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Metal-based drugs for malaria, trypanosomiasis and leishmaniasis: recent achievements and perspectives

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Tropical diseases today constitute a major health problem and a big challenge for drug discovery. Because of the limited arsenal of effective antiparasitic agents and the frequent appearance of chemoresistance, there is an urgent and continuous need to develop new drugs against these ailments. Metal compounds still offer excellent opportunities to find new 'leads' against the major protozoan diseases such as malaria, leishmaniasis and trypanosomiasis. A few metal-based drugs are already available in this therapeutic area, and others are currently being developed. Recent progress in parasite genomics and the identification of a few biomolecular targets hold great promise for the discovery of new 'mechanism-based' antiparasitic metallodrugs. The trends and perspectives for this exciting research field are outlined here.

Introduction

Undoubtedly, tropical diseases today are a major health problem. They affect more than two billion people worldwide (about one-third of the total population) and cause nearly two million deaths per year, mostly in the poorest areas of the planet. The wide diffusion of these diseases, the small number of effective drugs and the frequent emergence of resistance make drug discovery in this therapeutic area a very urgent and challenging task. Until recently, low financial returns greatly discouraged big pharmaceutical companies from investing in drug discovery programs against tropical diseases. Over the past decade, however, this gap has (fortunately) started to reduce considerably as several international non-profit organizations have intervened heavily and efficaciously to sustain tropical disease research, paying specific attention to the clinical development of new chemotherapeutics. Among the several known tropical diseases, we will restrict our attention here to three illnesses with protozoa as their causative agent: malaria, trypanosomiasis and leishmaniasis. These three diseases are among the major tropical diseases characterized by very high morbidity and lethality and by a widespread diffusion across the world.

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This review article specifically aims to consider the several opportunities that metal-based compounds – still a relatively unexplored area of modern medicinal chemistry – might offer today as a rich source of effective chemotherapeutics against the major protozoan diseases.

Remarkably, metal-based drugs have had a major role as therapeutic agents in the ancient history of medicine and in the pioneering times of modern pharmacology, especially as anti-infective agents. Afterward, they were largely abandoned because of (partially grounded) concerns about their systemic toxicity and because of the rapid advent of modern (organic) medicinal chemistry. The most notable exceptions to this trend were the use of platinum-based drugs in cancer chemotherapy after the introduction in the clinics of cisplatin (Fig. 1a) and a few success stories (e.g. auranofin; Fig. 1b) in the treatment of rheumatoid arthritis.

During the past 25 years, however, this situation has changed substantially. There has been a strong resurgence of interest in metal-based drugs with potential applications in a variety of therapeutic areas, especially within the academic bioinorganic community. It has been recognized that metal compounds provide a great variety of different and peculiar chemistries that the reactivity of the metal centers toward target biomolecules can be finely tuned through an appropriate choice of metal ligands, and

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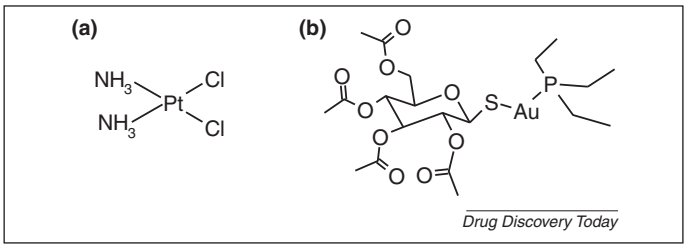

FIGURE 1

Two representative metallodrugs: **(a)** cisplatin and **(b)** auranofin.

that systemic toxic effects can be effectively countered by specific strategies (even in terms of pharmaceutical technology). Several different metal-based compounds were thus investigated, with a renewed interest, especially as anticancer agents, and some of them provided excellent results. Such a return of interest in metal-based drugs can be witnessed in several recent review articles [1–3].

Metal compounds seem to be particularly suitable for the treatment of tropical parasitic diseases because they can show a pronounced selectivity for selected parasites' biomolecules compared to the host's biomolecules.

The application of metal compounds against parasitic diseases is basically grounded on the following considerations:

(i) Metal compounds have already found extensive application in the treatment of parasitic diseases in the pioneering times of modern pharmacology, mostly based on an empirical use. Various inorganic salts were thus administered against the major tropical diseases, sometimes with very good results. Notably, as a consequence of those ancient observations, a few antimony compounds still constitute the treatment of choice for some forms of leishmaniasis. Bismuth is still used sporadically in the prophylaxis of malaria. By contrast, arsenicals, although effective, were withdrawn completely because of toxicity. However, no detailed structure/function studies were ever performed on antiparasitic metal-based compounds. These arguments open the way to new mechanistic investigations in this research area for the optimization of the identified metal leads. In particular, antimony and bismuth compounds, already in clinical use, might be further improved through the modern technologies of synthetic inorganic and coordination chemistry, upon concomitant evaluation of their respective biological profiles. Similar metal-based compounds might be developed – showing, we hope, better biological profiles.

(ii) Metals might be a part of novel antiparasitic agents based on the strategies mentioned below, well documented by a few relevant examples.
- The insertion of a metal center into the scaffold of an established antiparasitic drug to enhance its pharmacological actions, for instance through redox cycling (e.g. ferroquine).
- The metal complexation of classical antiparasitic drugs to modulate activity and pharmacokinetic parameters (e.g. gold–chloroquine and ruthenium–benznidazole).
- The use of stable metal complexes as antiparasitic agents *per se* (e.g. metalloporphyrins).

(iii) New antiparasitic metal compounds could be developed as prodrugs in analogy with metal-based anticancer agents. Indeed, a strict similarity was postulated between parasite and cancer biology. Typically, these substances are able to deliver highly reactive metal-containing molecular fragments (e.g. platinum compounds and ruthenium compounds) capable of hitting parasite targets.

