The antimalarial ferroquine: from bench to clinic.
Christophe Biot, F. Nosten, L. Fraisse, D. Ter-Minassian, Jamal Khalife, Daniel Dive

To cite this version:

Christophe Biot, F. Nosten, L. Fraisse, D. Ter-Minassian, Jamal Khalife, et al.. The antimalarial ferroquine: from bench to clinic.. Parasite, EDP Sciences, 2011, 18 (3), pp.207-214. 10.1051/parasite/2011183207. hal-00642112

HAL Id: hal-00642112
https://hal.archives-ouvertes.fr/hal-00642112
Submitted on 16 Sep 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution 4.0 International License
THE MALARIA PROBLEM

With approximately 243 million cases and more than 800,000 deaths reported in 2009, malaria remains the most important human parasitic disease. Among the five *Plasmodium* species able to infect human, *P. falciparum* is responsible for most cases of severe disease and death, mainly in African children below the age of five. The morbidity caused by *P. vivax* in tropical countries outside of Africa has long been underestimated (Anstey et al., 2009, Baird, 2009). Malaria is a factor of poverty in endemic countries (Stratton et al., 2008). In the absence of an effective vaccine and reliable approaches for vector control, chemotherapy remains the cornerstone of malaria control. Quinine has been the first widely used antimalarial drug. Synthetic derivatives of quinine were the 8-aminoquinoline primaquine and the 4-aminoquinoline chloroquine (CQ). When resistance to CQ emerged in the late 1950s, the strategy was to modify the chemical structure of the existing compounds. The synthesis of CQ-like drugs led to the discovery of amodiaquine (AQ) and later mefloquine (MQ), halofantrine in the United States and lumefantrine in China (Baird, 2005). But the pace of new drug development has been slow and no new antimalarial drugs have been introduced into clinical practice since artemether-lumefantrine registered in 1998 (Olliaro & Wells, 2009). For all new antimalarial drugs introduced the risk of resistance can be reduced by combination therapy (White, 1999; Nosten & White, 2007). In 2006, the WHO guidelines recommended new treatments combining two drugs with different mechanisms of action. Treatments containing an artemisinin derivative (artemisinin-combination therapies, ACTs) are now standard treatment for *P. falciparum* malaria. However, a decline of susceptibility to artemisinate has been recently reported in the Thai-Cambodian border region (Dondorp et al., 2010). So the search for new molecules with antimalarial activity is more important than ever.

Summary:
Ferroquine (FQ, SSR97193) is currently the most advanced organometallic drug candidate and about to complete phase II clinical trials as a treatment for uncomplicated malaria. This ferrocene-containing compound is active against both chloroquine-susceptible and chloroquine-resistant *Plasmodium falciparum* and *P. vivax* strains and/or isolates. This article focuses on the discovery of FQ, its antimalarial activity, the hypothesis of its mode of action, the current absence of resistance in vitro and recent clinical trials.

**KEY WORDS:** malaria, bioorganometallics, drug candidate, ferroquine, mechanism of action, resistance.

The Antimalarial Ferroquine: From Bench to Clinic


**Summary:**
Ferroquine (FQ, SSR97193) is currently the most advanced organometallic drug candidate and about to complete phase II clinical trials as a treatment for uncomplicated malaria. This ferrocene-containing compound is active against both chloroquine-susceptible and chloroquine-resistant *Plasmodium falciparum* and *P. vivax* strains and/or isolates. This article focuses on the discovery of FQ, its antimalarial activity, the hypothesis of its mode of action, the current absence of resistance in vitro and recent clinical trials.

**KEY WORDS:** malaria, bioorganometallics, drug candidate, ferroquine, mechanism of action, resistance.

**The Antimalarial Ferroquine: From Bench to Clinic**


**Summary:**
Ferroquine (FQ, SSR97193) is currently the most advanced organometallic drug candidate and about to complete phase II clinical trials as a treatment for uncomplicated malaria. This ferrocene-containing compound is active against both chloroquine-susceptible and chloroquine-resistant *Plasmodium falciparum* and *P. vivax* strains and/or isolates. This article focuses on the discovery of FQ, its antimalarial activity, the hypothesis of its mode of action, the current absence of resistance in vitro and recent clinical trials.

