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Gold complexes as antimicrobial agents: an overview of different biological activities in relation to the oxidation state of gold ion and ligand structure

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Abstract

Interest for antimicrobial gold complexes originated from the work of Robert Koch in the end of 19th century, who demonstrated that potassium dicyanidoaurate(I), K[Au(CN)$_2$], showed activity against *Mycobacterium tuberculosis*, a causative agent of tuberculosis. Subsequently, a large number of gold(I) and gold(III) complexes have been evaluated as possible antimicrobial agents against a broad spectrum of bacteria, fungi and parasites. The first part of the present review article summarizes the results achieved in the field of antibacterial and antifungal activity of gold(I) and gold(III) complexes. The represented gold(I) complexes have been divided into three distinct classes based on the type of coordinated ligand: *(i)* complexes with phosphine-type ligands, *(ii)* complexes with *N*-heterocyclic carbene ligands and *(iii)* various other gold(I) complexes, while the results related to the antibacterial and antifungal gold(III) complexes have been mainly focused on the organometallic-type of complexes. The second section of this article represents findings obtained from the evaluation of antimalarial activity of gold complexes against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* parasite. Antimalarial gold(I) and gold(III) complexes have been divided into the following classes, based on the nature of the coordinated ligand: *(i)* complexes with chloroquine and its derivatives, *(ii)* complexes with *N*-heterocyclic carbene ligands, *(iii)* complexes containing functionalised alkynes and *(iv)* thiosemicarbazonato ligands, as well as *(v)* other gold(I) and gold(III) complexes. In the last section of the review, gold(I) and gold(III) complexes have been reported as potential agents against parasites that cause amoebiasis, leishmaniasis and trypanosomiasis. A systematic summary of these results could contribute to the future design of new gold(I) and gold(III) complexes as potential antimicrobial agents.

Keywords: Gold(I); Gold(III); Antibacterial; Antifungal; Antimalarial; Antiamoebic; Antileishmanial; Antitrypanosomial.

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1. Introduction

The chemistry of gold is very interesting and has some unique aspects, most likely as a consequence of the important electronic properties of the gold atom. The most important oxidation states of gold in its complexes are +1 and +3.[1-4] As a soft Lewis acid, Au(I) ion (d^{10} electronic configuration) favours complexation with ligands containing soft donor atoms. Thus, thiolates, thioethers, cyanide, phosphines and arsines form stable complexes with Au(I) ion. X-ray crystallography has shown that gold(I) complexes can adopt linear, trigonal or tetrahedral geometries. Gold(I) complexes are stable in non-aqueous aprotic solvents such as acetonitrile. On the other hand, in aqueous solution, gold(I) complexes have a strong tendency to disproportionate forming Au(III) and metallic Au(0)[5-7] according to the following equation:

$$3Au(I)_{(aq)} \rightarrow Au(III)_{(aq)} + 2Au_{(s)} \quad \log K \approx 10.$$

Gold(III) ion has a d^8 closed-shell configuration ($[Xe]4f^{14}5d^8$). The ionic radius of the Au(III) (85 pm) is less than Au(I) (137 pm) which renders the Au(III) ion much less polarisable. Consequently, Au(III) ion has a preference for ligands containing nitrogen and oxygen donor atoms (hard Lewis bases). Other important ligands which form complexes with Au(III) ion are chloride, bromide and cyanide. The dominant coordination geometry for gold(III) complexes is square planar, although trigonal bipyramidal and octahedral geometries are also observed. Trigonal bipyramidal and octahedral structures typically exhibit elongated axial bond lengths perpendicular to the square plane.

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Beside the many applications of gold in dentistry, monetary systems, jewellery and electronics, this metal and its complexes have been used in medicine throughout the history of civilisation for the treatment of a wide range of diseases. In the middle of 20th century gold(I) complexes found clinical use as antiarthritic agents for the treatment of rheumatoid arthritis and a variety of rheumatic diseases including psoriatic arthritis, juvenile arthritis, palindromic rheumatism and discoid lupus erythematosus.[8] Subsequently, a large number of gold(I) and gold(III) complexes have been evaluated for their potential use in the treatment of cancer, bronchial asthma, as anti-HIV and antimicrobial agents.[9] The purpose of this review is to present the results achieved in the field of gold(I) and gold(III) complexes as potential antibacterial, antifungal, antimalarial, antiamoebic, antileishmanial and antitrypanosomial agents.

2. Antibacterial and antifungal activity of gold(I) and gold(III) complexes

Interest for antimicrobial gold complexes originated from the work of Robert Koch in the end of 19th century, who demonstrated that potassium dicyanidoaurate(I), K[Au(CN)$_2$], showed activity against *Mycobacterium tuberculosis*, a causative agent of tuberculosis.[10,11] Subsequently, a large number of gold(I) and gold(III) complexes have been tested and shown the activity against a broad spectrum of microorganisms.

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2.1. Antibacterial and antifungal gold(I) complexes

So far, a relatively large number of gold(I) complexes have been synthesized and evaluated for their antibacterial and antifungal activity, and the obtained results are summarized herein. For a better understanding of the data, the represented gold(I) complexes have been divided into three distinct classes based on the type of coordinated ligand: *complexes with phosphine-type ligands, complexes with N-heterocyclic carbene ligands* and *various other gold(I) complexes.*

Gold(I) complexes with phosphine-type ligands

Seven linear phosphine gold(I) complexes having a sulfur atom in the coordination sphere (**1-7**, Fig. 1 and Table 1) exhibited a different spectrum of *in vitro* activity against several strains of Gram-positive and Gram-negative bacteria, *Staphylococcus aureus* (*Staph. aureus*), *Staphylococcus epidermidis* (*Staph. epidermidis*), *Escherichia coli* (*Esch. coli*) and *Pseudomonas aeruginosa* (*Ps. aeruginosa*), and fungi *Candida albicans* (*Ca. albicans*) and *Aspergillus niger* (*A. niger*).[12] As it can be seen in Table 1, the exchange of the phenyl groups (Ph) on the phosphorus atoms of the dinuclear complex **4** with methyl groups (Me), resulting in the formation of complex **3**, significantly reduced the antimicrobial activity, while gold(I) complexes **1**, **6** and **7**, containing triethylphosphine (PEt_3), were the most active against the investigated strains of bacteria and fungi. However, the presence of different thiol ligands in complexes **1**, **6** and **7** caused the difference in the activity

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against *Esch. coli*, *Ca. albicans* and *A. niger*. Thus, complex **1**, containing the bulky and lipophilic lupinylthiol, showed the highest activity against fungi, comparable to that of miconazole nitrate, while the more hydrophilic complex **6** was more active than **1** against *Esch. coli* (Table 1). As it can be seen at the end of Table 1, the antibiotic piperacillin, used as the reference drug, was more active than the investigated gold(I) complexes **1**, **6** and **7** against Gram-negative bacteria, but less against Gram-positive strains. On the other hand, chloramphenicol was slightly more active than **6** against *Esch. coli,* but much less active than these gold(I) complexes against Gram-positive bacteria. Auranofin (complex **8**, Fig. 1), widely used for the treatment of rheumatoid arthritis, was comparably active as complexes **1** and **6** against Gram-positive bacteria and *A. niger*, but less active against *Esch. coli* and *Ca. albicans* (Table 1).[12]

Gold(I) complex [Au(SCN)(PMe_3)] (complex **9**, Fig. 1) was found to be active *in vitro* against meticillin-resistant *Staph. aureus*, enterococci *Enterococcus faecalis* (*Ent. faecalis*) and *Proteus mirabilis* (*Pr. mirabilis*) at low concentration (MIC[1] $\leq$ 4 μg/mL) and less active against *Ps. aeruginosa* and *Ca. albicans* (Table 1).[13,14] Moreover, this complex was remarkably selective in its action toward bacteria over mammalian cells and showed an excellent *in vivo* activity in the treatment of antibiotic resistant Gram-positive bacteria. Also, it is worth mentioning that the phosphine gold(I) complexes with sulfur-containing ligands such as 2-mercaptopropionic acid (2-H_2mpa), 6-mercaptonicotinic acid (6-H_2mna), 2-mercaptonicotinic acid (2-H_2mna),

[1]Minimum inhibitory concentration

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penicillamine (H_2pen), 2-mercaptobenzoic acid (2-H_2mba), 3-mercaptobenzoic acid (3-H_2mba) and 4-mercaptobenzoic acid (4-H_2mba) (**10**-**17**, Fig. 2) showed a different spectrum of antimicrobial activity.[15] [Au(2-Hmna)(PPh_3)] complex **12** and [Au(D-Hpen)(PPh_3)] complex **13** were effective against Gram-positive bacteria *Bacillus subtilis* (*B. subtilis*) and *Staph. aureus*, but not against Gram-negative bacteria *Esch. coli* and *Ps. aeruginosa* (Table 1).[15] [Au(D,L-Hpen)(PPh_3)]·0.5MeOH complex **14** was active against *Staph. aureus*, while complexes [Au(2-Hmpa)(PPh_3)] **(10)** and [Au(4-Hmba)(PPh_3)]·0.3$(CH_3)_2$CO **(17)** showed only modest activities against *B. subtilis*. No activity against the investigated strains of bacteria, yeasts *Ca. albicans* and *Saccharomyces cerevisiae* (*Sacch. cerevisiae*) and molds *A. niger* and *Penicillium citrinum* (*Pen. citrinum*) was found for [Au(2-Hmba)(PPh_3)] **(15)** and [Au(3-Hmba)(PPh_3)] **(16)** complexes,[15] as well as for different phosphine gold(I) complexes containing monoanionic thiourea ligands (against bacteria *B. subtilis*, *Esch. coli* and *Ps. aeruginosa*, as well as fungi *Ca. albicans*, *Trichophyton mentagrophytes* (*T. mentagrophytes*) and *Cladosporium resinae* (*Cl. resinae*).[16] Moreover, like most of the abovementioned gold(I) complexes, (aminophosphane)gold(I) thiolate complexes were more effective against Gram-positive *Ent. faecalis* and *Staph. aureus* than against Gram-negative bacteria *Esch. coli*.[17]

The exchange of sulfur-containing ligands in the abovementioned phosphine gold(I) complexes with heterocyclic nitrogen-containing ligands led to the formation of four linear gold(I) complexes, [Au(pz)(PPh_3)] (**18**, Hpz is

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pyrazole), [Au(im)(PPh_3)] (**19**, Him is imidazole), [Au(1,2,3-triz)(PPh_3)] (**20**, Htriz is triazole) and [Au(1,2,4-triz)(PPh_3)]$_2$ (**21**) (Fig. 3a).[18] All these complexes showed selective and high activity against two Gram-positive bacteria *B. subtilis* and *Staph. aureus* and modest activity against yeasts *Ca. albicans* and *Sacch. cerevisiae*. No activity of complexes **18**-**21** was observed toward Gram-negative bacteria *Ps. aeruginosa* and *Esch. coli* and molds *A. niger* and *Pen. citrinum* (Table 1). On the other hand, the coordination of tetrazole (Htetz) to Au(I) resulted in the formation of [Au(tetz)(PPh_3)] complex **22** (Fig. 3a), that had a modest activity only against the investigated Gram-positive bacteria (Table 1).[19]

The [Au(smtz)(PPh_3)] complex **23** (smtz is sulfamethoxazolato anion; Fig. 3a and Table 1) was demonstrated strong activity against Gram-negative *Esch. coli* (MIC = 8.0 μg/mL) and Gram-positive *Staph. aureus* (MIC = 2.0 μg/mL) being much more potent than the polymeric silver(I) complex, [Ag(smtz)]$_n$, and starting smtz ligand.[20]

Essentially consistent with the above results for Au(I)-PPh_3 complexes with sulfur and nitrogen-containing ligands,[15,18] the phosphine gold(I) complexes with oxygen donors (Fig. 3b), [Au(*R,S*-Hpyrrld)(PPh_3)] (complex **24**, H_2pyrrld is 2-pyrrolidone-5-carboxylic acid) and [Au(*R,S*-othf)(PPh_3)] (complex **25**, Hothf is 5-oxo-2-tetrahydrofurancarboxylic acid) were effective exclusively against the investigated Gram-positive bacteria *B. subtilis* and *Staph. aureus*, and poorly active against yeasts *Ca. albicans* and *Sacch. cerevisiae* (Table 1).[21]

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Out of a series of five gold(I) complexes **26**-**30** (Fig. 4a) with alkyl-*bis*(*m*-sulfonated-phenyl) (*m*-$C_6H_4SO_3Na)_2$ and dialkyl-(*m*-sulfonated-phenyl) (*m*-$C_6H_4SO_3Na$) phosphanes (alkyl = n-butyl (^{n}Bu) or cyclopentyl (Cp)), complex **29** turned out to be the most active one against the growth of Gram-positive bacteria *Bacillus cereus* (*B. cereus*) and *Staph. aureus*, one hundred times more active than against Gram-negative ones, *Esch. coli* and *Salmonella typhimurium* (*Sal. typhimurium*).[22] Gram-negative *Esch. coli* was the most sensitive one to the action of **26**, whereas the cyclopentyl group in **28** and **30** increased the activity against *Sal. typhimurium*. Moreover, only complexes **29** and **30** were active against fungi *Sacch. cerevisiae*. Thus, the plasma membrane of the investigated fungi was shown to be an effective barrier for more hydrophilic complexes **26**-**28**, whereas more lipophilic complexes **29** and **30** were able to penetrate the plasma membrane and suppress growth of the yeast.

Antimicrobial activity of gold(I) complexes with diphosphanes, dppe (1,2-*bis*(diphenylphosphano)ethane) and dppy (1,2-*bis*(di-3-pyridylphosphano)ethane) (**31**-**34**, Fig. 4b) has been also evaluated.[23] The obtained results showed that complex **31** was inactive against all investigated bacteria and a yeast species at a concentration of 100 μg/mL, while its dppy analogue **32** was active against both Gram-positive and Gram-negative strains at the same concentration (Table 1). Complexes **33** and **34**, having a mesityl ligand, were found to be inactive toward Gram-negative bacteria at concentrations of 100 μg/mL or lower, and only **33** was active against Gram-positive *Staph. aureus* with the MIC value being 10 μg/mL (Table 1).

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Interestingly, the reactions of complexes **33** and **34** with silver(I), leading to the formation of heterometallic Au_2Ag clusters, resulted in greater antibacterial potency against both Gram-positive and Gram-negative bacteria.

Regarding tetrahedral gold(I) complexes, [Au(*cis*-$Ph_2P(CH=CH)PPh_2)_2$]Cl (**35**) and [Au($Ph_2P(CH_2)_3PPh_2)_2$]Cl (**36**) (Fig. 4b), with chelating diphosphine ligands have been reported to manifest modest activities against *Staph. aureus*, and no activity against *Esch. coli* and *Ps. aeruginosa*.[24]

Gold(I) complexes containing N-heterocyclic carbene ligands

N-heterocyclic carbenes (NHC) are neutral two-electron donor ligands with binding ability for both hard and soft metal ions, making them more versatile than phosphines.[25] These ligands interact with metal ions primarily through strong σ-donation, and to a lesser degree through π-backdonation, forming more stable complexes than metal phosphine complexes. Among others, gold complexes with NHC ligands have gained special attention due to their stability toward biologically important thiols,[26] as well as their potential applications in medicine as antiarthritic,[27] antitumor[28,29] and antimicrobial agents.[25]

Antibacterial and antifungal activity of gold(I) complexes having coordinated NHC ligands (complexes **37**-**39**, Fig. 5) has been reported by Özdemir *et al*.[30] It was found that the activity of the investigated gold(I) complexes against bacteria and fungi was strongly dependent on the nature of the substituents on the nitrogen atoms of the corresponding NHC ligand. Thus,

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complexes **37** and **39** were found to inhibit growth of Gram-positive bacteria *Staph. aureus* and *Ent. faecalis* (MIC = 12.5 μg/mL; see Table 2), while having no effect toward Gram-negative bacteria *Esch. coli* and *Ps. aeruginosa* and fungi *Ca. albicans* and *Ca. tropicalis*. On the other hand, the incorporation of a pentamethylbenzyl group as a substituent on nitrogen atoms (complex **38**), resulted only in good antifungal activity (MIC = 12.5 μg/mL; Table 2). Like **37** and **39**, gold(I) complex **40** (Fig. 5) was active against Gram-positive *B. subtilis*, but did not inhibit the growth of Gram-negative *Esch. coli*.[31] It was found that this complex produced over 80% inhibition of *B. subtilis* growth after 12 h incubation at low concentration (IC_{50}[2] and MIC values were 4.0 ± 0.8 μM and 15.0 ± 2.3 μM, respectively).

