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# New orally active spiro 1,2,4-trioxanes with high antimalarial potency☆

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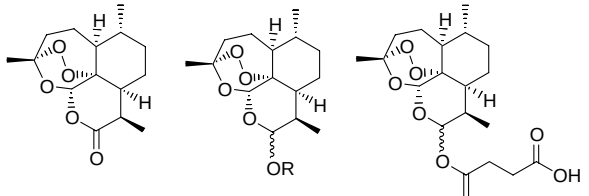
**Abstract**—A new series of functionalized 1,2,4-trioxanes **10**–**21** have been prepared and assessed for antimalarial activity in mice. Several of these trioxanes show significant activity. Trioxane **16**, the most active compound of the series, has shown activity by oral route which is comparable with that of the clinically used drug, β-arteether.


## 1. Introduction

Malaria is a major parasitic disease affecting over 100 countries of the tropical and subtropical regions of the world including India. Around 300–500 million clinical cases of malaria are reported every year of which around 2–3 million die due to complicated cases of malaria.[1] The situation is getting worse with the emergence of multi-drug resistant parasites. Against this background, isolation of artemisinin **1** by the Chinese as the active principle of their traditional antimalarial drug, *Artemisia annua*, has been a major breakthrough in malaria chemotherapy. Artemisinin is active against both chloroquine sensitive and chloroquine resistant malaria.[2]

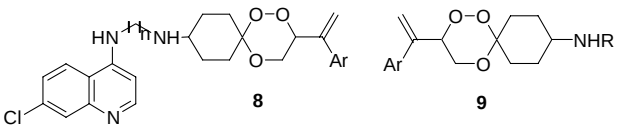


**1** **2** R = Me, **3** R = Et **4**

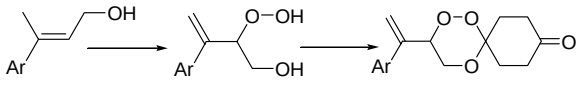
Several derivatives of artemisinin with better activity profile, for example, artemether **2**, arteether **3** and artesunic acid **4** are being clinically used.[3] The peroxide group present in the form of 1,2,4-trioxane is essential for the antimalarial activity of artemisinin and its derivatives. Several synthetic trioxanes originating from different laboratories including our group have shown promising antimalarial activity both in vitro and in vivo.[4,5]

Earlier we have shown that β-hydroxyhydroperoxides **6a**,**b** prepared by photooxygenation of allylic alcohols[5a] **5a**,**b** react with 1,4-cyclohexanedione to give keto-functionalized 1,2,4-trioxanes **7a**,**b** (Scheme 1) and that these trioxanes undergo facile reductive amination with various amines to give amino functionalized 1,2,4-trioxanes (prototype **8** and **9**).[6]

Some of these amino functionalized 1,2,4-trioxanes showed high order of activity against chloroquine resistant *Plasmodium yoelii* in mice.[6b]



**8** **9**



**5a-b** **6a-b** **7a-b**

**Scheme 1.** Reagents and conditions: (a) h$\nu$ (light produced by 500 W tungsten halogen lamp), $O_2$, methylene blue, MeCN, −10 to 0 °C. (b) 1,4-Cyclohexanedione, concd HCl, 5 °C.

*Keywords*: Artemisinin; Arteether; 1,2,4-Trioxanes; Multi-drug resistant; Antimalarial.

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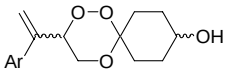
We have further explored the chemistry of the carbonyl group of these keto-trioxanes and report herein the synthesis of a new series of functionalized 1,2,4-trioxanes **10**–**21**. Several of these trioxanes show better activity profile than the parent trioxanes **7a**,**b**. Trioxane **16**, the most active compound of the series, has shown activity by oral route which is comparable with that of the clinically used drug, β-arteether.

