Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Organometallic Chemistry 688 (2003) 144–152
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Synthesis and antimalarial activity in vitro of new heterobimetallic complexes: Rh and Au derivatives of chloroquine and a series of ferrocenyl-4-amino-7-chloroquinolines

Margaret A.L. Blackie [a], Paul Beagley [a], Kelly Chibale [a], Cailean Clarkson [b], John R. Moss [a,*], Peter J. Smith [b]

[a] Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa
[b] Division of Pharmacology, Department of Medicine, University of Cape Town Medical School, Observatory 7925, South Africa

Received 4 March 2003; accepted 30 July 2003

Abstract

The reaction of chloroquine and several ferrocenyl derivatives of chloroquine with $Au(PPh_3)NO_3$, $Au(C_6F_5)(tht)$ and $[Rh(COD)Cl]_2$ have been investigated. The resulting products have been characterised by a range of techniques including NMR, mass spectrometry, elemental analysis, IR and cyclic voltammetry. The data suggests that the products are heterobimetallic complexes where the quinoline nitrogen coordinates to the Au or Rh. In vitro studies against *Plasmodium falciparum* are reported.

Keywords: Antimalarial activity; Heterobimetallic complexes; Chloroquine

1. Introduction

Malaria continues to be a major health problem, especially in the Third World. Malaria is a vector-borne parasitic disease, transmitted to humans by the female *Anopheles* mosquito. Forty years ago, less than 10% of the world's population was at risk of contracting the disease, today over 40% of the world's population is at risk [1] since various species of *Plasmodium*, the causative agent of malaria, have developed resistance to drugs like chloroquine (**1**).

The advent of cisplatin [2] sparked a worldwide interest in metal-containing drugs, and as a result, numerous inorganic/organometallic compounds have been screened for anti-tumour activity. In many cases, the platinum or organometallic moiety has been co-ordinated to or incorporated into vectors like hormones, drugs and metabolites [3]. Accumulation of these complexes in the vicinity of the tumour results in higher selectivity for the cancer cells. Metal complexes have now been investigated to treat numerous diseases including malaria. This approach has been successfully explored with 4-aminoquinolines, an important class of antimalarial agents exemplified by chloroquine. A number or transition metals e.g. Rh, Ru [4] and Au [5] have been coordinated to chloroquine and other aminoquinolines [6]. It has also been shown that ferrocene [7] and a ruthenocene [8] unit can also be incorporated into the aminoalkyl side chain of chloroquine. The coordination of a metal and the incorporation of an organometallic moiety has a positive effect resulting in higher activity against both the chloroquine-sensitive and chloroquine-resistant strains of the parasite.

Metallic chloroquine analogues and derivatives show considerable promise but the role of the metals is not completely understood. The mechanism by which the organometallic and coordination complexes operate is likely to be different and we thought it would be interesting to see if the two approaches were complementary. We wished to investigate the synthesis of complexes of the type $[Au(L)(PPh_3)]NO_3$, $[Au(C_6F_5)(L)]$ and $[Rh(Cl)(COD)(L)]$ where L is either chloroquine (**1**), ferroquine (**2**), *N*-(7-chloro-quinolin-4-yl)-*N*′-[2-

* Corresponding author. Tel.: +27-21-650-2535; fax: +27-21-689-7499.
E-mail address: jrm@science.uct.ac.za (J.R. Moss).

0022-328X/03/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0022-328X(03)00917-3

(*N″*,*N″*-dimethylaminomethyl)ferrocenylmethyl]-ethane-1,2-diamine (**3**), or 3-benzyl-1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N″*,*N″*-dimethylaminomethyl)-ferrocenylmethyl]urea (**4**) (Fig. 1). The presence of the two metal centres in the molecule could have an additive, synergistic or antagonistic effect as far as the antimalarial activity is concerned and we wished to explore this.

2. Experimental

2.1. General experimental

The syntheses were performed using standard Schlenk techniques. When applicable reactions were performed in a centrifuge tube fitted with a nitrogen inlet. MeCN and CH_2Cl_2 were distilled from CaH_2; Et_2O was distilled from Na/benzophenone/tetraglyme. Chloroquine, free base, was obtained from chloroquine diphosphate according to a literature procedure [4]. Ferroquine (**3**) [7a], $[Au(PPh_3)]NO_3$ [9], $[Au(C_6F_5)(tht)]$ [10], $[Rh(Cl)(COD)]_2$ [11] and **13** [4] were prepared according to literature procedures The synthesis of the previously reported complexes **3** and 3-benzyl-1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N″*,*N″*-dimethylamino-methyl)-ferrocenylmethyl]urea **4** are described in the supplementary information.

Melting points were recorded on a Kofler hotstage microscope (Reichart Thermovar). Microanalyses were performed using a Carlo Erba EA1108 elemental analyser in the microanalytical laboratory at the University of Cape Town. Infrared spectra were recorded as KBr discs on a Perkin–Elmer Paragon 1000 FT-IR spectrometer. NMR spectra were recorded on either a Varian Unity-400 (^{1}H: 400 MHz; ^{13}C: 100.6 MHz; ^{19}F: 376 MHz) spectrometer or a Varian Mercury-300 (^{1}H: 300 MHz; ^{13}C: 75.5 MHz; ^{31}P: 121 MHz) spectrometer

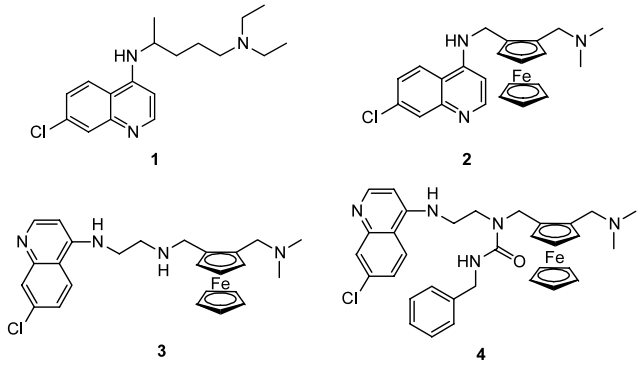

Fig. 1. Ligands for metal complexation (chloroquine (**1**); ferroquine (**2**); *N*-(7-chloro-quinolin-4-yl)-*N′*-[2-(*N″*,*N″*-dimethylamino-methyl)ferrocenylmethyl]-ethane-1,2-diamine (**3**); 3-benzyl-1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N″*,*N″*-dimethylamino-methyl)-ferrocenylmethyl]urea) (**4**).

at ambient temperature. ^{1}H-NMR spectra were referenced internally using the residual protons in the deuterated solvent ($CDCl_3$: δ 7.27; CD_3OD: δ 5.84) and are reported relative to Me_4Si (δ 0.00). ^{13}C-NMR spectra were referenced internally to the solvent resonance ($CDCl_3$: δ 77.0; CD_3OD: δ 49.1) and are reported relative to Me_4Si (δ 0.0). ^{19}F-NMR spectra were referenced externally to $CFCl_3$. ^{31}P-NMR spectra were referenced externally to H_3PO_4. All chemical shifts are quoted in δ (ppm) and coupling constants, J, are given in Hertz (Hz). Mass spectra were determined by Dr Boshoff of the mass spectrometry unit at the Cape Technikon. In all cases the isotopic distribution pattern was checked against the theoretical distribution. Cyclic voltammetry (CV) was carried out on a BAS-100B electrochemical analyser in a one-compartment-three-electrode system, comprising Ag/Ag^+ (0.01 M) as the reference electrode, platinum wire as the auxiliary electrode and a platinum disc as the working electrode. The supporting electrolyte was a solution of 0.1 M tetrabutylammonium perchlorate in anhydrous MeCN. The potentials E were recorded without IR compensation. All potentials reported are relative to the half wave potential ($E_{1/2}$) of the ferrocene/ferrocenium couple run under the same conditions. The experiments were performed in 1.0 mM solutions under an atmosphere of Ar at room temperature (r.t.). The solutions were degassed by bubbling Ar through the solution for 5 min prior to the CV run. The platinum disc electrode was polished after every run. Conductivity measurements were performed on a Metrohm 660 conductometer in 1.0 mM nitrobenzene solutions at 20 °C. 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 [12]. Parasite viability was assessed using the lactate dehydrogenase assay [13].

