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Review

Pincer Complexes Derived from Tridentate Schiff Bases for Their Use as Antimicrobial Metallopharmaceuticals

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Abstract: Within the current challenges in medicinal chemistry, the development of new and better therapeutic agents effective against infectious diseases produced by bacteria, fungi, viruses, and parasites stands out. With chemotherapy as one of the main strategies against these diseases focusing on the administration of organic and inorganic drugs, the latter is generally based on the synergistic effect produced by the formation of metal complexes with biologically active organic compounds. In this sense, Schiff bases (SBs) represent and ideal ligand scaffold since they have demonstrated a broad spectrum of antitumor, antiviral, antimicrobial, and anti-inflammatory activities, among others. In addition, SBs are synthesized in an easy manner from one-step condensation reactions, being thus suitable for facile structural modifications, having the imine group as a coordination point found in most of their metal complexes, and promoting chelation when other donor atoms are three, four, or five bonds apart. However, despite the wide variety of metal complexes found in the literature using this type of ligands, only a handful of them include on their structures tridentate SBs ligands and their biological evaluation has been explored. Hence, this review summarizes the most important antimicrobial activity results reported this far for pincer-type complexes (main group and d-block) derived from SBs tridentate ligands.

Keywords: metallopharmaceuticals; Schiff bases; tridentate ligands; pincer ligands; antimicrobial activity; metal-based drugs

1. Introduction

Currently, many drugs used for the treatment of various diseases caused by bacteria, fungi or parasitic agents (Appendix A) exhibit adverse effects affecting the health of patients, the most common being: hypersensitivity reactions (allergies), neurological effects, respiratory, gastrointestinal, hepatic, haematological, and renal effects [1,2]. To this situation, we have to add the resistance developed by pathogenic microorganisms and the

high toxicity that some of the active components in drugs have towards specific cells [3]. Due to this, besides the extensive research focused on the development of biologically active organic compounds, metal complexes in the realm of bioinorganic chemistry have shown interesting physicochemical properties useful not only in the preparation of new materials, but also for their potential medicinal applications. For instance, one of the great contributions of coordination chemistry to medicinal chemistry was the discovery of cisplatin (*cis*-diaminodichloroplatin(II)) and its derivatives that have shown a good anticancer effect, which has led to arouse interest in the development of new molecules based on metals with biological activity, thus building a bridge between inorganic and medicinal chemistry [4]. Other successful examples are the ^{99m}Tc and Gd^{3+} complexes that have been used in scintigraphy and magnetic resonance imaging, respectively, while complexes based on platinum and ruthenium represent some of the most used metallodrugs for cancer treatments. In fact, historically, one of the first therapeutic metallopharmaceuticals used for the treatment of syphilis was salvarsan, an arsenic-based antimicrobial agent developed by Paul Ehrlich, which was used since its discovery at the beginning of the 20th century and until it was replaced by penicillin after World War II. Another relevant example can be found in silver complexes widely used to treat infections, as well as topical sulphonamide ointments, such as silver sulfadiazine, which are applied as cream formulations or as aqueous solutions (1% silver salt) to prevent and treat infections resulting from second- or third-degree burns, decreasing bacterial colonization [5]. As mentioned above, the resistance of some microorganisms to conventional drugs has caused an accelerated development of metallopharmaceuticals that include the therapeutic agent as ligand. A clear example of this is the ferroquine, a metallodrug combining ferrocene with the well-known chloroquine (antimalarial drug), a complex that makes it possible to overcome the resistance to chloroquine developed by the pathogen *P. falciparum* [4]. As expected, several studies involving the various proposed potential mechanisms of action in the antiparasitic activity of coordination complexes have been performed, including the formation of hemozoin as the main target for the action of antimalarial drugs [6,7]. Besides the examples illustrated above, there are many others that include metals such as iron, gold, ruthenium, and rhodium exhibiting very interesting properties and biological activities [8,9], and more recently a lot of attention has been placed on the development of complexes including multidentate ligands (for stability purposes) coordinated to metals(III), as is the case for heterometallic species of Rh(III) and Ir(III) [10].

1.1. General Characteristics of Metallopharmaceuticals

The development of new metal complexes with different molecular architectures continues to be an important chemotherapeutic tool that has notably improved patient survival rates around the world [11,12]. Among the new drugs that are being developed for the control of different diseases, great attention has been placed on drugs containing metals [13,14], since metal centres of positively charged complexes favour the binding to negatively charged biomolecules, including proteins and nucleic acids that act as ligands in the presence of metal ions [15]. A characteristic generally found in investigations of biological applications of metal complexes is the synergistic effect between the metal and the organic ligand that accompanies it, as even in many treatments with triple or quadruple therapy, the presence of a metalopharmaceutical is necessary to increase drug efficacy [4].

In the design of metallopharmaceuticals, it is important to consider the organic compounds to be used as ligands, such as the biological activity of the molecules, their uptake, trajectory, function, and metal excretion in biological systems, the results of which can be determined by metallomic studies. Here, the species of interest for metallomics are complexes of trace elements and their compounds with endogenous or bio-induced biomolecules, such as organic acids, proteins, sugars, or DNA fragments [16]. Seven of the twenty-one amino acids, considered the building blocks of peptides and proteins, have donor atoms such as nitrogen, oxygen, or sulphur in their side chains, providing the opportunity to interact or bind to a metalopharmaceutical. Another advantage of metal-based drugs is that thanks

to the versatility of metal ions in the formation of different hybrid orbitals, it is possible to play with the geometries of their complexes to obtain more convenient structures to be a perfect fit to target biomolecules, a fact that can be achieved by modifying the type of ligand to be coordinated to the metal. Many ligands with the aforementioned characteristics (biologically active and with metal ion binding sites) have been studied in medicinal organic chemistry, so there is a wide variety of potential candidates to be used in the design of metallopharmaceuticals. In the case of antibiotics, due to their activity/concentration relationship, we find organic compounds classified into the following categories: β-lactams, glycopeptides, aminoglycosides, fluoroquinolones, macrolides, tetracyclines, and chloramphenicol. They can also be found classified by type of structure, some of them being peptides, carbapenems, cephalosporins, penicillins, quinolones, sulphonamides, and azoles. All of these are of great interest in medicinal chemistry, ultimately seeking to synthesize, based on structural variations, derivatives able to exhibit good antibacterial activity overcoming the phenomenon of resistance. This strategy rendering several metal complexes exhibits enhanced antibacterial and antiparasitic properties with low toxicities [4,17–19].

1.2. Importance of Multidenticity of Ligands

Currently, there is a great diversity of biological studies with metal complexes of almost the entire transition series and the main group, including both coordination and organometallic complexes, among which complexes with bidentate, tridentate, and tetradentate ligands stand out, conferring greater stability to these molecules in biological systems and allowing them to be selective. The variety of multidentate ligands has led to cataloguing them into different types according to their conformations and structures. For example, we find "pincer" tridentate ligands, which offer three binding sites to metal centres; these sites are generally separated from each other by two atoms. As a result of the chelate effect, pincer ligands form very stable complexes with transition metals, preventing decomposition in a physiological environment. Complexes containing this type of ligands have turned out to be increasingly interesting for biological applications, which is why the number of related studies has increased in recent years. CNS-Pt(II)-type pincer complexes derived from iminophosphorans have shown antitumor activity, with IC_{50} values lower than cisplatin [20], while complexes of the NCN-Pd(II) type derived from peptides, the NNN-Ni(II) type derived from bis-pyrazolyl-*s*-triazines, and the SNN-Cu(II) type derived from thiosemicarbazones, have shown antimicrobial activity [21–23]. Figure 1 presents structures of reported pincer complexes, highlighting the presence of biologically active functional groups, for example, imines, pyrimidines, or imidazoles derivatives with a known antimicrobial activity, even giving place to bimetallic structures of gold and palladium that have shown good cytotoxic activities [24]. In this sense, Schiff bases (SBs) are among the ligands with the capacity to have multiple coordination sites. SBs have an azomethine unit (-HC=N-) with a lone pair of electrons on the nitrogen atom that provide a binding site to metal ions. In addition to bonding via the nitrogen, SBs can connect to metals through other heteroatoms such as oxygen and/or sulphur.

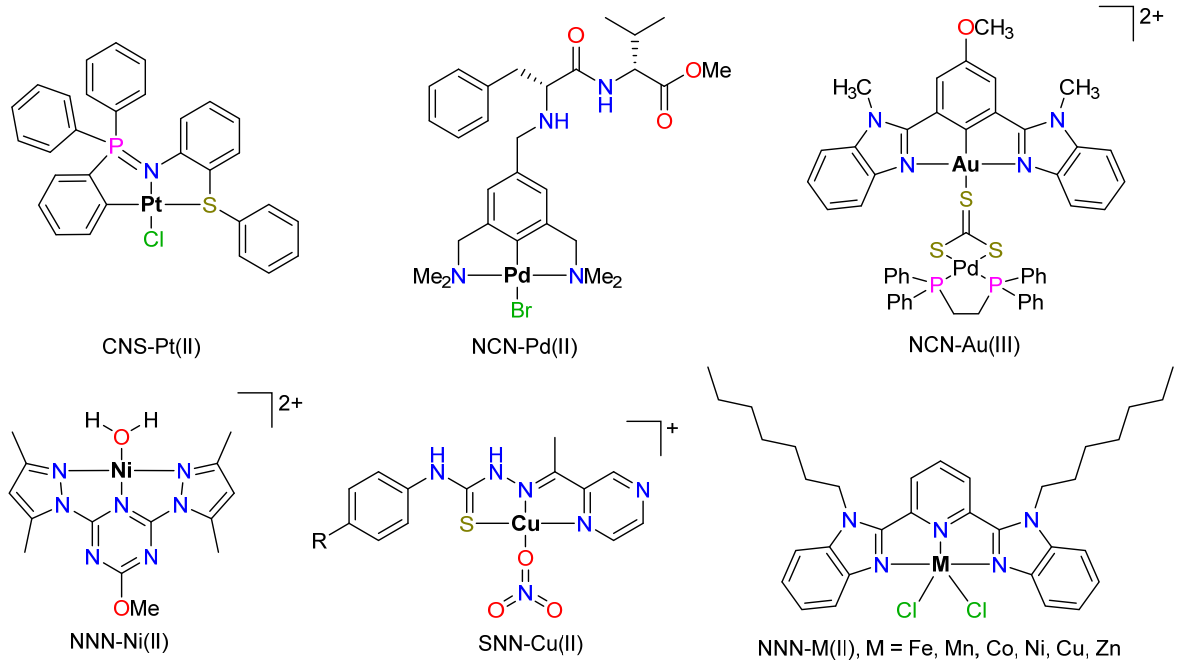


Figure 1. Pincer complexes with tridentate ligands that have shown biological activity.

2. General Aspects of Schiff Bases

The azomethine group is the common structural feature of SBs, where the substituents can be alkyl, cycloalkyl, aryl, or heterocyclic groups. The carbon atom of the C=N_{imine} bond is prone to nucleophilic addition, while the nitrogen atom possesses a highly reactive free electron pair that can form stable complexes with metal ions.

The real interest in compounds derived from SBs is due to the ease of their preparation and the possibility of modifying their structure with different substituents, given the existing diversity of amines and compounds with carbonyl groups. Therefore, SBs are among the most widely used organic compounds, showing a wide range of applications as intermediates in organic synthesis [25], chemosensors, and polymeric stabilizers [26], in the food [27], dye, and pigment industry [28], as well as as catalysts [29] and, in recent years, for their recognized biological properties [30].

2.1. Biological Importance of Schiff Bases

The presence of a single pair of electrons in the nitrogen of the azomethine group has chemical and biological importance since, by having sp^2 hybridization, it interferes in normal cellular processes through hydrogen bonds with the active centres of the cellular constituents. Furthermore, in biological systems, the azomethine nitrogen of SBs provides a binding site for metal ions to bind with various biomolecules such as proteins and amino acids which demonstrates its biological capacity.

Among the properties exhibited by SBs is autofluorescence, which is attributed to the $n \rightarrow \pi^*$ transition of the C=N_{imine} bond. This property is beneficial for monitoring the efficacy of pharmacological carriers in vivo, avoiding the use of fluorochromes. Furthermore, the bond present in the SBs is a dynamic covalent bond that presents reversibility against external factors such as pH. The stability of these bonds decreases as the pH decreases, a useful characteristic at the time of drug release through a specific pH [31]. Another aspect of the biological importance of SBs is their presence in biological systems. Different classes of proteins have been discussed in which SBs play an important role in the function and catalytic mechanisms related to retinylidene proteins, pyridoxal phosphate (PLP)-dependent enzymes, and aldolases, which catalyse aldol cleavage during glycolysis [32].

On the other hand, various investigations have shown that compounds derived from SBs present pharmacological activity as anti-inflammatory, analgesic, antimicrobial, anti-

convulsant, antitubercular, anticancer, antioxidant, and anthelmintic agents [33]. However, the precise mechanisms of action of SBs are not yet fully defined and therefore continue to be investigated. Some bioactive imine-containing molecules are commercially available, and these can be of natural, synthetic, or semi-synthetic origin [34]. Da Silva et al. highlighted the antimalarial activity exhibited by ancistrocladidine, a secondary metabolite produced by plants with the capacity to inhibit the growth of *P. falciparum* strains K1 and 3D7 at minimal inhibitory concentrations (MIC) < 1.0 $\mu g \cdot mL^{-1}$ [35,36]. This review also highlights the antibacterial activity of the compound N-(salicylidene)-2-hydroxyaniline, which is active against *M. tuberculosis* H37Rv (MIC = 8 µg/mL) [35,37]. Other promising compounds that contain imines are semi-synthetics molecules (or derived from natural sources), since chitosan-derived SBs have been shown to have an antifungal activity by inhibiting the growth of *B. cinerea* and *C. lagenarium* in percentages between 26 and 38%.

2.2. Schiff Bases as Tridentate Ligands

Due to their highly modular synthesis that makes it possible to control the nature of donor atoms, denticity, and chelating capacity, as well as their electronic and steric properties, SBs are considered "privileged ligands". The binding to the metal centre depends to a great extent on the nature of the donor atoms that act as coordination sites, that is, on the presence of donor heteroatoms, which generally appear in their structures as nitrogen and oxygen molecules. In this way, it is possible to obtain highly stable complexes with metal ions of different oxidation states, modulating their pharmacological action [38,39].

During the last decade, metal complexes with SBs that have exhibited electroluminescent, fluorescent, as well as non-linear optical and biological properties such as antiviral, antibacterial, antiapoptotic, antifungal, anti-inflammatory and as urease inhibitors have been developed. They have also generated great interest for their applications as polymeric materials, sensors, organic photovoltaic materials, energy materials, nuclear materials in medicine, and as components of pharmaceutically active products. In the literature, there are different studies with SBs used as chelate ligands with the ability to form stable complexes, as reported in the work of Alterhoni et al. who synthesized metal complexes of Co(II), Pd(II), Cu(II), and Zn(II) with SBs (Figure 2) and evaluated their biological activity on six bacterial and three fungal strains, finding that the MIC on *S. aureus* was lower compared to the ligand when metal ions were present (36 µg/mL) [40].

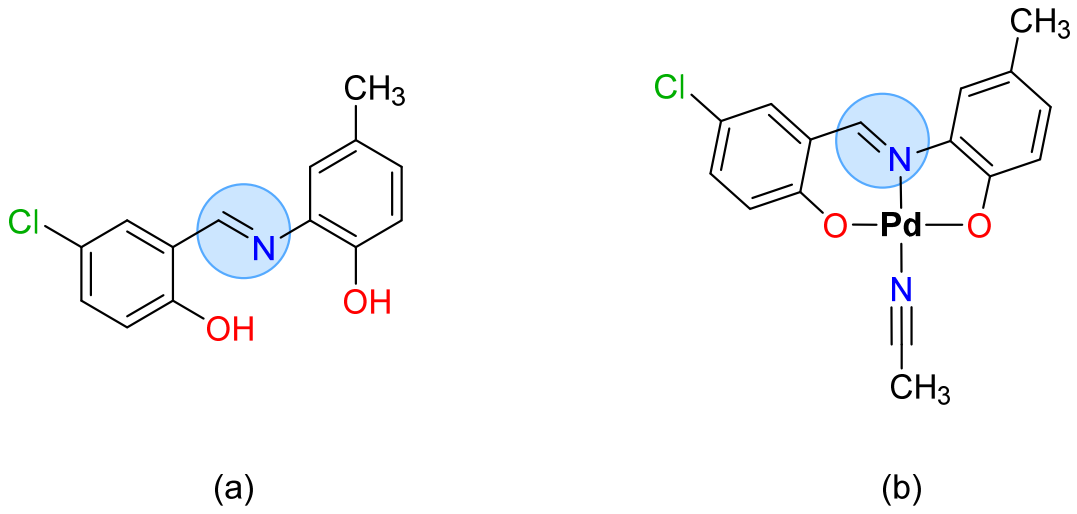


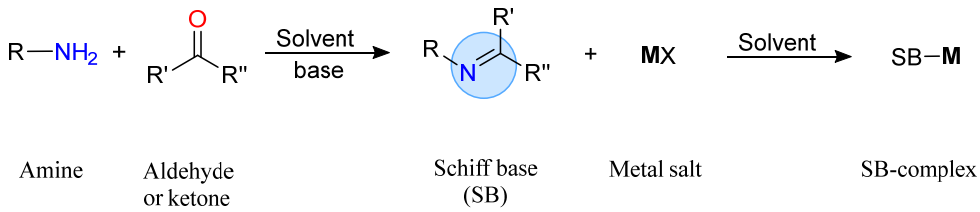
Figure 2. Structure of (**a**) tridentate Schiff base and (**b**) its palladium pincer complex with antimicrobial activity.

2.3. Synthesis of Metal Complexes Using Schiff Bases

To prepare the metal complexes derived from SBs, triethylamine is generally used to guarantee a basic medium and thus promote the deprotonation of ligands, while the metal is protected by adding weak acids that prevent the precipitation.

2.3.1. Traditional Chemical Method

SBs complexes can be prepared by mixing metal salts and a selected SB on the appropriate solvent. The mixture is stirred and refluxed, and the formed complex is washed and dried (Scheme 1).



Scheme 1. General synthesis of Schiff Bases Complexes.

This method is by far the most widely used and has been used to prepare a number of metal complexes with tridentate SBs that have been the subject of several reviews in recent years [41]. This method was used to prepare a series of ruthenium chelate complexes with SBs reported by Singh and Barman [42], Cu(II), Co(II), Ni(II), and Zn(II) complexes using SBs obtained by the condensation of *p*-nitrobenzaldehyde and 2-(aminomethyl)benzimidazole dihydrochloride [43]. Some chelate dianionic metal (Co(II), Ni(II), Cu(II), and Zn(II)) complexes with tetradentate SBs have been prepared with the ligand derived from the condensation of 2,5-thiophenedicarboxaldehyde with 2-aminobenzoic acid [44].

SBs complexes derived from N-(salicylidene)-*L*-alanine and N,N,N′,N′-tetramethylethylene-1,2-diamine (tmen) with Co(II), Ni(II), Cu(II), and Zn(II) were reported and screened against *Culex quinquefasciatus*, the southern house mosquito, which is the primary vector of the St. Louis encephalitis virus and the West Nile virus. The synthesis was carried out in an aqueous solution of L-alanine and KOH, to which a salicylaldehyde ethanolic solution was added. When the solution turned yellow, an ethanolic solution of the metal salt was added under stirring at 333 K and then N,N,N′N′-tetramethylethylene-1,2-diamine was added. The product was filtered, washed with ethanol, and dried [45]. A similar pathway was followed in the reaction of the SB ligand obtained via condensation of pyridine-2,6-dicarboxaldehyde with -2-aminopyridine with several metal ions, i.e., Cr(III), Fe(III), Co(II), Ni(II), Cu(II), Th(IV), Mn(II), Cd(II), Zn(II), and UO_2(II) [46]. In this case, a metal complex with an SB ligand was prepared by the addition of metal salt to a hot solution of the SB in an ethanol–water mixture, stirring for 1 h, and the precipitated product was collected, filtered, and washed with an ethanol–water mixture and diethyl ether. The synthesis of a series or M(II) complexes with cephalothin SBs resulting in the reaction of cephalothin antibiotic and sulfadiazine was also reported. The complexes with the general formula $[ML(H_2O)_3]$ were screened against two bacterial strains (*E. coli* and *S. aureus*) [47]. The transition metal complexes of an asymmetrical tetradentate SB ligand, derived from dehydroacetic acid, 4-methyl-*o*-phenylenediamine, and salicylic aldehyde, were produce by a one-pot reaction of the ligand and metal chloride under stirring and reflux temperature. The biological activity of these compounds was tested for antibacterial activity against *S. aureus* and *E. coli* and for fungicidal activity against *A. niger* and *T. viride* [48]. In another report, four transition-metal complexes $[Co^{II}(L)_2]$, $[Zn^{II}(L)_2]$, $[Ni^{II}(L)_2]$, and $[Cu^{II}(L)_2]$ were synthetized using this method from the reaction of metal salts with a tridentate SB ligand (HL = 2-((E)-(2-methoxyphenylimino)methyl)-4-bromophenol) and its biological activity studied against *B. subtilis*, *S. aureus*, *E. cloacae,* and *E. coli* [49].

The synthesis of transition metal(III) complexes using the one-pot reaction of the SB and the metal salt has also been reported. In a recent report, an Fe(III) complex was achieved

by this methodology using an unsymmetrical tetradentate SB and $FeCl_3 \cdot 6H_2O$ [50]. In the same way, the reaction of $Ln(NO_3)_3 \cdot xH_2O$ (x = 5 or 6) and the tridentate SB ligand N-(2-carboxyphenyl)salicylideneimine in a 1:2 methanol/acetonitrile mixture was carried out. The reported complexes were binuclear and showed catalytic properties [51].

The main group of metal compounds with tridentate SBs are not as common as transition metal complexes; however, the magnesium benzyl alkoxy complex of general formula $[LMg(\mu\text{-}OBn)]_2$, where L is an NNO-tridentate SB ligand, has been reported. The synthetic steps are similar to those of transition metal complexes, but the stirring occurs at room temperatures. This report showed how the strong coordination between the amino group and the Mg atom stabilizes the compound and prevents further ligand exchange [52]. Dimeric quinoline complexes with SBs $[Cr(DPPMHQ)Cl]_2 \cdot 2Cl$ and $[M(DPPMHQ)Cl]_2$ (where M = Cr(III), Cu(II), Co(II), Ni(II), and Zn(II)) have also been prepared by this method and their properties have been studied. The SB ligand (H-DPPMHQ) is derived from 2-hydrazineylquinoline and 1,3-diphenyl-1H-pyrazole-5-carbaldehyde [53].

2.3.2. Microwave and Sonochemical Synthesis

Non-traditional synthesis has gained a lot of ground in the chemical field of eco-friendly processes. Microwave-assisted synthesis has emerged as a useful and economic tool, with high yields and good atomic economy. The major advantage of this method is the homogeneous heating produced by the rotation and vibrational motion of the polar molecules [54]. Conventional and microwave methods were used to prepare metal complexes of Cr(III), Co(II), Ni(II), and Cu(II) with SBs derived from 5-chlorosalicylidene-2-amino-5-methylthiazole and 2-hydroxy-1-naphthylidene-2-amino-5-methylthiazole [55]. Likewise, a comparison was carried out between both methods to prepare biologically active donor SBs and their Cr(III) complexes, using azomethine ligands 1-(2-pyridyl) ethanoneisonicotinoylhydrazone and 1-(2-naphthyl)ethenoneisonicotinoylhydrazone. Microwave synthesis showed higher yields in shorter reaction periods [56].

Moreover, ultrasound irradiation has gained attention because it is a versatile technique to achieve high yield, short reaction times, simple processes, green chemistry, and a cost–efficiency relation [57]. This technique has been used to prepare the oxovanadium(IV) complex of the tetradentate SB ligand derived from the condensation of diaminoethane and 2-hydroxy-1-naphthaldehyde. The reaction was carried out in a reaction flask where the organic molecules and the bis(acetylacetonate)oxovanadium, previously mixed in a mortar, were heated at 50 °C for 40 min in an ultrasonic bath. Ultrasonic synthesis showed a better yield (95.4%) compared to the traditional synthesis (70–90%), and shorter reaction times—40 min vs. 3 h [58]. The synthesis of a series of complexes of Fe(II), Cd(II), and Zn(II) with SB obtained from 2-amino-3-hydroxypyridine and 3-methoxysalicylaldehyde has been carried out via ultrasonic synthesis [59].

The microwave method was used along with the traditional method to synthesize di- and triorganotitanium(IV) complexes with the SB 2-{[(E)-(2-hydroxy-3-methoxyphenyl) methylidene]amino}-2-methylpropanoic acid. In this experience, the microwave method provides, once again, a better reaction time and yield percentage than the traditional method [60].

3. Antimicrobial Metallopharmaceuticals with Tridentate Schiff Bases

Since the standard treatment for many infectious diseases faces drug resistance, high cost, and severe side effects, the need to develop new treatments with high efficiency and low toxicity is a global concern and a main goal for pharmaceutical companies. In that regard, SBs have shown a biological activity against a variety of human ailments and have become important molecules in the field of drug discovery. The use of tridentate SBs ligands in different organometallic and coordination complexes containing main-group metals and transition metals has been an option in recent years to study the biological activity of new possible metallopharmaceuticals that contribute to increase activity and to counteract the effect of microbial resistance.

In order to obtain metal complexes, the SB ligands NNO and ONO have been extensively studied, as have been, to a lesser extent, the NNS or NOS ligands. The potential application of these compounds involves experimentation in catalysis [61,62], electronic [63], and biological areas [64,65]. The importance of achieving antimicrobial studies arises from the multiresistance observed in recent years; moreover, there are some unattended diseases and severe human health cases. In general, the assays to evaluate the bactericide and fungicide activity are performed with agar diffusion method, disc diffusion method, and less frequently agar cup plate method, which are reported according to inhibition zone expressed in mm. Besides this, quantitative experiments such as MIC and MIB determinations are constantly reported, which are the lowest concentration of the compound that generates the inhibition of microbial growth and the lowest concentration at which the compound will kill a microorganism, respectively, and are expressed in g/mL or μg/mL. In the same way, there is a general strategy to perform these experiments, such as including Gram-positive and Gram-negative bacteria in the research. This is due to their differences in cellular wall that demonstrate major resistance to antimicrobial drugs by Gram-negative species which is reflected in the MIC values or in the mm of the inhibition diameter obtained. The most studied Gram-negative strains are *E. coli* and *S. typhi*, which are habitually found as contaminants in water and food, and for this reason *P. aeruginosa* is also a relevant microorganism. The Gram-positive bacteria *S. aureus* and *B. subtilis*, as well as the fungi *A. niger* and *C. albicans*, are the most studied. The importance of these strains stems from relevance in food and clinical safety. It is important to highlight that the results reported by the authors in all cases are expressed according to internal parameters such as concentrations, references, methods, and selected and employed strains. It is highly recommended to revise the *Performance Standards for Antimicrobial Susceptibility Testing* document [66] emitted by the Clinical and Laboratory Standards Institute (CLSI) that include the updates on microbiological experiments.

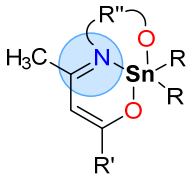
3.1. Main Group Elements

Medicinal inorganic chemistry is a growing field that has proven to be very effective in the treatment and diagnostic of many diseases [4]. Nowadays, transition metal complexes are the most known and most used compounds in the design of metallodrugs. However, main group elements have received extensive attention since the discovery of salvarsan, also known as arsphenamine or Ehrlich 606, a mixture of 3-amino-4-hydroxyphenyl-As(I) and As(V) compounds synthetized by Paul Ehrlich as an effective cure for syphilis. Salvarsan is acknowledged as the first pharmaceutic cure for a disease and opened the door to the research of new molecules that target specific cells to treat many infections [67]. Arsenic was widely used to treat parasite infections, skin diseases, and anaemia in the early 20th century. Livingstone reported the effective action of arsenic in trypanosomiasis, and subsequent reports showed the beneficial action of arsenic against the parasites in the blood stream, but also acknowledged that since the known forms of arsenic were toxic, its use could be lethal to the patient. Organic arsenicals were recognized as less toxic that their inorganic counterpart and were used to treat syphilis and sleeping sickness [68]. Atoxyl, melarsoprol, and melarsonyl are examples of chemotherapeutic drugs for the treatment of infectious diseases [68–70]. Furthermore, antimony-based chemotherapy drugs are the main treatment for Leishmaniosis [71]. The pentavalent antimonial compounds that had traditionally been used as treatment for Leishmaniosis (meglumine antimoniate and sodium stibogluconate) had important side effects, and over time the parasite became resistant, so the available drug was not safe enough nor effective [71,72].

Research about the synergic effect of SBs with metals has been addressed mainly for transition metals, and the main group has received less attention, mostly due to the toxicological effects that these kinds of compounds have historically shown. However, in recent decades, the number of reports of medicinal research of SBs with the main group have been increasing. Tin is a main group metal that shares some characteristics with the transition metals. It can form complexes with several organic molecules bound

through donor heteroatoms as oxygen, sulphur, or nitrogen, in a wide range of geometries. Organotin complexes have been the subject of interest for decades due to their prospective use in pharmacology, industry, or medicine. In the field of complexes of SBs with tin, many reports about their biological activities can be found in the literature. Even though most research on organotin focuses on its anti-cancer activity, the biological activity of SBs with Sn(IV) with a variety of coordination geometries can be found in reports showing their potential antibacterial, cytotoxic, and antifungal activity [73–79].

