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Synthesis and antimalarial activities of rhenium bioorganometallics based on the 4-aminoquinoline structure

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ABSTRACT

A bioorganometallic approach to malaria therapy led to the discovery of ferroquine (FQ, SSR97193). To assess the importance of the electronic properties of the ferrocenyl group, cyclopentadienyltricarbonylrhenium analogues related to FQ, were synthesized. The reaction of [*N*-(7-chloro-4-quinolinyl)-1,2-ethanodiamine] with the cyrhetrenylaldehyde complexes $(\eta^5\text{-}C_5H_4CHO)Re(CO)_3$ and $[\eta^5\text{-}1,2\text{-}C_5H_3(CH_2OH)(CHO)]Re(CO)_3$ produces the corresponding imine derivatives $[\eta^5\text{-}1,2\text{-}C_5H_3(R)(CH{=}N{-}CH_2CH_2NH{-}QN)]Re(CO)_3$ R = H **3a**; R = CH_2OH **3b**; QN = *N*-(7-Cl-4-quinolinyl). Reduction of **3a** and **3b** with sodium borohydride in methanol yields quantitatively the amine complexes $[\eta^5\text{-}1,2\text{-}C_5H_3(R)(CH_2{-}NH{-}CH_2CH_2NH{-}QN)]Re(CO)_3$ R = H **4a**; R = CH_2OH **4b**. To establish the role of the cyrethrenyl moiety in the antimalarial activity of this series, purely organic parent compounds were also synthesized and tested. Evaluation of antimalarial activity measured in vitro against the CQ-resistant strains (W2) and the CQ-susceptible strain (3D7) of *Plasmodium falciparum* indicates that these cyrhetrene conjugates are less active compared to their ferrocene and organic analogues. These data suggest an original mode-of-action of FQ and ferrocenyl analogues in relationship with the redox pharmacophore.

1. Introduction

Malaria continues to be one of the major infectious disease killers throughout the tropical regions of the planet, despite being preventable and curable.[1] Several antimalarial drugs have been used, notably 4-aminoquinolines (chloroquine, CQ), amino-alcohol quinolines (mefloquine, quinine) and artemisinin. CQ has been the most successful and widely used antimalarial drug for several decades but its efficacy is now severely compromised by the spread of resistance, particularly for *Plasmodium falciparum*.[2,3]

Since the mid-1980s, organometallic compounds have attracted attention for medicinal applications, mainly as anticancer and antimalarial agents.[4–7] Indeed, bioorganometallics may overcome resistance to established drugs via new and possibly metal-specific modes of action. Two well-known examples are: (i) the ferrocene-modified tamoxifens, named ferrocifens, developed by Jaouen and co-workers, that exhibited activity against hormone-independent breast cancer, where hydroxytamoxifen and tamoxifens are

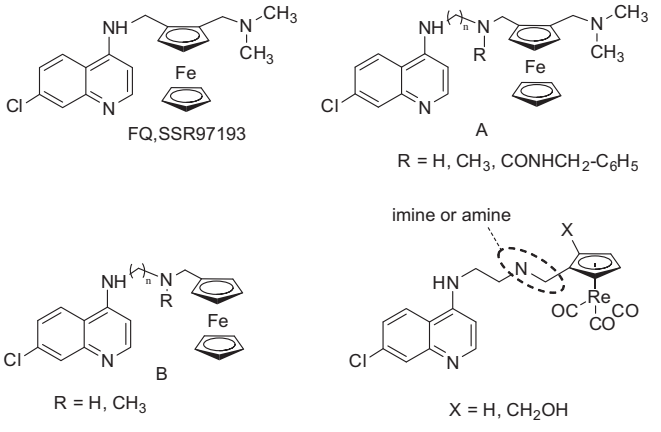

Figure 1. Chemical structure of FQ, related compounds A and B, and designed cyrhetrene analogues.

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inactive[8] and (ii) a ferrocene analogue of CQ named ferroquine (FQ, SSR97193, Fig. 1), which was highly active against all *P. falciparum* clones tested, whatever their level of resistance to CQ and, moreover, did not show any significant cross-resistance with other currently used antimalarials.[9–16] More recently, FQ was shown to have a potent ex vivo effect on *Plasmodium vivax* schizont maturation. Thus, it was suggested that FQ could also be a suitable replacement for CQ in the treatment of drug resistant vivax malaria.[17]

FQ cannot be no longer considered as just a CQ-like derivative but represents a new antimalarial drug. FQ is currently being developed by Sanofi-Aventis and entered phase II clinical trials in association with artesunate in September 2007.[18]

Even though the participation of ferrocene in the biological activity of FQ is still not well understood, comparative studies on the behavior of FQ and CQ have led to the conclusion that the ferrocenyl moiety plays an important role in the observed antimalarial activity.[19–21] To probe the role of the electron donating ferrocenyl moiety, we prepared and evaluated new organometallic analogues of CQ bearing a cyclopentadienyltricarbonylrhenium moiety with an electron withdrawing effect (Fig. 1). Additionally, suitable properties of radioisotopes ^{186}Re and ^{188}Re for nuclear medicine make the cyrhetrenyl moiety interesting for the synthesis of radiopharmaceuticals.[22]

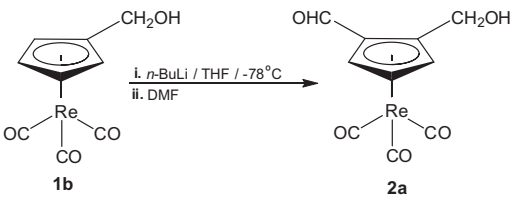
The initial concept was to replace the disubstituted ferrocene in FQ by a cyrhetrenyl moiety. As this synthesis appeared very challenging, we then designed more easily obtainable analogues where the cyrhetrenyl moiety was introduced at the extremity of a lateral side chain of a 4-aminoquinoline derivative (Fig. 1).[23] As short chain CQ analogues were found to retain activity against CQ-resistant *P. falciparum*, we designed this new series where the *iso*pentyl side chain has been replaced by an ethyl.[24] The lipophilicity of the new compounds was studied with respect to the parasite vacuolar and cytosolic pHs, thus gaining a first insight into possible vacuolar accumulation. Antimalarial activity was tested in vitro on *P. falciparum*. To establish the role of metal in the antiplasmodial activity, purely organic derivatives with some larger lipophilic moieties were also synthesized and tested.

