New Mono and Bimetallic Chloroquine Derivatives: Synthesis and Evaluation as Antiparasitic Agents

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Synthesis and Evaluation as Antiparasitic Agents

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by

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Abstract

Several series of new ferrocenyl-quinoline antimalarial agents have been synthesised and fully characterised using standard spectroscopic and analytical techniques. The molecular structure of *N*-(7-Chloro-quinolin-4-yl)-*N'*-[2-(*N'',N''*-dimethylaminomethyl)ferrocenylmethyl]-ethane-1,2-diamine has been determined by x-ray crystallography.

N-(7-Chloro-quinolin-4-yl)-*N'*-[2-(*N'',N''*-dimethylaminomethyl)ferrocenylmethyl]-alkyl-1,n-diamine compounds were made where n = 2-6. These compounds contain a reactive secondary amine centre through which derivatisation to form aryl urea and aryl sulfonamide compounds was achieved.

Complexes of the types: triphenylphosphine(L)gold(I) nitrate, pentafluorophenyl(L)gold(I) and chloro(cyclooctadiene)(L)rhodium(I) have been synthesised (where L = chloroquine, ferroquine, *N*-(7-chloro-quinolin-4-yl)-*N'*-[2-(*N'',N''*-dimethylaminomethyl)ferrocenylmethyl]-ethane-1,2-diamine, 3-benzyl-1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethylaminomethyl)-ferrocenylmethyl]urea).

All compounds have been evaluated against chloroquine sensitive and chloroquine resistant strains of *Plasmodium falciparum*. In most cases good activity was found in both strains of the parasite.

N-(7-Chloro-quinolin-4-yl)-*N'*-[2-(*N'',N''*-dimethylaminomethyl)ferrocenylmethyl]-alkyl-1,n-diamine compounds have been made where n = 2-6. It was found that *in vitro* efficacy against *P. falciparum* diminished with increasing spacer length. The introduction of the aryl urea moiety served to influence efficacy towards *P. falciparum* and toxicity towards mammalian cells. In some cases the toxicity was significantly reduced accompanied by an improvement in efficacy.

The coordination complexes where L = chloroquine showed improved efficacy in the chloroquine resistant K1 strain of *P. falciparum*. In the heterobimetallic complexes, the ligand L showed equivalent or better *in vitro* efficacy than the coordination complexes of L against both chloroquine sensitive D10 and chloroquine resistant K1 strains of *P. falciparum*

Preliminary structure-activity studies were carried out on some of the prepared compounds. Phenylene analogues of some of the ferrocenyl compounds have been synthesized and it was found that the analogues show similar *in vitro* efficacy to each other in both chloroquine sensitive 3D7 and chloroquine resistant K1 strains of *P. falciparum*. The presence of a ferrocenyl moiety in the side chain of chloroquine analogues appears to have a synergistic or additive effect on *in vitro* efficacy.

Acknowledgements

The development of this thesis has not been entirely my own effort. While I have done the laboratory described herein, there are many people I have to thank for helping me to get to this point. At the start I presumed I would learn a lot of chemistry, but I did not anticipate that my learning of interpersonal relationships would overshadow the chemistry completely. Everyone with whom I have come into contact over the last three years has contributed in varying degrees to this process, but some I must thank individually.

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I am who I am today because of all of you. I thank you and I pray this thesis pays tribute to you all. AMDG.

List of Abbreviations

BU	–	abbreviation for compound **37**
COD	–	cyclooctadiene
COSY	–	correlation spectroscopy
Cp	–	cyclopentadienyl
CQ	–	chloroquine
CQR	–	chloroquine resistant
CQS	–	chloroquine sensitive
CV	–	cyclic voltametry
DMF	–	dimethylformamide
$E_{1/2}$	–	half wave potential
ED	–	effective dose
EI	–	electron impact
E_{pa}	–	anodic peak potential
E_{pc}	–	cathodic peak potential
Et_3N	–	triethylamine
FAB	–	fast atom bombardment
F2Q	–	abbrevation for compound **20**
FnQ	–	general abbrevation for compounds **20** – **24**
Fc	–	ferrocene
FQ	–	ferroquine
GR	–	glutathione reductase
HRMS	–	high resolution mass spectrometry
IC	–	inhibitory concentration
MeOH	–	methanol
mp	–	melting point
m/z	–	mass to charge ratio
n-BuLi	–	n-butyllithium
NMP	–	1-methyl-2-pyrrolidinone
R_f	–	ratio of movement of solute to solvent in TLC
tert-BuLi	–	*tertiary*-butyllithium
THF	–	tetrahydrofuran
tht	–	tetrahydrothiophene
TLC	–	thin layer chromatography
TyrR	–	trypanothione reductase

Infra-red spectroscopy (IR)

br	–	broad band
m	–	medium band
s	–	strong band
v	–	very strong band
w	–	weak band
ν-s	–	ymmetric stretch
ν-as	–	asymmetric stretch
δ-s	–	symmetric bend

Nuclear Magnetic Resonance Spectroscopy (NMR)

A	–	signal arises from amide or amine group
Ar	–	signals arise from aromatic group (usually quinoline)
B	–	signals arises from phenylene group
d	–	doublet
dd	–	doublet of doublets
^{iv}C	–	quaternary carbon atom
m	–	multiplet
U	–	signals arise from urea group
S	–	signals arise from sulfonamide group
t	–	triplet

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Chapter 1

Introduction

This project describes the development of new monometallic and heterobimetallic compounds as antiparasitic agents. It is necessary to establish a foundation for this project in this chapter. Essentially, this foundation requires the development of some understanding of the problems faced in the treatment of parasitic diseases today, in particular malaria. In addition to this, it is of interest to look at the development of the use of organometallic compounds and coordination complexes in medicine.

Malaria

Malaria has been one of the major health problems faced by humanity throughout recorded history.[1] It is purported to be the number one killer of people after natural causes.[2] Even today, with the advances of modern medicine, between 400 million and 600 million people are diagnosed with the disease annually, resulting in 1.5 to 2.7 million deaths per annum.[1] This approximates to three deaths every minute.[2] The problem is most prevalent in sub-Saharan Africa, where over 90% of the cases of the disease are reported, the majority of which occur in young children.[3] It is estimated that two billion people are at risk of contracting malaria.[4]

Malaria, also known as 'marsh fever' has long been associated with wetlands.[5] Initially it was thought that exposure to the miasmata that rose from swamps and marshes caused the disease. The name 'malaria' is, in fact, derived from the Italian for 'bad air'.[6] It was only in 1880 that Alphonse Laveran discovered the parasitic causal agent.[5] Sir Ronald Ross established the role of mosquitoes in the transmission of the disease shortly before the turn of the century some twenty years later.[6]

Four species of the *Plasmodium* parasite are responsible for causing malaria in humans, namely, *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae* and *Plasmodium ovale*.[5] Of these *P. falciparum* accounts for up to 90% of the fatalities[7] and is the prevalent species in sub-Saharan Africa.[2]

In the 1950's and 1960's there was a massive drive to try and eradicate malaria worldwide, following the successful eradication of the disease in the United States. This effort resulted in the reduction of those potentially at risk to 10% of the world's population.[8] Essentially, the main idea was to destroy the vector, the female *Anopheles* mosquito, by the use of DDT and other insecticides. Unfortunately, this program was thwarted by financial constraints and the lack of trained personnel in affected areas. At the same time, insecticide resistant mosquitoes began to

emerge.[1] In addition to this, there was mounting evidence of the emergence of the development of resistance to chloroquine in some strains of the parasite.[9] Today, malaria is clearly on the increase with as much as 40% of the world's population living in so-called 'malaria areas'[8] and the efficacy of the current antimalarial drugs is diminishing.[10] It is estimated that the annual cost of the problem to developing countries is in excess of US$ two billion.[8]

In order to understand some of the current chemotherapies of the disease it is necessary to look at the life cycle of the parasite.

Life Cycle of the Parasite

In order to survive and propagate, *Plasmodium* parasites require two organisms, the human host and the mosquito vector. The parasite undergoes various changes in the bodies of both species. The mosquito is unaffected by the presence of the parasite, while humans suffer chills, shaking and bouts of intense fever.[1] As treatment of malaria deals only with the parasitic presence in the human host, only this section of the life cycle is of interest with regard to the topic of this thesis.

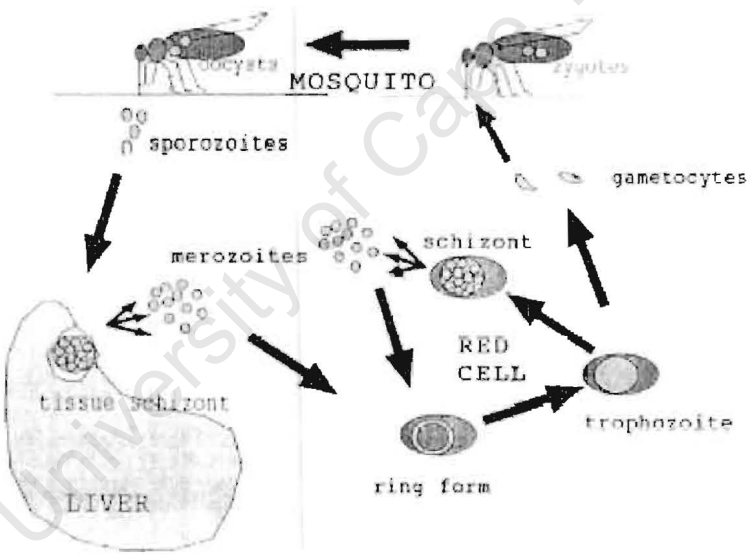

Figure 1: A representation of the life cycle of the malarial parasite[11]

Sporozoites present in the saliva of a carrier mosquito are injected into the human host when the mosquito inserts its proboscis into a human. These travel through the blood stream to the liver where they rapidly divide forming tens of thousands of merozoites, which are released into the bloodstream again after a period of 7-14 days. The merozoites invade red blood cells and again undergo rapid multiplication until the red blood cell bursts, releasing more merozoites into the blood stream. These then invade more red blood cells and the cycle continues. The release of the merozoites into the blood stream precipitates a massive immune response, which results in an intense fever.[1] The blood stages of the cycle comprise the ring forms, trophozoites and blood schizonts.[11]

Treatment

The first treatment for malaria in Western medicine was a fine powder made from the bark of the cinchona tree. It had been used by the Inca civilisation and was brought back to Europe by Spanish Jesuits in 1638.[12] Quinine **1**, Figure 2, was isolated from the cinchona tree bark in 1820 and was used as an antimalarial agent.[4] Shortly thereafter, the commercial growth of cinchona trees started in the islands of the South Pacific.[6] Selective breeding of the trees resulted in an improvement of the quinine content of the bark of up to 13%.[4] The structure of quinine was determined in 1908.[13] Quinine is not considered to be a 'cure' for malaria because its toxicity to the parasite is limited to certain periods of the life cycle of the parasite.[12] Whilst quinine is still an effective antimalarial, it has a bitter taste[6] and can have severe side effects, which make it unsuitable for prophylaxis or use in routine treatment.[4]

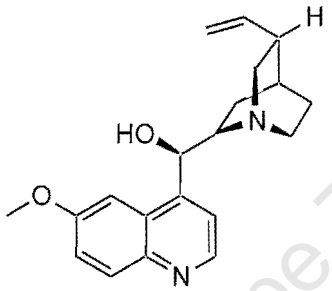

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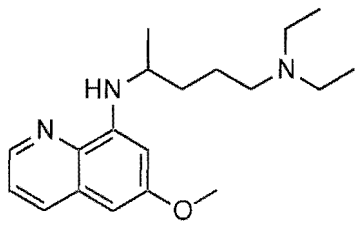
Figure 2: Structure of Quinine (**1**)

The blockade of Germany by the Allied forces cut off supplies of quinine during World War I and thus, precipitated research into the development of synthetic analogues of this drug.[13] The production of analogues was favoured as the total synthesis of quinine has proved to be rather complicated. The first complete stereoselective synthesis of quinine was only published in 2001.[14] Pamaquine **2** was released in 1932 and quinacrine **3** in 1933, [13] but it was not until World War II that widespread use of the synthetic drugs gained favour as supply of cinchona bark was cut off from the Allies by the Japanese presence in the South Pacific.[13]



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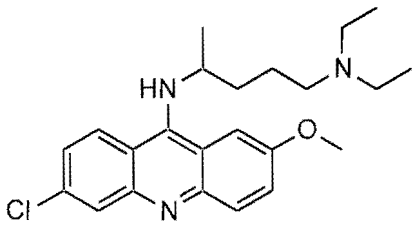

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Figure 3: Pamaquine (**2**) and Quinacrine (**3**)

Today, there are several classes of antimalarial drugs.[1] Chloroquine **4**, primaquine **5** and mefloquine **6**, Figure 4, are all basically quinine analogues falling within the group of quinoline antimalarials.[15] They are thought to have similar modes of action and target the blood stage of the parasite i.e. the merozoite. Another class of antimalarials are the antifolate drugs which

prevent the parasite from metabolizing human folic acid, which is necessary for its reproduction.[1] The major problem is the development of resistance to the drugs in the parasite.[4] Whilst it is unlikely that any single strain of the parasite will exhibit multiple drug resistance, the use of combination drug therapies can be expensive.[1]

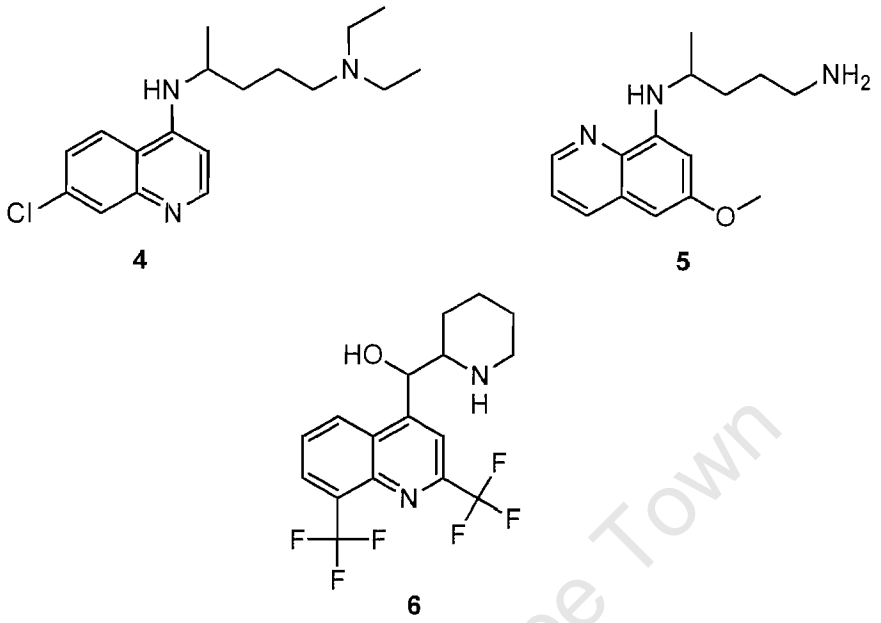


Figure 4: Chloroquine (**4**), primaquine (**5**) and mefloquine (**6**)

There remains much debate as to the mechanism of chloroquine resistance. The focus of this thesis has been the development of new compounds that have the potential to act as antimalarial agents. If the results obtained herein aid to the understanding of drug resistance in the malarial parasites by those better schooled in that particular avenue of research it is fortuitous. Therefore, it is not within the bounds of this thesis to discuss the varying theories of how chloroquine resistance occurs.

β-Haematin Inhibition

Despite the widespread use of 4-aminoquinolines as antimalarial agents, the mode of action of this class of drugs has not been unambiguously determined although much research has been carried out in this area.[16] There is some debate as to whether their action occurs in the cytosol or in the food vacuole of the parasite. Arguments can be made for both extravacuolar[17] and intravacuolar[18] activity of these drugs.

In 1964 it was suggested that the target of chloroquine could be haematin.[19] In the blood stage of the *P. falciparum* life cycle, haemoglobin is used as the food source for the parasite.[20] The parasite has enzymes which break down the protein,[21] and the haem is autooxidised to haematin (aquaferriprotoporphyrin IX, H_2O-Fe(III)PPIX), this substance is potentially toxic to the parasite[22] and is converted to haemozoin.[7] β-haematin is the synthetic form of naturally produced haemozoin and it has been shown that this substance comprises dimeric subunits of ferriprotoporphyrin IX (Fe(III)PPIX) which then combine to form a polymeric chain.[23] The mode

of formation of haemozoin is still unclear although some *in vitro* evidence indicates that it may be a kind of biomineralisation process.[24]

Whilst, the mode of action of chloroquine and other 4-aminoquinolines has not been specifically determined, it is known that some of these compounds, most notably, the 4-amino-7-chloroquinolines, inhibit the formation of β-haematin.[25] This inhibition can easily be monitored by infrared spectroscopy as β-haematin has characteristic bands at 1660 and 1210 cm^{-1}, which are not observed if the synthesis of β-haematin is attempted in the presence of chloroquine.[16] In addition to this, there is accumulation of the 4-aminoquinolines in the food vacuole of the parasite which has been directly related to the antimalarial activity of these compounds.[26]

The characteristic features necessary for the inhibition of β-haematin formation by 4-aminoquinolines has been well established, and there does appear to be a correlation between β-haematin inhibition and *in vitro* efficacy against chloroquine sensitive strains of *P. falciparum*.[27] However, it is notable that other compounds having completely different structures such as octahedral amine phenol complex of gallium(III), [{1,12-bis-(2-hydroxy-3-methoxybenzyl)-1,5,8,12-tetraazododecane}gallium(III)], has also been shown to inhibit the formation of β-haematin.[28] Similar activity has been observed with a ferrocenyl artemisinin derivative.[29]

Other Parasitic Diseases

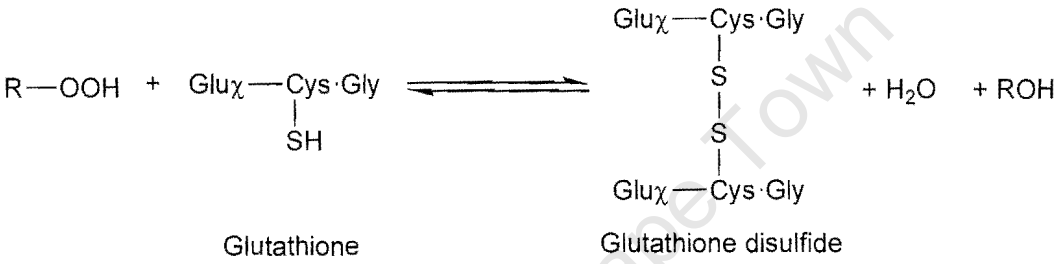
There is evidence to suggest that compounds that are found to be active antimalarials can also exhibit efficacy against the causative agents of other parasitic diseases,[30] for example, *Leishmania spp.*, *Trypanosoma brucei spp.* and *Trypanosoma cruzi.* Whilst there are several classes of parasitic diseases, defined by the causative agent,[2] the main focus here is on protozoan diseases. The aforementioned protozoa cause Leishmaniasis, African Sleeping Sickness and Chagas' Disease respectively.

Leishmaniasis is a broad term covering a group of vector-borne diseases caused by parasites of the genus *Leishmania.* It is transmitted through female phlebotomine sand flies.[31] There are various forms of the disease which have varying degrees of severity. The most severe form, visceral leishmaniasis, is fatal and is caused by members of the *L. donovani* species.[2] Leishmaniasis is essentially a tropical disease, and over 90% of cases of visceral leishmaniasis are reported in India, Bangladesh, Nepal, Sudan and Brazil.[31]

Chagas' Disease is the South American form of Trypanosomiasis. It is caused by parasites of the species *Trypanosoma cruzi*.[2] It is transmitted by reduviid insects commonly known as 'kissing bugs'.[32] The disease has an acute phase, which may cause fatalities especially in children, but its chronic effects may last decades before resulting in organ failure or the onset of cancer.[2]

are responsible for human infection, *Trypanosoma brucei gambiense* and *T. b. rhodisiense*. The former is prevalent in Central and West Africa and results in a more chronic illness, whilst the latter, found in Southern and East Africa causes a far more acute infection.[2] The disease can be cured if diagnosed and treated in time, but the neuronal damage caused by the disease will prove fatal if left untreated.[32]

Leishmaniasis, Chagas' Disease and African Sleeping Sickness are all related diseases, as the causative agents fall in the same broad class of flagellate protozoa known as sarcomastigophora.[2] These protozoa share a common enzyme called trypanothione reductase which functions in much the same way that glutathione reductase does in humans. When a cell undergoes oxidative stress it produces peroxides which are highly reactive species, unless the cell finds a way to break these down they will kill the cell. Glutathione reductase facilitates the breakdown of peroxides in humans.[33]



Scheme 1: Mode of action of glutathione reductase[34]

Trypanothione reductase is therefore a good enzyme to target. If it is possible to inhibit the enzyme activity the cell will die, and as the enzyme is present and virtually identical in the causative agents of all three diseases, a molecule capable of inhibiting this enzyme could potentially be a curative agent for all these diseases.

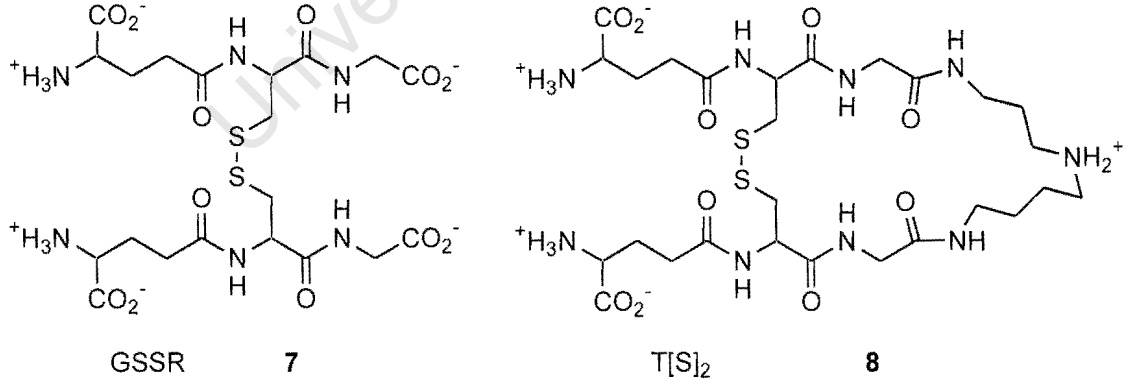


Figure 5: Structures of glutathione disulfide (**7**) and trypanothione disulfide (**8**)[35]

Whilst the function of glutathione reductase and trypanothione reductase are analogous in human and parasite respectively, there is a fundamental difference between the two enzymes. Human glutathione reductase is incapable of processing trypanothione disulfide **8** and parasite trypanothione reductase is incapable of processing glutathione disulfide **7**. This indicates the possibility of selective inhibitor design for trypanothione reductase.[35] The aim then is to achieve

a molecule that has high inhibition on trypanothione reductase, but very little effect on the activity of glutathione reductase. It is known that the active site of glutathione reductase carries a positive charge and is smaller than the active site of trypanothione reductase which carries a negative charge. The presence of a protonable nitrogen in a potential drug could aid its selectivity for trypanothione reductase. In addition to this, as shown in Scheme 1, the whole mechanism of the enzyme is based on a series of redox reactions. The question then arises as to whether the presence of a redox active moiety in the drug molecule could interfere with this process, especially *in vivo*.

The Use of Metals in Chemotherapy

Metal containing compounds have been used for aeons in traditional medicines for a wide variety of complaints.[36] Much of this traditional knowledge was forgotten and no longer in use by the late nineteenth century. This coupled with the development of the Food and Drug Administration in the late 1800's resulted in less emphasis on metallo-drugs. Interestingly, one of the important factors in the development of the FDA was the egregious abuse of malarial remedies. Vendors of quinine-containing cinchona bark powder were mixing the powder with alum and clay masked poor wheat powder, amongst other things, to improve their profit margin.[37] The development and growth of the FDA was, of course, necessitated by the passing of the Food and Drugs Act in June 1906.[38] Whilst the Act only holds legal standing in the United States of America, most countries acknowledge the need for such regulation and have developed similar legislation. So, over the last century, there has been a move towards more stringent control on the use of substances as medicines. This resulted in the domination of the pharmaceutical industry by organic compounds for most of the twentieth century.[39]

The earliest metallo-drugs include iron complexes used in the treatment of hypochronic anaemia caused by iron deficiency.[40] However, the fortuitous discovery of the inhibition of cell division by *cis*-diamminedichloroplatinum(II) **9**, Figure 6, in 1965[41] and the subsequent discovery of the inhibition of tumour growth by the same complex[42] stimulated much interest in the field of bioinorganic medicinal chemistry. Cisplatin and its analogues have since become the most successful drugs for the treatment of testicular and ovarian cancers.[40]

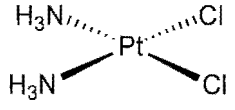


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Figure 6: Structure of cisplatin (**9**)

The use of both organometallic and coordination complexes in a wide variety of medical applications has increased significantly in recent years. The use of such compounds covers two broad areas of research, that of bioanalysis and biomedical research.[43]

Coordination Complexes

Most metallo-drugs are, in fact, coordination complexes. Prior to the discovery of ferrocene in 1951, there were no organometallic compounds that possessed sufficient stability to be used in medicinal chemistry. Cisplatin, as described above, has been one of the major success stories of bioinorganic medicinal chemistry.

Gold complexes were used in chemotherapy in the 1920's against tuberculosis.[44] Later auranofin, 2,3,4,6-tetra-*O*-acetyl-1-thio-β-glucopyranosato-*S*-triethylphosphine-gold **10**, Figure 7, was found to be effective against rheumatoid arthritis. More recently the same drug has been found to be active against leukaemia P388.[45] The efficacy of auranofin against these diseases started a trend of testing numerous gold compounds against a variety of microbial agents.[46] Gold complexes have also been used against such varying disorders as syphilis and alcoholism.[47]

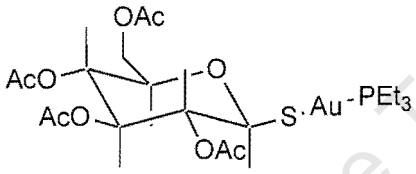

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Figure 7: Structure of auranofin (**10**)

Not surprisingly, the success of metallo-drugs in cancer therapy led to investigation into the use of coordination complexes in other areas, including their use as antimalarial agents,[48,49] anti-inflammatories[50] and antifungal agents.[51] In most cases, the new metallo-drug is simply a coordination complex of a transition metal and a known commercial drug. This approach has had varying success. For example, coordination of gold to chloroquine, Figure 8, results in a marked increase in efficacy in the metal complex relative to the free drug in both chloroquine sensitive and chloroquine resistant strains of *Plasmodium*.[49]

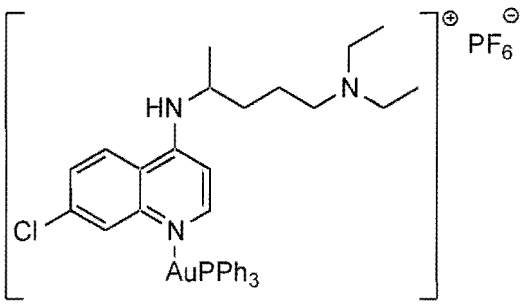

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Figure 8: Structure of $[Au(CQ)PPh_3]PF_6$ (**11**)

The speciation of coordination complexes in the incredibly complex aqueous medium of the human body remains a crucial question.[40] Whilst some work has been done in trying to answer this question for various well known commercial drugs, such as auranofin[52] and cisplatin there is

still much work to be done in this field. When developing a new metallo-drug the question of speciation cannot be disregarded.

This is demonstrated well in the case of auranofin **10** in which it is known that acetate groups undergo hydrolysis in acidic media and it has been shown that auranofin undergoes deacetylation on passing through everted intestinal walls.[53] Thiol exchange is known to occur *in vivo* to form gold-protein-thiol adducts and the triethylphosphine group can undergo oxidation to form triethylphosphine oxide.[54] The question as to what species are active and responsible for the efficacy of the drug therefore arises. One study[52] showed that gold(I) tertiary phosphine complexes were more active than gold(I) thiolates against *Pseudomonas putida*, suggesting that the tertiary phosphine plays a role in the activity of the drug. The speciation of cisplatin has similarly been the subject of much study.

Little is known about the speciation of metallo-antimalarial drugs. The reason for this is primarily because they are still essentially an area of academic interest, rather than being a real prospect of a commercial drug. As a result, the requirement for knowledge of the speciation is limited and the question of speciation therefore remains unanswered. However, the implication from studies on other coordination complexes used as drugs indicates that the coordination complex is in fact a pro-drug. That means that between administration and reaching the site of action, the metal complex undergoes some change *in vivo* and it is the newly formed species that is the active drug.

Organometallic Compounds

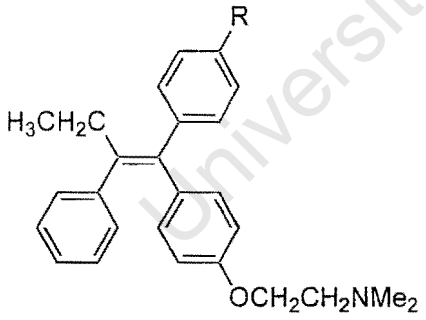
An organometallic compound must contain at least one direct metal-carbon bond.[55] Many of these compounds are sensitive to air and moisture, making their synthesis, isolation and characterisation difficult and clearly precluding their use as drugs.

The discovery of ferrocene in 1951[56] opened a new field of transition metal chemistry than could not possibly have been imagined from the paradigm of Werner type coordination chemistry.[57] The structure of ferrocene determined in 1952[58] showed it to contain iron(II) sandwiched between two η^5-cyclopentadienyl rings. The π bonding in ferrocene imparts great stability to the structure, subliming at 500°C and remains intact in the presence of strong acids or alkalis.[59] Few coordination complexes exhibit such stability, and up until 1951, it was assumed that no organometallic compound of a transition metal could exhibit such characteristics. From a biological perspective, it is known that in some ferrocenyl compounds, iron can be released from the ferrocenyl moiety in the liver.[60] However, it is still quite likely that the drug will reach the site of action intact, thereby making ferrocenyl compounds ideal candidates for metallo-drugs.

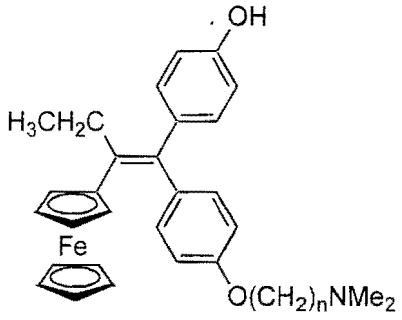
Ferrocene

In recent years there have been several medicinal applications of ferrocene derivatives. Most notable is the work done on ferrocenyl derivatives of known antimalarial drugs.[62] It has been shown, for example, that the introduction of a ferrocenyl moiety into the side chain of chloroquine results in a significant improvement in efficacy against both chloroquine sensitive and chloroquine resistant strains of the parasite. Whilst the incorporation of the ferrocenyl moiety into such molecules seems to have a positive influence on the efficacy of the drugs, the role that this moiety plays in the process has yet to be established. It may be that the ferrocenyl moiety itself plays a crucial role, or it may be that it is simply a large hydrophobic group.

However, there is some precedent for assuming that ferrocenyl moiety itself is important. A recent study on the differences in efficacy of tamoxifen **12** and ferrocifen **14** exemplify the effect ferrocene can have.[63] Tamoxifen is used in the treatment of breast cancer. It acts as a selective oestrogen receptor modulator (SERM), meaning that it competes with oestradiol for the oestradiol receptor (ER). There appear to be two different types of oestradiol receptors, α-ER and β-ER, which occur in different cell lines. In cell lines that have the α-ER, there is no significant difference in the efficacy of tamoxifen and ferrocifen. They appear to have the same mode of action, both fitting into the receptor site in a similar manner with no distortion. However, in the cell lines having the β-ER, against which tamoxifen exhibits limited activity, ferrocifen shows good activity. There are a number of possible reasons for this, but it has been suggested that the redox activity of the ferrocenyl moiety is crucial. It is also noted that ferrocene by itself shows no activity.



12 R = H; Tamoxifen
13 R = OH; Hydroxytamoxifen



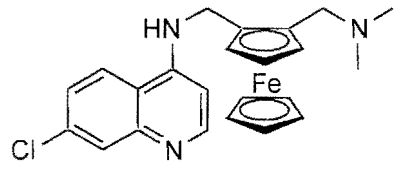
14 Ferrocifens
(n = 2, 3, 4, 5, 8)

Figure 9: Structure of Tamoxifen (**12**) and Ferrocifen (**14**)

Ferrocene in Antimalarial Chemotherapy

As mentioned previously the use of ferrocene in antimalarial compounds has proved to be successful. Ferroquine **15** was developed using a simple 'bait and hook' approach. It is known that *Plasmodium* has an avidity for free iron. It was postulated that the resistance to chloroquine could be overcome by the incorporation of a stable iron moiety into the active drug molecule.[64]

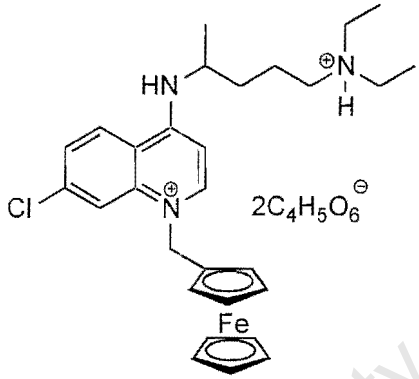
This approach has certainly been effective, with ferroquine exhibiting excellent efficacy against both chloroquine sensitive and chloroquine resistant strains of *Plasmodium* in *in vitro* and *in vivo* studies.[62]



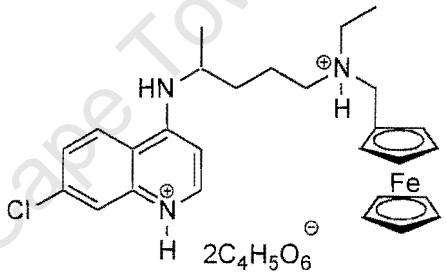
15

Figure 10: Structure of Ferroquine (**15**)

Ferrocene has also been incorporated into other known antimalarials such as mefloquine and artemisinin.[29] However, the presence of the ferrocenyl moiety does not significantly enhance the efficacy of the drugs in question. Furthermore, it appears that the positioning of the ferrocenyl moiety in the 4-aminoquinolines is crucial to its efficacy.



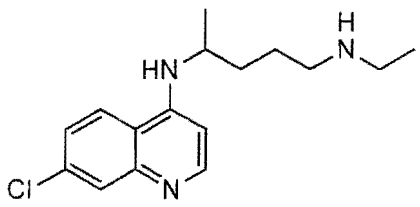
16



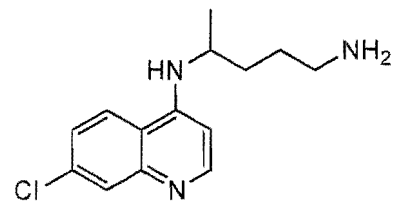
17

Figure 11: Alternative positions of ferrocene in chloroquine derivatives[65]

It is interesting to note that **16**, with ferrocene attached at the quinoline nitrogen shows a significant decrease in efficacy with respect to chloroquine. It has been postulated that the quaternisation at the quinoline nitrogen prevents the inhibition of β-haematin formation normally characteristic of 7-chloroquinoline compounds.[65] The quaternisation of the quinoline nitrogen is also likely to have a significant effect on the weak base properties of the resultaing drug complex. This may adversely effect the cellular accumulation of the drug molecule and thereby reduce its efficacy. The efficacy of **17** is also interesting to consider. It is known that chloroquine is metabolised in the liver to form monodesethylchloroquine (DECQ) and didesethylchloroquine (di-DECQ).[66]



18 DECQ



19 di-DECQ

Compound **17** shows enhanced efficacy with respect to chloroquine in both resistant and sensitive strains of *Plasmodium* in *in vitro* and *in vivo* studies. This indicates that despite the fact that some of the active drug compound may be metabolised to DECQ **18** or di-DECQ **19**, enough of the drug remains intact or with removal of the ethyl group rather than the methylferrocenyl group to have a significant effect on efficacy. This change in efficacy may be attributed to the lipophilicity of the ferrocenyl unit resulting in an increased cellular accumulation of the drug.[64]

It has been suggested that the ferrocenyl unit must be covalently bound to the rest of the molecule in order to display improved efficacy against *P. falciparum.*[63] It has been observed that ferroquine is highly active against a wide variety of strains of *Plasmodium spp.* even in areas where chloroquine resistance is as high as 95% and multi-drug resistance is known.[66] In addition to this, there is little evidence of toxicological side effects of ferroquine and oral administration of the drug appears to be viable, making ferroquine a good candidate for further drug trials.[66] Furthermore, there appears to be no difference in activity of the two enantiomers of ferroquine which means that costly chiral resolution of the drug can be avoided.[67]

Preliminary studies into the synthesis, characterisation and biological evaluation of novel ferrocenyl sugars indicate that the overall structure of the sugar molecule is important to the efficacy of the drug.[68] This could imply that whilst ferrocene may have an additive or synergistic effect when covalently bonded to an biologically active molecule, it has limited efficacy on its own.

The electrochemistry of ferrocene provides an interesting avenue of research. As implied in the discussion on ferrocifen and tamoxifen, ferrocene exhibits a characteristic fully reversible one-electron wave. This means that ferrocene, η^5-$(C_5H_5)_2Fe$, is oxidised relatively easily to the ferrocenium ion, η^5-$(C_5H_5)_2Fe^+$,[55] which, in turn, is reduced back to ferrocene. In fact, this process is often used as a standard in cyclic voltametry experiments. In the human blood stream, *P. falciparum* use haemoglobin as a food source. The haemoglobin is broken down to release amino acids required by the parasite. In the process haem is liberated and the iron of the haem moiety is oxidised from iron(II) to iron(III).[8] It is possible that the presence of a ferrocenyl moiety in a potential antimalarial drug may have some effect on this process as it is capable of undergoing redox reactions.

There is little doubt that the introduction of ferrocene into the field of bioorganometallic chemistry opens the door to several possibilities. However, there is still a great deal of uncertainty as to the role played by the ferrocenyl moiety in the efficacy of these drugs. There is therefore, still much scope for research in this area.

Aims and Objectives

It should be noted that the focus of the project has been to develop new compounds that have the potential to be antimalarial agents. The first priority has been to synthesise, characterise and explore the chemistry of new compounds. For the most part, this has required the adaptation of known techniques and synthetic pathways in order to make and isolate new compounds. Most of the new compounds developed and characterised were then tested for some form of antiparasitic activity.

The second chapter outlines the rationale used for the development of ferroquine analogues. This required the development of appropriate synthetic methodology.

The third chapter outlines the development of ferroquine analogues containing urea and sulfonamide substituents in the side chain. Both classes of compounds have been used in antiparasitic drugs in the past, and it was thought that combining them with the active ferrocenyl-quinoline compounds would be worth examining.

The fourth chapter outlines the development of coordination complexes of various 4-amino-7-chloroquinoline compounds. In particular gold and rhodium were used for complexation, and chloroquine and ferroquine analogues were used as ligands. Gold and rhodium complexes of chloroquine have been shown to be efficacious against both chloroquine sensitive and chloroquine resistant strains of *Plasmodium* in various *in vitro* and *in vivo* studies.

The fifth chapter deals with the biological evaluation of the compounds detailed in Chapters 2, 3 and 4. Most compounds were tested for *in vitro* antiplasmodial activity. A few compounds were also tested for *in vivo* antiplasmodial activity. Some enzyme inhibition assays were also carried out on the antioxidative enzyme trypanothione reductase. While some compounds were tested against the causative agents of Chagas' disease, African Sleeping Sickness and Leishmaniasis.

The sixth chapter outlines the synthesis of a series of related compounds designed to determine the role of ferrocene in the efficacy of ferroquine and its analogues. The *in vitro* antiplasmodial activity of these compounds was also assessed.

The seventh chapter gives an overview of conclusions from the work carried out for this thesis and suggests avenues for future research arising from this work.

The eighth chapter is the general experimental section.

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Chapter 2

Ferroquine Analogues

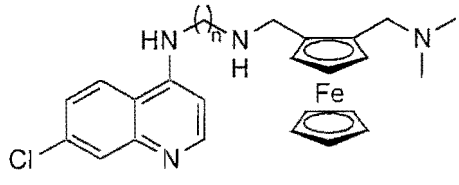
Introduction

In this chapter the synthesis and characterisation of novel ferroquine analogues is described.[1] A rationale is provided for the synthesis of this class of compounds and the use of a variety of possible synthetic routes is discussed. The synthesis of the known compound ferroquine, **15**, is discussed and the synthetic route actually employed is detailed. Several aspects of the characterisation of the compounds are then discussed. This is followed by a brief exploration of some of the chemical properties of these compounds, for example, cyclic voltametry. The biological activity of these compounds is discussed in Chapter 5.

Rationale

Whilst there has been a growing emergence of resistance to chloroquine, small variations in the structure of the side chain of 7-chloroquinolines have been shown to overcome this resistance. Most noteworthy and relevant to this study is the incorporation of a ferrocenyl moiety into such molecules.[2,3] These types of compounds have been found to be active against chloroquine resistant strains of malaria. The incorporation of the ferrocenyl moiety into other known antimalarials has also been successful.[4]

It has previously been demonstrated that the length of the methylene spacer between the two nitrogen atoms in the side chain of chloroquine has a significant effect on the efficacy of the compound.[5] For this reason, it was envisaged that investigation into the determination of the effect of introducing methylene spacers of various lengths into the side chain of ferroquine was a worthwhile endeavour. This led to the design of derivatives **20-24**, shown in Figure 1. The presence of the secondary amine group in the side chain of **20-24** provides a site for introducing chemical diversity which is important for structure-activity studies within this series of compounds.[1]

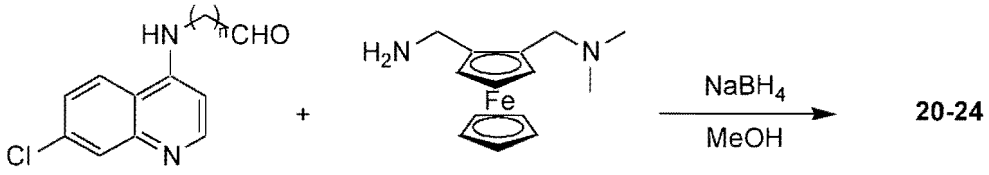


n = 2, **20**
n = 3, **21**
n = 4, **22**
n = 5, **23**
n = 6, **24**

Figure 1: Ferroquine analogues

Possible Synthetic Routes

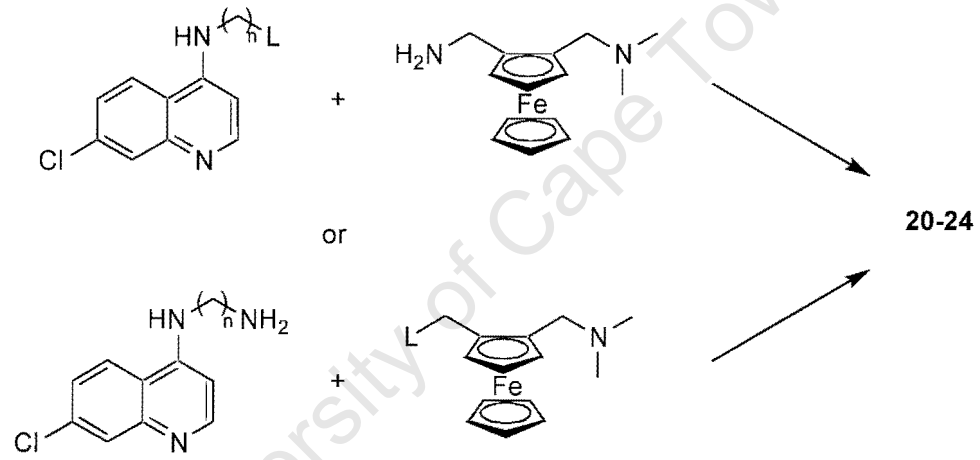
1. Reductive amination of 7-chloroquinoline aldehydes and a ferrocene containing amine.



Scheme 1: Reductive amination from 7-chloroquinoline aldehyde

This is a simple method from known compounds. The main drawback is that the synthesis of the ferrocenyl amine requires a three step synthesis.[2] In total, the process would therefore require at least six steps to achieve the synthesis of the desired products (cf option 3).

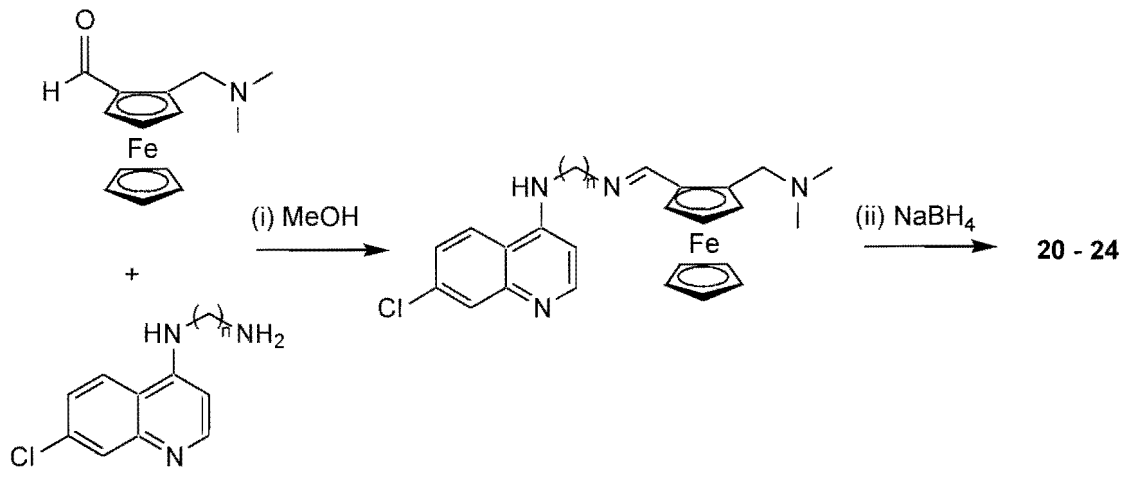
2. Displacement of leaving group (L) e.g. iodide or tosylate, by primary amine



Scheme 2: Use of a Leaving Group, L

The displacement of a leaving group e.g. iodide or tosylate by the incoming primary amine could facilitate the preparation of the required compounds. The leaving group could be incorporated by reduction of the relevant aldehyde to the alcohol, followed by substitution of the alcohol group by the iodide or tosylate group. The major problem with this route would be over alkylation i.e. the secondary amine formed in the first step would readily undergo further alkylation. The reaction would, therefore, be difficult to control unless a large excess (4-5 equivalents) of the primary amine is used. As all the reagents require initial preparation prior to the reaction and are made from starting materials that may not be cheap, the process would be both labour intensive and costly.

3. Reductive amination of 7-chloroquinoline amine and ferrocene carboxaldehyde



Scheme 3: Reductive amination from ferrocene carboxaldehyde

This approach would require a one-step synthesis of both starting materials using known methodology.[2,5] In addition to this, polymer supported borohydride could be used in the reduction of the imine to the amine, which could facilitate a simple and quick method of preparation of these compounds. This approach had the added advantage that a reduced number of steps were required in the synthesis. Although, once again, there were two potentially reactive amine centres that could compete, the aniline amine attached to the chloroquinoline moiety was deactivated by the mesomeric release of the lone pair of electrons into the π system of the chloroquinoline moiety. This is shown in Figure 2 and discussed below.

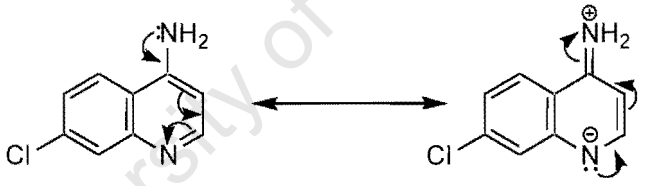


Figure 2: Two of the possible resonance structures of 4-amino-7-chloroquinoline **25**

4. Use of 4,7-dichloroquinoline and ferrocene amine with methylene spacer

As shown in Figure 3, if a similar nucleophilic substitution reaction of 4,7-dichloroquinoline **25** was attempted in the final step of the reaction, there could be competition between the primary and secondary amines present in the ferrocenyl fragment **26**.

The separation of the products, **20** and **27**, would ostensibly be fairly simple using silica gel chromatography, as the primary amine **27** would have a far greater affinity for the silica gel. However, the competition would probably result in lower yields of the desired product **20**. The conditions of the analogous reaction to form ferroquine[2] requires the use of a five fold excess of 4,7-dichloroquinoline. Given the possibility of the reaction at more than one amine centre, the use of an excess of 4,7-dichloroquinoline could result in the formation of a wide variety of products.

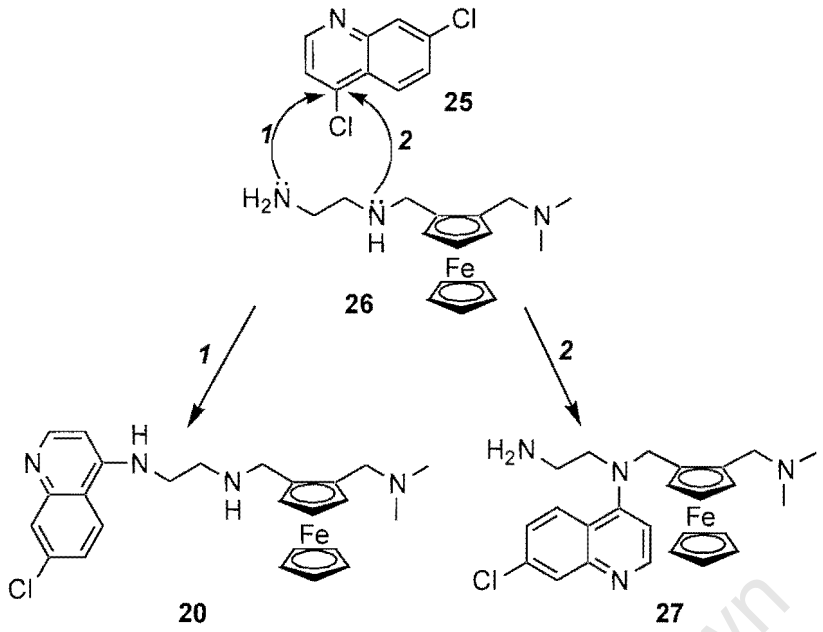
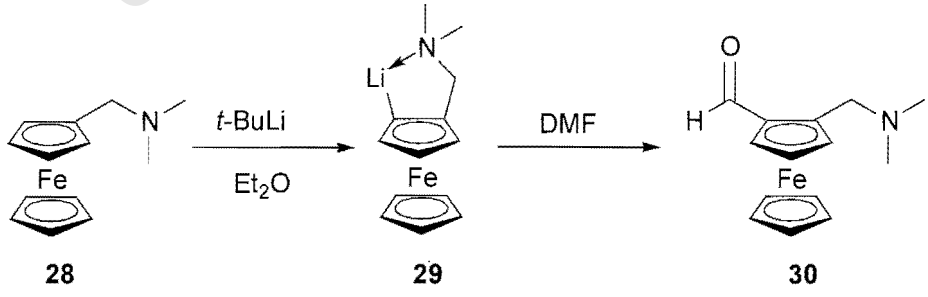


Figure 3: Potential products of formed by using method 4

Synthesis of Ferroquine Derivatives

Lithiation of Ferrocene

The synthesis of the ferroquine analogues required the synthesis of *N,N*-dimethylaminomethylferrocenecarboxaldehyde, **30** via *ortho*-lithiation of the starting material **28** to give **29** *in situ*. It is well known that the dimethylamino group has a strongly *ortho*-directing effect in metalation reactions.[6] Initially this reaction was carried out as described[2] using *n*-butyllithium (*n*-BuLi). A subsequent publication[7] detailed the use of *tert*-butyllithium (*t*-BuLi) in place of *n*-BuLi. This significantly reduced the reaction time and improved the yield. The presence of the lithio-species **29** was easily observed as it formed a bright orange precipitate.



Scheme 4: Synthesis of **30**

The difference in the reaction rates between *n*-butyllithium and *tert*-butyllithium could result from the differences in their structures in solution. In paraffinic or aromatic solvents, the organolithium reagents tend to form aggregates. The monomeric species is primarily the species that reacts although the dimeric species can also show some activity. The aggregate must, therefore, totally

or at least partially break down before any reaction could occur. In diethyl ether at room temperature, *n*-butyllithium exists as a tetramer, whilst *tert*-butyllithium exists as a dimer. This difference in structure can be explained on the basis of the steric bulk of the *tert*-butyl group relative to the *n*-butyl group. This means that the reaction with *tert*-butyllithium will be significantly faster, because the deaggregation of the dimer is expected to be more rapid relative to that of the tetramer.[8] The increased rate of reaction using the *tert*-butyllithium results in a higher yield because there is a significant decrease in reaction time.[7]

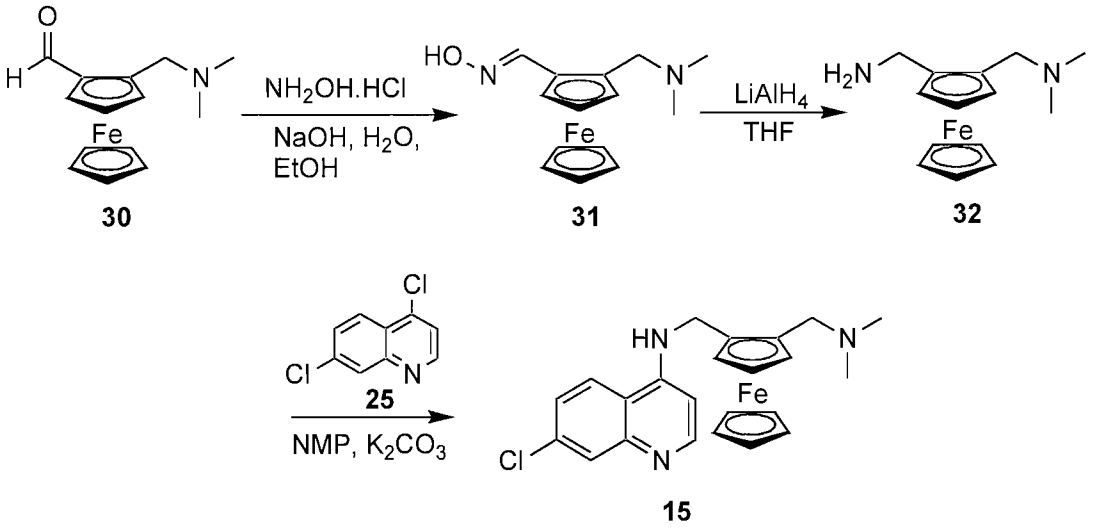
In addition to this, the kinetic product appears to be the 1,2-disubstituted product.[9] So the shorter reaction time reduces the probability of forming either the 1,1'- product or the dialdehyde. Furthermore, whilst it cannot be generally stated that a decreased reaction time will necessarily result in an increased yield, in this case it holds true because decomposition of the product does occur over time. Therefore, if the reaction time can be minimised, the amount of decomposition can likewise be reduced thus resulting in an overall improved yield.

The use of both *n*-butyllithium and *tert*-butyllithium resulted in the formation of the 1,2-disubstituted ferrocene as the major product. There was no obvious evidence of dilithiation or the formation of the 1,1'- derivative. As these species were not the desired product, little time was spent on trying to ascertain whether they were forming or not. The preference of the 1,2-product can be attributed to the stabilising effect of the tertiary amine on the lithiated intermediate (Scheme 4). The single carbon linker facilitates and stabilises the formation of the 1,2-lithiated species which ensures the production of the 1,2-disubstituted ferrocene as the major product. It is interesting to note that such preference for the 1,2-disubstituted metallocene does not extend to the ruthenocene analogues. Work done in our laboratory[10] indicates that the preference for the production of the 1,1'-disubstituted ruthenocene over the 1,2- isomer or vice versa, can be controlled to some degree by variation of the solvent and base used.

The *ortho*-lithio species **29** was reacted *in situ* with *N,N*-dimethylformamide (DMF),[11] forming the desired product **30** in good yield (84%). The product was characterised using NMR and IR spectroscopy and the results compared well with literature results.[2]

Synthesis of Ferroquine

The synthesis of ferroquine **15** was carried out according to literature procedures.[2]



Scheme 5: Formation of ferroquine from ferrocenecarboxaldehyde

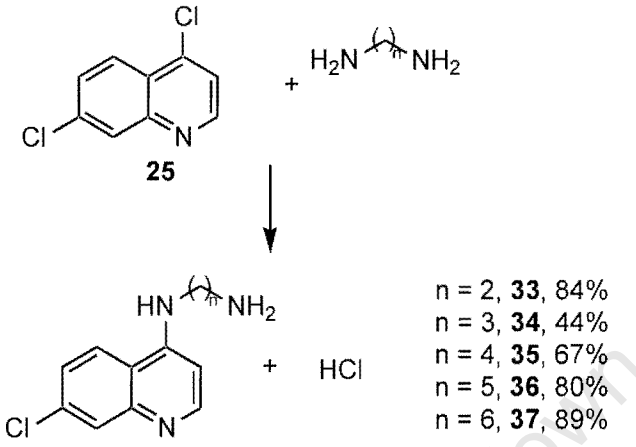
The conversion of **30** to **32** *via* the oxime **31**, shown in Scheme 5 is relatively straightforward and each step has a yield of greater than 95%. The coupling of the ferrocenyl amine **32** to the 4,7-dichloroquinoline **25** gives **15** in 53% yield. The use of *N*-methyl-2-pyrrolidinone (NMP) as a solvent is necessary to achieve dissolution of the starting materials, but requires numerous washings of the organic phase with brine in order to isolate the product. It was found that the use of the less dense, ethyl acetate was preferable to dichloromethane because the organic layer could then be retained in the separating funnel while the brine is repeatedly added and removed. This seemed to have little effect on the overall yield of the reaction, but made the work-up far less tedious. It was observed that the yield of ferroquine, **15**, was adversely affected by the storage of NMP over molecular sieves.

A five-fold excess of 4,7-dichloroquinoline was used to drive the reaction to completion. The possibility of formation of the disubstituted product is unlikely as the presence of the quinoline system significantly diminishes the available charge on the newly formed aniline nitrogen due to a resonance or mesomeric effect shown in Figure 2. This effect also means that this amine centre is unlikely to act as a site of metal co-ordination. This consideration will be elaborated upon in Chapter 4.

Synthesis of Ferroquine Analogues

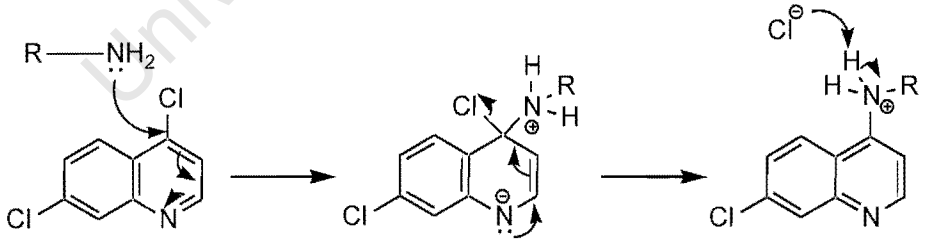
It is apparent from Scheme 3 that 4,7-dichloroquinoline required modification to the alkyldiamine, before use in the reaction. The formation of the diamines, **33-37** are all simple reactions that can be carried out in relatively high yield. The neat 1,n-alkyldiamine is reacted directly with 4,7-dichloroquinoline, in the melt, to form the desired products.[12] Reported procedures[12] favour the use of ethyl acetate in the work-up, but it was found that dichloromethane was more convenient to use. The aqueous layer tended to form an emulsion and a better separation was achieved by using the more dense dichloromethane, although this had no marked effect on the yield. As the compounds are all primary amines, purification by

silica gel chromatography is not an easy option, albeit possible. The presence of the product was determined by TLC. The product remains on the base line whilst 4,7-dichloroquinoline moves close to the solvent front. The compounds **33-37** were used without further purification. A proton NMR spectrum was run on the crude product to ensure the formation of the desired product had indeed occurred. This was compared with literature values.[12]



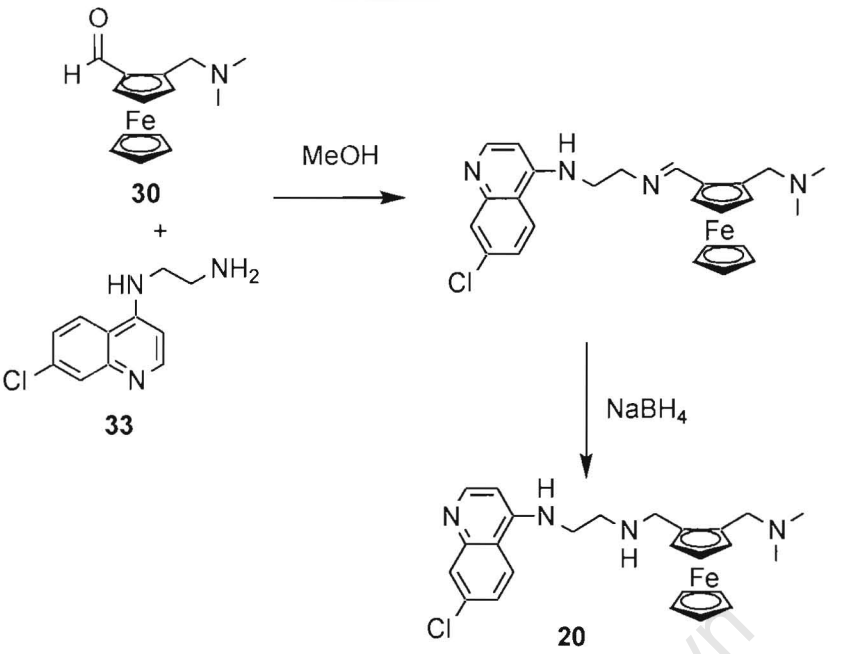
Scheme 6: Synthesis of 7-chloroquinolinyl-1,n-alkyldiamines

It should be noted that in 4,7-dichloroquinoline, the relative positions of the chlorine atom at the carbon 4 position and the quinoline nitrogen is crucial to the leaving group ability of this chlorine atom, Scheme 7. The quinoline nitrogen acts as an electron 'sink' which allows the nucleophilic attack of the incoming amine at the closer carbon 4. The resulting resonance stabilisation and proximity of the 4-chloro to the quinoline nitrogen are a major driving force. There is absolutely no competition from the chlorine atom at the 7 position in this reaction. Substitution at the 7 position, though possible, requires specialised conditions, such as palladium-catalysed aminations with appropriate catalysts.



