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Journal Name

ARTICLE

Antimalarial activity of ruthenium(II) and osmium(II) arene complexes with mono- and bidentate chloroquine analogue ligands, reviewed by the authors

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Eight new ruthenium and five new osmium *p*-cymene half-sandwich complexes have been synthesized, characterized and evaluated for antimalarial activity. All complexes contain ligands that are based on a 4-chloroquinoline framework related to the antimalarial drug chloroquine. Ligands HL¹⁻⁸ are salicylaldimine derivatives, where HL¹ = *N*-(2-(2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine, and HL²⁻⁸ contain non-hydrogen substituents in the 3-position of the salicylaldimine ring, viz. F, Cl, Br, I, NO₂, OMe and ^tBu for HL²⁻⁸, respectively. Ligand HL⁹ is also a salicylaldimine-containing ligand with substitutions in both 3- and 5-positions of the salicylaldimine moiety, i.e. *N*-(2-(2-hydroxy-3,5-di-*tert*-butylphenyl)methyl-imino)ethyl)-7-chloroquinolin-4-amine, while HL¹⁰ is *N*-(2-(1-methyl-1*H*-imidazol-2-yl)methylamino)ethyl)-7-chloroquinolin-4-amine. The half sandwich metal complexes that have been investigated are [Ru(η^6 -cym)(L¹⁻⁸)Cl] (Ru-1 - Ru-8, cym = *p*-cymene), [Os(η^6 -cym)(L^{1-3,5,7})Cl] (Os-1 - Os-3, Os-5, and Os-7), [M(η^6 -cym)(HL⁹)Cl₂] (M=Ru, Ru-HL⁹; M=Os, Os-HL⁹) and [M(η^6 -cym)(L¹⁰)Cl]Cl (M=Ru, Ru-10; M= Os, Os-10). In complexes Ru-1 - Ru-8 and Ru-10, Os-1 - Os-3, Os-5 and Os-7 and Os-10, the ligands were found to coordinate as bidentate *N,O*- and *N,N*-chelates, while in complexes Ru-HL⁹ and Os-HL⁹, monodentate coordination of the ligands through the quinoline nitrogen was established. The antimalarial activity of the new ligands and complexes was evaluated against chloroquine sensitive (NF54 and D10) and chloroquine resistant (Dd2) *Plasmodium falciparum* malaria parasite strains. Coordination of ruthenium and osmium arene moieties to the ligands resulted in lower antiplasmodial activities relative to the free ligands, but the resistance index is better for the ruthenium complexes compared to chloroquine. Overall, osmium complexes appeared to be less active than the corresponding ruthenium complexes.

Introduction

The development of organometallic complexes for medicinal purposes has progressed rapidly during the last decade.¹⁻³ Although the development of anticancer agents is one of the largest research areas within the field, other applications, e.g. organometallics as antimalarial agents, have also generated scientific interest.⁴⁻⁶ Approximately half the world's population

is at risk of contracting malaria and the disease kills around 600 000 people per year. An African child dies from malaria every 45 seconds and widespread resistance to many of the available antimalarial drugs is undermining malaria control efforts.⁷ The recent reports of developing resistance against artemisinins have added renewed urgency to the development of new antimalarials.⁸ Chloroquine (CQ, Figure 1) was the mainstay of malaria chemotherapy in large parts of the world for decades, but resistance has now prompted its replacement in most malaria-endemic countries.⁹ Ferroquine (FQ, Figure 1), a ferrocene analogue of chloroquine, is a particularly successful organometallic antimalarial agent that has completed phase IIb clinical trials.^{10,11}

Organometallic ruthenium arene complexes are a class of organometallic half-sandwich compounds that show both catalytic activity and promising anti-tumor activity, and such compounds have consequently been the subject of much research effort.^{12,13} It has been shown that ruthenium coordination complexes and organometallic ruthenium arene

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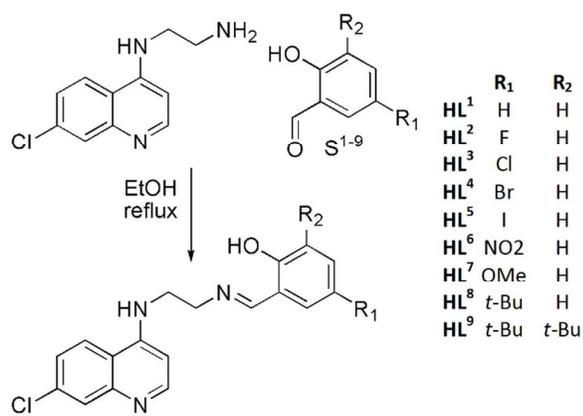
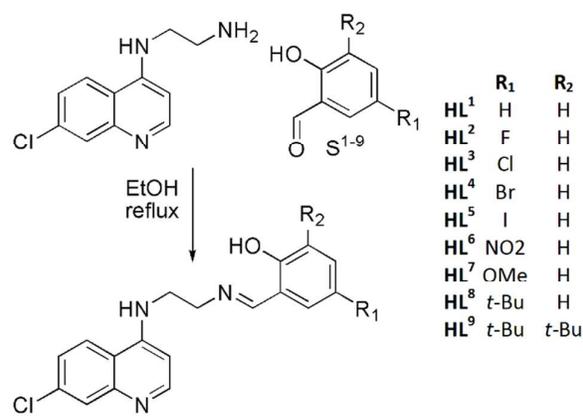
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Electronic Supplementary Information (ESI) available: additional electrochemical details, Hammett's σ -plots, ¹H-NMR assignment of Ru-HL⁹ and Os-HL⁹, and additional structure drawings of Ru-1. CCDC 992172, CCDC 1005351, CCDC 1005352, CCDC 1408709, CCDC 1408710. See DOI: 10.1039/x0xx00000x

Scheme 1. Synthesis of ligands HL¹⁻⁹.Scheme 1. Synthesis of ligands HL¹⁻⁹.

complexes of chloroquine (Figure 1) exhibit increased activity towards chloroquine resistant malaria strains compared to chloroquine itself.^{14,15} In addition, the arene ruthenium chloroquine complexes showed anticancer activity against several tumor cell lines.¹⁶ In an earlier study, we reported half-sandwich ruthenium arene complexes with bidentate chloroquine analogue ligands.¹⁷ Relative to corresponding compounds with *N,N*-chelating ligands, a complex (**Ru-1**, Figure 1) containing a chloroquine analogue with an *N,O*-chelating salicylaldimine unit (**HL¹**, Figure 1) was shown to have the highest antimalarial activity.¹⁷

In comparison to the above-mentioned ruthenium half-sandwich complexes, arene complexes of the heavier congener osmium are much less studied, but recently osmium arene complexes with biological activity have been reported.¹⁸⁻²⁵ Sadler and co-workers have synthesized and evaluated the anticancer activity of a large number of osmium arene complexes with bidentate ligands, including *N,N*-, *N,O*- and *O,O*-chelates.¹⁸⁻²⁰ In addition, Keppler, Arion and co-workers have reported antiproliferative osmium arene complexes with ligands based on biologically active so-called paullones, an indolo-benzazepine that can be modified to create *N,N*-chelating ligands.^{23,24,26,27} Recently Pfeffer *et al.* have reported cyclometallated osmium arene complexes with *C,N*-chelating ligands that show activity against glioblastoma cells.²⁵ In all three groups of compounds, the nature of the ligand and its mode of coordination have great impact on the anticancer activity of the complex.

Here, we wish to present the synthesis and characterization of a group of new ruthenium and osmium arene compounds with chloroquine analogue ligands similar to that used for **Ru-1** (Figure 1), which coordinate to the metal in bidentate or monodentate modes. This new set of complexes enables the study of i) the effect of changing the metal from Ru to Os, ii) the effect of the coordination mode of the ligand and iii) the effect of the electronic properties of the substituent in *para*-position to the coordinating phenoxy group on antimalarial activity. The activity of the complexes was tested *in vitro* on *Plasmodium*

falciparum malaria parasites; to our knowledge, these are the first osmium compounds tested for antimalarial activity.

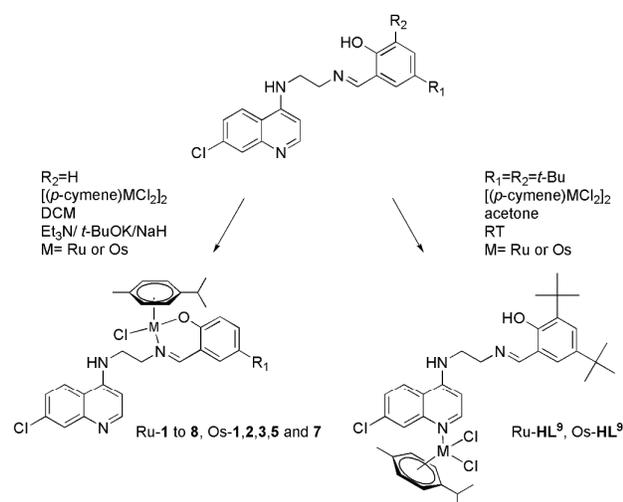
Results and discussion

Synthesis.

Considering the relatively good antimalarial activity exhibited by the ligand **HL¹** and its Ru *p*-cymene complex **Ru-1** (*vide supra* and Fig. 1), we chose to explore this ligand framework for possible electronic influence exerted by substituent groups on the antimalarial activity of the ligands and their metal complexes. Thus, reaction of *N*¹-(7-chloroquinolin-4-yl)ethane-1,2-diamine with the substituted salicylaldehydes **S¹⁻⁹** in refluxing ethanol yielded the Schiff bases **HL¹⁻⁹** in fair to excellent yields (51% to 99 %) (Scheme 1), and these ligands were characterized by ¹H-NMR and ¹³C NMR spectroscopy, IR spectroscopy and mass spectrometry (*cf.* Experimental Section). Deprotonation of the (pro)ligands **HL¹⁻⁸** with Et₃N, *t*-BuOK or NaH in dichloromethane followed by addition of [Ru(*p*-cymene)Cl₂]₂ gave the complexes [Ru(L)(*p*-cymene)Cl] (L=**L¹⁻⁸**; **Ru-1** - **Ru-8**, respectively) in fair to excellent yields (53% to 93%), and in the corresponding reactions of **HL¹⁻³**, **HL⁵** and **HL⁷** with [Os(*p*-cymene)Cl₂]₂, the analogous [Os(L)(*p*-cymene)Cl] complexes **Os-1** - **Os-3**, **Os-5** and **Os-7** were obtained in fair yields (36% to 72 %, Scheme 2, *cf.* Experimental Section).

The choices of base, workup and purification procedures were found to have only limited effect on the yields and purities of the complexes. Synthesis of the imidazolyl-containing ligand *N*-(2-((1-methyl-1H-imidazol-2-yl)methylamino)ethyl)-7-chloroquinolin-4-amine (**L¹⁰**) and its ruthenium *p*-cymene derivative, **Ru-10**, have been reported earlier.¹⁷ The complex [Os(*p*-cymene)(**L¹⁰**)Cl]Cl (**Os-10**) was synthesized by stirring [Os(*p*-cymene)Cl₂]₂ with ligand **L¹⁰** in 1:2 molar ratio in acetone at room temperature (Scheme 3).

Under the conditions used to synthesize the above-mentioned half-sandwich ruthenium and osmium complexes, the 2,5-di-

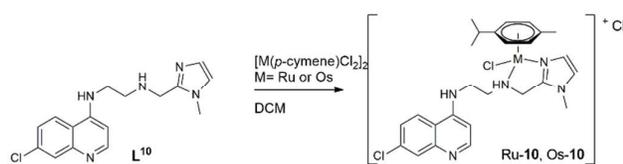


Scheme 2. Synthesis of complexes Ru-1 to 8, Os-1, 2, 3, 5 and 7 and Ru-HL⁹ and Os-HL⁹, M= Ru or Os.

tert-butyl substituted ligand HL⁹ failed to give analogous ruthenium/osmium complexes; instead, inseparable mixtures of products were obtained. However, reaction of HL⁹ with half an equivalent of metal dimer in the absence of base gave products whose ¹H-NMR spectra and mass spectrometry data (*vide infra*) were consistent with complexes of formulation [Ru(*p*-cymene)(HL⁹)Cl₂], Ru-HL⁹, and [Os(*p*-cymene)(HL⁹)Cl₂], Os-HL⁹. An NMR spectroscopy scale reaction showed that reaction of HL¹ with the osmium dimer under the same conditions did not yield a monodentate complex analogous to Os-HL⁹, but rather resulted in a mixture of species that could not be properly identified. This is most likely due to the relative availability of the hydroxyl group, which is sterically protected by the *tert*-butyl groups in HL⁹ but available for coordination in HL¹ which in the absence of base leads to competing coordination reactions that result in a complex mixture of products, including coordination through the salicylaldimine moiety and the quinoline nitrogen and coordination to both coordination sites. There are no examples in the literature of osmium-arene complexes with salicylaldimine ligands containing a *tert*-butyl substituent in the 2 position, *ortho* to the phenolic group, and the few examples of ruthenium complexes are reported to be unstable in solution.^{28–30}

Characterization

Coordination of unsymmetrical bidentate ligands to the Ru(η^6 -*p*-cymene)Cl and Os(η^6 -*p*-cymene)Cl moieties induces chirality at the metal atom, which results in loss of two-fold symmetry of the *p*-cymene ring. Hence, the observation of the aromatic



Scheme 3. Synthesis of complex Ru-10 and Os-10.

protons of the *p*-cymene as four separate doublets and the *p*-cymene isopropyl group as two doublets in the ¹H-NMR spectra of Ru-1 - Ru-8 is consistent with a bidentate coordination mode of the salicylaldimine ligand. An upfield shift of the imine proton of approximately 1.1 ppm and the disappearance of the phenolic proton resonance between 13.5 and 12.5 ppm upon coordination of the ruthenium arene moiety strongly indicates that the structures of Ru-1 - Ru-8 are as shown in Scheme 2. The IR-spectra of complexes Ru-1 - Ru-8 show the imine C=N stretch as a shoulder at 1617-1632 cm⁻¹ and the phenolic C-O stretch at 1315-1330 cm⁻¹, compared to 1640-1650 cm⁻¹ and 1250 cm⁻¹ in the free ligands. The distinct new vibration frequencies of the coordinated imine and phenoxyate moieties, as well as the disappearance of an O-H band around 3200 cm⁻¹, further support the proposed structures of complexes Ru-1 - Ru-8. The ESI mass spectra of complex Ru-1 - Ru-8 all show molecular peaks ([M+H]⁺) (cf. Experimental Section) as well as peaks corresponding to ([M-Cl]⁺) i.e. loss of a chloride ligand.

The NMR and IR spectra for the osmium complexes Os-1 - Os-3, Os-5 and Os-7 closely resembles those for the corresponding ruthenium congeners. Their ¹H-NMR spectra show the same features as the spectra for the ruthenium complexes: diastereotopic splitting of the aromatic and isopropyl protons of the *p*-cymene, an upfield shift of the imine proton resonance and the absence of the phenolic proton resonance. The one noteworthy difference is that the aromatic protons on the *p*-cymene ring appear slightly downfield from their positions in the ruthenium complexes; between 5.8 to 5.4 ppm for the osmium complexes, as compared to 5.5 to 5.0 ppm in the ruthenium complexes. This difference is similar to the one observed in the parent dimers, where the osmium dimer has two doublets at 5.74 and 5.55 ppm while the lighter congener displays the same pattern at 5.46 and 5.33 ppm. Similar to the ruthenium analogues, a shift to lower frequency is noted for the C=N vibration; from ~1645 cm⁻¹ in the free ligand to ~1610 cm⁻¹ in Os-1 - Os-3, Os-5 and Os-7, indicative of coordination of the imine nitrogen to osmium. Mass spectral analysis of Os-1 - Os-3, Os-5 and Os-7 revealed that for each complex the base peak corresponds to the metal complex after loss of a chlorido ligand ([M-Cl]⁺). A peak for the protonated complex ([M+H]⁺) was also observed.

