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FULL PAPER

Synthesis and antimalarial activity *in vitro* of new ruthenocene–chloroquine analogues

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The syntheses of the new compounds (7-chloroquinolin-4-yl)(2-dimethylaminomethylruthenocen-1-ylmethyl)amine **3** and *N*-(7-chloroquinolin-4-yl)-*N′*-(2-dimethylaminomethylruthenocen-1-ylmethyl)ethane-1,2-diamine **5** are reported. The reactions are compared to those previously reported for the preparation of the ferrocene analogues. The key step in the reaction is the regioselective synthesis of 2-dimethylaminomethylruthenocene carboxaldehyde **10** by deprotonation of dimethylaminomethylruthenocene with *t*-BuLi in diethyl ether, followed by the addition of DMF. In addition, 1′-dimethylaminomethylruthenocene carboxaldehyde **11** was also prepared leading to the unexpected synthesis of the 1,1′-isomers (7-chloroquinolin-4-yl)(1′-dimethylaminomethylruthenocen-1-ylmethyl)amine **17** and *N*-(7-chloroquinolin-4-yl)-*N′*-(1′-dimethylaminomethylruthenocen-1-ylmethyl)ethane-1,2-diamine **18**. X-Ray crystal and molecular structures for compounds **3** and **17**·H_2O are reported. The 4-aminoquinoline complexes show high efficacy against the chloroquine sensitive and resistant strains of the *Plasmodium falciparum* parasite *in vitro*; these results are compared with those obtained for the analogous ferrocene compounds.

Introduction

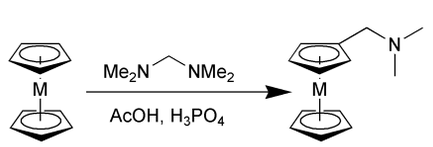
Chloroquine **1** (Fig. 1) has for sometime been an effective antimalarial agent. Unfortunately, in most affected areas the causative agent *P. falciparum* has developed resistance to chloroquine and other quinoline antimalarials.[1] Since malaria affects between 300 and 500 million people each year and is responsible for 1.5 to 2.7 million fatalities,[2] the emergence of quinoline drug resistance is a major problem. To overcome this problem numerous aminoquinolines[3] and aminoquinoline metal complexes[4–7] have been screened against *P. falciparum*. When chloroquine is complexed to a metal (*e.g.* Ru or Rh),[7] or if a ferrocenyl group is included in the side chain[4] (**2** and **4**), high antimalarial activity against chloroquine resistant strains has been observed *in vitro* (*P. falciparum*)[4] and *in vivo* (*P. berghei*).[4a] Since the chemistry of ferrocene and ruthenocene is similar, it was envisaged that compounds **3** and **5** could be synthesised. It is also important to establish whether the metal itself plays a role in the antimalarial activity of these complexes.

Results and discussion

Synthesis

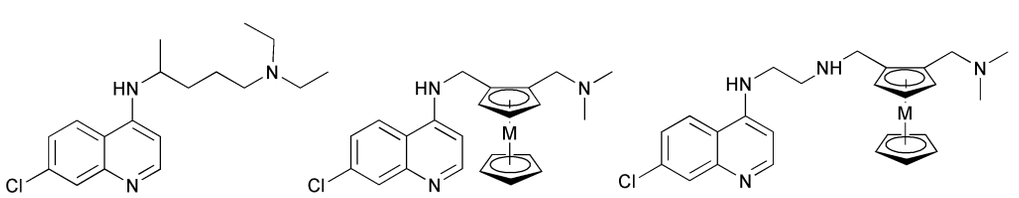
Modification of ruthenocene using the methodology developed for the synthesis of **2** and **4**[4] proved to be difficult since ferrocene and ruthenocene exhibit similar chemistry but very different reactivity. Ferrocene is more susceptible to electrophilic addition than ruthenocene[8] and the ferrocenyl Cp protons are less acidic than the corresponding ruthenocenyl protons; hence it is difficult to generate monolithioruthenocene without forming significant quantities of dilithioruthenocene.[8,9] In contrast both mono- and di-lithioferrocene can be readily prepared.[9–11a]

The synthesis of the first key intermediate dimethylaminomethylruthenocene **7** by the electrophilic addition of the iminium ion $[CH_2{=}NMe_2]^+$, generated *in situ* from *N,N,N′N′*-tetramethylaminomethane (Scheme 1) was achieved in significantly lower yields than for the analogous ferrocene complex **6**. Increasing the temperature, duration of the reaction or altering the stoichiometry led to no appreciable improvement in the yield. To develop a higher yielding synthesis, monolithioruthenocene was generated by the method reported by Sanders



6 M = Fe 79%
7 M = Ru 35%

Scheme 1



1

2 M = Fe
3 M = Ru

4 M = Fe
5 M = Ru

Fig. 1 Chloroquine and organometallic 4-aminoquinolines.

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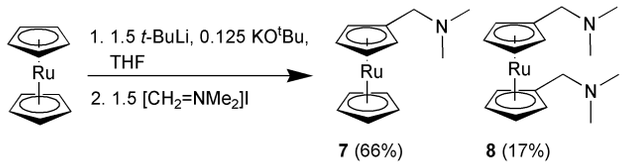
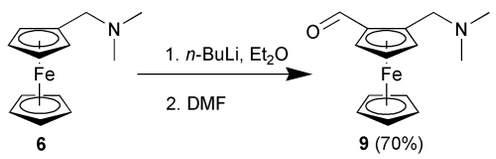
and Mueller-Westerhoff[9] and reacted with Eschenmoser's salt ([CH_2=NMe_2]I).[11] This reaction yielded a mixture of the monosubstituted product **7** and the disubstituted product bis(dimethylaminomethylruthenocene) **8** (Scheme 2).



Scheme 2

Complex **9** is the key intermediate for the syntheses of both **2** and **4** (see Scheme 3). The preparation was originally performed by treating **6** with *n*-BuLi in diethyl ether; deprotonation occurs exclusively at the 2-position since the Me_2NCH_2– moiety has a strong *ortho*-directing effect and the resulting dimethylaminomethylferrocenyl-2-lithium is reacted with DMF to form **9**.



Scheme 3

This reaction was repeated with the ruthenocene analogue **7** with much lower regioselectivity. The three products shown in Scheme 4 were isolated *i.e.* the 1,2- and 1,1′-disubstituted isomers **10** and **11** respectively and a dialdehyde **12**. The separation of the 1,2- and 1,1′-isomers proved to be a difficult and lengthy process. In addition all three complexes decomposed † thus, the yields quoted are isolated yields and do not accurately represent the product distribution. The synthesis of compounds **3** and **5** was achieved from complex **10**[12] ‡ but the yields were extremely low.

