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Metal-based compounds and Chagas disease treatment: current knowledge and therapeutic perspectives

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Chagas disease (CD) is a parasitic infection caused by the protozoan *Trypanosoma cruzi*. CD treatment is restricted to benznidazole (BZN) and nifurtimox, with the former being the treatment of choice in many countries. Unfortunately, BZN demonstrates limited efficacy in the chronic phase of CD and leads to several side effects that often result in patients discontinuing the treatment. The emergence of BZN-resistant *T. cruzi* strains is also a major concern. Metal compounds have gained importance due to their unique physicochemical properties. Therefore, we conducted a 5-year systematic review, analysing 22 articles with the aim of compiling the results of the anti-trypanocidal effect of 113 compounds. Our results show that the majority of the compounds centre on Cu (17%), followed by Zn (12%) and Sn (9%). Most exhibit an anti-*T. cruzi* effect across all life-cycle forms, with epimastigotes generally being more resistant than trypomastigotes. Only 43 compounds (38%) had their mode of action elucidated, which included disruption of mitochondrial membrane potential, an increase in reactive oxygen species generation, and inhibition of ergosterol synthesis, cruzain, trypanothione reductase, and fumarate reductase. Despite our inability to establish the most effective metal compound due to a lack of standardisation in the methods used, this review seeks to outline a path for the design of new metallodrugs, a class of compounds that warrants further investigation for its promising anti-*T. cruzi* activity.

KEYWORDS

 Chagas disease, metallodrugs, review, treatment, *Trypanosoma cruzi*

Introduction

An ideal treatment for a disease should be specific to the etiological agent, resulting in minimal side effects for the host. Unfortunately, this is not true for Chagas disease (CD), a crucial public health issue in Latin America, which is also found in non-endemic countries (DNDi, 2025). Benznidazole (BZN), the first-line therapy for CD, is effective in the acute phase of infection (Kratz, 2019) but demonstrates limited efficacy in the chronic stage. Its use can lead to side effects that compromise patient adherence to treatment. Although its mechanism of action is not fully understood, it appears to involve the covalent binding of BZN-derived reduced metabolites to parasite macromolecules (Trochine et al., 2014), with BZN lacking specificity for a parasite-exclusive target. Therefore, the search for a specific and less toxic compound to treat CD patients is urgently needed.

Metal-based compounds are promising for CD treatment due to their distinct physical and chemical properties, which enable their use in diverse biological systems. Examples include cisplatin, a broad-spectrum anticancer agent, and auranofin, a gold(I) complex clinically utilised for treating rheumatoid arthritis (Boros et al., 2020). The coordination of transition metals with ligands further enhances these properties (Zhang and Guo, 2023).

In this study, we conducted a 5-year systematic review of published research to discuss different metal-based compounds with promising anti-*Trypanosoma cruzi* activity, focusing on their structural features and mechanisms of action.

Methods

The methodology involved a systematic literature search conducted within the PubMed database. The temporal filter included publications between September 2020 and September 2025 (inclusive). We utilised six distinct search strategies for this process, considering only experimental articles and excluding review articles. (1) Search terms: “metallo drugs” AND “CD”; initial retrieval (IR): eight articles; exclusion: three due to temporal filter; and title/abstract/review screening (T/A/R): three excluded and two selected. (2) Search terms: “metallic compounds” AND “CD”; IR: 123 articles; exclusion: 79 due to temporal filter; and T/A/R: 21 excluded and 23 selected. (3) Search terms: “metallic complexes” AND “CD”; IR: 130 articles; exclusion: 88 due to temporal filter; and T/A/R: 21 excluded and 21 selected. (4) Search terms: “metallo drugs” AND “*Trypanosoma cruzi*”; IR: seven articles; exclusion: two due to temporal filter; and T/A/R: three excluded and two selected. (5) Search terms: “metallic compounds” AND “*Trypanosoma cruzi*”; IR: 151 articles; exclusion: 110 due to temporal filter; and T/A/R: 18 excluded and 23 selected. (6) Search terms: “metallic complexes” AND “*Trypanosoma cruzi*”; IR: 175 articles; exclusion: 138 due to temporal filter; and T/A/R: 15 excluded and 22 selected. A total of 22 articles were selected for comprehensive full-text review and subsequent data analysis (Page et al., 2021) (Supplementary Figure S1).