Among six gold(I) complexes **41**-**46** (Fig. 6a) of the general formula $[Au(NHC)_2]^+$ with 1,3-diorganylimidazolidin-2-ylidenes as ligands, complex **42** was highly active against Gram-negative *Ps. aeruginosa* (MIC = 3.12 μg/mL; see Table 2), while complex **43** inhibited the growth of Gram-negative *E. coli* (MIC = 3.12 μg/mL; Table 2).[26] As it can be seen (Fig. 6a and Table 2), the variation of the *para* substituent on the *N*-benzyl group resulted in a significant difference in the antimicrobial activity of these gold(I) complexes. Thus, complex **42** was active against all investigated bacteria, while, on the other hand, complex **44** was almost completely inactive.

The coordination of *bis*(imino)acenaphthene-supported *N*-heterocyclic carbene ligand to Au(I) ion led to the formation of complexes **47** and **48** (Fig. 6b), having modest activity against Gram-positive bacteria (MIC = 630 μg/mL

[2] The half-maximal inhibitory concentration

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against *Staph. aureus*; Table 2).[32] At variance with this, chlorido[2,6-*bis*(1-methylimidazol)pyrazine]gold(I) manifested more potent antimicrobial activity than several conventionally used antibiotics.[33] This complex inhibited biofilm formation by Gram-positive bacteria *Streptococcus mutans* (*Strept. mutans*) and Gram-negative bacteria *Esch. coli* causing damage of the bacterial cell wall and increasing membrane permeability.

Furthermore, $[Au(NHC)_2][AuCl_2]$-type complexes **49-54** (Fig 7; NHC = *N,N'*-dialkylbenzimidazol-2-ylidene) exhibited antimicrobial activity when tested against bacteria and fungi at concentrations of 12.5-400.0 μg/mL (Table 2).[34] Among these complexes, **50** and **51** were effective in inhibiting the growth of all investigated strains (MICs were between 12.5 and 100.0 μg/mL), being particularly active against Gram-positive strains *Staph. aureus* and *Ent. faecalis* and fungi *Ca. albicans* and *Ca. tropicalis*.

Various other gold(I) complexes

Various other gold(I) complexes, which cannot be classified into the above described groups, showed promising antibacterial and antifungal activity. Some relevant examples are reported below.

Polymeric gold(I) complex in which *N*-acetyl-L-cysteine is coordinated to Au(I) ion through the sulfur atom, was found to be effective against Gram-positive *Staph. aureus* and Gram-negative *Esch. coli* bacteria, being comparable to the standard antibiotics, oxacilin, gentamycin and tetracycline.[35] The activity, similar to that of the latter complex, was also observed for gold(I)

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complex with monodentately coordinated ibuprofen through the oxygen atom of the C=O group,[36] as well as for [Au(CN)(mtz)] complex (mtz is coordinated 2-mercaptothiazoline through the nitrogen atom).[37] Moreover, gold(I) complex with coordinated rimantadine through the nitrogen atom of the amino group, showed promising antibacterial activity, comparable to ofloxacin and imipenem, with MIC values against Gram-positive and Gram-negative bacteria being in the range 6.25-100.00 μg/mL.[38] On the other hand, coordination of D-penicillamine to gold(I) resulted only in modest antibacterial activity against *Esch. coli*.[39]

It is worth noting that some gold(I) complexes showed potent activity against *Mycobacterium tuberculosis* (*M. tuberculosis*), the pathogen responsible for tuberculosis that still remains a leading cause of morbidity and mortality in the developing countries. The initial therapy of tuberculosis with sodium *bis*(thiosulfato)aurate(I) (Sanocrysin) was abandoned, due to the high systemic toxicity of this complex and the lack of a statistically significant antitubercular effect at tolerable doses.[40] On the other hand, cationic gold(I) complexes **55-60** (Fig. 8), containing 1-[2-(acridin-9-ylamino)ethyl]-1,3-dimethylthiourea, manifested considerable potential as relatively nontoxic agents for *M. tuberculosis*.[41] Complexes **55-57**, having +1 charge, showed better selectivity towards *M. tuberculosis* over mammalian cells than +2 charged complexes **58** and **59**, while complex **60** with two acridine moieties, turned out to be inactive toward *M. tuberculosis*. On the basis of DNA binding data, it was found that the investigated gold(I) complexes did not form stable

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adducts with this biomolecule. Furthermore, complex **57** was evaluated *in vivo*, but at a maximum tolerated dose of 300 mg/kg administrated *via* oral gavage, it did not inhibit the growth of *M. tuberculosis*, indicating limited oral bioavailability of this complex. A good antitubercular activity *in vitro* was also observed for gold(I) complexes (Fig. 8) with 6-mercaptopurine (complex **61**)[42] and 2-(2-thienyl)benzothiazole (complex **62**) as ligands.[43]

2.2. Antibacterial and antifungal gold(III) complexes

Although gold(III) complexes have been intensively investigated as potential antitumor agents due to the similarities with platinum(II) complexes,[44-47] there are few reports related to their antibacterial and antifungal activity. The results of these investigations are listed in the following paragraphs, mainly focusing on the organometallic type of gold(III) complexes.

Organometallic gold(III) complexes

All gold(III) complexes described in this section have the same general formula $[AuX_2(L)]$, in which L is a bifunctional ligand that forms a Au–C σ-bond, as well as a coordinate Au–N bond.[11] The two remaining positions at the square planar gold(III) center are usually occupied by two monodentate or one bidentate anion, leading to the formation of neutral complex.

Parish *et al*. have carried out a range of biological tests to evaluate $[AuCl_2(damp)]$ (damp is 2-((dimethylamino)methyl)phenyl; complex **63**) and $[AuCl_2(ppy)]$ (ppy is 2-pyridylphenyl; complex **64**) for antimicrobial activity

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(Fig. 9).[48,49] *In vitro* antimicrobial activity was assessed using a panel of bacteria, *Staph. aureus*, *Ent. faecalis*, *Klebsiella pneumoniae* (*K. pneumoniae*), *Esch. coli* and *Ps. aeruginosa*, and fungi, *Ca. albicans*, *Cryptococcus neoformans* (*Cr. neoformans*), *A. niger* and *Aspergillus fumigatus* (*A. fumigatus*), representing microorganisms of clinical importance. The range between the highest concentration of the complex which allowed the growth and the lowest which inhibited the growth is presented in Table 3. As it can be seen, **63** was a little more active than **64**, but neither was as active as control drugs, ciprofloxacin and amphotericin B, when tested against selected bacteria and fungi, respectively. Also, **63** displayed only marginal selectivity for the microorganisms over mammalian cells, indicating that this complex is not suitable as an antimicrobial chemotherapeutic, rather as an antiseptic or biocide agent due to the broad spectrum of antimicrobial activity.

In order to improve the antimicrobial activity of complex **63**, two chlorido were replaced with acetato ligands, leading to the formation of a water-soluble complex **65** (Fig. 9).[49,50] As it can be seen in Table 3, this complex, like its chlorido analogue, showed a broad spectrum of antimicrobial activity, with some preference towards Gram-positive *Staph. aureus* and *Ent. faecalis* (as mentioned above, this preference was also found for most of the active gold(I) complexes). In contrast with complex **63**, MIC values of **65** against Gram-positive bacteria were an order of magnitude lower than the cytotoxic concentrations against Chinese hamster ovary cells, indicating *in vitro* selectivity for these microorganisms.

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Only moderate activity against bacteria *Esch. coli*, *B. subtilis* and *Ps. aeruginosa* and fungi *Ca. albicans*, *T. mentagrophytes* and *Cl. resinae* was found for gold(III) thiosalicylate complex **66** (Fig. 9).[51] On the other hand, gold(III) complexes **67** and **68** (Fig. 9), containing chelating thiosalicylate and salicylate anions, respectively, showed significantly higher activity against the investigated microorganisms.[51] Also, the substitution of the thiosalicylate ligand in complex **66** with *N,N'*-diaacetylureate anion, leading to the formation of complex **69** (Fig. 9), resulted in higher potency against the same strains of bacteria and fungi.[52]

Gold(III) complexes with catechol and its derivative, as well as with 2-acetamidophenol, have been also evaluated for antibacterial and antifungal activity.[53] Catecholate and acetamidophenolate gold(III) complexes showed high activity against the investigated bacteria *B. subtilis*, *Esch. coli* and *Ps. aeruginosa* and fungi *Ca. albicans*, *T. mentagrophytes* and *Cl. resinae*, with preference toward *B. subtilis* and *Ps. aeruginosa*.

Out of series of organogold(III) complexes containing imidate[54] and *bis*(amidate) ligands,[55] only two complexes **70** and **71** (Fig. 10a) showed significant antimicrobial activity, which was ascribed to the presence of gold metallacycle, as 1,2-diacetamidobenzene ligand was not active against the investigated strains.[55] A broad spectrum of antimicrobial activity was also found for the trimetallic complex **72**, with $\{Pt_2Au(\mu\text{-}S)_2\}^{2+}$ core containing a *C,N*-donor ligand (Fig. 10b).[56]

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Other gold(III) complexes

Among other gold(III) complexes that have been tested for antimicrobial potential, worth noting are gold(III) complexes with dithiocarbamates derived from amino acids (D,L-alanine, D,L-valine, L-valine and D,L-leucine), that exhibited a larger activity against *Streptococcus pneumoniae* (*Strept. pneumoniae*) than the reference antimicrobial agents.[57] Gold(III) complex $[Au(Nor)_2(H_2O)_2]Cl_3$ (Nor is norfloxacin, a drug used for the treatment of bacterial infections of the urinary and respiratory tracts, diarrhoea and conjunctivitis), in which norfloxacin is coordinated to gold(III) in a monodentate fashion through the nitrogen atom of the piperidyl ring, was evaluated against bacteria *B. subtilis*, *Esch. coli* and *Ps. aeruginosa* and fungi *Aspergillus flavus* (*A. flavus*), *Fusarium solani* (*F. solani*) and *Penicillium verrucosum* (*Pen. verrucosum*).[58] For comparison, norfloxacin was also tested against the same strains. On the basis of the obtained results, it was concluded that the coordination of norfloxacin to gold(III) resulted in greater potency only toward the bacterium *Ps. aeruginosa* and the fungus *Pen. verrucosum*.

Remarkable antibacterial and antifungal activity comparable to the standard drugs was found for tetrachloridoaurate(III) complex having protonated thioterpy (4'-(2-thienyl)-2,2':6',2''-terpyridine) as the counter-cation.[59]

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3. Antimalarial activity of gold(I) and gold(III) complexes

Malaria is an infectious disease caused by protozoan parasites of the genus *Plasmodium* and is still a major cause of illness and death in tropical countries.[60] Of the five species that cause malaria (*P. falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi*), the most serious form of the disease is caused by *P. falciparum*. Malaria parasites are transmitted by the bite of an infected female mosquito of the *Anopheles* genus. The World Health Organization estimates that 3.3 billion people were at risk of malaria in 2011, with an approximately 80% of malarial cases and 90% of deaths occurring in the African region.[61]

Several organic compounds have been successfully used in the treatment of malaria, such as quinine, chloroquine, primaquine, amodiaquine, mefloquine and artemisinin.[62] Among them, chloroquine (CQ) represents the most widely used antimalarial drug, which is thought to act against the parasite by accumulating in its acid vesicles and interfering with their function.[63] However, this drug has become less effective, due to emerging and spreading of CQ-resistant *Plasmodium* parasites.[64] In order to overcome CQ resistance and to obtain improved antimalarial agents, the concept of metal-drug synergism has been developed.[64] This concept implies the coordination of previously used organic drugs to different metal ions, resulting in enhanced antimalarial activity. Among numerous metal complexes, gold(I) and gold(III) complexes have gained considerable attention as potential antimalarial agents.

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3.1. Antimalarial gold(I) complexes

Gold(I) complexes with chloroquine and its derivatives

A few gold(I) complexes with chloroquine as ligand have been synthesized, characterized by fast atom bombardment mass spectrometry (FAB-MS), IR and NMR spectroscopy, and evaluated for *in vitro* and *in vivo* antimalarial activity (Table 4).[65,66] The $[Au(CQ)(PPh_3)][PF_6]$ complex **73** (CQ is coordinated through the nitrogen atom of the quinoline ring; Fig. 11a), displayed high *in vitro* activity against two CQ-resistant FcB1 and FcB2 strains of *P. falciparum*, as well as *in vitro* and *in vivo* activity against the rodent malaria parasite *P. berghei*.[65] This complex was found to be considerably more active than CQ diphosphate, showing that the coordination of CQ to Au(I) ion caused a significant enhancement of its efficacy. *In vivo* experiments demonstrated that parasitemia of infected mice was suppressed by 84% after the treatment with complex **73** in comparison with untreated controls, and no toxicity was observed.[65] The proposed mechanism of antimalarial action of complex **73** against CQ-resistant strains of *P. falciparum* was inhibition of *β*-haematin formation.[67] Thus, this complex displayed a greater ability than CQ diphosphate to inhibit *β*-haematin formation both in aqueous medium and near water/n-octanol interfaces, due to the enhanced lipophilicity achieved by introducing a gold-triphenylphosphine fragment.

In order to investigate whether the nature of the counter-anion or phosphine ligand had an influence on the enhancement of the antimalarial activity of the gold(I) coordinated chloroquine, the following complexes

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$[Au(CQ)(PPh_3)]NO_3$ (**74**), $[Au(CQ)(PMe_3)][PF_6]$ (**75**) and $[Au(CQ)(PEt_3)][PF_6]$ (**76**) (Fig. 11a) were synthesized and evaluated *in vitro* against CQ-sensitive (F32) and CQ-resistant (FcB1, K1 and W1) strains of *P. falciparum* (Table 4).[66] The obtained results showed that complex **74** containing nitrate as the counter-anion was more active than complex **73** against W2 and K1 strains.[66] No significant differences in the activity of complexes **73** and **74** against FcB1 strain were found. Variation of the phosphine substituents had no significant effect on the increase of antimalarial activity, except in the case of $[Au(CQ)(PEt_3)][PF_6]$ complex **76**, which was found to be four and five times more active against FcB1 strain than complex **73** and CQ diphosphate, respectively (Table 4).[66] Furthermore, ^{198}Au(I)-labelled gold chloroquine complex, $[^{198}Au(CQ)(PPh_3)][PF_6]$, has been prepared and examined as a potential antimalarial agent.[68]

The incorporation of ferrocenyl moiety into the aminoalkyl side chain of chloroquine resulted in the formation of a potent CQ analogue named ferroquine (FQ).[69] The *in vitro* activity of FQ against *P. falciparum* was similar to CQ diphosphate for CQ-sensitive strains. However, it showed excellent activity against CQ-resistant strains, both *in vitro* and *in vivo*. Moss *et al.* have synthesized gold(I) complexes of the general formulae $[Au(L)(PPh_3)]NO_3$ and [Au(Ph)(L)], where L is chloroquine, ferroquine, *N*-(7-chloro-quinolin-4-yl)-*N'*-[2-(*N'',N''*-dimethylaminomethyl)ferrocenylmethyl]-ethane-1,2-diamine and 3-benzyl-1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N'',N''*-dimethylaminomethyl)ferrocenylmethyl]urea, and evaluated for *in vitro*

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antimalarial activity against CQ-sensitive D10 and CQ-resistant K1 strain of *P. falciparum*.[70] [Au(Ph)(CQ)] complex **77** (Fig. 11a) showed improved activity against K1 strain in respect to CQ, and comparable activity to CQ against D10 strain of *P. falciparum* (Table 4). Among all gold(I) complexes with coordinated ferrocenyl ligands, [Au(Ph)(FQ)] complex **78** was the most effective one (Fig. 11b and Table 4). On the other hand, gold(I) complexes, obtained in the reactions of ruthenocenyl and ferrocenyl phosphine ligands with two equivalents of chlorido(tetrahydrothiophene)gold(I), turned out not to be good candidates for CQ-resistant malaria parasites, due to the fact that their IC_{50} values were much higher than that for chloroquine.[71]

Gold(I) complexes with N-heterocyclic carbene ligands

Gold(I) complex, formed in the reactions of ylideneamine functionalised heterocyclic ligand with [Au(NO_3)(1,3-^{t}BuIm-2-ylidene)], was found to be much less active than CQ against 3D7 strain.[72] Similarly, among few dinuclear gold(I) complexes containing *bis*(*N*-heterocyclic carbene) ligands, only complex **79** (Fig. 12a) manifested moderate antiplasmodial activity with IC_{50} value being 15 μM, when tested against the CQ-resistant *P. falciparum* strain FcM29-Cameroon, but considerably lower than CQ (IC_{50} = 0.445 μM).[73] Other investigated gold(I) complexes with coordinated *bis*(*N*-heterocyclic carbene) ligands showed no activity with IC_{50} values higher than 39 μM. In contrast with these results, mononuclear gold(I) complexes containing nitrogen heterocyclic functionalised arms, namely quinoline (complex **80**) and bipyridine (complex

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81) moieties (Fig. 12a) displayed significantly better antiplasmodial activity with IC_{50} values of 1.1 and 0.33 μM, respectively.[73]

Gold(I) complexes containing functionalised alkynes

Only low activity against 3D7 CQ-sensitive and K1 CQ-resistant strains of malaria parasite was found for gold(I) complexes, obtained in the reactions of [AuCl(PPh_3)] with propargyl ethers 7-chloro-(4-propargyloxy)quinoline, 1-propargyloxynaphthlene and 2-propargyloxybenzophenone in the presence of potassium hydroxide.[74] IC_{50} values of the investigated complexes were in the range of 7.2-14.8 μM against 3D7 and 14.8-23.6 μM against K1 strain, in comparison with IC_{50} value of 0.01 and 0.3 μM, respectively, determined for chloroquine. The low activity of these complexes was ascribed to the presence of considerably strong gold-carbon bond, which prevented hydrolysis under physiological conditions.