2. Chemistry

2.1. Disubstitution of the cyclopentadienyl ring

The synthesis of the new disubstituted complex **2a** was carried out by using the precursor [η^5-$C_5H_4CH_2OH$]Re(CO)$_3$ **1b** (Scheme 1). Compound **1b** was reacted with *n*-butyllithium.[25,26] The lithium derivative was then treated with *N*,*N*-dimethylformamide at −10 °C giving, after workup, compound **2a** in respectable yields (70%). The 1,2 orientation of the substituents of the cyclopentadienyl ring was established unambiguously by ^{1}H and ^{13}C NMR spectroscopies. The parameters were in agreement with other 1,2-disubstituted cyrhetrene complexes.[26]

The IR spectra of this compound showed three absorptions [2034 (νCO), 1943 (νCO), and 1674 (CHO) cm^{-1}]. Similar frequency shifts have been reported for formylcyrhetrene [2033 (νCO), 1940 (νCO), and 1694 (CHO) cm^{-1}] in CH_2Cl_2.[27] The ^{1}H and ^{13}C NMR spectra were in accordance with the carboxaldehyde group, showing a sharp singlet at 9.65 and 186.54 ppm, respectively. In addition, ^{1}H spectra exhibit three multiplets at high field, corresponding to the magnetically non-equivalent hydrogens, present in the disubstituted ring. These resonances were in accordance with three signals in the ^{13}C NMR spectra at 82.1, 87.1, and 90.8 ppm. The mass spectra of **2a** exhibited the molecular ion, and the successive loss of three CO ligands. In addition, a fragment observed at (*m*/*z* 308) was assigned to the loss of the [CH_2OH] group.



Scheme 1. Synthesis of compound **2a**.

2.2. Synthesis of cyrhetrenylimine complexes

The imine complexes were easily accessible following the same procedure to that described for analogous ferrocenylimines and cyrhetrenylimine derivatives,[28,29] that is by condensation of the corresponding cyrhetrenilcarboxaldehyde complexes with *N*-(7-chloro-quinolin-4-yl)-ethane-1,2-diamine in methanol (Scheme 2). In both cases the products were isolated as crystalline solids after crystallization from CH_2Cl_2/hexane mixture (1:5).

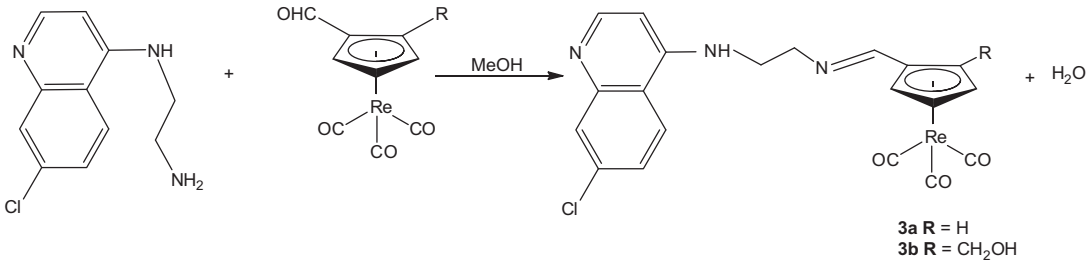
The IR spectra of these compounds showed the expected value of the νC=N stretch in the range 1610–1630 cm^{-1} in CH_2Cl_2. Similar νC=N frequency shifts have been reported for Schiff bases derived from formylferrocene[28–30] and formylcyrhetrene.[29]

The ^{1}H NMR spectra showed a sharp singlet around 8.00–8.50 ppm due to the iminic proton (C*H*=N). The proton resonances of the Cp group of compound **3a** are observed as two apparent triplets around 5.31 and 5.65 ppm, in agreement with the data reported for the complexes [C_5H_4CH=NAr]Re(CO)$_3$.[29] On the other hand, complex **3b** showed three resonances for the non-equivalent hydrogens, as expected for 1,2-disubstitution of the cyclopentadienyl ring. Similar values have been measured for other disubstituted cyrhetrenyl complexes.[26] ^{13}C NMR data were also in accordance with the existence of a single compound. Despite the fact that these types of compounds could adopt two different forms (*E*- or *Z*-), their ^{1}H and ^{13}C NMR spectra, which agreed with those reported for related ferrocenyl and cyrhetrenyl Schiff bases,[28,29] revealed that only one isomer (*E*-form) was present in solution. The most important feature of these spectra is the presence of a low field resonance (δ 143–148) assigned to the iminyl carbon. This resonance occurs at almost the same δ as those reported for the ferrocene analogues[28,30] and is indicative of some degree of conjugation of the C_5H_4 fragment and the HC=N entity in **3a** and **3b**. These assignments were confirmed by ^{1}H/^{13}C NMR COSY. It is important to note that the ^{1}H and ^{13}C resonances of the quinoline moiety showed no noticeable shift when compared with those reported for analogous ferrocene derivates.[19–23]

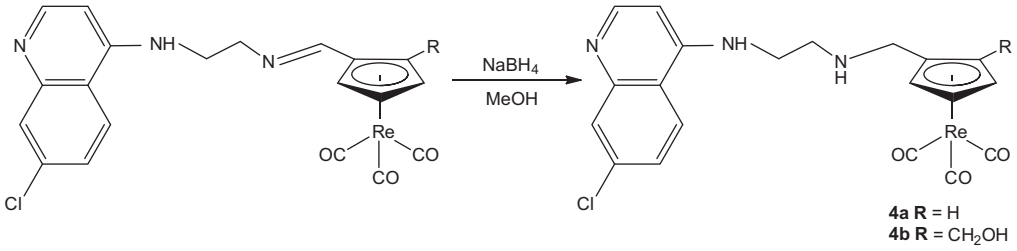
2.3. Cyrhetrenylamine complexes

These compounds were prepared according to the general procedure described for most ferrocenylamines[31] and cyrhetrenylamines,[29] that is by direct reduction of the corresponding cyrhetrenyl imine complex with $NaBH_4$ in anhydrous methanol, at room temperature (Scheme 3).

