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Antiplasmodial activities of gold(I) complexes involving functionalized *N*-heterocyclic carbenes

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Abstract

A series of twenty five molecules, including imidazolium salts functionalized by N-, O- or S-containing groups and their corresponding cationic, neutral or anionic gold(I) complexes were evaluated on *Plasmodium falciparum in vitro* and then on Vero cells to determine their selectivity. Among them, eight new compounds were synthesized and fully characterized by spectroscopic methods. The X-ray structures of three gold(I) complexes are presented. Except one complex (**18**), all the cationic gold(I) complexes show potent antiplasmodial activity with IC_{50} in the micro- and submicromolar range, correlated with their lipophilicity. Structure-activity relationships enable to evidence a lead-complex (**21**) displaying a good activity ($IC_{50} = 210$ nM) close to the value obtained with chloroquine ($IC_{50} = 514$ nM) and a weak cytotoxicity.

1. Introduction

According to the latest estimates, malaria led to about 500 000 deaths in 2015 with 70 % of all deaths for children aged under 5 years.¹ Thanks to global fight against vectors and the large use of artemisinin-based combination therapies (ACT), estimated malaria mortality rates decreased by 60 % worldwide between 2000 and 2015.¹ Unfortunately, ACT resistance is now reported in many South-east Asia countries whereas there are no other antiplasmodial drugs to replace them.¹ New drugs with alternative chemical structures are urgently needed.

The peculiar biological properties of some organometallic compounds have helped in the development of new drugs based on metal complexes for major medical human problems including mainly cancer along with bacterial, viral and parasitic infections.² Generally, metal complexes are subject to modifications (ligand substitution and/or redox reactions) during uptake and transport inside the human body; this will influence the reactivity of the metal, but also greatly affect the absorption and delivery of the complex, and sometimes even the specificity of target recognition so they are therefore almost always “pro-dugs”. Metals may also be used to enhance the efficacy of known organic drugs and the metal-drug synergism results in the enhancement of the activity of the parental organic drug due to binding to the metal ion. More specifically, numerous metal-containing compounds have been evaluated as antimalarial agents and a recent review overviewed the advancements in this field during the last three decades.³ Among metal coordination complexes in which the metal center is directly coordinated to a known organic drug, gold and ruthenium complexes containing chloroquine (CQ) or analogs were the most active (with IC_{50} in the nM range), with improved efficacy, when compared to the drug, against CQ-sensitive and CQ-resistant strains, *in vitro* and *in vivo*.⁴ In particular, the principal mechanism proposed for the antimalarial action of $[Au(CQ)(PPh_3)]PF_6$ against resistant strains of *P. falciparum* is the interaction with heme and the inhibition of β -hematin formation. Both the enhanced activity and the ability of this

compound to lower CQ-resistance are related to the high lipophilicity of the metal complex and the important structural modification of the CQ structure imposed by the presence of the metal-containing fragment.^{4a} A great success was obtained by C. Biot and coll. with impressive biological results in the introduction of a ferrocenyl moiety into the lateral side chain of CQ, leading to the bioorganometallic drug Ferroquine (FQ) which is more active than CQ, and equally active against CQ-susceptible and CQ-resistant clones.⁵ The potent activity of FQ and the absence of cross-resistance with other antimalarials were reported both *in vitro* on a large number of clones and field isolates of *P. falciparum*, and *in vivo* on rodent models that demonstrated the high bioavailability of the product.^{5d} FQ has been developed by Sanofi and is the only metallodrug that has entered clinical trials (Phase IIb) against malaria, currently evaluated in combination with Artefenomel (OZ439).^{5f} FQ has a multi-mode of action: a capacity to target lipids, an ability to inhibit the formation of hemozoin, and to generate reactive oxygen species.^{5e, 6}

NHCs represent one of the most important classes of ligands in organometallic chemistry. The easy preparation of NHC-precursors has allowed an almost infinite access to new organometallic complexes, in which the nitrogen atoms of the azoliums rings can be functionalized by organic groups, organometallic moieties and biologic entities. NHCs are extremely good σ -donors, making strong metal-carbene bonds and giving stable complexes in biological medium. Numerous NHC-metal complexes exhibit very interesting biological activities as reflected in several review articles.⁷ By varying the properties of the NHCs and the nature of the metals (mainly Cu, Ag, Au, Ni, Pd, Pt and Ru), different important diseases have been targeted, mainly fungi^{7b, 7i}, bacteria^{7b-d, 7i}, and cancer.^{7a-f, 7h-k}. We focused our research on heteroditopic *N*-heterocyclic carbene (NHC) gold(I) complexes for their biomedical potential in anticancer and parasitic diseases such as malaria and leishmaniasis.⁸ New gold(I) complexes containing two 1-[2-(diethylamino)ethyl]imidazolylidene ligands have been synthesized and

their anticancer activity reported in five representative human cancer cell cancers (prostate, breast, brain, lung and liver) lines.^{8a} Very recently, we have demonstrated that mononuclear cationic and especially neutral gold(I) NHC-quinoline proved to be promising metallodrugs with potent and selective action against the pathological relevant form (intramacrophagic amastigote) of *Leishmania*.^{8d} Moreover, we have previously synthesized and tested against *Plasmodium falciparum* dinuclear dimeric and mononuclear gold(I) complexes and we have shown that mononuclear cationic gold(I) complexes containing aromatic amino-functionalized NHC exhibit *in vitro* potent and non-toxic antiplasmodial activity against the chloroquine-resistant strain FcM29-Cameroon with IC₅₀ values up to 330 nM.^{8c}

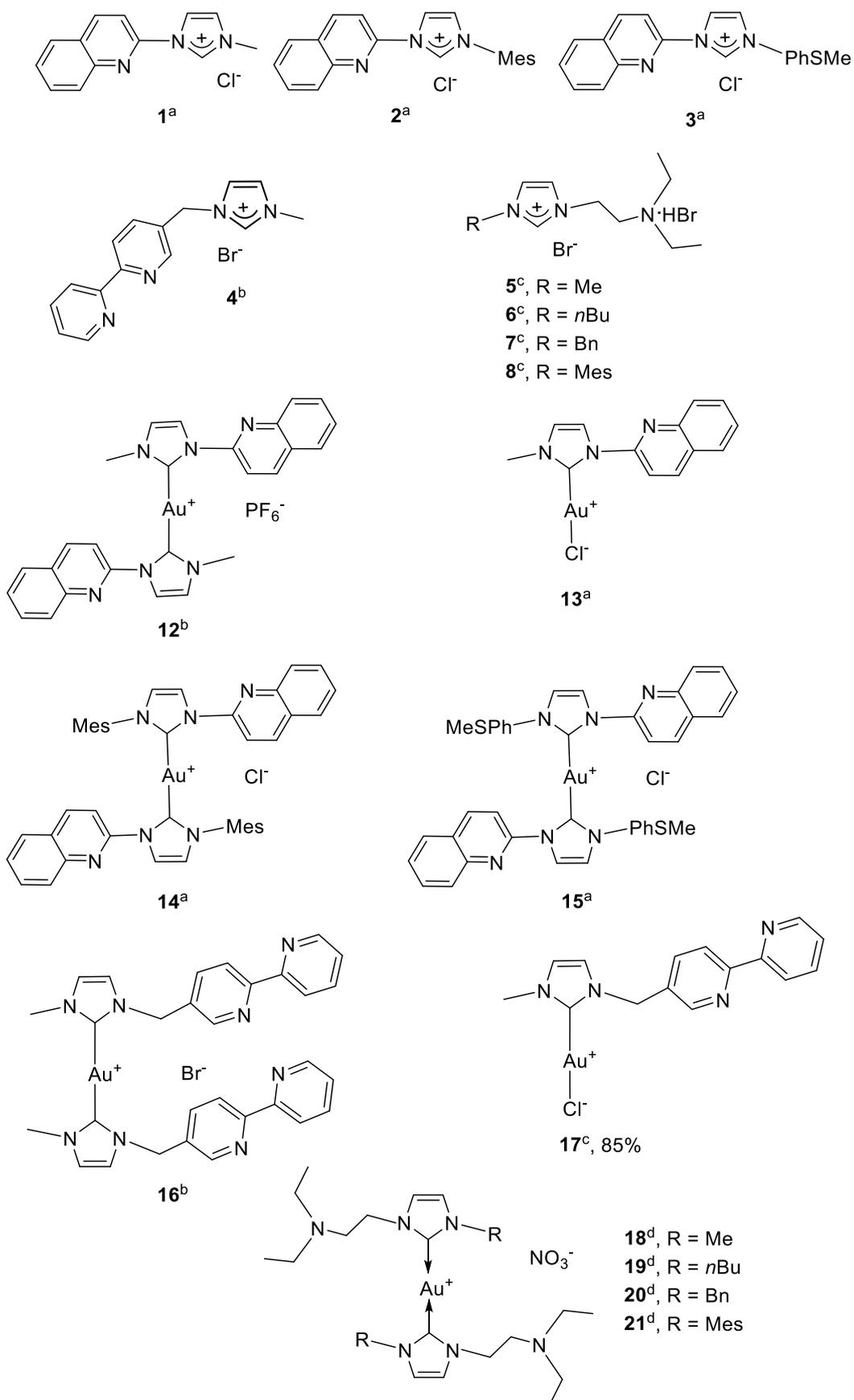
The rational design of new gold *N*-functionalized NHCs complexes with specific and/or selective parasite targets appear thus as a very useful avenue in the antiplasmodial drug research.

