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Synthesis and biological evaluation of a new trioxaquine containing a trioxane moiety obtained by halogenocyclisation of a hemiperoxyacetal

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Abstract

The preparation and the biological evaluation of a new antimalarial modular drug, named trioxaquine are reported. The trioxane moiety of this trioxaquine is prepared through the halogenocyclisation of a hemiperoxyacetal derived from the allylic hydroperoxide of 2,3-dimethyl-2-butene. ***To cite this article: O. Dechy-Cabaret et al., C. R. Chimie 6 (2003) 153–160.***

Résumé

Les trioxaquines constituent une nouvelle classe de composés antipaludiques. Ces molécules duales comportent une entité trioxane, liée de façon covalente à une 4-aminoquinoléine. Une nouvelle voie de synthèse de trioxaquines est décrite ici. Un hémiperoxyacétal est produit par condensation d'un aldéhyde avec un hydroperoxyde allylique, lui-même issu de la réaction de $^1O_2$ avec le 2,3-diméthyl-2-butène. L'halogénocyclisation de cet hémiperoxyacétal en présence de *N*-iodosuccinimide produit un 1,2,4-trioxane. L'utilisation d'un aldéhyde fonctionnalisé par une cétone produit un trioxane–cétone, qui est couplé à l'aminoquinoléine par amination réductrice. L'activité antipaludique de la trioxaquine ainsi synthétisée a été testée in vitro sur trois souches différentes de *Plasmodium falciparum* ***Pour citer cet article : O. Dechy-Cabaret et al., C. R. Chimie 6 (2003) 153–160.***

Keywords: malaria; trioxaquine; 1,2,4-trioxane

Mots clés : paludisme ; trioxaquine ; 1,2,4-trioxane

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1. Introduction

Because of the widespread resistance of many *Plasmodium falciparum* strains to widely used drugs, malaria's incidence is dramatically increasing [1]. There is therefore an urgent need for efficient drugs with new chemical structure [2, 3]. Combination of drugs is now recommended both to increase the efficiency of the treatment and to impede the development of resistance [4, 5].

Trioxaquines are a new class of antimalarial compounds that we have recently synthesised [6, 7]: they covalently combine a trioxane moiety known to be responsible for artemisinin activity [8–12] and a 4-aminoquinoline entity contained in chloroquine.

Encouraged by the excellent antimalarial activity of the first trioxaquine 1 (DU-1102, Fig. 1) [7, 13], we began a program of structural modulations to find out the structure–activity relationship and to explore for more potent antimalarials [14, 15].

Here we report the convergent synthesis and the biological evaluation of a new trioxaquine named DU-1202 in which the elaboration of the trioxane moiety is done through the halogenocyclisation of a hemiperoxyacetal derived from an allylic hydroperoxide.

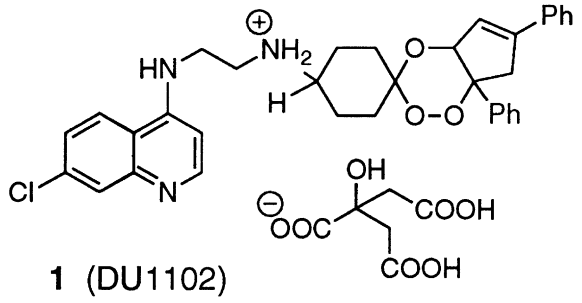

Fig. 1. Structure of trioxaquine **1** (DU-1102).

2. Results and discussion

2.1. Synthesis of trioxaquine DU-1202

In the synthesis of the first trioxaquine DU-1102, the trioxane moiety was obtained via an initial [4+2] cycloaddition of singlet oxygen with 1,4-diphenyl-1,3-cyclopentadiene, and the trioxane–ketone was finally obtained through the Me_3 SiOTf-catalyzed condensation with 1,4-cyclohexanedione [7]. Another major reaction of the singlet oxygen is the ene-reaction with olefins having allylic hydrogen atoms [16]. This reaction has been used for the synthesis of a 1,2,4-trioxane by Bloodworth et al. [17, 18] or by Singh [19]. One of the syntheses proposed by Bloodworth is depicted in Fig. 2 [18]. The ene-reaction of singlet oxygen on 2,3-dimethyl-2-butene **5** leads to the formation of the 2,3-dimethyl-1-buten-3-yl hydroperoxide **6**, that is further condensed with an aldehyde to provide the unsaturated hemiperoxyacetal **7**. Finally, the electrophile-mediated cyclisation of **7** involving *N*-iodosuccinimide (NIS) leads to the 1,2,4-trioxane **8**.

