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Review Article

Metallo-Drugs as Promising Antibacterial Agents and Their Modes of Action

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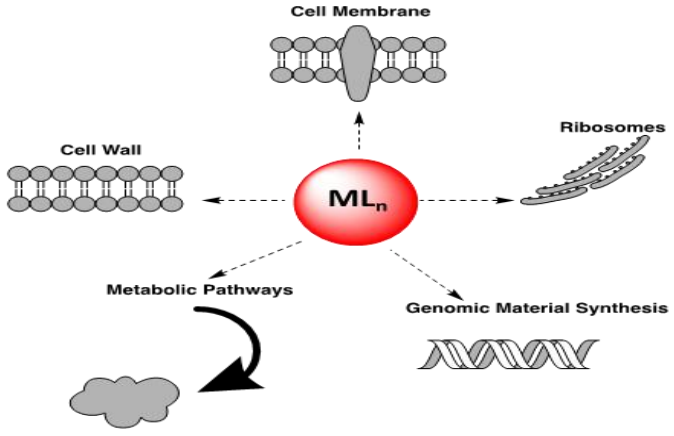
ABSTRACT

Antibiotic resistance has been a growing worldwide public health issue. The World Health Organization (WHO) has stated that the search for new antibiotics is slow, while antibiotic resistance is growing. WHO has also declared that antibiotic resistance is one of the top 10 global public health threats facing humanity in the 21st century. Therefore, this review discusses the potential of metal-based drugs as antibacterial agents from the period of the early 2000s to date. The review reveals that a lot of preliminary work has been done to assess these as potential drugs. However, their mode of action is faintly described. Furthermore, a few examples of metal-based drugs assessed for their modes of action are described. These compounds are ideal as they have been observed to work with one or more modes of action and they are also able to induce or increase activity of free organic compounds once bound to the metal. Nonetheless, more studies are needed to understand the modes of action of other transition metal compounds.

GRAPHICAL ABSTRACT



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Introduction

Bacteria are microscopic organisms made up of a single cell, that grow in colonies consisting of millions of bacteria. They may exist in or out of other organisms. Bacterial organisms can exist as pathogenic or non-pathogenic species. Pathogenic bacteria are those that cause disease while non-pathogenic do not progress to cause disease. However, non-pathogenic bacteria may sometimes cause disease in other people. These non-pathogens may become infectious when one's immune system is compromised. Pathogenic bacteria multiply by entering the host's body to acquire nutrients and thus causing infections [1]. Commensal enteric bacteria may also become pathogenic and thus cause mild infections. This mostly happens when these commensals move from their normal host location to a different location in the host [1].

They are prokaryotic cellular organisms that do not have some cellular organelles as compared with the eukaryotic cells. Bacteria do not have a nucleus but rather have the nucleoid to accommodate their piece of double stranded DNA [2]. Furthermore, these organisms are classified as either Gram-positive or Gram-negative, which explains their outer membranes structures. Gram-positive bacteria have a cell wall while Gram-negative bacteria do not. This is observed through a technique called Gram staining [2]. The Gram-positive bacteria have a larger peptidoglycan layer that makes up the cell wall, while the Gram-negative bacteria have a smaller peptidoglycan layer. However, Gram-negative bacteria also have a lipopolysaccharide plasma membrane. The Gram-negative bacterial membranes are generally challenging to access as compared with the Gram-positive cell walls. Hence, they use a porin/efflux pump to accept essentials into the cell and remove waste out of the cell [3]. There are other organelles found in both the Gram-positive and Gram-negative bacteria, such as a polysaccharide membrane called a capsule around their outer membrane. This capsule prevents bacteria from phagocytosis by other organisms or human phagocytic cells. It is an important virulence factor for pathogenic bacteria [2, 3]. The bacterial cell also has a gel matrix called a cytoplasm where all the cellular processes take place. It is composed of enzymes, water, nutrients, gases and wastes. The cytoplasm contains all the important cellular organelles and macromolecules such as ribosomes, plasmids, and the chromosome [2]. The bacterial cell also has a cytoplasmic membrane made up of proteins and phospholipids. This is an important membrane in bacteria that regulates the flow of materials going in and out of the cell. Some bacteria have a flagellum, which are hairlike structures that aid bacteria in locomotion [3]. Since the bacteria only have one chromosome, their double stranded DNA is found in a membrane-less region called a nucleoid. Most bacteria also have pili which assists them in attachment to surfaces. Pili are hairlike growths from the outer membrane of the bacterial cell. Lastly, all bacteria have ribosomes. These are factories that translate the bacterial genetic code to produce amino acids which are the building blocks of proteins.

Conventional Antibacterial Agents

An ideal antibiotic drug is one that has toxicity towards bacterial cells and no or less activity towards animal cells. Bacteria have many unique targets for antimicrobials as shown in Figure 1 and each antibacterial class has a unique mode of action against the survival of the bacterial cell. There are antibacterial drugs that mechanically disrupt the integrity of the cell membrane, which spills out the cell organelles and thus killing the bacteria [1]. Other antibacterial drugs inhibit the synthesis of macromolecules which stops the bacteria from growing or surviving. These are the cell wall growth inhibitors [2–4], metabolic pathway synthesis inhibitors [5-6], ribosome function inhibitors and DNA synthesis inhibitors [7-8]. Examples of classes of these antibacterial drugs are shown on Figure 1.

As observed in Figure 1, different classes of antibacterial drugs affect bacterial cells in many ways, some of which affect the bacterial cells mechanically by physically disrupting structures of the bacterial cell, such as the cell membrane disrupting drugs. On the other hand, some antibacterial drugs affect the bacteria by inhibiting biosynthesis of some macromolecules in the survival and growth of the bacterial cells.

Table 1 shows the different antibacterial drug classes, their modes of action and biological targets.

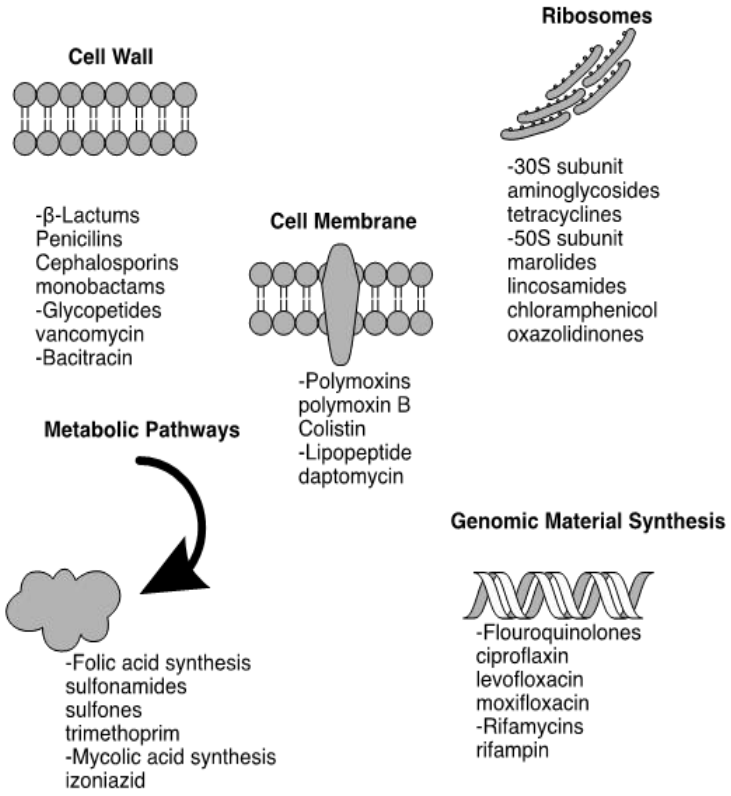


Figure 1: Antibiotic classes and their targets in the bacterial cell

Table 1: Antibacterial Drug Classes their Targets and Modes of Actions

Mode of Action	Target	Drug Class	References
Inhibit cell wall biosynthesis	Penicillin-binding proteins	β-lactams: penicillin, cephalosporins, monobactams, carbapenems, Glycopeptides	[2–4]
	Peptidoglycan subunits		
	Peptidoglycan subunit transport	Bacitracin	[9–11]
Membrane disruption	Lipopolysaccharide, inner and outer membranes	Polymyxin B, colistin, daptomycin	[1], [12–14]
Antimetabolites	Folic acid synthesis enzyme	Sulfonamides, trimethoprim	[5], [6], [15]
Inhibit biosynthesis of proteins	30S ribosomal subunit 50S ribosomal subunit	Aminoglycosides, tetracyclines Macrolides, lincosamides, chloramphenicol, oxazolidinones	[7], [8]
Inhibit nucleic acid synthesis	RNA DNA	Rifamycin Fluoroquinolones	[16–20]

