Coordination Chemistry Reviews 255 (2011) 2193–2203

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Potentiality of vanadium compounds as anti-parasitic agents

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Contents

ARTICLE INFO

Article history:
Received 4 November 2010
Accepted 22 December 2010
Available online 11 January 2011

Keywords:
Vanadium complexes
Neglected parasitic diseases
Trypanosomiasis
Chagas disease
Leishmaniasis
Amoebiasis

ABSTRACT

Research efforts on the medicinal chemistry of vanadium have been mainly focused whether on improving biodistribution and tolerability of the vanadium insulin-enhancing core or on developing potential anti-tumor compounds. Despite the fact that the World Health Organization statistics show that parasitic diseases are among the most prevalent illnesses worldwide, work on vanadium compounds for the potential treatment of some of these diseases has only recently arisen. This review focuses on recent attempts to develop vanadium-based potential anti-parasitic agents, mainly active against the parasites causing American trypanosomiasis (Chagas disease), leishmaniasis and amoebiasis. In addition, the search for new therapeutic uses of some previously known bioactive vanadium compounds is included.

1. Introduction

Metal compounds have been used in medicine since ancient times. Nevertheless, organic drugs have traditionally dominated modern medicinal chemistry and pharmacology. Inorganic medicinal chemistry is a growing research area whose current development has been triggered by the serendipitous discovery of the anti-tumor activity of cisplatin. This discipline exploits the singular properties of metal ions for designing metal compounds with therapeutic and diagnostic applications. Either coordination or organometallic chemistry offer wide possibilities to develop novel metal-based drugs bearing quite different mechanisms of action aiming at different targets. Most significant investigations on inorganic medicinal chemistry have been directed to the development of anti-tumor compounds of different metals (Pt, Ru, Sn, Ga, Au, Ti, Sn, among others) that could show improved therapeutic indexes and wider activity spectra [1–7].

Research efforts on the medicinal chemistry of vanadium have been mainly focused whether on improving biodistribution, oral bioavailability and tolerability of the vanadium insulin-enhancing core or on developing potential anti-tumor compounds [8–15]. Studies performed in the last decades established the ability of vanadium(V) and (IV) inorganic species and vanadium chelates to exert different insulin-mimetic and antidiabetic effects either *in vitro* or *in vivo*. For instance, extensive work on bis(maltolato derivative)oxovanadium(IV) complexes (Fig. 1), first vanadium-based insulin enhancing agents deserving to enter clinical trials, showed that modification of the vanadium core upon chelation improved biodistribution and tolerability with respect to $VOSO_4$ or $NaVO_3$. Phase I clinical trials of bis(ethylmaltolato) oxovana-

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doi:10.1016/j.ccr.2010.12.028

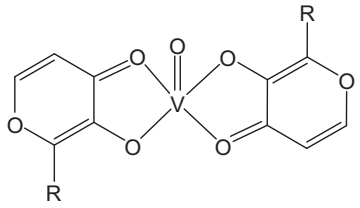

Fig. 1. General formula of the insulin-enhancing family of bis(maltolato derivative)oxovanadium(IV) complexes [16].

dium(IV) (BEOV) have been completed. Since a carrier function of the bioactive vanadium core coordination was suggested, extensive chelation work was conducted mainly pursuing fine-tuning of the physicochemical and biological properties of the vanadium center [5,16–18]. Biochemical studies have demonstrated that vanadium compounds exert their action through mechanisms involving generation of radical oxygen species (ROS) and inhibition of enzymes, especially certain regulatory phosphatases. More recently, it has been proposed that some anti-diabetic effects due to the vanadium compounds could result from the induction of changes in the membrane function [8–10,12,19]. On the other hand, anti-tumor properties of vanadium complexes are based on different cellular effects that depend primarily on vanadium core but also on the nature of the ligands and on the vanadium entity as a whole [12–15]. Evidence supports that they produce whether inhibition of cell cycle or induction of tumor cells death mediated by inhibition of PTPases and generation of ROS that damage some cellular components such as DNA [12].

According to the World Health Organization (WHO), infectious and parasitic ailments are major causes of human disease worldwide. Although representing a tremendous burden, some of these diseases have historically received low investment by the pharmaceutical industry as they are associated with little prospect of generating financial profit. Therefore, some parasitosis like malaria, schistosomiasis, Chagas disease, human African trypanosomiasis and leishmaniasis are considered by the international health authorities as neglected diseases [20–23]. They affect about one-third of the total world population that mostly inhabit the poorest areas of the planet. Due to the small number of available effective drugs, together with their high toxicity and low efficiency and the emergence of resistance, new drugs are urgently needed. In recent years some international non-profit organizations have pushed forward programs to sustain basic and clinical research involved in the development of new chemotherapeutics that could result in useful drugs for the treatment of these tropical neglected diseases [24–26].

Among other current efforts, inorganic medicinal chemistry offers the development of bioactive metal complexes as a promising and attractive approach in the search for a pharmacological control of some of these diseases [27–32]. Pioneering research by Sánchez-Delgado and Brocard led to some interesting potential metallopharmaceuticals for Chagas disease and malaria [27,28,33]. Several attempts to develop anti-parasitic metal-based drugs are currently in progress. They are mainly based on one of the following strategies [24]:

- Inclusion of a metal center into the moiety of an established anti-parasitic drug to enhance its pharmacological properties by using the bioorganometallic strategy of analogue generation. A clear example of this strategy is the first organometallic drug ferroquine, a novel anti-malarial drug candidate that is currently being developed by Sanofi-Aventis (Fig. 2) [33].
- Metal complexation of anti-parasitic compounds to modulate their activity and circumvent resistance mechanisms. The work performed by Sánchez-Delgado on Ru chloroquine complexes exemplifies this approach (Fig. 2) [27,28,34].
- Metal complexation of DNA intercalating ligands, intending this biomolecule to be a target in the parasite (see Gambino's work in Section 2).
- Metal coordination compounds of non bioactive ligands to be tested as metal inhibitors of parasite specific enzymes. Enzymes are natural targets for inorganic drugs as they can affect enzyme activity in different ways. In particular, metal ions can coordinate to active site residues blocking the interaction with the substrate or can affect enzyme structure by coordination to residues outside the active site [35]. McKerrow et al. tested several metal compounds with innocent ligands as potential inhibitors of trypanosomatid cysteine proteases [32].

