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New heterobimetallic ferrocenyl derivatives: Evaluation of their potential as prospective agents against trypanosomatid parasites and *Mycobacterium tuberculosis*

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ABSTRACT

Searching for prospective agents against infectious diseases, four new ferrocenyl derivatives, [M(L)(dppf)4] (PF_6), with M = Pd(II) or Pt(II), dppf = 1,1′-bis(dipheny1phosphino) ferrocene and HL = tropolone (HTrop) or hinokitiol (HHino), were synthesized and characterized. Complexes and ligands were evaluated against the bloodstream form of *T. brucei*, *L. infantum* amastigotes, *M. tuberculosis* (MTB) sensitive strain and MTB clinical isolates. Complexes showed a significant increase of the anti-*T. brucei* activity with respect to the free ligands (> 28- and > 46-fold for Trop and 6- and 22-fold for Hino coordinated to Pt-dppf and Pd-dppf, respectively), yielding IC_{50} values < 5 μM. The complexes proved to be more potent than the antitrypanosomal drug Nifurtimox. The new ferrocenyl derivatives were more selective towards the parasite than the free ligands. The Pt compounds were less toxic on J774 murine macrophages (mammalian cell model), than the Pd ones, showing selectivity index values (*SI* = IC_{50} murine macrophage/IC_{50} *T. brucei*) up to 23. Generation of the {M-dppf} compounds lead to a slightly positive impact on the anti-leishmanial potency. Although the ferrocenyl derivatives were more active on sensitive MTB than the free ligands (MIC_{90} = 9.88–14.73 μM), they showed low selectivity towards the pathogen. Related to the mechanism of action, the antiparasitic effect cannot be ascribed to an interference of the compounds with the thiol-redox homeostasis of the pathogen. Fluorescence measurements pointed at DNA as a probable target of the new compounds. [Pt(Trop)(dppf)](PF_6) and [Pt(Hino)(dppf)](PF_6) could be considered prospective anti-*T. brucei* agents that deserve further research.

1. Introduction

Infectious diseases represent a tremendous health burden worldwide. Among them, a group of twenty communicable and poverty-related diseases, that affect about one billion people living in 149 countries, have received low attention from the pharmaceutical industry mainly due to little prospect of generating financial profit. Among these neglected diseases, three parasitic illnesses caused by genetically related trypanosomatid protozoa are major health concerns in the developing world: American Trypanosomiasis (Chagas' disease), Human African Trypanosomiasis (HAT, sleeping sickness) and Leishmaniasis. The genome of the three main parasites responsible of these diseases (*Trypanosoma cruzi*, *Trypanosoma brucei* and *Leishmania major*) shows a high percentage of inter-species conservation of genes encoding for indispensable and, sometimes, unique proteins. This offers the opportunity to develop wide spectrum drugs that could affect several related parasites. Additionally, these diseases are often co-endemic in certain regions of the world, Leishmaniasis and Chagas´ disease in South America and Leishmaniasis and HAT in Africa. This fact has led to the interest in developing drugs suitable for the treatment of multiple and biologically related pathogens [1–4]. HAT and Leishmaniasis are both parasitic diseases of interest in this work. HAT, caused by two strains of *Trypanosoma brucei* (*T. brucei*) (*Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*), is currently a resurgent disease with epidemic character in many regions of sub-Saharan Africa that can be fatal if not treated. The lack of surveillance, health care and new treatments and the emergence of resistance to old drugs favored the reappearance of the disease. The drugs currently available for the treatment show

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toxicity problems and variable efficacy depending on the type and stage of the disease [5–8]. Leishmaniases are a group of diseases caused by more than twenty *Leishmania* species. The parasites are transmitted to humans by the bite of an infected female phlebotomine sandfly insect vector. There are three main forms of the disease: cutaneous, visceral or kala-azar, and mucocutaneous. Leishmaniasis currently threatens 350 million people in 88 countries around the world being prevalent in four continents. *Leishmania*–HIV co-infection has been reported in 34 countries in Africa, Asia, Europe and South America and it intensifies the burden of visceral and cutaneous leishmaniasis by causing severe forms that are more difficult to manage [9–11]. Overall, available drugs for the treatment of both diseases are decades old and/or suffer from limited efficacy, undesirable collateral effects and development of resistance.

