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Biological activity of vanadium pincer complexes†

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This review focuses on the biological activity of vanadium pincer complexes, exploring their applications as activators or inhibitors of enzymatic function, antioxidants, and agents with potential therapeutic effects. Specifically, their capacities as antidiabetic, antibacterial, antiviral, antiparasitic, and anticancer agents are examined in detail. The use of pincer ligands for biological applications has grown enormously in the last ten years, as these ligands can confer to the complexes they form properties such as enhanced stability, improved bioavailability, and greater specificity for pharmacological targets, potentially leading to pharmacological synergy. Additionally, the use of vanadium in the development of pharmacologically active compounds has gained attention due to its role in certain biological processes and its ability to interact with proteins by mimicking phosphorus atoms, making vanadium-containing molecules of significant interest for further study.

Introduction

Vanadium is a transition metal widely distributed in the Earth's crust and located in the first transition series of the periodic table, specifically in group 5.[1] It exhibits a broad range of oxidation states, from −3 to +5, with V(III), V(IV), and V(V) species being the most biologically relevant.[2] Vanadium is considered a trace element with essential roles in both biology and medicine, typically in the form of coordination complexes, where its oxidation state is +5 or +4.[2]

The biological importance of vanadium is underscored by the evolution of several enzyme systems that contain this metal in their active sites.[3] Examples include vanadium-dependent haloperoxidases[4] and vanadium-containing nitrogenases.[5–9] Additionally, vanadium plays an important role in insulin regulation in higher organisms, though the exact mechanisms remain unclear.[10–12]

Over the past three decades, the development of metallodrugs based on coordination compounds has expanded rapidly, incorporating a variety of transition metals and ligands with specific structures.[13–22] Given vanadium's biological relevance,[23,24] it is not surprising that many vanadium-based complexes have been proposed for the treatment of various diseases.[25–33] Vanadium complexes have shown promising activities as anticancer agents[18,26,27,34–39] due to their ability to inhibit biological processes, crucial for cancer cell growth. Furthermore, they have been tested for the treatment of diabetes,[40,41] antibacterial,[35,42,43] antifungal,[43,44] and parasitic diseases (*vide infra*).[45–49]

The biological activity of these complexes can be modulated by selecting the appropriate ligand.[49,50] In this review, we focus on pincer ligands,[51] which provide a robust platform that stabilizes different oxidation states of the metal center and can be easily functionalized and tuned.[52] Pincer ligands are tridentate compounds that coordinate to a metal fragment in a meridional fashion. When a pincer ligand coordinates with a metal center, forms a pincer complex, which is typically stable under thermal and moisture conditions due to the chelation effect. Although these properties have traditionally been valued in the design of catalysts[53–81] and materials,[82–84] recent studies have explored their use in tailoring complexes with anticancer,[85–93] antiparasitic,[94] and antibacterial activities.[45–96]

Thus, in this review, we examine vanadium pincer complexes with biological applications, specifically focusing on their biodistribution, enzyme inhibition and activation capabilities,

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antioxidant properties, and their potential as antidiabetic, antibacterial, antiviral, antiparasitic, and anticancer agents. For comparative purposes, we have also included complexes with tetra- and penta-dentate ligands.

Biodistribution of vanadium

Vanadium was identified as a trace element[96] essential for certain organisms such as ascidians,[97] polychaete worms,[98,99] and Amanita mushrooms.[100,101] However, information regarding its essentiality for mammals and humans remained limited. Vanadium occurred in nature in oxidation states ranging from +2 to +5 and played a role in some biochemical processes in mammals. Importantly, vanadium is not considered carcinogenic, although it has been detected in cancer cells interacting with enzymes.[34] While vanadium compounds proved toxic in high quantities,[102] they have been investigated for therapeutic uses, particularly in treating diseases such as cancer and diabetes (*vide infra*).

Studies in mice provided insights into the absorption, distribution, and excretion of vanadium. Analyses showed that vanadium was primarily absorbed in the bone, followed by the liver, kidneys, and spleen. The extent of vanadium absorption depended on particle size and dosage. Smaller particle sizes and higher doses led to increased vanadium accumulation in the bone and liver, particularly in diabetic mice compared to non-diabetic mice.[96] Additionally, a study with vanadium dioxide derivatives demonstrated differential absorption, with the unabsorbed portion excreted through faeces within 28 days.[96] After treatment cessation, the concentration of accumulated vanadium in organs decreased over 14 days until reaching basal levels in some tissues.

Simple inorganic vanadium salts like sodium metavanadate (Na_2VO_3) and vanadyl sulphate ($VOSO_4$) demonstrated medical potential but exhibited low absorption, higher toxicity, and were primarily excreted through faeces and urine. Given these limitations, researchers developed new vanadium compounds to improve their biological activity.[33]

An example of biodistribution and pharmacokinetics in vanadium-based anticancer agents was performed using vanadocene dichloride (VDC).[103] Studies in mice revealed that VDC levels decreased in the blood and small intestine, while vanadium accumulated in the kidneys and liver. It was also well-established that some vanadium species interacted with various biomolecules, including citrate, lactate, oxalate, and amino acids. Vanadium also bounds to proteins such as transferrin, albumin, and immunoglobulins.[104]

Vanadium pincer complexes were identified in biological systems.[51] A vanadium-pyrroloquinoline quinone complex was found in methanol dehydrogenase and a bacterial dehydrogenase enzyme. Tridentate dioxidovanadium complexes were evaluated for their antidiabetic activity as inhibitors of insulin-related enzymes. These complexes, with promising inhibition of α-amylase and α-glucosidase, suggested potential as insulin enzyme inhibitors.[105]

The biodistribution of vanadium compounds is influenced by factors such as stability, coordination geometry, electric charge, hydrolipophilicity balance, substituents, and redox properties. Vanadium pincer complexes, in particular, were explored for their potential to improve solubility, absorption, and biodistribution in humans. These compounds offered versatile therapeutic potential, with better absorption and targeted intra-/intercellular interactions, which enhanced therapeutic efficacy.[33]

Overall, research on the biodistribution of vanadium has provided fundamental knowledge on the pharmacokinetic and pharmacodynamic parameters of vanadium compounds. However, further studies are needed on this topic to deepen our knowledge of vanadium pincer complexes specifically, and thus the following sections explore their potential in the treatment of diseases such as cancer and diabetes, as well as their interactions at the enzymatic level (*vide infra*).

Vanadium-mediated enzyme activation and inhibition

The exploration of vanadium-mediated enzyme activation and inhibition systems is of vital importance to understand the mechanisms by which the desired pharmacological action occurs.

In 2019, Lu and coworkers reported the synthesis of three vanadium pincer complexes (Fig. 1, complexes **1**–**3**) and their evaluation as inhibitors of lysine-specific demethylase **1** (LSD1),[106] an enzyme implicated in the progression of various diseases, including several types of cancer.