In this work, we aim to extend our preliminary work concerning gold(I) NHCs complexes against *Plasmodium falciparum* by fine tuning and studying the key building blocks of these organometallic molecules. For this purpose, we report the antiplasmodial activity of our gold(I) complexes already described for other biomedical applications.^{8c} In addition, we report the preparation, characterization and antimalarial potential of new mononuclear cationic, anionic and neutral gold(I) NHC or bis(NHC) complexes.

2. Results and discussion

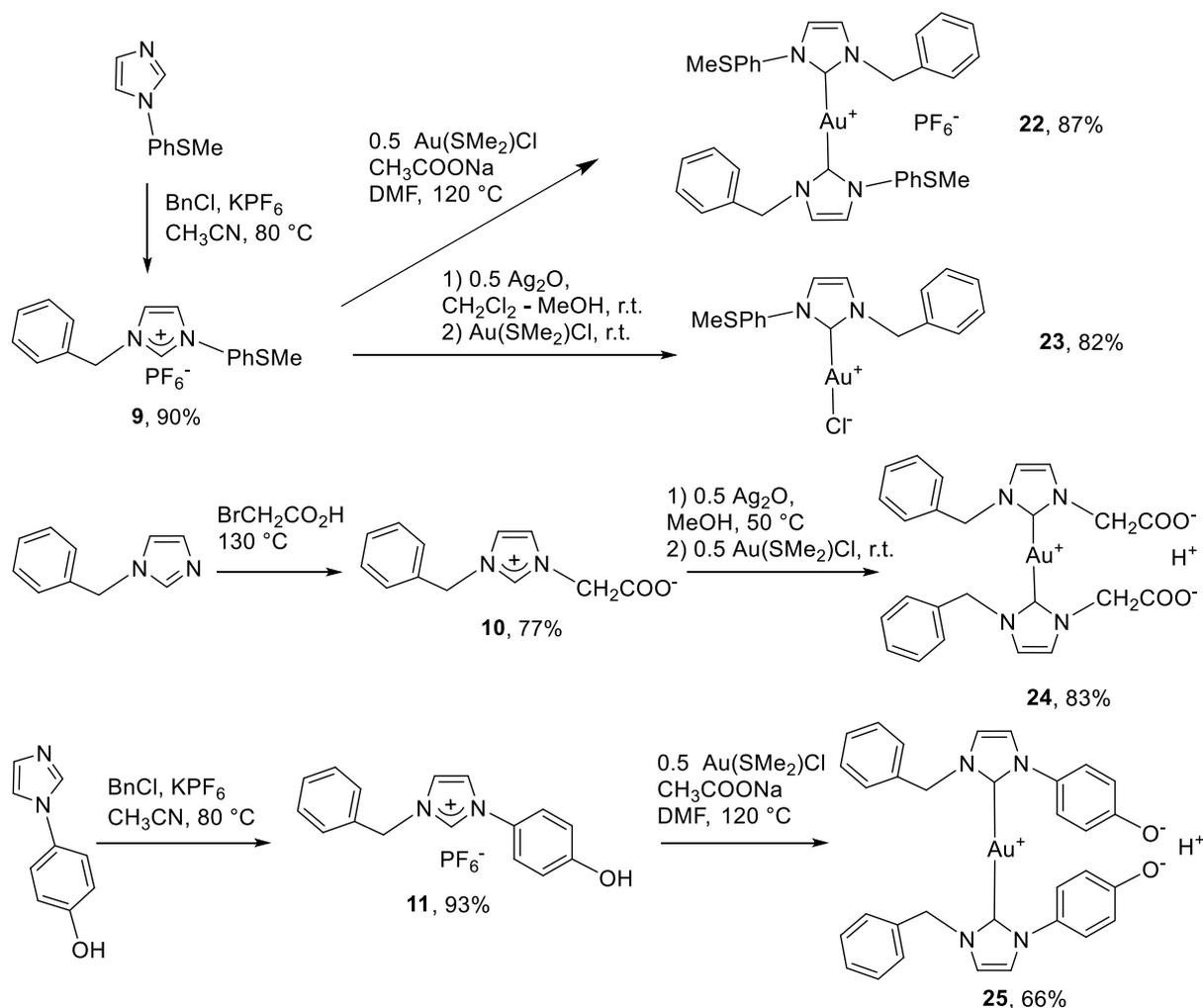
2.1. Chemistry and structural characterization

The synthesis of proligands **1-8** was already described (Scheme 1).^{8a, 8c, 8d} The imidazolium salts **9** and **11** were simply obtained after a quaternization step of 1-arylimidazole, namely 1-(4-methylthiophenyl)-1*H*-imidazole and 1-(4-hydroxyphenyl)imidazole, respectively, with one



Scheme 1. Proligands and gold(I) complexes used in this study. ^a Ref. 8d, ^b Ref. 8c, ^c this work and ^d Ref. 8a.

equivalent of benzylchloride and KPF₆ at 80 °C in acetonitrile (Scheme 2). The zwitterionic proligand **10** was easily synthesized by heating stoichiometric amounts of benzylimidazole and bromoacetic acid at 130 °C, following by deprotonation of the acidic proton by addition of Na₂CO₃ under reflux in water. The most notable features in the ¹H and ¹³C NMR spectra of the imidazolium salts are the resonances for imidazolium protons (*H*₂) located at 9.97, 9.21 and 10.16 ppm and the corresponding imidazolium carbons (*C*₂) in the range of 135.6-164.0 ppm, for **9**, **10** and **11** respectively. The high resolution mass spectra (ES) of proligands **9** and **11** exhibit the classical peak corresponding to the cation [M – PF₆]⁺ and that of zwitterion **10** shows the cation [M + H]⁺.



Scheme 2. Synthesis of imidazolium salts **9-11** and gold(I) bis(NHC) complexes **23-25**.

