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Synthesis, characterization and pharmacological evaluation of ferrocenyl azines and their rhodium(I) complexes

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ABSTRACT

Ferrocenyl azines containing salicylaldimine motifs were prepared by Schiff-base condensation of salicylaldehyde hydrazones and (dimethylamino)methyl ferrocenecarboxaldehyde. Their corresponding Rh(I) complexes were prepared by reaction of the various ferrocenyl azines with $[RhCl(COD)]_2$ (where COD = 1,5-cyclooctadiene) to yield heterobimetallic complexes. The compounds were characterized using standard spectroscopic and analytical techniques. The characterization data suggests that the ferrocenyl azine acts as a bidentate donor. The rhodium(I) centre binds to the imine nitrogen and phenolic oxygen of the salicylaldimine, forming a neutral complex. The compounds were screened against the NF54 chloroquine-sensitive (CQS) and K1 chloroquine-resistant (CQR) strains of *Plasmodium falciparum*. The ferrocene-containing salicylaldimines exhibited weak to moderate activity across both parasite strains. The heterometallic complexes exhibited enhanced activity compared to the ferrocenyl azines in both strains. Most of the compounds exhibited enhanced activity in the resistant strain compared to the sensitive strain. Inhibition of haemozoin formation was considered as a possible mechanism of action of these compounds and indeed they exhibited β-haematin inhibition activity, albeit weaker than chloroquine. All compounds were also screened against the G3 strain of *Trichomonas vaginalis*. The compounds inhibited no more than 50% parasite growth at the tested concentration. One complex exhibited moderate cytotoxicity against WHCO1 oesophageal cancer cells.

Introduction

Multinuclear complexes are compounds that consist of two or more metal centers and have attracted interest in many areas of chemistry. In the case of medicinal chemistry, these complexes are used because they may impart different properties compared to their mononuclear derivatives including charge, redox activities and selectivity towards various biomolecules [1]. Ruthenium-arene poly(propyleneimine) (PPI) dendrimers have been screened for their antitumoral activity *in vitro* and it was found that the multinuclear derivatives exhibited enhanced activity compared to their mononuclear analogues [2–4]. First-generation ferrocenylthiosemicarbazone dendrimers based on a PPI scaffold were screened for *in vitro* antiplasmodial activity against *Plasmodium falciparum* and showed increased efficacy compared to non-conjugated thioester precursors [5]. This has also been observed when similar ferrocenyl thiourea compounds were tested against the G3 strain of *Trichomonas vaginalis* [6]. The polyamine-conjugated derivatives exhibited enhanced parasitic activity compared to the free thioester. Heterometallic complexes containing ferrocene have also proved to exhibit biological activities. For example, ruthenium–arene complexes based on a ferrocenoyl pyridine displayed moderate cytotoxicity towards human ovarian carcinoma cells, with the binuclear complexes being more active than their mononuclear derivatives [7]. In another case, heterometallic palladium(II) and gold(III) ferrocenylphosphane complexes have also exhibited antiproliferative activity against ovarian and breast cancer cells [8].

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Ferrocene is often incorporated as part of bioactive compounds due to its robust nature, low toxicity and redox properties [9,10]. Ferrocene is able to undergo one-electron reversible oxidation to the ferrocenium cation at various potentials [11]. Incorporation of ferrocene as part of potential bioactive compounds may lead to interesting properties. Ferrocene-containing compounds can exhibit antitumour activities [12–15]. For example, hydroxyferrocifen was discovered when hydroxytamoxifen (the active metabolite of tamoxifen) was altered by substituting its phenyl ring with a ferrocene unit and screened for activity. This particular complex exhibited promising antiproliferative activity against various breast cancer cell lines [13]. In another case, Ferroquine (Fig. 1) (ferrocene analogue of chloroquine) has the ability to overcome resistance experienced by CQ, a once widely used antimalarial drug. Ferroquine (FQ) has recently completed phase IIb clinical trials [16]. Its mode of action is not yet fully understood, but it is believed that this compound is able to hinder haemozoin formation due to the presence of the 4-aminoquinoline moiety [17]. Ferroquine is also able to accumulate more efficiently inside of the digestive vacuole of the parasite compared to CQ; and once inside, ferroquine inhibits haemozoin formation strongly. In addition to this, it is also able to generate reactive oxygen species (ROS) which permanently damages the parasite [18–20]. Incorporating ferrocene as part of these systems is therefore an attractive approach to afford promising antimalarial candidates. Various other complexes possessing metals such as rhodium, ruthenium and iridium have also been screened as potential antiplasmodial agents [21–23]. In one case, a Rh(I)-CQ complex exhibited comparable activity to its parent compound. *In vivo*, the complex reduced parasitemia to a greater extent to that of CQ, further supporting the use of metal-based compounds for malaria [24].