Despite the fact that vanadium inorganic medicinal chemistry has been extensively investigated and that parasitic diseases are among the most prevalent illnesses worldwide, work on development of vanadium compounds for the potential treatment of some of these diseases has only been performed in recent years. Vanadium offers interesting chemical and biochemical properties for the development of anti-parasitic drugs. For instance, *in vivo* V(V) and V(IV) coexist intra- and extra-cellularly as oxo species, being both cationic and anionic cores present in the physiologically pH range. V(V) forms vanadate and other related species in aqueous solution and vanadate mimics phosphate both structurally and electronically, which is very significant due to the role of phosphates in biology [8,36]. Additionally, vanadium in its tri-, tetra-, and pentavalent oxidation states has the ability to interact with biomolecules, which may be responsible for important biological effects. Inhibition of phosphatases by vanadium compounds has been established as part of their mechanism of action. Relevant ATPases present in the parasites that cause malaria, trypanosomiasis, leishmaniasis, amoebiasis and other tropical diseases could be potential targets for vanadium species. Other parasite-specific enzymes could be also inhibited, counting for potential additional targets for vanadium compounds. Furthermore, owing to the high sensitivity of these parasites to oxidative stress [37], the generation of ROS could be another mechanism of anti-parasitic action. Further biological details of potential parasite targets related to enzymatic inhibition and ROS generation have been previously discussed [29]. The development of vanadium compounds as anti-parasitic agents could be an innovative and cost effective approach to anti-parasite drug discovery providing less expensive and more accesible metal-based drugs for the treatment of neglected diseases than those currently under research containing ruthenium, palladium, platinum or gold. Moreover, vanadium is currently considered an ultra trace metal with low nutritional requirements and is present in almost all-living organisms including man. Most foods destined for humans contain vanadium in non-toxic forms. Although some toxic effects of vanadium have been reported at high doses, it seems to be relatively innocuous when compared to other metals. For instance, vanadium supplementation is widely used by athletes for increasing muscle mass, without any toxicity reports [38–40]. Even if these properties represent an additional advantage for the development of vanadium-based drugs, toxicological profile will obviously not only depend on vanadium itself and its oxidation state but also on the route of administration, the speciation and the biological behavior of the whole vanadium coordination compound. Therefore, toxicity must be studied for each new potential drug.

This review focuses on recent attempts to develop vanadium-based potential anti-parasitic agents, mainly active against the parasites causing American trypanosomiasis (Chagas disease), leishmaniasis and amoebiasis. In addition, some efforts in the

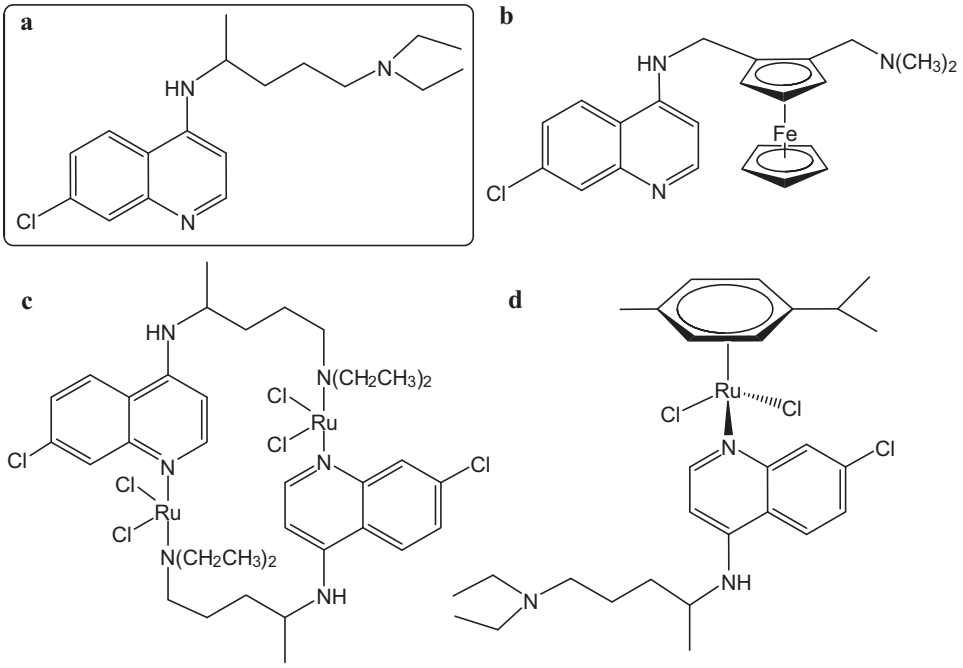

Fig. 2. Structure of some successful examples of metal-based anti-parasitic compounds related to the anti-malarial drug chloroquine (a): ferroquine (b), $[RuCl_2(chloroquine)]_2$ (c) and $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2(chloroquine)]$ (d) [28,33,34].

search for new therapeutic uses of previously known bioactive vanadium compounds are included.

2. Vanadium compounds as anti-trypanosomal agents

Trypanosomatids are single-celled protozoan parasites belonging to the kinetoplastida order. They cause various diseases including American trypanosomiasis, human African trypanosomiasis and leishmaniasis which are among the top neglected diseases [41]. American trypanosomiasis (Chagas disease) and human African trypanosomiasis (sleeping sickness) constitute major health concerns in the poorest tropical or subtropical regions of the world [23,42–44]. American trypanosomiasis is the third largest occurring parasitic disease worldwide after malaria and schistosomiasis. It is endemic throughout Latin America infecting about 10 million people and causing more deaths in this region than any other parasitic disease. The situation is becoming worse as globalization and immigration of unknowingly infected people from Latin America lead to the spreading of the disease to developed countries mainly due to the lack of controls and screening in blood and organ banks [43,45,46]. Although eradicated in the 1960s, human African trypanosomiasis is currently a resurgent disease with epidemic character in many regions of Africa. Its dramatic reappearance is attributed to the lack of surveillance and health care especially in conflicting regions, the lack of new treatments and the emergence of resistance to old drugs. The prevalence of the disease is currently as high as it was in the 1920s [42]. The etiologic agents of Chagas disease and human African trypanosomiasis, *Trypanosoma cruzi* and *Trypanosoma brucei* (*Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*), respectively, are mainly transmitted to the mammalian host by infected insects [47]. Treatment of Chagas disease is based on the old and quite unspecific nitroheterocyclic drugs nifurtimox and benznidazole that have significant activity only in the acute phase of the disease and, when associated with long-term treatments, give rise to severe side effects [43–48]. Although new improved treatments against this disease are urgently needed, no drugs are currently under clinical development. Only antifungal triazoles have demonstrated enough therapeutic potentiality in preclinical development to be worth beginning of clinical trials [44]. The drugs currently available for the treatment of human African trypanosomiasis, pentamidine, suramin, eflornithine and melarsoprol, also suffer from toxicity problems. Additionally, they are not universally active showing variable efficacy depending on the type and stage of the disease, and/or they have generated high levels of resistance to treatment [23,48].

In 1905 early inorganic medicinal chemistry attempts showed that the organoarsenical Atoxyl, although very toxic, is effective for the treatment of African trypanosomiasis. More recently, a correlation between anti-trypanosomal and anti-tumor activities has been observed probably due to the similarity of metabolic pathways in kinetoplastid parasites and tumor cells [27,28,49,50]. For instance, cisplatin has demonstrated activity on trypanosomatids (either *T. cruzi* or *T. brucei rhodesiense*) [51,52]. Some Pt, Rh and Os complexes, mainly developed by Osuna et al., showed *in vitro* anti-*T. cruzi* activity [53–58]. Novel results on anti-*T. cruzi* activity and potential mechanism of action of Ru, Au, Rh and other metal complexes of the well known drugs clotrimazole and ketoconazole were reported by Sánchez-Delgado [27,28,59–62]. Moreover, a group of platinum complexes are active against *T. cruzi*, acting as irreversible inhibitors of the parasite specific enzyme trypanothione reductase [63,64]. More recently Gambino et al. have developed several anti-trypanosome metal complexes by coordination of bioactive ligands, *i.e.* 5-nitrofurane and 5-nitrofurylacroleine thiosemicarbazone derivatives, bisphosphonates, aromatic ammine *N*-oxides, with biologically relevant metal centers, *i.e.* Pd(II), Pt(II), Au(I), Ru(II), Ru(III), Cu(II), Co(II), Mn(II) and Ni(II) [65–75]. The design of anti-parasite compounds by combining ligands bearing anti-trypanosomal activity and pharmacologically active metals takes advantage of the medicinal chemistry emerging drug discovery paradigm, based on the development of single chemical entities as dual inhibitors capable of modulating multiple targets simultaneously [30,31,76]. This strategy aims to enhance efficacy or improve safety relative to drugs that address only a single target. The obtained metal compounds could act through dual or even multiple mechanisms of action by combining the pharmacological

properties of both, the ligand and the metal. The development of single agents that provide maximal anti-protozoa activity by acting against multiple parasitic targets could diminish toxic effects in the host by lowering therapeutic dose and/or circumvent the development of drug resistance [30,31,76,77].

