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Metal-Based Antiparasitic Therapeutics

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Abstract

This review discusses the potential of metal-based compounds to act as safe and affordable drugs in the treatment of important tropical parasitic illnesses such as Chagas disease, leishmaniasis, and malaria. Currently, half the world's population is estimated to be at risk of contracting these vector-borne diseases, and almost one million people die annually from these diseases. No effective vaccine exists to treat these infectious diseases and available treatments are far from ideal. Coordination metal complexes offer potential in the development of new antiparasitic drugs. Indeed, coordination compounds in medicine are a growing and exciting research field, having been used successfully in cancer therapy. As an antiparasitic agent, ferroquine has entered phase II clinical trials against malaria and is an excellent example to encourage the development of antiparasitic metal-based drugs. Insights into the mechanism of actions of metal-based antiparasitic drugs are discussed.

Introduction

Metals have been used for medicinal purposes since prehistoric and ancient times. Many metals fulfil essential roles in the human body, and deficiency of some metals can lead to disease. Moreover, metals such as iron, zinc, copper, manganese, and cobalt are incorporated into proteins or enzymes which facilitate a number of crucial functions in the body.

It is also well known that metals can induce toxicity in humans. Attention to this undesirable effect was brought to light through Paul Ehrlich's seminal work in 1910 on chemotherapy (the use of drugs to injure an invading organism without injury to the host). Ehrlich's formulation of Salvarsan—an arsenic compound—not only provided a successful treatment for syphilis, it marked the entry of metallotherapeutic agents into broad clinical usage.

Based on the advances in coordination chemistry, a variety of metal-containing drugs have since been proposed, and some have progressed to clinical

use. Well-known examples are platinum complexes (cisplatin, carboplatin, nedaplatin, and oxaliplatin) used to treat cancer; gold complexes (auranofin, solganol and myocrisin) used as antiarthritic drugs; silver used as an antimicrobial; and antimony (sodium stibogluconate and meglumine antimoniate) used to treat leishmaniasis. Currently, experimental clinical trials are underway to test several metal-based drugs that are based on titanium, ruthenium, iron, or platinum to treat cancer; bis(ethylmaltolato)oxovanadium(IV) as an antidiabetic drug; and ferroquine to treat malaria (Figure 10.1) (Alessio 2011; de Almeida et al. 2013; Farrell 2002; Guo and Sadler 1999; Thompson and Orvig 2003).

There is growing interest in metal-based drugs with potential application in a variety of therapeutic areas. Most efforts have been focused on developing drugs for cancer therapies, due to the success of cisplatin in the treatment of testicular and ovarian cancer. This success has inspired and led researchers to search for new metal-based chemotherapies for other illnesses, such as parasitic diseases. Unfortunately, though, the use of the metal complexes in the treatment of tropical parasitic diseases has not advanced at the same speed as cancer research.

Parasitic diseases constitute a major public health problem, particularly in the poorest areas of the world. Together they affect about one-third of the world's total population, causing more than one million deaths per year. Most of the available treatments are often toxic, not very effective, expensive, and sometimes difficult to administer. To make things worse, strains resistant to drugs currently in use have emerged (Aguiar et al. 2012; Bhargava and Singh

