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New functionalized 1,2,4-trioxepanes: Synthesis and antimalarial activity against multi-drug resistant *P. yoelii* in mice ☆

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ABSTRACT

A series of new amino functionalized 1,2,4-trioxepanes **8–16** and ester functionalized 1,2,4-trioxepanes **17–19** have been synthesized and evaluated against multi-drug resistant *Plasmodium yoelii* in Swiss mice. Amino functionalized trioxepanes **14**, the most active compound of the series, showed 100% clearance of parasitaemia by oral route on day 4 and 75% protection to the treated mice beyond day 28.

Artemisinin **1**, the antimalarial principle of the Chinese traditional herb, *Artemisia annua*, and its semi-synthetic derivatives, for example, artemether **2**, arteether **3**, and artesunic acid **4** are potent antimalarials and are currently being used clinically to treat multi-drug resistant malaria (Fig. 1).[1] The endoperoxide linkage, present as 1,2,4-trioxane, is the active pharmacophore responsible for the antimalarial activity and currently the focus is on synthesis and antimalarial assessment of structurally simple peroxides, including 1,2,4-trioxanes,[2] 1,2,4-trioxepanes,[3] 1,2,4,5-tetraoxanes[4] and ozonides.[5]

Recently, we have reported a photooxygenation route for the preparation 1,2,4-trioxepanes.[3j] Some of the trioxepanes prepared using this method have shown significant suppression of parasitaemia but did not provide any long term survival advantage to the treated animals.[3k] In our search for trioxepanes showing better activity profile, we have prepared a series of new amino functionalized trioxepanes **8–16** and ester functionalized trioxepanes **17–19** and assessed them for antimalarial activity against multi-drug resistant *Plasmodium yoelii* in mice. Some of the amino functionalized trioxepanes have shown promising antimalarial activity. Herein, we report the results of this study.

Keto trioxepanes **7a–c** were prepared by the published procedure, via condensation of γ-hydroxyhydroperoxides **6a–c** with cyclohexane-1,4-dione[6] in the presence of conc. HCl (Scheme 1). γ-Hydroxyhydroperoxides **6a–c** were prepared by the photooxygenation of homoallylic alcohols **5a–c**.[3k]

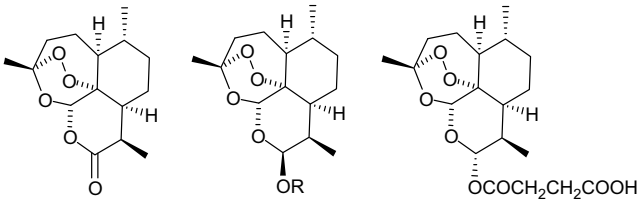

Figure 1. Artemisinin and its derivatives.

Reductive amination of keto-trioxepane **7a** with aniline, 4-fluoroaniline and 4-trifluoromethylaniline in the presence of $NaBH(OAc)_3$ furnished amino functionalized trioxepane **8**, **9** and **10** as inseparable mixture of diastereomers in 84%, 85% and 62% yield, respectively. Similarly, keto-trioxepane **7b** on reductive amination with aniline, 4-fluoroaniline and 4-trifluoromethylaniline furnished trioxepanes **11, 12** and **13** as inseparable mixture of diastereomers in 82%, 77% and 60% yields, respectively. Similar reductive amination of **7c** with aniline, 4-fluoroaniline and 4-trifluoromethylaniline furnished trioxepanes **14**, **15** and **16** as mixture of diastereomers in 83%, 86% and 67% yields, respectively

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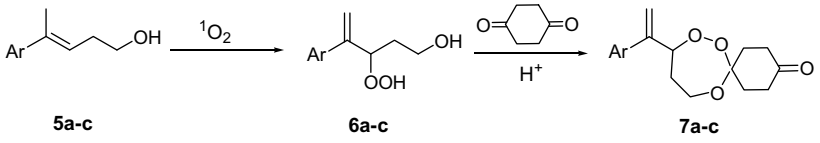

Scheme 1.