For complexes Ru-HL⁹ and Os-HL⁹, the ¹H-NMR signals corresponding to the *p*-cymene show that the complex retains its two-fold symmetry, indicating monodentate coordination of the ligands. Sánchez-Delgado and co-workers have shown that coordination of chloroquine to ruthenium in [Ru(arene)(CQ)Cl₂], Ru-CQ, (Figure 1) occurs through the quinoline nitrogen.¹⁴ These authors argued that the largest variations in the ¹H chemical shifts ($\Delta\delta$) of a bound ligand with respect to the values for the free form are observed for the nuclei in close vicinity of the coordination site.^{15,31} In Ru-HL⁹ and Os-HL⁹, the proton signals of ligand HL⁹ shift to a varying degree upon coordination, and $\Delta\delta$ values and signal assignments are reported in the electronic supplementary information. The largest ¹H $\Delta\delta$ value for Ru-HL⁹ and Os-HL⁹ is

observed for H14, which is adjacent to the nitrogen atom in the heterocyclic ring. This corresponds well

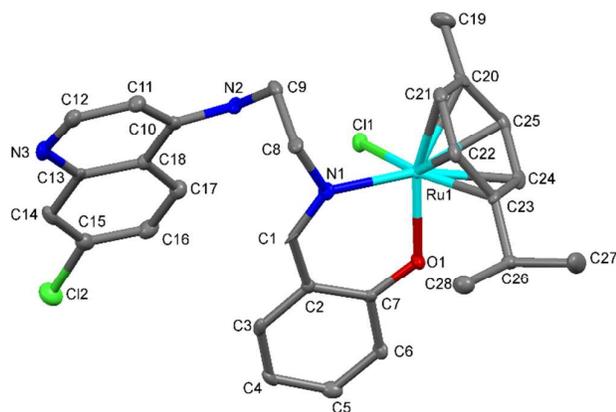


Figure 2. A Mercury plot of the molecular structure of complex $[Ru(\eta^6\text{-cym})(L^1)Cl]$, Ru-1. Hydrogen atoms have been omitted for the sake of clarity. Only one of the molecules in the asymmetric unit of the major polymorph is shown, see Figure S-6 in the ESI for the structure at the stacking fault. Thermal ellipsoids at the 50 % level.

with the $^1H \Delta\delta$ values observed for the dichloro species $[Ru(p\text{-cymene})(CQ)Cl_2]$.¹⁴ In addition, $^1H \Delta\delta$ values for all protons on quinoline are large, while none of the protons of the di-*tert*-butyl phenyl moiety are shifted. The $^1H \Delta\delta$ values strongly suggest that the coordination mode of the ligand in Ru-HL⁹ and Os-HL⁹ is monodentate through the quinoline nitrogen, as illustrated in Scheme 2.

The 1H -NMR and IR spectra of Os-10 correspond closely to those of the reported ruthenium analogue.¹⁷ The bidentate bonding of L¹⁰ in the ruthenium complex Ru-10 was confirmed by X-ray diffraction¹⁷ and all the data strongly support the proposed structure for Os-10.

The spectroscopic and mass spectrometric data for complexes Ru-1 - Ru-8, Ru-HL⁹ and Ru-10 and Os-1 - Os-3, Os-5, Os-7, Os-HL⁹ and Os-10 are in full agreement with the proposed structures as depicted in Schemes 1 and 2. The exact bonding mode of ligand HL⁹ in complexes Ru-HL⁹ and Os-HL⁹ is difficult to assign with certainty on the basis of available data, but the $^1H \Delta\delta$ values clearly indicate that coordination occurs through the quinoline nitrogen.

Single Crystal X-ray Diffraction

The proposed coordination mode of the ligands was confirmed for complexes Ru-1, Ru-3, Ru-5, Os-5 and Os-7 by single crystal X-ray diffraction studies. Single crystals of Ru-1, Ru-3 and Ru-5 were grown by slow evaporation of a DCM-petroleum ether solution of the respective complexes while for Os-5 and Os-7, crystals were grown by vapor diffusion of diethyl ether into a solution of the appropriate complex in DCM. Figures 2 - 6 show the molecular structures of Ru-1, Ru-3, Ru-5, Os-5 and Os-7 and Tables 1 and 2 contain a selection of relevant bond lengths and angles. Relevant crystal data and structure refinement parameters are listed in Table 5 in the experimental section.

When solving the structure of Ru-1 it was noticed that the refinement converges nicely for a solution that agrees well with expectations, but despite the good agreement between

model and data ($R1=4.37\%$ $Rw2=10.39\%$, $GOOF= 1.84$) there are some conspicuous residual electron densities that indicate that the

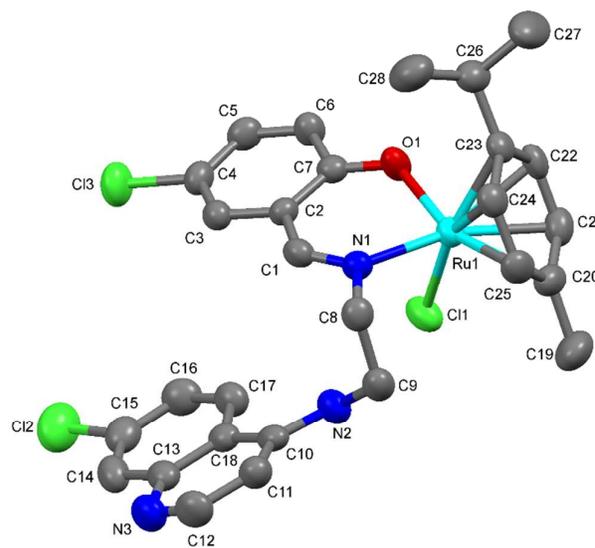


Figure 3. A Mercury plot of the molecular structure of complex $[Ru(\eta^6\text{-cym})(L^1)Cl]$ Ru-3. Hydrogen atoms have been omitted for the sake of clarity. Thermal ellipsoids at the 50 % level.

solution is incomplete. Interestingly, these residuals appear in what seems to be random locations, neither close to the heavy atoms, nor in volumes where partially occupied solvent molecules may be expected. This seems to rule out local disorder and rather points to twinning or extended defects. It was noted that the five most prominent residual peaks fall into two categories, two having electron densities close to $4e^- \text{Å}^{-3}$ and the remaining three having values less than half of this. Moreover, the two more pronounced residuals are both located at the same distance and direction ($-0.785, 0., 0.171$) from the two independent Ru positions in the structure. In the same way, the three smaller peaks correspond to the translation of Cl positions. Translating the entire molecules along this vector in fact generates a packing without any short interatomic distances and with a packing efficiency comparable to that of the original structure. It thus seems probable that the residuals are generated by an alternative molecular packing in the ac-plane.

To test this hypothesis, a split model was introduced where copies of the two independent molecules in the unit cell appear at positions given by the vector between the main electron densities and the Ru atom positions. To avoid introducing a large number of new refinable parameters, the original model was fixed and the only refinable parameters (14) in the split model were the occupancies of the split positions and the rotations and translations of the major components to the new positions. These were allowed to refine independently and both occupancies came out very close to 5%, the translation vectors were essentially identical, and the rotations as expected were close to 0.

The refinement converged at $R1=2.79\%$, $Rw2=6.70\%$, $GOOF=1.20$ with an essentially featureless electron difference density map. Despite the small number of refined parameters, this constitutes a major improvement on the original model and

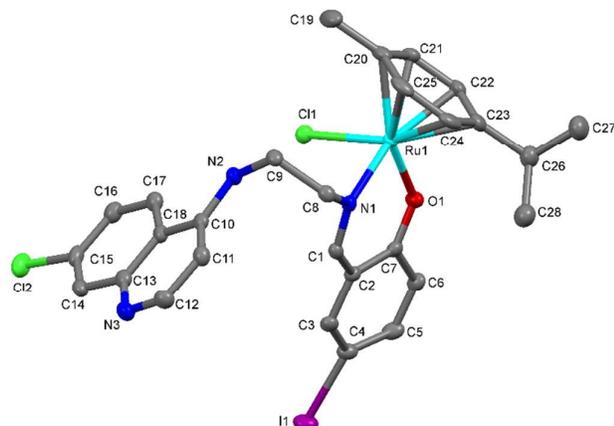


Figure 4. A Mercury plot of the molecular structure of complex $[\text{Ru}(\eta^6\text{-cym})(\text{L}^5)\text{Cl}]$ Ru-5. Hydrogen atoms have been omitted for the sake of clarity. Thermal ellipsoids at the 50 % level.

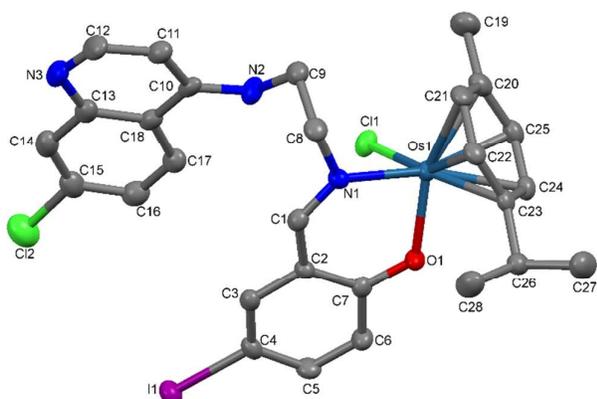


Figure 5. A Mercury plot of the molecular structure of complex $[\text{Os}(\eta^6\text{-cym})(\text{L}^5)\text{Cl}]$ Os-5. Hydrogen atoms have been omitted for the sake of clarity. Thermal ellipsoids at the 50 % level.

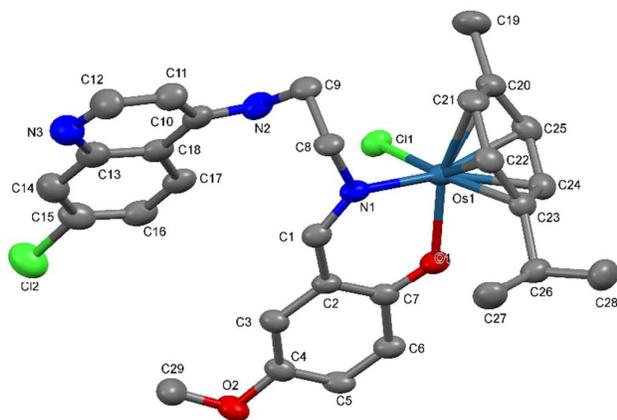


Figure 6. A Mercury plot of the molecular structure of complex $[\text{Os}(\eta^6\text{-cym})(\text{L}^7)\text{Cl}]$ Os-7. Hydrogen atoms have been omitted for the sake of clarity. Thermal ellipsoids at the 50 % level.

there is little doubt that this model correctly describes the local structure of the compound. Moreover, the same residual electron density in the same locations, corresponding to the same stacking fault, were observed in three other crystals of Ru-1, from two different batches of crystals. Figure 2 shows the structure of one of the two non-equivalent molecules in the main morphology, see the ESI, Figure S-6 for a representation of the two polymorphs in the crystal. The space group $P2_1$ would normally be associated with a single-enantiomer structure, but here of course, Ru-1 is stereogenic at the metal center but is present as the racemate, so the space group was surprising.³² Rather than finding a single enantiomer of Ru-1 in the asymmetric unit, both enantiomers were present, but with non-crystallographic inversion symmetry. That is, the two enantiomers were present in the asymmetric unit but with many minor conformational differences. Crystallization of a racemic mixture in a Sohnke space group was until recently thought to be extremely rare, with perhaps fewer than 50 examples.^{32,33} However, improved search methods have shown the number of these examples, referred to as kryptoracemates, to be a bit higher, and two recent publications describe 181 organic and 26 organometallic kryptoracemates.^{34,35} We now add Ru-1 to this list, although there is no particular reason that it crystallizes in this non-centrosymmetric space group. Bernal and Watkins have speculated that the crystallographic enantiomers in a non-Sohnke space group at room temperature could be converted to a non-crystallographic inversion pair at low temperature, but Ru-1 exhibits the same structure at room temperature as at 100 K.³⁵ It is noteworthy that even though the structure in general is acentric the local structure at the stacking-fault is centrosymmetric.

Complexes Ru-3, Ru-5, Os-5 and Os-7 crystallize in centric monoclinic point groups, Ru-3, Ru-5 and Os-7 in $P2_1/c$ and Os-5 in $P2_1/n$. They all refine well with standard procedures.

As suggested by the spectroscopic characterization, in all complexes the salicylaldimine ligand (L^1 , L^3 , L^5 and L^7) coordinates to the metal in a bidentate manner via the phenolate oxygen and the imine nitrogen. The metal center adopts a typical 'piano-stool' conformation with the chlorido ligand and nitrogen and oxygen atoms of the salicylaldimine ring acting as the legs.

The metal is bound to the p-cymene ring in the expected η^6 coordination mode. The bond lengths observed between the metal and the centroid of the p-cymene ring ($\text{M-Cy}_{\text{centroid}}$) as well as the chlorido (M-Cl), oxygen (M-O) and nitrogen (M-N) atoms within each molecular structure agree with similar Ru(II) and Os(II)-arene complexes.^{17,36-40} For the osmium complexes Os-5 and Os-7, the bond angles formed between the centroid of the arene ring and the other atoms coordinated to the metal are in the range of $124 - 133^\circ$ and bond angles close to 90° are noted for O1-Os1-Cl1 , O1-Os1-N1 and Cl1-Os1-N1 in agreement with previously reported osmium arene

structures.^{36–39} Torsion angles close to 90° are formed by the bonds of the imine and the aminoethyl chain (C8-C9-N2-C10 and C1-N1-C8-C9) as a consequence of the salicylaldehyde and quinoline rings sitting in planes that are almost parallel to each other.

The bond lengths and angles as well as the observed geometries around the metals in Os-5 and Os-7 are comparable Ru-1, Ru-3

Table 1. Selected bond lengths (Å) and angles (°) for complex Ru-1, Ru-3 and Ru-5.

	Ru-1	Ru-3	Ru-5		Ru-1	Ru-3	Ru-5
Bond Lengths (Å)							
Ru1-Cy _{centroid}	1.672	1.668	1.680	Ru1-O1	2.052(5)	2.064(3)	2.077(2)
Ru1-N1	2.105(5)	2.098(4)	2.100(2)	Ru1-Cl3	2.457(2)	2.4502(12)	2.4561(8)
Bond Angles (°)							
Cl1- Ru1-Cy _{centroid}	128.74	128.78	126.32	O1- Ru1-Cl1	85.6(1)	84.00(10)	86.46(6)
O1- Ru1-Cy _{centroid}	123.54	123.60	124.17	O1- Ru1-N1	88.1(2)	87.33(15)	87.43(8)
N1- Ru1-Cy _{centroid}	132.11	132.22	133.29	Cl1- Ru1-N1	83.7(2)	82.30(11)	84.36(6)
Torsion Angles (°)							
C8-C9-N2-C10	73.9(7)	-84.2(4)	-73.9(3)	C1-N1-C8-C9	-99.6(6)	98.7(4)	98.8(3)

Table 2. Selected bond lengths (Å) and angles (°) for complex Os-5, and Os-7.