The products were purified by column chromatography and isolated in quantitative yields. The IR spectra, in CH_2Cl_2 solution, showed as expected the presence of two νCO bands that are slightly shifted to lower wavelengths compared to their imine precursors **3a** and **3b**. In addition, the proton resonances of the cyclopentadienyl and aryl groups, observed in the ^{1}H NMR spectra, in C_6D_6 solution, clearly showed at $\delta \sim$3.4, a doublet and a broad singlet for the CH_2 and NH groups, respectively.[29] The main feature of the ^{13}C NMR spectrum of each compound, in $CDCl_3$ solution, is a resonance at about 41 ppm which has been assigned to the CH_2 group on the basis of the reported chemical shifts for the methylene group in analogous ferrocenylamines.[32,33] The resonances of



Scheme 2. Synthesis of compounds **3a** and **3b**.



Scheme 3. Synthesis of compounds **4a** and **4b**.

CO groups (Re–CO) occurred at similar chemical shift reported for other tricarbonyl cyclopententadienyl functionalized complexes.[28] The mass spectra of **3a** exhibited the molecular ion, and the successive loss of three CO ligands. This fragmentation is similar to that observed for the complex (η^5-$C_5H_4CH_2NHC_6H_5$)$Re(CO)_3$.[29]

2.4. Purely organic analogues complexes

Purely organic compounds **5**–**7** (Scheme 4) were prepared according to the general procedures previously described.[23a–e] This series were also designed to cover a wide range of log *D* values (Table 1). Note here that during this study, Ray et al. also reported on the development of a new generation of 4-aminoquinoline antimalarial compounds with log *D* values ranging from 1.7 to 5.5.[23e]

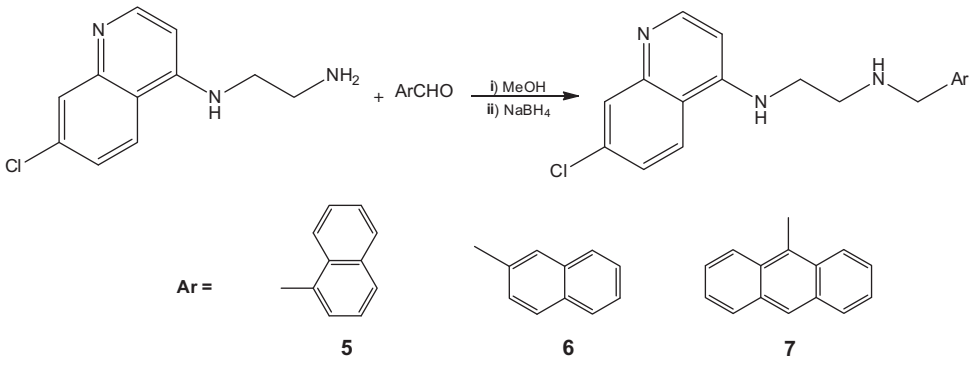
Table 1
Experimental log *D* values at two different pHs reflecting the vacuolar (5.2) and cytosolic (7.4) environment

Compd	log *D* 5.2 ± SD	log *D* 7.4 ± SD
3a	2.22 ± 0.04	2.33 ± 0.06
4a	0.95 ± 0.01	3.96 ± 0.01
3b	1.84 ± 0.01	1.98 ± 0.06
4b	0.82 ± 0.01	3.54 ± 0.06
5[a]	2.72	3.83
6[a]	2.77	3.83
7[a]	3.80	4.80
FQ[b]	−0.77	2.95
CQ[b]	−1.2	0.85

[a] Calculator Plugins were used for structure property prediction and calculation, Marvin 5.3.1, 2010, ChemAxon (http://www.chemaxon.com).
[b] Values taken from Ref. 19.

2.5. Lipophilicity

HPLC determination of log *D*s was achieved for cyrhetrenylimine (**3a** and **3b**) and cyrhetrenylamine (**4a** and **4b**) derivatives at two distinct pHs (5.2, considered close to the probable pH of the digestive vacuole and 7.4, assumed to be the cytosolic pH). The values show distinct behaviors for the two families of products **3** and **4** (Table 1). First, the imines **3** present very similar log *D* values at the two pHs. The presence of the imine group in the structure of compounds **3** induces a lower basicity.[34] Consequently, these molecules will have a different protonation profile than the reference product FQ. At both pHs, compounds **3** seem to exist in the same state of protonation, which is expressed by a lipophilicity independent of pH in the range explored. On another hand, the amines **4** have a similar lipophilic behavior at both pHs



Scheme 4. Synthesis of compounds **5**–**7**.

compared to FQ. They are hydrophilic at vacuolar pH and lipophilic at cytosolic pH. This property proceeds from a similar protonation profile of derivatives **4** and FQ.

The presence of the cyrhetrenyl moiety in **3** and **4**, contributes to the increased lipophilicity of the molecules at vacuolar pH. Reference molecules FQ and CQ remain the most hydrophilic compounds at pH 5.2 with log *D* values of −0.77 and −1.2, respectively. The substitution of the hydrogen atom (**3a**, **4a**) on the cyrhethrenyl moiety by a hydroxymethylene group (**3b**, **4b**) reduces the lipophilicity by half.