SBs with Sn(IV) in vitro antimicrobial activities have been studied against Gram-positive bacteria, Gram-negative bacteria, and fungal strains. In many cases, these complexes showed better activity against Gram-positive strains, such as *S. aureus* and *B. subtilis*, than Gram-negative strains, such as *E. coli* and *P. aeruginosa* [76,79–81]. This result can be explained by the chelation theory that sustains that chelation increases the lipophilic character of the complexes, allowing the permeation of the compound through the cell wall of the bacteria. Through chelation, the metal polarity is reduced by sharing its positive charge with the heteroatom in the ligand, originating an electron delocalization over the metallo-ring. As such, the biological activity of organotin(IV) complexes depend on the donor ligand, the geometry, and the coordination number over the tin atom [78,79]. Synthesis of pentacoordinate Sn(IV) complexes with SBs and general formulas $R_2Sn[OC(R'):CH(CH_3)C:NR''O]$ were reported (Figure 3) [76]. As stated before, structure affects how well the complex penetrates the bacterial cell, making the compounds more active against Gram-positive strains (*S. aureus* and *B. subtilis*) than Gram-negative strains (*E. coli* and *P. aeruginosa*), which could be related to the composition of the cell wall. In this study, complexes (inhibition zone values < 25 mm) were more active compared to the free ligands (inhibition zone values < 15 mm) and the starting salts (inhibition zone values < 14 mm), indicating that chelation generates a synergistic effect on the antimicrobial activity. In general, the antimicrobial activity was moderate and low, highlighting the activity of complex **1l**, which presented zones of inhibition > 20 mm against *B. subtilis*, *P. funiculosum*, and *A. niger*. Besides the structure, concentration plays a vital part in activity, with a higher concentration giving better antimicrobial activity, affecting a bigger number of enzymes and therefore killing the organism more rapidly.



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(a) R = Me, R' = Me, R'' = $(CH_2)_2$
(b) R = Me, R' = Me, R'' = $(CH_2)_3$
(c) R = Me, R' = Ph, R'' = $(CH_2)_2$
(d) R = Me, R' = Ph, R'' = $(CH_2)_3$
(e) R = Bu, R' = Me, R'' = $(CH_2)_2$
(f) R = Bu, R' = Me, R'' = $(CH_2)_3$
(g) R = Bu, R' = Ph, R'' = $(CH_2)_2$
(h) R = Bu, R' = Ph, R'' = $(CH_2)_3$
(i) R = Ph, R' = Me, R'' = $(CH_2)_2$
(j) R = Ph, R' = Me, R'' = $(CH_2)_3$
(k) R = Ph, R' = Ph, R'' = $(CH_2)_2$
(l) R = Ph, R' = Ph, R'' = $(CH_2)_3$

Figure 3. Diorganotin(IV) derivatives of some bioactive bifunctional tridentate Schiff base ligands.

Prasad et al. obtained a similar result [80] when a series of four diorganotin(IV) complexes were synthetized using biologically active 4(3H)-quinazolinone derivatives as ligands (Figure 4) and the obtained compounds were screened against bacteria (*E. coli*, *S. aureus*, *R. solanacearum*, and *X. vesicatoria*) and fungi (*A. niger*, *A. flavus*, *F. oxysporum*, and *A. solani*). Compared to the free ligand, under the same conditions and microorganism, the complex performed better. Of the four complexes, those with the hydroxyl group on the organic moiety showed better activity, with complex **2b** reporting the highest activity against three bacteria and two fungi. DNA binding studies indicated that the complexes bind to DNA via intercalative mode. The reported results are consistent with those of Sonika and Malhotra [82], who reported a series of Tin(IV) complexes of the type $R_2Sn(L)_nCl_{2-n}$ [R = butyl and phenyl, n = 1 or 2, HL = bidentate SB derived from the condensation of methyl/ethyl pyruvate with substituted acid hydrazides. Both the ligands and their complexes were screened against the phytopathogenic fungi *C. albicans* and *A. niger*, and the bacteria *B. subtilis*, *E. coli*, and *S. aureus*, concluding that complexation improves the activity of the ligand.

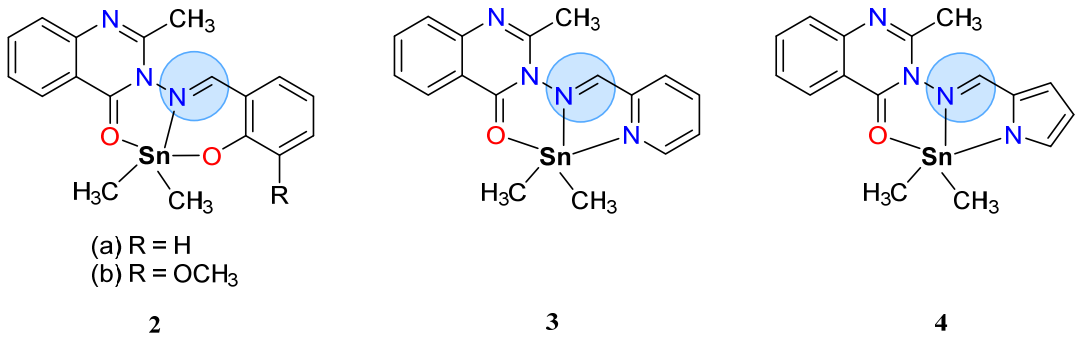


Figure 4. Organotin(IV) complexes with ligands derived from 4(3*H*)-quinazolinone.

More recently, a series of sixteen pentacoordinated diorganotin(IV) complexes with dianionic tridentate SB hydrazones (ONO) as ligands (complex **5**) was reported (Figure 5) [83]. The complexes were tested against four bacterial strains, the Gram-positive *B. cereus* and *S. aureus*, and the Gram-negative *E. coli* and *P. aeruginosa*, as well as the three fungal strains *A. flavus*, *A. niger*, and *C. albicans*. As in previous reports, the complexes were more active against Gram-positive than Gram-negative bacteria, which have a more complex outer membrane containing lipopolysaccharides that hinder the diffusion of the complex through the membrane. The same group reported a series of diorganotin(IV) complexes (complex **6**), [R'_2SnL], obtained by the reaction of 2-benzoyl-1*H*-indene-1,3(2*H*)-dione SBs with R'_2SnCl_2, (R′ = Me, Et, n-Bu, Ph). The complexes were studied against the same bacteria and fungi as in the previous report, with a consistent result of a higher activity against Gram-positive than against Gram-negative strains [84]. In both reports, the complexes present a higher antifungal than antibacterial activity, which was explained by the fact that the metal centre increases its lipophilic character, facilitating the diffusion through the cell membrane and the DNA binding that eventually kills the microbe. Recently, Devi et al. [79] reported a series of four organotin(IV) complexes of general formula R_2SnL, with SBs derived from salicylaldehyde, namely, 4-((2-hydroxybenzylidene)amino)-[1,1′-biphenyl]-3-ol, 4-((2-hydroxy-5-nitrobenzylidene)amino)-[1,1′-biphenyl]-3-ol, 4-((3-bromo-2-hydroxy-5-nitrobenzylidene)amino)[1,1′-biphenyl]-3-ol, and 4-((3,5-dibromo-2-hydroxybenzylidene)amino)[1,1′-biphenyl]-3-ol, where R is methyl, ethyl, butyl, or phenyl. The complexes were pentacoordinated with the SB coordinated through the imine nitrogen and the two phenolic oxygens; complex **7**. All complexes showed better antimicrobial activities than the organic molecule alone. As in the aforementioned reports, the complexes present a higher activity against Gram-positive bacteria (*S. aureus* and *B. subtilis*) than against Gram-negative bacteria (*E. coli* and *P. aeruginosa*) for the previously explained reason. The analysis of the results showed that the phenyl derivatives have an improved activity since the aromatic π cloud helps the diffusion through the lipidic cell wall by improving the lipophilicity of the Sn atom. As such, a lower activity was observed in the methyl derivative, followed by the ethyl and butyl derivatives, respectively. The phenyl derivatives presented an even better activity than the standard drug, fluconazole. Other reports focus on binuclear organotin complexes. The activities of four binuclear diphenyl- and dimethyl-tin(IV) complexes (**8** and **9**) with general formula $(R_2Sn)_2L$ showed a pentacoordinate structure of tin coordinated to an SBs bis-acylhydrazone obtained from the reaction of adipic dihydrazide with 5-bromosalicylaldehyde and 2-hydroxynaphtaldehyde; they were screened against bacteria (*B. subtilis*, *S. aureus*, *E. coli*, and *P. aeruginosa*). The result was compared to those of known drugs, nalidixic acid and vancomycin. X-ray structure showed that the SB ligand is coordinated to Sn through the imine nitrogen and oxygens of the phenolic and enolic moieties. The geometry can be described as a distorted trigonal-bipyramidal with the oxygen in the axial position and the nitrogen in the equatorial position [81]. As in the former reports, the studied activities showed that the organotin(IV) complexes were more effective that the free ligand, and that complex **8b** is even more active (inhibition zone = 23 mm) than the standard drugs (inhibition zone = 12 mm and

17 mm for nalidixic acid and vancomycin, respectively) when an antibacterial activity was determined for *S. aureus*. As in other reports, the complexes were more active against Gram-positive bacteria than against Gram-negative strains. This is another example of the effect of chelation on the penetrability of the compound on the bacterial cell wall. The highlight of this report is the effect of the complex on *P. aeruginosa*, a bacterium that is known to be resistant to the known drugs, making these complexes possible candidates for drug development. These reports showed that the structure of the complex affects the antimicrobial activity, with significant differences due to small modifications in the R group, with the phenyl and butyl group having a bigger impact on the effectiveness of the complex against microbes when compared to the ethyl or methyl groups. Among the diverse biological applications of organotin complexes, they are considered promising molecules in the field of drug development for the treatment of human illness, such as trypanosomiasis and other neglected diseases, due to their ability to interact with DNA.

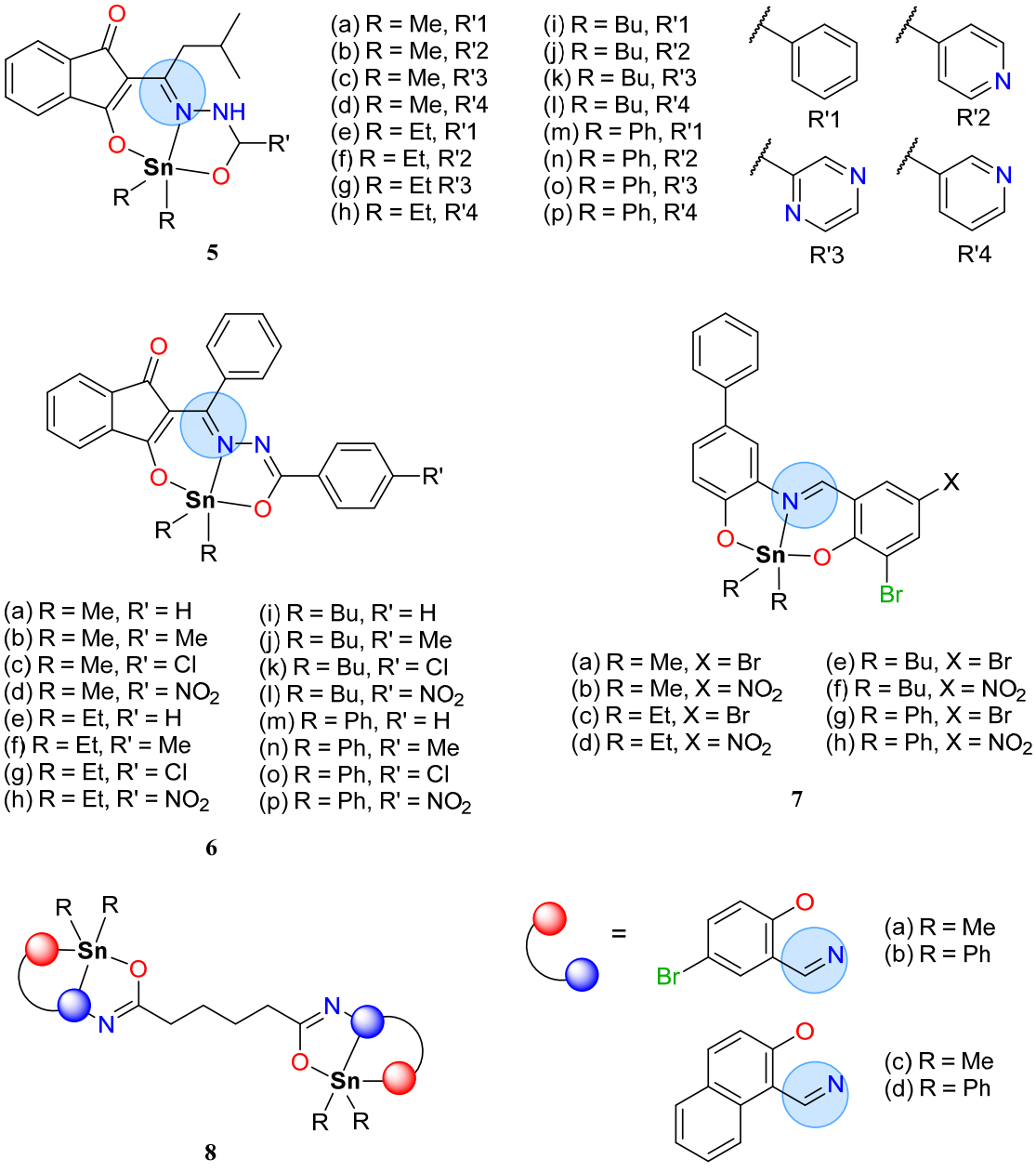


Figure 5. Organotin(IV) complexes with tridentate ONO donor Schiff base ligands tested for antimicrobial activity.

Organotin(IV) complexes with tridentate SB ligands (ONO), obtained from N′-(2-hydroxybenzylidene)formohydrazide with the general formula [SnR_2L] (L = [$OC_6H_4CHNNCHO$]), complex **9** (Figure 6), were tested against *L. major* promastigotes. The study used amphotericin B (IC_{50} = 0.50 µg/mL) and pentamidine (IC_{50} = 5.78 µg/mL) as standard drugs for the control. Compared to the control, three complexes presented good results: complex **9f** showed the best activity with IC_{50} = 0.90 µg/mL, followed by complex **9c** with IC_{50} = 0.96 µg/mL, and complex **9e** with IC_{50} = 0.98 µg/mL. No cytotoxic studies were reported; therefore, the selectivity was not determined [85]. The anti-leishmania activity of six diorganotin(IV) compounds with general formula [R_2SnL] (complex **10**) and one monoorganotin(IV) derivate, C_4H_9SnClL (complex **11**), where L = N′-(5-bromo-2-oxidobenzylidene)-N-(oxidomethylene)hydrazine (with ONO tridentate chelation capability), were reported against *L. major* using amphotericin B (IC_{50} = 0.50 µg/mL) as a standard drug [86]. Two complexes, **10c** (IC_{50} = 0.41 µg/mL) and **10f** (IC_{50} = 1.22 µg/mL), showed good activity, and the highest activity was noted for complex **10c** which exceeded the standard drug. The complexes with a more planar geometry and lipophilicity had the best activities, while those with other geometries and higher molecular weight presented the lowest activity. Additionally, diorganotin complexes are more toxic than mono-organotin compounds. The anti-leishmania activity of organotin complexes derived from N-(2-hydroxy-3-methoxybenzylidene) formohydrazide ligand was reported [87] using amphotericin B as a standard drug. All six tin complexes were screened against *L. major*, and presented a better activity than the free ligand, showing again the importance of the tin atom in the biological activity. Complexes **12e** (IC_{50} = 1.26 µg/mL) and **12c** (IC_{50} = 2.03 µg/mL), *tert*-dibutyltin(IV), and diphenyltin(IV), respectively, were as active as the standard drug due to their lipophilic nature. The geometry of the **12c** complex plays a role in the high activity of the compound along with a low molecular weight that aids in the diffusion across the membrane. The same factor explains the low action of complex **12d** (IC_{50} = 8.25 µg/mL). **12a–e** complexes were also active against various bacterial and fungal strains, highlighting the antibacterial activity of all the studied complexes (except **12d**) against *B. subtilis*, which presented inhibition zones between 5 and 20 mm, while in the antifungal activity, complex **12c** was the most active with inhibition percentages > 50% against *C. albicans* and *C. glaberata* fungi.

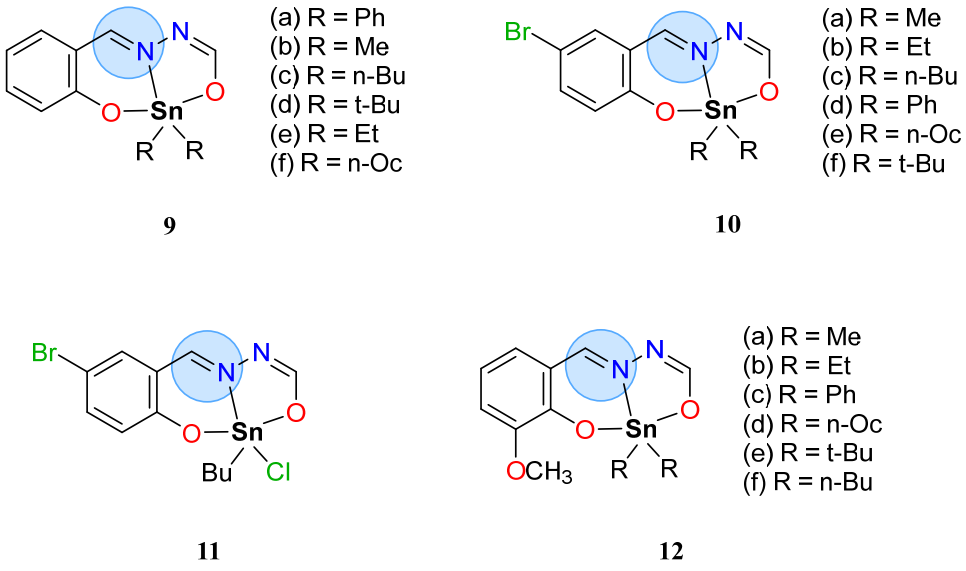
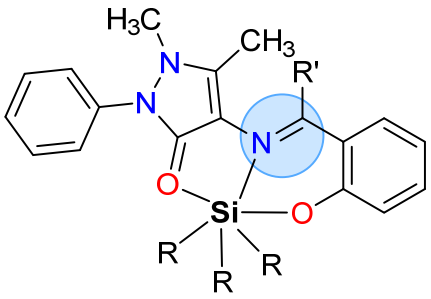


Figure 6. Organotin(IV) complexes with tridentate Schiff base ligands (ONO) tested for antileishmanial activity.

Along with the chemistry of organotin(IV) complexes, the biological activities of hypercoordinated silicon compounds with SB ligands have also been studied [75,88]. Sil-

icon compounds with tridentate SBs are scarce, with some early reports by Puri et al. looking to examine the physical and chemical properties of these compounds. In this report, a series of complexes, which exhibit a hexacoordinate Si(IV) atom and the ligand N,N′-diethylenetriamine-bis(salicylideneimine), are reported [89]. A report by Devi et al. explored the biological activity of some triorganosilicon(IV) complexes coordinated to tridentate SBs with the general formula [$R_3Si(L)$], where L is an SB obtained by the reaction of 4-aminoantipyrine with 2-hydroxyacetophenone, 2-hydroxybenzophenone, 2-hydroxybenzaldehyde, and 2-hydroxynapthaldehyde, and R = butyl, phenyl, ethyl [90]. The complexes were fully characterized by spectroscopic techniques (IR, ^{1}H, ^{13}C, and ^{29}Si NMR), in addition to elemental analysis and molar conductance. The result points to an ONO tridentate coordination (Figure 7), complex **13**, since the band of the azomethine group moves to lower frequencies by 10–15 cm^{-1}, compared to the free ligand, evidencing a coordination through the lone pair of the nitrogen atom to the central atom. Then, the ν(C=O) shifted 20–30 cm^{-1} to lower frequencies, indicating the coordination of the oxygen atom to the silicon atom. Furthermore, NMR analysis points towards a tricoordinate ligand as shown in Figure 7. The silicon complexes, as well as the ligands, were tested against fungi (*A. niger* and *C. albicans*), against Gram-positive bacteria (*S. aureus* and *B. subtilis*), and Gram-negative bacteria (*E. coli*). The standards to determine the effectiveness of the complexes and their ligands were known as bactericides tetracycline, chloramphenicol, kanamycin, cefazoline sodium, and cefotaxime, as well as the fungicides cycloheximide, carbendazim, and fluconazole. As with the organotin complexes, the silicon compounds showed higher activities (MIC up to 3.12 μg/mL) compared to their free ligands. Additionally, as with tin complexes, the presence of a bulky R group bonded to the silicon atom increases the activity by improving the lipophilicity of the complex. Therefore, the phenyl complexes (Ph_3SiL) (**13g**, **13h,** and **13i**) showed better activity values against *E. coli* and *A. niger* fungi. In general, under the same experimental conditions, the silicon complexes showed better bactericidal and fungicidal actions than the free ligand and some of the commercial drugs.



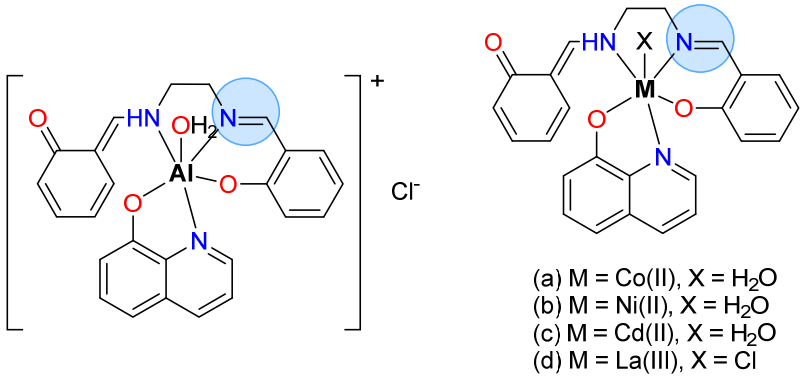
13

(a) R = Et, R' = H
(b) R = Et, R' = Me
(c) R = Et, R' = Ph
(d) R = Bu, R' = H
(e) R = Bu, R' = Me
(f) R = Bu, R' = Ph
(g) R = Ph, R' = H
(h) R = Ph, R' = Me
(i) R = Ph, R' = Ph

Figure 7. Silicon complex from a tridentate Schiff base ligand (ONO) with antimicrobial activity.

Reports of tridentate SBs forming aluminium complexes are scarce. A recent work of Al(III) complex with a SB and 8-hydroxyquinoline was reported (Figure 8) [91]. The complexes were obtained from the reaction of (2,2′-{1,2-ethanediylbis[nitrile(*E*)methylylidene]} diphenol, 8-hydroxyquinoline with the aluminium salt. Beside the Al(III) complex, Co(II), Ni(II), Cd(II), and La(III) complexes were synthetized. The complexes were evaluated against the bacteria *E. coli*, *P. vulgaris*, *S. aureus*, and *B. subtilis*, as well as the fungi *C. albicans* and *A. flavus*. The activities were compared to the regular drugs gentamicin (antibiotic) and ketoconazole (antifungal). Of all complexes, free ligands, and commercial drugs, complex **14** showed better antibacterial and antifungal effectiveness, achieving an inhibition zone of up to 31 mm for *S. aureus* and 37 mm for *A. flavus*. Complexes **15c** and **15d** showed a moderate–high activity for both fungi and bacteria, while complexes **15a** and **15b** showed a

moderate–low activity for bacteria, and no antifungal activity, which demonstrates a clear dependence on the nature of the metal centre.



14 **15**

Figure 8. Salen-metal complexes with antibacterial and antifungal activity.

Arsenic has historically played an important role in the treatment of human illness and has been used to treat ailments such as syphilis, trypanosomiasis, or malaria. Some of the first metallodrugs that were developed as antiparasitic and antimicrobial agents were arsenic compounds, such as atoxyl (arsanilic acid) used to treat trypanosomiasis or sleeping sickness. Additionally, chemotherapy started with the development by Ehrlich et al. of salvarsan, a drug that was the standard treatment for syphilis and trypanosomiasis before being replaced by less toxic drugs such as penicillin. Even today, melarsoprol (2-(4-amino)-(4,6-diamino-1,3,5-triazin-2-yl)-phenyl-1,2,3-dithiarsolan-4-methanol (Mel B, arsobal) is still used for the treatment of the two known forms of human African sleeping sickness. Antimony has been used to combat microbes and parasites, standing out as a component of drugs for cutaneous and mucocutaneous leishmaniosis, such as stibosan, neostibosan, pentostam, or glutantime. The anti-leishmanial activity of the toxic antimony(III) ion is associated to its ability to bind to the trypanothione reductase, the enzyme responsible to protect the parasite from free radicals and consequently necessary for the persistence and virulence of the parasite [92]. On the other hand, bismuth is known as a non-toxic element that can be used in high doses and its effect on gastric diseases is well known, but it has also been used to deal with the *H. pylori* bacteria. Since the treatment for parasitic infections and other illnesses extends over a long period of time, the toxic side effects and the growing drug resistance have aroused interest in the research for more efficient and less toxic metallodrugs with these elements. In this regard, the use of SBs is of pharmacological interest due to their wide biological activities. The Beraldo group carried out an extensive study on the antitrypanosomal, antimicrobial, and antifungal activity of a series of thiosemicarbazones derivatives of the main metal groups [93–100]; the report presented complexes of gallium, antimonium, tin, indio, and beryllium.

Antimony(III) complexes with thiosemicarbazone ligands have been reported and tested for their biological activity as antitrypanosomal compounds [93]. The compounds had the general formula [$SbLCl_2$], when L was N(4)-phenyl-2-pyridine derived from thiosemicarbazones. FTIR spectra showed a ν(C≡N) signal at 1611 and 1596 cm^{-1}, consistent with a bond through the N-imine atom. Moreover, the ν(C-S) bond moves at 730 and 753 cm^{-1}, indicating an S-Sb coordination. The NMR and XRD results confirm the tridentate bonding of the SB to the Sb(III) central atom. The coordination sphere was completed with two Cl atoms (Figure 9). The complexes dichloro(N(4)-phenyl-2-formylpyridinethiosemicarbazonato)antimony(III) (complex **16a**), dichloro(N(4)-phenyl-2-acetylpyridinethiosemicarbazonato)antimony(III) (complex **16b**), and dichloro(N(4)-phenyl-2-benzoylpyridinethiosemicarbazonato)antimony(III), (complex **16c**), were screened against trypomastigote and epimastigote forms of *T. cruzi* and the result was compared with the

activity of benznidazole and nifurtimox. The complexes and their free ligands showed an activity against the epimastigote and trypomastigote forms of *T. cruzi*. Compared to the commercial drugs benznidazole (IC_{50} = 6.65 μM) and nifurtimox (IC_{50} = 1.88 μM), the compounds **16a** and **16b** showed a better activity with IC_{50} = 1.27 μM and IC_{50} = 1.23 μM, respectively (for the trypamastigote form), but the cytotoxicity of doses around 1 μM made them not appropriate candidates for new drugs. The organic molecules were active, but their respective complexes had higher activities. Regarding the complex **16c**, the free ligand was the least cytotoxic of all three and the activity against the trypomastigote form was moderate (IC_{50} = 14.41 μM), while the Sb complex showed a better activity against the epimastigote (IC_{50} = 2.10 μM) than the trypamastigote form (IC_{50} = 8.39 μM). Continuing with this line of research, the same group reported six thiosemicarbazones antimony(III) derived from 2-acetylpyridine and 2-benzoylpyridine, complex **17** (Figure 9) [94]. The observed antitrypanosomal activity follows the order: Cl ~ F > NO_2 for thiosemicarbazones derived from 2-acetylpyridine; and Cl > F > NO_2 for analogues derived from 2-benzoylpyridine, both for the ligand and for the Sb(III) complexes. Despite the antileishmanial activity, the complexes were more toxic than the organic molecules. In a subsequent report, the complexes were tested against fungi [101], with the complex **17d** (IC_{50} = 4.91 ± 1.20 μM) being as active as nystatin (IC_{50} = 4.44 ± 0.76 μM) and twice as active as the free ligand (IC_{50} = 10.05 ± 0.67 μM) against *C. dubliniensis*, while the same complex had a higher activity (IC_{50} = 10.11 ± 0.64 μM) than the miconazole nitrate (IC_{50} = 19.50 ± 4.53 μM) and the free ligand (inactive) against *C. glabrata*.

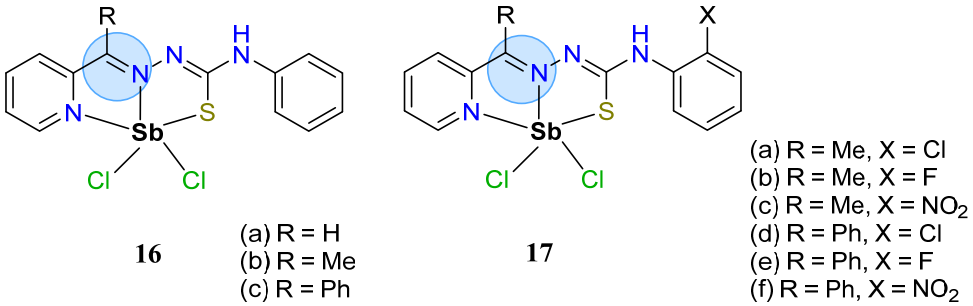


Figure 9. Antimony(III) complexes with N(4)-phenyl-2-pyridine-derived thiosemicarbazones ligands studied in antimicrobial activity.

Hydrazones derived from 2-acetylpyridine- and 2-benzoylpyridine form eight complexes with bismuth(III) (Figure 10) that were screened against Gram-positive and Gram-negative bacterial strains, showing that the coordination to Bi(III) improved the activity compared to the organic moiety in all cases but one. This observation suggests that the ligand could be acting as a carrier to help penetrate the cell wall, allowing the entrance of Bi(III) that is well known, allowing it to act as antimicrobial and bactericide, increasing its bioavailability [102].

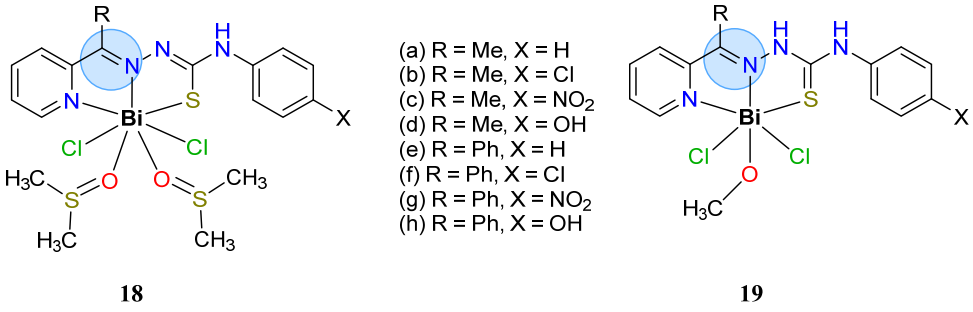


Figure 10. Bismuth(III) complexes with 2-acetylpyridine- and 2-benzoylpyridine-derived hydrazones ligands studied in antimicrobial activity.

