Dalton Transactions

PAPER

View Article Online
View Journal | View Issue

Cite this: *Dalton Trans.*, 2016, **45**, 3905

Pentamethylcyclopentadienyl-rhodium and iridium complexes containing (N^N and N^O) bound chloroquine analogue ligands: synthesis, characterization and antimalarial properties†

Erik Ekengard,‡[a] Kamlesh Kumar,‡[a] Thibault Fogeron,[a] Carmen de Kock,[b] Peter J. Smith,[b] Matti Haukka,[c] Magda Monari[d] and Ebbe Nordlander*[a]

Received 24th September 2015,
Accepted 23rd December 2015

DOI: 10.1039/c5dt03739e

www.rsc.org/dalton

The synthesis and characterization of twenty new pentamethylcyclopentadienyl-rhodium and iridium complexes containing N^N and N^O-chelating chloroquine analogue ligands are described. The *in vitro* antimalarial activity of the new ligands as well as the complexes was evaluated against the chloroquine sensitive (CQS) NF54 and the chloroquine resistant (CQR) Dd2 strains of *Plasmodium falciparum*. The antimalarial activity was found to be good to moderate; although all complexes are less active than artesunate, some of the ligands and complexes showed better activity than chloroquine (CQ). In particular, rhodium complexes were found to be considerably more active than iridium complexes against the CQS NF54 strain. Salicylaldimine Schiff base ligands having electron-withdrawing groups (F, Cl, Br, I and NO_2) in *para* position of the salicyl moiety and their rhodium complexes showed good antiplasmodial activity against both the CQS-NF54 and the CQR-Dd2 strains. The crystal structures of (η^5-pentamethylcyclopentadienyl){N^1-(7-chloroquinolin-4-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine} chlororhodium(III) chloride and (η^5-pentamethylcyclopentadienyl){(4-chloro-2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl)phenolate)}chlororhodium(III) chloride are reported. The crystallization of the amino-pyridyl complex (η^5-pentamethylcyclopentadienyl){(N^1-(7-chloroquinolin-4-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine)}chloroiridium(III) chloride in acetone resulted in the formation of the imino-pyridyl derivative (η^5-pentamethylcyclopentadienyl){(N1-(7-chloroquinolin-4-yl)-N2-(pyridin-2-ylmethylene)ethane-1,2-diamine)}chloroiridium(III) chloride, the crystal structure of which is also reported.

Introduction

Malaria is a parasitic disease and constitutes a serious societal problem in many countries in the tropical and sub-tropical regions of Africa, Asia and Latin America. There are around 200 million cases of malaria each year, and malaria leads to more than half a million deaths every year worldwide.[1] The causative agents for malaria are five *Plasmodium* species, *viz.* *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Out of these five species, *P. falciparum* is the most lethal and responsible for most of the deaths from malaria.[2]

Quinoline-based drugs, in particular chloroquine (CQ, structure a, Fig. 1), have been widely used for the treatment of malaria,[3] but resistance to chloroquine and other antimalarial agents has become a major obstacle in the efforts to control malaria.[4] It has been postulated that 4-aminoquinoline-based antimalarial agents bind with haematin, which is formed by the degradation of hemoglobin in the food vacuole of the parasite and is toxic to the parasite, and prevent detoxification of haematin. This process inhibits the formation of haemozoin (β-haematin; malaria pigment) in the food vacuole of the parasite, thus causing a build-up of haematin that eventually leads to the death of parasites by haematin poisoning.[5–12] Therefore, inhibition of haemozoin formation remains an excellent target for new antimalarial drug discovery.

After the discovery of cisplatin (*cis*-[$(NH_3)_2PtCl_2$]), an anticancer agent commonly used for the treatment of testicular and ovarian cancer,[13,14] in the 1960s a wide variety of metal

[a]*Inorganic Chemistry Research Group, Chemical Physics, Center for Chemistry and Chemical Engineering, Lund University, Box 124, SE-221 00 Lund, Sweden. E-mail: Ebbe.Nordlander@chemphys.lu.se*
[b]*Division of Pharmacology, Department of Medicine, University of Cape Town Medical School, Observatory 7925, South Africa*
[c]*Department of Chemistry, University of Jyväskylä, P.O. Box-35, Jyväskylä, FI-40014, Finland*
[d]*Dipartimento di Chimica "G. Ciamician", Alma Mater Studiorum Università di Bologna, Via Selmi 2, 40126 Bologna, Italy*
†CCDC 1426906–1426908. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c5dt03739e
‡These authors contributed equally to the paper.

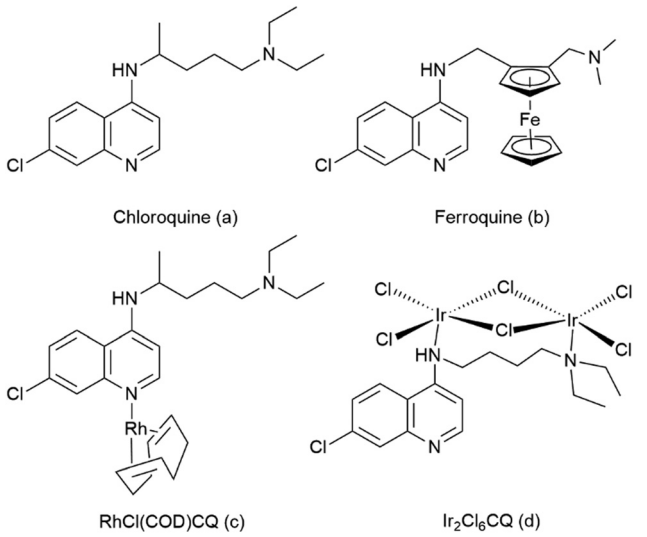


Fig. 1 Structures of chloroquine, ferroquine, RhCl(COD)CQ and Ir_2Cl_6CQ.

complexes have been synthesized and tested for a number of medical purposes. During the last three decades there has been increased interest in expanding the pharmaceutical potential of coordination compounds, especially organometallic complexes. This has been achieved by the incorporation of organometallic moieties into a large number of bioactive compounds. The focus of this research has mainly been the development of organometallic anticancer compounds, but other classes of bioactive organometallics, *e.g.* antibacterial and antimalarial, have also been investigated.[15,16]

A large number of 7-chloro-4-aminoquinoline derivatives have been evaluated in the search for chloroquine analogues that overcome the widespread chloroquine resistance developed by malaria parasites. In 1997, Biot *et al.* synthesized ferroquine (FQ, structure b, Fig. 1), a chloroquine analogue with a ferrocene moiety in the side chain that shows no cross resistance with chloroquine.[17–19] Ferroquine has entered phase IIb clinical trials in association with artesunate.

Other attempts to create metal-containing chloroquine derivatives that overcome chloroquine resistance include ruthenocene compounds and half sandwich compounds of chromium and rhenium, as well as ruthenium, rhodium, iridium and gold coordination complexes.[5] Sanchez-Delgado *et al.* have shown that Ru^{II} coordination complexes with CQ enhance the antimalarial activity against resistant parasite strains as compared to free chloroquine.[20,21] Hence, there is sustained interest to synthesize new metal conjugates of chloroquine with enhanced antimalarial activity. We have previously investigated ruthenium- and osmium cymene complexes with N^O- and N^N-coordinating chloroquine analogue ligands.[22,23] The initial results were promising and indicated that Ru cymene complexes of the N^O-coordinating ligand were more active than the free ligand, while further studies and expanding the ligand scope indicated lowered antimalarial activity *in vitro* on coordinating the Ru cymene moiety to both the N^N- and N^O-coordinating ligands. Furthermore, we observed that the heavier osmium congeners of a subset of these complexes exhibited a further reduction in anti-plasmodial activity.[22,23]

The square planar Rh(I) complex [RhCl(COD)CQ] (structure c, Fig. 1) has been found to exhibit antimalarial activity similar to chloroquine diphosphate (CQDP)[20] while the iridium chloroquine conjugate, $[Ir_2Cl_6(CQ)]$ (structure d, Fig. 1) shows only moderate activity against *P. bergei in vitro*.[24] The rhodium(III) and iridium(III) pentamethylcyclopentadienyl (Cp*) moieties are isoelectric to the ruthenium(II) and osmium(II) arene moieties and have similar coordination chemistry. The Cp* complexes of Rh and Ir are generally more stable than the corresponding cyclopentadienyl (Cp) complexes, a fact that is normally attributed to a combination of steric shielding of the metal center and the greater electron density in the Cp* ring compared to unsubstituted Cp. The large lipophilic Cp* also ought to increase the overall lipophilicity of the potential antimalarial complex, something that is generally believed to be beneficial to overcome chloroquine resistance.[25–27] Smith and coworkers have recently presented a number of Rh and Ir Cp* complexes with anti-malarial properties, based on both quinoline containing ligands and ligands not bearing a quinoline moiety.[28–32] In general, these complexes were found to be less active than the corresponding ruthenium-arene complexes, but in several cases it is evident that the RhCp* moiety is preferable over the Ru-arene moiety for anti-plasmodial activity.

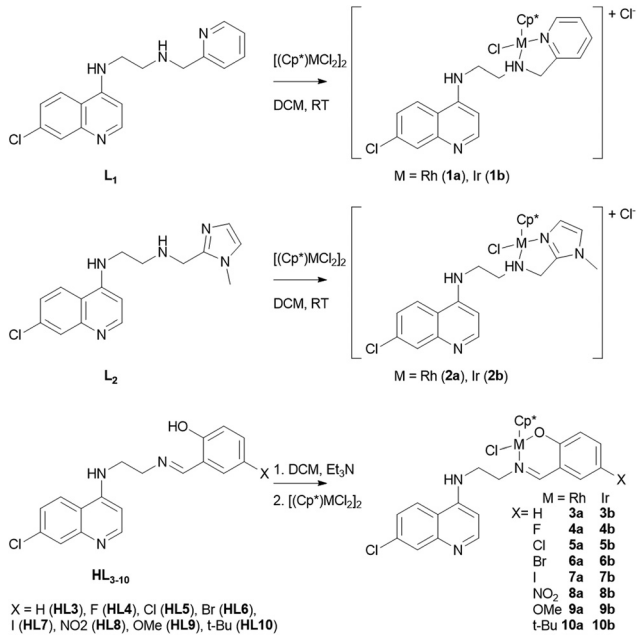
We have thus decided to investigate the anti-malarial properties of Rh- and Ir-Cp* complexes of the same family of chloroquine-mimicking ligands used in the studies with ruthenium and osmium. In this study, we have synthesized and characterized twenty new rhodium and iridium-Cp* complexes containing (N^N and N^O)-bound chloroquine analogue ligands. These complexes have been examined against the chloroquine sensitive (CQS) NF54 and the chloroquine resistant (CQR) Dd2 strains of *P. falciparum*.

Results and discussion

Synthesis and characterization

The ligands, **L1**, **L2** and **HL3–10** were synthesized according to a recently reported procedure.[23] Reaction of **L1** or **L2** with the chloro-bridged dimeric rhodium complex $[Cp^*RhCl_2]_2$ or the structurally analogous iridium complex $[Cp^*IrCl_2]_2$ in 2 : 1 molar ratio in dichloromethane at room temperature gave the complexes [RhCp*(L1)Cl]Cl (**1a**), [IrCp*(L1)Cl]Cl (**1b**), [RhCp*(L2)Cl]Cl (**2a**) and [IrCp*(L2)Cl]Cl (**2b**) in good yields. The rhodium complexes **3a–10a** and their iridium analogues **3b–10b** were synthesized by deprotonating the ligands **HL3–10** with triethylamine followed by reaction with $[Cp^*MCl_2]_2$ (M = Rh and Ir) (Scheme 1). All complexes were found to be air-stable yellow/orange-colored solids that exhibit good solubility in polar solvents.