Aiming to extend the field of anti-parasitic metal complexes to other not yet explored metal centers, different vanadium species were studied. As explained above, bioactivity and/or bioavailability of organic bioactive ligands could be favorably modified through their coordination to vanadium due to changes in their electronic and physicochemical properties upon complexation. In addition, new parasite targets could be affected either by coordinated vanadium or by simple ionic vanadium species resulting from metabolism of the original vanadium-bioactive ligand entity. Potential *T. cruzi* targets for vanadium compounds have been previously discussed [29]. Trypanosomes diverged early from the eukaryotic lineage, which led to a quite different biochemistry from that of the mammalian host. Biochemistry and physiology of *T. cruzi* has been exhaustively studied and several enzymes crucial for the parasite survival have been validated as potential drug targets [37,78,79]. These parasite specific enzymes could be potential targets for the vanadium-based compounds. For instance, vanadium species could affect calcium homestasis of the parasite. Calcium presence, at specific concentrations, is critical for a variety of essential functions during the parasite life cycle and for host cell invasion process. Calcium regulation differs from that in the mammalian cells providing a potential target for anti-parasitic drugs. Its concentration is regulated by concerted calcium pumps, some of them present in parasite specific calcium and polyphosphates storage organelles called acidocalcisomes [80–82]. Acidocalcisomes possess vanadate sensitive plasma membrane-type Ca(II) ATPases, involved in the Ca(II) influx [29]. Vanadium-based drugs and/or vanadium species emerging from their metabolism could interact with ATPases relevant for calcium homestasis of the parasite. On the other hand, trypanosomatids are particularly sensitive to oxidative stress and, as previously mentioned, vanadium species can induce ROS in biological media. In this sense, Douglas et al. studied vanadate as a futile superoxide ion-producing substrate of trypanothione reductase, an essential and specific enzyme involved in the defense against oxidative stress in trypanosomatids [83]. The host glutathione/glutathione reductase system is replaced in the parasite by this trypanothione/trypanothione reductase system rendering an attractive parasite target. Authors suggested that vanadate and probably other vanadium species acting as subversive substrates for this enzyme might increase the effects of anti-*T. cruzi* drugs like nifurtimox, that act producing toxic ROS. However, bisperoxovanadium species of 1,10-phenanthroline, bipyridine and oxalate as well as bis(maltolato)oxovanadium(IV) were also tested but they did not inhibit trypanothione reductase even at concentration as high as 6 mM [83].

2.1. Vanadium compounds of bioactive aromatic ammine N-oxides

Gambino et al. reported the first research on developing novel anti-*T. cruzi* vanadium-based compounds [84]. A family of structurally related bioactive 6(7)-substituted-3-aminoquinoxaline-2-carbonitrile N^1,N^4-dioxides was coordinated to vanadium(IV) leading to [VO(L-H)$_2$] complexes (Fig. 3) [84]. Quinoxaline N^1,N^4-dioxides had displayed several biological activities. In particular, some amino substituted-3-amino-2-carbonitrile derivatives showed interesting *in vitro* anti-*T. cruzi* activity [85,86]. Oxovanadium compounds of the selected 6(7)-substituted-3-aminoquinoxaline-2-carbonitrile N^1,N^4-dioxides (mixture of 6(7) isomers) showed significantly increased ability to inhibit growth of the epimastigote form of *T. cruzi* (Tulahuen 2 strain) compared to the corresponding free ligands (Table 1). Structure–activity relationship studies showed that the biological response of this structurally related series depended mainly on the lipophilic properties of the compounds as well as on the electronic effects of the 6(7) substituent. This electronic effect of the R substituent on the quinoxaline moiety (see Fig. 3) played a role in the activity of the oxovanadium(IV) complexes, which increased whenever the ligands bore electron-withdrawing halogen substituents (**L3**, ***L4***, **L5**, Fig. 3). IC_{50} values of the halogen substituted ligands (**L3**, ***L4***, **L5**, Fig. 3) vanadium complexes were of the same order than those of the reference anti-trypanosome drugs nifurtimox and benznidazole. [VO(acac)$_2$] is almost non active, suggesting that the activity observed for the complexes can be attributed to the presence of the quinoxaline ligands. The complexation to vanadium apparently increases activity by improving bioavailability of the bioactive entity, *i.e.* the quinoxaline N^1,N^4-dioxide moiety [29].

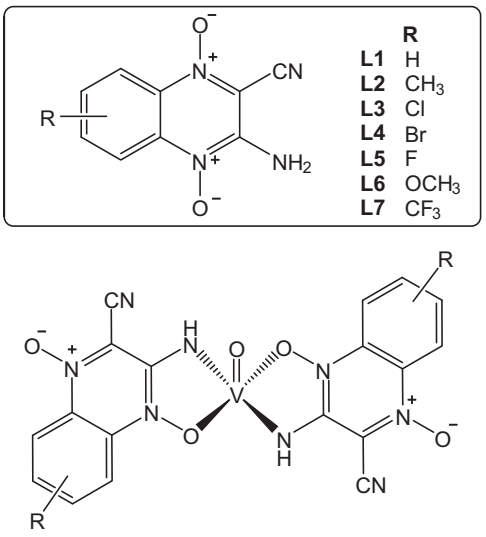

Fig. 3. Structure of the selected bioactive 6(7)-substituted-3-aminoquinoxaline-2-carbonitrile N^1,N^4-dioxides and their oxovanadium(IV) complexes [84].

Further work performed with these ligands and other metal centers, *i.e.* Pd(II) and Cu(II), led to similar [M(L-H)$_2$] complexes, and demonstrated that the anti-*T. cruzi* activity was dependent on the nature of the metal center M (Fig. 4) [87]. Vanadium compounds were significantly more active than the Pd and Cu analogues highlighting the potentiality of vanadium in the search of metal-based antichagasic drugs.

Following the same strategy, Gambino et al. worked with metal coordination compounds of the bioactive pyridine-2-thiol *N*-oxide

Table 1
In vitro anti-*T. cruzi* activity on epimastigotes (Tulahuen 2 strain) of selected 6(7)-substituted-3-aminoquinoxaline-2-carbonitrile N^1,N^4-dioxides and their oxovanadium(IV) complexes.

