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Original article

Synthesis and *in vitro* antiplasmodial activity of ferrocenyl aminoquinoline derivatives

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ABSTRACT

The aim of this study was to synthesize a series of ferrocenyl 4-aminoquinolines and to evaluate their activities against *Plasmodium falciparum* F32 (chloroquine-sensitive) and FCB1 and K1 (chloroquino-resistant). Some of the ferrocenyl compounds exhibited *in vitro* antiplasmodial activity in the nM range. In particular, (1*R*,4*R*)-*N*1-(7-chloroquinolin-4-yl)-*N*4-(ferrocenylmethyl)-*N*4-methylcyclohexane-1,4-diamine **17** presented the lowest IC_{50} value (26 nM) against CQ-resistant strains.

1. Introduction

Malaria remains the most common parasite disease in tropical and subtropical regions affecting more than 207 million people with 627.000 deaths in 2013 [1,2]. Human malaria, transmitted by female Anopheles mosquitoes, is caused by five species of *Plasmodium*, which are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*. However, most cases of malaria and deaths are caused by *P. falciparum*. Since its discovery, Chloroquine (CQ) was the best antimalarial drug according to its safety, affordability, and efficacy. Despite this, the emergence and rapid widespread of *P. falciparum* CQ resistance have created an urgent need to discover new antimalarial agents [3,4]. Nowadays, most important antimalarial drugs include diaminopyrimidines (e.g. pyrimethamine), biguanides (e.g. proguanil), sulfonamides (e.g. sulfadoxine) and sulfones, quinolines (quinine, primaquine), arylaminoalcohols (mefloquine, halofantrine, lumefantrine), hydroxynaphthoquinones (e.g. atovaquone), artemisinin and its semisynthetic derivatives [5,6]. Among these, the interesting 4-aminoquinoline scaffold continues to be introduced in synthesized compounds [7–10]. Particularly, hybrid molecules are obtained by combining 4-aminoquinoline with other pharmacophore possessing an antimalarial activity [11–16]. This type of molecules may overcome drug resistance problems.

The use of metal complexes enhancing the biological activity of compounds has become a relevant strategy of research in both organometallic chemical and biological communities. In fact, the introduction of metals leads to profound changes in drugs biological activities [17–22]. Many different metal complexes have been incorporated into antimalarial drugs. Particularly, Ferroquine (FQ, SSR97193), a molecule with a ferrocenyl moiety inserted within the side chain of CQ is currently developed by Sanofi-Aventis [23–27]. Following this work, a variety of ferrocenyl antimalarial compounds was investigated and validated the ferrocene as an important entity for the design of new drugs [28–33]. A representative series of Ferroquine analogous is presented in Fig. 1. Usually, the ferrocenyl

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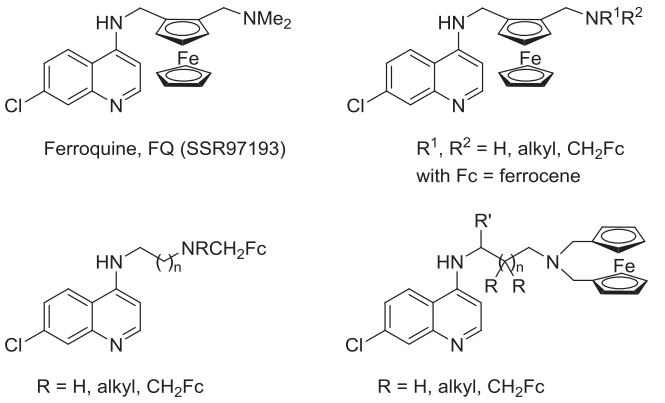


Fig. 1. Structures of Ferroquine (FQ) and analogous.

moiety is introduced between the two amino groups or at the end of the linear or branched aliphatic *N*-alkylamino side chain of the 4-aminoquinoline. To our knowledge, no ferrocenyl compounds possessing a cyclic entity have been previously synthesized.

However, previous studies have shown that the incorporation of a cyclohexane, piperidine or piperazine group in the side chain of the 4-aminoquinoline provided good antimalarial drugs [34–36]. As part of our ongoing interest in development of novel ferrocenyl drugs [37–39], we introduced cyclic moiety in the design of ferrocenyl compounds (Fig. 2). Their antiplasmodial activity was evaluated on CQ-sensitive- and CQ-resistant *P. falciparum* strains.

2. Results and discussion

2.1. Chemistry

Ferrocenyl ketone **3** was first synthesized by reaction of ferrocenyl ammonium salt **1** with 4-piperidone chloride **2** in the presence of potassium carbonate (Scheme 1). In addition, condensation of diamines with 4,7-dichloroquinoline **4** afforded the primary amines **5**–**8** [40]. Ferrocenyl quinoline amines **9**–**12** were then obtained in 74–95% yields by condensation of amines **5**–**8** on the ketone **3**, followed by a reduction with $NaBH_4$ (Scheme 1).

The ferrocenyl diamines **14** and **16** were prepared by a two-step reaction in 86 and 83% global yield respectively including a nucleophilic substitution of 4,7-dichloroquinoline **4** and a reductive amination in the presence of ferrocene carboxaldehyde (Scheme 2). The methylation of the secondary amine **16** by reaction of formaldehyde followed by a reduction with $NaBH_4$ afforded to **17** in 90% yield. Finally, condensation of amine **15** with either *N*-Boc-2-bromoethylamine or 3-bromopropylamine followed by *N*-Boc deprotection led to amines **18** and **19** in 26 and 56% global yields. The incorporation of a ferrocenyl group in **18** and **19** was achieved by reductive amination in the presence of ferrocene carboxaldehyde and furnished the ferrocenyl amines **20** and **21** in 95% yield (Scheme 2).