**KEY WORDS:** malaria, bioorganometallics, drug candidate, ferroquine, mechanism of action, resistance.

The Antimalarial Ferroquine: From Bench to Clinic

Many strategies can be used for the search of affordable and efficient antimalarial drugs. These strategies include ethnopharmacology (i.e. bio-evaluation of the efficiency of traditional medicines), medicinal chemistry, combinatorial chemistry and chemical libraries screening by high throughput screening, and drug design. These strategies have led to the discovery of potential antimalarials such as the synthetic endoperoxides and others (Dhanawat et al., 2009). But the clinical development of new compounds is often stopped for various reasons: toxicity, chemistry, pharmacology, or economics, and less than one in ten promising molecules that have entered the pipeline reaches the stage of clinical studies. In the mid-90s, we extended the strategy developed by Gérard Jaouen (Vessieres et al., 1988) in anticancer therapy to antimalarial therapy (see Chavain & Biot, 2010 for review). The main antimalarials in current use (CQ, quinine, mefloquine, artemisinin, atovaquone) were modified by introduction of a ferrocenyl moiety in their chemical structure. More than 150 ferrocenic analogues have been synthesized, by us and others (Biot & Dive, 2010). The ferrocenic analogues were systematically tested against in vitro cultures of P. falciparum with CQ-susceptible and CQ-resistant strains. Ferroquine (FQ, SSR97193) was rapidly identified as a lead compound to meet candidate nomination requirements (Biot et al., 1997). The clinical phase IIb study (efficacy/safety in adults, adolescents and children) began in 2009 in Africa.

This mini-review will focus on the discovery of FQ, its antimalarial activity, the hypothesis of its modes of action and recent clinical trials.

THE ORGANOETALIC ANTIMALARIAL COMPOUND SET

Since 1993, we and others have systematically prepared organometallic versions of the antimalarials in current use such as CQ, primaquine, mepacrine, mefloquine, quinine, artemisinin, and atovaquone (see Dive & Biot, 2008 for review). New sandwiches and half-sandwich metal complexes (Dunitz et al., 1956) have been synthesized and characterized. In vitro tests of their antimalarial activity were performed. Other organometallic compounds with a priori unknown antimalarial activity were still screened. A collection of almost 150 compounds was made available. Among the organometallic-drug hybrids, the most interesting compounds were the ferrocene-drug hybrids and among those the ferrocene-chloroquine hybrids were the most promising (Fig. 1).

Note here that the ferrocene-artemisitene hybrids showed also interesting properties with activities equal to artemisinin (Delhaes et al., 2000, Dive & Biot, 2008). In the ferrocene-CQ hybrids series, we have shown that the ferrocene moiety has to be covalently flanked by a 4-aminoquinoline and an alkylamine (Biot et al., 2006). Ferroquine (FQ, SSR97193) was the first compound synthesized by us (Biot et al., 1997). Later, a second generation of analogues of FQ was designed and investigated. For example, we synthesized dual molecules including a FQ analogue conjugated with a glutathione reductase inhibitor or a glutathione depletory (Chavain et al., 2009) Nevertheless, this strategy failed to identify a “new” lead for a further development. More interestingly, amino-alcohols based on the FQ structure are active against CQ-susceptible (CQ8) and CQ-resistant (CQ8) clones of P. falciparum. In addition, in this second generation of analogues the ferrocenec amino-alcohols exert antiviral effects with some selectivity toward SARS-CoV infection (Biot et al., 2006b).

ANTIMALARIAL ACTIVITY OF FERROQUINE

ANTIMALARIAL ACTIVITY ON LABORATORY CLONES

FQ antimalarial activity was compared to that of CQ with standard in vitro parasite growth inhibition method, based on tritiated hypoxanthin incorporation in erythrocytes parasite infected with P. falciparum, incubated 48 hours (Desjardins et al., 1978). Preliminary studies have shown that FQ was equally active as a base, ditartrate or dichlorhydrate salts (unpublished results).

Tests results available from 11 studies performed in different laboratories and using 19 CQ5 and CQ8 P. falciparum laboratory adapted clones are represented in Fig. 2. The results show that the response to CQ can be easily dissociated between susceptible and resistant clones, which are spread respectively on either sides of the 100 nM IC50 for CQ. However, FQ is equally active on both types of clone and is at least equally active and often more active than CQ on CQ5 parasites. No resistance to FQ occurred in CQ8 clones and no correlation was found between susceptibility to FQ and polymorphism in transport proteins implicated in quinoline resistance (Henry et al., 2008).

