THE DESIGN AND SYNTHESIS OF NEW TRANSITION METAL COORDINATION COMPLEXES AS POTENTIAL ANTI-MALARIAL AGENTS

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University of Cape Town
February 2011

THE DESIGN AND SYNTHESIS OF NEW TRANSITION METAL COORDINATION COMPLEXES AS POTENTIAL ANTI-MALARIAL AGENTS

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A thesis submitted in fulfilment of the requirements for the degree of
Doctor of Philosophy

Department of Chemistry
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DECLARATION

I declare that **"The design and synthesis of new transition metal coordination complexes as potential anti-malarial agents"** is my own work and to the best of my knowledge has never been submitted for examination for any degree at any university. All sources of information are cited and fully referenced at the end of each chapter.

……………………………………..

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February 2011

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ABSTRACT

New Rh(I), Rh(III), Ir(III) and Pd(II) coordination complexes bearing 1,10-phenanthroline (phen) or 2,2'-bipyridyl (bipy) ligands have been investigated for potential anti-malarial activity. A wide range of different complexes, varying in the metal centre, geometry, charge, diimine ligand, ancillary ligand and counterion have been synthesized. These include [Rh(COD)(N-N)]X (X = PF_6, BPh_4), [Cp*M(N-N)Cl]PF_6, [Pd(N-N)(L-L)].nCl (n = 0,1,2) and [Pd(N-N)PR_3Cl].nPF_6 (n = 1, 2), where COD = 1,5-cyclooctadiene, N-N = diimine, Cp* = pentamethylcyclopentadienyl, L-L = chelating ligand and PR_3 = tertiary phosphine. Chelating ligands (L-L) used were ethylenediamine (en), ethanolamine (EA) and ethylene glycolate (EG), while diimine ligands included 4,4'-R_2-bipy (R = H, Me, ^{t}Bu), 5-R'-phen (R' = H, Me, NH_2, Cl), 4,7-dichloro-1,10-phenanthroline (Cl_2-phen) and 3,4,7,8-tetramethyl-1,10-phenanthroline (TM-phen).

The complexes were characterized by various techniques, including ^1H, ^{13}C and ^{31}P NMR spectroscopy and elemental analysis. X-ray crystal structures were determined for five of the complexes: [Rh(COD)(Me-phen)]BPh_4, [Cp*Rh(Me-phen)Cl]PF_6, [Pd(phen)(ED)]2Cl, [Pd(bipy)(PPh_3)Cl]PF_6 and [Pd(phen)(PPh_3)$_2$]2PF_6.

The free diimine ligands and their complexes have been tested for biological activity against chloroquine-sensitive *P. falciparum* strain D10. The Rh(III) and Ir(III) complexes were completely inactive. The square planar complexes exhibited better anti-malarial activity, with most displaying IC_{50} values in the range 1 – 3 μM. Several more active complexes showed IC_{50} values below 1 μM, with [(TM-phen)Rh(COD)]PF_6 having the strongest activity with an IC_{50} of 0.22 μM. The unsubstituted bipy complexes were the least active of all the compounds, with IC_{50}s of 10 μM and above.

Several ligands and complexes have been further tested against chloroquine-resistant *P. falciparum* strain Dd2. The compounds exhibited little to moderate cross-resistance, with resistance indices ranging from 0.7 for [Pd(Me-phen)PPh_3)Cl]PF_6 to

4.6 for free ligand 5-Me-phen, a range usually considered to indicate that there is no significant cross-resistance.

Some compounds have also been tested against human cancer cell line WHCO1. Most showed good cytotoxicity (IC_{50} range of 2 – 8 μM) and hence were shown to have poor selectivity for malaria cells over human cancer cells.

The diimine ligand was found to be the main determinant of anti-malarial efficacy and the alkylated phenanthrolines, 5-Me-phen and TM-phen, were found to be particularly potent. Variations in metal centre, charge and ancillary ligands had little effect on biological activity. It appears that the anti-malarial action of the complexes occurs as a result of general cytotoxicity against living cells. It is likely that the complexes exert their cytotoxic effect through DNA intercalation and damage.

ABBREVIATIONS

°	degrees
δ	chemical shift
μM	micromolar
Å	angstrom
Ar	aromatic
bipy	2,2’-bipyridyl
br	broad
ca	approximately
COD	1,5-cyclooctadiene
Cp*	pentamethylcyclopentadienyl
CQ	chloroquine
CQR	chloroquine-resistant
CQS	chloroquine-sensitive
d	doublet
dd	doublet of doublets
D_2O	deuterium oxide
DCM	dichloromethane
decomp.	decomposition
DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
Eq.	equation
equiv.	equivalents
ESI-MS	electrospray ionization mass spectrometry

m	multiplet
M	mol/dm^3
mg	milligrams
mmol	millimoles
m/z	mass to charge ratio
nM	nanomolar
NMR	nuclear magnetic resonance
phen	1,10-phenanthroline
ppm	parts per millions
q	quartet
s	singlet
sept	septet
t	triplet
td	triplet of doublets
UV	ultraviolet
UV-Vis	ultraviolet-visible spectroscopy

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Chapter 1

A history of malaria and its treatment

1.1 Malaria: Introduction

There are an estimated 300 – 600 million cases of malaria,[1] resulting in at least 1 million deaths,[2] worldwide each year. The developing regions of Sub-Saharan Africa are worst affected (Figure 1.1),[3] with up to 90 % of all fatalities occurring here.[4]

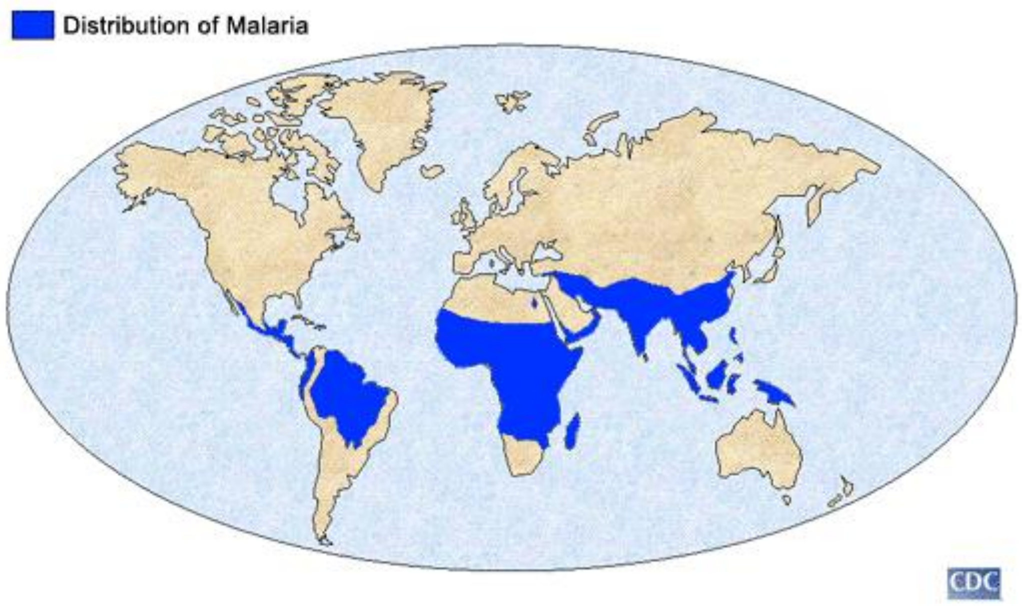


Figure 1.1 Global distribution of malaria; reproduced from reference [5]

The causative agents of malaria are protozoan parasites of the genus *Plasmodium*. By far the most virulent is *Plasmodium falciparum,* which is responsible for the majority of deaths reported.[2,6,7] The disease is characterized by recurring bouts of chills and fever, headaches, nausea and anaemia. In more severe cases, it results in cerebral malaria, coma and subsequent death. Autopsies on malaria victims reveal the presence of large quantities of a dark-coloured solid substance, known as "malaria pigment", in the spleen, brain and other organs.[8]

1.2 Life cycle of *Plasmodium*

Malaria is transmitted by female *Anopheles* mosquitoes. The bite of an infected mosquito leads to introduction of the *Plasmodium* parasite, in the form of thread-like sporozoites, into the human bloodstream (Figure 1.2).[2,9,10] The sporozoites are rapidly transported via the circulatory system to the liver, where they invade and infect liver cells. For several days the parasites develop and multiply within the liver cells; the descendent merozoites are then liberated and re-enter the bloodstream to rapidly bind to and invade red blood cells (erythrocytes).

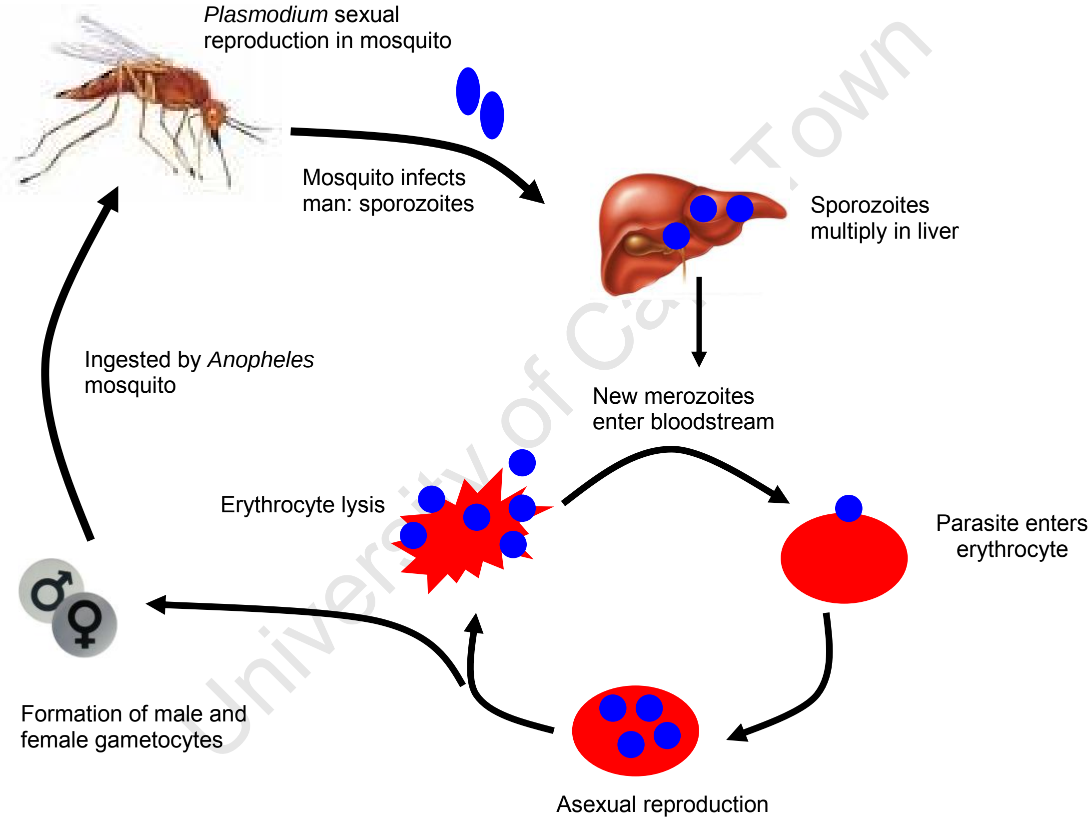


Figure 1.2 Life cycle of *Plasmodium*

Once inside an erythrocyte, the parasite can ingest and utilize its host's haemoglobin as a food source. The merozoite grows into a trophozoite, which then reproduces asexually and forms a schizont containing 8 to 24 offspring.[2] The schizont eventually ruptures (in the process destroying its host blood cell)[11] to release a wave of new parasites that can invade more red blood cells. This cycle continues, and as more and more parasites are formed and released, more and more erythrocytes are infected and ultimately destroyed.

Some blood stage parasites develop into male and female gametocytes, sexual forms of the parasite.[2,9-11] These forms do not themselves cause any symptoms of malaria but do play a role in its transmission. Mosquitoes ingesting blood from an infected human host inadvertently pick up the gametocytes, and sexual reproduction can ensue in the insect midgut. The result of this is the production of sporozoites which migrate to the mosquito salivary glands, and the process of mosquito-to-man infection can begin again.

1.3 Anti-malarial drugs

There is a wide spectrum of anti-malarial drugs available for use today. Different drugs have different targets and therefore different mechanisms of action. However, anti-malarials can be grouped into several broad classes.

1.3.1 Quinolines

The quinolines comprise the best-known anti-malarial drugs, and will be discussed at length.

1.3.1.1 Discovery of quinoline anti-malarial drugs

According to legend, in 1630 in Peru the Countess of Chinchon was successfully treated for malaria with the powdered bark of a certain tree, which later became known as the *Cinchona* tree.[2,12] Thereafter, during the 17th century cinchona bark was distributed as an anti-malarial throughout Europe.

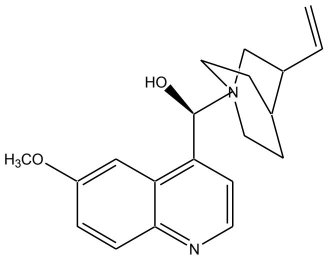


Figure 1.3 Structure of quinine

In 1820 French scientists Pelletier and Caventou isolated the active ingredient, quinine, from *Cinchona* tree bark. To this day quinine can be used in cases of severe malaria,[13] although there may be several unpleasant or dangerous side effects associated with its use.[14] Elucidation of the structure of quinine (Figure 1.3) has led to the discovery of new quinoline compounds. Several 4-amino-substituted quinolines and quinoline methanols have shown excellent activity against the disease in terms of both prevention (prophylaxis) and treatment. Among the most potent of these are mefloquine, amodiaquine and, in particular, chloroquine (Figure 1.4).[15] Inexpensive, readily available, safe [16] and effective, chloroquine became the most extensively used anti-malarial drug and has prevented countless malaria fatalities.[17] However, the emergence of strains of *Plasmodium* that are resistant to chloroquine (and to other quinolines as well) has compromised the efficacy of this drug in many regions.[4]

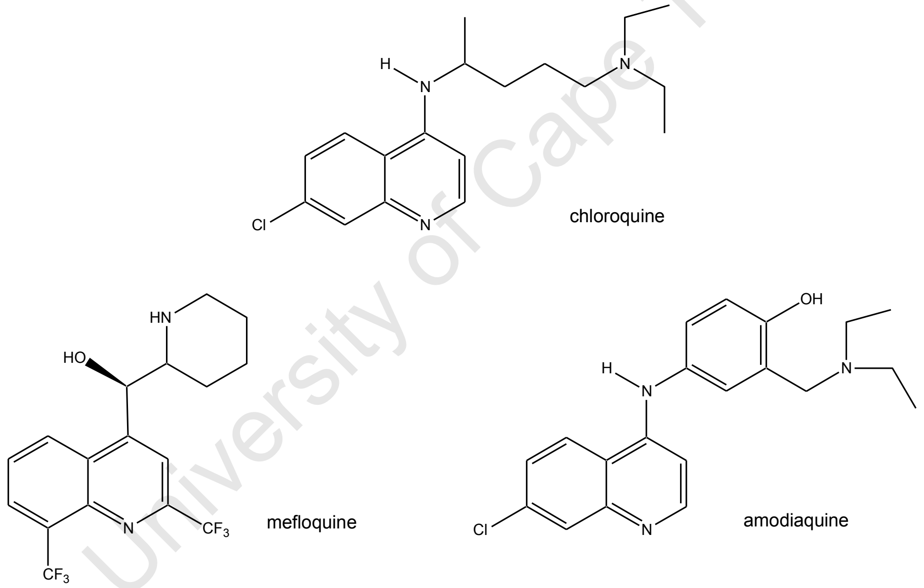


Figure 1.4 Quinoline anti-malarial compounds

1.3.1.2 Mechanism of action of quinolines

In order to understand how quinoline (and related aryl methanol) anti-malarials act, some biology of the *Plasmodium* parasite must first be understood.

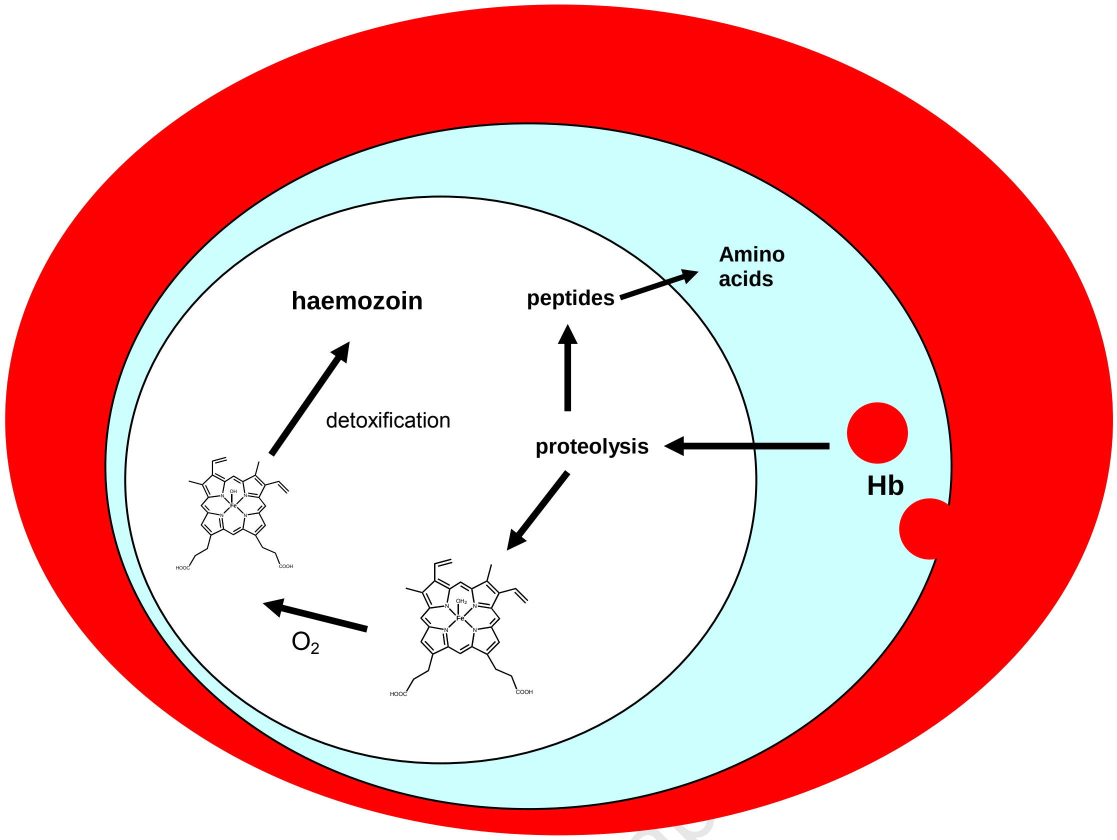


Figure 1.5 Uptake and digestion of haemoglobin in *Plasmodium*

During the blood stage of its life cycle, the parasite digests haemoglobin (Hb, Figure 1.5), taken from the host blood cell, inside its acidic digestive vacuole (DV, Figure 1.5). The peptides produced are further degraded into amino acids which are used as a food source.[18,19] The degradation of haemoglobin leads to the release of haem, iron(II) protoporphyrin IX; this is oxidized to Fe(III) protoporphyrin IX (haematin), which is toxic to the parasite and is believed to be able to damage cell membranes via lipid peroxidation [20,21] and generate harmful radical species.[22] Haematin is therefore detoxified through a biocrystallization process [23] into an insoluble, innocuous form known as haemozoin (malaria pigment).

Through the use of IR, ESR and x-ray absorption experiments, Slater and co-workers concluded that haemozoin consists exclusively of haematin molecules bonded through ferric-carboxylate bonds.[24] In 2000, Pagola *et al*. reported the crystal structure of β-haematin through Rietveld refinement of the high resolution powder diffraction pattern.[25] β-haematin is a synthetic form of the substance, previously shown through x-ray diffraction experiments to be chemically and structurally identical to haemozoin.[26] β-haematin, or haemozoin, consists of dimers of Fe(III) protoporphyrin, connected through reciprocal iron-propionate bonds. Dimers are then linked together in an extended hydrogen-bonded chain (Figure 1.6) to form the crystal. It has been shown that β-haematin, or haemozoin, formation is an enzyme-independent chemical process.[27] More recently, Egan *et al*. have explained the rapid formation of this biocrystal in the malaria parasite, showing that haematin can undergo rapid self-assembly into β-haematin at lipid-water boundaries.[28] It has been suggested that approximately 95 % of haem liberated as a result of haemoglobin degradation is sequestered in this way.[19] Haemozoin is significantly less harmful than haematin and causes little damage in the form of radical production and lipid peroxidation.[29] Thus, haemozoin formation is an efficient and necessary method for the disposal of toxic haematin in the parasite.

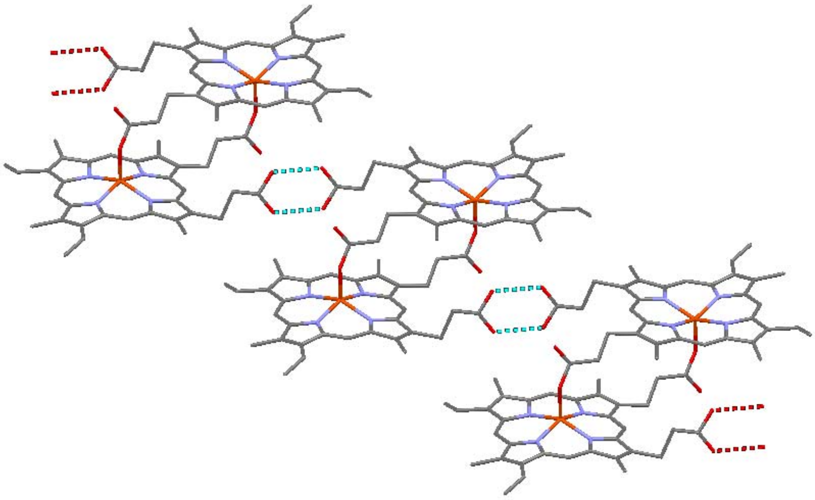


Figure 1.6 The structure of haemozoin, reproduced with permission from the author [30]

In 1994 Egan and co-workers showed that those 4-aminoquinolines and quinoline methanols active against malaria inhibit β-haematin formation, whereas inactive quinolines had no effect.[31] They were later able to show graphically the direct relationship between the normalized *in vitro* anti-plasmodial IC_{50} value (where relative vacuolar accumulation ratio was taken into account) and the β-haematin inhibition ($BHIA_{50}$) value,[32a] as quantified according to the previously-reported β-haematin inhibitory assay.[32b] It is now widely accepted that the 4-aminoquinoline anti-malarials act by accumulating within the acidic food vacuole, and forming complexes with haematin to block the haematin detoxification pathway. Various studies, including UV-Vis, NMR and circular dichroism studies, have highlighted the ability of anti-malarial active aminoquinolines to form strong complexes with haematin and other iron porphyrin analogues.[33-37] It is also known that those related quinolines that do not form measurable complexes with haematin in solution do not inhibit β-haematin formation and do not exhibit good anti-malarial activity.[38] Thus, the action of the 4-aminoquinoline drugs and related compounds can be described as follows.

1) The neutral drug enters the digestive vacuole of the parasite by passive diffusion across cell membranes, where the two weakly basic moieties (amines) are protonated in the acidic environment. The now doubly positively-charged molecule can no longer diffuse easily across cell membranes and out of the vacuole; thus the drug accumulates within that organelle, in part, as a result of this "pH-trapping". Both chloroquine and amodiaquine are believed to exist at near-millimolar concentrations within the acidic digestive vacuole, compared to the nanomolar concentrations at which it is found in the parasite as a whole.[39]

2) The drug forms a complex with free haematin, principally through π-π interactions.[33,38,40] The presence of a coordinating group, such as the hydroxyl group in quinine, may permit an additional mode of binding through coordination to the iron centre.[33,34] This has also been shown for related non-quinoline compounds. De Villiers *et al*. recently published the crystal structure of a halofantrine-haematin complex.[41]

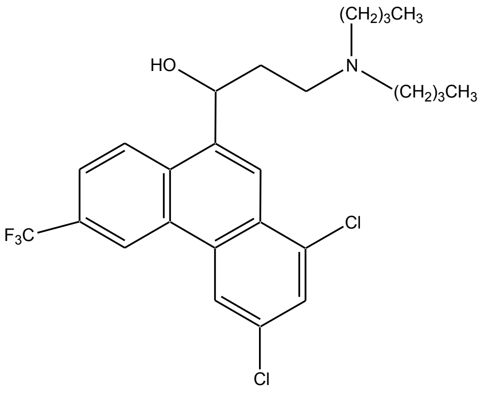


Figure 1.7 Structure of the anti-malarial halofantrine

The aryl methanol anti-malarial drug halofantrine (Figure 1.7) was shown to bind to monomeric haematin through both π-π stacking and coordination of the deprotonated oxygen to the iron centre (Figure 1.8). In this case, hydrogen bonding between the protonated nitrogen of halofantrine and the propionate side chain of haematin provided a third mode of binding.

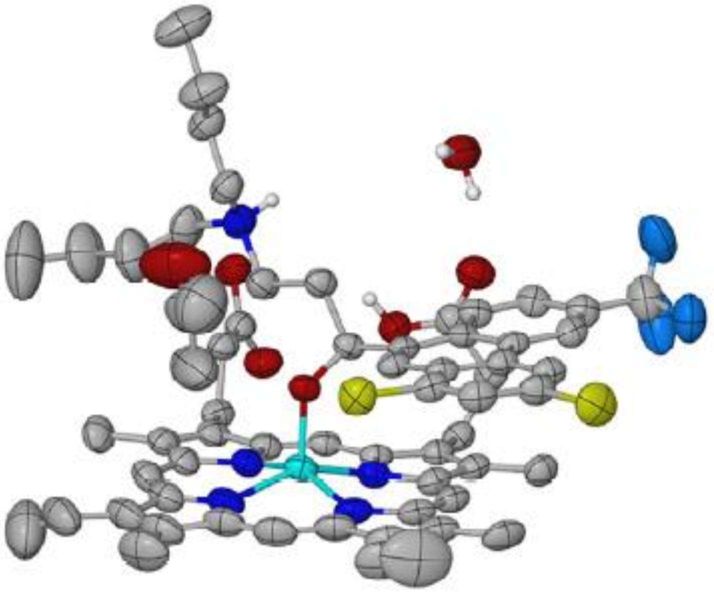


Fig. 1.8 The halofantrine–haematin crystal structure, reproduced with permission from the author [41]

3) The drug-haematin adduct presents a threat to the parasite. In the first place, it prevents the biocrystallization of toxic free haematin into non-toxic haemozoin: binding of the drug to the growing haemozoin surface caps crystal growth, preventing further detoxification of free haematin into haemozoin.[42] Second, the formation of drug-haematin adducts may present a toxic effect in much the same way as free haematin.[37,43-45] Fitch *et al*. have shown that *P. falciparum* cells are lyzed by chloroquine-haematin complex as well as by free haematin.[46] Studies by Tilley *et al*. suggest that chloroquine enhances the binding of haematin to lipid membranes;[20] this could promote accelerated lipid peroxidation.

1.3.1.3 Structure-activity relationships for 4-aminoquinolines and related compounds

It has been established that in order for a quinoline drug to display good anti-malarial activity it must possess all of the following: the ability to form a strong complex with haematin, the ability to inhibit haemozoin formation, and the ability to accumulate to therapeutic concentrations in the *Plasmodium* digestive vacuole.[38]

Several research groups have conducted structure-activity investigations on 4-aminoquinolines, with a special focus on chloroquine derivatives. The elucidation of the structural requirements for the three properties outlined above are particularly important in light of the widespread resistance of malaria parasites to anti-malarial drugs (including quinolines) that threatens the efforts of the World Health Organization to eradicate the disease.

Egan *et al.* proposed the following structure-activity relationships [38] (Figure 1.9) :

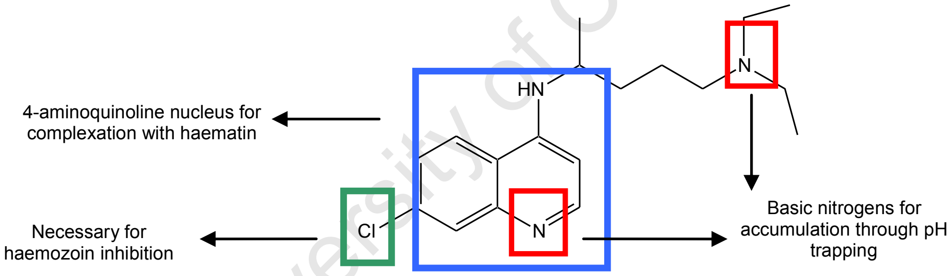
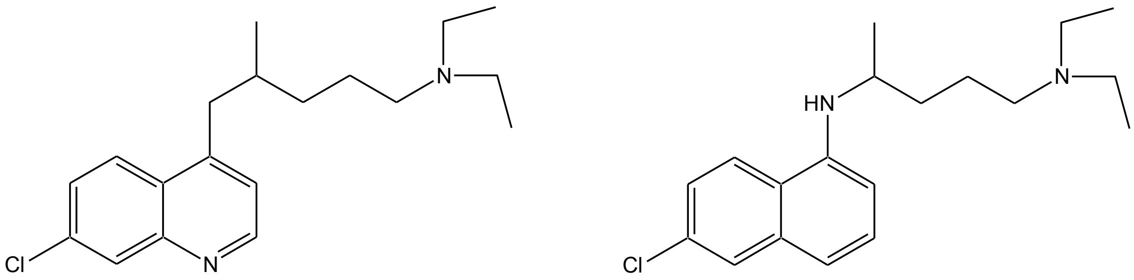


Figure 1.9 Structure-activity relationships for chloroquine

(i) The 4-aminoquinoline pharmacophore

Binding to haematin occurs via π-π stacking through the 4-aminoquinoline pharmacophore.[38] Carbon isosteres of chloroquine (Figure 1.10) are not active against malaria,[47] as reported by Cheruku *et al.* Compound **1**, in which the aniline nitrogen was replaced by a methylene carbon, was seen to bind haematin less strongly than chloroquine, and also inhibited β-haematin only weakly. For **2**, in which a carbon was substituted for the quinoline nitrogen, no binding to haematin was detected at all and no β-haematin inhibition occurred. Neither compound showed anti-malarial activity *in vitro*.



1 **2**

Figure 1.10 Carbon isosteres of chloroquine

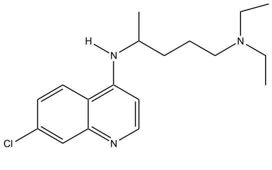
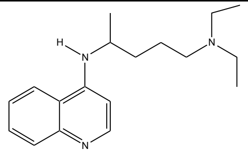
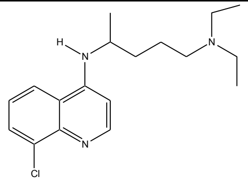
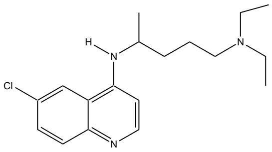
The importance of the amino substitution at the 4-position particularly was observed by Egan *et al.* who determined drug-haematin association constants for a series of aminoquinolines. It was found that 2- and 4-aminoquinolines form strong complexes with β-haematin while 3-, 5-, 6- and 8-aminoquinolines do not.[38]

(ii) The chloro substituent at the 7-position

It has been observed that the presence of the chloro substituent at the 7-position of chloroquine is a minimum structural requirement for anti-plasmodial activity.[32,38,48] The Krogstad group showed that removal of the chloro group to the 6- or 8-position caused, respectively, a decrease in or a total loss of anti-malarial activity [48] (Table 1.1).

The 7-bromo and 7-iodo analogues of chloroquine have been synthesized; these showed activities comparable to chloroquine against a chloroquine-sensitive plasmodial strain, and activities better than chloroquine against a chloroquine-resistant strain.[16] However, the fluoro-, trifluoromethyl- and methoxy-substituted analogues generally exhibited poorer activities.

Table 1.1 Importance of the position of chloro substituent on anti-malarial activity of chloroquine (CQ)

Structure	IC_{50} (nM)	
	Haiti 135 (CQ-senstive)	Indo-China 1 (CQ-resistant)
 **chloroquine**	8	95
	90	5000
	1000	1050
	30	250

A different study showed that the presence of a chloro group at position 7 of a 4-aminoquinoline compound does not necessarily increase the strength of association between the compound and haematin (Figure 1.11), but is necessary for β-haematin inhibition activity,[38] the proposed mechanism of action of quinoline anti-malarials.

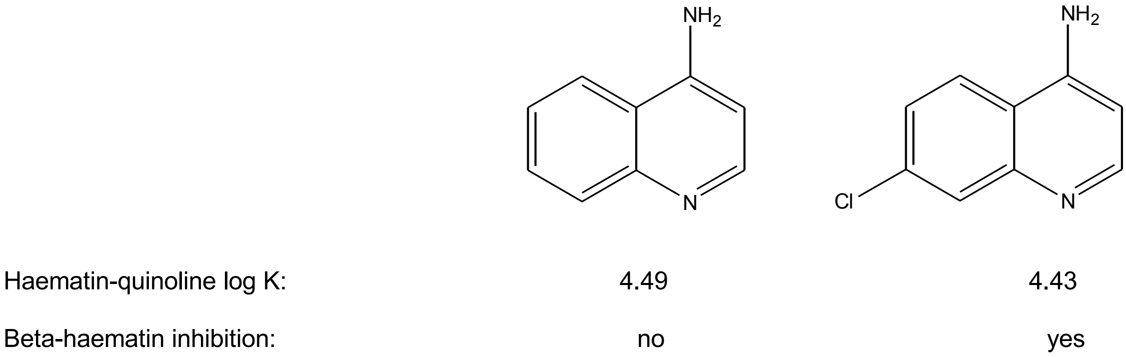
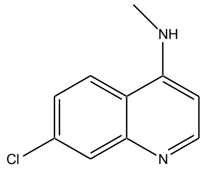
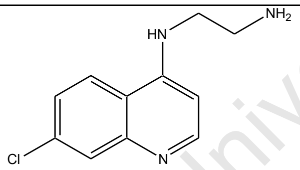
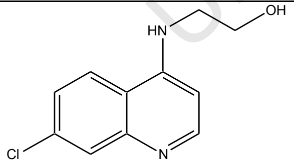
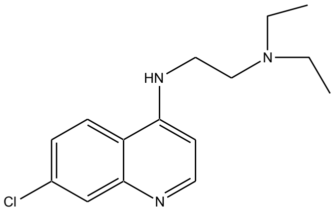


Figure 1.11 The 7-chloro substituent is necessary for β-haematin inhibition

(iii) The aminoalkyl side chain

There is a direct relationship between the accumulation of quinoline in the *Plasmodium* food vacuole and its anti-malarial activity.[49] While the 4-amino side chain does not appear to play a role in β-haematin inhibition, the presence of amino functionalities in the side chain is believed to be necessary for drug accumulation through pH trapping. Although accumulation of drug inside the food vacuole may be in part due to drug-haematin association,[43] it is believed that pH trapping is necessary to drive the equilibrium.[32] Table 1.2 shows the *in vitro* anti-malarial IC_{50} values of selected 4-aminoquinolines.[38] All of the compounds shown inhibit β-haematin formation, however, only those containing a basic side chain show good anti-malarial activity *in vitro*.

Table 1.2 IC_{50} values for selected 4-aminoquinolines against CQ-sensitive D10 strain of *P. falciparum*

Compound	**β-haematin inhibition**	**In vitro IC_{50} (nM)**
	yes	4000
	yes	92
	yes	5070
	yes	49

The Krogstad group found that varying the length of the chloroquine diaminoalkyl side chain (C2 – C12) had little effect on activity against chloroquine-sensitive malaria strains. However analogues with the shortest side chains (ethyl, propyl, isopropyl) and longest side chains (decyl, dodecyl) showed good activity against chloroquine-resistant strains.[16,48] These results suggested that chloroquine analogues with modified side chains are not as susceptible to mechanisms of chloroquine resistance. Later studies have also shown that variation of the amine side chain may be a useful method to circumvent chloroquine resistance.[15]

1.3.1.4 Resistance to chloroquine and other quinolines

Chloroquine remained the most successful anti-malarial globally for several decades.[50] Resistance to the drug in certain regions was first reported in the late 1950's [51] and early 1960's;[52] however, widespread and lasting resistance did not occur until decades later. As chloroquine resistance increased, the cases of severe malaria and mortality likewise increased.[53] It has been shown that, although child mortality due to malaria in Africa declined between the 1960's and late 1980's, it began to increase again from the 1990's.[54]

Previous studies by Krogstad *et al.* showed that, due to an unusually fast rate of chloroquine efflux in chloroquine-resistant (CQR) parasites, chloroquine accumulates only to very low levels; 40 to 50 times lower than in sensitive (CQS) strains.[55] Several research groups noted that verapamil, a calcium channel blocker, can enhance chloroquine accumulation in CQR parasites.[56] These findings indicated the possibility that a transporter or channel protein is involved in chloroquine resistance. Other researchers suggested that chloroquine resistance is associated with a change in the pH of the digestive vacuole, leading to changes in chloroquine influx.[57,58] However, the results of later studies seem to suggest that the former hypothesis is most likely correct.

In 2000 Fidock *et al.* linked chloroquine resistance to mutations in a gene coding for a protein called PfCRT, which was then presumed to be a membrane transporter or channel protein.[59] Later studies showed that PfCRT does indeed belong to a superfamily of drug/metabolite transporter proteins[60,61,62] and that it is located in the membrane of the acidic digestive vacuole.[63] It is hypothesized that in CQS *Plasmodium* strains a positive charge at the first trans-membrane segment of PfCRT prevents the interaction of doubly protonated chloroquine with the protein, thus preventing its efflux through this channel. In CQR the absence of a positive charge in mutated PfCRT removes any source of repulsion, thus chloroquine can interact with and be exported by the protein.[62,63] The efflux of chloroquine in this way reduces the amount of chloroquine inside the digestive vacuole (its presumed site of action) to levels far below therapeutic concentration, and the drug is no longer effective against *Plasmodium*. In 2009 Martin *et al*. presented direct evidence of chloroquine transport by PfCRT in a frog oocyte (female gametocyte) model.[64]

Following the increasing failure of chloroquine since the 1980's, the highly active amodiaquine was used as prophylaxis for and treatment of chloroquine-resistant malaria.[13] However there have been many cases of chloroquine and amodiaquine cross-resistance.[65] Moreover, there has been concern that amodiaquine can cause toxic effects such as hepatitis and agranulocytosis (a shortage of granulocytes, a type of white blood cell) in some people,[66] especially with prophylactic use,[67] and is therefore not used for that indication today. Recent evidence has suggested that the toxicity is not as bad as originally believed [66,67] and it is now being used as treatment in combination with other anti-malarials such as artesunate.[68, 69]

Resistance to chloroquine is global; there is also widespread resistance to mefloquine and some evidence of resistance to quinine in certain regions.[57] The main determinant of mefloquine resistance is the pfmdr1 gene [70] encoding the transporter protein P-glycoprotein homologue 1 (Pgh1), which is believed to actively expel chemotherapeutic compounds from the parasite cell.[71] Numerous studies have shown that point polymorphisms and overexpression of pfmdr1 are linked to resistance to mefloquine [70,72-75] as well as other drugs including quinine,[73,75] halofantrine [73,75] and some non-quinoline anti-malarials.[75] It is also believed to play a role in chloroquine resistance, although it is not the primary cause of chloroquine resistance.[76] Thus pfmdr1 is responsible for multi-drug resistance in some strains of *P. falciparum*.

With the loss of anti-malarial efficacy of the quinolines, there is increasing interest in the use of other classes of drugs as anti-malarial agents.

1.3.2 Artemisinins

The natural extract qinghaosu, (commonly known as artemisinin) and the compounds derived from it (Figure 1.12) form another class of effective anti-malarial drugs.[77,78] The derivatives are much more active than the parent artemisinin itself.[2] These compounds are believed to trigger oxidative stress in the parasite.[78 - 80] Cleavage of the peroxide bond leads to the eventual production of harmful oxygen radicals that destroy the parasite. Analogues that lack the peroxo functionality have no anti-malarial activity.[81]

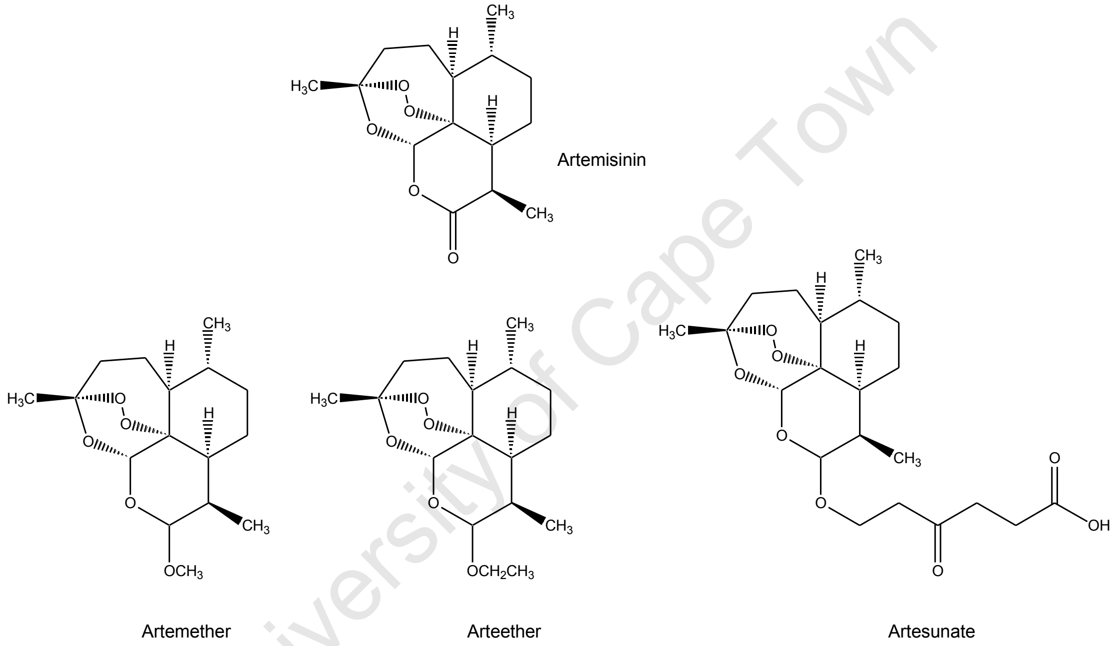


Figure 1.12 Artemisinin and its derivatives

Artemisinins are powerful, fast-acting anti-malarials,[4] effective against both chloroquine-susceptible and chloroquine-resistant *Plasmodium* strains. Some disadvantages of these compounds are their high cost relative to other anti-malarial drugs,[4] and their short half-lives *in vivo*,[82] which can lead to recurrence of the disease after it seemingly has been suppressed. Thus artemisinins must be administered in conjunction with other anti-malarial drugs with longer half-lives as combination therapies. [83]

Until very recently, no clinically proven resistance to artemisinins had been reported. In 2008 and 2009 clinical studies in Cambodia, where artemisinin monotherapy has been in use for over 30 years,[84] indicated that *P. falciparum* has reduced sensitivity to artemisinins *in vivo* in this region.[84,85] Parasite clearance time was significantly prolonged and failure rates somewhat higher compared to other regions of the world. However, resistance to artemisinins is not yet widespread.[85]

1.3.3 Folate antagonists

While humans must obtain folate from dietary sources,[86] microorganisms like *Plasmodium* must synthesize this essential vitamin [87] in a pathway involving several enzymes. Anti-malarial anti-folates act by inhibiting one of two key enzymes, either dihydrofolate reductase (DHFR) or dihydropteroate synthase (DHPS),[88,89] thus disrupting folate synthesis. Drugs are usually administered as a complementary combination of one DHFR and one DHPS inhibitor to slow drug resistance [88] and improve efficacy.[87] Pyrimethamine-sulfadoxine (Figure 1.13) became a frequently-used first-line treatment in regions of chloroquine resistance.[66,87] Other anti-folate combinations used include chlorproguanil-dapsone and trimethoprim-sulfamethoxazole.[90]

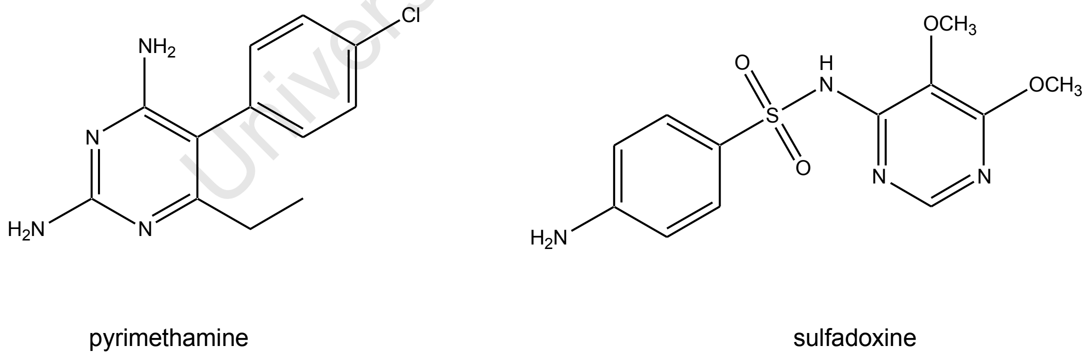


Figure 1.13 Pyrimethamine/sulfadoxine, a combination anti-folate anti-malarial therapy

Anti-folate anti-malarials provide an affordable alternative to chloroquine in areas of high chloroquine resistance.[4,90] Unfortunately, the appearance of resistant *Plasmodium* strains can often occur very soon after introduction of these therapies and resistance to pyrimethamine/sulfadoxine is now widespread.[91]

1.3.4 Atovaquone

The napthoquinone anti-malarial drug atovaquone (Figure 1.14) acts by disrupting mitochondrial functions in the parasite.[91, 92] Resistance to atovaquone, when used as a single drug, develops rapidly. It is therefore commonly used in combination with the anti-folate drug proguanil,[89] and sometimes with the antibiotics tetracycline or doxycycline. These combinations show enhanced anti-malarial activity relative to atovaquone on its own.[91]

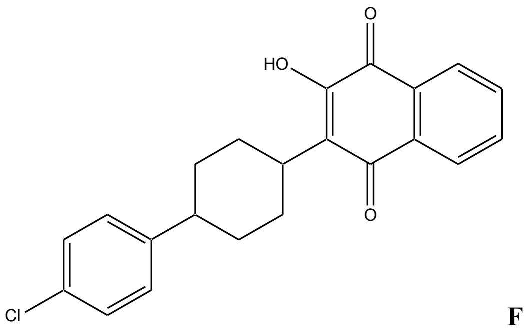


Figure 1.14 Structure of atovaquone

1.3.5 Antibiotics

Antibiotics such as tetracycline and its derivative doxycycline can be used as preventative agents.[2] They may also be used in conjunction with other anti-malarials, such as quinine, to improve efficacy. Clindamycin is a reasonably effective anti-malarial [93, 94] and is more useful in that it is safe for pregnant women and infants.[94] However it shows slow clinical response times and the relatively demanding treatment regimen increases the risk of non-compliance.[94] Nevertheless, it is still useful in combination therapy to help improve the cure rates of faster-acting anti-malarial agents.

1.4 Summary

Despite global efforts, malaria remains a serious threat to developing nations worldwide. The ultimate failure of chloroquine, the most widely used and inexpensive anti-malarial drug, has been a great drawback in eradication of the disease. Some related quinolines, like mefloquine, are no longer effective against drug-resistant *Plasmodium*. Yet others, like amodiaquine, may produce potentially fatal side effects in malaria patients.

Other classes of drugs have been developed and used for treatment of malaria. The artemisinins are very active but are much more expensive than chloroquine, a major disadvantage considering that most malaria sufferers are found in poor countries. Also, resistance to artemisinins has just begun to appear. Others, like the anti-folate combination drug sulfadoxine/pyrimethamine, are cheaper, but resistance develops rapidly and the useful lifetime of the drug is short.

Therefore there is ongoing interest in the discovery and development of new anti-malarial agents that are safe, inexpensive, and most importantly, effective.

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Chapter 2
The use of metals in medicine

2.1 Introduction

Traditionally the field of medicinal chemistry and pharmaceutics has been dominated by organic compounds.[1] However metal–based complexes have more recently gained great interest as potential therapeutic or diagnostic agents,[2] particularly since the remarkable success of the anti-cancer drug cisplatin (see section 2.2.1). The variability of metal complex characteristics (eg. coordination number, oxidation state, ligands) and their unique reactivities may allow for the design of drugs with optimal properties for specific biological actions.

Although there are as yet relatively few examples of metal-based drugs used clinically, the field is growing and much research is being dedicated to the discovery of new drugs of this type. In this brief review, the focus is primarily on metal complexes that have been used successfully to treat or diagnose various diseases.

2.2 Metal complexes in cancer research

2.2.1 Platinum anti-cancer complexes

Following the observation by Rosenberg and others in the 1960's that certain platinum (and other metal) compounds inhibited cell growth in Gram-negative rod bacteria,[3-5] several platinum compounds were screened for antitumor activity.[6] The complex *cis*-diamminedichloroplatinum(II), which later became known as cisplatin (Figure 2.1), proved particularly efficacious. It was entered into clinical trials in 1971,[7] and was eventually approved for the treatment of testicular and ovarian cancers in 1978.[8] Since then cisplatin increasingly has been used to treat bladder, cervical, head and neck and small lung cell cancers.[9]

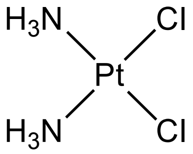
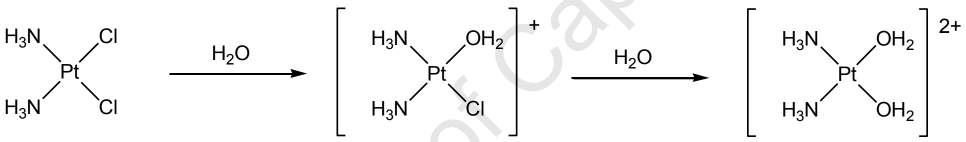


Figure 2.1 Structure of cisplatin

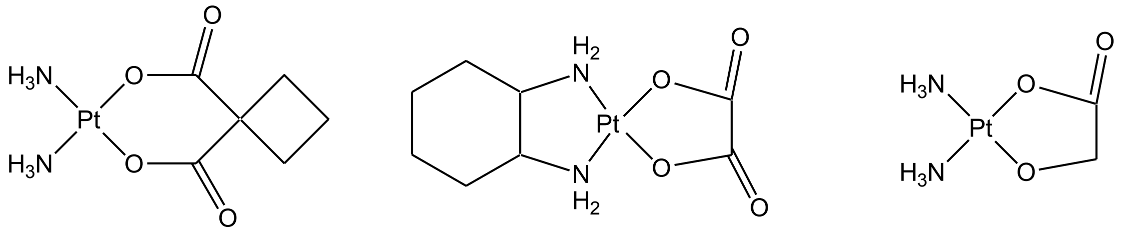
Cisplatin has been shown to act by binding to DNA, leading to DNA damage and cell death. Crystal structures of drug-DNA adducts support this. However the exact mechanism of action is still under debate.[10] One theory is that cisplatin undergoes hydrolysis in the aqueous biological environment to form first the aqua and, eventually, the diaqua species (Scheme 2.1). The aqua complexes then bind to DNA, primarily at the guanine functionalities, with concomitant loss of water ligands.[11] This binding to DNA leads to conformational distortion of the biomolecule, eventually leading to cell death.



Scheme 2.1

Despite its excellent efficacy, which has led to its becoming one of the most successful and best-selling anti-cancer drugs worldwide,[8] cisplatin induces severe side effects including nephrotoxicity (kidney damage), neurotoxicity, ototoxicity (hearing loss), nausea and vomiting.[8] A second disadvantage is its limited solubility in water.[8] The development of cisplatin-resistant tumors may also be a problem; ovarian cancer patients, for example, often develop resistance to cisplatin.[12] For these reasons, there has been a drive to develop new cisplatin analogues with comparable or better anti-cancer activity and decreased toxicity relative to the parent compound.

From the thousands of platinum compounds screened for anti-cancer activity, three more have been approved for clinical use: carboplatin, oxaliplatin and nedaplatin (Figure 2.2).[13]



carboplatin oxaliplatin nedaplatin

Figure 2.2 Platinum anticancer compounds

Carboplatin has similar activity to cisplatin, but reduced nephrotoxicity, neurotoxocity and ototoxicity.[14] However it does induce myelosuppression (impaired bone marrow activity) and there may be cross-resistance with cisplatin-resistant tumors. Nevertheless, carboplatin is a highly successful anti-cancer therapy used worldwide today.

Oxaliplatin is a diaminocyclohexane analogue of cisplatin. Importantly, it is the only platinum-based drug that is clinically active against colorectal cancer.[15] An added advantage is that it is not cross-resistant with cisplatin or carboplatin.[15]

Nedaplatin became available as a treatment in Japan in the late 1980's.[16] It can be used to treat a range of cancers, including head and neck, testicular, cervical and others. It is cross-resistant with cisplatin, and causes little nephrotoxicity but increased myelosuppression relative to cisplatin.[16]

Since the discovery of platinum-based anti-cancer drugs, numerous other transition metals have been screened for anti-tumor/anti-cancer activity. As yet no metal compounds other than platinum compounds are used clinically; however, the complexes discussed below have shown promising activity and have entered clinical trials.

2.2.2 Ruthenium anti-cancer complexes

Of the numerous ruthenium complexes screened, only two have entered clinical trials. NAMI-A (Figure 2.3) was reported by Sava *et al.*[17] Its precursor, NAMI (Figure 2.3) was previously shown to have very good activity against metastatic cancers in mice. Metastasis [18] occurs when cells from the primary tumour break away and enter the blood or lymph systems, from where they can travel to other organs to start new tumours. Metastatic tumours pose a great difficulty in cancer treatment as they can invade all areas of the body, and are often not sensitive to clinically used drugs.[19]

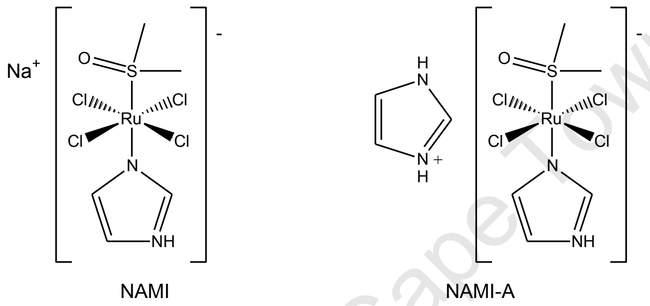
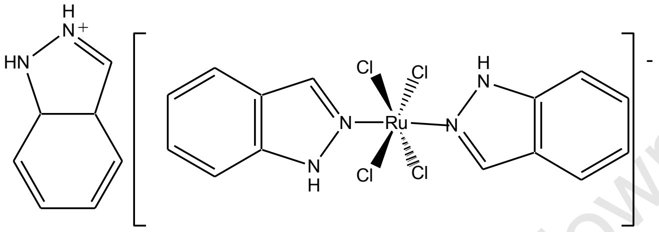


Figure 2.3 Anti-metastatic ruthenium complexes

Studies showed that in tumours NAMI affected the activity of certain enzymes crucial to metastasis formation. At the same time, there was an increase in the amount of connective tissue surrounding the tumour blood vessels, impeding the movement of metastatic cells away from the primary site.[19] Thus, while no significant cytotoxic effect on primary tumours was observed, it was concluded that NAMI actively prevented new metastasis formation and controlled the growth of metastases that had already formed.[19]

NAMI-A was synthesized in order to improve on the chemical properties of NAMI, such as increased stability in air.[17] Like its precursor, NAMI-A showed significant anti-metastatic activity in rodents transplanted with tumours.[17,20,21] NAMI-A underwent a successful phase I clinical trial in 2004.[22] Some side effects, including blisters, nausea and vomiting were observed. However the drug was in general well-tolerated. NAMI-A therefore entered phase II clinical trials in 2008.[22a]

A second ruthenium complex, KP1019 (Figure 2.4), was prepared in 1996 and was shown to possess excellent anti-tumour activity in animal models,[23] particularly against colorectal cancers.[23,24] In a rat tumour model it showed significantly better activity than even 5-fluorouracil, which is the most effective drug for treatment of colorectal cancer.[23] Phase I clinical trials were conducted and most patients experienced disease stabilization. The drug was well-tolerated, with no serious side-effects observed.[23]



KP1019

Figure 2.4 Ruthenium complex active against colorectal cancer

The drug may act by binding to DNA subsequent to its activation by reduction in the relatively acidic environment of tumour cells; Ru(II) is believed to bind more strongly to biomolecules than does Ru(III).[23] KP1019 will proceed to Phase II clinical trials.

2.2.3 Other potential anti-cancer metal complexes

The complexes of numerous metals have been and continue to be evaluated for anti-cancer activity. Palladium,[25] gold,[26] titanium[27] and gallium [28,29] are only a few examples of metals whose complexes are being studied. Some have even reached clinical trial stage. Titanocene dichloride (Figure 2.5), for instance, reached phase II trials in the late 1990's, but showed weak activity against renal-cell cancer and was therefore not pursued as a clinical chemotherapeutic agent.[30] However, countless other complexes are still in the stages of preclinical and early clinical investigation, and it is very possible that these efforts may yield new lead compounds for anti-cancer chemotherapy.

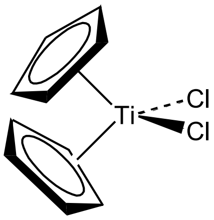


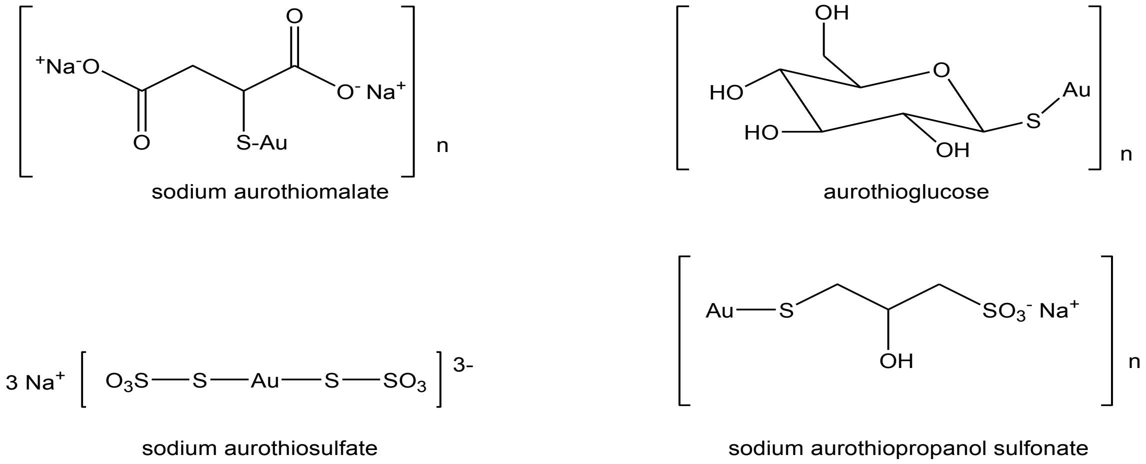
Figure 2.5 Titanocene dichloride

2.3 Gold drugs for rheumatoid arthritis

Rheumatoid arthritis (RA) is a debilitating autoimmune disease primarily characterized by inflammation and pain of the joints.[31] The exact cause is unknown, but the result is a disruption in the immune system,[31] leading to the over-production of lymphocytes (immune cells) that attack the body's tissues.[32]

For decades, gold thiolate complexes have been used for the alleviation of symptoms of rheumatoid arthritis.[33] The chemical formulations of the first-generation gold thiolates are shown in Figure 2.6, although it must be noted that the actual chemical structures are not well-defined.[31,34] The compounds (with the exception of sodium aurothiomalate) are believed to be polymeric with the bidentate sulfur donor atoms bridging two gold centres, and each gold atom bonded to two sulfurs to form -S-Au-S- arrays.[31] They are water-soluble,[31] and are administered via intramuscular injection.[31,33]

The precise mechanism of action of gold compounds against rheumatoid arthritis is not well understood. It is known that the compounds undergo rapid ligand displacement reactions *in vivo*, and thus should be considered as prodrugs.[31,34] Upon displacement of the ligands, the gold binds to proteins; most extracellular gold is bound to albumin,[34] the most abundant blood plasma protein. The protein-bound gold can thus be transported, via the vascular system, to the target site (inflamed joints). The gold reacts with the cyanide that is abundant in inflamed areas [31] to form the metabolite aurocyanide, $[Au(CN)_2]^-$, which is then taken up into cells. It is believed that aurocyanide is the biologically active species and may suppress the activation of the lymphocytes.[32,35]



sodium aurothiomalate

aurothioglucose

sodium aurothiosulfate

sodium aurothiopropanol sulfonate

Figure 2.6 First-generation gold anti-arthritic compounds

Common side-effects of these drugs are rashes and mouth ulcers. More serious effects like aplastic anaemia may occur less frequently.[35] Perhaps it is for this reason that gold drugs are usually used to treat progressive rather than early-onset RA.

The single second-generation drug triethylphosphinegold(I) tetraacetylthioglucose, or auranofin (Figure 2.7), is a well-defined monomeric compound and is administered orally, usually in the form of capsules.[31] It is somewhat less effective than the first-generation parent compounds, but also causes less severe side effects.[35]

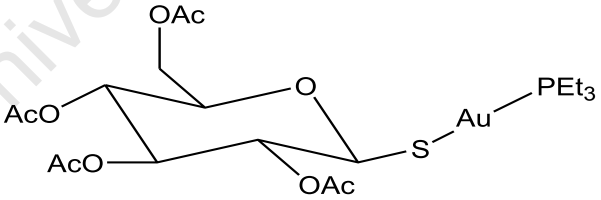


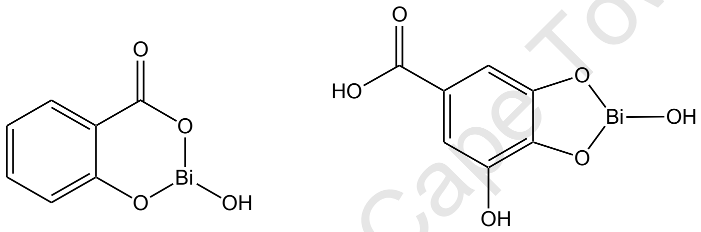
Figure 2.7 Gold-containing drug auranofin

Gold complexes have found application not only in the treatment of RA, but have also been investigated for anti-HIV, anti-asthma and particularly anti-cancer properties.[31] There is thus great scope for the discovery of new gold-based drugs to treat disease.

