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A new therapeutic perspective on metal-based drugs

Rodrigo Castro-Ramírez and Norah Barba-Behrens *

Metal-based drugs have been at the forefront of research and development in laboratories around the world for several decades. Within the area of medicinal inorganic chemistry, many potential pharmaceuticals have been obtained and evaluated, with some notable examples making their way into therapy. In this Perspective article, we discuss notable examples of metal-based drugs and their mechanisms of action. These mechanisms are predicated on properties unique to coordination compounds, making them relevant to their evaluation as therapeutics for many diseases. Herein, we discuss our research as an example of the design, structural features and biological evaluation of these types of compounds. We present a proposal for the mechanism of action based on a series of experimental and computational studies of our most active compounds in an effort to highlight the potential of metal complexes of small molecules in the development of accessible treatments for infectious diseases.

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Introduction

Inorganic chemistry applied to the therapy or diagnosis of diseases is within the field of medicinal inorganic chemistry, where metal-based drugs have a prominent role in the search for new compounds for the treatment of infectious diseases and cancer, among many others. This has proven to be a challenging yet promising area of research, where the biological activity of metallodrugs is related to the metal itself, the ligands and the properties of the complexes.

Since the early reports of cisplatin and its anticancer properties, a lot of effort has been put into the research and development of similar therapeutic agents. Ranging from antibacterial to anti-Alzheimer's applications, these metal-based compounds have been thoroughly studied, not only for their biological activity but also for their potential mechanisms of action, side effects and toxicity. Such studies have been adequately summarised in recent reviews.[1–3] Among them, we consider the recent review by Gasser *et al.* as one of the most appropriate classifications of the diverse mechanisms of action shown by metal complexes because of the wide range of therapeutic targets it applies to. Herein, we will primarily focus on three mechanisms, namely, covalent binding to biomolecules, inhibition of enzymes and the redox activity of compounds. Although some of these modes of action are shared across many therapeutic agents, the versatility seen in metal-based drugs is due to some properties unique to these complexes.[4] Such properties are illustrated in Fig. 1a and b, which depict the mechanisms of action.

Covalent binding to biomolecules

Due to the unique capability of metal complexes to exchange the types and number of ligands, stabilising different geome-

Departamento de Química Inorgánica, Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Coyoacán, 04510 Ciudad de México, Mexico. E-mail: norah@unam.mx

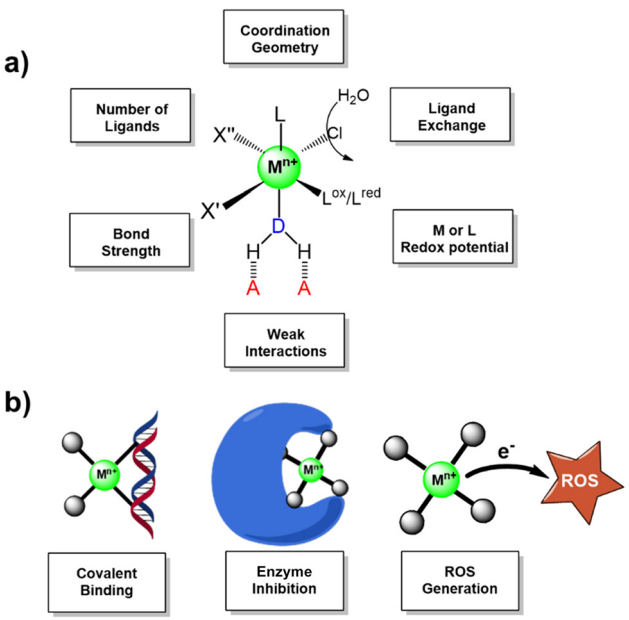


Fig. 1 (a) Properties of metal complexes that can be used for therapy. (b) Types of mechanisms by which metal-based drugs are active.

tries, metal-based drugs are uniquely equipped for covalent binding to biomolecules. The most notable examples of therapeutic agents with this type of mechanism are cisplatin and its later-generation analogues, oxaliplatin and carboplatin. The mode of action of these compounds has been well-studied and generally consists of a few key steps: entry into the cell through passive diffusion or by transmembrane enzymes such as CTR1, ligand exchange (aquation) caused by the concentration gradient of chloride, and site-specific coordination to N(7) of guanine.[5–10] When looking at their clinical use, however, a key difference between these Pt complexes becomes apparent. Oxaliplatin has been mostly used to treat gastrointestinal cancers, for which cisplatin and carboplatin have low efficacy.[11] This has been attributed to a different mechanism of action, where oxaliplatin induces ribosome biogenesis stress through the inhibition of rRNA synthesis.[12] This further highlights how some minor modifications to a metal-based drug can alter its biological activity. Furthermore, there are different mechanisms by which the cell does not allow these compounds to reach the DNA, *i.e.* a decrease in complex assimilation, an increase of complex efflux and inhibition and excretion by covalent binding to various proteins.[13] Thus, the need for better targeting in the design of similar compounds is still paramount.

Alternatively, some metal complexes are capable of binding to enzymes rather than DNA, most notably, some gold-based compounds. Since 1985, the gold complex auranofin has been used for the treatment of rheumatoid arthritis (RA) due to its anti-inflammatory activity. In this compound, Au(I) acts as a soft Lewis acid, able to covalently bind to soft bases such as sulphur and selenium, making its main targets cysteine and selenocysteine residues within glycoproteins that mediate inflammation, *i.e.* thioredoxin reductase (TrxR) and glutathione reductase. Despite being FDA approved for RA for more than 40 years, new therapeutic applications have been studied for these types of compound. Auranofin is currently under clinical trials as a repurposed therapeutic agent for cancer, given its ability to bind covalently to TrxR. This enzyme is overexpressed in several types of cancers and dysregulates reactive oxygen species inside cancerous cells, leading to an increase of reactive oxygen species (ROS) and inducing cell death.[14] Moreover, novel coordination and organometallic compounds with this metal ion have been studied for their ability to act as antiparasitic agents. In such studies, auranofin showed an EC_{50} value comparable to amphotericin B against *L. amazonensis* promastigotes. Similar activity was found *in vitro* against the amastigote form of *L. major* and *L. amazonensis* and *in vivo* against *L. major* promastigotes.[15] Similarly, a series of $Au^{I/III}$ N-heterocyclic carbene compounds were tested against *L. amazonensis* and *L. braziliensis*. Within this report, a cationic bis-NHC Au(I) complex with a benzylated caffeine scaffold showed high activity against the promastigote and amastigote forms of these parasites, as well as high selectivity when compared to BALB/c mouse primary macrophages (BMDMs).[16] Although studies are still needed to fully understand the mechanisms of action of such compounds, the inhibition of trypanothione reductase (TR) and parasite membrane permeability could induce a cell death process similar to apoptosis.[17,18]

The examples described above using gold ions illustrate another advantage of these types of therapeutic agents, as they can be used for the treatment of a wide range of diseases, given the different properties of the metal complexes (Fig. 1a).

Such properties are perhaps best illustrated in the recent strategies employed for the treatment of Alzheimer's disease (AD). AD is a progressive neurodegenerative disease characterised by the formation of senile plaques in the brain, formed by fibrils of the Aβ peptide. These aggregates are known to affect the homeostasis of metal ions in the brain, disrupt membrane-bound synaptic receptors and interrupt electrochemical signals essential for synapsis.[19,20] To tackle the problem of Aβ aggregation, metal complexes have been designed and tested against this disease, with some notable results in three main mechanisms of action:[21]

- Oxidation of amino acids in Aβ: involves using metal complexes with known redox properties to produce ROS that target residues susceptible to oxidative stress like histidine and methionine. Iridium(III) and ruthenium(II) complexes with aromatic ligands have been proved to trigger the oxidation of amino acids due to their ability to generate $^1O_2$ *via* photoactivation.[22,23]

- Hydrolysis of the Aβ peptide: metal complexes are used to activate otherwise stable amide bonds. Here, Co(III) complexes have been proposed as hydrolytic catalysts, as they readily bind to water molecules. These H_2O molecules are deprotonated, and the resulting hydroxo ligand can carry out a nucleophilic attack on the carbonyl of the amide group, making the resulting amine a good leaving group.[24–26]

- Coordination to Aβ amyloid: within the brains of patients with AD, a high amount of ions such as Cu, Zn and Fe has been found.[27] These ions are usually coordinated to His residues. Thus, metal-based drugs can be designed to take advantage of these binding amino acids and inhibit Aβ aggregation.