Scheme 7: Attack of 4,7-dichloroquinoline by primary amine

Having made the required 7-chloroquinoline-1,n-alkyldiamines, the reductive amination with ferrocenecarboxaldehyde, **30**, could then be carried out, Scheme 8. Initially it was hoped that the work-up and isolation of the product could be simplified by using polymer supported borohydride to reduce the imine Schiff base. However, despite the use of the polymer supported reagent it was still necessary to purify the product by silica gel chromatography. Sodium borohydride was then used as a reducing agent as there was deemed to be no real advantage to using the polymer supported reagent.



Scheme 8: Synthesis of **20**

The synthesis of the ferroquine analogues was achieved in moderate yield. It was found that the yield was improved by using freshly prepared ferrocenylcarboxaldehyde. The compounds were all fully characterised using standard methods. The results were compared as far as possible with known compounds e.g. ferroquine[2] and 7-chloroquinoline-1,n-alkyldiamines[12] in order to validate their structures.

Chirality

At this point, it is important to establish the fact that 1,2-disubstituted metallocenes are chiral. They exhibit planar chirality and are subject to a modification of the (*R,S*) nomenclature. The ferrocenyl moiety is viewed from above along the C_5 axis whereby the disubstituted ring is uppermost. In moving from R to R' in a clockwise direction through the smallest possible angle, if R' has a lower priority than R, the metallocene is designated *R* configuration. If R' has a greater priority than R, the metallocene is designated *S* configuration.[13]

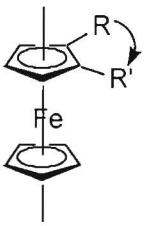


Figure 4: Illustration of assignment of stereochemistry of compounds exhibiting planar chirality

Ferroquine analogues are therefore chiral. The method of preparation outlined above results in the formation of the racemate. The racemate can be resolved using *L*-tartaric acid. Both

ferroquine **15** and **20** were resolved in this manner to form the respective tartrate salts. The compounds were characterised by NMR spectroscopy.

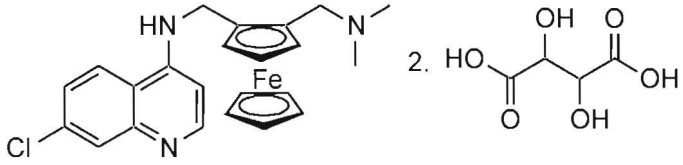


Figure 5: Tartaric acid derivative of **15**

X-ray Crystal Structure

The crystal structure of **20** has been determined. The compound crystallises in the monoclinic crystal system with a $P2_1/c$ space group. There are four repeating units per unit cell. As implied by the space group, the crystal structure of **20** was determined as a racemate.

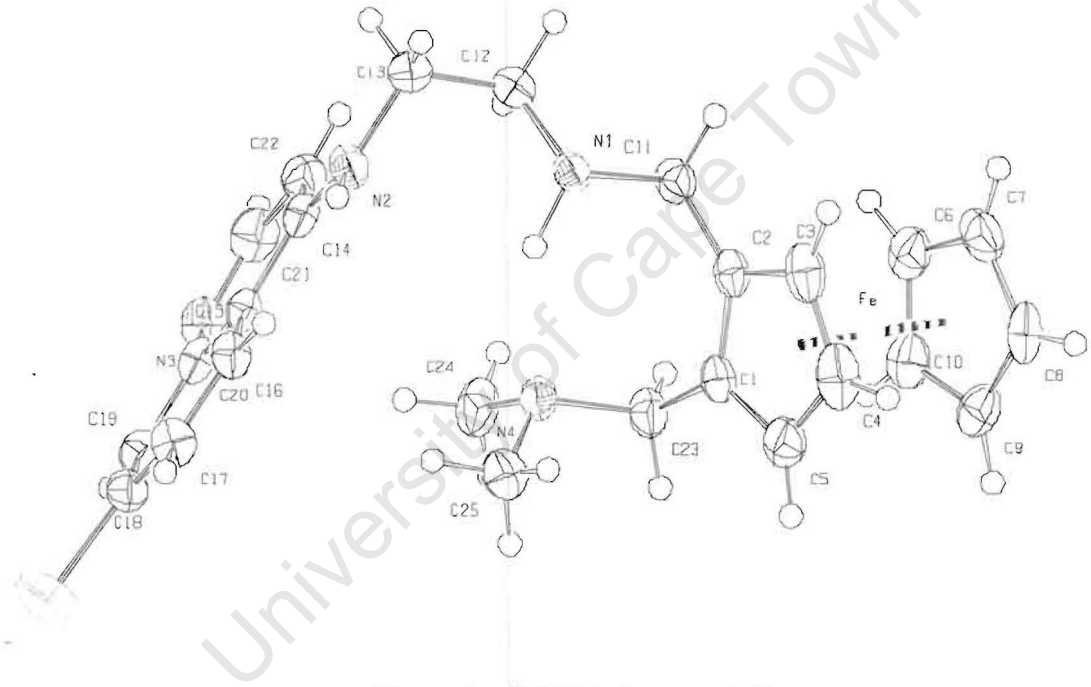


Figure 6: ORTEP diagram of **20**

The distances from the iron to the centre of the Cp rings are not equal (1.643 and 1.652 Å) with the shorter bond to the substituted Cp ring. However, this slight difference is unlikely to be of significance. The crystal structure confirms the *ortho*-substitution of the Cp ring. The position of the unsubstituted ring is well defined in this structure, this means that it occupies the same eclipsed orientation throughout the crystal lattice (Figure 6). There is one strong intramolecular hydrogen bond between N4 of the tertiary aliphatic amine and the H1 atom of the secondary amine with an N···H bond distance of 2.190(4)Å. There is an intermolecular hydrogen bond between the H2 of the secondary amine and N1 of a neighbouring molecule, resulting in hydrogen bonded dimers (Figure 7). The angle of this intermolecular hydrogen bond is 160°. There is a weaker intermolecular hydrogen bond between the quinoline N and H17 belonging to a neighbouring quinoline ring (N3···H17, 2.419(4)Å).

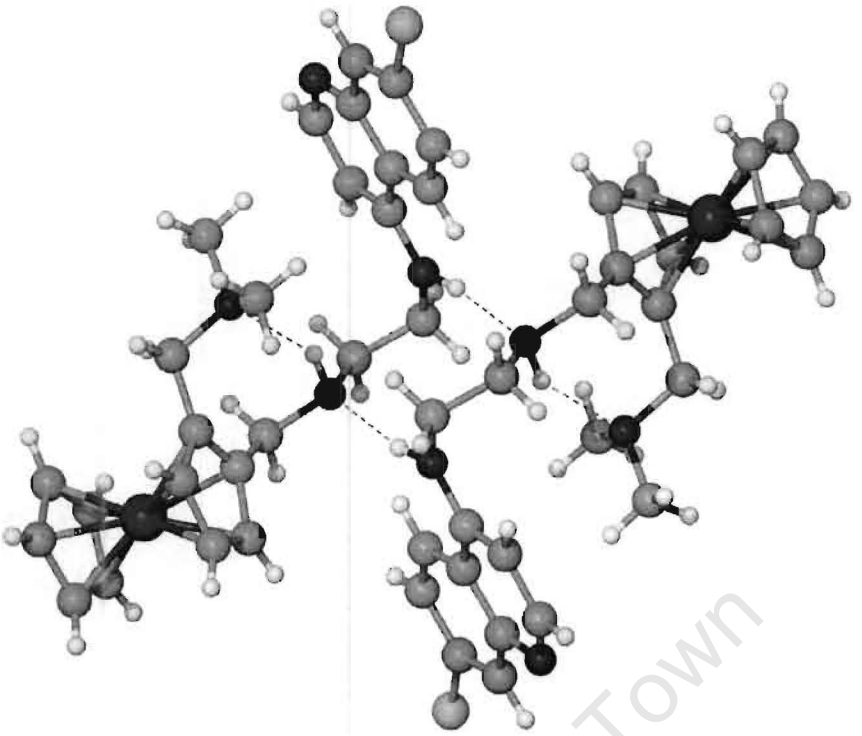


Figure 7: Hydrogen bonded dimers of **20**

Figure 7 shows the hydrogen bonding between the two enantiomers of **20** to form a loosely associated dimer. The dimers then pack together as shown in the packing diagram Figure 8, to give four molecules per unit cell.

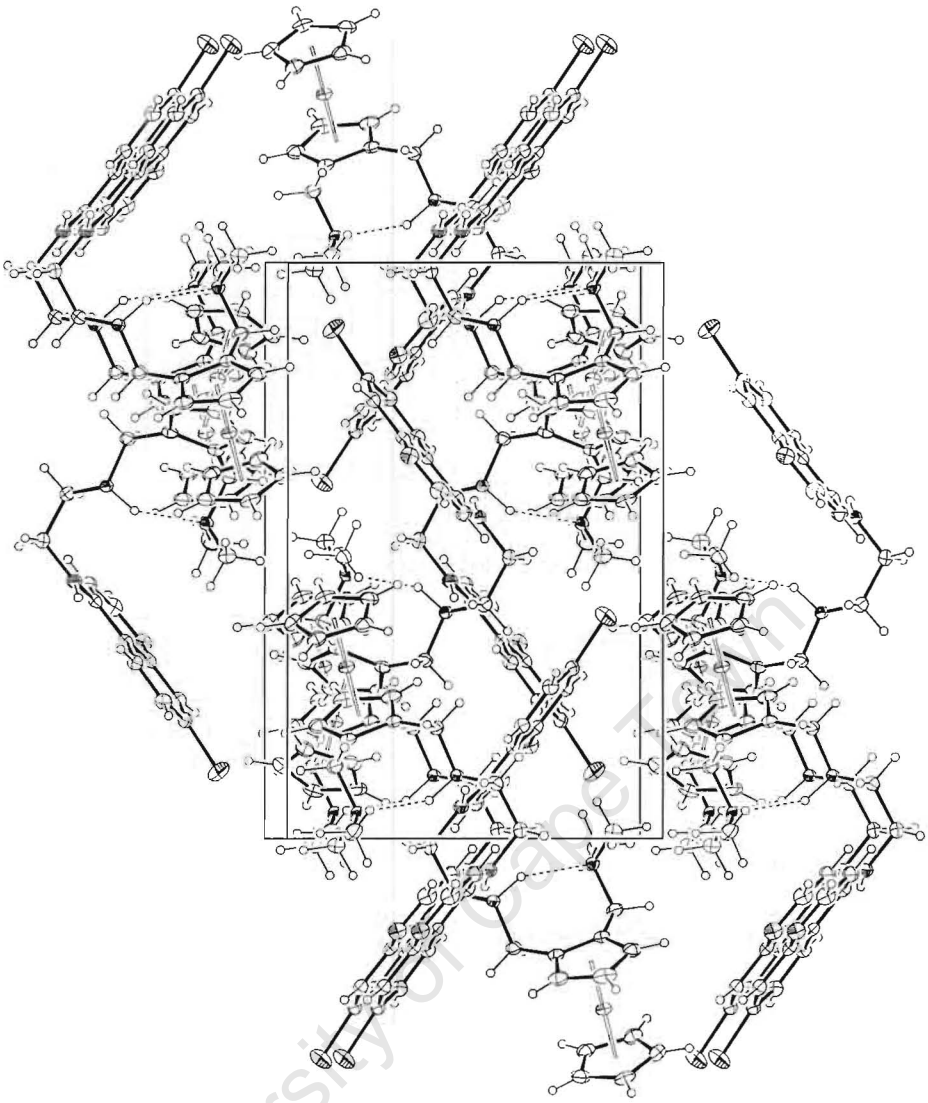


Figure 8: Packing diagram of **20**

NMR Spectroscopy

All compounds were characterised using ^{1}H and ^{13}C NMR spectroscopy and assignment of peaks was facilitated by use of COSY and HSQC two-dimensional NMR spectroscopy. The full detail of the NMR data can be found in Chapter 8. The x-ray crystal structure of **20** was crucial to the interpretation of the NMR data. As the structural conformation was known, any ambiguity in the assignment of the data arose from the inability to distinguish between similar signals and not from different possible structural conformations.

^{1}H NMR Spectroscopy

The proton NMR data of ferroquine is consistent with literature values.[2] The proton NMR data of the ferroquine analogues that we have prepared is also consistent with literature values for

similar compounds i.e. ferroquine[2] and other related chloroquinoline derivatives,[12] in as far as reasonable comparison could be made.

The chirality of these molecules is clearly evident in the ^{1}H NMR spectra, Figure 9. For example, if one considers the diastereotopic 2' protons this is demonstrated as follows: in a non-chiral environment the two protons would appear as a singlet. In these compounds there are two signals separated by a chemical shift of 1ppm. This is because the environment above and below the plane of the cyclopentadienyl ring is different, as one proton will be in close proximity to the iron centre, whilst the other will not. These protons are therefore diastereotopic and couple to one another. Hence the two signals are both doublets having a coupling constant of 12 – 13 Hz. The 3' protons show similar behaviour.

The 3' protons in the ferroquine analogues show a significant upfield shift with respect to **15**. This is consistent with the fact that in **15** the electron density on the adjacent aniline amine is reduced by the partial incorporation of the electrons on the nitrogen into the quinoline ring. This results in a deshielding of the 3' protons and hence in **20**, 3'a and 3'b appear at 4.09ppm and 4.35ppm respectively. In the ferroquine analogues there is some variation in the positioning of the 3' protons, but they consistently appear below 4ppm.

The quinoline protons of all compounds, **20-24**, occur in expected positions with regular coupling patterns. The alkyl protons adjacent to amine centres are observed downfield relative to those in the centre of the alkyl chain as would be expected.

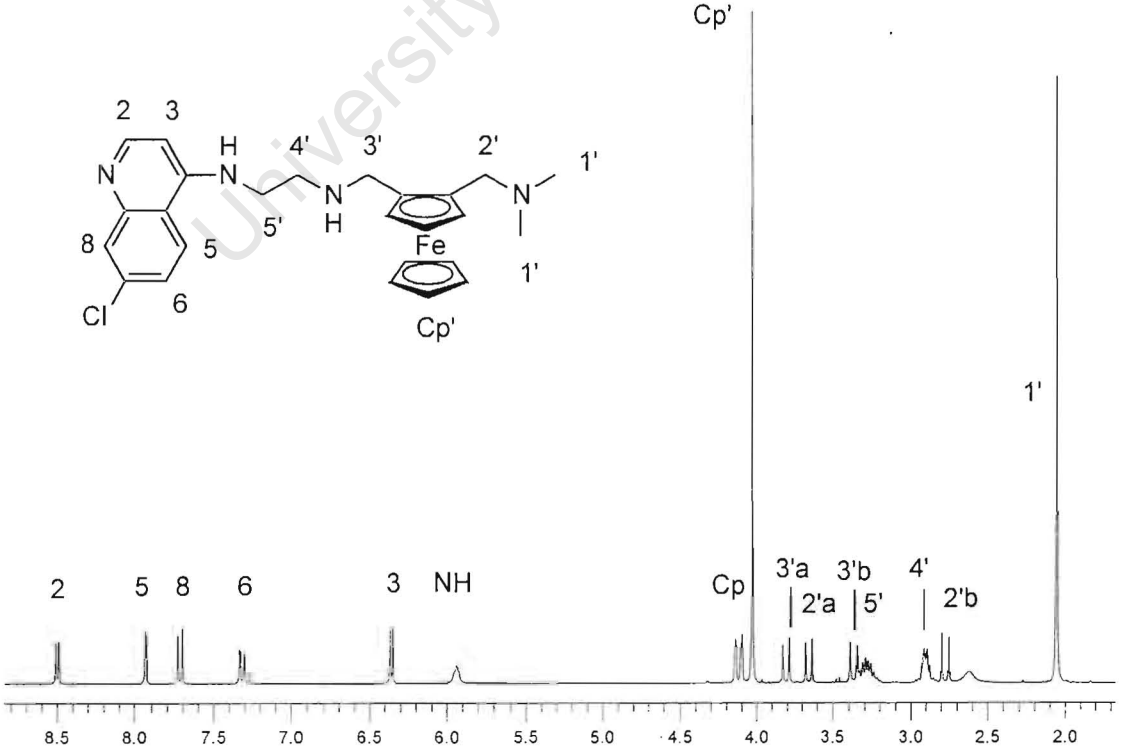


Figure 9: ^{1}H NMR spectrum of **20** in $CDCl_3$

The ^{1}H NMR spectra of the resolved salts showed a distinct shift in the 2' protons from 3.80ppm and 2.89ppm to approximately 4.2ppm. The 1' protons, normally observed as a 6 proton singlet, split into two 3 proton singlets, so 1'a and 1'b become distinguishable. This is seen quite clearly in Figure 10.

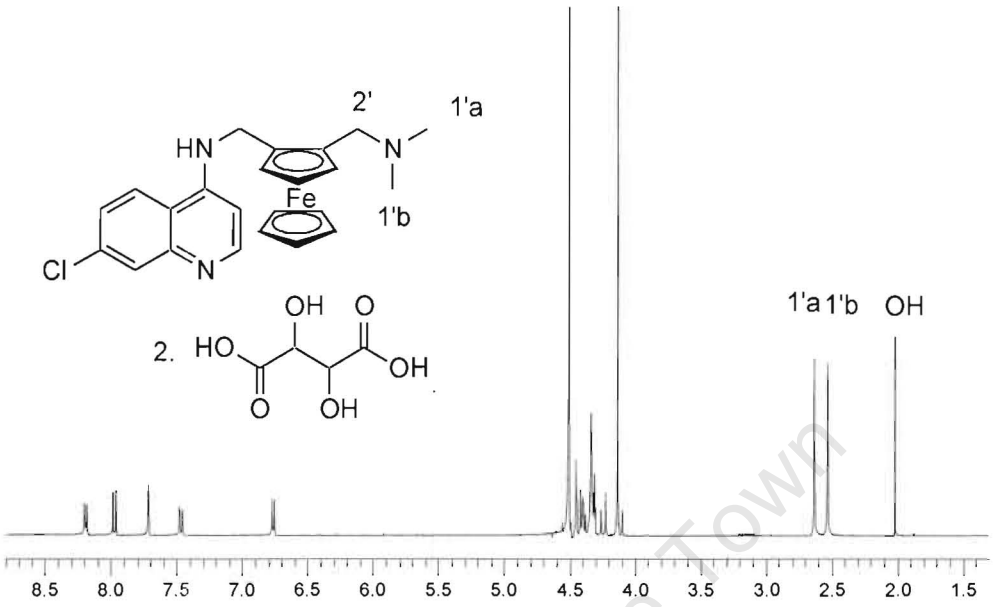


Figure 10: ^{1}H NMR spectrum of the resolved *L*-tartrate salt of **15**

^{13}C NMR Spectra

The carbon-13 NMR data for compounds **20-24** found to be was consistent with data found in the literature for similar compounds,[2] in as far as reasonable comparison could be made. Figure 11 shows the ^{13}C NMR for **20**, the only changes on increasing spacer length was the increment of one signal below 50ppm for each additional methylene group. It appears that the chemical shifts of carbon signals are far less susceptible to shielding and deshielding as there is little change in the positions of any of the signals irrespective of the length of the carbon spacer. HSQC was an invaluable tool in the assignment of the spectra. It was most useful for the unambiguous assignment of 2' and 3' protons, and assignment in the aromatic region.

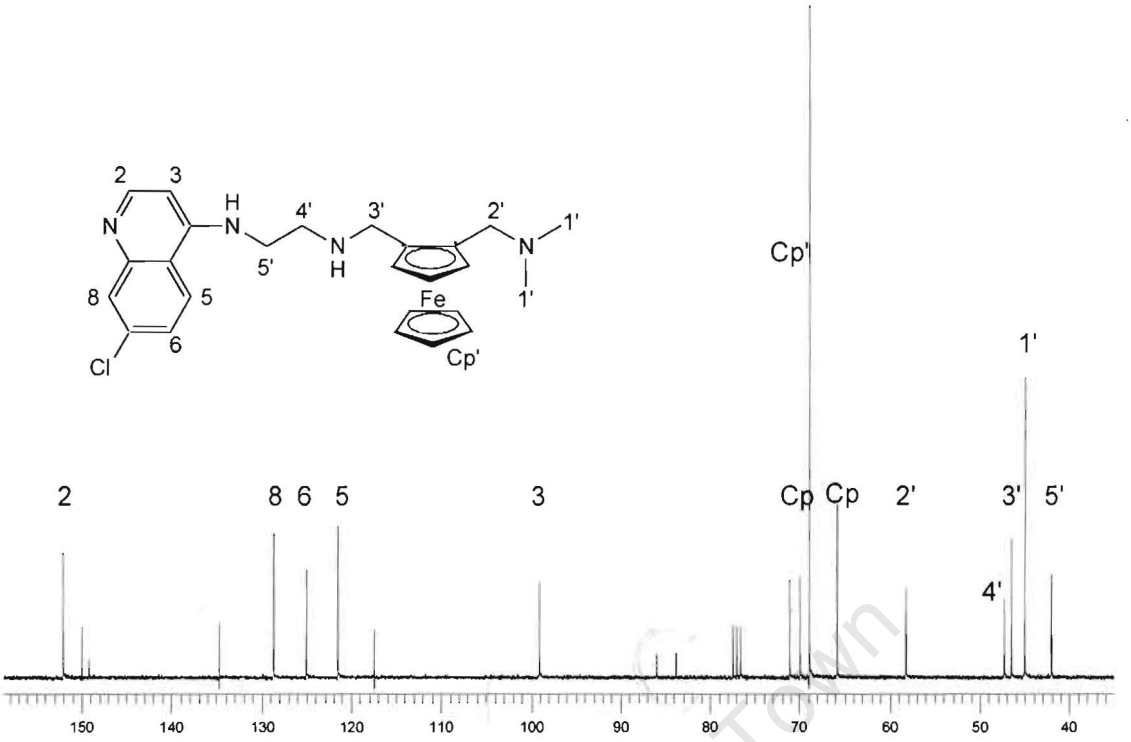


Figure 11: ^{13}C NMR Spectrum of **20** in $CDCl_3$

Mass Spectrometry

High resolution mass spectrometry (HRMS) was used principally to determine and confirm the accurate molecular mass of the compound. In all cases the accurate mass of the parent ion was determined within acceptable limits of error. In addition to this, the isotopic distribution of the parent ion was checked to determine whether it was consistent with calculated values. Furthermore, some attempt was made to ascertain the identity of the major fragments given that the structure of **20** was known. All these factors were used simply to determine whether the proposed compound had been formed or not. Together, these data provided further support that the desired compounds had indeed been successfully synthesised.

Infrared Spectroscopy

As with mass spectrometry the infrared spectra were very complex and it was not possible to assign all the absorption bands unambiguously. Some groups present in the molecules exhibit characteristic absorption patterns that were relatively easy to identify. For example, the presence of the ferrocenyl moiety may be ascertained by four clear bands at 1104, 1000, 830, 490 cm^{-1}. The 7-chloroquinoline moiety similarly showed three characteristic strong bands at approximately 1610, 1580 and 1540 cm^{-1}. Once again, this technique was used simply to confirm the proposed structures as far as possible and to provide the unique fingerprint for each compound.

Studies into Activity of the Compounds

Cyclic Voltametry

Ferrocene derivatives have been investigated as potential electrochemical probes because they are stable and relatively easy to synthesise.[14]

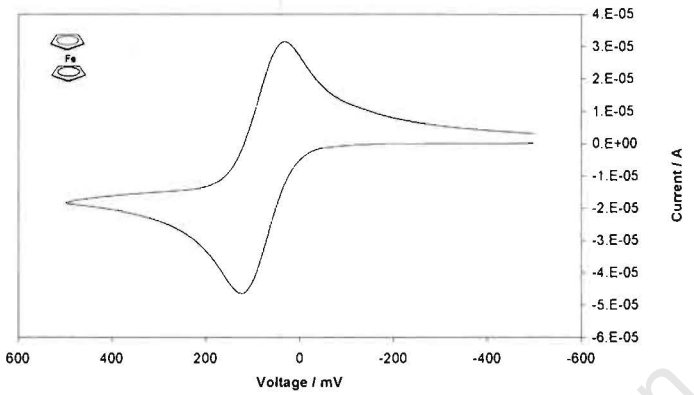


Figure 12: Cyclic voltamogram of ferrocene

In a cyclic voltametry experiment, ferrocene exhibits a characteristic fully reversible one-electron wave, Figure 12. In fact, ferrocene is usually used as the standard for cyclic voltametry. As these compounds all contain a substituted ferrocenyl moiety it was of interest to examine the redox activity of these complexes. The picture obtained was far more complex than anticipated. In general, it is accepted that a fully reversible one-electron wave will have a peak separation (ΔE_p) within the range of 70-90 mV. Furthermore, it is required that the anodic and cathodic peak current values should be approximately the same. This can be seen in Figure 12.

Table 1: Cyclic Voltametry Data for Ferroquine Analogues

Compound	E_{pa}	E_{pc}	$E_{1/2}$[a]	ΔE_p[b]
Ferrocene	123	34	79	89
15	181	113	147	70
20	150	(30)		120
21	120	(13)		107
22	106	(14)		92
23	92	(12)		80
24	Indistinct	(12)		

[a]$E_{1/2} = (E_{pa} + E_{pc})/2$; [b]$\Delta E_p = E_{pa} - E_{pc}$

Ferroquine, **15**, exhibited a fully reversible one electron oxidation but it is far more difficult to oxidise than ferrocene, as indicated by the significant increase in $E_{1/2}$ value.

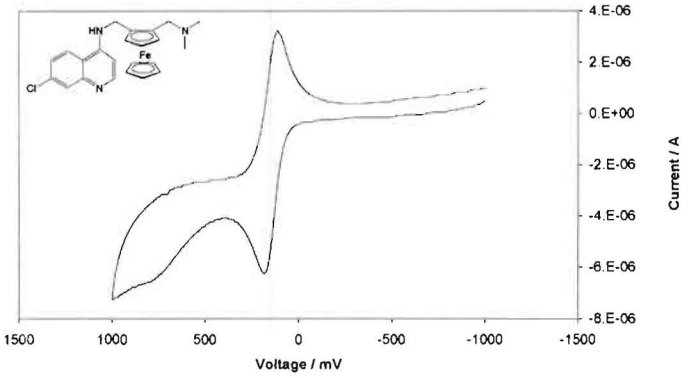


Figure 13: Cyclic voltamogram of Ferroquine

The ferroquine analogues all show, at best, quasi-reversible oxidation of the ferrocenyl moiety. The ease of reversibility of the reaction increased with increasing spacer length, as indicated by the decrease in peak separation (ΔE_p). While the value of the peak separation of the ferroquine analogues with longer chain length does fall within the required range, the cathodic peak current is consistently significantly smaller than the anodic peak current, so these cannot be regarded as fully reversible redox reactions, thus, no half-wave potential is calculated.

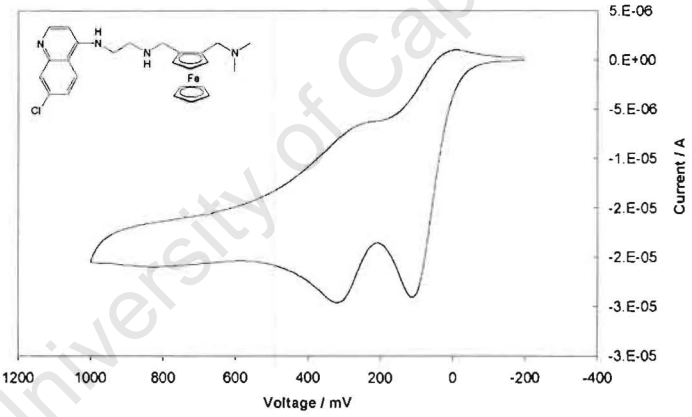


Figure 14: Cyclic voltamogram of **20**

The oxidation of all compounds resulted in the deposition of some species on the electrode. This was observed by the decrease in peak currents on each successive sweep cycle in a single experiment.

While there are still a number of questions surrounding the cyclic voltametry of these compounds, several points have been established.

- 4,7-dichloroquinoline does not exhibit any redox behaviour in the solvent window.
- Chloroquine shows an irreversible oxidation curve at 750mV which results in deposition on the electrode. This suggests that the redox activity exhibited by chloroquine is a function of the side chain rather than the 7-chloroquinoline system.
- Ferroquine **15** shows a fully reversible one electron oxidation.

- Whilst the ΔE_p values of the longer chain ferroquine analogues fall within the range required for a fully reversible oxidation, the cathodic peak current is significantly smaller than the anodic peak current and therefore these can only be regarded as quasi-reversible oxidations.
- The ease of reversibility increases with increasing spacer length, shown by the lower ΔE_p values.
- The ferroquine analogues all cause deposition on the electrode. This is shown by running a single experiment with several sweeps. Each successive sweep shows diminished peak currents.
- The ferroquine analogues also exhibit a second redox event at about 300mV.
- The anodic peak current of the second redox event diminishes with respect to the ferrocenyl oxidation on increasing the scan rate.

These results, when considered alongside the cyclic voltametry results discussed in Chapters 3 and 4, indicate several possible explanations.

1. The irreversible oxidation is related to the aniline amine. This event is observed in all compounds that have the 7-chloroquinoline system we have tested with the exception of 4,7-dichloroquinoline. Deposition on the electrode appears to be related to this event.
2. The reversibility of the oxidation of the ferrocenyl moiety is impaired by the presence of the NH β to this entity.
3. The aniline amine and the secondary amine β to ferrocene exhibit different redox activity. This is demonstrated by the reversibility of the oxidation of the ferrocenyl moiety in ferroquine, **15**, and the lack thereof in the ferroquine analogues.

It should also be observed that the electronic effect of the side chain is known to have an impact on the redox behaviour of ferrocene. In particular, the oxidation potential increases with increasing electon acceptor strength of the substituent.[15] This is clearly demonstrated in the significant increase in the cathodic peak potential in moving from ferrocene to ferroquine, **15**.

Whilst it is of interest to look at the cyclic voltametry of these compounds in itself as part of their characterisation, it was suggested that there may be a correlation between the electrochemical behaviour of these compounds and their *in vitro* biological activity. Some correlation could be drawn between potency of trypanothione reductase inhibition (results given in chapter 5) and ease of oxidation, following increasing methylene spacer length. However, no such correlation was observed with glutathione reductase inhibition.

Molar Conductivity

The molar conductivity of some of the compounds was determined and, as expected, these compounds were found to be neutral. This is consistent with the structure of the compounds as determined by x-ray crystallography.

Conclusions

The x-ray crystal structure of **20** was determined and thus provided the basis for interpretation of the spectroscopic data obtained. In all cases the NMR data was clear and simple to interpret. As the methylene spacer increased in length some ambiguity arose as to the absolute assignment of methylene groups in both ^{1}H and ^{13}C NMR. This was not deemed to be a problem as the rest of the data was consistent across the series of compounds and consistent with the literature as far as reasonable comparison could be made.[2,12] Data from mass spectrometry and infra-red spectroscopy was used to support the other analytical data obtained, and to provide further characterisation data for the new compounds described.

Ferrocene exhibits a fully reversible one-electron redox wave in acetonitrile. Ferroquine exhibits similar behaviour, but it is far more difficult to oxidise than ferrocene. The ferroquine analogues, **20-24** do not display such fully reversible events. The ease of reversibility increases with increasing spacer length.

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Chapter 3

Urea and Sulfonamide Derivatives of Ferroquine

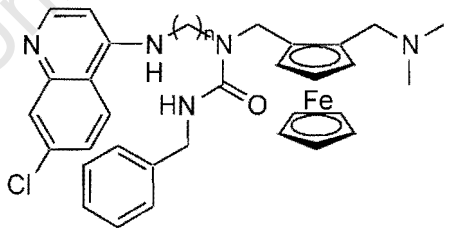
Introduction

This chapter deals with the synthesis and characterisation of various organic derivatives of the ferroquine analogues detailed in Chapter 2. Part of the rationale for the design of the ferroquine analogues was the inclusion of a reactive secondary amine centre as a site for introducing chemical diversity. This was used specifically in this work for the functionalisation of the ferroquine analogues to make urea and sulfonamide derivatives.

The purpose of this study was to ascertain whether potential high throughput synthetic methodologies could be applied to these systems in order to rapidly obtain modest libraries of compounds that could then be screened for biological activity. It is well known that small differences in the structure of potential drug candidates can have significant effects on the efficacy.[1]

Rationale

The aim here was to functionalise the ferroquine analogues using the reactive secondary amine centre. In particular, urea and sulfonamide derivatives were targeted. The use of ureas and sulfonamides[2,3] in compounds that exhibit antimalarial activity has been established.[4] In addition to this, the possibility of using appropriate quenching reagents and resin bound substrates[5,6] could facilitate the synthesis of modest libraries of these compounds relatively quickly.



n = 2; **37**
n = 3; **38**
n = 4; **39**
n = 6; **40**

Figure 1: Benzyl ureas with varying spacer length

A series of benzyl ureas, Figure 1, with varying methylene spacer lengths[7] would serve to determine the effect, if any, of the length of the methylene spacer on the efficacy of the compounds as antimalarial agents.[8,9] This effect was also examined with regard to the ferroquine analogues (Chapter 5).

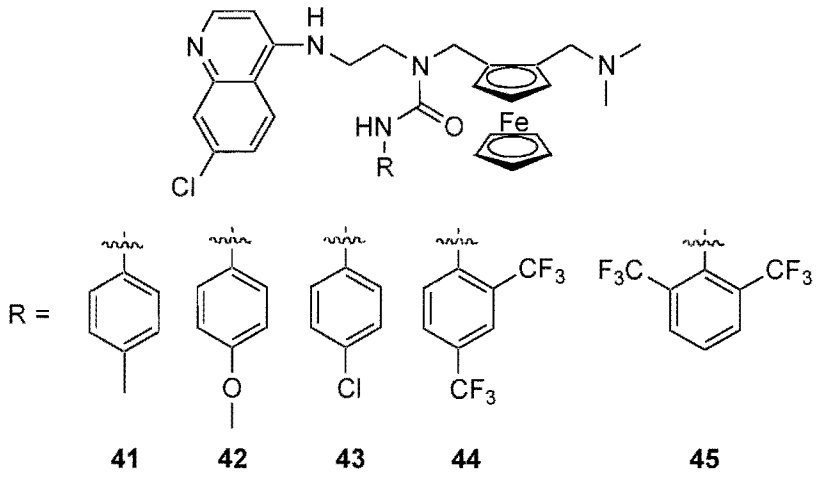


Figure 2: Urea derivatives of **20** with varying side chains

The effect of aromatic substituents in the urea compounds was examined (Figure 2). Here the methylene spacer length was kept constant, in order to determine the effect due to the substituted aromatic ring alone.

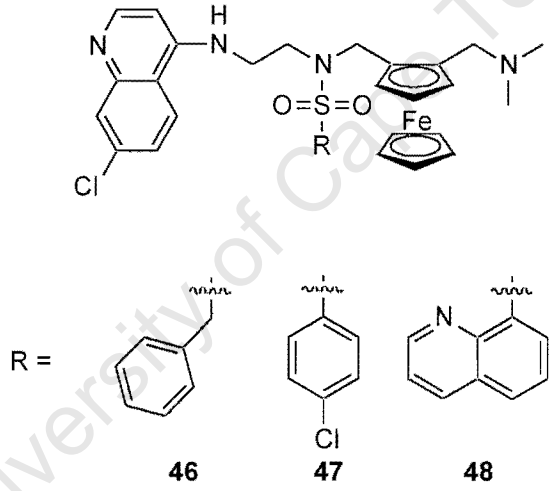


Figure 3: Sulfonamide derivatives of **20** with varying side chains

The introduction of the aromatic sulfonamide moiety was carried out for two purposes. Firstly, to further determine the effect aromatic substituents. Secondly, to determine whether there was any major difference in efficacy in moving from the urea series to sulfonamide series. Again, the methylene spacer was kept constant, in order to minimise the number of changes.

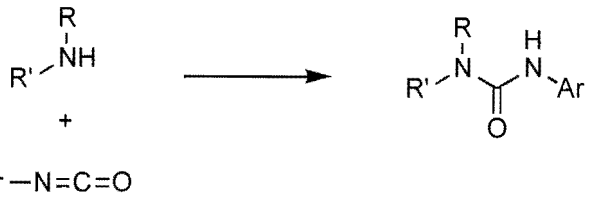
General Synthesis of Ureas

There are many possible synthetic routes for the synthesis of urea compounds, only two are examined here.

1. Synthesis from isocyanates and amines

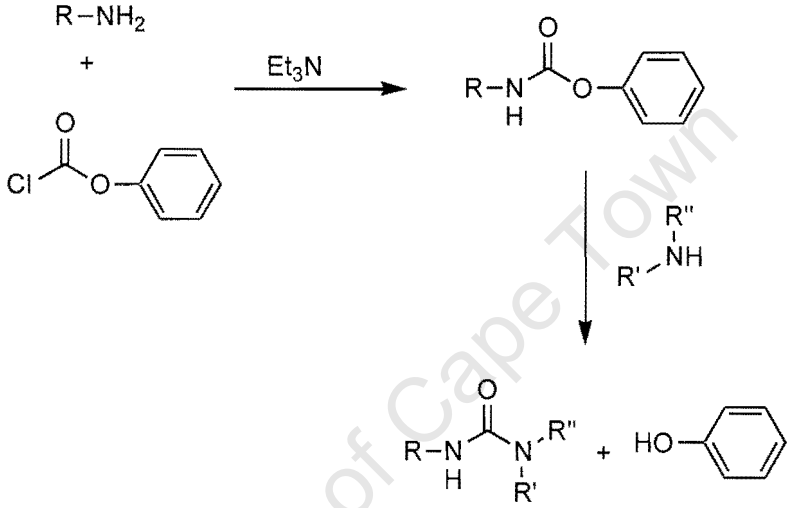
Using this method, urea compounds can be made quickly and under ambient conditions to give the product in high yields. The main drawback of this approach is the limited range of

commercially available isocyanates. Although isocyanates can be synthesised from phosgene and amines, this diminishes the advantages of using this particular methodology by introducing an extra step in the synthesis.



Scheme 1: Synthesis of ureas from amines and isocyanates

2. Synthesis from a carbamate intermediate

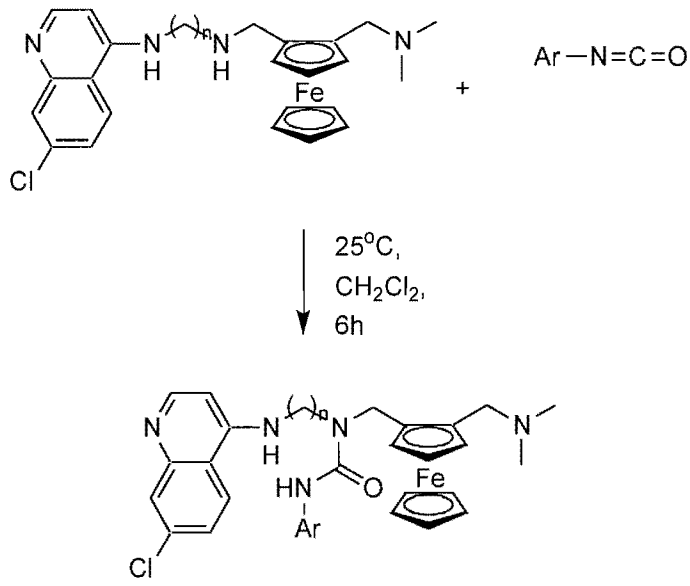


Scheme 2: Synthesis of urea compounds *via* carbamate intermediate

The reaction of amines with chloroformates, exemplified in Scheme 2, in the presence of a base such as triethylamine gives carbamate intermediates. These intermediates are then reacted with a range of primary and secondary amines. As both primary and secondary amines can be used and a wide variety of these reagents are commercially available, many different urea compounds can be synthesised.

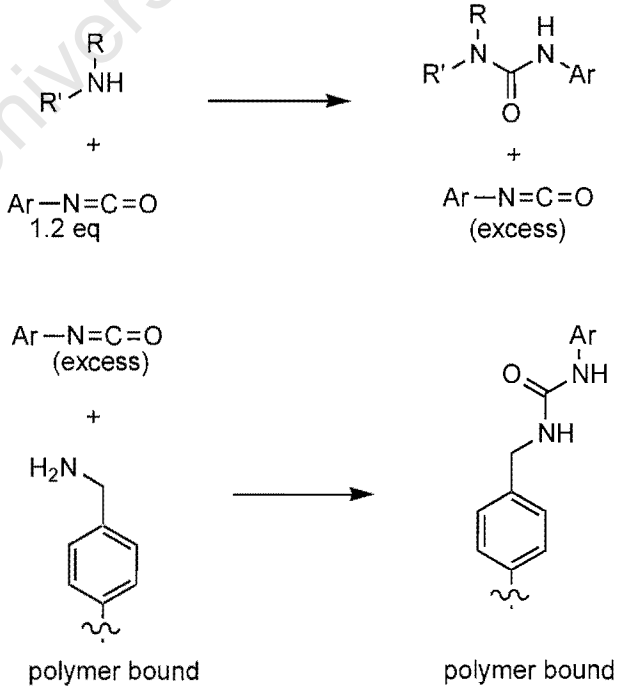
Formation of Ferroquine Urea Derivatives

The synthesis of the urea compounds was relatively simple and was achieved in high yields (up to 90%). The ferroquine compounds were reacted with the relevant isocyanate to form the corresponding ureas.



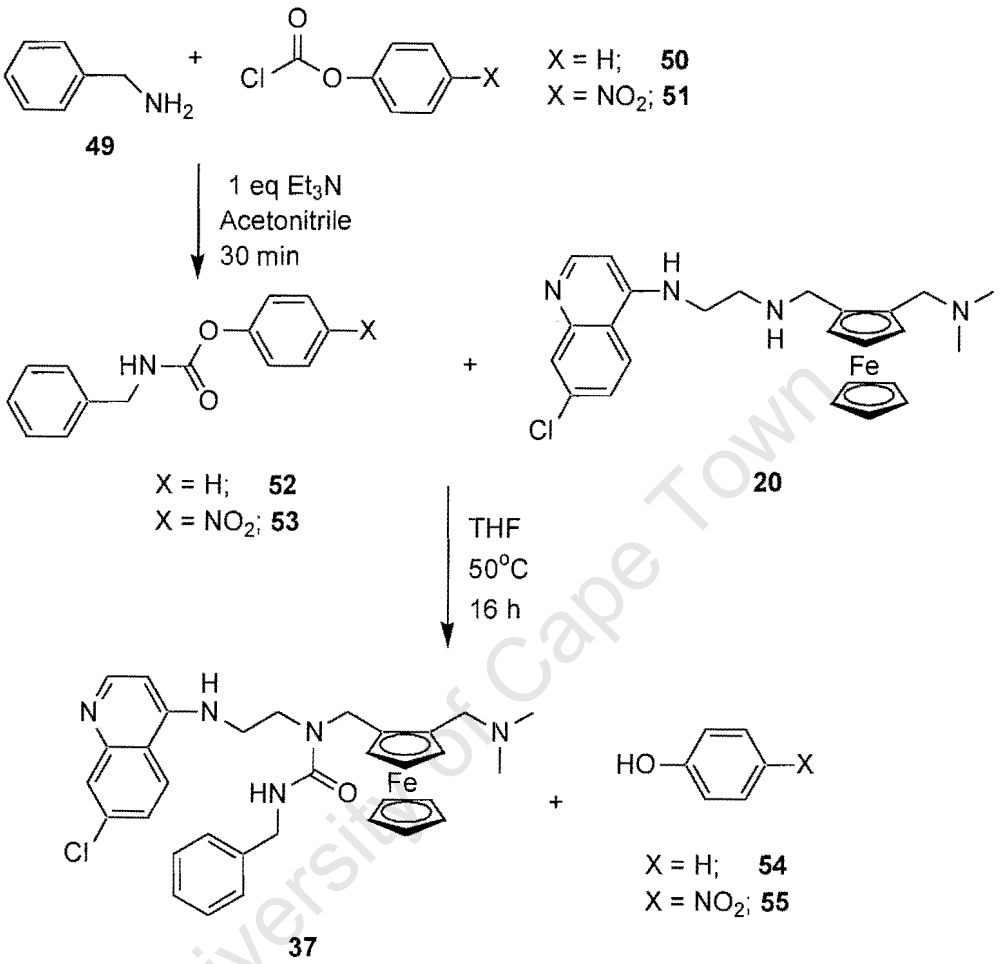
Scheme 3: Synthetic route employed to produce substituted ureas

The use of solid phase quenchers in the synthesis of urea compounds is known.[5] The product could be isolated by filtration and removal of the solvent. This would mean that a variety of products could be made simply and rapidly, allowing for the development of a modest library of compounds. It was hoped that (aminomethyl)polystyrene could be used to trap the excess isocyanate used in the reaction leaving the pure product in solution, Scheme 4. However, it was found that purification by silica gel chromatography was still necessary. Decomposition of the starting isocyanates under the reaction conditions was the major problem. The use of the polymer-supported reagent was therefore superfluous and so it was not used for most of the syntheses.



Scheme 4: Synthesis of ureas using trapping agents.

The synthesis of ureas depicted in Scheme 3 worked consistently well. However, as the reaction still required purification by silica gel chromatography, it was reasoned that exploration of an alternative synthesis of the benzyl urea derivatives *via* the carbamate intermediate route, Scheme 5, was worthwhile. The reason being, the synthesis of several benzyl urea analogues was required for the structure-activity relationship studies described in Chapter 6.



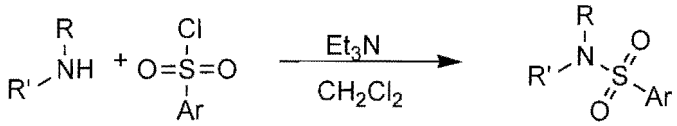
Scheme 5: Formation of urea compounds *via* carbamate intermediate

The carbamate intermediates (X = H and X = NO_2) were prepared in high yields (80-85%) from the corresponding chloroformates by reaction with benzylamine in the presence of triethylamine. The difference between use of the nitrophenylchloroformate- and the phenylchloroformate- derived carbamates was significant in the synthesis of the benzyl urea. The presence of the electron-withdrawing nitro group renders the carbonyl group highly electrophilic. Coupled with the resonance stabilisation of the nitrophenoxide anion, the reaction proceeded at a faster rate and could be carried out at a lower temperature. This was important because prolonged heating of **20** results in decomposition and therefore significantly reduces the yield of the reaction. The yields with respect to **20** obtained by this methodology were similar to those found with the isocyanate methodology.

General Synthetic Routes for Sulfonamides

The chemistry of RSO_2X is similar to that of RCOX (X = Cl). In the same way as carboxylic acid amides can be made by a substitution reaction between the acid chloride and an amine, so sulfonamides can also be made from the corresponding sulfonyl chloride. However, it should be noted that the sulfonyl halides are less reactive than the carboxylic acid halide analogues.[10]

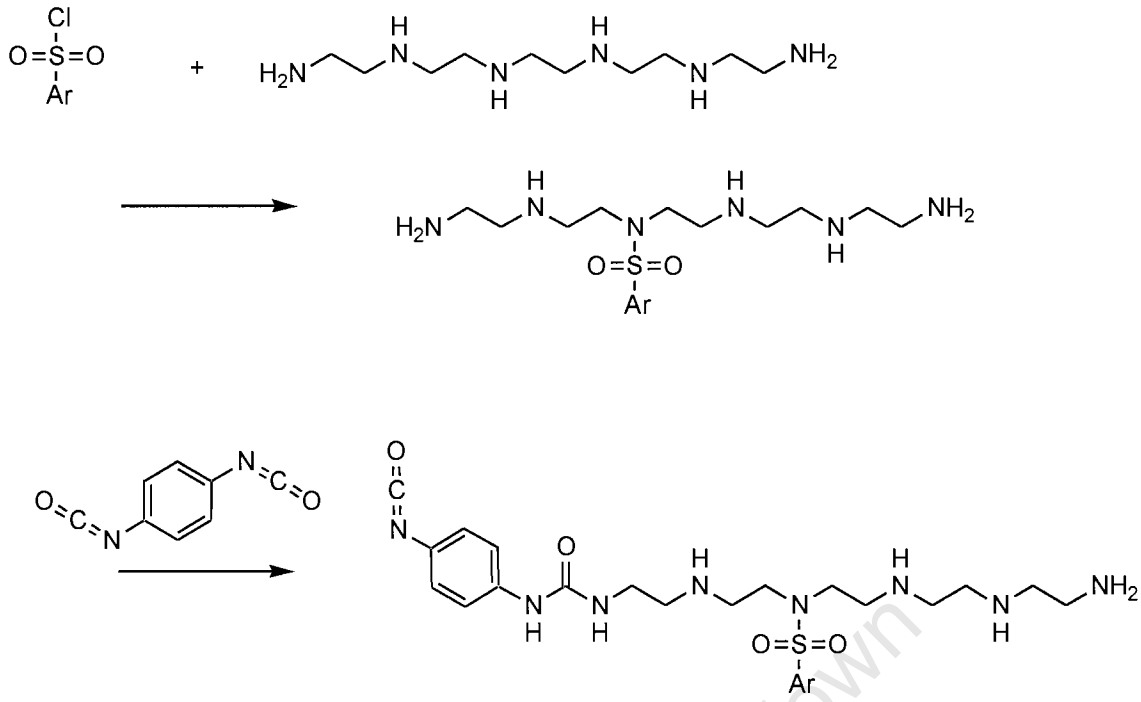
Only one synthetic route was explored using trapping reagents and polymer supported reagents to provide an efficient synthesis of sulfonamide derivatives of ferroquine analogues.



Scheme 6: Synthesis of sulfonamides from amines and sulfonyl chlorides

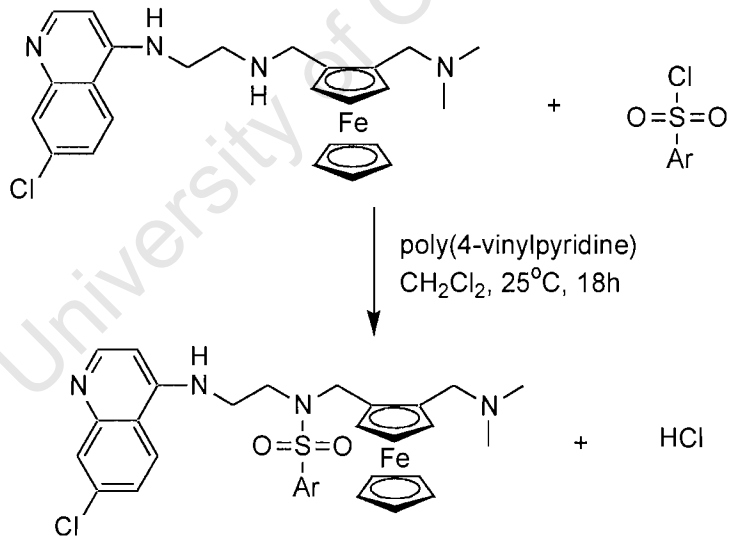
This methodology requires the use of readily available starting materials under mild conditions to give the product in high yield. This type of reaction is well suited to the use of trapping reagents. An excess of sulfonyl chloride in the presence of a suitable base is used to ensure as much of the amine reacts as possible.[6] The base removes the hydrochloric acid formed in solution and is best achieved using a polymer supported base exemplified by poly(4-vinylpyridine). Triethylamine can also be used, but the removal of this reagent can sometimes prove difficult, whereas the polymer supported reagent can be removed by filtration. In on of the protocols, pentaethylenehexamine is then used to react with the excess sulfonyl chloride. 1,4-phenylene diisocyanate is then added to form a polymeric product with the pentaethylenehexamine through the formation of a polyurea.[6]

Scheme 7 shows representative reactions with the three reagents. It is clear that there are many potential reactive sites on the pentaethylenehexamine, and two reactive sites on the 1,4-phenylene diisocyanate. This facilitates the formation of the polyurea which can be removed by filtration.[6]



Scheme 7: Trapping of excess sulfonyl chloride

Formation of Ferroquine Sulfonamide Derivatives



Scheme 8: Synthetic scheme for the formation of the sulfonamide derivatives

The aforementioned use of trapping agents was attempted. Pentaethylenehexamine was added to trap any remaining sulfonyl chloride. The excess pentaethylenehexamine was then trapped by the addition of 1,4-phenylenediisocyanate. Both these reactions resulted in the formation of insoluble products which could then be removed by filtration. However, once again the use of silica gel chromatography was necessary to obtain a pure product, so the use of trapping agents was superfluous.

Characterisation

^{1}H NMR Spectroscopy

The proton NMR data is consistent with the proposed structures of the new compounds. Figure 4 and Figure 5 show the ^{1}H NMR spectra of **37** and **20**, respectively. Only the significant points of difference are labelled. There are several points to note:

- The presence of the aromatic protons originating from the isocyanate fragment (7.13-7.07 ppm)
- The absence of the broad triplet of the NH (5.9ppm)
- The presence of the 1'' protons (4.24-4.16ppm)
- The upfield shift of the 3'a, 3'b in the urea derivative, which shift from the left of the Cp peak in **20** to the right of the Cp peak in the urea.
- The upfield shift of the 4' protons.

The latter two points are consistent with the close proximity of the electron withdrawing urea group causing deshielding of the 3' and 4' protons and hence the upfield shift.

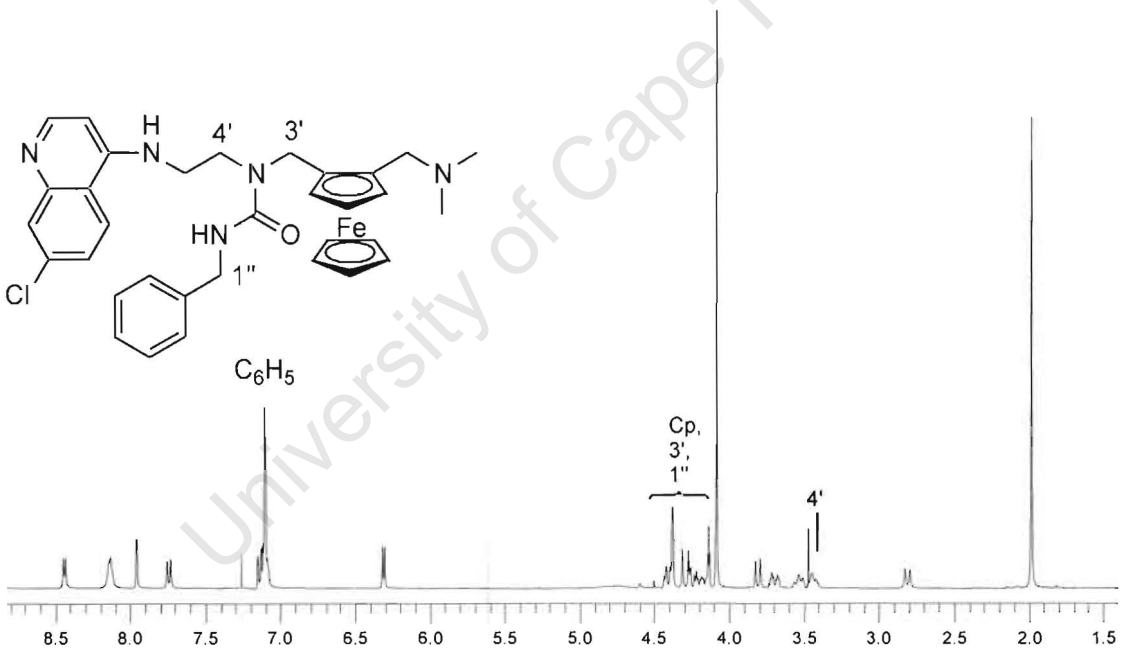


Figure 4: ^{1}H NMR Spectrum of **37** in $CDCl_3$

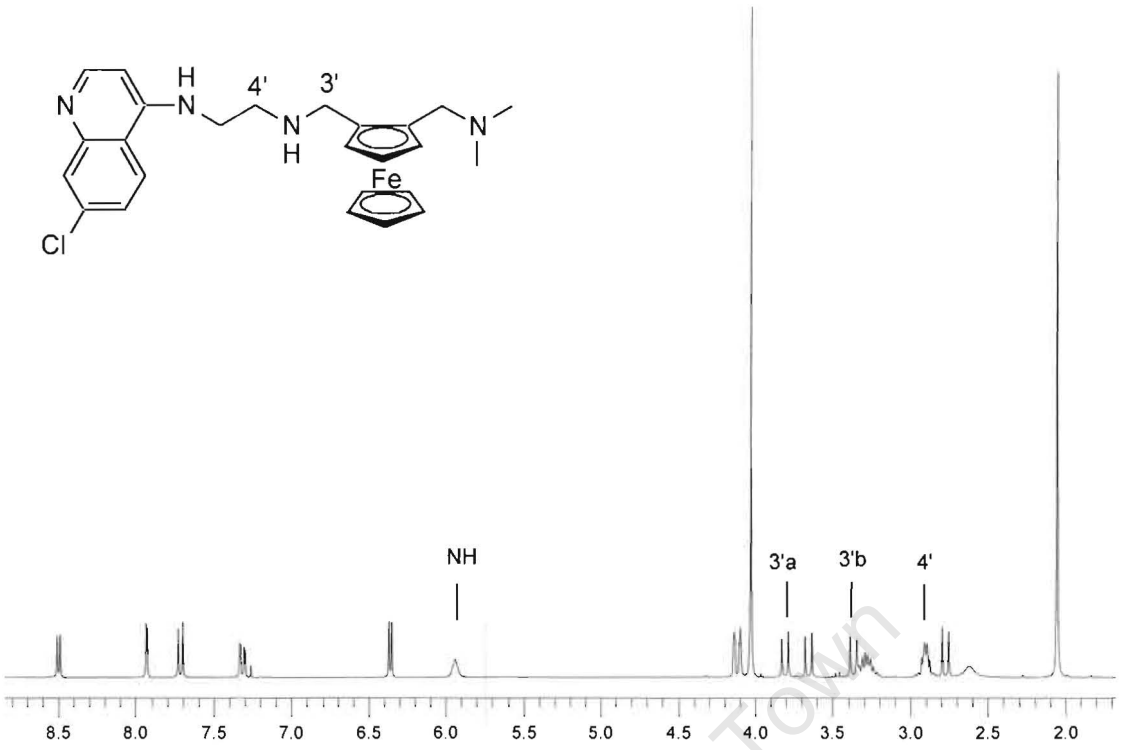


Figure 5: ^{1}H NMR Spectrum of **20** in $CDCl_3$

The data for the sulfonamide derivatives show a similar trend in the ^{1}H NMR spectra. A comparison can therefore be drawn between the benzyl urea derivative **37** and the benzyl sulfonamide derivative **45**. Again the downfield shift of 3' and 4' protons is observed, once more consistent with the deshielding by electron withdrawing effect of the sulfonamide group.

^{13}C NMR Spectroscopy

The carbon-13 NMR data of all compounds was consistent with expected values. There was no significant change in the chemical shifts of carbon atoms in the ferroquine analogue scaffolds. There were new signals arising from the urea or sulfonamide groups, but their values were all found to be consistent within the group when reasonable comparison could be made.