Table 1
Functionalized 1,2,4-trioxepanes

Compound	Ar	*R*	Time (h)	Yield (%)
8	Phenyl	Phenyl	2.5	84
9	Phenyl	4-Fluorophenyl	2.5	85
10	Phenyl	4-Trifluoro methyl phenyl	2	62
11	4-Chloro phenyl	Phenyl	2.5	82
12	4-Chloro phenyl	4-Fluorophenyl	2.5	77
13	4-Chloro phenyl	4-Trifluoro methyl phenyl	2.5	60
14	4-Biphenyl	Phenyl	3	83
15	4-Biphenyl	4-Fluorophenyl	2.5	86
16	4-Biphenyl	4-Trifluoro methyl phenyl	3	67
17	Phenyl	—	5	58
18	4-Chloro phenyl	—	5	57
19	4-Biphenyl	—	6	55

(Scheme 2, Table 1). Only amino trioxepane **16** could be separated into pure diastereomers **16a** (less polar) and **16b** (more polar).[7]

Horner wordsworth emmons wittig reaction of keto-trioxepanes 7**a–c** furnished inseparable diastereomeric mixtures of ester functionalized trioxepanes **17–19** in 55–58% overall yields (Scheme 3).[8]

All the trioxepanes **8–19** were screened for antimalarial activity against multi-drug resistant *P. yoelii nigeriensis* in Swiss mice at a dose of 96 mg/kg by oral and intramuscular (im) routes. [9a] The results are shown in Table 2.

As can be seen from Table 2, several of these trioxepanes exhibited significant suppression of parasitaemia on day 4. Amino functionalized trioxepanes **14** was the most active compound of the series. It showed 100% clearance of parasitaemia by oral route on day 4 and provided 75% protection to the treated mice beyond day 28.[9b] It also showed 99% clearance of parasitaemia on day 4 by i.m. route. Next in order of activity is compound **10** which showed 100% suppression of parasitaemia on day 4 and 40% of the treated mice survived beyond day 28. Trioxepanes **11** and **15** exhibited 98% suppression of parasitaemia by oral route on day 4. Trioxepane **19** exhibited 95% clearance of parasitaemia on day 4 by oral route. Compound **13** showed 87% suppression of parasitaemia by oral route and 73% suppression of parasitaemia by im route. While, the remaining compounds showed only moderate activity.

In conclusion we have prepared a series of functionalized trioxepanes **8–19**, several of which exhibited significant antimalarial activity by oral route. However, these functionalized trioxepanes show only moderate activity by im route. Amino functionalized trioxepane **14** is the most active compound of the series. It showed 100% clearance of parasitaemia by oral route on day 4 and provided 75% protection to the treated mice.

Acknowledgments

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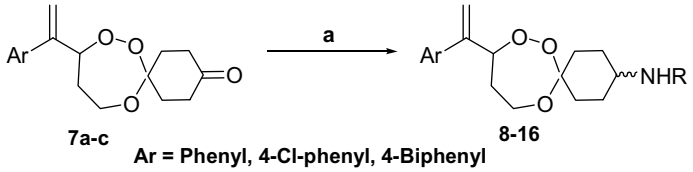
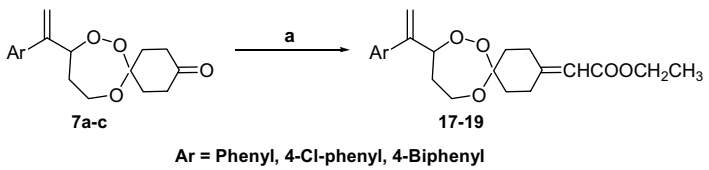
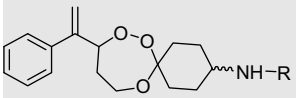
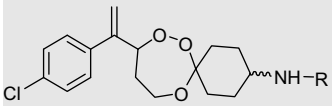
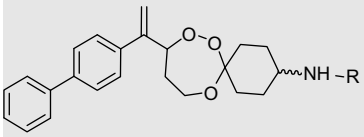
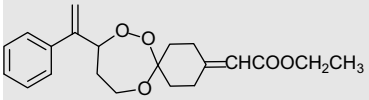
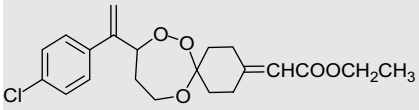
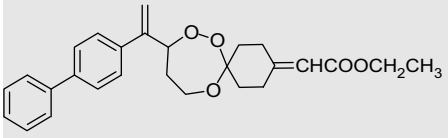
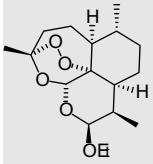


