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Synthesis and antiplasmodial activity *in vitro* of new ferrocene–chloroquine analogues †

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The synthesis of the new compounds (7-chloroquinolin-4-yl)-*N*′-(1′-dimethylaminomethylferrocen-1-ylmethyl)-amine (**4a**) and *N*-(7-chloroquinolin-4-yl)-*N*′-(1′-dimethylaminomethylferrocen-1-ylmethyl)-ethane-1,2-diamine (**6a**) is reported. The key step in the synthesis is the cleavage of a ferrocene–Sn bond with *n*-BuLi to give a lithiumferrocenide species (**10**), which is then treated with an electrophile. Thus, 1′-dimethylaminomethyl-1-tri-*n*-butylstannyl-ferrocene (**11**) and subsequently 1′-dimethylaminomethylferrocene-1-carbaldehyde (**7a**) were synthesised from 1,1′-bis(tri-*n*-butylstannyl)ferrocene, employing [CH_2=NMe_2]I and DMF to introduce the amine and then the aldehyde functionalities. In addition, the compound 1′-dimethylaminomethyl-1-lithiumferrocenide was isolated and the ^{1}H and ^{13}C NMR data are reported. X-Ray crystal and molecular structures are reported for compound **4a** and the related compound *N*-(7-chloroquinolin-4-yl)-*N*′-(2-dimethylaminomethylferrocen-1-ylmethyl)-ethane-1,2-diamine (**5a**). The antiplasmodial activity *in vitro* against chloroquine sensitive and resistant strains of *Plasmodium falciparum* is reported and compared to a series of ferrocene, ruthenocene and phenylene analogues.

Introduction

Chloroquine (**1**, see Fig. 1) has been an effective antimalarial agent since the late 1940s. Unfortunately, in most affected areas, the causative agent *Plasmodium falciparum* has developed resistance to chloroquine and other quinoline antimalarials.[1] Since malaria affects between 300 and 500 million people each year and is responsible for 1.5 to 2.7 million fatalities, the emergence of quinoline drug resistance is a major problem.[2] To overcome this problem numerous aminoquinolines[3] and aminoquinoline metal complexes[4] have been screened against *P. falciparum*; of these ferroquine (**2a**)[5] shows the greatest promise and clinical trials are currently in progress.

To establish the role of the iron/ferrocene in ferroquine we have performed preliminary structure–activity relationship studies.[6] As part of this work we have prepared a series of 7-chloro-4-aminoquinolines with amino alkyl side chains containing the ferrocene,[7] ruthenocene[8] and phenylene[6] moieties. The synthesis of the ruthenocene analogues resulted in the unexpected synthesis of 4-aminoquinolines with 1,1′-disubstituted ruthenocenes in the side chain *e.g.* **4b** (isoruthenoquine) and **6b**.[8] To extend structure–activity relationships, we have now synthesised the corresponding ferrocene complexes **4a** (isoferroquine) and **6a**. We have also had to develop a new synthetic route since ferrocene and ruthenocene differ significantly in reactivity.

Results and discussion

The key intermediate for the synthesis of isoruthenoquine (**4b**), and **6b** is the complex **7b** (see Scheme 1).[8] Unfortunately, the corresponding iron complex **7a** is not readily accessible. When the methodology employed to synthesise **7b** was applied to the ferrocene system the 1,2-isomer was formed exclusively and not the desired 1,1′-isomer. Although **7a** is described in the literature, poor selectivity and low yields were reported.[9]

We have now achieved a higher yielding synthesis of **7a** by employing 1,1′-bis(tri-*n*-butylstannyl)ferrocene (**9**). The key to this route is the selective and sequential removal of the tri-*n*-butylstannyl groups with *n*-BuLi in THF at −78 °C.[10] Firstly, 1′-tri-*n*-butylstannyl-1-lithiumferrocenide (**10**) is generated and reacted with Eschenmoser's salt, ([CH_2=NMe_2]I), to introduce

† Electronic supplementary information (ESI) available: NMR scale synthesis of **7a** and ^{1}H NMR spectrum of **12**. See http://www.rsc.org/suppdata/dt/b3/b303335j/

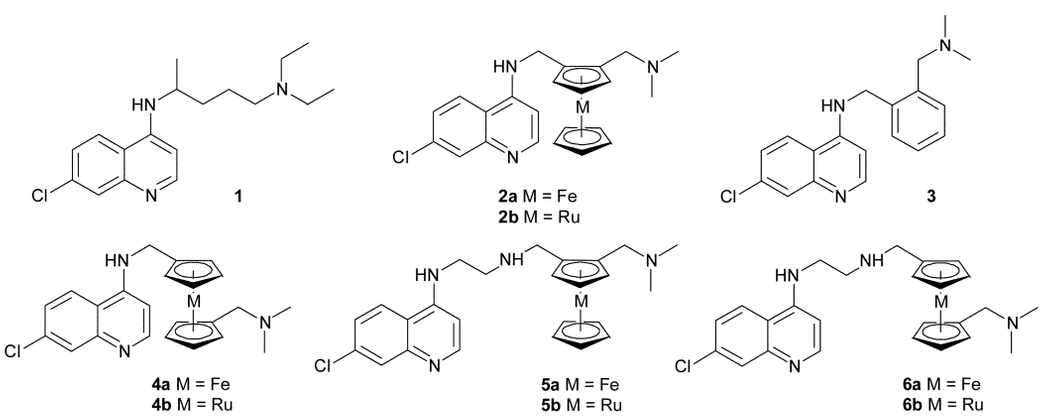

Fig. 1 Chloroquine (**1**) and analogues of current interest (**2a**–**6b**).

