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

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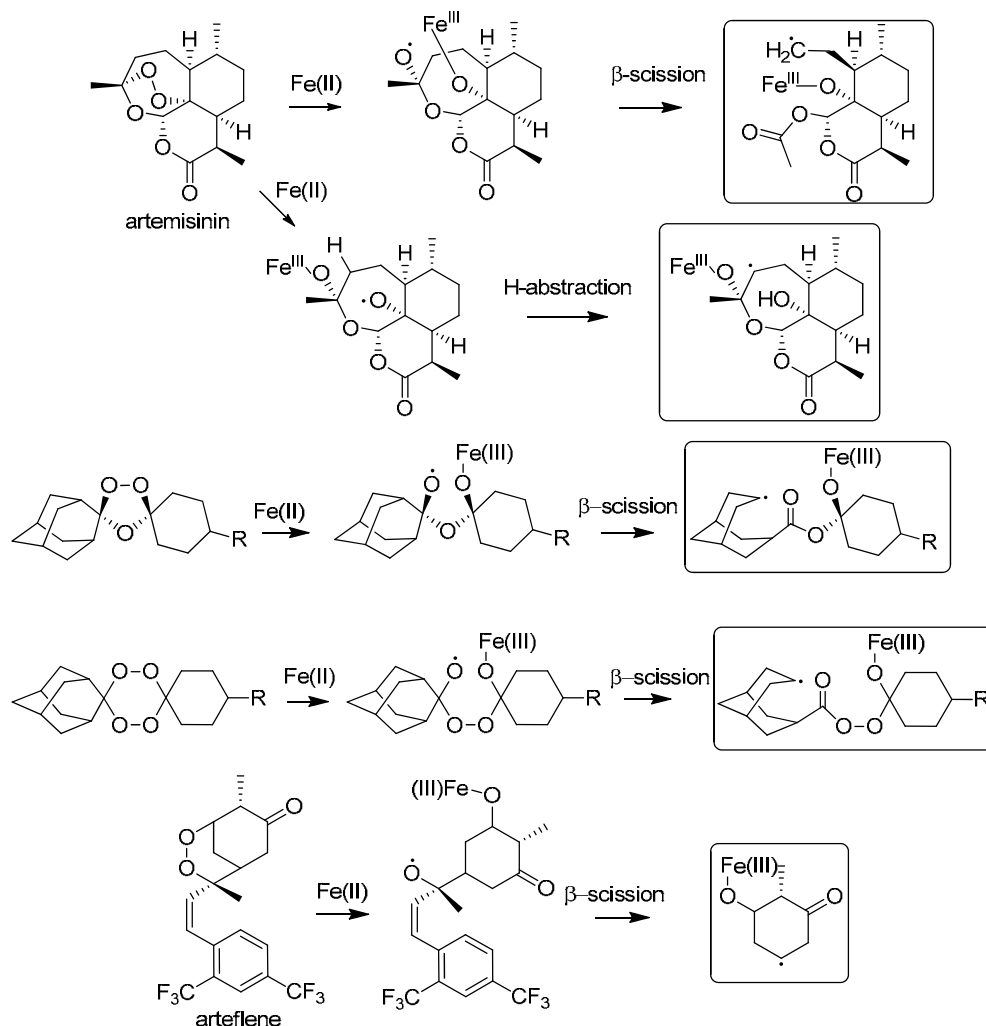
Key Words: malaria, endoperoxide, C-centered radical, hybrid molecule, *Plasmodium falciparum*, G-factor.

Abstract

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 constituted 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 search of 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 Primary or/and secondary C-centered radicals have been described after Fe(II) induced reduction of artemisinin or its derivatives,² trioxanes,³ trioxolanes,⁴ tetraoxanes⁵ or arteflene.⁶ (Scheme 1)



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

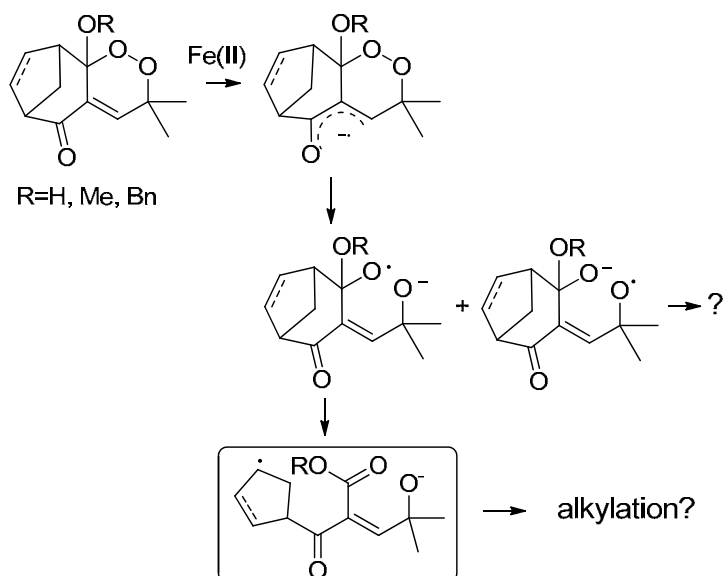
Previous studies have shown that endoperoxides belonging to the G-factor family, natural compounds extracted from leaves of *Eucalyptus grandis*,⁷ possess interesting antimalarial properties after methylation of the hydroxyl group of the peroxyhemiketal moiety. The concentration of the methylated endoperoxide to inhibit by 50% the growth of chloroquine sensitive and resistant *P. falciparum* strains (IC₅₀) was in the range of 200-300 nM i.e. was 100-fold better than the hydroxylated one, the fluorinated being inactive.^{8,9} A study of the Fe(II)-induced reduction of these three compounds¹⁰ has shown the presence of a tertiary C-centered radical which cyclizes in 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 lead 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