The above results may indicate that the cyrhetrenyl moiety plays an important role in log *D* values in cyrhetrenyl imines and amines, in comparison to FQ and CQ. This could be related to the amine fragment. Similar results have been reported for ferrocenyl and cyrhetrenyl compounds derivates from tamoxifen.[35]

The purely organic compounds **5**–**7** in the panel differ significantly in their predicted permeability (Table 1). As expected, the log *D* values increase with the size of the aromatic moiety from the naphtalenyl group to the anthracenyl group. Ray et al. reported a similar behavior for other aromatic moieties.[23e]

3. In vitro antimalarial activities

In vitro, the cyrhetrenylimines **3** were more active than the amines **4** against the CQ-susceptible 3D7 clone (Table 2), but only amine **4a** showed a significant activity on the CQ-resistant W2 clone (twice as active as CQ). All compounds were less active than FQ against the two clones tested. The substitution of a hydrogen atom in **3a** by a hydroxymethylene group in **3b** did not modify the activity of the compound toward either strain whereas the same substitution in the amine series **4** decreased the antimalarial activity 10-fold toward both strains.

A similar trend was observed for the purely organic analogues **5**–**7**. These compounds were more active against the CQ-susceptible 3D7 clone than against the CQ-resistant W2 clone. A curious observation was that compound **5** bearing the 1-naphtyl substituent was 10-fold less active than its 2-naphtyl analogue against the CQ-susceptible 3D7 clone. The difference in activity was reduced against the CQ-resistant W2 clone.

From these two series (cyrhetrenyl and organic), the observed decreased activities toward the CQ-resistant strain W2 suggested that cross-resistance might develop rapidly for these compounds.

As recently studied by Ray et al., these data could be related to their chemical stability.[23e] Indeed, the corresponding primary amine, which resulted from N-dealkylation reaction, is inactive. The methylenic hydrogen atoms close to the organometallic moiety (with electron withdrawing effect) are significantly more acidic than those of the organic analogues. They are therefore more efficient in abstracting the hydrogen α to the nitrogen atom.[23e]

Table 2
In vitro susceptibilities of *P. falciparum* strains

Compd	Strain	
	3D7	W2
	IC_{50} (nM) ± SD	
3a	64 ± 14	2563 ± 772
4a	497 ± 42	267 ± 83
3b	85 ± 17	2167 ± 306
4b	5500 ± 557	2533 ± 153
5	471 ± 163	1203 ± 363
6	48 ± 11	820 ± 170
7	84 ± 27	797 ± 114
FQ	3.4 ± 0.6	6.8 ± 0.7
CQ	23 ± 5	563 ± 85

Values are means of IC_{50} of 5–7 experiments for each strain.

Therefore, the cyclopentadienyltricarbonylrhenium moiety should be more chemically labile than its organic analogues.

4. Discussion

In order to study the influence of the metallocene substitution in 4-aminoquinoline antimalarials, we synthesized derivatives carrying a cyclopentadienyltricarbonylrhenium moiety with an electron withdrawing effect. The electronic properties of these derivatives could then be compared to those of the electron donating ferrocene derivatives. Facing the difficulties of synthesizing a cyclopentadienyltricarbonylrhenium equivalent of FQ, we designed and prepared derivatives with a cyrhetrenyl moiety at the extremity of a shortened CQ lateral chain (two carbon atoms). Similar ferrocene conjugates had been previously synthesized and tested.[23c]

We have found that the carboxaldehyde complexes **1a** and the unreported 1,2 disubstituted **2a** are useful precursors to condensate the terminal amino group of *N*-(7-chloroquinolin-4-yl) ethane-1,2-diamine to yield the corresponding imine derivates **3a** and **3b** in only one isomeric form (*E*-isomer). Further reduction of the imine groups in **3a** and **3b** easily and quantitatively produced the amine complexes **4a** and **4b**.

Concerning the lipophilicity of the molecules as a function of pH, the introduction of the cyrhetrenyl moiety at the end of the lateral chain of the 4-aminoquinoline scaffold dramatically increased lipophilicity at the pH of the parasite digestive vacuole (5.2). Compounds **4a** and **4b** remained 10-fold less hydrophilic than the corresponding ferrocene conjugates.[23] The difference is even much dramatic with FQ and CQ. Therefore the cyrhetrenyl moiety appears to modulate the log *D* of conjugates much more strongly than does ferrocene.

It was shown in previous studies that the log *D* at pH 5.2 was critical for antimalarial activity of ferrocene derivatives.[23a,c] Due to the properties of rhenium bioorganometallics (more lipophilic and less chemically stable than ferrocene equivalents previously examined[23c]) studied here, it is not surprising to observe only a moderate or a slight activity on *P. falciparum*. Compared to its ferrocenic analogue (series B, $n = 2$ and R = H), **4a** is less active (IC_{50} = 63.5 nM against W2).[23c] This also indicates that the rhenium atom, via the electron withdrawing properties of the cyrhetrenyl moiety, has a decisive influence on the antimalarial activity of these conjugates. A plot of antimalarial IC_{50} values against log *D* values showed that there is no correlation between *P. falciparum* culture growth inhibition and lipophilicity of the compounds. Therefore differences in the antiplasmodial activity of the ferrocenyl, cyrhetrenyl or organic derivatives could not only be attributed to the effect of the lipid/aqueous distribution ratio. In addition to their capacity to inhibit hemozoin formation, the activity of the compounds should be related not only to a preferential localization at the lipid-water interface but also to the capacity to generate reactive oxygen species (as for FQ). Insertion of cyclopentadienyltricarbonylrhenium at a position similar to that of ferrocene in FQ might perhaps provide more significant complementary information on the possible influence of this moiety, but this goal appears very difficult to achieve experimentally and would not present a great interest in the context of the development of affordable new antimalarials. Other organometallic-based antimalarial compounds have already been reported,[23b] comparison of their antimalarial activity and their precise mode-of-action will be discussed elsewhere.

In conclusion, we succeeded in synthesizing rhenium organometallic antimalarials based on the structures of the ferrocene conjugates already described. The cyrhetrenyl moiety appears to modulate the lipophilicity and chemical stability of conjugates

and has direct consequences on the activity of compounds toward *P. falciparum*. Compared to ferrocenic analogues, the nature of metal and the withdrawing effect of this metallocenic moiety have a significant effect on antimalarial properties.

