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Organometallics in Medicinal Chemistry: Antiparasitic Agents

Dinorah Gambino *,[a]

[a]*Área Química Inorgánica, Facultad de Química, Universidad de la República, 11800 Montevideo, Uruguay*

Neglected tropical diseases (NTDs) encompass a diverse group of 20 medical conditions triggered by various pathogens, including viruses, bacteria, protozoa, and parasitic worms. Diseases caused by parasitic protozoa and parasitic worms show the highest incidence worldwide. NTDs predominantly afflict impoverished communities in tropical regions, although some exhibit a broader geographic reach. It is estimated that over 1 billion people suffer from NTDs, spanning 149 countries. Additionally, malaria is caused by protozoa of the genus *Plasmodium* and is highly prevalent in similar geographic regions. New drugs are urgently needed for the treatment of these diseases. In the last decades, various research groups have endeavored to develop organometallic compounds with potential applications as drugs against malaria and NTDs diseases caused by trypanosomatid parasites and parasitic helminths. This perspective highlights selected efforts from these groups in the pursuit of innovative therapeutic solutions. Relevant bioorganometallic compounds belonging to the typical classes of metallocenes, "half sandwich" M-arenes and metal carbonyls will be particularly described.

Keywords: organometallics, neglected diseases, malaria, trypanosomatid parasites, parasitic helminths

1. Introduction

Although human life relies on at least ten essential metals, more than forty non-essential metals, including radionuclides, currently find different applications in therapy and diagnostics.[1,2] Classical Inorganic Medicinal Chemistry involves five main research areas (Figure 1): chelation therapy that looks for designing proper ligands to remove excess of metals causing disease, supplementation of essential metals that are present *in vivo* in deficient levels causing disease, development of contrast agents mainly as tools for magnetic resonance imaging (MRI) diagnostics, radiopharmaceuticals for diagnosis or therapy and the wider area of development of therapeutic agents for the treatment of varied diseases.

The later aims to design, identify and prepare new metal-based drugs or prospective drugs. Additionally, it includes the study of the chemical changes that these compounds suffer in the biological media, the unraveling of their mechanism of action at molecular level and the establishment of structure activity relationships that could guide in the drug discovery process. Recently, this area is paying increasing attention to metallomics as the comprehensive analysis of the metal species within a cell or tissue type relevant to the unveiling of the mechanism of action.[3]

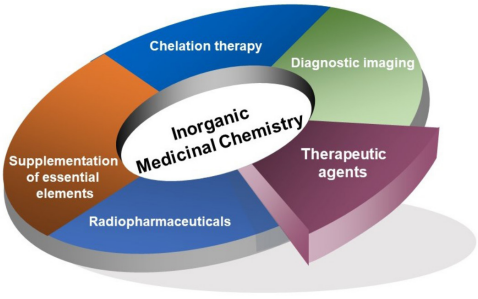

Figure 1. Main classical areas of Inorganic Medicinal Chemistry.

Although therapeutical properties of metals and metal compounds for the treatment of different pathologies have been known since ancient times, the serendipity discovery of the antineoplastic properties of the very simple cisplatin compound in 1965 (Figure 2) led to the explosive development of the modern era of Medicinal Inorganic Chemistry, which is marked by the rational design of new compounds searching for selected therapeutical properties not restricted to antitumoral activity.[4]

*e-mail: dgambino@fq.edu.uy
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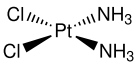


Figure 2. Structure of cisplatin (*cis*-diamminedichloroplatinum(II)).

Novel metal-based compounds are being currently investigated against viruses, parasites, bacteria and fungi and diseases such as diabetes, Parkinson and Alzheimer, among others. Different metal compounds have been approved by different pharmacopeias for clinical use and are daily used in medicine. Many others are in drug development advanced clinical phases waiting for entering the pharmaceutical market in the next years. Multitude of prospective metallodrugs has been explored for their potential as anticancer agents, antimicrobials, antivirals, and various other indications. Despite this extensive investigation, only a limited number of metal compounds have been successfully translated into clinical applications.[1,5,6] A detailed list of medicines including a metal can be found in the supplementary file of Anthony *et al*.[1] Most common examples in this list are some simple metallic salts, like lithium carbonate, silver sulfadiazine, bismuth subcitrate potassium and magnesium sulfate or classical coordination compounds, like cisplatin, oxaliplatin, carboplatin, sodium nitroprusside, cyanocobalamin, ibritumomab tiuxetan, glucantime, pentostam, auranofin and Sm-153 lexidronam.

In modern era this discipline has left behind serendipity and involves a rational design of new drugs based on Inorganic Chemistry knowledge. The chemical characteristics associated with both the central metal (oxidation state, acidity, geometry, coordination number, kinetic and thermodynamic stability, among others) and the ligand (basicity, donor atoms, denticity, hapticity, chirality, reactivity in biological environments) are of particular importance for this design. If all these aspects are considered, metal compounds offer broad possibilities for designing potentially bioactive compounds. Furthermore, considering that many of these compounds may undergo redox reactions of the central metal ion, ligand substitution reactions, or reactions at the level of organic ligands in biological environments, they can effectively serve as prodrugs that will be activated *in vivo*. In this sense, metal compounds offer a wider range of possibilities compared to organic compounds developed by Medicinal Organic Chemistry. This poses a challenge in both the design of potential metal-based drugs and the elucidation of their mechanism of action. As the pursuit of innovative and improved drugs becomes increasingly pressing, the existing drug discovery and development pipelines designed for organic drugs, relying on target identification or high-throughput screening of libraries of compounds, prove to be less effective when applied to metallodrugs. Metal-based drugs or prospective metal-based drugs include simple metal salts, classical coordination compounds and organometallic compounds.

2. Bioorganometallics

At the end of the 20th century, it was demonstrated that organometallic compounds usually used in catalysis could themselves be used to treat diseases. In this context, Bioorganometallic Chemistry is a relatively recent and deeply interdisciplinary field, focusing on authentic organometallic compounds featuring at least one σ metal-carbon bond, with relevance in a biological context. This area was described as such for the first time more than 20 years ago by the pioneer French researcher Gerard Jaouen.[7-13] Specifically, it encompasses organometallic drugs and prospective organometallic drugs. These compounds provide a promising and innovative approach to designing new drugs with unique modes of action, offering distinct advantages compared to traditional coordination compounds and purely organic substances. Notably, these advantages include highly diverse structural possibilities, the ability to modulate their lability to achieve kinetically stable compounds, a lipophilic nature that could favor the *in vivo* behavior, and a rich redox chemistry. Although the primary focus of the field has been on the development of potential anticancer drugs, attempts to expand generating bioactive compounds for other purposes have been successful.[10-12,14-19]

Figure 3 shows the main types of organometallic compounds investigated in Medicinal Chemistry during the last decades: metallocenes, metal-arenes (M-arenes), metal-carbonyls (M-carbonyls) and metal-carbenes (M-carbenes).[6]

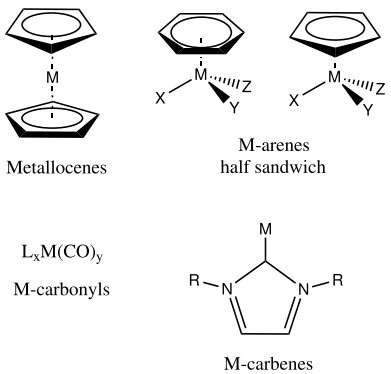


Figure 3. Main types of organometallics investigated in Medicinal Chemistry.

Organometallic compounds of these primary categories emerged as alternative chemotherapeutic agents against tumors, pathogenic fungi and bacteria and viruses, like severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2), thanks to their distinct and specific physicochemical properties.[6,9,11,14,19-27]

Metallocenes consist of two cyclopentadiene (Cp) anions that exhibit a robust binding to certain metals such as iron, adopting a side-on orientation. Due to this typical configuration, these compounds are frequently referred to as "sandwich complexes" due to the manner in which the Cp ligands envelop the metal ion.

Demonstrating broad antitumor activity, titanocene dichloride became the first non-platinum complex to undergo clinical trials for its potential use as a chemotherapy drug (Figure 4).[28] A quite different mechanism of action to that of cisplatin was proposed for it involving the binding to transferrin which transports it to tumor cells that usually show overexpressed receptors of this protein due to high iron requirements. After preferentially entering into the tumor cells, Ti^{IV} accumulates in nucleic acids rich regions probably generating a deoxyribonucleic acid (DNA) adduct by binding to the phosphate skeleton of this biomolecule.[29] Reaching phase II in Germany, trials were later on abandoned due to the uncontrolled and complex hydrolysis of the compound in biological medium that complicated its pharmacokinetic study and the characterization of its active metabolite, among other drawbacks.

Among metallocenes, the ferrocene moiety has undoubtedly played a pivotal role in the advancement of bioorganometallic drugs, showcasing several physicochemical advantages tailored for this purpose (Figure 4). It boasts affordability, easy derivatization, stability in aqueous solutions under aerobic conditions, high lipophilicity, and non-cytotoxicity. Furthermore, it possesses the capability to generate reactive oxygen species (ROS) through Fenton-like reactions, adding an additional mechanism of action. Considering these advantages, the integration of the ferrocene moiety into organic drugs has emerged as a successful strategy to reduce cytotoxicity in normal cells and enhance the therapeutic index of such drugs. Consequently, a long series of antitumor ferrocenyl compounds, exemplified by ferrocifen, the organometallic analogue of the anticancer drug tamoxifen developed by the French group headed by Jaouen,[30,31] has been successfully developed (Figure 4). First reported in 1996,[32] ferrocifen stands out as one of the earliest organometallic selective estrogen receptor modulators. The inclusion of the ferrocenyl moiety into the organic drug resulted in enhanced activity compared to the parent drug and in a broader spectrum of activity. Notably, it exhibits antiproliferative effects on both hormone-dependent (MCF-7) and hormone-independent (MDA-MB-231) breast cancer cells with significant efficacy. In contrast, tamoxifen demonstrates antiestrogenic activity exclusively in hormone-dependent MCF-7 breast cancer cells. Ferrocifen has been in pre-clinical studies as antitumoral agent. Cell death mechanism induced by ferrocifen and its derivatives differs depending on structure, cell line and concentration. Generation of ROS through Fenton reaction and effects on thioredoxine reductase have been described as part of it. Ferrocifen is highly insoluble in water and requires a formulation stage before being administered *in vivo*. Lipid nanocapsules including ferrocifen are currently under study as potential nanomedicines.[32-34]

The same strategy was followed by Jaouen and co-workers[31,34] to get more than 200 ferrocenyl derivatives with antitumoral activity, perform structure activity relationships (SAR) studies and make attempts to unravel the mechanism of action. Other groups[33] have also adopted the strategy of generation of ferrocene-containing hybrids of different organic drugs to get compounds with a diversity of activities.

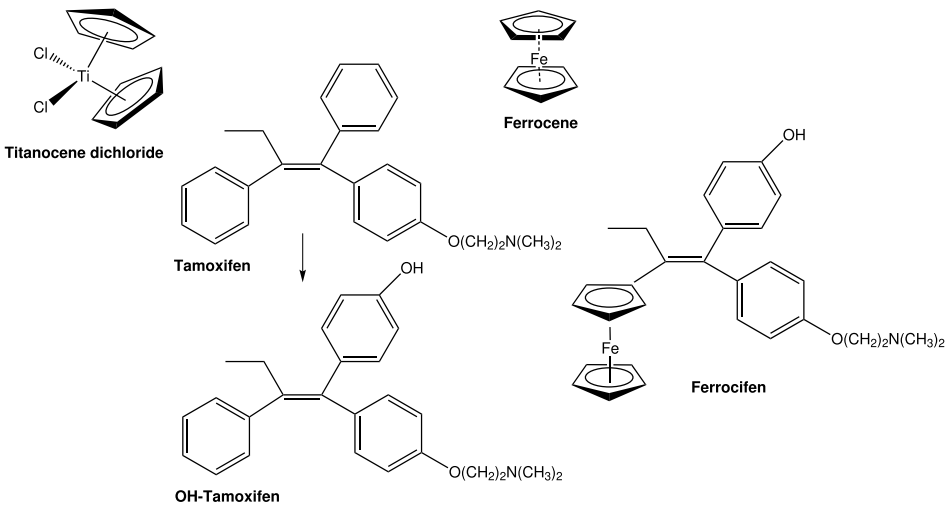


Figure 4. Structures of titanocene dichloride, ferrocene, tamoxifen and its biological active species hydroxy-tamoxifen and the analogous organometallic compound ferrocifen.

Half sandwich ruthenium arenes have been by far the most studied M-arenes in organometallic medicinal chemistry. This type of organometallic compounds (Figure 5) offers ample possibilities for designing new compounds by incorporating a range of ligands X, Y and Z, different arene types (cyclopentadienyl or aryl and substituted) or functional groups onto the arene moiety. These modifications have the capability to influence the physicochemical and biological characteristics of the compounds, leading to a diverse array of mechanisms of action.[6,16]

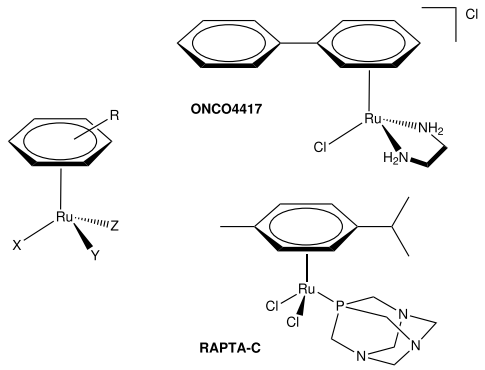


Figure 5. General structure of Ru^{II}-arene half sandwich (piano stool) complexes (right) and main examples of compounds entering clinical trials by Sadler's (ONCO 4417)[35] and Dyson's (RAPTA-C)[35,36] groups.