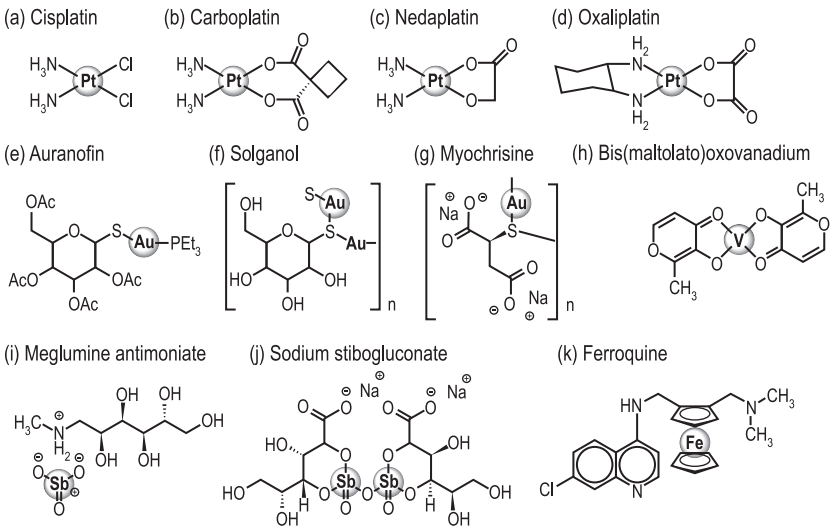

Figure 10.1 Selected metal-based drugs that are currently used clinically for cancer (a, b, c, d), arthritis (e, f, g), and leishmaniasis (i, j), and in the experimental clinical phase for diabetes (h) and malaria (k).

2012). Thus, there is an urgent need to develop new effective, adequate, affordable, and safe chemotherapies to treat parasitic diseases. Metal-based drugs offer a rich source of effective chemotherapeutic agents against the major protozoan diseases, especially when the drugs are designed to attack specific parasitic targets. Here, we review efforts to discover novel metal-based antiparasitic agents for the treatment of Chagas disease, leishmaniasis, and malaria—important representatives of tropical diseases.

Metal-Based Therapeutics for Trypanosomatidae

Trypanosomatidae are parasitic protists that cause Chagas disease and various manifestations of leishmaniasis in humans in many tropical and subtropical parts of the world. Even though these infectious diseases constitute a major global health problem, they have been classified as neglected tropical diseases (NTDs), due to the minimal levels of investment, on the part of both public and privates sectors, to develop new drugs for treatment. NTDs are concentrated among the world's poorest populations; worldwide they threaten more than 350 million people, affect up to 20 million, and are responsible for a significant number of deaths annually.

American trypanosomiasis, also known as Chagas disease, is endemic throughout Latin America. It is primarily transmitted to humans through the feces of triatomine bugs, also known as "kissing bugs." Occasionally, the responsible parasite, *Trypanosoma cruzi*, is transmitted through contaminated food, blood transfusion, and/or passage from an infected mother to her newborn during pregnancy or at childbirth.

Leishmaniasis is caused by protozoa parasites from over twenty *Leishmania* species and is transmitted to humans through the bite of infected female phlebotomine sandflies. It is currently estimated that 12 million people are infected worldwide.[1] There are three main types of the disease: cutaneous and mucocutaneous leishmaniasis are the most common, and visceral leishmaniasis is fatal if left untreated. An estimated 200,000–400,000 new cases of visceral leishmaniasis occur worldwide each year.

Current treatment for Chagas disease is based on nitroheterocyclic drugs (e.g., nifurtimox and benznidazole), which show significant activity only in the acute phase. The first line of treatment for leishmaniasis relies on pentavalent antimonials: sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime®) are the most representative drugs in use (see Figure 10.1). Although effective, these antimonials can cause severe side effects. When antimonials fail, Amphotericin B, pentamidine, or miltefosine are recommended as a second line of treatment for all three forms of leishmaniasis.

[1] http://www.who.int/leishmaniasis/burden/magnitude/burden_magnitude/en/

At present, there is no effective vaccine for either leishmaniasis or trypanosomiasis and, unfortunately, the treatments for trypanosomatid infections are far from ideal. This situation clearly calls for the development of new, effective, and nontoxic antiparasitic drugs. Since most of the drugs currently available for both diseases are characterized by poor efficacy, high toxicity, and increasing resistance, research into metal complexes as potent chemotherapeutic agents against trypanosomiasis and leishmaniasis is, and must remain, a priority.