2.2. In vitro antiplasmodial activities

The *in vitro* antiplasmodial activity of ferrocenyl 4-aminoquinolines were evaluated against the CQ-sensitive F32 (IC_{50} CQ = 0.019 μM) and CQ-resistant FcB1 (IC_{50} = 0.111 μM) and K1 (IC_{50} = 0.160 μM) *P. falciparum* strains. The potencies of the ferrocenyl compounds, as indicated by their IC_{50} values, are summarized in Table 1. The IC_{50} values were compared to Chloroquine (CQ), Ferroquine (FQ) and Artemesinine (ART). In parallel, the cytotoxicity of the compounds was evaluated with human MCR-5 cells (Table 1). The selectivity index of the compounds was calculated as the ratio of cytotoxicity LD_{50} to antiplasmodial IC_{50}.

All tested compounds exhibited modest to excellent activities on the CQ-sensitive F32, CQ-resistant FCB1 and K1 strains with IC_{50} ranging from 26 to 292 nM for F32, 18–217 μM for FCB1 and 26–261 nM for K1. Except for molecules **11** and **21**, all ferrocenyl quinolines were more efficient than CQ in inhibiting the CQ-resistant strains FcB1 and K1 with IC_{50} ranging from 18 to 34 and 25–32 nM respectively. Furthermore, they displayed similar IC_{50} values than FQ and ART toward all strains tested.

Increasing the length of the side alkyl chain from two or three to four methylene units in compounds **9**–**11** decreased the antiplasmodial activity (entries 4 and 5 *vs* 6). Similar effect was observed for **20** and **21** (entries 11 *vs* 12). But the effect of chain length was not observed with the linear **10** and branched **12** propylamino chain derivatives (entries 10 and 12). As already described [34], 1,4-diaminocyclohexyl compounds showed an increase of relative activity against CQ. Indeed, ferrocenyl derivative **16** exhibited excellent activities of 31–32 nM for the three strains (entry 9). Changing the position of the two amines in the cyclohexyl for **14** led to similar activities than **16** (entries 8 and 9). The antiplasmodial activity is not affected by the *N*-methylation of the nitrogen atom in compound **16** (entries 9 *vs* 10).

The resistance index values provide a quantitative measurement of the antimalarial activity against chloroquine-resistant strains (FcB1 and K1) relative to that against sensitive strain (F32). All ferrocenyl compounds exhibited lower resistance index than those of CQ in a range of 0.6–1.2 (FcB1) and 0.7–1.1 (K1) (Table 1).

2.3. Cytotoxicities on MCR-5 cells

The cytotoxicities of the ferrocenyl compounds were evaluated upon MCR-5 cells. The values allowed us to calculate the selectivity index corresponding to the ratio of cytotoxicity and antimalarial activity for the different strains. The results are summarized in Table 1.

Unfortunately, most of the ferrocenyl derivatives appeared to be cytotoxic with LD_{50} ranging from 17 to 683 nM. Although **11** and **21** were the less cytotoxic compounds, they were also the less active on *P. falciparum* strains. Only ferrocenyl compound **17** could constitute good candidate for further pharmacological studies with selectivity indexes over 259 upon the CQ-sensitive strain F32 and over 317 upon CQ-resistant strains FcB1 and K1.

3. Conclusion

Novel series of ferrocenyl 4-aminoquinolines were synthesized and tested for their activities against *P. falciparum* F32 (chloroquine-sensitive) and FCB1 and K1 (chloroquine-resistant). Most of the ferrocenyl compounds showed interesting antiplasmodial activity in the nM range. In particular, the biological results led to highlight the ferrocenyl quinoline **17** as a lead compound in this series and could be a good candidate for further pharmacological studies. In addition, this work emphasizes the importance of the ferrocenyl entity as a good scaffold for designing antimalarial compounds. Further in vivo testing of ferrocenyl quinoline **17** will also be performed on murine models of malaria.

4. Experimental

4.1. Chemistry

All commercial reagents and solvents were used without further purification. Melting points were determined with a Barnstead Electrothermal (BI 9300) capillary melting point apparatus and are