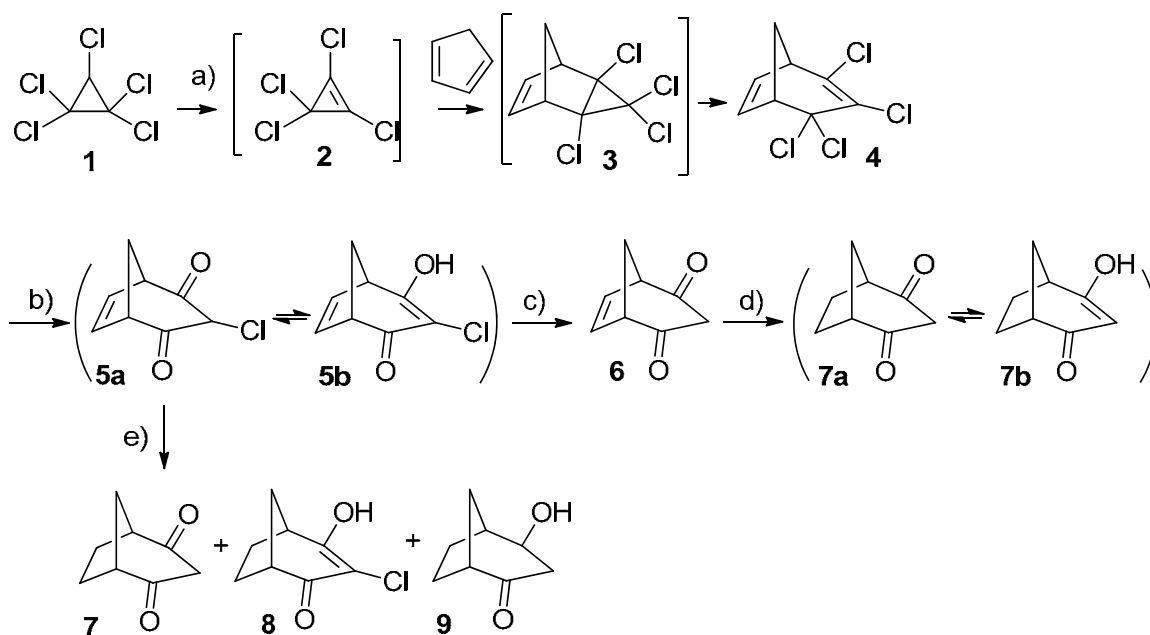


Scheme 2: Hypothesis of Fe(II)-induced reduction

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

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 Product **5** was then obtained after chloride substitution by hydroxide, using sodium hydroxide in water/dioxane mixture. The C-Cl bond of 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).



Scheme 3: Synthesis of diones **6**, **7**: a) KOH, dioxane, RT, 1h then cyclopentadiene, 85°C, 2h, 81% b) NaOH/H₂O, 90°C, 18h, 59% c) Zn, 3 eq, RT, dioxane/AcOH 6/4, 20 h, 62% d) Pd/C H₂ dioxane/EtOAc, 1h e) Pd/C, H₂, 55°C dioxane/EtOAc

The patent also describes the bicyclo[3.2.1]octane-2,4-dione **7** in 59% yield, by hydrogenation and reduction of 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 H₂.

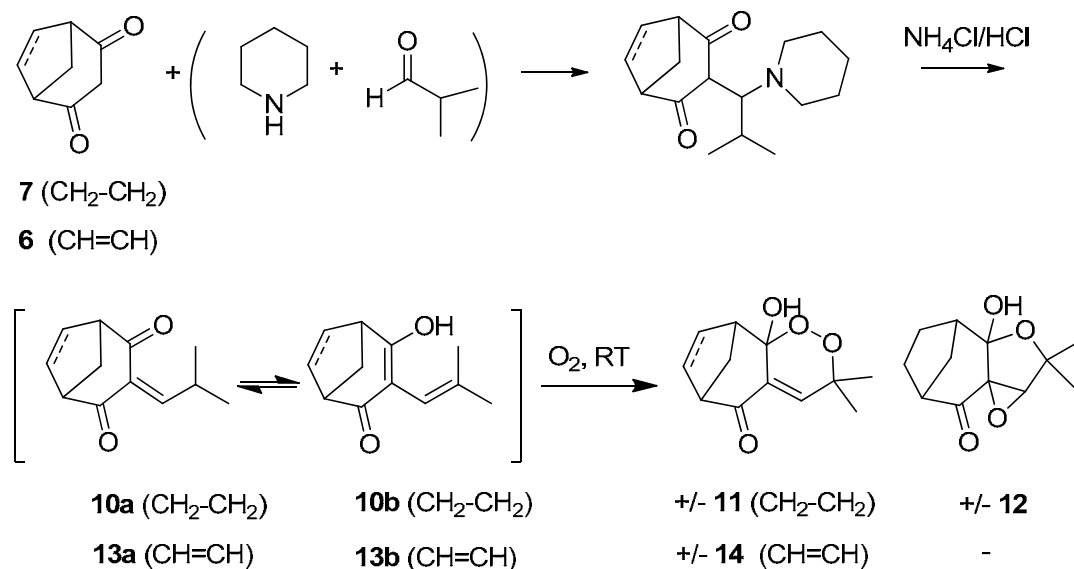
Following these conditions product **8** was obtained in 58% yield after 6 hours of hydrogenation. If the reaction is left longer (17 hours) the alcohol **9** was isolated in lower yield (34%). Finally the dione **7** was obtained in good yield from the unsaturated dione **6** after one hour of catalytic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

II. Syntheses of tricyclic peroxides

Tricyclic peroxides were synthesized following a previously described procedure¹¹ 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 NH₄Cl in HCl (1M), 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 (ethyl acetate or benzene), O₂ pressure (air, 1 and 5 bars), UV irradiation (300 nm or 350 nm).

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



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

Autoxidation under O₂ (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 O₂ pressure of 1 bar or after only 4 hours under O₂ pressure of 5 bars.

Photoenolization of **10** using a Rayonet apparatus equipped with 350 nm low pressure mercury lamps, under O₂ (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 ¹H NMR spectroscopy. After 3 hours, the peroxide **11** was then obtained with 48% yield.

Concerning precursor **13**, ¹H NMR did not indicate the presence of the dienol form **13b**. As autoxidation proceeds on this form, oxygen uptake proved to be very slow in this case as it

took several days (50% after 30 days in ethyl acetate). O₂ pressure did not accelerate the overall kinetics.

As previously described, photoenolization was then attempted using ethyl acetate or benzene as solvent. At 350 nm dienol **13b** in mixture with the enone form **13a** along with its deconjugated form, was detected by ¹H NMR. Then autoxidation occurred quickly in competition with displacement of the equilibrium towards the enone form. So, several cycles consisting of irradiation for 15 mn followed by autoxidation under O₂ (1 bar) for 45 mn, 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.

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 ($a = 6.47 \text{ \AA}$, $b = 8.74 \text{ \AA}$, $c = 10.93 \text{ \AA}$, $\alpha = 110.2^\circ$, $\beta = 95.6^\circ$, $\gamma = 101.3^\circ$).¹⁵ Using numbering indicated in figure 1 and used in X-ray diffraction analysis, its configuration is 1S,4R,5R or 1R,4S,5S.

Endoperoxide **14** crystallizes in a monoclinic structure ($a = 6.50 \text{ \AA}$, $b = 20.28 \text{ \AA}$, $c = 8.37 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 99.7^\circ$, $\gamma = 90^\circ$).¹⁶ Its configuration is also 1S,4R,5R or 1R,4S,5S.

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 level of the two diastereoisomers **11cis** and **11trans** on the one hand, and **14cis** and **14trans** 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 figure 2. The gaps between the two enthalpy levels of **11cis** and **11trans** on the one hand and **14cis** and **14trans** 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 **11trans** (**14trans**) than **11cis** (**14cis**).

