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Design, synthesis and evaluation of new tricyclic endoperoxides as potential antiplasmodial agents†

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Diastereoselective autoxidation allowed preparation of new tricyclic endoperoxides. These compounds and their methylated analogs were evaluated against the *in vitro* growth of *Plasmodium falciparum*, the malaria-causing parasite, showing moderate activities. However, hybrid molecules composed of the tricyclic peroxide moiety and 7-chloro-4-aminoquinoline were synthesized and displayed a marked increase in antiplasmodial activity.

Introduction

The emergence of artemisinin-resistant *Plasmodium falciparum* in Southeast Asia has exacerbated the need and stimulated the search for new synthetic molecules that possess antimalarial activity. Consequently, we continue our efforts to design and synthesize new G-factor analog endoperoxides. The new compounds will act as artemisinin or artemisinin-like compounds. They will have to form, after Fe(II) induced reduction, C-centered radicals potentially able to alkylate heme or to react with vital biomolecules.[1] The formation of primary and/or secondary C-centered radicals has been described after Fe(II) induced reduction of artemisinin or its derivatives,[2] trioxanes,[3] trioxolanes,[4] tetraoxanes[5] or arteflene[6] (Scheme 1).

Previous studies have shown that endoperoxides belonging to the G-factor family, natural compounds extracted from leaves of *Eucalyptus grandis*,[7] possess interesting antimalarial properties after methylation of the hydroxyl group of the peroxyhemiketal moiety. The concentration of the methylated endoperoxide to inhibit by 50% the growth of chloroquine sensitive and resistant *P. falciparum* strains (IC_{50}) was in the range of 200–300 nM, *i.e.* 100-fold better than the hydroxylated one, the fluorinated one being inactive.[8,9] A study of the Fe(II)-induced reduction of these three compounds[10] has shown the presence of a tertiary C-centered radical which cyclizes in a 5-*exo*-trig manner in all cases. Only in the case of the G3Me, competition between 5-*exo*-trig cyclisation and disproportionation of the radical does occur, favoring disproportionation, which becomes the prevalent mechanism (disproportionation–cyclization: 70/30). So, this tertiary C-centered radical can indeed interact with vital biomolecules of the parasite, for instance alkylating the heme, explaining the effect observed on antimalarial activity. In contrast, in the case of G3 or G3F, the radical is more reactive and leads to self-quenching *via* cyclization in a 5-*exo*-trig manner, finally giving rise to Fe(II) and a neutral molecule.

So, in order to obtain secondary radicals as described for known antimalarial peroxides acting like artemisinin, we designed tricyclic endoperoxide analogs of known G-factor derivatives. Fe(II)-induced reduction could indeed afford secondary C-centered radicals. In this case, the 5-*exo*-trig cyclisation could be preferentially replaced by an intermolecular addition on heme or parasite vital biomolecules (Scheme 2).

Results and discussion

The aim of this work was to synthesize and evaluate antimalarial properties of these new tricyclic endoperoxides. Synthesis is based on an autoxidation step on dienol intermediates as previously described for the G-factors and analogs.[11] These precursors were obtained following a modified Knoevenagel-type procedure in two steps from bicyclic dienone.

Furthermore, a patent from Syngenta described the synthesis of bicyclic diones used as precursors in herbicide synthesis.[12]

I. Synthesis of bicyclo[3.2.1]oct-6-ene-2,4-diones 6 and 7

Synthesis of bicyclo[3.2.1]oct-6-ene-2,4-dione **6** was optimized following the patent description.[12]

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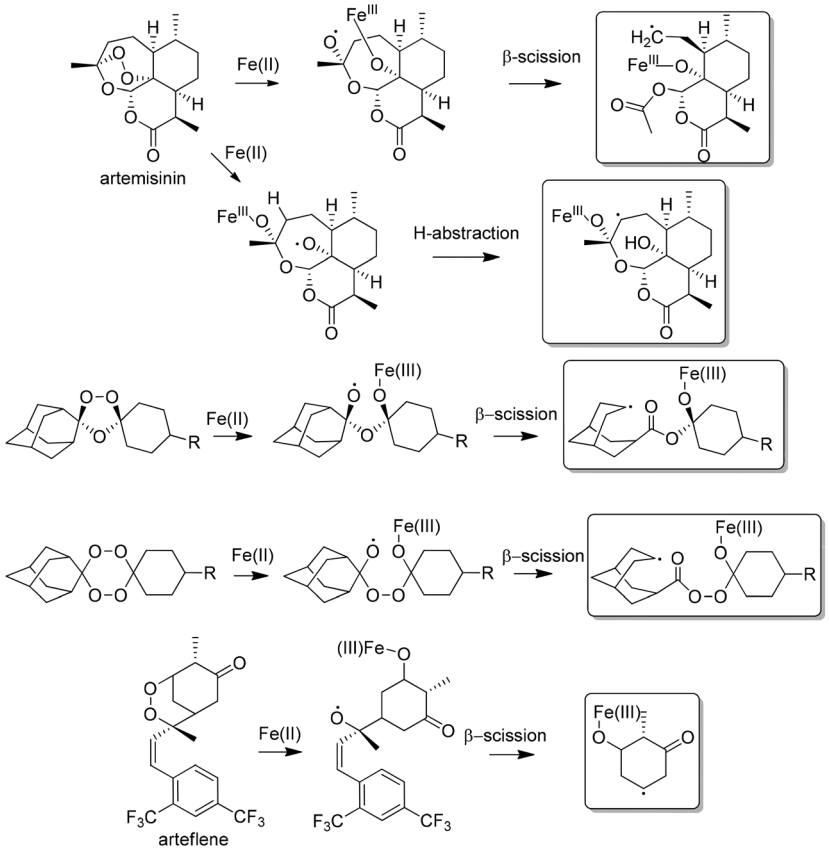
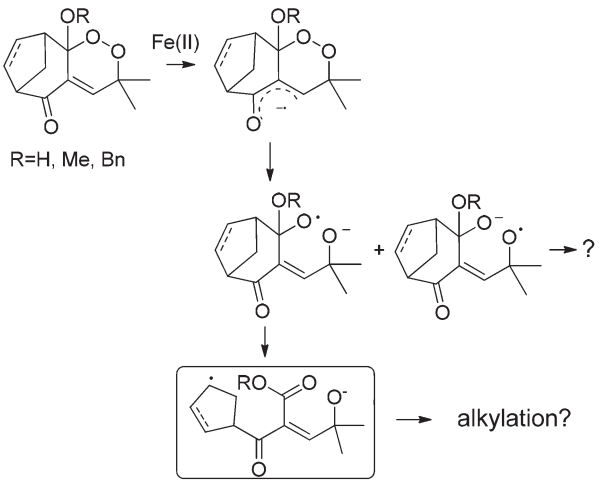


Scheme 1 Fe(II)-induced primary or secondary C-centered radical formation.



Scheme 2 Hypothesis of Fe(II)-induced reduction.

The first step was a [4 + 2] cycloaddition reaction between cyclopentadiene and perchloropropene **2** previously obtained *in situ* after HCl elimination from pentachlorocyclopropane **1**. The Diels–Alder adduct **3** rearranged itself into tetrachlorinated product **4**.[13] The product **5** was then obtained after chloride substitution by hydroxide, using sodium hydroxide in a water–dioxane mixture. The C–Cl bond of the product **5** was reduced by Zn(0) in acetic acid–dioxane 4/6 to afford dione **6** in 30% yield in a three-step reaction (Scheme 3).