Antibacterial Resistance

This is a process of bacterial species losing susceptibility to an antibiotic. This bacterial defence mechanism occurs when there is a mutation in the bacteria resulting in the reduction or total elimination of drug efficacy. This is

sometimes caused by patients who wrongfully take antibiotics. This failure to take drugs correctly leads to the drug resistant bacteria to pass their resistant mutation to the non-drug resistant species [21]. According to WHO (2014), antibiotic resistance has become one of the world's greatest public health issues. WHO reports that in the last 25 years, no new anti-biotics has been developed. However, there has been an increase in antibiotic resistance while the conventional effective antibiotics are decreasing in efficacy [22]. Bacteria may resist antibiotics by two important ways: Through reducing the concentration of the antibiotic before it reaches the target or by improving the bacterial organelles the antibiotic works on to avoid cell death. Figure 2 illustrates this phenomenon.

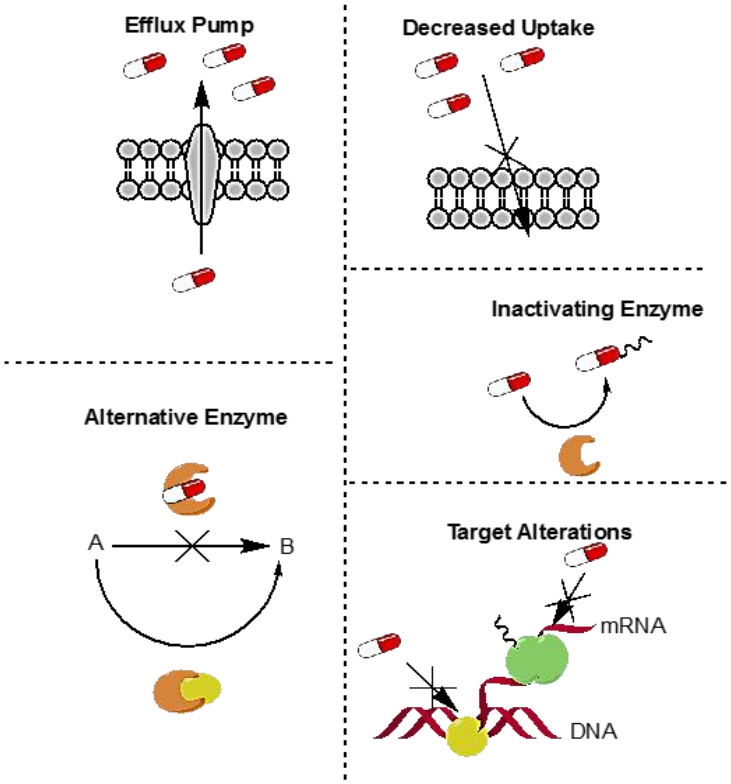


Figure 2: Bacterial antibiotic resistance [23-24]

In their race to avoid antibiotics, some bacteria have been reported to decrease permeability of their membrane. This becomes difficult for the antibiotics to enter the cell and attack at the target [25]. Gram-negative bacteria have an efflux pump, which is vital for sending out important information from the bacterium and even essential nutrients and waste materials. However, in terms of resistance, this pump releases some antibiotics before they reach their target [26]. Some bacteria genetically encode for enzymes that can destroy antibiotics before they reach the target in the cell. An important example is the beta-lactamase producing bacterial species. These species destroy most of the beta-lactam containing antibiotics. The most common beta-lactam is penicillin [27]. Bacteria are also reported to change chemical groups on their surface to alter the binding nature of antibiotics from their target in the cell. Some bacteria can genetically encode for production of alternative target molecules of the antibiotics. An example is *Staphylococcus aureus* (*S. aureus*); this organism, through its virulent mecA gene genetically, encodes a new penicillin binding protein. This protein has low affinity to beta-lactam antibiotics; thus, the cell synthesis of this bacterial species is continued. This is the basis in MRSA resistance [24].

Transition Metal Chemistry in Medicine

Metal based drugs in Medicine

Coordination compounds have been widely researched for their potential application in medicine and drug discovery [28, 33]. Due to the

coordinated metallic centre, their physical and chemical properties may in most cases induce their efficacy as potential drugs. These properties include their variable oxidation states, ligand exchange kinetics, genomic binding properties and protein binding properties [34, 38]. The alkylating agent *cis*-diamminedichloridoplatinum(II) (cisplatin) is an excellent example of a metallodrug. This platinum complex has been used as an antitumor agent since the 1970s [39]. The properties listed above are traits this complex could exhibit. This complex specifically works by binding to the DNA of the cancerous cell. Firstly, the complex enters the cell through the membrane. Thereafter, with its good ligand exchange kinetics cisplatin it substitutes one of the chlorides with a water molecule to enables the complex to now bind to a single nitrogen on the DNA nucleobase. This is followed by replacement of the second chloride by another water molecule to enables further binding to another nucleobase by cisplatin. This characteristic binding of cisplatin distorts the DNA molecule thus preventing effective repair mechanisms to the DNA which further results in apoptosis of the cancerous cell. This whole process is based on the physical and chemical properties of the transition metal compound [40]. Ever since the success of cisplatin many transition metal chemists have explored other metal centres for various diseases. However, in this study the focus will be on their antibacterial activity.

Research in Potential Metallo-Antibacterial Agents

Research in Metal Based Complexes with Preliminary Antibacterial Activity

Silver Compounds as Antimicrobial Agents

According to Alexander (2009), the Greek have been documented to have used silver to treat ulcers and to stimulate wound healing. He also stated that silver has been used over millennia as one of the most effective antimicrobial agents to treat and prevent infections [41]. An example of a silver antibiotic in use is the ionic (4-amino-*N*-2-pyrimidinyl-benzene-sulfonamidato-*NN*,01)-silver or simply silver sulfadiazine, as shown in Figure 3. This drug is used to prevent infections in severe burns. This compound works by the slow release of the antibacterial silver ions, which are reported to disrupt the thiol function in the bacterial cell wall [22].

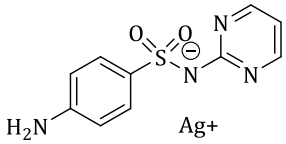


Figure 3: Silver anti-bacterial organo salt

Cardoso *et al.* (2016) reported the synthesis and characterization of camphorimine complexes of silver with the general formula $[Ag(NO_3)YL]$. They used the disk diffusion method and Minimal Inhibitory Concentrations (MIC) assays to study the antimicrobial properties of the new complexes [42]. They achieved this by testing the compounds against bacterial strains of both Gram-positive and Gram-negative nature; *Staphylococcus aureus, Escherichia coli (E. coli), Pseudomonas aeruginosa (P. aeruginosa),* and *Burkholderia contaminans (B. contaminans)*. One of their new compounds showed the lowest MIC for *S. aureus, E. coli, B. contaminans,* and *P. aeruginosa*. However, this compound showed similar results with silver nitrate on their antimicrobial properties with *S. aureus*. Finally, their MIC data showed that their compounds were bactericidal [42].