Scheme 2. Reagents and condition: (a) $ArNH_2$,[$NaBH_4$ + AcOH = $NaBH(OAc)_3$], benzene, rt.



Scheme 3. Reagents and conditions: (a) $(OEt)_2P(O)$ CH_2 CO_2 Et/NaH, THF, 0 °C-rt.

Table 2
In vivo antimalarial activity against *P. yoelii* in Swiss mice

Structure	R	Compound	Dose (mg/kg/day)	Route	% Suppression on day 4	Mice survived on day 28
	Phenyl	**8**	96	Oral	78.58	0/4
			96	im	75.47	0/4
	4-F-Phenyl	**9**	96	Oral	63.18	0/4
			96	im	50	0/4
	4-CF_3-Phenyl	**10**	96	Oral	100	2/5
			96	im	24.32	0/4
	Phenyl	**11**	96	Oral	98.49	0/4
			96	im	32.07	0/4
	4-F-	**12**	96	Oral	41.51	0/4
	Phenyl		96	im	58.37	0/4
	4-CF_3-Phenyl	**13**	96	Oral	87.17	0/4
			96	im	73.36	0/4
	Phenyl	**14**	96	Oral	100	3/4
			96	im	99.01	0/4
	4-F-	**15**	96	Oral	98.08	0/4
	Phenyl		96	im	57.69	0/4
	4-CF_3-Phenyl	**16**	96	Oral	68.3	0/4
			96	im	75.84	0/4
	—	**17**	96	Oral	88.76	0/4
			96	im	43.58	0/4
	—	**18**	96	Oral	85.87	0/4
			96	im	41.11	0/4
	—	**19**	96	Oral	95.18	0/4
			96	im	35.32	0/4
	β-Arteether	**3**	48	Oral	100	5/5

