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Synthesis and Antimalarial Activity In Vitro of Potential Metabolites of Ferrochloroquine and Related Compounds

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Abstract—In man, the two major metabolites of the antimalarial drug chloroquine (CQ) are monodesethylchloroquine (DECQ) and didesethylchloroquine (di-DECQ). By analogy with CQ, the synthesis and the in vitro tests of some amino derivatives of ferrochloroquine (FQ), a ferrocenic analogue of CQ which are presumed to be the oxidative metabolites of FQ, are reported. Desmethylferrochloroquine **1a** and didesmethylferrochloroquine **2** would be more potent against schizontocides than CQ in vitro against two strains (HB3 and Dd2) of *Plasmodium falciparum*. Other secondary amino derivatives have been prepared and proved to be active as antimalarial agents in vitro, too. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Introduction

Approximately 300 million people world-wide are affected by malaria and between 2 and 2.5 million people die from it every year.[1–3] This disease is caused by an intracellular parasite of the genus *Plasmodium*. *Plasmodium falciparum* is responsible for the life threatening form of the disease. The situation has become even more complex over the last few years with the increase in resistance due to the drugs (chloroquine, mefloquine, pyrimethamine etc.) normally used against *P. falciparum*.[1–3]

In previous patents and papers we have described the synthesis and antimalarial activity of a ferrocene–chloroquine analogue (Chart 1), i.e. ferrochloroquine **1** (FQ: 7-chloro-4[2-(*N*′,*N*′-dimethylaminomethyl)-*N*-ferrocenylmethylamino]quinoline).[4–7] In vitro, FQ proved to be more schizontocide than CQ against chloroquino-resistant strains of *P. falciparum* and showed high activity in vivo on mice infected with *P. berghei* N and *P. yoelii* NS.[6,7] It is imperative to understand the mechanisms that the parasite may use to evade the toxic effect of the drug. Unfortunately, virtually nothing is known about the metabolism of ferrochloroquine (**1**).

Several metabolites of chloroquine (CQ) have been isolated and studied.[8,9] Chloroquine is metabolized in the liver, mostly by oxidation via the cytochrome P-450 enzyme system. A side-chain de-ethylation (Chart 2), leading first to the monodesethylchloroquine (DECQ), and to the didesethylchloroquine (di-DECQ) which is a primary amine, represents the main metabolization way.[10–12] Literature data showed that the in vitro activity of DECQ was lower than that of chloroquine against chloroquine-resistant, but not sensitive, strains.[8,9,13,14] In vivo, both metabolites exhibited a quite similar antimalarial activity against *P. berghei berghei* but remained less active than CQ.[13]

Considering this information and assuming that ferrochloroquine may have a similar metabolic behavior, we hypothesized that FQ leads to the corresponding demethyl metabolites: **1a** and **2**.

We have also synthesized a series of compounds bearing various secondary amino groups (Chart 3) instead of the *N*,*N*-dimethylamino residue, in order to examine the

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Key words: Malaria; ferrocene; chloroquine; metabolites; synthesis; in vitro activity; *Plasmodium falciparum*.

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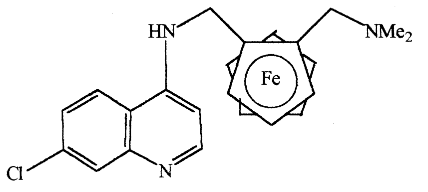

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Chart 1. Ferrochloroquine, i.e. 7-chloro-4[2-(*N*′,*N*′-dimethylaminomethyl)-*N*-ferrocenylmethylamino]quinoline, FQ (**1**).

effect of the substitution pattern of **1a**, **1b** or **1c** on the antimalarial activity.