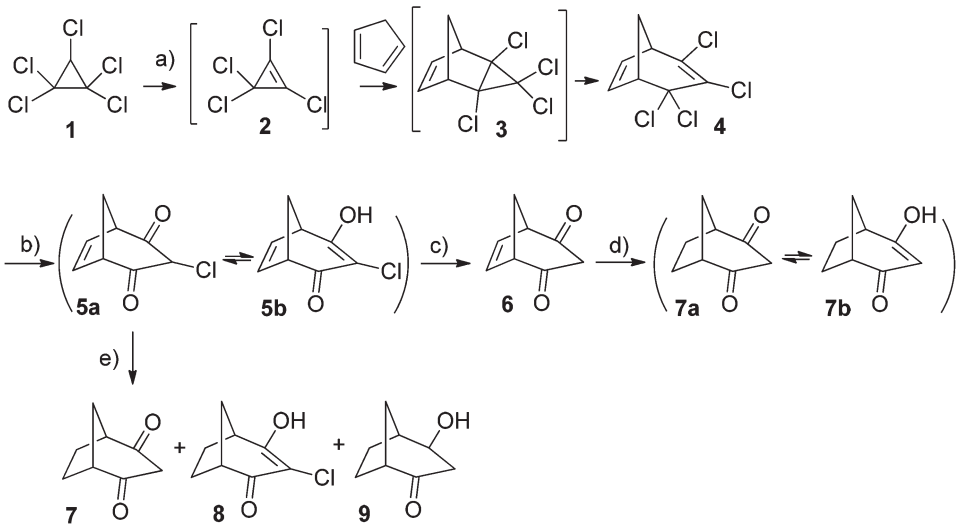
The patent also describes the bicyclo[3.2.1]octane-2,4-dione **7** in 59% yield by hydrogenation and reduction of the product **5** in the presence of acetic acid and a catalytic amount of Pd/C (0.1 eq.) at 55 °C in dioxane under 1 bar H_2.

Following these conditions, the product **8** was obtained in 58% yield after 6 hours of hydrogenation. If the reaction is left longer (17 hours) the alcohol **9** was isolated in lower yield (34%). Finally the dione **7** was obtained in good yield from the unsaturated dione **6** after one hour of catalytic hydrogenation at room temperature in the dioxane–ethyl acetate mixture.

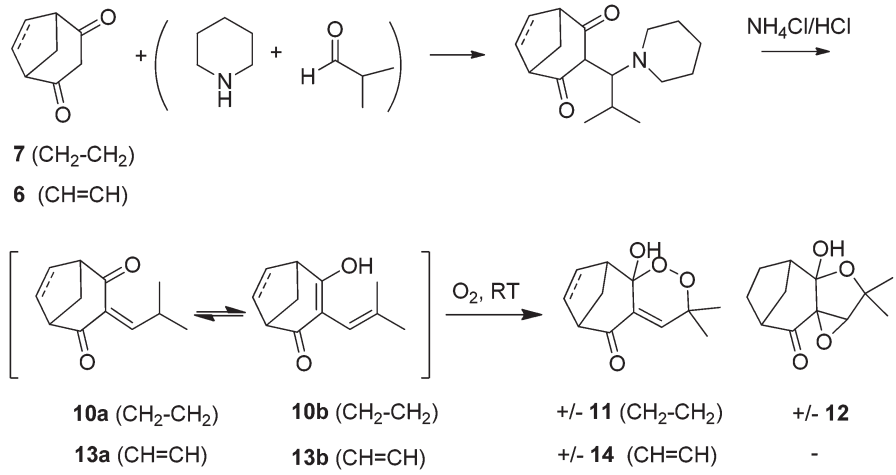
II. Syntheses of tricyclic peroxides

Tricyclic peroxides were synthesized following a previously described procedure[11] with autoxidation as a key step. Mannich bases were prepared by reaction of the bicyclooctanediones **6** or **7** with the iminium obtained from isobutyraldehyde and piperidine. After treatment with saturated NH_4Cl in HCl (1 M), precursors **10** and **13** were obtained in 89% and 98% yields respectively (Scheme 4).

Autoxidation reactions on precursors **10** and **13** were then optimized by varying different conditions: solvent



Scheme 3 Synthesis of diones **6** and **7**: (a) KOH, dioxane, RT, 1 h then cyclopentadiene, 85 °C, 2 h, 81%; (b) NaOH–H_2O, 90 °C, 18 h, 59%; (c) Zn, 3 eq., RT, dioxane–AcOH 6/4, 20 h, 62%; (d) Pd/C H_2 dioxane–EtOAc, 1 h; (e) Pd/C, H_2, 55 °C dioxane–EtOAc.



Scheme 4 Synthesis of endoperoxides **11** and **14**.

(ethyl acetate or benzene), O_2 pressure (air, 1 and 5 bars), UV irradiation (300 nm or 350 nm).

The precursor **10** is in equilibrium between its dienone form **10a** and dienol **10b** as shown by the ^{1}H NMR spectroscopy analysis of the precursor **10**.

Autoxidation under O_2 (1 bar) in ethyl acetate was quite slow and led to the formation of endoperoxide **11** in 60% yield along with epoxide **12** in 7% yield after 4 days. The reaction was accelerated in benzene as endoperoxide was observed alone in around 50% yield after one day under O_2 pressure of 1 bar or after only 4 hours under O_2 pressure of 5 bars.

Photoenolization of **10** using a Rayonet apparatus equipped with 350 nm low pressure mercury lamps under O_2 (1 bar) in deuterated benzene allowed the formation of dienol **10b** in a 1/1 mixture with enone **10a** after 15 minutes of irradiation as indicated by ^{1}H NMR spectroscopy. After 3 hours, the peroxide **11** was then obtained with 48% yield.

Concerning precursor **13**, ^{1}H NMR did not indicate the presence of the dienol form **13b**. As autoxidation proceeds in this form, oxygen uptake proved to be very slow in this case as it took several days (50% after 30 days in ethyl acetate). O_2 pressure did not accelerate the overall kinetics.

As previously described, photoenolization was then attempted using ethyl acetate or benzene as a solvent. At 350 nm, dienol **13b** in mixture with the enone form **13a** along with its deconjugated form was detected by ^{1}H NMR. Then autoxidation occurred quickly in competition with displacement of the equilibrium towards the enone form. So, several cycles consisting of irradiation for 15 min followed by autoxidation under O_2 (1 bar) for 45 min allowed endoperoxide formation with roughly 45% yield after 8 cycles. Whatever the solvent, yield and reaction time were similar. In this case, enolization seems to be the rate-limiting step of the global kinetics.

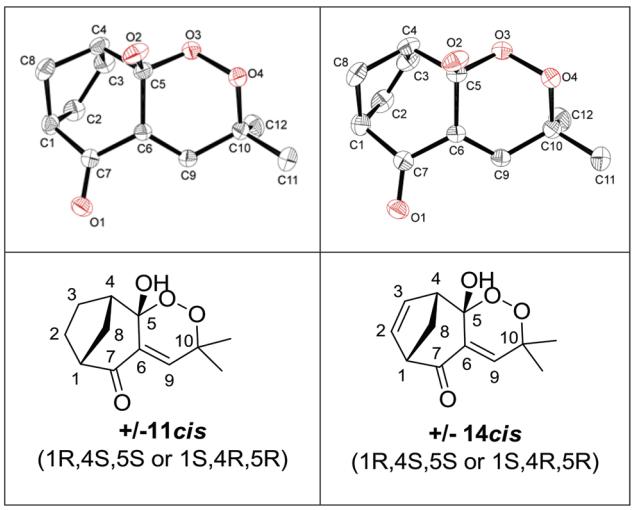


Fig. 1 ORTEP molecular view of endoperoxides **11** and **14** in the solid state (thermal ellipsoids at 50% probability; hydrogen atoms are omitted for clarity).

Both endoperoxides **11** and **14** were obtained as single diastereoisomers. Both compounds could be crystallized and crystals were analyzed by X-ray diffraction.[14]

Endoperoxide **11** crystallizes in a triclinic structure (a = 6.47 Å b = 8.74 Å, c = 10.93 Å, α = 110.2°, β = 95.6°, γ = 101.3°).[15] Using the numbering indicated in Fig. 1 and used in X-ray diffraction analysis, its configuration is 1*S*,4*R*,5*R* or 1*R*,4*S*,5*S*.

Endoperoxide **14** crystallizes in a monoclinic structure (a = 6.50 Å, b = 20.28 Å, c = 8.37 Å, α = 90°, β = 99.7°, γ = 90°).[16] Its configuration is also 1*S*,4*R*,5*R* or 1*R*,4*S*,5*S*.

The hydroxyl and the methylene C8 groups are on the same side for both endoperoxides, so the diastereoisomers are called **11*cis*** and **14*cis*** respectively.

To compare the energy levels of the two diastereoisomers **11*cis*** and **11*trans***, on the one hand, and **14*cis*** and **14*trans***, on the other hand, the four structures were fully optimized using density functional theory (DFT) and the GAUSSIAN 09 software package.[17] We chose the B3LYP hybrid functional.[18] The computations were done with the B3LYP/6-311+G(d,p) scheme and the stationary points were characterized as minima by a vibrational analysis. Geometries and enthalpies of the four compounds are presented in Fig. 2. The gaps between the two enthalpy levels of **11*cis*** and **11*trans*** on the one hand and **14*cis*** and **14*trans*** on the other hand are 0.8 kcal mol^{-1} and 0.3 kcal mol^{-1} respectively. Those values are too low to explain the selectivity observed. Probably a higher transition state must be reached in both cases during the reaction path leading to **11*trans*** (**14*trans***) than **11*cis*** (**14*cis***).