An appropriate example of this third mechanism is provided by ruthenium(III) complexes using azoles as ligands. The metal complexes NAMI-A, KP1019 and PMRU20 appear as anionic distorted octahedral complexes (Fig. 2a). These complexes were initially evaluated as anti-cancer agents and, more recently, have been used as inhibitors of the aggregation of the Aβ amyloid, responsible for Alzheimer's disease (AD).[28,29] As mentioned above, AD is characterised by the formation of senile plaques in the brain, formed by fibrils of the Aβ peptide. Fig. 2b depicts the aggregated peptide and the monomer after treatment, as well as the primary structure of $A\beta_{42}$.[30] Given the primary structure of this peptide, histidines in positions 13 and 14 have been the target of many potential anti-aggregation agents. The previously mentioned Ru(III) compounds and novel complexes using azoles with various substituents have proven to be effective at inhibiting peptide aggregation. This is due to the displacement of chloride atoms in the axial position of the octahedron by H_{13-14}, allowing the metal ion to covalently bind to the peptide. Furthermore, both the substituents and the azole ring used in these compounds

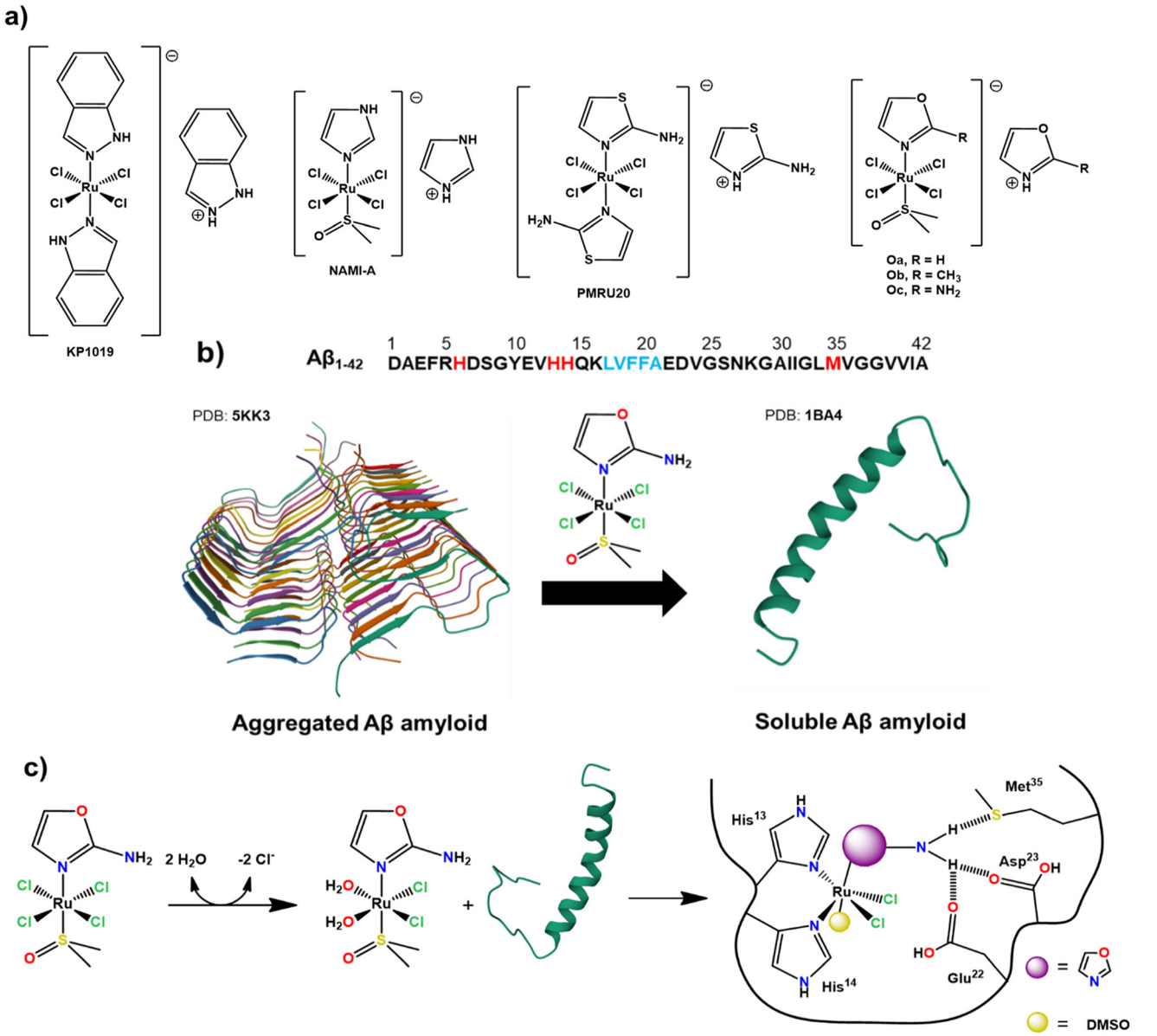


Fig. 2 Treatment of Alzheimer's disease with ruthenium derivatives. (a) Ru(III)-azole derivatives tested as anti-AD agents. (b) Treatment of aggregated Aβ amyloid with a Ru(III)-azole derivative into a soluble monomer. The primary structure of peptide $A\beta_{42}$ is shown here, with the main coordination target depicted in red and the self-recognition site depicted in light blue. (c) Proposed mechanism of action of some anti-AD agents: aquation of Cl, coordination of Ru(III) to target residues and aggregation inhibition by ligand–peptide weak interactions.

play a key role in their activity. Metal complexes with oxazole rings are more effective at inhibiting peptide aggregation than those with benzimidazole, thiazole and imidazole, and compounds featuring amine functionalisation were also among the most active. This is due to the ability of the ligand, and especially its $-NH_2$ group, to potentially interact with the peptide through hydrophobic contacts and hydrogen bonds (Fig. 2c).[31–33]

Using benznidazole (bnz), one of the main treatments for Chagas disease, a series of metal complexes have been reported with ruthenium,[34,35] as well as Cu(I/II) and Ag(I),[36] aiming to reduce its toxicity to humans and resistance to the *T. cruzi* protozoan. Overall, these bnz–metal complexes showed improved activity against the parasite compared to the free ligand, with compound $[Ag(BZN)_2]NO_3$ being the most promising with low IC_{50} values against epimastigotes and amastigotes, low LD_{50} values for trypomastigotes and high selectivity towards these forms of the parasite over human foreskin fibroblasts (HFF1) or the human liver carcinoma cell line (HEPG2). Although no definitive mechanism of action has been discussed, a significant modification of kinetoplastid DNA (kDNA) was proposed, as a topological modification of the kinetoplast was observed through TEM. For compound $[Ag(BZN)_2]NO_3$, this could involve binding of Ag(I) to DNA bases, as has been previously reported.[37,38]

Inhibition of enzymes

Within metal-based drugs, the mechanism of action that entails the inhibition of enzymes, vanadate and its derivatives are perhaps the most prominent example. Vanadium compounds have long been used as anti-diabetic agents due to their ability to enhance insulin assimilation, especially in type II diabetes.[39] Regardless of the vanadate compound administered, the initial step is the speciation of the prodrug to generate $H_2VO^{4-}/VO^{2+}L$. These species bind covalently to a cysteine residue in the protein tyrosine phosphatase (PTPase), inhibiting its activity. When there is not enough insulin present, PTPase dephosphorylates tyrosines in the transmembrane insulin receptor (IR) enzyme, halting cellular glucose uptake. Thus, the inhibition of this phosphatase reactivates insulin assimilation, allowing the activation of the glucose transporter (GLUT4), essential for glycolysis.[40,41]