The synthesis of complexes **12-16** and **18-21** was previously reported in the literature (Scheme 1).^{8a, 8c, 8d} The mononuclear gold(I) bis(NHC) complexes **22** and **25** (Scheme 2) were prepared according a classical way, from the *N*-functionalized imidazolium salts **9** or **11**, respectively and one half equivalent of Au(SMe₂)Cl with sodium acetate as a mild base in hot *N,N*-dimethylformamide (120 °C) and were isolated as white or beige powders with good yields (66-87%). It has to be mentioned that in the ¹H NMR of complex **24**, both protons of the CH₂COO⁻ become inequivalent. This could be due to the interaction of the two carboxylate with a proton, which may impede the free rotation of the CH₂. Moreover, for complex **25** the phenol functions are deprotonated during the complexation process which is supported by the absence of the OH proton in the ¹H NMR spectrum (the OH proton of proligand **11** was located at 10.16 ppm) and by the ES-HRMS spectrum showing the molecular peak [M + H⁺] at *m/z* 697.1874 with M = Au^Ibis(NHC-phenolato). The neutral gold(I) NHC complexes **17** and **23** and the anionic complex gold(I) bis(NHC) **24** (Schemes 1 and 2) were synthesized *via* the convenient transmetalation route. Firstly, the silver precursor complexes were prepared by deprotonation of the imidazolium salts **4**, **9** or **10**, with one half equivalent of the mild base Ag₂O in a mixture of CH₂Cl₂-MeOH at room temperature or in MeOH at 50 °C. For **17**, the silver species Ag(4)₂Br^{8c} was isolated before the carbene transfer reaction while for compounds **23** and **24**, the transmetalation was carried out *in situ*, by adding one (for **17** and **23**) or one half equivalent (for **24**) of Au(SMe₂)Cl, with respect to the ligand. The three later compounds were obtained as grey solids with high yields (82-85%) and all complexes are stable towards air and moisture. NMR spectroscopy unequivocally demonstrates the formation of the gold(I) complexes; the ¹³C spectra show the resonance for the carbene carbon atoms between 181.6 and 184.5 ppm for the gold(I) bis(NHC) complexes **22**, **24** and **25**, and at 172.0 and 168.9 ppm for the neutral species **17** and **23**, respectively. These values are in the range of reported values for Au^I-NHC complexes having C-Au-X (X = halide) or C-Au-C motifs.⁹ The elemental

analysis of the gold(I) complexes are in agreement with the proposed structures and the high resolution mass spectra (ES) exhibit the classical peaks corresponding to the cationic fragments $[M + H]^+$ for the neutral and the anionic complexes **17**, **23-25** and $[M - PF_6^-]^+$ for the cationic compound **22**.

Crystals of **17** suitable for X-ray diffraction analysis were obtained by slow evaporation of a chloroform solution of **17**.

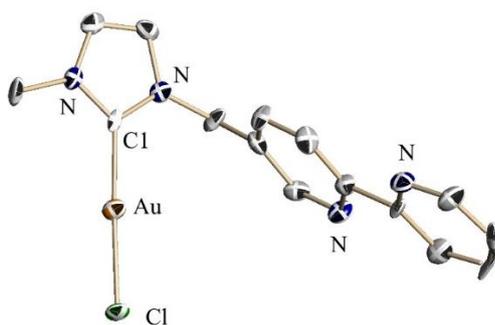


Figure 1. Structure of **17** in the solid state, thermal ellipsoids are depicted at a 50% level. Hydrogen atoms have been omitted for clarity. Selected bond lengths [\AA] and angles [$^\circ$]: C1-Au = 1.99(2), Au-Cl = 2.30(1), C1-Au-Cl = 177.7(4).

Slow evaporation of a MeOH solution of **22** gave crystals suitable for X-ray diffraction analysis.

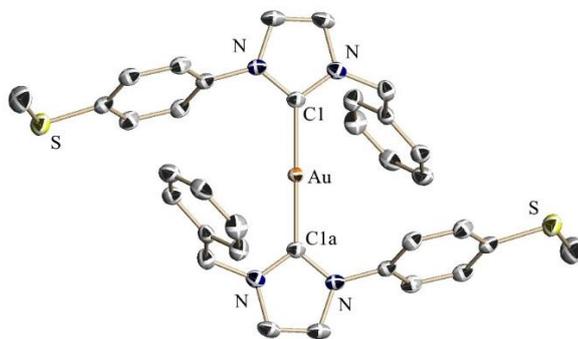


Figure 2. Structure of the cationic part of **22** in the solid state, thermal ellipsoids are depicted at a 50% level. Hydrogen atoms and the uncoordinated PF_6^- anion have been omitted for clarity. Selected bond lengths [\AA] and angles [$^\circ$]: C1-Au = 2.013(2), Au-C1a = 2.013(2), C1-Au-C1a = 180.

Crystals of **23** suitable for X-ray diffraction analysis were obtained by slow evaporation of an acetonitrile solution of **23**.

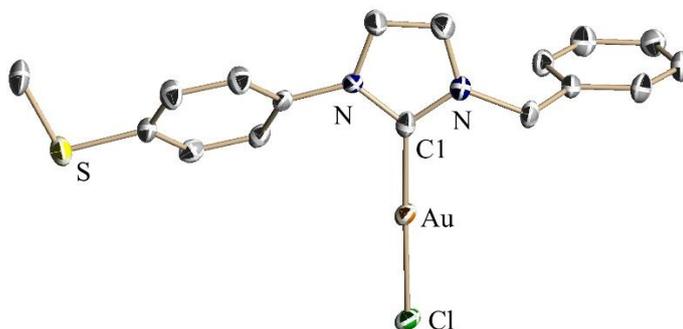


Figure 3. Structure of **23** in the solid state, thermal ellipsoids are depicted at a 50% level. Hydrogen atoms have been omitted for clarity. Selected bond lengths [\AA] and angles [$^\circ$]: C1-Au = 1.972(5), Au-Cl = 2.287(2), C1-Au-Cl = 178.2(2).

All carbon-gold and chlorine-gold distances, as well as the carbon-gold-carbon and carbon-gold-chlorine angles are in the normal range for such compounds. In **22** the gold cation is located on an inversion center and both NHC ring systems are absolutely coplanar. Moreover, the benzyl substituents are in trans position.

2.2. Anti-malarial activity and selectivity

Twenty five molecules, involving imidazolium salts **1-11** and mononuclear gold(I) complexes **12-25** were screened *in vitro* against *P. falciparum* strains (Table 1) by determining their 50% inhibitory concentrations (IC_{50}) and compared to the antimalarial reference-drugs chloroquine and artemisinin. As expected, proligands **1** and **4-11** showed weak or no activity with IC_{50} values ranging from 6.4 to $> 230 \mu\text{M}$, the worst value being obtained for the neutral zwitterionic species **10**, all other imidazolium salts being cationic. More surprising, the two proligands **2** and **3** containing both a quinoline entity and an aryl directly branched on the azolium ring exhibit interesting antiplasmodial potency with IC_{50} values of 1.4 and 1.5 μM ,

respectively. As expected, an enhanced activity was observed for the tested gold(I) complexes **12**, **15-16** and **19-22** when compared to the corresponding starting proligands, except for the couple **2/14** showing similar activity. This set of results corroborates in most cases the key role of the gold cation in antiprotozoal activity against *P. falciparum*. The three neutral complexes **13**, **17** and **23** showed moderate activity with IC₅₀ comprised between 4.1 and 6.6 μM and the IC₅₀ values of the two anionic compounds **24** and **25** are in the same order of magnitude, 5.6 μM and 3.7 μM, respectively. With the exception of complex **18**, the best values on *P. falciparum* were obtained for the cationic Au(I)bis(NHC) species with IC₅₀ in the micromolar and submicromolar range, with 2.1 μM (**19**), 0.48 μM (**20**), 0.21 μM (**21**), and 0.32 μM (**22**). A first insight can emerge from these results and confirm our preliminary published results (concerning **12** and **16**^{8c}): the global charge of the complex constitutes an important factor and cationic compounds are correlated with an increase antiplasmodial activity. The same antiplasmodial properties were reported with albitiazolium, a bis cationic compound which reached the clinical 2b step for antimalarial drug development. Albitiazolium had shown its entry facilitated by a poly-specific cation transporter present in the parasite membrane.¹⁰ The cationic property could facilitate the accumulation of the molecules inside the parasite where the pH of the cytoplasm is approximately 7.15 but certainly not in the malaria digestive vacuole where pH is about 5.¹¹ Moreover, even if the carbenic ligand acts mainly as a carrier for the metal center towards its target(s), as it is generally the case for gold complexes with biological potential, the two substituents on the NHC plays a crucial role with regard to the antiparasitic efficiency. This is well illustrated for the gold(I) series **18-21** where the antiplasmodial activity dramatically increases from methyl- (**18**: 22 μM) to mesityl-substituted (**21**: 0.21 nM) systems. By raising the sterically hindrance, the antimalarial activity was highly improved, reflecting an increase of the protective effect of the ligand around the metal and probably this allows to avoid releasing of the gold cation before reaching its target.

