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Synthesis, Characterization, and Pharmacological Evaluation of Silicon-Containing Aminoquinoline Organometallic Complexes As Antiplasmodial, Antitumor, and Antimycobacterial Agents

Yiqun Li,[†] Carmen de Kock,[‡] Peter J. Smith,[‡] Hajira Guzgay,[§] Denver T. Hendricks,[§] Krupa Naran,[⊥,∥] Valerie Mizrahi,[⊥,∥] Digby F. Warner,[⊥,∥] Kelly Chibale,*[,†,∥] and Gregory S. Smith*[,†]

[†]Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa

[‡]Division of Pharmacology, Department of Medicine, University of Cape Town, K45, OMB, Groote Schuur Hospital, Observatory 7925, South Africa

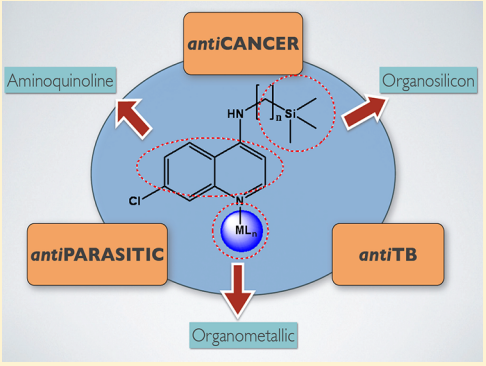
[§]Division of Medical Biochemistry, Department of Clinical and Laboratory Sciences, University of Cape Town, Rondebosch 7701, South Africa

[⊥]MRC/NHLS/UCT Molecular Mycobacteriology Research Unit, DST/NRF Centre of Excellence for Biomedical TB Research, University of Cape Town, Rondebosch 7701, South Africa

[∥]Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Rondebosch 7701, South Africa

Supporting Information

ABSTRACT: Two silicon-containing analogues (**1**, **2**) of chloroquine, modified in the lateral side chain with organosilicon moieties, were synthesized. Compounds **1** and **2** were 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 neutral mononuclear Ru(II), Rh(I), and Rh(III) silicon-aminoquinoline complexes (**3**−**12**). Compounds **1** and **2** act as monodentate donors that coordinate to the transition metals via the quinoline nitrogen of the aminoquinoline scaffold. All the compounds were characterized using various analytical and spectroscopic techniques, and the molecular structures of compounds **2** and **11** were elucidated by single-crystal X-ray diffraction analysis. Furthermore, the *in vitro* pharmacological activities of compounds **1**−**12** were established against chloroquine-sensitive (NF54) and chloroquine-resistant (Dd2) strains of the malarial parasite *Plasmodium falciparum* and against the pathogenic bacterium *Mycobacterium tuberculosis* $H_{37}R_v$, as well as an esophageal (WHCO1) cancer cell line.



INTRODUCTION

The medical successes of cisplatin and related platinum-based drugs pioneered research into the synthesis of new transition metal complexes with interesting and occasionally multifunctional biological properties.[1−3] Under this umbrella, the field of bioorganometallic chemistry has certainly thrived through the combination of organometallic complexes with organic compounds of known therapeutic value or through the development of new bioorganometallic chemotherapeutics in their own right.[4−10]

Malaria is an infectious disease found mostly in tropical and subtropical countries, and it is responsible for 1−3 million deaths each year.[11,12] The causative agent is a parasite of the genus *Plasmodium*, the most virulent strain being *P. falciparum*.[13] The parasite is transmitted by an infected female Anopheles mosquito and is extremely infectious to humans and pathogenic when it invades the host red blood cells.[14] The most common treatment is through the use of chemotherapeutics, most of which have historically been based on the quinoline class of drugs, exemplified by chloroquine.[15−20] The antimalarial activity of quinoline-based antimalarial drugs stems from their ability to form strong complexes with hematin and inhibit hemozoin formation by accumulating in the parasite's digestive vacuole.[21,22] However, chloroquine and other quinoline drugs show reduced efficacy due to increased drug resistance, which has rendered drugs like chloroquine virtually useless and malaria impossible to treat in many parts of the world. Previous conventional quinoline- and non-quinoline-based antimalarial medicines have largely been replaced by new fixed-dose combination therapies containing a derivative of the Chinese natural product artemisinin and a 4-aminoquinoline or amino alcohol in the now popular artemisinin combination therapy, ACT.[23]

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To combat this resistance, new strategies in drug design are required. In this regard, several transition metal complexes of chloroquine have been synthesized and evaluated for antiplasmodial activity with varying degrees of success.[24−26] In some instances transition metals seem to provide additional stability to the drug and a better means of delivery to their desired targets.[27−33] The most notable example of an organometallic antimalarial drug is ferroquine (Figure 1),

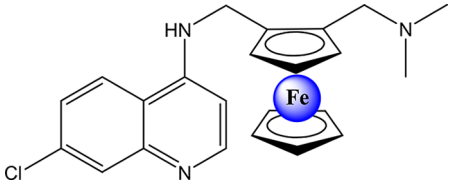


Figure 1. Chemical structure of ferroquine with known antimalarial activity.

which has a ferrocene moiety incorporated into the lateral side chain of chloroquine. Ferroquine and its derivatives display high antimalarial activity against chloroquine-resistant strains[34−38] and is currently in phase IIb clinical trials.[39] The hydrophobic ferrocene core is thought to enhance lipophilicity and, in turn, enhances transmembrane interactions.[22] Several research groups have also introduced various organometallic fragments in the basic amine side chain in an attempt to enhance the antimalarial activity.[24,26−32,35b]

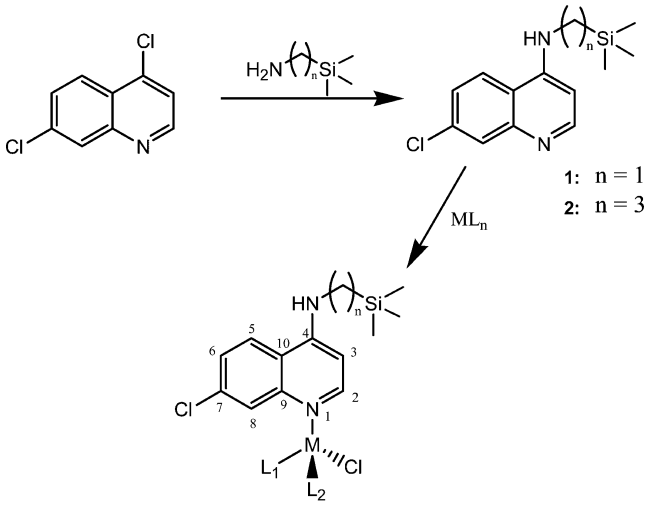
The basis for our study is a series of recent publications illustrating that bioorganosilicon chemistry provides a novel and powerful source of chemical diversity in medicinal drug design.[40−43] There are several examples of silicon-containing drugs in the literature. For example, polydimethylsiloxanes are well known for their unusual rheological properties.[44] The structure of cyclohexyl(phenyl)(3-piperidin-1-yl)propyl)silanol contains some interesting silicon chiral centers,[44,45] and sila-derived phthalocyanine has shown some promising results in photodynamic cancer therapy.[44,45] In addition, many silicon-containing drugs such as silperisone,[45a] Tac101,[45b] and BNP 1350[45c] have entered human clinical trials. This strategy of incorporating organosilicon moieties has been used to augment biological activity and reduce toxicity in a bid to enhance the therapeutic value of existing drugs.[46,47] Many organosilicon compounds remain chemically stable under physiological conditions, their ease of synthesis from a number of commercially available precursors facilitates chemical modification of existing drugs, and silicon analogues are generally more lipophilic, which can markedly increase the distribution of a molecule.[41−47] An increase in lipophilicity of a drug molecule can provide several physiological benefits, including an increase in bioavailability and better tissue and cell penetration, which may result in an increase in permeability.[46,47] Their selective uptake by tumors could result in a greater drug payload in tumorous cells.