Although this is still a developing strategy for the design of new metal-based drugs, the inhibition of enzymes shows great potential. For example, within the cell cycle, there are numerous crucial enzymes that allow the cell to go from phase to phase. If, at any stage, the cell is under stress (*e.g.* oxidative stress or DNA damage) or any of the proteins involved in the process are inhibited, the cell goes through different processes, such as cell cycle arrest, senescence or cell death (apoptosis).[42] Some of the targeted enzymes are the CDK1/cyclin B1 complex, which is in charge of allowing the cell to enter its mitotic phase; kinases (Aurora A, B or C) that play crucial roles within mitosis; or the αβ tubulin dimer, which is key in spindle formation and chromosome alignment.[43,44] Recently, a series of Cu(II) thiosemicarbazone complexes have been reported with antiproliferative activity against uterine sarcoma (MES-SA) and multidrug-resistant uterine sarcoma (MES-SA/Dx5). The copper(II) thiosemicarbazone complex depicted in Fig. 3 proved to be the most cytotoxic against the aforementioned cell lines and was mostly active in the G2/M phase of the cycle, due to its ability to inhibit tubulin polymerization by binding to the colchicine site (Fig. 3). Despite its promising anti-mitotic activity, these complexes also inhibit the tyrosyl radical in ribonucleotide reductase (RNR), crucial for the transformation of nucleoside 5′-diphosphates to their deoxy form.[45] Given that RNR is crucial for mDNA replication, cell cycle regulation and apoptosis, further studies are needed to ascertain its selectivity towards cancerous cells without affecting the cellular processes of healthy cells.

Other complexes with second- and third-row transition metals have also shown cytotoxic activity against cancerous cell lines, acting in the G2/M phase. Half-sandwich Ru(II) and Os(II) latonduine *p*-cymene complexes acted similarly to the copper(II) thiosemicarbazone complex, whereas two Ru(II) complexes with lapachol induced cell cycle arrest in mitosis by downregulating Aurora-B kinase overexpression in cancerous cell lines.[46–48]

Recently, Navarro *et al.* published a series of hybrid Cu(II) complexes and tested them against *Leishmania brasiliensis* and *Sporothrix brasiliensis*. The complexes reported therein depicted two biologically active ligands: dipyridophenazine (dppz), a planar DNA intercalator, and three antifungal and antiprotozoan imidazole-based ligands, namely, ketoconazole (KTZ), clotrimazole (CTZ), fluconazole (FLZ).

The synthesised copper complexes, $[Cu(dppz)(CTZ)(NO_3)](NO_3)$ **1**, $[Cu(dppz)(KTZ)(H_2O)(NO_3)](NO_3)$ **2** and $[Cu(dppz)(FLZ)(NO_3)]_2(NO_3)_2$ **3** (Fig. 4), interacted strongly with DNA *via* intercalation, according to spectroscopic titrations, DNA viscosity measurements and electrophoresis.

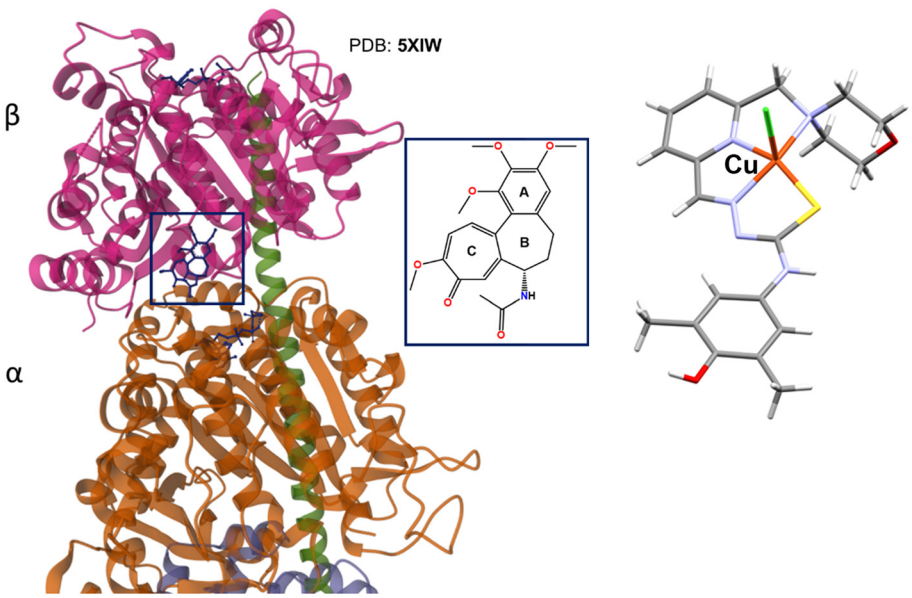


Fig. 3 Left: Tubulin crystal structure depicting the colchicine binding site and the α (orange) and β (pink) subunits. Right: Copper(II) thiosemicarbazone complex (complex **6**), reported to inhibit microtubule formation by binding tubulin at the colchicine recognition site.

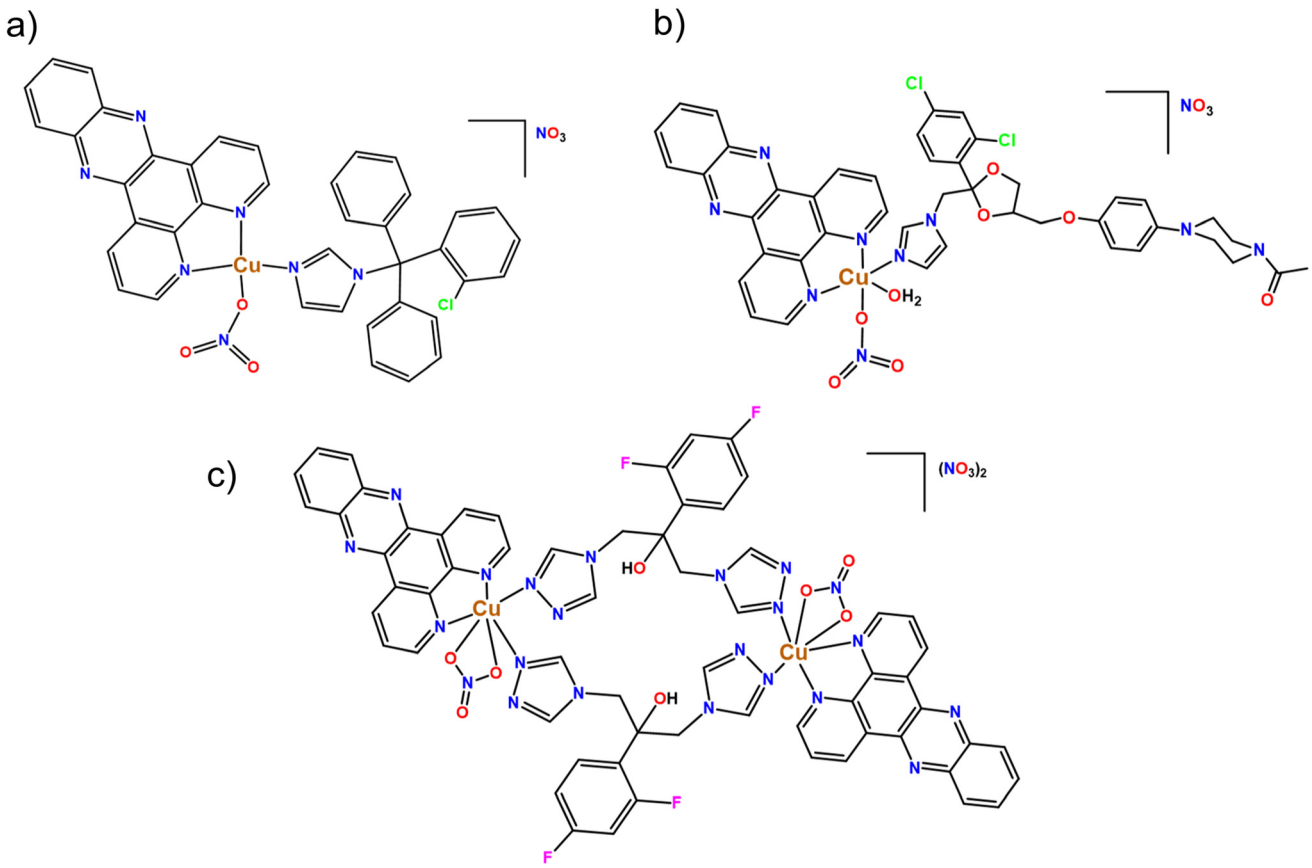


Fig. 4 Proposed structure for the copper(II) hybrid complexes (a) $[Cu(dppz)(CTZ)(NO_3)](NO_3)$, (b) $[Cu(dppz)(KTZ)(H_2O)(NO_3)](NO_3)$ and (c) $[Cu(dppz)(FLZ)(NO_3)]_2(NO_3)_2$.

