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Synthesis, characterization, antiplasmodial evaluation and electrochemical studies of water-soluble heterobimetallic ferrocenyl complexes

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ABSTRACT

Three new ferrocenyl-containing heterobimetallic complexes were synthesized using a sodium sulfonate-salicylaldimine mononuclear ferrocenyl complex and various metal precursors. Complexation with ruthenium(II), rhodium(III) and iridium(III) precursors yielded the heterobimetallic complexes, which display good water-solubility. The ferrocenyl ligand acts as a *N,O*-bidentate chelating ligand, coordinating to the metal center via the imine nitrogen and the deprotonated phenolic oxygen. The complexes were characterized using analytical and spectroscopic techniques. The compounds were evaluated for *in vitro* antiplasmodial activity against the NF54 chloroquine-sensitive strain of *Plasmodium falciparum*. The mono- and bimetallic complexes exhibit enhanced activity compared to the salicylaldimine hydrazone. The compounds were evaluated for their ability to inhibit β-haematin formation but were inactive, suggesting an alternative reason for their antiplasmodial activity. Electrochemical studies on the bimetallic complexes revealed a voltammetric wave corresponding to the oxidation of the ferrocenyl group and another at a more positive potential which inhibited the reversibility of the ferrocenyl oxidation.

1. Introduction

Malaria is one of the most prevalent infectious diseases worldwide. In 2013, the World Health Organization (WHO) reported 198 million cases of malaria globally. Of these cases, 584,000 deaths were documented [1]. The disease is caused by parasites of the genus *Plasmodium*, with *Plasmodium falciparum* being responsible for most fatalities. Quinoline-based antimalarials have been used successfully for many years to treat this disease, but have been rendered almost useless in recent years due to the increase in resistance [2,3]. More recently, artemisinin-based combination therapy (ACT) has been used to treat uncomplicated malarial infections [4]. This involves the use of artemisinin or a derivative thereof with a second drug not having the same mechanism of action, to lower the risk of resistance occurring. Despite this, reports of resistance to ACTs have been reported [5–9]. Therefore there is an urgent need to obtain alternative therapies that will be able to overcome this resistance. A metal-based compound, ferroquine (FQ), has displayed promising activity *in vitro* and *in vivo* and has reached phase IIb clinical trials [10]. Its success has prompted investigations of many other ferrocene-containing compounds for malaria treatment over the past few years [11–13]. Heterobimetallic ferrocenyl salicylaldimine complexes (Fig. 1) have yielded some promising results against *P. falciparum* [14,15]. Ferrocenyl-based heterobimetallic complexes have been known to exhibit other biological properties as well, such as cytotoxicity against cancer cells [16,17]. Along with ferrocenyl derivatives, other metal-containing complexes have also exhibited promising antimalarial activity. These metals include ruthenium, iridium, osmium and rhodium, to name but a few [11–13,18–20]. This further supports the use of metal-based drugs as potential antimalarials. This study aims to evaluate water-soluble heterobimetallic complexes as antiplasmodial agents. Our previous studies on non-water-soluble heterobimetallic complexes yielded encouraging results, but these complexes were not comparable in activity to chloroquine (CQ), a common antimalarial agent [14,15]. Lipophilicity may have been a factor contributing to the lower activity, so in this study water-soluble versions were prepared, characterized and evaluated for their antiplasmodial activity against the NF54 strain of *P. falciparum* in order to probe the effect of this factor on activity.