Structural differences in the pincer ligands had a significant impact on the inhibition rates. Hence, complexes **1** and **3** containing an ONS pincer ligand exhibited greater inhibition compared to complex **2** including in its structure an ONO pincer ligand. Complex **1** demonstrated the highest inhibition rate, reaching 70%, followed by complex **3** at 44%, and complex **2** with the lowest inhibition rate of 28%. The presence of a sulfur atom in the pincer ligand (ONS) resulted in a significantly enhanced activity compared to the oxygen derivative (ONO), as observed in the comparison between complexes **2** and **3**. Additionally, the introduction of an extra *tert*-butyl group in the pincer ligand further boosted the activity, with complex 1 being more active than complex **3**.

In contrast, the free pincer ligands showed no significant inhibitory activity against LSD1 under the same conditions, highlighting the crucial role of the vanadium center in the complexes. All compounds were tested under similar conditions using a concentration of 30 μM.

The IC_{50} value of complex **1** was determined to be 19.0 μM, which is lower than that of the reference compound tranylcypromine (TCP) (26.1 μM for TCP *vs.* 19.0 μM for complex **1**). Furthermore, complex **1** was evaluated for its inhibition of monoamine oxidases (MAO), as LSD1 shares a similar amino acid sequence with MAO. Only weak inhibition of MAO-A/B was observed at concentrations of 30 μM and 60 μM, demonstrating that complex **1** is selective for LSD1.

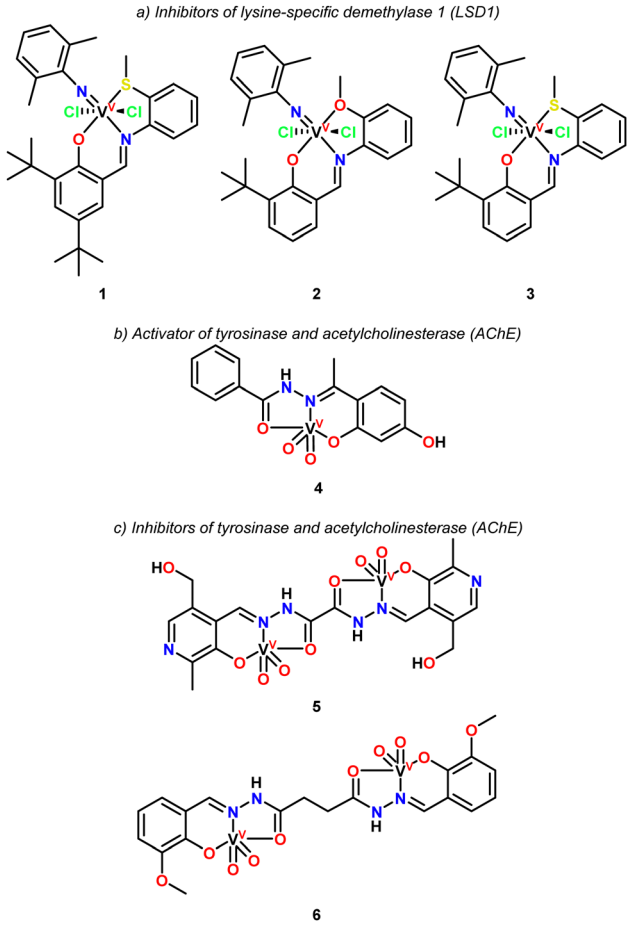

Fig. 1 Vanadium compounds used as: (a) LSD1 inhibitor, (b) tyrosinase and acetylcholinesterase (AChE) activator, and (c) enzyme inhibitors. The counterions of complexes **4–6** were omitted for clarity. Complexes **4** and **6** are triethylammonium derivatives, while complex **5** is a protonated DBU salt.

While some vanadium compounds can act as enzyme inhibitors, the presence of vanadium in organisms is essential for the functionality and activation of numerous proteins and enzymes. In particular, several vanadium complexes, primarily based on vanadate $(VO_4)^{3-}$, have the ability to activate enzymes due to their remarkable chemical similarity to phosphate groups, allowing vanadate to act as a phosphate competitor. Furthermore, vanadate compounds can form stable complexes with target enzymes such as phosphatases, kinases, nucleases, ATPases, glucose-6-phosphate dehydrogenase, and tyrosine kinases, all of which play critical roles in cell regulation processes.[107]

In the specific case of vanadium complexes with pincer-type ligands, with the capacity to act as enzymatic activators, Back and coworkers reported the activation properties of a series of pentacoordinated dioxidovanadium(v) complexes (**4–6**) on tyrosinase and acetylcholinesterase (AChE).[108] Among these, only complex **4** demonstrated ability to activate tyrosinase and AChE by 11.5% and 47%, respectively, while complexes **5** and **6** exhibited inhibitory effects. An *in silico* evaluation of complex **4** suggested that the presence of a hydroxyl group mediates its interaction with the enzymes through hydrophobic and van der Waals forces. Reports on enzyme activation by vanadium complexes are scarce, as most studies focus on their inhibitory effects on specific enzymes.

Antioxidant activity of vanadium pincer complexes

An important part to consider for a better therapeutic treatment is the reduction of oxidative stress, which occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize these harmful molecules or repair the resulting damage. ROS, including free radicals like superoxide and hydroxyl radicals, are highly reactive and can cause significant harm to cellular components such as lipids, proteins, and DNA. This oxidative damage is closely associated with the development and progression of several chronic diseases, including cancer, cardiovascular conditions, neurodegenerative disorders, and diabetes.

To counteract oxidative stress, the body relies on a complex antioxidant defence system consisting of enzymatic antioxidants (such as superoxide dismutase and catalase) and non-enzymatic antioxidants (such as vitamins C and E). However, when oxidative stress overwhelms these natural defences, external antioxidants may be required to restore balance and prevent further cellular damage.

Vanadium compounds have recently gained attention for their potential antioxidant properties.[109] This interest stems from their ability to scavenge free radicals, reduce ROS production, and enhance the activity of endogenous antioxidant enzymes. Studies suggest that vanadium may help mitigate oxidative damage in various biological systems, presenting potential therapeutic applications in conditions where oxidative stress plays a critical role.[110] Fig. 2 shows some representative examples of vanadium pincer complexes with antioxidant activity.

Adam and coworkers reported the synthesis of a series of oxovanadium(iv) complexes with salicylideneamino ligands (complexes **7–11**).[111] The antioxidant activity of these vanadium complexes was evaluated, focusing on their effectiveness in inhibiting superoxide radicals, a major component of ROS. Excessive ROS production can lead to cellular damage when it exceeds the body's antioxidant defense mechanisms, such as superoxide dismutase (SOD). The results indicated that the vanadium complexes effectively inhibit superoxide anion radical formation. Notably, complexes **7**, **8** and **9** exhibited significant SOD-like activity, with inhibition percentages of 87%, 85%, and 91%, respectively, highlighting their strong antioxidant potential.