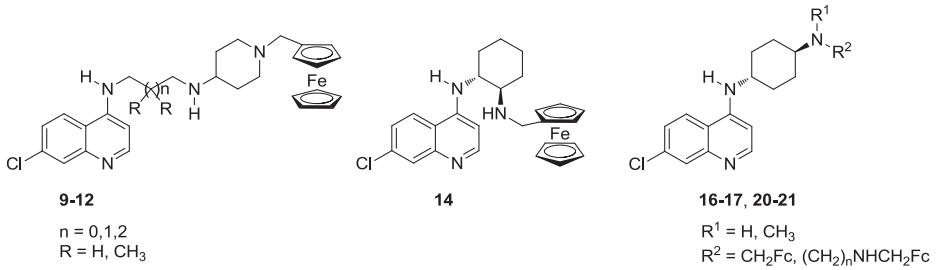
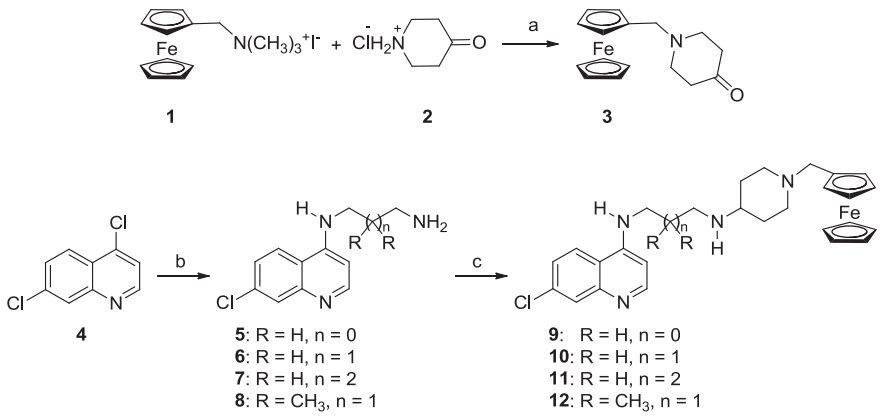
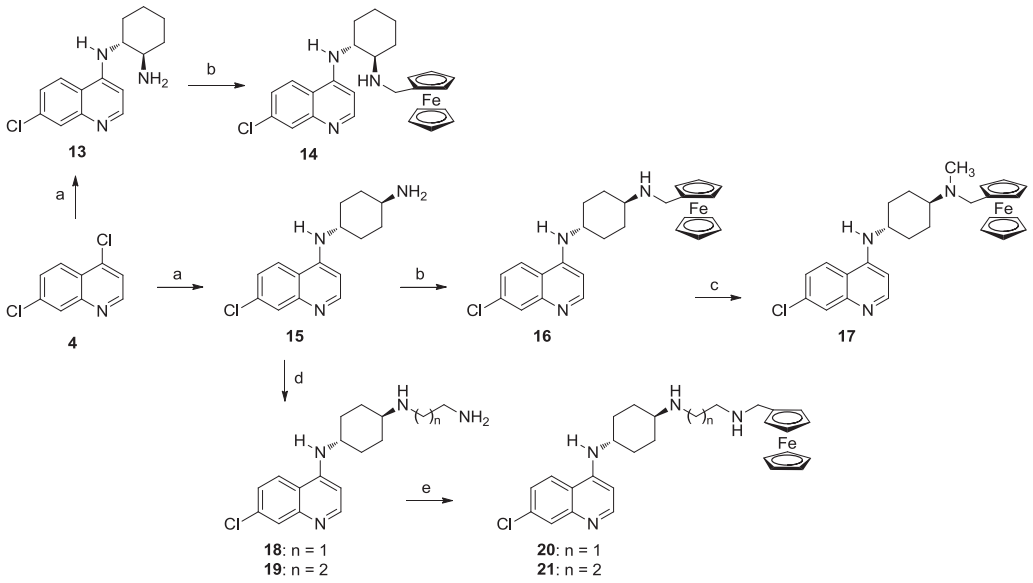


Fig. 2. Structures of ferrocenyl 4-aminoquinolines.



Scheme 1. Reagents and conditions: (a) K_2CO_3, methanol, reflux, 12 h (98%); (b) diamine, 135 °C, 4 h (80–98%); (c) **3**, methanol, reflux, 4 h then $NaBH_4$ (74–95%).



Scheme 2. Reagents and conditions: (a) 1,2- or 1,4-diaminocyclohexane, ethanol, reflux, 24 h (90% for **13** and 87% for **15**); (b) Ferrocene carboxaldehyde, methanol, reflux, 4 h then $NaBH_4$ (95%); (c) Formaldehyde (37% aq), methanol, 2 h, reflux then $NaBH_4$, 0 °C, 2 h (90%); (d) *N*-Boc aminoalkyl bromide, dioxane, potassium carbonate, 100 °C then 12 h HCl, *i*-PrOH, $CHCl_3$, rt, 12 h (26% for **18** and 56% for **19**, two steps); (e) Ferrocene carboxaldehyde, methanol, reflux, 4 h then $NaBH_4$ (95%).

uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC300 spectrometer at 300 and 75.5 MHz respectively. Thin layer chromatography (TLC) was carried out on aluminum-baked Macherey–Nagel silica gel 60. Column chromatography was performed on silica gel (230–400 mesh). Elemental analyses were performed with a varioMICRO analyzer.

4.1.1. *N-ferrocenylmethyl-4-piperidone* ***3***

Ferrocenyl ammonium iodide **1** (8.8 mmol, 3.38 g) and 4-piperidone chloride (4.6 mmol, 0.455 g) were dissolved in acetonitrile (30 mL) in the presence of K_2CO_3 (4.6 mmol, 0.634 mg). The resulting solution was heated at reflux for 12 h. The mixture was hydrolyzed by an aqueous NaOH solution (1 M, 20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give a yellow solid. The

Table 1
In vitro sensitivity of *P. falciparum* strains and *in vitro* cytotoxicity on MRC-5 cells of ferrocenyl compounds **9**–**12**, **14**, **16**–**17** and **20**–**21**.

Entry	Compd	*P. falciparum* strains IC_{50} values (nM)[a]			MRC-5 cells LD_{50} (nM)[b]	Selectivity index[c]			Resistance index[d]	
		F32	FcB1	K1		F32	FcB1	K1	FcB1	K1
1	**CQ**	19	111	160	50000					
2	**FQ**	29	20	31	NT	–	–	–	0.7	1.1
3	**ART**	31	18	29	NT	–	–	–	0.6	0.9
4	**9**	26	32	27	17	0.7	0.5	0.6	1.2	1.0
5	**10**	30	32	25	683	22.7	21.3	27.3	1.1	0.8
6	**11**	319	217	215	5520	17.3	25.4	25.6	0.7	0.7
7	**12**	35	27	30	551	15.7	20.4	18.3	0.8	0.9
8	**14**	33	34	30	59	1.8	1.7	2.0	1.0	0.9
9	**16**	31	32	32	52	1.7	1.6	1.6	1.0	1.0
10	**17**	33	27	26	8570	259.7	317.4	329.6	0.8	0.8
11	**20**	33	33	32	67	2.0	2.0	2.1	1.0	0.9
12	**21**	292	174	261	8900	30.5	51.1	34.1	0.6	0.9

