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Metal Complexes as Antimicrobial Agents

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1. Introduction

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens. In spite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotic resistance created in the last decades revealed a substantial medical need for new classes of antimicrobial agents. There is a real perceived need for the discovery of new compounds endowed with antimicrobial activity, possibly acting through mechanism of action, which is distinct from those of well-known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant.

Due to the outbreak of infectious diseases caused by different pathogenic bacteria and the development of antibiotic resistance, researchers are searching for new antibacterial agents. Therefore, new antimicrobial agents and nanotechnological materials have to be synthesized for the treatment of resistant bacterial diseases.

Historically, medicinal inorganic chemistry is rich in metal- or metalloid-based drugs, including Paul Erlich's organoarsenic compound for the treatment of syphilis, antiarthritic gold preparations, and diagnostic agents for magnetic resonance imaging (Gd, Mn, Fe) among others.

Some metals have been used as drugs and diagnostic agents to treat a variety of diseases and conditions. Platinum compounds, cisplatin ($\text{cis-[Pt(NH}_3)_2\text{Cl}_2]$), carboplatin and oxaliplatin are among the most widely used cancer therapeutic agents. Gold drugs, myocrisin and auranofin are used for the treatment of rheumatoid arthritis. Another important aspect of medicinal inorganic chemistry is the development of radiopharmaceuticals and diagnostic agents. A technetium radiopharmaceutical, cardiolite supplies $^{99\text{m}}\text{Tc}$, which is selectively taken up by myocardial tissue and is used to image the heart. $^{186}\text{Re}/^{188}\text{Re}$ has been identified as important radionuclides with therapeutic potential. The use of lanthanides and transition metals (Gd, Fe, Mn) as paramagnetic contrast agents for magnetic resonance imaging is becoming more exciting with the development of new complexes having the ability to target specific tissues and physiological states.

The field of bioinorganic chemistry, which deals with the study of role of metal complexes in biological systems, has opened a new horizon for scientific research in coordination compounds. A large number of compounds are important from the biological point of view.

Some metals are essential for biological functions and are found in enzymes and cofactors required for various processes. For example, hemoglobin in red blood cells contains an iron porphyrin complex, which is used for oxygen transport and storage in the body. Chlorophyll in green plants, which is responsible for photosynthetic process, contains a magnesium porphyrin complex. Cobalt is found in the coenzyme B12, which is essential for the transfer of alkyl groups from one molecule to another in biological systems. Metals such as copper, zinc, iron and manganese are incorporated into catalytic proteins (the metalloenzymes), which facilitate a multitude of chemical reactions needed for life. Today medicinal inorganic chemistry remains a field of great promise with many challenges. The potential for a major expansion of chemical diversity into new structural and reactivity motifs of high therapeutic impact is unquestionable.

Biological metal ions play key roles in the structural organization and activation of certain enzymes, which are involved in the transfer of genetic information from DNA, leading to the synthesis of specific proteins. Transition metal complexes have attracted attentions of inorganic, metallo-organic as well as bio-inorganic chemists because of their extensive applications in wide ranging areas from material to biological sciences.

Some chelating agents have been developed for metal intoxication, e.g., water soluble phosphine chelating agents are designed for chelating metals such as technetium, rhenium, platinum and gold. Many organic compounds used in medicine do not have a purely organic mode of action; some are activated or biotransformed by metal ions including metalloenzyme, others have a direct or indirect effect on metal ion metabolism. The pharmacological activities of these metal compounds depend on the metal ion, its ligands and the structure of the compounds. These factors are responsible for reaching them at the proper target site in the body. It is known that certain metal ions penetrate into bacteria and inactivate their enzymes, or some metal ions can generate hydrogen peroxide, thus killing bacteria.

Biologically relevant metal complexes have several requirements in terms of their synthetic design. First, a biologically active metal complex should have a sufficiently high thermodynamic stability to deliver the metal to the active site. The metal-ligand binding should be hydrolytically stable. The kinetics with which the metal ion undergoes ligation or deligation reactions is of great importance. The molecular weight of the metal complex is also critical. The compounds of low molecular weight with neutral charge and some water solubility are soluble in almost any medium and may slip through biological membranes by passive diffusion.

Generally, drug combinations have proven to be an essential feature of antimicrobial treatment due to a number of important considerations: (i) they increase activity through the use of compounds with synergistic or additive activity; (ii) they thwart drug resistance; (iii) they decrease required doses, reducing both cost and the chances of toxic side effects; (iv) they increase the spectrum of activity.

Various biological aspects of the metal based drugs/ligands entirely depend on the ease of cleaving the bond between the metal ion and the ligand. As a consequence, it is essential to understand the relationship between ligand and the metal in biological systems. Several metal complexes are known to accelerate the drug action and the efficacy of the organic therapeutic agent. The efficacy of the various organic therapeutic agents can often be

enhanced upon coordination with a suitable metal ion. The pharmacological activity of metal complexes is highly dependent on the nature of the metal ions and the donor sequence of the ligands because different ligands exhibit different biological properties. There is a real perceived need for the discovery of new compounds endowed with antimicrobial activities. The newly prepared compounds should be more effective and possibly act through a distinct mechanism from those of well-known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant.

2. Metal complexes of sulfonamides

Sulfonamides were the first effective chemotherapeutic agents employed systematically for the prevention and cure of bacterial infections in humans. Among the many and so different families of organic-inorganic chemicals being currently investigated today because of their applications, sulfonamides and their N-derivatives are one of the outstanding groups. Sulfonamides represent an important class of medicinally important compounds which are extensively used as antibacterial agent. It interferes with PABA (p-aminobenzoic acid) in the biosynthesis of tetrahydrofolic acid, which is a basic growth factor essential for the metabolic process of bacteria.

N-Substituted sulfonamides are still among the most widely used antibacterial agents in the world, mainly because of their low cost, low toxicity, and excellent activity against bacterial diseases.