Geometries of both diastereoisomers were compared with the geometry of endoperoxides **6-Endo** and **7-Endo** (Figure 2) obtained after autoxidation of 2-alkylidene cyclohexane dione and 2-alkylidene cycloheptane dione. The geometry obtained for **11cis** (**14cis**) is similar to that of **6-Endo** with a chair conformation for the 6-membered cycle while for **11trans** (**14trans**), 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 **11cis** and **14cis** obtained are the kinetic products.¹⁹

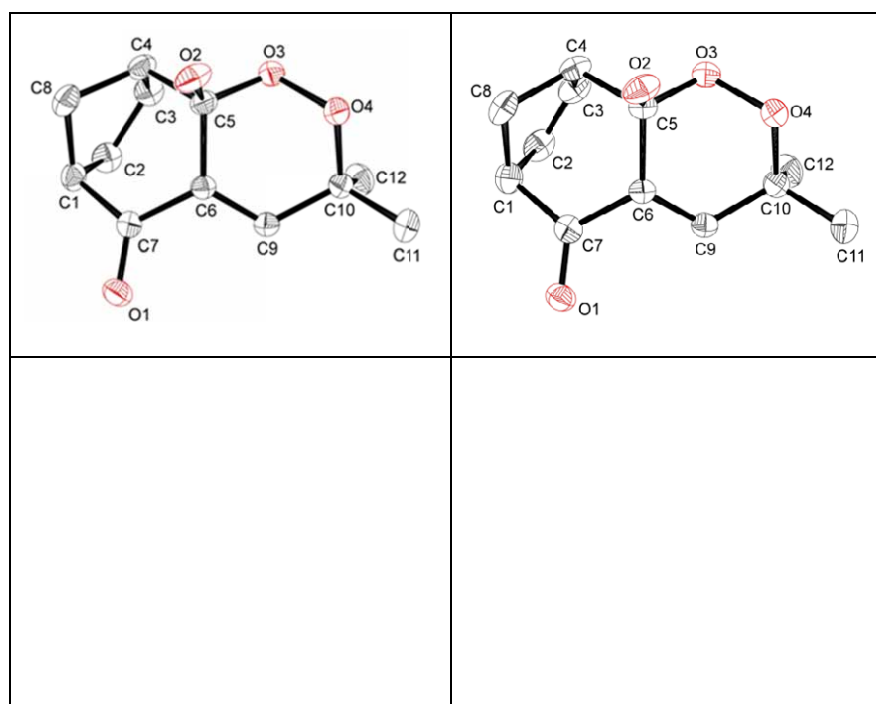


Figure 1 : ORTEP molecular view of endoperoxides **11** and **14** in the solid state (thermal ellipsoids at 50% probability; hydrogen atoms are omitted for clarity).

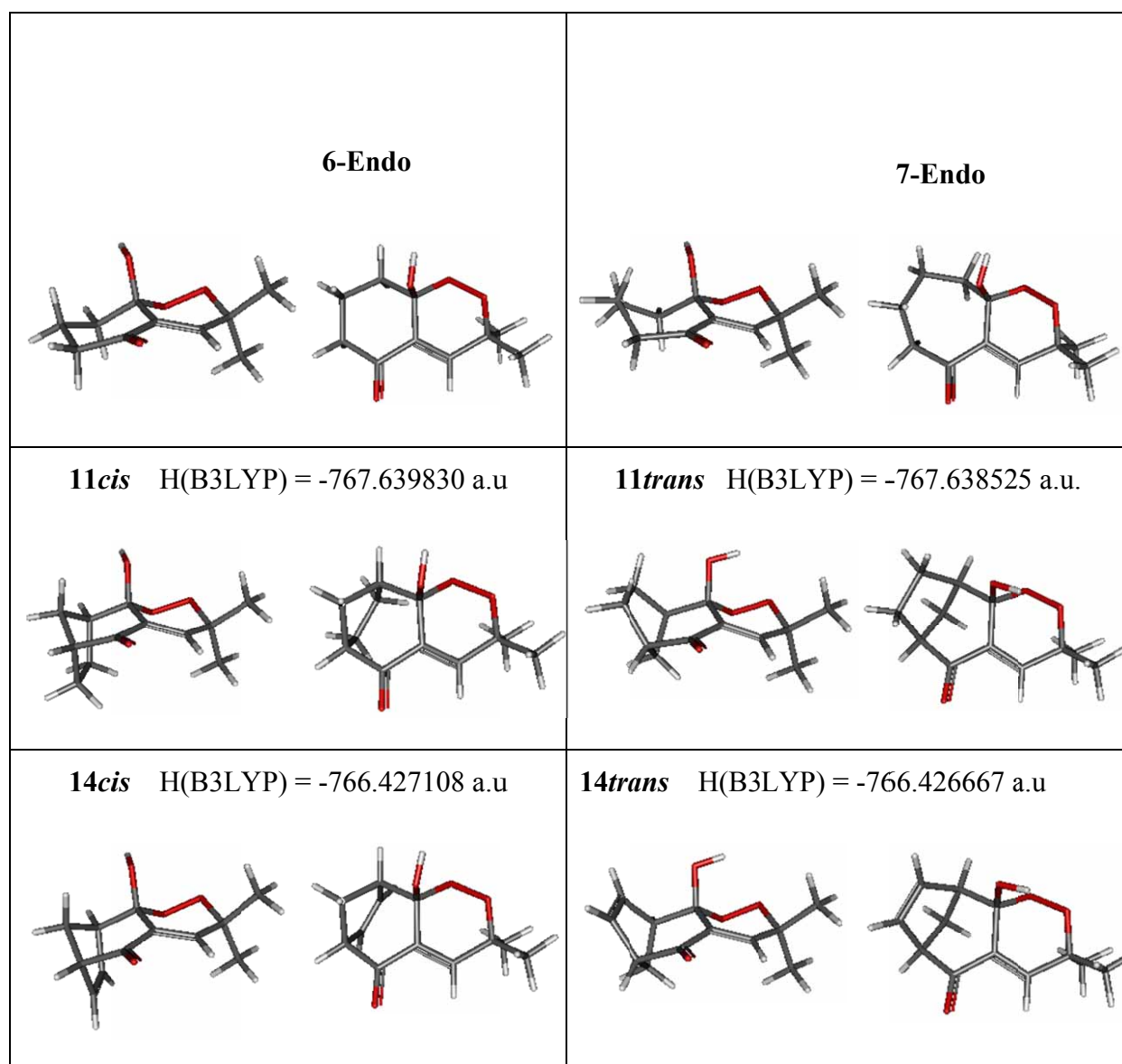
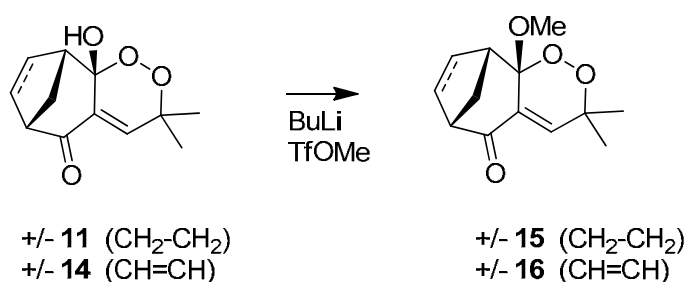


Figure 2: Optimized geometries and enthalpies of **6-Endo**, **7-Endo**, **11cis** and **11trans**, **14cis** and **14trans** at the B3LYP 6-311+G(d,p) level of theory

Previous works have shown the crucial role of the methylation of the peroxyhemiketal position^{9,11} so, methylation of **11** and **14** was planned.