On the other hand, Tuberculosis (TB) is a highly contagious infectious disease caused by *Mycobacterium tuberculosis* (MTB). Although curable and preventable, it remains on the leading causes of death in the world being the most deadly infectious disease worldwide. Over 95% of the deaths occur in low- and middle-income countries. According to the World Health Organization 10.4 million people developed TB in 2016. In addition, it is estimated that 2 to 3 billion people have MTB latently in the lungs and about 5 to 15% of these people will develop the disease at some point [12,13]. The risk of infection is higher in persons with impaired immune system. Therefore, TB is a leading killer of HIV-positive people. Only few drugs are active against *M. tuberculosis* bacilli. Moreover, there is an increasing emergence of multi-drug resistant (MDR, resistant to isoniazid and rifampicin) and extensively drug resistant (XDR, resistant to isoniazid and rifampicin and, also to fluoroquinolones and second-line drugs) MTB strains. For instance, about half million people developed MDR-TB in the world in 2016 and, additionally, 110,000 people with rifampicin-resistant TB also required second line treatment in the same year. The continuing spread of drug-resistant TB is one of the most urgent and difficult challenges facing the control of the disease. This leads to an urgent need of developing new drugs acting through unprecedented mechanisms [14–18].

Our group is currently focused on the rational design of prospective metal-based drugs for the treatment of diseases caused by trypanosomatids and tuberculosis based on bioactive ligands, pharmacologically active metals and selected organometallic *cores*. This strategy, based on the paradigm of the metal-ligand synergism, could provide drugs capable of modulating multiple targets simultaneously and bearing improved biological properties [19–21]. According to this interest, we have developed organometallic compounds bearing antitrypanosomal activity including {Ru^{II}-*p*-cymene}, {Ru^{II}-cyclopentadienyl}, {*fac*-$Re^{I}(CO)_3$} and {M^{II}-dppf} *cores*, where M = Pd or Pt and dppf = 1,1′-bis (diphenylphosphino) ferrocene [22–30].

In particular, the “sandwich type” ferrocene moiety has shown high potential in the development of novel organometallic drugs. For instance, compounds including it, like the antitumoral ferrocifen and the antimalarial ferroquine, have entered the phase of clinical trials. Ferrocene derivatives are usually stable in air and in solution. In addition, they usually show low cytotoxicity and adequate lipophilicity that favor compound's penetration across cell membranes [31–33].

In this context, we identified a {Pt^{II}-dppf} compound including the bioactive ligand pyridine-2-thiolate-1-oxide (Hmpo), [Pt^{II}(mpo)(dppf)] (PF_6), as a hit compound and performed metallomics and proteomics on *T. cruzi* for the first time for a metal-based prospective drug [29,34]. The promising results obtained for this Pt complex encouraged us to further study the physicochemical and biological behavior of other series of related complexes obtained by modifying the hit compound. The new families of compounds retained the M-dppf co-ligand and different families of bioactive bidentate ligands were included instead of mpo. Among these bioactive ligands two tropolone derivatives were selected in the current work: Tropolone (HTrop) and Hinokitiol (HHino) (Fig. 1).

Tropolones are considered lead-like natural products in Medicinal Chemistry. The tropolone scaffold is characterized by a relatively low molecular weight, ample sites for chemical modifications and metal-binding functionality. Tropolone, hinokitiol and their derivatives, including metal compounds, have shown antitumoral and antimicrobial activities, among others [35,36].