2.4 Bismuth for the treatment of gastrointestinal problems

The bacterium *Helicobacter pylori* is associated with several gastrointestinal disorders in humans, including peptic ulcers, gastritis, and even gastric cancer.[36,37]

Complexes of the heavy element bismuth have been used to treat gastrointestinal disorders for many years. Two common examples are bismuth subsalicylate (Figure 2.8), the active component in the commonly-used formulation Pepto-Bismol which is used for treatment of diarrhoea and dyspepsia, and colloidal bismuth subcitrate for treatment of peptic ulcers.[36] The success of these drugs is attributed to their anti-microbial action against *H. pylori*.[36]



Bismuth subsalicylate
(in Pepto-Bismol)

Bismuth subgallate

Figure 2.8 Bismuth compounds for treatment of gastrointestinal disorders

The anti-bacterial properties of bismuth compounds can be exploited in other areas. For instance, bismuth oxide[38] and bismuth subgallate[39] (Figure 2.8) can be used to treat wound infection.

2.5 Radiopharmaceuticals

Over the past few decades, transition metal complexes have become increasingly useful in the field of nuclear medicine, both for diagnostic imaging of diseases and tumours, and for radiotherapy.[40] Radiopharmaceuticals for diagnostic imaging are made up of a radionuclide (that emits gamma rays) and a ligand. The radiopharmaceutical is injected into the patient and allowed to distribute throughout the body; images may then be collected with a special gamma camera.[40,41] These images provide information about different areas in the body, including diseased or infected tissues.

By far the most common radionuclide used for imaging is ^{99m}Tc.[40,42,43] Its gamma emission energy of 140 keV is ideal for imaging by gamma cameras, and its half-life of 6 hours is long enough to allow for preparation and administration of the radiopharmaceutical but short enough to minimize patient exposure to radiation.[41-43]

Different ^{99m}Tc complexes are used to image different areas of the body. $^{99m}TcO_4^-$ has been used to image the thyroid and salivary glands. For brain imaging the ideal complex is neutral and lipophilic, able to cross the blood-brain barrier. Ceretec,[44] incorporating the hexamethyl propyleneamine oxime ligand, and Neurolite,[45] incorporating a 1-ethylcysteinate dimer (Figure 2.9), are commonly used to visualize regional cerebral blood flow.

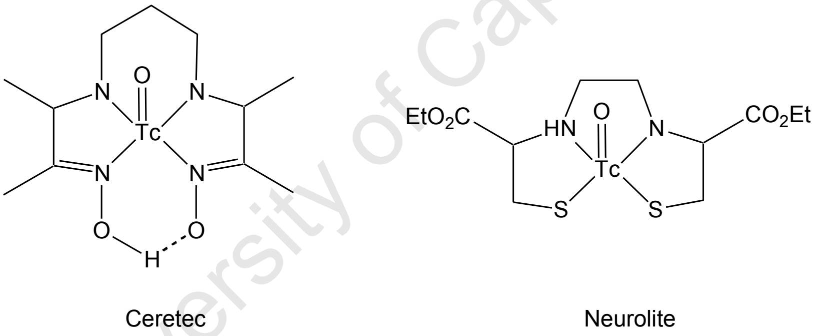
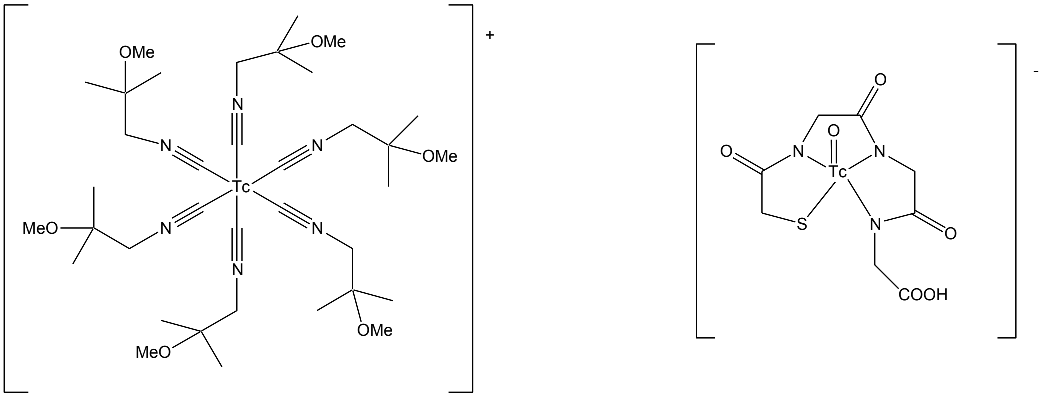


Figure 2.9 Neutral technetium brain-imaging agents

On the other hand, lipophilic monocationic complexes are believed to accumulate better in the myocardial tissue, thus radiopharmaceuticals such as ^{99m}Tc-hexakis(methoxyisobutyl isonitrile), Tc-MIBI [46] (Figure 2.10) and ^{99m}Tc-hexakis(t-butylisonitrile), Tc-TBI,[47] have been used for heart imaging. Tc-MIBI has also proved useful in the detection of breast cancer.[46] Anionic complexes like ^{99m}Tc-MAG$_3$ (MAG$_3$ = mercaptoacetyltriglycine, Figure 2.10) are utilized in kidney imaging.[48] Other Tc complexes are used in the imaging of bone and even tumours.[40, 43]



Tc-MIBI

Tc(MAG$_3$)

Figure 2.10 Ionic technetium imaging agents

More recent work has focused on tagging of ^{99m}Tc onto biomolecules (peptides, antibodies, steroids) to increase specificity of the radiopharmaceutical to the area of interest.[43,49] Radiolabelled monoclonal antibodies, for instance, have a high specificity for cancers rather than normal tissue.[43]

Although ^{99m}Tc is the most common radionuclide used in diagnostic imaging, it is by no means the only transition metal used. ^{67}Ga and ^{111}In are two examples of radiometals used for imaging.[41,42,50]

Radiotherapy involves the use of radioactive complexes to actually treat a disease, such as a tumour. Beta-emitting nuclides accumulate in the tumour tissue; β-electrons are emitted and react with water molecules, producing ionized atoms and free radicals. These reactive species damage DNA, leading to eventual tumour cell death.[42] ^{186}Re and ^{188}Re are two β-emitting isotopes that can be exploited for this purpose, in bone metastases, for example.[41]

2.6 Pentavalent antimony for leishmaniasis

The parasitic disease leishmaniasis is caused by protozoans of the genus *Leishmania*, transmitted to human hosts by the bite of female phlebotomine sandflies.[51,52] Cutaneous leishmaniasis causes disfiguring skin lesions while the mucocutaneous form of the disease affects the mucous membranes of the mouth, nose and throat and may cause lifelong deformity.[51] Visceral leishmaniasis usually results in death when left untreated.[52] The disease is most prevalent in developing countries in South America and the Middle East, including Brazil, Peru, Afghanistan, Saudi Arabia, India and others. An estimated 1 – 1.5 million people are afflicted with cutaneous leishmania, around 500 000 with visceral leishmania, and there are tens of thousands of fatalities each year.[52]

Pentavalent compounds of the metalloid antimony have been the mainstay of leishmansiasis treatment for over fifty years.[53,54] The common clinically used formulations are sodium stibogluconate (Figure 2.11) and meglumine antimoniate.[53,55] These prodrugs are reduced *in vivo* to form the active Sb(III) species.[53,54] Although for a long time the mechanism of action of antimonials had not been well understood, there is evidence that trivalent antimony binds to and disrupts the function of trypanothione reductase (TR), an enzyme present in the parasite but not in the host.[53,54] Baiocco *et al.* recently reported a crystal structure highlighting the binding of Sb(III) to trypanothione reductase.[53]

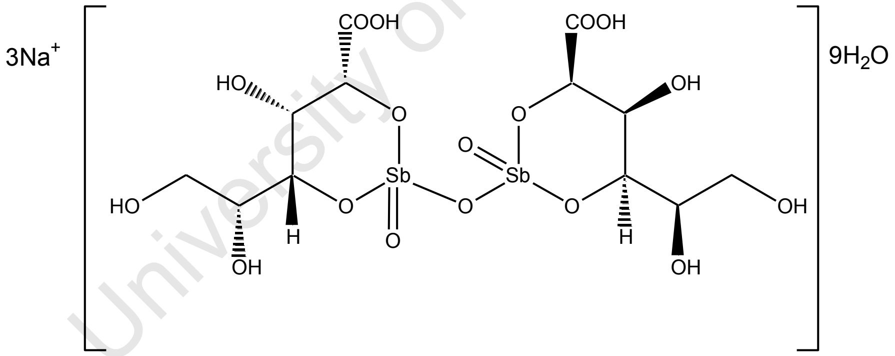


Figure 2.11 Sodium stibogluconate

Unfortunately, although the emergence of drug resistance has been slow, there are now certain areas (eg. Bihar, India)[56] where the efficacy of antimonials has decreased dramatically due to resistant forms of leishmaniasis.

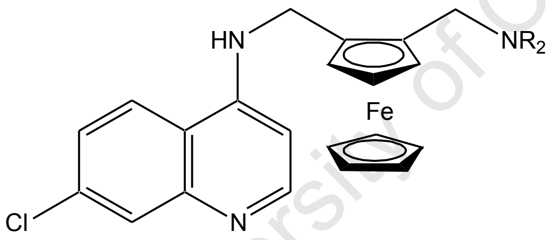
2.7 Metal-containing anti-malarial compounds

With the alarming prevalence of *Plasmodium* strains that are resistant to known drugs (see Chapter 1), there is an increasing need for the discovery of new and effective anti-malarial compounds. One approach in anti-malarial drug development is the modification of existing drugs (eg. chloroquine) by the incorporation of a metal moiety into the compound. With the preservation of the chloroquine substructure it could be assumed that the mechanism of action (haemozoin inhibition) would be retained, while the presence of the metal fragment, hopefully, would improve anti-malarial activity and/or reduce drug resistance.

2.7.1 Metallocene-containing 4-aminoquinolines

2.7.1.1 Discovery of ferroquine and its analogues

In 1997 Biot *et al.* reported the synthesis of a series of chloroquine analogues (Figure 2.12), each bearing a ferrocenyl group in the aminoalkyl side chain.[57]



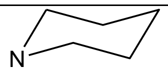
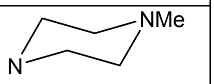
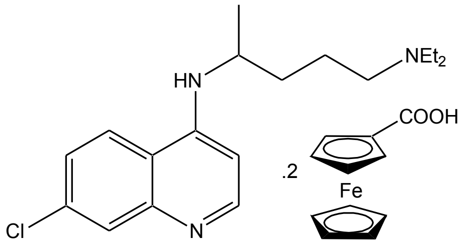
Compound	$-NR_2$
3	NMe_2
4	NEt_2
5	
6	

Figure 2.12 Ferrocene-containing chloroquine analogues

The water-soluble tartaric acid salt of **3** showed activity comparable to chloroquine against chloroquine-sensitive (CQS) *P. falciparum* strains *in vitro*, but showed significantly better activity against chloroquine-resistant (CQR) strains. The compound, later known as ferrochloroquine, or ferroquine, also displayed good anti-malarial activity *in vivo* against the mouse malaria strains *P. berghei* and *P. yoelli*.[57]

Since this discovery, various analogues of ferroquine have been synthesized and tested for anti-plasmodial activity. Domarle *et al.* showed that it was necessary to have the ferrocene molecule covalently bonded to chloroquine in order for anti-malarial activity to be observed; compound **7** (Figure 2.13) was not effective against CQR *P. falciparum*.[58]



7

Figure 2.13

The Biot research group have reported a range of derivatives with variations in the tertiary amine, length of the methylene side chain, and position of ferrocene and presence of substituents in the side chain.[59] Hydroxyferroquine compounds have also been synthesized.[60] Chibale and Moss reported new amine and urea analogues (Figure 2.14) and related their redox potentials to their *in vitro* anti-malarial activities against a CQS strain.[61]

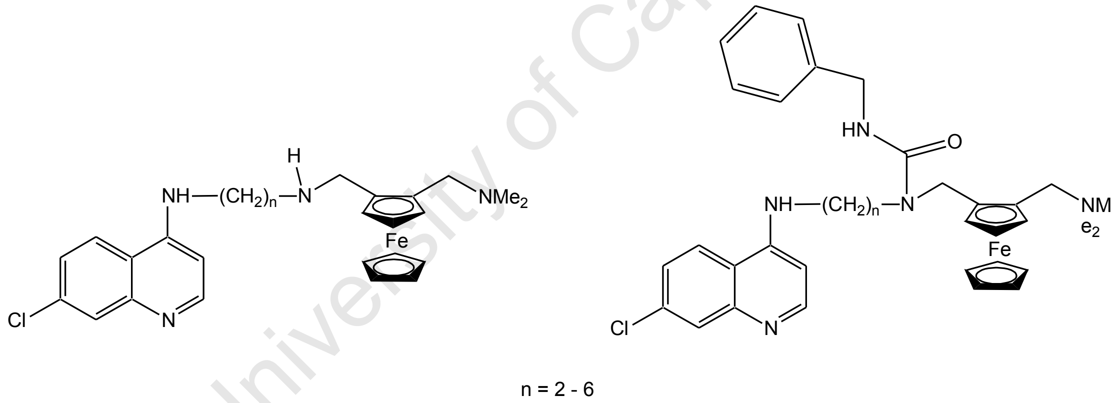


Figure 2.14 A series of amino and urea analogues of ferroquine

A ruthenocence derivative has also been synthesized [62] and shows very similar anti-plasmodial activity to ferroquine in *in vitro* experiments.[62–64]

Despite all the work being done on metallocene-containing 4-aminoquinolines, ferroquine alone has been extensively evaluated as a potential alternative to chloroquine. Numerous studies have been carried out using strains of *P. falciparum* isolated from malaria patients in regions of Gabon,[65-67] Senegal,[68] and the Thai-Burmese border.[69] In all cases ferroquine showed anti-plasmodial activity far superior to chloroquine, especially in areas of high chloroquine resistance. It also often showed better activity than most other known anti-malarial drugs. At the Thai-Burmese border, for instance, multi-drug resistance is prevalent, but there the excellent anti-malarial activity of ferroquine was exceeded only by artesunate.[69] There appeared to be little or no cross-resistance between ferroquine and chloroquine, and drug pressure studies have indicated a low likelihood of rapid development of ferroquine resistance in *P. falciparum*.[70]

These excellent results have prompted the evaluation of ferroquine in clinical trials. Phase II clinical trials were successfully completed in 2008.[71]

2.7.1.2 Mechanism of action of ferroquine

The strong activity of ferroquine against *P. falciparum*, particularly against CQR strains, may result from any of a number of factors. Ferroquine might have a mechanism of action different to other 4-aminoquinolines, or it may be unaffected by the known resistance mechanisms (protein transporters), allowing it to accumulate to therapeutic concentrations in CQR malaria parasites.[72] In addition, the presence of the metallocene could induce physicochemical changes, in turn altering drug accumulation, activity or availability.

The Biot research group showed that, like chloroquine, ferroquine associates strongly with haematin in solution and inhibits β-haematin formation.[73] In fact, ferroquine showed a significantly better β-haematin inhibition IC_{50}. These and other results suggested that the two compounds share a common anti-malarial mechanism of action. Their lipophilicities and basicities, though, were found to be quite different. Chloroquine, with pKa_1 and pKa_2 values of 7.94 and 10.03 respectively, is considerably more basic than ferroquine with pKa values of 6.99 and 8.19. Thus, ferroquine might be expected to accumulate in the digestive vacuole less efficiently than chloroquine does.[73] However, vacuolar accumulation is a function of both pKa and lipophilicity.[73] Results from a later study, indicated that ferroquine accumulates better than chloroquine due to the more lipophilic nature of the former.[74]

Ferroquine is more strongly lipophilic than chloroquine even in the very acidic environment of the food vacuole, and the concentration of its neutral or monoprotonated forms (rather than diprotonated) is higher than that for chloroquine. For these reasons, chloroquine is distributed mainly in the aqueous region of the food vacuole, whereas ferroquine should be localized in lipid regions or at lipid-water interfaces.[74] Lipid-water interfaces are the putative site of action of 4-aminoquinoline anti-malarials, so concentration of the compound here would likely promote anti-malarial action.

An x-ray crystal structure obtained for neutral ferroquine highlighted the strong intramolecular hydrogen bond (2.95 Å) between the anilino and tertiary amino atoms.[73] Later, NMR experiments showed that the hydrogen bond was present in less polar solvents ($CDCl_3$) but not in deuterated water.[74] Thus in apolar environments (eg. lipid) it appears that ferroquine is locked into a specific conformation (Figure 2.15) where the ferrocene group is extruded toward the exterior, allowing its interaction with the lipid layer, while the quinoline moiety interacts with haematin.[74]

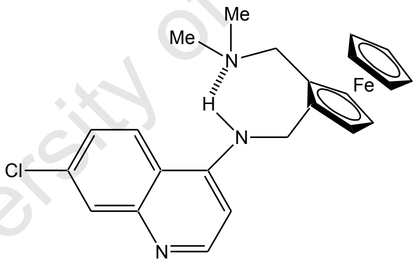


Figure 2.15 Conformation of ferroquine in apolar environment

Biot *et al.* studied a series of analogues of ferroquine substituted with alkyl chains on the anilino nitrogen (Figure 2.16). They found that complexes **8** – **12**, which were unable to form intramolecular hydrogen bonds, had significantly lower *in vitro* anti-plasmodial activity than the parent ferroquine. Complex **8** has physicochemical properties similar to ferroquine (lipophilicity, vacuolar accumulation etc.), but was nevertheless many times less active in both sensitive and resistant strains.[74] The forced conformation of ferroquine in the lipid environment may therefore enhance interaction with and binding to haematin, partly explaining its excellent anti-plasmodial activity.

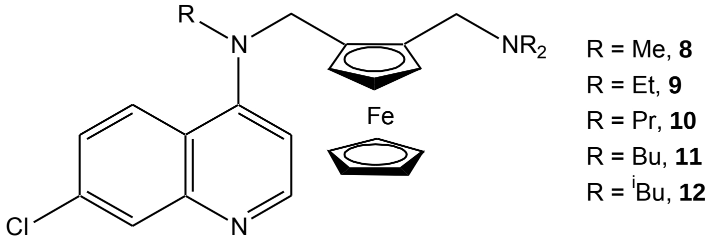


Figure 2.16 Anilino-substituted ferroquine derivatives

The activity of ferroquine against chloroquine-resistant *P. falciparum* is also of interest. It has been suggested that the bulky metallocene moiety changes the shape or volume of the chloroquine substructure to the extent where it can no longer interact with and be expelled by the membrane protein transporters believed to be responsible for 4-aminoquinoline resistance.[73] This idea is supported by the observation that gene polymorphisms for the quinoline protein transporters (PfCRT, Pfmdr and others) have no effect on *in vitro* ferroquine IC_{50} values.[75] The lipophilicity of ferroquine may also be a factor in overcoming resistance, where studies have shown that more lipophilic drugs tend to show better biological activity in resistant parasite strains.[76]

Finally, ferroquine may have an additional mode of action not possible with chloroquine. Hydrogen peroxide, H_2O_2, is produced during haemoglobin degradation in the parasite digestive vacuole. Chavain and co-workers hypothesized that the Fe(II) centre in ferrocene might catalyze the reduction of H_2O_2 to yield hydroxyl radicals (Eq. 1).[77]

$$\text{FQ(II)} + H_2O_2 \longrightarrow \text{FQ(III)} + OH^- \; OH^\bullet \qquad \textbf{Eq. 1}$$

Through the use of cyclic voltammetry, EPR and spin trapping experiments it was shown that the ferroquine Fe(II) centre undergoes a one-electron redox reaction in the presence of H_2O_2. The hydroxyl radicals formed as a result are known to be highly reactive and particularly damaging to lipid membranes.[78] With ferroquine supposedly localized near the lipid layer of the digestive vacuole, it is possible that the compound acts not only by inhibiting haemozoin formation, but by destruction of the parasite lipid membrane through the production of reactive radical species.[77]

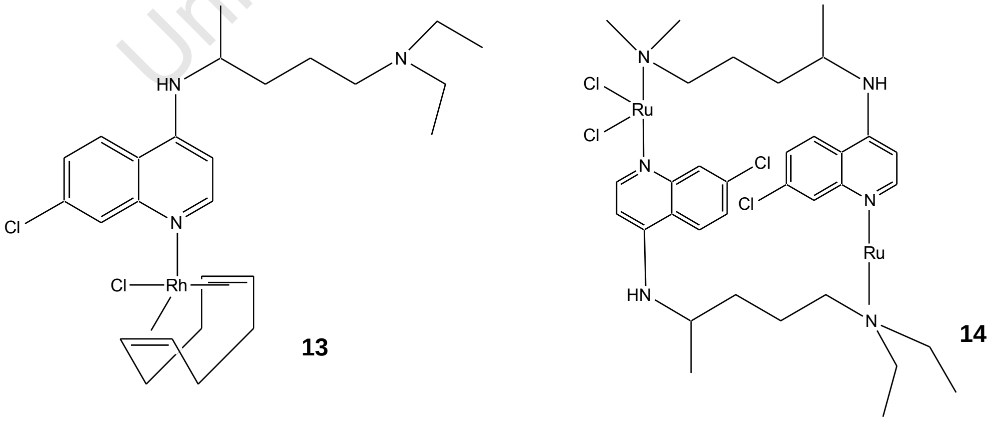
There are therefore many factors that may influence the activity of ferroquine relative to chloroquine; however, more evidence is needed to either prove or disprove any of the theories discussed.

2.7.2 Other metal-containing anti-malarial compounds

2.7.2.1 Chloroquine-based complexes

In the case of ferroquine, the anti-malarial drug chloroquine was modified by the covalent inclusion of a metal moiety into the side chain of the drug. Other research has focused on the coordination of chloroquine to transition metal complexes.

In 1996 the Sánchez-Delgado research group reported the synthesis of the rhodium and ruthenium chloroquine complexes **13** and **14**. The complexes were tested against the rodent malaria parasite, *P. berghei*. Both were found to be active against the blood stage of malaria during *in vivo* testing. Ruthenium complex **14**, showing superior activity, was also tested against chloroquine-resistant strains, and was found to be several times more active than chloroquine in these cases.[79]



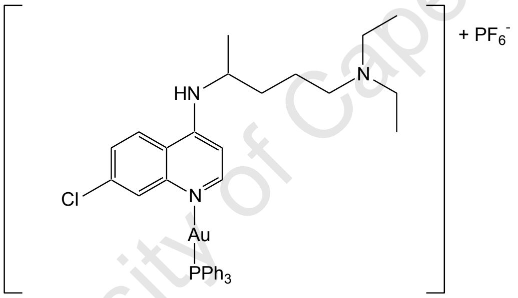
13

14

Figure 2.17 Rhodium- and ruthenium-chloroquine complexes

In a later study, the mechanism of action of **14** was probed.[80] With the basic amine and quinoline groups coordinated to ruthenium, the compound showed a decrease in basicity relative to chloroquine; basicity was previously shown to be necessary for 4-aminoquinoline accumulation and, therefore, activity. However, it was also found that while chloroquine is strongly hydrophilic at a pH less than 6, **14** was relatively lipophilic at pH as low as 5. Therefore, at the digestive vacuole pH, **14** would be expected to concentrate near lipid-water interfaces, the proposed sites of haemozoin (β-haematin) formation, whereas chloroquine would probably be found in the aqueous region.

Sánchez-Delgado *et al.* have also reported the synthesis of several gold-chloroquine complexes. The cationic Au(I) complex **15** (Figure 2.18) was shown to be more active than chloroquine in an *in vivo* experiment on parasitized mice. Furthermore, **15** was up to 9 times more active than chloroquine in chloroquine-resistant strains of *P. berghei* in *in vitro* studies.[81]



15

Figure 2.18 A cationic gold-chloroquine complex

Later, a series of derivatives of **15** was prepared for the purpose of comparison, along with two Au(III) chloroquine complexes (Figure 2.19).[82] The complexes were tested against a range of *P. falciparum* strains, of different levels of chloroquine sensitivity, *in vitro*. All had anti-malarial activity comparable to that of chloroquine against the CQS strain. In most cases the gold compounds showed somewhat better activity than chloroquine against the various moderately-resistant strains.

It was found that overall, variation of the counterion, phosphine ligand or oxidation state of gold (+1 or +3) did not significantly affect IC_{50} values.[82] Due to the limited number of complexes studied, no clear structure-activity relationships could be deduced.

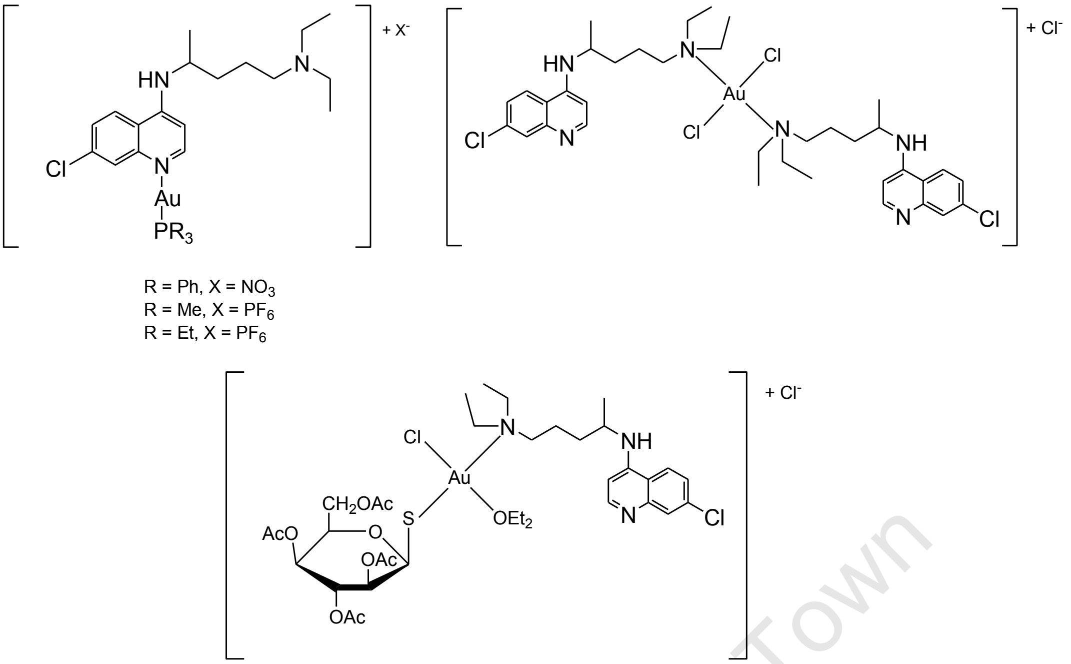
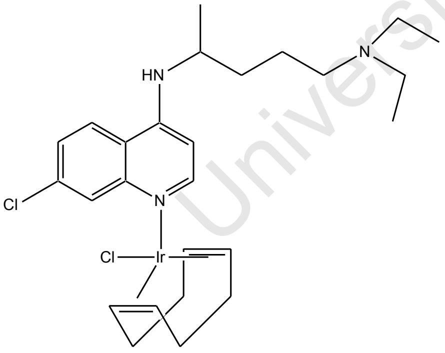
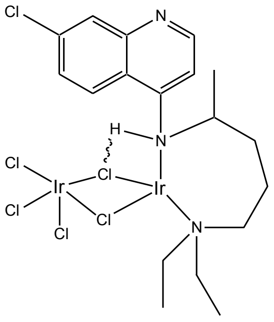


Figure 2.19 Gold-chloroquine complexes

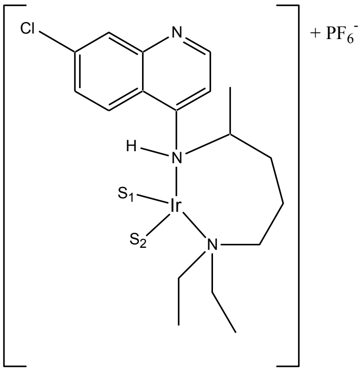
Iridium-chloroquine complexes **16** - **18** (Figure 2.20) were recently reported by Navarro *et al*. All complexes showed *in vitro* anti-plasmodial activities similar to chloroquine against *P. berghei.*[83]



16



17

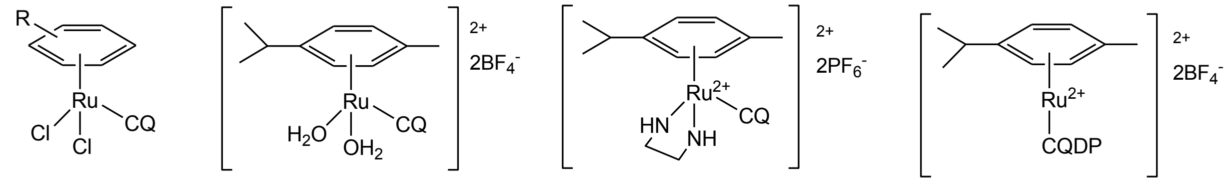


S = $(CH_3)_2CO$

18

Figure 2.20 Iridium-chloroquine complexes

More recently, new ruthenium(II) arene complexes of chloroquine (Figure 2.21) were prepared and evaluated.[84] For complexes **19** - **22** the ligand is bound to the ruthenium centre through the quinoline nitrogen; in **23** it is bound through the π-electron system of the quinoline ring.



Arene = *p*-cymene, **19**
Arene = benzene, **20**

21 **22** **23**

CQ = chloroquine
CQDP = chloroquine diphosphate

Figure 2.21 Ruthenium arene chloroquine complexes

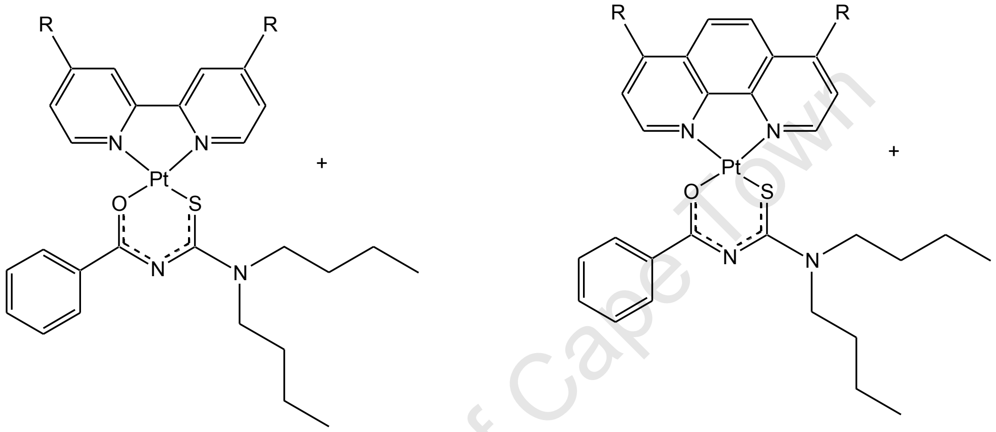
Four of the compounds (**19** – **21** and **23**) were tested for anti-malarial activity *in vitro*. All showed activity against both chloroquine-sensitive and chloroquine-resistant parasite forms. Regarding the CQR *P. falciparum* strains, the compounds were considerably more active than chloroquine in almost all cases.[84]

The mechanism of anti-malarial action was investigated.[85] The complexes bind to haematin almost as strongly as chloroquine does. β-haematin growth inhibition was measured both in aqueous medium and at water-octanol interface (ie. mimicking the lipid membrane/aqueous medium of the parasite digestive vacuole). Among complexes **19** – **23** and chloroquine there was a good correlation between lipophilicity and β-haematin inhibition activity as determined from the water-octanol experiment.[85]

In conclusion, it is clear that the incorporation of metal-containing groups into existing anti-malarial drugs is a promising strategy for overcoming malaria drug resistance. The physical or chemical characteristics, mechanism of action or susceptibility to drug resistance mechanisms may be altered, leading to a compound that is effective against all strains of malaria parasite.

2.7.2.2 Non-quinoline metal complexes as potential anti-malarial agents

In 1998 Koch *et al*. reported a series of cationic diimine platinum complexes (Figure 2.22) that, like porphyrins, exhibit a marked tendency to self-aggregate into dimers in solution. The dimers are most probably held together through non-covalent π-π stacking interactions between the planar aromatic rings of the bipyridyl or phenanthroline ligands, as well as cation-π interactions between cationic complex and aromatic ligand.[86]



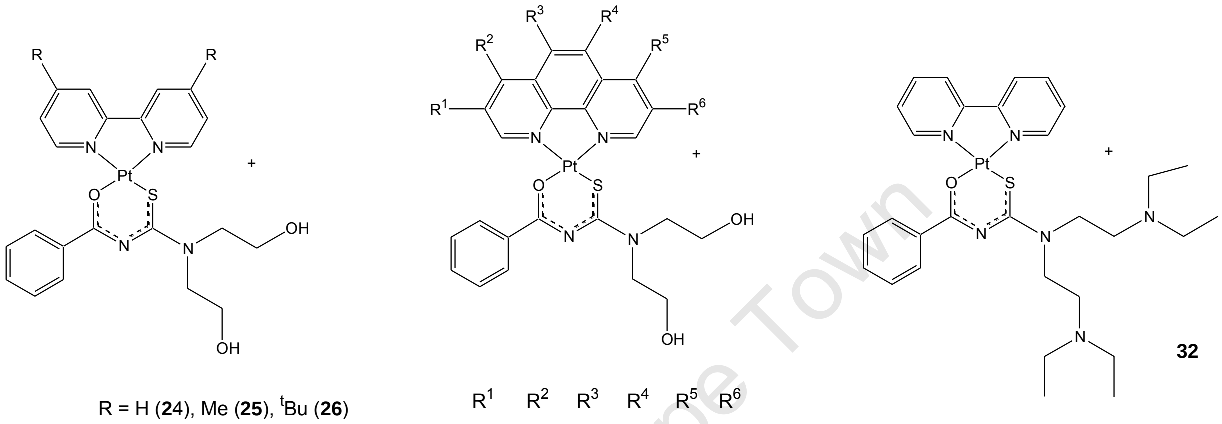
R = H, Ph   R = H, Me, ^{t}Bu

Figure 2.22 Mixed-ligand platinum complexes showing self-aggregation in solution

These results suggested that the platinum complexes might undergo π-stacking with haematin in the same way as aromatic anti-malarial drugs such as chloroquine. Thus a series of similar cationic complexes, each containing a substituted bipyridyl or phenanthroline ligand and a benzoylthiourea ligand, were prepared and tested for haematin binding, β-haematin inhibition and *in vitro* anti-malarial activity.[87]

A range of different bipyridyl and phenantholine ligands, bearing various substituents, were used (Figure 2.23). Hydroxyl and amino moieties were incorporated in order to achieve improved water-solubility. Most of the complexes were isolated as hydrated salts. In the case of complexes **27**, **28**, **30** and **31** a mixture of *syn* and *anti* isomers were obtained; these could not be separated.

The haematin association constants for the free ligands and the complexes were determined. The acylthiourea and phenanthroline ligands form very weak complexes with haematin, while the bipyridyl ligands formed no complexes. However, the platinum compounds were found to form strong complexes with haematin, even stronger than chloroquine-haematin complexes. Binding interactions occur through π-π stacking between the extended π-system of the diimine ligand and that of haematin, and possibly cation-π interactions of the cationic metal complex with the porphyrin.[87]



R = H (**24**), Me (**25**), ^{t}Bu (**26**)

32

	R^1	R^2	R^3	R^4	R^5	R^6
27	H	Me	H	H	H	H
28	H	H	Me	H	H	H
29	Me	Me	H	H	Me	Me
30	H	H	Cl	H	H	H
31	H	H	NO_2	H	H	H

Figure 2.23 Cationic platinum complexes showing anti-malarial activity

The platinum compounds also inhibit β-haematin formation whereas the free ligands do not; in general the bipyridyl complexes are weaker inhibitors than the phenanthroline analogues.

The platinum complexes were tested for anti-malarial activity against CQR and CQS *P. falciparum*. Unlike chloroquine, the complexes carry a permanent charge and would therefore not be expected to cross the cell membranes as easily. Most also do not carry the basic groups assumed to be necessary for 4-aminoquinoline anti-malarial action. However, many of the complexes showed good anti-malarial activity *in vitro*. In almost all cases they were equally active against chloroquine-sensitive and chloroquine-resistant parasites (Table 2.1). One unexpected observation was that there was no clear-cut correlation between β-haematin inhibition activity and anti-plasmodial action.[87] This raises the possibility of a different or additional mechanism of action compared to chloroquine.

Table 2.1 β-haematin inhibition activity and *in vitro* anti-malarial activity against chloroquine-sensitive (D10) and chloroquine-resistant (K1) *P. falciparum* for platinum cationic complexes [87]

Compound	**β-haematin inhibition**	**D10 IC_{50} (nM ± SD)**	**K1 IC_{50} (nM ± SD)***
24	+	336 ± 76	295 ± 56
25	+/-	295 ± 42	824 ± 102
26	+/-	141 ± 29	119 ± 33
27	+	282 ± 45	488 ± 130
28	+	308 ± 64	557 ± 89
29	+	602 ± 44	706 ± 95
30	+	594 ± 93	666 ± 79
31	+	2927 ± 736	1925 ± 309
32	+/-	1958 ± 85	2378 ± 513
Chloroquine	+	35 ± 7	156 ± 34

* SD = standard deviation

It is difficult to make any definite conclusions considering the limited number of complexes presented here. In order for any structure-activity relationships to be established, a much wider range of similar complexes would have to be synthesized and assessed for anti-malarial activity.

The methyl-phenanthroline, dimethyl-bipyridyl and di^{t}butyl-pyridyl complexes gave the best biological results in this study. It would be interesting to see, in an analogous series, whether complexes containing these particular diimines give consistently better results than those incorporating the other diimines.

The chemistry described here can also be extended to other metals, such as palladium(II) and other square planar metal centres. Any influence of the metal centre itself could thus be observed. Similarly, the ancillary ligand can be altered or replaced with completely different ligands in order to study any ligand effects. In this study it was proposed that the benzoylthioureas have no effect on the activities of the complexes, but it is possible that other types of ligands could work synergistically with the diimine ligands and enhance the activity of the complexes. All the complexes described in this paper are monocationic; it would be of interest to synthesize similar complexes that are neutral or perhaps dicationic. In this way the importance of charge on the metal complex can be established.

The information gained from such experiments would be extremely useful in understanding the roles that the different factors (metal, charge, ligand factors) play in imparting anti-malarial activity to the overall complex. With this information one can begin to design a metal diimine complex with the optimal structure for anti-malarial activity. It is then possible that such a complex, incorporating all the best features, may show good enough anti-malarial activity *in vivo* to make it a viable candidate for drug development.

2.8 Aims and objectives of this study

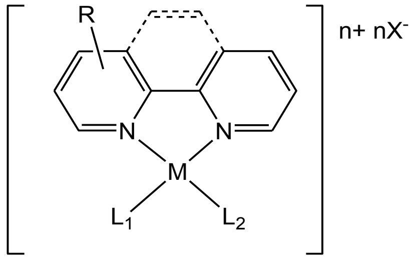
2.8.1 Aims

There is much scope for the design or discovery of non-quinoline metal complexes with anti-malarial activity. The aims of this project are:

1) The design and synthesis of square planar metal complexes containing diimine (1,10-phenanthroline or 2,2'-bipyridyl) ligands
2) Evaluation of the anti-malarial activity of the complexes by *in vitro* biological testing and by physicochemical methods such as β-haematin inhibition assays
3) Development of structure-activity relationships for the complexes

2.8.2 Specific objectives

The specific goals of this project are to synthesize a wide range of different square planar metal complexes containing diimine ligands. A basic model of the type of complex of interest is shown below in Figure 2.24.



M = Rh, Pd
L_1, L_2 = ancillary ligands
n = 0, 1, 2
X = Cl, PF_6, BPh_4

Figure 2.24 Simple model of the complexes prepared in this study

In order to develop any kind of structure-activity relationships, each aspect of the complexes should be systematically varied.

1) The metal: Any metal effects will be determined by variation of the metal centre. Specifically, the focus will be on square planar metal centres. This is because of the possibility that, like quinoline compounds, the platinum complexes discussed in section 2.7.2.2 act by binding to haematin through π-π or cation-π interactions. If this is the case, then such binding would be optimized in a planar system. Thus, square planar metal centres Rh(I) and Pd(II) are ideal. These are isoelectronic with the Pt(II) systems discussed above, would have similar structures, and therefore might be expected to exhibit similar (anti-malarial) activity.

2) The diimine ligand: The diimine ligand will be varied in two ways. Firstly, both 2,2'-bipyridyl (a 2-ring π system) and 1,10-phenanthroline (a 3-ring π system) would be used. Secondly, substituents on the two ring systems could be varied, for example, electron-donating versus electron-withdrawing substituents. It would be worthwhile to include some chloro-substituted diimines, as the presence of the chloro group in chloroquine has been shown to be essential for β-haematin inhibition. At the same time, the importance of drug lipophilicity has also been discussed, therefore more lipophilic alkyl-substituted ligands should also be examined.

3) The ancillary ligands: Both monodentate and chelating bidentate ancillary ligands will be incorporated in this part of the study. A definite decision to exclude benzoylthiourea ligands from this study was made at the outset, since a comprehensive programme of investigation on platinum benzoylthiourea

complexes is currently being carried out in the group of Klaus Koch (Stellenbosch University, South Africa). Simple and strongly-coordinating ligands, that are not known to possess biological activity themselves, should be used. These would help to stabilize the entire complex while not directly participating in any anti-malarial mechanisms of action, thus allowing for a more accurate assessment of the roles of metal and diimine in anti-malarial action. For example, phosphines are common monodentate ligands that are known to stabilize metal centres.[88] On the other hand, 1,2-hydroxy- or amino-substituted ethyl ligands would be suitable bidentate ligands, as the use of these would result in the formation of stable 5-membered metal chelate complexes.

4) Charge on the complex: By altering the nature of the ancillary ligands (neutral or anionic) it is possible to produce neutral, monocationic, or dicationic complexes. If, as it is believed, cation-π interactions do play a role in the anti-malarial activity of the cationic platinum complexes, then it might be expected that mono- or dicationic complexes would show improved activity relative to their neutral counterparts.

5) The counterion (X^-): In the case of the cationic complexes, it is possible that the use of different counterions could impact on the activity of the complexes, although this is not necessarily expected.

After synthesis of a suitable number of complexes, taking into account all the variations described above, it would be necessary to test for anti-malarial activity. Firstly, physicochemical methods would be used; β-haematin inhibition ability would be determined. Next, the *in vitro* anti-malarial IC_{50} values would be ascertained. Possible relationships between β-haematin inhibition ability and biological activity could be determined. Thus, structure-activity relationships could be established.

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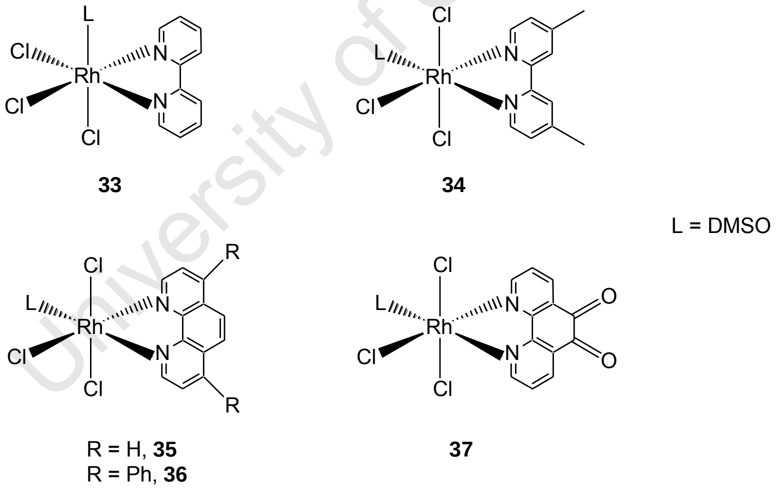
Chapter 3

The synthesis and characterization of rhodium and iridium complexes containing diimine ligands

3.1 Introduction

Since the advent of cisplatin, rhodium, like other transition metals, has been investigated for potential applications in medicine. The anti-tumoral and anti-bacterial properties of rhodium complexes have been well-studied.[1-5] For example, the Rh(III) complexes **33** - **37** (Figure 3.1) were found to be very active against colon tumour cells, with **36** showing greater activity than both cisplatin and the known anti-cancer compound doxorubicin. Complexes **34** – **36** also showed promising anti-bacterial activity against Gram-positive bacteria.[2] Numerous rhodium(I) complexes have also been screened for anti-cancer activity against various cancer cell lines, and many have exhibited good biological activity.[5]



33

34

L = DMSO

R = H, **35**
R = Ph, **36**

37

Figure 3.1 Rhodium diimine complexes showing biological activity

Little research has been done on the use of rhodium complexes as potential anti-malarial therapies, aside from the example discussed in Chapter 2.7.2.1. That particular case concerned a chloroquine compound modified through coordination to a rhodium centre. In this chapter, the synthesis and characterization of non-quinoline rhodium complexes as potential anti-malarial agents are discussed.

3.2 Attempted synthesis of rhodium(I) complexes containing planar diimine and tertiary phosphine ligands

Following the model outlined in Chapter 2, the initial aim was to synthesize complexes of the type shown in Figure 3.2. Complex **A** represents a neutral square planar rhodium(I) complex, while **B** could be prepared from **A** by the abstraction of the chloride by a silver salt such as $AgPF_6$ or $AgBF_4$, for example. The tertiary phosphine ligand, PR_3, could be varied to include simple, commonly-used phosphines such as triphenylphosphine, or ligands such as 1,3,5-triazaphosphaadamantane, which is water-soluble and often used to solubilize complexes for biological or catalytic use.[6] Synthesis of these complexes would allow for the comparison of the anti-malarial efficacy of neutral and monocationic complexes.

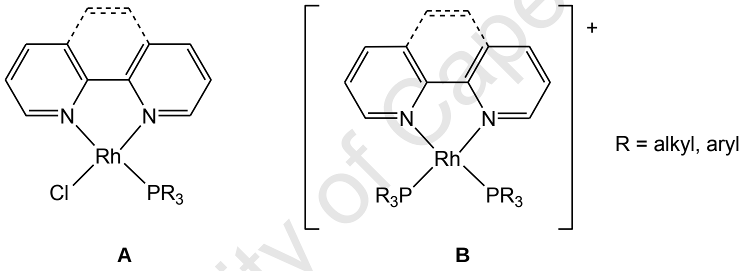
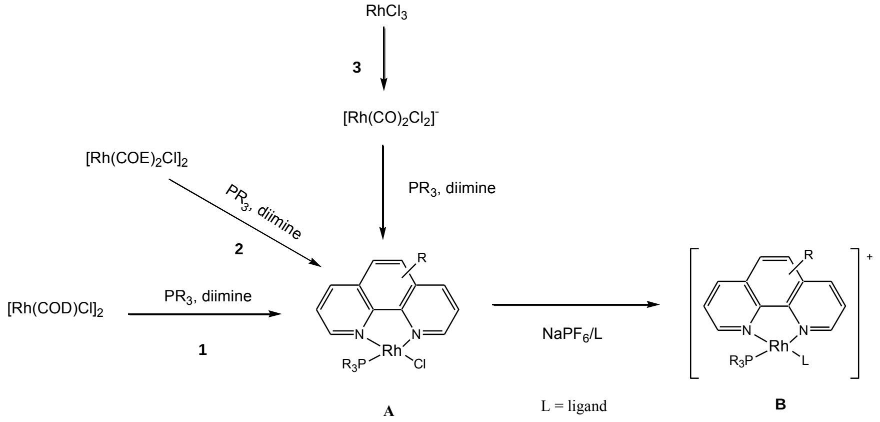


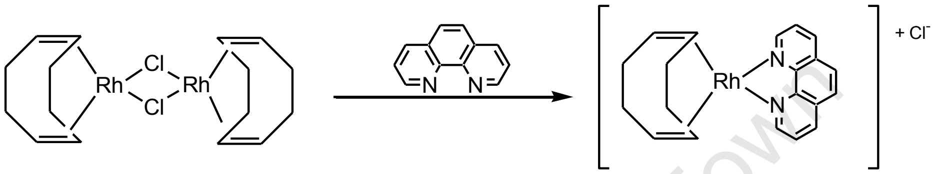
Figure 3.2 General structure of proposed rhodium(I) complexes

Several methods were employed in an attempt to synthesize complexes of type **A** (Scheme 3.1). All reactions were carried out using PPh_3 as the phosphine initially, as it is commonly available and inexpensive compared to other phosphines.



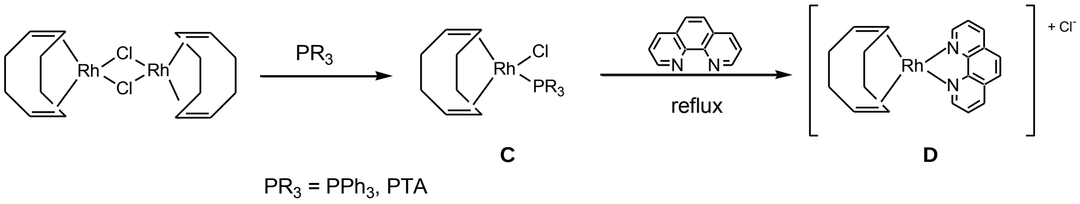
Scheme 3.1

Each method required the preparation of a square planar rhodium(I) starting material. Method 1 involved the use of the rhodium cyclooctadiene dimer [Rh(COD)Cl]$_2$, a well-known complex synthesized by the reduction of $RhCl_3$ in refluxing ethanol in the presence of cyclooctadiene.[7] [Rh(COD)Cl]$_2$ reacts readily with monodentate or bidentate ligands in chloride bridge-splitting reactions to form mononuclear complexes, and there are numerous examples in the literature of these kinds of reactions.[8-10] Reactions of the complex with diimine ligands such as 1,10-phenanthroline are known, and produce cationic complexes,[11-14] as shown in Scheme 3.2.



Scheme 3.2

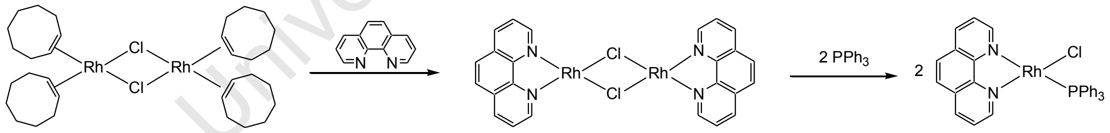
Therefore the starting dimer was reacted first with a phosphine (PPh_3), in order to produce the monomeric rhodium(I) phosphine complex as shown in Scheme 3.3 (complex **C**). The diimine ligand was then added to the reaction mixture in an attempt to displace the cyclooctadiene. However, the cyclooctadiene (COD) ligand is very strongly bound to the rhodium centre and cannot be substituted, even under more rigorous reaction conditions (refluxing at high temperatures, for example). In fact, when refluxing a mixture of complex **C** and 1,10-phenanthroline in dichloromethane, the triphenylphosphine and chloride ligands, rather than the COD, are displaced by the incoming diimine, resulting in the formation of cationic complex **D**. This was confirmed by ^1H NMR (see section 3.4.2 for examples and discussion of rhodium(I) cyclooctadiene spectra).



Scheme 3.3

A more strongly-coordinating phosphine was used in place of triphenylphosphine, in an attempt to prevent the formation of the cationic complex. The compound 1,3,5-triazaphosphaadamantane (PTA) is known to be strongly basic;[15] it should therefore bind more strongly than triphenylphosphine to rhodium and be less easily replaced by a diimine. It is also air-stable, not prone to oxidation, and is water-soluble, and was therefore chosen as an ideal ligand for studies of this type. Unfortunately, as in the case of the PPh_3 reactions, the PTA and chloride ligands of complex **C**, rather than the cyclooctadiene ligand, were displaced by 1,10-phenanthroline, leading to the cationic complex being formed once again. Thus, method 1 was not deemed a viable synthetic route for the preparation of the desired complexes.

For method 2 a rhodium starting material with more labile ligands was used. The rhodium cyclooctene (COE) dimer $[Rh(COE)_2Cl]_2$ was prepared according to literature procedures [16] and isolated as a yellow solid. The cyclooctene ligands are much more readily displaced than cyclooctadiene; the reaction of $[Rh(COE)_2Cl]_2$ with excess dimethylsulfoxide (DMSO), for example, results in the formation of the complex $Rh(DMSO)_3Cl$.[17] The envisaged reaction progression was first, replacement of the two pairs of cyclooctenes with two diimines, and second, cleavage of the halide bridge by a phosphine to yield the mononuclear diimine phosphine complex (Scheme 3.4) in a one-pot reaction.



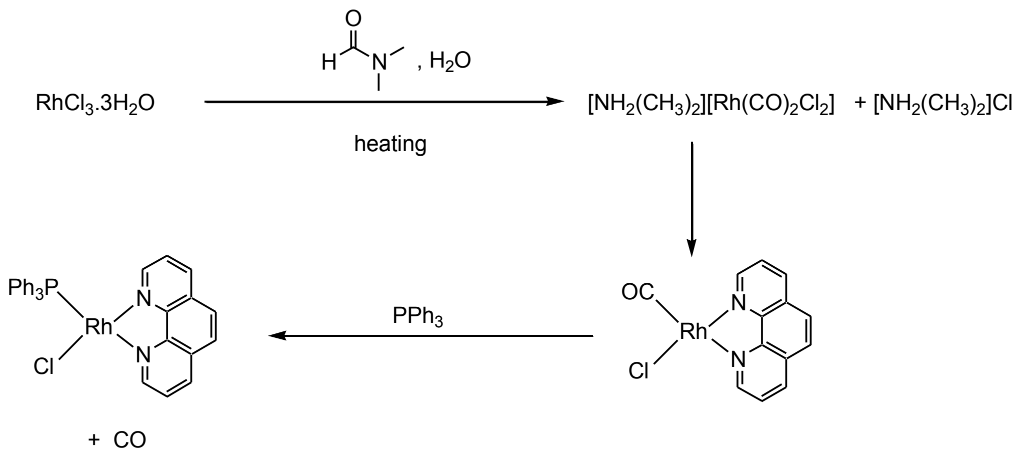
Scheme 3.4

The reactions were carried out using nitrogen-purged solvent and under nitrogen atmosphere using standard Schlenk line techniques. Reactions were attempted using different solvents, including tetrahydrofuran, dichloromethane and acetonitrile and were carried out at room temperature. In all cases, upon addition of the diimine (1,10-phenanthroline) to the $[Rh(COE)_2Cl]_2$ solution, there was an immediate colour change to red. After addition of PPh_3, light brown powdery precipitates were formed and isolated from the reaction mixtures. ^1H NMR indicated a complex mixture of products. ^{31}P NMR showed a main product as a singlet in the region 27 – 29 ppm. This indicates that the phosphine present was not coordinated to the rhodium centre; from the literature it can be seen that phosphines coordinated to either Rh(I) or Rh(III) exhibit relatively large ^{31}P-^{103}Rh couplings of around 150 – 250 Hz.[18] The peak at *ca* 28 ppm could be due to triphenylphosphine oxide, which resonates at the same chemical shift in the ^{31}P NMR spectrum.[19] Therefore it seems that there is oxidation of triphenylphosphine under the reaction conditions described, possibly even mediated by the rhodium centre itself. Attempts to isolate the expected reaction intermediate [Rh(diimine)Cl]$_2$ were also unsuccessful. This route was therefore also eventually abandoned.

The final method used involves the generation of a rhodium(I) intermediate *in situ*, according to a procedure described by Kalck *et al.*: A red solution of $RhCl_3.3H_2O$ in deaerated dimethylformamide (DMF) and a small quantity of water is heated with stirring under nitrogen. The reaction lightens to a yellow-orange colour over several minutes, signalling conversion to the $[Rh(CO)_2Cl_2]^-$ anion, where the carbonyl ligands are derived from decarbonylation of DMF.[20] Thereafter, ligands may be added to the reaction solution to yield the desired product, with concomitant release of CO and Cl^-. This method can be used for the facile preparation of *trans* chlorocarbonyl diphosphine complexes $[Rh(CO)(PR_3)_2Cl]$ for example, where 2 equivalents of PR_3 are added to the solution of $[Rh(CO)_2Cl_2]^-$.[20]

Thus the expected reaction progression as described in Scheme 3.5 was firstly generation of the anion, followed by addition of the diimine and then the phosphine.

The light orange solution obtained on heating rhodium trichloride in DMF-water indicated the successful formation of the rhodium dicarbonyl anion. However, when 1,10-phenanthroline was added to the solution, there was immediate formation of a solid black decomposition product. A slightly different route was then followed. One equivalent of triphenylphosphine was first added to the rhodium anion solution, and the reaction solution remained yellow. Upon addition of 1,10-phenanthroline, however, a black decomposition product once again immediately precipitated from the reaction mixture.



Scheme 3.5

Three different synthetic methods were followed in attempts to prepare and isolate complex **A**, each requiring a different rhodium(I) starting material. In each case the reaction conditions (reaction time, solvent, heating) were varied to optimize the method. Despite this, complex **A** and its derivative **B** were not obtained. It is possible that the desired rhodium(I) complexes are inherently unstable and cannot be isolated or even synthesized at all.

The initial aim, to synthesize neutral metal phosphine diimine complexes of type **A** and compare them with their cationic derivatives, was consequently not achieved. However, Method 1 (using $[Rh(COD)Cl]_2$ as starting material), as discussed previously, led to cationic diimine complexes that do possess most of the characteristics of interest in this project:

1) square planar geometry
2) presence of the diimine ligand
3) a stable, strongly-bound ancillary ligand (cyclooctadiene)
4) positive charge on the complex

By reacting $[Rh(COD)Cl]_2$ with a wide range of different diimines (both unsubstituted and substituted 1,10-phenanthroline and 2,2'-bipyridyl) it therefore is possible to synthesize a series of cationic complexes bearing ligands with different substituents. By comparing the anti-malarial properties of the different complexes in the series one could determine the effects of the different parameters on anti-malarial activity, and perhaps gain more insight into a possible mechanism of action.

3.3 Synthesis of cationic rhodium(I) cyclooctadiene complexes

There are a few literature reports outlining the reaction of the rhodium cyclooctadiene dimer with unsubstituted 1,10-phenanthroline or substituted 2,2'-bipyridines to form cationic complexes of the type shown in Scheme 3.3.[11-14] However, there are many substituted 1,10-phenanthroline compounds that have not been used in these reactions. Consequently, there was much scope for the preparation of new rhodium(I) cyclooctadiene diimine complexes.

Addition of 2 molar equivalents of a diimine ligand (1, 10-phenanthroline, 5-chloro-1,10-phenanthroline, 1,10-phenanthroline-5-amine) to a methanolic suspension of $[Rh(COD)Cl]_2$ at room temperature resulted in immediate formation of a red solution. The solution was stirred at room temperature for 30 minutes to ensure reaction completion; the solvent was then removed to give the ionic [Rh(N-N)(COD)]Cl (where N-N is the diimine) product as an amorphous or powdery red or orange solid.

When the ligand was neocuproine (2,9-dimethyl-1,10-phenanthroline, Figure 3.3), there was no reaction to form the cationic product, even after several hours of stirring at elevated temperature. No formation of the red solution or water-soluble product was observed, and ^1H NMR indicated that coordination to rhodium had not occurred. This may be due to the steric hindrance imposed by the methyl groups near the neocuproine site of reaction.

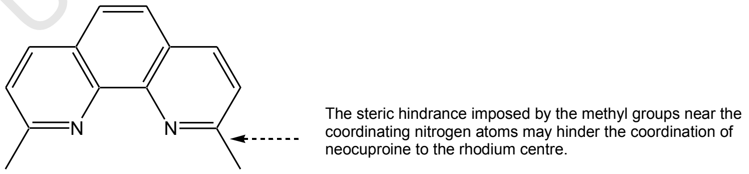
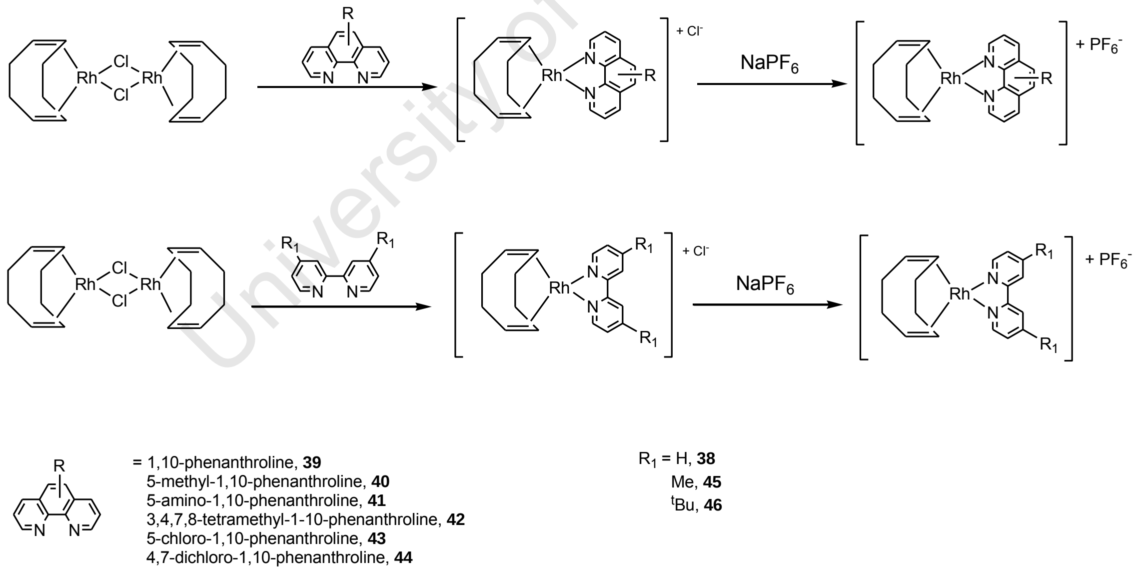


Figure 3.3 The structure of neocuproine (2,9-dimethyl, 1,10-phenanthroline)

The complexes [Rh(N-N)(COD)]Cl are very soluble in methanol and somewhat soluble in ethanol and water , which would make them ideal for a biological study. ^1H NMR spectra were clean, showing no signs of impurities. However, satisfactory microanalytical data could not be obtained, despite repeated attempts at purification by recrystallization. Researchers have previously reported this particular problem with rhodium complexes of this type.[11,13] It is possible that these complexes, like many water-soluble salts, are hygroscopic and absorb water from the air,[21] facilitated by electrostatic attractions between the complex ions and the positive or negative ends of the polar water molecule. This would affect microanalysis results. However, substitution of the chloride anion with, for example, PF_6^- or BF_4^-, has been shown to lead to the formation of analytically pure compounds. Thereafter, the various [Rh(N-N)(COD)]Cl species were generated *in situ* and then converted to the corresponding PF_6^- salts.