One promising and attractive approach to the development of metallotherapeutic agents to treat parasitic infection was achieved through the application of metal-drug synergism. This concept consists of designing metal compounds that are based on the coordination of a transition metal into organic compounds with known or potential biologic activity. This modification is important within biological systems, due to the binding capability and reactivity of the transition metals, which are determined by the d-orbitals. These d-orbitals allow the design and preparation of a wide variety of coordination and organometallic compounds with different geometries (coordination spheres), oxidation states (redox potential), and use of diverse kinds of ligands. These geometries lead to metal complexes with enhanced lipophilicity, different kinetic and thermodynamic properties toward biological receptors, and the ability to interact with intracellular biomolecules, etc.

Such combinations can translate into enhanced activity of the parental organic drug. This activity enhancement may be related to the stabilization of the organic drug by coordination to the metal ion, which leads to a longer residence time of the drug in the organism, thus allowing it to reach the biological targets more efficiently. Another important effect of this combination is that 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. Furthermore, these metallodrugs are capable of affecting multiple parasitic targets simultaneously.

This approach was followed by Sánchez-Delgado and colleagues, and led to the discovery of metal complexes through the coordination of metal-fragment complex to clotrimazole (CTZ) and ketoconazole (KTZ). These ligands, CTZ and KTZ, have been shown to inhibit effectively the growth of the *T. cruzi* parasite. Several metal complexes were achieved using metals such as ruthenium, copper, rhodium, platinum, and gold. All of these metal-CTZs and metal-KTZs were able to inhibit the proliferation of the epimastigotes form of *T. cruzi* considerably better than the CTZ and KTZ ligands. The most active compound of this group of metal-CTZ complexes was $RuCl_2(CTZ)_2$ (Figure 10.2a). This promising metal complex affects the regular function of the sterol biosynthesis when CTZ is liberated and attacks the parasite's DNA through covalent interaction of the Ru motif, thus demonstrating the metal-drug synergistic concept defined above (Sánchez-Delgado and Anzellotti 2004; Navarro et al. 2010; Gambino and Otero 2012).

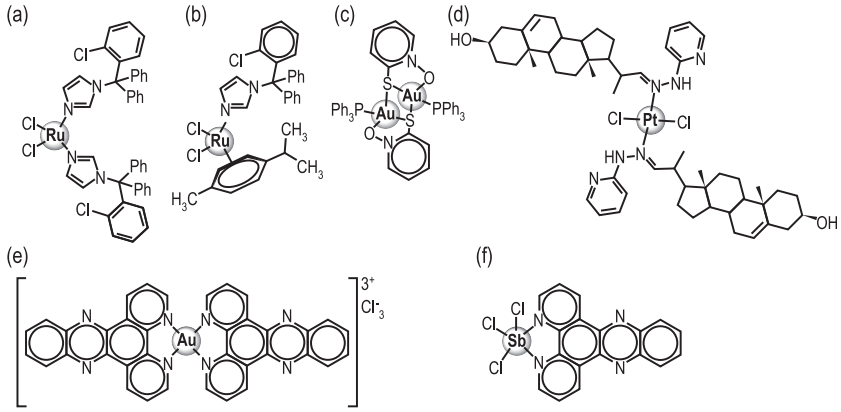

Figure 10.2 Selected metal-based therapeutic agents for trypanosomiasis (a, b) and leishmaniasis (c, d, e, f).

The Sánchez-Delgado group has continued to use this successful concept and has recently extended it to include the use of ancillary ligands, which provide the leader Ru-CTZ complex with better and desirable physicochemical and biological properties. Accordingly, organometallic Ru-CTZs were developed that displayed high antiparasitic activity *in vitro* against *T. cruzi* epimastigotes and *Leishmania major* promastigotes. Ru[(η^6-pcymene)Cl_2(CTZ)$_2$] (Figure 10.2b) was the most promising complex; it increased the activity of CTZ against *L. major* and *T. cruzi*, with no appreciable toxicity to human osteoblasts (Martínez et al. 2012). Similar organometallic compounds have been reported for Ru-KTZ (Iniguez et al. 2013).