Table 1. Antiplasmodial and cytotoxicity of imidazolium salts and their gold(I) *N*-heterocyclic compounds.

Compounds	Antiplasmodial activity CI₅₀ (μM) on <i>P. falciparum</i>*[‡]	Cytotoxicity activity CI₅₀ (μM) on Vero cell line[‡]	Selectivity index
1	17.9 ± 1.3		
2	1.4 ± 0.2	> 140	>100
3	1.5 ± 0.1	69.7 ± 5.6	46
4	73.2 ± 4.5 [¶]		
5	> 145 [¶]		
6	> 130 [¶]		
7	59.6 ± 1.4		
8	11.3 ± 0.6		
9	6.4 ± 0.1		
10	>230		
11	9.3 ± 0.3		
12^l	1.1 ± 0.1	< 1 ^δ	< 0.9
13	5.2 ± 2.0		
14	1.1 ± 0.2	6.6 ± 0.4	6
15	0.47 ± 0.1	3.6 ± 0.3	8
16^l	0.33 ± 0.03	1 ^δ	3
17	6.6 ± 0		
18	22 ± 3.8 [¶]		
19	2.1 ± 0.3 [¶]		
20	0.48 ± 0.06	1.9 ± 0	4
21	0.21 ± 0.04	3.7 ± 0.1 [§]	18

22	0.32 ± 0.08	3.6 ± 0.7	11
23	4.1 ± 0.4		
24	5.6 ± 0.8		
25	3.7 ± 0.7		
Chloroquine[#]	0.514 ± 0.02 0.187 ± 0.02 [¶]	134 ± 20	261 717 [¶]
Artemisinin[#]	0.010 ± 0.7	ND	

* Antiplasmodial activity of the compounds were evaluated against the *P. falciparum* strain FcM29-Cameroon, except compounds noted (¶) evaluated against the *P. falciparum* strain FcB1-Columbia.

‡ Data represented the mean of 2 to 5 independent experiments.

¶ Reference 8c.

δ Cytotoxicity activity of the compounds were evaluated against Vero cell lines, except compounds noted (δ) evaluated on the McF7 line.

§ Compound **21** was also tested against other cell lines and showed the following results: 0.4 μM (PC-3 cell line); 0.8 μM (MCF-7 cell line); 0.8 μM (U87 cell line); 0.9 μM (A549 cell line); 1 μM (Hep3B cell line); > 5 μM (Huvec cell line).^{8a}

Both antiplasmodial control drugs artemisinin and chloroquine were routinely tested.

We have previously reported that the selective cytotoxic activity of this family was directly correlated with the lipophilic properties^{8a} and this trend is also verified here: the highest lipophilic complex **21** is the most active against *P. falciparum*. We can hypothesize that lipophilic properties could permit to compounds to better cross the different membranes (red blood cell membrane, parasitophorous vacuole membrane, parasite plasma membrane and eventually digestive vacuole membrane) to target the parasite. Concerning the aromatic nitrogen-containing *N*-functionalized NHC complexes **12**, **14** and **15**, the two quinoline moieties are positioned in trans-arrangement with respect to each other and thus provide already a good protection to the gold(I) center, in contrast to the previous complexes. That could also

explain the less antiplasmodial activity with only one quinoline moiety (**13**: 5.2 μM). This feature can explain the same antiplasmodial activity for **12** (1.1 μM) and **14** (1.1 μM), differing in their non-functionalized substituents, methyl and mesityl, respectively. Introducing a second functionalized entity involving a thioether group (**15**) leads to an improvement of the antiproliferative activity with an IC_{50} of 0.47 μM . Moreover, it should be noted that the use of the methylthiophenyl group as the only functionalized group is also very interesting as evidenced by the antimalarial potency of complex **22** ($\text{IC}_{50} = 0.32 \mu\text{M}$).

Compounds **15**, **16**, **20**, **21** and **22** showed thus very high antiplasmodial activity with IC_{50} below the micromolar range. Compounds with the most promising antimalarial properties were also evaluated on culture cell lines in order to determine the specificity of their activity. The selectivity index are ranging from <0.9 to 18. The best selectivity index was found with the compound **21**. These results confirmed those already reported with various cell lines^{8a} with IC_{50} values below 1 μM for all cancer cell lines tested whereas the value was superior to 5 μM on non-tumor cells (primary cultures of human umbilical vein endothelial cells (HUVEC)). These data highlight that complex **21** is specifically active against pathogen cells such as *P. falciparum* or multiple cancer cell lines but shows restricted effects on normal human cells.

The potential of organometallic gold complexes without incorporation of known antimalarial organic drugs against parasitic diseases has been little explored until very recently.^{3, 12} Messori and coll. used a panel of structurally diverse gold(I) and (III) complexes involving N, O or P heterocyclic ligands and the clinically established gold-based antiarthritic drug auranofin, to evaluate them as possible inhibitors of the parasite enzyme Falcipain 2 (Fp2) which is an important protease of *P. falciparum* and represents one of the most promising targets for antimalarial drug discovery.¹³ This protein is mainly involved in the degradation of host's hemoglobin (thus providing a substantial amount of peptides and amino acids to sustain parasite growth) and its proteolytic activity is more pronounced at the early trophozoite stage of parasite

development. Remarkably, most tested gold compounds caused pronounced but reversible inhibition of Fp2 and important parasite growth inhibition of *P. falciparum* was observed *in vitro*. However, any direct correlation between enzyme inhibition and reduction of *P. falciparum* growth was established, suggesting that Fp2 inhibition represents just one of the various mechanisms through which gold compounds effectively antagonize *P. falciparum* replication. Chibale and coll. reported gold(I) and gold(III) thiosemicarbazone (TSCs) compounds which exhibit moderate *in vitro* activity against two *P. falciparum* strains, CQ-sensitive D10 (IC₅₀ of CQ = 0.0173 μM) and CQ-resistant W2 (IC₅₀ of CQ = 0.095 μM) with IC₅₀ ranging from 1.36 to 6.92 μM for the gold(I) compounds and IC₅₀ ranging from 3.04 to > 20 μM for the gold(III) complexes; the gold(I) TSCs complexes also inhibit the Fp2 but no correlation was found between their antiplasmodial activity and the ability to inhibit Fp2.¹⁴ Mohr and coll. reported gold(I) complexes involving functionalized alkynes that have shown low *in vitro* activity against falciparum malaria parasite strains CQ-sensitive 3D7 (IC₅₀ of CQ = 0.01 μM) and CQ-resistant K1 (IC₅₀ of CQ = 0.3 μM) with IC₅₀ values between 7.2 and 23 μM.¹⁵ The same authors described also a series of mono- and dinuclear gold(I) phosphine complexes containing mono-anionic seleno- and thiosemicarbazones ligands; the IC₅₀ results showed that two sulfur containing mononuclear compounds exhibit activity similar to CQ against the 3D7 strain with IC₅₀ of 7.06 and 10.7 nM (IC₅₀ of CQ = 8.84 nM).¹⁶ Unfortunately, neither the IC₅₀ of the thiosemicarbazones ligands nor the toxicity of the corresponding complexes were evaluated. Previous studies realized by C. Lambros and co-workers revealed that the two involved ligands themselves already exhibit high *in vitro* antimalarial activity (CQ-resistant *P. falciparum* Smith strain with ID₅₀ below 10 ng/mL (ID₅₀ of CQ = 60 ng/mL) and moreover they are toxic *in vivo* (on *P. berghei* at doses > 20 or 40 mg/kg).¹⁷ Cronje and coll. reported preliminary *in vitro* antimalarial activities of *N*-heterocyclic ylideneamine gold(I) against *P. falciparum*; the coordination of ancillary phosphine or NHC ligands to these

complexes results in better activities with an IC₅₀ value of 5.1 µg/ml for the NHC derivative.¹⁸ In light of the available literature concerning gold compounds, some of our Au(I)-NHC complexes display improved efficacy.