## 2. Chemistry

Reduction of **7a** with $NaBH_4$ in MeOH furnished alcohol **10** in 96% yield as an inseparable mixture of diastereomers, which on reaction with succinic anhydride and $Et_3N$ in $CH_2Cl_2$ at rt gave hemisuccinate **12** in 93% yield, again as an inseparable mixture of diastereomers. Similarly keto-trioxane **7b** on reduction furnished alcohol **11** in 95% yield as an inseparable mixture of diastereomers, which on reaction with succinic anhydride and $Et_3N$ in $CH_2Cl_2$ at rt gave hemisuccinate **13** in 95% yield, again as an inseparable mixture of diastereomers. Reaction of **7a** with $BrCH_2COOEt$/Zn in dry benzene furnished a mixture of diastereomers **14a**,**b** in 83% yield. Compounds **14a**,**b** were separated by column chromatography. Similar reaction of **7b** with $BrCH_2COOEt$/Zn in dry benzene furnished a mixture of diastereomers **15a**,**b** in 88% yield. The pure isomers were separated by column chromatography. Keto-trioxane **7a** when reacted with triethylphosphonoacetate in the presence of NaH as base in dimethoxyethane furnished the Wittig product **16** in 93% yield as an inseparable mixture of geometrical isomers. Reaction of keto-trioxane **7a** with triethylphosphono-2-propionate under the same conditions furnished **17** in 83% yield again as an inseparable mixture of geometrical isomers. Keto-trioxane **7b** on reaction with triethylphosphonoacetate and triethylphosphono-2-propionate under similar reaction conditions furnished **18** and **19** as an inseparable mixture of geometrical isomers in 93% and 84% yields, respectively. Reaction of keto-trioxane **7a** with MeMgBr in diethylether furnished a diastereomeric mixture of **20a**,**b** in 54% yield which were separated by column chromatography and characterized as pure isomers. Similar reaction of **7a** with PhMgBr furnished trioxane **21a**,**b** as a diastereomeric mixture in 59% yield, which were separated into pure isomers by column chromatography and characterized separately,[7,8] while they were screened as mixture for biological activity.

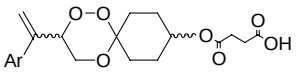
## 3. Antimalarial activity

1,2,4-Trioxanes **10**–**21** were initially screened for their antimalarial activity against multi-drug resistant *P. yoelii* in Swiss mice at a highest dose of 96 mg/kg[9] by oral and intramuscular (im) routes. The trioxanes showing activity at 96 mg/kg by either route were further evaluated at 48 and 24 mg/kg. The results are shown in Table 1.



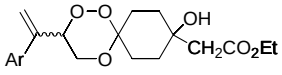
**10-11**

**10** Ar = phenyl
**11** Ar = 4-biphenyl



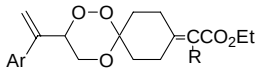
**12-13**

**12** Ar = phenyl
**13** Ar = 4-biphenyl



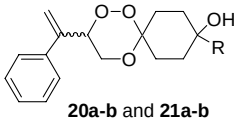
**14a-b** and **15a-b**

**14a** Ar = phenyl (higher $R_f$)
**14b** Ar = phenyl (lower $R_f$)
**15a** Ar = 4-bihenyl (higher $R_f$)
**15b** Ar = 4-biphenyl (lower $R_f$)



**16-19**

**16** Ar = phenyl, R = H
**17** Ar = phenyl, R = $CH_3$
**18** Ar = 4-biphenyl, R = H
**19** Ar = 4-biphenyl, R = $CH_3$



**20a-b** and **21a-b**

**20a** R = methyl (higher $R_f$)
**20b** R = methyl (lower $R_f$)
**21a** R = phenyl (higher $R_f$)
**21b** R = phenyl (lower $R_f$)