These "piano stool" shaped compounds exhibit the ability to covalently interact with guanine residues in DNA through the substitution of labile ligands and, additionally, by intercalating via selected expanded bicycle arene moieties, or minor groove binding. Two distinct families of anticancer compounds have undergone thorough investigation in the last decades: Ru-arene compounds $[Ru(\eta^6\text{-arene})(en)(Cl)]^+$, where en = ethylenediamine, and the RAPTA series of complexes ($[Ru(\eta^6\text{-arene})(PTA)(Cl)_2]$), with PTA = 1,3,5-triaza-7-phosphoadamantane. These compounds have demonstrated significant efficacy in both primary tumors or metastasis, leading to the selection of certain candidates for further *in vivo* studies. Selected compounds that have entered clinical trials as antitumorals are shown in Figure 5.[12]

Although osmium and iridium half-sandwich complexes have not garnered as much focus as their ruthenium counterparts in terms of their potential applications in medicinal chemistry, considerable research has been conducted to investigate the therapeutic potential, biological properties, and mechanisms of action of these complexes.[37-41]

Within metal-carbonyls, rhenium(I) tricarbonyls have demonstrated the most encouraging antitumoral outcomes. The prevalent structural motif of Re utilized in biological systems is the stable Re^I tricarbonyl core (Figure 6). These organometallic compounds exhibit several intrinsic properties that are advantageous for the development of innovative anti-cancer drug candidates. Moreover, their straightforward synthesis enables the generation of a diverse array of compounds, allowing for the tuning of properties to optimize biological activity.

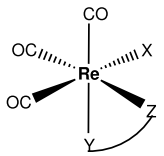


Figure 6. Rhenium(I) tricarbonyls common structure: X monodentate ligand, YZ bidentate ligand.[41-44]

Additionally, leveraging their rich spectroscopic properties these compounds have also been utilized for *in vitro* in cell fluorescence and vibrational microscopic imaging. The French group headed by Policar[45-47] has developed front-line research in this sense.

Concerning the main types of organometallics explored in Medicinal Chemistry (Figure 3), metal-*N*-heterocyclic carbenes have demonstrated notably robust antitumoral activity, particularly those of gold. Casini and co-workers[48] have extensively worked on the topic.

While the primary emphasis in bioorganometallic research has traditionally centered on the development of antitumor agents, the advent of the SARS-CoV-2 pandemic has prompted several research groups to redirect their focus toward viral infections. Although this area has been relatively underexplored in terms of metal-based bioactive compounds, an expanding body of reports[26,49-55] detailing metal complexes exhibiting activity in SARS-CoV-2 infection models affirms the potential efficacy of metal complexes in this particular area. In particular, Ott and co-workers[56,57] together with other organometallic groups[26] have recently reported on gold and silver *N*-heterocyclic carbene complexes with antiviral effects against SARS-CoV-2 in infected cells as potent inhibitors of the SARS-CoV-2 papain-like protease PLpro, which is a key enzyme in the virus replication in infected cells.

Having delineated the most relevant medicinal chemistry applications of the main classes of organometallics, this perspective will focus on the major strides made in the advancement of therapeutic organometallic antiparasitic agents over the past three decades, not providing a comprehensive or exhaustive review. The pioneering work performed by selected leading and representative groups for the development of agents against highly prevalent parasitic diseases, like malaria and diseases caused by trypanosomatid parasites and parasitic helminths, are

highlighted. Outcomes by those groups having done efforts to modify structures through rational design, to get at least qualitative structure-activity relationships and to identify molecular targets and mode of action are emphasized.

2.1. Organometallics as antiparasitic compounds

Neglected tropical diseases (NTDs) encompass a diverse group of 20 medical conditions triggered by various pathogens, including viruses, bacteria, protozoa, and parasitic worms. NTDs predominantly afflict impoverished communities in tropical regions, although some exhibit a broader geographic reach. It is estimated that over 1 billion people suffer from NTDs, spanning 149 countries. The epidemiology of these diseases is intricate, often intertwined with environmental factors. Many are vector-borne, involve animal reservoirs, and entail complex life cycles, rendering public health control challenging. NTDs disproportionately impact already vulnerable populations, whether due to poverty, marginalization, geographic location, or living conditions, leading to considerable suffering, disability, and death and posing severe health and economic challenges. The majority of drugs used against NTDs are old and frequently yield undesired side effects. Regrettably, major pharmaceutical companies exhibit limited interest in developing new drug candidates or vaccines for NTDs. Despite the substantial size of the target population, it is primarily situated in developing countries with low socioeconomic status, making them unable to afford expensive medicines. Consequently, much of the research on NTDs is conducted by academia, open sources, and nonprofit organizations.[58-61]

On the other hand, PLoS Neglected Tropical Diseases,[61] in alignment with the World Health Organization (WHO)[62] and several other international agencies, does not classify malaria produced by *Plasmodium falciparum* as an NTD because much attention has been put on it by the pharmaceutical industry and the health authorities. Accordingly, the *P. falciparum* caused malaria disease does not fulfill the definition of NTD. Transmission occurs through the bites of infected female *Anopheles* mosquitoes. In 2022, the Medicines for Malaria Venture[63] documented 249 million cases of malaria, reflecting a rise of 5 million compared to 2021. This increase was attributed to various factors, including severe weather events, population expansion, and conflict-driven forced migration. Notably, 76% of malaria-related deaths worldwide occurred in children under the age of 5. Malaria in humans is caused by four *Plasmodium* species: *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovae*. Its prevalence is particularly pronounced in tropical and subtropical regions, with the African Region carrying the predominant burden of both cases and fatalities. The majority of instances in this region can be attributed to the *Plasmodium falciparum* parasite. Despite being preventable and treatable, timely diagnosis and effective treatment are essential. Failure to address an uncomplicated malaria case promptly can result in the progression to a severe form of the disease, often leading to fatal outcomes without timely intervention. Artemisinin-based combination therapies emerge as the most efficacious antimalarial medications presently accessible and constitute the primary recommended treatment for *Plasmodium falciparum* malaria, the most lethal malaria parasite globally. They combine two active pharmaceuticals with distinct mechanisms of action, featuring derivatives of artemisinin and a complementary drug. Artemisinin element plays a pivotal role in reducing the parasite count during the initial days of treatment, while the companion drug focuses on eliminating the remaining parasites. Nevertheless, this strategy faces challenges such as drug interactions and drug resistance.

Various research groups have endeavored to develop organometallic compounds with potential applications as drugs against malaria and NTDs diseases caused by trypanosomatid parasites and parasitic helminths. This perspective highlights selected efforts from these groups in the pursuit of innovative therapeutic solutions.

2.2. Organometallic antimalarials

Many research groups[64-66] have developed novel organometallics as prospective antimalarials. In particular, the advantages demonstrated by the ferrocene scaffold for the development of bioorganometallic drugs, as outlined in the preceding section, have led to the successful incorporation of this moiety into organic drugs. This design strategy has paved the way for the development of ferrocenyl analogues of existing antimalarial drugs to improve antimalarial activity, reduce cytotoxicity in normal cells and enhance the therapeutic index of such drugs. Additionally, this modification can induce favorable alterations in the properties of the compounds, including changes in solubility, hydrophobicity, and lipophilicity.

The most notable and groundbreaking example has been the development by the Brocard and Biot French group[67-70] of the ferrocenyl derivative of the antimalarial drug chloroquine, known as ferroquine (Figure 7). The ferrocene moiety was incorporated into the lateral side-chain of the chloroquine skeleton. Chloroquine (Figure 7) was initially introduced as a main antimalarial drug in 1945, owing to its affordability, ease of use, and potent antimalarial efficacy. However, widespread resistance among *P. falciparum*

parasites led to the withdrawal of chloroquine from malaria treatment in the majority of malaria-endemic countries.[71] *In vitro*, ferroquine exhibited noteworthy activity against both chloroquine-sensitive and chloroquine-resistant *P. falciparum* strains, with no discernible cytotoxic effects. Ferroquine is presently undergoing clinical development and completed phase II trials for the treatment of malaria. It is under development for addressing uncomplicated *Plasmodium falciparum* malaria, administered orally in capsule form.[72-74]

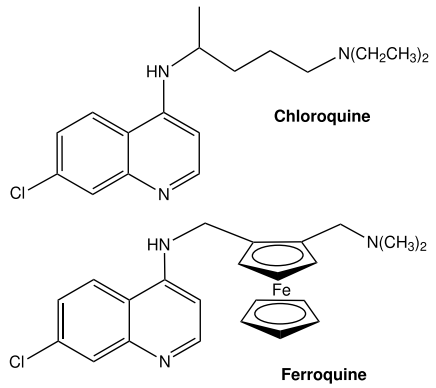


Figure 7. Structures of the antimalarial drug chloroquine and the organometallic analogue ferroquine (Biot-Brocard).[67-70]

Plasmodium parasite breaks down host hemoglobin in its digestive vacuole to obtain a nutrient supply. This process releases free heme, which is toxic to the parasite. Within the vacuole, the parasite detoxifies heme by converting it into hematin, ultimately forming the insoluble hemozoin, which is non-toxic to the parasite. Chloroquine accumulates in the parasite's digestive vacuole, preventing the conversion of toxic heme into its harmless crystalline form, hemozoin. To achieve this, the drug crosses the host red cell membrane, as well as the membranes of the parasite and its digestive vacuole. Ferroquine also targets beta-hematin and inhibits hemozoin formation, but additionally induces the generation of reactive oxygen species as part of its antimalarial mechanism. The heightened activity observed in respect to chloroquine was demonstrated to be, among other factors, a consequence of the generation of these reactive oxygen species through the reversible ferrocene/ferrocenium redox couple. Moreover, the enhanced lipophilic profile of ferroquine contributes to the prolonged retention of the drug within the digestive vacuole of the parasite.[75,76]

Following this success, a multitude of ferrocene-containing compounds exhibiting favorable pharmacological profiles have been developed for the treatment of malarial infections by the same group and others.[64-66]

2.3 Organometallic agents against trypanosomatid parasites

Gambino and co-workers[77-83] has performed since more than 20 years ago pioneering work on the development of metal-based potential drugs against diseases caused by trypanosomatid parasites. The group has been particularly interested in the development of bioactive compounds for the treatment of Chagas disease or American trypanosomiasis. This is an ancient endemic disease in Latin America caused by the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*). It is considered an NTD by WHO. In the endemic Latin-American countries, it is mainly transmitted to humans and other mammalian hosts by infected blood-sucking insects. The disease expanded to non-endemic regions due to migration of unknowingly infected people that transmit the disease by blood transfusion, organ transplants and from mother to child. *T. cruzi* cycles between four biologically and morphologically distinct stages. Metacyclic trypomastigotes, released in the feces during an insect's blood meal, enter the mammalian host through skin wounds or mucosa and initiate invasion of surrounding cells. Following cell invasion, they undergo a transformation into amastigotes and undergo multiplication within the host cells. Subsequently, amastigotes differentiate into highly mobile infective trypomastigotes, which are released into the bloodstream upon cell lysis. These trypomastigotes can infect adjacent cells, invade various tissues, or be ingested by an insect vector, completing the cycle by transforming into the rapidly dividing non-infective epimastigote form in the insect's gut.

The group's design strategy for developing new compounds has involved metal coordination of various families of structurally related bioactive ligands, each exhibiting antiparasitic activity by themselves. Compounds are rationally designed by changing the bioactive ligands family, the metal center, its oxidation state and geometry, and by including adequate coligands to improve relevant biological properties. The group[77,82,83] has explored numerous families of bioactive ligands, various metal centers, and even organometallic centers in their research endeavors (Figure 8). The aim of this strategy is to modulate physicochemical and biological properties of the bioactive ligands and to identify hit metal compounds that affect multiple targets in the parasite.

In more recent years the group extended the interest to two other diseases caused by trypanosomatid parasites: human African trypanosomiasis (HAT, caused by *Trypanosoma brucei*) and leishmaniasis (caused by more than 20 species of *Leishmania*). Both diseases are also included in the list of NTDs.[60,84-87] There are reasons for this expanded research interest. These diseases rank among the

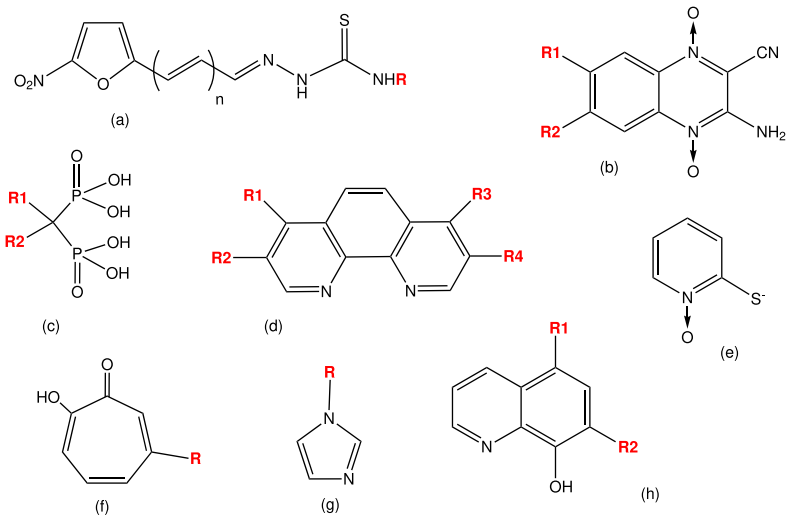


Figure 8. Different families of bioactive ligands used by Gambino group for the development of agents against trypanosomatid parasites: (a) 5-nitrofuryl thiosemicarbazones; (b) 3-aminoquinoxaline-2-carbonitrile N^1,N^4-dioxide derivatives; (c) bisphosphonates; (d) 1,10-phenanthroline derivatives; (e) pyridine-2-thiolate-1-oxide (mpo); (f) tropolones; (g) azoles; (h) 8-hydroxyquinoline derivatives.

most significant neglected illnesses, posing an urgent health crisis in developing countries. They frequently coexist in different poor regions of the world, such as leishmaniasis and Chagas' disease in South America and leishmaniasis and HAT in Africa, spreading worldwide due to human migration and globalization. Despite being highly life-threatening infections, the available chemotherapy remains old and deficient. While these trypanosomatid protozoan parasites exhibit significant differences, being transmitted by distinct insect vectors and causing clinically diverse human diseases, research[88-91] has demonstrated noteworthy similarities in their biology. Specifically, these parasites share more than 6,100 closely related genes encoding proteins out of a total gene count ranging from 8,000 to 12,000. This opens avenues for strategically planning the development of broad-spectrum compounds that could be trypanosomatid-specific, impacting all three major parasites rather than targeting only one. Such an approach could result in drugs affecting common targets across various parasites. In summary, the current aim of the group is to develop broad spectrum drugs affecting multiple trypanosomatid parasites but multifunctional drugs that affect multiple targets in the same parasite.