Many activities apart from carbonic anhydrase have been recently reviewed that include endothelin antagonism, anti-inflammatory, tubular transport inhibition, insulin release and saluretic activity. It is well documented that toxicological and pharmacological properties are enhanced when sulfonamides are administered in the form of their metal complexes

In 2006 the synthesis, characterization and comparative biological study of a series of antibacterial copper complexes with heterocyclic sulfonamides (L) were reported. Two kinds of complexes were obtained with the stoichiometries $[\text{Cu}(\text{L})_2] \cdot \text{H}_2\text{O}$ and $[\text{Cu}(\text{L})_2(\text{H}_2\text{O})_4] \cdot n\text{H}_2\text{O}$, which were characterized by infrared and electronic spectroscopies. The antimicrobial activity was evaluated for all the synthesized complexes and ligands using the agar dilution test. The results showed that the complexes with five-membered heterocyclic rings were more active than the free sulfonamides while the pyrimidine, pyridine and pyridazine complexes had similar or less activity than the free ligands. In order to find an explanation for this behavior lipophilicity and superoxide dismutase-like activity were tested, showing that the $[\text{Cu}(\text{sulfamethoxazol})_2(\text{H}_2\text{O})_4] \cdot 3\text{H}_2\text{O}$ presented the highest antimicrobial potency and a superoxide dismutase-like activity comparable with pharmacological active compounds. In spite of the fact that the different species were added in the agar as a suspension, due to their low solubility, all the compounds were active against *S. aureus* and *E. coli*. They acted as antibacterial agents with different behaviors. $[\text{Cu}(\text{sulfadiazine})_2] \cdot \text{H}_2\text{O}$, $[\text{Cu}(\text{sulfamerazine})_2] \cdot \text{H}_2\text{O}$ and $[\text{Cu}(\text{sulfapyridine})_2] \cdot \text{H}_2\text{O}$ were less efficient than the corresponding sulfonamides, while $[\text{Cu}(\text{sulfamethoxypyridazine})_2] \cdot \text{H}_2\text{O}$ had the same microbiological activity. On the contrary, $[\text{Cu}(\text{sulfisoxazole})_2(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}$, $[\text{Cu}(\text{sulfamethoxazole})_2(\text{H}_2\text{O})_4] \cdot 3\text{H}_2\text{O}$, $[\text{Cu}(\text{sulfamethoxazole})_2] \cdot \text{H}_2\text{O}$ and $[\text{Cu}(\text{sulfamethizole})_2] \cdot \text{H}_2\text{O}$ were more efficient than the free sulfonamides (MIC from 4 to 32 $\mu\text{g}/\text{mL}$). In this last group all the ligands have a five membered heterocycle (isoxazole and

diazomethyazole) and all the corresponding complexes coordinate through the heterocyclic N. None of the copper sulfate dilutions, used as controls, inhibited the growth of bacteria. Taking into account the previous knowledge, it could be suggest that one reason for the higher activity of the last four complexes may be due to higher lipophilicity in relation with free sulfonamides. The complexes with five-membered heterocyclic rings showed more activity than free ligands, in particular $[\text{Cu}(\text{sulfamethoxazole})_2(\text{H}_2\text{O})_4] \cdot 3\text{H}_2\text{O}$ provided the highest antimicrobial potency (4 $\mu\text{g}/\text{mL}$ against *Staphylococcus aureus* ATCC 29213, *S. aureus* and *Escherichia coli* (from patient exudates).

In 2007, tri- and di-positive metal complexes of the sulfa-drugs, Schiff base namely 2-thiophene carboxaldehyde-sulfametrole (HL) and its have been synthesized and characterized. The proposed general formulae of the prepared complexes are $[\text{M}_2\text{X}_4(\text{HL})(\text{H}_2\text{O})_4]$ (where $\text{M} = \text{Mn(II)}, \text{Co(II)}, \text{Ni(II)}, \text{Cu(II)}, \text{Zn(II)}$ and Cd(II) , $\text{X} = \text{Cl}$, $[\text{Fe}_2\text{Cl}_6(\text{HL})(\text{H}_2\text{O})_2]$, $[(\text{FeSO}_4)_2(\text{HL})(\text{H}_2\text{O})_4]$ and $[(\text{UO}_2)_2(\text{HL})(\text{NO}_3)_4] \cdot \text{H}_2\text{O}$. Chloramphenicol and Grisofluline were used as reference compounds for antibacterial and antifungal activities, respectively. *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtilis* (bacteria) or *Aspergillus terreus* and *Aspergillus flavus* (Fungi) were used as the test organisms. Results have been recorded in the form of inhibition zones (diameter, cm). It can be seen that the antibacterial and antifungal of HL ligand are more or similar to that of the standards. Further the antibacterial and antifungal actions of HL ligand may be significantly enhanced on chelation with transition metal ions. Also, complexes showed more or same antibacterial activity and moderate antifungal activity comparable to that of the standards. So, the results suggest that metallation increases activity.

Based on the significant biological and pharmacological properties that the indole moiety possesses, a new class of such compounds was reported by combining the chemistry of sulfonamides with indole-3-carbaldehyde and to explore their biological activities with the aim of obtaining more potent antibacterial and/or antifungal compounds. Synthesis of seven new indolenyl sulfonamides, have been prepared by the condensation reaction of indole-3-carboxaldehyde with different sulfonamides such as, sulphanilamide, sulfaguanidine, sulfathiazole, sulfamethoxazole, sulfisoxazole, sulfadiazine and sulfamethazine. These synthesized compounds have been used as potential ligands for complexation with some selective divalent transition metal ions (cobalt, copper, nickel & zinc). Structure of the synthesized ligands has been deduced from their physical, analytical (elemental analyses) and spectral (IR, ^1H NMR and ^{13}C NMR & UV-vis) data. All the compounds have also been assayed for their in vitro antibacterial and antifungal activities examining six species of pathogenic bacteria (*Escherichia coli*, *Shigella flexneri*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtilis*) and six of fungi (*Trichophyton longifusus*, *Candida albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusarium soloni* and *Candida glabrata*). Antibacterial and antifungal results showed that all the compounds showed significant antibacterial activity whereas most of the compounds displayed good antifungal activity (MIC from 1.3 to 0.65×10^{-4} M).