3. Conclusion

In summary, a series of N-, O- or S-functionalized proligands and their corresponding mononuclear cationic, anionic or neutral gold(I) bisNHC complexes, including eight new fully characterized compounds, were tested *in vitro* for their antimalarial potency against chloroquine-resistant *P. falciparum* strains. Moreover, cytotoxicity of the most active compounds was assessed on Vero cell line, in order to determine their selectivity of action. From this screening, the importance of the charge of the molecules tested in the antiplasmodial activity was observed. Cationic lipophilic gold(I)-NHC complexes are more active than similar neutral and anionic complexes. Moreover, an active complex has to be highly lipophilic and the presence of nitrogen or sulphur atoms in the ligands seems to have a positive influence on the antiplasmodial activity.

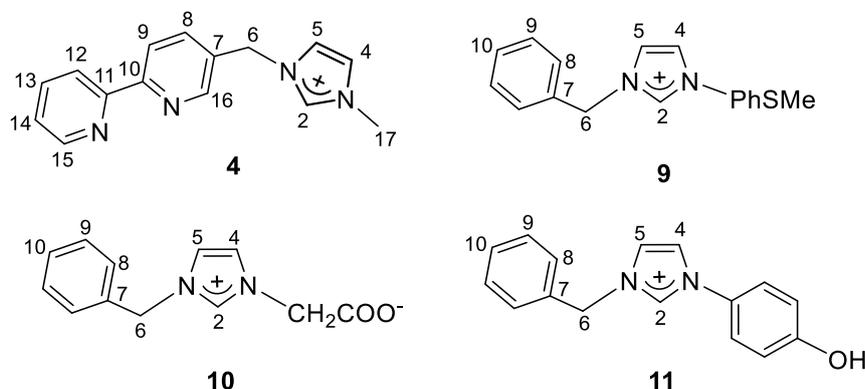
The pharmaco-modulation, by fine tuning either the global charge of the complexes and the key substituents on the NHC ligands, permitted to increase the antiplasmodial activity with promising selectivity indexes and highlighted the interest for gold cationic compounds which can be considered as a good scaffold for the optimisation of a new antimalarial chemistry.

4. Experimental

4.1. Chemistry

4.1.1. General methods

All manipulations were performed under an inert atmosphere of dry nitrogen by using standard vacuum line and Schlenk tube techniques. 3-Methyl-1-[[6-(pyridin-2-yl)pyridin-3-yl]methyl]-1*H*-imidazol-3-ium bromide (**4H**), Ag(**4**)₂Br^{8c} and 1-(4-methylthiophenyl)-1*H*-imidazole^{8d} were synthesized according to literature procedures. All reagents were used as received from commercial suppliers. Reactions involving silver compounds were performed with the exclusion of the light. ¹H (300 or 400 MHz) and ¹³C NMR spectra (75 or 101 MHz) were recorded at 298 K on Bruker AV300 or Bruker AV400 spectrometers in CDCl₃, CD₃CN, DMSO-*d*₆ and D₂O as solvents. Elemental analyses were carried out by the “Service de Microanalyse du Laboratoire de Chimie de Coordination (Toulouse). High Resolution Mass Spectrometry (HRMS) analysis were performed with a Thermo Finnigan MAT 95 XL spectrometer using electrospray ionization (ESI) or with a TOF mass analyzer by desorption chemical ionization with methane gas (DCI) by the “Service de Spectrométrie de Masse de Chimie UPS-CNRS” (Toulouse).



Numbering of H (¹H NMR) and C (¹³C NMR). These notations are used in the following section.

4.1.2. 1-(4-Methylthiophenyl)-3-benzylimidazolium chloride (**9**)

1-(4-Methylthiophenyl)-1*H*-imidazole (1.00 g, 5.26 mmol), benzylchloride (605 μ L, 5.26 mmol) and KPF₆ (967 mg, 5.26 mmol) were stirred in CH₃CN (20 mL) at 80 °C for 3 days.

After cooling to room temperature, the solvent was evaporated and the yellow solid obtained was washed with CH₂Cl₂ and diethyl ether and dried under vacuum (2.018 g, 90% yield). Anal. Calcd. For C₁₇H₁₇N₂SPF₆: C, 47.89; H, 4.02; N, 6.57. Found: C, 47.93; H, 4.06; N, 6.55. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.44 (s, 1H, *H*₂), 8.38 (d, *J* = 1.6 Hz, 1H, *H*₅), 8.11 (d, *J* = 1.6 Hz, 1H, *H*₄), 7.79 (d, *J* = 8.6 Hz, 2H, *H*_{PhSM_e}), 7.99 (d, *J* = 6.6 Hz, 2H, *H*₈), 7.49 (d, *J* = 8.6 Hz, 2H, *H*_{PhSM_e}), 7.45 – 7.37 (m, 3H, *H*₉, *H*₁₀), 5.57 (s, 2H, *H*₆), 2.54 (s, 3H, *H*_{PhSM_e}). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 141.37 (1C, *C*_{PhSM_e}), 135.73 (1C, *C*₂), 134.79 (1C, *C*₇), 131.93 (1C, *C*_{PhSM_e}), 129.47 (2C, *C*₉), 129.34 (1C, *C*₁₀), 128.95 (2C, *C*₈), 127.09 (2C, *C*_{PhSM_e}), 123.58 (1C, *C*₅), 122.86 (2C, *C*_{PhSM_e}), 122.12 (1C, *C*₄), 52.93 (1C, *C*₆), 14.92 (1C, *C*_{PhSM_e}). HRMS (ES⁺) calculated for C₁₇H₁₇N₂S (M – PF₆)⁺ 281.1112, found 281.1120.

4.1.3. 1-(Carboxymethyl)-3-benzylimidazolium (10)

Benzylimidazole (419 mg, 2.65 mmol) and bromoacetic acid (368 mg, 2.65 mmol) were heated at 130 °C for 24 h. After the mixture was cooled to room temperature, the oily product was dissolved in 20 ml H₂O and Na₂CO₃ was added (281 mg, 2.65 mmol). The mixture was refluxed at 100 °C for 30 min. After evaporation of the solvent, the resulting solid was partially dissolved in MeOH, filtered and the filtrate was evaporated to dryness. The crude product was washed with CH₂Cl₂ and dried under vacuum to afford a white solid (0.44 g, 77% yield). Anal. Calcd. For C₁₂H₁₂N₂O₂: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.58; H, 5.66; N, 12.90. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.21 (s, 1H, *H*₂), 7.69 (s, 1H, *H*₅), 7.60 (s, 1H, *H*₄), 7.40 (m, 5H, *H*₈, *H*₉, *H*₁₀), 5.43 (s, 2H, *H*₆), 4.45 (s, 2H, *H*_{CH₂COO}). ¹³C NMR (75 MHz, D₂O) δ 172.10 (1C, *C*_{COO}), 163.97 (1C, *C*₂), 133.44 (1C, *C*₇), 129.36 (2C, *C*₉), 129.31 (1C, *C*₁₀), 128.70 (2C, *C*₈), 123.71 (1C, *C*₅), 121.94 (1C, *C*₄), 52.89 (1C, *C*₆), 52.01 (1C, *C*_{CH₂COO}). HRMS (ES⁺) calculated for C₁₂H₁₃N₂O₂ (M + H)⁺ 217.0977, found 217.0978.