Geometries of both diastereoisomers were compared with the geometry of the endoperoxides **6-Endo** and **7-Endo** (Fig. 2) obtained after autoxidation of 2-alkylidene cyclohexane dione and 2-alkylidene cycloheptane dione. The geometry obtained for **11*cis*** (**14*cis***) is similar to that of **6-Endo** with a chair conformation for the 6-membered cycle while for **11*trans*** (**14*trans***), the 6-membered cycle adopts a boat conformation. We have previously shown that kinetics of autoxidation is considerably lower in the case of 2-alkylidene cycloheptane dione. So it seems that both **11*cis*** and **14*cis*** obtained are kinetic products.[19]

Previous studies have shown the crucial role of the methylation of the peroxyhemiketal position,[9,11] so methylation of **11** and **14** was planned (Scheme 5).

First attempts with K_2CO_3, Li_2CO_3 in DMF using MeI or $(MeO)_2SO_2$ as a methylating agent at room temperature did not work, and only the starting material was totally recovered. When Cs_2CO_3 was used as a base, whatever the methylating agent used (MeI or $(MeO)_2SO_2$), degradation occurred. Finally, butyl lithium (1 eq.) at −78 °C, in THF, followed by addition of TfOMe afforded endoperoxides **15** and **16** in about 50% yield, and 50% of the starting material was recovered. Increasing equivalents of BuLi (2 eq.) due to the presence of another acidic proton in the α-position of the carbonyl did not increase the yield of methylated endoperoxides and starting material recovery decreased too.

III. Hybrid molecules

Our recent work concerning the synthesis of hybrid molecules containing an endoperoxide moiety belonging to the G-factor family linked to a second pharmacophore, *e.g.* a streptocyanine or a 7-chloro-4-aminoquinoline, has shown that this approach can increase antiplasmodial activity.[20] So we decided to prepare hybrid molecules with a dual mode of action containing the tricyclic endoperoxide and a 7-chloro-4-aminoquinoline mimicking chloroquine. We designed and synthesized a functionalized aldehyde which could easily lead to the enone precursor of autoxidation. A piperidine linker was chosen to avoid the formation of diastereoisomers after autoxidation.

Starting from 4,7-dichloroquinoline, alcohol **17** was first obtained after substitution of the chloride by 4-piperidinylmethanol. Oxidation of **17** by 2-iodoxybenzoic acid (IBX) in refluxing acetone led to aldehyde **18** quantitatively (Scheme 6).

Then this aldehyde **18** was added to diones **6** and **7** following the previous Knoevenagel modified procedure: formation of the iminium by condensation of one equivalent of piperidine on the aldehyde, addition of this iminium to diones **6** and **7** furnishing the Mannich bases, and then aqueous acidic treatment allowing the formation of precursors **19** and **20** in 99% and 67% yields respectively in the three-step reaction.

^{1}H NMR spectra of these precursors indicated in both cases that they were present only in the enone form. As previously observed, autoxidation occurred very slowly on both structures and endoperoxides **21** and **22** were obtained in respectively 19% and 34% yield, after 33 and 15 days in ethyl acetate under O_2 (1 bar). An increase of the O_2 pressure to 10 bars did not enhance the rate of oxygen uptake. So, photoenolization was attempted at 350 nm, 300 nm and 254 nm but no dienol form appeared as shown by ^{1}H NMR spectroscopy. Incidentally we realize that deposing the precursor **20** on silica gel allowed its enolization. The dienol was then trapped by O_2, helping to shift the equilibrium in favor of the dienol, thus allowing for-

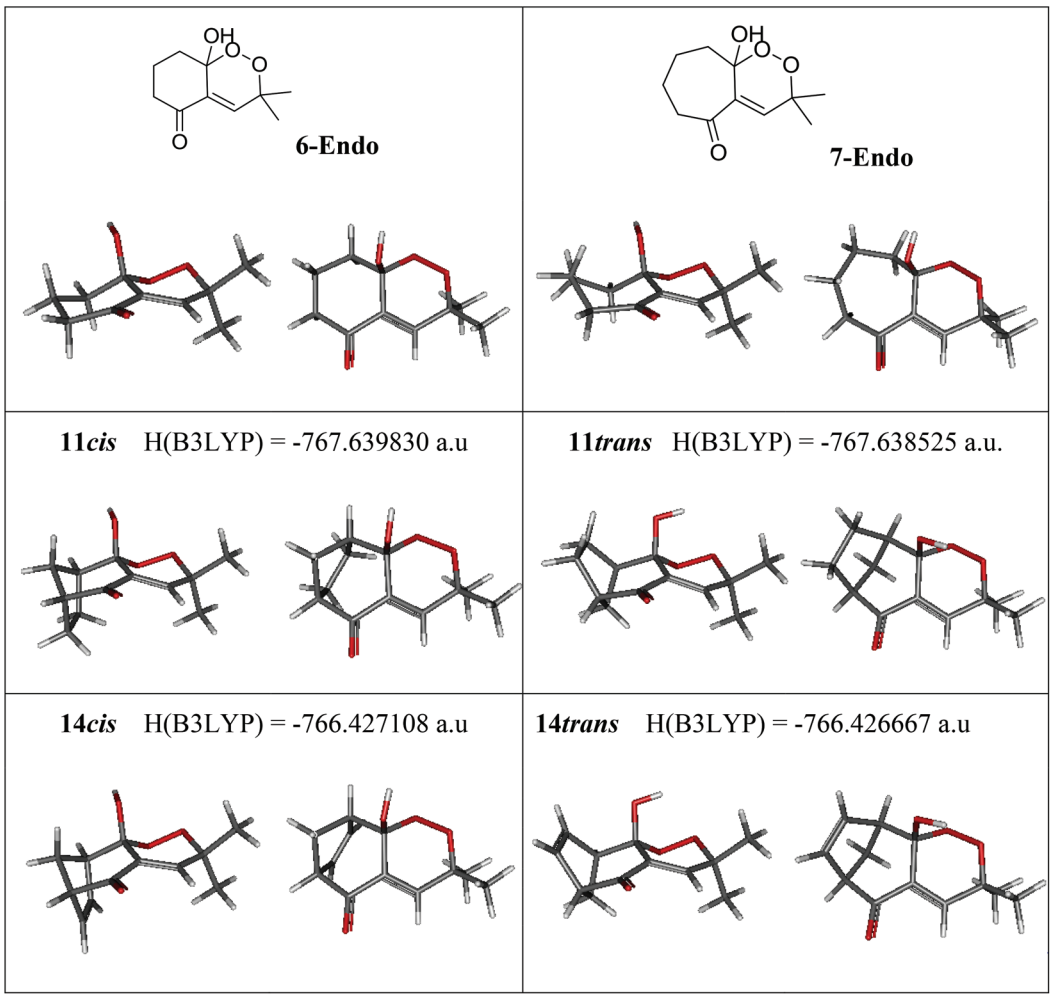
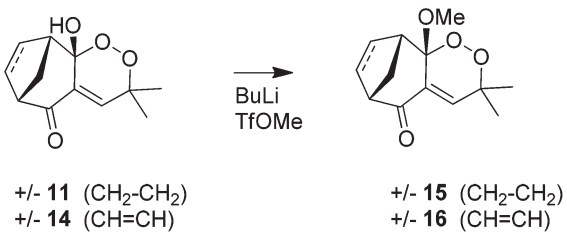


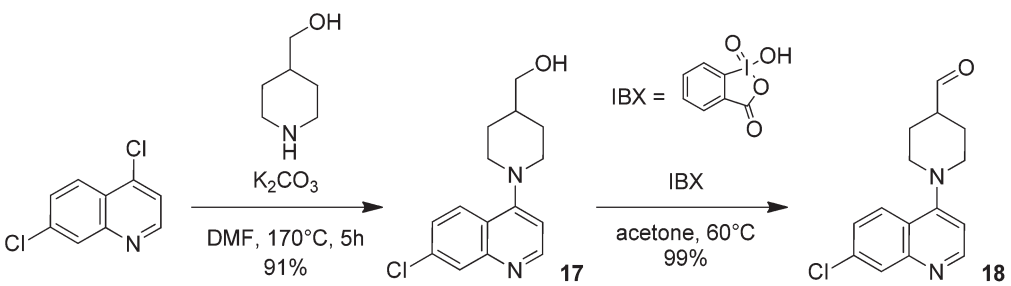
Fig. 2 Optimized geometries and enthalpies of **6-Endo**, **7-Endo**, **11*cis*** and **11*trans***, **14*cis*** and **14*trans*** at the B3LYP 6-311+G(d,p) level of theory.



