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Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities.

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Abstract: Three ferroquine (FQ) derivatives, closely mimicking the antimalarial drug hydroxychloroquine (HCQ) have been prepared. Whereas these organometallic compounds provide the expected reduced cytotoxic effects compared to FQ, they inhibit *in vitro* growth of *Plasmodium falciparum* far better than chloroquine (CQ). Moreover, this new class of bioorganometallic compounds exert antiviral effects with some selectivity towards SARS-CoV infection. These new drugs may offer an interesting alternative for Asia where SARS originated and malaria has remained endemic.

Keywords: Bioorganometallics, Ferroquine, Malaria, SARS-CoV

Introduction

Malaria is a major international public health problem, causing 300-500 million infections worldwide and a death toll of approximately 1.1-2.7 million annually.¹ *Plasmodium falciparum* accounts for most of the mortality, and its resistance to antimalarial drugs has developed in many regions of the world.^{2,3} Chemists and biologists have combined their efforts in an attempt to find efficient and affordable drugs for the developing countries. Several approaches have been investigated^{4,5} and new projects at various stages of development have emerged.⁶ Besides, apart from these classical organic schemes, an atypical strategy based on modification of the old drug chloroquine (CQ) by a ferrocenyl fragment led to the identification of FQ (Figure 1).^{7,8}

Ferroquine has been shown to be remarkably effective against CQ-resistant *P. falciparum*.⁷ Moreover, no observable immunotoxic effects were detected in naïve and infected young rats.⁹ The mode of action of FQ is believed to be similar to that of CQ and probably involves hemozoin as the drug target and inhibition of hemozoin formation.¹⁰ A recent study of FQ metabolism in animal and human hepatic models revealed similarities to that of CQ.¹¹ One notable difference is that while the two main CQ metabolites are not active against CQ-resistant *P. falciparum*, FQ metabolites still exhibited a significant activity. Also, it is important to note that the close parent of CQ, hydroxychloroquine (HCQ)

was reported to be less toxic than CQ, but was found inactive on CQ-resistant *P. falciparum*.¹² On the other hand, aminoquinoline-based antimalarials like CQ or mefloquine (MF) also had antiviral efficacy and showed a synergistic action with HIV protease inhibitors (PIs).¹³⁻¹⁶ CQ has been reported to possess strong antiviral effects on the severe acute respiratory syndrome (SARS) causative agent.¹⁷ SARS is a febrile respiratory illness caused by a novel coronavirus, SARS-associated coronavirus (SARS-CoV),¹⁸⁻²¹ which emerged in southern China in November 2002. SARS-CoV is believed to be of zoonotic origin. Although several animal species (e.g., civet) sold for human consumption in markets in southern China have demonstrated evidence of SARS-CoV infection, the wild reservoir of SARS-CoV is still unknown.²² As of today, no efficacious therapy is available, although many candidate anti-SARS-CoV agents have been identified.^{17,23,24,25}

Encouraged by the strong antimalarial activity of FQ on CQ-resistant clones and field isolates, we aimed to study if hydroxyferroquine (HFQ) might retain a significant activity against *P. falciparum* and a set of different viruses. A series of new bioorganometallics (Figure 1) was designed and synthesized in an effort to combine specific properties of both drugs: an assumed lower toxicity of HFQ associated with a restored antimalarial activity against CQ-resistant parasites. Such molecules would be an interesting alternative to ferroquine for malaria therapy and provide an additional interest in areas where malaria and viruses infection co-exist.

Results and Discussion

Synthesis. Like FQ, the hydroxyl FQ derivatives **2-4** can be synthesized easily from inexpensive starting materials.⁷ Quaternization of the terminal nitrogen atom of FQ was performed with methyl iodide in acetone at room temperature (Scheme 1). The resulting quaternary ammonium is the leaving group that was displaced by the appropriate amino-alcohol in acetonitrile under reflux. This nucleophilic substitution afforded products **2**, **3** and **4** in 46%, 46% and 51% yield, respectively.