In 2010 a new series of sulfonamide derived Schiff bases has been synthesized by a condensation reaction of various sulfonamides with aromatic aldehydes. The so obtained sulfonamide were further investigated for their chelation and biological properties with first row d-transition metal ions [cobalt(II), copper(II), nickel(II) and zinc(II)]. An octahedral geometry has been suggested for all the complexes. The ligands and their metal complexes

have been screened for in vitro antibacterial, antifungal and cytotoxic properties. The result of these studies have revealed that all compounds showed moderate to significant antibacterial activity against one or more bacterial strains and good antifungal activity against various fungal strains. All the synthesized compounds exhibited varying degree of inhibitory effect on the growth of different tested strains. A significant activity was observed by all the compounds against *E. coli*. Antibacterial activity is overall enhanced after complexation of the ligands. However, the Zinc (II) complexes ($[\text{Zn}(\text{L1-H})_2(\text{H}_2\text{O})_2] \cdot \text{C}_{38}\text{H}_{36}\text{N}_8\text{O}_8\text{S}_2 \cdot \text{Br}_2\text{Zn}$) and ($[\text{Zn}(\text{L2-H})_2(\text{H}_2\text{O})_2] \cdot \text{C}_{34}\text{H}_{28}\text{N}_8\text{O}_8\text{S}_2\text{Br}_2 \cdot \text{Zn}$) of both the ligands were observed to be the most active against all strains (MIC was in the range of 3.204×10^{-8} to 1.341×10^{-7} M). The antifungal screening of all compounds was carried out against *T. longifusus*, *C. albican*, *A. .avus*, *M. canis*, *F. solani* and *C. glaberata* fungal strains according to the literature protocol. Majority of the synthesized compounds showed good antifungal activity against different fungal strains. Compounds $[\text{Zn}(\text{L1-H})_2(\text{H}_2\text{O})_2]$, $[\text{Ni}(\text{L2-H})_2(\text{H}_2\text{O})_2]$ and $[\text{Zn}(\text{L2-H})_2(\text{H}_2\text{O})_2]$ showed excellent while all other compounds showed moderate to excellent activities against various fungal strains. The results of inhibition were compared with the results of inhibition with the standard drugs miconazole and amphotericin B.

The reaction between phthalylsulfathiazolate (PST) and cobalt(II) aqueous solutions leads to a stable complex compound, $[\text{Co}^{\text{II}}(\text{PST})(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}$ (Co-PST). Reflectance diffuse spectrum is in agreement with a distorted octahedral environment of the Co(II) ion. Vibrational FTIR and Raman spectroscopic data reveal that the ligand would be doubly deprotonated. Spectroscopic and chemical data let us suggest that the Nthiazolic and the Nsulfonamide atoms could be the binding sites for the Co(II) ion to the phthalylsulfathiazole moiety. The following strains from the American Type Culture Collection (ATCC), Rockville, MD, USA, Malbrán Institute (MI), Pasteur Institute (PI) and from the Laboratorio de Microbiología (LM, Facultad de Ciencias Médicas, Universidad Nacional de Cuyo, Mendoza, Argentina) were used: Gram-negative bacteria: *Escherichia coli* ATCC 25922, LM1-*Escherichia coli*, LM2-*Escherichia coli*, *Pseudomonas aeruginosa* ATCC 27853 and Gram-positive bacteria: LM-*Staphylococcus aureus*, *Staphylococcus aureus* methicillin-sensitive ATCC 29213 and *Staphylococcus aureus* methicillin-resistant ATCC 43300 were used for the antibacterial evaluation. Bacteria were grown on Müller-Hinton agar medium. Co-PST showed antibacterial activity similar to the ligand (20-30 µg/mL). Activity against *Candida albicans*, if moderate (125 µg/mL), was better than the ligand one (>250 µg/mL). Co-PST did not show direct mutagenicity with the Ames test in the range of assay doses nor hemolytic effects to human erythrocytes in vitro at concentrations in which it is active. The phytotoxicity of the complex, evaluated with the Allium test, was similar to the phthalylsulfathiazole one in the whole tested range.

More recently (2011), copper(II) and nickel(II) complexes of sulfadimethoxine, sulfadiazine, sulfamerazine and sulfamethazine were synthesized and characterized by single-crystal X-ray diffraction and electrochemistry. Structural inspections showed that the antibacterial entity of ligands remains non-coordinated to metal ions in the complex high-lighting the fact that in each cluster, antiseptic activity of the metal has been associated to the antibiotic activity of the ligand. The antibacterial activity of the complex is as important as the ligands one with the addition of antiseptic activity via the incorporation of copper ions. Bacterial strains tested were *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*. The MICs of *E. faecalis* and *P. aeruginosa* are equal to or

greater than 128 µg/mL. The MICs of *E. coli*, *S. aureus* and *K. pneumoniae* are between 32 and 128 µg/mL. All the results obtained with the complexes are thus at least identical or greater than those observed for the free ligands.

3. Antibacteria in materials

Bacteria can grow in different materials that are in close contact with humans, foods, etc., so, it is very important to control this matter in order to prevent risk of infections. The three following investigations are examples in this way.

The growth of bacteria on cellulosic textile is one of its inherent properties. Infection by bacteria causes cross-infection by pathogens, development of odour, staining and loss of the performance properties of textile, so application of antimicrobial finishing agents are necessary for many textiles such as hygienic, medical textiles and odour free sport wear. The antimicrobial function can be incorporated into textile either by chemical finishing of fabrics with biocidal agents or by physical incorporation of the agents into fibers. An area of polymer research that presents great current interest is that of the development of polymers with antimicrobial activities, generally known as polymeric biocides. In the area of health care and hygienic applications, biocidal polymers may be incorporated into fibers, or possibly extruded into fibers themselves, and used for contact disinfectants in many biomedical applications. One method of achieving antimicrobial polymers is to add an organic or inorganic biocide to the polymers during processing of the material. The antimicrobial study emphasise that Cu/oxidized polyvinyl pyridine (PVP) and Ag/oxidized PVP have retarded the growth of bacteria significantly, and Ag/oxidized PVP has a far better biocidal activity. The antibacterial activity of both metal ions survived after washing 10 times.