First attempts with K_2CO_3 , Li_2CO_3 in DMF, using MeI or $(MeO)_2SO_2$ as methylating agent at room temperature did not work, only starting material was totally recovered. When Cs_2CO_3 was used as base, whatever the methylating agent used (MeI or $(MeO)_2SO_2$), degradation occurred. Finally, butyl lithium (1 eq.) at $-78^\circ C$, in THF, followed by addition of TfOMe afforded endoperoxides **15** and **16** in about 50% yield, 50% of the starting material was

recovered. Increasing equivalent of BuLi (2 eq) due 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.

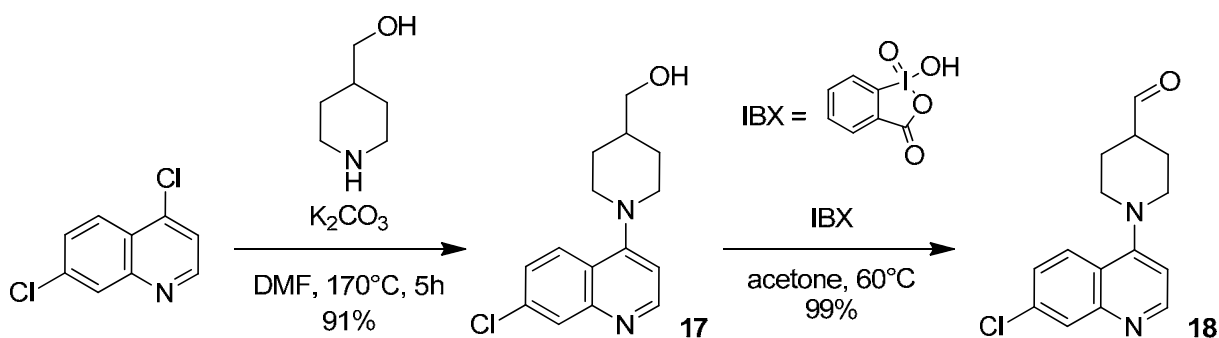


Scheme 5 : Methylation of endoperoxides **11** and **14**

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 this approach can increase antiparasitic 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 enone precursor of autoxidation. A piperidine linker was chosen to avoid the formation of diastereoisomers after autoxidation.

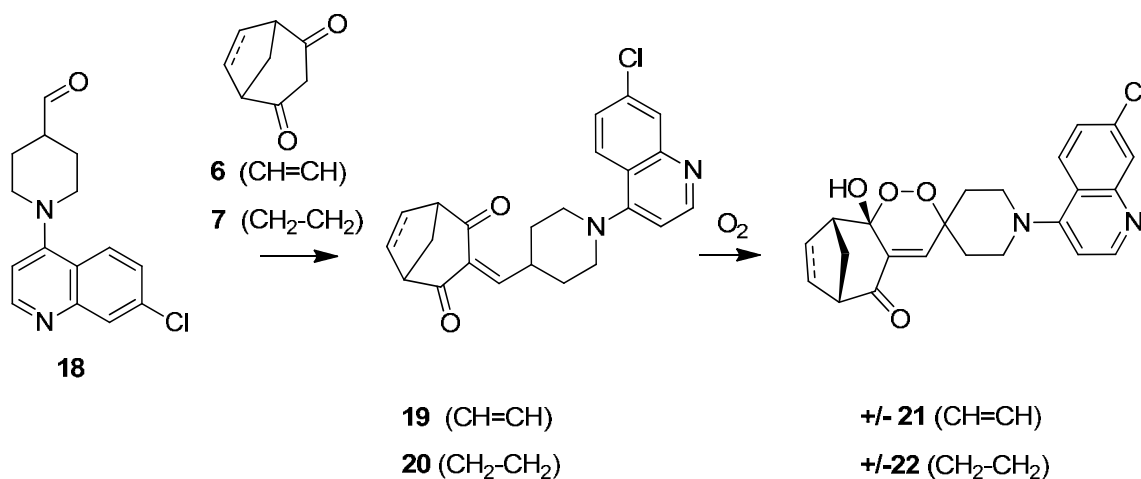
Starting from 4,7-dichloroquinoline, alcohol **17** was first obtained after substitution of the chloride by 4-piperidinyl-methanol. Oxidation of **17** by 2-iodoxybenzoic acid (IBX) in refluxing acetone led to aldehyde **18** quantitatively.



Scheme 6: Preparation of aldehyde **18**

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, then aqueous acidic treatment allowing the formation of precursors **19** and **20** in 99% and 67% yields respectively in the three-step reaction.

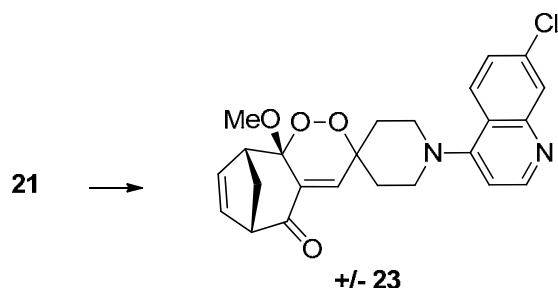
^1H NMR spectra of these precursors indicated in both cases that they were present only in the enone form. As previously, autoxidation occurred very slowly on both structures and endoperoxides **21** and **22** were obtained in respectively 19% and 34% yield, after 33 and 15 days in ethyl acetate under O_2 (1bar). 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 ^1H NMR spectroscopy. Incidentally we realize that depositing 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, so allowing formation of endoperoxide **22** with a great increase of the global rate: 3 hours over 2 weeks. The same procedure was tried for 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 ^1H NMR spectra present the same pattern as for **11** and **14**.



Scheme 7: Synthesis of hybrid endoperoxides +/- **21** and +/- **22**

Methylation in this series was particularly risky and delicate as several positions could be methylated. After several trials, 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: Methylation of endoperoxide **21**: BuLi/THF, -78 °C, then TfOMe, 16%

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 Desjardins et al. using [³H] hypoxanthine incorporation to assess parasite growth. Parasitic viability was expressed as IC₅₀, 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 IC₅₀ below 1 μM, both on 3D7 and W2 parasite strains.