Our recent studies into the synthesis of potential antimalarial agents[48,49] prompted us to explore the effect of introducing silicon in the lateral side chain of chloroquine, in an attempt to identify new antimalarial compounds. In addition, the quinoline nucleus represents an important class of heterocyclic compounds known to possess a range of pharmacological activities, including antiviral,[50] anticancer,[51] antibacterial,[52] antifungal,[53] antiobesity,[54] and anti-inflammatory.[55] Thus, due to the promising activity of quinolines against infectious agents and their activity against certain types of cancers, our study also includes an investigation of their antitumor and antimycobacterial properties. To the best of our knowledge, there are no reports on the use of silicon-containing aminoquinoline transition metal complexes as chemotherapeutic agents in the field of bioorganometallic antimalarial research. Herein we report the synthesis and characterization of a series of new organometallic silicon-containing compounds based on an aminoquinoline scaffold along with their *in vitro* antiplasmodial, antitumor, and antimycobacterial activities. Results from turbidimetric solubility and inhibition of β-hematin formation studies are also described.

RESULTS AND DISCUSSION

Synthesis of Silicon-Containing Aminoquinolines (1, 2). Two aminoquinolines (**1**, **2**) with organosilicon moieties in the lateral side chain were synthesized via a simple nucleophilic substitution reaction of 4,7-dichloroquinoline with the appropriate amine-terminated silane (Scheme 1). Compounds **1** and **2** were isolated in relatively good yields and are

Scheme 1. Synthetic Route to Compounds 1−12



Compound	n	M	L_1	L_2
3	1	Ru	η^6-benz	Cl
4	1	Ru	η^6-*p*-cymene	Cl
5	1	Ru	η^6-$C_6H_5C_2H_4OH$	Cl
6	1	Rh	COD	-
7	1	Rh	Cp*	Cl
8	3	Ru	η^6-benz	Cl
9	3	Ru	η^6-*p*-cymene	Cl
10	3	Ru	η^6-$C_6H_5C_2H_4OH$	Cl
11	3	Rh	COD	-
12	3	Rh	Cp*	Cl

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moderately soluble in most organic solvents. Both compounds were characterized using ^{1}H and ^{13}C NMR and IR spectroscopy, electron-impact mass spectrometry, and elemental analysis.

Synthesis of Ruthenium and Rhodium Complexes (3−12). Neutral mononuclear ruthenium and rhodium silicon-containing aminoquinoline complexes (**3**−**12**) were synthesized by the reaction of the aforementioned compounds (**1**, **2**) with the well-known dimers $[Ru(\eta^6\text{-arene})Cl_2]_2$ (arene = benzene, *p*-cymene, $C_6H_5OC_2H_4OH$), $[Rh(\eta^4\text{-cyclooctadiene})Cl]_2$, or $[RhCp^*Cl]_2$, as depicted in Scheme 1. The transition metal complexes were isolated in good yields and display good solubility in a range of organic solvents. For each complex, the reaction proceeds via coordination of the metal to the quinoline nitrogen. This is attested to in the IR spectra by a shift of the absorption band due to C═N aromatic vibration of the quinoline ring from 1575 cm^{-1} in the metal-free compound to around 1610 cm^{-1} for the metalated compounds. Both the ^{1}H and ^{13}C NMR spectra of **3**−**12** further confirm the incorporation of the organometallic fragments. The chemical shifts of the ^{1}H NMR signals for the silicon-aminoquinoline in the spectra of **3**−**12** are similar to those observed in **1** and **2**. Additional peaks due to the ancillary ligands coordinated to the metal are also observed. ESI-MS generally shows the molecular ion peak with the loss of a chloride ligand.

Single-Crystal X-ray Crystallography Study. In addition to the spectroscopic and analytical data, the incorporation of an organosilane moiety and coordination of rhodium to the silicon-containing aminoquinoline was further established by single-crystal X-ray diffraction analysis of compounds **2**[56] and **11**.[57] Crystal data for complexes **2** and **11** are summarized in the reference section, and selected bond angles and lengths are presented in Table 1. Single crystals of compound **2** were obtained by exposing a DMSO solution of **2** to air. The molecular structure of compound **2** (Figure 2) crystallizes in a *Pbca* space group, with an orthorhombic system, displaying the planar aromatic aminoquinoline nucleus and the flexible propyl side chain. The molecular structure shows positional disorder in two places (C11 and C12), due to increased flexibility of the propyl side chain that can be oriented in different ways.

Table 1. Selected Bond Lengths and Angles for Compounds 2 and 11

atoms	**2**	atoms	**11**
Interatomic Distances (Å)			
Cl1−C7	1.745(3)	Rh1−N1	2.103(18)
Si1−C13	1.851(4)	Rh1−C1	2.108(2)
Si1−C14	1.844(4)	Rh1−C4	2.146(3)
Si1−C15	1.856(3)	Rh1−C5	2.136(2)
Si1−C12A	1.919(4)	Rh1−C8	2.125(2)
Si1−C12B	1.861(12)	Rh1−Cl	2.370(6)
N1−C1	1.321(3)	Si1−C21	1.861(4)
N1−C9	1.364(3)	Si1−C22	1.870(4)
N2−C10A	1.455(3)	Si1−C23A	1.874(12)
N2−C10B	1.455(3)	Si1−C23B	1.875(16)
Angles (deg)			
C13−Si1−C14	108.12(17)	Cl1−Rh1−N1	88.84(5)
C13−Si1−C15	111.14(15)	Cl1−Rh1−C1	158.89(8)
C14−Si1−C15	110.10(15)	Cl1−Rh1−C4	93.38(6)
C1−N1−C9	115.80(19)	Cl1−Rh1−C5	90.13(6)
N2−C3−C2	123.2(2)	Cl1−Rh1−C8	162.57(8)
Cl1−C7−C8	120.23(19)	N1−Rh1−C1	89.55(9)
C3−C4−C5	123.7(2)	N1−Rh1−C4	162.28(9)

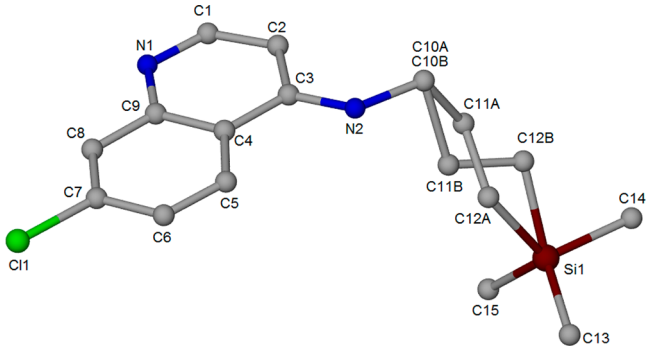

Figure 2. Molecular structure of **2** showing the atomic numbering scheme.