Antimalarial activity. Metallocenes **2-4** were evaluated *in vitro* against the CQ-sensitive HB3 strain and the CQ-resistant W2 strain of *P. falciparum* (Table 1). The three hydroxy-derivatives **2-4** were more active than CQ against the resistant strain. Among these amino-alcohol derivatives, the activity increased from the unsubstituted **2** to the N-ethyl-substituted **4**. Note also that the most active product **4** was even more active than mefloquine and only slightly less active than FQ against both *P. falciparum* strains.

The screening performed on 25 Cambodian field isolates confirmed the high potent antimalarial activity of the novel metallocenic compound **4** against *P. falciparum* (Table 2). Hydroxyferroquine derivative **4** was much more active than CQ and only slightly less active than FQ and MF. Although no cross resistance was found with MF ($r^2 = 0.021$), Q ($r^2 = 0.00005$) and ARS ($r^2 = 0.0732$), a slight cross response was observed with CQ ($r^2 = 0.32$). Metallocene **4** showed almost the same level of activity as that of FQ. As expected, a high correlation ($r^2 = 0.7129$) between the IC_{50} of FQ and **4** was noted within the isolates tested. This suggests that the two compounds have a similar mode of action and/or uptake by the parasite.

Studies concerning toxicity and antimalarial activity of HCQ are controversial and HCQ appears as lacking activity against CQ resistant strains of *P. falciparum*.¹² Our goal, on the basis of the high activity of FQ, was to synthesize a potentially less toxic molecule which would exhibit significant antimalarial activity. Among the three hydroxyferroquine-type derivatives synthesized, the results obtained for both laboratory clones and field isolates confirmed the strong antimalarial activity of compound **4** which is only 1.5 fold less active than FQ against all strains and isolates of *P. falciparum* tested and much more active than CQ (6 fold). This product is the most lipophilic of the three compounds synthesized, and the results observed are in accordance with the hypothesis already proposed to explain the strong activity of FQ against *P. falciparum* CQ resistant strains.¹⁰ Moreover, the mechanism of action of the hydroxyferroquine derivatives is probably multifactorial, and involves pharmacokinetic parameters. Indeed, oxidative metabolism of tertiary amines like CQ,²⁶ HCQ,²⁷ and FQ¹¹ occurs via the cytochrome P-450 system. The main metabolites are generated by side-chain de-

alkylation leading first to the monodesalkyl and then to the didesalkyl derivatives. The biotransformation of FQ has been recently studied *in vitro* in animal and human models.¹¹ Even if mono-*N*-desmethyl- and di-*N,N*-desmethyl-FQ showed a decreased *in vitro* activity compared to the parent molecule, they remained more active than CQ on *P. falciparum* CQ-resistant strains.^{11,28} It is notably that the metabolites of CQ showed no activity against CQ-resistant strains. The dramatic activity of FQ metabolites against CQ-resistant *P. falciparum* parasites growth enables us to expect a long-acting antimalarial activity during chemotherapy of malaria. Oxidative pathways should mediate the de-alkylation of bioorganometallics **3** and **4** as previously shown for HCQ²⁷ and FQ¹¹ (Scheme 2). The loss of the ethanol fragment generates the secondary amine **2**. The other C-N cleavage generates the active mono-*N*-desmethyl- (**dmFQ**)¹¹ and mono-*N*-desethyl-FQ (**dEFQ**)²⁸, respectively. By comparison with HCQ and FQ, it is tempting to suggest that during a clinical use of metallocenes **3** and **4**, formation of these active metabolites may occur and participate in the global activity of the parent products. These results, together with the fact that compound **4** was five fold less toxic than FQ (see Table 1 and 2 in Supporting Information) indicate that bioorganometallics **4** can be considered as a promising alternative to FQ for chemotherapy of CQ-resistant malaria.

Antiviral activity. CQ, HCQ and the metallocenes (FQ and **2-4**) were also tested against HIV-1. CQ and compound **3** exhibited some activity against HIV-1 with a selectivity index of 3 and 6, respectively (Table 3).