Table 1: IC₅₀ 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

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 to 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 IC₅₀ between 100 to 250 nM against both the chloroquine-susceptible and/or -resistant strains of *Plasmodium falciparum*. It seems that 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 radical 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 inert atmosphere. The suspension was stirred at room temperature for 1h. 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; Rf = 0.65 (petroleum ether); ¹H NMR (300 MHz, CDCl₃) δ 2.23 (1H, *td*, CH-CH₂-CH), 2.49 (1H, *d*, CH-CH₂-CH), 3.17-3.20 (1H, *m*, CCl=CCl-CH), 3.76-3.79 (1H, *m*, CCl₂-CH), 6.19 (1H, *dd*, CCl-CH-CH=CH), 6.67 (1H, *dd*, CH=CH-CH-CCl₂); ¹³C NMR (75.47 MHz, CDCl₃) δ 42.2 (CH₂, CH-CH₂-CH), 49.1 (CH, CCl-CH-CH₂), 58.4 (CH, CCl₂-CH-CH₂) 88.9 (C, CCl₂), 127.7 (C, CCl₂-CCl=CCl), 132.7 (CH, CCl-CH-CH=CH), 140.6 (C, CH-CCl=CCl), 141.8 (CH, CCl₂-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 (2M), (3.0 mmol, 30 eq.) was added. The reaction was stirred at 90°C for 18h. The reaction was extracted with 10 ml of EtOAc. The aqueous layer was adjusted to pH 1 with HCl (6M) aqueous solution and extracted with 3x10

mL of EtOAc. Combined organic layers were washed with 15 mL of brine, dried over MgSO₄ and concentrated to give 30 mg of a crude brownish solid (59 % yield).

mp = 137°C; Rf = 0.1 (petroleum ether/AcOEt; 50/50); ¹H NMR (300 MHz, CDCl₃) (**5a** and **5b** mixture) δ 2.33-2.50 (2H, *m*, CH-CH₂-CH), 2.59-2.76 (2H, *m*, CH-CH₂-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); ¹H NMR (300 MHz, MeOD) (**5b** major product) δ 2.38-2.44 (1H, *m*, AA'MX system, CH-CH₂-CH), 2.55-2.57 (1H, *m*, AA'MX system, CH-CH₂-CH), 3.43-3.45 (2H, *m*, AMXX' systems, CH-CH₂-CH), 6.54 (2H, *s*, CH-CH=CH-CH); ¹³C NMR (75.47 MHz, MeOD) (**5b** major product) δ 50.9 (CH₂, CH-CH₂-CH), 53.2 (CH, CH-CH₂-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 (6M) to pH 2 and separated. The aqueous layer was extracted with 3x60 mL of EtOAc. Combined organic layers were washed with 2x20 mL of brine, dried over MgSO₄ and concentrated to give 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 yellow oil (62% yield). Rf = 0.3-0.4 (petroleum ether/AcOEt; 80/20); ¹H NMR (300 MHz, CDCl₃) δ 2.44-2.48 (1H, *m*, CH-CH₂-CH), 2.52-2.60 (1H, *m*, CH-CH₂-CH), 3.20 (1H, *d*, CO-CH₂-CO), 3.48-3.50 (2H, *m*, CH-CH₂-CH), 3.51 (1H, *d*, CO-CH₂-CO), 6.19-6.23 (2H, *m*, CH=CH); ¹³C NMR (75.47 MHz, CDCl₃) δ 37.0 (CH₂, CH-CH₂-CH), 50.4 (CH₂, CO-CH₂-CO), 55.3 (CH, CH-CH₂-CH), 134.9 (CH, CH=CH), 201.6 (C, CO-CH₂-CO); IR (KBr blades) ν: 3512, 1708, 1638, 1587, 1244, 1223 cm⁻¹; HR-MS (DCI/CH₄): calculated for C₈H₉O₂⁺ 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 then the mixture was bubbled with H₂ for 5 min. The reaction was stirred under H₂ at atmospheric pressure at room temperature (23 °C) for 1h. 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 expected product (99%).

mp = 122-123°C; Rf = 0.1 (petroleum ether/EtOAc; 50/50); ¹H NMR (300 MHz, CDCl₃) (**7a** major product) δ 1.87-1.98 (4H, *m*, CH-CH₂-CH₂-CH), 2.11-2.16 (2H, *m*, CH-CH₂-CH), 3.01-3.05 (2H, *m*, CH-CH₂-CH), 3.15 (1H, *dd*, CO-CH₂-CO), 3.31 (1H, *d*, CO-CH₂-CO); ¹H NMR (300 MHz, CD₃OD) (**7b** major product) δ 1.58-1.70 (3H, *m*, CH-CH₂-CH, CH-CH₂-CH₂-CH), 2.00 (1H, *d*, *J* = 11.5 Hz, CH-CH₂-CH), 2.06-2.18 (2H, *m*, CH-CH₂-CH₂-CH), 2.79-2.83 (2H, *m*, CH-CH₂-CH), 4.90 (1H, *s*, CO-CH=COH); ¹³C NMR (75.47 MHz, CDCl₃) (**7a** and **7b** mixture) δ 26.1 (CH₂, A, CH-CH₂-CH₂-CH), 27.9 (CH₂, B, CH-CH₂-CH₂-CH), 31.3 (CH₂, A, CH-CH₂-CH), 38.7 (CH₂, B, CH-CH₂-CH), 45.6 (CH, B, CH-CH₂-CH), 49.6 (CH, A, CH-CH₂-CH), 51.4 (CH₂, A, CO-CH₂-CO), 99.7 (CH, B, CO-CH=COH), 197.8 (C, B, CO-CH=CO), 207.2 (C, A, CO-CH₂-CO); ¹³C NMR (75.47 MHz, CD₃OD) (**7b** major product) δ 28.8 (CH₂, CH-CH₂-CH₂-CH), 39.5 (CH₂, CH-CH₂-CH), 46.9 (CH, CH-CH₂-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/CH₄): calculated for C₈H₁₁O₂⁺ 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 H₂. The reaction was heated to 55 °C under H₂ at atmospheric pressure for 6h. 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 (6M) and extracted with 3x15 mL of EtOAc. The combined organic layers were washed with 15 mL of brine, dried over MgSO₄ 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); ¹H NMR (300 MHz, CDCl₃) δ 1.60 (1H, *td*, CH-CH₂-CH), 1.73-1.80 (2H, *m*, CH-CH₂-CH₂-CH), 2.08-2.12 (3H, *m*, CH-CH₂-CH₂-CH, CH-CH₂-CH), 3.11-3.15 (2H, *m*, CH-CH₂-CH); ¹³C NMR (75.47 MHz, CDCl₃) δ 27.5 (CH₂, CH-CH₂-CH₂-CH), 38.0 (CH₂, CH-CH₂-CH), 45.8 (CH, CH-CH₂-CH), 106.1 (C, CCl), 186.5 (C, CO-CCl=COH); IR (KBr pellet) ν : 1638, 1567 cm^{-1} ; HR-MS (DCI/CH₄): calculated for C₈H₁₁O₂Cl⁺ 173.0369, found 173.0368