It is important for a drug to be able to dissolve in water because most of the plasma is made up of water. A water-soluble silver complex, shown on Figure 4 $[Ag_2(phen)_3(udda)]$ (where $uddaH_2$= undecanedioic acid), was against both bacterial and mammalian cells. The complex showed antibacterial activity against three bacteria *E. coli*, *S. aureus* and *P. aeruginosa* [43]. The complex was seen to be toxic to the bacterial organism *E. coli* where it had an IC_{50} of 9.54 μM, while for *S. aureus* and *P. aeruginosa* the potency was IC_{50} = 14.18 μM and IC_{50} was 32.47 μM, respectively. As for the mammalian cell, the complex was tested on the breast cancer cell line MCF-7 and ovarian cell line SKOV-3. The complex continued to show potency for these cells as with the bacterial organisms. Furthermore, they studied the DNA binding properties of the complex and found out that it had some excellent intercalative DNA binding capabilities for the bacterial DNA, and these were

greater than those of ethidium bromide. Fortunately, the complex did not show any DNA damage in mammalian cells [43].

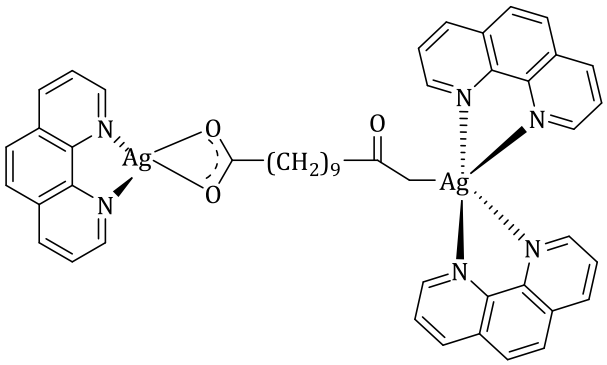
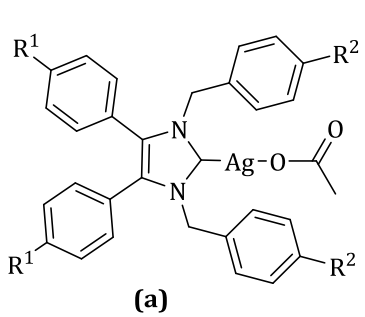
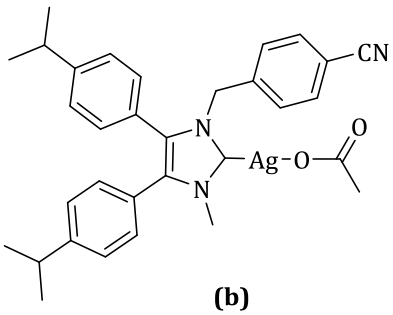


Figure 4: Water soluble silver complex with antibacterial activity [43]

Further, Pöthig *et al.* (2018) described complexes termed silver pillarplexes that had antimicrobial and antifungal activity. Their pillarplexes also showed some moderate cytotoxicity on human HepG2 cells. However, they observed that the same ligand coordinated with gold showed lower cytotoxicity and low antimicrobial activity compared with the silver pillerplexes. They assumed the difference to be because of the increased stability of the gold pillarplexes contrary to the silver pillarplexes. They further concluded that stability and non-toxicity of the gold complexes may make them find use as drug carriers in selective drug delivery biology [44]. Streciwilk *et al* (2012) described the synthesis and application of complexes of p-benzyl-substituted NHC–silver(I) acetate compounds derived from 4,5-di-p-diisopropylphenyl- or 4,5-di-p-chlorophenyl-1H-imidazole. All these compounds are shown in Figure 5 [45]. The complexes and their ligand's antibiotic properties against the Gram-negative bacteria *E. coli* and the Gram-positive bacteria *S. aureus* were studied using the disc diffusion assay. The imidazolium halide compounds had some antibiotic activity towards these organisms. The Imidazolium halide precursor were seen to have weak zones of inhibition of the range of 1–5 mm, while the NHC–silver(I) acetate derivatives similarly had weak to medium zones of inhibition in the range 2–6 mm. Furthermore, their NHC–silver(I) acetate complexes showed cytotoxic properties towards the breast cancer cell line MCF-7. This is because they produced IC_{50} values of 4.7 to 50 µM. Moreover, the same NHC–silver(I) complexes were also observed to have cytotoxicity against the renal cancer cell-line Caki-1 with IC_{50} values of 8.7 to 140 µM [45].



(a)



(b)

4a = R^1 = $CH(CH_3)_2$, R^2 = H
4b = R^1 = $CH(CH_3)_2$, R^2 = CH_3
4c = R^1 = $CH(CH_3)_2$, R^2 = OCH_3
4d = R^1 = $CH(CH_3)_2$, R^2 = CO_2CH
4e = R^1 = $CH(CH_3)_2$, R^2 = CN
4f = R^1 = Cl, R^2 = H
4g = R^1 = Cl, R^2 = CH_3
4h = R^1 = Cl, R^2 = OCH_3
4i = R^1 = Cl, R^2 = CN

Figure 5: **(a)** Symmetrically substituted NHC-silver(I) acetate complexes 4a-I, **(b)** the un-symmetrically substituted NHC-silver(I) acetate complex 5c [45]

Ruthenium Compounds as Antimicrobial Agents

Ruthenium compounds have been found to have biological activity and this has led to growing interest in finding potential ruthenium-based drugs for various diseases. Researchers have been exploring these bioactive properties of ruthenium complexes as potential antimicrobial, anticancer and antiviral agents [46–51]. Even though

ruthenium does not have any specific biochemical role, it has been observed to show low toxicity in biological systems [49]. There is currently no known conventional ruthenium based antimicrobial drugs, but there has been increasing research interest in that field. Li *et al.* (2016) synthesized some asymmetric dinuclear ruthenium (II) polypyridyl complexes that are shown in Figure 6. They reported these complexes to have potent antibacterial properties [51]. Their interesting data revealed that one of the ruthenium centers in the diatomic complex was inert while the other ruthenium center was labile. These were coordinated and linked by the ligand *bis*-[4(4'-methyl-2,2'-bipyridyl)]-1,n-alkane].

These complexes had antibacterial properties towards the bacterial organisms *S. aureus,* MRSA*, E. coli (E. coli)* and *P. aeruginosa* [51]. They further tested these complexes' toxicity towards normal eukaryotic cells and they were generally less toxic. Meaning that these complexes were generally better active against prokaryotic cells opposed to eukaryotic cells. Genomic material binding studies with the normal eukaryotic cells suggested that their toxicity was due to their affinity to the eukaryotic cell genomic material [51]. Some mixed ligand ruthenium polypyridyl complexes have been shown to possess antibacterial activity towards Gram-positive and Gram-negative bacteria. More activity was observed for the Gram-positive bacteria *S. aureus* and its drug resistant clinical isolate counterpart Methicillin-resistant *Staphylococcus aureus.* The active complexes were also observed to have genomic material damaging effects; this was shown with gel electrophoresis when the bacterial genomic material was completely damaged. The compounds were analogues of pyridine based 2-chloromethyl pyridine-based complexes mixed 2,2-dipyridylamine [52, 53].