Jute, a lignocellulosic natural fiber, has 58–68% α-cellulose, 12–14% lignin and 21–24% hemicellulose as a major constituent. Traditionally and due to its inherent coarseness property, jute is being used as a low cost packaging material and also to some extent for producing floor covering and decorative items. A study was carried out using chitosan-metal complex aiming to impart the jute fabric antimicrobial properties. In this regards, Ag⁺, Zn²⁺ and Zr²⁺ ions were allowed separately to form a complex with chitosan. It has been found that, jute fabrics treated with chitosan-metal complex show better antimicrobial properties than those fabrics treated with either chitosan or metal salt separately. Moreover, the jute fabrics treated with chitosan-Zn complex have higher antimicrobial properties compared with those samples treated with chitosan-Zr or chitosan-Ag complexes. It has been found that, jute fabrics treated with chitosan-metal complex show better antimicrobial properties than those fabrics treated with either chitosan or metal salt separately. Moreover, the jute fabrics treated with chitosan-Zn complex have higher antimicrobial properties compared with those samples treated with chitosan-Zr or chitosan-Ag complexes.

Antimicrobial ceramics (ACs) are becoming increasingly important because of their wide range of applications, including fabrics, building materials, cosmetics, electrical appliances, etc. The antimicrobial ceramics (AC) based on hydroxyapatite (HA) were made in a wet chemical process with additions of AgNO₃, Cu(NO₃)₂·3H₂O and Zn(NO₃)₂·6H₂O. The aerobic *Escherichia coli* was used in the study. An obvious antimicrobial effect against *E. coli* was observed in Ag(I) AC. In contrast to Ag(I) AC, it was difficult to ascertain any

bactericidal effect in the case of Cu(II) and Zn(II) AC. This suggests that Ag(I) dissolved out and reacted with *E. coli* and inactivated the *E. coli* metabolism, thus inhibiting its growth.

4. Cu, Co, Ni, Zn

Many biologically active compounds used as drugs possess modified pharmacological and toxicological potentials when administered in the form of metal based compounds. Various metal ions potentially and commonly used are cobalt, copper, nickel and zinc because of forming low molecular weight complexes and therefore, prove to be more beneficial against several diseases.

The antibiotic activity of metal complexes of N-methylthioformohydroxarnic acid against gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus* was investigated. The kinetically labile, square-planar, divalent (Cu, Ni, and Pd) and octahedral, trivalent (Fe, Co, and Cr) complexes displayed activity (0.5 to 5 μM against *S. aureus*), whereas the more inert platinum(II) or rhodium(III) complex displayed no activity, or activity only at elevated concentrations. The free ligand did not suppress the growth of the above organisms, and the sulfur atom of the ligand in its metal complexes appears crucial for activity.

Neutral thiabendazole (TBZH) when uncoordinated to a metal centre is a poor anti-Candida agent and has very little chemotherapeutic potential. Complexes of Cu(II), in which the TBZH is present as a neutral chelating ligand, are all potent anti-candida agents with activity comparable to the prescription drug ketoconazole. Coordination of neutral TBZH to a copper centre in two of these complexes resulted in a significant increase in its chemotherapeutic potential.

Synthesis and antimicrobial activity of new metal [Co(II), Ni(II), Zn(II)] complexes from 2-(1'-hydroxynaphthyl)benzoxazoles have been described in 2007. The cobalt complex $\text{C}_{34}\text{H}_{20}\text{CoN}_2\text{O}_4$ showed significant antifungal activity (MIC 6.25-12.5 $\mu\text{g/mL}$).

Interaction of norfloxacin (Nor) and ofloxacin (OfI) with copper(II) and copper(II)/phenanthroline has been studied in aqueous solution and the stability constants of the binary complexes Cu(II)/fluoroquinolone and of the ternary complexes Cu(II)/phenanthroline/fluoroquinolone have been determined by potentiometry and UV-vis spectrophotometry. The stability constants for the binary and ternary complexes of norfloxacin were always higher than those found for ofloxacin and comparing the values obtained for the binary and ternary species (logK) it is possible to conclude that the ternary complexes are more stable than the binary ones, suggesting that an interaction occurs between the ligands in the ternary complexes. From the distribution diagrams it is possible to state that at physiological pH 7.4, the copper ternary complexes, are the main species in solution not only at the concentration used to determine the stability constants but also at the minimum inhibitory concentration. The antibacterial activity of these complexes, in different bacterial strains, was determined, at physiological pH, and the results obtained show that these complexes may be good candidates as metalloantibiotics. (MIC against *Escherichia coli* ATCC 25922: Cu.OfI. 0.015 and Cu.OfI.Phe: 0.03 $\mu\text{g/mL}$). This work shows that copper(II)/phenanthroline complexes with fluoroquinolones are very stable, at physiological pH and they seem to be a good approach for the development of drugs with similar activity against bacteria but with the possibility of lowering their level of resistance.

A novel copper(II) complex of the fluoroquinolone antibacterial drug *N*-propyl-norfloxacin (Hpr-norf) in the presence of 1,10-phenanthroline (Phen) has been synthesized, characterized and studied its biological properties as antitumor antibiotic and antimicrobial agent. The antimicrobial activity of the complex has been tested, revealing an increased potency in comparison to the free Hpr-norf. (MIC: 4-16 µg/mL)

A few mixed ligand transition metal carbodithioate complexes of the general formula $[M(4\text{-MPipzcdt})_x(\text{phen})_y]Y$ ($M = \text{Mn(II)}, \text{Co(II)}, \text{Zn(II)}$; 4-MPipzcdt = 4-methylpiperazine-1-carbodithioate; phen = 1,10-phenanthroline; $x = 1$ and $y = 2$ when $Y = \text{Cl}$; $x = 2$ and $y = 1$ when $Y = \text{nil}$) were synthesized and screened for their antimicrobial activity against *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecalis* by disk diffusion method. All the complexes exhibited prominent antimicrobial activity against tested pathogenic strains with the MIC values in the range <8-512 µg/mL. The complexes $[\text{Mn}(4\text{-MPipzcdt})_2(\text{phen})]$ and $[\text{Co}(4\text{-MPipzcdt})(\text{phen})_2]\text{Cl}$ inhibited the growth of *Candida albicans* at a concentration as low as 8 µg/mL. The complexes were also evaluated for their toxicity towards human transformed rhabdomyosarcoma cells (RD cells). Moderate cell viability of the RD cells was exhibited against the metal complexes.