Gold(I) complexes containing thiosemicarbazonato ligands

The coordination of the thiosemicarbazones to gold(I) ion resulted in enhanced efficacy of the starting ligands against the malaria parasite.[75,76] However, the activity of the obtained gold(I) complexes was less or similar to chloroquine. Only gold(I) complex **82** (Fig. 12b), containing thiosemicarbazonato and triphenylphosphino ligands, showed slightly higher activity against 3D7 CQ-sensitive strain of *P. falciparum* (IC_{50} = 7.06 nM) than CQ (IC_{50} = 8.84 nM).[76] The exchange of thiosemicarbazonato with selenosemicarbazonato ligands

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resulted in moderate activity of the formed gold(I) complexes against 3D7 strain.[76]

Other gold(I) complexes

The antimalarial effects of auranofin (complex **8**, Fig. 1) and complexes presented in Fig. 12c, sodium aurothiomalate (complex **83**; Myochrysine), $[AuCl(PEt_3)]$ (**84**), $K[Au(sac)_2]$ (complex **85**; sac is saccharinate ligand) and [Au(sac)(tpa)] (complex **86**; tpa is 1,3,5-triaza-7-phosphaadamantane), were tested *in vitro* against CQ-sensitive 3D7 strain of *P. falciparum* (Table 4).[77,78] As it can be seen in Table 4, the antiarthritic gold(I) drug auranofin caused a strong and nearly complete inhibition of *P. falciparum* growth with IC_{50} value of 0.142 μM.[77] The complex **84** was approximately 15 times less active than auranofin (IC_{50} value of 2.1 μM), while **83** displayed far less significant antiplasmodial activity with IC_{50} values being 168 μM (Table 4).[77] Furthermore, auranofin manifested an additive antimalarial effect when used against 3D7 strain in combination with one of the most potent antimalarial drugs, artemisinin. The observed antiplasmodial effects were ascribed to the direct inhibition of *P. falciparum* thioredoxin reductase.[77] Moreover, it was found that auranofin, as well as complexes **85** and **86**, caused significant, but reversible inhibition of Falcipain 2 (Fp2, a cysteine protease from *P. falciparum*) with K_i values in the micromolar range, coordinating to the enzyme active site thiol.[78]

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3.2. Antimalarial gold(III) complexes

Gold(III) complexes with chloroquine

Gold(III) complexes with two well-known antimalarial dugs, amodiaquine and primaquine, were synthesized and screened by an *in vitro* microtechnique for the antimalarial activity.[79] However, no increase in the activity of [$AuCl_3$(amodiaquine)] and [$AuCl_3$(primaquine)] against *P. falciparum* in respect to the corresponding organic drugs was found. On the other hand, gold(III) complexes with chloroquine (Fig. 13a), [$AuCl_2(CQ)_2$]Cl (**87**) and [AuCl(SR)(CQ)(Et_2O)]Cl (**88**; RS^- is 1-thio-*β*-D-glucose-2,3,4,6-tetraacetate), proved to be more active than CQ diphosphate against the resistant K1 strain (Table 4).[66] Additionally, the effect of preincubation of red blood cells in 0.100 mM CQ diphosphate, above described gold(I) complex **73** (Fig. 11a) and presently discussed gold(III) complexes **87** and **88**, during 3 h at 37 ^oC on the *in vitro* reinvasion of the K1 strain of *P. falciparum* was investigated.[66] The obtained results showed that CQ diphosphate and gold(III) complex **87** with coordinated two chloroquine ligands, did not offer any protection against subsequent infection under investigated experimental conditions. However, no parasitemia was found in the red blood cells after preincubation with gold(I) complex **73**. Regarding complex **88,** a lower parasitemia was observed (3.75%) in comparison with CQ diphosphate preincubated cells (5.67%).

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Gold(III) complexes containing N-heterocyclic carbene ligands

Two gold(III) complexes **89** and **90** with coordinated *bis*(*N*-heterocyclic carbene) ligands (Fig. 13b) showed only moderate activity against *P. falciparum* strain FcM29 with IC_{50} values of 9 and 13 μM, respectively, which was significantly lower than the activity of CQ against the same strain (IC_{50} = 0.445 μM).[73]

Gold(III) complexes containing thiosemicarbazonato ligands

The coordination of thiosemicarbazonato ligands to gold(III) ion resulted in the formation of seven complexes **91**-**97** (Fig. 14), which showed lower antimalarial activity against W2 strain in comparison with CQ.[80] However, these complexes, with the exception of **91**, **92** and **97,** had improved antimalarial properties than the corresponding ligands. Also, it was concluded that replacing of the chloro with a bromo substituent on the aromatic ring resulted in improvement of antimalarial activity, while an exchange of the methyl group with an ethyl on the imine carbon atom had no influence on the activity.

Other gold(III) complexes

Mono- and dinuclear gold(III) complexes with coordinated 2,2'-bipyridine ligand (bipy), $[Au(bipy)(OH)_2][PF_6]$ (**98**), $[Au_2(\mu\text{-}O)_2(6\text{-}CH_2CMe_3bipy)_2][PF_6]_2$ (**99**), $[Au_2(\mu\text{-}O)_2(6\text{-}(2,6\text{-}Me_2C_6H_3)bipy)_2][PF_6]_2$ (**100**) and $[Au_2(\mu\text{-}O)_2(6,6'\text{-}diMebipy)_2][PF_6]_2$ (**101**) caused a inhibition of growth of 3D7 strain of *P.*

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falciparum parasite with IC_{50} values in the range of 2.3-12.2 μM,[81] whereas [Au(cyclam)]$(ClO_4)_2Cl$ complex **102** (cyclam is 1,4,8,11-tetraazacyclotetradecane) displayed far less significant antiplasmodial activity against the same strain with IC_{50} value being 439 μM (Fig. 15 and Table 4).[77] Moreover gold(III) complex **101**, as well as [Au(pyoxaz^{iPr})Cl_2][PF_6] (**103**; pyoxaz^{iPr} is 4-isopropyl-2-(pyridine-2-yl)-4,5-dihydrooxazole), [Au(pyoxaz^{Bn})Cl_2][PF_6] (**104**; pyoxaz^{Bn} is 4-benzyl-2-(pyridine-2-yl)-4,5-dihydrooxazole) and [Au(L-*N,N,O*)Cl] (**105**; L is *N*-(1-hydroxy-3-isopropyl-2-yl)pyridine-2-carboxamide) (Fig. 15) were evaluated as possible inhibitors of Falcipain 2 (Fp2).[78] It was found that all investigated gold complexes caused significant, but reversible inhibition of Fp2 enzyme with K_i values in the micromolar range. Enzyme inhibition was ascribed to the reduction of gold(III) to gold(I) leading to the formation of the gold(I)-protein species, in which Au(I) was anchored to the Fp2 active site cysteine. Moreover, gold(III) complexes **103**-**105** were potent inhibitors of *P. falciparum* growth *in vitro* with IC_{50} values falling in the range of 1.33-5.11 μM (Table 4).

4. Antiamoebic activity of gold(I) complexes

Amoebiasis is an infection of the large intestine caused by *Entamoeba histolytica* (*E. histolytica*), a single celled protozoan parasite.[82] It is common in tropical areas of the world where sanitation is poor, allowing food and water supplies to be exposed to faecal contamination. Amoebiasis is one of the leading causes of death from parasitic diseases worldwide, with an estimated

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70000 deaths each year.[83] The most preferred drug for the treatment of amoebiasis is metronidazole ([1-(2-hydroxyethyl)-2-methyl-5-nitro-1*H*-imidazole).[84] However, due to its side-effects (peripheral neuropathy with sensory disturbances) and the emergence of parasite resistance, there is a need for the development of new antiamoebic agents.[85]

Gold(I) complex **106** with metronidazole (Fig. 16a) has been evaluated *in vitro* as the growth inhibitor of *E. histolytica* (HM1:IMSS strain).[85] The IC_{50} value for this complex (0.32 ± 0.04 μM) was found to be 5.6-fold lower than that for metronidazole (1.81 ± 0.01 μM). This indicated that the coordination of metronidazole to gold(I), leading to the formation of complex **106**, resulted in the increased activity against *E. histolytica*. The enhanced activity of the gold(I) complex in respect to the free metronidazole was explained as a consequence of a chelation process, which reduced the polarity of the metal ion, favouring permeation of the complex through the lipid layers of cell membranes.[86] Due to the fact that [$AuCl(PPh_3)$] complex showed significantly lower activity against *E. histolytica* (IC_{50} = 3.19 ± 0.05 μM) than complex **106,** the antiamoebic activity of the complex **106** was ascribed to the presence of coordinated metronidazole ligand.[85]

5. Antileishmanial activity of gold(I) and gold(III) complexes

Leishmaniasis is a disease caused by protozoan parasites that belong to the genus *Leishmania*.[87] There are three main forms of the disease caused by different organisms, namely cutaneous leishmaniasis (Oriental sore),

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mucocutaneous leishmaniasis (Espundia) and the most severe visceral leishmaniasis (Kala-azar). Pentavalent antimony compounds, sodium stibogluconate (Pentostam) and meglumine antimonate (Glucantime) are widely used for the treatment of this disease. However, due to the toxicity of antimony compounds and the emergence of resistant parasites, new drugs have been developed for the treatment of leishmaniasis.[88] Until now, several complexes of rhodium, iridium, platinum and copper have been evaluated and shown excellent antileishmanial activity.[63] On the other hand, gold complexes have been poorly examined against *Leishmania* parasites and the results obtained from these investigations will be presented in the following sections.

5.1. Antileishmanial gold(I) complexes

Dinuclear gold(I) complex **107** (Fig. 16b), with the bioactive pyridine-2-thiol *N*-oxide as coligand, was evaluated *in vitro* against promastigotes of two different species of the genus *Leishmania*, namely *L. mexicana* and *L. braziliensis*.[89] At 1 μM concentration, the complex **107** was found to induce a potent leishmanicidal effect (LD_{50}) against promastigotes of *L. mexicana* after 30 min, while on *L. braziliensis*, at the same concentration, only a leishmanistatic effect (IC_{75}) was observed after 48 h. Similar differential susceptibilities were found for the sodium salt of pyridine-2-thiol *N*-oxide, but using a five-fold higher concentration (5 μM), indicating that the coordination of this ligand to Au(I) significantly improved the activity against *Leishmania* promastigotes. Moreover, this gold(I) complex showed low unspecific

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cytotoxicity on mammalian macrophages, being highly selective to parasites. The mechanism of its action was ascribed to the inhibition of nicotinamide adenine dinucleotide (NADH) fumarate reductase, a kinetoplastid parasite-specific enzyme absent in the host.[89]

In order to verify whether auranofin (complex **8** in Fig. 1) and [AuCl(PEt_3)] (complex **84** in Fig. 12c) might be used as antileishmanial agents, *Colotti et al.* tested their ability to *in vitro* inhibit trypanothione reductase as an important target of *Leishmania* parasites.[90] The strong inhibition of trypanothione reductase was observed for both auranofin and **84** with a K_i of 0.155 and 0.018 μM, respectively. The inhibition constants measured for these two gold(I) complexes were significantly lower than that of Sb(III) (K_i = 1.5 μM)[91] indicating that gold(I) complexes were more effective than antimony(III) *in vitro*. Moreover, both gold(I) complexes induced a dose-dependent antiproliferative effect on promastigotes of *L. infantum* and *L. major*.[90] Auranofin produced a slightly higher activity against both *Leishmania* species (IC_{50} = 9.68 ± 1.02 μM for *L. infantum* and 15.66 ± 1.24 μM for *L. major*) than **84** (IC_{50} = 16.59 ± 1.03 μM for *L. infantum* and 17.48 ± 1.02 μM for *L. major*).

5.2. Antileishmanial gold(III) complexes

Like gold(I), gold(III) complexes have not been intensively examined as potential antileishmanial agents. One of the examples is a gold(III) complex **108**, [Au(dppz)$_2$]Cl_3 (Fig. 16c), containing DNA intercalating dppz ligand (dppz is dipyrido[3,2-a:2',3'-c]phenazine).[92] It was found that this complex

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induced a potent dose-dependent antiproliferative activity toward *L. mexicana* with a MIC value of 3.4 nM and a lethal dose (LD_{26}) of 17 nM after 48 h. The activity of this complex was associated to its interaction with the parasite DNA. On the other hand, cyclometallated gold(III) complex **109** (Fig. 16c) was not effective against promastigotes of *L. major*, *L. mexicana* and *L. donovani*, at a concentration of 10 μM.[93]

6. Antitrypanosomial activity of gold(I) and gold(III) complexes

Trypanosomiasis is a parasitic disease caused by protozoan parasites of the genus *Trypanosoma*.[94] There are two forms of this disease that affect humans. African trypanosomiasis, known as the sleeping sickness, is caused by *T. brucei* and transmitted by the bite of tsetse flies. Four drugs, namely pentamidine, eflornithine, melarsoprol and suramin, have been used for the treatment of African trypanosomiasis, depending on the disease stage and causative pathogen.[94] The other form is the American trypanosomiasis, also known as Chagas disease.[95] The causative agent of Chagas disease is *T. cruzi*, a protozoan parasite, transmitted to humans by reduviid bugs in a stercorarian mode. Treatment of this disease is based on nifurtimox and benznidazole, two nitroheterocyclic drugs, that show significant activity only in the acute phase of the disease and numerous side-effects, such as allergic dermopathy, peripheral polyneuropathy, anorexia, loss of weight, vomiting, nausea and diarrhoea.[64]

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6.1. Antitrypanosomial gold(I) complexes

Coordination of clotrimazole (CTZ) and ketoconazole (KTZ) to gold(I) ion resulted in the formation of $[Au(CTZ)(PPh_3)][PF_6]$ (**110**) and $[Au(KTZ)(PPh_3)][PF_6]$ (**111**) complexes, respectively (Fig. 17a).[96] The effects of these two complexes on the proliferation of *in vitro* cultures of the epimastigotes of *T. cruzi* were evaluated. It was found that both complexes **110** and **111** showed considerably higher activity than the uncoordinated ligands. Thus, at 1 μM concentration of ligands and complexes, no effect was observed for CTZ, while gold(I) complex **110** produced a 66% inhibition. In the case of KTZ, the percentage of inhibition increased from 39% for free ligand to 71% after its coordination to gold(I).

