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Semi-synthetic and synthetic 1,2,4-trioxaquines and 1,2,4-trioxolaquines: synthesis, preliminary SAR and comparison with acridine endoperoxide conjugates

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ABSTRACT

A novel series of semi-synthetic trioxaquines and synthetic trioxolaquines were prepared, in moderate to good yields. Antimalarial activity was evaluated against both the chloroquine-sensitive 3D7 and resistant K1 strain of *Plasmodium falciparum* and both series of compounds were shown to be active in the low nanomolar range. For comparison the corresponding 9-amino acridine analogues were also prepared and shown to have low nanomolar activity like their quinoline counterparts.

In spite of numerous efforts to fight Malaria, approximately 40% of the world's population remains at risk of contracting the disease. Malaria causes more than 300 million acute illnesses and at least one million deaths annually, a number that continues to rise since resistance[1] against common drugs used in malaria chemotherapy (4-aminoquinolines and sulfadoxine-pyrimethamine) has developed by *Plasmodium falciparum* in most endemic countries. It is estimated that in the absence of adequate solutions the number of victims may double by 2010.[2]

Natural artemisinin (**1**) (Fig. 1) is extracted from the herb *Artemisia annua* (Sweet wormwood) and the structure of this sesquiterpene 1,2,4-trioxane was elucidated in the late 1970s.[3] Although the detailed mechanism of action of artemisinin remains a matter of debate,[4–7] it is accepted that the process is dependent on initial cleavage of the endoperoxide function, which has been shown to be catalysed by monomeric heme[8,9] (ferriprotoporphyrin IX; present in *Plasmodium*-infected erythrocytes as a product of haemoglobin digestion). Upon endoperoxide cleavage, carbon-centred free radicals are formed, leading to alkylation of heme and other essential parasite biomolecules.[7]

Artemisinin-based combination therapy (ACT) has been recommended by the World Health organisation (WHO) as a priority treatment in the fight against malaria. The rationale for this combination is that the artemisinin derivative rapidly clears ~95% of the parasites and the remaining 5% are cleared by the longer half-life partner drug.[10] Therefore, it is established that combinations of chemotherapeutic agents can accelerate therapeutic response, improve cure rates and protect the component drugs against resistance. Although artemisinin is highly potent and has been used clinically for the treatment of multidrug resistant *P. falciparum* malaria, its use is limited by poor solubility in both oil and water.[11,12] As a result several soluble derivatives of the parent drug have been prepared and investigated. The first generation artemisinin analogues such as artemether (**2**) and arteether (**3**) have proven to be highly active but have short plasma half-lives and have been reported to be neurotoxic in animal models.[13] Sodium artesunate (**4**) has been developed as a water-soluble alternative to artemether and arteether.[7]

In response to the growing burden of resistance to quinolines,[14] there have been many attempts to develop synthetic alternatives to the semi-synthetic artemisinin derivatives; perhaps the most significant discovery has been the revelation by Vennerstrom and co-workers that ozonides (1,2,4-trioxolanes) substituted with an adamantane ring are not only chemically stable but are active against *P. falciparum* in the low nanomolar range.[15,16] Later find-

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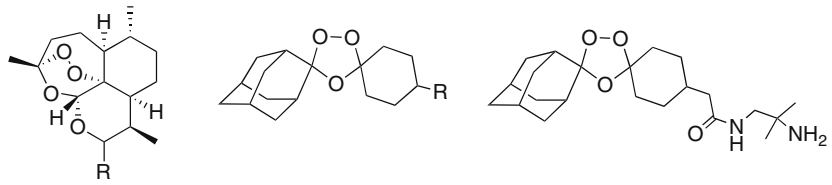


Artemisinin **1**, R = =O
Artemether **2**, R = β-OMe
Artemether **3**, R = β-OEt
Artesunate **4**, R = α-OC(O)-$CH_2CH_2CO_2Na$