Results and Discussion

Chemistry

Ferrochloroquine was obtained according to previously described synthetic methods.[4–6] Briefly, commercially available *N*,*N*-dimethyl(ferrocenylmethyl)amine was metalated with *t*-butyllithium in anhydrous diethylether under nitrogen atmosphere. The lithio derivative was condensed with *N*,*N*-dimethylformamide to give the resulting 2-(*N*,*N*-dimethylaminomethyl)ferrocene-carboxaldehyde in 92% yield. The latter was converted to the corresponding [2-(*N*,*N*-dimethylaminomethyl)ferrocenyl]methylamine in 93% yield via the 2-(*N*,*N*-dimethylamino-methyl)ferrocenecarboxaldehyde-oxime. Condensation of the amine with 4,7-dichloroquinoline in *N*-methylpyrrolidin-2-one produced ferrochloroquine in 60% yield.

As outlined in Scheme 1, quaternization of the ferrochloroquine with methyl iodide followed by reaction with methylamine, ethylamine or *t*-butylamine, in a sealed tube, in acetonitrile gave the corresponding secondary amino derivatives **1a**, **1b** and **1c**, respectively.[15]

A similar reaction of the methiodide derivative **1d** from ferrochloroquine with 2-aminopropanol under reflux in acetonitrile gave amino-alcohols **1e**.[16] Oxidative cleavage of **1e** with periodic acid in methanol containing 10 equiv of methylamine followed by aminolysis liberated the amine in 70% yield, as illustrated in Scheme 2.[17]

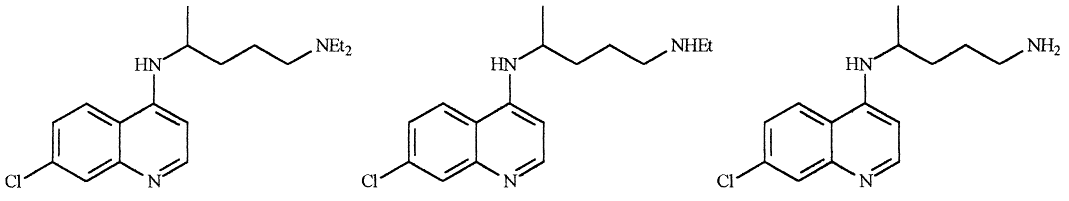
Biological activities

The assessments of in vitro antimalarial activity were proceeding against a chloroquine-sensitive (HB3, Honduras) and a chloroquine-resistant (Dd2, Indochina) strains of *P. falciparum*. The screening procedure is briefly described in Experimental.

For several years our laboratory has been involved in an investigation of the antimalarial properties of transition-metal organometallic compounds, particularly π-arene complexes such as ferrocenic derivatives.

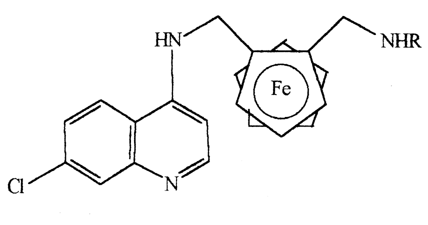
The target compound **1** differs from chloroquine in the nature of the side-chain attached to the amino-4-quinoline moiety. Instead of the *N*,*N*-diethylaminoisopentyl side-chain of CQ, compound **1** bears a 2-(*N*′,*N*′-dimethylaminomethyl)ferrocenylmethyl side-chain. This organometallic derivative has an elongated cylindrical shape rather than the carbon chain of CQ and might offer different interactions with the drug target and/or receptor.[18]

The selected compounds differed from **1** only in the nature of the amino group attached to the terminal