5. Materials and methods

5.1. Chemistry

All manipulations were conducted under an N_2 atmosphere using Schlenk techniques. (η^5-C_5H_4CHO)$Re(CO)_3$ **1a** and [*N*-(7-Chloro-4-quinolinyl)-1,2-etanodiamine] were prepared according to procedures described in the literature.[27,36] 4,7-Dichloroquinoline, ethylenediamine and $NaBH_4$ were obtained commercially (Aldrich). All the solvents were purified according standard methods prior to use. Infrared spectra were recorded in solution (NaCl cell) on a Perkin–Elmer FT-1605 spectrophotometer, and ^1H and ^{13}C NMR spectra on a Bruker AVANCE 400 spectrometer. ^1H NMR chemical shifts were referenced using the chemicals shifts of residual solvent resonances, and ^{13}C chemical shifts to solvent peaks. Elemental analyses were measured on a Perkin–Elmer CHNS Analyser 2400. Mass spectra were obtained on a Thermo-Finnigan MAT 900XP, at the Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile.

5.1.1. (η^5-$C_5H_4CH_2OH$)$Re(CO)_3$ (1b)

Compound **1b** was prepared following a modification of the procedure described by Kolobova et al.[36]

Complex **1a** (200.0 mg, 0.55 mmol) was dissolved in anhydrous methanol (10 ml) followed by addition in excess of solid $NaBH_4$ (84.0 mg, 2.2 mmol). The mixture was stirred under nitrogen atmosphere for 2 h. After this time, the IR spectrum showed the complete disappearance of the carboxaldehyde complex and the presence of two new absorption bands shifted to low energy (2024 and 1924 cm^{-1}). The white solid obtained after evaporation of methanol was chromatographed on a silica gel column. The column was washed with hexanes and **1b** eluted with CH_2Cl_2. The complex **1b** was isolated quantitatively as white solid, after crystallization from CH_2Cl_2/hexane (1:5) at −18 °C. IR (CH_2Cl_2, νCO, cm^{-1}): 2023 (s), 1926 (vs). ^1H NMR ($CDCl_3$) δ: 4.43 (s, 2H, CH_2); 5.25 (t, 2H, J = 2.3 Hz, C_5H_4); 5.40 (t, 2H, J = 2.3 Hz, C_5H_4); O*H* (not observed). Mass spectrum (based on ^{187}Re) *m*/*z*: 366 [M^+]; 338 [M^+−CO]; 310 [M^+−2CO]; 282 [M^+−3CO].

5.1.2. [η^5-1,2-$C_5H_3(CH_2OH)(CHO)$]$Re(CO)_3$ (2a)

Complex **1b** (0.1 g, 0.27 mmol) was dissolved in anhydrous THF (10 mL) in a Schlenk tube. The flask was cooled at −50 °C, and *n*-BuLi 1.6 M in hexane (0.822 ml, 3 equiv) was slowly added. The mixture was stirred 15 min at −50 °C, and then cooled to −70 °C. Freshly distilled DMF (0.1 ml, 0.27 mmol) was then added dropwise. The reaction mixture was stirred for 4 h at −10 °C. The reaction was quenched with saturated aqueous ammonium chloride (5 mL). The aqueous phase was extracted with diethyl ether (4 × 5 mL) and dried over $MgSO_4$. Column chromatography on silica gel (eluent hexane/CH_2Cl_2, 80:20) afforded compound **2a** as an off-white powder (76 mg, 70%). IR (CH_2Cl_2, cm^{-1}): 2034 (s) (νCO), 1943 (vs) (νCO), 1674 (w) (CHO). ^1H NMR ($CDCl_3$) δ: 3.53 (br t, 1H, O*H*); 4.58 (m, 2H, CH_2OH); 5.30 (m, 1H, C_5H_3); 5.57 (m, 1H, C_5H_3); 5.94 (m, 1H, C_5H_3); 9.65 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$) δ: 57.4 (*C*H_2); 82.1 (C_5H_3); 87.1 (C_5H_3); 90.8 (C_5H_3); 93.0 (C_5H_3 ipso); 112.8 (C_5H_3 ipso); 186.5 (*C*HO); 190.8 (*C*O). Mass spectrum (based on ^{187}Re) *m*/*z*: 394 [M^+]; 366 [M^+−CO]; 338 [M^+−2CO]; 308 [M^+−2CO–CH_2OH]; 280 [M^+−2CO–CH_2OH–CO]. EA, Found: C, 30.54; H, 1.81. Calcd for $C_{10}H_7O_5Re$: C, 30.53; H, 1.79.

5.1.3. Cyrhetrenylimine complexes 3a and 3b

5.1.3.1. To a solution of (η^5-C_5H_4CHO)$Re(CO)_3$ 1a (0.138 mmol) in methanol (10 mL) was added *N*-(7-chloroquinolin-4-yl) ethane-1,2-diamine 17.0 mg (0.138 mmol). The mixture was refluxed under nitrogen atmosphere for 1 h. After this point, the solution changed color from yellow to colorless. The IR spectrum showed the complete disappearance of the starting complex and two new absorption bands for the terminal CO groups. The solvent was removed under vacuum and a white solid was obtained. Crystallization from CH_2Cl_2/hexane (1:5) at −18 °C produced off-white microcrystals of **3a** (yield: 61 mg, 0.130 mmol, 94%). IR (CH_2Cl_2, cm^{-1}): 2026 (s) (νCO); 1933 (vs) (νCO); 1628 (w) (νC=N). ^1H NMR ($CDCl_3$) δ: 3.58 (dd, 2H, J = 5.5 Hz, J = 11.1 Hz, –NH–CH_2–CH_2–); 3.78 (t, 2H, J = 5.5 Hz, –NH–CH_2–CH_2–); 5.37 (t, 2H, J = 2.2 Hz, C_5H_4); 5.81 (t, 2H, J = 2.2 Hz, C_5H_4); 6.43 (d, 1H, J = 5.4 Hz, QN–H); 7.35 (dd, 1H, J = 2.1 Hz, J = 8.9 Hz, QN–H); 7.67 (d, 1H, J = 8.9 Hz, QN–H); 7.91 (s, 1H, CH=N); 7.93 (d, 1H, J = 2.1 Hz, QN–H); 8.51 (d, 1H, J = 5.3 Hz, QN–H). ^{13}C NMR ($CDCl_3$) δ: 43.4 (CH_2–NH); 58.6 (NH–CH_2–*C*H_2–); 84.8 (C_5H_4); 85.6 (C_5H_4); 98.9 (C_5H_{4ipso}); 99.2 (QN–C); 117.3 (QN–C); 121.1 (QN–C); 125.3 (QN–C); 128.7 (QN–C); 134.8 (QN–C); 149.1 (QN–C); 149.4 (QN–C); 151.9 (QN–C); 155.0 (CH=N); 192.9 (*C*O). Mass spectrum (based on ^{187}Re) *m*/*z*: 567 [M^+]; 539 [M^+−CO]. EA, Found: C, 42.12; H, 2.59; N, 7.38. Calcd for $C_{20}H_{15}N_3O_3ClRe$: C, 42.36; H, 2.66; N, 7.41.