## 4. Results and discussion

As can be seen from Table 1, the Wittig product **16**, is the best compound in the series. At 48 mg/kg given orally, this compound shows complete clearance of parasitaemia on day 4 and all the animals survive beyond day 28. Even at 24 mg/kg, this compound shows complete clearance of parasitaemia on day 4 though none of the animals survive beyond day 28. This trioxane also shows complete clearance of parasitaemia on day 4 at 96 mg/kg by im route and 40% of the animals survive beyond day 28. Surprisingly, Wittig product **17**, which is structurally very close to **16** except that olefinic proton is replaced by a methyl group, is completely inactive by both the routes. Trioxane **18** is the next best compound in the series. It shows 100% clearance of parasitaemia at 96 and 48 mg/kg by oral route and provides 100% protection at 96 mg/kg in the 28-day observation period. It also shows 96% clearance of parasitaemia on day 4 at 96 mg/kg by im route but none of the animals survive beyond day 28. Here again the corresponding methyl substituted derivative **19** is less active. It provides only 40% protection to the mice treated at 96 mg/kg by oral route and no protection when given by im route. Compounds **11** and **20** provide 100% suppression by im route on day 4 and 40% protection to the treated mice. The rest of the functionalized trioxanes **10**, **12**–**15** and **21** show only moderate activity.

The moderate order of activity of trioxanes **16** and **18**, the two most orally active compounds of this series, by im route could be due to their poor solubility in water which restricts their absorption from the site of injection.[10] We have also observed such difference in activity between oral and im routes earlier in a related series of amino functionalized 1,2,4-trioxanes.[6b]

**Table 1.** In vivo antimalarial activity of functionalized 1,2,4-trioxanes against *P. yoelii* in Swiss mice

| Compound | Dose (mg/kg/day) | Route | % Suppression on day 4[a] | Mice alive on day 28 |
|---|---|---|---|---|
| **7a** | 96 | Oral | 7 | 0/5 |
| | 96 | im | 99 | 0/5 |
| **7b** | 96 | Oral | 92 | 0/5 |
| | 96 | im | 100 | 1/5 |
| **10** | 96 | Oral | 78 | 0/5 |
| | 96 | im | 82 | 0/5 |
| **11** | 96 | Oral | 91 | 0/5 |
| | 96 | im | 100 | 2/5 |
| **12** | 96 | Oral | 82 | 0/5 |
| | 96 | im | 14 | 0/5 |
| **13** | 96 | Oral | 99 | 0/5 |
| | 96 | im | 74 | 0/5 |
| **14a** (higher $R_f$) | 96 | Oral | 87 | 0/5 |
| | 96 | im | 30 | 0/5 |
| **14b** (lower $R_f$) | 96 | Oral | 37 | 0/5 |
| | 96 | im | 62 | 0/5 |
| **15a** (higher $R_f$) | 96 | Oral | 93 | 0/5 |
| | 96 | im | 84 | 0/5 |
| **15b** (lower $R_f$) | 96 | Oral | 97 | 0/5 |
| | 96 | im | 86 | 0/5 |
| **16** | 96 | Oral | 100 | 5/5 |
| | 48 | Oral | 100 | 5/5 |
| | 24 | Oral | 100 | 0/5 |
| | 96 | im | 100 | 2/5 |
| **17** | 96 | Oral | 39 | 0/5 |
| | 96 | im | 40 | 0/5 |
| **18** | 96 | Oral | 100 | 5/5 |
| | 48 | Oral | 100 | 0/5 |
| | 96 | im | 96 | 0/5 |
| **19** | 96 | Oral | 100 | 2/5 |
| | 48 | Oral | 100 | 0/5 |
| | 96 | im | 78 | 0/5 |
| **20a** and **20b** | 96 | Oral | 92 | 0/5 |
| | 96 | im | 100 | 2/5 |
| **21a** and **21b** | 96 | Oral | 95 | 0/5 |
| | 96 | im | 93 | 0/5 |
| β-Arteether | 48 | Oral | 100 | 5/5 |
| | 24 | Oral | 100 | 1/5 |
| Vehicle control | — | — | — | 0/15 |

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

## 5. Conclusion

A new series of functionalized trioxanes have been prepared using the chemistry of carbonyl group of trioxanes **7a**,**b**. Several of these trioxanes show better activity profiles than the parent trioxanes **7a**,**b**. Trioxane **16**, the most active compound of the series, has shown activity by oral route which is comparable with that of the clinically used drug, β-arteether.