The reaction was examined under different conditions, and the ratio of the 1,2- and the 1,1′-isomers was determined using the characteristic aldehyde signals in the ^{1}H NMR. It was quickly established that *t*-BuLi in diethyl ether produced the 1,2-isomer exclusively with a yield of 32–40%. An improved synthesis of complex **9** was reported by Brocard and co-workers employing 1.5 equivalents of *t*-BuLi in diethyl ether.[13] Using this new methodology the yield of **10** was increased to 70%. Small quantities of compounds **11** (<0.5%) and **12** (<3%) were observed in the ^{1}H NMR spectrum of the crude mixture. The procedure has been repeated several times and both the yield and regioselectivity are reproducible. The high regioselectivity can be rationalised by considering the composition of alkyllithium reagents in solution. *t*-BuLi in diethyl ether is primarily a dimer,[14a] this results in deprotonation at the sterically hindered but *ortho*-directed 2-position. An excess of *t*-BuLi leads to higher yields of **10** but it is not clear why it does not lead to significant quantities of compound **12**.

With this rationale in mind, a large sterically hindered base would favour the formation of the 1,1′-isomer. When the reaction was performed in pentane employing *n*-BuLi, deprotonation occurred predominantly at the 1′-position.§ The reaction was performed several times and 85–93% selectivity for **11** over **10** was observed by ^{1}H NMR of the crude sample. Since large oligomeric alkyl lithium reagents are less reactive than their solvated counterparts, longer reaction times are required and lower yields 35–47% are observed. The lower regioselectivity may be due to the *ortho*-directing effect of the –CH_2NMe_2 moiety or the dimethylaminomethylruthenocene-1′-lithium may isomerise to the 1,2-isomer before the DMF is added.[14b,c] When the ferrocene complex **6** was deprotonated with *n*-BuLi in pentane and reacted with DMF, the 1,2-disubstituted ferrocene **9** was formed exclusively in 42% yield.

Compounds **10** and **11** were converted to the oximes **13** and **14** which were reduced to the primary amines **15** and **16** with $LiAlH_4$ (Scheme 5).[4a] Condensation of **15** and **16** with 4,7-dichloroquinoline (Scheme 6) yielded complexes **3** and **17** respectively.[4a]

Complexes **5** and **18** were prepared in 77 and 65% yields respectively, by reductive amination of **10** or **11** with N^1-(7-chloroquinolin-4-yl)ethane-1,2-diamine (Scheme 7).[4b]

Complexes **3** and **17** were crystallised from ethyl acetate/hexane and complex **5** was crystallised from acetonitrile/diethyl ether to yield analytically pure cream solids. Complex **18** was isolated as a cream coloured oil. Complexes **3** and **5** were spectroscopically similar to complexes **2** and **4**.[4]

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

	D10		K1	
Compound	IC_{50}/ng mL^{-1}	IC_{50}/nM	IC_{50}/ng mL^{-1}	IC_{50}/nM
1·$2H_3PO_4$	11.83	22.9	181.76	352.3
2	7.05	16.3	2.15	5.0
3	10.94	23.8	3.02	6.3
4	12.50	26.2	14.59	30.6
5	10.54	20.2	10.84	20.8
17	8.24	17.2	12.13	25.3
18	39.24	75.1	92.26	176.7

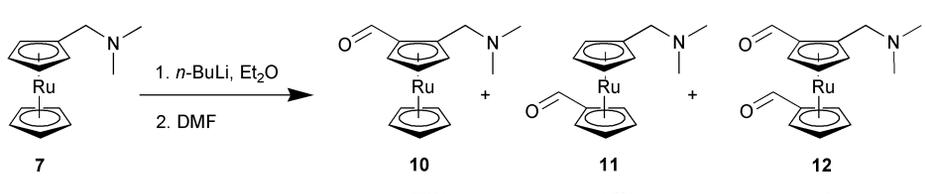
Assessment of antimalarial activity *in vitro*

The data for the *in vitro* antimalarial activity of the new derivatives is presented in Table 1. Data for chloroquine, ferroquine **2** and compound **4** is included for comparison purposes. The results summarised in Table 1 show that the new ruthenocenyl complexes show high *in vitro* activity against both chloroquine sensitive (D10) and resistant strains (K1) of *P. falciparum*. The ferroquine-type structures (compounds **2** and **3**) were found to be the most active, since introducing a two carbon methylene

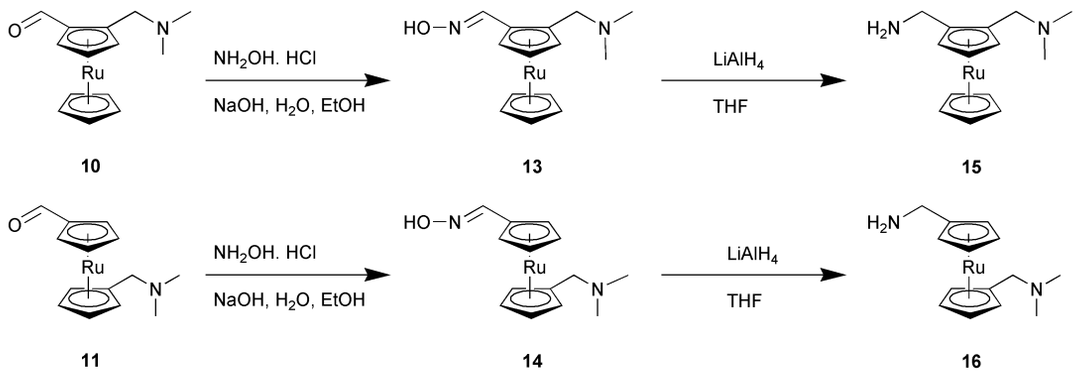
† The yellow complexes decomposed turning light brown and the ^{1}H NMR spectra contained broad reasonances due to paramagnetic impurities. The paramagnetic impurities could sometimes be removed by extraction into hexane and filtering. Unfortunately, this method could not be applied successfully to compound **12** which exhibited lower stability than the monoaldehyde complexes **10** and **11**.