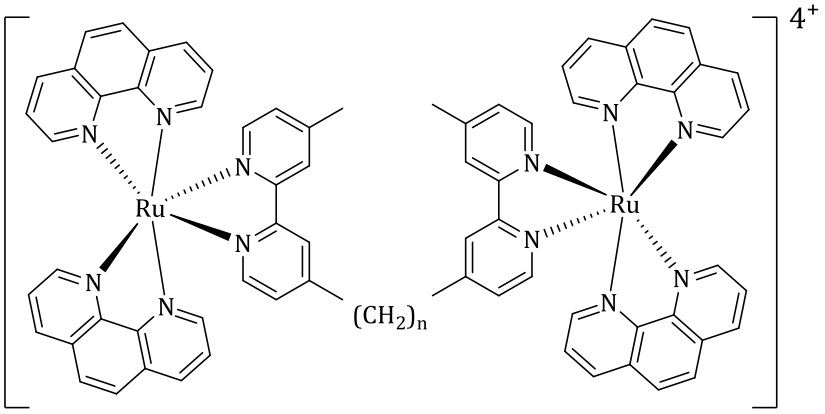


Figure 6: Asymmetric dinuclear ruthenium (II) polypyridyl complexes [51]

Patel *et al* (2014) reported some interesting complexes of ruthenium (II/III) coordinated to fluoroquinolones shown in Figure 7 [54]. They tested their DNA binding properties, DNA cleavage properties and antibacterial properties [54]. Their results indicated that the ruthenium coordinated fluoroquinolones were more active against bacteria than the free fluoroquinolones. This observation suggested that the fluoroquinolones were activated by the introduction of the ruthenium centre to have the antibacterial activity. Patel and his associates further realized that the ruthenium (III) complexes had better antibacterial activity than those of the ruthenium (II). The complexes also partially intercalated DNA as shown by their UV/Vis DNA binding experiments. DNA cleaving studies of the ruthenium complexes using gel electrophoresis suggested that they have DNA cleaving properties as compared to the free fluoroquinolones [54]. Antibacterial studies also displayed the complexes to have low toxicity towards bacterial cells. However, they realized that with increased concentration of the complexes there was increased antibacterial activity. They suggested the toxicity towards these cells to be because of the lipophilicity of the compounds, meaning that the more lipophilic the compound the easier, it is to enter the bacterial outer lipopolysaccharide (LPS) membrane and the host lipid bilayer/cell membrane [54].

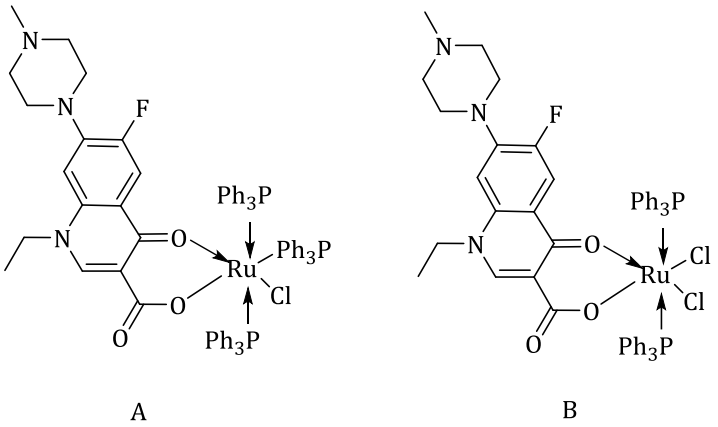


Figure 7: Ruthenium (II/III) coordinated to fluoroquinolones [54]

Sun *et al.* (2015) made a ruthenium (II) mixed ligand polypyridyl complex (see Figure 8) and found it to have antibacterial activity against *S. aureus* and *Micrococcus tetragenus* [55]. The complex was observed to be efficiently taken up by the bacterial cell, which was achieved through cellular uptake studies and laser confocal microscopy. Scanning electron microscopy was also used to assess cell wall damage of the bacterial cell and they identified the cell membrane of the bacteria to be damaged by the ruthenium complex. Because of this cell wall damage together with gel electrophoretic studies, the complex was assumed to work by easy membrane permeability and genomic material nucleation as the gel electrophoretic studies showed the disappearance of genomic material [55].

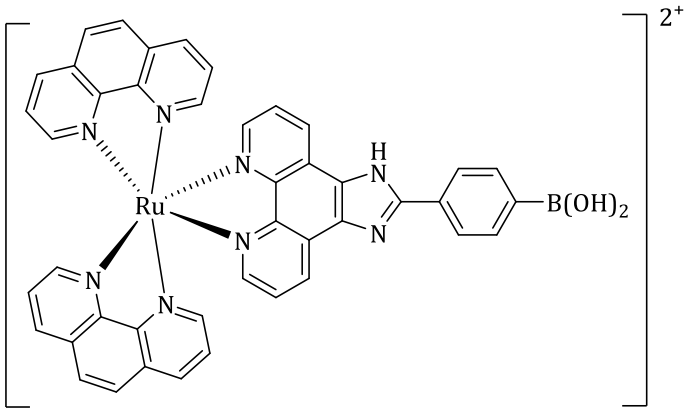


Figure 8: Ruthenium (II) mixed ligand polypyridyl complex [55]

Some ruthenium (II) bipyridyl complexes were observed to show activity towards some drug resistant bacteria [56]. The complexes in this study had a varied aromatic moiety bound to a diazo bidentate nitrogen ligand as seen in Figure 9. The complex bearing the heptoxy chain had more activity towards MRSA as opposed to the positive control. They also discovered that the hexoxy bearing ligand had similar antibacterial activity towards MRSA. However, the activity was not as potent as compared with the heptoxy chain bearing ligand, as seen by the smaller zones of inhibition to the hexoxy bearing ligand. The MIC study also corroborated the disc diffusion assay data, showing that the heptoxy chain bearing complex was more potent than the hexoxy chain bearing ligand by having a smaller MIC. This means that the heptoxy complex is more active at lower concentrations as opposed to the hexoxy ligand [56].

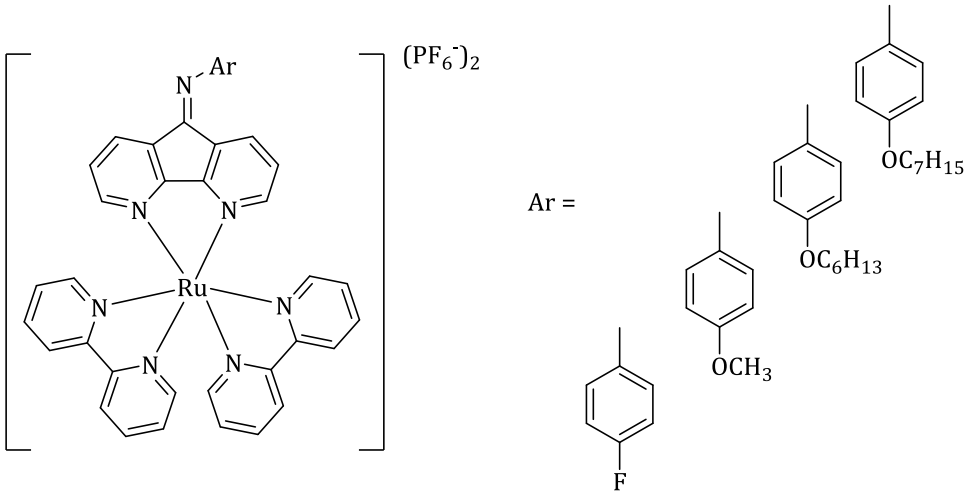


Figure 9: Ruthenium (II) complexes of various N-phenyl substituted 4,5 diazoflourenes [56]

Cobalt Compounds as Antimicrobial Agents

A survey of literature indicated that cobalt medicinal chemistry research is not as common as that of other transition metal compounds such as platinum and ruthenium. Even though that is the case, this metal possesses some useful properties that may be favourable in drug design. One of these important properties includes the accessibility of the metal's two oxidation states under physiological conditions (Co (II/III)). This means that under hypoxic conditions Co (III), pro-drugs may be reduced to the more active Co (II) [57]. Co (III) is known to be kinetically inert, but it is also known to undergo ligand exchange reactions like that of Pt (II) and Ru (III). These reactions include aquation, which may allow these cobalt complexes to be activated through aquation mechanism [58]. Cobalt metal is also an essential trace element in the human body. Therefore, it is relatively less toxic. In that case this allows the design and development of cobalt metal drugs with lower potential of toxicity on host cells. Furthermore, the bioavailability of cobalt in the human body may allow for drugs of this metal to use bioavailable cobalt transport mechanisms, to exploit this trait for improved drug delivery. Transport mechanisms such as those for the movement of cobalt containing molecules like cobalamin may be employed by the body in terms of drug delivery [58]. Several cobalt complexes of various structural nature such as the dilapacholate diaquo cobalt (II) di-dimethylformamide complex have been shown to have bioactivity. This complex showed potential bioactivity at a concentration of 25 ppm. This metal complex showed biological activity against *S. aureus* strains [59].