[a] IC_{50} values were measured on the chloroquine-sensitive strain F32/Tanzania and the chloroquine-resistant strains FcB1/Colombia and K1/Thailand. The results are expressed as IC_{50} values at least one experiment for F32, three independent experiments for FCB1, two experiments for K1.
[b] LD_{50} lethal dose, indicating concentration which reduced the number of viable cells by 50%.
[c] Selectivity index (SI) was defined as the ratio between the LD_{50} value on the MRC-5 cells and the IC_{50} value against the *P. falciparum* F32, FcB1 et K1 strains.
[d] IC_{50}(FcB1)/IC_{50}(F32) and IC_{50}(K1)/IC_{50}(F32).

product was purified by recrystallization to give **3** (1.33 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (s, 2H, Cp), 4.12 (s, 2H, Cp), 4.11 (s, 5H, Cp′), 3.50 (s, 2H, $FcCH_2$), 2.70 (t, J = 6.0 Hz, 2H, CH_2), 2.41 (t, J = 6.0 Hz, 2H, CH_2). ^{13}C (75.5 MHz, $CDCl_3$) δ 209.2, 82.3, 70.2, 68.6, 68.3, 57.4, 52.4, 41.1. HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{16}H_{20}FeNO$: 298.0894, found: 297.0881.

4.1.2. General procedure for ferrocenyl amines **9**–**12**

To a solution of amine (1.3 mmol) in methanol (20 mL) was added ferrocene carboxaldehyde (1.3 mmol). After stirring under reflux for 4 h, the mixture was allowed to reach to room temperature and $NaBH_4$ (4 mmol) was slowly added. After 1 h 30, the mixture was hydrolyzed by an aqueous NaOH solution (1 M, 20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give a yellow solid. The crude product was purified by recrystallization or by column chromatography (eluant: ethyl acetate/triethylamine: 7/3).

4.1.2.1. *N1-(1-ferrocenylmethylpiperidin-4-yl)-N2-(7-chloroquinolin-4-yl)ethane-1,2-diamine* ***9***.

Yield: 95%, yellow solid, mp 66 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 5.4 Hz, 1H, H_{Ar}), 7.81 (d, J = 2.1 Hz, 1H, H_{Ar}), 7.64 (d, J = 8.9 Hz, 1H, H_{Ar}), 7.20 (dd, J = 8.7 and 2.1 Hz, 1H, H_{Ar}), 6.27 (d, J = 5.4 Hz, 1H, H_{Ar}), 5.20 (s, 1H, NH), 4.07 (s, 2H, Cp), 4.02 (s, 2H, Cp), 4.01 (s, 5H, Cp′), 3.29 (s, 2H, $FcCH_2$), 3.18 (t, J = 6.0 Hz, 2H, CH_2), 2.74 (t, J = 6.0 Hz, 2H, CH_2), 2.35 (m, 4H, CH_2), 1.85 (m, 1H, CH), 1.78 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 149.9, 148.9, 134.7, 128.4, 125.1, 121.5, 117.4, 99.1, 82.2, 70.3, 68.5, 68.0, 58.3, 54.2, 51.7, 44.2, 42.3, 32.7. Anal. Calcd for $C_{27}H_{31}ClFeN_4$: C 64.49, H 6.21, N 11.14, found: C 64.58, H 6.01, N 11.23.

4.1.2.2. *N1-(1-ferrocenylmethylpiperidin-4-yl)-N3-(7-chloroquinolin-4-yl)propane-1,3-diamine* ***10***.

Yield: 80%, yellow solid, mp 64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 5.3 Hz, 1H, H_{Ar}), 7.88 (d, J = 2.0 Hz, 1H, H_{Ar}), 7.81 (d, J = 8.9 Hz, 1H, H_{Ar}), 7.32 (dd, J = 9.2 and 2.0 Hz, 1H, H_{Ar}), 6.25 (d, J = 5.4 Hz, 1H, H_{Ar}), 5.22 (s, 1H, NH), 4.15 (s, 2H, Cp), 4.11 (s, 2H, Cp), 4.09 (s, 5H, Cp′), 3.39 (s, 2H, $FcCH_2$), 3.29 (t, J = 5.7 Hz, 2H, CH_2), 2.85 (m, 4H, CH_2), 2.79 (t, J = 7.1 Hz, 2H, CH_2), 2.5 (m, 1H, CH), 1.50 (m, 2H, CH_2), 1.21 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 150.7, 144.4, 134.9, 127.8, 125.1, 125.6, 122.5, 117.4, 98.2, 82.1, 70.3, 68.5, 68.1, 58.1, 55.4, 51.6, 43.5, 34.4, 31.9, 27.2. Anal. Calcd for $C_{28}H_{33}ClFeN_4$: C 65.06, H 6.44, N 10.84, found: C 65.24, H 6.31, N 10.65.

4.1.2.3. *N1-(1-ferrocenylmethylpiperidin-4-yl)-N4-(7-chloroquinolin-4-yl)butane-1,4-diamine* ***11***.