Organotin(IV) complexes with 2-pyridineformamide thiosemicarbazone and its N(4)-methyl and N(4)-ethyl derivatives (Figure 11) were evaluated against *C. albicans* and *S. typhimurium*, showing an activity for both the organic moiety alone, and for the complexes. In addition to the microbial activity, the complexes presented a high activity against malignant glioblastoma [99]. The interesting result of this report was the unusual activity of the 2-pyridineformamide-derived, which proved to be more active against *S. typhimurium* bacteria than against *C. albicans*, in contradiction to other reports in the literature. The complex **20a** had a higher activity against *S. typhimurium* (MIC = 165 μM). All reported complexes had similar antifungal activities (MIC = 270–290 μM) and neither had a better action than the reference drugs chloramphenicol or nystatin.

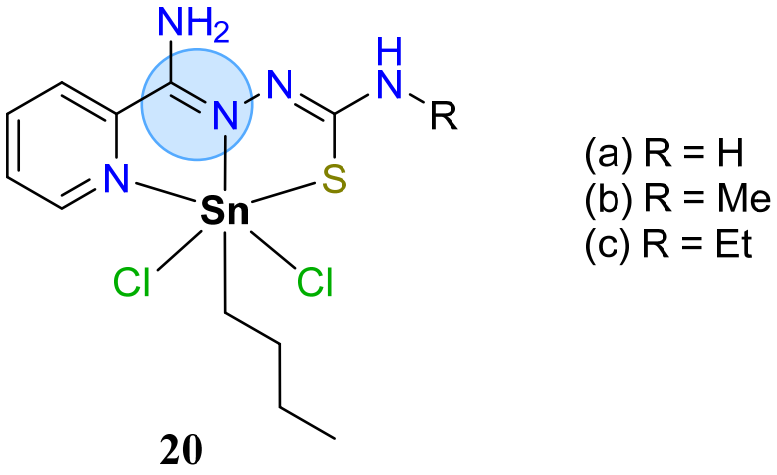


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Figure 11. n-Butyltin(IV) complexes with ligands derived from 2-pyridineformamide thiosemicarbazone studied in antimicrobial activity.

A series of Bi(III) complexes coordinated to tridentate thiosemicarbazone ligands in which the ligands are bound through the 2N and 1S atoms, complexes **21** and **22** (Figure 12), were studied as potential antimicrobial agents [103]. The complexes were active against different bacterial strains, and since the starting bismuth salts did not show any activity, the activity was due to the coordination of the organic moiety to the Bi(III) atom. It is important to note that for *B. subtilis* and *S. aureus*, the activity of the complexes was improved compared to the free ligand. The results provide a clear relationship between structure and antimicrobial activities: complex **21** (general formula [$BiLCl_2$]) was effective and selective against *B. subtilis* (MIC = 7.9 μg/mL), whereas complex **22** (general formula [$BiL_2(NO_3)$]) had a high activity against the Gram-positive bacteria *B. subtilis* and *S. aureus* (MIC = 4.0 μg/mL for both). It is important to note that the presence of nitrate ions improves the activity compared to chloride ions, so the choice of the starting bismuth salt is a criterion to take into account in the design of future molecules. Another factor that could improve the antibacterial activity is the number of ligands bound to the Bi(III) centre, since it was observed that the activity was higher for complex **21** (with two ligands) than for complex **22** (with one ligand) in the antibacterial activity results against *E. coli*, *B. subtilis*, *S. aureus*, and *P. aeruginosa* [103]. A recent report studied the biological activity of eight bismuth complexes with a hydrazone ligand and the general formula [$Bi(RCONNCHC_5H_4N)Cl_x$] and [$Bi(RCONNCHC_9H_6N)Cl_x$] (R = $C_{10}H_7O$, C_4H_3S, C_6H_5O, C_7H_7, C_5H_4N, and x = 2 or 3), complexes **23**–**26** (Figure 12), against two Gram-positive bacteria (*B. subtilis* and *S. aureus*) and two Gram-negative bacteria (*K. pneumoniae* and *E. coli*). As in other reports, the data indicate that complexation induces a bigger biological activity than free ligands. All complexes showed good activity against all strains studied (MIC = 3.125–50 μg/mL) compared to the organic moiety, while the results of the antifungal activity showed MIC values between 12.5 and 50 μg/mL for most of the compounds against fungal strains, and

only complex **25b** presented an MIC of 6.25 µg/mL against *A. flavus*, a value lower than that of the reference drug (MIC = 10 µg/mL) [104].

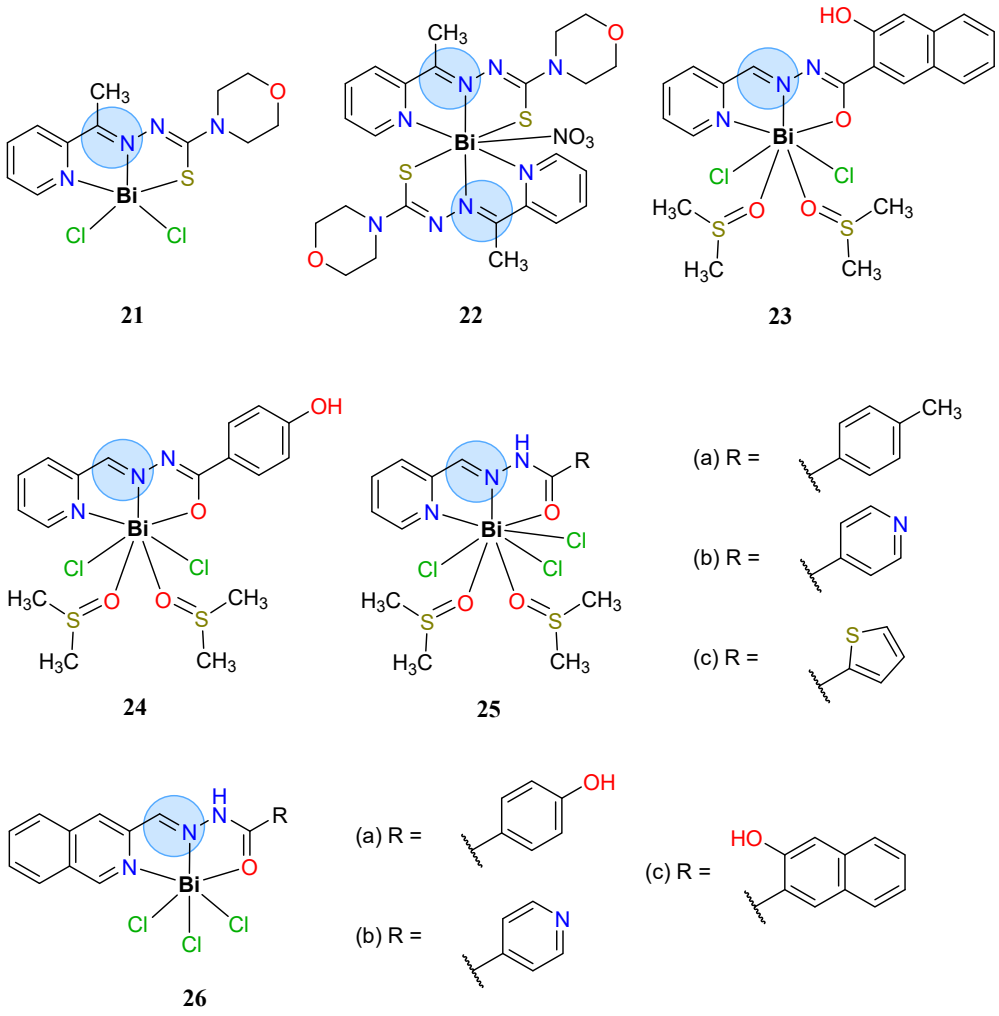


Figure 12. Bi(III) complexes with NNO and NNS asymmetric ligands studied in antimicrobial activity.

On the other hand, the antimicrobial activity of indium(III) complexes with thiosemicarbazone ligands has also been reported (Figure 13) [105,106]. The [In(III)(L)Cl_2(MeOH)] complexes **27** have as ligands thiosemicarbazones obtained from 2-acetylpyririne and have been reported to be effective against several strains of *Candida*, i.e., *C. albicans*, *C. parapsilosis*, *C. lusitaniae,* and *C. dubliniensis* [106], with better results than free ligands in all cases, highlighting the activity of complex **27b** with an IC_{50} value of 3.0 ± 1 µM against *C. parapsilosis*, which was more effective than the reference drug nystatin (IC_{50} = 5.1 ± 0.4 µM). In the case of *C. lusitaniae*, the complexes had an equal or better activity than the reference drug nystatin (IC_{50} = 2.0 ± 0.3 µM), while for *C. dubliniensis,* all the complexes had a better activity (except **27b**) than the reference drug nystatin (IC_{50} = 2.3 ± 0.3 µM). The indium(III) complex with 2-acetylpyridine-N(4)-phenylthiosemicarbazone (complex **28a**) and its gallium(III) homologue (complex **28b**) has low to moderate antibacterial activity (MIC > 62.5 µg/mL) against Gram-positive bacteria (*B. cereus*, *B. subtilis*, *S. aureus*, and *S. lutea*) and Gram-negative bacteria (*E. coli*, *A. tumefaciens*, *S. typhimurium*, and *P. aeruginosa*), but great cytotoxicity against HepG2 cells. However, it should be noted that in all cases, the antibacterial activity was improved in the presence of the metal compared to the MIC values for the free ligand [105]. The gallium complex with tridentate thiosemicarbazones has also been reported to show antimicrobial activity. Beraldo's group also reported an enhanced activity against fungi as a consequence of the coordination of thiosemicarbazones derivatives to Ga(III) [96,97,107].

Complex **29** (Figure 13) and its derivatives were tested against *Cryptococcus* strains; however, they did not show a fungicidal but rather a fungistatic activity, meaning that once the treatment is stopped, the strains grow again [96]. In a previous report, the same group published the results of the screening of this kind of compounds against *Pseudomonas aeruginosa*, reporting that complexation has an important role in the increase in biological activity relative to the free ligand [97]. Additionally, a recent report presented a lead(II) complex with quinoline-2-carboxaldehyde-4-methyl-3-thiosemicarbazone derivative as ligand, complex **30**, and its biological activity was tested against *B. subtilis*, *S. aureus*, *P. aeruginosa*, and *E. coli*, with slight inhibition for *S. aureus* (inhibition zone diameter = 11 mm) [108].

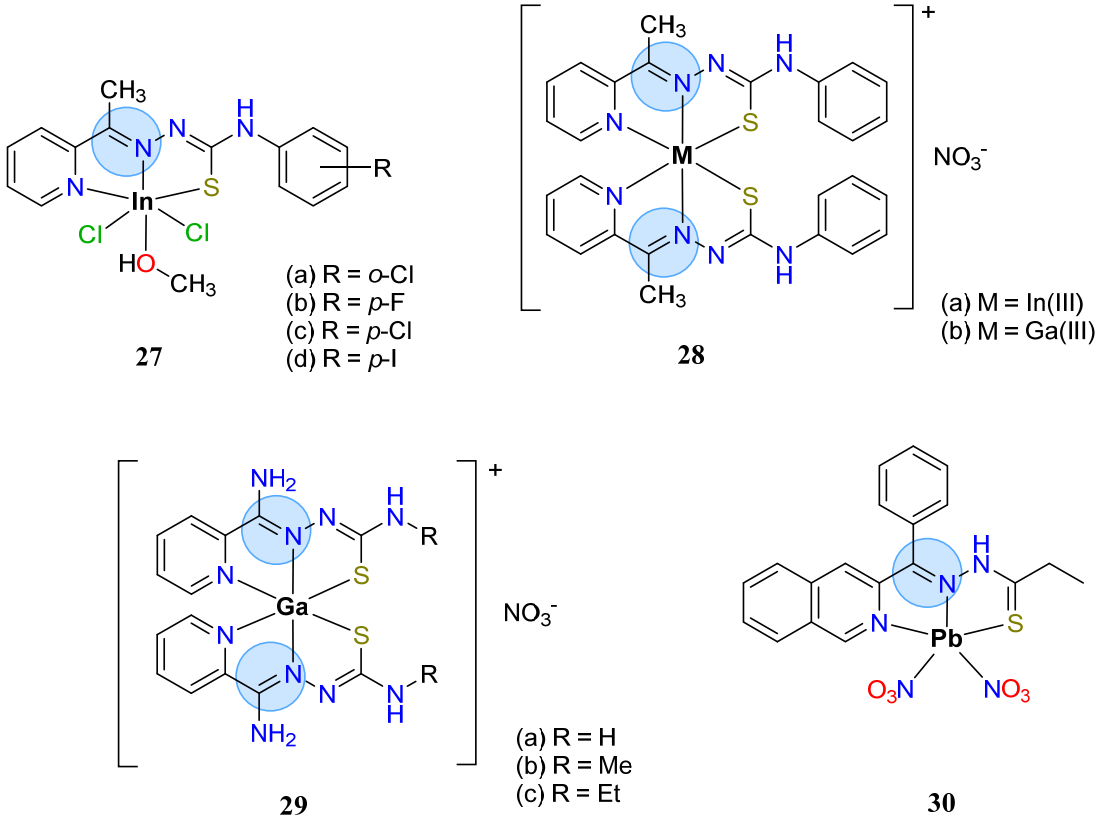


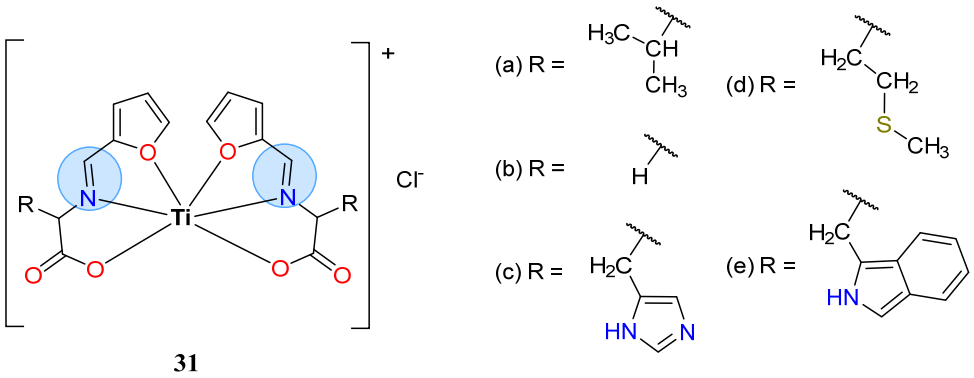
Figure 13. Indium(III), gallium(III), and lead(II) complexes with NNS thiosemicarbazones ligands studied in antimicrobial activity.

3.2. Titanium Group

Group IV is the second group of transition metals in the periodic table. It contains four elements: titanium, zirconium, hafnium, and rutherfordium. Due to the small amounts produced and its short half-life, there are currently no uses for rutherfordium outside of basic scientific research, so there are no metal complexes. Hafnium easily absorbs neutrons and is used to control nuclear reactor rods and as an alloying agent with iron, titanium, niobium, and other metals. There are complexes reported but there are no biological evaluations [109]. Zirconium is a corrosion-resistant metal that is used in pumps, valves, and some types of surgical equipment. Zirconium has been used in some complexes of which few have biological evaluations [110].

The most widely used metal of this group for synthesis of SBs complexes is titanium, an extremely corrosion-resistant metal, widely distributed, and the ninth most abundant element in the earth's crust. Several structures with this metal such as carboxaldehydes, hydroxyacetophenones, and aroylhydrazines present antibiotic properties. Titanium complexes have shown antibacterial, fungicidal, and antioxidant properties mainly in oxidation states of III and IV. Antibacterial and antifungal activities of Ti(III) complexes with SBs de-

rived from furan-2-carboxaldehyde with L-histidine, L-tryptophan, L-valine, L-methionine, and L-glycine (Figure 14) have been determined by single disc method against *B. subtilis*, *E. coli*, *A. fumigatus*, and *A. niger* using streptomycin as the control [111]. The results show that the activity of the complexes increases with respect to the metal used, in the order Cu(II) > Ni(II) > Ti(III). Interestingly, all the complexes showed moderate activities, whereas the ligands did not present any significant activity against the evaluated microorganisms.



31

Figure 14. Ti(III) complexes with 2- furfuraldehyde studied for their antimicrobial activity. Complex with (a) Valine; (b) Glycine; (c) Histidine; (d) Methionine; (e) Tryptophan.

The fungicidal activity of bis(cyclopentadienyl) titanium(IV) chloride compounds with SBs derived from 2-amino-5-phenyl-1,3,4-thiadiazole with 2-hydroxybenzaldehyde or 2-hydroxyacetophenone was evaluated (Figure 15). The compounds exhibited a moderate activity against the evaluated species of fungi (*A. niger*, *A. alternata*, and *H. oryzae*), with inhibition percentages between 60.2 and 76.2% when evaluated at 1000 ppm. In this study, complex **32a** was found to be more active than complex **32b** for all three fungi, suggesting that the antifungal activity depends on the *R* group in the molecule [112]. On the other hand, the antibacterial activity against *B. subtilis* and *E. coli* was also studied, observing greater inhibition for the Gram-negative strain in relation to the Gram-positive strain (zone of inhibition = 17 mm and 16 mm, respectively), with the two Ti(IV) complexes. For both antifungal and antibacterial activity, the complexes were more active than the free ligands.

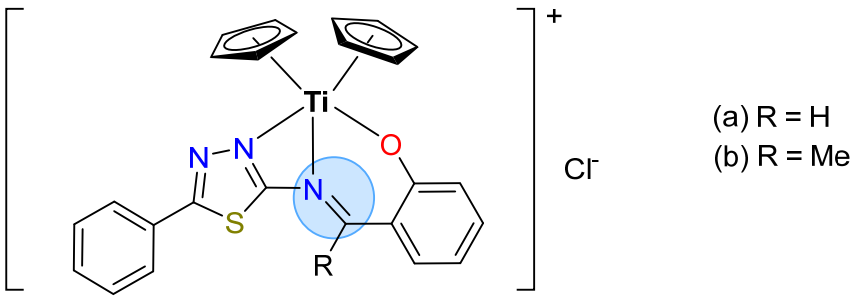


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Figure 15. Bis(cyclopentadienyl)titanium(IV) derivatives with antimicrobial activity.

Mononuclear complexes of Ti(III), Cr(III), Mn(III), and Fe(III) with tridentate hydrazone ligands 2-hydroxy-5-chloroacetophenonebenzoylhydrazone and 2-hydroxy-3,5-dichloroacetophenone-4-nitrobenzoylhydrazone (Figure 16) were screened for their antimicrobial activity on a nutrient agar medium. In all cases, the complexes showed greater inhibition compared to the free ligands [113]. The Ti(III) complexes, as well as the other complexes, showed a moderate activity against the bacterial strains *E. coli*, *S. abony*, *P. aeruginosa*, *S. aureus*, and *B. subtilis*, as well as against the fungal strains *A. niger* and *C. albicans*, with complex **34b** being the most active against *A. niger* (inhibition zone = 16.50 mm) and for the

bacterial strains *E. coli* and *S. aboni* (inhibition zone = 13.50 and 13.00 mm, respectively). It is suggested that the antibacterial activity is related to the structure of the C=N bond that reduces the polarity of the metal atom, as chelation favours the lipophicity of the metal and increases the permeability of the cell membrane.

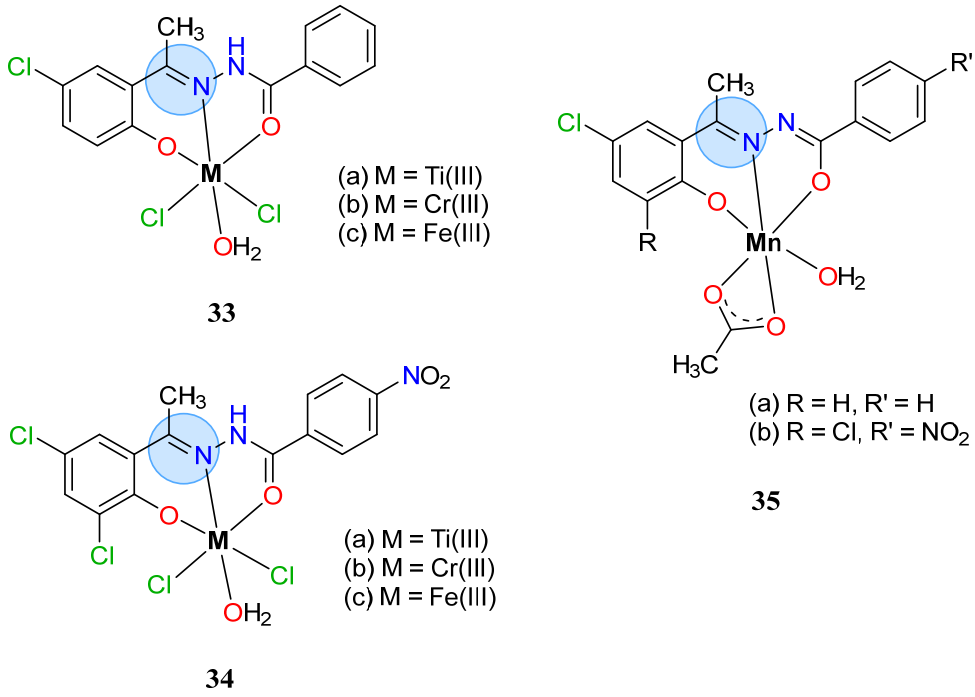


Figure 16. Ti(III), Cr(III), Fe(III), and Mn(III) complexes containing tridentate hydrazone with antibacterial activity.

The antimicrobial and antioxidant properties of titanium(IV) complexes from aroylhydrazines (benzoylhydrazine, salicyloylhydrazine, and nicotinic acid hydrazide) were evaluated (Figure 17). Complex **36c** showed the maximum activity against *B. cereus*, *S. aureus*, *C. albicans*, and *S. paratyphi* [114]. Complex **38c** showed the highest activity against the four microorganisms, and the highest activity was observed in the case of *C. albicans* and *S. aureus.* Unfortunately, the activity induced by the ligands and the complexes, rather than inhibiting the bacteria and fungi, increased the bacterial growth and the microbial biomass of the Fusarium species. Complex **38a** induced the growth of the test organism and showed the maximum inducing capacity with *C. albicans* and *S. paratyphi* and showed the minimum enhancing capacity with *B. cereus* and *S. aureus.* On the other hand, the complexes have excellent antioxidant properties because they have a high phenolic content.

Nasir Uddin et al. had previously published the antibacterial activity of Ti(IV) complexes with non-symmetrical SB ligands derived from ethylenediamine with salicylaldehyde, o-hydroxyacetophenone, and o-hydroxynapthaldehyde (Figure 18). The antibacterial study against *B. cereus* (BTCC 19), *B. cereus* (AE 14612), *B. cereus* (AE 14396), and *B. cereus* (ATCC 25922) showed that complexes **39b**, **39c**, **39d**, and **39d** were the most effective against bacteria; however, complex **39d** was shown to be the most active (inhibition zone = 18 mm) [115]. The results showed that the compounds have the maximum growth against all evaluated fungi and are less active towards the selected two fungi *M. phaseolin* and *M. phaseolina*; however, complex **39e** was able to inhibit more than 50% of phytopathogenic fungi, a better result compared to the studied compounds **40** and **41**. The improved activity of the complexes in relation to the free ligands is explained by the chelation theory, but it is clear that it is not the only important criterion when defining the antimicrobial activity, since the nature of the ligand and the presence of co-ligands influences the results of such activity.

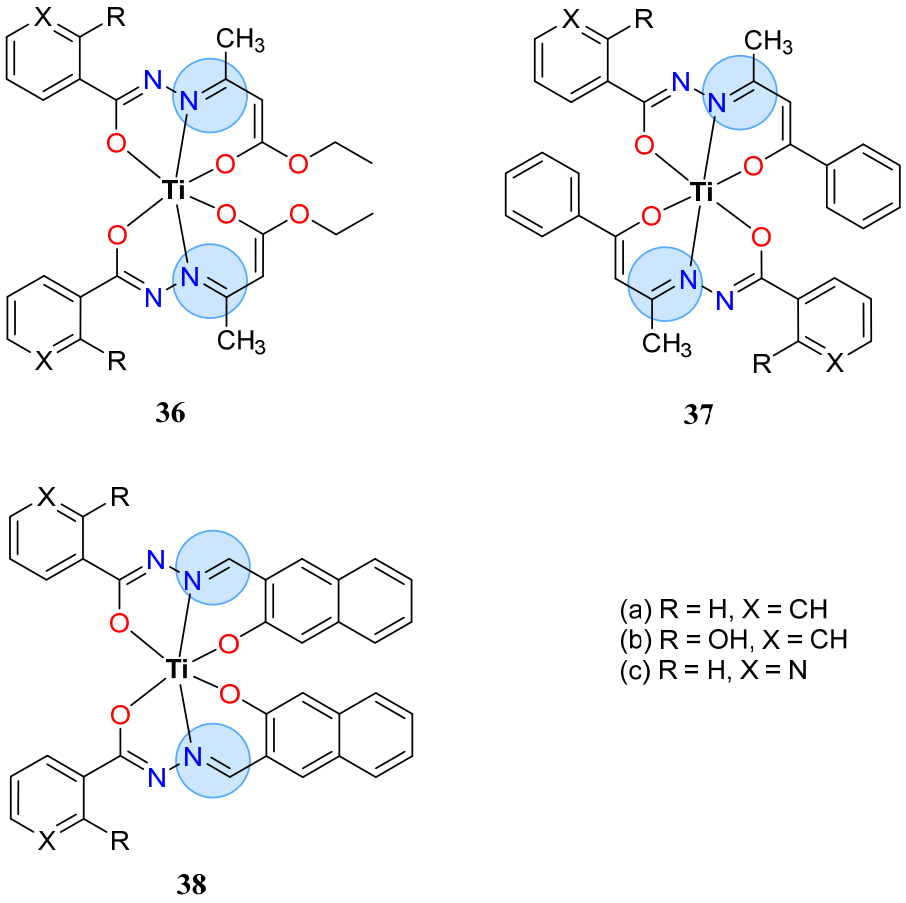


Figure 17. Ti(IV) complexes with Schiff Bases derived from aroylhydrazine with antimicrobial and antioxidant properties.

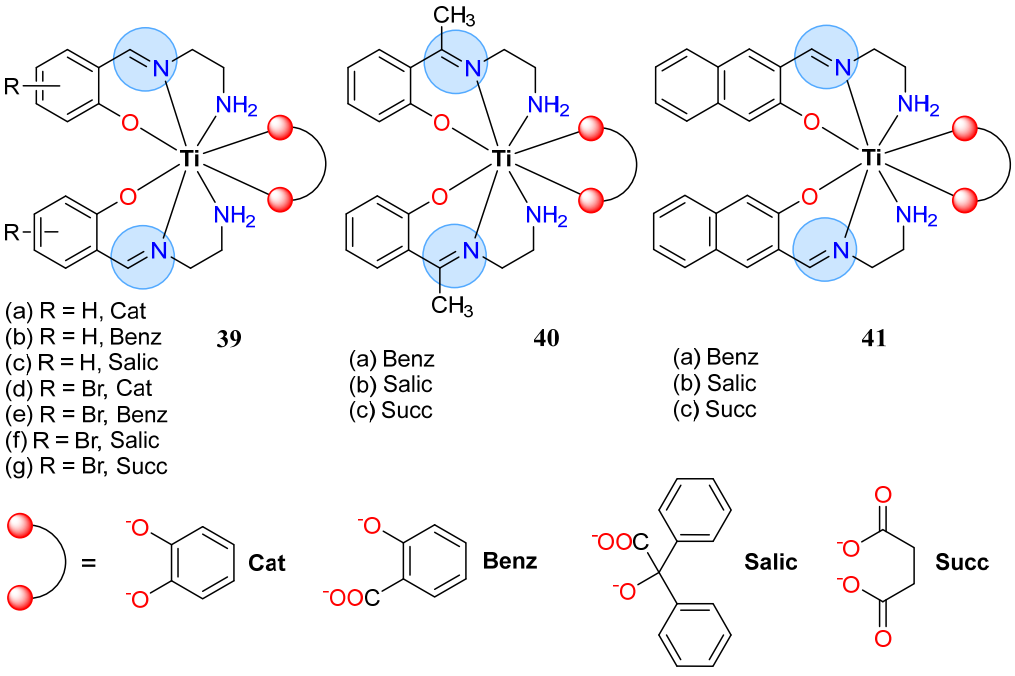
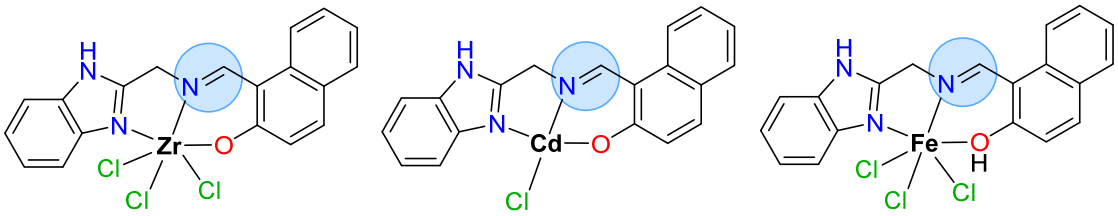


Figure 18. Ti(IV) complexes with non-symmetrical Schiff base ligands derived from ethylenediamine with antimicrobial properties.

Recently, Al-Hakimi et al. studied the biological activity of zirconium (IV), cadmium (II), and iron (III) complexes with an SB synthetized from 2-aminomethylbenzimidazole and 2-hydroxynaphtadehyde (Figure 19) [110]. The antimicrobial activity of the compounds was examined in vitro against *E. coli*, *B. subtilis*, and *A. niger* (fungus), and in this case, the activity of the ligand was higher in most of the studies compared to the metal complexes, which is explained by the increase in the polarity of the metal ion after complexation. The values of the inhibition zones varied between 15 and 32 mm, highlighting the activity of complex **43**, which presented the best activity among the three studied complexes.



42 **43** **44**

Figure 19. Zr(IV), Cd(II), and Fe(III) complexes with a Schiff base synthetized from 2-aminomethylbenzimidazole and 2-hydroxynaphtadehyde.

3.3. Vanadium Group

Group V of the periodic table contains vanadium, niobium, tantalum, and dubnium. There are complexes with SBs that contain niobium but do not report biological activity [116]. Small amounts of dubnium (Db) are produced and its half-life is short; therefore, there are currently no uses for dubnium outside of basic scientific research, so no complexes are reported. Tantalum is a transition metal with properties very similar to niobium and a very low abundance in the Earth's crust (0.7 parts per million), which could explain why it is not used to produce complexes.

