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# New ferrocenic pyrrolo[1,2-*a*]quinoxaline derivatives: Synthesis, and in vitro antimalarial activity

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ABSTRACT

Following our search for antimalarial compounds, novel series of ferrocenic pyrrolo[1,2-*a*]quinoxaline derivatives **1–2** were synthesized from various substituted nitroanilines and tested for in vitro activity upon the erythrocytic development of *Plasmodium falciparum* strains with different chloroquine-resistance status. The pyrrolo[1,2-*a*]quinoxalines **1** were prepared in 6–8 steps through a regioselective palladium-catalyzed monoamination by coupling 4-chloropyrrolo[1,2-*a*]quinoxalines with 1,3-bis(aminopropyl)piperazine or -methylamine using Xantphos as the ligand. The ferrocenic bispyrrolo[1,2-*a*]quinoxalines **2** were prepared by reductive amination of previously described bispyrrolo[1,2-*a*]quinoxalines **9** with ferrocene-carboxaldehyde, by treatment with $NaHB(OAc)_3$. The best results were observed with ferrocenic pyrrolo[1,2-*a*]quinoxalines linked by a bis(3-aminopropyl)piperazine. Moreover, it was observed that a methoxy group on the pyrrolo[1,2-*a*]quinoxaline nucleus and no substitution on the terminal *N*-ferrocenylmethylamine function enhanced the pharmacological activity. Selected compounds **1b**, **1f–h**, **1l** and **2a** were tested for their ability to inhibit β-haematin formation, the synthetic equivalent of hemozoin, by using the HPIA (heme polymerization inhibitory activity) assay. Of the tested compounds, only **2a** showed a β-haematin formation inhibition, but no inhibition of haem polymerization was observed with the other selected ferrocenic monopyrrolo[1,2-*a*]quinoxaline derivatives **1b**, **1f–h** and **1l**, as the $IC_{50}$ values were superior to 10 equivalents.



## 1. Introduction

Parasitic infections caused by *Plasmodium* species are responsible for malaria, a severe disease causing 300–500 millions of cases and 1.1 million deaths per years in tropical zones worldwide according to World Health Organization estimations.[1–3] The most virulent protozoa, *P. falciparum* is the main cause of severe clinical malaria and death and shows an increasing prevalence of resistance to standard antimalarial drugs.[4,5] Chloroquine (CQ)[6] is, after 50 years, still a mainstream drug in the fight against malaria, but its efficacy is being eroded by the emergence of resistant parasites. This resistance to antimalarial drugs like CQ is widespread throughout much of Africa and other parts of the developing world where malaria transmission is high.[7,8] The need of active antiplasmodial drugs with new mode of action becomes more and more urgent to replace ineffective drugs. This has led to the search for novel antimalarial drugs that might circumvent the resistance mechanism of the parasite. Two series of compounds that show promise in this regard are the bisquinoline and bisacridine antimalarial drugs **A** and **B** (Fig. 1).[9–12] These drugs show much lower resistance indices than chloroquine, indicating that the bisquinoline or bisacridine structures are less efficiently excluded by drug-resistant parasites. An other method to overcome CQ efflux consists of designing monoquinolines **C** linked by a 1,4-bis(3-aminopropyl)piperazine substituted by a large variety of terminal groups.[13–16]For several years, it was proposed a strategy for the development of organometallic-based antimalarial drugs.[17–19] Given the avidity of *Plasmodium* for free iron, it was postulated that an effective way of removing the chloroquine resistance of parasites might be the addition of iron to a chloroquine molecule and that a ferrocene moiety will permit to vectorize the drug to the selected target. Hence, some new organometallic compounds including a ferrocene nucleus (dicyclopentadienyl iron) incorporated on

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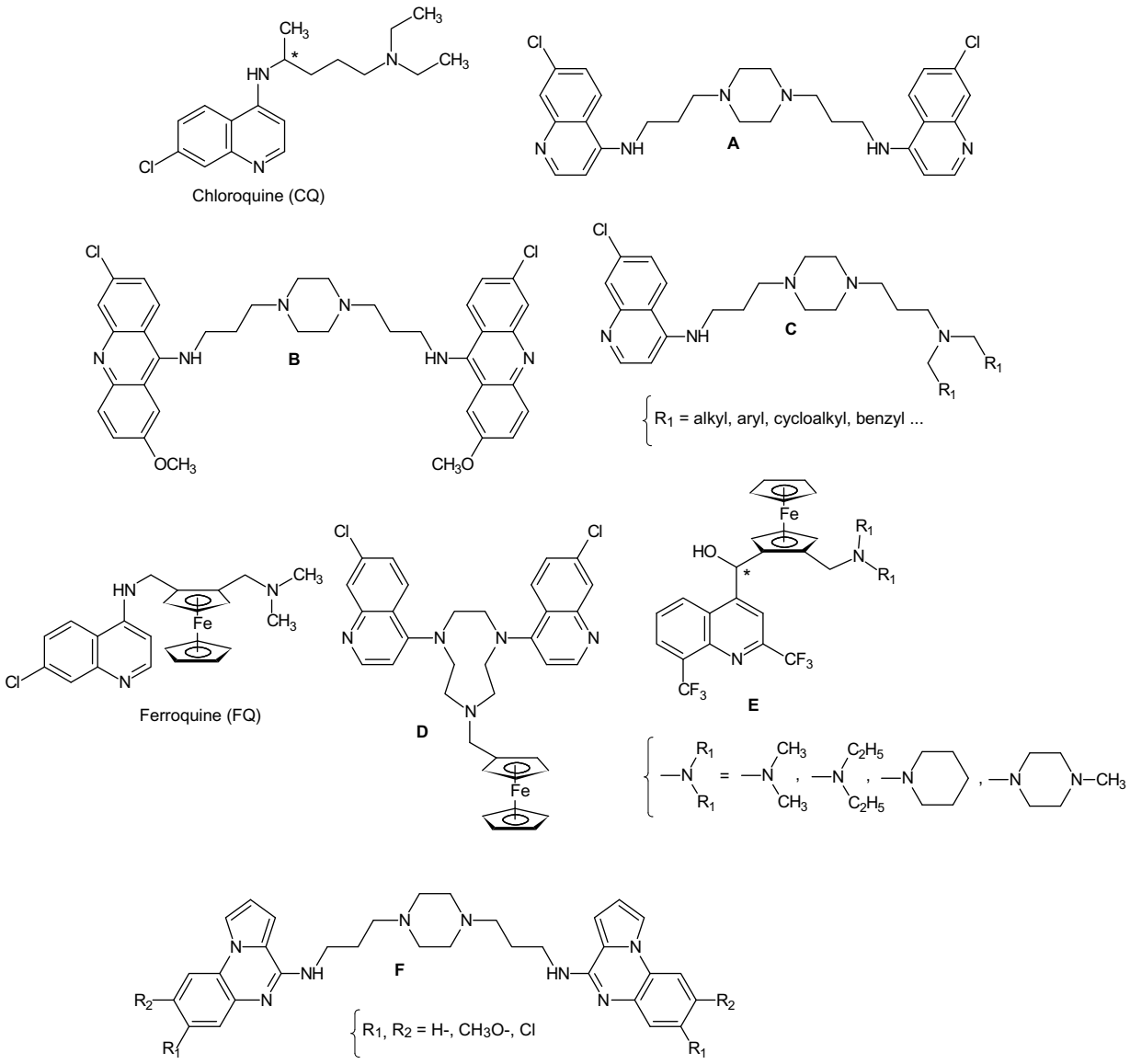



**Figure 1.** Structure of chloroquine (CQ), bisquinolines **A**, bisacridines **B**, quinolinylpiperazines **C**, ferroquine (FQ), ferrocenyl triazacyclononanes **D**, ferrocenic mefloquine analogues **E**, and bispyrrolo[1,2-*a*]quinoxalines **F**.

chloroquine were designed, which led to the discovery of ferroquine (FQ) and of structural analogues.[20–25] Then, new organometallic antimalarial compounds were investigated, for example, ferrocene triazacyclononane quinolines **D** and ferrocenic mefloquine analogues **E**.[26,27]

As we previously described a novel synthetic approach to pyrrolo[1,2-*a*]quinoxalines as analogues of quinoline derivatives[28–30] such as antimalarial bis{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}piperazines **F** (Fig. 1)[31] we used the pyrrolo[1,2-*a*]quinoxaline moiety as a template for the design of new antimalarial ferrocenic monoquinoline bioisostere compounds. Hence, we report here the synthesis and in vitro antiparasitic activity upon *Plasmodium falciparum* or a series of ferrocenic pyrrolo[1,2-*a*]quinoxalines **1–2** in which the heterocyclic and ferrocenic moieties are linked through a bis(3-aminopropyl)amine via a "pseudo-amidinic" bond (Fig. 2). The choice of the linker was based, in particular, on previous results obtained for bispyrrolo[1,2-*a*]quinoxalines **F**. From biological results obtained for the new ferrocenic pyrrolo[1,2-*a*]quinoxaline derivatives **1–2**, preliminary structure-affinity relationships may be drawn, in relation to the chemical nature of both linker and substituents on the pyrroloquinoxaline moiety. Finally, pharmacological results will be discussed in terms of the lipophilic behaviour of synthesized compounds quantified through the partitioning theory.

## 2. Results and discussion

### 2.1. Chemistry

The new ferrocenic pyrrolo[1,2-*a*]quinoxaline derivatives **1a–n**, and **2a–b** were synthesized from substituted 2-nitro-anilines (Scheme 1). The Clauson–Kaas reaction achieved on anilines with 2,5-dimethoxytetrahydrofuran (DMTHF) in acetic acid gave the pyrrolic derivatives **3a–b** (75–81% yields), which were then reduced using a $BiCl_3$–$NaBH_4$ treatment to provide the attempted 1-(2-aminophenyl)pyrroles **4a–b** (Scheme 1). Cyclization between the $NH_2$ and the C-α of the pyrrole ring was performed by reacting **4a–b** with triphosgene in toluene to give the lactams **5a–f**, which were subsequently chlorodehydroxylated with

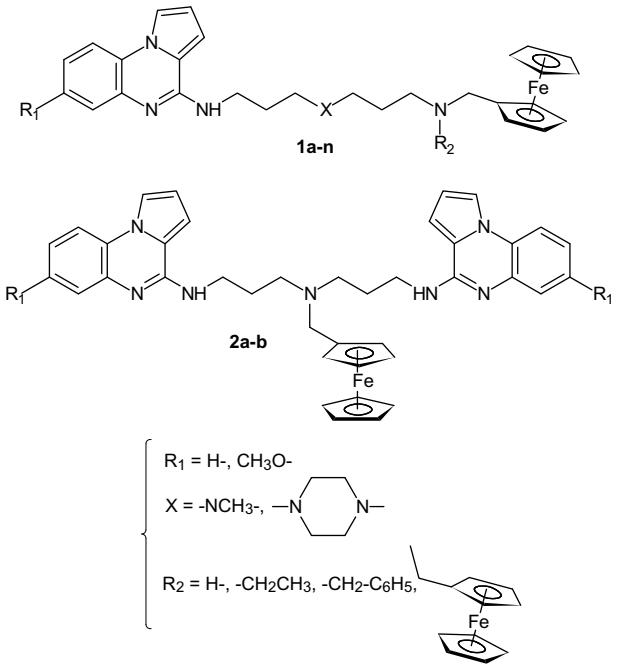



**Figure 2.** Structure of synthesized ferrocenyl pyrrolo[1,2-*a*]quinoxaline derivatives **1a**–**n** and **2a**–**b**.

phosphorous oxychloride to obtain the chloroquinoxalines **6a–b**.[28,31] Instead of the previously adopted method for bis{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}piperazines **F** employing DMF and $K_2CO_3$,[31] the key intermediates **7a–d**, used as precursors for synthesis of compounds **1**, were obtained by coupling 4-chloropyrrolo[1,2-*a*]quinoxalines **6a–b** to 1,3-bis(aminopropyl)piperazine or -methylamine in an efficient and regioselective procedure using catalytic amounts of $Pd(OAc)_2$ and the chelating ligand 9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene (Xantphos). This $Pd(OAc)_2$/Xantphos system behaved as a very efficient and selective catalyst for these mono *N*-heteroarylations, giving 49–60% yields.[32–34] The pyrrolo[1,2-*a*]quinoxalines **7a–d** were also prepared in 1-pentanol without base by condensation of 4-chloropyrrolo[1,2-*a*]quinoxalines **6a–b** with 1,3-bis(aminopropyl)piperazine or -methylamine according to an aromatic nucleophilic substitution mechanism.[15,35] The excess of amine (3 equiv) led to a moderate yield (32–45%) of the *N*-monosubstituted derivatives **7a–d**. In both methods, formation of the dicoupling bis{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl} amines **F**[31] was also observed as side-products. The ferrocene-carboxaldehyde was then condensed with amines **7a–d** in refluxing ethanol giving the imines **8a–d**.[21] Reduction of **8a–d** by sodium borohydride in methanol gave the 1-{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4[*N*-(ferrocenylmethyl)-3-aminopropyl]piperazines or methylamines **1a–d**.[36,37] These secondary amines **1a–d** were then engaged in a reductive amination with sodium triacetoxyborohydride and acetaldehyde or benzaldehyde to give the ferrocenic pyrrolo[1,2-*a*]quinoxaline derivatives **1e–j**.[15] The diferrocenic pyrrolo[1,2-*a*]quinoxaline derivatives **1k–n** were also obtained by reductive amination between intermediates **7a–d** and ferrocene-carboxaldehyde (3 equiv) using $NaHB(OAc)_3$ in methylene chloride at room temperature (Scheme 2).[15]

The bispyrrolo[1,2-*a*]quinoxalines **9a–b** were synthesized by reacting 3,3'-diamino-*N*-methyldipropylamine with a two equivalents amount of **6a–b** in DMF at 130 °C, in the presence of potassium carbonate as an inorganic base.[31] The ferrocenic bispyrrolo[1,2-*a*]quinoxalines **2a–b** were then prepared by treating these secondary amines **9a–b** with ferrocene-carboxaldehyde in the presence of $NaHB(OAc)_3$ (Scheme 3).