The use of metal-containing substances for the treatment of protozoan diseases was extensively described by Sánchez-Delgado *et al.* [4,5] a few years ago in a couple of comprehensive review articles. Here, we illustrate the state of the art today and report some major achievements that have occurred during the past few years.

Remarkably, the knowledge of the biology of these parasites in our postgenomic era has greatly increased, and several protein targets have been identified against which novel metal compounds might be specifically developed and tested. These advancements could have an important impact on the general strategy for the discovery and development of metal-based antiparasitic agents. Whereas in the past the screening of novel compounds was usually based on the assessment of efficacy against cultured protozoa *in vitro* (simply by measuring inhibition of parasite growth), there is now the opportunity to screen and select the active compounds through specific *in vitro* assays directed against a selected biomolecular target.

In the following paragraphs, we briefly describe the state of knowledge in the application of metal-based compounds against malaria, trypanosomiasis and leishmaniasis with an emphasis on the most representative and recent compounds (2005–2010). Afterward, attention is paid to a few parasitic targets for which metal-based inhibitors might be developed. In a few cases, structural information on the actual metal–target interactions is already available. The expected future trends for this fascinating research area are outlined.

Metal-based drugs for malaria

Malaria is a major cause of morbidity and death in children and adults in tropical countries. Currently, half of the world's population is at risk of malaria. An estimated 243 million malarial cases and 863,000 malarial deaths occurred in 2008, 767,000 of which were in Africa (http://www.who.int/research/en/).

The fight against malaria is largely based on chemotherapy. Historically, several organic compounds have been used as antimalarial drugs, including quinine, chloroquine, hydroxychloroquine, mefloquine, primaquine, proguanil, cotrifazid, doxycycline, sulfadoxine, pyrimethamine, artemether, lumefantrine, artesunate and amodiaquine (the most important are shown in Fig. 2). Current malaria treatments are still based on the combination of two or three of these drugs [6].

Chloroquine (CQ) represents one of the most successful drugs ever used to treat an infectious disease; it was considered a 'wonder drug' because of its low cost, high efficacy and lack of significant side-effects. After twenty years of successful use, however, CQ-resistant malarial parasites started to emerge and spread from Asia to Africa and South America. The loss of activity of CQ as a first-line antimalarial drug is a major setback to the control of malaria; fortunately, effective artemisinin-based drugs are quickly replacing CQ, but the risk of insurgence of resistance even against new endoperoxide antimalarials is very high.

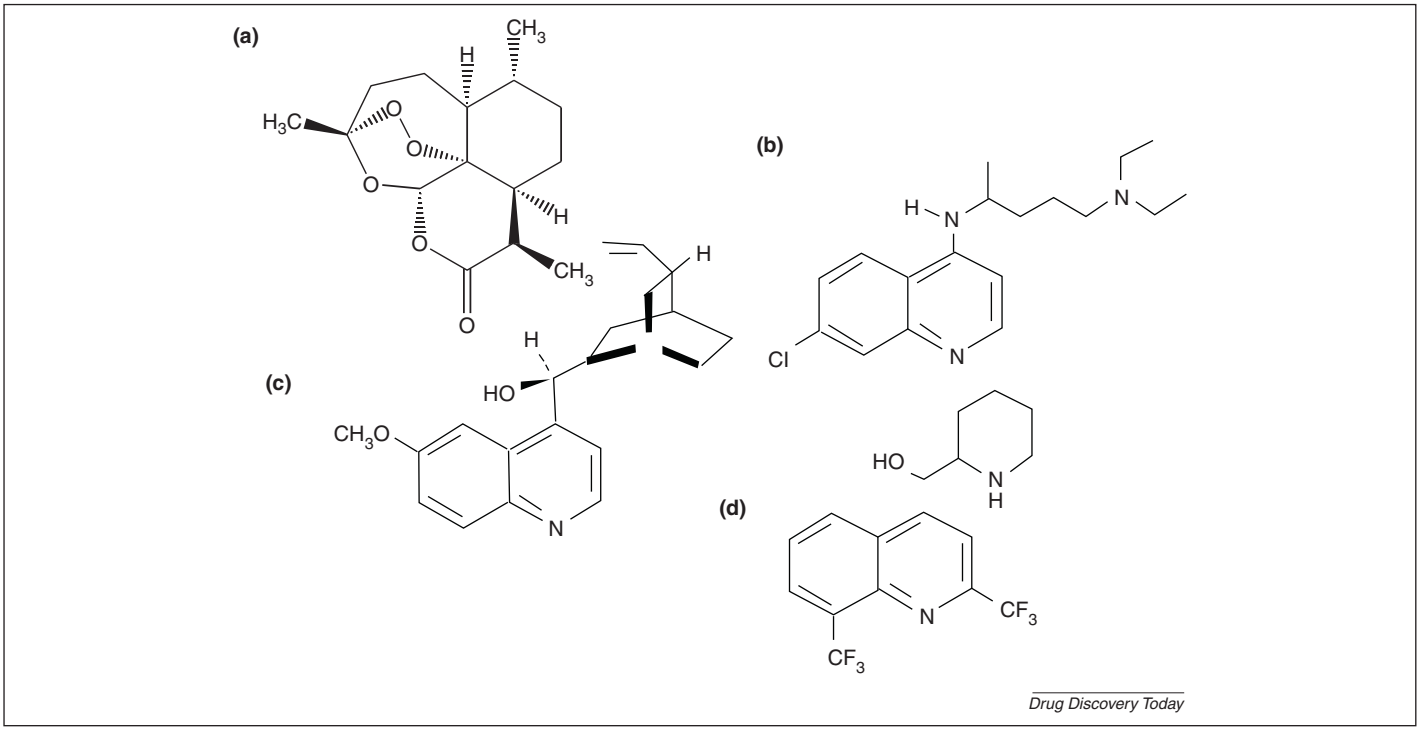

FIGURE 2

Chemical structure of the main antimalarial drugs used in therapy: **(a)** artemisinin, **(b)** chloroquine, **(c)** quinine and **(d)** mefloquine.