4.1.4. 1-(4-Hydroxyphenyl)-3-benzylimidazolium hexafluorophosphate (11)

1-(4-Hydroxyphenyl)imidazole (1.642 g, 9.760 mmol), benzylchloride (1.15 mL, 9.760 mmol) and KPF₆ (1.800 g, 9.760 mmol) were heated in acetonitrile (20 mL) at 80 °C for 3 days. The white solid obtained was filtered and dried under vacuum (3.595 g, 93% yield). Anal. Calcd. For C₁₆H₁₅N₂OPF₆: C, 48.50; H, 3.82; N, 7.07. Found: C, 48.47; H, 3.95; N, 7.01. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.31 (s, 1H, *H*_{PhOH}), 9.74 (t, *J* = 1.8 Hz, 1H, *H*₂), 8.11 (t, *J* = 1.9 Hz, 1H, *H*₅), 7.90 (t, *J* = 1.9 Hz, 1H, *H*₄), 7.56 (d, *J* = 8.9 Hz, 2H, *H*_{PhOH}), 7.53 – 7.36 (m, 5H, *H*₈, *H*₉, *H*₁₀), 6.98 (d, *J* = 8.9 Hz, 2H, *H*_{PhOH}), 5.47 (s, 2H, *H*₆). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 159.09 (1C, *C*_{PhOH}), 135.58 (1C, *C*₂), 135.01 (1C, *C*₇), 129.49 (2C, *C*₉), 129.32 (1C, *C*₁₀), 128.89 (2C, *C*₈), 126.94 (1C, *C*_{PhOH}), 124.23 (2C, *C*_{PhOH}), 123.43 (1C, *C*₅), 122.52 (1C, *C*₄), 116.74 (2C, *C*_{PhOH}), 52.83 (1C, *C*₆). HRMS (ES⁺) calculated for C₁₆H₁₅N₂O (M – PF₆)⁺ 251.1184, found 251.1189.

4.1.5. {1-[(2,2'-Bipyridin]-5-yl)methyl]-3-methylimidazol-2-ylidene}(chloro)gold(I) (17)

Complex **17** was obtained by transmetalation of Ag(**4**)₂Br (81 mg, 0.118 mmol) with Au(SMe₂)Cl (69.2 mg, 0.235 mmol) in a mixture of CH₂Cl₂-MeOH (4 mL / 2 mL) at r.t.. After stirring for 1 h, the solution was filtered through a pad of celite and the solvent removed under reduced pressure to give a grey solid (0.72 g, 63% yield). Anal. Calcd. For C₁₅H₁₄N₄AuCl: C, 37.32; H, 2.92; N, 11.61. Found: C, 37.27; H, 3.06; N, 11.57. ¹H NMR (400 MHz, CDCl₃) δ 8.73 – 8.67 (m, 2H, *H*₁₅, *H*₁₆), 8.48 (d, *J* = 8.2 Hz, 1H, *H*₁₂), 8.43 (d, *J* = 8.0 Hz, 1H, *H*₉), 7.95 – 7.80 (m, 2H, *H*₈, *H*₁₃), 7.39 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H, *H*₁₄), 7.00 (d, *J* = 1.9 Hz, 1H, *H*₅), 6.96 (d, *J* = 1.9 Hz, 1H, *H*₄), 5.49 (s, 2H, *H*₆), 3.90 (s, 3H, *H*₁₇). ¹³C NMR (101 MHz, CDCl₃) δ 171.99 (1C, *C*₂), 156.78 (1C, *C*₁₀), 155.25 (1C, *C*₁₁), 149.25 (1C, *C*₁₅), 148.50 (1C, *C*₁₆), 137.05 (1C, *C*₁₃), 136.68 (1C, *C*₈), 130.61 (1C, *C*₇), 124.11 (1C, *C*₁₄), 122.70 (1C, *C*₅), 121.31

(1C, C₉), 121.25 (1C, C₁₂), 120.21 (1C, C₄), 52.41 (1C, C₆), 38.41 (1C, C₁₇). HRMS (ES⁺) calculated for C₁₅H₁₄N₄Au (M – Cl)⁺ 447.0884, found 447.0887.

4.1.6. Bis{1-benzyl-3-[4-(methylsulfanyl)phenyl]imidazol-2-ylidene}gold(I) hexafluorophosphate (22)

Under a nitrogen atmosphere, sodium acetate (69.3 mg, 0.844 mmol) was added to a mixture of **9** (300 mg, 0.704 mmol) and Au(SMe₂)Cl (104 mg, 0.352 mmol) in dry DMF (6 mL) at 100°C. The mixture was then heated to 120 °C and this temperature was maintained for 2 h. After cooling to room temperature, the solution was filtered through a pad of celite and the solvent removed under reduced pressure to give a white solid (0.277 g, 87% yield). Anal. Calcd. For C₃₄H₃₂N₄S₂PF₆Au: C, 45.24; H, 3.57; N, 6.21. Found: C, 45.29; H, 3.62; N, 6.24. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.88 (d, *J* = 1.9 Hz, 2H, *H*₅), 7.82 (d, *J* = 1.9 Hz, 2H, *H*₄), 7.63 (d, 4H, *J* = 8.6 Hz, *H*_{PhSMe}), 7.37 – 7.28 (m, 6H, *H*₉, *H*₁₀), 7.26 (d, 4H, *J* = 8.6 Hz, *H*_{PhSMe}), 7.24 – 7.17 (m, 4H, *H*₈), 5.35 (s, 4H, *H*₆), 2.45 (s, 6H, *H*_{PhSMe}). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 181.57 (2C, C₂), 140.26 (2C, *C*_{PhSMe}), 136.62 (2C, C₇), 135.92 (2C, *C*_{PhSMe}), 129.21 (4C, C₉), 128.66 (2C, C₁₀), 127.94 (4C C₈), 126.64 (4C, *C*_{PhSMe}), 125.71 (4C, *C*_{PhSMe}), 123.93 (2C, C₅), 123.61 (2C, C₄), 54.35 (2C, C₆), 14.95 (2C, *C*_{PhSMe}). HRMS (ES⁺) calculated for C₃₄H₃₂N₄S₂Au (M – PF₆)⁺ 757.1734, found 757.1744.

4.1.7. {1-Benzyl-3-[4-(methylsulfanyl)phenyl]imidazol-2-ylidene}(chloro)gold(I) (23)

Under a nitrogen atmosphere and protection of the light, a Schlenk tube was charged with **9** (261 mg, 0.612 mmol) in a mixture of CH₂Cl₂-MeOH (5 mL / 1 mL), Ag₂O (71 mg, 0.306 mmol) and KCl (68 mg, 0.918 mmol). The reaction mixture was stirred at r.t. for 6 h. After that Au(SMe₂)Cl (180 mg, 0.612 mmol) was added and the mixture was stirred for 4 h. The solution was filtered through a pad of celite and the solvent removed under reduced pressure to give a

grey solid (0.267 g, 82% yield). Anal. Calcd. For $C_{17}H_{16}N_2SClAu$: C, 39.82; H, 3.15; N, 5.46. Found: C, 39.76; H, 3.22; N, 5.48. 1H NMR (300 MHz, CD_3CN) δ 7.63 (d, $J = 8.8$ Hz, 2H, H_{PhSMe}), 7.48 – 7.38 (m, 8H, H_{PhSMe} , H_5 , H_8 , H_9 , H_{10}), 7.36 (d, $J = 2.0$ Hz, 1H, H_4), 5.48 (s, 2H, H_6), 2.56 (s, 3H, H_{PhSMe}). ^{13}C NMR (75 MHz, $DMSO-d_6$) δ 168.90 (1C, C_2), 140.10 (1C, C_{PhSMe}), 136.84 (1C, C_7), 136.18 (1C, C_{PhSMe}), 129.30 (2C, C_9), 128.69 (1C, C_{10}), 128.23 (2C, C_8), 126.73 (2C, C_{PhSMe}), 125.93 (2C, C_{PhSMe}), 123.57 (1C, C_5), 123.01 (1C, C_4), 54.62 (1C, C_6), 15.00 (1C, C_{PhSMe}). HRMS (DCI) calculated for $C_{17}H_{16}N_2SAu$ ($M - Cl$) $^+$ 477.0700, found 477.0710.