A range of different 1,10-phenanthroline and 2,2'-bipyridyl ligands were reacted with $[Rh(COD)Cl]_2$ to form the red methanol solution of [Rh(N-N)(COD)]Cl (Scheme 3.6). The dropwise addition of excess aqueous sodium hexafluorophosphate to the solution led to the precipitation of the corresponding PF_6^- complex in the form of bright orange or red solids (except when the diimine was a dialkyl-subsituted 2,2'-bipyridyl; these complexes remained in solution).



Scheme 3.6

In some cases, if the $NaPF_6$ is added slowly and carefully enough, microcrystals may be obtained. In other cases the product is an air- and moisture-stable amorphous solid which can be recrystallized from hot acetonitrile to form microcrystals. The phenanthroline PF_6^- complexes are all insoluble in water and in most organic solvents, but are somewhat soluble in dimethylsulfoxide (DMSO). However, the 4,4'-di-alkylated bipyridyl analogues, especially **46**, are soluble in chlorinated organic solvents dichloromethane and chloroform as well as in DMSO. Complexes **38**, **39**, **42** and **46** have all been reported previously; the remaining compounds are new.

Due to the extreme insolubility of the PF_6^- complexes in most organic solvents, it was difficult to obtain suitable crystals for structure determination. Even the more soluble di-alkyl-substituted bipyridyl complexes yielded poor crystals unsuitable for crystallography. Therefore, tetraphenylborate analogues of some of the complexes (**38**, **40** – **42**) were also prepared in the hope that a change in counterion would allow for the isolation of superior single crystals. A methanol solution of the [Rh(N-N)(COD)]Cl species was reacted with sodium tetraphenylborate, $NaBPh_4$, in an anion-exchange reaction to yield $[Rh(N\text{-}N)(COD)]BPh_4$. The BPh_4^- salts were isolated as powdery, analytically pure red and orange solids (Figure 3.4). They are insoluble in water and non-polar organic solvents, sparingly soluble in alcohols and chloroform, and soluble in dichloromethane and dimethylsulfoxide. The improved physical properties of the BPh_4^- analogues allowed for x-ray quality crystals to be obtained for some of the complexes (see section 3.4.5 for full discussion).

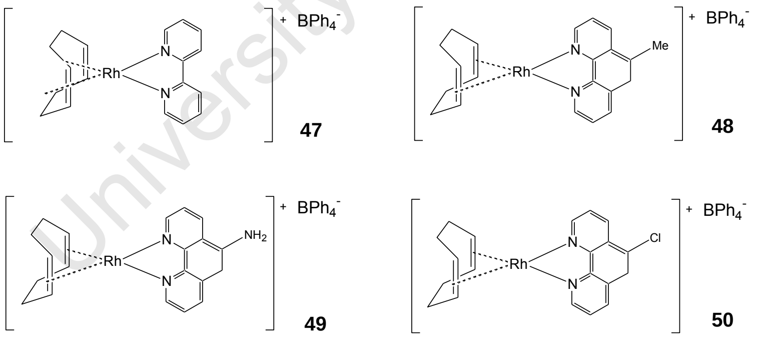


Figure 3.4 Rhodium(I) cyclooctadiene complexes containing the tetraphenylborate counterion

3.4 Characterization of rhodium(I) cationic complexes

3.4.1 Thermal stability

All the hexafluorophosphate rhodium complexes are highly thermally stable and melt or decompose at temperatures above 200 °C. The compounds containing phenanthroline derivatives generally decompose without melting at close to 300 °C, except for complex **44** (N-N = 4,7-dichloro-1,10-phenanthroline) which melts at a somewhat lower temperature of 225 – 227 °C. The bipyridyl complexes melt above 200 °C.

The tetraphenylborate complexes melt at significantly lower temperatures than their PF_6^- analogues (ranging between *ca* 190 and 250 °C), and generally melt following decomposition.

3.4.2 NMR spectroscopy

The ^{1}H NMR data for complexes **38** and **45** agree with the data reported for similar complexes.[14] The corresponding hexafluorophosphate and tetraphenylborate compounds containing the same diimine ligand yield similar NMR spectra, with only minor differences in the observed chemical shifts due to the presence of a different anion. There are also additional peaks due to the phenyl protons of BPh_4^-. Tables 3.1 and 3.2 show the ^{1}H chemical shifts of the free bipyridyl and phenanthroline ligands and their corresponding rhodium hexafluorophosphate complexes. Figure 3.5 gives the numbering scheme for protons on the diimine ligands. Figure 3.6 shows the main ^{1}H NMR regions for representative complex **50**, [Rh(Cl-phen)(COD)]BPh_4.

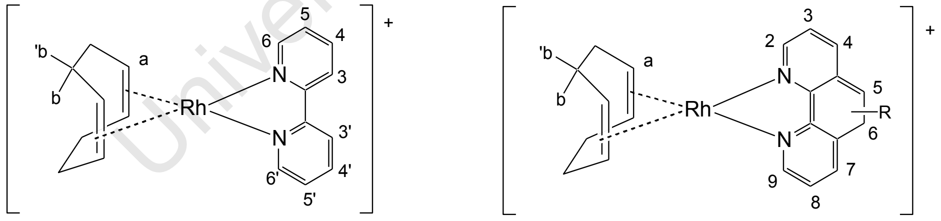


Figure 3.5 ^{1}H NMR numbering scheme for bipyridyl and phenanthroline free ligands and complexes

A first point of interest is that long-range coupling (^4J, four-bond coupling) is usually present in the free ligand but disappears upon its coordination to the metal centre. For instance, in free 5-methyl-1,10-phenanthroline protons H2 and H9 couple to H4 and H7 respectively, with coupling constants of around 1.7 Hz (Table 3.2). However, this is not observed in the case of the metal-coordinated form of the ligand.

There are significant upfield shifts (~ 0.6 – 0.8 ppm) of the imine hydrogen atoms (H2 and H9 of phenanthroline, H6 and H6’ of bipyridyl) upon coordination of the diimine to the rhodium centre. This is probably due to shielding by the electrons of the newly-formed Rh-N bond. The chemical shifts of the remaining aryl protons move noticeably downfield, probably due to the electron-withdrawing positively charged metal centre. For instance, H3 and H8 of the phenanthroline ligands are shifted 0.2 to 0.3 ppm downfield, H4 and H7 approximately 0.4 ppm downfield, and H5 and H6 shift by 0.1 to 0.4 ppm depending on the ligand in question.

Table 3.1 ^{1}H NMR chemical shifts (ppm), multiplicity and coupling constants for 2,2’-bipyridyl ligands in free and complexed form

	Bipy ligand [a]	Bipy complex [a]	di-Mebipy ligand [a]	di-Mebipy complex [a]	di-tBubipy ligand [b]	di-tBubipy complex [b]
H3/H3’	8.37, dt 7.98, 1.0 Hz	8.62, d 8.0 Hz	8.22	8.44, s	8.41, dd 1.95, 0.65 Hz	8.59, d 1.53 Hz
H4/H4’	7.92, td 7.75, 1.8 Hz	8.34, t, 7.8 Hz	-	-	-	-
H5/H5’	7.42, ddd 7.5, 4.79, 1.8 Hz	7.76, t 6.2 Hz	7.26, dd 4.95, 1.65 Hz	7.54, d 5.48 Hz	7.30, dd 5.25, 1.99 Hz	7.71, dd 5.8, 1.4 Hz
H6/H6’	8.67, ddd 4.74, 1.67, 0.86 Hz	8.05, d 5.3 Hz	8.52, d 4.94 Hz	7.85, d 5.66 Hz	8.59, dd 5.25, 0.63 Hz	7.93, d 5.95 Hz
Other	-	-	2.41, s, CH_3	2.51, s, CH_3	1.39, s, CH_3	1.45, s, CH_3

[a] in DMSO-d_6
[b] in $CDCl_3$

There are three distinct ^{1}H NMR signals for the cyclooctadiene protons. A broad peak at approximately 4.8 ppm (Figure 3.6) represents the alkenyl protons, H_a (Figure 3.5).

Table 3.2 ^{1}H NMR chemical shifts (ppm, in DMSO-d_6), multiplicity and coupling constants for 1,10-phenathroline ligands in free and complexed form*

	Free Phen	Phen complex	Free Me-phen	Me-phen complex	Free NH_2-phen	NH_2-phen complex	Free Cl-phen	Cl-phen complex	Free TM-phen	TM-phen complex
H2	9.09, dd 4.29, 1.74 Hz	8.41, d, 4.93 Hz	9.08, dd 4.25, 1.69 Hz	8.46, d, 5.08 Hz	9.06, dd 4.23,1.61 Hz	8.41, d, 5.6 Hz	9.17, dd 4.29, 1.65 Hz	8.58, d, 5.4 Hz	8.81, s	8.09, s
H3	7.74, dd 8.08, 4.29H z	8.01, dd, 8.18, 5.1Hz	7.77, dd 8.31, 4.35 Hz	8.1 – 7.8 m	7.72, dd 8.37, 4.24 Hz	7.99, br s	7.89, dd 8.35, 4.31 Hz	8.17, dd, 8.3, 5.1 Hz	-	-
H4	8.46, dd 8.08, 1.73 Hz	8.87, d, 8.13 Hz	8.51, dd 8.31, 1.64 Hz	8.95, d, 8.42 Hz	8.65 – 8.71 complex	9.06, d, 8.2 Hz	8.65, dd 8.36, 1.63 Hz	9.05, d, 8.6 Hz	-	-
H5	7.96, s	8.20, s	-	-	-	-	-	-	8.14, s	8.28, s
H6	7.96, s	As H5	7.75, s	8.1 – 7.8, m	6.88, s	7.0, s	8.24, s	8.60, s	8.14, s	8.28, s
H7	8.46, dd 8.08, 1.73 Hz	As H4	8.33, dd 8.06, 1.67 Hz	8.79, d 7.46 Hz	8.03, dd 8.13, 1.65 Hz	8.45, d, 8.8 Hz	8.45, dd 8.11, 1.69 Hz	8.88, d, 8.6 Hz	-	-
H8	7.74, dd 8.08, 4.29H z	As H3	7.69, dd 8.05, 4.30 Hz	8.1 – 7.8 m	7.50, dd 8.11, 4.22 Hz	7.74, dd, 8.2, 5.0 Hz	7.77, dd 8.11, 4.32 Hz	8.09, dd, 7.6, 4.8 Hz	-	-
H9	9.09, dd 4.29, 1.74 Hz	As H2	9.00, dd 4.29, 1.69 Hz	8.39, d 5.11 Hz	8.65 – 8.71 complex	8.02, d 5.3 Hz	9.10, dd 4.32, 1.74 Hz	8.50, d, 5.0 Hz	8.81, s	8.09, s
Other	-	-	CH_3	2.92, s, CH_3	6.05, s NH_2	6.81, s, NH_2	-	-	2.85, s, CH_3 2.49, s, CH_3	2.75, s, CH_3 2.51, s, CH_3

* 4,7-dichloro-1,10-phenanthroline is extremely insoluble even in DMSO and an NMR spectrum could not be obtained

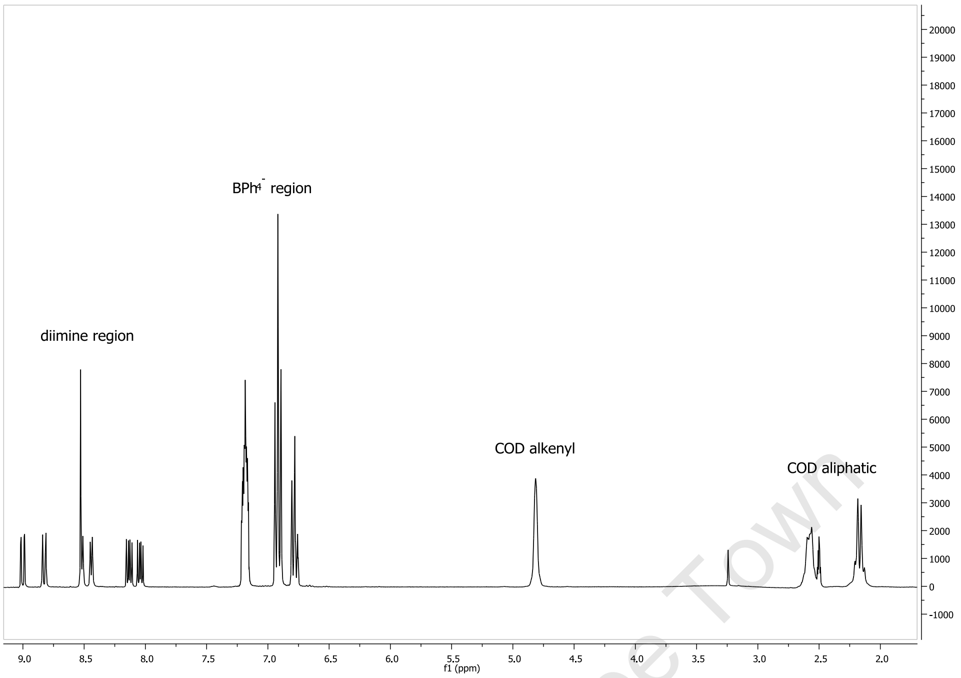


Figure 3.6 ^{1}H NMR spectrum of 50, [(Cl-phen)Rh(COD)]BPh$_4$

The aliphatic hydrogen atoms $H_{b'}$, directed "outwards" (away from the interior of the cyclooctadiene cavity), occur at around 2.6 ppm, while the H_b protons are more shielded and occur at about 2.1 – 2.2 ppm. This difference in the NMR chemical environment of H_b and $H_{b'}$ hydrogens has been observed in other rhodium cyclooctadiene complexes, and has been attributed to magnetic anisotropy.[14,22]

Magnetic anisotropy refers to the through-space influence of π-electrons on the chemical shifts of nearby nuclei.[23-25] The electron clouds induce magnetic fields that can lead to either shielding or deshielding of those nuclei. The effects are different depending on the location of the nucleus in the space around the π-cloud. In the case of alkenes, the deshielding zone occurs in the plane of the double bond (hence the higher chemical shifts observed with alkenyl protons) while the shielding zone occurs in a cone-shaped area above and below the double bond (Figure 3.7).

The aliphatic H_b protons of cyclooctadiene, directed inwards, should be located inside the cone-shaped shielding areas induced by the circulating electrons of the COD double bonds, whereas $H_{b'}$ would not (Figure 3.5). This accounts for both the inequivalence of the two sets of protons, and for the more upfield δ values observed for H_b.

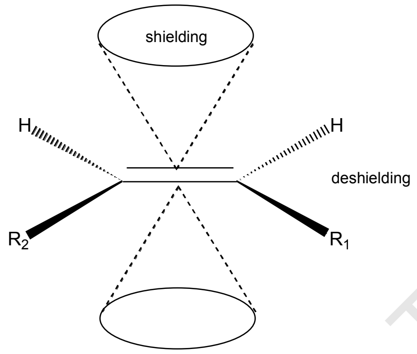


Figure 3.7 Diagram indicating areas of shielding and deshielding around the circulating π-electrons of an alkene double bond

Although complexes of the type described in this chapter are known, it does not appear that their ^{13}C NMR spectra have been reported anywhere in the literature. This may be due to their poor solubility in most available solvents. In this section, the ^{13}C spectra of cationic rhodium(I) cyclooctadiene complexes are described. Figure 3.8 depicts the principal regions of the ^{13}C NMR spectrum of representative complex **50**, [Rh(Cl-phen)(COD)]BPh_4.

The carbon spectra of all the complexes show the expected number of peaks, all singlets, in the aromatic region. Spectra of the BPh_4^- complexes are more complicated than those of the PF_6^- complexes, due to the contribution of that counterion to the aromatic region of the spectrum. The peak representing the *ipso* carbons of the tetraphenylborate moiety is especially recognizable as it occurs as a 1:1:1:1 quartet (J = 50 Hz) at about 163 ppm. The multiplicity of this peak is due to coupling of the carbon to the ^{11}B atom, which is a quadrupolar nucleus with a spin of 3/2.[26] Similar results have been reported for other tetraphenylborate complexes.[27]

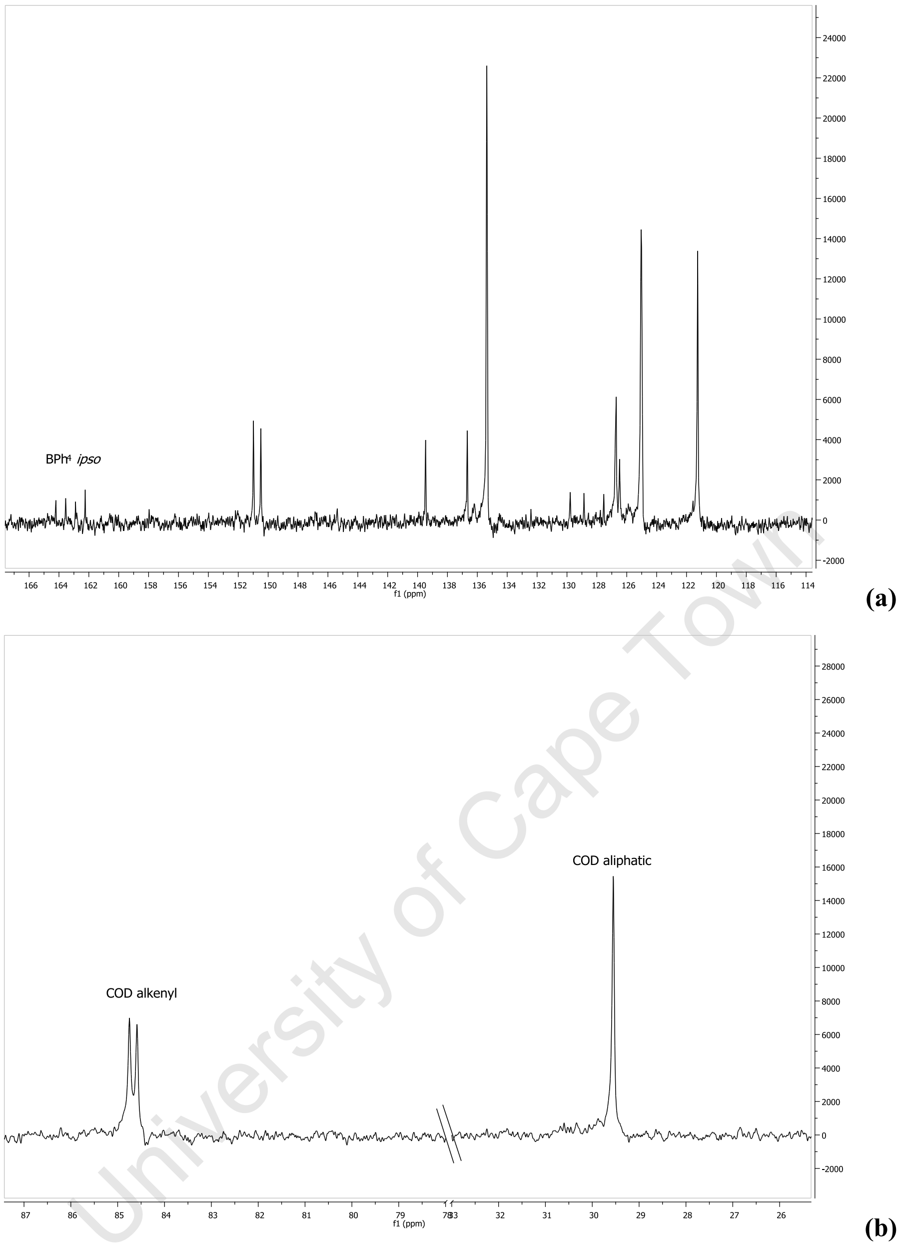


Figure 3.8 ^{13}C NMR spectrum of complex 50 **depicting (a) aromatic and (b) cyclooctadienyl proton regions**

The signal for the aliphatic cyclooctadiene carbons (-CH_2) occurs as a singlet at approximately 30 ppm. The peak for the alkenyl cyclooctadiene carbons is found much more downfield at around 90 ppm, and occurs as a doublet with a coupling constant of about 12 Hz. As ^{103}Rh has a spin of ½ [28] it couples to the alkenyl carbons that are directly bonded to it, resulting in a noticeable coupling constant of $J = 12$ Hz.

The PF_6^- cationic complexes all show a single peak in the ^{31}P spectrum. A high-field septet at -144 ppm represents the phosphorus atom of the counterion; this couples to the six fluorine atoms with $^1J_{P-F}$ = 711 Hz. Similar ^{31}P NMR splitting patterns and coupling constants for hexafluorophosphate complexes have been reported in the literature.[29]

3.4.3 Elemental analysis and mass spectrometry

The elemental analysis results of all complexes agree with the proposed formulations and indicate a high degree of purity. The mass spectra (obtained using electrospray ionization, or ESI) of all complexes show the expected parent ion peaks minus the non-coordinating counterion; that is, representing the cation $[Rh(N\text{-}N)(COD)]^+$. Compounds **43** and **44** contain chlorine, which exists as two stable isotopes, ^{35}Cl and ^{37}Cl.[30] Thus two and three parent peaks respectively are observed for these complexes. Figure 3.9 shows representative mass spectra of complexes **46** and **50**.

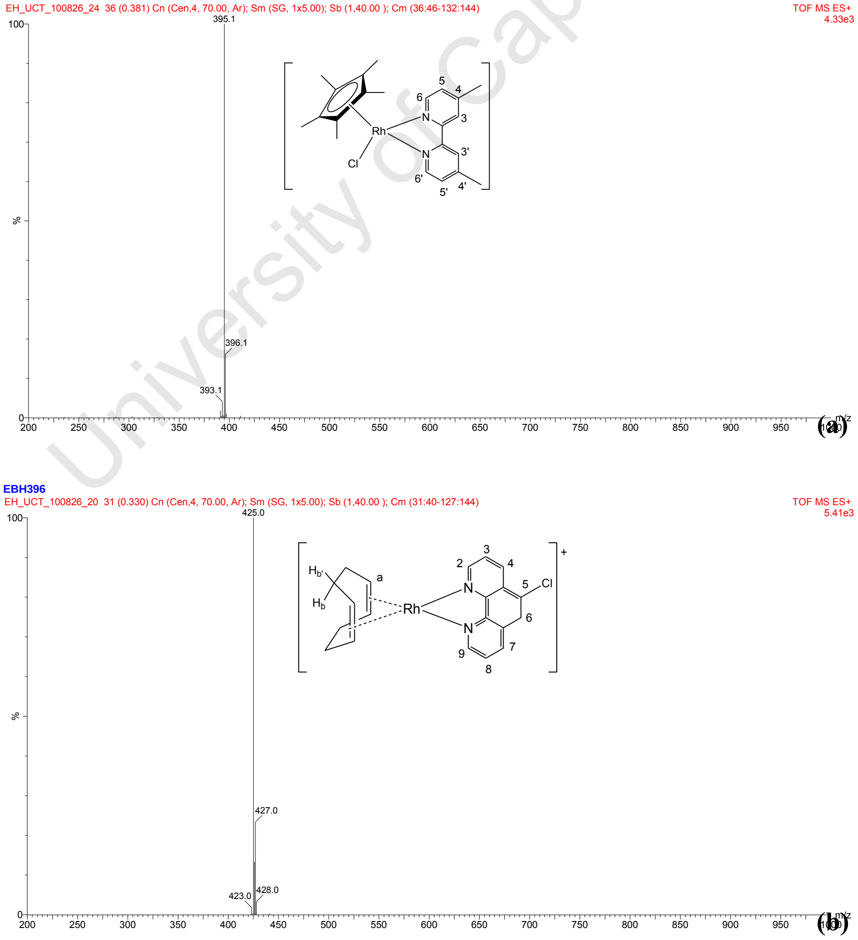


Figure 3.9 Mass spectra of rhodium complex 46 **(a) and complex** 50 **(b)**

No peaks other than those of the parent ion are observed, except for some small peaks clustered closely around the main peak. These could correspond to protonated or deprotonated forms of the cation.

The dearth of peaks representing lower molecular weight fragments suggests that the complexes are highly stable under the experimental conditions. The fact that the tetraphenylborate peak is not observed at 321 g/mol for complex **50** (Figure 3.9b) might indicate that the ion is readily broken down to its phenyl fragments under these particular experimental conditions.

3.4.4 Conductivity

The molar conductivities (or conductances) of rhodium(I) complexes in nitrobenzene (2 mM solution) at 20 °C were determined. Molar conductivity, Λ_m, is calculated as a function of the specific conductivity of the solution (K)[31] and the molar concentration (c_M) of the solution according to the equation:

$$\Lambda_m = K/c_M$$

Thus at larger concentrations a proportionally larger K value will be obtained. This means that Λ_m should remain constant over a concentration range. Nevertheless, it is desirable to perform conductivity measurements of different complexes at the same concentration, in order to facilitate a direct comparison of the results.[31]

The normal range for 1:1 electrolytes in nitrobenzene is approximately 20 – 30 $\Omega^{-1}.cm^2.mol^{-1}$.[31] The conductivity values of the PF_6^- complexes all fall within the range 24.3 – 27.1 $\Omega^{-1}.cm^2.mol^{-1}$, confirming their identity as 1:1 electrolytes. However, the conductivities of the corresponding BPh_4^- complexes are significantly lower at between 16.8 and 18.6 $\Omega^{-1}.cm^2.mol^{-1}$. The complexes are clearly ionic in solution, but show values outside the normal range for 1:1 electrolytes in nitrobenzene.

This can be explained by the large bulk of the tetraphenylborate ion. Conductivity is proportional to ionic mobility in solution,[32] and bulky electrolytes would be expected to have reduced mobility. Experimental data from various conductance studies done have revealed that compounds containing larger ions (both anions like BPh_4^- and cations like NBu_4^+) show consistently lower conductance values than other, simpler compounds in the same solvent system.[33-36] In general, the ionic conductance of an individual ion decreases as particle size increases. For example, in a conductivity study using trimethylurea as solvent, it was determined that the limiting equivalent conductance of the tetraphenylborate ion, $\lambda_o(BPh_4^-)$, was 13.72, while those of Br^-, ClO_4^- and SCN^- were 30.38, 28.71 and 33.44 respectively.[37] Thus, electrolytes containing BPh_4^- will often display molar conductivities that appear below the normal range of a specific type of electrolyte in a given solvent.[31]

3.4.5 X-ray crystallography

A literature search has not revealed any previous reports of crystal structure determinations of cationic rhodium(I) cyclooctadiene complexes bearing phenanthroline or bipyridyl ligands. The slow diffusion of hexane into a dichloromethane solution of **48** produced x-ray quality crystals of the complex. Previous attempts to grow crystals of the PF_6^- analogue **40** had been unsuccessful.

It has been observed that the nature of the counterion is a contributing factor to the acquirement of good quality single crystals of an ionic complex.[38, 39] The use of the BPh_4^- rather than the PF_6^- ion may have been advantageous in several ways. Firstly, relatively small and symmetrical ions, such as PF_6^- and BF_4^-, can rotate within unit cells, leading to disorder which is unfavourable for crystal structure refinement. Bulky ions like BPh_4^- have much less flexibility, cannot move freely, and disorder is therefore minimized.[38] Secondly it is known that ions of similar size pack together better, leading to higher-quality crystals.[39] In this case, the larger BPh_4^- may have provided a better match for the rhodium complex cation in terms of size.

Another possible factor is the fact that the presence of phenyl groups often allows for better crystallization.[38] A study conducted by Hatase *et al.* on low-temperature crystallization in liquids showed that crystal growth occurred only for those molecules containing at least one phenyl ring.[40] It was postulated that intermolecular C-H…π interactions between phenyl rings increased order within those regions, leading to crystal nucleation.

The crystal structure of **48** is depicted in Figure 3.10, while Table 3.3 lists selected bond lengths and angles. A full list of bond lengths and angles can be found in the Appendix. The x-ray data collection parameters are found in Chapter 7 (experimental details).

Figure 3.10 clearly shows both the cationic rhodium complex and its tetraphenylborate counterion. The geometry around the metal centre is essentially pseudo-square planar with respect to the two nitrogen atoms of the diimine ligand and the centres of the two C=C double bonds. The C-Rh-C bond angles involving the directly opposing sp^2 carbons of the COD double bonds are close to 90 °. However the N(1)-Rh-N(2) bite angle of 78.94 ° represents significant distortion from a strictly square complex. The complex is forced into this conformation due to the rigidity of the chelating diimine ligand.

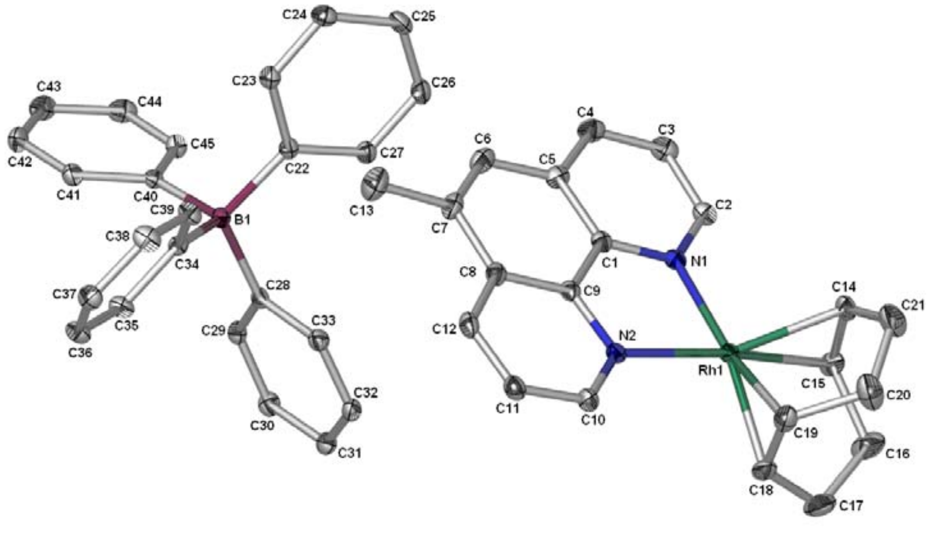


Figure 3.10 Molecular structure of 48 **showing the rhodium complex and its tetraphenylborate counterion**. **Hydrogen atoms have been omitted for clarity**

The Rh-C bond distances (involving the sp^2 carbon atoms of the cyclooctadiene ligand) are in the same range as those of other cationic rhodium COD complexes.[41-44] The Rh-N bond distances are also comparable to literature values for Rh-N(imine) bonds in cationic Rh(I) complexes, where these occur in a range of 2.07 – 2.14 Å.[41,42]

Table 3.3 Selected bond lengths and angles for complex **48**

Bond lengths (Å)		**Angles (°)**	
Rh(1) – N(1)	2.0947(19)	N(1)-Rh(1)-N(2)	78.94(7)
Rh(1) – N(2)	2.1097(18)	C(14)-Rh(1)-C(18)	95.90(10)
Rh(1) – C(14)	2.135(2)	C(15)-Rh(1)-C(19)	90.82(10)
Rh(1) – C(15)	2.145(2)	N(1)-C(1)-C(9)-N(2)	-1.2(3)
Rh(1) – C(18)	2.138(2)	C(7)-C(8)-C(9)-N(2)	178.5(2)
Rh(1) – C(19)	2.145(2)	C(3)-C(4)-C(5)-C(1)	-0.2(4)

The cyclooctadiene double bond lengths are 1.387 and 1.384 Å, where a normal C=C bond length of a simple alkene is somewhat shorter at approximately 1.33 ˚Å.[45-47] The lengthening of the C=C bond distance could be due to weakening of the bond upon its coordination to the rhodium centre. When alkenes bond to a metal centre, electron density is donated into the unfilled metal d-orbitals. At the same time, electron density may be back-donated into the alkene's empty anti-bonding π* orbitals.[48] The back-donation would cause the Rh-alkene bond to strengthen further, and the C=C bond simultaneously to weaken.

From Figure 3.10 it is obvious that the cyclooctadiene ligand is not especially bulky and should therefore not interfere with potential π-π stacking with haematin. Torsion angles indicate that the diimine ligand is, as expected, almost completely planar within itself, which is ideal for π-π stacking.

True face-to-face π-π stacking (Figure 3.11a) is rare; this conformation is unfavourable due to strong π-π repulsive forces.[49a,49b] Stacking generally occurs either as offset face-to-face stacking (Figure 3.11b) or so-called T-shaped stacking (Figure 3.11c). In both instances σ-π attraction overcomes π-π repulsion. Evidence has shown that the introduction of heteroatoms such as nitrogen into the aromatic ring increases the strength of the offset facial interaction by decreasing π-electron density in the ring, and subsequently reducing π-electron repulsion.[49a,49b] Electron-withdrawing substituents on a ring are believed to strengthen aromatic stacking in the same way.[49a]

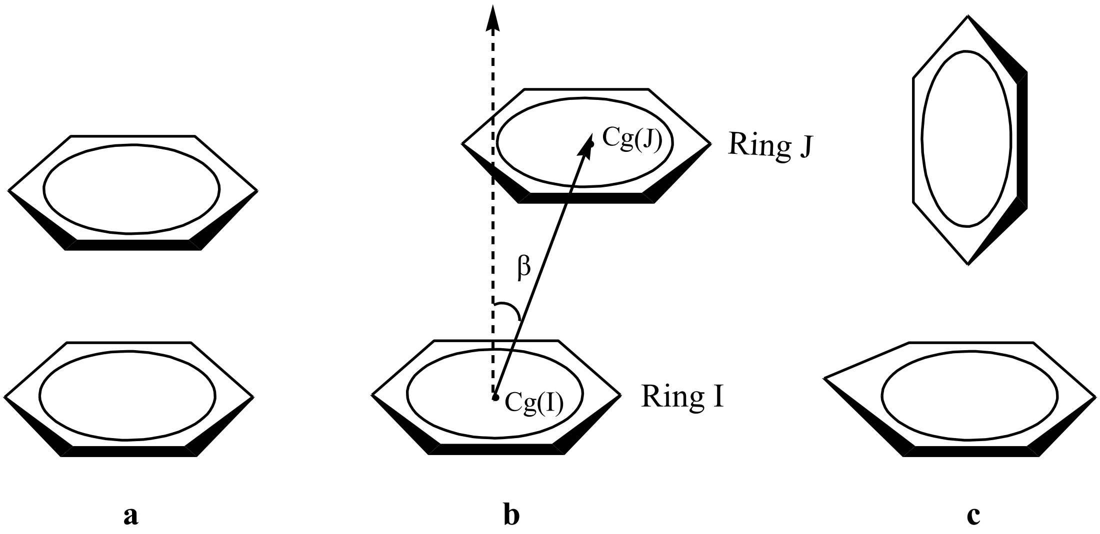


Figure 3.11 Simplified diagram of (a) true face-to-face stacking (b) offset stacking and (c) T-shaped or edge-to-face stacking between two aromatic rings

Intermolecular stacking in metal-ligand complexes is also possible. There are numerous literature examples of intermolecular (and intramolecular) aromatic π interactions in the crystal structures of metal-ligand complexes, where ligands comprise large nitrogen-containing aromatic heterocycles such as phenanthroline.[49a,c,d] Requirements for offset stacking interactions between aromatic ligands of metal complexes are generally considered to be: One, a centroid-centroid (Cg-Cg) distance of about 3.4 – 3.8 Å. Two, an interplanar angle α of close to zero (in other words, the two ring planes are almost completely parallel). Three, a displacement angle β (Figure 3.11b) of 20 – 30 ° (although this is sometimes found to reach up to 40 °). In the case where the planes are not completely parallel, there are two displacement vectors, β and γ, as obtained from two different planes. Interplanar distances correspond to the perpendicular distance between the centroid of one ring and the plane of the other, and are approximately 3.3 – 3.8 Å.[49a]

Taking into account these rules it can be seen that there are probably offset stacking interactions in the crystal structure of **48**. Table 3.4 lists the interactions that fulfil the necessary requirements. All three rings of the phenanthroline ligand appear to be involved in stacking, although the Cg11-Cg12 interactions are rather weak, with distances of almost 4 Å. This is slightly longer than the maximum 3.8 Å that is usually specified for aromatic stacking interactions.

Table 3.4 Geometric parameters for stacking in **48**

Cg(I)-Cg(J)	$d_{c\text{-}c}$ (Å)	α (°)	β (°)	γ (°)	d⊥[Cg(I)-P(J)] (Å)	d⊥[Cg(J)-P(I)] (Å)
Cg10-Cg11	3.6713(13)	1.36	13.07	11.86	3.595	3.578
Cg11-Cg12	3.9833(13)	0.45	25.92	26.36	3.569	3.583
Cg12-Cg11	3.9833(13)	0.45	25.92	26.36	3.583	3.569
Cg11-Cg10	3.6713(13)	1.36	11.86	13.07	3.578	3.595

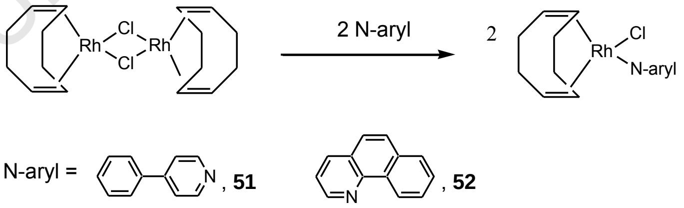
$d_{c\text{-}c}$ = distance between ring centroids
α = dihedral angle between planes
β = angle between Cg(I)-Cg(J) vector and normal to plane I
d⊥[Cg(I)-P(J)] =perpendicular distance of Cg(I) on ring J

Cg10: N1-C2-C3-C4-C5-C1
Cg11: N2-C9-C8-C12-C11-C10
Cg12: C1-C5-C6-C7-C8-C9

Thus it can be concluded that the cationic complexes synthesized theoretically possess the characteristics necessary for anti-malarial action by haemozoin inhibition. However, it can not be concluded that haemozoin inhibition is indeed the mechanism of action of these complexes, should they show any significant biological activity.

3.5 Synthesis and characterization of neutral rhodium(I) cyclooctadiene complexes

Two neutral rhodium(I) cyclooctadiene compounds were synthesized to provide a comparison with the cationic analogues. The ligands 4-phenylpyridine and benzo(h)quinoline are structurally very similar to 2,2'-bipyridyl and 1,10-phenanthroline respectively, but contain only one imine nitrogen and can therefore coordinate to the rhodium centre in only a monodentate fashion, leading to a neutral product (Scheme 3.7).



Scheme 3.7

Although the geometry around the metal itself would be square planar, it is likely that the η^1-coordinated ligand would not be bound in a plane with the rest of the complex. A crystal structure of a related complex reported by Rajput and Moss *et al.* showed that the ligands were bonded in an essentially square planar manner about the rhodium centre. However the aromatic plane of the pyridine moiety was not in line with the plane around the metal centre, nor with that of the second aromatic ring substituted on the pyridine ring (Figure 3.12).[8] A similar type of structure would be expected for **51** and **52**, especially for **51,** the ligand of which has increased flexibility about the C-C single bond.

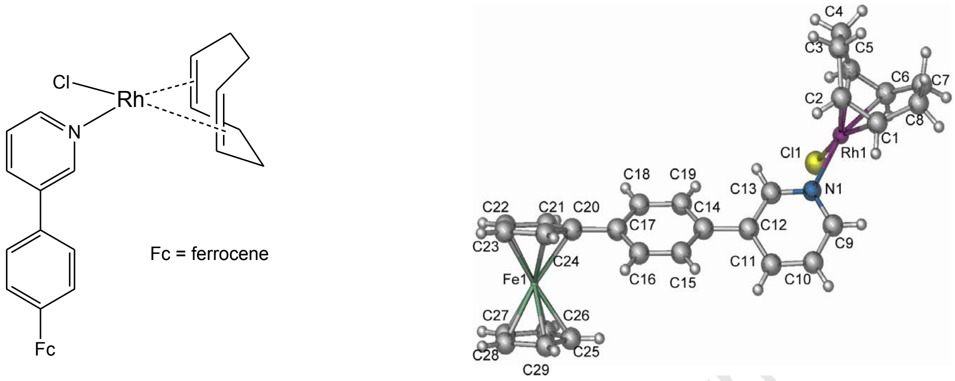


Figure 3.12 Crystal structure of a rhodium(I) cyclooctadiene complex with substituted pyridyl ligand, reported by Rajput *et al.*

If the mechanism of anti-malarial activity of metal phenanthroline complexes is indeed β-haematin inhibition stemming from planar π-π or cation-π interactions, then these complexes with their reduced planarity may be inherently less active than the planar cationic complexes before even taking into account the possible contribution of charge. However, if complete planarity is not essential for anti-malarial activity, as may be the case, then it is worth looking at the potential activity of these neutral complexes.

Complexes **51** and **52** are air- and moisture-stable yellow compounds. Compound **52** is new, while **51** has been reported previously. Both are solids at room temperature; however, **52**, having a very low melting point (31 – 34 °C) is somewhat oily. They are soluble in chlorinated solvents and dimethyl sulfoxide.

The ^{1}H NMR spectrum for **51** is similar to that reported in the literature.[8] In both the free ligand and the complex the –C_5H_4N protons are observed as two distinct peaks, while the remaining protons, on the phenyl substituent, are seen as a complicated multiplet integrating for five atoms. There are no obvious changes in the NMR spectrum of **51** relative to the uncoordinated 4-phenylpyridine, other than the presence of the cyclooctadiene proton signals. Similarly, there appear to be no major NMR shift changes in going from free to coordinated benzo(h)quinoline. This is unlike what is seen in the NMR spectra of cationic rhodium(I) complexes, where coordination of the ligand to the metal centre resulted in significant shifts of the ligand proton peaks. However, in the case of both complexes, the NMR spectra support the proposed structures.

One interesting aspect is that the cyclooctadiene protons of the neutral rhodium complexes occur at chemical shifts noticeably upfield compared to the cationic complexes. H_a and $H_{b'}$ occur between 4.6 – 4.8 ppm and 2.1 – 2.2 ppm respectively in cationic complexes, whereas they occur at about 4.2 and 1.8 ppm in the neutral complexes. A reasonable explanation for this is that the postively-charged metal centres withdraw electrons more strongly than the neutral centres, leading to greater deshielding and higher chemical shifts in those complexes.

The elemental analysis and mass spectrometry results for the neutral rhodium complexes confirm the proposed chemical formulations and molecular weights respectively.

3.6 Attempted synthesis of iridium(I)cyclooctadiene complexes

In order to ascertain any contribution by the metal centre to anti-malarial activity, we attempted to prepare the iridium(I) analogues of the cationic rhodium cyclooctadiene complexes. The unsubstituted bipyridyl and phenanthroline derivatives of these complexes had been reported in the literature before.[50-51]

Initially, the preparations were carried out under the same reaction conditions as the rhodium complexes, using $[Ir(COD)Cl]_2$ as starting material. A quantity of iridium dimer was suspended in methanol and stirred at room temperature. Two equivalents of the diimine were added; the reaction turned a bluish-black colour. After stirring at room temperature for about 30 minutes an orange-red solution was formed. Excess aqueous $NaPF_6$ was added and the solution turned yellow. The solvent was reduced and the resultant yellow precipitate collected on a filter.

The ^{1}H NMR spectrum of the iridium product in DMSO-d_6 was complicated and seemed to point to, possibly, some decomposition or complex product formation. The reactions were repeated under different sets of reaction conditions. The solvent was changed to DCM (as indicated in a literature procedure [51b]) and the reactions carried out under inert atmosphere and using deaerated DCM. The diimine ligand was varied and the sequence of reaction events altered (for instance, the $NaPF_6$ could be added before or after the blue-black solution turned orange). In all cases the end product was a yellowish solid that gave a ^{1}H NMR spectrum that did not indicate the desired product formation, and that was impossible to decipher.

According to literature reports, iridium(I) complexes of type $[Ir(N\text{-}N)(COD)]^+$ are prone to coordinative and oxidative addition reactions with small molecules under mild conditions. For example, $[Ir(phen)(COD)]^+$ can form pentacoordinated adducts with small alkenes at room temperature [50,51b] and reacts with dilute HCl in methanol to form $[Ir(phen)(COD)HCl]^+$.[51b] The ease with which numerous such reactions can occur may lead to difficulties in isolating the pure product. The fact that rhodium(I) complexes are less likely to undergo these kinds of reactions [51] explains why $[Rh(N\text{-}N)(COD)]^+$ compounds are easily isolated, whereas the iridium analogues are not. However, it is strange that it was not possible to obtain $[(N\text{-}N)Ir(COD)]^+$ in pure form, when these complexes have been described in the literature.

Eventually the attempted preparation of iridium(I) cyclooctadiene complexes was discontinued, with no iridium complexes having been obtained.

3.7 Synthesis of cationic rhodium(III) and iridium(III) complexes

As mentioned previously, this study focused primarily on the use of square planar transition metal complexes as potential anti-malarial agents, although in the case of neutral rhodium(I) complexes we submitted to some loss in planarity in order to examine the effects of charge on anti-malarial activity.

Rhodium(III) complexes are generally octahedral around the metal nucleus, and were not originally considered for this study. Still it would be interesting to study the differences between Rh(I) and Rh(III) in terms of biological activity.

Pentamethylcyclopentadienyl (Cp*) complexes of both trivalent rhodium and iridium are well-known (Figure 3.13).[52, 53]

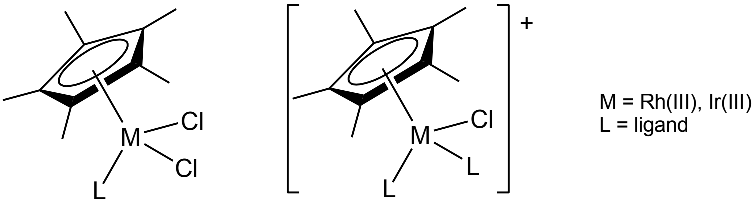
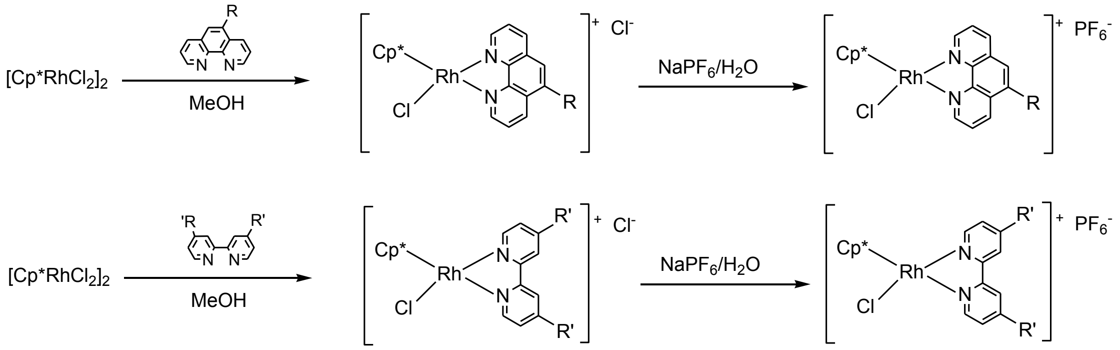


Figure 3.13 Basic structure of Group 9 metal complexes containing Cp* ligand

Such complexes possess a “piano-stool” geometry. This means that they are pseudo-octahedral rather than square planar, but it would be worthwhile to explore the anti-malarial activity of compounds with the formulation [Cp*Rh(N-N)Cl]$^+$, where N-N is a derivative of 2,2-bipyridyl or 1,10-phenanthroline. Even if they are only weakly active, it might still be possible to compare the trends between Rh(III) and Rh(I) complexes; to determine whether, for instance, the same diimine ligands give the best results in both cases. An added attraction is the fact that the iridium analogues should be stable and isolable, allowing for an investigation into the effects of the metal centre on anti-malarial activity. This was not possible in the case of the univalent metal ions.

The complexes [Cp*Rh(R-phenanthroline)Cl]Cl (R = H, NH_2, NO_2) have been prepared and used in catalytic studies by other research groups.[54] To our knowledge, no biological studies of these compounds have been conducted. Therefore a series of cationic Rh(III) complexes bearing pentamethylcyclopentadienyl and diimine ligands have been prepared (Scheme 3.8).

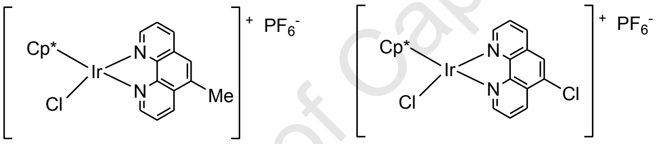
The $[Cp^*RhCl_2]_2$ dimer was suspended in methanol and reacted with two equivalents of the appropriate diimine, forming a yellow solution within 10 minutes. The product was precipitated by the addition of excess aqueous sodium hexafluorophosphate. The complexes were isolated as stable yellow microcrystalline solids in reasonably good yields. They possess better solubility properties than the cyclooctadiene compounds, and are soluble in acetone and acetonitrile as well as in dimethylsulfoxide.



Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl
R = H (**53**), Me (**54**), NH_2 (**55**), Cl (**56**)
R' = H (**57**), Me (**58**), ^{t}Bu (**59**)

Scheme 3.8

Iridium(III) analogues of **54** and **56** (Figure 3.14) were prepared in a similar manner. They were obtained as bright yellow solids, in slightly lower yields than the rhodium complexes.



60 **61**

Figure 3.14 Iridium(III) complexes synthesized

It should be noted here that complexes **54** – **56** and **60** and **61** are chiral due to the asymmetry of the phenanthroline ligands and the geometry around the metal centre. However all were obtained and used as racemic mixtures, and all subsequent characterization and testing were assumed to be unaffected by the presence of enantiomers.

3.8 Characterization of cationic rhodium(III) and iridium(III) complexes

3.8.1 Thermal stability

The cationic rhodium(III) and iridium(III) complexes melt or decompose at temperatures close to 300 °C.

3.8.2 NMR spectroscopy

The ^{1}H NMR data for the Rh(III) phenanthroline complexes are similar to literature values [54] and confirmed the proposed chemical structures. Most of the phenanthroline protons occur at chemical shifts similar to (but slightly downfield of) those of the corresponding phenanthroline protons in the Rh(I) complexes. However the imine protons H2 and H9 of all Rh(III) complexes are significantly more downfield than in the analogous Rh(I) cyclooctadiene complexes. This is clearly illustrated in Table 3.5, in which the H2 and H3 protons of the ligands in Rh(I) and Rh(III) hexafluorophosphate complexes are compared as an example.

In the case of the Rh(I) complexes, the chemical shifts of H2 and H9 of the coordinated ligand were more upfield than those of the free ligand. This was attributed to magnetic anisotropy (section 3.4.2). The corresponding chemical shifts in the Rh(III) complexes are much higher than in the free ligand, probably due to deshielding by the electron-poor Rh(III) centre. A single peak integrating for the methyl hydrogens of the Cp* ligand was found between 1.6 and 1.8 ppm in all cases.

The ^{1}H NMR spectra for the two iridium complexes **60** and **61** are similar to those of the analogous rhodium complexes.

Table 3.5 Comparison of ^{1}H NMR (DMSO-d_6) chemical shifts of protons H2 and H3 in Rh(I) and Rh(III) phenanthroline-containing complexes

Ligand (N-N)	**[Rh(N-N)(COD)]PF_6**		**[Cp*Rh(N-N)Cl]PF_6**	
	δ H2 (ppm)	δ H3 (ppm)	δ H2 (ppm)	δ H3 (ppm)
1,10-phen	8.41	8.01	9.35	8.17
5-Me-1, 10-phen	8.46	8.1 –7.8	9.39	8.23
5-NH_2-1, 10-phen	8.41	7.99	9.28	8.10
5-Cl-1, 10-phen	8.58	8.17	9.58	8.34

The ^{13}C NMR spectra of rhodium and iridium complexes give the expected number of singlet peaks in the aromatic region. Complexes containing asymmetrical phenanthroline ligands exhibit twelve individual aryl signals, while those bearing symmetrical phenanthroline ligands show six distinct peaks. The 2,2'-bipyridyl ligands are all symmetrical and have five chemically distinct aryl carbons. The cyclopentadienyl carbon atoms appear as a singlet at around 90 ppm in the iridium complexes. However, in the case of rhodium, this peak, occurring at ~ 97 ppm, is a doublet with coupling constant of ~ 8 Hz, due to coupling of carbon with ^{103}Rh. The methyl substituents on the Cp* ring appear as a singlet between 8 and 9 ppm in both rhodium and iridium complexes.

All cationic PF_6^- complexes show a septet at -144 ppm in the ^{31}P spectrum. The $^1J_{\text{P-F}}$ value is constant at 711 Hz.

3.8.3 Elemental analysis and mass spectrometry

Elemental analysis results for rhodium and iridium complexes agree with the proposed formulae. In some cases the complexes are partially hydrated, containing 0.5 or 1 molecule of water per complex molecule. This is fairly common for ionic compounds.

The ESI mass spectra of the rhodium compounds show two sets of peaks. The main signal, corresponding to the parent cation $[Cp^*Rh(N\text{-}N)Cl]^+$, occurs as a doublet due to the isotopic distribution of chlorine. There is also a peak consistent with the fragment $[Cp^*Rh(N\text{-}N)]^+$, where the chloride ligand has been lost.

The mass spectra of iridium complexes show only the peak for the parent cation. No other peaks consistent with the $[Cp^*Ir(N\text{-}N)]^+$ fragment, or with any other fragment, are observed.

3.8.4 Conductivity

The conductivities of the cyclopentadienyl complexes were determined in nitrobenzene at 20 °C. Initially, solutions of concentration 2 mM were used, as was the procedure with the Rh(I) cyclooctadiene complexes. However, it was later found that in some instances there was insufficient sample to make up a 2 mM solution of a particular complex. Thus, a 1 mM solution was used where indicated.

As molar conductivity values are calculated taking molar concentration into account, the Λ_M value for a given electrolyte in solution should remain constant over a concentration range. However, in order to confirm that the results obtained for different complexes obtained at different concentrations are comparable, further experiments were carried out. Some of the complexes were tested at different molarities in order to assess the reproducibility of Λ_M. The results are tabulated in Table 3.6.

The molar conductivities of all three complexes appear to remain constant (within experimental error) over the relevant concentration range. Thus it is possible to compare values determined for different complexes at different molarities (2 mM or 1 mM).

Table 3.6 Comparison of molar conductivities ($\Omega^{-1}.cm^2.mol^{-1}$) of Rh(III) complexes in nitrobenzene solutions of varying molar concentrations

Complex	Concentration		
	2 mM	1 mM	0.5 mM
53	24.7	24.9	25.2
54	26.0	25.9	nd*
56	26.9	26.7	nd*

* not determined

The Λ_M values indicated that all complexes tested were 1:1 electrolytes. This was particularly important to ascertain, as the complexes contain a coordinated chloride, and, as noted by previous researchers, there is the risk of slow hydrolysis in aqueous solution, [54] potentially leading to the formation of a $[Cp^*Rh(diimine)(H_2O)]^{2+}$ species, a 2:1 electrolyte. As the preparation of these complexes takes place partly in a methanol-water solution, this was a relevant concern. However, results confirm that the complexes are 1:1 electrolytes and thus no hydrolysis had taken place under the experimental conditions.

3.8.5 X-ray crystallography

High quality single crystals of **54** were obtained by the slow evaporation of diethyl ether into an acetone solution of the complex, and x-ray structural analysis was performed. Figure 3.15 shows the molecular structure of the complex. Table 3.7 lists selected bond lengths and angles; a full list is found in the Appendix. The x-ray crystallographic data collection parameters can be found in Chapter 7.

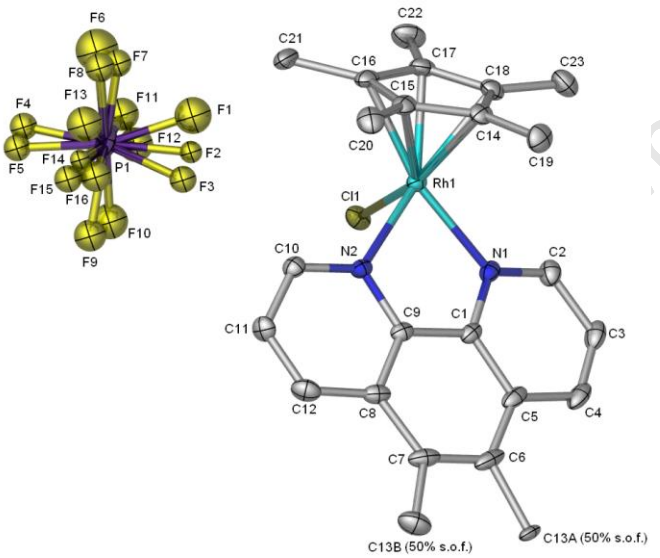


Figure 3.15. Molecular structure of complex 54 **showing the rhodium complex and its hexafluorophosphate counterion**. **Hydrogen atoms have been omitted for clarity**

Table 3.7 Selected bond lengths and angles for **54**

Bond lengths (Å)		**Angles (°)**	
Rh(1) – N(1)	2.112(3)	N(1)-Rh(1)-N(2)	77.79(11)
Rh(1) – N(2)	2.101(3)	N(1)-Rh(1)-Cl(1)	87.10
Rh(1) – Cl(1)	2.3995(8)	N(2)-Rh(1)-Cl(1)	89.46(7)
Rh(1) – C(15)	2.162(3)	N(2)-Rh(1)-C(16)	111.08(13)
C(17) – C(18)	1.419(5)	N(1)-Rh(1)-C(15)	132.16(12)
C(15) – C(16)	1.433(5)		

The geometry of the complex is pseudo-octahedral. This is illustated by the two N-Rh-Cl bonds of close to the 90 ° that would be found in an octahedral arrangement. The methyl group on the phenanthroline ring system is disordered over two positions with site occupancies of 50 % each. This is probably due to the different enantiomeric forms of the complex, which, as mentioned previously, is chiral.

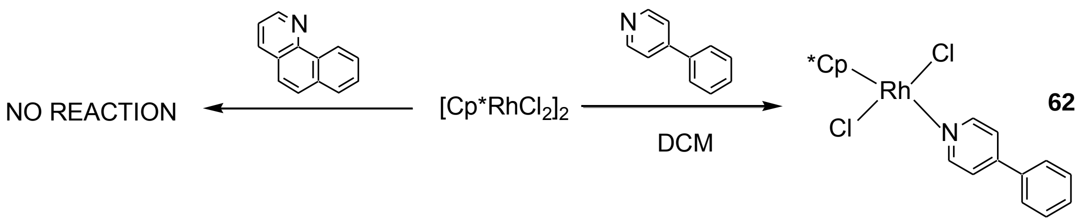
There is one interesting anomaly in the crystal structure of **54**; the PF_6^- anion is depicted as containing *sixteen* fluorine atoms, rather than six (Figure 3.15). This particular anion is disordered, with each fluorine atom occupying 2 to 4 positions with equal site occupancy factors, due to the high thermal motions. Hexafluorophosphate ions are known to be relatively disordered compared to more bulky ions such as tetraphenylborate, and this can sometimes preclude the successful achievement of x-ray quality crystals or successful x-ray structural refinement (see section 3.4.5 for discussion).[38, 39] There are numerous literature examples of crystal structures in which hexafluorophosphate ions exhibit such disorder, with one or more of the fluorine atoms occupying different positions in the crystal.[55]

The Rh-Cl and Rh-N bond distances, and the bond angles (Table 3.7), are consistent with those of other cationic Cp* rhodium complexes containing bidentate nitrogen-donor ligands.[56-58] The ring C-C bond distances range between 1.40 and 1.44 Å; these values lie between accepted bond length values for C-C single bonds and C-C double bonds, indicating aromaticity of the ring.

Due to the presence of enantiomers in the crystal structure of **54**, it is difficult to detect the offset aromatic stacking interactions that are of interest.

3.9 Synthesis and characterization of neutral rhodium(III) complex

The rhodium pentamethylcyclopentadienyl dimer was reacted with mono-imine ligands (4-phenylpyridine or benzo(h)quinoline) in dichloromethane in an attempt to synthesize uncharged Rh(III) complexes (Scheme 3.9).



Scheme 3.9

However, no product was obtained from the reaction involving benzo(*h*)quinoline despite a prolonged reaction time. Only starting material was isolated from the reaction mixture after 4 hours reaction time; this was confirmed by ^{1}H NMR. It is possible that the shape and rigidity of the organic ligand and the position of the donor nitrogen atom would impose some steric strain within the complex (Figure 3.16a). Perhaps the use of benzo(*q*)quinoline (which is structurally similar to the former but contains the nitrogen donor at a different position, Figure 3.16b) would result in less steric hindrance and allow for successful isolation of a neutral mononuclear product.

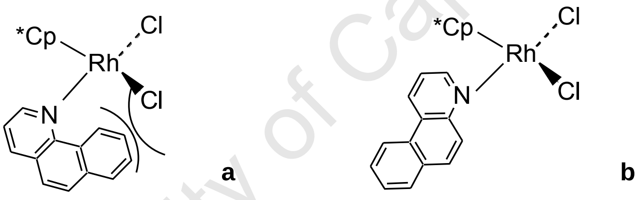


Figure 3.16 The proposed structures of theoretical Rh(III) complexes containing (a) benzo(*h*)quinoline and (b) benzo(*q*)quinoline

The rhodium dimer reacted readily with 4-phenylpyridine at room temperature to produce **62**. The complex was isolated as a yellow solid in good yield after 60 minutes reaction time. NMR data agree with the proposed structure. The ^{13}C NMR spectrum shows six distinct aromatic carbon signals where seven might be expected; however, this may be due to two of the peaks overlapping. This is fairly likely, as in the free 4-phenylpyridine ligand, two of the peaks lie very close, almost overlapping at 129.0 and 129.1 ppm. A very low conductivity measurement of 0.4 $\Omega^{-1}.\mathrm{cm}^2.\mathrm{mol}^{-1}$ (2 mM concentration in nitrobenzene) confirms that the complex is neutral. Elemental analysis also confirms the proposed chemical formula.