## Acknowledgments

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7. Selected data: *Trioxane* **10**. mp 68–70 °C; IR (KBr, $cm^{-1}$) 3394; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.57–1.90 (m, 7H), 1.98–2.12 (m, 1H), 2.36–2.45 and 2.54–2.64 (m, 1H), 3.78 and 3.80 (2 × dd, 1H, $J$ = 11.8, 3.3 Hz, together integrating for 1H) 3.93 and 3.95 (2 × dd, 1H, $J$ = 11.8, 10.1 Hz, together integrating for 1H), 5.25 (dd, 1H, $J$ = 10.1, 3.3 Hz), 5.32 and 5.50 (2 × s, 2H), 7.31–7.39 (m, 5H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$: 25.32 and 25.80 (t), 30.41 and 30.58 (t), 30.83 and 30.95 (t), 31.17 and 31.85 (t), 63.17 and 63.53 (t), 68.28 and 68.79 (d), 80.72 and 80.77 (d), 102.26 and 102.37 (s), 116.84 and 116.88 (t), 126.79 (d, integrating for 2 carbons), 128.60 (d), 128.99 (d, integrating for 2 carbons), 139.00 (s), 143.79 (s); FAB-MS (*m*/*z*) 277 $[M+H]^+$; Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54%; H, 7.30%. Found: C, 69.47%; H, 7.36%. *Trioxane* **15a**. mp 140–141 °C; IR (KBr, $cm^{-1}$) 1713, 3510; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$: 1.27 (t, 3H, $J$ = 7.1 Hz), 1.49–1.78 (m, 5H), 1.90–2.15 (m, 2H), 2.45 (s, 2H), 2.49–2.57 (m, 1H), 3.44 (s, 1H, OH), 3.80 (dd, 1H, $J$ = 11.9, 3.5 Hz), 3.90 (dd, 1H, $J$ = 11.9, 9.7 Hz), 4.17 (q, 2H, $J$ = 7.1 Hz), 5.29 (dd, 1H, $J$ = 9.7, 3.5 Hz), 5.35 and 5.56 (2 × s, 2H), 7.34–7.60 (m, 9H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$: 14.60 (q), 24.31 (t), 29.96 (t), 33.40 (t), 33.67 (t), 45.60 (t), 61.15 (t), 63.35 (t), 69.49 (s), 80.69 (d), 102.67 (s), 116.79 (t), 127.22 (d, integrating for 2 carbons), 127.41 (d, integrating for 2 carbons), 127.66 (d, integrating for 2 carbons), 127.92 (d), 129.24 (d, integrating for 2 carbons), 137.84 (s), 140.82 (s), 141.43 (s), 143.40 (s), 173.20 (s); FAB-MS (*m*/*z*) 439 $[M+H]^+$; Anal. Calcd for $C_{26}H_{30}O_6$: C, 71.21%; H, 6.90%.