2.2. Preparation of $[Au(L)(PPh_3)]NO_3$ complexes [14]

Complex **5**. Chloroquine (**1**) (62 mg, 0.19 mmol) and triphenylphosphinegold(I) nitrate (100 mg, 0.19 mmol) were dissolved in CH_2Cl_2 (5 cm^3). Light was excluded and the mixture was allowed to stir for 3 h at 25 °C. The reaction vessel was cooled to −78 °C and ~90% of the solvent was removed in vacuo. The mixture was allowed to warm to r.t. and Et_2O (1 cm^3) was added resulting in a slurry which was cooled to −4 °C and allowed to stand for 1 h. The mixture was then filtered, and the solid washed with Et_2O before drying the solid in vacuo to yield a cream crystalline product (134 mg, 82%); m.p.: 89–90 °C; Found: C, 51.72; H, 5.01; N, 6.50. Calc. for $[C_{35}H_{40}N_3AuClP][NO_3]$: C, 51.47; H, 4.80; N, 6.67%; δ_H (300 MHz; $CDCl_3$) 8.44 (1H, d, $^3J_{HH} = 9$, ArC_5-H), 8.33

(1H, d, $^3J_{HH} = 6$, ArC$_2$-H), 8.06 (1H, d, $^4J_{HH} = 2$, ArC$_8$-H), 7.63–7.49 (15H, m, Ph), 7.38 (1H, dd, $^3J_{HH} = 2$ and $^3J_{HH} = 9$, ArC$_6$-H), 6.48 (1H, d, $^3J_{HH} = 6$, ArC$_3$-H), 3.76 (1H, m, 6′), 2.79–2.56 (6H, m, 2′, 3′), 1.78–1.57 (4H, m, 5′, 4′), 1.35 (3H, d, $^3J_{HH} = 6$, 1′′), 1.09 (6H, t, $^3J_{HH} = 6$, 1′); $\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 152.3 (ArC_2), 151.8 (C^{IV}), 147.5 (C^{IV}), 136.3 (C^{IV}), 134.1 (Ph), 134.0 (Ph), 132.5 (Ph), 129.7 (Ph), 129.5 (Ph), 126.1 (ArC_5), 125.3 (ArC_6), 124.7 (ArC_8), 117.9 (C^{IV}), 99.1 (ArC_3), 52.6 (2′), 49.3 (6′), 47.0 (3′), 33.5 (5′), 23.1 (4′), 19.7 (1′′), 10.6 (1′); $\delta_{P\{H\}}$ (121 MHz, $CDCl_3$) 30.81 (PPh$_3$); ν_{max} 3404br m (ν N–H), 3070m, 2966m, 1579s (7-chloroquinoline, ν C=N), 1534m (7-chloroquinoline), 1478m, 1436m, 1382vs (ν N–O), 1200w (NR), 1152m, 1100m, 1025w, 996w (ν P–C), 807w, 749m, 711m, 693s, 546s, 503s; *m/z* (FAB) 781 (M(^{37}Cl)+H, 16), 780 (M(^{37}Cl), 40), 779 (M+H, 16), 778 (M, 40), 748 (M − Me, 3), 721 (13), 459 (AuPPh$_3$, 21), 320 (CQ, 8), 249 (CQ^{37}Cl − 2CH$_2$CH$_3$, 13), 247 (^{35}Cl-CQ − 2-CH$_2$CH$_3$, 36), 183 (39), 165 (12), 152 (15), 140 (30), 136 (17), 128 (11), 115 (18), 105 (11), 91 (26), 89 (30), 86 (47), 77 (60), 64 (27), 63 (59); Λ ($C_6H_5NO_2$, 20 °C) = 17 Ω^{-1} cm^2 mol^{-1}.

Compound **6** was prepared by an analogous procedure to **5** from ferroquine (**2**) and triphenylphosphinegold(I) nitrate and obtained as an orange crystalline solid (84%); m.p. 110–112 °C; δ_H (400 MHz; $CDCl_3$) 8.68 (1H, d, $^3J_{HH} = 7$, ArC$_2$-H), 8.26 (1H, d, $^4J_{HH} = 2$, ArC$_8$-H), 7.94 (1H, d, $^3J_{HH} = 9$, ArC$_5$-H), 7.60 (15H, m, Ph), 7.39 (1H, d, $^4J_{HH} = 2$ and $^3J_{HH} = 9$, ArC$_6$-H), 6.97 (1H, d, $^3J_{HH} = 7$, ArC$_3$-H), 4.59 (1H, d, $^2J_{HH} = 14$, 3′a), 4.48 (1H, d, $^2J_{HH} = 14$, 3′b), 4.37 (1H, m, Cp), 4.22 (1H, m, Cp), 4.16 (5H, s, Cp′), 4.09 (1H, m, Cp), 3.99 (1H, d, $^2J_{HH} = 12$, 2′a), 3.11 (1H, d, $^2J_{HH} = 12$, 2′b), 2.32 (6H, s, 1′); $\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 154.2 (ArC_2), 152.5 (C^{IV}), 146.8 (C^{IV}), 136.7 (C^{IV}), 134.2 (Ph), 134.1 (Ph), 132.6 (Ph), 128.8 (Ph), 126.7 (Ph), 126.1 (ArC_8), 124.6 (ArC_6), 124.0 (ArC_5), 118.0 (C^{IV}), 100.4 (C^{IV}), 95.5 (ArC_3), 83.0 (C^{IV}, Cp), 71.4 (Cp), 70.8 (Cp), 69.6 (5C, Cp′), 66.7 (Cp), 57.8 (2′), 44.7 (2C, 1′), 42.5 (3′); $\delta_{P\{H\}}$ (121 MHz, $CDCl_3$) 30.60 (PPh$_3$); ν_{max} 3430br s (ν N–H), 3079s, 2941s, 2826s, 2776s, 1592vs (7-chloroquinoline, ν C=N), 1480m, 1434m (δ-as NCH$_3$), 1384vs (ν N–O), 1332s, 1209w, 1141w, 1102s (ferrocene), 1032w, 996m (ν P–C), 815m (ferrocene), 749m (δ C–H aromatic, five adjacent hydrogens), 711m (δ C–H aromatic, five adjacent hydrogens), 544s, 505m, 456w; *m/z* (EI) 892 (M$^+$, 79%), 848.1 (M − NMe$_2$, 5), 757 (5), 721 (23), 637 (5), 459 (100), 432 (M$^+$ − AuPPh$_3$, 14), 388 (25), 262 (PPh$_3$, 12), 213 (94), 185 (65), 183 (65), 134 (51), 91 (28); $E_{1/2} = 147$ mV; ferrocene redox: $E_{pa} = 252$ mV and $E_{pc} = 162$ mV; Λ ($C_6H_5NO_2$, 20 °C) = 21 Ω^{-1} cm^2 mol^{-1}.