In vivo antimalarial activity in rodent models

Antimalarial activity of FQ was tested on various rodent malaria strains (P. berghei, P. yoelii, P. vinckei) by the standard four day test of Peters (1987) adapted
to determine the curative dose. On *P. berghei* N and *P. yoelii* NS strains, FQ and CQ had a close EC\(_{50}\) (treatment with a decrease in parasitaemia of 50 % at the end of assay) and the simple four days test could not lead to conclude to a better efficacy of FQ versus CQ. But the curative tests are more significant and showed that *P. berghei* and *P. vinckei* infections were cured in presence of 8.3 mg/kg/d of FQ for four days when with CQ 30 to 55 mg/kg/d were necessary to cure CQ\(^6\) strains and the drug was unable to cure resistant strains, even at a toxic dose (Biot *et al.*, 1997, Delhaes *et al.*, 2001, Dive & Biot, 2008, Biot & Dive, 2010). Moreover, it has been shown that FQ was active not only by subcutaneous administration, but also by oral route, which was an interesting indication concerning the bioavailability of the drug by digestive tract. This was further confirmed by additional pharmacokinetic studies (Biot & Dive, 2010).
ENANTIOMERS

As FQ is a racemic compound. The two stereoisomers were synthetized and showed an antimalarial activity similar to that of the parent compound in vitro (Delhaes et al., 2002).

METABOLIZATION AND ACTIVITY OF METABOLITES

It was first postulated that the metabolism of FQ may share a common pathway with that of CQ and potential metabolites (N-monodemethyl-FQ and N-didemethyl-FQ) were synthesized and tested (Biot et al., 1999). The metabolism of FQ was then studied in details in vitro and enabled to determine its degradation pathway (Daher et al., 2006a). In vitro FQ is mainly metabolized to a major N-monodemethylated metabolite, SSR97213 (EVT0233) and to a further potential metabolite that is an N-didemethylated compound. Antimalarial activity of N-monodemethyl-FQ was found to be comparable to that of parent compounds on two CQ8 clones and remained much more active than CQ on two CQ8 clones. On the other hand, N-didemethyl-FQ had a decreased activity on CQ8 clones, mainly if IC99 of compounds is taken into account (Daher et al., 2006a).

EFFICACY ON CLINICAL ISOLATES

Compounds were evaluated with standard in vitro parasite growth inhibition methods, in erythrocytes infected with P. falciparum, incubated at least 24 hours with the drugs. The antimalarial activity of FQ (SSR97193) on blood clinical isolates (CQ8, CQ8, and multi-drug resistant isolates) infected by P. falciparum was assessed in seven different studies of African patients (Senegal, Gabon) (Pradines et al., 2001 & 2002; Attak et al., 2003; Kreidenweiss et al., 2006), or southeast Asian patients (Chim et al., 2004; Barends et al., 2007) in comparison with existing antimalarial drugs. Data on FQ, CQ, and artesunate are reported in Table I.

Taking all these studies together, FQ was evaluated on 534 clinical isolates, 220 from Southeast Asia and 314 from Africa. In all these studies, FQ, like artesunate, displayed a very potent antimalarial activity against P. falciparum (range IC50 below 30 nM [13 ng/mL] for FQ and below 4 nM [1.5 ng/mL] for artesunate) with equal efficacy upon CQ8 and CQ8 clinical isolates (resistant isolates, with IC50 over 100 nM, represented from 32 % to 100 % of samples).