In particular, Gambino group has ventured in the development of organometallic compounds against trypanosomatid parasites of the metallocene, metal-arene and metal-carbonyl classes (Figure 3). Eleven series of bioactive organometallic compounds were rationally designed, synthesized, characterized and evaluated on *T. cruzi*, *T. brucei* or both parasites. *T. brucei brucei* (nagana cattle disease was used as a parasite model for African trypanosomiasis). An insight into the probable mechanism of action of the compounds was also provided. Metallomics, proteomics and transcriptomics studies in *T. cruzi* were performed for the first time in this parasite to unravel the main pathways affected by prospective organometallic drugs. Hit compounds of all these new families of compounds were selected based on their IC_{50} (half-maximal inhibitory concentration) and selectivity index values (SI = IC_{50} mammalian cells/IC_{50} parasite) (Table 1). Their structures are depicted in Figure 9.

While the various hit compounds presented in Table 1 cannot be strictly compared in terms of their activity against *T. cruzi* since they were evaluated at different stages of research by the Gambino group using different forms and strains of the parasite, practically all IC_{50} values presented in the table fall within the submicromolar range, demonstrating a high antitrypanosomal activity of the organometallic compounds developed compared to the reference drug nifurtimox.

The first attempts by the group to develop organometallic antitrypanosomal compounds involved Ru-arene half-sandwich compounds including 5-nitrofuryl derived thiosemicarbazones as ligands and *p*-cymene or cyclopentadienyl (Cp) as arene cores. The thiosemicarbazone moiety has been identified as a privileged structure in medicinal chemistry and particularly in the development of antiparasitic compounds.[78,80,108,109] The thiosemicarbazones, which incorporate the 5-nitrofurane pharmacophore illustrated in Figure 10, were designed as analogues of the commercial antitrypanosomal drug nifurtimox. In the majority of cases, these compounds exhibited greater activities against *T. cruzi* compared to the reference drug. Their mechanism of antiparasitic action involves the bioreduction of the nitro moiety, subsequently leading to the generation of ROS.[110]

Table 1. Hit organometallic compounds and their IC_{50} (half-maximal inhibitory concentrations) and selectivity index values (SI). Free ligands are included for comparison

Compound	*T. cruzi*		*T. brucei*		Reference
	IC_{50} / μM	SI	IC_{50} / μM	SI	
1, $[Ru^{II}_2(\eta^6\text{-}p\text{-cymene})_2(TSC4\text{-}H)_2]Cl_2$	8.7[a]	3[c]	0.5[b]	52[c]	92,93
TSC4	22.7[a]	> 100[c]	> 100[b]	–	92,93
2, $[Ru^{II}Cp(PPh_3)(TSC3\text{-}H)]$	0.41[a]	> 49[c]	3.5[b]	> 6[c]	94
TSC3	18.5[a]	2[c]	17.0[b]	2[c]	92,93
3, $[Ru^{II}Cp(PPh_3)_2(CTZ)](CF_3SO_3)$	0.25[d]	8[c]	0.6[b]	3[c]	95
CTZ	1.8[d]	31[c]	> 25[b]	< 2[c]	95
4, $[RuCl(\eta^6\text{-}p\text{-cymene})(phendione)](PF_6)$	–	–	0.19[b]	169[c]	96
Phendione	–	–	0.018[b]	53[c]	96
5, *fac*-$[Re^{I}(CO)_3Br(TSC5)]$	2.01[a]	22[e]	–	–	97
TSC5	12.7[a]	3[e]	–	–	97
6, *fac*-$[Re^{I}(CO)_3(tmp)(CTZ)](PF_6)$	0.61[f]	8.4[g]	–	–	98,99
CTZ	10.2[f]	3.6[g]	–	–	98,99
7, $[Pd(mpo)(dppf)](PF_6)$	0.64[h]	39[g]	–	–	100,101
8, $[Pt(mpo)(dppf)](PF_6)$	0.28[h]	18[g]	–	–	100,102
Na mpo	1.33[h]	–	–	–	100
9, $[Pt(TSC3\text{-}H)(dppf)](PF_6)$	0.76[a]	> 66[e]	0.52[b]	> 56[e]	103
10, $[Pt(trop)(dppf)](PF_6)$	–	–	2.1[b]	18[c]	104
Htrop	–	–	> 60[b]	ca. 1[c]	104
11, $[Pd(8HQNO_2\text{-}H)(dppf)](PF_6)$	–	–	0.33[b]	102[c]	105
$8HQNO_2$	–	–	0.8[b]	38.9[c]	105
12, $[Pt(8HQClI\text{-}H)(dppf)](PF_6)$	–	–	0.14[b]	48[c]	106
8HQClI	–	–	2.4[b]	16.2[c]	106
13, [Ru(8HQII-H)(dppf)(bipy)]Cl	–	–	0.13[b]	38[c]	107
8HQII	–	–	1.7[b]	29[c]	107

[a]Dm28c strain *T. cruzi* trypomastigotes; [b]bloodstream *T. brucei brucei* strain 427; [c]J774 murine macrophages; [d]Y strain *T. cruzi* epimastigotes; [e]human-derived endothelial cell line (EA.hy926); [f]CL Brener strain *T. cruzi* trypomastigotes; [g]VERO cells (ATCC CCL81); [h]Dm28c strain *T. cruzi* epimastigotes. TSC: 5-nitrofurylthiosemicarbazone (Figures 8 and 9); CTZ: clotrimazole; phendione: 1,10-phenanthroline-5,6-dione; tmp: 3,4,7,8-tetramethyl-1,10-phenanthroline; mpo: pyridine-2-thiolate-1-oxide; dppf: 1,1'-bis(dipheny1phosphino) ferrocene; trop: tropolone; 8HQ: 8-hydroxyquinoline; $8HQNO_2$: 5-nitro-8-quinolinol; 8HQClI: 5-chloro-7-iodo-8-quinolinol; bipy: 2,2'-bipyridine; 8HQII: 5,7-diiodo-8-quinolinol. SI: IC_{50} mammalian cell model/ IC_{50} parasite; IC_{50} nifurtimox (*T. cruzi*): 24.7 μM (Dm28c trypomastigotes), 8.0 μM (Y strain epimastigotes), 20.1 μM (CL Brener strain trypomastigotes), 6.0 μM (Dm28c epimastigotes); IC_{50} nifurtimox (*T. brucei brucei*): 6 μM (SI J774: 23).[107]

Complexes of the formula $[Ru^{II}Cp(PPh_3)(TSC\text{-}H)]$ and $[Ru^{II}_2(\eta^6\text{-}p\text{-cymene})_2(TSC\text{-}H)_2]X_2$, with X = chloride and/or hexafluorophosphate as counterions, were obtained.[92-94]

The Ru-cyclopentadienyl compounds exhibited *in vitro* activity against the blood circulating trypomastigote form of *T. cruzi* and the infective form of *T. brucei brucei*, displaying IC_{50} values in the micromolar range. A majority of these compounds demonstrated greater activity compared to the corresponding free TSC ligands and the antitrypanosomal drug nifurtimox. $[Ru^{II}Cp(PPh_3)(TSC3\text{-}H)]$ with the *N*-ethyl derivative TSC3 as ligand (Figure 10) was the most active one on both parasites showing an excellent selectivity towards *T. cruzi* and a good selectivity towards *T. brucei* (Table 1, Figure 9).[94]

Among the Ru-*p*-cymene compounds, only $[Ru^{II}_2(\eta^6\text{-}p\text{-cymene})_2(TSC4\text{-}H)_2]Cl_2$ demonstrated significant activity against the relevant life cycle forms of both parasites, particularly showing high selectivity towards *T. brucei*. The remaining compounds displayed limited activity against *T. cruzi* and exhibited a similar level of effectiveness as the corresponding free ligands (TSC1-TSC3) against *T. brucei*. Furthermore, the results highlighted the influence of the counterion nature on the activity, with the more soluble chloride complexes being more active than the hexafluorophosphate ones.[93]

In general, the complexation of the TSC ligands with the $\{RuCp(PPh_3)\}$ moiety yielded superior results in terms of antiparasitic activity compared to the Ru-*p*-cymene counterpart. The biological findings

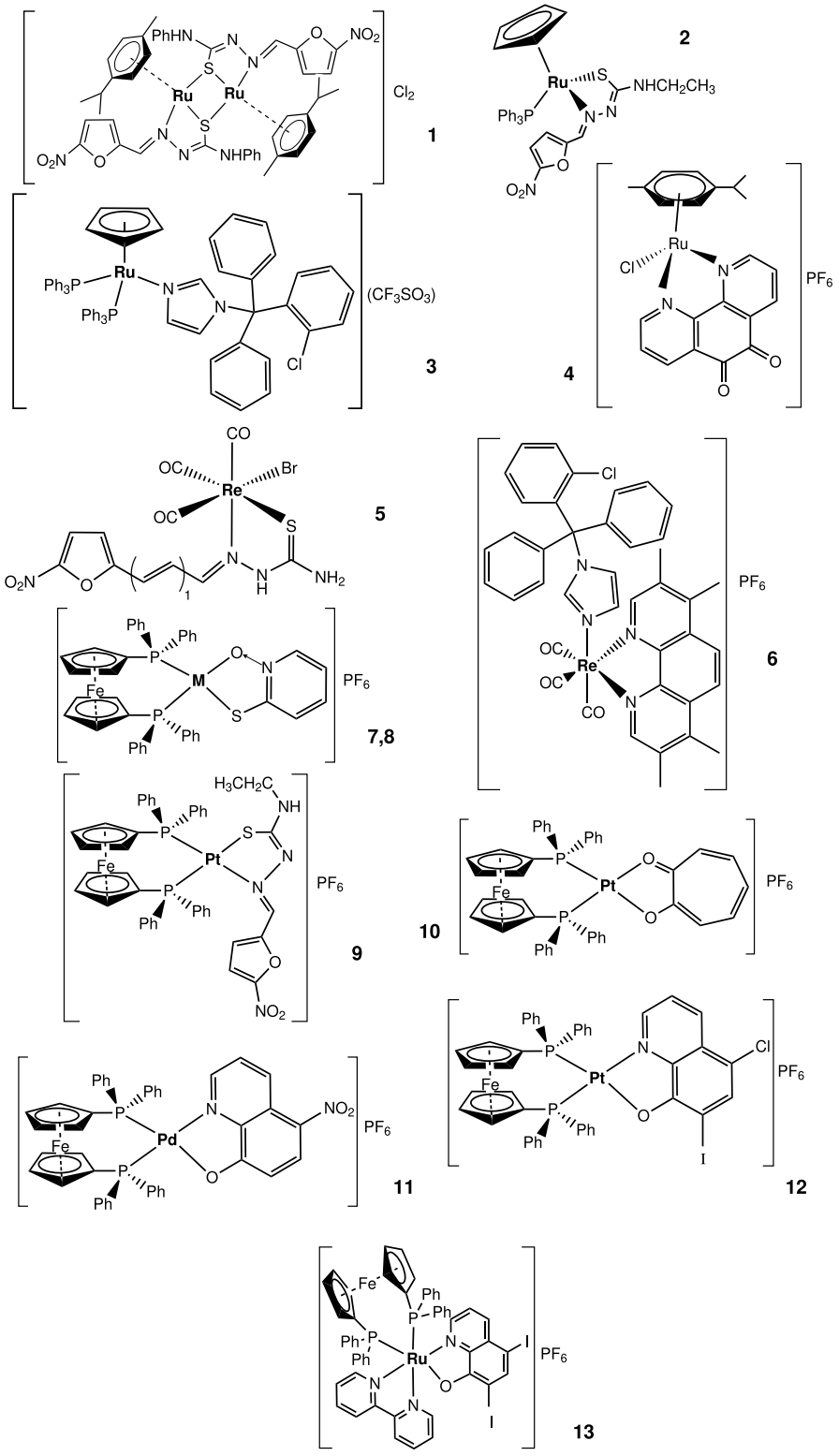
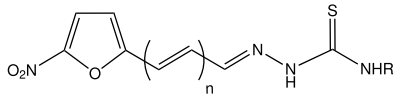


Figure 9. Hit organometallic antitrypanosomal compounds obtained by Gambino and co-workers.[92-107] Compounds are numbered as in Table 1.