3.10 Summary

A range of different rhodium(I) complexes containing 1,5-cyclooctadiene and an imine or diimine ligand were synthesized and characterized using standard spectroscopic and analytical techniques, including x-ray crystallography. Imine-containing complexes carried no overall charge (neutral complexes) while diimine complexes were monocationic.

Within the cationic series, many variations were made. A range of different diimines was used, including both unsubstituted and substituted 2,2'-bipyridyl and 1,10-phenanthroline compounds. The substituents themselves were wide-ranging, encompassing electron-releasing and electron-withdrawing, hydrophobic and hydrophilic groups. Secondly, the counterion was changed (PF_6^- versus BPh_4^-) in order to tailor the chemical properties as well as ascertain any effect of the counterion on anti-malarial activity.

Cationic rhodium(III) complexes containing pentamethylcyclopentadienyl ligand and diimine ligands were prepared. All complexes contained the hexafluorophosphate counterion. Two cationic iridium analogues were also prepared in order to determine metal effects on any potential biological activity. A neutral rhodium(III) complex was synthesized in order to provide a comparison to the ionic derivatives. All the complexes were characterized by standard techniques.

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Chapter 4: The synthesis and characterization of palladium(II) complexes containing diimine ligands

4.1 Introduction

Although complexes of palladium have been intensively studied for potential anti-tumor and anti-microbial properties, there are to date few clinical uses for compounds of this metal. In most cases, palladium compounds (for example, in anti-cancer research) have been found to be less active than their platinum analogues, due to their inferior stability profiles.[1] However, where the ideal ligands are used, palladium complexes may be sufficiently stable to be able to exert the required biological effect.

In this chapter, the focus is on the synthesis of square planar palladium(II) complexes as potential anti-malarial compounds.

4.2 Palladium chelate complexes

A range of palladium complexes, each containing one diimine ligand and one chelating ligand were prepared. Bidentate chelating ligands were used due to their added stability compared to monodentate ligands. Those used in this study are simple compounds that are easily available (Figure 4.1). Slight variations in the ligand employed allowed for the preparation of neutral, monocationic or dicationic metal complexes. For instance, coordination of a doubly negative ligand to a divalent Pd(II) centre would yield a neutral complex, while a neutral ligand like ethylenediamine would produce a dicationic species.

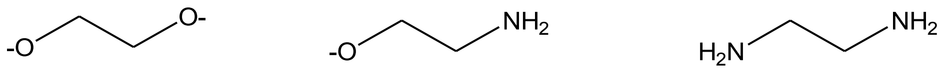
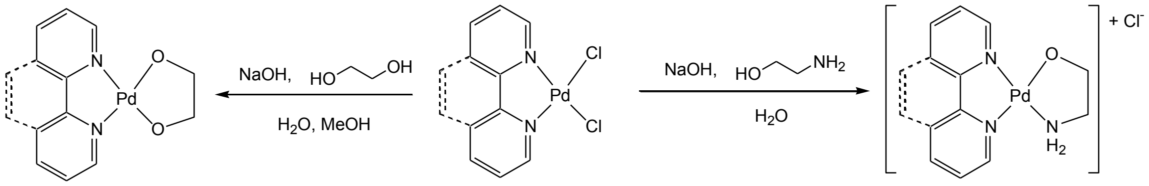


Figure 4.1 Chelating ligands used in this study

According to the hard-soft acid base rules, palladium is a “soft” Lewis acid [2] and should bind more strongly to sulfur and phosphorus ligands than to the hard-base ligands O-R and NH_2-R.[1] However we chose to work with oxygen donor ligands rather than sulphur ligands in this study for several reasons. Sulfur-donor ligand-containing complexes (especially the neutral complexes) are likely to be much less water-soluble than the oxygen-containing complexes. Secondly, the oxygen-containing starting materials are cheaper and more readily available. They are also not odorous like sulfur compounds, and all of these are considerations in dealing with potential drug molecules. It was to be hoped that, even though the individual oxygen atoms themselves might not form very strong bonds with palladium, there would be extra stability conferred by the fact that the ligands are chelating molecules. Chelate compounds, especially those containing 5-membered chelate rings (such as the ones discussed in this chapter), are in general much more stable than compounds containing monodentate ligands.[2-4]

4.2.1 Synthesis of palladium chelate complexes

Neutral palladium diimine compounds were prepared according to Scheme 4.1. A quantity of palladium diimine dichloride was suspended in methanol. A solution of excess ethylene glycol (EG) and NaOH in water was added dropwise to the suspension and the reaction mixture was then stirred at room temperature. Over the course of a few hours the suspension was transformed into a yellow-orange solution. This was filtered by gravity to remove any remaining starting material or insoluble by-product. The solvent was reduced *in vacuo*, to leave only a small amount of solvent (water) behind. The solution was stored at 4 °C and fine needle-like crystals were formed. These were collected and washed with small quantities of ice-cold water. The yields were quite low (30 - 40 %), possibly due to the compounds being partially soluble in water. Compounds **63** and **64** have been reported previously in the literature.[5]

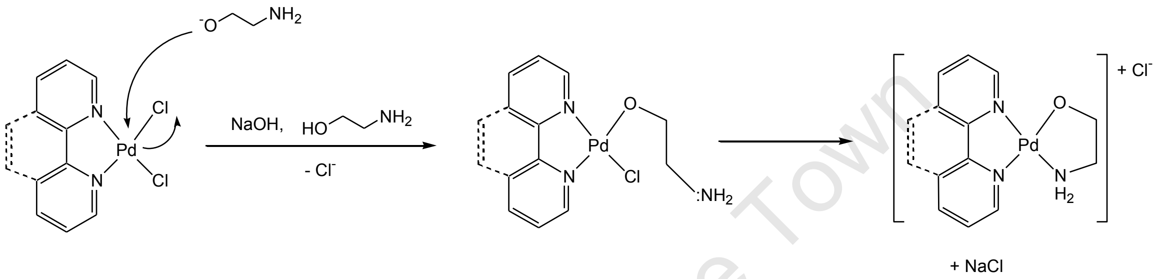


Diimine = bipy, **63**
phen, **64**

Diimine = bipy, **65**
phen, **66**

Scheme 4.1

The monocationic chelate complexes were prepared from the reaction of ethanolamine (EA) and palladium diimine dichloride in the presence of a base (Scheme 4.1). The mixture was refluxed in distilled water; a yellow solution was formed within 30 minutes. Presumably the reaction proceeds first from attack of the deprotonated, anionic oxygen on the palladium centre with loss of a chloride ion, followed by the slower substitution of the second chloride by the neutral amine group, yielding a cationic product (Scheme 4.2).



Diimine = bipy, **65**
phen, **66**

Scheme 4.2

The product was isolated by concentration of the reaction solvent *in vacuo*, whereafter it was allowed to crystallize slowly at 4 °C. The crystals were collected on a filter and washed with small amounts of ice-cold water to remove any salt by-product or unreacted ethanolamine. The compounds are obtained as hydrated salts. Compounds **65** and **66** are new and have not been found in the literature; however, similar complexes, incorporating the simple amino acid glycine rather than ethanolamine, have been synthesized previously (Figure 4.2).[6,7]

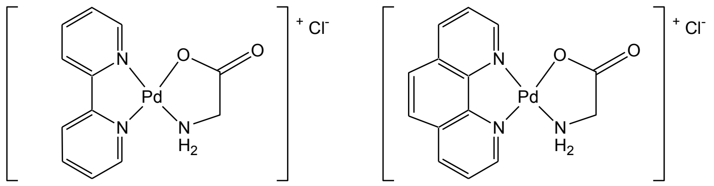
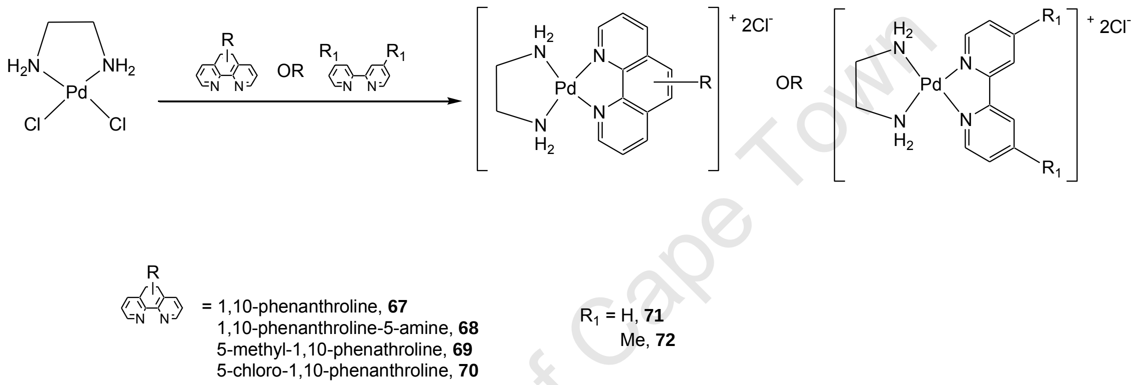


Figure 4.2 Cationic palladium complexes containing bidentate anionic glycinate ligand

Dicationic chelate complexes were obtained by refluxing (ethylenediamine)dichloropalladium(II) with an equimolar amount of the appropriate diimine in distilled water (Scheme 4.3). The reaction was quite rapid, with formation of the water-soluble product to give a pale yellow or colourless solution within 10 minutes of refluxing time. The reaction was refluxed approximately 30 minutes further, and allowed to cool to room temperature. The solvent was reduced or removed *in vacuo*, and methanol and ether were added to obtain the white or pale yellow precipitate. The product was collected on a vacuum filter and washed with methanol and diethyl ether.



Scheme 4.3

The yields of the dicationic complexes are moderate, but higher compared to the neutral and monocationic complexes, greater than 60 %. In the case of the neutral and cationic complexes, the required reaction conditions (presence of base) leads to the formation of a salt by-product. There is also some ethylene glycol or ethanolamine starting material present: these compounds are liquids and the tiny amounts required are difficult to control accurately, therefore they are generally added in excess. The salt and excess starting material must be removed by washing with distilled water. Because the neutral and monocationic complexes are slightly water-soluble and highly water-soluble respectively, washing with water, albeit ice-cold water, would cause some of the product to be lost. The syntheses of the dicationic complexes do not require addition of base, no salt by-product is formed and washing with water thus is not required. All the starting materials are solids and can therefore be measured exactly, so no one starting material is in excess.

That the yields of the dicationic compounds are not higher than they are, may be due to two reasons. Firstly, not all the starting material might react, and the insoluble reactants would then be removed by filtration. Secondly, the complexes are only really soluble in water and dimethylsulfoxide, but do seem to show some solubility in polar solvents such as alcohols. Washing with methanol and diethyl ether after collection by filtration would therefore lead to some loss of product. However, it was necessary to wash with these solvents in order to ensure that no traces of starting material remained in the sample.

The unsubstituted diimine dications have previously been reported in the literature.[8-14] For example, the complex [Pd(bipy)(en)][(NO_3)]$_2$ has been used in ligand-exchange reactions and NMR or computational studies.[8-11] The compounds [Pd(bipy)(en)][(ClO_4)]$_2$ and [Pd(di-Me-bipy)(en)][(ClO_4)]$_2$ were included in a study on the interaction of square planar complexes with DNA.[12] Both **67** and **71** have also been used in anti-cancer research.[13] However, complexes **68**, **69** and **70** are new compounds, and none of the complexes **67** – **72** have ever been tested for anti-malarial activity.

4.3 Characterization of palladium(II) chelate complexes

4.3.1 Thermal stability

The neutral palladium chelate complexes decompose below 200 °C. The dicationic complexes are thermally stable, and all melt or decompose only at temperatures well above 200 °C.

4.3.2 NMR spectroscopy

The NMR spectra of neutral and dicationic palladium chelate complexes are simpler than those of monocationic complexes due to the higher degree of symmetry. All neutral and dicationic complexes display only one singlet for the aliphatic protons (2 x CH_2) of the ethylene glycolate and ethylenediamine (en) ligands, as the coupling of equivalent nuclei is not observed in NMR spectra.[15,16] There are four magnetically inequivalent signals for the phenanthroline or bipyridyl protons. In the case of the dicationic compounds containing asymmetrical phenanthrolines, the equivalence of the two methylene groups indicates that position-5 substitutions on the phenanthroline ring do not influence the chelating ancillary ligand in terms of chemical or magnetic environment.

The spectra of aminoethanolate complexes containing unsubstituted 2,2'-bipyridyl and 1,10-phenanthroline are somewhat more complicated. As expected, there are two triplets in the lower-field aliphatic regions, indicating that the two methylene groups, each adjacent to a different heteroatom, are coupling to each other. Then, due to the asymmetry introduced by the asymmetrical chelating ligand, eight instead of four distinct aromatic signals (corresponding to the diimine ligand) are observed. This effect has been reported with similar palladium diimine complexes (see section 4.2.1).[6] The presence of a nitrogen atom directly opposite one side of the phenanthroline or bipyridyl ring, and the presence of the oxygen opposite the other, removes the plane of symmetry of the diimine and results in differences in the chemical shifts of previously equivalent atoms (for example, H2 and H9 of 1,10-phenanthroline). It is therefore not easy to unambiguously assign ^{1}H NMR spectra of the compounds.

The ^{13}C NMR of the chelate complexes similarly reflect the symmetry of the environment opposite the diimine ligand. The carbon spectra of the neutral and dicationic complexes show five and six aromatic signals for the 2,2'-bipyridyl and 1,10-phenanthroline ligands respectively. There is a doubling up of signals for the monocationic aminoethanolate complexes, however, with five or six sets of two closely-related signals. In most cases the difference between the two related signals is small (0.1 – 0.4 ppm), but one pair (presumably the imine carbons, which are directly opposite and closest to the aminoethanolate chelate) differ by about 2 ppm.

4.3.3 Elemental analysis and mass spectrometry

The elemental analysis results of the monocationic and dicationic chelate complexes showed lower carbon and nitrogen percentages, and higher hydrogen percentages, than were expected from the proposed chemical formulae. Further examination of the results indicated that the complexes exist as hydrated salts, with the different complexes containing two to four water molecules per molecule of palladium complex. The neutral complexes **63** and **64** are also obtained in highly hydrated form, despite prolonged drying under vacuum.

The ESI mass spectra showed the expected peaks for each compound. Each signal occurs as a cluster of individual peaks (one or two main peaks and several smaller, surrounding peaks), corresponding, probably, to the various stable isotopes of palladium: ^{106}Pd and ^{108}Pd (the most abundant forms), ^{105}Pd, ^{110}Pd, ^{104}Pd and ^{102}Pd (least abundant).[17]

In the case of the neutral EG complexes **63** and **64**, the intensity of the cluster of peaks corresponding to the parent ion is rather weak. A much larger cluster is found corresponding to $[M - O]^+$, possibly indicating the dissociation of one end of the chelate ring from palladium, and subsequent fragmentation of the free oxygen atom.

The dicationic ethylenediamine complexes display more complicated mass spectra. In all cases the $[M - 2Cl]^+$ fragment, corresponding to the palladium-containing dication, is observed. This is expected because the term $[M]^+$ includes the two chloride counterions, which are not expected to be coordinated to the metal centre. Thus [M – 2Cl] should be the main fragment in the spectrum. However, the spectra usually also appear to indicate fragments in which one or two chloride counterions have become coordinated to the palladium centre, yielding peaks corresponding to $[M - Cl]^+$ or $[M]^+$.

A number of other fragments are also observed. A peak corresponding to $[M - 2Cl - en]^+$ is evident in most cases. In some cases there may be a peak that correlates to $[M - 2Cl - NH_2]^+$, suggesting that one amino group of the chelate ring has dissociated from the metal centre and broken away from the ethylenediamine chain. There are also peaks occurring at higher *m/z* ratios, which cannot easily be assigned. These may represent a complex reconfiguration of ionic fragments, perhaps dimerization of palladium fragments. A sample mass spectrum of complex **72** is shown in Figure 4.3.

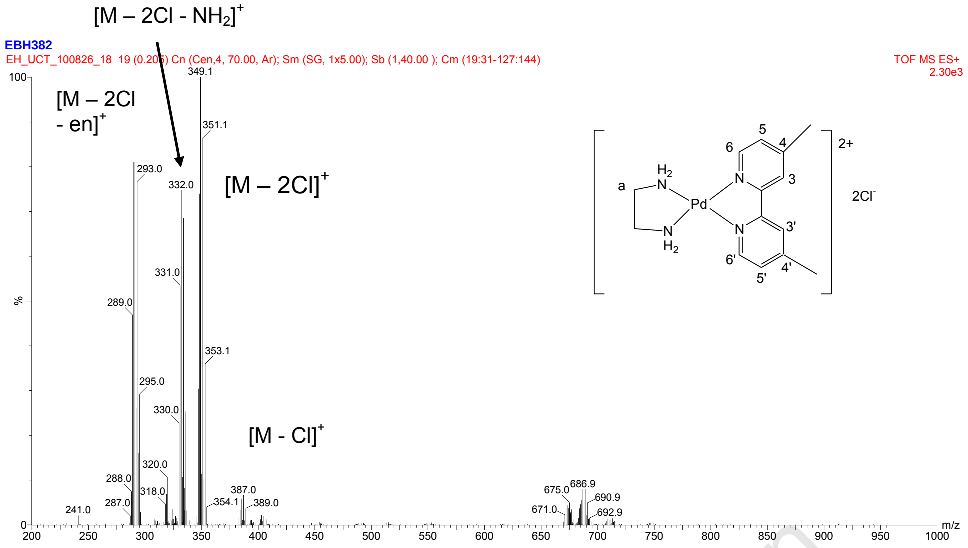


Figure 4.3 Mass spectrum of complex 72 **indicating individual fragment masses**

4.3.4 X-ray crystallography

The recrystallization of [Pd(phen)(en)].2Cl (**67**) from slow evaporation of a water solution led to the formation of x-ray quality crystals. The molecular structure of the complex was determined by x-ray crystallography and is shown in Figure 4.4. Selected bond lengths and angles are listed in Table 4.1.

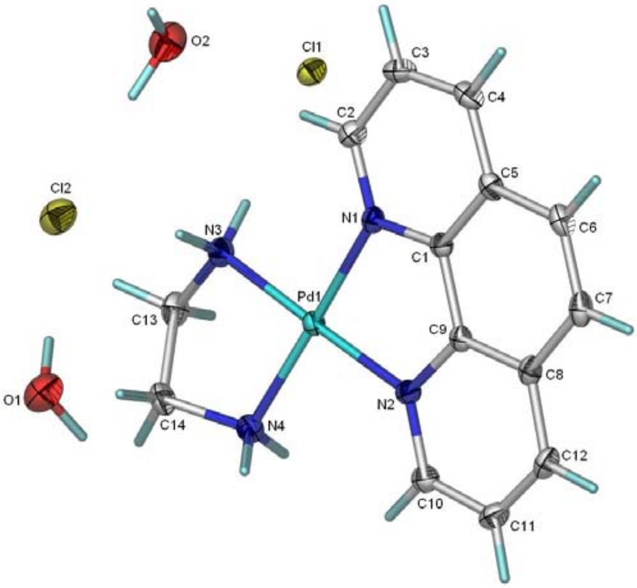


Figure 4.4 X-ray crystal structure of 67**, showing the palladium complex and its chloride counterions crystallizing with two water molecules**

Table 4.1 Selected bond lengths and angles for complex **67**

Bond lengths (Å)		**Angles (°)**	
Pd(1) – N(1)	2.031(2)	N(3)-Pd(1)-N(1)	97.15(8)
Pd(1) – N(3)	2.030(2)	N(3)-Pd(1)-N(2)	178.69(8)
Pd(1) – N(4)	2.043(2)	N(1)-Pd(1)-N(2)	81.54(8)
Pd(1) – N(2)	2.034(2)	N(3)-Pd(1)-N(4)	83.40(9)
N(3) – C(13)	1.492(3)	N(1)-Pd(1)-N(4)	176.4(8)
C(14) – C(13)	1.51(4)	C(14)-N(4)-Pd(1)	108.82(16)

Complex **67** crystallizes with two water molecules per palladium atom. The complex is square planar around the metal centre, as expected for a Pd(II) compound.[2] There is some distortion due to the strain imposed by the two chelate rings; the two Pd-N bonds of each chelate system are pushed closer together to form angles closer to 80 ° than the ideal 90 °. This decrease of the N-Pd-N bond angle due to chelating ring strain has been reported in other palladium diimine complexes containing phenathroline- or bipyridyl-type ligands.[18-20]

Bond angles centering on the ethylenediamine nitrogen atoms are close to 109.5 °, indicating the tetrahedral arrangement about these atoms.[21] The palladium-amine bond distances of about 2.04 Å are within the same range as those of other cationic palladium ethylenediamine complexes.[22] The palladium-imine bond distances are also similar to those reported in the literature for other palladium phenanthroline complexes.[18-20, 23, 24]

There is an extensive hydrogen bonding network (Table 4.2) where the acceptor atom is, in most cases, a chloride counterion. The donor molecules comprise the ethylenediamine nitrogen and water oxygen atoms; one of the water molecules also acts as acceptor from an N-H bond. Figure 4.5 depicts a packing diagram of the complex with hydrogen bonds included.

Table 4.2 Hydrogen bond distances and angles for complex **67**

D-H…A	d(D-H) (Å)	d(H…A) (Å)	d(D…A) (Å)	< DHA (°)
O(1)-H(1B)...Cl(1)	0.951(18)	2.39(2)	3.298(2)	160(3)
O(1)-H(1A)...Cl(2)	0.939(17)	2.209(18)	3.138(2)	177(3)
N(3)-H(3A)...Cl(2)	0.943(17)	2.257(19)	3.177(2)	165(2)
N(3)-H(3B)...Cl(1)	0.936(18)	2.417(18)	3.346(2)	172(3)
N(4)-H(4A)...O(1)	0.948(18)	2.20(2)	3.006(3)	143(2)
N(4)-H(4B)...Cl(1)	0.938(18)	2.37(2)	3.253(2)	158(3)
O(2)-H(2A)...Cl(1)	0.965(18)	2.31(2)	3.257(2)	166(3)
O(2)-H(2B)-Cl(2)	0.965(18)	2.16(18)	3.123(2)	173(3)

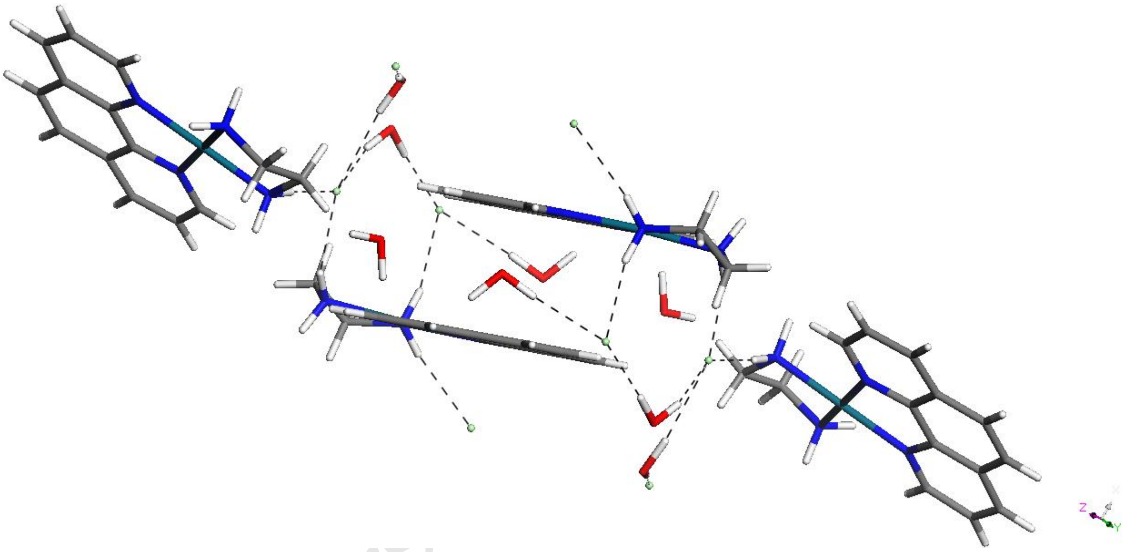


Figure 4.5 Packing diagram of 67 **showing hydrogen bonding network**

The crystal structure of **67** also indicates the occurrence of planar aromatic stacking interactions between the various rings of the phenanthroline ligand. Table 4.3 lists the geometric parameters for these interactions (see 3.4.5 for a detailed description).

Table 4.3 Geometric parameters for π-π stacking in **67**

Cg(I)-Cg(J)	d_{c-c} (Å)	α (°)	β (°)	γ (°)	d⊥[Cg(I)-P(J)] (Å)	d⊥[Cg(J)-P(I)] (Å)
Cg3-Cg4	3.6431(13)	0.53	23.50	23.91	3.330	3.341
Cg3-Cg4	3.8569(13)	0.53	28.17	28.11	3.402	3.400
Cg3-Cg5	3.6234(13)	0.24	20.23	20.42	3.396	3.400
Cg4-Cg3	3.6430(13)	0.53	23.91	23.50	3.341	3.330
Cg4-Cg5	3.6591(13)	0.76	23.21	23.90	3.345	3.363
Cg4-Cg3	3.8570(13)	0.53	28.11	28.17	3.400	3.402

d_{c-c} = distance between ring centroids
α = dihedral angle between planes
β = angle between Cg(I)-Cg(J) vector and normal to plane I
d⊥[Cg(I)-P(J)] = perpendicular distance of Cg(I) on ring J

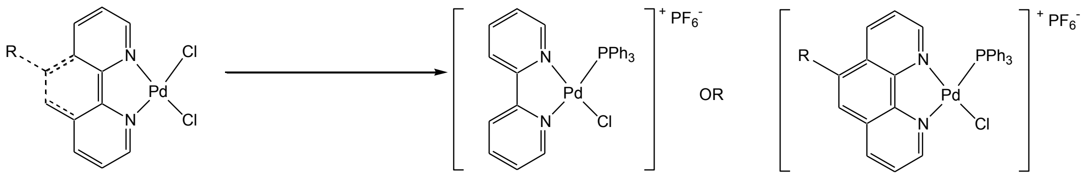
Cg3: N1-C1-C5-C4-C3-C2
Cg4: N1-C9-C8-C12-C11-C1
Cg5: C1-C5-C6-C7-C8-C9

4.4 Palladium phosphine complexes

Complexes containing monodentate phosphines ligands were prepared for comparison to the chelate complexes. Phosphines form stable complexes with many transition metals in different oxidation states.[25] They are versatile ligands, and their properties (steric, electronic, solubility) can be tuned to a specific purpose. Phosphines have thus found wide application as ligands in the areas of transition metal catalysis as well as in biological research.

4.4.1 Synthesis of palladium phosphine complexes

Monocationic palladium triphenylphosphine complexes were synthesized from the reaction of the palladium diimine dichlorides with PPh_3 in the presence of a halide-abstracting agent. Equal molar amounts of palladium precursor, sodium hexafluorophosphate and triphenylphosphine were refluxed in acetonitrile (Scheme 4.4). After approximately 10 minutes of refluxing a bright yellow solution was formed. After cooling the reaction mixture, the solvent was reduced and methanol added to precipitate the product, which was filtered and washed with water and methanol.



73 R = H (**74**), Me (**75**), NH_2 (**76**), Cl (**77**)

Scheme 4.4

In the case of the complexes containing 5-substituted phenanthroline derivatives there is the possibility of forming a mixture of isomers (Figure 4.6), depending on at which position the phosphine coordinates. However the asymmetry induced by the replacement of a chloride with triphenylphosphine does not appear to lead to inequivalence of the protons of the unsubstituted diimines. The spectra of 1,10-phenanthroline and 2,2'-bipyridyl compounds still give only four distinct signals in the aromatic region. Therefore, despite the likelihood of a mixture of isomers being formed in the case of the 5-substituted phenanthroline complexes, this is not observed in NMR spectra, which simplifies the assignments of NMR peaks for these complexes.

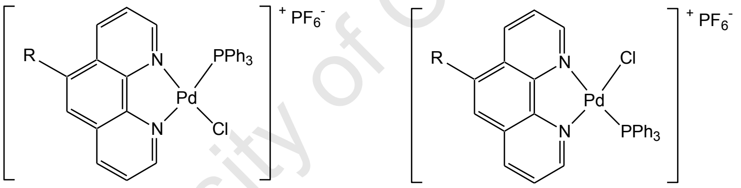
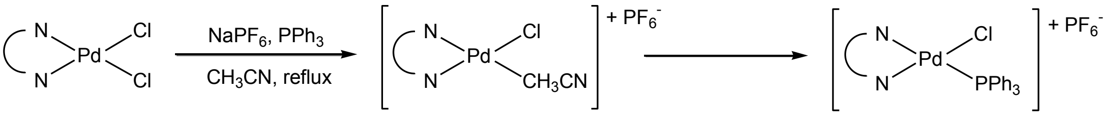


Figure 4.6 Two possible isomers formed for [Pd(R-phen)(PPh_3)Cl]$^+$ complexes (R = Me, NH_2, Cl)

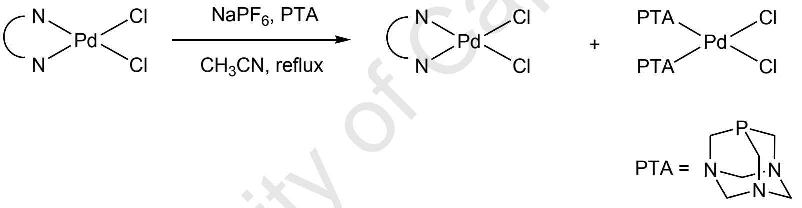
This is different to the situation concerning the chelate complexes, where asymmetry in the chelating spectator ligand caused differences in the NMR environments of the diimine ligand. However there is precedence for this in the literature. Phosphine complexes similar to **74** have been reported previously [26] and it has been found that the effects of asymmetry are small, and that the phenanthroline resonances are not always resolved in the ^1H NMR spectrum.[26a]

A complex containing a different phosphine ligand, 1,3,5-triazaphosphaadamantane (PTA), was prepared. The synthesis of this complex required a procedure slightly different to that of the PPh_3 complexes. In the case of PPh_3 complexes, the three reactants (the palladium starting complex, triphenylphosphine and sodium hexafluorophosphate) can all be added to the reaction mixture simultaneously; the reaction then, presumably, progresses as shown in Scheme 4.5:



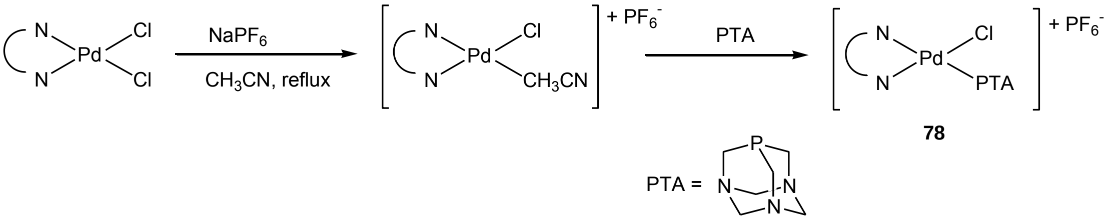
Scheme 4.5

However, if this reaction procedure is followed using PTA in place of PPh_3, the corresponding cationic phosphine product is not formed. Instead, there is rapid formation of a yellow water-soluble complex, $Pd(PTA)_2Cl_2$ (Scheme 4.6). This probably occurs as a result of the strongly-binding PTA ligand displacing the less strongly-bound diimine. This would not happen when using PPh_3, which is a much weaker ligand.



Scheme 4.6

Therefore, it was necessary first to generate the cationic intermediate before adding the PTA (Scheme 4.7). In that event, the most weakly bound ligand of the palladium complex upon introduction of the PTA would be the acetonitrile solvent molecule, which would then be displaced by the phosphine, leaving the diimine ligand intact.



Scheme 4.7

This approach was more successful, and the new complex [Pd(phen)PTA(Cl)]PF_6 was synthesized. Despite the incorporation of the water-soluble ligand, the complex itself is not water-soluble, probably due to the extreme hydrophobicity of the PF_6^- counterion. However, the complex is more soluble in general than the triphenylphosphine complexes, and, unlike them, dissolves in alcohols and in alcohol-water mixtures.

A dicationic phosphine complex, [Pd(phen)(PPh_3)$_2$].2PF_6 (**79**) was also prepared. The removal of two chloride ligands required the use of a stronger halide abstracting agent, and thus silver hexafluorophosphate, $AgPF_6$, was used in place of $NaPF_6$. The reaction of Pd(phen)Cl_2, $AgPF_6$ and PPh_3 in dry acetonitrile at room temperature and under nitrogen atmosphere led to the rapid formation of an orange-yellow solution and a greyish precipitate (AgCl). The filtration of silver chloride, removal of solvent from mother liquor *in vacuo*, and re-dissolution of the product in dichloromethane were repeated several times to ensure that all AgCl was removed. The product was finally isolated as a yellow solid. A similar compound [Pd(phen)(PPh_3)$_2$].2ClO_4 has been reported in the literature, but was prepared using a different method to that described here.[27]

4.5 Characterization of palladium(II) phosphine complexes

4.5.1 Thermal stability

The cationic palladium phosphine complexes are thermally stable and melt or decompose at temperatures exceeding 200 °C.

4.5.2 NMR spectroscopy

Due to the high numbers of aryl protons in the triphenylphosphine complexes, most of the ^{1}H NMR signals are not distinct, but appear in an extended multiplet comprising numerous overlapping peaks. However, protons H4 and H7 of the phenanthroline complexes, which are significantly more downfield than the others, are distinguishable as two doublets, with coupling constants of 8 – 9 Hz, close to 9 ppm. Proton H6 is usually also observed as a single peak. Table 4.4 compares the differences in the chemical shifts for protons H4 and H7 in the free ligand and the palladium-coordinated ligand complex.

There is a large downfield shift of both H4 and H7 upon ligand coordination to palladium. This indicates the electron-withdrawing ability of the positively-charged metal centre, and consequent inductive deshielding of the hydrogen atoms on the phenanthroline ligand.

Table 4.4 ^{1}H NMR chemical shifts (ppm) of protons H4 and H7 for 1,10-phenanthroline ligands in free and complexed form where complex is $[Pd(R\text{-}phen)Cl(PPh_3)]PF_6$

	H4 (free ligand)	H4 (complex)	H7 (free ligand)	H7 (complex)
phen	8.46	8.96	8.46	8.96
5-Cl-phen	8.65	9.14	8.45	8.68
5-Me-phen	8.51	9.02	8.33	8.83
5-NH_2-phen	8.65 – 8.71	9.15	8.03	8.48

The PTA complex **78** containing phenanthroline gives a well-defined spectrum and all peaks are readily assigned. Again, the asymmetry of the overall complex does not affect the phenanthroline ligand, in that there is no doubling of the phenanthroline signals. There are two main resonances for the PTA ligand itself. The 6 protons of –P-CH_2-N- are represented as a singlet at 4.80 ppm. In the free ligand, this resonance is observed as a doublet with P-H coupling, but coordination to a metal centre decreases $J_{P\text{-}H}$ to a negligible value.[28] The -N-CH_2-N- protons display the two doublets of an AB spin system (with J_{HAHB} = 13 Hz), corresponding to the axial and equatorial atoms of that methylene group, at a slightly more upfield shift (Figure 4.7). This type of ^{1}H NMR pattern has previously been observed in other transition metal-PTA complexes.[29,30]

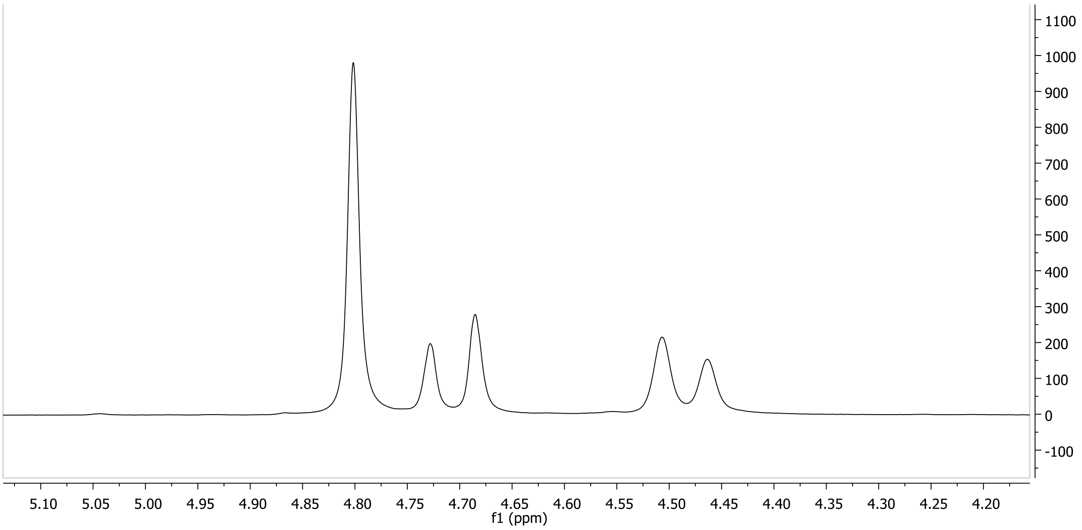


Figure 4.7 ^{1}H NMR aliphatic region showing PTA protons for 78

Dicationic complex **79** gives a spectrum indicative of a mixture of products and individual peaks could not be assigned. It was observed that a dichloromethane or DMSO solution of **79** darkened from yellow to deep orange fairly quickly at room temperature. It is possible that the steric strain of the bulky *cis*-positioned phosphine groups causes instability in the complex and leads to reversible dissociation of one or both of the phosphines in solution. This could explain both the complicated NMR spectrum and the observed colour change of **79** in solution.

The ^{31}P NMR spectrum of each triphenylphosphine complex contains a singlet between 30 and 35 ppm. Free PPh_3 occurs at roughly -5 ppm, and the large downfield shift is evidence for coordination to the palladium nucleus. The ^{31}P spectrum of the PTA complex shows a singlet at -24 ppm, whereas free PTA occurs at -98 ppm;[31] once again this indicates that the phosphine is palladium-bound.

Each complex also shows a septet occurring in the high-field region at approximately – 144 ppm. This is assigned to the phosphorus atom of the counterion (hexafluorophosphate) that couples with six ^{19}F atoms to yield the septet. The coupling constant of 711 Hz is typical for the PF_6^- ion.[32]

Due to the poor solubility of the triphenylphosphine complexes in available deuterated solvents, good ^{13}C NMR spectra could not be obtained. Therefore there are no data for these complexes. The PTA complex **78** is more soluble in all solvents by virtue of its more soluble ligand, and this is the only phosphine complex for which the ^{13}C NMR data are presented.

4.5.3 Elemental analysis and mass spectrometry

The elemental analysis results are consistent with the proposed structures. The PTA complex **78** is found to exist as a triply hydrated complex, possibly due to the three nitrogen atoms of the phosphine ligand forming hydrogen bonds with water.

Mass spectrometry results (ESI-MS) indicated peaks for the parent complexes at the expected molecular masses. Each compound shows a fairly complex isotope pattern, possibly due in part to the fact that palladium can exist in several stable isotopic forms.[17] The two main parent ion peaks correspond to ^{106}Pd (the most common isotope of palladium) [17] containing either one of the two naturally-occurring isotopes of chlorine, ^{35}Cl or ^{37}Cl.

In the case of complex **77** containing two chlorine atoms in the chemical formulation, three main peaks (617, 619, 621 g/mol) were observed. These correspond to a ^{106}Pd complex containing a $^{35}Cl/^{35}Cl$, $^{35}Cl/^{37}Cl$, or $^{37}Cl/^{37}Cl$ combination respectively.

4.5.4 X-ray crystallography

X-ray quality crystals of **73** were obtained from the slow diffusion of diethyl ether into an acetonitrile solution of the complex. The crystal structure of the complex was elucidated by x-ray diffraction and is depicted with atomic numbering in Figure 4.8. Table 4.5 shows selected bond lengths and angles for the complex.

The complex is essentially square planar around the metal centre, as expected for a Pd(II) compound. However bond angles around the palladium centre that deviate quite significantly from the ideal 180 ° or 90 ° indicate some distortion. A rather small N-Pd-N angle of 79.4 ° is attributed to the chelating diimine ring strain (see section 4.2.2.4). A much larger N-Pd-P angle of 98.6 ° is probably forced by the large steric bulk of the triphenylphosphine ligand.

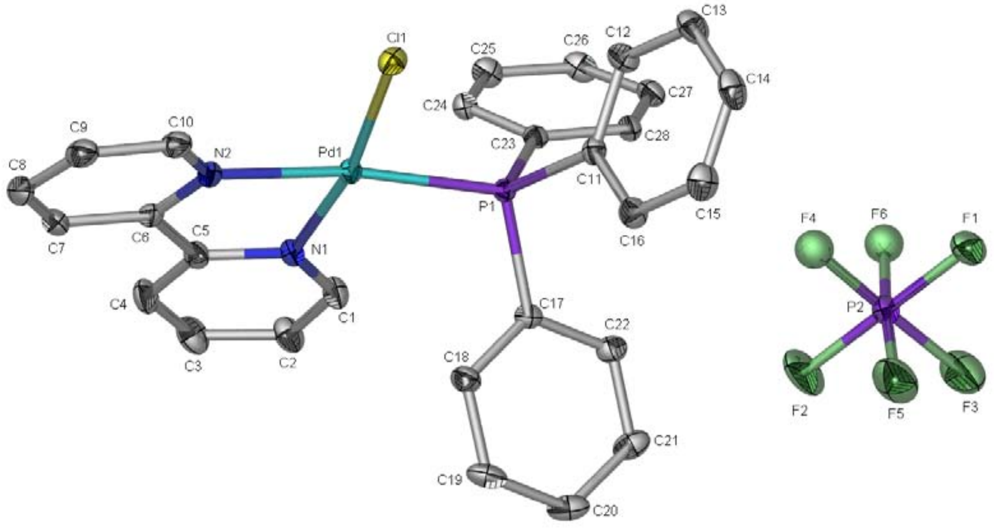


Figure 4.8 X-ray crystal structure of 73 **showing the palladium complex and its hexafluorophosphate counterion**

Table 4.5 Selected bond lengths and angles for complex **73**

Bond lengths (Å)		**Angles (°)**	
Pd(1) – (N1)	2.065(4)	N(1)-Pd(1)-N(2)	79.40(15)
Pd(1) – N(2)	2.092(4)	N(1)-Pd(1)-P(1)	98.62(10)
Pd(1) – P(1)	2.2743(11)	N(2)-Pd(1)-P(1)	171.12(10)
Pd(1) – Cl(1)	2.2808(11)	N(1)-Pd(1)-Cl(1)	169.06(10)
P(1) – C(23)	1.815(4)	N(2)-Pd(1)-Cl(1)	93.74(11)
P(1) – C(11)	1.817(4)	P(1)-Pd(1)-Cl(1)	89.43(4)
		Pd(1)-P(1)-C(17)	108.41(14)
		C(23)-P(1)-C(17)	107.65(19)

The Pd-N bond lengths are in the same range as those found in other palladium diimine complexes, both neutral and cationic.[18-20, 23, 24] The metal bond distance to phosphorus was found to be similar to those observed in other palladium triphenylphosphine complexes where crystal structures have been reported.[33-37] The Pd-Cl bond length of approximately 2.3 Å is also in accordance with literature reports.[18, 23] Phosphorus-carbon bonds of about 1.8 Å are likewise consistent with literature values.[33, 34] No aromatic stacking interactions are observed.

Dicationic complex **79** was recrystallized by the slow diffusion of pentane into a dichloromethane solution of the complex. Although previously the complex had appeared to be unstable in solution, it was possible to isolate x-ray quality single crystals using this method. The solid state structure of the complex was confirmed by x-ray diffraction and is shown with atomic numbering in Figure 4.9. Table 4.6 shows selected bond lengths and angles for the complex.

Table 4.6 Selected bond lengths and angles for complex **79**

Bond lengths (Å)		**Angles (°)**	
Pd(1) – N(1)	2.1346(19)	N(2)-Pd(1)-N(1)	79.24(7)
Pd(1) – N(2)	2.0976(19)	N(2)-Pd(1)-P(1)	167.24(5)
Pd(1) – P(1)	2.2825(6)	N(1)-Pd(1)-P(1)	95.02(6)
Pd(1) – P(2)	2.2861(6)	N(1)-Pd(1)-P(2)	160.67(5)
P(1) – C(31)	1.828(2)	P(1)-Pd(1)-P(2)	94.63(2)
N(1) – C(12)	1.366(3)	C(21)-P(1)-C(31)	108.91(10)

Complex **79** has distorted square planar geometry. The small N-Pd-N bond angle of 79 ° is due to constraints imposed by the chelating bipyridyl ring system. The bond distances are similar to the corresponding distances in complex **73**, and are consistent with literature values.[18 - 20, 33 - 37]

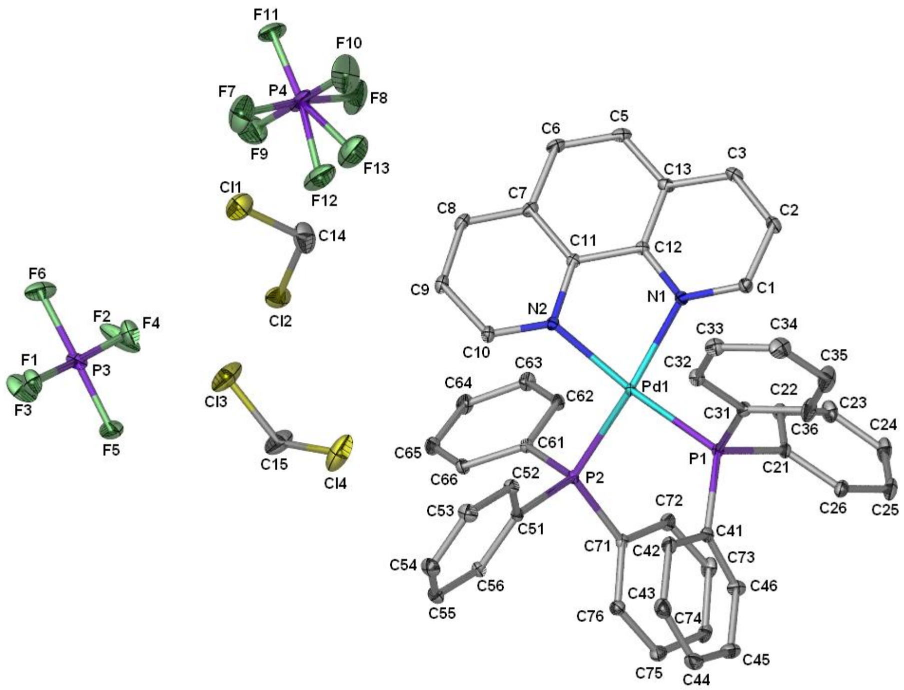


Figure 4.9 Molecular structure of 79 **showing the palladium complex and its hexafluorophosphate counterions crystallizing with two dichloromethane molecules**

One of the hexafluorophosphate counterions is depicted as containing seven fluorine atoms rather than six, where three of the fluorines shown (F10, F12, F13) are disordered over two sites. This type of disorder is fairly common among hexafluorophosphate complexes [38-40] and has previously been discussed in section 3.8.5 of this thesis.

Figure 4.10 shows the packing diagram for 79. Some intermolecular stacking between the phenanthroline ligands is observed. Table 4.7 lists the relevant interactions. The angle α of 4.10 ° indicates that the interacting rings are not perfectly parallel. However, the remaining parameters all fall within the accepted range for π-π stacking.

Table 4.7 Geometric parameters for π-π stacking in **79**

Cg(I)-Cg(J)	$d_{c\text{-}c}$ (Å)	α (°)	β (°)	γ (°)	d⊥[Cg(I)-P(J)] (Å)	d⊥[Cg(J)-P(I)] (Å)
Cg2-Cg4	3.7508(15)	4.10	23.41	25.75	3.378	3.442
Cg4-Cg2	3.7508(15)	4.10	25.75	23.41	3.442	3.378

$d_{c\text{-}c}$ = distance between ring centroids
α = dihedral angle between planes
β = angle between Cg(I)-Cg(J) vector and normal to plane I
d⊥[Cg(I)-P(J)] = perpendicular distance of Cg(I) on ring J

Cg2: N1-C1-C2-C3-C12-C13
Cg4: C5-C6-C7-C11-C12-C13

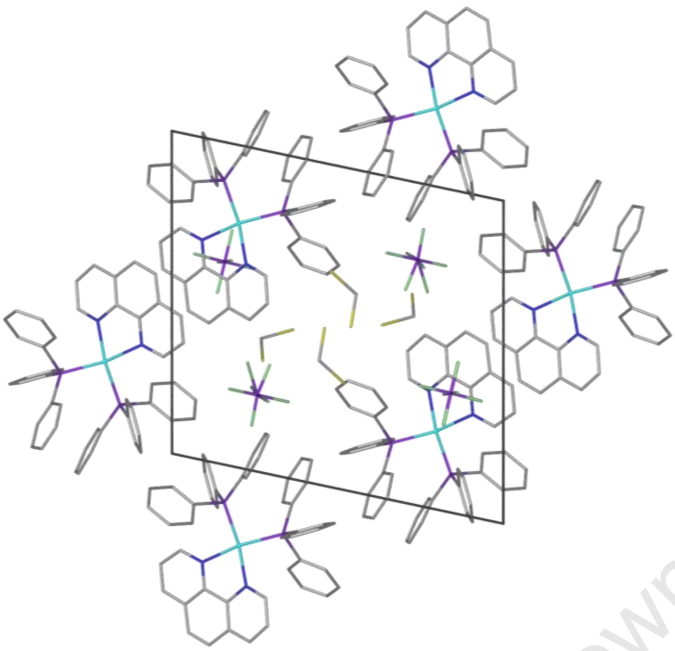


Figure 4.10 Projection of 79 **viewed down [100]**

The full lists of bond lengths and angles for **73** and **79** are found in the Appendix.

4.6 Summary

Two separate series of palladium(II) complexes containing diimine ligands were synthesized. In both series several different diimine ligands were used. For the first set of compounds, the ancillary ligand consisted of a simple bidentate chelating ligand. Neutral, monocationic and dicationic complexes were prepared. The cationic complexes incorporate chloride counterions, are water-soluble and were isolated as hydrated salts. All complexes were characterized by NMR, elemental analysis and mass spectrometry. The molecular structure of **67** was confirmed by x-ray crystallography.

The second series consisted of cationic palladium complexes containing monodentate phosphine ligands. As the counterion in this case, PF_6^-, is very hydrophobic, these complexes are not water-soluble, even where a water-soluble phosphine was used. The complexes were characterized by NMR, elemental analysis and mass spectrometry. The molecular structures of **73** and **79** were determined by x-ray crystallography.

4.7 References

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Chapter 5

Biological activity of rhodium and palladium complexes

5.1 Introduction

There are numerous considerations regarding the action of any drug in a biological system. One is cell uptake. In order for drugs to exert their required action, they must be able to cross the cellular membrane, a phospholipid bilayer surrounding the cell. Small, neutral, and hydrophobic organic molecules pass easily across the membrane by passive diffusion along a concentration gradient.[1,2] Hydrophilic or charged particles often must be actively transported across the lipid bilayer by membrane transport proteins [1,3] or enter the cell through ion channels.[1] Therefore, the positive charge carried by most of the complexes in this study, and the added hydrophilicity of some (the palladium chelates, for example), might be expected to hinder their uptake and thereby inhibit their function.

There are few comprehensive reports on the cellular uptake and accumulation properties of metal-based drugs.[4] A number of these studies deal with cisplatin and its analogues, where it is believed that the small, neutral Pt(II) complexes traverse the cell membrane by passive diffusion.[5,6] However, some studies have indicated that many cationic metal complexes are taken up and retained within cells as a result of diffusion or by other uptake mechanisms.[4,7,8] It has been observed that increasing the lipophilicity of ancillary ligands can increase the movement of a charged metal complex into a cell by passive diffusion.[4,9,10] One particular case study is that of Puckett and Barton, who investigated the uptake into HeLa cells of luminescent dicationic ruthenium(II) complexes containing dipyridophenazine (Figure 5.1).[4] [*]

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[*] HeLa cells are a human cell line derived from cervical cancer cells, and are often used in scientific research.

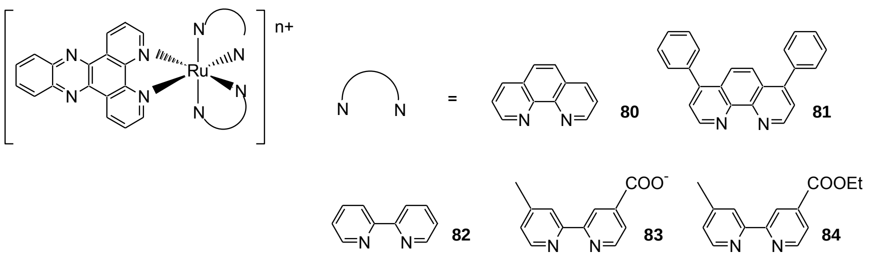


Figure 5.1 Ru(II) complexes in cell uptake study

Luminescence experiments showed significant uptake of the highly lipophilic **81** even at low concentrations. There was some uptake of **80**, **82** and **84**, but less for the much more hydrophilic **83** despite its overall neutral charge. Another observation is that smaller and more flexible ligands also facilitate passive diffusion.[8]

Therefore it cannot be assumed that these complexes will experience poor cellular uptake due to their positive charges. The hydrophobic ligands (diimines, COD, phosphines) and small flexible ligands (chelating aliphatic ligands) may help facilitate passive diffusion. In addition, there may be other modes of transport across the cell membrane. Organic cation transporters situated within the membrane are believed to play a role in the transport of some platinum-based drugs.[11,12] Self-assisted membrane transport is also possible, where metal complexes can bind to the plasma membrane, affecting the physical properties of the membrane and increasing its permeability.[5,13] There are thus a number of potential modes of uptake that might be available to the compounds from this study.

A second issue is the stability of the drug. The integrity of the complexes under possibly harsh biological conditions cannot be confirmed. As in the case of any metal-containing compound, they could be prone to processes such as ligand dissociation, ligand exchange, oxidative reactions and others. Still, it is possible and is to be hoped that these complexes remain intact under conditions of biological testing. The fact that most of the ligands are strongly-bound chelating ligands leads to the possibility that ligand dissociation and exchange, at least, are not likely. In any event, the results of anti-malarial testing of these complexes may provide some clues as to their behaviour *in vitro*.

5.2 Biological testing: Overview of results

The β-haematin inhibition activity of each ligand and complex was determined by physiochemical means, using a procedure reported by Egan *et al.*[14] Few of the compounds showed any inhibition, thus β-haematin inhibition IC_{50} values have not been reported here except in the case of the palladium phosphine complexes, which were found to exhibit this activity (Table 5.4).

The compounds were assessed for their *in vitro* anti-malarial activity against a chloroquine-sensitive strain of malaria parasite *Plasmodium falciparum*. These results are shown in Tables 5.1 – 5.4. Some of the more active compounds were tested against the chloroquine-resistant Dd2 strain in order to determine whether there was any cross-resistance. Selected compounds were also tested against human oesophageal cancer cell line WHCO1 in order to establish any possible relationship between anti-malarial activity and general cytotoxicity.

A brief account of the more general points regarding activity against the CQS malaria strain is given here; the results and trends are discussed in more detail in section 5.3.

Table 5.1 *In vitro* anti-malarial activity of diimine ligands against chloroquine-sensitive D10 strain of *P. falciparum*

Entry	**Ligand**	***In vitro* IC_{50} (μM)**
1	4-phenylpyridine	45 ± 6
2	Benzo(h)quinoline	28 ± 7
3	2,2’-bipyridyl	33 ± 14
4	4,4’-dimethyl-2,2’-bipyridyl	20 ± 6
5	4,4’-^{t}Butyl-2,2’-bipyridyl	9.8 ± 0.8
6	1,10-phenathroline	1.6 ± 0.1
7	5-methyl-1,10-phenanthroline	0.51 ± 0.05
8	5-chloro-1,10-phenanthroline	3.5 ± 0.1
9	chloroquine	0.04 ± 0.01

The $[Cp^*M(N\text{-}N)Cl]PF_6$ compounds (M = Rh, Ir) showed no anti-malarial activity whatsoever. Of all the different complexes synthesized these were the only ones that possess pseudo-octahedral rather than square planar geometry. This may be a factor contributing to their poor activity, if the mechanism of action for metal complexes is affected by the geometry of the drug compound.

Table 5.2. *In vitro* anti-malarial activity of rhodium diimine cyclooctadiene complexes against chloroquine-sensitive D10 strain of *P. falciparum*

Entry	Complex no.	Imine ligand	Charge	Counterion	*In vitro* IC_{50} (μM)
1	**51**	4-phenylpyridine	0	-	32 ± 4
2	**38**	Bipy	+1	PF_6^-	11 ± 1
3	**47**	Bipy	+1	BPh_4^-	> 15
4	**45**	4,4-diMebipy	+1	PF_6^-	15 ± 2
5	**46**	4,4-di^{t}Bubipy	+1	PF_6^-	1.3 ± 0.5
6	**52**	Benzo(h)quinoline	0	-	13 ± 1
7	**39**	Phen	+1	PF_6^-	1.7 ± 0.3
8	**40**	Me-phen	+1	PF_6^-	1.56 ± 0.04
9	**48**	Me-phen	+1	BPh_4^-	0.9 ± 0.2
10	**41**	NH_2-phen	+1	PF_6^-	2.6 ± 0.3
11	**49**	NH_2-phen	+1	BPh_4^-	0.6 ± 0.2
12	**42**	TM-phen	+1	PF_6^-	0.22 ± 0.02
13	**43**	Cl-phen	+1	PF_6^-	2.0 ± 0.3
14	**50**	Cl-phen	+1	BPh_4^-	2.2 ± 0.4
15	**44**	Cl_2-phen	+1	PF_6^-	3.1 ± 0.2

The other ligands and compounds show reasonable anti-plasmodial activity with IC_{50} values of between 0.22 and 45 μM, many falling in the region of 1.5 – 3 μM. In general, those compounds with IC_{50} values less than 1 μM would be of most interest, as showing good biological activity. The most active compounds overall are the ligand 5-methyl-1,10-phenanthroline and rhodium(I) complexes **42** and **49**, with IC_{50}

values of 0.51, 0.22 and 0.62 μM respectively. None of the compounds show values close to that of chloroquine, which has an IC_{50} of 0.04 μM (Table 5.1, entry 9).

Table 5.3 *In vitro* anti-malarial activity of palladium chelate complexes against chloroquine-sensitive D10 strain of *P. falciparum*

Entry	Complex no.	Imine ligand	Ancillary ligand	Charge	*In vitro* IC_{50} (μM)
1	**63**	Bipy	EG	0	9.6 ± 0.3
2	**64**	Phen	EG	0	2.3 ± 0.3
3	**65**	Bipy	EA	+1	13 ± 2
4	**66**	Phen	EA	+1	2.3 ± 0.2
5	**71**	Bipy	en	+2	12 ± 2
6	**72**	diMebipy	en	+2	1.8 ± 0.3
7	**67**	Phen	en	+2	1.7 ± 0.2
8	**69**	Me-phen	en	+2	0.89 ± 0.01
9	**68**	NH_2-phen	en	+2	2.2 ± 0.8
10	**70**	Cl-phen	en	+2	1.5 ± 0.1

Table 5.4 *In vitro* anti-malarial activity of palladium chelate complexes against chloroquine-sensitive D10 strain *P. falciparum*

Entry	Complex no.	Diimine ligand	Phosphine	β-haematin IC_{50} (eq.)	*In vitro* IC_{50} (μM)
1	**73**	Bipy	PPh_3	1.7	1.7 ± 0.3
2	**74**	Phen	PPh_3	1.3	1.0 ± 0.2
3	**78**	Phen	PTA	1.1 ± 0.3	1.0 ± 0.1
4	**75**	Me-phen	PPh_3	Nd	2.1 ± 0.6
5	**76**	NH_2-phen	PPh_3	No inhibition	2.4 ± 0.2
6	**77**	Cl-phen	PPh_3	0.21 ± 0.04	1.1 ± 0.5

The palladium phosphine complexes are the only compounds from this study that inhibit β-haematin formation (Table 5.4). An interesting observation is that the 5-

chloro-phenanthroline complex **77** shows by far the highest activity. Free 5-chloro-phenanthroline itself is also the only ligand that shows good β-haematin inhibition, with an IC_{50} of 2.0 ± 0.9 equivalents (compared to chloroquine with an IC_{50} of 1.9 ± 0.3 equiv.).[14] As mentioned in chapter 3, it would be expected that the ligand with the most electron-withdrawing substituent would form stronger π-π interactions with haematin in solution, and thus better inhibit the formation of β-haematin. However, it does not appear that this enhanced inhibition ability translates into better *in vitro* anti-malarial activity, as the IC_{50} value of **77** is about the same as those of the other phosphine complexes. This, and the fact that almost none of the other compounds show significant β-haematin inhibitory activity indicates that the anti-malarial activity that is observed is not due to β-haematin inhibition, but to some other mechanism of action.

5.3 Trends in biological activity: anti-malarial activity against the chloroquine-senstive strain of **P. falciparum**

The aim of this project was to determine the effect of different parameters, including metal effects, charge on complex and counterion effects, on anti-malarial activity. One way of doing this is to look at a specific example of a diimine ligand and to track the anti-malarial activity from the free ligand to the different metal-complexed forms.

If one considers 1,10-phenanthroline as a model, it can be seen that there is no substantial change in the IC_{50} values of the free ligand compared to either the rhodium- or palladium-complexed forms (Figure 5.2). There is only a 2-fold difference between the most active and least active compounds, and standard deviations associated with these measurements make the difference still less significant. Whether the phenanthroline is bound to rhodium or palladium, therefore, appears not to affect anti-malarial activity. This opens up the possibility that the ligand dissociates from the metal centre under biological conditions, and that the ligand itself is then the active component in biological activity. For the reasons stated previously, however, this is not necessarily the case.