Yield: 85%, yellow solid, mp 62 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 6.7 Hz, 1H, H_{Ar}), 8.12 (d, J = 9.3 Hz, 1H, H_{Ar}), 7.79 (s, 1H, H_{Ar}), 7.23 (d, J = 9.3 Hz, 1H, H_{Ar}), 6.19 (d, J = 7.0 Hz, 1H, H_{Ar}), 5.9 (s, 1H, NH), 4.12 (s, 2H, Cp), 4.11 (s, 7H, Cp, Cp′), 3.39 (s, 2H, $FcCH_2$), 3.21 (m, 2H, CH_2), 2.85 (m, 4H, CH_2), 2.71 (m, 1H, CH), 2.18 (m, 2H, CH_2),2.01 (m, 4H, CH_2), 1.95 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 151.5, 147.9, 135.8, 125.4, 123.4, 126.7, 111.4, 98.2, 81.3, 70.4, 68.6, 68.3, 57.6, 54.8, 50.9, 42.5, 30.9, 29.2, 25.2, 24.0. HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{29}H_{36}ClFeN_4$: 531.1978, found: 531.1988.

4.1.2.4. *N1-(1-ferrocenylmethylpiperidin-4-yl)-N3-(7-chloroquinolin-4-yl)2,2-dimethyl propane-1,3-diamine* ***12***.

Yield: 74%, yellow solid, mp 58 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, J = 6.9 Hz, 1H, H_{Ar}), 8.33 (s, 1H, NH), 7.91 (d, J = 2.1 Hz, 1H, H_{Ar}), 7.70 (d, J = 9.2 Hz, 1H, H_{Ar}), 7.29 (dd, J = 8.9 and 2.1 Hz, 1H, H_{Ar}), 6.26 (d, J = 6.9 Hz, 1H, H_{Ar}), 4.16 (m, 2H, Cp), 4.11 (s, 2H, Cp), 4.10 (s, 5H, Cp′), 3.37 (s, 2H, $FcCH_2$), 3.13 (s, 2H, CH_2), 2.85 (m, 2H, CH_2), 2.69 (s, 2H, CH_2), 2.37 (m, 1H, CH),1.95 (m, 4H, CH_2), 1.21 (m, 2H, CH_2), 1.06 (s, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 150.8, 149.1, 134.5, 128.5, 124.7, 122.4, 117.7, 97.8, 82.7, 70.4, 68.5, 68.0, 58.2, 55.9, 51.9, 33.5, 32.7, 25.0. Anal. Calcd for $C_{30}H_{37}ClFeN_4$: C 66.12, H 6.84, N 10.28, found: C 66.01, H 6.79, N 10.20.

4.1.3. *(1R,2R)-N1-(7-chloroquinolein-4-yl)cyclohexane-1,2-diamine* ***13***

A mixture of 4,7-dichloroquinoline (0.28 g, 1.4 mmol) and (1*R*,2*R*)-1,2-diaminocyclohexane (0.5 mL, 4.2 mmol) was heated to 110 °C for 24 h. After cooling to room temperature, water (30 mL) was then added and the mixture was extracted with CH_2Cl_2. The organic layers were washed with water (50 mL), dried over anhydrous $MgSO_4$. The mixture was evaporated to give a brown oil (0.346 g, 90%). ^{1}H NMR (300 MHz, MeOD-d4) δ 8.38 (d, J = 5.6 Hz, 1H, H_{Ar}), 8.21 (d, J = 9.0 Hz, 1H, H_{Ar}), 7.75 (s, 1H, H_{Ar}), 7.38 (d, J = 8.9 Hz, 1H, H_{Ar}), 6.67 (d, J = 5.7 Hz, 1H, H_{Ar}), 5.50 (s, 3H, NH), 3.65 (m, 1H, CH), 3.22 (m, 1H, CH), 2.16 (m, 2H, CH_2), 1.84 (m, 2H, CH_2), 1.44 (m, 4H, CH_2). ^{13}C NMR (75 MHz, MeOD-d4) δ 152.5, 152.2, 149.5, 136.5, 127.3, 126.1, 124.9, 119.1, 100.2, 57.2, 54.9, 32.9, 31.9, 25.6, 25.5.

4.1.4. (1R,2R)-N1-(7-chloroquinolin-4-yl)-N2-(ferrocenylmethyl) cyclohexane-1,2-diamine **14**

To a solution of diamine **13** (1.2 mmol, 0.300 g) in methanol (20 mL) was added ferrocene carboxaldehyde (1.3 mmol, 0.286 g). After stirring under reflux for 4 h, the mixture was allowed to reach to room temperature and $NaBH_4$ (2.6 mmol, 100 mg) was slowly added. After 1h30, the mixture was hydrolyzed by an aqueous NaOH solution (1 M, 20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give a yellow solid. The crude product was purified by column chromatography (eluant: ethyl acetate/triethylamine: 7/3) to give a yellow solid (0.539 g, 95%). M.p. 50 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 5.4 Hz, 1H, H_{Ar}), 7.85 (d, J = 2.1 Hz, 1H, H_{Ar}), 7.41 (d, J = 8.9 Hz, 1H, H_{Ar}), 7.19 (dd, J = 8.9 and 2.1 Hz, 1H, H_{Ar}), 6.40 (d, J = 5.4 Hz, 1H, H_{Ar}), 5.10 (s, 1H, NH), 4.05 (m, 4H, Cp), 3.95 (s, 5H, Cp′), 3.57 (d, J = 13.1 Hz, 1H, $FcCH_2$), 3.31 (d, J = 13.4 Hz, 1H, $FcCH_2$), 3.16 (m, 1H, CH), 2.19 (m, 4H, CH_2), 1.75 (m, 1H, CH), 1.35 (m, 4H, CH_2), 1.16 (m, 4H, CH_2). ^{13}C NMR (75 MHz, MeOD-d4) δ 152.0, 149.9, 149.3, 134.7, 128.8, 125.2, 121.3, 117.6, 99.8, 87.3, 68.4, 68.1, 67.8, 60.5, 56.7, 45.6, 31.7, 24.7. HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{26}H_{28}ClFeN_3$: 473.1321, found: 473.1302.

