Design and synthesis of orally active dispiro 1,2,4,5-tetraoxanes; synthetic antimalarials with superior activity to artemisinin†‡

Richard Amewu,[a] Andrew V. Stachulski,[a] Stephen A. Ward,[b] Neil G. Berry,[a] Patrick G. Bray,[b] Jill Davies,[b] Gael Labat,[a] Livia Vivas[c] and Paul M. O'Neill*[a]

Unsymmetrical dispiro- and spirotetraoxanes have been designed and synthesized *via* acid-catalyzed cyclocondensation of bis(hydroperoxides) with ketones. Incorporation of water-soluble and polar functionalities, *via* reductive amination and amide bond formation, produces several analogues with low nanomolar *in vitro* antimalarial activity. Several analogues display an unprecedented level of oral antimalarial activity for this class of endoperoxide drug.

The discovery of artemisinin[1,2] and the establishment that the endoperoxide bridge is crucial for antimalarial activity[3,4] has led to many attempts by chemists to synthesise simple but effective synthetic endoperoxides.[5,6] Artemisinin (**1**) is a naturally occurring endoperoxide sesquiterpene lactone compound of *Artemisia annua*, a herbal remedy used in Chinese medicine. Although artemisinin derivatives are extensively used against malaria, cost, supply and high recrudescent rates remain issues with this class of drug.[7,8] Other known cyclic peroxides with antimalarial potency include Yingzhaosu A (**2**) and the 1,2,4,5-tetraoxanes WR148999[9](**3**) and steroid amide (**4**) (Fig. 1).[10]

Tetraoxanes are cyclic peroxides that have received considerable attention in the literature. Initially, these systems were used industrially for the production of macrocyclic hydrocarbons and lactones.[11,12] Subsequent pioneering work by the Vennerstrom group in the early 1990s demonstrated that symmetrical dispiro 1,2,4,5-tetraoxanes such as (**3**) possess impressive *in vitro* antimalarial activity.[9] It has been proposed that these compounds share a similar antimalarial mode of action to the naturally occurring peroxides such as artemisinin.[13–15]

Surprisingly, in spite of the development of a variety of synthetic methodologies for the synthesis of the tetraoxane heterocycle,[16–29] there has been little success in the discovery of molecules with high stability and good oral bioavailability in rodent models of malaria. One notable exception is the steroidal-based 1,2,4,5-tetraoxanes, such as **4**.[10] Many of the first generation tetraoxane derivatives are highly lipophilic, suggesting that poor absorption is the key factor affecting bioavailability, but it is also apparent
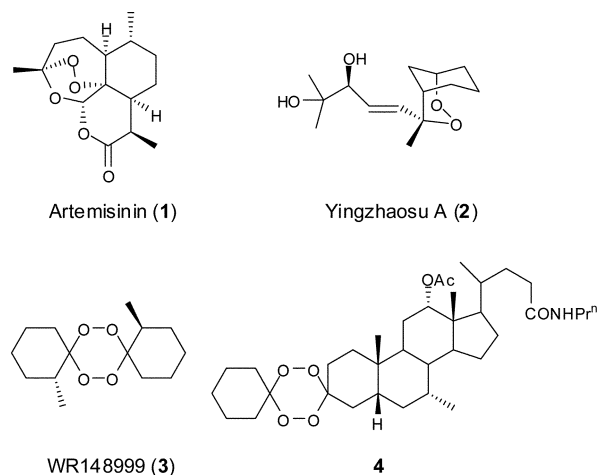

Fig. 1 Naturally occurring endoperoxides artemisinin (**1**), Yingzhaosu A (**2**) and synthetic tetraoxanes (**3**) and (**4**).

that first pass metabolism plays a role in reducing effective drug absorption.[8,30] Therefore, our aim was to prepare more stable unsymmetrical 1,2,4,5-tetraoxanes functionalised by polar water-solubilising functionalities. The synthetic routes described in this paper have been designed to be modular to enable many different analogues to be prepared from common achiral synthetic intermediates. Key reactions employed include reductive amination and mixed anhydride amide coupling reactions.

The synthesis of 1,2,4,5-tetraoxanes is dependent on several factors such as the structure of the ketone or aldehyde, temperature, solvent, pH, the catalyst, concentration of the substrate as well as the equilibria between the ketone and the precursors of cyclic peroxides.[31] All of these factors result in variable yields being achieved from selected carbonyl starting materials. Having surveyed the literature, our initial target molecule was prepared by the method reported by Iskra *et al.*[32] (Scheme 1) in which cyclohexanone **5** and 1,4-cyclohexanedione **6** are allowed to react in a two-step sequence.