Mixed-ligand ternary transition metal (i.e., Cu, Co and Ni) complexes bearing iminodiacetic acid ligand and 1,10-phenanthroline co-ligand, were synthesized and characterized from spectral methods. The complexes usually adopt a distorted octahedral geometry around the metal ion. Among the synthesized ternary complexes, copper and cobalt complexes showed remarkable antibacterial and antifungal activities (6.25 to 12.5 µg/mL).

Transition metal complexes of the type $[M(L)_2]$ and those containing monodentate phosphines of the type $[M(L)_2(PPh_3)]$ ($M = \text{Ni}, \text{Co}, \text{Cu}$ and Zn ; $L = \text{cyclohexylamine-}N\text{-dithiocarbamate}$; $PPh_3 = \text{triphenylphosphine}$) have been synthesized. The spectral studies in all compounds revealed that the coordination of metals occurs via the sulphur atom of the dithiocarbamate ligand in a bidentate fashion. The ligand and their metal complexes were screened in vitro for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Bacillus cereus* and antifungal activities against *Aspergillus flavus*, *Aspergillus carbonarius*, *Aspergillus niger* and *Aspergillus fumigatus*. The metal complexes exhibited higher antimicrobial activity than the parent ligands. Generally, the zinc complexes were effective against the growth of bacteria with $\text{Zn}(L)_2$ displaying broad spectrum bacteriocidal activity at concentrations of 50 µg/mL; and $\text{Ni}(L)_2$ was more effective against the growth of fungi at concentrations of 100-400 µg/mL under laboratory conditions.

Condensation of *o*-acetoacetylphenol and 1,2-diaminopropane in 1:1 molar ratio under condition of high dilution yielded the mono-condensed dibasic Schiff base ligand with a N_2O_2 donors. Reactions of the ligand with metal salts yielded mono- and homo-bi-nuclear complexes formulated as $[M(HL)]$, where $M = \text{Co(II)}, \text{Ni(II)}$ and Cu(II) , $[M_2(L)Cl(H_2O)_2] \cdot \frac{1}{2}H_2O$, where $M: \text{Co(II)}$ and Ni(II) and $[\text{Cu}(H_2L)Cl]$. The mononuclear Ni(II) complex, $[\text{Ni}(HL)]$, was used to synthesize homo- and hetero-bi- and tri-nuclear complexes with the molecular formulae $[\text{Ni}_2(L)Cl(H_2O)_2]$, $[\text{Ni}_2(L)_2\text{FeCl}(H_2O)] \cdot H_2O$ and $[\text{Ni}_2(HL)_2\text{CoCl}_2]$. The structures of the complexes were characterized by various techniques such as elemental and thermal analyses, IR, 1H and ^{13}C NMR, mass and electronic spectra as well as conductivity and magnetic moment measurements. Square-planar and octahedral

geometries are suggested for the Cu(II), Co(II) and Ni(II) complexes. The Schiff base and its metal complexes were evaluated for antimicrobial activity against Gram positive bacteria (*Staphylococcus aureus*), Gram negative bacteria (*Escherichia coli*) and fungi (*Candida albicans* and *Aspergillus flavus*). The ligand and some of its complexes were found to be biologically active. Results recorded revealed that among all the compounds $Zn(L)_2$ was effective at lower concentration (50 $\mu\text{g/mL}$) and also exhibit bactericidal activity against all the bacteria. On the other hand $Co(L)_2$ was the compound with the weakest activity against bacteria and mostly static except with *P. aeruginosa*.

The transition metal (Fe, Co, Ni or Cu) ternary complexes containing pyridine-2,6-dicarboxylate dianion as primary ligand and 4-picoline as an auxiliary ligand were synthesized and characterized from spectral methods. The spectral data are consistent with a distorted octahedral geometry. The iron, copper and cobalt complexes showed remarkable antibacterial and antifungal activities while nickel complex showed these activities up to less extent. The antimicrobial activities investigated against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Candida albicans*, *Aspergillus fumigatus* and *Penicillium marneffeii* showed significant activities (6.25 to 12.5 $\mu\text{g/mL}$).

Equilibrium studies on the ternary complex systems involving ampicillin (amp) as ligand (A) and imidazole containing ligands viz., imidazole (Him), benzimidazole (Hbim), histamine (Hist) and histidine (His) as ligands (B) at 37 °C show the presence of CuABH, CuAB and CuAB₂. The antimicrobial activity of Cu(II)-amp(A) and Cu(II)-amp(A)-Him/Hist/His(B) complexes were tested against bacteria *S. typhi*, yeast *S. cerevisiae* and fungi *L. theobrome* and *F. oxysporum*. The bacteria and yeast were tested by "agar diffusion method" and the fungal activity have been tested using "potato dextrose agar method" using DMF as control. The zone inhibition against the growth of bacteria, yeast and fungi for the binary and ternary complexes show that the inhibition zone of ternary complexes (6.7-9.1 mm) is higher than the binary complex and control (3.6-7.9). On chelation, the polarity of Cu(II) ion will be reduced to a greater extent due to the overlap of ligand orbital and partial sharing of the positive charge of the Cu(II) ion with donor groups. Further, it increases the delocalization of π -electrons over the whole chelate ring and enhances lipophilicity of the complexes. This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganism. These complexes also disturb the respiration process of the cell and thus block the synthesis of protein that restricts further growth of the organism.