The mechanism of the anti-HIV activity of CQ and HCQ is still not fully understood. But it has been linked with the viral entry and related to inhibition of HIV surface envelope glycoprotein gp120. Indeed, these compounds are supposed to increase endosomal pH and alter enzymes required for gp120 production.^{14,24} Based on their chemical structures, hydroxyferroquine derivatives **2-4** might target the complex entry process in a similar manner.

Whereas CQ has been shown to inhibit SARS-CoV replication *in vitro*, the mode of action of this compound is currently still unknown.¹⁷ In this context, the metallocenic compounds **2-4** were evaluated for their activity against feline and human (SARS) coronavirus (Table 4) and compared to their parent

drugs, CQ, HCQ and FQ. All compounds, except for HCQ, were effective inhibitors of SARS-CoV replication in Vero cells within the 1-10 μ M concentration range. Compounds **3**, **4**, FQ and CQ exhibited a selectivity index of approximately 15. These data confirm the anti-SARS-CoV activity noted previously with CQ.^{17,25,29} In fact, CQ had been quoted as potentially active against SARS-CoV.²⁴ The current data supports this hypothesis and extend the anti-SARS-CoV potential further to CQ derivatives such as, in particular, the metallocenes FQ, **3** and **4**. CQ, HCQ, FQ and compounds **2-4** were evaluated against parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus, respiratory syncytial virus, herpes simplex virus-1 (HSV-1; KOS), herpes simplex virus-2 (HSV-2; G), vaccinia virus, vesicular stomatitis virus, herpes simplex virus-1 (TK/KOS ACV) and influenza A virus (H3N2). Unfortunately, no significant activity was noted (SI Table 1, 2, 3 and 4). This indicates that these compounds present a higher specificity for HIV and SARS-CoV viruses.

Our results showed that HFQ derivatives appear as promising new antimalarial molecules, since they are active with their potential metabolites against CQ-resistant *P. falciparum*. Moreover, we showed that these drugs have anti-HIV and anti-SARS-CoV activities. These findings highlighted the potential interest of metallocenes FQ, **3** and **4** use in all countries where malaria coinfection with HIV and SARS viruses will occur.

Experimental section

Chemistry. Nuclear magnetic resonance (¹H and ¹³C NMR) spectra were recorded at ambient temperature on a Bruker AC 300 spectrometer and TMS was used as an internal standard. ¹H NMR analyses were obtained at 300 MHz (s: singlet, d: doublet, t: triplet, dd: double doublet, m: multiplet); whereas ¹³C NMR analyses were obtained at 75.4 MHz. The chemical shifts (δ) are given in parts per million relative to TMS ($\delta = 0.00$). Diverse solvents were used in the determination of spectra for different compounds. Mass spectra were recorded by mean of a Waters Micromass Quattro II triple quadrupole LC mass spectrometer equipped with electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) sources. Melting points were determined by a Kopfler and are uncorrected. Column chromatography, carried out on silica gel (Merck Kieselgel 60) was used in purification of

samples. Reactions were monitored by thin-layer chromatography (TLC) using coated silica gel plates, detection by an ultra-violet lamp.

General Procedure for Preparation of 2-4. A mixture of the corresponding amino-alcohol (2-amino-1-ethanol, 2-amino-1-propanol or 2-amino-1-butanol, 10 mmol) and *N*-(7-chloro-4-quinolyl)-*N*-2-[(1,1,1-trimethylammonio)methyl]ferrocenylmethylamine iodide recently prepared (0.41 mmol) was dissolved in acetonitrile (25 mL). Potassium carbonate (10 mmol) was added in excess, and the mixture was stirred for 3-7 h at reflux. After cooling to room temperature, the reaction was quenched with water (25 mL). The aqueous layer was then extracted with dichloromethane (3 × 50 mL). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc, 5% triethylamine).