Mass Spectrometry

In all cases the accurate mass of the parent ion was determined within acceptable limits of error using HRMS. In addition to this, the isotopic distribution around the parent ion was checked to determine whether it was consistent with calculated values. Furthermore, some attempt was made to ascertain the identity of the major fragments. These compared well with the data obtained for the ferroquine scaffolds. Together these data provided further support that the desired compounds had indeed been successfully synthesised.

Infrared Spectroscopy

As in Chapter 2, infrared spectroscopy was used principally to ascertain the presence of the major functional groups in the molecules. In all cases, characteristic ferrocenyl (1104, 1000, 830, 490 cm^{-1}) and 7-chloroquinoline bands (1610, 1580 and 1540 cm^{-1}) were observed.

In the urea compounds the carbonyl stretching frequency occurs at about 1640cm^{-1}. In some cases a distinct peak was observed, but in other cases, the presence of this absorption band was noted only by a distinct broadening of the strong C=C stretching frequency present at about 1610 cm^{-1}.

The methoxyphenylurea shows most characteristic strong R-O-R' symmetric and asymmetric stretching bands at 1032cm^{-1} and 1232 cm^{-1} respectively.

The trifluoromethyl groups, CF_3, show distinctive strong symmetric and asymmetric stretching bands at 1323cm^{-1}, 1166cm^{-1} and 1136cm^{-1} as well.

Cyclic Voltametry

Cyclic voltamograms were obtained for the compounds in acetonitrile solution. It is noted that a fully reversible one-electron wave will have a peak separation within the range of 70-90mV. In addition to this, it is required that the anodic and cathodic peak currents are of similar magnitude. The benzyl urea series can all be considered to show such reversible redox events, Figure 6.

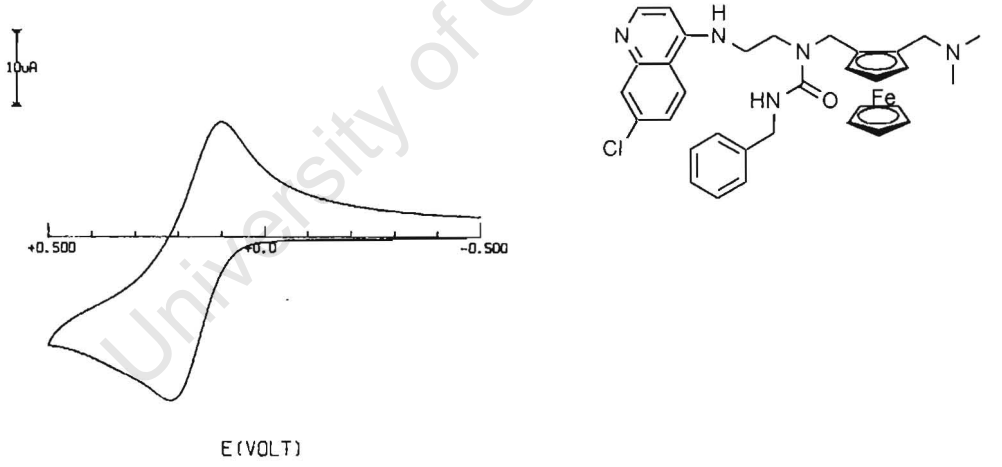


Figure 6: Cyclic voltamogram of **37**

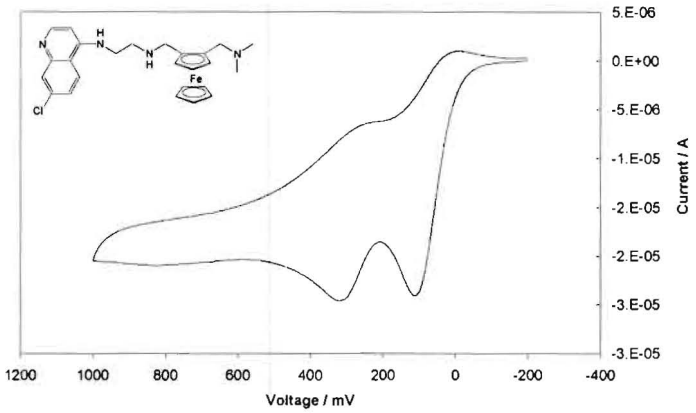


Figure 7: Cyclic voltamogram of **20**

These results are remarkably different from the parent amines (see Table 1, Chapter 2). The presence of the benzyl urea moiety seems to have two effects. Firstly, the ferrocenyl moiety is far more difficult to oxidise, shown by the high half wave potentials. This is consistent with the increase in electron acceptor strength of the side chain relative to hydrogen.[11] Secondly, the redox event is fully reversible in the benzyl ureas, Figure 6, whilst in the parent ferroquine analogues it is, at best, quasi reversible, Figure 7. (NB – the differences in appearance of the diagrams are simply due to the acquisition of more user friendly software for processing data. The CV experiments were performed using the same instrumentation)

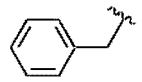
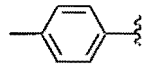
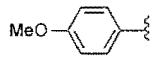
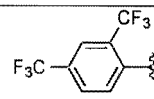
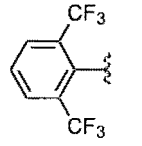
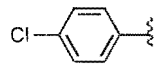
Table 1: Cyclic Voltametric Data of Selected Compounds

Compound	n	E_a (mV)[a]	E_c (mV)[b]	$E_{1/2}$ (mV)[c]	ΔE_p (mV)[d]
37	2	198	115	158	83
38	3	171	91	131	80
39	4	149	82	116	67
40	6	164	81	123	83

[a]anodic potential; [b]cathodic potential; [c]half wave potential $(E_a + E_c)/2$; [d]$\Delta E_p = E_a - E_c$

Table 2 shows the results of the cyclic voltametry experiments performed in the urea series with varying side chain. With the exception of **42** and **45** all the compounds showed similar redox behaviour to that exhibited by the benzyl ureas.

Table 2: Electrochemistry of urea derivatives of **20**

Compound	Side chain	E_{pa} (mV)[a]	E_{pc} (mV)[b]	$E_{1/2}$ (mV)[c]	ΔE_p (mV)[d]
37		198	115	157	83
41		195	115	155	80
42		170	5		160
43		204	125	165	79
44		218	139	179	79
45		214	111		103

[a]anodic potential; [b]cathodic potential; [c]half wave potential $(E_{pa} + E_{pc})/2$; [d]$\Delta E_p = E_a - E_c$

Overall, it is noted that there seems to be little correlation between the half wave potential and the biological activity (detailed in Chapter 4).Note that the half wave potentials of **42** and **45** were not calculated, because $\Delta E_p > 90$, so these curves were not fully reversible and thus it is misleading to quote an $E_{1/2}$ value.

Conclusions

A limited series of urea and sulfonamide compounds have been synthesised. The synthetic strategy employed was relatively simple for each series and in most cases the desired product was obtained in good yield. Unfortunately, the use of high throughput methodology, such as polymer supported reagents or trapping agents, was found to be superfluous. This was as a result of the decomposition of starting materials and/or reaction products particular to the given system rather than a problem with the general methodology.

All of the compounds made have been fully characterised. In all cases the characterisation data was consistent with the proposed structure of the compounds. The cyclic voltametry of the compounds was interesting. It was found that these compounds show fully reversible one-electron redox curves. As discussed in Chapter 2, the ferroquine analogues do not show such activity. It is proposed that the lack of reversibility in the ferroquine analogues is due to the presence of the reactive secondary amine centre. Further studies would need to be done to substantiate this theory.

References

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Chapter 4

Metal Complexes of 4-Amino-7-chloroquinoline Compounds

Introduction

The synthesis and characterisation of metal complexes of various 4-amino-7-chloroquinoline ligands is detailed in this chapter. The ligands used in this work were chloroquine, ferroquine, **20** and **37**. (Note in the metal complexes **20** is referred to as **F2Q** and **37** as **BU**)

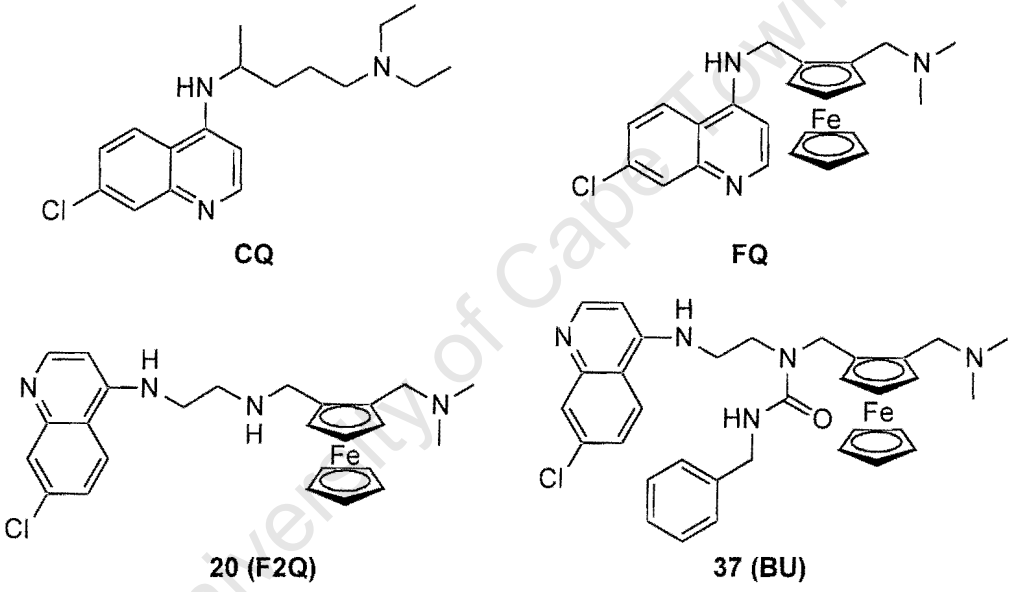


Figure 1: 4-Amino-7-chloroquinoline ligands used for complexation

Three series of metal complexes have been made using the ligands shown in Figure 1. Firstly, a series of ionic gold complexes of the type $[Au(L)PPh_3]^+NO_3^-$; secondly, a series of neutral gold complexes of the type $[Au(C_6F_5)L]$; and thirdly, a series of neutral rhodium complexes of the type [RhCl(COD)L], (where L = 4-amino-7-chloroquinoline ligand).

Rationale

The concept of coordinating metal complexes to existing antimalarial drugs is known.[1] There have been several publications regarding the complexation of metals to chloroquine in particular.[2,3] In these papers, it is clearly demonstrated that the introduction of the metal complex has a positive influence on the efficacy of chloroquine. The biological evaluation studies were carried out *in vitro* and *in vivo* on various chloroquine sensitive and chloroquine resistant strains of the parasite.[2,3]

The advantages of incorporating ferrocene into 4-amino-7-chloroquinoline derivatives have already been established in previous chapters. The question posed here is whether the incorporation of the second metal centre to form heterobimetallic complexes could provide synergistic, additive or antagonistic effects. Taking $[Au(FQ)PPh_3]NO_3$ as an example, ferroquine **15** shows good efficacy against chloroquine resistant *P. falciparum*, exhibiting a 100 fold improvement[4] in efficacy versus chloroquine. Similarly, the $[Au(CQ)PPh_3]PF_6$ is reported to show a 22 fold improvement in efficacy.[3]

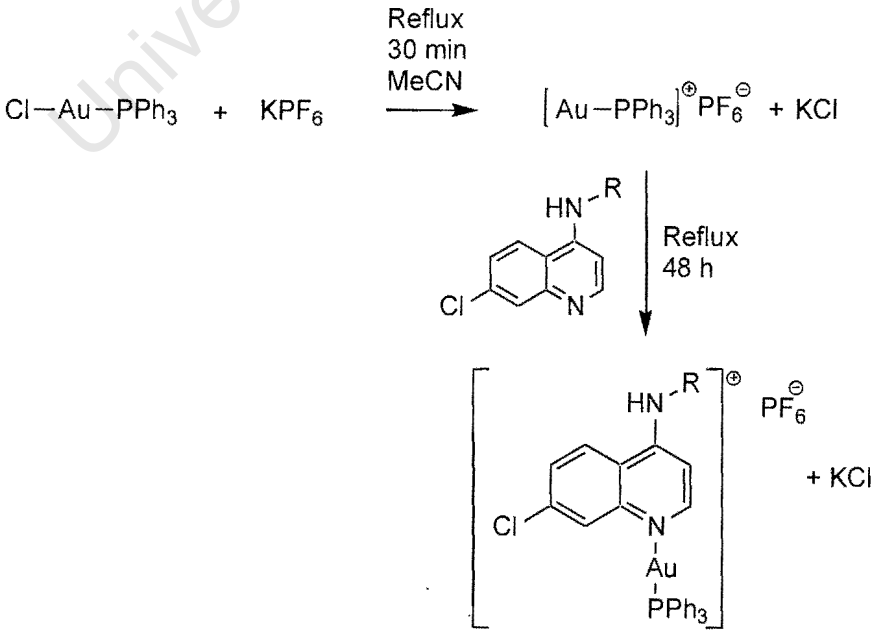
In order to establish whether the aforementioned effects exist, a series of compounds were targeted for preliminary investigation. Compounds of the type $[Au(CQ)PPh_3]PF_6$[3] and $[Rh(COD)Cl(CQ)]$[2] have been shown to be more effective than chloroquine against chloroquine resistant strains of *P. falciparum* and are thought to have simple well-defined structures. Therefore, these complexes provide a good basis for investigation of the type described. In addition to this, a neutral series of gold complexes was also targeted.

Ionic Gold Complexes

Synthetic Routes to Ionic Gold Complexes

The most convenient starting point for the synthesis of these types of complexes is chloro(triphenylphosphine)gold(I). The (4-amino-7-chloroquinoline)(triphenylphosphine)gold complexes could then be synthesised using two different routes.

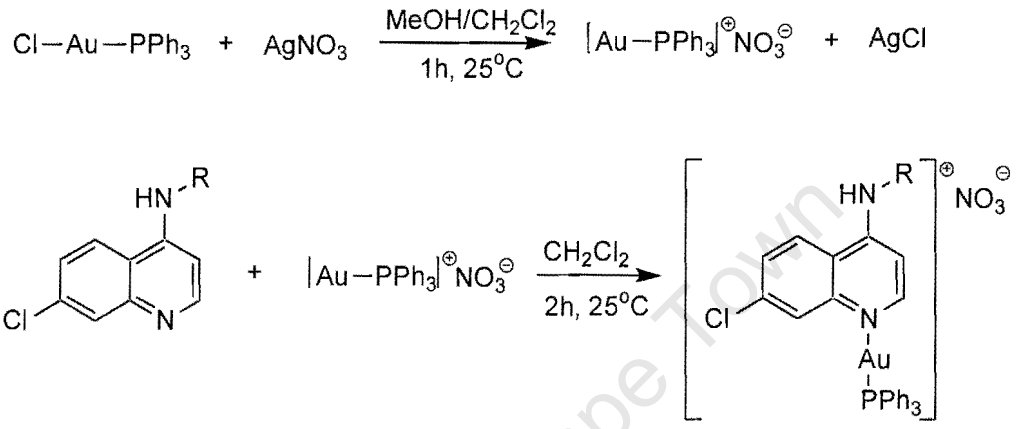
1. A one-pot synthesis from chloro(triphenylphosphine)gold(I) with potassium hexafluorophosphate.



Scheme 1: Synthesis of quinoline-gold complexes from $[Au(Cl)PPh_3]$ and KPF_6

This method of synthesis has been used to prepare chloroquine(triphenylphosphine)gold(I) hexafluorophosphate.[3] While this method does not require isolation of the gold hexafluorophosphate salt, the conditions used are rather vigorous. It has already been established (Chapter 2) that prolonged heating of ferroquine derivatives results in some decomposition, so heating the reaction mixture under reflux in acetonitrile (bp 82°C) for 48 hours was not deemed to be a suitable route for the synthesis of these compounds.

2. A two step synthesis from chloro(triphenylphosphine)gold(I) *via* (triphenylphosphine)gold(I) nitrate

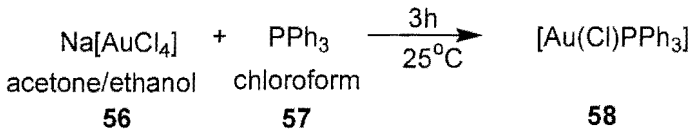


Scheme 2: Synthesis of gold triphenylphosphine complexes using a two step synthesis

The isolation of the gold nitrate salt could easily be achieved as silver chloride precipitates out of solution. The gold nitrate salt can therefore be isolated by a well known simple filtration and crystallisation protocol.[5] This is then reacted with the 4-amino-7-chloroquinoline derivative under mild conditions to form the desired gold complex.[6]

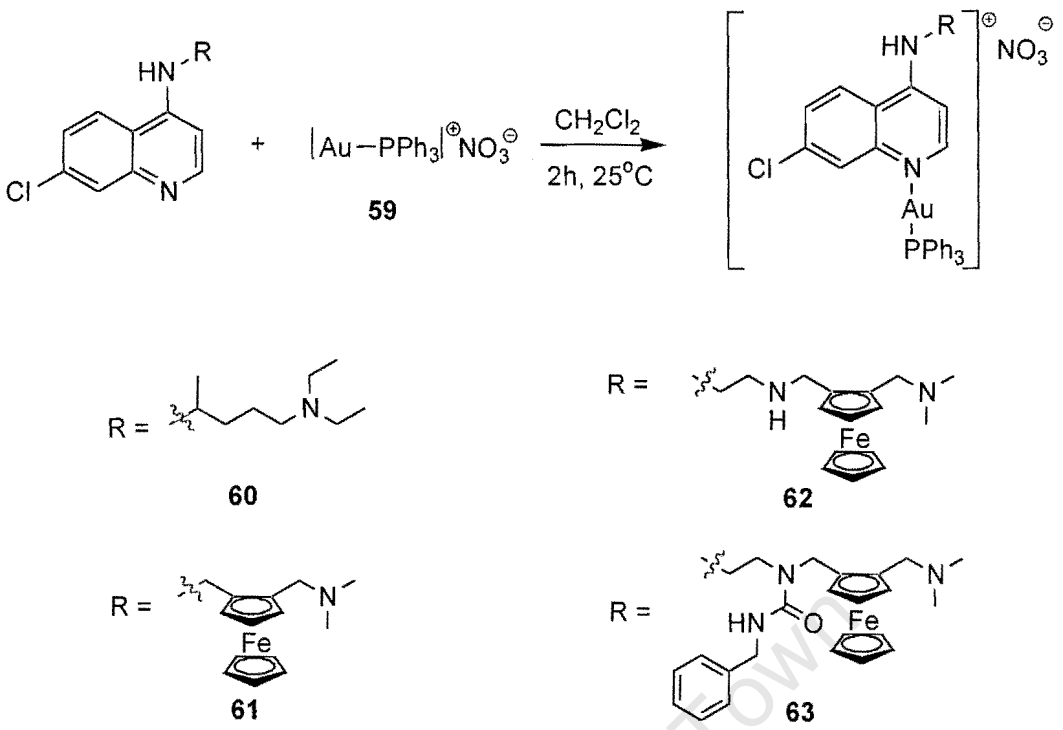
Formation of ionic gold complexes

The synthesis of the 4-amino-7-chloroquinoline-gold complexes was achieved in relatively high yield using the second methodology outlined above. Chloro(triphenylphosphine)gold(I) **58** was synthesised from sodium tetrachloroaurate(III) **56**.[7]



Scheme 3: Synthesis of chloro(triphenylphosphine)gold(I)

Chloro(triphenylphosphine)gold(I) **58**, was then converted to (triphenylphosphine)gold(I) nitrate **59**,[5] Scheme 2. (Triphenylphosphine)gold(I) nitrate **59** was then reacted with the relevant 4-amino-7-chloroquinoline ligand to give the desired products **60 – 63** in moderate yields under mild conditions.



Scheme 4: Synthesis of (4-amino-7-chloroquinoline) triphenylphosphinegold complexes **60 – 63**

Neutral Gold Complexes

There was no obvious literature precedent for making neutral gold complexes of known antimalarial drugs. It was decided, therefore, to use some of the expertise available in our laboratory.[8] There is also some literature available on ferrocene containing complexes of this type.[10]

There were two classes of neutral gold complexes which could possibly be synthesised viz., [Au(Cl)L] and [Au(C_6F_5)L].

1. [Au(Cl)L]

These complexes had the advantage of requiring fewer steps in the synthesis. However, it has been observed that compounds of this type are light sensitive.[9] Given that the compounds were being synthesised with a view to evaluating them in a biological testing protocol, stability is an important criterion to consider.

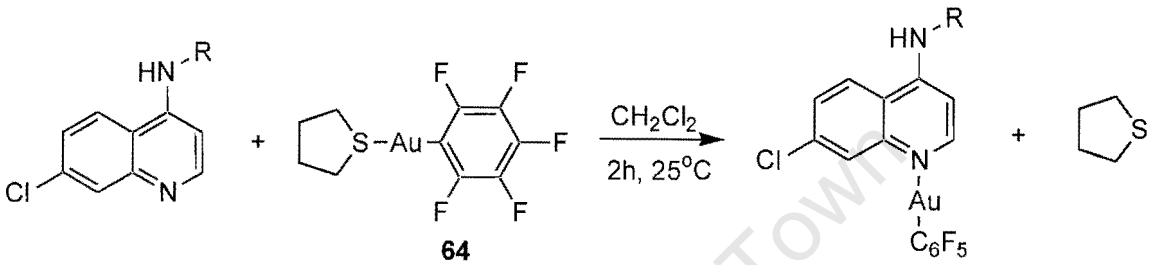
2. [Au(C_6F_5)L]

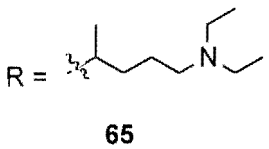
These compounds required a more lengthy preparation, as the precursor, [Au(C_6F_5)tht], is made from [Au(Cl)tht]. However, the pentafluorophenyl complexes are generally more stable that the corresponding chloro complexes. This can be attributed, in part, to the lower stability of the $C_6F_5^-$ ion when compared to the chloride ion. In addition to this, the presence of the Au(C_6F_5) unit

could be detected by ^{19}F NMR spectroscopy whereas Au(Cl) cannot be detected directly by NMR spectroscopy.

Synthetic Route to Neutral Gold Complexes

A well established methodology for the synthesis of these type of compounds requires pentafluorophenyl(tetrahydrothiophene)gold(I) **64** as a starting material.[10] The tetrahydrothiophene (tht) is known to be a labile ligand, and the 4-amino-7-chlorochloroquinoline derivatives would be expected to displace it relatively easily. The reaction can therefore be carried out under mild conditions. The tht is volatile and can be removed *in vacuo*, thereby providing a simple route to a pure product provided the synthesis goes to completion.





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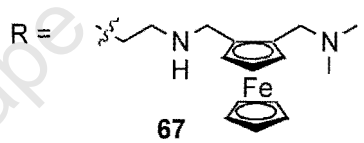

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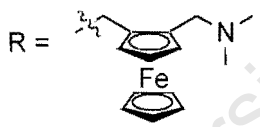

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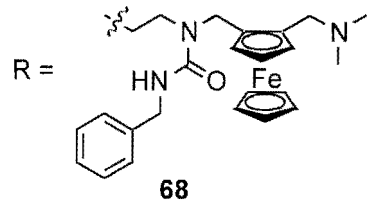
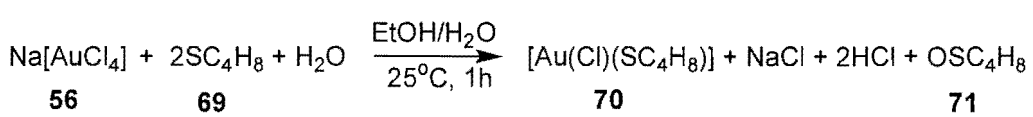


68

Scheme 5: Synthesis of neutral gold complexes **65 - 68**

The synthesis of the 4-amino-7-chloroquinoline(pentafluorophenyl)gold(I) complexes **65 – 68** required a multistep synthesis. The available starting material was sodium tetrachloroaurate(III). Chloro(tetrahydrothiophene)gold(I) **70** was prepared from sodium tetrachloroaurate **56** according to a literature procedure.[11] The product was obtained in over 90% yield (Scheme 6).



56 **69** **70** **71**

Scheme 6: Synthesis of chloro(tetrahydrothiophene)gold(I)

Chloro(tht)gold(I) **70** was then converted into pentafluorophenyl(tht)gold(I) **64** as reported.[12,13] This reaction requires a two step synthesis as shown in Scheme 7.

$$C_6F_5Br + n\text{-BuLi} \xrightarrow[-78^oC,\ 1h]{Et_2O} C_6F_5Li + n\text{-BuBr}$$

$$C_6F_5Li + \underset{\mathbf{70}}{[Au(Cl)(tht)]} \xrightarrow[1h^*]{Et_2O} \underset{\mathbf{64}}{[Au(C_6F_5)(tht)]} + LiCl$$

* Mixture allowed to warm from -78°C to 25°C over this time

Scheme 7: Synthesis of pentafluorophenyl(tht)gold(I) (**64**)

The reaction progress could be monitored quite easily using TLC (10% MeOH in CH_2Cl_2). The crystalline product was quite stable if isolated as a pure product, but the presence of impurities resulted in fairly rapid decomposition. The product was stored at 4°C to minimise decomposition and was always used in the complexation reaction with the 4-amino-7-chloroquinoline ligands within a few days. The product was characterised using ^1H and ^{19}F NMR spectroscopy.

The complexation to the 4-amino-7-chloroquinoline ligands was achieved in reasonable yield under fairly mild reaction conditions as shown in Scheme 5. The volatile tht was removed *in vacuo*. The purification of the products was achieved either by preparative TLC or by recrystallisation. The latter technique was found to be far superior both qualitatively and quantitatively.

It was observed that the reaction did not go to completion. The TLC (10% MeOH in CH_2Cl_2) of the final reaction mixture consistently showed a mixture of product and the two starting materials. The reaction time was increased to 24 hours, but the TLC showed little change in the reaction mixture composition. The tht was removed *in vacuo* and further solvent added to ensure that the problem was not associated with an equilibrium reaction. Again, there was no noticeable difference in the reaction mixture composition. The use of toluene was attempted in order to facilitate raising the temperature of the reaction. However, at room temperature, the 4-amino-7-chloroquinoline ligands are sparingly soluble in toluene and at elevated temperatures decomposition of the gold complexes occurred. The net result was a lowering in the overall yield of the reaction. The use of dichloromethane was continued despite the relative instability of gold complexes in chlorinated solvents. In order to minimise decomposition the reaction vessels were protected from light. There were two reasons for this; firstly, it is possible that these compounds are sensitive to light, as it has been demonstrated for chloro(quinine)gold(I).[9] Secondly, it is known that chlorinated solvents form radicals when exposed to light. These radicals could then react with either reactants or products resulting in diminished yields.

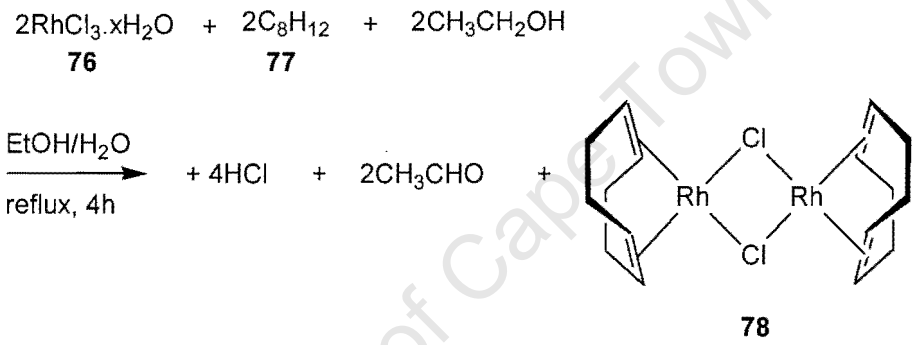
It is possible that increasing the ratio of pentafluorophenyl(tetrahydrothiophene)gold(I) **64** might drive the reaction to completion. This approach was not attempted because of the number of potential nitrogen donor sites on the 4-amino-7-chloroquinoline derivatives. As it was, despite the fact that the reaction did not go to completion, yields as high as 75% were obtained and it was decided not to attempt to increase the yield further by using excess ligand.

Rhodium Complexes

A rhodium cyclooctadiene complex of chloroquine has been prepared previously.[2] The method used starts from di-μ-chloro-bis(η^4-1,5-cyclooctadiene)dirhodium(I), $[RhCl(COD)]_2$ **78** which is a well established route to the preparation of complexes of the type [Rh(Cl)(COD)L], where L is a nitrogen or phosphorus donor ligand.[14] The required reaction conditions were mild and the yields reasonably good.

Synthetic Routes to Rhodium Complexes

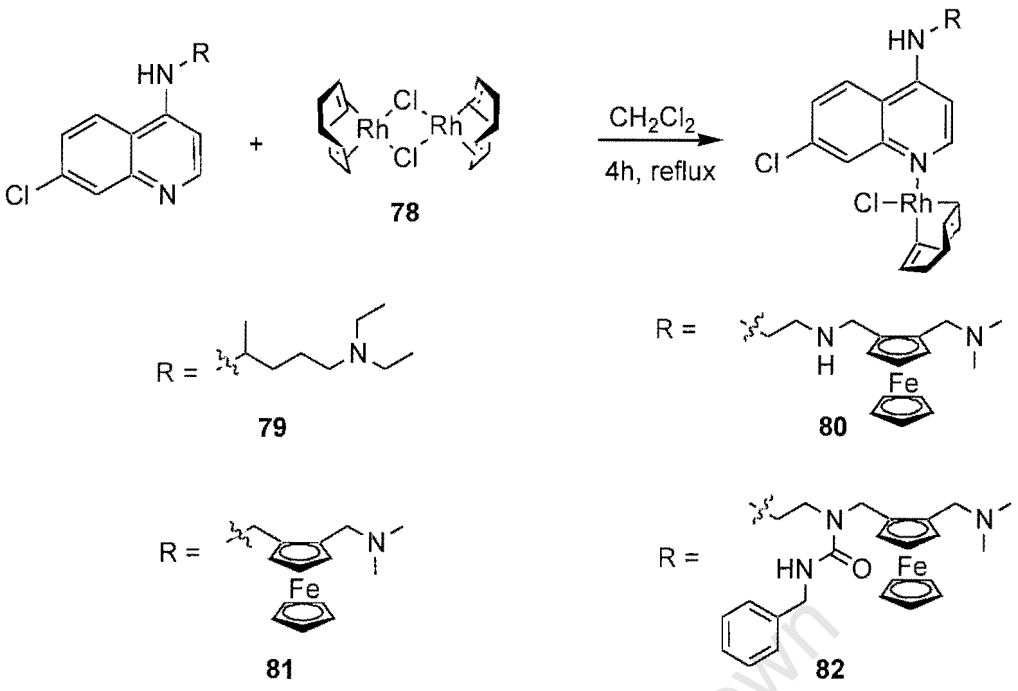
The complexes were prepared as outlined above. This required the preparation of $[RhCl(COD)]_2$, **78**. The available starting material was hydrated rhodium trichloride, and the synthesis was carried out according to a literature procedure.[14] A yield of 83% was obtained and the ^1H and ^{13}C NMR spectra were found to be consistent with literature values.[15]



Scheme 8: Preparation of $[RhCl(COD)]_2$ **78**

The syntheses of the 4-amino-7-chloroquinoline-rhodium complexes **79 – 82**, Scheme 9, were carried out according to a literature procedure,[2] with the only change being the choice of solvent. Dichloromethane was used instead of 2-methoxyethanol.

There was no significant difference in the yield or the ^1H and ^{13}C NMR spectra of the chloroquine–rhodium complex **79** formed and the reported literature values,[2] so all other reactions were carried out in a similar manner, using the appropriate 4-amino-7-chloroquinoline starting material. In all cases, a yellow/orange crystalline complex was formed.



Scheme 9: Synthesis of rhodium complexes of 4-amino-7-chloroquinolines

NMR Spectroscopy

All complexes were characterised using ^{1}H and ^{13}C NMR spectroscopy, using COSY and HSQC two dimensional NMR spectroscopy to assign the spectra. In addition, the complexes of the type $[Au(L)(PPh_3)]NO_3$ were characterised using ^{31}P NMR spectroscopy and complexes of the type $[Au(C_6F_5)L]$ were characterised using ^{19}F NMR spectroscopy. The full assignment of data is given in the general experimental (Chapter 8)

^{1}H NMR Spectroscopy

For the gold complexes, ^{1}H NMR spectroscopy could not provide a direct method of establishing whether the complex has in fact been formed as opposed to having a mixture of starting materials. The reason for this is that while there is a change in chemical environment of both the incoming $[Au(PPh_3)]$ fragment of the 4-amino-7-chloroquinoline ligand, these changes do not have a significant effect on the chemical shifts of the proton signals in either of the gold ligands. Figure 2 shows the protons which would be expected to show the greatest change in chemical shift on complexation.

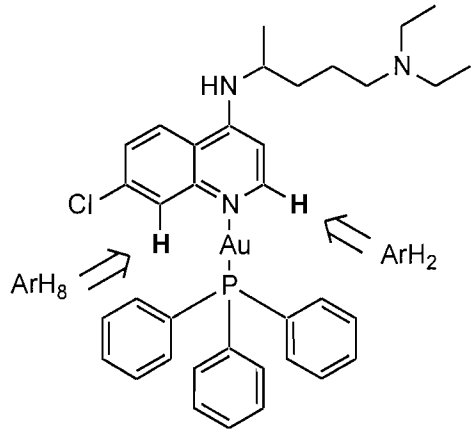


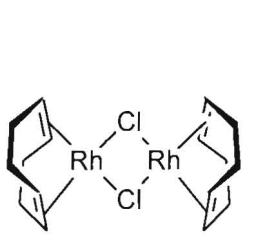
Figure 2: $[Au(CQ)PPh_3]^+$ showing protons expected to be most affected by complexation

There appears to be little long range electronic disturbance within either fragment on complexation. This means that the through-bond effect of the complexation reaction may not necessarily be evident in the ^1H NMR spectrum. In both the ionic and the neutral series of gold complexes small changes (> 0.6ppm) in the chemical shift of ArH_8 were observed. The chemical shifts of the protons of the remainder of the ligand were largely unchanged. In analogous $[Au(L)(PPh_3)]$ complexes having pyridyl ligands, it is observed that only the proton in position 4, para to the nitrogen, shows significant changes in the chemical shift between the free ligand and that which is complexed to gold triphenylphosphine. [16]

In the gold triphenylphosphine complexes the presence of the triphenylphosphine is evidenced by the 15 proton signal between 7.6 and 7.5 ppm. This is consistent with literature values observed for similar complexes.[3, 16] The ^1H NMR spectrum of $[Au(CQ)PPh_3]NO_3$ **60** was similar to that of $[Au(CQ)PPh_3]PF_6$ **11**.[3] The remaining three complexes of the series i.e. **61 - 63** showed changes that were reasonably consistent with those observed between chloroquine and $[Au(CQ)PPh_3]PF_6$ in as far as reasonable comparison could be made.[3]

In the pentafluorophenylgold complexes **65 - 68**, there were no additional protons observed due to the incoming $[Au(C_6F_5)]$ group, although the presence of the group was detected by ^{19}F NMR spectroscopy. It should be noted though, that there was no evidence of the tht group in the ^1H NMR spectrum. This suggests that the 4-amino-7-chloroquinoline ligand has replaced the tht.

The ^1H NMR spectral data of the rhodium complexes **79 - 82** showed the formation of the 4-amino-7-chloroquinoline-metal complexes far more clearly. The reason being that the chemical environment experienced by the cyclooctadiene protons changes significantly on complexation, Figure 3.



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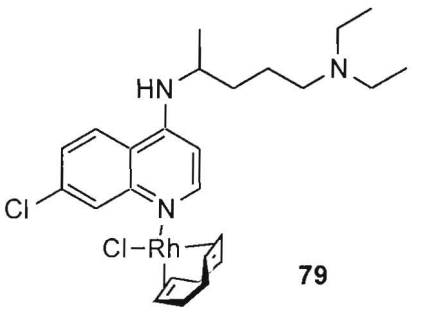

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Figure 3: Significant difference in chemical environment of COD protons between the dimer **78** and the chloroquine complex, **79**

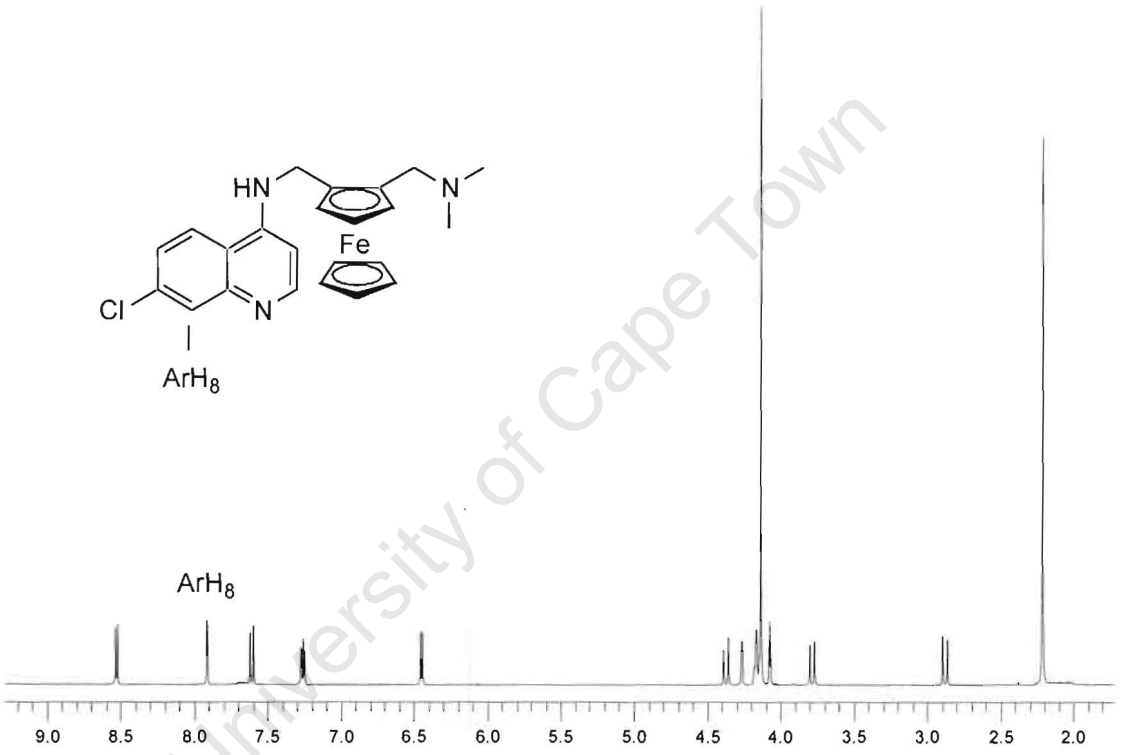


Figure 4: ^{1}H NMR spectrum of **15** in $CDCl_3$

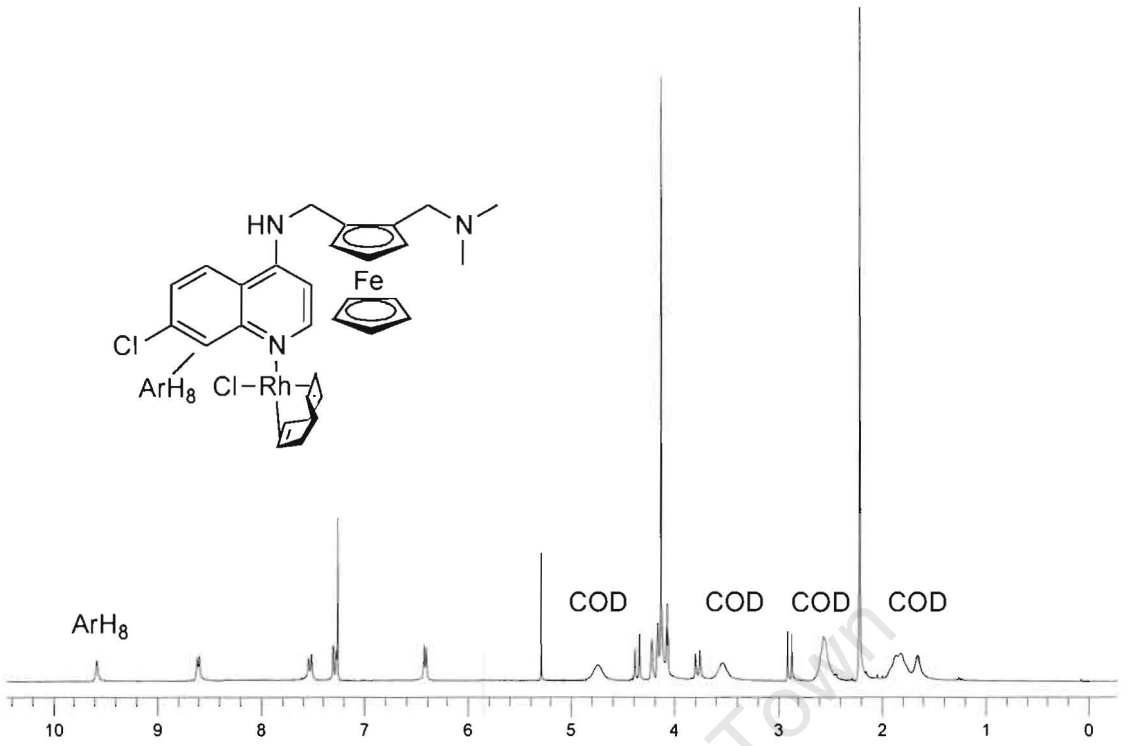


Figure 5: ^{1}H NMR spectrum of **80** in $CDCl_3$

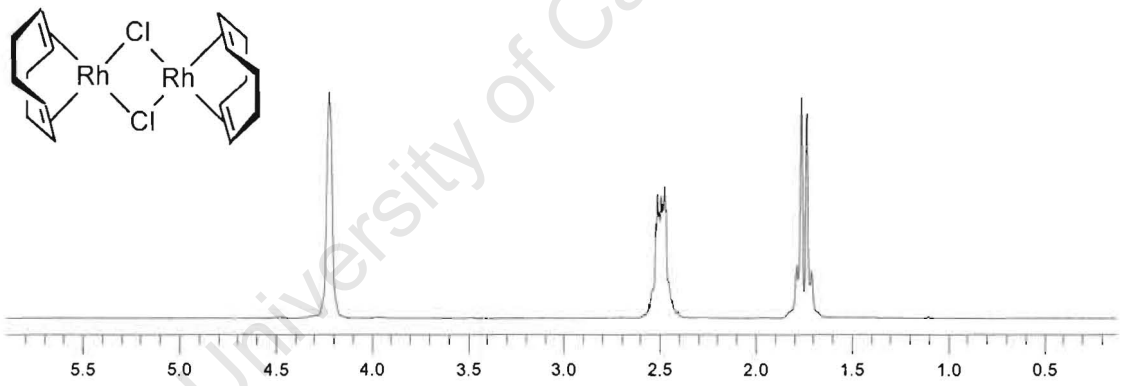


Figure 6: ^{1}H NMR spectrum of $[Rh(Cl)(COD)]_2$ **78** in $CDCl_3$

Figure 4, 5 and 6 show the shifts in proton signals on complexation of ferroquine and rhodium cyclooctadiene. Only those protons of particular relevance have been labelled. It is clear that there is a significant change in the position of ArH_8 of the ferroquine ligand ($\Delta\delta$ 1.6ppm). The other point to note is the change in position of the cyclooctadiene protons. In particular the methylene protons; in $[Rh(Cl)(COD)]_2$ **78** these are indistinguishable and appear at 4.25ppm. In the complex, the methylene protons now exist in different chemical environments, and hence two distinct signals are observed at 4.8 and 3.5ppm. The observed changes in the cyclooctadiene chemical shifts are consistent through the series and in agreement with reported values for 4-amino-7-chloroquinoline complexes.[2] The splitting of the methylene cyclooctadiene protons is also consistent with the ^{1}H NMR spectra obtained for a variety of rhodium complexes with nitrogen donor ligands.[17]

^{13}C NMR Spectroscopy

In the gold complexes, **60 – 63** and **65 – 68**, there is no significant difference in the ^{13}C NMR spectra between the complex and the free ligands. In the triphenylphosphine complexes, the resonances due to the phenyl carbons are observed in positions similar to those reported previously.[6,16] In the pentafluorophenyl complexes, however, no new signals are seen. This is because the relaxation time of the carbon-fluorine coupling is of greater duration than the NMR time scale. Again this observation is consistent with literature reports.[10]

In the rhodium complexes, **79 – 82**, the presence of the [Rh(Cl)(COD)] fragment is clearly seen. There are four new signals in the spectrum as the eight cyclooctadiene carbons exist in four different environments when complexed to an asymmetric nitrogen donor ligand.

^{31}P NMR Spectroscopy

The ^{31}P NMR spectra consistently show a singlet at approximately 30 ppm for all complexes. Again this is consistent with values reported for similar complexes.[6,16] There seems to be no significant shift in the signal in changing from chloro(triphenylphosphine)gold(I) **58** to the 4-amino-7-chloroquinoline(triphenylphosphine)gold(I) complexes **60 – 63**.

^{19}F NMR Spectroscopy

The ^{19}F NMR spectra of all complexes, **65 – 68**, clearly show the presence of the pentafluorophenyl group. There are slight changes in the chemical shifts observed between the gold tetrahydrothiophene complex **64** and the 4-amino-7-chloroquinoline complexes **65 – 68** (± 1ppm for all signals). The fluorine atoms may seem relatively remote from the site of complexation to be so affected, but it must be noted that there is a change from a sulfur donor ligand (tht) to a nitrogen donor ligand (quinoline). There is a large difference in the electron donor properties of sulfur and nitrogen.[18] This could have a large effect on the electron density of the phenyl moiety and hence cause a change in the chemical shifts of the fluorine atoms.

While these shifts are small, they are significant. This is shown by the fact that the spectrum of the crude reaction mixture clearly shows the presence of the two different species. The ^{19}F spectra show two mulitplets corresponding to fluorine atoms in *ortho* and *meta* positions, whilst the fluorine atom in the *para* position forms a triplet with a coupling constant of approximately 20Hz.

Infrared Spectra

The bands corresponding to the 4-amino-7-chloroquinoline ligands do not change significantly on complexation to gold or rhodium and have already been discussed in chapters 2 and 3.

The infrared spectra are also useful in identifying the presence of the complexes. The nitrate ion of the gold triphenylphosphine complexes is clearly observed by a strong absorption band at 1369 cm^{-1}. The phosphorus-carbon stretching frequency is also observed with a weak band at 998 cm^{-1}. Two bands at 750 and 700 cm^{-1} correspond to C-H aromatic bending frequencies with 5 adjacent protons, arising from the phenyl group. Several strong absorption bands resulting from the pentafluorophenyl group are observed in the spectra of the gold pentafluorophenyl complexes at approximately 1500, 1460 and 960 cm^{-1}.

Mass Spectrometry

In all cases the molecular ion was observed corresponding to the proposed structures, whereby one 4-amino-7-chloroquinoline ligand complexes to a single gold or rhodium centre.

Structure of Compound

Throughout this chapter it has been assumed that all the metal complexes of the ferroquine compounds have the analogous structure to those of the chloroquine complexes.[2,3]

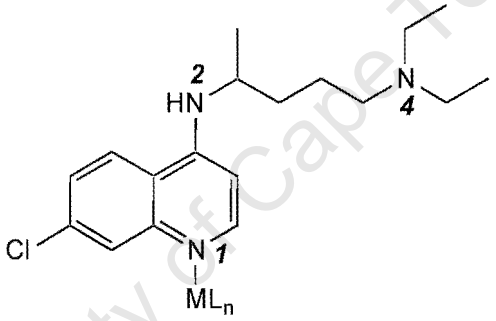
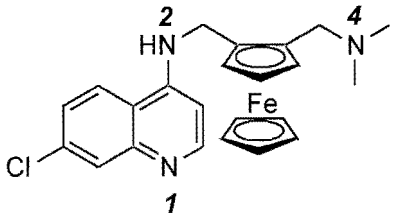


Figure 7: Suggested structure of metal complexes of chloroquine

The structure of the chloroquine complexes **60**, **65** and **79** were proposed on the basis of NMR spectral data.[2,3] In the case of ferroquine, Figure 8, there are similarly three nitrogen donor sites which exist in similar chemical environments to the nitrogen donor sites found in chloroquine. The changes in chemical shifts on complexation are similar to those found in the analogous chloroquine complex, so it is reasonable to suggest that the structures are similar i.e. complexation occurs through the quinoline nitrogen.



15

Figure 8: Possible sites of metal coordination on ferroquine (**15**)

However, in the case of **20**, there is an additional potential nitrogen donor site (***3***), Figure 9. Nitrogens ***1***, ***2*** and ***4*** are analogous to those found in chloroquine and ferroquine. The question

arises as to whether nitrogen ***3*** competes with nitrogen ***1*** or not. The NMR spectral evidence suggests that nitrogen ***1*** is still the site of coordination, as there are no major changes observed in chemical shifts arising from the side chain of **20**.

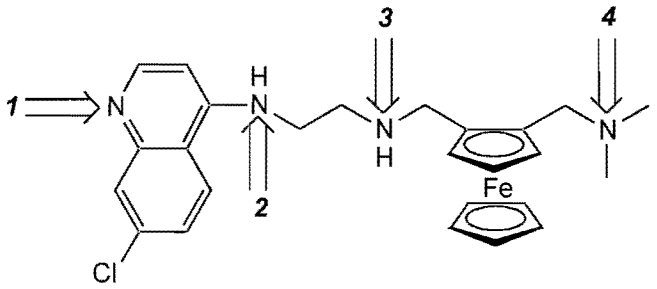
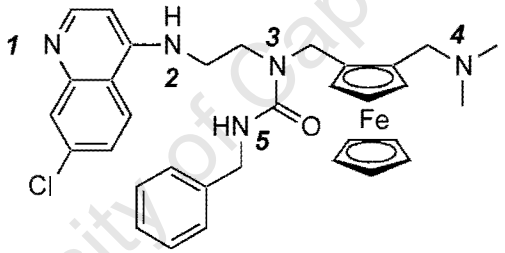


Figure 9: Possible sites of metal coordination on **20**

In the case of **37**, Figure 10, nitrogens ***1***, ***2*** and ***4*** are again analogous to those in chloroquine. Nitrogens ***3*** and ***5*** could ostensibly be sites of metal coordination, but this is unlikely as the carbonyl moiety of the urea is strongly electron withdrawing, which would result in a lowering of electron density on both of these nitrogens. As coordination to a metal is dependent of the availability of electron density, it is likely that the quinoline nitrogen will be favoured. The NMR spectral data obtained for the metal complexes of this compound supports this proposal.



37

Figure 10: Possible sites of coordination of **37**

Conductivity Measurements

Table 1: Molar conductivity of selected gold complexes

Compound	**Compound Number**	**κ ($\mu\Omega^{-1}$)**	**Concentration (mol dm^{-3})**	**Λ ($\Omega^{-1}cm^2mol^{-1}$)**
$[Au(CQ)PPh_3]^+NO_3^-$	**60**	55.0	0.00316	17
$[Au(FQ)PPh_3]^+NO_3^-$	**61**	38.9	0.00184	21
$[Au(F2Q)PPh_3]^+NO_3^-$	**62**	33.7	0.00267	13
$[Au(BU)PPh_3]^+NO_3^-$	**63**	23.4	0.00131	18
$[Au(C_6F_5)CQ]$	**65**	0.425	0.00208	0.2
$[Au(C_6F_5)F2Q]$	**67**	2.043	0.00227	0.9
$[Au(BU)C_6F_5]$	**68**	0.703	0.00140	0.4

Measurements made in nitrobenzene at 20°C.

As part of their characterisation, the molar conductivities were measured for the two series of gold complexes. A molar conductivity, Λ, of below $1\Omega^{-1}cm^2mol^{-1}$ under the aforementioned conditions is consistent with neutral compounds. The molar conductivities of the salts fall within the range of salts of unipositive cations and uninegative anions. These values are at the lower end of the range, but as the $[Au(L)PPh_3]$ cation is large its motion through the solvent is likely to be impeded, so such a salt is likely to exhibit a lower conductivity than sodium chloride for example.

The results obtained here are consistent with the proposed structure of the complexes i.e. metal complexation at the quinoline nitrogen. If one considers the $[Au(F2Q)PPh_3]NO_3$ **62**, there are three possible scenarios:

1. The gold is attached to the quinoline nitrogen ***1*** *via* a coordination bond – the complexes will be unipositive and will show a molar conductivity greater than 10.
2. The gold is attached to nitrogen ***3*** *via* a coordination bond – the complexes will be unipositive and have a similar conductivity as scenario 1.
3. The gold is attached to nitrogen ***3*** *via* a covalent bond having displaced the hydrogen. This would result in a neutral complex having a molar conductivity less than 1.

As the triphenylphosphine gold complexes have all have similar molar conductivities and all are greater than 10. The molar conductivities indicate that either a coordination bond nitrogen ***1*** or a coordination bond at nitrogen ***3*** is the likely structure. However, the aforementioned NMR spectral evidence suggests that the coordination bond at nitrogen ***1*** is the correct structure.

The pentafluorophenyl gold(I) complexes could be similarly bonded. This would result in neutral complexes in the first two instances and a uninegative ion in the final scenario. Molar conductivity will be able to distinguish between the formation of a coordinate bond or a covalent bond, but will not distinguish between the formation of coordination complexes at nitrogen ***1*** and nitrogen ***3***. The fact that the complexes of this type were found to be neutral suggests coordination bonding. Again, the coordination at nitrogen ***1*** is proposed on the basis of NMR evidence.

Cyclic Voltametry of the Gold Complexes

The focus of this section was on the cyclic voltametry of the gold triphenylphosphine complexes of FQ, F2Q and BU, **61** – **63**. It should be noted that chloroquine exhibits an irreversible oxidation at approximately 750mV. This oxidation event results in deposition on the electrode. 4,7-Dichloroquinoline shows no redox activity which could imply that the redox event observed in chloroquine is associated with the side chain. Triphenylphosphinegold(I) nitrate **59** shows no redox activity within the solvent window.

Table 2: Cyclic voltametry of gold complexes and 4-amino-7-chloroquinoline ligands

Compound	Cpd No	E_{pa} (mV)[a]	E_{pc} (mV)[b]	$E_{1/2}$ (mV)[c]	ΔE_p (mV)[d]
FQ	**15**	181	113	147	70
$[Au(FQ)PPh_3]^+NO_3^-$	**61**	252	162	207	90
F2Q	**20**	150	30		120
$[Au(F2Q)PPh_3]^+NO_3^-$	**62**	294	186		108
$[Au(C_6F_5)F2Q]$	**67**	315	210		105
BU	**37**	198	115	158	83
$[Au(BU)PPh_3]^+NO_3^-$	**63**	219	141	180	78

[a]anodic potential; [b]cathodic potential; [c]half wave potential $(E_{pa} + E_{pc})/2$;

[d] $\Delta E_p = (E_{pa}-E_{pc})$;

It is apparent from the results in Table 2 that the coordination of the gold to the ferroquine derivatives has an effect on the redox behaviour of the ferrocenyl moiety. This can be seen by the marked increase in both anodic and cathodic peak potentials in moving from free ligand to metal complex. In all cases, the incorporation of gold into the molecule resulted in an increase in half wave potential, $E_{1/2}$, which indicates that the gold complexes are more difficult to oxidise. The effect was most marked in the case of the F2Q complexes. There also appeared to be a trend towards reversibility shown by the lowering in peak separation, ΔE_p. This was also observed in the shape of the voltamograms, Figure 11-13, below show that the cathode peak currents have a greater magnitude in the gold complexes. In a fully reversible oxidation the anodic and cathodic peak currents should be of equal magnitude.

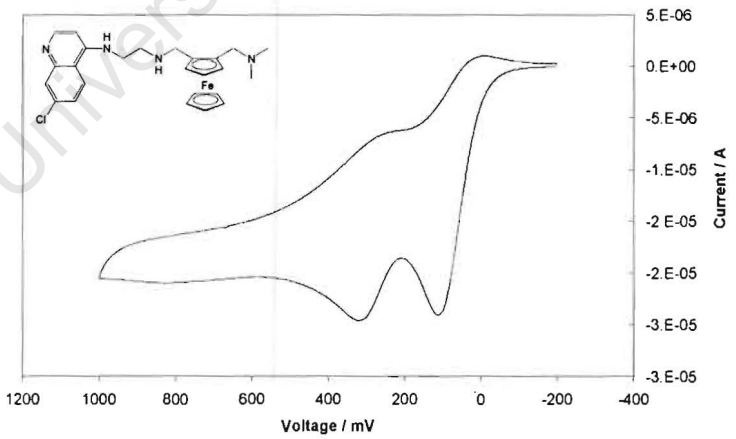


Figure 11: Cyclic voltamogram of **20**

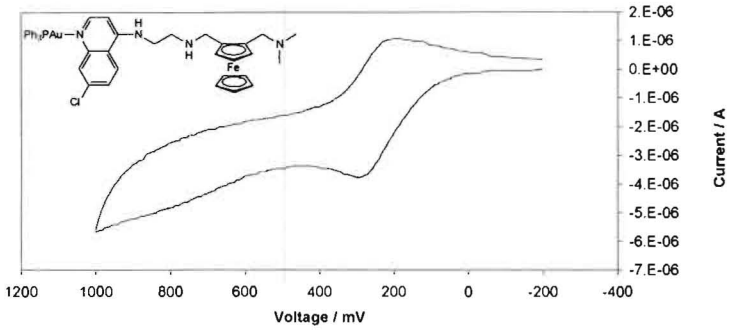


Figure 12: Cyclic voltamogram of **62**

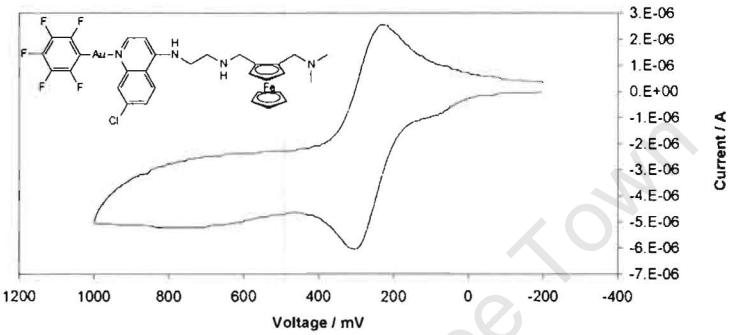


Figure 13: Cyclic voltamogram of **67**

As the general trends observed are the same for all the compounds i.e. $E_{1/2}$ for the ferrocenyl moiety increases on moving from ligand to complex, it is likely that the interaction is a 'through-space' interaction rather than a 'through-bond' interaction. There is no conjugated link between the quinoline and the ferrocenyl moieties that would facilitate a 'through-bond' interaction. If it were a 'through-bond' interaction it would follow that the effect of the gold moiety would be most marked in **61** as the gold atom is in closest proximity to the iron in this complex. However, **61** does not exhibit the greatest increase in peak potentials.

Inhibition of β-Haematin Formation

It has been well established that 4-amino-7-chloroquinolines prevent the formation of β-haematin. As the site of coordination of the gold or rhodium appears to be the quinoline nitrogen, it could be postulated that the presence of the metal atom at this position could have an adverse effect on this mechanism. $[Au(CQ)(PPh_3)]NO_3$ **60**, $[Au(FQ)(PPh_3)]NO_3$ **61**, $[Au(F2Q)(PPh_3)]NO_3$ **62**, [Rh(Cl)(COD)(CQ)] **79**, [Rh(Cl)(COD)(FQ)] **80** and [Rh(Cl)(COD)(CQ)] **81** were all tested for β-haematin inhibition activity. In all cases, the metal complexes inhibited the formation of β-haematin.

The assay used to determine the inhibition of β-haematin in this case uses a three fold excess of the drug relative to haemin. The observed results do not give an indication of either kinetic or thermodynamic factors which may play a crucial role.

Conclusions

Three series of metal complexes of a variety of 4-amino-7-chloroquinoline ligands have been successfully synthesised and characterised using standard spectroscopic methods. The characterisation data obtained are consistent through the series as far as reasonable comparison could be made. It has been proposed that despite there being from three to five potential nitrogen donor sites on the various 4-amino-7-chloroquinoline ligands, the quinoline nitrogen is the most likely site of coordination in all cases. This has been demonstrated on the basis of NMR spectroscopy. In all cases the mass spectral data and the elemental analytical data (where available) have served to confirm the presence of the desired coordination complexes. Furthermore, the molar conductivity studies indicate that the complexes of the type $[Au(L)(PPh_3)]^+NO_3^-$ are ionic and the complexes of the type $[Au(C_6F_5)(L)]$ are neutral as required by their proposed structures.