4.1.8. Hydrogen bis[1-benzyl-3-(carboxylatomethyl)imidazol-2-ylidene]gold(I) (24)

Under a nitrogen atmosphere and protection of the light, a Schlenk tube was charged with **10** (338 mg, 1.563 mmol) in 10 ml of dry MeOH and Ag_2O (181 mg, 0.782 mmol). The mixture was stirred for 12 h at 50 °C. After cooling to r.t., $Au(SMe_2)Cl$ (230 mg, 0.782 mmol) was added and the mixture was stirred at r.t. for 2 h. The solution was filtered through a pad of celite and the solvent removed under reduced pressure to give a grey solid (0.407 g, 83% yield). Anal. Calcd. For $C_{24}H_{23}N_4O_4Au$: C, 45.87; H, 3.69; N, 8.92. Found: C, 45.90; H, 3.90; N, 8.93. 1H NMR (300 MHz, $DMSO-d_6$) δ 7.45 (s, 2H, H_5), 7.39-7.28 (m, 12H, H_4 , H_8 , H_9 , H_{10}), 5.32 (s, 4H, H_6), 4.50 (s, 2H, H_{CH_2COO}), 4.42 (s, 2H, H_{CH_2COO}). ^{13}C NMR (75 MHz, D_2O) δ 184.51 (2C, C_2), 174.02 (2C, C_{COO}), 136.53 (2C, C_7), 128.83 (4C, C_9), 128.15 (2C, C_{10}), 127.40 (4C, C_8), 123.05 (2C, C_5), 121.74 (2C, C_4), 53.91 (2C, C_6), 53.85 (2C, C_{CH_2COO}). HRMS (ES^+) calculated for $C_{24}H_{24}N_4O_4Au$ ($M + H$) $^+$ 629.1463, found 629.1478.

4.1.9. Hydrogen bis[1-benzyl-3-[(4-oxidophenyl)]imidazol-2-ylidene]gold(I) (25)

Under a nitrogen atmosphere, sodium acetate (74.5 mg, 0.908 mmol) was added to a mixture of **11** (300 mg, 0.757 mmol) and $Au(SMe_2)Cl$ (112 mg, 0.379 mmol) in dry DMF (5 mL) at

100 °C. The mixture was then heated to 120 °C and this temperature was maintained for 2 h. After cooling to room temperature, CH₂Cl₂ (5 mL) and hexane (10 mL) were added to the solution to afford a beige solid, which was filtered and dried under vacuum (0.175 g, 66% yield). Anal. Calcd. For C₃₂H₂₇N₄O₂Au: C, 55.18; H, 3.91; N, 8.04. Found: C, 55.23; H, 3.96; N, 8.10. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.77 – 7.76 (m, 4H, *H*₄, *H*₅), 7.37 (d, *J* = 8.8 Hz, 4H, *H*_{PhO}), 7.31 – 7.29 (m, 6H, *H*₉, *H*₁₀), 7.19 (dd, *J* = 6.7, 2.9 Hz, 4H, *H*₈), 6.82 (d, *J* = 8.8 Hz, 4H, *H*_{PhO}), 5.31 (s, 4H, *H*₆). ¹³C NMR (101 MHz, DMSO) δ 181.55 (2C, *C*₂), 158.36 (2C, *C*_{PhO}), 136.66 (2C, *C*₇), 130.71 (2C, *C*_{PhO}), 129.22 (4C, *C*₉), 128.69 (2C, *C*₁₀), 127.94 (4C, *C*₈), 126.43 (4C, *C*_{PhO}), 123.88 (2C, *C*₅), 123.12 (2C, *C*₄), 116.24 (4C, *C*_{PhO}), 54.19 (2C, *C*₆). HRMS (ES⁺) calculated for C₃₂H₂₈N₄O₂Au (M + H)⁺ 697.1878, found 697.1874.

4.2. Crystallographic data for 17, 22 and 23

All data were collected at low temperature using oil-coated shock-cooled crystals on a Bruker-AXS APEX II diffractometer with MoK α radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods¹⁹ and all non hydrogen atoms were refined anisotropically using the least-squares method on F^2 .^{3, 20}

CCDC-1441512 (**17**), CCDC-1441513 (**22**) and CCDC-1441514 (**23**) contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

17: C₁₅H₁₄AuClN₄, Mr = 482.72, crystal size = 0.30 x 0.30 x 0.10 mm³, monoclinic, space group *P*2₁/*c*, *a* = 5.6934(3) Å, *b* = 11.8070(6) Å, *c* = 21.8435(12) Å, β = 92.646(3)°, *V* = 1466.8(2) Å³, *Z* = 4, *T* = 173(2) K, 2506 unique reflections, *R*1 = 0.0554, *wR*2 = 0.1535 [*I* > 2 σ (*I*)], *R*1 = 0.0759, *wR*2 = 0.1659 (all data), residual electron density = 2.400 e Å⁻³.

22: C₃₄H₃₂AuF₆N₄PS₂, Mr = 902.69, crystal size = 0.30 x 0.30 x 0.10 mm³, monoclinic, space group *P2₁/n*, *a* = 11.7142(5) Å, *b* = 11.6965(5) Å, *c* = 12.7877(6) Å, β = 108.408(1)°, *V* = 1662.5(2) Å³, *Z* = 2, *T* = 173(2) K, 24252 reflections collected, 6058 unique reflections (*R*_{int} = 0.0409), *R*₁ = 0.0228, *wR*₂ = 0.0551 [*I* > 2σ(*I*)], *R*₁ = 0.0324, *wR*₂ = 0.0613 (all data), residual electron density = 1.811 e Å⁻³.

23: C₁₇H₁₆AuClN₂S, Mr = 512.79, crystal size = 0.30 x 0.20 x 0.05 mm³, triclinic, space group *P* $\bar{1}$, *a* = 9.545(1) Å, *b* = 9.931(1) Å, *c* = 10.044(1) Å, α = 103.547(4)°, β = 112.197(4)°, γ = 97.717(4)°, *V* = 830.4(2) Å³, *Z* = 2, *T* = 173(2) K, 11653 reflections collected, 4054 unique reflections (*R*_{int} = 0.0366), *R*₁ = 0.0276, *wR*₂ = 0.0679 [*I* > 2σ(*I*)], *R*₁ = 0.0320, *wR*₂ = 0.0702 (all data), residual electron density = 2.108 e Å⁻³.

4.3 Biological material and methods

4.3.1. In vitro antimalarial activities

The *in vitro* antimalarial activities of the 25 synthesized compounds were tested comparatively to their ligands in order to determine the influence of the different structure modulations on the biological activities. Both chloroquine-resistant *P. falciparum* strains FcM29-Cameroon and FcB1-Colombia, were cultured continuously according to the modified Trager and Jensen's method.²¹ The antimalarial activity was evaluated by the radioactive micro-method described by Desjardins *et al.*²² with modifications as reported.²³

Drug testing was performed from 2 to 5 times in triplicate in 96-well culture plates on D-sorbitol synchronized cultures. Compounds were dissolved in dimethylsulfoxide (DMSO) (stock solution: 10 mg/mL) and further diluted in culture medium so that the final DMSO concentration never exceeded 2 %. For each assay, it was verified that the 2 % concentration of

DMSO did not affect parasite growth. Parasite growth was estimated by [³H]hypoxanthine incorporation (Perkin Elmer, France).

The control parasite culture (culture medium with or without 2 % DMSO) was referred to as 100 % growth. The IC₅₀ values were determined graphically by plotting the log of the drug concentration versus the percentage inhibition of parasite growth. Results are summarized in Table 1.

4.3.2. Cytotoxicity assays

Evaluation of the cytotoxicity of selected compounds was performed on Vero cell lines (Monkey epithelial cell line, Sigma-Aldrich) or on McF7 cell line with the same dilution protocol used for antiplasmodial assays. Cell lines were distributed in 96-well plates in 100 µL MEM medium with 10% foetal calf serum at 37 °C under a humidified atmosphere (5% CO₂). After 24 h-culture, the cells were supplemented with 100 µL of the compounds dilutions and [³H]hypoxanthine was also added for 48 h more. Cell growth was estimated by [³H]hypoxanthine incorporation read by β counter (1450-Microbeta Trilux, Wallac-Perkin Elmer) as reported for antiplasmodial assays.²⁴ Selectivity index was then calculated by the Cytotoxicity/Activity ratio.

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References and notes

1. WHO, *World Health Organization*. World Malaria Report 2015. **2015**. 280 p.
2. Alessio, E., *Bioinorg Med Chem*. Germany 2011; Vol. 10.
3. Salas, P. F.; Herrmann, C.; Orvig, C. *Chem. Rev.* **2013**, *113*, 3450.

