Probing the Role of the Covalent Linkage of Ferrocene into a Chloroquine Template

Christophe Biot,*,† Wassim Daher,‡ Cheikh M. Ndiaye,† Patricia Melnyk,§ Bruno Pradines,|| Natascha Chavain,† Alain Pellet,⊥ Laurent Fraisse,⊥ Lydie Pelinski,† Christian Jarry,⊗ Jacques Brocard,† Jamal Khalife,‡ Isabelle Forfar-Bares,⊗ and Daniel Dive‡

Unité de Catalyse et Chimie du Solide - UMR CNRS 8181, ENSCL, Bâtiment C7, USTL, B.P. 90108, 59652, Villeneuve d' Ascq Cedex, France, Inserm, U547, Institut Pasteur, 1 rue du Pr Calmette, B.P. 245, 59019 Lille Cedex, France, UMR CNRS 8161, Universités Lille1 et Lille2, IPL, 1 rue du Pr. Calmette, B.P. 245, 59019 Lille Cedex, France, Institut de Médecine Tropicale du Service de Santé des Armées, Unité de Parasitologie, Bd Charles Livon, Parc le Pharo, BP 46, 13998 Marseille Armées, France, Sanofi-Aventis Recherche, Discovery Department, 31000 Toulouse Cedex, France, and EA 2962 Pharmacochimie Université Victor Segalen Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France

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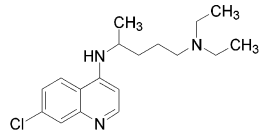
A new therapeutic approach to malaria led to the discovery of ferroquine (FQ, SR97276). To assess the importance of the linkage of the ferrocenyl group to a 4-aminoquinoline scaffold, two series of 4-aminoquinolines, structurally related to FQ, were synthesized. Evaluation of antimalarial activity, physicochemical parameters, and the β-hematin inhibition property indicate that the ferrocene moiety has to be covalently flanked by a 4-aminoquinoline and an alkylamine. Current data reinforced our choice of FQ as a drug candidate.

Introduction

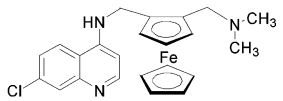
Malaria is one of the most prevalent causes of morbidity and mortality worldwide. Therefore, chemotherapy is a major element of malaria control[1,2] in the absence of an active vaccine.[3,4] Owing to the widespread occurrence of drug resistance to *Plasmodium falciparum*, many ways are being currently explored to develop new antimalarials.[5−7]

We have previously reported the design, synthesis and antimalarial activity of FQ (SR97276), a metallocenic compound (Figure 1).[8] The probable mechanism of action of FQ has been partially studied and should be in part similar to that of chloroquine (CQ). It probably involves hematin as the drug target and inhibition of hemozoin formation.[9] Subsequently, variation of the attachment position of the ferrocenic moiety on the quinoline ring of CQ has been investigated, but unfortunately such a strategy afforded no improvement of the antiplasmodial activity.[8] Besides, it has been shown in many studies that CQ[10,11] and FQ[12,13] analogues with shortened side chains may be good schizontocides. All these results prompted us to investigate the role of the covalent linkage of the ferrocenyl moiety to CQ-like drugs.

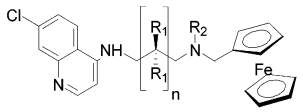
In this work we describe two series of 4-aminoquinolines structurally related to FQ (Figure 1) designed in order to study the structural basis for in vitro effects on *P. falciparum* and on β-hematin formation. Moreover, low-cost preparation and easy accessibility were the main criteria for the design of molecules in series A. Such compounds would indeed meet the current need for cheap, novel antimalarials. For that purpose, the ferrocene moiety was introduced at the extremity of a (branched) lateral side chain of a 4-aminoquinoline derivative. In addition, these structures allow the modulation of the substituent on the amino group. Compounds of series B were designed through the variation of the side chain of FQ. Not only do these new analogues offer new therapeutic possibilities, but they will also



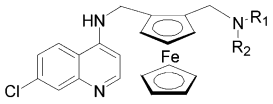
Chloroquine, CQ



Ferroquine, FQ



FQ Analogues, Series A



FQ Analogues, Series B

compd	R_1	R_2	n
1a	H	H	0
1b	H	H	1
1c	H	H	2
1d	H	H	4
2a	H	CH_3	0
2b	H	CH_3	1
2c	H	CH_3	2
2d	H	CH_3	4
3a	H	C_2H_5	0
3b	H	C_2H_5	1
3c	H	C_2H_5	2
3d	H	C_2H_5	4
4a	H	$FcCH_2$	0
4b	H	$FcCH_2$	1
4c	H	$FcCH_2$	2
4d	H	$FcCH_2$	4
5a	CH_3	H	1
5b	CH_3	CH_3	1
5c	CH_3	C_2H_5	1

compd	R_1	R_2
6	C_2H_5	C_2H_5
7a	CH_3	H
7b	CH_3	C_2H_5
8a	$FcCH_2$	H
8b	$FcCH_2$	CH_3
8c	$FcCH_2$	C_2H_5

with Fc = ferrocenyl

Figure 1. Structure of chloroquine, ferroquine, and ferroquine analogues (Series A and B).

* To whom correspondence should be addressed. Phone: +33-(0)-320434893. Fax: +33-(0)320436585 E-mail: christophe.biot@ensc-lille.fr.
† Unité de Catalyse et Chimie du Solide - UMR CNRS 8181.
‡ Inserm, U547, Institut Pasteur.
§ Universités Lille1 et Lille2.
|| Institut de Médecine Tropicale du Service de Santé des Armées.
⊥ Sanofi-Aventis Recherche.
⊗ EA 2962 Pharmacochimie Université Victor Segalen Bordeaux 2.

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Scheme 1. Series A: Synthesis of Ferroquine Analogues

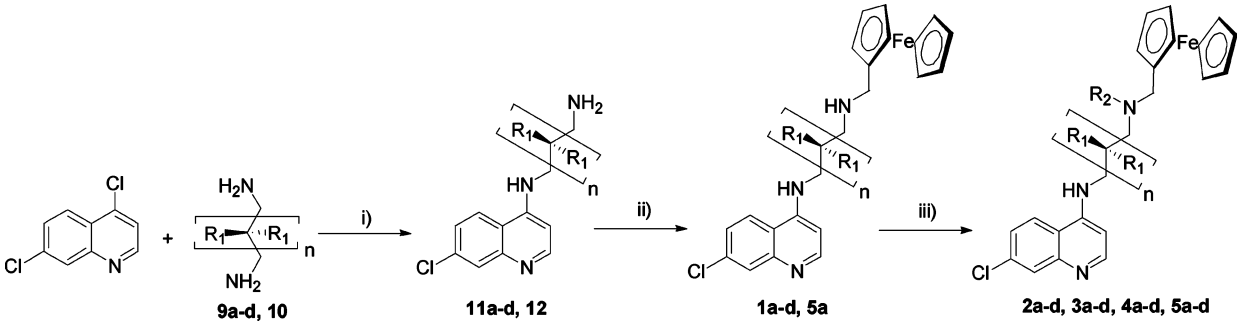

Table 1. Series A: In Vitro Sensitivities of *P. falciparum* Strains

compd	strains	IC_{50} (nM)	±SEM	n^a	IC_{90} (nM)	±SEM	n^a
CQ	HB3	**21.8**[d]	4.52	10	**45.7**	13.9	10
	Dd2	**61.8**	28.7	4	166.7	45.2	4
	W2	452.4	92.7	8	802.2	151.9	8
FQ	HB3	**20.2**	6.1	10	**28.6**	7.3	10
	Dd2	**18.9**	4.3	4	**28.4**	7.9	4
	W2	**8.1**	2.1	8	**13.8**	3.0	8
1a	HB3	**73.0**		2	>3800		2
	Dd2	**29.3**	12.2	3	>3800		3
	W2	**63.5**	83.0	3	>2000		3
1b	HB3	**65.1**		2	2643		2
	Dd2	**63.0**	10.8	3	>700		3
1c	HB3	**58.8**		2	1844.0		2
	Dd2	**68.1**	25.6	3	630.0	368.2	3
1d	Dd2	127.0	13.3	3	>274		3
2a	HB3	>274			>274		
	Dd2	**55.9**	8.3	3	>274		3
2b	HB3	**45.7**		2	**66.4**		2
	Dd2	**50.6**	14.7	4	**66.2**	21.8	3
	W2	**26.7**	11.4	4	>500		4
2c	HB3	118.3		2	>319		3
	Dd2	120.1	36.9	4	182.8	70.3	3
2d	HB3	**80.0**		2	>356		2
	Dd2	**78.3**	5.1	3	114.5		2
3a	Dd2	**63.6**	5.8	3	>274		3
3b	HB3	**50.3**		2	**70.9**		2
	Dd2	**61.5**	18	3	**79.0**		2
	W2	**24.0**	5.7	3	>500		3
3c	HB3	**61.8**		2	103.8		2
	Dd2	**96.5**	8.9	4	140.6	13.2	3
	W2	134.4	33.6	3	>500		3
3d	HB3	93.9		2	>356		2
	Dd2	86.9	9.7	4	192.6	49.4	4
5a	HB3	**53.0**		2	1451.5		2
	Dd2	**54.5**	21.0	3	7322.5		2
	W2	**50.6**	30.6	4	>500		4
5b	HB3	181.0		2	442.6		2
	Dd2	212.9	81.5	3			
5c	HB3	268.0		2	962.5		2
	Dd2	399.2	229.7	4	>400		4