‡ Complex **3** has been synthesised independently by Brocard and co-workers and the same problems with regioselectivity were encountered.[12b]

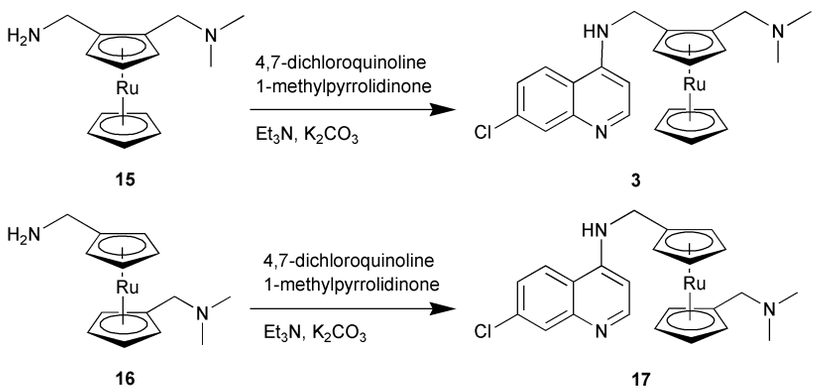
§ *n*-BuLi in hydrocarbon solvents exists predominantly as a hexamer.[14a]



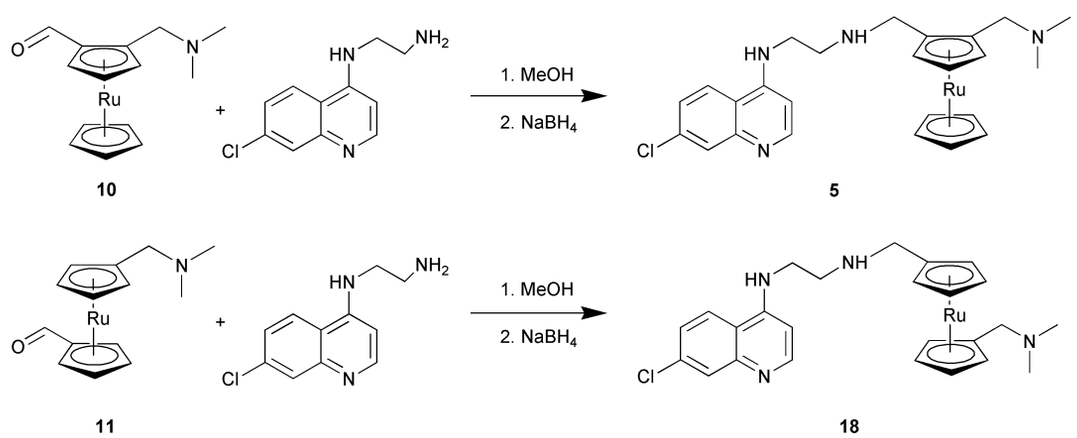
Scheme 4



Scheme 5



Scheme 6



Scheme 7

spacer or changing the position of the metallocene substituents leads to a drop in antimalarial activity against the K1 strain. This is consistent with the observation that a major factor in determining the antimalarial activity of 4-aminoquinolines is the distance between the amines in the side chain.[15] Altering the substitution pattern around the metallocene (compounds **17** and **18**), or including an aminoalkyl spacer (compounds **5** and **18**) increases the distance between the terminal nitrogen and the 4-aminoquinoline nitrogen. There is essentially no difference between the antimalarial activity of the ferrocene and ruthenocene analogues.

X-Ray crystallography

Racemic (7-chloroquinolin-4-yl)(2-dimethylaminomethylruthenocen-1-ylmethyl)amine 3. The molecular structure of **3** appears in Fig. 2 and confirms that the regioselective lithiation of dimethylaminomethylruthenocene with *t*-BuLi was *ortho*-directed since the ruthenocene is 1,2-disubstituted. The Ru

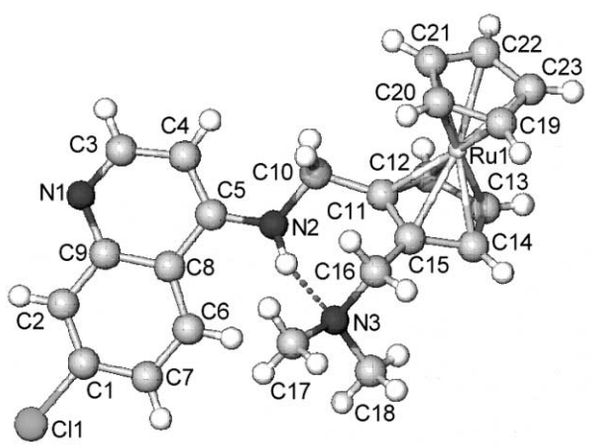


Fig. 2 Molecular structure and numbering scheme for complex **3**.

distances to the two Cp rings differ slightly (1.807(2) and 1.818(2) Å), with the shorter metal–Cp centroid distance being to the disubstituted cyclopentadienyl ring. The unsubstituted ring is disordered and has been refined with larger displacement ellipsoids. This could indicate that there is free rotation around the Cp–Ru bond with several energy minima, or that there is static disorder in the crystal. The orientation of the disubstituted ring is fixed within the crystal lattice since the dimethylaminomethyl and 4-aminomethylquinolyl moieties are large and result in an unsymmetrical fragment. The crystal structure also confirms the presence of the strong, intramolecular hydrogen bond which was observed by infrared spectroscopy (3668 cm^{-1}); this hydrogen bond is shown in Fig. 2 by the dashed bond. The N(3) of the dimethylamino group accepts a strong intramolecular hydrogen bond from the secondary amine with a N ··· H distance of 2.098(4) Å. There is also a weaker intermolecular hydrogen bond interaction between the quinoline N and an H atom belonging to the fused phenyl ring (N1 ··· H7′, 2.587(5) Å).

(7-Chloroquinolin-4-yl)(1′-dimethylaminomethylruthenocen-1-ylmethyl)amine hydrate 17·H_2O. The molecular structure of **17**, excluding the water molecule, is shown in Fig. 3. The 1,1′-substitution pattern elucidated by ^{1}H and ^{13}C NMR is confirmed. The ruthenocene has adopted an eclipsed conformation but unlike **3** the two Ru–Cp distances are the same (1.814(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 atoms, with N ··· H distances of 1.871(3) and 2.002(4) Å, respectively. The water molecule also accepts a hydrogen bond from the secondary amine with a N ··· H distance of 2.176(4) Å. Unlike the structure determined for compound **3** there are no intramolecular hydrogen bonds, due to both the presence of water and the large distance between potential donor and acceptor atoms. It is unlikely that the water is required to facilitate crystallisation but the inclusion of water results in hydrogen bonding, leading to a highly ordered structure (see Fig. 4).