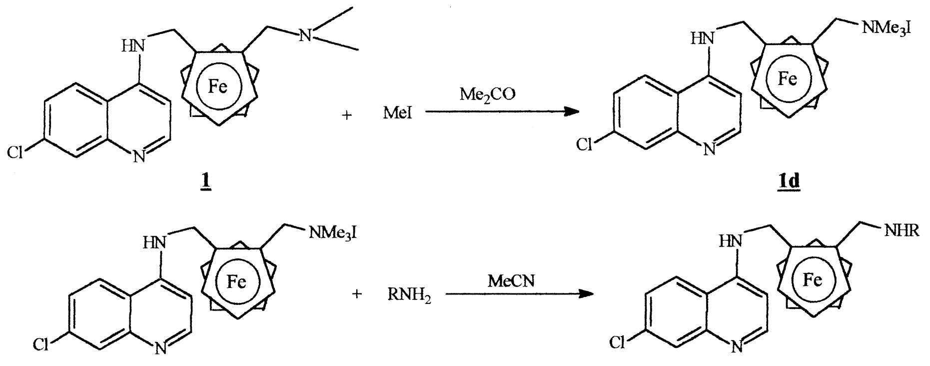
CQ **DECQ** **di-DECQ**

Chart 2. Chloroquine (CQ) and its main oxidative metabolites in man: monodesethylcholoroquine (DECQ) and didesethylchloroquine (di-DECQ).

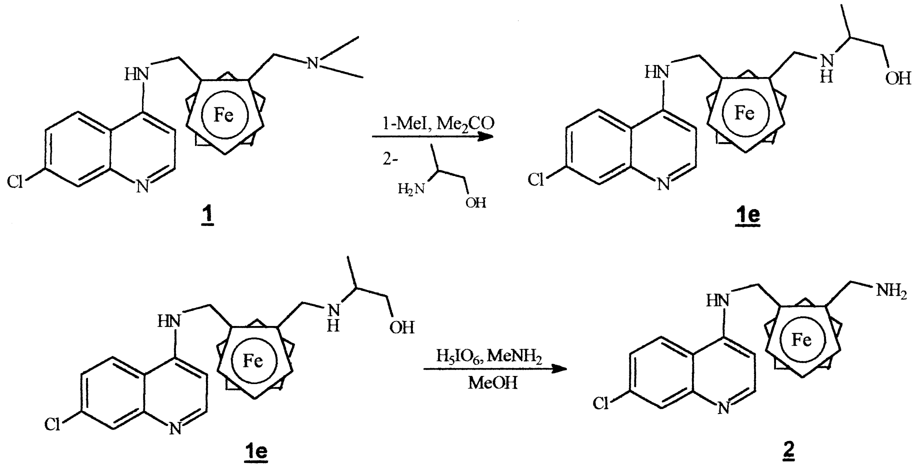


compd.	R
1a	Me
1b	Et
1c	*t*-Bu
2	H

Chart 3. 7-Chloro-4-[2-(*N*′-substituted aminomethyl)-*N*-ferrocenylmethylamino]quinoline.



Scheme 1. Synthesis of the monodesmethylferrochloroquine (**1a**) and related secondary amino derivatives (**1b** and **1c**).



Scheme 2. Synthesis of the didesmethylferrochloroquine (**2**).

nitrogen atom. The compounds bear *N*-methylamino **1a**, *N*-ethylamino **1b**, *N*-*tert*-butylamino **1c** and NH_2 residue **2**, instead of the *N*,*N*-dimethylamino residue.

The activities of compounds **1a**, **1b**, **1c** and **2** against parasite growth in vitro are presented in Table 1, where they are compared with chloroquine and the parent compound: ferrochloroquine (**1**). The results indicate that all the new secondary amino derivatives possess antimalarial activity comparable to that of the parent compound: FQ. All compounds exhibit better inhibitory activity against the chloroquine-resistant lineage Dd2 than CQ itself. Compound **1b**, containing a NHEt moiety instead of the NMe_2 residue, retained the strongest activity against Dd2 whereas compound **1c**, containing a NH*t*-Bu group, showed the weakest activity against the same strain. Surprisingly, the primary amine **2** is found twice less potent against Dd2 strain, and as potent against HB3 strain as ferrochloroquine. But the most remarkable observation made in this and earlier work is the in vitro activity of **1a**, **1b**, **1c** and **2** against chloroquine-resistant *P. falciparum* lineage. Compound **2** has a lower potency against chloroquine-resistant strain of *P. falciparum* compared to the parent drug **1** but remains more active than CQ itself. Moreover, the didesthylferrochloroquine **2** is less active than monodesethylferrochloroquine **1a**. These results are similar to those done for chloroquine and its major metabolites.[8–14]