The straightforward condensation of 3-acetyl-2-one indol and hydrazinecarbothioamide to yield the novel Schiff base ligand has been reported. Its flexible back bone, together with the presence of N, S and O donor atoms, renders this compound interesting for studying its coordination behaviour with transition metals ion. In this work some complexes with copper, nickel and cobalt have been characterized. The spectral data indicate that ligand behaves as a neutral pentadentate ligand, with two different coordinating sites, one provided by a nitrogen and an oxygen donor atoms and one by the C=N, C=O and C=S groups, each one accommodating a metal ion. Antimicrobial study reveals that, metal complexes have more biological activity than free ligand. Complex $HLNi_2(OAc)_4(H_2O)_3$ shows best antimicrobial activity against all microorganism (MIC: 10-12 $\mu\text{g/mL}$, while Imipenem = standard drug: 6-8 $\mu\text{g/mL}$, ligand: 65-125 $\mu\text{g/mL}$).

The antibactericidal activity of the cupric chloride, fluoroquinolones and its complexes were tested against two Gram(+) *S. aureus*, *B. subtilis*, and three Gram(–) *S. marcescens*, *E. coli* and *P. aeruginosa* organisms using double dilution method. An acceptable reason for this increase in bactericidal activity may be considered in the light of Overtone's concept and chelation theory. According to Overtone's concept of cell permeability, the lipid membrane that surrounds cell favors the passage of only lipid soluble materials so that liposolubility is an important factor which controls bactericidal activity. This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocks the metal binding sites in bacterial enzymes. The antimicrobial activity of all complexes against five microorganisms (MIC from 0.36 to 2.07 µg/mL) is much higher than metal salt. The complex shows better antimicrobial activity than the metal salt ≈ 3000 µg/mL), another quinilones (1.1-5.7 µg/mL), and enrofloxacin (1.4-3.9 µg/mL).

The study provides useful information about the nature of bonding in zinc-thione complexes. We have shown that thiones react with ZnCl_2 to form the complexes of the type, L_2ZnCl_2 in which the ligands coordinate in the thione form in solution as well as in the solid state. Antimicrobial activities of the complexes were evaluated by minimum inhibitory concentration and the results showed that some complexes exhibited significant activities against gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*: $[\text{Zn}(\text{Dmtu})_2\text{Cl}_2]$ 50-40 µg/mL) and yeasts ($[\text{Zn}(\text{Tmtu})_2\text{Cl}_2]$ 80 µg/mL against *Saccharomyces cerevisiae*). However, moderate activity was observed against molds (*Aspergillus niger*, *Penicillium citrinum*).

5. Silver antimicrobial agents

Silver and its compounds have long been used as antimicrobial agents in medicine. Silver is active at low concentrations and has a low toxicity. Silver sulfadiazine is a widely used broad-spectrum antibiotic ointment, effective against a broad range of bacteria and some yeasts. It is used to prevent and treat skin infections on the areas of burnt skin. Silver complexes of oxygen donor ligands such as, $[\text{Ag}(\text{hino})]_2$ (where hino = 4-isopropyltopolone) and water-soluble silver(I) complexes of 2-pyrrolidone-2-carboxylic acid displayed wide ranging and effective activities against some bacteria, yeasts and moulds. It has been found that the silver-oxygen bonding properties rather than the chiral helical or achiral polymer structure play a role in exhibiting antimicrobial activities. The antimicrobial activities of the silver(I)-oxygen bonding complexes are independent of whether the ligand itself possesses antimicrobial activities. Examples of such complexes are $\{[\text{Ag}(\text{L-Hasp})]_2\}$ and $\{[\text{Ag}(\text{LHasp})]_2\}_n$, where the ligand showed no activity. Similarly, salicylic acid (salH) did not prevent the growth of a fungal pathogen, while the silver complexes, $[\text{Ag}(\text{salH})]_2$ and $[\text{Ag}(\text{NH}_3)(\text{salH})]_2$ greatly inhibited cell reproduction. These complexes also produced a cytotoxic response against human cancer cells. The biological action of the silver(I) oxygen complexes comes from a weaker bonding property of the Ag–O bond. In the biological system, the ease of ligand replacement of the silver(I) complexes would result in further replacement with biological ligands. The Ag–O bonding complexes can readily undergo ligand replacement with O-, N- or S-donor atoms. The antimicrobial activities by silver(I)-oxygen bonding complexes are due to the silver(I) ion itself, i.e., due to a direct interaction between the silver(I) ion and biological ligands such as protein, enzymes and membrane. The coordinating ligands of the silver(I) complexes play the role of carrier for the silver(I)

ion to the biological system. The magnitude of antimicrobial properties of silver complexes is related to the ease with which they participate in ligand exchange reactions. For example, it has been speculated that the weak Ag-O and Ag-N bond strengths might play an important role in exhibiting wider spectrum of antimicrobial and antifungal activities and that the potential target sites for inhibition of bacterial and yeast growth by silver complexes might be the sulfur containing residues of proteins. Generally, Ag-S complexes have been shown to have a narrower spectrum of antibacterial activity than Ag-N complexes but no antifungal activity. In contrast, the compounds with Ag-P bonds have shown no activity against bacteria, yeast or molds. A sulfur coordinated, water soluble silver(I) complex of thiomalic acid showed remarkable antimicrobial activity against some bacteria, yeast and moulds. Although aqueous silver nitrate itself has similar activities for bacteria, the complexation of silver(I) with thiomalate leads to appreciably high activities for some moulds. Antimicrobial activities have been observed for sulfur bonded silver complexes of 2-mercaptosuccinic acid, $[\text{Ag}(\text{Hmna})]_6 \cdot 4\text{H}_2\text{O}$ and 2-mercaptobenzoic acid, $[\text{Ag}(\text{Hmba})]_n$ and $[\text{Na}\{\text{Ag}(\text{Hmba})\} \cdot \text{H}_2\text{O}]_n$. The spectra of antimicrobial activities observed in Ag-S bonded compounds have so far been narrower than those in the Ag-N bonded compounds such as $[\text{Ag}(\text{im})]_n$ (im = imidazole) and $[\text{Ag}(\text{triaz})]_n$ (triaz = 1,2,4-triazole). The key factor determining the spectra of antimicrobial activity is the nature of atom coordinated to the silver(I) atom and its bonding properties, (i.e., the ease of ligand replacement), rather than the solid state structure, solubility, charge and degree of polymerization of the complexes