Compound	PGI (%)[a,b]	IC_{50} (μM)[b,c]	Compound	PGI (%)[a,b]	IC_{50} (μM)
L1	25.0	nd	[$V^{IV}O$(**L1**-H)$_2$]	59.5	20.0
L2	5.0	nd	[$V^{IV}O$(**L2**-H)$_2$]	47.5	27.0
L3	0.0	nd	[$V^{IV}O$(**L3**-H)$_2$]	95.0	16.8
L4	31.5	nd	[$V^{IV}O$(**L4**-H)$_2$]	91.5	12.8
L5	5.0	nd	[$V^{IV}O$(**L5**-H)$_2$]	84.0	19.9
L6	25.0	nd	[$V^{IV}O$(**L6**-H)$_2$]	43.5	35.0
L7	0.0	nd	[$V^{IV}O$(**L7**-H)$_2$]	15.5	nd
Nifurtimox	92.0	7.7	[$V^{IV}O$(acac)$_2$]	13.5	nd
Benznidazole	93.0	8.5			

[a] PGI, percentage of growth inhibition at 25 μM dose.
[b] Data from Ref. [84].
[c] 50% inhibitory concentration; nd, not determined.

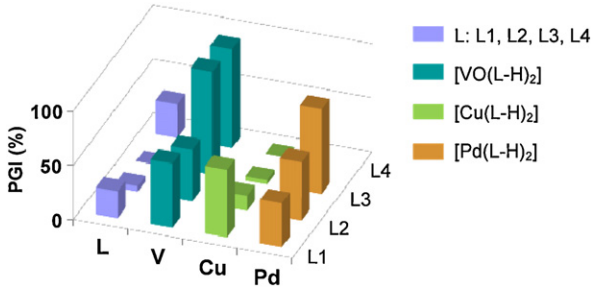

Fig. 4. Comparison of the percentage of growth inhibition (PGI %) at 25 μM dose for different 3-amino-2-carbonitrile quinoxaline N^1,N^4-dioxides metal complexes, [M(L-H)$_2$], and the free ligands [84,87].

(mpo, 2-mercaptopyridine *N*-oxide) as potential anti-trypanosome compounds (Fig. 5) [24,74,71]. Turrens et al. had previously demonstrated that mpo blocks *T. cruzi* growth in all stages of the parasite's life cycle without affecting mammalian cells [88]. The parasite specific NADH dependent enzyme fumarate reductase was identified as the main target. This enzyme, involved in the generation of energy as it turns fumarate to succinate, is absent in mammalian cells thus providing an interesting and specific target against *T. cruzi*. The dimeric gold(I) complex [Au$_2$(mpo-H)$_2$(PPh$_3$)$_2$] and the bis(pyridine-2-thiol *N*-oxide) platinum(II) and palladium(II) complexes, [Pt(mpo-H)$_2$] and [Pd(mpo-H)$_2$], showed improved activities towards epimastigotes of *T. cruzi* compared to the mpo sodium salt and nifurtimox (39, 67 and 115-fold more active than nifurtimox, respectively). All IC$_{50}$ values were in the nanomolar range. A clear correlation between parasite growth inhibition and NADH-fumarate reductase inhibitory effects has been observed which once again suggested this parasite enzyme as the main target of these complexes.

According to a current pharmaceutical development practice, efforts are being made to get new therapeutic tools for neglected parasitic diseases by evaluating well established drugs, previously tested for the treatment of other pathologies, or well known bioactive compounds [89]. This approach would have the advantage of shortening the pharmaceutical development process as well as lowering costs. The bis(pyridine-2-thiol *N*-oxide) oxovanadium(IV) complex, [VO(mpo-H)$_2$] (Fig. 5), had been previously studied as a potential insulin mimetic agent. It had proven to decrease the blood glucose levels with relatively high efficiency in streptozotocin-induced diabetic rats (STZ rats) and had shown relatively low toxicity [90–92]. Following the previously mentioned idea, this complex was evaluated *in vitro* on *T. cruzi* epimastigotes [93] and showed higher *in vitro* activity than the antichagasic reference

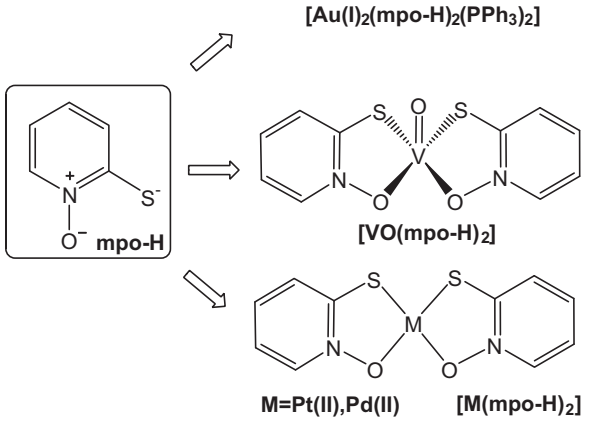

Fig. 5. Pyridine-2-thiol *N*-oxide and its Pt(II), Pd(II), Au(I) and VO(IV) complexes [71,74].

Table 2
In vitro activities of pyridine-2-thiol *N*-oxide sodium salt, Na(mpo-H), and [VO(mpo-H)$_2$] against *T. cruzi* epimastigotes and mammalian cells lines [93].

Compound	IC$_{50}$ *T. cruzi*[a]	IC$_{50}$ J774 macrophages[a]	IC$_{50}$ NCTC 929 fibroblasts[a]	SI[b]
Na(mpo-H)	3.35	>256	144.1	43.01
[VO(mpo-H)$_2$]	1.27	67.80	77.65	61.14
Benznidazole	30.89	>384.24	>384.24	12.44

[a] IC$_{50}$, 50% inhibitory concentration on *T. cruzi* epimastigotes (transfected Clone CL-B5) in μM.
[b] SI (selectivity index) = IC$_{50}$ on NCTC929 mammalian cells/IC$_{50}$ on *T. cruzi*.

drug benznidazole (Table 2). Furthermore, it showed low toxicity on mammalian cells with a high selectivity index (IC$_{50}$ on NCTC fibroblasts/IC$_{50}$ *T. cruzi* = 61.14) and low cytoxicity on J774 macrophages (IC$_{50}$ 67.80 μM), thus deserving to undergo an *in vivo* evaluation. *In vivo* acute phase model studies on experimentally infected Swiss albino mice are currently in progress.

2.2. Vanadium compounds with DNA intercalating ligands

Gambino et al. developed other vanadium compounds bearing anti-*T. cruzi* activity through the strategy of metal complexation of DNA intercalating ligands, aiming for this biomolecule as a parasite target [94–96].

As previously mentioned, metabolic pathways of kinetoplastid parasites (*Leishmania* and *Trypanosoma* parasites) are supposed to be similar to those present in tumor cells leading to a correlation between anti-trypanosome and anti-tumor activities. Moreover, it has been proposed that compounds that efficiently interact with DNA in an intercalative mode could also show anti-trypanosomatid activity [28,49,97]. Based on this hypothesis, some work had been done designing metallointercalators as anti-leishmania drugs, including metals of pharmacological interest, *i.e.* Cu(II), Cu(I), Au(III) or Ag(I), and dppz (dipyrido[3,2-a:2′,3′-c]phenazine) or dpq (dipyrido[3,2-a: 2′,3′-h]quinoxoline) as intercalating ligands [98]. All of them showed leishmanicidal activity against the promastigote form of *Leishmania* (*V*) *braziliensis* and *Leishmania (L) mexicana*. More recently (Fig. 6), an oxovanadium(IV) complex [V^{IV}O(SO$_4$)(H$_2$O)$_2$(dppz)]·2H$_2$O showing a slightly higher *in vitro* activity than nifurtimox on *T. cruzi* Dm28c strain epimastigotes has been obtained (Table 3) [95]. In addition, some mixed-ligand oxovanadium(IV) complexes including polypyridyl chelators (N$_{py}$,N$_{py}$ donors) (dppz, bipy = 2,2′-bipyridine or phen = 1,10-phenanthroline), capable of intercalating DNA as ligands, have been developed as potential anti-trypanosome agents [94,96]. These mixed-ligand complexes [V^{IV}O(L-2H)(N–N)]

Table 3
In vitro activities of vanadium(IV)-DNA intercalating ligand complexes against *T. cruzi* and HL-60 acute promyelocytic leukemia cell line. L8–L12 semicarbazone ligands are shown in Fig. 6.