5.1.3.2. The synthesis of the complex 3b was carried out in a similar manner to that described for complex 3a using (η^5-1,2-$C_5H_3(CH_2OH)(CHO)$)$Re(CO)_3$ (50.0mg, 0.138 mmol) and *N*-(7-chloroquinolin-4-yl)ethane-1,2-diamine (19.0 mg, 0.138 mmol). Compound **3b** was obtained as white-yellow crystals (yield: 61, 0.126 mmol, mg, 91%). IR (CH_2Cl_2, cm^{-1}): 2027 (s) (νCO); 1935 (vs) (νCO); 1625 (w) (νC=N). ^1H NMR ($CDCl_3$) δ: 3.58 (pst, 2H, –NH–CH_2–CH_2–); 3.84 (m, 2H, –NH–CH_2–CH_2–); 4.42 (s, 2H, CH_2–OH); 5.14 (s, 1H, C_5H_3); 5.48 (s, 1H, C_5H_3); 5.65 (s, 1H, C_5H_3); 6.43 (d, 1H, J = 5.2 Hz, QN–H); 7.35 (d, 1H, J = 8.6 Hz, QN–H); 7.68 (d, 1H, J = 8.6 Hz, QN–H); 7.92 (s, 1H, CH=N); 7.99 (s, 1H, QN–H); 8.51 (d, 1H, J = 5.2 Hz, QN–H). ^{13}C NMR ($CDCl_3$) δ: 41.0 (*C*H_2–NH); 56.3 (*C*H_2OH); 58.6 (NH–CH_2–*C*H_2–); 83.6 (C_5H_3); 87.7 (C_5H_3); 90.5 (C_5H_3); 98.9 (C_5H_{3ipso}); 113.1 (C_5H_{3ipso}); 117.2 (QN–C); 121.1 (QN–C); 125.2 (QN–C); 128.6 (QN–C); 134.6 (QN–C); 149.2 (QN–C); 149.0 (QN–C); 151.6 (QN–C); 155.0 (CH=N); 192.9 (*C*O). Mass spectrum (based on ^{187}Re) *m*/*z*: 597 [M^+]; 569 [M^+−CO]. EA, Found: C, 42.29; H, 2.81; N, 7.02. Calcd for $C_{21}H_{17}N_3O_4ClRe$: C, 42.25; H, 2.85; N, 7.04.

5.1.4. Cyrhetrenylamine complexes [η^5-1,2-C_5H_3(R)(CH_2–NH–CH_2CH_2NH–QN)]$Re(CO)_3$ (4)

5.1.4.1. Complex 3a (50.0 mg, 0.114 mmol) was dissolved in anhydrous methanol (10 ml) followed by addition of an excess of solid $NaBH_4$ (16.0 mg, 0.423 mmol). The mixture was stirred under nitrogen atmosphere for 2 h. After this time, the IR spectrum showed the complete disappearance of the imine complex **3a**, and the presence of two new absorption bands shifted to low energy (2020 and 1924 cm^{-1}). The white solid obtained after evaporation of methanol was chromatographed on a silica gel column; elution with CH_2Cl_2 moved the amine complex. The complex **4a** was isolated quantitatively as white solid, after crystallization from CH_2Cl_2/hexane (1:5) at −18 °C. IR (CH_2Cl_2, νCO, cm^{-1}): 2022 (s), 1926 (vs). ^1H NMR ($CDCl_3$) δ: 3.08 (m, 2H, –NH–CH_2–CH_2–); 3.35 (dd, 2H, J = 5.1 Hz, J = 11.1 Hz, –NH–CH_2–CH_2–); 3.60 (s, 2H, –CH_2–C_5H_4); 5.27 (t, 2H, J = 2.1 Hz, C_5H_4); 5.37 (t, 2H, J = 2.1 Hz, C_5H_4); 6.43 (d, 1H, J = 5.4 Hz, QN–H); 7.35 (dd, 1H, J = 2.1 Hz, J = 8.9 Hz, QN–H); 7.67 (d, 1H, J = 8.9 Hz, QN–H); 7.93 (d, 1H, J = 2.1 Hz, QN–H); 8.51 (d, 1H, J = 5.3 Hz, QN–H). ^{13}C NMR ($CDCl_3$) δ: 41.9 (–NH–*C*H_2–CH_2–); 46.2 (–*C*H_2–C_5H_4); 47.5 (–NH–CH_2–

CH_2–); 83.2 (C_5H_4); 84.1 (C_5H_4); 99.1 (QN–C); 109.5 (C_{ipso}); 117.2 (QN–C); 121.1 (QN–C); 125.3 (QN–C); 128.7 (QN–C); 134.8 (QN–C); 149.1 (QN–C); 149.4 (QN–C); 151.9 (QN–C); 192.9 (*C*O). Mass spectrum (based on ^{187}Re) *m*/*z*: 569 [M^+]; 349 [M^+–QN–$NHCH_2CH_2NH$]; 321 [M^+–QN–$NHCH_2CH_2NH$–CO]; 293 [M^+–QN–$NHCH_2CH_2NH$–2CO]. EA, Found: C, 42.25; H, 3.01; N, 7.45. Calcd for $C_{20}H_{17}N_3O_3ClRe$: C, 42.21; H, 2.99; N, 7.39.