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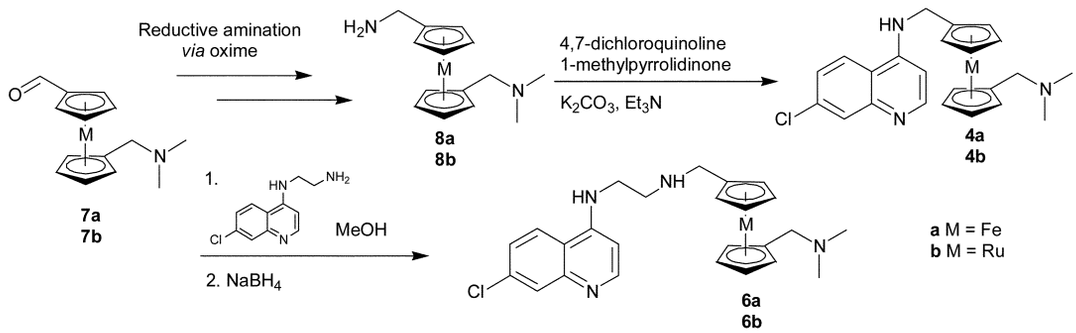
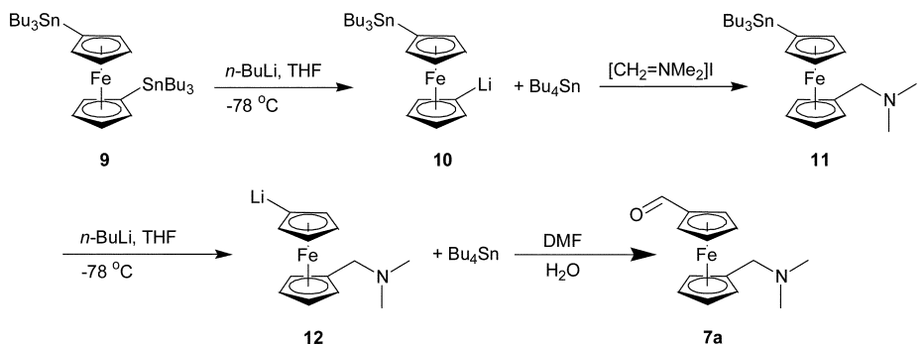


Scheme 1



Scheme 2

the dimethylaminomethyl moiety. The resulting complex 1′-dimethylaminomethyl-1-tri-*n*-butylstannylferrocene (**11**) is then reacted with *n*-BuLi in THF at −78 °C to generate 1′-dimethylaminomethyl-1-lithiumferrocenide (**12**) which is reacted with DMF to yield the desired product **7a** in high yield (see Scheme 2). ‡

The aldehyde **7a** was then converted to the oxime and reduced to the primary amine **8a** with $LiAlH_4$ (Scheme 1). Condensation of **8a** with 4,7-dichloroquinoline yielded **4a** as a yellow crystalline solid in 74% yield. Complex **6a** was prepared as an orange oil in 66% yield by reductive amination of **7a** with N^1-(7-chloroquinolin-4-yl)-ethane-1,2-diamine (see Scheme 1).

Since we were able to prepare **7a** in high yield from **11** without forming any of the 1,2-isomer, and we have previously isolated lithiated carbosilane dendrimers[11] using this methodology, we thought it would be interesting to isolate **12**. Compound **12** was generated in THF at −78 °C as before, the solvent was removed *in vacuo* and the Bu_4Sn was washed out with pentane to yield **12** as an orange–red solid. This solid was stable at room temperature (24 h) but was air- and moisture-sensitive; reaction of this solid with DMF yielded **7a** quantitatively. The ^{1}H NMR spectrum of **12**, thus isolated, did not contain THF which is known to coordinate strongly to RLi compounds.[12] NMR spectra of pure **12** were run at 60 °C to ensure dissolution in C_6D_6, possibly causing the Me_2N-group to dissociate from the lithium. When the synthesis of **7a** from **11** was performed on an NMR scale (see ESI†), coordination of THF was observed. The NMR scale synthesis of **7a** also revealed that all reactions were selective, fast and quantitative.