2-[(2-[(7-chloro-4-quinolyl)amino]methyl]ferrocenylmethyl)amino]-1-ethanol (2). Following the general procedure, a yellow solid was obtained: yield 46 %; mp: decomposed before melting; ¹H NMR (CDCl₃) δ 8.41 (d, 1H, *J* = 5.5 Hz), 7.79 (d, 1H, *J* = 2.0 Hz), 7.68 (d, 1H, *J* = 9.1 Hz), 7.11 (dd, 1H, *J* = 2.0, 9.8 Hz), 6.89 (m, 1H), 6.38 (d, 1H, *J* = 5.5 Hz), 4.28 (d, 1H, *J* = 13.0 Hz), 4.19 (m, 1H), 4.14 (m, 1H), 4.09 (s, 5H), 4.03 (m, 2H), 3.67 (m, 3H), 3.49 (d, 1H, *J* = 12.4 Hz), 2.73 (m, 2H); ¹³C NMR (CDCl₃) δ 150.7 (CH), 149.0 (C^{IV}), 147.8 (C^{IV}), 133.7 (C^{IV}), 126.9 (CH), 123.7 (CH), 121.5 (CH), 116.5 (C^{IV}), 97.8 (CH), 84.3 (C^{IV}), 82.2 (C^{IV}), 69.5 (CH), 69.2 (CH), 68.2 (5CH), 65.4 (CH), 59.8 (CH₂), 50.1 (CH₂), 46.6 (CH₂), 41.1 (CH₂); MS *m/z* 452 (MH⁺ ³⁷Cl), 451 (M^{o+} ³⁷Cl), 450 MH⁺ ³⁵Cl, 449 (M^{o+} ³⁵Cl), 391 (M ³⁷Cl – NHCH₂CH₂OH)⁺, 389 (M ³⁵Cl – NHCH₂CH₂OH)⁺, 271 (M – NH₂Q).

2-[(2-[(7-chloro-4-quinolyl)amino]methyl]ferrocenylmethyl)(methyl)amino]-1-ethanol (3). A yellow solid was obtained: yield 46 %; mp 164 ± 1 °C; ¹H NMR (CDCl₃) δ 8.45 (d, 1H, *J* = 5.5 Hz), 7.86 (d, 1H, *J* = 2.2 Hz), 7.71 (d, 1H, *J* = 8.9 Hz), 7.23 (d, 1H, *J* = 2.2 Hz), 6.77 (m, 1H), 6.46 (d, 1H, *J* = 5.5 Hz), 4.32 (m, 2H), 4.20 (m, 2H), 4.15 (s, 5H), 4.11 (m, 1H), 3.88 (d, 1H, *J* = 12.9 Hz), 3.67 (m, 2H), 3.07 (d, 1H, *J* = 12.9 Hz), 2.74 (m, 1H), 2.48 (m, 1H), 2.19 (s, 3H); ¹³C NMR (CDCl₃) δ 151.4 (CH), 150.1 (C^{IV}), 148.5 (C^{IV}), 134.8 (C^{IV}), 127.6 (CH), 124.8 (CH), 122.4 (CH), 117.4 (C^{IV}), 98.8 (CH), 84.0 (C^{IV}), 83.8 (C^{IV}), 71.5 (CH), 70.3 (CH), 69.3 (5CH), 66.4 (CH), 59.2 (CH₂), 59.1 (CH₂), 56.4 (CH₂), 42.4 (CH₂), 41.9 (CH₃); MS *m/z* 466 (MH⁺ ³⁷Cl), 465 (M^{o+} ³⁷Cl), 464 MH⁺ ³⁵Cl, 463 (M^{o+} ³⁵Cl), 391 (M ³⁷Cl – NHCH₂CH₂OH)⁺, 389 (M ³⁵Cl – NHCH₂CH₂OH)⁺.