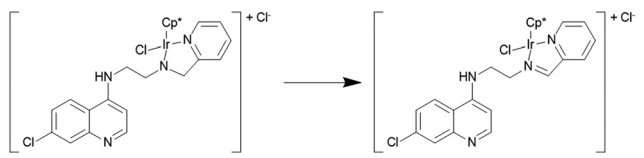
All complexes have been fully characterized by infrared, ^{1}H- and ^{13}C-NMR spectroscopy and mass spectrometry. Further-



Scheme 1 Synthesis of rhodium (**1a–10a**) and iridium (**1b–10b**) complexes.

more, the molecular structures of complexes **1a** and **5a** have been authenticated by single crystal X-ray diffraction analysis. Efforts to grow single crystals of complex **1b** in acetone gave X-ray quality crystals, but not of **1b** but rather the corresponding imino-iridium(III) complex **11** (Scheme 2), in which the ligand has been oxidized to form the imine analogue of **L1** (*vide infra*). The ^{1}H spectra of the complexes show the expected differences relative to the uncoordinated ligands; *i.e.* a downfield shift of ligand protons close to the coordinating sites and diastereotopic splitting of the methylene (CH_2) protons. The diastereotopic splitting can be ascribed to the coordination of the ligand with the metal in a bidentate coordination mode, inducing chirality at the metal center.[22]

The most abundant peaks in the ESI mass spectra of complexes **1a** and **1b** occur at *m*/*z* 585 and 675, respectively, which are attributed to the $[M]^+$ peak for each complex. While the iridium complex **2b** showed the most abundant peak at *m*/*z* 642 ($[M - HCl]^+$), the analogous rhodium complex **2a** showed the most abundant peak at *m*/*z* 276 which is attributed to $[M - HCl]^{2+}$. These results suggest cleavage of the M–Cl bond and loss of a chloride ligand for both **2a** and **2b**. The complexes **3a–10a** and **3b–10b** all showed $[M + 1]^+$ molecular peaks, but all except **6a** and **9a** showed $[M - Cl]^+$ as the most abundant peak, indicating that complexes based on salicylaldimine ligands, like the imidazole in **L2**, are prone to lose a chloride.



Scheme 2 Spontaneous ligand dehydrogenation of **1b** to **11**.

Molecular structures of complexes 1a, 5a and 11

The molecular structures of complexes **1a**, **5a** and **11** have been determined by X-ray crystallography. Single crystals suitable for X-ray crystallographic analyses were obtained by layering hexane on a dichloromethane solution of **1a** kept at low temperature (−20 °C) and by slow evaporation of a dichloromethane/hexane solution of **5a** at room temperature. When an acetone solution of complex **1b** was allowed to slowly evaporate at low temperature (−20 °C), single crystals suitable for X-ray crystallography were obtained. However, as already mentioned, it was found that the crystal structure showed the structure of an imino-iridium(III) complex, **11** (Scheme 2), as a result of oxidation of the ligand in the corresponding amino-iridium(III) complex **1b**. Relevant crystallographic data and structure refinement parameters are compiled in Table 1. Selected bond lengths and bond angles are given in Table 2 and molecular structures with numbering schemes are shown in Fig. 2–4, for **1a**, **5a**, and **11**, respectively. The three complexes adopt the expected piano stool geometry, with all bond lengths and angles around the metal centers similar to reported structures of RhCp* and IrCp* complexes with amino-pyridyl, salicylaldimine-based and imino-pyridyl ligands.[33–36] The distances of the Rh atom from the Cp* centroid are 1.779 and 1.816 Å in **1a** and **5a**, respectively. For **1a**, the Rh–Cl, Rh–N_{amine} and Rh–N_{py} bond distances are 2.4203(6), 2.1729(19) and 2.1089(19) Å, respectively, and for **5a** the Rh–Cl, Rh–N and Rh–O bond distances are 2.4212(8), 2.098(3) and 2.080(2) Å, respectively.

As discussed above, coordination of the bidentate quinoline derivatives renders the complexes chiral at the metal (in addition to the stereogenic centers at N2 and N3 for **1a**, at N2 for **5a** and at N3 for **11**), but the complexes crystallize as racemic mixtures of enantiomers, and the NMR spectra of the complexes indicate that no diastereomers are present in solution.

The structure of **11** closely resembles that of **1a**, exhibiting a distorted piano-stool geometry around the iridium center; an η^5-Cp* group occupies three facial positions of an ideal metal-octahedral environment, and the chelating pyridine-imine ligand and a terminal chloride complete the octahedral coordination sphere. The crystal structure reveals that the Ir1–N1–C5–C6–N2 metallacycle is essentially planar, and coplanar with the plane of the pyridine ring, while in the structure of **1a** the corresponding metallacycle is in a classic envelope conformation with N2 in the *endo* position. The Ir–Cl, Ir–N_{imine}, Ir–N_{py}, Ir–centroid(Cp*), and Ir–C5(Cp*) bond distances are similar to the distances in complex **1a** and these bond distances are comparable to the values reported for (η^5-Cp*)Ir(III)-complexes in the literature.[36] However, the major structural differences observed between complexes **1a** and **11** are the bond angles and bond distances around the C6 and N2 atoms. The C6–N2 bond length in complex **11** is 1.296(6) Å, which is

Table 1 Crystal data and structure refinement for complexes **1a**, **5a** and **11**

Complex	**1a**	**5a**	**11**
Empirical formula	$C_{28.50}H_{35}Cl_6N_4Rh$	$C_{28}H_{29}Cl_3N_3ORh{\cdot}CH_2Cl_2$	$C_{27}H_{36}Cl_3IrN_4O_3$
Formula weight	749.21	717.73	763.15
Temperature (K)	170(2)	293	120(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Triclinic	Monoclinic	Triclinic
Space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
Unit cell dimensions			
a (Å)	11.6470(6)	12.3489(2)	11.5226(10)
b (Å)	12.1871(5)	13.4149(2)	11.8000(9)
c (Å)	13.4363(5)	18.5804(3)	12.6405(8)
α (°)	76.108(3)	90.00	92.389(6)
β (°)	89.564(4)	99.424(1)	98.090(6)
γ (°)	61.569(5)	90.00	118.661(8)
Volume (Å^3)	1615.33(14)	3036.47(8)	1481.3(2)
Z	2	4	2
Density (calculated, Mg m^{-3})	1.540	1.570	1.711
Absorption coefficient (mm^{-1})	1.051	1.031	4.813
F(000)	762	1456	756
Crystal size (mm^3)	0.432 × 0.167 × 0.115	0.30 × 0.25 × 0.10	0.932 × 0.047 × 0.023
Theta range for data collection	3.148 to 30.747°	1.672 to 28.454°	2.850 to 26.499°
Index ranges	$-16 \le h \le 16$	$-16 \le h \le 16$	$-13 \le h \le 14$
	$-17 \le k \le 17$	$-17 \le k \le 17$	$-14 \le k \le 14$
	$-19 \le l \le 19$	$-24 \le l \le 24$	$-15 \le l \le 13$
Reflections collected	18 611	55 008	10 684
Independent reflections	10 031 [R(int) = 0.0229]	7557 [R(int) = 0.0515]	6081 [R(int) = 0.0458]
Completeness to theta = 25.242°	99.8%	100.0%	99.5%
Absorption correction	Analytical	Multi-scan	Gaussian
Max. and min. transmission	0.913 and 0.752	0.725 and 0.920	0.898 and 0.762
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	10 031/14/366	7557/5/430	6081/0/348
Goodness-of-fit on F^2	1.036	0.974	0.966
Final R indices [$I > 2\mathrm{sigma}(I)$]	$R_1{}^a = 0.0409$, $wR_2{}^b = 0.0974$	$R_1{}^a = 0.0368$, $wR_2{}^b = 0.0824$	$R_1{}^a = 0.0395$, $wR_2{}^b = 0.0603$
R indices (all data)	$R_1 = 0.0468$, $wR_2 = 0.1030$	$R_1 = 0.0634$, $wR_2 = 0.0971$	$R_1 = 0.0607$, $wR_2 = 0.0649$
Largest diff. peak and hole (e Å^{-3})	1.461 and −1.571	0.514 and −0.551	1.190 and −0.885

$^a R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. $^b wR_2 = [\sum w(F_o{}^2 - F_c{}^2)^2/\sum w(F_o{}^2)^2]^{1/2}$ where $w = 1/[\sigma^2(F_o{}^2) + (aP)^2 + bP]$ where $P = (F_o{}^2 + F_c{}^2)/3$.

Table 2 Selected bond lengths (Å) and bond angles (°) for complexes **1a**, **5a** and **11**

Complex **1a**	Complex **5a**	Complex **11**
Rh1–N1 = 2.1089(19)	Rh1–O1 = 2.080(2)	Ir1–N1 = 2.093(4)
Rh1–N2 = 2.1729(19)	Rh1–N1 = 2.098(3)	Ir1–N2 = 2.104(4)
Rh1–Cl1 = 2.4203(6)	Rh1–Cl1 = 2.4212 (8)	Ir1–Cl1 = 2.4051(13)
Rh1–C18 = 2.160(2)	Rh1–C19 = 2.178(8)	Ir1–C18 = 2.187(5)
Rh1–C19 = 2.175(2)	Rh1–C20 = 2.128(7)	Ir1–C19 = 2.167(5)
Rh1–C20 = 2.148(2)	Rh1–C21 = 2.143(8)	Ir1–C20 = 2.188(4)
Rh1–C21 = 2.162(2)	Rh1–C22 = 2.250(7)	Ir1–C21 = 2.181(5)
Rh1–C22 = 2.143(2)	Rh1–C23 = 2.202(9)	Ir1–C22 = 2.158(5)
Rh1–C5(Cp*) (avg) = 2.157	Rh1–C5(Cp*) (avg) = 2.180	Ir1–C5(Cp*) (avg) = 2.176
Rh1–centroid (Cp*) = 1.779	Rh1–centroid (Cp*) = 1.816	Ir1–centroid (Cp*) = 1.802
N1–C1 = 1.352(3)	O1–C1 = 1.303(4)	N1–C1 = 1.323(6)
N1–C5 = 1.346(3)		N1–C5 = 1.366(6)
C5–C6 = 1.501(3)	C6–C7 = 1.455(4)	C5–C6 = 1.431(7)
C6–N2 = 1.494(3)	C7–N1 = 1.280(4)	C6–N2 = 1.296(6)
N2–C7 = 1.489(3)	N1–C8 = 1.486(4)	N2–C7 = 1.447(6)
N1–Rh1–N2 = 77.52(7)	O1–Rh–N1 = 83.20(9)	N1–Ir1–N2 = 76.11(15)
N1–Rh1–Cl1 = 85.28(5)	Cl1–Rh–N1 = 90.06 (7)	N1–Ir1–Cl1 = 85.16(12)
N2–Rh1–Cl1 = 95.90(5)	Cl1–Rh–O1 = 88.84 (6)	N2–Ir1–Cl1 = 88.74(12)
Rh1–N1–C5 = 115.80(15)	Rh1–O1–C1 = 118.6(2)	Ir–N1–C5 = 115.7(3)
N1–C5–C6 = 114.2(2)	O1–C1–C6 = 124.2(3)	N1–C5–C6 = 114.1(4)
C5–C6–N2 = 109.10 (18)	C1–C6–C7 = 120.8(3)	C5–C6–N2 = 117.4(4)
	C6–C7–N1 = 125.2(3)	
Rh1–N2–C6 = 104.88(13)	Rh–N1–C7 = 121.8(2)	Ir1–N2–C6 = 116.4(3)
Rh1–N2–C7 = 117.74(15)	Rh–N1–C8 = 120.5(2)	Ir1–N2–C7 = 125.2(3)
C6–N2–C7 = 110.27(18)	C7–N1–C8 = 117.4(3)	C6–N2–C7 = 118.5(4)

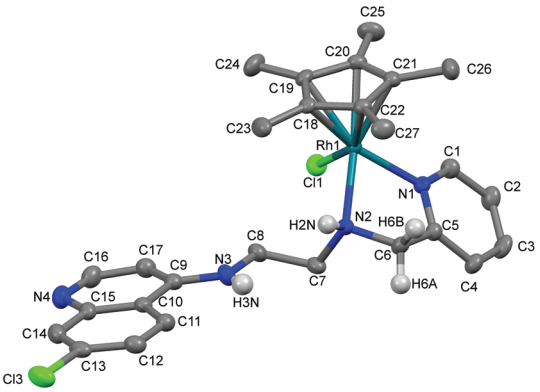


Fig. 2 Crystal structure of **1a** with atom numbering schemes (thermal ellipsoids drawn at 50% probability level). Solvent of crystallization, counter anion (Cl^-) and most of the hydrogen atoms have been omitted for clarity (hydrogen atoms attached to C6, N2 and N3 are shown).