Vanadium is a ubiquitous metal and exists in +2, +3, +4, and +5 oxidation states, most commonly in tetravalent and pentavalent forms, which can form several compounds and act as an anion or cation. It is present in trace amounts in plant and animal tissues such as bones, kidneys, liver, spleen, and in less quantity in the brain. In cells, vanadium can be found in the pentavalent form in the nucleus, mitochondria, and cytosol. Intracellularly, it is reduced to vanadyl (VO(IV); VO(II); V(IV)) affecting cellular metabolism. Vanadium forms compounds mainly in +3, +4, and +5 oxidation states, and different structures have previously been evaluated and reviewed [33,117,118]. Structures such as aminoantipyrines, antipyrines, and pyridinecarboxaldehyde, among others, have been evaluated mainly for their antibacterial and antidiabetic activity with good results. P. K. Panchal et al. presented the synthesis of oxovanadium(IV) complexes with SBs: salicylidene-*o*-aminothiophenol, bis(benzylidene)ethylenediamine, bis(acetophenone)ethylenediamine, 2,2′-bipyridylamine, bis(benzylidene)-1,8-diaminonaphthalene, thiophene-*o*-carboxaldeneaniline, and thiophene-*o*-carboxaldene-*p*-anisidine (Figure 20). The bactericidal activity of these compounds was evaluated against *S. typhi*, *E. coli*, and *S. mercescens* using the disc diffusion method, finding that the VO(IV) complexes were more active (40–60% inhibition) than the free ligands (10–25% inhibition), but not as effective as the tetracycline control drug (70–100% inhibition). The explanation for the synergistic effect with the presence of oxovanadium(IV) was based on the Overtone concept and the Tweedy chelation theory, where the liposolubility of the molecule is improved, while the polarity of the metal ion is reduced [117].

On the other hand, transition metal complexes of VO(IV) from the SB ligand derived from 4-aminoantipyrine and 5-bromosalicylaldehyde have been screened for antimicrobial activity (Figure 21). The results indicate that VO(IV), Ni(II), and Zn(II) complexes did not show activity, observing no inhibition growth against *E.coli* and *S.aureus* at concentrations of 200 µg/mL, 100 µg/mL, and 50 µg/mL in DMSO by paper disc method. However, with the same ligand, the Cu(II) and Co(II) complexes (complexes **49d** and **49e**) were active

at 200 μg/mL, inhibiting the growth of the two bacteria studied on the paper disc [119]. Bhattacharjee et al. reported other studies with oxovanadium(IV) complexes of ONO donor tridentate SB ligands (Figure 21). On this occasion, binuclear complexes were obtained from the ligand prepared with 2-aminophenol (complex **50**), and mononuclear complexes from the ligand prepared with 2-aminobenzoic acid (complex **51**) [120]. The antibacterial activity was evaluated by measuring the inhibition zone in mm, while the minimum inhibitory concentrations were determined by the broth microdilution method. The complexes showed high antibacterial activity (MIC = 28–48 μg/mL) against *K. pneumoniae*, *S. aureus*, *P. aeruginosa*, and *P. vulgaris*, but the activity of complex **50a** (oxovanadium(IV)) stood out, since it showed the highest inhibition zone against *P. vulgaris* (14.3 mm) and the lowest MIC value (28 μg/mL) against *K. pneumoniae* and *P. vulgaris*. The enhanced activity of the complexes relative to the ligands was explained on the basis of the Overtone concept and Tweedy's chelation theory.

The coordination complexes of VO(II), Cu(II), Co(II), and Ni(II) derived from 2-pyridinecarboxaldehyde with 4-aminoantipyrine (Figure 22) showed a good biological activity when the minimum inhibitory concentration was determined on three bacteria (*S. aureus*, *E. coli*, and *S. faecalis*) and four fungi (*A. niger*, *T. polysporum*, *C. albicans*, and *A. flavus*) [121]. The results indicate that the metal complexes are better antibacterial agents (MIC = 12–35 μg/mL) compared to the SBs (MIC = 60–75 μg/mL). In the case of the antifungal activity, the complexes presented high zones of inhibition, especially in the case of complex **52**, which obtained almost twice the value of the zone of inhibition of the ligand, reaching values of up to 30 mm of activity against *A. niger* and *C. albicans*, the same result as for complex **53b** against *A. niger*. These good results of antimicrobial activity of the complexes compared to the ligand were explained by the Overtone concept and the chelation theory, according to which by reducing the polarity of the metal ion due to a charge exchange with donor groups, it is possible to improve the penetration into lipid membranes.

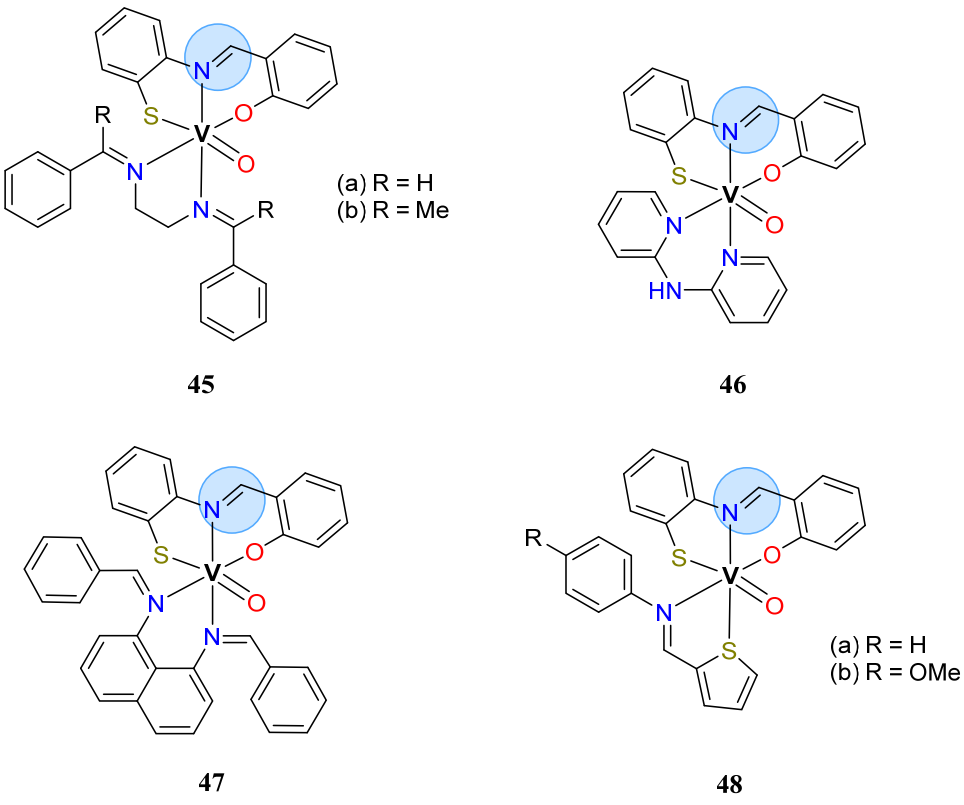


Figure 20. Oxovanadium(IV) complexes with Schiff bases SNO for antimicrobial activity.

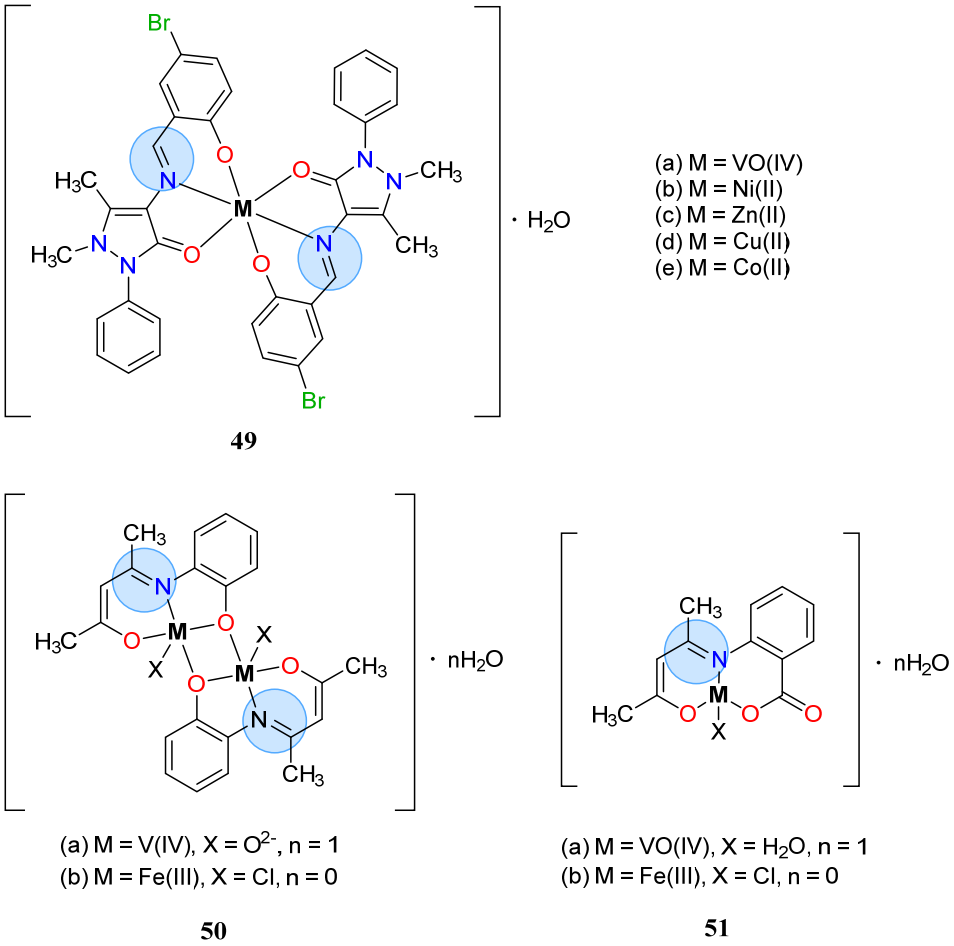


Figure 21. Metal complexes with ONO donor tridentate Schiff base ligands tested as antimicrobial agents.

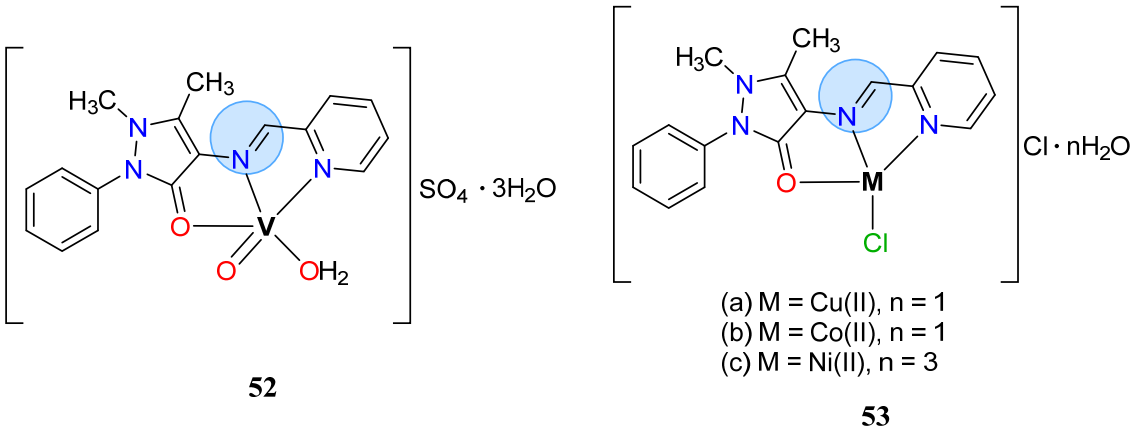
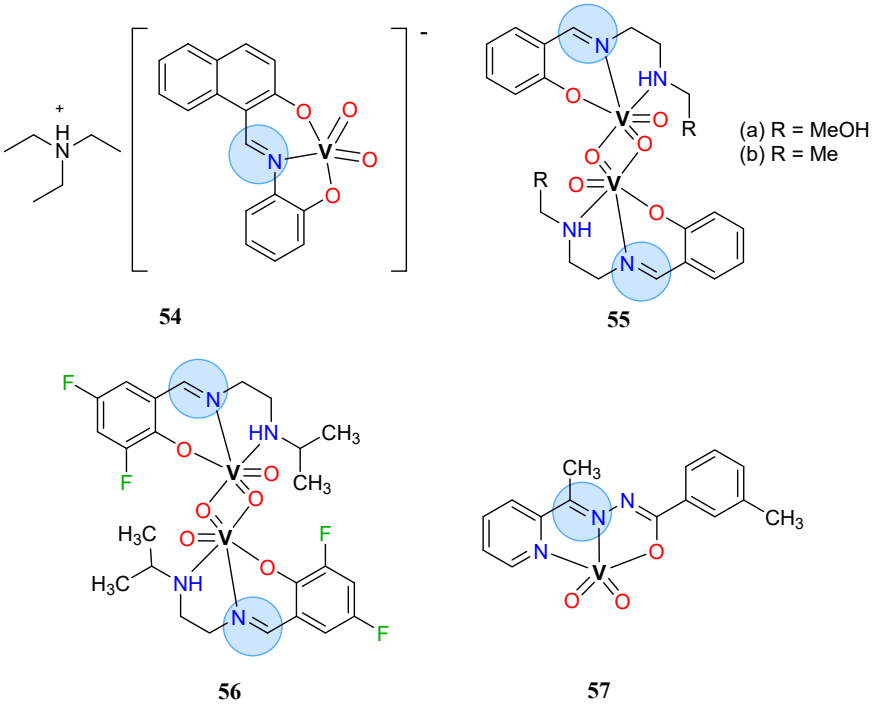


Figure 22. Metal complexes from 2-pyridinecarboxylidene-4-aminoantipyrine ligand with antimicrobial activity.

On the other hand, vanadium(V) complexes have also been interesting for their antimicrobial activity. In a recent study by M. Khosravan et al., the antimicrobial activities of a tridentate ONO SB ligand named 1-[(((2-hydroxyphenyl)imino)methyl)]naphthalen-2-ol and its di-oxido vanadium(V) complex (Figure 23) were evaluated against *E. coli*, *S. aureus*, *P. aeruginosa*, and *B. cereus*, observing that the compounds were active against all bacteria strains (except the ligand for *E. coli*) [122]. Interestingly, complex **54** presented a higher antibacterial activity against Gram-negative and Gram-positive bacteria, especially *S. aureus* (inhibition zone = 35 mm at 500 µg/mL). The reported MIC val-

ues against *P. aeruginosa* showed that the complex (125 μg/mL) is more active than the free ligand (250 μg/mL), which is attributed to the positive charge of the central atom and the delocalization of the π electrons on the chelate ring, which would improve the penetration capacity of the molecule in the membranes of microorganisms [122]. The dimeric oxovanadium(V) complexes (Figure 23) were obtained with the mono-anionic forms of 2-{1-[2-(2-hydroxyethylamino)ethylimino]ethyl}phenol (complex **55a**) and 2-[1-(2-ethylaminoethylimino)ethyl]phenol (complex **55b**), which showed stronger activities than SBs and tetracycline for *C. albicans* [123]. The activities of the complexes were stronger than those of free SBs for *S. aureus* (MIC = 2–8 μg/mL) and *E. coli* (MIC = 16–32 μg/mL) and still much lesser than tetracycline (MIC = 0.32 and 2.12 μg/mL, respectively). Another dimeric oxovanadium(V) complex was reported by Xiao-Qiang et al. (complex **56**), using 2,4-difluoro-6-[(2-isopropylaminoethylimino)methyl]phenolate as SB ligand [124]. The comparative study of minimum inhibitory concentration values of the ligand and of the complex indicates that the vanadium(V) complex had a higher activity than the free SB, an activity improved by the greater lipophilic nature of the complex. The MIC values for complex **56** were: 0.5 μg/mL (*S. aureus*), 1.0 μg/mL (*E. coli*) and 64 μg/mL (*C. albicans*), which exceeded the activity values of the control drug (tetracycline) that obtained an MIC of 2.12 μg/mL for *E. coli* and > 512 μg/mL for *C. albicans* [124]. The vanadium(V) complex **57**, obtained from the anionic form of 3-methyl-N′-(1-(pyridin-2-yl)ethylidene)benzohydrazide, showed a better activity than penicillin B against *S. aureus* (MIC = 2.3 μg/mL for complex **57** and 4.7 μg/mL for penincillin B), *E. coli* (MIC = 18.8 μg/mL for complex **57** and >150 μg/mL for penincillin B), and *P. fluorescens* (MIC = 75 μg/mL for complex **57** and >150 μg/mL for penincillin B) [125]. In general, complex **57** had a strong activity against *B. subtilis* and *S. aureus*, a moderate activity against *E. coli*, and a weak activity against *P. fluorescens*. However, antibacterial activity studies for this same tridentate ligand coordinated with copper and zinc showed that the copper complex is the most active, presenting the lowest MIC values (0.30–18.8 μg/mL) and being even lower than the reference drugs (penicillin B and kanamycin G).



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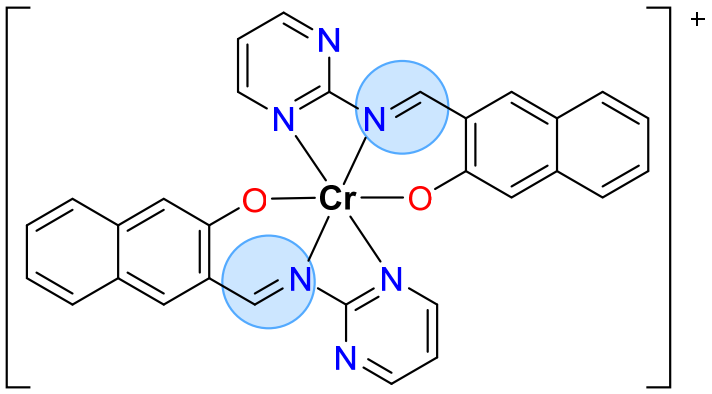
56 57

Figure 23. Monomeric and dimeric oxovanadium(V) complexes from Schiff base ligands with antimicrobial activity.

3.4. Chromium Group

Group VI contains the elements of molybdenum, tungsten, and chromium. There are several complexes containing molybdenum and tungsten but no biological evaluations of them have been available so far [126–128]. Molybdenum is an essential trace element that is present in the human body in the liver, kidney, adrenal glands, and bone, and is required for the function of many enzymes. Tungsten is naturally found in rocks and minerals, always combined with other chemicals, and it is used as a catalyst to speed up chemical reactions and several products, such as X-ray tubes, light bulbs, high-speed tools, and others. There are other complexes with SBs but the biological activity is not evaluated [129,130]. Chromium is the most used and biologically evaluated element of this group. It is a natural element in biologic systems, such as animals and plants, predominantly in oxidation states: trivalent chromium, Cr(III), or hexavalent chromium, Cr (VI). Cr(III) is an essential nutrient to normal glucose, proteins, and fats metabolism. The body has systems for reducing chromium(VI) to chromium(III). A chromium(VI) detoxification leads to an increase in the chromium(III) levels. Humans are generally exposed to chromium(III) by eating food, drinking water, and inhaling air that contains the chemical. Some structures with SBs of metformin, aminopyridines, and aminophenols have been obtained and several biological activities have been evaluated, such as the antidiabetic activity [131], but principally the antimicrobial activity against bacterial and fungal species [132]. The biological activity of a complex obtained by the reaction of $Cr(NO_3)_3 \cdot 6H_2O$ with the SB named (Pyrimidin-2-yliminomethyl)-naphthalen-2-ol (complex **58**) was reported by A.M. Abu-Dief et al. (Figure 24), testing the antimicrobial activity using the well diffusion method. The results obtained at 10 µg/mL were moderate (inhibition zone = 14.0 mm for *S. marcescence*, 11.5 mm for *E. coli*, 18.0 mm for *M. luteus*, 9.0 mm for *A. flavus*, 16.0 mm for *G. candidum*, and 10.5 mm for *F. oxysporum*) compared to the standards used (Ofloxacin for bacteria and Fluconazol for fungi). However, the ligand reveals a lower antimicrobial activity than the complexes, suggesting the antibacterial activity is enhanced after chelation [132].



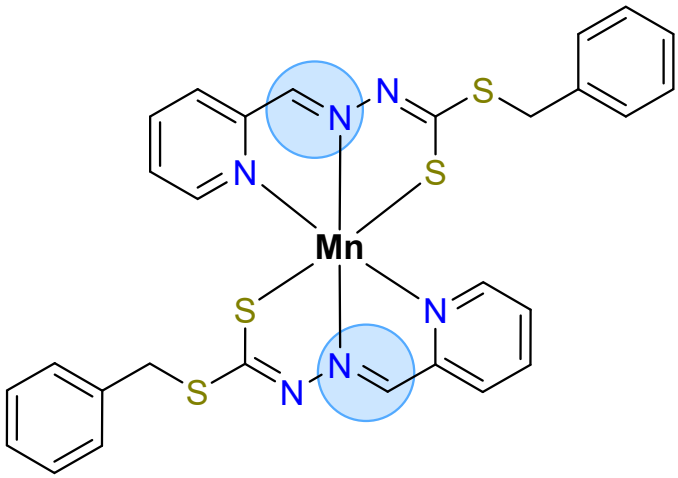
58

Figure 24. Cr(III) complex from the Schiff base (Pyrimidin-2-yliminomethyl)-naphthalen-2-ol with antibacterial activity.

3.5. Manganese Group

From group VII, manganese has been used in the synthesis of different complexes with ligands derived from tridentate Schiff bases that have exhibited an antimicrobial activity, especially when the metal is present as Mn(II). As for technetium and rhenium, there are still no biological studies of complexes with tridentate SBs that support proposing them as potential antimicrobial agents. In 2011, Zhang et al. reported a tridentate SB ligand (pyridine-2-carbaldehyde S-benzyldithiocarbazate) and its Mn(II) complex. The novel NNS-complex **59** was structurally characterized, showing a distorted octahedral geometry and a complex with 1:2 (M:L) stoichiometry (Figure 25) [133]. In order to test

the new compounds as microbiological agents, they were analysed by the disc diffusion method against eleven pathogenic strains to determine the MIC (μg/mL), obtaining the following results: Gram-positive (*B. subtilis*, *S. aureus*, and *A. tumefaciens*), Gram-negative (*E. coli*, *S. thyphimurium*, and *P. aeruginosa*), and fungi (*C. lusitaniae*, *C. albicans*, *A. niger*, *M. mucedo*, and *P. oxalicum*). The MIC determination demonstrated that the Mn(II) complex does not have significant microbiological activity with values from 100 to 250 μg/mL, being the lowest for *B. subtilis* and the highest for *P. aeruginosa* and *C. lusitaniae.* The results are as expected, considering the differences in the cell wall between Gram-positive and Gram-negative strains.

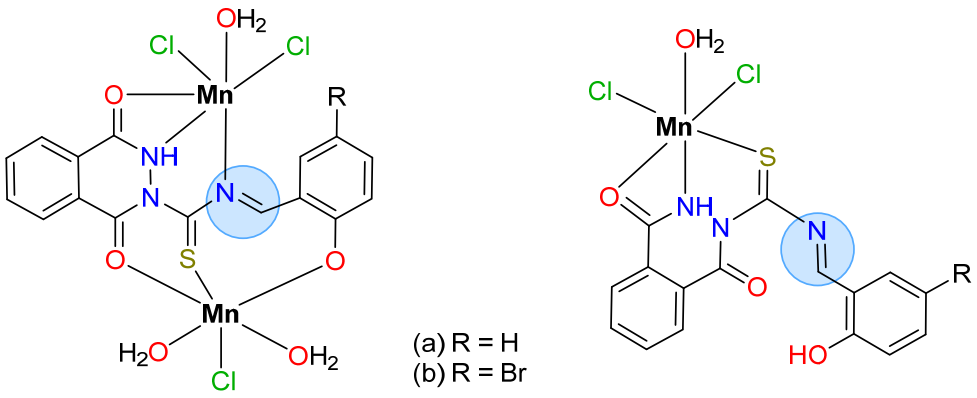


59

Figure 25. Mn(II) complex from an NNS Schiff base ligand with antimicrobial activity.

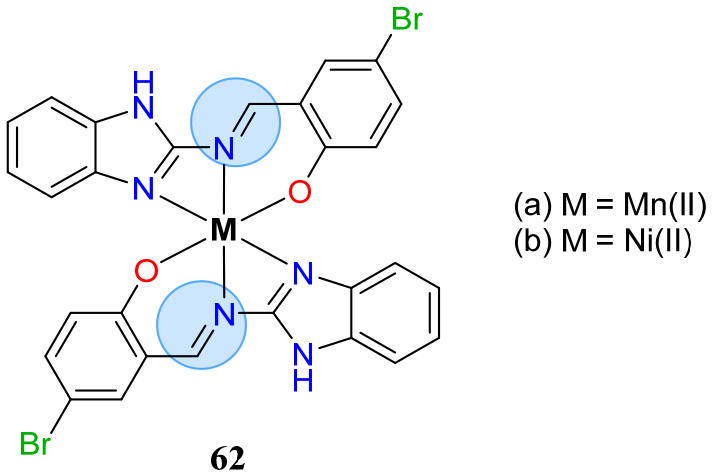
Refat's research group reported two SB ligands and their Mn(II) complexes to evaluate their biological properties [134]. Through analytical characterization and molecular modelling, Mn(II) complexes were proposed with an octahedral geometry, where manganese coordinates with ONN/OSO and ONS atoms to generate dinuclear and mononuclear complexes, respectively (Figure 26). To evaluate the antimicrobial activity, only complex **61** was studied. The agar disc diffusion method was used to test the uncoordinated ligands and their metal complexes at a 100 μg concentration against the Gram-positive strains *B. subtilis*, *S. pneumoniae,* and *S. aureus*, the Gram-negative bacteria *E. coli* and *Pseudomonas sp.*, as well as the fungi and yeasts strains *A. niger* and *Penicillium sp*. From the observed inhibition zone (in mm), it was evidenced that the complex **61** did not display a significant antimicrobial effect, and specifically for *P. aeruginosa,* the activity was null. The results for the *B. subtilis* and fungi strains were similar. The authors suggest that the results were due to the steric hindrance and the chelate effect.

Ahmed et al. obtained a tridentate SB ligand (NNO) and its Mn(II) and Ni(II) complexes, which were elucidated with octahedral geometry and a 1:2 stoichiometry M:L (Figure 27) [135]. Once the compounds were completely characterized, the authors carried out biological assays to test this compound as a possible antifungal agent. An agar well diffusion method was used to evaluate the antifungal activity of the new compound against *C. albicans* and *A. niger*, using grisofulvin as a positive control. The measurement of the inhibition zone, in mm, showed the complexes **62** as moderate agents against the two strains tested with values of the inhibition zone (13.45–14.33 mm for **62a** and 17.00–21.22 mm for **62b**) near to the standard drug (inhibition zone = 18.22–19.38 mm) employed and in both cases superior to the free ligand (inhibition zone = 10.38–11.48 mm).



60 **61**

Figure 26. Mn(II) complex from ONN/OSO and ONS Schiff base ligand with antimicrobial activity.



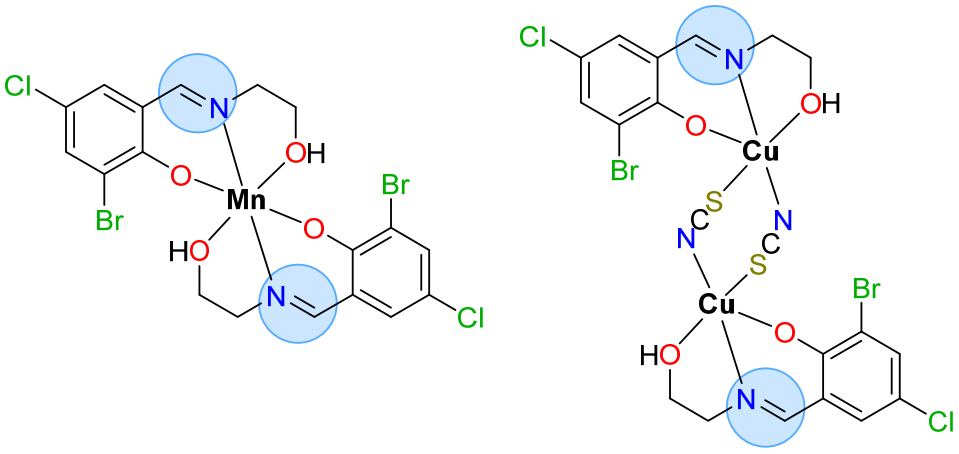
62

Figure 27. Mn(II) and Ni(II) complexes from tridentate Schiff base ligand (NNO) with antifungal activity.

Zhang and co-workers synthesised an SB ligand and its manganese and copper complexes (Figure 28) to test the antimicrobial activity against the Gram-negative bacteria *E. coli* and *P. fluorescens* and the Gram-positive bacteria *S. aureus* and *B. subtilis* by the MTT method reported as MIC (µg/mL) [136]. The results revealed that the complex **63** showed a moderate activity on the Gram-positive strains (MIC = 3.12–6.25 µg/mL) and a weak effect on *E. coli* (MIC = 12.5 µg/mL). On the other hand, complex **64** obtained better results with MIC values below the reference drug (penicillin), highlighting the MIC value of 0.20 µg/mL against *B. subtilis*. In this study, it is clear that the chelate effect improves the antibacterial activity of the complexes in relation to the free ligand.