Assessment of antimalarial activity *in vitro*

The data for the *in vitro* activity against both chloroquine sensitive and resistant strains of *P. falciparum* is shown in Table 1. Data for chloroquine, and a number of ferrocene, ruthenocene and phenylene compounds have also been included for comparison. It is difficult to delineate meaningful structure–activity relationships from the small statistical group presented in Table 1 however it is evident that: (i) despite the diverse range of side-chains employed, all the compounds show moderate to strong antiplasmodial activity against the chloroquine sensitive (D10) strain of the parasite. (ii) The 1,1′-disubstituted compounds **4a**, **4b**, **6a** and **6b** exhibited lower antiplasmodial activity against the chloroquine resistant (K1) than against the chloroquine sensitive (D10) strain of the parasite. Nevertheless, it is noteworthy that these compounds were still more active than chloroquine in the K1 strain. (iii) Compared to the 1,1′-disubstituted compounds (**4a** and **4b**), the 1,2-disubstituted metallocenes (**2a** and **2b**) exhibited high activity in the chloroquine resistant (K1) strain of the parasite. (iv) These results confirm the previously reported equipotency of ruthenocene and ferrocene analogues.[8]

Table 1 Results of *in vitro* antimalarial tests conducted on the chloroquine sensitive (D10) and resistant (K1) strains of *P. falciparum*

	D10		K1	
Compound	IC_{50}/ng mL^{-1}	IC_{50}/nM	IC_{50}/ngm L^{-1}	IC_{50}/nM
1·$2H_3PO_4$	12	23	182	352
2a	8	18	18	14
2b	9	19	6	13
3	4	13	2	7
4a	8	19	21	49
4b	12	25	14	29
5a	16	33	18	37
5b	10	20	10	20
6a	7	16	31	65
6b	18	34	66	127

In view of the data obtained for the phenylequine **3** this work suggests that the primary role of the metallocene is to act as a hydrophobic spacer. The increased lipophilicity may aid passage through membranes or may lead to a greater affinity for β-haematin. Whether a secondary toxicity is associated with the ferrocene is not clear. The stereochemistry around the metallocene appears to influence the capacity of these compounds to

‡ Despite the strong *ortho*-directing effect of the Me_2NCH_2-moiety the 1,1′-disubstituted ferrocene **11** was the only product observed when the crude mixture was analysed using ^{1}H NMR spectroscopy.

Table 2 Hydrogen bonding interactions for complexes **4a**·H_2O, **4b**·H_2O and **5a**

Compound	Donor(D)–H ··· Acceptor(A)	Bond distances/Å			Bond angles/°
		D–H	H ··· A	D ··· A	D–H ··· A
4a	N2–H2 ··· O1W	0.97(2)	2.01(1)	2.957(3)	164(3)
	O1W–H1W ··· N3[a]	0.99(2)	1.89(1)	2.835(3)	159(4)
	O1W–H2W ··· N1[b]	0.99(2)	1.98(1)	2.967(3)	174(3)
4b	N2–H2 ··· O1W[a]	0.97(1)	2.02(2)	2.962(2)	164(2)
	O1W–H1W ··· N3	0.99(1)	1.87(2)	2.853(3)	171(3)
	O1W–H2W ··· N1[c]	0.99(1)	2.01(2)	2.983(2)	167(2)
5a	N2–H2 ··· N1[d]	0.97(1)	2.11(1)	3.050(2)	163(2)
	N1–H1 ··· N4	0.97(1)	2.29(1)	3.171(2)	151(1)

Symmetry code: a $x + 1/2, -y + 3/2, z + 1/2$. b $x, y + 1, z$. c $x - 1/2, -y + 5/2, z - 1/2$. d $-x + 1, -y + 1, -z + 1$.

circumvent the parasite's resistance mechanism. The results in the D10 strain suggest the stereochemistry has a less significant effect on the antiplasmodial activity.

X-Ray crystallography

Molecular structure of (7-chloroquinolin-4-yl)-*N*′-(1′-dimethylferrocen-1-ylmethyl)-amine hydrate 4a·H_2O. The molecular structure of **4a**, excluding the water molecule, is shown in Fig. 2. It is isostructural to that of the monohydrated ruthenocene analogue, **4b**·H_2O, which has been previously reported.[8] The conformation of the ferrocene is almost eclipsed with torsional angles varying from 9.5(4)° to 11.8(3)°. The Fe–Cp centroid distances are 1.653(2) and 1.654(2) Å. The asymmetric unit of this compound contains a water molecule which behaves as a hydrogen bond donor for the tertiary amine and the quinoline N atom, and also accepts a hydrogen bond from the secondary amine. This hydrogen bonding pattern closely resembles that observed for **4b**·H_2O. The hydrogen bonding geometries for both **4a**·H_2O and **4b**·H_2O are given in Table 2 for comparison.

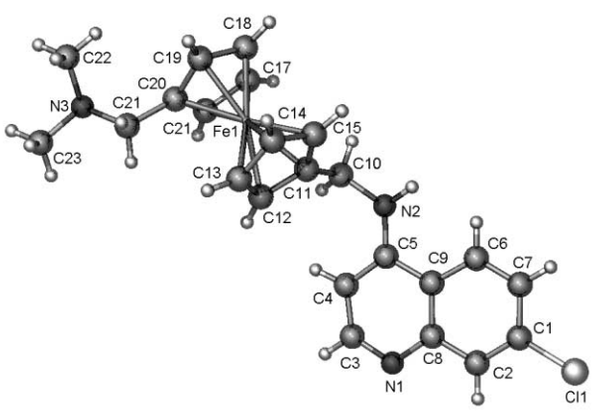


Fig. 2 Molecular structure and numbering scheme for complex **4a**·H_2O, the water molecule is omitted.