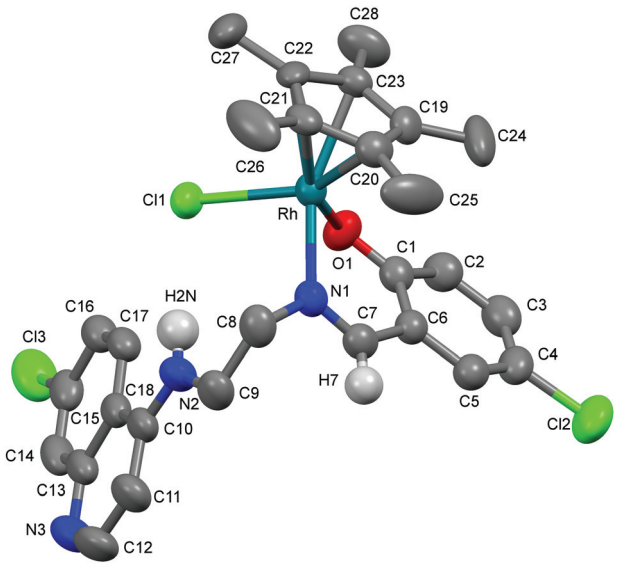


Fig. 3 Crystal structure of complex **5a** with atom numbering schemes (thermal ellipsoids drawn at 50% probability level). Solvent of crystallization, hydrogen atoms and disorder at the pentamethylcyclopentadienyl ring have been omitted for clarity (hydrogen atoms attached to N2 and C7 are shown).

considerably smaller than the corresponding distance in complex **1a**, 1.494(3) Å, indicative of an imine rather than an amine functionality. Also, the bond angles around both C6 and N2 in complex **11** are ~120°. The short N–C distance and the angles around C6 and N2 unambiguously indicate the sp^2 nature of the C6 carbon in complex **11** and a double bond between C6 and N2. However, **1b** can still be assumed to be the amino complex indicated in Scheme 1 as the combined spectroscopic data agree very well with this formulation. There is very good agreement between the ^{1}H- and ^{13}C-NMR spectra of **1a** and **1b**, suggesting an un-oxidized state of $\mathbf{L_1}$ in **1b**. Additionally, there is no trace of an imine C–H signal in the

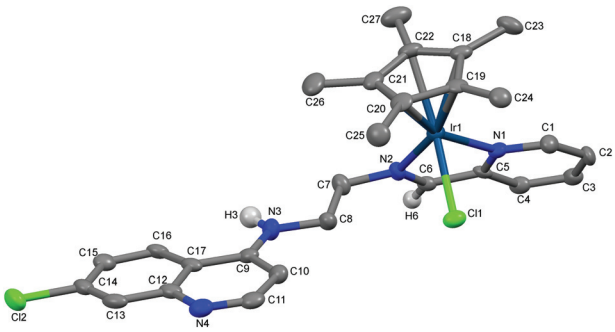


Fig. 4 Crystal structure of **11** with atom numbering schemes (thermal ellipsoids drawn at 50% probability level). Solvent of crystallization, counter anion (Cl^-) and hydrogen atoms have been omitted for clarity (hydrogen atoms attached to C6 and N3 are shown).

^{1}H-NMR spectrum, or of an imine N=C stretch in the IR-spectrum of **1b**. Thus the oxidation of complex **1b** to **11** must be assumed to have occurred during the crystallization. Metal-assisted dehydrogenation of coordinated amines to form imines is a well-known phenomenon, especially for Ru(II) and Os(II) complexes.[37] However, this is a relatively rare phenomenon for iridium complexes, and only a few examples of amino iridium pentamethylcyclopentadienyl complexes undergoing ligand dehydrogenation to form the corresponding imine complex are known. Jerphagnon *et al.*[38] observed that the ligand in the metallacycle formed from $[IrCp^*Cl_2]_2$ and *N*-methylbenzylamine slowly oxidizes to the imine *N*-benzylidenemethylamine during catalytic experiments or on standing in $CDCl_3$. Similarly, Barloy *et al.*[39] obtained significant amounts of the oxidized pyrroline complex from the reaction between (2*R*,5*R*)-2,5-diphenylpyrrolidine and $[IrCp^*Cl_2]_2$ even when the reaction was performed under anaerobic conditions, and only the oxidized product was obtained when the reaction was run under air.

Assessment of anti-malarial activity *in vitro*

The anti-malarial activity of all rhodium (**1a–10a**) and iridium (**1b–10b**) complexes has been evaluated against the chloroquine-sensitive (CQS) NF54 and the chloroquine-resistant (CQR) Dd2 strains of *Plasmodium falciparum*. Chloroquine and artesunate have been used as reference drugs in this study and the antiplasmodial activity was determined *in vitro* using the parasite lactate dehydrogenase assay. The results are given in Fig. 5 and 6, and Table 3. The anti-malarial properties of all ligands and *p*-cymene-ruthenium complexes analogous to the complexes presented in this work, and *p*-cymene-osmium complexes of ligands **L1**, **L3**, **L4**, **L5** and **L7**, have been reported previously.[22,23] All ligands display good to moderate activity against both the CQS-NF54 and CQR-Dd2 strains. In particular, the Schiff base ligands **HL3–HL10** exhibit higher antimalarial activity than the amine ligands **L1** and **L2** and in some cases, the Schiff base ligands even showed better activity than chloroquine. However, the coordination of a ruthenium arene moiety was found to be detrimental for anti-malarial activity,

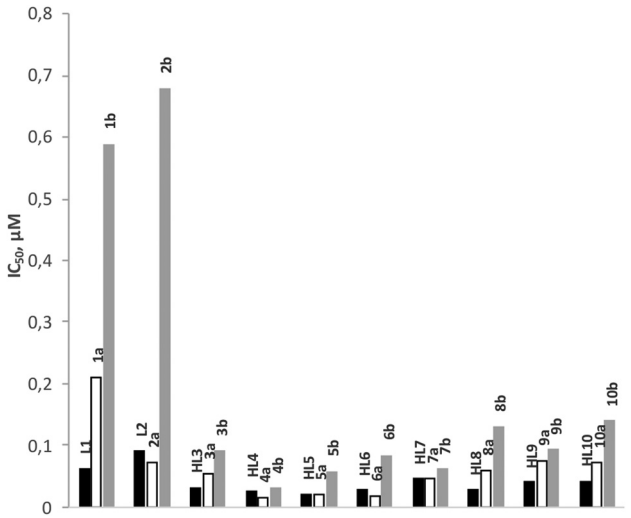


Fig. 5 IC_{50} values of ligands (**L1–HL10**, black bars), rhodium (**1a–10a**, hollow bars) and iridium complexes (**1b–10b**, grey bars) tested *in vitro* for antiplasmodial activity against the chloroquine sensitive NF54 strain of *P. falciparum*.

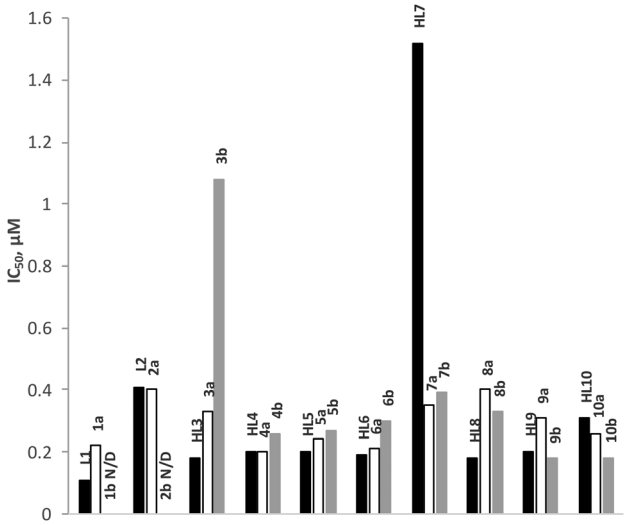


Fig. 6 IC_{50} values of ligands (**L1–HL10**, black bars), rhodium (**1a–10a**, hollow bars) and iridium complexes (**1b–10b**, grey bars) tested *in vitro* for antiplasmodial activity against the chloroquine resistant Dd2 strains of *P. falciparum*. N/D = not determined.

and the osmium arene complexes exhibited a further decrease in activity.

In this study, the rhodium complexes **1a** to **10a** exhibited lower IC_{50} values against the CQS NF54 strain relative to their iridium congeners. The same holds for the activity against the CQR Dd2 strain, with the exception of complexes **8a**, **9a** and **10a**, which showed slightly lower activity than their iridium analogues. The N^N-coordinating cationic complexes **1b** and **2b** were found to be inactive against the CQR Dd2 strain. In almost all cases there was no significant difference in activity between the free ligands and the rhodium complexes, while the activities of the iridium complexes were statistically different from both the free ligands and the rhodium complexes.