The covalent link between an aminoquinoline entity and the trioxane **8** could be achieved through a nucleophilic substitution of the iodide by an amine. Attempts to substitute the iodine atom of the trioxane **9** (Fig. 3) prepared from acetaldehyde [18] were unsuccessful under a variety of conditions described in Table 1. We

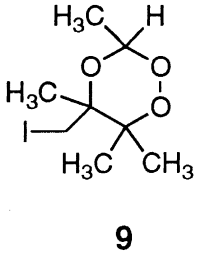

Fig. 3. Structure of trioxane **9** prepared from acetaldehyde.

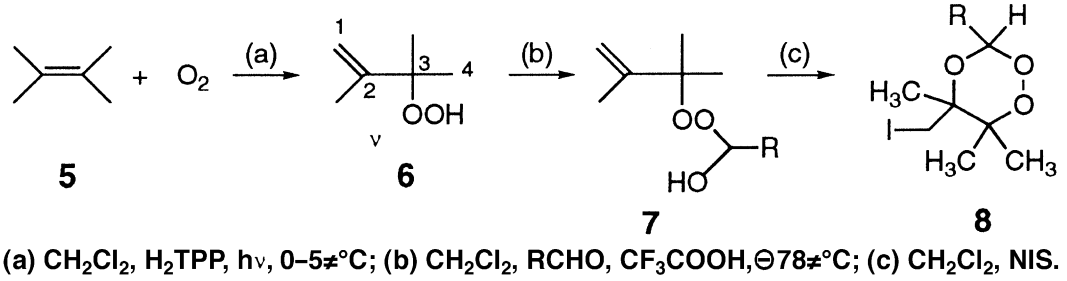

Fig. 2. Synthesis of a 1,2,4-trioxane via an initial ene-reaction of singlet oxygen on an olefin.

Table 1
Attempts of nucleophilic substitution of the iodide atom of the trioxane 9

Nucleophile	Solvent, temperature	Additive
Chloroquine	CH_2Cl_2, 20 °C	no
Chloroquine	CH_3CN, 80 °C	no
$MeO(CH_2)_3NH_2$	CH_3CN, 80 °C	no
$MeO(CH_2)_3NH_2$	CH_3CN, 80 °C	CH_3COOAg
$MeO(CH_2)_3NH_2$	CH_3CN, 80 °C	AgOTf
$HO(CH_2)_2NHCH_3$	CH_3CN, 80 °C	no
$Bu_4N^+OH^-$	CH_3CN, 80 °C	no

then focused our attention on the use of a functionalised aldehyde that can be engaged in a coupling reaction with an aminoquinoline functionalised by a primary amine **13** (Fig. 4), previously prepared for the trioxaquine DU-1102 [7]. As depicted in Fig. 4, we prepared an oxo-aldehyde to link the trioxane entity to the aminoquinoline by reductive amination [7].

The oxo-aldehyde 4-oxopentanal **11** was easily prepared by the pyridinium chlorochromate oxidation of the 5-hydroxypentan-2-one **10** [20]. Then the synthesis of the 1,2,4-trioxane **12** was carried out in a one-pot procedure as described by Bloodworth: the crude hydroperoxide **6** obtained by tetraphenylporphyrin-sensitised photooxygenation of 2,3-dimethyl-2-butene **5** was condensed on the aldehyde **11** using trifluoroacetic acid as a catalyst and the resulting unsaturated hydroperoxyacetal was cyclised with *N*-iodosuccinimide. The trioxane **12** consists of a pair of diastereoisomeric racemates **12a** and **12b**, as expected from the presence of chiral centres at C3 and C5 (Fig. 5). The reaction is diastereoselective with the isomer ratios, as determined by NMR, ranging from 4:1 to 5:1 in the different syntheses. By analogy to what Bloodworth described for the trioxane **9**, we propose that the major isomer **12a** has the alkyl group at C3 and the iodomethyl group at C5 *cis* to one another, so that they are both equatorial in the favoured conformation, as depicted in Fig. 5 [18]. These two diastereoisomeric racemates were not separated and their mixture was used in the next step.