Results and discussion

A total of 113 compounds with potential activity against *T. cruzi* have been reported in the last 5 years (Supplementary Table S1; Supplementary Figure S2). Among the 16 metals investigated, transition elements from the first and second series predominate. Sn stands as the sole post-transition exception, while third-row transition metals and lanthanides, the latter primarily explored for theranostic purposes, are less frequently reported. The high prevalence of copper-based compounds may be attributed to the metal’s endogenous trace status in humans, its low cost and abundance, and its ability to exist in both reduced Cu(I) and oxidised Cu(II) forms, which facilitates oxidative cell injury through a free-radical-mediated pathway (Iakovidis et al., 2011).

A broad spectrum of ligands was utilised, with some explored across multiple metal centres to evaluate how the nature of the metal influences biological activity. One strategy was based on the metal’s effects, with ligands modulating the complex for targeting, drug-like

properties, and stability. Examples include the class of N-heterocyclic carbenes (NHCs) and the Schiff base (SB) derivatives of BZN (De França et al., 2024).

Another strategy in metallo drug design is the coordination of an active ligand to the metal, seeking synergistic/complementary effects. For example, fluconazole (FLZ) and clotrimazole (CTZ) inhibit *T. cruzi* sterol 14-demethylase, disrupting ergosterol synthesis, which is critical for parasite viability (Bukner and Urbina, 2012). Collectively, these ligands exemplify the sophisticated design principles employed to optimise metal-based therapeutics by integrating chemical stability, biological targeting, and physicochemical balance (Abbehausen et al., 2024).

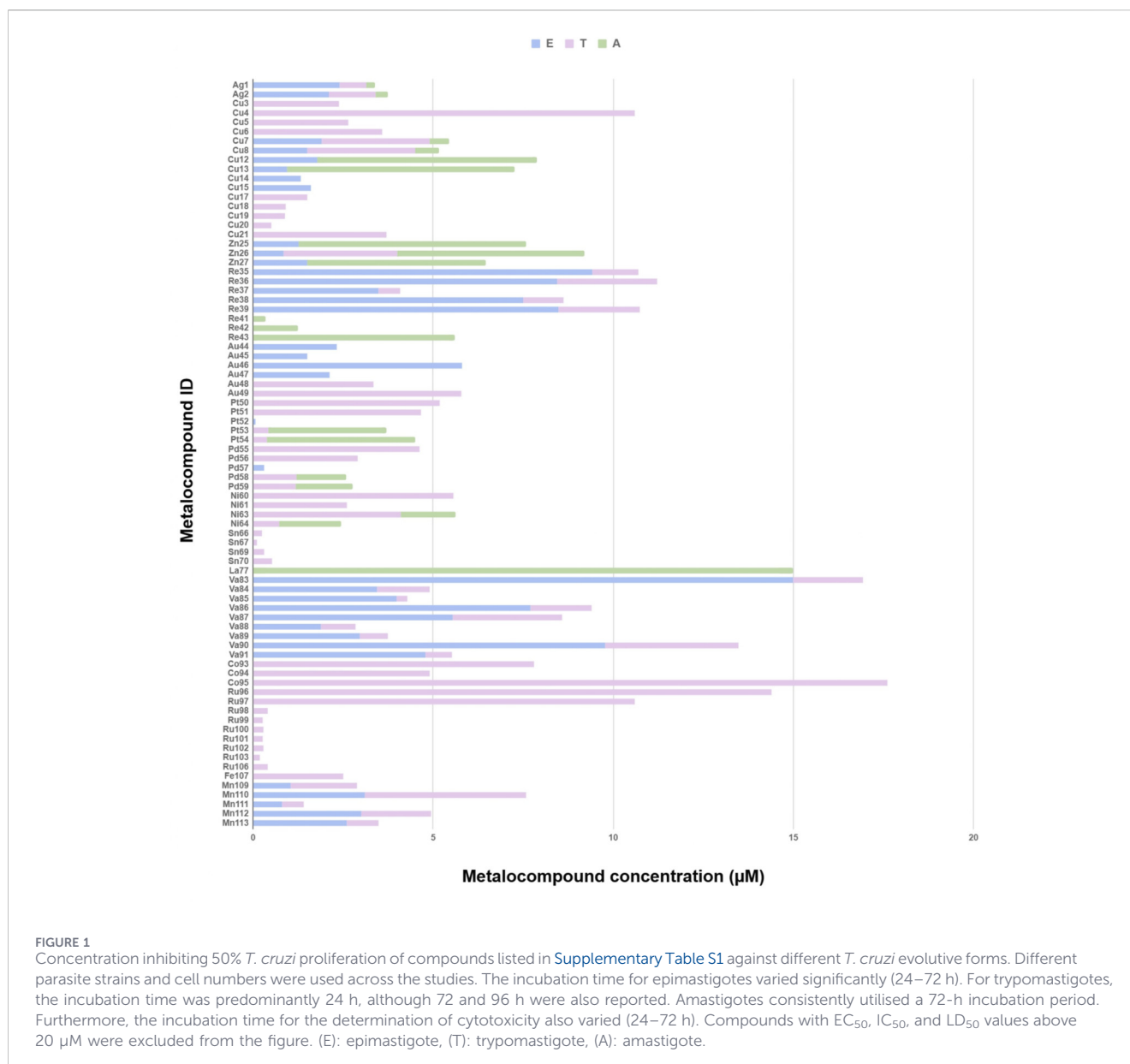
No uniformity was observed in the parameters used for cell viability assays, making it difficult to determine the most effective trypanocidal compound (Supplementary Table S1). Compound testing showed the following distribution: 53% against trypomastigotes, 28% against epimastigotes, and only 19% against the clinically relevant amastigote form. Furthermore, those compounds tested against multiple stages generally showed increased sensitivity in trypomastigotes compared to epimastigotes (Figure 1). We noted the frequent misuse of the terms IC₅₀, EC₅₀, CC₅₀, LC₅₀, and LD₅₀ values. The appropriate definitions for these metrics are discussed in detail by Du and Li (2025).