	R	n
TSC1	H	0
TSC2	methyl	0
TSC3	ethyl	0
TSC4	phenyl	0
TSC5	H	1

Figure 10. Bioactive 5-nitrofuryl containing thiosemicarbazones.

indicate that both, $[RuCp(PPh_3)(TSC\text{-}H)]$ and $[Ru^{II}_2(\eta^6\text{-}p\text{-cymene})_2(TSC\text{-}H)_2]^{2+}$ complexes, generate deleterious free radicals through bioreduction within the parasite, resembling the free TSC. Moreover, these

compounds display DNA interaction. Nevertheless, the observed biological activity does not seem to align straightforwardly with the magnitude of these effects, suggesting a more intricate "multiple-target" mechanism of action.[94]

Later on, clotrimazole (CTZ) was selected as ligand for the development of the ruthenium cyclopentadienyl compound $[RuCp(PPh_3)_2(CTZ)](CF_3SO_3)$ (Figure 9).[95] The formation of azole-metal complexes has been suggested as a strategy for creating agents targeting trypanosomatid parasites. Notably, complexes involving CTZ have exhibited promising outcomes. CTZ functions by inhibiting the sterol 14-α-demethylase enzyme, which plays a crucial role in converting lanosterol to zymosterol during the biosynthetic pathway leading to the parasite-specific sterol ergosterol.[111] The novel compound demonstrated significant cytotoxic activity against *T. cruzi*, exhibiting a sixfold increase compared to free CTZ. While CTZ alone lacks activity against *T. brucei brucei* (IC_{50} > 25 μM), its complexation with the {RuCp} moiety resulted in a 40-fold higher activity than free CTZ (Table 1). The compound displayed only moderate selectivity toward both parasites, *T. cruzi* and *T. brucei*, in comparison to mammalian cells. Despite the anticipation of a dual antiparasitic mechanism arising from the presence of Ru^{II} and CTZ in a single molecule, the compound does not impact DNA but inhibits the sterol biosynthetic pathway in *T. cruzi*, specifically at the conversion of squalene to squalene oxide.[95]

On the other hand, Moreno and co-workers[96] developed in collaboration with Gambino's group five novel ruthenium(II)-*p*-cymene compounds with bidentate and monodentate polycyclic aromatic ligands. While the free ligands exhibited higher activity against *T. brucei* compared to the Ru^{II} compounds, the latter demonstrated reduced toxicity on mammalian cells. In all examined compounds, the complexation to the ruthenium-*p*-cymene core significantly decreased the cytotoxicity of the free ligands by a minimum of 30-fold. $[RuCl(\eta^6\text{-}p\text{-cymene})(phendione)][PF_6]$, with phendione = 1,10-phenanthroline-5,6-dione, showed the highest activity (IC_{50} of nM value) of the series on the infective form of *T. brucei* together with the highest selectivity towards the parasite (Figure 9, Table 1). According to the criteria defined by the Special Programme for Research and Training in Tropical Diseases (TDR),[112] this compound was considered as a hit drug for African trypanosomiasis. These ruthenium-*p*-cymene compounds, featuring polycyclic aromatic ligands, were observed to associate with DNA, and their interaction with this biomolecule was primarily believed to occur through the intercalation of the aromatic ligand.[96]

Since the *fac*-tricarbonyl metal(I) moiety, *fac*-$\{M(CO)_3\}^+$, had been scarcely explored for the development of antiparasitic drugs, Re tricarbonyl complexes with different bioactive ligands were also developed by the group. In a first attempt a series of *fac*-$[Re^I(CO)_3Br(semicarbazone)]$ compounds was reported[113] that showed only low *in vitro* activity on *T. cruzi* (IC_{50} values 57-67 μM).

Later on, three *fac*-$[Re^I(CO)_3Br(TSC)]$ compounds were obtained. The chosen TSC ligands comprised two derivatives characterized by varying chain length linking the thiosemicarbazone and nitrofuran moieties (TSC1 and TSC5), along with the more voluminous and lipophilic compound TSC4 (Figure 10). The compounds demonstrated a 4- to 17-fold enhancement in activity compared to the TSC ligands and proved to be 8-15 times more potent than nifurtimox. Furthermore, these compounds exhibited moderate to good selectivity indexes, falling within the range of 11-22. Although the most lipophilic TSC4 compound was the most active one, *fac*-$[Re^I(CO)_3Br(TSC5)]$ showed a similarly low IC_{50} value and the highest SI value of the series (Table 1).[81,97] Through ^1H NMR (^1H nuclear magnetic resonance) and MS (mass spectroscopy) studies conducted over time, it was observed that *fac*-$[Re(CO)_3Br(TSC)]$ species underwent conversion into dimers $[Re_2(CO)_6(TSC\text{-}H)_2]$ in solution. Spin trapping ESR (electron spin resonance) investigations indicated that the studied compounds did not generate radical oxygen species in the parasite, unlike 5-nitrofuryl-derived thiosemicarbazones TSC. This difference is likely attributed to the unfavorable nitro reduction potential observed for the generated dimeric species $[Re_2(CO)_6(TSC\text{-}H)_2]$. Conversely, the compounds led to a reduction in the oxygen consumption rate of the parasites, possibly by inhibiting their mitochondrial respiration.[97]

In a recent advancement, Gambino and co-workers[98] devised a series of six multifunctional Re^I tricarbonyl compounds. Each compound integrated two distinct bioactive ligands: a polypyridyl NN derivative and a monodentate azole (CTZ or ketoconazole, KTZ). The chosen NN ligands encompassed 2,2'-bipyridine (bpy), 4,4'-dimethyl 2,2'-bipyridine (dmb), 1,10-phenanthroline (phen), 3,4,7,8-tetramethyl-1,10-phenanthroline (tmp), and 5-amino-1,10-phenanthroline (aminophen). The collection of five *fac*-$[Re(CO)_3(NN)(CTZ)]PF_6$ compounds displayed remarkable efficacy against *T. cruzi* trypomastigotes, with IC_{50} values in the low μM range. Notably, they displayed heightened activity compared to the free ligands and nifurtimox, being their IC_{50} values approximately ten times lower than that of the reference antitrypanosomal drug. Furthermore, these compounds exhibited a moderate to favorable selectivity towards the parasites when compared

to the VERO mammalian cell model. Among the series, $[Re(CO)_3(tmp)(CTZ)]PF_6$ emerged as the most active and selective compound (Table 1, Figure 9). Despite exhibiting increased lipophilicity compared to the free bioactive ligands, no clear correlation between antitrypanosomal activity and lipophilicity was identified. Metallomics studies[99] were conducted on the compound using Raman confocal microscopy and MP-AES (microwave plasma atomic emission spectrometry). The results revealed a low overall uptake of rhenium by parasites (ca. 1.2%) and a notable accumulation preference within the soluble proteins fraction of the parasite (ca. 82.8%) in respect to insoluble, DNA and RNA (ribonucleic acid) fractions. Two potential molecular targets, DNA and the enzyme CYP51 (lanosterol 14-α-demethylase), underwent both experimental and theoretical investigations. The compound demonstrated an ability to interact with DNA while also influencing the membrane sterol biosynthesis of the parasite. This led to the accumulation of squalene and lanosterol in the treated parasites, accompanied by a simultaneous reduction in ergosterol levels. Molecular docking calculations were employed to gain insights into the mechanism underlying the interaction with DNA and the inhibition of CYP51. The calculated free energy of binding to CYP51 for the compound was more favorable than for CTZ, aligning with the observed experimental activity order.[111]

The success of ferrocenes in antitumoral and antimalarial drugs design lead to the interest of the group in searching for novel ferrocenyl derivatives as prospective agents against trypanosomatid parasites. In addition to the advantages of ferrocene in drug design previously described, ferrocene and its derivatives exhibit enhanced bioaccumulation compared to ionic forms of iron, being iron supply very important for parasites survival. Moreover, the induced generation of ROS by ferrocene derivatives, such as ferroquine, in a Fenton-like manner may hold therapeutic significance, given the heightened sensitivity of trypanosomatid parasites to radical species.[6,70,77]

Rather than the conventional approach of coupling the ferrocene scaffold to an organic skeleton, as seen in ferroquine or ferrocifen, our synthetic strategy involved incorporating the ferrocene fragment as a co-ligand within the platinum(II), palladium(II), or ruthenium(II) coordination sphere. The chosen co-ligand, 1,1'-bis(diphenylphosphino)ferrocene, abbreviated as dppf (Figure 11a), serves as a bidentate ligand by binding to the additional metal center through its two phosphorus donor atoms. This arrangement leaves the remaining coordination positions of the metal center available for coordination with the selected bioactive bidentate ligand.

Twenty-four structurally related Pd^{II} or Pt^{II} ferrocenyl compounds $[M(L)(dppf)](PF_6)$ (4 series with different families of ligands with the general structure depicted in Figure 11b) were synthesized and thoroughly characterized. Their impact was evaluated on both trypanosomes and mammalian cell models. Their effects on selected molecular targets were studied, and for the most promising pyridine-2-thiolato-1-oxide (mpo) compounds, omic studies were performed. Overall, the incorporation of the ferrocene moiety resulted in interesting effects on the biological profile of the compounds. The selected hit compounds of each series are depicted in Figure 9 and Table 1.

At a first stage $[M(L)(dppf)](PF_6)$ compounds, where L represents the bioactive ligand pyridine-2-thiolato-1-oxide (mpo) (Figure 8e), were synthesized and characterized.[100] Earlier studies by Turrens *et al*.[114] showed that mpo hinders the growth of *T. cruzi*, both in culture and within infected mammalian myoblasts, inhibiting the parasite-specific enzyme NADH (nicotinamide adenine dinucleotide) fumarate reductase (*Tc*FR). The compound affects all stages of the parasite's life cycle, without causing any harm to mammalian cells. *Tc*FR catalyzes the conversion of fumarate to succinate. Because succinate plays a vital role as a respiratory substrate for *T. cruzi*, supporting essential energy production, the absence of this enzyme in mammalian cells provides an appealing target for the development of drugs aimed at combating *T. cruzi*.[114]

Both $[M(mpo)(dppf)](PF_6)$ compounds exhibited IC_{50} values in the nanomolar range against *T. cruzi* epimastigotes (Dm28c and CL Brener strains) while demonstrating low cytotoxicity on a mammalian cell model (VERO epithelial cells, ATCC CCL81), which led to excellent selectivity

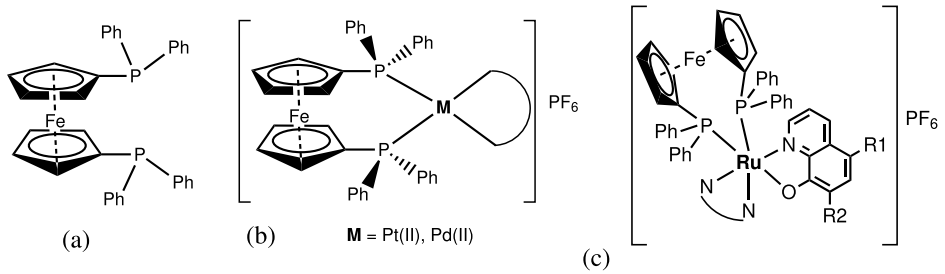


Figure 11. (a) 1,1'-Bis(dipheny1phosphino) ferrocene, dppf; (b) structure of $[M(L)(dppf)](PF_6)$ compounds, where M = Pt^{II} or Pd^{II} and L = mpo, trop, hino, TSC, 8HQs and (c) structure of $[Ru^{II}(8HQs)(dppf)(NN)](PF_6)$, where NN = 1,10-phenanthroline derivatives.

toward the parasite (Table 1). The complexes were approximately 10-20 times more potent than nifurtimox and two- to five-fold more active than mpo sodium salt. Notably, the compounds demonstrated 2-4 times greater susceptibility against epimastigotes of the CL Brener strain (type VI) compared to the type I Dm28c strain. This underscores the well-known fact that the genetic diversity of the parasite can result in varying susceptibility to drugs. Both complexes also affected the trypomastigote infection process as well as the intracellular amastigotes replication.[101,102]

While both metal compounds exhibited nanomolar IC_{50} values against the epimastigote stage of the parasite and demonstrated an enhanced inhibitory effect on the activity of *Tc*FR compared to the free mpo ligand, the IC_{50} values for enzyme inhibition were several times higher than those for *T. cruzi*. This suggested that *Tc*FR may not be the sole molecular target of the compounds within the parasite.[100]

To uncover the mechanism of action of both analogous prospective drugs, high-throughput omics approaches were employed on treated *T. cruzi* parasites.[101,102,115] Inorganic chemists have conventionally sought to discover and analyze molecular targets of metal-based drugs through *in vitro* methodologies. This process primarily hinged on the mechanistic characteristics of organic ligands and the central metal. On the other hand, omics studies serve as crucial tools for comprehensively unraveling the entire mechanism of action of metal-based drugs. Through proteomics, the identification and quantification of upregulated and downregulated cellular proteins resulting from drug effects and molecular target interactions, coupled with metallomics for quantifying cell uptake and subcellular distribution, and transcriptomics for assessing changes in gene expression, the whole omics approach provides a profound understanding of cellular events following the administration of a metallodrug.[116]

Globally, this study marked the first omics contribution aimed at unraveling the comprehensive spectrum of effects involved in the mechanism of action of potential metal-based drugs for the treatment of Chagas disease. Metallomics investigations revealed a significant uptake of Pt and Pd by the parasites. Comparing equal doses, the Pt compound exhibited a greater uptake compared to its Pd analogue. The distribution pattern of metals across the four examined macromolecular fractions (DNA, RNA, soluble proteins, and insoluble proteins, including membrane lipids) remained consistent, showcasing a preferential affinity for DNA. Proteomics and transcriptomics studies unveiled a multimodal mechanism of action, identifying several significant candidates as potential targets within the parasite. The comprehensive dataset suggested that the antitrypanosomal mechanism of action for both compounds is likely multimodal. Intriguingly, notable biological distinctions were observed between the two structurally analogous compounds, underscoring the importance of the metal center's nature in influencing their biological behavior. Notably, the transcriptomics study indicated that the treatment with both compounds resulted in the downregulation of most genes coding for enzymes involved in the ergosterol biosynthesis pathway, among effects on other important parasite pathways.[115] The identification of this biosynthesis route as a target for both compounds was validated through the determination of sterol levels in treated parasites using HPLC (high-performance liquid chromatography). The inhibitory effect on enzymes of the route resulted in the accumulation of intermediate sterols, specifically lanosterol and squalene, along with a dose-dependent decrease in ergosterol. Two enzymes in the entire pathway, phosphomevalonate kinase (PMK) and lanosterol 14-α demethylase (CYP51), exhibited reduced transcript levels, and no protein was detected in treated parasites according to the earlier proteomic studies.[117] The status of both enzymes as molecular targets of the compounds was confirmed using a gain-of-function strategy, involving the generation of parasites overexpressing PMK and CYP51. As anticipated, the overexpression resulted in heightened drug resistance. Moreover, molecular docking analyses suggested an energetically favorable interaction between the compounds and CYP51 and PMK and a mechanism of competitive inhibition.[117]

Building upon the encouraging outcomes achieved with these [M(mpo)(dppf)](PF_6) compounds, three additional series of ferrocenyl Pd and Pt compounds were developed. These new series of [M(L)(dppf)](PF_6) compounds incorporated TSC, tropolones, or 8-hydroxyquinoline derivatives as bioactive ligands (Figures 8, 10 and 12), instead of mpo.[103-106]

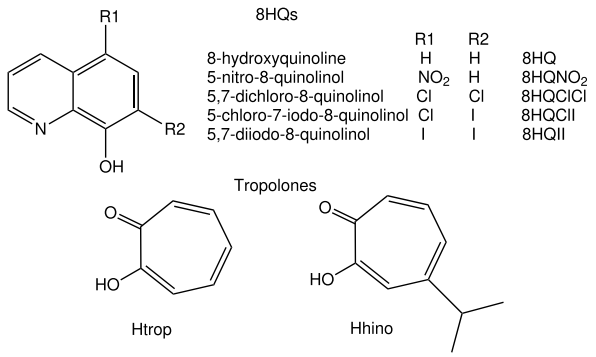


Figure 12. Structures of the selected 8-hydroxyquinoline derivatives (8HQs) and tropolones (tropolone, Htrop; hinokitiol, Hhino).