Compounds **1a–n** and **2a–b** were then converted into their oxalate salts in 63-86% yields by treatment with oxalic acid in refluxing isopropanol (Table 1).

## 2.2. Pharmacology

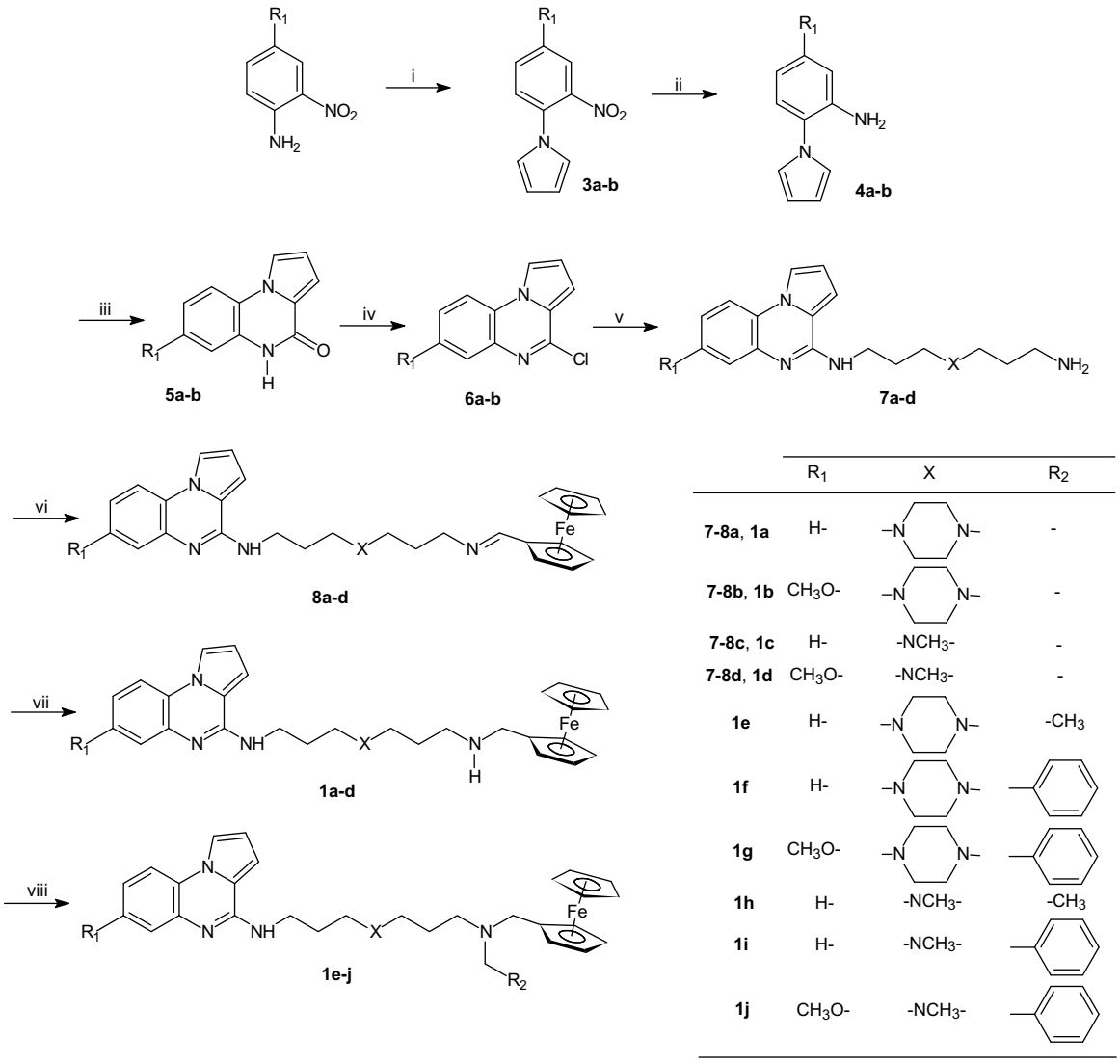
All new ferrocenic pyrrolo[1,2-*a*]quinoxaline derivatives **1–2** were evaluated for their antimalarial activity in vitro upon the *P. falciparum* CQ-sensitive strain F32 ($IC_{50}$ CQ = 19.5 nM) and the CQ-resistant strains FcB1 and PFB ($IC_{50}$ CQ = 105.3 and 225.7 nM, respectively). As shown in Table 2, they were found to have $IC_{50}$s between 9.1–167.5 nM upon F32, 16.6–173.1 nM upon FcB1, and 30.8-240.8 nM upon PFB *P. falciparum* strains, respectively.

By comparing activities for compounds bearing one same substituent on the pyrroloquinoxaline moiety and on the *N*-ferrocenylmethylamino function, it appears that compounds with a bis(3-aminopropyl)piperazine linker (**1b**, **1e–f**, **1k–l**) were generally more active (up to 2–8 times) than their counterparts with bis(3-aminopropyl)methylamine linkage (compounds **1d**, **1h–j**, **1m–n**), with the exception of **1a** and **1c**, that showed similar antimalarial activities. The presence of a two proton-acceptor site in the linker, such as a piperazine ring likely to increase vacuolar pH, was found to be favorable to antimalarial activity, when compared with a mono proton-acceptor site such as a methylamine function.

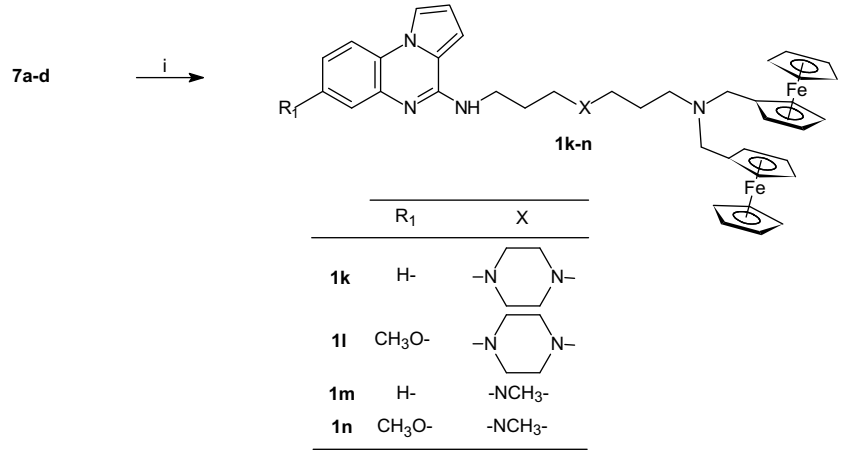
Antimalarial activity also clearly depended on the nature of the substituent on the pyrrolo[1,2-*a*]quinoxaline nucleus. Nevertheless, whatever the nature of the linker, the introduction of a methoxy substituent on C-7 carbon of the pyrroloquinoxaline moiety (compounds **1b**, **1d**, **1g**, **1j**, **1l**, **1n** and **2b** generally increased the antimalarial activity, when compared to the non-substituted counterparts (**1a**, **1c**, **1e–f**, **1h–i**, **1k**, **1m** and **2a**). On the other hand, secondary ferrocenyl amines **1a–d** were found to be more active than corresponding tertiary ones (ferrocenyl amines) **1e–n**.

Concerning the introduction of an aliphatic ethyl group on the terminal *N*-ferrocenylmethylamino moiety (compounds **1e** and **1h**), an elongation of the chain tends to decrease compounds activity, in comparison with **1a** and **1c**, respectively. A similar behaviour was noticed among derivatives with to a benzyl (**1f–g** and **1i–j**) or ferrocenylmethyl (**1k–n**) substitution on this terminal *N*-ferrocenylmethylamino function. For these compounds with a tertiary amine moiety, the isosteric replacement of the benzyl group by a ferrocenylmethyl one was found to be beneficial in terms of antimalarial activity (i.e., **1f** compared to **1k**, **1g** to **1l**, **1i** to **1m**, and **1j** to **1n,** respectively). On the other hand, compound **1b** displayed a remarkable activity ($IC_{50}$ = 9.1–22.2 nM) against the three *P. falciparum* strains showing different degrees of CQ-resistance. This result seems to corroborate the first preliminary structure–activity relationships in terms of substitution on the pyrroloquinoxaline skeleton and on the *N*-ferrocenylmethylamine function, and also in terms of linker's nature.

As seen in Table 2, almost all compounds (except **1f** and **2a**) have lower $IC_{50}$ values for growth inhibition of CQ-sensitive strain F32 than for growth inhibition of CQ-resistant strains FcB1 and PFB. A comparison of the $IC_{50}$ values for the growth inhibition of the resistant between sensitive strains of *P. falciparum* suggests relatively low levels of cross-resistance to CQ. The resistance index values (Table 2), calculated from the ratio between $IC_{50}$ for the resistant and $IC_{50}$ for sensitive strains of *P. falciparum*, were lower than those for CQ, in a 0.4–2.2 range (FcB1) and a 0.5–2.4 range (PFB), excepted for **1a** (4.3 on PFB). As it was already reported for

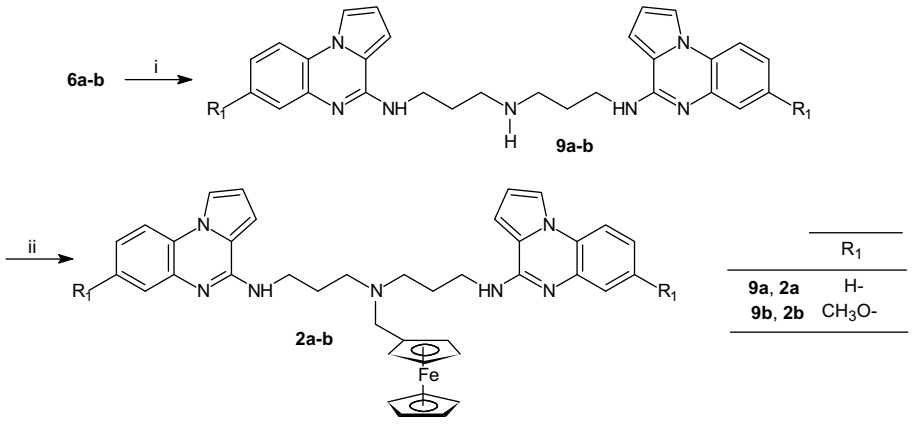



**Scheme 1.** Synthesis of 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives **1a**–**j**. Reagents and conditions: (i) DMTHF, Δ; (ii) $BiCl_3$, $NaBH_4$, EtOH; (iii) $CO(OCCl_3)_2$, toluene, Δ; (iv) $POCl_3$, Δ; (v) *Method A:* Xantphos, $H_2N–(CH_2)_3–X–(CH_2)_3–NH_2$, $K_2CO_3$, $Pd(OAc)_2$, dioxane, Δ; *Method B:* $H_2N–(CH_2)_3–X–(CH_2)_3–NH_2$, 1-pentanol, Δ; (vi) ferrocene-carboxaldehyde, EtOH, Δ; (vii) $NaBH_4$, MeOH, rt; (viii) $R_2–CHO$, $NaHB(OAc)_3$, $CH_2Cl_2$, rt.