Vamsikrishn *et al.* (2016) synthesized some new bivalent metal complexes of M = Cu(II), Ni(II), Co(II) with the formula $M(L1)_2$ and $M(L2)_2$ displayed in Figure 10. On the basis of the ligands used, L1 = 2-((benzo [d] thiazol-6-ylimino)methyl)-4-bromophenol, L2 = 1-((benzo [d] thiazol-6-ylimino)methyl)naphthalen-2-ol. They tested DNA binding properties of these complexes using electronic absorption spectroscopy, fluorescence, and viscosity measurements. Their complexes were shown to intercalate calf thymus DNA. Gel electrophoresis was used to study DNA cleavage efficacy of these complexes. Gel electrophoresis was done in the presence of H_2O_2 and UV light. This study showed all the complexes possessed nuclease activity. Their complexes were tested for *in vitro* antibacterial activities Gram-positive (*Bacillus subtilis*) and Gram-negative bacteria (*E. coli*, *Pseudomonas putida*, *K. pneumonia.*). They found out that the complexes had potent bactericidal activity compared to the free ligands [60].

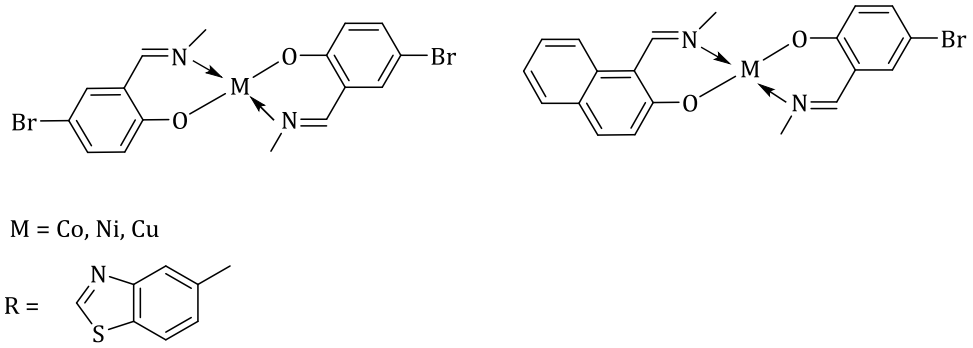


Figure 10: Square planar Complexes of Cu, Ni, and Co with DNA binding and antibacterial properties [60]

Miodragovic *et al* (2006) described a crystal structure of a new Co (III) complex that is shown in Figure 11. Cobalt was coordinated with the antiulcer drug famotidine and ethylenediamine [61]. They noticed that their complex possessed a different mode of complexation with famotidine as compared with other metal complexes. The drug is complexed as a tetradentate ligand using the nitrogen and sulfur donor atoms from guanidine at position N6, thiazole at position N4, thioether at position S2 and the terminal N3 atom. The other binding positions are the two NH_2 groups being on positions $N3H_2$ and $N6H_2$, which are deprotonated to allow the drug to coordinate as a dianion. The asymmetric unit of this complex includes a chloride anion and a water molecule to stabilize the stoichiometry of the complex. Furthermore, they realized that the complex structure had a lot of atoms, which could be hydrogen acceptors or donors in hydrogen bonding. In that regard, their crystal structure revealed dominance of hydrogen bonding. The complex also displayed some interesting noncovalent bonds within the famotidine anion (CH···π and NH···π) [61]. These were seen as stabilizing factors to the crystal structure. They also recognized stacked π···π interactions of neighboring complex cations [61]. Lastly, these observed chemical and physical properties play a pivotal role in their biological activity. These antibacterial and antifungal properties of complexes together with the famotidine ligand were studied against *E. coli*, *S. aureus* and *Micrococcus lysodeikticus.* The fungi studied were *Aspergillus niger* and *Candida albicans*. Their results indicated that the coordinated famotidine cobalt complex had a better activity as compared with the free famotidine ligand. This was shown by the low MIC values [61].

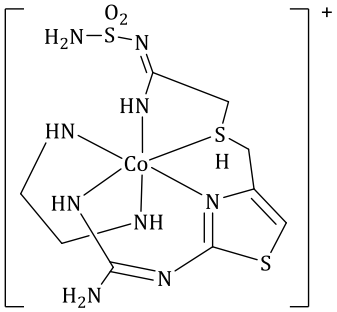


Figure 11: The Co (III) complex with the ulcer drug famotidine and its crystal structure molar ellipsoids showing hydrogen bonds [61]

Moreover, Cohan *et al.* (2003) synthesized cobalt complexes that showed some antibacterial properties against *E. coli, S. aureus, and P. aeruginosa.* The cobalt complexes were formed using a variety of benzothiazole-derived ligands [62]. They prepared these by reacting 2 - acetamido benzaldehyde with the following: 2-amino-4-methoxy-, 2-amino-4-chloro-, 2-amino-6-nitro- and 2-amino-6-methylsulfonylbenzothiazole. These congeners were thus coordinated to cobalt to produce Co (II) complexes. They elucidated their compound's structures using electronic spectra and elemental analysis. They discovered their complexes to show

an octahedral geometry on the central metal atom while the ligands were observed to act as tridentate ligands [62].

Copper Compounds as Antimicrobial Agents

Copper is an essential trace metal in the human body, which helps in various bodily functions such as the production of red blood cells with iron. Copper is also vital in the proper functioning of the organs and metabolic processes of the body. This metal may exist in at least two oxidation states (I and II). However, copper mostly exists as Cu (II) in the human body. Copper can accept electrons, and this is vital in oxidative reduction processes in the disposal of free radicals from the body [63]. Copper is also a medically functional metal, and it has been applied in medicine in ancient times. There has always been folklore belief of copper jewellery helping against rheumatoid arthritis [64]. However, there are some examples with copper that has shown to possess some medicinal properties. An example of these is the copper complexes described by Nleonu *et al* (2020), who synthesized ciprofloxacin complexes of cobalt, copper, iron and zinc (II) ions. After their preparation, the complexes were characterized by using physicochemical and spectroscopic studies. Furthermore, they examined the complexes for their antibacterial properties. Their antibacterial experiments showed better efficacy with the ciprofloxacin as complexes as compared with free ligands against *S. aureus* [65].

Khalil *et al* (2020) reported six derivatives of ciplofloxacin and their complexes of copper, as shown in Figure 12. They examined antibacterial properties of these compound against Gram-negative and Gram-positive bacteria. The structural elucidation data revealed that the ligands were bound as bidentate ligands while the metal centres complexed using the pyridone carbonyl donor groups and through the carboxylate oxygen donor atoms [66]. The ligand complex fields were thus assumed to be *tetragonally-distorted-octahedral* for all the complexes. The antibacterial properties of the Cu (II) complexes with the ciprofloxacin derivatives presented higher antibacterial properties towards both Gram-positive and Gram-negative bacterial organisms. The free ciprofloxacin antibiotic drug had lower activity compared with the complexes. Interestingly, the scientists studied the three-dimensional quantification structure-activity relationship (3D-QSAR) by using 30 antibiotic conventional compounds of the quinolone class. Computational calculations using the Density functional theory (DFT) calculations were used to understand the optimized geometrical structures using the hybrid functional B3LYP method and 6-311G(d,p) basis set [66]. The 3D-QSAR calculations showed eight optimum parameters that gave good predictive modulation (R2 = 0.996, F = 12.004, sigma = 0.426). Finally, the in silico molecular docking was studied on the derivatives which thus showed that there were two types of interactions between the *E. coli* and the compounds, and these were hydrogen bonding and Van der Waals interactions, with also inhibition at the docked site [66].