The reductive amination of the trioxane 12 by the aminoquinoline **13** under previously reported conditions [7] provided the trioxaquine **14**. The acyclic ketone function of the trioxane exhibited a poor reactivity in this step. The reductive amination of trioxane **12** was completed in two weeks, whereas that of the trioxane used in the synthesis of DU-1102 1 was completed in

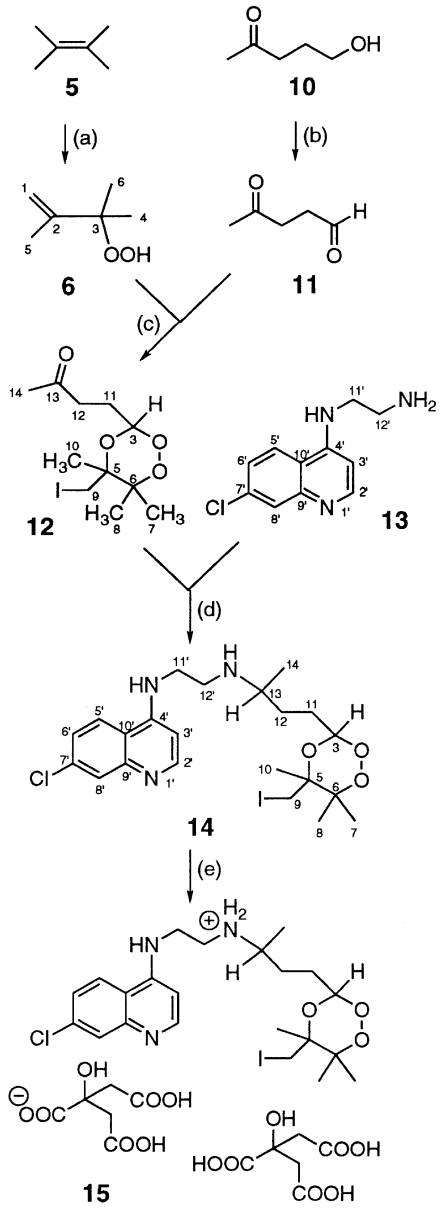

Fig. 4. Convergent synthesis of **15** (DU-1202).

18 h, and the yield was only 30% after purification. All attempts to improve this sluggish reaction failed: heating the reaction mixture (up to 90 °C), adding an acid (acetic acid) or using a stronger reducing agent ($NaBH_3$ CN) led to the formation of by-products or to

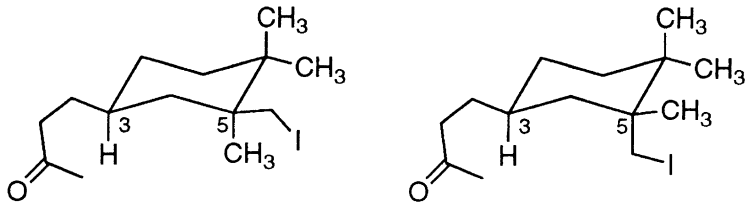

Fig. 5. Structure of trioxanes **12a** and **12b** prepared from 4-oxopentanal. Compounds **12a** and **12b** are diastereoisomeric racemates; only one enantiomer of each is depicted.

the degradation of the starting material. The trioxaquine **14** consists a priori in a mixture of eight stereoisomers, as expected from the presence of chiral centres at C3, C5 and C13: at this stage of the study, the separation of the isomers was not performed and the mixture of the stereoisomers was used for the next step.

In the final step, trioxaquine **14** was protonated by citric acid in acetone to provide the trioxaquine citrate **15** (DU-1202). As attested by both elemental analysis and ^{1}H NMR, the monoprotonated trioxaquine was obtained with one additional citric acid molecule (Fig. 4). This feature has already been observed for trioxaquine 1 (DU-1102) [7] and for the trioxaquines prepared from cis-bicyclo[3.3.0]octane-3,7-dione [14].

2.2. Biological evaluation of DU-1202

The trioxaquine citrate **15** (DU-1202, mixture of eight stereoisomers) was tested against three different strains of *P. falciparum*: a Nigerian chloroquine-sensitive (CQS) strain, FcB1 and FcM29 (CQ-resistant and highly CQ-resistant, respectively). The inhibition concentrations able to reduce the parasitemia by 50% within 48 h (IC_{50} values) were determined and compared to those of trioxaquine **1** (DU-1102), chloroquine and artemisinine (Table 2).