Single crystals of complex **11** suitable for single-crystal X-ray diffraction were obtained by exposing a DMSO solution of the complex to air. The molecular structure of **11** (Figure 3) shows the rhodium atom to be in a typical square-planar geometry surrounded by the aminoquinoline, a terminal chloro, and the cyclooctadienyl ligand. The molecular structure confirms that the planar aminoquinoline motif coordinates to the metal center through the quinoline nitrogen in a monodentate manner. The geometrical parameters around the rhodium atom are comparable to those found in analogous reported mononuclear Rh(I)-cyclooctadienyl complexes.[58,59] Complex **11** crystallizes with a monoclinic system.

***In Vitro* Antitumor Activity.** The *in vitro* antitumor activity of compounds **1**−**12** were evaluated against the WHCO1 esophageal cancer cell line. Table 2 summarizes the IC_{50} values obtained. With the exception of compounds **6** and **12**, all the compounds show cytotoxic activities, with IC_{50} values below 100 μM. Compounds **2** and **8**−**10** show the highest antiproliferative effect, with IC_{50} values less than 10 μM. Of these, complex **10**, containing the 2-hydroxyethoxy moiety tethered to the arene, showed the strongest cytotoxic activity, with an IC_{50} value of 4.41 μM. Compounds **1**, **3**−**5**, **7**, and **11** are moderately active, with IC_{50} values ranging between 25 and 52 μM. The general trend indicates that the ruthenium complexes display better activity in comparison with the rhodium complexes, and the compounds containing a three-carbon chain spacer show better activity when compared to those containing a one-carbon spacer. The presence of the metal did not appear to significantly enhance the biological activity in comparison with the free ligand.

***In Vitro* Antiplasmodial Activity.** The *in vitro* antiplasmodial activity of compounds **1**−**12** was evaluated against the choloroquine-sensitive (NF54) and chloroquine-resistant (Dd2) strains of *P. falciparum*, and the results are listed in Table 3. In general, the new silicon-containing derivatives show moderate to weak inhibitory effects relative to chloroquine. Compound **2**, with the three-carbon methylene spacer, displayed better activity compared to compound **1**, with a one-carbon methylene spacer. In the organometallic series, introduction of a transition metal, in somes cases (**3**−**5**, **7**, **10**), resulted in improved antiplasmodial activity, with the ruthenium complexes generally showing better activity than the rhodium complexes. In the chloroquine-sensitive (NF54) strain, the results revealed that the ruthenium complexes **3**, **8**, and **9** are the most active, with IC_{50} values less than 100 nM.

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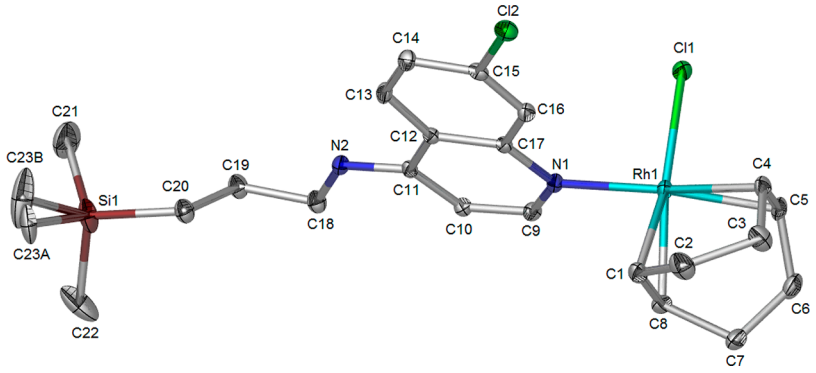

Figure 3. Molecular structure of **11** with 30% probability ellipsoids.

Table 2. IC_{50} Values Determined against WHCO1 Cancer Cells

compound	WHCO1 cell lines (IC_{50}, μM)	95% confidence intervals
1	51.92	45.49−59.27
2	5.86	4.75−7.24
3	25.16	18.83−33.62
4	31.46	25.77−38.40
5	33.08	28.85−37.94
6	inactive	
7	21.9	18.22−26.31
8	5.70	4.98−6.53
9	7.03	6.34−7.79
10	4.41	4.06−4.79
11	31.62	26.44−37.83
12	inactive	

Table 3. Antiplasmodial Activities of Compounds 1−12

	P. falciparum (IC_{50}, nM)		
compound	NF54	Dd2	RI
1	248.08 ± 28.7	524.74 ± 187.29	2.11
2	97.65 ± 9.6	269.74 ± 27.31	2.76
3	61.40 ± 10.3	>1749	
4	276.83 ± 31.0	526.56 ± 70.85	1.90
5	270.23 ± 35.9	835.09 ± 190.03	3.09
6	459.54 ± 92.5	>1955	
7	306.69 ± 112.2	>1742	
8	71.70 ± 4.8	211.77 ± 22.68	2.95
9	81.61 ± 7.4	228.96 ± 4.06	2.81
10	151.92 ± 14.1	385.61 ± 8.48	2.54
11	101.22 ± 19.7	721.13 ± 75.45	7.12
12	134.73 ± 28.6	370.48 ± 26.08	2.75
CQ	23.26	294.62	12.67
artesunate	22.63		

Compounds **1**, **4**−**7**, and **10**−**12** display moderate activities, with IC_{50} values ranging between 100 and 460 nM. In general, compounds were less active in Dd2, suggesting that these compounds show potential cross resistance in an analogous fashion to chloroquine, although all compounds had lower resistance indices than chloroquine.

***β*-Hematin Inhibition Studies.** It has been suggested in the literature that in spite of the resistance to chloroquine in several *P. falciparum* strains, hemozoin remains a unique target for most antimalarial drugs.[60,61] Using a modified NP-40 detergent-mediated assay, the ability of compounds **1**−**12** to inhibit hemozoin formation was evaluated. The results are shown in Table 4. From the log-based dose−response curves obtained, all of the compounds were shown to inhibit *β*-hematin formation at the concentration (1000 ng/mL) tested. The compounds generally show comparable IC_{50} values (10.64−28.52 μM), which are either comparable to or slightly better than chloroquine. This is not surprising since compounds **1**−**12** contain the 4-aminochloroquinoline motif, which has been shown to be important in the inhibition of *β*-hematin formation by chloroquine.[62]

Table 4. IC_{50} Values Determined against *β*-Hematin

compound	IC_{50} (μM)	95% confidence intervals
1	18.08	16.62−19.66
2	17.75	16.44−19.18
3	14.38	14.02−14.74
4	22.44	21.14−24.13
5	24.19	22.43−26.09
6	22.46	19.62−25.72
7	28.52	27.49−29.58
8	18.01	16.74−19.66
9	19.58	18.46−20.78
10	14.66	13.87−15.49
11	10.64	10.39−10.89
12	15.73	15.17−16.31
chloroquine	27.87	

***In Vitro* Antimycobacterial Activity.** Compounds **1**−**12** were screened for their *in vitro* antimycobacterial activity against *M. tuberculosis* $H_{37}R_v$. The MIC_{99} ranges are summarized in Table 5. In general, these compounds display weak to moderate antimycobacterial activity. Compounds **2**, **3**, and **11** are the most active, with MIC_{99} values of 20 μM. These results are not too dissimilar from other compounds containing a quinoline moiety and that were shown to confer antimycobacterial activity.[63]