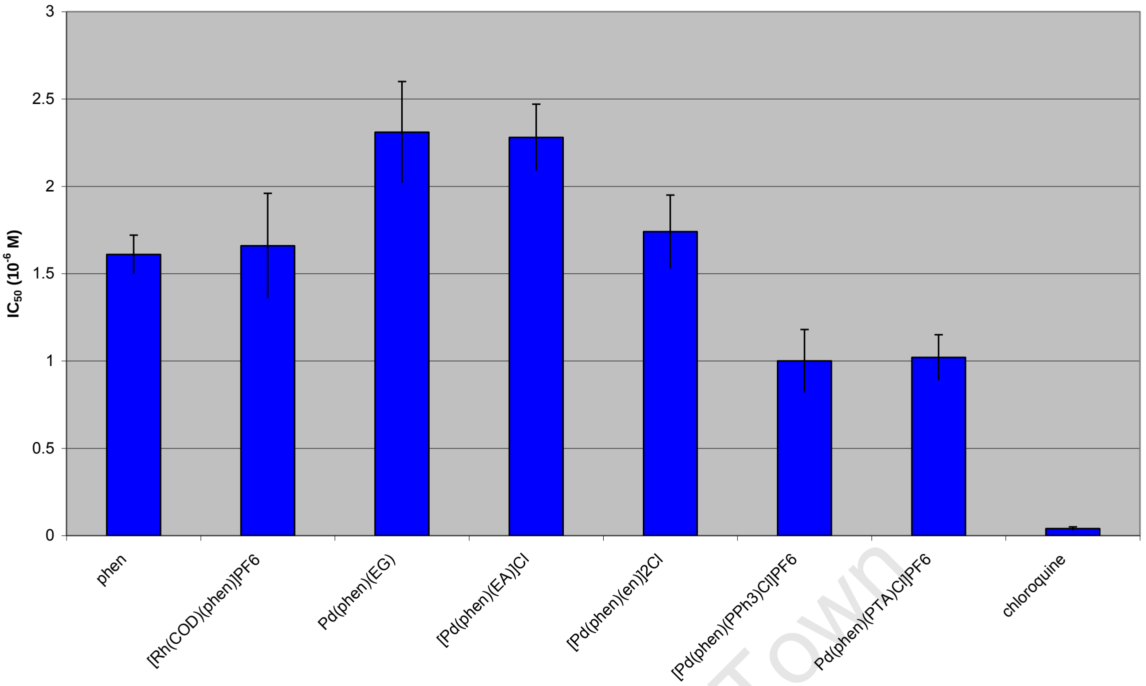
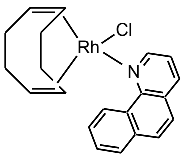


Figure 5.2 *In vitro* anti-malarial activity of 1,10-phenanthroline and its metal complexes against a chloroquine-sensitive D10 *P. falciparum*

There also does not appear to be any effect imposed by the charge on the complex. The IC$_{50}$ values of the neutral, monocationic and dicationic palladium chelate complexes are very similar. Statistical analysis of the results (two-tailed *t*-tests) reveals that there is no significant difference between these three mean IC$_{50}$ values at a 95 % probability level. There *is* a marked difference in the activities of the chemically similar rhodium(I) neutral and cationic complexes (Figure 5.3, Table 5.2, entries 6 and 7), but this is probably due more to the effect of the (di)imine ligands themselves, where the monoimine compound benzo(h)quinoline shows poor anti-malarial activity compared to the diimine compound 1,10-phenanthroline (Table 5.1, entries 2 and 6).



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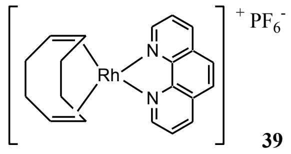

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Figure 5.3 Neutral and cationic Rh(I) complexes containing similar imine ligands

Therefore the anti-malarial activity in this case seems to be due primarily to the activity of the phenanthroline ligand. The anti-cancer testing shows that the ligand

and its complex **78**, [Pd(phen)(PTA)Cl]PF_6, have similar cytotoxicity, with IC_{50} values of 4.94 and 2.68 μM respectively against the WHCO1 cell line (Table 5.5, entries 2 and 9). Since the anti-malarial activities of the two compounds are also quite similar, this is an indication that cytotoxicity may be the mechanism of anti-malarial action. A compound that is generally cytotoxic will act against all types of cells, both human and malaria. In fact, all the compounds on which anti-cancer testing was done show poor selectivity for malaria (Table 5.5), further supporting this argument. The platinum phenanthroline complexes reported by Egan *et al.* were tested against Chinese hamster cell lines, and showed selectivity indices for malaria of above 100, confirming that those complexes are strongly selective for malaria over mammalian cells.[15] All of the compounds in this study have selectivity indices of only 2 - 5.

Table 5.5 Biological activity of diimine compounds against D10 *P. falciparum* and WHCO1 human oesophageal cancer line

Entry	**Compound**	***In vitro* IC_{50} (μM) D10**	***In vitro* IC_{50} (μM) WHCO1**	**95 % confidence interval (μM) WHCO1**	**Selectivity index***
1	2,2'-bipyridyl	33 ± 14	No activity	-	-
2	1,10-phenanthroline	1.6 ± 0.1	4.9	3.7 – 6.6	3.1
3	5-methyl-1,10-phen	0.51 ± 0.05	2.5	1.9 – 3.4	4.9
4	5-chloro-1,10-phen	3.5 ± 0.1	7.5	6.2 – 8.9	2.1
5	**41**	2.6 ± 0.3	4.6	4.0 – 5.2	1.8
6	**44**	3.1 ± 0.2	8.3	7.6 – 8.9	2.7
7	**49**	0.6 ± 0.2	2.8	2.2 – 3.5	4.6
8	**78**	1.0 ± 0.1	2.7	2.2 – 3.3	2.7

* Selectivity index (SI) = IC_{50} (WHCO1)/ IC_{50} (D10)

The suggestion that the ligand is the defining component in anti-malarial activity is reinforced when considering the compounds of 5-methyl-1,10-phenanthroline (Figure 5.4). Again, there is no significant variation between the activity of free Me-phen and its complexes.

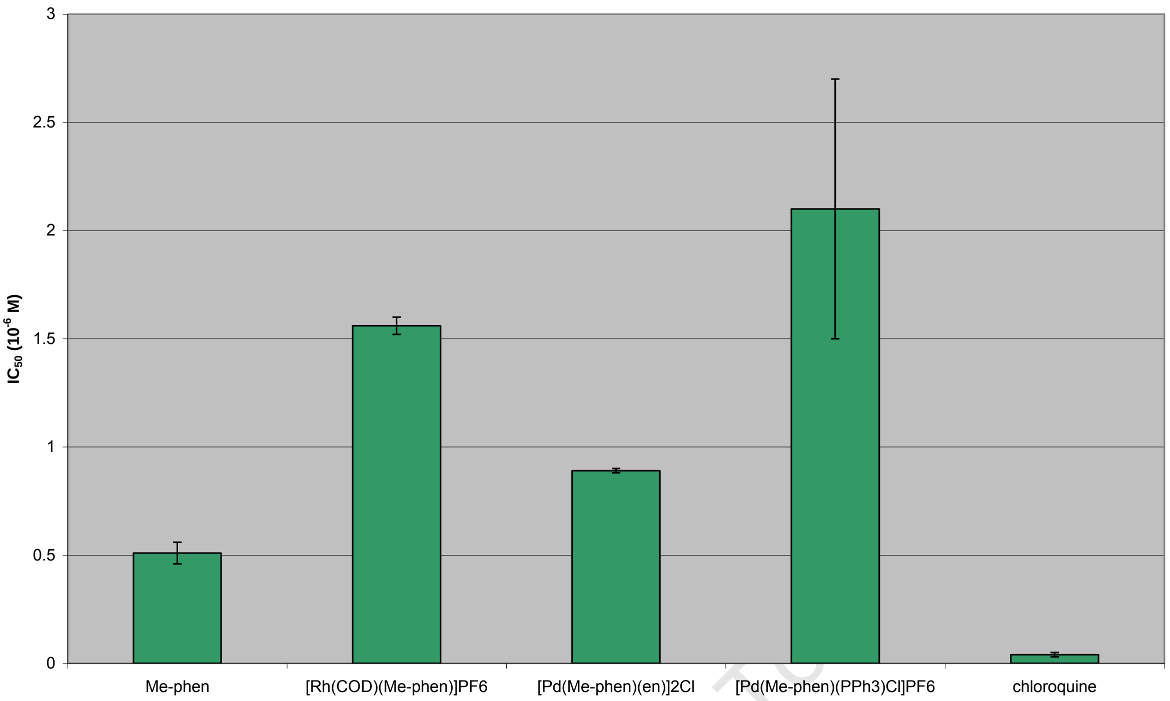


Figure 5.4 ***In vitro*** **anti-malarial activity of 5-methyl-1,10-phenanthroline and its metal complexes against a chloroquine-sensitive D10** ***P. falciparum***

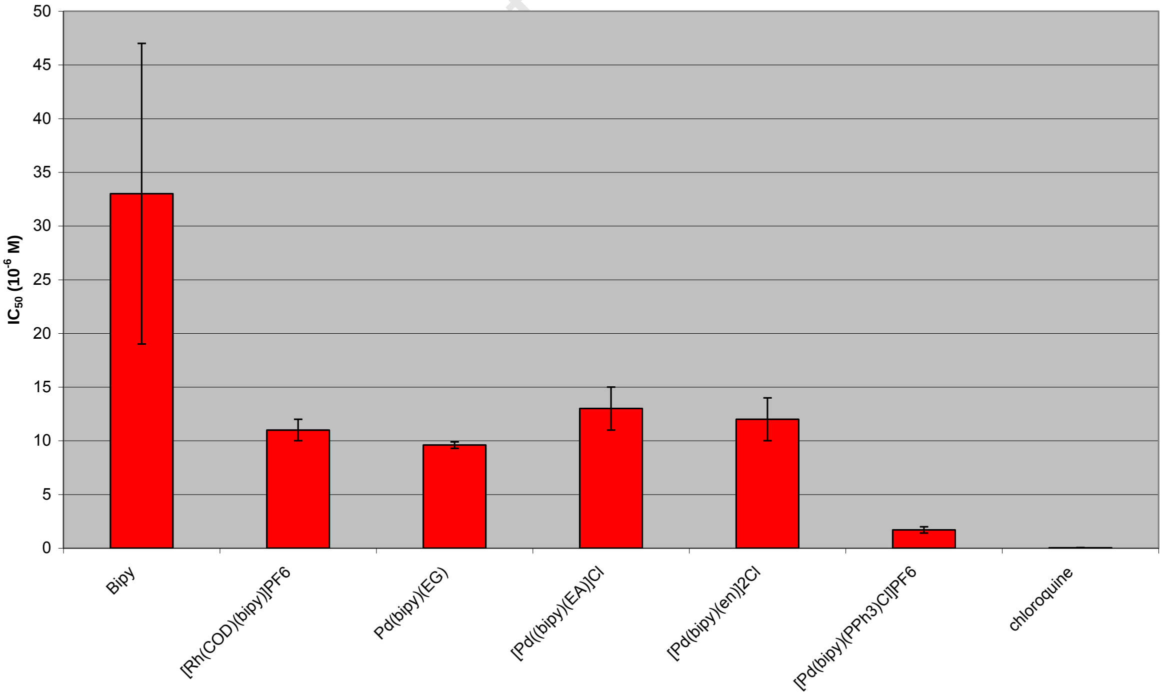


Figure 5.5 ***In vitro*** **anti-malarial activity of 2,2-bipyridyl complexes against a chloroquine-sensitive D10 strain of** ***P. falciparum***

A similar trend is observed in the case of 2,2'-bipyridyl, where the IC_{50} values of the complexes are nearly unchanged with regard to metal centre or charge on the complex, as seen in Figure 5.5 (Note that there is a question as to the accuracy of the cationic triphenylphosphine complex; its IC_{50} is 5 times lower than all other bipy complexes). However, in this case, there is a noticeable improvement of biological activity upon coordination of the 2,2'-bipyridyl to a metal centre, and this is observed for the alkyl-substituted bipy complexes as well. One possible reason for this is compound geometry.

Phenanthroline ligands, containing three fused rings, are planar both in free and complexed form. Bipyridyl ligands, on the other hand, may rotate freely around the C-C single bond when in free form, and are therefore not planar. However, when a bipyridyl ligand coordinates to a square planar metal centre, it is forced into a planar mode. This enforced change may contribute to an improvement in biological activity, which would seem to suggest that geometry plays a role in biological action.

One last factor to be considered is the counterion. Table 5.2 gives the IC_{50} values of several sets of rhodium(I) complexes (where ligand = bipy, Me-phen, NH_2-phen or Cl-phen) containing either the hexafluorophosphate or tetraphenylborate counterions. There is no clear indication that one or the other counterion is superior to the other. In the case of the bipyridyl complex (Table 5.2, entries 2 and 3) there is a decrease in anti-malarial activity in moving from the PF_6^- to the BPh_4^- complex; this effect is reversed for the NH_2-phen compounds (Table 5.2, entries 10 and 11). The IC_{50} values of the Cl-phen complexes are nearly identical. There is thus no evidence that the nature of the counterion affects activity in any way. This statement is further supported by the fact that $NaBPh_4$ shows no anti-malarial activity at all (the salt $NaPF_6$ was not tested due to its extremely hygroscopic nature).

It can be concluded that the imine ligand is the main factor influencing anti-malarial activity in these complexes, and that the metal centre, charge on complex and nature of the counterion do not play a major role in biological activity in this case.

5.4 Anti-malarial action against chloroquine-resistant **P. falciparum**

A few compounds, including some of the more active ones, were tested for anti-plasmodial activity against the CQR Dd2 strain of the parasite in order to establish whether there is any cross-resistance with chloroquine. The results are shown in Table 5.6, along with resistance indices (RI) for each compound.

Table 5.6 Anti-malarial activity of compounds against CQR Dd2 strain of *P. falciparum*

Entry	**Compound**	***In vitro* IC$_{50}$ (µM) D10**	***In vitro* IC$_{50}$ (µM) Dd2**	**Resistance index***
1	1,10-phenanthroline	1.6 ± 0.1	2.4 ± 0.3	1.5
2	5-methyl-1,10-phen	0.51 ± 0.05	2.4 ± 0.4	4.7
3	5-chloro-1,10-phen	3.5 ± 0.1	5 ± 1	1.4
4	**48**	0.9 ± 0.2	7 ± 1	7.8
5	**49**	0.6 ± 0.2	2.15 ± 0.04	3.6
6	**73**	1.7 ± 0.3	10.1 ± 0.5	5.9
7	**75**	2.1 ± 0.6	1.5 ± 0.2	0.7
8	chloroquine	0.04 ± 0.01	0.57 ± 0.04	14.3

* Resistance index (RI) = 1C$_{50}$ (CQR)/IC$_{50}$ (CQS)

The ligands 1,10-phenanthroline and 5-chloro-1,10-phenanthroline do not show significant cross-resistance with chloroquine, having resistance indices of only 1.5 and 1.4 respectively. However, 5-methyl-1,10-phenanthroline does display some cross-resistance (Table 5.6, entry 3).

Rhodium(I) complexes containing Me-phen and NH$_2$-phen (Table 5.6, entries 4 and 5), display quite strong and moderate cross-resistance respectively. In the case of Me-phen, this is interesting because this was the only ligand tested that also shows a fairly high RI value. On the other hand, the Me-phen palladium complex, **75** (Table 5.6, entry 5), seems to be slightly more active in the resistant stain, although this is probably not statistically significant if one considers the standard deviations associated with these IC_{50} values.

The bipy palladium(II) complex **73** has a fairly high RI value of 5.9. However, the CQS IC_{50} is questionable (as previously mentioned), and this RI value might not be accurate.

5.5 Possible mechanism of biological action

Now that it has been established that the imine ligand is probably the main contributing factor to anti-malarial activity it is important to look more closely at the compounds and how they might act in biological systems, and also how changes in the ligands themselves lead to changes in biological activity.

Firstly, from the results discussed in section 5.2, it seems that compound-haematin association and subsequent β-haematin inhibition do not play a role in the anti-malarial activity of these compounds. The hypothesis put forward at the start of this project, that planar π-interactions and cation-π interactions between the compound and haematin are important is, then, incorrect. Secondly, it appears that cytotoxicity is the main mechanism leading to anti-malarial action. Thirdly, it was observed that planar (phenanthroline) ligands and their various planar complexes have similar activity; however the non-planar (bipyridyl) diimine ligands were less active in free form than when forced into planarity by bidentate coordination to a metal centre. At first glance it therefore seems feasible that a mechanism of action in place here is that of cytotoxic activity via DNA intercalation by planar molecules.

Cytotoxicity by drug molecules can be induced in various ways: disruption of enzymes or proteins, DNA binding and damage (the mode of action of metal anti-cancer drug cis-platin) and DNA intercalation. Intercalation refers to the reversible insertion of small, planar aromatic molecules between adjacent base pairs of a nucleic acid.[16,17] These molecules can associate with the nucleobases through various interactions, including aromatic π-stacking. If the molecule carries a positive charge, the association may be intensified by an electrostatic attraction to the negatively charged phosphate groups of the DNA backbone.[16,17] This induces conformational changes in the DNA strand, resulting in DNA damage and consequent cell death. Some square planar metal complexes, notably platinum(II) and palladium(II) complexes containing phenanthroline or other aromatic ligands, have been found to intercalate with DNA.[16-18]

Some of the biological data shown here would seem to support the proposal that the compounds in this study also may intercalate with DNA. In the first place all the planar compounds and complexes show moderate anti-malarial activity and cytotoxic activity, whereas the non-planar compounds (bipy free ligands and pseudo-octahedral Rh(III) complexes) show low or no activity. However, when a bipy ligand is constrained into a planar conformation by its bidentate coordination to palladium or rhodium it shows a marked improvement in activity. This is consistent with results from research that has shown that $[(bipy)Pt(ED)]^{2+}$ intercalates but $[(py)_2Pt(ED)]^{2+}$ (py = pyridyl) does not, due probably to the inability of the two separate py rings to rotate into the metal coordination plane.[19,20]

Secondly, in all cases the 2,2'-bipyridyl compounds are significantly less active than the corresponding 1,10-phenanthroline derivatives, even when coordinated to a metal centre. Planar π-stacking requires the overlap of aromatic rings; larger ring systems will have a greater area of overlap and thus associate more strongly. Literature evidence for this includes studies on the intercalation ability of bisquinoline, phenanthroline and bipyridyl metal complexes, where it has been proven that a larger ring size leads to stronger binding.[16,17] It is interesting that π-stacking was observed in the crystal structures of the phenanthroline complexes (chapters 3 and 4) but not in the crystal structure of the bipyridyl complex **73** (chapter 4).

Of course, it may be possible that the metal complexes act both by intercalation and by covalently binding to DNA as in the case of cisplatin. Still, the fact that the metal-free ligands display cytotoxicity values reasonably close to those of the metal complexes implies that intercalation would be the preferred mode of binding. In addition, DNA binding requires the presence of a labile ligand that can dissociate, leaving a vacant site for the metal centre to bind to the nucleic acid. The Rh(I) complexes, with their very strongly bound COD ligands and chelating diimines are not likely to undergo ligand dissociation. The palladium chelate complexes should also be fairly stable and inert in solution, although this needs to be verified. The neutral complexes **63** and **64** in particular, with their weakly-bound oxygen donors, may not remain intact under aqueous conditions. There may also be some question as to the integrity of the palladium phosphine complexes, which contain a chloride ligand that is potentially labile given the right conditions.

One result that is perhaps unexpected (if DNA intercalation was the mode of action in this case) is that the anti-malarial (and by inference, cytotoxic) activities of the neutral, monocationic and dicationic palladium chelate complexes are all comparable. As mentioned before, though, a compound bearing a positive charge should experience stronger intercalation due to the added effect of electrostatic attraction. There may be a few explanations for this. One possible scenario is the dissociation of the ethylene glycolate ligand from the neutral complex, resulting in aquation at the newly-freed coordination sites and leading to a cationic species that ultimately is the biologically active species. However, more research would have to be done in order to assess the integrity of the complexes under these conditions.

Another apparent inconsistency is the fact that none of the rhodium(III) or iridium(III) complexes showed any biological activity. Even though the complexes themselves are not planar, the presumed intercalating moiety is planar in itself, and would be presumed to be able to protrude from the metal centre and insert itself between DNA base pairs. Certainly, other octahedral Rh(III) complexes have proven to be efficient intercalators.[21,22] It may be that in the case of the Cp* complexes, the steric bulk of the pentamethylcyclopentadienyl ring simply prevents the complex from the approaching the large DNA molecule closely enough for non-covalent interactions to be established.

In conclusion, a number of circumstantial pieces of evidence for an intercalating mechanism of action have been presented here. Taking into account the number of literature reports of palladium and platinum complexes that intercalate DNA, it is very possible that the complexes in this study intercalate with and disrupt DNA, leading to cell death. Importantly however, it must be noted that there are examples of 1,10-phenanthroline metal complexes that were found *not* to intercalate, although exerting cytotoxic effect against cancer cells by some other mechanism.[23] Therefore, more research must be done in order both to verify this assumption, and to determine whether other mechanisms of action may be at play.

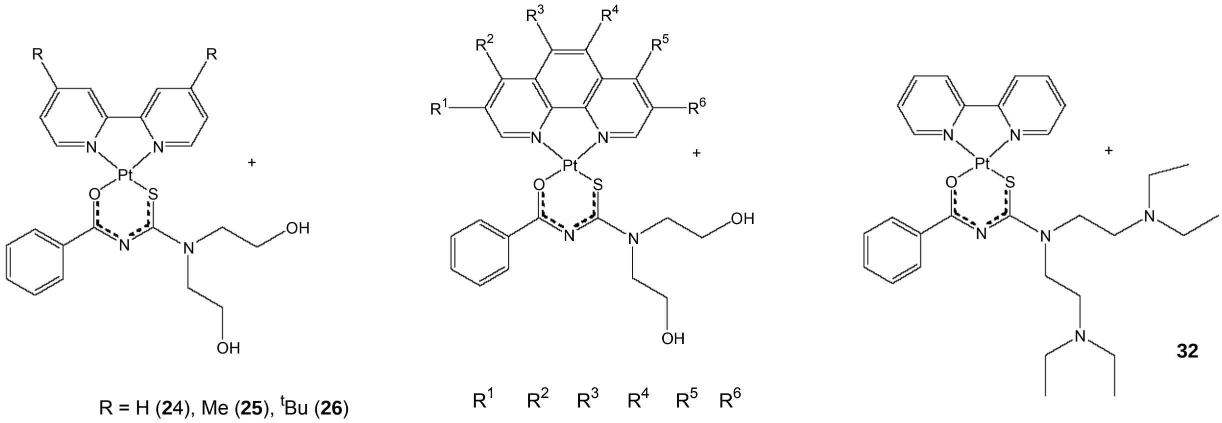
5.6 Comparison of complexes *38 – 79* with other transition metal diimine complexes

The platinum diimine benzoylthiourea complexes reported by Egan *et al.* (discussed in section 2.7.2.2) [15] showed good anti-malarial activity *in vitro* and inspired the more detailed investigation of transition metal diimine complexes that formed the basis of this project.

In general the platinum complexes (Figure 5.6) are quite active against *P. falciparum*, displaying IC_{50} values of 0.1 – 0.6 μM. Two complexes, **31** and **32**, have relatively high IC_{50}s of 3 and 2 μM respectively, but for the most part the platinum compounds are more active than the rhodium and palladium compounds, with the best ones displaying selective activity relative to mammalian cells. Despite the results of the current study suggesting that the identity of the metal centre and ancillary ligand play little role in biological activity, it would appear that the thiourea ligands may be different. Even though the benzoylthiourea ligands from this study were not tested as free ligands, it is possible that they themselves possess biological activity. This is particularly likely in view of the fact that a number of acylthiourea compounds and their metal complexes display good anti-bacterial, anti-viral, anti-fungal and anti-cancer activity.[24-30]

The most active platinum complex was the di-^{t}butyl-2,2'-bipyridyl compound **26**. This may be due to its higher lipophilicity which would facilitate uptake into the cell. On the other hand, a tetramethyl-1,10-phenanthroline platinum complex was less active than many of the others containing less lipophilic ligands. This is in contrast to the results obtained from the current study, where the most active compound was a rhodium(I) complex of the tetra-alkylated phenanthroline ligand.

Another inconsistency is that unsubstituted bipy platinum complexes are almost as efficient as the di-^{t}butyl-2,2'-bipyridyl compound, and are as efficient as (or more so than) the corresponding phenanthroline complexes. Also, unlike the rhodium and palladium complexes, most of the platinum complexes showed some β-haematin inhibition activity, but showed weak cytotoxicity towards mammalian cells.



R = H (**24**), Me (**25**), ^{t}Bu (**26**)

	R^1	R^2	R^3	R^4	R^5	R^6
27	H	Me	H	H	H	H
28	H	H	Me	H	H	H
29	Me	Me	H	H	Me	Me
30	H	H	Cl	H	H	H
31	H	H	NO_2	H	H	H

Figure 5.6 Platinum diimine complexes

It is difficult to explain the conflicting results from the two studies, more so because only a few platinum benzoylthiourea complexes were examined, making it difficult to establish overall trends. It is possible that the modes of action are different. It has been proposed that rhodium and palladium complexes act against *P. falciparum* by cytotoxicity due to DNA intercalation. The structurally similar platinum complexes would be expected to intercalate approximately as efficiently, unless there is perhaps an additional, competing mechanism of action such as haemozoin inhibition.

A second possibility is that the stability of the metal complex is important, where Pt(II) complexes are known to be particularly stable under biological conditions compared to many other metals. The third and most likely scenario (as discussed previously) is that the thiourea ligands themselves are biologically active and contribute to the activity of the entire complex.

It would be necessary to synthesize and evaluate a wider range of platinum complexes in order to determine the validity of these hypotheses. It would be especially useful to compare exactly analogous platinum and palladium complexes containing the same ancillary ligands (for example, to prepare palladium(II) benzoylthiourea complexes);

this will help elucidate any potential effects of the ancillary ligand on activity. Cytotoxicity studies should also be carried out using the same cell lines. In addition, further tests such as DNA binding should be done in order to ascertain the mechanisms of action of the different sets of complexes.

5.7 Metal complexes as anti-cancer agents

Although the ligands and rhodium and palladium complexes are not active enough against malaria to warrant further study, they and similar compounds could be of interest in the field of anti-cancer research. There are countless journal articles describing the investigation of different metal complexes for potential cytotoxic activity.[23,31-38] and a very recent review by Gasser *et al*. highlights the important advances made in organometallic anti-cancer research in the past decade.[39] Many complexes act against cancer cells via different mechanisms, sometimes with activity comparable to or better than cisplatin and other commercial drugs. IC_{50} values in the range of 1 – 10 μM are common, which is the same range as for the complexes from this study.

In this study it was shown that there was little difference in the anti-cancer activity of the free phenanthroline ligands and the metal complexes. There are several such findings, involving the activity of phenanthroline-type compounds and their metal complexes, in the literature.[33,36] This then begs the question of why one would even consider investigating the metal complex for anti-cancer activity when the free ligand might do just as well.

In the first place, it cannot be assumed that cytotoxicity will not be enhanced by coordination to a metal centre until a new ligand and its complex are tested. This study showed a noticeable improvement in cytotoxicity of the bipyridyl ligand when complexed to rhodium or palladium, although this *was* due more to geometric constraint rather than to metal effect. Secondly, metal compounds may display additional modes of action such as covalent binding to DNA, or photoinduced DNA cleavage in photodynamic therapy.[37] Metallodrugs may also have photophysical or electrochemical properties that allow their use as probes for studying molecules or processes at the cellular level.[22]

Metal complexes are easily modified by manipulation of ligands, charge or oxidation state to suit a certain purpose. For example, they can be fine-tuned for properties like water-solubility, lipophilicity or steric or electronic properties.

Another point is that the selectivity of an anti-cancer agent is very important. Drug compounds must be proven to act specifically against tumour cells rather than healthy human cells. It could well be that the metal complexes are more selective than the ligands for cancer. It would be interesting to determine whether the compounds from this study are indeed highly specific for cancerous cells.

Therefore, there is much scope for the discovery of new metal-based compounds in biological research, both as drugs for various diseases and as probes for studying them. For now, there have been few real applications in the field of malaria research. Nevertheless, it is certain that the keen interest in metal complexes in all areas of medicine will continue, and will produce some great successes in the future.

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Chapter 6

Conclusions and future work

6.1 Conclusions

During this project new transition metal diimine complexes were successfully prepared, isolated and characterized. The metal centre (Rh(I), Rh(III), Ir(III) and Pd(II)), charge (0, +1, +2) and identity of the ligands were varied to produce a wide range of different complexes. In general the synthetic procedures are fairly straightforward and the results highly reproducible. There were, however, a number of difficulties encountered in the synthesis of some of the complexes.

One of the original aims was the preparation of Rh(I) complexes of the type [Rh(N-N)(PR_3)Cl] and $[Rh(N\text{-}N)(PR_3)_2]^+$. Various attempts to prepare these complexes, using several different synthetic methods, were unsuccessful and led only to decomposition or undesired products. These results, together with the absence of any structures of this type in the literature, lead to the conclusion that they are simply not stable and can not be isolated.

A second difficulty concerned the preparation of $[Ir(COD)(N\text{-}N)]^+$ complexes. Unlike the rhodium analogues, the iridium(I) compounds could not be isolated as air-stable compounds. This is probably a result of the higher reactivity of iridium with small molecules under mild conditions. It should have been possible to prepare and isolate $[Ir(COD)(N\text{-}N)]^+$ complexes, as these have previously been reported in the literature.[1] However, their high reactivity (and therefore lower stability) would immediately preclude their usefulness in a biological study, where an important property for any potential drug compound is its stability under biological conditions. Therefore, the fact that these complexes were not included in this study should not be seen as a major disadvantage.

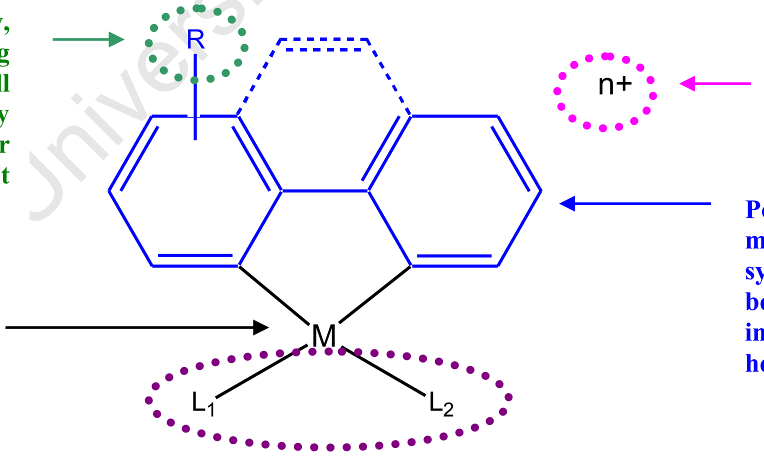
None of the free diimine ligands or their complexes show strong β-haematin inhibition activity, with the exception of the Pd(II) phosphine complexes. It may be that the presence of the phosphine enhances β-haematin inhibition in some way, either in itself, or by imparting certain properties to the complex as a whole. The overall requirements for a compound to exhibit β-haematin inhibition activity are not yet well-understood, and therefore it is difficult to speculate as to why the phosphine complexes alone show activity. Phosphines are widely used as ligands in transition metal chemistry due to the ease with which steric and electronic properties can be manipulated.[2] In the case of the palladium complexes it may be that the presumed larger steric bulk of the phosphines relative to the simple chelate ligands contributes to stronger β-haematin inhibition. Alternatively, it may be simply that the phosphine stabilizes the whole complex in such a way as to facilitate association of the complex with β-haematin. It is well-known that phosphine ligands stabilize many transition metals in a variety of oxidation states,[2] and, being relatively soft donor molecules,[2b] should form particularly stable bonds with the soft Pd(II) centre.

Notwithstanding the poor β-haematin inhibition activity, most of the ligands and complexes have some *in vitro* activity against chloroquine-sensitive *Plasmodium falciparum*. The phenanthroline compounds are more active than the bipyridyl compounds; complexes containing alkylated diimines are more active than the others. These points may be kept in mind during possible future studies on other such complexes for biological application. However all the complexes from this study are significantly less efficient than chloroquine and other anti-malarial drugs which, together with the high cost of the platinum-group metals involved, rules out any potential use as anti-malarial agents.

An important finding is that the complexes are also less active than the series of cationic platinum diimine complexes on which this research project was based.[3] It has been shown that the identity of the metal centre has little effect on activity. Therefore it would appear that the benzoylthiourea ligands do in fact play a central role in the biological activity of these compounds. Interestingly, some acylthiourea ligands and their complexes have been found to possess anti-microbial properties.[4 - 10]

Of the seven complexes tested against chloroquine-resistant *P. falciparum* none show strong cross-resistance, and some show none at all. Unfortunately no definitive conclusions regarding resistance can be drawn from the relatively limited data set. However, if *in vitro* activity against CQR malaria can be obtained for all the complexes, further insight into the role of certain properties (eg. type of diimine ligand) in avoiding resistance might be gained.

Unfortunately, the anti-malarial action of the compounds in this study is apparently primarily a result of their general cytotoxicity against living cells. Eight compounds were tested against human oesophageal cancer cell line WHCO1 and all showed strong *in vitro* activity with IC_{50} values below 10 µM. Given the planar structure of the compounds, it may be expected that the cytotoxic effects are induced by DNA intercalation and consequent damage. DNA intercalation involves the association of planar rings by π-π stacking.[11,12] The crystal structures for some of the complexes do indeed show intermolecular π stacking. It may be expected that compounds containing electron-withdrawing groups would intercalate better and be more cytotoxic, as electron-withdrawing groups are believed to improve stacking. However in this case, the methyl- and ^{t}butyl-substituted diimine complexes are the most efficient, and this may be due to their increased lipophilicity which facilitates their uptake through the phospholipid cell membrane and toward the site of action. This highlights the importance of bioavailability and drug transport in these compounds. Figure 6.1 summarizes the structure-activity relationships for the metal diimine complexes.



Lipophilic substituents increase cytotoxicity, probably by increasing lipophilicity of overall complex and probably allow for better cellular uptake – an important feature

No apparent effect

Possible intercalating moiety; larger, π-ring systems will allow for better overlap and intercalating ability; hence cytotoxicity.

Does not appear to affect activity

Ancillary ligand does not affect activity of the complex *unless* it possesses intrinsic biological activity as in the case of the benzoylthiourea ligands

Figure 6.1 Structure-activity relationships for anti-malarial activity of transition metal diimine complexes (if anti-malarial activity is due to general cytotoxicity as proposed, then this set of structure-activity relationships apply to cytotoxicity as well)

6.2 Future work

The immediate work resulting from this study should include the following:

1. The testing of all synthesized complexes against CQR *P. falciparum*: It may be possible to observe some trends regarding cross-resistance, leading to insights into circumventing drug resistance in malaria.

2. In view of their cytotoxicity, all complexes should be tested against the human cancer cell line. In addition, the selectivity of the compounds for cancer cells over healthy human cells should be determined. These experiments will have an impact on the possible further investigation of these compounds for anti-cancer applications. DNA binding studies will also help determine the mode of action of the complexes, and confirm or disprove the theory of DNA intercalation. These may include DNA melting or viscosity experiments to determine interaction with DNA, and UV absorption spectra experiments to determine binding constants.

It has been inferred from this work that the benzoylthiourea ligand is important for anti-malarial activity in the previously reported Pt(II) complexes. Therefore later work on these complexes in the field of malaria should involve the use of these and other benzoylthiourea ligands. It would be of special interest to synthesize the exact palladium analogues of the platinum benzoylthiourea complexes reported by Egan *et al*.[3] In this way the hypothesis that the nature of metal centre is not particularly important for biological activity can be tested.

It would also be useful to develop some type of structure-activity relationships for the thiourea ligands themselves. There are now some ideas concerning structure-activity relationships for the diimine ligands, where a larger ring system and a more lipophilic ligand are advantageous. Similarly, the stability, lipophilicity, solubility, steric and electronic properties of thiourea ligands (and their metal complexes) can be fine-tuned to produce the best results for anti-malarial activity.

Lastly, other biologically active multidentate ligands, such as thiosemicarbazones, can potentially be used in place of the acylthiourea ligands. Again, the various properties of these compounds can be manipulated to improve biological activity.

Therefore, despite the somewhat disappointing anti-malarial activity of the current series of compounds, they have opened new avenues for the investigation and discovery of new metal diimine complexes with interesting biological activity in the fields of both malaria and cancer research.

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Chapter 7

Experimental Details

7.1 General considerations and instrumentation

All reactions were carried out in air unless otherwise stated. Solvents used were reagent grade and were not distilled prior to use unless otherwise stated. $RhCl_3$, $IrCl_3$ and $PdCl_2$ were obtained from Johnson Matthey. All other chemicals were purchased from Aldrich and used as received.

Melting points were recorded using a Kofler hot stage microscope (Reichert Thermovar). ^1H, ^{31}P and ^{13}C NMR spectra were recorded on a Varian Mercury-300 MHz (^1H: 300 MHz; ^{13}C: 75.5 MHz; ^{31}P: 121 MHz) or Varian Unity-400 MHz (^1H: 400 MHz; ^{13}C: 100.6 MHz) spectrometer and values reported relative to the internal standard tetramethylsilane (δ 0.00).

Elemental analyses were carried out on a Fisons EA 1108 CHNS Elemental Analyzer at the University of Cape Town. Mass spectral analyses were carried out at the University of Stellenbosch on a Waters Q-TOF Ultima API or Waters Quattro Micro API mass spectrometer and using the electrospray ionization technique. Conductivity in nitrobenzene (1 or 2 mM concentration) was measured using a Metrohm 660 conductometer.

7.2 X-ray structure determination

X-ray single crystal intensity data for complexes **48**, **54**, **67** and **73** were collected on a Nonius Kappa-CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å). 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.[1] An empirical absorption correction using the program SADABS [2] was applied.

Table 7.1 X-ray crystallographic data collection parameters for rhodium complexes

Complex	**48**	**54**
Empirical formula	$C_{45}H_{42}BN_2Rh$	$C_{23}H_{25}ClN_2RhPF_6$
Formula weight (g/mol)	724.53	612.78
Temperature	173(2) K	173(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Triclinic
Space group	P21/n	P-1
Unit cell dimensions:		
a (Å)	13.3485(2)	8.0073(2)
b (Å)	14.4283(4)	11.9166(4)
c (Å)	18.3977(5)	12.9209(3)
α (°)	90	85.460(2)
β (°)	105.012(2)	82.498(2)
γ (°)	90	77.8400(1)
Volume (Å^3)	3422.40(14)	1193.23(6)
Z	4	2
Calculated density (g/cm^3)		1.706
Absorption coefficient (mm^{-1})	0.535 mm	0.956
F(000)	1504	616
Crystal size (mm)	0.19 x 0.12 x 0.11 mm	0.22 x 0.15 x 0.12
Theta range for data collection	2.82 – 26.38 °	3.06 – 28.23
Limiting indices	-16<=h<=16 -18<=k<=18 -22<=l<=22	0<=h<=10 -15<=k<=15 -16<=l<=17
Reflections collected/ Unique	13702/6996 [R(int) = 0.0148]	5887/5887 [R(int) = 0.0000]
Completeness to theta	99.8 %	99.7 %
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.9435 and 0.9051	0.8939 and 0.8172
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	6996/0/443	5887/0/327
Goodness-of-fit on F^2	1.051	1.063
Final R indices [l>2σ(l)]	R1 = 0.0308, Wr2 = 0.0778	R1 = 0.0418, wR2 = 0.1088
R indices (all data)	R1 = 0.0436, Wr2 = 0.0844	R1 = 0.0521, wR2 = 01166
Extinction coefficient	None	0.0028
Largest diff. peak and hole	0.691 and -0.561e.A^{-3}	0.840 and -0.827e.A^{-3}

Table 7.2 X-ray crystallographic data collection parameters for palladium complexes

Complex	**67**	**73**	**79**
Empirical formula	$C_{14}H_{20}Cl_2N_4O_2Pd$	$C_{28}H_{23}ClF_6N_2P_2Pd$	$C_{50}H_{42}Cl_4F_{12}N_2P_4Pd$
Formula weight (g/mol)	454.64	705.27	1270.94
Temperature	173(2) K	173(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	P21/n	$P2_1/n$	P-1
Unit cell dimensions:			
a (Å)	a = 7.3231(2)	14.1147(2)	9.5225(7)
b (Å)	b = 15.5338(4)	9.3513(2)	16.5355(12)
c (Å)	c = 14.9922(3)	20.7817(5)	17.1565(12)
α (°)	90	90	99.6030(10)
β (°)	95.0980(10)	94.707(2)	98.434(2)
γ (°)	90	90	102.6290(10)
Volume ($Å^3$)	1698.70(7) $Å^3$	2733.74(10)	2551.6(3)
Z	4	4	2
Calculated density (g/cm^3)	1.774	1.714	1.654
Absorption coefficient (mm^{-1})	1.421 mm^{-1}	0.957	0.781
F(000)	912	1408	1276
Crystal size (mm)	0.13 x 0.09 x 0.06 mm	0.23 x 0.22 x 0.22	0.48 x 0.37 x 0.25
Theta range for data collection	3.00 – 26.37 °	1.97 – 26.38 °	2.23 – 30.54 °
Limiting indices	-9<=h<=9	-17<=h<=17	-13<=h<=13
	-19<=k<=19	-11<=k<=11	-23<=k<=23
	-18<=l<=18	-25<=l<=25	-24<=l<=24
Reflections collected/ Unique	6801/ 3467 [R(int) = 0.0151]	131603/5590 [R(int) = 0.0659]	68243/15553 [R(int) = 0.0210]
Completeness to theta	99.8 %	99.9 %	99.5 %
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.9196 and 0.8369	1.0000 and 0.8826	0.8274 and 0.7544
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	3467/ 10/ 241	5590/0/351	15553/0/667
Goodness-of-fit on F^2	1.108	1.056	1.056
Final R indices [$I>2\sigma(I)$]	R1 = 0.0254, wR2 = 0.0584	R1 = 0.0490, wR2 = 0.1251	R1 = 0.0451, wR2 = 0.1192
R indices (all data)	R1 = 0.0334, wR2 = 0.0619	R1 = 0.0623, wR2 = 0.1365	R1 = 0.0484, wR2 = 0.1218
Extinction coefficient	0.0014(3)	None	None
Largest diff. peak and hole	0.930 and -0.854 $e.A^{-3}$	2.383 and -1.624 $e.A^{-3}$	2.452 and -2.132 $e.A^{-3}$

The structure was solved by direct methods and refined employing full-matrix least-squares with the program SHELXL-97 [3] refining on F^2. Packing diagrams were produced using the program PovRay and graphic interface X-seed.[4] All non-hydrogen atoms were refined anisotropically. In most cases the hydrogen atoms were placed in idealized positions in a riding model with U_{iso} set at 1.2 or 1.5 times those of their parent atoms and fixed C-H bond lengths. In the case of hydrogen atoms on H_2O and $–NH_2$, these were located in electron-density maps and refined with simple bond length constraints.

X-ray single crystal intensity data for complex **79** were collected on a Bruker Kappa APEX II DUO diffractometer. Cell refinement and data reduction were carried out using the program SAINT.[5] In all other respects, the procedure for structure determination was the same as for **48**, **54**, **67** and **73** (above). The x-ray data collection parameters for all five complexes are listed in Tables 7.1 and 7.2.

7.3 Starting materials for synthesis of coordination complexes

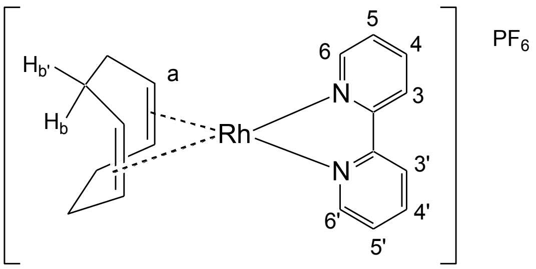
$[Rh(COD)Cl]_2$, $[Cp^*RhCl_2]_2$, $[Cp^*IrCl_2]_2$, and $Pd(COD)Cl_2$ were prepared from known literature procedures.[6-9] Pd(diimine)Cl_2 complexes were prepared from reaction of $Pd(COD)Cl_2$ with the appropriate diimine.

7.4 Synthesis of rhodium(I) diimine complexes

*7.4.1 General method for the preparation of **38 – 44***

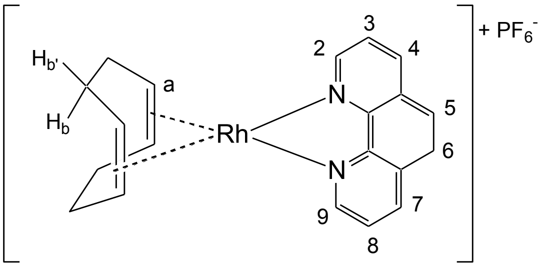
To a suspension of $[Rh(COD)Cl]_2$ in methanol was added 2 equivalents of the relevant diimine ligand. There was immediate formation of a red or orange solution. The reaction was stirred for 30 minutes to ensure completion. Excess aqueous sodium hexafluorophosphate, $NaPF_6$, was added drop-wise to the solution over several minutes. An insoluble orange or red product precipitated; this was filtered and washed with water, methanol and diethyl ether to yield the product as an air- and moisture-stable solid.

[Rh(bipy)COD]PF$_6$ (**38**)



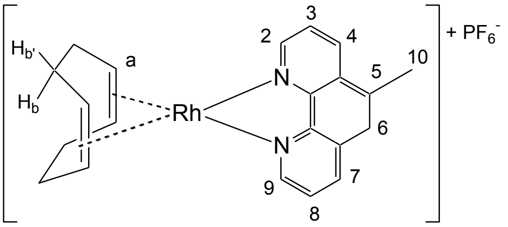
The reaction between $[Rh(COD)Cl]_2$ (50 mg, 0.10 mmol), 2,2'-bipyridine (32 mg, 0.20 mmol), and excess $NaPF_6$ yielded a red solid (86 mg, 84 % yield). Mp. 268 – 288 °C (slow decomp. with melting). ^1H NMR (DMSO-d$_6$): δ 8.62 (d, ^3J = 8.0 Hz, 2H, H3/H3'), 8.34 (t, ^3J = 7.8 Hz, 2H, H4/H4'), 8.05 (d, ^3J = 5.3 Hz, 2H, H6/H6'), 7.76 (t, ^3J = 6.2 Hz, 2H, H5/H5'), 4.65 (s, 4H, H$_a$), 2.55 (br s, 4H, H$_b$'), 2.15 (m, 4H, H$_b$). ^{13}C NMR (DMSO-d$_6$): δ 156.0 (s, Ar-C), 149.9 (s, Ar-C), 141.9 (s, Ar-C), 128.2 (s, Ar-C), 124.0 (s, Ar-C), 85.2 (d, $^1J_{Rh-C}$ = 12.2 Hz, COD –$\underline{C}$H), 30.1 (s, COD –$\underline{C}H_2$). ^{31}P NMR (DMSO-d$_6$): δ -144 (sept, $^1J_{P-F}$ = 711 Hz). Calculated for $C_{18}H_{20}N_2RhPF_6$: C, 42.16; H, 3.90; N, 5.47 %. Found: C, 42.19; H, 3.99; N, 5.14 %. ESI-MS: *m/z* 367 $[M - PF_6]^+$. Λ_M = 27.4 $\Omega^{-1}.cm^2.mol^{-1}$ (2 x 10^{-3} M in nitrobenzene, 20 °C).

[Rh(phen)(COD)]PF$_6$ (**39**)



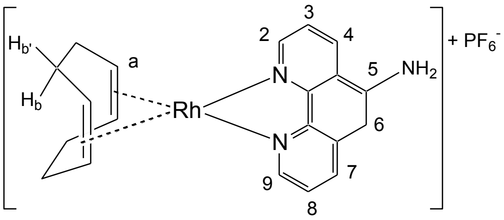
The reaction between $[Rh(COD)Cl]_2$ (45 mg, 0.091 mmol), 1,10-phenanthroline (33 mg, 0.183 mmol) and excess $NaPF_6$ yielded a red solid (82 mg, 84 % yield). Mp. 295 °C (decomp.). ^1H NMR (DMSO-d$_6$): δ 8.87 (d, ^3J = 8.13 Hz, 2H, H4/H7), 8.41 (d, ^3J = 4.93 Hz, 2H, H2/H9), 8.20 (s, 2H, H5/H6), 8.01 (dd, ^3J = 8.18, ^3J = 5.1 Hz, 2H, H3/H8), 4.79 (s, 4H, H$_a$), 2.57 (br s, 4H, H$_{b'}$), 2.15 (m, 4H, H$_b$). ^{31}P NMR (DMSO-d$_6$): δ -144 (sept, $^1J_{P-F}$ = 711 Hz). Calculated for $C_{20}H_{20}N_2RhPF_6$: C, 44.76; H, 3.72; N, 5.22 %. Found: C, 44.68; H, 4.52; N, 5.95 %.

[Rh(Me-phen)(COD)]PF$_6$ (**40**)



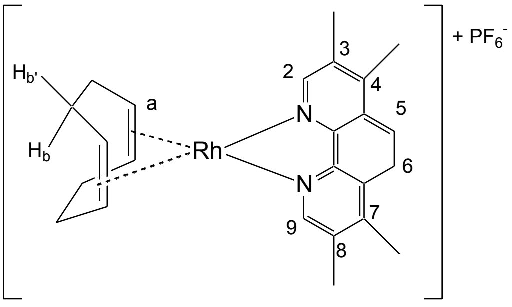
The reaction between [Rh(COD)Cl]$_2$ (36 mg, 0.073 mmol), 5-methyl-1,10-phenanthroline (28 mg, 0.144 mmol) and excess NaPF$_6$ yielded an orange solid (69 mg, 86% yield). ^{1}H NMR (DMSO-d$_6$): δ 8.95 (d, ^3J = 8.42 Hz, 1H, H4), 8.79 (d, ^3J = 7.46 Hz, 1H, H7), 8.46 (d, ^3J = 5.08 Hz, 1H, H2), 8.39 (d, ^3J = 5.11 Hz, 1H, H9), 8.1 – 7.8 (m, 3H, H3/H6/H8), 4.81 (br s, 4H, H$_a$), 2.92 (s, 3H, H10), 2.59 (br s, 4H, H$_{b'}$), 2.17 (m, 4H, H$_b$). ^{13}C NMR (DMSO-d$_6$): δ 150.5 (s, Ar-C), 150.0 (s, Ar-C), 146.8 (s, Ar-C), 145.8 (s, Ar-C), 137.9 (s, Ar-C), 135.7 (s, Ar-C), 130.3 (s, Ar-C), 129.9 (s, Ar-C), 126.7 (s, Ar-C), 126.6 (s, Ar-C), 126.4 (s, Ar-C), 85.1 (d, $^1J_{\text{Rh-C}}$ = 12.17 Hz, COD –$\underline{\text{C}}$H), 30.2 (s, COD –$\underline{\text{C}}$H$_2$), 18.8 (s, C10). ^{31}P NMR (DMSO-d$_6$): δ -144 (sept, $^1J_{\text{P-F}}$ = 711 Hz). Calculated for $C_{21}H_{22}N_2RhPF_6$: C, 45.83; H, 4.00; N, 4.98 %. Found: C, 45.56; H, 4.36; N, 5.09 %. ESI-MS: *m/z* 405 [M – PF$_6$]$^+$. Λ_M = 26.7 Ω^{-1}.cm^2.mol^{-1} (2 x 10^{-3} M in nitrobenzene, 20 °C).

[Rh(NH$_2$-phen)(COD)]PF$_6$ (**41**)



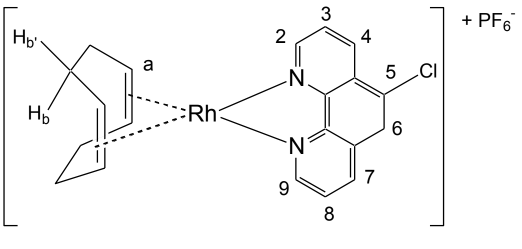
The reaction between [Rh(COD)Cl]$_2$ (44 mg, 0.09 mmol), 1,10-phenanthroline-5-amine (35 mg, 0.18 mmol) and NaPF$_6$ yielded a red solid, (93 mg, 95 % yield). Mp. 268 – 270 °C (decomp.). ^{1}H NMR (DMSO-d$_6$): δ 9.06 (d, ^3J = 8.2 Hz, 1H, H4), 8.45 (d, ^3J = 8.8 Hz, 1H, H7), 8.41 (d, ^3J = 5.6 Hz, 1H, H2), 8.02 (d, ^3J = 5.3 Hz, 1H, H9), 7.99 (br, 1H, H3), 7.74 (dd, ^3J = 8.2, ^3J = 5.0 Hz, 1H, H8) 7.0 (s, 1H, H6), 6.81 (s, 2H, -NH$_2$), 4.78 (s, 4H, H$_a$), 2.59 (br s, 4H, H$_{b'}$), 2.16 (m, 4H, H$_b$). ^{13}C NMR (DMSO-d$_6$): δ 150.3 (s, Ar-C), 147.3 (s, Ar-C), 144.9 (s, 2 Ar-C), 140.2 (s, Ar-C), 137.1 (s, Ar-C), 135.7 (s, Ar-C), 132.4 (s, Ar-C), 126.0 (s, Ar-C), 125.0 (s, Ar-C), 123.1 (s, Ar-C), 101.8 (s, Ar-C), 84.8 (d, $^1J_{\text{Rh-C}}$ = 12.07 Hz, COD –$\underline{\text{C}}$H), 30.2 (s, COD –$\underline{\text{C}}$H$_2$). ^{31}P NMR (DMSO-d$_6$): δ -144 (sept, $^1J_{\text{P-F}}$ = 711 Hz). Calculated for $C_{20}H_{21}N_2RhPF_6$: C, 43.58; H, 3.84; N, 7.62 %. Found: C, 43.47; H, 4.11; N, 7.50 %. ESI-MS: *m/z* 406 [M – PF_6]$^+$. Λ_M = 25.7 Ω^{-1}.cm^2.mol^{-1} (2 x 10^{-3} M in nitrobenzene, 20 °C).

[Rh(TM-phen)(COD)]PF_6 (**42**)



The reaction between $[Rh(COD)Cl]_2$ (52 mg, 0.105 mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (50 mg, 0.211 mmol) and excess $NaPF_6$ yielded a yellow solid (111 mg, 89 %). Mp. > 300 °C. ^{1}H NMR (DMSO-d_6): δ 8.28 (s, 2H, H5/H6), 8.09 (s, 2H, H2/H9), 4.78 (br s, 4H, H_a), 2.75 (s, 6H, -CH_3), 2.55 (br s, 4H, $H_{b'}$), 2.51 (s, 6H, -CH_3), 2.16 (m, 4H, H_b). ^{13}C NMR (DMSO-d_6): δ 150.1 (s, Ar-C), 147.8 (s, Ar-C), 144.5 (s, Ar-C), 134.2 (s, Ar-C), 127.8 (s, Ar-C), 123.5 (s, Ar-C), 84.0 (d, $^1J_{Rh-C}$ = 12.15 Hz, COD –$\underline{C}$H), 29.5 (s, COD –$\underline{C}H_2$), 16.8 (s, -CH_3), 14.8 (s, -CH_3). ^{31}P NMR (DMSO-d_6): δ -144 (sept, $^1J_{P-F}$ = 711 Hz). Calculated for $C_{24}H_{28}N_2RhPF_6$.½H_2O: C, 47.96; H, 4.86; N, 4.66. Found: C, 48.15; H, 4.88; N, 4.32. ESI-MS: *m/z* 447 [M – PF_6]$^+$. Λ_M = 27.1 Ω^{-1}.cm^2.mol^{-1} (2 x 10^{-3} M in nitrobenzene, 20 °C).

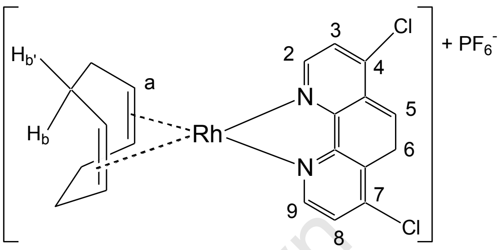
[Rh(Cl-phen)(COD)]PF_6 (**43**)



The reaction between $[Rh(COD)Cl]_2$ (48 mg, 0.097 mmol), 5-chloro-1,10-phenanthroline (42 mg, 0.196 mmol) and excess $NaPF_6$ yielded a purple solid (90 mg, 81 % yield). Mp. 297 - 300°C (decomp.). ^{1}H NMR (DMSO-d_6): δ 9.05 (d, ^3J = 8.6 Hz, 1H, H4), 8.88 (d, ^3J = 8.6 Hz, 1H, H7), 8.60 (s, 1H, H6), 8.58 (d, ^3J = 5.4 Hz, 1H, H2), 8.50 (d, ^3J = 5.0 Hz, 1H, H9), 8.17 (dd, ^3J = 8.3, ^3J = 5.1 Hz, 1H, H3), 8.09 (dd, ^3J = 7.6, ^3J = 4.8 Hz, 1H, H8), 4.84 (br s, 4H, H_a), 2.60 (br s, 4H, $H_{b'}$), 2.19 (m, 4H, H_b). ^{13}C NMR (DMSO-d_6): δ 151.7 (s, Ar-C), 151.2 (s, Ar-C), 147.4 (s, Ar-C), 145.9 (s, Ar-C), 140.1 (s, Ar-C), 137.4 (s, Ar-C), 130.4 (s, Ar-C), 129.5 (s, Ar-C), 128.1 (s, Ar-C), 127.5 (s, Ar-C), 127.3 (s, Ar-C), 127.2 (s, Ar-C), 85.4 (d, $^1J_{Rh-C}$ = 12.23 Hz, COD –$\underline{C}$H), 30.2 (s, COD –$\underline{C}H_2$). ^{31}P NMR (DMSO-d_6): δ -144 (sept, $^1J_{P-F}$ = 711 Hz). Calculated for

$C_{20}H_{19}N_2ClRhPF_6$: C, 41.94; H, 3.34; N, 4.89 %. Found: C, 41.21; H, 3.28; N, 4.84 %. ESI-MS: *m/z* 425/427 $[M - PF_6]^+$. $\Lambda_M = 24.8\ \Omega^{-1}.cm^2.mol^{-1}$ (2 x 10^{-3} M in nitrobenzene, 20 °C) .

[Rh(4,7-Cl$_2$-phen)(COD)]PF$_6$ (**44**)

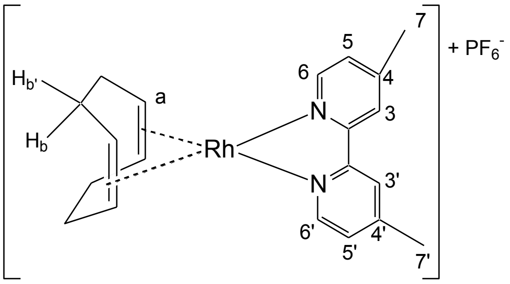


The reaction between $[Rh(COD)Cl]_2$ (44 mg, 0.09 mmol), 4,7-dichloro-1,10-phenanthroline (45 mg, 0.18 mmol) and excess $NaPF_6$ yielded a purple solid (97 mg, 89 %). Mp. 225 – 227 °C. ^{1}H NMR (DMSO-d$_6$): δ 8.46 (s, 2H, H5/H6), 8.41 (d, ^3J = 5.60 Hz, 2H), 8.26 (d, ^3J = 5.57 Hz, 2H), 4.70 (s, 4H, H$_a$), 2.56 (br s, 4H, H$_{b'}$), 2.16 (m, 4H, H$_b$). ^{13}C NMR (DMSO-d$_6$): δ 151.0 (s, Ar-C), 146.8 (s, Ar-C), 145.4 (s, Ar-C), 127.9 (s, Ar-C), 126.6 (s, Ar-C), 124.4 (s, Ar-C), 84.9 (d, $^1J_{Rh\text{-}C}$ = 12.38 Hz, COD –$\underline{C}$H), 29.6 (s, COD -$\underline{C}H_2$). ^{31}P NMR (DMSO-d$_6$): δ -144 (sept, $^1J_{P\text{-}F}$ = 711 Hz). ESI-MS: *m/z* 459/461/463 $[M - PF_6]^+$. $\Lambda_M = 24.3\ \Omega^{-1}.cm^2.mol^{-1}$ (2 x 10^{-3} M in nitrobenzene, 20 °C).

*7.4.2 General method for the preparation of **45 – 46***

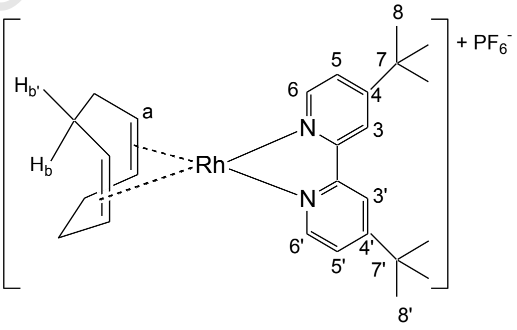
A quantity of $[Rh(COD)Cl]_2$ was dissolved in dichloromethane at room temperature and 2 equivalents of the relevant diimine ligand were added. There was immediate formation of a red or orange solution. The reaction was stirred for 30 minutes to ensure completion. Excess sodium hexafluorophosphate, $NaPF_6$, in methanol, was added drop-wise to the solution over several minutes. The solution was allowed to stir for a further 30 minutes, and was then filtered by gravity to remove any unreacted $NaPF_6$ or NaCl by-product. The solvent was removed *in vacuo*, to yield red or orange stable crystalline solids.