	Os-5	Os-7		Os-5	Os-7
Bond Lengths (Å)					
Os1-Cy _{centroid}	1.656	1.659	Os1-O1	2.059(2)	2.064(3)
Os1-N1	2.103(3)	2.098(4)	Os1-Cl1	2.4310(9)	2.4502(12)
Bond Angles (°)					
Cl1-Os1-Cy _{centroid}	129.37	130.37	O1-Os1-Cl1	83.76(8)	84.00(10)
O1-Os1-Cy _{centroid}	124.48	124.13	O1-Os1-N1	87.45(10)	87.33(15)
N1-Os1-Cy _{centroid}	132.73	132.50	Cl1-Os1-N1	82.91(8)	82.30(11)
Torsion Angles (°)					
C8-C9-N2-C10	93.5(4)	77.3(6)	C1-N1-C8-C9	-96.2(4)	-96.5(5)

and Ru-5 as well as other analogous [N,O]- and [N,N]-ruthenium arene complexes.^{17, 40}

Antimalarial activity

The antimalarial activity of ligands HL¹⁻⁸ and complexes Ru-1 - Ru-8, Os-1 - Os-3, Os-5 and Os-7 was evaluated *in vitro* against chloroquine sensitive (CQS) NF54 and chloroquine resistant (CQR) Dd2 strains of *Plasmodium falciparum* (Table 3). The antimalarial activity of ligands L¹⁰ and HL¹ as well as their ruthenium complexes Ru-10 and Ru-1 against the chloroquine sensitive (CQS) D10 and Dd2 strains has been reported previously¹⁷ and is included in Table 4 for comparison, together with the osmium analogues, Os-1 and Os-10, as well as HL⁹, Ru-HL⁹ and Os-HL⁹. The relative biological activities are illustrated in Figure 7.

Ligands HL¹⁻⁸ exhibit *in vitro* antiplasmodial activities similar to chloroquine, i.e. IC₅₀^(NF54) ≈ 30 nM and IC₅₀^(Dd2) ≈ 200 nM. The sole exception is HL⁵ (X=I), which shows very poor activity

against the chloroquine resistant strain of *P. falciparum* (Dd2) (IC₅₀^(Dd2) = 1520 nM). The ruthenium arene complexes Ru-1 to Ru-8 exhibit activities approximately an order of magnitude worse than the free ligands against the chloroquine sensitive strain, IC₅₀^(NF54) = 140–730 nM. Against the chloroquine resistant strain two of the complexes, Ru-5 (X=I) and Ru-6 (X=NO₂), showed no activity up to the highest concentration tested. The complexes that were active, displayed antiplasmodial behavior at concentrations 4 to 6 times higher than chloroquine and 3 to 7 times higher than the free ligands. However, the resistance index, i.e. the quotient of the activity against chloroquine resistant and chloroquine sensitive *P. falciparum*, is better compared to chloroquine for the complexes that were active against the resistant strain. While this is a promising result, it

Table 3. Results from *in vitro* tests on chloroquine sensitive (NF54) and chloroquine resistant (Dd2) strains of *P. falciparum* for Ru-1 – Ru-8, Os-1 – Os-3, Os-5 and Os-7 with chloroquine, CQ, as reference. Resistance index, $RI = IC_{50}^{Dd2} / IC_{50}^{NF54}$.

compound	R ¹	NF54: IC ₅₀ (μM)	Dd2: IC ₅₀ (μM)	RI
HL ¹	H	0.032±0.004	0.18±0.02 ¹	5.5
HL ²	F	0.025±0.007	0.2±0.02	8
HL ³	Cl	0.021±0.003	0.2±0.04	9.6
HL ⁴	Br	0.027±0.009	0.19±0.03	7.2
HL ⁵	I	0.046±0.006	1.52±0.3	32.9
HL ⁶	NO ₂	0.028±0.008	0.18±0.009	6.5
HL ⁷	OMe	0.04±0.002	0.2±0.03	5.2
HL ⁸	<i>t</i> -Bu	0.041±0.002	0.31±0.03	7.8
Ru-1	H	0.52±0.09	0.82±0.05	1.6
Ru-2	F	0.14±0.04	0.66±0.1	4.5
Ru-3	Cl	0.27±0.1	1.08±0.3	4
Ru-4	Br	0.49±0.12	1.44±0.07	2.9
Ru-5	I	0.68±0.2	ND ²	N/A
Ru-6	NO ₂	0.55±0.15	ND ²	N/A
Ru-7	OMe	0.35±0.07	0.84±0.2	2.4
Ru-8	<i>t</i> -Bu	0.73±0.2	1.04±0.1	1.4
Os-1	H	0.28±0.1	2.56±0.3	9.3
Os-2	F	0.44±0.07	2.6±0.5	5.9
Os-3	Cl	0.61±0.09	2.75±0.6	4.5
Os-5	I	0.58±0.09	4.37±0.3	7.5
Os-7	OMe	0.49±0.05	1.64±0.04	3.3
CQ	N/A	0.027±0.01	0.22±0.05	8.1

Note: 1) at another occasion no activity could be detected against Dd2 for HL¹, 2) ND = no activity detected/IC₅₀>30 μM, N/A=Not applicable.

should not be over interpreted, considering the relatively poor activities exhibited against the chloroquine sensitive strain.

The osmium complexes Os-1 – Os-3 and Os-7 showed activities or slightly lower than their ruthenium analogues, but against the chloroquine resistant Dd2 strain they are consistently less active. The iodo-substituted complex Os-5 stands out, with slightly better activity than the ruthenium analogue Ru-5 against the CQS strain ($IC_{50}^{(NF54)} = 580$ nM and $IC_{50}^{(NF54)} = 680$ nM

respectively) and some, although poor, activity against the CQR strain ($IC_{50}^{(Dd2)} = 4370$ nM), against which the ruthenium analogue shows no activity.

Ligand HL⁹ was found to be significantly more active than the unsubstituted HL¹, $IC_{50}^{(D10)} = 32$ nM and $IC_{50}^{(Dd2)} = 550$ nM respectively, and is almost as active as chloroquine against the CQS D10 strain. However, the dramatic increase in activity against the D10 strain that is observed upon coordination of Ru or Os to HL¹ is not seen for HL⁹; metal coordination of HL⁹ results in a slight decrease in activity against the CQS strain for both Os-HL⁹ and Ru-HL⁹ relative to the free ligand and a slight increase in activity against the CQR strain in the case of Os-HL⁹. The small difference in activity for the complexes compared to the free ligand may indicate partial decomposition of the complexes under physiological conditions, and that the resultant antiparasitodal effect observed is primarily caused by the dissociated ligand, HL⁹. Coordination of L¹⁰ to osmium results in a complex (Os-10) which is less active than its free ligand against both parasite strains but is much more active than its ruthenium analogue, Ru-10.

Table 4. Results from *in vitro* tests on chloroquine sensitive (D10) and chloroquine resistant (Dd2) strains of *P. falciparum* for L¹⁰, Ru-10 and Os-10, HL¹, Ru-1 and Os-1 and HL⁹, Ru-HL⁹ and Os-HL⁹ with chloroquine, CQ, as reference. Resistance index, $RI = IC_{50}^{Dd2} / IC_{50}^{NF54}$.

	R ¹ & R ²	D10: IC ₅₀ (μM)	Dd2: IC ₅₀ (μM)	RI
L ¹⁰	N/A	0.19±0.03	0.25±0.06	1.3
Ru-10	N/A	4.5±0.7	19.7±0.4	4.3
Os-10	N/A	0.64±0.06	0.5±0.1	0.8
HL ¹	H	0.55±0.3	0.18±0.02 ¹	0.32
Ru-1	H	0.07±0.007	0.82±0.05	1.6
Os-1	H	0.059±0.01	0.43±0.04	7.3
HL ⁹	<i>t</i> -Bu	0.032±0.009	0.42±0.09	13
Ru-HL ⁹	<i>t</i> -Bu	0.059±0.01	0.43±0.04	7.3
Os-HL ⁹	<i>t</i> -Bu	0.042±0.01	0.3±0.04	7.2
CQ	N/A	0.025±0.009	0.14±0.01	5.7

Note: 1) at another occasion no activity could be detected against Dd2 for HL¹, N/A=Not applicable.

Comparing osmium and ruthenium compounds, all the ruthenium salicylaldimine complexes performed better against the Dd2 strain (CQR) than their osmium congeners, while against NF54 (CQS) two complexes, Ru-1 and Ru-5, have lower activities than the osmium equivalents. For the compounds tested against D10 and Dd2, the imidazole containing ruthenium complex Ru-10 is 7 and 40 times less active than Os-10 against the D10 and Dd2 strains, respectively. Both Ru-1 and Ru-HL⁹ have similar activities to Os-1 and Os-HL⁹ against the chloroquine sensitive D10 strain and are slightly less active against the Dd2 chloroquine resistant strain than Os-1 and Os-HL⁹. While several osmium complexes exhibited better activity than their ruthenium congeners, replacement of ruthenium by

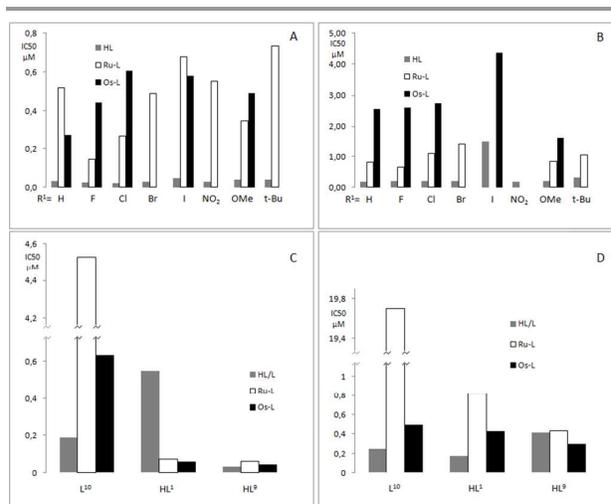


Figure 7. IC₅₀ values for: A) CQS, NF54 strain, HL¹ to 8, Ru-1 to 8, and, Os-1,2,3,5 and 7, B) CQR, Dd2 strain, HL¹ to 8, Ru-1 to 8, and, Os-1,2,3,5 and 7, C) CQS, D10 strain, L¹⁰, Ru-10 and Os-10, HL¹, Ru-1 and Os-1 and HL⁹, Ru-HL⁹ and Os-HL⁹, D)

CQR, Dd2 strain, **L**¹⁰, Ru-**10** and Os-**10**, **HL**¹, Ru-**1** and Os-**1** and **HL**⁹, Ru-**HL**⁹ and Os-**HL**⁹

osmium in these complexes does not appear to offer a significant advantage for antiplasmodial activity.

If the antiplasmodial activities of ligands **HL**^{1 to 8} are plotted against the Hammett σ -constants of the substituents in R_1 (cf. Scheme 1), a weak negative correlation can be seen (see ESI) with the electron-withdrawing F, Cl, Br and NO_2 substituted ligands, **HL**^{2, 3, 4 and 6}, having the highest activities and **HL**^{7 and 8}, bearing the electron donating methoxy and *tert*-butyl groups having some of the lowest activities. However, no such trend can be seen for the corresponding ruthenium or osmium complexes. Similarly **HL**⁹ shows higher activity against the D10 strain than **HL**¹, while the opposite is true for the CQR Dd2 strain. It is worth noting that the activity of **HL**¹ and its complexes Ru-**1** and Os-**1** vary considerably between the two different chloroquine sensitive strains. The free ligand is almost 20 times more active against NF54 than D10, while the ruthenium (Ru-**1**) and osmium (Os-**1**) complexes are 7 and 5 times less active against NF54 than Dd2, respectively.

Since the overall trend is that the uncoordinated ligands are significantly more active than the metal complexes, it is possible that the complexes in themselves are inactive, while the active species are the decoordinated ligands. If this is the case, the differences in antiplasmodial activity between the ruthenium and osmium complexes could be the result of the greater lability of the coordinated ligands in the former, resulting in a higher concentration of free ligand at equal concentrations of the complexes. For the ligand **HL**⁹ and its complexes Ru-**9** and Os-**9**, the IC_{50} data for the Dd2 *P. Falciparum* strain suggest a reverse trend, but the activities are actually not statistically different (cf. Table 4). The fact that there is no significant difference between the activities of this ligand and its complexes may indicate that the ligand is fully decoordinated from the metal under physiological conditions, and that the free ligand determines the activity.

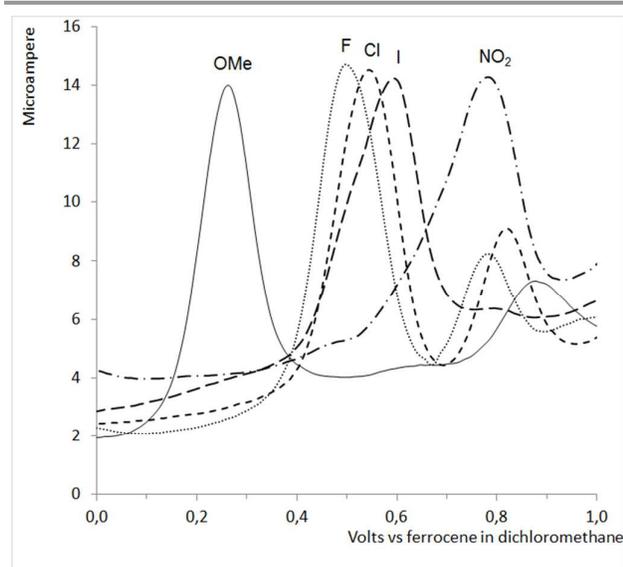


Figure 8. A differential pulse voltammetry (DPV) trace for complexes Ru-**2**, -**3**, -**5**, -**6** and -**7**, showing the increase in oxidation potential when more electron withdrawing groups are introduced on the salicylaldimine moiety

Electrochemistry

The ruthenium complexes Ru-**2**, -**3**, -**5**, -**6** and -**7** were studied by cyclic and differential pulse voltammetry, see Figure 8. All 5 complexes showed a single irreversible oxidation not present in the corresponding free ligand, presumed to be the oxidation of

Ru^{II} to Ru^{III} . The oxidation potential correlates well ($\rho=0.98$) with the Hammett σ -constants of the substituents in the R_1 position, i.e. R (cf. Scheme 1). However, as might be anticipated, no correlation between the oxidation potentials of the complexes and their anti-malarial activities could be observed.

Experimental

General information.

Ruthenium and osmium complexes were synthesized under dry argon or 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. Acetone was dried over molecular sieves overnight, followed by storage under argon. All chemicals were purchased from Sigma Aldrich, except $\text{OsCl}_3 \cdot x\text{H}_2\text{O}$ which was purchased from Strem and used as received. $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$,⁴¹ $[\text{Os}(p\text{-cymene})\text{Cl}_2]_2$,^{42,43} N^1 -(7-chloroquinolin-4-yl)ethane-1,2-diamine,⁴⁴ N -((1-methyl-1H-imidazol-2-yl)methylamino)ethyl)-7-chloroquinolin-4-amine (**L**¹⁰) and N -((2-(2-hydroxyphenyl)methyl-imino)ethyl)-7-chloroquinolin-4-amine (**HL**¹)¹⁷ were prepared according to literature methods. NMR spectra were recorded on a Varian Inova 500 MHz (^1H at 499.76 MHz, ^{13}C at 125.68 MHz), a Varian Unity XR400 MHz (^1H at 399.95 MHz, ^{13}C at 100.58 MHz), Varian Mercury XR300 (^1H at 300.08 MHz, ^{13}C at 75.46 MHz) or Bruker Biospin GmbH (^1H at 400.22 MHz, ^{13}C at 100.65 MHz) spectrometer at ambient temperature using the residual solvent peak as internal standard for ^1H -NMR and ^{13}C NMR. IR spectra were recorded on a Nicolet Avatar 360 FT-IR instrument or Perkin-Elmer Spectrum 100 FT-IR Spectrometer as KBR pellets. Electrospray ionization (ESI) mass spectra were recorded using a Waters Micromass Q-TOF micro mass spectrometer or a Waters API Quattro Micro instrument in either the positive or negative mode.