Following this approach, the bioactive ligand, 5-nitrofuryl- and 5-nitroacroleine-containing thiosemicarbazones, has been incorporated into Ru, Pt, and Pd complexes, and it was found that Pt(II) and Pd(II) complexes were more active *in vitro* on *T. cruzi* epimastigotes than Nifurtimox and the corresponding free ligand. Another interesting ligand, 2-mercaptopyridine N-oxide (mpo), also coordinated to several metals (e.g., palladium, vanadium, and gold; Figure 10.2c) and showed significantly increased activity compared to mpo sodium salt on epimastigotes of different *T. cruzi* strains. Reported metal-mpo complexes showed a clear correlation between parasite inhibition and NADH fumarate reductase inhibition, thus highlighting this enzyme as the main target of these complexes as well.

Other organometallic compounds of iridium and rhodium with pentamidine (antileishmanial agents) have also been shown to be active against *L. donovani* promastigotes; some were even more active than pentamidine isethionate. A synergistic effect was noted when this complex was administered in combination with pentamidine, amphotericin B, or paromomycin. The Pt(II)-pentamidine complexes appear to be less active than Rh(I) and Ir(I) analogs

against amastigotes of *L. donovani.* In addition, nitroimidazole dithiocarbamates, benznidazole dithiocarbamates, and related ligands coordinated to platinum, osmium, and rhodium displayed a moderate activity against *L. donovani*.

An interesting approach has been developed using gold(III), palladium (II), and rhenium(V) cyclometallated complexes against *T. cruzi* and three *Leishmania* species: *L. major*, *L. mexicana*, and *L. donovani.* Preliminary data indicate that these metal complexes target parasite cysteine proteases.

Another rational strategy was based on the coordination of sterol hydrazone ligands to platinum (Figure 10.2d). These steroid ligands have been shown to be specific inhibitors of (S)-adenosyl-L-methionine: Δ^{24}-sterol methyl transferase (SMT), an enzyme which catalyzes the incorporation of this alkyl group to produce the main sterol leishmania's parasites (ergosterol and 24-alkylated sterol analogs), is necessary for their survival and growth. SMT inhibitors should only affect parasitic cells, without damaging cells from higher eukaryotes, therefore bypassing any undesirable clinical side effect (Visbal et al. 2008).

Other types of metal complexes were developed as antiparasitic agents based on two facts:

1. The metabolic pathways of kinetoplastid parasites are similar to those present in tumor cells.
2. Selected antitumor metal-containing complexes, such as cisplatin (functions by binding to DNA and disrupting DNA replication), have been evaluated against *T. rhodiense* and *T. cruzi*.

These results, along with the fact that many antiprotozoal drugs bind to DNA, have led some to propose that, in general, every DNA-interacting compound could be active against parasites (Kinnamon et al. 1979). This motivated us to design DNA metallointercalators that could show activity against some of these pathogenic parasites through their interaction with DNA. This strategy was based on the use of polypyridyl ligands (typically intercalators), such as phen (phenantroline), 1,10-phenantroline-5,6-dione (phendione), dppz (dipyrido[3,2-a:2′,3′-c]phenazine), and dpq (dipyrido[3,2-a:2′,3′-h]quinoxoline), which were coordinated to copper, silver, gold, palladium, and ruthenium to obtain a series of metal compounds:

- $[Cu(dpq)(NO_3)]NO_3$
- $[Cu(dpq)_2(NO_3)]NO_3$
- $[Cu(dppz)(NO_3)]NO_3$
- $[Cu(dppz)_2(NO_3)]NO_3$
- $[Ag(dpq)_2]NO_3$
- $[Ag(dppz)_2]NO_3$
- $[Cu(dppz)_2]BF_4$
- $[Au(dppz)_2]Cl_3$
- $PdCl_2$(Phen)
- $[Ru(phen)_2phendione](PF_6)_2$.