In contrast, complexes **10** and **11** showed relatively lower inhibition values, at 65% and 59%, respectively, indicating a lesser but still notable antioxidant capacity. Further analysis using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical assay revealed that complex **9** demonstrated substantial antioxidant

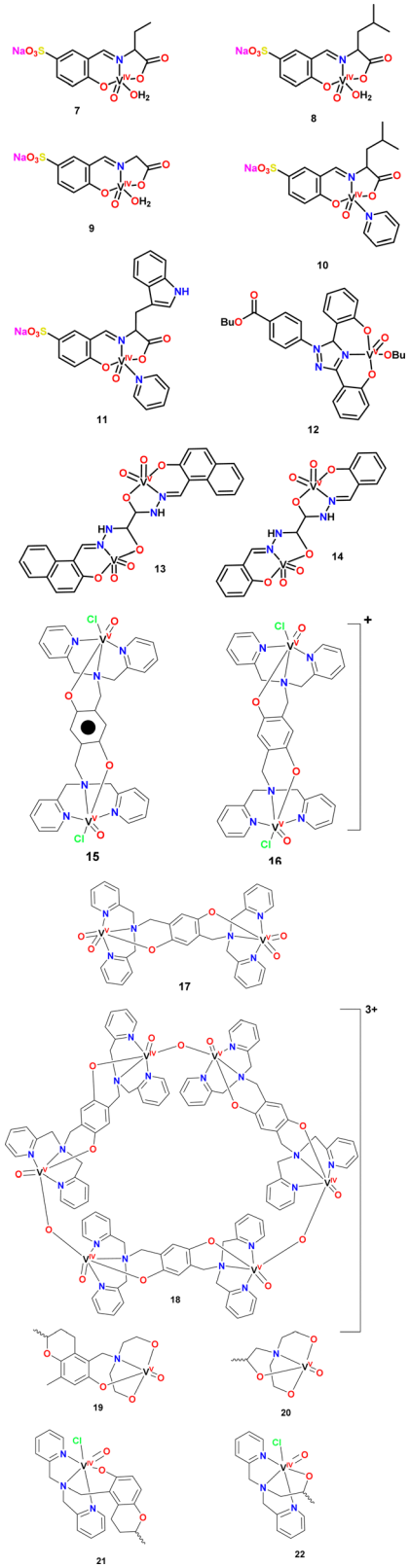

Fig. 2 Vanadium pincer complexes with antioxidant (7–14) and oxidant (15–22) activity.

activity, with a 55% inhibition rate. This value, exceeding the 50% threshold, confirms the superior antioxidant potential of complex **9** compared to the other vanadium pincer complexes analyzed for Adam and coworkers.

The antioxidant efficacy of complex **12** and its deferasirox (DFX) ligand was evaluated through the reduction of DPPH absorbance, with the IC_{50} parameter used for quantification.[112] The analysis showed that complex **12** exhibits significantly higher antioxidant activity compared to the standard antioxidant, butylated hydroxytoluene (BHT). Also, complex **12** demonstrated a remarkable IC_{50} value of 0.1 mM, substantially lower than that of BHT (IC_{50} = 3.6 mM). A lower IC_{50} value signifies greater radical scavenging capacity and enhanced antioxidant activity, highlighting the strong efficacy of complex **12**.[113]

This finding is consistent with previous studies on metal complexes, suggesting that the high activity is likely due to the metal complex and the inherent properties of the metal ion itself. In contrast, the free DFX ligand showed a high IC_{50} value, indicating minimal antioxidant activity.

Shi and coworkers presented the antioxidant activity of the vanadium pincer complexes **13** and **14**,[114] which were evaluated using various assays to assess its ability to mimic SOD activity, scavenge ABTS radicals, and neutralize hydroxyl radicals. The complexes demonstrated notable SOD-like activity, with specific values ranging from 0.24 to 0.89 U mg^{-1}. Remarkably when these complexes were conjugated with bovine serum albumin (BSA) to form hybrid proteins, their SOD activity increased significantly. This enhancement suggests that the protein environment provided by BSA stabilizes the active form of the complexes, enabling more efficient catalysis of superoxide radicals. Moreover, the hybrid proteins exhibit greater antioxidant activity compared to the standalone complexes, likely due to a combination of factors such as stabilization, improved solubility, and potentially altered electronic properties within the protein microenvironment.

From the reviewed works regarding the antioxidant activity of pincer-type vanadium complexes, this property appears to operate through two distinct pathways, (1) enhancing the activity of enzymes that catalyse free radical reduction (particularly SOD), and (2) directly acting as free radical reducing agents, such as DPPH.

Despite this, it is important to remember that vanadium can act as an oxidizing agent and produce reactive species H_2O_2, such is the case described by Stylianou *et al.*[115] for pincer-type complexes derived from iminopyridine hydroquinonate (complexes **15–18**). The authors suggest that O_2 is activated by vanadium metal, in such a way that the coordination of O_2 with metal ions produces an increase in one-electron the reduction potential of O_2 making it kinetically more reactive. Which is resumed in the interaction of O_2 with V(IV) and then the oxidation of hydroquinone to semiquinone giving place to the production of H_2O_2 in the process. Keeping this in mind, we can deduce that vanadium complexes have a protective effect against oxidative stress, and also an oxidizing effect that can be direct or indirect. As exemplified by the complexes studied by Ioanna Hadjiadamouy *et al.*,[116] who prepared vitamin E derivatives (α-tocopherol) that coordinate as pincer-type ligands to vanadium IV and V species. The authors performed the assessment of the radical scavenging

capacity (RSC), to eliminate the DPPH• radical. The study showed that β-tocDEA and β-tocDPA exhibit antioxidant activity almost five times lower than α-tocopherol. Contrary to expectations, where the inhibition of the DPPH radical was the goal, the results indicated that complexes **19–22** seemingly acted as initiators in the formation of radicals rather than inhibiting the DPPH radical in solution. These results, beyond being counterproductive, are of great interest since examination of the cytotoxicity of these complexes, demonstrated great cytotoxic activity in both normal and cancer cells in μM (MRC5, LMS and U2OS cells) and nM concentrations (HeLa and HEK293). The same authors commented that detailed analysis of the mechanism by which the cytotoxic activity proceeds is necessary, but they also suggest that the complexes cause oxidative stress in cancer cell lines.[116]

Having reviewed the enzyme inhibitory and activating activity of vanadium pincer-type complexes, in addition to the possible behaviours they may have with respect to their capacity as oxidizing or antioxidant agents. The use of this type of compounds as antidiabetic, antibacterial, antiviral, antiparasitic and anticancer agents is reviewed in more detail next.