The cyclic voltametry of the ferrocene containing gold triphenylphosphine complexes have been determined and it was found that the presence of the gold had a significant influence on the ferrocene redox curve. In all cases, large increases in both cathodic and anodic peak potentials were observed indicating that the ferrocenyl moiety was significantly more difficult to oxidise when the gold atom was present. As the molecule is not fully conjugated it is proposed that this change is a through-space effect rather than a through-bond effect. This is also consistent with the observation that the degree of increase in peak potential is not related to the methylene spacer length.

The presence of the gold or rhodium attached to the quinoline nitrogen had no effect on the ability of the 4-amino-7-chloroquinolines to inhibit β-haematin formation.

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Chapter 5

Biological Results and Discussion

Introduction

As mentioned earlier, the main aim of this project was to make potential new antiparasitic agents. It was therefore of interest to test the efficacy of these compounds in this regard. Before discussing the results in detail, it is worthwhile explaining several general points about biological testing and to define some terms.

It must be noted that biological testing is a complicated process and, as a result, there are many possible variables. For this reason, most laboratories will run the assays on new compounds and use a standard commercially available drug as a reference control. It is therefore not always appropriate to compare results from two different laboratories without reference to the standard control drug. It should also be noted that small differences in values are rarely significant unless observed as part of a general trend.

The IC_{50} and ED_{50} values used in this chapter to express biological activity give essentially the same information. IC means inhibitory concentration and is usually used when the assay is carried out by measuring the inhibition of a certain compound. For example, in *Plasmodium* assays, the measurement is of the inhibition of a purine precursor, specifically the reduction in uptake of radiolabelled hypoxanthine. ED means effective dose and is used when the actual numbers of parasites are counted. The IC_{50} then is the drug concentration required to cause the measured parameter to fall to 50% of its original value. The ED_{50} similarly is the dosage of the drug required to kill half the parasite population or to inhibit 50% of the enzyme activity. The lower the values of the IC_{50} or ED_{50} the greater the efficacy of the drug.

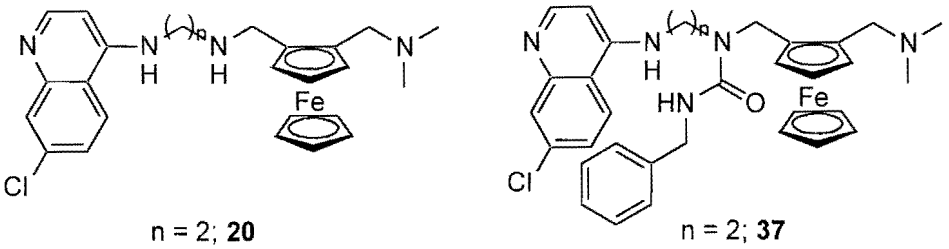
The IC or ED values are calculated from the percentage inhibition at varying concentrations. Normally the percentage inhibitions are not quoted in the literature. They are included here in order to preserve as full a record of this work as possible, as some useful information may sometimes be gleaned from these values.

Testing was carried out at four different facilities as specified in the results given below.

Toxicity of a drug can refer to toxicity towards the parasite or toxicity towards mammalian cells. The ideal drug has high toxicity or efficacy towards the parasite and low or no toxicity towards mammalian cells. The toxicity referred to in this chapter is toxicity towards mammalian cells.

In Vitro Testing against *Plasmodium falciparum* strains

Ferroquine and urea derivatives



n = 2; **20**
n = 3; **21**
n = 4; **22**
n = 6; **24**

n = 2; **37**
n = 3; **38**
n = 4; **39**
n = 6; **40**

Figure 1: Ferroquine analogues and urea derivatives tested against *P. falciparum*

Table 1: IC_{50} values of compounds on chloroquine sensitive (D10) and chloroquine resistant (K1) strains of *P. falciparum* (Dept of Pharmacology, University of Cape Town)[1]

Compound	n	D10 (CQS) IC_{50} (nM)	K1 (CQR) IC_{50} (nM)
CQ		41.86 ± 1.25	125.38 ± 4.53
20	2	41.70 ± 2.60	73.46 ± 6.40
21	3	51.37± 3.85	36.93 ± 1.70
22	4	61.16 ± 1.53	111.5 ± 12.9
24	6	86.92 ± 7.30	81.39 ± 5.57
37	2	21.35 ± 1.99	37.50 ± 7.35
38	3	16.20 ± 0.54	47.41 ± 2.41
39	4	16.74 ± 4.25	75.23 ± 8.49
40	6	19.01 ± 6.24	110.2 ± 9.46

All compounds tested showed comparable activity to chloroquine against the chloroquine sensitive D10 strain, although the general trend in the ferroquine compounds shows a decrease in efficacy with increasing methylene spacer length, terminating with **24** showing half as good activity as chloroquine. All the urea compounds show comparable efficacy to one another and are approximately twice as efficacious as chloroquine. However, their efficacy against K1 varied substantially. Compound **21** was the most effective having an activity three times that of chloroquine in the resistant strain. In both the ferroquine and urea series it is apparent that the methylene spacer length plays a role in the efficacy of the drug against the chloroquine resistant strain (Figure 2).[1] These results lend further support to previous observations that the

length of the methylene spacer between the nitrogens in the side chain of 7-substituted 4-aminoquinolines is a major determinant of activity against chloroquine resistant *P. falciparum*.[2,3]

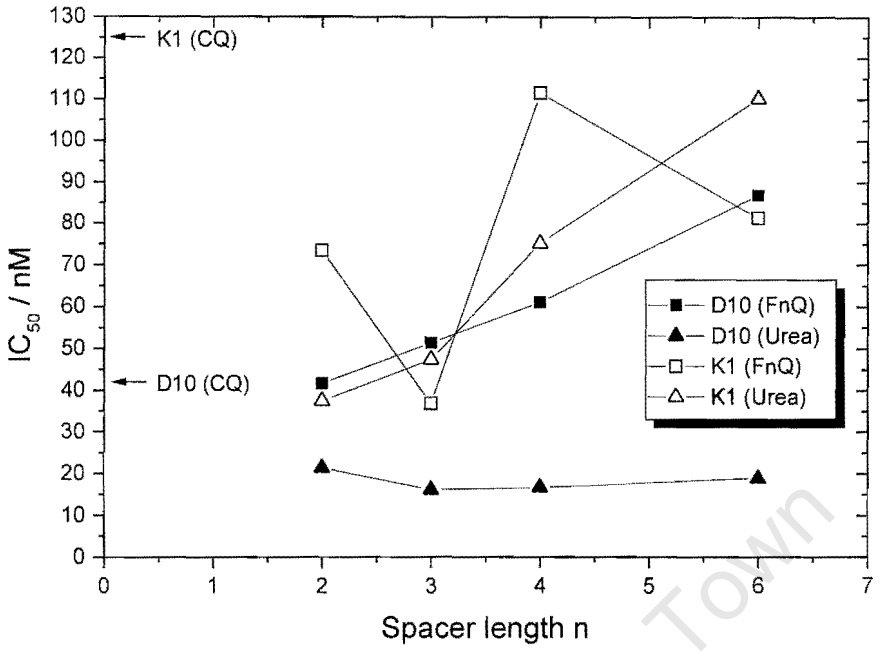


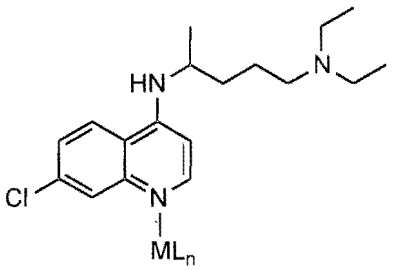
Figure 2: Graph showing correlation between methylene spacer length and IC_{50} in ferroquine analogues (FnQ) and ureas (UCT)

In a separate determination carried out at the Department of Infectious and Tropical Disease, London School of Hygiene and Tropical Medicine, compound **23**, with a methylene spacer of 5, showed an ED_{50} of 0.03μg/ml (58nM) against the chloroquine sensitive 3D7 strain of *P. falciparum* and 0.19μg/ml (367nM) against the chloroquine resistant K1 strain.

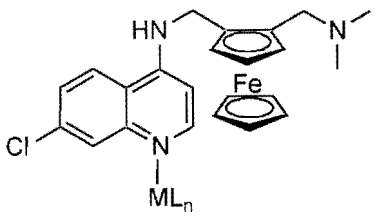
Compound **20** and ferroquine were tested in a separate determination against choroquine resistant strain, W2, and the sensitive D10 strain of *P. falciparum*. Ferroquine, **15**, was approximately twice as effective as **20** and three times as effective as the resolved tartrate salt of **20** (Dept of Pharmacology, University of Cape Town).

Coordination Complexes of 4-Amino-7-Chloroquinolines

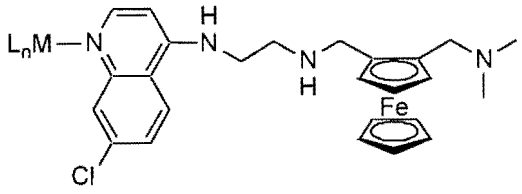
The series of gold and rhodium complexes shown in Figure 3 were also submitted for *in vitro* testing against a chloroquine sensitive and a chloroquine resistant strain of *Plasmodium falciparum*. The parent 4-amino-7chloroquinoline ligands were all tested in the same series of assays.



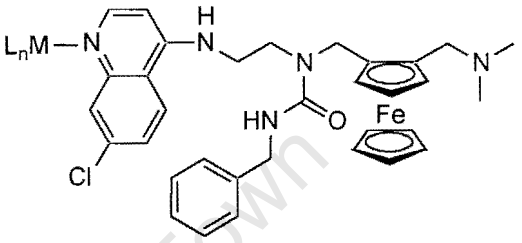
CQ-ML_n
60 - $AuPPh_3NO_3$
65 - AuC_6F_5
79 - Rh(COD)Cl



FQ-ML_n
61 - $AuPPh_3NO_3$
66 - AuC_6F_5
80 - Rh(COD)Cl



F2Q-ML_n
62 - $AuPPh_3NO_3$
67 - AuC_6F_5
81 - Rh(COD)Cl



BU-ML_n
63 - $AuPPh_3NO_3$
68 - AuC_6F_5
82 - Rh(COD)Cl

Figure 3: Structures of metal complexes used in *in vitro* assays

It should be noted that the tartrate salts of ferroquine[4] and $[Rh(Cl)(COD)(CQ)]$[5] and $[Au(CQ)(PPh_3)]PF_6$[6] have been synthesised and tested previously. The results obtained here cannot be directly compared to the reported values, but it worthwhile noting that our results are reasonably consistent with those previously reported.

Several trends can be observed from the results in Table 2. The ferrocenyl 4-amino-7-chloroquinoline ligands, FQ (**15**), F2Q (**20**) and BU (**37**), all show good activity in both chloroquine sensitive and chloroquine resistant strains of *P. falciparum*. Compounds **20** and **37** show similar efficacy in both strains, whilst **15** shows improved efficacy in the chloroquine resistant strain. However, the results clearly show that the 4-amino-7-chloroquinoline ligands are more efficacious than the metal complexes in the D10 chloroquine sensitive strain. The exception to this is chloroquine, as the gold and rhodium coordination complexes of chloroquine all exhibit a slightly better efficacy than chloroquine. The presence of the coordinated metal only has a significant advantageous effect in the case of the chloroquine complex when used against the chloroquine resistant K1strain. It can be seen that the presence of the gold moiety is in most cases superfluous, whilst in the case of the gold triphenylphosphine salt of **20** and **37** it actually serves to reduce the efficacy of the ligand. The rhodium complexes are significantly less active than the gold complexes. They have a moderate to strong antagonistic effect on the efficacy of the ferrocenyl containing ligands.

Table 2: *In vitro* activity of metal complexes against *P. falciparum* (Dept of Pharmacology, University of Cape Town)

		D10 (CQ sensitive)		K1 (CQ resistant)	
Compound	**No**	**IC_{50} (ng/ml)**	**IC_{50} (nM)**	**IC_{50} (ng/ml)**	**IC_{50} (nM)**
CQ	**4**	11.83	37.10	181.76	570.0
$[Au(C_6F_5)(CQ)]$	**60**	12.36	18.07	41.78	61.09
$[Au(CQ)(PPh_3)]NO_3$	**65**	17.74	21.09	51.76	61.53
[Rh(Cl)(COD)(CQ)]	**79**	12.16	21.50	46.03	81.31
FQ	**15**	7.05	16.30	2.15	4.96
$[Au(C_6F_5)(FQ)]$	**61**	8.05	10.08	3.16	3.96
$[Au(FQ)(PPh_3)]NO_3$	**66**	10.02	10.50	5.42	5.68
[Rh(Cl)(COD)(FQ)]	**80**	10.57	15.80	7.05	10.55
F2Q	**20**	5.38	11.30	5.98	12.56
$[Au(C_6F_5)(F2Q)]$	**62**	11.53	13.70	12.33	14.65
$[Au(PPh_3)(F2Q)]NO_3$	**67**	33.19	33.27	33.81	33.89
[Rh(Cl)(COD)(F2Q)]	**81**	145.88	202.00	431.52	597.59
BU	**37**	10.09	16.54	9.48	15.54
$[Au(BU)(C_6F_5)]$	**63**	22.75	23.36	12.59	12.92
$[Au(BU)(PPh_3)]NO_3$	**68**	32.14	30.32	32.96	31.09
[Rh(BU)(Cl)(COD)]	**82**	47.32	56.10	40.27	47.70

Inhibition of Trypanothione Reductase

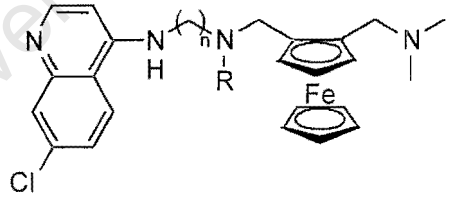
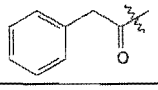
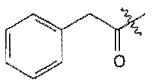
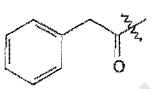
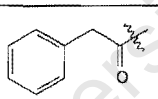
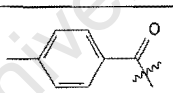
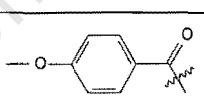
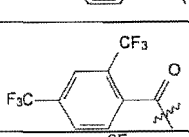
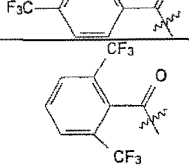
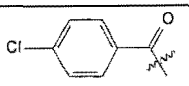


Figure 4: Structure of compounds used in enzyme inhibition assays

It is clear from Table 3 that the ferroquine analogues have enhanced inhibitory activity against both trypanothione reductase and glutathione reductase relative to chloroquine. Changing the methylene spacer length did appear to have an effect on the potency against trypanothione reductase with **21** and **22** being most efficacious in the amine series. This is consistent with similar trends shown for acridine, sulfonamide and urea compounds.[7] A similar effect was observed with the potency and selectivity against glutathione reductase. Here **21** had the lowest potency and the greatest selectivity. However, compared to chloroquine although the potency was approximately 20 times greater with **21**, it was at best only a third as selective for trypanothione reductase. So while the potency indices might indicate that the ferrocenyl compounds are promising, the selectivity counts severely against them.

Table 3: Inhibition of Trypanothione Reductase and Glutathione Reductase by the Ferroquine and Urea Compounds (Wellcome Trust Biocentre, University of Dundee)

Compound	n	Side chain R	IC_{50} TyrR (μM)	IC_{50} GR (μM)	Selectivity Indexes[a]	Potency Indexes[b]
CQ			47.60 ± 3.81	> 2000[c]	> 42.02	N/A
20	2	H	6.78 ± 0.67	14.11 ± 1.36	2.08	7.0
21	3	H	2.70 ± 0.17	39.60 ± 2.23	14.6	17.6
22	3	H	2.11 ± 0.08	19.97 ± 1.84	9.5	22.6
24	4	H	15.00 ± 1.96	8.53 ± 0.78	0.57	3.17
37	2		3.20 ± 0.27	25.01 ± 2.32	7.8	14.9
38	3		3.33 ± 0.16	83.80 ± 3.11	25.2	14.3
39	4		5.39 ± 0.29	18.38 ± 0.90	3.41	8.8
40	6		2.40 ± 0.093	16.77 ± 0.86	6.99	19.8
41	2		6.44 ± 0.41	142.55 ± 38.87	22.1	7.4
42	2		2.32 ± 0.16	76.30 ± 7.77	32.9	20.5
43	2		10.46 ± 0.20	143.99 ± 29.44	13.77	4.6
44	2		2.02 ± 0.15	15.17 ± 0.98	7.5	23.6
45	2		2.50 ± 0.20	34.43 ± 5.45	13.8	19.0

[a] IC_{50} in GR / IC_{50} in TryR; [b] IC_{50} of CQ (TyrR) / IC_{50} of FnQ (TryR); [c] no significant inhibition at 2000μM.

The more potent the compound the better as lower concentrations can be used, reducing the potential of problems with toxicity towards mammalian cells. In addition, with lower selectivity, the likelihood of the compound being toxic towards mammalian cells is greater. Therefore the higher the selectivity and potency indices the better. By this reckoning **42** shows the most promise. It showed selectivity slightly lower than that of chloroquine but is significantly more potent. Whilst the lower selectivity may count against the compound, the greater potency means that lower concentrations of the drug could be used to achieve the same efficacy.

In Vitro tests against *Leishmania* and *Trypanosoma* Parasites

Following the results of the aforementioned enzyme inhibition assays, three of the urea compounds, **37**, **42** and **45** and the parent ferroquine derivative **20** (Figure 5) were selected for *in vitro* testing against *Leishmania donovani*, *Trypanosoma cruzi* and *Trypanosoma brucei rhodesiense*. These tests were all carried out at the Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine.

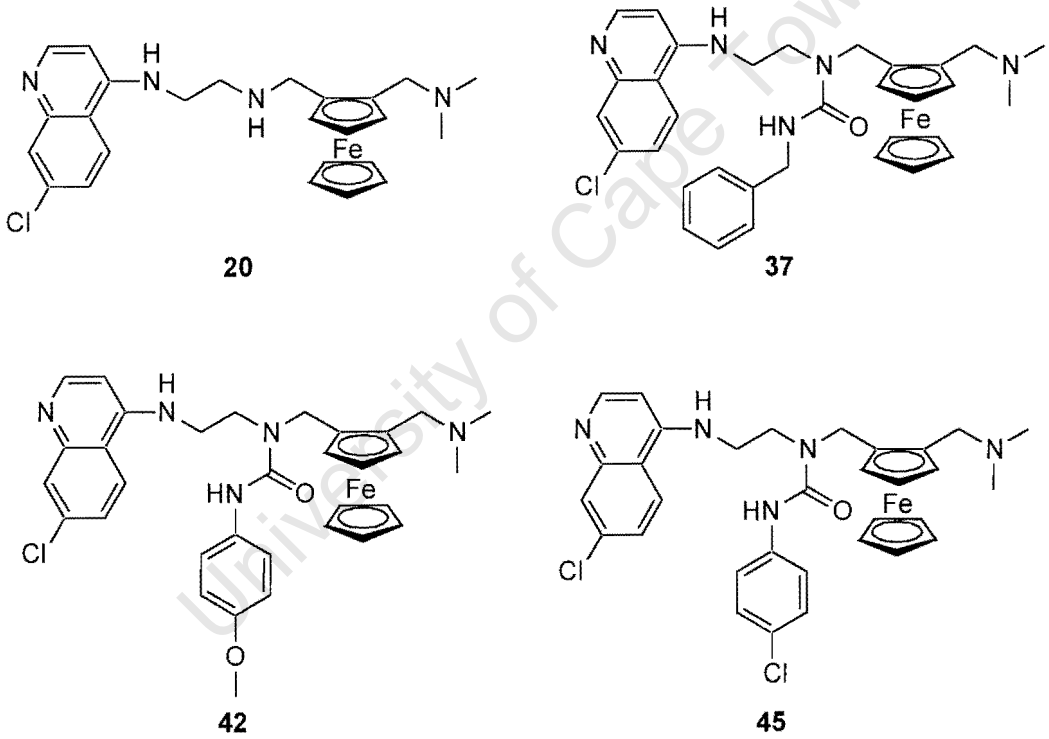


Figure 5: Four ferrocenyl compounds tested against a *Leishmania* and *Trypanosoma* parasites

Leishmaniasis

Table 4: *In vitro* tests against *L. donovani*

	ED_{50} (ED_{90})	ED_{50} (ED_{90})	% Inhibition			
Compound	**μg/ml**	**μM**	**30μM**	**10μM**	**3μM**	**1μM**
Pentostam	8.9[a]	144.2				
20	9.95 (12.6)	20.9 (26.5)	T/100[b]	T/100	T/+	0
37	5.8 (6.6)	9.5 (10.8)	T/100	T/100	0	
42	14.0 (16.6)	22.4 (26.5)	T/100	0		
45	14.0 (16.6)	22.2 (26.3)	T/100	0		

[a]Pentostam is sodium stibgluconate and the ED_{50} value is expressed as μg Sb^{v}/mL or μM Sb^{v}

[b]T/100 – toxic to macrophages, no parasite present.

The ED values indicate that these drugs show some potential against *Leishmania donovani.* All the new compounds exhibit an efficacy of 7-fold greater than the standard drug, Pentostam. Compound **37** was found to be most active. However, although the drugs are toxic to the parasite, they also show toxicity to the macrophages. Since *L. donovani* parasites exists as intracellular amastigotes, the drug must pass through the macrophage to reach the parasite. Selective toxicity is thus crucial.

Chagas' Disease

Table 5: *In vitro* studies against *T. cruzi*

	ED_{50} (ED_{90})	ED_{50} (ED_{90})	% Inhibition			
Compound	**μg/ml**	**μM**	**30μM**	**10μM**	**3μM**	**1μM**
Benznidazole	12.4	47.7				
20	>30	>63	32.8	7.3	1.2	0
37 (1)[a]	3.7 (>30)	6.1 (>49)	82.5	52.6	48.0	44.1
37 (2)	1.5 (>30)	2.5 (>49)	80.11	65.53	58.71	47.54
42	>30	>48	41.5	13.9	10.9	0
45	>30	>48	46.7	27.9	0	

[a] **37** tests repeated

With the exception of **37** these compounds show very little activity against *Trypanosoma cruzi.* The assays of **37** were repeated because they are anomalous with the rest of the series. This compound was found to be more active than the standard drug, Benznidazole. *T. cruzi* parasites also exist as intracellular amastigotes.

African Sleeping Sickness

Table 6: *In vitro* activity against *T. b. rhodesiense* STIB900

	ED_{50}	ED_{50}	% Inhibition			
Compound	**μg/ml**	**μM**	**30μM**	**10μM**	**3μM**	**1μM**
Pentamidine	0.012	0.025				
20	2.55	5.36	99.3	98.8	97.3	0
37	1.55	2.54	98.5	98.0	58.6	46.0
42	1.71	2.73	98.1	97.4	50.0	47.4
45	4.41	7.00	99.6	98.2	22.3	9.7

The results against *Trypanosoma brucei rhodesiense* show good promise. However, the standard drug, Pentamidine, is at worst 100-fold better than any of the new compounds. *T. brucei* exists in the bloodstream as extracellular trypamastigotes, so the problems associated with drug penetration of the macrophage are not present and the drug is far more likely to reach the site of action intact.

If the mode of action of these compounds was solely attributed to trypanothione reductase inhibition then there is no correlation as **42** and **45** since show superior efficacy as inhibitors of trypanothione reductase. However, **37** is consistently the best candidate from this series, having ED_{50} values for *in vitro* antiparasitic activity superior to **42** and **45**. As mentioned previously, it is possible that other factors such as cell penetration and metabolism could be playing a significant role in accounting for the greater efficacy of **37**.

In Vitro tests against a variety of strains of *P. falciparum*

Selected compounds were tested against a variety of strains of *P. falciparum* and their efficacy compared to various standard antimalarial drugs. All strains are sensitive to mefloquine, artelinic acid, artemisinin and dihydroartemisinin. Strain W2 is resistant to chloroquine. Strains W2, TM91-C235 and TM90C2b are all resistant to quinine.

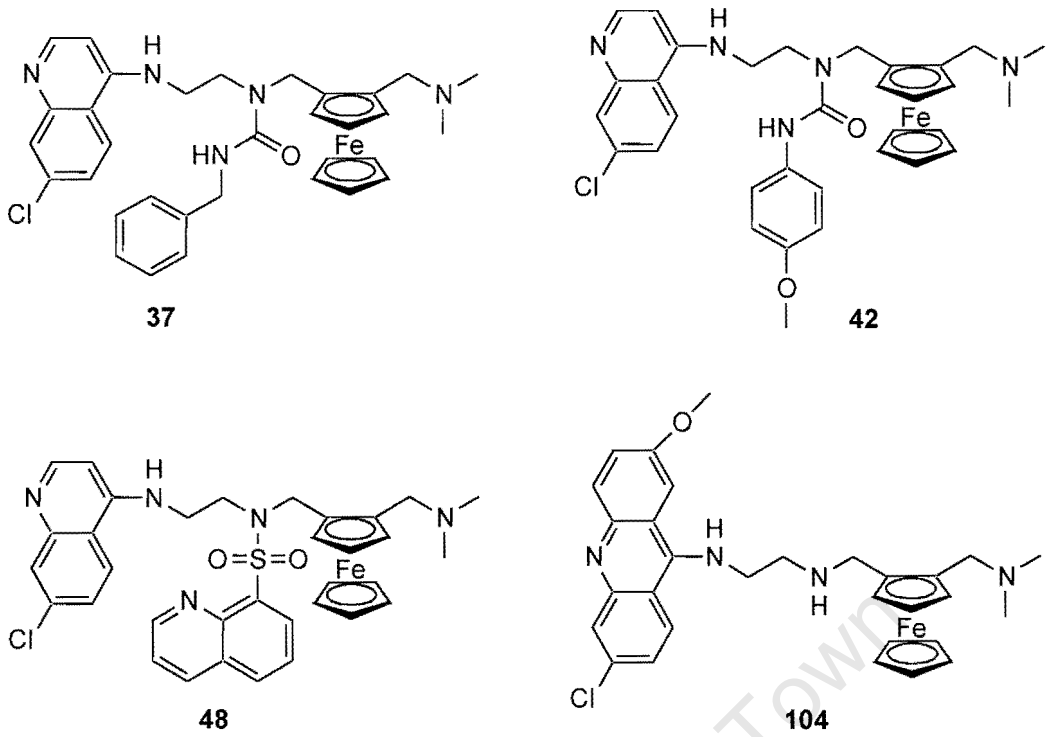


Figure 6: Selected compounds tested against a variety of strains of *P. falciparum*

Table 7: Comparative results of urea, sulfonamide, and acridine compounds with standard antimalarial drugs against various strains of *P. falciparum* (Walter Reed Army Institute of Research)

	IC_{50} (ng/ml)					
Strain	**D6**	**W2**	**WR87**	**TM91-C235**	**TM90C2b**	**RCS**
CQ	2.81	153.85	5.96	59.78	76.13	83.33
Mefloquine	10.71	3.80	9.83	14.48	12.78	1.61
Quinine	17.90	134.28	44.26	197.97	184.08	92.84
Artelinic acid	4.51	2.63	4.37	5.41	0.5	1.3
Artemisinin	2.26	1.11	2.7	2.02	1.9	0.84
Dihydroartemisinin	1.12	0.75	0.77	0.97	0.84	0.6
37	4.85	7.30	8.33	6.1	7.59	8.79
42	5.80	13.18	4.25	8.65	12.02	7.13
48	14.12	> 100	13.25	43.58	46.07	80
104	7.46	9.05	7.06	7.94	9.45	7.03

The results in Table 7 show that against the chloroquine sensitive, D6, ureas show comparable efficacy to chloroquine. Whilst against the chloroquine resistant strain, W2, they are in general at least ten times better than chloroquine. These urea compounds show comparable activity to mefloquine, but are not as good as artelinic acid, artemisinin or dihydroartemisinin. Compounds

37 and **42** show fairly consistent efficacy throughout all the strains of *P. falciparum*. This implies that there is little cross-resistance between these compounds and either quinine or chloroquine. The sulfonamide compound showed efficacy of a similar magnitude to chloroquine with much variation of efficacy between strains of the parasite. Compound **104** is a quinacrine analogue and its preparation is discussed in Chapter 6. It shows consistently good activity against all strains.

In Vivo Studies

It has been mentioned in Chapter 1 that malaria is caused by parasites of the genus *Plasmodium*. *Plasmodium falciparum* is the main species found in Africa and is the species in which chloroquine resistance is most prevalent and is therefore of greatest interest to this study. For *in vivo* studies it is normal to test the potential antimalarial drugs against *Plasmodium berghei*, a species of the parasite that has been developed for use in mice. *P. berghei* is sensitive to chloroquine. All *in vivo* testing was carried out at the Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine.

Table 8: *In vivo* activity of selected compounds against *P. berghei*

Group	Dose (mg/kg)	Dose (μmol/kg)	Schedule	Mean Parasitemia %	St Err	Mean Survival Time (days)	St Err
Control	-	-	-	16.99	1.30	5.00	0.00
CQ	10	31.3	x4	0.00	0.00	28.00	0.00
20	25	52.4	x4	0.00	0.00	15.20	1.24
37	25	41.0	x4	0.00	0.00	>30	N/A
42	25	39.9	x4	0.00	0.00	>30	N/A
45	25	39.7	x4	0.42	0.37	23.00	1.30

Table 8 indicates that in accordance with the *in vitro* results, all the compounds tested show good antimalarial activity *in vivo*. This is demonstrated by the mean parasitaemia. For all compounds, except **45**, no parasitaemia could be detected in the blood at the indicated doses. This implies that **20**, **37** and **42** all kill the parasite in the blood stage of the disease, which is consistent with the mode of action of 4-amino-7-chloroquinolines.[8] The mean survival time of the mice is a good indication of the toxicity of the compounds towards the mice, the longer the survival time, the lower the drug toxicity. Thus, it would appear that **20** is more toxic than **37** or **42**.

The functionalisation at the secondary amino group of **20** to form the ureas appears to play an important role in reducing the toxicity of the drug candidates towards mice. Within this limited series of compounds, **37** and **42** are the most efficacious.

Compounds **37** and **42** were carried through to another phase of *in vivo* trials in a different malaria mode. This time *P. chabaudi*, a chloroquine sensitive strain of the parasite was used. The drug was administered orally and as a subcutaneous injection in different groups. The determination of the efficacy is therefore particularly important because it sheds some light on the stability of the compounds in the harsh environment of the gastro-intestinal tract.

Table 9: *In vivo* trials against *P. chabaudi*

Compound	Route	ED_{50} (range) mg/kg x 4	ED_{90} (range) mg/kg x 4	% suppression at 10mg/kg
CQ	Subcutaneous	1.9 (2.3-2.6)	3.5 (2.3-4.6)	100
CQ	Oral	1.6 (1.0-2.8)	2.9 (1.8-5.3)	100
37	Subcutaneous	16.0 (13.0-20.0)	20.0 (16.0-25.0)	99.9
37	Oral	10.0 (5.0-13.0)	16.0 (7.2-17.0)	46.4
42	Subcutaneous	2.7 (1.4-4.8)	6.5 (3.5-12.5)	96.6
42	Oral	17.5 (12.5-25.0)	22.5 (16.0-32.0)	Nil

In the case of chloroquine, it is noted that there is very little difference between the subcutaneous and oral results. However, it is clear that the route of administration of the urea compounds has a marked effect on their *in vivo* efficacy. Compound **37** shows similar activity to chloroquine in the subcutaneous trial. However, oral administration of the drug results in a marked decrease in efficacy. Compound **42** also exhibits a similar trend in moving from subcutaneous to oral administration. However, the efficacy of chloroquine is still superior.

Conclusions

It is quite clear that the incorporation of the ferrocenyl moiety in the side chain of 4-amino-7-chloroquinolines has a beneficial effect on the efficacy of these compounds against chloroquine resistant strains of *Plasmodium*. As previously demonstrated,[2] the length of the methylene spacer has an effect on the efficacy of the compounds. In the ferroquine analogues it has been demonstrated that the compound with the three-carbon methylene spacer between aniline and secondary amine nitrogens was the most efficacious, whilst in the urea derivatives the compound with the two-carbon methylene spacer was favoured.[1]

The *in vivo* studies show that the ferroquine amine analogues appear to be fairly toxic. The toxicity can be reduced by the incorporation of a urea moiety. The urea compounds, in particular the benzyl urea **37** and the *p*-methoxyphenyl urea **42** show good activity *in vivo* provided they are administered by subcutaneous injection.

The coordination of a metal centre to chloroquine showed improved efficacy in chloroquine resistant strains of the parasite relative to uncomplexed chloroquine. However, the effect of complexing gold or rhodium to the ferroquine analogues and derivatives was, at best,

negligible. In some cases the complexation of the second metal resulted in an apparent antagonistic effect.

Overall compounds **37** and **42** appear to be the most promising drug candidates within this limited series of compounds. They show good efficacy against a variety of both chloroquine sensitive and chloroquine resistant strains of *P. falciparum* in *in vitro* tests. Compound **37** in particular shows a broad spectrum of *in vitro* activity against the causative agents of several tropical diseases. They also show good inhibition of trypanothione reductase whilst maintaining a high selectivity for the same enzyme relative to glutathione reductase. Finally, they show similar activity to chloroquine against chloroquine sensitive *P. berghei* in an *in vivo* study, but display a better mean survival time.

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Chapter 6

Preliminary Structure – Activity Relationships

Introduction

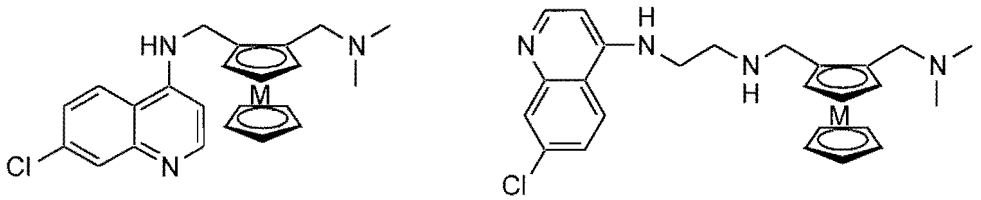
The synthesis, characterisation and biological evaluation of ferroquine analogues has been detailed in previous chapters. The formation of organometallic derivatives and coordination complexes between the ferroquine compounds have also been studied. The aim of this chapter is to explore the relationship of the chemical structure and the biological activity with a view to determining those sub structural motifs which may be important for biological activity either on their own or in combination with others. It should be noted that the intention of this study was not to determine the necessary features for the activity of 4-aminoquinolines, as this arena has been looked at carefully and the results of such studies have been established.[1] Rather, the focus here is to conduct preliminary studies into the structure-activity relationships of ferroquine analogues. Whatever the mode of action of the compounds under study, structure-activity relationships could arise from the specificity or non-specificity of these compounds.

This chapter deals with the synthesis and characterisation of some new compounds and the biological activity thereof. From these results some conclusions can be drawn as to the relative importance of several component parts of the molecules in question. As the emphasis of this section is on structure-activity relationships within this series of compounds, the synthetic routes employed to make the required compounds were, as far as possible, analogous to those previously used.

The characterisation data is detailed in the general experimental section (Chapter 8).

Rationale

The principle question arising from the study of ferroquine derivatives and related compounds is to establish the role of the ferrocenyl moiety in the efficacy of these compounds. Ferroquine **15** is indisputably a remarkable compound. It is more efficacious than chloroquine in both sensitive and resistant strains of the parasite, it has low toxicity, both enantiomers are equipotent and it appears that there is no sustained build-up of resistance to the drug so far.[2] The development of ferroquine followed a 'bait and hook' rationale. It is known that *P. falciparum* has an avidity for iron.[3] The presence of the iron in the ferrocenyl moiety in the side chain of chloroquine could provide the 'bait' whilst the presence of the chloroquine framework i.e. the 4-amino-7-chloroquinoline and terminal tertiary amine groups provides the 'hook'.[2]



M = Fe: **15**
M = Ru: **83**

M = Fe: **20**
M = Ru: **84**

Figure 1: Ruthenocene and ferrocene analogues

Results from our laboratory suggest that there is no significant difference in *in vitro* efficacy between analogous compounds containing ruthenocene, Figure 1.[4] On this basis, it could therefore be suggested that the efficacy of these compounds could be attributed to the large hydrophobic group present in the ferroquine or ruthenoquine molecules rather than the effect of the metal centre.* It was then postulated that replacing ferrocene with phenylene could result in a compound which showed similar efficacy to ferroquine.

Table 1: *In vitro* activity of ferrocene and ruthenocene analogues against *P. falciparum* (Dept of Pharmacology, University of Cape Town)[4]

		D10 (CQS)	K1 (CQR)
Compound	**Metal**	**IC_{50} nM**	**IC_{50} nM**
CQ		37.0	568
15	Fe	16.3	5.0
83	Ru	23.8	6.3
20	Fe	26.3	30.6
84	Ru	20.2	20.8

In Chapter 5, the biological activity of a number of ferrocenyl compounds is reported. On the basis of the variation in efficacy of those compounds and the efficacy of the ruthenocene compounds it was thought that various structural motifs in these compounds could contribute to the overall efficacy of these molecules in an additive or synergistic manner. The envisaged structure-activity relationships are summarised in Figure 2.

* Note that ruthenoquine (**83**) has also been synthesised independently in the laboratory of Prof JS Brocard.

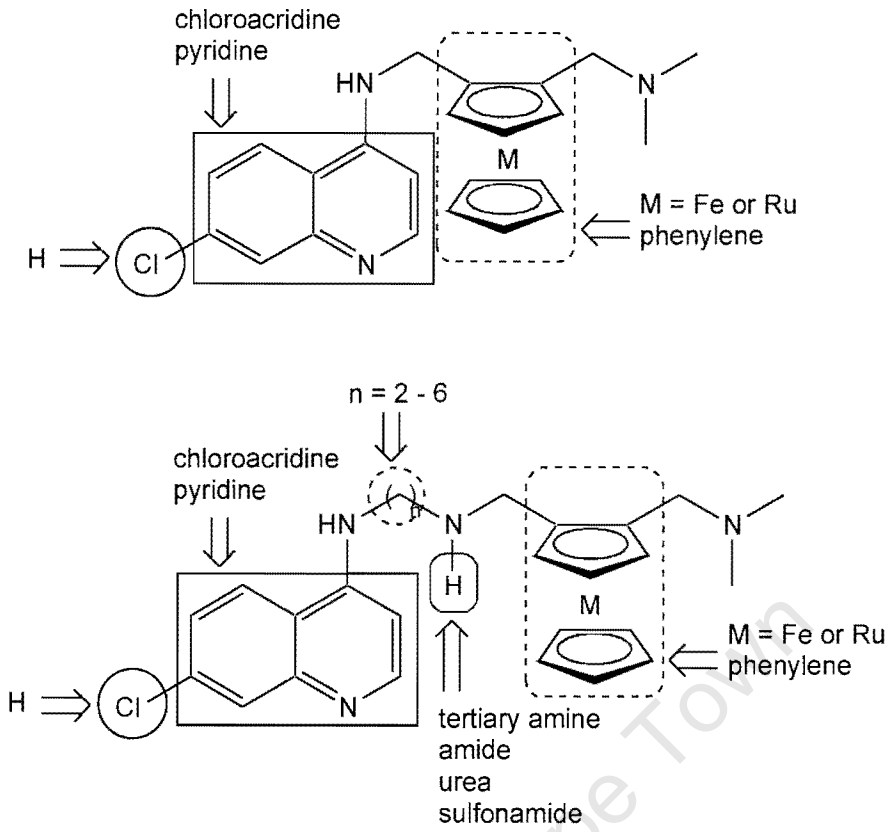
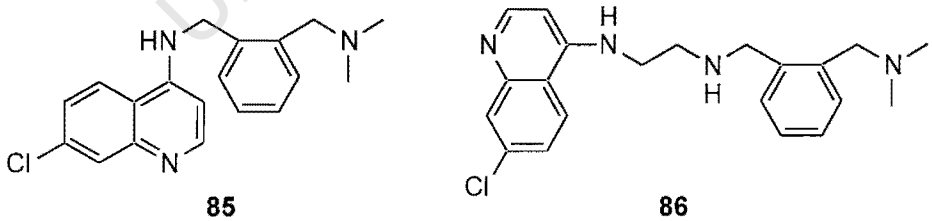


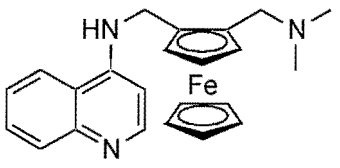
Figure 2: Preliminary structure-activity relationships

The variation in the length of the methylene spacer, n, has already been discussed in Chapter 5. Here three basic structural motifs are used: one motif based on ferroquine, a second motif, based on **20**, in which there is a reactive secondary amine centre and a third motif based on **37** in which an organic substituent has been introduced at the reactive secondary amine centre. The compounds synthesised for this series of preliminary structure-activity studies are summarised in below.



85 **86**

Figure 3: Substituting metallocene with phenylene moiety



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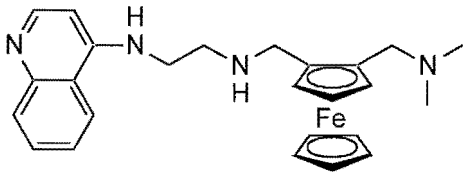

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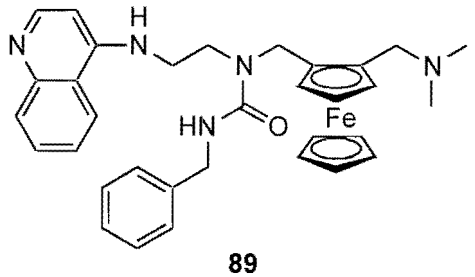

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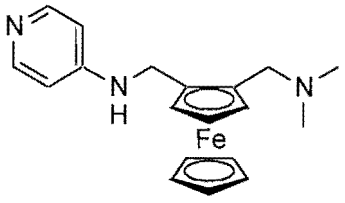
Figure 4: Substitution of 7-chloroquinoline by quinoline



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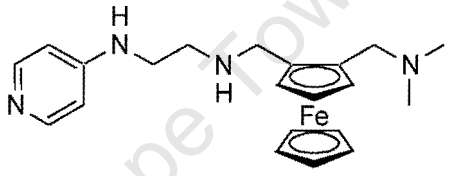

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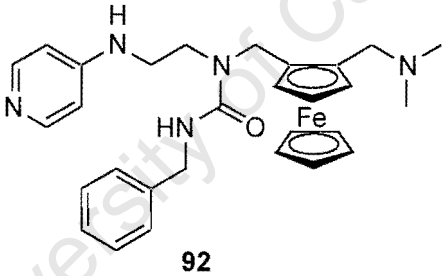

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Figure 5: Substitution of quinoline by pyridine

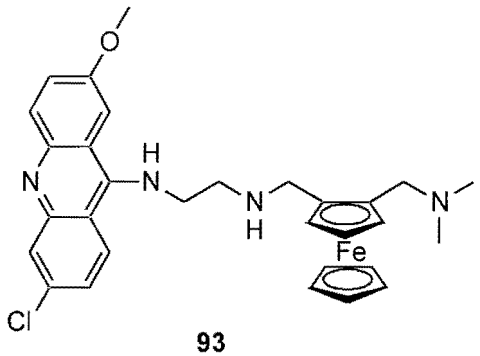

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Figure 6: Substitution of quinoline by chloroacridine

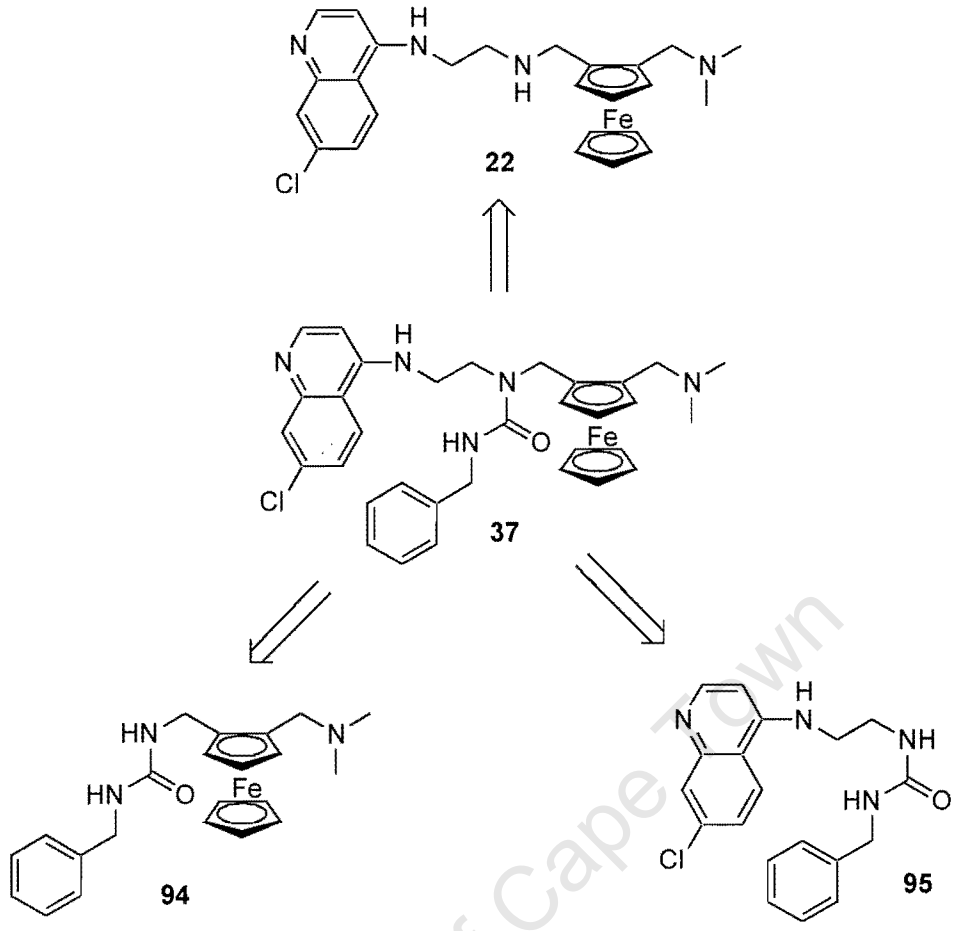

Figure 7: Importance of components of **37**

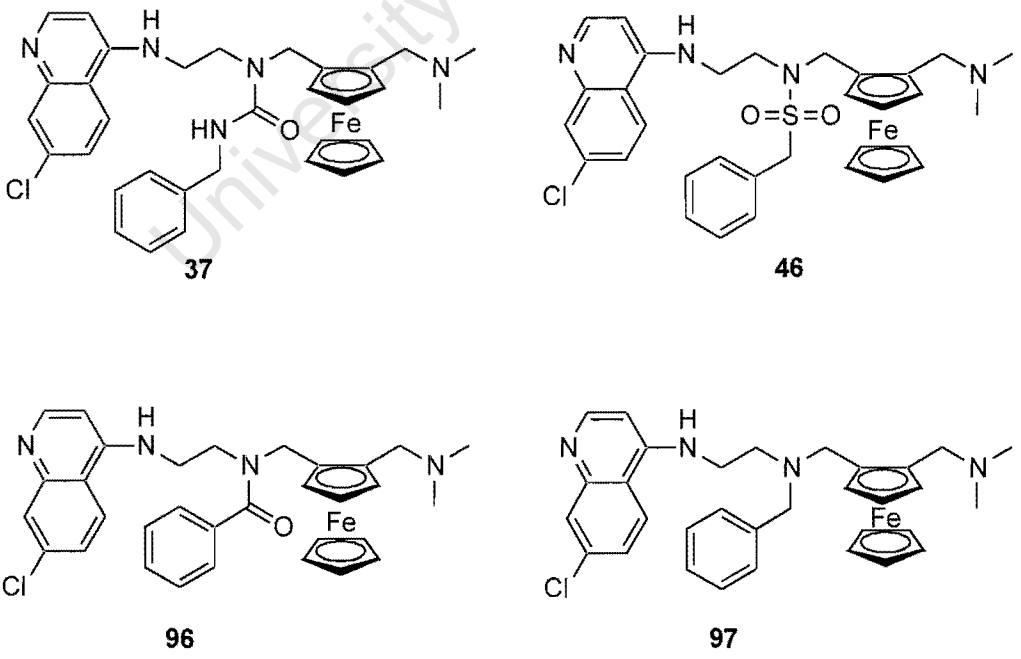

Figure 8: Importance of urea linkage

Synthesis of Structure-Activity Compounds

Substitution of Ferrocenyl Moiety by Phenylene Moiety

The synthesis of 'benzoquine' **85** and corresponding analogue **86** could be carried out in the same manner as ferroquine **15** and **20** respectively. Compound **85** bears some resemblance to amodiaquine **98**. However, as amodiaquine is a Mannich base the *in vivo* chemistry of benzoquine is likely to be different to that of amodiaquine.

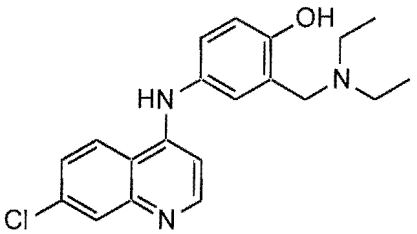

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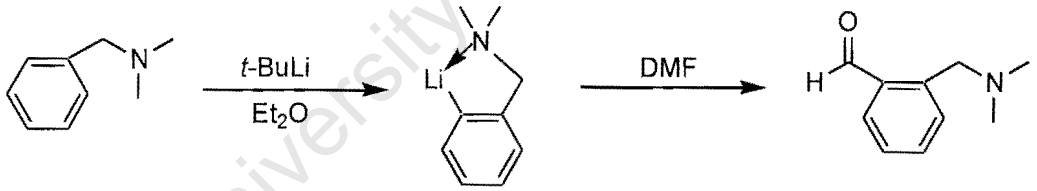
Figure 9: Amodiaquine

Synthesis of Benzoquine Analogues

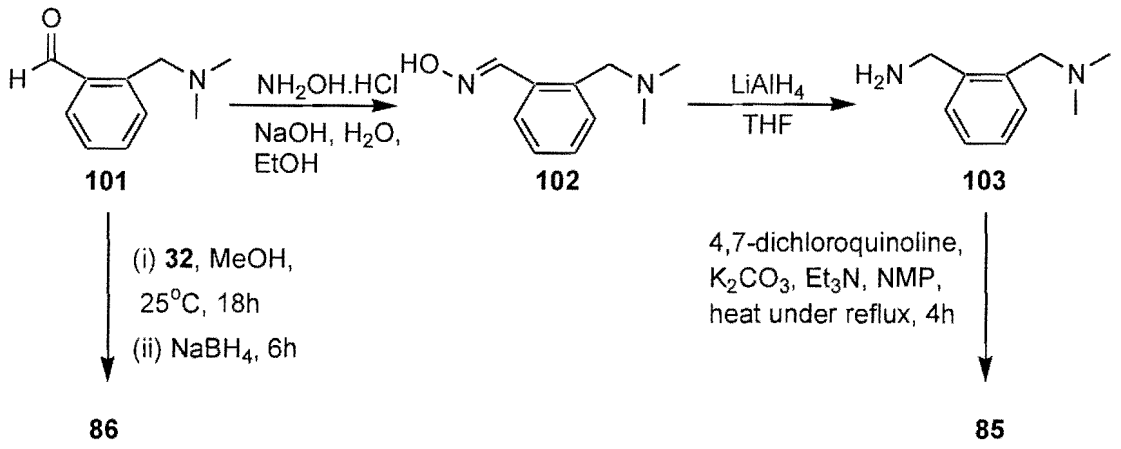
Dimethylaminomethylbenzene **99** is commercially available, and as the chemistry of ferrocene and benzene is known to be very similar, it was decided that a similar method of preparation would be used for making intermediates leading to benzoquine if possible.



99 **100** **101**

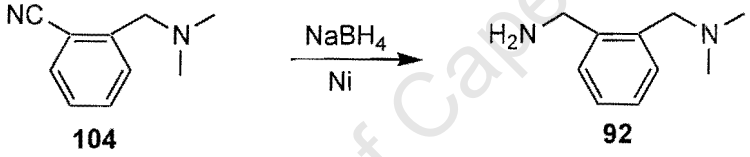
Scheme 1: Synthesis of **101**

The first step in the synthetic scheme requires the synthesis of 2-dimethylaminomethylbenzaldehyde **101**, Scheme 1. This compound is known, but was previously prepared using *n*-butyllithium in hexane and isolated using vacuum distillation after work-up (yield 53%).[5] As indicated in Scheme 1, *tert*-butyllithium was used in the synthesis and silica gel chromatography used to isolate the product after work-up (yield 60%).



Scheme 2: Preparation of **85** and **86**

Compounds **102** and **103** are known.[6,7] The synthetic route employed to prepare **103** is quite different to that used to prepare the compound previously.[7] As shown in Scheme 2, **103** was made *via* the benzyl oxime **102**. It is possible to make **103** from the benzonitrile **104**, Scheme 3, but as **101** was required for the synthesis of **86**, it was decided to use a similar methodology to that used for a related ferrocenyl compound (Chapter 2).



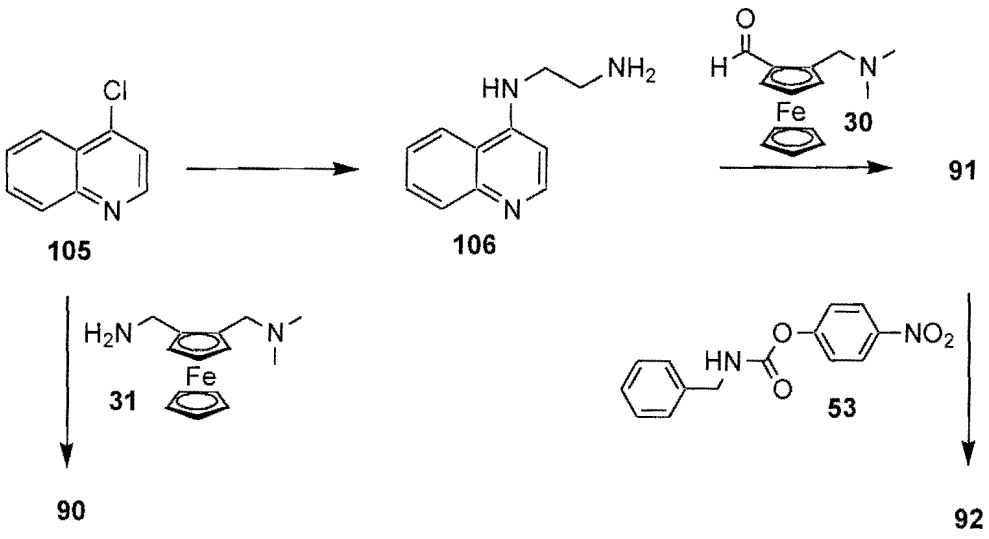
Scheme 3: Alternative synthetic methodology to **92**[7]

As mentioned earlier, the synthesis of **85** and **86**, Scheme 2, followed the same methodology as that described in Chapter 2 for the synthesis of ferroquine and the ferroquine analogues. No significant difference was found in the reactivity between analogous phenylene and ferrocene compounds.

Substitution of the 7-Chloroquinoline Moiety

Synthesis of Quinoline Compounds

As would be expected these compounds are synthesised in exactly the same manner as 7-chloroquinoline compounds. The absence of the chlorine in the 7-position has no noticeable effect on the reactivity of these compounds. Reaction conditions are not given in Scheme 4 as these have been detailed in Chapter 2.

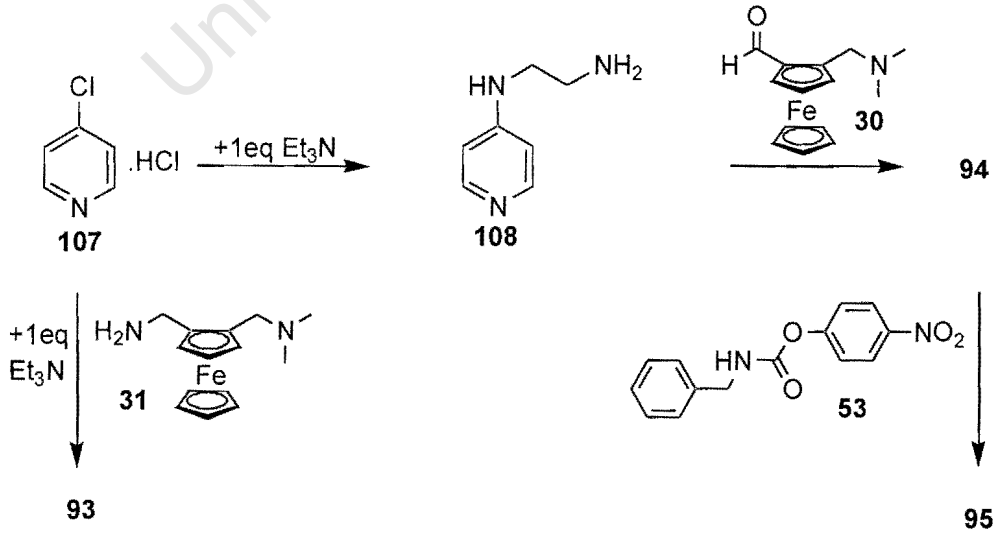


Conditions for all reactions have been described previously

Scheme 4: Synthesis of **90**, **91** and **92**

Synthesis of Pyridyl Compounds

The reactivity of 4-chloropyridine is similar to that of 4,7-dichloroquinoline because in both molecules, the reactive chlorine lies *para* to the nitrogen in an aromatic system. This facilitates a nucleophilic substitution reaction. The pyridyl compounds were then synthesised in a manner similar to the chloroquinoline compounds. The only significant difference here was that 4-chloropyridine hydrochloride as used as a starting material. This meant that the hydrogen chloride had to be removed from the reaction mixture. This was achieved by stirring the starting material with triethylamine for a few minutes prior to addition of the other reagents. The synthesis of compounds **93**, **94** and **95** is detailed in Scheme 5, but only amendments to the previously described synthetic methodologies are noted.



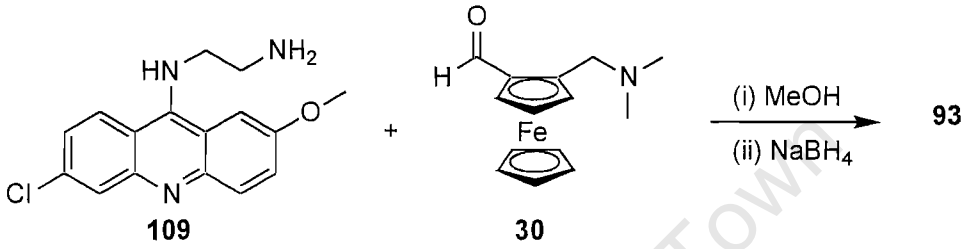
Conditions for all reactions have been described previously

Scheme 5: Synthesis of **93**, **94** and **95**

The other point to note is that the pyridine derivatives appear to be significantly more basic than the quinoline analogues. The pyridine compounds all had lower R_f values than the analogous quinoline compounds on silica gel TLC plates.

Synthesis of acridine derivative

This compound was synthesised in similar manner to that described for **20**. The only difference was in the synthesis of the tricyclic diaminoethane **109**, starting material. This was carried out in high yield according to a literature procedure.[8] This was then reacted with the ferrocene carboxaldehyde **30** under the reactions conditions used for **20**. There was no significant difference in yield or R_f value of **109** when compared to **20**.



Scheme 6: Synthesis of **93**

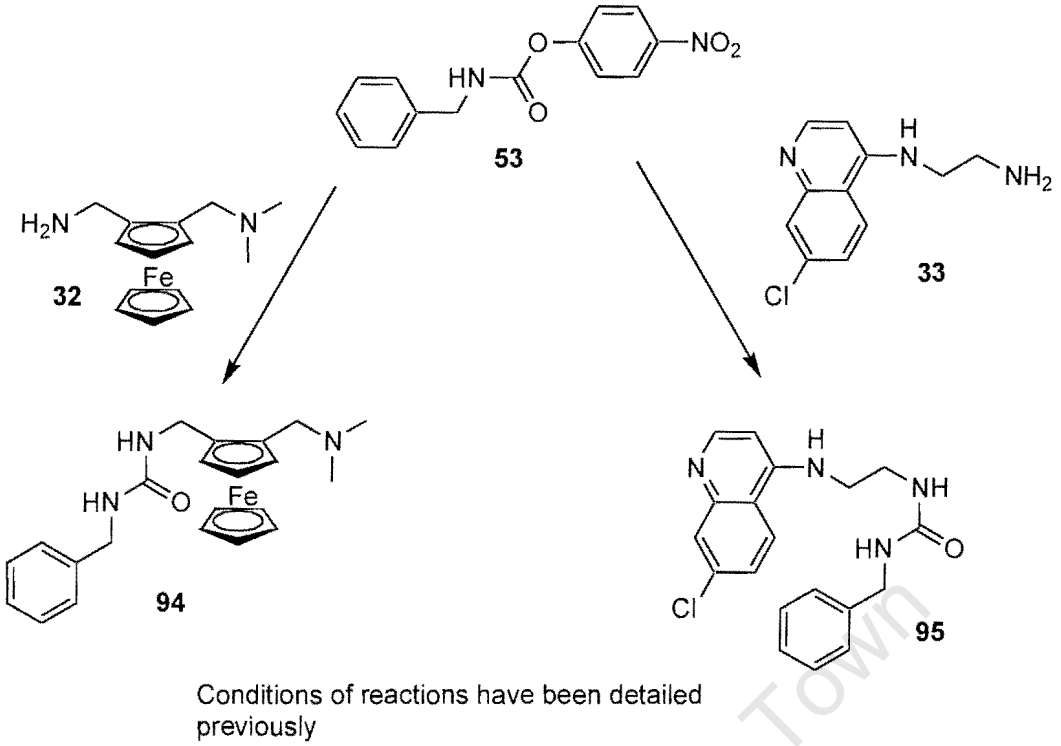
Effect and Nature of the Urea Moiety

Much study was carried out on the benzyl urea ferroquine derivative **37**. It was therefore deemed appropriate to try and ascertain which components are most necessary for high efficacy and low toxicity. The benzyl urea is essentially a trisubstituted urea, the substituents being N^1-(7-Chloro-quinolin-4-yl)-ethane-1,2-diamine, (2-dimethylaminomethylferrocenyl)-methylamine and benzylamine, Figure 7.