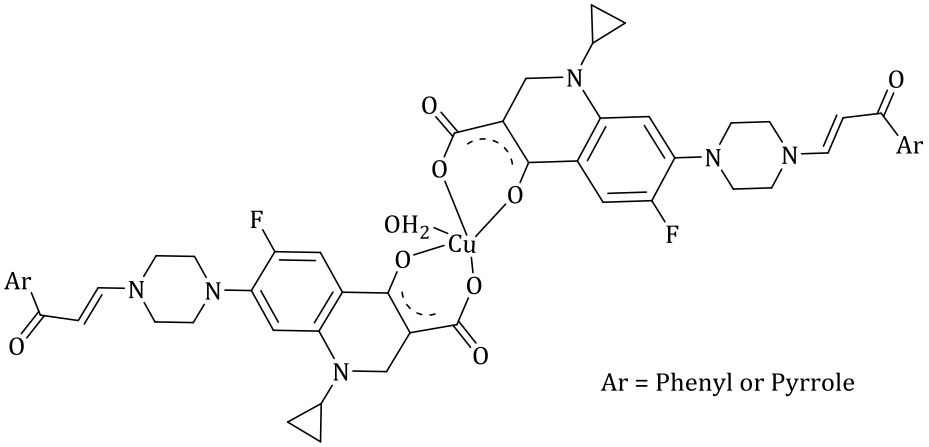
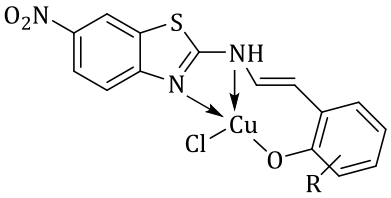


Figure 12: Copper antibacterial ciploflaxin complex [66]

Kolate *et al* (2020) prepared Cu (II) complexes using two hydrazone ligands, 2-[(6-Nitro-benzothiazole-2-yl)-hydrazonomethyl]-4,6-dichloro-phenol (BHD5) and 2-[(6-Nitro-benzothiazole-2-yl)-hydrazonomethyl]-4-chloro-phenol (BH5C) that are shown in Figure 13. They prepared their copper complexes in a stoichiometry of 1:1 metal to ligand ratio [67]. The ligand was observed to bond as a tridentate ligand towards the metal ion using the NNO donor atoms. Furthermore, through their spectroscopic characterization, they realized that the complexes had a tetrahedral geometry. Finally, they assayed their compounds for potential antimicrobial properties towards Gram-positive bacteria *Bacillus subtilis*, Gram-negative bacteria *Salmonella typhi* and two funguses *Candida tropicalis* and *Kluyveromyces marxianus*. They discovered that the complexes had better antimicrobial activity as opposed to their free ligands. Furthermore, their DPPH antioxidant assay also showed that the copper complexes had much better biological activity as compared to the free ligand [67].



R = 3,5 Cl_2 and 5Cl

Figure 13: Antimicrobial copper complexes with hydrazone derivative ligands [67]

Mandal *et al.* (2020) reported three mononuclear Cu (II) complexes of the formula CuL_n and one Ni (II) complex of the formula NiL_n, where the ligands were H_2L_1 = 3,3'-{(methylazanediyl)-*bis*-[(propane-3,1-diyl)-azanylylidene-methanylylidene]}-*bis*-(4-bromophenol), H_2L_2 = 2,2'-[1,2-phenylene-*bis*-(azanylylidene-methanylylidene)]-*bis*-(4-bromophenol) and H_2L_3 = 3,3'-{(methylazanediyl)-*bis*-[(propane-3,1-diyl)-azanylylidene-methanylylidene]}-*bis*-(4,6-dibromophenol) [68]. The Complexes were prepared using the metal salts copper perchlorate for the complexes made with ligand 1 to 3 while nickel perchlorate with ligand 4. All these complexes were made on a stoichiometry of 1:1 of metal to ligand. From these structural studies of the compound, they were able to realize that the complexes of ligands 1, 3 and 4 had a distorted trigonal bipyramidal geometry. However, the complex of ligand 2 adopted a distorted square planar geometry [68]. Finally, they assessed these ligands and their corresponding Ni (II) and Cu (II) complexes for their antibacterial properties against two Gram-positive bacteria *S. aureus B. subtilis* and two Gram-negative *P. aeruginosa E. coli*. They found out that the complexes had much better activity compared with their free ligands, while they also realized that the complexes exhibited an increase in bactericidal properties with an increase in dose. Unfortunately, their data revealed that the complexes did not fare well with the conventional medicines, as these medicines had better activity than the new complexes [68].

Nickel Compounds as Antimicrobial Agents

Nickel is an important transition metal that may exist in the +2-oxidation state in aqueous solutions [69]. This transition metal has been observed to possess some important biological properties. In the human body, Nickel interacts biologically with biological iron to assist in oxygen transport in the haemoglobin. Nickel also stimulates metabolic process in the body and is also an important cofactor in several plants and animal enzyme [70]. Furthermore, nickel may not only help in certain enzymes as a cofactor in the metabolism of sugars but additionally in genetic code transmission (Poonkothai & Vijayavathi, 2012). With that said, researchers have surveyed the idea of using nickel-based compounds as potential drugs for various diseases including infectious diseases.

Subramanian and Sakunthala (2013) presented some new complexes of Cu (II), Zn (II), Ni (II) and

Mn (II) with a new Schiff base ligand. The ligand was observed to be a tetradentate ligand in its binding to the metal centres. The complexes were assayed for their antibacterial properties towards one Gram-positive and two Gram negative bacteria *S. aureus, K. pneumoniae* and *E. coli* [71]. The conventional antibiotic streptomycin was used as a control standard while the ligand and the complexes were the test studies. From their data, the zones of inhibition of the synthesized complexes showed that they had higher activity than the free ligand and the antibiotic standard [71]. They prepared the tetradentate Schiff base complexes by reacting the Schiff base ligand on the stoichiometry of metal salt in 2:1 mole ratio. The ligands were derived from 2-hydroxy-1-naphthaldehyde and 5-amino-1-naphthol. Finally, the ligand and the complexes of Cu (II), Zn (II), Ni (II) and Mn (II) ions were characterized by elemental analysis, FTIR and UV/Vis and conductivity measurements, which all showed their successful preparation [71].

Mondelli *et al.* (2007) described the synthesis, Single Crystal-X ray Diffraction (SC-XRD) structural analysis, voltametric analysis and the antibacterial activity of some nickel sulfonamide-based complexes; $[Ni(sulfisoxazole)_2(H_2O)_4]\bullet 2H_2O$ and $[Ni(sulfapyridine)_2]$. SC-XRD analysis of $[Ni(sulfisoxazole)_2(H_2O)_4]\bullet 2H_2O$ showed the central nickel ion possessed a slight distorted octahedral geometry. The nickel center complexed with two sulfisoxazole molecules using the donor nitrogen atoms, and the structure indicated four water molecule co-ligands to the sulfonamide ligands [72]. However, the second complex $[Ni(sulfapyridine)_2]$ also had a distorted octahedral geometry on the nickel ion. The donor atoms that coordinated the metal center were the two-aryl amine nitrogens from two sulfonamides ligands. The ligands bonded as multidentate ligands because of the monodentate moiety groups, the other two bidentate moieties from the four nitrogen atoms in the sulfonamidic ligand and lastly the other two from the heterocyclic nitrogens [72]. Finally, they tested the antibacterial properties of these two complexes. $[Ni(sulfapyridine)_2]$ had less activity against *E. coli* and *S. aureus* than the free ligand. They assumed this to be due to the poor solubility of the complex and the strong covalent bonds attributed to bigger molecular weights that may affect permeability of the compound into the bacterial cell. The other complex $[Ni(sulfisoxazole)_2(H_2O)_4]\bullet 2H_2O$ showed similar activity to its ligand sulfisoxazole against *S. aureus* and *E. coli* [72].