Similar to the above complexes, dinuclear gold(I) complex with the bioactive pyridine-2-thiol *N*-oxide (complex **107** in Fig. 16b) was significantly more active *in vitro* (IC_{50} = 0.09 μM) against Dm28c strain epimastigotes of *T. cruzi* than the reference drug nifurtimox (IC_{50} = 6 μM), as well as the sodium salt of the ligand (IC_{50} = 0.19 μM).[89] As in the case of *Leishmania* species, this complex was found to be a potent inhibitor of NADH fumarate reductase of *T. cruzi*.

6.2. Antitrypanosomial gold(III) complexes

Gold(III) complex with clotrimazole, $[AuCl_3(CTZ)]$ (**112**, Fig. 17b), showed slightly enhanced activity toward the epimastigotes of *T. cruzi* in comparison to the free clotrimazole.[97] Thus, at 10 μM concentration, the coordination of CTZ

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to gold(III) resulted in the increase of the percentage of inhibition growth from 58 to 60%.

The effectiveness of sodium tetrachloridoaurate(III) ($Na[AuCl_4]$) and Au(III) complex with coordinated *tetrakis*(1-methylpyridinium-4-yl)porphyrin (complex **113**, Fig. 17b) to inhibit the growth of *T. brucei brucei* has been studied.[98] While gold(III) porphyrin complex **113** was effective against the parasites above the concentration of 4.8 μM, $[AuCl_4]^-$ was effective against the parasites above 0.2 μM. The higher antitrypanosomial activity of $[AuCl_4]^-$ was attributed to the generation of free radicals, which enhanced its activity toward *T. brucei brucei* parasite compared to the gold(III) porphyrin complex **113**.

In contrast with the above findings, cyclometallated gold(III) complex **109** (Fig. 16c) was ineffective against *T. cruzi*, as the parasites completed the intracellular life cycle within five days, with no signs of toxicity to the host cells.[93]

7. Concluding remarks

This article presents an overview of the results achieved in the studies of antimicrobial activity of gold(I) and gold(III) complexes. From the presented data it can be concluded that, so far, a large number of gold(I) and gold(III) complexes have been tested *in vitro* against a broad spectrum of bacteria, fungi and parasites, while complexes with +1 oxidation state of gold have attracted much more attention. In general, gold(I) complexes having phosphine and *N*-heterocyclic carbene ligands showed relevant antibacterial and antifungal

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activity. Among antibacterial and antifungal gold(III) complexes, the most important ones are those containing bifunctional ligands that form a Au–C σ-bond and a coordinate Au–N bond (organometallic complexes). Regarding antimalarial gold(I) and gold(III) complexes, the best candidates for future biological evaluation are the complexes containing chloroquine and its potent analogue ferroquine as ligands, that display a higher activity than the corresponding antimalarial drugs. Moreover, a few gold complexes offer excellent opportunities for the treatment of other parasitic diseases, such as amoebiasis, leishmaniasis and trypanosomiasis. In spite of numerous data related to *in vitro* investigations, so far only a few gold(I) complexes have been evaluated for *in vivo* activity.

The content of this review article could direct future developments of new gold(I) and gold(III) complexes as potential antimicrobial agents, as an exciting area of research that should be encouraged worldwide.

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Table and Figure Captions

Table 1 Antibacterial and antifungal activity (MIC) of the gold(I) complexes containing phosphine-type ligands, as well as some reference drugs

Table 2 Antibacterial and antifungal activity (MIC) of the gold(I) complexes containing *N*-heterocyclic carbene ligands, as well as some reference drugs

Table 3 In vitro antibacterial and antifungal activity (MIC) of organometallic gold(III) complexes **63-65**[48,50]

Table 4 *In vitro* antimalarial activity (IC_{50}) of some gold(I) and gold(III) complexes against different strains of *P. falciparum*

Fig. 1 Antibacterial and antifungal phosphine gold(I) complexes containing a sulfur atom in the coordination sphere.[12-14]

Fig. 2 Phosphine gold(I) complexes with sulfur-containing ligands such as 2-mercaptopropionic acid (**10**), 6-mercaptonicotinic acid (**11**), 2-mercaptonicotinic acid (**12**), penicillamine (**13, 14**), 2-mercaptobenzoic acid (**15**), 3-mercaptobenzoic acid (**16**) and 4-mercaptobenzoic acid (**17**) showing a different spectrum of antibacterial and antifungal activity.[15]

Fig. 3 Phosphine gold(I) complexes with nitrogen **(a)** and oxygen **(b)** donor ligands showing a different spectrum of antibacterial and antifungal activity.[18-21]

Fig. 4 Gold(I) complexes containing mono- **(a)** and diphosphine **(b)** ligands as potential antibacterial and antifungal agents.[22-24]

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Fig. 5 Antibacterial and antifungal gold(I) complexes having coordinated *N*-heterocyclic carbene ligands.[30,31]

Fig. 6 Gold(I) complexes with 1,3-diorganylimidazolidin-2-ylidenes **(a)** and *bis*(imino)acenaphthene-supported *N*-heterocyclic carbene ligand **(b)** as potential antibacterial and antifungal agents.[26,32]

Fig. 7 Antibacterial and antifungal gold(I) complexes of the general formula $[Au(NHC)_2][AuCl_2]$ (NHC = *N,N'*-dialkylbenzimidazol-2-ylidene).[34]

Fig. 8 Gold(I) complexes with promising activity toward *M. tuberculosis*.[41-43]

Fig. 9 Organometallic gold(III) complexes showing a broad spectrum of antibacterial and antifungal activity.[48-52]

Fig. 10 (a) Organogold(III) complexes with *bis*(amidate) ligands[55] and **(b)** trimetallic complex with $\{Pt_2Au(\mu\text{-}S)_2\}^{2+}$ core containing a *C,N*-donor ligand[56] showing a broad spectrum of antibacterial and antifungal activity.

Fig. 11 Antimalarial gold(I) complexes with chloroquine **(a)** and ferroquine **(b)** as ligands.[66,70]

Fig. 12 Antimalarial gold(I) complexes with *N*-heterocyclic carbenes **(a)**,[73] thiosemicarbazone **(b)**[76] and other type of ligands **(c)**.[77,78]

Fig. 13 Antimalarial gold(III) complexes with chloroquine **(a)**[66] and *N*-heterocyclic carbene ligands **(b)**.[73]

Fig. 14 Gold(III) complexes containing thiosemicarbazonato ligands evaluated as antimalarial agents.[80]

Fig. 15 Gold(III) complexes evaluated as potential antimalarial agents.[77,78,81]

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Fig. 16 Antiamoebic gold(I) complex with metronidazole **(a)**[85] and antileishmanial gold(I) **(b)** and gold(III) **(c)** complexes.[89,92,93]

Fig. 17 (a) Gold(I) complexes with clotrimazole **(110)** and ketoconazole **(111)** and **(b)** gold(III) complexes with clotrimazole **(112)** and *tetrakis*(1-methylpyridinium-4-yl)porphyrin **(113)** showing activity against *Trypanosoma* parasites.[96-98]

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Table 1 Antibacterial and antifungal activity (MIC) of the gold(I) complexes containing phosphine-type ligands, as well as some reference drugs

Compound	MIC (μg/mL)								Ref.
	Gram-positive bacteria		Gram-negative bacteria		Yeasts		Molds		
	Staph. aureus	*B. subtilis*	*Esch. coli*	*Ps. aeruginosa*	*Ca. albicans*	*Sacch. cerevisiae*	*A. niger*	*Pen. citrinum*	
1	0.122		15.63	> 250	7.81		15.63		12
2	1.95		125	250	125		> 250		12
3	125		> 250	> 250	> 250		> 250		12
4	7.81		> 250	> 250	> 250		> 250		12
5	7.81		250	> 250	250		> 250		12
6	0.122		7.81	250	125		31.25		12
7	0.244		15.63	> 250	15.63		31.25		12
8	0.122		31.25	250	> 250		15.6		12
9	0.33			26.4	27.3				13
10	1000	500	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	15
11	500	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	15
12	62.5	62.5	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	15
13	31.3	125	> 1000	> 1000	250	500	> 1000	> 1000	15
14	31.3	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	15
15	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	15
16	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	15
17	> 1000	125	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	15
18	7.9	15.7	> 1000	> 1000	250	500	> 1000	> 1000	18
19	125	125	> 1000	> 1000	500	> 1000	> 1000	> 1000	18
20	7.9	7.9	> 1000	> 1000	250	500	> 1000	> 1000	18
21	7.9	7.9	> 1000	> 1000	31.3	125	> 1000	> 1000	18
22	500	250	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	19

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23	2.0		8.0	256					20
24	62.5	62.5	> 1000	> 1000	500	500	> 1000	> 1000	21
25	31.3	31.3	> 1000	> 1000	125	125	> 1000	> 1000	21
31	> 100		> 100			> 100			23
32	100		100			> 100			23
33	10		*			*			23
34	> 100		> 100			> 100			23
Piperacillin	0.49		0.98	1.95					12
Chloramphenicol	3.90		3.90	> 250					12
Miconazole					15.6		7.8		12

*the complex **33** was insoluble in aqueous solution at concentration above 10 μg/mL.

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Table 2 Antibacterial and antifungal activity (MIC) of the gold(I) complexes containing *N*-heterocyclic carbene ligands, as well as some reference drugs

Compound	MIC (μg/mL)						Ref.
	Staph. aureus	*Ent. faecalis*	*Esch. coli*	*Ps. aeruginosa*	*Ca. albicans*	*Ca. tropicalis*	
37	12.5	12.5	400	400	200	200	30
38	200	200	400	800	12.5	12.5	30
39	12.5	12.5	200	400	200	200	30
41	3.12	800	800	1600	800		26
42	3.12	3.12	1600	3.12	200		26
43	> 1600	> 1600	3.12	> 1600	> 1600		26
44	200	> 1600	200	> 1600	> 1600		26
45	50	800	1600	> 1600	1600		26
46	50	> 1600	400	> 1600	> 1600		26
47	630		630	630			32
48	630		> 20000	10000			32
49	100	100	400	400	100	100	34
50	12.5	12.5	100	50	12.5	12.5	34
51	12.5	25	100	100	12.5	12.5	34
52	50	50	100	100	50	50	34
53	25	100	25	100	25	25	34
54	50	100	50	100	50	50	34
Ampicillin	3.12	1.56	3.12				30, 34
Ciprofloxacin	0.39	0.78	1.56	3.12			30, 34
Fluconazole					3.12	3.12	30, 34

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Table 3 *In vitro* antibacterial and antifungal activity (MIC) of organometallic gold(III) complexes **63-65**[48,50]

Compound	**MIC (µg/mL)**				
	Antibacterial activity				
	Staph. aureus	*Ent. faecalis*	*K. pneumoniae*	*Esch. coli*	*Ps. aeruginosa*
$[AuCl_2(damp)]$ **63**	1.0 – 2.5	1.0 – 2.5	10 – 25	10 – 25	10 – 25
$[AuCl_2(ppy)]$ **64**	1.0 – 2.5	2.5 – 10	25 – 100	25 – 100	25 – 100
$[Au(CH_3COO)_2(damp)]$ **65**	0.25 – 1.0	0.25 – 1.0		2.5 – 10	50 – 100
Ciprofloxacin	< 0.25	1.0 – 2.5	< 0.25	< 0.25	< 0.25
	Antifungal activity				
	Ca. albicans NCFC 3153	*Ca. albicans*	*Cr. neoformans*	*A. niger*	*A. fumigatus*
$[AuCl_2(damp)]$ **63**	10 – 25	25 – 100	25 – 100	10 – 25	2.5 – 10
$[AuCl_2(ppy)]$ **64**	25 – 100	25 – 100	1.0 – 2.5	25 – 100	25 – 100
Amphotericin B	< 0.25	< 0.25	< 0.25	0.25 – 1.0	0.25 – 1.0

damp = 2-((dimethylamino)methyl)phenyl; ppy is 2-pyridylphenyl.

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Table 4 *In vitro* antimalarial activity (IC_{50}) of some gold(I) and gold(III) complexes against different strains of *P. falciparum*

Ligand/Gold complex	IC_{50} x10^{-2} (μM)					Ref.
	Strains of *P. falciparum*					
	FcB1	K1	F32	D10	3D7	
Gold(I) complexes						
CQ diphosphate	5.0	9.1	1.0	2.3	1.0	66,70,74
$[Au(CQ)(PPh_3)][PF_6]$ **73**	4.0	9.9	1.8			66
$[Au(CQ)(PPh_3)]NO_3$ **74**	4.0	5.8	1.0	2.1		66,70
$[Au(CQ)(PMe_3)][PF_6]$ **75**	4.0	9.3	1.7			66
$[Au(CQ)(PEt_3)][PF_6]$ **76**	1.0	9.9	1.3			66
[Au(Ph)(CQ)] **77**		6.1		1.8		70
FQ		0.5		1.6		70
[Au(Ph)(FQ)] **78**		0.4		1.0		70
ART					1.6	77
auranofin **8**					14.2	77
ART/0.05 μM auranofin					1.2	77
ART/0.10 μM auranofin					0.9	77
sodium aurothiomalate **83**					16800	77
$[AuCl(PEt_3)]$ **84**					210	77
$K[Au(sac)_2]$ **85**					482	78
[Au(sac)(tpa)] **86**					516	78
Gold(III) complexes						
$[AuCl_2(CQ)_2]Cl$ **87**		4.3	1.3			66
$[AuCl(SR)(CQ)(Et_2O)]Cl$ **88**		5.4	1.8			66
$[Au(bipy)(OH)_2][PF_6]$ **98**					1220	81
$[Au_2(\mu\text{-}O)_2(6\text{-}CH_2CMe_3bipy)_2][PF_6]_2$ **99**					770	81
$[Au_2(\mu\text{-}O)_2(6\text{-}(2,6\text{-}Me_2C_6H_3)bipy)_2][PF_6]_2$ **100**					420	81
$[Au_2(\mu\text{-}O)_2(6,6'\text{-}diMebipy)_2][PF_6]_2$ **101**					230	81
$[Au(cyclam)](ClO_4)_2Cl$ **102**					43900	77
$[Au(pyoxaz^{iPr})Cl_2][PF_6]$ **103**					511	78
$[Au(pyoxaz^{Bn})Cl_2][PF_6]$ **104**					451	78
[Au(L-*N,N,O*)Cl] **105**					133	78

CQ = chloroquine; FQ = ferroquine; ART = artemisinin; sac = saccharinate; tpa = 1,3,5-triaza-7-phosphaadamantane; cyclam = 1,4,8,11-tetraazacyclotetradecane; bipy = 2,2'-bipyridine; $pyoxaz^{iPr}$ = 4-isopropyl-2-(pyridine-2-yl)-4,5-dihydrooxazole; $pyoxaz^{Bn}$ = 4-benzyl-2-(pyridine-2-yl)-4,5-dihydrooxazole; L = *N*-(1-hydroxy-3-isopropyl-2-yl)pyridine-2-carboxamide.