Turbidimetric Solubility Studies. The turbidimetric solubility assay investigates the kinetic solubility of the compounds through a series of dilutions of the tested compound in DMSO into an aqueous buffer. The solubility of a compound is an important factor in determining its absorption from the gastrointestinal tract and ultimately its bioavailability.[64,65] Compounds with poor solubility can often pose a development challenge.[66] The quality of the data generated from the *in vitro* assays can also be affected by poor solubility. In the turbidimetric solubility assay as used in drug discovery, compounds with solubility less than 1 μM are considered to be highly insoluble, a compound with solubility

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Table 5. Antimycobacterial Activities of Compounds 1−12

compound	MIC_{99} at day 7 (μM)	MIC_{99} at day 14 (μM)
1	40	40
2	20	20
3	20	20
4	40	40
5	40	40
6	40	40
7	40	40
8	80	80
9	40	40
10	40	80
11	20	20
12	40	40
rifampicin		0.0121
kanamycin		5.40

between 1 and 100 μM is considered to be moderately soluble, and that with solubility above 100 μM is considered highly soluble.[64−66] Although poor solubility is obviously an undesirable situation, it does not necessarily preclude the development of an otherwise promising compound.[66] If the compound has high permeability and is highly potent *in vivo*, then solubility may become less limiting. From the data obtained (Table 6), all compounds showed moderate solubility,

Table 6. Turbidimetric Solubility Values Determined against PBS Buffer at pH 7.4

compound	turbidimetric solubility (μM)
1	20−40
2	20−40
3	60−80
4	80−100
5	4−5
6	10−20
7	80−100
8	5−10
9	20−40
10	1−2
11	5−10
12	10−20
niclosamide	20−40

with compounds **5**, **8**, and **10**−**11** displaying the poorest solubility and compounds **3**, **4**, and **7** the best solubility properties, as determined at physiological pH in a PBS buffer and at ambient temperature.

CONCLUSIONS

Two aminoquinoline ligands (**1** and **2**) containing organosilicon moieties in the lateral side chain and a corresponding series of Ru(II), Rh(I), and Rh(III) neutral complexes (**3**−**12**) have been synthesized and fully characterized. Compounds **1**−**12** are air-stable, and consequently stability studies show that they are stable in DMSO at least up to a month. In addition, the antiplasmodial, antimycobacterial, and antitumor activities of compounds **1**−**12** were evaluated *in vitro*. Compounds containing the longer alkyl (propyl) side chain generally showed better activity. β-Hematin inhibition studies suggest that the compounds act in a similar manner to chloroquine. However, there was no correlation between the β-hematin inhibition and antiplasmodial activity. This may suggest that this new class of silicon-containing 4-aminoquinolines exert their antiplasmodial effects through multiple mechanisms, including inhibition of hemozoin formation. The lack of correlation may also point to physicochemical and/or transport properties, as the drugs have to cross the membrane of the infected host red blood cells and the parasite in order to reach the site of action, the food vacuole.

EXPERIMENTAL SECTION

General Methods. Reagents were purchased from commercial suppliers, either Sigma-Aldrich or ABCR, and used as received without further purification. Ruthenium trichloride and rhodium trichloride were kindly donated by AngloAmerican Platinum Limited. The dimers, $[Ru(II)(\eta^6\text{-}p\text{-}^iPrC_6H_4Me)(\mu\text{-}Cl)Cl]_2$,[67] $[Ru(II)(\eta^6\text{-}C_6H_6)(\mu\text{-}Cl)Cl]_2$,[68] $[Ru(II)(\eta^6\text{-}C_6H_5OCH_2CH_2OH)(\mu\text{-}Cl)Cl]_2$,[69] $[Rh(I)(\eta^4\text{-}C_8H_{12})(\mu\text{-}Cl)]_2$,[70] and $[Rh(III)(\eta^5\text{-}C_{10}H_{15})(\mu\text{-}Cl)_2Cl]_2$,[71] were all prepared according to literature methods. All solvents used were analytical grade and dried over molecular sieves. Nuclear magnetic resonance spectra were recorded on a Varian Unity XR400 MHz (^{1}H at 399.95 MHz, ^{13}C at 100.58 MHz), Varian Mercury XR300 (^{1}H at 300.08 MHz, ^{13}C at 75.46 MHz), or Bruker Biospin GmbH (^{1}H at 400.22 MHz, ^{13}C at 100.65 MHz) spectrometer at ambient temperature. Chemical shifts for ^{1}H and ^{13}C{^{1}H} NMR are reported using tetramethylsilane (TMS) as the internal standard. NMR spectra were recorded in deuterated dimethylsulfoxide (DMSO-D_6) unless otherwise stated. Infrared absorptions were measured on a Perkin-Elmer Spectrum 100 FT-IR spectrometer as KBr pellets. Microanalyses for C, H, and N were carried out using a Thermo Flash 1112 Series CHNS-O analyzer, and melting points were determined using a Büchi melting point apparatus B-540. Mass spectrometry determinations were carried out on all new compounds using either electron impact (EI) on a JEOL GC Matell instrument or electrospray ionization (ESI) on a Waters API Quattro Micro instrument in either the positive or negative mode.

General Method for the Synthesis of 1 and 2. 4,7-Dichloroquinoline (0.98 g, 4.95 mmol) was added to an excess amount of 3-aminopropyltrimethylsilane (2.01 mL, 12.0 mmol). The air-sensitive neat reaction was carried out under argon. The light yellow suspension solution mixture was heated slowly to 80 °C without stirring in an oil-bath. After an hour, the light yellow homogeneous solution mixture was heated further to 140 °C with stirring over a 30-minute interval and subsequently refluxed for a further 6 hours at 140 °C. The reaction mixture was then cooled to room temperature, and the resulting white solid isolated by vacuum filtration. The white solid (**2**) was washed with distilled H_2O (5 × 10.0 mL) and dried.

Compound 1. A neat mixture of 4,7-dichloroquinoline (1.08 g, 5.10 mmol) was reacted together with aminomethyltrimethylsilane (1.51 mL, 15.1 mmol). The reaction yielded **1** as a white solid. Yield = 1.07 g (79.2%). Mp: 125−129 °C. ^{1}H NMR (300.006 MHz, DMSO): δ (ppm) −0.37 (9H, s, 3*CH_3); 2.36 (2H, s, CH_2); 6.01 (1H, d, $^3J_{HH}$ = 5.59 Hz, H_3); 6.97 (1H, d, $^3J_{HH}$ = 8.82 Hz, H_6); 7.10 (1H, s, NH); 7.31 (1H, s, H_8); 7.89 (2H, m, H_5, H_2). ^{13}C NMR (75.46 MHz, CD_3OD): δ (ppm) −3.1 ($\underline{C}H_3$); 32.4 ($\underline{C}H_2$); 98.6, 118.9, 121.2, 122.9, 123.4, 137.2,, 148.6, 149.8, 151.9 (ArC). IR (KBr, cm^{-1}): ν(NH) 3341; ν(CH aromatic) 3030; ν(C═N) 1615; ν(C═C aromatic) 1578. Anal. Calcd for $C_{13}H_{17}N_2ClSi\cdot H_2O$ (282.85): C, 55.20; H, 6.06; N, 9.90. Found: C, 55.83; H, 6.51; N, 10.11. MS (EI$^+$-MS, m/z): 264.1 $[M - H]^+$.