The *T. cruzi* population is highly genetically divergent, being classified into six discrete typing units (DTUs: TcI–TcVI) and Tcbat (Zingales and Macedo, 2023). Three DTUs were employed in the studies: TcI (47%), TcII (23%), and TcVI (31%). TcI is the most prevalent in Latin American countries, followed by TcII and TcVI (Zingales and Macedo, 2023). DTUs can induce distinct host immune responses that affect disease progression and may differ in parasitemia and host tissue tropism (Silvestrini et al., 2024). The SI, a parameter used to determine therapeutic potential, was erroneously calculated using the epimastigote form, which is the parasite stage found solely within the insect vector. We employed 14 mammalian cell lines in these assays, among which the VERO cell line predominated (41%). In some studies, inconsistent cell and parasite incubation times may mislead cytotoxicity conclusions. Based on parameters previously established (Chatelain, 2015), SIs were classified as low ≤10, good >10–50, and great >50. For the compounds reported herein, 36% had a good SI and 28% a great SI (Supplementary Table S1).

Silver

Ag1 has silver coordinated to two molecules of BZN and, in Ag2, also to a phosphine (PR₃) (De Souza et al., 2023). When BZN was associated with silver (Ag1), SI in amastigotes was increased approximately 18 times compared to BZN alone, but the addition of the PR₃ ligand (Ag2) did not enhance its biological activity (Supplementary Table S1). Binding with azoles boosts antimicrobial effects, while PR₃ ligands enhance selectivity and reduce toxicity by modifying lipophilicity (Medici et al., 2019).

Ag1 was capable of inducing a decrease in the mitochondrial membrane potential of epimastigotes ($\Delta\Psi_m$), which is essential for ATP production (Fidalgo and Gille, 2011), and caused cell division problems in amastigotes. Autophagy was also suggested to occur in both evolutionary forms (Supplementary Table S1).



Copper

Cu(II) forms stable complexes with nitrogen ligands such as phenanthroline (Phen), especially using bi- and tridentate ligands to reduce lability in biological environments. In contrast, Cu(I), due to its large size/low charge, prefers phosphorus- and sulphur-based ligands and is easily oxidised to Cu(II) under physiological conditions (Latorre et al., 2019).

Cu(I) was used with different ligands from PR₃ and semi-carbazone (s-CBZ) classes Cu3–Cu6. Cu3, Cu5, and Cu6 were the most potent Cu(I) complexes, showing the lowest IC₅₀ value against tryptomastigotes and good SIs (Machado et al., 2023). Compounds Cu7 and Cu8 are analogues of Ag1 and Ag2, respectively (De Souza et al., 2023). Interestingly, Ag1 and Ag2 demonstrated slightly higher activity in amastigotes and tryptomastigotes than Cu7 and Cu8. Cu9 and Cu10 had similar activity in tryptomastigotes, while in amastigotes, Cu9 had a lower IC₅₀ value than Cu10 (Silva-Oliveira et al., 2023). Classes