Table 3 IC_{50} values of ligands and complexes tested *in vitro* for antiplasmodial activity against chloroquine sensitive (NF54) and chloroquine resistant (Dd2) strains of *P. falciparum*

Compound	NF54: IC_{50} (μM)	Dd2: IC_{50} (μM)	RI
L1	0.063 ± 0.002	0.11 ± 0.04	1.7
L2	0.091 ± 0.016	0.41 ± 0.01	4.5
HL3	0.032 ± 0.004	0.18 ± 0.02	5.5
HL4	0.025 ± 0.007	0.20 ± 0.02	8
HL5	0.021 ± 0.003	0.20 ± 0.04	9.5
HL6	0.027 ± 0.009	0.19 ± 0.03	7.2
HL7	0.046 ± 0.006	1.52 ± 0.27	33
HL8	0.028 ± 0.008	0.18 ± 0.01	6.5
HL9	0.040 ± 0.002	0.20 ± 0.03	5.2
HL10	0.041 ± 0.002	0.31 ± 0.03	7.8
1a	0.209 ± 0.038	0.22 ± 0.13	1.1
2a	0.072 ± 0.021	0.40 ± 0.035	5.7
3a	0.054 ± 0.002	0.33 ± 0.08	6.1
4a	0.016 ± 0.002	0.20 ± 0.004	12
5a	0.020 ± 0.006	0.24 ± 0.01	12
6a	0.018 ± 0.006	0.21 ± 0.03	12
7a	0.047 ± 0.011	0.35 ± 0.08	7.5
8a	0.060 ± 0.014	0.40 ± 0.02	6.6
9a	0.076 ± 0.012	0.31 ± 0.04	4.1
10a	0.073 ± 0.009	0.26 ± 0.07	3.5
1b	0.587 ± 0.143	>1.4 ± ND	ND
2b	0.677 ± 0.029	>1.4 ± ND	ND
3b	0.091 ± 0.006	1.08 ± 0.35	12
4b	0.030 ± 0.007	0.26 ± 0.02	8.8
5b	0.058 ± 0.017	0.27 ± 0.05	4.7
6b	0.084 ± 0.013	0.30 ± 0.03	3.6
7b	0.061 ± 0.016	0.39 ± 0.06	6.3
8b	0.13 ± 0.03	0.33 ± 0.12	2.5
9b	0.093 ± 0.002	0.18 ± 0.05	1.9
10b	0.14 ± 0.04	0.18 ± 0.02	1.3
CQ	0.027 ± 0.011	0.22 ± 0.05	8.1
Artesunate	<0.005	0.011 ± 0.001	—

ND (not determined), RI (resistance index) = $IC_{50(CQR)}/IC_{50(CQS)}$.

Activity against both the CQS-NF54 and CQR-Dd2 strains

It is interesting to note that electronic variation in the Schiff base (N^O) ligand systems also has a significant effect on the antiplasmodial activity of the ligands as well as the rhodium and iridium complexes. The ligands having electron-withdrawing groups (F, Cl, Br, I and NO_2) in *para* position to the phenolic OH and their rhodium complexes showed good antiplasmodial activity. Indeed, some of these rhodium complexes (**4a**, **5a** and **6a**) are more active than chloroquine against the CQS NF54 strain. If the IC_{50} values for ligands **HL3** to **HL10** and complexes **3a** to **10a** and **3b** to **10b** are plotted as a function of Hammett's σ_p parameter (Fig. 7), a clear trend that the compounds bearing electron-withdrawing groups are more active against the CQS strain can be seen, but the same trend is not evident for the CQR strain. The reason for the observed correlation in the case of the CQS strain remains unclear.

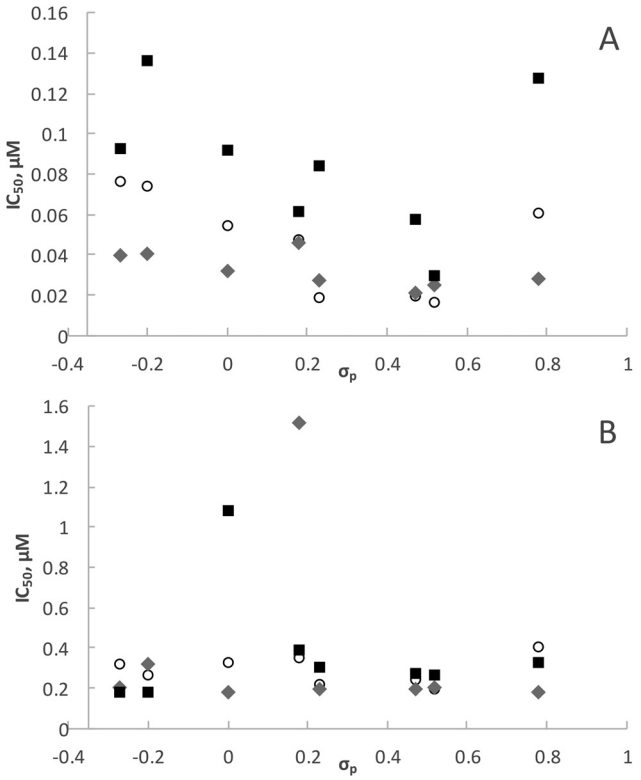


Fig. 7 A plot of the IC_{50} values *vs.* Hammett's σ_p parameter for the substituent *para* to the phenolic group in **HL3** to **HL10**. (A) CQS NF54 strain, (B) CQR Dd2 strain. Ligands **HL3** to **HL10**: grey diamonds. Rhodium complexes **3a** to **10a**: hollow circles. Iridium complexes **3b** to **10b**: black squares.

Experimental

All synthetic procedures were performed under dry nitrogen using standard Schlenk and vacuum-line techniques. Solvents used were dried by distillation over appropriate drying reagents and stored over molecular sieves under nitrogen. All chemicals were purchased from Sigma-Aldrich and used as received. N^1-(7-chloroquinolin-4-yl)ethane-1,2-diamine was prepared according to a literature method.[40] Ligands **L1**, **L2** and **HL3–10** were synthesized according to published procedures.[22,23] NMR spectra were recorded on a Varian Inova 500 MHz spectrometer using the solvent resonance as internal standard for ^{1}H NMR and ^{13}C NMR shifts. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. Electrospray ionization (ESI) mass spectra were recorded using a Waters Micromass Q-Tof micro mass spectrometer or an LC-MS Agilent 6220-TOF spectrometer coupled with a 1200 series HPLC. Elemental analysis was performed by Mikroanalytische Laboratorium Kolbe, Mülheim an der Ruhr.

Synthesis of complexes

(η^5-Pentamethylcyclopentadienyl){(N^1-(7-chloroquinolin-4-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine)}chlororhodium(III) chloride, [RhCp*(L1)Cl]Cl (1a). A solution of **L1** (0.031 g, 0.099 mmol) in dry dichloromethane (3 mL) was added dropwise to a solution of $[RhCp^*Cl_2]_2$ (0.030 g, 0.049 mmol) in dry dichloromethane (7 mL) under nitrogen, and the reaction mixture was stirred for 3 h at room temperature. After reducing the solvent volume to approximately 2 mL, the reaction mixture was poured into petroleum ether (15 mL), yielding a yellow precipitate. The precipitate was filtered, washed with petroleum ether and dried under vacuum. Suitable single crystals for X-ray diffraction were obtained by layering hexane on a dichloromethane solution of the complex. Yield: 0.053 g (~86%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.90 (d, 1H, J = 9.0 Hz, ArH), 8.50 (d, 2H, J = 5.5 Hz, ArH), 8.37 (br s, 1H, NH), 8.11(br s, 1H, NH), 7.95 (s, 1H, ArH), 7.87 (t, 1H, J = 7.7 Hz, ArH), 7.50–7.42 (m, 3H, ArH), 6.35 (d, 1H, J = 5.5 Hz, ArH), 4.86 (dd, 1H, J = 15.8 Hz, 5.9 Hz), 4.04 (dd, 1H, J = 15.6 Hz, 5.1 Hz), 3.76–3.70 (m, 1H), 3.65–3.60 (m, 1H), 3.35–3.30 (m, 1H), 3.26–3.21 (m, 1H), 1.64 (s, 15H, Cp^*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 161.04, 151.00, 150.71, 150.42, 148.47, 139.48, 135.36, 127.09, 125.69, 125.46, 125.05, 122.42, 117.71, 97.98, 95.93 (d, $J_{c\text{-}Rh}$ = 8.7 Hz, Cp*), 59.59, 53.12, 41.39, 9.08 (Cp^*CH_3). IR (KBr) ν_{max}/cm^{-1}: 3438w, 3237w, 3099w, 2910m, 1609m, 1580s, 1538m, 1486m, 1449w, 1377m, 1365m, 1329m, 1282m, 1251m, 1143m, 1082m, 1027m, 917m, 880m, 884m, 820m, 771m. MS (ES+, m/z): 585 [M]$^+$. Elemental analysis (%) calcd For $C_{27}H_{32}Cl_3N_4Rh$: C, 52.15; H, 5.19; N, 9.01; Found: C, 52.75; H, 5.10; N 8.85.

(η^5-Pentamethylcyclopentadienyl)(N^1-(7-chloroquinolin-4-yl)-N^2-((1-methyl-1*H*-imidazol-2-yl)methyl)ethane-1,2-diamine) chlororhodium(III) chloride, [RhCp*(L2)Cl]Cl (2a). This compound was synthesized from **L2** (31 mg, 0.098 mmol) and $[Rh(Cp^*)Cl_2]_2$ (30 mg, 0.049 mmol) by the procedure used for the synthesis of **1a**. The product **2a** was obtained as a yellow precipitate. Yield: 56 mg (~91%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.72 (d, 1H, J = 9.1 Hz, ArH), 8.52 (d, 1H, J = 5.1 Hz, ArH), 8.26 (br s, 1H, NH), 7.99 (br s, 1H, NH), 7.93 (s, 1H, ArH), 7.47 (dd, 1H, J = 8.8 Hz, 1.7 Hz, ArH), 7.02 (d, 1H, J = 1.5 Hz, Imz-H), 6.93 (d, 1H, J = 1.0 Hz, Imz-H), 6.34 (d, 1H, J = 5.1 Hz, ArH), 4.78 (dd, 1H, J = 14.8 Hz, 6.8 Hz), 3.80–3.74 (m, 1H), 3.68–3.60 (m, 5H), 3.49–3.44 (m, 1H), 3.37 (t, 1H, J = 11.6 Hz), 1.60 (s, 15H, Cp^*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 151.32, 150.09, 149.84, 149.10, 135.35, 127.57, 125.76, 124.63, 124.04, 123.05, 117.82, 97.59, 94.67 (d, $J_{c\text{-}Rh}$ = 8.7 Hz, Cp*), 54.57, 47.20, 39.60, 34.55. 8.88 (Cp^*CH_3). IR (KBr) ν_{max}/cm^{-1}: 3385w, 3096w, 2958m, 1610m, 1579s, 1539m, 1513m, 1451w, 1426m, 1369m, 1329m, 1139m, 1078m, 1022m, 820w. MS (ES+, m/z): 552 ([M − HCl]$^+$). Elemental analysis (%) calcd For $C_{26}H_{32}Cl_3N_5Rh$: C, 50.06; H, 5.17; N, 11.23; Found: C, 50.21; H, 5.12; N, 11.32.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((2-hydroxyphenyl) methylimino)ethyl)-7-chloroquinolin-4-amine)}chlororhodium(III), [RhClCp*(L3)] (3a). Ligand **HL3** (19.8 mg, 0.061 mmol) was stirred with Et_3N (12.7 μl, 0.091 mmol) in dichloromethane (5 mL) for 30 minutes before the solution was cooled in an acetone-dry ice bath (−78 °C) followed by the addition of $[Cp^*RhCl_2]_2$ (18.7 mg, 0.0304 mmol) in dichloromethane (1 mL). The reaction mixture was stirred overnight at ambient temperature under nitrogen. The solvent was evaporated