The biological activity of these metal complexes against *L. (V.) braziliensis and L. (L) mexicana* was evaluated, and all of them showed leishmanicidal activity. This biological activity was higher for the metal-dppz complexes. In addition, the complexes with two coordinated molecules of the planar ligand were more active than those with one. $[Cu(dppz)_2]BF_4$, which corresponds to Cu(I) complex, displayed a higher leishmanicidal effect than those observed with Cu(II). In contrast, Ag complexes were less active than complexes of Cu(II), whereas complexes of palladium and ruthenium showed moderate activity. $[Au(dppz)_2]Cl_3$ was the most effective complex in the series (Figure 10.2e): its strong *in vitro* activity against *L. (L) mexicana* could be related to its ability to interact with DNA through an intercalative mode. Other DNA metallointercalator (2,2′:6′2″-terpyridine) Pt(II) complexes and analogs have produced remarkable growth inhibition of *L. donovani*. These complexes exploit the intercalative DNA properties of the terpyridine ligand along with the covalent binding ability of the Pt(II) center. Similar complexes using mixed-ligand vanadyl complexes, $[V^{IV}O(L_2\text{-}2H)(L_1)]$—where L_1 is a tridentate salycylaldehyde semicarbazone derivative and L_2 is dppz as coligand—showed significant activity against *T. cruzi* and were as active as Nifurtimox. A recent report showed $[Cu(CH_3COO)(dppz)_2]CH_3COO$ and $[Zn(dppz)_2](BF_4)_2$ to have significant activity against a visceratropic *L. infantum* strain and to be more active than the reference drug miltefosine. In addition, their DNA–intercalation interaction correlates with leishmanicidal activity. Trivalent antimony(III) and bismuth(III) complexes with the dppz were synthesized, characterized, and evaluated against the promastigote form of Sb(III)-sensitive and Sb(III)-resistant *L. infantum chagasi* and *L. amazonensis* strains. Both complexes were more effective than dppz alone in inhibiting the growth of *Leishmania* promastigotes. The lack of cross-resistance to the Sb(III)-dppz (Figure 10.2f) complex together with the much lower activity of antimonyl tartrate, $SbCl_3$, and $BiCl_3$ strongly support the model that the metal is not active by itself but rather it improves the activity of dppz through complexation (Benítez et al. 2013; Lizarazo-Jaimes et al. 2012; Madureira et al. 2013; Navarro 2009; Navarro et al. 2007).

Using a different approach, Cu complexes with fluorinated β-diketones were synthesized and tested against promastigotes of *L. amazonensis* and showed inhibition of trypanosomatid-specific trypanothione reductase. It was found that the highly lipophilic and redox activity of these Cu derivatives increased toxicity toward promastigotes (Portas et al. 2012). Copper and zinc with sulfonamides that contain 8-aminoquinoline ligands showed activity against *L. chagasi* and *L. brasilensis* (Everson da Silva et al. 2010).

Interesting results have been reported for Ag nanoparticles (Baiocco et al. 2011) and Au nanoparticles (de Almeida and Carabineiro 2013) in the inhibition of leishmaniasis promastigotes.

In summary, based on the above discussion, it is clear that the presented metal-based drugs are designed to attack important and specific parasitic targets of the *T. cruzi* and *Leishmania*. Due to the well-known complexity of these

parasites, these drugs do not have a unique target to attack. Further research and efforts are thus needed to develop a rational design for an affordable and safe drug that will simultaneously attack several specific and/or selective targets in these parasites. Taking into account the metal-drug synergism strategy, metal-based drugs could play an important role in this research and drug design.

Metal-Based Therapeutics for Malaria

Malaria is a major cause of illness and death in children and adults who live in tropical countries, in particular, Africa. It is one of the world's most ancient diseases and is one of the most devastating parasitic infections known to affect humans. According to the World Health Organization (2013), an estimated 207 million episodes of malaria occurred in 2012 and approximately 627,000 people died. Despite important efforts made in research and the investment in its control, prevention, and treatment, malaria remains a primary cause of mortality and morbidity throughout the Tropics.

Malaria is transmitted to humans through the bite of infected female mosquitoes from more than thirty anopheline species. Five species of parasites of the genus *Plasmodium* are infectious to humans*: P. falciparum, P. vivax, P. ovale, P. malariae*, and *P. knowlesi.* Malaria caused by *P. falciparum* is the most deadly.