Compound	IC$_{50}$ *T. cruzi*[a]	IC$_{50}$ HL-60 cells[b] 24 h	Reference
[V^{IV}O(SO$_4$)(H$_2$O)$_2$(dppz)]	*c.a.* 3	6.87	[94]
[V^{IV}O(**L8**-2H)(dppz)]	13	–	[95]
[V^{IV}O(**L9**-2H)(dppz)]	19	–	[95]
[V^{IV}O(**L8**-2H)(bipy)]	73	–	[92]
[V^{IV}O(**L9**-2H)(bipy)]	84	–	[95]
[V^{IV}O(**L8**-2H)(phen)]	2.0	17.14	[96]
[V^{IV}O(**L9**-2H)(phen)]	3.1	24.30	[96]
[V^{IV}O(**L10**-2H)(phen)]	2.3	16.80	[93]
[V^{IV}O(**L11**-2H)(phen)]	1.6	32.30	[93]
[V^{IV}O(**L12**-2H)(phen)]	3.8	13.90	[96]
Nifurtimox	6.0	–	[94–96]
Cisplatin	–	15.61	[95,96]

[a] IC$_{50}$, 50% inhibitory concentration on *T. cruzi* epimastigotes (Dm28c) in μM.
[b] IC$_{50}$, 50% inhibitory concentration on HL-60 acute promyelocytic leukemia cells in μM.

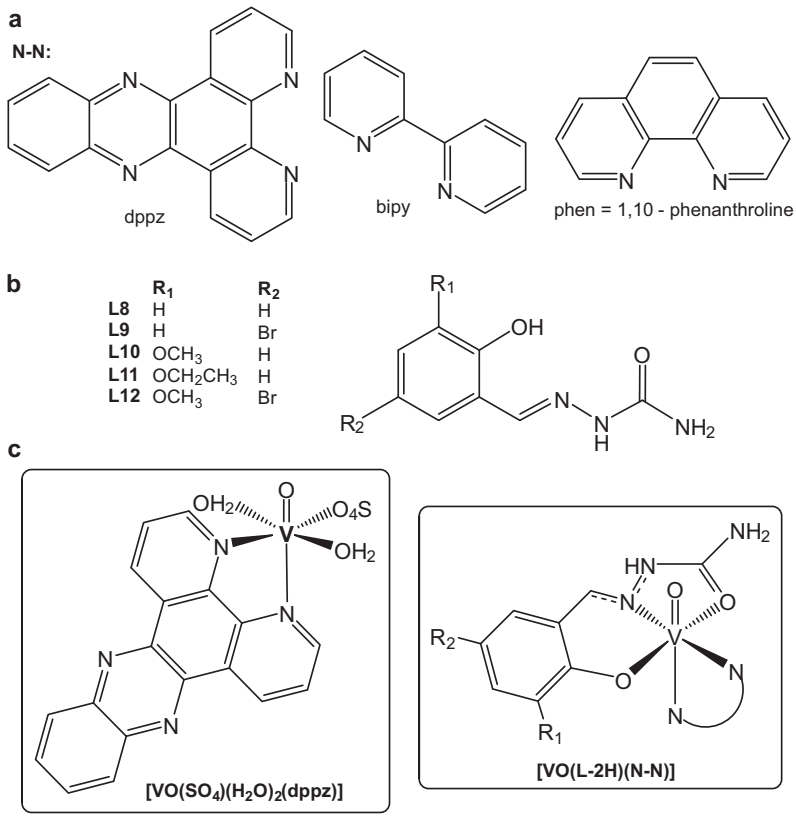

Fig. 6. Structure of selected DNA intercalating ligands (a), semicarbazone co-ligands (b) and the developed oxovanadium(IV) complexes (c) [94–96].

included a bidentate polypyridyl DNA intercalator (N–N) and a tridentate salycylaldehyde semicarbazone derivative (L) as co-ligand (Fig. 6). Previous work reported by the same group had shown $[V^{V}O_2(L\text{-}H)]$ complexes, where L = tridentate salycylaldehyde semicarbazone derivative, to have cytotoxic effects on kidney tumor cells (TK-10 cell line) and biological effects on osteoblasts in culture, promoting this series of semicarbazones to be further used as co-ligands [99,100]. All [VO(L-2H)(N–N)] oxovanadium(IV) complexes were active *in vitro* against the epimastigote form of *T. cruzi* (Dm28c strain) (Table 3). The relevance of the nature of the polypyridyl ligand was clearly stated when comparing the IC_{50} values of those complexes with the same semicarbazone derivative (**L8** or **L9**), resulting those with phen the most active ones followed by dppz complexes. In addition, complexes presenting the same polypyridyl ligand but a different semicarbazone showed similar IC_{50} values demonstrating a low incidence of the substituents on the semicarbazone aromatic ring on the anti-*T. cruzi* activity. All phen complexes showed a slightly higher *in vitro* activity than nifurtimox against the selected *T. cruzi* strain. Both dppz complexes showed IC_{50} values of the same order than nifurtimox. The semicarbazone ligands showed no inhibitory *in vitro* effect on *T. cruzi* epimastigotes even up to 100 μM concentration. Although phen and dppz showed growth inhibitory effects, bipy showed a high IC_{50} value of *ca.* 70 μM. Results indicated that coordination to vanadium to yield these mixed-ligand complexes was relevant to achieve the final anti-*T.cruzi* activity.

The hypothesized correlation between anti-trypanosomatid and anti-tumor activities was explored on six out of the ten compounds by evaluating them *in vitro* on the human acute promyelocytic leukemia cell line HL-60. Their cytotoxicity and ability to induce apoptosis were compared to those of cisplatin on the same cell line. The tested complexes showed IC_{50} values of the same order of magnitude as cisplatin (Table 3).

The interaction of $[V^{IV}O(SO_4)(H_2O)_2(dppz)]$ and the nine $[V^{IV}O(L\text{-}2H)(N\text{–}N)]$ complexes with DNA was demonstrated by using different techniques (plasmid DNA gel electrophoresis, plasmid DNA atomic force microscopy (AFM) and calf thymus DNA (CT-DNA) viscosity measurements). Results suggested that this biomolecule could be one of the potential targets either in the parasites or in tumor cells. AFM studies showed more intense effects on plasmid DNA for $[V^{IV}O(SO_4)(H_2O)_2(dppz)]$ than for free dppz. Additionally, the effects on DNA produced by this complex arose significantly more rapidly than those produced by the [VO(L-2H)(phen)] compounds [94,96]. Further work is proposed by the authors to get more potent and stable related oxovanadium(IV) compounds and to better identify the active species in solution.