[Rh(Me$_2$-bipy)(COD)]PF$_6$ (**45**)



The reaction between [Rh(COD)Cl]$_2$ (38 mg, 0.077 mmol), 4,4'-dimethyl-2,2'-bipyridyl (29 mg, 0.157 mmol) and excess NaPF$_6$ yielded a red crystalline solid (75 mg, 90 %). Mp. 251 – 258 °C (decomp. with melting). ^{1}H NMR (DMSO-d$_6$): δ 8.44 (s, 2H, H3/H3'), 7.85 (d, ^3J = 5.66 Hz, 2H, H6/H6'), 7.54 (d, ^3J = 5.48 Hz, 2H, H5/H5'), 4.55 (s, 4H, H$_a$), 2.51 (s, 6H, H7/H7'), 2.49 (s, 4H, H$_{b'}$), 2.08 (m, 4H, H$_b$). ^{13}C NMR (DMSO-d$_6$): δ 156.0 (s, Ar-C), 154.0 (s, Ar-C), 149.1 (s, Ar-C), 128.5 (s, Ar-C), 124.5 (s, Ar-C), 84.8 (d, $^1J_{Rh-C}$ = 12.24 Hz, COD -$\underline{C}$H), 30.2 (s, COD –$\underline{C}H_2$), 21.4 (C7/C7'). ^{31}P NMR (DMSO-d$_6$): δ -144 (sept., $^1J_{P-F}$ = 711 Hz). ESI-MS: *m/z* 395 [M + 2H$^+$ – PF$_6$]$^+$, 393 [M – PF$_6$]$^+$. Λ_M = 24.3 Ω^{-1}.cm^2.mol^{-1} (2 x 10^{-3} M in nitrobenzene, 20 °C).

[Rh(^{t}Bu$_2$-bipy)(COD)]PF$_6$ (**46**)

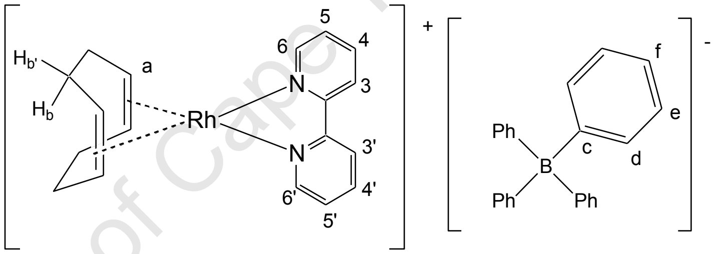


The reaction between [Rh(COD)Cl]$_2$ (58 mg, 0.118 mmol), 4,4'-di-^{t}butyl-2,2'-bipyridyl (64 mg, 0.238 mmol) and excess NaPF$_6$ yielded a bright orange crystalline solid (122 mg, 83 %). Mp. = 236 – 237 °C. ^{1}H NMR (CDCl$_3$): δ 8.59 (d, ^4J = 1.53 Hz, 2H, H3/H3'), 7.93 (d, ^3J = 5.95 Hz, 2H, H6/H6'), 7.71 (dd, ^3J = 5.8, ^4J = 1.4 Hz, 2H, H5/H5'), 4.61 (s, 4H, H$_a$), 2.53 (br s, 4H, H$_{b'}$), 2.13 (br m, 4H, H$_b$), 1.45 (s, 18H, H8/H8'). ^{13}C NMR (CDCl$_3$): δ 166.3 (s, Ar-C), 156.3 (s, Ar-C), 148.2 (s, Ar-C), 124.9 (s, Ar-C), 119.5 (s, Ar-C), 85.2 (d, $^1J_{Rh-C}$ = 12.25 Hz, COD -$\underline{C}$H), 35.9 (s, C7/C7'), 30.2 (s, C8/C8'), 30.1 (s, COD –$\underline{C}H_2$). ^{31}P NMR (CDCl$_3$): δ -144 (sept, $^1J_{P-F}$ = 711 Hz). Calculated for $C_{26}H_{36}N_2RhPF_6$: C, 50.01; H, 5.81; N, 4.48 %. Found: C, 49.60; H, 6.00; N, 4.18 %. ESI-MS: *m/z* 479 [M – PF$_6$]$^+$. Λ_M = 26.2 Ω^{-1}.cm^2.mol^{-1} (2 x 10^{-3} M in nitrobenzene, 20 °C).

*7.4.3 General method for preparation of complexes **47** – **50***

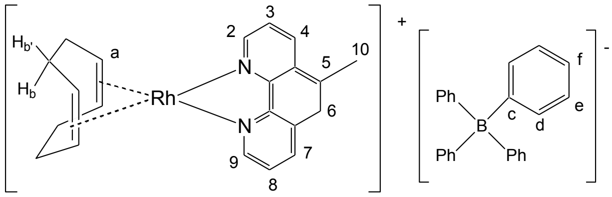
The general method of synthesis is similar to that used to synthesize complexes **38** – **44**, except that sodium tetraphenylborate, $NaBPh_4$, is used in place of $NaPF_6$. To a suspension of $[Rh(COD)Cl]_2$ in methanol was added 2 equivalents of the relevant diimine ligand. There was immediate formation of a red or orange solution. The reaction was stirred for 30 minutes to ensure completion. A slight excess of $NaBPh_4$ in water was added drop-wise to the solution. An insoluble orange or red product precipitated; this was filtered and washed with small amounts of water, methanol and diethyl ether to yield the product as an air- and moisture-stable powdery solid.

[Rh(bipy)(COD)]BPh₄ (**47**)



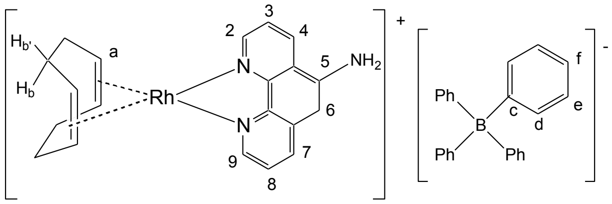
The reaction between $[Rh(COD)Cl]_2$ (35.5 mg, 0.072 mmol) and 2,2'-bipyridyl (23 mg, 0.147 mmol) and $NaBPh_4$ (52 mg, 0.15 mmol) yielded an orange solid (85 mg, 86 % yield). Mp. 188 – 190 °C (melts with decomp.). ^{1}H NMR (DMSO-d_6): δ 8.56 (d, ^3J = 8.15 Hz, 2H, H3/H3'), 8.28 (t, ^3J = 7.88 Hz, H4/H4'), 8.00 (d, ^3J = 5.24 Hz, H6/H6'), 7.71 (t, ^3J = 6.6 Hz, H5/H5'), 7.17 (br, 8H, H_d), 6.94 – 6.75 (complex, 12H, H_e/H_f), 4.59 (s, 4H, H_a), 2.52 (br m, 4H, $H_{b'}$), 2.11 (m, 4H, H_b). ^{13}C NMR (DMSO-d_6): δ 163.9 (q, $^1J_{B\text{-}C}$ = 49.65 Hz, C_c), 149.2 (s, Ar-C), 141.2 (s, Ar-C), 141.2 (s, Ar-C), 136.4 (s, Ar-C), 127.5 (s, Ar-C), 125.0 (s, Ar-C), 123.3 (s, Ar-C), 121.3 (s, Ar-C), 84.6 (d, $^1J_{Rh\text{-}C}$ = 12.40 Hz, COD -$\underline{C}$H), 29.6 (s, COD $\underline{C}H_2$-) . Calculated for $C_{42}H_{40}N_2RhB$: C, 73.49; H, 5.87; N, 4.08 %. Found: 73.35; H, 5.18; N, 3.31 %. ESI-MS: *m/z* 367 $[M - BPh_4]^+$. Λ_M = 18.6 $\Omega^{-1}.cm^2.mol^{-1}$ (2 x 10^{-3} M in nitrobenzene, 20 °C).

[Rh(Me-phen)(COD)]BPh_4 (**48**)



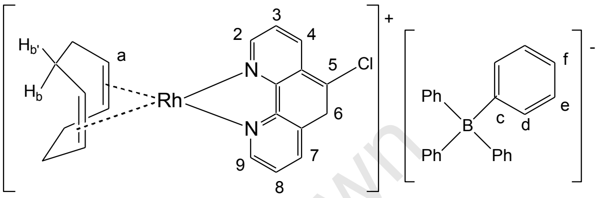
The reaction between $[Rh(COD)Cl]_2$ (40 mg, 0.081 mmol) and 5-methyl-1,10-phenanthroline (32 mg, 0.165 mmol) and $NaBPh_4$ (60 mg, 0.175 mmol) yielded an orange solid (100 mg, 85 % yield). Mp. 219 – 223 °C (melt with decomp.). ^{1}H NMR (DMSO-d_6): δ 8.92 (d, ^3J = 8.46 Hz, 1H, H4), 8.76 (d, ^3J = 8.22 Hz, 1H, H7), 8.43 (d, ^3J = 4.86 Hz, 1H, H2), 8.36 (d, ^3J = 4.98 Hz, 1H, H9), 8.26 – 8.02 (complex, H3, H6), 7.97 (dd, ^3J = 7.94, ^3J = 4.87 Hz, 1H, H8), 7.16 (br s, 8H, H_d), 6.93 – 6.74 (complex, 12H, H_e/H_f), 4.78 (s, 4H, H_a), 2.79 (s, 3H, H10), 2.56 (br m, 4H, $H_{b'}$), 2.14 (complex, 4H, H_b). ^{13}C NMR (DMSO-d_6): δ 163.3 (q, $^1J_{B\text{-}C}$ = 49.30 Hz, C_c), 149.8 (s, Ar-C), 149.2 (s, Ar-C), 146.3 (s, Ar-C), 144.3 (s, Ar-C), 139.3 (s, Ar-C), 137.3 (s, Ar-C), 135.4 (s, Ar-C), 135.0 (s, Ar-C), 129.7 (s, Ar-C), 129.4 (s, Ar-C), 126.1 (s, Ar-C), 126.0 (s, Ar-C), 125.7 (s, Ar-C), 125.0 (s, Ar-C), 121.3 (s, Ar-C), 84.4 (d, $^1J_{Rh\text{-}C}$ = 12.27 Hz, COD -$\underline{C}$H), 29.6 (s, COD –$\underline{C}H_2$), 18.1 (s, C10). Calculated for $C_{45}H_{42}N_2RhB$: C, 74.61; H, 5.84; N, 3.86 %. Found: C, 74.70; H, 6.06; N, 3.13 %. ESI-MS: *m/z* 405 $[M – BPh_4]^+$. $\Lambda_M = 17.9\ \Omega^{-1}.cm^2.mol^{-1}$ (2 x 10^{-3} M in nitrobenzene, 20 °C).

[Rh(NH_2-phen)(COD)]BPh_4.½ H_2O (**49**)



The complex was synthesized from the reaction of $[Rh(COD)Cl]_2$ (37 mg, 0.075 mmol) with 1,10-phenanthroline-5-amine (29 mg, 0.15 mmol) and $NaBPh_4$ (57 mg, 0.17 mmol) according to the general method. The product is an orange solid (96 mg, 88 %). Mp. 215 – 221 °C (decomp. followed by melt). ^{1}H NMR (DMSO-d_6): δ 9.00 (d, ^3J = 8.54 Hz, 1H, H4), 8.38 (d, ^3J = 8.11 Hz, 1H, H7), 8.31 (d, ^3J = 4.95 Hz, 1H, H2), 7.94 (dd, ^3J = 8.42, 5.12 Hz, 1H, H3), 7.89 (d, ^3J = 4.75 Hz, 1H, H9), 7.67 (dd, ^3J = 8.30, 4.93 Hz, 1H, H8), 7.17 (complex, 8H, H_d), 6.93 – 6.75 (complex, 13H, H_e/H_f/H6), 4.70 (s, 4H, H_a), 2.54 (br, 4H, $H_{b'}$), 2.11 (m, 4H, H_b). ^{13}C NMR (DMSO-d_6): δ 163.9 (q, $^1J_{B\text{-}C}$ = 49.50 Hz, C_c), 150.3 (s, Ar-C), 147.4 (s, Ar-C), 145.0 (s, Ar-C), 144.9 (s, Ar-C), 140.2 (s, Ar-C), 137.1 (s, Ar-C), 136.0 (s, Ar-C), 135.7 (s, Ar-C), 132.4 (s, Ar-C), 127.7 (br m, Ar-C), 126.1 (s, Ar-C), 125.0 (s, Ar-C), 123.1 (s, Ar-C), 122.0 (s, Ar-C), 101.8 (s, 1C, Ar-C), 84.8 (d, $^1J_{Rh\text{-}C}$ = 12.16 Hz, COD -$\underline{C}$H), 30.2 (s, COD –$\underline{C}H_2$). Calculated for $C_{44}H_{41}N_3RhB.½ H_2O$: C, 72.00; H, 5.76; N, 5.72 %. Found: C, 72.20; H, 5.43; N, 5.12 %. ESI-MS: *m/z* 406 [M – $BPh_4]^+$. $\Lambda_M = 17.5\ \Omega^{-1}.cm^2.mol^{-1}$ (2 x 10^{-3} M in nitrobenzene, 20 °C).

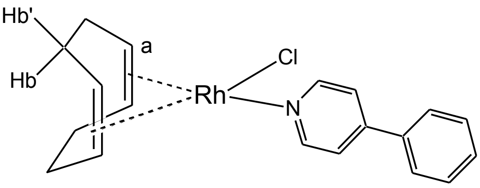
[Rh(Cl-phen)(COD)]BPh₄ (**50**)



Complex **50** was synthesized from the reaction of $[Rh(COD)Cl]_2$ (37 mg, 0.075 mmol) with 5-chloro-1,10-phenanthroline (32 mg, 0.15 mmol) and $NaBPh_4$ (58 mg, 0.17 mmol) according to the general method. The product is an orange-red solid (100 mg, 85 % yield). Mp. 210 – 220 °C (decomp. with some melting). ^{1}H NMR (DMSO-d$_6$): δ 9.00 (dd, ^3J = 8.48, ^4J = 1.19 Hz, 1H, H4), 8.83 (dd, ^3J = 8.28, ^4J = 1.24 Hz, 1H, H7), 8.53 (s, 1H, H6), 8.52 (dd, ^3J = 5.43, ^4J = 1.12 Hz, 1H, H2), 8.44 (dd, ^3J = 5.16, ^4J = 1.02 Hz, H9), 8.13 (dd, ^3J = 8.50, ^3J = 5.14 Hz, 1H, H3), 8.04 (dd, ^3J = 8.25, ^3J = 5.14 Hz, 1H, H8), 7.18 (complex, 8H, H_d), 6.95 – 6.75 (complex, 12H, H_e/H_f), 4.81 (s, 4H, H_a), 2.57 (s, 4H, $H_{b'}$), 2.17 (s, 4H, H_b). ^{13}C NMR (DMSO-d$_6$): δ 163.2 (q, $^1J_{B\text{-}C}$ = 49.34 Hz, C_c), 151.0 (s, Ar-C), 150.5 (s, Ar-C), 139.5 (s, Ar-C), 136.7 (s, Ar-C), 135.4 (s, Ar-C), 132.4 (s, Ar-C), 129.8 (s, Ar-C), 128.9 (s, Ar-C), 127.8 (s, Ar-C), 127.5 (s, Ar-C), 126.8 (s, Ar-C),126.7 (s, Ar-C), 126.5 (s, Ar-C), 125.0 (br, Ar-C), 121.3 (s, Ar-C), 84.7 (d, $^1J_{Rh\text{-}C}$ = 12.24 Hz, COD -$\underline{C}$H), 29.6 (s, COD –$\underline{C}H_2$). Calculated for $C_{44}H_{39}N_2RhBCl$: C, 70.95; H, 5.28; N, 3.76 %. Found: C, 71.37; H, 5.03; N, 3.19 %. ESI-MS: *m/z* 425/427 [M – $BPh_4]^+$. $\Lambda_M = 16.8\ \Omega^{-1}.cm^2.mol^{-1}$ (2 x 10^{-3} M in nitrobenzene, 20 °C).

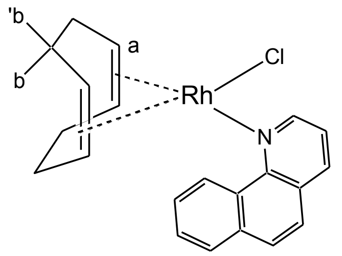
7.4.4 Neutral Rh(I) complexes

[Rh(4-phenylpyridine)(COD)] (**51**)



Ligand 4-phenylpyridine (40 mg, 0.258 mmol) was added to a solution of $[Rh(COD)Cl]_2$ (63 mg, 0.128 mmol) in dichloromethane (10 cm^3). The yellow solution was stirred at room temperature for 1 hour. There was no visible change to the reaction mixture. After an hour the solvent was reduced *in vacuo* and hexane was added to precipitate a yellow crystalline solid. The product was collected on a filter and washed with hexane. Yield 65 mg (63 %). Mp. 174 – 178 °C (melts with decomp.). ^{1}H NMR ($CDCl_3$): δ 8.77 (d, $^3J = 5.46$ Hz, 2H), 7.61 (d, $^3J = 7.73$ Hz, 2H), 7.55 – 7.48 (m, 5H), 4.20 (br, 4H, H_a), 2.54 (br, 4H, $H_{b'}$), 1.88 (m, 4H, H_b). ^{13}C NMR ($CDCl_3$): δ 151.0 (s, Ar-C), 149.6 (s, Ar-C), 137.0 (s, Ar-C), 129.9 (s, Ar-C), 129.3 (s, Ar-C), 127.0 (s, Ar-C), 122.4 (s, Ar-C), 77.4 (d, $^1J_{Rh\text{-}C} = 13.10$ Hz, COD -$\underline{C}$H), 30.9 (s, COD –$\underline{C}H_2$). Calculated for $C_{19}H_{21}NRhCl$: C, 56.80; H, 5.27; N, 3.48 %. Found: C, 56.28; H, 5.36; N, 2.65 %.

[Rh(Benzo(h)quinoline)(COD)] (**52**)



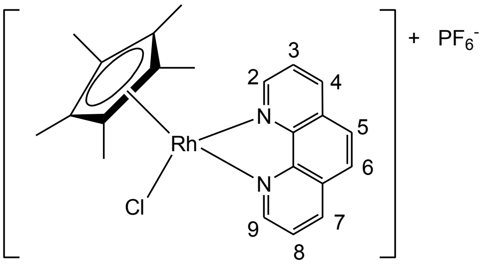
Benzo(h)quinoline (26 mg, 0.145 mmol) was added to a solution of $[Rh(COD)Cl]_2$ (36 mg, 0.073 mmol) in 5 cm^3 dichloromethane. No visible change occurred. The yellow solution was stirred for 3 hours at room temperature. A small amount of diethyl ether was added and the solution left to stand open for 48 hours, whereafter the solvent had evaporated to yield an orange crystalline solid. Yield 58 mg (94 %). Mp. 31 - 34°C. ^{1}H NMR ($CDCl_3$): δ 9.33 (d, $^3J = 7.99$ Hz, 1H), 9.02 (br, 1H), 8.19 (d, $^3J = 7.83$ Hz, 1H), 7.92 (d, $^3J = 7.40$ Hz, 1H), 7.83 (d, $^3J = 7.40$ Hz, 1H), 7.78 – 7.68 (m, 3H) 7.54 (dd, $^3J = 7.5$ and 4.3 Hz, 1H), 4.25 (br s, 4H, H_a), 2.52 (br, 4H, $H_{b'}$), 1.77 (br m, 4H, H_b). ^{13}C NMR ($CDCl_3$): δ 148.8 (s, Ar-C), 146.6 (s, Ar-C), 135.8 (s, Ar-C), 133.6 (s, Ar-C), 131.5 (s, Ar-C), 128.2 (s, Ar-C), 127.80 (s, Ar-C), 127.78 (s, Ar-C), 127.1 (s, Ar-C), 126.4 (s, Ar-C), 125.3 (s, Ar-C), 124.4 (s, Ar-C), 121.8 (s, Ar-C), 78.7 (d, $^1J_{Rh\text{-}C} = 13.93$ Hz, COD -$\underline{C}$H), 30.9 (s, COD -$\underline{C}H_2$). Calculated for $C_{21}H_{21}NClRh.CH_2Cl_2.1.5H_2O$: C, 49.22; H, 4.88 %. Found: C, 49.42; H, 5.16 %.

7.5 Synthesis of rhodium(III) and iridium(III) diimine complexes

7.5.1 General method for preparation of ***53*** *-* ***61***

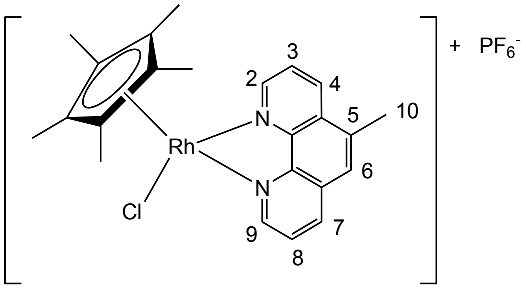
A suspension of of $[Cp^*RhCl_2]_2$ or $[Cp^*IrCl_2]_2$ (approximately 40 - 60 mg) in *ca* 5 – 10 cm^3 methanol was stirred at room temperature in a round-bottomed flask. Two equivalents of the appropriate diimine were added, and a yellow solution formed within 1 – 2 minutes. The reaction was allowed to stir for 10 min, whereafter an excess of sodium hexafluorophosphate dissolved in about 10 cm^3 water was added slowly. A yellow precipitate formed almost immediately. The reaction mixture was stirred at room temperature for 30 minutes. The yellow precipitate was filtered by suction and washed with water, cold methanol and diethyl ether. The products were isolated as stable yellow solids (usually microcrystalline) in moderate to good yields.

$[Cp^*Rh(phen)Cl]PF_{6..}½H_2O$ (**53**)



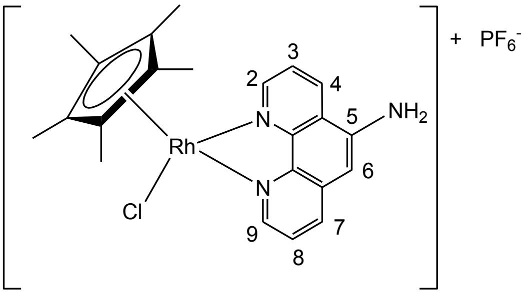
The reaction of $[Cp^*RhCl_2]_2$ (42 mg, 0.068 mmol) with 1,10-phenanthroline (25 mg, 0.139 mmol) and excess $NaPF_6$ yielded complex **53** as a yellow microcrystalline solid (72 mg, 88 % yield). Mp. = 298 – 301 °C (decomp.). ^1H NMR (DMSO-d_6): δ 9.35 (dd, ^3J = 5.15, ^4J = 1.24 Hz, 2H, H2/H9), 8.90 (dd, ^3J = 8.20, ^4J = 1.28 Hz, 2H, H4/H7), 8.26 (s, 2H, H5/H6), 8.17 (dd, ^3J = 8.19, ^3J = 5.16 Hz, 2H, H3/H8), 1.69 (s, 15H, Cp* Me). ^{13}C NMR (DMSO-d_6): δ 152.8 (s, Ar-C), 145.2 (s, Ar-C)139.5 (s, Ar-C), 130.6 (s, Ar-C), 128.1 (s, Ar-C), 127.5 (s, Ar-C), 97.4 (d, $^1J_{Rh\text{-}C}$ = 8.05 Hz, Cp* C=C), 8.99 (s, Cp* Me). ^{31}P NMR (DMSO-d_6): δ -144 (sept, $^1J_{P\text{-}F}$ = 711 Hz). Calculated for $C_{22}H_{23}N_2ClRhPF_6.½H_2O$: C, 43.48; H, 3.98; N, 4.61 %. Found: C, 43.54; H, 3.75; N, 4.23 %. ESI-MS: *m/z* 453/455 $[M – PF_6]^+$, 417 $[M – PF_6 – Cl – H]$. Λ_M = 24.7 $\Omega^{-1}.cm^2.mol^{-1}$ (2 x 10^{-3} M in nitrobenzene, 20 °C).

*[Cp*Rh(Me-phen)Cl]PF$_6$* (**54**)



The reaction of [Cp*RhCl$_2$]$_2$ (60 mg, 0.097 mmol) with 5-methyl-1,10-phenanthroline (38 mg, 0.196 mmol) and excess NaPF$_6$ yielded **54** as a microcrystalline solid (74 mg, 62 % yield). Mp. = 294 – 296 °C (melts with decomp.). ^{1}H NMR (DMSO-d$_6$): δ 9.39 (dd, ^3J = 5.01 Hz, ^4J = 0.63 Hz, 1H, H2), 9.31 (dd, ^3J = 5.03 Hz, ^4J = 0.71 Hz, 1H, H9), 8.97 (dd, ^3J = 8.41 Hz, ^4J = 1.07 Hz, 1H, H4), 8.82 (dd, ^3J = 8.20 Hz, ^4J = 1.07 Hz, 1H, H7), 8.23 (dd, ^3J = 8.40 Hz, ^3J = 5.15 Hz, 1H, H3), 8.17 (dd, ^3J = 8.19, ^3J = 5.17 Hz, 1H, H8), 8.12 (s, 1H, H6), 2.85 (s, 3H, H10), 1.73 (s, 15H, Cp* Me). ^{13}C NMR (DMSO-d$_6$): δ 152.6 (s, Ar-C), 152.0 (s, Ar-C), 145.5 (s, Ar-C), 144.5 (s, Ar-C), 138.7 (s, Ar-C), 136.8 (s, Ar-C), 136.0 (s, Ar-C), 130.7 (s, Ar-C), 130.3 (s, Ar-C), 127.6 (s, Ar-C), 127.3 (s, Ar-C), 126.7 (s, Ar-C), 97.4 (d, $^1J_{\text{Rh-C}}$ = 8.09 Hz, Cp* C=C), 18.7 (s, C10), 9.0 (s, Cp* Me). ^{31}P NMR (DMSO-d$_6$): δ -144 (sept, $^1J_{\text{P-F}}$ = 711 Hz). ESI-MS: *m/z* 467/469 [M – PF$_6$]$^+$, 431 [M – PF$_6$ – Cl – H]. Λ_M = 26.0 Ω^{-1}.cm^2.mol^{-1} (2 x 10^{-3} M in nitrobenzene, 20 °C).

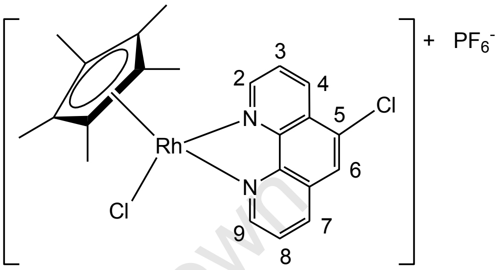
*[Cp*Rh(NH$_2$-phen)Cl]PF$_6$* (**55**)



The reaction of [Cp*RhCl$_2$]$_2$ (56 mg, 0.091 mmol) with 1,10-phenanthroline-5-amine (36 mg, 0.184 mmol) and excess NaPF$_6$ yielded **55** as a yellow precipitate (82 mg, 73 %). Mp. = 288 – 292 °C (melt with decomp.). ^{1}H NMR (DMSO-d$_6$): δ 9.28 (dd, ^3J = 5.10 Hz, ^4J = 0.83 Hz, 1H, H2), 9.03 (dd, ^3J = 8.46 Hz, ^4J = 0.99 Hz, 1H, H4), 8.86 (dd, ^3J = 5.03 Hz, ^4J = 1.0 Hz, 1H, H9), 8.40 (dd, ^3J = 8.33 Hz, ^4J = 1.01 Hz, 1H, H7), 8.10 (dd, ^3J = 8.44 Hz, ^3J = 5.13 Hz, 1H, H3), 7.84 (dd, ^3J = 8.31 Hz, ^3J = 5.05 Hz, 1H, H8), 6.99 (s, 1H, H6), 6.79 (s, 2H, -NH$_2$), 1.65 (s, 15H, Cp* Me). ^{13}C NMR (DMSO-d$_6$): δ 152.6 (s, Ar-C), 147.2 (s, Ar-C), 146.1 (s, Ar-C), 145.2 (s, Ar-C), 138.2 (s, Ar-C), 135.6 (s, Ar-C), 134.6 (s, Ar-C), 132.8 (s, Ar-C), 127.04 (s, Ar-C), 125.9 (s, Ar-C), 123.6 (s, Ar-C), 101.5 (s, Ar-C), 97.2 (d, $^1J_{\text{Rh-C}}$ = 7.89 Hz, Cp*

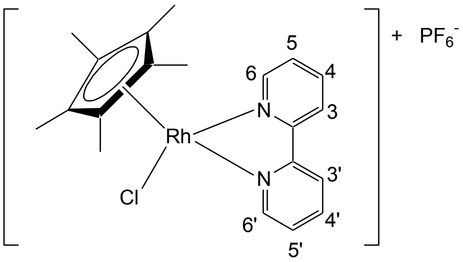
C=C), 8.95 (s, Cp* Me). ^{31}P NMR (DMSO-d$_6$): δ -144 (sept., $^1J_{P\text{-}F}$ = 711 Hz). Calculated for $C_{22}H_{24}N_3ClRhPF_6.H_2O$: C, 41.82; H, 4.15; N, 6.65 %. Found: C, 41.80; H, 4.21; N, 6.10 %. ESI-MS: *m/z* 468/470 [M – PF$_6$]$^+$, 432 [M – PF$_6$ – Cl – H]. Λ_M = 24.8 Ω^{-1}.cm^2.mol^{-1} (2 x 10^{-3} M in nitrobenzene, 20 °C).

*[Cp*Rh(Cl-phen)Cl]PF$_6$* (**56**)



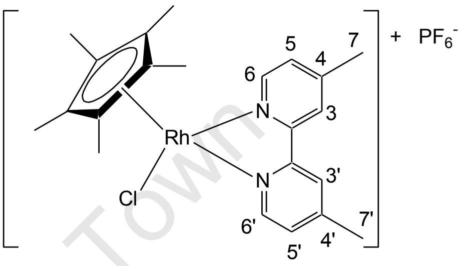
Complex **56** was prepared from the reaction of [Cp*RhCl$_2$]$_2$ (50 mg, 0.081 mmol) with 5-chloro-1,10-phenanthroline (35 mg, 0.163 mmol) and excess aqueous NaPF$_6$ in 76 mg (74 %) yield. Mp. 303 – 307 °C (melt with decomp.). ^{1}H NMR (DMSO-d$_6$): δ 9.48 (d, ^3J = 5.10 Hz, 1H, H2), 9.40 (d, ^3J = 5.13 Hz, 1H, H9), 9.07 (dd, ^3J = 8.42 Hz, ^4J = 0.93 Hz, 1H, H4), 8.90 (dd, ^3J = 8.20 Hz, ^4J = 0.95 Hz, 1H, H7), 8.63 (s, 1H, H6), 8.34 (dd, ^3J = 8.46, ^3J = 5.16 Hz, 1H, H3), 8.24 (dd, ^3J = 8.23, ^3J = 5.17 Hz, 1H, H8), 1.74 (s, 15H, Cp* Me). ^{13}C NMR (DMSO-d$_6$): δ 153.0 (s, Ar-C), 152.5 (s, Ar-C), 147.1 (s, Ar-C), 145.1 (s, Ar-C), 138.3 (s, Ar-C), 135.7 (s, Ar-C), 129.3 (s, Ar-C), 127.6 (s, Ar-C), 127.4 (s, Ar-C), 126.7 (s, Ar-C), 122.7 (s, Ar-C), 121.8 (s, Ar-C), 96.99 (d, $^1J_{Rh\text{-}C}$ = 8.24 Hz, Cp* C=C), 8.3 (s, Cp* Me). ^{31}P NMR (DMSO-d$_6$): δ -144 (sept., $^1J_{P\text{-}F}$ = 711 Hz). ESI-MS: *m/z* 487/489/491 [M – PF$_6$]$^+$, 451/453 [M – PF$_6$ – Cl]. Λ_M = 26.9 Ω^{-1}.cm^2.mol^{-1} (2 x 10^{-3} M in nitrobenzene, 20 °C).

*[Cp*Rh(bipy)Cl]PF$_6$.½H$_2$O* (**57**)



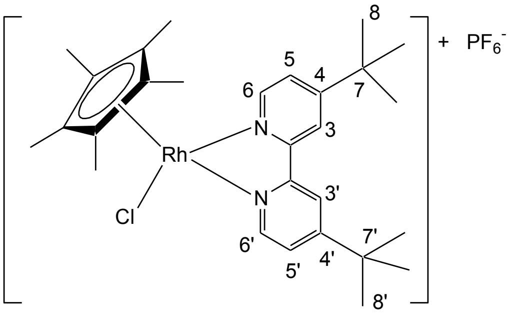
Complex **57** was prepared from the reaction of [Cp*RhCl$_2$]$_2$ (56 mg, 0.091 mmol) with 2,2'-bipyridyl (30 mg, 0.192 mmol) and excess aqueous NaPF$_6$ to give a yellow solid product in 49 mg (47 %) yield. Mp. 294 – 297 °C (melt with decomp.). ^{1}H NMR (DMSO-d$_6$): δ 8.98 (d, ^3J = 5.21 Hz, 2H, H6/H6'), 8.67 (d, ^3J = 8.03 Hz, 2H, H3/H3'), 8.33 (td, ^3J = 7.85 Hz, ^4J = 1.38 Hz, 2H, H4/H4'), 7.88 (td, ^3J = 5.58 Hz, ^4J = 1.12 Hz, 2H, H5/H5'), 1.67 (s, 15H, Cp* Me). ^{13}C NMR (DMSO-d$_6$): δ 153.8 (s, Ar-C), 152.0 (s, Ar-C), 140.2 (s, Ar-C), 128.2 (s, Ar-C), 123.5 (s, Ar-C), 96.7 (d, $^1J_{Rh\text{-}C}$ = 8.03 Hz, Cp* C=C), 8.21 (s, Cp* Me). ^{31}P NMR (DMSO-d$_6$): δ -144 (sept, $^1J_{P\text{-}F}$ = 711 Hz). Calculated for $C_{20}H_{23}N_2ClRhPF_6$.½H_2O: C, 41.15; H, 4.14; N, 4.80 %. Found: C, 40.98; H, 3.88; N, 4.35 %. ESI-MS: *m/z* 429/431 [M – PF$_6$]$^+$, 393 [M – PF$_6$ – Cl – H]$^+$.

*[Cp*Rh(Me$_2$-bipy)Cl]PF$_6$* (**58**)



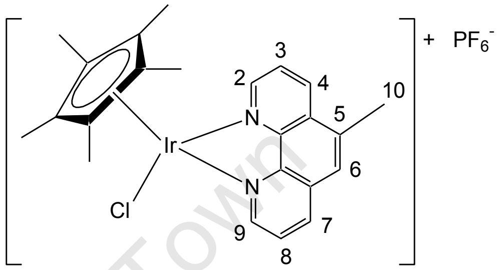
Complex **58** was prepared from the reaction of [Cp*RhCl$_2$]$_2$ (40 mg, 0.065 mmol) with 4,4'-dimethyl-2,2'-bipyridyl (24 mg, 0.130 mmol) and excess aqueous NaPF$_6$ to give a yellow microcrystalline solid in 71 mg (91 %) yield. Mp. = 285 – 290 °C (decomp.). ^{1}H NMR (DMSO-d$_6$): δ 8.75 (d, ^3J = 5.72 Hz, 2H, H6/H6'), 8.49 (br, 2H), 7.64 (br, 2H), 2.53 (s, 6H, H7/H7'), 1.60 (s, 15H, Cp* Me). ^{13}C NMR (DMSO-d$_6$): δ 154.1 (s, Ar-C), 152.7 (s, Ar-C), 151.9 (s, Ar-C), 129.4 (s, Ar-C), 124.7 (s, Ar-C), 97.1 (d, $^1J_{Rh\text{-}C}$ = 8.04 Hz), 21.2 (s, C7/C7'), 8.9 (s, Cp* Me). ^{31}P NMR (DMSO-d$_6$): δ -144 (sept, $^1J_{P\text{-}F}$ = 711 Hz). Calculated for $C_{22}H_{27}N_2ClRhPF_6$.½$NaPF_6$.½ H_2O: C, 37.98; H, 4.06; N, 4.02 %. Found: C, 38.05; H, 4.14; N, 3.57 %. ESI-MS: *m/z* 457/459 [M – PF$_6$]$^+$, 421 [M – PF$_6$ – Cl – H]$^+$. Λ_M = 22.3 Ω^{-1}.cm^2.mol^{-1} (1 x 10^{-3} M in nitrobenzene, 20 °C).

*[Cp*Rh(^{t}Bu$_2$-bipy)Cl]PF$_6$* (**59**)



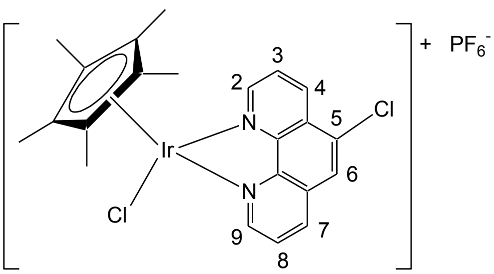
Complex **59** was prepared from the reaction of [Cp*RhCl$_2$]$_2$ (41 mg, 0.066 mmol) with 4,4'-di^{t}butyl-2,2'-bipyridyl (36 mg, 0.134 mmol) and excess aqueous NaPF$_6$ to give a yellow microcrystalline solid in 86 mg (95 %) yield. Mp. 304 – 306 °C (melt with decomp.). ^{1}H NMR (DMSO-d$_6$): δ 8.82 (d, ^3J = 5.96 Hz, 2H, H6/H6'), 8.65 (d, ^4J = 1.98Hz, 2H, H3/H3'), 7.77 (dd, ^3J = 5.97 Hz, ^4J = 2.03 Hz, 2H, H5/H5'), 1.61 (s, 15H, Cp* Me), 1.40 (s, 18H, H8/H8'). ^{13}C NMR (DMSO-d$_6$): δ 164.8 (s, Ar-C), 154.4 (s, Ar-C), 152.2 (s, Ar-C), 125.4 (s, Ar-C), 121.7 (s, Ar-C), 97.2 (d, $^{1}J_{\text{Rh-C}}$ = 7.98 Hz), 36.1 (s, C7/C7'), 30.5 (s, C8/C8'), 8.9 (s, Cp* Me). ^{31}P NMR (DMSO-d_6): δ -144 (sept, $^{1}J_{\text{P-F}}$ = 711 Hz). Calculated for $C_{28}H_{39}N_2ClRhPF_6$: C, 48.95; H, 5.72; N, 4.08 %. Found: C, 48.87; H, 5.63; N, 3.56 %. ESI-MS: *m/z* 541/543 $[M - PF_6]^+$, 506 $[M - PF_6 - Cl]^+$. Λ_M = 24.8 $\Omega^{-1}.cm^{2}.mol^{-1}$ (2 x 10^{-3} M in nitrobenzene, 20 °C).

*[Cp*Ir(Me-phen)Cl]PF$_6$* (**60**)



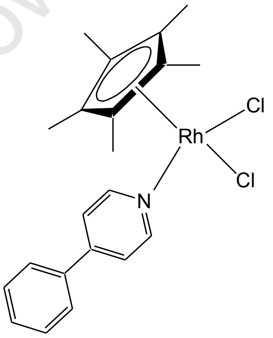
The reaction of $[Cp^*IrCl_2]_2$ (53 mg, 0.066 mmol) with 5-methyl-1,10-phenanthroline (26 mg, 0.134 mmol) and excess $NaPF_6$ according to the general procedure produced bright yellow microcrystals of **60** (60 mg, 65 %). Mp. 300 – 302 °C (decomp. with melting). ^{1}H NMR (DMSO-d_6): δ 9.41 (dd, ^{3}J = 5.23 Hz, ^{4}J = 0.79 Hz, 1H, H2), 9.34 (dd, ^{3}J = 5.25 Hz, ^{4}J = 0.83 Hz, 1H, H9), 9.01 (dd, ^{3}J = 8.37 Hz, ^{4}J = 0.78 Hz, 1H, H4), 8.86 (dd, ^{3}J = 8.21 Hz, ^{4}J = 0.77 Hz, 1H, H7), 8.25 (dd, ^{3}J = 8.41, ^{3}J = 5.25 Hz, 1H, H3), 8.21 (s, 1H, H6), 8.19 (dd, ^{3}J = 8.22, ^{3}J = 5.28 Hz, 1H, H8), 2.90 (s, 3H, H10), 1.75 (s, 15H, Cp* Me). ^{13}C NMR (DMSO-d_6): δ 152.3 (s, Ar-C), 151.7 (s, Ar-C), 146.8 (s, Ar-C), 145.9 (s, Ar-C), 138.7 (s, Ar-C), 137.0 (s, Ar-C), 136.5 (s, Ar-C), 131.1 (s, Ar-C), 130.6 (s, Ar-C), 128.0 (s, Ar-C), 127.7 (s, Ar-C), 126.8 (s, Ar-C), 89.6 (s, Cp* C=C), 18.6 (s, C10) 8.7 (s, 15H Cp* Me). ^{31}P NMR (DMSO-d_6): δ -144 (sept, $^{1}J_{\text{P-F}}$ = 711 Hz). ESI-MS: *m/z* 557/559 $[M - PF_6]^+$. Λ_M = 22.9 $\Omega^{-1}.cm^{2}.mol^{-1}$ (1 x 10^{-3} M in nitrobenzene, 20 °C).

*[Cp*Ir(Cl-phen)Cl]PF$_6$* (**61**)



The reaction of $[Cp^*IrCl_2]_2$ (46 mg, 0.058 mmol) with 5-chloro-1,10-phenanthroline (25 mg, 0.117 mmol) and excess $NaPF_6$ according to the general procedure produced bright yellow microcrystals of **61** (53 mg, 63 %). Mp. > 310 °C. ^{1}H NMR (DMSO-d_6): δ 9.46 (dd, ^{3}J = 5.28 Hz, ^{4}J = 1.00 Hz, 1H, H2), 9.39 (dd, ^{3}J = 5.28 Hz, ^{4}J = 1.10 Hz, 1H, H9), 9.07 (dd, ^{3}J = 8.44 Hz, ^{4}J = 1.00 Hz, 1H, H4), 8.91 (dd, ^3J = 8.27 Hz, ^4J = 1.03 Hz, 1H, H7), 8.70 (s, 1H, H6), 8.33 (dd, ^3J = 8.46, ^3J = 5.29 Hz, 1H, H3), 8.23 (dd, ^3J = 8.25, ^3J = 5.29 Hz, 1H, H8), 1.72 (s, 15H, Cp* Me). ^{13}C NMR (DMSO-d$_6$): δ 152.8 (s, Ar-C), 152.2 (s, Ar-C), 146.7 (s, Ar-C), 145.2 (s, Ar-C), 138.4 (s, Ar-C), 135.8 (s, Ar-C), 130.4 (s, Ar-C), 129.4 (s, Ar-C), 128.3 (s, Ar-C), 127.9 (s, Ar-C), 126.9 (s, Ar-C), 89.1 (s, Cp* C=C), 8.0 (Cp* Me). ^{31}P NMR (DMSO-d$_6$): δ -140 (sept, $^1J_{P-F}$ = 711 Hz). Calculated for $C_{22}H_{22}N_2Cl_2IrPF_6$: C, 36.57; H, 3.10; N, 3.88 %. Found: C, 36.53; H, 3.51; N, 2.60 %. ESI-MS: *m/z* 575/577/579 [M – PF$_6$ - H]$^+$. Λ_M = 26.4 Ω^{-1}.cm^2.mol^{-1} (1 x 10^{-3} M in nitrobenzene, 20 °C).

*[Cp*Rh(4-phenylpyridine)Cl$_2$]* (**62**)

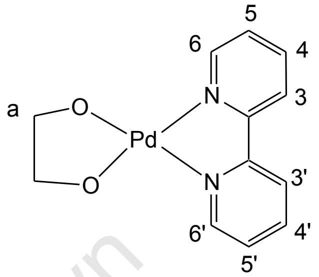


Rhodium dimer [Cp*RhCl$_2$]$_2$ (39 mg, 0.063 mmol) was dissolved in 5 cm^3 DCM in a round-bottomed flask. Ligand 4-phenylpyridine (20 mg, 0.129 mmol) was added. The red solution turned orange. The reaction was stirred at room temperature for 60 minutes. Hexane was added slowly to precipitate a yellow compound, which was filtered and washed with hexane. The product was isolated as a yellow precipitate in 50 mg (85 %) yield. Mp. 215 – 250 °C (slow decomp.). ^{1}H NMR (DMSO-d$_6$): δ 8.64 (d, ^3J = 4.74 Hz, 2H), 7.81 (d, ^3J = 7.5 Hz, 2H), 7.71 (d, ^3J = 4.69 Hz, 2H), 7.56 – 7.46 (m, 3H), 1.64 (s, 15H, Cp* Me). ^{13}C NMR (DMSO-d$_6$): δ 150.7 (s, Ar-C), 147.2 (s, Ar-C), 136.3 (s, Ar-C), 129.8 (s, Ar-C, 2C), 127.3 (s, Ar-C), 121.6 (s, Ar-C), 98.2 (d, $^1J_{Rh-C}$ = 7.88 Hz, Cp* C=C), 9.0 (s, Cp* Me). Λ_M = 0.4 Ω^{-1}.cm^2.mol^{-1} (2 x 10^{-3} M in nitrobenzene, 20 °C).

7.6 Synthesis of palladium(II) chelate complexes

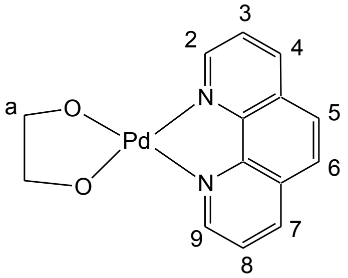
7.6.1 Neutral Pd(II) complexes

[Pd(bipy)(EG)].7H$_2$O (**63**)



An orange suspension of (2,2'-bipyridyl)dichloropalladium(II) (72 mg, 0.22 mmol) in methanol (5 cm^3) was stirred at room temperature in a round-bottomed flask. An aqueous solution of *ca* 0.1 g KOH and 5 drops of ethanediol was added drop-wise. The reaction mixture was stirred at room temperature and gradually turned to a yellow solution within an hour. The solution was stirred a further 4 hours to ensure reaction completion. The solvent was then reduced *in vacuo* and the product was allowed to crystallize overnight at 4 °C. The very fine yellow needle-like crystals were collected and washed with very small amounts of ice-water and cold acetonitrile. Yield 33 mg (33 %). ^{1}H NMR (DMSO-d$_6$) δ: 8.58 (d, ^3J = 5.02 Hz, 2H, H6/H6'), 8.46 (d, ^3J = 8.07 Hz, 2H, H3/H3'), 8.23 (td, ^3J = 8.04 Hz, ^4J = 1.46 Hz, 2H, H4/H4'), 7.68 (td, ^3J = 7.48 Hz, ^4J = 1.40 Hz, 2H, H5/H5'), 3.46 (s, 4H, H$_a$). Calculated for $C_{12}H_{12}N_2O_2Pd.7H_2O$: C, 32.12; H, 5.84; N, 6.24 %. Found: C, 32.37; H, 5.11; N, 6.85 %.ESI-MS: *m/z* 338 [M + O]$^+$, 332 [M]$^+$, 306/307 [M – O]$^+$.

[Pd(phen)(EG)].8H$_2$O (**64**)

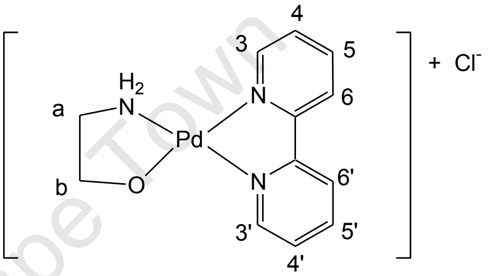


An orange suspension of (1,10-phenanthroline)dichloropalladium(II) (70 mg, 0.20 mmol) in methanol (5 cm^3) was stirred at room temperature in a round-bottomed flask. An aqueous solution of excess KOH and 6 drops ethanediol in distilled water was added and the reaction mixture was stirred for 6 hours, during which time a yellow solution formed. After the reaction the solvent was reduced *in vacuo* and the product was allowed to crystallize overnight at 4 °C. The fine pale yellow needle-like crystals were collected and washed with very small amounts of ice-water and cold acetonitrile. Yield 42 mg (43 %). Mp. = 175 –

180 °C (decomp.). ^{1}H NMR (DMSO-d$_6$): δ 8.90 – 8.85 (br m, 4H, H2/H4/H7/H9), 8.23 (s, 2H, H5/H6), 8.04 (dd, ^3J = 5.1, ^3J = 8.05 Hz, 2H, H3/H8), 3.51 (s, 4H, H$_a$). ^{13}C NMR (DMSO-d$_6$): δ 149.2 (s, Ar-C), 145.0 (s, Ar-C), 137.8 (s, Ar-C), 129.3 (s, Ar-C), 126.9 (s, Ar-C), 125.6 (s, Ar-C), 75.9 (s, C$_a$). Calculated for $C_{14}H_{12}N_2O_2Pd.8H_2O$: C, 34.28; H, 5.75; N, 5.75 %. Found: C, 34.13; H, 5.14; N, 5.86 %. ESI-MS: *m/z* 345 [M – H]$^+$, 330 [M – O]$^+$.

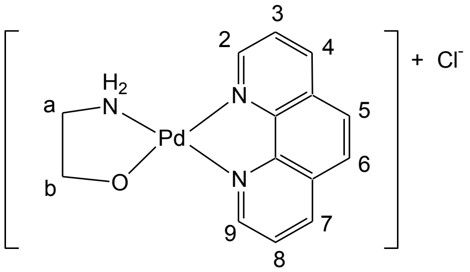
7.6.2 Monocationic Pd(II) complexes

[Pd(bipy)(EA)] Cl.2½H$_2$O (**65**)



An aqueous solution of ethanolamine (15 mg, 0.25 mmol) and KOH (14 mg, 0.25 mmol) was added to a suspension of (2,2'-bipyridyl)dichloropalladium(II) (74 mg, 0.22 mmol) in water. The mixture was refluxed and formed a clear solution within 15 minutes. The reaction mixture was heated for a further 60 minutes, then cooled to room temperature. The reaction flask was kept at - 4°C to encourage crystallization of the product, which was collected on a filter and washed with small amounts of ice-cold water. Yield of beige crystalline product was 35 mg (43 %). Mp. 123 – 154 °C (slow decomp.). ^{1}H NMR (D$_2$O): δ 8.31 - 8.22 (m, 4H), 7.77 (t, ^3J = 6.5 Hz, 1H, H4/H4'), 7.70 (t, ^3J = 6.5 Hz, 1H, H5/H5'), 3.60 (t, ^3J = 5.3 Hz, 2H, H$_b$), 2.98 (t, ^3J = 5.3 Hz, 2H, H$_a$). ^{13}C NMR (D$_2$O): δ 155.3 (s, Ar-C), 155.2 (s, Ar-C), 150.9 (s, Ar-C), 148.6 (s, Ar-C), 141.8 (s, Ar-C), 141.3 (s, Ar-C), 127.9 (s, Ar-C), 127.5 (s, Ar-C), 123.6 (s, Ar-C), 123.3 (s, Ar-C), 69.2 (s, C$_b$), 50.7 (s, C$_a$). Calculated for $C_{12}H_{14}N_3OClPd.2.5H_2O$: C, 35.78; H, 4.75; N, 10.43 %. Found: C, 35.51; H, 4.69; N, 10.28 %.

[Pd(phen)(EA)]Cl.4H$_2$O (**66**)

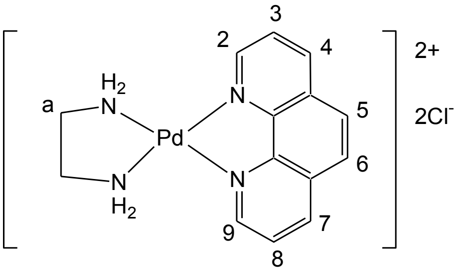


An aqueous solution of ethanolamine (17 mg, 0.28 mmol) and KOH (16 mg, 0.28 mmol) was added to a suspension of (1,10-

phenanthroline)dichloropalladium(II) (87 mg, 0.24 mmol) in water. The mixture was refluxed and formed a clear solution within 10 minutes. The reaction mixture was heated for a further 60 minutes, then cooled to room temperature. The reaction flask was kept at - 4°C to encourage crystallization of the product, which was collected on a filter and washed with small amounts of ice-cold water. Yield of white microcrystalline product 39 mg (39 %). Mp. 112 – 170 °C (slow decomp.). ^{1}H NMR (D_2O): δ 8.59 – 8.56 (m, 2H, H4/H7), 8.41 (dd, ^3J = 5.27, ^4J = 1.08 Hz, 1H), 8.36 (dd, ^3J = 5.25, ^4J = 1.19 Hz, 1H), 7.90 (dd, ^3J = 8.29, ^3J = 5.25 Hz, 1H), 7.82 (dd, ^3J = 8.32, ^3J = 5.30 Hz, 1H), 7.80 (br s, 2H, H5/H6), 3.57 (t, ^3J = 5.54 Hz, 2H, H_b), 2.94 (t, ^3J = 5.53 Hz, 2H, H_a). ^{13}C NMR (D_2O): δ 151.3 (s, Ar-C), 149.0 (s, Ar-C), 144.8 (s, Ar-C), 144.6 (s, Ar-C), 140.1 (s, Ar-C), 139.8 (s, Ar-C), 129.8 (s, Ar-C), 129.6 (s, Ar-C), 127.4 (s, Ar-C), 127.3 (s, Ar-C), 126.3 (s, Ar-C), 125.9 (s, Ar-C), 69.7 (s, C_b), 50. 7 (s, C_a). Calculated for $C_{14}H_{14}N_3OClPd.4H_2O$: C, 37.02; H, 4.89; N, 9.25 %. Found: C, 37.09; H, 5.00; N, 9.18 %.

7.6.3 Dicationic Pd(II) complexes

[Pd(phen)(en)]$Cl_2.3H_2O$ (**67**)



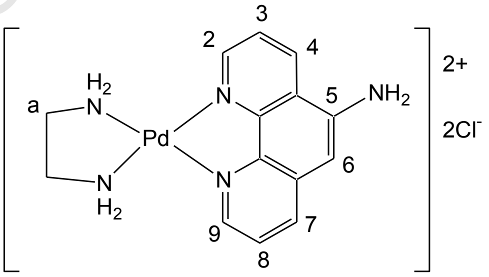
Dichloro(1,10-phenanthroline)palladium (95 mg, 0.27 mmol) was added to a solution of ethylenediamine (16 mg, 0.27 mmol) in 10 cm^3 distilled water, and the suspension was heated to reflux. Within 10 minutes the solid (phen)$PdCl_2$ disappeared, and a clear solution was formed. The mixture was heated for a further 60 minutes, cooled to room temperature, then filtered to remove any unreacted starting material. The solvent was reduced, and ethanol was added to precipitate the white solid product, which was filtered and washed with cold ethanol (3 x 5 cm^3). Yield 95 mg (75 %). Mp. = slow decomp. from 285 °C. ^{1}H NMR (D_2O): δ 8.57 (d, ^3J = 8.3 Hz, 2H, H4/H7), 8.38 (d, ^3J = 5.6 Hz, 2H, H2/H9), 7.86 (s, 2H, H5/H6), 7.73 (dd, ^3J = 8.2 Hz, ^3J = 5.4 Hz, 2H, H3/H8), 2.82 (s, 4H, H_a). ^{13}C NMR (D_2O): δ 151.3 (s, Ar-C), 146.7 (s, Ar-C), 141.2 (s, Ar-C), 130.9 (s, Ar-C), 128.0 (s, Ar-C), 126.3 (s, Ar-C), 47.0 (br, C_a). Calculated for $C_{14}H_{16}N_4PdCl_2.3H_2O$: C, 35.66; H, 4.70; N, 11.87 %.

Found: C, 35.68; H, 4.49; N, 12.15 %. ESI-MS: *m/z* 381/383 [M - Cl]$^+$, 345/347 [M – 2Cl ± H]$^+$, 285 [M – 2Cl - en]$^+$.

7.6.3.1 General method of preparation of complexes **68 - 72**

A quantity of (ethylenediamine)dichloropalladium(II) was suspended in *ca* 10 - 15 cm^3 distilled water in a round-bottomed flask fitted with reflux condenser. An equimolar amount of diimine was added, and the mixture was heated to reflux. Within 10 minutes the reaction suspension had changed to a clear or pale yellow solution. The reaction mixture was heated for a further 30 – 60 minutes to ensure reaction completion. The solvent was removed *in vacuo*, the residue was taken up in methanol and ether and the precipitate was filtered and washed with ether. The product was isolated as a white or pale yellow solid.

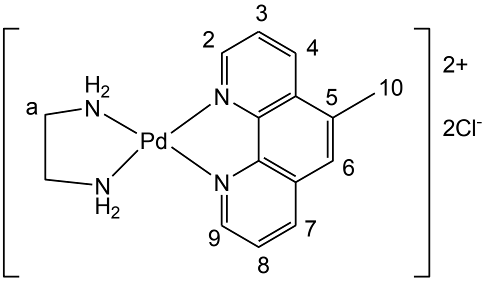
[Pd(NH$_2$-phen)(en)]Cl$_2$.3H$_2$O (**68**)



Complex **68** was prepared from the reaction of (ethylenediammine)dichloropalladium (68 mg, 0.29 mmol) and 1,10-phenanthroline-5-amine (57 mg, 0.29 mmol) to yield the compound as an orange solid (70 mg, 65 %). Mp. = 275 °C (decomp.). ^{1}H NMR (D$_2$O): δ 8.39 (d, ^3J = 8.8 Hz, 1H), 8.29 (d, ^3J = 5.2 Hz, 1H), 7.95 -7.94 (m, 2H), 7.64 (dd, ^3J = 8.4, ^3J = 5.2 Hz, 1H), 7.48 (dd, ^3J = 8.4, ^3J = 5.2 Hz, 1H), 6.48 (s, 1H), 3.00 (s, 4H). ^{13}C NMR (D$_2$O): δ 150.9 (s, Ar-C), 146.4 (s, Ar-C), 145.3 (s, Ar-C), 143.1 (s, Ar-C), 138.7 (s, Ar-C), 137.3 (s, Ar-C), 134.8 (s, Ar-C), 131.3 (s, Ar-C), 126.1 (s, Ar-C), 125.1 (s, Ar-C), 102.3 (s, Ar-C), 47.0 (C$_a$). Calculated for $C_{14}H_{17}N_5PdCl_2.3H_2O$: C, 34.56; H, 4.76; N, 14.39 %. Found: C, 34.88; H, 4.59; N, 15.90 %. ESI-MS: *m/z* 396/398 [M - Cl]$^+$, 360/362 [M – 2Cl ± H]$^+$.

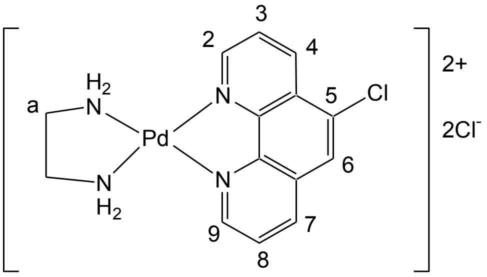
[Pd(Me-phen)(en)]Cl$_2$.3.5H$_2$O (**69**)

Complex **69** was prepared from the reaction of (ethylenediammine)dichloropalladium (68 mg, 0.29 mmol) and 5-methyl-1,10-phenanthroline (56 mg, 0.29 mmol) to yield the compound as a white solid (98 mg, 68 %). Mp. 225 – 229 °C (decomp.). ^{1}H NMR (D$_2$O): δ 8.89 (dd, ^3J = 8.52, ^4J = 1.19 Hz, 1H, H4), 8.73 – 8.71 (m, 2H, H7/H2) 8.66 (dd, ^3J = 5.30, ^4J = 1.21 Hz, 1H, H9), 8.12 (dd, ^3J = 8.49, ^3J = 5.29 Hz, 1H, H3), 8.07 (dd, ^3J = 8.28, ^3J = 5.31 Hz, 1H, H8), 7.75 (br, 1H, H6), 3.20 (s, 4H, H$_a$), 2.78 (d, ^4J = 1.12 Hz). ^{13}C NMR (D$_2$O): δ 151.0 (s, Ar-C), 150.4 (s, Ar-C), 146.1 (s, Ar-C), 145.2 (s, Ar-C), 140.2 (s, Ar-C), 138.1 (s, Ar-C), 136.3 (s, Ar-C), 126.4 (s, Ar-C), 126.2 (s, Ar-C), 130.6 (s, Ar-C), 130.2 (s, Ar-C), 47.0 (s, C$_a$). Calculated for $C_{15}H_{18}N_4PdCl_2.3.5H_2O$: C, 36.41; H, 5.06; N, 11.33 %. Found: C, 36.46; H, 4.72; N, 12.38 %. ESI-MS: *m/z* 395/397 [M - Cl]$^+$, 361 [M – 2Cl + H]$^+$, 344 [M – 2Cl – NH$_2$]$^+$, 301 [M – 2Cl - en]$^+$.

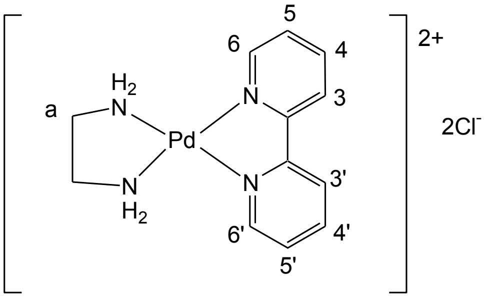


[Pd(Cl-phen)(en)]Cl$_2$.3H$_2$O (**70**)

Complex **70** was prepared from the reaction of (ethylenediamine)dichloropalladium (79 mg, 0.33 mmol) and 5-chloro-1,10-phenanthroline (72 mg, 0.34 mmol) to yield the compound as a white solid (128 mg, 77 %). ^{1}H NMR (D$_2$O): δ 9.07 (d, ^3J = 8.48 Hz, 1H, H4), 8.82 (d, ^3J = 5.18 Hz, 1H, H2), 8.80 – 8.77 (m, 2H, H7 and H9), 8.29 (s, 1H, H6), 8.16 (dd, ^3J = 8.49, 5.47 Hz, 1H, H3), 8.12 (dd, ^3J = 7.87, 5.68 Hz, 1H, H8), 3.21 (s, 4H, H$_a$). ^{13}C NMR (D$_2$O): δ 152.2 (s, Ar-C), 151.7 (s, Ar-C), 146.6 (s, Ar-C), 145.3 (s, Ar-C), 140.4 (s, Ar-C), 138.1 (s, Ar-C), 131.3 (s, Ar-C), 129.6 (s, Ar-C), 128.6 (s, Ar-C), 127.0 (s, Ar-C), 126.7 (s, Ar-C), 47.1 (s, C$_a$). ESI-MS: *m/z* 452/453/455 [M]$^+$, 379/381 [M – 2Cl - H]$^+$, 364/366 [M – 2Cl – NH$_2$]$^+$, 321 [M – 2Cl – en]$^+$. Calculated for $C_{14}H_{15}N_4PdCl_3.3H_2O$: C, 33.22; H, 2.99; N, 11.07 %. Found: C, 33.74; H, 3.08; N, 11.82 %.