in vacuo and the crude product was purified by column chromatography on silica eluting with dichloromethane/methanol (9 : 1 v/v) to afford compound **3a** as an orange solid. Yield: 22 mg (~61%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.23 (s, 1H), 8.01 (s, 1H), 7.91 (s, 1H), 7.75 (s, 1H), 7.29 (d, 1H, J = 9.0 Hz), 7.15 (td, 1H, J = 1.89, J = 7.3 Hz), 6.86 (d, 1H, J = 8.3 Hz), 6.78 (d, 1H, J = 6.8 Hz), 6.51 (d, 1H, J = 4.1 Hz), 6.37 (t, 1H, J = 7.1 Hz), 4.40 (m, 1H), 4.29 (m, 1H), 4.20 (m, 1H), 3.81 (m, 1H), 1.58 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 166.17, 166.12, 151.62, 148.61, 145.82, 136.28, 135.03, 134.45, 126.00, 125.36, 124.06, 123.59, 120.94, 116.83, 114.84, 98.35, 93.31 (d, $J_{c\text{-}Rh}$ = 8.2 Hz, Cp*), 61.60, 42.88, 8.81. IR (KBr) ν_{max}/cm^{-1}: 3434 (br), 2920w, 1620sh (C═N), 1615s (7-chloroquinoline), 1580s (7-chloroquinoline), 1537w (7-chloroquinoline), 1447m, 1330m, 1141w, 1023m, 810m 759w. MS (ES+, m/z): 562 ($[M - Cl]^+$) 100%, 598 ($[M + H]^+$) 68%.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((5-fluro-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chlororhodium(III), [RhClCp*(L4)] (4a). This compound was synthesized from **HL4** (23.3 mg, 0.065 mmol) and $[RhCp^*Cl_2]_2$ (20 mg, 0.032 mmol) by the procedure used for the synthesis of **3a**. The product **4a** was obtained as an orange solid. Yield: 23 mg (~58%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.25 (s, 1H), 8.11 (s, 1H), 7.90 (s, 1H), 7.62 (s, 1H),7.51 (br, 1H) 7.24 (d, 1H, J = 1.0 Hz), 6.93 (dt, 1H, J = 3.1 Hz, J = 8.9 Hz), 6.84 (dd, 1H, J = 4.4 Hz, J = 9.1 Hz), 6.46 (s, 1H), 6.45 (s, 1H), 4.30 (m, 2H), 4.12 (m, 1H), 3.79 (m, 1H), 1.59 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 165.22, 163.12, 153.76, 150.99 (d, J = 230.5 Hz), 150.89, 135.92, 126.61, 126.57, 125.90, 124.62 (d, J = 6.9 Hz), 123.80, 123.20 (d, J = 23.7 Hz), 119.55 (d, J = 6.6 Hz), 117.46 (d, J = 22.2 Hz), 117.27, 98.45, 93.53 (d, $J_{c\text{-}Rh}$ = 8.6 Hz), 61.85, 42.77, 8.99. IR (KBr) ν_{max}/cm^{-1} 3425 (br), 2923m, 1633sh (C═N), 1623s (7-chloroquinoline), 1578s (7-chloroquinoline), 1541w (7-chloroquinoline), 1460s, 1376w, 1307w, 1261w, 1243w, 1210w, 1139s, 1081s, 804w. MS (ES+, m/z): 580 ($[M - Cl]^+$) 100%, 616 ($[M + H]^+$) 34%.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((5-chloro-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chlororhodium(III), [RhClCp*(L5)] (5a). This compound was synthesized from **HL5** (22.3 mg, 0.064 mmol) and $[RhCp^*Cl_2]_2$ (20 mg, 0.032 mmol) by the procedure used for the synthesis of complex **3a**. The product **5a** was obtained as an orange solid. Yield: 19 mg (~50%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.40 (s, 1H), 7.96 (d, 1H, J = 8.6 Hz), 7.88 (d, 1H, J = 1.6 Hz), 7.49 (s, 1H), 7.21 (dd, 1H, J = 1.9 Hz, J = 8.9 Hz), 7.14 (br, 1H), 7.08 (dd, 1H, J = 2.7 Hz, J = 9.0 Hz), 6.86 (d, 1H, J = 9.1 Hz), 6.62 (d, 1H, J = 2.2 Hz), 6.40 (d, 1H, J = 5.4 Hz), 4.27 (m, 2H), 4.06 (m, 1H), 3.75 (m, 1H), 1.59 (s, 15H, Cp*CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.19, 165.01, 150.91, 150.29, 148.49, 135.58, 134.98, 132.70, 127.39, 125.76, 125.35, 123.52, 120.92, 118.43, 117.45, 98.42, 93.65 (d, J = 8.2 Hz), 62.03, 42.50, 9.03. IR (KBr) ν_{max}/cm^{-1} 3444 (br), 2921w, 2852w, 1621s (7-chloroquinoline), 1581s (7-chloroquinoline), 1557w (7-chloroquinoline), 1520w, 1456m, 1384w, 1317m, 1172w, 1138w, 1025w, 878w, 810m. MS (ES+, m/z): 596 ($[M - Cl]^+$) 100%, 634 ($[M + H]^+$) 28%.

(η5-Pentamethylcyclopentadienyl){(*N*-(2-((5-bromo-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chlororhodium(III), [RhClCp*(L6)] (6a). This compound was synthesized from **HL6** (21.6 mg, 0.061 mmol) and $[RhCp^*Cl_2]_2$ (18.3 mg, 0.030 mmol) by the procedure used for the synthesis of complex **3a**. The product **6a** was obtained as an orange solid. Yield: 36 mg (~89%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.32 (d, 1H, J = 3.1 Hz), 8.05 (d, 1H, J = 8.8 Hz), 7.82 (s, 1H), 7.58 (s, 1H), 7.34 (s, 1H), 7.18 (d, 1H, J = 8.8 Hz), 7.14 (dd, 1H, J = 2.1 Hz, J = 9.0 Hz), 6.79 (s, 1H), 6.76 (d, 1H, J = 9.0 Hz), 6.44 (d, 1H, J = 5.1 Hz), 4.23 (m, 2H), 3.96 (m, 1H), 3.77 (m, 1H), 1.53 (s, 15H, (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 165.60, 165.01, 150.91, 149.82, 147.43, 137.50, 136.03, 135.70, 126.42, 125.95, 125.74, 123.79, 122.06, 117.19, 105.12, 98.43, 93.65 (d, $J_{c\text{-}Rh}$ = 7.9 Hz), 61.91, 42.74, 8.99. IR (KBr) ν_{max}/cm^{-1} 3432 (br), 2923m, 2854w, 1626sh (C═N), 1619s (7-chloroquinoline), 1578s (7-chloroquinoline), 1542w (7-chloroquinoline), 1509w, 1459s, 1375w, 1261w, 1024m, 800w. MS (ES+, m/z): 678 ($[M + H]^+$) 100%, 642 ($[M - Cl]^+$) 91%.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((5-iodo-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chlororhodium(III), [RhClCp*(L7)] (7a). This compound was synthesized from **HL7** (24.3 mg, 0.065 mmol) and $[RhCp^*Cl_2]_2$ (20 mg, 0.032 mmol) by the procedure used for the synthesis of complex **3a**. The product **7a** was obtained as an orange solid. Yield: 35 mg (~75%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.25 (s, 1H), 8.09 (d, 1H, J = 7.4 Hz), 7.91 (d, 1H, J = 1.7 Hz), 7.59 (s, 1H), 7.32 (dd, 1H, J = 2.3 Hz, J = 8.9 Hz), 7.24 (d, 1H, J = 1.7 Hz), 6.98 (s, 1H), 6.68 (d, 1H, J = 8.9 Hz), 6.48 (d, 1H, J = 5.8 Hz) 4.36 (m, 2H), 4.13 (m, 1H), 3.82 (m, 1H), 1.59 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 166.06, 165.29, 151.55, 148.99, 146.30, 143.05, 142.18, 136.56, 126.37, 126.22, 125.67, 124.07, 123.46, 117.04, 98.65, 93.70 (d, $J_{c\text{-}Rh}$ = 8.2 Hz), 73.60, 61.95, 42.96, 9.02. IR (KBr) ν_{max}/cm^{-1}: 3427 (br), 2922m, 1624sh (C═N), 1618s (7-chloroquinoline), 1588s (7-chloroquinoline), 1541w (7-chloroquinoline), 1509w, 1458m, 1375w, 1318w, 1023m, 806w. MS (ES+, m/z): 688 ($[M - Cl]^+$) 100%, 724 ($[M + H]^+$) 24%.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((2-hydroxy-5-nitrophenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chlororhodium(III), [RhClCp*(L8)] (8a). This compound was synthesized from **HL8** (22.5 mg, 0.061 mmol) and $[RhCp^*Cl_2]_2$ (18.5 mg, 0.030 mmol) by the procedure used for the synthesis of complex **3a**. The product **8a** was obtained as an orange solid. Yield: 11 mg (~28%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.33 (d, 1H, J = 5.4 Hz), 8.05 (d, 1H, J = 9.1 Hz), 8.01 (dd, 1H, J = 2.8 Hz, J = 9.4 Hz), 7.97 (s, 1H), 7.90 (s, 1H), 7.85 (d, 1H, J = 2.1 Hz), 7.69 (br, 1H), 7.24 (d, 1H, J = 1.8 Hz), 6.88 (d, 1H, J = 9.4 Hz), 6.55 (d, 1H, J = 6.3 Hz), 4.35 (m, 2H), 4.10 (m, 1H), 3.95 (m, 1H), 1.56 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 171.81, 165.95, 152.26, 147.63, 144.34, 137.20, 135.85, 132.96, 132.58, 129.58, 126.65, 124.20, 123.97, 119.33, 116.68, 98.62, 94.39 (d, $J_{c\text{-}Rh}$ = 8.6 Hz), 62.60, 43.02, 9.10. IR (KBr) ν_{max}/cm^{-1}: 3444 (br), 2921w, 1644sh (C═N), 1627s (7-chloroquinoline), 1598s (7-chloroquinoline), 1542w (7-chloroquinoline), 1473w, 1456m, 1138w, 1101w, 1025w, 1019w. MS (ES+, m/z): 607 ($[M - Cl]^+$) 100%, 643 ($[M + H]^+$) 40%.

(η5-Pentamethylcyclopentadienyl){(*N*-(2-((2-hydroxy-5-methoxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chlororhodium(III), [RhClCp*(L9)] (9a). This compound was synthesized from **HL9** (23 mg, 0.064 mmol) and $[RhCp^*Cl_2]_2$ (20 mg, 0.032 mmol) by the procedure used for the synthesis of complex **3a**. The product **9a** was obtained as an orange solid: Yield: 8 mg (~26%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.20 (s, 1H), 7.98 (s, 1H), 7.82(s, 2H), 7.66 (s, 1H), 7.22 (d, 1H, J = 8.3 Hz), 6.82 (dd, 1H, J = 2.2 Hz, J = 8.8 Hz), 6.78 (d, 1H, J = 8.9 Hz), 6.52 (s, 1H), 6.22 (s, 1H), 4.38 (m, 1H), 4.23 (m, 1H), 4.15 (m, 1H), 3.77 (m, 1H), 3.59 (s, 3H, OCH3), 1.59 (s, 15H, Cp*CH3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 165.1, 161.7, 151.66, 149.74, 149.3, 148.89, 134.9, 127.87, 125.26, 124.95, 124.52, 123.38, 118.93, 117.57, 114.39, 98.35, 93.18 (d $J_{c\text{-}Rh}$ = 8.4 Hz), 61.42, 55.85, 42.16, 8.82. IR (KBr) ν_{max}/cm^{-1}. 3443 (br), 2926m, 1623sh (C═N), 1610s (7-chloroquinoline), 1578s (7-chloroquinoline), 1512w (7-chloroquinoline), 1459s, 1374w, 1290w, 1261s, 1213w, 1136w, 1093w, 1022m, 818w. MS (ES+, m/z): 592 ([M − Cl]$^+$) 96%, 628 ([M + H]$^+$) 100%.

