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Research paper

Ferrocene-pyrimidine conjugates: Synthesis, electrochemistry, physicochemical properties and antiplasmodial activities

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ABSTRACT

The promise of hybrid antimalarial agents and the precedence set by the antimalarial drug ferroquine prompted us to design ferrocene-pyrimidine conjugates. Herein, we report the synthesis, electrochemistry and anti-plasmodial evaluation of ferrocenyl-pyrimidine conjugates against chloroquine susceptible NF54 strain of the malaria parasite *Plasmodium falciparum*. Also their physicochemical properties have been studied.

1. Introduction

Ferroquine (SSR97193) **1** is an effective 4-aminoquinoline-ferrocene conjugate antimalarial agent [1–6], which is active *in vitro* as well as *in vivo* against both chloroquine resistant (CQ^R) as well as chloroquine susceptible (CQ^S) *Plasmodium falciparum* strains. Although ferrocene itself lacks any antimalarial activity [7], the antimalarial activity of ferroquine presumably takes advantage of the affinity of the *P. falciparum* for the metal (Fe^{2+}) center of ferrocene core. Also the redox (Fe^{2+}/Fe^{3+}) behavior of the ferrocene based compounds is known to influence the bioactivity of the ferrocenyl derivatives [8–11]. Since the antimalarial activity of **1** is superior to that of chloroquine **2** (Fig. 1), this may suggest that the mode of action of **1** is not essentially same as that of **2**. Within the context of the mode of action of **1**, it has also been suggested that **1** makes a strong complex with hematin and blocks the hemozoin based detoxification process of the parasite [5] or even act as a resistance reversing agent through blocking of the *P. falciparum* transmembrane protein (*Pf*CRT) [12] by virtue of its lipophilic properties. A carbosilane analog (**3**) of ferroquine (Fig. 1) with potent antiplasmodial activity has been recently reported [13,14].

Malaria has posed a serious threat to the human health as nearly 1 million people face death due to malaria every year [15]. Besides, being epidemic in sub-Saharan Africa, the disease has slowly gained its ground in Asia and Latin America also. In fact, on the borders of Thailand, *P. falciparum* has become resistant to almost all the available antimalarial drugs [16–18]. The weak immune system of pregnant women and/or children below the age of 5 exposes them to greater risk from this killer disease. The activity of the one-time most active antimalarial drugs (mostly quinoline based) has been compromised owing to growing drug resistance [19,20]. Resistance to the artemisinin class of drugs as well as to primaquine has been reported [21–23]. Thus, the burden of malaria is further expected to rise, which necessitates an urgent need for effective new drugs [24–28] or drug combinations to combat the growing resistance.

Hybrid drugs have been portrayed as drugs of the future owing to the potential advantages over single drug and/or multicomponent combination therapy. As part of our continuing interest in the synthesis, biology, structure-activity relationship and mode of action studies of hybrid antimalarials [29–34], recently we have reported [35–37] a series of pyrimidine-quinoline hybrids, with antiplasmodial activity against both CQ^s as well as CQ^R strains of *P. falciparum*. We now report the synthesis of new hybrids in which

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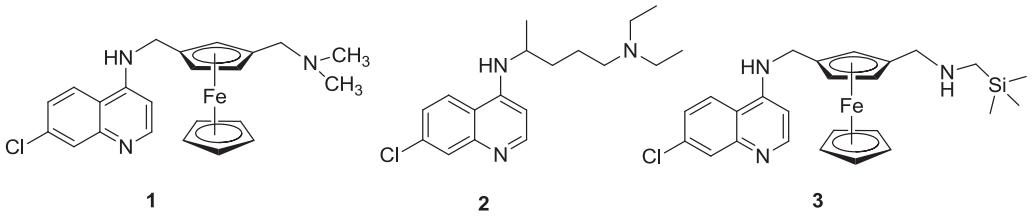


Fig. 1. Antimalarial agents: ferroquine **1**, chloroquine **2** and carbosilane analog **3**.

ferrocene and pyrimidine moieties are linked through five-membered heterocyclic units. The choice of these heterocycles was guided by the fact that many of these systems are present in molecules, which possess antimalarial activity [13,14,38]. Additionally, we discuss the electrochemical behavior, physico-chemical and antiplasmodial properties of the title compounds.