Syntheses.

N-((5-fluoro-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine (**HL**²) 5-Fluoro-2-hydroxybenzaldehyde (0.140 g, 1.0 mmol) and N^1 -(7-chloroquinolin-4-yl)ethane-1,2-diamine (0.222 g, 1.0 mmol) were refluxed in ethanol (25 mL) overnight. The solvent was evaporated and the product was dried under vacuum. The product was obtained as a yellow powder (0.307 g, 89%). ^1H -NMR (CDCl_3) δ 12.72 (s, 1H), 8.55 (d, 1H, $J=5.4\text{Hz}$), 8.34 (s, 1H), 7.99 (d, 1H, $J=4.3\text{Hz}$), 7.65 (d, 1H, $J=9.0\text{Hz}$), 7.37 (dd, 1H, $J=2.1\text{Hz}$, $J=8.9\text{Hz}$), 7.06 (m, 1H), 6.94 (t,

1H, J=3.9Hz), 6.92 (t, 1H, J=3.5Hz), 6.51 (d, 1H, J=5.4Hz), 5.40 (m, 1H), 3.99 (dd, 2H, J=6.0Hz, J=12.5Hz), 3.76 (dd, 2H, J=5.8Hz, J=11.6Hz); ¹³C{1H} NMR (125.68 MHz, DMSO) δ 165.73, 156.74, 155.50, 153.64, 151.91, 149.94, 149.09, 133.42, 127.54, 124.15, 123.99, 118.72, 117.67, 117.46, 98.95, 56.80, 42.88; Found 62.61% C, 4.31% H and 12.32% N. C₁₈H₁₅ClFN₃O requires 62.89% C, 4.40% H and 12.22% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3240s (O-H), 2960w, 1644s (N=C), 1614w (7-chloroquinoline), 1580s (7-chloroquinoline), 1547w (7-chloroquinoline), 1582m, 1449w, 1431w, 1380w, 1273m, 1257m, 1143m, 811m, 782w; MS (ES+) m/z 344 ([M+H]⁺, 100 %).

N-(2-((5-chloro-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine (HL³) 5-Chloro-2-hydroxybenzaldehyde (0.157 g, 1.0 mmol) and N'-(7-chloroquinolin-4-yl)ethane-1,2-diamine (0.222 g, 1.0 mmol) were refluxed in ethanol (25 mL) overnight. The solvent was evaporated and the product was dried under vacuum. The product was obtained as a yellow powder (0.340 g, 94%). ¹H-NMR (CDCl₃) δ 12.94 (s, 1H), 8.54 (d, 1H, J=5.4Hz), 8.32 (s, 1H), 7.98 (d, 1H, J=1.9Hz), 7.69 (d, 1H, J=8.7Hz), 7.36 (dd, 1H, J=2.0Hz, J=8.9Hz), 7.29 (d, 1H, J=2.6Hz), 7.19 (d, 1H, J=2.5Hz), 6.92 (d, 1H, J=8.8Hz), 6.51 (d, 1H, J=5.4Hz), 3.99 (t, 2H, J=5.8Hz), 3.77 (dd, 2H, J=5.8Hz, J=11.5Hz); ¹³C{1H} NMR (125.68 MHz, DMSO) δ 165.71, 159.67, 151.86, 149.94, 149.05, 133.44, 132.01, 130.50, 127.53, 124.20, 123.98, 121.68, 119.70, 118.60, 117.88, 117.46, 98.95, 56.52, 42.84; Found 60.38% C, 4.31% H and 6.25% N. C₁₈H₁₅Cl₂N₃O requires 60.01% C, 4.20% H and 11.66% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3212s (O-H), 2974w, 1641s (N=C), 1616w (7-chloroquinoline), 1584s (7-chloroquinoline), 1477m, 1369w, 1279m, 1146w, 804m; MS (ES+) m/z 360 ([M+H]⁺, 100 %).

N-(2-((5-bromo-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine (HL⁴) 5-Bromo-2-hydroxybenzaldehyde (0.209 g, 1.0 mmol) and N'-(7-chloroquinolin-4-yl)ethane-1,2-diamine (0.222 g, 1.0 mmol) were refluxed in ethanol (25 mL) overnight. The precipitate was filtered off and washed with chloroform and dried under vacuum. The product was obtained as an off-white powder (0.240 g, 58%). ¹H-NMR (DMSO) δ 13.49 (s, 1H), 8.51 (s, 1H) ppm, 8.40 (d, 1H, J=4.2Hz), 8.23 (d, 1H, J=8.6Hz), 7.78 (s, 1H), 7.61 (s, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.44 (s, 1H), 6.83 (d, 1H, J=8.4Hz), 6.61 (d, 1H, J=3.9Hz), 3.89 (m, 2H), 3.64 (m, 2H); ¹³C{1H} NMR (125.68 MHz, DMSO) δ 165.63, 160.17, 151.91, 149.94, 149.09, 134.80, 133.43, 127.51, 124.15, 123.98, 120.32, 119.10, 118.96, 117.47, 108.96, 98.96, 56.47, 42.85; Found 52.25% C, 3.00% H and 6.63% N. C₁₈H₁₅BrClN₃O requires 53.14% C, 3.74% H and 10.38% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3208s (O-H), 3063w, 3008w, 2969w, 2874w, 1639s (N=C), 1615w (7-chloroquinoline), 1583s (7-chloroquinoline), 1474w, 1453w, 1432w, 1369m, 1280m, 1211w, 1145m, 1083w, 1049w, 1010w, 902w, 865w, 802m, 779w; MS (ES+) m/z 406 ([M+H]⁺, 100 %).

N-(2-((5-iodo-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine (HL⁵) 5-Iodo-2-hydroxybenzaldehyde (0.248 g, 1.0 mmol) and N'-(7-chloroquinolin-4-yl)ethane-1,2-diamine (0.222 g, 1.0 mmol) were refluxed in ethanol (25 mL) overnight. The precipitate was filtered off and washed with chloroform and dried under vacuum. The product was obtained as an off-white powder (0.348 g, 77%). ¹H-NMR

(DMSO) δ 13.49 (s, 1H), 8.49 (s, 1H), 8.39 (d, 1H, J=5.4Hz), 8.22 (d, 1H, J=9.0Hz), 7.78 (d, 1H, J=2.1Hz), 7.73 (d, 1H, J=2.1Hz), 7.57 (dd, 1H, J=2.2Hz, J=8.7Hz), 7.47 (d, 1H, J=4.9Hz), 7.44 (dd, 1H, J=2.1Hz, J=9.0Hz), 6.70 (d, 1H, J=8.7Hz), 6.60 (d, 1H, J=5.4Hz), 3.88 (t, 1H, J=5.7Hz), 3.62 (dd, 1H, J=5.9Hz, J=11.6Hz); ¹³C{1H} NMR (125.68 MHz, DMSO) δ 165.61, 160.74, 151.90, 149.93, 149.08, 140.42, 139.37, 133.43, 127.52, 124.18, 123.98, 121.02, 119.50, 117.46, 99.01, 79.49, 56.43, 42.86; Found 47.77% C, 3.39% H and 8.84% N. C₁₈H₁₅ClIN₃O requires 47.86% C, 3.33% H and 9.30% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3434s (O-H), 2964w, 1637s (N=C), 1618w (7-chloroquinoline), 1582s (7-chloroquinoline), 1560w, 1542w (7-chloroquinoline), 1473w, 1366w, 1282m, 1145m, 802m; MS (ES+) m/z 452 ([M+H]⁺, 100 %).

N-(2-((2-hydroxy-5-nitro-phenyl)methylimino)ethyl)-7-chloroquinolin-4-amine (HL⁶) 2-Hydroxy-5-nitrobenzaldehyde (1.43 g, 8.57 mmol) and N'-(7-chloroquinolin-4-yl)ethane-1,2-diamine (1.89 g, 8.57 mmol) were refluxed in ethanol (100 ml) overnight. The solvent was evaporated and the product was dried under vacuum. The product was obtained as a yellow powder (3.17 g, 99%). ¹H-NMR (500 MHz, DMSO) δ 8.66 (s, 1H), 8.42 (d, J = 5.3 Hz, 1H), 8.36 (d, J = 3.0 Hz, 1H), 8.22 (d, J = 9.1 Hz, 1H), 7.98 (dd, J = 9.6, 3.1 Hz, 1H), 7.79 (s, 1H), 7.52 (s, 1H), 7.46 (d, J = 8.9 Hz, 1H), 6.64 (d, J = 5.3 Hz, 1H), 6.54 (d, J = 9.6 Hz, 1H), 3.90 (m, 2H), 3.66 (m, 2H); ¹³C{1H} NMR (125.68 MHz, DMSO) δ 177.45, 166.99, 152.37, 150.50, 149.44, 133.94, 133.73, 131.57, 129.37, 127.98, 124.72, 124.38, 122.70, 117.88, 115.75, 99.53, 52.76, 42.82; Found 57.62% C, 4.43% H and 15.11% N. C₁₈H₁₅ClN₄O₃ requires 58.31% C, 4.08% H and 15.11% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3238m (O-H), 3062w, 2919w, 1660s, 1642m (N=C), 1607m (7-chloroquinoline), 1583s (7-chloroquinoline), 1541m (7-chloroquinoline), 1515w, 1481w, 1451w, 1327s, 1281w, 1231m, 1173w, 1094m, 892w, 841w, 800w; MS (ES-) m/z 369 ([M-H]⁻, 100 %).

N-(2-((2-hydroxy-5-methoxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine (HL⁷) 2-Hydroxy-5-methoxybenzaldehyde (150 μL, 0.183 g, 1.2 mmol) and N'-(7-chloroquinolin-4-yl)ethane-1,2-diamine (0.222 g, 1.0 mmol) were refluxed in ethanol (25 mL) overnight. The solvent was removed *in vacuo* and residual aldehyde was removed by heating at 80°C under vacuum. The product was obtained as a grey powder (0.304 g, 85%). ¹H-NMR (CDCl₃) δ 12.49 (s, 1H), 8.54 (d, 1H, J=5.3Hz), 8.31 (s, 1H), 7.96 (s, 1H), 7.65 (d, 1H, J=8.9Hz), 7.33 (d, 1H, J=7.5Hz), 6.95 (dd, 1H, J=2.8Hz, J=9.0Hz), 6.91 (d, 1H, J=8.9Hz), 6.71 (d, 1H, J=2.6Hz), 6.50 (d, 1H, J=5.3Hz), 5.43 (s, 1H), 3.94 (t, 2H, J=5.5Hz), 3.75 (s, 3H), 3.73 (m, 2H); ¹³C{1H} NMR (125.68 MHz, DMSO) δ 166.52, 154.33, 151.86, 151.40, 149.98, 149.09, 133.42, 127.46, 124.12, 123.91, 119.22, 118.49, 117.46, 117.10, 114.82, 98.99, 98.95, 56.91, 43.00; Found 62.36% C, 5.78% H and 10.72% N. C₁₉H₁₈ClN₃O₂ requires 64.13% C, 5.10% H and 10.55% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3192s (O-H), 3055w, 2935w, 2846w, 1643s (N=C), 1614w (7-chloroquinoline), 1582s (7-chloroquinoline), 1548w (7-chloroquinoline), 1489w, 1451w, 1430w, 1371w, 1271s, 1209w, 1153w, 1143w, 1053w, 852w, 766m; MS (ES+) m/z 356 ([M+H]⁺, 100 %).

N-(2-((5-tert-butyl-2-hydroxy-phenyl)methylimino)ethyl)-7-chloroquinolin-4-amine (HL⁸)

2-Hydroxy-5-tert-butylbenzaldehyde (0.500 g, 2.81 mmol) and N'-(7-chloroquinolin-4-yl)ethane-1,2-diamine (0.518 g, 2.34 mmol) were refluxed in ethanol (30 mL) overnight. The crude product was purified by column chromatography on silica (Et3N:Heptane:EtOAc 5:25:70) to yield the desired product as a grey powder (0.523 g, 51 %). ¹H-NMR (500 MHz, CDCl₃) δ 12.75 (s, 1H), 8.55 (d, J = 5.2 Hz, 1H), 8.37 (s, 1H), 7.97 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.39 (dd, J = 8.7, 1.9 Hz, 1H), 7.34 (dd, J = 8.8, 1.2 Hz, 1H), 7.18 (s, 1H), 6.92 (d, J = 8.6 Hz, 1H), 6.51 (d, J = 5.2 Hz, 1H), 5.40 (s, 1H), 3.95 (m,), 3.74 (m, 2H); ¹³C{1H} NMR (125.68 MHz, DMSO) δ 167.30, 158.24, 151.97, 149.95, 149.00, 140.69, 133.35H, 129.36, 127.88, 127.49, 124.10, 123.97, 117.96, 117.47, 115.93, 99.06, 56.79, 43.02, 33.66, 31.27; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3229s (O-H), 2963m, 1639s (N=C), 1609w (7-chloroquinoline), 1590s (7-chloroquinoline), 1543w (7-chloroquinoline), 1494w, 1455w, 1428w, 1367w, 1327w, 1254m, 1214w, 1139m, 1064w, 911w, 878w, 832m, 803w; MS (ES+) m/z 382 ([M+H]⁺, 100 %).

N-(2-((2-hydroxy-3,5-di-tert-butylphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine (HL⁹)

3,5-Di-tert-butyl-2-hydroxybenzaldehyde (0.614 g, 2.62 mmol) and N1-(7-chloroquinolin-4-yl)ethane-1,2-diamine (0.523 g, 2.37 mmol) were refluxed in ethanol (50 mL) overnight. The solvent was evaporated and residual aldehyde was removed by heating the residue at 80 °C under vacuum. The product was obtained as a yellow solid (0.970 g, 95 %). ¹H-NMR (500MHz, CDCl₃) δ 13.45 (br s, 1H), 8.59 (d, 1H, J=5.3Hz), 8.40 (s, 1H), 7.98 (d, 1H, J=2.1Hz), 7.66 (d, 1H, J=8.9Hz), 7.43 (d, 1H, J=2.4) 7.37 (dd, 1H, J= 8.9 Hz, J=2.1 Hz), 7.06 (d, 1H, J=2.4Hz), 6.53 (d, 1H, J=5.3Hz), 5.29 (br s, 1H), 3.95 (m, 2H), 3.74 (m, 2H), 1.47 (s, 9 H), 1.31 (s, 9H); ¹³C{1H} NMR (125 MHz, CDCl₃) δ 168.2, 157.8, 152.0, 149.3, 149.2, 140.5, 136.8, 135.0, 128.9, 127.5, 126.1, 125.6, 120.9, 117.6, 117.2, 99.4, 57.6, 43.6, 35.0, 34.1, 31.4, 29.4; IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3253s (O-H), 2960w, 2907w, 2867w, 1634m, 1613m (7-chloroquinoline), 1574s (7-chloroquinoline), 1540m (7-chloroquinoline), 1471, 1443, 1363, 1306, 1274, 1251, 1135, 794; MS (ES+) m/z 438.2 ([M+H]⁺, 100 %).