By synthesising and testing the efficacy of the three basic components indicated in Figure 7 separately, it may be possible to elucidate which components are necessary for the activity.

Synthesis of Urea Compounds

The urea compounds were synthesised in much the same manner as described in Chapter 3. In all cases, the urea moiety was introduced using nitrophenylbenzylcarbamate **53** (described as method 4 of urea preparation in the general experimental) and reacting it with the appropriate primary or secondary amine.

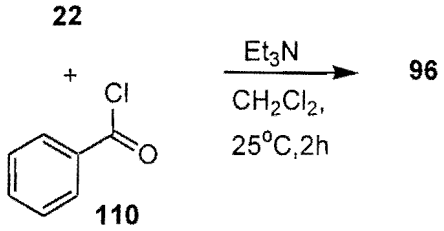


Scheme 7: Synthesis of **94** and **95**

Comparison of Amide, Amine and Urea Moieties

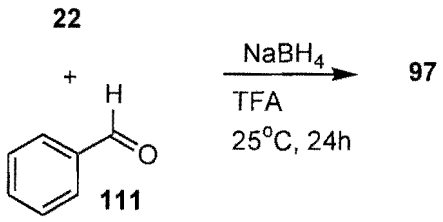
Synthesis of Benzyl Compounds

Whilst looking at the compounds described above is of importance, it is also necessary to look at the significance of the urea moiety in the efficacy of the compounds. This was achieved by looking at three different benzyl derivatives, Figure 7.



Scheme 8: Synthesis of **96**

The urea compound was synthesised as previously discussed (Chapter 3). The amide derivative **96** was synthesised by condensation of **20** and benzoyl chloride in the presence of triethylamine.

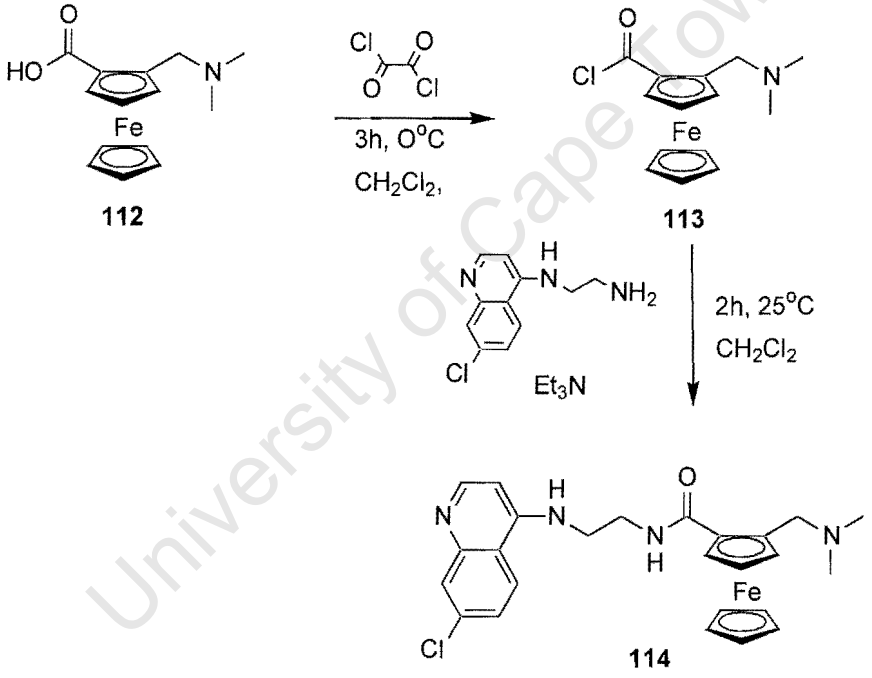


Scheme 9: Synthesis of **97**

The amine **97** was synthesised, using an adapted literature procedure,[9] from **20** and benzaldehyde in the presence of sodium borohydride and trifluoroacetic acid.

Introduction of amide linkage into 20

The introduction of a carbonyl group in position 3' could be expected to have an influence on the reactivity of the adjacent secondary amine centre. The compound was made by condensation of the ferrocene carboxylic acid chloride with **20** in the presence of triethylamine.

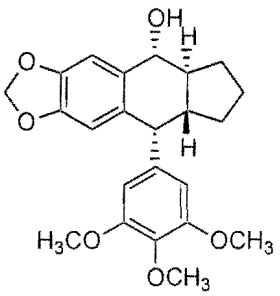


Scheme 10: Synthesis of amide **114**

The IC_{50} value in the D10 chloroquine sensitive strain was determined for this compound at the Department of Pharmacology, University of Cape Town. It was determined to be 623 nM (306 ng/ml) whilst the original amine compound **20** was determined to have an efficacy of 26.3 nM (5.38 ng/ml) in the series of assays (Chloroquine 37.0nM, 11.83ng/ml). The efficacy in the chloroquine resistant K1 strain was not determined. It is surprising that such a small difference in structural change could result in such a significant difference in *in vitro* efficacy against *P falciparum*. This result is anomalous with the rest of the structure activity results reported below and is therefore, probably worth repeating before any major conclusions could be drawn.

Structure-Activity Relationships

All the biological results detailed below were obtained from the Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine. *In vitro* assays were carried out against 3D7, a chloroquine sensitive strain, and K1, a chloroquine resistant strain of *Plasmodium falciparum*. Toxicity was determined against mammalian cells. The standard control drug used for this assay is podophyllotoxin **115**.



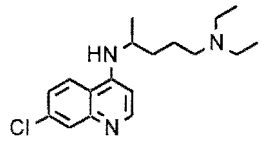
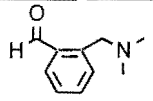
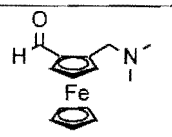
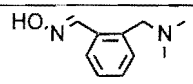
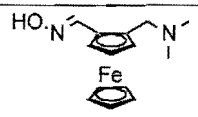
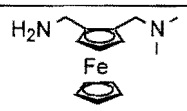
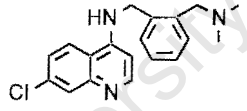
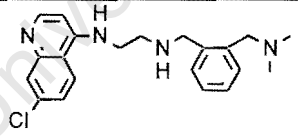
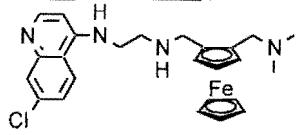
115

Figure 10: Structure of podophyllotoxin

Comparison of Ferroquine, Benzoquine analogues and advanced intermediates

Ferroquine **15** was not tested in the same series of assays. Both **15** and **20** have been tested against the K1 chloroquine resistant strain of *P. falciparum* previously at the Department of Pharmacology, University of Cape Town. The results of these assays are given in Table 1 above. It is apparent in those assays, that **15** showed a three fold improvement in efficacy in the K1 chloroquine resistant strain, whilst **20** showed similar efficacy in both the D10 chloroquine sensitive strain and in the K1 chloroquine resistant strain. The intermediates **30**, **31**, **32**, **101** and **102** were screened in the same series of assays. This was deemed worthwhile as the intention of the study is structure-activity relationships and the activity of the phenylene or ferrocenyl moieties in the quinoline system was of particular interest. Whilst it is apparent that the 4-amino-7-chloroquinoline moiety is necessary for an efficacy against *P. falciparum* in the above assays, there appears to be little difference in the efficacy between phenylene and ferrocene analogues. Perhaps the oxime compounds demonstrate this most effectively. It is noteworthy that both phenylene and ferrocene oximes exhibit no activity against the chloroquine sensitive 3D7 strain, but show efficacy, albeit modest, towards the chloroquine resistant K1 strain. Both **85** and **86** exhibit similar efficacy to chloroquine in the chloroquine sensitive 3D7 strain. On the other hand, both **86** and **20** showed significantly diminished efficacy in the chloroquine resistant K1 strain. This would suggest that there is a degree of cross resistance.

Table 2: *In vitro* studies on phenylene and ferrocenyl analogues

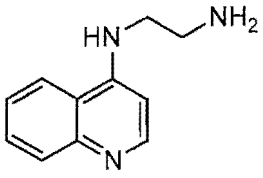
Compound	Structure	3D7 (CQS) μM (μg/ml)	K1 (CQR) μM (μg/ml)	Toxicity μM (μg/ml)
Podophyllotoxin				0.00024
Chloroquine		0.00138 (0.0044)	0.47 (0.15)	
101		>184 (>30)	>184 (>30)	160 (26.1)
30		134 (28.9)	>139 (>30)	450 (96.8)
102		>168 (>30)	36.5 (6.5)	773 (137.6)
31		>130 (>30)	46 (10.8)	17 (4)
32		>139 (>30)	76.7 (16.6)	11.6 (2.5)
85		0.0014 (0.00047)	0.0031 (0.010)	70 (22.9)
86		0.0068 (0.0025)	0.461 (0.170)	14 (5.1)
20		<0.2 (<0.1)	0.650 (0.310)	133 (63.6)

Although the exact mode of action of phenylene and ferrocene derivatives is unknown as yet, these results do suggest that the ferrocenyl moiety might simply be acting as a hydrophobic group. If that is the case, the phenylene derivatives offer a promising new avenue of research.

Effect of substitution of the 7-chloroquinoline moiety

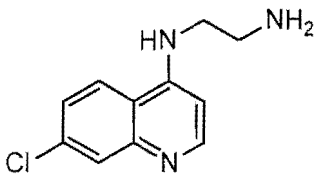
7-Chloroquinoline versus Quinoline

It well known that the presence of the chlorine atom in the 7 position of the quinoline ring plays an important role in the binding of quinoline compounds to haematin and hence influences the ability of the compounds to inhibit β-haematin formation. This has a significant effect on the efficacy of analogous compounds against a chloroquine sensitive strain of *P. falciparum*, Figure 11.



106

Does not inhibit ß-haematin formation
IC_{50} in D10 strain of *P. falciparum* = 3 800 ± 500nM



33

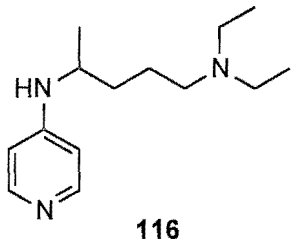
Does inhibit ß-haematin formation
IC_{50} in D10 strain of *P. falciparum* = 92 ± 12nM

Figure 11: Effect of presence of chlorine atom in the 7 position[10]

The results shown in Figure 11 indicate that there is a 40 fold difference in efficacy between the two compounds shown. The only difference between them is the presence of the chlorine atom in the 7 position. Presuming inhibition of β-haematin formation to be the mode of action of these antimalarials and the ferrocenyl moiety to have no influence on the inhibition of β-haematin formation, it could be postulated that the compounds shown in Figure 4 would show a similar decrease in efficacy as antimalarial agents with respect to **15**, **20** and **37**. If, however, the ferrocenyl unit enhances the antimalarial activity and/or β-haematin inhibition in some way, the efficacy may not be so severely affected.

7-Chloroquinoline versus Pyridine

There have been various reports on the use of pyridine derivatives in antimalarial compounds.[11,12] A brief perusal of the results reported indicate that 4-aminopyridines show no antimalarial activity.



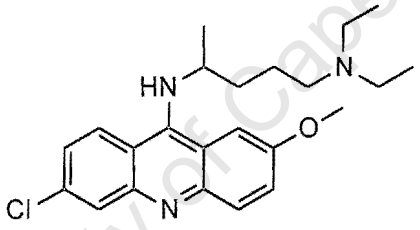
116

Figure 12: Pyridine analogue of chloroquine (inactive against *P. relictum*)[12]

If the pyridine analogues of **15**, **20** and **37** show activity, it could indicate that the ferrocenyl moiety itself is playing some role in the antimalarial activity of these compounds.

7-Chloroquinoline versus Acridine derivatives

Quinacrine **3**,[13] also known as mepacrine, was the antimalarial drug of choice before chloroquine.[14,15] Again, the incorporation of ferrocene in the side chain of this compound was deemed worthy of investigation to ascertain whether the beneficial influence of the ferrocenyl moiety exhibited in the ferroquine analogues is also observed in acridine derivatives.

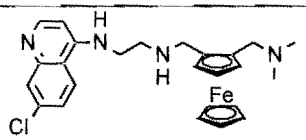
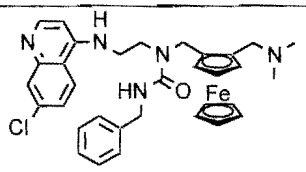
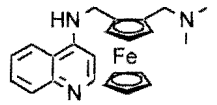
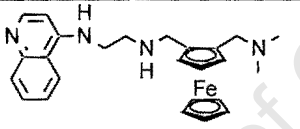
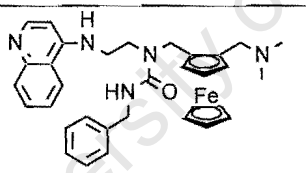
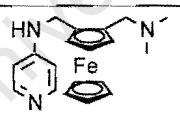
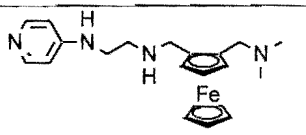
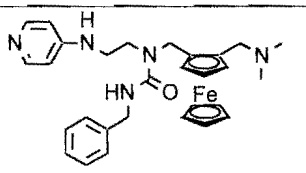
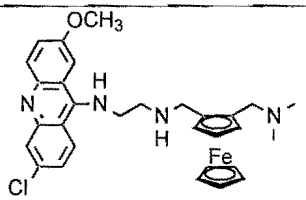


3

Figure 13: Quinacrine (**3**)

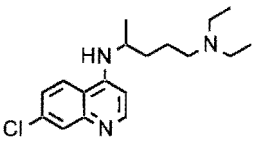
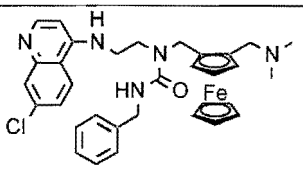
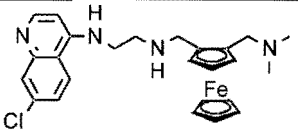
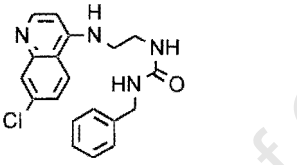
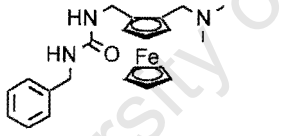
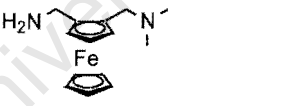
There are several points to note from the results reported in Table 3. The efficacies of **87** and **89** are superior to those of chloroquine in the chloroquine sensitive 3D7 strain despite the lack of the chlorine atom in the 7- position of the quinoline ring. There is a slight decrease in activity in moving from the 7-chloroquinoline to the quinoline but the effect is not as marked as would be expected when compared to previous studies e.g. Figure 11. This suggests these results may be strain specific. The pyridine derivatives show limited efficacy while the acridine derivative shows good efficacy, albeit they display high toxicity towards mammalian cells. It should be noted that neither the pyridine derivatives **92** nor the quinoline derivatives **87** and **88** inhibit β-haematin formation, but the acridine derivative **93** does. It would appear that the presence of the ferrocene in the side chain does have a positive influence on the efficacy of these compounds, indicated by the good efficacy of the quinoline compounds. However, the quinoline moiety is still necessary for activity. This may suggest that there is an additive or synergistic effect arising from the incorporation of the ferrocenyl moiety.

Table 3: Effect of modifications to 7-chloroquinoline on *in vitro* efficacy

Compound	Structure	3D7 (CQS) μM (μg/ml)	K1 (CQR) μM (μg/ml)	Toxicity μM (μg/ml)
Podophyllotoxin				0.00024
Chloroquine		0.0137 (0.0044)	0.47 (0.15)	
20		<0.2 (<0.1)	0.65 (0.31)	133 (63.6)
37		0.007 (0.004)	0.29 (0.18)	24 (14.5)
87		0.0083 (0.0033)	0.125 (0.050)	13 (5.2)
88		<0.23 (<0.1)	0.927 (0.410)	13.8 (6.1)
89		0.0121 (0.0068)	0.59 (0.33)	8.0 (4.5)
90		6.37 (2.50)	16 (5.6)	133 (46.3)
91		4.3 (1.7)	38.2 (15.0)	105 (41.4)
92		0.837 (0.44)	21.7 (11.4)	42.0 (21.9)
93		0.0013 (0.0007)	0.0077 (0.0043)	0.90 (0.50)

Effect of urea moiety

Table 4: Efficacy of the components of the urea

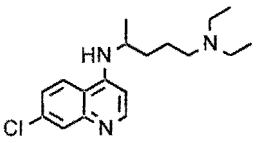
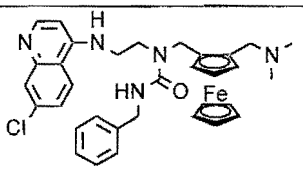
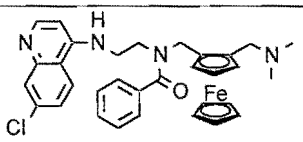
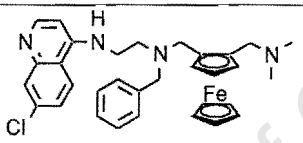
Compound	Structure	3D7 (CQS) μM (μg/ml)	K1 (CQR) μM (μg/ml)	Toxicity μM (μg/ml)
Podophyllotoxin				0.00024
Chloroquine		0.0137 (0.0044)	0.47 (0.15)	
37		0.007 (0.004)	0.29 (0.18)	24.0 (14.5)
22		<0.20 (<0.1)	0.65 (0.31)	133 (63.6)
94		0.113 (0.04)	3.4 (1.2)	73.0 (25.9)
95		70.6 (28.6)	29.9 (12.1)	7.2 (2.9)
32		>139 (>30)	76.7 (16.6)	11.6 (2.5)

It is quite clear that the most efficacious of the benzyl ureas are those containing the 7-chloroquinoline moiety. Those molecules lacking the 7-chloroquinoline show significantly higher ED values. However, it does appear that incorporation of benzyl urea unit is also advantageous in that there is a moderate to good improvement in both efficacy and toxicity observed in moving from **32** to **95** and **20** to **37**.

Comparison of amide, amine and urea moieties

It is clear from Table 5 that the nature of substitution at the secondary amine group of **20** does have an effect on the efficacy of the benzyl derivatives. Compound **97** shows the greatest efficacy in both strains of the parasite. This is most significant in the chloroquine resistant K1 strain. The toxicity of all the compounds is moderate.

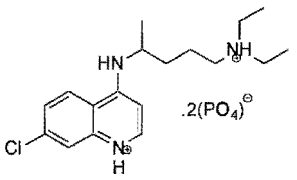
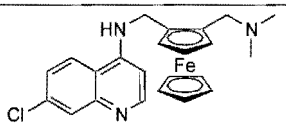
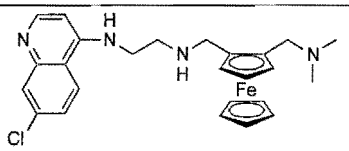
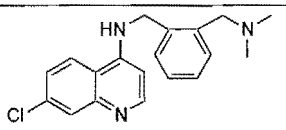
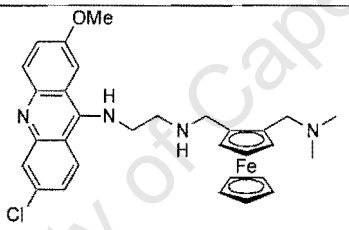
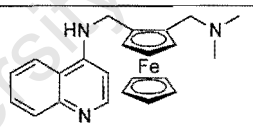
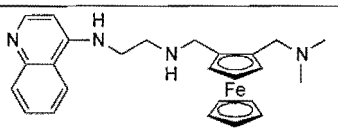
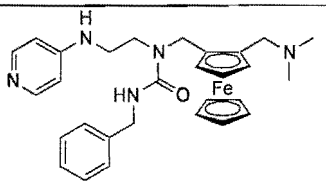
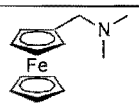
Table 5: Effect of nature of substituent on reactive secondary amine centre on *in vitro* efficacy of benzyl derivatives

Compound	Structure	3D7 (CQS) μM (μg/ml)	K1 (CQR) μM (μg/ml)	Toxicity μM (μg/ml)
Podophyllotoxin				0.00024
Chloroquine		0.0137 (0.0044)	0.47 (0.15)	
37		0.007 (0.004)	0.29 (0.18)	24.0 (14.5)
96		<0.17 (<0.1)	0.10 (0.06)	9.7 (5.6)
97		0.006 (0.0034)	0.017 (0.0098)	10.2 (5.8)

β-Haematin Inhibition Studies

β-Haematin inhibition can be determined by carrying out a simple assay and monitoring the product by infrared spectroscopy. β-haematin has characteristic bands at 1660 and 1210 cm^{-1}. These bands are not observed if the synthesis of β-haematin is attempted in the presence of chloroquine. This assay has been well documented and has been used to screen many potential antimalarial compounds. In general, in 4-aminoquinolines there is a correlation between the *in vitro* efficacy of a given compound against chloroquine sensitive *P. falciparum* and its ability to inhibit β-haematin formation.[10]

Table 6: Inhibition of β-haematin formation

Compound	Structure	Inhibition of β-haematin formation
[CQ]diphosphate		Yes
15		Yes
20		Yes
85		Yes
93		Yes
87		No
88		No
92		No
28		No

It is clearly demonstrated from Table 6 that the only compounds that are capable of inhibiting the formation of β-haematin are those compounds which contain the 7-chloroquinoline moiety. The acridine compound, **93**, is capable of this inhibition because it contains the necessary substituent.

Conclusions

The presence of a hydrophobic group in the side chain of chloroquine derivatives has a beneficial effect on the efficacy of these compounds particularly in chloroquine resistant strains of the *P. falciparum*. The nature of this hydrophobic group does not appear to be important in *in vitro* studies but it remains to be seen whether there is a difference in *in vivo* activity between phenylene, ferrocene and ruthenocene analogues.

The presence of the ferrocenyl moiety in the side chain of quinoline derivatives shows a marked increase in *in vitro* efficacy compared with those compounds with an aliphatic organic side chain. Moving from quinoline to pyridine results in a large decrease in efficacy, but the pyridine derivatives have a greater efficacy than expected. This suggests that the presence of the ferrocenyl moiety is important, and that it does have a beneficial influence on the efficacy of the compounds. It remains to be seen whether the phenylene or ruthenocene analogues would have a similar effect.

The presence of the benzyl urea results in a lowering of toxicity particularly in the ferroquine compounds. Whilst it is acknowledged that the lower the molecular mass of drugs the better, the addition of the benzyl urea is justified because it does appear to have a significant influence on the toxicity. There also seems to have a beneficial influence on the efficacy of these compounds. However, the benzyl amine derivative appears to have a similar efficacy although it does exhibit an increased toxicity

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Chapter 7

Conclusions and Future Work

Conclusions

The aim of this project was to synthesise new monometallic and heterobimetallic compounds as antiparasitic agents. A number of ferroquine type compounds have been synthesised. The incorporation of a reactive secondary amine centre in the side chain facilitated the derivatisation to form urea and sulfonamide compounds. Two of the new compounds together with ferroquine and chloroquine were used to make a series of coordination complexes with gold and rhodium. All these compounds were characterised using ^{1}H and ^{13}C NMR spectroscopy, infrared spectroscopy, mass spectrometry and elemental analysis (where possible). In addition, ^{19}F and ^{31}P NMR spectroscopy, molar conductivity and cyclic voltametry were used for further characterisation of selected compounds. The x-ray crystal structure of one of the ferroquine compounds was determined.

These compounds were then tested for *in vitro* antiparasitic activity with some being tested against the antioxidative enzyme trypanothione reductase. In particular most compounds were tested against *Plasmodium falciparum*, the causative agent of malaria. The incorporation of ferrocene into the side chain of 4-amino-7-chloroquinolines is clearly advantageous. Many of the ferroquine compounds and derivatives showed good efficacy both in chloroquine sensitive and in chloroquine resistant strains of the parasite. It was noted that in general the longer the methylene spacer between 4-amino-7-chloroquinoline and the ferrocenyl moiety the less efficacious the compound. It was also found that introducing a urea group at the reactive secondary amine centre resulted in a decrease in toxicity towards mammalian cells.

The incorporation of a gold or rhodium centre into chloroquine shows an improvement in efficacy against chloroquine resistant *P. falciparum*. However, incorporation of the same into the ferroquine compounds resulted in, at best, no effect on the efficacy of the compounds in either chloroquine sensitive or chloroquine resistant strains of the parasite. However, in some cases an antagonistic effect in the heterobimetallic system was apparent.

The cyclic voltametry of selected complexes was measured. Ferroquine itself gave a fully reversible one electron wave, but the ferroquine analogues showed at best quasi-reversible behaviour. The urea derivatives showed fully reversible behaviour. The incorporation of gold or rhodium resulted in a large increase in both anodic and cathodic potentials indicating that the *in vitro* ferrocenyl moiety is much more difficult to oxidise when the second metal centre is

present. There did not appear to be any real correlation between the half wave potential and the antimalarial activity.

The urea compounds were also tested for enzyme inhibition against trypanothione reductase and glutathione reductase. Those compounds which showed good selectivity for trypanothione reductase were tested against the causative agents of Leishmaniasis, African Sleeping Sickness and Chagas's Disease, all of which require trypanothione reductase to reduce peroxides in the parasitic cell. Little correlation was found between antiprotozoal activity and inhibition of trypanothione reductase.

Having established the efficacy of the aforementioned ferroquine compounds and derivatives, it was clear that the presence of ferrocenyl moiety in the side chain was advantageous. However, the role of the ferrocene was not well defined. As ruthenocene derivatives show similar efficacy to the ferrocene analogues of these compounds, it was suggested that the metallocene could simply be acting as a large hydrophobic group. A small selection of compounds were made in order to glean some understanding of the role of the ferrocenyl moiety in the ferroquine compounds.

Various phenylene derivatives were synthesised and tested against *P. falciparum* alongside the analogous ferrocene compounds. In all cases, there was little difference in efficacy between phenylene and ferrocene derivatives. 4-Aminoquinoline derivatives and 4-aminopyridine analogues of three 4-amino-7-chloroquinoline derivatives were also made and tested. The 4-aminoquinolines were significantly more efficacious than the 4-aminopyridines, but both series showed that the presence of the ferrocenyl moiety in the side chain gave a significantly greater efficacy than would be expected for compounds lacking the 4-amino-7-chloroquinoline moiety on the basis of β-haematin inhibition as the primary mechanism accounting fro antimalarial activity in the chloroquine sensitive strain of the parasite. It is therefore suggested that the presence of the ferrocenyl moiety enhances the efficacy of these compounds.

An analysis of the benzyl urea ferroquine analogue showed that whilst the inclusion of the benzyl urea had a minor advantageous effect on the efficacy of these compounds, there was a significant lowering in toxicity in mammalian cells associated with inclusion of this group. It was also shown that the benzyl amine derivative showed similar behaviour but the benzyl amide analogue did not. It is therefore concluded that the presence of the reactive secondary amine centre is advantageous, for the purpose of improving toxicity.

Future Work

Whilst it is apparent that the phenylene and metallocene derivatives show similar behaviour in *in vitro* assays, it remains to be seen whether this correlation is observed in *in vivo* studies. While it is also apparent that 4-aminoquinoline compounds with ferrocene in the side chain

exhibit unusually high antiplasmodial efficacy, it would be worth making the phenylene analogues and testing their efficacy in a similar assay.

It is noted that the inclusion of a benzyl urea or benzyl amine in the ferroquine derivatives is advantageous, however, this system has not been optimised. It would therefore be important to make a large series of urea and amine derivatives in order to find the most suitable compound. This would also serve to determine whether or not the urea and amine linkages are, in fact, equivalent in the biological system, or whether this is simple coincidental of the benzyl derivatives. Again, increasing the study to the phenylene analogues would be useful to provide further evidence to support or refute the similarity between phenylene and ferrocene analogues.

Closing Remarks

In 1947, my grandfather, William Kerr Blackie, wrote a book entitled 'Malaria with special reference to the African forms'. He was a general practitioner in Harare, Zimbabwe (Salisbury, Rhodesia, as it was then). He ended the historical review with these comments:

"The disease (malaria) continues to be widespread throughout the length and breadth of the Tropics and beyond, and in consequence is responsible for a heavy toll on life, both amongst the indigenous inhabitants and amongst European settlers. In addition it is responsible for much in the way of chronic ill-health and invalidism.

But recent advances in chemo-therapy have provided the clinician with new powerful drugs for the more efficient treatment of the disease in all its phases, and at the same time refinements in laboratory technique have enhanced the accuracy of laboratory diagnosis.

Again, in the sphere of preventative medicine, the hygienist is now in the possession of highly potent insecticides by means of which he can strike at the very heart of the malaria problem – the malaria vector.

None the less, the scientific control and elimination of malaria will long remain a task of the first magnitude, but the balance is now more definitely weighted in favour of those who a grappling with this elusive biological challenge to human life and enterprise."

Despite the great advances in medical technology in the last 55 years, the problem of malaria remains. Its significance is perhaps being overshadowed by the HIV/AIDS pandemic, but the poorest countries in the world continue to battle against a problem in which the First World has little interest. Much of the development of antimalarial drugs historically has occurred during periods such as the two World Wars, when soldiers from the First World countries were being directly affected by this disease. In addition to this, it is the children who are most severely affected so the economic effect of the disease is not as obvious as the effect of HIV/AIDS. Meanwhile the areas where malaria is endemic slowly grow and drug resistance is increasing even more rapidly. If the parasite had not developed resistance to drugs and the mosquito resistance to pesticides, I could not have produced this project, as there would have been no real need for much further research in this area. However, these problems are real and once

again nature is one step ahead of us. The real key to solving the problem of malaria is education in the Third World. Prevention is always far superior to a cure, and the only way to achieve prevention is through education. In the mean time, it is my fervent hope that this project will serve to increase understanding of the mode of action ferrocenyl-quinoline derivatives, thereby sheddding some further light on this specialised field of research.

On a personal note

Before commencing this section, I acknowledge that this is not usual to include such a section in scientific writing, but I feel it is perhaps important to review the process of producing this thesis. The chemistry is, of course, important, and I would like to think that I have made some small contribution to the field of medicinal chemistry. I have learnt a great deal about the chemistry involved in this project but also something of the chemistry in which my fellow students have been involved in. I think I have a far better idea of the nature of chemistry and chemistry research than I did three years ago. But in some ways this project has been a part of me, and in producing this thesis I have put some of myself on paper for review.

In addition to the chemistry I have learnt, the personal skills that I have developed will be invaluable. I would think it impossible to spend three years in such an environment and not learn something about interpersonal relationships. It is also impossible not to learn something about self-discipline and self-motivation. It has been for the most part a good and fruitful experience and I am grateful for having had this marvellous opportunity.

Chapter 8

General Experimental

General Procedures

Unless clearly stated otherwise all manipulations were carried out under an atmosphere of nitrogen using common Schlenk techniques. Syringes were stored at 60°C and all other glassware was thoroughly dried for at least 4 h at 210°C prior to use.

Materials

The solvents used in reactions for the preparation of compounds in the experimental were purified, dried and distilled as described in Table 1, according to literature procedures.[1] *N,N*-Dimethylformamide, 1-methyl-2-pyrrolidinone and triethylamine were stored in dry glass storage vessels equipped with Teflon valve closures and stored under nitrogen. All other solvents were freshly distilled before use.

Table 1: Solvent Purification and Drying Procedures

Solvent	Drying Agent	Distillation	Colour
Acetonitrile	CaH_2	Yes	-
Dichloromethane	CaH_2	Yes	-
Diethyl Ether	Sodium/benzophenone	Yes	Blue
N,N-Dimethylformamide (DMF)	Drierite at 15-20mm Hg	Yes	-
Methanol	I_2/Mg turnings	Yes	-
1-Methyl-2-pyrrolidinone (NMP)	Azeotropic distillation with toluene	Yes	-
Tetrahydrofuran (THF)	Sodium/benzophenone /tetraglyme	Yes	Blue
Toluene	Sodium	Yes	-
Triethylamine	Dried over K_2CO_3, distilled from CaH_2	Yes	-

The solvents used for work-up procedures and silica gel chromatography were of analytical grade and used without further purification. The only exceptions to this were hexane and dichloromethane, both of which were obtained as chemically pure grade reagents and distilled in air prior to use.

n-Butyllithium (1.6*M* in hexanes) and *tert*-butyllithium (1.7*M* in pentane) were purchased from Sigma Aldrich and transferred into Teflon valved storage flasks. The storage flasks were wrapped in aluminium foil, and stored at room temperature.

Chloroquine, free base, was obtained from chloroquine diphosphate by the addition of a strong ammonia solution, followed by extraction into diethyl ether. The solvent was removed under reduced pressure before dissolving in acetonitrile and allowing to stand at -6°C overnight. A white precipitate of chloroquine formed which was then filtered and washed with acetonitrile before drying *in vacuo*.[2]

Sodium tetrachloroaurate and rhodium trichloride were provided by Johnson-Matthey. Dimethylaminomethylferrocene was obtained from Strem. All other commercial reagents were obtained commercially used without further purification.

Chromatography

Column chromatography was carried out on silica gel (Particle size: 0.063 mm – 0.200 mm) obtained from Merck. The ratio of product to silica used was approximately 1:80. The column was packed by making a slurry of silica gel and the starting solvent system. The sample was loaded onto the column in a concentrated solution. It was found that gradually increasing polarity to the required solvent system provided good separation of all products.

Table 2: Starting Solvent System and Final Solvent System for Silica Gel Chromatography

Starting Solvent System	Required Solvent System
Et_2O:Hexane (50:50)	Et_2O:Hexane:Et_3N (70:20:10)
CH_2Cl_2:MeOH (95:5)	CH_2Cl_2:MeOH:Et_3N (80:20:1)
CH_2Cl_2:MeOH (95:5)	CH_2Cl_2:MeOH (80:20)

Instrumentation

Melting points were recorded on a Kofler hotstage microscope (Reichart Thermovar). Microanalysis data were performed using a Carlo Erba EA1108 elemental analyser. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer in the range 400 to 4000 cm^{-1}. Samples were either prepared neat between NaCl discs for oils, or as KBr discs for solids. All data are given in wavenumbers (cm^{-1}).

NMR spectra were recorded on either a Varian Unity-400 (^1H: 400 MHz; ^{13}C: 100.6 MHz; ^{19}F: 376 MHz) spectrometer or a Varian Mercury-300 (^1H: 300 MHz; ^{13}C: 75.5 MHz; ^{31}P: 121 MHz) spectrometer at ambient temperature. ^1H NMR spectra were referenced internally using the residual protons in the deuterated solvent ($CDCl_3$: δ 7.27; CD_3OD: δ 5.84; D_2O: δ 4.79; DMSO:

2.50) and values are reported relative to tetramethylsilane (δ 0.00). ^{13}C NMR spectra were either referenced internally to the solvent resonance ($CDCl_3$: δ 77.0; CD_3OD: δ 49.1; DMSO: δ 39.4) or sodium 3-(trimethylsilyl)-1-propanesulfonate was used as an external reference and values are reported relative to tetramethylsilane (δ 0.0). ^{19}F NMR spectra were referenced externally to $CFCl_3$. ^{31}P NMR spectra were referenced externally to H_3PO_4. All chemical shifts are quoted in δ (ppm) and coupling constants, *J*, are given in Hertz (Hz).

Mass spectra were determined by Dr Boshoff of the mass spectrometry unit at the Cape Technikon. In all cases the isotopic distribution pattern was checked against the theoretical distribution.

Cyclic voltametry (CV) was carried out on a BAS-100B electrochemical analyser in a one-compartment-three-electrode system, comprising Ag/Ag^+ (0.01M) as the reference electrode, platinum wire as the auxiliary electrode and a platinum disc as the working electrode. The supporting electrolyte was a solution of 0.1M tetrabutylammonium perchlorate in anhydrous acetonitrile. The potentials E were recorded without IR compensation. All potentials reported are relative to the half wave potential ($E_{1/2}$) of the ferrocene/ferrocenium couple run under the same conditions. The experiments were performed in 1.0mM solutions under an atmosphere of argon at room temperature. The solutions were saturated with argon, by bubbling argon through the solution for 5 minutes prior to the CV run. The platinum disc electrode was polished after every run.

Conductivity measurements were performed on a Metrohm 660 conductometer in 1.0mM nitrobenzene solutions at 20°C.

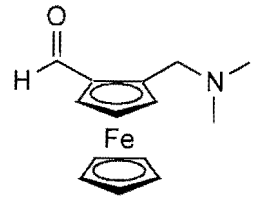
X-ray diffraction data was collected at room temperature using a Nonius Kappa CCD with 1.5kW graphite-monochromated Mo radiation. The strategy for the data collection was evaluated using COLLECT.[3] Several sets of data were collected with both 360°C phi and omega scans to collect the cusp data. These data were integrated using DENZO-SMN.[4] Unit cell dimensions were refined on all data. The program SCALEPACK[4] was used for the scaling and treating the data for absorption. The structure was solved and refined using SHELX97.[5]

Note

It is acknowledged that the characterisation data given below is in excess of that required by most journals. For example, all the infrared bands observed are written down whilst only some can be assigned unambiguously. The reason for this is to provide as detailed a record of this work as possible as only a small part of this work has been published to date.

Experimental Details Pertaining to Chapter 2

Compound 30



[(*N*,*N*-Dimethylamino)methyl]ferrocenecarboxaldehyde

Method 1:[6]

(Dimethylamino)methylferrocene **28** (2ml, 2.43g, 10mmol) was added to anhydrous diethyl ether (20ml) in a Schlenk tube. *n*-Butyllithium (7.5ml, 12.5mmol) was added and the mixture allowed to stir at 25°C for 18 h under nitrogen. A bright orange suspension was formed. Anhydrous DMF was added dropwise and the mixture allowed to stir for a further 4 h. A deep red solution was formed. The reaction was quenched by adding deionised water (20ml). The organic layer was separated off and the aqueous layer washed with diethyl ether (3 x 15ml). The organic extracts were collected, combined and dried over sodium sulfate. The solution was filtered and the sodium sulfate residue washed with diethyl ether. The solvent was removed under reduced pressure. The product was purified by silica gel chromatography eluting with diethyl ether: hexane: triethylamine (70:20:10). The product was collected and the solvent removed under reduced pressure before drying *in vacuo* to give the required product as a deep red oil. Yield: 1.195g (44%).

Method 2:[7]

(Dimethylamino)methylferrocene **28** (2ml, 2.43g, 10mmol) was added to anhydrous diethyl ether (20ml) in a Schlenk tube. *tert*-Butyllithium (7.5ml, 12.5mmol) was added and the mixture allowed to stir at 25°C for 30 min under nitrogen. A bright orange suspension was formed. Anhydrous DMF was added dropwise and the mixture allowed to stir for 30 min, after which time a deep red solution had formed. Diethyl ether was added slowly to dilute the reaction mixture before quenching with deionised water. The reaction was then worked up in the manner described above. Yield: 2.278g (84%).

The products from the two methods were indistinguishable by ^{1}H and ^{13}C NMR.

R_f (silica/diethyl ether: hexane: Et_3N = 70:20:10) 0.26;

δ_H (300 MHz; $CDCl_3$) 10.09 (1H, s, C*H*O), 4.76 (1H, m, Cp*H*-αCHO), 4.60 (1H, m, Cp*H*-βCHO), 4.54 (1H, m, Cp*H*-αCH_2NMe_2), 4.21 (5H, s, Cp'), 3.81 (1H, d, $^{2}J_{HH}$ = 13, 2'a), 3.36 (1H, d, $^{2}J_{HH}$ = 13, 2'b) and 2.20 (6H, s, 1');

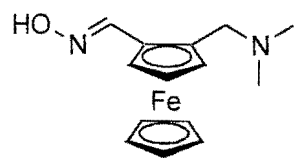
$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 193.2 (*C*HO), 75.9 (^{IV}C, Cp), 71.8 (Cp*C*-αCHO), 72.0 (Cp*C*-βCHO), 70.2 (5C, Cp'), 68.5 (^{IV}C, Cp), 68.0 (Cp*C*-αCH_2NMe_2), 56.5 (2') and 44.7 (2C, 1');

IR (thin film) ν_{max} 3332w, 3095m, 2938s, 2855s, 2816s, 2770s, 2722m, 1674vs (ν C=O), 1443s (NCH_3), 1411m, 1384m, 1353m, 1289m, 1251m, 1206w, 1173m, 1147m, 1106m (ferrocene), 1034s, 1013s (ferrocene), 957w, 842s (aryl $CH_2N(CH_3)$), 823s (ferrocene), 791m and 741m;

$E_{1/2}$ = 88 mV.

^{1}H NMR in agreement with literature.[6,8]

Compound 31



2-[(*N,N*-Dimethylamino)methyl]ferrocenecarboxaldehyde Oxime[6] **30** (2.00g, 7.40mmol) was placed in a 100ml round bottomed flask. Absolute ethanol (50ml) was added followed by hydroxylamine hydrochloride (0.84g, 12mmol). Sodium hydroxide (0.96g, 24.4mmol) was dissolved in deionised water (10ml) and the solution added to the reaction mixture. The mixture was allowed to heat under reflux for 2 h in an atmosphere of nitrogen. The reaction mixture was allowed to cool to room temperature before adding sufficient dry ice to neutralise the solution. Dichloromethane was then added and the organic layer separated off. The aqueous layer was washed with dichloromethane (3 x 20ml). The organic fractions were collected, combined and dried over sodium sulfate. The solution was then filtered and the sodium sulfate residue washed with dichloromethane. The solvent was removed under reduced pressure before drying *in vacuo*. The product was a hygroscopic deep orange crystalline solid. Yield: 0.737g (98%);

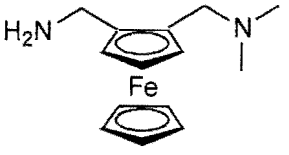
δ_H (300 MHz; $CDCl_3$) 8.02 (1H, s, 3'), 4.55 (1H, m, Cp), 4.38 (1H, m, Cp), 4.30 (1H, t, $^3J_{HH}$ = 2, Cp), 4.13 (5H, s, Cp'), 3.94 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.45 (1H, d, $^2J_{HH}$ = 13, 2'b), 2.28 (6H, s, 1') and 2.19 (1H, s, O*H*);

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 148.0 (3'), 80.9 (^{IV}C), 72.6 (Cp), 69.8 (5C, Cp'), 69.0 (Cp), 68.0 (Cp), 56.6 (2') and 44.0 (2C, 1');

HRMS (EI) *m/z* 286.07641 [M^+, $C_{14}H_{18}N_2OFe$ requires 286.07685], 268.1, 241.0 [Fp-CH_2-NMe_2], 224.0, 211.0, 187.0, 163.0, 121.0 [Cp-Fe], 104.0 and 58.1 [CH_2NMe_2].

^{1}H NMR and mass spectral data in agreement with literature.[6]

Compound 32



2-[(*N,N*-Dimethylamino)methyl]ferrocenemethylamine[6] **31** (1.913g, 6.638mmol) was placed in a 100ml round bottomed flask. Anhydrous THF (50ml) was added followed by lithium aluminium hydride (836mg, 21.74mmol). The mixture was heated under reflux in an atmosphere of nitrogen for 15 h. The mixture was allowed to cool to room temperature before diluting with diethyl ether (10ml) and adding a saturated brine solution (30ml). The product was extracted into the organic phase. The aqueous layer was washed with diethyl ether (3 x 50ml). The organic extracts were collected, combined and dried over potassium carbonate. The product was filtered to remove potassium carbonate and the solvent was removed under reduced pressure. The deep red oil product was dried *in vacuo*. Yield: 1.802g (95%)

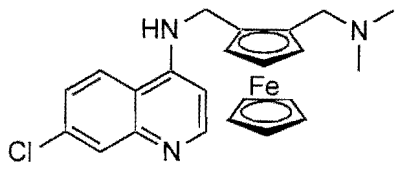
δ_H (300 MHz; $CDCl_3$) 4.10 (1H, m, Cp), 4.08 (1H, m, Cp), 4.02 (5H, s, Cp'), 3.99 (1H, m, Cp), 3.66 (1H, d, $^2J_{HH}$ = 14, 3'a), 3.61 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.45 (1H, d, $^2J_{HH}$ = 14, 3'b), 2.88 (1H, d, $^2J_{HH}$ = 13, 2'b) and 2.12 (6H, s, 1');

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 90.3 (^{IV}C, Cp), 83.1 (^{IV}C, Cp), 70.7 (Cp), 68.7 (5C, Cp'), 68.1 (Cp), 65.7 (Cp), 58.0 (2'), 44.9 (2C, 1') and 40.4 (3');

IR (thin film) ν_{max} 3352s (NH), 3093s (NH), 2933s, 2855s, 2816s, 2771s, 1641m, 1456s (NCH_3), 1353m, 1286w, 1258m, 1172m, 1105m (ferrocene), 1037m, 1001s (ferrocene), 952w, 843s (aryl $CH_2N(CH_3)_2$) and 816s (ferrocene);

^1H NMR and mass spectral data in agreement with literature.[6]

Compound 15



(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenylmethyl)amine, ferroquine (FQ)

32 (4.742g, 17.42mmol) was placed in a 50ml round bottomed flask together with 4,7-dichloroquinoline (17.42g, 87.1mmol), anhydrous potassium carbonate (10.10g, 25.26mmol), anhydrous triethylamine (7ml) and anhydrous NMP (20ml). The flask was fitted with a reflux condenser and nitrogen inlet and the mixture heated to 135°C for 4 h. The reaction mixture was allowed to cool to room temperature before adding ethyl acetate. The mixture was then transferred to a separating funnel and washed with a saturated brine solution (10 x 30ml). The organic layer was then dried over sodium sulfate before removing the solvent under reduced pressure. The product was then purified by silica gel chromatography. The orange glassy solid obtained was recrystallised from ethyl acetate/hexane to give a bright orange crystalline solid. Yield: 3.987g (53%);

mp: 196-197°C (from ethyl acetate/hexane)

R_f (silica/ethyl acetate: hexane: Et_3N = 45:50:5) 0.18;

δ_H (400 MHz; $CDCl_3$) 8.53 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 7.91 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.62 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.27 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.46 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 4.38 (1H, d, $^2J_{HH}$ = 13, 3'a), 4.26 (1H, m, Cp), 4.16 (1H, m, Cp), 4.14 (1H, m, 3'b), 4.13 (5H, s, Cp'), 4.08 (1H, t, $^3J_{HH}$ = 2, Cp), 3.80 (1H, d, $^2J_{HH}$ = 13, 2'a), 2.89 (1H, d, $^2J_{HH}$ = 13, 2'b) and 2.21 (6H, s, 1');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 152.3 (ArC_2), 150.5 (^{IV}C), 149.5 (^{IV}C), 134.8 (^{IV}C), 128.6 (ArC_8), 124.9 (ArC_6), 122.4 (ArC_5), 118.1 (^{IV}C), 102.8 (^{IV}C), 99.1 (ArC_3), 84.2 (2C, ^{IV}C), 71.6 (Cp), 70.8 (Cp), 69.5 (5C, Cp'), 66.2 (Cp), 58.3 (2'), 45.1 (2C, 1') and 42.7 (3');

IR (KBr) ν_{max} 3425br w (NH), 3192br w (NH), 3091m, 3046m, 2976m, 2944m, 2901m, 2865m, 2831m, 2787m, 1609s (7-chloroquinoline), 1578vs (7-chloroquinoline), 1541s (7-chloroquinoline), 1488w, 1463m (NCH_3), 1442m, 1426m, 1379w, 1365w, 1348s, 1330s (ν C-N aromatic), 1280w, 1250w, 1224w, 1195m, 1165m, 1131s, 1105m (ferrocene), 1076m, 1033m, 1006m (ferrocene), 906m, 879m, 859m (aryl $CH_2N(CH_3)_2$), 813m (ferrocene), 798s, 765m, 725w, 694m, 640m, 623w, 614w, 548w, 510m, 490s (ferrocene), 454m, 433m, 418m and 405m;

HRMS (EI) *m/z* 433.09928 [M^+, $C_{23}H_{24}N_3{}^{35}ClFe$ requires 433.10081], 388.0 [M^+ - $N(Me)_2$], 307.2, 255.1 [HC-Fp-CH_2-NMe_2], 213.0, 167.0, 149.0, 120.1 [Cp-Fe], 91.0 [CH_2-Cp-CH_2] and 57.1 [CH-NMe_2];

Found: C, 63.89; H, 5.38; N, 9.40. Calc. for $C_{23}H_{24}N_3ClFe$: C, 63.67; H, 5.58; N, 9.67%.

$E_{1/2}$ = 147 mV; ferrocene redox: E_{pa} = 181 mV and E_{pc} = 113 mV.
^{1}H NMR, ^{13}C NMR, IR and MS in agreement with literature values.[6]

Tartrate salt of **15**

15 was dissolved in hot methanol. *L*-tartaric acid was dissolved in hot acetone and then added slowly to the solution of ferroquine forming a yellow precipitate. The precipitate was filtered and washed with hot acetone. The product was then dried *in vacuo*.

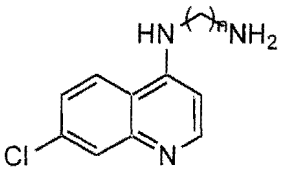
δ_H (300 MHz; D_2O) 8.12 (1H, d, $^3J_{HH}$ = 7, ArC_2-H), 7.82 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.50 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.30 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.66 (1H, d, $^3J_{HH}$ = 7, ArC_3-H), 4.40-4.31 (3H, m, 3'a, 3'b, Cp), 4.28 (4H, m, tartaric acid), 4.22 (1H, d, $^3J_{HH}$ = 3, Cp), 4.13 (3H, m, 2'a, 2'b, Cp), 4.03 (5H, s, Cp'), 2.57 (3H, s, 1'a), 2.48 (3H, s, 1'b) and 2.164 (1H, s, O*H*);

$\delta_{C\{H\}}$ (75.5 MHz; D_2O) 176.1 (2C, tartaric acid, *C*OOH), 155.2 (ArC_2), 142.4 (^{IV}C), 139.2 (ArC_6), 137.8 (^{IV}C), 127.7 (ArC_6), 123.7 (ArC_5), 119.0 (ArC_8), 114.8 (^{IV}C), 98.7 (ArC_3), 82.9 (^{IV}C), 73.8 (Cp), 72.6 (2C, tartaric acid, *C*HOH) 71.9 (Cp), 70.6 (Cp), 69.9 (5C, Cp'), 55.3 (2'), 41.9 (1'a), 41.3 (1'b) and 40.7 (3').

^{1}H NMR in agreement with literature values.[6]

Compounds 33 – 37

33: *N*-(7-chloro-quinolin-4-yl)-ethane-1,2-diamine[9]
34: *N*-(7-chloro-quinolin-4-yl)-propane-1,3-diamine
35: *N*-(7-chloro-quinolin-4-yl)-butane-1,4-diamine
36: *N*-(7-chloro-quinolin-4-yl)-pentane-1,5-diamine
37: *N*-(7-chloro-quinolin-4-yl)-hexane-1,6-diamine



Synthesis of Compound 33

A mixture of 4,7-dichloroquinoline and 4.5 mol equivalents of the appropriate alkyldiamine was placed in a round bottomed flask fitted with reflux condenser and nitrogen inlet. The mixture was heated to 80°C for 1 h before raising the temperature to 145°C for a further 3 h. A cream precipitate formed in the bottom of the flask. The reaction mixture was allowed to cool to room temperature with stirring.

Work-up 1: Sodium hydroxide (1M, 10ml) was added forming an emulsion. The product was then extracted into ethyl acetate. The solvent was then removed under reduced pressure giving a pale yellow powder. Yield: 1.118g (82%).

Work-up 2: Sodium hydroxide (1M, 10ml) was added forming an emulsion. The product was then extracted into dichloromethane. The solvent was then removed under reduced pressure giving a pale yellow powder. Yield: 1.254g (84%).

Compounds **34** – **37** were prepared in a similar manner starting from 1,3-diaminopropane, 1,4-diaminobutane, 1,5-diaminopentane and 1,6-diaminohexane respectively. All products were pale yellow powders.

Compound **34** Yield: 44%;

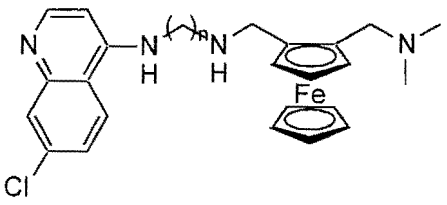
Compound **35** Yield: 67%;

Compound **36** Yield: 80%;

Compound **37** Yield: 89%.

Compounds 20 – 24

Synthesis of Compound 20

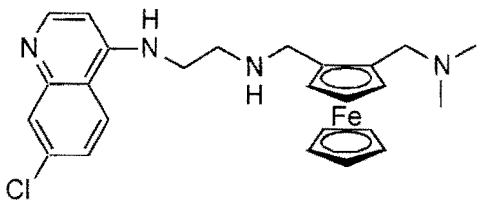


[(*N,N*-dimethylamino)methyl]ferrocenecarboxaldehyde, **30** was dissolved in anhydrous methanol in a round bottomed flask. 1 mol equivalent of the appropriate 7-chloroquinoline-4-alkyldiamine (**33** – **37**) was added and the mixture allowed to shake for 16 h at 200rpm at 20°C. 2 mol equivalents of Amberlite, IRA 400, borohydride exchange resin (2.5g $mmol^{-1}$) was added and the mixture allowed to shake for a further 6 h. The mixture was filtered and the resin washed with methanol. The solvent was removed under reduced pressure and the product purified using silica gel chromatography eluting with dichloromethane: methanol: triethylamine (80:20:1) to give the product *amine*. Yield: 1.498g (64%).

Method 2: [(*N,N*-dimethylamino)methyl]ferrocenecarboxaldehyde, **30**, was dissolved in anhydrous methanol in a round bottomed flask. 1 mol equivalent of the appropriate 7-chloroquinoline-4-alkyldiamine was then added and the mixture allowed to stir for 16 h at 20°C. Sodium borohydride (10 mol equivalents) was added and the mixture stirred for a further 6 h. Residual sodium borohydride was destroyed by the slow addition of deionised water. The product was extracted into dichloromethane and dried over sodium sulfate before removing the solvent under reduced pressure. The purification procedure used followed that detailed in method 1. Yield: 1.356g (61%).

Similar reaction procedures were used to make **21**, **22**, **23** and **24** from **34**, **35**, **36** and **37** respectively.

Compound 20



N-(7-Chloro-quinolin-4-yl)-*N'*-[2-(*N'',N''*-dimethylaminomethyl)ferrocenylmethyl]-ethane-1,2-diamine, F2Q

Bright orange crystalline solid; Yield: 5.067g (74%); mp: 118-120°C (from acetonitrile/diethyl ether);

R_f (silica/CH_2Cl_2: MeOH: Et_3N = 80:20:1) 0.27;

δ_H (400 MHz; $CDCl_3$) 8.50 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 7.93 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.73 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.33 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.27 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 4.14 (1H, m, Cp), 4.10 (1H, m, Cp), 4.04 (6H, m, Cp, 5Cp'), 3.83 (1H, d, $^2J_{HH}$ = 13, 3'a), 3.67 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.38 (1H, d, $^2J_{HH}$ = 13, 3'b), 3.48-3.40 (2H, m, 5'), 2.98-2.92 (2H, m, 4'), 2.79 (1H, d, $^2J_{HH}$ = 13, 2'b) and 1.95 (6H, s, 1');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 152.0 (ArC_2), 149.9 (^{IV}C), 149.2 (^{IV}C), 134.7 (^{IV}C), 128.6 (ArC_8), 125.0 (ArC_6), 121.5 (ArC_5), 117.4 (^{IV}C), 99.1 (ArC_3), 86.0 (^{IV}C, Cp), 83.8 (^{IV}C, Cp), 71.1 (Cp), 69.9 (Cp), 68.9 (5C, Cp'), 65.8 (Cp), 58.2 (2'), 47.3 (4'), 46.4 (3'), 45.0 (2C, 1') and 42.0 (5');

IR (KBr) ν_{max} 3314br w, (N-H), 3090s (N-H), 2970s, 2939s, 2853s, 2825s, 2780s, 1608m (7-chloroquinoline), 1579vs (7-chloroquinoline), 1538s (7-chloroquinoline), 1487m, 1471m, 1452s (NCH_3), 1434m (δ-as (NCH_3)), 1370m, 1354m, 1327m (ν C-N aromatic), 1287m, 1254m, 1211w, 1198w, 1172w, 1159w, 1140s, 1113w, 1103m (ferrocene), 1087m, 1076m, 1032m, 1008m (ferrocene), 970w, 954w, 872s, 854s, 845s (aryl $CH_2N(CH_3)_2$), 824s (ferrocene), 804s, 771m, 742w, 647m, 613m, 562m, 528w, 508m, 488m (ferrocene), 474m (ferrocene) and 429w;

HRMS (EI) *m/z* 476.14119 [M^+, $C_{25}H_{29}N_4{}^{35}ClFe$ requires 476.0891], 431.1 [M^+ - (NMe_2)], 366.0 [M^+ - (Cp + NMe_2)], 255.1 [HC-Fp-CH_2-NMe_2], 240.0 [Fp-CH_2-NMe_2], 213.0, 191.0 [ClC_9NH_5-NH-CH_2], 163.0 [ClC_9NH_5], 155.0 [C_9NH_5-NH-CH_2] 121.0 [Cp-Fe], 91.0 [CH_2-Cp-CH_2], 58.1 [CH_2-NMe_2] and 55.9 [Fe];

Found: C, 63.11; H, 5.97; N, 11.61. Calc. for $C_{25}H_{29}N_4ClFe$: C, 62.97; H, 6.130; N, 11.75%;

$E_{1/2}$ = not found, ferrocene redox: E_{pa} = 150 mV, E_{pc} = ± 30 mV; second redox: E_{pa} = ± 300 mV and E_{pc} = ± 250 mV;

Λ = 0.6 $\Omega^{-1}cm^2mol^{-1}$;

Crystal Data: $C_{25}H_{29}N_4ClFe$, M = 476.82, monoclinic, a = 10.7013(3), b = 16.2573(4), c = 13.7853(3) Å, β = 92.727(1)°, U = 2395.55 Å^3, T = 173(2) K, space group $P2_1/c$, Z = 4, μ = 0.760 mm^{-1}, 10265 reflections collected, 5429 unique (R_{int} = 0.0240), final R_1 = 0.0552 and wR_2 = 0.0843 (all data).

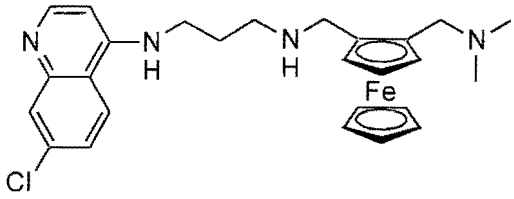
Tartrate salt of **20**

20 was dissolved in hot methanol. *L*-tartaric acid was dissolved in hot acetone and then added slowly to the solution of **20** forming a yellow precipitate. The precipitate was filtered and washed with hot acetone. The product was then dried *in vacuo*.

δ_H (300 MHz; D_2O) 8.16 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 7.92 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.65 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.42 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.62 (1H, d, $^3J_{HH}$ = 7, ArC_3-H), 4.28 (4H, m, tartaric acid), 4.21-4.15 (5H, m, 2'a, 2'b, Cp), 4.04 (5H, s, Cp'), 3.94 (1H, d, $^2J_{HH}$ = 13 Hz, 3'a), 3.74 (2H, m, 5'), 3.29 (3H, m, 3'b, 4'), 2.66 (3H, s, 1'a) and 2.50 (3H, s, 1'b);

$\delta_{C\{H\}}$ (75.5 MHz; D_2O) 177.1 (2C, tartaric acid, *C*OOH), 156.1 (^{IV}C), 142.7 (ArC_2), 139.5 (ArC_6), 138.0 (^{IV}C), 127.8 (ArC_8), 124.0 (^{IV}C), 119.2 (ArC_5), 115.4 (^{IV}C), 98.4 (ArC_3), 74.5 (Cp), 73.5 (Cp), 73.1 (2C, tartaric acid, *C*HOH), 71.0 (Cp), 70.3 (5C, Cp'), 57.2 (2'), 45.4 (4'), 44.8 (1'a), 43.5 (1'b), 40.8 (3') and 39.3 (5').