In addition, in the study from Thailand the main FQ in vivo metabolite (SSR97213) was investigated (Barends et al., 2007). SSR97213 was shown to be highly potent against P. falciparum (range IC50 below 30 nM [13 ng/mL] for FQ and below 4 nM [1.5 ng/mL] for artesunate) with equal efficacy upon CQ8 and CQ8 clinical isolates (resistant isolates, with IC50 over 100 nM, represented from 32 % to 100 % of samples).
**THE ANTIMALARIAL FERROQUINE**

### The Antimalarial Ferroquine

#### Ferroquine vs. Chloroquine

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>95% CI</th>
<th>n</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>95% CI</th>
<th>% resistance</th>
<th>n</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>95% CI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabon</td>
<td>103</td>
<td>10.8</td>
<td>8.6-13.5</td>
<td>102</td>
<td>370</td>
<td>319-429</td>
<td>95 (a)</td>
<td>65</td>
<td>2.9</td>
<td>2.3-3.7</td>
<td>Biot et al., 1999</td>
</tr>
<tr>
<td></td>
<td>12.6</td>
<td>3.8-5.9</td>
<td></td>
<td>118.4</td>
<td>102-137</td>
<td></td>
<td></td>
<td>1.1</td>
<td>0.9-1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senegal</td>
<td>99 &gt; 30 nM for the HRP2</td>
<td>75 % CIs = 99 &gt; 30 nM for the HRP2</td>
<td></td>
<td>51</td>
<td>1.9</td>
<td>1.5-2.3</td>
<td>Biot et al., 2006a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.9</td>
<td>6.5-9.7</td>
<td></td>
<td>53</td>
<td>102</td>
<td>74-140</td>
<td>55 (a)</td>
<td>70-285</td>
<td>nt</td>
<td>nt</td>
<td>nt</td>
</tr>
<tr>
<td>Gabon</td>
<td>56</td>
<td>16</td>
<td>14.4-17.8</td>
<td>56</td>
<td>141</td>
<td>70-285</td>
<td>52 (a)</td>
<td>nt</td>
<td>nt</td>
<td>nt</td>
<td>Daher et al., 2006a</td>
</tr>
<tr>
<td></td>
<td>6.9</td>
<td>6.3-7.8</td>
<td></td>
<td>45.1</td>
<td>22.4-91.2</td>
<td></td>
<td></td>
<td>155</td>
<td>29</td>
<td>26.3-31.6</td>
<td></td>
</tr>
<tr>
<td>Gabon</td>
<td>60</td>
<td>27.9</td>
<td>2.3-33.2</td>
<td>60</td>
<td>398</td>
<td>166-956</td>
<td>97 (a)</td>
<td>nt</td>
<td>nt</td>
<td>nt</td>
<td>Daher et al., 2006a</td>
</tr>
<tr>
<td></td>
<td>12.1</td>
<td>1.0-14.5</td>
<td></td>
<td>127.3</td>
<td>53.1-306</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>65</td>
<td>9.3</td>
<td>8.7-10.0</td>
<td>62</td>
<td>341</td>
<td>304-382</td>
<td>100 (a)</td>
<td>56</td>
<td>4.0</td>
<td>3.1-6.3</td>
<td>Daher et al., 2006b</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>3.8-4.4</td>
<td></td>
<td>109.1</td>
<td>87.2-122</td>
<td></td>
<td></td>
<td>1.5</td>
<td>1.2-2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabon</td>
<td>40</td>
<td>1.9</td>
<td>0.6-6.7</td>
<td>43</td>
<td>113</td>
<td>12.4-332</td>
<td>100 (b)</td>
<td>43</td>
<td>1.0</td>
<td>0.2-6.0</td>
<td>Delhaes et al., 2001</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>0.3-3.0</td>
<td></td>
<td>36.1</td>
<td>40-106</td>
<td></td>
<td></td>
<td>0.4</td>
<td>0.1-2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cambodia</td>
<td>155</td>
<td>29</td>
<td>26.3-31.6</td>
<td>155</td>
<td>135</td>
<td>121-151</td>
<td>32 (a)</td>
<td>150</td>
<td>1.1</td>
<td>1.0-1.2</td>
<td>EVT0231</td>
</tr>
<tr>
<td></td>
<td>12.6</td>
<td>11.6-13.8</td>
<td></td>
<td>43.1</td>
<td>38.7-48.2</td>
<td></td>
<td></td>
<td>0.4</td>
<td>0.4-0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = number of clinical sites; nt = not tested; CI = confidence interval; IC<sub>50</sub> = inhibitory concentration decreasing a response by 50 %; (a) = % of resistance using the threshold level of resistance IC<sub>50</sub> > 100 nM; (b) = % of resistance using the threshold of IC<sub>50</sub> > 30 nM for the HRP2 detection assay. For values in *italics*, units = ng/mL, calculated for translation to a free-base or free-acid gravimetric concentration.