In this work, 1,1′-bis(dipheny1phosphino) ferrocene hexafluorophosphate compounds [M^{II}(Trop)(dppf)](PF_6) and [M^{II}(Hino)(dppf)](PF_6), where M = Pd or Pt, were synthesized and fully characterized in the solid state and in solution. The biological activity of the four compounds was evaluated against *T. brucei*, *L. infantum* and *M. tuberculosis* (MTB) as well as on murine macrophages and human lung cells, both considered suitable mammalian cell models for determining selectivity towards trypanosomatids and MTB, respectively. Effects on redox metabolism of *T. brucei* and interaction with DNA were explored to get insight into the potential mechanism of action on the parasite.

2. Materials and methods

2.1. Materials

All common laboratory chemicals were purchased from commercial sources and used without further purification. Tropolone and Hinokitiol were purchased from Sigma Aldrich. Hinokitiol and tropolone sodium salts (NaHino·$2H_2O$ and NaTrop) were prepared according to a literature procedure [37]. [MCl_2(dppf)]·$CHCl_3$ precursors were synthesized according to a previously reported procedure by heating for 30 min an equimolar mixture of [MCl_2(dmso)$_2$] and dppf in $CHCl_3$ [38].

2.2. Synthesis of [M^{II}(Trop)(dppf)](PF_6) and [M^{II}(Hino)(dppf)](PF_6) compounds

The [M(Trop)(dppf)](PF_6) and [M(Hino)(dppf)](PF_6) compounds were synthesized by the following procedure: 50 mg of the precursor [MCl_2(dppf)] (0.059 mmol [$PdCl_2$(dppf)]·$CHCl_3$ or 0.053 mmol [$PtCl_2$(dppf)]·$CHCl_3$) were dissolved in 10 mL methanol. To this solution, an equimolar amount of NaHino·$2H_2O$ (13.1 mg for the Pd compound and 11.8 mg for the Pt compound) or NaTrop (8.5 mg for the Pd compound and 7.7 mg for the Pt compound) dissolved in 5 mL methanol was added. The mixture was shaken at room temperature for 24 h for the Trop compounds and 6 h at reflux for the Hino compounds. The solution was evaporated up to 5 mL and centrifugated. $NaPF_6$ dissolved in a minimal volume of methanol (14.8 mg, 0.88 mmol, for the Pd compounds and 13.4 mg, 0.079 mmol, for the Pt compounds) was added. The solution was kept in refrigerator during 24 h. Pd compounds were isolated by centrifugation as brown reddish solids and the Pt analogues as orange-yellow ones. Solids were washed with small portions of methanol. The four compounds were recrystallized from a dichloromethane solution of the compounds by diffusion with hexane. Single crystals suitable for X ray diffraction studies were obtained in the four cases.

[Pd(Trop)(dppf)] (PF_6), **Pd-dppf-Trop**. Yield: 27 mg, 49%. Anal. calc. for $C_{41}H_{33}F_6FeO_2P_3Pd$: C, 53.13; H, 3.59. Found: C, 52.93; H, 3.57.

[Pt(Trop)(dppf)] (PF_6), **Pt-dppf-Trop**. Yield: 22 mg, 41%. Anal. calc. for $C_{41}H_{33}F_6FeO_2P_3Pt$: C, 48.49; H, 3.28. Found: C, 48.51; H, 3.19.

[Pd(Hino)(dppf)] (PF_6), **Pd-dppf-Hino**. Yield: 25 mg, 44%. Anal. calc. for $C_{44}H_{39}F_6FeO_2P_3Pd$: C, 54.56; H, 4.03. Found: C, 54.26; H, 3.98.

[Pt(Hino)(dppf)] (PF_6), **Pt-dppf-Hino**. Yield: 20 mg, 35%. Anal. calc. for $C_{44}H_{39}F_6FeO_2P_3Pt$: C, 49.98; H, 3.69. Found: C, 49.86; H, 3.74.

2.3. Physicochemical characterization

C and H analyses were carried out with a Thermo Scientific Flash 2000 elemental analyzer. Conductimetric measurements were done

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