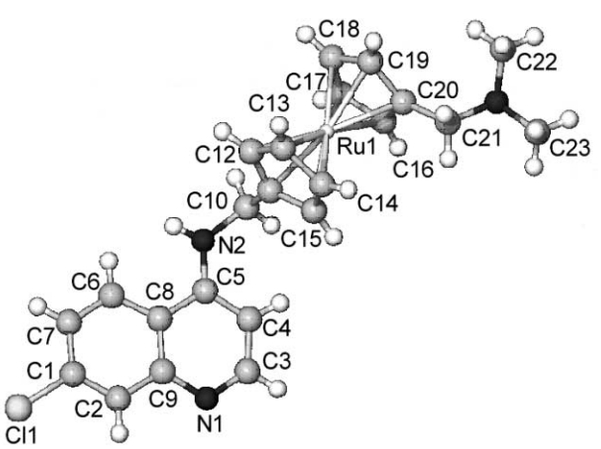


Fig. 3 Molecular structure and numbering scheme for complex **17**·H_2O, the water molecule is omitted.

Conclusions

Complexes **3**, **5**, **17** and **18** have been synthesised and the crystal structures determined for complexes **3** and **17**·H_2O. This work illustrates that whilst the chemistry of ferrocene and ruthenocene are similar, they differ in reactivity. Biological evaluation against both chloroquine sensitive and resistant strains of *P. falciparum* show that organometallic 4-aminoquinolines exhibit good potential as antimalarials, however, no significant difference between the ferrocenyl and ruthenocenyl analogues

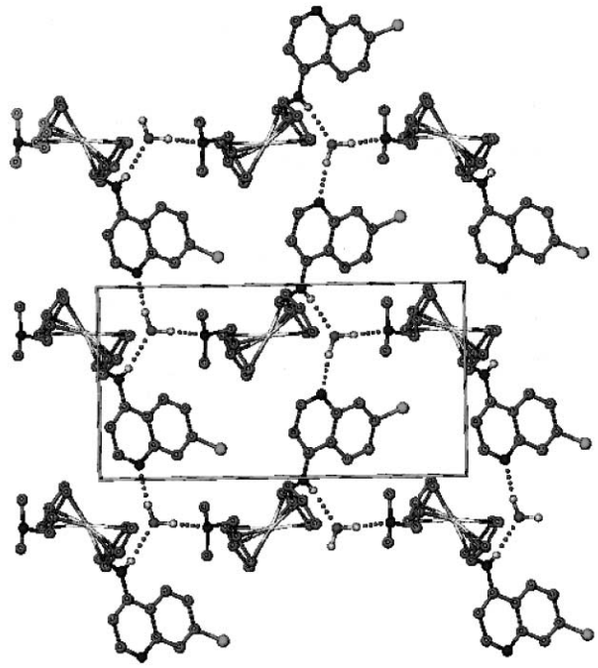


Fig. 4 The extended network of hydrogen bonds parallel to the [100] axis is shown for complex **17**·H_2O.

was observed. The activity against the chloroquine resistant strain of the parasite K1 diminished when the 1,1′-ruthenocenyl complexes **17** and **18** were employed indicating that the stereochemistry around the metal centre does have an effect on the antimalarial activity.

Experimental

The syntheses were performed using standard Schlenk techniques; ruthenocene,[16] *N,N,N′,N′*-tetramethyldiaminomethane,[17] dimethylaminomethylruthenocene[18] and *N*^{1}-(7-chloroquinolin-4-yl)ethane-1,2-diamine[19] were prepared according to literature methods. Diethyl ether and THF were 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/39mmHg). The concentration of alkyllithium reagents was determined by the Gilman double titration method prior to use.[20] 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) 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) 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 Boshoff of the mass spectrometry unit at the Cape Technikon. Elemental analyses were performed using a Carlo Erba EA1108 elemental analyser in the microanalytical laboratory of the University of Cape Town. Parasite viability was determined using the parasite lactate dehydrogenase assay according to Makler and Hinrichs.[21]

Synthesis

Dimethylaminomethylruthenocene 7 and bis(dimethylaminomethylruthenocene) 8. Ruthenocene (3.97 g, 17 mmol) and K*t*-BuO (250 mg, 2.13 mmol) was dissolved in THF (450 cm^3)

and cooled to −78 °C. *t*-BuLi (14.7 cm^3, 25.5 mmol, 1.7 M solution in pentane) was added over 10 min and stirred for a further 0.5 h maintaining a temperature below −70 °C. Eschenmoser's salt (4.81 g, 26 mmol) was then added *via* a Merlic addition funnel and the mixture was stirred for 12 h allowing the mixture to warm to 25 °C. The reaction was quenched with HCl (20 cm^3, 1 M), then the reaction was treated with NaOH until the aqueous phase was pH 10. The organic layer was removed and the aqueous layer washed with diethyl ether (2 × 75 cm^3), the organic portions were combined, dried over anhydrous Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude mixture was purified by column chromatography on deactivated alumina (Brockmann V). Hexane was used to elute the unreacted ruthenocene first (0.58 g, 15%), followed by hexane–diethyl ether; 70 : 30 to elute **7** (3.22 g, 66%) and finally diethyl ether–methanol 97 : 3 was used to elute **8** (1.02 g, 17%), recrystallisation from hexane at −15 °C yielded cream needles of **7** and **8**. Compound **7** mp 38–39 °C (lit.[18a] 39–42 °C) (Found: C, 54.18; H, 5.82; N, 4.78. Calc. for $RuC_{13}H_{17}N$ C, 54.15; H, 5.94; N, 4.86%); $\tilde{\nu}_{max}/cm^{-1}$ 3083m, 2966m, 2934m, 2819m, 2777m, 1467m, 1431w, 1407w, 1321w, 1303w, 1264m, 1218w, 1157w, 1120w, 1090w, 1023w, 994m, 914w, 841m, 816m, 800w, 743w, 504w (KBr); δ_H(400 MHz; solvent $CDCl_3$) 4.55 (2 H, m), 4.47 (5 H, s, Cp), 4.45 (2 H, m), 3.05 (2 H, s), 2.17 (6 H, s); δ_C(100 MHz; solvent $CDCl_3$) 87.1 (Cp^{IV}), 72.4 (Cp–H), 70.5 (Cp′–H), 70.2 (Cp–H), 59.0 (NCH_2), 45.5 (NMe_2); *m*/*z* (FAB) 288 (M^+, 11%), 245 (100, M − Me_2N). Compound **8** mp 65–67 °C (Found: C, 56.11; H, 6.81; N, 7.95. Calc. for $RuC_{16}H_{24}N_2$ C, 55.63 H, 7.00; N, 8.11%); $\tilde{\nu}_{max}/cm^{-1}$ 3093m, 3061m, 2986m, 2959m, 2937m, 2852m, 2816m, 2772m, 1699w (br), 1450m, 1351, 1262m, 1230m, 1171w, 1134w, 1097m, 1064w, 1038m, 1019m, 957w, 930m, 919w, 839w, 815w (KBr); δ_H(400 MHz; solvent $CDCl_3$) 4.47 (4 H, m, Cp–H), 4.40 (4 H, m, Cp–H), 2.98 (4 H, s, CH_2N), 2.14 (12 H, s, (NMe_2); δ_C(100 MHz; solvent $CDCl_3$) 86.8 (Cp^{IV}), 72.9 (Cp–H), 70.8 (Cp–H), 58.9 (NCH_2), 44.8 (NMe_2), *m*/*z* (FAB) Found 347.10612 (M + H — $RuC_{16}H_{25}N_2$ requires 347.108996) 302 (M − NMe_2, 55%), 259 (M − $2NMe_2$, 100%).