5

OZ 277, **6**

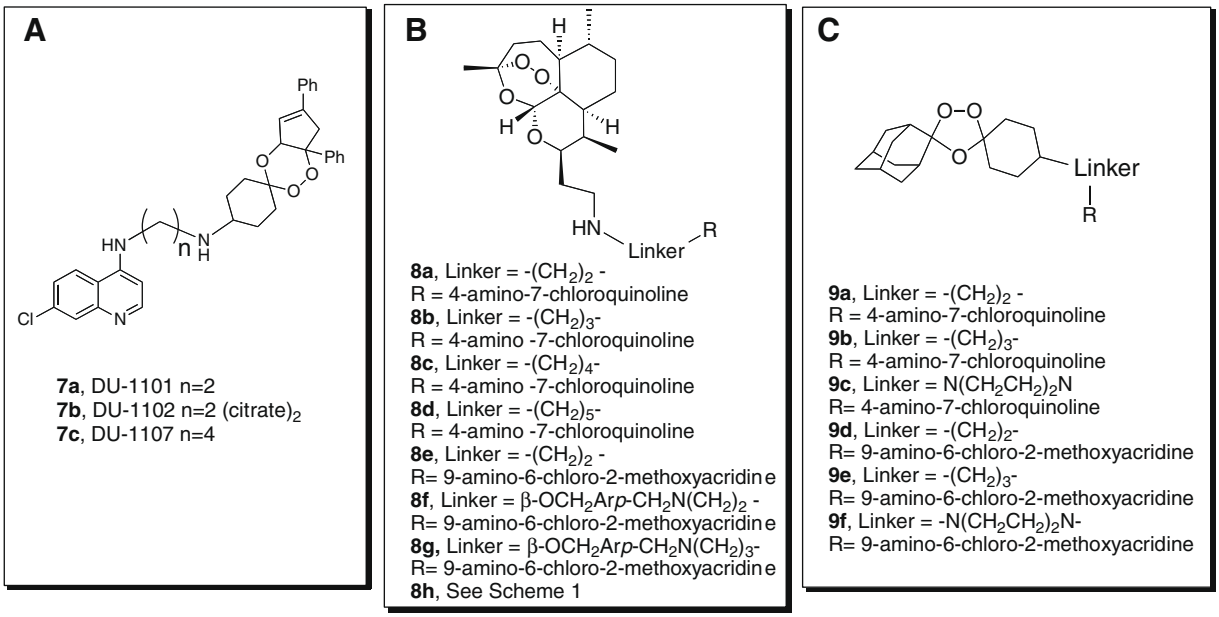
Figure 1. Artemisinin (**1**) and derivatives **2**–**4** and synthetic ozonides (**5**) and (**6**).

ings indicated that the clinical candidate OZ277/RBx11160 (**6**) Fig. 2) was non-toxic, orally active in mice and effective for a prolonged period of action.[17] Due to the high efficacy and improved properties of this drug, it has been accelerated to Phase II dose range studies in India, Thailand and Africa.[17] Further work in this area has indicated that novel trioxolanes with a wide range of neutral and basic (but not acidic) functional groups possess good antimalarial profiles.[18,19] Based on the proposed mechanisms of action of artemisinin and chloroquine, a new class of drugs named 'trioxaquines' were developed by Meunier in a 'covalent bitherapy' approach.[20–23] Trioxaquines were obtained by covalent attachment of a 1,2,4-trioxane entity, responsible for the activity of artemisinin, to an aminoquinoline entity, necessary for the accumulation of the drug within the parasite. The antimalarial activity of first generation trioxaquines, such as DU-1101 (**7a**), DU-1102 (**7b**) and DU-1107 (**7c**) (see A, Fig. 2) on sensitive and resistant strains are significantly higher than the activity of each of the individual fragments, indicating a synergistic effect of the trioxaquine and aminoquinoline components.[20,24] Recent studies have shown a second-generation trioxolane analogue, DU1302, exhibits potent activity against gameocytes, the form of malaria parasites transmitted by mosquitoes.[25]

Singh have also synthesised a series of novel trioxaquines incorporating the trioxane and 4-aminoquinoline moieties, some of which are more orally active than the parent trioxane and 4-aminoquinoline derivatives.[26] However, these hybrid molecules suffer from limitations such as poor stability and poor solubility.

In this Letter we describe our efforts in the area of quinoline endoperoxide hybrids and include for the first time the synthesis and evaluation of both semi-synthetic artemisinin derivatives (Fig. 2 B) and synthetic analogues (based on the 1,2,4-trioxolane heterocycle, Fig. 2 C). Incorporation of the 4-aminoquinoline or 9-aminoacridine unit in the final hybrid drug should act to increase the drug concentration in the 'acidic' ferrous rich food vacuole thus inducing a greater turnover of potentially toxic free radicals by endoperoxide bioactivation.[27,28] The 9-aminoacridine unit is a component of the antimalarial mepacrine, a drug used prior to chloroquine for malaria chemotherapy in humans. A useful property of these derivatives is their fluorescence and we have recently reported the distribution of both acridine containing semi-synthetic and synthetic endoperoxides in infected human red blood cells using laser scanning confocal microscopy.[29] The potential advantage of both sets of compound may be their capacity to target the parasite by two distinctive mechanisms. Indeed, any chemical or metabolic degradation of the endoperoxide bridge will result in metabolites that may act as alkylating agents or inhibitors of hematin polymerisation, provided that they do not become covalently attached to proteins in the bioactivation process.