3. Vanadium compounds as anti-leishmanial agents

Leishmaniasis involves a group of diseases produced by different protozoa of the genus *Leishmania*. There are three main distinct types of the disease: cutaneous, mucocutaneous and visceral leishmaniasis, the latter also known as kala azar. The parasite is mainly transmitted to humans through the bite of infected female hematophagous phlebotomine sandflies. The disease currently affects about 12 million people worldwide with 1.5–2 million new cases per year, including approximately half a million cases of the visceral type, which is nearly 100% fatal if untreated. Visceral leishmaniasis is caused by three different *Leishmania* species depending on the geographical area (*L. donovani*, *L. chagasi* and *L. infantum*). Approximately 350 million people live at risk of infection with *Leishmania* parasites. Leishmaniasis is endemic in 88 countries, mainly from Africa, Asia, and Latin America. Poverty and malnutrition are partially responsible for the high prevalence of visceral leishmaniasis in developing countries. Since it affects the immune system, in the last 20–30 years it has also become relevant in the south of Europe due to co-infection in patients

affected by HIV-AIDS [101–104]. As no vaccination is available, treatment of leishmaniasis is strictly based on chemotherapeutic drugs. First-line treatment has relied for almost 75 years on pentavalent antimonial drugs, sodium stibogluconate and meglumine antimoniate. These antimonials may cause severe side effects and development of resistance is now observed in several cases and geographical regions, emphasizing the urgent need for new treatments. The emergence of resistance has led to the use of alternative drugs, like pentamidine, amphotericin B and paromomycin. More recently, miltefosine, initially developed for cancer treatment, became the first oral drug for the treatment of visceral leishmaniasis [31,100,101]. Although these alternatives have proved to be effective, they show several drawbacks, such as high cost and low availability.

The reference drugs themselves, antimony compounds, are clear examples of well established anti-*leishmania* metal-based drugs. Furthermore, some iridium(I), rhodium(I), osmium(III) and platinum(II) compounds have also shown anti-*leishmania* activity [55–57,63,105–107]. More recently, gold(III), palladium(II) and rhenium(V) complexes have been tested against *L. major*, *L. mexicana*, *L. donovani* and *T. cruzi*, as potential inhibitors of parasite-specific cysteine proteases, some of them showing growth inhibitory effects on these parasites [32].

As vanadium compounds could inhibit *T. cruzi* growth by affecting essential enzymes and processes, they could also inhibit growth of other trypanosomatids (see Section 2). In particular, *Leishmania* parasites show phosphatases of high significance for their survival. For instance, sodium stibogluconate is a potent inhibitor of protein tyrosine phosphatases of the parasite [108,109]. Nevertheless, potentiality of vanadium compounds as anti-*leishmania* agents has been almost unexplored until very recently.

3.1. Peroxovanadium compounds

Since peroxovanadium compounds are potent inhibitors of protein tyrosine phosphatases and inducers of anti-leishmania effectors like ROS and NO, some peroxo and diperoxovanadate compounds have been studied *in vitro* and also *in vivo* as anti-leishmania agents [110,111]. Treatment of infected mice with bis-peroxovanadium-1,10-phenanthroline or bis-peroxovanadium-picolinate completely controlled progression of leishmaniasis in an NO-dependent manner. After injection, compounds rapidly triggered the expression of inducible NO synthase in liver of mice infected with *L. major*. *In vivo* functional and immunological events associated with this peroxovanadium protective process have been identified [111].

More recently, three dinuclear triperoxovanadate complexes, two mononuclear diperoxovanadate complexes with aminoacids or dipeptides as ancillary ligands and bis-peroxovanadate have been tested for their ability to kill *Leishmania* parasites *in vitro*, being $K[VO(O_2)_2(H_2O)]$ the most potent one [112]. Combined administration of this last complex with sub-optimal doses of sodium antimony gluconate on BALB/c mice experimentally infected with antimony resistant (SbR) *L. donovani* are highly effective in reducing the organ parasite burden. The effect was mainly associated with the generation of ROS and nitrogen species that could kill intracellular parasites [112].

3.2. Vanadium compounds of bioactive ligands

The unique reference of vanadium complexation to a compound bearing anti-leishmania activity involves the oxovanadium(IV) core and the water soluble galactomannan (GMPOLY), isolated from the southern Brazil lichen *Ramalina celastri* [113]. Complexation highly increased the leishmanicidal effect of galactomannan on amastigotes of *L. amazonensis* infecting peritoneal macrophages. This effect of GMPOLY on amastigotes, the only proliferative form of the parasite in the host, could be attributed to the activation of the nitric oxide pathway. Nitric oxide is secreted by macrophages in response to IFN-γ (interferon γ) stimulation and it is regulated by tyrosine phosphatase events. Since the effect detected for GMPOLY oxovanadium(IV) complex occurred at concentrations where GMPOLY was non active, authors suggested the involvement of the oxovanadium(IV) ion in the anti-parasite action.

3.3. Vanadium compounds against multiple trypanosomatid parasites

It has been proposed that the development of broad spectrum drugs acting against multiple protozoan parasites could offer an innovative approach for anti-parasite drug discovery that could lead to more accesible drugs for the treatment of neglected diseases affecting the poorest and least developed tropical regions of the world [77]. This approach involves the recognition of chemical scaffolds that could be active against multiple parasites by acting towards common or similar targets present in the different parasites. Moreover, some enzymes and metabolic or catalytic pathways are common to different pathogenic parasites. In particular, in 2005 the so called *Tritryp* genome, involving the genomes of *T. cruzi*, *T. brucei* and *L. major*, was published [114]. The comparison of the three genomes showed high similarities between these trypanosomatid parasites, *i.e.* each genome contains 8300–12,000 protein encoding genes of which almost 6500 are common to the three species. It is then reasonable to assume that broad spectrum clinically useful anti-trypanosomatid drugs could be developed to affect similar targets in the different parasites. Thus considering this background, Gambino et al. tested some metal compounds showing anti-*T. cruzi* activity on *Leishmania* parasites [74,95]. Since it has been demonstrated that the NADH-fumarate reductase enzyme could also be a suitable target for anti-leishmanial drugs [115], bis(pyridine-2-thiol *N*-oxide) oxovanadium(IV) complex, $[VO(mpo\text{-}H)_2]$, and the pyridine-2-thiol *N*-oxide gold(I) complex $[Au_2(mpo\text{-}H)_2(PPh_3)_2]$ were evaluated on *L.(L) mexicana* and *L.(V.) braziliensis* promastigotes. In particular, improved *in vitro* activity of $[VO(mpo\text{-}H)_2]$ was observed compared to the pyridine-2-thiol *N*-oxide sodium salt (unpublished results).

As discussed in Section 2.2, some platinum, copper and silver DNA intercalating compounds have shown interesting anti-leishmania activities [98]. The five oxovanadium(IV) complexes, $[V^{IV}O(L\text{-}2H)(phen)]$, discussed there were selected to be now evaluated *in vitro* against promastigotes and intracellular amastigotes of *L. panamensis* and *L. chagasi*, while selectivity towards the parasite was determined by testing toxicity on mammalian cells (human acute monocytic leukemia cell line THP-1 cells) [95]. Unexpectedly, not all the oxovanadium(IV) complexes turned out active against the tested *Leishmania* species. Results pointed out mixed-ligand compounds [VO(**L8**-2H)(phen)] and [VO(**L10**-2H)(phen)] (Fig. 6) as promising anti-leishmania agents showing low IC_{50} values and high parasite/mammalian cells selectivities (Table 4).

Table 4
In vitro activity on *L. panamensis* promastigotes and intracellular amastigotes of selected $[V^{IV}O(L\text{-}2H)(phen)]$ complexes and their selectivity indexes.