The antibacterial property of silver has been known for thousands of years. Silver nanoparticles have proved to be most effective as they have good antimicrobial efficacy against bacteria, viruses and other eukaryotic microorganisms. Silver is toxic to microorganisms by poisoning respiratory enzymes and components of electron transport system, and it also binds to bacterial surface, altering the membrane function and inhibiting replication. Silver compounds are used as antimicrobial agents in a variety of applications, including coating of catheters, dental resin composites, burn wounds and homeopathic medicine, antimicrobial matter with a minimal risk of toxicity in humans. The synthesis, spectroscopic, thermal and antimicrobial properties and characterization of five new (saccharinato)silver(I) complexes with diverse diamine derivatives, N,N,N',N'-tetramethylethylenediamine, N,N'-diethylethylenediamine, N,N'-dimethylethylenediamine, N,N-diethylethylenediamine and 1,3-diamino-2,2-dimethylpropan ligands, namely $[\text{Ag}_2(\text{sac})_2(\text{tmen})_2]$ (1), $[\text{Ag}_2(\text{sac})_2(\text{deten})_2]$ (2), $[\text{Ag}_2(\text{sac})_2(\text{dmen})_2]_n$ (3), $[\text{Ag}(\text{sac})(\text{N,N-eten})]$ (4) and $[\text{Ag}(\text{sac})(\text{dmpen})]_n$ (5) and Ag(I)-saccharin complex (6) were reported. There are no significant differences among antimicrobial activities of new complexes. Complex 6 is more efficient against all bacteria and yeast than the new complexes except *P. aeruginosa*. While the values of MIC for 6 are in the range of 13.5–27.5 $\mu\text{g}/\text{mL}$, value of MIC for *P. aeruginosa* is 45 $\mu\text{g}/\text{mL}$. But the values of MIC for new complexes (1–5) are in the range of 30–55 $\mu\text{g}/\text{mL}$. Antimicrobial activities of complexes 1–5 and 6 did not show differences between gram (+), gram (-) and eukaryotes in point of effective dose. It is known that there are a disparity between prokaryotes (gram +, gram -) and eukaryotes. But this difference is not important for antimicrobial effect of silver-saccharinate complexes. This suggests that they are potent as broad spectrum topical antimicrobial agents, but they need to be investigated with respect to their toxicity.

Two water-soluble, silver(I) complexes showing a wide spectrum of effective antibacterial and antifungal activities, i.e., $\{[Ag(Hhis)]0.2Et(OH)\}_2$ (**1**; H_2his = L-histidine) and $[Ag(Hpyrrld)]_2$ (**2**; $H_2pyrrld$ = (S)-(-)-2-pyrrolidone-5-carboxylic acid) were prepared. Antimicrobial activities of the free ligands, H_2his and $H_2pyrrld$, were estimated as $>1000 \mu\text{g/mL}$ for bacteria, yeast, and mold and, thus, showed no activity. The Ag^+ ion, as aqueous $AgNO_3$, has shown remarkable activities against Gram-negative bacteria (*E. coli*, *P. aeruginosa*), moderate activities against one Gram-positive bacteria (*B. subtilis*), and no activity ($>1600 \mu\text{g/mL}$) against 2 yeasts and 10 molds. The complex **2**, on the contrary, showed remarkable and excellent activities against a wide spectrum of Gram-negative and -positive (*B. subtilis* and *S. aureus*) bacteria and yeast (*C. albicans* and *S. cerevisiae*) and even against many molds except *A. niger* and *A. terreus*. A similar wide spectrum was also obtained in **1**. Of particular note is the fact that in **1** and **2** activities against many molds are observed. The antibacterial and antifungal activities of **1** and **2** were remarkable ($7.9\text{--}62.5 \mu\text{g/mL}$) and comparable to another silver(I)-N-heterocycle complexes ($6.3\text{--}50 \mu\text{g/mL}$).

The alkanol *N*-functionalized silvercarbene complexes Silver(I)-2,6-bis(ethanolimidazolemethyl)pyridine hydroxide and silver(I)-2,6-bis(propanolimidazolemethyl)pyridine hydroxide are soluble in aqueous media. The solubility and stability of silver complexes in chloride solution are key factors that limit the use of silver complexes for in vivo application. The bactericidal activities of the water-soluble silver(I)-carbene complexes were found to be improved over that of silver nitrate, so the use of Ag-C donor (carbene) compounds has demonstrated its potential as a therapeutic agent.

The antimicrobial activity of the bis(*N*-heterocyclic carbene) (NHC) silver acetate complex, was evaluated against a variety of test organisms including a panel of highly resistant opportunistic pathogens recovered, primarily, from the respiratory tract of patients with cystic fibrosis (CF). The silver complex was also found to be a very effective antimicrobial agent when tested on fungi. Against *A. niger* and *S. cerevisiae*, it was found to be effective with a fungicidal MIC values of $13 \mu\text{g/mL}$ and $4 \mu\text{g/mL}$. It shows a fungistatic effect on *C. albicans* with a MIC value of $4 \mu\text{g/mL}$. Application of this NHC silver complex to primary cultures of murine respiratory epithelial cells followed by microarray analysis showed minimal gene expression changes at the concentrations effective against respiratory pathogens. Furthermore, methylated caffeine without silver showed some antibacterial and antifungal activity.

Preliminary in vivo toxicity studies demonstrated very low toxicity for both the parent methylated caffeine and the silver complex. Given the water solubility of this silver complex and its low toxicity, it may prove useful as a nebulized therapy in patients colonized with these resistant organisms.