Whilst tested against *L. brasiliensis* promastigotes, all three copper complexes where more active than their respective ligands. However, only **2** and **3** (both showing distorted octahedral geometry, while **1** depicted a square planar geometry) were more active than the free ligands when tested against the intracellular amastigote form of the protozoan parasite. On the other hand, when exposing *S. brasiliensis* to these complexes and the free azole ligands, the ligands probed to be more active than the complexes themselves at inhibiting fungal growth.

Although no further studies were conducted in this report to evaluate a plausible mechanism of action, the authors point towards enzymatic inhibition and sterol metabolism disruption, as both trypanosomatids and fungi produce ergosterol rather than cholesterol. Thus, inhibiting sterol C14 α-demethylase (CYP51), as the azole ligands have been proven to do, can selectively target the parasites' metabolism without damaging the human host. This is clear when testing complexes **1–3** against RAW-246.7 mammalian cells, as the complexes were 4 to 50 times more active against intracellular amastigotes than the mammalian cells, according to their selectivity indexes (SI).[49]

These conclusions echo some promising results with similar compounds. The same group has also published Zn-based complexes with a known antimycotic, itraconazole, showing promising results against *Trypanosoma cruzi*, *Leishmania amazonensis*, *Toxoplasma gondii* and *Sporothrix* spp.[50]

Redox-based mechanisms

The third and final mechanism of action is the generation of ROS to oxidatively damage DNA and other biomolecules. Redox active molecules are ubiquitous in biological systems and are responsible for crucial metabolic reactions. These redox processes depend on a delicate balance of these reactive species, which have been proven to be disrupted in many diseases such as cancer, Alzheimer's disease, diabetes, among many others.[51] In fact, it has recently been demonstrated that ROS increase throughout the growth of pathogens such as *T. cruzi* (responsible for Chagas disease) and that these species are key for the programmed death of these parasites.[52–54] Due to such findings, one major area of pharmaceutical development of novel drugs is based on the generation of ROS. In this context, metal-based drugs are uniquely tailored for this type of mechanism of action. Not only are many of the metal ions used for their development redox-active, but they can also act as prodrugs, where the ligands themselves can show redox properties and be active.[55,56]

Some examples of drugs with this mechanism of action go all the way back to second- and third-generation platinum-based anticancer drugs, in which several platinum(IV) complexes were designed to act as prodrugs. The octahedral geometry and the axial ligands chosen increased stabilisation and inertness, making them less susceptible to deactivation by thiol-containing molecules. The Pt(IV) metal centre is reduced within the cell, producing an active Pt(II) compound. This strategy has also been applied to the notable NAMI-A-type and Kepler-type compounds, as well as satraplatin, which are currently under clinical trials.[57,58] However, for those ruthenium compounds and many others inspired by them, the reduction process from Ru(III) to Ru(II) has recently been discarded as a key step in their mechanism of action.[59] This has been demonstrated using X-ray absorption near edge structure (XANES) spectroscopy in tissues such as liver, kidney and tumor of mice with human colorectal adenocarcinoma (SW480), with no trace of Ru(II) species even after 24 h of treatment with these compounds.[60] Despite this, ruthenium(II) compounds have proven to be good pro-drug compounds in photoactivated chemotherapy (PACT) for the treatment of tumors. Generally, these compounds include polyaromatic ligands, which aid in the absorption of light; a ligand that, upon release, can interact with biomolecules and show some pharmacological effect; and the Ru(II) ion, which can itself interact with some biological targets such as DNA.[61]

Recently, a protoporphyrin IX ruthenium(II)-based compound was synthesised and tested against human gastric cancer cells (AGS) using photodynamic therapy (PDT). In the dark, low activity was observed from the compound and the free ligand. However, upon irradiation, the compound was able to induce caspase 3-mediated apoptosis and cell death *via* C/EBP homologous protein (CHOP), due to its ability to generate both superoxide radical $O_2^{\bullet -}$ and $^1O_2$ even under hypoxic conditions.[62]

Additionally, several compounds have been developed based on a crucial metabolic reaction known as the Fenton reaction. This reaction, alongside the Haber–Weiss reaction, is in charge of the regulation of ROS inside the cell (Fig. 5). Therefore, many complexes have been designed using Fe(III) and Cu(II) metal ions, which, upon entering the cell, are able to react with hydrogen peroxide to yield a hydroxyl radical that can oxidatively damage DNA by breaking the phosphate chains.[63–65]

In addition to its redox capabilities, a novel copper-dependent mechanism has been put forward by Tsvetkov *et al.* This mechanism consists of an over-accumulation of copper or its ionophores (*e.g.* elesclomol, disulfiram or NSC319726) inside the cell. This accumulation, especially in the mitochondria, is able to disrupt a group of enzymes present in the tricarboxylic acid (TCA) cycle by a process known as lipoylation, in which a sulfur-lipoic acid metabolite attaches to certain proteins: dihydrolipoamide *S*-acetyltransferase (DLAT), dihydrolipoamide branched chain transacylase E2 (DBT), glycine cleavage system protein H (GCSH) and dihydrolipoamide *S*-succinyltransferase (DLST). This results in copper binding to the lipoyl moiety,

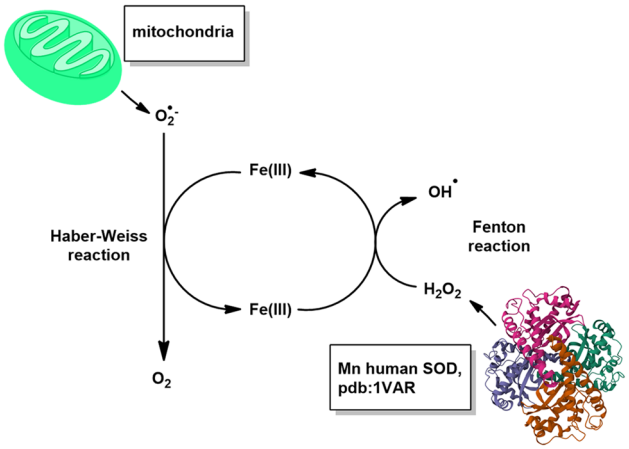


Fig. 5 Fe-dependent reactive oxygen species regulation reactions. Superoxide deactivation by the Haber–Weiss reaction (left) and hydroxyl radical generation through the Fenton reaction (right).

protein aggregation and loss of Fe–S cluster proteins, eventually leading to cell death. This opens the door to the design of new Cu-based compounds targeting tumour cell lines with high lipoylated protein content.[66]

A series of vanadium compounds with 8-hydroxyquinoline (L-H) derivatives and 2-mercaptopyridine (mpo) have been reported as potential antitrypanosomatid agents. These complexes, with the general formula $[V^{IV}O(L\text{-}H)(mpo)]$, were able to inhibit the growth of *T. cruzi* and *L. infantum* with IC_{50} values lower than those of nifurtimox and amphotericin B. In terms of the potential mechanism of action, the ROS generation was evaluated, showing a significant increase in the presence of the complexes compared to the control. This oxidative stress resulted in mitochondria-dependent apoptosis. Additionally, the effect of these complexes as inhibitors of the parasite-specific *T. cruzi* fumarate reductase (*TcFR*) was evaluated. Through molecular docking and molecular dynamics studies, it was concluded that these compounds bind to the enzyme far from the active site. However, the binding of the compounds significantly modified the *TcFR* structure, inhibiting a key step in the parasite's metabolism.[67]

