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Review

Gold complexes as potential anti-parasitic agents

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ABSTRACT

The medical uses of gold have a long history; rheumatoid arthritis is currently treated with gold-based drugs and there is increasing interest in the application of gold complexes as potential anticancer agents. However, the potential use of gold derivatives as drugs against parasitic diseases, also called neglected diseases, has so far been very little explored. This review focuses on recent advances in developing gold anti-parasitic agents and new uses of existing gold drugs against these old ailments, with emphasis on the major tropical diseases, malaria, leishmaniasis, trypanosomiasis and schistosomiasis. These illnesses afflict millions of people around the world with very limited therapeutic options for their treatment.

1. Introduction

Nowadays, compounds of gold and platinum are being used as pharmaceutical drugs. Although their medical applications are the result of serendipitous discoveries, advances in the rational design of metal-based therapeutic agents have become an increasingly important research effort towards the development of new compounds with less toxic side effects and with an understanding of their mechanisms of action [1–5].

Arguably medicinal inorganic chemistry research has been more focused in the development of drugs for cancer due to the important discovery of cisplatin (Fig. 1), and its second and third generation analogues, developed to make better pharmaceutical agents. More recently, there has been intense interest in the potential use of compounds of other metals, such as ruthenium and titanium complexes, as anti-tumor drugs. Several excellent and encouraging reviews in this field have already appeared [6–15].

Gold complexes have also attracted considerable attention as anti-tumor agents [16–19]. A number of gold (I) complexes have shown potent *in vitro* and *in vivo* cytotoxic activity [20–24]. Gold (III) complexes, isoelectronic and isostructural with platinum (II) appear as potential candidates as anticancer agents [25–27]. There is evidence that the cytotoxic effects of a range of gold (I) and gold (III) complexes are related to the inhibition of mitochondrial thioredoxin reductase and mitochondrial function [28–30].

The modern medical applications of gold complexes stem from 1890 with the discovery of $[KAu(CN)_2]$ as a bacteriostatic agent on the tubercle bacillus. Subsequently, gold compounds were used in the treatment of tuberculosis in the 1920s without providing an effective therapy. However, in 1935 reports appeared that gold salts reduce inflammation especially related to rheumatoid arthritis [31]. After that, gold drugs entered into the clinic to treat this disease and have been employed for more than seven decades. The most commonly used drugs for the treatment of rheumatoid arthritis are gold (I) thiolates (Fig. 2), such as sodium aurothioma-

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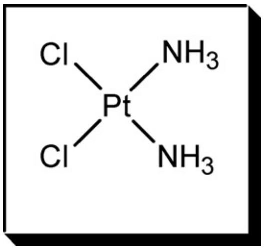

Fig. 1. Structure of cisplatin.

late (Myocrisin^{TM}) and aurothioglucose (Solganol^{TM}), both given by intramuscular injection. More recently auranofin (Ridaura^{TM}) was introduced into the clinic, as an orally bioavailable drug. Gold therapy has been extended to treat a variety of other diseases such as psoriasis, pemphigus, asthma, urticaria among others [32–35].

Despite the important research advances in the field of inorganic medicinal chemistry to fight cancer, the use of metal containing drugs as antiparasitic agents has been very little explored. There is an urgent need for new effective and non-toxic anti-parasitic drugs and an immense number of rational combinations of appropriate organic molecules (used in traditional medicine) with different transition metals are available. This approach makes use of the concept of metal–drug synergism, which is the enhancement of the activity of the parental organic drug due to binding to the metal ion. This activity enhancement is possibly related to the stabilization of the drug by coordination to the metal ion, which leads to a longer residence time of the drug in the organism and more efficient biological targeting. It may also result in a decrease in the toxicity of the metal ion due to complexation with the organic drugs, which makes it less available for undesirable reactions that lead to toxicity [6,36].

This review focuses on recent advances in developing gold complexes as anti-parasitic agents, based primarily on our work using the metal–drug synergism approach as a powerful tool which could provide effective treatment for parasitic diseases. Also, reviewed here is related literature on the use of new gold complexes or existing gold-based drugs for treatment of tropical diseases such as malaria, leishmaniasis, trypanosomiasis and schistosomiasis.

2. Gold complexes as antimalarial agents

Malaria is a very old disease, which is still a major cause of illness and death in children and adults in tropical countries. It currently affects an estimated 400 million people and is threatening more than one billion people around the world [37,38]. The disease is caused by protozoan parasites of the genus *Plasmodium*. There are four types of human pathogenic *Plasmodium* (*falciparum*, *vivax*, *ovale* and *malariae*) species, usually referred to as malaria parasites. The most serious forms of the disease are caused by *Plasmodium falciparum* and *Plasmodium vivax*. Malaria parasites are transmitted to human by the bite of the infected female *Anopheles* mosquitoes.

This huge public health problem has been addressed by at least three different approaches. The first uses insecticides. DDT (dichloro-diphenyl-trichloroethane) was originally used in order to control the insects, but this practice was discarded due to environmental impact, indiscriminate spraying and development of resistance to DDT in some populations of malaria vector Anopheles mosquitoes. However, today there is renewed interest in the use of indoor residual spraying (IRS) as one of the primary vector control interventions for reducing and interrupting malaria transmission in Africa countries. Secondly, immunological methods are implemented in order to obtain the vaccines which are one of the most effective modes of treatment available, but, so far, despite these efforts there are no available vaccines that effectively target a parasitic infection. The third approach employs chemotherapy. A number of organic compounds have been used as antimalarial drugs such as quinine, chloroquine, hydroxychloroquine, mefloquine, primaquine, proguanil, cotrifazid, doxycycline, sulfadoxine, pyrimethamine, artemether, lumefantrine, artesunate, amodiaquine. The current treatment is based on the combination of two or three of these drugs [38–40].

Chloroquine (CQ) was one of the most successful drugs ever used to treat an infectious disease, it was considered a wonder drug due its low cost, high efficacy against malaria parasites and lack of significant side effects. However, after twenty years of successful use in the clinic, the chloroquine resistant parasite emerged and spread from Asia to Africa and South America. The loss of the usefulness of CQ as a first line antimalarial drug is one of the major setbacks to the effective control of malaria. Currently, the therapeutic tools for the treatment of malaria are very limited, therefore new anti-malarial