$[Ag(2\text{-amino-3-methylpyridine})_2]NO_3$ (**1**) and $[Ag(\text{pyridine-2-carboxaldoxime})NO_3]$ (**2**) were prepared from corresponding ligands and $AgNO_3$ in water/ethanol solutions, and the products were characterized by IR, elemental analysis, NMR, and TGA. The X-ray crystal structures of the two compounds show that the geometry around the silver(I) ion is bent for complex **1** with nitrate as an anion and trigonal planar for complex **2** with nitrate coordinated. The geometries of the complexes are well described by DFT calculations using the ZORA relativistic approach. The compounds were tested against 14 different clinically isolated and four ATCC standard bacteria and yeasts and also compared with 17 commonly

used antibiotics. Both 1 and 2 exhibited considerable activity against *S. lutea*, *M. lutea*, and *S. aureus* (0.6-17.9 µg/mL) and against the yeast *Candida albicans* (2.3 µg/mL), while 2-amino-3-methylpyridine is slightly active and pyridine-2-carboxaldoxime shows no antimicrobial activity. In addition, the interaction of these metal complexes with DNA was investigated. Both 1 and 2 bind to DNA and reduce its electrophoretic mobility with different patterns of migration, while the ligands themselves induce no change.

The two compounds show antibacterial effects against different bacteria and yeast, quite comparable to commercial antibiotics in vitro, but their activity spectrum is different, on both a microgram per milliliter basis and a Ag per milliliter basis.

6. Metal ions from the 5^o and 6^o periods

Dimers of vancomycin (Van), linked by a rigid metal complex, [Pt(en)(H₂O)₂]²⁺, (en: ethylenediamine) exhibit potent activities (MIC: 0.8 µg/mL, 720 times more potent than that of Van itself) against vancomycin resistant enterococci (VRE). The result suggests that combining metal complexation and receptor/ligand interaction offers a useful method to construct multivalent inhibitors. In summary, metal complex can be used as a new platform to construct multivalent inhibitors, which are as effective as other rigid linkers used for multivalency. One of the concerns on platinum-based complexes is its cytotoxicity. Preliminary study has shown that these *cis*-platin based divalent Vans are not toxic toward mammalian cells. Our future work will examine other metal complex linkers, which may help further elucidate the structural basis of vancomycin resistance, as well as the mechanism of multivalent Vans binding to vancomycinsensitive strains, which has yet to be established.

Cationic gold(I) complexes containing 1-[2-(acridin-9-ylamino)ethyl]-1,3-dimethylthiourea [AuL(1)]ⁿ⁺ (where L is Cl⁻, Br⁻, SCN⁻, PEt₃, PPh₃, or 1), derived from a class of analogous platinum(II) antitumor agents, have been synthesized. Unlike platinum, gold does not form permanent adducts with DNA, and its complexes are 2 orders of magnitude less cytotoxic in non-small-cell lung cancer cells than the most active platinum-based agent. Instead, several gold analogues show submicromolar and selective antimicrobial activity against *Mycobacterium tuberculosis* (MIC: 0.49-0.82 µM). In conclusion, the current set of complexes shows considerable potential as relatively nontoxic anti-Mtb agents. Given the urgent need for effective treatment options for multidrug resistant forms of TB, novel gold(I) complexes based on improved prodrug design and delivery may represent a promising approach to combating this disease.

A series of novel palladium(II) chloride and bromide complexes with three types of quinolinylaminophosphonates have been synthesized and structurally characterized. All organophosphorus ligands contain three potential donor atoms, quinoline nitrogen, amino nitrogen and phosphoryl oxygen, but their coordination behaviour towards palladium(II) ion is different. In complexes either quinoline or both quinoline and amino nitrogens are involved in metal(s) bonding forming mononuclear dihalide adducts either with *cis*- or *trans*-configuration as well as dinuclear tetrahalide complexes. Phosphoryl oxygen is not coordinated and is free to be involved in hydrogen bonding, which is the main feature of crystal structures of complexes. The stereochemistry of the complexes, the nature of metal-ligand binding and hydrogen bond interactions are investigated by spectroscopy and X-ray structure analysis. Biological properties of complexes were examined by screening of their ability to inhibit the cancer growth in vitro in a panel of human tumor cell lines and their

antimicrobial activity in a wide spectrum of bacterial and fungal strains. While no specific antimicrobial effects of both the free organophosphorus ligands and their palladium(II) halide complexes were noted, the majority of complexes demonstrated cytostatic activity, which was especially pronounced in the case of dipalladium tetrahalide complexes with IC_{50} :10 μ M. It may be concluded that palladium complexes of investigated quinolinylaminophosphonates represent an interesting class of new complex compounds from the viewpoint of their physicochemical, structural and biological properties.

Some organotin(IV) complexes containing benzil bis(benzoylhydrazone) and different numbers of bipyridyl units have been synthesised and fully characterized. In all the complexes the bis(hydrazone) ligand is doubly deprotonated and behaves as N_2O_2 tetradentate chelate. The in vitro antimicrobial activity against bacteria and fungi was evaluated. Methyl derivatives are devoid of antimicrobial properties, whereas all butyltin(IV) complexes show a good activity against bacteria that increases with the number of bipyridyl units (12-25 μ g/mL).

7. Conclusions

In general, when the antimicrobial activity of metal complexes is concerned, the following five principal factors may be considered:

- i. The chelate effect, i.e. bidentate ligands, such as the quinolones, show higher antimicrobial efficiency towards complexes with monodentate ligands
- ii. The nature of the ligands
- iii. The total charge of the complex; generally the antimicrobial efficiency decreases in the order cationic > neutral > anionic complex
- iv. The nature of the counter ion in the case of the ionic complexes
- v. The nuclearity of the metal center in the complex; dinuclear centers are more active than mononuclear ones.

The antimicrobial activities of metal complexes depended more on the metal center itself than on the geometry around the metal ion.

The biological activity of new silver(I) complexes is potentially important, and these compounds are developed not only with wound care in mind but some cases of antibiotic resistance, and also with, for example, the treatment of lungs chronically infected with cystic fibrosis.

Because of the broad spectrum activity displayed by some of the tested compounds, it is would be necessary to evaluate the cytotoxicity of these compounds as their applications in the formulation of novel antimicrobial therapeutic drugs seem promising. Useful test in the preclinical phase of medicaments are bioassays like the Ames test and a micronucleus test (*Allium cepa* test for example).

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