5.1.4.2. Complex 4b was obtained following the same procedure described for 4a. It was isolated quantitatively as a yellow oil. IR (CH_2Cl_2, *v*CO, cm^{-1}): 2023 (s), 1928 (vs). ^{1}H NMR ($CDCl_3$) δ: 3.18 (pst, 2H, –NH–CH_2–CH_2–); 3.44 (m, 2H, –NH–CH_2–CH_2–); 3.66 (s, 2H, NH–CH_2–C_5H_3); 4.42 (s, 2H, CH_2–OH); 5.01 (s, 1H, C_5H_3); 5.22 (s, 1H, C_5H_3); 5.40 (s, 1H, C_5H_3); 6.43 (d, 1H, *J* = 5.2 Hz, QN–H); 7.35 (d, 1H, *J* = 8.6 Hz, QN–H); 7.68 (d, 1H, *J* = 8.6 Hz, QN–H); 7.92 (s, 1H, CH=N); 7.99 (s, 1H, QN–H); 8.51 (d, 1H, *J* = 5.2 Hz, QN–H). ^{13}C NMR ($CDCl_3$) δ: 41.9 (–NH–CH_2–CH_2–); 46.2 (–CH_2–C_5H_3); 47.5 (–NH–CH_2–CH_2–); 56.3 (CH_2OH); 83.6 (C_5H_3); 87.7 (C_5H_3); 90.5 (C_5H_3); 98.9 (C_5H_{3ipso}); 113.1 (C_5H_{3ipso}); 116,.3 (QN–C); 121.4 (QN–C); 124.7 (QN–C); 128.7 (QN–C); 134.8 (QN–C); 149.1 (QN–C); 149.4 (QN–C); 151.9 (QN–C); 193.2 (CO). EA, Found: C, 42.15; H, 3.20; N, 7.06. Calcd for $C_{21}H_{19}N_3O_4ClRe$: C, 42.10; H, 3.17; N, 7.02.

5.1.5. Organic derivatives

Equimolar amounts of aromatic aldehydes and *N*-(7-chloroquinolin-4-yl)-ethane-1,2-diamine were dissolved in anhydrous methanol (30 ml). The mixture was refluxed under nitrogen atmosphere for 6 h. After this time, an excess of solid $NaBH_4$ was added and the mixture was stirred for 2 h. The reaction was quenched with H_2O (500 μl) and solvent was removed under vacuum. The white solid obtained was extracted with CH_2Cl_2 (3 × 20 ml). The organic extracts were combined, dried over Na_2SO_4, and evaporated to dryness to give a white solid. The amine compounds were isolated quantitatively as solids, after crystallization from CH_2Cl_2/hexane (1:5) at −18 °C.

5.1.5.1. N^1-(7-Chloroquinolin-4-yl)-N^2-(naphthalen-1-ylmethyl) ethane-1,2-diamine 6. ^{1}H NMR ($CDCl_3$) δ: 3.05 (t, 2H, *J* = 6.0 Hz, –NH–CH_2–CH_2–); 3.20 (q, 2H, *J* = 6.0 Hz, –NH–CH_2–CH_2–); 4.24 (s, 2H, NH–CH_2-Ar); 5.80 (brs, 1H, NH); 6.23 (d, 1H, *J* = 5.3 Hz, QN–H); 7.19 (dd, 1H, *J* = 9.0 Hz, 2.0 Hz, QN–H); 7.28 (d, 1H, *J* = 8.8 Hz, Ar-H); 7.41 (m, 2H, Ar-H); 7.49 (m, 2H, Ar-H); 7.78 (m, 1H, QN–H); 7.87 (m, 1H, Ar-H); 7.92 (d, 1H, *J* = 2.0 Hz, QN–H); 8.17 (d, 1H, *J* = 8.8 Hz, Ar-H); 8.44 (d, 1H, *J* = 5.3 Hz, QN–H). Mass spectrum *m*/*z*: 364 [^{37}Cl MH^+]; 362 [^{35}Cl MH^+]; 363 [^{37}Cl $M^{\cdot+}$]; 361 [^{35}Cl $M^{\cdot+}$]. EA, Found: C, 72.94; H, 5.49; N, 11.67. Calcd for $C_{22}H_{20}N_3Cl$: C, 73.03; H, 5.53; N, 11.62.

5.1.5.2. N^1-(7-Chloroquinolin-4-yl)-N^2-(naphthalen-2-ylmethyl) ethane-1,2-diamine 6. ^{1}H NMR ($CDCl_3$) δ: 3.06 (t, 2H, *J* = 6.1 Hz, –NH–CH_2–CH_2–); 3.30 (q, 2H, *J* = 6.1 Hz, –NH–CH_2–CH_2–); 4.00 (s, 2H, NH–CH_2-Ar); 5.85 (brs, 1H, NH); 6.33 (d, 1H, *J* = 5.0 Hz, QN–H); 7.32 (dd, 1H, *J* = 9.0 Hz, 2.0 Hz, QN–H); 7.47 (m, 3H, Ar-H); 7.65 (m, 1H, QN–H); 7.79 (m, 4H, Ar-H); 7.95 (d, 1H, *J* = 2.0 Hz, QN–H); 8.49 (d, 1H, *J* = 5.0 Hz, QN–H). Mass spectrum *m*/*z*: 364 [^{37}Cl MH^+]; 362 [^{35}Cl MH^+]; 363 [^{37}Cl $M^{\cdot+}$]; 361 [^{35}Cl $M^{\cdot+}$]. EA, Found: C, 73.10; H, 5.50; N, 11.65. Calcd for $C_{22}H_{20}N_3Cl$: C, 73.03; H, 5.53; N, 11.62.