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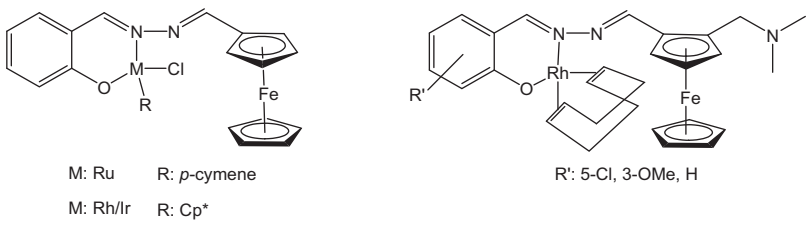
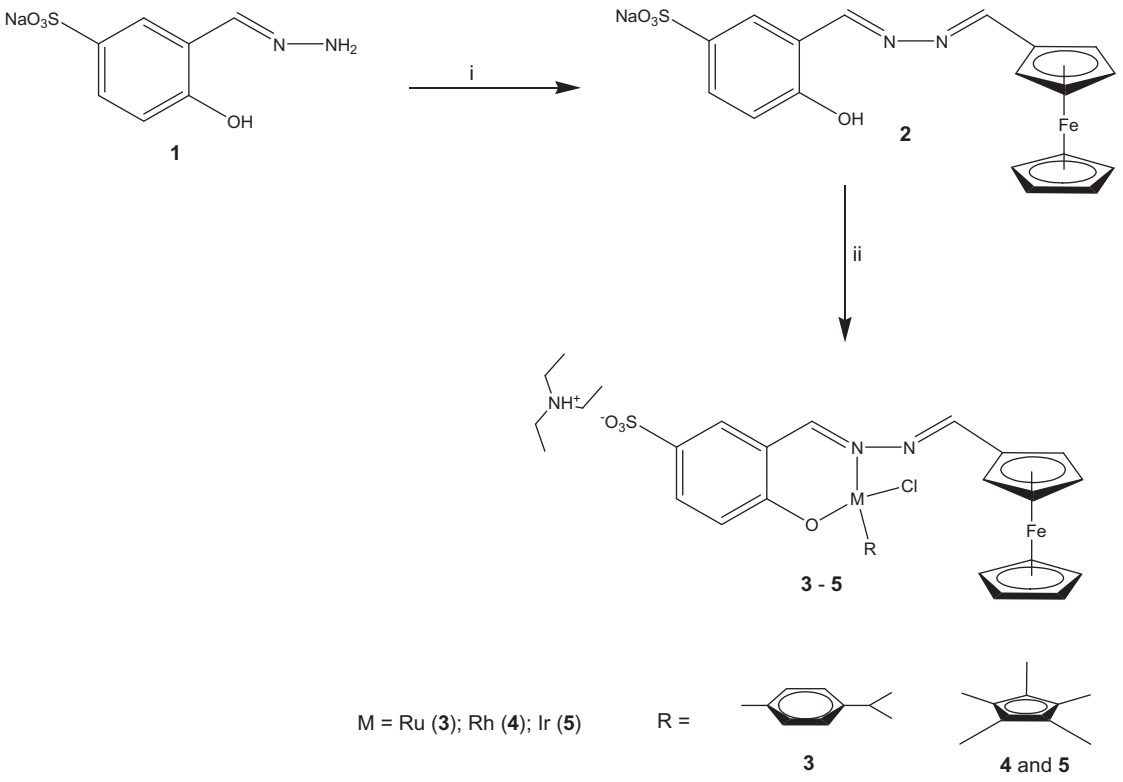


Fig. 1. Heterobimetallic complexes previously studied for antiplasmodial activity [14,15].

2. Results and discussion

2.1. Synthesis and characterization

The synthesis of the heterobimetallic complexes (**3**–**5**) involves the preparation of the monosulfonated salicylaldimine hydrazone (**1**) and then the ferrocenyl-containing sulfonated ligand (**2**) using published methods [21]. The heterobimetallic complexes (**3**–**5**) were synthesized by a bridge-cleavage reaction of the dimeric complexes $[Ru(\eta^6\text{-}p\text{-cymene})(\mu\text{-Cl})Cl]_2$, $[Rh(\eta^5\text{-}Cp^*)(\mu\text{-Cl})Cl]_2$ or $[Ir(\eta^5\text{-}Cp^*)(\mu\text{-Cl})Cl]_2$ with **2** (Scheme 1). Compounds **3**–**5** were isolated in good yields (83–89%) as orange-red solids. The bimetallic complexes display solubility in water, dichloromethane and alcoholic solvents. The characterization data confirm that the anionic sulfonato-salicylaldimine ferrocenyl complex (**2**) coordinates to the platinum group metal (M = Ru, Rh, Ir) in a bidentate chelating manner via the imine nitrogen and deprotonated hydroxyl oxygen, which is facilitated by the addition of triethylamine. The complexes were characterized using standard techniques such as NMR and IR spectroscopy and mass spectrometry. The ^{1}H NMR spectra of complexes **3**–**5** display signals for two imine protons in each case. The ^{1}H NMR spectra also exhibit additional signals corresponding to protons of a Et_3NH^+ counter-ion and the integration is also consistent with the proposed structure. For the ruthenium complex (**3**), signals for the *p*-cymene moiety are observed at 1.15, 2.10 and between 5.26 and 5.50 ppm for the isopropyl, CH_3 and arene groups, respectively. In the case of complexes **4** and **5**, signals for the Cp^* protons are observed at 1.5 ppm as a singlet, confirming complexation. Signals corresponding to the ferrocenyl protons are also observed in the expected region, with a singlet for the unsubstituted Cp ring observed around 4.3 ppm. Signals for the protons of the substituted Cp ring are observed between 4.56 and 4.87 ppm. The $^{13}C\{^1H\}$ NMR spectra also confirm that the desired compounds were afforded as the expected number of signals are observed in each case. Infrared spectra show a shift in the imine ν(C=N) absorption bands to lower wavenumbers compared to the free ligand (**2**), which gives evidence of coordination of this moiety to the platinum group metal centers. The ESI mass spectra of **3**–**5** reveal peaks at *m*/*z* 647, 649 and 739, respectively, which correspond to the $[M\text{-}Et_3NH{+}H\text{-}Cl]^+$ ions.



Scheme 1. (i) Ferrocenecarboxaldehyde (1 eq.), EtOH, 45 °C, 16 h [21]; (ii) $[Ru(\eta^6\text{-}p\text{-cymene})(\mu\text{-Cl})Cl]_2$ (0.5 eq.), $[Rh(\eta^5\text{-}Cp^*)(\mu\text{-Cl})Cl]_2$ (0.5 eq.) or $[Ir(\eta^5\text{-}Cp^*)(\mu\text{-Cl})Cl]_2$ (0.5 eq.), Et_3N (1 eq.), EtOH, r.t., 16 h.