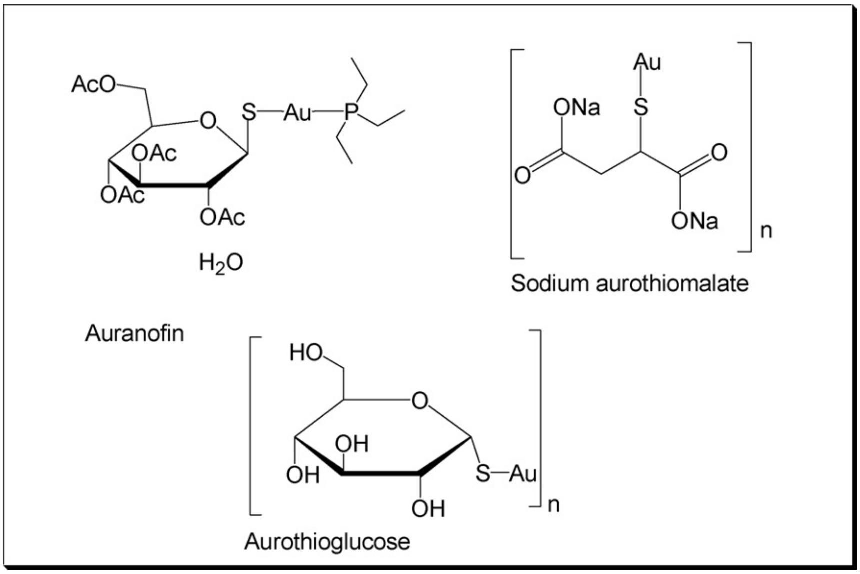

Fig. 2. Gold-based drugs most commonly used for the treatment of rheumatoid arthritis.

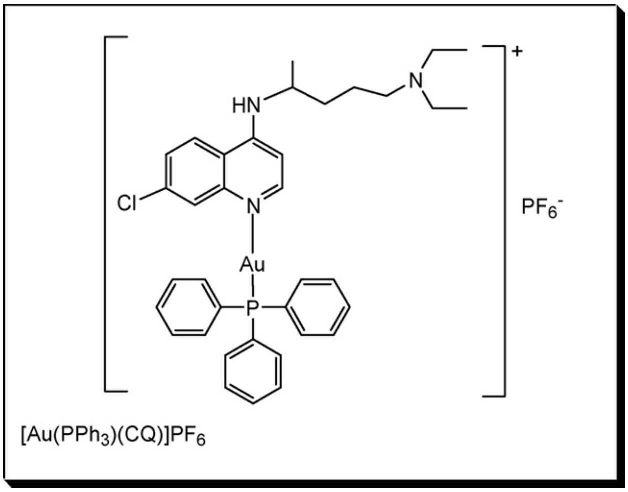

Fig. 3. Proposed structure of chloroquine (triphenylphosphine) gold (I) hexafluorophosphate, which has potent antimalarial activity.

drugs, preferably with new structure and or mode of action, are urgently needed.

Metal–drug synergic effects have been used in order to obtain antimalarial metal agents. In 1987, the drugs primaquine and amodiaquine were employed as ligands in the synthesis of 32 metal complexes and two of those were based on gold (III). All compounds were found to be active against *P. falciparum* (Table 1) to the same extent as the parental drugs [41]. Attaching a gold-containing fragment to chloroquine (CQ) results in a strong modification of the electronic properties. Moreover, the almost unlimited variety of possible gold–ligand fragments that can be coordinated to base CQ or chloroquine diphosphate (CQDP) represents a very extensive area for exploring their anti-malarial properties.

The complex $[Au(PPh_3)(CQ)]PF_6$ (Fig. 3, AuCQ) caused marked inhibition of the *in vitro* growth of *P. berghei* and was also very effective against two chloroquine resistant FcB1 and FcB2 strains of *P. falciparum* (Table 1). It displayed a 5–10-fold greater activity than the corresponding CQDP, demonstrating that gold coordination results in a significant enhancement of the activity of the parental drug against resistant parasites. Further in vivo series of experiments against *P. berghei* showed that AuCQ is also active against this type of rodent malaria. The parasitemia of infected mice after treatment with AuCQ at a dose of 1 mg of CQ per kg of body weight was reduced by 84% as compared to untreated controls, while the reduction in parasitemia of mice treated with an equivalent concentration of CQDP was only 44%; this shows that complexation of Au to CQ significantly increased the in vivo susceptibility of *P. berghei* to CQ. No apparent adverse reaction or apparent acute toxic responses were observed [42].

The enhancement of activity of CQ caused by the coordination to gold, stimulated the development of new gold-CQ antimalarial agents with different changes in the structure of the $[Au(PPh_3)(CQ)]PF_6$ complex, thereby generating a series of CQ-Au derivatives. The changes included variation of the phosphine ligand with the purpose of inducing changes in the electronic and steric properties, variation of the counteranion (for example nitrate), variation of the gold oxidation state (both Au (I) and Au (III)) and the use of other biological important ligands such as 1-thio-β-D-glucose-2,3,4,6-tetraacetate. Fig. 4 summarizes the gold–chloroquine complexes obtained through these variations. All of the complexes were evaluated against CQ-sensitive and CQ-resistant strains of *P. falciparum* (Table 1). Gold (III) complexes were found to be more active than CQDP against CQ-resistant strain K1. The highest activity for this series was found for complex $[Au(PEt_3)(CQ)]PF_6$, which is 5-fold more active than CQDP against CQ-resistant strain FcB1, although no clear structure activity correlations could be established for this series of compounds. Interestingly, on pre-incubating uninfected red blood cells (RBC's) with the gold $[Au(PPh_3)(CQ)]PF_6$, protection against subsequent infection was observed [43].

Table 1
IC_{50} of Au (I) and Au (III) complexes against several strains of *P. falciparum*.

Compounds	IC_{50} (nM)	Strain *P falciparum*	Reference
CQDP	50	FcB1	[43]
	110	FcB2	[42]
	70	W2	[43]
	91	K1	[43]
	10	F32	[43]
	23	D10	[53]
	352	K1	[53]
FQ	16	D10	[53]
	5	K1	[53]
Amodiaquine	100	FAN-5	[41]
Primaquine	1000	FAN-5	[41]
Au (I) compounds			
Auranofin	142	3D7	[55]
$Au(PEt_3)Cl$	21×10^2	3D7	[55]
Aurothiomalate	168×10^3	3D7	[55]
$[Au(PPh_3)(CQ)]PF_6$	5	FcB1	[42]
	40	FcB1	[43]
	23	FcB2	[42]
	70	W2	[43]
	99	K1	[43]
	18	F32	[43]
$[Au(PPh_3)(CQ)]NO_3$	40	FcB1	[43]
	40	W2	[43]
	58	K1	[43]
	10	F32	[43]
	21	D10	[53]
	62	K1	[53]
$[Au(PEt_3)(CQ)]PF_6$	10	FcB1	[43]
	50	W2	[43]
	99	K1	[43]
	13	F32	[43]
$[Au(PMe_3)(CQ)]PF_6$	40	FcB1	[43]
	50	W2	[43]
	93	K1	[43]
	17	F32	[43]
$[Au(FQ)(PPh_3)]NO_3$	11	D10	[53]
	6	K1	[53]
$[Au(L1)(PPh_3)]NO_3$	33	D10	[53]
	34	K1	[53]
$[Au(L2)(PPh_3)]NO_3$	30	D10	[53]
	31	K1	[53]
$[Au(C_6F_5)(CQ)]$	18	D10	[53]
	61	K1	[53]
$[Au(C_6F_5)(FQ)]$	10	D10	[53]
	4	K1	[53]
$[Au(C_6F_5)(L1)$	14	D10	[53]
	15	K1	[53]
$[Au(C_6F_5)(L2)]$	23	D10	[53]
	13	K1	[53]
Au (III) compounds			
$[Au(CQ)_2(Cl)_2]Cl$	43	K1	[43]
	13	F32	[43]
[Au(CQ)(SR)(Cl)(Solv)]Cl	54	K1	[43]
	18	F32	[43]
$KAuCl_4$	100	FAN-5	[41]
$Au(Primaquine)Cl_3$	1000	FAN-5	[41]
$Au(amodiaquine)Cl_3$	100	FAN-5	[41]
AuCyclam	439×10^3	3D7	[55]