Molecular structure of racemic *N*-(7-chloroquinolin-4-yl)-*N*′-(2-dimethylaminomethylferrocene-1-ylmethyl)-ethane-1,2-diamine 5a. The molecular structure of complex **5a** is shown in Fig. 3. The ferrocene adopts an eclipsed conformation with torsion angles in the range 8.1(3)–9.0(4)°. The Fe–Cp centroid distances are 1.643(2) Å and 1.652(2) Å with the shorter distance to the substituted Cp ring. The dashed line in Fig. 3 shows an intramolecular hydrogen bond with a N ··· N distance of 3.171(2) Å between the tertiary and secondary amines of the ferrocene. The opposing enantiomers associate as dimers within the crystal lattice since intermolecular hydrogen bonds form between the secondary amines (Fig. 4). The details of H-bonding interactions are in Table 2.

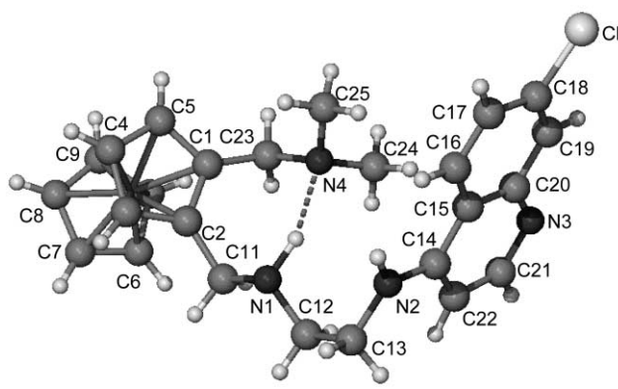


Fig. 3 Molecular structure and numbering scheme for complex **5a**.

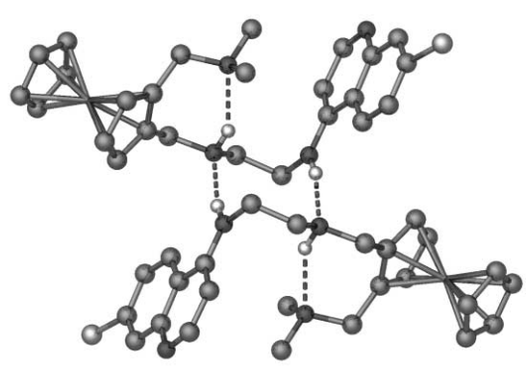


Fig. 4 Hydrogen bond dimers of **5a**.

Conclusions

The new complexes **4a** and **6a** have been synthesised and the crystal structures of **4a**·H_2O and **5a** have been determined. Most of the compounds including **4a** exhibited moderate to strong antiplasmodial activity when tested against both chloroquine sensitive (D10) and chloroquine resistant (K1) strains of *P. falciparum*. Employing a 1,1′-disubstituted metallocene in the side chain instead of a 1,2-disubstituted metallocene does not lead to a more effective anti-plasmodial agent. However, administering a combination of compounds in this class may prevent the emergence of drug resistance. These results are consistent with previous structure–activity relations performed on aminoquinolines where a hydrophobic group *e.g.* an alkyl spacer and an amino group for pH trapping are essential for high anti-plasmodial activity.[3]

Experimental

The syntheses were performed using standard Schlenk techniques; *N*[1]-(7-chloroquinolin-4-yl)-ethane-1,2-diamine[13] and 1,1′-bis(tri-*n*-butylstannyl)ferrocene[14] were prepared according

to literature methods. Tetrahydrofuran was distilled from Na/benzophenone; pentane was distilled from Na/benzophenone/tetraglyme; methanol was distilled from magnesium activated by iodine, 1-methylpyrrolidinone was purified by an azeotropic distillation from toluene and DMF was distilled from $CaSO_4$ (76 °C/39 mmHg). The concentration of alkyllithium reagents was determined by the Gilman double titration method prior to use.[15] TMEDA was distilled from sodium. C_6D_6 was distilled from Na/K. All other chemicals were used as supplied by Aldrich. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on Varian EM 400 or 300 MHz spectrometers. ^{1}H NMR spectra were referenced internally using the residual protons in the deuterated solvent ($CDCl_3$: δ 7.27, C_6D_6: δ 7.16) and are reported relative to tetramethylsilane (δ 0.00). ^{13}C NMR spectra were referenced internally to the solvent resonance ($CDCl_3$: δ 77.0, C_6D_6: δ 128.0) and are reported relative to tetramethylsilane (δ 0.0). Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Melting points were performed on a Kofler hot-stage microscope (Reichert-Thermovar). Mass spectra were determined by Dr P. Boshof at the Cape Technikon. The *m*/*z* values quoted refer to the most abundant isotopes, in all cases the isotopic distribution corresponded to theoretical distribution. Elemental analyses were performed using a Carlo Erba EA1108 elemental analyser in the microanalytical laboratory of the University of Cape Town.