(η⁶-p-cymene)(N-(2-((5-fluoro-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)chlororuthenium(II), [Ru(p-cymene)(L²)Cl] (Ru-2)

Ligand HL² (20.1 mg, 65.6 μmol) was dissolved in dichloromethane (10 mL) and triethylamine (13.7 μL, 98.4 μmol) was added. The solution was stirred at room temperature for 30 min, cooled to -78 °C and [Ru(p-cymene)Cl₂]₂ (20.0 mg, 32.8 μmol) was added. The reaction mixture was stirred for 16 h, during which the solution was allowed to warm to room temperature. The crude product was purified by column chromatography on silica (~50 g, DCM:MeOH, 9:1 v/v) and the product (Ru-2) was dried under vacuum and obtained as a brown solid (24 mg, 65%). ¹H-NMR (CDCl₃) δ 8.48 (s, 1H), 7.93 (s, 1H), 7.72 (d, 1H, J=8.9Hz), 7.21 (s, 1H), 7.20 (s, 1H), 6.92 (t, 1H, J=9.7Hz), 6.84 (dd, 1H, J=4.6Hz, J=9.3Hz), 6.82 (br, 1H), 6.44 (s, 1H), 6.09 (d, 1H, J=6.1Hz), 5.55 (d, 1H, J=6.2Hz), 5.50 (d, 1H, J=6.1Hz), 5.43 (d, 1H, J=4.6Hz), 5.02 (d, 1H, J=4.8Hz), 4.52 (m, 1H), 4.23 (m, 2H), 3.88 (m, 1H), 2.75 (td, 1H, J=6.9Hz, J=14.0Hz), 2.30 (d, 3H),

1.25 (d, 3H, J=6.9Hz), 1.15 (d, 3H, J=6.8Hz); ¹³C{1H} NMR (125.68 MHz, CDCl₃) δ 164.78, 161.60, 152.46 (d, J= 232.4 Hz), 150.26, 147.59, 135.94, 126.82, 126.00, 123.77 (d, J= 23.7 Hz), 123.09, 122.93 (d, J= 7.4 Hz), 117.37 (d, J= 232.4 Hz), 117.04, 116.61 (d, J=7.8 Hz), 100.68, 99.08, 98.22, 88.45, 83.15, 80.84, 80.47, 66.87, 42.30, 30.63, 22.92, 21.61, 18.87; Found 53.01% C, 4.83% H and 5.68% N. C₂₈H₂₈Cl₂FN₃ORu requires 54.82% C, 4.60% H and 06.85% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3452 (br), 2962m, 1623sh (N=O), 1613s (7-chloroquinoline), 1583s (7-chloroquinoline), 1541m (7-chloroquinoline), 1466s, 1427w, 1389w, 1316w, 1243w, 1210w, 1027w, 870w, 817m; MS (ES+) m/z 614 ([M+H]⁺, 100 %).

(η⁶-p-cymene)(N-(2-((5-chloro-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)chlororuthenium(II), [Ru(p-cymene)(L³)Cl] (Ru-3)

Ligand HL³ (24.0 mg, 0.066 mmol), triethylamine (13.7 μL, 98.4 μmol) and [Ru(p-cymene)Cl₂]₂ (20.0 mg, 32.8 μmol) were reacted using the same method employed for the synthesis of Ru-2. The product (Ru-3) was isolated as a brown solid (35 mg, 84 %). ¹H-NMR (CDCl₃) δ 8.49 (br, 1H), 7.96 (s, 1H), 7.70 (d, 1H, J=8.3Hz), 7.22 (d, 1H, J=8.6Hz), 7.18 (s, 1H), 7.06 (d, 1H, J=8.9Hz), 6.84 (d, 1H, J=8.9Hz), 6.82 (br, 1H), 6.46 (br, 1H), 6.32 (s, 1H), 5.56 (d, 1H, J=5.7Hz), 5.52 (d, 1H, J=6.3Hz), 5.44 (d, 1H, J=4.2Hz), 5.02 (d, 1H, J=4.2Hz), 4.51 (m, 1H), 4.23 (m, 2H), 3.89 (m, 1H), 2.75 (td, 1H, J=6.6Hz, J=13.4Hz), 2.30 (s, 3H), 1.25 (d, 3H, J=6.8Hz), 1.15 (d, 3H, J=6.6Hz); ¹³C{1H} NMR (126 MHz, CDCl₃) δ 164.92, 163.83, 150.52, 150.32, 147.58, 136.28, 135.46, 132.97, 126.82, 126.28, 123.69, 123.27, 118.67, 118.41, 117.15, 100.92, 99.31, 98.49, 88.73, 83.38, 80.94, 80.73, 67.05, 42.46, 30.80, 23.09, 21.77, 19.02. Found 51.69% C, 4.75% H and 5.97% N. C₂₈H₂₈Cl₃N₃ORu requires 53.38% C, 4.48% H and 6.67% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3434 (br), 2922m, 2854w, 1619sh (N=O), 1614s (7-chloroquinoline), 1581s (7-chloroquinoline), 1527w (7-chloroquinoline), 1460m, 1389w, 1322w, 1262w, 1090w, 1026m, 872w, 805m; MS (ES-) m/z 630 ([M-H]⁻, 100 %).

(η⁶-p-cymene)(N-(2-((5-bromo-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)chlororuthenium(II), [Ru(p-cymene)(L⁴)Cl] (Ru-4)

Ligand HL⁴ (24.2 mg, 0.060 mmol), triethylamine (13.7 μL, 98.4 μmol) and [Ru(p-cymene)Cl₂]₂ (20.0 mg, 32.8 μmol) were reacted using the same method employed for the synthesis of Ru-2. The product (Ru-4) was isolated as a brown solid (24 mg, 59 %). ¹H-NMR (CDCl₃) δ 8.50 (s, 1H), 7.96 (m, 1H), 7.70 (d, 1H, J=8.8Hz), 7.22 (d, 1H, J=8.4Hz), 7.17 (dd, 1H, J=2.2Hz, J=9.1 Hz), 7.15 (s, 1H), 6.80 (br, 1H), 6.79 (d, 1H, J=9.1Hz), 6.44 (s, 2H,), 5.56 (d, 1H, J=6.2Hz), 5.51 (d, 1H, J=6.1Hz), 5.44 (d, 1H, J=4.2Hz), 5.02 (d, 1H, J=4.3Hz), 4.50 (m, 1H), 4.21 (m, 2), 3.88 (m, 1H), 2.75 (td, 1H, J=6.8Hz, J=13.7Hz), 2.30 (s, 1H), 1.25 (d, 1H, J=6.9Hz), 1.15 (d, 1H, J=6.8Hz); ¹³C{1H} NMR (125.68 MHz, CDCl₃) δ 164.65, 164.11, 150.32, 150.21, 147.63, 147.51, 137.92, 136.14, 135.95, 126.72, 126.15, 123.97, 123.07, 119.39, 117.00, 104.86, 100.76, 99.16, 98.31, 88.59, 83.23, 80.60, 66.87, 42.22, 30.60, 22.94, 21.59, 18.88; Found 48.15% C, 4.33% H and 5.57% N. C₂₈H₂₈BrCl₂N₃ORu requires 49.86% C, 4.18% H and 6.23% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3433 (br), 2960w, 2922w, 1617sh (N=O), 1611s (7-chloroquinoline), 1581s (7-

chloroquinoline), 1523w (7-chloroquinoline), 1459m, 1388w, 1320m, 1172w, 1137w, 1078w, 1028m, 872w, 819m; MS (ES+) m/z 676 ([M+H]⁺, 100 %).

(η^6 -p-cymene)(N-(2-((5-iodo-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)chlororuthenium(II), [Ru(p-cymene)(L⁵)Cl] (Ru-5) Ligand HL⁵ (29.6 mg, 0.066 mmol), triethylamine (13.7 μ L, 98.4 μ mol) and [Ru(p-cymene)Cl₂]₂ (20.0 mg, 32.8 μ mol) were reacted using the same method employed for the synthesis of Ru-2. The product (Ru-5) was isolated as a brown solid (44 mg, 93 %). ¹H-NMR (CDCl₃) δ 8.48 (s, 1H), 7.95 (s, 1H), 7.71 (d, 1H, J=9.0Hz), 7.30 (dd, 1H, J=2.1Hz, J=9.0Hz), 7.24 (d, 1H, J=8.8Hz), 7.16 (s, 1H), 6.97 (s, 1H), 6.68 (d, 1H, J=9.0Hz), 6.62 (s, 1H), 6.51 (s, 1H), 5.56 (d, 1H, J=6.1Hz), 5.51 (d, 1H, J=6.0Hz), 5.45 (d, 1H, J=5.0Hz), 5.04 (d, 1H, J=4.9Hz), 4.53 (m, 1H), 4.22 (m, 2H), 3.93 (m, 1H), 2.74 (td, 1H, J=6.7Hz, J=13.4Hz), 2.30 (s, 3H), 1.24 (d, 3H, J=7.0Hz), 1.14 (d, 3H, J=6.8Hz); ¹³C-NMR (125.68 MHz, CDCl₃) δ 164.71, 164.67, 151.20, 149.23, 146.28, 143.34, 142.46, 136.80, 126.55, 125.79, 124.74, 123.49, 120.94, 116.89, 100.88, 99.24, 98.55, 88.63, 83.35, 80.99, 80.79, 73.31, 67.03, 42.58, 30.77, 23.09, 23.05, 21.80, 19.02. Found 43.15% C, 4.14% H and 4.65% N. C₂₈H₂₈Cl₂IN₃ORu requires 46.62% C, 3.91% H and 5.82% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3422 (br), 2961w, 1618sh (N=O), 1612s (7-chloroquinoline), 1581s (7-chloroquinoline), 1541w, 1522w (7-chloroquinoline), 1459m, 1386w, 1320m, 1173w, 1139w, 1081m, 874w, 819m; MS (ES+) m/z 722 ([M+H]⁺, 100 %).

(η^6 -p-cymene)(N-(2-((2-hydroxy-5-nitrophenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)chlororuthenium(II), [Ru(p-cymene)(L⁶)Cl] (Ru-6) Ligand HL⁶ (22.2 mg, 0.060 mmol), triethylamine (13.7 μ L, 98.4 μ mol) and [Ru(p-cymene)Cl₂]₂ (20.0 mg, 32.8 μ mol) were reacted using the same method employed for the synthesis of Ru-2. The product (Ru-6) was isolated as a brown solid (24 mg, 57 %). ¹H-NMR (CDCl₃) δ 8.46 (s, 1H), 7.98 (d, 1H, J=2.4Hz), 7.97 (s, 1H), 7.77 (d, 1H, J=8.6Hz), 7.61 (s, 1H), 7.57 (s, 1H), 7.23 (d, 1H, J=8.5Hz), 7.19 (br, 1H), 6.87 (d, 1H, J=9.4Hz), 6.60 (s, 1H), 5.62 (d, 1H, J=6.0Hz), 5.59 (d, 1H, J=6.2Hz), 5.55 (d, 1H, J=5.0Hz), 5.14 (d, 1H, J=4.4Hz), 4.56 (m, 1H), 4.31 (m, 1H), 4.16 (m, 1H), 3.88 (m, 1H), 2.76 (td, 1H, J=6.2Hz, J=13.4Hz), 2.33 (s, 3H), 1.26 (d, 3H, J=6.9Hz), 1.17 (d, 3H, J=6.8Hz); ¹³C{¹H} NMR (125.68 MHz, CDCl₃) δ 170.22, 165.37, 159.49, 151.36, 148.67, 144.48, 137.02, 135.61, 132.89, 129.52, 126.59, 125.09, 123.15, 122.65, 117.29, 116.55, 101.78, 99.40, 88.37, 83.70, 81.10, 80.79, 67.40, 42.47, 30.72, 22.92, 21.62, 18.86; Found 51.78% C, 4.69% H and 7.95% N. C₂₈H₂₈Cl₂N₄O₃Ru requires 52.50% C, 4.41% H and 8.75% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3434 (br), 2921w, 1632sh (N=O), 1623s (7-chloroquinoline), 1603s (7-chloroquinoline), 1548w (7-chloroquinoline), 1474w, 1355m, 1195w, 1102m, 1034w; MS (ES+) m/z 641 ([M+H]⁺, 100 %).

(η^6 -p-cymene)(N-(2-((2-hydroxy-5-methoxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)chlororuthenium(II), [Ru(p-cymene)(L⁷)Cl] (Ru-7) Ligand HL⁷ (21.3 mg, 0.060 mmol), triethylamine (13.7 μ L, 98.4 μ mol) and [Ru(p-cymene)Cl₂]₂ (20.0 mg, 32.8 μ mol) were reacted using the same method employed for the synthesis of Ru-2. The product (Ru-7) was isolated as a brown solid (20 mg, 53 %). ¹H-

NMR (CDCl₃) δ 8.47 (s, 1H), 7.97 (s, 1H), 7.74 (d, 1H, J=8.8Hz), 7.20 (d, 1H, J=9.2Hz), 7.05 (br, 1H), 6.86 (s, 2H), 7.14 (s, 1H), 6.47 (s, 1H), 5.73 (s, 1H), 5.56 (d, 1H, J=6.0Hz), 5.50 (d, 1H, J=5.4Hz), 5.42 (s, 1H), 5.02 (s, 1H), 4.51 (m, 1H), 4.23 (m, 2H), 3.88 (m, 1H), 3.43 (s, 3H), 2.76 (m, 1H), 2.30 (s, 3H), 1.25 (d, 3H, J=6.6Hz), 1.15 (d, 3H, J=6.4Hz); ¹³C{¹H} NMR (125.68 MHz, CDCl₃) δ 165.39, 160.62, 150.96, 149.95, 148.86, 136.50, 133.81, 126.34, 126.28, 123.63, 123.05, 117.18, 116.52, 114.31, 100.47, 99.12, 98.73, 88.67, 83.23, 81.20, 80.53, 66.83, 55.89, 42.56, 30.79, 29.84, 23.12, 21.80, 19.06; Found 53.60% C, 5.27% H and 6.00% N. C₂₉H₃₁Cl₂N₃O₂Ru requires 55.68% C, 4.99% H and 6.72% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3434 (br), 2924m, 2852w, 1623sh (N=O), 1610s (7-chloroquinoline), 1582s (7-chloroquinoline), 1560w, 1540m (7-chloroquinoline), 1466m, 1314w, 1261w, 1091w, 1027m, 869w, 804m; MS (ES+) m/z 626 ([M+H]⁺, 100 %).

(η^6 -p-cymene)(N-(2-((5-tert-butyl-2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)chlororuthenium(II), [Ru(p-cymene)(L⁸)Cl] (Ru-8) Ligand HL⁸ (25.0 mg, 0.066 mmol), triethylamine (13.7 μ L, 98.4 μ mol) and [Ru(p-cymene)Cl₂]₂ (20.0 mg, 32.8 μ mol) were reacted using the same method employed for the synthesis of Ru-2. The product (Ru-8) was isolated as a brown solid (25 mg, 58 %). ¹H-NMR (CDCl₃) δ 8.50 (d, 1H, J=4.4Hz), 7.96 (s, 1H), 7.70 (d, 1H, J=9.0Hz), 7.22 (dd, 1H, J=2.5Hz, J=8.9Hz), 7.16 (dd, 1H, J=1.4Hz, J=8.91Hz), 7.14 (s, 1H), 7.00 (br, 1H), 6.84 (d, 1H, J=9.0Hz), 6.50 (d, 1H, J=3.8Hz), 6.13 (d, 1H, J=1.9Hz), 5.56 (d, 1H, J=6.2Hz), 5.49 (d, 1H, J=6.3Hz), 5.42 (d, 1H, J=5.5Hz), 5.02 (d, 1H, J=5.7Hz), 4.50 (m, 1H), 4.23 (m, 2H), 3.91 (m, 1H), 2.76 (td, 1H, J=6.8Hz, J=13.6Hz), 2.30 (s, 3H), 1.25 (d, 3H, J=6.9Hz), 1.16 (d, 3H, J=6.8Hz), 1.02 (s, 9H); ¹³C{¹H} NMR (125.68 MHz, CDCl₃) δ 166.06, 163.17, 150.87, 149.79, 147.17, 136.66, 136.23, 133.84, 130.08, 126.15, 123.38, 121.37, 116.98, 116.77, 100.42, 98.87, 98.47, 88.27, 82.97, 80.98, 80.47, 66.14, 42.09, 33.35, 31.07, 30.60, 22.90, 21.62, 18.92, 17.09; Found 50.33% C, 4.48% H and 2.57% N. C₃₂H₃₇Cl₂N₃ORu requires 58.98% C, 5.72% H and 6.45% N. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3449 (br), 2959m, 1623sh (N=O), 1618s (7-chloroquinoline), 1578s (7-chloroquinoline), 1541w (7-chloroquinoline), 1474m, 1457w, 1421w, 1389w, 1322m, 1255w, 1180w, 1142w, 1023w, 834w; MS (ES+) m/z 651 ([M+H]⁺, 100 %).