Compound **7** was prepared by an analogous procedure to **5** from **3** and triphenylphosphinegold(I) nitrate as an orange crystalline solid (90%); m.p.: 106–108 °C; δ_H (300 MHz; $CDCl_3$) 8.41 (1H, d, $^3J_{HH} = 6$, ArC$_2$-H), 8.14 (1H, d, $^3J_{HH} = 9$, ArC$_5$-H), 7.85 (1H, d, $^4J_{HH} = 2$, ArC$_8$-H), 7.53 (15H, m, Ph), 7.12 (1H, dd, $^4J_{HH} = 2$ and $^3J_{HH} = 9$, ArC$_6$-H), 6.49 (1H, d, $^3J_{HH} = 6$, ArC$_3$-H), 4.31 (1H, m, Cp), 4.24 (1H, m, Cp), 4.12 (1H, m, Cp), 4.08 (5H, m, Cp′), 3.90 (1H, d, $^2J_{HH} = 13$, 2′a), 3.64 (3H, m, 3′a, 5′), 3.50 (3H, m, 3′b, 4′), 2.82 (1H, d, $^2J_{HH} = 13$, 2′b), 2.09 (6H, s, 1′); $\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 152.1 (ArC_2), 151.0 (C^{IV}), 148.2 (C^{IV}), 135.4 (C^{IV}), 134.0 (Ph), 133.9 (Ph), 132.3 (Ph), 129.5 (Ph), 129.3 (Ph), 128.0 (C^{IV}), 127.1 (C^{IV}), 126.7 (ArC_8), 125.8 (ArC_6), 123.7 (ArC_5), 117.7 (C^{IV}), 99.0 (ArC_3), 71.4 (Cp), 69.4 (5C, Cp′), 66.5 (Cp), 65.8 (Cp), 58.0 (2′), 44.4 (2C, 1′), 41.6 (5′); $\delta_{P\{H\}}$ (121 MHz; $CDCl_3$) 30.71 (PPh$_3$); ν_{max} 3331br m (NH), 3054m, 2940m, 1580s (7-chloroquinoline, ν C=N), 1478m (NCH$_3$), 1436m, 1383vs (ν N–O), 1329s, 1205w, 1139w, 1102m (ferrocene), 1029w, 996m, 811m (ferrocene), 747m (δ C–H aromatic), 714m (δ C–H aromatic), 695s, 618w, 544s and 506m; *m/z* (FAB) Found 935.20071 (M$^+$, $C_{43}H_{44}N_4Au^{35}ClFeP^+$ requires 935.20069), 841.5 (2%), 770.6 (2), 721.5 (M$^+$ − 3Ph+Me, 25), 680.5 (3), 649.4 (3%), 475.3 (M$^+$ − AuPPh$_3$, 5), 459.3 (AuPPh$_3$, 100), 213.1 (18), 185.1 (23); $E_{1/2}$: not found; ferrocene redox: $E_{pa} = 294$ mV and $E_{pc} = 186$ mV; Λ ($C_6H_5NO_2$, 20 °C) = 13 Ω^{-1} cm^2 mol^{-1}.

Compound **8** was prepared by an analogous procedure to **5** from **4** and triphenylphosphinegold(I) nitrate as an orange crystalline solid (75%); m.p.: 102–105 °C; Found: C, 54.05; H, 4.14; N, 7.16. Calc. for $C_{51}H_{50}AuClFeN_5OPNO_3$: C, 54.15; H, 4.54; N, 7.43%; δ_H (300 MHz; $CDCl_3$) 8.31 (1H, d, $^3J_{HH} = 7$, ArC$_2$-H), 8.18 (1H, d, $^4J_{HH} = 2$, ArC$_8$-H), 8.11 (1H, d, $^3J_{HH} = 9$, ArC$_5$-H), 7.66–7.50 (15H, m, Ph), 7.28–7.10 (8H, m, 1′′, ArC$_6$-H, U), 6.81 (1H, d, $^3J_{HH} = 7$, ArC$_3$-H), 4.51–4.20 (6H, m, 3Cp, 3′a, 4′), 4.12 (5H, s, Cp′), 4.11–3.61 (5H, m, 2′a, 2′b, 3′b, 5′), 2.01 (6H, s, 1′); $\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 159.9 (*C*O), 153.6 (C^{IV}), 153.3 (ArC_2), 146.3 (C^{IV}), 140.5 (C^{IV}), 136.8 (C^{IV}), 134.2 (Ph), 134.0 (Ph), 132.6 (Ph), 129.8 (Ph), 129.6 (Ph), 128.2 (2C, U), 127.1 (U), 126.6 (2C, U), 124.9 (ArC_8), 123.7 (ArC_5) 117.8 (C^{IV}), 99.5 (ArC_3), 84.3 (C^{IV}, Cp), 70.6 (Cp), 69.7 (Cp′), 68.6 (Cp), 67.8 (Cp), 58.7 (2′), 49.7 (3′), 45.5 (4′), 44.6 (1′′), 44.2 (2C, 1′), 43.1 (5′); $\delta_{P\{H\}}$ (121 MHz; $CDCl_3$) 30.58 (PPh$_3$); ν_{max} 3309br m (ν N–H), 3057m, 2934m, 2820m, 2775m, 1595vs (7-chloroquinoline, ν C=N), 1542s (7-chloroquinoline), 1480w, 1452m (NCH$_3$), 1437m (δ-as (NCH$_3$)), 1381vs (ν N–O), 1336s, 1283m, 1205m, 1101m (ferrocene), 1028m, 999w (ν P–C), 814w (δ C–H aromatic), 748m (δ C–H aromatic), 695s, 609w, 544s, 510m, 454w; *m/z* (FAB) 1068.2548 (M$^+$+H, $C_{51}H_{51}N_5Au^{35}ClFeOP^+$ requires 1068.2535), 917 (2%), 721 (36), 610 (M$^+$ − AuPPh$_3$, 12), 565 (8), 459 (100), 213 (33), 185 (33), 91 (CH$_2$–Cp–CH$_2$, 54); $E_{1/2} =$ 180 mV; ferrocene redox: $E_{pa} = 219$ mV and $E_{pc} = 141$ mV; Λ ($C_6H_5NO_2$, 20 °C) = 31 Ω^{-1} cm^2 mol^{-1}.

2.3. Preparation of [Au(L)(C_6F_5)] complexes

Synthesis of complex **9**. (Pentafluorophenyl)(tetrahydrothiophene)gold (58 mg, 0.95 mmol) and chloroquine (**1**) (100 mg, 0.18 mmol) were dissolved in CH_2Cl_2 (3 cm^3) and stirred at 25 °C for 2 h in the absence of light. Addition of hexane (2 cm^3) resulted in a suspension which was centrifuged and the supernatant was decanted off the crystalline solid. The crystals were dried in vacuo to yield a white crystalline solid; (91 mg, 63%); m.p.: 114–116 °C; δ_H (400 MHz; CD_3OD) 8.58 (1H, d, $^4J_{HH} = 2$, ArC_8-H), 8.37 (1H, d, $^3J_{HH} = 6$, ArC_2-H), 8.23 (1H, d, $^3J_{HH} = 9$, ArC_5-H), 7.44 (1H, dd, $^4J_{HH} = 2$ and $^3J_{HH} = 9$, ArC_6-H), 6.66 (1H, d, $^3J_{HH} = 6$, ArC_3-H), 3.95–3.91 (1H, m, 6′), 3.24–3.12 (6H, m, 2′, 3′), 1.92–1.74 (4H, m, 4′, 5′), 1.42 (3H, d, $^3J_{HH} = 6$, 1″), 1.32 (6H, t, $^3J_{HH} = 7$, 1′); $\delta_{C\{H\}}$ (100 MHz; CD_3OD) 153.5 (ArC_2), 151.8 (C ^{IV}), 147.4 (C^{IV}), 136.2 (C^{IV}), 125.9 (ArC_5), 125.6 (ArC_6), 123.4 (ArC_8), 117.8 (C^{IV}), 99.3 (ArC_3), 51.8 (2′), 49.0 (6′), 46.9 (3′), 32.7 (5′), 21.0 (4′), 18.9 (1″), 8.2 (1′); $\delta_{F\{H\}}$ (376 MHz; CD_3OD) −117.26 to −117.38 (2F, m, *o*-F), −165.78 (1F, t, $^3J_{FF} = 19$, *p*-F), −166.80 to −166.97 (2F, m, *m*-F); IR (KBr) ν_{max} 3431m (NH), 2972m, 2923m, 2874m, 2852m, 2791m, 1594vs (7-chloroquinoline, *ν* C=N), 1541m (7-chloroquinoline), 1505s (*ν* C–F), 1455vs (*ν* C–F), 1442s, 1381m, 1367m, 1341m, 1282m, 1263m, 1219w, 1198m, 1068m, 1017m, 956vs (*ν* C–F), 866m, 803s, 754m, 647w, 514m and 454m; *m/z* (FAB) 684[M^+, 23), 332 (19), 320 ($M^+ - AuC_6F_5$, 57), 247 ($M^+ - AuC_6F_5 + N(CH_2CH_3)_2$, 27), 205 (8), 179 (13), 142 (40), 86 (100) and 58.0 (53); Λ ($C_6H_5NO_2$, 20 °C) = 0.2 Ω^{-1} cm^2 mol^{-1}.