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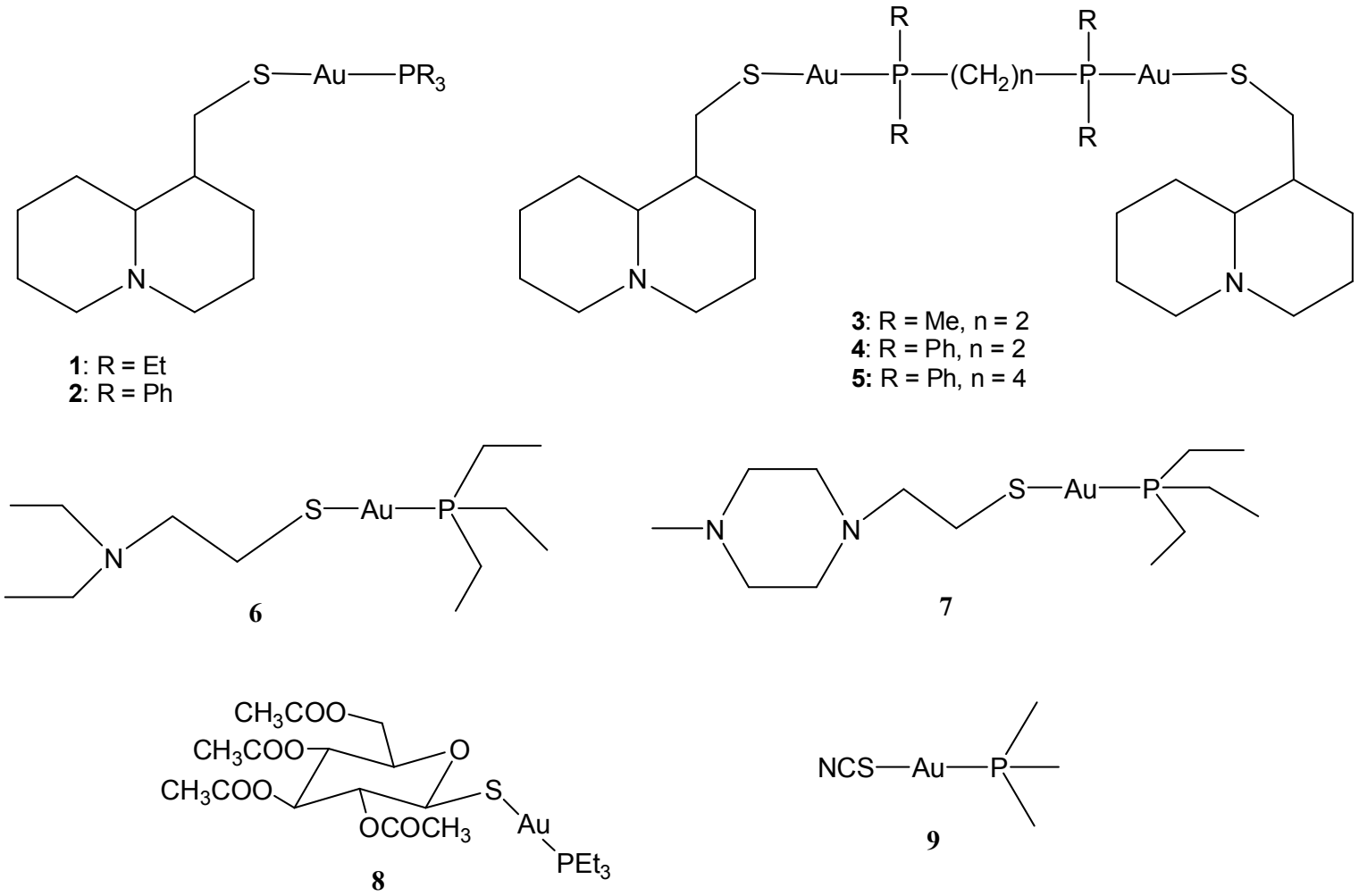

Fig. 1 Antibacterial and antifungal phosphine gold(I) complexes containing a sulfur atom in the coordination sphere.[12-14]

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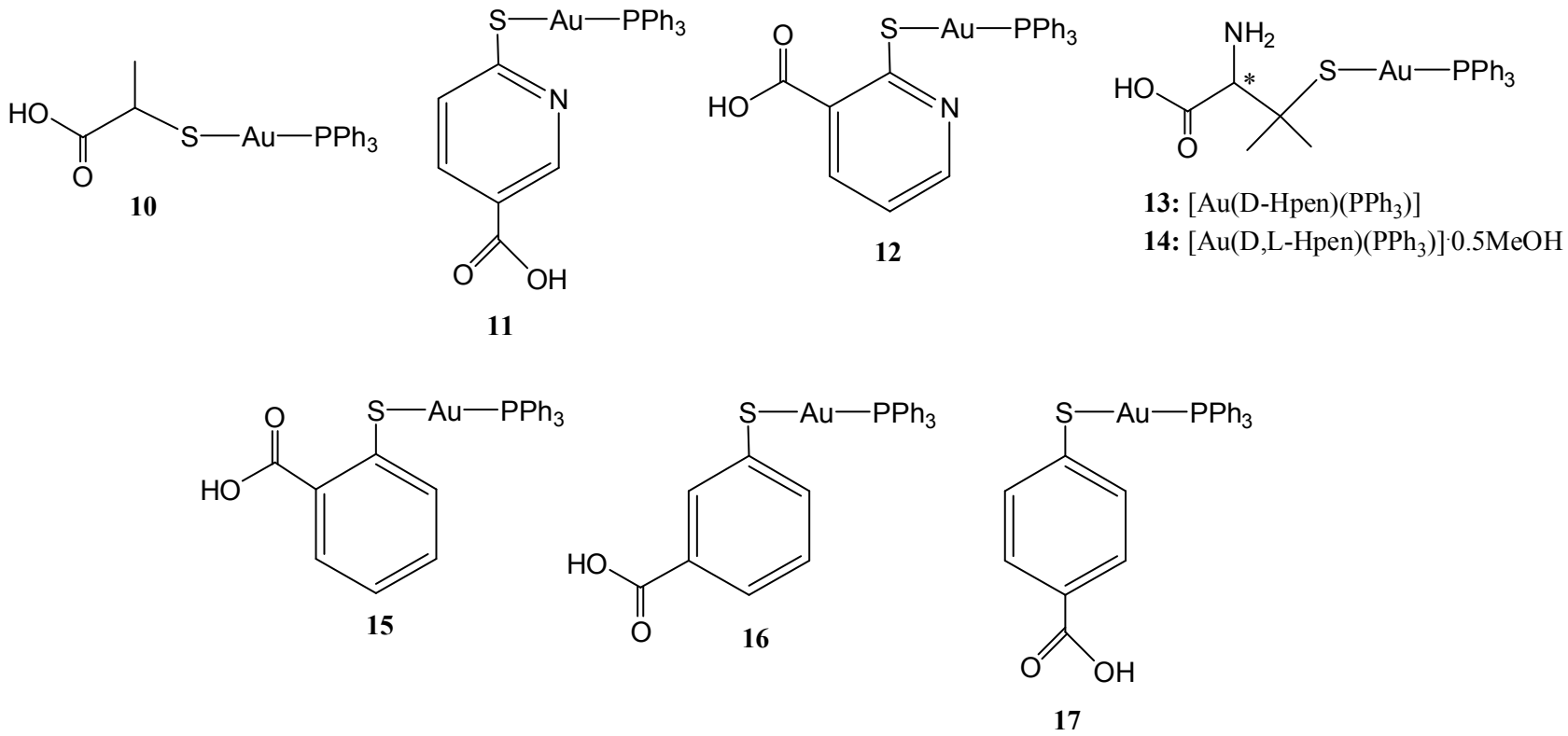

Fig. 2 Phosphine gold(I) complexes with sulfur-containing ligands such as 2-mercaptopropionic acid (**10**), 6-mercaptonicotinic acid (**11**), 2-mercaptonicotinic acid (**12**), penicillamine (**13, 14**), 2-mercaptobenzoic acid (**15**), 3-mercaptobenzoic acid (**16**) and 4-mercaptobenzoic acid (**17**) showing a different spectrum of antibacterial and antifungal activity.[15]

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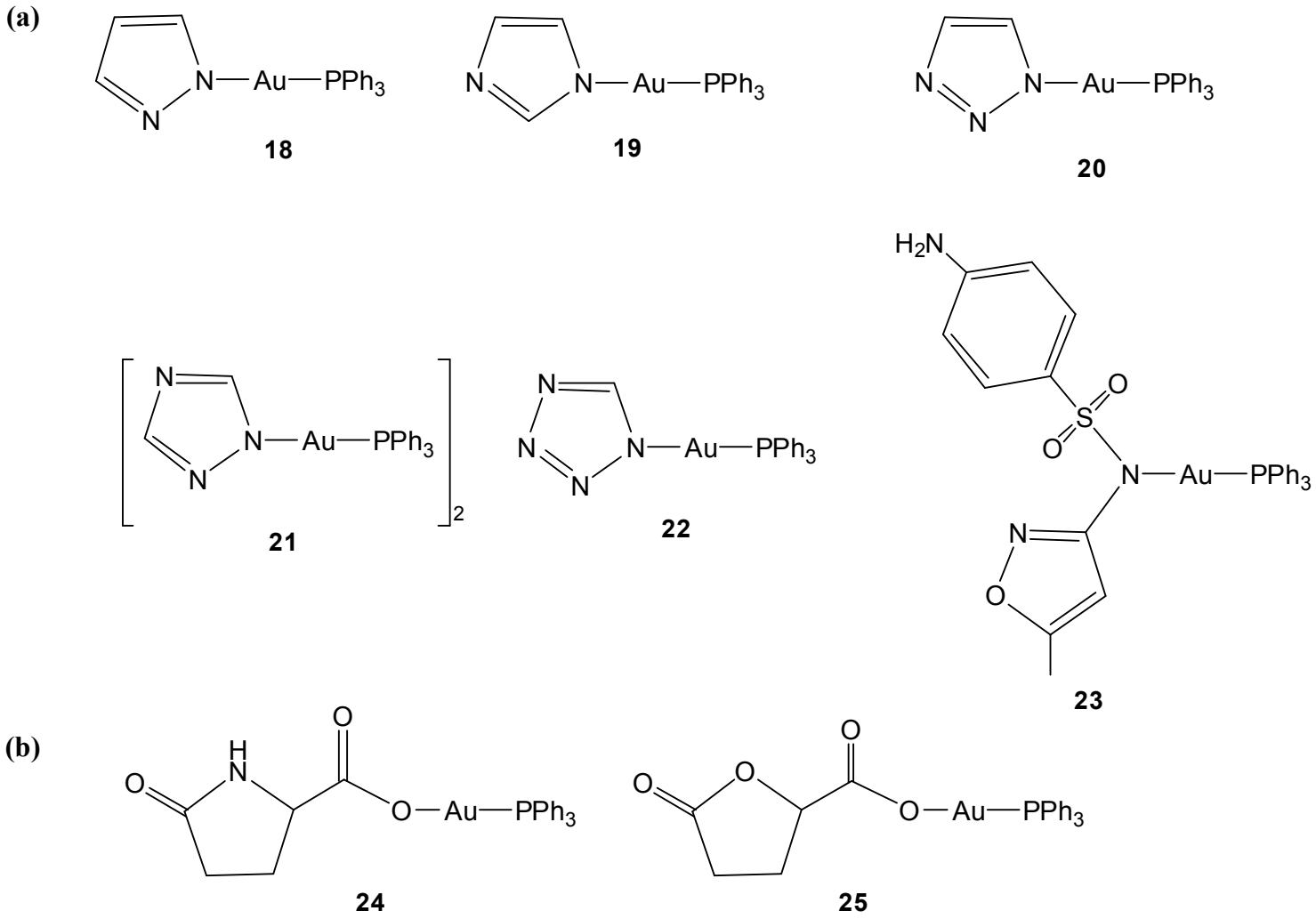

Fig. 3 Phosphine gold(I) complexes with nitrogen **(a)** and oxygen **(b)** donor ligands showing a different spectrum of antibacterial and antifungal activity.[18-21]

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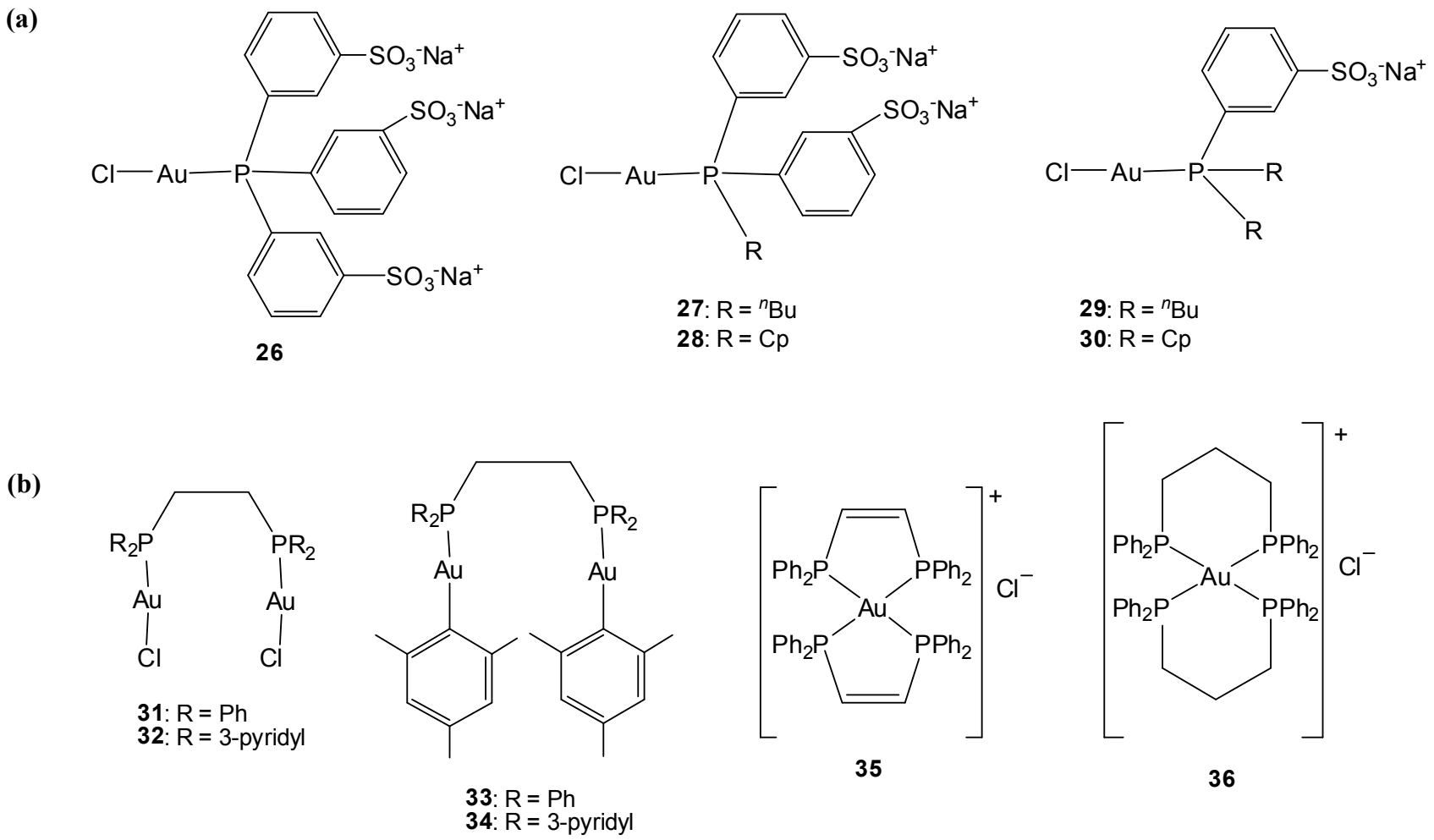

Fig. 4 Gold(I) complexes containing mono- **(a)** and diphosphine **(b)** ligands as potential antibacterial and antifungal agents.[22-24]

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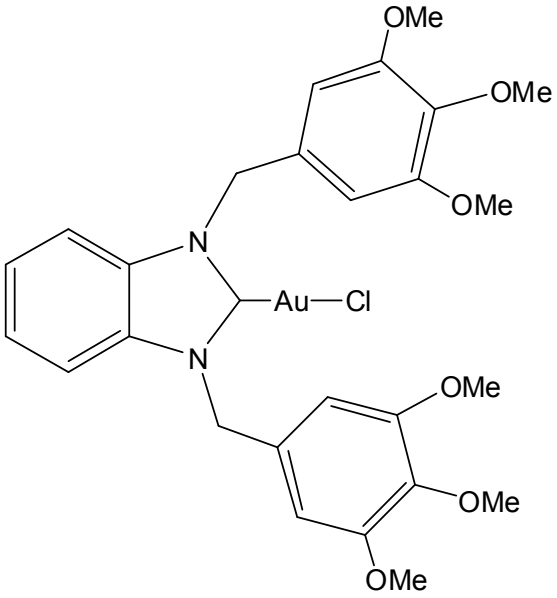