Racemic 2-dimethylaminomethylruthenocene carboxaldehyde 10. *t*-BuLi (5.57 cm^3, 7.8 mmol, 1.4 M solution in pentane) was added to a solution of **7** (1.50 g, 5.2 mmol) in diethyl ether (150 cm^3) at 25 °C and stirred for 0.5 h. To this mixture *N,N*-dimethylformamide (4 cm^3) was added and stirred for a further 1 h at 25 °C. Then water (35 cm^3) was added, the organic layer was removed and the aqueous layer washed with diethyl ether (2 × 75 cm^3). The organic portions were combined, dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo.* Only the title product was isolated by chromatography on silica gel eluting with diethyl ether–hexane–triethylamine 70 : 20 : 10 (R_f **7** 0.68, **10** 0.35, **11** 0.11, **12** 0.0). The crude product was extracted into hexane, filtered and the solvent removed *in vacuo* to yield a yellow oil **10** (1.164 g, 70%) (Found: C, 53.27; H, 5.63; N, 4.49. $RuC_{13}H_{17}NO$ requires C, 53.16; H, 5.42; N, 4.43%); $\tilde{\nu}_{max}/cm^{-1}$ 3096w (br), 2939m, 2854m, 2816m (CHO), 1676s (C=O), 1442m (NMe_2), 1408w, 1350w, 1286w, 1248w, 1172w, 1100w, 1031w, 813w (neat NaCl); δ_H(400 MHz; solvent $CDCl_3$) 9.86 (1 H, s, CHO), 5.03 (1 H, m, Cp), 4.87 (1 H, m, Cp), 4.77 (1 H, m, Cp), 4.58 (5 H, s, Cp′), 3.64 (1 H, d, ^2J(HH) 13 Hz), 3.12 (1 H, d, ^2J(HH) 13 Hz), 2.15 (6 H, s, NMe_2); δ_C(75 MHz; solvent $CDCl_3$) 189.8 (CHO), 89.0, 83.2 (Cp^{IV}), 77.1, 73.0, 72.4 (Cp–H), 71.8 (Cp′–H), 56.4, 44.7; *m*/*z* (EI) Found 317.03362 (M^+ — $RuC_{14}H_{17}ON$ requires 317.03536), 302 (M − Me, 75%), 288 (M − CHO, 32), 245 (M − NMe_2, CHO 100), 166 (Ru–Cp, 80).

Racemic 2-dimethylaminomethylruthenocene carboxaldehyde oxime 13. A solution of sodium hydroxide (0.48 g, 12.2 mmol) in water (3 cm^3) was added to a stirred mixture of 2-dimethylaminomethylruthenocene carboxaldehyde **10** (1.04 g, 3.29 mmol) and hydroxylamine hydrochloride (0.42 g, 6 mmol) in ethanol (25 cm^3) at room temperature. The resulting mixture was heated under reflux for 2 h and allowed to cool. Water (1 cm^3) was added to the reaction mixture which was then 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 **13** as a cream semi-solid (1.04 g, 96%), $\tilde{\nu}_{max}/cm^{-1}$ 3208w (br –OH), 3098m, 2950m, 2858m, 2821m, 2775m, 1626m (C=N), 1465m (NMe_2), 1253w, 1173w, 1100w, 1034w, 1000w, 953m, 810m, 731w (NaCl neat); δ_H(400 MHz; solvent $CDCl_3$) 7.87 (1 H, s), 4.91 (1 H, m), 4.76 (1 H, m), 4.62 (1 H, m), 4.50 (5 H, s), 3.65 (1 H, d, ^2J(HH) 13 Hz), 3.21 (1 H, d, ^2J(HH) 13 Hz), 2.28 (6 H, s); δ_C(100 MHz; solvent $CDCl_3$) 147.0 (CH=NOH), 85.1, 82.0 (Cp^{IV}), 70.2, 71.0, 72.15 (Cp–H), 73.8 (Cp′–H), 56.8 (CH_2N), 44.5 (Me_2N); *m*/*z* (FAB) Found 333.055231 (M^+ — $RuC_{14}N_{19}N_2O$ requires 333.05410), 315 (M − OH, 8%), 288 (M − CHNOH 100), 270 (M − NMe_2 − OH, 35), 245 (M − NMe_2 − CHNOH, 9).