Today, the available therapeutic tools for malaria are limited: new anti-malarial drugs, preferably with new structures and/or modes of action, are urgently needed. Metal–drug synergism has been exploited to obtain effective antimalarial metal agents [4,7,8]. Remarkable success came from the modification of CQ through metal-containing fragments, a strategy intensely pursued by Sánchez-Delgado *et al.* Several metal complexes were thus synthesized with encouraging antimalarial activities [8–10]. Among them, ruthenium(II) chloroquine $[RuCQCl_2]_2$ (Fig. 3a) and gold(I) chloroquine $[Au(PPh_3)(CQ)]PF_6$ (Fig. 3b) cause marked inhibition of *Plasmodium berghei* and are very effective against CQ-resistant FcB1 and FcB2 *Plasmodium falciparum* strains. Typically, ruthenium and gold coordination to CQ resulted in a significant enhancement of the parental drug against resistant parasites. Upon pre-incubating uninfected red blood cells with $[Au(PPh_3)(CQ)]PF_6$, protection against subsequent infection was also afforded [8]. Iridium–CQ derivatives showed activity against rodent malaria [9]. Recently, a series of organo-Ru(II)-CQ complexes were synthesized and tested against several *P. falciparum* strains (Fig. 4); they displayed higher activities against resistant parasites than chloroquine diphosphate [10]. Thus, metal complexation of existing antimalarial drugs represents an effective option for drug improvement that merits further exploration. In particular, ruthenium(II) complexation offers the chance of contrasting effectively some of the biochemical mechanisms responsible for CQ resistance, as highlighted by Martinez *et al.*

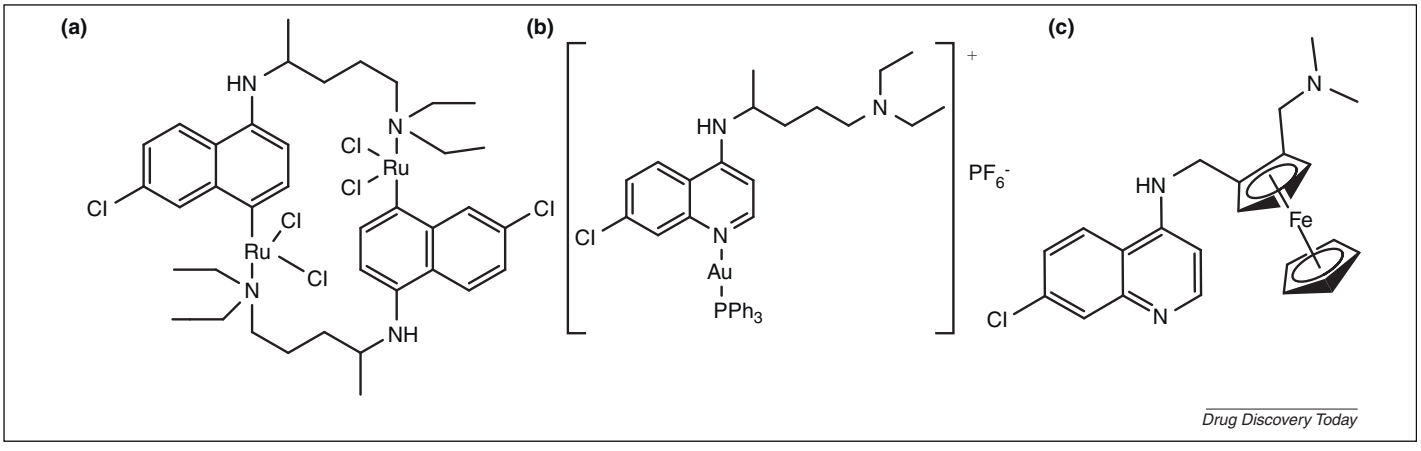

FIGURE 3

Structures of metal derivatives of chloroquine with antimalarial properties: **(a)** ruthenium chloroquine $[RuCQCl_2]_2$, **(b)** gold chloroquine $[Au(PPh_3)(CQ)]PF_6$ and **(c)** ferroquine.

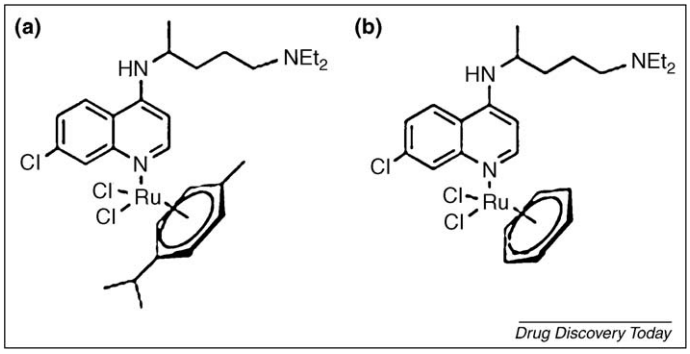

FIGURE 4

Schematic drawings: **(a)** [$Ru^{II}(\eta^6$-p-cymene)Cl_2(CQ)]. **(b)** [$Ru^{II}(\eta^6$-benzene)Cl_2(CQ)].