Cu11–Cu13 (AD ligand) were more active in epimastigotes than in amastigotes. Complexes combining Phen and s-CBZ (Cu17–Cu20), as well as Cu21 containing only s-CBZ ligand, exhibited low SI, independent of the mammalian cell lines tested (Ortega-Campos et al., 2025) (Supplementary Table S1). The possible mechanism of action of Cu14 and Cu15 is the inhibition of farnesyl diphosphate synthase (TcFPPS) (Romero-Solano et al., 2025). Cu20 promoted a decrease in ΔΨ_m, an increase in reactive oxygen species (ROS) production, and an induction of necrosis (Supplementary Table S1).

Throughout its life cycle, *T. cruzi* is exposed to multiple sources of ROS and other free radicals (Machado-Silva et al., 2016). At moderate levels, ROS can act as signalling molecules involved in parasite differentiation and host–parasite interactions; however, under oxidative stress, they may interact with essential biomolecules, leading to parasite death (Maldonado et al., 2020). These processes could lead to a collapse of the ΔΨ_m and the activation of apoptosis-like processes (Supplementary Table S1). TcFPPS is responsible for

catalysing the condensation reaction to form farnesyl diphosphate, which in *T. cruzi* is essential for the biosynthesis of sterols and ubiquinones (Docampo and Moreno, 2017).

Zinc

Zn(II) complexes exhibit marked lability and readily change geometry, participating in diverse cellular roles as the second most abundant endogenous trace element in the human body (Costa et al., 2023).

Low SIs were observed for most complexes (65%) under the different experimental conditions employed (Méndez-Arriaga et al., 2022). Zn-Pyr complexes (Zn22–Zn24) were highly cytotoxic. Zn-AD complexes (Zn25–Zn27) exhibited the highest SIs (De Azevedo-França et al., 2022). This AD is FLZ, a triazole compound with a good half-life and bioavailability; it is commonly used as an anti-fungal (Lin et al., 2024). In *T. cruzi*, autophagic processes induced by the FLZ-coordinated complexes were observed in epimastigotes. The Zn32 complex containing Phen and s-CBZ ligands promoted a decrease in $\Delta\Psi_m$ and induction of necrosis in trypomastigotes (Ortega-Campos et al., 2025). It had a similar mechanism of action as Cu20, although with lower SI than Cu20. Zn28 (Martín-Montes et al., 2023), Zn33, and Zn34 had IC_{50} above 46 μM ; Zn29–Zn31 had low SIs (Supplementary Table S1).

Rhenium

Rhenium, most commonly found in the +1 state, forms stable complexes with chelating ligands. Non-radioactive Re(I) tricarbonyl complexes show strong antimicrobial activity (Towett et al., 2025).

Re35-Re43 had an AD in their structure, alone or combined with Phen or Bipy. Great SIs were observed for Re41 and Re42, coordinated with megazol and its derivatives (Supplementary Table S1). Megazol is a nitroimidazole similar to BZN that displays activity against both *T. cruzi* and *Trypanosoma brucei*, the etiological agent of African trypanosomiasis (De Carvalho et al., 2014). The Re(I)-megazol complex with the best SI (Re41) appears to interact with the *T. cruzi* Old Yellow Enzyme, involved in the prostaglandin metabolism (Supplementary Table S1). Although prostaglandins are important mediators of physiological and pathological responses, their precise roles in *T. cruzi* remain poorly understood (Gonçalves et al., 2024). Re37 showed inhibition of sterol pathways, which are essential for the biosynthesis of ergosterol in *T. cruzi* (Soba et al., 2023; Dumoulin et al., 2022) (Supplementary Table S1).

Gold

Gold is a chemically inert precious metal, mainly in the +1 and +3 oxidation states. Au(I) is stabilised in complexes with phosphines and carbenes, and Au(III) complexes are often stabilised by cyclometalated ligands (Castro et al., 2025).

The classes of ligands explored were combinations of NHC and Pyr for Au(I) (Au44–Au47) (Oliveira et al., 2024) and PR₃ and dithiolane (DTC) for Au(III) complexes (Au48 and Au49) (Hachem et al., 2025). Although Au48 and Au49 displayed low SIs (Supplementary Table S1), gold compounds still exhibit promising biological potential. This is largely attributed to the structural diversity of their ligands and the varied coordination

environments afforded by Au(I)/Au(III), giving them multi-target properties that enable interactions with DNA and thiol-containing biomolecules, such as trypanosomatid trypanothione reductase (TR) (Navarro et al., 2021). TR is a unique key enzyme in the parasite's defence against ROS; it is essential for maintaining redox homeostasis as it feeds into multiple downstream detoxification pathways. It is known to be a target for metal-based compounds, such as Ag(I) and Au(I) (Battista et al., 2020).