Racemic 2-(dimethylamino)methylruthenocen-1-ylmethylamine 15. A mixture of $LiAlH_4$ (0.21 g, 5.7 mmol) and 2-dimethylaminomethylruthenocene carboxaldehyde oxime **13** (0.95 g, 2.85 mmol) in THF (75 cm^3) was heated under reflux for 6 h. The cooled solution was diluted with diethyl ether (25 cm^3), washed with brine (2 × 10 cm^3), dried over anhydrous K_2CO_3, filtered and the solvent removed *in vacuo* to yield a yellow oil (813 mg, 90%), $\tilde{\nu}_{max}/cm^{-1}$ 3354m (br), 3094m, 2938m, 2853m, 2814m, 2769m, 1598w (br), 1458m, 1409w, 1351m, 1283w, 1257m, 1171m, 1099m, 1030m, 1009m, 841m, 805m (NaCl neat); δ_H(400 MHz; solvent $CDCl_3$) 4.54 (1 H, m), 4.53 (1 H, m), 4.45 (5 H, s), 4.38 (1 H, m), 3.45 (1 H, d, ^2J(HH) 14 Hz), 3.37 (1 H, d, ^2J(HH) 13 Hz), 3.27 (1 H, d, ^2J(HH) 14 Hz), 2.76 (1 H, d, ^2J(HH) 13 Hz), 2.15 (6 H, s); δ_C(100 MHz; solvent $CDCl_3$) 95.1, 87.3 (Cp^{IV}), 73.4, 71.1, 70.9, 68.6 (Cp–H), 58.0 (CH_2), 45.2 (NMe_2), 40.5 (CH_2). (FAB) Found 318.06605 (M + H — $RuC_{14}H_{20}N_2$ requires 318.06700), 301 (M − NH_2, 26%), 288 (M − CH_2NH_2, 24), 273 (M − NMe_2, 100), 244 (M − CH_2NH_2 − Me, 38), 179 (M − CH_2NH_2 − NMe_2, 20).

Racemic (7-chloroquinolin-4-yl)(2-dimethylaminomethylruthenocen-1-ylmethyl)amine 3. A mixture of **15** (0.758 g, 2.4 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 45 : 50 : 5 (R_f 4,7-dichloroquinoline 0.76, **3** 0.28). Recrystallisation from ethyl acetate and hexane gave cream needles (509 mg, 44%), mp 214–215 °C (Found: C, 58.02; H, 4.62; N, 8.58. $RuC_{23}H_{24}N_3Cl$ requires C, 57.68; H, 5.05; N, 8.77%); $\tilde{\nu}_{max}/cm^{-1}$ 3668w (br) (shifts to 3683 when diluted, intramolecular H-bond), 3242 (br) (intermolecular H-bond), 3100w (br), 3048w, 2948w, 2858w, 2825w, 2783w, 1734w, 1614m (7-chloroquinoline), 1580s (7-chloroquinoline), 1544m (7-chloroquinoline), 1460m (NMe_2), 1446m, 1426m, 1381w, 1361w, 1348s, 1329w (*ν* C–N aromatic), 1271m, 1269vs, 1262vs, 1222w, 1197w, 1169w, 1132w, 1098w (ruthenocene), 1079w, 1037w, 1006w, 906w, 883w (ruthenocene), 852w, 844w, 810w (CH_2Cl_2); δ_H(400 MHz; solvent $CDCl_3$) 8.50 (1 H, d, ^3J(HH) 5 Hz), 7.92 (1 H, d, ^3J(HH) 2 Hz), 7.64 (1 H, ^3J(HH) 9 Hz), 7.50 (1 H, br s, NH), 7.29 (1 H, dd, ^3J(HH) 9 Hz, ^4J(HH) 2 Hz), 6.41 (1 H, d, ^3J(HH) 5 Hz), 4.71 (1 H, m), 4.60 (1 H, m), 4.54 (5 H, m), 4.44 (1 H, m), 4.14 (1 H, d, ^2J(HH) 13 Hz), 4.01 (1 H, d, ^2J(HH) 14 Hz), 3.57 (1 H, d, ^2J(HH) 13 Hz), 2.77 (1 H, d, ^2J(HH) 13 Hz), 2.36 (6 H, s); δ_C(100 MHz, solvent $CDCl_3$) 152.1 (CH), 150.2 (C^{IV}), 149.4 (C^{IV}), 134.6 (C^{IV}), 128.5 (CH), 124.8 (CH), 122.0 (CH), 117.9 (C^{IV}), 98.9 (CH), 87.9, 87.7 (Cp^{IV}), 72.9, 73.6, 68.7 (Cp–H), 71.4 (Cp′–H), 57.9 (CH_2), 45.0

(NMe_2), 42.5 (CH_2), *m/z* (FAB) Found 480.07811 (M + H — $RuC_{23}H_{25}N_3Cl$ requires 480.07805), 435 (M − NMe_2, 88%), 302 (M − $C_9H_7ClN_2$, 40), 259 (100).

Racemic *N*-(7-chloroquinolin-4-yl)-*N′*-(2-dimethylaminomethylruthenocen-1-ylmethyl)ethane-1,2-diamine 5. Compound **10** (1.10 g, 3.46 mmol) and *N*[1]-(7-chloroquinolin-4-yl)ethane-1,2-diamine (776 mg, 3.46 mmol) was dissolved in methanol (30 cm^3) and stirred for 16 h. Sodium borohydride (0.26 g, 6.92 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 (150 cm^3) and washed with brine (3 × 50 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 the title product as a glassy white solid. Recrystallisation from acetonitrile and diethyl ether at −15 °C yielded white rhombic crystals (1.4 g, 77%), mp 126–127 °C (Found: C, 57.54; H, 5.33; N, 10.62. $RuC_{25}H_{29}N_4Cl$ requires C, 57.52; H, 5.60; N, 10.73%); $\tilde{\nu}_{max}/cm^{-1}$ 3656vw (br) (intramolecular H-bond), 3405w (br) (intermolecular H-bond), 3088w (br), 3058m, 2977w, 2856m, 2820m, 2774w, 1614m (7-chloroquinoline), 1582s (7-chloroquinoline), 1526m (7-chloroquinoline), 1472m (NMe), 1448m (*δ*-asym (NMe)), 1370w, 1329w, 1274vs, 1268vs, 1266vs, 1261vs, 1257vs, 1253vs, 1239w, 1168w, 1156w, 1137w, 1099w, 1081w, 888w, 841w, 813w (CH_2Cl_2); δ_H(400 MHz; solvent $CDCl_3$) 8.48 (1 H, d, ^3J(HH) 5 Hz), 7.92–7.94 (2 H, m), 7.35 (1 H, dd, ^3J(HH) 9 Hz, ^4J(HH) 2 Hz), 6.51 (1 H, br s, NH), 6.33 (1 H, d, ^3J(HH) 5 Hz), 4.62 (1 H, m), 4.55 (1 H, m) 4.46 (5 H, s), 4.43 (1 H, m), 3.76 (1 H, d ^2J(HH) 13 Hz), 3.51 (1 H, d, ^2J(HH) 13 Hz), 3.49–3.65 (2 H, m), 3.33 (1 H, d, ^2J(HH) 13 Hz), 2.88–3.04 (2 H, m), 2.68 (1 H, d, ^2J(HH) 13 Hz), 2.05 (6 H, s); δ_C(100 MHz; solvent $CDCl_3$) 151.9 (CH) 149.9 (C^{IV}), 149.2 (C^{IV}), 135.0 (C^{IV}), 128.5 (CH), 125.3 (CH), 122.1 (CH), 117.5 (C^{IV}), 98.6 (CH), 87.4, 87.2 (Cp^{IV}), 73.7, 72.8, (Cp–H), 71.3 (Cp′–H), 68.9 (Cp–H), 57.9, 46.8, 45.8, (CH_2), 44.6 (–NMe_2), 41.5 (–CH_2N); *m/z* (FAB) Found 523.1202 (M + H — $RuC_{25}H_{31}N_4Cl$ requires 523.12016), 478 (M − NMe_2, 17%), 303 (14), 286 (17), 259 (46), 150 (100).