The required 1,2,4,5-tetraoxane **7a**, formed by cross-condensation of the bis(hydroperoxide) **5a** and the 1,4-cyclohexanedione **6**, was obtained in rather low yield. A significant amount of the symmetrical 1,2,4,5-tetraoxane **7b**, resulting from competitive homo-cyclocondensation of bis(hydroperoxide), also was recovered, with a small amount of trimeric cyclic peroxide by-product **7c**. It was earlier reported,[33] that the presence of excess hydrogen peroxide after the formation of the bis(hydroperoxide) leads to the formation of this trimeric cyclic by-product. As a result, we decided to remove any excess hydrogen peroxide by

[a]Department of Chemistry, University of Liverpool, PO Box 147, Liverpool, UK L69 3BX. E-mail: P.M.oneill01@liv.ac.uk; Fax: (+44) 151 794 3588; Tel: (+44) 151 794 3553

[b]Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, UK L3 5QA

[c]Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK WC1E 7HT

† The HTML version of this article has been enhanced with colour images.

‡ Electronic supplementary information (ESI) available: Experimental procedures and characterization details. See DOI: 10.1039/b613565j
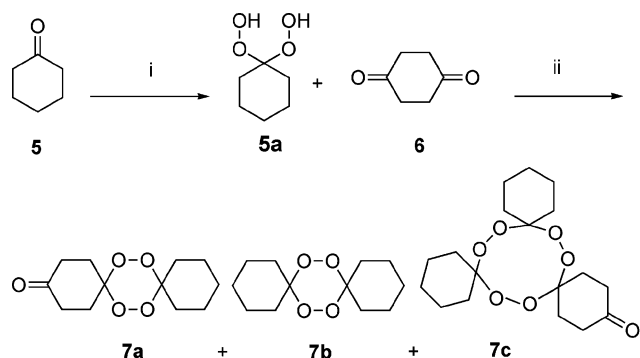
Scheme 1 *Reagents and conditions*: (i) 30% H_2O_2 (2 equiv.), methyltrioxorhenium (MTO) (0.1 equiv.)–TFE (0.5 M); (ii) **6** (2 equiv.), EtOAc, HBF_4 (1 equiv.), 28%.

carrying out a two-step synthesis of the tetraoxanes; first, by preparing the bis(hydroperoxide) and removing any unreacted hydrogen peroxide, then followed by the tetraoxane formation reaction (Scheme 2). The yield of the required tetraoxane was improved slightly. We then investigated various methodologies available for the formation of the bis(hydroperoxide) and examined the method reported by Ledaal.[34] Performing the reaction in acetonitrile led to the elimination of the formation of a solid mass in the flask, leading to quantitative conversion of the ketone to the bis(hydroperoxide). While some methodologies led to an exclusive formation of the symmetrical tetraoxanes, others led to the formation of compound **8** (Fig. 2). Several attempts to form the cyclic product according to existing literature[34] procedures failed.
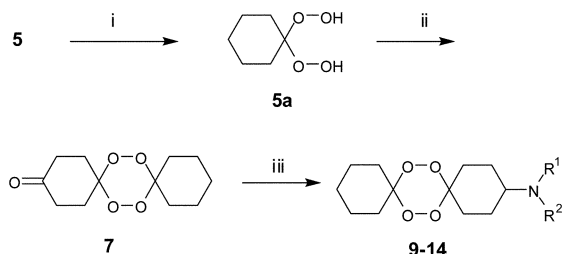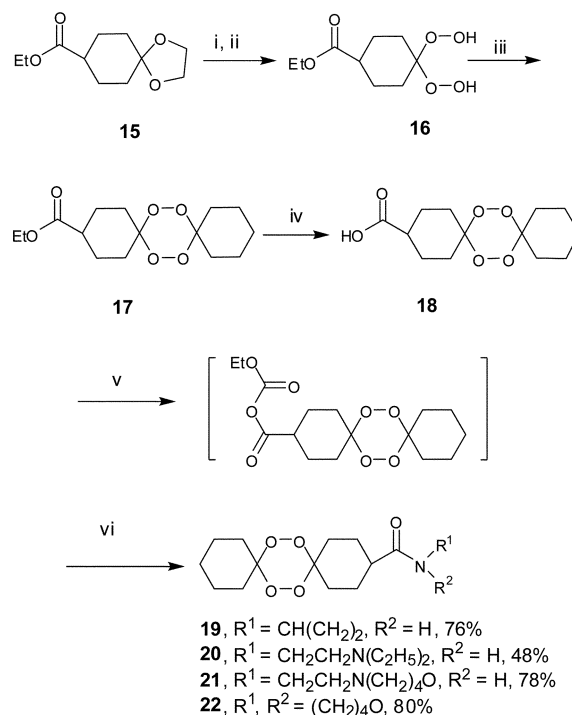

9, $R^1 = CH(CH_2)_2$, $R^2 = H$, 55%
10, $R^1 = CH_2CH_2N(CH_2)_4$, $R^2 = H$, 85%
11, $R^1 = CH_2CH_2N(CH_2)_5$, $R^2 = H$, 60%
12, $R^1 = CH_2CH_2N(CH_2)_4O$, $R^2 = H$, 47%
13, $R^1 = CH_2CH_2N(C_2H_5)_2$, $R^2 = H$, 20%
14, $R^1, R^2 = (CH_2)_4O$, 56%

Scheme 2 *Reagents and conditions*: (i) 30% H_2O_2(2 equiv.), CH_3CN, 0 °C, 4 min, 76%; (ii) 1,4-cyclohexanedione **6** (2 equiv.), EtOAc, HBF_4 (1 equiv.), 38%; (iii) R^1R^2NH (1.3 equiv.), $NaBH(OAc)_3$ (1.3 equiv.), CH_2Cl_2, 18 h.
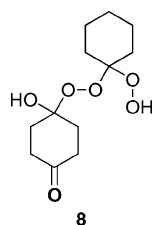
Fig. 2 Open chain dimeric peroxide.