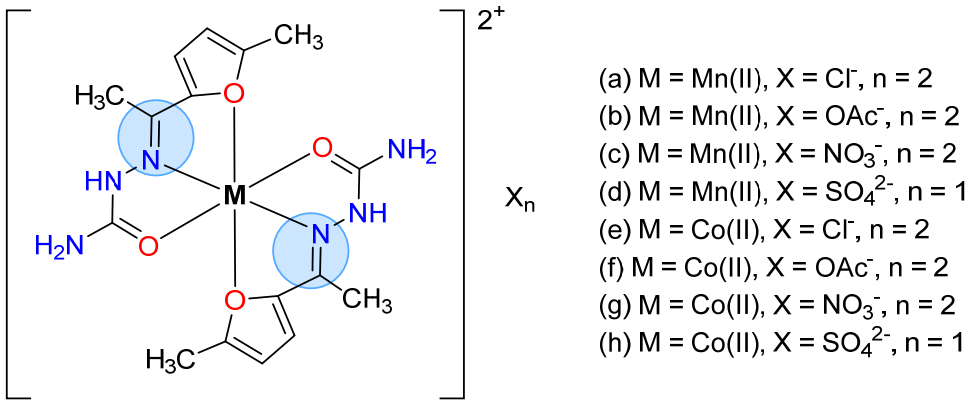
The SB ligand derived from semicarbazone was reported by Misra et al. as well as, consequently, the metal complexes that include those of Mn(II) and Co(II). The new compounds were synthesized by varying anionic species (X= Cl^-, NO_3^-, CH_3COO^-, $1/2SO_4^{2-}$), suggesting by analytical and theoretical methods that all complexes have octahedral geometry and a formula $[MnL_2]X_2$ (Figure 29) [137]. In order to evaluate their antimicrobial activities, all complexes were tested against representative bacteria and fungi strains, the Gram-positive *S. aureus*, the Gram-negative *P. aeruginosa*, and the two yeast strains *C. krusei* and *C. tropicalis* by well diffusion method and using four solutions of different concentrations from 250 to 1000 µg/mL. The results expressed in mm obtained by the measurement of the inhibition zone confirmed that the metal complexes presented major inhibition of bacterial and fungi growth (inhibition zone < 43 mm for fungi and <34 mm for bacteria) than the uncoordinated ligand (inhibition zone < 18 mm for fungi and <9 mm for bacteria). It was observed that the effect is highly dependent on the applied dose,

and in general it gives a better result for the yeast strains and a worse one for *P. aeruginosa*. On the other hand, complexes **65c**, **65d**, **65g**, and **65h** (with NO_3^- and SO_4^{2-}) show the highest values in the inhibition zone, and even values close to the reference drug (inhibition zone = 44–45 mm) were observed. The authors suggest that these results were consistent with Overtone and Tweedy's theory.



63 **64**

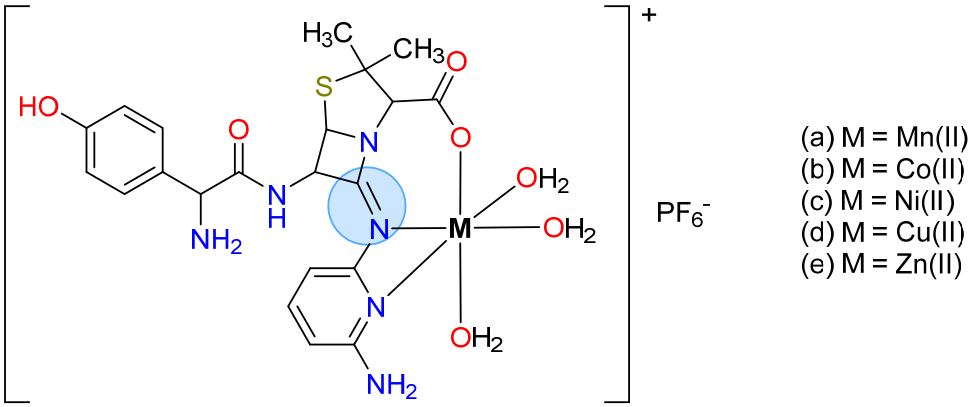
Figure 28. Mn(II) and Cu(II) complexes with a Schiff base derived from 2-bromo-4-chloro-6-[(2-hydroxyethylimino)methyl]phenol.



65

Figure 29. Mn(II) and Co(II) complexes with Schiff base ligand derived from semicarbazone with antimicrobial activity.

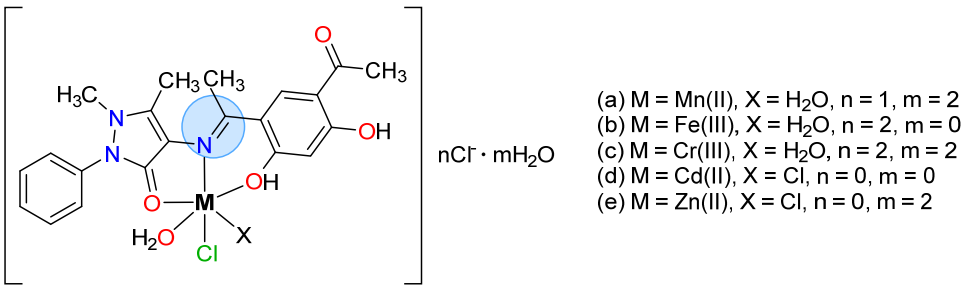
Anacona et al. synthesized a derived amoxicillin ligand (NNO) and its metal complex to carry out a microbiological evaluation using the disc diffusion method (Figure 30) [138]. M(II) complexes were tested as antimicrobial agents in *S. aureus*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *S. epidermis*. From the measurement of the inhibition zone, the authors observed a clear tendency to mainly inhibit Gram-positive bacteria. Among the metal complexes synthesized, complexes **66c** and **66e** possess pronounced bactericidal activity against *S. aureus* and *E. coli* (inhibition zone = 27–30 mm). Most of the coordination compounds showed little or no activity against *P. aeruginosa* and *S. epidermidis* bacteria with the exception of complexes **66b** and **66d**, which showed a slight activity.



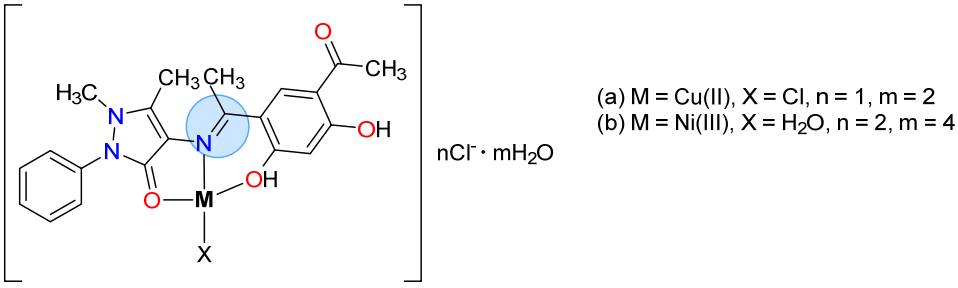
66

Figure 30. Metal(II) complexes with a Schiff base ligand derived from amoxicillin studied for antibacterial activity.

Recently, Ahmed's group reported an SB ligand (ONO) and obtained seven metal complexes [139]. The experimental procedures demonstrated that Mn(II), Fe(III), Cr(III), Cd(II), and Zn(II) complexes have an octahedral geometry and 1:1 stoichiometry (Figure 31). The antimicrobial activity was examined by the well diffusion method against the *S. aureus* and *E. coli* bacterial strains, while the fungi strains evaluated were *C. albicans* and *A. flavus*. The negative control was DMSO and the standard reference drugs were amikacine and ketokonazole. The results reported as inhibition zones in mm reveal that all metal complexes have better antimicrobial activity than the free ligand. Additionally, complex **67d** showed a better antimicrobial activity than the other octahedral complexes, with inhibition zones of 24 mm for *E. coli*, 20 mm for *S. aureus*, and 20 mm for *C. albicans*. It is clear from this study that the geometry of the complexes and the nature of the metal play an important role in the antimicrobial activity.



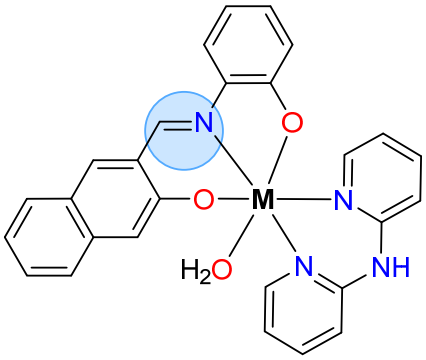
67



68

Figure 31. Mononuclear chelates of Mn(II), Fe(III), Cr(III), Cd(II), Zn(II), Cu(II), and Ni(II) from a new tridentate Schiff base ligand with antimicrobial properties.

Patel and co-workers reported a brief microbiological study that includes manganese(II), iron(II), cobalt(II), nickel(II), copper(II), zinc(II), and cadmium(II) complexes (Figure 32) [140]. The antimicrobial effect was evaluated with the agar diffusion method and expressed as percentage of inhibition. The species studied included fungi (*C. utilis* and *S. pulverlentum*) and one bacteria strain (*P. fluorescens*). A concentration of 5×10^{-4} M was used, and all the complexes showed a moderate to good result without a clear tendency; however, in all the cases, the metal complex was better than the free ligand. Another interesting finding was the major effect of bacteria over the fungi strains in almost all the complexes evaluated. This fact was expected due to the difference between the cell membrane and the associated lability.

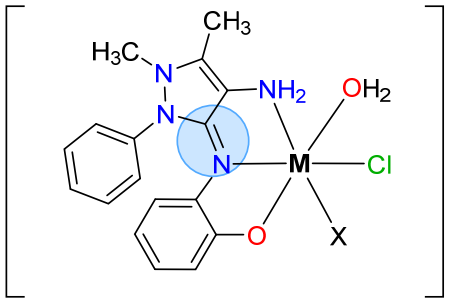


(a) M = Mn(II)
(b) M = Fe(III)
(c) M = Co(III)
(d) M = Ni(II)
(e) M = Cu(II)
(f) M = Zn(II)
(g) M = Cd(II)

69

Figure 32. Metal(II) complexes with ONO tridentate Schiff bases and 2,2′-bipyridylamine.

Mohamed et al. synthesized a new NNO ligand from 4-aminoantipyrine and 2-aminophenol and their coordination compounds with a variety of transition metals, including Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), and Fe(III), all of them with octahedral geometry (Figure 33) [141]. The antibacterial activity was evaluated against *B. simplex*, *E. acetylicum*, *E. coli, and P. putida*, using the agar diffusion technique and DMF and cefepime as internal controls. The results (reported as cm of inhibition values) showed that the Fe(III) complex exhibited a good antibacterial activity against *B. subtilis*, *E. acetylicum*, and *P. putida*, better in all cases than the free ligand and cefepime. On the other hand, complex **70b** showed a great selectivity with the best antibacterial activity against *E. coli*, more than the free ligand and cefepime; however, the most active compound was the copper compound (complex **70d**) that managed to reach an inhibition value between 11 and 15 mm against *P. putida*, surpassing the activity of the reference drug.



(a) M = Mn(II), X = H_2O, n = 3
(b) M = Co(II), X = H_2O, n = 4
(c) M = Ni(II), X = H_2O, n = 4
(d) M = Cu(II), X = H_2O, n = 4
(e) M = Zn(II), X = H_2O, n = 3
(f) M = Cd(II), X = H_2O, n = 3
(g) M = Fe(III), X = Cl, n = 3

70

Figure 33. M(II) and Fe(III) complexes with a Schiff base ligand prepared via condensation of 4-aminoantipyrine and 2-aminophenol.

In 2014, Chondhekar et al. obtained an SB tridentate ligand (ONO) from dehydroacetic acid with *o*-phenylene diamine and fluorobenzaldehyde, which is highly recognized and employed as a bactericidal and fungicidal compound [142]. The authors reported the

formation of their metal complexes with five transition metals (Mn(II), Cu(II), Ni(II), Co(II), and Fe(III)). All the complexes were obtained with 1:2 stoichiometry (M:L) and exhibited an octahedral geometry (Figure 34). The antimicrobial activity of the metal complexes was tested against fungi (*A. niger* and *Trichoderm*) and bacterial strains (*S. aureus* and *E. coli)*, employing the dry mycelium method for the antifungal activity and the paper disc plate method for the antibacterial activity with 0.5 and 1.0 mg/mL concentrations. From the measurement of the inhibition zone or the percentage of inhibition, it was observed that in all cases, the metal complex showed a higher activity than the free ligand, but a lower one than ciprofloxin, concluding that the novel complex exhibited a very weak activity against the bacterial strains tested and a higher activity against fungal strains. The results observed with fungi species were in accordance with the stability constants of the complexes determined by the authors following the order: Cu(II) > Ni(II) > Co(II) > Fe(III) > Mn(II). Later, the same research group reported a tautomeric ligand derived from hidrazone and its cobalt, iron, and manganese complexes used to evaluate the antimicrobial activity, this time including bacteria and fungi species [143]. The manganese complex (complex **73**) was obtained with enol form while the keto ligand generated the cobalt and iron complexes, all of them with octahedral geometry (Figure 34). The authors performed their biological experiments through a less used methodology such as the agar cup method and the poison plate method for bacteria and fungi, respectively, with a fixed concentration of 1% in DMSO as solvent, and reported the activity as mm of inhibition zones. *E. coli*, *S. aureus*, *B. subtilis*, *A. niger*, *P. chrysogenum*, *F. moniliforme,* and *A. flavus* were tested. The results showed no activity through Gram-negative strains with any complex; however, the Gram-positive strains were seriously affected by both metal complexes as free ligands (to a lesser extent), including the manganese complex that showed a relevant activity against *S. aureus* and *B. subtilis* with comparable results to the standard used (penicillin). The antifungal activity showed that free ligand had no effect on growth inhibition, and by way of contrast, complex **72** demonstrated the highest antifungal activity against almost all strains, except for *A. flavus*, while complex **73** was only active against *F. monilifirme.*

Zahan et al. prepared an SB ligand and its metal complexes including Mn(II), Fe(II), Co(II), and Sn(II), all with a suggested octahedral geometry (Figure 35) [144]. The antibacterial activity was measured through the paper disc diffusion method, using 40 µg/0.01 mL of each complex, in DMSO. The strains tested were the Gram-negative strains *E. coli*, *P. aeruginosa,* and *A. aceti*. The latter is unfrequently studied; nevertheless, it is industrially and commercially important. The results showed that the formation of a metal complex enhanced the antibacterial activity, where complexes **74a** and **74b** presented the best activity against *E. coli* (inhibition zone = 12 mm), while complex **74c** presented the best activity against *P. aeruginosa* (inhibition zone = 13 mm). Although there is no comparison with the Gram-positive strain, the effect of the complexes would be expected to be better.

Sumrra et al. presented two tridentate triazole (NNO) derived SB ligands and seven transition metal complexes which possess 1:2 stoichiometry (Figure 36) [145]. The novel compounds were tested as antimicrobial agents against six bacterial strains and six fungi strains: *H. halophila*, *H. salina*, *C. israelensis*, *C. salexigens*, *S. aureus*, *N. gonorrhoeae*, *T. longifusus*, *C. albicans*, *A. flavus*, *M. canis*, *F. solani,* and *C. glabrata.* Biological experiments were carried out using the agar diffusion method and reported as mm of inhibition zone, using streptomicin, ampicillin, and miconazole as standard references for bacterial and fungi species. Almost all the tested complexes showed a moderate to weak activity, with the best result for complex **76e** against *S. aureus* (inhibition zone = 20 mm), outperforming the activity of control drugs (15 mm for streptomycin and 12 mm for ampicillin). The antifungal results revealed that, in general, the complex **75g** was the best antifungal agent, the inhibition percentage varying from 73 to 82%. The results evidenced the free ligand and the metal complexes showed an antimicrobial activity without a clear tendency.

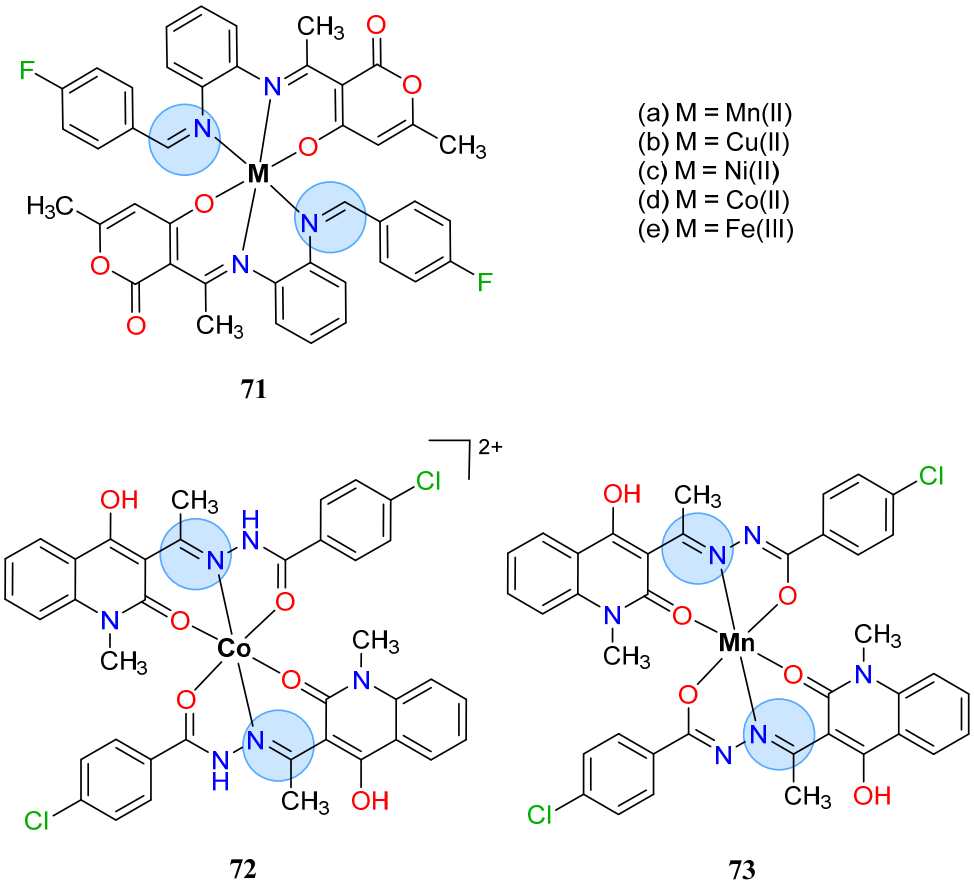


Figure 34. Metal complexes with Schiff base ligands (NNO and ONO) reported by Chondhekar group, studied for their antimicrobial activity.

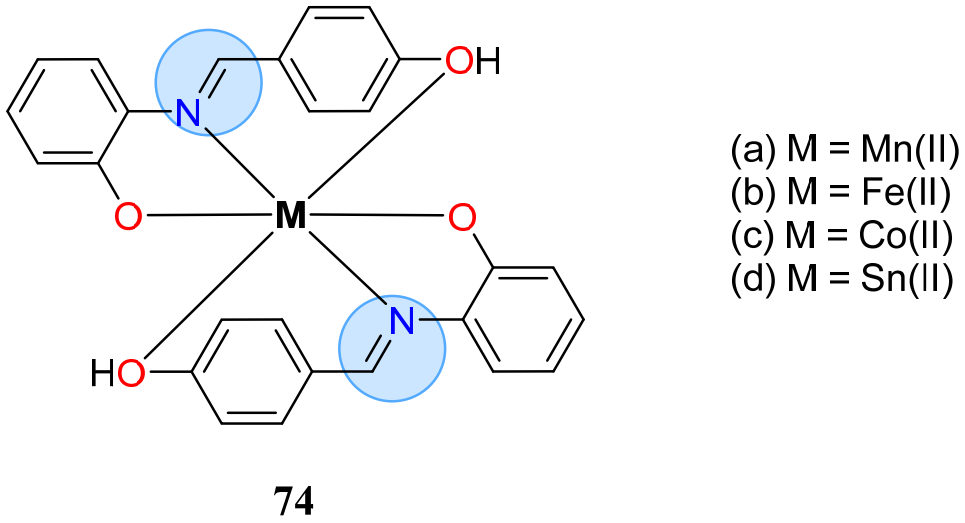
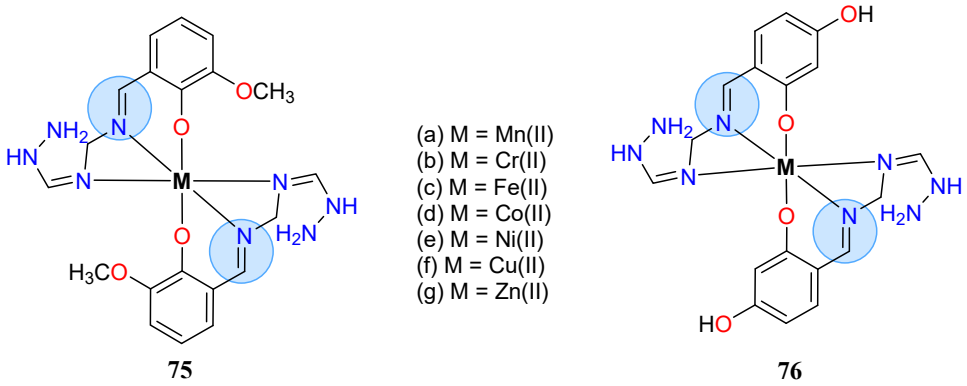


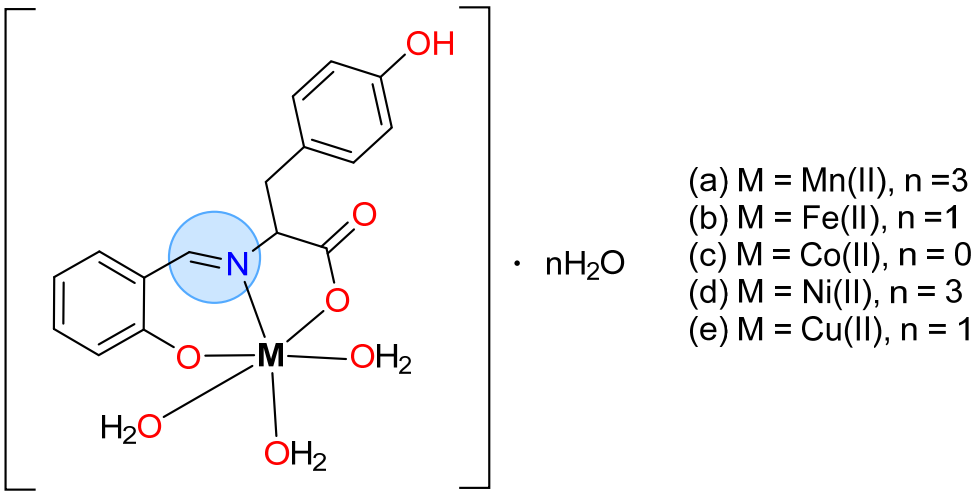
Figure 35. Transition metal complexes of Mn(II), Fe(II), Co(II), and Sn(II) ions with tridentate Schiff base ligand 2-{(4-hydroxybenzylidene) amino}phenol.



75 **76**

Figure 36. Metal complexes with Schiff base ligands (NNO) derived from 3-amino-1,2,4-triazole evaluated for their antimicrobial activity.

Osoikhia and co-workers reported in 2019 an ONO ligand derived from aromatic aminoacid, L-tyrosine, as well as the formation of its metal complexes to evaluate their antimicrobial properties [146]. The Mn(II), Fe(II), Co(II), Ni(II), and Cu(II) complexes obtained showed a 1:1 stoichiometry and an octahedral geometry (Figure 37). To evaluate the antimicrobial activity, the authors performed the agar diffusion method. To demonstrate their antibacterial potential, the metal complexes were tested against the bacterial strains (*E. coli*, *P. aeruginosa*, *S. typhy*, *K. pneumoniae*, *B. subtilis*, and *S. aureus*) including gentamycin as reference, and the fungi strains (*C. albicans*, *P. notatum*, *R. stolonifer*, and *A. niger*) were employed to evaluate the novel compounds as antifungal agents, using tioconazole as standard reference. Apparently, all the strains were chosen due to their importance, whether in public health, clinical areas, food safety, among others. Nevertheless, the metal complexes showed no activity against *K. pneumoniae*, *S. typhi*, and *R. stolonifer*, as well as an insignificant activity for the other strains. The antimicrobial screening of the complexes showed that complex **77e** was the most active of the complexes against all the microorganisms tested at all concentrations.

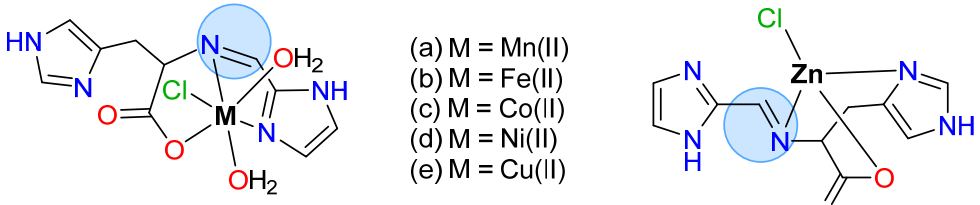


77

Figure 37. Transition metal complexes with a Schiff base derived from salicylaldehyde and L-tyrosine amino acid, evaluated for their antimicrobial activity.

Reshma et al. reported a series of metal complexes formed with transition metals including Mn(II), Fe(II), Co(II), Ni(II), Cu(II), and Zn(II) as well as an SB ligand derived from imidazole, which presented in all cases an octahedral geometry, except for the Zn(II) complex that exhibited a tetrahedral geometry (Figure 38) [147]. The biological evaluation

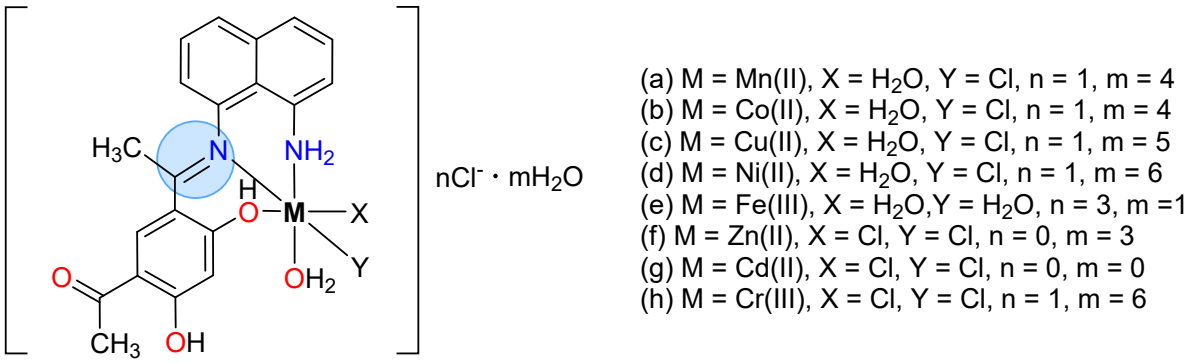
was tested by the disc diffusion method and MIC determination, using *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, *A. niger,* and *C. albicans* strains. In general, the results showed a superior activity of the metal complex vs the free ligand; nevertheless, Mn(II), Fe(II), Co(II), and Ni(II) showed a weak or moderate result on the studied strains, while complexes **78e** and **79** were the most active, even exceeding the activity of the control drug (ciprofloxacin).



78 **79**

Figure 38. Metal complexes of an imidazole-derived tridentate Schiff base ligand reported for their antimicrobial activity.

Ahmed and co-workers obtained an NNO ligand and eight transition metal complexes to evaluate their antibacterial potential (Figure 39) [148]. The new complexes were characterized through spectroscopic, analytical, and theoretical methods, which suggests that the complexes had an octahedral geometry. Antibacterial experiments were performed using the modified Kirby-Bauer method (disc diffusion) and amikacin as the positive control, while DMSO was the negative control employed. Four pathogenic strains were chosen (*S. aureus*, *B. subtilis*, *E. coli*, and *P. aeruginosa*). The results showed that the complexes **80c**, **80g**, and **80h** had the highest activity against *E. coli*, while the complexes **80d** and **80g** had the highest activity against *B. Subtilis*. Complex **80b** had the highest activity against *S. aureus* and complex **80g** had the highest activity against *P. aeruginosa*; moreover, the free ligand demonstrated a good activity against all tested species, even better than the complexes.

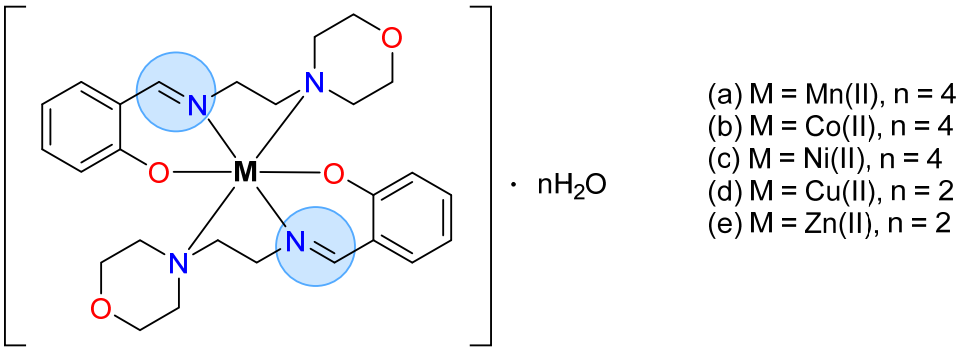


80

Figure 39. Transition metal complexes with an SB ligand derived from 4,6-diacetylresorcinol and 1,8-naphthalenediamine with antibacterial properties.

In the same way, Raja et al. performed biological experimentation to evaluate the NNO ligand and its cobalt and manganese complexes (Figure 40) including DNA intercalation and microbiological studies [149]. The bacterial strains employed were *S. aureus*, *B. cereus*, *E. coli*, *S. typhi,* and *Chromo bacteri*, while *A. niger*, *A. flavus,* and *C. albicans* were chosen to evaluate the antifungal effect. The disc diffusion method was also used by this research group, and the result showed that there was no difference between Gram-positive bacteria strains, Gram-negative bacteria strains, or fungi strains. It was also observed that there was no clear behaviour in the compounds used as antimicrobial agents to kill a specific kind of microbial species. As expected, according to Tweedy's chelation theory, the complexes

have a better result than the uncoordinated ligand. Complexes **81b**, **81d**, and **81e** showed a significant antimicrobial activity compared to the others (inhibition zone = 13–17 mm); however, they are less active than the standard drugs amikacin and ketoconazole (inhibition zone = 15–19 mm).