Found: C, 71.43%; H, 6.94%. *Trioxane* **15b**. mp 124–125 °C; IR (KBr, $cm^{-1}$) 1700, 3515; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$: 1.27 (t, 3H, $J = 7.1$ Hz), 1.54–1.72 (m, 5H), 1.85–2.09 (m, 2H), 2.46 (s, 2H), 2.67 (dd, 1H, $J = 13.4$, 2.4 Hz), 3.51 (s, 1H, OH), 3.82 (dd, 1H, $J = 11.9$, 2.9 Hz), 4.06 (dd, 1H, $J = 11.9$, 10.2 Hz), 4.17 (q, 2H, $J = 7.1$ Hz), 5.28 (dd, 1H, $J = 10.2$, 2.9 Hz), 5.33 and 5.56 (2 × s, 2H), 7.34–7.61 (m, 9H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$: 14.57 (q), 24.50 (t), 30.57 (t), 33.50 (t), 33.73 (t), 45.69 (t), 61.16 (t), 63.29 (t), 69.37 (s), 80.63 (d), 102.64 (s), 116.69 (t), 127.15 (d, integrating for 2 carbons), 127.43 (d, integrating for 2 carbons), 127.69 (d, integrating for 2 carbons), 127.91 (d), 129.23 (d, integrating for 2 carbons), 137.85 (s), 140.83 (s), 141.47 (s), 143.31 (s), 173.40 (s); FAB-MS (*m*/*z*) 439 $[M+H]^+$; Anal. Calcd for $C_{26}H_{30}O_6$: C, 71.21%; H, 6.90%. Found: C, 70.89%; H, 6.97%. *Trioxane* **16**. An oil: IR (neat, $cm^{-1}$) 1711; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$: 1.26 (t, 3H, $J = 7.1$ Hz), 1.77–1.84 (m, 2H), 2.08–2.19 (m, 1H), 2.27–2.45 (m, 3H), 2.84–3.13 (m, 2H), 3.79 (dd, 1H, $J = 12.1$, 2.9 Hz), 3.94 and 3.96 (2 × dd, 1H, $J = 12.1$, 10.0 Hz, together integrating for 1H), 4.14 (q, 2H, $J = 7.1$ Hz), 5.28 (dd, 1H, $J = 10.0$, 2.9 Hz), 5.33 and 5.50 (2 × s, 2H), 5.68 (s, 1H), 7.30–7.38 (m, 5H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 14.69 (q), 24.82 and 24.97 (t), 29.18 and 29.90 (t), 33.06 and 33.28 (t), 34.82 and 35.46 (t), 60.04 (t), 63.41 (t), 80.77 (d), 102.14 (s), 115.08 (d), 116.85 and 117.00 (t), 126.80 (d, integrating for 2 carbons), 128.62 (d), 128.99 (d, integrating for 2 carbons), 138.96 (s), 143.78 (s), 159.97 (s), 166.78 (s); FAB-MS (*m*/*z*) 345 $[M+H]^+$; HR-EIMS calcd for $C_{20}H_{24}O_5$, 344.1625; found: 344.1624. *Trioxane* **17**. An oil: IR (neat, $cm^{-1}$) 1709; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.29 and 1.30 (2 × t, 3H, $J = 7.2$ Hz, together integrating for 3H), 1.72–1.78 (m, 3H), 1.89 (s, 3H), 2.00–2.16 (m, 1H), 2.28–2.43 (m, 2H), 2.51–2.71 (m, 2H), 3.79 (dd, 1H, $J = 11.7$, 3.1 Hz), 3.96 (dd, 1H, $J = 11.7$, 10.8 Hz), 4.19 and 4.20 (2 × q, 2H, $J = 7.2$ Hz, together integrating for 2H), 5.28 (dd, 1H, $J = 10.8$, 3.1 Hz), 5.33 and 5.50 (2 × s, 2H), 7.28–7.37 (m, 5H); FAB-MS (*m*/*z*) 359 $[M+H]^+$; HR-EIMS calcd for $C_{21}H_{26}O_5$, 358.1780; found, 358.1780. *Trioxane* **18**. mp 143–145 °C; IR (KBr, $cm^{-1}$) 1707; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$: 1.27 (t, 3H, $J = 7.1$ Hz), 1.79–1.86 (m, 2H), 2.08–2.45 (m, 4H), 2.81–2.95 (m, 1H), 3.04–3.14 (m, 1H), 3.84 (dd, 1H, $J = 11.7$, 3.3 