Reductive amination[35] of the ketone **7a** with various amino compounds afforded compounds **9–14** in moderate to good yields (20–85%) (Scheme 2). Next, we examined the reaction between **5a** and ethyl-4-oxocyclohexane carboxylate (the acetal deprotected product of **15**) and also the reaction between **16** and cyclohexanone. The latter gave a significant reduction in the trimeric by-product. Intermediate **16** was formed either by hydrolysing the ketal **15**, followed by formic acid catalysed formation of the bis(hydroperoxide) and subsequent acid catalyzed condensation with cyclohexanone or *via* tungstic acid catalysed[25] formation directly from the ketal (Scheme 3).
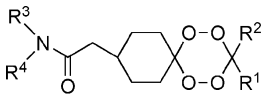

19, $R^1 = CH(CH_2)_2$, $R^2 = H$, 76%
20, $R^1 = CH_2CH_2N(C_2H_5)_2$, $R^2 = H$, 48%
21, $R^1 = CH_2CH_2N(CH_2)_4O$, $R^2 = H$, 78%
22, $R^1, R^2 = (CH_2)_4O$, 80%

Scheme 3 *Reagents and conditions*: (i) 20% H_2SO_4, ethanol; (ii) 30% H_2O_2 (4 equiv.), HCOOH (4 equiv.), CH_3CN, 0 °C, 63% or (i,ii) H_2WO_4 (2 equiv.), THF, 30% H_2O_2, 0 °C, 48 h; (iii) cyclohexanone (2 equiv.), EtOAc, HBF_4 (1 equiv.), 35%; (iv) KOH (5.5 equiv.), CH_3OH, 70 °C, 1 h, 85%; (v) NEt_3 (1 equiv.), $ClCO_2C_2H_5$ (1.3 equiv.), CH_2Cl_2, 0 °C, 1 h; (vi) R^1R^2NH (2 equiv.), 0 °C–rt.

The ester was hydrolysed to the corresponding acid (Scheme 3) by a procedure reported by Opsenica *et al.*[10] The resulting acid was coupled with a selection of amino compounds *via* a mixed anhydride intermediate to give the corresponding amides (Scheme 3).

Considering the relatively high cost of **15**, we prepared the higher homologue *via* an alternative route, by first carrying out a Wittig reaction between 1,4-cyclohexanedione monoethylketal and ethyl (triphenylphosphoranylidene)acetate (Scheme 4). Hydrogenation in the presence of palladium on carbon afforded the required starting material **25**. The bis(hydroperoxide) formed was condensed with various ketones to afford the corresponding tetraoxanes **27a**, **28a** and **29a**. Hydrolysis, followed by amide coupling reactions led to various water-soluble analogues listed in Table 1.

For analogues **27h** and **29h** crystals were grown by slowly evaporating a dichloromethane–hexane mixture and the single crystal X-ray structures were solved for these two tetraoxanes (Fig. 3).§

Table 1 Yields for amide synthesis

27c-27h, R^1 and R^2 = $(CH_2)_5$
28c-28h, R^1 and R^2 = $(CH_2)_{11}$
29c-29h, R^1 and R^2 = Adamantylidine