1′-(*N*,*N*-Dimethylamino)methylruthenocene carboxaldehyde 11. *n*-BuLi (4.5 cm^3, 7.26 mmol, 1.6 M solution in hexane) was added to a solution of **7** (1.9 g, 6.6 mmol) in pentane (150 cm^3) at 25 °C and stirred for 6 h. To this mixture *N*,*N*-dimethylformamide (4 cm^3) was added and stirred for a further 1 h at 25 °C. Water (35 cm^3) was added, the organic layer was removed and the aqueous phase was washed with diethyl ether (2 × 75 cm^3). The organic fractions were combined, dried over Na_2SO_4, filtered and the solvent removed *in vacuo.* The title product was purified using silica gel chromatography eluting with diethyl ether–hexane–triethylamine 70 : 20 : 10. The solvent was removed *in vacuo* and the product was crystallised from hexane at −15 °C as yellow needles¶ (980 mg, 47%), mp 49–50 °C (Found: C, 53.18; H, 5.28; N, 4.39. $RuC_{14}H_{17}NO$ requires C, 53.16; H, 5.42; N, 4.43%); $\tilde{\nu}_{max}/cm^{-1}$ 3092m, 2939m, 2856m, 2817m, 2771m, 1682vs (CHO), 1445s (NMe_2), 1368m, 1242m, 1170w, 1038w, 818w, 738w (neat NaCl); δ_H(400 MHz, solvent $CDCl_3$) 9.57 (1 H, s), 4.95 (2 H, m), 4.73 (2 H, m), 2.59 (2 H, m), 4.49 (2 H, m), 2.88 (2 H, s), 2.10 (6 H, s); δ_C(100 MHz; solvent $CDCl_3$) 189.7 (CHO), 89.0 (Cp^{IV}), 84.7, 74.7, 74.2, 72.2, 71.3, (Cp–H's), 58.1 (–CH_2N), 44.7 (–NMe_2), *m/z* (FAB) M + H 318 (M^+ 35%), 273 (100, M − NMe_2), 245 (M − NMe_2 − CHO, 9).

1′-Dimethylaminomethylruthenocene carboxaldehyde oxime 14. This compound was synthesised from **11** using the same procedure employed for **13** as a light yellow solid (96%), mp 104–105 °C; $\tilde{\nu}_{max}/cm^{-1}$ 3751w (br), 3103m, 3088m, 2976m, 2946m, 2849w, 2775w, 1702m, 1635m, 1560m, 1463m, 1359w, 1232w, 1172w, 1135w (KBr); δ_H(400 MHz, solvent $CDCl_3$) 7.72 (1 H, s), 4.86 (2 H, m), 4.65 (2 H, m), 4.59 (2 H, m), 4.51 (2 H, m), 3.10 (2 H, s), 2.22 (6 H, s); δ_C(100 MHz, solvent $CDCl_3$) 86.8, 81.6 (Cp), 44.3 (Me_2N), 58.2 (CH_2N), 69.9, 71.5, 71.9, 73.8 (Cp–H); *m/z* (EI) Found 332.04663 (M — $RuC_{14}H_{18}ON_2$ requires 332.04626), 299 (M − Me − OH − H, 18%), 270 (M − NMe_2 − NOH − H, 100).

1′-(Dimethylamino)methylruthenocen-1-ylmethylamine 16. This compound was synthesised from **14** using the same procedure employed for **15** and obtained as a yellow oil (92%), $\tilde{\nu}_{max}/cm^{-1}$ 3358w (br) (H-bond), 3088m, 2936s, 2854s, 2816s, 2771s, 1984w (br), 1886m, 1585m (br), 1456m, 1398m, 1381w, 1347w, 1258w, 1229w, 1170w, 1037s, 1019m, 841m, 807m (NaCl neat); δ_H(400 MHz; solvent $CDCl_3$) 4.56 (2 H, m), 4.52 (2 H, m), 4.48 (2 H, m), 4.42 (2 H, m), 3.27 (2 H, s), 3.05 (2 H, s), 2.18 (6 H, s), δ_C(100 MHz; solvent $CDCl_3$) 87.3 (Cp^{IV}), 72.9 70.7, 70.6, 70.5, (Cp–H), 59.0 (CH_2N), 44.7 (Me_2N–), 40.8 (CH_2NH_2); (FAB) Found 318.06508 (M + H — $RuC_{14}H_{20}N_2$ requires 318.06700), 301 (M − NH_2, 23%), 288 (M − CH_2NH_2, 26), 273 (M − Me_2N, 100), 244 (M − CH_2NH_2 − Me, 34), 179 (M − CH_2NH_2 − NMe_2, 27), 167 (Cp–Ru).