Compound 2. Yield = 0.91 g (63.0%). Mp: 165−168 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) −0.02 (9H, s, 3*CH_3); 0.56 (2H, m, CH_2); 1.64 (2H, m, CH_2); 3.26 (2H, m, CH_2); 6.48 (1H, d, $^3J_{HH}$ = 5.74 Hz, H_3); 7.45 (1H, dd, $^4J_{HH}$ = 2.23 Hz, $^3J_{HH}$ = 8.99 Hz, H_6); 7.62 (1H, s, NH); 7.79 (1H, d, $^3J_{HH}$ = 2.74 Hz, H_8); 8.31 (1H, d, $^3J_{HH}$ = 9.05 Hz, H_5); 8.38 (1H, d, $^3J_{HH}$ = 5.68 Hz, H_2). ^{13}C NMR (100.58 MHz, CD_3OD): δ (ppm) −3.1 (Si$\underline{C}H_3$); 13.5 ($\underline{C}H_2$); 22.6 ($\underline{C}H_2$); 45.9 ($\underline{C}H_2$); 98.2, 118.5, 122.9, 124.0, 126.2, 135.1, 149.1, 150.9, 151.5 (ArC). IR (KBr, cm^{-1}): ν(NH) 3246; ν(C═N) 1615; ν(C═C

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aromatic) 1578. Anal. Calcd for $C_{15}H_{21}N_2ClSi\cdot(1/2)H_2O$ (301.89): C, 59.68; H, 7.01; N, 9.28. Found: C, 59.54; H, 7.09; N, 9.15. MS (EI^+-MS, m/z): 292.1 $[M]^+$.

General Method for Synthesis of Ru(II), Rh(I), and Rh(III) Complexes. As an example, a solution of **2** (0.15 g, 0.49 mmol) dissolved in dry DCM (5.0 mL) was added dropwise to a solution mixture of the appropriate metal dimer (in this case $[Ru(p\text{-cymene})Cl_2]_2$) (0.15 g, 0.25 mmol) dissolved in dry DCM (5.0 mL). The red-orange solution was heated at 45 °C for 2 hours. Upon cooling to room temperature, the red-orange solution was reduced to less than half of its initial volume by rotary evaporation. The residual sticky red-orange solution was placed on ice to aid precipitation, yielding the product (**8**) as a yellow-orange solid. Compound **8** was recrystallized using a minimum amount of hot DCM, filtered and washed with a minimum amount of cold DCM (3 × 5.0 mL), and then dried under vacuum. Complexes **3**–**7** were synthesized by reacting **1** with the appropriate Ru(II)-arene (benzene, *p*-cymene, $C_6H_5C_2H_4OH$) and Rh(I) or Rh(III) dimers, and complexes **8**–**12** were synthesized by reacting **2** with the appropriate Ru(II) or Rh(I/III) dimers.

Compound ***3***. Orange solid, yield = 0.24 g (55.5%). Mp: 261–265 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) 0.12 (9H, s, 3*C$\underline{H}_3$); 2.91 (2H, d, $^3J_{HH}$ = 9.6 Hz, CH_2); 5.97(6H, s, ArH benz); 6.56 (1H, d, $^3J_{HH}$ = 6.1 Hz, H_3); 7.52 (1H, dd, $^4J_{HH}$ = 9.0 Hz, ^3J_H = 2.1 Hz, H_6); 7.82 (1H, d, $^3J_{HH}$ = 2.0 Hz, H_8); 7.90 (1H, s, NH); 8.39–8.43 (2H, m, H_5 and H_2). ^{13}C NMR (100.58 MHz, DMSO): δ (ppm) −1.72 (Si$\underline{C}H_3$); 33.75 (CH_2); 87.84 (Ar$\underline{C}$ benz); 98.76, 117.47, 124.80, 124.81, 135.05, 147.11, 147.10, 148.83, 152.27 (ArC). IR (KBr, cm^{-1}): ν(NH) 3287; ν(C═N) 1619; ν(C═C aromatic) 1588. Anal. Calcd for $C_{19}H_{23}N_2Cl_3SiRu\cdot H_2O$ (532.93): C, 42.82; H, 4.35; N, 5.26. Found: C, 42.52; H, 4.24; N, 4.74. MS (ESI^+-MS, m/z): 479.0 $[M - Cl]^+$.

Compound ***4***. Golden solid, yield = 0.18 g (60.1%). Mp: 238–241 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) 0.10 (9H, s, 3*C$\underline{H}_3$); 1.19 (6H, m, 2*CH_3 *p*-cym); 2.09 (3H, m, CH_3 *p*-cym); 2.83 (1H, m, CH *p*-cym); 2.90 (2H, m, CH_2); 5.77 (2H, d, $^3J_{HH}$ = 6.3 Hz, 2*CH *p*-cym); 5.81 (2H, d, $^3J_{HH}$ = 6.3 Hz, 2*CH *p*-cym); 6.56 (1H, d, $^3J_{HH}$ = 6.0 Hz, H_3); 7.51 (1H, dd, $^4J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 2.1 Hz, H_6); 7.81 (2H, m, H_8 and NH); 8.39 (2H, m, H_5 and H_2). ^{13}C NMR (100.58 MHz, DMSO): δ (ppm) −1.17 (Si$\underline{C}H_3$); 18.04, 21.68, 30.16, (C *p*-cym); 33.84 (CH_2); 85.69, 86.54, 98.75, 101.42 (Ar$\underline{C}$ *p*-cym); 108.54, 117.87, 124.42, 124.90, 135.05, 147.21, 148.10, 148.36, 152.27 (ArC). IR (KBr, cm^{-1}): ν(NH) 3297; ν(C═N) 1611; ν(C═C aromatic) 1590. Anal. Calcd for $C_{23}H_{31}N_2Cl_3SiRu\cdot H_2O$ (589.04): C, 46.90; H, 5.30; N, 4.76. Found: C, 47.06; H, 5.27; N, 4.61. MS (ESI^+-MS, m/z): 572.0 $[M]^+$, 536.5 $[M - Cl]^+$.