Syntheses

1′-(*N,N*-Dimethylaminomethyl)-1-tri-*n*-butylstannyl-ferrocene 11. *n*-BuLi (12.8 cm^3, 18 mmol of a 1.4 M solution in hexanes) was added to a solution of 1,1′-bis(tri-*n*-butylstannyl)ferrocene (13.1 g, 17 mmol) in THF (160 cm^3) at −78 °C and stirred for 0.5 h. Eschenmoser's salt (3.35 g, 18 mmol) was added *via* a Merlic addition funnel. The reaction mixture was allowed to warm to 25 °C and stirred for a further 16 h. The solvent was removed *in vacuo* and the red oil was dissolved in diethyl ether (150 cm^3) and washed with water (50 cm^3), the aqueous phase was removed and washed with diethyl ether (2 × 50 cm^3), the organic fractions were combined, dried over Na_2SO_4, filtered and the solvent removed *in vacuo.* Purification by column chromatography on alumina (Brockman V) eluting with hexane to remove unreacted 1,1′-bis(tri-*n*-butylstannyl)ferrocene first, followed by hexane–diethyl ether–triethylamine 70 : 29 : 1 to elute the title product as an orange oil (6.45 g, 67%) (Found: C, 56.77; H, 8.27; N, 2.65. $FeSnC_{25}H_{43}N$ calculated C, 56.42; H, 8.14; N, 2.63%); $\tilde{\nu}_{max}$/cm^{-1} 3093w (br), 2950s, 2923s, 2860m, 2808m, 2705m (br), 1461m, 1382w, 1345w, 1265w, 1176w, 1138w, 1037w, 1026w, 824w (NaCl neat); δ_H (400 MHz; solvent C_6D_6) 4.15 (2 H, m), 4.12 (2 H, m), 4.01 (2 H, m), 3.95 (2 H, m), 3.25 (2 H, s), 2.09 (6 H, s, NMe_2), 1.58–1.68 (6 H, m), 1.30–1.45 (6 H, m), 1.01–1.10 (6 H, m), 0.91 (9 H, t, ^3J(HH) 8 Hz); δ_C (100 MHz; solvent $CDCl_3$) 84.1 (Cp^{IV}), 75.1 (^2J(CC$^{117/119}$Sn) 42 Hz Cp–H), 71.5 (^3J(CCC$^{117/119}$Sn) 35 Hz), 70.3 (Cp–H), 68.7 (Cp^{IV}), 68.1 (Cp–H), 59.6 (CH_2–N), 44.8 (–NMe_2), 29.5 (^3J(CCC$^{117/119}$Sn) 19 Hz), 27.6 (^2J(CC$^{117/119}$ 56 Hz), 13.7 (Me), 10.5 (^1J(C$^{117/119}$Sn) 346/329 Hz); *m*/*z* (FAB) found 533.1767 (100%), $Fe^{120}SnC_{25}H_{43}N$ requires 533.1767, 489 (M − NMe_2, 85), 476 (M − CH_2NMe_2, 86), 431 (M − NMe_2 − Bu, 61), 362 (M − 3Bu) 319 (M − NMe_2 − 3Bu), 242 (M − $SnBu_3$, 49), 235 (54), 199 (87), 179 (79).

1′-Dimethylaminomethylferrocene-1-carbaldehyde 7a. *n*-BuLi (4.4 cm^3, 6.2 mmol, of a 1.4 M solution in hexanes) was added to a mixture of 1′-dimethylaminomethyl-1-tri-*n*-butylstannylferrocene (3.0 g, 1.5 mmol) in THF (15 cm^3) at −78 °C and stirred for 0.5 h. To this mixture *N,N*-dimethylformamide (5 cm^3) was added and stirred for a further 3 h allowing the mixture to warm to 25 °C. The solvent was removed *in vacuo* and the red oil was dissolved in diethyl ether (100 cm^3) and washed with water (30 cm^3), the aqueous phase was removed and washed with diethyl ether (2 × 50 cm^3), the organic fractions were combined, dried over Na_2SO_4, filtered and the solvent removed *in vacuo.* Column chromatography on silica eluting with diethyl ether–hexane–triethylamine 70 : 20 : 10 yielded the title product as an orange oil (1.4 g, 92%), $\tilde{\nu}_{max}$/cm^{-1} 3092w, 2933w (br), 2862w, 2827w, 2770w, 1679s (CO), 1455m (NMe_2), 1245m, 1040w, 1028w, 846m, 743w (neat NaCl); δ_H (solvent $CDCl_3$; 300 MHz) 9.88 (1 H, s), 4.62 (2 H, m), 4.49 (2 H, m), 4.21 (2 H, m), 4.16 (2 H, m), 3.12 (2 H, s), 2.09 (6 H, s); δ_C (solvent $CDCl_3$, 75 MHz) 193.1 (CHO), 85.5, 79.6 (Cp^{IV}), 73.6, 71.4, 69.9, 69.5 (Cp–H), 58.2 (–CH_2), 44.6 (–NMe_2); *m*/*z* (FAB) found 271.0660, $C_{14}H_{17}NOFe$ requires 271.0660, 256 (M − Me, 22%), 242 (M − 30), 227 (M − NMe_2, 100), 199 (M − NMe_2 − CHO, 49), 154 (19), 136 (23).