Conclusion

The results, obtained with ferrochloroquine potential metabolites, compared to these observed with CQ metabolites[8–14] suggest that, if the metabolization pathway of **1** is similar to those of CQ, the resulting products will remain more active than CQ against *P. falciparum*. Therefore, a potential metabolization of ferrochloroquine cannot disprove the interest of this compound as an antimalarial drug.

Nevertheless, further studies (such as the use of FQ as substrate for microbial fermentation to obtain the oxidative metabolites or the detection of the metabolites in plasma after FQ administration) are necessary to verify this supposed metabolization pathway of **1**. And at least, pharmacokinetic studies and optimization of ferrochloroquine therapy should consider the antimalarial activity of these putative metabolites.

Experimental

Chemistry

Melting points (mp) are uncorrected. The ^1H NMR spectra were recorded on a Brucker AC300 spectrometer using tetramethylsilane (TMS) as the internal

Table 1. Mean of IC_{50} of chloroquine (CQ), ferrochloroquine (**1**), **1a**, **1b**, **1c** and **2** for each *Plasmodium falciparum* strain

Compounds[b]	IC_{50} (nmmol/l)[a]	
	HB3	Dd2
CQ[c]	25.8 ± 2.7	136.5 ± 21.9
1	23.6 ± 5.5	27.2 ± 2.9
1a	13.2 ± 1.0	23.2 ± 1.7
1b	18.8 ± 5.3	16.1 ± 1.9
1c	38.5 ± 12.9	29.3 ± 1.2
2	21.4 ± 7.0	54.2 ± 9.4

[a] Values are the arithmetic mean ± standard deviation of three independent experiments.

[b] CQ was applied as phosphate salt, **1**, **1a**, **1b**, **1c** and **2** as the free bases.

[c] Chloroquine sensitive threshold adopted is 100 nmol/L.

standard and $CDCl_3$ or DMSO-d_6 as the solvent. MS MALDI TOF spectra were obtained using a Vision 2000 time-of-flight instrument (Finnigan MAT, Bremen, Germany) equipped with a nitrogen laser operating at wavelength of 337 nm. Between 20 and 30 single-shot spectra in either the reflector or linear mode were accumulated to obtain a good signal-to-noise ratio. The matrix used was dihydroxybenzoic acid (dhb) or trihydroxyacetophenone (thap). Merck's Kieselgel 60 PF254 was used for the chromatography.

***N,N,N*-Trimethyl{2-[4-*N*′-(7-chloroquinolyl)aminomethyl]}ferrocenylmethylammonium iodide (1d).** To a solution of 7-chloro-4-[2-(*N*′,*N*′-dimethylaminomethyl)-*N*-ferrocenylmethylamino]-quinoline (60 mg, 0.14 mmol) in acetone (20 mL, dried over molecular sieves) were added dropwise methyl iodide (75 µL, 1.20 mmol). The mixture was stirred at room temperature during 4 h and then evaporated to dryness under reduced pressure. Compound **1d** was isolated as a brown solid (79 mg, 0.14 mmol, 99%), mp decomposed. ^{1}H NMR (DMSO-d_6) δ 8.47 (1H, d, *J* = 5.21 Hz, H2), 8.32 (1H, d, *J* = 9.06 Hz, H5), 7.80 (1H, d, *J* = 1.95 Hz, H8), 7.46 (1H, dd, *J* = 2.11 and 8.98 Hz, H6), 7.21 (1H, m, NH), 6.72 (1H, d, *J* = 5.47 Hz, H3), 4.64 (1H, *J* = 13.36 Hz, 1C*H*NHQ), 4.60–4.29 (6H, m, 3 CH and 3H Cp), 4.26 (5H, s, Cp′), 2.96 (6H, s, NMe_3). MS MALDI TOF (thap) positive ions: 450 (M ^{37}Cl)$^{\cdot+}$, 448 (M ^{35}Cl)$^{\cdot+}$, 405 (M–Me_3 ^{37}Cl)$^+$, 403 (M–Me_3 ^{35}Cl)$^+$, 391 (M–NMe_3 ^{37}Cl)$^+$, 389 (M–NMe_3 ^{35}Cl)$^+$, 285 [MH–(FeCp + Me_3) ^{37}Cl]$^+$, 283 [MH–(FeCp + Me_3) ^{35}Cl]$^+$; negative ions: 127 (I)$^-$.