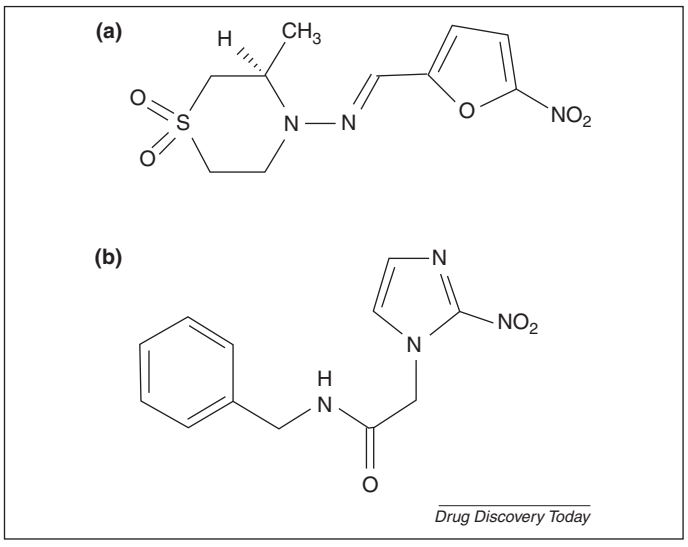

FIGURE 5

Drugs used in American trypanosomiasis: **(a)** nifurtimox and **(b)** benznidazole.

[11,12] in two recent papers. They found that Ru–CQ complex binds to hematin in solution and inhibits aggregation to β-hematin at <!–pH ~5. The heme aggregation inhibition induced by Ru–CQ is significantly higher than that of CQ. This suggests that heme aggregation is the principal target of the Ru–CQ complex and that this additional molecular mechanism permits it to overcome CQ resistance [11,12].

Another interesting metal-based strategy for malaria treatment was disclosed in 1997, when ferroquine (FQ) was first synthesized [13]. FQ, containing a ferrocene moiety (Fig. 3c), shares some biological features with CQ, but their respective activities on *P. falciparum* are very different. FQ, now in phase II clinical trials, is the most advanced antimalarial project of Sanofi-Aventis (http://clinicaltrialsfeeds.org/clinical-trials/show/NCT00563914) [14]. The activity of FQ can be ascribed to a dual mechanism: first, FQ is a strong inhibitor of β-hematin formation, more potent than CQ, and second, redox activation from ferrocene [iron(II)] to ferricinium [iron(III)] and consequent radical generation is probably to occur. Currently, new and interesting FQ derivatives, even bearing a second metal center, are under active investigation.

Recently, selected metallodrugs such as auranofin (Fig. 1b), aurothiomalate, triethylphosphine gold(I) chloride, cisplatin (Fig. 1a), NAMI A [i.e. a ruthenium(III) complex], mononuclear and dinuclear gold(III) complexes, and bismuth and antimony compounds were evaluated for their antiplasmodial properties. All tested metal compounds, although with different potencies, effectively reduced *P. falciparum* growth *in vitro*, implying a high and broad parasite sensitivity to these metals [15,16]. Good candidate molecular targets for these metal compounds are parasite biomolecules containing functionally relevant thiol groups such as thioredoxin reductase, an ubiquitous protein involved in intracellular redox balance, and falcipain, a cysteine protease typical of *P. falciparum* [17,18]. These issues are discussed later in more detail.

Metal-based drugs for trypanosomiasis

American trypanosomiasis (Chagas disease) and human African trypanosomiasis (sleeping sickness) are important health problems of the poorest tropical and subtropical regions of the planet [19–22]. American trypanosomiasis is endemic throughout Latin America, infecting 8–14 million people and causing more deaths (14,000 per year) in this region than any other parasitic disease. After being eradicated in the 1960s, human African trypanosomiasis is now a resurgent disease with epidemic character in many regions of Africa [20]. *Trypanosoma cruzi* and *Trypanosoma brucei*, the etiologic agents of American trypanosomiasis and human African trypanosomiasis, respectively, are protozoan parasites that belong to the trypanosomatid genus and the kinetoplastida order. Both are transmitted to the mammalian host by insects: *T. brucei* by the tsetse fly through saliva and *T. cruzi* by hematophagus triatomine bugs through the insect feces [4,5,23].

Chemotherapy for trypanosomatid infections mostly relies on drugs that are more than 50 years old and suffer from poor efficacy, high toxicity and increasing resistance. Treatment of American trypanosomiasis is based on nifurtimox and benznidazole (Fig. 5), two unspecific nitroheterocyclic drugs that show significant activity only in the acute phase of the disease [21–24]. Conversely, the principal drugs for human African trypanosomiasis, namely pentamidine, suramin, eflornithine and melarsoprol, suffer from severe toxicity, are not universally active and have already generated conspicuous levels of resistance [20,25].

Several attempts are under way to develop new trypanocidal metal-based compounds [25–27], mostly inspired by the three following strategies: the metal coordination of trypanocidal ligands, the metal coordination of DNA intercalators and metal compounds as direct inhibitors of parasite enzymes. Examples of these approaches are given below (Figs. 6 and 7).

Metal complexes of trypanocidal ligands

The design of antiparasitic compounds by combining anti-trypanosomal ligands with pharmacologically active metals follows the concept of developing new chemical entities as dual inhibitors, capable of affecting multiple targets simultaneously. Indeed, single agents acting against multiple parasitic targets might diminish host toxicity. Pioneering work by Sánchez-Delgado *et al.* [4,5] led to the discovery of metal complexes of clotrimazole and ketoconazole intended for anti-trypanosome therapy. More recently, Gambino *et al.* developed several ruthenium, platinum and palla-

