Antimicrobial Metallopharmaceuticals with Tridentate Schiff Bases

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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. SBs are among the most widely used organic compounds, showing a wide range of applications as intermediates in organic synthesis, chemosensors, and polymeric stabilizers, in the food, dye, and pigment industry, as well as as catalysts and, in recent years, for their recognized biological properties. The use of tridentate SBs ligands in different organometallic and coordination complexes containing main-group metals and transition metals has been an option to study the biological activity of new possible metallopharmaceuticals that contribute to increase activity and to counteract the effect of microbial resistance.

Keywords: metallopharmaceuticals ; Schiff bases ; tridentate ligands ; pincer ligands ; antimicrobial activity

1. Schiff Bases

1.1. 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 [1]. 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 [2].

On the other hand, various investigations have shown that compounds derived from SBs present pharmacological activity as anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antitubercular, anticancer, antioxidant, and anthelmintic agents [3].

1.2. 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 [4][5].

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 1**) 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) [6].

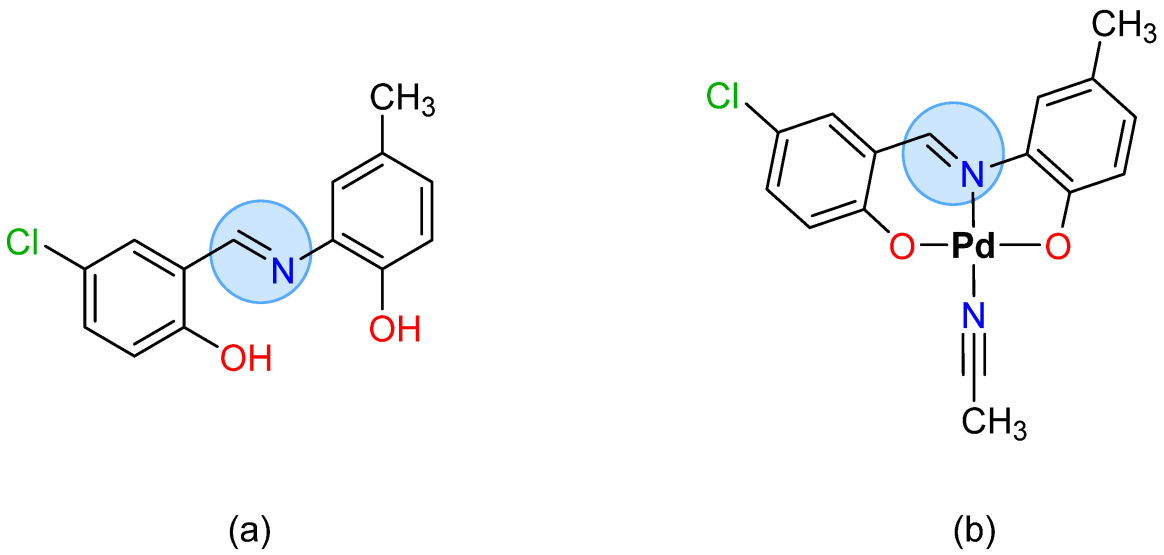
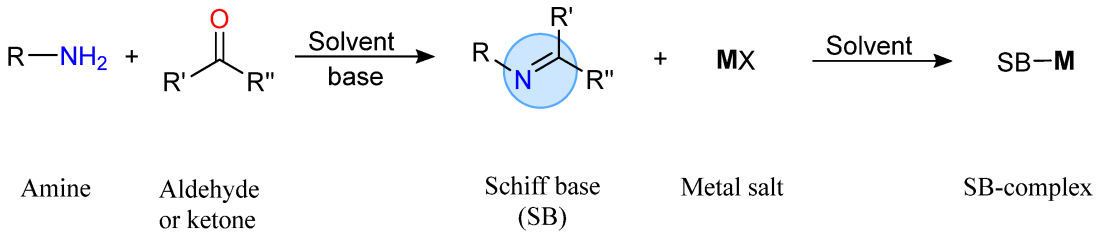


Figure 1. Structure of (**a**) tridentate Schiff base and (**b**) its palladium pincer complex with antimicrobial activity.

1.3. 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.

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.

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 [7]. 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 [8]. 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 [9].

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 [10]. 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 [11]. 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 [12].

2. Antimicrobial Metallopharmaceuticals with Tridentate Schiff Bases

2.1. 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 [13]. 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 [14]. 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 [15]. Atoxyl, melarsoprol, and melarsonyl are examples of chemotherapeutic drugs for the treatment of infectious diseases [15][16][17]. Furthermore, antimony-based chemotherapy drugs are the main treatment for Leishmaniosis [18]. 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 [18][19].

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.

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* [20][21][22][23]. 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 [21][24].

Along with the chemistry of organotin(IV) complexes, the biological activities of hypercoordinated silicon compounds with SB ligands have also been studied [25][26]. Silicon 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 [27].

Organotin(IV) complexes with 2-pyridineformamide thiosemicarbazone and its N(4)-methyl and N(4)-ethyl derivatives 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 [28]. 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.

2.2. 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 [29]. 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 [30].

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 derived from furan-2-carboxaldehyde with L-histidine, L-tryptophan, L-valine, L-methionine, and L-glycine have been determined by single disc method against *B. subtilis*, *E. coli*, *A. fumigatus,* and *A. niger* using streptomycin as the control [31]. 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.

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 were screened for their antimicrobial activity on a nutrient agar medium. In all cases, the complexes showed greater inhibition compared to the free ligands [32]. 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 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.

2.3. 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 [33]. 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 [3][34][35]. 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. 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 [34].

2.4. 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 [36][37][38]. 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 [39][40]. 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 [41], but principally the antimicrobial activity against bacterial and fungal species [42]. 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 was reported by A.M. Abu-Dief et al. 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 [42].

2.5. 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 was structurally characterized, showing a distorted octahedral geometry and a complex with 1:2 (M:L) stoichiometry [43]. 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.

2.6. 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) [44]. 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. 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). As expected, in all cases the metal complexes demonstrated a better antibacterial activity than the free ligand.

2.7. 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 [45]. The antimicrobial activity was measured by the disc diffusion method (Kirby-Bauer). The scholars 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 turned out to be more active with the inhibition zones between 14 and 15 mm.

2.8. 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 [46]. 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. 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 showed promising MIC values, even lower than the control drugs (doxymicine and fluconazole) for *K. pnemonie* and *C. albicans*.

3. 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.

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.

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