The first series of trioxaquines were designed to incorporate the metabolically stable C-10 carba linkage. The synthetic route to C-

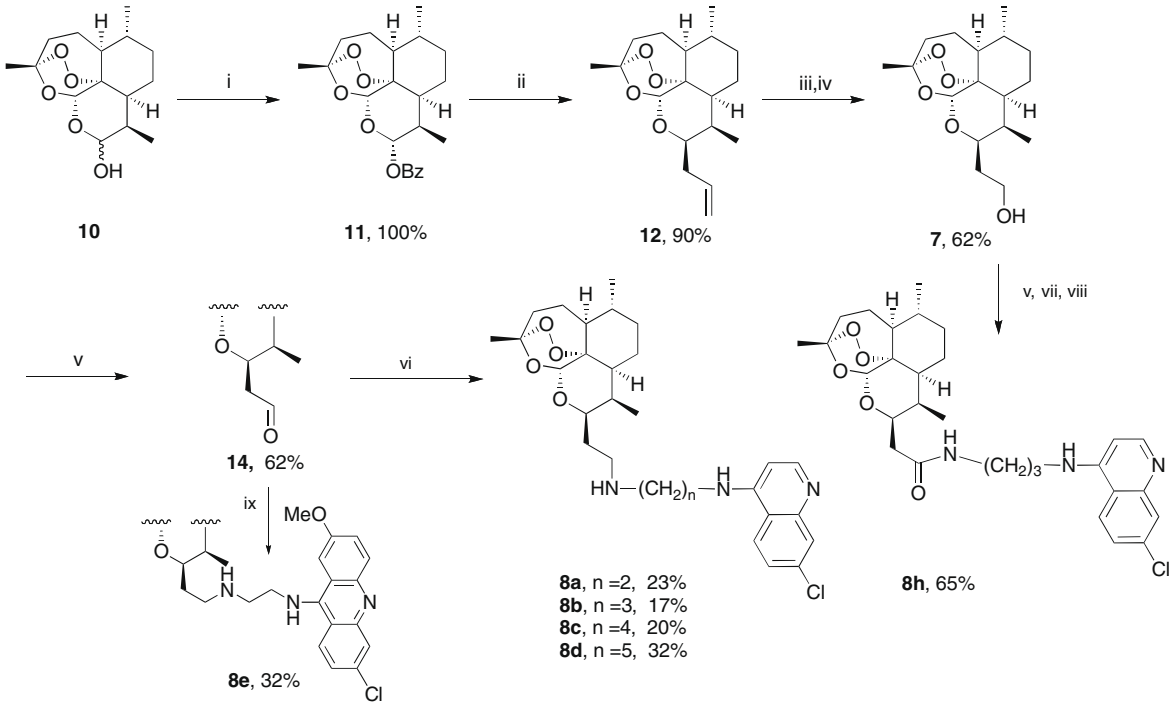


7a, DU-1101 n=2
7b, DU-1102 n=2 $(citrate)_2$
7c, DU-1107 n=4

8a, Linker = $-(CH_2)_2-$
R = 4-amino-7-chloroquinoline
8b, Linker = $-(CH_2)_3-$
R = 4-amino -7-chloroquinoline
8c, Linker = $-(CH_2)_4-$
R = 4-amino -7-chloroquinoline
8d, Linker = $-(CH_2)_5-$
R = 4-amino -7-chloroquinoline
8e, Linker = $-(CH_2)_2-$
R= 9-amino-6-chloro-2-methoxyacridine
8f, Linker = β-OCH_2Ar*p*-$CH_2N(CH_2)_2-$
R= 9-amino-6-chloro-2-methoxyacridine
8g, Linker = β-OCH_2Ar*p*-$CH_2N(CH_2)_3-$
R= 9-amino-6-chloro-2-methoxyacridine
8h, See Scheme 1

9a, Linker = $-(CH_2)_2-$
R = 4-amino-7-chloroquinoline
9b, Linker = $-(CH_2)_3-$
R = 4-amino-7-chloroquinoline
9c, Linker = $N(CH_2CH_2)_2N$
R= 4-amino-7-chloroquinoline
9d, Linker = $-(CH_2)_2-$
R= 9-amino-6-chloro-2-methoxyacridine
9e, Linker = $-(CH_2)_3-$
R= 9-amino-6-chloro-2-methoxyacridine
9f, Linker = $-N(CH_2CH_2)_2N-$
R= 9-amino-6-chloro-2-methoxyacridine

Figure 2. Trioxaquines and trioxolaquines.