(η5-Pentamethylcyclopentadienyl){(*N*-(2-((5-*tert*-butyl-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chlororhodium(III), [RhClCp*(L10)] (10a). This compound was synthesized from **HL10** (29.7 mg, 0.064 mmol) and $[RhCp^*Cl_2]_2$ (20 mg, 0.032 mmol) by the procedure used for the synthesis of **3a**. The product **10a** was obtained as an orange solid. Yield: 27 mg (~64%). ^{1}H NMR (500 MHz, CDCl3, δ ppm): 8.19 (s, 1H), 8.10 (s,1H), 8.01 (s,1H), 7.70 (br, 1H), 7.62 (s, 1H), 7.20 (dd, 1H, J = 2.6 Hz, J = 8.7 Hz), 7.19 (br,1H), 6.79 (d, 1H, J = 8.7 Hz), 6.58 (s,1H), 6.53 (d, 1H, J = 4.8 Hz), 4.37 (m, 1H), 4.27 (m, 1H), 4.19 (m, 1H), 3.80 (m, 1H), 1.58 (s, 15H, Cp*CH_3), 1.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 166.58, 164.17, 151.73, 148.99, 146.58, 137.50, 136.32, 133.35, 130.06, 126.08, 125.70, 124.44, 124.37, 122.96, 119.83, 117.15, 98.71, 93.40 (d, $J_{c\text{-}Rh}$ = 8.0 Hz), 61.72, 42.92, 33.55, 31.31, 8.95. IR (KBr) ν_{max}/cm^{-1}: 3433 (br), 2960m, 1633sh (C═N), 1618s (7-chloroquinoline), 1580s (7-chloroquinoline), 1528w (7-chloroquinoline), 1458w, 1362w, 1323w, 1075m, 835w. MS (ES+, m/z): 618 ([M − Cl]$^+$) 100%, 654 ([M + H]$^+$) 57%.

(η^5-Pentamethylcyclopentadienyl){(N^1-(7-chloroquinolin-4-yl)-N^2-(pyridin-2-ylmethyl)ethane-1,2-diamine)}chloroiridium(III) chloride, [IrCp*(L1)Cl]Cl (1b). This compound was synthesized from **L1** (24 mg, 0.075 mmol) and $[IrCp^*Cl_2]_2$ (30 mg, 0.037 mmol) by the procedure used for the synthesis of **1a**. The product **1b** was obtained as a yellow precipitate. Slow evaporation of an acetone solution of **1b** in a freezer (−20 °C) yielded yellow crystals of **11**. Yield: 45 mg (~84%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.92 (d, 2H, J = 8.6 Hz, ArH), 8.52 (d, 1H, J = 5.0 Hz, ArH), 8.49 (d, 1H, J = 5.4 Hz) 8.36 (br s, 1H, NH), 8.03(br s, 1H, NH), 7.90 (dt, 1H, J = 7.7 Hz, J = 1.3 Hz), 7.54 (d, 1H, J = 7.8 Hz), 7.51 (d, 1H, J = 8.8 Hz), 7.41 (t, 1H, J = 6.3 Hz), 6.36 (d, 1H, J = 5.6 Hz, ArH), 4.86 (dd, 1H, J = 16.0 Hz, 5.7 Hz), 4.28 (dd, 1H, J = 16.0 Hz, 4.7 Hz), 3.76–3.70 (m, 1H), 3.66–3.60 (m, 1H), 3.41–3.34 (m, 2H), 1.61 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 162.20, 151.05, 150.63, 150.29, 148.58, 139.48, 135.42, 127.21, 125.77, 125.72, 124.95, 122.31, 117.75, 97.84, 87.78 (Cp*), 60.94, 53.75, 41.14, 8.80 (Cp*CH_3). IR (KBr) ν_{max}/cm^{-1}: 3398w, 3060w, 2917m, 1611m, 1579s, 1540m, 1450m, 1370w, 1330m, 1282m, 1243w, 1139m, 1079m, 1032m, 769m. MS (ES+) m/z 675 [M]$^+$. Elemental analysis (%) calcd For $C_{27}H_{32}Cl_3N_4Ir$: C, 45.60; H, 4.54; N, 7.88; Found: C, 45.48; H, 4.47; N, 7.95.

(η^5-Pentamethylcyclopentadienyl){(N^1-(7-chloroquinolin-4-yl)-N^2-((1-methyl-1*H*-imidazol-2-yl)methyl)ethane-1,2-diamine)}chloroiridium(III) chloride, [IrCp*(L2)Cl]Cl (2b). This compound was synthesized from **L2** (24 mg, 0.075 mmol) and $[IrCp^*Cl_2]_2$ (30 mg, 0.037 mmol) by the procedure used for the synthesis of **1a**. The product **2b** was obtained as a light purple precipitate. Yield: 65 mg (~81%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.84 (d, 1H, J = 8.0 Hz, ArH), 8.60 (br s, 1H, NH), 8.48 (d, 1H, J = 5.7 Hz, ArH), 8.16 (s, 1H, ArH), 7.53 (d, 1H, J = 8.7, ArH), 7.01 (s, 1H, Imz-H), 6.94 (s, 1H, Imz-H), 6.39 (d, 1H, J = 6.1 Hz, ArH), 4.84 (dd, 1H, J = 14.1 Hz, 6.2 Hz), 3.81–3.73(m, 7H), 3.42 (t, 1H, J = 12.8 Hz), 1.59 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 153.59, 151.25, 150.04, 149.03, 135.38, 127.55, 125.79, 124.57, 123.81, 123.04, 117.82, 97.59, 86.24 (Cp*), 55.21, 47.77, 39.60, 34.91, 8.69 (Cp*CH_3). IR (KBr) ν_{max}/cm^{-1}: 3398w, 3098w, 2918w, 1611m, 1580m, 1540m, 1516m, 1451m, 1426m, 1369w, 1329m, 1284m, 1169m, 1139m, 1080w, 1031m, 820w, 767w. MS (ES+, m/z): 642 ([M − HCl]$^+$). Elemental analysis (%) calcd For $C_{26}H_{32}Cl_3N_5Ir$: C, 43.79; H, 4.52; N, 9.82; Found: C, 43.81; H, 4.58; N, 9.90.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chloroiridium(III), [IrClCp*(L3)] (3b). This compound was synthesized from **HL3** (16.3 mg, 0.050 mmol) and $[IrCp^*Cl_2]_2$ (20 mg, 0.025 mmol) by the procedure used for the synthesis of complex **3a**. The product **3b** was obtained as a yellow solid. Yield: 14 mg (~41%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.24 (s, 1H), 8.05 (d, 1H, J = 6.9 Hz), 7.86 (s, 1H), 7.59 (s, 1H), 7.53 (br, 1H), 7.21 (dd, 1H, J = 1.7 Hz, J = 7.2 Hz), 7.18 (dd, 1H, J = 1.4 Hz, J = 6.7 Hz), 6.81 (d, 1H, J = 8.5 Hz), 6.68 (d, 1H, J = 7.5 Hz), 6.51 (d, 1H, J = 5.3 Hz), 6.28 (t, 1H, J = 7.3 Hz), 4.43 (m, 1H), 4.19 (m, 1H), 4.09 (m, 1H), 3.79 (m, 1H), 1.56 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 164.54, 163.19, 151.61, 148.63, 146.09, 136.64, 135.21, 133.97, 126.35, 125.52, 124.02, 122.68, 121.02, 117.07, 115.70, 98.46, 85.54, 64.79, 42.90, 9.14. IR (KBr) ν_{max}/cm^{-1}: 3448 (br), 2922w, 1624sh (C═N), 1618s (7-chloroquinoline), 1578s (7-chloroquinoline), 1560w (7-chloroquinoline), 1541w, 1508w, 1449m, 1325w, 1143w, 1029w, 809w, 758w. MS (ES+, m/z): 652 ([M − Cl]$^+$) 100%, 688 ([M + H]$^+$) 15%.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((5-fluro-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chloroiridium(III), [IrClCp*(L2)] (4b). This compound was synthesized from **HL4** (17.3 mg, 0.050 mmol) and $[IrCp^*Cl_2]_2$ (20 mg, 0.025 mmol) by the procedure used for the synthesis for complex **3a**. The product **4b** was obtained as a yellow solid: Yield: 28 mg (79%). ^{1}H NMR (500 MHz, CDCl3, δ ppm): 8.31 (d, 1H, J = 5.3 Hz), 8.00 (d, 1H, J = 8.8 Hz), 7.88 (d, 1H, J = 1.4 Hz), 7.52 (s, 1H), 7.46 (s, 1H) 7.24 (dd, 1H, J = 1.7 Hz, J = 9.2 Hz), 6.99 (dt, 1H, J = 3.3 Hz, J = 9.1 Hz), 6.78 (dd, 1H, J = 4.6 Hz, J = 9.2 Hz), 6.50 (d, 1H, J = 5.7 Hz), 6.41 (dd, 1H, J =