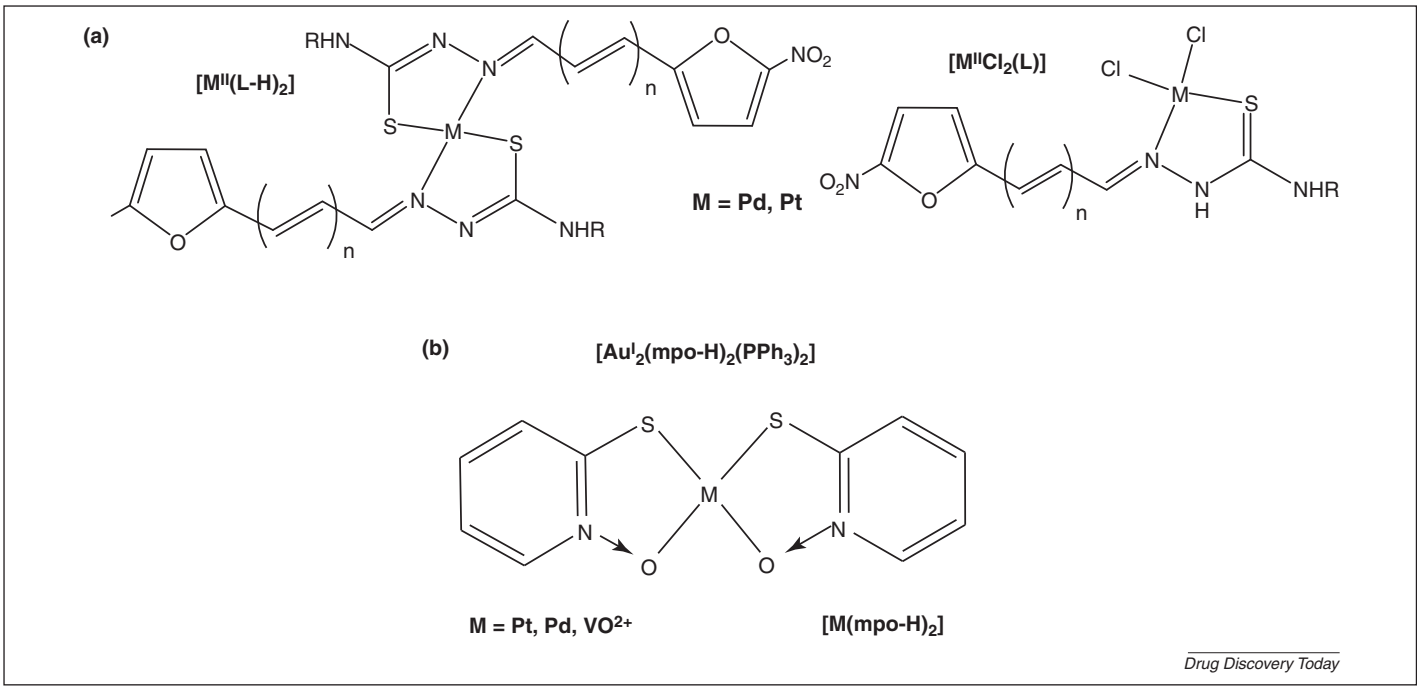

FIGURE 6

A few representative metal-based drugs for trypanosomiasis: **(a)** metal compounds of 5-nitrofuryl-derived thiosemicarbazones. **(b)** 2-Mercaptopyridine N-oxide metal complexes.

dium complexes of bioactive 5-nitrofuryl and 5-nitroacroleine containing thiosemicarbazones. These ligands had shown higher *in vitro* activity against *T. cruzi* than nifurtimox based on a similar mechanism. In turn, platinum, palladium and ruthenium compounds had proven and conspicuous antitumor effects caused by their ability to bind DNA. Coordination of selected bioactive ligands to these metals seemed interesting because of the postulated metabolic similarities between tumor cells and *T. cruzi* cells. As a proof of concept, *in vitro* evaluation of *T. cruzi* epimastigotes showed that many of these Pt(II) and Pd(II) complexes were more