(η^6 -p-cymene)(N-(2-((2-hydroxyphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)chloroosmium(II), [Os(p-cymene)(L¹)Cl] (Os-1) Ligand HL¹ (33 mg, 0.1 mmol) was dissolved in dichloromethane (5 mL) and KOtBu (13 mg, 0.11 mmol) was added at room temperature. The solution was stirred for 30 min, cooled to -78°C and [Os(p-cymene)Cl₂]₂ (40 mg, 0.05 mmol) was added. The reaction mixture was stirred for 16 h, during which the solution was allowed to warm to room temperature. The reaction mixture was loaded on a short column of Celite and SiO₂ and eluted with dichloromethane-methanol 9:1 (v/v). The solvent was evaporated to give the product (Os-1) as a red solid (50 mg, 72%). ¹H-NMR (500 MHz, CDCl₃) δ 8.53 (d, 1H, J=5.1Hz), 7.91 (s, 1H), 7.66 (d, 1H, J=8.9Hz), 7.22 (m, 2H), 7.18 (d, 1H, J=8.9Hz), 6.85 (d, 1H, J=8.5Hz), 6.53 (br s, 1H), 6.43 (d, 1H, J=5.1Hz), 6.32 (d, 1H, J=7.4Hz), 6.27 (t, 1H, J=7.4Hz), 5.81 (m, 2H), 5.79 (d, 1H,

J=5.0Hz), 5.39 (d, 1H, J=5.0Hz), 4.38 (m, 1H), 4.30 (m, 1H), 4.11 (m, 1H), 3.77 (m, 1H), 2.64 (sept, 1H, J=6.8Hz), 2.38 (s, 3H), 1.26 (d, 3H, J=6.8Hz), 1.13 (d, 3H, J=6.8Hz); ^{13}C -NMR; IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3300m (br), 2960m, 2923w, 2858w, 1633sh (N=C) 1613s (7-chloroquinoline), 1588s (7-chloroquinoline), 1539m (7-chloroquinoline), 1469m, 1447m, 1322m, 1200w, 1142w, 1084w, 1034w; MS (ES+) m/z 686 ([M+H]⁺, 3%), 650 ([M-Cl]⁺, 30%), 325.6 ([M-Cl+H]²⁺, 100%).

(η^6 -p-cymene)(2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl)-4-fluoro-phenol)chloroosmium(II), [Os(p-cymene)(L²)Cl] (Os-2) Ligand HL² (40.2 mg, 0.117 mmol) and sodium hydride (8.10 mg, 0.352 mmol) was added to DCM (10 mL) and allowed to stir at room temperature for 30 minutes. DCM (60 mL) was then added and a solution of [Os(p-cymene)Cl₂]₂ (46.1 mg, 0.0583 mmol) in DCM (15 mL) was added dropwise over 75 min with stirring. The resulting orange solution was transferred to a separating funnel and washed with water (4 x 30 mL), dried over magnesium sulphate and filtered. The solvent was then reduced under reduced pressure to approximately 2 mL and the product (Os-2) was precipitated by addition of petroleum ether and collected by vacuum filtration as an orange-red solid (31.4 mg, 38%). ^1H -NMR (400 MHz, CDCl₃) δ 8.54 (d, 1H, J = 5.31 Hz), 7.92 (s, 1H), 7.69 (d, 1H, J = 8.79 Hz), 7.23 (d, 1H, J = 8.79 Hz), 7.16 (s, 1H), 7.00 (m, 1H), 6.80 (m, 1H), 6.43 (m, 2H), 6.03 (m, 1H), 5.79 (m, 3H), 5.39 (d, 1H, J = 5.31 Hz), 4.33 (m, 2H), 4.11 (m, 1H), 3.77 (m, 1H), 2.63 (m, 1H), 2.37 (s, 3H), 1.27 (d, 3H, J = 6.96 Hz), 1.15 (d, 3H, J = 6.77 Hz); ^{13}C -NMR; IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3317 (br, N-H), 1613 (s, C=N), 1589 (s, C=N). MS (ES+) m/z 668.15 ([M-Cl]⁺, 100%), 704.12 ([M+H]⁺, 40%).

(η^6 -p-cymene)(2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl)-4-chloro-phenol)chloroosmium(II), [Os(p-cymene)(L³)Cl] (Os-3) Ligand HL³ (47.0 mg, 0.130 mmol), sodium hydride (7.10 mg, 0.308 mmol) and [Os(p-cymene)Cl₂]₂ (51.5 mg, 0.0651 mmol) were reacted using the same method employed for the synthesis of Os-2. The product (Os-3) was isolated as an orange-red solid (51.3 mg, 55%). ^1H -NMR (400 MHz, CDCl₃) δ 8.54 (br s, 1H), 7.91 (s, 1H), 7.65 (d, 1H, J = 10.25 Hz), 7.20-7.11 (m, 3H), 6.78 (d, 1H, J = 8.79 Hz), 6.41 (m, 2H), 6.21 (s, 1H), 5.78 (m, 3H), 5.37 (d, 1H, J = 4.76 Hz), 4.37 (m, 2H), 4.07 (m, 1H), 3.78 (m, 1H), 2.61 (m, 1H), 2.36 (s, 3H), 1.25 (d, 3H, J = 6.95 Hz), 1.13 (d, 3H, J = 6.77 Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.65 MHz, CDCl₃) δ 162.9, 151.8, 149.2, 135.72, 132.7, 128.4, 125.9, 122.8, 119.2, 117.4, 104, 1, 98.5, 91.2, 90.7, 80.8, 74.3, 73.7, 70.8, 68.2, 41.8, 31.2, 23.4, 22.2, 18.9. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3307 (br, N-H), 1613 (s, C=N), 1580 (s, C=N). MS (ES+) m/z 684.1 ([M-Cl]⁺, 100%), 720.09 ([M+H]⁺, 50%).

(η^6 -p-cymene)(2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl)-4-iodo-phenol)chloroosmium(II), [Os(p-cymene)(L⁵)Cl] (Os-5) Ligand HL⁵ (39.9 mg, 0.083 mmol), sodium hydride (4.0 mg, 0.174 mmol) and [Os(p-cymene)Cl₂]₂ (35.0 mg, 0.0443 mmol) were reacted using the same method employed for the synthesis of Os-2. The product (Os-5) was isolated as an orange-red solid (25.6 mg, 36%). ^1H -NMR (400 MHz, CDCl₃) δ 8.54 (d, 1H, J = 5.13 Hz), 7.97 (s, 1H), 7.68 (d, 1H, J = 8.98 Hz), 7.40 (dd, 1H, J = 2.38, 8.97 Hz), 7.24 (m, 1H), 7.09 (s, 1H), 6.64 (d, 1H, J = 8.98 Hz), 6.51 (s, 1H), 6.45 (d, 1H, J =

5.49 Hz), 5.80 (m, 3H), 5.39 (d, 1H, J = 5.49 Hz), 4.39-4.29 (m, 2H), 4.09 (m, 1H), 3.81 (m, 1H), 2.65 (m, 1H), 2.37 (s, 3H), 1.27 (d, 3H, J = 6.96 Hz), 1.14 (d, 3H, J = 6.96 Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.65 MHz, CDCl₃) δ 164.0, 162.4, 151.7, 149.5, 149.2, 143.7, 142.1, 135.6, 128.4, 126.0, 123.8, 122.5, 121.3, 117.3, 98.4, 91.2, 90.7, 80.7, 74.3, 72.7, 70.8, 67.9, 41.6, 31.2, 23.4, 22.2, 18.9. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 1610 (s, C=N), 1583 (s, C=N). MS (ES+) m/z.

(η^6 -p-cymene)(2-(((2-((7-chloroquinolin-4-yl)amino)ethyl)imino)methyl)-4-methoxy-phenol)chloroosmium(II), [Os(p-cymene)(L⁷)Cl] (Os-7) Ligand HL⁷ (50.3 mg, 0.141 mmol), sodium hydride (5.50 mg, 0.239 mmol) and [Os(p-cymene)Cl₂]₂ (55.3 mg, 0.0699 mmol) were reacted using the same method employed for the synthesis of Os-2. The product (Os-7) was isolated as an orange-red solid (42.4 mg, 42%). ^1H -NMR (400 MHz, CDCl₃) δ 8.55 (d, 1H, J = 5.31 Hz), 7.91 (s, 1H), 7.69 (d, 1H, J = 8.79 Hz), 7.20 (d, 1H, J = 10.81 Hz), 7.06 (s, 1H), 6.94 (dd, 1H, J = 3.29, 9.16 Hz), 6.81 (d, 1H, J = 9.16 Hz), 6.50-6.44 (m, 2H), 5.78 (m, 3H), 5.60 (d, 1H, J = 3.11 Hz), 5.37 (d, 1H, J = 4.76 Hz), 4.35 (m, 2H), 4.11 (m, 1H), 3.76 (m, 1H), 3.39 (s, 3H), 2.63 (m, 1H), 2.38 (s, 3H), 1.27 (d, 3H, J = 6.77 Hz), 1.14 (d, 3H, J = 6.78 Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (100.65 MHz, CDCl₃) δ 163.1, 159.9, 151.8, 149.3, 135.4, 128.07, 126.6, 125.8, 122.9, 122.1, 117.5, 117.0, 113.9, 98.5, 91.0, 90.1, 80.7, 74.2, 72.5, 70.9, 67.6, 55.6, 41.7, 31.2, 23.4, 22.2, 18.91. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3325 (br, N-H), 1607 (s, C=N), 1587 (s, C=N). MS (ES+) m/z 680.2 ([M-Cl]⁺, 100%), 716.14 ([M+H]⁺, 20%).

(η^6 -p-cymene)(N-(2-(((2-hydroxy-3,5-di-tert-butylphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)dichloroosmium(II), [Os(p-cymene)(HL⁹)Cl₂] (Os-HL⁹) Dimer [Os(p-cymene)Cl₂]₂ (30 mg, 0.038 mmol) and HL⁹ (33 mg, 0.076 mmol) were dissolved in dichloromethane (4 mL) and stirred at room temperature for 1h. The reaction mixture was filtered through a plug of Celite and the solvent was removed in vacuo. The product (Os-HL⁹), a yellow solid, was dried under vacuum (51 mg, 81%). ^1H -NMR (500 MHz, CDCl₃) δ 13.58 (s, 1H), 8.77 (d, 1H, J=6.8Hz), 8.48 (d, 1H, J=1.8Hz), 8.39 (s, 1H), 7.33 (d, 1H, J=2.2Hz), 7.24 (d, 1H), 7.03 (d, 1H, J=2.2Hz), 6.92 (dd, 1H, J=1.8Hz, J=9.1Hz), 6.26 (br s, 1H), 6.09 (d, 1H, J=6.8Hz), 6.00 (m, 2H), 5.68 (d, 2H, J=5.3Hz), 3.91 (m, 2H), 3.61 (m, 2H), 2.86 (m, 1H), 1.85 (s, 3H), 1.41 (s, 9H), 1.29 (d, 6H, J=6.9Hz), 1.26 (s, 9H); ^{13}C -NMR; IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3319w (br), 2955m, 2903w, 2862w, 1630w, 1612m (7-chloroquinoline), 1590s (7-chloroquinoline), 1543w (7-chloroquinoline), 1441w, 1360w, 1331w, 1251w, 1172w, 1141w, 802w; MS (ES+) m/z 798 ([M-Cl]⁺, 3%), 399.6 ([M-Cl+H]²⁺, 50%).

(η^6 -p-cymene)(N-(2-(((2-hydroxy-3,5-di-tert-butylphenyl)methylimino)ethyl)-7-chloroquinolin-4-amine)dichlororuthenium(II), [Ru(cymene)(HL⁹)Cl₂] (Ru-HL⁹) This compound was synthesised from [Ru(p-cymene)Cl₂]₂ (50 mg, 0.08 mmol) and HL⁹ (71 mg, 0.16 mmol) using the same procedure employed for synthesis of Os-HL⁹. The product (Ru-HL⁹) was obtained as a red solid (105 mg, 87%). ^1H -NMR (500 MHz, CDCl₃) δ 13.63 (s, 1H), 8.80 (d, 1H, J=6.5Hz), 8.60 (d, 1H, J=1.8Hz), 8.39 (s, 1H), 7.33 (d, 1H, J=2.2Hz), 7.14 (d, 1H, J=8.9Hz), 7.03 (d, 1H, J=2.2Hz), 6.88 (dd, 1H, J=1.8Hz, J=8.9Hz), 6.25 (br s, 1H), 6.10 (d, 1H, J=6.5Hz), 5.51 (m, 2H), 5.20 (d, 2H,

$J=5.7\text{Hz}$), 3.90 (m, 2H), 3.55 (m, 2H), 3.02 (m, 1H), 1.87 (s, 3H), 1.41 (s, 9H), 1.28 (d, 1H, $J=6.9\text{Hz}$), 1.26 (s, 9H); $^{13}\text{C-NMR}$; IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3310w, 2958m, 2906w, 2864w, 1631w, 1612w (7-chloroquinoline), 1588s (7-chloroquinoline), 1542w (7-chloroquinoline), 1441w, 1360w, 1332w, 1247w, 1167w, 1141w, 803w; MS (ES+) m/z 746 ([M+H]⁺, 5%), 708 ([M-Cl]⁺, 3%).

(η^6 -p-cymene)(N-(2-((1-methyl-1H-imidazol-2-yl)methylamino)ethyl)-7-chloroquinolin-4-amine)chloroosmium(II)

chloride, [Os(cymene)(L¹⁰)Cl] (Os-10) Dimer [Os(p-cymene)Cl₂]₂ (30 mg, 0.038 mmol) and L¹⁰ (24 mg, 0.076 mmol) were dissolved in acetone (4 mL) and stirred at room temperature for 1h. The solvent was removed under reduced pressure and the residue was recrystallized from dichloromethane/diethyl ether. The product (Os-10) was obtained as a fine, yellow solid (28 mg,

Table 5. Selected crystal data for complexes Ru-1, Ru-3, Ru-7, Os-5 and Os-7.