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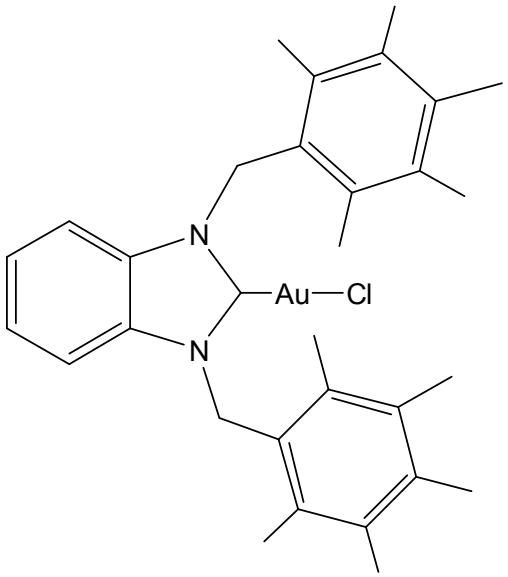

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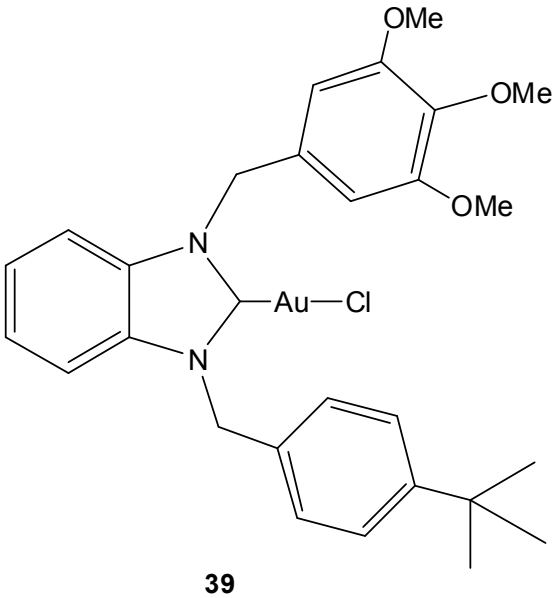

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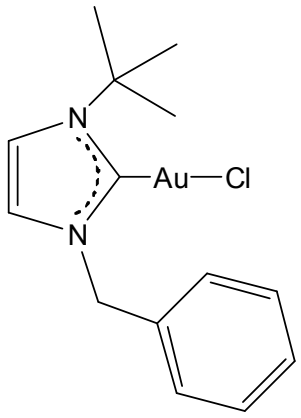

40

Fig. 5 Antibacterial and antifungal gold(I) complexes having coordinated *N*-heterocyclic carbene ligands.[30,31]

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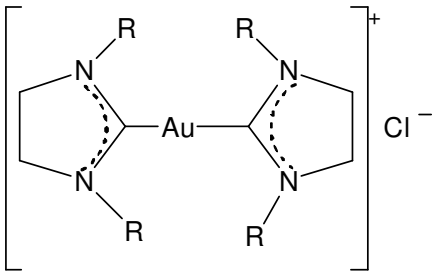
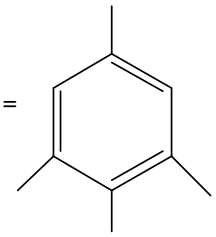
(a)



41-46

41: R =



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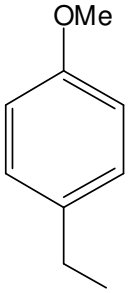
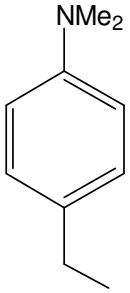
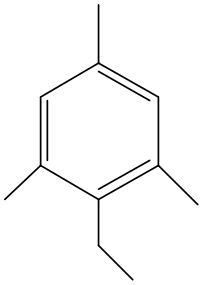


43: R =



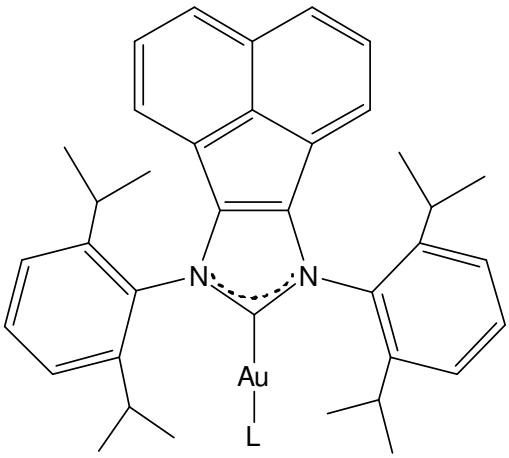
44: R =



45: R =C_5H_9-

46: R =C_2H_5-

(b)



47: L = Cl^-
48: L = AcO^-

Fig. 6 Gold(I) complexes with 1,3-diorganylimidazolidin-2-ylidenes **(a)** and *bis*(imino)acenaphthene-supported *N*-heterocyclic carbene ligand **(b)** as potential antibacterial and antifungal agents.[26,32]

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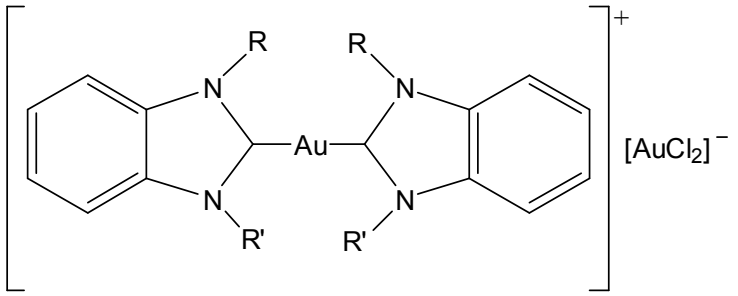


49-54

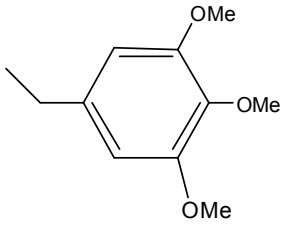
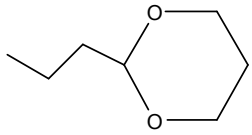
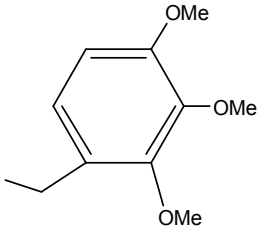
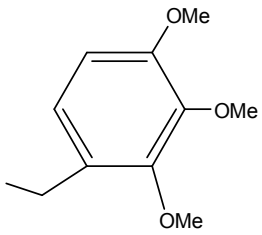
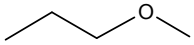
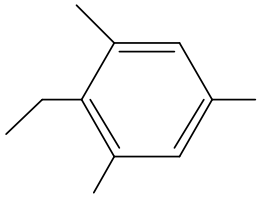
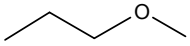
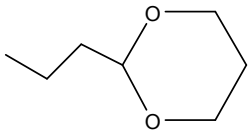
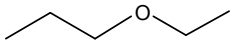
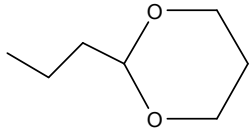
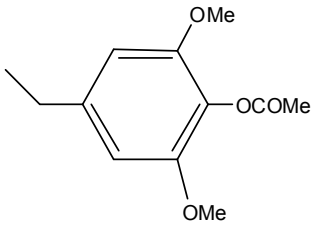
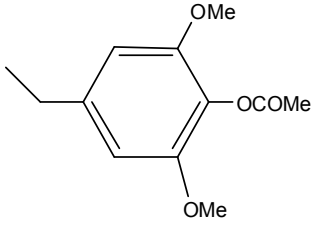
	R	R'
49		
50		
51		
52		
53		
54		

Fig. 7 Antibacterial and antifungal gold(I) complexes of the general formula $[Au(NHC)_2][AuCl_2]$ (NHC = *N,N'*-dialkylbenzimidazol-2-ylidene).[34]

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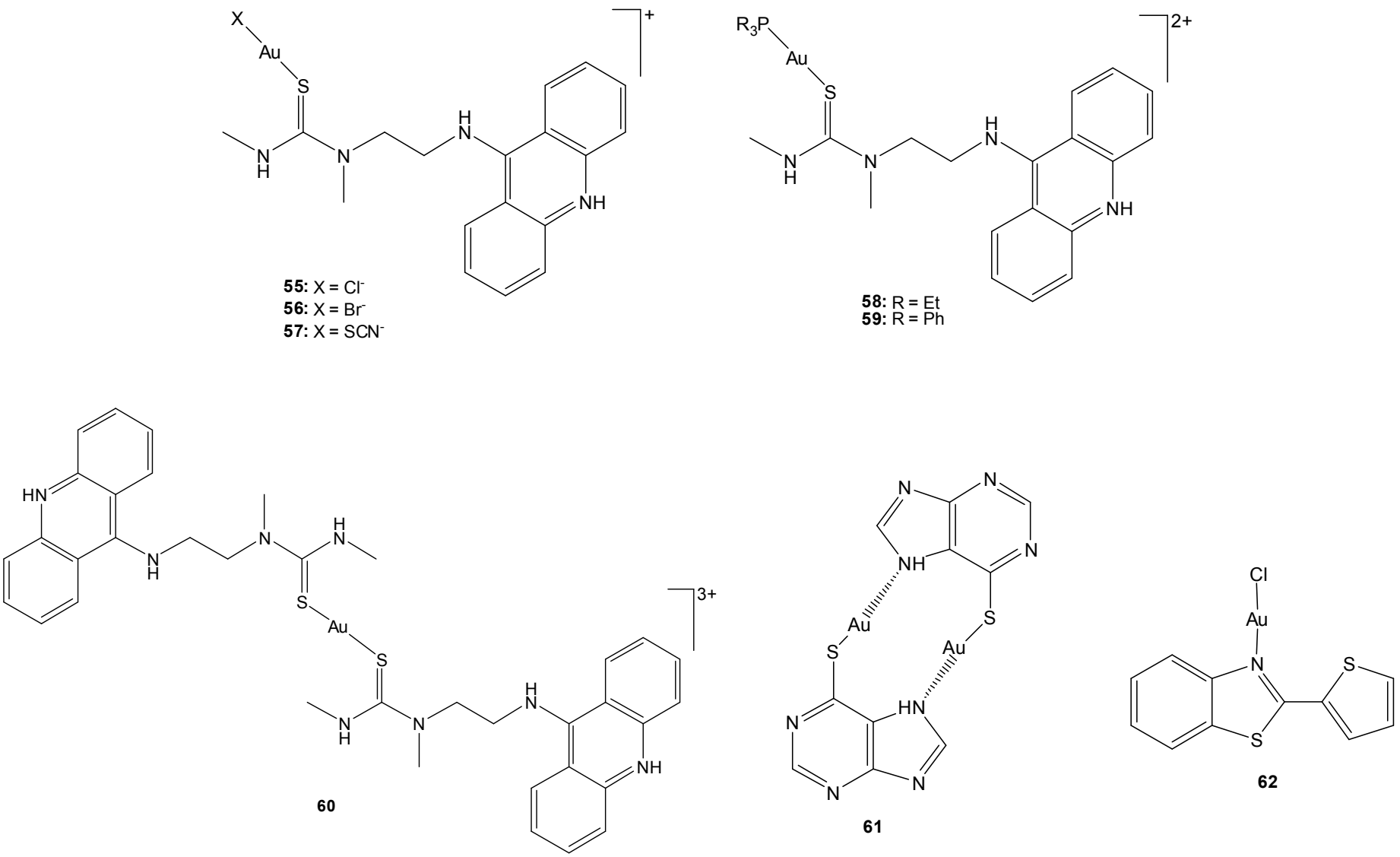

Fig. 8 Gold(I) complexes with promising activity toward *M. tuberculosis*.[41-43]

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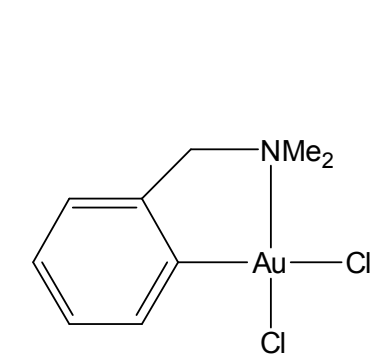

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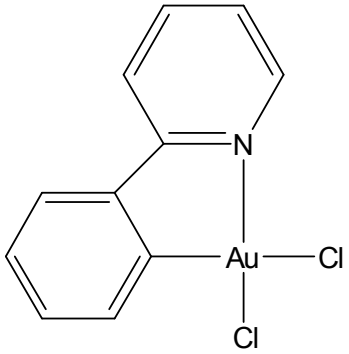

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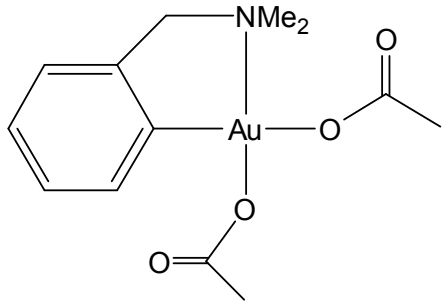

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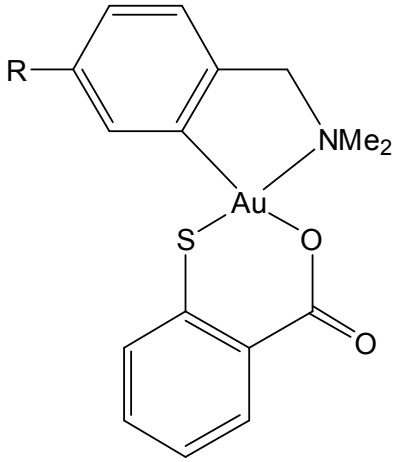
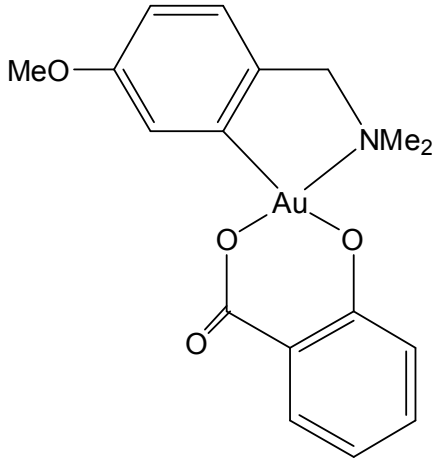


66: R = OMe
67: R = H



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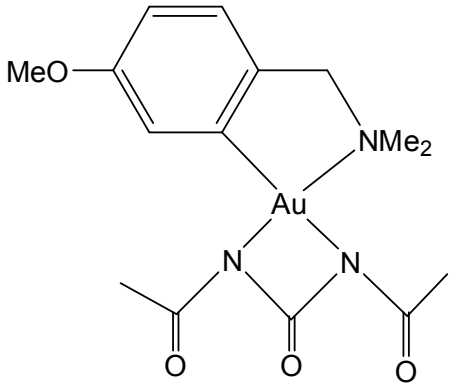

69

Fig. 9 Organometallic gold(III) complexes showing a broad spectrum of antibacterial and antifungal activity.[48-52]

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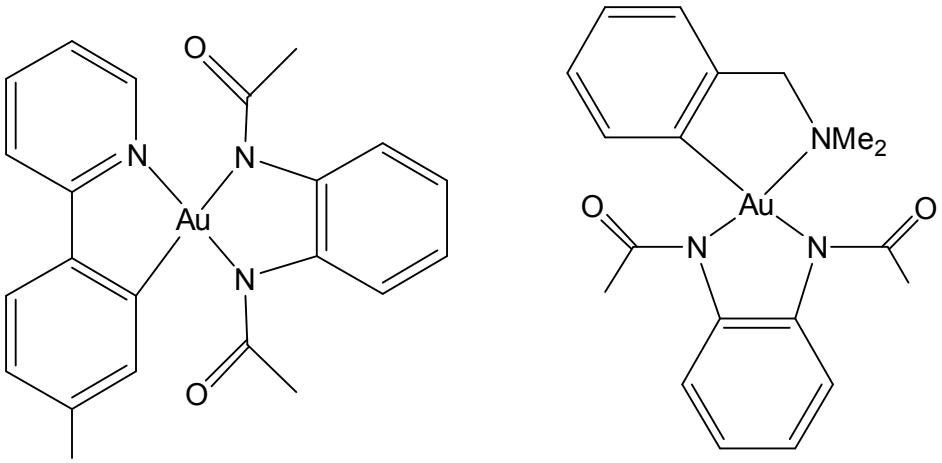
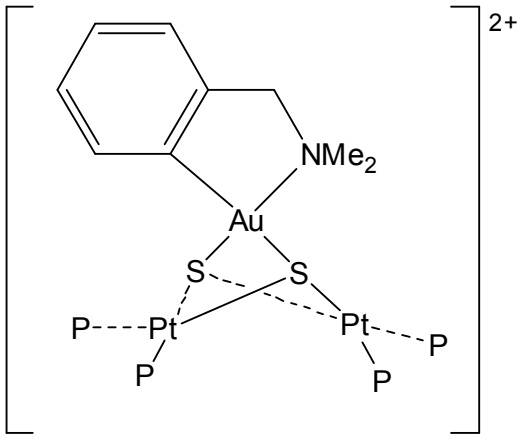
(a)



70 **71**

(b)



72

Fig. 10 (a) Organogold(III) complexes with *bis*(amidate) ligands[55] and **(b)** trimetallic complex with $\{Pt_2Au(\mu\text{-}S)_2\}^{2+}$ core containing a *C,N*-donor ligand[56] showing a broad spectrum of antibacterial and antifungal activity.

