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Synthesis and Evaluation of a Carbosilane Congener of Ferroquine and Its Corresponding Half-Sandwich Ruthenium and Rhodium Complexes for Antiplasmodial and β-Hematin Inhibition Activity

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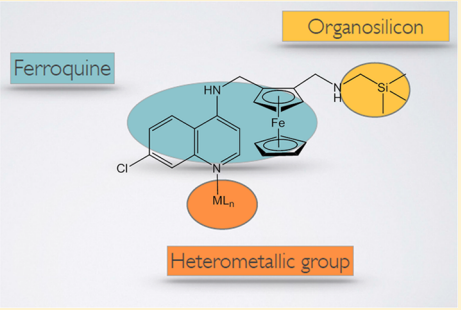
Supporting Information

ABSTRACT: A silicon-containing congener of ferroquine (**1**) was synthesized by incorporating an organosilicon motif in the lateral side chain of ferroquine. Compound **1** was then further reacted with dinuclear half-sandwich transition-metal precursors $[Ru(Ar)(\mu\text{-}Cl)Cl]_2$ (Ar = η^6-*p*-^{i}PrC$_6$H$_4$Me, η^6-C$_6$H$_6$, η^6-C$_6$H$_5$OCH$_2$CH$_2$OH), $[Rh(COD)(\mu\text{-}Cl)]_2$, and $[RhCp^*(\mu\text{-}Cl)Cl]_2$, to yield a series of heterometallic organometallic complexes (**2**−**6**). Compound **1** coordinates selectively in a monodentate manner to the transition metals via the quinoline nitrogen of the aminoquinoline scaffold. All of the compounds were characterized using various analytical and spectroscopic techniques, and the molecular structure of compound **1** was elucidated by single-crystal X-ray diffraction analysis. Furthermore, the *in vitro* antiplasmodial activity of compounds **1**−**6** was established against the chloroquine-sensitive (NF54) and chloroquine-resistant (Dd2) strains of the malaria parasite *Plasmodium falciparum*.



Malaria remains one of the most devastating and problematic infectious diseases in the world today. Over 40% of the world's population is at risk of infection, and it is estimated that malaria infections result in approximately 1 million fatalities annually.[1] Chloroquine had been the clinical drug of choice for treatment of malaria due to its high efficacy, safety, and low cost.[2−7] Unfortunately, due to widespread resistance, chloroquine has been rendered useless in many malaria endemic regions, thus creating a major setback in antimalarial treatment.[4] In many instances, the parasite's recurring resistance to antimalarial drugs has resulted in the exploration of new chemical entities that encompass different mechanisms of action from existing clinically used drugs.[3−5] Conventional quinoline-based and non-quinoline-based antimalarial medicines have largely been replaced by the now popular artemisinin combination therapy, ACT.[8] Unfortunately, resistance to ACTs has been reported, necessitating the search for novel regimens to stem the tide of resistance.

Transition-metal derivatization of existing drugs has become a popular strategy in drug design to combat rising resistance. Interest in the combination of organometallic compounds with compounds of known therapeutic value, such as ferroquine, has thrived in the field of bioorganometallic chemistry.[9−15] This is largely due to the ability of drugs such as ferroquine to overcome resistance experienced by the parent drug chloroquine. The higher lipophilicity of ferroquine allows for greater trans membrane permeation and higher accumulation in the parasite. As a consequence, ferroquine displays higher activity *in vitro* and *in vivo* and has recently completed phase IIb clinical trials.[16−21] Several transition-metal complexes of chloroquine and other non-quinoline-based compounds have been synthesized and evaluated for antiplasmodial activity with varying degrees of success.[22−24]

The strategy of incorporating organosilicon moieties, which generally results in an increase in lipophilicity, has been used to augment biological activity and reduce toxicity in a bid to enhance the therapeutic value of existing drugs.[25−27] We recently reported the synthesis of a series of silicon-containing analogues of chloroquine and corresponding organometallic complexes (Figure 1), in an attempt to enhance lipophilicity by derivatizing the basic amine side chain of chloroquine.[25] As a follow-up to this study, we now report on the synthesis and characterization of a carbosilane congener of ferroquine and its corresponding heterometallic complexes along with their *in vitro* antiplasmodial activities.