Platinum

Platinum is known for its inertness and mainly exists in the +2 and +4 oxidation states, forming stable compounds, especially in coordination complexes with ligands such as chloride and ammonia (Navarro et al., 2021).

The best SIs in trypomastigotes were observed for Pt53 and Pt54, complexes coordinated with PR₃ and a combination of PR₃ and thiophene (TS), respectively (De Oliveira et al., 2022). The Pt50 complex coordinated with PR₃ and DTC (radical Et) had a lower SI in trypomastigotes than Pt51, which was also coordinated with these ligands but with *t*Bu as the radical (Hachem et al., 2025). As a mechanism of action, the compound Pt52 inhibits ergosterol synthesis, like Re37 (Mosquillo et al., 2023).

Palladium

Palladium resembles platinum chemically and is often used in similar compounds. Pd(II) is more reactive than Pt(II), with kinetics 10⁵ times faster, requiring chelating ligands for stabilisation (Czarnomysy et al., 2021).

For complexes coordinated with PR₃-DTC (Pd55 and Pd56), better SIs are in trypomastigotes than the Pt(II) analogues (Pt50 and Pt51) and Au analogues (Au48 and Au49) (Hachem et al., 2025). The same was also true for the PR₃-TS compounds, where Pd59 had a higher SI in amastigotes than Pt54. Pd58 had a similar SI to Pd59, which contained, in addition to PR₃, TS as a ligand (De Oliveira et al., 2022). Pd57, an analogue of Pt52, also inhibited the synthesis of ergosterol pathways (Mosquillo et al., 2023) (Supplementary Table S1).