Hz), 3.97 and 3.99 (2 × dd, 1H, $J = 11.7$, 10.2 Hz, together integrating for 1H), 4.15 (q, 2H, $J = 7.1$ Hz), 5.32 (dd, 1H, $J = 10.2$, 3.3 Hz), 5.35 and 5.57 (2 × s, 2H), 5.69 (s, 1H), 7.34–7.60 (m, 9H); FAB-MS (*m*/*z*) 421 $[M+H]^+$; Anal. calcd for $C_{26}H_{28}O_5$: C, 74.26%; H, 6.71%. Found: C, 74.37%; H, 6.82%. *Trioxane* **19**. mp 68–70 °C; IR (KBr, $cm^{-1}$) 1705; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$: 1.29 and 1.30 (2 × t, 3H,$J = 7.0$ Hz, together integrating for 3H), 1.75–1.82 (m, 3H), 1.89 (s, 3H), 2.06–2.13 (m, 1H), 2.33–2.46 (m, 2H), 2.56–2.68 (m, 2H), 3.83 (dd, 1H, $J = 11.7$, 3.1 Hz), 4.00 (dd, 1H, $J = 11.7$, 10.3 Hz), 4.19 and 4.20 (2 × q, 2H, $J = 7.0$ Hz, together integrating for 2H), 5.30 (dd, 1H, $J = 10.3$, 3.1 Hz), 5.35 and 5.57 (2 × s, 2H), 7.30–7.60 (m, 9H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$: 14.71 (q), 15.80 (q), 26.46 and 26.64 (t), 27.23 and 27.43 (t), 29.22 and 29.76 (t), 34.83 and 35.34 (t), 60.72 (t), 63.46 (t), 80.69 and 80.73 (d), 102.65 (s), 116.82 and 116.90 (t), 122.09 (s), 127.22 (d, integrating for 2 carbons), 127.43 (d, integrating for 2 carbons), 127.70 (d, integrating for 2 carbons), 127.95 (d), 129.27 (d, integrating for 2 carbons), 137.81 (s), 140.81 (s), 141.47 (s), 143.31 (s), 145.11 and 145.24 (s), 170.40 (s); FAB-MS (*m*/*z*) 435 $[M+H]^+$; Anal. calcd for $C_{27}H_{30}O_5$: C, 74.63%; H, 6.96%. Found: C, 74.84%; H, 6.82%. *Trioxane* **20a**. An oil: IR (neat, $cm^{-1}$) 3419; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$: 1.26 (s, 3H), 1.63–1.93 (m, 6H), 2.03–2.18 (m, 1H), 2.37–2.44 (m, 1H), 3.76 (dd, 1H, $J = 11.6$, 3.1 Hz), 3.88 (dd, 1H, $J = 11.6$, 10.1 Hz), 5.25 (dd, 1H, $J = 10.1$, 3.1 Hz), 5.33 and 5.50 (2 × s, 2H), 7.31–7.36 (m, 5H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$: 24.94 (t), 29.94 (q), 30.68 (t), 35.31 (t), 35.60 (t), 63.36 (t), 69.56 (s), 80.76 (d), 102.73 (s), 116.83 (t), 126.43 (d, integrating for 2 carbons), 127.65 (d), 128.57 (d, integrating for 2 carbons), 139.02 (s), 143.87 (s); ES-MS ($ES^+$+Na) 313; Anal. calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.37; H, 7.24. *Trioxane* **20b**. An oil: IR (neat, $cm^{-1}$) 3381; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$: 1.25 (s, 3H), 1.58–2.03 (m, 7H), 2.58 (dd, 1H, $J = 6.2$, 2.2 Hz), 3.77 (dd, 1H, $J = 11.9$, 2.9 Hz), 4.01 (dd, 1H, $J = 11.9$, 10.3 Hz), 5.25 (dd, 1H, $J = 10.3$, 2.9 Hz), 5.31 and 5.50 (2 × s, 2H), 7.29–7.48 (m, 5H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$: 25.04 (t), 30.48 (q), 31.13 (t), 35.35 (t), 35.51 (t), 63.27 (t), 69.44 (s), 80.72 (d), 102.71 (s), 116.79 (t), 126.78 (d, integrating for 2 carbons), 128.58 (d), 128.98 (d, integrating for 2 carbons), 139.04 (s), 143.82 (s); ES-MS ($ES^+$+Na) 313; Anal. calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.76; H, 7.36. *Trioxane* **21a**. mp 96–98 °C; IR (KBr, $cm^{-1}$) 3448; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 1.70–1.78 (m, 4H), 1.95–2.26 (m, 3H), 2.71 (d, 1H, $J = 12.0$ Hz), 3.80 (dd, 1H, $J = 12.0$, 3.0 Hz), 3.91 (dd,1H, $J = 12.0$, 9.9 Hz), 5.28 (dd, 1H, $J = 9.9$, 3.0 Hz), 5.34 and 5.50 (2 × s, 2H), 7.23–7.50 (m, 10H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 24.3 (t), 29.9 (t), 34.5 (t), 35.0 (t), 62.9 (t), 72.5 (s), 80.3 (d), 102.1 (s), 116.4 (t), 124.5 (d, integrating for 2 carbons), 126.4 (d, integrating for 2 carbons), 127.0 (d), 128.1 (d), 128.3 (d, integrating for 2 carbons), 128.5 (d, integrating for 2 carbons), 138.5 (s), 143.3 (s), 148.0 (s); FAB-MS (*m*/*z*) 353 $[M+H]^+$; Anal. calcd for $C_{22}H_{24}O_4$: C, 74.98%; H, 6.86%. Found: C, 74.66%; H, 6.71%. *Trioxane* **21b**. mp 104–106 °C; IR (KBr, $cm^{-1}$) 3449; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$: 1.69–2.21 (m, 7H), 2.84 (d, 1H, $J = 12.5$ Hz), 3.81 (dd, 1H, $J = 11.9$, 2.8 Hz), 4.07 (dd, 1H, $J = 11.9$, 10.4 Hz), 5.29 (dd, 1H, $J = 10.4$, 2.8 Hz), 5.34 and 5.52 (2 × s, 2H), 7.28–7.52 (m, 10H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$: 25.11 (t), 31.25 (t), 35.49 (2 × t), 63.39 (t), 73.46 (s), 80.78 (d), 102.50 (s), 116.92 (t), 124.91 (d, integrating for 2 carbons), 126.81 (d, integrating for 2 carbons), 127.46 (d), 128.67 (d), 128.76 (d, integrating for 2 carbons), 129.05 (d, integrating for 2 carbons), 139.04 (s), 143.78 (s), 148.66 (s); FAB-MS (*m*/*z*) 353 $[M+H]^+$; Anal. calcd for $C_{22}H_{24}O_4$: C, 74.98%; H, 6.86%. Found: C, 74.72%; H, 6.53%.

8. In all cases ratio of the diastereomers and geometrical isomers, as assessed by $^1H$ NMR and $^{13}C$ NMR, is around 50:50.
9. The in vivo efficacy of compounds was evaluated against *P. yoelii* (MDR) in Swiss mice model. The colony bred Swiss mice (25 ± 1 g) were inoculated with $1 \times 10^6$ parasitized RBC on day zero and treatment was administered to a group of five mice at each dose, from day 0 to 3, in two divided doses daily. The drug dilutions of compounds **10** and **11**, **14**–**21** were prepared in groundnut oil while hemisuccinates **12** and **13** were dissolved in 5% $NaHCO_3$ so as to contain the required amount of the drug (1.2 mg for a dose of 96 mg/kg, 0.6 mg for a dose of 48 mg/kg and 0.3 mg for a dose of 24 mg/kg) in 0.1 ml and administered either intramuscularly or orally for each dose. Parasitaemia level was recorded from thin blood smears between days 4 and 28.[11] Mice treated with β-arteether served as positive controls.
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