4.1.5. Trans-N1-(7-chloroquinolein-4-yl)cyclohexane-1,4-diamine **15**

A mixture of 4,7-dichloroquinoline (1.4 mmol, 0.28 g) and *trans*-1,4-diaminocyclohexane (4.2 mmol, 0.5 mL) was heated to 110 °C for 24 h. After cooling to room temperature, water (30 mL) was then added and the mixture was extracted with CH_2Cl_2. The organic layers were washed with water (50 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The mixture was purified by flash chromatography (eluent: ethyl acetate/MeOH/triethylamine: 7/1/2) to give a brown oil (0.335 g, 87%). ^{1}H NMR (300 MHz, MeOD-d4) δ 8.29 (d, J = 5.6 Hz, 1H, H_{Ar}), 8.07 (d, J = 8.8 Hz, 1H, H_{Ar}), 7.73 (s, 1H, H_{Ar}), 7.30 (d, J = 9.0 Hz, 1H, H_{Ar}), 6.47 (d, J = 5.6 Hz, 1H, H_{Ar}), 4.94 (s, 3H, NH), 3.48 (m, 1H, CH), 2.69 (m, 1H, CH), 2.09 (m, 2H, CH_2), 1.94 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.30 (m, 2H, CH_2). ^{13}C NMR (75 MHz, MeOD-d4) δ 150.9, 150.3, 148.4, 134.8, 126.1, 124.3, 123.0, 117.3, 98.5, 50.9, 49.5, 34.0, 30.4.

4.1.6. Trans-N1-(7-chloroquinolin-4-yl)-N4-(ferrocenylmethyl) cyclohexane-1,4-diamine **16**

To a solution of diamine **15** (1.2 mmol, 0.300 g) in methanol (20 mL) was added ferrocene carboxaldehyde (1.3 mmol, 0.286 g). After stirring under reflux for 4 h, the mixture was allowed to room temperature and $NaBH_4$ (2.6 mmol, 100 mg) was slowly added. After 1h30, the mixture was hydrolyzed by an aqueous NaOH solution (1 M, 20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give a yellow solid. The crude product was purified by column chromatography (eluant: ethyl acetate/MeOH/triethylamine: 7/1/2) to give a yellow solid (0.539 g, 95%). M.p. 187 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 6.7 Hz, 1H, H_{Ar}), 8.12 (d, J = 9.3 Hz, 1H, H_{Ar}), 7.79 (s, 1H, H_{Ar}), 7.23 (d, J = 9.4 Hz, 1H, H_{Ar}), 6.39 (d, J = 7.0 Hz, 1H, H_{Ar}), 4.88 (d, J = 7.2 Hz, 1H, NH), 4.22 (s, 2H, Cp), 4.11 (s, 2H, Cp), 4.10 (s, 5H, Cp′), 3.60 (s, 2H, $FcCH_2$), 3.21 (m, 1H, CH), 2.85 (m, 1H, CH), 2.18 (m, 2H, CH_2), 2.01 (m, 2H, CH_2), 1.83 (s, 1H, NH), 1.37 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 149.3, 148.6, 134.8, 129.7, 125.2, 120.8, 117.1, 99.4, 87.0, 68.4, 68.3, 67.8, 55.7, 53.4, 51.5, 46.3, 31.8, 31.3. HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{26}H_{29}ClFeN_3$: 474.1399, found: 474.1407.

4.1.7. (1R,4R)-N1-(7-chloroquinolin-4-yl)-N4-(ferrocenylmethyl)-N4-methylcyclohexane-1,4-diamine **17**

To a solution of amine **16** (0.84 mmol, 0.400 g) in methanol (20 mL) was added methanal (1 mL, 37% in H_2O). After stirring under reflux for 2 h, the mixture was allowed to room temperature and $NaBH_4$ (1.68 mmol, 63 mg) was slowly added at 0 °C. After 2 h, the mixture was hydrolyzed by water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give a yellow solid. The crude product was purified by column chromatography (eluant: ethyl acetate/triethylamine: 7/3) to give a yellow solid (367 mg, 90%). M.p. 90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 5.3 Hz, 1H, H_{Ar}), 7.87 (d, J = 1.8 Hz, 1H, H_{Ar}), 7.53 (d, J = 8.9 Hz, 1H, H_{Ar}), 7.25 (dd, J = 8.8 and 1.8 Hz, 1H, H_{Ar}), 6.35 (d, J = 5.4 Hz, 1H, H_{Ar}), 4.72 (d, J = 7.1 Hz, 1H, NH), 4.10 (s, 2H, Cp), 4.00 (s, 7H, Cp + Cp′), 3.49 (s, 2H, $FcCH_2$), 3.48 (m, 1H, CH), 2.52 (m, 1H, CH), 2.25 (s, 3H, CH_3), 2.18 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 1.26 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 149.3, 148.6, 134.8, 128.9, 125.2, 120.7, 117.0, 99.3, 84.0, 70.2, 68.8, 68.2, 60.4, 53.7, 51.7, 37.9, 31.9, 27.2. Anal. Calcd for $C_{27}H_{30}ClFeN_3$: C 66.47, H 6.20, N 8.61, Found 66.21, H 6.12, N 8.45.