Ferroquine was synthesized as previously described.[28] The tertiary amine of ferroquine was quaternized using methyl iodide,

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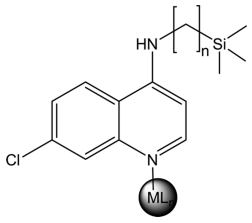
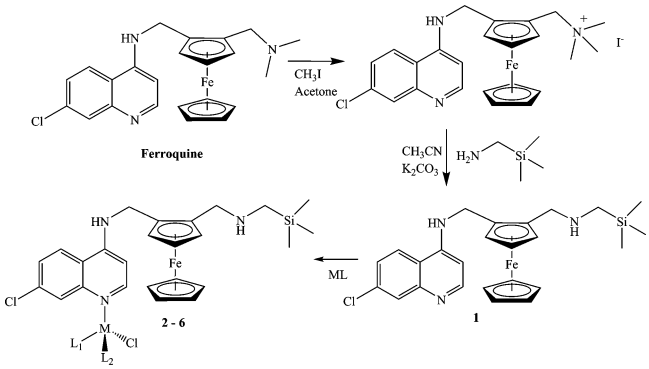


Figure 1. Silicon-containing organometallic analogues of chloroquine previously synthesized.[25]

to yield the corresponding trimethylammonium intermediate, which was then further reacted with aminomethyltrimethylsilane to deliver the silicon-containing ferroquine congener **1** (Scheme 1).

Scheme 1. Synthetic Route to Compounds 1−6



Compound	M	L_1	L_2
2	Ru	η^6-benzene	Cl
3	Ru	η^6-*p*-cymene	Cl
4	Ru	η^6-$C_6H_5OC_2H_4OH$	Cl
5	Rh	COD	-
6	Rh	Cp*	Cl

Heterometallic ruthenium and rhodium silicon-containing ferroquine complexes **2−6** were formed by reacting compound **1** with the metal dimers $[Ru(\eta^6\text{-arene})Cl_2]_2$ (arene = benzene, *p*-cymene, $C_6H_5OC_2H_4OH$), $[Rh(\eta^4\text{-cyclooctadiene})Cl]_2$, and $[Rh(Cp^*)Cl]_2$ (Scheme 1). The bimetallic complexes were isolated in moderate yields and display good solubility in a range of organic solvents. In the synthesis of the heterometallic complexes, the reaction proceeds via selective coordination of the platinum group metal (PGM) to the quinoline nitrogen. Analogous compounds using these metals have been reported by Sanchez-Delgado et al.,[23b] who have evaluated their *in vitro* antiplasmodial and *in vivo* antimalarial activities. Infrared spectral analysis reveals that the absorption bands due to C=N and C=C aromatic vibrations of the quinoline ring shift from 1613 and 1582 cm^{-1} in the ferroquine congener **1** to around 1609 and 1590 cm^{-1} for the heterometallic compounds, respectively. This is analogous to what was observed for the chloroquine series of compounds reported previously.[25] Both the ^1H and ^{13}C NMR spectra of complexes **2−6** further confirm the incorporation of the organometallic PGM fragments. In the ^1H NMR spectra of complexes **2−6**, resonances for the silicon−aminoquinoline moiety are similar to those observed in compound **1**. In addition, resonances due to the ancillary ligands (benzene, *p*-cymene, $C_6H_5OC_2H_4OH$, η^4-cyclooctadiene, pentamethylcyclopentadienyl) coordinated to the PGM metal are also observed.

The molecular structure of compound **1** (Figure 2) was elucidated by single-crystal X-ray diffraction analysis. Single