1′-Dimethylaminomethylferrocene-1-carbaldehyde oxime. A solution of sodium hydroxide (0.72 g, 18 mmol) in water (4.5 cm^3) was added to a stirred mixture of freshly prepared 1′-dimethylaminomethylferrocene-1-carbaldehyde **7a** (1.20 g, 4.4 mmol) and hydroxylamine hydrochloride (625 mg, 9 mmol) in ethanol (35 cm^3) at room temperature. The resulting mixture was heated under reflux for 4 h and allowed to cool. Water (3 cm^3) was added and the mixture was neutralised by the addition of CO_2(s). The product was extracted with dichloromethane (3 × 20 cm^3), dried with Na_2SO_4, filtered and the solvent removed *in vacuo* to yield an orange semi-solid (1.23 g, 98%), $\tilde{\nu}_{max}$/cm^{-1} 3774w (br), 3185w (br), 3088w, 2976w, 2964m, 2939m, 2864m, 2820m, 2685w, 1598s, 1448s, 1374m, 1344m, 1344m, 1292m, 1158s, 1039s, 956w, 830w, 733m, 695m (NaCl neat); δ_H (solvent $CDCl_3$; 300 MHz) 7.89 (1 H, s), 4.49 (2 H, m), 4.26 (4 H, m), 4.16 (2 H, m), 3.36 (2 H, s), 2.20 (6 H, s); δ_C (solvent $CDCl_3$, 75 MHz) 148.0 (C=NOH), 83.0, 77.6 (Cp^{IV}), 71.4, 70.2, 69.4, 67.8 (Cp–H), 58.3 (–CH_2), 44.0 (–NMe_2); *m*/*z* (FAB) found 286.0777, $C_{14}H_{18}ON_2Fe$ requires 286.0786, 269 (M − OH, 21%), 242 (M − NMe_2, 100), 225 (M − NMe_2 − OH, 31), 194 (11), 176 (6).

1′-Aminomethyl-1-dimethylaminomethylferrocene 8. A mixture of $LiAlH_4$ (0.6 g, 16 mmol) and 1-dimethylaminomethylferrocene-1′-carboxaldehyde oxime (1.2 g, 4 mmol) in THF (100 cm^3) was heated under reflux for 6 h. The cooled solution was diluted with diethyl ether (25 cm^3), quenched with water, washed with brine (2 × 10 cm^3), dried over anhydrous K_2CO_3, filtered and the solvent removed *in vacuo* to yield a brown oil (1.05 g, 97%), $\tilde{\nu}_{max}$/cm^{-1} 3371m (br), 3289m (br), 2931s, 2857s, 2820s, 2767s, 1637w, 1597w, 1456w, 1381w, 1351w, 1262w, 1240w, 1173w, 1038s, 912m, 830s, 733s (NaCl neat); δ_H (solvent $CDCl_3$; 400 MHz) 4.09 (2 H, m), 4.05 (4 H, m), 4.02 (2 H, m) 3.51 (2 H, s), 3.23 (2 H, s), 2.13 (6 H, s); δ_C (solvent $CDCl_3$, 100 MHz) 91.0, 83.5 (Cp^{IV}), 70.3, 68.3, 68.2, 67.6 (Cp–H), 59.0 (CH_2NMe_2), 44.7 (–NMe_2), 41.1 (–CH_2NH_2); *m*/*z* (FAB) found 272.0970, $C_{14}H_{20}N_2Fe$ requires 272.0976, 256 (M − NH_2, 43%), 242 (M − 2Me, 17), 228 (M − NMe_2, 100), 213 (M − NMe_2, NH_2), 199 (M − CH_2NMe_2, NH_2, 17), 178 (11) 135 (15).

Isoferroquine 4a. A mixture of **8a** (0.60 g, 2.2 mmol), 4,7-dichloroquinoline (2.38 g, 12 mmol), Na_2CO_3 (50 mg), triethylamine (3 cm^3) and 1-methylpyrrolidinone (8 cm^3) was heated to 130 °C and stirred for 6 h. The product was extracted with ethyl acetate (75 cm^3) and washed with brine (10 × 40 cm^3), the organic layer was then dried over anhydrous Na_2SO_4, filtered and the solvent was removed *in vacuo*. The product was purified by silica gel chromatography eluting with ethyl acetate–hexane–triethylamine 80 : 15 : 5. Recrystallisation from ethyl acetate and hexane gave yellow microcrystals (703 mg, 74%), mp 118 °C (Found: C, 63.94; H, 5.50; N, 9.46. $FeC_{23}H_{24}N_3Cl$ requires C, 63.69; H, 5.58; N, 9.69%); $\tilde{\nu}_{max}$/cm^{-1} 3685m (br) (intermolecular H-bond), 3609 (br) (intermolecular H-bond), 3437w (br),