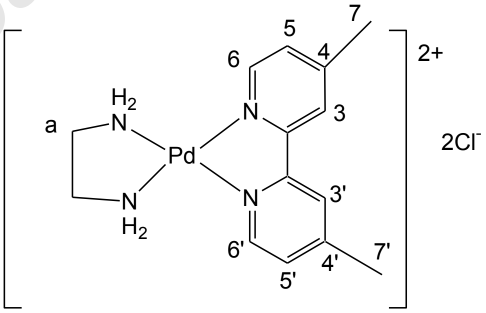


[Pd(bipy)(en)]Cl$_2$.3H$_2$O (**71**)



The reaction of (ethylenediamine)-dichloropalladium (76 mg, 0.32 mmol) with 2,2'-bipyridyl (51 mg, 0.32 mmol) according to the general procedure produced a white solid compound in 117 mg (79 %) yield. ^{1}H NMR (D_2O): δ 8.35 – 8.20 (m, 6H, H3/H3', H4/H4', H6/H6'), 7.68 (t, ^4J = 6.4 Hz, 2H, H5/H5'), 2.95 (s, 4H, H_a). ^{13}C NMR (D_2O): δ 156.4 (s, Ar-C), 150.6 (s, Ar-C), 142.3 (s, Ar-C), 128.0 (s, Ar-C), 124.2 (s, Ar-C), 46.7 (s, C_a). Calculated for $C_{12}H_{16}N_4PdCl_2.3H_2O$: C, 32.20; H, 4.95; N, 12.51 %. Found: C, 29.91; H, 4.69; N, 12.25 %.

[Pd(Me$_2$-bipy)(en)]Cl$_2$.4H$_2$O (**72**)



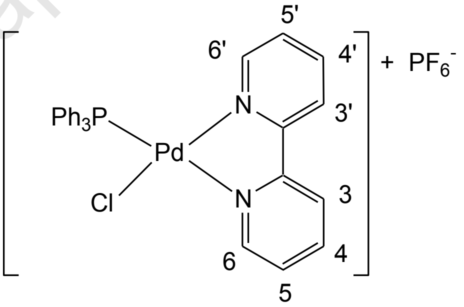
The reaction of (ethylenediamine)-dichloropalladium (74 mg, 0.31 mmol) with 2,2'-bipyridyl (58 mg, 0.31 mmol) according to the general procedure produced a pale yellow solid compound in 101 mg (66 %) yield. Mp. 264 – 268 °C (decomp. with melting). ^{1}H NMR (D_2O): δ 8.11 (br, 2H, H3/H3'), 8.01 (d, ^3J = 5.89 Hz, 2H, H6/H6'), 7.47 (d, ^3J = 5.88 Hz, 2H, H5/H5'), 2.93 (s, 4H, H_a), 2.51 (s, 6H, H7/H7'). ^{13}C NMR (D_2O): δ 155.8 (s, Ar-C), 155.5 (s, Ar-C), 149.7 (s, Ar-C), 128.4 (s, Ar-C), 124.6 (s, Ar-C), 46.7 (s, C_a), 21.1 (s, C7/C7'). Calculated for $C_{14}H_{20}N_4PdCl_2.4H_2O$: C, 34.07; H, 5.72; N, 11.35 %. Found: C, 34.08; H, 5.48; N, 12.01 %. ESI-MS: *m/z* 403/405/407 $[M – NH_2 - H]^+$, 385/387 $[M - Cl]^+$, 349/351 $[M – 2Cl \pm H]^+$, 334 [M – 2Cl – NH$_2$]+, 290/291 $[M – 2Cl – en]^+$.

7.7 Synthesis of palladium phosphine complexes

7.7.1 General method for preparation of **73 - 77**

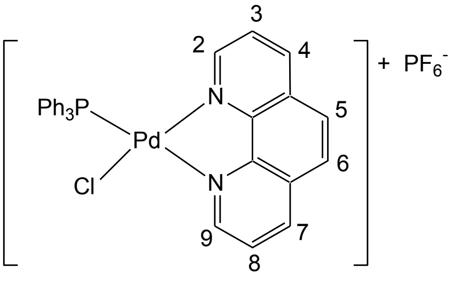
A quantity (80 – 100 mg) of the appropriate palladium diimine dichloride precursor and approximately 15 – 20 cm^3 acetonitrile were placed in a round-bottomed flask fitted with condenser. Equimolar amounts of sodium hexafluorophosphate and triphenylphosphine were added, and the mixture heated to reflux. After approximately 10 minutes of refluxing a bright yellow solution was formed. The reaction mixture was heated for a further 60 minutes. After cooling to room temperature, the solvent was reduced and methanol added to precipitate the product, which was filtered and washed with portions of water and methanol and ether.

[Pd(bipy)(PPh$_3$)Cl]PF$_6$ (**73**)



The reaction of Pd(bipy)Cl$_2$ (100 mg, 0.3 mmol) with triphenylphosphine (79 mg, 0.3 mmol) and NaPF$_6$ (52 mg, 0.3 mmol) according to the general procedure yielded **73** as a bright yellow solid in 136 mg (64 %) yield. Mp. = 221 – 225 °C (melting with decomp.). ^{1}H NMR (DMSO-d$_6$): δ 8.67 (d, ^3J = 7.95 Hz, 2H), 8.34 (d, ^3J = 7.80 Hz, 2H), 7.94 - 7.54 (m, 19H). ^{31}P NMR (DMSO-d$_6$): δ 35.5 (s), -143 (sept, $^1J_{\text{P-F}}$ = 711 Hz). Calculated for $C_{28}H_{23}N_2ClPdP_2F_6$: C, 47.68; H, 3.29; N, 3.97 %. Found: C, 47.35; H, 3.31; N, 3.35 %. ESI-MS: *m/z* 559/561 [M – PF$_6$]$^+$.

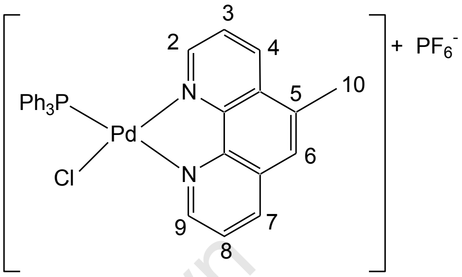
[Pd(phen)Cl(PPh$_3$)]PF$_6$ (**74**)



The reaction of Pd(phen)Cl$_2$ (95 mg, 0.27 mmol) with triphenylphosphine (71 mg, 027 mmol) and NaPF$_6$ (46 mg, 0.27 mmol) according to the general procedure yielded **74** as a yellow solid in 142 mg (72 %) yield. ^{1}H NMR (DMSO-d$_6$): δ 8.96 (d, ^3J = 8.10 Hz, 2H, H4/H7), 8.40 (s, 2H, H5/H6), 7.96 – 7.53

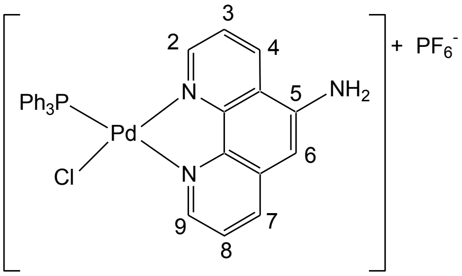
(m, 19H). ^{31}P NMR (DMSO-d_6): δ 32 (s), -143 (sept, $^1J_{P\text{-}F}$ = 711 Hz). Calculated for $C_{30}H_{23}N_2ClPdP_2F_6$: C, 49.40; H, 3.18; N, 3.84 %. Found: C, 49.58; H, 3.43; N, 3.67 %. ESI-MS: *m/z* 583/585 $[M - PF_6]^+$.

[Pd(Me-phen)(PPh$_3$)Cl]PF$_6$ (**75**)



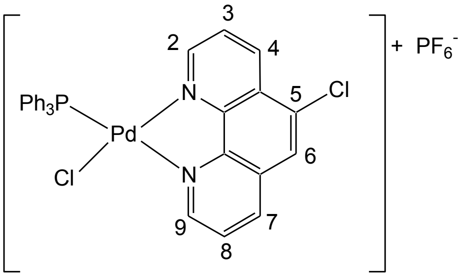
The reaction of Pd(Me-phen)Cl$_2$ (92 mg, 0.25 mmol) with triphenylphosphine (66 mg, 0.25 mmol) and NaPF$_6$ (43 mg, 0.26 mmol) according to the general procedure yielded **75** as a yellow solid in 106 mg (57 %) yield. Mp. 250 – 253 °C (melting with decomp.). ^{1}H NMR (DMSO-d_6): δ 9.02 (d, ^3J = 8.18 Hz, 1H, H4), 8.83 (d, ^3J = 7.60 Hz, 1H, H7), 8.14 (s, 1H, H6), 8.00 – 7.50 (m, 19H), 2.86 (s, 3H, H10). ^{31}P NMR (DMSO-d_6) δ: 35.4 (s), -143 (sept., $^1J_{P\text{-}F}$ = 711 Hz). Calculated for $C_{31}H_{25}N_2ClPdP_2F_6.2H_2O$: C, 47.78; H, 3.75; N, 3.59 %. Found: C, 47.92; H, 3.75; N, 3.25 %. ESI-MS: *m/z* 597/599 $[M - PF_6]^+$.

[Pd(NH$_2$-phen)(PPh$_3$)Cl]PF$_6$ (**76**)



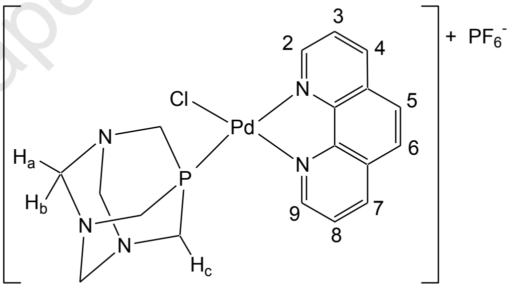
The reaction of Pd(NH$_2$-phen)Cl$_2$ (85 mg, 0.23 mmol) with triphenylphosphine (61 mg, 0.23 mmol) and NaPF$_6$ (39 mg, 0.23 mmol) according to the general procedure yielded **76** as a yellow solid in 118 mg (69 %) yield. Mp. slow decomposition from 230 °C (decomp. complete 280 °C). ^{1}H NMR (DMSO-d_6): δ 9.15 (d, ^3J = 8.78 Hz, 1H, H4), 8.48 (d, ^3J = 8.09 Hz, 1H, H7), 7.96 – 7.50 (m, 19H), 7.07 (s, -NH$_2$). ^{31}P NMR (DMSO-d_6): δ 32.3 (s), -143 (sept, $^1J_{P\text{-}F}$ = 711 Hz). Calculated for $C_{30}H_{24}N_3ClPdP_2F_6$: C, 48.41; H, 3.25; N, 5.64 %. Found: C, 48.37; H, 3.56; N, 5.24 %. ESI-MS: *m/z* 598/600 $[M - PF_6]^+$.

[Pd(Cl-phen)l(PPh$_3$)Cl]PF$_6$ (**77**)



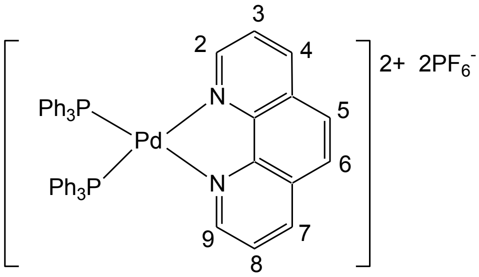
The reaction of Pd(Cl-phen)Cl$_2$ (88 mg, 0.22 mmol) with triphenylphosphine (58 mg, 0.22 mmol) and NaPF$_6$ (37 mg, 0.22 mmol) according to the general procedure yielded **77** as a yellow solid in 118 mg (70 %) yield. Mp. 274 – 276 °C. ^{1}H NMR (DMSO-d$_6$): δ 9.14 (d, ^3J = 8.32 Hz, 1H, H4), 8.93 (d, ^3J = 8.14 Hz, 1H, H7), 8.68 (s, 1H, H6), 8.16 – 7.56 (m, 19H). ^{31}P NMR (DMSO-d$_6$): δ 32.5 (s), -143 (sept., $^1J_{P-F}$ = 711 Hz). ESI-MS: *m/z* 617/619/621 [M – PF$_6$]$^+$.

[(phen)PdCl(PTA)]PF$_6$.3H$_2$O (**78**)



A round-bottomed flask fitted with a reflux condenser was charged with Pd(phen)Cl$_2$ (100 mg, 0.28 mmol) and NaPF$_6$ (50 mg, 0.3 mmol) in 15 cm^3 acetonitrile. The suspension was refluxed for 15 minutes, and PTA (43 mg, 0.28 mmol) dissolved in a little water/ethanol mixture was added. There was immediate formation of a yellow solution. The reaction mixture was heated 15 minutes longer, then cooled to room temperature. The solvent was reduced *in vacuo*, whereupon a yellow precipitate appeared. This was collected by suction filtration and washed with water and ether. The sticky orange product was dried under vacuum for 2 hours to yield an orange solid (107 mg, 56 %). Mp. = 208 – 211 °C. ^{1}H NMR (DMSO-d$_6$): δ 9.08 (br s, 2H, H2/H9), 9.00 (dd, ^3J = 8.22, 0.93 Hz, 2H, H4/H7), 8.30 (s, 2H, H5/H6), 8.19 (dd, ^3J = 8.19, 5.28 Hz, 2H, H3/H8), 4.80 (s, 6H, H$_c$), 4.71 (d, $^2J_{HA-HB}$ = 12.9 Hz, 3H), 4.49 (d, $^2J_{HA-HB}$ = 13.0 Hz, 3H). ^{13}C NMR (DMSO-d$_6$): δ 141.3 (s, Ar-C), 131.0 (s, Ar-C), 128.3 (s, Ar-C), 127.1 (s, Ar-C), 72.3 (d, $^3J_{PC}$ = 8.18 Hz, N-$\underline{C}$H$_2$-N), 52.5 (d, $^1J_{PC}$ = 15.25 Hz, N-$\underline{C}$H$_2$-P). ^{31}P NMR (DMSO-d$_6$) δ: -140 (sept, $^1J_{P-F}$ = 711 Hz), -23.6 (s, PTA). Calculated for $C_{18}H_{20}N_5ClPdP_2F_6.3H_2O$: C, 31.93; H, 3.87; N, 10.34 %. Found: C, 32.03; H, 3.33; N, 10.71 %. ESI-MS: *m/z* 478/480 [M – PF$_6$]$^+$.

[Pd(phen)(PPh$_3$)$_2$]2PF$_6$ (**79**)



This reaction was performed under moisture- and oxygen-free conditions. A Schlenk tube was charged with AgPF$_6$ (129 mg, 0.51 mmol) inside a glovebox. The tube was transferred to a vacuum-nitrogen line and Pd(phen)Cl$_2$ (90 mg, 0.25 mmol) and PPh$_3$ (135 mg, 0.51 mmol) were added. Dry acetonitrile (10 cm^3) was added, and the mixture was stirred at room temperature for 2 hours, to give an orange solution with greyish AgCl precipitate. The AgCl was removed by filtration through celite. The solvent was removed from the mother liquor to give an oily orange product. The oil was dissolved in DCM, and filtered again through celite to remove residual AgCl and the solvent was removed. This step was repeated in order to remove all traces of AgCl. The yellow oil was recrystallized from DCM/hexane to give yellow crystals in 82 mg (30 %) yield. No NMR data are recorded due to the apparent instability of the complexe in solution. Calculated for $C_{48}H_{38}N_2PdP_4F_{12}.½CH_2Cl_2$: C, 50.94; H, 3.44; N, 2.45 %. Found: C, 50.33; H, 3.47; N, 1.94 %. Chemical structure confirmed by x-ray crystallography.

7.8 β-haematin inhibition assays

β-haematin inhibition testing was carried out according to the procedure published by Ncokazi and Egan.[10] An appropriate mass of each compound was dissolved in either DMSO or water to give 100 µl of a 0.168 M solution. Serial dilutions of the drug solutions were performed in triplicate in a 96-well plate. Each well contained 10 µl of drug solution (except for the last row of wells, which contained 10 µl drug solvent), where the final concentrations of the drug solutions corresponded to 0 – 10 equivalents relative to haematin in the final mixture. To each well 101.2 µl haematin stock solution (0.00168 M in 0.1 M NaOH) was added, followed by 10 µl of 1 M HCl to neutralize the base, and the mixtures were homogenized. Then 58.7 µl acetate solution (12.9 M, pH 5), preincubated at 60 °C, was added to each well. After mixing the plates were incubated in a water-bath at 60 °C for one hour. Thereafter 80 µl of a pyridine solution (30 % in 0.02 mM Hepes) was added at room temperature. The mixtures were allowed to settle overnight whereafter 38 µl of the supernatant from each well was transferred to the corresponding well in a new 96-well plate. The aliquots were diluted to 250 μl with 30 % pyridine solution (in 0.02 M Hepes). Data were collected using a microplate reader and absorbances read at 405 nm. The sigmoidal dose response curve was analyzed using GraphPad Prism software [11] and the IC_{50} of drug (in equivalents) was determined.

7.9 In vitro *anti-malarial testing*

In vitro anti-malarial testing was carried out by the research group of Prof. Pete Smith at the UCT Pharmacology Department (Medical Campus). The test samples were tested in triplicate on one occasion against chloroquine-sensitive (CQS) D10 strain and chloroquine-resistant Dd2 strain of *Plasmodium falciparum*. Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen.[12] Quantitative assessment of anti-plasmodial activity *in vitro* was determined via the parasite lactate dehydrogenase assay using a modified method described by Makler.[13]

The test samples were prepared to a 2mg/ml stock solution in 10% DMSO and sonicated to enhance solubility. Samples were tested as a suspension if not completely dissolved. Stock solutions were stored at -20ºC. Further dilutions were prepared on the day of the experiment. Chloroquine (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 (IC_{50}–value). Test samples were tested at a starting concentration of 10 μg/ml, which was then serially diluted 2-fold in complete medium to give 10 concentrations; with the lowest concentration being 0.02 μg/ml. The same dilution technique was used for all samples. CQ was tested at a starting concentration of 100 ng/ml. The highest concentration of solvent to which the parasites were exposed to 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.

7.10 In vitro *anti-cancer testing*

In vitro anti-cancer testing was carried out by the research group of Dr Denver Hendricks at UCT Medical Campus. The WHCO1 cell line was derived from biopsies of primary oesophageal squamous cell carcinomas. All cultures were maintained in Dulbecco's Modified Eagle Medium containing 10% Foetal Calf Serum and 100U/ml streptomycin and 100µg/ml penicillin. Cells were maintained in a humidified 37°C, 5% CO_2 incubator.

IC_{50} determinations were carried out using the MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Briefly, 3000 cells were seeded per well in 96-well plates. Cells were incubated at 37°C and 5% CO_2 (24 h), then aqueous DMSO solutions of each compound (10µL, with a constant final concentration of DMSO = 0.2%) were plated at various concentrations. After 48 h incubation, observations were made, and MTT (10µL) solution added to each well. After 4 h incubation, solubilization solution (100µL) was added to each well, and plates were incubated overnight. Plates were read at 595nm on a BioTek microplate reader.

7.11 References

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APPENDIX

Tables containing the full lists of bond lengths and angles (x-ray crystallographic data) for complexes **48**, **54**, **67**, **73** and **79** are provided. Please refer to the attached disk.

APPENDIX

X-ray crystallographic data: Full list of bond lengths and angles for rhodium and palladium complexes

Complex **48**

Table 1. Bond lengths (Å) and angles (°) for **48**

Rh(1)-N(1)	2.0947(19)
Rh(1)-N(2)	2.1097(18)
Rh(1)-C(14)	2.135(2)
Rh(1)-C(18)	2.138(2)
Rh(1)-C(15)	2.145(2)
Rh(1)-C(19)	2.145(2)
N(1)-C(2)	1.331(3)
N(1)-C(1)	1.369(3)
N(2)-C(10)	1.332(3)
N(2)-C(9)	1.367(3)
C(1)-C(5)	1.400(3)
C(1)-C(9)	1.429(3)
C(2)-C(3)	1.394(3)
C(2)-H(2)	0.9500
C(3)-C(4)	1.366(4)
C(3)-H(3)	0.9500
C(4)-C(5)	1.413(3)
C(4)-H(4)	0.9500
C(5)-C(6)	1.434(3)
C(6)-C(7)	1.358(4)
C(6)-H(6)	0.9500
C(7)-C(8)	1.445(3)
C(7)-C(13)	1.506(4)
C(8)-C(9)	1.408(3)
C(8)-C(12)	1.409(3)
C(10)-C(11)	1.396(3)
C(10)-H(10)	0.9500
C(11)-C(12)	1.367(3)
C(11)-H(11)	0.9500
C(12)-H(12)	0.9500
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-C(15)	1.387(4)
C(14)-C(21)	1.508(4)
C(14)-H(14)	1.0000
C(15)-C(16)	1.515(4)
C(15)-H(15)	1.0000

C(16)-C(17)	1.489(4)
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(17)-C(18)	1.514(4)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-C(19)	1.384(4)
C(18)-H(18)	1.0000
C(19)-C(20)	1.515(4)
C(19)-H(19)	1.0000
C(20)-C(21)	1.497(4)
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-C(27)	1.399(3)
C(22)-C(23)	1.400(3)
C(22)-B(1)	1.647(3)
C(23)-C(24)	1.392(3)
C(23)-H(23)	0.9500
C(24)-C(25)	1.384(3)
C(24)-H(24)	0.9500
C(25)-C(26)	1.378(3)
C(25)-H(25)	0.9500
C(26)-C(27)	1.390(3)
C(26)-H(26)	0.9500
C(27)-H(27)	0.9500
C(28)-C(29)	1.398(3)
C(28)-C(33)	1.409(3)
C(28)-B(1)	1.644(3)
C(29)-C(30)	1.396(3)
C(29)-H(29)	0.9500
C(30)-C(31)	1.379(3)
C(30)-H(30)	0.9500
C(31)-C(32)	1.388(3)
C(31)-H(31)	0.9500
C(32)-C(33)	1.382(3)
C(32)-H(32)	0.9500
C(33)-H(33)	0.9500
C(34)-C(39)	1.390(3)
C(34)-C(35)	1.406(3)
C(34)-B(1)	1.651(3)
C(35)-C(36)	1.382(3)
C(35)-H(35)	0.9500
C(36)-C(37)	1.382(3)
C(36)-H(36)	0.9500
C(37)-C(38)	1.380(3)
C(37)-H(37)	0.9500
C(38)-C(39)	1.395(3)
C(38)-H(38)	0.9500
C(39)-H(39)	0.9500
C(40)-C(45)	1.399(3)
C(40)-C(41)	1.401(3)

C(40)-B(1)	1.651(3)
C(41)-C(42)	1.394(3)
C(41)-H(41)	0.9500
C(42)-C(43)	1.372(4)
C(42)-H(42)	0.9500
C(43)-C(44)	1.385(4)
C(43)-H(43)	0.9500
C(44)-H(44)	0.9500
C(45)-H(45)	0.9500

N(1)-Rh(1)-N(2)	78.94(7)
N(1)-Rh(1)-C(14)	94.45(8)
N(2)-Rh(1)-C(14)	152.71(9)
N(1)-Rh(1)-C(18)	161.42(9)
N(2)-Rh(1)-C(18)	98.27(9)
C(14)-Rh(1)-C(18)	95.90(10)
N(1)-Rh(1)-C(15)	98.11(9)
N(2)-Rh(1)-C(15)	168.64(9)
C(14)-Rh(1)-C(15)	37.80(10)
C(18)-Rh(1)-C(15)	80.99(10)
N(1)-Rh(1)-C(19)	160.14(9)
N(2)-Rh(1)-C(19)	95.47(9)
C(14)-Rh(1)-C(19)	81.78(9)
C(18)-Rh(1)-C(19)	37.72(12)
C(15)-Rh(1)-C(19)	90.82(10)
C(2)-N(1)-C(1)	117.5(2)
C(2)-N(1)-Rh(1)	128.92(16)
C(1)-N(1)-Rh(1)	113.36(14)
C(10)-N(2)-C(9)	117.80(19)
C(10)-N(2)-Rh(1)	128.74(16)
C(9)-N(2)-Rh(1)	113.13(14)
N(1)-C(1)-C(5)	123.1(2)
N(1)-C(1)-C(9)	117.3(2)
C(5)-C(1)-C(9)	119.7(2)
N(1)-C(2)-C(3)	123.2(2)
N(1)-C(2)-H(2)	118.4
C(3)-C(2)-H(2)	118.4
C(4)-C(3)-C(2)	119.4(2)
C(4)-C(3)-H(3)	120.3
C(2)-C(3)-H(3)	120.3
C(3)-C(4)-C(5)	119.6(2)
C(3)-C(4)-H(4)	120.2
C(5)-C(4)-H(4)	120.2
C(1)-C(5)-C(4)	117.2(2)
C(1)-C(5)-C(6)	119.3(2)
C(4)-C(5)-C(6)	123.6(2)
C(7)-C(6)-C(5)	121.8(2)
C(7)-C(6)-H(6)	119.1
C(5)-C(6)-H(6)	119.1
C(6)-C(7)-C(8)	119.8(2)
C(6)-C(7)-C(13)	119.9(2)
C(8)-C(7)-C(13)	120.4(2)
C(9)-C(8)-C(12)	117.1(2)

C(9)-C(8)-C(7)	119.3(2)
C(12)-C(8)-C(7)	123.6(2)
N(2)-C(9)-C(8)	123.0(2)
N(2)-C(9)-C(1)	116.80(19)
C(8)-C(9)-C(1)	120.2(2)
N(2)-C(10)-C(11)	122.8(2)
N(2)-C(10)-H(10)	118.6
C(11)-C(10)-H(10)	118.6
C(12)-C(11)-C(10)	119.6(2)
C(12)-C(11)-H(11)	120.2
C(10)-C(11)-H(11)	120.2
C(11)-C(12)-C(8)	119.7(2)
C(11)-C(12)-H(12)	120.2
C(8)-C(12)-H(12)	120.2
C(7)-C(13)-H(13A)	109.5
C(7)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(7)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(15)-C(14)-C(21)	126.2(3)
C(15)-C(14)-Rh(1)	71.46(14)
C(21)-C(14)-Rh(1)	109.71(17)
C(15)-C(14)-H(14)	113.8
C(21)-C(14)-H(14)	113.8
Rh(1)-C(14)-H(14)	113.8
C(14)-C(15)-C(16)	122.7(3)
C(14)-C(15)-Rh(1)	70.73(13)
C(16)-C(15)-Rh(1)	113.18(17)
C(14)-C(15)-H(15)	114.3
C(16)-C(15)-H(15)	114.3
Rh(1)-C(15)-H(15)	114.3
C(17)-C(16)-C(15)	114.0(2)
C(17)-C(16)-H(16A)	108.7
C(15)-C(16)-H(16A)	108.7
C(17)-C(16)-H(16B)	108.7
C(15)-C(16)-H(16B)	108.7
H(16A)-C(16)-H(16B)	107.6
C(16)-C(17)-C(18)	14.0(2)
C(16)-C(17)-H(17A)	108.8
C(18)-C(17)-H(17A)	108.8
C(16)-C(17)-H(17B)	108.8
C(18)-C(17)-H(17B)	108.8
H(17A)-C(17)-H(17B)	107.7
C(19)-C(18)-C(17)	125.6(3)
C(19)-C(18)-Rh(1)	71.44(14)
C(17)-C(18)-Rh(1)	111.33(18)
C(19)-C(18)-H(18)	113.6
C(17)-C(18)-H(18)	113.6
Rh(1)-C(18)-H(18)	113.6
C(18)-C(19)-C(20)	123.3(3)
C(18)-C(19)-Rh(1)	70.84(14)
C(20)-C(19)-Rh(1)	112.48(17)

C(18)-C(19)-H(19)	114.2
C(20)-C(19)-H(19)	114.2
Rh(1)-C(19)-H(19)	114.2
C(21)-C(20)-C(19)	113.5(2)
C(21)-C(20)-H(20A)	108.9
C(19)-C(20)-H(20A)	108.9
C(21)-C(20)-H(20B)	108.9
C(19)-C(20)-H(20B)	108.9
H(20A)-C(20)-H(20B)	107.7
C(20)-C(21)-C(14)	115.0(2)
C(20)-C(21)-H(21A)	108.5
C(14)-C(21)-H(21A)	108.5
C(20)-C(21)-H(21B)	108.5
C(14)-C(21)-H(21B)	108.5
H(21A)-C(21)-H(21B)	107.5
C(27)-C(22)-C(23)	114.59(19)
C(27)-C(22)-B(1)	124.52(19)
C(23)-C(22)-B(1)	120.78(18)
C(24)-C(23)-C(22)	123.3(2)
C(24)-C(23)-H(23)	118.4
C(22)-C(23)-H(23)	118.4
C(25)-C(24)-C(23)	120.1(2)
C(25)-C(24)-H(24)	119.9
C(23)-C(24)-H(24)	119.9
C(26)-C(25)-C(24)	118.4(2)
C(26)-C(25)-H(25)	120.8
C(24)-C(25)-H(25)	120.8
C(25)-C(26)-C(27)	120.8(2)
C(25)-C(26)-H(26)	119.6
C(27)-C(26)-H(26)	119.6
C(26)-C(27)-C(22)	122.8(2)
C(26)-C(27)-H(27)	118.6
C(22)-C(27)-H(27)	118.6
C(29)-C(28)-C(33)	114.9(2)
C(29)-C(28)-B(1)	125.43(19)
C(33)-C(28)-B(1)	119.57(19)
C(30)-C(29)-C(28)	122.4(2)
C(30)-C(29)-H(29)	118.8
C(28)-C(29)-H(29)	118.8
C(31)-C(30)-C(29)	120.9(2)
C(31)-C(30)-H(30)	119.6
C(29)-C(30)-H(30)	119.6
C(30)-C(31)-C(32)	118.4(2)
C(30)-C(31)-H(31)	120.8
C(32)-C(31)-H(31)	120.8
C(33)-C(32)-C(31)	120.3(2)
C(33)-C(32)-H(32)	119.8
C(31)-C(32)-H(32)	119.8
C(32)-C(33)-C(28)	123.1(2)
C(32)-C(33)-H(33)	118.5
C(28)-C(33)-H(33)	118.5
C(39)-C(34)-C(35)	114.48(19)
C(39)-C(34)-B(1)	127.16(18)

C(35)-C(34)-B(1)	118.34(18)
C(36)-C(35)-C(34)	123.6(2)
C(36)-C(35)-H(35)	118.2
C(34)-C(35)-H(35)	118.2
C(37)-C(36)-C(35)	119.9(2)
C(37)-C(36)-H(36)	120.1
C(35)-C(36)-H(36)	120.1
C(38)-C(37)-C(36)	118.6(2)
C(38)-C(37)-H(37)	120.7
C(36)-C(37)-H(37)	120.7
C(37)-C(38)-C(39)	120.5(2)
C(37)-C(38)-H(38)	119.7
C(39)-C(38)-H(38)	119.7
C(34)-C(39)-C(38)	122.8(2)
C(34)-C(39)-H(39)	118.6
C(38)-C(39)-H(39)	118.6
C(45)-C(40)-C(41)	114.8(2)
C(45)-C(40)-B(1)	120.40(18)
C(41)-C(40)-B(1)	124.83(19)
C(42)-C(41)-C(40)	123.0(2)
C(42)-C(41)-H(41)	118.5
C(40)-C(41)-H(41)	118.5
C(43)-C(42)-C(41)	120.5(2)
C(43)-C(42)-H(42)	119.8
C(41)-C(42)-H(42)	119.8
C(42)-C(43)-C(44)	118.8(2)
C(42)-C(43)-H(43)	120.6
C(44)-C(43)-H(43)	120.6
C(43)-C(44)-C(45)	120.1(2)
C(43)-C(44)-H(44)	120.0
C(45)-C(44)-H(44)	120.0
C(40)-C(45)-C(44)	122.9(2)
C(40)-C(45)-H(45)	118.6
C(44)-C(45)-H(45)	118.6
C(28)-B(1)-C(22)	111.13(17)
C(28)-B(1)-C(34)	106.19(17)
C(22)-B(1)-C(34)	112.93(17)
C(28)-B(1)-C(40)	110.94(17)
C(22)-B(1)-C(40)	106.28(17)
C(34)-B(1)-C(40)	109.43(17)

Table 2. Torsion angles (°) for **48**

N(2)-Rh(1)-N(1)-C(2)	-179.25(19)
C(14)-Rh(1)-N(1)-C(2)	27.48(19)
C(18)-Rh(1)-N(1)-C(2)	-96.2(3)
C(15)-Rh(1)-N(1)-C(2)	-10.4(2)
C(19)-Rh(1)-N(1)-C(2)	105.6(3)
N(2)-Rh(1)-N(1)-C(1)	5.67(13)
C(14)-Rh(1)-N(1)-C(1)	-147.59(15)
C(18)-Rh(1)-N(1)-C(1)	88.7(3)
C(15)-Rh(1)-N(1)-C(1)	174.54(15)
C(19)-Rh(1)-N(1)-C(1)	-69.5(3)
N(1)-Rh(1)-N(2)-C(10)	-179.4(2)
C(14)-Rh(1)-N(2)-C(10)	-101.3(2)
C(18)-Rh(1)-N(2)-C(10)	19.2(2)
C(15)-Rh(1)-N(2)-C(10)	104.7(4)
C(19)-Rh(1)-N(2)-C(10)	-18.7(2)
N(1)-Rh(1)-N(2)-C(9)	-6.29(14)
C(14)-Rh(1)-N(2)-C(9)	71.8(2)
C(18)-Rh(1)-N(2)-C(9)	-167.66(16)
C(15)-Rh(1)-N(2)-C(9)	-82.2(5)
C(19)-Rh(1)-N(2)-C(9)	154.44(16)
C(2)-N(1)-C(1)-C(5)	-1.0(3)
Rh(1)-N(1)-C(1)-C(5)	174.70(16)
C(2)-N(1)-C(1)-C(9)	179.99(19)
Rh(1)-N(1)-C(1)-C(9)	-4.3(2)
C(1)-N(1)-C(2)-C(3)	0.0(3)
Rh(1)-N(1)-C(2)-C(3)	-174.87(17)
N(1)-C(2)-C(3)-C(4)	0.8(4)
C(2)-C(3)-C(4)-C(5)	-0.7(4)
N(1)-C(1)-C(5)-C(4)	1.1(3)
C(9)-C(1)-C(5)-C(4)	-179.9(2)
N(1)-C(1)-C(5)-C(6)	-177.5(2)
C(9)-C(1)-C(5)-C(6)	1.5(3)
C(3)-C(4)-C(5)-C(1)	-0.2(4)
C(3)-C(4)-C(5)-C(6)	178.3(2)
C(1)-C(5)-C(6)-C(7)	-0.1(4)
C(4)-C(5)-C(6)-C(7)	-178.5(2)
C(5)-C(6)-C(7)-C(8)	-1.6(4)
C(5)-C(6)-C(7)-C(13)	177.1(2)
C(6)-C(7)-C(8)-C(9)	1.9(3)
C(13)-C(7)-C(8)-C(9)	-176.9(2)
C(6)-C(7)-C(8)-C(12)	-179.1(2)
C(13)-C(7)-C(8)-C(12)	2.2(4)
C(10)-N(2)-C(9)-C(8)	1.0(3)
Rh(1)-N(2)-C(9)-C(8)	-172.90(16)
C(10)-N(2)-C(9)-C(1)	179.9(2)
Rh(1)-N(2)-C(9)-C(1)	6.0(2)
C(12)-C(8)-C(9)-N(2)	-0.6(3)
C(7)-C(8)-C(9)-N(2)	178.5(2)
C(12)-C(8)-C(9)-C(1)	-179.53(19)
C(7)-C(8)-C(9)-C(1)	-0.4(3)
N(1)-C(1)-C(9)-N(2)	-1.2(3)
C(5)-C(1)-C(9)-N(2)	179.75(19)
N(1)-C(1)-C(9)-C(8)	177.78(18)
C(5)-C(1)-C(9)-C(8)	-1.3(3)
C(9)-N(2)-C(10)-C(11)	-0.3(3)
Rh(1)-N(2)-C(10)-C(11)	172.49(18)
N(2)-C(10)-C(11)-C(12)	-0.7(4)
C(10)-C(11)-C(12)-C(8)	1.1(4)
C(9)-C(8)-C(12)-C(11)	-0.4(3)
C(7)-C(8)-C(12)-C(11)	-179.5(2)

N(1)-Rh(1)-C(14)-C(15)	-97.51(15)
N(2)-Rh(1)-C(14)-C(15)	-171.90(17)
C(18)-Rh(1)-C(14)-C(15)	67.04(17)
C(19)-Rh(1)-C(14)-C(15)	102.11(17)
N(1)-Rh(1)-C(14)-C(21)	139.7(2)
N(2)-Rh(1)-C(14)-C(21)	65.3(3)
C(18)-Rh(1)-C(14)-C(21)	-55.8(2)
C(15)-Rh(1)-C(14)-C(21)	-122.8(3)
C(19)-Rh(1)-C(14)-C(21)	-20.7(2)
C(21)-C(14)-C(15)-C(16)	-4.5(4)
Rh(1)-C(14)-C(15)-C(16)	-105.7(2)
C(21)-C(14)-C(15)-Rh(1)	101.3(2)
N(1)-Rh(1)-C(15)-C(14)	86.79(15)
N(2)-Rh(1)-C(15)-C(14)	160.9(4)
C(18)-Rh(1)-C(15)-C(14)	-111.98(17)
C(19)-Rh(1)-C(15)-C(14)	-75.42(16)
N(1)-Rh(1)-C(15)-C(16)	-155.0(2)
N(2)-Rh(1)-C(15)-C(16)	-80.9(5)
C(14)-Rh(1)-C(15)-C(16)	118.2(3)
C(18)-Rh(1)-C(15)-C(16)	6.3(2)
C(19)-Rh(1)-C(15)-C(16)	42.8(2)
C(14)-C(15)-C(16)-C(17)	89.0(4)
Rh(1)-C(15)-C(16)-C(17)	7.7(4)
C(15)-C(16)-C(17)-C(18)	-24.0(5)
C(16)-C(17)-C(18)-C(19)	-53.2(4)
C(16)-C(17)-C(18)-Rh(1)	28.7(4)
N(1)-Rh(1)-C(18)-C(19)	-168.1(2)
N(2)-Rh(1)-C(18)-C(19)	-88.24(15)
C(14)-Rh(1)-C(18)-C(19)	68.38(16)
C(15)-Rh(1)-C(18)-C(19)	103.23(17)
N(1)-Rh(1)-C(18)-C(17)	70.0(4)
N(2)-Rh(1)-C(18)-C(17)	149.8(2)
C(14)-Rh(1)-C(18)-C(17)	-53.5(2)
C(15)-Rh(1)-C(18)-C(17)	-18.7(2)
C(19)-Rh(1)-C(18)-C(17)	-121.9(3)
C(17)-C(18)-C(19)-C(20)	-1.5(4)
Rh(1)-C(18)-C(19)-C(20)	-104.8(2)
C(17)-C(18)-C(19)-Rh(1)	103.4(3)
N(1)-Rh(1)-C(19)-C(18)	168.9(2)
N(2)-Rh(1)-C(19)-C(18)	96.46(15)
C(14)-Rh(1)-C(19)-C(18)	-110.89(16)
C(15)-Rh(1)-C(19)-C(18)	-74.06(16)
N(1)-Rh(1)-C(19)-C(20)	-72.1(3)
N(2)-Rh(1)-C(19)-C(20)	-144.5(2)
C(14)-Rh(1)-C(19)-C(20)	8.2(2)
C(18)-Rh(1)-C(19)-C(20)	119.0(3)
C(15)-Rh(1)-C(19)-C(20)	45.0(2)
C(18)-C(19)-C(20)-C(21)	87.6(4)
Rh(1)-C(19)-C(20)-C(21)	6.4(4)
C(19)-C(20)-C(21)-C(14)	-24.9(4)
C(15)-C(14)-C(21)-C(20)	-50.1(4)
Rh(1)-C(14)-C(21)-C(20)	30.9(4)
C(27)-C(22)-C(23)-C(24)	-1.4(3)
B(1)-C(22)-C(23)-C(24)	-177.67(19)
C(22)-C(23)-C(24)-C(25)	0.4(3)
C(23)-C(24)-C(25)-C(26)	0.6(3)
C(24)-C(25)-C(26)-C(27)	-0.5(4)
C(25)-C(26)-C(27)-C(22)	-0.5(4)
C(23)-C(22)-C(27)-C(26)	1.4(3)
B(1)-C(22)-C(27)-C(26)	177.5(2)
C(33)-C(28)-C(29)-C(30)	1.1(3)
B(1)-C(28)-C(29)-C(30)	-175.4(2)
C(28)-C(29)-C(30)-C(31)	-1.1(3)
C(29)-C(30)-C(31)-C(32)	-0.1(3)

C(30)-C(31)-C(32)-C(33)	1.4(3)
C(31)-C(32)-C(33)-C(28)	-1.4(3)
C(29)-C(28)-C(33)-C(32)	0.2(3)
B(1)-C(28)-C(33)-C(32)	176.9(2)
C(39)-C(34)-C(35)-C(36)	2.2(3)
B(1)-C(34)-C(35)-C(36)	-176.2(2)
C(34)-C(35)-C(36)-C(37)	-0.6(4)
C(35)-C(36)-C(37)-C(38)	-1.3(4)
C(36)-C(37)-C(38)-C(39)	1.4(4)
C(35)-C(34)-C(39)-C(38)	-2.1(3)
B(1)-C(34)-C(39)-C(38)	176.1(2)
C(37)-C(38)-C(39)-C(34)	0.4(4)
C(45)-C(40)-C(41)-C(42)	-1.0(3)
B(1)-C(40)-C(41)-C(42)	178.0(2)
C(40)-C(41)-C(42)-C(43)	0.8(4)
C(41)-C(42)-C(43)-C(44)	-0.4(4)
C(42)-C(43)-C(44)-C(45)	0.4(4)
C(41)-C(40)-C(45)-C(44)	1.0(3)
B(1)-C(40)-C(45)-C(44)	-178.1(2)
C(43)-C(44)-C(45)-C(40)	-0.7(4)
C(29)-C(28)-B(1)-C(22)	-121.3(2)
C(33)-C(28)-B(1)-C(22)	62.3(2)
C(29)-C(28)-B(1)-C(34)	115.5(2)
C(33)-C(28)-B(1)-C(34)	-60.9(2)
C(29)-C(28)-B(1)-C(40)	-3.3(3)
C(33)-C(28)-B(1)-C(40)	-179.68(18)
C(27)-C(22)-B(1)-C(28)	9.9(3)
C(23)-C(22)-B(1)-C(28)	-174.22(18)
C(27)-C(22)-B(1)-C(34)	129.1(2)
C(23)-C(22)-B(1)-C(34)	-55.0(3)
C(27)-C(22)-B(1)-C(40)	-110.9(2)
C(23)-C(22)-B(1)-C(40)	65.0(2)
C(39)-C(34)-B(1)-C(28)	126.6(2)
C(35)-C(34)-B(1)-C(28)	-55.3(2)
C(39)-C(34)-B(1)-C(22)	4.6(3)
C(35)-C(34)-B(1)-C(22)	-177.31(19)
C(39)-C(34)-B(1)-C(40)	-113.6(2)
C(35)-C(34)-B(1)-C(40)	64.5(2)
C(45)-C(40)-B(1)-C(28)	-67.3(2)
C(41)-C(40)-B(1)-C(28)	113.8(2)
C(45)-C(40)-B(1)-C(22)	53.7(2)
C(41)-C(40)-B(1)-C(22)	-125.3(2)
C(45)-C(40)-B(1)-C(34)	175.90(19)
C(41)-C(40)-B(1)-C(34)	-3.1(3)

Complex **54**

Table 3.Bond lengths (Å) and angles (°) for **54**

Rh(1)-N(2)	2.101(3)	Rh(1)-N(1)	2.112(3)
Rh(1)-C(16)	2.140(3)	Rh(1)-C(14)	2.149(3)
Rh(1)-C(15)	2.162(3)	Rh(1)-C(17)	2.165(3)
Rh(1)-C(18)	2.171(3)	Rh(1)-Cl(1)	2.3995(8)
P(1)-F(13)	1.512(15)	P(1)-F(16)	1.512(15)
P(1)-F(12)	1.530(8)	P(1)-F(7)	1.540(9)
P(1)-F(10)	1.548(8)	P(1)-F(2)	1.568(6)
P(1)-F(8)	1.570(10)	P(1)-F(4)	1.582(6)
P(1)-F(5)	1.625(6)	P(1)-F(14)	1.626(11)
P(1)-F(11)	1.658(7)	P(1)-F(1)	1.661(12)
F(1)-F(2)	0.675(12)	F(1)-F(3)	1.266(14)
F(2)-F(3)	0.627(8)	F(6)-F(7)	0.674(18)
F(6)-F(8)	0.873(18)	F(9)-F(10)	0.586(10)
F(11)-F(12)	0.612(9)	F(13)-F(14)	0.656(16)
F(13)-F(16)	0.97(3)	F(13)-F(15)	1.04(2)
F(15)-F(16)	0.515(19)	N(1)-C(2)	1.329(4)
N(1)-C(1)	1.357(4)	N(2)-C(10)	1.328(4)
N(2)-C(9)	1.362(4)	C(1)-C(5)	1.407(4)
C(1)-C(9)	1.425(5)	C(2)-C(3)	1.403(5)
C(2)-H(2)	0.9500	C(3)-C(4)	1.350(7)
C(3)-H(3)	0.9500	C(4)-C(5)	1.413(6)
C(4)-H(4)	0.9500	C(5)-C(6A)	1.436(6)
C(8)-C(12)	1.397(6)	C(8)-C(9)	1.404(5)
C(8)-C(7A)	1.441(5)	C(10)-C(11)	1.418(5)
C(10)-H(10)	0.9500	C(11)-C(12)	1.352(5)
C(11)-H(11)	0.9500	C(12)-H(12)	0.9500
C(14)-C(15)	1.430(5)	C(14)-C(18)	1.445(5)
C(14)-C(19)	1.495(5)	C(15)-C(16)	1.433(5)
C(15)-C(20)	1.493(5)	C(16)-C(17)	1.437(6)
C(16)-C(21)	1.503(5)	C(17)-C(18)	1.419(5)
C(17)-C(22)	1.491(5)	C(18)-C(23)	1.494(6)
C(19)-H(19A)	0.9800	C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800	C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800	C(20)-H(20C)	0.9800
C(21)-H(21A)	0.9800	C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800	C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800	C(22)-H(22C)	0.9800
C(23)-H(23A)	0.9800	C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800	C(6A)-C(7A)	1.347(6)
C(6A)-C(13A)	1.522(6)	C(7A)-H(7A)	0.9500
C(13A)-H(13A)	0.9800	C(13A)-H(13B)	0.9800
C(13A)-H(13C)	0.9800	C(13B)-H(13D)	0.9800
C(13B)-H(13E)	0.9800	C(13B)-H(13F)	0.9800
N(2)-Rh(1)-N(1)	77.79(11)	N(2)-Rh(1)-C(16)	111.08(13)
N(1)-Rh(1)-C(16)	165.95(12)	N(2)-Rh(1)-C(14)	113.59(12)
N(1)-Rh(1)-C(14)	101.09(12)	C(16)-Rh(1)-C(14)	65.64(14)
N(2)-Rh(1)-C(15)	94.85(12)	N(1)-Rh(1)-C(15)	132.16(12)
C(16)-Rh(1)-C(15)	38.92(14)	C(14)-Rh(1)-C(15)	38.76(14)
N(2)-Rh(1)-C(17)	149.63(14)	N(1)-Rh(1)-C(17)	132.52(14)
C(16)-Rh(1)-C(17)	38.99(15)	C(14)-Rh(1)-C(17)	64.71(14)
C(15)-Rh(1)-C(17)	64.42(15)	N(2)-Rh(1)-C(18)	152.50(12)
N(1)-Rh(1)-C(18)	101.64(13)	C(16)-Rh(1)-C(18)	65.34(14)
C(14)-Rh(1)-C(18)	39.07(14)	C(15)-Rh(1)-C(18)	64.81(14)
C(17)-Rh(1)-C(18)	38.19(14)	N(2)-Rh(1)-Cl(1)	89.46(7)
N(1)-Rh(1)-Cl(1)	87.10(7)	C(16)-Rh(1)-Cl(1)	103.47(10)
C(14)-Rh(1)-Cl(1)	156.62(10)	C(15)-Rh(1)-Cl(1)	140.54(10)
C(17)-Rh(1)-Cl(1)	93.56(10)	C(18)-Rh(1)-Cl(1)	118.04(10)
F(13)-P(1)-F(16)	37.4(10)	F(13)-P(1)-F(12)	165.7(8)
F(16)-P(1)-F(12)	153.2(7)	F(13)-P(1)-F(7)	63.1(8)
F(16)-P(1)-F(7)	97.6(8)	F(12)-P(1)-F(7)	102.8(5)
F(13)-P(1)-F(10)	128.0(8)	F(16)-P(1)-F(10)	91.6(8)
F(12)-P(1)-F(10)	65.6(4)	F(7)-P(1)-F(10)	166.6(6)
F(13)-P(1)-F(2)	95.1(6)	F(16)-P(1)-F(2)	84.4(7)
F(12)-P(1)-F(2)	80.6(4)	F(7)-P(1)-F(2)	84.3(5)
F(10)-P(1)-F(2)	86.9(4)	F(13)-P(1)-F(8)	48.4(7)
F(16)-P(1)-F(8)	84.9(8)	F(12)-P(1)-F(8)	118.0(5)
F(7)-P(1)-F(8)	16.5(5)	F(10)-P(1)-F(8)	176.4(5)
F(2)-P(1)-F(8)	93.4(5)	F(13)-P(1)-F(4)	89.6(6)
F(16)-P(1)-F(4)	103.7(6)	F(12)-P(1)-F(4)	93.1(4)
F(7)-P(1)-F(4)	91.3(4)	F(10)-P(1)-F(4)	96.0(4)
F(2)-P(1)-F(4)	171.3(4)	F(8)-P(1)-F(4)	84.2(5)
F(13)-P(1)-F(5)	86.7(6)	F(16)-P(1)-F(5)	92.5(6)
F(12)-P(1)-F(5)	99.4(4)	F(7)-P(1)-F(5)	103.4(4)
F(10)-P(1)-F(5)	85.9(4)	F(2)-P(1)-F(5)	172.1(4)
F(8)-P(1)-F(5)	93.5(5)	F(4)-P(1)-F(5)	15.3(3)
F(13)-P(1)-F(14)	23.8(6)	F(16)-P(1)-F(14)	15.8(7)
F(12)-P(1)-F(14)	168.8(6)	F(7)-P(1)-F(14)	86.7(7)
F(10)-P(1)-F(14)	104.2(6)	F(2)-P(1)-F(14)	94.7(5)
F(8)-P(1)-F(14)	72.2(6)	F(4)-P(1)-F(14)	92.5(5)
F(5)-P(1)-F(14)	83.9(5)	F(13)-P(1)-F(11)	147.1(8)

F(16)-P(1)-F(11)	174.8(7)	F(12)-P(1)-F(11)	21.7(3)
F(7)-P(1)-F(11)	85.8(5)	F(10)-P(1)-F(11)	84.3(4)
F(2)-P(1)-F(11)	92.1(4)	F(8)-P(1)-F(11)	99.2(5)
F(4)-P(1)-F(11)	80.1(3)	F(5)-P(1)-F(11)	90.5(3)
F(14)-P(1)-F(11)	169.4(5)	F(13)-P(1)-F(1)	93.6(7)
F(16)-P(1)-F(1)	97.7(8)	F(12)-P(1)-F(1)	76.8(5)
F(7)-P(1)-F(1)	62.9(6)	F(10)-P(1)-F(1)	106.3(6)
F(2)-P(1)-F(1)	23.9(4)	F(8)-P(1)-F(1)	74.9(6)
F(4)-P(1)-F(1)	148.6(5)	F(5)-P(1)-F(1)	163.8(5)
F(14)-P(1)-F(1)	102.8(6)	F(11)-P(1)-F(1)	80.4(5)
F(2)-F(1)-F(3)	13.0(9)	F(2)-F(1)-P(1)	70.3(12)
F(3)-F(1)-P(1)	67.8(7)	F(3)-F(2)-F(1)	153.0(19)
F(3)-F(2)-P(1)	87.7(10)	F(1)-F(2)-P(1)	85.8(13)
F(2)-F(3)-F(1)	14.0(10)	F(2)-F(3)-P(1)	70.2(10)
F(1)-F(3)-P(1)	67.5(6)	F(7)-F(6)-F(8)	30.3(14)
F(7)-F(6)-P(1)	64.1(17)	F(8)-F(6)-P(1)	65.9(12)
F(6)-F(7)-P(1)	92.6(19)	F(6)-F(8)-P(1)	83.6(13)
F(10)-F(9)-P(1)	64.6(12)	F(9)-F(10)-P(1)	95.4(13)
F(12)-F(11)-P(1)	67.3(11)	F(11)-F(12)-P(1)	91.0(12)
F(14)-F(13)-F(16)	23.0(18)	F(14)-F(13)-F(15)	10.6(17)
F(16)-F(13)-F(15)	29.4(13)	F(14)-F(13)-P(1)	87.9(19)
F(16)-F(13)-P(1)	71.3(12)	F(15)-F(13)-P(1)	85.4(12)
F(13)-F(14)-P(1)	68.3(17)	F(16)-F(15)-F(13)	68(3)
F(16)-F(15)-P(1)	53(2)	F(13)-F(15)-P(1)	58.7(10)
F(15)-F(16)-F(13)	83(4)	F(15)-F(16)-P(1)	111(3)
F(13)-F(16)-P(1)	71.3(13)	C(2)-N(1)-C(1)	118.4(3)
C(2)-N(1)-Rh(1)	127.5(3)	C(1)-N(1)-Rh(1)	114.0(2)
C(10)-N(2)-C(9)	118.7(3)	C(10)-N(2)-Rh(1)	127.2(2)
C(9)-N(2)-Rh(1)	114.0(2)	N(1)-C(1)-C(5)	123.5(3)
N(1)-C(1)-C(9)	116.5(3)	C(5)-C(1)-C(9)	120.0(3)
N(1)-C(2)-C(3)	121.4(4)	N(1)-C(2)-H(2)	119.3
C(3)-C(2)-H(2)	119.3	C(4)-C(3)-C(2)	120.7(4)
C(4)-C(3)-H(3)	119.6	C(2)-C(3)-H(3)	119.6
C(3)-C(4)-C(5)	119.7(3)	C(3)-C(4)-H(4)	120.1
C(5)-C(4)-H(4)	120.1	C(1)-C(5)-C(4)	116.2(4)
C(1)-C(5)-C(6A)	118.7(3)	C(4)-C(5)-C(6A)	125.1(3)
C(12)-C(8)-C(9)	117.1(3)	C(12)-C(8)-C(7A)	124.8(3)
C(9)-C(8)-C(7A)	118.1(4)	N(2)-C(9)-C(8)	122.6(3)
N(2)-C(9)-C(1)	116.8(3)	C(8)-C(9)-C(1)	120.5(3)
N(2)-C(10)-C(11)	121.6(3)	N(2)-C(10)-H(10)	119.2
C(11)-C(10)-H(10)	119.2	C(12)-C(11)-C(10)	119.4(3)
C(12)-C(11)-H(11)	120.3	C(10)-C(11)-H(11)	120.3
C(11)-C(12)-C(8)	120.5(3)	C(11)-C(12)-H(12)	119.7
C(8)-C(12)-H(12)	119.7	C(15)-C(14)-C(18)	107.7(3)
C(15)-C(14)-C(19)	125.4(4)	C(18)-C(14)-C(19)	126.6(4)
C(15)-C(14)-Rh(1)	71.14(18)	C(18)-C(14)-Rh(1)	71.30(18)
C(19)-C(14)-Rh(1)	127.4(3)	C(14)-C(15)-C(16)	108.5(3)
C(14)-C(15)-C(20)	124.2(3)	C(16)-C(15)-C(20)	127.3(3)
C(14)-C(15)-Rh(1)	70.10(18)	C(16)-C(15)-Rh(1)	69.68(19)
C(20)-C(15)-Rh(1)	126.5(3)	C(15)-C(16)-C(17)	107.0(3)
C(15)-C(16)-C(21)	126.5(4)	C(17)-C(16)-C(21)	126.3(4)
C(15)-C(16)-Rh(1)	71.40(18)	C(17)-C(16)-Rh(1)	71.5(2)
C(21)-C(16)-Rh(1)	127.1(2)	C(18)-C(17)-C(16)	109.2(3)
C(18)-C(17)-C(22)	125.8(4)	C(16)-C(17)-C(22)	125.0(4)
C(18)-C(17)-Rh(1)	71.12(19)	C(16)-C(17)-Rh(1)	69.53(19)
C(22)-C(17)-Rh(1)	126.4(3)	C(17)-C(18)-C(14)	107.5(3)
C(17)-C(18)-C(23)	125.9(4)	C(14)-C(18)-C(23)	126.4(3)
C(17)-C(18)-Rh(1)	70.69(19)	C(14)-C(18)-Rh(1)	69.63(19)
C(23)-C(18)-Rh(1)	128.4(3)	C(14)-C(19)-H(19A)	109.5
C(14)-C(19)-H(19B)	109.5	H(19A)-C(19)-H(19B)	109.5
C(14)-C(19)-H(19C)	109.5	H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5	C(15)-C(20)-H(20A)	109.5
C(15)-C(20)-H(20B)	109.5	H(20A)-C(20)-H(20B)	109.5
C(15)-C(20)-H(20C)	109.5	H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5	C(16)-C(21)-H(21A)	109.5
C(16)-C(21)-H(21B)	109.5	H(21A)-C(21)-H(21B)	109.5
C(16)-C(21)-H(21C)	109.5	H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5	C(17)-C(22)-H(22A)	109.5
C(17)-C(22)-H(22B)	109.5	H(22A)-C(22)-H(22B)	109.5
C(17)-C(22)-H(22C)	109.5	H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5	C(18)-C(23)-H(23A)	109.5
C(18)-C(23)-H(23B)	109.5	H(23A)-C(23)-H(23B)	109.5
C(18)-C(23)-H(23C)	109.5	H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5	C(7A)-C(6A)-C(5)	121.0(3)
C(7A)-C(6A)-C(13A)	113.2(4)	C(5)-C(6A)-C(13A)	125.7(4)
C(6A)-C(7A)-C(8)	121.5(3)	C(6A)-C(7A)-H(7A)	119.2
C(8)-C(7A)-H(7A)	119.2	C(6A)-C(13A)-H(13A)	109.5
C(6A)-C(13A)-H(13B)	109.5	H(13A)-C(13A)-H(13B)	109.5
C(6A)-C(13A)-H(13C)	109.5	H(13A)-C(13A)-H(13C)	109.5
H(13B)-C(13A)-H(13C)	109.5	H(13D)-C(13B)-H(13E)	109.5
H(13D)-C(13B)-H(13F)	109.5	H(13E)-C(13B)-H(13F)	109.5

Table 4. Torsion angles (°)for **54**.