Compound	IC_{50}[a] promastigotes	SI[b]	IC_{50}[a] amastigotes	SI[b]	Reference
$[V^{IV}O(\mathbf{L8}\text{-}2H)(phen)]$	2.74	68.7	19.52	9.66	[95]
$[V^{IV}O(\mathbf{L10}\text{-}2H)(phen)]$	2.75	32.0	20.75	4.25	[95]

[a] 50% inhibitory concentration in μM.
[b] SI: selectivity index, 50% cytotoxic concentration CC_{50} of mammalian THP-1 cells/IC_{50} of parasites.

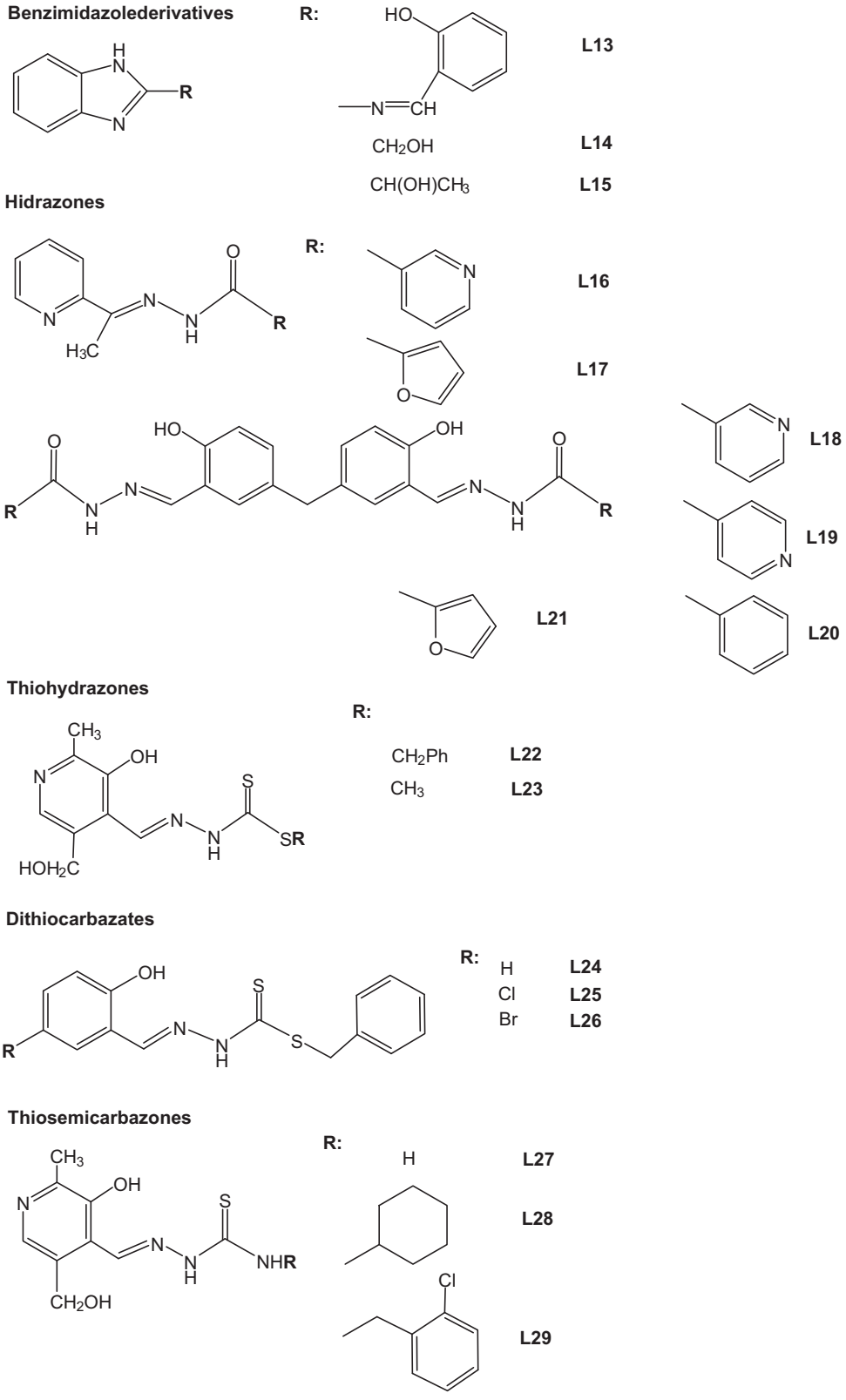

Fig. 7. Structure of the ligands coordinated to vanadium in the compounds tested as anti-*Entamoeba histolytica* agents [120–126].

4. Vanadium compounds as anti-amoebic agents

Amoebiasis is the second leading cause of human death by a parasitic disease worldwide, accounting for about 110,000 deaths annually. It remains a major threat to public health in most countries of the world and it is considered a re-emergent disease in many areas. Although distributed throughout the world, it is a substantial burden in almost every country where the barriers between human feces, food and water are inadequate. Amoebiasis occurs mainly in the tropical and subtropical regions of Africa, Central America,

South America, India and Southeast Asia affecting more than 10% of the world's population. It is mainly an infection of the human gastrointestinal tract produced by the potent pathogenic protozoa *Entamoeba histolytica* and transmitted by ingestion of contaminated food or water. Infections occurring exclusively in the bowel lumen are asymptomatic. Clinical amoebiasis takes place when the parasite penetrates the colon wall, causing ulcers that lead to amoebic dysentery. The protozoa can also breach the mucosal barrier and cause amoebic liver abscesses. Untreated infection may lead to severe complications including hepatic amoebiasis and intestinal tissue destruction. The many anti-amoebic drugs used in clinical practice act either as tissue or as luminal amoebicides. Luminal amoebicides, like iodoquinol, paromomycin and diloxanide furoate, are poorly absorbed and therefore only active in the intestinal lumen. Among tissue amoebicides 5-nitroimidazoles, like metronidazole, tinidazole and ornidazole, are current drugs used for the treatment of this disease, since they remain cheap and effective. Nevertheless, they show significant side effects such as gastrointestinal and neurological complications and the emergence of resistance. In addition, metronidazole are mutagenic in bacteria and carcinogenic in rodents [29,116–119].

Many attempts to develop metal complexes that could lead to new drugs against *E. histolytica* have been reported and reviewed [29,119]. Among them, Pd(II), Pt(II), Cu(II) and Ru(II) complexes of thiosemicarbazones, Schiff bases of S-alkyldithiocarbazates, and pyrazolines, and Mo(VI) and W(VI) complexes of 2-(salicylideneimine) benzimidazole and benzimidazole derivatives have shown increased *in vitro* activity against *E. histolytica* compared to the free ligands. In addition, they have presented growth inhibitory effects at lower doses than the drug metronidazole. Moreover, Pd, Pt, Cu, Au, and Ru metronidazole (mnz) complexes displayed 4- to 18-fold increase *in vitro* activity against *E. histolytica* compared to the free drug. In addition, *trans*-[$PdCl_2(mnz)_2$], *trans*-[$PtCl_2(mnz)_2$] and *trans*-[$Cu_2(OAc)_4(mnz)_2$], are potent inhibitors of *E. histolytica in vivo* when administered orally to infected male golden hamsters bearing an experimental amoebic hepatic abscess [119]. These antecedents show that the inorganic medicinal chemistry approach could lead to interesting bioactive metal-based compounds in this field.