[a] *n*: number of experiments. [b] Values in bold indicated IC < 100 nM.

be helpful in providing an understanding of the mode of action of FQ. The lipophilicity behavior dependence of new compounds was studied with respect to the parasite vacuolar and cytosolic pHs.

Chemistry. A rapid and cost-effective procedure was developed for syntheses of all FQ analogues of series A. Condensation of diamines **9a**−**d** and **10** with 4,7-dichloroquinoline afforded the primary amines **11a**−**d** and **12** (Scheme 1).[10] Upon further reaction with ferrocenecarboxaldehyde, the intermediate imines were converted to the corresponding amines **1a**−**d** and **5a** in 62−84% global yields by addition of $NaBH_4$. The ferrocenic amines **2a**−**d**, **3a**−**d**, **4a**−**d**, and **5b**,**c** were then obtained in 14−88% yields by a typical Borch's mechanism.[14,15] Compounds of series B were obtained as previously reported.[8] Metallocene **6** was synthesized in a similar way to FQ (Scheme 2). Quaternerization of the tertiary amine of FQ was achieved by reaction with methyl iodide. The resulting salt was then condensed with methylamine or ferrocenylmethyl-amine to afford **7a** and **8a**.[9] These secondary amines **7a** and **8a** were then converted to the corresponding tertiary amines **7b** and **8b**,**c** (25−80% yields).

Results and Discussion

The new compounds were evaluated in vitro against *P. falciparum* strains (Tables 1 and 2). As limitation to the IC_{50} values could lead to erroneous conclusions in the supposed efficacy of the compounds, the IC_{90} also have to be evaluated and discussed.

Compounds **2b** and **3b** inhibited parasite development of HB3 and Dd2 clones (IC_{50} and IC_{90} at or below 100 nM). Nevertheless, the efficacy decreased (IC_{90} > 500 nM) against the more resistant strain W2, suggesting that these molecules will probably be inefficient on strongly resistant *P. falciparum* strains. Whereas compounds **1a**-**d** and **5a** displayed potential activity (*I*C_{50} < 150 nM on both tested *P. falciparum* strains), they were less active than CQ (and FQ) against the CQ-sensitive strain HB3. All showed superior IC_{90} values to CQ and FQ. Striking differences were observed for **1a** and **5a** between their low IC_{50} (roughly 50 nM) and their high IC_{90} (>500 nM). A decrease of the efficacy was observed between the linear (**1b**, **2b**, and **3b)** and branched (**5a**−**c**) propylamino chain derivatives. Introduction of methyl groups in the side chain was not favorable to the antimalarial activity. Finally compounds **4a**−**d**, bearing two ferrocenic moieties in their skeleton, gave erratic and inconsistent results in a range of concentrations varying from 10 to 1000 nM which did not allow a precise determination of their IC_{50}. In conclusion, none of the series A compounds exhibited a global antimalarial activity similar (or better) to that of FQ on the three tested strains.

In series B, metallocenes **8a**−**c** including two ferrocenic nuclei showed lower activity than CQ (Table 2). The IC values observed for the first FQ metabolite **7a** were in accordance with those previously reported.[16,17] Its antimalarial activity against the Dd2 clone has also been included here for comparison. Tertiary amines **6** and **7b** showed strong antimalarial activity (IC_{50} and IC_{90} < 42 nM) on the three laboratory strains and appeared as efficient as CQ against the HB3 strain and much more active against the Dd2 and W2 strains (2 to 10-fold). These structure−activity relationship studies on the side chain of the basic amino group of FQ revealed that the in vitro antimalarial activity was not disturbed by slight chemical modifications (from hydrogen to ethyl).

Next, compounds were tested for their ability to inhibit β-hematin formation (Figure 2 and Table 4), the synthetic equivalent of hemozoin, induced by lipids in 96-well plate format.[18,19] Low solubility in DMSO of compounds **1d**, **3c**, **4a**,

Scheme 2. Series B: Synthesis of FQ Analogues

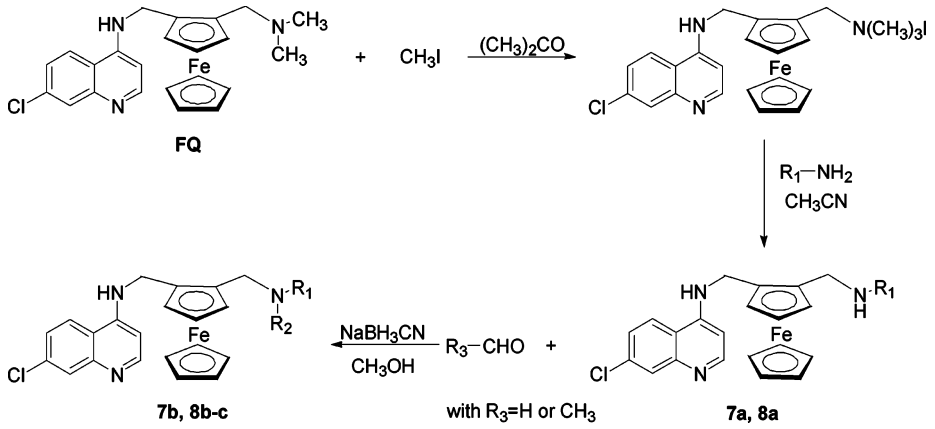

Table 2. Series B: In Vitro Sensitivities of *P. falciparum* Strains

compd	strains	IC_{50} (nM)	±SEM	n^a	IC_{90} (nM)	±SEM	n^a
CQ	HB3	**21.8**[b]	4.5	10	45.7	13.9	10
	Dd2	**61.8**	28.7	4	166.7	45.2	4
	W2	452.4	92.7	8	802.2	151.9	8
FQ	HB3	**20.2**	6.1	10	**28.6**	7.3	10
	Dd2	**18.9**	4.3	4	**28.4**	7.9	4
	W2	**8.1**	2.1	8	**13.8**	3.0	8
6	HB3	**12.4**	3.6	4	**18.0**	3.7	4
	Dd2	**17.7**	3.7	5	**28.3**	6.4	5
	W2	**16.8**	5.1	6	**25.3**	6.4	6
7a	HB3	**29.6**	8.7	7	**45.7**	12.6	7
	Dd2[b]	**23.2**	1.7	3	ND[c]	ND	ND
	W2	**23.1**	6.1	6	**42.1**	17.8	6
7b	HB3	**23.6**	3.6	3	**34.1**	1.2	3
	Dd2	**17.0**	6.1	6	**30.2**	8.2	6
	W2	**19.2**	4.6	6	**30.9**	7.0	6
8a	HB3	155.5	39.7	3	>582		3
	Dd2	169.5	70.0	6	>582		6
8b	HB3	204.8	84.0	3	>582		3
	Dd2	**88.5**	7.4	3	>582		3
8c	HB3	156.4	39.6	3	>582		3
	Dd2	**51.3**	2.6	3	>582		3

[a] *n*: number of experiments [b] For IC_{50} determination, see ref 16. [c] ND = not determined. [d] Values in bold indicated IC < 100 nM.