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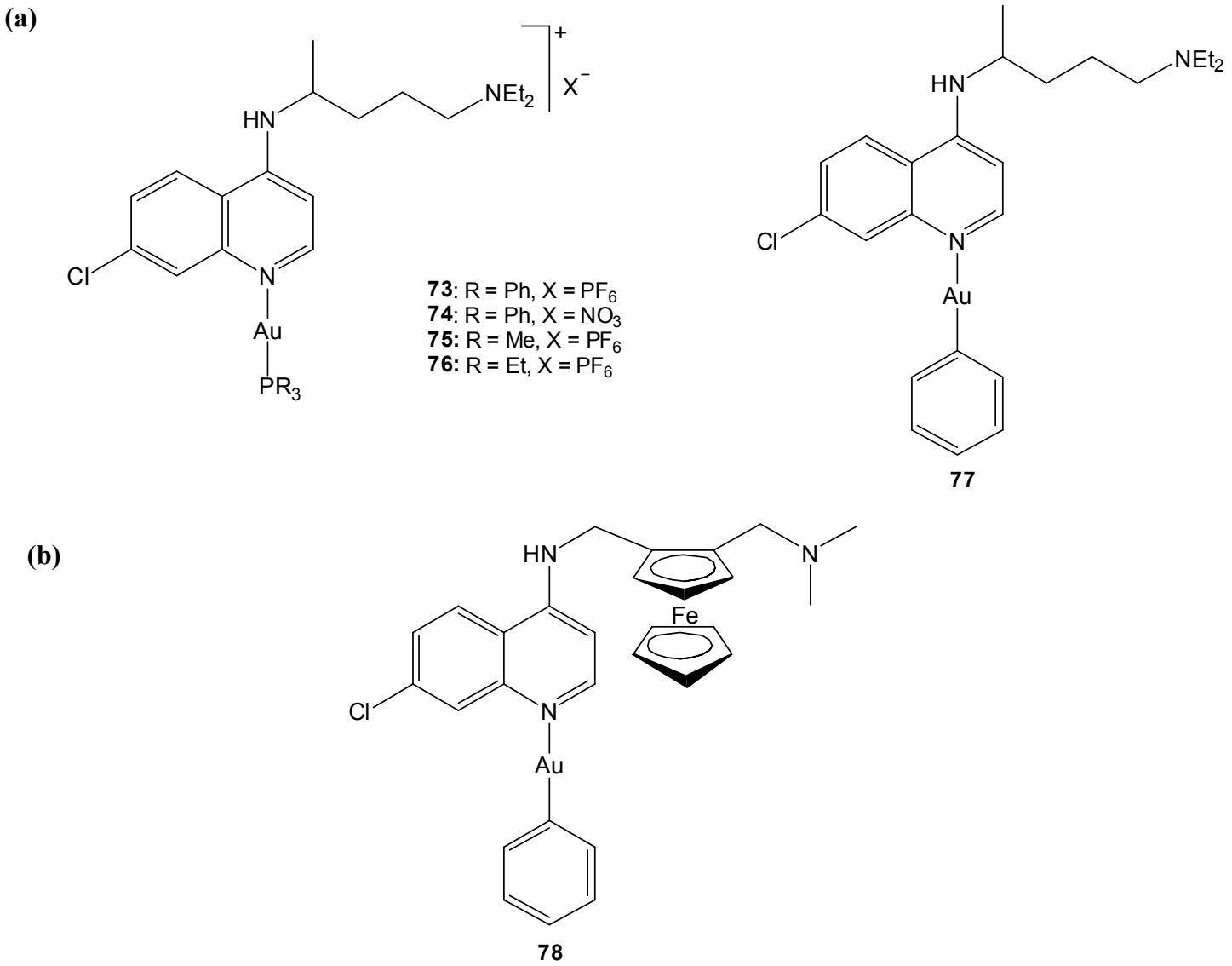

Fig. 11 Antimalarial gold(I) complexes with chloroquine **(a)** and ferroquine **(b)** as ligands.[66,70]

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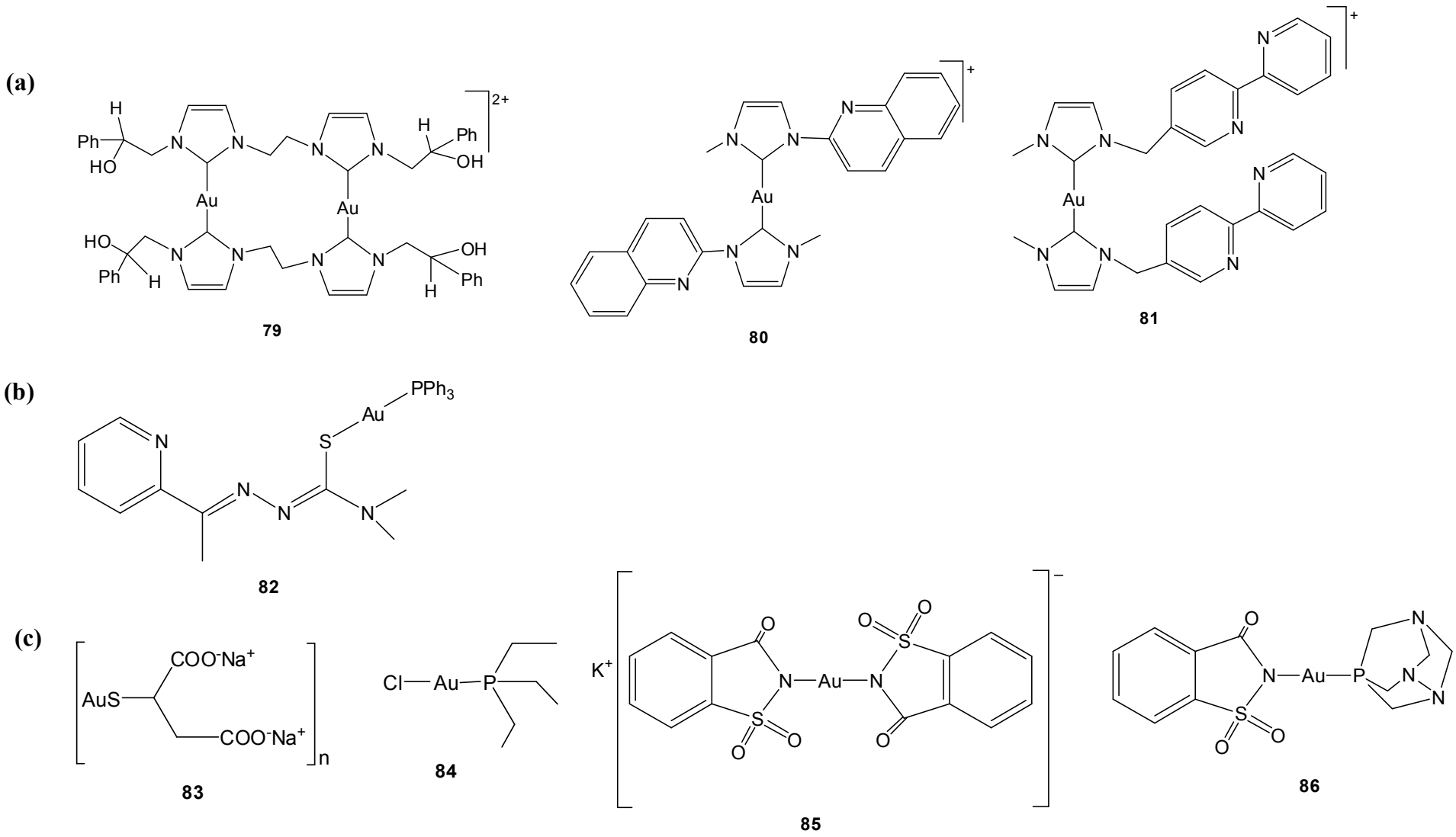

Fig. 12 Antimalarial gold(I) complexes with *N*-heterocyclic carbenes **(a)**,[73] thiosemicarbazone **(b)**[76] and other type of ligands **(c)**.[77,78]

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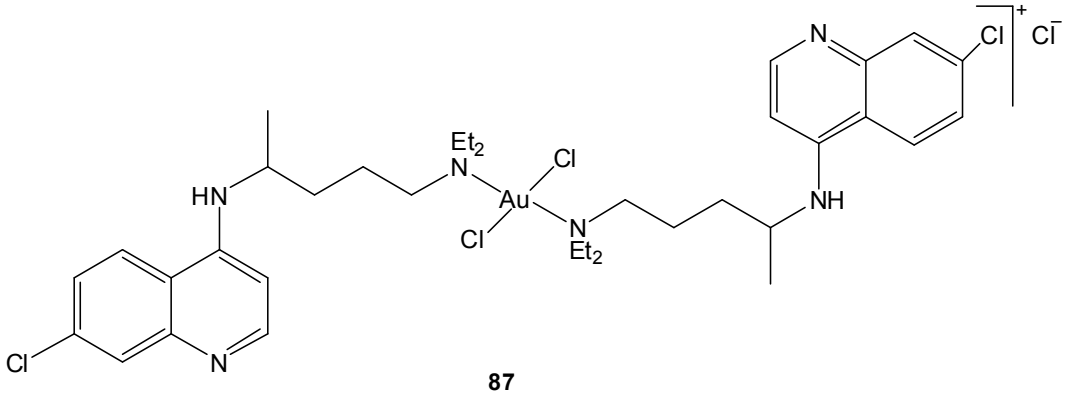
(a)



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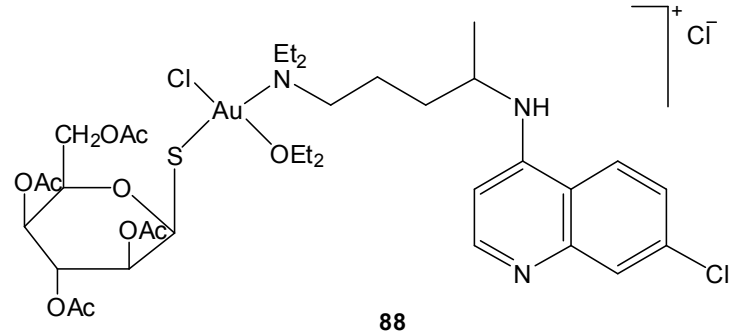

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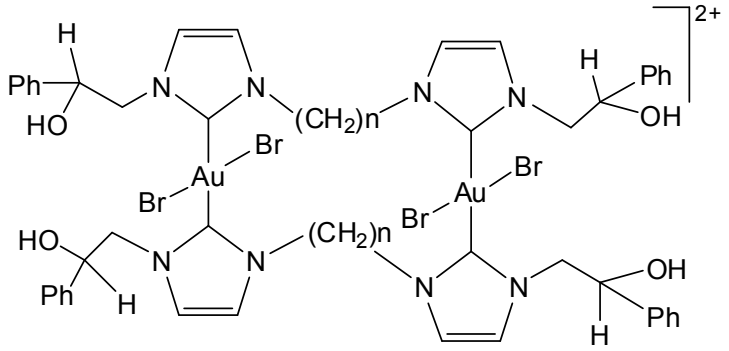
(b)



89: n = 2
90: n = 3

Fig. 13 Antimalarial gold(III) complexes with chloroquine **(a)**[66] and *N*-heterocyclic carbene ligands **(b)**.[73]

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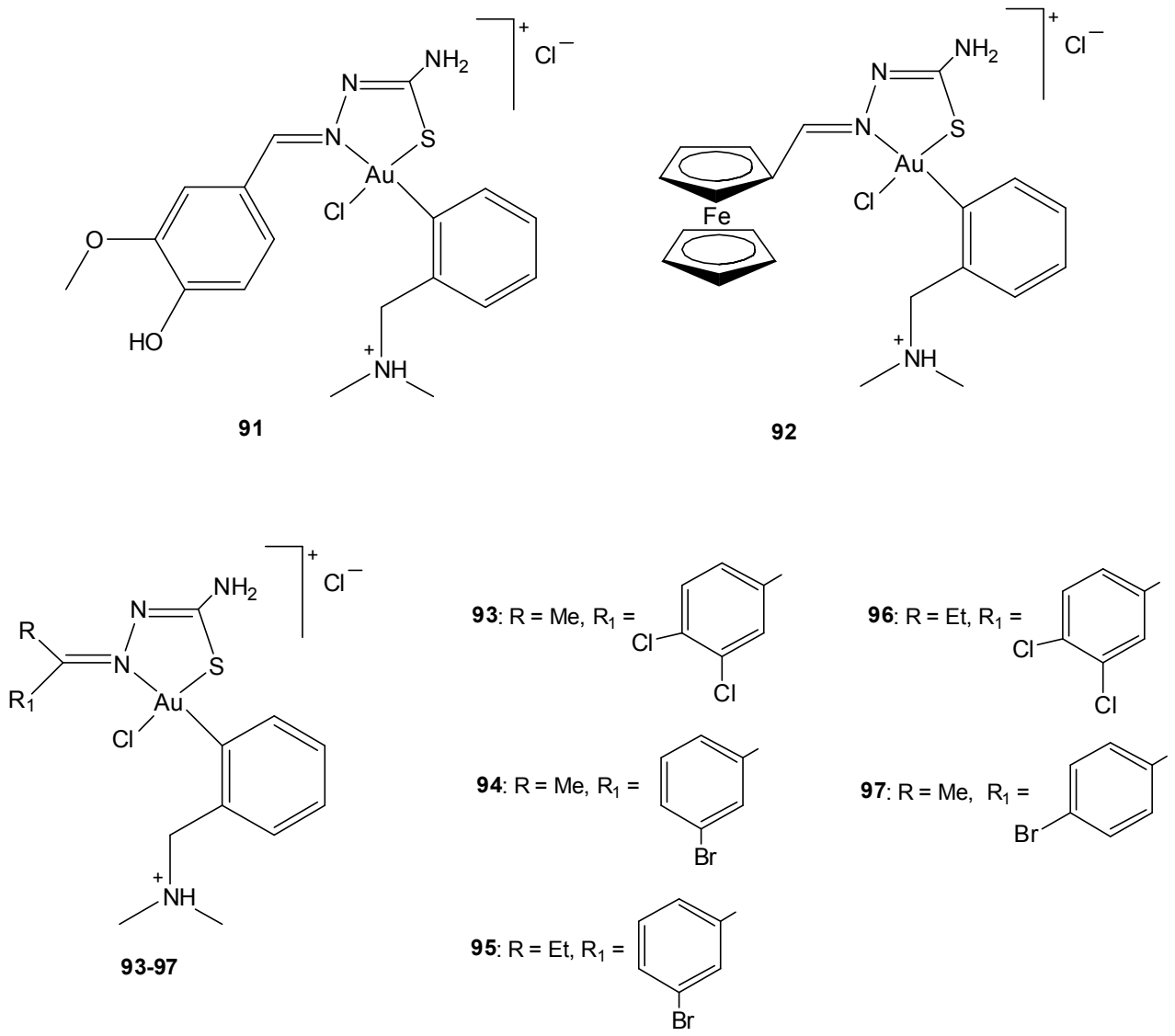