Antidiabetic activity of vanadium pincer complexes

Vanadium compounds have also garnered attention for their insulin-mimetic[117] or insulin-enhancing properties by stimulating glucose uptake in glucose-metabolizing cells, making them ideal candidates for the treatment of diabetes mellitus—a prevalent metabolic disorder characterized by elevated blood glucose levels.[40,41] Several vanadium compounds have shown promising potential for the development of orally administered treatments, which could replace insulin injections, offering a less painful and more cost-effective option.[118] The vanadium complexes studied exhibit various oxidation states and ligand types. In this review, we focus specifically on vanadium pincer complexes, which, although still underexplored as antidiabetic agents, have shown promising properties that could expand their therapeutic use in managing this metabolic disorder.

El-Gammal and coworkers reported the synthesis and potential medicinal application of two new VO(IV) complexes featuring pincer ligands (Fig. 3, complexes **23** and **24**), derived from thiosemicarbazide ligands, for the oral treatment of diabetes.[119] The complexes were tested in diabetic rats, which were administered a water suspension at a dose of 5 mg kg^{-1} body weight per day, orally, for 30 days. The results showed that complex **23** exhibited a stronger hypolipidemic effect, which the authors attributed to the normalization of glucose metabolism, inhibition of lipolysis by vanadyl ions through tyrosine phosphorylation, inhibition of HMG-CoA synthase, and the regulation of lipogenic enzyme gene expression.

Patel and coworkers on the other hand synthesized and studied the antidiabetic potential of a new mixed-ligand oxovanadium(IV) complex with a tridentate Schiff base (Fig. 3, complex **25**).[120] The activity of complex **25** was assessed using an α-glucosidase inhibition assay, with acarbose as the standard.

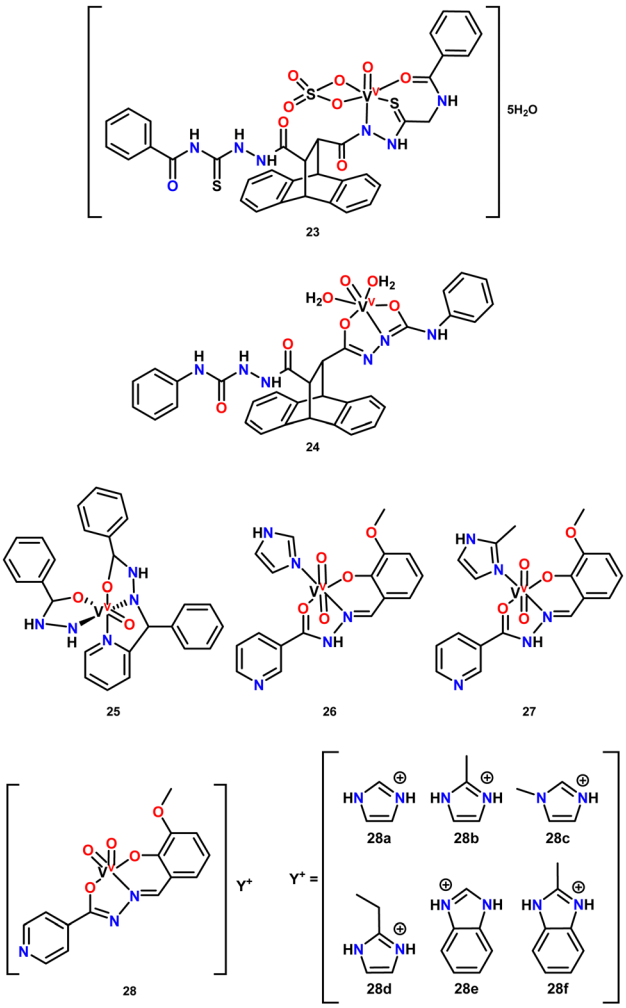

Fig. 3 Vanadium pincer complexes with antidiabetic activity.

The results demonstrated moderate inhibition activity, with percentage inhibition at 200 μM and IC_{50} values of 14.75 μM for the complex compared to 18.59 μM for acarbose. Based on these findings, the authors suggested that this complex could serve as a potential α-glucosidase inhibitor.

In another study by Patel and coworkers, two new dioxidovanadium(V) complexes (**26** and **27**) bearing a tridentate ONO donor nicotinic acid ligand and imidazoles were investigated for their *in vitro* antidiabetic activity.[106] The activity was evaluated through α-amylase and α-glucosidase inhibition assays. Both complexes showed inhibitory effects against α-glucosidase, with IC_{50} values of 153.037 and 32.542 μg mL^{-1} for **26** and **27**, respectively, with **27** demonstrating a potency comparable to the standard, acarbose, suggesting its potential as a potent α-glucosidase inhibitor.

Contrarily, in the α-amylase inhibition assay, complex **26** exhibited the lowest IC_{50} value (23.669 μg mL^{-1}), while complex **27** had the highest IC_{50} value (182.901 μg mL^{-1}), indicating a varied response. Lastly, for β-glucosidase inhibition, **27** displayed the highest IC_{50} value (2021.770 μg mL^{-1}), whereas **26** exhibited a moderate IC_{50} value (282.050 μg mL^{-1}).

These results led the researchers to conclude that both complexes, **23** and **24**, hold promise as potential antidiabetic agents due to their significant inhibition activities, which were concentration-dependent.

More recently, the same research group investigated the *in vitro* antidiabetic activity of new anionic dioxidovanadium(v) complexes with a hydrazone as pincer ligand (**28a–f**) using α-glucosidase, β-glucosidase, and α-amylase inhibition assays.[121] The α-glucosidase inhibition assay revealed that complex **28f** was the most active in the series, with an IC_{50} value of 53.88 μg mL^{-1}. However, in the β-glucosidase inhibition assay, this complex displayed the lowest inhibition (IC_{50} = 843.41 μg mL^{-1}), while complex **28c** was the most potent β-glucosidase inhibitor, with an IC_{50} value of 227.45 μg mL^{-1}.

Additionally, in the α-amylase inhibition study, complex **28d** exhibited the lowest IC_{50} value (82.99 μg mL^{-1}), while the other complexes showed moderate activity compared to the control acarbose, with IC_{50} values ranging from 100 to 270 μg mL^{-1}. The inhibition activity of these complexes was concentration-dependent, consistent with findings from their previous work.

Interestingly, the researchers observed that complexes containing electron repelling moieties exhibited better inhibition activity, leading them to conclude that these vanadium complexes hold promise as potential antidiabetic agents.