**Scheme 2.** Synthesis of 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives **1k**–**n**. Reagents and conditions: (i) ferrocene-carboxaldehyde, $NaHB(OAc)_3$, $CH_2Cl_2$, rt.

bisquinolines or bisacridines, these results could be related to the bulky structure of studied bispyrroloquinoxalines with respect to recognition difficulties by the parasite efflux proteins, involved in CQ resistance.[38,39]




**Scheme 3.** Synthesis of bispyrrolo[1,2-*a*]quinoxaline derivatives **2a**–**b**. Reagents and conditions: (i) ferrocene-carboxaldehyde, $NaHB(OAc)_3$, $CH_2Cl_2$, rt.

**Table 1**
Physical properties of the final amines **1**–**2**

| Compound | Salt[a] | Mp (°C)[b] | %Yield[c] |
|---|---|---|---|
| **1a** | 4 $(COOH)_2$, 4 $H_2O$ | 191 | 86 |
| **1b** | 4 $(COOH)_2$, 4 $H_2O$ | 203 | 84 |
| **1c** | 3$(COOH)_2$, 3$H_2O$ | 174 | 81 |
| **1d** | 3$(COOH)_2$, 3$H_2O$ | 216 | 75 |
| **1e** | 4 $(COOH)_2$, 4 $H_2O$ | >260 | 63 |
| **1f** | 4 $(COOH)_2$, 4 $H_2O$ | 248 | 82 |
| **1g** | 4 $(COOH)_2$, 4 $H_2O$ | 178 | 85 |
| **1h** | 3$(COOH)_2$, 3$H_2O$ | 126 | 75 |
| **1i** | 3$(COOH)_2$, 3$H_2O$ | 96 | 69 |
| **1j** | 3$(COOH)_2$, 3$H_2O$ | 123 | 64 |
| **1k** | 4 $(COOH)_2$, 4 $H_2O$ | 218 | 76 |
| **1l** | 4 $(COOH)_2$, 4 $H_2O$ | 210 | 71 |
| **1m** | 3$(COOH)_2$, 3$H_2O$ | 99 | 73 |
| **1n** | 3$(COOH)_2$, 3$H_2O$ | 170 | 77 |
| **2a** | 3$(COOH)_2$, 3$H_2O$ | 147 | 75 |
| **2b** | 3$(COOH)_2$, 3$H_2O$ | 156 | 76 |

[a] The amines **1**–**2** were dissolved in 30 mL of 2-propanol, heated to boiling, and treated with oxalic acid (4 or 5 equiv, based on the amount of the starting material). The oxalate salts crystallized upon cooling, were collected by filtration, and were washed with 2-propanol and $Et_2O$.
[b] Crystallization solvent: 2-PrOH–$H_2O$.
[c] The yields included the conversions into the oxalates.

### 2.3. Cytotoxicity test on MRC-5 cells

All bispyrrolo[1,2-*a*]quinoxalines showed cytotoxicity upon the MRC-5 cells in the micromolar range. The different substituent modulations had less influence on the cytotoxicity $IC_{50}$ values than that observed for the antimalarial activity. Hence, for the piperazine series $IC_{50}$s on the MRC-5 cells varied only from 620 to 1480 nM (Table 2). The substitution of the *N*-ferrocenylmethylamine function of compounds **1** by a benzyl group (compounds **1f**, **1g**, **1i–j**) induced decreases in the cytotoxicity upon MRC-5 cells. Indexes of selectivity are defined as the ratio between the $IC_{50}$ value on the MRC-5 cells and the $IC_{50}$ value on the CQ-sensitive or CQ-resistant *P. falciparum* strains. Compounds that demonstrated high selectivity (high indexes of selectivity) should offer a potential of safer therapy. This led to identify only compound **2b**, with selectivity indexes >86, that could constitute suitable candidate for further pharmacological studies.

### 2.4. Inhibition of β-haematin formation

In vitro experiment studies have previously established that quinoline antimalarial drugs, such as CQ, are associated with the crystallization of haemazoin.[40–43] In fact, present evidence indicates that drugs act by inhibiting the formation of haemazoin, thus preventing haem detoxification. Three mechanisms of action can be proposed: (1) direct binding of the drug to haem monomers or dimers in solution which interferes with the crystallization of haemazoin[42]; (2) enzymatic inhibition of a protein that catalyses haemazoin crystallization[44]; and (3) chemiabsorption of the drug onto crystallised haemazoin, leading to inhibition of further haem aggregation.[45] Thus, a panel of selected active compounds **1b**, **1f–h**, **1l** and **2a**, representing various substitutions on the pyrroloquinoxaline nucleus, was tested for its ability to inhibit β-haematin formation (Table 3), the synthetic equivalent of hemozoin, by using the HPIA (heme polymerization inhibitory activity) assay.[46] Experiments were conducted by mixing haematin (0.4 μmol/well) with 0–10 compounds equivalents, previously dissolved in the appropriate solvent, immediately before adding acetic acid. Plates were then incubated for 20 h at 37 °C, and the β-haematin content was determined by spectrophotometry at 405 nm. Artemisinin and other endoperoxide antimalarials also act through their binding with haem (Table 3). The binding of artemisinin to haem both potentiates the redox activity of haem and inhibits hemoglobin digestion as well as heme detoxification function.[47] Using this microassay, 50% inhibition of haem polymerization ($IC_{50}$) was obtained using 1.63 ± 0.21 equivalent of chloroquine in aqueous solution and 1.50 ± 0.28 equivalent of artemisinin in DMSO, data in general agreement with previous reports.[46,47] On the other hand, sulfadimethoxine belonging to the antimalarial antifolates family, inhibits dihydropteroate synthase (DHPS), a key enzyme in folate biosynthesis pathway,[48] and is also used as reference. As expected, no inhibition of β-haematin formation was observed at any tested dose for compounds **1b**, **1f–h** and **1l**, as also for the reference sulfadimethoxine. Of the tested compounds, only **2a** showed a β-haematin formation inhibition, with a 5.85 ± 0.10 equivalents $IC_{50}$ value (for **1b**, **1f–h** and **1l** $IC_{50}$ values were superior to 10 equiv). Hence, it could be hypothesized that activity of **2a** could be related to the inhibition of β-haematin formation.

### 2.5. Lipophilicity

Preliminary pharmacological results of tested compounds could be discussed in terms of their physicochemical behaviour through the partitioning theory, evaluated here by the distribution coefficient *D* (usually expressed as log*D*).[49] Consequently, HPLC determination of log*D* was achieved for ferrocenic pyrrolo[1,2-*a*]quinoxaline derivatives **1–2** at two distinct pHs (5.0 considered close to the probable pH of the digestive vacuole, and 7.4 assumed to be the cytosol pH). A plot of antimalarial $IC_{50}$ versus log*D* values at pH 7.4 and 5.0 was presented in Figures 3 and 4, respectively,

**Table 2**
In vitro sensitivity of P. falciparum strains and in vitro cytotoxicity on MRC-5 cells

| Compound | $IC_{50}$ values (nM)[a] | | | | Index of selectivity[b] | | | Resistance index | |
|---|---|---|---|---|---|---|---|---|---|
| | *P. falciparum* strains | | | MRC-5 cells | F32 | FcB1 | PFB | FcB1[c] | PFB[d] |
| | F32 | FcB1 | PFB | | | | | | |
| CQ | 19.5 ± 4.2 | 105.3 ± 16.2 | 225.7 ± 52.6 | 50,000 ± 6000 | 2564.1 | 474.8 | 221.5 | 5.4 | 11.6 |
| **1a** | 11.9 ± 2.6 | 26.4 ± 3.5 | 51.4 ± 18.7 | 750 ± 10 | 63.0 | 28.4 | 14.6 | 2.2 | 4.3 |
| **1b** | 9.1 ± 1.5 | 16.6 ± 1.2 | 22.2 ± 10.5 | 730 ± 20 | 80.2 | 44.0 | 32.9 | 1.8 | 2.4 |
| **1c** | 23.8 ± 4.1 | 23.0 ± 0.8 | 50.2 ± 13.1 | 1310 ± 40 | 55.0 | 57.0 | 26.1 | 0.9 | 2.1 |
| **1d** | 36.8 ± 10.0 | 52.5 ± 11.0 | 68.8 ± 13.7 | 1550 ± 130 | 42.1 | 29.5 | 22.5 | 1.4 | 1.9 |
| **1e** | 22.3 ± 3.2 | 28.8 ± 7.9 | 30.8 ± 6.6 | 680 ± 30 | 30.5 | 23.6 | 22.1 | 1.3 | 1.4 |
| **1f** | 52.9 ± 10.5 | 61.9 ± 13.1 | 28.5 ± 29.0 | 1380 ± 50 | 26.1 | 22.3 | 48.4 | 1.2 | 0.5 |
| **1g** | 36.5 ± 5.9 | 52.3 ± 14.4 | 78.4 ± 19.8 | 1480 ± 40 | 40.5 | 28.3 | 18.9 | 1.4 | 2.1 |
| **1h** | 55.4 ± 13.3 | 59.1 ± 19.3 | 67.7 ± 16.7 | 1220 ± 170 | 22.0 | 20.6 | 18.0 | 1.0 | 1.2 |
| **1i** | 167.5 ± 17.7 | 173.1 ± 16.8 | 240.8 ± 51.4 | 2720 ± 100 | 16.2 | 15.7 | 11.3 | 1.0 | 1.4 |
| **1j** | 85.8 ± 8.3 | 132.0 ± 16.4 | 133.7 ± 24.4 | 1430 ± 100 | 16.7 | 10.8 | 10.7 | 1.5 | 1.5 |
| **1k** | 34.3 ± 8.9 | 46.7 ± 10.3 | 48.7 ± 15.1 | 660 ± 20 | 19.2 | 14.1 | 13.6 | 1.3 | 1.4 |
| **1l** | 23.1 ± 2.8 | 24.9 ± 8.2 | 30.9 ± 8.5 | 620 ± 130 | 26.8 | 24.9 | 20.1 | 1.1 | 1.3 |
| **1m** | 93.2 ± 10.0 | 133.0 ± 24.8 | 179.9 ± 18.3 | 1340 ± 40 | 14.4 | 10.1 | 7.4 | 1.4 | 1.9 |
| **1n** | 64.7 ± 16.6 | 77.4 ± 2.5 | 86.8 ± 13.8 | 1470 ± 50 | 22.7 | 19.0 | 16.9 | 1.2 | 1.3 |
| **2a** | 143.6 ± 42.2 | 58.9 ± 12.9 | 106.3 ± 20.8 | 2350 ± 60 | 16.4 | 39.9 | 22.1 | 0.4 | 0.7 |
| **2b** | 29.2 ± 7.6 | 27.2 ± 10.3 | 61.4 ± 22.8 | 2530 ± 60 | 86.6 | 93.0 | 41.2 | 0.9 | 2.1 |

[a] $IC_{50}$ values were measured on the chloroquine-sensitive strain F32/Tanzania and the chloroquine-resistant strains FcB1/Colombia and PFB/Brazil. The $IC_{50}$ (nM) values correspond to the mean ± standard deviation from three independent experiments.
[b] Index of selectivity (IS) was defined as the ratio between the $IC_{50}$ value on the MRC-5 cells and the $IC_{50}$ value against the *P. falciparum* F32, FcB1 and PFB strains.
[c] $IC_{50}$ (FcB1)/$IC_{50}$ (F32).
[d] $IC_{50}$ (PFB)/$IC_{50}$ (F32).