4c, **5c** and series B did not allow the study of their influence on β-hematin formation. FQ is a 2-fold more potent inhibitor of β-hematin formation than CQ.[9] In general, the introduction of a second ferrocenyl substituent (compounds **4b** and **4d**) resulted in a dramatic increase of the IC_{50} values. The majority of the other compounds were potent inhibitors with IC_{50} lower than 50 μM. Four of the metallocenic complexes **1c**, **2a**, **2b**, and **2c** inhibit the process similarly to CQ. Four other compounds **1b**, **3b**, **3d**, and **5a** are better inhibitors than CQ, with IC_{50} values close to that of FQ. The best β-hematin formation inhibitor is **1a** which showed an IC_{50} value equal to 9.3 μM.

HPLC determination of log D[9,20] was achieved for these compounds at two distinct pHs (5.2 considered close to the probable pH of the digestive vacuole and 7.4 assumed to be the cytosol pH).

It can be seen on Figure 2 that, at pH 7.4, all of the compounds studied were found to be highly lipid soluble with a difference near 300-fold between them. Introduction of a ferrocenic moiety in the lateral chain considerably increased the lipophilicity, compared to the purely organic CQ molecule. Moreover, compounds **4a**, **4b**, **5b**, **5c**, **8a**, and **8b** were found the most lipophilic (log D > 4). This can be explained by the fact that **4a**, **4b**, **8a**, and **8b** include a second ferrocenic group in their chemical structure, and **5b** and **5c** are sterically hindered due to the branched side chain.

At pH 5.2, a large difference can be noticed (more than 1000-fold) between the log D values. All compounds except products **4a**, **4b**, **5b**, **5c**, **8a**, and **8b** have hydrophilic properties. Reference molecules CQ and FQ presented the most hydrophilic behavior with log D values of −1.2 and −0.77, respectively. An increase of lipophilicity can be noticed for **1a**, **2a**, **3a**, and **4a** where a hydrogen atom (**1a**) was replaced by a methyl (**2a**), an ethyl (**3a**), and a $FcCH_2$ group (**4a**). The same statement can be made for **2b**, **3b**, and **4b**. Log D values of FQ and compound **6** are similar (Table 3); indeed, methyl groups of FQ have just been replaced by ethyl groups. Expectedly, log D increased upon introduction of a second ferrocenyl moiety, as exemplified by compounds **8a** and **8b**. In conclusion, either the introduction of a second bulky group such as a ferrocene or the introduction of

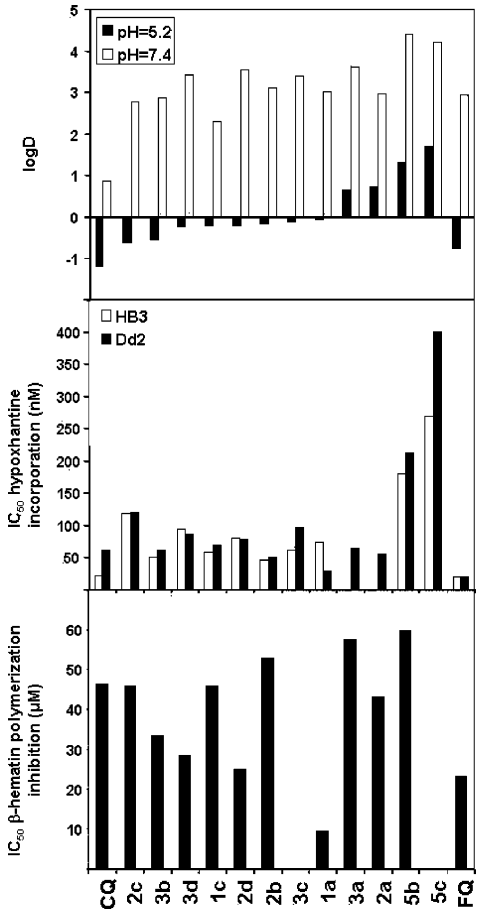

Figure 2. Series A analogues:[a] Relationship between in vitro antimalarial activity, (pH 5.2 and 7.4) log D, and in vitro β-hematin inhibition.

three alkyl substituents on the lateral chain led to compounds with a particularly lipophilic behavior. On the other hand, the relative position of the ferrocenic group on the lateral chain of the 4-aminoquinoline ring seemed to have no significant influence in terms of lipophilicity results.

A plot of antimalarial IC_{50} values against log *D* values showed that there is no correlation between *P. falciparum* culture growth inhibition and lipophilicity of the ferrocenic compounds ($r^2 = 0.0184$).[21] Similarly, a plot of antimalarial IC_{50} values against β-hematin formation inhibition IC_{50} values did not show any linear correlation ($r^2 = 0.184$).[22] The high lipophilicity of the ferrocene nucleus should mask the influence of the alkyl part. Note here that we were unable to obtain pK_a values (owing to the low aqueous solubility of the FQ analogues) and thereafter to correct for the extent of pH trapping.[22]

The in vitro behavior of the FQ analogues (series A) with low IC_{50} and high IC_{90} values could not be easily explained and is undoubtly multifactorial. Evidently, the remarkable activity of FQ depends on the position of the ferrocenic nucleus in the side chain. 4-Aminoquinolines **6**, **7a**, and **7b** (series B) closely related to FQ, and designed to influence its physicochemical properties, showed similar antimalarial activity against both CQ-susceptible and CQ-resistant strains of *P. falciparum*.

This study supports the continued synthesis and investigation of ferrocenic CQ-like compounds in the search for "back-up" 4-aminoquinolines. Further studies on the relationship between bioorganometallics accumulation and activity (implicating or not the involvement of additional mechanisms) will be needed for drug design and development.

Experimental Section

Chemistry. The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC 300 MHz spectrometer using tetramethylsilane (TMS) as the internal standard and $CDCl_3$ or DMSO-d_6 as the solvent. D_2O was added to remove exchangeable protons. 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 a wavelength of 337 nm. Between 20 and 30 single-shot spectra in the reflector mode were accumulated to obtain a good signal-to-noise ratio. The matrix used was 2,4,6-trihydroxyacetophenone (thap). EI mass spectra were acquired with a quadrupole instrument (Nermag R 10-10 H). Melting points are uncorrected. Merck's Kieselgel 60 PF254 was used for the chromatography.

Ferroquine Analogues. Series A. *N*1-(7-Chloro-4-quinolyl)-2,2-dimethyl-1,3-propanediamine 12. 4,7-Dichloroquinoline (1,98 g, 10 mmol) and 2,2-dimethyl-1,3-propanediamine (4.59 g, 45 mmol) were placed in a round-bottom flask The mixture was stirred at 85 °C for 5 h. The mixture was allowed to cool to 50 °C before adding an aqueous solution of 1 N NaOH (10 mL). The mixture was stirred until it cooled to room temperature. The product was extracted with dichloromethane (3 × 50 mL). The combined organic fractions were washed with distilled water (5 × 50 mL). The organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure yielding the product (1.7 g, 6.45 mmol) as a white solid. Yield: 63%. M.p.: 94 °C. ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, $J = 5.3$ Hz, ArC_2-H), 7.93 (1H, d, $J = 1.7$ Hz, ArC_8-H), 7.73 (1H, d, $J = 8.8$ Hz, ArC_5-H), 7.33 (1H, dd, $J = 1.7$ and 8.8 Hz, ArC_6-H), 6.27 (1H, d, $J = 5.3$ Hz, ArC_3-H), 3.16 (2H, s, $ArNDCH_2$), 2.85 (2H, s, CH_2ND_2), 1.06 (6H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 151.9 150.9, 149.1, 134.5, 128.2, 124.7, 122.4, 117.7, 97.7, 55.6, 52.6, 33.7, 24.4.

Synthetic Procedure for 1a−d and 5a. A mixture of ferrocenecarboxaldehyde (1.02 equiv) and the appropriate *N*1-(7-chloro-4-quinolyl)-1,ω-alkyldiamine (1 equiv) were dissolved in dry methanol (50 mL) with 4 Å molecular sieves (7 g). The mixture was stirred for 1 to 5 h at room temperature depending on the diamine. An excess of sodium borohydride (15 equiv) was added slowly, and the resulting mixture was stirred for an additional 1 h. After addition of 0.6 N hydrochloric acid (100 mL) and water (100 mL), the aqueous layer was washed with diethyl ether (3 × 100 mL). The aqueous layer was basified by sodium carbonate (pH 7) and was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$. The product was purified by column chromatography on silica gel.