Antibacterial and antiviral activity of vanadium pincer complexes

In 2014, Pessoa and coworkers leveraged the well-established biological activity of hydroxyquinolines to prepare six vanadium complexes featuring this naturally occurring ligand (Fig. 4, complexes **29–34**).[122,123] Complex **29** is a dinuclear complex, bridged by two oxygen atoms from the ONO pincer ligands and does not contain a hydroxyquinoline ligand. The other five complexes are mononuclear, including two non-pincer complexes, **32** and **34**. Notably, the pincer ONO ligands are Schiff bases, which are easily synthesized and can be readily tuned for specific applications.

The biological evaluation of complexes **29–34** aimed to assess their antibacterial and anti-tumor activities. The antituberculosis effect of the complexes was specifically studied to determine their antibacterial properties. For this purpose, the Resazurin assay was employed to determine the minimal inhibitory concentration (MIC). A *Mycobacterium tuberculosis* strain was prepared and incubated for 7–10 days, with the vanadium complexes tested at concentrations ranging from 0.25 to 250 μg mL^{-1} in DMSO as solvent. The bacterial cultures and the complexes were mixed in microplates and incubated for 7 days at 37 °C. Resazurin was then added, and the plates were incubated for an additional 24 h. The results demonstrated good antituberculosis activity, with the vanadium complexes showing bacterial growth inhibition like that of commercial antibiotics. Complexes **30**, **32**, **33**, and **34** exhibited MIC values of 1.5 μg mL^{-1}, while the commercial antibiotics

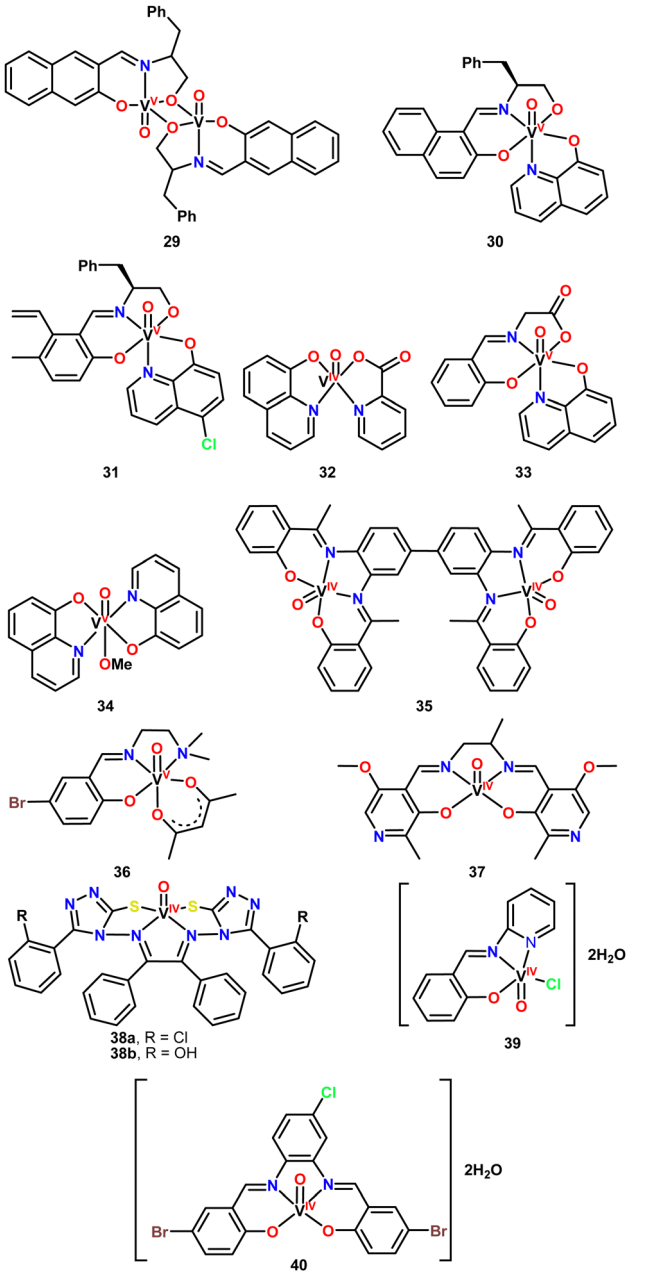

Fig. 4 Vanadium pincer complexes with antibacterial and antiviral activity.

gentamicin and ciprofloxacin had MIC values of 1 μg mL^{-1} and 2–4 μg mL^{-1}, respectively, under similar conditions.

Interestingly, the presence of a chlorine atom in the 8-hydroxyquinoline ligand negatively impacted the activity of complex **31**, which showed no activity against *M. tuberculosis*. Similar results were observed for the dimeric complex **29**. Furthermore, other complexes lacking 8-hydroxyquinoline also demonstrated no activity, indicating that the presence of the hydroxyquinoline ligand is fundamental to the antibacterial efficacy of these complexes.

The essential role of vanadium in the biological activity was confirmed by testing copper analogues of the complexes under similar conditions, which showed no activity. This suggests

that vanadium, the pincer ligand, and 8-hydroxyquinoline work synergistically to produce active species.

Despite the promising activity of the vanadium complexes against some strains, their potency remains lower than that of drugs currently used for tuberculosis treatment, such as isoniazid, which has a MIC of 0.03 μg mL^{-1}. Further structural modifications of the complexes could enhance their activity and elucidating the mechanism of action may provide insights for designing more effective vanadium-based complexes.

Rajavel and coworkers reported the synthesis of a new tetradentate Schiff base ligand and its dinuclear metal complexes.[124] They described the vanadium derivative (Fig. 4, complex **35**), along with complexes of other transition metals such as copper, zinc, and nickel. The Schiff base ligand and its complexes were obtained in good yields and thoroughly characterized using various spectroscopic techniques.

The biological activity of the complexes was tested as bacterial growth inhibitors against Gram-negative *Klebsiella pneumoniae* and Gram-positive Staphylococcus pyogenes strains using the disk agar diffusion method. The complexes and the free ligand were evaluated at concentrations of 50, 100, and 150 μg mL^{-1}, with tetracycline and chloramphenicol serving as reference drugs for the Gram-positive and Gram-negative strains, respectively. The complexes exhibited higher antibacterial activity compared to the free ligand, with a clear concentration-dependent effect, as indicated by the measured inhibition zones.

Interestingly, the vanadium complex demonstrated better performance against the Gram-negative strain compared to the Gram-positive strain, which is known for its thicker lipopolysaccharide cell wall. This behaviour aligns with chelation theory, which suggests that the inclusion of the metal increases the lipophilicity of the complex, facilitating its penetration through the bacterial cell wall. However, despite the increased activity of the complexes, their efficacy was still lower than that of the reference drugs.