2.9 Hz, J = 8.6 Hz), 4.40 (m, 1H), 4.23 (m, 1H), 4.11 (m, 1H), 3.78 (m, 1H), 1.59 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 162.03, 161.20, 153.46 (d, J = 230.1 Hz), 150.66, 150.02, 136.01, 126.78, 126.04, 123.66 (d, J = 7.0 Hz), 123.48, 123.35 (d, J = 23.5 Hz), 119.53 (d, J = 7.1 Hz), 117.27, 116.78 (d, J = 22.9 Hz), 116.77, 98.39, 85.64, 64.97, 42.57, 9.16. IR (KBr) ν_{max}/cm^{-1} 3444 (br), 2921w, 1633sh (C═N), 1614s (7-chloroquinoline), 1581s (7-chloroquinoline), 1538w (7-chloroquinoline), 1464s, 1384w, 1313w, 1140w, 1028m, 813w. MS (ES+, m/z): 670 ([M − Cl]$^+$) 100%, 706 ([M + H]$^+$) 7%.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((5-chloro-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chloroiridium(III), [IrClCp*(L5)] (5b). This compound was synthesized from **HL5** (18 mg, 0.050 mmol) and $[IrCp^*Cl_2]_2$ (20 mg, 0.025 mmol) by the procedure used for the synthesis of complex **3a**. The product **5b** was obtained as a yellow solid. Yield: 27 mg (75%). ^{1}H NMR (500 MHz, CDCl3, δ ppm): 8.37 (d, 1H, J = 4.2 Hz), 7.98 (d, 1H, J = 8.4 Hz), 7.94 (d, 1H, J = 1.6 Hz), 7.50 (s, 1H), 7.39 (s, 1H), 7.24 (d, 1H, J = 1.7 Hz), 7.16 (dd, 1H, J = 2.7 Hz, J = 9.1 Hz), 6.80 (d, 1H, J = 9.0 Hz), 6.63 (d, 1H, J = 1.9 Hz), 6.49 (d, 1H, J = 5.9 Hz), 4.41 (m, 1H), 4.21 (m, 1H), 4.11 (m, 1H), 3.81 (m, 1H), 1.59 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 163.12, 161.96, 151.03, 149.23, 146.63, 136.31, 134.86, 131.93, 126.11, 125.97, 124.13, 123.51, 121.27, 119.36, 116.94, 98.37, 85.59, 64.85, 42.55, 8.99. IR (KBr) ν_{max}/cm^{-1}: 3433 (br), 2920w, 1621sh (C═N), 1615s (7-chloroquinoline), 1580s (7-chloroquinoline), 1558w (7-chloroquinoline), 1520w 1456s, 1383w, 1314m, 1173w, 1138w, 1079w, 1028w, 876w, 821w. MS (ES+, m/z): 686 ([M − Cl]$^+$) 100%, 722 ([M + H]$^+$) 18%.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((5-bromo-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chloroiridium(III), [IrClCp*(L6)] (6b). This compound was synthesized from **HL6** (20.3 mg, 0.050 mmol) and $[IrCp^*Cl_2]_2$ (20 mg, 0.025 mmol) by the procedure used for the synthesis of complex **3a**. The product **6b** was obtained as a yellow solid. Yield: 19 mg (~46%). ^{1}H NMR (500 MHz, CDCl3, δ ppm): 8.35 (d, 1H, J = 4.0 Hz), 7.99 (d, 1H, J = 8.7 Hz), 7.94 (d, 1H, J = 1.7 Hz), 7.50 (s, 1H), 7.39 (br, 1H), 7.27 (d, 1H, J = 2.6 Hz), 7.24 (dd, 1H, J = 1.9 Hz, J = 9.0 Hz), 6.75 (d, 1H, J = 6.8 Hz), 6.76 (s, 1H), 6.50 (d, 1H, J = 5.8 Hz), 4.43 (m, 1H), 4.22 (m, 1H), 4.11 (m, 1H), 3.81 (m, 1H), 1.59 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 163.54, 162.14, 151.17, 149.38, 146.60, 137.79, 136.61, 135.25, 126.36, 126.11, 124.76, 123.66, 122.21, 117.08, 106.19, 98.52, 85.78, 65.05, 42.65, 9.15. IR (KBr) ν_{max}/cm^{-1}: 3427 (br), 2920w, 1621sh (C═N), 1615s (7-chloroquinoline), 1580s (7-chloroquinoline), 1557w (7-chloroquinoline), 1520w, 1456s, 1384w, 1315w, 1171w, 1137w, 1029m, 875w, 820w. MS (ES+, m/z): 732 ([M − Cl]$^+$) 100%, 768 ([M + H]$^+$) 12%.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((5-iodo-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chloroiridium(III), [IrClCp*(L7)] (7b). This compound was synthesized from **HL7** (22.7 mg, 0.050 mmol) and $[IrCp^*Cl_2]_2$ (20 mg, 0.025 mmol) by the procedure used for the synthesis of complex **3a**. The product **7b** was obtained as a yellow solid. Yield: 43 mg (~98%). ^{1}H NMR (500 MHz, CDCl3, δ ppm): 8.50 (d, 1H, J = 5.4 Hz), 7.92 (d, 1H, J = 1.6 Hz), 7.83 (d, 1H, J = 9.0 Hz), 7.41 (dd, 1H, J = 2.2 Hz, J = 8.9 Hz), 7.31 (br, 1H), 7.20 (dd, 1H, J = 1.9 Hz, J = 9.0 Hz), 6.84 (s, 1H), 6.80 (d, 1H, J = 1.8 Hz), 6.67 (d, 1H, J = 9.0 Hz), 6.41 (d, 1H, J = 5.4 Hz), 4.32 (m, 1H), 4.18 (m, 1H), 4.05 (m, 1H), 3.75 (m, 1H), 1.60 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 164.18, 161.94, 151.42, 149.04, 146.40, 142.97, 141.53, 136.52, 126.25, 125.78, 125.32, 123.80, 123.61, 116.97, 102.60, 98.67, 85.69, 74.44, 64.91, 42.80, 9.09. IR (KBr) ν_{max}/cm^{-1}: 3449 (br), 2920m, 1637sh (C═N), 1612s (7-chloroquinoline), 1578s (7-chloroquinoline), 1541w (7-chloroquinoline), 1522w, 1458s, 1382m, 1315m, 1170w, 1030m, 875w, 820w. MS (ES+, m/z): 778 ([M − Cl]$^+$) 100%, 814 ([M + H]$^+$) 15%.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((2-hydroxy-5-nitrophenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chloroiridium(III), [IrClCp*(L8)] (8b). This compound was synthesized from **HL8** (18.6 mg, 0.050 mmol) and $[IrCp^*Cl_2]_2$ (20 mg, 0.025 mmol) by the procedure used for the synthesis of complex **3a**. The product **8b** was obtained as an orange solid. Yield: 15 mg (~36%). ^{1}H NMR (500 MHz, CDCl3, δ ppm): 8.43 (d, 1H, J = 5.8 Hz), 8.11 (dd, 1H, J = 2.8 Hz, J = 9.3 Hz), 7.98 (d, 1H, J = 1.6 Hz), 7.90 (d, 1H, J = 8.7 Hz), 7.82 (br, 1H), 7.78 (d, 1H, J = 2.7 Hz), 7.34 (br, 1H), 7.23 (dd, 1H, J = 1.8 Hz, J = 8.7 Hz), 6.86 (d, 1H, J = 9.6 Hz), 6.54 (d, 1H, J = 5.8 Hz), 4.46 (m, 1H), 4.26 (m, 1H), 4.10 (m, 1H), 3.88 (m, 1H), 1.62 (s, 5H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 169.19, 162.42, 150.32, 149.15, 136.54, 136.46, 131.98, 129.38, 126.26, 126.19, 123.24, 122.96, 119.22, 116.82, 115.81, 98.34, 86.27, 65.50, 42.28, 9.01. IR (KBr) ν_{max}/cm^{-1}: 3433 (br), 2921w, 1636sh (C═N), 1623s (7-chloroquinoline), 1603s, 1578s (7-chloroquinoline), 1547w (7-chloroquinoline), 1473m, 1458w, 1382w, 1363w, 1313s, 1130w, 1100m, 1029m, 947w, 904w, 875w, 831w, 804w. MS (ES+, m/z): 697 ([M − Cl]$^+$) 100%, 733 ([M + H]$^+$) 16%.

(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((2-hydroxy-5-methoxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chloroiridium(III), [IrCl(Cp)*(L9)] (9b). This compound was synthesized from **HL9** (17.9 mg, 0.050 mmol) and $[IrCp^*Cl_2]_2$ (20 mg, 0.025 mmol) by the procedure used for the synthesis of complex **3a**. The product **9b** was obtained as a yellow solid. Yield: 13 mg (~34%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.20 (br, 1H), 8.05 (br, 1H), 7.99 (s, 1H), 7.61 (s, 1H), 7.60 (br, 1H), 7.34 (d, 1H, J = 8.0 Hz), 6.90 (dd, 1H, J = 2.8 Hz, J = 9.1 Hz), 6.74 (d, 1H, J = 7.9 Hz), 6.60 (s, 1H), 6.17 (s, 1H), 4.56 (m, 1H), 4.21 (m, 2H), 4 3.82 (m, 1H), 1.58 (s, 15H, Cp*CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 177.03, 161.95, 159.89, 151.69, 149.66, 149.44, 127.94, 125.42, 125.34, 123.48, 123.16, 118.83, 118.8, 117.55, 113.47, 98.43, 85.33, 64.53, 55.8, 42.03, 8.98 IR (KBr) ν_{max}/cm^{-1}: 3432 (br), 2920w, 1633sh (C═N), 1611s (7-chloroquinoline), 1580s (7-chloroquinoline), 1539m (7-chloroquinoline), 1469s, 1377w, 1309w, 1263w, 1219w, 1155w, 1140w, 1031m, 875w, 818w, 775w. MS (ES+, m/z): 682 ([M − Cl]$^+$) 100%, 718 ([M + H]$^+$) 25%.

**(η^5-Pentamethylcyclopentadienyl){(*N*-(2-((5-*tert*-butyl-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)}chloro-

iridium(III), [IrClCp*(L10)] (10b). This compound was synthesized from **HL10** (19.1 mg, 0.050 mmol) and $[IrCp^*Cl_2]_2$ (20 mg, 0.025 mmol) by the procedure used for the synthesis of complex **3a**. The product **10b** was obtained as an orange solid. Yield: 19 mg (~47%). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.26 (s, 1H), 8.00 (d, 1H, J = 7.6 Hz), 7.88 (d, 1H, J = 1.4 Hz), 7.57 (br, 1H), 7.43 (s, 1H), 7.27 (dd, 1H, J = 2.5 Hz, J = 8.8 Hz), 7.16 (d, 1H, J = 8.7 Hz), 6.76 (d, 1H, J = 8.8 Hz), 6.51 (d, 1H, J = 5.2 Hz), 6.44 (s, 1H), 4.43 (m, 1H), 4.19 (m, 1H), 4.09 (m, 1H), 3.79 (m, 1H), 1.59 (s, 15H, Cp*CH_3), 1.09 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 163.26, 162.62, 152.50, 151.15, 149.50, 137.90, 136.30, 133.57, 129.34, 126.34, 126.10, 123.92, 122.08, 119.49, 117.26, 98.67, 85.50, 64.65, 42.53, 33.46, 31.31, 9.12. IR (KBr) ν_{max}/cm^{-1}: 3423 (br), 2959m, 2921w, 1637sh (C═N), 1618s (7-chloroquinoline), 1578s (7-chloroquinoline), 1533w (7-chloroquinoline), 1474m, 1458w, 1380w, 1363w, 1320w, 1256w, 1178w, 1141w, 1030m, 829w. MS (ES+, m/z): 708 ($[M - Cl]^+$) 100%, 744 ($[M + H]^+$) 12%.

X-ray structure determinations

[RhL1Cp*Cl]Cl 1a and [Ir(L1^{ox})Cp*Cl]Cl 11. The crystals of **1a** and **11** were immersed in cryo-oil, mounted in a nylon loop and the X-ray diffraction data were collected on a Bruker AXS Kappa ApexII Duo diffractometer using Mo Kα radiation (λ = 0.71073 Å) at a temperature of 170(2) and 120(2) K for complexes **1a** and **11**, respectively. The APEX2 program package was used for cell refinement and data reduction. The structures were solved by direct methods using SHELXS-97.[41] A semi-empirical absorption correction based on equivalent reflections (SADABS) was applied to the data.[42] Structural refinements were carried out using SHELXL-97. The NH hydrogen atoms were located from the difference Fourier map but constrained to ride on their parent atom, with U_{iso} = 1.5U_{eq} (parent atom). Other hydrogen atoms were positioned geometrically and were also constrained to ride on their parent atoms, with C–H = 0.95–1.00 Å, and U_{iso} = 1.2–1.5U_{eq} (parent atom).

[RhL5Cp*Cl], 5a. The X-ray intensity data for complex **5a** were measured on a Bruker Apex II CCD diffractometer at room temperature. Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in three sets of 20 exposures, collected in three different ω regions, and eventually refined against all data. A full sphere of reciprocal space was scanned by 0.3° ω steps. The software SMART[43] was used for collecting frames of data, indexing reflections and determination of lattice parameters. The collected frames were then processed for integration by the SAINT program,[43] and an empirical absorption correction was applied using SADABS.[42] The structures were solved by direct methods (SIR 97)[44] and subsequent Fourier syntheses and refined by full-matrix least-squares on F^2 (SHELXTL)[45] using anisotropic thermal parameters for all non-hydrogen atoms. The pentamethylcyclopentadienyl ligand was found to be disordered over two sites. The atomic positions of this fragment were split to model the disorder, and occupancy was allowed to refine. At the latest stages of refinement, occupancy was fixed at 61% and 39%, respectively, providing satisfactory anisotropic thermal motion parameters. One solvent molecule (CH_2Cl_2) is present in the asymmetric unit. The aromatic, methylene and methyl H atoms were placed in calculated positions and refined with isotropic thermal parameters U(H) = 1.2U_{eq}(C) or U(H) = 1.5U_{eq}(C–Me), respectively and allowed to ride on their carrier carbons whereas the imine H atom in **5a** was located in the Fourier map and refined isotropically [U(H) = 1.2U_{eq}(N)]. Crystal data and details of the data collections for compounds **1a**, **5a** and **11** are reported in Table 1.