**Table 3**
Haem polymerisation inhibitory activity (HPIA) of different compounds used in the microtitre assay

| Compound | Inhibition[a] | $IC_{50}$ (drug:haematin molar ratio)[b] |
|---|---|---|
| CQ-diphosphate | + | 1.63 ± 0.21 |
| Artemisinin | + | 1.50 ± 0.28 |
| Sulfadimethoxine | – | – |
| **1b** | – | – |
| **1f** | – | – |
| **1g** | – | – |
| **1h** | – | – |
| **1l** | – | – |
| **2a** | + | 5.85 ± 0.10 |

[a] Inhibition: +, positive; –, negative.
[b] The $IC_{50}$ represents the molar equivalents of test compounds, relative to haematin, required to inhibit haem polymerisation by 50% (data are expressed as mean ± standard deviation from at least three different experiments in triplicate).

permitting to classify compounds in various subsets. At pH 7.4, all of studied compounds were found to be highly lipid-soluble. Introduction of a ferrocenic moiety in the lateral chain considerably increased the lipophilicity, compared to the purely organic CQ reference drug. The most active pyrrolo[1,2-*a*]quinoxaline derivatives without substituent on the terminal *N*-ferrocenylmethylamino function of the amino linker (**1a–d**), or substituted by an ethyl group (**1e** and **1h**) have log*D* values between 2.58 and 4.25. An heterogenous behaviour was found for less active compounds **1i**, **1j** and **1m**, with log *D* between 4.88 and 5.08. In this last case, introduction of a bulky benzyl or a second ferrocenic moiety on the terminal *N*-ferrocenylmethylamino function of the amino linker considerably increases lipophilicity. Finally, a third group of compounds (**1f**, **1g**, **1k** and **1l**) with log*D* values in the 5.13–5.18 range showed appreciable potency with $IC_{50}$s < 80 nM. Comparatively with **1i**, **1j** and **1m**, they included a piperazine ring linker instead of an *N*-methyl function.

At pH 5.0, a larger dispersion of log*D* values can be noticed. The most active compounds **1a–h** and **1k–l** were found the less lipophilic with log*D* values inferior to 0.5. Conversely, the slightly less active five compounds (**1i–j**, **1m–n** and **2a**) are more lipophilic with the exception of **2b**: they were found slightly less active ($IC_{50}$ = 58.9–40.8 nM) on *P. falciparum* strains.

These results clearly indicate that the choice and the substitution of the terminal *N*-ferrocenylmethylamino function in the amino linker of the pyrrolo[1,2-*a*]quinoxaline moiety correlated with a particular lipophilic behaviour, and seem to be fundamental for the antimalarial activity of these new compounds.

## 3. Conclusion

In conclusion, novel series of ferrocenic pyrrolo[1,2-*a*]quinoxaline derivatives **1–2** were synthesized from various substituted nitroanilines and tested for in vitro activity upon the erythrocytic development of *Plasmodium falciparum* strains with different chloroquine-resistance status. Promising pharmacological results were obtained, leading to the selection of **1b** as the most potent candidate, but further development was suspended for toxicity purpose. Nevertheless, it appears that these new ferrocenic pyrrolo[1,2-*a*]quinoxaline derivatives could open the way to original valuable medicinal chemistry scaffolding. Furthermore, this work contributes to validate the choice of the ferrocene moiety as a template useful for designing new antimalarial compounds.

## 4. Experimental

### 4.1. Chemistry

Commercially, reagents were used as received without additional purification. Melting points were determinated with an SM-LUX-POL Leitz hot-stage microscope and are uncorrected. IR spectra were recorded on a BRUKER IFS-25 spectrophotometer. NMR spectra were recorded with tetramethylsilane as an internal standard using a BRUKER AVANCE 300 spectrometer ($^1$H, $^{13}$C, 2D COSY). Splitting patterns have been designated as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; qt, quintuplet; sex, sextuplet; m, multiplet. Analytical TLC was carried out on 0.25 precoated silica gel plates (POLYGRAM SIL G/$UV_{254}$) with visualisation by irradiation with a UV lamp. Silica gel 60 (70–230 mesh) was used for column chromatography. Elemental analyses (C, H, N) for new compounds were performed by CNRS

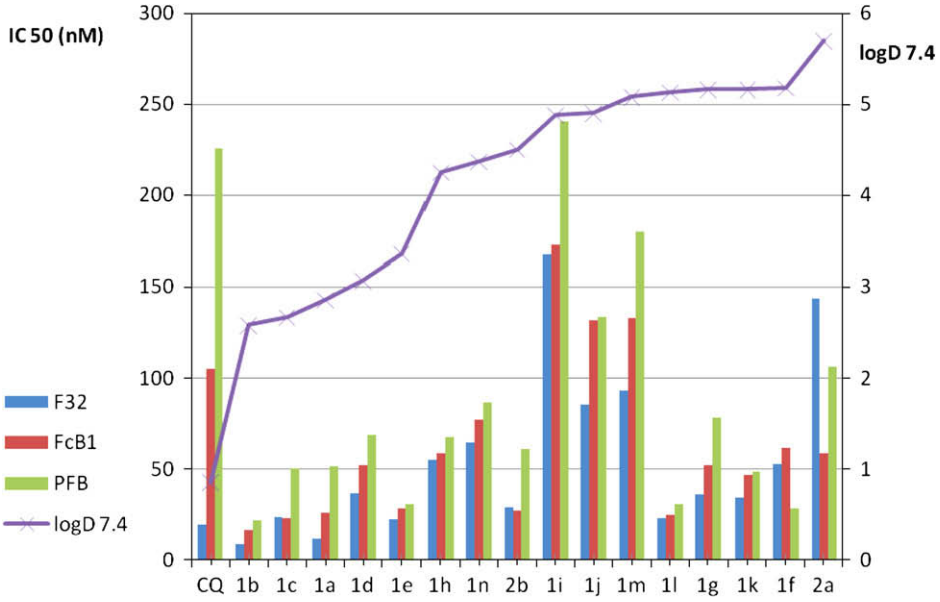



**Figure 3.** Log *D*/activity relationship for pyrrolo[1,2-*a*]quinoxalines **1**–**2** at pH 7.4.

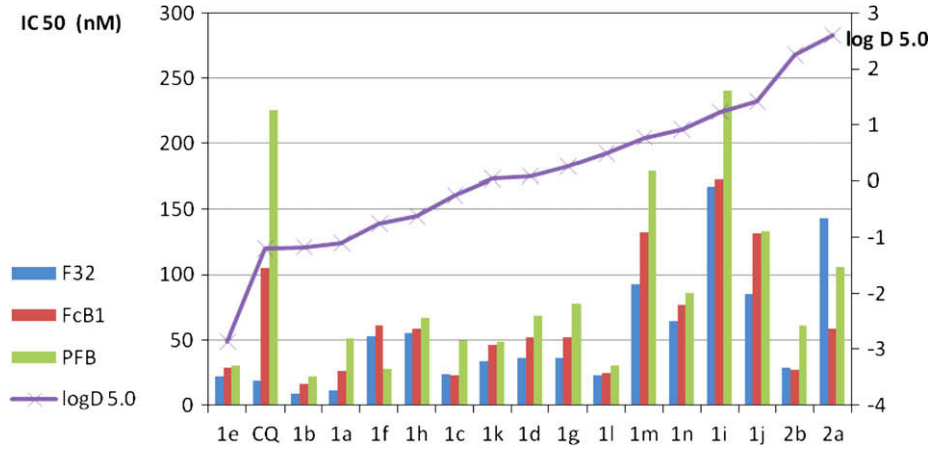



**Figure 4.** Log *D*/activity relationship for pyrrolo[1,2-*a*]quinoxalines **1**–**2** at pH 5.0.

(Vernaison-France) and agreed with the proposed structures within ±0.3% of the theoretical values.

#### 4.1.1. General procedure for 1-{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-(3-aminopropyl)piperazine (7a–b) and {*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-(3-aminopropyl)methylamine (7c–d)

*Method A:* A three-necked flask was flushed with nitrogen and charged with Xantphos (3.0 mmol, 1.2 equiv) and dry dioxane (25 mL). After degassing, $Pd(OAc)_2$ (0.5 mmol, 0.2 equiv) was charged, and the mixture was stirred under nitrogen for 10 min. In another three-necked round-bottom flask, 4-chloropyrrolo[1,2-*a*]quinoxaline **6a–b** (2.46 mmol), 1,4-bis(3-aminopropyl)piperazine or 3,3'-diamino-*N*-methyldipropylamine (3.0 mmol, 1.2 equiv), and $K_2CO_3$ (49.3 mmol, 20 equiv) were poured into dry dioxane (35 mL). Then, the $Pd(OAc)_2$/Xantphos solution was added with a double syringe. The resulting mixture was subsequently heated to reflux under $N_2$ with vigorous stirring for 3 h. After cooling, the solid material was filtered-off and washed with $CH_2Cl_2$ and methanol. The solvent was evaporated, and the resulting crude product was purified by flash column chromatography using $CH_2Cl_2$/methanol/$NH_4OH$ (80:20:1 v/v/v) as eluent to give **7a–d** as yellow oil. *Method B:* A solution of 4-chloropyrrolo[1,2-*a*]quinoxaline **6a–b** (20 mmol, 1 equiv) and 1,4-bis(3-aminopropyl)piperazine or 3,3'-diamino-*N*-methyldipropylamine (60 mmol, 3 equiv) in 33 mL of 1-pentanol was heated and held at reflux (160 °C) for 24 h. After cooling to room temperature, the mixture was diluted with 45 mL of $CH_2Cl_2$. The organic layer was washed with 10% NaOH (3× 45 mL), then with 45 mL of water, and dried over $Na_2SO_4$. The solvents were evaporated, and the residue was purified by flash column chromatography using $CH_2Cl_2$/methanol/$NH_4OH$ (80:20:1 v/v/v) as eluent to afford **7a–d**.

**4.1.1.1. 1-{*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-(3-aminopropyl)piperazine (7a).** Yellow oil (Method A: 52%, Method B: 49%). IR (KBr) 3350, 3280 ($NH_2$ and NH). $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (dd, 1H, $J$ = 2.65 and 1.45 Hz, H-1), 7.70 (dd, 1H, $J$ = 8.05 and 1.40 Hz, H-9), 7.64 (dd, 1H, $J$ = 8.05 and 1.40 Hz, H-6), 7.30 (ddd, 1H, $J$ = 8.05, 7.35 and 1.40 Hz, H-8), 7.19 (ddd, 1H, $J$ = 8.05, 7.35 and 1.40 Hz, H-7), 6.91 (t, 1H, $J$ = 5.40 Hz, NH), 6.74 (dd, 1H, $J$ = 3.90 and 1.45 Hz, H-3), 6.72 (dd, 1H, $J$ = 3.90 and 2.65 Hz, H-2), 3.79 (m, 2H, $NCH_2$), 2.80 (t, 2 H, $J$ = 6.60 Hz, $NCH_2$), 2.60 (t, 8H, $J$ = 6.00 Hz, $CH_2$ pip.), 2.50 (t, 4H, $J$ = 6.60 Hz, $NCH_2$), 1.89 (qt, 2H, $J$ = 6.60 Hz, $CH_2$), 1.73 (br s, 2H, $NH_2$), 1.69 (qt, 2H, $J$ = 6.60 Hz, $CH_2$). Anal. Calcd for $C_{21}H_{30}N_6$: C, 68.82; H, 8.25; N, 22.93. Found: C, 69.03; H, 8.39; N, 22.78.

**4.1.1.2. 1-{*N*-(7-Methoxypyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-(3-aminopropyl)piperazine (7b).** Yellow crystals (Method A: 60%, Method B: 43%); mp 72 °C. IR (KBr) 3385, 3290 ($NH_2$ and NH). $^1H$ NMR ($CDCl_3$) $\delta$ 7.71 (m, 1H, H-1), 7.60 (d, 1H, $J$ = 8.85 Hz, H-9), 7.15 (d, 1H, $J$ = 2.45 Hz, H-6), 6.84 (m, 1H, NH), 6.81 (dd, 1H, $J$ = 8.85 and 2.45 Hz, H-8), 6.70 (m, 2H, H-3 and H-2), 3.89 (s, 3H, $CH_3O$), 3.78 (m, 2H, $NCH_2$), 3.76 (br s, 2H, $NH_2$), 2.93 (t, 2H, $J$ = 6.20 Hz, $NCH_2$), 2.61 (t, 8H, $J$ = 6.10 Hz, $CH_2$ pip.), 2.56 (t, 4H, $J$ = 6.20 Hz, $NCH_2$), 1.90 (qt, 2H, $J$ = 6.20 Hz, $CH_2$), 1.78 (qt, 2H, $J$ = 6.20 Hz, $CH_2$). Anal. Calcd for $C_{22}H_{32}N_6O$: C, 66.63; H, 8.13; N, 21.19. Found: C, 66.38; H, 8.05; N, 20.87.