Biological targets for tinidazole complexes

In the search for new active coordination compounds, we have been interested in the design and synthesis of a wide variety of transition metal coordination compounds with biologically active ligands that could present antibacterial, antiparasitic or anticancer activities.[68–71] In this context, a little over a decade ago, we started to investigate 5-nitroimidazole derivatives due to their diverse biological properties and their coordination chemistry towards transition metal ions. In particular, one 5-nitroimidazole derivative, tinidazole (tnz), has proven to be a versatile ligand towards transition metal ions (*i.e.* Co, Ni, Cu, Zn, Cd, Ag), giving rise to a variety of coordination compounds and stabilising a wide range of geometries.[72–74]

Interestingly, it was found that, despite the potential coordinating sites, this nitroimidazole only coordinated through the

N(3) in the heterocycle. This unique mode of coordination allows the other groups (NO_2 and SO_2) to interact inter- and intramolecularly. In the tetrahedral $[Cu(tnz)_2Cl_2]$ complex, two different conformers, kinetic and thermodynamic, were obtained and fully characterised. In the thermodynamic conformer, the sulfone group interacts intramolecularly, yielding a stabilising bifurcated lone pair···π contact.[72] Similarly, single crystal X-ray structures for the thermodynamic conformers of Co(II) and Zn(II), with both Cl and Br, as well as the $[Ni(tnz)_2Br_2]$ compound, were obtained. It is noteworthy that all these distorted tetrahedral compounds stabilised the same bifurcated lp···π interaction, regardless of the metal ion,[73,74] which, upon computational studies, was proven to be an attractive, localised and directional interaction (Fig. 6).[75] Additionally, when modifying the reaction conditions, $[Cu(tnz)_2Br_2]$ can be reduced to a trigonal planar $[Cu(tnz)_2Br]$ compound. According to its X-ray structure, this copper(I) complex presents a novel intermolecular lone pair···π hole interaction between one oxygen from the sulfone with a $-NO_2$ group, due to its resonance structures.[75,76]

The fact that this lp···π contact is a weak interaction, and not a covalent bond, provides stabilisation in solution for the complexes while allowing them to be modified as they interact with their target molecules (see the Discussion and perspective section). Similar complexes with chelating ligands are limited by their covalent bonds, thus making them less versatile when interacting with biomolecules.

These properties unique to tnz metal complexes allowed us to test them against different diseases. Initially, the evaluation of the biological activity of these compounds aimed at their potential use in aquaculture as anthelmintic agents for fish.[73] Within those studies, the $[Cu(tnz)_2Br_2]$ compound was the most effective, followed by $[Zn(tnz)_2Br_2]$. When the compound was given orally to the fish, it was metabolised and mainly found in the liver. As Cu(II) is an essential element, many biological organisms have specifically designed mechanisms to deal with an excess or external source of copper.[77–79] In our studies, the compounds were not toxic, but rather they were deactivated by fish metabolism. Hence, a more direct route of administration was implemented by adding the compound to the water tanks holding the fish. This allowed the compound to go directly to the parasite, which mainly localises in the gills, achieving over 90% effectiveness. Given these results, we further assessed the anticancer ability of these compounds. Against several cell lines, the Cu(II)-tinidazole compounds presented good activity, especially $[Cu(tnz)_2Br_2]$ and the dinuclear $[Cu(tnz)_2(\mu\text{-}Cl)Cl]_2$, which dissociates in solution into the mononuclear $[Cu(tnz)_2Cl_2]$. Additionally, these compounds exchange the halogen ligands with water molecules in solution. One of the most interesting results was the selectivity of these compounds, as they were considerably more cytotoxic towards cancerous cells (MCF-7) than healthy cells (MCF-10A).[74] Fig. 7 depicts some notable results of these compounds as multi-target therapeutic agents.

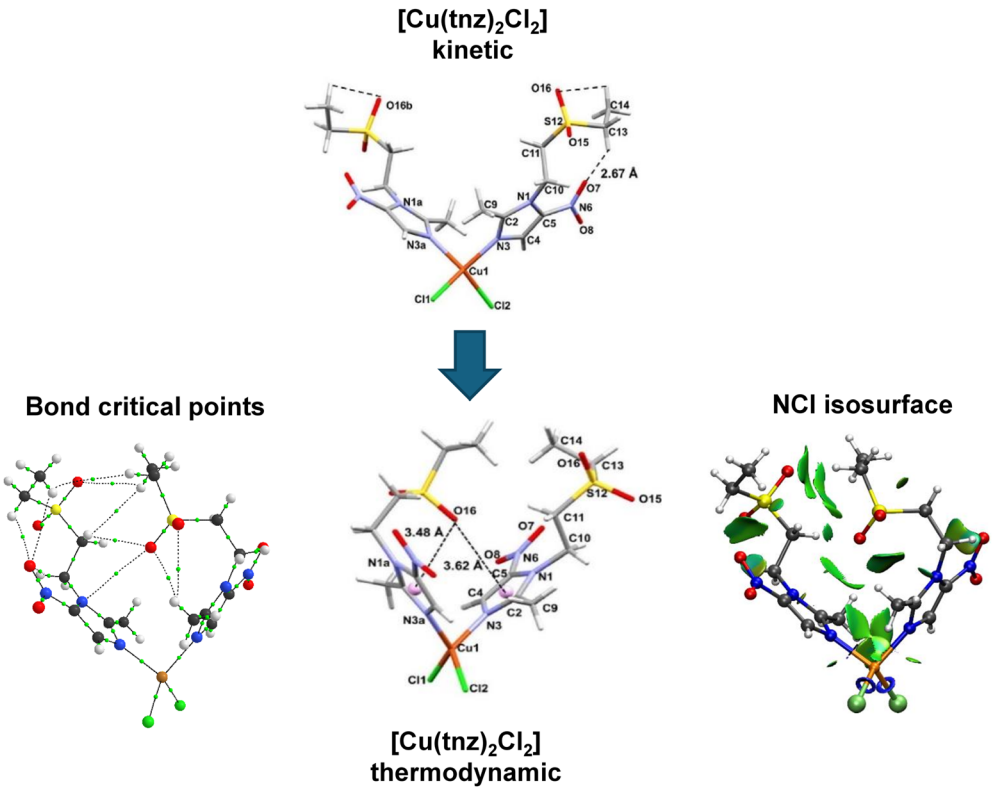
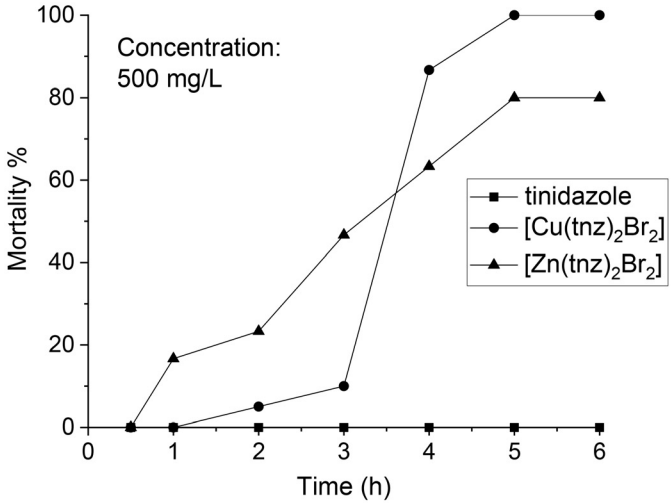


Fig. 6 Transformation of $[Cu(tnz)_2Cl_2]$ from the kinetic conformer into the thermodynamic conformer, with bond critical points (green dots) and NCI isosurface studies for the evaluation of the stabilising lp···π interaction.