4.1.8. (1R,4R)-N1-(2-aminoethyl)-N4-(7-chloroquinolin-4-yl) cyclohexane-1,4-diamine **18**

To a solution of diamine **15** (1.21 mmol, 0.332 g) in dioxane (20 mL) was added ter-butyl-2-bromoethylcarbamate (1.33 mmol, 0.296 g) in the presence of K_2CO_3 (400 mg). After stirring at 100 °C for 12 h, the mixture was allowed to room temperature and the solvent was evaporated. The residue was hydrolyzed by HCl (1 M, 20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give yellow oil. The crude product was purified by column chromatography (eluant: ethyl acetate/triethylamine: 7/3) to give a yellow oil (0.258 g, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 4.7 Hz, 1H, H_{Ar}), 8.10 (d, J = 9.1 Hz, 1H, H_{Ar}), 8.03 (s, 1H, H_{Ar}), 7.52 (d, J = 8.9 Hz, 1H, H_{Ar}), 7.52 (d, J = 4.6 Hz, 1H, H_{Ar}), 4.92 (s, 1H, NH), 4.52 (s, 1H, NH), 3.63 (m, 2H, CH_2), 3.52 (m, 2H, CH_2), 3.39 (m, 1H, CH), 3.21 (m, 1H, CH), 2.18 (m, 2H, CH_2), 2.01 (m, 2H, CH_2), 1.95 (m, 4H, CH_2), 1.38 (s, 9H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 150.9, 150.4, 148.4, 134.8, 126.1, 124.3, 123.0, 117.4, 98.5, 85.3, 50.9, 49.5, 42.3, 35.2, 33.6, 32.4, 28.3.

To a solution of *N*-protected amine (0.500 mg, 1.18 mmol) in $CHCl_3$ (10 mL) was added HCl (10 M in *i*-PrOH, 10 mL). After stirring at 20 °C for 18 h, the mixture was hydrolyzed by water (50 mL), neutralized by NaOH and extracted with $CHCl_3$ (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give yellow oil. The crude product was purified by column chromatography (eluant: ethyl acetate/triethylamine: 7/3) to give a yellow oil (193 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 5.5 Hz, H_{Ar}), 8.04 (d, J = 9.0 Hz, H_{Ar}), 7.65 (s, 1H, H_{Ar}), 7.27 (d, J = 9.0 Hz, H_{Ar}), 6.46 (d, J = 5.9 Hz, H_{Ar}), 3.45 (s, 1H, NH), 2.90 (m, 1H, CH), 2.60 (m, 1H, CH), 2.10 (m, 2H, CH_2), 2.08 (m, 2H, CH_2), 1.45 (m, 4H, CH_2), 1.06 (m, 2H, CH_2), 1.04 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 151.8, 148.7, 136.4, 127.5, 125.9, 124.5, 118.8, 100.0, 51.8, 50.8, 49.8, 48.1, 32.3, 31.2.

4.1.9. (1R,4R)-N1-(2-aminopropyl)-N4-(7-chloroquinolin-4-yl) cyclohexane-1,4-diamine **19**

To a solution of diamine **15** (1.21 mmol, 0.332 g) in dioxane (20 mL) was added ter-butyl-2-bromopropylcarbamate (1.33 mmol, 0.315 g) in the presence of K_2CO_3 (400 mg). After stirring at 100 °C for 12 h, the mixture was allowed to reach to room temperature and the solvent was evaporated. The residue was hydrolyzed by HCl (1 M, 20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give yellow oil. The crude product was purified by column chromatography (eluant: ethyl acetate/triethylamine: 7/3) to give a yellow oil (355 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 5.3 Hz, 1H, H_{Ar}), 7.86 (s, 1H, ArH), 7.56 (d, J = 8.9 Hz, 1H, H_{Ar}), 7.26 (d, J = 8.5 Hz, 1H, H_{Ar}), 6.35 (d, J = 5.2 Hz, 1H, H_{Ar}), 5.23 (s, 1H, NH), 4.60 (s, 1H,

NH), 3.45 (m, 2H, CH_2), 3.16 (m, 1H, CH), 2.49 (m, 2H, CH_2), 2.10 (m, 1H, CH), 2.04 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 1.41 (m, 2H, CH_2), 1.38 (s, 9H, CH_3), 1.28 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 151.9, 149.3, 148.5, 134.8, 128.8, 125.2, 120.0, 117.0, 99.3, 85.1, 50.9, 49.5, 42.3, 35.2, 35.1, 32.7, 31.2, 28.4.

To a solution of *N*-protected amine (1 mmol, 0.432 g) in $CHCl_3$ (10 mL) was added HCl (10 M in *i*-PrOH, 10 mL). After stirring at 20 °C for 18 h, the mixture was hydrolyzed by water (50 mL), neutralized by NaOH and extracted with $CHCl_3$ (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give yellow oil. The crude product was purified by column chromatography (eluant: ethyl acetate/triethylamine: 7/3) to give a yellow oil (272 mg, 82%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.93 (d, J = 5.5 Hz, H_{Ar}), 8.36 (d, J = 9.7 Hz, H_{Ar}), 8.15 (s, 1H, H_{Ar}), 7.98 (d, J = 9.6 Hz, H_{Ar}), 7.84 (d, J = 5.9 Hz, H_{Ar}), 3.5 (s, 1H, NH), 3.45 (s, 2H, NH), 2.92 (m, 1H, CH), 2.65 (m, 1H, CH), 2.10 (m, 2H, CH_2), 2.08 (m, 2H, CH_2), 1.45 (m, 4H, CH_2), 1.36 (m, 2H, CH_2), 1.24 (m, 2H, CH_2), 0.86 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9; 149.3, 148.5, 134.8, 128.8, 125.2, 120.0, 117.0, 99.3, 50.9, 49.5, 42.3, 35.2, 35.1, 32.7, 31.2.