**4.1.1.3. {*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-(3-aminopropyl)methylamine (7c).** Yellow oil (Method A: 54%, Method B: 41%). IR (KBr) 3400, 3290 ($NH_2$ and NH). $^1H$ NMR ($CDCl_3$) $\delta$ 7.77 (dd, 1H, $J$ = 2.75 and 1.45 Hz, H-1), 7.70 (dd, 1H, $J$ = 8.00 and 1.35 Hz, H-9), 7.65 (dd, 1H, $J$ = 8.00 and 1.35 Hz, H-6), 7.31 (ddd, 1H, $J$ = 8.00, 7.30 and 1.35 Hz, H-8), 7.27 (br s, 1H, NH), 7.20 (ddd, 1H, $J$ = 8.00, 7.30 and 1.35 Hz, H-7), 6.71 (dd, 1H, $J$ = 4.05 and 1.45 Hz, H-3), 6.58 (dd, 1H, $J$ = 4.05 and 2.75 Hz, H-2), 3.79 (m, 2H, $NCH_2$), 2.78 (t, 2 H, $J$ = 7.20 Hz, $NCH_2$), 2.60 (t, 2H, $J$ = 7.20 Hz, $NCH_2$), 2.50 (t, 2H, $J$ = 7.20 Hz, $NCH_2$), 2.34 (s, H, $NCH_3$), 1.88 (qt, 2H, $J$ = 7.20 Hz, $CH_2$), 1.73 (qt, 2H, $J$ = 7.20 Hz, $CH_2$), 1.37 (br s, 2H, $NH_2$). Anal. Calcd for $C_{18}H_{25}N_5$: C, 69.42; H, 8.09; N, 22.49. Found: C, 69.57; H, 8.01; N, 22.63.

**4.1.1.4. {*N*-(7-Methoxypyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-(3-aminopropyl)methylamine (7d).** Yellow oil (Method A: 49%, Method B: 40%). IR (KBr) 3390, 3280 ($NH_2$ and NH). $^1H$ NMR ($CDCl_3$) $\delta$ 7.68 (dd, 1H, $J$ = 2.70 and 1.35 Hz, H-1), 7.59 (d, 1H, $J$ = 8.85 Hz, H-9), 7.33 (br s, 1H, NH), 7.15 (d, 1H, $J$ = 2.75 Hz, H-6), 6.80 (dd, 1H, $J$ = 8.85 and 2.75 Hz, H-8), 6.66 (dd, 1H, $J$ = 3.90 and 2.70 Hz, H-2), 6.55 (dd, 1H, $J$ = 3.90 and 1.35 Hz, H-3), 3.89 (s, 3H, $CH_3O$), 3.78 (m, 2H, $NCH_2$), 2.77 (t, 2H, $J$ = 7.05 Hz, $NCH_2$), 2.59 (t, 2H, $J$ = 7.05 Hz, $NH_2$), 2.49 (t, 2H, $J$ = 7.05 Hz, $NCH_2$), 2.34 (s, 3H, $NCH_3$), 1.88 (qt, 2H, $J$ = 7.05 Hz, $CH_2$), 1.72 (qt, 2H, $J$ = 7.05 Hz, $CH_2$), 1.34 (br s, 2H, $NH_2$). Anal. Calcd for $C_{19}H_{27}N_5O$: C, 66.83; H, 7.97; N, 20.51. Found: C, 67.05; H, 8.08; N, 20.69.

### 4.1.2. General procedure for 1-{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*-(ferrocenylmethylene)-3-aminopropyl]-piperazine (8a–b) and {*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*-(ferrocenylmethylene)-3-aminopropyl]methylamine (8c–d)

To a solution of compound **7a–d** (5.46 mmol) in ethanol (40 mL) was added ferrocene-carboxaldehyde (5.46 mmol). The reaction mixture was then refluxed for 4 hours. The mixture was evaporated to dryness under reduced pressure. After cooling, the residue was extracted with methylene chloride (150 mL). The organic layer was dried over $Na_2SO_4$ and evaporated to dryness. The oily residue was used without further purification.

**4.1.2.1. 1-{*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*-(ferrocenylmethylene)-3-aminopropyl]piperazine (8a).** Orange oil (83%). IR (KBr) 3270 (NH), 1620 (C=N). $^1H$ NMR ($CDCl_3$) $\delta$ 8.16 (s, 1H, CH=N), 7.77 (dd, 1H, $J$ = 2.75 and 1.25 Hz, H-1), 7.70 (dd, 1H, $J$ = 8.05 and 1.30 Hz, H-9), 7.65 (dd, 1H, $J$ = 8.05 and 1.30 Hz, H-6), 7.30 (ddd, 1H, $J$ = 8.05, 7.40 and 1.30 Hz, H-8), 7.20 (ddd, 1H, $J$ = 8.05, 7.40 and 1.30 Hz, H-7), 6.92 (t, 1H, $J$ = 5.35 Hz, NH), 6.76 (dd, 1H, $J$ = 3.85 and 1.25 Hz, H-3), 6.71 (dd, 1H, $J$ = 3.85 and 2.75 Hz, H-2), 4.65 (t, 2H, $J$ = 1.85 Hz, Cp-*ortho*), 4.38 (t, 2H, $J$ = 1.85 Hz, Cp), 4.20 (s, 5H, Cp'), 3.80 (m, 2H, $NCH_2$), 3.53 (t, 2H, $J$ = 7.20 Hz, $NCH_2$), 2.63 (t, 8H, $J$ = 5.90 Hz, $CH_2$ pip.), 2.51 (t, 4H, $J$ = 7.20 Hz, $NCH_2$), 1.91 (m, 4H, $CH_2$). Anal. Calcd for $C_{32}H_{38}N_6Fe$: C, 68.32; H, 6.81; N, 14.94. Found: C, 68.56; H, 7.03; N, 15.11.

**4.1.2.2. 1-{*N*-(7-Methoxypyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*-(ferrocenylmethylene)-3-aminopropyl]piperazine (8b).** Orange crystals (89%); mp 73 °C. IR (KBr) 3280 (NH), 1620 (C=N). $^1H$ NMR ($CDCl_3$) $\delta$ 8.16 (s, 1H, CH=N), 7.71 (m, 1H, H-1), 7.61 (d, 1H, $J$ = 8.85 Hz, H-9), 7.17 (d, 1H, $J$ = 2.40 Hz, H-6), 6.84 (br s, 1H, NH), 6.80 (dd, 1H, $J$ = 8.85 and 2.40 Hz, H-8), 6.77 (m, 1H, H-3), 6.68 (m, 1H, H-2), 4.66 (m, 2H, Cp-*ortho*), 4.39 (m, 2H, Cp-*meta*), 4.18 (s, 5H, Cp'), 3.90 (s, 3H, $CH_3O$), 3.81 (m, 2H, $NCH_2$), 3.53 (t, 2H, $J$ = 6.95 Hz, $NCH_2$), 2.69 (m, 8H, $CH_2$ pip.), 2.52 (t, 4H, $J$ = 6.95 Hz, $NCH_2$), 1.92 (m, 4H, $CH_2$). Anal. Calcd for $C_{33}H_{40}N_6OFe$: C, 66.89; H, 6.80; N, 14.18. Found: C, 66.97; H, 7.00; N, 14.33.

**4.1.2.3. {*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*-(ferrocenylmethylene)-3-aminopropyl]methylamine (8c).** Orange oil (96%). IR (KBr) 3275 (NH), 1625 (C=N). $^1H$ NMR ($CDCl_3$) $\delta$ 8.09 (s, 1H, CH=N), 7.74 (dd, 1H, $J$ = 2.80 and 1.30 Hz, H-1), 7.69 (dd, 1 H, $J$ = 8.00 and 1.30 Hz, H-9), 7.65 (dd, 1H, $J$ = 8.00 and 1.30 Hz, H-6), 7.31 (ddd, 1H, $J$ = 8.00, 7.35 and 1.30 Hz, H-8), 7.22 (br s, 1H, NH), 7.20 (ddd, 1H, $J$ = 8.00, 7.35 and 1.30 Hz, H-7), 6.70 (dd, 1H, $J$ = 3.95 and 1.30 Hz, H-3), 6.59 (dd, 1H, $J$ = 3.95 and 2.80 Hz, H-2), 4.61 (t, 2H, $J$ = 1.30 Hz, Cp-*ortho*), 4.35 (t, 2H, $J$ = 1.30 Hz, Cp-*meta*), 4.15 (s, 5H, Cp'), 3.83 (m, 2H, $NCH_2$), 3.52 (t, 2H, $J$ = 6.95 Hz, $NCH_2$), 2.64 (t, 2H, $J$ = 6.95 Hz, $NCH_2$), 2.54 (t, 2H, $J$ = 6.95 Hz, $NCH_2$), 2.38 (s, 3H, $NCH_3$), 1.95 (m, 4H, $CH_2$). Anal. Calcd for $C_{29}H_{33}N_5Fe$: C, 68.64; H, 6.55; N, 13.80. Found: C, 68.51; H, 6.32; N, 13.96.

**4.1.2.4. {*N*-(7-Methoxypyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*-(ferrocenylmethylene)-3-aminopropyl]methylamine (8d).** Orange oil (97%). IR (KBr) 3275 (NH), 1620 (C=N). $^1H$ NMR ($CDCl_3$) $\delta$ 8.08 (s, 1H, CH=N), 7.68 (dd, 1H, $J$ = 2.65 and 1.25 Hz, H-1), 7.59 (d, 1H, $J$ = 8.90 Hz, H-9), 7.24 (t, 1H, $J$ = 5.35 Hz, NH), 7.17 (d, 1H, $J$ = 2.70 Hz, H-6), 6.80 (dd, 1H, $J$ = 8.90 and 2.70 Hz, H-8), 6.66 (dd, 1H, $J$ = 3.90 and 2.65 Hz, H-2), 6.58 (dd, 1H, $J$ = 3.90 and 1.25 Hz, H-3), 4.60 (t, 2H, $J$ = 1.75 Hz, Cp-*ortho*), 4.34 (t, 2H, $J$ = 1.75 Hz, Cp-*meta*), 4.14 (s, 5H, Cp'), 3.89 (s, 3H, $CH_3O$), 3.80 (m, 2H, $NCH_2$), 3.51 (t, 2H, $J$ = 6.70 Hz, $NCH_2$), 2.64 (t, 2H, $J$ = 6.70 Hz, $NCH_2$), 2.54 (t, 2H, $J$ = 6.70 Hz, $NCH_2$), 2.38 (s, 3H, $NCH_3$), 1.92 (m, 4H, $CH_2$). Anal. Calcd for $C_{30}H_{35}N_5OFe$: C, 67.04; H, 6.56; N, 13.03. Found: C, 66.94; H, 6.45; N, 13.23.

### 4.1.3. General procedure for 1-{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*-(ferrocenylmethyl)-3-aminopropyl]-piperazine (1a–b) and {*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*-(ferrocenylmethyl)-3-aminopropyl]methylamine (1c–d)

To a solution of compound **8a–d** (4.0 mmol) in methanol (40 mL) at 0 °C was added $NaBH_4$ (20 mmol) in small portions over 30 min. After the mixture was stirred at 0 °C for 1.5 h, the reaction was quenched by addition of 40 mL of a 0.5 M NaOH aqueous solution. Then the mixture was extracted with dichloromethane (2x 50 mL). The organic layers were combined, washed with brine, dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure to give **1a–d**.