Compound 21



N-(7-Chloro-quinolin-4-yl)-*N'*-[2-(*N'',N''*-dimethylaminomethyl)ferrocenylmethyl]-propane-1,3-diamine, F3Q

Red glassy solid; Yield: 1.204g (61%);

mp: 108-110°C;

R_f (silica/CH_2Cl_2: MeOH: Et_3N = 80:20:1) 0.2;

δ_H (400 MHz; $CDCl_3$) 8.44 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 7.86 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.50 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.11 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.22 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.19-4.15 (2H, m, Cp), 4.12 (1H, t, $^3J_{HHH}$ = 2, Cp), 4.05 (5H, s, Cp), 3.79 (1H, d, $^2J_{HH}$ = 12, 2'a), 3.74 (1H, d, $^2J_{HH}$ = 12, 3'a), 3.42 (1H, d, $^2J_{HH}$ = 12, 3'b), 3.36-3.31 (2H, m, 6'), 2.99-2.92 (2H, m, 4'), 2.79 (1H, d, $^2J_{HH}$ = 12, 2'b), 2.11 (6H, s, 1') and 1.94-1.72 (2H, m, 5');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 152.1 (ArC_2), 150.7 (^{IV}C), 149.1 (^{IV}C), 134.4 (^{IV}C), 128.2 (ArC_8), 124.8 (ArC_6), 122.9 (ArC_5), 117.7 (^{IV}C), 97.9 (ArC_3), 85.9 (^{IV}C, Cp), 84.1 (^{IV}C, Cp), 71.2 (Cp), 70.3 (Cp), 68.0 (5C, Cp'), 65.8 (Cp), 58.3 (2'), 49.3 (4'), 48.3 (3'), 44.9 (2C, 1'), 44.3 (6') and 26.9 (5');

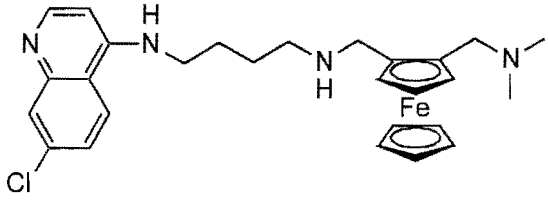
IR (KBr) ν_{max} 3249br w (NH), 2970s, 2940s, 2850s, 2816s, 2766s, 1610s (7-chloroquinoline), 1586vs (7-chloroquinoline), 1544s (7-chloroquinoline), 1491m, 1457s (NCH_3), 1439s, 1386m, 1367s, 1329m (ν C-N aromatic), 1285m, 1253m, 1236w, 1203m, 1174m, 1156w, 1138m, 1104m (ferrocene), 1079m, 1034w, 1016m, 999m (ferrocene), 954w, 908m, 878m, 856s (aryl $CH_2N(CH_3)_2$), 819m (ferrocene), 809m, 798m, 768m, 646m, 613m, 598w, 558w, 528w, 489m (ferrocene), 458w, 438w and 426w;

HRMS (EI) *m/z* 490.15824 [M^+, $C_{26}H_{31}N_4{}^{35}ClFe$ requires 490.11590], 445.1 [M^+ - ($HNMe_2$)], 380.0 [M^+ - (Cp + NMe_2)], 255.1 [HC-Fp-CH_2-NMe_2], 241.1, 227.0 [Fp-CH_2-NMe], 213.0, 191.0 [ClC_9NH_5-NH-CH_2], 154.0 [C_9NH_5-NH-CH_2], 134.0 [Fe-Cp-CH_2], 121.0 [CpFe], 91.0 [CH_2-Cp-CH_2], 58.1 [CH_2-NMe_2] and 55.9 [Fe];

$E_{1/2}$ = not found; ferrocene redox: E_{pa} = ± 120 mV, E_{pc} = 13 mV; second redox: E_{pa} = 318 mV and E_{pc} = 210 mV;

Found: C, 63.89; H, 6.39; N, 11.15. Calc. for $C_{26}H_{31}N_4ClFe$: C, 63.62; H, 6.365; N, 11.41%.

Compound 22



N-(7-Chloro-quinolin-4-yl)-*N'*-[2-(*N'',N''*-dimethyl-aminomethyl)ferrocenylmethyl]-butane-1,4-diamine, F4Q

Red glassy solid; Yield: 1.337g (65%);

mp: 103-104°C;

R_f (silica/CH_2Cl_2: MeOH: Et_3N = 80:20:1) 0.17;

δ_H (400 MHz; $CDCl_3$) 8.44 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.14 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.88 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.31 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.29 (1H, d, $^3J_{HH}$ = 6, ArC_3-H),

4.20-4.07 (3H, m, Cp), 4.06 (5H, s, Cp), 3.77 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.53 (1H, d, $^2J_{HH}$ = 13, 3'a), 3.33-3.29 (3H, m, 3'b, 7'), 2.83 (1H, d, $^2J_{HH}$ = 13, 2'b), 2.69-2.66 (2H, m, 4'), 2.10 (6H, s, 1'), 1.85-1.80 (2H, m, 5' or 6') and 1.75-1.70 (2H, m, 5' or 6');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 151.8 (ArC_2), 150.4 (^{IV}C), 149.2 (^{IV}C), 134.7 (^{IV}C), 128.2 (ArC_8), 125.0 (ArC_6), 123.0 (ArC_5), 117.7 (^{IV}C), 98.5 (^{IV}C), 83.7 (^{IV}C), 71.6 (Cp), 71.0 (Cp), 69.4 (5C, Cp'), 66.6 (Cp), 57.9 (2'), 47.0 (4'), 46.0 (3'), 44.4 (2C, 1'), 42.3 (7'), 25.4 (5' or 6') and 25.3 (5' or 6');

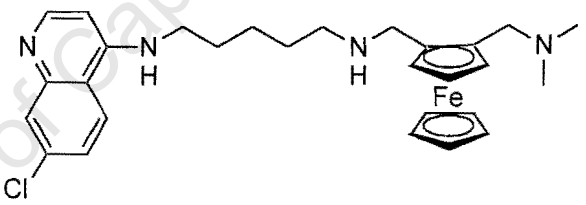
IR (KBr) ν_{max} 3285br s, 3087s, 2939s, 2857s, 2819s, 2774s, 2362m, 1653m, 1610m (7-chloroquinoline), 1581vs (7-chloroquinoline), 1540m (7-chloroquinoline), 1451m (NCH_3), 1367m, 1331m, 1282m, 1252m, 1170w, 1137m, 1105m (ferrocene), 1080w, 1033w, 1000m (ferrocene), 877w, 851m (aryl $CH_2N(CH_3)$), 809m (ferrocene), 768w, 645w and 489w (ferrocene);

HRMS (EI) *m/z* 504.1746 [M^+, $C_{27}H_{33}N_4{}^{35}ClFe$ requires 504.1427], 460.1 [M^+ - ($HNMe_2$)], 394.1 [M^+ - (Cp + NMe_2)], 255.1 [HC-Fp-CH_2-NMe_2], 240.0, 213.0, 134.0 [Fe-Cp-CH_2], 121.0 [CpFe], 91.0 [CH_2-Cp-CH_2], 58.1 [CH_2-NMe_2] and 55.9 [Fe];

$E_{1/2}$ = not found; ferrocene redox: E_{pa} = 106 mV, E_{pc} = 14 mV; second redox: E_{pa} = 328 mV, E_{pc} = 220 mV.

Compound 23

N-(7-Chloro-quinolin-4-yl)-*N'*-[2-(*N'',N''*-dimethyl-aminomethyl)ferrocenylmethyl]-pentane-1,5-diamine



Red glassy solid; Yield: 541mg (60%);

mp: 74-75°C;

R_f (silica/CH_2Cl_2: MeOH: Et_3N = 80:20:1) 0.1;

δ_H (400 MHz, $CDCl_3$) 8.50 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 7.93 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.76 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.32 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.37 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 4.16-4.15 (1H, m, Cp), 4.10-4.09 (1H, m, Cp), 4.03 (5H, s, Cp), 3.80 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.67 (1H, d, $^2J_{HH}$ = 13, 3'a), 3.38 (1H, d, $^2J_{HH}$ = 13, 2'b), 3.32 (2H, m, 8'), 2.82 (1H, d, $^2J_{HH}$ = 13, 3'b), 2.67-2.65 (2H, m, 4'), 2.10 (6H, s, 1') and 1.78-1.40 (6H, m, 5', 6', 7');

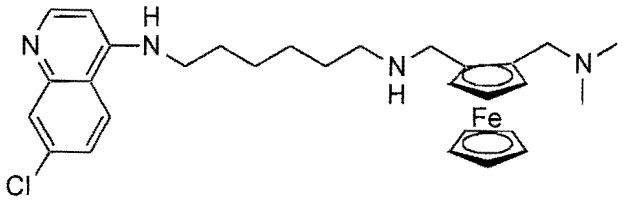
$\delta_{C\{H\}}$ (100.6 MHz, $CDCl_3$) 151.9 (ArC_2), 150.0 (^{IV}C), 149.1 (^{IV}C), 134.7 (^{IV}C), 128.5 (ArC_8), 125.0 (ArC_6), 121.7 (ArC_5), 117.3 (^{IV}C), 98.8 (^{IV}C), 84.9 (^{IV}C, Cp), 83.6 (^{IV}C, Cp), 71.1 (Cp), 70.1 (Cp), 69.0 (5C, Cp'), 66.1 (Cp), 57.9 (2'), 48.1 (4'), 47.7 (3'), 44.8 (2C, 1'), 42.9 (8'), 28.9 (5' or 7'), 28.1 (5' or 7') and 24.4 (6');

IR (KBr) ν_{max} 3244br s, 3092m, 2939m, 2856m, 2819m, 2772m, 1610m (7-chloroquinoline), 1580vs (7-chloroquinoline), 1534m (7-chloroquinoline), 1457m (NCH_3), 1367m, 1352m, 1329m, 1283w, 1255w, 1201w, 1174w, 1136m, 1104m (ferrocene), 1082w, 1001w (ferrocene), 880w, 855m (aryl $CH_2N(CH_3)$), 805m (ferrocene), 770w, 649w, 598w, 533w, 487w, 458w and 426w;

HRMS (EI) *m/z* 518.1886 [M^+, $C_{28}H_{35}N_4{}^{35}ClFe$ requires 518.1655], 473.1 [M^+ - ($HNMe_2$)], 408.1 [M^+ - (Cp + NMe_2)], 255.1 [HC-Fp-CH_2-NMe_2], 240.0, 213.0, 134.0 [Fe-Cp-CH_2], 121.0 [CpFe], 91.0 [CH_2-Cp-CH_2], 58.1 [CH_2-NMe_2] and 55.9 [Fe];

$E_{1/2}$ = not found; ferrocene redox: E_{pa} = 92 mV, E_{pc} = 12 mV, second redox: E_{pa} = 332 mV and E_{pc} = 210 mV.

Compound 24



N-(7-Chloro-quinolin-4-yl)-*N'*-[2-(*N'',N''*-dimethyl-aminomethyl)ferrocenylmethyl]-hexane-1,6-diamine, F6Q

Red glassy solid; Yield: 1.729g (60%);

mp: 92-95°C;

R_f (silica/CH_2Cl_2: MeOH: Et_3N = 80:20:1) 0.07;

δ_H (400 MHz; $CDCl_3$) 8.46 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.16 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.90 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.24 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.34 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.28-4.15 (3H, m, Cp), 4.09 (5H, s, Cp), 3.81 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.53 (1H, d, $^2J_{HH}$ = 13, 3'a), 3.55-3.50 (2H, m, 9'), 3.33 (1H, d, $^2J_{HH}$ = 13, 3'b), 2.86 (1H, d, $^2J_{HH}$ = 13, 2'b), 2.64 (2H, m, 4'), 2.14 (6H, s, 1'), 1.76-1.73 (2H, m, 5' or 8'), 1.60-1.54 (2H, m, 5' or 8') and 1.45-1.38 (4H, m, 6' and 7');

$\delta_{C\{H\}}$ (100.6 MHz, $CDCl_3$) 151.8 (ArC_2), 150.3 (^{IV}C), 149.2 (^{IV}C), 134.7 (^{IV}C), 128.3 (ArC_8), 125.0 (ArC_6), 122.6 (ArC_5), 117.5 (^{IV}C), 98.7 (ArC_3), 83.8 (^{IV}C), 71.6 (Cp), 71.2 (Cp), 69.5 (5C, Cp'), 66.8 (Cp), 57.8 (2'), 46.7 (4'), 45.5 (3'), 44.3 (2C, 1'), 42.5 (9'), 27.9 (5' – 8')*, 27.0 (5' – 8'), 26.2 (5' – 8') and 25.9 (5' – 8');

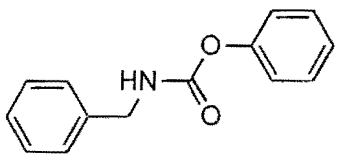
IR (KBr) ν_{max} 3300br m (NH), 3084m, 2934m, 2857m, 1610s (7-chloroquinoline), 1580vs (7-chloroquinoline), 1540s (7-chloroquinoline), 1453s (NCH_3), 1425m, 1367s, 1331m (ν C-N aromatic), 1282m, 1250m, 1205w, 1175w, 1137m, 1105m (ferrocene), 1080w, 1033w, 1000m (ferrocene), 900w, 877w, 850m (aryl $CH_2N(CH_3)$), 810s (ferrocene), 769w, 726w, 646w, 600w, 547w, 489m (ferrocene) and 424w;

HRMS (EI) *m/z* 532.20585 [M^+, $C_{29}H_{37}N_4{}^{35}ClFe$ requires 532.20561], 515.2, 487.1 [M^+ - ($HNMe_2$)], 422.1 [M^+ - (Cp + NMe_2)], 255.1 [HC-Fp-CH_2-NMe_2], 240.0, 213.0, 121.0, [CpFe], 91.0 [CH_2-Cp-CH_2], 58.1 [CH_2-NMe_2] and 55.9 [Fe];

$E_{1/2}$ = not found; ferrocene redox: E_{pa} = indistinct, E_{pc} = 12 mV, second redox: E_{pa} = 330 mV, E_{pc} = 210 mV.

Experimental Details Pertaining to Chapter 3

Compound 52



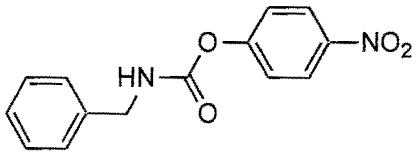
Phenylbenzylcarbamate

Anhydrous DMF (0.77ml, 10mmol) was placed in a centrifuge tube fitted with nitrogen inlet and dropping funnel, followed by anhydrous dichloromethane (10ml). The mixture was cooled to

* (5' – 8') indicates that these proton or carbon signals could be the 5', 6', 7' or 8' signals.

0°C and allowed to stir for 10 min. Phenylchloroformate **50** (1.26ml, 10mmol) was added dropwise and the mixture allowed to stir for 40 min. Benzylamine **49** (1.2ml, 11mmol) was then added dropwise and the mixture allowed to stir for 4 h. The mixture was allowed to warm to room temperature before removing the solvent under reduced pressure. The product was used without further purification. (TLC checked; 20:80; ethyl acetate: hexane).

Compound 53

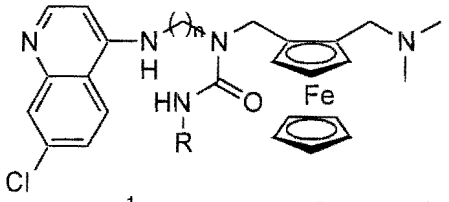


Nitrophenylbenzylcarbamate

Nitrophenylchloroformate **51**, (2.016g, 10mmol) was placed in a 2-necked 100ml round bottomed flask fitted with nitrogen inlet and dropping funnel, followed by anhydrous acetonitrile (10ml). Benzylamine **49** (1.09ml, 10mmol) and anhydrous triethylamine (1.40ml, 10mmol) were mixed and placed in a pressure-compensated dropping funnel followed by anhydrous acetonitrile (10ml). The mixture was added dropwise to the reaction vessel. A white suspension (ammonium salt) formed immediately. The mixture was allowed to stir at 25°C for 30 min, after which time a bright yellow precipitate had formed. Dichloromethane (30ml) was added followed by deionised water (30ml). The mixture was extracted into dichloromethane and dried over magnesium sulfate. The organic extract was then filtered and the residual magnesium sulfate washed with dichloromethane. The solvent was removed under reduced pressure leaving a yellow solid. The product was used without further purification. (TLC checked: ethyl acetate: hexane; 20:80).

Synthesis of Urea Compounds

Method 1:



20 was dissolved in anhydrous dichloromethane in a small sample vial. 1.2 mol equivalents of the required isocyanate was added and the sample vial was placed on a shaker at 200 rpm for 2 h at 25°C. 1 mol equivalent of aminomethylpolystyrene (polymer loading: 1.1g mol^{-1}) was added, followed by anhydrous dichloromethane and the mixture allowed to shake for a further hour. The mixture was then filtered and washed with 10% methanol in dichloromethane. The product was then purified by silica gel chromatography eluting with 10% methanol in dichloromethane. The product was isolated as a yellow crystalline solid. Yield: 143mg (75%).

Method 2:

As for method 1, but use of aminomethylpolystyrene omitted. The reaction mixture was placed directly onto the column. Yield: 452mg (90%).

Method 3:

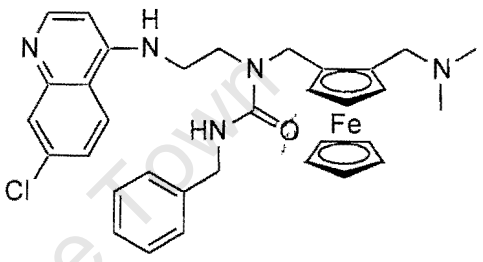
Phenylbenzylcarbamate **52** was placed in a 50ml round bottomed flask. Anhydrous THF was added followed by 0.9 mol equivalents of **20**. The mixture was allowed to stir at 50°C for 16 h. The reaction progress was monitored by TLC (20% methanol in dichloromethane). Only a small amount of product was observed so the reaction was allowed to heat under reflux for a further

24 h. The solvent was then removed under reduced pressure and the mixture purified by silica gel chromatography (20% methanol in dichloromethane) without further workup. Yield: 58mg (35%).

Method 4:

Nitrophenylbenzylcarbamate **53** and 1 mol equivalent of **20** were placed in a 100ml round bottomed flask and anhydrous THF was added. The mixture was heated to 50°C and the reaction allowed to proceed for 16 h before allowing to cool to room temperature. The solvent was then removed under reduced pressure and the product purified using silica gel chromatography as described in previous methods. Yield: 531mg (83%).

Compound 37



3-Benzyl-1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethylaminomethyl)-ferrocenylmethyl]urea

Yellow crystalline solid; Yield: 345mg (90%);

mp: 95-96°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.51;

δ_H (400 MHz; $CDCl_3$) 8.45 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.12 (1H, t, $^3J_{HH}$ = 6, $ArCH_2NHCO$), 7.96 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.75 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.15 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 7.13-7.07 (5H, m, U_2, U_3, U_4), 6.32 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.24-4.16 (7H, m, Cp, 1'', 3'a, 3b'), 4.08 (5H, s, Cp'), 3.82 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.73-3.68 (2H, m, 4'), 3.58-3.40 (2H, m, 5'), 2.82 (1H, d, $^2J_{HH}$ = 13, 2'b) and 1.98 (6H, s, 1'');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 160.4 (^{IV}C, CO), 151.7 (^{IV}C), 149.7 (ArC_2), 146.7 (^{IV}C), 140.2 (^{IV}C), 135.7 (^{IV}C), 128.2 (2C, U), 126.6 (ArC_6), 126.5 (2C, U), 126.2 (U_4), 125.7 (ArC_5), 123.1 (ArC_8), 116.9 (^{IV}C), 97.5 (ArC_3), 83.9 (^{IV}C, Cp), 70.6 (Cp), 69.5 (5C, Cp'), 69.0 (Cp), 67.7 (Cp), 57.8 (2'), 47.0 (3'), 45.6 (4'), 44.6 (1''), 44.4 (2C, 1') and 43.7 (5');

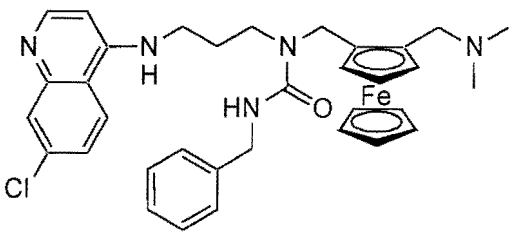
IR (KBr) ν_{max} 3268br w (NH), 3061m, 3027m, 2940m, 2858m, 2821m, 2777m, 1611s (7-chloroquinoline), 1582vs (7-chloroquinoline), 1539s (7-chloroquinoline), 1452m (NCH_3), 1430m, 1405m, 1365m, 1332m (ν C-N aromatic), 1302m, 1270m, 1241m, 1205m, 1170m, 1135m, 1105m (ferrocene), 1079m, 1038m, 1005m (ferrocene), 960w, 917w, 874m, 842m (aryl $CH_2N(CH_3)$), 808m (ferrocene), 768m, 731m, 698m, 608w, 526m, 487m (ferrocene), 454w and 424w;

HRMS (FAB) *m/z* 610.2030 [M^+ + H, $C_{33}H_{36}N_5ClOFe$ + H requires 610.2034], 565.1 [M^+ - ($HNMe_2$)], 432.2 [M^+ - ($HNMe_2$ + $C_6H_5CH_2NHCO$)], 409.1 [M^+ - (Cp + $C_6H_5CH_2NHCO$)], 304.0, 255.1 [HC-Fp-CH_2-NMe_2], 213.1, 191.0 [ClC_9NH_5-NH-CH_2], 154.0 [C_9NH_5-NH-CH_2], 134.1 [Fe-Cp-CH_2] and 91.1 [CH_2-Cp-CH_2];

$E_{1/2}$ = 157 mV; ferrocene redox: E_{pa} = 198 mV, E_{pc} = 115 mV; second redox: barely noticeable;

Found: C, 65.01; H, 5.83; N, 11.50. Calc. for $C_{23}H_{24}N_3ClFe$: C, 64.98; H, 5.95; N, 11.48%.

Compound 38



3-Benzyl-1-[3-(7-chloro-quinolin-4-ylamino)-propyl]-1-[2-(*N'',N''*-dimethylaminomethyl)-ferrocenylmethyl]urea

Yellow crystalline solid; Yield: 33mg (34%);

mp: 88-89°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.46;

δ_H (400 MHz; $CDCl_3$) 8.47 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.05 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.95 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.30 (1H, dd, $^3J_{HH}$ = 2 and $^4J_{HH}$ = 9 Hz, ArC_6-H), 7.25-7.13 (5H, m, U_2, U_3, U_4), 6.39 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.48 (1H, m, Cp), 4.39-4.38 (1H, m, Cp), 4.33 (1H, d, $^2J_{HH}$ = 16, 3'a), 4.26-4.21 (1H, m, Cp), 4.22 (1H, d, $^2J_{HH}$ = 16, 3'b), 4.14 (1H, t, $^3J_{HHH}$ = 3, Cp), 4.03 (5H, s, Cp'), 4.07 (2H, m, 1''), 3.91-3.82 (1H, m, 4'), 3.80 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.48-3.43 (2H, m, 6'), 3.36-3.27 (2H, m, 4'), 2.77 (1H, d, $^2J_{HH}$ = 13, 2'b), 1.97 (6H, s, 1') and 1.91-1.85 (2H, m, 5');

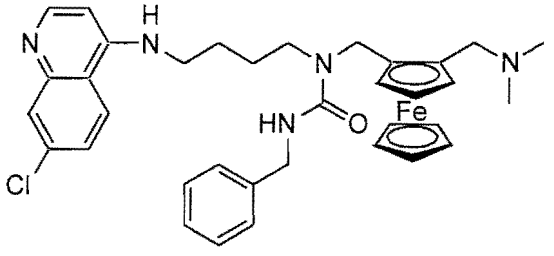
$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 159.1 (^{IV}C, CO), 151.2 (^{IV}C), 150.7 (ArC_2), 140.7 (^{IV}C), 135.8 (^{IV}C), 128.2 (2C, U), 127.2 (ArC_6), 126.7 (2C, U), 126.6 (U_4), 125.4 (ArC_5), 122.9 (ArC_8), 117.6 (^{IV}C), 97.8 (ArC_3), 84.3 (^{IV}C, Cp), 70.4 (Cp), 69.5 (5C, Cp'), 69.0 (Cp), 67.4 (Cp), 58.0 (2'), 45.4 (3'), 45.2 (4' or 6'), 44.7 (4' or 6'), 44.6 (2C, 1'), 39.4 (1'') and 26.7 (5');

IR (KBr) ν_{max} 3437br s (NH), 3322br s (NH), 3087m, 3027m, 2936m, 2857m, 2820m, 2761m, 1611s (7-chloroquinoline), 1578vs (7-chloroquinoline), 1538s (7-chloroquinoline), 1494w, 1455m (NCH_3), 1428w, 1369m, 1331w, 1272m, 1242w, 1169w, 1139w, 1106w (ferrocene), 1078w, 1037w, 1005w (ferrocene), 903w, 878w, 850m (aryl $CH_2N(CH_3)$), 809m (ferrocene), 770w, 731w, 702m, 647w, 625w, 604w, 530w, 511w and 487w;

HRMS (FAB) *m/z* 624.1890 [M^+ + H, $C_{34}H_{38}N_5ClOFe$ + H requires 624.1908], 579.1 [M^+ - ($HNMe_2$)], 446.1 [M^+ - ($HNMe_2$ + $C_6H_5CH_2NHCO$)], 423.1 [M^+ - (Cp + $C_6H_5CH_2NHCO$)], 318.0, 255.1 [HC-Fp-CH_2-NMe_2], 213.1, 191.0 [ClC_9NH_5-NH-CH_2], 154.0 [C_9NH_5-NH-CH_2], 134.1 [Fe-Cp-CH_2] and 91.1 [CH_2-Cp-CH_2];

$E_{1/2}$ = 131 mV; ferrocene redox: E_{pa} = 171 mV, E_{pc} = 91 mV; second redox: E_{pa} = ± 300 mV and E_{pc} = 240 mV.

Compound 39



3-Benzyl-1-[4-(7-chloro-quinolin-4-ylamino)-butyl]-1-[2-(*N'',N''*-dimethylaminomethyl)-ferrocenylmethyl]urea

Yellow crystalline solid; Yield: 75mg (58%);

mp: 84-86°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.4;

δ_H (400 MHz; $CDCl_3$) 8.47 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 8.07 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.91 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.38-7.09 (6H, m, ArC_6-H, U_2, U_3, U_4), 6.35 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.42-4.09 (5H, m, 3Cp, 3'a, 3'b), 4.06 (5H, s, Cp'), 4.05-4.04 (2H, m, 1''), 3.79 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.43 (4H, m, 4', 7'), 2.77 (1H, d, $^2J_{HH}$ = 13, 2'b), 1.96 (6H, s, 1') and 1.79-1.65 (4H, m, 5', 6');

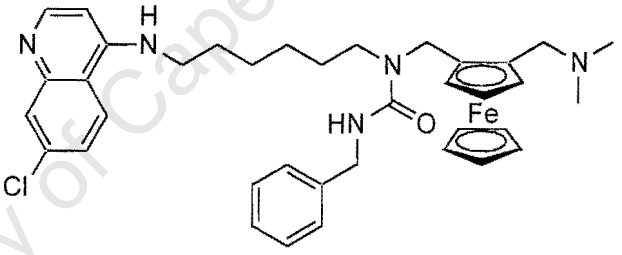
$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 158.7 (^{IV}C, *C*O), 151.3 (^{IV}C), 150.8 (ArC_2), 144.2 (^{IV}C), 140.8 (^{IV}C), 134.9 (^{IV}C), 128.2 (2C, U), 127.8 (U_4), 126.6 (2C, U), 126.5 (ArC_6), 125.1 (ArC_5), 122.9 (ArC_8), 117.6 (^{IV}C), 98.5 (ArC_3), 84.6 (^{IV}C), 70.3 (Cp), 69.4 (5C, Cp'), 69.2 (Cp), 67.3 (Cp), 57.9 (2'), 47.8 (3'), 45.2 (4'), 44.7 (2C, 1'), 44.5 (7'), 43.1 (1''), 26.7 (5' or 6') and 24.3 (5' or 6');

IR (KBr) ν_{max} 3437br s (NH), 3322br s (NH), 3087m, 3027m, 2936m, 2857m, 2820m, 2761m, 1611s (7-chloroquinoline), 1578vs (7-chloroquinoline), 1538s (7-chloroquinoline), 1494w, 1455m (NCH_3), 1428w, 1369m, 1331w, 1272m, 1242w, 1169w, 1139w, 1106w (ferrocene), 1078w, 1037w, 1005w (ferrocene), 903w, 878w, 850m (aryl $CH_2N(CH_3)$), 809m (ferrocene), 770w, 731w, 702m, 647w, 625w, 604w, 530w, 511w and 487w;

HRMS (FAB) *m/z* 638.2333 [M^+ + H, $C_{35}H_{40}N_5ClOFe$ + H requires 638.2347], 593.0 [M^+ - ($HNMe_2$)], 505.2 [M^+ - ($C_6H_5CH_2NHCO$)], 460.0 [M^+ - ($HNMe_2$ + $C_6H_5CH_2NHCO$)], 437.0 [M^+ - (Cp + C_6H_5NHCO)], 255.1 [HC-Fp-CH_2-NMe_2], 213.0, 191.0 [ClC_9NH_5-NH-CH_2], 154.0 [C_9NH_5-NH-CH_2], 134.1[Fe-Cp-CH_2] and 91.1 [CH_2-Cp-CH_2];

$E_{1/2}$ = 116 mV; ferrocene redox: E_{pa} = 149 mV, E_{pc} = 82 mV; second redox: E_{pa} = 303 mV and E_{pc} = 240 mV.

Compound 40



3-Benzyl-1-[6-(7-chloro-quinolin-4-ylamino)-hexyl]-1-[2-(*N'',N''*-dimethylaminomethyl)-ferrocenylmethyl]urea

Yellow crystalline solid; Yield: 78mg (57%); mp: 85-87°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.46;

δ_H (400 MHz; $CDCl_3$) 8.39 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.14 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 8.02 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.16-7.12 (5H, m, U_2, U_3, U_4), 7.04 (1H, d, $^3J_{HH}$ = 9, ArC_6-H), 6.32 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.41-4.17 (4H, m, 2Cp, 3'a, 3'b), 4.16 (1H, t, $^3J_{HHH}$ = 3, Cp), 4.09 (5H, s, Cp'), 4.08-4.07 (2H, m, 1''), 3.77 (1H, m, 2'a), 3.31-3.21 (2H, m, 4'), 3.19 (2H, m, 9'), 2.89 (1H, d, $^2J_{HH}$ = 13, 2'b), 2.05 (6H, s, 1') and 1.74-1.33 (8H, m, 5', 6', 7', 8');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 158.5 (^{IV}C, *C*O), 151.9 (^{IV}C), 149.1 (ArC_2), 140.7 (^{IV}C), 135.6 (^{IV}C), 128.2 (2C, U), 126.5 (2C, U), 126.5 (U_4), 125.6 (ArC_5), 123.0 (ArC_8), 117.1 (^{IV}C), 98.0 (ArC_3), 84.7 (^{IV}C, Cp), 70.4 (Cp), 69.5 (5C, Cp'), 69.4 (Cp), 67.5 (Cp), 57.8 (2'), 46.6 (3'), 44.6 (2C, 1'), 44.3 (4'), 41.6 (9'), 27.7 (5' – 8')*, 27.6 (5' – 8'), 25.0 (5' – 8') and 24.6 (5' – 8');

IR (KBr) ν_{max} 3306br s (NH), 3095m, 3027m, 2931s, 2859m, 2822m, 2780m, 1612s (7-chloroquinoline), 1582vs (7-chloroquinoline), 1540s (7-chloroquinoline), 1492w, 1457m (NCH_3), 1425w, 1407w, 1367m, 1333w, 1281m, 1266m, 1209w, 1171w, 1135w, 1106w (ferrocene), 1076w, 1036w, 1005w (ferrocene), 933w, 903w, 879w, 852m (aryl $CH_2N(CH_3)$), 813m (ferrocene), 770w, 734w, 701m, 606w, 530w, 512w, 490m (ferrocene), 453w and 437w;

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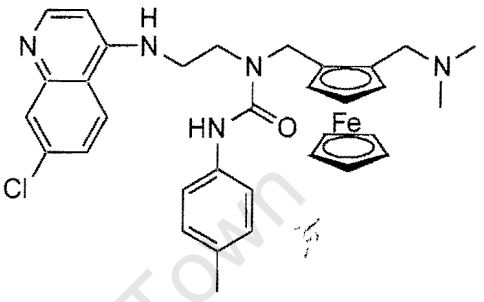
* As for **24**, 5' – 8' indicates that signals could correspond to 5', 6', 7' or 8' carbon atoms

HRMS (FAB) *m/z* 666.2648 [M^+ + H, $C_{37}H_{44}N_5ClOFe$ + H requires 666.2660], 621.1 [M^+ - ($HNMe_2$)], 547.4, 502.2 [M^+ - (HNMe + $C_6H_5CH_2NHCO$)], 488.0 [M^+ - ($HNMe_2$ + $C_6H_5CH_2NHCO$)], 465.0 [M^+ - (Cp + $C_6H_5CH_2NHCO$)], 422.1, 360.0 [C_9NH_5-NH-$(CH_2)_4$-N-CH_2-C_5H_3-CH_2NMe], 304.0, 255.1 [HC-Fp-CH_2-NMe_2], 213.1, 191.0 [ClC_9NH_5-NH-CH_2], 154.0 [C_9NH_5-NH-CH_2], 134.1 [Fe-Cp-CH_2] and 91.1 [CH_2-Cp-CH_2];

$E_{1/2}$ = 123 mV; ferrocene redox: E_{pa} = 164 mV, E_{pc} = 81 mV, second redox: E_{pa} = 317 mV and E_{pc} = 260 mV.

Compound 41



1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethylaminomethyl)-ferrocenylmethyl]-3-*p*-tolyl-urea

Yellow crystalline solid; Yield: 145mg (75%);

mp: 81-84°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.51;

δ_H (400 MHz; $CDCl_3$) 8.51 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 7.91 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.69 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.15-7.08 (5H, m, U_2, U_3, ArC_6-H), 6.31 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.43 (1H, d, $^2J_{HH}$ = 16, 3'a), 4.40-4.39 (1H, m, Cp), 4.36-4.34 (1H, m, Cp), 4.28 (1H, d, $^2J_{HH}$ = 16, 3'b), 4.15 (1H, t, $^3J_{HHH}$ = 3, Cp), 4.10 (5H, s, Cp'), 3.80 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.71-3.68 (2H, m, 5'), 3.55-3.40 (2H, m, 4'), 2.77 (1H, d, $^2J_{HH}$ = 13, 2'b) and 1.98 (9H, s, 1', $ArCH_3$);

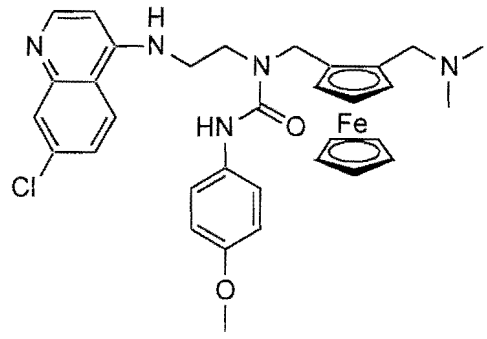
$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 160.5 (^{IV}C, *C*O), 151.5 (^{IV}C), 150.8 (ArC_2), 140.3 (^{IV}C), 134.9 (^{IV}C), 128.3 (2C, U), 127.7 (^{IV}C), 126.6 (ArC_6) 126.5 (2C, U), 125.3 (ArC_5), 122.7 (ArC_8), 117.3 (^{IV}C), 97.6 (ArC_3), 85.0 (^{IV}C, Cp), 82.1 (^{IV}C, Cp), 70.5 (Cp), 69.5 (5C, Cp'), 68.9 (Cp), 67.6 (Cp), 57.9 (2'), 47.2 (3'), 45.6 (4'), 44.7 (2C, 1'), 44.7 (3') and 43.7 (5');

IR (KBr) ν_{max} 3266br m (NH), 3061m, 3027m, 2827m, 2940m, 2821m, 2777m, 1610s (7-chloroquinoline), 1582vs (7-chloroquinoline), 1537s (7-chloroquinoline), 1452m (NCH_3), 1430m, 1404w, 1365m, 1332m (ν C-N aromatic), 1302m, 1270s, 1241s, 1204m, 1170m, 1135m, 1105m (ferrocene), 1079m, 1029m, 1005s (ferrocene), 960w, 917w, 873m, 841m (aryl $CH_2N(CH_3)$), 808s (ferrocene), 768m, 730m, 698m, 644w, 608w, 526m, 488m (ferrocene), 456w and 426w;

HRMS (FAB) *m/z* 610.2025 [M^+ + H, $C_{33}H_{36}N_5ClFeO$ + H requires 610.2034], 565.1 [M^+ - ($HNMe_2$)], 432.1 [M^+ - ($HNMe_2$ + $CH_3C_6H_4NHCO$)], 409.0 [M^+ - (Cp + $CH_3C_6H_4CH_2NHCO$)], 304.0 [C_9NH_5-NH-$(CH_2)_2$-N-CH_2-C_5H_3-CH_2NMe], 255.1 [HC-Fp-CH_2-NMe_2], 213.1, 134.1 [Fe-Cp-CH_2] and 91.0 [CH_2-Cp-CH_2 or $C_6H_4CH_3$];

$E_{1/2}$ = 155 mV; ferrocene redox: E_{pa} = 195 mV, E_{pc} = 115 mV; second redox: not observed.

Compound 42



1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethylaminomethyl)-ferrocenylmethyl]-3-*p*-methoxyphenyl-urea

Yellow crystalline solid; Yield: 101mg (51%);

mp: 99-100°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.49;

δ_H (400 MHz; $CDCl_3$) 8.53 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 7.94 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.81 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.29 (1H, dd, $^4J_{HH}$ = 2 Hz and $^3J_{HH}$ = 9 Hz, ArC_6-H), 6.99 (2H, d, $^3J_{HH}$ = 9, U), 6.84 (2H, d, $^3J_{HH}$ = 9, U), 6.31 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 4.48 (1H, d, $^2J_{HH}$ = 16, 3'a), 4.43 (1H, m, Cp), 4.34 (1H, d, $^2J_{HH}$ = 16, 3'b), 4.17 (1H, t, $^3J_{HH}$ = 2, Cp), 4.13-4.12 (1H, m, Cp), 4.11 (5H, s, Cp'), 3.87 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.81 (3H, s, OCH_3), 3.71-3.67 (2H, m, 5'), 3.60-3.40 (2H, m, 4'), 2.82 (1H, d, $^2J_{HH}$ = 13, 2'b) and 2.05 (6H, s, 1');

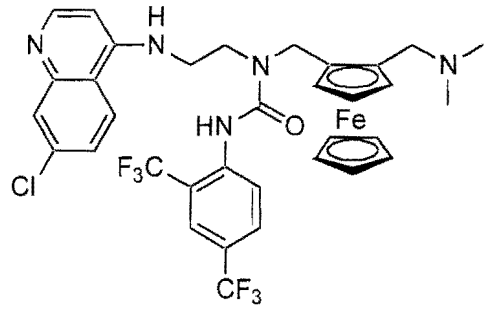
$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 159.8 (^{IV}C, *CO*), 157.1 (^{IV}C, U_4), 151.5 (ArC_2), 150.8 (^{IV}C), 132.2 (^{IV}C), 127.8 (^{IV}C), 126.8 (2C, U_2), 125.3 (ArC_5), 122.9 (ArC_8), 117.4 (^{IV}C), 113.9 (2C, U_3), 98.0 (ArC_3), 83.8 (^{IV}C, Cp), 82.1 (^{IV}C, Cp), 70.7 (Cp), 69.5 (5C, Cp'), 69.0 (Cp), 67.6 (Cp), 58.0 (2'), 55.5 (OCH_3), 46.7 (4'), 45.7 (3'), 45.0 (2C, 1') and 43.4 (5');

IR (KBr) ν_{max} 3284br m (NH), 3087m, 2950m, 2858m, 2823m, 2780m, 1636m (ν C=O), 1610m (7-chloroquinoline), 1583vs (7-chloroquinoline), 1510vs (OCH_3), 1481m, 1458m (NCH_3), 1416m, 1391m, 1365m, 1332m (ν C-N aromatic), 1295m, 1277m, 1232s (ν-as R-O-R'), 1169m, 1149m, 1136m, 1105m (ferrocene), 1089w, 1075w, 1032m (ν-s R-O-R'), 1006m (ferrocene), 916w, 875m, 824s (ferrocene), 767w, 736w, 645w, 576w, 524m, 492m (ferrocene), 456w and 436w;

HRMS (FAB) *m/z* 626.1995 [M^+ + H, $C_{33}H_{36}N_5ClFeO_2$ + H requires 626.1983], 581.1 [M^+ - ($HNMe_2$)], 530.9, 477.0 [M^+ - ($CH_3OC_6H_3NHCO$)], 432.0 [M^+ - ($HNMe_2$ + $CH_3OC_6H_3NHCO$)], 365.9, 334.0, 270.1, 213.0, 191.0 [ClC_9NH_5-NH-CH_2], 134.1 [Fe-Cp-CH_2] and 91.0 [CH_2-Cp-CH_2];

$E_{1/2}$ = not found; ferrocene redox: E_{pa} = 170 mV, E_{pc} = ± 30 mV; second redox: E_{pa} = 342 mV and E_{pc} = 205 mV.

Compound 43



1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethylaminomethyl)-ferrocenylmethyl]-3-[2,4-bis-(trifluoromethyl)-phenyl]-urea

Yellow crystalline solid; Yield: 138mg (65%);

mp: 94-96°C;

R_f (silica/ CH_2Cl_2: MeOH = 80:20) 0.63;

δ_H (400 MHz; $CDCl_3$) 8.52 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 7.91 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.63 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.38 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 7.24-7.14 (3H, m, U_3, U_5, U_6), 6.33 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 4.52 (1H, d, $^2J_{HH}$ = 16, 3a'), 4.42-4.40 (1H, m, Cp), 4.34 (1H, d, $^2J_{HH}$ = 16, 3b'), 4.20 (1H, t, $^3J_{HHH}$ = 3, Cp), 4.14 (1H, m, Cp), 4.13 (5H, s, Cp'), 3.85 (1H, d, $^2J_{HH}$ = 13, 2a'), 3.76-3.70 (2H, m, 5'), 3.61-3.39 (2H, m, 4'), 2.80 (1H, d, $^2J_{HH}$ = 13, 2b') and 1.94 (6H, s, 1');

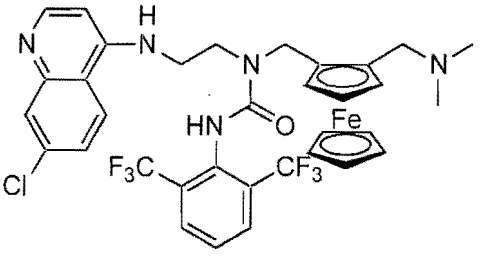
$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 159.8 (^{IV}C, CO), 151.6 (ArC_2), 150.6 (^{IV}C), 133.3 (U), 133.2 (U), 127.9 (ArC_6), 125.0 (U), 122.6 (ArC_8), 119.5 (^{IV}C), 117.3 (^{IV}C), 114.3 (^{IV}C, U_4), 114.0 (^{IV}C, U_2), 97.8 (ArC_3), 83.5 (^{IV}C, Cp), 82.0 (^{IV}C, Cp), 71.0 (Cp), 69.5 (5C, Cp'), 69.3 (Cp), 67.7 (Cp), 57.7 (2'), 46.2 (4'), 45.6 (3'), 44.6 (2C, 1') and 43.1 (5');

IR (KBr) ν_{max} 3312br w, 3013m, 2949s, 2823w, 2779m, 1636m (ν C=O), 1612m (7-chloroquinoline), 1583vs (7-chloroquinoline), 1505s, 1470m (NCH_3), 1431s, 1405m, 1368m, 1319s (ν-as CF_3), 1280s (ν-as CF_3), 1250m, 1202m, 1163s (ν-s CF_3), 1136s (ν-s CF_3), 1047m (ν C-F), 1005m (ferrocene), 956w, 918m, 876m, 820m (ferrocene), 767w, 745w, 668w, 647w, 608w, 530m and 488m (ferrocene);

HRMS (FAB) *m/z* 682.1669 [M^+ + H, $C_{33}H_{32}N_5ClF_4FeO$ + H requires 682.1658], 636.9 [M^+ - ($HNMe_2$)], 597.0, 531.0, 477.0, 431.9, 367.0, 321.9, 256.1 [HC-Fp-CH_2-NMe_2], 213.0, 191.0 [ClC_9NH_5-NH-CH_2], 134.1 [Fe-Cp-CH_2] and 91.0 [CH_2-Cp-CH_2];

$E_{1/2}$ = 165 mV; ferrocene redox: E_{pa} = 204 mV, E_{pc} = 125 mV; second redox: not observed.

Compound 44



1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethyl-aminomethyl)-ferrocenylmethyl]-3-[2,6-bis-(trifluoromethyl)-phenyl]-urea

Yellow crystalline solid; Yield: 96mg (43%);

mp: 113-115°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.79;

δ_H (400 MHz; $CDCl_3$) 8.50 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 7.98 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.65 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.51-7.32 (3H, m, U_3, U_4), 7.17 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.35 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.64 (1H, d, $^2J_{HH}$ = 16, 3'a), 4.45-4.44 (1H, m, Cp), 4.38 (1H, d, $^2J_{HH}$ = 16, 3'b), 4.21 (1H, t, $^3J_{HHH}$ = 2, Cp), 4.15 (1H, m, Cp), 4.13 (5H, s, Cp'), 3.91 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.74-3.72 (2H, m, 5'), 3.66-3.41 (2H, m, 4'), 2.81 (1H, d, $^2J_{HH}$ = 13, 2'b) and 1.95 (6H, s, 1');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 159.9 (^{IV}C, CO), 151.6 (^{IV}C), 149.8 (ArC_2), 146.9 (^{IV}C), 135.6 (^{IV}C), 128.5 (U), 126.3 (ArC_6), 125.3 (ArC_5), 123.1 (ArC_8), 122.0 (U), 119.8 (U), 119.6 (U), 116.9 (^{IV}C), 97.7 (ArC_3), 83.3 (^{IV}C, Cp), 81.8 (^{IV}C, Cp), 71.1 (Cp), 69.7 (5C, Cp'), 67.8 (Cp), 66.1 (Cp), 57.6 (2'), 53.0 (2C, CF_3), 46.0 (4'), 45.8 (3'), 44.1 (2C, 1') and 43.0 (5');

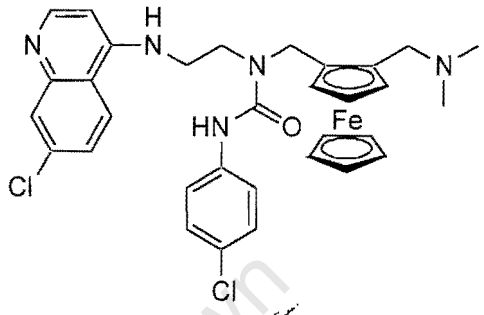
IR (KBr) ν_{max} 3296br w (NH), 3092m, 2950m, 2861m, 2824m, 2780m, 1637m (ν C=O), 1616m (7-chloroquinoline), 1582vs (7-chloroquinoline), 1522s (7-chloroquinoline), 1476s (NCH_3), 1406m, 1368m, 1323vs (ν-as CF_3), 1276m (ν-as CF_3), 1203w, 1166s (ν-s CF_3), 1136s (ν-s

CF_3), 1076w, 1039w (ν C-F), 1005m (ferrocene), 904m, 876w, 844m (aryl $CH_2N(CH_3)$), 804m (ferrocene), 766w, 729w, 668w, 507w, 488w (ferrocene) and 422w;

HRMS (FAB) *m/z* 682.1666 [M^+ + H, $C_{33}H_{32}N_5ClF_4FeO$ + H requires 682.1658], 637.0 [M^+ - ($HNMe_2$)], 477.1 [M^+ - ($CF_3C_6H_3NHCO$)], 432.1 [M^+ - ($HNMe_2$ + $CF_3C_6H_3NHCO$)], 367.1, 322.0, 213.1, 205.0, 134.1 [Fe-Cp-CH_2] and 91.0 [CH_2-Cp-CH_2];

$E_{1/2}$ = 179 mV, ferrocene redox: E_{pa} = 218 mV, E_{pc} = 138 mV, second redox: not observed.

Compound 45



1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethyl-aminomethyl)-ferrocenylmethyl]-3-*p*-chloro-phenyl-urea

Yellow crystalline solid; Yield: 115mg (56%);

mp: 115-116°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.62;

δ_H (400 MHz; $CDCl_3$) 8.52 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 7.95 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.79 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.31 (1H, dd, $^3J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 7.28-7.24 (4H, m, U), 6.35 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.54 (1H, d, $^2J_{HH}$ = 16, 3a'), 4.42-4.41 (1H, m, Cp), 4.38 (1H, d, $^2J_{HH}$ = 16, 3b'), 4.19 (1H, t, $^3J_{HH}$ = 3, Cp), 4.16-4.14 (1H, m, Cp), 4.12 (5H, s, Cp'), 3.89 (1H, d, $^2J_{HH}$ = 13, 2a'), 3.74-3.72 (2H, m, 5'), 3.66-3.41 (2H, m, 4'), 2.80 (1H, d, $^2J_{HH}$ = 13, 2b') and 1.97 (6H, s, 1');

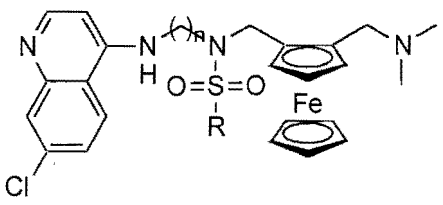
$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 159.1 (^{IV}C, CO), 151.5 (^{IV}C), 150.7 (ArC_2), 138.0 (^{IV}C), 135.5 (^{IV}C), 128.7 (2C, U), 127.9 (2C, U), 125.9 (ArC_6), 125.4 (ArC_5), 122.6 (ArC_8), 117.3 (^{IV}C), 97.9 (ArC_3), 83.4 (^{IV}C, Cp), 82.0 (^{IV}C, Cp), 70.8 (Cp), 69.6 (5C, Cp'), 69.0 (Cp), 67.7 (Cp), 58.1 (2'), 46.7 (4'), 45.8 (3'), 45.3 (2C, 1') and 43.2 (5');

IR (KBr) ν_{max} 3306s (NH), 3089m, 2980m, 2934m, 2853m, 2820m, 2771m, 1634s (ν C=O), 1608m (7-chloroquinoline), 1579vs (7-chloroquinoline), 1528s (7-chloroquinoline), 1482s (NCH_3), 1413m, 1364m, 1329m, 1310m, 1288m, 1259m, 1237m, 1176m, 1150w, 1137m, 1098m, 1087m, 997m, 912w, 874m, 844m (aryl $CH_2N(CH_3)$), 820m (ferrocene), 809m, 766w, 742w, 644w, 593w, 507m and 460w;

HRMS (FAB) *m/z* 630.1479 [M^+ + H, $C_{32}H_{33}N_5Cl_2FeO$ + H requires 630.1489], 585.0 [M^+ - ($HNMe_2$)], 477.1 [M^+ - (ClC_6H_3NHCO)], 432.0, 366.0, 307.1, 274.1, 256.1 [HC-Fp-CH_2-NMe_2], 213.0 and 91.0 [CH_2-Cp-CH_2];

$E_{1/2}$ = not found; ferrocene redox: E_{pa} = 214 mV, E_{pc} = 111 mV; second redox: E_{pa} = 300 mV and E_{pc} = ± 210 mV;

Synthesis of Sulfonamide Derivatives



Method 1:

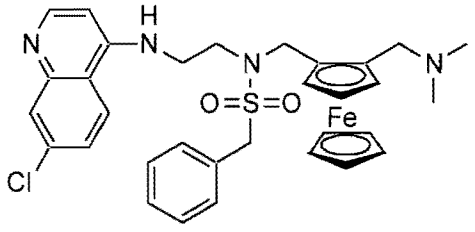
20 was placed in a large sample vial followed by anhydrous dichloromethane. 5 mol equivalents of poly(4-vinylpyridine) (2% cross-linked) was added followed by 3

mol equivalents the appropriate sulfonyl chloride resulting in a vigorous, exothermic reaction. The sample vial was placed on the shaker overnight at 200 rpm at 20°C. Pentaethylenehexamine (3 mol equivalents) was added followed by a further anhydrous dichloromethane, and the sample vial was returned to the shaker for 1 h. 1,4-phenylene diisocyanate (3 mol equivalents) was added followed by anhydrous dichloromethane and returned to the shaker for 1 h. The mixture was then filtered under gravity. The solvent was removed from the filtrate under reduced pressure. The product was then purified using silica gel chromatography eluting with 20% methanol in dichloromethane. The product *sulfonamide* was isolated as a yellow crystalline solid.

Method 2:

20 was placed in a large sample vial followed by anhydrous dichloromethane. 5 mol equivalents of poly(4-vinylpyridine) (2% cross-linked) was added followed by 3 mol equivalents the appropriate sulfonyl chloride resulting in a vigorous, exothermic reaction. The sample vial was placed on the shaker overnight at 200 rpm at 20°C. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The product then purified using silica gel chromatography eluting with 20% methanol in dichloromethane. The product *sulfonamide* was isolated as a yellow crystalline solid.

Compound 46



3-Benzyl-sulfonic acid-1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethylaminomethyl)-ferrocenylmethyl]amide

Yellow crystalline solid; Yield: 38mg (40%); mp: 114-116°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.60;

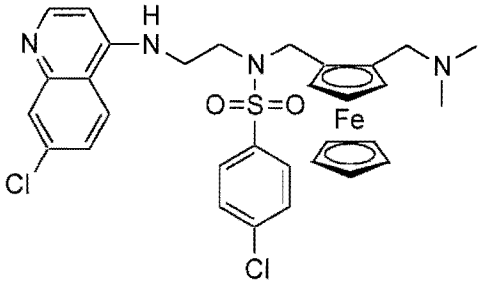
δ_H (400 MHz; $CDCl_3$) 8.41 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 7.90 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.79 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.38-7.27 (6H, m, ArC_6-H, S_2, S_3, S_4), 6.27 (1H, br s, NH), 6.10 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.51 (1H, d, $^2J_{HH}$ = 14, 3a'), 4.36-4.09 (7H, m, Cp, 1'', 4', 3b'), 4.04 (5H, s, Cp'), 3.62 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.43-3.27 (2H, m, 5'), 2.95 (1H, d, $^2J_{HH}$ = 13, 2'b) and 2.17 (6H, s, 1'');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 151.2 (^{IV}C), 150.2 (ArC_2), 135.2 (^{IV}C), 130.8 (2C, S), 130.7 (^{IV}C), 128.9 (S_4), 128.8 (2C, S), 128.1 (^{IV}C), 127.8 (ArC_6), 125.5 (ArC_5), 122.3 (ArC_8), 117.2 (^{IV}C), 98.2 (ArC_3), 83.7 (^{IV}C, Cp), 81.9 (^{IV}C, Cp), 72.1 (Cp), 70.7 (Cp), 69.4 (5C, Cp'), 67.9 (Cp), 58.3 (2'), 57.4 (1''), 46.4 (2C, 3', 4'), 45.0 (2C, 1') and 41.4 (5');

IR (KBr) ν_{max} 3392m (NH), 3078m, 3035m, 2932m, 2856m, 2813m, 2771m, 1610m (7-chloroquinoline), 1582vs (7-chloroquinoline), 1538m (7-chloroquinoline), 1494m, 1456m (NCH_3), 1367m, 1329s, 1231m, 1184m, 1146s, 1124m, 1106m (ferrocene), 1076m, 1040m, 1014w (ferrocene), 992m, 913w, 895w, 800m, 732w, 694m, 624w, 602w, 563w, 535m, 511m and 491m (ferrocene);

HRMS (EI) *m/z* 630.1520 [M^+, $C_{32}H_{35}N_4ClFeO_2S$ requires 630.1519], 585.1 [M^+ - NMe_2], 475.1 [M^+ - $SO_2CH_2C_6H_5$], 430.1, 375.0, 311.0, 255.1 [HC-Fp-CH_2-NMe_2], 240.0 [Fp-CH_2-NMe_2], 213.0, 191.0 [ClC_9NH_5-NH-CH_2], 121.0 [Cp-Fe], 91.0 [CH_2-Cp-CH_2] and 58.1 [CH_2-NMe_2].

Compound 47



1-[2-(7-Chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethyl-aminomethyl)-ferrocenylmethyl]-3-*p*-chloro-phenyl-sulphonamide

Yellow crystalline solid; Yield: 63mg (51%); mp: 119-121°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.57;

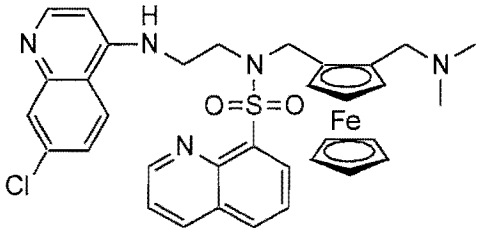
δ_H (400 MHz; $CDCl_3$) 8.42 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 7.90 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.88 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.78 (4H, m, S_2, S_3), 7.24 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.25 (1H, br s, NH), 6.11 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 4.30-4.19 (4H, m, Cp, 3a', 3b'), 4.10-4.06 (1H, m, Cp), 4.05 (5H, s, Cp'), 3.60 (1H, d, $^2J_{HH}$ = 13, 2a'), 3.38-3.32 (2H, m, 5'), 3.01-2.98 (2H, m, 4'), 2.89 (1H, d, $^2J_{HH}$ = 13, 2b') and 2.09 (6H, s, 1');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 151.4 (ArC_2), 150.2 (^{IV}C), 139.4 (^{IV}C), 135.1 (^{IV}C), 129.6 (2C, S), 129.3 (^{IV}C), 128.5 (2C, S), 128.6 (ArC_5), 128.4 (^{IV}C) 125.4 (ArC_6), 122.1 (ArC_8), 117.4 (^{IV}C), 98.4 (ArC_3), 81.3 (^{IV}C, Cp), 72.0 (Cp), 70.6 (Cp), 69.4 (5C, Cp'), 67.8 (Cp), 57.4 (2'), 47.6 (4'), 46.3 (3'), 45.2 (2C, 1') and 42.0 (5');

IR (KBr) ν_{max} 3393m (NH), 3091m, 2931m, 2858m, 2816m, 2776m, 1611s (7-chloroquinoline), 1582vs (7-chloroquinoline), 1540m (7-chloroquinoline), 1476m, 1453m (NCH_3), 1336s, 1281m, 1216m, 1158s, 1123m, 1088m, 1035m, 1004m (ferrocene), 910w, 872w, 828m (aryl $CH_2N(CH_3)$), 767m, 729m, 650w, 615m, 561w and 483m (ferrocene);

HRMS (EI) *m/z* 650.10164 [M^+ + H, $C_{31}H_{32}N_4Cl_2FeO_2S$ requires 650.09724], 475.1 [M^+ - $SO_2C_6H_4Cl$], 430.1, 395.0, 311.0, 240.0 [Fp-CH_2-NMe_2], 213.0, 191.0 [ClC_9NH_5-NH-CH_2], 156.0, 91.0 [CH_2-Cp-CH_2] and 57.1 [CH-NMe_2].