5.1.5.3. N^1-(Anthracen-9-ylmethyl)-N^2-(7-chloroquinolin-4-yl)ethane-1,2-diamine 7. ^{1}H NMR ($CDCl_3$) δ: 3.18 (m, 2H, –NH–CH_2–CH_2–); 3.23 (m, 2H, –NH–CH_2–CH_2–); 4.76 (s, 2H, NH–CH_2-Ar); 5.87 (brs, 1H, NH); 6.25 (d, 1H, *J* = 5.0 Hz, QN–H); 7.18 (dd, 1H, *J* = 9.0 Hz, 2.0 Hz, QN–H); 7.28 (m. 1H, Ar-H); 7.48 (m, 4H, 3Ar-H, 1H QN); 7.93 (d, 1H, *J* = 2.0 Hz, QN–H); 8.01 (m, 2H, Ar-H); 8.32 (m, 2H, Ar-H); 8.40 (s, 1H, Ar-H); 8.46 (d, 1H, *J* = 5.0 Hz, QN–H). Mass spectrum *m*/*z*: 414 [^{37}Cl MH^+]; 412 [^{35}Cl MH^+]; 413 [^{37}Cl $M^{\cdot+}$]; 411 [^{35}Cl $M^{\cdot+}$]. EA, Found: C, 75.51; H, 5.30; N, 10.25. Calcd for $C_{26}H_{22}N_3Cl$: C, 75.82; H, 5.35; N, 10.21.

5.2. Partition coefficients log *D* (pHs 7.4 and 5.2)

In this study, the relative log *D*s were assessed at pHs 7.4 and 5.2 by the micro-HPLC method. Determinations were performed with a chromatographic apparatus (Spectra Series, San Jose, USA) equipped with a model P1000XR pump and a model SCM 1000 vacuum membrane degasser, a model UV 150 ultraviolet detector (λ = 215 nm) and a ChromJet data module integrator (ThermoFinnigan, San Jose, USA). The reversed phase column was a WatersXTerra™MS C_{18} (3.9 × 150 mm; 5 μm particle size) with a mobile phase consisting of acetonitrile—potassium dihydrogenophosphate 6.24×10^{-2} M [KH_2PO_4/K_2HPO_4] (pH 7) (50:50, v/v (**3a**, **4a**)), (40:60, v/v (**3b**, **4b**)). The compounds were partitioned between *n*-octanol (HPLC grade) and phosphate buffer (pH 7.4 or 5.2). Octanol was presaturated with the adequate phosphate buffer (1%), and conversely. An amount of 1 mg of each compound was dissolved in an adequate volume of methanol in order to produce 1 mg/mL stock solutions. Then, an appropriate aliquot of these methanolic solutions was dissolved in buffer to obtain a final concentration of 50 μg/mL. Under the above described chromatographic conditions, 50 μL of aqueous phase was injected into the chromatograph, leading to the determination of a peak area before partitioning (W_0). In screw-capped tubes, 1000 μL of the aqueous phase (V_{aq}) were then added to 5 μL of *n*-octanol (V_{oct}) when measuring at pH 7.4 or $V_{aq} = V_{org}$ = 500 μL when working at pH 5.2. The mixture was shaken by mechanical rotation during 20 min, followed by centrifugation at 3000 rpm during 10 min. An amount of 50 μL of the lower phase was injected into the chromatograph column. This led to the determination of a peak area after partitioning (W_1). For each compound, the log *D* value was calculated using the formula:

$$\log D = \log[(W_0 - W_1)V_{aq}/W_1V_{oct}]$$

5.3. *P. falciparum* cultures and in vitro assay

The 3D7 (chloroquine-susceptible) and the W2 (chloroquine-resistant) parasite strains were maintained in culture in RPMI 1640 (Invitrogen, Paisley, United Kingdom), supplemented with 10% human serum (Abcys S.A. Paris, France) and buffered with 25 mM HEPES and 25 mM $NaHCO_3$. Parasites were grown in A-positive human blood (Centre de Transfusion Sanguine, Marseille, France) under controlled atmospheric conditions that consist of 10% O_2, 5% CO_2 and 85% N_2 at 37 °C with a humidity of 95%.

FQ base was obtained from Sanofi-Aventis (France). CQ diphosphate was purchased from Sigma (Saint Louis, MO). FQ and synthetic compounds were resuspended and then diluted in RPMI-DMSO (99v/1v) to obtain final concentrations ranging from 0.125 to 500 nM and 1 nM to 100 μM, respectively. CQ was resolubilized in water at concentrations ranging between 5 and 3200 nM.

The isotopic, micro drug susceptibility test used was based on the microdilution radioisotope technique of Desjardins. For in vitro isotopic microtests, 25 μl/well of antimalarial drug and 200 μl/well of the parasitized red blood cell suspension (final parasitemia, 0.5%; final hematocrit, 1.5%) were distributed into 96 well plates. Parasite growth was assessed by adding 1 μCi of tritiated hypoxanthine with a specific activity of 14.1 Ci/mmol (Perkin–Elmer, Courtaboeuf, France) to each well at time zero. The plates were then incubated for 48 h in controlled atmospheric conditions. Immediately after incubation, the plates were frozen and thawed to lyse erythrocytes. The contents of each well were collected on standard filter microplates (Unifilter GF/B; Perkin–Elmer) and washed using a cell harvester (Filter-Mate Cell Harvester; Perkin–Elmer). Filter

microplates were dried, and 25 μl of scintillation cocktail (Microscint O; Perkin–Elmer) was placed in each well. Radioactivity incorporated by the parasites was measured with a scintillation counter (Top Count; Perkin–Elmer).

The IC_{50}, the drug concentration able to inhibit 50% of parasite growth, was assessed by identifying the drug concentration corresponding to 50% of the uptake of tritiated hypoxanthine by the parasite in the drug-free control wells. The IC_{50} values were determined by non-linear regression analysis of log-based dose–response curves (Riasmart™, Packard, Meriden, USA).

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