Tropolones and their derivatives were chosen as bioactive ligands due to being considered as lead-like natural products in medicinal chemistry. The tropolone moiety offers significant potential for derivatization, allowing for improvements in metal binding abilities. Compounds such as tropolone, hinokitiol, and their derivatives, along with the corresponding metal complexes, have exhibited diverse biological activities.[118-120]

On the other hand, medicinal chemists have shown keen interest in the 8-hydroxyquinoline moiety, thanks to its noteworthy biological activities. It is widely regarded as a privileged structure in the realm of drug development.[121-123]

[M(dppf)(L)](PF_6) compounds, with M = Pd^{II} or Pt^{II} and HL = tropolone (Htrop) or hinokitiol (Hhino), demonstrated IC_{50} values ranging from 1.2 to 4.5 μM against the bloodstream form of *T. brucei*. There was a significant increase in activity, along with enhanced selectivity towards the parasite compared to the free ligands. Platinum complexes were more selective than palladium ones. Figure 9 and Table 1 illustrate the structure, IC_{50} value on *T. brucei*, and selectivity index (SI) value of the hit compound of the series, [Pt(trop)(dppf)](PF_6). Moreover, coordination of the tropolones to the {M-dppf} moiety also led to a slight increase of the activity against *Leishmania infantum* amastigotes. No effect on the thiol-redox homeostasis of the parasites is produced by the complexes' action. DNA could be a probable, but not main, target of these compounds.

Eight novel heterobimetallic [M(dppf)(TSC-H)](PF_6) compounds, featuring Pt^{II} or Pd^{II}, were synthesized. Figure 9 and Table 1 illustrate the structure, IC_{50} values on *T. cruzi* and *T. brucei*, and SI values of the most active and selective compound in the series, [Pt(TSC3-H)(dppf)](PF_6). The majority of these compounds exhibited potent activity, with IC_{50} values falling within the low micromolar or submicromolar range against both *T. cruzi* and *T. brucei*. Interestingly, the platinum compounds demonstrated higher activities when compared to their palladium counterparts. The antiparasitic activities of these compounds surpassed those of the free thiosemicarbazone ligands, exhibiting a 3- to 24-fold increase against *T. cruzi* and up to a remarkable 99-fold increase against *T. brucei*. The compounds exhibited activity up to 26 times higher against *T. cruzi* and up to 30 times against *T. brucei* than nifurtimox. Moreover, the incorporation of the organometallic dppf co-ligand seems to contribute to decreased toxicity on mammalian cells and enhanced selectivity towards both parasites when compared to the free thiosemicarbazone compounds. Both the Pd and Pt compounds were found to interact with DNA and to impact the redox metabolism of *T. cruzi*, suggesting that they retained the anti-*T. cruzi* mechanism of action observed for the free ligands described earlier. However, there was no observed correlation between oxygen uptake and the generation of free oxygen radical species in the parasite or the interaction with DNA and the anti-*T. cruzi* activity. [Pt(TSC3-H)(dppf)](PF_6) exhibited no *in vivo* toxicity in Zebrafish (*Danio rerio*) embryos, which are commonly employed as a toxicity model in drug development, throughout the tested concentration range of 1-100 μM. There were no apparent signs of toxicity even after 48 h of treatment.

Furthermore, the ten [M(8HQs-H)(dppf)](PF_6) compounds, encompassing five 8-hydroxyquinoline derivatives (8HQs) as bioactive bidentate co-ligands (Figure 12), demonstrated IC_{50} values against bloodstream *T. brucei* form within the submicromolar or micromolar range (IC_{50}: Pt compounds 0.14-0.93 μM; Pd compounds 0.33-1.2 μM). Notably, these compounds exhibited strong selectivity towards the parasite (SI: Pt compounds **11**-**48**; Pd compounds **4**-**102**) in comparison to murine macrophages (cell line J774) selected as model mammalian cells. Figure 9 and Table 1 illustrate the structure, IC_{50} values on *T. brucei*, and SI values of the hit Pt and Pd compounds of the series, [Pt(8HQClI-H)(dppf)](PF_6) and [Pd(8HQNO_2-H)(dppf)](PF_6). In most cases, the coordination of the bioactive 8HQs to the {Pt-dppf} moiety resulted in a significant increase in activity (11- to 41-fold). While some Pd compounds surpassed the corresponding 8HQ ligands in activity, the majority of Pd compounds displayed lower activity than their Pt analogues. Interestingly, the Pd compounds proved to be 2- to 45-fold more potent than the drug nifurtimox, whereas platinum complexes exhibited a striking 16- to 107-fold increase in potency compared to this reference drug. The findings from the conducted studies indicate that the mechanism of action for these complexes against *T. brucei* may involve DNA interaction, with an additional contribution of oxidative stress specifically for the Pt compounds.

Having identified [Pt(8HQClI-H)(dppf)](PF_6) as the most promising compound from the 8HQs series (Table 1), an exploratory pre-clinical therapeutic efficacy study was conducted in an acute murine model for HAT. The study involved mice infected with a bioluminescent cell line of *T. brucei*, enabling non-invasive *in vivo* imaging (Figure 13). While preliminary, the *in vivo* investigation indicated that the tested compound did not exhibit acute toxicity to the animals. Furthermore, the results suggested that although the compound demonstrated antiproliferative activity, leading to an extension of animal survival, it did not possess a curative effect.

A comprehensive investigation was conducted on the whole family of twenty-two structurally related

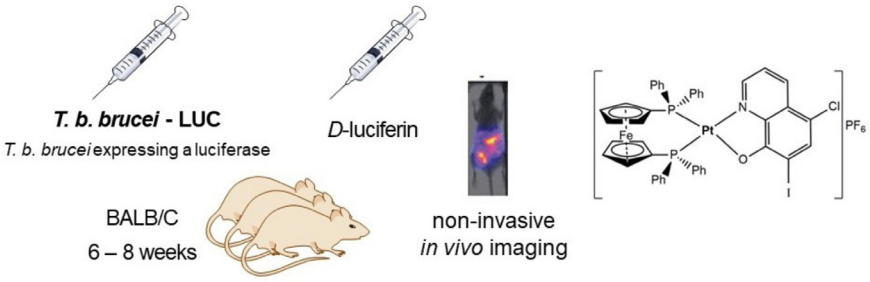


Figure 13. Scheme of the non-invasive *in vivo* study.

M-dppf-L compounds, featuring the diverse bioactive ligands L. The focus of the study was to delve into the quantitative structure-activity relationships (QSAR) and discern the key structural parameters influencing anti-*T. brucei* activity. Such analyses are infrequent in inorganic medicinal chemistry, primarily due to the requisite abundance of structurally analogous compounds. Various physicochemical characteristics, encompassing lipophilic, electronic, and steric/topological properties, were considered as independent variables. Among the descriptors, electronic properties and the nature of the metal ion emerged as the most pivotal factors in determining efficacy. The QSAR findings indicate that ligands bearing electron-withdrawing substituents, coupled with high lipophilicity and platinum as the central atom, contribute to complexes exhibiting heightened anti-*T. brucei* activity.[77,105]

The latest rationally designed modification of these promising M-dppf-L compounds has focused on creating multifunctional Ru^{II} ferrocenyl compounds as potential agents against trypanosomatid parasites. Having Ru^{II} center a six coordination, these compounds were designed to incorporate the bidentate dppf and two bioactive bidentate ligands, 8-hydroxyquinoline derivatives (8HQs) and polypyridyl ligands (NNs), within a single molecule. The three [Ru(8HQs)(dppf)(NN)](PF_6) compounds exhibited *in vitro* activity against bloodstream *T. brucei*, with IC_{50} values ranging from 140 to 310 nM. Additionally, they demonstrated activity against *Leishmania infantum* promastigotes, with IC_{50} values ranging from 3.0 to 4.8 μM. Notably, these compounds displayed favorable selectivity towards *T. brucei* compared to J774 murine macrophages, with SI ranging from 15 to 38. Figure 9 and Table 1 illustrate the structure, IC_{50} value on *T. brucei*, and SI value of the hit compound of this series, [Ru(8HQII-H)(dppf)(bipy)]Cl. Changing the hexafluorophosphate counterion by chloride resulted in a three-fold enhancement in activity against both parasites and a two to three-fold increase in selectivity towards the pathogens. The compounds affect *in vitro* at least the targets of the individual bioactive moieties included in the new chemical entities: DNA and generation of ROS. The compounds demonstrate stability in solution and possess higher lipophilicity compared to the free bioactive ligands. However, no clear correlation was observed between lipophilicity, interaction with DNA, generation of ROS, and activity. This observation aligns with their overall similar potency against trypanosoma and selectivity. This new scaffold could serve as a starting point for expanding this family of compounds by replacing 8HQs with other bioactive ligands.[107]

In summary, the approach by Gambino group for designing new ferrocene derivatives by including the ferrocene scaffold as the organometallic co-ligand 1,1'-bis(diphenylphosphino)ferrocene (dppf) resulted in the development of highly active and selective anti-*T. cruzi* and/or *T. brucei* compounds, in the form of Pd-Fe, Pt-Fe and Ru-Fe heterobimetallic compounds. This family of organometallics deserves further study as a source of prospective antitrypanosomal drugs.

2.4. Organometallic agents against parasitic diseases by helminths

In the last decade, there has been a growing interest in the design and development of organometallics as prospective drugs against parasitic diseases by helminths.[60,124] Helminths are parasitic worms that can infect humans and animals. Main worm-induced NTDs encompass soil-transmitted helminthiases, schistosomiasis, lymphatic filariasis, and onchocerciasis. These NTDs account for 45% of the global NTDs burden.[125]

Schistosomiasis, a parasitic disease caused by Schistosoma worms, manifests as both acute and chronic conditions. Its prevalence is notable in tropical and subtropical regions of Africa, Asia, and Latin America, particularly affecting impoverished communities lacking access to safe drinking water, proper sanitation, and adequate hygiene. The transmission of schistosomiasis is linked to the contamination of freshwater sources by infected individuals who urinate and defecate in open water bodies. To combat schistosomiasis, the WHO employs a

strategy focused on reducing the disease burden through periodic, targeted large-scale treatment with praziquantel, administered as preventive chemotherapy. Praziquantel, while recommended for its effectiveness, safety, and cost-efficiency, has limitations due to its minimal impact on eggs and immature worms and rather low metabolic stability *in vivo*. Given that praziquantel is currently the sole treatment for schistosomiasis, and that there are occasional reports of treatment failure and the risk of resistance development, there is an urgent need to explore and develop alternative drugs.[124-128]

On the other hand, soil-transmitted helminth infections rank among the most widespread infections globally, impacting approximately 1.5 billion individuals, which accounts for 24% of the world's population. These infections disproportionately affect the most impoverished and underserved communities, where access to clean water, sanitation, and hygiene is lacking, particularly in tropical and subtropical regions. Sub-Saharan Africa, China, South America, and Asia report the highest prevalence of these infections. The transmission of these helminths occurs through eggs present in the feces of infected individuals, contaminating the soil in areas marked by inadequate sanitation.[125,129]

Lymphatic filariasis, also known as elephantiasis, stands as a painful and severely disfiguring NTD. It stems from an infection with nematodes (roundworms) transmitted through mosquito bites. The larvae find their way onto the skin and enter the body. Subsequently, these larvae migrate to the lymphatic vessels, maturing into adult worms and perpetuating a cycle of transmission. This disease affects more than 120 million individuals across 72 countries in the tropical and sub-tropical regions of Asia, Africa, the Western Pacific, and certain areas of the Caribbean and South America.[130]

Among the efforts to develop organometallic drugs for treating diseases by parasitic helminths, like schistosomiasis, lymphatic filariasis and soil-transmitted helminthiases, Gasser and co-workers[60,124,131] have made notable strides in this field. Following a methodology akin to the one detailed in previous sections for developing the antitumoral drug ferrocifen and the antimalarial drug ferroquine, an organometallic moiety was incorporated into an anthelmintic organic drug. Figure 14 displays the chosen drugs, including praziquantel, monepantel, oxamniquine and albendazole.