IC_{50}: 50% inhibitory concentration; CQ: Chloroquine; SR: -thio-β-D-glucose-2,3,4,6-tetraacetate; L1: N-(7-chloro-quinolin-4-yl)-N′-[2-(N″,N″-dimethylaminomethyl) ferrocenylmethyl]-ethane-1,2-diamine; L2: 3-benzyl-1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1-[2-(N″,N″ dimethylaminomethyl)-ferrocenylmethyl]urea). FcB1 and FcB2: CQ-resistant Strains of *P. falciparum* [42]; FcB1, W2, and K1 strains are considered of medium CQ resistance, while F32 is CQ sensitive [43]. D10 is CQ-sensitive and K1 CQ-resistance [53].

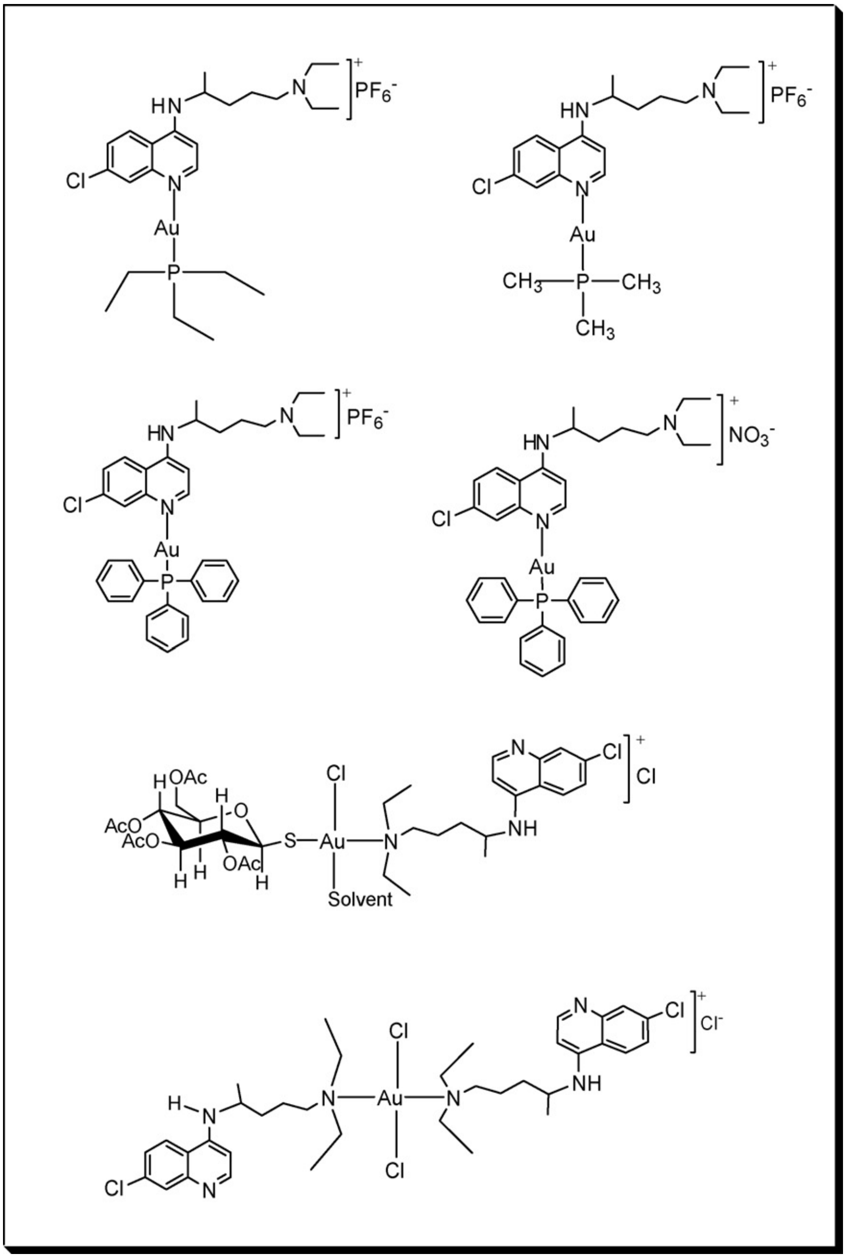

Fig. 4. Gold–chloroquine complexes active against malaria parasites.

The possible mechanisms of action of this promising complex [Au(PPh$_3$)(CQ)]PF$_6$ are currently under investigation [44]. Two targets have been evaluated, based on the accepted mechanisms of action for the CQ, viz. the inhibition of haemozoin (malarial pigment) formation and DNA interaction [45–49]. The most accepted explanation of the CQ mode of action is based on the interference of the drug with the detoxification of haem. CQ accumulates in the food vacuole of the intraerythrocytic parasite where the digestion of the haemoglobin takes place. CQ has been shown to be able to counteract haem aggregation inside the vacuole by blocking the sequestration of toxic haem into haemozoin, thus promoting accumulation of toxic levels of haem resulting in parasite death. Many excellent reviews are available on this exciting area of research [37,45–48]. Several other theories have been proposed such as inhibition of DNA and RNA synthesis and inhibition of protein synthesis, but these explanations seem unlikely since the concentration of drug required for a lethal effect on the parasite would have to be much higher than those observed *in vivo* [49]. Unfortunately, there is no direct proof of the putative mechanism of CQ action, but there is considerable evidence in favour of the targets evaluated for this complex. The preliminary results obtained [44] show that the complex [Au(PPh$_3$)(CQ)]PF$_6$ can interact with DNA by an intercalative mode, no covalent DNA interaction was detected. Also, this complex inhibited the β-hematin (synthetic haemozoin) formation at comparable concentration to CQ [44]. The evaluation of this complex on the haeme aggregation inhibition in the water–lipid interface is in progress [50].