Khalaji and Grivani synthesized a Schiff base pincer ligand and its vanadium(IV) complex (Fig. 4, complex **36**).[125] The pincer ligand coordinates to oxovanadium through the imine nitrogen, phenolic oxygen, and amino nitrogen in the equatorial plane, with two oxygen atoms from the acetylacetone ligand completing the metal center's coordination sphere.

The antimicrobial activity of complex **36** and its free pincer ligand was evaluated using the disk agar diffusion method. The activity was tested against Gram-negative strains (*Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella enteritidis*) and Gram-positive strains (*Staphylococcus aureus* and *Bacillus cereus*). For this experiment, a solution with a concentration of 100 mg mL^{-1} of each compound was prepared and applied to bacterial cultures, which were then incubated for 24 h at 37 °C.

Contrary to expectations, the free ligand demonstrated better antibacterial activity than complex **36**, with inhibition zones of 45.3 mm compared to 20.3 mm, respectively. Additionally, no significant differences in activity were observed between Gram-positive and Gram-negative strains.

In 2021, Azizi and coworkers published a study on a vanadium complex featuring a tetradentate Schiff base with N, N, O, O donor atoms.[126] The structure of complex **37** exhibits a square pyramidal geometry, where the vanadium is coordinated by two nitrogen and two oxygen atoms from the ligand, with an oxo group (V═O) occupying the apical position (Fig. 4).

The biological activity of complex **37** was evaluated through antibacterial screening using the determination of MIC *via* the dilution method and minimal bactericidal concentration (MBC) in agar medium. Serial dilutions of the complex in the micromolar range were prepared to assess its ability to inhibit bacterial growth in Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) strains. The complex, controls, and reference drug (tetracycline) were incubated with bacterial cultures for 24 h at 37 °C, after which the MIC and MBC values were determined.

Complex **37** did not exhibit antibacterial activity against *E. coli*. However, slight bacterial growth inhibition was observed for *P. aeruginosa* and *S. aureus*, though the complex was less active than tetracycline. The likely reason for the limited activity is that the lipophilic character of complex **37** may not have been sufficient to facilitate strong interactions with the bacterial cell walls.

In 2021, Sharma and coworkers reported the synthesis of two triazole ligands and their corresponding oxovanadium complexes (Fig. 4, complexes **38a–b**).[127] The Schiff base ligands contain two triazole units, with either a hydroxyl or methyl substituent on the adjacent aromatic ring. These ligands coordinate the oxovanadium moiety in a tetradentate fashion *via* nitrogen and sulfur atoms, resulting in a square pyramidal geometry. Triazole moieties are commonly found in biologically active compounds,[128–134] which prompted the researchers to evaluate the antibacterial activity of both the free ligands and their vanadium complexes.

The antibacterial activity was assessed using the agar diffusion method, targeting Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*. The compounds were tested at concentrations ranging from 4 mg mL^{-1} to 0.05 mg mL^{-1} in DMSO, with neomycin serving as the reference drug.

The results showed that the antibacterial activity of the free ligands and their vanadium complexes was comparable, with inhibition zones for both Gram-negative and Gram-positive strains being similar. This is notable, as Gram-positive bacteria typically show greater susceptibility to antibiotics due to their thinner cell wall. However, the observed activities were lower than those of neomycin.

Recently, Abdel-Rahman and coworkers synthesized an ONN pincer ligand and its corresponding vanadium complex (Fig. 4, complex **39**).[135] The biological activity of these compounds was investigated through antibacterial, cytotoxic, and antioxidant assays, as well as molecular docking studies. The antibacterial activity was assessed using the disc diffusion and microdilution methods. Solutions of the free ligand and the vanadium complex were prepared in DMSO at a final concentration of 20 μM and tested against four bacterial strains: two Gram-negative (*Escherichia coli*, *Klebsiella pneumoniae*) and two Gram-positive (*Staphylococcus aureus*, *Streptococcus mutans*). Gentamicin and ampicillin were used as reference drugs for Gram-negative and

Gram-positive bacteria, respectively. After 24 h of incubation, the inhibition zones were measured.

The free ligand exhibited lower antibacterial activity compared to complex **39**. Interestingly, complex **39** showed similar activity to its cobalt and chromium analogs, although it was less effective than the nickel derivative. It is important to note that the concentration used in this assay was lower than those reported in other studies, making direct comparisons with emerging compounds challenging. The authors suggest that the observed results are consistent with previous studies, where the enhanced activity of metal complexes is attributed to the chelation theory. They also propose that the azomethine group plays a crucial role in interacting with the bacterial cell wall through hydrogen bonding.

Abdel-Rahman and coworkers synthesized a tetracoordinated Schiff base ligand and its corresponding oxovanadium complex (Fig. 4, complex **40**).[136] To investigate the biological activity of the ligand and complex **40**, the authors conducted antibacterial, antifungal, antioxidant, cytotoxic, and DNA binding assays. The antibacterial tests were performed using the agar disc diffusion method and MIC determination by dilution. The compounds were tested at concentrations of 15 and 30 μM against Gram-negative *Serratia marcescens* and *Escherichia coli*, as well as Gram-positive *Micrococcus luteus*, with ofloxacin serving as the positive control. The results were reported as an activity index (%), which compared the inhibition zones of the compounds to those of the reference drug.

Consistent with previous studies, complex **40** exhibited greater antibacterial activity than the free ligand, with the highest efficacy observed against *Micrococcus luteus*. The inhibition zone for this strain was similar to that of ofloxacin and larger than those observed for other metal complexes, such as zinc.

Antiparasitic activity of vanadium pincer compounds

The antiparasitic activity of vanadium complexes has been extensively studied in recent years, targeting various species of parasites, including *Entamoeba histolytica*, *Leishmania* species, and *Trypanosoma*.[45,108,137] Among the earliest studies of vanadium complexes with antiparasitic properties in the 21st century, their action against *Entamoeba histolytica*, *Leishmania amazonensis*, *Leishmania donovani*, and *Trypanosoma cruzi* has been reported.[138–141]

The use of coordination or organometallic vanadium compounds for the treatment of parasitic diseases has emerged as a promising alternative, showing encouraging results. However, a review of recent literature indicates that, over the past decade, vanadium compounds featuring pincer-type ligands have been reported only sparingly.[142–144] Fig. 5 presents some representative examples. Despite their limited number, the compounds that have been studied exhibit intriguing properties, maintaining them as a focal point of ongoing research.