Praziquantel, monepantel, oxamniquine and albendazole underwent derivatization and assessment as antischistosomal agents by the Keiser and Gasser group. To narrow down the scope, this review showcases the research conducted by the Gasser and co-workers[132] on the use of praziquantel in this field. Within the 18 praziquantel ferrocenyl derivatives synthesized, only four compounds, devoid of the cyclohexane ring and featuring the ferrocenyl moiety linked to praziquanamine through various connectors, retained some level of activity. The alternative approach of inclusion of a chromium tricarbonyl moiety at the aromatic ring of praziquantel successfully led to two chromium tricarbonyl-praziquantel racemate derivatives **14** and **15** with remarkable *in vitro* antischistosomal activity (Figure 15). Both $Cr(CO)_3$-praziquantel racemates **14** and **15** showed *in vitro* IC_{50} values of 0.25 and 0.27 μM, respectively, on adult *S. mansoni* worms (IC_{50} praziquantel 0.1 μM). Additionally, they showed high selectivity towards the parasite in respect to MRC-5 human fibroblasts as mammalian cell model.[133] Interestingly, to discern the activity difference between *R*-diastereomers and *S*-diastereomers, four diastereomers of these compounds were synthesized. Similar to praziquantel, both *R*-diastereomers exhibited significant *in vitro* activity against adult *S. mansoni* (IC_{50} = 0.08-0.13 μM), whereas the *S*-enantiomers displayed no detectable activity.[134,135]

In vivo studies conducted on mice infected with adult *S. mansoni* demonstrated lower efficacy for racemic mixtures of both complexes compared to racemic praziquantel.[134] To identify the biological targets of the most potent chromium compound **14** (depicted in Figure 15), researchers employed combined imaging by X-ray fluorescence (XRF) and infrared (IR) absorption spectromicroscopy. This approach

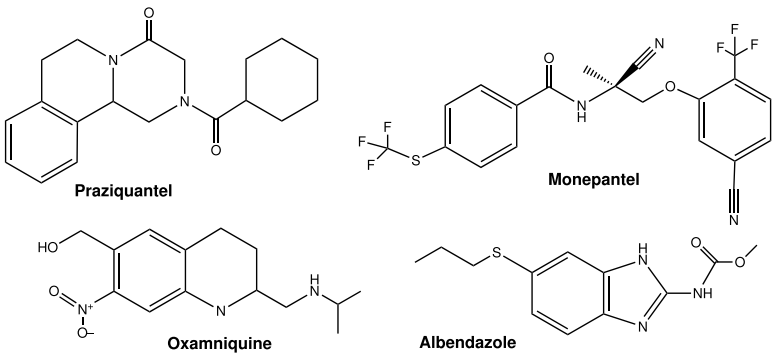


Figure 14. Antihelminthic drugs selected by Gasser and co-workers.[60,124,131]

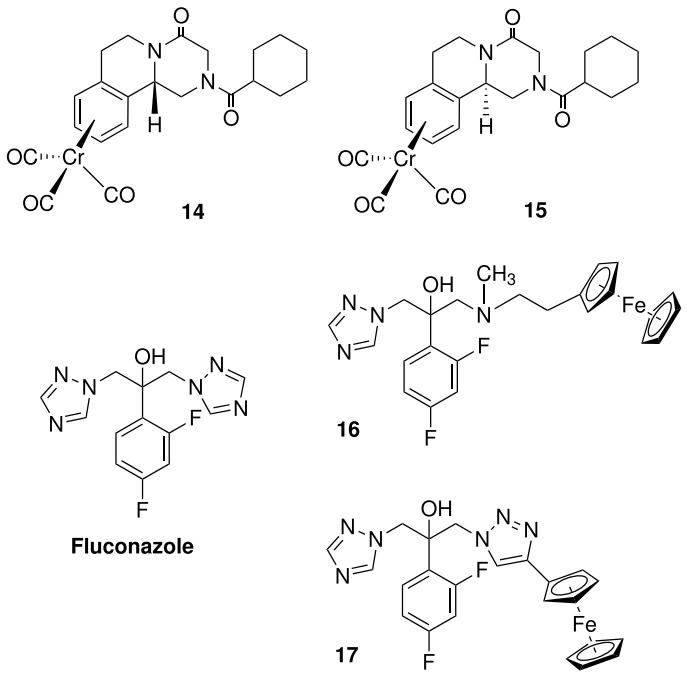


Figure 15. Selected organometallic compounds reported by Gasser and co-workers:[133] chromium tricarbonyl-praziquantel racemate derivatives **14** and **15**; fluconazole and derivatives **16** and **17**.

revealed the organometallic compound's localization within the schistosome. Distinctive IR CO stretchings and the chromium XRF feature indicated a notable accumulation of the compound in the worm's tegument, the site where biological targets for praziquantel are thought to reside.[136]

Related strategies were developed by Gasser and co-workers to derivatize the anthelmintic drugs monepantel,[137-139] oxamniquine,[140,141] and albendazole.[142] Further new antischistosomal drug candidates were also obtained by the organometallic derivatization of non-antifungal drugs like the antimalarial mefloquine.[143] The findings affirm the potential of developing organometallic derivatives of organic drugs as therapeutic agents against medically and veterinary significant parasites.

Gasser group have expanded its research by developing organometallic derivatives of the well-established antifungal drug fluconazole that showed promise as potential agents against parasitic helminths responsible for both soil-transmitted helminthiasis and lymphatic filariasis. The incorporation of organometallic moieties into the organic drug's structure not only enhanced the antifungal activity of the original drug but also broadened its spectrum of action. Ten organometallic derivatives were obtained by replacement of one of the triazole rings of fluconazole by ferrocene or ruthenocene together with changes on the aliphatic linker. *In vivo* studies have demonstrated the compounds' high effectiveness against pathogenic fungal infections, while *in vitro* experiments have revealed their potency against parasitic nematodes such as *Brugia pahangi*, causative agent of lymphatic filariasis, and *Trichuris muris*, a useful model for *Trichuris trichiura* (whipworm), one of the principal soil-transmitted helminths affecting humans. The ferrocenyl compound showing best performance of the series, compound **16** (Figure 15), displayed improved antifungal activity together with IC_{50} values in μM of 9 on *Brugia pahangi* and 23.9 on *Trichuris muris*.[144] It effectively reduced the reproductive output and fecundity of *B. pahangi in vivo*. These new compounds target specific molecular pathways, differing in their mechanism of action from fluconazole. Importantly, they exert their effects on biosynthetic pathways that are not present in the human host, enhancing their specificity and minimizing potential adverse effects.[145]

In a subsequent approach, a similar strategy was employed, but with the substitution with the metallocenyl moieties ferrocene, ruthenocene, and cobaltocenium on one of the two identical triazoles in fluconazole. The incorporation of different metallocenes was intended to deepen the understanding of the impact of the metallocene moiety on the biological properties. Two synthetic methodologies were employed to produce fluconazole analogues, which depended on the type of linker, either 1,2,3-triazole or amide, connecting the organometallic group to the fluconazole core.[146]

Although ruthenocene and ferrocene are isoelectronic and possess very similar geometry and steric demands, ruthenocene exhibits distinct redox properties compared to ferrocene.[147] The utilization of the isoelectronic

cobaltocenium in existing drugs has been considerably less explored compared to the extensively studied ferrocene-containing bioactive compounds.[148]

The hit compound **17** (Figure 15) proved effective in inducing worm death against both *Brugia pahangi* and *Trichuris muris* at concentrations of 50 and 100 μM, respectively. Toxicity assessment on the free-living nematode *C. elegans*, commonly utilized for testing the toxicity of potential drugs, indicated that this compound is non-toxic up to a dose of 100 μM, as it did not exhibit any noticeable impact on motility, viability, or development in this invertebrate animal. Additionally, this compound showed micromolar activity on *T. cruzi* and also some antifungal activity.

Overall, both studies underscore that the organometallic derivatization of known antifungal drugs can yield novel, easily synthesizable compounds with potent biological activity and broad spectrum. This type of organometallics should be further investigated to get novel compounds active against neglected diseases by parasitic helminths.

3. Conclusions

According to the findings highlighted in this review, organometallic compounds present a promising avenue for drug development that remains relatively untapped. Bioorganometallic chemistry holds significant potential for the creation of innovative drugs targeting prevalent neglected diseases caused by trypanosomatid parasites and parasitic worms, and malaria. This potential stems from the diverse bonding modes and structures available, as well as the adaptability this field offers in design. Generally, these compounds have demonstrated adequate stability in biological environments and suitable lipophilicity for *in vivo* applications. According to Lipinski's rule, drugs typically have physicochemical and structural properties within certain ranges. Although metal compounds often do not follow the guidelines for drug-like properties of organic molecules, a balanced lipophilicity plays a significant role in determining pharmacokinetics properties of the compounds. Metal compounds with an appropriate level of lipophilicity are more likely to exhibit favorable ADME (absorption, distribution, metabolism, and excretion) profiles, leading to a suitable bioavailability.[1]

The identification of the parasite targets affected is crucial to understand activity, unspecific cytotoxicity and selectivity towards the parasites and for the design of compounds with improved biological performance. Leveraging omics studies in parasites provides deeper insights into the potential antiparasitic actions of these compounds.

While this review highlights selected examples of established classes of organometallic compounds, there is ample opportunity for further research focused on rational design using these organometallic cores. Such endeavors would be of great interest to the fields of Medicinal Inorganic Chemistry and, particularly, Bioorganometallic Chemistry.

Dinorah Gambino *is Full Professor of Inorganic Chemistry (2010) at the Facultad de Química, Universidad de la República (UdelaR), Montevideo, Uruguay. She obtained a Pharmaceutical Chemist degree (1981), a doctoral degree in Pharmaceutical Sciences (1986) and a doctoral degree in Chemistry (2001) from the UdelaR. She spent a short postdoctoral stay with Malcolm Frier, Radiopharmacy Unit, Queen's Medical Centre, Nottingham University, UK. Her current research focuses on the design and development of new metal-based prospective drugs for the treatment of neglected diseases caused by trypanosomatid parasites. She is an elected member of the Academia de Ciencias de América Latina (ACAL, 2023) and of the council of SBIC (2021-2025) and a senior researcher of the National Research System (SNI-ANII) and PEDECIBA (Program for the Development of Basic Sciences) of Uruguay. She got the 2023 Vanadis award. She currently joins the editorial boards of Anti-Infective Agents - Frontiers in Drug Discovery (Associate Editor), New Journal of Chemistry (Advisory Board), Journal of Inorganic Biochemistry and Inorganics. She has served as guest editor of several themed issues of various international scientific journals and as editor of a book in Spanish entitled "Applications of Metal Compounds in Medicine" (2012). She was Chair of VII Latin American Meeting on Biological Inorganic Chemistry (LABIC, 2021), 11th International Vanadium Symposium (IVS, V11, 2018) and XII International Symposium on Metal Ions in Biology and Medicine (2013, co-chair).*

References

1. Anthony, E. J.; Bolitho, E. M.; Bridgewater, H. E.; Carter, O. W. L; Donnelly, J. M.; Imberti, C.; Lant, E. C.; Lermyte, F.; Needham, R. J.; Palau, M.; Sadler, P. J.; Shi, H.; Wang, F.-X.; Zhang, W.-Y.; Zhang, Z.; *Chem. Sci.* **2020**, *11*, 12888. [Crossref]
2. Kostenkova, K.; Scalese, G.; Gambino, D.; Crans, D. C.; *Curr. Opin. Chem. Biol.* **2022**, *69*, 102155. [Crossref]
3. Scalese, G.; Kostenkova, K.; Crans, D. C.; Gambino, D.; *Curr. Opin. Chem. Biol.* **2022**, *67*, 102127. [Crossref] and references therein.

4. Rosenberg, B.; Van Camp, L.; Krigas, T.; *Nature* **1965**, *205*, 698. [Crossref]
5. Van Cleave, C.; Crans, D. C.; *Inorganics* **2019**, *7*, 111. [Crossref]
6. Gasser, G.; Ott, I.; Metzler-Nolte, N.; *J. Med. Chem*. **2011**, *54*, 3. [Crossref]
7. Fish, R. H.; Jaouen, G.; *Organometallics* **2003**, *22*, 2166. [Crossref]
8. Jaouen, G.; *Bioorganometallics*; John Wiley & Sons: Weinheim, Germany, 2006.
9. Hillard, E. A.; Jaouen, G.; *Organometallics* **2011**, *30*, 20. [Crossref]
10. Noffke, A. L.; Habtemariam, A.; Pizarro, A. M.; Sadler, P. J.; *Chem. Commun.* **2012**, *48*, 5219. [Crossref]
11. Hartinger, C. G.; Dyson, P. J.; *Chem. Soc. Rev.* **2009**, *38*, 391. [Crossref]
12. Allardyce, C. S.; Dorcier, A.; Scolaro, C.; Dyson, P. J.; *Appl. Organomet. Chem.* **2005**, *19*, 1. [Crossref]
13. Dyson, P. J.; Sava, G.; *Dalton Trans.* **2006**, 1929. [Crossref]
14. Chellan, P.; Sadler, P. J.; *Chem. - Eur. J.* **2020**, *26*, 8676. [Crossref]
15. Zhang, P.; Sadler, P. J.; *J. Organomet. Chem.* **2017**, *839*, 5. [Crossref]
16. van Rijt, S. H.; Sadler, P. J.; *Drug Discovery Today* **2009**, *14*, 1089. [Crossref]
17. Yan, Y. K.; Melchart, M.; Habtemariam, A.; Sadler, P. J.; *Chem. Commun.* **2005**, 4764. [Crossref]
18. Braga, S. S.; Silva, A. M. S.; *Organometallics* **2013**, *32*, 5626. [Crossref]
19. Ong, Y. C.; Gasser, G.; *Drug Discovery Today: Technol.* **2020**, *37*, 117. [Crossref]
20. Gasser, G.; *Chimia* **2015**, *69*, 442. [Crossref]
21. Patra, M.; Gasser, G.; *ChemBioChem* **2012**, *13*, 1232. [Crossref]
22. Gasser, G.; Metzler-Nolte, N.; *Curr. Opin. Chem. Biol.* **2012**, *16*, 84. [Crossref]
23. Frei, A.; Elliott, A. G.; Kan, A.; Dinh, H.; Bräse, S.; Bruce, A. E.; Bruce, M. R.; Chen, F.; Humaidy, D.; Jung, N.; King, A. P.; Lye, P. G.; Maliszewska, H. K.; Mansour, A. M.; Matiadis, D.; Muñoz, M. P.; Pai, T.-Y.; Pokhrel, S.; Sadler, P. J.; Sagnou, M.; Taylor, M.; Wilson, J. J.; Woods, D.; Zuegg, J.; Meyer, W.; Cain, A. K.; Cooper, M. A.; Blaskovich, M. A. T.; *JACS Au* **2022**, *2*, 2277. [Crossref]
24. Lin, Y.; Betts, H.; Keller, S.; Cariou, K.; Gasser, G.; *Chem. Soc. Rev.* **2021**, *50*, 10346. [Crossref]
25. Oehninger, L.; Rubbiani, R.; Ott, I.; *Dalton Trans.* **2013**, *42*, 3269. [Crossref]
26. Gil-Moles, M.; Türck, S.; Basu, U.; Pettenuzzo, A.; Bhattacharya, S.; Rajan, A.; Ma, X.; Büssing, R.; Wölker, J.; Burmeister, H.; Hoffmeister, H.; Schneeberg, P.; Prause, A.; Lippmann, P.; Kusi-Nimarko, J.; Hassell-Hart, S.; McGown, A.; Guest, D.; Lin, Y.; Notaro, A.; Vinck, R.; Karges, J.; Cariou, K.; Peng, K.; Qin, X.; Wang, X.; Skiba, J.; Szczupak, Ł.; Kowalski, K.; Schatzschneider, U.; Hemmert, C.; Gornitzka, H.; Milaeva, E. R.; Nazarov, A. A.; Gasser, G.; Spencer, J.; Ronconi, L.; Kortz, U.; Cinatl, J.; Bojkova, D.; Ott, I.; *Chem. - Eur. J.* **2021**, *27*, 17928. [Crossref]
27. Karges, J.; Giardini, M. A.; Blacque, O.; Woodworth, B.; Siqueira-Neto, J. L.; Cohen, S. M.; *Chem. Sci.* **2023**, *14*, 711. [Crossref]
28. Köpf, H.; Köpf-Maier, P.; *Angew. Chem.* **1979**, *91*, 509. [Crossref]
29. Guo, M.; Sun, H.; McArdle, H. J.; Gambling, L.; Sadler, P. J.; *Biochemistry* **2000**, *39*, 10023. [Crossref]
30. Top, S.; Dauer, B.; Vaissermann, J.; Jaouen, G.; *J. Organomet. Chem.* **1997**, *541*, 355. [Crossref]
31. Jaouen, G.; Vessières, A.; Top, S.; *Chem. Soc. Rev.* **2015**, *44*, 8802. [Crossref]
32. Top, S.; Tang, J.; Vessières, A.; Carrez, D.; Provot, C.; Jaouen, G.; *Chem. Commun.* **1996**, 955. [Crossref]
33. Wang, R.; Chen, H.; Yan, W.; Zheng, M.; Zhang, T.; Zhang, Y.; *Eur. J. Med. Chem.* **2020**, *190*, 112109. [Crossref]
34. Idlas, P.; Lepeltier, E.; Jaouen, G.; Passirani, C.; *Cancers* **2021**, *13*, 2291. [Crossref]
35. Coverdale, J. P.; Laroiya-McCarron, T.; Romero-Canelón I.; *Inorganics* **2019**, *7*, 31. [Crossref]
36. Rausch, M.; Dyson, P. J.; Nowak-Sliwinska, P.; *Adv. Ther.* **2019**, *2*, 1900042. [Crossref]
37. Hanif, M.; Babak, M. V.; Hartinger, C. G.; *Drug Discovery Today* **2014**, *19*, 1640. [Crossref]
38. Meier-Menches, S. M.; Gerner, C.; Berger, W.; Hartinger, C. G.; Keppler, B. K.; *Chem. Soc. Rev.* **2018**, *47*, 909. [Crossref]
39. Hearn, J. M.; Romero-Canelón, I.; Qamar, B.; Liu, Z.; Hands-Portman, I. Sadler, P. J.; *ACS Chem. Biol.* **2013**, *8*, 1335. [Crossref]
40. Liu, Z.; Sadler, P. J.; *Acc. Chem. Res.* **2014**, *47*, 1174. [Crossref]
41. Konkankit, C. C.; Marker, S. C.; Knopf, K. M.; Wilson, J. J.; *Dalton Trans.* **2018**, *47*, 9934. [Crossref]
42. Leonidova, A.; Gasser, G.; *ACS Chem. Biol.* **2014**, *9*, 2180. [Crossref]
43. Jürgens, S.; Herrmann, W. A.; Kühn, F. E.; *J. Organomet. Chem.* **2014**, *751*, 83. [Crossref]
44. Bauer, E. B.; Haase, A. A.; Reich, R. M.; Crans, D. C.; Kühn, F. E.; *Coord. Chem. Rev.* **2019**, *393*, 79. [Crossref]
45. Clède, S.; Policar, C.; *Chem. - Eur. J.* **2015**, *21*, 942. [Crossref]
46. Policar, C.; Bouvet, J.; Bertrand, H. C.; Delsuc, N.; *Curr. Opin. Chem. Biol.* **2022**, *67*, 102109. [Crossref]
47. Hostachy, S.; Policar, C.; Delsuc, N.; *Coord. Chem. Rev.* **2017**, *351*, 172. [Crossref]
48. Cinellu, M. A.; Ott, I.; Casini, A. In *Bioorganometallic Chemistry*; Jaouen, G.; Salmain, M., eds.; Wiley-VCH: Weinheim, 2015, p. 117-140.
49. de Paiva, R. E. F.; Marçal Neto, A.; Santos, I. A.; Jardim, A. C. G.; Corbi, P. P.; Bergamini, F. R. G.; *Dalton Trans.* **2020**, *49*, 16004. [Crossref]