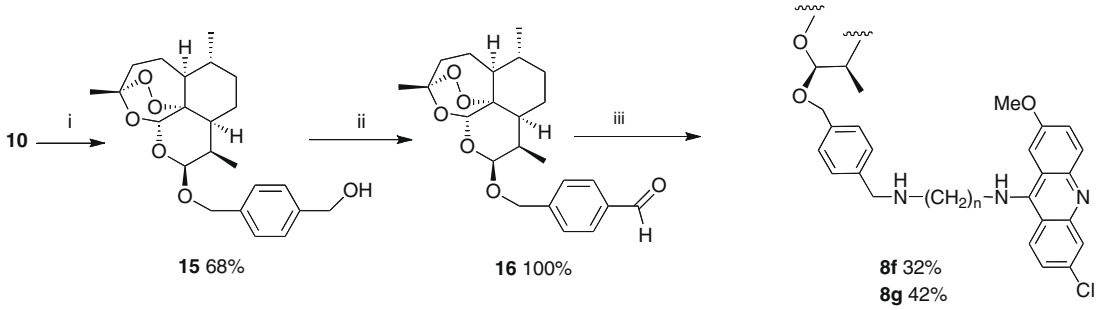


Scheme 1. Reagents and conditions: (i) BzCl, py, CH_2Cl_2, 0 °C, 16 h; (ii) allyl trimethylsilane, $ZnCl_2$, 4·molecular sieves, DCE, 0 °C, 3 h; (iii) O_3, CH_2Cl_2, −78 °C, 1 h; (iv) $NaBH_4$, THF/MeOH (9:1), 0 °C; (v) (i) 4 h Oxalyl chloride, DMSO, −78 °C, DCM; (ii) TEA; (vi) 7-Chloro-4-[*N*-(aminoalkyl)amino]quinoline, $NaHB(OAc)_3$, DCM, rt; (vii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH/H_2O, rt, 2 h; (viii) (a) $(COCl)_2$, CH_2Cl_2, 0 °C to rt, 1.5 h; (b) N^1-(7-chloroquinolin-4-yl)propane-1,3-diamine, CH_2Cl_2, Et_3N, 24 h; (ix) N^1-(2-chloro-6-methoxyacridin-9-yl)ethane-1,2-diamine, $NaHB(OAc)_3$, CH_2Cl_2, rt.

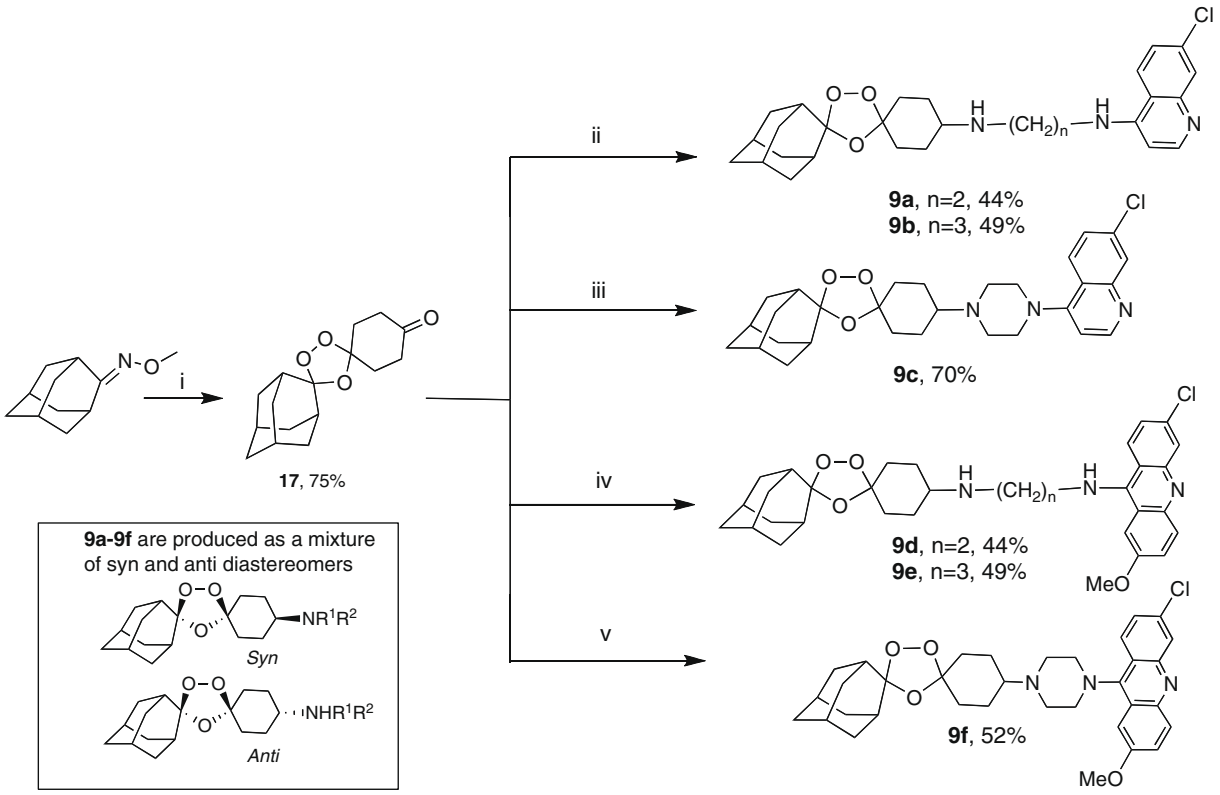
10 artemisinin carba linked 4-aminoquinolines is shown in Scheme 1 and involved methodology already developed within the group.[30,31] Dihydroartemisinin (**10**) was converted into its C-10 benzoate **11** and the ester was allowed to react with allyltrimethylsilane, in the presence of anhydrous zinc chloride to give the C-10 allyl derivative **12**. Synthesis of the C-10 aldehyde (**14**) was achieved by ozonolysis of allyl deoxoartemisinin followed by reductive work up with sodium borohydride to give alcohol **7**. Alcohol **7** was then oxidised to the corresponding aldehyde **14** via Swern methodology. The final chemical step involved reductive amination of the aldehyde **14**, prepared using a 1:1.25 mixture of aldehyde and respective alkylaminoquinoline to provide products **8a–8d**.[32,33] Reductive amination of aldehyde **14** with N^1-(2-chloro-6-methoxyacridin-9-yl)ethane-1,2-diamine gave **8e** in moderate yield. In all of these reactions, yields were compromised by the formation of by-product dimers. To circumvent this problem we explored the synthesis of an amide-linked analogue **8h** where the key step involved the synthesis of an intermediate acyl chloride derived from **7** (by oxidation to carboxylic acid and treatment with oxalyl chloride). This provided target molecule **8h** in good yield.