**4.1.3.1. 1-{*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*-(ferrocenylmethyl)-3-aminopropyl]piperazine (1a).** Yellow oil (81%). IR (KBr) 3280 (NH). $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (dd, 1H, $J$ = 2.75 and 1.30 Hz, H-1), 7.71 (dd, 1H, $J$ = 8.05 and 1.25 Hz, H-9), 7.65 (dd, 1H, $J$ = 8.05 and 1.25 Hz, H-6), 7.31 (ddd, 1H, $J$ = 8.05, 7.35 and 1.25 Hz, H-8), 7.20 (ddd, 1H, $J$ = 8.05, 7.35 and 1.25 Hz, H-7), 6.88 (t, 1H, $J$ = 5.40 Hz, NH), 6.72 (m, 2H, H-3 and H-2), 4.22 (m, 2H, Cp-*ortho*), 4.14 (s, 5H, Cp'), 4.12 (m, 2H, Cp-*meta*), 3.79 (m, 2H, $NCH_2$), 3.56 (s, 2H, $CH_2Fc$), 2.73 (t, 2H, $J$ = 6.80 Hz, $NCH_2$), 2.61 (t, 8H, $J$ = 5.95 Hz, $CH_2$ pip.), 2.49 (t, 4H, $J$ = 6.80 Hz, $NCH_2$), 2.32 (br s,

1H, NH), 1.89 (qt, 2H, $J$ = 6.80 Hz, $CH_2$), 1.75 (qt, 2H, $J$ = 6.80 Hz, $CH_2$). $^{13}$C NMR ($CDCl_3$) $\delta$ 149.6 (C-4), 137.3 (C-5a), 126.5 (C-6), 125.2 (C-7), 125.1 (C-9a), 122.4 (C-8), 119.8 (C-3a), 114.1 (C-9), 113.3 (C-1), 112.0 (C-3), 102.6 (C-2), 86.2 (Cp-1), 68.5 (Cp'), 68.4 (Cp-*ortho*), 67.9 (Cp-*meta*), 58.4 ($NCH_2$), 57.0 ($NCH_2$), 53.4 ($CH_2$ pip.), 53.3 ($CH_2$ pip.), 48.8 ($NCH_2$), 48.0 ($NCH_2$), 41.5 ($NCH_2$), 26.4 ($CH_2$), 24.6 ($CH_2$). Anal. Calcd for $C_{32}H_{40}N_6Fe$: C, 68.08; H, 7.14; N, 14.88. Found: C, 67.97; H, 7.26; N, 15.08.

**4.1.3.2. 1-{*N*-(7-Methoxypyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*-(ferrocenylmethyl)-3-aminopropyl]piperazine (1b).** Orange oil (88%). IR (KBr) 3275 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.71 (dd, 1H, $J$ = 2.80 and 1.30 Hz, H-1), 7.60 (d, 1H, $J$ = 8.85 Hz, H-9), 7.16 (d, 1H, $J$ = 2.65 Hz, H-6), 6.89 (t, 1H, $J$ = 5.35 Hz, NH), 6.81 (dd, 1H, $J$ = 8.85 and 2.65 Hz, H-8), 6.69 (m, 2H, H-3 and H-2), 4.21 (m, 2H, Cp-*ortho*), 4.14 (s, 5H, Cp'), 4.12 (m, 2H, Cp-*meta*), 3.90 (s, 3H, $CH_3O$), 3.80 (m, 2H, $NCH_2$), 3.55 (s, 2H, $CH_2Fc$), 2.73 (t, 2H, $J$ = 6.85 Hz, $NCH_2$), 2.52 (m, 8H, $CH_2$ pip.), 2.50 (t, 4H, $J$ = 6.85 Hz, $NCH_2$), 2.35 (br s, 1H, NH), 1909 (qt, 2H, $J$ = 6.85 Hz, $CH_2$), 1.75 (qt, 2H, $J$ = 6.85 Hz, $CH_2$). Anal. Calcd for $C_{33}H_{42}N_6OFe$: C, 66.66; H, 7.12; N, 14.13. Found: C, 66.87; H, 7.01; N, 13.88.

**4.1.3.3. {*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*-(ferrocenylmethyl)-3-aminopropyl]methylamine (1c).** Yellow crystals (85%); mp 31 °C. IR (KBr) 3280 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.77 (dd, 1H, $J$ = 2.85 and 1.35 Hz, H-1), 7.70 (d, 1H, $J$ = 8.00 Hz, H-9), 7.67 (d, 1H, $J$ = 8.00 Hz, H-6), 7.31 (t, 1H, $J$ = 8.00 Hz, H-8), 7.24 (br s, 1H, NH), 7.20 (t, 1H, $J$ = 8.00 Hz, H-7), 6.71 (dd, 1H, $J$ = 4.00 and 2.85 Hz, H-2), 6.60 (dd, 1H, $J$ = 4.00 and 1.35 Hz, H-3), 4.14 (m, 2H, Cp-*ortho*), 4.08 (m, 7H, Cp-*meta* and Cp'), 3.77 (m, 2H, $NCH_2$), 3.49 (s, 2H, $CH_2Fc$), 2.72 (t, 2H, $J$ = 6.50 Hz, $NCH_2$), 2.57 (t, 2H, $J$ = 6.50 Hz, $NCH_2$), 2.49 (t, 2H, $J$ = 6.50 Hz, $NCH_2$), 2.37 (br s, 1H, NH), 2.33 (s, 3H, $NCH_3$), 1.88 (qt, 2H, $J$ = 6.50 Hz, $CH_2$), 1.77 (qt, 2H, $J$ = 6.50 Hz, $CH_2$). $^{13}$C NMR ($CDCl_3$) $\delta$ 149.6 (C-4), 137.4 (C-5a), 126.4 (C-6), 125.2 (C-7), 125.0 (C-9a), 122.2 (C-8), 119.9 (C-3a), 113.9 (C-9), 113.3 (C-1), 112.2 (C-3), 102.5 (C-2), 86.2 (Cp-1), 68.5 (Cp-*ortho*), 68.3 (Cp'), 67.8 (Cp-*meta*), 56.9 ($NCH_2$), 56.8 ($NCH_2$), 49.0 ($NCH_2$), 48.1 ($NCH_2$), 42.3 ($NCH_3$), 40.9 ($NCH_2Fc$), 27.4 ($CH_2$), 25.3 ($CH_2$). Anal. Calcd for $C_{29}H_{35}N_5Fe$: C, 68.37; H, 6.92; N, 13.74. Found: C, 68.45; H, 7.12; N, 13.98.

**4.1.3.4. {*N*-(7-Methoxypyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*-(ferrocenylmethyl)-3-aminopropyl]methylamine (1d).** Yellow oil (83%). IR (KBr) 3280 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.70 (dd, 1H, $J$ = 2.85 and 1.30 Hz, H-1), 7.60 (d, 1H, $J$ = 8.90 Hz, H-9), 7.26 (br s, 1H, NH), 7.17 (d, 1H, $J$ = 2.75 Hz, H-6), 6.80 (dd, 1H, $J$ = 8.90 and 2.75 Hz, H-8), 6.67 (dd, 1H, $J$ = 3.95 and 2.85 Hz, H-2), 6.56 (dd, 1H, $J$ = 3.95 and 1.30 Hz, H-3), 4.14 (t, 2H, $J$ = 1.70 Hz, Cp-*ortho*), 4.08 (m, 7H, Cp-*meta* and Cp'), 3.90 (s, 3H, $CH_3O$), 3.77 (m, 2H, $NCH_2$), 3.48 (s, 2H, $CH_2Fc$), 2.72 (t, 2H, $J$ = 6.40 Hz, $NCH_2$), 2.58 (t, 2H, $J$ = 6.40 Hz, $NCH_2$), 2.50 (t, 2H, $J$ = 6.40 Hz, $NCH_2$), 2.41 (br s, 1H, NH), 2.33 (s, 3H, $NCH_3$), 1.88 (qt, 2H, $J$ = 6.40 Hz, $CH_2$), 1.77 (qt, 2H, $J$ = 6.40 Hz, $CH_2$). Anal. Calcd for $C_{30}H_{37}N_5OFe$: C, 66.79; H, 6.91; N, 12.98. Found: C, 66.58; H, 6.83; N, 13.04.

**4.1.4. General procedure for 1-{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*-alkyl-*N*-(ferrocenylmethyl)-3-aminopropyl]piperazine (1e–g) and {*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*-alkyl-*N*-(ferrocenylmethyl)-3-aminopropyl]methylamine (1h–j)**

To a solution of compounds **1a–d** (0.8 mmol) in 10 mL of dry $CH_2Cl_2$ were added acetaldehyde (2.40 mmol, 3 equiv) or benzaldehyde (1.7 mmol, 1.5 equiv) and $NaHB(OAc)_3$ (1.2 mmol, 1.5 equiv). After the mixture was stirred at room temperature for 24 h, a total of 15 mL of aqueous 1 M NaOH solution was introduced. The mixture left for 15 min, the organic layer was separated, and the aqueous layer was washed with $CH_2Cl_2$. Then the organic layers were mixed and dried over $Na_2SO_4$, the solvent was evaporated, and the residue was purified by column chromatography using $CH_2Cl_2$/methanol/$NH_4OH$ (80:20:1 v/v/v) as eluent to yield **1e–j**.

**4.1.4.1. 1-{*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*-alkyl-*N*-(ferrocenylmethyl)-3-aminopropyl]piperazine (1e).** Yellow oil (76%). IR (KBr) 3280 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.79 (m, 1H, H-1), 7.70 (d, 1H, $J$ = 7.75 Hz, H-9), 7.67 (d, 1H, $J$ = 7.75 Hz, H-6), 7.31 (t, 1H, $J$ = 7.75 Hz, H-8), 7.20 (t, 1H, $J$ = 7.75 Hz, H-7), 6.82 (br s, 1H, NH), 6.72 (m, 2H, H-3 and H-2), 4.18 (m, 4H, Cp-*ortho* and Cp-*meta*), 4.13 (s, 5H, Cp'), 3.81 (m, 2H, $NCH_2$), 3.56 (s, 2H, $CH_2Fc$), 2.60 (m, 10H, $NCH_2$ and $CH_2$ pip.), 2.40 (m, 6H, $NCH_2$), 1.91 (m, 2H, $CH_2$), 1.72 (m, 2H, $CH_2$), 1.07 (t, 3H, $J$ = 6.95 Hz, $CH_3$). Anal. Calcd for $C_{34}H_{44}N_6Fe$: C, 68.91; H, 7.48; N, 14.18. Found: C, 69.06; H, 7.61; N, 13.94.

**4.1.4.2. 1-{*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*-benzyl-*N*-(ferrocenylmethyl)-3-aminopropyl]piperazine (1f).** Yellow oil (71%). IR (KBr) 3280 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.79 (m, 1H, H-1), 7.70 (d, 1H, $J$ = 8.00 Hz, H-9), 7.66 (d, 1H, $J$ = 8.00 Hz, H-6), 7.36-7.27 (m, 6H, Ar-H and H-8), 7.21 (t, 1H, $J$ = 8.00 Hz, H-7), 6.94 (t, 1H, $J$ = 5.30 Hz, NH), 6.74 (m, 2H, H-3 and H-2), 4.17 (m, 2H, Cp-*ortho*), 4.13 (m, 2H, Cp-*meta*), 4.07 (s, 5H, Cp'), 3.80 (m, 2H, $NCH_2$), 3.52 (s, 4H, $CH_2Fc$ and $CH_2Ph$), 2.59 (m, 10H, $NCH_2$ and $CH_2$ pip.), 2.42 (m, 4H, $NCH_2$), 1.89 (m, 2H, $CH_2$), 1.72 (m, 2H, $CH_2$). $^{13}$C NMR ($CDCl_3$) $\delta$ 149.5 (C-4), 139.9 (C-1'), 137.2 (C-5a), 128.7 (C-2' and C-6'), 128.1 (C-3' and C-5'), 126.7 (C-4'), 126.5 (C-6), 125.2 (C-7), 125.1 (C-9a), 122.4 (C-8), 119.8 (C-3a), 114.0 (C-9), 113.2 (C-1), 112.0 (C-3), 102.6 (C-2), 82.9 (Cp-1), 70.0 (Cp-*ortho*), 68.4 (Cp'), 67.7 (Cp-*meta*), 58.5 ($NCH_2$), 57.6 ($NCH_2$), 56.6 ($NCH_2$), 53.4 ($CH_2$ pip.), 53.3 ($CH_2$ pip.), 52.6 ($NCH_2$), 50.7 ($NCH_2$), 41.5 ($NCH_2$), 24.5 ($2CH_2$). Anal. Calcd for $C_{39}H_{46}N_6Fe$: C, 71.55; H, 7.08; N, 12.84. Found: C, 71.64; H, 7.20; N, 13.07.

**4.1.4.3. 1-{*N*-(7-Methoxypyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*-benzyl-*N*-(ferrocenylmethyl)-3-aminopropyl]-piperazine (1g).** Yellow oil (73%). IR (KBr) 3275 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.71 (dd, 1H, $J$ = 2.65 and 1.30 Hz, H-1), 7.61 (d, 1H, $J$ = 8.85 Hz, H-9), 7.36-7.25 (m, 5H, Ar-H), 7.18 (d, 1H, $J$ = 2.75 Hz, H-6), 6.94 (t, 1H, $J$ = 5.35 Hz, NH), 6.82 (dd, 1H, $J$ = 8.85 and 2.75 Hz, H-8), 6.74 (dd, 1H, $J$ = 3.90 and 1.30 Hz, H-3), 6.69 (dd, 1H, $J$ = 3.90 and 2.65 Hz, H-2), 4.18 (t, 2H, $J$ = 1.75 Hz, Cp-*ortho*), 4.14 (t, 2H, $J$ = 1.75 Hz, Cp-*meta*), 4.08 (s, 5H, Cp'), 3.90 (s, 3H, $CH_3O$), 3.81 (m, 2H, $NCH_2$), 3.53 (s, 4H, $CH_2Fc$ and $CH_2Ph$), 2.61 (m, 10H, $NCH_2$ and $CH_2$ pip.), 2.42 (m, 4H, $NCH_2$), 1.90 (m, 2H, $CH_2$), 1.72 (m, 2H, $CH_2$). Anal. Calcd for $C_{40}H_{48}N_6OFe$: C, 70.17; H, 7.07; N, 12.27. Found: C, 70.22; H, 7.01; N, 12.35.