81

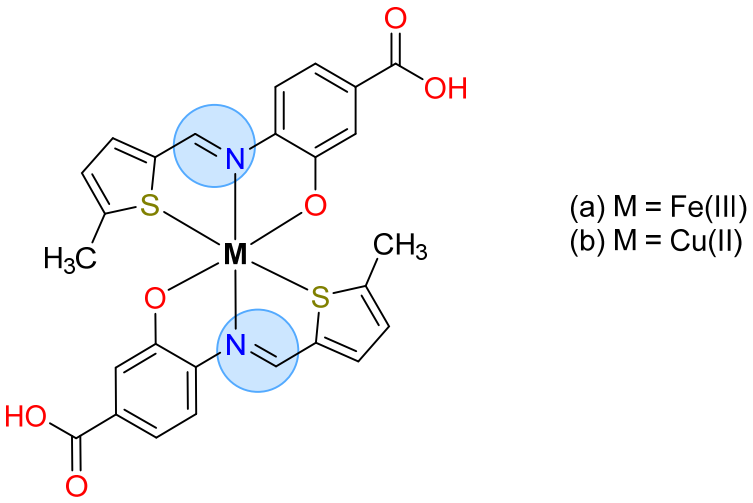
Figure 40. Transition metal(II) complexes from tridentate SB condensed with morpholine with antimicrobial activity.

3.6. Iron Group

The transition metals iron, ruthenium, and osmium are located in the group VIII of the periodic table. The complexes of Fe and Ru, di- and trivalent, with ligands derived from tridentate SBs have been reported and studied for their antimicrobial activity; however, as far as osmium is concerned, there are still no biological studies to support its use as potential antibacterial or antifungal agents. Seshaiah et al. synthesized a tridentate SB ligand (NOS) and its metal complexes of Fe(III) and Cu(II) [150]. Through spectroscopic methods, it was revealed that the new thiophene derivative ligand coordinated to the metal through iminic nitrogen, phenolic oxygen, and thiophene sulphur to generate a 1:2 (M:L) stoichiometry complex with a proposed octahedral geometry (Figure 41). The measurement of its antibacterial activity was evaluated at different concentrations of 0.5, 1, and 2 mg through the diffusion method using three bacterial strains, two Gram-negative (*E. coli* and *E. aerogenes*) and one Gram-positive (*S. aureus*), and all strains were isolated from the patients (clinical strains). The results expressed as mm of inhibition zone concluded that complex **82a** had weak activity against all the tested strains, with a clear dependence on the concentration employed, showing a very slight effect on Gram-positive strains. The high dose of complex **82b** showed good antibacterial activity against *E. coli*, *E. aerogenes*, and *S. aureus* (inhibition zone = 22, 14, and 19 mm, respectively). As expected, in all cases the metal complexes demonstrated a better antibacterial activity than the free ligand.

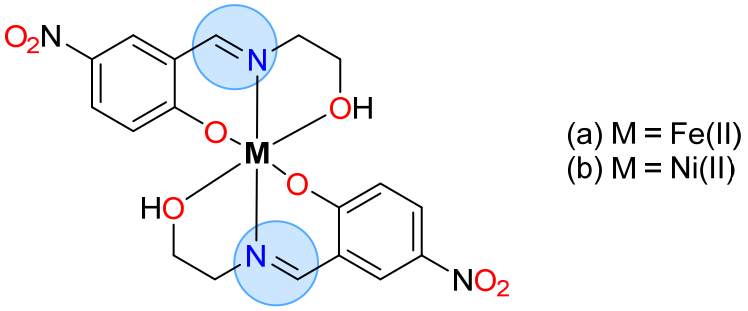
Gungor et al. synthesised a tridentate SB ligand (ONO), and its Fe(II) and Ni(II) complexes, which presented a distorted octahedral geometry (Figure 42) [151]. After complete characterization, the new compounds were tested as antimicrobial agents through a very complete experiment that includes ten bacteria strains (*C. jejuni*, *E. aerogenes*, *E. coli*, *L. monocytogenes*, *P. aeruginosa*, *P. vulgaris*, *S. aureous*, *S. marcescens*, *S. sonei*, and *K. pneumoniae*), two yeast (*C. albicans* from clinical isolate and reference strains), and five fungi (*A. flavus*, *A. niger*, *P. expansum*, *P. lanosum*, and *A. alternata*) strains. The authors used the disc diffusion method, the microdilution broth assay (for MIC determination), and the single pore culture method. The complexes exhibited similar levels of antimicrobial activity and presented a higher antibacterial activity than the free ligand, which is explained by the efficient diffusion of the metal complexes into the bacterial cell or the interaction with the bacterial cell. Complex **83a** was most effective against *P. vulgaris* and *S. marcescens* with an MIC value of 125 µg/mL. The results of these experiments were interesting because all the studied strains showed an inhibition zone equal to or very close to that observed with the standard drugs (chloramphenicol and ketoconazole), and the MIC determination was in

accordance with this result; however, the percentage of inhibition on fungi and yeast was not as expected. This result was in accordance with all the previous ones and was related to the difference in metabolism, action mechanism, and structural difference between bacteria and fungi.



82

Figure 41. Iron(III) and copper (II) complexes of Schiff base ligand named (Z)-3-hydroxy-4-((5-methylthiophen-2-yl) methyleneamino)benzoic acid with antibacterial properties.

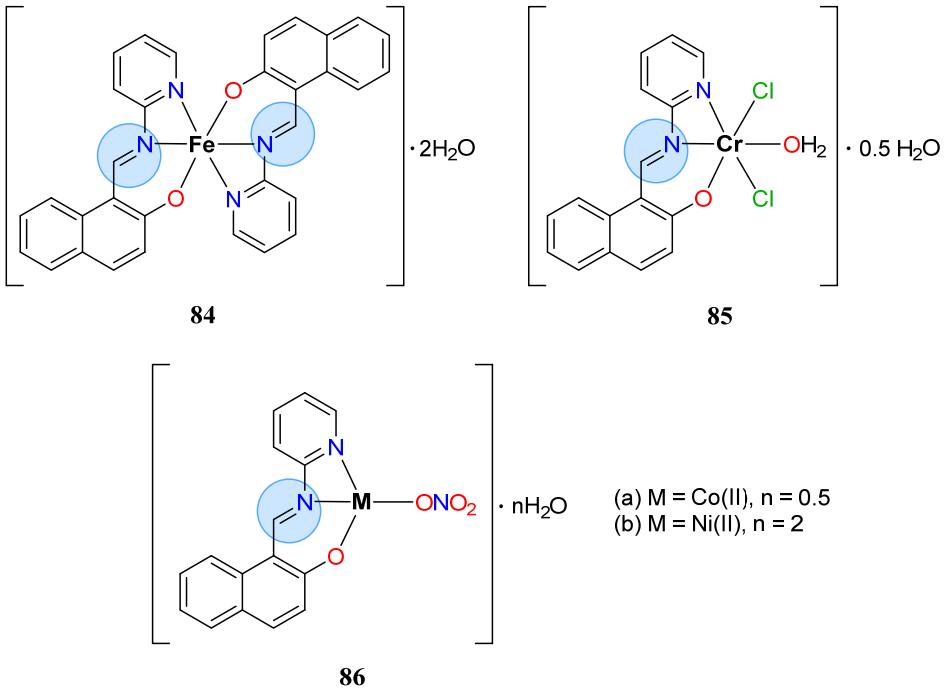


83

Figure 42. Fe(II) and Ni(II) complexes with N-(2-hydroxyethyl)-5-nitrosalicylaldimine.

In 2016, Abdel-Rahman and co-workers reported a new tridentate ligand (NNO) and its nanosized metal complexes with four transition metals, including Fe(II), Cr(III), Co(II), and Ni(II) [152]. The complexes presented tetrahedral and octahedral geometries, as well as 1:1 and 1:2 stoichiometry, respectively (Figure 43). The authors tested the biological activity of these complexes by performing cytotoxic, antioxidant, antiviral, antibacterial, and antifungal activities, as well as DNA binding. To evaluate the antibacterial activity against the two Gram-negative strains (*E. coli* and *P. aeruginosa*) and the one Gram-positive strain (*S. aureus*), the agar well diffusion method was employed, and tetracyclin and DMF acted as the positive and negative controls. The results were reported as mm of inhibition zone and as expected, the metal complexes showed a better activity than the free ligand. Complex **86b** was better than the others, achieving zones of inhibition > 35 mm at 25 mg/mL for *P. aeruginosa* and *S. aureus*. On the other hand, *A. flavus*, *C. albicans*, and *T. rubrum* were the strains used to evaluate the antifungal activity through the disc diffusion method, showing higher activity index values for metal complexes than for the free ligand, particularly the complexes **84** and **85** for *C. albicans*. According to the author discussion, the nature of metal ion, the stability of the complexes, the differences between cell membrane,

and a probable iminic nitrogen–hydrogen bond interfering with cell membrane synthesis, could be the determining factors.



84 **85** **86**

Figure 43. Complexes incorporating the 2-((*E*)-(pyridine-2-ylimino)methyl)napthalen-1-ol ligand studied for their antimicrobial activity.

Anacona et al. synthesized an NNO ligand derived from penicillin and five metal complexes M(II) (Figure 44) [153]. The antibacterial evaluation was measured by the disc diffusion method and MIC determination [138], and the strains tested were only Gram-positive strains (*E. faecalis*, *S. aureus*, and clinical isolates *S. viridans*, *Enterococcus* sp., and methicillin-resistant *S. aureus*). After the measurement of the inhibition zone, it was revealed that complexes **87a**,**c** were effective for all strains, with inhibitory zones of 15–30 mm and 10–40 mm, respectively, which was confirmed through MIC determination. Complex **87a** showed to be the most effective (MIC = 0.042 µmol/mL). As the previous reports [138], the disc diffusion method did not have the best result on the growth inhibition; this could be attributed to the solvent (DMSO), the diffusion capacity, and the characteristic solubility of the compound.

Zabin and co-workers prepared three tridentate SB ligands (NOS) and their metal complexes for screening of their antimicrobial activity [154]. The new ligands were structurally characterized by spectroscopic techniques and suggested complexes with 1:2 (M:L) stoichiometry and octahedral geometry (Figure 45). The antimicrobial potential was measured by the agar disc diffusion method, using seven pathogenic strains, six of them bacterial, and one fungi strain: *E. coli*, *P. aeruginosa*, *P. mirabalis*, *S. aureus*, *S. epidermis*, *E. faecalis*, and *C. albicans*. The result of the experiment carried out showed a weak to null activity of the new compounds; nevertheless, the complexes were in all cases better than the uncoordinated ligand. Particularly for complex **88f**, the results, expressed in mm of inhibition zone, suggest that it was the best result for Gram-positive strains, reaching inhibition zones of 24 and 25 mm for *S. epidermidis* and *E. faecalis*, respectively; the values close to the reference drug (amoxicillin) presented inhibition zones of 28 and 26 mm, respectively.

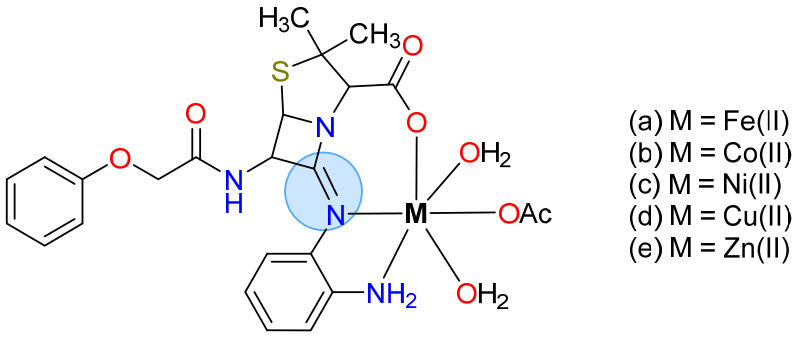


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Figure 44. Metal complexes containing a tridentate SB ligand (NNO) based on phenoxymethylpenicillin studied for their antibacterial activity.

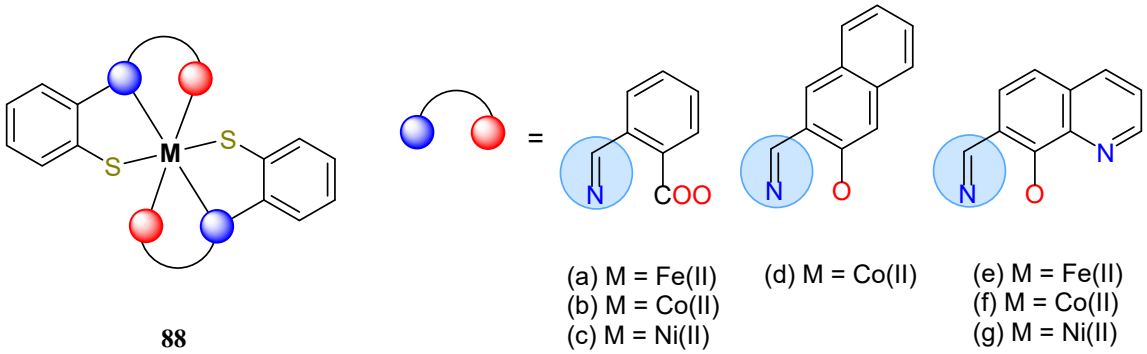

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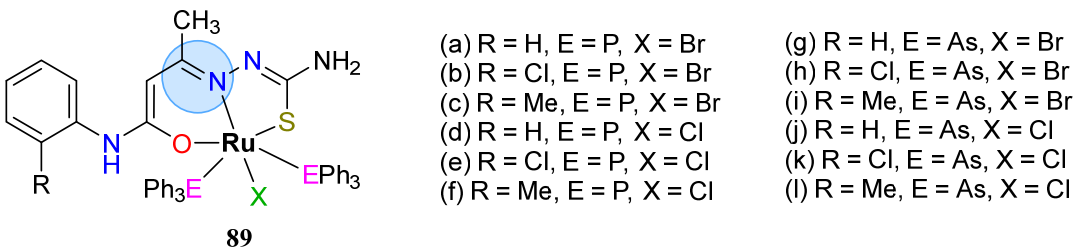
Figure 45. Fe(II), Co(II), and Ni(II) complexes with unsymmetrical tridentate Schiff base ligands prepared from 2-aminothiophenol with aldehydes.

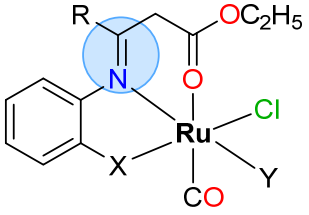
On the other hand, in this same group VIII we find ruthenium. Regarding the chemistry of ruthenium in terms of its possible applications in biological areas, it has not been studied as extensively; however, there are a few reports that can contribute to review and analyse its potential as a microbial agent. In 2005, Natarajan et al. reported the synthesis and characterization of three Schiff base ligands (NOS) from thiosemicarbazide in which the substituent in the aromatic ring (H, Me, Cl) was varied [155]. These ligands were used to obtain their Ru(III) complexes (Figure 46), which once characterised were evaluated as bacterial growth inhibitors. The antimicrobial assay was performed at concentrations of 0.25%, 0.5%, and 1%, using the disc diffusion method against only Gram-negative strains (*E. coli*, *A. hydrophila,* and *S. typhi*) and using streptomycin as the standard drug. From the results expressed as diameter of inhibition zone in mm, it is observed that the new Ru(III) complexes displayed from moderate to weak activities, which depend on the applied dose, and all the metal complexes showed a better activity than the free ligand; however, none came close to the result obtained with the standard drug.



89

Figure 46. Ruthenium(III) complexes containing dibasic tridentate Schiff bases with antibacterial activity.

Later, Jayabalakrichnan and co-workers synthesized four new SB ligands, two of which were NOS and two ONO [156]. After the ligands were fully characterised, they were used to generate the Ru(II) complexes. The authors proposed that these metal complexes had an octahedral geometry, where mononuclear and coordination occur through imine nitrogen, carbonyl oxygen, and the SH or OH group (Figure 47). To evaluate their ability as an antibacterial agent, the new complexes, uncoordinated ligands, metal salts, DCM (dichloromethane), and amikacin were tested against *S. aureus* and *E. coli* employing the Kirby-Bauer method. The assay was carried out at different concentrations, from 0.5% to 1.0%, 1.5%, and 2.0%, and the results reported in mm of inhibition zone revealed that the Ru(II) complexes have a lower effect on bacterial growth, but higher than the free ligand, metal salts, and DCM with a dependence on the dose used. The results also showed that the complexes with R = C_6H_5 and X = S (complexes **90h**, **90j**, and **90l**) presented a greater inhibition zone (15–19 mm) against *S. aureus*, while against *E. coli*, the activity was improved (inhibition zone = 15–17 mm) with the presence of pyridine (Py) coordinated to the metal centre (complexes **90e**, **90f**, **90k**, and **90l**), which indicated that the activity depends largely on the substituent group located on the carbon of the imine, as well as on the base coordinated to Ru(II).

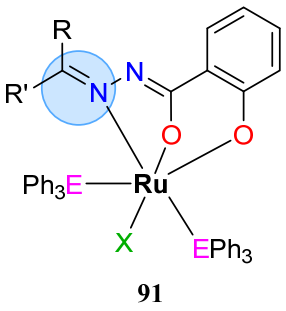


90

(a) R = CH_3, Y = PPh_3, X = O
(b) R = CH_3, Y = PPh_3, X = S
(c) R = CH_3, Y = $AsPh_3$, X = O
(d) R = CH_3, Y = $AsPh_3$, X = S
(e) R = CH_3, Y = Py, X = O
(f) R = CH_3, Y = Py, X = S
(g) R = C_6H_5, Y = PPh_3, X = O
(h) R = C_6H_5, Y = PPh_3, X = S
(i) R = C_6H_5, Y = $AsPh_3$, X = O
(j) R = C_6H_5, Y = $AsPh_3$, X = S
(k) R = C_6H_5, Y = Py, X = O
(l) R = C_6H_5, Y = Py, X = S

Figure 47. Diamagnetic ruthenium(II) complexes with monobasic tridentate Schiff base ligands derived from *o*-aminophenol or *o*-aminothiophenol.

Another contribution was reported by Balasubramaniam et al. from the synthesis of twelve octahedral Ru(II) complexes (Figure 48) [157]. The complexes presented 1:1 stoichiometry and the coordination of the ONO ligand to ruthenium occurred from imine nitrogen, carbonyl oxygen, and deprotonated phenolic oxygen. Once fully characterised, the catalytic and biological activities of these Ru(II) complexes were tested. The interest in the biological field was to test them as possible inhibitors of bacterial growth. This evaluation was performed by the disc diffusion method against *S. aureus*, *E. coli*, *P. aeruginosa*, and *S. typhi* at three different concentrations of 0.25, 0.50, and 1.0% and employing streptomycin as a positive control. Through the measurement of the diameter of the inhibition zone in mm, it was determined that the complexes **91** were more effective than the free ligand; however, they did not exceed the activity of the standard drug. It was also observed that there is no substantial difference between Gram-negative and Gram-positive strains, and with regard to the dose, a clear dependence was observed, as at higher concentrations of the complex used, the inhibition of bacterial growth was greater. Finally, regarding the structural differences, it was observed that the weakest antibacterial effect was presented when the ligand had two methyl groups (complexes **91a**, **91b**, **91g**, and **91h**), while in all groups of synthesized complexes the best result was when bromine was found in the coordination sphere (X = Br).



91

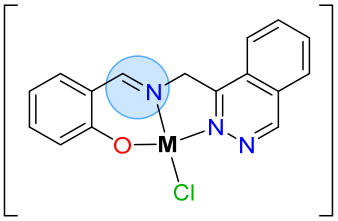
(a) R = Me, R' = Me, E = P, X = Br
(b) R = Me, R' = Me, E = P, X = Cl
(c) R = Me, R' = Et, E = P, X = Br
(d) R = Me, R' = Et, E = P, X = Cl
(e) R = H, R' = PhOH, E = P, X = Br
(f) R = H, R' = PhOH, E = P, X = Cl
(g) R = Me, R' = Me, E = As, X = Br
(h) R = Me, R' = Me, E = As, X = Cl
(i) R = Me, R' = Et, E = As, X = Br
(j) R = Me, R' = Et, E = As, X = Cl
(k) R = H, R' = PhOH, E = As, X = Br
(l) R = H, R' = PhOH, E = As, X = Cl

Figure 48. Ruthenium(III) complexes with tridentate Schiff base ligands (ONO) derived from salicyloyl hydrazide with antibacterial activity.

3.7. Cobalt Group

Group IX corresponds to cobalt, rhodium, and iridium; however, studies on antimicrobial potential were only found for cobalt when coordinated with tridentate ligands derived from SBs. The most commonly observed geometries when cobalt(II) and cobalt(III) were used to obtain metal complexes with NNO and ONO ligands was octahedral, and the less frequently observed one was square planar. The antimicrobial activities of cobalt complexes were studied, considering bacteria, fungi, and yeast, and in almost all cases including other metals, such as manganese, copper, nickel, zinc, and less frequently iron; however, there were a few assays that were exclusive to cobalt.

Shoukry et al. reported a hidrazone SB ligand (NNO) and its metal complex that included cobalt(II) as metal centre (Figure 49) [158]. The antimicrobial activity was measured by the disc diffusion method (Kirby-Bauer). The authors employed four bacteria species (*S. aureus*, *B. subtillis*, *E. coli*, and *P. aeruginosa*) and two fungi species (*A. flavus* and *C. albicans*). The results reported for bacteria in mm for the measurement of the inhibition zone showed that complexes were better than the free ligand over all microbiological strains, but only in *E. coli* was the result moderate for the Co(II) complex, while the complex **92b** turned out to be more active with the inhibition zones between 14 and 15 mm. The effect of complex **92b** on fungi was also better, comparable to that found for complexes **92a** and **92c**.



92

(a) M = Co(II), n = 2
(b) M = Cu(II), n = 1
(c) M = Ni(II), n = 1

Figure 49. Metal(II) complexes with a tridentate hydrazone ligand derived from hydralazine with antimicrobial activity.

Abdel-Satar et al. synthesized a tridentate SB ligand and four metal complexes including Co(II), Pd(II), and Cu(II) [159]. The stoichiometry observed for the monobasic complexes was 1:1 (Figure 50). Antimicrobial experiments were performed using the disc diffusion method against four bacterial strains (*B. subtilis*, *S. aureus*, *E. caratovora*, and *P. vulgaris*), including DMS and streptomycin as controls and reference. The results revealed that the novel metal complexes had a weak or null activity against the studied pathogenic strains. In the first place, all complexes showed a weak activity against *E. caratovora*; meanwhile, the complexes **94** and **95** exhibited an activity against all bacterial strains, which suggested that the antibacterial activity of this series of compounds depended largely on the nature of the metal centre.

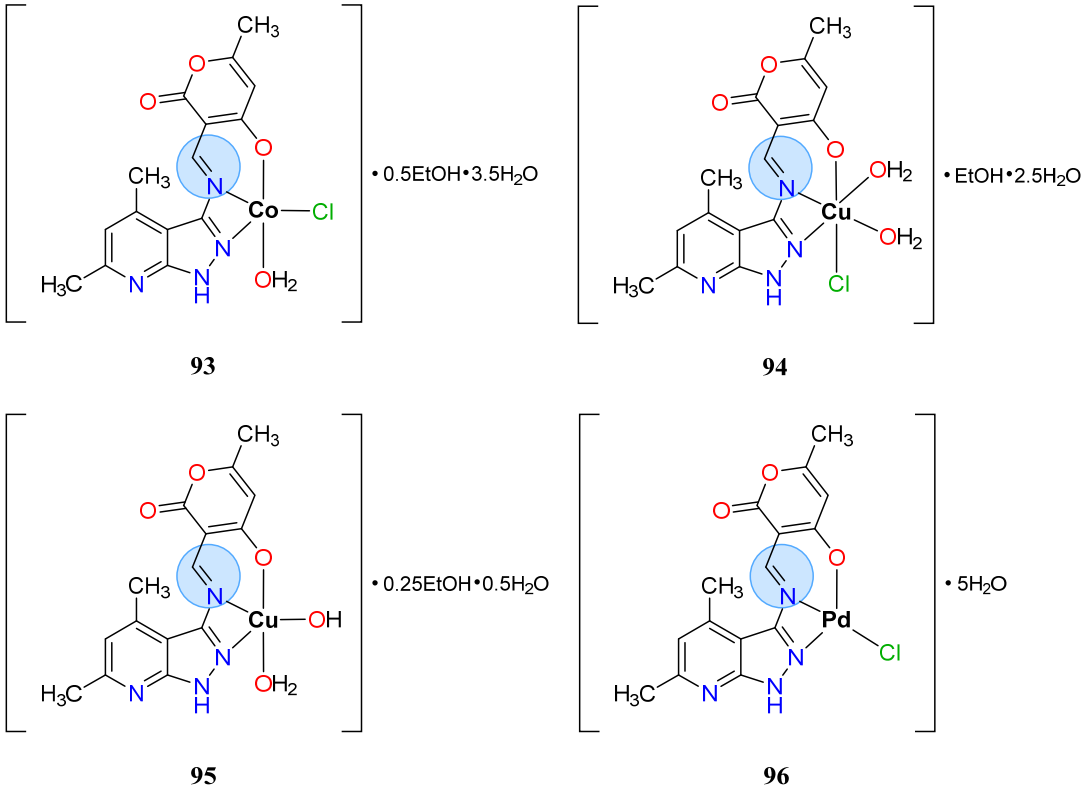


Figure 50. Metal complexes containing Schiff base ligand named (Z)-3-(1-((4,6-dimethyl-1*H*-pyrazolo [3,4-b] pyridin-3-yl)imino)ethyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one.

Kubicki and co-workers presented a ligand and its cobalt(III) complex with distorted octahedral geometry, where Co(III) was coordinated to ONO heteroatoms from the ligand and three nitrogen from pyridine (Figure 51) [160]. The biological properties were measured by the Kirby-Bauer disc diffusion method to analyse the antibacterial activity against Gram-positive and Gram-negative species; the selected strains were *B. subtilis*, *S. aureus*, *E. coli*, and *P. aeruginosa*. The Kirby-Bauer experiment showed moderate results against the bacteria; however, the MIC obtained for complex **97** was 30 mg/mL, concluding that there was no activity for this complex. Subsequently, Salehi et al. published two works about the synthesis of ONO ligands and their cobalt complexes (Figure 51), which presented in all cases a distorted octahedral geometry (complexes **98**–**100**). The authors reported the evaluation of the antimicrobial activity through the Bauer method and MIC determination in their 2014 work [161], as well as MIC and MBC determination for their 2018 publication [162], using almost the same strains as the previous report; however, *P. aeruginosa* was substituted by *S. typhi*. The antimicrobial effect in both reports, as predicted, was better for the complexes (MIC = 4.0–8.2 µg/mL for **98**–**100** and 3.2–279 µg/mL for **101**) than for the free ligand (MIC = 6.0–16.4 µg/mL for SB of **98**–**100** and 104–558 µg/mL for SB of **101**), and a better activity was exhibited on Gram-positive than on Gram-negative strains. Even then, when no reference standard is used, the MIC value obtained showed lower concentrations of complex **101**, which was used at a 10^{-6} M concentration. According to Tweedy's theory, the observed result was expected to show a higher activity of the ligand with the phenyl group over that with the -NH_2 group.

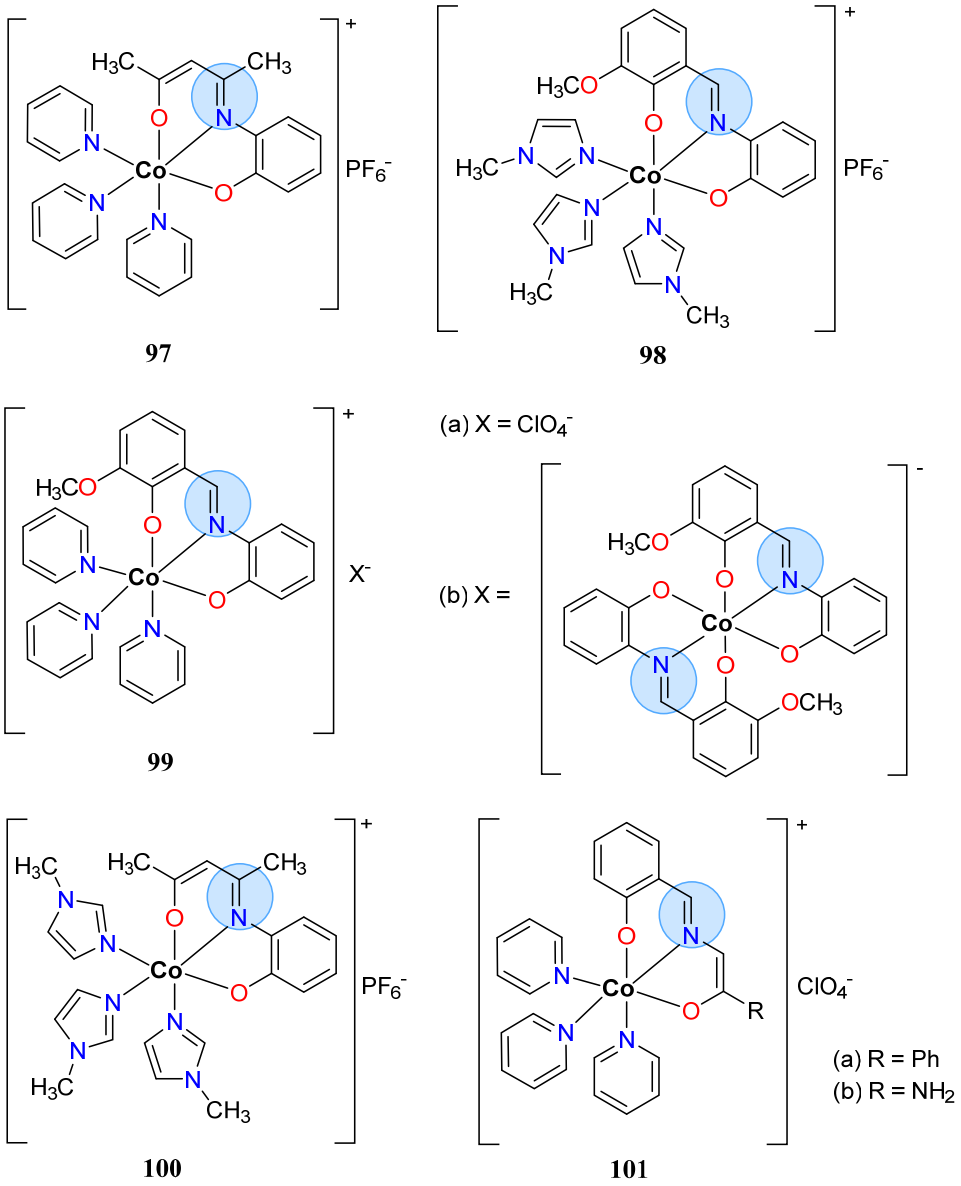
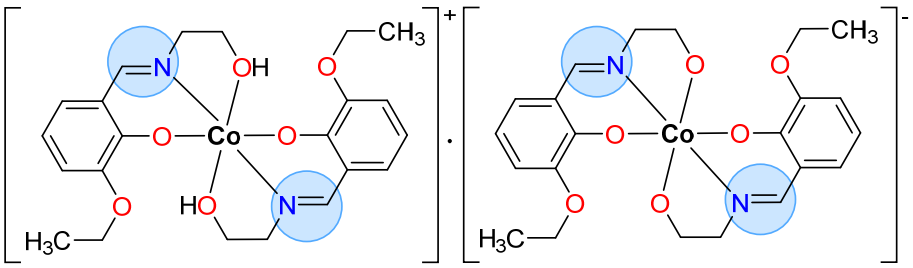


Figure 51. Co(III) complexes with Schiff base ligands (ONO) reported by Kubicki et al. studied for their antibacterial properties.