A second series of peroxide hybrid molecules (derived from acridine) were prepared by a shorter chemical route as depicted in Scheme 2. Alcohol **15** was obtained in good yield and diastereoselectivity (β/α, 5:1) by the reaction of dihydroartemisinin with 1,4-bis(hydroxymethyl)benzene in the presence of $BF_3{\cdot}Et_2O$ as catalyst. Swern oxidation afforded the expected aldehyde **16**, in excellent yields and subsequent reductive amination with the appropriate aminoalkyl acridines provided **8f** and **8g** as shown.

For the 1,2,4-trioxolane series a head to head quinoline/acridine series was produced to examine the effect of (a) the length of the linker and (b) which of the two heterocyclic ring systems provided analogues with the best antimalarial profiles. The synthetic pathway to 1,2,4-trioxolane hybrid molecules is depicted in Scheme 3 and involves only three synthetic steps from adamant-2-one as shown. Thus, ozonolysis of the methyl oxime[15] derived from adamant-2-one in the presence of 1,4-cyclohexadione provided key intermediate **17**. Target trioxolaquines were obtained through



Scheme 2. Reagents and conditions: (i) $BF_3{\cdot}Et_2O$, diethyl ether, 1,4-phenylenedimethanol rt; (ii) 4 h, oxalyl chloride, DMSO, −78 °C, DCM; (ii) TEA; (iii) 6-chloro-9-[*N*-(aminoalkyl)amino]-6-methoxyacridine, $NaHB(OAc)_3$, DCM, rt.



Scheme 3. Reagents and conditions: (i) O_3 (−78 °C)pentane/CH_2Cl_2, 1,4-cyclohexadione, 0 °C, 1–2 h; (ii) $NaHB(OAc)_3$,CH_2Cl_2, for **9a** N^1-(7-chloroquinolin-4-yl)ethane-1,2-diamine and for **9b**, N^1-(7-chloroquinolin-4-yl)propane-1,3-diamine; (iii) $NaHB(OAc)_3$, ,CH_2Cl_2, rt, 7-chloro-4-(piperazin-1-yl)quinoline; (iv) $NaHB(OAc)_3$, CH_2Cl_2, rt, for **9d** N^1-(6-chloro-2-methoxyacridin-9-yl)ethane-1,2-diamine and for **9e** N^1-(6-chloro-2-methoxyacridin-9-yl)ethane-1,2-diamine; (v) $NaHB(OAc)_3$, CH_2Cl_2, rt, 6-chloro-2-methoxy-9-(piperazin-1-yl)acridine.

reductive amination of **30** and aminoquinoline/acridine derivatives (Scheme 3) as shown for analogues **9a–9f**.[34] As for the semi-synthetic trioxaquines, this series of compounds could be readily formulated as water-soluble salts. Thus, compound **9a** was treated with citric acid in acetone to afford the corresponding di-citrate salt in high yield. Apart from **9f** all products were produced as a 1:1 mixture of diastereomers (see inset in Scheme 3) that could not be separated by normal chromatographic methods. Using HPLC we were able to separate the two distereomers of **9f** but it was not possible to assign the stereochemistry of the *trans* and *cis* diastereomers by 1 or 2D NMR methods.