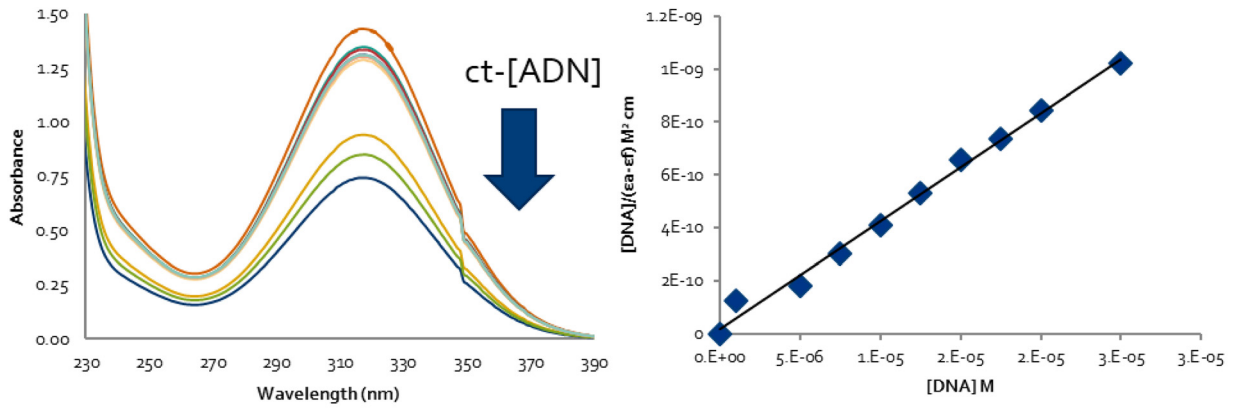


Compounds	MCF-7	MCF-10A
	IC_{50} (μM)	IC_{50} (μM)
tinidazole	>100	>100
$[Cu(tnz)_2Br_2]$	14.9	33.1
$[Cu(tnz)_2(\mu\text{-}Cl)Cl]_2$	6.9	28.6
$[Cu(tnz)_2Cl_2]$	64.3	45.0
$[Cu(tnz)_2(NO_3)_2]$	37.0	31.8
$[Cu(tnz)(\mu\text{-}AcO)_2]_2$	22.1	31.7

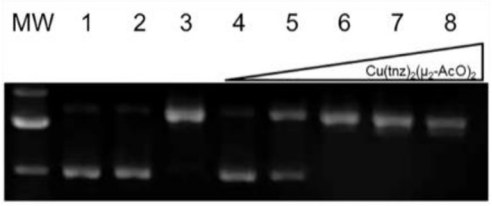
Fig. 7 Tinidazole complexes were evaluated as antihelminthic and anticancer agents with high activity and selectivity.

In parallel to these *in vivo* and *in vitro* studies, the way these compounds could interact with DNA was evaluated by UV–Vis and fluorescence titration essays,[74] showing electrostatic or minor groove complex–DNA interactions. When performing the ethidium bromide assay, a quenching of fluorescence was observed due to the strong interaction with DNA.[80] Given the known ability of copper to perform Fenton-like reactions, the ability of the compounds to oxidatively damage DNA was evaluated both in the presence and absence of H_2O_2, showing promising results. Most notably, the compounds were able to damage DNA even when hydrogen peroxide was not added. This suggests that there might be another species capable of stabilising radicals, such as the nitroimidazole, as its mechanism of action involves the generation of a radical anion in the nitro group. Fig. 8 depicts the DNA binding abilities and ROS generation for some of these complexes.

Furthermore, we have performed theoretical studies to determine a plausible mechanism of action for these tinidazole complexes.[76] A summary of all these results and the insights obtained from them can be found in the Discussion and perspective section.



Complex	Binding constant, K_b (*10^5)
$[Cu(tnz)_2(\mu\text{-}Cl)Cl]_2$	26
$[Cu(tnz)_2Cl_2]$	6.67
$[Cu(tnz)_2Br_2]$	8.89
$[Cu(tnz)_2(NO_3)_2]$	500
$[Cu(tnz)(\mu\text{-}AcO)_2]_2$	14.3



$$[Cu^{I}(tnz)_2(H_2O)]^{+} + ROs \longrightarrow [Cu^{II}(tnz)_2(H_2O)]^{2+} + ROs^{\bullet}$$

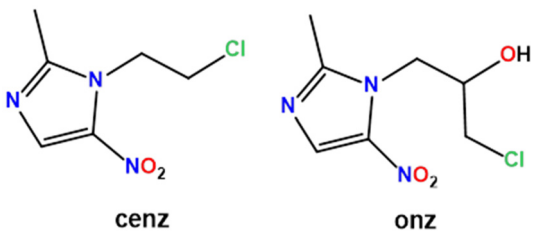
Fig. 8 The tinidazole–copper complexes interact with DNA in the minor groove with high binding constants. The biologically accessible $Cu^{I/II}$ redox potential in the complexes is used to oxidatively damage DNA.

Based on the promising results with tinidazole metal complexes, we designed and synthesised derivatives of benzimidazole (2-mfsbz, sfabz and seabz) and imidazole (2-mfsiz) to further study the influence of different functional groups on the structural, electronic and chemical properties of their metal complexes, as well as their potential biological activity. Using halides as counterions, distorted tetrahedral complexes were obtained with the general formula $[M(L)_2X_2]$. Those complexes stable in solution were evaluated for their cytotoxic properties. Among all these compounds, both $[Cu(sfabz)_2Cl_2]$ and $[Cu(sfabz)_2Br_2]$ showed activity comparable to cisplatin, specifically against HeLa.[81,82]

From a first nitroimidazole generation to potential antiparasitic coordination compounds

One of the huge setbacks that nitroimidazoles have faced in their use as therapeutic agents is the resistance that some of the target microorganisms have developed over time.[83,84] Such is the case with metronidazole, a first-generation 5-nitroimidazole. In order to overcome this resistance, strategic modifications have been made to the heterocycle scaffold, yielding compounds such as tinidazole and ornidazole, second- and third-generation pharmaceuticals, respectively.[85,86]

Because of this, we recently investigated several Cu(II) and Zn(II) complexes using the later-generation nitroimidazole ornidazole (**onz**) and a chlorinated metronidazole derivative, 1-(2-chloroethyl)-2-methyl-5-nitroimidazole (**cenz**), which was synthesised (Scheme 1).[87]



Scheme 1 Chemical structures of **cenz** and **onz** ligands.

Coordination compounds with the general formula $[M(L)_2X_2]$ (M = Cu(II), Zn(II); L = **cenz**, **onz**; X = Cl, Br) were obtained (Fig. 9, top). These complexes did not show any intramolecular lp···π interactions, despite having Cl and OH with free pairs of electrons. However, using **cenz** as a ligand, the complexes do interact intermolecularly through a series of lp···π contacts. For $[Zn(\mathbf{cenz})_2Cl_2]$, the donating groups of the lone pair are both the chlorido and the oxygen of the nitro group. Whereas for $[Cu(\mathbf{cenz})_2Cl_2]$, the donor is also the oxygen in the nitro group, albeit in a very different supramolecular arrangement. This is due to a larger distortion that the copper(II) complex shows around the metal ion, with $\tau_4 = 0.32$. In contrast, the zinc(II) compound has $\tau_4 = 0.9$, indicative of a regular tetrahedral geometry (Fig. 9, bottom).