7-Chloro-4[2-(*N*′-methylaminomethyl)-*N*-ferrocenylmethylamino]quinoline (1a). Under nitrogen, a tube was charged with **1d** (80 mg; 0.14 mmol) in acetonitrile (20 mL), freshly distilled methylamine (2 mL) and K_2CO_3 (200 mg; 0.14 mmol). The tube was sealed, and then heated at 75°C for 2 h. After cooling to room temperature, a solution of H_2O:$CHCl_3$ (60 mL) (1:1) was added. The organic layer was separated, and the remaining aqueous phase was washed with small portions of chloroform (2×50 mL). The $CHCl_3$ extracts were combined, dried over Na_2SO_4, and evaporated to dryness to give a yellow solid, which was purified by silica gel chromatography. Elution with AcOMe: triethylamine (95:5) gave **1a** (21 mg; 34%): mp 185–186°C; ^{1}H NMR ($CDCl_3$ + D_2O) δ 8.52 (1H, d, *J* = 5.40 Hz, H2), 7.91 (1H, d, *J* = 2.13 Hz, H8), 7.79 (1H, d, *J* = 8.98 Hz, H5), 7.27 (1H, dd, *J* = 2.17 and 8.96 Hz, H6), 6.45 (1H, d, *J* = 5.45 Hz, H3), 4.34 (1H, d, *J* = 13.10 Hz, 1CHNDQ), 4.26 (1H, m, 1HCp), 4.19 (1H, m, 1HCp), 4.15 (6H, m, 1CHNDQ, Cp′), 4.09 (1H, m, 1HCp), 3.68 (1H, d, *J* = 12.25 Hz, 1CHNDR), 3.47 (1H, d, *J* = 12.25 Hz, 1CHNDR), 2.44 (3H, s, CH_3). MS MALDI TOF (thap) 442 (M + Na ^{35}Cl)$^+$, 422 (MH ^{37}Cl)$^+$, 420 (MH ^{35}Cl)$^+$, 391 (M–HNMe ^{37}Cl)$^+$, 389 (M–HNMe ^{35}Cl)$^+$, 388. Anal. found: C, 63.03; H, 5.52; N. $C_{22}H_{22}N_3FeCl$. Calcd: C, 62.95; H, 5.28; N, 10.01.

7-Chloro-4-[2-(*N*′-ethylaminomethyl)-*N*-ferrocenylmethylamino]quinoline (1b). The preparation is analogous to the synthesis of **1a**. 45°C, 64 h, purification: AcOMe: hexane:triethylamine (50:45:5) (28%): mp 206–208°C; ^{1}H NMR ($CDCl_3$ + D_2O) δ 8.53 (1H, d, *J* = 5.39 Hz, H2), 7.92 (1H, d, *J* = 2.06 Hz, H8), 7.83 (1H, d, *J* = 8.95 Hz, H5), 7.25 (1H, dd, *J* = 2.13 and 9.07 Hz, H6), 6.47 (1H, d, *J* = 5.44 Hz, H3), 4.36 (1H, d, *J* = 13.06 Hz, 1CHNDQ), 4.26 (1H, m, 1HCp), 4.20 (1H, m, 1HCp), 4.15 (5H, s, Cp′), 4.09 (1H, m, 1HCp), 3.70 (1H, d, *J* = 12.22 Hz, 1CHNDR), 3.52 (1H, d, *J* = 12.22 Hz, 1CHNDR), 2.70 (2H, q, *J* = 7.13 Hz, CH_2), 1.13 (3H, t, *J* = 7.14 Hz, CH_3). MS MALDI TOF (dhb) 436 (MH ^{37}Cl)$^+$, 434 (MH ^{35}Cl)$^+$, 391 (M–HNEt ^{37}Cl)$^+$, 389 (M–HNEt ^{35}Cl)$^+$, 388. Anal. found: C, 63.35; H, 5.83; N, 9.37. $C_{23}H_{24}N_3FeCl$. Calc.: C, 63.69; H, 5.58; N, 9.37.