Due to the interesting activity found for gold- and rhodium-chloroquine [42,51] and ferrocenyl derivatives against malarial parasites [52], another interesting approach has been investigated using heterobimetallic complexes through the combinations of rhodium and gold-containing fragments with *ferrochloroquine* (FQ) in contrast to chloroquine [53]. The biological data showed that the coordination of the CQ to gold (I) or rhodium (I) increases the efficacy with respect to CQ, most notably in chloroquine-resistant strains of the *P. falciparum* (Table 1) confirming the concept

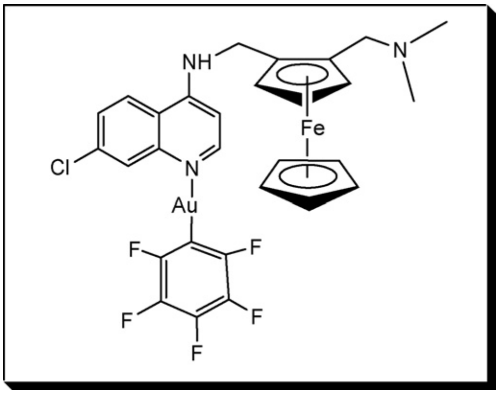

Fig. 5. Heterobimetallic gold–ferroquine complex active against CQ-sensitive and CQ-resistant strains.

of metal–drug synergism [6,36] previously proposed. Ferrocenyl ligands are more active than CQ against both CQ-sensitive and CQ-resistant strains of the parasite. Furthermore, FQ displayed better activity than metal-chloroquine complexes against the resistant strains of *P. falciparum*. The most active of the 16 compounds studied is the complex Au(C_6F_5)(FQ) (Fig. 5), the rhodium complexes evaluated were significantly less active than the gold complexes. However, the presence of two metal centers in the molecules at best has little effect on the overall efficacy of the compounds. At worst, there appears to be a significant antagonistic effect on the complexation of the second metal. Although, this antagonistic effect was not deeply explored, the presence of the second metal made the ferrocenyl moiety far more difficult to oxidise [53,54].

Recently, the antiarthritic drugs auranofin and aurothiomalate (Fig. 2) as well as triethylphosphine gold (I) chloride and a gold (III) cyclam (Fig. 6) have been tested against 3D7 *P. falciparum* strain (Table 1). Auranofin causes strong and nearly completed inhibition of *P. falciparum* growth, at 142 nM while Et_3PAuCl showed a similar trend but at higher concentration (2.1 μM). In contrast, aurothiomalate and AuCyclam were less effective. The strong effect found for auranofin against *P. falciparum* is probably mediated by severe oxidative stress originating from this parasite thioredoxin reductase inhibition [55].

3. Gold complexes as potential anti-leishmaniasis agents

Leishmaniasis, an emerging and uncontrolled category I disease, constitutes a major public health problem, causing significant morbidity and mortality in Africa, Asia and the Americas. The disease currently threatens about 350 million people around the world. It is caused by flagellated protozoans of the genus *Leishmania* (Sarcomastigophora, Kinetoplastida) and ranges from self-healing cutaneous leishmaniasis to progressive mucocutaneous infections, and fatal visceral leishmaniasis also called kala-azar. The annual incidence is estimated at 1-1.5 million cases of cutaneous leishmaniasis and 500,000 cases of visceral leishmaniasis [56].

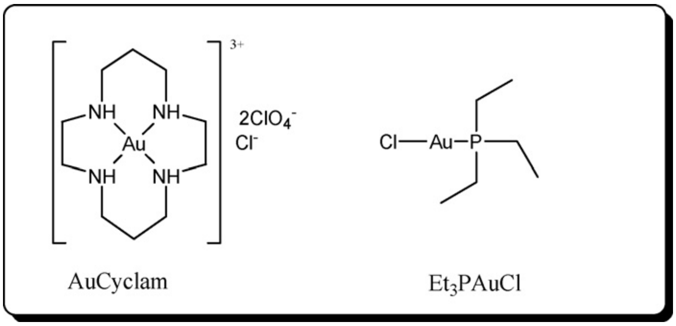

Fig. 6. Structures of Au (III) cyclam and chloro(triethylphosphine) gold (I) tested against 3D7 *P. falciparum* strain.

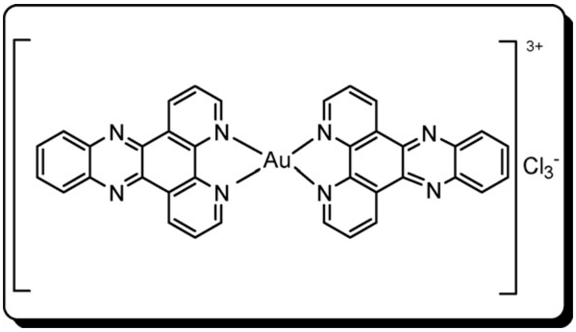

Fig. 7. The proposed structure of $[Au(dppz)_2]Cl_3$.

Treatments for leishmaniasis available at present are far from ideal. The classic first line treatment is based on pentavalent antimonials (Sb(V)), particularly sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime). Both drugs only exist in their parental forms and have been used for over 60 years [57]. Although these antimonials are successfully employed worldwide, they have been shown to induce severe side effects. The second-line compounds, used during the treatment of unresponsive cases, generally include pentamidine and amphotericin B [58], and a new anti-leishmanial, miltefosine [59], originally developed as an antineoplastic agent. Another potentially useful compound, Paramomycin (an aminoglycoside antibiotic) has been clinically tested for treating the disease [60,61].

The development of metal complexes as potent chemotherapeutic agents against leishmaniasis remains a priority since the drugs currently available are not totally safe or active. Moreover, the appearance of drug-resistant strains of *Leishmania* spp. justifies the screening of new compounds. Some organometallic and coordination complexes of iridium, rhodium and platinum and zinc sulfate have been tested against the leishmania parasite [62–72]. Also, some metallointercalators of DNA based on platinum, copper and silver have been evaluated and have shown remarkable antileishmanial activity [73]. Gold compounds have been very little explored against leihmaniasis.

Since metabolic pathways of kinetoplastid parasites are similar to those present in tumor cells [74,75], there has been some interest in the design of metallointercalators that could show activity against some of these pathogenic parasites through their interaction with DNA. The metal complexes designed to be DNA intercalating molecules with potential leishmanicidal activity are based on metals of known clinical application such as copper [76,77], silver [78] and gold [79] with ligands typically employed in the synthesis of metallointercalators such as the planar organic compounds dppz (dipyrido[3,2-a:2′,3′-c]phenazine) and dpq (dipyrido[3,2-a:2′,3′-h]quinoxoline). The compounds of this series are $[Cu(dpq)(NO_3)]NO_3$, $[Cu(dpq)_2(NO_3)]NO_3$, $[Cu(dppz)(NO_3)]NO_3$, $[Cu(dppz)_2(NO_3)]NO_3$, $[Ag(dpq)_2]NO_3$, $[Ag(dppz)_2]NO_3$, $[Cu(dppz)_2]BF_4$ and $[Au(dppz)_2]Cl_3$. The biological activity of these eight complexes against the promastigote form of *Leishmania* (*V*) *braziliensis* and *L.* (L) *mexicana* was evaluated, all of them showing leishmanicidal activity. This biological activity was higher for the metal-dppz complexes than for the metal-dpq complexes. Additionally the complexes with two coordinated molecules of the planar ligand were more active than those with one.