The most successful treatment used to be chloroquine (CQ); it was considered the ideal drug, due to its low cost, high efficacy against all species of the *Plasmodium* parasite, and lack of significant side effects. However, CQ-resistant malaria parasites started to emerge in the late 1950s, spreading from Asia to Africa and South America, reducing its efficiency as a first line antimalarial drug and resulting in major setbacks to the effective control of malaria. Fortunately, very effective artemisinin-derivative (dihydroartemisinin, artesunate, and artemethe) drugs replaced chloroquine. However, monotherapy is not recommended for different reasons. Currently, malaria is treated with a combination of two or more drugs that have different modes of action to provide an adequate cure rate and delay development of resistance. Artemisinin-based compounds are combined with drugs including lumefantrine, mefloquine, amodiaquine, piperaquine, and chlorproguanil/dapsone (Sinclair et al. 2009; WHO 2013b). At least three different strategies have been developed to address this public health problem:

1. The indiscriminate use of insecticides has been discontinued, due to insects' resistance to these chemicals and environmental impact. It should be noted, however, that renewed interest has been shown in the use of indoor residual spraying as a primary vector control intervention to reduce and interrupt transmission in African countries.

2. Vaccination is one of the most effective modes of treatment available, yet despite many efforts, effective vaccines are lacking. At the time of writing this review, encouraging results have been announced for the clinical trial of a new malaria vaccine developed by GlaxoSmithKline, which has shown some effectiveness in children over an 18-month period.
3. The use of chemotherapy, discussed here, focusing on metal-based drugs.

Metal-drug synergism has been exploited to obtain effective antimalarial metal agents. In line with this, chloroquine was modified through the incorporation of a transition metal into the molecular structure. Several metal complexes were synthesized, characterized, and evaluated. The first ones, RhCl(COD)CQ and $[RuCl_2(CQ)]_2$ (Figure 10.3a), demonstrated that coordination to ruthenium is effective in circumventing the resistance of two CQ-resistant strains of *P. falciparum* (FcB1 and FcB2). *In vivo* experiments showed that $[RuCl_2(CQ)]_2$ caused a reduction of the parasitemia by 94% at a concentration equivalent to 1 ED_{50} (50% effective levels) of chloroquine diphosphate. Encouraged by these results, the Sanchez-Delgado group varied the ancillary ligands and overall charge of the complexes, leading to new organometallic Ru-CQ complexes (Figure 10.3b), which showed an enhanced activity against CQ-resistant strains of the parasite.

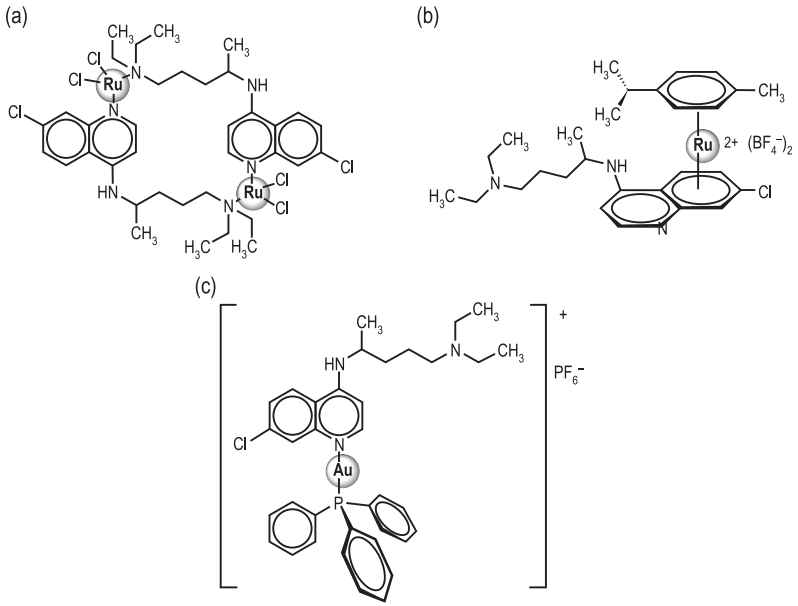

Figure 10.3 Selected metal-based therapeutic agents for malaria. The main mechanism of the action found for these metal-CQ complexes is the inhibition of the β-hematin formation.