Fig. 14 Gold(III) complexes containing thiosemicarbazonato ligands evaluated as antimalarial agents.[80]

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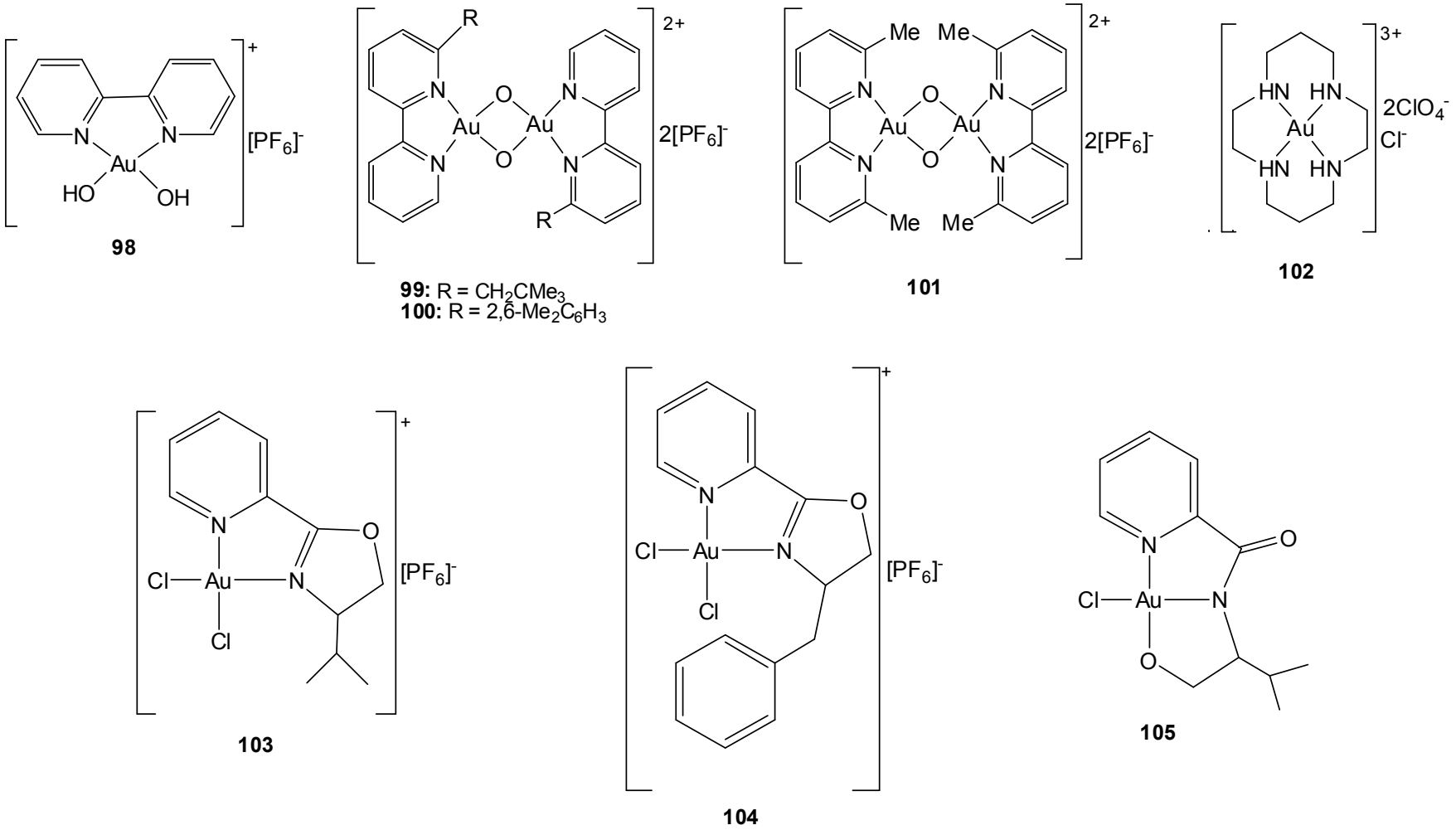

Fig. 15 Gold(III) complexes evaluated as potential antimalarial agents.[77,78,81]

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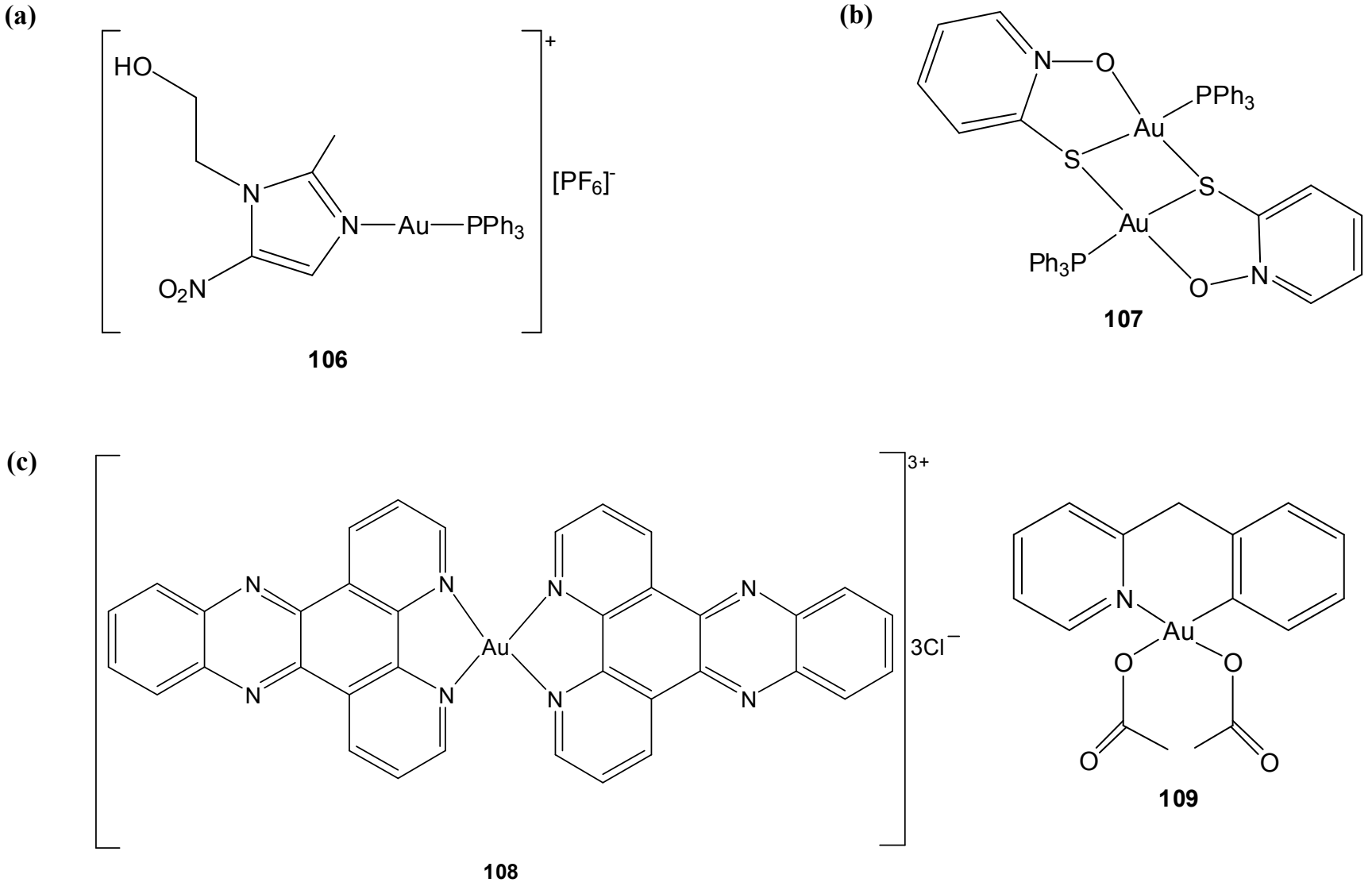

Fig. 16 Antiamoebic gold(I) complex with metronidazole **(a)**[85] and antileishmanial gold(I) **(b)** and gold(III) **(c)** complexes.[89,92,93]

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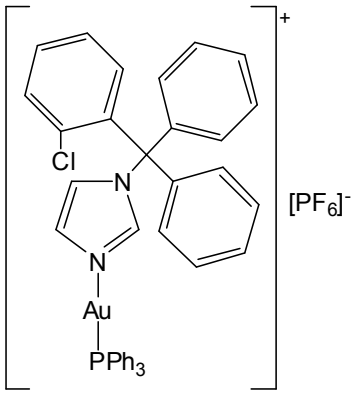
(a)



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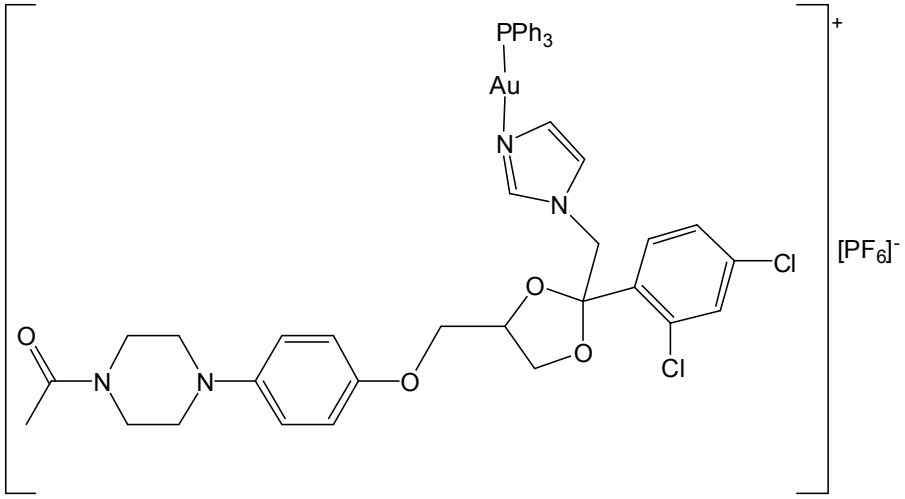

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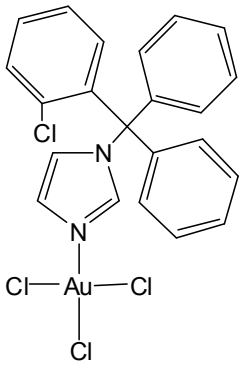
(b)



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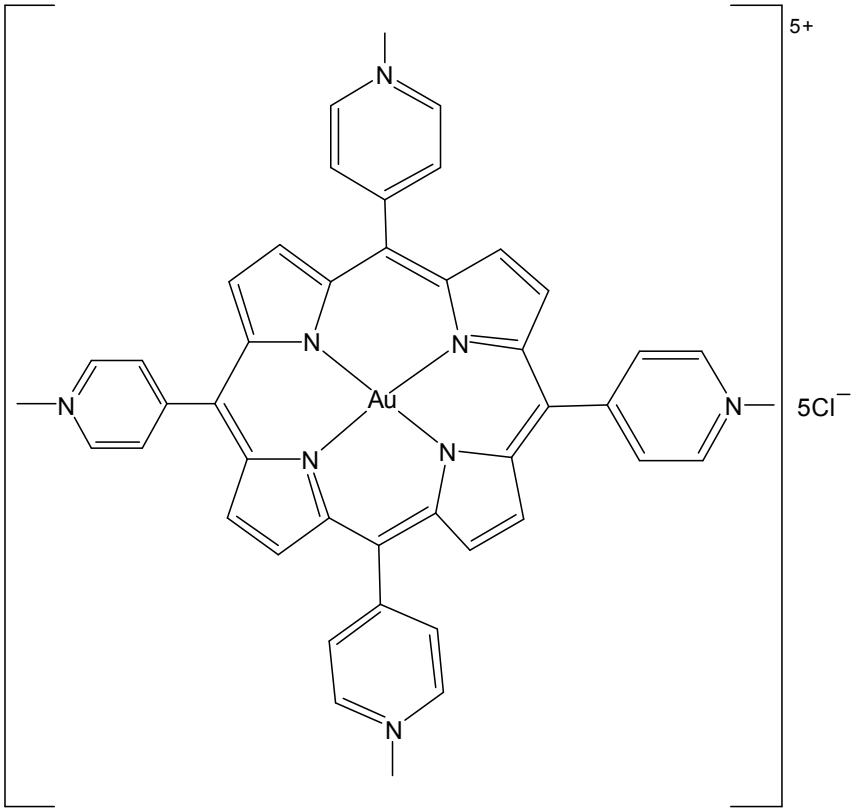

113

Fig. 17 **(a)** Gold(I) complexes with clotrimazole **(110)** and ketoconazole **(111)** and **(b)** gold(III) complexes with clotrimazole **(112)** and *tetrakis*(1-methylpyridinium-4-yl)porphyrin **(113)** showing activity against *Trypanosoma* parasites.[96-98]

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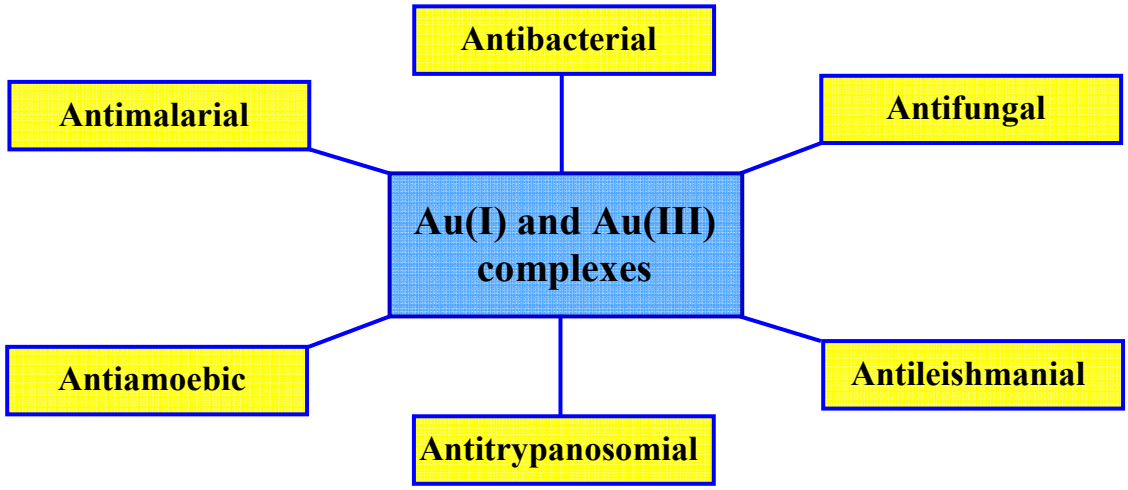
Manuscript ID **DT-PER-01-2014-000022** (revised version)

Graphical contents entry

Gold complexes as antimicrobial agents: an overview of different biological activities in relation to the oxidation state of gold ion and ligand structure

Biljana Đ. Glišić and Miloš I. Djuran



A survey of the results achieved in the field of gold(I) and gold(III) complexes as potential antimicrobial agents.

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