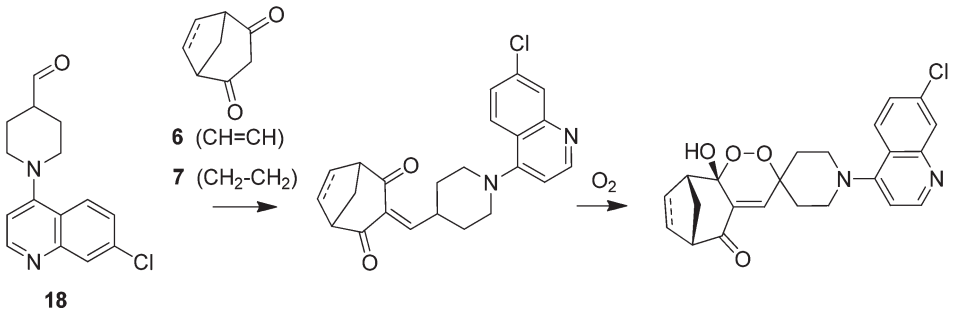
Scheme 5 Methylation of endoperoxides **11** and **14**.

mation of endoperoxide **22** with a great increase of the global rate: 3 hours over 2 weeks. The same procedure was tried for the precursor **19** without success, the starting material being entirely recovered in the enone form. As previously, a single diastereoisomer was obtained in both cases. NMR spectroscopy analysis allowed concluding that the hydroxyl and the methylene are on the same side, as their ^{1}H NMR spectra present the same pattern as those for **11** and **14** (Scheme 7).

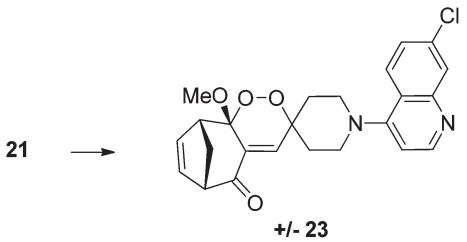
Methylation in this series was particularly risky and delicate as several positions could be methylated. After several trials,



Scheme 6 Preparation of aldehyde **18**.



Scheme 7 Synthesis of hybrid endoperoxides +/− **21** and +/− **22**.



Scheme 8 Methylation of endoperoxide **21**: BuLi–THF, −78 °C, then TfOMe, 16%.

and several conditions, only endoperoxide **21** was methylated using BuLi–TfOMe (1 eq./1 eq.) at low temperature in THF, affording **23** in a low yield after purification by silica gel chromatography (16%) (Scheme 8).

IV. Antimalarial activity

Endoperoxides **11**, **14**, **21** and **22** and their methylated analogs **15**, **16** and **23** were tested *in vitro* against the chloroquine-sensitive 3D7 strain and the chloroquine-resistant W2 strain of *Plasmodium falciparum* (Table 1). The activities were determined according to the method of Desjardins *et al.* using [^{3}H] hypoxanthine incorporation to assess parasite growth. Parasitic viability was expressed as IC_{50}, the drug concentration causing 50% parasite growth inhibition.[21]

In contrast to previous results,[9,11] methylation of **11** and **14** allowed only a slight increase in activity (respectively 4-fold and 2-fold for the methylated endoperoxides **15** and **16**). However, as previously, methylation of **21** provided endoperoxide **23** which was 28–32 fold more potent. The introduction of 7-chloro-4-aminoquinoline improved the activity. Indeed the hybrid endoperoxide **23** was 16-fold to 25-fold more potent than **16**, with an IC_{50} below 1 μM, both on 3D7 and W2 parasite strains.

Conclusion

Endoperoxides were prepared following an autoxidation step in moderate to good yields. Oxygen uptake proved to be diastereoselective leading to peroxides **11** and **14**, with the same configuration (+/−)-*cis*. Unfortunately, those compounds presented very low activity whether methylated or not. The same methodology was followed for the preparation of hybrid molecules **21** and **22** combining the 7-chloro-4-aminoquinoline with the tricyclic endoperoxide moiety. The same diastereoselectivity during the autoxidation step was observed. After methylation of the peroxyhemiketal function, the hybrid compound **23** displayed a marked increase in its antiplasmodial activity, with an IC_{50} between 100 and 250 nM against both the chloroquine-susceptible and/or -resistant strains of *Plasmodium falciparum*. It seems that the 7-chloro-4-aminoquinoline moiety can interact with heme by π–π interaction, leading to the localization of the compound near its target, the heme. The heme provides iron(II) for reduction of the peroxide; the production of C-centered radicals in the vicinity of heme renders alkylation feasible.

Experimental part

2,3,4,4-Tetrachlorobicyclo[3.2.1]octa-2,6-diene (4)

KOH pellets (369 mg, 5.60 mmol, 4.00 eq.) were powdered in 20 mL of dry toluene. Pentachlorocyclopropane **1** (0.7 mL, 4.9 mmol, 1.0 eq.) was added at room temperature under an

Table 1 IC_{50} values of several endoperoxides, artemisinin (ART) and chloroquine on chloroquine-susceptible (3D7) and chloroquine-resistant (W2) strains of *Plasmodium falciparum*

	11	**14**	**15**	**16**	**21**	**22**	**23**	G3	G3Me	ART	Chloroquine
IC_{50} (μM) (3D7)	31.5	10.55	7.75	3.85	6.75	2.45	0.24	62	0.40	0.019	0.019
IC_{50} (μM) (W2)	—	8.45	6.35	4.55	6.05	1.40	0.185	38	0.23	0.019	0.42

inert atmosphere. The suspension was stirred at room temperature for 1 h. Freshly distilled cyclopentadiene was added dropwise. The reaction was heated at 85 °C for 2 h. The mixture was filtered through celite. The filtrate was concentrated to give 965 mg of a yellowish crystal (81%). mp = 91 °C; R_f = 0.65 (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (1H, td, CH–CH_2–CH), 2.49 (1H, d, CH–CH_2–CH), 3.17–3.20 (1H, m, CCl=CCl–CH), 3.76–3.79 (1H, m, CCl_2–CH), 6.19 (1H, dd, CCl–CH–CH=CH), 6.67 (1H, dd, CH=CH–CH–CCl_2); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 42.2 (CH_2, CH–$C$$H_2$–CH), 49.1 (CH, CCl–$C$H–$CH_2$), 58.4 (CH, CCl_2–CH–CH_2) 88.9 (C, CCl_2), 127.7 (C, CCl_2–CCl=CCl), 132.7 (CH, CCl–CH–CH=CH), 140.6 (C, CH–CCl=CCl), 141.8 (CH, CCl_2–CH–CH=CH).

3-Chlorobicyclo[3.2.1]oct-6-ene-2,4-dione (5a) and its enol isomer 5b

2,3,4,4-Tetrachlorobicyclo[3.2.1]octa-2,6-diene (**4**) (72 mg, 0.3 mmol, 1.0 eq.) was dissolved in 2 mL of dioxane. Then 1.5 mL of NaOH solution (2 M) (3.0 mmol, 30 eq.) was added. The reaction was stirred at 90 °C for 18 h. The reaction was extracted with 10 mL of EtOAc. The aqueous layer was adjusted to pH 1 with HCl (6 M) aqueous solution and extracted with 3 × 10 mL of EtOAc. Combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$ and concentrated to give 30 mg of a crude brownish solid (59% yield).

mp = 137 °C; R_f = 0.1 (petroleum ether–AcOEt; 50/50); ^{1}H NMR (300 MHz, $CDCl_3$) (**5a** and **5b** mixture) δ 2.33–2.50 (2H, m, CH–CH_2–CH), 2.59–2.76 (2H, m, CH–CH_2–CH), 3.53 (2H, t, CO–CH), 3.71–3.73 (1H, m, CO–CH), 3.82 (1H, dd, CO–CH), 5.22 (1H, d, COH–CH–CH=CH), 5.55 (1H, d, COH–CH–CH=CH), 6.19 (1H, d, CO–CH–CH=CH), 6.41–6.42 (1H, m, CO–CH–CH=CH), 6.52 (1H, s, CHCl); ^{1}H NMR (300 MHz, MeOD) (**5b** major product) δ 2.38–2.44 (1H, m, AA′MX system, CH–CH_2–CH), 2.55–2.57 (1H, m, AA′MX system, CH–CH_2–CH), 3.43–3.45 (2H, m, AMXX′ systems, CH–CH_2–CH), 6.54 (2H, s, CH–CH=CH–CH); ^{13}C NMR (75.47 MHz, MeOD) (**5b** major product) δ 50.9 (CH_2, CH–$C$$H_2$–CH), 53.2 (CH, CH–CH_2–CH), 101.0 (C, CCl), 138.5 (CH, CH=CH), 187.3 (C, CO–CCl=COH).