	Ru-1	Ru-3	Ru-5	Os-5	Os-7
Formula	C ₂₈ H ₂₉ Cl ₂ N ₃ ORu	C ₂₈ H ₂₈ Cl ₃ N ₃ ORu	C ₂₈ H ₂₈ Cl ₂ IN ₃ ORu	C ₂₈ H ₂₈ Cl ₂ IN ₃ OOS	C ₂₉ H ₃₁ Cl ₂ N ₃ O ₂ Os
Formula weight	595.53	629.97	721.40	810.56	714.67
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	<i>P</i> 2 ₁	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> (Å)	8.9756(16)	9.3205(14)	6.5071(11)	9.6159(6)	8.9203(2)
<i>b</i> (Å)	15.207(3)	15.822(5)	18.214(3)	15.6469(10)	15.7392(4)
<i>c</i> (Å)	18.917(3)	18.804(5)	22.628(4)	18.6189(12)	19.7232(4)
β (deg.)	103.018(2)	103.675(18)	91.422(2)	104.1850(10)	99.676(2)
<i>V</i> (Å ³)	2515.7(8)	2694.3(12)	2681.0(8)	2716.0(3)	2729.71(11)
<i>Z</i>	4	4	4	4	4
<i>D_c</i> (g·cm ⁻³)	1.572	1.5527	1.787	1.982	1.739
μ (mm ⁻¹)	0.863	0.906	1.963	6.055	4.899
θ range for data collection (deg.)	2.329 to 27.079	3.018 to 28.79	1.435 to 27.262	1.70 to 28.50	2.46 to 27.50
Limiting indices	-11 < <i>h</i> < 11 -19 < <i>k</i> < 19 -24 < <i>l</i> < 24	-12 < <i>h</i> < 12 -20 < <i>k</i> < 21 -25 < <i>l</i> < 25	-8 < <i>h</i> < 8 -23 < <i>k</i> < 23 -29 < <i>l</i> < 29	-12 < <i>h</i> < 12 -20 < <i>k</i> < 20 -25 < <i>l</i> < 24	-11 < <i>h</i> < 11 -20 < <i>k</i> < 20 -25 < <i>l</i> < 25
no. of reflexions measured	29412	29607	31278	84625	12294
no. of unique reflexions	11009	6414	6003	6859	6261
<i>R</i> _{int}	0.032	0.0817	0.0371	0.071	0.017
no. of parameters	644	328	331	328	342
<i>R</i> ₁	0.0433	0.0415	0.0282	0.0266	0.0374
<i>wR</i> ₂	0.1088	0.0647	0.0719	0.0462	0.0750
goodness of fit on <i>F</i> ²	1.066	1.05	1.06	1.06	1.510

52%). $^1\text{H-NMR}$ (500 MHz, CDCl₃) δ 9.31 (br s, 1H), 8.91 (d, 1H, $J=9.1\text{Hz}$), 8.54 (d, 1H, $J=5.4\text{Hz}$), 8.27 (br s, 1H), 7.95 (d, 1H, $J=1.6\text{Hz}$), 7.48 (dd, 1H, $J=1.6\text{Hz}$, $J=9.1\text{Hz}$), 7.12 (s, 1H), 6.89 (s, 1H), 6.34 (d, 1H, $J=5.4\text{Hz}$), 5.99 (d, 1H, $J=5.4\text{Hz}$), 5.76 (d, 1H, $J=5.4\text{Hz}$), 5.58 (m, 2H), 4.38 (dd, 1H, $J=6.4\text{Hz}$, $J=14.1\text{Hz}$), 3.78 (m, 4H), 3.66 (s, 3H), 3.57 (m, 1H), 2.76 (sept, 1H, $J=6.9\text{Hz}$), 2.20 (s, 3H), 1.16 (d, 3H, $J=6.9\text{Hz}$), 1.14 (d, 3H, $J=6.9\text{Hz}$); $^{13}\text{C-NMR}$; IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3375m, 2962m, 2923w, 2869w, 1701w, 1611w (7-chloroquinoline), 1580s (7-chloroquinoline), 1538w (7-chloroquinoline), 1515w, 1451m, 1426w, 1370w, 1330w, 1138w, 807w; MS (ES+) m/z 676 ([M]⁺, 5%), 640 (5, [Os(cymene)(L¹⁰)⁺], 320.4 ([M-Cl]²⁺, 100 %).

X-Ray Structure Analysis.

An orange-red crystal of Ru-1 was cut from a long spar and mounted on a 200 micron MiTeGen MicroMount in Paratone-N oil, and then cooled with an Oxford Cryosystems Series 700 low-temperature device; a single crystal of Ru-5 was found and treated in the identical manner. The X-ray intensity data were measured on a Bruker Smart Breeze CCD system equipped with a graphite monochromator ($\lambda = 0.71073 \text{ \AA}$) at 100(2) K. A total of 1464 frames were collected with a total exposure time

of 4.07 hours for Ru-1 and 3.25 hours for Ru-5. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm, and data were corrected for absorption effects using the multi-scan method (SADABS).

The structure of Ru-1 was first solved using the Bruker SHELXTL Software Package with anisotropic full-matrix least-squares refinement on *F*². Hydrogen atom positions were calculated for all CH hydrogen atoms but thermal parameters were allowed to refine isotropically. The NH hydrogen atoms were located in the difference maps and then refined with isotropic thermal parameters and distance restraints (0.91 Å at 100 K).

Copies of the two independent molecules in the unit cell was then created and placed in positions given by the vector between the main residual electron densities and the Ru atom positions. This model was refined with respect to only the occupancies of the split positions and the rotations and translations of the major components to the new positions to yield the final structure. The final refinements were performed using the JANA2006 software.⁴⁵

The red crystals of Ru-3 were fixed to glass fiber using Epoxy glue and the single crystal data was collected at room temperature on an Oxford Diffraction Xcalibur EOS CCD diffractometer with graphite monochromatised Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$) operated at 50 kV and 40 mA, with a detector distance of 50 mm and 2θ range $3.0 - 28.8^\circ$. The Oxford CrysAlisPro RED software was used for data processing, including numerical absorption correction based on Gaussian integration over a multifaceted crystal model.⁴⁶

Structural solution was accomplished using charge flipping as implemented in Superflip.⁴⁷ All refinements were performed using the JANA2006 software.⁴⁶ All non-hydrogen atoms were refined anisotropically and all hydrogen atoms were theoretically generated.

The structure of Ru-5 was solved (intrinsic phasing method) and refined using the Bruker SHELXTL Software Package with anisotropic full-matrix least-squares refinement on F₂. Hydrogen atom positions were calculated for all CH hydrogen atoms but thermal parameters were allowed to refine isotropically. The NH hydrogen atoms were located in the difference maps and then refined with isotropic thermal parameters and distance restraints (0.91 \AA at 100 K).

For Os-5 and Os-7, X-ray single crystal intensity data were collected on a Nonius Kappa-CCD diffractometer using graphite monochromated MoK α radiation ($\lambda = 0.71073 \text{ \AA}$). Temperature was controlled by an Oxford Cryostream cooling system (Oxford Cryostat). The strategy for the data collections was evaluated using the Bruker Nonius "Collect" program. Data were scaled and reduced using DENZO-SMN software.⁴⁸ Absorption correction was performed using SADABS.⁴⁹

The structures of Os-5 and Os-7 were solved by direct methods and refined employing full-matrix least-squares with the program SHELXL-97 refining on F².⁵⁰ Figures were produced using the program PovRay and graphic interface X-seed.⁵¹ All non-hydrogen atoms were refined anisotropically.

For Os-5, all hydrogen atoms were placed in idealized positions and refined in riding models with U_{iso} assigned to be 1.2 or 1.5 times those of their parent atoms and the distance of C-H constrained ranging from 0.95 \AA to 0.99 \AA and N-H 0.88 \AA . The structure was refined to R factor of 0.0266.

For Os-7, all hydrogen atoms, except H2, were placed in idealised positions and refined in riding models with U_{iso} assigned the values to be 1.2 or 1.5 times U_{eq} of the atoms to which they are attached and the constraint distances of C-H ranging from 0.95 \AA to 1.00 \AA . The hydrogen H2 was located in the difference Fourier maps and refined with bond length constraint $d(\text{N2-H2}) = 0.88 \text{ \AA}$. The structure was refined to R factor of 0.0374. Selected crystal data and structure refinement parameters are listed in Table 5.

Electrochemistry.

The electrochemical analyses were performed using a WaveNow potentiostat (Pine Research). The solvent was anhydrous dichloromethane stored over molecular sieves and the supporting electrolyte was 0.1 M tetrabutylammonium perchlorate. Measurements were carried out using a 2 mm diameter glassy carbon working electrode, a Pt wire auxiliary electrode and a Ag/AgCl reference electrode separated from

the working solution by a glass frit. Differential pulse measurements used a 10 mV increment. Oxygen was excluded during measurement by a flow of nitrogen gas. All potentials are reported versus the ferrocene/ferrocenium potential (0.400 V vs NHE) as an internal standard.

Determination of *in vitro* antiplasmodial activity.

Three strains of *Plasmodium falciparum* were used in this study: the chloroquine sensitive strains D10 and NF54 and the chloroquine resistant strain Dd2. Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen.⁵² Quantitative assessment of antiplasmodial activity *in vitro* was determined via the parasite lactate dehydrogenase assay using a modified method described by Makler.⁵³ The samples were tested in triplicate on two separate occasions; HL¹⁻⁸, Ru-1 - Ru-8 and Os-1 - Os-3, Os-5 and Os-7, were tested against NF54 (CQS) and Dd2 (CQR) strains and HL¹, Ru-1 and Os-1, HL⁹, Ru-HL⁹ and Os-HL⁹ and L¹⁰, Ru-10 and Os-10 were tested against D10 (CQS) and Dd2 (CQR) strains. The test samples were prepared as a 20 mg/ml stock solution in 100% DMSO. 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 diphosphate (CQ) was used as the reference drug in all experiments. A full dose-response was performed for all compounds to determine the concentration inhibiting 50% of parasite growth (IC₅₀-value). Samples were tested at a starting concentration of $10 \mu\text{g/ml}$, which was then serially diluted 2-fold in complete medium to give 10 concentrations with the lowest concentration being $0.02 \mu\text{g/ml}$. The same dilution technique was used for all samples. Samples were also tested at a starting concentration of 1000 ng/ml, which was then serially diluted 2-fold in complete medium to give 10 concentrations; with the lowest concentration being 2 ng/ml . CQ was tested at a starting concentration of 100 ng/ml . The highest concentration of solvent to which the parasites were exposed had no measurable effect on the parasite viability (data not shown). The IC₅₀-values were obtained using a non-linear dose-response curve fitting analysis via Graph Pad Prism v.4.0 software.

Summary and Conclusions

Eight new ligands, HL²⁻⁹, and the previously known HL¹, which contain a 7-chloroquinoline framework functionalized with a salicylaldehyde moiety in position 4, have been synthesized. These ligands and the related ligand HL¹⁰, in which the salicylaldehyde moiety is replaced by an amine-(N-methyl) imidazolyl chelating unit, have been used to prepare the ruthenium complexes $[\text{Ru}(\eta^6\text{-cym})(\text{L}^{1-8})\text{Cl}]$ (Ru-1 - Ru-8, cym = *p*-cymene) and the previously known $[\text{Ru}(\eta^6\text{-cym})(\text{L}^{10})\text{Cl}]\text{Cl}$ (Ru-10), in which the ligands coordinate to the metal via the bidentate chelating functionality. In the case of ligand HL⁹, spectroscopic evidence indicates that the metal coordinates to the quinoline nitrogen of the ligand to form $[\text{Ru}(\eta^6\text{-cym})(\text{HL}^9)\text{Cl}_2]$ (Ru-9) presumably due to the steric hindrance of

the *tert*-butyl group in 2-position on the salicylaldimine moiety. Furthermore, the direct osmium analogues Os-1 – Os-3, Os-5, Os-7, Os-9, and Os-10 were synthesized and characterized.

All ligands and metal complexes were (or have previously been) evaluated *in vitro* for antimalarial activity against both chloroquine sensitive and chloroquine resistant strains of *P. falciparum*. Ligands HL¹⁻⁸ exhibited antiplasmodial activities on par with chloroquine. The corresponding ruthenium complexes did also exhibit antiplasmodial activities, but at IC₅₀ concentrations that were consistently higher than the corresponding ligands. Two complexes, Ru-5 and Ru-6, did not show any activity against a chloroquine resistant strain. However, the resistance indices for the active ruthenium complexes were better than that of chloroquine. The osmium analogues that were investigated gave antiplasmodial activities that were similar, but in most cases worse, than their ruthenium congeners. A weak correlation of antiplasmodial activity to the electronic influence of the substituent in *para* position on the salicylaldimine moiety in the ligands HL¹⁻⁸ could be detected, with more electron-withdrawing substituents giving higher activity; however, this correlation is not borne out in the analogous metal complexes.

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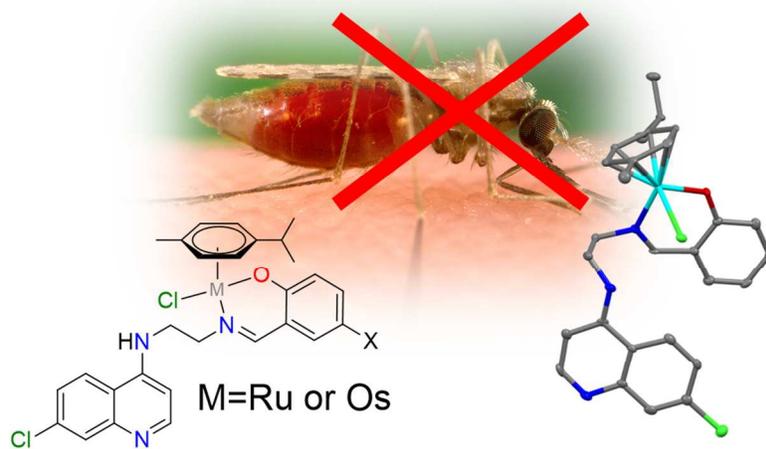
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Thirteen new ruthenium and osmium half-sandwich complexes with chloroquine analogue ligands have been synthesized and evaluated for anti-malarial properties.
338x190mm (96 x 96 DPI)

Supporting Information

Antimalarial activity of ruthenium(II) and osmium(II) arene complexes with mono- and bidentate chloroquine analogue ligands

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Electrochemistry

Table S-1. Oxidation potentials for Ru complexes.

Complex	Volts vs Ferrocene	Hammett value
Ru-HL ⁷ , OMe	0.2568	-0.268
Ru-HL ² , F	0.4972	0.062
Ru-HL ³ , Cl	0.5439	0.227
Ru-HL ⁵ , I	0.5957	0.276
Ru-HL ⁶ , NO ₂	0.7795	0.778

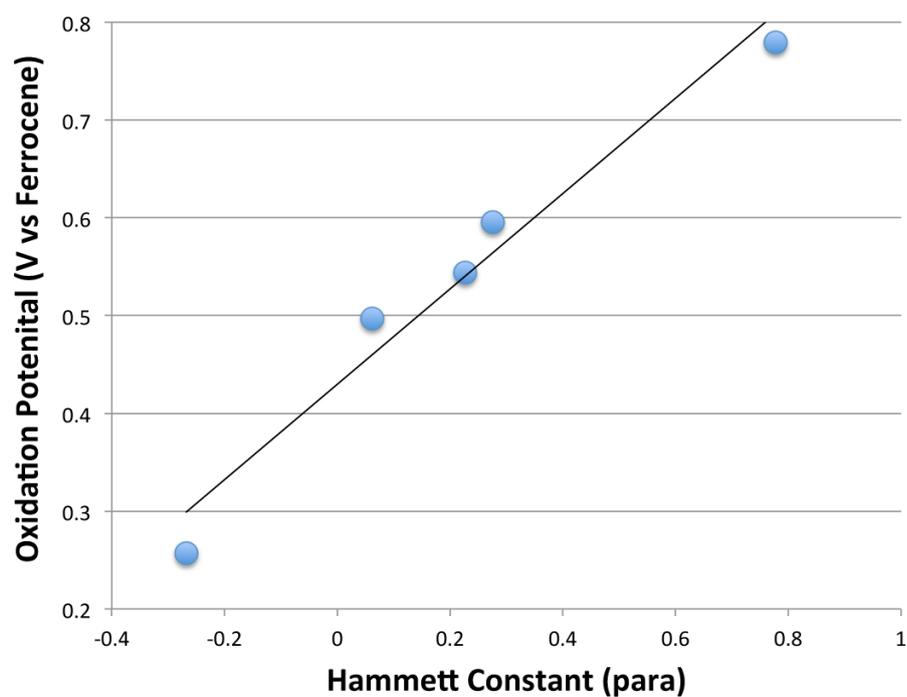


Figure S-1. The oxidation potentials for Ru^{II} to Ru^{III} correlate with the Hammett constants, as the greater electron-withdrawing groups raise the oxidation potential. The data is also shown in Table 1.