Compound **10** was prepared by an analogous procedure to complex **9** from **2** and (pentafluorophenyl)(tetrahydrothiophene)gold. The product obtained as an orange crystalline solid (79 mg, 54%); m.p.: 83–86 °C; δ_H(300 MHz; CD_3OD) 8.37 (1H, d, $^3J_{HH} = 6$, ArC_2-H), 7.91 (1H, d, $^3J_{HH} = 9$, ArC_5-H), 7.76 (1H, d, $^4J_{HH} = 2$, ArC_8-H), 7.45 (1H, dd, $^4J_{HH} = 2$ and $^3J_{HH} = 9$, ArC_6-H), 6.75 (1H, d, $^3J_{HH} = 6$, ArC_3-H), 4.58 (1H, d, $^2J_{HH} = 14$, 3′a), 4.55 (1H, d, $^2J_{HH} = 14$, 3′b), 4.37 (1H, m, Cp), 4.31–4.29 (1H, m, Cp) 4.19–4.18 (1H, m, Cp), 4.17 (5H, s, Cp′), 3.92 (1H, d, $^2J_{HH} = 13$, 2′a), 3.29 (1H, d, $^2J_{HH} = 13$, 2′b), 2.34 (6H, s, 1′); $\delta_{C\{H\}}$ (75.5 MHz; CD_3OD) 153.3 (ArC_2), 150.2 (C^{IV}), 149.5 (C^{IV}), 126.7 (ArC_8), 125.7 (ArC_6), 124.4 (ArC_5), 118.2 (C^{IV}), 100.2 (ArC_5), 84.9 (C^{IV}, Cp), 82.9 (C^{IV}, Cp), 72.5 (Cp), 71.5 (Cp), 70.6 (5C, Cp′), 68.2 (Cp), 58.3 (2′), 44.7 (2C, 1′), 42.8 (3′); $\delta_{F\{H\}}$ (376 MHz; CD_3OD) −117.25 to −117.45 (2F, m, *o*-F), −165.88 (1F, t, $^3J_{FF} = 19$, *p*-F) −166.90 to −167.05 (2F, m, *m*-F); ν_{max} 3400br m (NH), 3088m, 2945m, 2826m, 2783m, 1591s (7-chloroquinoline, *ν* C=N), 1554m (7-chloroquinoline), 1502s (*ν* C–F), 1457s (*ν* C–F), 1362m, 1325m, 1285w, 1259w, 1226w, 1203w, 1141w, 1105w (ferrocene), 1062m, 1003w (ferrocene), 955s (*ν* C–F), 862m, 804m, 605w, 527w and 490w (ferrocene); *m/z* (FAB) 798.0672 ($M^+ + H$, $C_{29}H_{25}N_3Au^{35}ClFeF_5$ requires 798.0672), 753 (8), 459 (9), 434 (71), 389 (100), 256 (27, HC-Fp-CH_2-NMe_2), 213 (65), 134 (29, Fe-Cp-CH_2), 91 (66, CH_2-Cp-CH_2).

Compound **11** was prepared by an analogous procedure to **9** from **3** and pentafluorophenyl(tetrahydrothiophene)gold(I) as a orange crystalline solid; (132 mg, 75%); m.p.: 76–78 °C; δ_H (300 MHz; CD_3OD) 8.35 (1H, d, $^3J_{HH} = 6$, ArC_2-H), 8.09 (1H, d, $^3J_{HH} = 9$, ArC_5-H), 7.78 (1H, d, $^4J_{HH} = 2$, ArC_8-H), 7.40 (1H, dd, $^4J_{HH} = 2$ and $^3J_{HH} = 9$, ArC_6-H), 6.57 (1H, d, $^3J_{HH} = 6$, ArC_3-H), 4.25–4.23 (1H, m, Cp), 4.15–4.13 (1H, m, Cp), 4.07 (1H, t, $^3J_{HHH} = 2$, Cp), 4.03 (5H, s, Cp′), 3.81 (1H, d, $^2J_{HH} = 13$, 3′a), 3.66 (1H, d, $^2J_{HH} = 13$, 2′a), 3.52 (2H, m, 5′), 3.44 (1H, d, $^2J_{HH} = 13$, 3′b), 2.95 (2H, m, 4′), 2.88 (1H, d, $^2J_{HH} = 13$, 2′b), 1.97 (6H, s, 1′); $\delta_{C\{H\}}$ (75.5 MHz; CD_3OD) 152.7 (C^{IV}), 152.5 (ArC_2), 149.7 (C^{IV}), 136.4 (C^{IV}), 127.7 (ArC_8), 126.1 (ArC_6), 124.3 (ArC_5), 119.3 (C^{IV}), 99.8 (ArC_3), 85.9 (C^{IV}, Cp), 84.0 (C^{IV}, Cp), 72.3 (Cp), 71.3 (Cp), 70.2 (5C, Cp′), 67.5 (Cp), 58.7 (2′), 44.8 (2C, 1′), 43.3 (5′); $\delta_{F\{H\}}$ (376 MHz; CD_3OD) −117.23 to −117.40 (2F, m, *o*-F), −165.86 (1F, t, $^3J_{FF} = 19$, *p*-F), −166.86 to −167.03 (2F, m, *m*-F); ν_{max} 3411br m (NH), 2955m, 1612w (7-chloroquinoline), 1583s (N=C, 7-chloroquinoline), 1536m (7-chloroquinoline), 1499s (*ν* C–F), 1450vs (*ν* C–F), 1384m, 1336m, 1278w, 1252w, 1139w, 1105w (ferrocene), 1048m, 1000w (ferrocene), 952s (*ν* C–F), 811m (ferrocene), 781m, 489m (ferrocene) and 452w; *m/z* (FAB) 841 ($M^+ + H$, 1%), 796 (2), 477 ($M^+ - AuC_6F_4Br$, 16), 432 (19), 256 (HC-Fp-CH_2-NMe_2, 31), 213 (100), 134 (Fe-Cp-CH_2, 4), 91 (CH_2-Cp-CH_2, 32); $E_{1/2}$: not found; ferrocene redox: $E_{pa} = 315$ mV and $E_{pc} = 210$ mV; Λ ($C_6H_5NO_2$, 20 °C) = 0.9 Ω^{-1} cm^2 mol^{-1}.