***N*1-(7-Chloro-4-quinolyl)-*N*2-ferrocenyl 1,2-ethanediamine 1a.** Yield: 80%. M.p.: 48 °C. ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, $J = 5.3$ Hz, ArC_2-H), 7.95 (1H, d, $J = 2.1$ Hz, ArC_8-H), 7.70 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.37 (1H, dd, $J = 2.1$ and 8.9 Hz, ArC_6-H), 6.40 (1H, d, $J = 5.4$ Hz, ArC_3-H), 4.18 (2H, m, Cp), 4.14 (2H, m, Cp), 4.12 (5H, s, Cp′), 3.58 (2H, s, $FcCH_2N$) 3.34 (2H, m, $ArNDCH_2$), 3.13 (2H, m, CH_2ND). ^{13}C NMR ($CDCl_3$) δ 151.9, 149.9, 149.0, 134.8, 128.5, 125.2, 121.4, 99.1, 86.2, 68.4, 68.4, 68.0, 48.3, 46.7, 41.9. MS-MALDI-TOF (thap): 444 (M ^{37}Cl + Na)$^+$, 442 (M ^{35}Cl + Na)$^+$, 421 (MH^+ ^{37}Cl), 420 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{22}H_{22}ClN_3Fe$) C, H, N.

***N*1-(7-Chloro-4-quinolyl)-*N*1-ferrocenyl-1,3-propanediamine 1b.** Yield: 69%. M.p.: 71 °C. ^{1}H NMR ($CDCl_3$) δ 8.47 (1H, d, $J = 5.3$ Hz, ArC_2-H), 7.90 (1H, d, $J = 2.2$ Hz, ArC_8-H), 7.60 (1H, d, $J = 9.0$ Hz, ArC_5-H), 7.21 (1H, dd, $J = 2.2$ and 9.0 Hz, ArC_6-H), 6.27 (1H, d, $J = 5.3$ Hz, ArC_3-H), 4.22 (2H, m, Cp), 4.20 (2H, m, Cp), 4.14 (5H, s, Cp′), 3.58 (2H, s, $FcCH_2N$), 3.37 (2H, m, $ArNDCH_2$), 2.96 (2H, m, CH_2ND), 1.91 (2H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ 152.1, 150.5, 134.5, 128.3, 124.8, 122.5, 98.0, 68.7, 68.5, 68.1, 49.5, 49.4, 44.2, 27.1. MS-MALDI-TOF (thap): 458 (M ^{37}Cl + Na)$^+$, 456 (M ^{35}Cl + Na)$^+$, 435 (MH^+ ^{37}Cl), 434 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal.($C_{23}H_{24}ClN_3Fe$) C, H, N.

***N*1-(7-Chloro-4-quinolyl)-*N*4-ferrocenyl-1,4-butanediamine 1c.** Yield: 77%. M.p.: 55 °C. ^{1}H NMR ($CDCl_3$) δ 8.47 (1H, d, $J = 5.3$ Hz, ArC_2-H), 7.90 (1H, d, $J = 2.0$ Hz, ArC_8-H), 7.64 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.27 (1H, dd, $J = 2.0$ and 8.9 Hz, ArC_6-H), 6.36 (1H, d, $J = 5.4$ Hz, ArC_3-H), 4.18 (2H, m, Cp), 4.14 (2H, m, Cp), 4.12 (5H, s, Cp′), 3.58 (2H, s, $FcCH_2N'$), 3.28 (2H, m, $ArNDCH_2$), 2.72 (2H, m, $CH_2N'D$), 1.86 (2H, m, CH_2), 1.67 (2H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ 152.0, 149.1, 134.6, 128.6, 125.0, 121.5, 98.8, 68.4, 68.2, 67.9, 49.0, 48.5, 43.1, 43.1, 27.7, 26.2. MS-MALDI-TOF(thap): 472 (M ^{37}Cl + Na)$^+$, 470 (M ^{35}Cl + Na)$^+$, 450 (MH^+ ^{37}Cl), 448 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{24}H_{26}ClN_3Fe$) C, H, N.

***N*1-(7-Chloro-4-quinolyl)-*N*6-ferrocenyl-1,6-hexanediamine 1d.** Yield: 62%. M.p.: 88 °C. ^{1}H NMR ($CDCl_3$) δ 8.52 (1H, d, $J = 5.3$ Hz, ArC_2-H), 7.95 (1H, d, $J = 2.0$ Hz, ArC_8-H), 7.75 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.37 (1H, dd, $J = 2.0$ and 8.9 Hz, ArC_6-H), 6.40 (1H, d, $J = 5.4$ Hz, ArC_3-H), 4.18 (2H, m, Cp), 4.14 (7H, m, Cp, Cp′), 3.58 (2H, s, $FcCH_2N'$) 3.32 (2H, m, $ArNDCH_2$), 2.72 (2H, m, $CH_2N'D$), 1.80 (2H, m, CH_2), 1.56 (6H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ 151.9, 128.5, 125.1, 121.2, 98.9, 68.5, 68.4, 67.8, 49.1, 48.9, 43.1, 29.7, 28.6, 26.9. MS-MALDI-TOF (thap): 500 (M ^{37}Cl + Na)$^+$, 498 (M ^{35}Cl + Na)$^+$, 478 (MH^+ ^{37}Cl), 476 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{26}H_{30}ClN_3Fe$) C, H, N.

***N*1-(7-Chloro-4-quinolyl)-*N*3-ferrocenyl-2,2-dimethyl-1,3-propanediamine 5a.** Yield: 84%. M.p.: 116 °C. ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, $J = 5.3$ Hz, ArC_2-H), 7.95 (1H, d, $J = 2.0$ Hz, ArC_8-H), 7.70 (1H, d, $J = 8.8$ Hz, ArC_5-H), 7.37 (1H, dd, $J = 2.0$ and 8.8 Hz, ArC_6-H), 6.40 (1H, d, $J = 5.6$ Hz, ArC_3-H), 4.18 (2H, m, Cp), 4.14 (2H, m, Cp), 4.12 (5H, s, Cp′), 3.58 (2H, s, $FcCH_2N'$), 3.16 (2H, s, $ArNDCH_2$), 2.72 (2H, s, CH_2ND_2), 1.09 (6H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 152.0, 150.9, 149.0, 134.4, 128.2, 124.7, 122.8, 117.7, 97.7, 85.6, 68.8, 68.5, 68.2, 61.0, 55.8, 50.2, 33.6, 24.9. MS-MALDI-TOF (thap): 486 (M ^{37}Cl + Na)$^+$, 484 (M ^{35}Cl + Na)$^+$, 464 (MH^+ ^{37}Cl), 462 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{25}H_{28}ClN_3Fe$) C, H, N.

Synthetic Procedure for 2a−d, 3a−d, and 5b,c. A mixture of the corresponding primary amine **1a−d** or **5a** (1 equiv) and aldehyde (see below, 10 equiv) was dissolved in dry methanol (10 mL). After addition of sodium cyanoborohydride (1.8 equiv), the mixture was stirred for 1 h at room temperature. The solvent was then removed under reduced pressure. The resulting oil was dissolved in dichloromethane and the solution filtered through

Celite. The product was purified using silica gel chromatography, eluting with diethyl ether−petroleum ether−triethylamine (6:3:1). Formaldehyde (37% solution in water) was used to introduce the methyl group, and acetaldehyde was used to introduce the ethyl group.

***N*1-(7-Chloro-4-quinolyl)-*N*2-ferrocenyl-*N*2-methyl-1,2-ethanediamine 2a.** Yield: 82%. M.p.: 163 °C. ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, J = 5.3 Hz, ArC_2-H), 7.95 (1H, d, J = 2.1 Hz, ArC_8-H), 7.70 (1H, d, J = 8.9 Hz, ArC_5-H), 7.37 (1H, dd, J = 2.1 and 8.9 Hz, ArC_6-H), 6.40 (1H, d, J = 5.3 Hz, ArC_3-H), 4.18 (2H, d, J = 2.0 Hz, Cp), 4.14 (2H, d, J = 2.0 Hz, Cp), 4.12 (5H, s, Cp′), 3.58 (2H, s, $FcCH_2N'$) 3.34 (2H, t, J = 5.0 Hz $ArNDCH_2$), 2.72 (2H, t, J = 5.0 Hz, $CH_2N'D$), 2.35 (3H, s, NCH_3). ^{13}C NMR ($CDCl_3$) δ 152.0, 128.5, 125.0, 121.5, 99.1, 83.0, 77.0, 68.5, 68.2, 57.0, 53.3, 41.5, 39.6. MS-MALDI-TOF (thap): 458 (M ^{37}Cl + Na)$^+$, 456 (M ^{35}Cl + Na)$^+$, 436 (MH^+ ^{37}Cl), 434 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{23}H_{24}ClN_3Fe$) C, H, N.