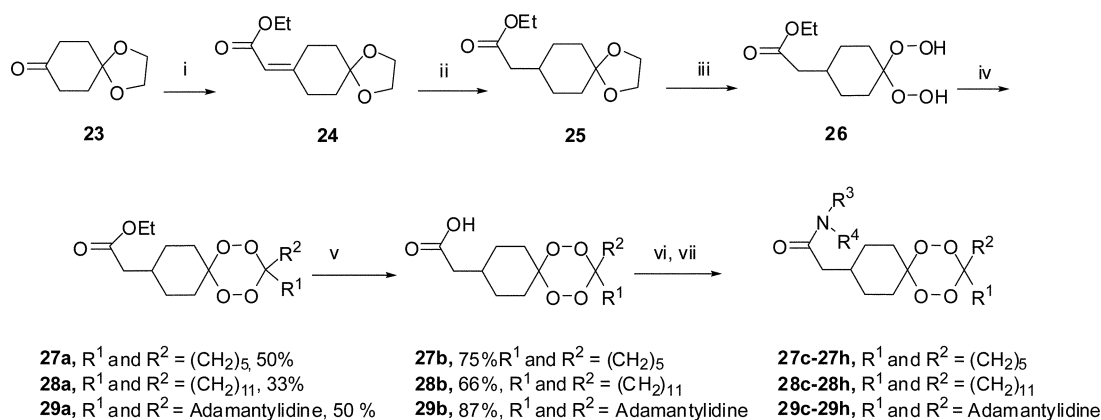| Acid	Amide product	Yield (%)
27b	27c, R^3 = CH(CH$_2$)$_2$, R^4 = H	85
27b	27d, R^3 = CH$_2$CH$_2$N(CH$_2$)$_4$, R^4 = H	78
27b	27e, R^3 = CH$_2$CH$_2$N(CH$_2$)$_5$, R^4 = H	81
27b	27f, R^3 = CH$_2$CH$_2$N(CH$_2$)$_4$O, R^4 = H	76
27b	27g, R^3 = CH$_2$CH$_2$N(C$_2$H$_5$)$_2$, R^4 = H	58
27b	27h, R^3, R^4 = (CH$_2$)$_4$O	84
28b	28c, R^3 = CH(CH$_2$)$_2$, R^4 = H	88
28b	28d, R^3 = CH$_2$CH$_2$N(CH$_2$)$_4$, R^4 = H	81
28b	28e, R^3 = CH$_2$CH$_2$N(CH$_2$)$_5$, R^4 = H	82
28b	28f, R^3 = CH$_2$CH$_2$N(CH$_2$)$_4$O, R^4 = H	78
28b	28g, R^3 = CH$_2$CH$_2$N(C$_2$H$_5$)$_2$, R^4 = H	74
28b	28h, R^3, R^4 = (CH$_2$)$_4$O	90
29b	29c, R^3 = CH(CH$_2$)$_2$, R^4 = H	83
29b	29d, R^3 = CH$_2$CH$_2$N(CH$_2$)$_4$, R^4 = H	80
29b	29e, R^3 = CH$_2$CH$_2$N(CH$_2$)$_5$, R^4 = H	78
29b	29f, R^3 = CH$_2$CH$_2$N(CH$_2$)$_4$O, R^4 = H	77
29b	29g, R^3 = CH$_2$CH$_2$N(C$_2$H$_5$)$_2$, R^4 = H	66
29b	29h, R^3, R^4 = (CH$_2$)$_4$O	81

In addition to the synthesis of dispiro derivatives we also decided to investigate the synthesis of some simple spiro derivatives. However, in the reaction of bis(hydroperoxide) **5a** and ethyl levulinate, only the trimeric cyclic product **31** (Scheme 5) was produced. Incorporation of amino functionalities into **31** was carried out to see if this class of cyclic endoperoxide had antimalarial properties; hydrolysis of the ester function of **31** to the carboxylic acid, followed by amide coupling gave analogues **32–34**.

By reversing this route, by preparing the bis(hydroperoxide) from ethyl levulinate and condensing with cyclohexanone (Scheme 6) the required tetraoxane was made in low yield; we attribute this low yield to the instability of the bis(hydroperoxide) **30a**.

The ester handle was converted into the corresponding amides **37–40** as shown in Scheme 6.

A selection of the 1,2,4,5-tetraoxanes was tested against the 3D7 strain of the *Plasmodium falciparum* and the results are summarized in Table 2 below. Most of the analogues have comparable antimalarial IC50 values to the naturally occurring endoperoxide artemisinin. The incorporation of a methylene spacer into **19–22** generally improves activity. The adamantane analogues of the tetraoxanes and their corresponding amide have a better activity than their cyclohexanone and cyclododecanone counterparts. Notably, the spiro-amides **37–40** have much lower potency than members of the dispiro series.

A 4-day Peter's suppressive test was performed on a selection of the compounds and the results are summarized in Table 3. The

27a, R^1 and R^2 = (CH$_2$)$_5$, 50%
28a, R^1 and R^2 = (CH$_2$)$_{11}$, 33%
29a, R^1 and R^2 = Adamantylidine, 50 %

27b, 75% R^1 and R^2 = (CH$_2$)$_5$
28b, 66%, R^1 and R^2 = (CH$_2$)$_{11}$
29b, 87%, R^1 and R^2 = Adamantylidine

27c-27h, R^1 and R^2 = (CH$_2$)$_5$
28c-28h, R^1 and R^2 = (CH$_2$)$_{11}$
29c-29h, R^1 and R^2 = Adamantylidine

Scheme 4 *Reagents and conditions*: (i) Ph$_3$P=CHCO$_2$Et (1.1 equiv.), benzene–toluene, reflux, 24 h, 90%; (ii) Pd/C, H$_2$, EtOAc, 95%; (iii) H$_2$WO$_4$ (2 equiv.), THF, 30% H$_2$O$_2$ (2 equiv.), 0 °C, 48 h, 88%; (iv) cyclohexanone/cyclododecanone/adamantanone (2 equiv.), EtOAc, HBF$_4$ (1 equiv.); (v) KOH (5.5 equiv.), CH$_3$OH, 70 °C, 1 h; (vi) Et$_3$N (1 equiv.), ClCO$_2$C$_2$H$_5$ (1.3 equiv.), 0 °C, 1 h; (vii) R^{3}R^{4}NH (2 equiv.), 0 °C–rt.