In other efforts to obtain metal complexes of greater efficacy, a Au complex of CQ—$[Au(PPh_3)(CQ)]PF_6$ (Figure 10.3c)—was synthesized. It caused marked inhibition of the *in vitro* growth of *P. berghei* and was also very effective against two CQ-resistant FcB1 and FcB2 strains of *P. falciparum*, displaying greater activity than the corresponding chloroquine diphosphate.

Motivated by this higher activity, a series of new Au-CQ complexes were developed by coordinating gold to chloroquine with different changes in the structure of the $[Au(PPh_3)(CQ)]PF_6$ complex. These changes included variations of the phosphine ligand with the purpose of inducing changes in the electronic and steric properties, variations of the counter anion (e.g., nitrate), variations of the Au oxidation state, such as Au(I) and Au(III), or using biologically important ligands such as 1-thio-β-D-glucose-2,3,4,6-tetraacetate. The highest activity in FcB1 and W2 strains was obtained for $[Au(PEt_3)(CQ)]PF_6$, while Au(III) complexes such as $[Au(Cl)_2(CQ)_2]Cl$ showed excellent activity in strains K1. Chloroquine has been coordinated to other metals such as iridium, platinum, titanium, and copper, which have displayed moderate activities.

To gain insight into the possible mechanism of action of the metal-CQ derivatives, two potential targets of action accepted for the chloroquine have been evaluated: the inhibition of hemozoin (malarial pigment) formation and DNA interaction. Chloroquine is believed to act by concentrating in the parasite digestive vacuole and preventing the crystallization of toxic heme into hemozoin, leading to membrane damage and parasite death. It is uncertain how this drug's mechanism operates, but it is well established that chloroquine forms complexes with hematin in solution and is an inhibitor of β-hematin formation. The main mechanism of the action found for the metal-CQ complexes that were evaluated address the inhibition of β-hematin formation, specifically in interfacing. In terms of Au and Ru concentrations in these drugs, and the likelihood of adverse effects on the patient, Au and Ru complexes have thus far only been tested *in vitro* and *in vivo* in mice. Thus, it is currently not possible to predict the likelihood of adverse effects in humans. More studies are needed before the possible concentration of these potential antimalarial drugs is known.

Using a similar strategy, primaquine, mefloquine, and amodiaquine metal derivatives were prepared and evaluated as antimalarial drugs. These compounds, however, did not show significant reduction in parasitemia.

Another interesting and successful metal-based strategy for malaria treatment involved the introduction of the ferrocenyl moiety into the lateral side chain of chloroquine, known as ferroquine (FQ, SSR97193; see Figure 10.1). FQ is extremely active against both CQ-susceptible and CQ-resistant *P. falciparum*, and is being developed by Sanofi-Aventis; it entered phase II clinical trials in September 2007. In contrast to conventional drugs, FQ is the first organometallic drug: a ferrocenyl group covalently flanked by a 4-aminoquinoline and a basic alkylamine. An extensive investigation was carried out in search of analogs with better activities; indeed a library of ~150

antimalarial complexes has been prepared based on ferrocene-conjugate analogs of known antimalarial drugs, such as artemesinin, atovaquone, mefloquine, and quinine, among others.

Ferroquine was also modified in the secondary and tertiary amines. It was combined with thiosemicarbazones and associated with glutathione reductase inhibitors. Another interesting approach was the study of chloroquine diphosphate associated with ferrocene carboxylic acid via a salt bridge. A ruthenocene analog of FQ was also reported. Mixed CQ and/or FQ metal complexes—$[RhCl(COD)L]$, $[Au(L)(C_6F_5)NO_3]$, and $[Au(L)(PPh_3)NO_3]$ where L = CQ or FQ—were also synthesized. All of these compounds have shown very promising antimalarial activities, which implies that the presence of the ferrocenyl moiety in these structures causes significant changes that moderate the attack by malaria parasites.