7-Chloro-4-[2-(*N*′-*t*-butylaminomethyl)-*N*-ferrocenylmethylamino]quinoline (1c). The preparation is analogous to the synthesis of **1a**. 45°C, 64 h, purification: AcOMe: hexane:triethylamine (40:50:10) (20%). ^{1}H NMR ($CDCl_3$ + D_2O) δ 8.56 (1H, d, *J* = 5.41 Hz, H2), 7.93 (1H, d, *J* = 2.09 Hz, H8), 7.85 (1H, d, *J* = 8.91 Hz, H5), 7.26 (1H, dd, *J* = 2.16 and 8.86 Hz, H6), 6.51 (1H, d, *J* = 5.46 Hz, H3), 4.34 (1H, d, *J* = 12.91 Hz, 1CHNDQ), 4.26 (1H, m, 1HCp), 4.20 (1H, m, 1HCp), 4.17 (5H, s, Cp′), 4.11 (2H, m, 1CHNDQ and 1HCp), 3.57 (2H, s, CH_2NDR), 1.10 (9H, s, CH_3); MS MALDI TOF (dhb) 484 (M + Na ^{35}Cl)$^+$, 462 (MH ^{37}Cl)$^+$, 461 (MH ^{35}Cl)$^+$, 391 (M–HNtBu ^{37}Cl)$^+$, 389 (M–HNtBu ^{35}Cl)$^+$, 388. Anal. found: C, 65.15; H, 6.46; N, 8.78. $C_{25}H_{28}N_3FeCl$. Calc.: C, 65.02; H, 6.11; N, 9.10.

2-*N*-{2-[4*N*′-(7-Chloroquinolyl)aminomethyl]ferrocenylmethylamino}propan-1-ol (3). A mixture of **1d** (80 mg; 0.14 mmol) and 3-aminopropanol (1 mL; 15.3 mmol) in acetonitrile was stirred under reflux for 1 h 30 min, quenched by the addition of a solution (80 mL) H_2O:$CHCl_3$ (1:1). The amino-alcohol was extracted with $CHCl_3$ (2×50 mL). The combined extracts were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The resulting oil was purified by TLC (silica gel, using AcOMe:hexane:triethylamine (50:40:10)) (55 mg; 85%). Diastereomers; ^{1}H NMR ($CDCl_3$ + D_2O) δ 8.47 (2H, d, *J* = 5.28 Hz, H2), 7.87 (2H, s broad, H8), 7.75 (2H, d, *J* = 8.88 Hz, H5), 7.19 (2H, dd, *J* = 1.81 and 9.02 Hz, H6), 6.46 (2H, d, *J* = 5.38 Hz, H3), 4.33 (2H, m, 2 1CHNDQ), 4.28 (2H, m, 2 1H Cp), 4.23 (2H, m, 2 1H Cp), 4.16 (10H, s, 2 Cp′), 4.12 (4H, m, 2 (1CHNDQ and 1H Cp)), 3.79 (1H, d, $J = 12.18$ Hz, 1CHNDR), 3.67–3.37 (4H, m, 2 (1CHNDR and 1CHOD)), 3.47 (1H, d, $J = 12.17$ Hz, 1CHNDR), 2.87 (2H, m, 2CHND), 1.20 (3H, d, $J = 6.90$ Hz, CH_3), 0.91 (3H, d, $J = 6.36$ Hz, CH_3); MS MALDI TOF (dhb): 488 (M + Na ^{37}Cl)$^+$, 486 (M + Na ^{35} Cl)$^+$, 466 (MH ^{37}Cl)$^+$, 464 (MH ^{35}Cl)$^+$, 392 (M–NHCH(CH_3)CH_2OH ^{37}Cl)$^+$, 392 (M–NHCH(CH_3)CH_2OH 35Cl)$^+$.