Bicyclo[3.2.1]oct-6-ene-2,4-dione (6)

3-Chlorobicyclo[3.2.1]oct-6-ene-2,4-dione (**5**) (1.47 g, 8.60 mmol, 1.0 eq.) was dissolved in 35 mL of dioxane. 23 mL of acetic acid was added, followed by zinc powder (1.64 g, 25.9 mmol, 3.0 eq.). The reaction was stirred at room temperature (20 °C) for 21 h. The reaction was filtered through a pad of celite. The residue was washed with water and EtOAc. Layers were acidified with HCl (6 M) to pH 2 and separated. The aqueous layer was extracted with 3 × 60 mL of EtOAc. Combined organic layers were washed with 2 × 20 mL of brine, dried over $MgSO_4$ and concentrated to give a brown oil. The crude was dry loaded to be purified by flash chromatography over silica gel (petroleum ether–AcOEt; 80/20 then 50/50) to give 729 mg of a yellow oil (62% yield). R_f = 0.3–0.4 (petroleum ether–AcOEt; 80/20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44–2.48 (1H, m, CH–CH_2–CH), 2.52–2.60 (1H, m, CH–CH_2–CH), 3.20 (1H, d, CO–CH_2–CO), 3.48–3.50 (2H, m, CH–CH_2–CH), 3.51 (1H, d, CO–CH_2–CO), 6.19–6.23 (2H, m, CH=CH); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 37.0 (CH_2, CH–$C$$H_2$–CH), 50.4 ($CH_2$, CO–$C$$H_2$–CO), 55.3 (CH, CH–CH_2–CH), 134.9 (CH, CH=CH), 201.6 (C, CO–CH_2–CO); IR (KBr blades) ν: 3512, 1708, 1638, 1587, 1244, 1223 cm^{-1}; HR-MS (DCI/CH_4): calculated for $C_8H_9O_2^+$, 137.0603, found 137.0607.

Bicyclo[3.2.1]octane-2,4-dione (7a) and its enol isomer 7b

Bicyclo[3.2.1]oct-6-ene-2,4-dione (**6**) (331 mg, 1.94 mmol, 1.0 eq.) was dissolved with 16 mL of 1,4-dioxane. The mixture was degassed with Ar for 20 min. Pd/C (10%, 104 mg, 0.10 mmol, 0.05 eq.) was added and then the mixture was bubbled with H_2 for 5 min. The reaction was stirred under H_2 at atmospheric pressure at room temperature (23 °C) for 1 h. The reaction was filtered through a pad of celite. The residue was washed with EtOAc. The filtrate was concentrated to give a white solid of the expected product (99%).

mp = 122–123 °C; R_f = 0.1 (petroleum ether–EtOAc; 50/50); ^{1}H NMR (300 MHz, $CDCl_3$) (**7a** major product) δ 1.87–1.98 (4H, m, CH–CH_2–CH_2–CH), 2.11–2.16 (2H, m, CH–CH_2–CH), 3.01–3.05 (2H, m, CH–CH_2–CH), 3.15 (1H, dd, CO–CH_2–CO), 3.31 (1H, d, CO–CH_2–CO); ^{1}H NMR (300 MHz, CD_3OD) (**7b** major product) δ 1.58–170 (3H, m, CH–CH_2–CH, CH–CH_2–CH_2–CH), 2.00 (1H, d, J = 11.5 Hz, CH–CH_2–CH), 2.06–2.18 (2H, m, CH–CH_2–CH_2–CH), 2.79–2.83 (2H, m, CH–CH_2–CH), 4.90 (1H, s, CO–CH=COH); ^{13}C NMR (75.47 MHz, $CDCl_3$) (**7a** and **7b** mixture) δ 26.1 (CH_2, A, CH–$C$$H_2$–$C$$H_2$–CH), 27.9 ($CH_2$, B, CH–$C$$H_2$–$C$$H_2$–CH), 31.3 ($CH_2$, A, CH–$C$$H_2$–CH), 38.7 ($CH_2$, B, CH–$C$$H_2$–CH), 45.6 (CH, B, CH–CH_2–CH), 49.6 (CH, A, CH–CH_2–CH), 51.4 (CH_2, A, CO–$C$$H_2$–CO), 99.7 (CH, B, CO–$C$H=COH), 197.8 (C, B, CO–CH=CO), 207.2 (C, A, CO–CH_2–CO); ^{13}C NMR (75.47 MHz, CD_3OD) (**7b** major product) δ 28.8 (CH_2, CH–$C$$H_2$–$C$$H_2$–CH), 39.5 ($CH_2$, CH–$C$$H_2$–CH), 46.9 (CH, CH–CH_2–CH), 100.1 (CH, CO–CH=COH), 198.3 (C, CO–CH=COH); IR (KBr pellet) ν: 1637, br. 1568 cm^{-1}; HR-MS (DCI/CH_4): calculated for $C_8H_{11}O_2^+$, 139.0759, found 139.0763.

3-Chloro-4-hydroxybicyclo[3.2.1]oct-3-en-2-one (8)

3-Chlorobicyclo[3.2.1]oct-6-ene-2,4-dione (**7**) (50 mg, 0.3 mmol, 1.0 eq.) was dissolved in 3.5 mL of dioxane. 2.5 mL of water and acetic acid were added. The mixture was degassed with Ar for 10 min. Pd/C 10% (3.2 mg, 0.03 mmol, 0.1 eq.) was added. The mixture was degassed with H_2. The reaction was heated to 55 °C under H_2 at atmospheric pressure for 6 h. The reaction was filtered through a pad of celite. The residue was washed with EtOAc and water. The aqueous layer was separated, acidified to pH 1 with HCl (6 M) and extracted with 3 × 15 mL of EtOAc. The combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$ and concentrated. The crude was purified by flash chromatography on silica gel (DCM, 0% to 3% of MeOH) to give 29 mg (58% yield). R_f = 0.1 (DCM–MeOH; 90/10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (1H, td, CH–CH_2–CH), 1.73–1.80 (2H, m, CH–CH_2–CH_2–CH), 2.08–2.12 (3H, m, CH–CH_2–CH_2–CH, CH–CH_2–CH), 3.11–3.15 (2H, m, CH–CH_2–CH); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 27.5 (CH_2, CH–$C$$H_2$–$C$$H_2$–CH), 38.0 ($CH_2$, CH–$C$$H_2$–CH), 45.8 (CH, CH–CH_2–CH), 106.1

(C, *C*Cl), 186.5 (C, *C*O–CCl=*C*OH); IR (KBr pellet) ν: 1638, 1567 cm^{-1}; HR-MS (DCI/CH_4): calculated for $C_8H_{11}O_2Cl^+$, 173.0369, found 173.0368.

4-Hydroxybicyclo[3.2.1]octan-2-one (9)

R_f = 0.5 (DCM–MeOH; 90/10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (1H, d, CHOH–CH–CH_2–CH$_2$), 1.64–1.73 (1H, m, CO–CH–CH_2–CH$_2$), 1.76 (1H, t, CH–CH_2–CH), 1.78–1.98 (2H, m, CH–CH_2–CH_2–CH), 2.04–2.13 (1H, m, CH–CH_2–CH), 2.25 (1H, dd, CO–CH_2–CHOH), 2.41–2.46 (1H, m, CHOH–C*H*), 2.58 (1H, dd, CO–CH_2–CHOH), 2.66 (1H, t, CO–C*H*), 2.81 (1H, br. s, CHO*H*), 4.04 (1H, ddd, C*H*OH); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 21.8 (CH$_2$, CH–*C*H$_2$–CH), 27.9 (CH$_2$, CO–CH–*C*H$_2$–CH$_2$), 32.9 (CH$_2$, CHOH–CH–*C*H$_2$–CH$_2$), 41.7 (CH, CHOH–*C*H), 44.4 (CH$_2$, CHOH–*C*H$_2$–CO), 49.3 (CH, CO–*C*H), 71.8 (CH, *C*HOH), 211.9 (C, *C*O); IR (KBr blades) ν: 3424 (br.), 1712, 1065 cm^{-1}; HR-MS (DCI/CH_4): calculated for $C_8H_{12}O_2^+$, 140.0837, found 140.0834.