The IC_{50} values obtained for **15** were ranging from 188 nM on FcM29 (CQR) to 536 nM on the Nigerian strain (CQS). This compound showed a significantly lower antimalarial activity than the first trioxaquine **1**, whose IC_{50} values were ranging from 22 to 27 nM. This loss of activity might be linked to the structural modification around the trioxane moiety. The major difference between the two trioxaquines is in the substitution of the C3 (Fig. 6): in **15**, C3 is a secondary carbon, bearing the hydrogen atom of the initial aldehyde RCHO, whereas in **1**, C3 is a spiro carbon atom linking the trioxane ring and the cyclohexyl ring. As depicted in Fig. 6, this difference can at least partly account for the differential antimalarial activity.

Trioxaquines with a high antimalarial activity are expected to have alkylating properties after activation of the peroxide bond by iron(II)-heme, as it has been established for artemisinin [8–12] or other related trioxanes [21, 22]. In the case of trioxaquine **1**, the reductive activation by Fe^{II}-heme results in the formation of the alkoxy radical **1a**. By subsequent homolysis of either C3–C10 or C3–C14 bond, **1a** can promptly rearrange to the sterically unhindered C-centred radical **1b**, which can be responsible for the alkylation of the heme and so for the antimalarial activity of **1** (Fig. 6a). In the case of trioxaquine **15**, the reductive activation by

Table 2
In vitro antimalarial activity of trioxaquine 15 on three different strains of *P. falciparum*. IC_{50} values in nM (SEM, standard error of the mean is given in parentheses). IC_{50} values are mean values of 2–4 independent experiments.

Trioxaquine	Nigerian CQS[a]	FcB1–Columbia CQR	FcM29–Cameroon CQR+
15 (DU-1202)	536 (212)	365 (161)	188 (27)
1 (DU-1102)	22 (1)	27 (3)	27 (10)
Chloroquine[b,c]	62 (10)	116 (57)	174 (26)
Artemisinin[b]	6 (1)	5 (1)	8 (1)

[a] CQS = chloroquine sensitive, CQR = chloroquine resistant, CQR+ = highly chloroquine resistant.
[b] Measured as reference.
[c] Chloroquine diphosphate was used.

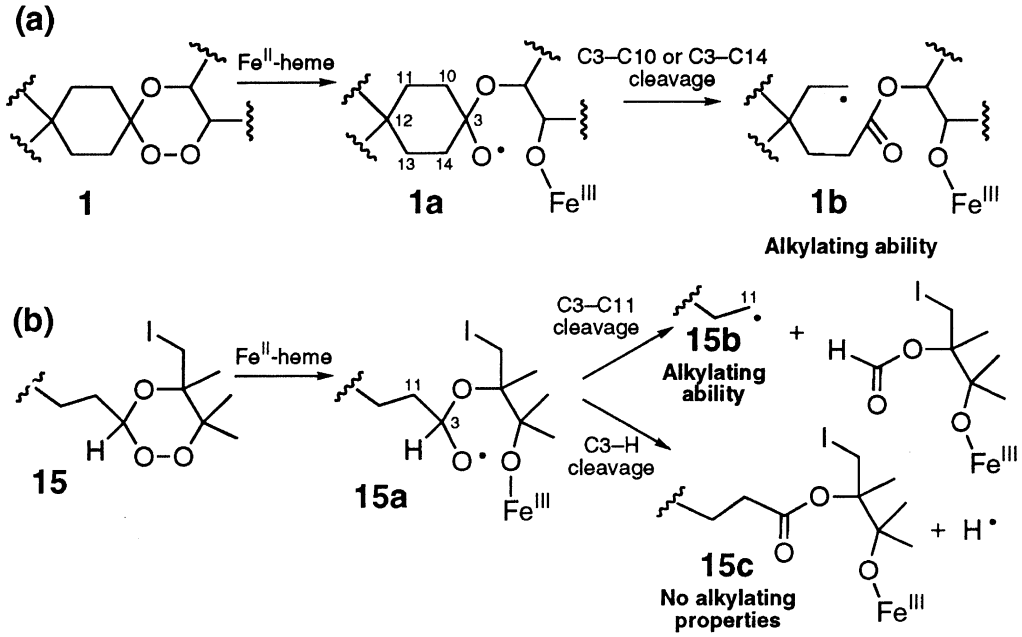

Fig. 6. Activation of the peroxide bond in trioxaquines **1** and **15**.