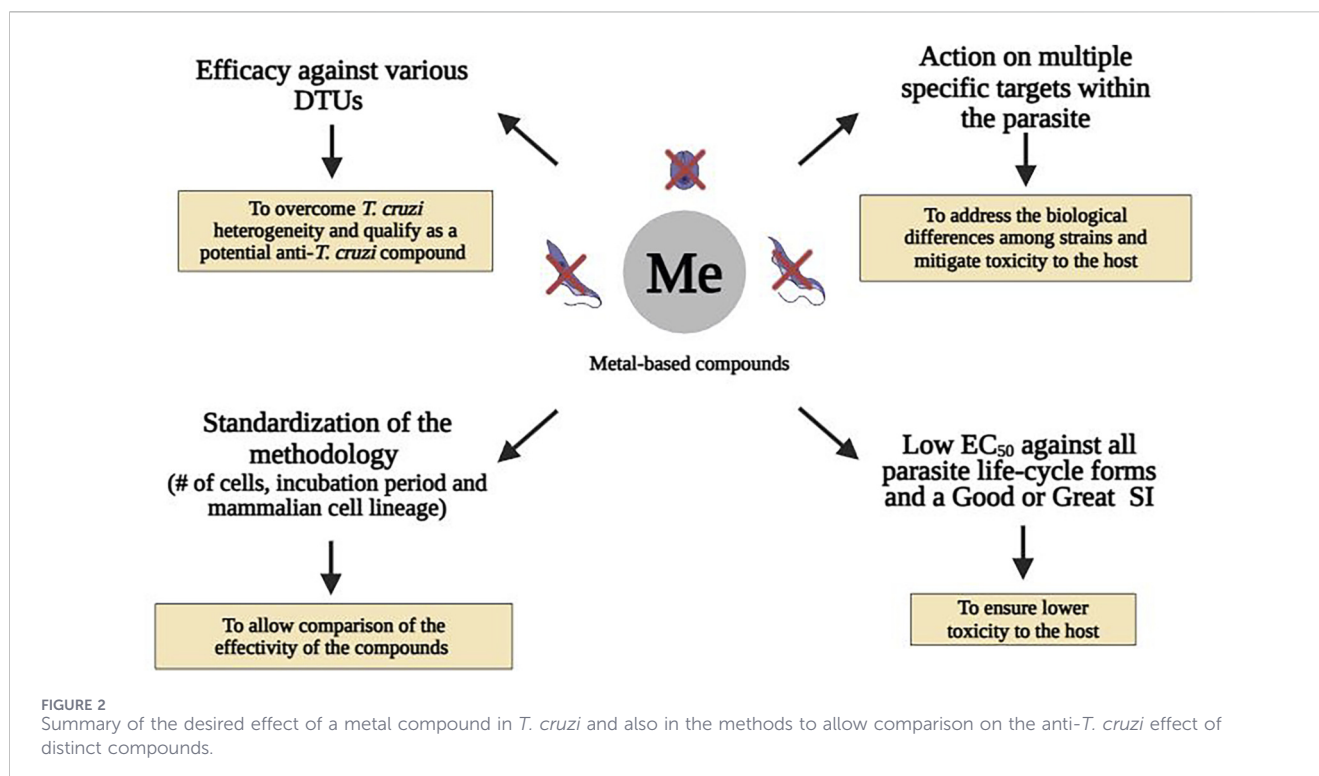
Nickel

Nickel mainly occurs as Ni(II), forming complexes with a variety of ligands and serving as a cofactor in numerous enzymes (Genchi et al., 2020).

Ni60 (PR₃-DTC(Et)) had lower SI against trypomastigotes than Ni61 (PR₃-DTC(*t*Bu)) (Hachem et al., 2025). Ni64 (coordinated with PR₃-TS) yielded a higher SI against trypomastigotes than Ni63 (PR₃ only) (Supplementary Table S1) (De Oliveira et al., 2022). Ni62, having Pyr as a ligand, had a high IC_{50} for epimastigotes (Martín-Montes et al., 2023). As shown by Prabhakara and Naik (2008), Ni(II)-TS compounds are capable of binding to the DNA helix, promoting its cleavage through oxidative mechanisms.

Tin

Tin is mainly found as Sn(II) and Sn(IV). Sn(IV) forms complexes with organic and inorganic ligands, showing covalent character (Martinez-Morata et al., 2023).



Only Sn66 among the 10 organotin(IV) compounds, all coordinated with carboxylic acid ligands, had a good SI, while Sn69 displayed a great SI to trypomastigotes (Supplementary Table S1). While the specific trypanocidal mechanism was not investigated for Sn66, proteomic analysis in monocytes infected with *Leishmania donovani* showed a reduction in the expression of the Rab7 enzyme (Hayat et al., 2022). Rab7, a conserved GTPase also present in *T. cruzi*, plays a critical role in vesicle trafficking (Araripe et al., 2004), which could be related to host cell invasion and parasite differentiation (Hayat et al., 2022).

Lanthanum and cerium

La and Ce are both rare-earth metals, with La existing mainly in the 3+ oxidation state and Ce in the +3 and +4 oxidation states. While La(III) needed bulky or chelating ligands to stabilise, Ce(III) readily cycles between the Ce³⁺/Ce⁴⁺ oxidation states, resulting in enzyme-mimetic activities (Boggiano et al., 2024; Bai et al., 2024).

The La75–La78 and Ce79–Ce82 series were coordinated with SB-AD ligands, all showing low SI in amastigotes (Aragón-Muriel et al., 2021). They appear to inhibit cruzain, a cysteine protease involved in *T. cruzi* growth, differentiation, and defence mechanisms (Supplementary Table S1). Cruzain and the sterol pathway enzymes have been identified as targets for the development of new chemotherapeutic agents against CD (Prates et al., 2024).

Vanadium

Vanadium is a biologically relevant transition metal with common oxidation states of +3, +4, and +5. Oxidovanadium(V)

with tridentate SB ligands exhibits diverse therapeutic effects, including antiparasitic activities (Hashmi et al., 2023).

Va83–Va91, coordinated with quinoline (QN) and SB ligands, showed substantial variability of effect in parasite and mammalian cells, resulting in a broad spectrum of SIs (Scalese et al., 2021; Scalese et al., 2025). Va85 and Va89 exhibited great SIs, while Va86 had a good SI for trypomastigotes. Although Va85 and Va89 have the same 8-hydroxyquinoline derivative in their structure, the SB ligand differs between them. They lead to an increase in ROS generation and a decrease in infection rates, and Va89 also led to a decrease in $\Delta\Psi_m$ and the induction of apoptosis and necrosis (Supplementary Table S1).

Cobalt

Cobalt is predominantly found as Co(II), an essential component of vitamin B₁₂, which has previously demonstrated activity against all evolutionary forms of *T. cruzi*. It could also exist as Co(III), stabilised by nitrogen and oxygen ligands (Ciccarelli et al., 2012).