General procedure for cyclic peroxide preparation

The aldehyde (1.20 eq.) (isobutyraldehyde or aldehyde **18**) was diluted in anhydrous DCM (0.12 M). Piperidine (1.20 eq.) was added dropwise and the mixture was stirred at room temperature for 10 min. A solution of diketone (1 eq.) (**6** or **7**) and piperidine (1.10 eq.) in anhydrous DCM (0.1 M) was added dropwise to the iminium solution. The reaction was stirred at room temperature for 30 min and then was concentrated. The excess of piperidine was removed under vacuum to give the Mannich base as a solid. The Mannich base was dissolved with DCM (0.1 M). The solution was stirred for 10 minutes with a saturated solution of NH_4Cl in 1 N HCl as a (1 : 1) mixture with DCM. Then the mixture was immediately extracted 3 times with EtOAc or DCM. The combined organic layers were washed with water, until pH 5–6 was reached, and brined, dried over $MgSO_4$ and concentrated to give the autoxidation precursor (**10**, **13**, **19**, **20**). The precursor was solubilized in benzene (0.1 M) and the reaction was stirred at room temperature under O_2 (1 bar). The reaction was followed by ^{1}H NMR spectroscopy analysis until consumption of the enol and enone forms of the precursor. The reaction was concentrated and purified by flash chromatography over silica gel.

Use of the Rayonet for photoenolization: the apparatus was equipped with 350 nm low pressure mercury lamps. Precursors (**10**, **13**, **19**, **20**) were solubilized in ethyl acetate or benzene (0.1 M). The solution was irradiated for 15 minutes and then analyzed by ^{1}H NMR. The peroxide **11** was obtained after 15 minutes of irradiation and then 3 h under an O_2 atmosphere. The peroxide **13** was obtained after 8 cycles of irradiation (15 minutes) followed by 45 minutes under an O_2 atmosphere.

(+/−)-(6*R*,9*S*,9a*S*)-9a-Hydroxy-3,3-dimethyl-3,6,7,8,9,9a-hexahydro-5*H*-6,9-methanocyclohepta[*c*][1,2]dioxin-5-one (11). See: general procedure for cyclic peroxide preparation (1 day, 48% yield); white crystal; mp = decomposition; R_f = 0.45 (petroleum ether–EtOAc, 80/20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (3H, s, C–CH_3), 1.45 (3H, s, C–CH_3), 1.55–1.64 (1H, m, CH_2–CH$_2$), 1.70–1.80 (3H, m, CH_2–CH_2, CH–CH_2–CH), 1.83–1.95 (1H, m, CH_2–CH$_2$), 2.45 (1H, d, J = 12.6 Hz, CH–CH_2–CH), 2.43–2.58 (1H, m, COH–C*H*), 2.82–2.86 (1H, m, CO–C*H*), 6.46 (1H, s, C=C*H*–C): ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 23.1 (CH$_2$, *C*H$_2$–CH$_2$), 23.5 (CH$_3$, C–*C*H$_3$), 24.5 (CH$_3$, C–*C*H$_3$), 28.6 (CH$_2$, CH$_2$–*C*H$_2$), 31.8 (CH$_2$, C–*C*H$_2$–C), 42.0 (CH, COH–*C*H), 50.2 (CH, CO–*C*H), 78.9 (C, (CH$_3$)$_2$*C*–O), 100.2 (C, CH–*C*OH), 135.3 (C, *C*=CH–C), 140.1 (CH, C=*C*H–C), 201.9 (C, CH–*C*O–C); IR (KBr pellet) ν: 3337 (br.), 1690, 1642, 1277, 1128, 1088, 1036 cm^{-1}; MS (DCI/NH_3^+): 207 (100, [MH − H_2O]$^+$), 224 (41, [M]$^+$), 242 (34, [MNH_4]$^+$); HR-MS (DCI/CH_4): calculated for $C_{12}H_{17}O_4^+$, 225.1127, found 225.1122.

(+/−)-3a-Hydroxy-2,2-dimethylhexahydro-4,7-methanocyclohepta[*b*]oxireno[2,3-*c*]furan-8(3a*H*)-one (12). White solid, mp = decomposition; R_f = 0.2 (petroleum ether–EtOAc, 80/20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (3H, s, C–CH_3), 1.42 (3H, s, C–CH_3), 1.66–1.78 (1H, m, CO–CH–CH_2–CH$_2$), 1.82–1.88 (1H, m, COH–CH–CH_2–CH$_2$), 1.93 (1H, td, CH–CH_2–CH), 2.05–2.21 (2H, m, CH–CH_2–CH_2–CH), 2.38 (1H, d, CH–CH_2–CH), 2.62 (1H, dd, COH–C*H*–CH$_2$), 3.00 (1H, dd, CO–C*H*–CH$_2$), 3.79 (1H, s, C*H*–O–C); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 24.4 (CH$_2$, CH–*C*H$_2$–CH$_2$–CH), 25.0 (CH$_3$, C–*C*H$_3$), 25.5 (CH$_3$, C–*C*H$_3$), 26.7 (CH$_2$, CH–CH$_2$–*C*H$_2$–CH), 34.2 (CH$_2$, CH–*C*H$_2$–CH), 44.8 (CH, *C*H–COH), 49.9 (CH, *C*H–CO), 70.3 (C, CO–*C*–COH), 74.9 (CH, C(CH$_3$)$_2$–*C*H–O–C), 81.2 (C, O–*C*(CH$_3$)$_2$–CHO), 106.9 (C, *C*OH), 203.3 (C, *C*O); IR (KBr pellet) ν: 3433, 1722, 1295, 1126, 1116, 1089, 1062, 1023 cm^{-1}; LR-MS (DCI/NH_3): 207.0 (100, [M − OH]$^+$), 224.0 (30, [M]$^+$), 242.0 (2%, [MNH_4]$^+$); HR-MS (DCI/CH_4): calculated for $C_{12}H_{17}O_4^+$, 225.1127, found 225.1132.

(+/−)-(6*S*,9*R*,9a*S*)-9a-Hydroxy-3,3-dimethyl-3,6,9,9a-tetrahydro-5*H*-6,9-methanocyclohepta[*c*][1,2]dioxin-5-one (14). See: general procedure for cyclic peroxide preparation (36 days, 49% yield); white crystal; mp=decomposition; R_f = 0.2 (petroleum ether–EtOAc, 80/20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, s, C–CH_3), 1.35 (3H, s, C–CH_3), 2.40 (1H, dt, J = 12 Hz, J = 5 Hz, CH–CH_2–CH), 2.66 (1H, d, J = 12 Hz, CH–CH_2–CH), 3.01 (1H, dd, J = 5 Hz, J = 3 Hz, COH–C*H*), 3.21 (1H, dd, J = 5 Hz, J = 3 Hz, CO–C*H*), 6.10 (1H, dd, J = 5.7 Hz, J = 3 Hz, CH–C*H*=C*H*–CH) 6.16 (1H, dd, J = 5.7 Hz, J = 3 Hz, CH–C*H*=C*H*–CH), 6.43 (1H, s, C=C*H*–C); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 23.6 (CH$_3$, C–*C*H$_3$), 24.2 (CH$_3$, C–*C*H$_3$), 37.7 (CH$_2$, CH–*C*H$_2$–CH), 46.6 (CH, COH–*C*H), 55.0 (CH, CO–*C*H), 79.5 (C, (CH$_3$)$_2$*C*–O), 98.9 (C, CH–*C*OH), 135.5 (CH, CH–*C*H=CH–CH), 136.2 (CH, CH–CH=*C*H–CH), 136.3 (C, *C*=CH–C), 140.5 (CH, C=*C*H–C), 197.1 (C, CH–*C*O–C); IR (KBr pellet) ν: 3363 (br.), 1694, 1639, 1263, 1110, 1085, 1052 cm^{-1}; HR-MS (DCI/CH_4): calculated for $C_{12}H_{15}O_4^+$, 223.0970, found 223.0979.