Joseph *et al.* (2010) prepared some antibacterial copper and nickel salicylidene thiosemicarbazone (SALTSC) and 5-bromosalicylidene thiosemicarbazone (5-Br SALTSC) Schiff based complexes. The Schiff base ligands were used to prepare the Cu (II) and Ni (II) complexes namely CuSALTSC, 5-BrCuSALTSC, NiSALTSC, and 5-BrNiSALTSC [73]. Furthermore, their antibacterial activity against the Gram-positive *S. aureus* and the Gram-negative *E. coli*. The 5-BrCuSALTSC was highly active against both the *S. aureus* and against *E. coli* bacteria at working concentrations of 100 mg/disk and 150 mg/disk respectively. The nickel complex 5-BrNiSALTSC on the other hand was only highly active against *E. coli* at a working concentration of 150 mg/disk [73].

Three trinuclear Ni (II) complexes namely $[Ni_3(abb)_3(H_2O)_3(\mu\text{-ttc})](ClO_4)_3$, $[Ni_3(tebb)_3(H_2O)_3(\mu\text{-ttc})](ClO_4)_3.H_2O$, and $[Ni_3(pmdien)_3(\mu\text{-ttc})](ClO_4)_3$ (where abb = 1-(1*H*-benzimidazol-2-yl)-N-(1H-benzimidazol-2-ylmethyl)methan-amine, $ttcH_3$ = trithiocyanuric acid, tebb = 2-[2-[2-(1*H*-benzimidazol-2-yl)ethylsulfanyl]ethyl]-1*H*-benzimidazole, and pmdien = *N,N,N′,N″,N*″-pentamethyldiethylenetriamine) were synthesized, characterized and examined for antibacterial and cytotoxic properties. The three complexes showed some antibacterial properties towards *S. aureus* and *E. coli* [74]. However, there was better activity towards Gram-negative bacteria than the Gram-positive bacteria. The abb ligand together with its complex had the best antibacterial activity [74]. Due to the $[Ni_3(pmdien)_3(\mu\text{-ttc})](ClO_4)_3$ having better bioactivity, they further tested for its cytotoxic activity together with its ligand $ttcNa_3$ on the cancer cell lines G-361, HOS, K-562, and MCF7. They detected cytotoxic properties of this complex against the cancer cell lines. However, the ligand

ttcNa$_3$ did not show any cytotoxic activity. They further studied the electrochemical redox behaviour of the three trinuclear Ni (II) complexes which was studied using cyclic voltammetry. This study revealed that the nickel was on the +2-oxidation state for all the complexes and showed the presence of ttc [74].

Islam *et al.* (2015) reported a simple yet potentially important nickel metal complex. The complex was synthesized using nickel chloride salt and pyridine ligand. This gave a complex of the stoichiometry 1:2 nickel to pyridine with the molecular formula [Ni(C_5H_5N)$_2$Cl$_2$]. They saw some interesting data on the complex using FTIR and carbon NMR the complex existed as both of *cis* and *trans* isomers as shown in Figure 14 [75]. Furthermore, they tested both the pyridine ligand and Ni (II) complex for antimicrobial properties against *Salmonella typhi*, *Shigella dysenteriae*, *E. coli*, *Bacillus cereus*, and phytopathogenic fungi *Macrophomina phaseolina*, *Alternaria alternata*, *Fusarium equiseti*, *Colletotrichums corcolei*, and *Botryodiplodia theobromae*. The results for these assays proved that the complex had better activity towards the bacteria as opposed to the free pyridine ligand. The results also indicated more activity against *E. coli* by the complex. As for the fungi, it has been shown that the complex shows inhibition of mycelial growth. Specifically, there was more activity of the ligand and the complex on the inhibition of growth of *Macrophomina phaseolina* as compared with the other fungi [75].

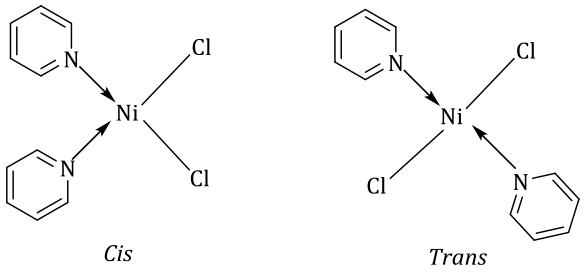


Figure 14: The Ni (II) complex existing as both cis and trans isomers [75]

Palladium Compounds as Antimicrobial Agents

Palladium as a chemical element with the symbol Pd is a rare metal of the platinum group metals. It is a lustrous silvery white metal with various uses and increasing research as potential therapeutics for various diseases [76–79]. Palladium has been known to have great potential in medicine because it belongs to the platinum group of metals, and it is a known antagonistic metal in the human body. It is generally a less toxic metal as seen through various animal model studies [80]. In that case, the literature was surveyed to assess the extent of palladium used as a potential antimicrobial agent. Pd (II) complexes with 2-pyrral amino acid Schiff ligands (Figure 15) have been investigated for antibacterial properties activity against six bacterial species being the Gram-positive *S. aureus*, MRSA, *Staphylococcus epidermidis* and *Streptococcus pyogenes* and the Gram-negative *P. aeruginosa* and *K. pneumoniae* using the disc difusion assay and MIC method. The Pd (II) complexes showed antibacterial properties against the bacteria with the 2-pyrral-l-histidine palladium (II) complex and the 2-pyrral-l-tryptophan palladium (II) complex displaying the best antibacterial properties. The compounds were all characterized using proton NMR, FTIR, Electronic spectra, elemental analysis, and conductivity measurements [81].

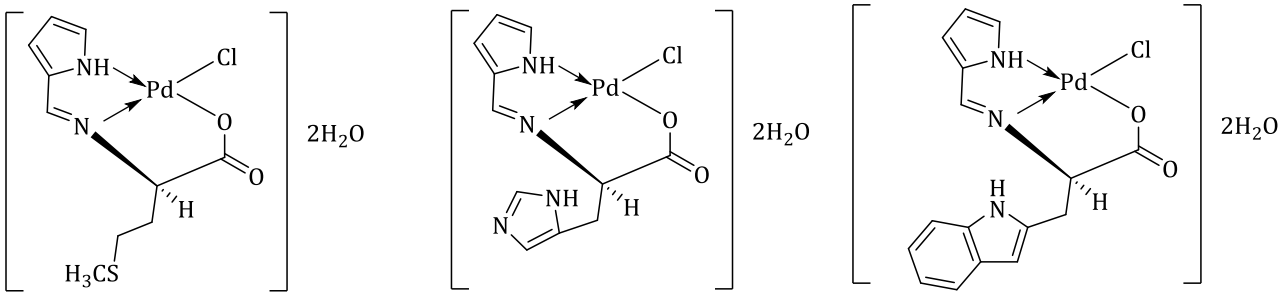


Figure 15: The antibacterial Pd (II) complexes with 2-pyrral amino acid Schiff ligands [81]

Zalevskaya *et al.* (2020) reported terpene-derived chiral palladium complexes and their antimicrobial and antifungal activities. The scientists studied the antibacterial properties against *S. aureus*, *P. aeruginosa, K. pneumoniae, Acinetobacter baumannii, E. coli, Candida albicans,* and *Cryptococcus neoformans*. They discovered that all the palladium complexes had good antifungal activities. However, the palladacycles with a palladium–carbon bond demonstrated activity towards the Gram-positive *S. aureus*. They discovered all the complexes to have poor activity towards the Gram-negative bacteria [82]. Three palladium complexes of the formulars $[PdL_4]2Cl$, PdL_2Cl_2 and $[PdL_4]_2Cl\bullet 4H_2O\bullet L$ (Figure 16) were synthesized and characterized by elemental analysis and spectral techniques. The ligand listed as L represented the imidazo [1,2-*α*]pyridine ligand. The study of biological activity on the palladium complexes were anticancer and antimicrobial activities. The other two complexes $[PdL_4]2Cl$ and $[PdL_4]2Cl\bullet 4H_2O\bullet L$ showed some antibacterial properties towards *S. aureus* [83].