27h

29h
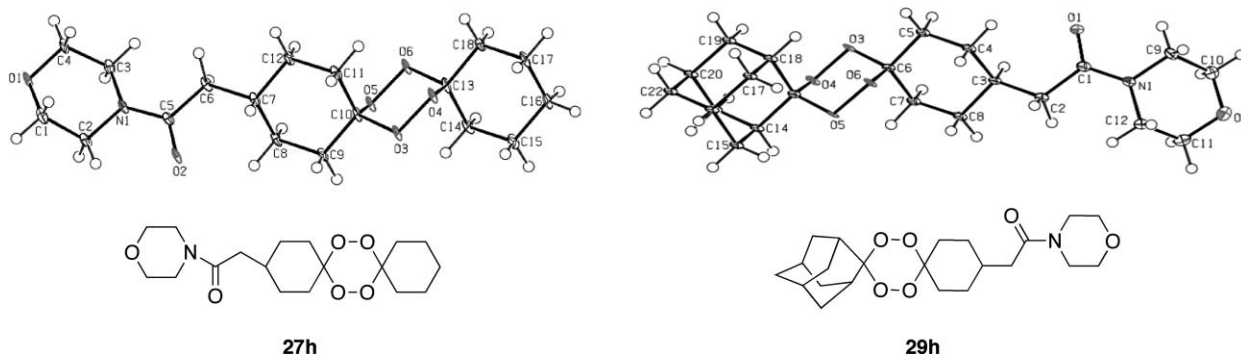
Fig. 3 Single crystal X-ray structures of compounds **27h** and **28h**.¶
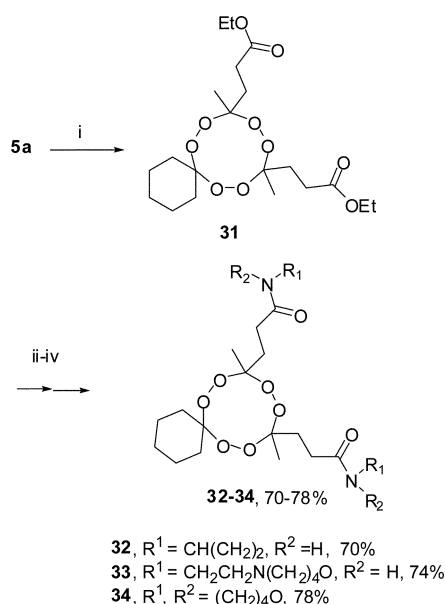
Scheme 5 *Reagents and conditions*: (i) ethyl levulinate (2 equiv.), EtOAc, HBF$_4$(1 equiv.), 68%; (ii) KOH (5.5 equiv.), CH$_3$OH, 70 °C, 1 h; (iii) Et$_3$N (1 equiv.), ClCO$_2$C$_2$H$_5$ (1.3 equiv.), CH$_2$Cl$_2$, 0 °C, 1 h; (iv) R^{1}R^{2}NH (2 equiv.), 0 °C–rt.
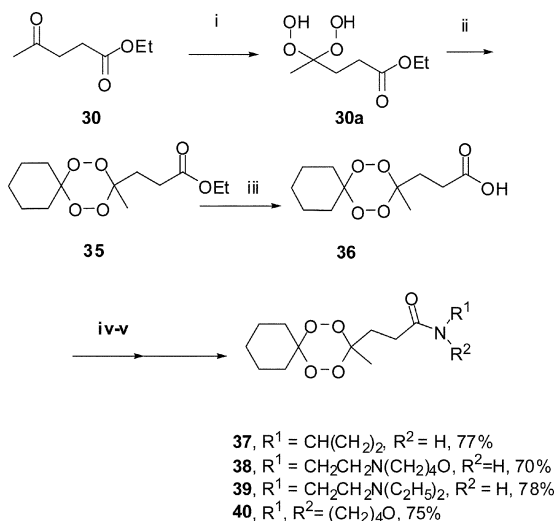
Scheme 6 *Reagents and conditions*: (i) 30% H$_2$O$_2$ (2 equiv.), CH$_3$CN, 0 °C, 4 min, (ii) cyclohexanone (2 equiv.), EtOAc, HBF$_4$ (1 equiv.), 18%; (iii) KOH (5.5 equiv.), CH$_3$OH, 70 °C, 1 h, 86%; (iv) Et$_3$N (1 equiv.), ClCO$_2$C$_2$H$_5$ (1.3 equiv.), CH$_2$Cl$_2$, 0 °C, 1 h; (v) R^{1}R^{2}NH (2 equiv.), 0 °C–rt.