***N*1-(7-Chloro-4-quinolyl)-*N*3-ferrocenyl-*N*3-methyl-1,3-propanediamine 2b.** Yield: 72%. M.p.: 82 °C. ^{1}H NMR ($CDCl_3$) δ 8.47 (1H, d, J = 5.3 Hz, ArC_2-H), 7.90 (1H, d, J = 2.1 Hz, ArC_8-H), 7.60 (1H, d, J = 8.9 Hz, ArC_5-H), 7.21 (1H, dd, J = 2.1 and 8.9 Hz, ArC_6-H), 6.27 (1H, d, J = 5.3 Hz, ArC_3-H), 4.22 (2H, m, Cp), 4.20 (2H, m, Cp), 4.14 (5H, s, Cp′), 3.58 (2H, s, $FcCH_2N'$), 3.45 (2H, t, J = 5.0 Hz, $ArNDCH_2$), 2.67 (2H, t, J = 5.0 Hz, $CH_2N'D$), 2.40 (3H, s, NCH_3), 1.91 (2H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ 153.1, 152.0, 149.0, 148.9, 141.1 134.3, 132.9, 128.2, 124.9, 122.4, 101.0, 98.1, 82.7, 70.3, 68.5, 68.3, 57.7, 57.4, 51.5, 44.4, 30.3. MS-MALDI-TOF (thap): 482 (M ^{37}Cl + Na)$^+$, 480 (M ^{35}Cl + Na)$^+$, 450 (MH^+ ^{37}Cl), 448 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{24}H_{26}ClN_3Fe$), C, H.

***N*1-(7-Chloro-4-quinolyl)-*N*4-ferrocenyl-*N*4-methyl-1,4-butanediamine 2c.** Yield: 78%. M.p.: 118 °C. ^{1}H NMR ($CDCl_3$) δ 8.52 (1H, d, J = 5.3 Hz, ArC_2-H), 7.90 (1H, d, J = 2.1 Hz, ArC_8-H), 7.64 (1H, d, J = 8.9 Hz, ArC_5-H), 7.27 (1H, dd, J = 2.1 and 8.9 Hz, ArC_6-H), 6.36 (1H, d, J = 5.3 Hz, ArC_3-H), 4.18 (2H, m, Cp), 4.14 (2H, m, Cp), 4.12 (5H, s, Cp′), 3.48 (2H, s, $FcCH_2N'$), 3.28 (2H, m, $ArNDCH_2$), 2.42 (2H, m, $CH_2N'D$), 2.19 (3H, s, NCH_3), 1.86 (2H, m, CH_2), 1.67 (2H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ 161.6, 152.0, 150.2, 149.1, 134.5, 128.4, 124.7, 121.8, 117.4, 98.7, 82.4, 70.2, 68.5, 68.1, 56.8, 55.7, 43.0, 42.1, 26.4, 25.2. MS-MALDI-TOF(thap): 496 (M ^{37}Cl + Na)$^+$, 494 (M ^{35}Cl + Na)$^+$, 464 (MH^+ ^{37}Cl), 462 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{25}H_{28}ClN_3Fe$) C, H.

***N*1-(7-Chloro-4-quinolyl)-*N*6-ferrocenyl-*N*6-methyl-1,6-hexanediamine 2d.** Yield: 78%. M.p.: 112 °C. ^{1}H NMR ($CDCl_3$) δ 8.52 (1H, d, J = 5.3 Hz, ArC_2-H), 7.95 (1H, d, J = 1.9 Hz, ArC_8-H), 7.75 (1H, d, J = 8.9 Hz, ArC_5-H), 7.37 (1H, dd, J = 1.9 and 8.9 Hz, ArC_6-H), 6.40 (1H, d, J = 5.3 Hz, ArC_3-H), 4.18 (2H, m, Cp), 4.14 (7H, m, Cp, Cp′), 3.58 (2H, s, $FcCH_2N'$), 3.32 (2H, m, $ArNDCH_2$), 2.32 (2H, t, J = 5.0 Hz, $CH_2N'D$), 2.15 (3H, s, NCH_3), 1.80 (2H, m, CH_2), 1.56 (6H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ 152.0, 149.7, 149.1, 134.7, 128.6, 125.1, 120.7, 121.0, 117.1, 99.0, 82.9, 70.2, 68.4, 67.9, 57.2, 56.3, 43.1, 41.8, 28.7, 27.2, 27.0. MS-MALDI-TOF (thap): 514 (M ^{37}Cl + Na)$^+$, 512 (M ^{35}Cl + Na)$^+$, 492 (MH^+ ^{37}Cl), 490 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{27}H_{32}ClN_3Fe$) C, H.

***N*1-(7-Chloro-4-quinolyl)-*N*3-ferrocenyl-*N*3-methyl-2,2-dimethyl-1,3-propanediamine 5b.** Yield: 61%. M.p.: 130 °C. ^{1}H NMR ($CDCl_3$) δ 8.48 (1H, d, J = 5.3 Hz, ArC_2-H), 7.92 (1H, d, J = 2.1 Hz, ArC_8-H), 7.22 (1H, d, J = 9.0 Hz, ArC_5-H), 7.05 (1H, dd, J = 2.1 and 8.9 Hz, ArC_6-H), 6.30 (1H, d, J = 5.4 Hz, ArC_3-H), 4.18 (4H, m, Cp), 4.12 (5H, s, Cp′), 3.48 (2H, s, $FcCH_2N'$), 3.06 (2H, s, $ArNDCH_2$), 2.52 (2H, s, CH_2ND_2), 2.25 (3H, s, NCH_3), 1.09 (6H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 151.9, 150.7, 149.0, 134.3, 128.1, 124.8, 122.4, 117.6, 97.6, 83.5, 70.2, 69.5, 68.4, 59.8, 55.6, 50.4, 44.3, 34.2, 25.6. MS-MALDI-TOF (thap): 500 (M ^{37}Cl + Na)$^+$, 498 (M ^{35}Cl + Na)$^+$, 478 (MH^+ ^{37}Cl), 476 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{26}H_{30}ClN_3Fe$) C, H.

***N*1-(7-Chloro-4-quinolyl)-*N*2-ethyl-*N*2-ferrocenyl-1,2-ethanediamine 3a.** Yield: 75%. M.p.: 138 °C. ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, J = 5.3 Hz, ArC_2-H), 7.95 (1H, d, J = 2.1 Hz, ArC_8-H), 7.63 (1H, d, J = 8.9 Hz, ArC_5-H), 7.37 (1H, dd, J = 2.1 and 8.9 Hz, ArC_6-H), 6.40 (1H, d, J = 5.3 Hz, ArC_3-H), 4.18 (2H, m, Cp), 4.14 (2H, m, Cp), 4.12 (5H, s, Cp′), 3.58 (2H, s, $FcCH_2N'$) 3.34 (2H, m, $ArNDCH_2$), 2.72 (2H, t, J = 5.0, $CH_2N'Et$), 2.67 (2H, q, $N'CH_2CH_3$), 1.13 (3H, t, $N'CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 152.1, 128.6, 125.0, 121.4, 99.1, 83.4, 69.9, 68.5, 68.2, 52.4, 50.0, 46.9, 39.7, 12.4. MS-MALDI-TOF (thap): 472 (M ^{37}Cl + Na)$^+$, 470 (M ^{35}Cl + Na)$^+$, 450 (MH^+ ^{37}Cl), 448 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{24}H_{26}ClN_3Fe$) C, H.