Compound **12** was prepared by an analogous procedure to **9** from **4** and pentafluorophenyl(tetrahydrothiophene)gold(I) as a yellow crystalline solid (130 mg, 60%); m.p.: 102–105 °C; δ_H (300 MHz; $CDCl_3$) 8.81 (1H, br s), 8.68 (1H, d, $^4J_{HH} = 2$, ArC_8-H), 8.42 (1H, $^3J_{HH} = 6$, ArC_2-H), 8.33 (1H, br s), 7.71 (1H, d, $^3J_{HH} = 9$, ArC_5-H), 7.17–7.02 (6H, m, U, ArC_6-H), 6.31 (1H, d, $^3J_{HH} = 6$, ArC_3-H), 4.50–4.15 (8H, m, Cp, 1″, 3′a, 4′), 4.11 (5H, s, Cp′), 3.81 (1H, d, $^2J_{HH} = 13$, 2′a), 3.75–3.66 (1H, m, 3′b), 3.56–3.40 (2H, m, 5′), 2.78 (1H, d, $^2J_{HH} = 13$, 2′b) and 1.99 (6H, s, 1′); $\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 160.5 (C^{IV}, *C*O), 153.3 (ArC_2), 152.0 (C^{IV}), 146.9 (C^{IV}), 139.7 (C^{IV}), 136.4 (C^{IV}), 128.2 (2C, U), 126.7 (ArC_6), 126.6 (U_4), 126.2 (2C, U), 125.7 (ArC_5), 123.0 (ArC_8), 117.4 (^{IV}C), 98.0 (ArC_3), 83.5 (C^{IV}, Cp), 70.6 (Cp), 69.9 (Cp), 69.5 (5C, Cp′), 67.6 (Cp), 57.7 (2′), 46.9 (3′), 45.8 (4′), 44.6 (1″), 44.5 (2C, 1′), 43.8 (5′); $\delta_{F\{H\}}$ (376 MHz; $CDCl_3$) −120.05 to −120.25 (2F, m, *o*-F), −164.518 (1F, t, $^3J_{FF} = 20$, *p*-F), −167.38 to −167.62 (2F, m, *m*-F); IR (KBr) ν_{max} 3409br m (NH), 3091m, 2928m, 2860m, 2823m, 2779m, 1592vs (7-chloroquinoline, *ν* C=

N), 1548m (N=C, 7-chloroquinoline), 1502s (ν C–F), 1457s (ν C–F), 1361m, 1335m, 1271m, 1204w, 1160w, 1142w, 1104w (ferrocene), 1062m, 1005w (ferrocene), 956s (ν C–F), 858w, 805m, 730w, 698w, 607w, 527w and 487w; *m/z* (FAB) 974 (M^+, 21), 929 ($M-HNMe_2$, 12), 610 ($M-AuC_6F_5$, 12) 565 ($M^+-AuC_6F_5+HNMe_2$, 19), 432 ($M^+-HNMe_2+C_6H_5CH_2NHCO$, 5), 409 (7), 304 (5), 213 (89), 134 (Fe-Cp-CH_2, 37) 91 (CH_2-Cp-CH_2, 100); Λ ($C_6H_5NO_2$, 20°C) = 0.7 Ω^{-1} cm^2 mol^{-1}.

When the compounds were purified by preparative TLC (silica) eluting with CH_2Cl_2–MeOH 9:1 the products were found to be spectroscopically consistent with those obtained by above but in slightly lower yields.

2.4. Preparation of complex [RhCl(COD)L]

Synthesis of complex **14**: A mixture of dichoro(dicyclooctadiene)dirhodium (56 mg, 0.11 mmol) and ferroquine (**1**) (150 mg, 0.34 mmol) in CHx_2Cl_2 (5 cm^3) was heated under reflux for 4 h. The solvent volume was reduced to half its original level in vacuo and Et_2O was then added dropwise until the solution became turbid. The mixture was then cooled to -15 °C for $\sim$14 h to yield a suspension. The mixture was filtered, washed with Et_2O and the orange microcrystalline solid was dried recrystallised from MeOH and dried in vacuo (156 mg, 60%); m.p.: 212 °C (dec.); Found: C, 55.01; H, 5.19; N, 6.18. $C_{31}H_{36}Cl_2FeN_3Rh$ requires C, 54.73; H, 5.33; N, 6.18%; δ_H(300 MHz; $CDCl_3$) 9.58 (1H, br s, ArC_8-H), 8.61 (1H, d, $^3J_{HH}=6$, ArC_2-H) 8.17 (1H, br s, NH), 7.54 (1H, d, $^3J_{HH}=9$, ArC_5-H), 7.30 (1H, d, $^4J_{HH}=2$ and $^3J_{HH}=9$ Hz, ArC_6-H), 6.42 (1H, d, $^3J_{HH}=6$, ArC_3-H), 4.74 (2H, br s, COD-CH trans to Cl), 4.38 (1H, d, $^2J_{HH}=13$, 3′a), 4.22 (1H, m, Cp), 4.16 (1H, m, Cp), 4.13 (6H, m, Cp′, 3′b), 4.08 (1H, t, $^3J_{HH}=2$, Cp), 3.79 (1H, d, $^2J_{HH}=13$, 2′a), 3.69 (2H, br s, COD-CH *cis* to Cl), 2.90 (1H, d, $^2J_{HH}=13$, 2′b), 2.56 (4H, m, COD-CH_2), 2.21 (6H, s, 1′), 1.85 (4H, m, COD-CH_2); $\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 152.7 (ArC_2), 150.7 (ArC_4), 128.7 (ArC_8), 125.6 (ArC_6), 122.4 (ArC_5), 112.4 (C^{IV}, ArC_{10}), 101.4 (C^{IV}), 99.5 (ArC_3), 84.2 (2C, CH, COD), 84.0 (2C, CH, COD), 71.5 (Cp), 70.5 (Cp), 69.3 (5C, Cp′), 66.1 (Cp), 58.0 (2′), 44.9 (2C, 1′), 42.5 (2′), 31.4 (2C, COD, CH_2), 30.5 (2C, COD, CH_2); ν_{max} 3442br m (NH), 3230br m, 3091m, 3077m, 2990m, 2932m, 2878m, 2822m, 2776m, 1590vs (7-chloroquinoline, ν C=N), 1545m (7-chloroquinoline), 1495m (ν C=C, COD), 1451m (NCH_3), 1427m, 1391w, 1367m, 1350m, 1333m, 1296w, 1282m, 1251m, 1228m, 1201m, 1170m, 1136m, 1105m (ferrocene), 1067w, 1029m, 1000m (ferrocene), 962w, 923w, 892w, 861s, 842m, 824s, 807s, 766m, 734m, 701w, 643w, 625w, 615w, 600w, 552w, 523m, 490m (ferrocene), 457w, and 434w; *m/z* (FAB) 680 (M+H, 2%), 644 (M − Cl, 98), 599 (5), 491 (9), 434 ($M^+-Rh(COD)Cl$, 22), 389 (54), 359 (15), 303 (15), 256 (HC-Fp-CH_2-NMe_2, 21), 213 (100), 134 (26), 91 (CH_2-Cp-CH_2).