Du obtained two ONO ligands and their cobalt and copper complexes (Figure 52) to evaluate their antimicrobial effect on *S. aureus*, *E. coli*, *P. aeruginosa*, and *S. typhi* by the well diffusion method and MIC determination using a concentration of 100 µg/mL in both experiments [163]. The observed effect was always better for the complexes (MIC = 10.1–21.0 µg/mL) compared to the free ligands (MIC > 27.3 µg/mL), which may be due to the coordination of the SBs to Co(III) and an efficient diffusion of the complexes **102** and **103** into the bacterial cell.

Mahalakshmi et al. reported a new NNO ligand to form metal complexes of Co(II), Cu(II), Ni(II), and Zn(II) [164]. The cobalt complex had 2:1 stoichiometry (Figure 53), with a hexacoordinated metal centre (octahedral geometry). The antimicrobial activity was tested by the well diffusion method and MIC determination using *S. aureus*, *B. subtilis*, and *P. vulgaris*, as well as *C. albicans* as the fungi strain. The authors used concentrations from 20 to 60 µL, and they observed a good to moderate and a dose-dependent effect, with better results for 40 and 60 µL solutions, highlighting the greater effect of the free ligand, comparable to all metal complexes, which could be attributed to the antipyrinyl fragment. Only for the activity against *P. vulgaris*, a greater inhibition zone was found for

the complexes (11–14 mm at 60 µL) compared to the free ligand (9 mm at 60 µL), with complexes **103a** and **103d** being more active; however, the inhibition values were far from the value obtained for the reference drug, tetracycline (24 mm at 60 µL).



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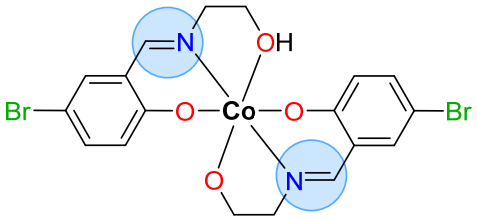

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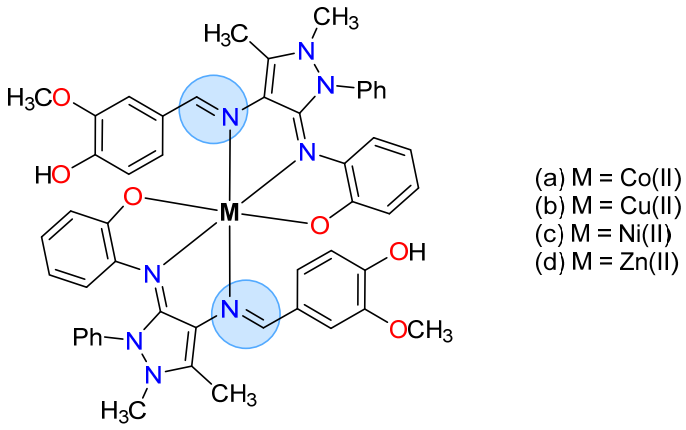
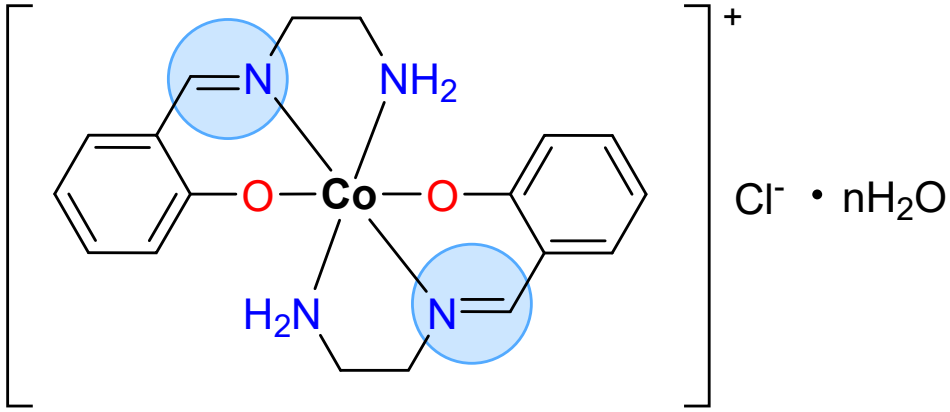
Figure 52. Cobalt complexes with Schiff base ligands (ONO) containing [(2-hydroxyethylimino) methyl]phenol studied for their antibacterial activity.



104

Figure 53. Metal(II) complexes with a tridentate Schiff base derived from 4-hydroxy-3-methoxybenzylidine-4-aminoantipyrine studied for their antimicrobial activity.

The NNO structurally simple ligand and its cobalt(III) complex was reported by Chitra et al. (Figure 54). The metal complex was fully characterized and tested through biological experiments to evaluate its potential application [165]. To realize the antimicrobial measurement, the authors performed the disc diffusion method including six different species: *S. aureus*, *B. subtilis*, *S. paratyphi*, *K. pneumoniae*, *A. niger*, and *C. albicans*. The result showed a significant enhancement in the activity of complex **105** versus its ligand, and a considerable activity against *S. aureus* (inhibition zone = 22 mm), *S. patratyphi* (inhibition zone = 23 mm), and *A. niger* (inhibition zone = 33 mm), even better than the standard reference drug (ciprofloxacin and clotrimazole).



105

Figure 54. Co(III) complex with a tridentate SB ligand derived from salicylaldehyde and ethylenediamine tested as antimicrobial agent.

Hao reported a new azido ligand, the formation of its cobalt(III) trinuclear complex and phenolato-bridged dinuclear copper(II) complex (Figure 55), as well as the antibacterial evaluation against bacterial strains (*S. aureus* and *E. coli*) and yeast (*C. parapsilosis*) by the macro-dilution method and MIC determination [166]. From the MIC values, the result revealed a better antimicrobial activity against the Gram-positive strain (0.54 mM for **106** and 0.28 mM for **107**), followed for the Gram-negative strain (1.03 mM for **106** and 0.65 mM for **107**), the last or least affected being the yeast species (>2.5 mM for **106** and 1.81 mM for **107**). That result is in agreement with the structural difference of cellular wall. In general, complexes were more active than the free ligand (MIC > 2.5 mM for bacteria and yeast).

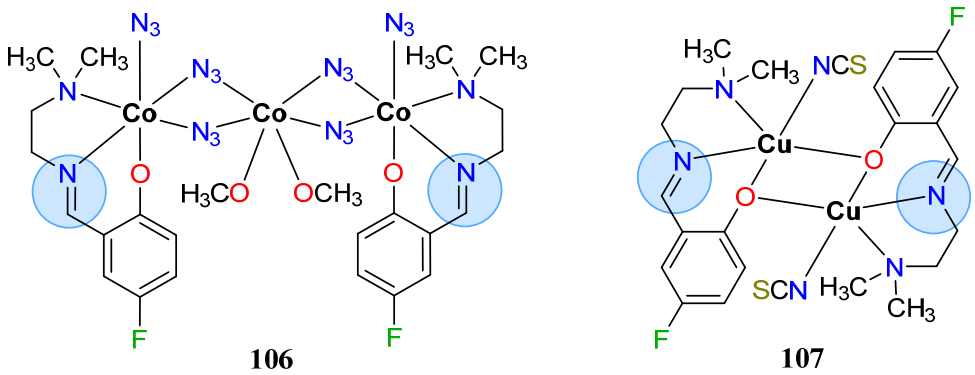
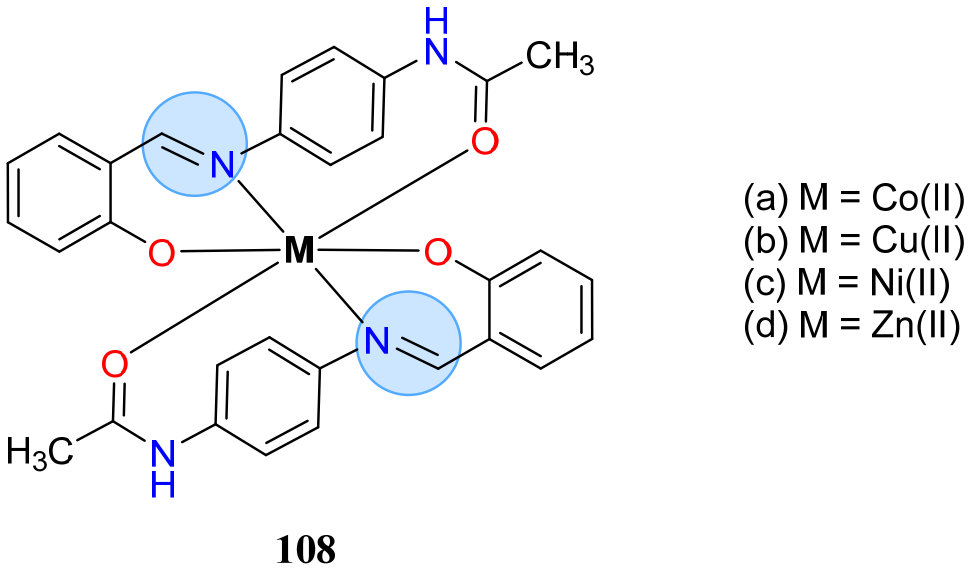


Figure 55. Polynuclear Co(III) and Cu(II) complexes derived from similar tridentate Schiff bases with antimicrobial activity.

In 2018, Munjal synthesised an ONO ligand derived from acetanilide and formed the distorted octahedral complexes of Co(II), Cu(II), Ni(II), and Zn(II) (Figure 56); however, for these complexes, the author only chose fungi species to test their biological activity, such as *A. niger*, *A. flavus*, *R. stolonifer*, *C. albicans*, *R. bataticola*, and *T. harzianum* [167]. All of them have a great importance in medical, food technology, and agroindustry areas. In general, the complexes caused a significant inhibition (MIC = 20–55 g/mL) compared to the free ligand (MIC = 50–85 g/mL). Due to the fact that the concentrations emerged from different experiments, there was no direct comparison between these investigations. Comparing the transition metals, a direct relationship was found between the antifungal activity and the nature of the metal ion, with complex **108b** being the most active against all strains (MIC = 20–30 g/mL).



108

Figure 56. Transition metal(II) complexes with Schiff base derived from *p*-amino-acetanilide and salicylaldehyde studied for their antifungal activity.

Similar results were obtained by Prajapati et al. who synthesized an ONO tridentate ligand to form two tetrahedral Co(II) and Cu(II) complexes and one octahedral Ni(II) complex (Figure 57) [168]. The antimicrobial evaluation was carried out by the well diffusion method and the studied strains were limited to bacteria, the Gram-positive group included *B. subtilis* and *B. cereus*, while the Gram-negative strains were *E. coli* and *P. aeruginosa*. It is important to highlight the concentrations employed to perform the biological experiment, which ranged from 100 to 400 µg/mL, and the results showed that the antimicrobial activity for complex **110** was highly dependent on the concentration. As seen in previous reports, the free ligand had no effect on bacterial growth, while complex **109** showed a weak or moderate effect and complex **111** showed a moderate effect (inhibition zone = 10–14 mm), with a slightly better result on *E. coli* and *B. subtilis* for complex **110** (inhibition zone > 14 mm). According to the authors, an inhibition zone of less than 6 mm was considered for an inactive compound. Despite the results being reported as moderate by the aforementioned research groups, none of the tested compounds were close to the concentrations of the standard employed (ciprofloxacin).

Sithique et al. presented a new Schiff base ligand (NNO) with hydrazine and a chitosan biopolymer, which formed their metal complexes with cobalt, nickel, and zinc (Figure 58) [169]. The aim of the study was the measurement of the biological activity for the potential application of the compounds. To perform the microbiological experiments, the agar plate method was chosen using an extended group of bacteria (*E. coli*, *P. aeruginosa*, *S. aureus*, and *B. subtilis*) and fungi species (*A. niger*, *A. clavatus*, and *C. albicans*). According to the inhibition zone observed at the 50 µL concentration, the results showed that the complexes were more active than the free ligand, with a better effect on *S. aureus*, achieving inhibition values greater than 30 mm for complexes **112b** and **112c** at the 250 µL concentration, while the fungi species were less affected by the complexes but with moderate results, highlighting that complex **112b** exhibited an inhibition of the growth of *C. albicans* of around 94.38%. This inhibition was greater than that of the Schiff base ligand due to the presence of the Ni(II) ion in the biopolymer.

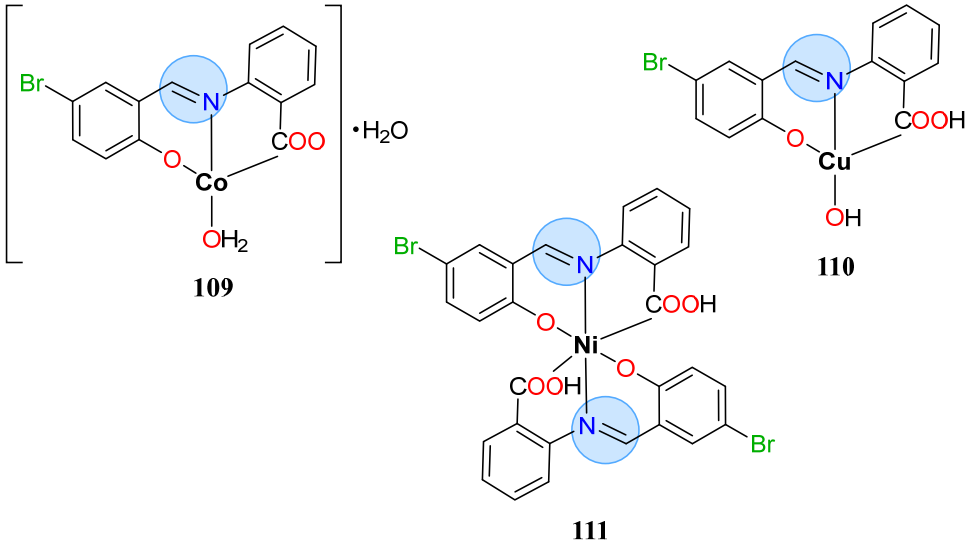


Figure 57. Metal(II) complexes with a Schiff base ligand (ONO) derived from anthranilic acid and 5-bromosalicylaldehyde.

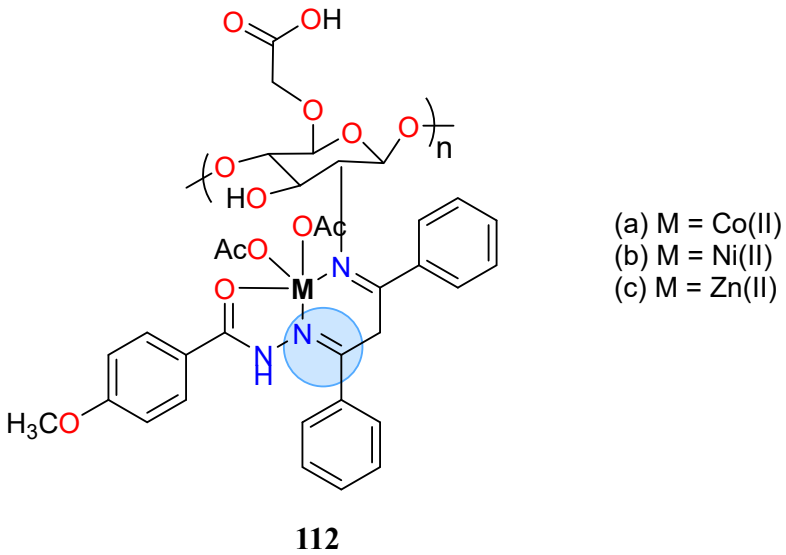
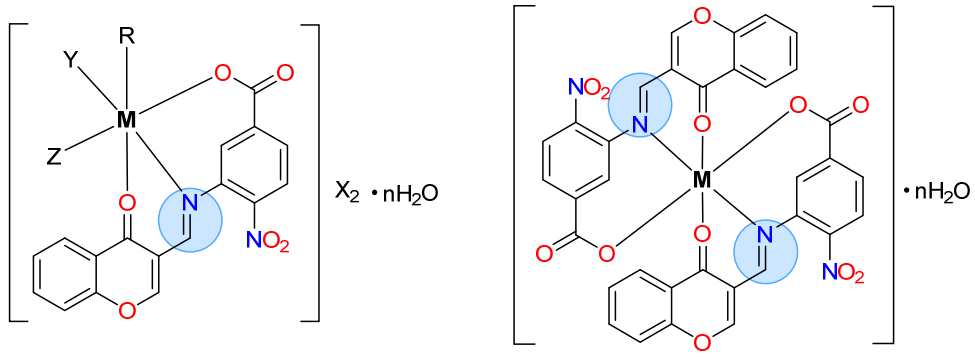


Figure 58. Co(II), Ni(II) and Zn(II) complexes with a tridentate Schiff base ligand (NNO) derived from hydrazide functionalized with a biopolymer.

3.8. Nickel, Copper, and Zinc Groups

In 2016, a new SB derived from chromene and its complexes of Ni(II), Cu(II), Co(II), Fe(III), Zn(II), Cd(II), and UO_2(VI) were reported [170]. The coordination sites with metal ion were γ-pyrone oxygen, azomethine nitrogen, and carboxylic oxygen. The metal complexes exhibited an octahedral geometry, except for the Cu(II) complex, which had a square planar geometry, and the UO_2(VI) complex, in which uranium ion was heptacoordinated (Figure 59). In general, the complexes were inactive against the studied bacterial strains (*E. coli*, *P. vulgaris*, *K. pnemonie*, and *S. aureus*) and had a moderate activity against *C. albicans*. However, complex **114b** showed promising MIC values, even lower than the control drugs (doxymicine and fluconazole) for *K. pnemonie* and *C. albicans*.



(a) M = Ni(II), R = OAc, Y = H_2O, Z = H_2O, n = 2
(b) M = Cu(II), R = OAc, n = 0.5
(c) M = Fe(III), R = EtOH, Y = H_2O, Z = H_2O, X = NO_3, n = 0
(d) M = UO_2(VI), R = OAc, Y = H_2O, n = 0.5

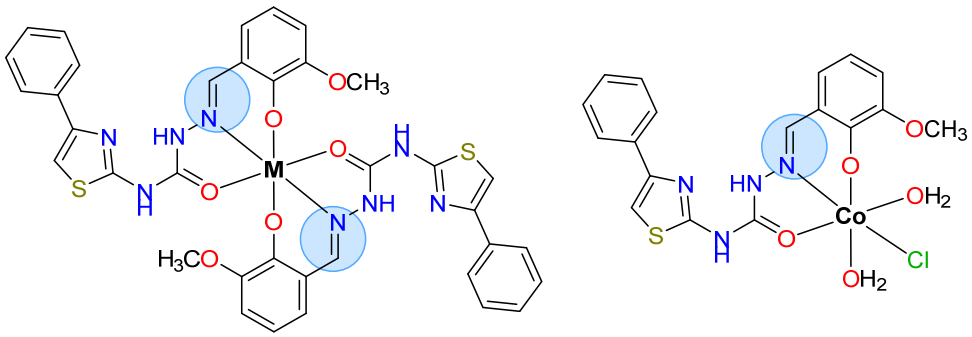
113

(a) M = Co(II), n = 3
(b) M = Zn(II), n = 3.5
(c) M = Cd(II), n = 1

114

Figure 59. A Schiff base derived from chromene and its transition-metal complexes.

The SB ligand named 2-(2-hydroxy-3-methoxybenzylidene)-N-(4-phenylthiazol-2 yl)hydrazinecarboxamide coordinated to Ni(II), Cu(II), and Zn(II), generating an octahedral complex of the type $[M(L)_2]$, while with Co(II) a complex of the type $[M(L)(H_2O)_2Cl]$ was obtained. Spectral results confirmed the binding of the donor tridentate ligand (ONO) involving an amide carbonyl oxygen atom, azomethine nitrogen, and hydroxyl oxygen via deprotonation (Figure 60) [171]. The electrophoresis analysis revealed that the ligand and its metal complex acted on DNA. The ligand and its complexes were good pathogenic microorganism inhibitors, as evidenced by the observation of pBR322 DNA cleavage. The ligand showed lower antimicrobial and antifungal activities (MIC = 50–75 µg/mL) than complexes **115** and **116** (MIC = 25–50 µg/mL). This enhancement in the antimicrobial activity of the complex over the free ligand can be explained on the basis of the chelation theory [172,173]. The antimicrobial activity may be rationalized on the basis that the positive charge of the metal(II) complex is partially shared with the donor heteroatoms (N and O) present in the ligand, and there may be a π-electron delocalization throughout the chelating system. Hence, the increase in the lipophilic character of the metal chelates favours their permeation through the lipoid layer of bacterial membranes and the blocking of metal binding sites in the enzymes of microorganisms [173].



(a) M = Ni(II)
(b) M = Cu(II)
(c) M = Zn(II)

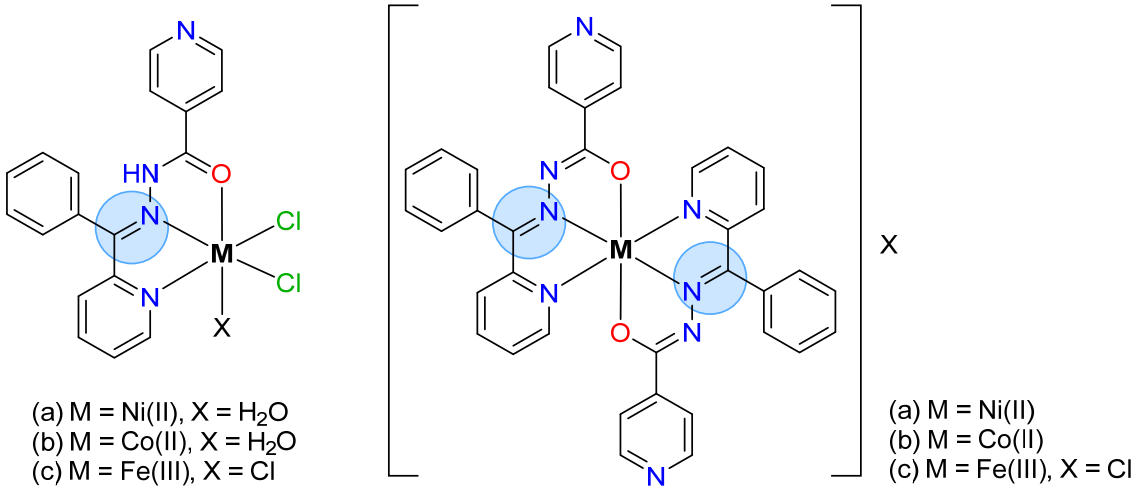
115

116

Figure 60. Ni(II) complex with the Schiff base ligand named 2-(2-hydroxy-3-methoxybenzylidene)-N-(4-phenylthiazol-2 yl)hydrazinecarboxamide.

In recent reports, the NNO pincer-like ligand named (E)-N′-(phenyl(pyridin-2-yl) methylene)isonicotinohydrazide reacted with the metal ion Ni(II) produced two metal derivatives (Figure 61) [174]. The antibacterial activity of the SB ligand and its metal complexes were screened against *B. subtilis* and *E. coli*. The popular drug amoxicillin was used

as a standard. Complexes **117** and **118** were more active than the ligand in the antibacterial study, whereas complex **118c** presented the best activity, achieving inhibition zones of 14 mm for *B. subtilis* and 18 mm for *E. coli*. The findings suggest that chelation facilitated the ability of these complexes to cross the cell membrane, which can be explained by Tweedy's chelation theory. On chelation, the polarity of the metal ion was reduced because it partially shares its positive charge with donor groups, increasing the delocalization of π-electrons throughout the chelate ring. This enhances the lipophilicity of the complex, favouring its penetration through the lipid membrane and blocking metal-binding sites in the enzymes of microorganisms. In other words, chelates may disturb the microbial cells' respiration process, which may lead to the inability of the microbial cells to synthesize their proteins that restrict the further growth of the organism.



117 **118**

Figure 61. Metal complexes with NNO pincer-like ligand named (E)-N′-(phenyl(pyridin-2-yl)methylene)isonicotinohydrazide studied for their antibacterial activity.

Additionally, recently, mononuclear complexes of nicotinohydrazone with Ni(II), Cu(II), and VO(II) (Figure 62) were investigated as antimicrobial agents against some commonly applicable microbial series, considering some bacterial strains (*S. marcescens*, *E. coli,* and *S.aureus*) and fungal strains (*C. albicans*, *A. flavus,* and *T. rubrum*). Interestingly, complexes **119** and **120** established a strong antimicrobial action (inhibition zone = 19–41 mm at 20 μM), more than the free ligand (inhibition zone = 10–14 mm at 20 μM). Such reactivity could be assigned to its positively charged metal centre, which could strongly develop its antibacterial potential with the chelation theory effect [175,176]. The slightly better results against Gram-positive bacteria than against Gram-negative bacteria were explained by the bacteria cell wall structure [177,178].

On the other hand, studies with binuclear compounds containing Ni(II) were also found in the literature. The binuclear metal complex of Ni(II), Cu(II), and Fe(III), with SBs in the presence of 8-hydroxyquinoline (8-HQ) or 1,10-phenanthroline (Phen) as secondary ligands (L_0), were obtained in two molar ratios of 1:2:2 and 1:2:1 (SB:M:L_0). The coordination sites with the metal ion were two azomethine nitrogens, two oxygens from phenolic groups, and two oxygens from carboxylic groups (Figure 63) [179]. SBs and their complexes **121**–**126** showed low antibacterial activity (inhibition zone < 7 mm at 2 mg/mL) against Gram-positive bacteria (*S. aureus* and *S. pyogenes*) and Gram-negative bacteria (*P. fluorescens* and *P. phaseolicola*). However, the antifungal activity against the fungi *F. oxysporium* and *A. fumigatus* presented better results (inhibition zone < 30 mm at 2 mg/mL), with the highest values for Fe(III) complexes.

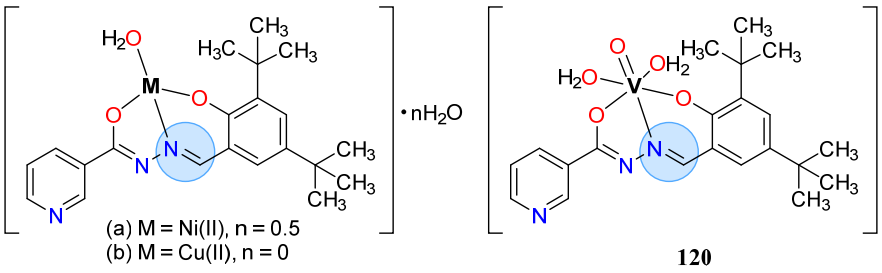
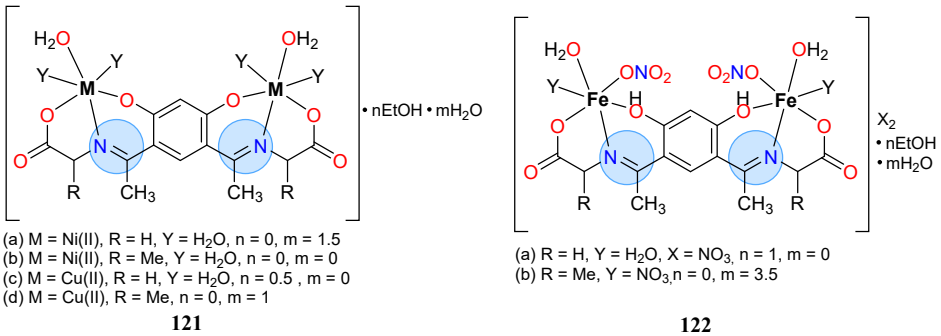
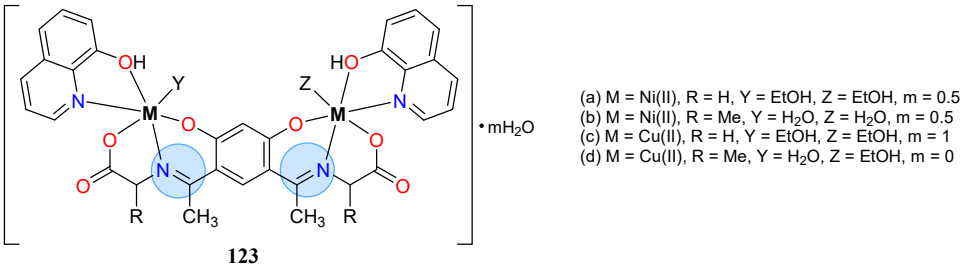
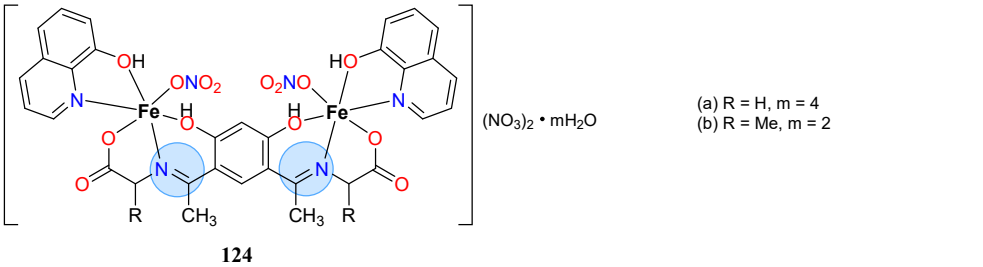


Figure 62. Structure of dibasic tridentate ligand derived from nicotinohydrazone and its Ni(II), Cu(II) and VO(II) complexes with antimicrobial activity.