Table I. – Effect of FQ (SSR97193 – IC<sub>50</sub>) and 95 % confidence intervals) on *P. falciparum* clinical isolates from different studies.

**vivo** effect on *P. vivax* schizont maturation (median IC<sub>50</sub> = 15 nM; 75 % CIs = 12 to 20 nM, n = 52) with SSR97213 being less active (IC<sub>50</sub> = 77 nM; 75 % CIs = 14 to 205 nM), and no significant cross-sensitivity between FQ and other antimalarials was detected; consequently FQ may be a suitable replacement for chloroquine in the treatment of drug-resistant *P. vivax* malaria (Leimanis *et al.*, 2010). In the Gabonese study (Kreidenweiss *et al.*, 2006), IC<sub>99s</sub> were reported in comparison with IC<sub>50s</sub> (Kreidenweiss *et al.*, 2006). For artesunate and FQ, the IC<sub>99s</sub> were 5.76 nM (95 % CIs = 0.57 to 49.1 nM) or IC<sub>50</sub> = 2.21 ng/mL (95 % CIs = 0.22 to 18.9 ng/mL), and 5.75 nM (95 % CIs = 1.10 to 56.9 nM) or IC<sub>50</sub> = 2.50 ng/mL (95 % CIs = 0.48 to 24.8 ng/mL). These values are close to the reported IC<sub>50s</sub>, indicating a strong potency and the ability to efficiently kill all parasites present in the field isolates.

Finally, the susceptibility of *P. falciparum* isolates from Madagascar (n = 21), Guyana (n = 65) and Cambodia (n = 62) to FQ was measured at the local Pasteur Institutes using the [3H]-hypoxanthine incorporation method. The mean IC<sub>50</sub> (with minimum and maximum IC<sub>50</sub> values), were 5.96 nM (0.2-43.2), 8.68 nM (3.05-55.77) and 10.18 nM (2.53-43.43), respectively (Eric Legrand, personal communication).

In all studies, no cross-resistance was observed with CQ and other antimalarials, although weak occurrences could be attributed, in one study to fluctuations of initial inoculums used for test (Kreidenweiss *et al.*, 2006). This absence of cross-resistance is supported by molecular studies, which showed that there was no association between polymorphisms of resistance of *pfcrt* gene, the main molecular marker for CQ, and FQ susceptibility in field isolates (Daher *et al.*, 2006b). This last observation was then extended to other markers of quinoline resistance (Henry *et al.*, 2008) and to *pymdr* and *pfcrt* genes of the rodent strain *P. yoelii* (Dive & Biot, 2008).

**Resistance Acquisition Under Ferroquine Pressure**

An *in vitro* study on *P. falciparum* resistance acquisition under ferroquine pressure was performed on human red blood cells infected with the W2 clone. After two months of FQ pressure we were unable to obtain a viable resistant strain. During these experiments however, we observed very few parasites, which were unable to develop when transferred in drug-free medium (Daher *et al.*, 2006b).

An attempt to obtain a rodent FQ<sup>R</sup> strain starting from *P. yoelii* resulted in a phenotype that was not fixed genetically the resistance disappearing as soon as FQ pressure was removed. Moreover, the phenotype was emerging very slowly and was confined strictly to reticulocytes and easily cleared by the host (Dive & Biot, 2008).

These results clearly show that the fitness cost of FQ resistance is very high for the parasite and that it would be detrimental for them in competition with non-resistant clones.
MODES OF ACTION: HYPOTHESES

CQ is thought to act by interfering with the digestion of haemoglobin in the blood stages of the malaria life cycle. Even if CQ and FQ share some similarities in their activity, FQ clearly showed an increased lipophilicity at pH 7.4 and the peculiar conformation provided by the intra-molecular hydrogen bond present in non-polar conditions result in a better potency for FQ to cross membranes and a higher accumulation in the digestive vacuole. At the pH in that organelle, the physicochemical properties of FQ evidenced a higher fraction of neutral and mono-protonated forms and suggested a more efficient inhibitory activity on hematin biocrystallization (Dubar et al., 2011), which was verified in vitro in BHIA (β-Hematin Inhibition Assay). Moreover, preferential localization of FQ at the site of crystallization of hemozoin close to the membrane of the acidic vacuole might induce two independent or concomitant behaviours: first FQ might inhibit the self-assembly of the hemozoin crystal and second FQ might specifically generate reactive oxygen species (per se, or via destruction of the hemozoin crystal) and induce lipid peroxidation and alteration of digestive vacuole (Chavain et al., 2008; Dubar et al., 2011).