Compound **15** was prepared by an analogous procedure to **14** from **3** and dichoro(dicyclooctadiene)dirhodium to yield an orange crystalline solid; (130 mg, 57%); m.p.: 213 °C (dec.); Found: C, 57.37; H, 5.28; N, 7.49. Calc. for $C_{33}H_{41}Cl_2FeN_4Rh$: C, 57.61; H, 5.36; N, 7.26%. δ_H (300 MHz; $CDCl_3$) 8.50 (1H, d, $^3J_{HH}=5$, ArC_2-H), 8.41 (1H, s, ArC_8-H), 7.73 (1H, d, $^3J_{HH}=9$, ArC_5-H), 7.33 (1H, dd, $^4J_{HH}=2$ and $^3J_{HH}=9$, ArC_6-H), 6.27 (1H, d, $^3J_{HH}=5$, ArC_3-H), 4.70 (2H, br s, COD-CH trans to Cl), 4.14 (1H, m, Cp), 4.10 (2H, m, Cp), 4.04 (5H, Cp′), 3.83 (1H, d, $^2J_{HH}=13$, 3′a), 3.67 (3H, m, 2′a, COD-CH cis to Cl), 3.38 (1H, d, $^2J_{HH}=13$, 3′b), 3.48–3.40 (2H, m, 5′), 2.98–2.92 (2H, m, 4′), 2.79 (1H, d, $^2J_{HH}=13$, 2′b), 2.52 (4H, m, COD-CH_2), 1.95 (6H, s, 1′), 1.76 (4H, m, COD-CH_2); $\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 152.0 (ArC_2), 149.9 (ArC_4), 149.2 (C^{IV}), 134.7 (C^{IV}), 128.6 (ArC_8), 125.0 (ArC_6), 121.5 (ArC_5), 117.4 (C^{IV}), 99.1 (ArC_3), 84.5 (2C, CH, COD), 84.2 (2C, CH, COD), 83.8 (C^{IV}, Cp), 71.1 (Cp), 69.9 (Cp), 68.9 (5C, Cp′), 65.8 (Cp), 58.2 (2′), 47.3 (4′), 46.4 (3′), 45.0 (2C, 1′), 42.0 (5′) 31.4 (2C, COD, CH_2), 30.5 (2C, COD, CH_2); ν_{max} 3311br m (NH), 3093m, 2940m, 2869m, 2830m, 1611s (7-chloroquinoline, ν C=N), 1584vs (7-chloroquinoline), 1541m (7-chloroquinoline), 1451m (NCH_3), 1424m, 1365m, 1331m, 1283w, 1251w, 1200w, 1171w, 1140m, 1105w (ferrocene), 1062w, 1035w, 998w, 879w, 854w, 815m (ferrocene), 766w, 647w and 493w (ferrocene); *m/z* (FAB) 723.3 (M^++H), (HRMS) 687.1436 (M^+-Cl, $C_{33}H_{41}N_4ClFeRh$ requires 687.1424), 477 ($M^+-Rh(COD)Cl$, 13), 432 (32), 307 (2), 213 (100), 179 (5), 107 (91), 89 (23).

Compound **16** was prepared by an analogous procedure to **14** from **4** and dichoro(dicyclooctadiene)dirhodium to yield an orange crystalline solid; (145 mg, 45%); m.p.: 210 °C (dec.); Found: C, 56.95; H, 5.60; N, 7.61. Calc. for $C_{41}H_{48}Cl_2N_5OFeRh$: C, 57.49; H, 5.65; N, 8.18%.δ_H (300 MHz; $CDCl_3$) 9.51 (1H, br s, ArC_8-H), 8.55 (1H, d, $^3J_{HH}=6$, ArC_2-H), 8.02 (1H, br s, $ArCH_2NHCO$), 7.57 (1H, d, $^3J_{HH}=9$, ArC_5-H), 7.14–7.05 (6H, m, U_2, U_3, U_4, ArC_6-H), 6.24 (1H, d, $^3J_{HH}=6$, ArC_3-H), 4.72 (2H, br s, COD-CH trans to Cl), 4.41–4.12 (7H, m, Cp, 1″, 3′a, 4′), 4.08 (5H, s, Cp′), 4.05 (1H, m, Cp), 3.77 (1H, d, $^2J_{HH}=13$, 2′a), 3.69–3.25 (5H, m, 3′b, 5′, COD-CH cis to Cl), 2.74 (1H, d, $^2J_{HH}=13$, 2′b), 2.50 (4H, m, COD -CH_2), 1.94 (6H, s, 1′), 1.77 (4H, m, COD-CH_2); $\delta_{c\{H\}}$ (75.5 MHz; $CDCl_3$) 160.5 (C^{IV}, *C*O), 152.5 (ArC_2), 151.2 (C^{IV}), 147.3 (C^{IV}), 140.1 (C^{IV}), 135.5 (C^{IV}), 128.3 (2C, U), 128.2 (ArC_6), 126.7 (U_4), 126.4 (2C, U), 126.0 (ArC_6), 123.0 (ArC_8), 119.0 (C^{IV}), 98.7 (ArC_3), 84.1 (2C, CH, COD), 83.8 (2C, CH, COD), 82.0 (C^{IV}, Cp), 70.4 (Cp), 69.5 (5C, Cp′), 68.8 (Cp), 67.6 (Cp), 57.9 (2′), 44.7 (2C, 1′), 44.6 (4′), 43.8 (1″), 31.4 (2C, COD, CH_2), 30.5 (2C, COD, CH_2); ν_{max} 3313m, 3084m, 2988m, 2934m, 2878m, 2828m, 2776m, 1590vs

(7-chloroquinoline, *v* C=N), 1539s (7-chloroquinoline), 1491m (*v* C=C, COD), 1452m (NCH_3), 1400m, 1359m, 1331m, 1300m, 1273m, 1256m, 1201m, 1172w, 1139w, 1104w (ferrocene), 1038w, 1005m (ferrocene), 962w, 856m, 810m (ferrocene), 764w, 742m, 695w, 513m, 492m (ferrocene), 462m; *m/z* (FAB) 856.2 ($M^+ + H$, 1%), 820 ($M^+ - Cl$, 3) 694 (3), 610 ($M^+ - Rh(COD)Cl$, 63), 565 (29), 409 (9), 307 (12), 237 (38), 213 (45), 150 (100), 91 (55).

3. Results and discussion

3.1. Synthesis

The reaction of ligands **1**–**4** with ionic $[Au(PPh_3)NO_3]$, and neutral $[Au(C_6F_5)(tht)]$ were investigated. The $[Au(L)(PPh_3)]NO_3$ complexes are soluble in water and were synthesised under milder conditions than the corresponding hexafluorophosphate salts [5]. The complexes **5**–**8** were prepared from triphenylphosphinegold(I) and the corresponding ligand (**1**–**4**) in CH_2Cl_2 (see Eq.(1)) and isolated as crystalline solids. The neutral complexes **9**–**12** were synthesised from $[Au(C_6F_5)(tht)]$ and the corresponding ligand (**1**–**4**) in CH_2Cl_2 (see Eq. (2)) and isolated as crystalline solids.

$$[Rh(Cl)(COD)]_2 + 2L \xrightarrow[4h,\ reflux]{CH_2Cl_2} \underset{\textbf{13-16}}{2[Rh(Cl)(COD)(L)]} \quad (1)$$

$$[Au(C_5F_5)(tht)] + L \xrightarrow[2h,\ 25\ ^oC]{CH_2Cl_2} [Au(C_6F_5)(L)] + tht \quad (2)$$

9-12

Complexes of the type [Rh(Cl)(COD)(L)] (**13**–**16**) were synthesised from $[Rh(Cl)(COD)]_2$ and the corresponding ligands (**1**–**4**) in CH_2Cl_2 and obtained as crystalline solids (see Eq. (3)).

$$[Au(PPh_3)]NO_3 + L \xrightarrow[2h,\ 25\ ^oC]{CH_2Cl_2} \underset{\textbf{5-8}}{[Au(L)(PPh_3)]NO_3} \quad (3)$$

The ligands (**1**–**4**) contain several sites that can potentially coordinate to a metal. We expected the metal to coordinate to the quinoline nitrogen since the 4-amino nitrogen donates electrons into the quinoline ring increasing the electron density at the quinoline nitrogen and rendering the 4-amino moiety unreactive. The possibility of the tertiary amine coordinating to the metal made unambiguous characterisation of these complexes difficult. Suitable crystals for X-ray diffraction studies have eluded us but there is strong evidence from NMR studies (see Section 3.2) that suggests that both the gold and rhodium coordinate to the quinoline nitrogen. In addition, the characteristic C=N stretch in the IR spectra shifts by ~ 20–$30\ cm^{-1}$ for most of the complexes. The exceptions to this rule are complexes **11** and **15** where a second secondary amine is present. The H_8 proton resonance in the ^{1}H-NMR shifts significantly for complex **15**, this indicates that the Rh coordinates to the quinoline amine (see Section 3.2). However, complex **11** cannot be identified unambiguously.