50. Karges, J.; Cohen, S. M.; *ChemBioChem* **2021**, *22*, 2600. [Crossref]
51. Ioannou, K.; Vlasiou, M. C.; *BioMetals* **2022**, *35*, 639. [Crossref]
52. Li, H.; Yuan, S. Wei, X.; Sun, H.; *Chem. Commun.* **2022**, *58*, 7466. [Crossref]
53. Rothan, H. A.; Stone, S.; Natekar, J.; Kumari, P.; Arora, K.; Kumar, M.; *Virology* **2020**, *547*, 7. [Crossref]
54. Cirri, D.; Marzo, T.; Tolbatov, I.; Marrone, A.; Saladini, F.; Vicenti, I.; Dragoni, F.; Boccuto, A.; Messori, L.; *Biomolecules* **2021**, *11*, 1858. [Crossref]
55. Chuong, C.; DuChane, C. M.; Webb, E. M.; Rai, P.; Marano, J. M.; Bernier, C. M.; Merola, J. S.; Weger-Lucarelli, J.; *Viruses* **2021**, *13*, 980. [Crossref]
56. Gil-Moles, M.; O'Beirne, C.; Esarev, I. V.; Lippmann, P.; Tacke, M.; Cinatl Jr., J.; Bojkova, D.; Ott, I.; *RSC Med. Chem.* **2023**, *14*, 1260. [Crossref]
57. Gil-Moles, M.; Basu, U.; Büssing, R.; Hoffmeister, H.; Türck, S.; Varchmin, A.; Ott, I.; *Chem. - Eur. J.* **2020**, *26*, 15140. [Crossref]
58. World Health Organization (WHO), *Neglected Tropical Diseases*, https://www.who.int/news-room/questions-and-answers/item/neglected-tropical-diseases, accessed in May 2024.
59. Drugs for Neglected Diseases initiative (DNDi), *Neglected Tropical Diseases - A Global Health Emergency*, https://dndi.org/diseases/neglected-tropical-diseases/, accessed in May 2024.
60. Ong, Y. C.; Roy, S.; Andrews, P. C.; Gasser, G.; *Chem. Rev.* **2019**, *119*, 730. [Crossref]
61. Hotez, P. J.; Aksoy, S.; Brindley, P. J.; Kamhawi, S.; *PLoS Neglected Trop. Dis*. **2020**, *14*, e0008001. [Crossref]
62. World Health Organization, *Malaria*, https://www.who.int/news-room/questions-and-answers/item/malaria, accessed in May 2024.
63. Medicines for Malaria Venture (MMV), *Malaria Facts and Statistics*, https://www.mmv.org/malaria/malaria-facts-statistics, accessed in June 2024.
64. Peter, S.; Aderibigbe, B. A.; *Molecules* **2019**, *24*, 3604. [Crossref]
65. Mangawa, S. K.; Singh, S.; *Curr. Top. Med. Chem.* **2023**, *23*, 1503. [Crossref]
66. Wani, W. A.; Jameel, E.; Baig, U.; Mumtazuddin, S.; Hun, L. T.; *Eur. J. Med. Chem.* **2015**, *101*, 534. [Crossref]
67. Biot, C.; Glorian, G.; Maciejewski, L. A.; Brocard, J. S.; Domarle, O.; Blampain, G.; Millet, P.; Georges, A. J.; Abessolo, H.; Dive, D.; Lebibi, J.; *J. Med. Chem.* **1997**, *40*, 3715. [Crossref]
68. Dubar, F.; Khalife, J.; Brocard, J.; Dive, D.; Biot, C.; *Molecules* **2008**, *13*, 2900. [Crossref]
69. Pierrot, C.; Lafitte, S.; Dive, D.; Fraisse, L.; Brocard, J.; Khalife, J.; *Int. J. Parasitol.* **2005**, *35*, 1601. [Crossref]
70. Biot, C.; *Curr. Med. Chem.: Anti-Infect. Agents* **2004**, *3*, 135. [Crossref]
71. Medicines for Malaria Venture (MMV), *Chloroquine*, https://www.mmv.org/malaria-medicines/history-antimalarials-drugs#:~:text=Chloroquine, accessed in May 2024.
72. NIH National Library of Medicine, *Ferroquine*, https://www.clinicaltrials.gov/search?term=ferroquine, accessed in May 2024.
73. Abd-Rahman, A. N.; Zaloumis, S.; McCarthy, J. S.; Simpson, J. A.; Commons, R. J.; *Antimicrob. Agents Chemother.* **2022**, *66*, e01659-21. [Crossref]
74. Medicines for Malaria Venture (MMV), *ZY19489+ Ferroquine*, https://www.mmv.org/mmv-pipeline-antimalarial-drugs/zy19489-ferroquine, accessed in May 2024.
75. Dubar, F.; Egan, T. J.; Pradines, B.; Kuter, D.; Ncokazi, K. K.; Forge, D.; Paul, J.-F.; Pierrot, C.; Kalamou, H.; Khalife, J.; Buisine, E.; Rogier, C.; Vezin, H.; Forfar, I.; Slomianny, C.; Trivelli, X.; Kapishnikov, S.; Leiserowitz, L.; Dive, D.; Biot, C.; *ACS Chem. Biol.* **2011**, *6*, 275. [Crossref]
76. Biot, C.; Taramelli, D.; Forfar-Bares, I.; Maciejewski, L. A.; Boyce, M.; Nowogrocki, G.; Brocard, J. S.; Basilico, N.; Olliaro, P.; Egan, T. J.; *Mol. Pharm.* **2005**, *2*, 185. [Crossref]
77. Gambino, D.; Otero, L.; *Front. Chem.* **2022**, *9*, 816266. [Crossref]
78. Navarro, M.; Gabbiani, C.; Messori, L.; Gambino, D.; *Drug Discovery Today* **2010**, *15*, 1070. [Crossref]
79. Gambino, D.; *Coord. Chem. Rev.* **2011**, *255*, 2193. [Crossref]
80. Gambino, D.; Otero, L.; *Inorg. Chim. Acta* **2012**, *393*, 103. [Crossref]
81. Gambino, D.; Otero, L.; *Inorg. Chim. Acta* **2018**, *472*, 58. [Crossref]
82. Gambino, D.; Otero, L. In *Essential Metals in Medicine: Therapeutic Use and Toxicity of Metal Ions in the Clinic*, vol. 19; Carver, P. L., ed.; De Gruyter: Berlin, Boston, 2019, p. 331. [Crossref]
83. Gambino, D.; Otero, L. In *Targeted Metallo-Drugs, Design, Development, and Modes of Action*, vol. 24, 1st ed.; Farkas, E.; Marmion, C. J., eds.; CRC Press: Boca Raton, 2023, ch. 7. [Crossref]
84. Ribeiro, I.; Sevcsik, A.-M.; Alves, F.; Diap, G.; Don, R.; Harhay, M. O.; Chang, S.; Pecoul, B.; *PLoS Neglected Trop. Dis.* **2009**, *3*, e484. [Crossref]
85. De Rycker, M.; Baragaña, B.; Duce, S. L.; Gilbert, I. H.; *Nature* **2018**, *559*, 498. [Crossref]
86. Santos, S. S.; de Araújo, R. V.; Giarolla, J.; El Seoud, O.; Ferreira, E. I.; *Int. J. Antimicrob. Agents* **2020**, *55*, 105906. [Crossref]
87. Kourbeli, V.; Chontzopoulou, E.; Moschovou, K.; Pavlos, D.; Mavromoustakos, T.; Papanastasiou, I. P.; *Molecules* **2021**, *26*, 4629. [Crossref]