For these complexes, their DNA binding properties were assessed using UV-Vis and fluorescence spectroscopy with ethidium bromide and Hoechst 33258. The results obtained suggested that the complexes interact through groove binding and electrostatic interactions. Additionally, a modification of the helicity of DNA, specifically with the copper(II) complexes, was observed in their circular dichroism spectra. This effect is

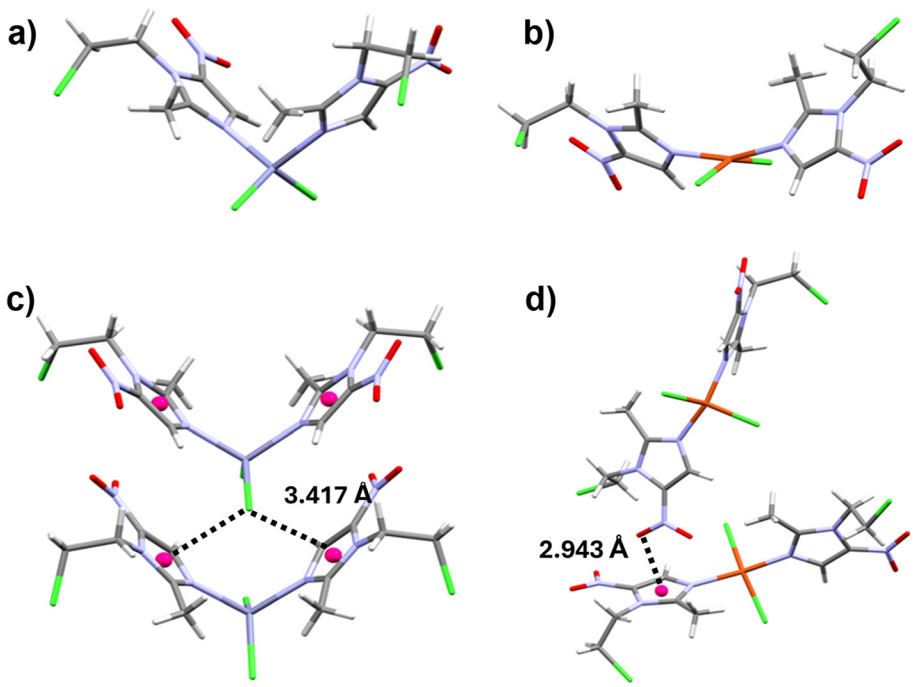


Fig. 9 Top: X-ray structures of (a) $[Zn(\mathbf{cenz})_2Cl_2]$ and (b) $[Cu(\mathbf{cenz})_2Cl_2]$. Bottom: Intermolecular lp···π interactions for (c) $[Zn(\mathbf{cenz})_2Cl_2]$ and (d) $[Cu(\mathbf{cenz})_2Cl_2]$.

often associated with a change in π stacking due to groove binding.[88] Zn(II) complexes showed a lower effect on the helical structure of DNA, favouring electrostatic interactions.[89] Further evaluation of the effect of these compounds on DNA through gel electrophoresis showed that not only are the Cu(II) complexes able to oxidatively damage DNA but also those compounds with Zn(II) as the metal ion. These results are significant, as oxidative damage by a non-redox metal ion is quite rare, as no Fenton-like reaction is carried out. Hence, a different mechanism for the generation of radicals must be in effect with these zinc(II) compounds, involving the reduction of the nitro group.

Finally, these **cenz** and **onz** coordination compounds were evaluated against *Toxoplasma gondii*. This study showed no significant activity for the ligands but promising results for their metal complexes. $[Cu(\mathbf{onz})_2Cl_2]$ and $[Cu(\mathbf{onz})_2Br_2]$ were the most active compounds, with IC_{50} values lower than the standard sulfadiazine agent, followed by the $[Zn(\mathbf{cenz})_2Br_2]$ compound. This effect is congruent with the results seen in gel electrophoresis; however, further studies are needed for the understanding of their antiparasitic activity.[87]

Discussion and perspective

Looking back at the last decade of research in our group, it is interesting how the initial results with tnz inspired us to focus on these types of molecules as ligands for biologically active metal complexes and how our most recent study with **cenz** and **onz** was aimed towards parasites. Going full circle in the targets chosen for our biological studies illustrates not only what we have learned throughout these years but also how medicinal inorganic chemistry has changed as well.

Throughout the years since cisplatin first became the drug of choice in chemotherapy for several types of cancers, many different techniques have been studied and developed for the diagnosis and treatment of diseases. Recent advances in this area have ranged from the use of precious metals (*e.g.* gold, ruthenium, and osmium),[90] nanoparticles,[91,92] to even immunotherapy[93,94] and gene editing.[95,96] Although huge leaps have been made in the advancement of these techniques, we firmly believe that the research and development of treatments based on small molecules is still paramount. This is especially the case for those diseases that do not get as much attention or funding from the global scientific community, such as parasitic infections. These are the so-called Neglected Tropical or Parasitic Diseases (NTPDs), a series of diseases caused by a wide variety of organisms. They are considered "neglected" as they mostly affect countries within Central and South America, Africa and South Asia, characterised by their tropical climates. However, the endemicity of these diseases is expected to change in the next years. As the planet becomes warmer because of climate change and northern countries start to develop a more tropical climate, the number of cases of these diseases will start to increase all over the world.[97]

One of the most popular strategies that has been used to fight these diseases is the repurposing of drugs. Simply put, it is the study of molecules with previous pharmacological use as new agents for the treatment of other diseases. A series of international organisations have been established with the purpose of finding potential agents for the treatment of NTPDs with promising results.[54]

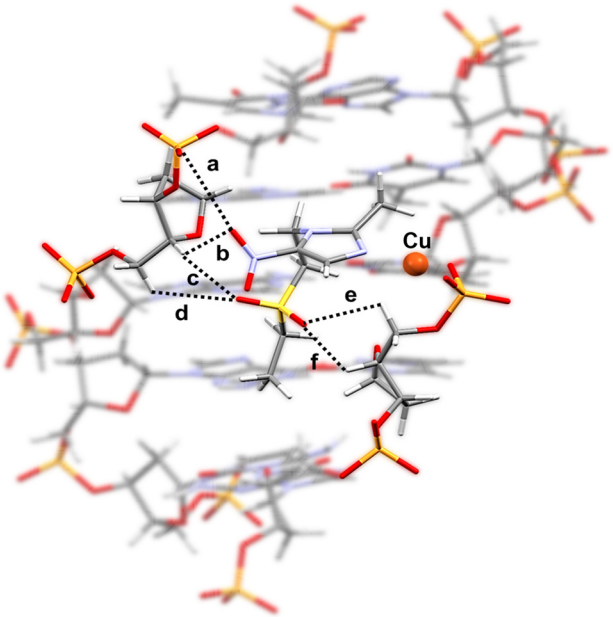
In a way, the compounds we have developed in the last years can be considered repurposed molecules, as we use biologically-active compounds as ligands for the synthesis of metal complexes, thus being able to take advantage of all the properties of these types of compounds (Fig. 1a).[4] Throughout our research, we have used most of these properties, allowing us to propose a mechanism of action for some of our most promising compounds.

In a previous section, we discussed the biological studies performed with Cu(II)–tnz complexes. Therein, we described the ability of such compounds to interact with DNA through electrostatic interactions and groove binding. Taking those results into account, a molecular dynamics (MD) study was carried out towards understanding a potential mechanism of action.[76] With the chloro and bromo Cu(II) complexes, over 20 geometries of these complexes interacting with DNA were obtained. The $[Cu(tnz)_2Cl_2]$ kinetic compound shows the most

Table 1 Summary of geometries and ligand interactions found in the MD studies of copper–tnz complexes

Complex	Geometry	Cycle	$-H_{cycle}$	$-CH_{3\ cycle}$	$-NO_{2\ cycle}$	CH_2CH_2	SO_2	CH_2CH_3
2	**A**	3	1	9	3	10	3	8
		7.7	2.6	23.1	7.7	25.6	7.7	20.5
		−3.6	−1.5	−10.3	−2.3	−13.7	−5.8	−8.8
E per interaction (kcal mol^{-1})		−1.2	−1.5	−1.14	−0.38	−1.37	**−1.93**	−1.1
3	**B**	2	0	5	3	8	4	7
		6.7	0	16.7	10.0	26.7	13.3	23.3
		−1.5	0	−4.0	−7.2	−11.4	−9.0	−10.6
E per interaction (kcal mol^{-1})		−0.75	0	−0.8	**−2.4**	−1.42	**−2.25**	−1.51