3.2. NMR spectroscopy

The ^{1}H-NMR spectra of complexes **5**–**8** gave rise to a 15 proton multiplet arising from triphenylphosphine. Both the H_8 and the H_2 protons of the quinoline shifted with respect to the parent ligand, this can be illustrated by ferroquine (**2**) where the H_8 (δ 7.91) and H_2 (δ 6.46) quinoline proton resonances shift to 8.26 and 6.97 in **6**, respectively. The second notable change in the spectra concerns the CH_2NMe_2 proton resonances, which shift significantly. This could be interpreted as evidence for coordination to the NMe_2 moiety but the resonances corresponding to the NMe_2 group do not shift significantly and a similar shift is observed for the $HNCH_2CH_2NH$ spacer not the CH_2NMe_2 protons when the gold is complexed to **3** and **4**. The presence of the triphenylphosphine was observed in the ^{13}C-NMR spectra and ^{31}P-NMR spectra of these complexes. Many aspects of the spectroscopic data obtained for the complex $[Au(CQ)(PPh_3)]NO_3$ (**5**) are similar to the data reported for the related complex $[Au(CQ)(PPh_3)]PF_6$ [5].

Upon coordination of the $Au(C_6F_5)$ a similar downfield shift in the H_8 quinoline proton resonance was observed in the ^{1}H-NMR spectra when compared to the free ligand. The tetrahydrothiophene was notably absent in both ^{1}H- and ^{13}C-NMR spectra indicating that this had been displaced by the 4-amino-7-chloroquinoline ligand. The ^{19}F-NMR spectra of **9**–**12** showed small, but consistent changes in the all three pentafluorophenyl resonances compared to the $[Au(C_6F_5)(tht)]$.

The formation of the rhodium complexes [Rh(Cl)(COD)(L)] could be clearly observed in the ^{1}H-NMR spectra as the chemical environment of the cyclooctadiene protons changes significantly on complexation, resulting in large changes in the chemical shifts of these protons. A large change in the chemical shift of the H_8 quinoline resonance (>1 ppm) was observed. Compound **13** [Rh(Cl)(COD)(CQ)] has previously been synthesized and the spectroscopic data that we obtained was consistent with that reported in the literature [4]

3.3. Biological testing

The data for the in vitro antimalarial activity of the new derivatives is presented in Table 1. Data for the ligands **1–4** and the previously prepared complex **13** are included for comparison purposes. The following trends are consistent with literature reports:

i) The coordination of gold or rhodium increases the efficacy of chloroquine (**1**); this is most notable in the chloroquine-resistant K1 strain.
ii) The ferrocenyl ligands **2–4** are more effective than chloroquine in both the chloroquine-sensitive and the chloroquine-resistant strains of the parasite.

Several new trends have emerged from these tests:

i) The ferrocenyl ligands are also more efficacious than the gold or rhodium complexes of chloroquine, particularly against the resistant strains of the parasite.
ii) The most active of the three types of coordination complexes studied are those of the type $[Au(C_6F_5)(L)]$. However, the gold moiety is in most cases superfluous when coordinated to the ferrocenyl ligands. In the case of the triphenylphosphine salts **7** and **8**, the presence of the gold moiety has a detrimental effect on the antiplasmodial activity of the ferrocenyl ligand.
iii) The rhodium complexes are significantly less active than the gold complexes and exhibit a moderate to strong antagonistic effect on the efficacy of the complexes **2–4**. It must be noted that Sánchez-Delgado and co-workers [4] reported higher activity in vivo against *P. berghei* for the Rh complexes than would be expected on the basis of the in vitro testing.

3.4. Cyclic voltammetry

The introduction of a ferrocene moiety into chloroquine may enhance the transport of a 4-aminoquinoline into the food vacuole or there maybe a toxicity associated with the metal fragment. One such mechanism is the generation free radicals by ferrocene (see Eq. (4)) [15].

$$Fe^{2+} + O_2 = Fe^{3+} + O_2^{\bullet -};$$
$$Fe^{2+} + O_2^{\bullet -} = Fe^{3+} + H_2O_2;$$
$$Fe^{2+} + H_2O_2 = Fe^{3+} + OH^- + OH^{\bullet} \quad (4)$$

Previous attempts to find a correlation between the antimalarial activity and the reduction potential of the ferrocene have been inconclusive [16]. We have continued to study the electrochemical properties of these complexes because recent work on ferroquine analogues has indicated that there maybe a secondary toxicity associated with the ferrocene. The ease with which the ferrocene is oxidised may have a bearing on a minor/secondary antiplasmodial activity that the primary chloroquine type action masks.

3.5. Cyclic voltammetry

Compounds **2** and **4** both show a fully reversible redox event whilst the behaviour of **3** is, at best, quasi-reversible, as it exhibits a greater reversibility with increasing scan rate (Table 2). The $E_{1/2}$ value of **7** is not quoted, because the $E_{pa} - E_{pc}$ value indicates that this compound does not exhibit a full reversible one

Table 1
In vitro antiplasmodial activity of metal complexes

Compound	Compound number	D10 (CQ-sensitive)		K1 (CQ-resistant)	
		IC_{50} (ng ml^{-1})	IC_{50} (nM)	IC_{50} (ng ml^{-1})	IC_{50} (nM)
1·H_3PO_4	**1**	11.83	22.93	181.76	352.33
2	**2**	7.05	16.30	2.15	4.96
3	**3**	5.38	11.30	5.98	12.56
4	**4**	10.09	16.54	9.48	15.54
$[Au(\mathbf{1})(PPh_3)]NO_3$	**5**	17.74	21.09	51.76	61.53
$[Au(\mathbf{2})(PPh_3)]NO_3$	**6**	10.02	10.50	5.42	5.68
$[Au(\mathbf{3})(PPh_3)]NO_3$	**7**	33.19	33.27	33.81	33.89
$[Au(\mathbf{4})(PPh_3)]NO_3$	**8**	32.14	30.32	32.96	31.09
$[Au(C_6F_5)(\mathbf{1})]$	**9**	12.36	18.07	41.78	61.09
$[Au(C_6F_5)(\mathbf{2})]$	**10**	8.05	10.08	3.16	3.96
$[Au(C_6F_5)(\mathbf{3})]$	**11**	11.53	13.70	12.33	14.65
$[Au(C_6F_5)(\mathbf{4})]$	**12**	22.75	23.36	12.59	12.92
[Rh(Cl)(COD)(**1**)]	**13**	12.16	21.50	46.03	81.31
[Rh(Cl)(COD)(**2**)]	**14**	10.57	15.80	7.05	10.55
[Rh(Cl)(COD)(**3**)]	**15**	145.88	202.00	431.52	597.59
[Rh(Cl)(COD)(**4**)]	**16**	47.32	56.10	40.27	47.70

Table 2
Cyclic voltammetry of selected ferrocene containing compounds

Compound	Compound number	E_{pa} (mV) [a]	E_{pc} (mV) [b]	$E_{1/2}$ (mV) [c]	$E_{pa} - E_{pc}$ (mV)
2	**2**	181	113	147	70
[Au(**2**)(PPh_3)]NO_3	**6**	252	162	207	90
3	**3**	150	30		120
[Au(**3**)(PPh_3)]NO_3	**7**	294	186		108
4	**4**	198	115	158	83
[Au(**4**)(PPh_3)]NO_3	**8**	219	141	180	78

[a] Anodic potential.
[b] Cathodic potential.
[c] Half wave potential ($E_{pa}+E_{pc}$)/2.

electron oxidation and therefore it is inappropriate to quote a $E_{1/2}$ value (Fig. 2). Coordination of the gold to the ferrocenyl ligands has an effect on the redox behaviour of the ferrocenyl moiety. Most notably, in all cases the incorporation of gold into the molecule resulted in an increase in half wave potentials, $E_{1/2}$, which indicates that the ferrocenyl moiety is more difficult to oxidise in the presence of the coordinated gold moiety. The effect was most marked when comparing compound **3** with compound **7** [Au(3)(PPh_3)]NO_3. There also appeared to be a trend towards reversibility shown by the lowering in peak separation, $E_{pa} - E_{pc}$. This effect is far more likely to be a 'through-space' interaction than a 'through-bond' interaction since the aromatic quinoline and ferrocenyl moieties are not linked by a conjugated chain.