2-[(2-[(7-chloro-4-quinolyl)amino]methyl]ferrocenylmethyl)(ethyl)amino]-1-ethanol (4). A yellow solid was obtained: yield 51 %; mp 180 ± 1 °C; ¹H NMR (CDCl₃) δ 8.43 (d, 1H, *J* = 5.5 Hz), 7.82 (d, 1H, *J* = 2.1 Hz), 7.70 (d, 1H, *J* = 8.9 Hz), 7.21 (dd, 1H, *J* = 8.9, 2.1 Hz), 6.42 (d, 1H, *J* = 5.5 Hz), 4.25 (m, 1H), 4.20 (s, 1H), 4.16 (m, 1H), 4.09 (s, 5H), 4.07 (m, 2H), 3.78 (d, 1H, *J* = 13.0 Hz), 3.50 (m, 2H), 3.13 (d, 1H, *J* = 13.0 Hz), 2.71 (m, 1H), 2.58 (m, 1H), 2.40 (m, 2H), 0.88 (t, 3H, *J* = 7.2 Hz). ¹³C NMR (CDCl₃) δ 151.2 (CH), 149.0 (C^{IV}), 148.4 (C^{IV}), 134.1 (C^{IV}), 127.4 (CH), 124.3 (CH), 121.6 (CH),

116.7 (C^{IV}), 98.6 (CH), 83.8 (C^{IV}), 82.9 (C^{IV}), 70.9 (CH), 69.4 (CH), 68.6 (5CH), 65.9 (CH), 58.5 (CH₂), 53.8 (CH₂), 51.8 (CH₂), 47.2 (CH₂), 40.9 (CH₂), 10.1 (CH₃); MS *m/z* 480 (MH⁺ ³⁷Cl), 479 (M^{o+} ³⁷Cl), 478 MH⁺ ³⁵Cl, 477 (M^{o+} ³⁵Cl), 391 (M ³⁷Cl – NHCH₂CH₂OH)⁺, 389 (M ³⁵Cl – NHCH₂CH₂OH)⁺.

Antiviral evaluation, as described in ref. 25, 30, 31 and 32: ref. 25 as to SARS-CoV; ref. 30 as to HSV-1, HSV-2, vaccinia virus; ref. 31 as to various other RNA viruses; ref. 32 as to HIV-1.

Antimalarial Activity. Laboratory Strains. The 3D7 and W2 strains of *P. falciparum* used as a control for sensitivity to CQ and FQ were cultured as previously described. Parasites were grown *in vitro* on O⁺ human red blood cells in RPMI 1640 medium (Invitrogen) supplemented with 10 % AB human serum (EFS), and 0.01 mg/ml gentamicin under an atmosphere of 90% nitrogen/ 5% oxygen/ 5% carbon dioxide.

Field isolates. Isolates of *P. falciparum* were collected from 25 subjects recruited, for *in vivo* trials of mefloquine–artesunate, by the Cambodian Ministry of Health. All the subjects came from malaria-endemic areas of Cambodia. Sampling and further treatment of samples were previously described.³³ All antimalarial measurements were done on fresh samples.

For antimalarial activity measurements, a microplate assay measuring [³H] hypoxanthine incorporation in parasite nucleic acids and derived from the method of Desjardins³⁴ was used to test FQ antimalarial properties on laboratory strains and Cambodian field isolates. Test procedures for laboratory strains were as previously described (0.5% hematocrit; 0.5% parasitaemia) (4, 5). IC₅₀ were calculated from response curves by linear interpolation.

Concerning field isolates, fresh blood samples were tested without prior culture adaptation. Erythrocyte suspensions (1.5% hematocrit; 0.1--1% parasitaemia) were cultivated as described above in an atmosphere enriched with 5% CO₂. Ranges of concentrations were 5-5120 nM for CQ and FQ. Test microplates were incubated for 42-46h at 37 °C. Only assays showing at least a 10 fold increase in parasite counts between drug free control wells containing uninfected or infected red blood cells were considered for IC₅₀ (Inhibitory concentration 50%) calculations which were done by log-probit approximation.