7-Chloro-4-[2-(aminomethyl)-*N*-ferrocenylmethylamino]-quinoline (2). A solution of diastereomeric amino-alcohol **3** (46 mg; 0.1 mmol) in methanol (20 mL) was stirred at room temperature, periodic acid (54 mg; 0.24 mmol) and 75 μL of 40% aqueous methylamine were added. After 2 h, the solution was extracted with diethyl ether (3×50 mL). The ether extracts were combined, dried over Na_2SO_4 and evaporated to dryness under reduced pressure to give **2** (30 mg; 70%). Kept at −25°C. ^{1}H NMR ($CDCl_3 + D_2O$) δ 8.58 (1H, d, $J = 5.31$ Hz, H2), 7.91 (1H, d, $J = 1.53$ Hz, H8), 7.81 (1H, d, $J = 8.96$ Hz, H5), 7.25 (1H, m, H6), 6.47 (1H, d, $J = 5.34$ Hz, H3), 4.35 (1H, d, $J = 13.13$ Hz, 1CHNDQ), 4.28 (1H, m, 1HCp), 4.21 (1H, m, 1HCp), 4.13 (5H, s, Cp′), 4.13 (1H, m, 1CHNDQ), 4.10 (1H, m, 1HCp), 3.73 (2H, 2s, 2CHND$_2$). MS MALDI TOF (dhb) 428 (M + Na ^{35}Cl)$^+$, 408 (MH ^{37}Cl)$^+$, 406 (MH ^{35}Cl)$^+$, 391 (M–NH$_2$ ^{37}Cl)$^+$, 389 (M–NH$_2$ ^{35}Cl)$^+$. Anal. found: C, 62.25; H, 5.23; N, 10.12. $C_{21}H_{20}N_3FeCl$. Calc.: C, 62.17; H, 4.97; N, 10.36.

Biology

Two culture-adapted strains of *Plasmodium falciparum* were used: the chloroquine-sensitive strain HB3 (Honduras) and the mefloquine chloroquine-resistant strain Dd2 (Indochina). All stock parasite culture were maintained using Tager and Jensen's method.[19,20]

The assays were conducted in vitro using a modification of the semiautomated microdilution technique of Desjardin et al. based on radiolabelled hypoxantine.[21] The parasites from asynchronous culture with a majority of young trophozoites stages were treated by chloroquine (CQ), ferrochloroquine (FQ), **1a**, **1b**, **1c** and **2** for 48 h in appropriate conditions. The stock solution of chloroquine diphosphate was prepared in 70 ° ethanol. The other compounds were dissolved in DMSO. Then, all the serial dilutions were realized in complete culture medium (RPMI 1640 supplemented with 10% pooled human A+ serum). The final concentrations ranged at 4.5 to 581.5 nmol. Growth of the parasites was measured in a liquid scintillation spectrometer (Beckman) by the incorporation of radiolabelled [G-H$_3$]Hypoxanthine into the nucleic acids of parasites. Fifty percent inhibitory concentrations (IC_{50}) refer to molar concentrations of drug causing 50% reduction in [G-H^3]-Hypoxanthine incorporation compared to drug-free control wells. They were estimated by linear regression analysis of log-dose–response curves.

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