Fe^{II}-heme results in the formation of the alkoxy radical **15a**, that can rearrange by β-scission of the C3–C11 bond, giving rise to the potentially alkylating radical **15b**. As a competitive reaction, the C3–H bond scission may give rise to $H^{\bullet}$ and **15c**, which is devoided of any alkylating properties towards heme (Fig. 6b). Further studies are being done in our laboratory to determine which part the mechanism of reductive activation/alkylation has in the antimalarial activity of the trioxaquines but nevertheless, it seems that the presence of the hydrogen atom in α-position of the endoperoxide, leading to the formation of a non-alkylating compound, resulted in a lower in vitro antimalarial activity.

3. Conclusion

A new trioxaquine **15** (DU-1202) has been prepared through a convergent synthesis exploiting a halogenocylisation route to the 1,2,4-trioxane moiety. The trioxaquine **15** exhibits a lower antimalarial activity than the first trioxaquine **1** on three different strains of *P. falciparum*, suggesting that the presence of an hydrogen atom in α-position of the endoperoxide is not recommended for a good antimalarial activity of trioxane-containing molecules.

4. Experimental section

4.1. Instrumentation, materials and methods

NMR spectra were recorded on Brucker AM 250 or DPX 300 spectrometers. DCI mass spectra were acquired on a Nermag R10-10H instrument and ES mass spectra on a API 365 Sciex Perkin Elmer instrument. Chromatography columns were done on silica gel 60 ACC Chromagel, 70–200 μm granulometry, SDS, or on neutral alumina, Brockman activity II-III, 63–200 μm granulometry, Merck. Silica plates (60 F_{254}, Merck) were used for thin layer chromatography.

4.2. Synthesis of the trioxane 12

*4.2.1. 2,3-Dimethyl-1-buten-3-yl hydroperoxide **6***

2,3-Dimethyl-2-butene **5** (2.8 g, 34 mmol) in dichloromethane (30 ml) was irradiated by a 600 W visible lamp in the presence of molecular oxygen (1.6 bar) during 6 h at 0–5 °C, using tetraphenylporphyrin (5 mg) as photosensitiser. The hydroperoxide **6** was quantitatively obtained and the crude dichloromethane solution was used in the next step without any further treatment. An aliquot was withdrawn and evaporated to dryness for NMR characterisation.

^{1}H NMR (250 MHz, $CDCl_3$) δ, ppm: 1.34 (s, 6H, H_3 C4, H_3 C6), 1.79 (dd, ^4J = 0.8 Hz and 1.5 Hz, 3H, H_3 C5), 4.94 (qd, ^4J = 0.8 Hz and ^2J = 1.5 Hz, 1H, H_b C1), 4.98 (qd, ^4J = 1.5 Hz and ^2J = 1.5 Hz, 1H, H_a C1), 7.47 (s, 1H, HOO).

*4.2.2. 4-Oxopentanal **11***

To a stirred solution containing 6.4 g (30 mmol) of pyridinium chlorochromate in 25 ml of dichloromethane was slowly added 2.0 g (20 mmol) of 5-hydroxypropan-2-one **10** at room temperature, and the solution was stirred for 2 h. The mixture was passed through a fritted-disk Büchner funnel using a short pad of silica gel. The residue was washed through the funnel with 100 ml of diethyl ether. The diethyl ether/dichloromethane solution was evaporated under reduced pressure. The expected aldehyde was obtained as a brown liquid (purity 82%, yield in aldehyde 58%, with 4'-oxopentyle-4-oxopentanoate as by-product) and was used in the next step without any further purification.

^{1}H NMR (250 MHz, $CDCl_3$) δ, ppm: 2.14 (s, 3H), 2.70 (unresolved m, 4H), 9.75 (s, 1H).

*4.2.3. Trioxane **12***

In a flask protected from light by aluminium foil, the hydroperoxide **6** (3.8 g, 33 mmol) and aldehyde **11** (7.0 g, 70 mmol) in dichloromethane (60 ml) were stirred with trifluoroacetic acid (5 drops) for 60 min before adding *N*-iodosuccinimide (10.0 g, 45 mmol). After 3 h, the reaction mixture was washed with 20 wt% aqueous sodium thiosulphate, then with water. The organic layer was dried, the solvent removed under reduced pressure and the 1,2,4-trioxane **12** isolated by chromatography on alumina gel using hexane/diethyl ether (from 90:10 to 50:50, v/v) as eluent. Two diastereomeric racemates **12a** and **12b** were obtained and were not separated (molar ratio **12a/12b** = 85/15 evaluated by ^{1}H NMR). The characterisation was performed on the mixture, but ^{1}H NMR of each diastereoisomer is described separately for clarity.