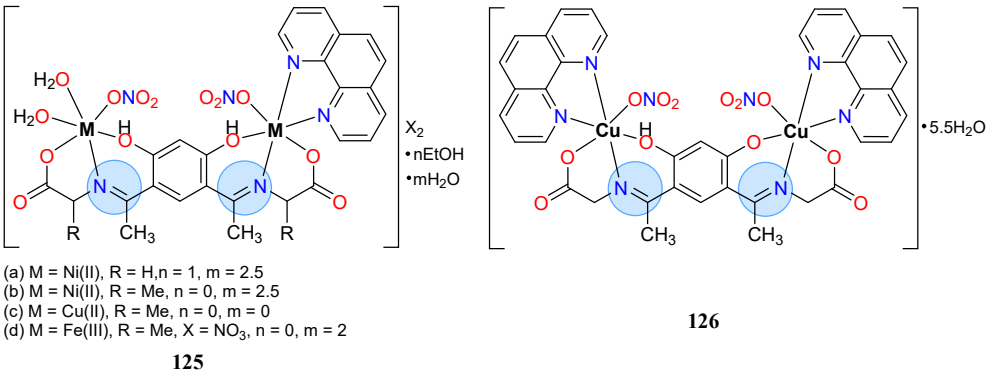


Figure 63. Representative structures of binuclear Ni(II), Cu(II), and Fe(III) complexes derived from Schiff bases with 8-hydroxyquinoline (8-HQ) or 1,10-phenanthroline (Phen) as secondary ligands.

Continuing with binuclear compounds, in 2017 Shebl reported three hydrazone ligands and sixteen complexes [180], which presented an octahedral or tetrahedral structure (Figure 64). The effect of coordinating sites on the spectra and magnetic moments can be studied by comparing complexes with the same geometry. Complexes **127** reflected this effect as follows: (i) a higher energy shift was observed in the case of O-bonded complexes compared to N-bonded complexes; (ii) a decrease in magnetic moment values was observed for O-bonded complexes compared to N-bonded complexes, suggesting a stronger interaction in the case of O-bonded complexes compared to N-bonded complexes. The complexes were assayed against the microorganisms *S. aureus*, *K. pnemonie*, *E. coli*, *P. vulgaris*, and *C. albicans* by the serial dilution method and the MIC was determined. The ligands possessed a lower activity towards all tested microorganisms (MIC > 50 µg/mL). Against *S. aureus*, complex **127b** had the best antibacterial activity (MIC = 6 µg/mL), comparable to the reference drug doximycin (MIC = 5 µg/mL). Against *E. coli* and *P. vulgaris*, complex **128f** was more active (MIC = 8 and 4 µg/mL, respectively) than other complexes; it was even more active than doximycin (MIC = 10 and 8 µg/mL, respectively). It is well-known that some factors such as nature of the ligand and its coordinating sites, nature of the metal ion, geometry of the complex, solubility, and other factors have significant effects on the antibacterial activity of a compound. For the antifungal activity, complexes **129e** (MIC = 3 µg/mL) and **130** (MIC = 2 µg/mL) were more active than reference drug fluconazole (MIC = 8 µg/mL).

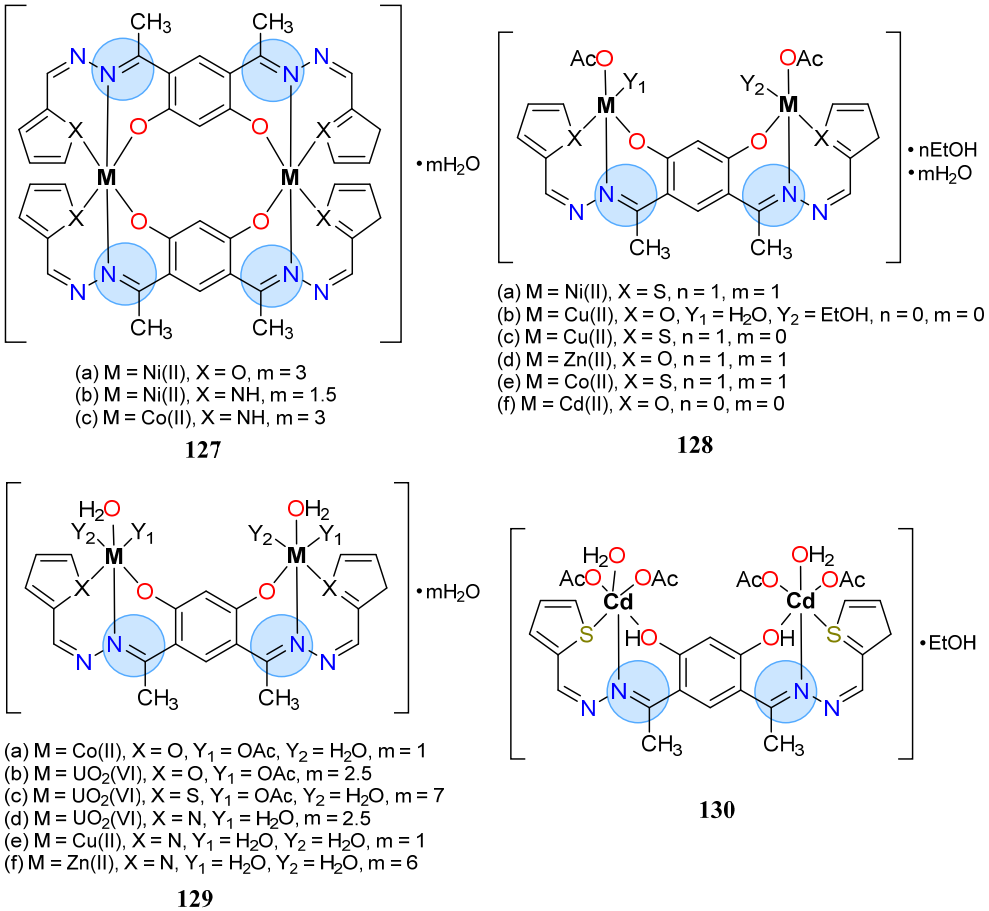


Figure 64. Dinuclear complexes with Schiff base ligands derived from hydrazones studied for their antimicrobial activity.

The hydrazone ligand named (*E*)-3-(2-(5,6-diphenyl-1,2,4-triazine-3-yl)hydrazono) butan-2-one oxime was allowed to react with metal salts to obtain new mononuclear Cu(II), Ag(I), Fe(III), ZrO(IV), and UO_2(VI) complexes. All complexes had octahedral geometries

except complex **131a**, which had a square planar geometry, and complex **132b**, with coordination number seven (Figure 65) [181]. The antimicrobial activity of the hydrazone ligand and its metal complexes against the microorganisms *S. aureus*, *B. subtilis*, S. *typhimurium*, *E. coli*, *C. albicans*, and *A. fumigates* was investigated. The hydrazone ligand and its complexes **131a**, **131b**, and **132b** were biologically inactive against all bacterial strains. Complex **133** showed a moderate activity against *S. aureus* and *E. coli* (inhibition zone = 19 and 18 mm, respectively at 1 mg/mL) and a low activity against *B. subtilis* (inhibition zone < 10 mm). Regarding the antifungal activity, complex **133** presented a high activity against *C. albicans* (inhibition zone = 23 mm at 1 mg/mL), but was inactive against *A. fumigates*. Complex **132b** was the best antifungal agent with inhibition zones of 23 and 24 mm at 1 mg/mL for *C. albicans* and *A. fumigates*, respectively. The antimicrobial activity observed for compounds may be due to the destruction of cell walls, which leads to a change in the cell permeability properties, thus causing cell death [182].

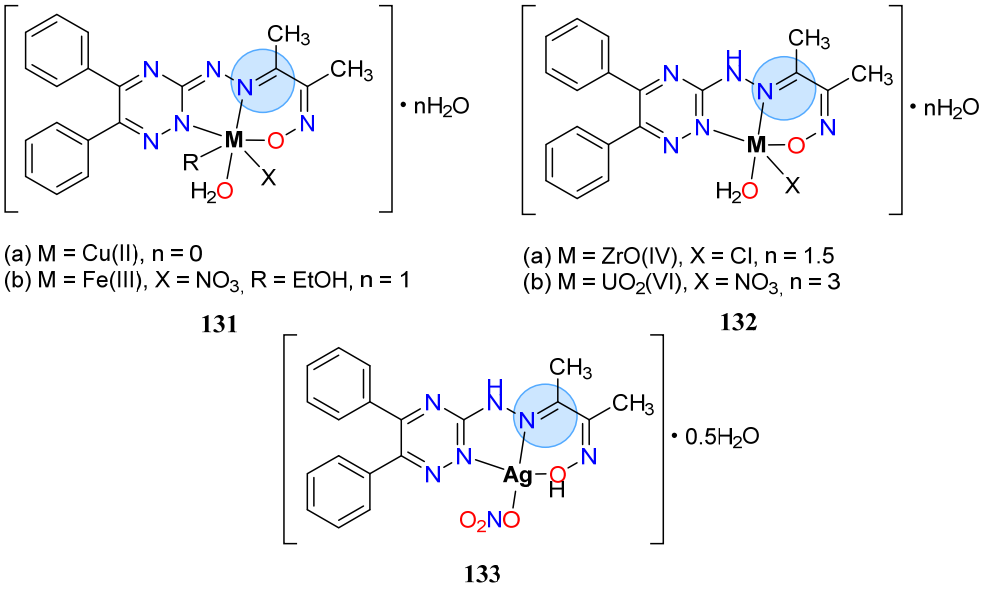
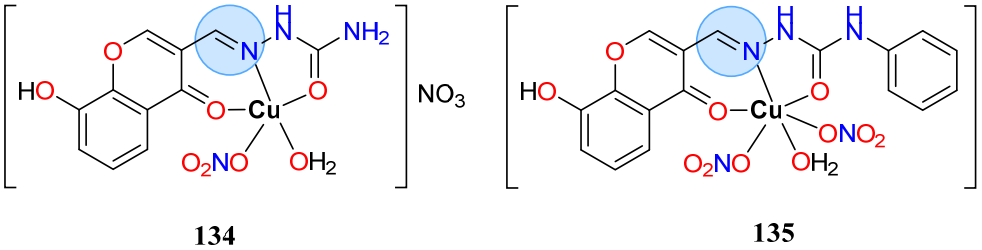


Figure 65. Mononuclear complexes derived from (*E*)-3-(2-(5,6-diphenyl-1,2,4-triazin-3-yl)hydrazono)butan-2-one oxime studied for their antimicrobial activity.

The semicarbazone ligands coordinated to the copper salts, generating complexes **134** and **135**. X-ray diffraction studies indicated that complex **134** had a square pyramidal geometry, where the nitrate ion occupies the apical vertex, the semicarbazone behaves as a tridentate pincer ligand that binds to the Cu(II) ion through the carbonyl oxygen atom, the azomethine nitrogen atom and semicarbazide oxygen atom form the basal plane, and the fourth basal position is occupied by the oxygen atom of the water molecule (Figure 66). The complex **135** had an octahedral geometry [183]. The antibacterial activities of semicarbazide ligands and their Cu(II) complexes were performed on the bacterial species such as *P. aeruginosa*, *S. aureus*, *S. pneumonie*, and *A. baumannii*. Cu(II) complexes were more active than the free ligand, finding moderate results for complex **135**, which was the most active in the bacterial strains (MIC = 20 μM). The in vitro antifungal activity of the complexes was studied with *C. albicans*, *A. niger*, *T. rubrum*, *C. tropicalis*, and *A. fumigatus*. Complex **135** was found to be more active against *A. niger* and *A. fumigatus*, while complex **134** was more toxic against *C. albicans*. The antimicrobial results on the activity of complexes compared to the SB ligands against all tested pathogens, which may be due to the chelation of the semicarbazone to metal ions, can be understood in terms of the increased lipophilicity of metal complexes, facilitating their easy entry into the cell membrane [183].



134 **135**

Figure 66. Cu(II) complexes with an ONO semicarbazone SB ligand studied for their antimicrobial activity.

Other semicarbazone ligands were synthesized and used to obtain Cu(II) and Ni(II) complexes, and their antibacterial activity and their interaction with DNA were studied [23]. Spectral data showed that the thiosemicarbazone behaved as an NNS tridentate ligand through the nitrogen atoms of the azomethine group and the pyrazine ring, as well as the sulphur atom of the thioamide group, forming a compound with 1:1 (M:L) stoichiometry (Figure 67). The complexes and free ligands were studied by microdilution against *S. aureus*, *L. monocytogenes*, *B. cereus*, *E. coli*, *S. typhimurium*, and *K. pneumonia*. In addition, ciprofloxacin was used as a standard control. The results show that the complexes were more active than the free ligands, which was explained by the decrease in metal ion polarity after coordination to the NNS donor system, which increased the lipophilicity of the molecules, allowing them to penetrate lipid membranes more easily and block essential enzymatic processes in microorganisms. Complexes **136a** and **136b** presented the best results with MIC values of 3.9 µg/mL for *S. aureus* and *B. cereus* strains, demonstrating that the activity depends on the nature of the metal centre, in this case suggesting that the redox capacity of copper could promote reactive oxygen species that would lead to the cell death of microorganisms.

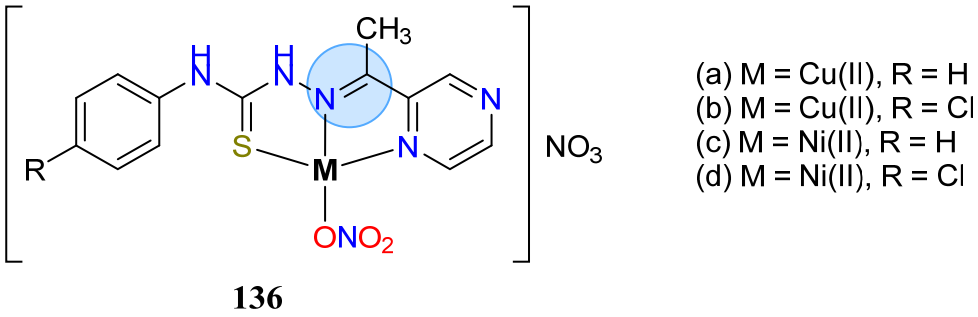


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Figure 67. Cu(II) and Ni(II) complexes with NNS tridentate thiosemicarbazones studied for their antibacterial activity.

In 2017, Pahontu presented the synthesis of several complexes (mainly copper compounds) with SB ligands derived from 4-aminoantipyrine (Figure 68), as well as the in vitro research of their antibacterial activities against *S. aureus*, *K. pneumoniae*, *E. coli*, and *P. aeruginosa* strains [184]. The results showed that the SB activity was more pronounced when it coordinated to the metal ion. For complexes **137**, **138e**, **140a**, **140e**, **141a**, **141c,** and **141e**, an increase in antibacterial action was observed, even reaching the same minimum inhibitory concentration values of the reference drug, streptomycin (MIC = 4–16 µg/mL), which suggested that the presence of the monomeric form in DMSO solution is an element that influences the antibacterial activity. On the other hand, the presence of large volume anions, in the outer coordination sphere of the complexes (ClO_4^- and SO_4^{2-}), can be deemed as another main element that can influence the antibacterial activity. Based on this study, the authors suggested that some synthetized complexes can be successfully used instead of streptomycin, due to the resistance to this antibiotic.

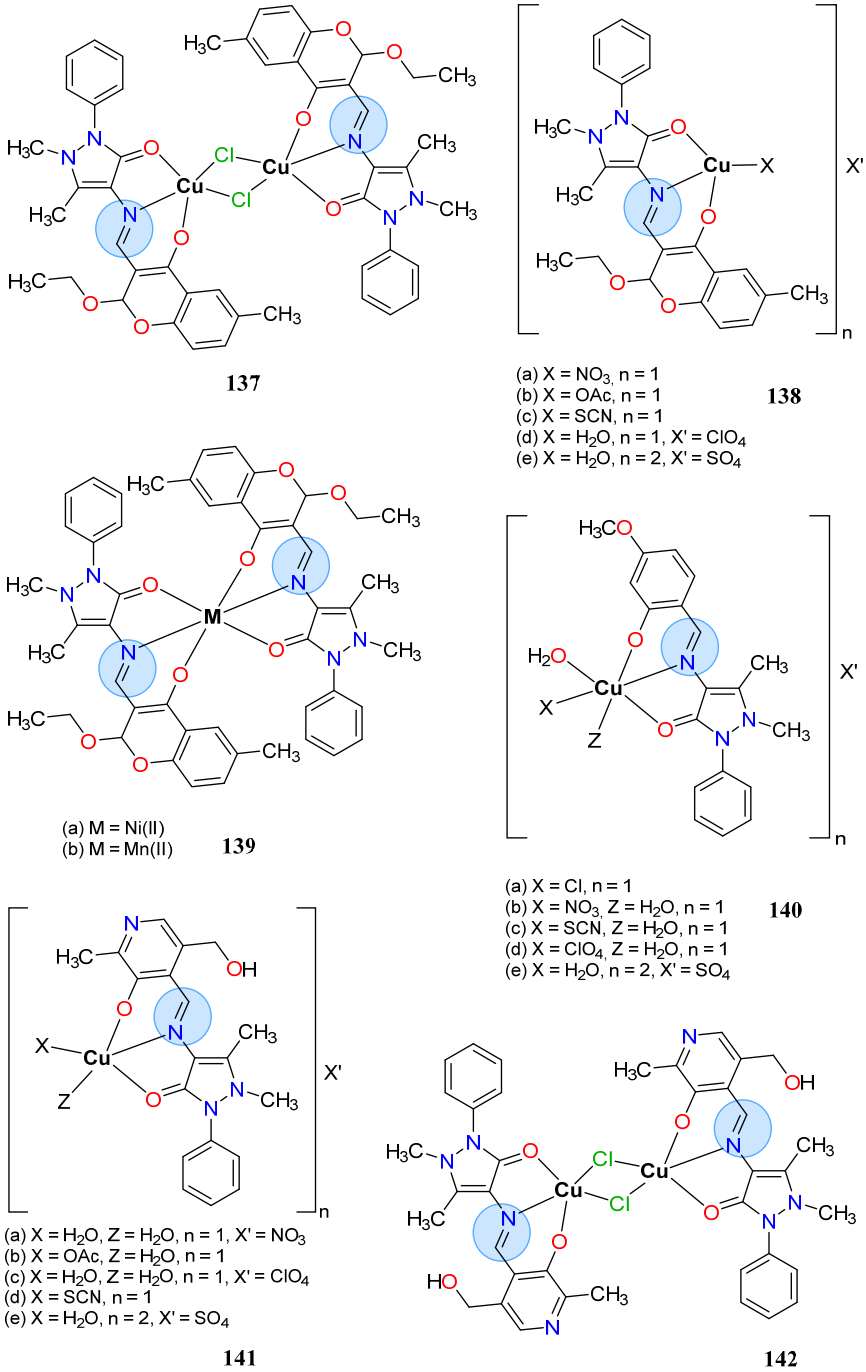

Figure 68. Transition metal complexes with Schiff base ligands derived from antipyrine studied for their antibacterial activity.

In one of the most recent works on metal complexes with tridentate SBs, Reiss et al. reported complexes of Cu(II), Ni(II), and Co(II) containing a tridentate SB (ONN) based on sulfathiazole obtained by the condensation of sulfathiazole with salicylaldehyde (Figure 69) [185]. The composition of the complexes was found to be of the $[ML_2]\cdot nH_2O$ type, having an octahedral geometry for complexes **143b** and **143c**, as well as a tetragonally distorted octahedral geometry for complex **143a**. The SB and its metal complexes were tested against some bacterial strains (*E. coli*, *P. aeruginosa*, *S. aureus*, and *B. subtilis*). The results indicated that the antibacterial activity of all metal complexes was better than that of the SB, which was explained based on the Overtone concept and Tweedy's chelation theory. In all cases, the complexes were more active than the reference drug (amoxi-

cillin); however, the complex **143a** presented higher inhibition values than its analogues (inhibition zone > 40 mm).

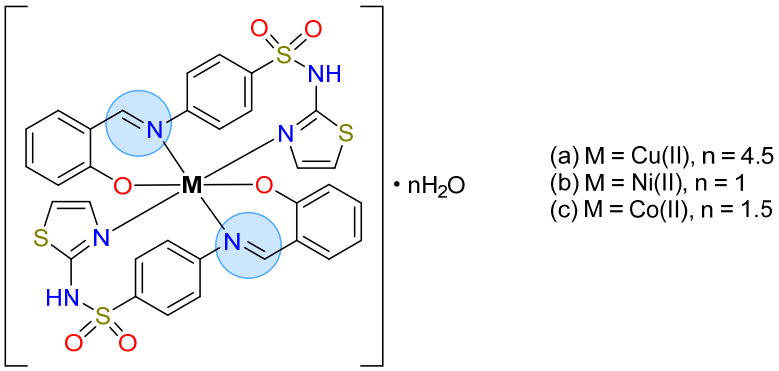

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Figure 69. Ni(II), Cu(II), and Co(II) complexes containing a tridentate Schiff base (ONN) based on sulfathiazole studied for their antimicrobial activity.

The results consolidated in the present review generally show a better activity for the complexes compared to the free ligands, exhibiting trends in the activity depending on the nature of the metal ion. Table 1 presents the most important results of the studied complexes showing greater advantages in relation to others within the same group, presenting a similar or even greater activity than the control drugs. One of the main characteristics found for the main group complexes is that the activity is generally higher when only one ligand is found in the structure of the complex, so that a 1:1 ratio of M:L (L = tridentate Schiff base ligand) represents an advantage when designing this type of complexes with antimicrobial activity. However, for the other groups, no clear trends are observed, although the complexes of elements of period 4 are the most active compared to the heaviest metals of d-block, except for zinc.

Table 1. Comparison of the pincer complexes derived from tridentate Schiff bases with best antimicrobial activity.

Group in Periodic Table	Complex	Best Activity
Main Group	Organotin(IV): **8b**	Inhibition zone = 23 mm for *S. aureus*
	Organotin(IV): **10c**	IC_{50} = 0.41 µg/mL for *L. major*
	Aluminium(III): **14**	Inhibition zone = 37 mm for *A. flavus*
	Antimony(III): **16b**	IC_{50} = 1.23 µM for *T. cruzi*
	Indium(III): **27b**	IC_{50} = 3.0 µM for *C. parapsilosis*
Titanium Group	Titanium (IV): **32**	Inhibition zone = 16 mm for *E. coli*
	Titanium (IV): **39d**	Inhibition zone = 18 mm for *B. cereus*
Vanadium Group	Oxovanadium(IV): **50a**	MIC = 28 µg/mL for *K. pneumoniae*
	Oxovanadium(V): **56**	MIC = 0.5 µg/mL for *S. aureus*
Chromium Group	Chromium(III): **34b**	Inhibition zone = 16.50 mm for *A. niger*
	Chromium(III): **58**	Inhibition zone = 18 mm for *M. luteus*
Manganese Group	Manganese(II): **65c**, **65d**	Inhibition zone = 44 mm for *P. aeruginosa*
	Manganese(II): **74a**	Inhibition zone = 12 mm for *E. coli*
Iron Group	Iron(II): **87a**	MIC = 0.042 µmol/mL for *S. aureus*
	Ruthenium(II): **90h**, **90l**	Inhibition zone = 15–17 mm for *S. aureus*
Cobalt Group	Cobalt(II): **88f**	Inhibition zone = 25 mm for *E. faecalis*
	Cobalt(III): **105**	Inhibition zone = 33 mm for *A. niger*
Nickel Group	Nickel(II): **76e**	Inhibition zone = 20 mm for *S. aureus*
	Nickel(II): **112b**	% of inhibition = 94.38% for *C. albicans*
	Nickel(II): **127b**	MIC = 6 µg/mL for *S. aureus*
Copper Group	Copper(II): **64**	MIC = 0.20 µg/mL for *B. subtilis*
	Copper(II): **70d**	Inhibition zone = 15 mm for *P. putida*
	Copper(II): **136a**, **136b**	MIC = 3.9 µg/mL for *S. aureus*/*B. cereus*
Zinc Group	Cadmium(II): **67d**	Inhibition zone = 24 mm for *E. coli*
	Cadmium(II): **128f**	MIC = 4 µg/mL for *P. vulgaris*
	Cadmium(II): **130**	MIC = 2 µg/mL for *C. albicans*

4. Conclusions

Bioinorganic chemistry is one of the most critical areas of modern medicinal chemistry. In addition to its breadth and complexity, it occupies a vital research space in the scientific community. The many reports in this field evidence its importance. Schiff bases are a promising class of bioactive compounds that, in addition to being molecules with a wide range of applications, are easy to obtain and allow their molecular architecture to be modulated, revealing new potential and better therapeutic agents.

This review clearly shows that metal complexes derived from tridentate Schiff base ligands exhibit broad-spectrum antimicrobial activity. Although the reported mechanisms of action are nonspecific, specific activity patterns can be elicited. Significant antimicrobial activity is generally shown more in the metal complexes than in the free ligands. This increase is a consequence of the rise in lipophilicity, making it easier for complexes to penetrate the cell membrane of microorganisms. In addition, the ability of the metal centre to generate reactive oxygen species and the geometry of the metal complex are other factors that must be considered for the design of new metallopharmaceuticals.

For future studies of the antimicrobial activity with metallic complexes, it is important to improve the methodologies used in terms of the controls used, since it was noticed that the metallic salts used as starting materials to produce the metal complexes are not considered in the experimental methods, the cases where no drug controls are reported being more serious. The more controls used in biological assays, the higher the quality of the reported results will be for the scientific community.

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Data Availability Statement: Not further data available.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Species of microorganisms mentioned in the review.

Species	Short Name	Long Name
Gram-positive Bacteria	*A. tumefaciens*	*Agrobacterium tumefaciens*
	B. cereus	*Bacillus cereus*
	B. simplex	*Bacillus simplex*
	B. subtilis	*Bacillus subtilis*
	E. faecalis	*Enterococcus faecalis*
	E. acetylicum	*Exiguobacterium acetylicum*
	M. tuberculosis	*Mycobacterium tuberculosis*
	L. monocytogenes	*Listeria monocytogenes*
	P. acnes	*Propionibacterium acnes*
	S. lutea	*Sarcina lutea*
	S. aureus	*Staphylococcus aureus*
	S. epidermis	*Staphylococcus epidermis*
	S. faecalis	*Streptococcus faecalis*
	S. pneumoniae	*Streptococcus pneumoniae*
	S. pyogenes	*Streptococcus pyogenes*
	S. viridans	*Streptococcus viridans*

Table A1. *Cont.*

Species	Short Name	Long Name
Gram-negative bacteria	*A. aceti*	*Acetobacter aceti*
	A. baumannii	*Acinetobacter baumannii*
	A. hydrophila	*Aeromonas hydrophila*
	A. tumefaciens	*Agrobacterium tumefaciens*
	C. jejuni	*Campylobacter jejuni*
	C. israelensis	*Chromohalobacter israelensis*
	C. salexigens	*Chromohalobacter salexigens*
	E. aerogenes	*Enterobacter aerogenes*
	E. cloacae	*Enterobacter cloacae*
	E. caratovora	*Erwinia caratovora*
	E. coli	*Escherichia coli*
	H. halophila	*Halomonas halophila*
	H.s salina	*Halomonas salina*
	K. pneumoniae	*Klebsiella pneumoniae*
	N. gonorrhoeae	*Neisseria gonorrhoeae*
	P. mirabalis	*Proteus mirabalis*
	P. vulgaris	*Proteus vulgaris*
	P. aeruginosa	*Pseudomonas aeruginosa*
	P. fluorescens	*Pseudomonas fluorescens*
	P. phaseolicola	*Pseudomonas phaseolicola*
	P. putida	*Pseudomonas putida*
	R. solanacearum	*Ralstonia solanacearum*
	S. abony	*Salmonella abony*
	S. paratyphi	*Salmonella paratyphi*
	S. typhimurium	*Salmonella typhimurium*
	S. marcescens	*Serratia marcescens*
	S. dysenteriae	*Shigella dysenteriae*
	S. sonnei	*Shigella sonnei*
	X. vesicatoria	*Xanthomonas vesicatoria*
Fungi	*A. alternata*	*Alternaria alternata*
	A. solani	*Alternaria solani*
	A. clavatus	*Aspergillus clavatus*
	A. flavus	*Aspergillus flavus*
	A. fumigatus	*Aspergillus fumigatus*
	A. niger	*Aspergillus niger*
	B. cinerea	*Botrytis cinerea*
	C. albicans	*Candida albicans*
	C. dubliniensis	*Candida dubliniensis*
	C. glaberata	*Candida glaberata*
	C. krusei	*Candida krusei*
	C. lusitaniae	*Candida lusitaniae*
	C. parapsilosis	*Candida parapsilosis*
	C. tropicalis	*Candida tropicalis*
	C. utilis	*Candida utilis*
	C. lagenarium	*Colletotrichum lagenarium*
	Cryptococcus	*Cryptococcus*
	D. hansenii	*Debaryomyces hansenii*
	F. moniliforme	*Fusarium moniliforme*
	F. oxysporum	*Fusarium oxysporum*
	F. solani	*Fusarium solani*
	H. guilliermondii	*Hanseniaspora guilliermondii*
	H. oryzae	*Heterodera oryzae*
	K. fragilis	*Kluyveromyces fragilis*
	M. phaseolin	*Macrophomina phaseolin*
	M. phaseolina	*Macrophomina phaseolina*

Table A1. *Cont.*

Species	Short Name	Long Name
Fungi	*M. canis*	*Microsporum canis*
	M. mucedo	*Mucor mucedo*
	P. chrysogenum	*Penicilium chrysogenum*
	P. expansum	*Penicillium expansum*
	P. funiculosum	*Penicillium funiculosum*
	P. lanosum	*Penicillium lanosum*
	P. notatum	*Penicillium notatum*
	P. oxalicum	*Penicillium oxalicum*
	R. bataticola	*Rhizoctonia bataticola*
	R. stolonifer	*Rhizopus stolonifer*
	R. stolonifera	*Rhizopus stolonifera*
	R. rubra	*Rhodotorula rubra*
	S. pulverlentum	*Sporotrichum pulverlentum*
	T. harzianum	*Trichoderma harzianum*
	T. polysporum	*Trichoderma polysporum*
	T. viride	*Trichoderma viride*
	T. longifolius	*Trichophyton longifolius*
	T. rubrum	*Trichophyton rubrum*
Parasite	*P. falciparum*	*Plasmodium falciparum*
	L. major	*Leishmania major*
	T. cruzi	*Trypanosoma cruzi*

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