Compound 48



Quinoline-8-sulphonic acid [2-(7-chloro-quinolin-4-yl)-ethyl]-(2-dimethylaminomethyl-ferrocenylmethyl)-amide

Deep orange crystalline solid; Yield: 204mg (90%); mp: 108-110°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.23;

δ_H (400 MHz; CD_3OD) 8.82 (1H, d, $^3J_{HH}$ = 4, S_7), 8.43 (1H, $^3J_{HH}$ = 7, S_2), 8.33 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.24 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 8, S_5), 7.98 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 8, S_4), 7.83 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.66 (1H, d, $^3J_{HH}$ = 2, ArC_8-H), 7.63 (1H, dd, $^3J_{HH}$ = 7 and $^3J_{HH}$ = 8, S_3), 7.38 (1H, d, $^3J_{HH}$ = 4 and $^3J_{HH}$ = 8, S_6), 6.92 (1H, dd, $^3J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.66 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.50 (1H, m, Cp), 4.46 (1H, d, $^2J_{HH}$ = 13, 3a'), 4.36 (1H, m, Cp), 4.35

(1H, d, $^{2}J_{HH}$ = 13, 2a'), 4.33 (1H, t, $^{3}J_{HH}$ = 2, Cp), 4.16 (5H, s, Cp'), 4.00 (1H, d, $^{2}J_{HH}$ = 13, 3b'), 3.85-3.64 (2H, m, 4'), 3.43 (1H, d, $^{2}J_{HH}$ = 13, 2b'), 3.37-3.23 (2H, m, 5') and 2.45 (6H, s, 1');
$\delta_{C\{H\}}$ (100.6 MHz; CD_3OD) 152.5 (^{IV}C), 150.5 (S_7), 148.5 (ArC_2), 145.1 (^{IV}C), 144.0 (^{IV}C), 140.8 (^{IV}C), 137.0 (S_5), 136.4 (^{IV}C), 131.7 (S_4), 129.5 (S_2), 129.3 (^{IV}C), 125.5 (S_8), 125.1 (ArC_6), 123.8 (ArC_5), 123.6 (ArC_8), 122.4 (S_6), 116.6 (^{IV}C), 98.6 (ArC_3), 79.8 (^{IV}C, Cp), 78.0 (^{IV}C, Cp), 72.2 (2C, Cp), 69.8 (5C, Cp'), 68.1 (Cp), 56.6 (2'), 46.2 (3'), 45.0 (5'), 42.4 (2C, 1') and 40.4 (4');
IR (KBr) ν_{max} 3448br s, 2973s, 2938s, 2739s, 2676s, 2489m, 1615s (7-chloroquinoline), 1582s (7-chloroquinoline), 1495m, 1455m (NCH_3), 1398m, 1384m, 1366m, 1334m, 1311w, 1208br vs, 1105m (ferrocene), 1048s, 980w, 900w, 832m (aryl $CH_2N(CH_3)$), 784m, 689m, 618s, 576m, 519m and 432m;
MS (FAB) *m/z* 686.1 [M^+ + H], 477.1 [M^+ - $SO_2C_9H_6N$], 432.1, 312.1, 253.9, 213.0, 191.0 [ClC_9NH_5-NH-CH_2], 102.1 and 91.0. [CH_2-Cp-CH_2].

Experimental Details Pertaining to Chapter 4

Preparation of Ionic Gold Complexes

Compound 58

Preparation of Chlorogoldtriphenylphosphine [10]

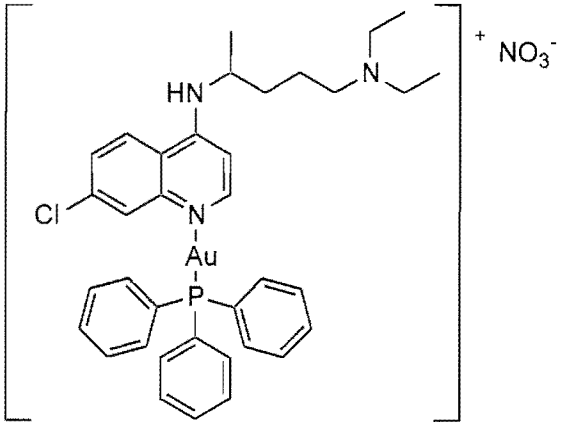
Compound 59

Preparation of Triphenylphosphinegold(I) nitrate[11]

Compounds 60 – 63

Coordination of gold triphenylphosphine to 4-amino-7-chloroquinoline derivatives
The 4-amino-7-chloroquinoline derivative was added to anhydrous dichloromethane in a centrifuge tube fitted with nitrogen inlet. 1 mol equivalent of triphenylphosphinegold(I) nitrate **59** was added. Light was excluded from the flask and the mixture was allowed to stir at 25°C for 3h. The reaction vessel was then cooled to -72°C in an ethanol/dry ice slurry. The volume of solvent was reduced to about 10% of the original volume *in vacuo*. The concentrated solution was transferred to a sample vial. Diethyl ether was added giving a precipitate. The slurry was allowed to stand at 4°C for 1 h before filtering and washing with diethyl ether.

Compound 60



(Chloroquine)(triphenylphosphine)gold nitrate; $[Au(CQ)PPh_3]NO_3$

Cream crystalline solid; Yield: 134mg (82%); mp: 89-90°C (from diethyl ether);

δ_H (300 MHz; $CDCl_3$) 8.44 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 8.33 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.06 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.63-7.49 (15H, m, Ph), 7.38 (1H, dd, $^3J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.48 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 3.76 (1H, m, 6'), 2.79-2.56 (6H, m, 2', 3'), 1.78-1.57 (4H, m, 5', 4'), 1.35 (3H, d, $^3J_{HH}$ = 6, 1'') and 1.09 (6H, t, $^3J_{HH}$ = 6, 1');

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 152.3 (ArC_2), 151.8 (^{IV}C), 147.5 (^{IV}C), 136.3 (^{IV}C), 134.1 (Ph), 134.0 (Ph), 132.5 (Ph), 129.7 (Ph), 129.5 (Ph), 126.1 (ArC_5), 125.3 (ArC_6), 124.7 (ArC_8), 117.9 (^{IV}C), 99.1 (ArC_3), 52.6 (2'), 49.3 (6'), 47.0 (3'), 33.5 (5'), 23.1 (4'), 19.7 (1'') and 10.6 (1');

$\delta_{P\{H\}}$ (121 MHz, $CDCl_3$) 30.81 (PPh_3);

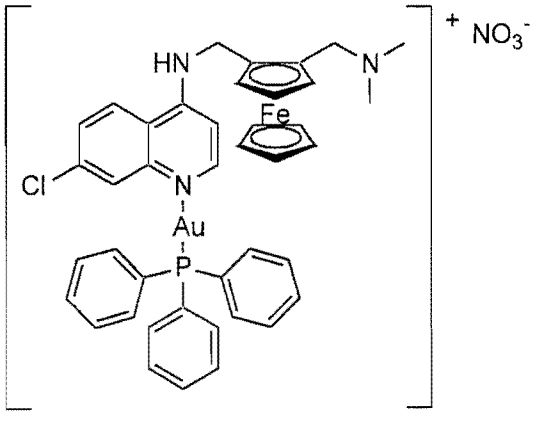
IR (KBr) ν_{max} 3404br m (ν N-H), 3070m, 2966m, 1579s (7-chloroquinoline), 1534m (7-chloroquinoline), 1478m, 1436m, 1382vs (ν N-O), 1200w (NCH_2CH_3), 1152m, 1100m, 1025w, 996w (ν P-C), 807w, 749m, 711m, 693s, 546s and 503s;

MS (FAB) *m/z* 779.142 [M^+, $C_{36}H_{40}N_3Au^{35}ClP^+$ requires 779.198], 747.9, 720.9, 662.9, 578.8, 458.8 [$AuPPh_3$], 320.0 [CQ], 249.0 [(Cl37 _ CQ – 2(CH2CH3)], 247.0 [Cl35_ CQ – 2 (CH2CH3)], 183.0, 165.0, 152.0, 140.1, 136.0, 128.0, 115.0, 105.0, 91.0, 89.0, 86.0, 76.9, 64.8, and 62.8;

Found: C, 51.72; H, 5.01; N, 6.50. Calc. for $[C_{35}H_{40}N_3AuClP]^+[NO_3]^-$: C, 51.47; H, 4.80; N, 6.67%;

Λ ($C_6H_5NO_2$, 20°C) = 17 $\Omega^{-1}cm^2mol^{-1}$.

Compound 61



(Ferroquine)(triphenylphosphine)gold nitrate $[Au(FQ)PPh_3]NO_3$

Orange crystalline solid; Yield: 185mg (84%); mp: 110-112°C;

δ_H (400 MHz; $CDCl_3$) 8.68 (1H, d, $^3J_{HH}$ = 7, ArC_2-H), 8.26 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.94 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.60 (15H, m, Ph), 7.39 (1H, d, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.97 (1H, d, $^3J_{HH}$ = 7, ArC_3-H), 4.59 (1H, d, $^2J_{HH}$ = 14, 3'a), 4.48 (1H, d, $^2J_{HH}$ = 14, 3'b), 4.37 (1H, m, Cp), 4.22 (1H, m, Cp), 4.16 (5H, s, Cp'), 4.09 (1H, m, Cp), 3.99 (1H, d, $^2J_{HH}$ = 12, 2'a), 3.11 (1H, d, $^2J_{HH}$ = 12, 2'b) and 2.32 (6H, s, 1');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 154.2 (ArC_2), 152.5 (^{IV}C), 146.8 (^{IV}C), 136.7 (^{IV}C), 134.2 (Ph), 134.1 (Ph), 132.6 (Ph), 128.8 (Ph), 126.7 (Ph), 126.1 (ArC_8), 124.6 (ArC_6), 124.0 (ArC_5), 118.0 (^{IV}C), 100.4 (^{IV}C), 95.5 (ArC_3), 83.0 (^{IV}C, Cp), 71.4 (Cp), 70.8 (Cp), 69.6 (5C, Cp'), 66.7 (Cp), 57.8 (2'), 44.7 (2C, 1') and 42.5 (3');

$\delta_{P\{H\}}$ (121 MHz, $CDCl_3$) 30.60 (PPh_3);

IR (KBr) ν_{max} 3430br s (ν N-H), 3079s, 2941s, 2826s, 2776s, 1592vs (7-chloroquinoline, ν C=N), 1480m, 1434m (δ-as NCH_3), 1384vs (ν N-O), 1332s, 1209w, 1141w, 1102s (ferrocene), 1032w, 996m (ν P-C), 815m (ferrocene), 749m (δ C-H aromatic, 5 adjacent hydrogens), 711m (δ C-H aromatic, 5 adjacent hydrogens), 544s, 505m and 456w;

MS (FAB) *m/z* 892.2 [M^+, $C_{41}H_{39}N_3{}^{35}CAuFeP$ requires 892.15851], 848.1 [M^+ - (NMe_2)], 757.1, 721.2, 637.1, 492.2, 432.2 [M^+ - ($AuPPh_3$)], 388.1, 262.2 [PPh_3], 213.1, 185.1, 183.1, 134.1 and 91.0 [CH_2-Cp-CH_2];

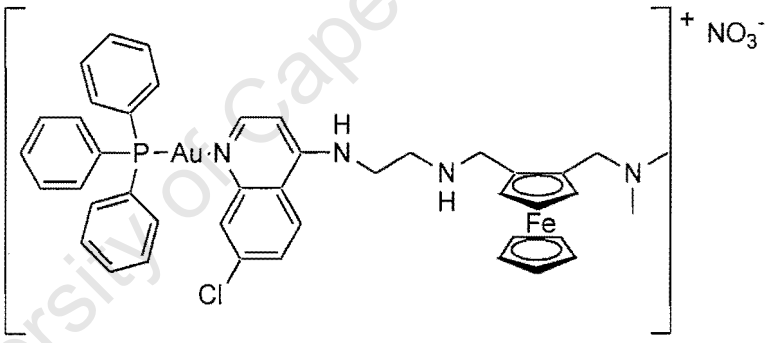
$E_{1/2}$ = 147 mV; ferrocene redox: E_{pa} = 252 mV and E_{pc} = 162 mV;

Λ ($C_6H_5NO_2$, 20°C) = 21 $\Omega^{-1}cm^2mol^{-1}$.

Compound 62

N-(7-Chloro-quinolin-4-yl)-*N'*-[2-[(*N''*,*N''*-dimethylaminomethyl) ferrocenylmethyl-ethane-1,2-diamine] (triphenylphosphine)gold nitrate

$[Au(F2Q)PPh_3]NO_3$



Deep orange crystalline solid; Yield: 343mg (90%); mp: 106-108°C;

δ_H (300 MHz; $CDCl_3$) 8.41 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.14 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.85 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.53 (15H, m, Ph), 7.12 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.49 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.31 (1H, m, Cp), 4.24 (1H, m, Cp), 4.12 (1H, m, Cp), 4.08 (5H, m, Cp'), 3.90 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.64 (3H, m, 3'a, 5'), 3.50 (3H, m, 3'b, 4'), 2.82 (1H, d, $^2J_{HH}$ = 13, 2'b) and 2.09 (6H, s, 1');

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 152.1 (ArC_2), 151.0 (^{IV}C), 148.2 (^{IV}C), 135.4 (^{IV}C), 134.0 (Ph), 133.9 (Ph), 132.3 (Ph), 129.5 (Ph), 129.3 (Ph), 128.0 (^{IV}C), 127.1 (^{IV}C), 126.7 (ArC_8), 125.8 (ArC_6), 123.7 (ArC_5), 117.7 (^{IV}C), 99.0 (ArC_3), 71.4 (Cp), 69.4 (5C, Cp'), 66.5 (Cp), 65.8 (Cp), 58.0 (2'), 44.4 (2C, 1') and 41.6 (5');

$\delta_{P\{H\}}$ (121 MHz; $CDCl_3$) 30.71 (PPh_3);

IR (KBr) ν_{max} 3331br m (NH), 3054m, 2940m, 1580s (7-chloroquinoline), 1478m (NCH_3), 1436m, 1383vs (ν N-O), 1329s, 1205w, 1139w, 1102m (ferrocene), 1029w, 996m, 811m (ferrocene), 747m (δ C-H aromatic), 714m (δ C-H aromatic), 695s, 618w, 544s and 506m;

HRMS (FAB) *m/z* 935.20071 [M^+, $C_{43}H_{44}N_4Au^{35}ClFeP^+$ requires 935.1396], 841.5, 770.6, 721.5 [M^+ - (3Ph + Me)], 680.5, 649.4, 475.3 [M^+ - ($AuPPh_3$)], 459.3 [$AuPPh_3$], 213.1 and 185.1;

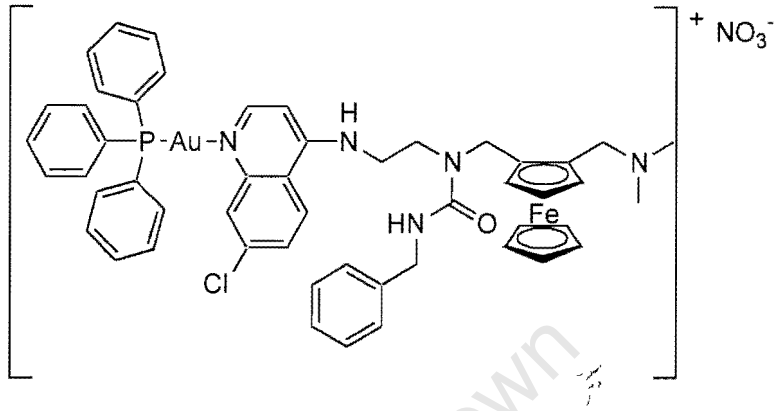
$E_{1/2}$: not found; ferrocene redox: E_{pa} = 294 mV and E_{pc} = 186 mV;

Λ ($C_6H_5NO_2$, 20°C) = 13 $\Omega^{-1}cm^2mol^{-1}$.

Compound 63

{3-Benzyl-1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethylaminomethyl)-ferrocenylmethyl]urea} (triphenylphosphine)gold nitrate

$[Au(BU)PPh_3]NO_3$



Yellow crystalline solid;

Yield: 190mg (75%); mp: 102-105°C;

δ_H (300 MHz; $CDCl_3$) 8.31 (1H, d, $^3J_{HH}$ = 7, ArC_2-H), 8.18 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 8.11 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.66-7.50 (15H, m, Ph), 7.28-7.10 (8H, m, 1'', ArC_6-H, U), 6.81 (1H, d, $^3J_{HH}$ = 7, ArC_3-H), 4.51-4.20 (6H, m, 3Cp, 3'a, 4'), 4.12 (5H, s, Cp'), 4.11-3.61 (5H, m, 2'a, 2'b, 3'b, 5') and 2.01 (6H, s, 1');

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 159.9 (*C*O), 153.6 (^{IV}C), 153.3 (ArC_2), 146.3 (^{IV}C), 140.5 (^{IV}C), 136.8 (^{IV}C), 134.2 (Ph), 134.0 (Ph), 132.6 (Ph), 129.8 (Ph), 129.6 (Ph), 128.2 (2C, U), 127.1 (U), 126.6 (2C, U), 124.9 (ArC_8), 123.7 (ArC_5) 117.8 (^{IV}C), 99.5 (ArC_3), 84.3 (^{IV}C, Cp), 70.6 (Cp), 69.7 (Cp'), 68.6 (Cp), 67.8 (Cp), 58.7 (2'), 49.7 (3'), 45.5 (4'), 44.6 (1''), 44.2 (2C, 1') and 43.1 (5');

$\delta_{P\{H\}}$ (121 MHz; $CDCl_3$) 30.58 (*P*Ph_3);

IR (KBr) ν_{max} 3309br m (ν N-H), 3057m, 2934m, 2820m, 2775m, 1595vs (7-chloroquinoline), 1542s (7-chloroquinoline), 1480w, 1452m (NCH_3), 1437m (δ-as (NCH_3)), 1381vs (ν N-O), 1336s, 1283m, 1205m, 1101m (ferrocene), 1028m, 999w (ν P-C), 814w (δ C-H aromatic), 748m (δ C-H aromatic), 695s, 609w, 544s, 510m and 454w;

HRMS (FAB) *m/z* 1068.2548 [M^+ + H, $C_{51}H_{50}N_5Au^{35}ClFeOP^+$ + H requires 1068.2535], 917.2, 721.2, 610.3 [M^+ - ($AuPPh_3$)], 565.2, 459.0, 213.0, 185.1 and 91.0 [CH_2-Cp-CH_2];

Found: C, 54.05; H, 4.14; N, 7.16. Calc. for [$C_{51}H_{50}N_5AuClFeOP^+$]$NO_3^-$: C, 54.15; H, 4.544; N, 7.429%;

$E_{1/2}$ = 180 mV; ferrocene redox: E_{pa} = 219 mV and E_{pc} = 141 mV;

Λ ($C_6H_5NO_2$, 20°C) = 31 $\Omega^{-1}cm^2mol^{-1}$.

Preparation of Neutral Gold Complexes

Compound 70

Preparation of (Chloro)(tetrahydrothiophene)gold(I)[12]

Compound 64

Preparation of (Pentafluorophenyl)(tetrahydrothiophene)gold(I)[13,14]

Compounds 65 – 68

Complexation of pentafluorophenylgold to 4-amino-7-chloroquinoline derivatives

Method 1:

A 1:1 molar ratio of (pentafluorophenyl)(tetrahydrothiophene)gold **64** and the 4-amino-7-chloroquinoline derivative were placed in a 25ml 2-necked round bottomed flask fitted with nitrogen inlet and stopper. Freshly distilled dichloromethane was added and the flask protected from light. The mixture was allowed to stir at 25°C for 2 h. The solvent was then removed *in vacuo*. The solid residue was then purified using preparative TLC, eluting with 10% methanol in dichloromethane.

Method 2:

A 1:1 molar ratio of (pentafluorophenyl)(tetrahydrothiophene)gold **64** and the 4-amino-7-chloroquinoline derivative were placed in a centrifuge tube fitted with 2-necked adaptor. Freshly distilled dichloromethane was then added. The tube was protected from light and the mixture allowed to stir at 25°C for 2 h. The stirrer bar was removed and hexane added. The product precipitated out of solution. The suspension was centrifuged and the supernatant decanted off. The solid product was then dried *in vacuo*.

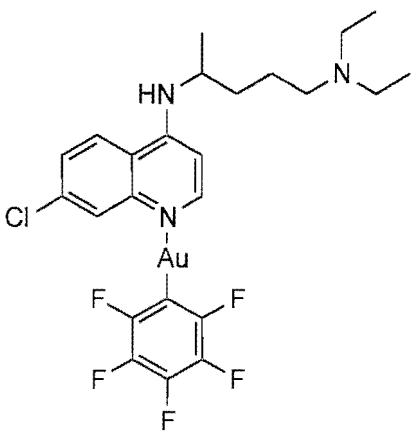
Compound 65

Chloroquine(pentafluorophenyl)gold

$[Au(C_6F_5)(CQ)]$

White crystalline solid; Yield: 91mg (63%);

mp: 114-116°C;



δ_H (400 MHz; CD_3OD) 8.58 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 8.37 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.23 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.44 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.66 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 3.95-3.91 (1H, m, 6'), 3.24-3.12 (6H, m, 2', 3'), 1.92-1.74 (4H, m, 4', 5'), 1.42 (3H, d, $^3J_{HH}$ = 6, 1'') and 1.32 (6H, t, $^3J_{HH}$ = 7, 1');

$\delta_{C\{H\}}$ (100.6 MHz; CD_3OD) 153.5 (ArC_2), 151.8 (^{IV}C), 147.4 (^{IV}C), 136.2 (^{IV}C), 125.9 (ArC_5), 125.6 (ArC_6), 123.4 (ArC_8), 117.8 (^{IV}C), 99.3 (ArC_3), 51.8 (2'), 49.0 (6'), 46.9 (3'), 32.7 (5'), 21.0 (4'), 18.9 (1'') and 8.2 (1');

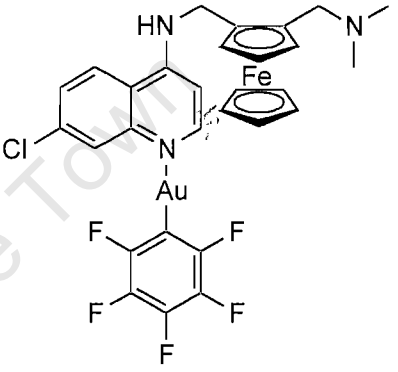
$\delta_{F\{H\}}$ (376 MHz; CD_3OD) -117.26 to -117.38 (2F, m, *o*-F), -165.78 (1F, t, $^3J_{FF}$ = 19, *p*-F) and -166.80 to -166.97 (2F, m, *m*-F);

IR (KBr) ν_{max} 3431m (NH), 2972m, 2923m, 2874m, 2852m, 2791m, 1594vs (7-chloroquinoline), 1541m (7-chloroquinoline), 1505s (ν C-F), 1455vs (ν C-F), 1442s, 1381m, 1367m, 1341m, 1282m, 1263m, 1219w, 1198m, 1068m, 1017m, 956vs (ν C-F), 866m, 803s, 754m, 647w, 514m and 454m;

MS (FAB) *m/z* 684.2 [M^+, $C_{24}H_{26}N_3AuClFe$ requires 684.2], 639.5, 595.4, 551.4, 507.3, 462.3, 332.4, 320.2 [M^+ - (AuC_6F_5)], 247.1 [M^+ - (AuC_6F_5 + $N(CH_2CH_3)_2$)], 205.0, 179.0, 142.1, 86.1 and 58.0;

Λ ($C_6H_5NO_2$, 20°C) = 0.2 $\Omega^{-1}cm^2mol^{-1}$.

Compound 66



Ferroquine(pentafluorophenyl)gold

[$Au(C_6F_5)$(FQ)]

Orange crystalline solid; Yield: 79mg (54%); mp: 83-86°C;

δ_H (300 MHz; CD_3OD) 8.37 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 7.91 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.76 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.45 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.75 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.58 (1H, d, $^2J_{HH}$ = 14, 3'a), 4.55 (1H, d, $^2J_{HH}$ = 14, 3'b), 4.37 (1H, m, Cp), 4.31-4.29 (1H, m, Cp) 4.19-4.18 (1H, m, Cp), 4.17 (5H, s, Cp'), 3.92 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.29 (1H, d, $^2J_{HH}$ = 13, 2'b) and 2.34 (6H, s, 1');

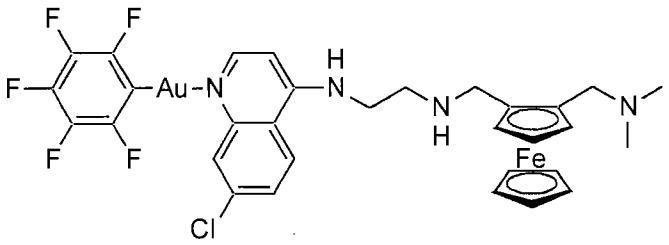
$\delta_{C\{H\}}$ (75.5 MHz; CD_3OD) 153.3 (ArC_2), 150.2 (^{IV}C), 149.5 (^{IV}C), 126.7 (ArC_8), 125.7 (ArC_6), 124.4 (ArC_5), 118.2 (^{IV}C), 100.2 (ArC_5), 84.9 (^{IV}C, Cp), 82.9 (^{IV}C, Cp), 72.5 (Cp), 71.5 (Cp), 70.6 (5C, Cp'), 68.2 (Cp), 58.3 (2'), 44.7 (2C, 1') and 42.8 (3');

$\delta_{F\{H\}}$ (376 MHz; CD_3OD) -117.25 to -117.45 (2F, m, *o*-F), -165.88 (1F, t, $^3J_{FF}$ = 19, *p*-F) and -166.90 to -167.05 (2F, m, *m*-F);

IR (KBr) ν_{max} 3400br m (NH), 3088m, 2945m, 2826m, 2783m, 1591s (7-chloroquinoline), 1554m (7-chloroquinoline), 1502s (ν C-F), 1457s (ν C-F), 1362m, 1325m, 1285w, 1259w, 1226w, 1203w, 1141w, 1105w (ferrocene), 1062m, 1003w (ferrocene), 955s (ν C-F), 862m, 804m, 605w, 527w and 490w (ferrocene);

HRMS (FAB) *m/z* 798.0672 [M^+ + H, $C_{29}H_{24}N_3Au^{35}ClFeF_5$ + H requires 798.3425], 753.0, 459.2, 434.2, 389.0, 256.1 [HC-Fp-CH_2-NMe_2], 213.0, 134.1 [Fe-Cp-CH_2] and 91.1 [CH_2-Cp-CH_2].

Compound 67



N-(7-Chloro-quinolin-4-yl)-*N'*-[2-[(*N'',N''*-dimethyl-aminomethyl)ferrocenylmethyl-ethane-1,2-diamine] (pentfluorophenyl)gold

[Au(C_6F_5)(F2Q)]

Orange crystalline solid; Yield: 132mg (75%); mp: 76-78°C;

δ_H (300 MHz; CD_3OD) 8.35 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.09 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.78 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.40 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.57 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.25-4.23 (1H, m, Cp), 4.15-4.13 (1H, m, Cp), 4.07 (1H, t, $^3J_{HHH}$ = 2, Cp), 4.03 (5H, s, Cp'), 3.81 (1H, d, $^2J_{HH}$ = 13, 3'a), 3.66 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.52 (2H, m, 5'), 3.44 (1H, d, $^2J_{HH}$ = 13, 3'b), 2.95 (2H, m, 4'), 2.88 (1H, d, $^2J_{HH}$ = 13, 2'b) and 1.97 (6H, s, 1');

$\delta_{C\{H\}}$ (75.5 MHz; CD_3OD) 152.7 (^{IV}C), 152.5 (ArC_2), 149.7 (^{IV}C), 136.4 (^{IV}C), 127.7 (ArC_8), 126.1 (ArC_6), 124.3 (ArC_5), 119.3 (^{IV}C), 99.8 (ArC_3), 85.9 (^{IV}C, Cp), 84.0 (^{IV}C, Cp), 72.3 (Cp), 71.3 (Cp), 70.2 (5C, Cp'), 67.5 (Cp), 58.7 (2'), 44.8 (2C, 1') and 43.3 (5');

$\delta_{F\{H\}}$ (376 MHz; CD_3OD) -117.23 to -117.40 (2F, m, *o*-F), -165.86 (1F, t, $^3J_{FF}$ = 19, *p*-F) and -166.86 to -167.03 (2F, m, *m*-F);

IR (KBr) ν_{max} 3411br m (NH), 2955m, 1612m (7-chloroquinoline), 1583s (7-chloroquinoline), 1536m (7-chloroquinoline), 1499s (ν C-F), 1450vs (ν C-F), 1384m, 1336m, 1278w, 1252w, 1139w, 1105w (ferrocene), 1048m, 1000w (ferrocene), 952s (ν C-F), 811m (ferrocene), 781m, 489m (ferrocene) and 452w;

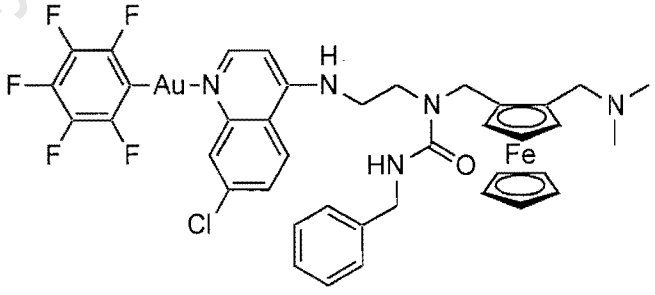
MS (FAB) *m/z* 841.2 [M^+ + H, $C_{31}H_{29}N_4Au^{35}ClFeF_5$ + H requires 841.2], 796.1, 477.2 [M^+ - AuC_6F_4Br], 432.2, 312.1, 256.1 [HC-Fp-CH_2-NMe_2], 213.0, 134.1 [Fe-Cp-CH_2] and 91.0 [CH_2-Cp-CH_2];

$E_{1/2}$: not found; ferrocene redox: E_{pa} = 315 mV and E_{pc} = 210 mV;

Λ ($C_6H_5NO_2$, 20°C) = 0.9 $\Omega^{-1}cm^2mol^{-1}$.

Compound 68

{3-Benzyl-1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethylaminomethyl)-ferrocenylmethyl]urea} (pentafluorophenyl)gold



[Au(BU)(C_6F_5)]

Yellow crystalline solid; Yield: 130mg (60%); mp: 102-105°C;

δ_H (300 MHz; $CDCl_3$) 8.81 (1H, br s), 8.68 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 8.42 (1H, $^3J_{HH}$ = 6, ArC_2-H), 8.33 (1H, br s), 7.71 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.17-7.02 (6H, m, U, ArC_6-H), 6.31 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.50-4.15 (8H, m, Cp, 1'', 3'a, 4'), 4.11 (5H, s, Cp'), 3.81 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.75-3.66 (1H, m, 3'b), 3.56-3.40 (2H, m, 5'), 2.78 (1H, d, $^2J_{HH}$ = 13, 2'b) and 1.99 (6H, s, 1');

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 160.5 (^{IV}C, *C*O), 153.3 (ArC_2), 152.0 (^{IV}C), 146.9 (^{IV}C), 139.7 (^{IV}C), 136.4 (^{IV}C), 128.2 (2C, U), 126.7 (ArC_6), 126.6 (U_4), 126.2 (2C, U), 125.7 (ArC_5), 123.0 (ArC_8), 117.4 (^{IV}C), 98.0 (ArC_3), 83.5 (^{IV}C, Cp), 70.6 (Cp), 69.9 (Cp), 69.5 (5C, Cp'), 67.6 (Cp), 57.7 (2'), 46.9 (3'), 45.8 (4'), 44.6 (1''), 44.5 (2C, 1') and 43.8 (5');

$\delta_{F\{H\}}$ (376 MHz; $CDCl_3$) -120.05 to -120.25 (2F, m, *o*-F), -164.518 (1F, t, $^3J_{FF}$ = 20, *p*-F) and

-167.38 to -167.62 (2F, m, *m*-F);

IR (KBr) ν_{max} 3409br m (NH), 3091m, 2928m, 2860m, 2823m, 2779m, 1592vs (7-chloroquinoline), 1548m (7-chloroquinoline), 1502s (ν C-F), 1457s (ν C-F), 1361m, 1335m, 1271m, 1204w, 1160w, 1142w, 1104w (ferrocene), 1062m, 1005w (ferrocene), 956s (ν C-F), 858w, 805m, 730w, 698w, 607w, 527w and 487w;

MS (FAB) 974.1 [M^+ + H, $C_{39}H_{37}N_5{}^{35}ClAuF_5FeO$ + H requires 974.16218], 929.0 [M^+ - ($HNMe_2$)], 806.2, 773.1, 610.3 [M^+ - (AuC_6F_5)], 565.2 [M^+ - (AuC_6F_5 + $HNMe_2$)], 499.1, 432.2 [M^+ - ($HNMe_2$ + $C_6H_5CH_2NHCO$], 409.1, 304.0, 213.0, 134.1 [Fe-Cp-CH_2] and 91.0 [CH_2-Cp-CH_2];

Λ ($C_6H_5NO_2$, 20°C) = 0.7 $\Omega^{-1}cm^2mol^{-1}$.

Preparation of Rhodium Complexes

Compound 78

$[RhCl(COD)]_2$ was prepared according to literature procedures.[15]

Compounds 79 – 82

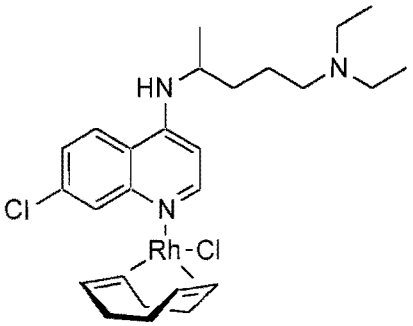
Dichoro(dicyclooctadiene)dirhodium **78** was placed in a Schlenk tube followed by 3 mol equivalents of the appropriate 4-amino-7-chloroquinoline compound. Anhydrous dichloromethane (5 ml) was added and the mixture allowed to heat under reflux for 4 h. There was no visible change in the solution. The solvent volume was reduced to half its original level *in vacuo*. Diethyl ether was then added dropwise until the solution became turbid. The mixture was then placed in the freezer overnight. The suspension was then filtered under reduced pressure and washed with diethyl ether. The solid product was then dried *in vacuo*.

Compound 79

[RhCl(COD)CQ]

Pale yellow crystalline solid; Yield: 321mg (45%);

mp: 171-173°C;



δ_H (300 MHz; $CDCl_3$) 9.49 (1H, br s, ArC_8-H), 8.39 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 7.68 (1H, d, $^3J_{HH}$ = 9 Hz, ArC_5-H), 7.09 (1H, d, $^3J_{HH}$ = 9, ArC_6-H), 6.21 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 6.04 (1H, br s, NH), 4.74 (2H, m, COD – CH trans to Cl), 3.66-3.54 (3H, m, 1', COD – CH cis to Cl), 2.53 (8H, m, 4', 5', COD – CH_2), 1.81 (6H, m, 2', 3'), 1.41 (3H, d, $^3J_{HH}$ = 6, 1'') and 0.98 (4H, br s, COD – CH_2);

$\delta_{C\{H\}}$ (75.5 MHz, $CDCl_3$) 152.1 (ArC_2), 149.6 (^{IV}C, ArC_9), 147.3 (^{IV}C, ArC_4), 135.1 (^{IV}C, ArC_7), 128.2 (ArC_8), 125.3 (ArC_6), 122.7 (ArC_5), 117.9 (^{IV}C, ArC_{10}), 99.6 (ArC_3), 84.2 (2C, CH, COD), 84.0 (2C, CH, COD), 52.6 (2C, 5'), 48.7 (1'), 46.8 (4'), 34.2 (2'), 31.3 (2C, COD), 30.5 (2C, COD), 23.8 (3'), 19.8 (1'') and 11.4 (2C, 6');

IR (KBr) ν_{max} 3320s (NH), 3061m, 2972s, 2935s, 2861s, 2833m, 2808m, 1588vs (7-chloroquinoline), 1540s (7-chloroquinoline), 1492m (ν C=C, COD), 1457s, 1423m, 1380m,

1368m, 1332m, 1280m, 1258m, 1213w, 1197m, 1143m, 1084m, 996m, 965m, 919m, 859m, 809s, 765m, 660w, 532m and 484m (ν Rh-COD);

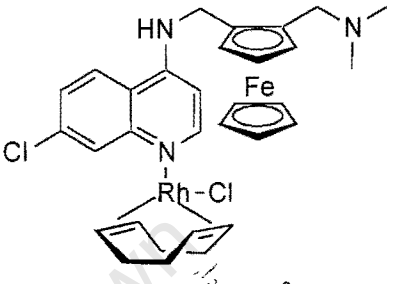
MS (FAB) *m/z* 566.1 [M^+], 530.1799 [(M^+ - Cl), $C_{26}H_{38}N_3ClRh$ requires 530.1809], 420.0, 348.9, 320.1 [M^+ - (Rh(COD)Cl)], 247.1, 211.0, 179.1, 142.2, 136.1, 112.1, 91.1, 86.0 and 77.1;

Found: C, 55.43; H, 6.71; N, 7.12. Calc. for $C_{26}H_{38}N_3Cl_2Rh$: C, 55.13; H, 6.76; N, 7.42%.

^{1}H NMR and IR in agreement with literature values.[2]

Compound 80

[RhCl(COD)FQ]



Orange crystalline solid; Yield: 156mg (60%);

mp: 212°C (dec);

δ_H (300 MHz; $CDCl_3$) 9.58 (1H, br s, ArC_8-H), 8.61 (1H, d, $^3J_{HH}$ = 6, ArC_2-H) 8.17 (1H, br s, NH), 7.54 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.30 (1H, d, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9 Hz, ArC_6-H), 6.42 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.74 (2H, br s, COD - CH trans to Cl), 4.38 (1H, d, $^2J_{HH}$ = 13, 3'a), 4.22 (1H, m, Cp), 4.16 (1H, m, Cp), 4.13 (6H, m, Cp', 3'b), 4.08 (1H, t, $^3J_{HH}$ = 2, Cp), 3.79 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.69 (2H, br s, COD - CH cis to Cl), 2.90 (1H, d, $^2J_{HH}$ = 13, 2'b), 2.56 (4H, m, COD - CH_2), 2.21 (6H, s, 1') and 1.85 (4H, m, COD - CH_2);

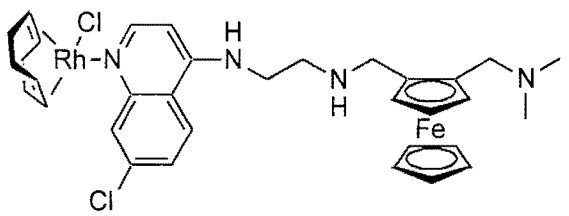
$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 152.7 (ArC_2), 150.7 (ArC_4), 128.7 (ArC_8), 125.6 (ArC_6), 122.4 (ArC_5), 112.4 (^{IV}C, ArC_{10}), 101.4 (^{IV}C), 99.5 (ArC_3), 84.2 (2C, CH, COD), 84.0 (2C, CH, COD), 71.5 (Cp), 70.5 (Cp), 69.3 (5C, Cp'), 66.1 (Cp), 58.0 (2'), 44.9 (2C, 1'), 42.5 (2'), 31.4 (2C, COD, CH_2) and 30.5 (2C, COD, CH_2);

IR (KBr) ν_{max} 3442br m (NH), 3230br m, 3091m, 3077m, 2990m, 2932m, 2878m, 2822m, 2776m, 1590vs (7-chloroquinoline), 1545m (7-chloroquinoline), 1495m (ν C=C, COD), 1451m (NCH_3), 1427m, 1391w, 1367m, 1350m, 1333m, 1296w, 1282m, 1251m, 1228m, 1201m, 1170m, 1136m, 1105m (ferrocene), 1067w, 1029m, 1000m (ferrocene), 962w, 923w, 892w, 861s, 842m, 824s, 807s, 766m, 734m, 701w, 643w, 625w, 615w, 600w, 552w, 523m, 490m (ferrocene), 457w, and 434w

MS (FAB) *m/z* 680.1 [M^+ + H, $C_{31}H_{37}N_3{}^{35}Cl_2FeRh$ requires 680.07690], 644.1 [M^+ - Cl], 599.1, 491.1, 434.1[M^+ - Rh(COD)Cl], 389.1, 359.8, 303.1, 256.1[HC-Fp-CH_2-NMe_2], 213.1, 134.1 and 91.1[CH_2-Cp-CH_2].

Compound 81

[RhCl(COD)F2Q]



Orange crystalline solid; Yield: 130mg (57%);

mp: 213°C (dec);

δ_H (300 MHz; $CDCl_3$) 8.50 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 8.41 (1H, s, ArC_8-H), 7.73 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.33 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 6.27 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 4.70 (2H, br s, COD - CH trans to Cl), 4.14

(1H, m, Cp), 4.10 (2H, m, Cp), 4.04 (5H, Cp'), 3.83 (1H, d, $^2J_{HH}$ = 13, 3'a), 3.67 (3H, m, 2'a, COD - CH cis to Cl), 3.38 (1H, d, $^2J_{HH}$ = 13, 3'b), 3.48-3.40 (2H, m, 5'), 2.98-2.92 (2H, m, 4'), 2.79 (1H, d, $^2J_{HH}$ = 13, 2'b), 2.52 (4H, m, COD - CH_2), 1.95 (6H, s, 1') and 1.76 (4H, m, COD - CH_2);

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 152.0 (ArC_2), 149.9 (ArC_4), 149.2 (^{IV}C), 134.7 (^{IV}C), 128.6 (ArC_8), 125.0 (ArC_6), 121.5 (ArC_5), 117.4 (^{IV}C), 99.1 (ArC_3), 84.5 (2C, CH, COD), 84.2 (2C, CH, COD), 83.8 (^{IV}C, Cp), 71.1 (Cp), 69.9 (Cp), 68.9 (5C, Cp'), 65.8 (Cp), 58.2 (2'), 47.3 (4'), 46.4 (3'), 45.0 (2C, 1'), 42.0 (5') 31.4 (2C, COD, CH_2) and 30.5 (2C, COD, CH_2);

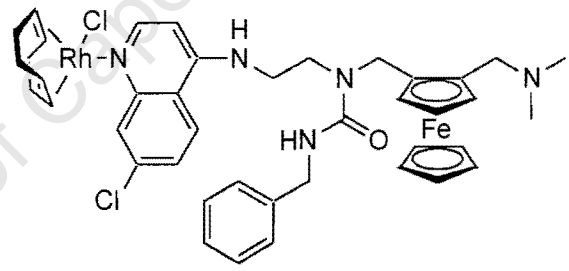
IR (KBr) ν_{max} 3311br m (NH), 3093m, 2940m, 2869m, 2830m, 1611s (7-chloroquinoline), 1584vs (7-chloroquinoline), 1541m (7-chloroquinoline), 1451m (NCH_3), 1424m, 1365m, 1331m, 1283w, 1251w, 1200w, 1171w, 1140m, 1105w (ferrocene), 1062w, 1035w, 998w, 879w, 854w, 815m (ferrocene), 766w, 647w and 493w (ferrocene);

HRMS (FAB) *m/z* 723.3 [M^+ + H], 687.1436 [(M^+ - Cl), $C_{33}H_{41}N_4ClFeRh$ requires 687.1424], 477.2 [M^+ - Rh(COD)Cl], 432.2, 307.1, 213.1, 179.1, 107.1 and 89.1;

Found: C, 57.37; H, 5.28; N, 7.49. Calc. for $C_{33}H_{41}N_4Cl_2FeRh$: C, 57.61; H, 5.36; N, 7.26%.

Compound 82

[Rh(BU)(Cl)(COD)]



Orange crystalline solid; Yield: 145mg (45%);

mp: 210°C (dec);

δ_H (300 MHz; $CDCl_3$) 9.51 (1H, br s, ArC_8-H), 8.55 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.02 (1H, br s, ArCH_2N*H*CO), 7.57 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.14-7.05 (6H, m, U_2, U_3, U_4, ArC_6-H), 6.24 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.72 (2H, br s, COD - CH trans to Cl), 4.41-4.12 (7H, m, Cp, 1'', 3'a, 4'), 4.08 (5H, s, Cp'), 4.05 (1H, m, Cp), 3.77 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.69-3.25 (5H, m, 3'b, 5', COD - CH cis to Cl), 2.74 (1H, d, $^2J_{HH}$ = 13, 2'b), 2.50 (4H, m, COD -CH_2), 1.94 (6H, s, 1') and 1.77 (4H, m, COD - CH_2);

$\delta_{c\{H\}}$ (75.5 MHz; $CDCl_3$) 160.5 (^{IV}C, *C*O), 152.5 (ArC_2), 151.2 (^{IV}C), 147.3 (^{IV}C), 140.1 (^{IV}C), 135.5 (^{IV}C), 128.3 (2C, U), 128.2 (ArC_6), 126.7 (U_4), 126.4 (2C, U), 126.0 (ArC_6), 123.0 (ArC_8), 119.0 (^{IV}C), 98.7 (ArC_3), 84.1 (2C, CH, COD), 83.8 (2C, CH, COD), 82.0 (^{IV}C, Cp), 70.4 (Cp), 69.5 (5C, Cp'), 68.8 (Cp), 67.6 (Cp), 57.9 (2'), 44.7 (2C, 1'), 44.6 (4'), 43.8 (1''), 31.4 (2C, COD, CH_2) and 30.5 (2C, COD, CH_2);

IR (KBr) ν_{max} 3313m, 3084m, 2988m, 2934m, 2878m, 2828m, 2776m, 1590vs (7-chloroquinoline), 1539s (7-chloroquinoline), 1491m (ν C=C, COD), 1452m (NCH_3), 1400m, 1359m, 1331m, 1300m, 1273m, 1256m, 1201m, 1172w, 1139w, 1104w (ferrocene), 1038w, 1005m (ferrocene), 962w, 856m, 810m (ferrocene), 764w, 742m, 695w, 513m, 492m (ferrocene) and 462m;

MS (FAB) *m/z* 856.2 [M^+ + H], 820.3 [M^+ - Cl] 694.1, 610.2 [M^+ - Rh(COD)Cl], 565.2, 409.1, 307.1, 237.9, 213.0, 150.1 and 91.0;

Found: C, 56.95; H, 5.60; N, 7.61. Calc. for $C_{41}H_{48}N_5Cl_2OFeRh$: C, 57.49; H, 5.65; N, 8.18%.

Experimental Details Pertaining to Chapter 5

Testing carried out at Department of Pharmacology, University of Cape Town

Cultivation of Malaria Parasites

Two strains of *P. falciparum* were used in this study, a chloroquine sensitive strain, D10, and a chloroquine resistant strain, K1. The *P. falciparum* strains were cultured using a modified version of the Trager and Jensen method.[16] The parasites were maintained in RPMI 1640 (BioWhittaker) culture medium, to which was added; 40 mg ml^{-1} gentamycin (Lennon); 1% sodium bicarbonate; 0.5% Albumax (lipid rich bovine serum) and O^+ human red blood cells (Transfusion Services and Haemotology, UCT/Groote Schuur Hospital). The cultures were contained in flat bottomed flasks and incubated at 37°C with a controlled atmosphere of 4% CO_2, 3% O_2 and 93% N_2. Medium was changed at frequent intervals and parasite cultures were fed to maintain an optimum 3-5% parasitaemia and a 2-4% haemocrit. The parasitaemia was determined using Giesma stained blood films of the cultures. Synchronisation of cultures was achieved by a brief exposure to 5% *D*-sorbitol solution.

Lactacte Dehydrogenase Assay for Parasite Viability

Sensitive assays are done in 96-well microtitre plates and the parasite lactate dehydrogenase (pLDH) assay[17] was used to evaluate drug susceptibility. This enzymatic assay is based on the ability of pLDH to utilise 3-acetyl pyridine NAD (APAD) as a coenzyme in the conversion of lactate to pyruvate. As human red blood cells LDH carry out this reaction at a very slow rate in the presence of APAD, pLDH activity is distinguishable from host LDH. The formation of APADH by pLDH can be monitored using the Malstat reagent, nitroblue tetrazolium (NBT) and phenazine ethosulfate (PES). As APADH is formed the yellow NBT is reduced to a blue formazan product, the absorbance of which can be measured at 620nm on a 7520 Microplate reader (Cambridge Technology). The amount of blue formazan produced is proportional to the pLDH activity and can, thus, be used to assess parasite viability.

Testing carried out at the Wellcome Trust Biocenter, University of Dundee

Trypanothione Reductase Inhibition

Recombinant *T. cruzi* trypanothione reductase (128 mU) was assayed using a Beckman DU640 spectrophotometer in 40mM HEPES, pH 7.5, 1mM EDTA and 200μM NADPH at 25°C followed by the addition of 100μM Try[SH]2. Human glutathione reductase, purified from human erythrocytes (42.3mU), was analysed in a similar manner and under identical conditions followed by the addition of glutathione disulfide (100μM). Enzyme mixtures were preincubated

with NADPH (10 min at 25°C) before the addition of varying concentrations of the inhibitor added in DMSO (1% v/v final concentration).

Testing carried out at Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine

In Vitro Trials against *L. donovani, T. cruzi* and *T. brucei*

L. donovani (MHOM/ET/67/L82) and *T. cruzi* (MHOM/BR/00/Y): Peritoneal macrophages were harvested from female CD1 mice (Charles River Ltd., Margate, UK) by peritoneal lavage 24 h after starch (Merck Ltd., Leics, UK) induced recruitment. After two washes in medium the exudate cells were dispensed in 16-well Lab-tek™ tissue culture slides (Nunc Inc., IL, USA) at 4 x 10^4/well in a volume of 200µL of RPMI-1640 medium (Sigma-Aldrich Company Ltd., Dorset, UK) and 10% inactivated foetal calf serum (Harlan-Sea-Lab Ltd., Crawley, UK). After 24 h, macrophages were infected at a ratio of 10:1 (4 x 10^5/well) with *L. donovani* amastigotes freshly isolated from hamster spleen or at a ratio of 5:1 (2 x 10^5/well) with *T. cruzi* trypomastigotes derived from the overlay of MDCK fibroblasts. Infected macrophages were then maintained in the presence of drug in a 3-fold dilution series, with quadruplicate cultures for each concentration, for 5 days for *L. donovani* cultures and for 3 days for *T. cruzi* cultures. After these periods of drug exposure slides were methanol fixed and Giemsa stained and drug activity determined by counting the percentage of macrophages cleared of amastigotes in treated cultures in comparison to untreated cultures.[18] Sodium stibgluconate ($NaSb^V$) (Glaxo-Wellcome, Dartford, UK) and nifurtimox (Bayer, UK) or benznidazole were used as the respective control drugs.

T. brucei (S427): Compounds were tested in a triplicate 3-fold dilution series from a top concentration of 30µM. Parasites were diluted to 2 x 10^5/ml and added in equal volumes to the test compounds in 96-well, flat bottom Microtest III tissue culture plates (Becton Dickinson and Company, NJ, USA). Appropriate controls with pentamidine isothionate (Rhone-Poulenc-Rorer) as the standard were set up in parallel. Plates were maintained for 3 days at 37°C in a 5% CO_2/air mixture. Compound activity was determined by the use of a tetrazolium salt colorimetric assay[19] on day 3.

P. falciparum: All compounds were tested against the chloroquine sensitive strain (3D7) and the chloroquine resistant strain (K1). The whole cell growth inhibition assay of *P. falciparum* growth in human red blood cells was carried out in a 48 h [^{3}H]-hypoxanthinine incorporation assay.[20,21]

In Vivo Trials

In vivo testing against *Plasmodium berghei*

Day 1: 5 Balb/c mice were inoculated with 1% (1 x 10^7 infected RBCs) parasitemia i.v.

2 h post infection drugs administered as follows

Chloroquine – 10mg/kg x 4 i.p

Test compounds – 25mg/kg x 4 i.p

Days 2-4: Drugs administered as per above stated dosing and schedule

Day 5: Tail smears were taken, methanol fixed, stained with 10% Giemsa stain and examined under x1000 and parasitemia calculated.

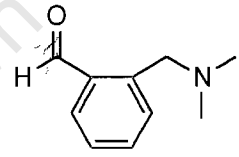
Day 6: Mean Survival Time was monitored and scored.

Experimental Details Pertaining to Chapter 6

Synthesis of Benzyl Derivatives

Compound 101

2-Dimethylaminomethylbenzaldehyde



N,N-Dimethylaminomethylbenzene **99** (3.0ml, 24.6mmol) was placed in a 2-necked round bottomed flask followed by 60ml freshly distilled diethyl ether. *tert*-Butyllithium (1.7M in pentane) (20ml) was added slowly. A white precipitate of lithiobenzyldimethylamine **100** formed immediately. The mixture was allowed to stir at room temperature for 30 min before the dropwise addition of anhydrous DMF (1.6ml). The mixture was allowed to stir for a further 30 min before diluting with diethyl ether and quenching with deionised water. The mixture was extracted into diethyl ether. The organic fractions were collected, combined and dried over sodium sulfate. The solvent was removed under reduced pressure. The product, a colourless oil, was then isolated by silica gel chromatography. Yield: 2.234g (60%);

R_f (silica/diethyl ether: hexane: Et_3N = 70:20:10) 0.25;

δ_H (300 MHz; $CDCl_3$) 10.40 (1H, s, C*H*O), 7.85 (1H, dd, $^3J_{HH}$ = 1 and $^3J_{HH}$ = 8, B_6), 7.50 (1H, m, B), 7.39 (2H, m, B), 3.72 (2H, s, 2') and 2.22 (6H, s, 1');

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 192.1 (*C*HO), 141.7 (^{IV}C), 135.1 (^{IV}C), 133.1 (B), 130.4 (B_6), 129.4 (B), 127.7 (B), 60.9 (2') and 45.1 (2C, 1');

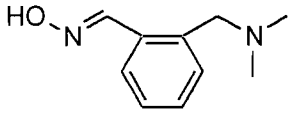
IR (thin film) ν_{max} 3366w, 3069w, 3028w, 2975s, 2943s, 2859s, 2819s, 2771s, 1690vs (ν C=O), 1599s, 1574w, 1457s (NCH_3), 1396m, 1362m, 1309w, 1290m, 1251m, 1213s, 1190m, 1174m, 1145m, 1097w, 1043m, 1023s, 974w, 954w, 882w, 844s (aryl $CH_2N(CH_3)_2$ group), 810m, 756s (4 adjacent aromatic H), 657m and 610m;

HRMS (EI) *m/z* 163.10011 [M^+, $C_{10}H_{13}NO$ requires 163.09971], 148.1 [M^+ - CH_3], 135.1, 119.0, 91.1, 77.0, 65.0, 58.0 [CH_2NMe_2] and 44.0.

^{1}H NMR in agreement with literature[22]

Compound 102

2-Dimethylaminomethylbenzaldehyde Oxime



2-Dimethylaminomethylbenzenecarboxaldehyde **101** (1.162g,

7.11mmol) was placed in a 250ml round bottomed flask followed by 75ml absolute ethanol and hydroxylamine hydrochloride (1.384g, 19.38mmol). A solution of sodium hydroxide (1.582g, 40.2mmol) in 20ml deionised water was added. The mixture was allowed to heat under reflux under nitrogen for 14 h. The mixture was allowed to cool and dry ice was added until neutralisation was achieved. The mixture was diluted with deionised water and extracted into dichloromethane. The organic layer was dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The product was then dried *in vacuo* and isolated as a colourless oil. Yield: 1.159g (91%);

δ_H (400 MHz; $CDCl_3$) 8.56 (1H, s, 3'), 7.76 (1H, m, B_6), 7.32 (3H, m, B), 3.56 (2H, s, 2'), 2.28 (6H, s, 1') and 2.24 (1H, s, O*H*);

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 148.8 (3'), 131.2 (B), 129.3 (B), 128.0 (B), 127.0 (B), 61.8 (2') and 45.2 (1');

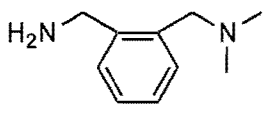
IR (thin film) ν_{max} 3224br s (OH), 3063s, 2816s (aliphatic CH), 2779s, 1927w, 1637w, 1600w, 1573w, 1464s (NCH_3), 1364s, 1315m, 1254m, 1222m, 1174m, 1149w, 1096m, 1044s, 1020s, 970s, 870m, 842s (aryl $CH_2N(CH_3)_2$ group), 760s (4 adjacent aromatic H), 738m, 701w and 638m;

HRMS (EI) *m/z* 161.10731 [(M^+ - OH), $C_{10}H_{13}N_2$ requires 161.10787], 145.1, 132.1, 118.1, 104.1, 89.0, 77.0, 58.1 and 44.0 (M^+, 178.1 not observed).

Infrared data is in agreement with literature[23]

Compound 103

2-Dimethylaminomethylbenzylamine



2-Dimethylaminomethylbenzaldehyde oxime **102** (1.100g, 6.171mmol) was placed in a 100ml round bottomed flask. 50ml anhydrous THF was added followed by lithium aluminium hydride (769mg, 20.00mmol). The mixture was heated under reflux under an atmosphere of nitrogen for 15 h. The mixture was allowed to cool to room temperature before adding diethyl ether and a saturated brine solution. The product was extracted into diethyl ether and dried over potassium carbonate. The solvent was removed under reduced pressure before drying the product *in vacuo*. The product was isolated as a colourless oil. Yield: 805mg (79%)

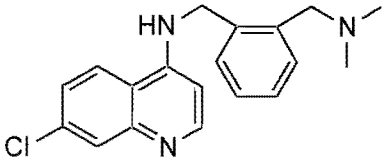
δ_H (400 MHz; $CDCl_3$) 7.26 (4H, m, B_3, B_4, B_5, B_6), 3.83 (2H, s, 2'), 3.42 (2H, s, 3'), 2.23 (2H, s, NH_2) and 2.20 (6H, s, 1');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 142.4 (^{IV}C, B_1), 137.0 (^{IV}C, B_2), 131.0 (B), 128.9 (B), 128.1 (B), 126.7 (B), 62.8 (2'), 45.3 (1') and 45.0 (3');

IR (thin film) ν_{max} 3349m (NH), 3264m (NH), 3063m, 3018m, 2914s, 2856s, 2815s, 2769s, 2714m, 1602m, 1465s (NCH_3), 1362s, 1311m, 1253s, 1215m, 1174s, 1147m, 1097m, 1042s, 1020s, 967m, 944m, 910m, 843s (aryl $CH_2N(CH_3)_2$) and 752s (4 adjacent aromatic H).

^{1}H NMR and IR spectra in agreement with literature.[24]

Compound 85



(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethyl-benzyl)-amine

2-Dimethylaminomethylbenzylamine **103** (0.805g, 4.9mmol), 4,7-dichloroquinoline (5.0g, 25mmol), potassium carbonate (1.0g, 7.25mmol), anhydrous triethylamine (5.0ml, 36mmol) and anhydrous NMP (7ml) were placed in a 25ml round bottomed flask and allowed to heat under reflux in an atmosphere of nitrogen for 15 h. The mixture was allowed to cool to room temperature before diluting with ethyl acetate. The product was washed 10 times with brine. The organic layer was dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The product was purified using silica gel chromatography and isolated as a white crystalline solid. Yield: 819mg (51%);

R_f (silica/ethyl acetate: hexane: Et_3N = 45:50:5) 0.24;

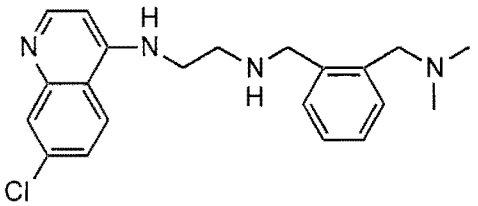
δ_H (400 MHz; $CDCl_3$) 8.53 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 8.31 (1H, br s, N*H*), 7.90 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.62 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.40-7.37 (1H, m, B), 7.31-7.22 (4H, m, ArC_6-H, B), 6.52 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 4.42 (2H, s, 3'), 3.46 (2H, s, 2') and 2.24 (6H, s, 1');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 152.3 (ArC_2), 150.7 (^{IV}C), 149.5 (^{IV}C), 137.5 (^{IV}C), 137.2 (^{IV}C), 134.7 (^{IV}C), 132.1 (B), 130.1 (B), 128.6 (ArC_8-H), 128.1 (B), 124.9 (ArC_6), 122.3 (ArC_5), 118.3 (^{IV}C), 99.0 (ArC_3), 62.7 (2'), 47.4 (3') and 45.1 (2C, 1');

IR (KBr) ν_{max} 3426br m (NH), 3212br m, 3065m, 3021m, 2968m, 2941m, 2858m, 2817m, 2790m, 2768m, 1662m, 1610m (7-chloroquinoline), 1575s (7-chloroquinoline), 1485m, 1449m (NCH_3), 1427m, 1367m, 1350m, 1326m, 1284m, 1237s, 1163m, 1147m, 1136m, 1082m, 1040w, 1014m, 967w, 901m, 882m, 840m (aryl $CH_2N(CH_3)_2$), 811s, 771m, 746s (4 adjacent aromatic H), 714w, 645m, 590m, 541m, 495w, 463w and 432w;

HRMS (EI) *m/z* 325.13380 [M^+, $C_{19}H_{20}N_3{}^{35}Cl$ requires 325.13458], 280.1 [M^+ - (NMe_2)], 263.0, 245.1, 163.0, 146.1, 132.1 and 118.1.

Compound 86



N-(7-Chloroquinolin-4-yl)-*N'*-(2-dimethylaminomethylbenzyl)-ethane-1,2-diamine

The compound was prepared in the manner described for **20**.