General procedure for methylation

To a solution of the peroxy-alcohol (1.0 eq.) in anhydrous THF (0.025 M) at −78 °C, BuLi (1.6 M, 1.0 eq.) was added dropwise under Ar. After 10 min, methyl-triflate (1.2 eq.) was added dropwise. The reaction was quenched with an aqueous saturated solution of NH_4Cl. The reaction was diluted with water and phases were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with

brine, dried over $MgSO_4$ and concentrated. The crude was purified by flash chromatography over silica gel.

(+/−)-(6*R*,9*S*,9a*S*)-9a-Methoxy-3,3-dimethyl-3,6,7,8,9,9a-hexahydro-5*H*-6,9-methanocyclohepta[*c*][1,2]dioxin-5-one (15). (−70 °C, 4 h, 48% yield); colorless oil; R_f = 0.45 (petroleum ether–EtOAc, 85/15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, s, C–CH_3), 1.43 (3H, s, C–CH_3), 1.58–1.73 (3H, m, CH_2–CH$_2$, CH–CH_2–CH), 1.78–1.95 (2H, m, CH_2–CH_2), 2.29 (1H, d, CH–CH_2–CH), 2.70 (1H, t, COH–C*H*), 2.85 (1H, t, CO–C*H*), 3.38 (3H, s, OCH_3), 6.51 (1H, s, C=C*H*–C); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 23.4 (CH_3, C–*C*H_3), 23.5 (CH_2, C–*C*H_2–C), 24.8 (CH_3, C–*C*H_3), 29.1 (CH_2, *C*H_2–*C*H_2), 31.4 (CH_2, *C*H_2–*C*H_2), 38.7 (CH, COCH$_3$–*C*H), 50.3 (CH, CO–*C*H), 50.4 (CH_3, O*C*H_3), 78.2 (C, $(CH_3)_2$*C*–O), 102.9 (C, CH–*C*OH), 133.5 (C, *C*=CH–C), 140.6 (CH, C=*C*H–C), 201.6 (C, CH–*C*O–C); IR (KBr blades) ν: 1701, 1649, 1270, 1126, 1091, 1074, 1003 cm^{-1}; HR-MS (DCI/CH_4): calculated for $C_{13}H_{19}O_4^+$, 239.1283, found 239.1287.

(+/−)-(6*S*,9*R*,9a*S*)-9a-Methoxy-3,3-dimethyl-3,6,9,9a-tetrahydro-5*H*-6,9-methanocyclohepta[*c*][1,2]dioxin-5-one (16). (−70 °C, 2.5 h, 50% yield); colorless oil; R_f = 0.4 (petroleum ether–EtOAc, 90/10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, s, C–CH_3), 1.32 (3H, s, C–CH_3), 2.30–2.37 (1H, m, AA′MX system, CH–CH_2–CH), 2.49 (1H, d, CH–CH_2–CH), 3.15–3.20 (2H, m, 2 × CH–CH$_2$–C*H*), 3.42 (3H, s, O–CH_3), 6.07–6.12 (2H, m, ABX systems, CH–C*H*=C*H*–CH), 6.43 (1H, s, C=C*H*–C); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 23.4 (CH_3, C–*C*H_3), 24.6 (CH_3, C–*C*H_3), 37.1 (CH_2, CH–*CH*$_2$–CH), 43.4 (CH, COH–*C*H), 50.5 (CH_3, O*C*H_3), 55.0 (CH, CO–*C*H), 78.9 (C, $(CH_3)_2$*C*–O), 101.5 (C, CH–*C*OH), 133.9 (C, *C*=CH–C), 135.8 (CH, CH–*C*H=CH–CH), 136.2 (CH, CH–CH=*C*H–CH), 141.1 (CH, C=*C*H–C), 197.0 (C, CH–*C*O–C); IR (KBr blades) ν: 1704, 1648, 1258, 1106, 1085, 1057 cm^{-1}; HRMS (DCI/CH_4): calculated for $C_{13}H_{17}O_4^+$, 237.1127, found 237.1126.

1-(7-Chloroquinolin-4-yl)piperidine-4-carbaldehyde (18). Alcohol **17** (200 mg, 0.72 mmol, 1.0 eq.) and IBX (407 mg, 1.45 mmol, 2.0 eq.) in 5 mL of acetone were heated at 60 °C for 5 h. Then the reaction was filtered. The white precipitate was washed with DCM. The filtrate was concentrated to give 237 mg (99% yield) of a yellow oil of aldehyde. R_f = 0.44 (DCM–EtOAc, 50/50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90–2.03 (2H, m, CH$_2$–CH_2–CH–CH_2–CH$_2$), 2.10–2.19 (2H, m, CH$_2$–CH_2–CH–CH_2–CH$_2$), 2.48–2.52 (1H, m, CH$_2$–CH$_2$–C*H*–CH$_2$–CH$_2$), 2.91–2.99 (2H, m, CH_2–CH$_2$–CH–CH$_2$–CH_2), 3.50 (2H, td, CH_2–CH$_2$–CH–CH$_2$–CH_2), 6.81 (1H, d, N=CH–C*H*), 7.41 (1H, dd, CCl=C*H*–CH), 7.87 (1H, CCl=CH–C*H*), 8.02 (1H, d, C*H*–CCl), 8.68 (1H, d, N=C*H*–CH), 9.76 (1H, d, C*H*O); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 25.4 (CH_2, CH$_2$–*C*H$_2$–CH–CH$_2$–CH$_2$), 25.5 (CH_2, CH$_2$–CH$_2$–CH–*C*H$_2$–CH$_2$), 47.6 (CH, CH$_2$–CH$_2$–*C*H–CH$_2$–CH$_2$), 51.7 (CH_2, *C*H$_2$–CH$_2$–CH–CH$_2$–*C*H$_2$), 109.1 (CH, N=CH–*C*H=C), 122.0 (C, C–*C*=CH), 125.0 (CH, CCl=*C*H–CH), 126.3 (CH, CCl=CH–*C*H), 128.7 (CH, CCl–*C*H=C), 134.9 (C, *C*Cl), 150.0 (C, CCl–CH=*C*), 151.8 (CH, N=*C*H–CH–C), 157.3 (C, N=CH–CH–*C*), 202.9 (CH, *C*HO); IR (ATR) ν: 3062, 2945, 2920, 2816, 1724, 1607, 1574, 1425 and 869 cm^{-1}; LR-MS (DCI/NH_3): 275 (100, $[MH]^+$), 277 (34%, $[MH + 2]^+$); HR-MS (ESI): calculated for $C_{15}H_{16}N_2OCl^+$, 275.0951, found 275.0953.

(+/−)-1-(7-Chloroquinolin-4-yl)-9a′-hydroxy-9′,9a′-dihydrospiro-[piperidine-4,3′-[6,9]methanocyclohepta[*c*][1,2]dioxin]-5′(6′*H*)-one (21). See: general procedure for cyclic peroxide preparation (DCM, 33 days, 19% yield); colorless oil; R_f = 0.11 (DCM–EtOAc, 80/20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84–2.00 (2H, m, C–CH_2–CH$_2$–N), 2.11–2.21 (2H, m, C–CH_2–CH$_2$–N), 2.42–2.49 (1H, m, CH–CH_2–CH), 2.71 (1H, d, CH–CH_2–CH), 3.04–3.07 (1H, m, C*H*–CH$_2$–CH), 3.13 (1H, dt, C–CH$_2$–CH_2–N), 3.23–3.28 (2H, m, CH–CH$_2$–C*H*, C–CH$_2$–CH_2–N), 3.30–3.38 (2H, m, C–CH$_2$–CH_2–N), 6.12–6.19 (2H, m, C*H*=C*H*), 6.48 (1H, s, C=C*H*–CO), 6.85 (1H, d, N–CH=C*H*–C), 7.42 (1H, dd, C–CH=C*H*–CCl), 7.86 (1H, d, C–C*H*=CH–CCl), 8.06 (1H, d, C–C*H*=CCl), 8.71 (1H, d, N–C*H*=CH–C); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 31.4 (CH_2, C(*C*H_2)$_2$), 33.1 (CH_2, C(*C*H_2)$_2$), 37.8 (CH_2, CH–*C*H$_2$–CH), 46.8 (CH, *C*H–CH$_2$–CH), 47.5 (CH_2, N(*C*H_2)$_2$), 48.0 (CH_2, N(*C*H_2)$_2$), 55.1 (CH, CH–CH$_2$–*C*H), 78.4 (C, CH–*C*–(CH$_2$)$_2$), 99.4 (C, *C*OH), 109.3 (CH, C=*C*H–CH=N), 122.0 (C, CH=C–*C*–CH), 125.0 (CH, C–*C*H=CH–CCl), 126.5 (CH, C–CH=*C*H–CCl), 128.9 (CH, C–*C*H=CCl), 135.2 (C, *C*Cl), 135.5 (CH, *C*H=CH), 136.2 (CH, CH=*C*H), 138.0 (C, COH–*C*=CH), 138.4 (CH, COH–C=*C*H), 150.0 (C, N–*C*–CH), 151.9 (CH, C=CH–*C*H=N), 157.3 (C, CH=*C*–C–CH), 196.6 (C, *C*O); IR (ATR) ν: 3060, 1700, 1572 cm^{-1}; MS (CI/NH_3): 424 (5, $[MH]^+$), 382 (5), 260 (100), 217 (21), 190 (23), 155 (30%); HR-MS (DCI/CH_4): calculated for $C_{23}H_{22}N_2O_4Cl^+$, 425.1268, found 425.1253.