$[Au(dppz)_2]Cl_3$ (Fig. 7) was the most effective complex in the series. This complex induced a dose dependent antiproliferative effect with a minimal inhibitory concentration (MIC) of 3.4 nM and lethal doses LD_{26} of 17 nM at 48 h. This strong *in vitro* activity against L*eishmania* (*L*) *mexicana* could be related to their ability to interact with DNA through an intercalative mode. Also, preliminary ultrastructural studies using Transmission Electron Microscopy (TEM) carried out with treated parasites at a sublethal concentration (IC_7 = 0.34 nM for 24 h) showed polynucleated cells with DNA fragmentation and drastic disorganization of the mitochondria [73,79].

In 1987, sodium aurothiomalate (Fig. 2) was used in the treatment of 10 patients with kala-azar and showed an excellent clinical response [80].

Recently, five selected gold (III), palladium (II) and rhenium(V) complexes have been tested against three *Leishmania* species (*L. major*, *L. mexicana*, *L. donovani*) and *Trypanosoma cruzi*, along with evaluation of the inhibitory effect against parasite cysteine proteases. All compounds were inhibitors of this parasite enzyme, and one of the palladium complexes assayed was the most active against these parasites. The preliminary data indicating that the metal complexes target parasite cysteine proteases [81].

4. Gold complexes as potential anti-trypanosomiasis agents

There are at least two groups of diseases caused by the infection with the protozoa parasites of the genus *Trypanosoma*. One of them is Chagas' disease also called American trypanosomiasis, which is the result of an infection caused by the flagellate protozoan *Trypanosoma cruzi*. This parasite is usually transmitted to humans through feces of blood-sucking of infected insect vectors (reduviid bugs). Currently, this illness afflicts over 17 million people in Latin America and ranks as the third largest parasitic disease worldwide after malaria and schistosomiasis. Nowadays, there are no prophylactic drugs to prevent infection with *T. cruzi*, the current treatment is very limited and far from ideal; commercially available drugs are benznidazol (nitroaromatic compounds) and nifurtimox (discontinued to the public). These drugs have proven efficient only through the acute phase; both drugs have important side effects including allergic dermopathy, peripheral polyneuropathy, anorexia, loss of weight, vomiting, nausea and diarrhea [82,83].

The other important disease caused by this family of parasite is African trypanosomiasis, also known as sleeping sickness, which is caused by *Trypanosoma brucei* (sub-species *T. gambiense and T. rhodesiense*), two species of flagellates transmitted by bites of infected tsetse flies (*Glossina* species). Sleeping sickness threatens millions of people in 36 countries of sub-Saharan Africa. Four drugs have been used for the treatment of this illness such as pentamidine, melarsoprol, eflornithine and suramin, the treatment used depends on the type and stage of African trypanosomiasis [84].

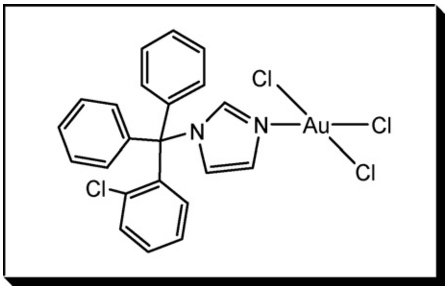

Fig. 8. The molecular structure of trichloro(clotrimazole) gold (III), active against *T. cruzi* parasite.

In view of the similarity between tumor cells and the pathogenic African trypanosomes both in metabolism and in drug reactivity, the trypanocidal activity of selected antitumor drugs and metal based complexes have been evaluated against *Trypanosomas*. In 1979, cisplatin showed significant activity against *T. rhodiense* [85] and *T. cruzi* [86]; cisplatin analogs and ruthenium, palladium, rhenium were also reported to be active against *Trypanosomes* parasites [81,87–93].

A different approach involves coordination of metals such as copper, ruthenium, platinum, rhodium, gold (I) and gold (III) to cotrimazole (CTZ) and ketoconazole (KTZ), known antifungal agents that are efficient Sterol Biosynthesis Inhibitors (SBIs) [94], to produce remarkably effective compounds that make use of the metal–drug synergism [95,96].

Coordination of clotrimazole to gold (III) produced the complex $AuCl_3(CTZ)$ (Fig. 8). This complex at 10^{-5} M inhibited 60% of the proliferation of the epimastigotes of *T. cruzi*, slightly higher than the free CTZ (58%) [97]. Gold (I) has been also coordinated to CTZ and KTZ to yield the complexes $[AuPPh_3(CTZ)]PF_6$ and $[AuPPh_3(KTZ)]PF_6$, respectively (Fig. 9). Both complexes showed considerable inhibition of the proliferation of the epimastigotes form of *T. cruzi* at a concentration of 1 μM (around 70%) while the parental compound CTZ has no effect on the growth and KTZ only inhibited 39% at the same concentration [98].

The trypanocidal effects of porphyrins bonded to different metals including gold (III) have been evaluated against *T. brucei brucei*

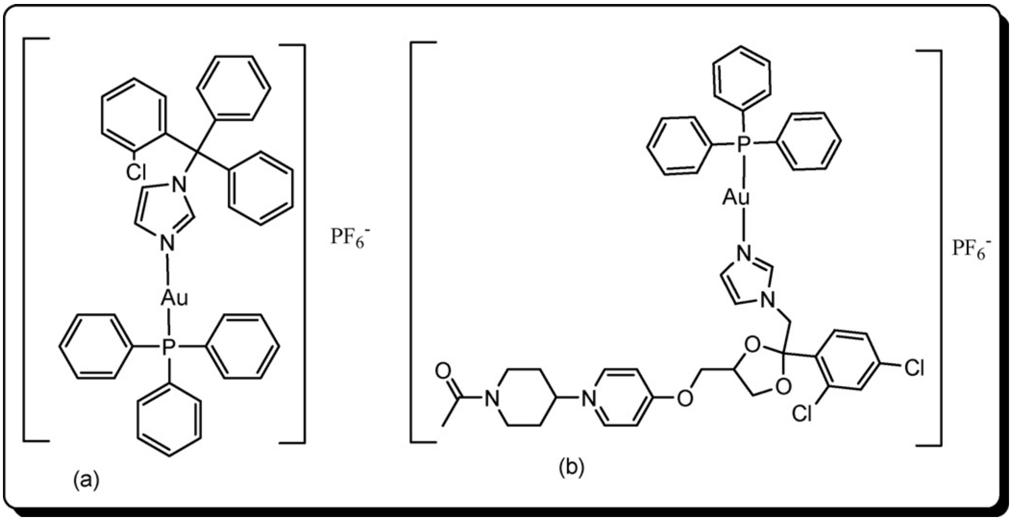

Fig. 9. (a) Molecular structure of clotrimazole(triphenylphosphine) gold (I) hexafluorophosphate and (b) structure of ketoconazole(triphenylphosphine) gold (I) hexafluorophosphate.

growth and sodium tetrachloaurate (III) was found to be more toxic to this parasite than the gold (III) porphyrin complex; this result was attributed to free radical generation in the presence of the gold (III) ion [99].