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

R_f = 0,5 (DCM/MeOH; 90/10); ¹H NMR (300 MHz, CDCl₃) δ 1.60 (1H, *d*, CHOH-CH-CH₂-CH₂), 1.64-1.73 (1H, *m*, CO-CH-CH₂-CH₂), 1.76 (1H, *t*, CH-CH₂-CH), 1.78-1.98 (2H, *m*, CH-CH₂-CH₂-CH), 2.04-2.13 (1H, *m*, CH-CH₂-CH), 2.25 (1H, *dd*, CO-CH₂-CHOH), 2.41-2.46 (1H, *m*, CHOH-CH), 2.58 (1H, *dd*, CO-CH₂-CHOH), 2.66 (1H, *t*, CO-CH), 2.81 (1H, br. *s*, CHOH), 4.04 (1H, *ddd*, CHOH); ¹³C NMR (75.47 MHz, CDCl₃) δ 21.8 (CH₂, CH-CH₂-CH), 27.9 (CH₂, CO-CH-CH₂-CH₂), 32.9 (CH₂, CHOH-CH-CH₂-CH₂), 41.7 (CH, CHOH-CH), 44.4 (CH₂, CHOH-CH₂-CO), 49.3 (CH, CO-CH), 71.8 (CH, CHOH), 211.9 (C, CO); IR (KBr blades) ν : 3424 (br.), 1712, 1065 cm^{-1} ; HR-MS (DCI/CH₄): calculated for C₈H₁₂O₂⁺ 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 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 NH₄Cl in 1N 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 MgSO₄ 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 O₂ (1 bar). The reaction was followed by ¹H NMR spectroscopy analysis until consumption of the enol and enone form 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 (0.1M). The solution was irradiated during 15 minutes then analyzed by ^1H NMR. The peroxide **11** was obtained after 15 minutes of irradiation then 3h under O_2 atmosphere. The peroxide **13** was obtained after 8 cycles of irradiation (15 minutes) followed by 45 minutes under O_2 atmosphere.

(+/-)-(6R,9S,9aS)-9a-hydroxy-3,3-dimethyl-3,6,7,8,9,9a-hexahydro-5H-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; Rf = 0.45 (petroleum ether/EtOAc, 80/20); ^1H 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*, $\text{CH}_2\text{-CH}_2$), 1.70-1.80 (3H, *m*, $\text{CH}_2\text{-CH}_2$, CH- $\text{CH}_2\text{-CH}$), 1.83-1.95 (1H, *m*, $\text{CH}_2\text{-CH}_2$), 2.45 (1H, *d*, $J = 12.6$ Hz, CH- $\text{CH}_2\text{-CH}$), 2.43-2.58 (1H, *m*, COH- CH), 2.82-2.86 (1H, *m*, CO- CH), 6.46 (1H, *s*, C= CH-C); ^{13}C NMR (75.47 MHz, CDCl_3) δ 23.1 (CH_2 , $\text{CH}_2\text{-CH}_2$), 23.5 (CH_3 , C- CH_3), 24.5 (CH_3 , C- CH_3), 28.6 (CH_2 , $\text{CH}_2\text{-CH}_2$), 31.8 (CH_2 , C- $\text{CH}_2\text{-C}$), 42.0 (CH, COH- CH), 50.2 (CH, CO- CH), 78.9 (C, (CH_3) $_2\text{C-O}$), 100.2 (C, CH-COH), 135.3 (C, C= CH-C), 140.1 (CH, C= CH-C), 201.9 (C, CH-CO-C); IR (KBr pellet) ν : 3337 (br.), 1690, 1642, 1277, 1128, 1088, 1036 cm^{-1} ; MS (DCI/ NH_3^+): 207 (100, $[\text{MH-H}_2\text{O}]^+$), 224 (41, $[\text{M}]^+$), 242 (34, $[\text{MNH}_4]^+$); HR-MS (DCI/ CH_4): calculated for $\text{C}_{12}\text{H}_{17}\text{O}_4^+$ 225.1127, found 225.1122

(+/-)-3a-hydroxy-2,2-dimethylhexahydro-4,7-methanocyclohepta[b]oxireno[2,3-c]furan-8(3aH)-one (12)

White solid, mp= decomposition; Rf= 0.2 (petroleum ether/EtOAc, 80/20); ^1H 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- $\text{CH-CH}_2\text{-CH}_2$), 1.82-1.88 (1H, *m*, COH- $\text{CH-CH}_2\text{-CH}_2$), 1.93 (1H, *td*, CH- $\text{CH}_2\text{-CH}$), 2.05-2.21 (2H, *m*, CH- $\text{CH}_2\text{-CH}_2\text{-CH}$), 2.38 (1H, *d*, CH- $\text{CH}_2\text{-CH}$), 2.62 (1H, *dd*, COH- CH-CH_2), 3.00 (1H, *dd*, CO- CH-CH_2), 3.79 (1H, *s*, CH-O-C); ^{13}C NMR (125.77 MHz, CDCl_3) δ 24.4 (CH_2 , CH- $\text{CH}_2\text{-CH}_2\text{-CH}$), 25.0 (CH_3 , C- CH_3), 25.5 (CH_3 , C- CH_3), 26.7 (CH_2 , CH- $\text{CH}_2\text{-CH}_2\text{-CH}$), 34.2 (CH_2 , CH- $\text{CH}_2\text{-CH}$), 44.8 (CH, CH-COH), 49.9 (CH, CH-CO), 70.3 (C, CO-C-COH), 74.9 (CH, C(CH_3) $_2\text{-CH-O-C}$), 81.2 (C, O-C(CH_3) $_2\text{-CHO}$), 106.9 (C, COH), 203.3 (C, CO); IR (KBr pellet) ν : 3433, 1722, 1295, 1126, 1116, 1089, 1062, 1023 cm^{-1} ; LR-MS (DCI/ NH_3): 207.0 (100, $[\text{M-OH}]^+$), 224.0 (30, $[\text{M}]^+$), 242.0 (2%, $[\text{MNH}_4]^+$); HR-MS (DCI/ CH_4): calculated for $\text{C}_{12}\text{H}_{17}\text{O}_4^+$ 225.1127, found 225.1132