Table 3 Crystal data and structural refinement for **4a** and **5a**

	4a	**5a**
Empirical formula	$FeC_{23}H_{24}ClN_3 \cdot H_2O$	$FeC_{25}H_{29}N_4Cl$
Formula weight	451.77	476.82
Temperature/K	193(2)	173(2)
Wavelength/Å	0.71073	0.71073
Space group	*C*2/*c*	$P2_1/c$
Crystal system	Monoclinic	Monoclinic
a/Å	26.3704(2)	10.7012(3)
b/Å	9.2289(3)	16.2573(4)
c/Å	21.7319(4)	13.7853(3)
β/°	127.221(1)	92.727(1)
Volume/Å^3	4211.6(2)	2395.6(1)
Z	8	4
Absorption coefficient/mm^{-1}	0.862	0.760
Reflections collected	32757	10265
Independent reflections	4830 [*R*(int) = 0.0670]	5459 [*R*(int) = 0.0240]
Final *R* indices [$I>2\sigma(I)$]	*R*1 = 0.0440, *wR*2 = 0.1069	*R1* = 0.0338, *wR*2 = 0.0750
R indices (all data)	*R*1 = 0.0763, *wR*2 = 0.1372	*R*1 = 0.0546, *wR*2 = 0.0825

3063s, 3049s, 2856w, 2821w, 2775w, 1611 (C=N quinoline), 1583m, 1521w, 1470w (br), 1421w, 1374w, 1334m, 1286s, 1274s, 1264s, 1132w, 1097s, 1024s (CH_2Cl_2); δ_H (solvent $CDCl_3$; 400 MHz) 8.57 (1 H, d ^3J(HH) 6 Hz), 7.98 (1 H, d ^3J(HH) 2 Hz), 7.68 (1 H, ^3J(HH) 9 Hz), 7.37 (1 H, dd, ^3J(HH) 9 Hz, ^4J(HH) 2 Hz), 6.49 (1 H, d, ^3J(HH) 5 Hz), 5.32 (1 H, br NH), 4.24 (2 H, m), 4.18 (6 H, m), 4.14 (2 H, d (HH) 5 Hz), 3.30 (2 H, s), 2.19 (6 H, s); δ_C (solvent $CDCl_3$; 75 MHz) 151.8 (CH), 149.2, 148.9, 134.7 (C^{IV}), 128.5, 125.1, 121.0 (CH) 117.0 (C^{IV}), 99.0 (CH), 84.4, 83.9 (Cp^{IV}), 70.4, 68.9, 68.7, 68.5 (Cp–H), 58.7 (CH_2), 44.7 (NMe_2), 41.2 (CH_2); *m*/*z* (FAB) found 434.1099, $C_{23}H_{25}N_3FeCl$ requires 434.1086, 386 (M − NMe_2, 100), 311 (M − $CpCH_2NMe_2$, 43), 256 (M − $CpFeCH_2NMe_2$, 25).

***N*-(7-Chloroquinolin-4-yl)-*N*′-(1′-dimethylaminomethylferrocene-1-ylmethyl)-ethane-1,2-diamine 6a.** Compound **7a** (271 mg, 1 mmol) and *N*^{1}-(7-chloroquinolin-4-yl)-ethane-1,2-diamine (222 mg, 1 mmol) were dissolved in methanol (10 cm^3) and stirred for 16 h. Sodium borohydride (0.100 mg, 2.6 mmol) was added and the mixture was stirred for a further 1 h. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate (40 cm^3) and washed with brine (3 × 10 cm^3), the organic layer was dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The product was purified by silica gel chromatography slowly increasing the polarity from EtOAc–MeOH–triethylamine; 94 : 4 : 2 to 75 : 15 : 10 to yield an orange oil (315 mg, 66%) (Found: C, 63.08; H, 6.72; N, 11.42. $FeC_{23}H_{24}N_3Cl$ requires C, 62.84; H, 6.33; N, 11.73%); $\tilde{\nu}_{max}$/cm^{-1} 3693 (intermolecular H-bond), 3597 (br) (intermolecular H-bond), 3055s, 3045s, 2932m (br), 2856w (br), 2770w, 1609 (C=N quinoline), 1583s, 1528m (br), 1472w, 1369w, 1333w, 1272s, 1261m, 1254s, 1136w, 1078w, 1040w, 905m, 890, 868s, 821s, 811, (CH_2Cl_2); δ_H (400 MHz; solvent $CDCl_3$) 8.37 (1 H, d, ^3J(HH) 5 Hz), 7.83 (1 H, d, ^4J(HH) 2 Hz), 7.70 (1 H, d, ^3J(HH) 9 Hz), 7.20 (1 H, dd, ^3J(HH) 9 Hz, ^4J(HH) 2 Hz), 6.23 (1 H, d, ^3J(HH) 5 Hz), 6.15 (1 H, br s, NH), 4.04 (4 H, m), 3.99–4.01 (4 H, m), 3.49 (2 H, s), 3.25 (2 H, m), 3.20 (2 H, s), 2.92 (2 H, m), 2.08 (6 H, s); δ_C (100 MHz; solvent $CDCl_3$) 151.6 (CH), 150.0, 148.7, 134.7 (C^{IV}), 128.0 (CH), 124.9 (C–H), 121.8 (CH), 117.3 (C^{IV}), 98.9 (CH), 85.9, 83.1 (Cp^{IV}), 70.5, 70.0, 68.6, 68.6 (Cp–H), 58.7, 48.1, 46.7 (CH_2), 44.4 (NMe_2), 42.0 (CH_2); *m*/*z* (FAB) found 477.15084 (M + H − $FeC_{25}H_{31}N_4Cl$ requires 477.151506), 432 (M − NMe_2, 41%), 354 (M − Cp − CH_2NMe_2 38), 276 (16), 256 (52), 240 (26), 213 (100), 191 (14), 178 (13), 162 (12), 135 (34).