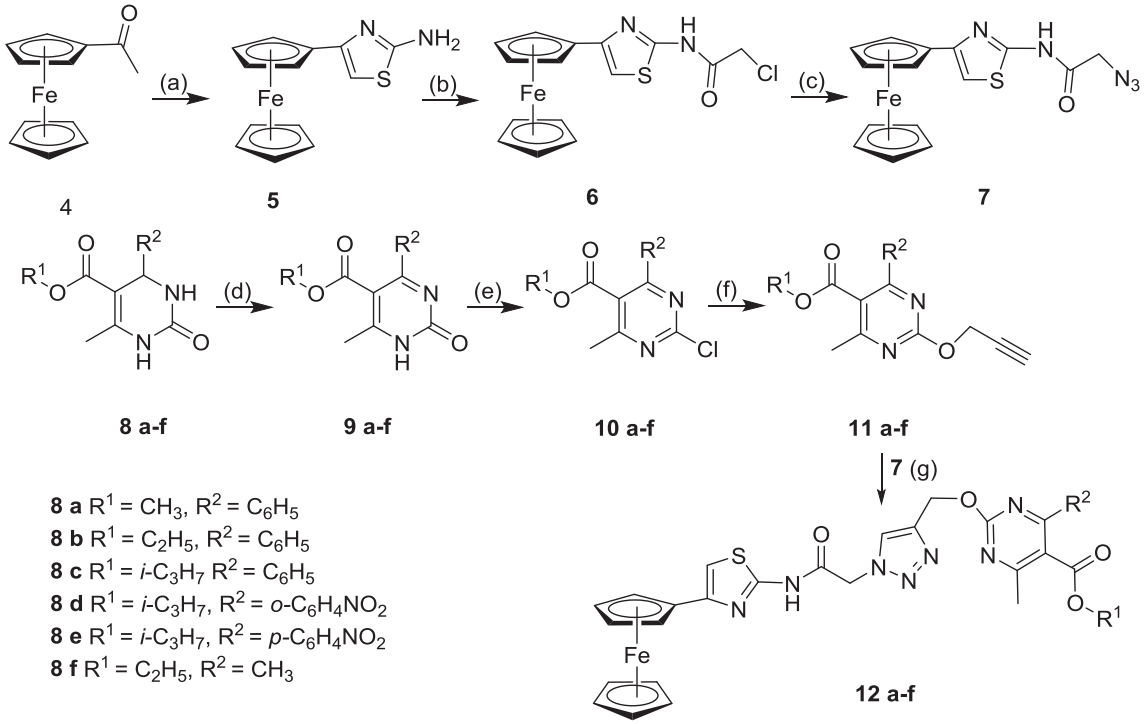
2. Results and discussion

2.1. Synthesis of pyrimidine-ferrocene conjugates

The synthetic pathway to pyrimidine-ferrocenyl conjugates **12a**–**f** commences with the synthesis of 2-amino-4-ferrocenylthiazole **5** from acetylferrocene [39]. Chloroacetylation of **5** upon refluxing with chloroacetyl chloride in dry toluene furnished **6** (Scheme 1), which upon a nucleophilic substitution reaction with NaN_3 in dry DMF at 60 °C gave **7**. On the other hand, C2-propargylated pyrimidines were synthesized by carrying out pyridinium chlorochromate (PCC) mediated dehydrogenation [40] of compound **8** prepared via conventional Bignelli condensation [41] to yield oxidized intermediate **9**. Subsequent chlorination of **9** using $POCl_3$ under reflux provided chloropyrimidines **10** [42]. Base-catalyzed nucleophillic substitution of **10** with propargyl alcohol led to the formation of C2-propargylated pyrimidines **11**. Finally, copper assisted azide-alkyne Huisgen 1,3-dipolar cycloaddition reaction between **7** and appropriate **11a**–**f** delivered click [43,44] condensed products **12a**–**f** in a synthetically useful manner (Table 2). All the compounds were characterized using spectroscopic techniques and microanalytical data and depicted correct spectral data (Fig. S1–S30). Additionally, purity of the hybrids was checked using HPLC (Fig. S31–S36).

2.2. Electrochemical properties

The redox behavior of the hybrids **12a**–**f** was determined using cyclic voltammetry (CV). The measurements were performed in nitrogen gas purged solutions of **12a**–**f** in anhydrous dichloromethane. The CV plots were recorded using Ag/Ag^+ (0.01 M n-$Bu_4N^+PF_6^-$) as a reference electrode, which was calibrated by a ferrocene/ferrocenium (Fc/Fc^+) redox couple. The hybrids depicted a single electron reversible oxidation peaks similar to ferrocene and the electrochemical data are presented in Table 1. As could be seen from the entries in Table 1, the hybrids show a one electron redox change. However, there is insignificant change in the redox behavior



8 a $R^1 = CH_3$, $R^2 = C_6H_5$
8 b $R^1 = C_2H_5$, $R^2 = C_6H_5$
8 c $R^1 = i\text{-}C_3H_7$ $R^2 = C_6H_5$
8 d $R^1 = i\text{-}C_3H_7$, $R^2 = o\text{-}C_6H_4NO_2$
8 e $R^1 = i\text{-}C_3H_7$, $R^2 = p\text{-}C_6H_4NO_2$
8 f $R^1 = C_2H_5$, $R^2 = CH_3$

Scheme 1. Synthetic route (a–c) to azidoacetamidoferrocenyl thiazole **7** and hybrids **12** (d–g): (a) thiourea, iodine 100 °C overnight, 88%, (b) chloroacetyl chloride, dry toluene, reflux, 85%, (c) NaN_3, dry DMF Δ 60 °C, 89%, (d) PCC, DCM, 24 h, 65%, (e) $POCl_3$, 105 °C, 95%, (f) 2-propyn-1-ol (propargyl alcohol), K_2CO_3, CH_3CN, 94%, (g) $CuSO_4 \cdot 5H_2O$, sodium-L-ascorbate, EtOH: H_2O (9:1 v/v), 92%.