Compound ***5***. Orange solid, yield = 0.20 g (53.9%). Mp: 222–225 °C. ^{1}H NMR (300.066 MHz, DMSO): δ (ppm) 0.14 (9H, s, 3*C$\underline{H}_3$); 3.01 (2H, s, CH_2); 3.74 (2H, t, $^3J_{HH}$ = 5.0 Hz, C$\underline{H}_2$ Glu); 4.23 (2H, t, $^3J_{HH}$ = 5.0 Hz, C$\underline{H}_2$ arene); 5.39 (1H, t, $^3J_{HH}$ = 5.4 Hz, C$\underline{H}$ arene); 5.55 (2H, d, $^3J_{HH}$ = 6.2 Hz, C$\underline{H}_2$ arene; 6.15 (2H, dd, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 5.4 Hz, C$\underline{H}_2$ arene); 6.65 (1H, d, $^3J_{HH}$ = 6.5 Hz, H_3); 7.59 (1H, dd, $^4J_{HH}$ = 9.0 Hz, ^3J_H = 2.2 Hz, H_6); 7.89 (1H, d, $^3J_{HH}$ = 2.2 Hz, H_8); 8.40 (1H, d, $^3J_{HH}$ = 6.4 Hz, H_2); 8.51 (1H, d, $^3J_{HH}$ = 9.0 Hz, H_5). ^{13}C NMR (100.58 MHz, DMSO): δ (ppm) −1.71 (Si$\underline{C}H_3$); 34.12 (CH_2); 59.18, 65.79 (C$\underline{H}_2$ arene); 71.71, 74.65, 86.71, 94.21, 98.72 (Ar$\underline{C}$); 116.23, 122.98, 125.16, 125.38, 136.81, 140.05, 143.57, 146.71, 153.18 (ArC). IR (KBr, cm^{-1}): ν(NH) 3417; ν(C═N) 1611; ν(C═C aromatic) 1588. Anal. Calcd for $C_{21}H_{25}N_2Cl_3SiO_2Ru\cdot 2H_2O$ (608.99): C, 41.42; H, 4.14; N, 4.60. Found: C, 41.90; H, 4.56; N, 4.21. MS (ESI^+-MS, m/z): 538.0 $[M - Cl]^+$.

Compound ***6***. Light yellow powder, yield = 0.20 g (61.2%). Mp: 268–270 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) 0.12 (9H, s, 3*C$\underline{H}_3$); 1.91 (4H, m, 2*CH_2 COD); 2.46 (4H, m, 2*CH_2 COD); 2.81 (4H, m, $^3J_{HH}$ = 5.6 Hz, CH_2); 4.27 (4H, s, 4*CH COD); 6.48 (1H, d, $^3J_{HH}$ = 5.9 Hz, H_3); 7.34 (1H, s, NH); 7.47 (1H, dd, $^4J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 2.1 Hz, H_6); 8.32 (1H, d, $^3J_{HH}$ = 9.1 Hz, H_5); 8.42 (2H, m, H_8 and H_2). ^{13}C NMR (100.58 MHz, DMSO): δ (ppm) 1.3 (Si$\underline{C}H_3$); 30.8 (C$\underline{H}_2$ COD); 32.9 (C$\underline{H}_2$); 83.5 (C$\underline{H}$ COD); 99.8, 119.2, 124.4, 128.1, 133.5, 149.4, 151.1, 153.4 (ArC). IR (KBr, cm^{-1}): ν(NH) 3311; ν(C═N) 1610; ν(C═C aromatic) 1590. Anal. Calcd for $C_{21}H_{29}N_2Cl_2SiRh$ (511.38): C, 49.32; H, 5.72; N, 5.48. Found: C, 49.03; H, 5.78; N, 5.26. MS (ESI^+-MS, m/z): 475.1 $[M - Cl]^+$.

Compound ***7***. Bright orange solid, yield = 0.19 g (51.6%). Mp: 285–289 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) 0.13 (9H, s, 3*C$\underline{H}_3$); 1.63 (15H, s, 5*CH_3 Cp*); 2.78 (2H, d, $^3J_{HH}$ = 5.5 Hz, CH_2); 6.46 (1H, d, $^3J_{HH}$ = 5.4 Hz, H_3); 7.09 (1H, s, NH); 7.41 (1H, m, H_6); 7.76 (1H, s, H_8); 8.31–8.33 (2H, m, H_5 and H_2). ^{13}C NMR (100.58 MHz, DMSO): δ (ppm) 1.3 (Si$\underline{C}H_3$); 9.0 (C Cp*); 32.9 (C$\underline{H}_2$); 99.8, 119.3, 124.4, 124.4, 128.2, 133.6, 149.3, 151.5, 153.4 (ArC). IR (KBr, cm^{-1}): ν(NH) 3268; ν(C═N) 1611; ν(C═C aromatic) 1587. Anal. Calcd for $C_{23}H_{32}N_2Cl_3SiRh$ (573.87): C, 48.09; H, 5.58; N, 4.88. Found: C, 47.82; H, 5.61; N, 4.81. MS (ESI^+-MS, m/z): 539.1 $[M - Cl]^+$, 572.0 $[M - H]^+$.

Compound ***8***. Mustard yellow-orange solid, yield = 0.28 g (61.8%). Mp: 282–285 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) −0.02 (9H, s, 3*C$\underline{H}_3$); 0.56 (2H, m, CH_2); 1.63 (2H, m, CH_2); 3.23 (2H, m, CH_2); 5.94 (6H, s, ArH benz); 6.45 (1H, d, $^4J_{HH}$ = 11.9 Hz, H_3); 7.33 (1H, s, NH); 7.43 (1H, dd, $^4J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 3.8 Hz, H_6); 7.75 (1H, d, $^3J_{HH}$ = 2.2 Hz, H_8); 8.25 (1H, d, $^3J_{HH}$ = 9.1 Hz, H_5); 8.36 (1H, d, $^3J_{HH}$ = 5.5 Hz, H_2). ^{13}C NMR (100.58 MHz, DMSO): δ (ppm) −3.5 (Si$\underline{C}H_3$); 13.1 (C$\underline{H}_2$); 22.3 (C$\underline{H}_2$); 46.7 (C$\underline{H}_2$); 76.1, 78.2, 79.5, 81.5 (Ar$\underline{C}$ benz); 98.8, 115.8, 118.6, 124.2, 127.0, 139.5, 139.7, 142.4, 156.1 (ArC). IR (KBr, cm^{-1}): ν(NH) 3305; ν(C═N) 1611; ν(C═C aromatic) 1592. Anal. Calcd for $C_{21}H_{25}N_2Cl_3SiRu$ (541.59): C, 46.75; H, 4.64; N, 5.19. Found: C, 46.20; H, 5.12; N, 4.90. MS (ESI^+-MS, m/z): 541.8 $[M]^+$, 542.8 $[M + H]^+$.

Compound ***9***. Light yellow-orange solid, yield = 0.24 g (62.1%). Mp: 171–172 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) 0.00 (9H, s, 3*C$\underline{H}_3$); 0.58 (2H, m, CH_2); 1.20 (6H, m, 2*CH_3 *p*-cym); 1.65 (2H, m, CH_2); 2.09 (3H, m, CH_3 *p*-cym); 2.84 (1H, m, CH *p*-cym); 3.36 (2H, m, CH_2); 5.77 (2H, d, $^3J_{HH}$ = 6.2 Hz, 2*CH *p*-cym), 5.81 (2H, d, $^3J_{HH}$ = 6.2 Hz, 2*CH *p*-cym); 6.46 (1H, d, $^3J_{HH}$ = 5.5 Hz, H_3); 7.36 (1H, s, NH); 7.44 (1H, dd, $^4J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 2.1 Hz, H_6); 7.77 (1H, d, $^4J_{HH}$ = 2.1 Hz, H_8); 8.28 (1H, d, $^3J_{HH}$ = 9.0 Hz, H_5); 8.39 (1H, d, $^3J_{HH}$ = 5.4 Hz, H_2). ^{13}C NMR (100.58 MHz, DMSO): δ (ppm) −3.5 (Si$\underline{C}H_3$); 13.0 (C$\underline{H}_2$); 18.1 (C$\underline{H}_3$ *p*-cym); 20.8 (C$\underline{H}_3$ *p*-cym); 22.2 (C$\underline{H}_2$); 31.0 (C$\underline{H}$ *p*-cym); 46.3 (C$\underline{H}_2$); 76.0, 77.1, 78.0, 92.1, 96.6 (Ar$\underline{C}$ *p*-cym); 98.0 (C_3); 115.6 (C_4); 118.8 (C_8); 124.2 (C_5); 126.9 (C_6); 139.4 (C_9); 139.7 (C_{10}); 142.2 (C_2); 156.4 (C_7). IR (KBr, cm^{-1}): ν(NH) 3303; ν(C═N) 1611; ν(C═C aromatic) 1591. Anal. Calcd for $C_{25}H_{35}N_2Cl_3SiRu$ (599.71): C, 50.25; H, 5.86; N, 4.09. Found: C, 50.00; H, 5.49; N, 3.90. MS (ESI^+-MS, m/z): 601.1 $[M + H]^+$.