Tables 1 and 2 contain data on the in vitro antimalarial activity of semi-synthetic analogues and 1,2,4-trioxolane counterparts versus the chloroquine-sensitive 3D7 strain and K1 resistant strain. All of the semi-synthetic analogues have nanomolar activity versus both strains of *P. falciparum* indicating a complete lack of cross-resistance with chloroquine. This lack of cross-resistance has also been noted by Meunier and other co-workers in studies with synthetic trioxaquines.[20]

Although many of the analogues are more potent than artemisinin none of the semi-synthetic analogues tested were more potent than artemether in these assays. This is somewhat surprising given the fact these molecules should accumulate within the acidic digestive vacuole (the site of free hematin generation) much more efficiently than the parent drug by an ion-trapping mechanism.[37] This observation may indicate that other targets outside the food vacuole such as PfATP6 (or other) may be more important for this

Table 1
In vitro antimalarial activity of semi-synthetic analogues versus the 3D7 and K1 strains of *Plasmodium falciparum*[a]

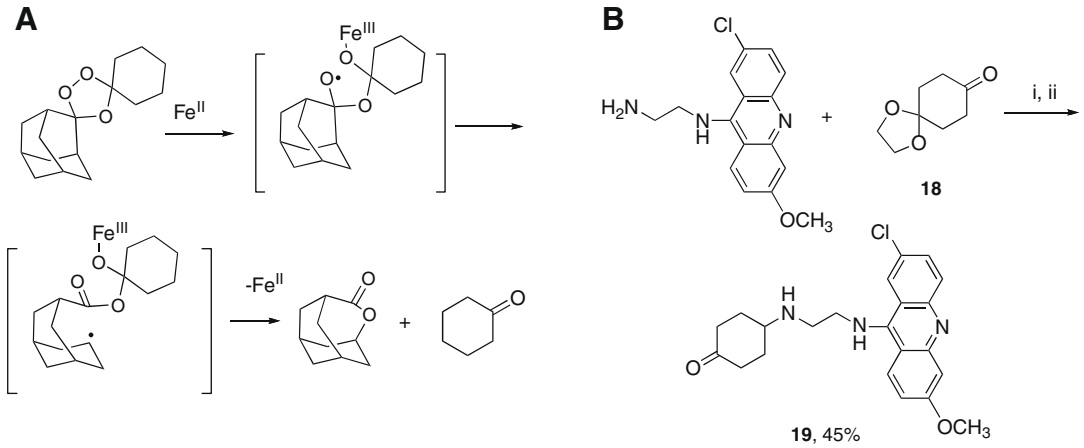
Endoperoxide	3D7 IC_{50}/nM	SD ± mean	K1 IC_{50}/nM	SD ± mean
Artemether	3.45	0.34	1.26	0.51
Artemisinin	11.23	2.23	9.54	1.10
Chloroquine	15.62	3.45	187.34	21.10
8a	5.40	2.34	8.70	2.23
8b	11.51	1.45	12.60	4.53
8c	12.61	2.43	13.23	1.23
8d	24.25	4.34	16.21	3.45
8e	12.52	1.01	14.34	3.49
8f	12.32	2.25	19.34	2.45
8g	16.34	4.56	20.22	4.39
8h	9.34	2.55	8.22	4.34

[a] Parasites were maintained in continuous culture according to the method of Trager and Jensen.[35] IC_{50} values were measured according to the methods described by Desjardins et al.[36] (3D7 is chloroquine sensitive and K1 is a chloroquine resistant strain).

Table 2
In vitro antimalarial activity of synthetic 1,2,4-Trioxolaquines versus the 3D7 and K1 strains of *Plasmodium falciparum*[a]

Endoperoxide	3D7 IC_{50}/nM	SD ± mean	K1 IC_{50}/nM	SD ± mean
Artemether	3.10	0.34	2.10	0.34
Artemisinin	9.30	1.22	12.35	2.23
Chloroquine	18.23	1.23	240.34	3.45
9a	6.56	4.23	3.60	2.34
9b	12.33	1.29	8.32	1.45
9c	12.61	2.43	26.21	4.21
9d	9.67	4.34	7.20	2.33
9e	12.52	1.01	11.10	5.22
9f	12.32	2.25	6.76	1.89
17	3.10	0.34	3.02	0.34

[a] Parasites were maintained in continuous culture according to the method of Trager and Jensen.[35] IC_{50} values were measured according to the methods described by Desjardins et al.[36] (3D7 is chloroquine sensitive and K1 is a chloroquine resistant strain).



Scheme 4. Reagents and conditions; (A) $FeBr_2$ (1 equiv) THF, rt (for full details see Ref. 39); (B) (i) $NaHB(OAc)_3$, CH_2Cl_2, 3 h, rt; (ii) CH_3OH/CH_2Cl_2 1:1, 10% HCl, 48 h reflux.

class of hybrid-drug.[38] Interestingly mono-protic amide **8h** was as active as the diprotic analogues **8a–8d** indicating that an additional protonation site within the hybrid drug has little impact on antimalarial activity. An increase in chain length decreases activity within the series **8a–8d** and comparing acridine **8e** there is little difference between a quinoline or acridine heterocycle in terms of absolute potency. By examining the activities of **8f** and **8g**, the SAR also seems to intolerant to the nature of the linker group or the C-10 anomeric substituent since both molecules have similar activity to other compounds tested in the series.