Many previously identified parasite-specific drug targets could be suitable for metal compounds, and particularly for vanadium compounds, *i.e.* calcium pathways and enzymes, like cysteine proteases, trypanothione synthase, among others [119]. Bharti et al. published the first work stating the improvement of amoebicidal activity of three benzimidazole derivatives upon complexation to vanadium, and leading to a dioxo- and two oxoperoxovanadium(V) active compounds (Table 5 and Fig. 7) [120]. After this initial work, Maurya et al. performed a significant research in this area [120–127]. Several mononuclear and binuclear dioxovanadium(V) species as well as binuclear μ-bis(oxo)bis{oxovanadium(V)} complexes, [$(VOL)_2(\mu\text{-}O)_2$], and μ-oxobis(oxovanadium(V)) complexes, [$(VOL)_2(\mu\text{-}O)$], have been developed. ONN, ONO and ONS ligands belonging to pharmacologically important organic scaffolds were used, namely benzimidazole derivatives, hydrazones, thiohydrazones, dithiocarbazates and thiosemicarbazones (Fig. 7). IC_{50} values on *E. histolytica* (HM1/1MSS strain) of these complexes are summarized in Table 5 together with IC_{50} values of the free ligands and the reference drug metronidazole. All of them presented *in vitro* activities in the micromolar range. Almost all vanadium complexes displayed enhanced activity and many of them showed significant improvement in their anti-amoebic activity as compared to their respective ligands. Even if all tested ligands were less active than metronidazole, some of their vanadium compounds showed higher activity than it. In particular, some recently developed binuclear **L18**–**L21** vanadium species (Fig. 7) displayed *in vitro* activities 3- to 4-fold higher than metronidazole [122,123]. In some cases complexation has not only increased the anti-amoebic activity of the parent ligand but it has also modified it from amoebostatic to amoebicidal. As commonly observed in medicinal chemistry research, the presence of sulfur functionality, like in dithiocarbazates and thiosemicarbazones, led to improved activities not only for the free ligands but also for their vanadium complexes [29,128]. Maurya et al. further characterized the biological behavior of the vanadium(V) bioactive compounds by testing their cytotoxicity on mammalian cells [122,123]. Deeper insight into the mechanism of action and the activity enhancement upon vanadium coordination is yet still missing. Authors suggested that vanadium complexation could directly or indirectly favor permeation of the compounds through the lipid layer of the cell membrane [122,123].

Table 5
In vitro activity on *E. histolytica* (HM1/1MSS strain) of vanadium complexes. Results for the free ligands and the reference drug metronidazole (mnz) are included for comparison (see structures of the ligands in Fig. 7).

Ligand	IC_{50}[a] (μM)	Vanadium compound	IC_{50}[a] (μM)	Reference
L13	9.20	$K[V^VO_2$ (**L13**)$_2]$	2.35	[120]
L14	9.59	$K[V^VO(O_2)$(**L14**)$_2]$	5.14	[120]
L15	10.12	$K[V^VO(O_2)$(**L15**)$_2]$	9.60	[120]
L16	9.63	$[(V^VO$**L16**$)_2(\mu\text{-}O)_2]$	1.68	[121]
L17	8.68	$[(V^VO$**L17**$)_2(\mu\text{-}O)_2]$	0.45	[121]
L18	8.97	$K_2[(V^VO_2)_2$(**L18**$)]\cdot 2H_2O$	0.47	[122]
		$Cs_2[(V^VO_2)_2$(**L18**$)]\cdot 2H_2O$	4.34	
L19	7.61	$Cs_2[(V^VO_2)_2$(**L19**$)]\cdot 2H_2O$	0.32	[122]
L20	9.08	$K_2[(V^VO_2)_2$(**L20**$)]\cdot 2H_2O$	2.21	[123]
		$Cs_2[(V^VO_2)_2$(**L20**$)]\cdot 2H_2O$	0.54	
L21	7.97	$K_2[(V^VO_2)_2$(**L21**$)]\cdot 2H_2O$	2.32	[123]
		$Cs_2[(V^VO_2)_2$(**L21**$)]\cdot 2H_2O$	0.36	
L22	9.45	$[V^VO_2$(**L22**$)]$	1.64	[124]
		$[\{V^VO$(**L22**$)\}_2(\mu\text{-}O)_2]$	1.25	
L23	11.05	$[VO_2$(**L23**$)]$	2.08	[124]
		$[\{V^VO$(**L23**$)\}_2(\mu\text{-}O)_2]$	1.67	
L24	5.19	$[K(H_2O)][V^VO_2$(**L24**$)]$	2.67	[125]
L25	3.57	$[K(H_2O)_2][V^VO_2$(**L25**$)]$	2.23	[125]
L26	4.19	$[K(H_2O)_2][V^VO_2$(**L26**$)]$	1.35	[125]
L27	10.4	$[V^VO_2$(**L27**$)]$	4.1	[126]
		$[\{V^VO$(**L27**$)\}_2(\mu\text{-}O)]$	1.9	
L28	4.6	$[V^VO_2$(**L28**$)]$	0.8	[126]
		$[\{V^VO$(**L28**$)\}_2(\mu\text{-}O)]$	0.5	
L29	5.2	$[V^VO_2$(**L29**$)]$	1.1	[126]
		$[\{V^VO$(**L29**$)\}_2(\mu\text{-}O)]$	0.7	
mnz	1.81–2.10	–	–	[120–126]

[a] IC_{50}, 50% inhibitory concentration; mnz, metronidazole.

5. Concluding remarks

Novel therapeutic tools for the treatment of neglected parasitic diseases are urgently needed. Among other current strategies, the inorganic medicinal chemistry approach offers the wide therapeutic potentialities of metal-based coordination compounds and bioorganometallic compounds that could affect specific parasite targets leading to parasite death or growth inhibition. Many metal-based compounds have been extensively studied as potential anti-parasite drugs, but the potentialities of the vanadium complexes in this area have been only poorly explored. This review highlights the investigation performed by bioinorganic chemists proving that vanadium compounds could also have suitable chemical and biological properties deserving further research in the pursuing of novel vanadium-based anti-parasite agents. In addition, the potentiality of vanadium compounds in the search of broad spectrum drugs acting against multiple protozoan parasites has been envisaged. This innovative approach, based on progress in knowledge of parasites biology and genomic discoveries of common enzymatic targets and metabolic pathways in related parasites, could lead to more accesible drugs for the treatment of these neglected diseases. Further research through this strategy is needed to increase the arsenal of vanadium compounds bear-

ing anti-parasite activity, aiming to identify novel vanadium lead species by detailed structure–activity studies.

Furthermore, studies of speciation under biologically relevant conditions as well as studies of interaction with biological ligands and biomolecules and of identification of cellular targets should be performed for the resulting vanadium compounds to get a deeper insight into the molecular basis of their actual mechanism of action. Altogether, this information will result of huge relevance for the designing of novel vanadium therapeutic agents. Hopefully, this review has highlighted unexplored opportunities in this research field for upcoming rational vanadium-based drug discovery.

Acknowledgements

Author would like to thank RIIDFCM (209RT0380) CYTED network and European Commission through Erasmus Mundus EMQAL for supporting collaborative research on development of anti-parasite vanadium-based compounds and the organizers of the 7th International Symposium on the Chemistry and Biological Chemistry of Vanadium for financial support.

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