5. Gold complexes as potential anti-schistosomiasis agents

Schistosomiasis (also known as bilharziasis) ranks as the second parasitic disease behind malaria. This disease is caused by the digenetic trematode *Schistosoma*. Three main species are pathogenic for humans, *Schistosoma mansoni*, responsible for hepatic bilharziasis, *Schistosoma haematobium* which leads to urinary bilharziasis, and *Schistosoma japonicum*, responsible for hepato-intestinal bilharziasis, these three forms are present in different geographical distributions. More than 200 million people are exposed to *Schistosoma* in 76 countries worldwide with a concentration in Asia, Africa, and South America [100]. Each year 280,000 people die of this disease [101]. No vaccine is available, and praziquantel, the only drug extensively utilized, is currently administered more than 100 million people yearly. Research for new antischistosome drugs is clearly needed.

Very recently, a study was undertaken of the evaluations of antiarthritic gold drugs such as auranofin, aurothiomalate, and aurothioglucose, among several others compounds, as potential inhibitors of the parasite enzyme thioredoxin glutathione reductase (TGR) based on the premise that *Schistosoma mansoni* TGR is an essential parasite enzyme. TGR (multifunctional enzyme) is a major if not the sole enzyme for thioredoxin reductase (TrxR) and glutathione reductase GR activities in the adult parasite *S. manzoni*. This contrasts with the mammals which have three distinct enzymes, TGR, TrxR and GR. TGR has a similar amino acid sequence and domain structure to mammalian TrxR and GR, with an additional amino-terminal extension of glutaredoxin (Grx) domain of ~100 amino acid, including the active site-Cys-Pro-Tyr-Cys motif. Like all mammalian TrxR isoforms, *S. mansoni* TGR is a selenoprotein with a carboxyl-terminal Gly-Cys-SeCys-Gly active site motif. TGR should be a key drug target for treatment of schistosomiasis [102,103]. Gold complexes were found to be potent *Schintosome* TGR inhibitors. Auranofin was the most potent inhibitor of TGR, with IC_{50} values in the low nanomolar range. Furthermore, the inhibition of TGR by auranofin in cultured worms greatly reduced the GSH:GSSG ratio and resulted in rapid worm death. There was a significant decrease in worm burden in infected mice treated with auranofin [103].

6. Conclusions

Gold is among the most ancient of all metals used in medicine; the most common medical use for gold compounds is the treatment of rheumatoid arthritis and there is emerging interest in the application of gold compounds as anticancer agents. Its current use in modern medicine has allowed information regarding toxicological and clinical administration to become available along with valuable studies concerning its metabolism and molecular targets. Therefore, gold has become one of the most promising metals for drug development in medicine. Due to the urgent need to develop new drugs, gold compounds are good candidates for parasitic diseases caused by *Plasmodium*, *Leishmania*, *Trypanosomes* and *Schistosomas*. The drugs currently used to treat these diseases have limited efficacies and/or are significantly toxic to humans. In addition, the occurrence of parasitic strains resistant to current drugs is a growing and extremely worrying phenomenon.

To treat the millions of people suffering from parasitic diseases and attack this immense health problem, the use of the existing gold-based drugs and/or rational design of new gold-based complexes with specific and/or selective parasite target appear as a very useful alternative, with the potential to develop a clinically acceptable drug, with high pharmacological potential and low toxicity. Research on gold-based antiparasitic agents is an area which has great prospects.

Metal–drug synergism is a powerful tool which could provide effective treatment for parasitic diseases in the future; however, it needs to be accompanied by studies involving the recognition of biomolecules as specific targets in order to understand the mechanisms of action of metal drugs and to facilitate the design of new metallodrugs.