88. Aslett, M.; Aurrecoechea, C.; Berriman, M.; Brestelli, J.; Brunk, B. P.; Carrington, M.; Depledge, D. P.; Fischer, S.; Gajria, B.; Gao, X.; Gardner, M. J.; Gingle, A.; Grant, G.; Harb, O. S.; Heiges, M.; Hertz-Fowler, C.; Houston, R.; Innamorato, F.; Iodice, J.; Kissinger, J. C.; Kraemer, E.; Li, W.; Logan, F. J.; Miller, J. A.; Mitra, S.; Myler, P. J.; Nayak, V.; Pennington, C.; Phan, I.; Pinney, D. F.; Ramasamy, G.; Rogers, M. B.; Roos, D. S.; Ross, C.; Sivam, D.; Smith, D. F.; Srinivasamoorthy, G.; Stoeckert Jr., C. J.; Subramanian, S.; Thibodeau, R.; Tivey, A.; Treatman, C.; Velarde, G.; Wang, H.; *Nucleic Acids Res.* **2010**, *38*, D457. [Crossref]
89. El-Sayed, N. M.; Myler, P. J.; Blandin, G.; Berriman, M.; Crabtree, J.; Aggarwal, G.; Caler, E.; Renauld, H.; Worthey, E. A.; Hertz-Fowler, C.; Ghedin, E.; Peacock, C.; Bartholomeu, D. C.; Haas, B. J.; Tran, A.-N.; Wortman, J. R.; Alsmark, U. C. M.; Angiuoli, S.; Anupama, A.; Badger, J.; Bringaud, F.; Cadag, E.; Carlton, J. M.; Cerqueira, G. C.; Creasy, T.; Delcher, A. L.; Djikeng, A.; Embley, T. M.; Hauser, C.; Ivens, A. C.; Kummerfeld, S. K.; Pereira-Leal, J. B.; Nilsson, D.; Peterson, J.; Salzberg, S. L.; Shallom, J.; Silva, J. C.; Sundaram, J.; Westenberger, S.; White, O.; Melville, S. E.; Donelson, J. E.; Andersson, B.; Stuart, K. D.; Hall, N.; *Science* **2005**, *309*, 404. [Crossref]
90. Ilari, A.; Genovese, I.; Fiorillo, F.; Battista, T.; De Ionna, I.; Fiorillo, A.; Colotti, G.; *Mol. Pharmaceutics* **2018**, *15*, 3069. [Crossref]
91. Stuart, K.; Brun, R.; Croft, S.; Fairlamb, A.; Gürtler, R. E.; McKerrow, J.; Reed, S.; Tarleton, R.; *J. Clin. Invest.* **2008**, *118*, 1301. [Crossref]
92. Demoro, B.; Sarniguet, C.; Sánchez-Delgado, R.; Rossi, M.; Liebowitz, D.; Caruso, F.; Olea-Azar, C.; Moreno, V.; Medeiros, A.; Comini, M. A.; Otero, L.; Gambino, D.; *Dalton Trans.* **2012**, *41*, 1534. [Crossref]
93. Demoro, B.; Rossi, M.; Caruso, F.; Liebowitz, D.; Olea-Azar, C.; Kemmerling, U.; Maya, J. D.; Guiset, H.; Moreno, V.; Pizzo, C.; Mahler, G.; Otero, L.; Gambino, D.; *Biol. Trace Elem. Res.* **2013**, *153*, 371. [Crossref]
94. Fernández, M.; Rodríguez Arce, E.; Sarniguet, C.; Morais, T. S.; Tomaz, A. I.; Olea Azar, C.; Figueroa, R.; Maya, J. D.; Medeiros, A.; Comini, M.; Garcia, M. H.; Otero, L.; Gambino, D.; *J. Inorg. Biochem.* **2015**, *153*, 306. [Crossref]
95. Rodríguez Arce, E.; Sarniguet, C.; Moraes, T. S.; Vieites, M.; Tomaz, A. I.; Medeiros, A.; Comini, M. A.; Varela, J.; Cerecetto, H.; González, M.; Marques, F.; García, M. H.; Otero, L.; Gambino, D.; *J. Coord. Chem.* **2015**, *68*, 2923. [Crossref]
96. Miserachs, H. G.; Cipriani, M.; Grau, J.; Vilaseca, M.; Lorenzo, J.; Medeiros, A.; Comini, M. A.; Gambino, D.; Otero, L.; Moreno, V.; *J. Inorg. Biochem.* **2015**, *150*, 38. [Crossref]
97. Rodríguez Arce, E.; Machado, I.; Rodríguez, B.; Lapier, M.; Zúñiga, M. C.; Maya, J. D.; Olea Azar, C.; Otero, L.; Gambino, D.; *J. Inorg. Biochem.* **2017**, *170*, 125. [Crossref]
98. Soba, M.; Scalese, G.; Casuriaga, F.; Perez, N.; Veiga, N.; Echeverría, G. A.; Piro, O. E.; Faccio, R.; Pérez-Díaz, L.; Gasser, G.; Machado, I.; Gambino, D.; *Dalton Trans.* **2023**, *52*, 1623. [Crossref]
99. Soba, M.; Scalese, G.; Pérez-Díaz, L.; Gambino, D.; Machado, I.; *Talanta* **2022**, *244*, 123413. [Crossref]
100. Rodríguez Arce, E.; Florencia Mosquillo, M.; Pérez-Díaz, L.; Echeverría, G. A.; Piro, O. E.; Merlino, A.; Coitiño, E. L.; Maríngolo Ribeiro, C.; Leite, C. Q. F.; Pavan, F. R.; Otero, L.; Gambino, D.; *Dalton Trans.* **2015**, *44*, 14453. [Crossref]
101. Florencia Mosquillo, M.; Bilbao, L.; Hernández, F.; Machado, I.; Gambino, D.; Garat, B.; Pérez-Díaz, L.; *Biometals* **2018**, *31*, 961. [Crossref]
102. Florencia Mosquillo, M.; Bilbao, L.; Hernández, F.; Tissot, F.; Gambino, D.; Garat, B.; Pérez-Díaz, L.; *Chem. Biol. Drug Des.* **2018**, *92*, 1657. [Crossref]
103. Rodríguez Arce, E.; Putzu, E.; Lapier, M.; Maya, J. D.; Olea Azar, C.; Echeverría, G. A.; Piro, O. E.; Medeiros, A.; Sardi, F.; Comini, M.; Risi, G.; Salinas, G.; Correia, I.; Pessoa, J. C.; Otero, L.; Gambino, D.; *Dalton Trans.* **2019**, *48*, 7644. [Crossref]
104. Rivas, F.; Medeiros, A.; Rodríguez Arce, E.; Comini, M.; Ribeiro, C. M.; Pavan, F. R.; Gambino, D.; *J. Inorg. Biochem.* **2018**, *187*, 73. [Crossref]
105. Rivas, F.; Medeiros, A.; Quiroga, C.; Benítez, D.; Comini, M.; Rodríguez-Arce, E.; Machado, I.; Cerecetto, H.; Gambino, D.; *Dalton Trans.* **2021**, *50*, 1651. [Crossref]
106. Rivas, F.; Medeiros, A.; Comini, M.; Suescun, L.; Rodríguez Arce, E.; Martins, M.; Pinheiro, T.; Marques, F.; Gambino, D.; *J. Inorg. Biochem.* **2019**, *199*, 110779. [Crossref]
107. Rivas, F.; Del Mármol, C.; Scalese, G.; Pérez-Díaz, L.; Machado, I.; Blacque, O.; Medeiros, A.; Comini, M.; Gambino, D.; *J. Inorg. Biochem.* **2022**, *237*, 112016. [Crossref]
108. Beraldo, H.; Gambino, D.; *Mini-Rev. Med. Chem.* **2004**, *4*, 31. [Crossref]
109. Kumar, A.; Mishra, R.; Mazumder, A.; Mazumder, R.; Kumar, A.; *Asian J. Chem.* **2021**, *33*, 1957. [Crossref]
110. Aguirre, G.; Boiani, L.; Cerecetto, H.; González, M.; Denicola, A.; Otero, L.; Gambino, D.; Rigol, C.; Olea-Azar, C.; Faundez, M.; *Bioorg. Med. Chem.* **2004**, *12*, 4885. [Crossref]
111. Scalese, G.; Florencia Mosquillo, M.; Pérez-Díaz, L.; Gambino, D.; *Coord. Chem. Rev.* **2024**, *503*, 215608. [Crossref]
112. Don, R.; Ioset, J. R. S.; *Parasitology* **2014**, *14*, 140. [Crossref]
113. Machado, I.; Fernández, S.; Becco, L.; Garat, B.; Gancheff, J. S.; Rey, A.; Gambino, D.; *J. Coord. Chem*. **2014**, *67*, 1835. [Crossref]
114. Turrens, J. F.; Newton, C. L.; Zhong, L.; Rafael Hernandez, F.; Whitfield, J.; Docampo, R.; *FEMS Microbiol. Lett.* **1999**, *175*, 217. [Crossref]
115. Florencia Mosquillo, M.; Smircich, P.; Ciganda, M.; Lima, A.; Gambino, D.; Garat, B.; Pérez-Díaz, L.; *Metallomics* **2020**, *12*, 813. [Crossref]

116. Wang, H.; Zhou, Y.; Xu, X.; Li, H.; Sun, H.; *Curr. Opin. Chem. Biol*. **2020**, *55*, 171. [Crossref]
117. Florencia Mosquillo, M.; Scalese, G.; Moreira, R.; Denis, P. A.; Machado, I.; Paulino, M.; Gambino, D.; Pérez-Díaz, L.; *ChemBioChem* **2023**, *24*, e202300406. [Crossref]
118. Ononye, S. N.; VanHeyst, M. D.; Oblak, E. Z.; Zhou, W.; Ammar, M.; Anderson, A. C.; Wright, D. L.; *ACS Med. Chem. Lett.* **2013**, *4*, 757. [Crossref]
119. Saniewski, M.; Horbowicz, M.; Kanlayanarat, S.; *J. Hortic. Res.* **2014**, *22*, 5. [Crossref]
120. El Hachlafi, N.; Lakhdar, F.; Khouchlaa, A.; Bakrim, S.; El Omari, N.; Balahbib, A.; Shariati, M. A.; Zengin, G.; Fikri-Benbrahim, K.; Orlando, G.; Ferrante, C.; Meninghi, L.; Bouyahya, A.; *Processes* **2021**, *9*, 1680. [Crossref]
121. Oliveri, V.; Vecchio, G.; *Eur. J. Med. Chem.* **2016**, *120*, 252. [Crossref]
122. Song, Y.; Xu, H.; Chen, W.; Zhan, P.; Liu, X.; *Med. Chem. Commun.* **2015**, *6*, 61. [Crossref]
123. Gupta, R.; Luxami, V.; Paul, K.; *Bioorg. Chem.* **2021**, *108*, 104633. [Crossref]
124. Hess, J.; Keiser, J.; Gasser, G.; *Future Med. Chem.* **2015**, *7*, 821. [Crossref]
125. Specht, S.; Keiser, J.; *Int. J. Parasitol.* **2023**, *53*, 411. [Crossref]
126. World Health Organization (WHO), *Schistosomiasis*, https://www.who.int/news-room/fact-sheets/detail/schistosomiasis, accessed in June 2024.
127. Hotez, P. J.; Brindley, P. J.; Bethony, J. M.; King, C. H.; Pearce, E. J.; Jacobson, J.; *J. Clin. Invest.* **2008**, *118*, 1311. [Crossref]
128. Greenberg, R. M.; *Parasitology* **2013**, *140*, 1534. [Crossref]
129. World Health Organization (WHO), *Soil-Transmitted Helminth Infections*, https://www.who.int/news-room/fact-sheets/detail/soil-transmitted-helminth-infections, accessed in May 2024.
130. World Health Organization (WHO), *Lymphatic Filariasis (Elephantiasis)*, https://www.who.int/health-topics/lymphatic-filariasis, accessed in May 2024.
131. Patra, M.; Gasser, G.; *Nat. Rev. Chem.* **2017**, *1*, 0066. [Crossref]
132. Patra, M.; Ingram, K.; Pierroz, V.; Ferrari, S.; Spingler, B.; Keiser, J.; Gasser, G.; *J. Med. Chem.* **2012**, *55*, 8790. [Crossref]
133. Patra, M.; Ingram, K.; Pierroz, V.; Ferrari, S.; Spingler, B.; Gasser, R. B.; Keiser, J.; Gasser, G.; *Chem. - Eur. J.* **2013**, *19*, 2232. [Crossref]
134. Patra, M.; Ingram, K.; Leonidova, A.; Pierroz, V.; Ferrari, S.; Robertson, M. N.; Todd, M. H.; Keiser, J.; Gasser, G.; *J. Med. Chem.* **2013**, *56*, 9192. [Crossref]
135. Meister, I.; Ingram-Sieber, K.; Cowan, N.; Todd, M.; Robertson, M. N.; Meli, C.; Patra, M.; Gasser, G.; Keiser, J.; *Antimicrob. Agents Chemother.* **2014**, *58*, 5466. [Crossref]
136. Clède, S.; Cowan, N.; Lambert, F.; Bertrand, H. C.; Rubbiani, R.; Patra, M.; Hess, J.; Sandt, C.; Trcera, N.; Gasser, G.; Keiser, J.; Policar, C.; *ChemBioChem* **2016**, *17*, 1004. [Crossref]
137. Hess, J.; Patra, M.; Jabbar, A.; Pierroz, V.; Konatschnig, S.; Spingler, B.; Ferrari, S.; Gasser, R. B.; Gasser, G.; *Dalton Trans.* **2016**, *45*, 17662. [Crossref]
138. Hess, J.; Patra, M.; Pierroz, V.; Spingler, B.; Jabbar, A.; Ferrari, S.; Gasser, R. B.; Gasser, G.; *Organometallics* **2016**, *35*, 3369. [Crossref]
139. Hess, J.; Patra, M.; Rangasamy, L.; Konatschnig, S.; Blacque, O.; Jabbar, A.; Mac, P.; Jorgensen, E. M.; Gasser, R. B.; Gasser, G.; *Chem. - Eur. J.* **2016**, *22*, 16602. [Crossref]
140. Hess, J.; Panic, G.; Patra, M.; Mastrobuoni, L.; Spingler, B.; Roy, S.; Keiser, J.; Gasser, G.; *ACS Infect. Dis.* **2017**, *3*, 645. [Crossref]
141. Buchter, V.; Hess, J.; Gasser, G.; Keiser, J.; *Parasites Vectors* **2018**, *11*, 580. [Crossref]
142. Lin, Y.; Ong, Y. C.; Keller, S.; Karges, J.; Bouchene, R.; Manoury, E.; Blacque, O.; Müller, J.; Anghel, N.; Hemphill, A.; Häberli, C.; Taki, A.; Gasser, R. B.; Cariou, K.; Keiser, J.; Gasser, G.; *Dalton Trans.* **2020**, *49*, 6616. [Crossref]
143. d'Orchymont, F.; Hess, J.; Panic, G.; Jakubaszek, M.; Gemperle, L.; Keiser, J.; Gasser, G.; *Med. Chem. Commun.* **2018**, *9*, 1905. [Crossref]
144. Klementowicz, J. E.; Travis, M. A.; Grencis, R. K.; *Semin. Immunopathol.* **2012**, *34*, 815. [Crossref]
145. Lin, Y.; Jung, H.; Bulman, C. A.; Ng, J.; Vinck, R.; O'Beirne, C.; Zhong, S.; Moser, M. S.; Tricoche, N.; Peguero, R.; Li, R. W.; Urban Jr., J. F.; Le Pape, P.; Pagniez, F.; Moretto, M.; Weil, T.; Lustigman, S.; Cariou, K.; Mitreva, M.; Sakanari, J. A.; Gasser, G.; *J. Med. Chem.* **2023**, *66*, 15867. [Crossref]
146. Lin, Y.; Scalese, G.; Bulman, C. A.; Vinck, R.; Blacque, O.; Paulino, M.; Ballesteros-Casallas, A.; Pérez Díaz, L.; Salinas, G.; Mitreva, M.; Weil, T.; Cariou, K.; Sakanari, J. A.; Gambino, D.; Gasser, G.; *ACS Infect. Dis.* **2024**, *10*, 938. [Crossref]
147. Swarts, J. C.; Nafady, A.; Roudebush, J. H.; Trupia, S.; Geiger, W. E.; *Inorg. Chem.* **2009**, *48*, 2156. [Crossref]
148. Chantson, J. T.; Falzacappa, M. V. V.; Crovella, S.; Metzler-Nolte, N.; *J. Organomet. Chem.* **2005**, *690*, 4564. [Crossref]

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