N(2)-Rh(1)-N(1)-C(2)	172.4(3)
C(16)-Rh(1)-N(1)-C(2)	-57.0(6)
C(14)-Rh(1)-N(1)-C(2)	-75.6(3)
C(15)-Rh(1)-N(1)-C(2)	-102.2(3)
C(17)-Rh(1)-N(1)-C(2)	-9.9(4)
C(18)-Rh(1)-N(1)-C(2)	-35.7(3)
Cl(1)-Rh(1)-N(1)-C(2)	82.3(3)
N(2)-Rh(1)-N(1)-C(1)	-7.7(2)
C(16)-Rh(1)-N(1)-C(1)	122.9(5)
C(14)-Rh(1)-N(1)-C(1)	104.3(2)
C(15)-Rh(1)-N(1)-C(1)	77.7(3)
C(17)-Rh(1)-N(1)-C(1)	170.0(2)
C(18)-Rh(1)-N(1)-C(1)	144.2(2)
Cl(1)-Rh(1)-N(1)-C(1)	-97.8(2)
N(1)-Rh(1)-N(2)-C(10)	-173.8(3)
C(16)-Rh(1)-N(2)-C(10)	17.6(3)
C(14)-Rh(1)-N(2)-C(10)	89.3(3)
C(15)-Rh(1)-N(2)-C(10)	54.0(3)
C(17)-Rh(1)-N(2)-C(10)	9.4(4)
C(18)-Rh(1)-N(2)-C(10)	94.4(4)
Cl(1)-Rh(1)-N(2)-C(10)	-86.7(3)
N(1)-Rh(1)-N(2)-C(9)	7.7(2)
C(16)-Rh(1)-N(2)-C(9)	-160.9(2)
C(14)-Rh(1)-N(2)-C(9)	-89.2(2)
C(15)-Rh(1)-N(2)-C(9)	-124.4(2)
C(17)-Rh(1)-N(2)-C(9)	-169.0(2)
C(18)-Rh(1)-N(2)-C(9)	-84.1(3)
Cl(1)-Rh(1)-N(2)-C(9)	94.88(19)
C(2)-N(1)-C(1)-C(5)	3.5(5)
Rh(1)-N(1)-C(1)-C(5)	-176.4(2)
C(2)-N(1)-C(1)-C(9)	-173.4(3)
Rh(1)-N(1)-C(1)-C(9)	6.7(3)
C(1)-N(1)-C(2)-C(3)	-2.6(5)
Rh(1)-N(1)-C(2)-C(3)	177.3(3)
N(1)-C(2)-C(3)-C(4)	-0.1(6)
C(2)-C(3)-C(4)-C(5)	2.0(6)
N(1)-C(1)-C(5)-C(4)	-1.7(5)
C(9)-C(1)-C(5)-C(4)	175.2(3)
N(1)-C(1)-C(5)-C(6A)	179.9(3)
C(9)-C(1)-C(5)-C(6A)	-3.2(4)
C(3)-C(4)-C(5)-C(1)	-1.2(5)
C(3)-C(4)-C(5)-C(6A)	177.2(3)
C(10)-N(2)-C(9)-C(8)	-2.7(4)
Rh(1)-N(2)-C(9)-C(8)	175.9(2)
C(10)-N(2)-C(9)-C(1)	174.6(3)
Rh(1)-N(2)-C(9)-C(1)	-6.8(3)
C(12)-C(8)-C(9)-N(2)	1.7(5)
C(7A)-C(8)-C(9)-N(2)	-179.8(3)
C(12)-C(8)-C(9)-C(1)	-175.5(3)
C(7A)-C(8)-C(9)-C(1)	3.1(4)
N(1)-C(1)-C(9)-N(2)	0.1(4)
C(5)-C(1)-C(9)-N(2)	-177.0(3)
N(1)-C(1)-C(9)-C(8)	177.4(3)
C(5)-C(1)-C(9)-C(8)	0.3(4)
C(9)-N(2)-C(10)-C(11)	0.7(5)
Rh(1)-N(2)-C(10)-C(11)	-177.7(2)
N(2)-C(10)-C(11)-C(12)	2.2(5)
C(10)-C(11)-C(12)-C(8)	-3.2(5)
C(9)-C(8)-C(12)-C(11)	1.3(5)
C(7A)-C(8)-C(12)-C(11)	-177.2(3)
N(2)-Rh(1)-C(14)-C(15)	-66.6(2)
N(1)-Rh(1)-C(14)-C(15)	-148.0(2)

C(16)-Rh(1)-C(14)-C(15)	36.8(2)
C(17)-Rh(1)-C(14)-C(15)	80.0(2)
C(18)-Rh(1)-C(14)-C(15)	117.1(3)
Cl(1)-Rh(1)-C(14)-C(15)	103.1(3)
N(2)-Rh(1)-C(14)-C(18)	176.25(19)
N(1)-Rh(1)-C(14)-C(18)	94.9(2)
C(16)-Rh(1)-C(14)-C(18)	-80.3(2)
C(15)-Rh(1)-C(14)-C(18)	-117.1(3)
C(17)-Rh(1)-C(14)-C(18)	-37.1(2)
Cl(1)-Rh(1)-C(14)-C(18)	-14.0(4)
N(2)-Rh(1)-C(14)-C(19)	54.0(4)
N(1)-Rh(1)-C(14)-C(19)	-27.4(4)
C(16)-Rh(1)-C(14)-C(19)	157.5(4)
C(15)-Rh(1)-C(14)-C(19)	120.6(4)
C(17)-Rh(1)-C(14)-C(19)	-159.4(4)
C(18)-Rh(1)-C(14)-C(19)	-122.3(4)
Cl(1)-Rh(1)-C(14)-C(19)	-136.3(3)
C(18)-C(14)-C(15)-C(16)	3.0(4)
C(19)-C(14)-C(15)-C(16)	177.7(3)
Rh(1)-C(14)-C(15)-C(16)	-59.3(2)
C(18)-C(14)-C(15)-C(20)	-176.5(3)
C(19)-C(14)-C(15)-C(20)	-1.8(5)
Rh(1)-C(14)-C(15)-C(20)	121.2(3)
C(18)-C(14)-C(15)-Rh(1)	62.3(2)
C(19)-C(14)-C(15)-Rh(1)	-123.0(4)
N(2)-Rh(1)-C(15)-C(14)	122.4(2)
N(1)-Rh(1)-C(15)-C(14)	44.5(3)
C(16)-Rh(1)-C(15)-C(14)	-119.6(3)
C(17)-Rh(1)-C(15)-C(14)	-80.8(2)
C(18)-Rh(1)-C(15)-C(14)	-38.3(2)
Cl(1)-Rh(1)-C(15)-C(14)	-142.55(18)
N(2)-Rh(1)-C(15)-C(16)	-118.0(2)
N(1)-Rh(1)-C(15)-C(16)	164.1(2)
C(14)-Rh(1)-C(15)-C(16)	119.6(3)
C(17)-Rh(1)-C(15)-C(16)	38.8(2)
C(18)-Rh(1)-C(15)-C(16)	81.3(2)
Cl(1)-Rh(1)-C(15)-C(16)	-22.9(3)
N(2)-Rh(1)-C(15)-C(20)	4.0(3)
N(1)-Rh(1)-C(15)-C(20)	-73.9(4)
C(16)-Rh(1)-C(15)-C(20)	122.0(4)
C(14)-Rh(1)-C(15)-C(20)	-118.4(4)
C(17)-Rh(1)-C(15)-C(20)	160.8(4)
C(18)-Rh(1)-C(15)-C(20)	-156.7(4)
Cl(1)-Rh(1)-C(15)-C(20)	99.1(3)
C(14)-C(15)-C(16)-C(17)	-3.5(4)
C(20)-C(15)-C(16)-C(17)	176.0(3)
Rh(1)-C(15)-C(16)-C(17)	-63.0(2)
C(14)-C(15)-C(16)-C(21)	-177.6(3)
C(20)-C(15)-C(16)-C(21)	1.9(6)
Rh(1)-C(15)-C(16)-C(21)	122.9(3)
C(14)-C(15)-C(16)-Rh(1)	59.6(2)
C(20)-C(15)-C(16)-Rh(1)	-121.0(4)
N(2)-Rh(1)-C(16)-C(15)	70.5(2)
N(1)-Rh(1)-C(16)-C(15)	-56.8(6)
C(14)-Rh(1)-C(16)-C(15)	-36.7(2)
C(17)-Rh(1)-C(16)-C(15)	-116.0(3)
C(18)-Rh(1)-C(16)-C(15)	-79.8(2)
Cl(1)-Rh(1)-C(16)-C(15)	165.24(19)
N(2)-Rh(1)-C(16)-C(17)	-173.49(19)
N(1)-Rh(1)-C(16)-C(17)	59.2(6)
C(14)-Rh(1)-C(16)-C(17)	79.3(2)
C(15)-Rh(1)-C(16)-C(17)	116.0(3)
C(18)-Rh(1)-C(16)-C(17)	36.2(2)
Cl(1)-Rh(1)-C(16)-C(17)	-78.8(2)

N(2)-Rh(1)-C(16)-C(21)	-51.6(4)
N(1)-Rh(1)-C(16)-C(21)	-178.9(4)
C(14)-Rh(1)-C(16)-C(21)	-158.8(4)
C(15)-Rh(1)-C(16)-C(21)	-122.1(5)
C(17)-Rh(1)-C(16)-C(21)	121.9(5)
C(18)-Rh(1)-C(16)-C(21)	158.1(4)
Cl(1)-Rh(1)-C(16)-C(21)	43.1(4)
C(15)-C(16)-C(17)-C(18)	2.7(4)
C(21)-C(16)-C(17)-C(18)	176.8(3)
Rh(1)-C(16)-C(17)-C(18)	-60.3(2)
C(15)-C(16)-C(17)-C(22)	-176.3(3)
C(21)-C(16)-C(17)-C(22)	-2.2(6)
Rh(1)-C(16)-C(17)-C(22)	120.7(4)
C(15)-C(16)-C(17)-Rh(1)	63.0(2)
C(21)-C(16)-C(17)-Rh(1)	-122.9(3)
N(2)-Rh(1)-C(17)-C(18)	131.9(3)
N(1)-Rh(1)-C(17)-C(18)	-43.7(3)
C(16)-Rh(1)-C(17)-C(18)	119.9(3)
C(14)-Rh(1)-C(17)-C(18)	38.0(2)
C(15)-Rh(1)-C(17)-C(18)	81.1(2)
Cl(1)-Rh(1)-C(17)-C(18)	-133.0(2)
N(2)-Rh(1)-C(17)-C(16)	12.1(3)
N(1)-Rh(1)-C(17)-C(16)	-163.57(18)
C(14)-Rh(1)-C(17)-C(16)	-81.9(2)
C(15)-Rh(1)-C(17)-C(16)	-38.8(2)
C(18)-Rh(1)-C(17)-C(16)	-119.9(3)
Cl(1)-Rh(1)-C(17)-C(16)	107.10(19)
N(2)-Rh(1)-C(17)-C(22)	-107.0(4)
N(1)-Rh(1)-C(17)-C(22)	77.3(4)
C(16)-Rh(1)-C(17)-C(22)	-119.1(5)
C(14)-Rh(1)-C(17)-C(22)	159.0(4)
C(15)-Rh(1)-C(17)-C(22)	-157.9(4)
C(18)-Rh(1)-C(17)-C(22)	121.0(5)
Cl(1)-Rh(1)-C(17)-C(22)	-12.0(4)
C(16)-C(17)-C(18)-C(14)	-0.9(4)
C(22)-C(17)-C(18)-C(14)	178.1(4)
Rh(1)-C(17)-C(18)-C(14)	-60.2(2)
C(16)-C(17)-C(18)-C(23)	-176.7(3)
C(22)-C(17)-C(18)-C(23)	2.3(6)
Rh(1)-C(17)-C(18)-C(23)	124.0(4)
C(16)-C(17)-C(18)-Rh(1)	59.3(2)
C(22)-C(17)-C(18)-Rh(1)	-121.7(4)
C(15)-C(14)-C(18)-C(17)	-1.3(4)
C(19)-C(14)-C(18)-C(17)	-175.9(3)
Rh(1)-C(14)-C(18)-C(17)	60.9(2)
C(15)-C(14)-C(18)-C(23)	174.5(3)
C(19)-C(14)-C(18)-C(23)	-0.1(6)
Rh(1)-C(14)-C(18)-C(23)	-123.3(4)
C(15)-C(14)-C(18)-Rh(1)	-62.2(2)
C(19)-C(14)-C(18)-Rh(1)	123.2(4)
N(2)-Rh(1)-C(18)-C(17)	-125.5(3)
N(1)-Rh(1)-C(18)-C(17)	148.7(2)
C(16)-Rh(1)-C(18)-C(17)	-36.9(2)
C(14)-Rh(1)-C(18)-C(17)	-118.0(3)
C(15)-Rh(1)-C(18)-C(17)	-80.0(2)
Cl(1)-Rh(1)-C(18)-C(17)	55.7(2)
N(2)-Rh(1)-C(18)-C(14)	-7.5(4)
N(1)-Rh(1)-C(18)-C(14)	-93.3(2)
C(16)-Rh(1)-C(18)-C(14)	81.1(2)
C(15)-Rh(1)-C(18)-C(14)	38.0(2)
C(17)-Rh(1)-C(18)-C(14)	118.0(3)
Cl(1)-Rh(1)-C(18)-C(14)	173.75(17)
N(2)-Rh(1)-C(18)-C(23)	113.5(4)
N(1)-Rh(1)-C(18)-C(23)	27.6(4)

C(16)-Rh(1)-C(18)-C(23)	-158.0(4)
C(14)-Rh(1)-C(18)-C(23)	120.9(4)
C(15)-Rh(1)-C(18)-C(23)	158.9(4)
C(17)-Rh(1)-C(18)-C(23)	-121.1(4)
Cl(1)-Rh(1)-C(18)-C(23)	-65.3(4)
C(1)-C(5)-C(6A)-C(7A)	2.8(5)
C(4)-C(5)-C(6A)-C(7A)	-175.5(3)
C(1)-C(5)-C(6A)-C(13A)	-178.9(4)
C(4)-C(5)-C(6A)-C(13A)	2.8(6)
C(5)-C(6A)-C(7A)-C(8)	0.6(5)
C(13A)-C(6A)-C(7A)-C(8)	-177.9(4)
C(12)-C(8)-C(7A)-C(6A)	174.9(3)
C(9)-C(8)-C(7A)-C(6A)	-3.6(5)

Complex **67**

Table 5. Bond lengths (Å) and angles (°) for **67**

Pd(1)-N(3)	2.030(2)
Pd(1)-N(1)	2.031(2)
Pd(1)-N(2)	2.034(2)
Pd(1)-N(4)	2.043(2)
O(1)-H(1A)	0.939(17)
O(1)-H(1B)	0.951(18)
O(2)-H(2A)	0.965(18)
O(2)-H(2B)	0.965(18)
N(1)-C(2)	1.334(3)
N(1)-C(1)	1.365(3)
N(2)-C(10)	1.331(3)
N(2)-C(9)	1.369(3)
N(3)-C(13)	1.492(3)
N(3)-H(3A)	0.943(17)
N(3)-H(3B)	0.936(18)
N(4)-C(14)	1.488(3)
N(4)-H(4A)	0.948(18)
N(4)-H(4B)	0.938(18)
C(1)-C(5)	1.397(3)
C(1)-C(9)	1.432(3)
C(2)-C(3)	1.399(4)
C(2)-H(2)	0.9500
C(3)-C(4)	1.364(4)
C(3)-H(3)	0.9500
C(4)-C(5)	1.412(4)
C(4)-H(4)	0.9500
C(5)-C(6)	1.431(4)
C(6)-C(7)	1.363(4)
C(6)-H(6)	0.9500
C(7)-C(8)	1.435(4)
C(7)-H(7)	0.9500
C(8)-C(9)	1.398(3)
C(8)-C(12)	1.413(4)
C(10)-C(11)	1.401(4)
C(10)-H(10)	0.9500
C(11)-C(12)	1.370(4)
C(11)-H(11)	0.9500
C(12)-H(12)	0.9500
C(13)-C(14)	1.510(4)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
N(3)-Pd(1)-N(1)	97.15(8)
N(3)-Pd(1)-N(2)	178.69(8)
N(1)-Pd(1)-N(2)	81.54(8)

N(3)-Pd(1)-N(4)	83.40(9)
N(1)-Pd(1)-N(4)	176.43(8)
N(2)-Pd(1)-N(4)	97.91(9)
H(1A)-O(1)-H(1B)	108(2)
H(2A)-O(2)-H(2B)	105(2)
C(2)-N(1)-C(1)	118.0(2)
C(2)-N(1)-Pd(1)	129.13(17)
C(1)-N(1)-Pd(1)	112.85(16)
C(10)-N(2)-C(9)	118.4(2)
C(10)-N(2)-Pd(1)	129.08(17)
C(9)-N(2)-Pd(1)	112.49(16)
C(13)-N(3)-Pd(1)	109.89(16)
C(13)-N(3)-H(3A)	108.8(18)
Pd(1)-N(3)-H(3A)	105.3(18)
C(13)-N(3)-H(3B)	107.9(19)
Pd(1)-N(3)-H(3B)	112.0(19)
H(3A)-N(3)-H(3B)	113(3)
C(14)-N(4)-Pd(1)	108.82(16)
C(14)-N(4)-H(4A)	111.1(18)
Pd(1)-N(4)-H(4A)	111.0(18)
C(14)-N(4)-H(4B)	111.6(19)
Pd(1)-N(4)-H(4B)	105.6(19)
H(4A)-N(4)-H(4B)	109(3)
N(1)-C(1)-C(5)	123.5(2)
N(1)-C(1)-C(9)	116.5(2)
C(5)-C(1)-C(9)	120.0(2)
N(1)-C(2)-C(3)	121.9(2)
N(1)-C(2)-H(2)	119.1
C(3)-C(2)-H(2)	119.1
C(4)-C(3)-C(2)	120.4(2)
C(4)-C(3)-H(3)	119.8
C(2)-C(3)-H(3)	119.8
C(3)-C(4)-C(5)	119.2(2)
C(3)-C(4)-H(4)	120.4
C(5)-C(4)-H(4)	120.4
C(1)-C(5)-C(4)	117.0(2)
C(1)-C(5)-C(6)	118.9(2)
C(4)-C(5)-C(6)	124.0(2)
C(7)-C(6)-C(5)	121.1(2)
C(7)-C(6)-H(6)	119.5
C(5)-C(6)-H(6)	119.5
C(6)-C(7)-C(8)	120.9(2)
C(6)-C(7)-H(7)	119.6
C(8)-C(7)-H(7)	119.6
C(9)-C(8)-C(12)	117.2(2)
C(9)-C(8)-C(7)	118.7(2)
C(12)-C(8)-C(7)	124.1(2)
N(2)-C(9)-C(8)	123.0(2)
N(2)-C(9)-C(1)	116.6(2)
C(8)-C(9)-C(1)	120.4(2)
N(2)-C(10)-C(11)	122.0(2)
N(2)-C(10)-H(10)	119.0
C(11)-C(10)-H(10)	119.0

C(12)-C(11)-C(10)	120.0(2)
C(12)-C(11)-H(11)	120.0
C(10)-C(11)-H(11)	120.0
C(11)-C(12)-C(8)	119.3(2)
C(11)-C(12)-H(12)	120.3
C(8)-C(12)-H(12)	120.3
N(3)-C(13)-C(14)	107.0(2)
N(3)-C(13)-H(13A)	110.3
C(14)-C(13)-H(13A)	110.3
N(3)-C(13)-H(13B)	110.3
C(14)-C(13)-H(13B)	110.3
H(13A)-C(13)-H(13B)	108.6
N(4)-C(14)-C(13)	107.5(2)
N(4)-C(14)-H(14A)	110.2
C(13)-C(14)-H(14A)	110.2
N(4)-C(14)-H(14B)	110.2
C(13)-C(14)-H(14B)	110.2
H(14A)-C(14)-H(14B)	108.5

Table 6. Torsion angles (°) for **67**

N(3)-Pd(1)-N(1)-C(2)	1.7(2)
N(2)-Pd(1)-N(1)-C(2)	-178.4(2)
N(4)-Pd(1)-N(1)-C(2)	-96.9(13)
N(3)-Pd(1)-N(1)-C(1)	179.21(16)
N(2)-Pd(1)-N(1)-C(1)	-0.88(15)
N(4)-Pd(1)-N(1)-C(1)	80.6(13)
N(3)-Pd(1)-N(2)-C(10)	-174(3)
N(1)-Pd(1)-N(2)-C(10)	-178.2(2)
N(4)-Pd(1)-N(2)-C(10)	5.4(2)
N(3)-Pd(1)-N(2)-C(9)	4(4)
N(1)-Pd(1)-N(2)-C(9)	0.62(15)
N(4)-Pd(1)-N(2)-C(9)	-175.81(16)
N(1)-Pd(1)-N(3)-C(13)	170.15(16)
N(2)-Pd(1)-N(3)-C(13)	166(3)
N(4)-Pd(1)-N(3)-C(13)	-13.40(17)
N(3)-Pd(1)-N(4)-C(14)	-15.67(17)
N(1)-Pd(1)-N(4)-C(14)	83.4(13)
N(2)-Pd(1)-N(4)-C(14)	164.33(16)
C(2)-N(1)-C(1)-C(5)	-0.7(3)
Pd(1)-N(1)-C(1)-C(5)	-178.52(18)
C(2)-N(1)-C(1)-C(9)	178.8(2)
Pd(1)-N(1)-C(1)-C(9)	1.0(3)
C(1)-N(1)-C(2)-C(3)	1.3(3)
Pd(1)-N(1)-C(2)-C(3)	178.67(17)
N(1)-C(2)-C(3)-C(4)	-0.6(4)
C(2)-C(3)-C(4)-C(5)	-0.6(4)
N(1)-C(1)-C(5)-C(4)	-0.5(3)
C(9)-C(1)-C(5)-C(4)	-180.0(2)
N(1)-C(1)-C(5)-C(6)	179.8(2)
C(9)-C(1)-C(5)-C(6)	0.4(3)
C(3)-C(4)-C(5)-C(1)	1.2(3)
C(3)-C(4)-C(5)-C(6)	-179.2(2)
C(1)-C(5)-C(6)-C(7)	0.4(4)

C(4)-C(5)-C(6)-C(7)	-179.2(2)
C(5)-C(6)-C(7)-C(8)	-0.7(4)
C(6)-C(7)-C(8)-C(9)	0.1(4)
C(6)-C(7)-C(8)-C(12)	179.6(2)
C(10)-N(2)-C(9)-C(8)	-1.4(3)
Pd(1)-N(2)-C(9)-C(8)	179.71(18)
C(10)-N(2)-C(9)-C(1)	178.6(2)
Pd(1)-N(2)-C(9)-C(1)	-0.3(3)
C(12)-C(8)-C(9)-N(2)	1.1(3)
C(7)-C(8)-C(9)-N(2)	-179.3(2)
C(12)-C(8)-C(9)-C(1)	-178.9(2)
C(7)-C(8)-C(9)-C(1)	0.7(3)
N(1)-C(1)-C(9)-N(2)	-0.5(3)
C(5)-C(1)-C(9)-N(2)	179.0(2)
N(1)-C(1)-C(9)-C(8)	179.5(2)
C(5)-C(1)-C(9)-C(8)	-0.9(3)
C(9)-N(2)-C(10)-C(11)	0.7(3)
Pd(1)-N(2)-C(10)-C(11)	179.42(17)
N(2)-C(10)-C(11)-C(12)	0.1(4)
C(10)-C(11)-C(12)-C(8)	-0.4(4)
C(9)-C(8)-C(12)-C(11)	-0.2(3)
C(7)-C(8)-C(12)-C(11)	-179.8(2)
Pd(1)-N(3)-C(13)-C(14)	39.3(2)
Pd(1)-N(4)-C(14)-C(13)	41.4(2)
N(3)-C(13)-C(14)-N(4)	-52.9(3)

Complex **73**

Table 7. Bond lengths (Å) and angles (°) for **73**

Pd(1)-N(1)	2.065(4)
Pd(1)-N(2)	2.092(4)
Pd(1)-P(1)	2.2743(11)
Pd(1)-Cl(1)	2.2808(11)
P(1)-C(23)	1.815(4)
P(1)-C(11)	1.817(4)
P(1)-C(17)	1.827(4)
P(2)-F(4)	1.569(6)
P(2)-F(2)	1.575(4)
P(2)-F(3)	1.584(4)
P(2)-F(6)	1.587(6)
P(2)-F(1)	1.593(3)
P(2)-F(5)	1.593(4)
N(1)-C(1)	1.331(6)
N(1)-C(5)	1.360(6)
N(2)-C(10)	1.338(6)
N(2)-C(6)	1.351(6)
C(1)-C(2)	1.387(7)
C(1)-H(1)	0.9500
C(2)-C(3)	1.371(7)
C(2)-H(2)	0.9500
C(3)-C(4)	1.381(8)
C(3)-H(3)	0.9500
C(4)-C(5)	1.390(7)
C(4)-H(4)	0.9500
C(5)-C(6)	1.480(6)
C(6)-C(7)	1.377(7)
C(7)-C(8)	1.384(8)
C(7)-H(7)	0.9500
C(8)-C(9)	1.373(8)
C(8)-H(8)	0.9500
C(9)-C(10)	1.382(7)
C(9)-H(9)	0.9500
C(10)-H(10)	0.9500
C(11)-C(16)	1.386(6)
C(11)-C(12)	1.392(7)
C(12)-C(13)	1.388(7)
C(12)-H(12)	0.9500
C(13)-C(14)	1.386(8)
C(13)-H(13)	0.9500
C(14)-C(15)	1.380(8)
C(14)-H(14)	0.9500
C(15)-C(16)	1.391(7)
C(15)-H(15)	0.9500
C(16)-H(16)	0.9500

C(17)-C(22)	1.389(6)
C(17)-C(18)	1.393(6)
C(18)-C(19)	1.404(7)
C(18)-H(18)	0.9500
C(19)-C(20)	1.365(8)
C(19)-H(19)	0.9500
C(20)-C(21)	1.393(8)
C(20)-H(20)	0.9500
C(21)-C(22)	1.391(6)
C(21)-H(21)	0.9500
C(22)-H(22)	0.9500
C(23)-C(24)	1.396(6)
C(23)-C(28)	1.399(6)
C(24)-C(25)	1.389(6)
C(24)-H(24)	0.9500
C(25)-C(26)	1.386(7)
C(25)-H(25)	0.9500
C(26)-C(27)	1.379(7)
C(26)-H(26)	0.9500
C(27)-C(28)	1.394(7)
C(27)-H(27)	0.9500
C(28)-H(28)	0.9500

N(1)-Pd(1)-N(2)	79.40(15)
N(1)-Pd(1)-P(1)	98.62(10)
N(2)-Pd(1)-P(1)	171.12(10)
N(1)-Pd(1)-Cl(1)	169.06(10)
N(2)-Pd(1)-Cl(1)	93.74(11)
P(1)-Pd(1)-Cl(1)	89.43(4)
C(23)-P(1)-C(11)	105.30(19)
C(23)-P(1)-C(17)	107.65(19)
C(11)-P(1)-C(17)	102.6(2)
C(23)-P(1)-Pd(1)	113.02(14)
C(11)-P(1)-Pd(1)	118.93(14)
C(17)-P(1)-Pd(1)	108.41(14)
F(4)-P(2)-F(2)	91.0(3)
F(4)-P(2)-F(3)	175.7(3)
F(2)-P(2)-F(3)	91.9(3)
F(4)-P(2)-F(6)	94.4(3)
F(2)-P(2)-F(6)	92.1(3)
F(3)-P(2)-F(6)	88.6(3)
F(4)-P(2)-F(1)	88.5(3)
F(2)-P(2)-F(1)	178.7(3)
F(3)-P(2)-F(1)	88.5(2)
F(6)-P(2)-F(1)	89.1(3)
F(4)-P(2)-F(5)	90.1(3)
F(2)-P(2)-F(5)	89.2(3)
F(3)-P(2)-F(5)	86.8(3)
F(6)-P(2)-F(5)	175.3(3)
F(1)-P(2)-F(5)	89.7(2)
C(1)-N(1)-C(5)	118.0(4)
C(1)-N(1)-Pd(1)	127.8(3)
C(5)-N(1)-Pd(1)	113.7(3)

C(10)-N(2)-C(6)	119.4(4)
C(10)-N(2)-Pd(1)	126.1(3)
C(6)-N(2)-Pd(1)	114.4(3)
N(1)-C(1)-C(2)	123.4(4)
N(1)-C(1)-H(1)	118.3
C(2)-C(1)-H(1)	118.3
C(3)-C(2)-C(1)	118.8(5)
C(3)-C(2)-H(2)	120.6
C(1)-C(2)-H(2)	120.6
C(2)-C(3)-C(4)	118.9(5)
C(2)-C(3)-H(3)	120.6
C(4)-C(3)-H(3)	120.6
C(3)-C(4)-C(5)	119.8(4)
C(3)-C(4)-H(4)	120.1
C(5)-C(4)-H(4)	120.1
N(1)-C(5)-C(4)	121.2(4)
N(1)-C(5)-C(6)	116.4(4)
C(4)-C(5)-C(6)	122.3(4)
N(2)-C(6)-C(7)	121.1(4)
N(2)-C(6)-C(5)	114.8(4)
C(7)-C(6)-C(5)	124.0(4)
C(6)-C(7)-C(8)	119.5(5)
C(6)-C(7)-H(7)	120.2
C(8)-C(7)-H(7)	120.2
C(9)-C(8)-C(7)	118.9(5)
C(9)-C(8)-H(8)	120.6
C(7)-C(8)-H(8)	120.6
C(8)-C(9)-C(10)	119.4(5)
C(8)-C(9)-H(9)	120.3
C(10)-C(9)-H(9)	120.3
N(2)-C(10)-C(9)	121.5(5)
N(2)-C(10)-H(10)	119.2
C(9)-C(10)-H(10)	119.2
C(16)-C(11)-C(12)	119.5(4)
C(16)-C(11)-P(1)	120.8(4)
C(12)-C(11)-P(1)	119.7(4)
C(13)-C(12)-C(11)	120.3(5)
C(13)-C(12)-H(12)	119.8
C(11)-C(12)-H(12)	119.8
C(14)-C(13)-C(12)	119.8(5)
C(14)-C(13)-H(13)	120.1
C(12)-C(13)-H(13)	120.1
C(15)-C(14)-C(13)	120.2(5)
C(15)-C(14)-H(14)	119.9
C(13)-C(14)-H(14)	119.9
C(14)-C(15)-C(16)	120.1(5)
C(14)-C(15)-H(15)	119.9
C(16)-C(15)-H(15)	119.9
C(11)-C(16)-C(15)	120.1(5)
C(11)-C(16)-H(16)	119.9
C(15)-C(16)-H(16)	119.9
C(22)-C(17)-C(18)	119.5(4)
C(22)-C(17)-P(1)	121.5(3)

C(18)-C(17)-P(1)	118.8(3)
C(17)-C(18)-C(19)	119.8(5)
C(17)-C(18)-H(18)	120.1
C(19)-C(18)-H(18)	120.1
C(20)-C(19)-C(18)	120.4(5)
C(20)-C(19)-H(19)	119.8
C(18)-C(19)-H(19)	119.8
C(19)-C(20)-C(21)	120.2(4)
C(19)-C(20)-H(20)	119.9
C(21)-C(20)-H(20)	119.9
C(22)-C(21)-C(20)	120.0(5)
C(22)-C(21)-H(21)	120.0
C(20)-C(21)-H(21)	120.0
C(17)-C(22)-C(21)	120.2(4)
C(17)-C(22)-H(22)	119.9
C(21)-C(22)-H(22)	119.9
C(24)-C(23)-C(28)	118.9(4)
C(24)-C(23)-P(1)	120.0(3)
C(28)-C(23)-P(1)	121.1(3)
C(25)-C(24)-C(23)	120.5(4)
C(25)-C(24)-H(24)	119.7
C(23)-C(24)-H(24)	119.7
C(26)-C(25)-C(24)	120.0(4)
C(26)-C(25)-H(25)	120.0
C(24)-C(25)-H(25)	120.0
C(27)-C(26)-C(25)	120.2(4)
C(27)-C(26)-H(26)	119.9
C(25)-C(26)-H(26)	119.9
C(26)-C(27)-C(28)	120.3(4)
C(26)-C(27)-H(27)	119.9
C(28)-C(27)-H(27)	119.9
C(27)-C(28)-C(23)	120.1(4)
C(27)-C(28)-H(28)	120.0
C(23)-C(28)-H(28)	120.0

Table 8. Torsion angles (°)for **73**

N(1)-Pd(1)-P(1)-C(23)	67.17(17)
N(2)-Pd(1)-P(1)-C(23)	143.6(7)
Cl(1)-Pd(1)-P(1)-C(23)	-105.38(15)
N(1)-Pd(1)-P(1)-C(11)	-168.6(2)
N(2)-Pd(1)-P(1)-C(11)	-92.2(8)
Cl(1)-Pd(1)-P(1)-C(11)	18.83(17)
N(1)-Pd(1)-P(1)-C(17)	-52.08(18)
N(2)-Pd(1)-P(1)-C(17)	24.3(8)
Cl(1)-Pd(1)-P(1)-C(17)	135.36(15)
N(2)-Pd(1)-N(1)-C(1)	-178.4(4)
P(1)-Pd(1)-N(1)-C(1)	-7.2(4)
Cl(1)-Pd(1)-N(1)-C(1)	129.8(5)
N(2)-Pd(1)-N(1)-C(5)	9.9(3)
P(1)-Pd(1)-N(1)-C(5)	-178.9(3)
Cl(1)-Pd(1)-N(1)-C(5)	-41.9(7)
N(1)-Pd(1)-N(2)-C(10)	169.4(4)

P(1)-Pd(1)-N(2)-C(10)	91.6(8)
Cl(1)-Pd(1)-N(2)-C(10)	-19.2(4)
N(1)-Pd(1)-N(2)-C(6)	-7.2(3)
P(1)-Pd(1)-N(2)-C(6)	-85.0(8)
Cl(1)-Pd(1)-N(2)-C(6)	164.2(3)
C(5)-N(1)-C(1)-C(2)	1.2(7)
Pd(1)-N(1)-C(1)-C(2)	-170.2(4)
N(1)-C(1)-C(2)-C(3)	0.2(8)
C(1)-C(2)-C(3)-C(4)	-1.8(8)
C(2)-C(3)-C(4)-C(5)	2.1(8)
C(1)-N(1)-C(5)-C(4)	-1.0(6)
Pd(1)-N(1)-C(5)-C(4)	171.6(4)
C(1)-N(1)-C(5)-C(6)	176.2(4)
Pd(1)-N(1)-C(5)-C(6)	-11.2(5)
C(3)-C(4)-C(5)-N(1)	-0.7(7)
C(3)-C(4)-C(5)-C(6)	-177.7(5)
C(10)-N(2)-C(6)-C(7)	3.4(6)
Pd(1)-N(2)-C(6)-C(7)	-179.7(4)
C(10)-N(2)-C(6)-C(5)	-173.4(4)
Pd(1)-N(2)-C(6)-C(5)	3.4(5)
N(1)-C(5)-C(6)-N(2)	5.2(6)
C(4)-C(5)-C(6)-N(2)	-177.7(4)
N(1)-C(5)-C(6)-C(7)	-171.6(4)
C(4)-C(5)-C(6)-C(7)	5.6(7)
N(2)-C(6)-C(7)-C(8)	-2.9(7)
C(5)-C(6)-C(7)-C(8)	173.7(4)
C(6)-C(7)-C(8)-C(9)	-0.2(8)
C(7)-C(8)-C(9)-C(10)	2.7(8)
C(6)-N(2)-C(10)-C(9)	-0.9(7)
Pd(1)-N(2)-C(10)-C(9)	-177.3(4)
C(8)-C(9)-C(10)-N(2)	-2.2(7)
C(23)-P(1)-C(11)-C(16)	-137.8(4)
C(17)-P(1)-C(11)-C(16)	-25.2(4)
Pd(1)-P(1)-C(11)-C(16)	94.3(4)
C(23)-P(1)-C(11)-C(12)	42.7(4)
C(17)-P(1)-C(11)-C(12)	155.3(4)
Pd(1)-P(1)-C(11)-C(12)	-85.2(4)
C(16)-C(11)-C(12)-C(13)	1.3(7)
P(1)-C(11)-C(12)-C(13)	-179.2(4)
C(11)-C(12)-C(13)-C(14)	-0.5(8)
C(12)-C(13)-C(14)-C(15)	-0.5(8)
C(13)-C(14)-C(15)-C(16)	0.7(8)
C(12)-C(11)-C(16)-C(15)	-1.1(7)
P(1)-C(11)-C(16)-C(15)	179.4(4)
C(14)-C(15)-C(16)-C(11)	0.1(8)
C(23)-P(1)-C(17)-C(22)	45.2(4)
C(11)-P(1)-C(17)-C(22)	-65.6(4)
Pd(1)-P(1)-C(17)-C(22)	167.7(3)
C(23)-P(1)-C(17)-C(18)	-140.5(4)
C(11)-P(1)-C(17)-C(18)	108.7(4)
Pd(1)-P(1)-C(17)-C(18)	-17.9(4)
C(22)-C(17)-C(18)-C(19)	-0.1(7)
P(1)-C(17)-C(18)-C(19)	-174.6(4)
C(17)-C(18)-C(19)-C(20)	-0.4(8)
C(18)-C(19)-C(20)-C(21)	0.5(8)
C(19)-C(20)-C(21)-C(22)	-0.2(8)
C(18)-C(17)-C(22)-C(21)	0.5(7)
P(1)-C(17)-C(22)-C(21)	174.8(4)
C(20)-C(21)-C(22)-C(17)	-0.3(7)
C(11)-P(1)-C(23)-C(24)	-143.8(3)
C(17)-P(1)-C(23)-C(24)	107.3(4)
Pd(1)-P(1)-C(23)-C(24)	-12.4(4)
C(11)-P(1)-C(23)-C(28)	38.4(4)
C(17)-P(1)-C(23)-C(28)	-70.5(4)

Pd(1)-P(1)-C(23)-C(28)	169.8(3)
C(28)-C(23)-C(24)-C(25)	3.4(6)
P(1)-C(23)-C(24)-C(25)	-174.5(3)
C(23)-C(24)-C(25)-C(26)	-1.7(7)
C(24)-C(25)-C(26)-C(27)	-1.1(7)
C(25)-C(26)-C(27)-C(28)	2.2(7)
C(26)-C(27)-C(28)-C(23)	-0.5(7)
C(24)-C(23)-C(28)-C(27)	-2.3(6)
P(1)-C(23)-C(28)-C(27)	175.5(3)

Table 9. Bond lengths (Å) and angles (°) for **79**

Pd(1)-N(2)	2.0976(19)
Pd(1)-N(1)	2.1346(19)
Pd(1)-P(1)	2.2825(6)
Pd(1)-P(2)	2.2861(6)
Cl(1)-C(14)	1.773(4)
Cl(2)-C(14)	1.752(4)
Cl(3)-C(15)	1.756(4)
Cl(4)-C(15)	1.757(4)
P(1)-C(21)	1.810(2)
P(1)-C(41)	1.818(2)
P(1)-C(31)	1.828(2)
P(2)-C(51)	1.803(2)
P(2)-C(71)	1.818(2)
P(2)-C(61)	1.820(2)
P(3)-F(5)	1.579(2)
P(3)-F(2)	1.596(2)
P(3)-F(3)	1.597(2)
P(3)-F(4)	1.602(2)
P(3)-F(1)	1.6037(18)
P(3)-F(6)	1.614(2)
P(4)-F(10)	1.506(4)
P(4)-F(11)	1.563(2)
P(4)-F(7)	1.591(3)
P(4)-F(8)	1.613(3)
P(4)-F(12)	1.619(3)
P(4)-F(9)	1.681(4)
P(4)-F(13)	1.745(7)
N(1)-C(1)	1.337(3)
N(1)-C(12)	1.366(3)
N(2)-C(10)	1.334(3)
N(2)-C(11)	1.367(3)
C(1)-C(2)	1.398(3)
C(1)-H(1)	0.9500
C(2)-C(3)	1.370(4)
C(2)-H(2)	0.9500
C(3)-C(13)	1.408(3)
C(3)-H(3)	0.9500
C(5)-C(6)	1.353(4)
C(5)-C(13)	1.433(3)
C(5)-H(5)	0.9500
C(6)-C(7)	1.438(3)
C(6)-H(6)	0.9500
C(7)-C(11)	1.401(3)
C(7)-C(8)	1.412(3)
C(8)-C(9)	1.372(4)
C(8)-H(8)	0.9500
C(9)-C(10)	1.400(3)
C(9)-H(9)	0.9500
C(10)-H(10)	0.9500
C(11)-C(12)	1.430(3)
C(12)-C(13)	1.405(3)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(21)-C(22)	1.398(3)
C(21)-C(26)	1.404(3)
C(22)-C(23)	1.386(3)

C(22)-H(22)	0.9500
C(23)-C(24)	1.381(4)
C(23)-H(23)	0.9500
C(24)-C(25)	1.387(5)
C(24)-H(24)	0.9500
C(25)-C(26)	1.388(4)
C(25)-H(25)	0.9500
C(26)-H(26)	0.9500
C(31)-C(36)	1.393(3)
C(31)-C(32)	1.396(3)
C(32)-C(33)	1.395(3)
C(32)-H(32)	0.9500
C(33)-C(34)	1.386(4)
C(33)-H(33)	0.9500
C(34)-C(35)	1.380(5)
C(34)-H(34)	0.9500
C(35)-C(36)	1.396(4)
C(35)-H(35)	0.9500
C(36)-H(36)	0.9500
C(41)-C(46)	1.396(3)
C(41)-C(42)	1.406(3)
C(42)-C(43)	1.384(4)
C(42)-H(42)	0.9500
C(43)-C(44)	1.395(4)
C(43)-H(43)	0.9500
C(44)-C(45)	1.387(4)
C(44)-H(44)	0.9500
C(45)-C(46)	1.390(4)
C(45)-H(45)	0.9500
C(46)-H(46)	0.9500
C(51)-C(52)	1.395(3)
C(51)-C(56)	1.405(3)
C(52)-C(53)	1.392(3)
C(52)-H(52)	0.9500
C(53)-C(54)	1.384(4)
C(53)-H(53)	0.9500
C(54)-C(55)	1.389(4)
C(54)-H(54)	0.9500
C(55)-C(56)	1.390(3)
C(55)-H(55)	0.9500
C(56)-H(56)	0.9500
C(61)-C(66)	1.400(3)
C(61)-C(62)	1.402(3)
C(62)-C(63)	1.387(3)
C(62)-H(62)	0.9500
C(63)-C(64)	1.392(4)
C(63)-H(63)	0.9500
C(64)-C(65)	1.395(4)
C(64)-H(64)	0.9500
C(65)-C(66)	1.388(3)
C(65)-H(65)	0.9500
C(66)-H(66)	0.9500
C(71)-C(76)	1.396(3)
C(71)-C(72)	1.402(3)
C(72)-C(73)	1.389(4)
C(72)-H(72)	0.9500
C(73)-C(74)	1.385(4)
C(73)-H(73)	0.9500
C(74)-C(75)	1.392(4)
C(74)-H(74)	0.9500
C(75)-C(76)	1.391(3)
C(75)-H(75)	0.9500
C(76)-H(76)	0.9500

N(2)-Pd(1)-N(1)	79.24(7)
N(2)-Pd(1)-P(1)	167.24(5)
N(1)-Pd(1)-P(1)	95.02(6)
N(2)-Pd(1)-P(2)	94.28(5)
N(1)-Pd(1)-P(2)	160.67(5)
P(1)-Pd(1)-P(2)	94.63(2)
C(21)-P(1)-C(41)	106.97(11)
C(21)-P(1)-C(31)	109.11(11)
C(41)-P(1)-C(31)	102.39(11)
C(21)-P(1)-Pd(1)	113.04(8)
C(41)-P(1)-Pd(1)	120.99(8)
C(31)-P(1)-Pd(1)	103.30(8)
C(51)-P(2)-C(71)	108.09(10)
C(51)-P(2)-C(61)	108.91(10)
C(71)-P(2)-C(61)	102.71(10)
C(51)-P(2)-Pd(1)	115.29(8)
C(71)-P(2)-Pd(1)	115.41(7)
C(61)-P(2)-Pd(1)	105.49(8)
F(5)-P(3)-F(2)	90.77(16)
F(5)-P(3)-F(3)	90.15(15)
F(2)-P(3)-F(3)	90.68(14)
F(5)-P(3)-F(4)	91.50(14)
F(2)-P(3)-F(4)	90.43(13)
F(3)-P(3)-F(4)	178.00(13)
F(5)-P(3)-F(1)	91.04(13)
F(2)-P(3)-F(1)	178.18(16)
F(3)-P(3)-F(1)	89.20(11)
F(4)-P(3)-F(1)	89.63(10)
F(5)-P(3)-F(6)	179.15(14)
F(2)-P(3)-F(6)	89.77(16)
F(3)-P(3)-F(6)	89.18(13)
F(4)-P(3)-F(6)	89.16(11)
F(1)-P(3)-F(6)	88.41(13)
F(10)-P(4)-F(11)	94.6(2)
F(10)-P(4)-F(7)	94.2(3)
F(11)-P(4)-F(7)	91.03(17)
F(10)-P(4)-F(8)	94.6(3)
F(11)-P(4)-F(8)	92.46(15)
F(7)-P(4)-F(8)	170.2(2)
F(10)-P(4)-F(12)	97.8(3)
F(11)-P(4)-F(12)	167.6(2)
F(7)-P(4)-F(12)	87.53(18)
F(8)-P(4)-F(12)	87.09(17)
F(10)-P(4)-F(9)	179.3(3)
F(11)-P(4)-F(9)	84.95(16)
F(7)-P(4)-F(9)	86.37(17)
F(8)-P(4)-F(9)	84.79(18)
F(12)-P(4)-F(9)	82.7(2)
F(10)-P(4)-F(13)	58.2(4)
F(11)-P(4)-F(13)	152.8(3)
F(7)-P(4)-F(13)	91.8(3)
F(8)-P(4)-F(13)	89.3(2)
F(12)-P(4)-F(13)	39.6(3)
F(9)-P(4)-F(13)	122.2(4)
C(1)-N(1)-C(12)	117.5(2)
C(1)-N(1)-Pd(1)	130.32(16)
C(12)-N(1)-Pd(1)	110.85(14)
C(10)-N(2)-C(11)	118.3(2)
C(10)-N(2)-Pd(1)	129.26(16)
C(11)-N(2)-Pd(1)	112.40(15)
N(1)-C(1)-C(2)	123.2(2)
N(1)-C(1)-H(1)	118.4
C(2)-C(1)-H(1)	118.4
C(3)-C(2)-C(1)	119.4(2)

C(3)-C(2)-H(2)	120.3
C(1)-C(2)-H(2)	120.3
C(2)-C(3)-C(13)	119.2(2)
C(2)-C(3)-H(3)	120.4
C(13)-C(3)-H(3)	120.4
C(6)-C(5)-C(13)	120.8(2)
C(6)-C(5)-H(5)	119.6
C(13)-C(5)-H(5)	119.6
C(5)-C(6)-C(7)	120.9(2)
C(5)-C(6)-H(6)	119.5
C(7)-C(6)-H(6)	119.5
C(11)-C(7)-C(8)	117.7(2)
C(11)-C(7)-C(6)	119.0(2)
C(8)-C(7)-C(6)	123.3(2)
C(9)-C(8)-C(7)	119.2(2)
C(9)-C(8)-H(8)	120.4
C(7)-C(8)-H(8)	120.4
C(8)-C(9)-C(10)	119.6(2)
C(8)-C(9)-H(9)	120.2
C(10)-C(9)-H(9)	120.2
N(2)-C(10)-C(9)	122.4(2)
N(2)-C(10)-H(10)	118.8
C(9)-C(10)-H(10)	118.8
N(2)-C(11)-C(7)	122.4(2)
N(2)-C(11)-C(12)	117.6(2)
C(7)-C(11)-C(12)	120.0(2)
N(1)-C(12)-C(13)	122.8(2)
N(1)-C(12)-C(11)	117.6(2)
C(13)-C(12)-C(11)	119.6(2)
C(12)-C(13)-C(3)	117.9(2)
C(12)-C(13)-C(5)	119.3(2)
C(3)-C(13)-C(5)	122.8(2)
Cl(2)-C(14)-Cl(1)	112.7(2)
Cl(2)-C(14)-H(14A)	109.0
Cl(1)-C(14)-H(14A)	109.0
Cl(2)-C(14)-H(14B)	109.0
Cl(1)-C(14)-H(14B)	109.0
H(14A)-C(14)-H(14B)	107.8
Cl(3)-C(15)-Cl(4)	110.7(2)
Cl(3)-C(15)-H(15A)	109.5
Cl(4)-C(15)-H(15A)	109.5
Cl(3)-C(15)-H(15B)	109.5
Cl(4)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	108.1
C(22)-C(21)-C(26)	118.9(2)
C(22)-C(21)-P(1)	118.74(18)
C(26)-C(21)-P(1)	122.32(19)
C(23)-C(22)-C(21)	120.4(2)
C(23)-C(22)-H(22)	119.8
C(21)-C(22)-H(22)	119.8
C(24)-C(23)-C(22)	120.1(3)
C(24)-C(23)-H(23)	120.0
C(22)-C(23)-H(23)	120.0
C(23)-C(24)-C(25)	120.5(2)
C(23)-C(24)-H(24)	119.7
C(25)-C(24)-H(24)	119.7
C(24)-C(25)-C(26)	119.9(3)
C(24)-C(25)-H(25)	120.1
C(26)-C(25)-H(25)	120.1
C(25)-C(26)-C(21)	120.2(3)
C(25)-C(26)-H(26)	119.9
C(21)-C(26)-H(26)	119.9
C(36)-C(31)-C(32)	119.4(2)
C(36)-C(31)-P(1)	121.57(19)

C(32)-C(31)-P(1)	119.02(18)
C(33)-C(32)-C(31)	120.2(2)
C(33)-C(32)-H(32)	119.9
C(31)-C(32)-H(32)	119.9
C(34)-C(33)-C(32)	120.0(3)
C(34)-C(33)-H(33)	120.0
C(32)-C(33)-H(33)	120.0
C(35)-C(34)-C(33)	120.0(3)
C(35)-C(34)-H(34)	120.0
C(33)-C(34)-H(34)	120.0
C(34)-C(35)-C(36)	120.5(3)
C(34)-C(35)-H(35)	119.8
C(36)-C(35)-H(35)	119.8
C(31)-C(36)-C(35)	119.9(3)
C(31)-C(36)-H(36)	120.0
C(35)-C(36)-H(36)	120.0
C(46)-C(41)-C(42)	119.3(2)
C(46)-C(41)-P(1)	123.08(18)
C(42)-C(41)-P(1)	117.56(19)
C(43)-C(42)-C(41)	119.9(3)
C(43)-C(42)-H(42)	120.0
C(41)-C(42)-H(42)	120.0
C(42)-C(43)-C(44)	120.5(3)
C(42)-C(43)-H(43)	119.8
C(44)-C(43)-H(43)	119.8
C(45)-C(44)-C(43)	119.7(2)
C(45)-C(44)-H(44)	120.2
C(43)-C(44)-H(44)	120.2
C(44)-C(45)-C(46)	120.3(3)
C(44)-C(45)-H(45)	119.9
C(46)-C(45)-H(45)	119.9
C(45)-C(46)-C(41)	120.3(2)
C(45)-C(46)-H(46)	119.9
C(41)-C(46)-H(46)	119.9
C(52)-C(51)-C(56)	119.6(2)
C(52)-C(51)-P(2)	118.04(17)
C(56)-C(51)-P(2)	122.36(17)
C(53)-C(52)-C(51)	120.1(2)
C(53)-C(52)-H(52)	119.9
C(51)-C(52)-H(52)	119.9
C(54)-C(53)-C(52)	120.1(2)
C(54)-C(53)-H(53)	120.0
C(52)-C(53)-H(53)	120.0
C(53)-C(54)-C(55)	120.3(2)
C(53)-C(54)-H(54)	119.8
C(55)-C(54)-H(54)	119.8
C(54)-C(55)-C(56)	120.2(2)
C(54)-C(55)-H(55)	119.9
C(56)-C(55)-H(55)	119.9
C(55)-C(56)-C(51)	119.7(2)
C(55)-C(56)-H(56)	120.2
C(51)-C(56)-H(56)	120.2
C(66)-C(61)-C(62)	119.1(2)
C(66)-C(61)-P(2)	122.87(17)
C(62)-C(61)-P(2)	117.87(17)
C(63)-C(62)-C(61)	120.5(2)
C(63)-C(62)-H(62)	119.8
C(61)-C(62)-H(62)	119.8
C(62)-C(63)-C(64)	120.0(2)
C(62)-C(63)-H(63)	120.0
C(64)-C(63)-H(63)	120.0
C(63)-C(64)-C(65)	119.8(2)
C(63)-C(64)-H(64)	120.1
C(65)-C(64)-H(64)	120.1

C(66)-C(65)-C(64)	120.3(2)
C(66)-C(65)-H(65)	119.9
C(64)-C(65)-H(65)	119.9
C(65)-C(66)-C(61)	120.1(2)
C(65)-C(66)-H(66)	119.9
C(61)-C(66)-H(66)	119.9
C(76)-C(71)-C(72)	119.0(2)
C(76)-C(71)-P(2)	124.29(17)
C(72)-C(71)-P(2)	116.70(18)
C(73)-C(72)-C(71)	120.4(2)
C(73)-C(72)-H(72)	119.8
C(71)-C(72)-H(72)	119.8
C(74)-C(73)-C(72)	120.3(2)
C(74)-C(73)-H(73)	119.9
C(72)-C(73)-H(73)	119.9
C(73)-C(74)-C(75)	119.7(2)
C(73)-C(74)-H(74)	120.2
C(75)-C(74)-H(74)	120.2
C(76)-C(75)-C(74)	120.4(2)
C(76)-C(75)-H(75)	119.8
C(74)-C(75)-H(75)	119.8
C(75)-C(76)-C(71)	120.1(2)
C(75)-C(76)-H(76)	119.9
C(71)-C(76)-H(76)	119.9

Table 10. Torsion angles (°) for **79**

N(2)-Pd(1)-P(1)-C(21)	-127.6(3)
N(1)-Pd(1)-P(1)-C(21)	-65.04(10)
P(2)-Pd(1)-P(1)-C(21)	98.19(8)
N(2)-Pd(1)-P(1)-C(41)	103.7(3)
N(1)-Pd(1)-P(1)-C(41)	166.25(11)
P(2)-Pd(1)-P(1)-C(41)	-30.52(9)
N(2)-Pd(1)-P(1)-C(31)	-9.9(3)
N(1)-Pd(1)-P(1)-C(31)	52.73(9)
P(2)-Pd(1)-P(1)-C(31)	-144.04(8)
N(2)-Pd(1)-P(2)-C(51)	-79.19(10)
N(1)-Pd(1)-P(2)-C(51)	-148.59(18)
P(1)-Pd(1)-P(2)-C(51)	91.67(8)
N(2)-Pd(1)-P(2)-C(71)	153.61(9)
N(1)-Pd(1)-P(2)-C(71)	84.21(18)
P(1)-Pd(1)-P(2)-C(71)	-35.53(8)
N(2)-Pd(1)-P(2)-C(61)	41.00(9)
N(1)-Pd(1)-P(2)-C(61)	-28.40(19)
P(1)-Pd(1)-P(2)-C(61)	-148.14(8)
N(2)-Pd(1)-N(1)-C(1)	-179.6(2)
P(1)-Pd(1)-N(1)-C(1)	11.9(2)
P(2)-Pd(1)-N(1)-C(1)	-107.8(2)
N(2)-Pd(1)-N(1)-C(12)	-13.37(15)
P(1)-Pd(1)-N(1)-C(12)	178.15(14)
P(2)-Pd(1)-N(1)-C(12)	58.5(3)
N(1)-Pd(1)-N(2)-C(10)	-166.6(2)
P(1)-Pd(1)-N(2)-C(10)	-102.4(3)
P(2)-Pd(1)-N(2)-C(10)	31.8(2)
N(1)-Pd(1)-N(2)-C(11)	10.93(15)
P(1)-Pd(1)-N(2)-C(11)	75.1(3)
P(2)-Pd(1)-N(2)-C(11)	-150.68(14)
C(12)-N(1)-C(1)-C(2)	-2.0(3)
Pd(1)-N(1)-C(1)-C(2)	163.53(18)
N(1)-C(1)-C(2)-C(3)	0.9(4)

C(1)-C(2)-C(3)-C(13)	1.4(4)
C(13)-C(5)-C(6)-C(7)	-2.0(4)
C(5)-C(6)-C(7)-C(11)	-3.4(4)
C(5)-C(6)-C(7)-C(8)	175.1(3)
C(11)-C(7)-C(8)-C(9)	-0.5(4)
C(6)-C(7)-C(8)-C(9)	-179.1(2)
C(7)-C(8)-C(9)-C(10)	-4.4(4)
C(11)-N(2)-C(10)-C(9)	1.7(3)
Pd(1)-N(2)-C(10)-C(9)	179.07(17)
C(8)-C(9)-C(10)-N(2)	4.0(4)
C(10)-N(2)-C(11)-C(7)	-6.9(3)
Pd(1)-N(2)-C(11)-C(7)	175.27(17)
C(10)-N(2)-C(11)-C(12)	170.8(2)
Pd(1)-N(2)-C(11)-C(12)	-7.0(2)
C(8)-C(7)-C(11)-N(2)	6.3(3)
C(6)-C(7)-C(11)-N(2)	-175.1(2)
C(8)-C(7)-C(11)-C(12)	-171.3(2)
C(6)-C(7)-C(11)-C(12)	7.3(3)
C(1)-N(1)-C(12)-C(13)	0.7(3)
Pd(1)-N(1)-C(12)-C(13)	-167.50(18)
C(1)-N(1)-C(12)-C(11)	-177.7(2)
Pd(1)-N(1)-C(12)-C(11)	14.1(2)
N(2)-C(11)-C(12)-N(1)	-5.1(3)
C(7)-C(11)-C(12)-N(1)	172.7(2)
N(2)-C(11)-C(12)-C(13)	176.4(2)
C(7)-C(11)-C(12)-C(13)	-5.8(3)
N(1)-C(12)-C(13)-C(3)	1.5(3)
C(11)-C(12)-C(13)-C(3)	179.9(2)
N(1)-C(12)-C(13)-C(5)	-178.0(2)
C(11)-C(12)-C(13)-C(5)	0.4(3)
C(2)-C(3)-C(13)-C(12)	-2.5(4)
C(2)-C(3)-C(13)-C(5)	177.0(2)
C(6)-C(5)-C(13)-C(12)	3.5(4)
C(6)-C(5)-C(13)-C(3)	-176.0(2)
C(41)-P(1)-C(21)-C(22)	139.21(19)
C(31)-P(1)-C(21)-C(22)	-110.7(2)
Pd(1)-P(1)-C(21)-C(22)	3.6(2)
C(41)-P(1)-C(21)-C(26)	-39.5(2)
C(31)-P(1)-C(21)-C(26)	70.5(2)
Pd(1)-P(1)-C(21)-C(26)	-175.17(18)
C(26)-C(21)-C(22)-C(23)	0.3(4)
P(1)-C(21)-C(22)-C(23)	-178.5(2)
C(21)-C(22)-C(23)-C(24)	0.8(4)
C(22)-C(23)-C(24)-C(25)	-0.8(4)
C(23)-C(24)-C(25)-C(26)	-0.5(4)
C(24)-C(25)-C(26)-C(21)	1.6(4)
C(22)-C(21)-C(26)-C(25)	-1.5(4)
P(1)-C(21)-C(26)-C(25)	177.3(2)
C(21)-P(1)-C(31)-C(36)	-30.2(3)
C(41)-P(1)-C(31)-C(36)	82.9(2)
Pd(1)-P(1)-C(31)-C(36)	-150.6(2)
C(21)-P(1)-C(31)-C(32)	151.61(19)
C(41)-P(1)-C(31)-C(32)	-95.3(2)
Pd(1)-P(1)-C(31)-C(32)	31.1(2)
C(36)-C(31)-C(32)-C(33)	-0.1(4)
P(1)-C(31)-C(32)-C(33)	178.22(19)
C(31)-C(32)-C(33)-C(34)	0.3(4)
C(32)-C(33)-C(34)-C(35)	-0.1(5)
C(33)-C(34)-C(35)-C(36)	-0.4(6)
C(32)-C(31)-C(36)-C(35)	-0.4(5)
P(1)-C(31)-C(36)-C(35)	-178.7(3)
C(34)-C(35)-C(36)-C(31)	0.7(6)
C(21)-P(1)-C(41)-C(46)	-12.9(2)
C(31)-P(1)-C(41)-C(46)	-127.6(2)

Pd(1)-P(1)-C(41)-C(46)	118.43(19)
C(21)-P(1)-C(41)-C(42)	164.45(18)
C(31)-P(1)-C(41)-C(42)	49.8(2)
Pd(1)-P(1)-C(41)-C(42)	-64.2(2)
C(46)-C(41)-C(42)-C(43)	1.5(4)
P(1)-C(41)-C(42)-C(43)	-175.9(2)
C(41)-C(42)-C(43)-C(44)	0.2(4)
C(42)-C(43)-C(44)-C(45)	-1.3(4)
C(43)-C(44)-C(45)-C(46)	0.7(4)
C(44)-C(45)-C(46)-C(41)	1.0(4)
C(42)-C(41)-C(46)-C(45)	-2.1(4)
P(1)-C(41)-C(46)-C(45)	175.2(2)
C(71)-P(2)-C(51)-C(52)	133.13(18)
C(61)-P(2)-C(51)-C(52)	-115.97(19)
Pd(1)-P(2)-C(51)-C(52)	2.3(2)
C(71)-P(2)-C(51)-C(56)	-48.4(2)
C(61)-P(2)-C(51)-C(56)	62.5(2)
Pd(1)-P(2)-C(51)-C(56)	-179.19(16)
C(56)-C(51)-C(52)-C(53)	0.2(4)
P(2)-C(51)-C(52)-C(53)	178.8(2)
C(51)-C(52)-C(53)-C(54)	0.2(4)
C(52)-C(53)-C(54)-C(55)	-0.5(4)
C(53)-C(54)-C(55)-C(56)	0.3(4)
C(54)-C(55)-C(56)-C(51)	0.2(4)
C(52)-C(51)-C(56)-C(55)	-0.5(3)
P(2)-C(51)-C(56)-C(55)	-178.94(19)
C(51)-P(2)-C(61)-C(66)	-18.3(2)
C(71)-P(2)-C(61)-C(66)	96.1(2)
Pd(1)-P(2)-C(61)-C(66)	-142.61(19)
C(51)-P(2)-C(61)-C(62)	165.76(18)
C(71)-P(2)-C(61)-C(62)	-79.8(2)
Pd(1)-P(2)-C(61)-C(62)	41.5(2)
C(66)-C(61)-C(62)-C(63)	-2.3(4)
P(2)-C(61)-C(62)-C(63)	173.7(2)
C(61)-C(62)-C(63)-C(64)	0.1(4)
C(62)-C(63)-C(64)-C(65)	1.9(4)
C(63)-C(64)-C(65)-C(66)	-1.5(4)
C(64)-C(65)-C(66)-C(61)	-0.8(4)
C(62)-C(61)-C(66)-C(65)	2.7(4)
P(2)-C(61)-C(66)-C(65)	-173.2(2)
C(51)-P(2)-C(71)-C(76)	-2.2(2)
C(61)-P(2)-C(71)-C(76)	-117.3(2)
Pd(1)-P(2)-C(71)-C(76)	128.53(18)
C(51)-P(2)-C(71)-C(72)	178.82(17)
C(61)-P(2)-C(71)-C(72)	63.8(2)
Pd(1)-P(2)-C(71)-C(72)	-50.44(19)
C(76)-C(71)-C(72)-C(73)	-1.7(4)
P(2)-C(71)-C(72)-C(73)	177.3(2)
C(71)-C(72)-C(73)-C(74)	1.1(4)
C(72)-C(73)-C(74)-C(75)	0.9(4)
C(73)-C(74)-C(75)-C(76)	-2.3(4)
C(74)-C(75)-C(76)-C(71)	1.6(4)
C(72)-C(71)-C(76)-C(75)	0.4(4)
P(2)-C(71)-C(76)-C(75)	-178.57(19)