The 1,2,4-trioxolane series were generally more potent than the semi-synthetic derivatives. As was the case for the semi-synthetic trioxaquines, increasing the linker length reduced activity slightly across the series **9a–9b**. The most potent analogue was **9a** with activity superior to artemisinin and chloroquine against the 3D7 and K1 strains of *P. falciparum*. As for the semi-synthetic analogues there was no observable cross-resistance with chloroquine indicating that the chloroquine resistance mechanism does not recognise these drug conjugates. Interestingly, ketone **17** had superior activity to many of the conjugates prepared indicating that the presence of the additional hematin-binding unit is not enhancing activity further as seen with the semi-synthetic series.

In spite of the lack of significant increase in antimalarial activity there are still some advantages of the hydrid drugs described here. Many of the derivatives prepared can be readily converted into water-soluble salts making them suitable for oral and iv formulations. Another potential advantage of the drug-hybrid is that even when the peroxide is 'chemically spent' the residual aminoquinoline or aminoacridine product can still act as an efficient antimalarial, provided that it is not covalently bound to protein. Recent studies by Tang and Vennerstrom have demonstrated that 1,2,4-trioxolanes readily fragment by an iron catalysed process leading to the formation of a secondary C-centred radical in tandem with cyclohexanone as shown in Scheme 4A.[39] Based on this mechanism it seems plausible that **9d** will release acridine ketone **19** following Fe(II) mediated degradation. Ketone **19** was prepared in two steps from ketal **18** by reductive amination and acid catalysed deprotection (Scheme 4B). Antimalarial assessment of this acridine indicated activity at the level of 450 nM versus the K1 strain of *P. falciparum*. This result provides some evidence that **9d** and other 1,2,4-trioxolane hybrids prepared here may have the capacity to function as a delivery system for an active hematin binder (i.e., aminoacridine or aminoquinoline) in tandem with a potentially cytotoxic secondary carbon-centred radical following Fe(II) mediated activation (Scheme 4A).

In conclusion, we have prepared two novel series of endoperoxide incorporating an aminoquinoline or acridine moiety. Both sets of hybrid molecule express high levels of antimalarial activity in vitro. Further work is required in this area to elucidate specific biochemical targets of both the trioxaquines and the trioxolaquines at inhibitory concentrations and to assess these molecules in rodent models of malaria. Recently, a synthetic trioxaquine (PA1103/SAR116242) was candidate selected for drug development indicating that this 'drug-hybrid' approach provides molecules with acceptable pharmacological and safety profiles to permit regulatory drug-development.[40]