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6. The corresponding dispiro-bis-1,2,4-trioxepanes are formed as minor products; data not included.
7. Spectral data of amino functionalized trioxepanes:
Phenyl-[9-(1-phenyl-vinyl)-7,8,12-trioxaspiro[5.6]dodec-3-yl]-amine (**8**): Yield: 84%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25–2.13 (m, 10H), 3.35 (brm, 1H), 3.78–3.80 (m, 1H), 3.98–4.04 (m, 1H), 5.06 (dd, 1H, J = 11.2, 3.1 Hz), 5.35 and 5.42 (2× s, 2H), 6.54–6.66 (m, 3H), 7.10–7.29 (m, 2H), 7.30–7.38 (m, 5H); EIMS (m/z) 366.2 $(M+H)^+$.
(4-Fluoro-phenyl)-[9-(1-phenyl-vinyl)-7,8,12-trioxa-piro [5.6]dodec-3-yl]-amine (**9**): Yield: 85%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46–2.05 (m, 10H), 3.29 (brm, 1H), 3.78 (td, 1H, J = 12.2, 3.2 Hz), 3.95–4.12 (m, 1H), 5.08 (dd, 1H, J = 11.0, 3.2 Hz), 5.36 and 5.44 (2× s, 2H), 6.48–6.55 (t, 2H, J = 8.6 Hz), 6.82–6.91 (m, 2H), 7.26–7.42 (m, 5H); EIMS (m/z) 384.2 $(M+H)^+$; HRMS Calcd. for $C_{23}H_{26}O_3NF$: 383.18967. Found: 383.18982. FT-IR (cm^{-1}) 1615.8, 3020.5.
9-(1-Phenyl-vinyl)-7,8,12-trioxa-spiro[5.6]dodec-3-yl]-(4-trifluoromethyl-phenyl)-amine (**10**): Yield: 53%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41–2.27 (m, 10H), 3.40 (brm, 1H), 3.76–3.82 (m, 1H), 3.97–4.10 (m, 1H), 5.07 (dd, 1H, J = 9.0, 3.0 Hz), 5.36 and 5.44 (2× s, 2H), 6.57 (d, 2H, J = 9.0 Hz), 7.25–7.42 (m, 7H); EIMS (m/z) 434.0 $(M+H)^+$.
{9-[1-(4-Chloro-phenyl)-vinyl]-7,8,12-trioxa-spiro[5.6]dodec-3-yl}-phenyl-amine (**11**): Yield: 82%; ^{1}H NMR (200 MHz, $CDCl_3$) δ1.41–2.10 (m, 10H), 3.37 (brm, 1H), 3.79 (td, 1H, J = 12.4, 3.1 Hz), 4.08 (m, 1H), 5.02 (dd, 1H, J = 11.3, 3.2 Hz), 5.38 and 5.44 (2× s, 2H), 6.56–6.67 (m, 3H), 7.12–7.20 (m, 2H), 7.25–7.37 (m, 5H); EIMS (m/z) 400.1 $(M+H)^+$, 402 $(M+2+H)^+$.
{9-[1-(4-Chloro-phenyl)-vinyl]-7,8,12-trioxa-spiro[5.6]dodec-3-yl}-(4-fluoro-phenyl)-amine (**12**): Yield: 77%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45–2.10 (m, 10H), 3.24–3.33 (brm, 1H), 3.78 (td, 1H, J = 12.3, 3.0 Hz), 4.00–4.11 (m, 1H), 5.00 (dd, 1H, J = 11.1, 3.2 Hz), 5.38 and 5.43 (2× s, 2H), 6.48–6.55 (m, 2H), 6.82–6.91 (t, 2H, J = 8.8 Hz), 7.24–7.37 (m, 4H); EIMS (m/z) 418.1 $(M+H)^+$.
{9-[1-(4-Chloro-phenyl)-vinyl]-7,8,12-trioxa-spiro[5.6]dodec-3-yl}-(4-trifluoromethyl-phenyl)-amine (**13**): Yield: 60%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91–2.10 (m, 10H), 3.65 (brm, 3H), 3.80–3.83 (m, 1H), 3.91–4.11 (m, 1H), 5.08 (dd, 1H, J = 11.2, 3.1 Hz), 5.39 and 5.57 (2× s, 2H), 6.51–6.53 (m, 2H), 7.23–7.60 (m, 6H); MS (m/z) 453 $(M)^+$, 476 $(M+Na)^+$.