Compound ***10***. Yellow solid, yield = 0.24 g (61.4%). Mp: 237–240 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) 0.00 (9H, s, 3*C$\underline{H}_3$); 0.58 (2H, m, CH_2); 1.64 (2H, m, CH_2); 3.25 (2H, m, CH_2); 3.73 (2H, dd, $^4J_{HH}$ = 7.20 Hz, $^3J_{HH}$ = 12.81 Hz, CH_2OH arene); 4.22 (2H, t, $^3J_{HH}$ = 4.99 Hz, OCH_2 arene); 5.37 (1H, m, CH arene); 5.54 (2H, d, $^3J_{HH}$ = 6.33 Hz, 2*CH arene); 6.14 (2H, m, 2*CH arene); 6.46 (1H, d, $^3J_{HH}$ = 5.55 Hz, H_3); 7.38 (1H, s, NH); 7.44 (1H, dd, $^4J_{HH}$ = 2.25 Hz, ^3J_H = 8.99 Hz, H_6); 7.77 (1H, d, ^4J_H = 2.21 Hz, H_8); 8.28 (1H, d, $^3J_{HH}$ = 9.04 Hz, H_5; 8.38 (1H, d, $^3J_{HH}$ = 5.47 Hz, H_2). ^{13}C NMR (100.58 MHz, DMSO): δ (ppm) −3.5 (Si$\underline{C}H_3$); 13.0 (C$\underline{H}_2$); 22.3 (C$\underline{H}_2$); 46.4 (C$\underline{H}_2$); 58.6 (C$\underline{H}_2$ arene); 60.1 (C$\underline{H}_2$ arene); 76.1, 78.2, 79.5, 81.1 (Ar$\underline{C}$ arene); 98.8, 115.8, 118.6, 124.2, 127.0, 139.5, 139.7, 142.4, 156.1 (ArC). IR (KBr, cm^{-1}): ν(NH) 3310; ν(C═N) 1609; ν(C═C aromatic) 1591. Anal. Calcd for $C_{23}H_{29}N_2Cl_3SiO_2Ru\cdot H_2O$ (619.02): C, 44.63; H, 4.72; N, 4.53. Found: C, 44.86; H, 5.13; N, 4.11. MS (ESI^+-MS, m/z): 566.1 $[M - Cl]^+$.

Compound ***11***. Bright yellow solid, yield = 0.19 g (59.4%). Mp: 270–272 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) −0.02 (9H, s, 3*C$\underline{H}_3$); 0.56 (2H, m, CH_2); 1.62 (2H, m, CH_2); 1.86 (4H, q, $^3J_{HH}$ = 7.4 Hz, 2*CH_2 COD); 2.44 (4H, d, $^3J_{HH}$ = 7.6 Hz, 2*CH_2 COD); 3.25 (2H, m, CH_2); 4.25 (4H, s, 4*CH COD); 6.46 (1H, d, $^3J_{HH}$ = 5.86 Hz, H_3); 7.46 (1H, dd, $^4J_{HH}$ = 2.22 Hz, $^3J_{HH}$ = 9.00 Hz, H_6); 7.52 (1H, s, NH); 8.25 (1H, d, $^3J_{HH}$ = 9.04 Hz, H_5); 8.41 (1H, m, H_8); 8.61 (1H, m, H_2). ^{13}C NMR (100.58 MHz, DMSO): δ (ppm) −1.5 (Si$\underline{C}H_3$); 13.7 (C$\underline{H}_2$); 22.6 (C$\underline{H}_2$); 45.9 (C$\underline{H}_2$); 30.6, 46.1 (C$\underline{H}$ COD); 83.8, 99.8, 119.1, 124.1, 128.0, 132.5, 149.7, 151.1, 153.1

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(ArC). IR (KBr, cm^{-1}): ν(NH) 3337; ν(C═N) 1613; ν(C═C aromatic) 1591. Anal. Calcd for $C_{23}H_{33}N_2Cl_2SiRh$ (539.43): C, 51.30; H, 6.13; N, 5.20. Found: C, 51.21; H, 6.33; N, 4.88. MS (ESI^+-MS, m/z): 503.1 $[M - Cl]^+$.

Compound **12**. Bright orange solid, yield = 0.21 g (53.7%). Mp: 263−266 °C. ^1H NMR (399.95 MHz, DMSO): δ (ppm) 0.01 (9H, s, 3*C$\underline{H}_3$); 0.59 (2H, m, CH_2); 1.63 (17H, m, 5*CH_3 Cp* and CH_2); 3.23 (2H, m, CH_2); 6.45 (1H, d, $^3J_{HH}$ = 4.9 Hz, H_3); 7.33 (1H, s, NH); 7.44 (1H, d, $^4J_{HH}$ = 8.6 Hz, H_6); 7.77 (1H, s, H_8); 8.27 (1H, d, $^3J_{HH}$ = 8.9 Hz, H_5); 8.39 (1H, d, $^3J_{HH}$ = 4.7 Hz, H_2). ^{13}C NMR (100.58 MHz, DMSO): δ (ppm) −1.15 (Si$\underline{C}H_3$); 9.03 ($\underline{C}H_3$ Cp*); 14.08 ($\underline{C}H_2$); 23.03 ($\underline{C}H_2$); 40.90 ($\underline{C}$ Cp*); 46.18 ($\underline{C}H_2$); 99.11, 119.10, 124.42, 124.54, 127.87, 133.5, 149.7, 151.1, 152.27 (ArC). IR (KBr, cm^{-1}): ν(NH) 3310; ν(C═N) 1612; ν(C═N) 1586. Anal. Calcd for $C_{25}H_{36}N_2Cl_3SiRh$ (601.93): C, 49.88; H, 5.99; N, 4.66. Found: C, 49.58; H, 6.10; N, 4.43. MS (ESI^+-MS, m/z): 601.1 $[M]^+$, 565.1 $[M - Cl - H]^+$.