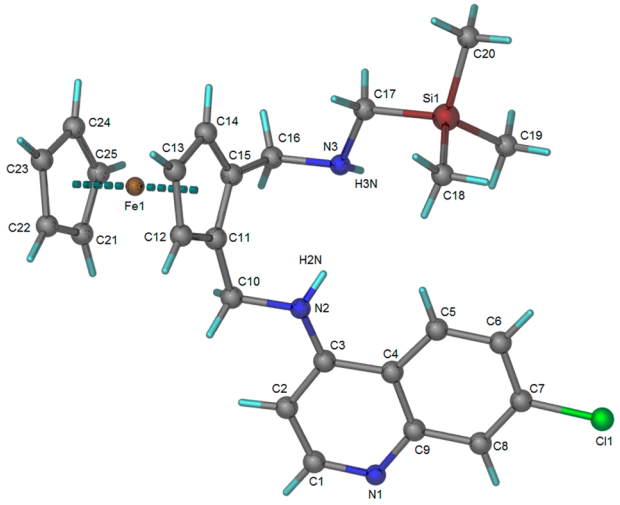


Figure 2. Molecular structure of compound **1** showing the atomic numbering scheme. Selected bond lengths (Å) and angles (deg): Fe1−C11, 2.032(19); Fe1−C21, 2.035(2); Fe1−C15, 2.047(2); Si1−C18, 1.859(3); Si1−C20, 1.862(3); N1−C1, 1.319(3); N1−C9, 1.370(3); N2−C10, 1.460(3); N3−C17, 1.473(3); C11−Fe1−C22, 123.4(10); C23−Fe1−C25, 67.62(11); C24−Fe1−C12, 162.6(11); C18−Si1−C19, 108.9(13); C20−Si1−C17, 106.6(12); C1−N1−C9, 115.5(18); C3−N2−C10, 119.9(18); C17−N3−C16, 111.7(16); C5−C4−C3, 123.4(18).

crystals of compound **1** were obtained by diffusion of hexane into a DCM solution of compound **1**. Compound **1** crystallizes in the space group $P\bar{1}$ with a triclinic system, displaying the planar aromatic aminoquinoline nucleus. Crystal data for complex **1** and the relevant geometrical parameters are given in the Supporting Information.

Solubility has a bearing on a compound's bioavailability and also validates the *in vitro* assay data obtained.[29−31] Since solubility is important for the reliable interpretation of data generated under specific assay conditions and affects the biovailability of a compound through solubility-limited absorption, turbidimetric solubility was determined for test compounds. We envisaged the use of turbidimetric solubility data to guide the synthesis of derivatives by establishing a solubility range for compounds in this class to remain in solution and not precipitate out of solution under the assay conditions. The data presented below would also be useful in establishing a solubility range for compounds in this class likely to have good absorption and permeation when administered to animals during future *in vivo* studies. For most turbidimetric solubility assays utilized in drug discovery programs, generally compounds with solubility less than 1 μM are considered to be highly insoluble, while a compound with a solubility value between 1 and 100 μM is considered to be moderately soluble, and a compound with a solubility value above 100 μM is considered to be highly soluble.[30,31] The turbidity was detected using UV−vis spectroscopy, generating the data obtained in Table 1. The drug niclosamide was used as a control. All compounds showed moderate solubility, with compounds **4** and **5** displaying the poorest solubility (1−5 μM) while compound **3** (20−40 μM) had the best solubility properties as determined at physiological pH in a PBS buffer and at room temperature. Overall, the data established suggests that these newly synthesized silicon-containing ferroquine derivatives are

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Table 1. Turbidimetric Solubility Values Determined against PBS Buffer at pH 7.4

compound	turbidimetric solubility (μM)
ferroquine	5−10
1	5−10
2	10−20
3	20−40
4	1−5
5	1−5
6	5−10
niclosamide	20−40

good candidates for *in vitro* pharmacological testing. The turbidity of these compounds from various biological assays would be highly unlikely, enforcing the IC_{50} values obtained from biological studies as a true reflection of their *in vitro* activity.

The *in vitro* antiplasmodial activity of all compounds was determined against the chloroquine-sensitive (NF54) and chloroquine-resistant (Dd2) strains of *P. falciparum*. The IC_{50} values obtained with standard deviation of the mean values are shown in Table 2. Chloroquine diphosphate and artesunate were

Table 2. *In Vitro* IC_{50} Data for Compounds 1−6 against *P. falciparum* Strains

	P. falciparum (IC_{50}, nM)		
compound	NF54	Dd2	RI[a]
ferroquine	42.65 ± 9.91	27.67 ± 6.46	0.65
1	7.32 ± 3.25	53.87 ± 1.83	7.36
2	30.73 ± 2.70	42.99 ± 1.08	1.40
3	8.27 ± 0.38	42.73 ± 12.78	5.17
4	4.96 ± 0.76	36.64 ± 4.33	7.39
5	28.03 ± 13.54	77.19 ± 12.46	2.75
6	10.36 ± 7.37	34.33 ± 3.37	3.31
chloroquine	5.43 ± 2.13	108.36 ± 1.10	19.95
artesunate	<5.20		

[a]Resistance index (RI) = IC_{50}(Dd2)/IC_{50}(NF54).

used as controls. In the NF54 strain, the results (Table 2) indicate that compound **1**, ruthenium complexes **3** and **4**, and rhodium complex **6** are the most active compounds, with IC_{50} values less than 10 nM. All remaining compounds display comparable activities relative to ferroquine, with IC_{50} values in the range 10−30 nM. In general, all compounds were less active in the Dd2 strain, suggesting cross resistance with chloroquine. However, it is noteworthy that the new compounds still display superior activity (IC_{50} values in the range 34−77 nM) relative to chloroquine (IC_{50} = 108.4 nM) in Dd2 and lower resistance index (RI) values of **1**−**6** in comparison to approximately 20 for chloroquine. While the presence of the trimethylsilyl group dramatically improved the activity of compound **1** (IC_{50} = 7.32 nM) relative to ferroquine (IC_{50} = 42.65 nM) in the NF54 strain, the addition of a metal group led to compounds with diverse activities (4.96−30.7 nM) in the same strain. On the other hand, none of the modifications resulted in improvement of the antiplasmodial activities of derivatives relative to ferroquine against the Dd2 strain.