4.1.10. (1R,4R)-N1-(7-chloroquinolin-4-yl)-N4-(3-(ferrocenylmethylamino)ethyl)cyclo hexane-1,4-diamine **20**

To a solution of amine **18** (0.34 mmol, 0.108 mg) in methanol (20 mL) was added ferrocene carboxaldehyde (0.37 mmol, 80 mg). After stirring under reflux for 4 h, the mixture was allowed to reach to room temperature and $NaBH_4$ (0.68 mmol, 26 mg) was slowly added. After 2 h, the mixture was hydrolyzed by water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give a yellow solid. The crude product was purified by column chromatography (eluant: ethyl acetate/triethylamine: 7/3) to give a yellow solid (115 mg, 95%). M.p. 155 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 8.8 Hz, H_{Ar}), 7.87 (s, 1H, H_{Ar}), 7.52 (d, J = 10.0 Hz, H_{Ar}), 7.25 (d, J = 10.0 Hz, H_{Ar}), 6.34 (d, J = 8.6 Hz, H_{Ar}), 4.76 (s, 1H, NH), 4.25 (s, 1H, NH), 4.15 (s, 2H, Cp), 4.08 (s, 2H, Cp), 4.06 (s, 5H, Cp′), 4.01 (s, 2H, $FcCH_2$), 2.55 (m, 2H, CH), 2.18 (m, 4H, CH_2), 1.99 (m, 4H, CH_2), 1.28 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 151.9, 144.7, 144.7, 129.0, 125.2, 122.5, 120.7, 114.0, 99.3, 81.7, 68.5, 68.3, 68.0, 60.7, 57.0, 55.5, 51.4, 46.1, 31.4, 31.2. Anal. Calcd for $C_{28}H_{33}ClFeN_4$: C 65.06, H 6.44, N 10.84, found: C 64.89, H 6.32, N 10.97.

4.1.11. (1R,4R)-N1-(7-chloroquinolin-4-yl)-N4-(3-(ferrocenylmethylamino)propyl)cyclo hexane-1,4-diamine **21**

To a solution of amine **19** (0.29 mmol, 0.096 g) in methanol (20 mL) was added ferrocene carboxaldehyde (0.32 mmol, 68 mg). After stirring under reflux for 4 h, the mixture was allowed to reach to room temperature and $NaBH_4$ (0.58 mmol, 22 mg) was slowly added. After 2 h, the mixture was hydrolyzed by water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated under vacuum to give a yellow solid. The crude product was purified by column chromatography (eluant: ethyl acetate/triethylamine: 7/3) to give a yellow solid (146 mg, 95%). M.p. 90 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 8.8 Hz, H_{Ar}), 7.96 (s, 1H, H_{Ar}), 7.62 (d, J = 10.2 Hz, H_{Ar}), 7.34 (d, J = 9.2 Hz, H_{Ar}), 6.44 (d, J = 8.1 Hz, H_{Ar}), 4.88 (s, 1H, NH), 4.35 (s, 1H, NH), 4.25 (s, 1H, NH), 4.20 (s, 2H, Cp), 4.17 (s, 2H, Cp), 4.14 (s, 5H, Cp′), 4.10 (s, 2H, $FcCH_2$), 2.70 (m, 2H, CH), 2.27 (m, 3H, CH + CH_2), 2.08 (m, 2H, CH_2), 1.35 (m, 4H, CH_2), 1.27 (m, 4H, CH_2), 0.86 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 149.4, 148.8, 128.8, 125.1, 120.9, 119.2, 117.2, 99.3, 79.6, 70.0, 68.5, 67.8, 60.6, 57.0, 57.0, 55.5, 51.4, 46.1, 31.8, 31.6, 31.1. Anal. Calcd for $C_{29}H_{35}ClFeN_4$: C 65.61, H 6.64, N 10.55, found: C 65.30, H 6.54, H 10.50.

4.2. Biological testing assay

4.2.1. In vitro P. falciparum culture and drug assays

P. falciparum strains were maintained continuously in culture on human erythrocytes [41]. *In vitro* antiplasmodial activity was determined by following [3H]hypoxanthine incorporation by the parasite [42]. *P. falciparum* CQ-sensitive (F32/Tanzania) and CQ-resistant (FcB1/Colombia and K1/Thailand) strains were used in sensitivity testing. Stock solutions of chloroquine diphosphate, artemisinine and test compounds were prepared in sterile distilled water and DMSO, respectively. Drug solutions were serially diluted with culture medium and introduced to asynchronous parasite cultures (1% parasitemia and 1% final hematocrit) in 96-well plates for 24 h at 37 °C prior to the addition of [3H]hypoxanthine (0.5 μCi per well, 1–5 Ci $mmol^{-1}$) 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. Inhibition concentration, IC_{50} (the drug concentration that reduced the number of *P. falciparum* parasites by 50%) and IC_{90} were obtained from the drug concentration–response curve and the results are expressed as the mean determined from several experiments. IC_{90} values were reported in Table 1 in Supporting information.

4.3. In vitro cytotoxicities against MCR-5 cells

Synthesized compounds were tested against MRC-5 human diploid embryonic lung cells, using tetrazolium salt MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; Sigma_) colorimetric method based on reagent cleavage by mitochondrial dehydrogenase in viable cells [43]. Five thousand cells per well were seeded into 96-well microplates containing culture medium (DMEM + 10% SVF + 2 mM L-glutamine + penicillin/streptomycin/neomycin: 0.5/0.5/1 μg /ml) as previously described [44]. The results were expressed as the median lethal dose LD50 (the drug concentration that reduced the number of viable human cells MCR-5 by 50%). LD_{50} were obtained from the drug concentration-response curve and the results are expressed as the mean determined from three experiments. A selectivity index (SI) corresponding to the ratio between the cytotoxic and antiparasitic activities of each compound was calculated as follows: $SI_{Plasmodium} = (LD50_{MRC\text{-}5})/(IC_{50Plasmodium})$.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.11.065.

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