Co92, coordinated with a Pyr ligand, inhibited proliferation in epimastigotes at a high concentration (Martín-Montes et al., 2023). In contrast, Co93–Co95, having ADs conjugated to cobaltocenium, showed good SI in trypomastigotes. Their mechanism of action appears to involve the inhibition of sterol pathways (Supplementary Table S1).

Ruthenium

Ruthenium is commonly found as Ru(II) and Ru(III). Ru(II) forms 18-electron metallocenes; unlike ferrocene, ruthenocene derivatives are not always electrochemically reversible (Navarro et al., 2021).

The 11 ruthenium complexes displayed a diverse set of ligands and ligand combinations (Ru96–Ru106), resulting in a variety of SI. Ru106 had the best SI for the Y strain (TcII), acting through DNA and mitochondrial damage associated with TR inhibition (Cezar et al., 2025). Ruthenocene-AD conjugates (Ru96 and Ru97) were designed to target sterol 14- α -demethylase, a mechanism suggested by molecular docking (Lin et al., 2024). Ru98, Ru100, and Ru102 inhibited NADH-fumarate reductase that catalyses the conversion of fumarate to succinate, a substrate for the electron transport chain, which is vital for parasite energy generation and survival (Merlino et al., 2014). In this series, Ru(II) is coordinated with Bis(diphenylphosphinoferrocene), which enhances lipophilicity and promotes radical generation by its reversible oxi-reduction. It contains a pyridine-2-thiolato-1-oxide (MPO) ligand known for inhibiting NADH-TcFR enzyme activity (Rivas et al., 2024).

Iron

Iron primarily exists as Fe(II) and Fe(III), and in *T. cruzi*, it is involved in growth and antioxidant defences. Ferrocene and its derivatives, such as ferrocenyl-chloroquine and ferrocenyl-tamoxifen, are effective against malaria and cancer due to their stability, lipophilicity, and ability to generate ROS with low toxicity (Dick et al., 2023).

Fe107 and Fe108, both conjugated with FLZ derivatives, exhibited different activities. Fe107 showed a good SI, whereas Fe108 displayed a low SI to trypomastigotes. The key structural difference between the two complexes is that Fe107 has a 1,2,3-triazole linker between the metal centre and the ligand, whereas Fe108 has an amide. This difference resulted in an approximately 12.7-times higher SI for Fe107. Molecular docking indicated that these compounds might inhibit the sterol pathways (Supplementary Table S1).

Manganese

Manganese is essential in *T. cruzi* for protein glycosylation, host-cell invasion, and intracellular replication (Ramakrishnan et al., 2021). The predominant oxidation state, Mn(II), acts as a critical cofactor for enzymes involved in signal transduction, DNA biosynthesis, and neurotransmitter production (Roth and Garrick, 2003).

Among the five Mn(II) compounds selected, three are coordinated with ADs and Phen (Mn109–Mn111), and two with ADs and Bipy (Mn112 and Mn113). All compounds showed a low SI towards trypomastigotes. Interestingly, Mn111 inhibited ergosterol synthesis and altered DNA compartmentalisation and localisation in treated parasites (Del Mármol et al., 2025).

Over the 5-year period, a limited number of studies (n = 22) were published focusing on the effect of 113 metal compounds on *T. cruzi*. In view of the factors discussed above, we propose a set of parameters (Figure 2) detailing the desired characteristics of a metal compound and the methodological parameters necessary to enhance the efficiency of cell viability assays for the search of active metallic compounds against *T. cruzi*. A good/great SI is paramount in order to minimise toxicity to the mammalian host. Given the effects of metal compounds on *T. cruzi*'s redox metabolism, bioenergetics, and ergosterol synthesis, along with

their observed multi-target activity, they represent promising candidates for addressing *T. cruzi* genetic variability. As such, they serve as a powerful weapon for the development of new strategies against CD.

Author contributions

VB: Formal analysis, Methodology, Writing – review and editing, Investigation, Validation, Writing – original draft, Data curation. JC: Writing – review and editing, Writing – original draft, Investigation, Validation, Formal analysis, Data curation. JF: Investigation, Writing – review and editing, Formal analysis, Data curation, Writing – original draft. CA: Writing – original draft, Formal analysis, Writing – review and editing, Data curation. FG: Writing – original draft, Formal analysis, Validation, Supervision, Data curation, Investigation, Conceptualization, Writing – review and editing.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. During the preparation of this work, the authors used IA/Gemini in order to correct their English. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fddsv.2026.1765208/full#supplementary-material>

SUPPLEMENTARY FIGURE S1

PRISMA Flow Diagram describing the selection of studies for the systematic review. Adapted from (Page et al. 2021).