4. (a) Navarro, M.; Castro, W.; Martínez, A.; Sánchez-Delgado, R. *J. Inorg. Biochem.* **2011**, *105*, 276; (b) Martinez, A.; Rajapakse, C. S. K.; Jalloh, D.; Dautriche, C.; Sanchez-Delgado, R. A. *J. Biol. Inorg. Chem.* **2009**, *14*, 863; (c) Navarro, M.; Vasquez, F.; Sanchez-Delgado, R. A.; Perez, H.; Sinou, V.; Schrevel, J. *J. Med. Chem.* **2004**, *47*, 5204; (d) Sánchez-Delgado, R.; Navarro, M.; Pérez, H. *J Chem Med* **1997**, *40*, 1937; (e) Sanchez-Delgado, R. A.; Navarro, M.; Perez, H.; Urbina, J. A. *J. Med. Chem.* **1996**, *39*, 1095.
5. (a) Biot, C.; Glorian, G.; Maciejewski, L. A.; Brocard, J. S.; Domarle, O.; Blampain, G.; Millet, P.; Georges, A. J.; Abessolo, H.; Dive, D.; Lebibi, J. *J. Med. Chem.* **1997**, *40*, 3715; (b) Chavain, N.; Vezin, H.; Dive, D.; Touati, N.; Paul, J. F.; Buisine, E.; Biot, C. *Mol. Pharm.* **2008**, *5*, 710; (c) Biot, C.; Nosten, F.; Fraisse, L.; Ter-Minassian, D.; Khalife, J.; Dive, D. *Parasite* **2011**, *18*, 207; (d) Biot, C.; Pradines, B.; Dive, D., *Drug Discovery in Infectious Diseases*. 2011; (e) Dubar, F.; Bohic, S.; Slomianny, C.; Morin, J. C.; Thomas, P.; Kalamou, H.; Guerardel, Y.; Cloetens, P.; Khalife, J.; Biot, C., *Chem Comm* **2012**, *48*, 910; (f) ClinicalTrials.gov, <http://clinicaltrials.gov/ct2/show/NCT00988507> & <https://clinicaltrials.gov/ct2/show/NCT02497612>
6. Chavain, N.; Davioud-Charvet, E.; Trivelli, X.; Mbeki, L.; Rottmann, M.; Brun, R.; Biot, C., *Bioorg. Med. Chem.* **2009**, *17*, 8048.
7. (a) Teyssot, M. L.; Jarrousse, A. S.; Manin, M.; Chevry, A.; Roche, S.; Norre, F.; Beaudoin, C.; Morel, L.; Boyer, D.; Mahiou, R.; Gautier, A. *Dalton Trans.* **2009**, 6894; (b) Hindi, K. M.; Panzner, M. J.; Tessier, C. A.; Cannon, C. L.; Youngs, W. J. *Chem. Rev.* **2009**, *109*, 3859; (c) John, A.; Ghosh, P. *Dalton Trans.* **2010**, *39*, 7183; (d) Merces, L.; Albrecht, M. *Chem. Soc. Rev.* **2010**, *39*, 1903; (e) Gasser, G.; Ott, I.; Metzler-Nolte, N., *J. Med. Chem.* **2011**, *54*, 3; (f) Gautier, A.; Cisnetti, F. *Metallomics* **2012**, *4*, 23; (g) Patra, M.; Gasser, G.; Metzler-Nolte, N. *Dalton Trans.* **2012**, *41*, 6350; (h) Liu, W. K.; Gust, R. *Chem. Soc. Rev.* **2013**, *42*, 755; (i) Oehninger, L.; Rubbiani, R.; Ott, I. *Dalton Trans.* **2013**, *42*, 3269; (j) Bertrand, B.; Casini, A. *Dalton Trans.* **2014**, *43*, 4209; (k) Tacke, M. *J. Organomet. Chem.* **2015**, 782, 17.
8. (a) Boselli, L.; Ader, I.; Carraz, M.; Hemmert, C.; Cuvillier, O.; Gornitzka, H. *Eur. J. Med. Chem.* **2014**, *85*, 87; (b) Boselli, L.; Carraz, M.; Mazerès, S.; Paloque, L.; Gonzalez, G.; Benoit-Vical, F.; Valentin, A.; Hemmert, C.; Gornitzka, H. *Organometallics* **2015**, *34*, 1046; (c) Hemmert, C.; Fabie, A.; Fabre, A.; Benoit-Vical, F.; Gornitzka, H. *Eur. J.*

- Med. Chem.* **2013**, *60*, 64; (d) Paloque, L.; Hemmert, C.; Valentin, A.; Gornitzka, H. *Eur. J. Med. Chem.* **2015**, *94*, 22.
9. Lin, J. C. Y.; Huang, R. T. W.; Lee, C. S.; Bhattacharyya, A.; Hwang, W. S.; Lin, I. J. B. *Chem. Rev.* **2009**, *109*, 3561.
 10. Wein, S.; Maynadier, M.; Bordat, Y.; Perez, J.; Maheshwari, S.; Bette-Bobillo, P.; Tran Van Ba, C.; Penarete-Vargas, D.; Fraisse, L.; Cerdan, R.; Vial, H. *Br. J. Pharmacol.* **2012**, *166*, 2263.
 11. Kuhn, Y.; Rohrbach, P.; Lanzer, M. *Cell Microbiol* **2007**, *9*, 1004.
 12. Glisic, B. D.; Djuran, M. I. *Dalton Trans.* **2014**, *43*, 5950.
 13. Micale, N.; Cinellu, M. A.; Maiore, L.; Sannella, A. R.; Severini, C.; Schirmeister, T.; Gabbiani, C.; Messori, L. *J. Inorg. Biochem.* **2011**, *105*, 1576.
 14. (a) Khanye, S. D.; Wan, B.; Franzblau, S. G.; Gut, J.; Rosenthal, P. J.; Smith, G. S.; Chibale, K. *J. Org. Chem.* **2011**, *696*, 3392; (b) Khanye, S. D.; Smith, G. S.; Lategan, C.; Smith, P. J.; Gut, J.; Rosenthal, P. J.; Chibale, K. *J. Inorg. Biochem.* **2010**, *104*, 1079.
 15. Schuh, E.; Valiahdi, S. M.; Jakupec, M. A.; Keppler, B. K.; Chiba, P.; Mohr, F. *Dalton Trans.* **2009**, 10841.
 16. Molter, A.; Rust, J.; Lehmann, C. W.; Deepa, G.; Chiba, P.; Mohr, F. *Dalton Trans.* **2011**, *40*, 9810.
 17. Lambros, C.; Childs, G. E.; Notsch, J. D.; Scovill, J. P.; Klayman, D. L.; Davidson, D. E. *Antimicrob. Agents Chemother.* **1982**, *22*, 981.
 18. Coetzee, J.; Cronje, S.; Dobrzanska, L.; Raubenheimer, H. G.; Joone, G.; Nell, M. J.; Hoppe, H. C. *Dalton Trans.* **2011**, *40*, 1471.
 19. Sheldrick, G. M. *Acta Cryst.* **1990**, *A46*, 467.
 20. Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112.
 21. Benoit-Vical, F.; Robert, A.; Meunier, B. *Antimicrob. Agents Chemother.* **2000**, *44*, 2836.
 22. Desjardins, R. E.; Canfield, C. J.; Haynes, J. D.; Chulay, J. D. *Antimicrob. Agents Chemother.* **1979**, *16*, 710.
 23. Benoit-Vical, F.; Lelievre, J.; Berry, A.; Deymier, C.; Dechy-Cabaret, O.; Cazelles, J.; Loup, C.; Robert, A.; Magnaval, J. F.; Meunier, B. *Antimicrob. Agents Chemother.* **2007**, *51*, 1463.
 24. Benoit-Vical, F.; Soh, P. N.; Salery, M.; Harguem, L.; Poupat, C.; Nongonierma, R., *J. Ethnopharmacol.* **2008**, *116*, 43.

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