(7-Chloroquinolin-4-yl)(1′-dimethylaminomethylruthenocen-1-ylmethyl)amine 17. This compound was prepared from **16** using the same procedure employed for the synthesis of complex **3**. Purification was performed by column chromatography on silica gel eluting with hexane–ethyl acetate–triethylamine 35 : 60 : 5 (R_f 4,7-dichloroquinoline, **17** 0.12). Crystallisation from ethyl acetate and hexane yielded the product as cream needles (39%), mp 94–95 °C (Found: C, 57.80; H, 4.84; N, 8.58. $RuC_{23}H_{24}N_3Cl$ requires C, 57.68; H, 5.05; N, 8.77%); $\tilde{\nu}_{max}/cm^{-1}$ 3928 vw (br), 3660w (br) (NH intramolecular H-bond), 3444m (sh), 3388w (br) (NH intermolecular H-bond), 3089w (br), 3044w, 2946m, 2861m, 2825m, 2771w, 1609w (7-chloroquinoline), 1582s, 1528s, 1477s, 1450s, 1370m, 1330s, 1274vs, 1276s, 1274vs, 1272vs, 1266s, 1265s (sh), 1263vs, 1259vs, 1257vs, 1255s, 1253m, 1236m, 1231, 1169w, 1137w, 1081w, 1040w, 1024w, 922w, 884w; 813w (CH_2Cl_2); δ_H (300 MHz; solvent $CDCl_3$) 8.53 (1 H, d, ^3J(HH) 5 Hz), 7.96 (1 H, d, ^4J(HH) 2 Hz), 7.65 (1 H, d, ^3J(HH) 9 Hz), 7.38 (1 H, dd, ^3J(HH) 9 Hz, ^4J(HH) 2 Hz), 6.41 (1 H, d, ^3J(HH) 5 Hz), 5.20 (1 H, br s, NH), 4.69 (4 H, m), 4.58 (2 H, m), 4.58 (2 H, m), 3.89 (2 H, d, ^3J(HH) 6 Hz), 3.09 (2 H, s), 2.19 (6 H, s); δ_C (75 MHz; solvent $CDCl_3$) 152.1 (CH), 149.2 (CH) 149.1 (C^{IV}), 134.9 (C^{IV}), 128.9 (CH), 125.4 (CH), 120.0 (CH), 117.1 (C^{IV}), 99.2 (CH), 89.7, 88.0 (Cp^{IV}), 72.9, 71.2, 71.0, 70.8 (Cp–H), 58.7 (CH_2), 44.7 (NMe_2), 41.2 (CH_2), *m/z* (EI) Found 479.07157 (M — $RuC_{23}H_{25}N_3Cl$ requires 479.07022), 433 (100%), 301 (47), 288 (28), 259 (55), 179 (21).

***N*-(7-Chloroquinolin-4-yl)-*N′*-(1′-dimethylaminomethylruthenocen-1-ylmethyl)ethane-1,2-diamine 18.** This compound was synthesised from **11** using the same procedure employed for **5**, and isolated as a cream coloured oil (65%) (Found: C, 57.81; H, 6.05; N, 10.61. $RuC_{25}H_{29}N_4Cl$ requires C, 57.52; H, 5.60; N, 10.73%); $\tilde{\nu}_{max}/cm^{-1}$ 3928vw (br), 3660vw (br) (NH, intramolecular H-bond), 3388w (br) (NH intermolecular H-bond), 2946m, 2861m, 2821m, 2771w, 1609s (7-chloroquinoline), 1582s (7-chloroquinoline), 1528s, 1477s, 1450s (*δ*-asym (NMe)), 1370m, 1330s (*ν* C–N aromatic), 1092, 1276s, 1274vs, 1272vs, 1266s, 1265s, 1263vs, 1259vs, 1257vs, 1255sd, 1253m, 1236m, 1231m, 1168w, 1137w, 1081w, 1040w, 1024w, 1016w, 922w, 884w, 842w, 813w (CH_2Cl_2); δ_H(400 MHz; solvent $CDCl_3$) 8.51 (1 H, d, ^3J(HH) 5 Hz), 7.94 (1 H, d, ^4J(HH) 2 Hz), 7.72 (1 H, d, ^3J(HH) 9 Hz), 7.34 (1 H, dd, ^3J(HH) 9 Hz, ^4J(HH) 2 Hz), 6.38 (1 H, d, ^3J(HH) 5 Hz), 5.93 (1 H, br s, NH), 4.56 (4 H, m), 4.46 (4 H, m), 3.35 (2 H, s), 3.31–3.34 (2 H, m), 3.06 (2 H, s), 3.04–

¶ If trace quantities of complex **10** are present these are removed by this selective crystallisation of compound **11**.

Table 2 Crystal data and structure refinement for **3** and **17**·H_2O

	3	**17**·H_2O
Empirical formula	$C_{23}H_{24}ClN_3Ru$	$C_{23}H_{24}ClN_3Ru.H_2O$
Formula weight	478.97	496.98
Temperature/K	173(2)	293(2)
Wavelength/Å	0.71073	0.71073
Space group	$P2_1/n$	$C2/c$
Crystal system	Monoclinic	Monoclinic
a/Å	7.8322(1)	26.463(5)
b/Å	12.6176(1)	9.2209(18)
c/Å	21.1164(2)	21.907(4)
β/°	92.526(1)	126.42(3)
Volume/Å^3	2084.77(4)	4301.5(15)
Z	4	8
Absorption coefficient/mm^{-1}	0.893	0.872
Reflections collected	32858	12057
Independent reflections	4768 [R(int) = 0.0223]	4910 [R(int) = 0.0214]
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0279, w$R2$ = 0.0674	$R1$ = 0.0253, w$R2$ = 0.0605
R indices (all data)	$R1$ = 0.0357, w$R2$ = 0.0715	$R1$ = 0.0385, w$R2$ = 0.0651

3.08 (2 H, m), 2.18 (6 H, s); δ_C(100 MHz; solvent $CDCl_3$) 152.2 (CH), 150.1 (C^{IV}), 149.3 (C^{IV}), 135.0 (C^{IV}), 128.9 (CH), 125.4 (C–H), 121.5 (CH), 117.6 (C^{IV}), 99.3 (CH), 87.1, 87.1 (Cp^{IV}), 73.0, 71.4, 70.9, 70.8 (Cp–H), 58.9, 47.8, 47.2 (CH_2), 44.7 (NMe_2), 42.2 (CH_2); *m*/*z* (FAB) Found 522.11309 (M + H — $RuC_{25}H_{31}N_4Cl$ requires 522.11242), 477 (M − NMe_2 − H, 30), 301 (M − $C_9H_7ClN_2$, 80), 286 (89), 259 (100).

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.[22] 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 complexes **3** and **17** were obtained by slow diffusion of hexane into an ethyl acetate solution of **3** or **17**. X-Ray diffraction data for compounds **3** and **17** 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.[23] The data were integrated, scaled and reduced with DENZO-SMN.[24] The structures were solved and refined with SHELX97.[25] 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.[26] The program PLATON[27] was used to prepare additional material for publication. A selection of crystal and refinement data is given in Table 2.

CCDC reference numbers 187087 and 187088.

See http://www.rsc.org/suppdata/dt/b2/b205432a/ for crystallographic data in CIF or other electronic format.

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