2-adamantanone derived analogues **29c** and **29h** showed 100% inhibition by oral administration at a dose of 30 mg kg^{-1}; in addition, the cyclododecylidene analogue **28h** displayed potent activity at this dosing level. Based on these exciting results, analogues **29c** and **29h** were assessed in the 4-day Peter's test to determine oral *in vivo* ED50 and ED90 values *versus Plasmodium berghei* (ANKA). Compound **29h** demonstrates outstanding oral activity and is superior to the semi-synthetic control artemether (Table 4). Compound **29c** was less potent in these tests.

A conformational search using a Monte-Carlo method with the MMFF94 force field was performed on molecules **28h** and **29h**.[41] Fig. 4 displays low energy conformations of **28h** and **29h**

Table 2 *in vitro* antimalarial activity of 1,2,4,5-tetraoxanes *versus* 3D7 strain of *Plasmodium falciparum*

Compound	Mean IC50^a/nM	Compound	Mean IC50^a/nM
Artemether	3.4	**27c**	19.9
Chloroquine	8.5	**27d**	19.1
Artemisinin	9.5	**27e**	19.2
7a	6.0	**27f**	19.1
9	20.0	**27g**	5.15
12	28.1	**27h**	22.2
14	29.4	**28c**	18.7
17	59.7	**28h**	15.5
19	26.1	**29c**	2.3
20	1.5	**29h**	5.2
21	21.3	**37**	469.2
22	23.6	**40**	473.7
27a	24.2		

^{a} The mean IC50 was calculated from triplicate results. Antimalarial activities were assessed by a previously published protocol.[38]

Table 3 Peter's suppressive test results *versus Plasmodium berghei* ANKA strain in mice.[39a]

Compound	R^1 and R^2	R^3 and R^4	Percentage of inhibition at 30 mg kg^{-1} (po^b)
27c	(CH$_2$)$_5$	H and CH(CH$_2$)$_2$	24.8
27h	(CH$_2$)$_5$	(CH$_2$)$_4$O	33.0
28c	(CH$_2$)$_{11}$	H and CH(CH$_2$)$_2$	50
28h	(CH$_2$)$_{11}$	(CH$_2$)$_4$O	99.6
29c	Adamantylidene	H and CH(CH$_2$)$_2$	100
29h	Adamantylidene	(CH$_2$)$_4$O	100
Artesunate	—	—	100
Artemether	—	—	100

^{a} Compounds were administered orally in a standard suspending vehicle (SSV). The aqueous formulation used contained medium-viscosity (CMC) (0.5%), '4-day' test benzyl alcohol (0.5%), Tween 80 (0.4%) and NaCl (0.9%). ^{b} po = oral route of administration.

respectively, rendered using DS Visualizer.[42] The polar surface area (PSA) was calculated for each conformation, and the Boltzmann weighted average calculated for the two compounds. Interestingly, the calculations revealed that the two molecules have very similar Boltzmann weighted polar surface areas, but very different logP values. Calculations demonstrate that compound **29h** is significantly more hydrophobic than **28h**.[43]

In summary, we have prepared a small array of tetraoxane derivatives that have remarkable antimalarial activities *in vitro*. Preliminary *in vivo* evaluation demonstrates that adamantylidene and cyclododecylidene derivatives have very promising oral activities; it is clear from this study that the cyclododecyl[27] and adamantyl functional groups are unique in imparting extra levels of antiparasitic activity. The latter observation follows on from studies with 1,2,4-trioxolanes (ozonides)[40] and 1,2,4-trioxanes,[44,45] where only systems containing this functional group had oral activities in mouse models of malaria. The 1,2,4,5-tetraoxanes described here have significant advantages over the racemic synthetic endoperoxides that have been prepared to date[5,6] since

Table 4 Oral activities of **29c** and **29h** *versus Plasmodium berghei* ANKA[39a]

Compound	R[1] and R[2]	R[3] and R[4]	ED50/mg kg^{-1}	ED90/mg kg^{-1}
29c	Adamantylidine	H and CH(CH$_2$)$_2$	10.27	20.33
29h	Adamantylidine	(CH$_2$)$_4$O	3.18	3.88
Artemether	—	—	5.88	10.57

[a] Compounds were administered orally in a standard suspending vehicle (SSV). The aqueous formulation used contained medium-viscosity CMC (0.5%), '4-day' test benzyl alcohol (0.5%), Tween 80 (0.4%) and NaCl (0.9%).