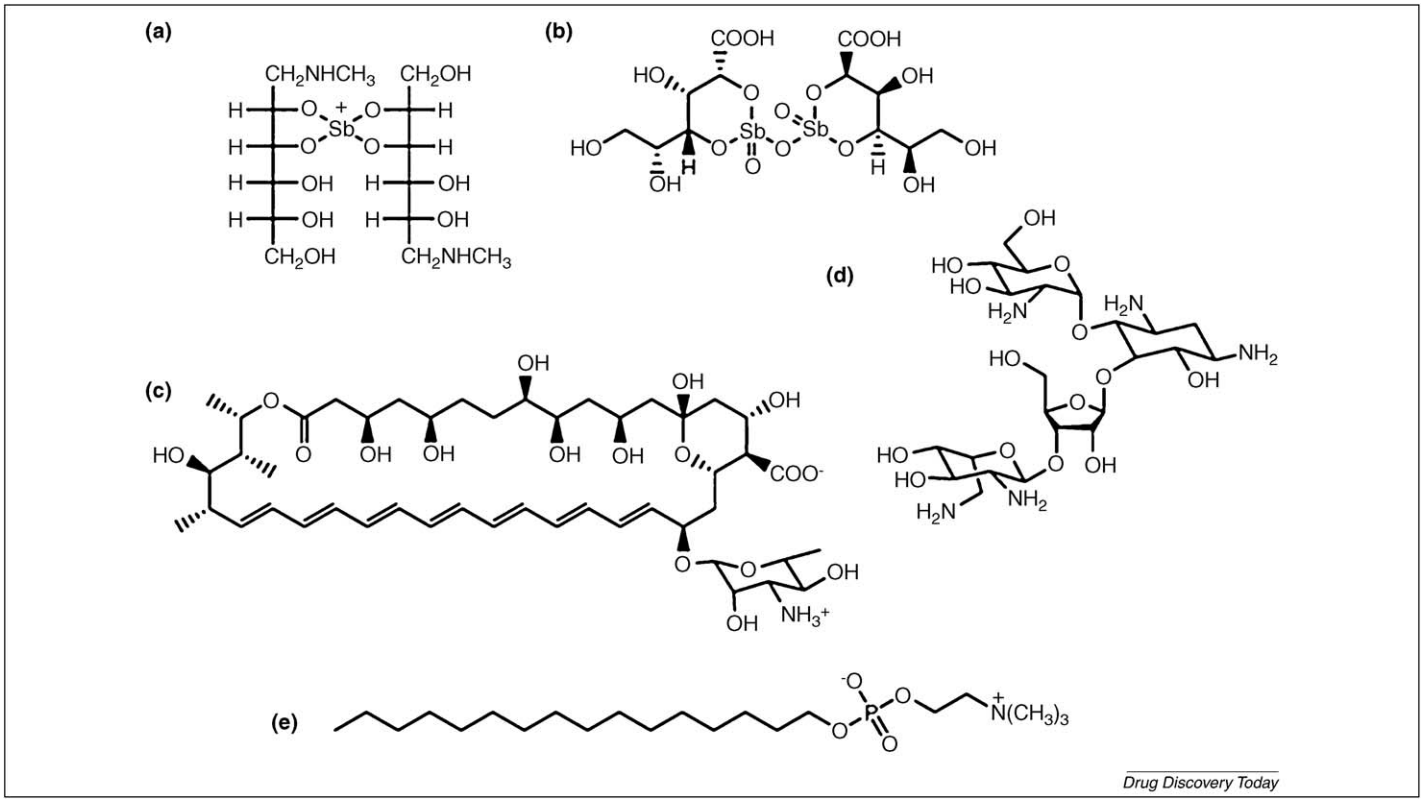

FIGURE 7

Drugs used for the treatment of leishmaniasis: **(a)** glucantine, **(b)** pentostam, **(c)** amphotericin B, **(d)** paromomycin and **(e)** miltefosine.

active than nifurtimox and the corresponding free ligand L [28–30], holding great promise for future drug development.

A similar situation was found in the case of 2-mercaptopyridine *N*-oxide (mpo). Turrens *et al*. demonstrated several years ago that mpo can block *T. cruzi* growth through inhibition of NADH–fumarate reductase affecting all stages of a parasite's cycle without affecting mammalian cells. Remarkably, $[Au_2(mpo\text{-}H)_2(PPh_3)_2]$, $[Pt(mpo\text{-}H)_2]$, $[Pd(mpo\text{-}H)_2]$ and $[VO(mpo\text{-}H)_2]$ showed significantly increased activities compared to mpo on epimastigotes of different *T. cruzi* strains. In particular, Pt(II), Au(I) and Pd(II) complexes were 39-, 67- and 115-fold more active, respectively, than nifurtimox. In turn, NADH–fumarate reductase inhibition studies showed a clear correlation between parasite inhibition and enzyme inhibition, highlighting NADH–fumarate reductase as the probable main target of these complexes [31,32].

Metal complexes of DNA intercalators

Compounds that efficiently interact with DNA through intercalation, beyond being potent antitumor agents, might show significant antitrypanosomal activity [33]. With this in mind, some homoleptic and heteroleptic vanadyl complexes with DNA intercalators as ligands (dppz = dipyrido[3,2-a:2′,3′-c]phenazine and bipy = 2,2́-bipyridine) were designed and tested as potential antitrypanosomal agents. The homoleptic vanadyl complex $[V^{IV}O(SO_4)(H_2O)_2(dppz)]\cdot 2H_2O$ showed slightly better *in vitro* activity than nifurtimox on *T. cruzi* Dm28c strain epimastigotes [34]. Mixed-ligand vanadyl complexes, $[V^{IV}O(L2\text{-}2H)(L1)]$, including the bidentate polypyridyl DNA intercalator (L1) and a tridentate salycylaldehyde semicarbazone derivative (L2) as ligands were also designed. Complexes including dppz as coligand showed IC_{50} values in the μM range against the Dm28c strain of *T. cruzi*, being as active as nifurtimox [35].

Metal complexes as metal inhibitors of parasite enzymes

Enzyme inhibition is one of the main modes of action of inorganic drugs. Indeed, metal ions might coordinate crucial active-site residues, thus blocking enzyme interaction with substrate, or might coordinate to external residues modifying enzyme structure. According to this strategy, many efforts were made to design metal coordination compounds that could specifically bind parasitic enzymes. Cruzipain, the major cysteine protease found in *T. cruzi*, is a validated target for the development of chemotherapeutics against American trypanosomiasis. Cruzipain inhibitory effects of some Pd(II) and Au(III) cyclometallated complexes and Re(V) complexes were initially explored with excellent results [27].

Metal-based drugs for leishmaniasis

Leishmaniasis is a disease with extensive morbidity and mortality. Its various forms are caused by protozoa of the genus *Leishmania* and range from self-healing cutaneous leishmaniasis to progressive mucocutaneous infections and fatal disseminating visceral leishmaniasis. Leishmaniasis currently affects some 12 million people worldwide with two million new cases per year. Approximately 350 million people live at risk of infection with *Leishmania* parasites; leishmaniases are prevalent in 88 countries, including 72 developing countries (http://www.who.int/emc).

The available treatments for leishmaniases are far from ideal. The classic first-line treatment relies on pentavalent antimonials with sodium stibogluconate (pentostam) and meglumine antimoniate (glucantine) as the most representative drugs. This is a clear example of clinically established metal-based drugs against a parasitic disease.

Although effective, these antimonials can cause severe side-effects such as cardiotoxicity, reversible renal insufficiency, pancreatitis, anemia, leucopenia, and others. When antimonials fail, amphotericin B is the recommended second-line treatment for visceral, cutaneous and mucocutaneous leishmaniasis. Aromatic diamidine pentamidine is a traditional alternative to pentavalent antimony. Recently, miltefosine was introduced as the first oral treatment for visceral leishmaniasis [36–38]. Another group of antileishmanial compounds are the sterol biosynthesis inhibitors, including terbinafin, imidazole derivatives (ketoconazole and clotrimazole), triazoles (fluconazole and itraconazole) and azasterols.