Isolation of 12. A solution of *n*-BuLi (0.65 cm^3, of a 1.54 M solution in hexanes, 1.0 mmol) was added to a solution of 1′-dimethylaminomethyl-1-tri-*n*-butylstannylferrocene (0.53 g, 1.0 mmol) in THF (5.0 cm^3) at −78 °C in the primary chamber of an H-type Schlenk-tube.[16] The mixture was stirred for 30 min at −78 °C, during which time a precipitate formed. Several drops of *n*-BuLi in hexane were added to the secondary chamber of the H-type Schlenk-tube. The volatiles were removed *in vacuo* to leave an orange–red solid and an oil. Pentane (2.0 cm^3) was added to the *n*-BuLi in the secondary chamber and distilled onto the reaction mixture (through this extra drying procedure pure solvents were guaranteed). Residual THF was removed by distilling pentane (3 × 2 cm^3) onto the mixture and then removing the pentane *in vacuo*. The mixture in the primary chamber was then washed with pentane (3 × 10 cm^3) by distilling the solvent onto the lithiated ferrocene and filtering to the secondary chamber. The volatiles were removed *in vacuo* to leave **12** as a red solid in the primary chamber and a red oil ($SnBu_4$ + BuLi + unreacted traces of starting material) in the secondary chamber. δ_H (300 MHz; solvent C_6D_6, 60 °C) 4.60 (2 H, m), 4.11–4.20 (4 H, m), 3.87 (2 H, m), 2.76 (2 H, s), 2.06 (6 H, s); δ_C (75 MHz; solvent C_6D_6) 83.6, 80.6 (Cp^{IV}), 72.1 (2Cp–H), 67.3 (4Cp–H), 67.1 (2Cp–H), 58.6 (CH_2N), 47.0 (NMe_2).

Cultivation of malaria parasites

Two strains of *P. falciparum* were used in this study, a chloroquine sensitive strain D10 and a chloroquine resistant strain K1. The *P. falciparum* strains were cultured using a modified version of the Trager and Jensen method.[17] The parasites are maintained in RPMI 1640 (BioWhittaker) culture medium, to which is added 40 mg cm^{-3} gentamycin (Lennon), 1% sodium bicarbonate, 0.5% Albumax (lipid rich bovine serum albumin) and O^+ human red blood cells (Transfusion Services and Haematology Department, UCT/Groote Schuur Hospital). The cultures are contained in flat bottom flasks and incubated at 37 °C with a controlled gas environment of 4% CO_2, 3% O_2 and 93% N_2. The medium is changed at frequent intervals and parasite cultures are fed to maintain an optimum 3–5% parasitaemia and a 2–4% haematocrit. The parasitaemia is determined using Giemsa stained blood films of the cultures. Synchronisation of cultures is achieved by a brief exposure to a 5% D-sorbitol solution.

X-Ray crystallography

Crystals of complex **4a**·H_2O were obtained by slow diffusion of hexane into a wet ethylacetate solution of **4a**. Crystals of **5a** were obtained by slow diffusion of diethyl ether into an acetonitrile solution of **5a**. X-Ray diffraction data for compounds **4a** and **5a** were collected on a Nonius Kappa CCD with 1.5 kW graphite monochromated Mo radiation. The strategy for the data collection was evaluated using COLLECT.[18] The data were integrated, scaled and reduced with DENZO-SMN.[19] The structures were solved and refined with SHELX97.[20] The H

atoms belonging to amino groups were located in the Fourier maps and refined with the N–H distances constrained. Although we could locate all other H atoms, they were placed in idealised positions and refined as riding atoms. Molecular graphics were obtained with POV-Ray using an X-Seed interface.[21] A selection of crystal and refinement data is given in Table 3.

CCDC reference numbers 206811 and 206812.

See http://www.rsc.org/suppdata/dt/b3/b303335j/ for crystallographic data in CIF or other electronic format.

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