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References

[1] P.C.A. Bruijnincx, P.J. Sadler, Curr. Opin. Chem. Biol. 12 (2008) 197.
[2] T.W. Hambley, Dalton Trans. (2007) 4929.
[3] K.H. Thompson, C. Orvig, Dalton Trans. (2006) 761.
[4] P.J. Dyson, G. Sava, Dalton Trans. (2006) 1929.
[5] S.P. Fricker, Dalton Trans. (2007) 4903.
[6] N. Farrell, Transition metal complexes as drugs and chemotherapeutic agents, in: B.R. James, R. Ugo (Eds.), Catalysis by Metal Complexes Series, Vol.11, Kluwer Academic Publishers, Dordrecht, 1989.
[7] Z. Guo, P.J. Sadler, Angew. Chem. Int. Ed. 38 (1999) 1512.
[8] N. Farrell, Compr. Coord. Chem. II 9 (2003) 809.
[9] M.J. Clarke, F. Zhu, D.R. Frasca, Chem. Rev. 99 (1999) 2511.
[10] N. Farrell, Coord. Chem. Rev. 232 (2002) 1.
[11] K.H. Thompson, C. Orvig, Science 300 (2003) 936.
[12] Z. Guo, P.J. Sadler, Adv. Inorg. Chem. 49 (2000) 183.
[13] M.J. Clarke, Coord. Chem. Rev. 232 (2002) 69.
[14] C.X. Zhang, S.J. Lippard, Curr. Opin. Chem. Biol. 7 (2003) 481.
[15] T. Storr, K.H. Thompson, C. Orvig, Chem. Soc. Rev. 35 (2006) 534.
[16] E.R.T. Tiekink, Inflammopharmacology 16 (2008) 138.
[17] I. Kostonova, Anti-Cancer Agents Med. Chem. 6 (2006) 19.
[18] X. Wang, Z. Guo, Dalton Trans. (2008) 1521.
[19] M.J. McKeage, L. Maharaj, S.J. Berners-Price, Coord. Chem. Rev. 232 (2002) 127.
[20] S.J. Berners-Price, C.K. Mirabelli, R.K. Johnson, M.R. Mattern, F.L. McCabe, L.F. Faucette, C. MeiSung, S. Mong, P.J. Sadler, S.T. Crooke, Cancer Res. 46 (1986) 5486.
[21] M.J. McKeage, S.J. Berners-Price, P. Galettis, W. Brouwer, L. Ding, L. Zhuang, B.C. Baguley, Cancer Chemother. Pharmacol. 46 (2000) 343.
[22] F. Caruso, M. Rossi, J. Tanski, C. Pettinari, F. Marchetti, J. Med. Chem. 46 (2003) 1737.
[23] N. Pillarsetty, K.K. Katti, T.J. Hoffman, W.A. Volkert, K.V. Katti, H. Kamei, T. Koide, J. Med. Chem. 46 (2003) 1130.
[24] D. Suresh, M.S. Balakrishna, K. Rathinasamy, D. Panda, S.M. Mobin, Dalton Trans. (2008) 2812.
[25] R.G. Buckley, A.M. Elsome, S.P. Fricker, G.R. Henderson, B.R.C. Theobald, R.V. Parish, B.P. Howe, L.R. Kelland, J. Med. Chem. 39 (1996) 5208.
[26] C. Gabbiani, A. Casini, L. Messori, Gold Bull. 40 (2007) 173.
[27] A. Casini, C. Hartinger, C. Gabbiani, E. Mini, P.J. Dyson, B.K. Keppler, L. Messori, J. Inorg. Biochem. 102 (2008) 564.
[28] P.J. Barnard, S.J. Berners-Price, Coord. Chem. Rev. 251 (2007) 1889.
[29] J.L. Hickey, R.A. Ruhayel, P.J. Barnard, M.V. Baker, S.J. Berners-Price, A. Filipovska, J. Am. Chem. Soc. 130 (2008) 12570.
[30] M.P. Rigobello, L. Messori, G. Marcon, M. Bragadin, A. Folda, G. Scutari, A. Bindoli, J. Inorg. Biochem. 98 (2004) 1634.
[31] J.J. Forestier, Lab. Clin. Med. 20 (1935) 827.
[32] C.F. Shaw III, Chem Rev. 99 (1999) 2589.
[33] E.R.T. Tiekink, Gold Bull. 36 (2003) 117.
[34] R. Eisler, Inflamm. Res. 52 (2003) 487.
[35] M.W. Whitehouse, Inflammopharmacology 16 (2008) 107.
[36] R.A. Sánchez-Delgado, A. Anzellotti, Mini Rev. Med. Chem. 4 (2004) 23.
[37] S.I. Hay, C.A. Guerra, A.J. Tatem, A.M. Noor, R.W. Snow, Lancet Infect. Dis. 4 (2004) 327.
[38] P. Cravo, R. Culleton, A. Afonso, I.D. Ferreira, V.E. do Rosário, Anti-Infect. Agents Med. Chem. 5 (2006) 63.
[39] http://www.who.int/malaria/wmr2008/malaria2008.pdf.
[40] A. Mital, Curr. Med. Chem. 14 (2007) 759.