With the exception of antimonials, the use of metal-containing drugs as antileishmanial agents (according to the metal–drug synergism concept) was scarcely explored and warrants further studies. Indeed, the appearance of drug-resistant strains of *Leishmania* spp. justifies intense screening of new compounds in parallel with deeper investigations of *Leishmania* biology to identify possible targets for rational drug design. In any case, the studies reported so far on metal compounds offer valuable hints for further research efforts.

Simple salts such as zinc sulfate were tested clinically against cutaneous leishmaniasis with very promising cure rates (>96.0%), using oral doses of 10 mg/kg for 45 days [39].

Several years ago, a DNA metallointercalator (2,2′:6′2″-terpyridine)platinum (II) showed remarkable antileishmanial activity, the most effective compound causing complete growth inhibition of *Leishmania donovani* amastigotes, at 1 μM concentration [40]. This complex exploits simultaneous DNA intercalation of terpyridine and platinum(II) binding to the enzyme active site. As the metabolic pathways of kinetoplastid parasites are similar to those of tumor cells [33], Navarro's group designed a group of metallointercalators showing significant antileishmanial activity, probably arising from DNA intercalation [41].

Another interesting approach was proposed by Fricker *et al*. [27], who developed various gold(III), palladium(II) and rhenium(V) cyclometallated complexes as potential inhibitors of different cysteine proteases in the search for metal-based drugs suitable not only for American trypanosomiasis but also for leishmaniasis [18,27].

Emerging druggable targets for metal compounds

The recent spectacular advancements in molecular biology and genomics have greatly expanded our understanding of parasite biology. Owing to such progress, a few parasite targets that are likely to be very sensitive to metal-based compounds have already been identified; some of the identified proteins indeed bear groups such as free thiols at their active sites that manifest a high propensity to react with 'soft' metals and are thus amenable to strong and selective inhibition by metallodrugs. A few examples will be described below.

Substantial work carried out by Krauth-Siegel *et al*. [42,43] revealed that dithiol reductases have crucial roles in the overall redox metabolism of parasites. Thioredoxin reductase in plasmo-

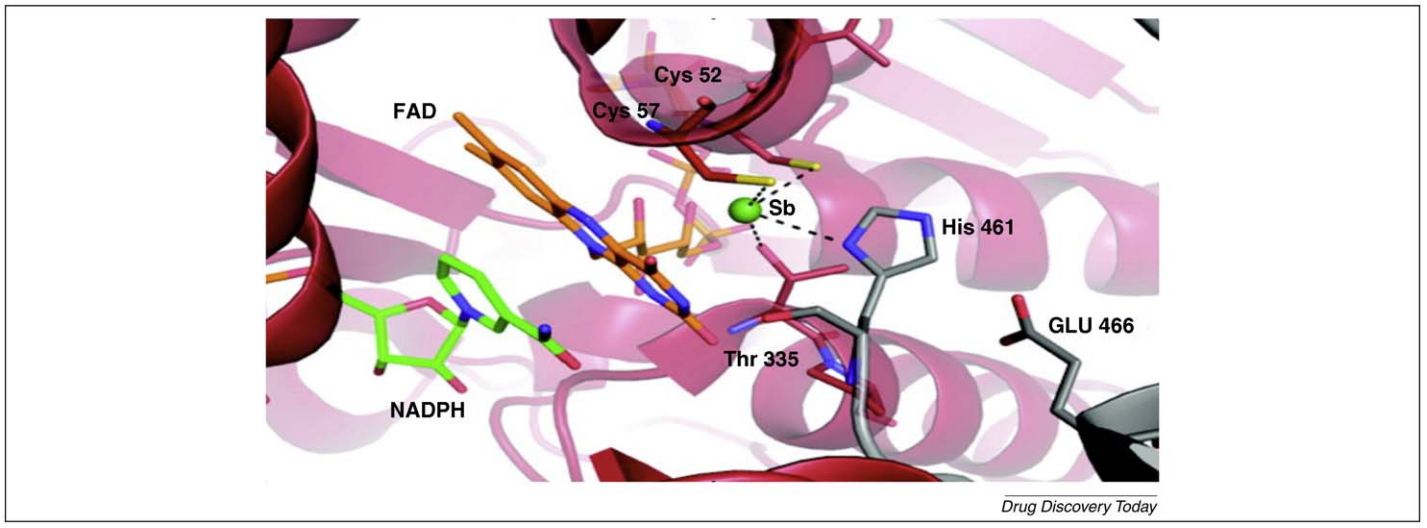

FIGURE 8

Crystal structure of the complex of trypanothione reductase (TR) from *Leishmania infantum* with NADPH and Sb(III) [44].

dia and trypanothione reductase in *Trypanosoma* and *Leishmania* are excellent examples of this kind of protein: because both proteins contain active-site thiol groups, they constitute primary druggable targets for metal compounds. Indeed, it is well known that parasites are particularly sensitive to oxidative stress arising from dithiol reductase inhibition.