**4.1.4.4. {*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*-ethyl-*N*-(ferrocenylmethyl)-3-aminopropyl]methylamine (1h).** Yellow oil (78%). IR (KBr) 3285 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.79 (dd, 1H, $J$ = 2.80 and 1.30 Hz, H-1), 7.70 (dd, 1H, $J$ = 7.95 and 1.30 Hz, H-9), 7.66 (dd, 1H, $J$ = 7.95 and 1.30 Hz, H-6), 7.43 (t, 1H, $J$ = 5.40Hz, NH), 7.31 (ddd, 1H, $J$ = 7.95, 7.30 and 1.30 Hz, H-8), 7.20 (ddd, 1H, $J$ = 7.95, 7.30 and 1.30 Hz, H-7), 6.72 (dd, 1H, $J$ = 3.85 and 2.80 Hz, H-2), 6.59 (dd, 1H, $J$ = 3.85 and 1.30 Hz, H-3), 4.08 (m, 4H, Cp-*ortho* and Cp-*meta*), 4.04 (s, 5H, Cp'), 3.80 (m, 2H, $NCH_2$), 3.48 (s, 2H, $CH_2Fc$), 2.61 (t, 2H, $J$ = 6.40 Hz, $NCH_2$), 2.41 (m, 6H, $NCH_2$), 2.34 (s, 3H, $NCH_3$), 1.88 (qt, 2H, $J$ = 6.40 Hz, $CH_2$), 1.75 (qt, 2H, $J$ = 6.40 Hz, $CH_2$), 1.01 (t, 3H, $J$ = 7.10 Hz, $CH_3$). Anal. Calcd for $C_{31}H_{39}N_5Fe$: C, 69.27; H, 7.31; N, 13.03. Found: C, 69.03; H, 7.18; N, 12.89.

**4.1.4.5. {*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*-benzyl-*N*-(ferrocenylmethyl)-3-aminopropyl]methylamine (1i).** Yellow oil (87%). IR (KBr) 3275 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.78 (dd, 1H, $J$ = 2.85 and 1.30 Hz, H-1), 7.71 (d, 1H, $J$ = 8.15 Hz, H-9),

7.67 (d, 1H, *J* = 8.15 Hz, H-6), 7.34–7.25 (m, 7H, Ar-H, H-8 and NH), 7.20 (t, 1H, *J* = 8.15 Hz, H-7), 6.71 (dd, 1H, *J* = 3.90 and 2.85 Hz, H-2), 6.62 (dd, 1H, *J* = 3.90 and 1.30 Hz, H-3), 4.09 (m, 4H, Cp-*ortho* and Cp-*meta*), 4.00 (s, 5H, Cp'), 3.80 (m, 2H, $NCH_2$), 3.48 (s, 4H, $CH_2Fc$ and $CH_2Ph$), 2.61 (m, 2H, $NCH_2$), 2.43 (m, 4H, $NCH_2$), 2.35 (s, 3H, $NCH_3$), 1.89 (m, 2H, $CH_2$), 1.75 (m, 2H, $CH_2$). Anal. Calcd for $C_{36}H_{41}N_5Fe$: C, 72.11 H, 6.89; N, 11.68. Found: C, 71.85; H, 6.95; N, 11.72.

**4.1.4.6. {*N*-(7-Methoxypyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*-benzyl-*N*-(ferrocenylmethyl)-3-aminopropyl]methylamine (1j).** Yellow oil (83%). IR (KBr) 3280 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.70 (dd, 1H, *J* = 2.70 and 1.30 Hz, H-1), 7.60 (d, 1H, *J* = 8.85 Hz, H-9), 7.47 (t, 1H, *J* = 5.35 Hz, NH), 7.32-7.24 (m, 5H, Ar-H), 7.18 (d, 1H, *J* = 2.70 Hz, H-6), 6.81 (dd, 1H, *J* = 8.85 and 2.70 Hz, H-8), 6.67 (dd, 1H, *J* = 3.85 and 2.70 Hz, H-2), 6.57 (dd, 1H, *J* = 3.85 and 1.30 Hz, H-3), 4.12 (m, 4H, Cp-*ortho* and Cp-*meta*), 4.00 (s, 5H, Cp'), 3.90 (s, 3H, $CH_3O$), 3.78 (m, 2H, $NCH_2$), 3.47 (s, 4H, $CH_2Fc$ and $CH_2Ph$), 2.61 (m, 2H, $NCH_2$), 2.44 (m, 4H, $NCH_2$), 2.34 (s, 3H, $NCH_3$), 1.88 (m, 2H, $CH_2$), 1.76 (m, 2H, $CH_2$). Anal. Calcd for $C_{37}H_{43}N_5OFe$: C, 70.58 H, 6.88; N, 11.12. Found: C, 70.54; H, 6.99; N, 11.02.

**4.1.5. General procedure for 1-{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*,*N*-bis(ferrocenylmethyl)-3-aminopropyl]-piperazine (1k–l) and {*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*,*N*-bis(ferrocenylmethyl)-3-aminopropyl]methylamine (1m–n)**

To a solution of compound **7a–d** (1.36 mmol) in 10 mL of dry $CH_2Cl_2$ were added ferrocene-carboxaldehyde (4.08 mmol, 3 equiv) and $NaHB(OAc)_3$ (4.08 mmol, 3 equiv). After the mixture was stirred at room temperature for 24 hours, a total of 15 mL of aqueous 1 M NaOH solution was introduced. The mixture left for 15 min, the organic layer was separated, and the aqueous layer was washed with $CH_2Cl_2$. Then the organic layers were mixed and dried over $Na_2SO_4$, the solvent was evaporated, and the residue was purified by column chromatography using $CH_2Cl_2$/methanol/$NH_4OH$ (80:20:1 v/v/v) as eluent to yield **1k–n**.

**4.1.5.1. 1-{*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[*N*,*N*-bis(ferrocenylmethyl)-3-aminopropyl]piperazine (1k).** Yellow oil (85%). IR (KBr) 3270 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.79 (m, 1H, H-1), 7.71 (d, 1H, *J* = 7.70 Hz, H-9), 7.66 (d, 1H, *J* = 7.70 Hz, H-6), 7.31 (t, 1H, *J* = 7.70 Hz, H-8), 7.21 (t, 1H, *J* = 7.70 Hz, H-7), 6.94 (t, 1H, *J* = 5.35 Hz, NH), 6.74 (m, 2H, H-3 and H-2), 4.20 (m, 4H, 2Cp-*ortho*), 4.14 (m, 4H, 2Cp-*meta*), 4.11 (s, 10H, 2Cp'), 3.80 (m, 2H, $NCH_2$), 3.45 (s, 4H, $2CH_2Fc$), 2.60 (m, 10H, $NCH_2$ and $CH_2$ pip.), 2.37 (m, 4H, $NCH_2$), 1.91 (m, 2H, $CH_2$), 1.69 (m, 2H, $CH_2$). $^{13}$C NMR ($CDCl_3$) $\delta$ 149.6 (C-4), 137.2 (C-5a), 126.5 (C-6), 125.2 (C-7), 125.1 (C-9a), 122.4 (C-8), 119.8 (C-3a), 114.0 (C-9), 113.3 (C-1), 112.0 (C-3), 102.6 (C-2), 83.2 (Cp-1), 70.1 (2Cp-*ortho*), 68.4 (2Cp'), 67.8 (2Cp-*meta*), 58.5 ($NCH_2$), 56.7 ($NCH_2$), 53.5 ($CH_2$ pip.), 53.4 ($CH_2$ pip.), 52.5 ($NCH_2$), 49.9 ($NCH_2$), 41.5 ($NCH_2$), 24.6 ($2CH_2$). Anal. Calcd for $C_{43}H_{50}N_6Fe_2$: C, 67.72; H, 6.61; N, 11.02. Found: C, 67.58; H, 6.75; N, 11.21.

**4.1.5.2. 1-{*N*-(7-Methoxypyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-4-[N,*N*-bis(ferrocenylmethyl)-3-aminopropyl]piperazine (1l).** Yellow oil (83%). Yellow oil (88%). IR (KBr) 3280 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.72 (m, 1H, H-1), 7.61 (d, 1H, *J* = 8.70 Hz, H-9), 7.16 (d, 1H, *J* = 2.15 Hz, H-6), 7.00 (t, 1H, *J* = 5.35 Hz, NH), 6.81 (dd, 1H, *J* = 8.70 and 2.15 Hz, H-8), 6.71 (m, 2H, H-3 and H-2), 4.20 (m, 4H, 2Cp-*ortho*), 4.15 (m, 4H, 2Cp-*meta*), 4.11 (s, 10H, 2Cp'), 3.90 (s, 3H, $CH_3O$), 3.80 (m, 2H, $NCH_2$), 3.45 (s, 4H, $2CH_2Fc$), 2.61 (m, 10H, $NCH_2$ and $CH_2$ pip.), 2.38 (m, 4H, $NCH_2$), 1.90 (m, 2H, $CH_2$), 1.69 (m, 2H, $CH_2$). Anal. Calcd for $C_{44}H_{52}N_6OFe_2$: C, 66.67; H, 6.61; N, 10.60. Found: C, 66.77; H, 6.72; N, 10.47.

**4.1.5.3. {*N*-(Pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*,*N*-bis(ferrocenylmethyl)-3-aminopropyl]methylamine (1m).** Yellow crystals (82%); mp 48 °C. IR (KBr) 3280 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.79 (m, 1H, H-1), 7.71 (d, 1H, *J* = 7.90 Hz, H-9), 7.68 (d, 1H, *J* = 7.90 Hz, H-6), 7.31 (m, 2H, H-8 and NH), 7.20 (t, 1H, *J* = 7.90 Hz, H-7), 6.74 (m, 1H, H-2), 6.60 (m, 1H, H-3), 4.13 (m, 4H, 2Cp-*ortho*), 4.10 (m, 4H, 2Cp-*meta*), 4.04 (s, 10H, 2Cp'), 3.80 (m, 2H, $NCH_2$), 3.41 (s, 4H, $2CH_2Fc$), 2.59 (m, 2H, $NCH_2$), 2.40 (m, 4H, $NCH_2$), 2.34 (s, 3H, $NCH_3$), 1.87 (m, 2H, $CH_2$), 1.71 (m, 2H, $CH_2$). Anal. Calcd for $C_{40}H_{45}N_5Fe_2$: C, 67.90; H, 6.41; N, 9.90. Found: C, 68.02; H, 6.46; N, 10.08.

**4.1.5.4. {*N*-(7-Methoxypyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-[*N*,*N*-bis(ferrocenylmethyl)-3-aminopropyl]methylamine (1n).** Yellow oil (83%). IR (KBr) 3275 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.71 (dd, 1H, *J* = 2.70 and 1.30 Hz, H-1), 7.60 (d, 1H, *J* = 8.90 Hz, H-9), 7.38 (t, 1H, *J* = 5.40 Hz, NH), 7.19 (d, 1H, *J* = 2.80 Hz, H-6), 6.80 (dd, 1H, *J* = 8.90 and 2.80 Hz, H-8), 6.70 (dd, 1H, *J* = 3.90 and 2.70 Hz, H-2), 6.57 (dd, 1H, *J* = 3.90 and 1.30 Hz, H-3), 4.14 (t, 4H, *J* = 1.75 Hz, 2Cp-*ortho*), 4.09 (t, 4H, *J* = 1.75 Hz, 2Cp-*meta*), 4.05 (s, 10H, 2Cp'), 3.92 (s, 3H, $CH_3O$), 3.80 (m, 2H, $NCH_2$), 3.40 (s, 4H, $2CH_2Fc$), 2.58 (t, 2H, *J* = 6.50 Hz, $NCH_2$), 2.39 (m, 4H, $NCH_2$), 2.33 (s, 3H, $NCH_3$), 1.87 (qt, 2H, *J* = 6.50 Hz, $CH_2$), 1.69 (qt, 2H, *J* = 6.50 Hz, $CH_2$). Anal. Calcd for $C_{41}H_{47}N_5OFe_2$: C, 66.77; H, 6.42; N, 9.49. Found: C, 67.04; H, 6.49; N, 9.55.