(+/−)-1-(7-Chloroquinolin-4-yl)-9a′-hydroxy-7′,8′,9′,9a′-tetrahydrospiro[piperidine-4,3′-[6,9]methanocyclohepta[*c*][1,2]-dioxin]-5′(6′*H*)-one (22). See: general procedure for cyclic peroxide preparation (DCM, 15 days, 34% yield); white solid; mp = 138 °C followed by decomposition at 140 °C; R_f = 0.28 (DCM–MeOH, 97/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62–1.71 (1H, m, CH–CH_2–CH$_2$–CH), 1.74–1.88 (3H, m, CH–CH_2–CH, CH–CH_2–CH$_2$–CH), 1.89–2.29 (5H, m, C–CH_2–CH$_2$–N, CH–CH_2–CH$_2$–CH), 2.54 (1H, d, C*H*–CH$_2$–CH), 2.61–2.65 (1H, m, C*H*–CH$_2$–CH), 2.90–2.94 (1H, m, CH–CH$_2$–C*H*), 3.27–3.43 (3H, m, C–CH$_2$–CH_2–N), 6.52 (1H, s, C=C*H*–CO), 6.85 (1H, d, N–CH=C*H*–C), 7.41 (1H, dd, C–CH=C*H*–CCl), 7.86 (1H, d, C–C*H*=CH–CCl), 8.07 (1H, s, C–C*H*=CCl), 8.70 (1H, br. s, N–C*H*=CH–C); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 23.3 (CH_2, *C*H$_2$–CH$_2$), 28.6 (CH_2, CH–*C*H$_2$), 31.7 (CH_2, C(*C*H$_2$)$_2$), 32.0 (CH_2, CH–*C*H$_2$–CH), 33.0 (CH_2, C(*C*H$_2$)$_2$), 42.3 (CH, *C*H–CH$_2$–CH), 47.6 (CH_2, N(*C*H$_2$)$_2$), 48.0 (CH_2, N(*C*H$_2$)$_2$), 50.3 (CH, CH–CH$_2$–*C*H), 77.7 (C, CH–*C*–(CH$_2$)$_2$), 100.8 (C, *C*OH), 109.3 (CH, C=*C*H–CH=N), 122.0 (C, CH=C–*C*–CH), 125.0 (CH, C–*C*H=CH–CCl), 126.5 (CH, C–CH=*C*H–CCl), 128.7 (CH, C–*C*H=CCl), 135.3 (C, *C*Cl), 137.2 (C, COH–*C*=CH), 137.9 (CH, COH–C=*C*H), 149.8 (C, N–*C*–CH), 151.8 (CH, C=CH–*C*H=N), 157.4 (C, CH=*C*–C–CH), 201.4 (C, *C*O); IR (ATR) ν: br. 3360, 1697, 1574, 1200, 1102, 1088 cm^{-1}; MS (CI/NH_3): 427 (5, $[MH]^+$), 429 (1, $[MH + 2]^+$), 261 (100, $C_{14}H_{14}ClN_2O^+$), 263 (32%, $[C_{14}H_{14}ClN_2O + 2]^+$); HR-MS (DCI/$CH_4$): calculated for $C_{23}H_{24}N_2O_4Cl^+$, 427.1425, found 427.1416.

(+/−)-1-(7-Chloroquinolin-4-yl)-9a′-methoxy-9′,9a′-dihydrospiro[piperidine-4,3′-[6,9]methanocyclohepta[*c*][1,2]dioxin]-5′-(6′*H*)-one (23). See: general procedure for methylation (−70 °C

to −65 °C, 2.5 h, 16%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92–1.99 (2H, m, C–(CH_2–CH_2)$_2$–N), 2.07–2.21 (2H, m, C–CH_2–CH_2–N), 2.35–2.43 (1H, m, CH–CH_2–CH), 2.54 (1H, d, CH–CH_2–CH), 3.10–3.18 (1H, m, C–(CH_2–CH_2)$_2$–N), 3.19–3.28 (3H, m, CH–CH_2–CH, C–(CH_2–CH_2)$_2$–N), 3.31–3.38 (2H, m, C–(CH_2–CH_2)$_2$–N), 3.48 (3H, s, OCH_3), 6.11–6.13 (2H, m, CH=CH), 6.48 (1H, s, C=CH–CO), 6.86 (1H, d, N–CH=CH–C), 7.43 (1H, dd, J = 2.1 Hz, C–CH=CH–CCl), 7.88 (1H, d, C–CH=CH–CCl), 8.05 (1H, d, C–CH=CCl), 8.71 (1H, d, N–CH=CH–C); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 31.7 (CH_2, C(CH_2)$_2$), 32.9 (CH_2, C(CH_2)$_2$), 37.2 (CH_2, CH–CH_2–CH), 43.3 (CH, CH–CH_2–CH), 47.7 (CH_2, N(CH_2)$_2$), 48.1 (CH_2, N(CH_2)$_2$), 50.5 (CH_3, OCH_3), 55.1 (CH, CH–CH_2–CH), 77.7 (C, CH–C–(CH_2)$_2$), 102.0 (C, COMe), 109.3 (CH, C=CH–CH=N), 122.0 (C, CH=C–C–CH), 125.0 (CH, C–CH=CH–CCl), 126.5 (CH, C–CH=CH–CCl), 128.9 (CH, C–CH=CCl), 135.2 (C, CCl), 135.8 (C, COH–C=CH), 136.1 (CH, CH=CH), 136.2 (CH, CH=CH), 139.0 (CH, COH–C=CH), 150.0 (C, N–C–CH), 151.9 (CH, C=CH–CH=N), 157.4 (C, CH=C–C–CH), 196.7 (C, CO); IR (ATR) ν: 3064, 1703, 1574 cm^{-1}; LR-MS (CI/NH_3): 438 (42, [MH]$^+$), 372 (46), 260 (100), 217 (52), 191 (66), 155 (66%); HR-MS (DCI/CH_4): calculated for $C_{24}H_{24}N_2O_4Cl^+$, 439.1425, found 439.1419.

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15 Crystal data for **11**: $C_{12}H_{16}O_4$, M = 224.25, triclinic, a = 6.4719(5), b = 8.7411(6), c = 10.9321(8) Å, V = 559.87(7) Å^3, T = 193 K, space group $P\bar{1}$, Z = 2, 10 737 reflections collected, 2765 unique (R_{int} = 0.0203), $R_1[I > 2\sigma(I)]$ = 0.0379. The final wR($F2$) was 0.1055 (all data). Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and have been assigned the deposition number CCDC 997078.
16 Crystal data for **14**: $C_{12}H_{14}O_4$, M = 222.23, monoclinic, a = 6.5048(5), b = 20.2812(16), c = 8.3695(6) Å, V = 1088.27(14) Å^3, T = 193 K, space group $P2_1/c$, Z = 4, 17567 reflections collected, 2338 unique (R_{int} = 0.0371), $R_1[I > 2\sigma(I)]$ = 0.0372. The final wR($F2$) was 0.0908 (all data). Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and have been assigned the deposition number CCDC 997079.
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