The pharmacokinetic profile of FQ seems to cover (together with appropriate partner) both cure and posttreatment of malaria prophylaxis. The mechanism of action and the induction of resistance to FQ have been studied in detail by Biot and colleagues. Its mechanism of action may be related to a strong inhibition of the hemozoin formation that leads to the accumulation of toxic heme (free or complexed with FQ), and thus to the death of malaria parasite. In addition, possible interactions between the malaria pigment and FQ may destabilize hemozoin, thereby irreversibly damaging the membrane. Evidence was found which shows that FQ accumulates within the digestive vacuole along with sulfur-containing compound(s). As accumulation of sulfur most likely arises from the influx of glutathione and its accumulation, FQ (under the oxidizing conditions of the digestive vacuole) should be capable of undergoing redox reactions, thus causing lipid oxidation. As a consequence, FQ (unlike CQ) might be capable of producing oxidative stress.

Trioxaquines represent a new class of antimalarial agents. These are hybrid molecules that contain two covalently linked pharmacophores: 1,2,4-trioxane, as in artemisinin, and 4-aminoquinoline, as in chloroquine. The first generation of trioxaquines was found to be highly active against CQ-resistant strains of *P. falciparum*. Ferrocene and trioxane derivatives have also been reported, as well as their biological studies which showed that they are active *in vitro* against CQ-resistant *P. falciparum*.

Selected metallodrugs (e.g., cisplatin, auranofin, aurothiomalate, and NAMI-A) have also been evaluated as antimalarial agents. They show different potencies but effectively reduce *P. falciparum* growth *in vitro*, implying high and broad parasite sensitivity to these metals.

Recent reviews have been published on metallopharmaceutics agents developed to fight against malaria parasites (Navarro et al. 2012; Biot et al. 2012; Salas et al. 2013).

Another rational strategy involves the use of Ru-based compounds designed to deliver carbon monoxide and confer robust protection against malaria (Pena et al. 2012). Interestingly, this class of metallodrugs, referred to as

CO-releasing molecules, provide host disease tolerance; that is, they protect the host from developing severe forms of disease without an overt effect on the pathogen itself (Medzhitov et al. 2012).

Conclusions and Outlook

It is clear that the commercially available drugs for the treatment of leishmaniasis, Chagas disease, and malaria are very limited and far from ideal. There is thus an urgent need to develop new, effective drugs to aid the millions of people suffering from these parasitic diseases, who are waiting for effective, safe, and affordable treatments.

Based on the knowledge that has been gained from analyzing the rationale behind metal-based antiparasitic agents designed to be more active and less toxic than the organic compounds described herein, it is possible to envisage that coordination metal complexes may offer an excellent way to discover and develop new antiparasitic drugs. However, metal-based therapeutics faces two hurdles: not only must they fight against parasitic disease, they must also overcome the prejudice that metals imply toxicity. Metal-based drugs should be treated separately according to their individual biological activity and toxicological properties. This might help attract the attention of pharmaceutical companies and spur more funding for this promising research field.

Undoubtedly, this important area of research needs to be accompanied by firm knowledge and understanding of the biology of these parasites. Fortunately, nowadays, a great number of protein targets have been identified, and novel metal compounds can be designed to attack specific parasitic targets. These advances may have an important impact on the general strategy for the discovery and development of effective metal-based antiparasitic agents with lower toxicity.

The ideal metal-based antiparasitic drug will only be achieved if future work is coordinated. Multidisciplinary groups are needed and should include organic and inorganic synthetic chemists, biologists, pharmacologists, toxicologists, and physicians. Research efforts should be combined and knowledge must be shared. Most importantly, these efforts must be able to rely on financial support from diverse research programs and the pharmaceutical industry.

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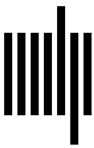

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