(+/-)-(6S,9R,9aS)-9a-hydroxy-3,3-dimethyl-3,6,9,9a-tetrahydro-5H-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; Rf = 0.2 (petroleum ether/EtOAc, 80/20); ^1H 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- $\text{CH}_2\text{-CH}$), 2.66 (1H, *d*, $J = 12$ Hz, CH- $\text{CH}_2\text{-CH}$), 3.01 (1H, *dd*, $J = 5$ Hz, $J = 3$ Hz, COH- CH), 3.21 (1H, *dd*, $J = 5$ Hz, $J = 3$ Hz, CO- CH), 6.10 (1H, *dd*, $J = 5.7$ Hz, $J = 3$ Hz, CH- CH=CH-CH) 6.16 (1H, *dd*, $J = 5.7$ Hz, $J = 3$ Hz, CH- CH=CH-CH), 6.43 (1H, *s*, C= CH-C); ^{13}C NMR (75.47 MHz, CDCl_3) δ 23.6 (CH_3 , C- CH_3), 24.2 (CH_3 , C- CH_3), 37.7 (CH_2 , CH- $\text{CH}_2\text{-CH}$), 46.6 (CH, COH- CH), 55.0 (CH, CO- CH), 79.5 (C, (CH_3) $_2\text{C-O}$), 98.9 (C, CH-COH), 135.5 (CH, CH- CH=CH-CH), 136.2 (CH, CH- CH=CH-CH), 136.3 (C, C= CH-C), 140.5 (CH, C= CH-C), 197.1 (C, CH-CO-C); IR (KBr pellet) ν : 3363 (br.), 1694, 1639, 1263, 1110, 1085, 1052 cm^{-1} ; HR-MS (DCI/ CH_4): calculated for $\text{C}_{12}\text{H}_{15}\text{O}_4^+$ 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.

(+/-)-(6R,9S,9aS)-9a-methoxy-3,3-dimethyl-3,6,7,8,9,9a-hexahydro-5H-6,9-methanocyclohepta[c][1,2]dioxin-5-one (15)

(-70°C , 4h, 48% yield); Colorless oil; $R_f = 0.45$ (petroleum ether/EtOAc, 85/15); ^1H 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*, $\text{CH}_2\text{-CH}_2$, $\text{CH-CH}_2\text{-CH}$), 1.78-1.95 (2H, *m*, $\text{CH}_2\text{-CH}_2$), 2.29 (1H, *d*, $\text{CH-CH}_2\text{-CH}$), 2.70 (1H, *t*, COH-CH), 2.85 (1H, *t*, CO-CH), 3.38 (3H, *s*, OCH_3), 6.51 (1H, *s*, C=CH-C); ^{13}C NMR (75.47 MHz, CDCl_3) δ 23.4 (CH_3 , C- CH_3), 23.5 (CH_2 , C- $\text{CH}_2\text{-C}$), 24.8 (CH_3 , C- CH_3), 29.1 (CH_2 , $\text{CH}_2\text{-CH}_2$), 31.4 (CH_2 , $\text{CH}_2\text{-CH}_2$), 38.7 (CH , $\text{COCH}_3\text{-CH}$), 50.3 (CH , CO-CH), 50.4 (CH_3 , OCH_3), 78.2 (C, $(\text{CH}_3)_2\text{C-O}$), 102.9 (C, CH-COH), 133.5 (C, C=CH-C), 140.6 (CH , C=CH-C), 201.6 (C, CH-CO-C); IR (KBr blades) ν : 1701, 1649, 1270, 1126, 1091, 1074, 1003 cm^{-1} ; HR-MS (DCI/ CH_4): calculated for $\text{C}_{13}\text{H}_{19}\text{O}_4^+$ 239.1283, found 239.1287

(+/-)-(6S,9R,9aS)-9a-methoxy-3,3-dimethyl-3,6,9,9a-tetrahydro-5H-6,9-methanocyclohepta[c][1,2]dioxin-5-one (16)

(-70°C , 2.5h, 50% yield); Colorless oil; $R_f = 0.4$ (petroleum ether/EtOAc, 90/10); ^1H 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, $\text{CH-CH}_2\text{-CH}$), 2.49 (1H, *d*, $\text{CH-CH}_2\text{-CH}$), 3.15-3.20 (2H, *m*, $2\times\text{CH-CH}_2\text{-CH}$), 3.42 (3H, *s*, O- CH_3), 6.07-6.12 (2H, *m*, ABX systems, CH-CH=CH-CH), 6.43 (1H, *s*, C=CH-C); ^{13}C NMR (75.47 MHz, CDCl_3) δ 23.4 (CH_3 , C- CH_3), 24.6 (CH_3 , C- CH_3), 37.1 (CH_2 , $\text{CH-CH}_2\text{-CH}$), 43.4 (CH , COH-CH), 50.5 (CH_3 , OCH_3), 55.0 (CH , CO-CH), 78.9 (C, $(\text{CH}_3)_2\text{C-O}$), 101.5 (C, CH-COH), 133.9 (C, C=CH-C), 135.8 (CH , CH-CH=CH-CH), 136.2 (CH , CH-CH=CH-CH), 141.1 (CH , C=CH-C), 197.0 (C, CH-CO-C); IR (KBr blades) ν : 1704, 1648, 1258, 1106, 1085, 1057 cm^{-1} ; HRMS (DCI/ CH_4): calculated for $\text{C}_{13}\text{H}_{17}\text{O}_4^+$ 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 5h. 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); ^1H NMR (300 MHz, CDCl_3) δ 1.90-2.03 (2H, *m*, $\text{CH}_2\text{-CH}_2\text{-CH-CH}_2\text{-CH}_2$), 2.10-2.19 (2H, *m*, $\text{CH}_2\text{-CH}_2\text{-CH-CH}_2\text{-CH}_2$), 2.48-2.52 (1H, *m*, $\text{CH}_2\text{-CH}_2\text{-CH-CH}_2\text{-CH}_2$), 2.91-2.99 (2H, *m*, $\text{CH}_2\text{-CH}_2\text{-CH-CH}_2\text{-CH}_2$), 3.50 (2H, *td*, $\text{CH}_2\text{-CH}_2\text{-CH-CH}_2\text{-CH}_2$), 6.81 (1H, *d*, N=CH-CH), 7.41 (1H, *dd*, CCl=CH-CH), 7.87 (1H, CCl=CH-CH), 8.02 (1H, *d*, CH-CCl), 8.68 (1H, *d*, N=CH-CH), 9.76 (1H, *d*, CHO); ^{13}C NMR (75.47 MHz, CDCl_3) δ 25.4 (CH_2 , $\text{CH}_2\text{-CH}_2\text{-CH-CH}_2\text{-CH}_2$), 25.5 (CH_2 , $\text{CH}_2\text{-CH}_2\text{-CH-CH}_2\text{-CH}_2$), 47.6 (CH , $\text{CH}_2\text{-CH}_2\text{-CH-CH}_2\text{-CH}_2$), 51.7 (CH_2 , $\text{CH}_2\text{-CH}_2\text{-CH-CH}_2\text{-CH}_2$), 109.1 (CH , N=CH-CH=C), 122.0 (C, C- C=CH), 125.0 (CH , CCl=CH-CH), 126.3 (CH , CCl=CH-CH), 128.7