MS (DCI/NH_3^+) *m/z* (%): 359 (22), 360 (MNH_4^+, 100), 361 (14), 362 (2)

^{1}H NMR for the diastereoisomer **12a** (300 MHz, $CDCl_3$) δ, ppm: 1.08 (s, 3H, H_3 C10), 1.49 (d, ^5J = 0.9 Hz, 3H, H_3 C7), 1.50 (s, 3H, H_3 C8), 1.82 (m, 2H, H_2 C11), 2.15 (s, 3H, H_3 C14), 2.57 (m, 2H, H_2 C12), 3.14 (d, ^2J = 10.0 Hz, 1H, HC9), 3.33 (dq, ^5J = 0.9 Hz and ^2J = 10.0 Hz, 1H, HC9), 5.41 (t, ^3J = 5.3 Hz, 1H, HC3).

^{13}C NMR for the diastereoisomer **12a** (75.4 MHz, $CDCl_3$) δ, ppm: 14.7 (C9), 20.9 (C10), 21.7 (C7), 21.8 (C8), 26.2 (C11), 30.4 (C14), 37.5 (C12), 75.5 (C5), 81.1 (C6), 98.2 (C3H), 207.9 (C13).

^{1}H NMR for the diastereoisomer **12b** (300 MHz, $CDCl_3$) δ, ppm: 1.08 (s, 3H, H_3 C10), 1.49 (m, 3H, H_3 C7), 1.50 (s, 3H, H_3 C8), 1.82 (m, 2H, H_2 C11), 2.15 (s, 3H, H_3 C14), 2.57 (m, 2H, H_2 C12), 3.31 (d, ^2J = 11.0 Hz, 1H, HC9), 4.09 (dq, ^5J = 1.2 Hz and ^2J = 11.0 Hz, 1H, HC9), 5.22 (dd, ^3J = 4.2 Hz and 6.2 Hz, 1H, HC3).

4.3. Synthesis of the trioxaquine citrate 15

Trioxaquine **14**. The trioxane **12** (500 mg, 1.5 mmol) and the aminoquinoline **13** (500 mg, 2.3 mmol) were dissolved in dichloromethane (75 ml) before addition of sodium triacetoxyborohydride (400 mg, 1.9 mmol). The reaction mixture was stirred at room temperature for two weeks and then washed with distilled water. The organic layer was then dried and evaporated under reduced pressure to dryness and the obtained trioxaquine **14** was purified by chromatography on silica gel using ethyl acetate/triethylamine (80:20, v/v) as eluent (yield 31%). Several isomers were obtained and not separated. The characterisation was performed on the mixture but NMR description is that of the major isomer (90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 1.07 (s, 3H, H_3 C10), 1.11 (d, ^3J = 6.2 Hz, 3H, H_3 C14), 1.47 (s, 3H, H_3 C7), 1.48 (s, 3H, H_3 C8), 1.56 (m, 2H, H_2 C12), 1.65 (m, 2H, H_2 C11), 1.97 (broad s, 1H, HNC12'), 2.74 (q, ^3J = 6.2 Hz, 1H, HC13), 2.99 (m, 2H, H_2 C12'), 3.12 (d, ^2J = 10.0 Hz, 1H, HC9), 3.30 (m, 3H, H_2 C11' and HC9), 5.36 (t, ^3J = 5.0 Hz, 1H, HC3), 6.06 (broad s, 1H, HNC4'), 6.35 (d, ^3J = 5.4 Hz, 1H, HC3'), 7.36 (dd, ^3J = 8.9 Hz and ^4J = 2.2 Hz, 1H, HC6'), 7.72 (d, ^3J = 8.9 Hz, 1H, HC5'), 7.91 (d, ^4J = 2.2 Hz, 1H, HC8'), 8.50 (d, ^3J = 5.4 Hz, 1H, HC2').