Malaria is the most common parasitic infectious disease in the world [25]. According to the World Health Organisation (WHO), in 2010, 216 million cases of malaria were reported worldwide and 655 000 cases of malaria-related deaths were documented [26]. This disease is caused by a protozoan of the genus *Plasmodium*; *P. falciparum* being the most deadly strain to humans [27]. Many treatments are available to combat this disease but drug-resistance is a major issue [28]. A recommended practice currently implemented is artemisinin combination therapy (ACT). This involves the treatment of an infected individual with artemisinin, or a derivative thereof, in conjunction with another drug of known efficacy, in order to delay the onset of drug resistance [29]. Recently, there have been reports of strains of *Plasmodium* that are resistant to artemisinin [30–33]. This problem therefore prompts the design of antiparasitics that can be used as an alternative to artemisinin-derived drugs. Previous work conducted on PGM ferrocenyl–salicylaldimine complexes (Fig. 1) yielded some encouraging results when these compounds (**L1**, **C1** – **C3**) were screened against a chloroquine-sensitive strain of *P. falciparum* [34]. In this study we report the synthesis, characterization and preliminary biological evaluation of (dimethylamino)methyl ferrocenyl-salicylaldimines and their Rh(I) complexes.

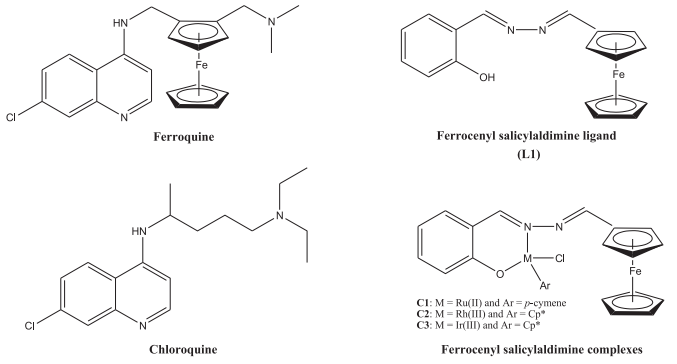


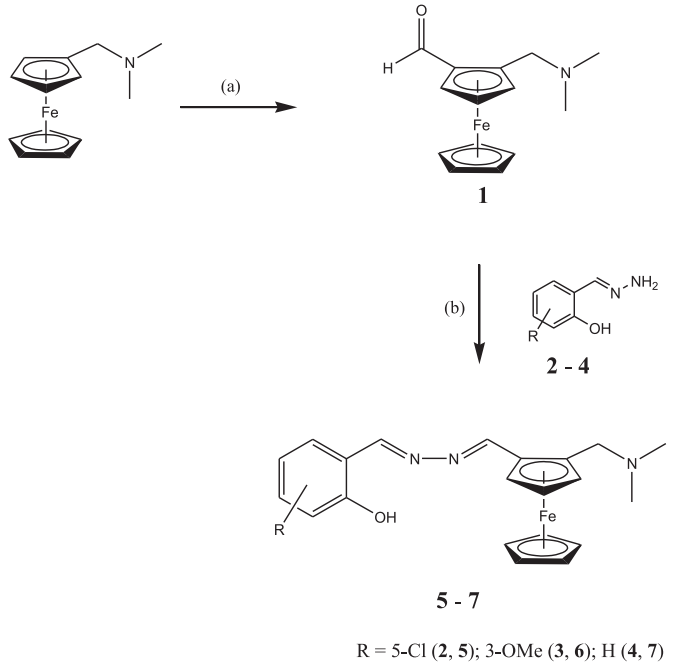
Fig. 1. Chloroquine, ferroquine and ferrocene-containing salicylaldimines (**L1**, **C1** – **C3**) [34] tested against *P. falciparum*.

Results and discussion

Synthesis and characterization

Compound **1** was prepared as described in the literature [35]. *Ortho*-lithiation of (dimethylamino)methyl ferrocene using *n*-butyllithium in hexanes afforded the lithiated species *in situ*. The lithium derivative was reacted with *N,N*-dimethylformamide giving the desired 1,2-disubstituted product **1** (Scheme 1). The salicylaldehyde hydrazones were prepared according to literature methods [36,37]. The aldehyde was reacted with either 5-chlorosalicylaldehyde hydrazone (**2**), 3-methoxysalicylaldehyde hydrazone (**3**) or salicylaldehyde hydrazone (**4**) in a 1:1 stoichiometric ratio in diethyl ether to afford salicylaldimine ferrocenes **5** – **7** as red oils in moderate to good yields (66 – 88%). The corresponding rhodium(I) cyclooctadiene complexes of **5** – **7** were also prepared (Scheme 2) in order to evaluate the effect of the metal on biological activity compared to the ferrocenyl azine. Rh(I) was chosen due to its square-planar geometry which may aid in complex-haem interactions. Complexes **8** – **10** were prepared by deprotonation of the hydroxyl group of the ferrocenyl azine using excess NaH in dichloromethane, followed by addition of 0.5 equivalents of $[RhCl(COD)]_2$ [38]. The complexes were obtained as orange-red powders in excellent yields (94 – 98%). All ferrocenyl azines and their complexes are soluble in common organic solvents such as dichloromethane, chloroform and dimethyl sulfoxide.

The ferrocenyl azines (**5** – **7**) and complexes (**8** – **10**) were characterized using standard techniques such as ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy, infrared spectroscopy and high-resolution (HR)



Scheme 1. (a) (Dimethylamino)methyl ferrocene (1 eq.), *n*-BuLi (1.45 eq.), Et_2O, 16 h, r.t., DMF (1.25 eq), 4 h, r.t. (b) appropriate salicylaldehyde hydrazone (1 eq.), Et_2O, 16 h, r.t.