X-ray Structure Analysis. Single-crystal X-ray intensity data were collected on a Nonius Kappa-CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Temperature was controlled by an Oxford Cryostream cooling system (Oxford Cryostat).[72] The strategy for the data collections was evaluated using the Bruker Nonius Collect program. Data were scaled and reduced using DENZO-SMN software.[73] Absorption correction was performed using SADABS.[74] The structure was solved by direct methods and refined employing full-matrix least-squares with the program SHELXL-97,[75] refining on F^2. The diagram was produced using the program PovRay and graphic interface X-seed.[72] For compound **2**, the hydrogen atoms in H_2N were located in the difference electron density maps and refined independently with a simple bond length constraint [d(N−H) = 0.97(1) Å]. The carbon atoms C_{11} and C_{12} were disordered over two places: C_{11A} and C_{12A} versus C_{11B} and C_{12B}, with refined site occupancy factors of 0.777(7) and 0.223(7), respectively. C_{10A} and C_{10B} are in fact one atom, and they were made for the purpose of refinements. The structure was refined to an R factor of 0.0500.

***P. falciparum in Vitro* Assay.** The test samples were tested in triplicate on one occasion against chloroquine-sensitive (CQS) NF54 strain and chloroquine-resistant (CQR) Dd2 strain of *P. falciparum*. Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method.[76] Quantitative assessment of antiplasmodial activity *in vitro* was determined via the parasite lactate dehydrogenase assay using a modified method.[77] The test samples were prepared to a 20 mg/mL stock solution in 100% DMSO and sonicated to enhance solubility. Samples were tested as a suspension if not completely dissolved. Stock solutions were stored at −20 °C. Further dilutions were prepared on the day of the experiment. Chloroquine (CQ) was used as the reference drug in all experiments. A full dose−response was performed for all compounds to determine the concentration inhibiting 50% of parasite growth (IC_{50} value). Test samples were tested at a starting concentration of 100 μg/mL, which was then serially diluted 2-fold in complete medium to give 10 concentrations, with the lowest concentration being 0.2 μg/mL. The same dilution technique was used for all samples. CQ was tested at a starting concentration of 100 ng/mL against the CQR strain and 1000 ng/mL against the CQS strain. The highest concentration of solvent to which the parasites were exposed had no measurable effect on the parasite viability (data not shown). The IC_{50} values were obtained using a nonlinear dose−response curve fitting analysis via Graph Pad Prism v.4.0 software.

Detergent-Mediated Assay for β-Hematin Inhibitors. The β-hematin formation assay method described by Carter et al.[78] was modified for manual liquid delivery. Stock solutions of the test compounds were prepared at 10, 2, and 0.4 mM by dissolving each sample in DMSO with sonication. Test compounds were delivered to a 96-well plate in triplicate from 0 to 500 μM (final concentration) with a total DMSO volume of 10 μL in each well. Deionized H_2O (70 μL) and NP-40 (20 μL; 30.55 μM) were then added. A 25 mM hematin stock solution was prepared by sonicating hemin in DMSO, for complete dissolution, and then suspending 177.76 μL of this in a 2 M acetate buffer (pH 4.8). The homogeneous suspension (100 μL) was then added to the wells to give final buffer and hematin concentrations of 1 M and 100 μM, respectively. The plate was covered and incubated at 37 °C for 5−6 h in a water bath. Analysis of the assay was carried out using the pyridine−ferrichrome method developed by Ncokazi and Egan.[79] A solution of 50% (v/v) pyridine, 30% (v/v) H_2O, 20% (v/v) acetone, and 0.2 M HEPES buffer (pH 7.4) was prepared, and 32 μL added to each well to give a final pyridine concentration of ±5% (v/v). Acetone (60 μL) was then added to assist with hematin dispersion. The UV−vis absorbance of the plate wells was read on a SpectraMax plate reader. Sigmoidal dose−response curves were fitted to the absorbance data using GraphPad Prism v3.02.

Broth Microdilution Method. The broth microdilution method[80] allows a range of antibiotic concentrations to be tested on a single 96-well microtiter plate in order to determine the minimum inhibitory concentration (MIC). Briefly, a 10 mL culture of *Mycobacterium tuberculosis* H37Rv MA[81] is grown to an OD_{600} of 0.6−0.7. The culture is then diluted 1:500 in liquid 7H9 medium supplemented with ADC (bovine albumin fraction V [5 mg/mL], D-glucose [2 mg/mL], sodium chloride [0.81 mg/mL]). In a 96-well microtiter plate, 50 μL of 7H9 medium is added to all wells in rows 2−12. The compounds to be tested are added to row 1 in duplicate, at a final concentration of 640 μM (stocks are made up to a concentration of 12.8 mM in DMSO, and diluted to 640 μM in 7H9 medium). A 2-fold serial dilution is prepared, using a multichannel pipet, by transferring 50 μL of the liquid in row 1 to row 2 and aspirating to mix. A 50 μL portion of the liquid in row 2 is then transferred to row 3 and aspirated, and so on. This procedure is repeated until row 12 is reached, from which 50 μL of the liquid is discarded so as to bring the final volume in all wells to 50 μL. Controls include media only, 5% DMSO, rifampicin, and kanamycin. Finally, 50 μL of the 1:500 diluted *M. tuberculosis* culture is added to all wells in rows 2−12. Cells are not added to row 1, as this serves as a contamination control. The microtiter plate is sealed in a ziplock bag and incubated at 37 °C with a humidifier to prevent evaporation of liquid. The lowest concentration of drug that inhibits growth of more than 99% of the bacterial population is considered to be the MIC_{99}. MIC_{99} values are scored visually at 7 days and 14 days postinoculation, and digital images captured and stored.

MTT Assay for Cancer Cells. The esophageal cancer cell line WHCO1, derived from a primary esophageal squamous cell carcinoma, was kindly provided by Professor Rob Veale (University of the Witwatersrand, Johannesburg, South Africa). IC_{50} determinations were carried out using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. Briefly, 3000 cells were seeded per well in 96-well plates. Cells were incubated at 37 °C under 5% CO_2 (24 h), after which aqueous DMSO solutions of each compound (10 μL, with a constant final concentration of DMSO of 0.2%) were plated at various concentrations. After 48 h incubation, observations were made, and MTT (10 μL) solution added to each well. After a further 4-hour incubation, solubilization solution (100 μL) was added to each well, and plates were incubated overnight. Plates were read at 595 nm on a BioTek microplate reader.

Turbidimetric Solubility Studies. The test samples were prepared to a 1% stock solution in 100% DMSO and sonicated to enhance solubility. All test samples were done in triplicates, and paracetamol and ncls were used as the reference drugs in all experiments, paracetamol being the positive control and ncls being the negative control. Test samples were then serially diluted in DMSO medium to give concentrations of 0.0, 0.1, 0.5, 1.0, 2.0, 4.0, 8.0, and 10.0 μM in a 96-well plate. After the predilution, the samples were further diluted in DMSO and 0.01 M phosphate-buffered saline pH 7.4 (PBS), final concentrations being 0.0, 1.0, 5.0, 10.0, 20.0, 40.0, 80.0, and 100.0 μM, in a second 96-well plate. After 2 hours of incubation at room temperature, turbidimetry was then used as the end-point by measuring absorbance at 620 nm. The plate curve fitting analyses via Microsoft Excel 2010, Graph Computation Data, were used to analyze the results.

■ ASSOCIATED CONTENT

Supporting Information

CCDC 876667 (**11**) and CCDC 881284 (**2**) contain the supplementary crystallographic data for this paper. 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, UK; fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk]. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +27-21-6505279. Fax: +27-21-6505195. E-mail: Gregory.Smith@uct.ac.za; Kelly.Chibale@uct.ac.za.

Notes

The authors declare no competing financial interest.

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