In 2014, Machado and coworkers reported the synthesis of new vanadium-based agents targeting *Trypanosoma cruzi*, using

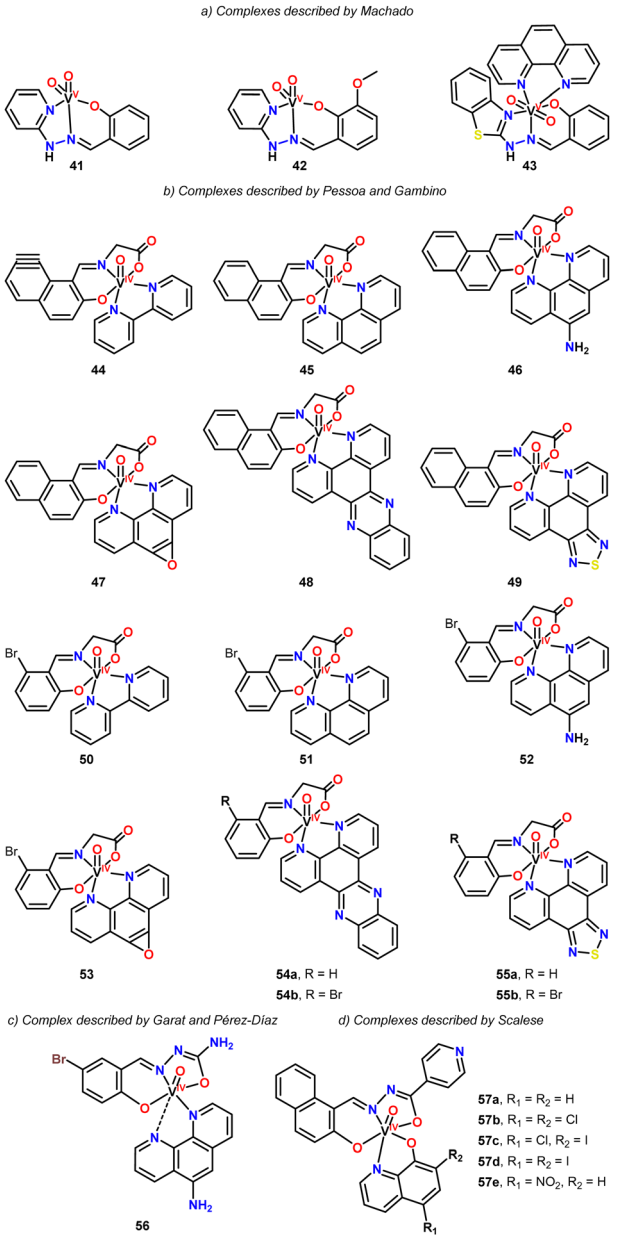

Fig. 5 Previously described vanadium pincer complexes with antiparasitic activity (a–d).

NNO pincer ligands (Fig. 5, complexes **41–43**).[50] These complexes were evaluated against the epimastigote form of the *Trypanosoma cruzi* strain Dm28c. Complexes **41** and **42** exhibited lower activity compared to their respective free pincer ligands. However, the incorporation of a benzothiazole fragment into the pincer ligand along with 1,10-phenanthroline produced a more potent compound. Complex **43**, in particular, demonstrated a 10-fold reduction in IC_{50} compared to the free ligands, achieving values similar to those of the reference drug, Nifurtimox. This enhanced activity is likely due to the interaction between DNA and the 1,10-phenanthroline ligand, as it is well known that the planarity of this ligand facilitates such interactions.

In 2017, Pessoa and Gambino investigated the anti-*Trypanosoma cruzi* activity of 14 vanadium complexes featuring ONO pincer ligands and N^N chelates (Fig. 5, complexes **44–55**).[38,145] The complexes were evaluated against the epimastigote form of the *T. cruzi* strain CL Brener, and their selectivity toward the parasite was assessed using VERO cells as a mammalian model. The complexes generally exhibited IC_{50} values in the low micromolar range (1.4 to 4.7 μM), which were comparable to or even lower than the activity of the reference drug, Nifurtimox (2.76 ± 0.19 μM). Additionally, the complexes demonstrated moderate to good selectivity toward the parasite, with selectivity indices (SI) ranging from 7 to 58.

The activity of the vanadium complexes was found to be influenced by the N^N chelate ligands. Complexes containing the bipyridine ligand were the least active, whereas those with the dipyridophenazine ligand exhibited the highest activity. The authors further concluded that these compounds induce apoptosis and cause alterations in the mitochondrial membrane potential in *T. cruzi*, suggesting this as the mechanism of cell death.

In 2020, Garat and Pérez-Díaz synthesized a pincer vanadium complex featuring 5-bromosalicylaldehyde semicarbazone as the pincer ligand, along with 1,10-phenanthrolin-5-amine as the chelating N^N ligand (Fig. 5, complex **56**).[146] The complex exhibited an IC_{50} value of 3.76 ± 0.08 μM in a proliferation assay against *T. cruzi*, a value comparable to that of the reference drug nifurtimox (2.8 ± 0.2 μM). Regarding the mechanism of parasite growth inhibition, the study determined that neither apoptosis nor necrosis were involved; instead, the complex induced a growth arrest phenomenon in the parasite.

In 2021, Scalese and coworkers synthesized five vanadium ONO-pincer complexes featuring 8-hydroxyquinoline derivatives (Fig. 5, complexes **57a–e**).[147] These complexes exhibited activity against both the epimastigote and trypomastigote forms of *T. cruzi* (CL Brener strain). The IC_{50} values for epimastigotes ranged from 3.45 to 7.70 μM, while for trypomastigotes, the IC_{50} values were comparable to those of Nifurtimox (0.29–3.02 μM). Notably, trypomastigotes were more sensitive to the vanadium complexes, showing IC_{50} values that were seven to 70 times lower than those of the reference drug. Additionally, the selectivity of the complexes towards the parasite increased significantly when halogen substituents were included in the hydroxyquinoline moiety.

Anticancer activity of vanadium pincer complexes

Over the past decade, research into the anticancer activity of vanadium compounds has intensified in response to the urgent need for new therapeutic agents to combat cancer. In this context, vanadium complexes with pincer-type ligands have gained attention. Many of these pincer-type vanadium compounds have been tested against various cancer cell lines, including human ovarian carcinoma cells (MCF-7),[50,106,148–152]