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Supporting Information Available. Elemental analyses, compared cytotoxicity and antiviral activity of HFQ derivatives on Viruses infecting Vero, HEL and HeLa cell cultures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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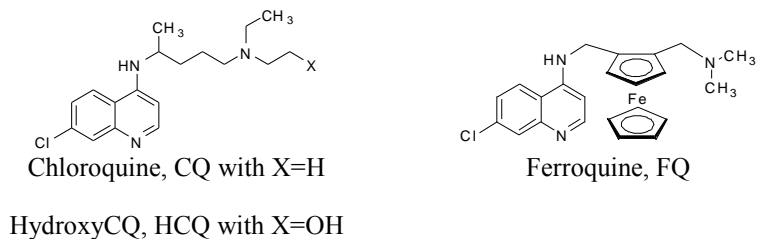
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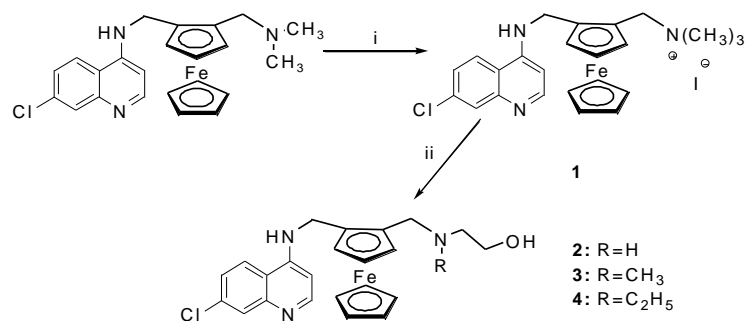
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Figure 1. Chemical structure of chloroquine, hydroxychloroquine, and ferroquine.



Scheme 1. Synthesis of hydroxyferroquine derivatives **2-4**.



^a (i) CH₃I, acetone; (ii) HOCH₂CH₂NHR, CH₃CN.

Scheme 2. Proposed conversion of hydroxyferroquine derivatives to active metabolites, **2**, **dMFQ** and **dEFQ**.

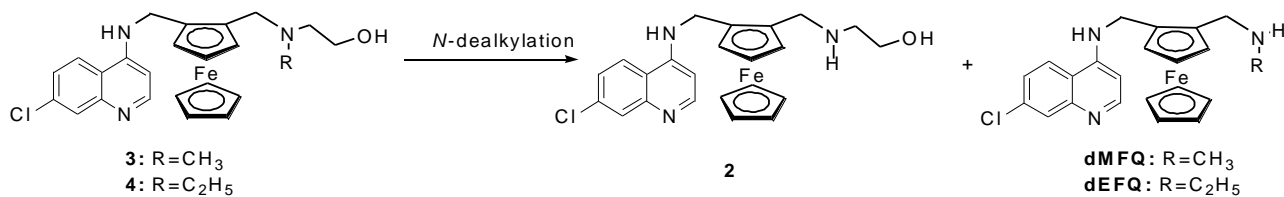


Table 1. *In vitro* sensitivities of *P. falciparum* strains.

| cpd ^a | strain | IC ₅₀ , nM | n | IC ₉₀ , nM | n |
|------------------|--------|-----------------------|----|-----------------------|----|
| 2 | 3D7 | 15.4 ± 5.5 | 4 | 25.7 ± 7.1 | 4 |
| | W2 | 133.2 ± 7.4 | 3 | 459.1 ± 53.3 | 3 |
| 3 | 3D7 | 21.5 ± 14.5 | 8 | 51.0 ± 22.2 | 8 |
| | W2 | 30 ± 8.8 | 3 | 99.9 ± 5.3 | 3 |
| 4 | 3D7 | 11.7 ± 5.7 | 9 | 29.19 ± 17.9 | 9 |
| | W2 | 20.4 ± 1.1 | 3 | 56 ± 1.9 | 3 |
| CQ | 3D7 | 10.6 ± 5.6 | 16 | 31 ± 16.5 | 16 |
| | W2 | 138.9 ± 20 | 11 | > 500 | 11 |
| MF | 3D7 | 38.7 ± 5.3 | 13 | 138.2 ± 29.7 | 4 |
| | W2 | 14.9 ± 0.4 | 4 | 66.1 ± 24.3 | 3 |
| ARS | 3D7 | 2.1 ± 0.3 | 13 | 9.1 ± 5.1 | 3 |
| | W2 | 2.1 ± 0.2 | 4 | 14 ± 1.6 | 4 |
| FQ | 3D7 | 7.8 ± 2.9 | 13 | 16.4 ± 9.4 | 13 |
| | W2 | 9.7 ± 2.4 | 4 | 24.6 ± 4.6 | 4 |