^{13}C NMR (75.4 MHz, $CDCl_3$) δ, ppm: 14.9 (C9), 20.9 (C10), 21.7 (C7), 21.8 (C8 and C14), 28.8 (C11), 31.1 (C12), 42.8 (C12'), 45.0 (C11'), 52.7(C13H), 75.4 (C5), 81.1 (C6), 99.5 (C3H), 99.6 (C3'H), 117.8 (C10'), 121.9 (C5'H), 125.7 (C6'H), 128.9 (C8'H), 135.2 (C7'), 149.4 (C9'), 150.3 (C4'), 152.3 (C2'H).

MS (DCI/NH_3^+) *m/z* (%): 547 (6), 548 (MH^+, 100), 549 (29), 550 (37), 551(9).

Trioxaquine citrate **15**. The trioxaquine **14** (125 mg, 0.23 mmol) was solubilised in acetone (6 ml) before adding a solution of citric acid (93 mg, 0.48 mmol) in acetone (5 ml). The trioxaquine citrate **15** precipitated spontaneously. After centrifugation, the solid precipitate was washed with diethyl ether and dried under vacuum.

^{1}H NMR (250 MHz, DMSO-d_6) δ, ppm: 1.04 (s, 3H, H_3 C10), 1.11 (d, 3H, H_3 C14), 1.40 (s, 6H, H_3 C7 and H_3 C8), 1.55 (m, 3H, H_2 C11 and HC12), 1.80 (m, 1H, HC12), 2.55 and 2.66 (2 × d, ^2J = 15.1 Hz, 2 × 4H, citric acid/citrate), 3.20 (m, 3H, HC13 and H_2 C12'), 3.25 (d, ^2J = 10.2 Hz, 1H, HC9), 3.54 (dd, J = 10.2 Hz and 1.5 Hz, 1H, HC9), 3.63 (m, 2H, H_2 C11'), 5.35 (t, ^3J = 4.4 Hz, 1H, HC3), 6.64 (d, ^3J = 5.5 Hz, 1H, HC3'), 7.57 (dd, ^3J = 8.9 Hz and ^4J = 2.0 Hz, 1H, HC6'), 7.85 (d, ^4J = 2.0 Hz, 1H, HC8'), 8.24 (d, ^3J = 8.9 Hz, 1H, HC5'), 8.50 (d, ^3J = 5.5 Hz, 1H, HC2'), 10.5 (br).

Anal. calc. for $C_{34}H_{47}O_{17}N_3$ ClI: C 43.81, H 5.08, N 4.51; found C 43.62, H 4.75, N 4.30.

MS (ESI$^+$) *m/z* (%): 548 (M^+, 100), 549 (30), 550 (45), 551(11).

*4.4. Antimalarial activity of the trioxaquine **15***

4.4.1. P. falciparum *strains and in vitro culture*

Three strains of *P. falciparum* were cultured according to a modified Trager and Jensen method in a 5% CO_2 atmosphere at 37 °C [23, 24]. The chloroquine-sensitive strain, Nigerian, and two chloroquine-resistant strains, FcB1-Columbia and FcM29-Cameroon were chosen for this study. The parasites were maintained in vitro in human red blood cells (O±) diluted to 1% hematocrit in RPMI 1640 medium (Bio-Media, France) supplemented with 25 mM Hepes and complemented with 5% human AB+ serum ('Centre de transfusion sanguine', Toulouse, France). Parasite cultures tested were not synchronised in vitro.

4.4.2. In vitro antimalarial activity

The antiplasmodial activity of the trioxaquine **15** was evaluated by the radioactive microdilution method described by Desjardins et al. and modified as follows [25, 26]. Drug dilutions were tested several times in triplicate in 96-well plates (TPP, Switzerland) with non-synchronised *P. falciparum* cultures at 1% parasitaemia with 1% hematocrit. For each test, the plates of parasite culture were incubated with drugs at decreasing concentrations for 48 h, radioactive [^{3}H]-hypoxanthine (Amersham Pharma Biotech, France) being added to the medium at 24 h after the beginning of incubation. The mother solution of the trioxaquine (5 mg ml^{-1}) was prepared in DMSO (Acros Organics, Belgium), and the following dilutions were done with RPMI 1640. Parasite growth was estimated by [^{3}H]-hypoxanthine incorporation. Concentrations of trioxaquine inhibiting 50% of the parasite growth (IC_{50}) were graphically determined by plotting the drug concentration versus percent of parasite growth inhibition curves at 48 h of incubation time [26]. The IC_{50} value given in the text represents the mean value of 2 to 4 independent experiments. The chloroquine and artemisinin sensitivities of the three strains were routinely tested.

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