9-(1-Biphenyl-4-yl-vinyl)-7,8,12-trioxa-spiro[5.6]dodec-3-yl]-phenyl-amine (**14**): Yield: 83%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50–2.33 (m, 10H), 3.37–3.42 (m, 1H), 3.81 (td, 1H, J = 12.3, 3.1 Hz), 3.97–4.14 (m, 1H), 5.11 (dd, 1H, J = 11.6, 3.1 Hz), 5.39 and 5.51 (2× s, 2H), 6.57–6.67 (m, 3H), 7.12–7.23 (m, 2H), 7.34–7.62 (m, 9H); EIMS (m/z) 442.1 $(M+H)^+$.
9-(1-Biphenyl-4-yl-vinyl)-7,8,12-trioxa-spiro[5.6]dodec-3-yl]-(4-fluoro-phenyl)-amine (**15**): Yield: 86%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48–2.16 (m, 10H), 3.29 (brm, 1H), 3.76–3.84 (m, 1H), 3.97–4.13 (m, 1H), 5.11 (dd, 1H, J = 11.1, 2.4 Hz), 5.39 and 5.51 (2× s, 2H), 6.48–6.54 (m, 2H), 6.82–6.91 (t, 2H, J = 8.6 Hz), 7.24–7.61 (m, 9H); EIMS (m/z) 460.2 $(M+H)^+$; FT-IR (cm^{-1}) 1620.9, 3400.8; HRMS Calcd. for $C_{29}H_{30}O_3NF$: 459.2210. Found: 459.2186.
9-(1-Biphenyl-4-yl-vinyl)-7,8,12-trioxa-spiro[5.6]dodec-3-yl]-(4-trifluoromethyl-phenyl)-amine (**16**): Yield: 62%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42–2.10 (m, 10H), 3.41 (m, 1H), 3.77–3.89 (m, 1H), 3.98–4.14 (m, 1H), 5.12 (dd, 1H, J = 10.9, 2.7 Hz), 5.39 and 5.52 (2× s, 2H), 6.54–6.59 (d, 2H, J = 8.4 Hz), 7.25–7.62 (m, 11H); EIMS (m/z) 510.1 $(M+H)^+$; FT-IR (cm^{-1}) 1620.9, 3400.8.
9-(1-Biphenyl-4-yl-vinyl)-7,8,12-trioxa-spiro[5.6]dodec-3-yl]-(4-trifluoromethyl-phenyl)-amine (**16a**, Less Polar), ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39–2.04 (m, 10H), 3.41 (brm, 1H), 3.78–3.85 (m, 2H, 1CH and 1NH), 4.03–4.15 (m, 1H), 5.12 (dd, 1H, J = 11.2, 3.0 Hz), 5.40 and 5.52 (2× s, 2H), 6.57 (d, 2H, J = 8.5 Hz), 7.25–7.62 (m, 11H); EIMS (m/z) 510.1 $(M+H)^+$; HRMS Calcd. for $C_{30}H_{30}O_3NF_3$: 510.2178 Found: 510.2170.
9-(1-Biphenyl-4-yl-vinyl)-7,8,12-trioxa-spiro[5.6]dodec-3-yl]-(4-trifluoromethyl-phenyl)-amine (**16b**, More Polar), ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.53–2.19 (m, 10H), 3.41 (brm, 1H), 3.82 (td, 1H, J = 12.4, 3.2 Hz), 3.90 (s, NH), 3.98–4.10 (m, 1H), 5.12 (dd, 1H, J = 11.2, 3.2 Hz), 5.39 and 5.57 (2× s, 2H), 6.58 (d, 2H, J = 8.5 Hz), 7.25–7.61 (m, 11H); EIMS (m/z) 510.2 $(M+H)^+$; HRMS Calcd. for $C_{30}H_{30}O_3NF_3$: 509.2178. Found: 509.2171.
8. *Spectral data of ester functionalized trioxepanes: 9-(1-biphenyl-4-yl-vinyl)-7,8,12-trioxa-spiro[5.6]dodec-3-ylidene]-acetic acid ethyl ester* (**19**): Yield 55%, mp 80–84 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.2 Hz), 1.70–2.35 (m, 8H), 2.86–3.04 (m, 2H), 3.82 (td, 1H, J = 10.9, 3.1 Hz), 4.01–4.19 (m, 3H), 5.13 (dd, 1H, J = 11.2, 2.8 Hz), 5.39 and 5.51 (2× s, 2H), 5.66 and 5.68 (s, together integrating for 1H), 7.24–7.60 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.66 (CH_3) 25.34 (CH_2), 25.51 (CH_2), 29.14 (CH_2), 29.78 (CH_2), 29.93 (CH_2), 