Acknowledgements

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32. Compound **8b** was obtained as a light yellow solid (0.19 g, 17% from 10β-carba aldehyde **14** (0.52 g, 2.21 mmol), *N*2-(-chloro-4-quinolinyl)-1,2-diaminopropane (0.55 g, 1.77 mmol) and sodium triacetoxyborohydride (0.38 g, 1.77 mmol). The mixture was allowed to stir for 22 h at room temperature and then washed with distilled water. The organic layer was dried and evaporated under vacuum to dryness. The residue was purified by flash chromatography using ethyl acetate/methanol (5–25%) mp 115 °C. ν_{max} (film)/cm^{-1} 1611, 1582, 1451, 1370, 1055, 877, 853. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.47 (d, J = 5.8 Hz, 1H), 8.00 (m,1H), 7.91 (d, J = 3.3 Hz, 1H), 7.36 (m, 1H), 6.29 (d, J = 5.8 Hz, 1H), 5.20 (s, 1H), 3.65 (m, 1H), 3.40 (m, 2H), 2.99 (m, 2H), 2.87 (m, 2H), 2.45 (m. 2H), 2.10–0.82 (m, 25H) including 1.41 (s, 3H, C-3-Me), 0.96 (d, J = 6.4 Hz, 3H, C-6-Me), 0.82 (d, J = 7.6 Hz, 3H, C-9-Me). ^{13}C (100 MHz, $CDCl_3$) δ 152.4, 150.9, 149.6, 134.9, 128.9, 125.0, 122.6, 118.0, 103.4, 98.6, 92.1, 89.7, 81.4, 74.0, 52.6, 49.9, 49.4, 44.5, 44.3, 37.8, 36.9, 34.7, 30.8, 29.9, 27.6, 26.4, 25.2, 25.0, 20.6, 13.2. MS m/z (CI, +ve): 530 ([M+H]$^+$, 2) 512(17) 179 (75) 145 (100); (FAB): 530 [M$^+$]. Found [M+H]$^+$ 530.2804, $C_{29}H_{41}O_4N_3$ requires 530.2785.
33. Compound **8c**: yellow solid; mp 133–134 °C; ν (film)/cm^{-1} 1711, 1612, 1582, 1453, 1376, 1056, 878, 853. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 5.3 Hz, 1H), 7.96 (br s, 1H), 7.52 (br d, 1H), 7.00 (br d, 1H), 6.39 (d, J = 5.5 Hz, 1H), 5.23 (s, 1H), 3.47 (m, 4H), 2.63 (m, 2H), 2.28 (m, 2H) 2.15–0.80 (m, 30H) including 1.39 (s, 3H, C-3-Me), 0.93 (d, 3H, J = 6.0 Hz, C-6-Me), 0.80 (d, 3H, J = 7.6 Hz, C-9-Me). MS m/z (FAB, +ve): Found [M+H]$^+$ 544.29430, $C_{30}H_{43}O_4N_3$ requires 544.2942.
34. Compound **9f**: Reductive amination of adamantane-2-spiro-3′-8′-oxo-1′, 4′-trioxaspiro[4.5] decane **17** (0.62 g, 2.2 mmol) with 6-chloro-2-methoxy-9-piperazin-1-yl-acridine (0.87 g, 2.8 mmol) and sodium trioacetoxyborohydride (0.6 g, 2.8 mmol) afforded the required trioxolaquine as a mixture of diastereomers. Orange solid (0.67 g, 52%). Mp 112 °C. ν_{max} (film)/cm^{-1} 1211 (R–O–CH_3), 1116 (C3′–O–C5′), 754 (C3′–O–O–C5′). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31–8.02 (m, 3H), 7.54–7.35 (m, 3H), 3.98 and 3.97 (2 × s, 3H), 3.62–3.60 (m, 4H) 2.90–2.88 (m, 5H), 2.55–2.49 (m, 1H), 2.03–1.70 (m, 21H). ^{13}C (100 MHz, $CDCl_3$) δ 157.1, 152.5, 149.2, 149.1, 148.4, 134.9, 132.0, 129.2, 128.9, 126.9, 126.3, 126.1, 125.5, 112.1111.8, 108.7, 108.6, 107.3, 100.8, 68.3, 62.6, 55.9, 53.9, 51.2, 50.9, 38.1, 37.1, 36.7, 35.2, 33.4, 32.4, 27.2, 26.8; MS (CI, +ve) 590 ([M+H]$^+$, 100), 360 (30). Found [M+H]$^+$ 590.2786, $C_{34}H_{41}N_3O_4Cl$ requires 590.2776. The two diastereomers were separated by HPLC using a 151/152 Gilson HPLC; mobile phase: ethyl acetate (channel A, 40%) and *n*-hexane (channel B, 60%); ramp time: 1 min; flow: 1.0 ml/min^{-1}; column: H1Chrom (normal phase), serial no. KR100-10-250004; detector: UV, 254 nm. For the less polar diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 9.2 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 8.07 (d, J = 9.4 Hz, 1H), 7.55 (d, J = 2.7 Hz, 1H), 7.46 (dd, J = 9.4 Hz, J = 2.7 Hz, 1H), 7.40 (dd, J = 9.3 Hz, J = 2.10 Hz, 1H), 3.99 (s, 3H), 3.64 (m, 4H), 2.91 (m, 4H), 2.56 (m, 1H), 2.04–1.68 (m, 22H). ^{13}C (100 MHz, $CDCl_3$) δ 157.2, 152.5, 148.4, 134.9, 132.1, 129.0, 126.1, 125.5, 123.5, 112.1, 108.7, 100.9, 66.2,62.3,55.9,53.0,51.3, 37.1, 36.8, 35.1, 33.2, 27.3, 26.8, 26.2, 15.6. For the more polar diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 9.2 Hz, 1H), 8.16 (d, J = 2.2 Hz, 1H), 8.07 (dd, J = 9.3 and J = 2.7 Hz, 1H), 7.53 (d, J = 2.7 Hz, 1H), 7.45 (d, J = 9.4 Hz, 1H), 7.39 (dd, J = 9.30 Hz, J = 2.7 Hz, 1H), 3.98 (s, 3H), 3.61 (m, 4H), 2.89 (m, 4H), 2.55 (m, 1H), 2.05–1.70 (m, 22H). ^{13}C (100 MHz, $CDCl_3$) δ 156.8, 148.8, 148.0, 134.5, 131.7, 128.6, 126.0, 125.3, 125.1, 123.1, 111.5, 108.3, 100.5, 65.8, 62.3, 55.6, 52.6, 50.5, 36.4, 34.8, 34.8, 33.3, 26.9, 25.5, 15.2.
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