero and treatment was administered to a group of five mice at each dose, from day 0–3, in two divided doses daily. The drug dilutions were prepared so as to contain the required amount of the drug (1.2 mg for a dose of 96 mg/kg) in 0.1 ml and administered either intramuscularly or orally for each dose. Parasitaemia levels were recorded from thin blood smears from day 4–17 by which time all the treated mice were dead.

Acknowledgments

We thank ICMR, New Delhi, for the financial support and SAIF (CDRI), Lucknow for providing spectral and analytical data. Shilpi Pandey is thankful to Council of Scientific and Industrial Research (CSIR), New Delhi, for the award of Senior Research Fellowship.

References and notes

1. WHO *Trans. R. Soc. Trop. Med. Hyg.*, **2000**, 94, 1.
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; (c) Zaman, S. S.; Sharma, R. P. *Heterocycles* **1991**, *32*, 1593; (d) Zhou, W. S.; Xu, X. X. *Acc. Chem. Res.* **1994**, *27*, 211; (e) Cumming,

J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1997**, *37*, 2253; (f) Bhattacharya, A. K.; Sharma, R. P. *Heterocycles* **1999**, *51*, 1681; (g) Borstnik, K.; Paik, I.; Shapiro, T. A.; Posner, G. H. *Int. J. Parasitol.* **2002**, *32*, 1661; (h) Ploypradith, P. *Acta Trop.* **2004**, *89*, 329; (i) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945.

3. (a) Jefford, C. W.; Jaggi, D.; Boukouvalas, J.; Kohmoto, S. *J. Am. Chem. Soc.* **1983**, *105*, 6498; (b) Kepler, J. A.; Philip, A.; Lee, Y. W.; Morey, M. C.; Caroll, F. I. *J. Med. Chem.* **1988**, *31*, 713; (c) Fujisakum, T.; Miura, M.; Nojima, M.; Kasabayashi, S. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1031; (d) Avery, M. A.; Jennings-White, C.; Chong, W. K. M. *J. Org. Chem.* **1989**, *54*, 1792; (e) Bloodworth, A. J.; Shah, A. *J. Chem. Soc. Chem. Commun.* **1991**, 947; (f) Posner, G. H.; Oh, C. H.; Milhous, W. K. *Tetrahedron Lett.* **1991**, *32*, 4235; (g) Bunnelle, W. H.; Isbell, T. A.; Barnes, C. L.; Qualls, S. *J. Am. Chem. Soc.* **1991**, *113*, 8168; (h) Bloodworth, A. J.; Johnson, K. A. *Tetrahedron Lett.* **1994**, *35*, 8057; (i) O'Neill, P. M.; Pugh, M.; Davies, J.; Ward, S. A.; Park, B. K. *Tetrahedron Lett.* **2001**, *42*, 4569; (j) O'Neill, P. M.; Mukhtar, A.; Ward, S. A.; Bickley, J. F.; Davies, J.; Bachi, M. D.; Stocks, P. A. *Org. Lett.* **2004**, *6*, 3035.
4. (a) Singh, C. *Tetrahedron Lett.* **1990**, *31*, 6901; (b) Singh, C.; Misra, D.; Saxena, G.; Chandra, S. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 497; (c) Singh, C.; Misra, D.; Saxena, G.; Chandra, S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1913; (d) Singh, C.; Gupta, N.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1913; (e) Singh, C.; Malik, H.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 1177; (f) Singh, C.; Srivastav, N. C.; Puri, S. K. *Bioorg. Med. Chem.* **2004**, *12*, 5745; (g) Singh, C.; Malik, H.; Puri, S. K. *Bioorg. Med. Chem.* **2004**, *14*, 459–462; (h) Singh, C.; Gupta, N.; Puri, S. K. *Bioorg. Med. Chem.* **2004**, *12*, 5553; (i) Singh, C.; Gupta, N.; Puri, S. K. *Tetrahedron Lett.* **2005**, *46*, 205; (j) Singh, C.; Malik, H.; Puri, S. K. *J. Med. Chem.* **2006**, *49*, 2794; (k) Singh, C.; Kanchan, R.; Srivastava, D.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 584; (l) Singh, C.; Kanchan, R.; Sharma, U.; Puri, S. K. *J. Med. Chem.* **2007**, *50*, 521.
5. (a) Adam, W.; Duran, N. *J. Chem. Soc. Chem. Comm.* **1972**, 798; (b) Dussault, P. H.; Trullinger, T. K.; Noor-e-Ain, F. *Org. Lett.* **2002**, *4*, 4591.
6. Oh, C. H.; Kang, J. H. *Tetrahedron Lett.* **1998**, *39*, 2771.
7. (a) Dussault, P. H.; Davies, D. R. *Tetrahedron Lett.* **1996**, *37*, 463; (b) Ushigoe, Y.; Kano, Y.; Nojima, M. *J. Chem. Soc. Perkin Trans. 1* **1997**, 5; (c) Ushigoe, Y.; Torao, Y.; Masuyama, A.; Nojima, M. *J. Org. Chem.* **1997**, *62*, 4949; (d) Ushigoe, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron Lett.* **1997**, *38*, 8753; (e) Ahmed, A.; Dussault, P. H. *Org. Lett.* **2004**, *6*, 3609.
8. For in vitro activity of 1,2,4-trioxepanes, see Amewu, R.; Stachulski, A. V.; Berry, N. G.; Ward, S. A.; Davies, J.; Labat, G.; Rossignol, J. F.; O'Neill, P. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6124.
9. Singh, C.; Pandey, S.; Saxena, G.; Srivastava, N.; Sharma, M. *J. Org. Chem.* **2006**, *71*, 9057.
10. Puri, S. K.; Singh, N. *Exp. Parasitol.* **2000**, *94*, 8.
11. Singh, C.; Gupta, N.; Tiwari, P. *Tetrahedron Lett.* **2005**, *46*, 4551.