All these properties might explain why FQ is more active than CQ in vitro even in a susceptible P. falciparum clone. The in vitro assays emphasized the specific importance of the intra-molecular hydrogen bond in FQ. Indeed in our studies based on methyl-FQ (an analogue of FQ without the intra-molecular hydrogen bond due to the presence of a methyl group on the 4-amino group), we clearly showed that the presence of the intra-molecular hydrogen bond allows FQ to escape resistance mechanisms and avoid cross-resistance with the current antimalarials (Biot et al., 2009; Dubar et al., 2011).

CONCLUSIONS AND PERSPECTIVES

In conclusion, FQ clinical trials will enable the definition of conditions of use of this new antimalarial drug, which appears to be well positioned in the pipeline. One remaining question is the cause of the potent activity of the drug, mainly towards CQ resistant parasites, and its relation with the structure of the molecule. Some clues (role of the hydrogen bond, role of redox activity, nature of the metal present in the metallocene moiety) are currently under examination to clarify the mechanisms of entry of FQ in the infected red blood cell, its site and mechanism of action and its relation with the transporters involved in resistance against different aminoquinolines, which appear ineffective to expel the molecule out of the

<table>
<thead>
<tr>
<th>Properties</th>
<th>CQ</th>
<th>FQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramolecular hydrogen bond</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Weak base properties (pK_a1 and pK_a2 values)</td>
<td>10.03 and 7.94</td>
<td>8.19 and 6.99</td>
</tr>
<tr>
<td>Neutral and protonated forms at vacuolar pH</td>
<td>One time</td>
<td>Ten times</td>
</tr>
<tr>
<td>Lipophilicity at pH 5.2</td>
<td>-1.2</td>
<td>-0.77</td>
</tr>
<tr>
<td>Lipophilicity at pH 7.4</td>
<td>0.85</td>
<td>2.95</td>
</tr>
<tr>
<td>Complex with hematin and stoichiometry</td>
<td>Yes (1:1)</td>
<td>Yes (1:1)</td>
</tr>
<tr>
<td>Interaction with monomeric hematin (log K)</td>
<td>Yes (5.52)</td>
<td>Yes (5.52)</td>
</tr>
<tr>
<td>Inhibition of β-hematin formation (IRS)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>BHIA_50</td>
<td>1.9</td>
<td>0.78</td>
</tr>
<tr>
<td>Production of hydroxyl radicals</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Activity on CQ^k clones and isolates</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Relation with specific molecular resistance markers</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

IRS = infrared spectroscopy. BHIA_50 = 50 % inhibitory concentration for β-hematin inhibition in equivalents of compounds to hemin (Biot et al., 2005).

Table II. – Comparative properties of chloroquine (CQ) and ferroquine (FQ).
parasite. On the clinical front, it remains to determine how this new drug will be best combined with a partner to limit the risk of resistance.

ACKNOWLEDGEMENTS

All searches on FQ carried out in laboratories * and **** were funded by Pierre Fabre Médicament and Sanofi-Aventis. The two labs are very grateful to all Ph.D. students who participated to this work (L. Delhaës, H. Abessolo, W. Daher, N. Chavain, and F. Dubar) and provided an excellent work. We acknowledge scientists who collaborated in the research: B. Pradines, T. Egan, K. Chibale, C. Slomianny, X. Trivelli, S. Bohic, E. Curis, and I. Forfar. F. Nosten is supported by the Wellcome Trust of Great Britain. We thank Ministère de l’Enseignement Supérieur, Université Lille Nord de France, CNRS and INSERM.

REFERENCES


Daher W., Biot C., Fandeur T., Joun H., Pelinski L., Viscogliosi E., Fraisse L., Pradines B., Brocard J., Khalife J. & Dive D. Assessment of P. falciparum resistance to ferro-
quine in field isolates and in W2 strain under pressure. Malaria J, 2006b, 5, 11.


Received on January 10th, 2011
Accepted on March 28th, 2011