[41] N. Wash, H.B. Singh, A. Gajanana, A.N. Raichowdhary, Inorg. Chim. Acta 135 (1987) 133.
[42] M. Navarro, H. Pérez, R.A. Sanchez-Delgado, J. Med. Chem. 40 (1997) 1937.
[43] M. Navarro, F. Vasquez, R.A. Sanchez-Delgado, H. Perez, V. Sinou, J. Schrevel, J. Med. Chem. 47 (2004) 5204.
[44] M. Navarro, W. Castro, unpublished result.
[45] J. Ziegler, R. Linck, D.W. Wright, Curr. Med. Chem. 8 (2001) 171.
[46] A.F.G. Slater, A. Cerami, Nature 355 (1992) 167.
[47] T.J. Egan, Targets 3 (2003) 115.
[48] T.J. Egan, J. Inorg. Biochem. 102 (2008) 1288.
[49] S.N. Cohen, K.L. Yielding, Proc. Natl. Acad. Sci. 54 (1965) 521.
[50] A. Martínez, C.S.K. Rajapakse, B. Naoulou, Y. Kopkalli, L. Davenport, R.A. Sánchez-Delgado, J. Biol. Inorg. Chem. 13 (2008) 703.
[51] R.A. Sanchez-Delgado, M. Navarro, H. Pérez, J. Urbina, J. Med. Chem. 39 (1996) 1095.
[52] C. Biot, G. Glorian, L. Maciejewski, J.S. Brocard, O. Domarle, M. Georgette, A.J. Georges, H. Abessolo, D. Dive, J. Lebibi, J. Med. Chem. 40 (1997) 3715.
[53] M.A.L. Blackie, P. Beagley, K. Chibale, C. Clarkson, J. Moss, P. Smith, J. Organometal. Chem. 688 (2003) 144.
[54] M.A.L. Blackie, P. Beagley, K. Chibale, Metal-Based Drugs ID 495123 (2008) 10 pages, doi:10.1155/2008/495123.
[55] A.R. Sannella, A. Casini, C. Gabbiani, L. Messori, A.R. Bilia, F.F. Vincieri, G. Majori, C. Severini, FEBS Lett. 582 (2008) 844.
[56] J. Blum, P. Desjeux, E. Schwartz, B. Beck, C. Hatz, J. Antimicrob. Chemother. 53 (2004) 158.
[57] J.D. Berman, B.D. Hanson, Rev. Infect. Dis. 10 (1988) 560.
[58] S.L. Croft, K. Seifert, V. Yardley, Indian J. Med. Res. 123 (2006) 399.
[59] J. Soto, J. Toledo, P. Gutierrez, R.S. Nicholls, J. Padilla, J. Engel, C. Fischer, A. Voss, J. Berman, Clin. Infect. Dis. 33 (2001) 57.
[60] J. Mishra, A. Saxena, S. Singh, Curr. Med. Chem. 14 (2007) 1153.
[61] M.C. O'Sullivan, Curr. Med. Chem. Anti-Infect. Agents 4 (2005) 355.
[62] C.M. Mesa-Valle, V. Moraleda-Lindez, D. Craciunescu, A. Osuna, Mem. Inst. Oswaldo Cruz 91 (1996) 625.
[63] N. Mbongo, P.M. Loiseau, F. Lawrence, C. Bories, D.G. Craciunescu, M. Robert-Gero, Parasitol. Res. 83 (1997) 515.
[64] P.M. Louiseau, N. Mbongo, C. Bories, Y. Boulard, D.G. Craciunescu, Parasite 7 (2000) 103.
[65] N. Mbongo, P.M. Loiseau, D.G. Craciunescu, M. Robert-Gero, Acta Tropica 70 (1998) 239.
[66] S.L. Croft, R.A. Neal, D.G. Craciunescu, G. Certad-Fombona, Trop. Med. Parasitol. 43 (1992) 24.
[67] N. Mbongo, P.M. Loiseau, F. Lawrence, D.G. Craciunescu, M. Robert-Gero, Arzneim.-Forsc./Drug Res. 48 (1998) 850.
[68] J.J. Castilla, M.C. Mesa-Valle, M. Sánchez-Moreno, T. Arnedo, M.J. Rosales, C. Mascaro, D. Craciunescu, A. Osuna, Arzneim.-Forsch./Drug Res. 46 (1996) 990.
[69] K.E. Sharquie, R.A. Najim, I.B. Farjou, Clin. Exp. Dermatol. 26 (2001) 21.
[70] G. Lowe, A.S. Droz, T. Vilaivan, J. Med. Chem. 42 (1999) 999.
[71] P.A. Nguewa, M.A. Fuertes, S. Iborra, N. Yousef, D. Gibson, E. Martinez, C. Alonso, J.M. Perez, J. Inorg. Biochem. 99 (2005) 727.
[72] M.A. Fuertes, P.A. Nguewa, J. Castilla, C. Alonso, J.M. Perez, Curr. Med. Chem. 15 (2008) 433.
[73] M. Navarro, G. Visbal, E. Marchan, in Programmed Cell Death in Protozoa', Editorial Landes Bioscience, Springer, Chapter 6 (2007) 59.
[74] K.E. Kinnamon, E.A. Steck, D.S. Rane, Antimicrob. Agents. Chemother. 15 (1979) 157.
[75] N.P. Farrell, J. Williamson, D.J.M. McLaren, Biochem. Pharmacol. (1984) 961.
[76] M. Navarro, E.J. Cisneros-Fajardo, A. Sierralta, M. Fernández-Mestre, P. Silva, D. Arrieche, E. Marchán, J. Biol. Inorg. Chem. 8 (2003) 401.
[77] M. Navarro, E.J. Cisneros-Fajardo, M. Fernández-Mestre, D. Arrieche, E. Marchán, J. Inorg. Biochem. 97 (2003) 364.
[78] M. Navarro, E.J. Cisneros-Fajardo, E. Marchan, Arzneim.-Forsch./Drug Res 56 (2006) 600.
[79] M. Navarro, C. Hernández, I. Colmenares, P. Hernández, M. Fernández, A. Sierraalta, E. Marchán, J. Inog. Biochem. 101 (2007) 111.
[80] M.P. Singh, M. Mishra, A.B. Khan, S.L. Ramdas, S. Panjiyar, Br. Med. J. 299 (1989) 1318.
[81] S.P. Fricker, R.M. Mosi, B.R. Cameron, I. Baird, Y. Zhu, V. Anastassov, J. Cox, P.S. Doyle, E. Hansell, G. Lau, J. Langille, M. Olsen, L. Qin, R. Skerlj, R.S.Y. Wong, Z. Santucci, J.H. Mckerrow, J. Inorg. Biochem. 102 (2008) 1839.
[82] World Health Organization. Technical Report Series No. 905, WHO, Geneva, 2002, pp. 1–109.
[83] Docampo, R. Chem. Biol. Interact. 73 (1990) 1.
[84] P.M.M. Guedes, J.L.R. Fietto, M. Lana, M.T. Bahia, Anti-Infect Agents Med. Chem. 5 (2006) 175.
[85] J. Williamson, N. Farrell, D.J. McLaren, Parasitology 14 (1982) 85.
[86] M.S. Wysor, L.A. Zwelling, J.E. Sanders, M.M. Grenan, Science 217 (1982) 454.
[87] G. Lowe, A.S. Droz, T. Vilaivan, G.W. Weaver, L. Tweedale, J.M. Pratt, P. Rock, V. Yardley, S.L. Croft, J. Med. Chem. 42 (1999) 999.
[88] S. Bonse, J.M. Richards, S.A. Ross, G. Lowe, R.L. Krauth-Siegel, J. Med. Chem. 43 (2000) 4812.
[89] G. Dreyfuss, B. Pénicaut, J.A. Nicolas, D. Craciunescu, P. Loiseau, Trop. Med. Parasitol. 44 (1993) 95.
[90] N.P. Farrell, J. Williamson, D.J.M. McLaren, Biochem. Pharmacol. 33 (1984) 961.
[91] M. Vieites, P. Smircich, B. Parajon-Costa, J. Rodriguez, V. Galaz, C. Olea-Azar, L. Otero, G. Aguirre, H. Cerecetto, M. Gonzalez, A. Gomez-Barrio, B. Garat, D. Gambino, J. Biol. Inorg. Chem. 13 (2008) 723.
[92] M. Vieites, L. Otero, D. Santos, J. Toloza, R. Figueroa, E. Norambuena, C. Olea-Azar, G. Aguirre, H. Cerecetto, M. Gonzalez, A. Morello, J.D. Maya, B. Garat, D. Gambino, J. Inorg. Biochem. 102 (2008) 1033.
[93] L. Otero, M. Vieites, L. Boiani, A. Denicola, C. Rigol, L. Opazo, C. Olea-Azar, J.D. Maya, A. Morello, R.L. Krauth-Siegel, O.E. Piro, E. Castellano, M. Gonzalez, D. Gambino, H. Cerecetto, J. Med. Chem. 49 (2006) 3322.
[94] J.A. Urbina, Parasitology 114 (1997) S91.
[95] R.A. Sánchez-Delgado, K. Lazardi, L. Rincon, J.A. Urbina, J. Med. Chem. 36 (1993) 2041.
[96] M. Navarro, T. Lehmann, E.J. Cisneros-Fajardo, A. Fuentes, R.A. Sánchez-Delgado, P. Silva, J.A. Urbina, Polyhedron 19 (2000) 2319.
[97] R.A. Sánchez-Delgado, M. Navarro, K. Lazardi, R. Atencio, M. Capparelli, F. Vargas, J.A. Urbina, A. Bouillez, A.F. Noels, D. Masi, Inorg. Chim. Acta 528 (1998) 275.
[98] M. Navarro, E.J. Cisneros-Fajardo, T. Lehmann, R.A. Sanchez-Delgado, R. Atencio, P. Silva, R. Lira, J.A. Urbina, Inorg. Chem. 40 (2001) 6879.
[99] E. Nyarko, T. Hara, D.J. Grab, A. Habib, Y. Kim, O. Nikolskaia, T. Fukumab, M. Tabata, Chem. Biol. Interact. 148 (2004) 19.
[100] L. Chitsulo, D. Engels, A. Montresor, L. Savioli, Acta Trop. 77 (2000) 41.
[101] J. Utzinger, J. Keiser, X. Shuhua, M. Tanner, B.H. Singer, Antimicrob. Agents Chemother. (2003) 1487.
[102] H.M. Alger, D.L. Williams, Mol. Biochem. Parasitol. 121 (2002) 129.
[103] A.N. Kuntz, E. Davioud-Charvet, A.A. Sayed, L.L. Califf, J. Dessolin, E.S.J. Arner, D.L. Williams, PLoS Med. 4 (2007) 206.