***N*1-(7-Chloro-4-quinolyl)-*N*3-ethyl-*N*3-ferrocenyl-1,3-propanediamine 3b.** Yield: 69%. M.p.: 99 °C. ^{1}H NMR ($CDCl_3$) δ 8.47 (1H, d, J = 5.3 Hz, ArC_2-H), 7.90 (1H, d, J = 2.1 Hz, ArC_8-H), 7.60 (1H, d, J = 8.9 Hz, ArC_5-H), 7.21 (1H, dd, J = 2.1 and 8.9 Hz, ArC_6-H), 6.27 (1H, d, J = 5.3 Hz, ArC_3-H), 4.22 (2H, m, Cp), 4.20 (2H, m, Cp), 4.14 (5H, s, Cp′), 3.58 (2H, s, $FcCH_2N'$), 3.45 (2H, m, $ArNDCH_2$), 2.67 (2H, m, $CH_2N'Et$), 2.60 (2H, q, J = 7.0 Hz, $N'CH_2CH_3$), 1.91 (2H, m, $ArNDCH_2CH_2CH_2N'D$), 1.13 (3H, t, J = 7.0 Hz, $N'CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 152.0, 128.3, 124.6, 122.6, 98.1, 82.7, 70.2, 68.5, 68.3, 53.3, 52.9, 47.0, 44.6, 24.2, 11.3. MS-MALDI-TOF (thap): 486 (M ^{37}Cl + Na)$^+$, 484 (M

Table 3. Measured Values of Drug Lipophilicity (log D) at Two Different pHs (pH 5.2 and pH 7.4)

compound	log D, pH = 5.2	log D, pH =7.4
FQ	−0.77	2.95
CQ	−1.2	0.85
1a	−0.08	3.02
1c	−0.21	2.29
2a	0.72	2.97
2b	−0.15	3.1
2c	−0.62	2.77
2d	−0.21	3.52
3a	0.65	3.61
3b	−0.54	2.87
3c	−0.12	3.39
3d	−0.24	3.42
4a	2.55	4.01
4b	1.83	4.78
5b	1.32	4.4
5c	1.69	4.2
6	−0.24	3.42
7a	−1.18	1.95
7b	−0.69	3.19
8a	1.07	4.13
8b	1.7	4.35

Table 4. Series A Analogues: In Vitro Inhibition of β-Hematin Formation

compd	IC_{50} (μM), β-hematin formation	±SEM	n^a
CQ	46.3	9.5	10
FQ.2 HCl	23.0	15.1	4
1a	9.3		2
1b	22.7		2
1c	45.9		2
1d	ND[b]		
2a	43.05	4.3	3
2b	52.7		2
2c	46.0		2
2d	24.8		2
3a	57.4		2
3b	33.5		2
3c	ND[b]		
3d	28.5		2
4a	ND[b]		
4b	>100		2
4c	ND[b]		
4d	>100		2
5a	35.6		2
5b	59.9		2
5c	ND[b]		

[a] n: number of experiments. [b] ND: Not determined. Compounds **1d**, **3c**, **4a**, **4c**, and **5c** showed (partial) insolubility under the experimental conditions used.

$^{35}Cl + Na)^+$, 464 (MH^+ ^{37}Cl), 462 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{25}H_{28}ClN_3Fe$) C, H.

***N*1-(7-Chloro-4-quinolyl)-*N*4-ethyl-*N*4-ferrocenyl-1,4-butanediamine 3c.** Yield: 88%. M.p.: 122 °C. ^1H NMR ($CDCl_3$) δ 8.52 (1H, d, $J = 5.3$ Hz, ArC_2-H), 7.90 (1H, d, $J = 2.1$ Hz, ArC_8-H), 7.64 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.27 (1H, dd, $J = 2.1$ and 8.9 Hz, ArC_6-H), 6.36 (1H, d, $J = 5.3$ Hz, ArC_3-H), 4.18 (2H, m, Cp), 4.14 (2H, m, Cp), 4.12 (5H, s, Cp′), 3.48 (2H, s, $FcCH_2N'$), 3.28 (2H, m, $ArNDCH_2$), 2.42 (4H, m, $CH_2N'Et$, $N'CH_2CH_3$), 1.86 (2H, m, CH_2), 1.67 (2H, m, CH_2), 1.13 (3H, t, $J = 7.0$ Hz, $N'CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 152.0, 128.5, 124.8, 121.6, 98.9, 70.2, 68.4, 68.0, 52.5, 51.7, 46.9, 42.9, 26.5, 25.1, 11.4. MS-MALDI-TOF (thap): 500 (M $^{37}Cl + Na)^+$, 498 (M $^{35}Cl + Na)^+$, 479 (MH^+ ^{37}Cl), 477 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{26}H_{30}ClN_3Fe$) C, H.

***N*1-(7-Chloro-4-quinolyl)-*N*6-ethyl-*N*6-ferrocenyl-1,6-hexanediamine 3d.** Yield: 78%. M.p.: 109 °C. ^1H NMR ($CDCl_3$) δ 8.52 (1H, d, $J = 5.3$ Hz, ArC_2-H), 7.95 (1H, d, $J = 2.1$ Hz, ArC_8-H), 7.75 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.37 (1H, dd, $J = 2.1$ and 8.9 Hz, ArC_6-H), 6.40 (1H, d, $J = 5.3$ Hz, ArC_3-H), 4.18 (2H, m, Cp), 4.14 (7H, m, Cp, Cp′), 3.58 (2H, s, $FcCH_2N'$) 3.32 (2H, m, $ArNDCH_2$), 2.32 (4H, m, $CH_2N'CH_2$), 1.80 (2H, m, $(CH_2)_4$), 1.56 (6H, m, $(CH_2)_4$), 1.08 (3H, t, $J = 7.1$ Hz, $N'CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ 152.0, 128.8, 125.2, 120.7, 99.0, 70.0, 68.4, 67.8, 52.4, 52.4, 46.8, 43.2, 28.8, 27.2, 27.0, 12.0. MS-MALDI-TOF (thap): 527 (M $^{37}Cl + Na)^+$, 525 (M $^{35}Cl + Na)^+$, 505 (MH^+ ^{37}Cl), 503 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{28}H_{34}ClN_3Fe$) C, H.

***N*1-(7-Chloro-4-quinolyl)-*N*3-ethyl-*N*3-ferrocenyl-2,2-dimethyl-1,3-propanediamine 5c.** Yield: 69%. M.p.: 155 °C. ^1H NMR ($CDCl_3$) δ 8.48 (1H, d, $J = 5.4$ Hz, ArC_2-H), 7.92 (1H, d, $J = 2.1$ Hz, ArC_8-H), 7.22 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.05 (1H, dd, $J = 2.1$ and 8.9 Hz, ArC_6-H), 6.30 (1H, d, $J = 5.4$ Hz, ArC_3-H), 4.18 (4H, m, Cp), 4.12 (5H, s, Cp′), 3.48 (2H, s, $FcCH_2N'$), 3.06 (2H, s, $ArNDCH_2$), 2.69 (2H, q, $J = 7.0$ Hz, $N'CH_2Me$), 2.52 (2H, s, CH_2NEt), 1.19 (3H, t, $J = 7.0$ Hz, $N'CH_2Me$), 1.09 (6H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 152.0, 150.7, 149.0, 134.3, 128.2, 124.6, 122.6, 117.7, 97.8, 83.5, 70.1, 68.5, 68.3, 65.6, 55.8, 55.2, 48.6, 34.1, 25.8, 10.6. MS-MALDI-TOF (thap): 514 (M $^{37}Cl + Na)^+$, 512 (M $^{35}Cl + Na)^+$, 492 (MH^+ ^{37}Cl), 490 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$. Anal. ($C_{27}H_{32}ClN_3Fe$) C, H.

Synthetic Procedure for 4a−d. Bisferrocene **4a−d** were obtained from the same procedure as reported above. A mixture of the corresponding primary amine **1a−d** (1 equiv) and ferrocene carboxaldehyde (3 equiv) was dissolved in dry methanol (10 mL). After addition of sodium cyanoborohydride (1.8 equiv), the mixture was stirred for 1 h at room temperature. The solvent was then removed under reduced pressure. The resulting oil was dissolved in dichloromethane and the solution filtered through Celite. The product was then purified using silica gel chromatography, eluting with diethyl ether−petroleum ether−triethylamine (6:3:1).

***N*1,*N*1-Bisferrocenyl-*N*2-(7-chloro-4-quinolyl)-1,2-ethanediamine 4a.** Yield: 14%. M.p.: 181 °C. ^1H NMR ($CDCl_3$) δ 8.50 (1H, d, $J = 5.3$ Hz, ArC_2-H), 7.95 (1H, d, $J = 2.1$ Hz, ArC_8-H), 7.50 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.32 (1H, dd, $J = 2.1$ and $J = 8.9$ Hz, ArC_6-H), 6.34 (1H, d, $J = 5.4$ Hz, ArC_3-H), 4.18 (8H, m, Cp), 4.12 (10H, s, Cp′), 3.48 (4H, s, $FcCH_2N'$) 3.11 (2H, m, $ArNDCH_2$), 2.75 (2H, m, $CH_2N'D$). ^{13}C NMR ($CDCl_3$) δ 151.9, 149.7, 134.7, 128.4, 124.9, 121.6, 99.0, 83.5, 69.9, 68.5, 68.2, 53.1, 48.9, 39.6. MS-MALDI-TOF (thap): 642 (M $^{37}Cl + Na)^+$, 640 (M $^{35}Cl + Na)^+$, 420 (MH^+ ^{37}Cl), 618 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$.