^a CQ = chloroquine; MF = mefloquine; ARS = artesunate; FQ = ferroquine

The results are expressed by the mean ± standard deviation of the mean.

Table 2. Comparison of the most active compound **4** with other antimalarials on Cambodian field isolates.

| cpd ^a | IC ₅₀ , nM ^b and range | n | Resistance , % |
|------------------|---|----|-------------------|
| 4 | 32.4 (17.9-83.6) | 25 | 3.8 |
| CQ | 191.8 (80-538) | 25 | 92 |
| MF | 25.2 (1.4-106.5) | 23 | 56 |
| Q | 146 (50-827) | 25 | 3.8 |
| ARS | 1.47 (0.41-5.35) | 25 | 7.6 |
| FQ | 22.94 (11.7-83.6) | 25 | 3.8 |

^a CQ = chloroquine; MF = mefloquine; Q = quinine; ARS = artesunate; FQ = ferroquine

^b IC₅₀ values are geometric means among isolates.

Table 3. Anti HIV-1 Activity, Cytotoxicity, and Selectivity Index in MT-4 Cells.

| cpd ^a | EC ₅₀ , μM ^b | CC ₅₀ , μM ^c | SI ^d |
|------------------|------------------------------------|------------------------------------|-----------------|
| 2 | > 2.3 | > 2.3 | - |
| 3 | 2.9 ± 1.1 | 9.1 ± 6.6 | 3 |
| 4 | 10 | > 10 | - |
| FQ | > 2.4 | > 2.4 | - |
| HCQ | > 12 | > 12 | - |
| CQ | 8.86 ± 1.18 | 54.4 ± 23.9 | 6 |

^a FQ = ferroquine; CQ = chloroquine; HCQ = hydroxychloroquine

^b Effective concentration required to reduce HIV-1-induced cytopathic effect by 50% in MT-4 cells.

^c Cytotoxic concentration required to reduce MT-4 cell viability by 50%.

^d Selectivity index: ratio CC₅₀/EC₅₀.

Table 4. Anti-coronavirus activity

| cpd ^a | Feline coronavirus ^b | | Human corona (SARS) virus ^c | | |
|------------------|---------------------------------|----------------------------|--|----------------------------|-----------------|
| | EC ₅₀ , μ M | CC ₅₀ , μ M | EC ₅₀ , μ M | CC ₅₀ , μ M | SI ^d |
| 2 | > 4 | 12 \pm 0 | 4.9 \pm 4.3 | 23 \pm 15 | 4 |
| 3 | \geq 10 | 12 \pm 0 | 1.9 \pm 0.1 | 30 \pm 3 | 16 |
| 4 | > 4 | 13 \pm 0 | 3.6 \pm 2.0 | 61 \pm 1 | 17 |
| FQ | 2.9 \pm 1.2 | 12 \pm 0 | 1.4 \pm 0.1 | 20 \pm 8.0 | 15 |
| HCQ | 28 \pm 27 | 84 \pm 14 | 34 \pm 5 | >100 | >3 |
| CQ | >0.8 | 3.6 \pm 0.3 | 6.5 \pm 3.2 | >100 | >15 |

^a FQ = ferroquine; CQ = chloroquine; HCQ = hydroxychloroquine

^b Feline corona virus in Crandell-Reese feline kidney (CRFK) cells

^c SARS-coronavirus in Vero cells

^d Selectivity index(for SARS-coronavirus): ratio CC₅₀/EC₅₀.

Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities.

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The SARS Co-V picture was taken from ref 19.