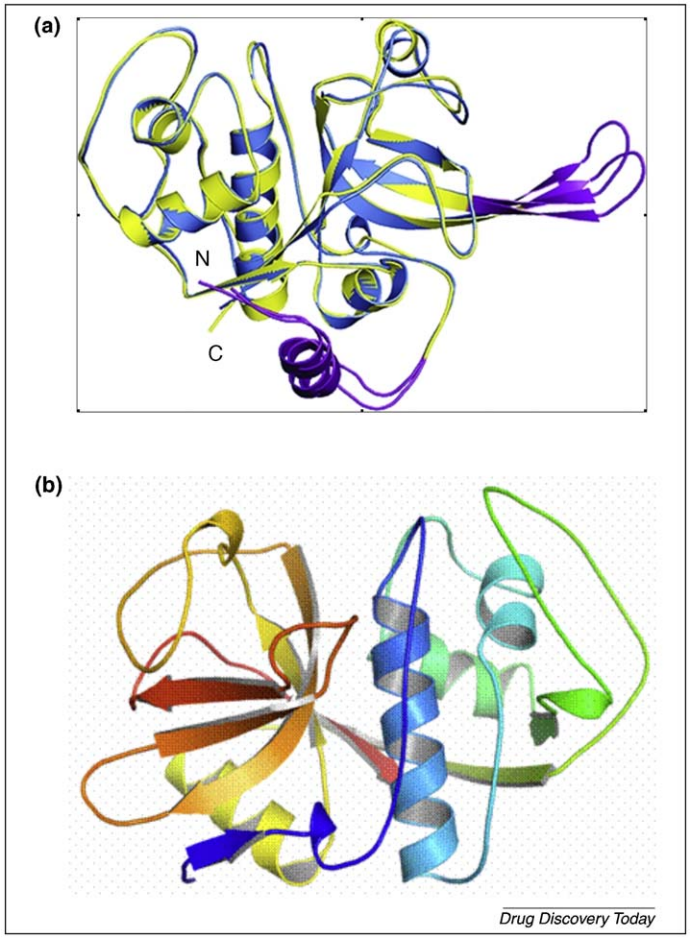

FIGURE 9

Two cysteine proteases as emerging parasite targets: **(a)** falcipain and **(b)** cruzipain has a dotted background.

Within this frame, Colotti *et al.* recently reported the crystal structure for *Leishmania* trypanothione reductase disclosing the actual mechanism of enzyme inhibition by antimonials. It was shown that trivalent antimony binds to the protein active site with high affinity, strongly inhibiting enzyme activity [44]. The metal binds directly to Cys52, Cys57, Thr335 and His461, thereby blocking hydride transfer and trypanothione reduction. Details of the structure are shown in Fig. 8. The observed Sb–protein interaction is consistent with the usual modalities of cysteine binding of thiophilic metals such as As(III), Sb(III) and Bi(III). Such metal-dependent inhibition of thiol reductases opens the way to combined metal therapy of leishmaniasis. It is very likely that this enzyme is similarly inhibited by other classes of metal complexes that are Lewis soft acids.

Pairwise, thioredoxin reductase is a crucial redox enzyme of plasmodia. It contains an active-site dithiol group [45]. This observation implies that thiophylic metals might act as potent enzyme inhibitors; however, because the mammalian enzyme contains pairwise an active-site selenol group and is very susceptible to inhibition by metal compounds (see, for instance, the several articles by the group of Berners Price [46–49]), extreme caution must be taken in developing metal-based thioredoxin reductase inhibitors capable of differential enzyme inhibition.

Cysteine proteases constitute another family of emerging parasite targets [50–52]. Fricker *et al.* proposed that metal-containing compounds might be developed as antiparasitic agents upon evaluating their ability to inhibit typical cysteine proteases [27]. Parasites typically contain a few important cysteine proteases, the strong inhibition of which might lead to the parasite's death. Important examples are given by falcipain and cruzipain. Because both these enzymes bear a thiol group at their active site, they are usually susceptible to inhibition by metal compounds (Fig. 9).

Concluding remarks and future perspectives

Metal-based compounds were largely neglected by the pharmaceutical industry and the medicinal chemistry community for a

long time; thus, several good opportunities for new drug discovery were probably lost. Many recent studies, however, mainly carried out in the fields of experimental oncology and bioinorganic chemistry have revealed that metal centers can be exploited pharmacologically to obtain innovative drugs, in different therapeutic areas. Metal-based drugs offer excellent opportunities for discovering new antiparasitic agents for which there is currently a great need. In particular, we have focused our attention on the major protozoan diseases of the tropical and subtropical areas. Notably, some metal compounds are already in clinical use against these diseases, whereas others are undergoing advanced clinical evaluation (e.g. FQ is now in phase II trials). Nonetheless, there are still great and unexplored opportunities in this research field for further metal-based drug discovery.

In this short review, we have considered several success stories in which metal centers have been incorporated into antiparasitic agents and the underlying strategies and rationale. From these stories, it has clearly emerged that the discovery of metal-based compounds as potential antiparasitic drugs has relied on various approaches over the course of time; analysis of these various approaches enables the depiction of some future trends in this research area.

In the past, the use of metal-based compounds was mainly driven by empiricism and by sporadic medical observations. Nonetheless, these activities and observations led to the discovery of important antiparasitic actions for a few metal compounds, such as bismuth in malaria prophylaxis and antimonials for leishmaniasis. In more recent times, starting from the 1980s, the design and discovery of metal-based antiparasitic agents were mainly governed by progress in coordination chemistry and its applications in medicine. Several metal-based compounds bearing antiparasitic activity were thus developed according to the strategies illustrated above.

In the past decade, however, coinciding with the advent of the so-called 'postgenomic era', the discovery of new metal-based agents seems to have been mostly driven by progress in the knowledge of parasite biology and by the identification of parasite targets susceptible to metal inhibition. Selected examples have been presented, such as dithiol reductases involved in parasite redox metabolism and a few parasite proteases. The availability of these parasite proteins in purified form might enable targeted screening *in vitro* of the best metal-based drug candidates out of large libraries. In turn, the knowledge of the molecular structure of the target will enable the rational design of novel metal-based antiparasitic agents according to *in silico* docking methods. These advanced strategies hold much promise for obtaining innovative metal-based compounds and for the optimization of known leads.

In conclusion, through this rapid excursus, we have tried to highlight the great potential and the real opportunities that metal-based drugs still offer today to the discovery and development of new antiparasitic agents.

Acknowledgements

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