***N*1,*N*1-Bisferrocenyl-*N*3-(7-chloro-4-quinolyl)-1,3-propanediamine 4b.** Yield: 79%. M.p.: 173 °C. ^1H NMR ($CDCl_3$) δ 8.47 (1H, d, $J = 5.3$ Hz, ArC_2-H), 7.90 (1H, d, $J = 2.1$ Hz, ArC_8-H), 7.82 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.15 (1H, dd, $J = 2.1$ and $J = 8.9$ Hz, ArC_6-H), 6.25 (1H, d, $J = 5.4$ Hz, ArC_3-H), 4.22 (8H, m, Cp), 4.14 (10H, s, Cp′), 3.48 (4H, s, $FcCH_2N'$), 3.27 (2H, m, $ArNDCH_2$), 2.65 (2H, m, $CH_2N'D$), 1.90 (2H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ 152.0, 150.6, 149.0, 134.4, 128.1, 123.0, 117.5, 98.1, 82.5, 70.3, 68.5, 68.3, 52.9, 44.4, 24.2. MS-MALDI-TOF (thap): 656 (M $^{37}Cl + Na)^+$, 654 (M $^{35}Cl + Na)^+$, 634 (MH^+ ^{37}Cl), 632 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$.

***N*1,*N*1-Bisferrocenyl-*N*4-(7-chloro-4-quinolyl)-1,4-butanediamine 4c.** Yield: 30%. M.p.: 191 °C. ^1H NMR ($CDCl_3$) δ 8.47 (1H, d, $J = 5.4$ Hz, ArC_2-H), 7.94 (1H, d, $J = 2.1$ Hz, ArC_8-H), 7.64 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.30 (1H, dd, $J = 2.1$ and $J = 8.9$ Hz, ArC_6-H), 6.36 (1H, d, $J = 5.4$ Hz, ArC_3-H), 4.18 (4H, m, Cp), 4.14 (4H, m, Cp), 4.12 (10H, s, Cp′), 3.48 (4H, s, $FcCH_2N'$), 3.28 (2H, m, $ArNDCH_2$), 2.41 (2H, m, $CH_2N'D$), 1.80 (2H, m, $(CH_2)_2$), 1.67 (2H, m, $(CH_2)_2$). ^{13}C NMR ($CDCl_3$) δ 152.0, 150.0, 135.9, 128.6, 124.7, 121.7, 117.3, 98.9, 82.8, 70.2, 68.5, 68.0, 52.9, 50.8, 42.8, 26.2, 24.9. MS-MALDI-TOF (thap): 670 (M $^{37}Cl + Na)^+$, 668 (M $^{35}Cl + Na)^+$, 648 (MH^+ ^{37}Cl), 646 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$.

***N*1,*N*1-Bisferrocenyl-*N*6-(7-chloro-4-quinolyl)-1,6-hexanediamine 4d.** Yield: 41%. M.p.: 158 °C. ^1H NMR ($CDCl_3$) δ 8.52 (1H, d, $J = 5.4$ Hz, ArC_2-H), 7.96 (1H, d, $J = 2.1$ Hz, ArC_8-H), 7.91 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.63 (1H, dd, $J = 2.1$ and 8.9 Hz, ArC_6-H), 6.39 (1H, d, $J = 5.4$ Hz, ArC_3-H), 4.16 (4H, m, Cp), 4.11 (4H, m, Cp), 4.08 (10H, s, Cp′), 3.41 (4H, s, $FcCH_2$), 3.26 (2H, m, $ArNDCH_2$), 2.27 (2H, m, CH_2N'), 1.71 (2H, m, CH_2), 1.40 (4H, m, CH_2), 1.30 (2H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ 152.03, 149.08, 128.78, 125.23, 120.89, 99.03, 83.48, 70.18, 68.51, 67.83, 52.74, 51.55, 43.04, 28.77, 27.01, 26.85. MS-MALDI-TOF (thap): 700 (M $^{37}Cl + Na)^+$, 698 (M $^{35}Cl + Na)^+$, 678 (MH^+ ^{37}Cl), 675 (MH^+ ^{35}Cl), 199 $(FcCH_2)^+$.

Ferroquine Analogues. Series B. The synthesis of compounds **7a−b** and **8a−c** is analogous to the synthesis of compounds **2a−d**, **3a−d**, and **4a−d**.

***N*4-{2-[Ethyl(methyl)amino]methylferrocenyl}-7-chloro-4-quinolinamine 7b.** Yield: 65%. M.p.: 130 °C. ^1H NMR ($CDCl_3$) δ 8.52 (1H, d, $J = 5.4$ Hz, ArC_2-H), 7.91 (1H, d, $J = 2.1$ Hz, ArC_8-H), 7.65 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.27 (1H, dd, $J = 2.1$ and 8.9 Hz, ArC_6-H), 6.46 (1H, d, $J = 5.4$ Hz, ArC_3-H), 4.35 (1H, d, $J = 13.1$ Hz, $ArNDCH_2$), 4.25 (1H, m, Cp), 4.17 (3H, m, $ArNDCH_2$, Cp), 4.13 (5H, s, Cp′), 4.06 (1H, m, Cp), 3.82 (1H, d, $J = 12.6$ Hz, $FcCH_2NRR'$), 2.90 (1H, d, $J = 12.6$ Hz, $FcCH_2NRR'$), 2.61 (1H, m, NCHMe), 2.37 (1H, m, NCHMe), 2.15 (3H, s, CH_3), 1.01 (3H, m, CH_3). ^{13}C NMR ($CDCl_3$) δ 125.0, 150.1, 149.3, 134.6, 128.2, 124.5, 122.5, 117.7, 98.9, 84.1, 83.8, 71.6, 70.4, 69.2, 65.9, 55.4, 51.1, 42.2, 41.3, 11.5. EIMS m/z 449 ($M^{\cdot+}$ 37Cl), 447 ($M^{\cdot+}$ 35Cl), 390 (M-HNEtMe)$^+$ ^{37}Cl, 388 (M-HNEtMe)$^+$ ^{35}Cl. Anal. ($C_{25}H_{28}ClN_3Fe$) C, H, N.

***N*4-{2-[(Ferrocenylamino)methyl]ferrocenyl}-7-chloro-4-quinolinamine 8a.** Yield: 45%. M.p.: 194 °C. ^1H NMR ($CDCl_3$) δ 8.49 (1H, d, $J = 5.4$ Hz, ArC_2-H), 7.87 (1H, d, $J = 2.1$ Hz, ArC_8-H), 7.55 (1H, d, $J = 8.9$ Hz, ArC_5-H), 7.05 (1H, dd, $J = 2.1$ and 8.9 Hz, ArC_6-H), 6.42 (1H, d, $J = 5.4$ Hz, ArC_3-H), 4.20 (1H, d, $J = 13.1$ Hz, $ArNDCH_2$), 4.23 (1H, m, Cp), 4.17 (1H, m, Cp), 4.15 (5H, s, Cp′), 4.08 (5H, s, Cp′), 4.10 (7H, m, Cp), 3.70 (1H, d, $J = 12.3$ Hz, $FcCH_2NRR'$), 3.53 (2H, m, CH_2Fc). ^{13}C NMR ($CDCl_3$) δ 151.9, 149.9, 149.1, 134.5, 128.5, 125.0, 122.8, 117.6, 98.8, 85.6, 85.2, 83.5, 70.5, 70.3, 69.2, 68.9, 68.7, 68.5, 68.2, 66.1, 48.9, 47.5, 42.0. EIMS m/z 605 ($M^{\cdot+}$ 37Cl), 603 ($M^{\cdot+}$ 35Cl), 390 (M-$FcCH_2NH_2$)$^+$ ^{37}Cl, 388 (M-$FcCH_2NH_2$)$^+$ ^{35}Cl. Anal. ($C_{32}H_{30}ClFe_2N_3$) C, H, N.