**4.1.6. Bis{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-amine (9a)**

To a solution of **6a** (7.4 mmol, 2 equiv) in dimethylformamide (20 mL) were added $K_2CO_3$ (8.1 mmol, 2.2 equiv) then *N*-(3-aminopropyl)-1,3-propanediamine (3.7 mmol, 1 equiv). The reaction mixture was heated at 120–130 °C for 4 h and, after cooling, was poured into water (100 mL). The precipitate was filtered, washed with water and dissolved in dichloromethane. The organic layer was washed with water (150 mL), dried over $Na_2SO_4$ and evaporated to dryness to give **9a**. Yellow crystals (81%), mp 89 °C. IR (KBr) 3415 and 3300 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.78 (dd, 2H, *J* = 2.75 and 1.25 Hz, H-1), 7.72 (dd, 2H, *J* = 8.05 and 1.35 Hz, H-9), 7.63 (dd, 2H, *J* = 8.05 and 1.35 Hz, H-6), 7.29 (ddd, 2H, *J* = 8.05, 7.35 and 1.35 Hz, H-8), 7.24 (ddd, 2H, *J* = 8.05, 7.35 and 1.35 Hz, H-7), 6.69 (m, 4H, H-2 and H-3), 6.21 (m, 2H, NH), 3.86 (m, 4H, $NCH_2$), 2.87 (t, 4H, *J* = 6.10 Hz, $NCH_2$), 2.00 (qt, 4H, *J* = 6.10 Hz, $CH_2$), 1.95 (br s, 1H, NH). Anal. Calcd for $C_{28}H_{29}N_7$: C, 72.54; H, 6.30; N, 21.15. Found: C, 72.61; H, 6.24; N, 21.20.

**4.1.7. General procedure for Bis{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-*N*-ferrocenylmethylamine (2a–b)**

To a solution of compound **9a–b** (1.00 mmol) in 10 mL of dry $CH_2Cl_2$ were added ferrocene-carboxaldehyde (1.5 mmol, 1.5 equiv) and $NaHB(OAc)_3$ (1.5 mmol, 1.5 equiv). After the mixture was stirred at room temperature for 24 h, a total of 15 mL of aqueous 1 M NaOH solution was introduced. The mixture left for 15 min, the organic layer was separated, and the aqueous layer was washed with $CH_2Cl_2$. Then the organic layers were mixed and dried over $Na_2SO_4$, the solvent was evaporated, and the residue was purified by column chromatography using $CH_2Cl_2$/methanol/$NH_4OH$ (80:20:1 v/v/v) as eluent to yield **2a–b.**

**4.1.7.1. Bis{*N*-(pyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-*N*-ferrocenylmethylamine (2a).** Pale-yellow crystals (76%); mp 94 °C. IR (KBr) 3300 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.58 (dd, 2H, *J* = 2.80 and 1.25 Hz, H-1), 7.70 (dd, 2H, *J* = 8.00 and 1.40 Hz, H-9), 7.66 (dd, 2H, *J* = 8.00 and 1.40 Hz, H-6), 7.30 (ddd, 2H, *J* = 8.00, 7.40 and 1.40 Hz, H-8), 7.20 (ddd, 2H, *J* = 8.00, 7.40 and 1.40 Hz, H-7), 6.65 (dd, 2H, *J* = 3.85 and 2.80 Hz, H-2), 6.53 (dd, 2H, *J* = 3.85 and 1.25 Hz, H-3), 6.17 (t, 2H, *J* = 5.45 Hz, NH), 4.22 (t, 2H, *J* = 1.75 Hz, Cp-*ortho*), 4.13 (t, 2H, *J* = 1.75 Hz, Cp-*meta*),

4.10 (s, 5H, Cp'), 3.75 (m, 4H, $NCH_2$), 3.65 (s, 2H, $CH_2Fc$), 2.65 (t, 4H, $J$ = 6.45 Hz, $NCH_2$), 1.95 (qt, 4H, $J$ = 6.45 Hz, $CH_2$). Anal. Calcd for $C_{39}H_{39}N_7Fe$: C, 70.80; H, 5.94; N, 14.82. Found: C, 70.96; H, 5.88; N, 14.75.

**4.1.7.2. Bis{*N*-(7-methoxypyrrolo[1,2-*a*]quinoxalin-4-yl)-3-aminopropyl}-*N*-ferrocenylmethylamine (2b).** Beige crystals (82%); mp 108 °C. IR (KBr) 3295 (NH). $^1$H NMR ($CDCl_3$) $\delta$ 7.58 (m, 2H, H-1), 7.59 (d, 2H, $J$ = 8.85 Hz, H-9), 7.14 (d, 2H, $J$ = 2.80 Hz, H-6), 6.81 (dd, 2H, $J$ = 8.85 and 2.80 Hz, H-8), 6.62-6.51 (m, 4H, H-2 and H-3), 6.26 (m, 2H, NH), 4.20 (m, 2H, Cp-*ortho*), 4.10 (m, 7H, Cp-*meta* and Cp'), 3.87 (m, 4H, $NCH_2$), 3.85 (s, 6H, $2CH_3O$), 3.73 (s, 2H, $CH_2Fc$), 2.65 (t, 4H, $J$ = 6.15 Hz, $NCH_2$), 1.94 (qt, 4H, $J$ = 6.15 Hz, $CH_2$). Anal. Calcd for $C_{41}H_{43}N_7O_2Fe$: C, 68.23; H, 6.01; N, 13.58. Found: C, 68.10; H, 6.23; N, 13.71.

### 4.2. Biological assays

#### 4.2.1. In vitro *P. falciparum* culture and drug assays

*Plasmodium falciparum* strains were maintained continuously in culture on human erythrocytes as described by Trager and Jensen.[50] In vitro antiplasmodial activity was determined using a modification of the semi-automated microdilution technique of Desjardins et al.[51] *P. falciparum* CQ-sensitive (F32/Tanzania) and CQ-resistant (FcB1R/Colombia and PFB/Brazil) strains were used in sensitivity testing. Stock solutions of CQ diphosphate and test compounds were prepared in sterile distilled water and DMSO, respectively. Drug solutions were serially diluted with culture medium and added to asynchronous parasite cultures (1% parasitemia and 1% final hematocrite) in 96-well plates for 24 h, at 37 °C, prior to the addition of 0.5 μCi of [$^3$H]hypoxanthine (1–5 Ci/mmol; Amersham, Les Ulis, France) *per* well, for 24 h. The growth inhibition for each drug concentration was determined by comparison of the radioactivity incorporated into the treated culture with that in the control culture (without drug) maintained on the same plate. The concentration causing 50% inhibition ($IC_{50}$) was obtained from the drug concentration–response curve and the results were expressed as the mean ± the standard deviations determined from several independent experiments. The DMSO concentration never exceeded 0.1% and did not inhibit the parasite growth.

#### 4.2.2. β-Haematin formation assay

Haematin (ferriprotoporphyrin IX hydroxide) (H-3281) and sulfadimethoxine (S-7385) were obtained from Sigma Co. (St. Louis, MO, USA), chloroquine diphosphate (25745) and acetic acid were from Fluka and dimethylsulfoxide (DMSO) and NaOH were from Fisher Scientific (UK). Methanol was purchased from Elvetec (Genas, France). Artemisinin was kindly provided by Pr Benakis (Geneva, Switzerland).

The drugs effects upon β-haematin formation were assessed according to Basilico et al. with minor modifications.[46] One hundred microlitres of a 4 mM solution of haematin, previously dissolved in 0.1 M NaOH, was distributed in 96-well microplates (0.4 μmol/well). Drugs were added from DMSO stock solutions (20 μl) at a drug:haem ratio between 0:1 and 10:1. Controls contained an equal amount of DMSO. Haematin polymerization was initiated by adding 0.8 mmol of acetic acid (50 μl) at a final pH of 3. The total volume of reaction was fitted to 200 μl with 0.1 M NaOH and the assay mixtures were incubated at 37 °C for 20 h. Plates were then centrifuged at 3300 g for 15 min and the soluble fraction of unprecipitated material collected. The remaining pellets were resuspended with 200 μl of DMSO to remove unreacted haematin. Plates were then centrifuged again at 3300*g* for 15 min. The DMSO-soluble fraction was collected and the pellets, consisting of a pure precipitate of β-haematin, were dissolved in 0.1 M NaOH for spectroscopic quantification. A 150-μl aliquot of each fraction was transferred onto a new plate and serial four-fold dilutions in 0.1 M NaOH were carried out. The amount of haematin was determinated by measuring the absorbance at 405 nm using an automatic plate reader (SAFIRE II, Tecan, Austria). The data are expressed as the molar equivalents of test compounds relative to haematin required to inhibit heme polymerization by 50%. Each compound was tested in triplicate. Chloroquine diphosphate in $H_2O$ and artemisinin in DMSO were used as positive controls. Sulfadimethoxine in DMSO was used as negative control.

#### 4.2.3. Cytotoxicity test upon human embryonic cells

A human diploid embryonic lung cell line (MRC-5, Bio-Whittaker 72211D) was used to assess the cytotoxic effects towards eukaryotic host cells. MRC-5 cells were seeded at 5,000 cells *per* well in 100 μl. After 24 h, the cells were washed and twofold dilutions of the drug were added in 200 μl standard culture medium (RPMI medium + 5% fetal calf serum) and maintained for five days under 5% $CO_2$ atmosphere. The final DMSO concentration in the culture remained below 0.1%. Untreated cultures were included as controls. The cytotoxicity was determined using the colorimetric MTT assay according to the manufacturer's recommendations (Cell proliferation kit I, Roche Applied Science, France) and scored as a percentage of reduction in absorption at 540 nm of treated cultures versus untreated control cultures. $IC_{50}$ values were obtained from the drug concentration–response curve. The results were expressed as the mean ± the standard deviations determined from several independent experiments. The index of selectivity was defined as the ratio of the $IC_{50}$ value on MRC-5 to that of *P. falciparum*.

### 4.3. Partition coefficients – log*D* (pH 7.4 and 5.0)

In this study, the relative log*D* (pH 7.4 and 5.0) were assessed at pH 7.4 and 5.0 by the micro-HPLC method. Determinations were performed with a chromatographic apparatus (Spectra Series, San Jose, USA) equipped with a model P1000XR pump and a model SCM 1000 vacuum membrane degasser, a model UV 150 ultraviolet detector ($\lambda$ = 210 nm) and a ChromJet data module integrator (ThermoFinnigan, San Jose, USA). The reversed phase column used, was a Stability (C.I.L. Cluzeau) $C_{18}$ (4.6 × 150 mm; 5 μm particle size) with a mobile phase consisting of acetonitrile—potassium dihydrogenophosphate $6.24 \times 10^{-2}$ M [$KH_2PO_4/K_2HPO_4$] (pH 5) (55:45, v/v (**1h–j**, **1m–n**, **2a–b**)), acetonitrile—phosphate buffer (pH 6) (35:65, v/v (**1c**)), (40:60, v/v (**1a–b, 1e**)), (50:50, v/v (**1f**)), (55:45, v/v (**1k–l**)), (60:40, v/v (**1g**)) acetonitrile—phosphate buffer (pH 7) (55:45, v/v (**1d**)). The compounds were partitioned between *n*-octanol (HPLC grade) and phosphate buffer (pH 7.4). Octanol was presatured with the adequate phosphate buffer (1%), 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 50 μg/mL. Under the above-described chromatographic conditions, 50 μL of aqueous phase was injected into the chromatograph, leading to the determination of a peak area before partitioning ($W_0$). In screw-capped tubes, 4000 μL of the aqueous phase ($V_{aq}$) was then added to 10 μL of *n*-octanol ($V_{oct}$). The mixture was shaken by mechanical rotation during 30 min, followed by centrifugation achieved at 3000 rpm during 15 min. An amount of 50 μL of the lower phase was injected into the chromatograph column. This led to the determination of a peak area after partitioning ($W_1$). For each compound, the log*D* value was calculated using the formula: $\log D = \log[(W_0 - W_1)V_{aq}/W_1V_{oct}]$.

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