SUPPLEMENTARY FIGURE S2

Structures of the metal-based complexes analysed (Table S1). Abbreviations: R₁ = Cl or PPh₃ (triphenylphosphine); R₂ = H₂O or BZN (benznidazole); R₃ = H or 4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy); R₄ = 7atp (7-amine-1,2,4-triazolo[1,5-a]pyrimidine) or dmtp (5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine); R₅ = dmtp (5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine) or H₂O; R₆ = acetate or polymer; R₇ = H or Me; R₈ = H or Me; R₉ = H, Cl, I or NO₂; R₁₀ = H, Cl or I; R₁₁ = Me or Et; R₁₂ = Cl, Hstzn (1,3-thiazolidine-2-thione), HSBtz (1,3-benzothiazole-2-thione), HSPym (pyrimidine-2-thione) or 2-tuH (2-thiouracil); R₁₃ = Me₃, Et₃, Bu₃, Ph₃, Cy₃, Bu₂, Ph₂, Vin₂, BuCl₂, Me₃(1,10-ph); R₁₄ = Cl or Hind (1H-indazole); R₁₅ = Cl or Hind (1H-indazole); R₁₆ = Ph, thiophene; R₁₇ = tBut, Et; R₁₈ = H or OH; X₁ = 7atp(SO₄); (NO₃)₂; X₂ = Cl₂ or (NO₃)₂; X₃ = PF₆ or Cl; Linker = 1,2,3-triazole or amide; NN_A = bipy

(2,2'-bipyridine), dmb (4,4'-dimethyl-2,2'-bipyridine), phen (1,10-phenanthroline), tmp (3,4,7,8-tetramethyl-1,10-phenanthroline), aminophen (5-amino-1,10-phenanthroline); NN_C = dmbp (dimethyl-2,2'-bipyridine); NN_D = phen, bipy, tmp; PP₁ = ddpe (1,2-bis(diphenylphosphano)ethane) or PPh₃; PP₂ = dppe; O_ANO = BrIS ((E)-N'-(5-bromo-2-hydroxybenzylidene)isonicotinohydrazide) or IN ((E)-N'-(2-hydroxynaphthalen-1-yl)methylene)isonicotinohydrazide); O_BNS or NS_A = coumarin; CTZ = clotrimazole; BZN = benznidazole; FLZ = fluconazole; Glu = (4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy); Ris = risedronate.

SUPPLEMENTARY TABLE S1

Characteristics of the metal-based compounds analysed. Abbreviations: Ligand class: ADs (Azole Drugs), Bipy (Bipyridine), BP (Bisphosphonates), DTC (Dithiolane), Glu (4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)), NHC (N-Heterocyclic carbene), Phen (Phenanthroline), PR₃ (Phosphine and/or Phosphane), Py (Pyridine), Pyr (Pyrimidine), QN (Quinoline), SB (Schiff base), s-CBZ (Semi-carbazone), TS (Thiophene), t-CBZ (Thiosemicarbazone). *T. cruzi* evolutive form: A (Amastigote), E (Epimastigote), T (Trypomastigote). Cell line: BMDM (Bone Marrow Derived Macrophages), C2C12 (Mouse myoblast), EA.hy926 (Somatic hybrid cell with endothelial morphology), H9c2 (Embryonic rat heart derived), HepG2 (Human liver carcinoma), HFF1 (Human Foreskin Fibroblasts), J774 (Murine macrophages), LLC-MK2 (Rhesus Monkey Kidney Epithelial Cell), MRC-5 (Lung fetal tissue derived), U-937 (Human promonocytic), VERO (*Chlorocebus* sp. kidney epithelial). Trypanocidal effect: ΔΨ_m (Mitochondrial membrane potential), NADH-TcFR (*T. cruzi* NADH-Fumarate Reductase), ROS (Reactive Oxygen Species), TcFPPS (*T. cruzi* farnesyl diphosphate synthase), TcOYE (*T. cruzi* Old Yellow Enzyme), TR (Trypanothione reductase). ND: Not determined. (-) Compound structure or results not reported in the *ms*.

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