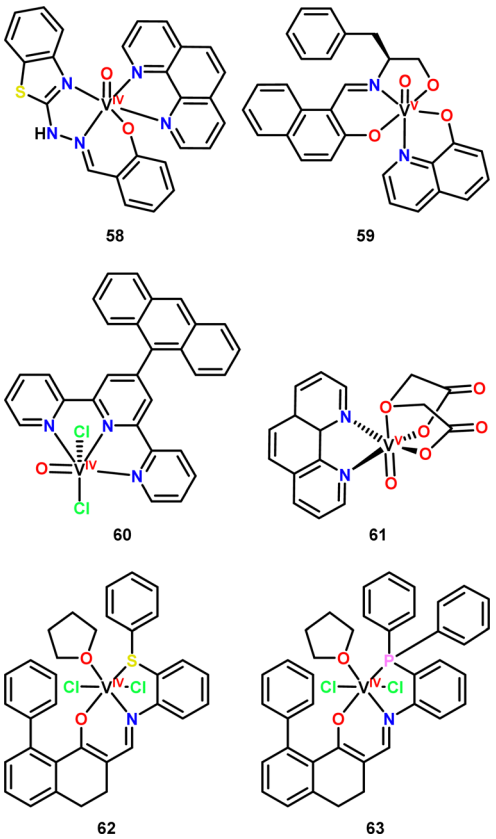

Fig. 6 Example of vanadium complexes with anticancer activity.

breast adenocarcinoma cells (A2780[38,50,122,148,153] and A2780 cisR[122]), prostate cancer cells (PC3),[38,50] cervical cancer cells (HeLa,[154–157] SiHa,[154] and C33A[154]), hepatocellular carcinoma cells (HEP G2),[107,158–161] lung carcinoma cells (A549),[151,158] colorectal adenocarcinoma cells (HT-29,[157] SW480,[153,158] and SW620[158]), epidermal carcinoma cells (KB-3-1),[153] epithelial human breast cancer cells (MDAMB231),[38] human osteosarcoma cells (MG-63 and HOS),[162] human gastric cancer cells (MGC803),[163] human esophageal cancer cells (EC109), colon carcinoma cells (HCT-116),[150] and ovary cells (CHO-K1).[159]

Vanadium pincer-type compounds commonly feature heteroatoms such as N, O, P, and S in various triad arrangements to coordinate with the metal centre. The most prevalent configurations include NNN, NNO, ONO, OOO, ONP, and ONS, as illustrated in Fig. 6,[50,122,162,163] highlighting the diverse possibilities available for the synthesis and exploration of these compounds in anticancer applications.

Some authors have highlighted the increase in anticancer activity of compounds when moving from the use of the ligands alone to the use of vanadium complexes,[150,151,155] even surpassing the cytotoxic capacity of cisplatin.[151] It is likely that several ligands exhibit little or no cytotoxic activity in such an way that many authors omit the comparison with their corresponding complexes, only highlighting the cytotoxic activity of the vanadium compounds. Thus, the selectivity or stability of the complex is directly dependant on the ligand used. And it is common to observe the use of co-ligands such as 1,10-phenantholine

(As observed in complexes **58** and **61**[50,162]) to increase the stability of the complexes, as shown in a study by Szklarzewics *et al.*[160] where they state that this type of co-ligands increases the lifetime of the complex by slowing down the oxidation process.

Conclusions

The use of vanadium complexes for pharmacological applications has seen a significant rise in recent years, particularly in addressing diseases such as cancer, diabetes, parasitic infections, and bacterial infections. Despite this progress, the number of studies focusing specifically on vanadium compounds with tridentate pincer-type ligands remains limited. Fortunately, there is a growing trend in exploring these compounds due to the unique properties they offer, particularly in terms of stability, selectivity, and tunability. Vanadium pincer complexes are distinguished by their strong chemical and biological properties, making them promising candidates for a variety of therapeutic applications. Pincer ligands, which commonly contain donor atoms such as nitrogen, oxygen, sulfur, or phosphorus, form highly stable chelating structures. This stability is crucial for ensuring the vanadium complexes remain intact in harsh biological environments, allowing them to exert their pharmacological effects. Additionally, the ease with which pincer ligands can be functionalized provides flexibility in tailoring these complexes for specific biological targets.

One notable aspect of vanadium pincer complexes is their multifunctionality. Several of these complexes have demonstrated efficacy in multiple therapeutic areas, such as showing both antiviral and antibacterial activity. This multifunctionality makes these complexes particularly attractive for further research, as they offer the potential for developing multi-targeted therapies. The ability to address multiple pathways or diseases with a single compound is increasingly important in precision medicine and could lead to more effective treatment strategies.

Vanadium's ability to exist in multiple oxidation states (III, IV, V) further enhances the potential of these pincer complexes in pharmacology. This redox flexibility allows vanadium to participate in a wide range of biological processes, including enzymatic regulation and modulation of oxidative stress. This is particularly relevant for diseases like cancer and diabetes, where oxidative stress and signaling dysregulation are key drivers of disease progression. The ability of vanadium pincer complexes to interact with these processes makes them valuable candidates for therapeutic intervention.

Despite the promising properties of vanadium pincer complexes, challenges remain in improving their specificity for biological targets. The use of molecular modeling, structure–activity relationship (SAR) studies, and high-throughput screening will likely play a critical role in addressing this issue. These tools will enable researchers to better understand how vanadium complexes interact with their biological targets, facilitating the design of more selective and potent compounds. Additionally, minimizing the toxicity of vanadium compounds is essential for their clinical use. Careful selection of ligands that enhance bioavailability and reduce the overall toxicity of the complexes will be important in moving these compounds forward in the drug development pipeline.

Hence, vanadium pincer complexes represent a valuable class of compounds for therapeutic development, offering stability, versatility, and multifunctionality. Bidentate N^N ligands further enhance their potential by providing a flexible framework for optimizing biological activity. While more research is needed to fully explore their potential, particularly in improving selectivity and reducing toxicity, vanadium pincer complexes hold great promise for the future of pharmacology, particularly in the treatment of complex diseases such as cancer, diabetes, and infections.

It is important to note that there are currently no drugs including vanadium compounds as active ingredients. It is possible that in the future drugs may be developed that include vanadium pincer-type complexes as active ingredients, emphasizing the relevance of pincer-type ligands to provide greater stability to the complexes they form without inhibiting their biological activity. To do this, it would be necessary to further continue the study of this type of molecules, both in terms of their biological activity and what involves the absorption and elimination of these compounds from the body, in order to shed further light into pharmacokinetic and pharmacodynamic studies.

Author contributions

Writing – original draft preparation, L. H. D.-R., V. R.-M., M. E. M.-N., A. A.-M., J. R. P.-V., J. A. C.-N., M. A. M.-T., H. V. and D. M.-M.; execution and drawing, L. H. D.-R., V. R.-M., M. E. M.-N., A. A.-M., J. R. P.-V., J. A. C.-N., M. A. M.-T., H. V. and D. M.-M.;. writing – review and editing, L. H. D.-R., H. V. and D. M.-M.; visualization and supervision, L. H. D.-R., H. V. and D. M.-M.; funding acquisition, D. M.-M. and H. V. All authors have read and agreed to the published version of the manuscript.

Data availability

The data supporting this article has been included as part of the ESI.†

Conflicts of interest

The authors declare no conflicts of interest.

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