***N*4-{2-[Ferrocenyl(methyl)amino]methylferrocenyl}-7-chloro-4-quinolinamine 8b.** Yield: 80%. M.p.: 90 °C. ^1H NMR ($CDCl_3$) δ 8.47 (1H, d, $J = 5.5$ Hz, ArC_2-H), 7.83 (1H, d, $J = 2.1$ Hz, ArC_8-H), 7.24 (1H, d, $J = 8.9$ Hz, ArC_5-H), 6.94 (1H, dd, $J = 2.1$ and 8.9 Hz, ArC_6-H), 6.43 (1H, d, $J = 5.5$ Hz, ArC_3-H), 4.24 (2H, m, $ArNDCH_2$), 4.16 (2H, m, Cp), 4.12 (5H, s, Cp′), 4.10 (2H, m, Cp), 4.07 (5H, s, Cp′), 3.97 (1H, m, Cp), 3.85 (1H, d, $J = 12.6$ Hz, $FcCH_2NRR'$), 3.51 (1H, d, $J = 12.8$ Hz, CH_2Fc), 3.25 (1H, d, $J = 12.8$ Hz, CH_2Fc), 2.91 (1H, d, $J = 12.6$ Hz, $FcCH_2NRR'$), 2.01 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 151.5, 150.4, 148.7, 134.7, 127.5, 124.9, 122.9, 117.7, 98.8, 84.0, 83.9, 82.5, 71.4, 70.6, 70.5, 70.3, 69.2, 68.5, 68.3, 65.9, 56.9, 56.1, 42.1, 41.1. EIMS m/z 619 (MH^+ ^{37}Cl), 618 (MH^+ ^{35}Cl), 389 (M − N($FcCH_2$)(CH_3))$^+$ ^{37}Cl, 387 (M − N($FcCH_2$)(CH_3))$^+$ ^{35}Cl. Anal. ($C_{33}H_{32}ClFe_2N_3$) C, H, N.

***N*4-{2-[Ferrocenyl(ethyl)amino]methylferrocenyl}-7-chloro-4-quinolinamine 8c.** Yield: 56%. M.p.: 67 °C. ^1H NMR ($CDCl_3$)

δ 8.48 (1H, d, J = 5.4 Hz, ArC_2-H), 7.84 (1H, d, J = 2.1 Hz, ArC_8-H), 7.27 (1H, d, J = 8.9 Hz, ArC_5-H), 6.97 (1H, dd, J = 2.1 and 8.9 Hz, ArC_6-H), 6.40 (1H, d, J = 5.4 Hz, ArC_3-H), 4.26 (1H, m, Cp), 4.21 (2H, m, $ArCH_2ND$), 4.11 (4H, m, Cp), 4.08 (5H, s, Cp′), 4.04 (5H, s, Cp′), 4.00 (1H, m, Cp), 3.86 (1H, m, Cp), 3.80 (1H, d, J = 12.8 Hz, $FcCH_2NRR'$), 3.64 (1H, d, J = 13.2 Hz, $FcCH_2$), 3.17 (1H, d, J = 13.2 Hz, $FcCH_2$), 2.98 (1H, d, J = 12.8 Hz, $FcCH_2NRR'$), 2.60 (1H, m, CH_2Me), 2.25 (1H, m, CH_2Me), 0.85 (3H, t, J = 7.1 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 151.9, 150.1, 149.1, 134.5, 128.0, 124.7, 123.0, 117.7, 98.9, 84.7, 83.8, 82.9, 71.6, 70.6, 70.5, 70.2, 69.2, 68.5, 68.1, 65.9, 52.2, 51.6, 46.4, 42.3, 10.1. EIMS m/z 634 (MH^+ ^{37}Cl), 632 (MH^+ ^{35}Cl), 389 ($M - N(FcCH_2)(C_2H_5)$)$^+$ ^{37}Cl, 387 ($M - N(FcCH_2)(C_2H_5)$)$^+$ ^{35}Cl. Anal. ($C_{34}H_{34}ClFe_2N_3$) C, H, N.

Antimalarial Activity. Chloroquine diphosphate was purchased from Sigma. Ferroquine base (SR97276) was obtained from Sanofi Synthélabo (France), and RPMI 1640 culture medium was purchased from Life Technologies. Human erythrocytes and plasma were obtained through the EFS (Etablissement Français du Sang, France).

The HB3, Dd2, and W2 clones of *P. falciparum* were used as a control for sensitivity to chloroquine and ferroquine. The subclone of *P. falciparum* clone W2 was provided by Dr B. Pradines (PHARO Marseille, France). Parasites were grown in vitro. The microdilution radioisotope technique of Desjardins was used. IC_{50} and IC_{90} were calculated from response curves by linear interpolation. The critical threshold for IC_{50} was considered as 100 nM, which is the critical value recognized for definition of CQ resistance in *P. falciparum*, and was considered equivalent for FQ resistance in field studies. Comparison within molecules was done using chloroquine as internal standard.

Inhibition of β-Hematin Formation. Experiments were carried out in duplicate, in 96-deep-wells. In each well, 250 μL of a solution of 700 μM of hemin in 25 mM NaOH were added to 250 μL of a suspension of 1 mM 1-monooleoylglycerol in 90 mM sodium acetate at pH 5. Drugs were added from DMSO stock solutions (5 μL). Microplates were incubated for 24 h at 37 °C. Controls contained an equal amount of DMSO. Following incubation, the samples were centrifuged at 4000 rpm at 4 °C for 30 min. The pellet of β-hematin was washed with 10 mM sodium phosphate, pH 7.4, containing 2.5% SDS, and was vortexed for 10 min at 20 °C before repelleting until the supernatant was colorless (five times). Dissolution of β-hematin was achieved by addition of 450 μL of 10 mM sodium phosphate, pH 7.4, containing 2.5% SDS and 25 μL of NaOH 1 M. Concentration of heme was calculated from absorbance at 405 nm.

Partition Coefficients: log *D* (pH 7.4 or pH 5.2). The relative log D (pH 7.4 or 5.2) in this study was assessed by the micro-HPLC method. These determinations were performed with a chromatographic apparatus (Spectra Series, San Jose, CA) equipped with a model P1000XR pump and a model SCM 1000 vacuum membrane degasser, a model UV 150 ultraviolet detector (λ = 330 nm), and a ChromJet data module integrator (ThermoFinnigan, San Jose, CA). A reversed phase column was used: a Waters XTerraMS C_{18} (3.9 × 150 mm; 5 μm particle size) with a mobile phase consisting of acetonitrile−phosphate buffer [KH_2PO_4/K_2HPO_4] (pH = 7) (60:40,v/v (FQ, **1a**, **1c**, **2a**−**d**, **3b**, **3d**, and **4a**), and 20:80, v/v (CQ)), acetonitrile−phosphate buffer (pH = 6) (60:40,v/v (**3c** and **8a**), 50:50, v/v (**3a** and **6** and **7b**) and 40:60,v/v (**7a**)), acetonitrile−phosphate buffer (pH = 5) (60:40,v/v (**4b**, **5b**, **5c**, and **8b**).

The compounds were partitioned between *n*-octanol (HPLC grade) and phosphate buffer (pH = 5.2 or 7.4). Octanol was presaturated with buffer, and conversely. An amount of 1 mg of each compound was dissolved in an adequate volume of methanol in order to achieve 1 mg/mL stock solutions. Then an appropriate aliquot of these methanolic solutions was dissolved in buffer to obtain final concentration of 100 μg/mL. Under the above-described chromatographic conditions, 20 μL of this aqueous phase was injected into the chromatograph, leading to the determination of a peak area before partitioning (W_0).

In screw-capped tubes, 500 μL of the aqueous phase (V_{aq}) was then added to 100 μL of *n*-octanol (V_{oct}) when working at pH = 5.2; V_{aq} = 2000 μL and V_{oct} = 10 μL for determination at pH = 7.4. The mixture was shaken by mechanical rotation during 30 min. Then the centrifugation was achieved at 3000 rpm in 15 min. An amount of 20 μL of the lower phase was injected into the chromatograph column. This led to the determination of a peak area after partitioning (W_1). The log D was determined by the formula:

$$\log D = \log [(W_0 - W_1)V_{aq}/W_1V_{oct}]$$

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Supporting Information Available: Combustion analyses for target compounds **1a**−**d**, **2a**−**d**, **3a**−**d**, **5a**−**c**, **7b**, and **8a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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