28h PSA (Å^2) = 59.25, logP = 3.67   **29h** PSA (Å^2) = 59.61, logP = 5.54
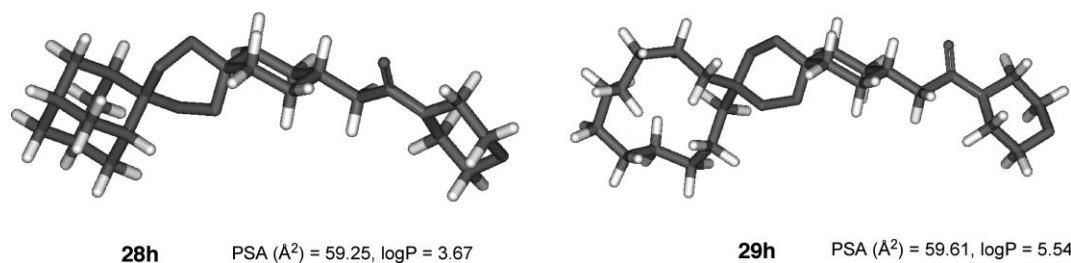
Fig. 4 Low energy conformations of tetraoxanes **28h** and **29h**.

they have equivalent activity to the natural product artemisinin, are achiral and can be synthesized in good yields from simple starting materials. Further studies will establish whether these 1,2,4,5-tetroxane derivatives are viable alternatives to the 1,2,4-trioxolane class of antimalarial recently described by Vennerstrom and co-workers.[40]

Acknowledgements

Notes and references

§ Crystal data for **27h**: C$_{18}$H$_{29}$NO$_6$; space group $P\bar{1}$, a = 5.9604(12) Å, a = 92.596(4)°, b = 8.5899(17) Å, β = 95.039(4)°, c = 17.360(3) Å, γ = 99.803(4)°; crystal size 0.5 × 0.4 × 0.1 mm; crystal system: triclinic; V = 870.8(3) Å^3; Z = 2; density (calculated) = 1.356 g cm^{-3}; reflections = 5294; angle range; 0.80 < θ < 28.13; $F(000)$ 384; number of reflections measured = 4499; number of observed reflections = 2270; independent reflections = 3017; refinement method: full-matrix least-squares on F^2; goodness-of-fit on F^2: 1.014; final R indices [I > 2σ(I)]: R_1 = 0.0761, wR_2 = 0.1793; R indices (all data): R_1 = 0.0948, wR_2 = 0.1924. CCDC 616879. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613565j

Crystal data for **29h**: C$_{22}$H$_{33}$NO$_6$; space group $P2_1/n$; a = 6.2610(6) Å, a = 90°, b = 37.479(3) Å, β = 90.841(2)°, c = 8.6291(8) Å, γ = 90°; crystal size 0.4 × 0.3 × 0.2 mm; crystal system: monoclinic; V = 2024.7(3) Å^3; density (calculated) 1.337 g cm^{-3}; reflections = 12387; angle range = 0.90 < θ < 28.12; number of reflections measured = 10349; independent reflections = 3562; refinement method: full-matrix least-squares on F^2; goodness-of-fit on F^2: 1.056; final R indices [I > 2σ(I)]: R_1 = 0.0707, wR_2 = 0.1875; R indices (all data): R_1 = 0.0779, wR_2 = 0.1943. CCDC 616880. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613565j

¶ The structures were solved using the SHELXS-97 program[36] and refined by full-matrix least-squares on F^2 with SHELXL-97.[37]

1 D. L. Klayman, *Science*, 1985, **228**, 1049–1055.
2 T. T. Hien and N. J. White, *Lancet*, 1993, **341**, 603–608.
3 S. R. Meshnick, *Int. J. Parasitol.*, 2002, **32**, 1655–1660.
4 S. Paitayatat, B. Tarnchompoo, Y. Thebtaranonth and Y. Yuthavong, *J. Med. Chem.*, 1997, **40**, 633–638.
5 P. M. O'Neill and G. H. Posner, *J. Med. Chem.*, 2004, **47**, 2945–2964.
6 Y. Q. Tang, Y. X. Dong and J. L. Vennerstrom, *Med. Res. Rev.*, 2004, **24**, 425–448.
7 L. P. D. Bishop, J. L. Maggs, P. M. O'Neill and B. K. Park, *J. Pharmacol. Exp. Ther.*, 1999, **289**, 511–520.
8 Y. L. Wu and Y. Li, *Med. Chem. Res.*, 1995, **5**, 569–586.
9 J. L. Vennerstrom, H. N. Fu, W. Y. Ellis, A. L. Ager, J. K. Wood, S. L. Andersen, L. Gerena and W. K. Milhous, *J. Med. Chem.*, 1992, **35**, 3023–3027.
10 D. Opsenica, D. E. Kyle, W. K. Milhous and B. A. Solaja, *J. Serb. Chem. Soc.*, 2003, **68**, 291–302.
11 M. J. C. Harding and D. M. Whalen, *Ind. Eng. Chem. Prod. Res. Dev.*, 1975, **14**, 232–239.
12 P. R. Story and P. Busch, in *Advances in Organic Chemistry*, ed. E. C. Taylor, Wiley, New York, 1972, vol. 8, pp. 67–95.
13 D. Opsenica, G. Pocsfalvi, Z. Juranic, B. Tinant, J. P. Declercq, D. E. Kyle, W. K. Milhous and B. A. Solaja, *J. Med. Chem.*, 2000, **43**, 3274–3282.
14 A. K. Bhattacharjee, K. A. Carvalho, D. Opsenica and B. A. Solaja, *J. Serb. Chem. Soc.*, 2005, **70**, 329–345.
15 S. Tonmunphean, A. Wijitkosoom and Y. Tantirungrotechai, *Bioorg. Med. Chem.*, 2004, **12**, 2005–2012.
16 Y. Hamada, H. Tokuhara, A. Masuyama, M. Nojima, H. S. Kim, K. Ono, N. Ogura and Y. Wataya, *J. Med. Chem.*, 2002, **45**, 1374–1480.
17 W. Adam, G. Asensio, R. Curci, J. A. Marco, M. E. González-Núñez and R. Mello, *Tetrahedron Lett.*, 1992, **33**, 5833–5836.
18 H. S. Kim, K. Tsuchiya, Y. Shibata, Y. Wataya, Y. Ushigoe, A. Masuyama, M. Nojima and K. J. McCullough, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1867–1870.
19 K. Griesbaum and K. Schlindwein, *J. Org. Chem.*, 1995, **60**, 8062.
20 N. Nakamura, M. Nojima and S. Kusabayashi, *J. Am. Chem. Soc.*, 1987, **109**, 4969–4973.
21 T. Tokuyasu, A. Masuyama, M. Nojima and K. J. McCullough, *J. Org. Chem.*, 2000, **65**, 1069–1075.
22 Y. Ito, M. Konishi and T. Matsuura, *Photochem. Photobiol.*, 1979, **30**, 53–57.
23 Y. Ito, H. Yokoya, Y. Umehara and T. Matsuura, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 2407–2408.
24 Y. X. Dong and J. L. Vennerstrom, *J. Org. Chem.*, 1998, **63**, 8582–8585.
25 C. W. Jefford, Y. Li, A. Jaber and J. Boukouvalas, *Synth. Commun.*, 1990, **20**, 2589–2596.
26 C. W. Jefford and A. J. J. Boukouvalas, *Synthesis*, 1988, 391–393.
27 H. S. Kim, Y. Shibata, Y. Wataya, K. Tsuchiya, A. Masuyama and M. Nojima, *J. Med. Chem.*, 1999, **42**, 2604–2609.