31.71 (CH_2), 32.43 (CH_2), 33.68 (CH_2), 33.91 (CH_2), 34.21 (CH_2), 34.97 (CH_2), 36.32 (CH_2), 37.30 (CH_2), 37.64 (CH_2), 59.97 (CH), 60.04 (CH), 60.94 (CH_2), 85.80 (CH), 106.20 (C), 114.96 (CH_2), 117.09 (CH_2), 127.50 (2× CH), 128.42 (2× CH), 128.76 (2× CH), 128.91 (3× CH), 134.07 (C), 138.31 (C), 144.00 (C), 145.28 (C), 159.94 (C), 160.39 (CH), 166.90 (C); MS (m/z) 435.2 $(M+H)^+$; FT-IR (cm^{-1}) 1717.
9-(1-Phenyl-vinyl)-7,8,12-trioxa-spiro[5.6]dodec-3-ylidene]-acetic acid ethyl ester (**17**): Yield 58%, ^{1}H NMR (200MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.1 Hz), 1.74–2.99 (m, 10H), 3.80 (td, 1H, J = 12.3, 3.3 Hz), 4.06–4.19 (m, 3H), 5.12 (dd, 1H, J = 11.2, 2.2 Hz), 5.36 and 5.43 (2× s, 2H), 5.67 and 5.69 (s, together integrating for 1H), 7.29–7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.71(CH_3) 25.42 (CH_2), 25.60 (CH_2), 31.80 (CH_2), 32.54 (CH_2), 33.78 (CH_2), 34.02 (CH_2), 34.27 (CH_2), 35.00 (CH_2), 36.39 (CH_2), 37.72 (CH_2), 60.06 (CH), 60.08 (CH), 61.06 (CH_2), 86.03 (CH), 106.20 (C), 115.00 (CH_2), 116.48 (CH_2), 127.07 (2× CH), 128.24 (CH), 128.82 (2× CH), 139.97 (C), 146.48 (C), 160.62 (C), 166.90 (C); MS (m/z) 359.2 $(M+H)^+$; FT-IR (cm^{-1}) 1720.
{9-[1-(4-Chloro-phenyl)-vinyl]-7,8,12-trioxa-spiro[5.6]dodec-3-ylidene}-acetic acid ethyl ester (**18**): Yield 57%, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 6.6 Hz), 1.42–2.41 (m, 8H), 2.98–3.04 (m, 2H), 3.78–4.20 (m, 4H), 5.04 (dd, 1H, J = 11.2, 3.1 Hz), 5.39 and 5.44 (2× s, 2H), 5.65–5.7 (m, 1H), 7.27–7.37 (m, 4H); MS (m/z) 393.2 $(M+H)^+$; FT-IR (cm^{-1}) 1721.
9. (a) The in vivo efficacy of compounds was evaluated against *Plasmodium yoelii* (MDR) in Swiss mice model. The colony bred Swiss mice (25±1 g) were inoculated with 1×10^6 parasitized RBC on day zero and treatment was administered to a group of five mice at each dose, from days 0 to 3, in two divided doses daily. The drug dilutions were prepared in groundnut oil 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 orally or intramuscularly for each dose. Parasitaemia level were recorded from thin blood smears between day 4 and 28. Mice treated with β-arteether served as positive controls.;
(b) 100% suppression of parasitaemia means no parasites were detected in 50 oil immersion microscopic fields (parasites if at all present are below the detection limit). The parasites present below the detection limit can multiply and eventually can be detected during observation on subsequent days. In such cases though the drug is providing near 100% suppression of the parasitaemia on day 4 but will not provide full protection to the treated mice in the 28 days survival assay.