Colourless oil; Yield: 1.881g (60%);

R_f (silica/CH_2Cl_2: MeOH: Et_3N = 80:20:1) 0.13;

δ_H (400 MHz; $CDCl_3$) 8.53 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 7.95 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.76 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.38 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H), 7.33-7.18 (4H, m, B_3, B_4, B_5, B_6), 6.41 (IH, d, $^3J_{HH}$ = 5, ArC_3-H), 3.85 (2H, s, 3'), 3.43 (2H, s, 2'), 3.34-3.29 (2H, m, 5'), 3.00-2.95 (2H, m, 4') and 2.11 (6H, s, 1');

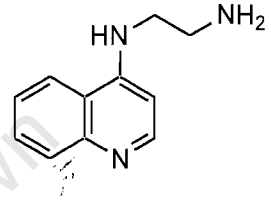
$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 152.0 (ArC_2), 131.1, 130.8, 128.7, 127.8, 125.3, 121.2, 99.2 (ArC_3), 62.5 (2'), 51.6 (4'), 45.0 (3'), 44.7 (2C, 1') and 40.2 (5');

IR (thin film) ν_{max} 3265m (NH), 3054m, 2944m, 2858m, 2820m, 2777m, 1611s (7-chloroquinoline), 1582vs (7-chloroquinoline), 1535s (7-chloroquinoline), 1450s (NCH_3), 1428m, 1367s, 1331s, 1265s, 1204w, 1172w, 1140m, 1081m, 1041w, 1017m, 878m, 843m (aryl $CH_2N(CH_3)_2$), 808m, 738s (4 adjacent aromatic H) and 703m;

HRMS (EI) *m/z* 368.17829 [M^+, $C_{21}H_{25}N_4{}^{35}Cl$ requires 368.17677], 323.1 [M^+ - NMe_2], 263.1, 205.1, 191.1 [ClC_9NH_5-NH-CH_2], 177.2 [ClC_9NH_5-NH], 156.0, 146.0, 132.1, 118.1, 105.1 and 58.0.

Synthesis of Quinoline Derivatives

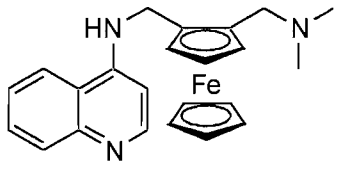
Compound 106



N^1-Quinolin-4-yl-ethane-1,2-diamine

This compound was synthesised according to literature procedures.[9] The final product was tested on TLC (ethyl acetate: hexane; 1:1) and no 4-chloroquinoline was observed.

Compound 87



(2-Dimethylaminomethyl-ferrocenyl)-quinolin-4-yl-amine

Compound prepared in the manner described for **15** using appropriate starting materials.

Deep orange crystalline solid; Yield: 716mg (70%); mp: 148-150°C;

R_f (silica/ethyl acetate: hexane: Et_3N = 45:50:5) 0.11;

δ_H (400 MHz; $CDCl_3$) 8.56 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 7.94 (1H, dd, $^4J_{HH}$ = 1 and $^3J_{HH}$ = 8, ArC_8-H), 7.70 (1H, dd, $^4J_{HH}$ = 1 and $^3J_{HH}$ = 8, ArC_5-H), 7.58 (1H, m, ArC_7-H), 7.33 (1H, m, ArC_6-H), 6.48 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 4.38 (1H, d, $^2J_{HH}$ = 13, 3'a), 4.27 (1H, m, Cp), 4.20-4.14 (2H, m, Cp, 3'b), 4.13 (5H, s, Cp'), 4.07 (1H, t, $^3J_{HHH}$ = 3, Cp), 3.79 (1H, d, $^2J_{HH}$ = 13, 2'a), 2.89 (1H, d, $^2J_{HH}$ = 13, 2'b) and 2.22 (6H, s, 1');

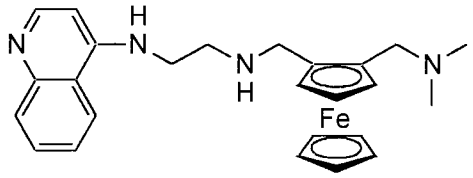
$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 151.2 (ArC_2), 150.4 (^{IV}C), 148.8 (^{IV}C), 129.7 (ArC_8), 128.9 (ArC_7), 124.2 (ArC_6), 120.7 (ArC_5), 119.6 (^{IV}C), 98.7 (ArC_3), 84.4 (^{IV}C, Cp), 84.2 (^{IV}C, Cp), 71.5 (Cp), 70.6 (Cp), 69.3 (5C, Cp'), 66.0 (Cp), 58.2 (2'), 45.1 (2C, 1') and 42.5 (3');

IR (KBr) ν_{max} 3185br m (NH), 3078m, 3058m, 2969m, 2943m, 2907m, 2861m, 2825m, 2781m, 1617m (quinoline), 1572vs (quinoline), 1540s (quinoline), 1500m, 1467s (NCH_3), 1433m, 1395m, 1362m, 1340m, 1288m, 1251m, 1221m, 1190m, 1170m, 1151w, 1117s, 1103m (ferrocene), 1032m, 1005m (ferrocene), 953w, 900w, 838m (aryl $CH_2N(CH_3)$), 822s (ferrocene), 805s, 780w, 757s, 726m, 694m, 619w, 594w, 550w, 530w, 497m (ferrocene), 480s (ferrocene) and 432m;

HRMS (EI) *m/z* 399.14058 [M^+, $C_{23}H_{25}N_3Fe$ requires 399.13979], 354.1 [M^+ - NMe_2], 288.0, 255.1 [HC-Fp-CH_2-NMe_2], 213.0, 198.0, 121.0[Cp-Fe], 91.1 [CH_2-Cp-CH_2] and 58.1 [NMe_2];

Found: C, 69.18; H, 6.17; N, 10.10. Calc. for $C_{23}H_{24}N_3ClFe$: C, 69.18; H, 6.31; N, 10.52%.

Compound 88



N-(2-Dimethylaminomethyl-ferrocenyl)-*N*-quinolin-4-yl-ethane-1,2-diamine

Compound prepared in the manner described for **20** using appropriate starting materials.

Yellow crystalline solid; Yield: 713mg (60%); mp: 128-129°C;

R_f (silica/CH_2Cl_2: MeOH: Et_3N = 80:20:1) 0.22;

δ_H (400 MHz; $CDCl_3$) 8.46 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 7.90 (1H, d, $^3J_{HH}$ = 8, ArC_8-H), 7.79 (1H, d, $^3J_{HH}$ = 8, ArC_5-H), 7.52 (1H, t, $^3J_{HHH}$ = 7, ArC_7-H), 7.30 (1H, t, $^3J_{HH}$ = 8, ArC_6-H), 6.29 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 6.14 (1H, s, N*H*), 4.05 (1H, m, Cp), 4.00 (1H, m, Cp), 3.94 (6H, s, Cp, Cp'), 3.75 (1H, d, $^2J_{HH}$ = 13, 3'a), 3.57 (1H, d, $^2J_{HH}$ = 12, 2'a), 3.31 (1H, d, $^2J_{HH}$ = 13, 3'b), 3.26-3.12 (2H, m, 5'), 2.87-2.77 (2H, m, 4'), 2.69 (1H, d, $^2J_{HH}$ = 12, 2'b) and 1.93 (6H, s, 1');

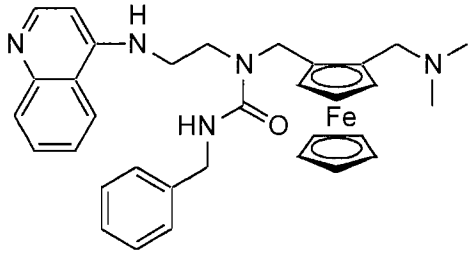
$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 151.1 (ArC_2), 150.1 (^{IV}C), 148.6 (^{IV}C), 129.7 (ArC_8), 128.9 (ArC_7), 124.5 (ArC_6), 120.3 (ArC_5), 119.2 (^{IV}C), 98.8 (ArC_3), 85.7 (^{IV}C, Cp), 83.9 (^{IV}C, Cp), 71.1 (Cp), 70.1 (Cp), 69.0 (5C, Cp'), 66.0 (Cp), 58.2 (2'), 47.4 (3'), 46.6 (4'), 45.0 (2C, 1') and 42.2 (5');

IR (KBr) ν_{max} 3235br m (NH), 3070m, 2950m, 2890m, 2839m, 2812m, 2764s, 1619m (quinoline), 1577vs (quinoline), 1550s (quinoline), 1500m, 1460s (NCH_3), 1435s, 1393s, 1366m, 1334s, 1276m, 1242m, 1213m, 1167m, 1152m, 1133m, 1104s (ferrocene), 1054m, 1033m, 1014m, 1000m (ferrocene), 948m, 927m, 878w, 864m, 828m (aryl $CH_2N(CH_3)$), 807s (ferrocene), 769s, 654m, 610w, 543m, 490m (ferrocene), 456m and 426w;

HRMS (EI) *m/z* 442.18181 [M^+, $C_{25}H_{30}N_4Fe$ requires 442.18199], 397.1, 332.1, 277.0, 255.0 [HC-Fp-CH_2-NMe_2], 240.0 [Fp-CH_2-NMe_2], 213.0, 157.1, 120.1, 91.0 [CH_2-Cp-CH_2] and 58.1 [NMe_2];

Found: C, 69.19; H, 6.84; N, 12.33. Calc. for $C_{23}H_{24}N_3ClFe$: C, 67.88; H, 6.84; N, 12.66%.

Compound 89



3-Benzyl-1-(2-dimethylaminomethyl-ferrocenyl-1-[2-(quinolin-4-ylamino)-ethyl]-urea

Compound prepared in the manner described for **37** (method 4) using appropriate starting materials.

Bright yellow crystalline solid; Yield: 150mg (80%);

mp: 88-89°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.47;

δ_H (300 MHz; $CDCl_3$) 8.52 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 8.03 (1H, t, $^3J_{HH}$ = 5, $ArCH_2NHCO$), 7.96 (1H, d, $^3J_{HH}$ = 8, ArC_8-H), 7.82 (1H, d, $^3J_{HH}$ = 8, ArC_5-H), 7.63-7.52 (1H, m, ArC_7-H), 7.27 (1H, t, $^3J_{HHH}$ = 7, ArC_6-H), 7.14-7.09 (5H, m, U_2, U_3, U_4), 6.34 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 4.49-4.16 (7H, m, Cp, 1'', 3'a, 3'b), 4.12 (1H, t, $^3J_{HH}$ = 2, Cp), 4.06 (5H, s, Cp'), 4.05-4.03 (1H, m, Cp), 3.76 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.71-3.63 (2H, m, 4'), 3.58-3.37 (2H, m, 5'), 2.74 (1H, d, $^2J_{HH}$ = 13, 2'b) and 1.94 (6H, s, 1');

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 160.3 (^{IV}C, CO), 150.9 (^{IV}C), 150.2 (ArC_2), 147.6 (^{IV}C), 140.3 (^{IV}C, U_1), 129.0 (ArC_8), 128.6 (ArC_7), 128.2 (2C, U), 126.6 (2C, U), 126.5 (U_4), 124.7 (ArC_6), 121.1 (ArC_5), 118.8 (^{IV}C), 97.4 (ArC_3), 84.0 (^{IV}C, Cp), 82.0 (^{IV}C, Cp), 70.4 (Cp), 69.4 (5C, Cp'), 68.8 (Cp), 67.4 (Cp), 57.9 (2'), 47.0 (3'), 45.4 (4'), 44.7 (2C, 1'), 44.6 (1'') and 43.6 (5');

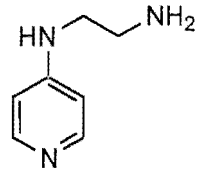
IR (KBr) ν_{max} 3280br m (NH), 3062m, 2942m, 2858m, 2823m, 2780m, 1618s (quinoline), 1584vs (quinoline), 1538s (quinoline), 1495m, 1456m (NCH_3), 1439m, 1402m, 1352m, 1303m, 1269m, 1172m, 1126m, 1070w, 1037m, 1004m (ferrocene), 959w, 911w, 810m (ferrocene), 765m, 731m, 699m, 607w, 527w and 487w (ferrocene);

HRMS (EI) *m/z* 575.23467 [M^+, $C_{33}H_{37}N_5OFe$ requires 575.23467], 530.2, 442.2, 397.1, 332.0, 277.0, 255.1 [HC-Fp-CH_2-NMe_2], 240.0 [Fp-CH_2-NMe_2], 213.0, 157.1, 133.1, 121.0 [Cp-Fe], 91.0 [CH_2-Cp-CH_2] and 58.1 [NMe_2].

Synthesis of Pyridine Derivatives

Compound 108

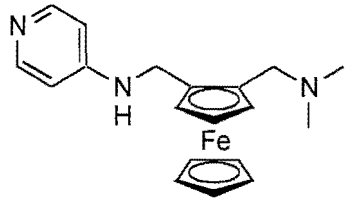
N^1-Pyridin-4-yl-ethane-1,2-diamine



4-Chloropyridine hydrochloride (2.500g, 15.7mmol) was stirred with triethylamine (10.0ml, 72mmol). Ethylene diamine (6.0ml, 8.4mmol) was added and the mixture allowed to heat under reflux under nitrogen for 24 h. The mixture was allowed to cool and then diluted with dichloromethane. 1M sodium hydroxide solution was added. The product was extracted into dichloromethane and dried over sodium sulfate before removing the solvent under reduced pressure. TLC (ethyl acetate: hexane; 1:1) showed a single spot on the base line, there was no evidence of 4-chloropyridine.

Yield: 60%.

Compound 90



(2-Dimethylaminomethyl-ferrocenyl)-pyridin-4-yl-amine

The synthetic route employed was similar to that of ferroquine.[6] However, the starting material was 4-chloropyridine hydrochloride, as opposed to 4-chloropyridine. To compensate for this an extra mol equivalent of triethylamine was added. The 4-chloropyridine was allowed to stir with the triethylamine for 15 minutes prior to addition of the other reagents.

Deep red oil; Yield: 60mg (35%);

R_f (silica/ethyl acetate: hexane: Et_3N = 45:50:5) 0.05;

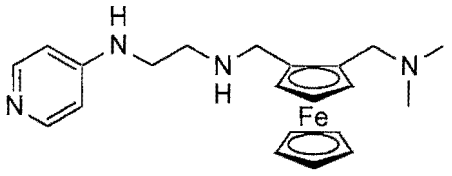
δ_H (400 MHz; $CDCl_3$) 8.15 (2H, br s, ArC_2-H), 6.45 (2H, br s, ArC_3-H), 4.31-4.13 (5H, m, Cp, 3'a, 3'b), 4.11 (5H, s, Cp'), 3.80 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.01 (1H, d, $^2J_{HH}$ = 13, 2'b) and 2.25 (6H, s, 1');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 155.1 (^{IV}C, ArC_4), 145.0 (2C, ArC_2), 107.5 (2C, ArC_3), 84.0 (^{IV}C, Cp), 82.5 (^{IV}C, Cp), 71.5 (Cp), 70.3 (5C, Cp'), 69.4 (Cp), 66.7 (Cp), 57.6 (2'), 44.3 (2C, 1') and 41.8 (3');

IR (thin film) ν_{max} 3267br s (NH), 2925s, 2854m, 2823m, 2777m, 1651s, 1606s (pyridine), 1573s, 1556s, 1469m (NCH_3), 1404m, 1266m, 1204m, 1172w, 1106m (ferrocene), 1038m, 1003m (ferrocene), 947w, 816m (ferrocene), 740m and 701m;

HRMS (EI) *m/z* 349.12487 [M^+, $C_{19}H_{23}N_3Fe$ requires 349.12414], 304.1, 255.1 [HC-Fp-CH_2-NMe_2], 238.0, 227.0, 213.0, 199.1, 134.1, 121.0 [Cp-Fe], 91.0 [CH_2-Cp-CH_2] and 58.1 [NMe_2].

Compound 91



N-(2-Dimethylaminomethyl-ferrocenyl)-*N*-pyridin-4-yl-ethane-1,2-diamine

The compound was prepared in the same manner described for **20** using appropriate starting materials.

Deep red oil; Yield: 515mg (60%);

R_f (silica/CH_2Cl_2: MeOH: Et_3N = 80:20:1) 0.22;

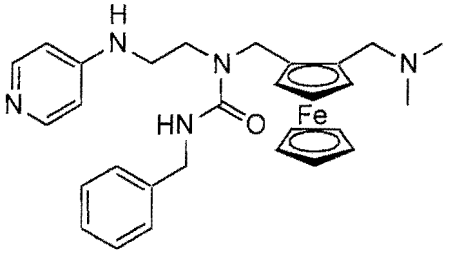
δ_H (400 MHz; $CDCl_3$) 8.10 (2H, d, $^3J_{HH}$ = 5, ArC_2-H), 6.40 (2H, d, $^3J_{HH}$ = 6, ArC_3-H), 4.12 (1H, m, Cp), 4.07 (1H, m, Cp), 4.00 (5H, s, Cp'), 3.98 (1H, m, Cp), 3.86 (1H, d, $^2J_{HH}$ = 13, 3'a), 3.66 (1H, d, $^2J_{HH}$ = 12, 2'a), 3.37 (1H, d, $^2J_{HH}$ = 13, 3'b), 3.24-3.10 (2H, m, 5'), 2.79-2.72 (3H, m, 4', 2'b) and 2.04 (6H, s, 1');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 153.6 (^{IV}C, ArC_4), 149.9 (2C, ArC_2),107.6 (2C, ArC_3), 84.1 (^{IV}C, Cp), 83.8 (^{IV}C, Cp), 71.3 (Cp), 70.4 (Cp), 69.2 (5C, Cp'), 66.2 (Cp), 58.2 (2"), 47.3 (3'), 46.6 (5'), 44.6 (2C, 1') and 41.5 (4');

IR (thin film) ν_{max} 3251br m (NH), 3149m, 3094m, 3046m, 2943m, 2855m, 2818m, 2773m, 1605vs (pyridine), 1545m, 1466m (NCH_3), 1402m, 1347m, 1323m, 1265m, 1217m, 1172w, 1155w, 1104m (ferrocene), 1034m, 998m, 811s (ferrocene), 735s and 701m;

HRMS (EI) *m/z* 392.16500 [M^+, $C_{21}H_{28}N_4Fe$ requires 392.16634], 373.1, 255.1 [HC-Fp-CH_2-NMe_2], 240.0 [Fp-CH_2-NMe_2], 213.0, 200.0, 163.0 [ClC_9NH_5], 134.1, 121.0 [Cp-Fe], 107.1, 91.0 [CH_2-Cp-CH_2] and 58.1 [NMe_2].

Compound 92



3-Benzyl-1-(2-dimethylaminomethyl-ferrocenyl)-1-[2-(pyridine-4-ylamino)-ethyl]-urea

Prepared in the same manner described for **37** (method 4) using appropriate starting materials.

Bright yellow crystalline solid; Yield: 236mg (71%);

mp: 70-72°C;

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.05;

δ_H (300 MHz; $CDCl_3$) 8.13 (2H, d, $^3J_{HH}$ = 6, ArC_2-H), 7.68 (1H, br s, NH), 7.25-7.08 (5H, m, U_2, U_3, U_4), 6.40 (2H, d, $^3J_{HH}$ = 6, ArC_3-H), 6.28 (1H, br s, NH), 4.43 (1H, d, $^2J_{HH}$ = 16, 3'a), 4.35-4.32 (1H, m, Cp), 4.23 (1H, d, $^2J_{HH}$ = 16, 3'b), 4.23-4.25 (1H, m, Cp), 4.13 (1H, t, $^3J_{HH}$ = 3, Cp), 4.06 (5H, s, Cp'), 4.00-3.89 (2H, m, 1''), 3.78 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.60-3.50 (2H, m, 4'), 3.40-3.20 (2H, m, 5'), 2.76 (1H, d, $^2J_{HH}$ = 13, 2'a) and 1.96 (6H, s, 1');

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 159.7 (^{IV}C, *C*O), 154.2 (^{IV}C, ArC_4), 148.3 (2C, ArC_2), 140.4 (^{IV}C, U_1), 128.3 (2C, U_3), 126.7 (2C, U_2), 126.6 (U_4), 107.2 (ArC_3), 84.2 (^{IV}C, Cp), 82.1 (^{IV}C, Cp), 70.5 (Cp), 69.4 (5C, Cp'), 69.0 (Cp), 67.4 (Cp), 57.9 (2'), 47.2 (3'), 45.6 (1''), 44.7 (2C, 1'), 44.6 (4') and 42.6 (5');

IR (KBr) ν_{max} 3263m (NH), 3028m, 2941m, 2859m, 2821m, 2776m, 1604vs (pyridine), 1529s, 1455m (NCH_3), 1428m, 1404m, 1353m, 1268m, 1240m, 1216m, 1105m (ferrocene), 1036m, 990m, 813m (ferrocene), 731m, 699m, 608w, 527m, 510m, 487m (ferrocene) and 457w;

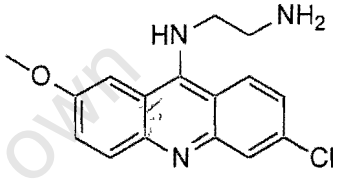
HRMS (EI) *m/z* 525.21853 [M^+, $C_{29}H_{35}N_5OFe$ requires 525.21910], 392.2, 347.1, 282.1, 255.1 [HC-Fp-CH_2-NMe_2], 240.0 [Fp-CH_2-NMe_2], 213.0, 133.1, 91.1 [CH_2-Cp-CH_2], 77.0 and 58.1 [NMe_2].

Compound 109

N^1-(6-Chloro-2-methoxy-acridine-9-yl)-ethane-1,2-diamine

Prepared according to literature procedure[25]

Bright yellow crystalline solid; Yield: 90%.

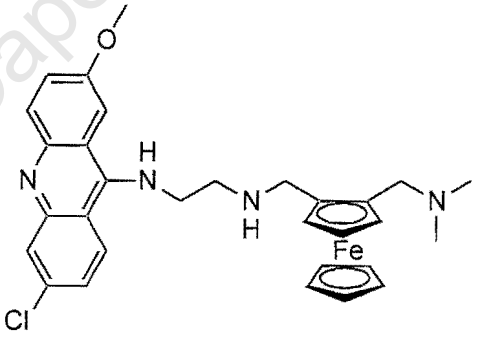


Compound 93

N-(6-Chloro-2-methoxy-acridine-9-yl)-*N'*-[2-(*N''*,*N''*-dimethylaminomethyl)ferrocenylmethyl]-ethane-1,2-diamine

Prepared in the same manner as that described for **20** using appropriate starting materials

Deep orange crystalline solid; Yield: 467mg (74%)



R_f (silica/CH_2Cl_2:MeOH:Et_3N = 80:20:1) 0.25;

δ_H (400 MHz; $CDCl_3$) 8.14 (1H, d, $^3J_{HH}$ = 9, ArC_8-H), 8.05 (1H, d, $^4J_{HH}$ = 2, ArC_5-H), 7.99 (1H, d, $^3J_{HH}$ = 10, ArC_1-H), 7.41-7.37 (2H, m, ArC_3-H, ArC_4-H), 7.28 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_7-H), 4.13-4.12 (2H, m, Cp), 4.05 (5H, s, Cp'), 4.04-4.03 (1H, m, Cp), 3.91 (1H, d, $^2J_{HH}$ = 13, 3'a), 3.90 (3H, s, O*C*H_3), 3.79-3.67 (2H, m, 5'), 3.73 (1H, d, $^2J_{HH}$ = 12, 2'a), 3.42 (1H, d, $^2J_{HH}$ = 13, 3'b), 2.87-2.84 (2H, m, 4'), 2.83 (1H, d, $^2J_{HH}$ = 12, 2'b) and 2.11 (6H, s, 1');

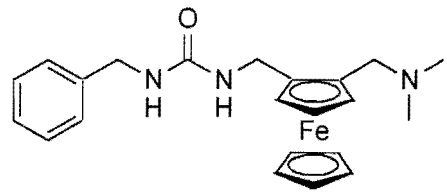
$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 131.4 (ArC_4), 128.3 (ArC_8), 124.9 (ArC_7), 124.6 (ArC_5), 124.3 (ArC_3), 99.8 (ArC_1), 71.3 (Cp), 70.1 (Cp), 69.1 (5C, Cp'), 66.0 (Cp), 58.4 (2'), 55.7 (OCH_3), 48.9 (4'), 48.4 (5'), 47.3 (3') and 46.4 (1');

IR (KBr) ν_{max} 3304br m, 3090m, 2938m, 2854m, 2817m, 2772m, 1631s (acridine), 1606m (acridine), 1561s (acridine), 1519m (OCH_3), 1467s (NCH_3), 1436s, 1347m, 1237s, 1168m, 1104m (ferrocene), 1074m, 1030m (ν-s R-O-R'), 1001m (ferrocene), 926m, 871w, 826m, 761m, 670w, 610w, 563w and 488m (ferrocene);

HRMS (EI) *m/z* 556.1685 [M^+, $C_{30}H_{33}N_4OClFe$ requires 556.4647], 511.1 [M^+ - ($HNMe_2$)], 468.1, 446.1 [M^+ - (Cp + NMe_2)], 311.0, 255.1 [HC-Fp-CH_2-NMe_2], 240.0 [Fp-CH_2-NMe_2], 213.0,] 191.0, 156.1, 121.0 [Cp-Fe], 91.1 [CH_2-Cp-CH_2], 58.1 [NMe_2] and 55.9 [Fe].

Preparation of disubstituted ureas

Compound 94



1-Benzyl-3-(2-dimethylaminomethylferrocenylmethyl)-urea

Prepared in the same manner as described for **37** (method 4) using appropriate starting materials.

Deep red oil;

Yield: 109mg (73%);

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.41;

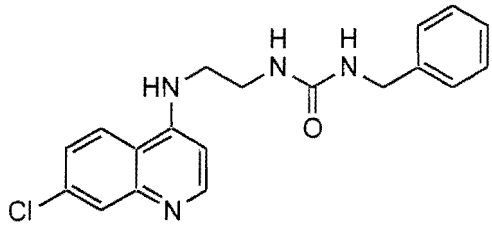
δ_H (400 MHz; $CDCl_3$) 7.30-7.22 (5H, m, U), 4.35-4.22 (4H, m, 1'', 3'a, Cp), 4.10-4.04 (3H, m, Cp, 3'b), 4.06 (5H, Cp'), 3.77 (1H, d, $^2J_{HH}$ = 13, 2'a), 2.86 (1H, d, $^2J_{HH}$ = 13, 2'b) and 2.11 (6H, s, 1'');

$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 128.5 (2C, U), 127.3 (U_4), 127.1 (2C, U), 85.6 (^{IV}C, Cp), 70.8 (Cp), 70.1 (Cp), 69.1 (5C, Cp'), 66.3 (Cp), 58.0 (2'), 44.6 (2C, 1''), 44.5 (1'') and 39.0 (3');

IR (thin film) ν_{max} 3311br m (NH), 3088m, 3030m, 2941m, 2857m, 2819m, 2775m, 1640s (ν C=O), 1565s, 1495m, 1454m (NCH_3), 1352m, 1265s, 1172w, 1105m (ferrocene), 1080w, 1029m, 1002m (ferrocene), 819m (ferrocene), 734s (5 adjacent aromatic H) and 700m (5 adjacent aromatic H);

HRMS (EI) *m/z* 405.1497 [M^+, $C_{22}H_{27}N_3OFe$ requires 405.315], 360.1 [M^+ - (NMe_2)], 296.1, 255.1 [HC-Fp-CH_2-NMe_2], 254.1, 240.1 [Fp-CH_2-NMe_2], 225.0, 199.0, 161.1, 134.1, 121.0 [Cp-Fe], 91.0 [CH_2-Cp-CH_2] and 58.1 [NMe_2].

Compound 95



1-Benzyl-3-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-urea

Prepared in the same manner as described for **37** (method 4) using appropriate starting materials.

White crystalline solid; Yield: 124mg (45%);

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.47;

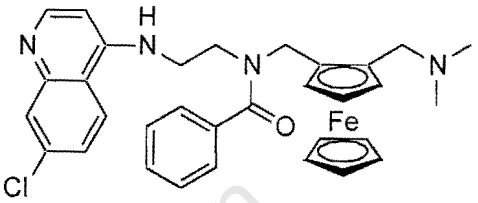
δ_H (400 MHz; DMSO) 8.38 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.16 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.77 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.52 (1H, br t, N*H*), 7.43 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_3-H), 7.28-7.15 (5H, m, B), 6.57 (1H, t, $^3J_{HHH}$ = 6, N*H*), 6.53 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 6.26 (1H, t, $^3J_{HH}$ = 6, N*H*), 4.22 (2H, d, $^3J_{HH}$ = 6, 1'') (note – 1' and 2' signals are obscured by the presence of the DMSO signal);

$\delta_{C\{H\}}$ (100.6 MHz; DMSO) 159.5 (^{IV}C, *C*O), 152.6 (ArC_2), 150.9 (^{IV}C), 149.7 (^{IV}C), 141.4 (^{IV}C), 134.1 (^{IV}C), 128.8 (2C, U), 128.2 (U_4), 127.7 (2C, U), 127.2 (ArC_6), 124.8 (ArC_5), 124.5 (ArC_8), 99.3 (ArC_3), 44.5, 43.7 and 38.8 (1'');

IR (KBr) ν_{max} 3353s (NH), 1612s (7-chloroquinoline), 1584s (7-chloroquinoline), 1537m (7-chloroquinoline), 1485m, 1451m, 1371w, 1334w, 1260w, 1198w, 1141m, 1097w, 1080w, 870m, 803m, 760w, 736m (5 adjacent aromatic H), 700m (5 adjacent aromatic H), 645m and 456w;
HRMS (EI) *m/z* 354.12527 [M^+, $C_{19}H_{19}N_4O^{35}Cl$ requires 354.12474], 248.1 [M^+ - (C_6H_5-CH_2-NH)], 204.0 [M^+ - (NHCONH-CH_2-C_6H_5)], 192.0, 164.0, 133.0, 107.1, 91.0 [C_6H_5-CH_2] and 51.0.

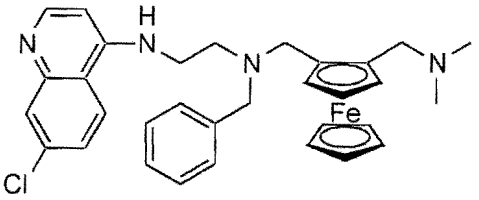
Synthesis of other derivatives

Compound 96



N-[3-(7-Chloro-quinolin-4-ylamino)-ethyl]-*N*-(2-dimethylaminomethyl-ferrocenyl)-benzamide **20** (200mg, 0.420mmol) was placed in a 50ml round bottomed flask followed by freshly distilled dichloromethane (10ml). Anhydrous triethylamine (0.1ml, 0.756mmol) was then added followed by benzoyl chloride (0.044ml, 0.378mmol). The mixture allowed to stir at 25°C for 2 h. The solvent was removed under reduced pressure and the product purified using silica gel chromatography. The product was isolated as yellow crystalline solid.
Yield: 123mg (67%); mp: 133-135°C;
R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.5;
δ_H (300 MHz; $CDCl_3$) 8.35 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 8.201 (2H, m, A_2), 7.87 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.48 (3H, m, A_3, ArC_5-H), 7.39 (1H, d, $^3J_{HH}$ = 10, A_4), 7.33 (1H, m, ArC_6-H), 6.19 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 4.72 (1H, d, $^2J_{HH}$ = 16, 3'a), 4.34- 4.10 (6H, m, 3'b, 4', Cp), 4.08 (5H, s, Cp), 3.56 (1H, d, $^2J_{HH}$ = 13, 2'a), 3.48-3.40 (2H, m, 5'), 2.97 (1H, d, $^2J_{HH}$ = 13, 2'b), 2.21 (6H, s, 1')
$\delta_{C\{H\}}$ (100.6 MHz; $CDCl_3$) 159.1 (CO), 152.3 (ArC_2), 150.5 (^{IV}C), 149.5 (^{IV}C), 134.8 (^{IV}C), 129.4, (A_4) 128.6 (ArC_8), 128.8 (A_3), 127.1 (A_2), 124.9 (ArC_6), 122.4 (ArC_5), 118.1 (^{IV}C), 102.8 (^{IV}C), 99.1 (ArC_3), 84.2 (2C, ^{IV}C), 71.6 (Cp), 70.8 (Cp), 69.5 (5C, Cp'), 66.2 (Cp), 57.2 (2'), 44.7 (2C, 1') and 42.7 (3');
IR (KBr) ν_{max} 3418br m (NH), 3061m, 2935m, 2765m, 1612s (7-chloroquinoline), 1580s (7-chloroquinoline), 1453m (NCH_3), 1425m, 1370m, 1286m, 1239m, 1210w, 1160m, 1138m, 1104w (ferrocene), 1022w, 930w, 814m (ferrocene), 703w, 603w and 489w (ferrocene);
HRMS (EI) *m/z* 580.16894 [M^+, $C_{32}H_{33}N_4O^{35}ClFe$ requires 580.16923], 535.1 [M^+ - (NMe_2)], 470.1, 430.1, 380.0, 331.1, 255.1 [HC-Fp-CH_2-NMe_2], 213.1, 191.0 [ClC_9NH_5-NH-CH_2], 105.0, 91.0 [CH_2-Cp-CH_2], 77.0 and 58.1 [CH_2-NMe_2].

Compound 97



N-Benzyl-*N*-(7-chloro-quinolin-4-yl)-*N*-(2-dimethylaminomethyl-ferrocenyl)-ethane-1,2-diamine

The compound was prepared by literature procedure.[26] The product was purified using silica gel chromatography.

Orange glassy solid; Yield: 25mg (30%)

R_f (silica/CH_2Cl_2: MeOH = 80:20) 0.4;

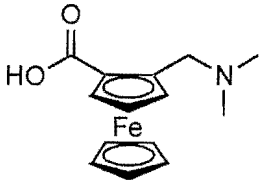
δ_H (400 MHz; $CDCl_3$) 8.41 (1H, d, $^3J_{HH}$ = 5, ArC_2-H), 7.91 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.53 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.35-7.16 (6H, m, ArC_6-H, Ph), 6.19 (1H, d, $^3J_{HH}$ = 5, ArC_3-H), 5.86 (1H, br, NH), 4.35-4.09 (3H, m, Cp), 4.00 (5H, s, Cp'), 3.75 (1H, d, $^2J_{HH}$ = 13, 3'a), 3.57 (1H, d, $^2J_{HH}$ = 12, 2'a), 3.47 (1H, d, $^2J_{HH}$ = 13, 3'b), 3.35 (2H, s, 1''), 3.20-3.04 (2H, m, 5'), 2.97 (1H, d, $^2J_{HH}$ = 12, 2'b), 2.90-2.78 (2H, m, 4') and 2.12 (6H, s, 1');

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 151.8 (ArC_2), 150.2 (^{IV}C), 139.6 (^{IV}C), 134.9 (^{IV}C), 129.1 (2C, Ph), 128.5 (2C, Ph), 128.4 (ArC_8), 127.3 (Ph), 124.9 (ArC_6), 122.1 (ArC_5), 100.0 (ArC_3), 84.4 (^{IV}C, Cp), 83.6 (^{IV}C), 71.5 (Cp), 70.9 (Cp), 69.4 (5C, Cp'), 69.3 (Cp), 59.4 (1''), 58.1 (2'), 53.0 (3'), 51.5 (4'), 45.6 (2C, 1') and 40.5 (5');

IR (thin film) ν_{max} 3323br m (NH), 3085m, 3025m, 2941m, 2853m, 2815m, 2772m, 1611m (7-chloroquinoline), 1581vs (7-chloroquinoline), 1529m (7-chloroquinoline), 1452m (NCH_3), 1368m, 1329m, 1262w, 1217w, 1170w, 1136m, 1105m (ferrocene), 1077w, 1035m, 1001m (ferrocene), 907w, 877m, 809m (ferrocene), 753s (5 adjacent aromatic H) and 700m (5 adjacent aromatic H);

HRMS (EI) *m/z* 566.19074 [M^+, $C_{32}H_{35}N_4{}^{35}ClFe$ requires 566.18996], 521.1 [M^+ - (NMe_2)], 455.1, 430.1, 375.1, 344.1, 317.1, 310.1, 255.1 [HC-Fp-CH_2-NMe_2], 213.0, 192.1, 163.0 [ClC_9NH_5], 121.0 [Cp-Fe], 91.0 [CH_2-Cp-CH_2] and 58.1 [CH_2-NMe_2].

Compound 112



[(*N,N*-Dimethylamino)methyl]ferrocenecarboxylic acid

The work-up procedure follows a literature procedure[27]

[(*N,N*-dimethylamino)methyl]ferrocene **28** (0.5ml, 2.509mmol) was placed in a centrifuge tube. Anhydrous diethyl ether (10ml) was added and the mixture cooled to -78°C. *tert*-Butyllithium (1.5ml, 1.7M solution in pentane, 2.509mmol) was then added. The mixture was allowed to stir for 20 minutes before adding crushed dry ice (± 1g). The mixture was allowed to stir at -78°C for a further 2 h. The mixture was then allowed to warm to room temperature. The centrifuge tube was then sealed with a rubber septum and centrifuged. The solvent was syringed off and the solid product washed with diethyl ether and centrifuged again. This process was repeated three times. The product was dissolved in methanol and the solvent removed under reduced pressure. The product was purified using silica gel chromatography eluting with 10% diethyl ether in methanol. The product was then

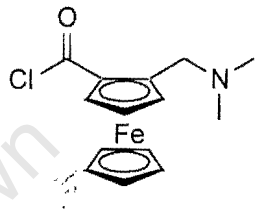
dissolved in dichloromethane, dried over sodium sulfate and filtered, before removing the solvent under reduced pressure. The product was dried *in vacuo* and isolated as a hygroscopic yellow crystalline solid. Yield: 470mg (67%);

δ_H (300 MHz; $CDCl_3$) 4.96 (1H, m, Cp*H*-αCOOH), 4.35 (1H, d, $^2J_{HH}$ = 13, 2'a), 4.26 (1H, t, $^3J_{HHH}$ = 2, Cp*H*-βCOOH), 4.20 (1H, m, Cp*H*-αCH_2NMe_2), 4.17 (5H, s, Cp), 3.21 (1H, d, $^2J_{HH}$ = 13, 2'b) and 2.37 (6H, s, 1');

$\delta_{C\{H\}}$ (75.5 MHz; $CDCl_3$) 173.6 (*C*OOH), 79.0 (^{IV}C, Cp), 76.4 (^{IV}C, Cp), 74.2 (Cp*C*-αCOOH), 72.0 (Cp*C*-βCOOH), 70.7 (5C, Cp), 68.6 (Cp*H*-αCH_2NMe_2), 58.0 (2') and 42.4 (2C, 1').

Compound 113

[(*N,N*-Dimethylamino)methyl]ferrocenecarboxylic acid chloride

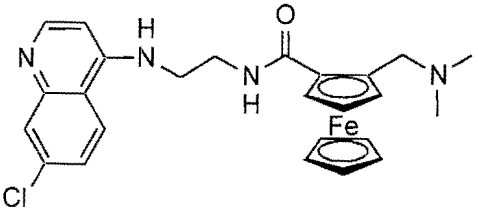


[(*N,N*-Dimethylamino)methyl]ferrocenecarboxylic acid **112** (0.934g, 3.256mmol) was placed in a 100 ml round bottomed flask. Anhydrous dichloromethane (10ml) was added. The mixture was then degassed before sealing with a rubber septum. The mixture was cooled to 0°C before adding oxalyl chloride (0.56ml, 6.506mmol) dropwise. The mixture was allowed to warm slowly to room temperature by stirring in an unlagged ice bath. After 3 h the solvent was removed under reduced pressure and the product dried *in vacuo*. The product was used without further purification or characterization.

Bright red glassy solid.

Compound 114

2-Dimethylaminomethyl-ferrocenecarboxylic acid [2-(7-chloro-quinolin-4-ylamino)-ethyl]-amide



32 (805mg, 3.582mmol) was placed in a 100ml round bottomed flask followed by anhydrous dichloromethane (15ml). Anhydrous triethylamine (0.85ml, 6.512mmol) was then added followed by a solution of **113** (3.256mmol) in anhydrous dichloromethane (15ml) and the mixture allowed to stir at 25°C for 2 h. The solvent was removed under reduced pressure and the product purified using silica gel chromatography. The product was isolated as a red oil. Yield: 756mg (43%);

R_f (silica/CH_2Cl_2: MeOH: Et_3N = 80:20:1) 0.33;

δ_H (300 MHz; CD_3OD) 8.39 (1H, d, $^3J_{HH}$ = 6, ArC_2-H), 8.22 (1H, d, $^3J_{HH}$ = 9, ArC_5-H), 7.80 (1H, d, $^4J_{HH}$ = 2, ArC_8-H), 7.56 (1H, dd, $^4J_{HH}$ = 2 and $^3J_{HH}$ = 9, ArC_6-H)), 6.73 (1H, d, $^3J_{HH}$ = 6, ArC_3-H), 5.00-4.99 (1H, m, Cp), 4.72 (1H, d, $^2J_{HH}$ = 13, 2'a), 4.61 (1H, m, Cp), 4.51 (1H, t, $^3J_{HHH}$ = 3, Cp), 4.17 (5H, s, Cp'), 3.86 (1H, d, $^2J_{HH}$ = 13, 2'b), 3.82-3.68 (2H, m, 4'), 3.44-3.52 (2H, m, 5') and 2.71 (6H, s, 1');

$\delta_{C\{H\}}$ (75.5 MHz; CD_3OD) 174.6 (3'), 154.2 (ArC_2), 150.2 (^{IV}C), 139.5 (^{IV}C), 137.8 (^{IV}C), 127.7 (ArC_8), 125.7 (ArC_6), 124.8 (ArC_5), 118.2 (^{IV}C), 99.9 (ArC_3), 72.1 (Cp), 71.8 (Cp), 71.7 (Cp), 69.0 (5C, Cp'), 53.9 (2'), 44.5 (2*C*, 1'), 42.8 (4') and 39.3 (5');

IR (thin film) ν_{max} 3426br s (NH), 1632s (7-chloroquinoline), 1582m (7-chloroquinoline), 1542m (7-chloroquinoline), 1452m (NCH_3), 1368w, 1313w, 1265m, 1141w, 1106w (ferrocene), 1004w (ferrocene), 896w, 737m and 701w;
MS (FAB) *m/z* 491.1 [M^+ $C_{25}H_{27}N_4ClFeO$ requires 491.1], 446.2 [M^+ - (NMe_2)], 371.1, 326.1, 315.2, 270.1 [OC-Fp-CH_2-NMe_2], 239.3, 199.0 and 179.1

β-Haematin Inhibition

Haemin (15mg, 0.023 mmol) was placed in a large sample vial followed by 0.1*M* NaOH (3.0ml). The solution was placed on a thermostatted hot plate situated on a shaker. This was allowed to equilibrate at 60°C. 3 mol equivalents (0.069mmol) of the relevant compound was added. 1.0*M* HCl (0.3ml) and 12.9*M* acetate buffer solution pH 5 (1.74ml) were also warmed to 60°C. These were then added to the haemin solution and the mixture allowed to shake for 30 min. The mixture was then cooled on ice. The product was then filtered on an 8μm cellulose acetate/nitrate Millipore filter type SC and extensively washed with water. The black product was transferred to a sample vial and dried in the presence of phosphorus pentoxide and silica in a vacuum desiccator 5 days.[28] The product was then analysed by IR spectroscopy.

These experiments were carried out on two separate occasions. In both cases a 'blank' experiment was performed with no addition of compound to ensure β-haematin formation was occurring. In addition to this, a 'control' was also performed, adding chloroquine diphosphate to ensure β-haematin inhibition was occurring.

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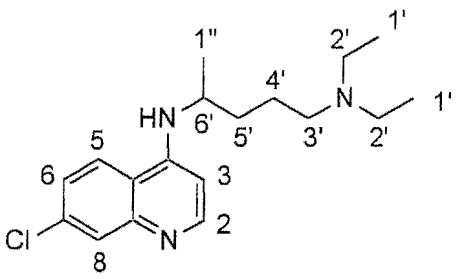
Appendix A

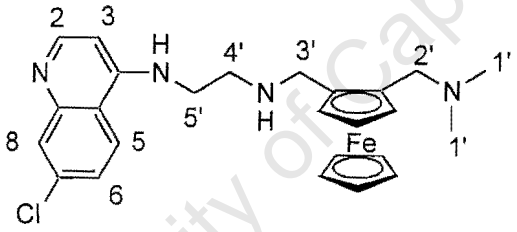
Numbering System for NMR

Chloroquine



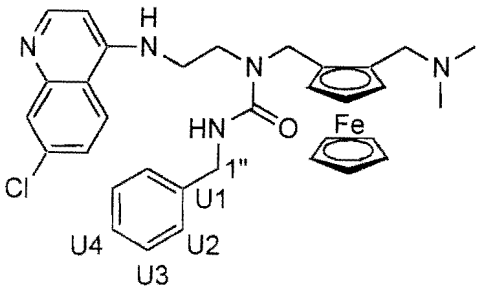
In the NMR assignment in Chapter 8, the aromatic protons are labelled as ArC_2-H, and the carbons are ArC_2. This is true for all quinoline systems. The other protons and carbons are labelled as indicated here.

Ferroquine analogues



In addition to the above numbering, the substituted Cp ring is denoted as Cp, and the free Cp ring is denoted as Cp'. Incremental CH_2 groups are placed between 5' and NH and are numbered sequentially as 6', 7' etc.

Substituted Ferroquine Derivatives



For the ureas and sulphonamides and other derivatives, the aromatic protons are labelled as U1 or S1 etc. from the point of attachment to linker unit i.e urea etc. In cases where unambiguous assignment of each proton or carbon is not possible, these are merely indicated as U or S etc, in order to distinguish them from the signals arising from the ferroquine analogue.

Appendix B

Data for xray crystal structure of 20

Table 1. Crystal data and structure refinement for **20**.

Identification code	20	
Empirical formula	Cl Fe C_{25} H_{29} N_4 O	
Formula weight	476.82	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 10.7012(3) Å	= 90°.
	b = 16.2573(4) Å	= 92.727(1)°.
	c = 13.7853(3) Å	= 90°.
Volume	2395.55(1) $Å^3$	
Z	4	
Density (calculated)	1.322 Mg/m^3	
Absorption coefficient	0.760 mm^{-1}	
F(000)	1000	
Crystal size	0.39 x 0.35 x 0.29 mm^3	
Theta range for data collection	1.91 to 27.49°.	
Index ranges	-13<=h<=13, -20<=k<=20, -17<=l<=17	
Reflections collected	10265	
Independent reflections	5459 [R(int) = 0.0240]	
Completeness to theta = 27.49°	99.3 %	
Max. and min. transmission	0.8097 and 0.7559	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5459 / 2 / 290	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0344, wR2 = 0.0768	
R indices (all data)	R1 = 0.0552, wR2 = 0.0843	
Largest diff. peak and hole	0.255 and -0.295 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 181. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Fe	1541(1)	2030(1)	4554(1)	29(1)
Cl	1423(1)	8834(1)	3377(1)	55(1)
C(1)	1580(3)	3279(2)	4410(2)	31(1)
C(18)	2310(3)	7946(2)	3248(2)	32(1)
N(1)	4464(2)	3902(1)	4152(2)	28(1)
C(2)	2811(3)	2965(2)	4614(2)	29(1)
C(16)	3690(3)	6956(2)	3988(2)	30(1)
C(6)	1933(3)	1311(2)	3392(2)	41(1)
C(19)	2416(3)	7598(2)	2358(2)	31(1)
C(20)	3213(3)	6919(2)	2243(2)	29(1)
C(15)	3870(3)	6591(2)	3074(2)	26(1)
N(3)	3324(3)	6623(2)	1321(2)	37(1)
C(8)	980(3)	840(2)	4741(2)	43(1)
C(11)	3897(3)	3080(2)	3988(2)	32(1)
N(2)	5297(2)	5557(1)	3730(2)	32(1)
C(14)	4687(3)	5900(2)	2946(2)	29(1)
C(5)	827(3)	3048(2)	5193(2)	41(1)
C(3)	2809(3)	2551(2)	5526(2)	40(1)
C(13)	6128(3)	4852(2)	3682(2)	38(1)
C(7)	2127(3)	865(2)	4269(3)	45(1)
C(12)	5461(3)	4037(2)	3483(2)	37(1)
C(22)	4802(3)	5623(2)	1998(2)	38(1)
C(21)	4108(3)	6004(2)	1243(2)	41(1)
C(17)	2935(3)	7625(2)	4080(2)	34(1)
C(10)	671(3)	1558(2)	3322(2)	39(1)
C(4)	1590(4)	2598(2)	5872(2)	48(1)
C(9)	83(3)	1271(2)	4155(2)	40(1)
N(4)	1779(2)	4556(1)	3455(2)	32(1)
C(23)	1181(3)	3744(2)	3508(2)	36(1)
C(25)	1255(3)	5122(2)	4140(3)	50(1)
C(24)	1604(3)	4876(2)	2465(2)	48(1)

Table 3. Bond lengths [Å] and angles [°] for 181.

Fe-C(4)	2.037(3)
Fe-C(2)	2.038(3)
Fe-C(7)	2.040(3)
Fe-C(1)	2.040(3)
Fe-C(5)	2.041(3)
Fe-C(6)	2.042(3)
Fe-C(9)	2.044(3)
Fe-C(3)	2.045(3)
Fe-C(8)	2.046(3)
Fe-C(10)	2.046(3)
Cl-C(18)	1.741(3)
C(1)-C(2)	1.428(4)
C(1)-C(5)	1.428(4)
C(1)-C(23)	1.500(4)
C(18)-C(19)	1.361(4)
C(18)-C(17)	1.402(4)
N(1)-C(12)	1.459(4)
N(1)-C(11)	1.481(3)
C(2)-C(3)	1.427(4)
C(2)-C(11)	1.491(4)
C(16)-C(17)	1.364(4)
C(16)-C(15)	1.414(4)
C(6)-C(10)	1.408(5)
C(6)-C(7)	1.417(5)
C(19)-C(20)	1.409(4)
C(20)-N(3)	1.369(4)
C(20)-C(15)	1.419(4)
C(15)-C(14)	1.439(4)
N(3)-C(21)	1.317(4)
C(8)-C(9)	1.411(5)
C(8)-C(7)	1.417(5)
N(2)-C(14)	1.356(4)
N(2)-C(13)	1.454(4)
C(14)-C(22)	1.394(4)
C(5)-C(4)	1.416(5)
C(3)-C(4)	1.412(5)

C(13)-C(12)	1.523(4)
C(22)-C(21)	1.395(4)
C(10)-C(9)	1.414(4)
N(4)-C(25)	1.450(4)
N(4)-C(24)	1.465(4)
N(4)-C(23)	1.469(3)

C(4)-Fe-C(2)	68.71(13)
C(4)-Fe-C(7)	126.68(14)
C(2)-Fe-C(7)	119.34(13)
C(4)-Fe-C(1)	68.66(12)
C(2)-Fe-C(1)	41.01(11)
C(7)-Fe-C(1)	153.85(14)
C(4)-Fe-C(5)	40.63(14)
C(2)-Fe-C(5)	68.92(13)
C(7)-Fe-C(5)	163.99(14)
C(1)-Fe-C(5)	40.98(12)
C(4)-Fe-C(6)	164.03(15)
C(2)-Fe-C(6)	107.29(13)
C(7)-Fe-C(6)	40.61(13)
C(1)-Fe-C(6)	119.18(12)
C(5)-Fe-C(6)	153.95(14)
C(4)-Fe-C(9)	120.02(14)
C(2)-Fe-C(9)	163.79(12)
C(7)-Fe-C(9)	68.00(14)
C(1)-Fe-C(9)	126.38(13)
C(5)-Fe-C(9)	107.99(14)
C(6)-Fe-C(9)	68.07(13)
C(4)-Fe-C(3)	40.47(14)
C(2)-Fe-C(3)	40.90(11)
C(7)-Fe-C(3)	108.07(14)
C(1)-Fe-C(3)	68.65(12)
C(5)-Fe-C(3)	68.35(14)
C(6)-Fe-C(3)	126.60(14)
C(9)-Fe-C(3)	154.21(13)
C(4)-Fe-C(8)	108.12(13)
C(2)-Fe-C(8)	154.07(13)
C(7)-Fe-C(8)	40.60(14)

C(1)-Fe-C(8)	163.87(14)
C(5)-Fe-C(8)	126.44(14)
C(6)-Fe-C(8)	68.30(13)
C(9)-Fe-C(8)	40.37(13)
C(3)-Fe-C(8)	119.89(13)
C(4)-Fe-C(10)	154.37(15)
C(2)-Fe-C(10)	126.14(12)
C(7)-Fe-C(10)	67.91(13)
C(1)-Fe-C(10)	107.65(12)
C(5)-Fe-C(10)	119.86(14)
C(6)-Fe-C(10)	40.30(13)
C(9)-Fe-C(10)	40.46(12)
C(3)-Fe-C(10)	163.88(14)
C(8)-Fe-C(10)	68.00(13)
C(2)-C(1)-C(5)	107.8(3)
C(2)-C(1)-C(23)	124.5(3)
C(5)-C(1)-C(23)	127.7(3)
C(2)-C(1)-Fe	69.41(16)
C(5)-C(1)-Fe	69.53(16)
C(23)-C(1)-Fe	125.22(19)
C(19)-C(18)-C(17)	121.8(3)
C(19)-C(18)-Cl	120.4(2)
C(17)-C(18)-Cl	117.8(2)
C(12)-N(1)-C(11)	110.2(2)
C(3)-C(2)-C(1)	107.6(3)
C(3)-C(2)-C(11)	127.1(3)
C(1)-C(2)-C(11)	125.3(3)
C(3)-C(2)-Fe	69.83(17)
C(1)-C(2)-Fe	69.58(16)
C(11)-C(2)-Fe	127.33(19)
C(17)-C(16)-C(15)	121.6(3)
C(10)-C(6)-C(7)	107.8(3)
C(10)-C(6)-Fe	70.01(18)
C(7)-C(6)-Fe	69.62(18)
C(18)-C(19)-C(20)	120.2(3)
N(3)-C(20)-C(19)	117.3(2)
N(3)-C(20)-C(15)	123.8(3)
C(19)-C(20)-C(15)	118.9(3)

C(16)-C(15)-C(20)	118.5(3)
C(16)-C(15)-C(14)	123.1(2)
C(20)-C(15)-C(14)	118.4(2)
C(21)-N(3)-C(20)	115.3(3)
C(9)-C(8)-C(7)	107.7(3)
C(9)-C(8)-Fe	69.74(17)
C(7)-C(8)-Fe	69.48(17)
N(1)-C(11)-C(2)	110.5(2)
C(14)-N(2)-C(13)	124.1(3)
N(2)-C(14)-C(22)	123.6(3)
N(2)-C(14)-C(15)	119.7(2)
C(22)-C(14)-C(15)	116.6(3)
C(4)-C(5)-C(1)	107.9(3)
C(4)-C(5)-Fe	69.56(18)
C(1)-C(5)-Fe	69.49(17)
C(4)-C(3)-C(2)	108.2(3)
C(4)-C(3)-Fe	69.47(18)
C(2)-C(3)-Fe	69.27(16)
N(2)-C(13)-C(12)	114.3(2)
C(6)-C(7)-C(8)	108.1(3)
C(6)-C(7)-Fe	69.77(17)
C(8)-C(7)-Fe	69.92(18)
N(1)-C(12)-C(13)	111.5(2)
C(14)-C(22)-C(21)	119.2(3)
N(3)-C(21)-C(22)	126.7(3)
C(16)-C(17)-C(18)	118.8(3)
C(6)-C(10)-C(9)	108.2(3)
C(6)-C(10)-Fe	69.69(18)
C(9)-C(10)-Fe	69.68(18)
C(3)-C(4)-C(5)	108.5(3)
C(3)-C(4)-Fe	70.06(18)
C(5)-C(4)-Fe	69.81(18)
C(8)-C(9)-C(10)	108.2(3)
C(8)-C(9)-Fe	69.89(18)
C(10)-C(9)-Fe	69.86(18)
C(25)-N(4)-C(24)	110.1(3)
C(25)-N(4)-C(23)	110.8(2)
C(24)-N(4)-C(23)	109.2(2)

N(4)-C(23)-C(1)	112.8(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 181. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Fe	39(1)	21(1)	28(1)	-1(1)	3(1)	-4(1)
Cl	65(1)	52(1)	48(1)	-3(1)	-7(1)	26(1)
C(1)	39(2)	20(1)	33(2)	-3(1)	0(1)	-4(1)
C(18)	29(2)	31(2)	35(2)	2(1)	-2(1)	0(1)
N(1)	27(1)	21(1)	36(1)	-1(1)	-3(1)	1(1)
C(2)	38(2)	21(1)	28(1)	-2(1)	-5(1)	-5(1)
C(16)	35(2)	30(2)	25(1)	4(1)	-8(1)	-3(1)
C(6)	50(2)	29(2)	43(2)	-11(1)	13(2)	-8(1)
C(19)	30(2)	35(2)	28(2)	7(1)	-4(1)	-5(1)
C(20)	31(2)	31(2)	24(1)	2(1)	0(1)	-10(1)
C(15)	26(2)	26(1)	26(1)	2(1)	-1(1)	-7(1)
N(3)	47(2)	41(2)	23(1)	4(1)	3(1)	-2(1)
C(8)	63(2)	26(2)	41(2)	4(1)	2(2)	-15(2)
C(11)	34(2)	26(1)	36(2)	-3(1)	-4(1)	-2(1)
N(2)	33(1)	26(1)	37(1)	1(1)	-5(1)	0(1)
C(14)	29(2)	28(1)	31(2)	2(1)	2(1)	-9(1)
C(5)	51(2)	29(2)	44(2)	-7(1)	16(2)	-2(1)
C(3)	57(2)	29(2)	32(2)	1(1)	-9(2)	-8(2)
C(13)	28(2)	35(2)	49(2)	3(2)	0(1)	1(1)
C(7)	52(2)	24(2)	59(2)	-5(2)	-3(2)	2(1)
C(12)	34(2)	29(2)	47(2)	0(1)	7(1)	5(1)
C(22)	39(2)	36(2)	39(2)	-1(1)	10(1)	-1(1)
C(21)	53(2)	46(2)	26(2)	-3(1)	10(1)	-6(2)
C(17)	39(2)	34(2)	27(2)	-3(1)	-4(1)	-2(1)
C(10)	50(2)	34(2)	33(2)	-5(1)	0(1)	-9(2)
C(4)	81(3)	34(2)	28(2)	-2(1)	9(2)	-8(2)
C(9)	42(2)	37(2)	41(2)	-6(1)	4(2)	-13(2)
N(4)	29(1)	26(1)	39(1)	6(1)	-4(1)	-3(1)
C(23)	38(2)	27(2)	42(2)	4(1)	-8(1)	-5(1)
C(25)	46(2)	33(2)	71(2)	-4(2)	7(2)	1(2)
C(24)	46(2)	44(2)	51(2)	19(2)	-15(2)	-12(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 181.

	x	y	z	U(eq)
H(16)	4104	6729	4551	36
H(6)	2546	1423	2934	49
H(19)	1951	7814	1811	37
H(8)	840	580	5344	52
H(11A)	4530	2649	4139	38
H(11B)	3614	3023	3297	38
H(5)	-33	3174	5250	49
H(3)	3507	2289	5846	48
H(13A)	6623	4808	4306	45
H(13B)	6721	4949	3165	45
H(7)	2893	623	4501	54
H(12A)	5102	4034	2808	44
H(12B)	6074	3582	3549	44
H(22)	5346	5179	1868	45
H(21)	4211	5796	608	50
H(17)	2836	7869	4698	41
H(10)	282	1864	2805	47
H(4)	1326	2367	6461	57
H(9)	-768	1354	4296	48
H(23A)	1393	3417	2932	43
H(23B)	262	3817	3488	43
H(25A)	1698	5648	4120	74
H(25B)	1345	4891	4796	74
H(25C)	366	5209	3966	74
H(24A)	708	4909	2287	72
H(24B)	2011	4508	2014	72
H(24C)	1976	5426	2432	72
H(2)	5230(30)	5844(18)	4434(11)	60(10)
H(1)	3712(17)	4332(13)	3982(19)	36(8)

Table 7. Hydrogen bonds for 181 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1) -- H(1) .. N(4) [Intra]	1.0828	2.1897	3.1691	149.27
N(2) -- H(2) .. N(1)' [symm.1]	1.0819	2.0043	3.0481	161.12
C(16) -- H(16) .. N(1)' [symm.1]	0.9500	2.5177	3.4561	169.49
C(17) -- H(17) .. N(3)'' [symm.2]	0.9500	2.4189	3.3301	160.64

'= 1-x,1-y,1-z
'' = x,3/2-y,1/2+z