28 A. O. Terent'ev, A. V. Kutkin, Z. A. Starikova, M. Y. Antipin, Y. N. Ogibin and G. I. Nikishina, *Synthesis*, 2004, 2356–2366.

29 K. Zmitek, S. Stavber, M. Zupan, D. Bonnet-Delpon and J. Iskra, *Tetrahedron*, 2006, **62**, 1479–1484.

30 Y. X. Dong, H. Matile, J. Chollet, R. Kaminsky, J. K. Wood and J. L. Vennerstrom, *J. Med. Chem.*, 1999, **42**, 1477–1480.

31 K. J. M. McCullough, A. R. Nonhebel, D. C. Pauson, P. L. White and G. J., *J. Chem. Res. (S)*, 1980, 601–628.

32 J. Iskra, D. Bonnet-Delpon and J. P. Begue, *Tetrahedron Lett.*, 2003, **44**, 6309–6312.

33 D. Yuxiang, *Mini-Rev. Med. Chem.*, 2002, **2**, 113–123.

34 T. Ledaal, *Acta Chem. Scand.*, 1967, **21**, 1656–1659.

35 O. Dechy-Cabaret, F. Benoit-Vical, A. Robert and B. Meunier, *Chem-BioChem*, 2000, **1**, 281–283.

36 G. M. Sheldrick, *SHELXS-97, Program for solution of crystal structures*, University of Göttingen, Germany, 1997.

37 G. M. Sheldrick, *SHELXL-97, Program for refinement of crystal structures*, University of Göttingen, Germany, 1997.

38 P. M. O'Neill, N. L. Searle, K. W. Kan, R. C. Storr, J. L. Maggs, S. A. Ward, K. Raynes and B. K. Park, *J. Med. Chem.*, 1999, **42**, 5487–5493.

39 W. Peters, S. L. Fleck, B. L. Robinson, L. B. Stewart and C. W. Jefford, *Ann. Trop. Med. Parasitol.*, 2002, **96**(6), 559–573.

40 J. L. Vennerstrom, S. Arbe-Barnes, R. Brun, S. A. Charman, F. C. K. Chiu, J. Chollet, Y. X. Dong, A. Dorn, D. Hunziker, H. Matile, K. McIntosh, M. Padmanilayam, J. S. Tomas, C. Scheurer, B. Scorneaux, Y. Q. Tang, H. Urwyler, S. Wittlin and W. N. Charman, *Nature*, 2004, **430**, 900–904.

41 *Spartan'04*, Wavefunction, Inc., Irvine, CA, 2004, http://www.wavefun.com/.

42 http://www.accelrys.com/products/downloads/ds_visualizer/.

43 A. K. Ghose and G. M. Crippen, *J. Chem. Inf. Comput. Sci.*, 1987, **27**, 21–35.

44 C. Singh, H. Malik and S. K. Puri, *J. Med. Chem.*, 2006, **49**, 2794–2803.

45 C. Singh, R. Kanchan, D. Srivastava and S. K. Puri, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 584–586.