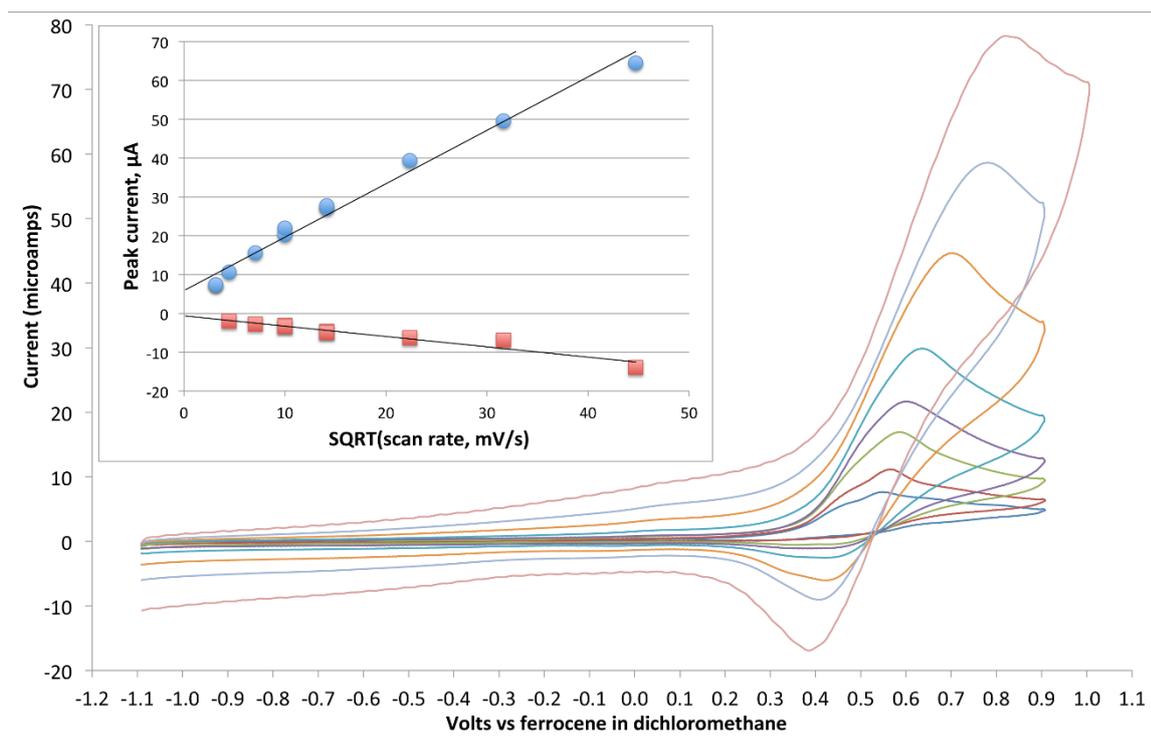


Figure S-2. The ruthenium complexes have a quasi-reversible oxidation with the cyclic voltammetry return wave having a smaller peak current. The figure shows the data for Ru-HL² at 10, 20, 50, 100, 200, 500, 1000, and 2000 mV/s scan rates. The peak current for the return wave is only 20% of that for the forward wave.

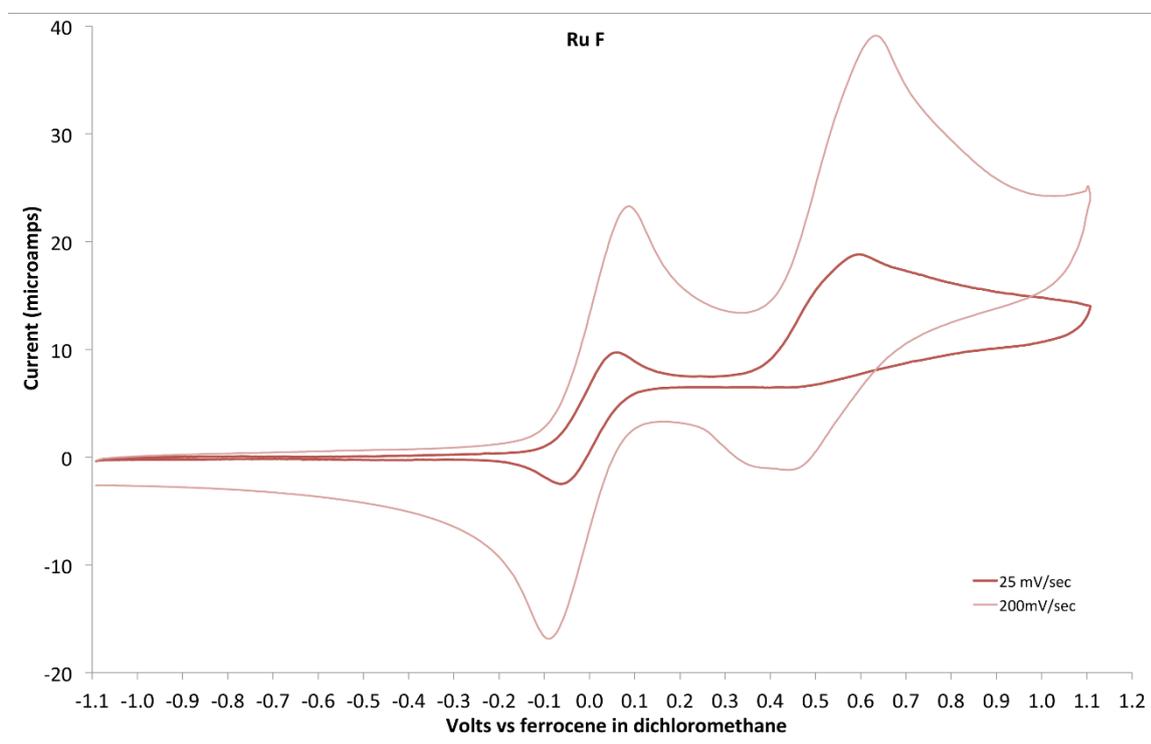


Figure S-3. Peak separations were similar to that of ferrocene. The cyclic voltammogram of Ru-HL² in dichloromethane is shown with added ferrocene at 25 and 200 mV/s scan rates.

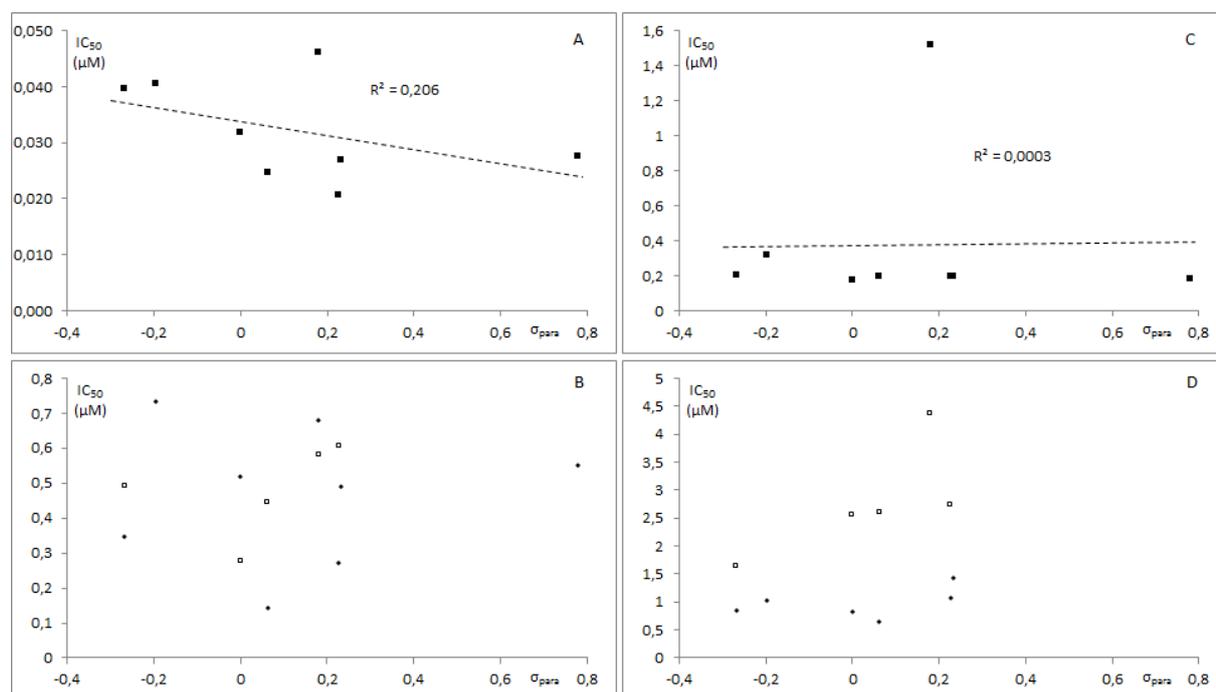
Anti-malarial activities as a function of σ_{para} 

Figure S-4. Antimalarial activities as a function of Hammett σ -para values. A) Ligands **HL**¹ to **HL**⁸ (solid squares), NF54 strain (CQS), B) Complexes Ru-1 to 8 (solid diamonds) and Os-1,2,3,5 and 7 (white squares) NF54 strain (CQS), C) Ligands **HL**¹ to **HL**⁸ (solid squares), Dd2 strain (CQR), D) Complexes Ru-1 to 8 (solid diamonds) and Os-1,2,3,5 and 7 (white squares), Dd2 strain (CQR). Notice the weak negative correlation between antimalarial activity versus the CQS strain for the ligands **HL**¹ to **HL**⁸ and the absence of the same trend in the the corresponding complexes.

¹H-NMR assignments used in the characterization of Ru-HL⁹ and Os-HL⁹Table S-2. Selected ¹H NMR data ($\Delta\delta$, ppm) for complexes Ru-HL⁹ and Os-HL⁹ in CD₂Cl₂.^a

	Ru-HL ⁹	Os-HL ⁹
H1	0.03	0.04
H3	-0.04	-0.05
H5	0.00	0.00
H8	-0.03	-0.04
H9	-0.10	-0.18
H11	0.31	0.33
H12	-0.34	-0.35
H14	0.68	0.77
H16	-0.35	-0.43
H17	-0.36	-0.48
H29	0.01	-0.01
H30	-0.02	-0.02
H31	0.09	0.14

^a $\Delta\delta$ is the displacement of the signal in the coordinated ligand with respect to the corresponding signal in the free ligand. Positive values denote downfield shifts. See figure S-5 for numbering.

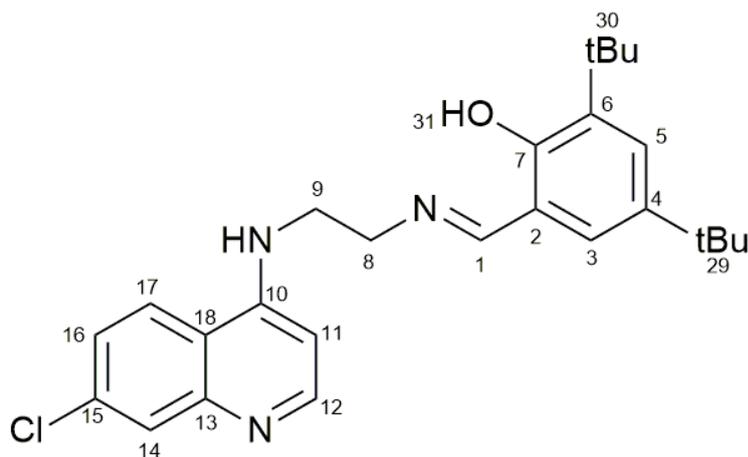


Figure S-5. Numbering scheme used for ¹H-NMR assignments in Table S-2. The same numbering is used for all crystal structures.

Stacking fault in Ru-1

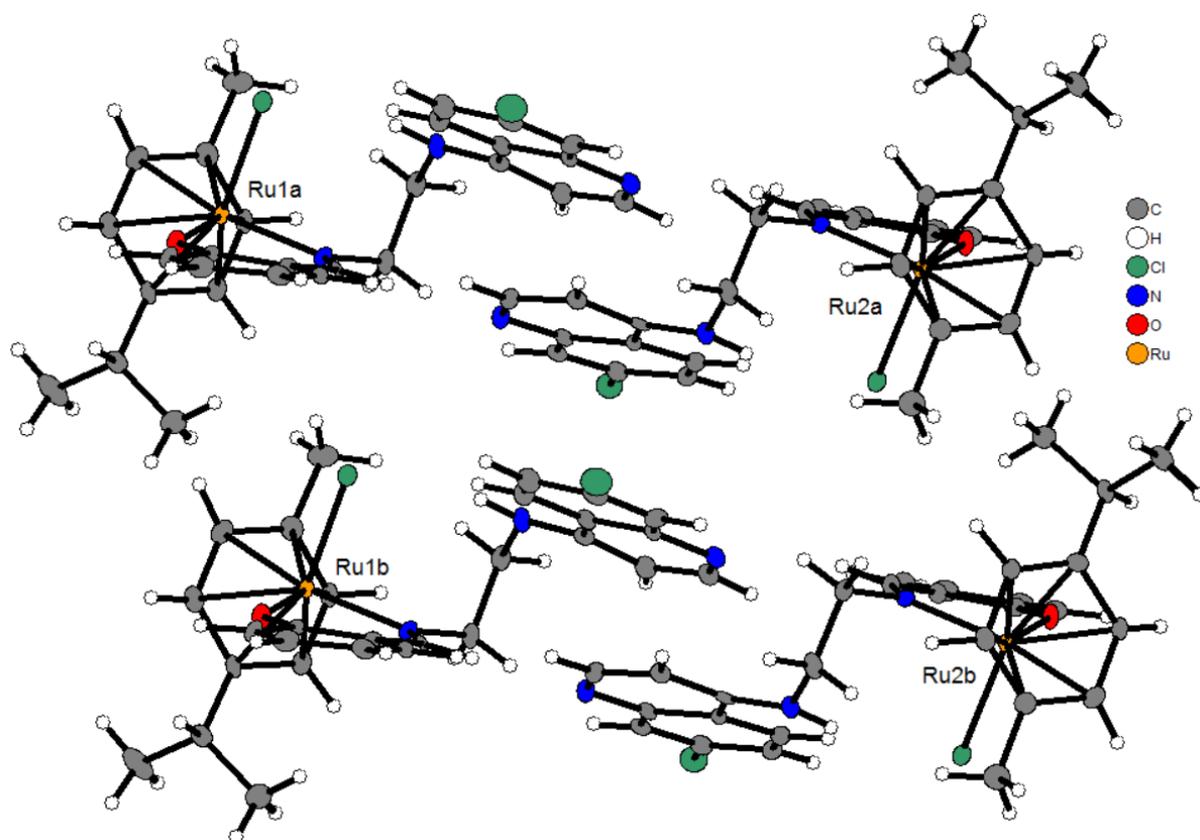


Figure S-6. Structure of the two different domains of Ru-1. Ru1a and Ru2a is in the main polymorph, Ru1b and Ru2b in the minor polymorph. Notice the local centrosymmetry at the interface between the polymorphs.