(CH, CCl-CH=C), 134.9 (C, CCl), 150.0 (C, CCl-CH=C), 151.8 (CH, N=CH-CH-C), 157.3 (C, N=CH-CH-C), 202.9 (CH, CHO); IR (ATR) ν : 3062, 2945, 2920, 2816, 1724, 1607, 1574, 1425 and 869 cm^{-1} ; LR-MS (DCI/NH₃): 275 (100, [MH]⁺), 277 (34%, [MH+2]⁺); HR-MS (ESI): calculated for C₁₅H₁₆N₂OCl⁺, 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); ¹H NMR (300 MHz, CDCl₃) δ 1.84-2.00 (2H, *m*, C-CH₂-CH₂-N), 2.11-2.21 (2H, *m*, C-CH₂-CH₂-N), 2.42-2.49 (1H, *m*, CH-CH₂-CH), 2.71 (1H, *d*, CH-CH₂-CH), 3.04-3.07 (1H, *m*, CH-CH₂-CH), 3.13 (1H, *dt*, C-CH₂-CH₂-N), 3.23-3.28 (2H, *m*, CH-CH₂-CH, C-CH₂-CH₂-N), 3.30-3.38 (2H, *m*, C-CH₂-CH₂-N), 6.12-6.19 (2H, *m*, CH=CH), 6.48 (1H, *s*, C=CH-CO), 6.85 (1H, *d*, N-CH=CH-C), 7.42 (1H, *dd*, C-CH=CH-CCl), 7.86 (1H, *d*, C-CH=CH-CCl), 8.06 (1H, *d*, C-CH=CCl), 8.71 (1H, *d*, N-CH=CH-C); ¹³C NMR (75.47 MHz, CDCl₃) δ 31.4 (CH₂, C(CH₂)₂), 33.1 (CH₂, C(CH₂)₂), 37.8 (CH₂, CH-CH₂-CH), 46.8 (CH, CH-CH₂-CH), 47.5 (CH₂, N(CH₂)₂), 48.0 (CH₂, N(CH₂)₂), 55.1 (CH, CH-CH₂-CH), 78.4 (C, CH-C-(CH₂)₂), 99.4 (C, COH), 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), 135.5 (CH, CH=CH), 136.2 (CH, CH=CH), 138.0 (C, COH-C=CH), 138.4 (CH, COH-C=CH), 150.0 (C, N-C-CH), 151.9 (CH, C=CH-CH=N), 157.3 (C, CH=C-C-CH), 196.6 (C, CO); IR (ATR) ν : 3060, 1700, 1572 cm^{-1} ; MS (CI/NH₃): 424 (5, [MH]⁺), 382 (5), 260 (100), 217 (21), 190 (23), 155 (30%); HR-MS (DCI/CH₄): calculated for C₂₃H₂₂N₂O₄Cl⁺, 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); ¹H NMR (300 MHz, CDCl₃) δ 1.62-1.71 (1H, *m*, CH-CH₂-CH₂-CH), 1.74-1.88 (3H, *m*, CH-CH₂-CH, CH-CH₂-CH₂-CH), 1.89-2.29 (5H, *m*, C-CH₂-CH₂-N, CH-CH₂-CH₂-CH), 2.54 (1H, *d*, CH-CH₂-CH), 2.61-2.65 (1H, *m*, CH-CH₂-CH), 2.90-2.94 (1H, *m*, CH-CH₂-CH), 3.27-3.43 (3H, *m*, C-CH₂-CH₂-N), 6.52 (1H, *s*, C=CH-CO), 6.85 (1H, *d*, N-CH=CH-C), 7.41 (1H, *dd*, C-CH=CH-CCl), 7.86 (1H, *d*, C-CH=CH-CCl), 8.07 (1H, *s*, C-CH=CCl), 8.70 (1H, *br. s*, N-CH=CH-C); ¹³C NMR (75.47 MHz, CDCl₃) δ 23.3 (CH₂, CH₂-CH₂), 28.6 (CH₂, CH-CH₂), 31.7 (CH₂, C(CH₂)₂), 32.0 (CH₂, CH-CH₂-CH), 33.0 (CH₂, C(CH₂)₂), 42.3 (CH, CH-CH₂-CH), 47.6 (CH₂, N(CH₂)₂), 48.0 (CH₂, N(CH₂)₂), 50.3 (CH, CH-CH₂-CH), 77.7 (C, CH-C-(CH₂)₂), 100.8 (C, COH), 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), 128.7 (CH, C-CH=CCl), 135.3 (C, CCl), 137.2 (C, COH-C=CH), 137.9 (CH, COH-C=CH), 149.8 (C, N-C-CH), 151.8 (CH, C=CH-CH=N), 157.4 (C, CH=C-C-CH), 201.4 (C, CO); IR (ATR) ν : *br.* 3360, 1697, 1574, 1200, 1102, 1088 cm^{-1} ; MS (CI/NH₃): 427 (5, [MH]⁺), 429 (1, [MH+2]⁺), 261 (100, C₁₄H₁₄ClN₂O⁺), 263 (32%, [C₁₄H₁₄ClN₂O+2]⁺); HR-MS (DCI/CH₄): calculated for C₂₃H₂₄N₂O₄Cl⁺ 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, 2.5h, 16%); ¹H NMR (300 MHz, CDCl₃) δ 1.92-1.99 (2H, *m*, C-(CH₂-CH₂)₂-N), 2.07-2.21 (2H, *m*, C-CH₂-CH₂-N), 2.35-2.43 (1H, *m*, CH-CH₂-CH), 2.54 (1H, *d*, CH-CH₂-CH), 3.10-3.18 (1H, *m*, C-(CH₂-CH₂)₂-N), 3.19-3.28 (3H, *m*, CH-CH₂-CH, C-(CH₂-CH₂)₂-N), 3.31-3.38 (2H, *m*, C-(CH₂-CH₂)₂-N), 3.48 (3H, *s*, OCH₃), 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); ¹³C NMR (75.47 MHz, CDCl₃) δ 31.7 (CH₂, C(CH₂)₂), 32.9 (CH₂, C(CH₂)₂), 37.2 (CH₂, CH-CH₂-CH), 43.3 (CH, CH-CH₂-CH), 47.7 (CH₂, N(CH₂)₂), 48.1 (CH₂, N(CH₂)₂), 50.5 (CH₃, OCH₃), 55.1 (CH, CH-CH₂-CH), 77.7 (C, CH-C-(CH₂)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/NH₃) : 438 (42, [MH]⁺), 372 (46), 260 (100), 217 (52), 191 (66), 155 (66%); HR-MS (DCI/CH₄): calculated for C₂₄H₂₄N₂O₄Cl⁺, 439.1425, found 439.1419

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