Despite the resistance to chloroquine in several *P. falciparum* strains, inhibition of hemozoin formation, the generally accepted mechanism of action of chloroquine and related compounds, remains an attractive unique target for antimalarial drug discovery.[32,33] The ability of a potential drug to inhibit the formation of hemozoin can be measured using the NP-40 mediated β-hematin (synthetic hemozoin) inhibition assay. The NP-40 mediated assay mimics the conditions of the acidic food vacuole in the parasite to give a better measure of hemozoin formation. Using a modified NP-40 detergent mediated assay, the ability of compounds **1**−**6** to inhibit hemozoin formation was evaluated (Table 3). The ferrocenyl rhodium-COD complex **5**

Table 3. IC_{50} Values Determined against β-Haematin

compound	IC_{50} (μM)	standard deviation
1	16.2	0.0923
2	4.98	0.140
3	4.92	0.139
4	5.36	0.123
5	4.84	0.231
6	6.81	0.128
ferroquine	15.1	0.330
amodiaquine	6.36	0.120

showed the highest inhibitory effect (IC_{50} = 4.84 μM), which was slightly better than that of amodiaquine (IC_{50} = 6.36 μM), another 4-aminoquinoline antimalarial drug known to target hemozoin formation. Compound **1** is comparable to ferroquine as far as inhibiting formation of β-hematin is concerned. All of the heteronuclear metal complexes are around 3-fold more potent at inhibiting β-hematin formation in comparison to the ferroquine congener **1** and ferroquine. However, no direct correlation between inhibition of β-hematin formation and parasite growth could be established. This is not surprising, since the antiplasmodial activity of 4-aminoquinolines such as chloroquine has more to do with accumulation within the acidic food vacuole compartment organelle of the parasite than inhibition of the target. All of the compounds screened using the NP-40 mediated assay contain several aromatic rings, making them capable of intermolecular $\pi-\pi$ interactions. It is possible that these compounds inhibit formation of hemozoin through $\pi-\pi$ stacking interactions with hematin.

In summary, a new carbosilane congener of ferroquine **1** and the corresponding series of neutral heterometallic ruthenium and rhodium metal complexes **2**−**6** have been successfully synthesized and characterized. Compound **1** acts as a monodentate donor ligand that coordinates to the transition metals selectively via the quinoline nitrogen of the aminoquinoline scaffold. The ferroquine-based series containing an organosilicon motif integrated into the lateral side chain have been evaluated for *in vitro* antiplasmodial activity. All of the compounds were found to exhibit high antiplasmodial activity against the NF54 and Dd2 *P. falciparum* strains. Selected compounds inhibited the growth of the malaria parasite in the low nanomolar range. Complex **4** was the most active in the NF54 and the Dd2 strains, with IC_{50} values of 4.86 and 35.91 nM, respectively. All of the metal complexes inhibited formation of synthetic hemozoin. Although none of the modifications resulted in derivatives with superior antiplasmodial activity relative to ferroquine on Dd2, compounds described in the present study would need to be tested against a larger panel of both sensitive and resistant strains of the malaria parasite before any meaningful structure−activity relationships, any beneficial effects, and evidence of cross resistance could be delineated. This is in view of the fact that antiplasmodial activity, like resistance, is both compound and strain specific. These preliminary results support the benefits of incorporating organosilicon moieties in exisiting drug leads. Coupled with the introduction of a ferrocenyl

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moiety, this results in heteronuclear metal complexes, which can further enhance biological properties. Investigations to further expand structure−activity relationships are currently in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Text, a table, and a CIF file giving experimental details and chemical data of the newly obtained compounds and crystallographic data for **1**. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 931518 also contains supplementary crystallographic data for **1**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K.; fax, (internat.) +44-1223/336-033; e-mail, deposit@ccdc.cam.ac.uk).

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Notes

The authors declare no competing financial interest.

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