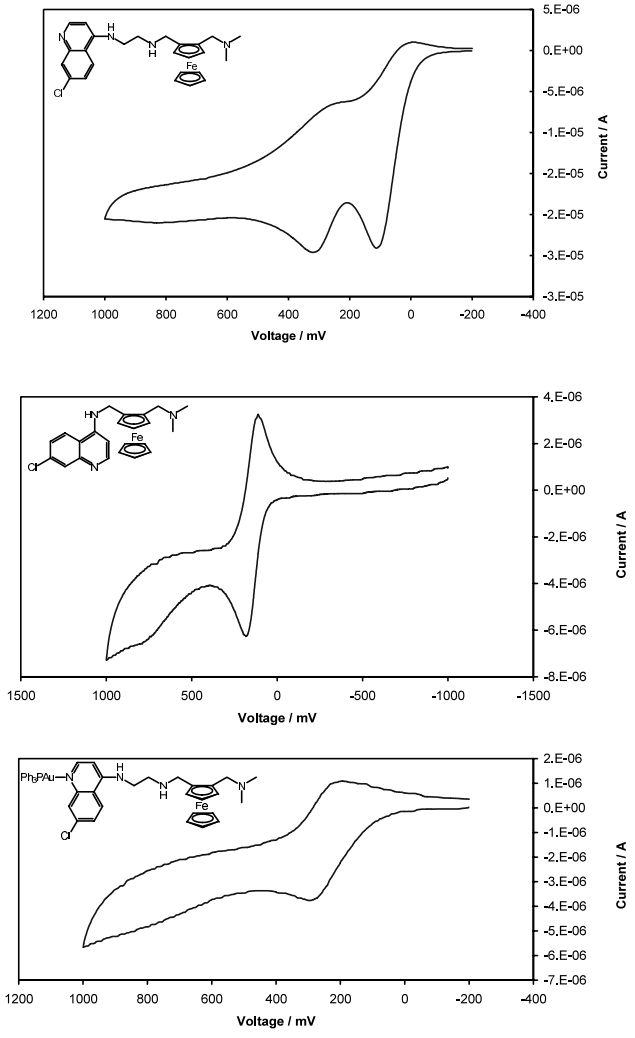

Fig. 2. Cyclic voltammograms of **2**, **3** and **7**.

Here it is observed that as the compounds become more difficult to oxidise, so they lose efficacy. Unfortunately, it is not possible to draw any conclusion about this correlation at this stage.

4. Conclusions

The reaction of 7-chloroquinolines **1**–**4** with [Au(PPh_3)NO_3], [Au(C_6F_5)(tht)] and [Rh(COD)Cl]$_2$ have been investigated. The coordination complexes of chloroquine show improved efficacy against chloroquine-resistant strains of the *P. falciparum* with respect to chloroquine. However, there is a threefold drop in efficacy in moving from the chloroquine sensitive to the chloroquine resistant strain.

The ferrocenyl 4-aminoquinolines all show improved efficacy with respect to chloroquine in both sensitive and resistant strains, ferroquine being the most efficacious. However, complexation of the second metal to these compounds at best has little effect on the overall efficacy of the compounds. At worst, there appears to be a significant antagonistic effect on complexation of the second metal. The presence of the second metal centre makes the ferrocenyl moiety far more difficult to oxidise.

It should be noted that whilst the gold and rhodium heterobimetallic compounds do not show additive or synergistic behaviour, this does not preclude this possibility with other metal combinations.

Acknowledgements

We would like to thank Professor Alan Hutton for assistance with cyclic voltammetry; UCT, the National Research Foundation (South Africa), THRIP and the Claude Harris Leon Foundation for financial support, Johnson Matthey for the loan of sodium tetrachloroaurate and rhodium trichloride, and Siyabonga Ngubane for help with preparing the final manuscripts.

References

[1] J. Zeigler, R. Linck, D.W. Wright, Curr. Med. Chem. 8 (2001) 171.
[2] B. Rosenburg, L. VanCamp, T. Krigas, Nature 205 (1965) 698.
[3] G. Jaouen, Chem. Ber. 37 (2001) 36.
[4] R.A. Sánchez-Delgado, M. Navarro, H Pérez, J Urbina, J. Med. Chem. 39 (1996) 1095.
[5] M. Navarro, H. Pérez, R.A. Sánchez-Delgado, J. Med. Chem. 40 (1997) 1937.
[6] N. Wasi, H.B. Singh, A. Gajanana, N. Raichowdhary, Inorg. Chim. Acta 135 (1987) 133.
[7] (a) C. Biot, G. Glorian, L.A. Maciejewski, J.S. Brocard, O. Domarle, G. Blampain, P. Millet, A.J. Georges, H Abessolo, D. Dive, J. Lebibi, J. Med. Chem. 40 (1997) 3715;
(b) K. Chibale, J.R. Moss, M. Blackie, D. van Schalkwyk, P.J. Smith, Tetrahedron Lett. 41 (2000) 6231.
[8] P. Beagley, M.A.L.. Blackie, K. Chibale, C. Clarkson, J.R. Moss, P.J. Smith, J. Chem. Soc. Dalton Trans. (2002) 4426.
[9] A.M. Meuting, B.D. Alexander, P.D. Boyle, A.I. Casanuovo, L.N. Ito, B.J. Johnson, L.H. Pignolet, Inorg. Synth. 29 (1992) 280.
[10] (a) R. Uson, A. Laguna, Inorg. Synth. 21 (1982) 71;
(b) R. Uson, M. Laguna, A Laguna, Inorg. Synth. 26 (1989) 86.
[11] G. Giordiano, R.H. Crabtree, Inorg. Synth. 28 (1990) 88.
[12] (a) W. Trager, J.B. Jensen, Science 193 (1976) 673;
(b) W. Trager, Methods Cell Biol. 45 (1994) 7.
[13] M.T. Makler, J.M. Ries, J.A. Williams, J.E. Bancroft, R.C. Piper, B.L. Gibbons, D.J. Hinrichs, Am. J. Trop. Med. Hyg. 48 (1993) 739.
[14] R. Hubel, K. Polborn, W. Beck, Eur. J. Inorg. Chem. (1999) 471.
[15] (a) H. Tamura, M. Miwa, Chem. Lett. 11 (1997) 1177;
(b) D. Osella, M. Ferrali, P. Zanello, F. Laschi, M. Fontani, C. Nervi, G. Cavigiolio, Inorg. Chim. Acta 306 (2000) 42.
[16] D. Osella, M. Ferrali, P. Zanello, F. Laschi, M. Fontani, C. Nervi, G. Cavigiolio, Inorg. Chim. Acta 306 (2000) 42–48.