Determination of the antiplasmodial activity

The test samples were tested in triplicate on one occasion against chloroquine-sensitive (CQS) NF54 and chloroquine-resistant (CQR) Dd2 strains of *Plasmodium falciparum*. Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen.[46] Quantitative assessment of antiplasmodial activity *in vitro* was determined *via* the parasite lactate dehydrogenase assay using a modified method described by Makler.[47] The test samples were prepared to a 20 mg ml^{-1} stock solution in 100% DMSO and sonicated to enhance solubility. Samples were tested as a suspension if not completely dissolved. Stock solutions were stored at −20 °C. Further dilutions were prepared on the day of the experiment. Chloroquine (CQ) and artesunate were used as the reference standards in all experiments. A full dose–response was performed for all compounds to determine the concentration inhibiting 50% of parasite growth (IC_{50}-value). Test samples were tested at a starting concentration of 10 μg ml^{-1}, which was then serially diluted 2-fold in complete medium to give 10 concentrations, with the lowest concentration being 0.02 μg ml^{-1}. The same dilution technique was used for all samples. Samples were also tested at a starting concentration of 1000 ng ml^{-1}. Reference standards were tested at a starting concentration of 1000 ng ml^{-1}. The highest concentration of solvent to which the parasites were exposed had no measurable effect on the parasite viability (data not shown). The IC_{50}-values were obtained using a non-linear dose–response curve fitting analysis *via* Graph Pad Prism v.4.0 software.

Conclusions

New pentamethylcyclopentadienyl-rhodium and -iridium complexes with chloroquine analogue ligands have been synthesized and fully characterized. Molecular structures of two complexes, [Rh(L1)Cp*Cl]Cl(**1a**), and [Rh(L5)Cp*Cl] (**5a**) have also been authenticated by X-ray crystallography. The iridium complex [Ir(L1)Cp*Cl]Cl (**1b**) underwent a ligand dehydrogenation reaction to yield the imine complex **11** during crystallization from acetone, and the structure of [Ir(L1^{ox})Cp*Cl]Cl **11** was elucidated by X-ray crystallography.

All complexes have been evaluated for antimalarial activity against the CQS-NF54 and CQR-Dd2 strains of the

P. falciparum malaria parasite. The rhodium complexes showed good antimalarial activity against both strains. The rhodium complexes [Rh(L4)Cp*Cl] (**4a**), [Rh(L5)Cp*Cl] (**5a**) and [Rh(L6)Cp*Cl] (**6a**) showed higher antimalarial activity than chloroquine against the CQS-NF54 strain. To the best of our knowledge, **4a** is the rhodium complex with the highest anti-plasmodial activity reported thus far that is not a ferroquine derivative. However, the iridium complexes showed only moderate activity against the CQS strain. The iridium complexes **1b** and **2b** are inactive against the CQR-Dd2 strain. A correlation between the nature (Hammett's σ_p parameter) of the electron-withdrawing groups on the salicylaldimine ligands and the anti-plasmodial activity against the CQSNF54 strain could be detected, but no such trend could be seen with the activities against the CQR-Dd2 strain.

Acknowledgements

EE thanks FLÄK, the Research School in Pharmaceutical Sciences at Lund University, for a PhD studentship. KK thanks the European Commission (Erasmus Mundus Europe Asia, EMEA) for a postdoctoral fellowship. Professor Steve Colbran, University of New South Wales, Australia, is thanked for inspiring the start of this project and for a gift of $[RhCp^*Cl_2]_2$ and $[IrCp^*Cl_2]_2$.

References

1 World Malarial Report 2014, World Health Organization, 2014.
2 L. H. Bannister, J. M. Hopkins, R. E. Fowler, S. Krishna and G. H. Mitchell, *Parasitol. Today*, 2000, **16**, 427–433.
3 M. Schlitzer, *Arch. Pharm.*, 2008, **341**, 149–163.
4 P. I. Trigg and A. V. Kondrachine, in *Malaria: Parasite Biology, Pathogenesis and Protection*, ASM Press, Washington DC, 1998.
5 C. Biot, W. Castro, C. Y. Botte and M. Navarro, *Dalton Trans.*, 2012, **41**, 6335–6349.
6 L. M. Ursos and P. D. Roepe, *Med. Res. Rev.*, 2002, **22**, 465–491.
7 K. A. de Villiers and T. J. Egan, *Molecules*, 2009, **14**, 2868–2887.
8 T. J. Egan and H. M. Marques, *Coord. Chem. Rev.*, 1999, **190–192**, 493–517.
9 A. Leed, K. DuBay, L. M. B. Ursos, D. Sears, A. de Dios and C. P. D. Roepe, *Biochemistry*, 2002, **31**, 10245–10255.
10 P. J. Rosenthal, *Antimalarial chemotherapy : mechanisms of action, resistance, and new directions in drug discovery*, Humana Press, New Jersey, 2001.
11 C. R. Chong and D. J. Sullivan Jr., *Biochem. Pharmacol.*, 2003, **66**, 2201–2212.
12 T. J. Egan, R. Hunter, C. H. Kaschula, H. M. Marques, A. Misplon and J. Walden, *J. Med. Chem.*, 2000, **43**, 283–291.
13 B. Rosenberg, L. Van Camp and T. Krigas, *Nature*, 1965, **205**, 698–699.
14 B. Rosenberg, L. Van Camp, J. E. Trosko and V. H. Mansour, *Nature*, 1969, **222**, 385–386.
15 C. Biot and D. Dive, in *Medicinal Organometallic Chemistry*, ed. G. Jaouen and N. Metzler-Nolte, Springer, Berlin Heidelberg, 2010, ch. 7, vol. 32, pp. 155–193.
16 C. G. Hartinger and P. J. Dyson, *Chem. Soc. Rev.*, 2009, **38**, 391–401.
17 C. Biot, G. Glorian, L. A. Maciejewski and J. S. Brocard, *J. Med. Chem.*, 1997, **40**, 3715–3718.
18 M. Henry, S. Briolant, A. Fontaine, J. Mosnier, E. Baret, R. Amalvict, T. Fusai, L. Fraisse, C. Rogier and B. Pradines, *Antimicrob. Agents Chemother.*, 2008, **52**, 2755–2759.
19 C. Biot, F. Nosten, L. Fraisse, D. Ter-Minassian, J. Khalife and D. Dive, *Parasite*, 2011, **18**, 207–214.
20 R. A. Sánchez-Delgado, M. Navarro, H. Pérez and J. A. Urbina, *J. Med. Chem.*, 1996, **39**, 1095–1099.
21 C. S. Rajapakse, A. Martinez, B. Naoulou, A. A. Jarzecki, L. Suarez, C. Deregnaucourt, V. Sinou, J. Schrevel, E. Musi, G. Ambrosini, G. K. Schwartz and R. A. Sanchez-Delgado, *Inorg. Chem.*, 2009, **48**, 1122–1131.
22 L. Glans, A. Ehnbom, C. de Kock, A. Martinez, J. Estrada, P. J. Smith, M. Haukka, R. A. Sanchez-Delgado and E. Nordlander, *Dalton Trans.*, 2012, **41**, 2764–2773.
23 E. Ekengard, L. Glans, I. Cassells, T. Fogeron, P. Govender, T. Stringer, P. Chellan, G. C. Lisensky, W. H. Hersh, I. Doverbratt, S. Lidin, C. de Kock, P. J. Smith, G. S. Smith and E. Nordlander, *Dalton Trans.*, 2015, **44**, 19314–19329.
24 M. Navarro, S. Pekerar and H. A. Pérez, *Polyhedron*, 2007, **26**, 2420–2424.
25 D. A. van Schalkwyk and T. J. Egan, *Drug Resist. Updates*, 2006, **9**, 211–226.
26 D. C. Warhurst, *Malar. J.*, 2003, **2**, 31.
27 D. C. Warhurst, J. C. Craig, I. S. Adagu, D. J. Meyer and S. Y. Lee, *Malar. J.*, 2003, **2**, 26.
28 M. Adams, C. de Kock, P. J. Smith, K. M. Land, N. Liu, M. Hopper, A. Hsiao, A. R. Burgoyne, T. Stringer, M. Meyer, L. Wiesner, K. Chibale and G. S. Smith, *Dalton Trans.*, 2015, **44**, 2456–2468.
29 P. Chellan, K. M. Land, A. Shokar, A. Au, S. H. An, D. Taylor, P. J. Smith, T. Riedel, P. J. Dyson, K. Chibale and G. S. Smith, *Dalton Trans.*, 2014, **43**, 513–526.
30 W. Nkoana, D. Nyoni, P. Chellan, T. Stringer, D. Taylor, P. J. Smith, A. T. Hutton and G. S. Smith, *J. Organomet. Chem.*, 2014, **752**, 67–75.
31 Y. Li, C. de Kock, P. J. Smith, K. Chibale and G. S. Smith, *Organometallics*, 2014, **33**, 4345–4348.
32 Y. Li, C. de Kock, P. J. Smith, H. Guzgay, D. T. Hendricks, K. Naran, V. Mizrahi, D. F. Warner, K. Chibale and G. S. Smith, *Organometallics*, 2013, **32**, 141–150.
33 D. Carmona, C. Vega, F. J. Lahoz, S. Elipe, L. A. Oro, M. P. Lamata, F. Viguri, R. García-Correas, C. Cativiela and M. P. López-Ram de Víu, *Organometallics*, 1999, **18**, 3364–3371.
34 R. Payne, P. Govender, B. Therrien, C. M. Clavel, P. J. Dyson and G. S. Smith, *J. Organomet. Chem.*, 2013, **729**, 20–27.

35 H. Brunner, A. Köllnberger, T. Burgemeister and M. Zabel, *Polyhedron*, 2000, **19**, 1519–1526.
36 D. Carmona, F. J. Lahoz, S. Elipe, L. A. Oro, M. P. Lamata, F. Viguri, C. Mir, C. Cativiela and M. P. L. R. de Viu, *Organometallics*, 1998, **17**, 2986–2995.
37 F. Richard Keene, *Coord. Chem. Rev.*, 1999, **187**, 121–149.
38 T. Jerphagnon, A. J. A. Gayet, F. Berthiol, V. Ritleng, N. Mršić, A. Meetsma, M. Pfeffer, A. J. Minnaard, B. L. Feringa and J. G. de Vries, *Chem. – Eur. J.*, 2009, **15**, 12780–12790.
39 L. Barloy, J.-T. Issenhuth, M. G. Weaver, N. Pannetier, C. Sirlin and M. Pfeffer, *Organometallics*, 2011, **30**, 1168–1174.
40 K. Yearick, K. Ekoue-Kovi, D. P. Iwaniuk, J. K. Natarajan, J. Alumasa, A. de Dios, C. P. D. Roepe and C. Wolf, *J. Med. Chem.*, 2008, **51**, 1995–1998.
41 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2008, **64**, 112–122.
42 G. M. Sheldrick, *SADABS, program for empirical absorption correction*, University of Göttingen, Göttingen, Germany, 1996.
43 *SMART & SAINT Software Reference Manuals, version 5.051 (Windows NT Version)*, Bruker Analytical X-ray Instruments Inc., Madison, WI, 1998.
44 A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115–119.
45 G. M. Sheldrick, *SHELXTLplus (Windows NT Version) Structure Determination Package*, Bruker Analytical X-ray Instruments Inc., 5.1 edn., 1998.
46 W. Trager and J. B. Jensen, *Science*, 1976, **193**, 673–675.
47 M. T. Makler and D. J. Hinrichs, *Am. J. Trop. Med. Hyg.*, 1993, **48**, 205–210.