Geometry **A**: copper atoms bound to two $O_{phosphate}$ groups and two tnz molecules in a tetrahedral geometry, with one of the tnz ligands intercalated into the DNA molecule. Geometry **B**: copper atoms bound to one $O_{phosphate}$ group and two tnz molecules in a trigonal geometry, with one of the tnz ligands intercalated into the DNA molecule.



a	b	c	d	e	f
3.619 Å	2.694 Å	2.650 Å	3.040 Å	2.750 Å	2.357 Å

Fig. 10 Tinidazole ligand intercalated in a DNA fragment. The table depicts the distance of the potential weak interactions (b–f) and the distance of an O_{nitro} to phosphorus in the DNA backbone, susceptible to radical nucleophilic attacks (a). The second tnz ligand has been omitted for clarity.

stable complex–DNA interaction, followed by the $[Cu(tnz)_2Cl_2]$ thermodynamic compound and, finally, $[Cu(tnz)_2Br_2]$. In terms of the ligands around the metal ion, the two tnz molecules are conserved, and either one or two $O_{phosphate}$ groups bind to the metal ion, giving a trigonal planar or distorted tetrahedral geometry, respectively. Upon further analysis of the results in this study, a few interesting conclusions can be drawn. In the MD study, a standard Dickerson–Drew dodecamer DNA fragment was used, where the C–G pair appears twice as often as the A–T pair. However, the preferred recognition site in most of the geometries depicts the Cu(II)-tnz compound at a thymine site, particularly next to adenine in the sequence.

In those geometries with the highest interaction energy (E_{int}), it is possible to evaluate which part of the tnz ligand contributed the most. Table 1 summarizes the number of interactions per fragment of the ligand (top), the percentage of the total E_{int} (middle) and the energy value per interaction in kcal mol^{-1} (bottom) for two different geometries. From this table, it is clear that the highest value per interaction in the $[Cu(tnz)_2Cl_2]$ kinetic conformer (geometry A) is for the $-SO_2$ group and the highest values per interaction in the $[Cu(tnz)_2Cl_2]$ thermodynamic conformer (geometry B) are for both the $-NO_2$ and $-SO_2$ groups.

Analysing geometry B for the $[Cu(tnz)_2Cl_2]$ thermodynamic compound, it is clear that the higher energy values for $-SO_2$ and $-NO_2$ are due to the potential weak interactions the ligand can present with the DNA. Fig. 10 depicts the interactions found for geometry B, with $-SO_2$ stabilising a

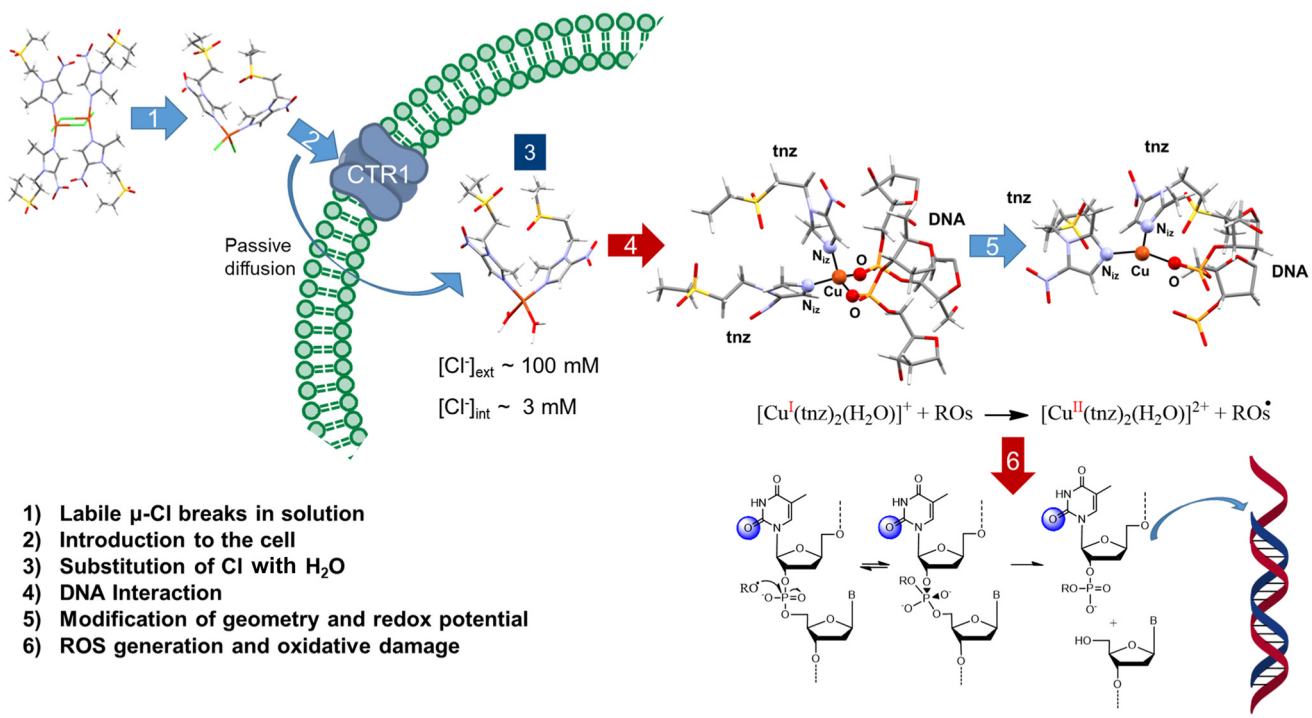


Fig. 11 Mechanism of action of Cu–tnz complexes proposed from a combination of experimental and theoretical studies.

series of hydrogen bonds with DNA and an interaction between the $-NO_2$ group and a phosphate group. It is noteworthy that one of the O_{nitro} is only 3.619 Å away from the phosphorus atom. From our oxidative damage studies using gel electrophoresis in the absence of H_2O_2, we proposed that the nitro group in the tnz molecules could be capable of generating ROS under biological conditions. In this case, the nitro group would be adequately positioned, as it is known in the mechanism of oxidative damage, where the first step is the radical electron attack on the phosphorus atom[63] (Fig. 11). Within that same study, we obtained a novel Cu(I) complex with a trigonal geometry similar to several geometries found through MD. A QSAR study with many copper complexes indicated that the redox potential of $[Cu(tnz)_2Br_2]$ is shifted to a positive potential well within the biological electrochemical window. This will make it even easier to obtain a Cu(I)–tnz complex *in situ*, and after binding to DNA, both the DNA interaction and ROS generation mechanism could act synergistically to make this type of compound highly active.

Based on all the experimental and theoretical results, Fig. 11 depicts our proposed mechanism of action for copper(II) complexes with tinidazole as a ligand.

According to recent cell cycle stage quantification data, the two most effective antiproliferative Cu(II)–tnz complexes act in early mitosis, similar to colchicine. Although further studies are needed to shed some light on these new developments, it has been reported that DNA damage and ROS can be major factors in inducing mitotic arrest, senescence and mitotic exit.[98–100] Regardless, this shows how versatile these types of compounds can be. Not only can Cu(II)–tnz complexes strongly interact with DNA and generate ROS, inducing cell death, but they can also target enzymes, particularly those with key roles in mitosis. This property makes these metal-based drug candidates therapeutic agents for a wider range of diseases, showing a synergy between the three mechanisms of action discussed in this Perspective article.

Conclusion

Taking into account the wide scope and contribution of several research groups on metal-based drugs, their broad therapeutic applications, and their different mechanisms of action, we are confident that, with clever design, accessible starting materials and non-toxic metal salts, the use of coordination compounds with biologically active ligands could re-emerge as a plausible treatment for many diseases, particularly those labelled as neglected. This, however, must be an internationally coordinated effort and not only the responsibility of those countries currently affected by these diseases. It is important to revisit the use of small molecules for the development of accessible treatments for infectious diseases.

Conflicts of interest

There are no conflicts of interest to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this perspectives.

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