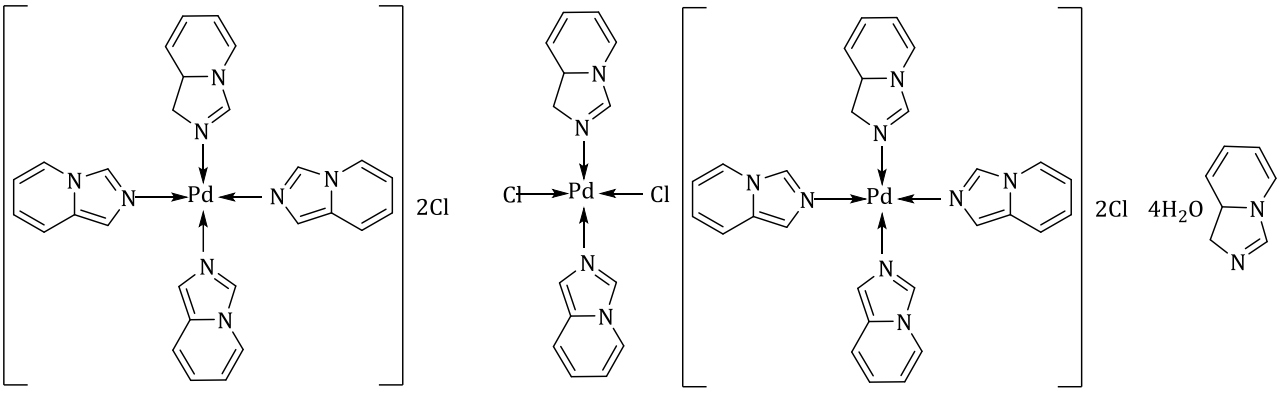


Figure 16: The anticancer and antibacterial activities of three palladium complexes $[PdL_4]2Cl$, PdL_2Cl_2 and $[PdL_4]2Cl.(4H_2O).L$ [83]

Another set of three Pd (II) complexes shown in Figure 17 were synthesized with the ofloxacin (OFL) drug, glycine and alanine amino acids (AA) as mixed chelate ligands. The characterization experiments showed that the molar ratio of the complexes was as follows 1:2 $[Pd(OFL)_2]Cl_2$ and 1:1:1 as $[Pd(OFL)(AA)]Cl$. Moreover, spectroscopic data indicated the OFL ligand as a bidentate ligand which coordinates using the nitrogen atoms of the piperazine ring [84]. Finally, these complexes antibacterial activity was studied against *K. pneumoniae, E. coli, S. aureus*, and *Staphylococcus epidermidis*. They determined that their new complexes indicated better potential when compared with the standard drugs ceftriaxone or gentamycin against all the four micro-organisms. They attributed the antimicrobial properties of the palladium complexes to chelation. In principle, this means that the donor atoms in the ligands may be partially sharing the positive charges from metal. Thus, increasing the possible π-electron delocalization over the metal complex, which may increase the lipophilic character of the metal complex. This then favours the metal complexes permeation into the cell wall and cell membrane [84].

Mode of action of metal-based Compounds

Not much data on the mode of action of metal based potential drugs is available. Most researchers in this field have only showed information of the preliminary antibacterial activity such as disc diffusion and minimum inhibitory concertation data such as the information seen in the previous section. However, attaching organic molecules to metal centers in most cases shows an increase in the antibacterial activity [85]. This section gives a brief preview of some metal based potential drugs and their proposed mode of action. Some iron complexes were observed to show activity towards Gram-positive and Gram-negative

bacteria. These complexes of the salen/ salophen ligand were seen to show more activity towards the Gram-positive bacteria. This was proposed to be due to the easier cell access of the Gram-positive bacteria. Furthermore, due to this easier cell access, it was proposed that the mode of action of these complexes was through ferroptosis. This is the oxidation of the lipid membranes, both Gram-positive and Gram-negative bacteria contain lipid membranes, which is a target for this mode of action [85]. Even though silver sulfadiazine is a conventional antibacterial drug, the mode of action of silver containing drugs was never conclusively known. It has always been suggested that these compounds work by the slow release of silver (I) irons through the dissociative mechanism of inorganic compounds. However, in 2019, Wang and his associates set out to find the possible mode of action of these silver-based drugs. They studied the protein binding of these compounds using a hyphenated system of gel electrophoresis inductively coupled plasma mass spectrometry (GE-ICP-MS). They focused on the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) binding as it is important in glycolysis. Through many techniques including protein single crystal structural analysis, they discovered that silver (I) ions coordinated with the cystine moieties in this protein, which may possibly be the target for these silver-based compounds [86].

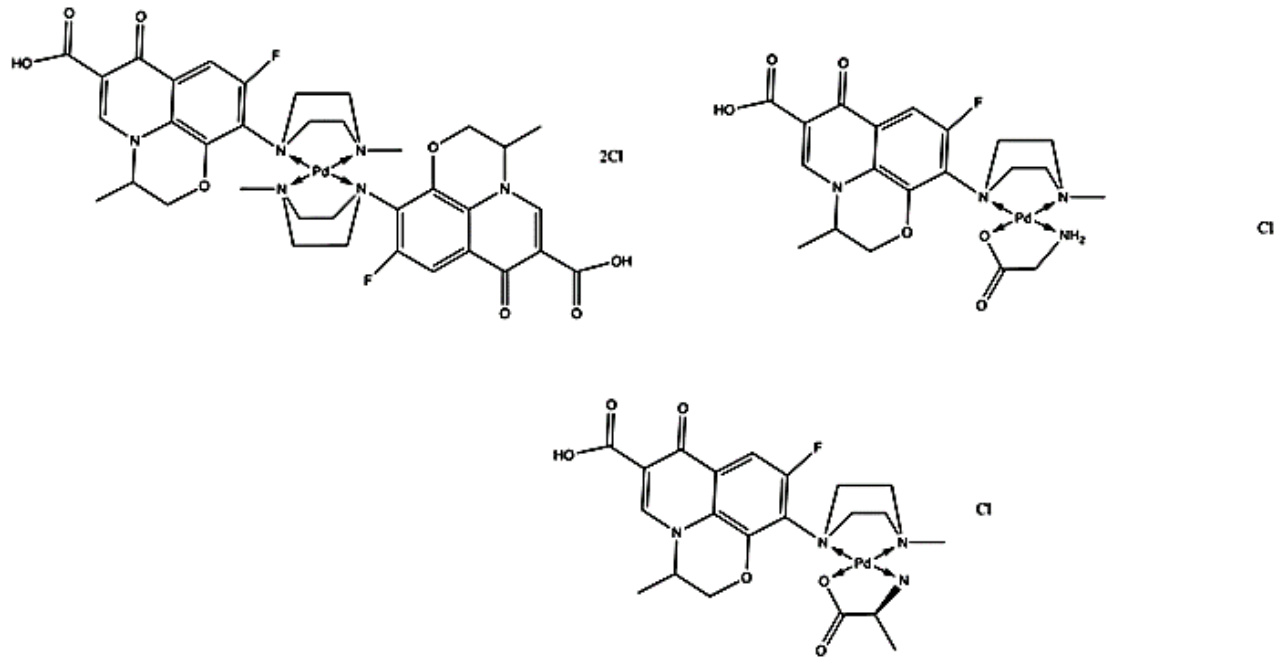


Figure 17: Palladium (II) complexes with ofloxacin (OFL) drug and glycine and alanine amino acids (AA) [84]

Auranofin is an approved antirheumatic drug of a gold complex. It has been studied for most biological activity including antibacterial activity. It has been observed to have antibacterial activity against clinically important bacterial isolates such as MRSA with less activity towards the Gram-negative counterparts [87]. Auranofin has been observed to target thioredoxin reductase (Trx). This target leads to oxidative stress in the cell and eventual death. However, this reduced activity of complexes towards Gram-negative bacteria was observed to be due to the glutathione system [87]. Gallium complexes are also promising metallo-antibacterials; they have been observed to work by affecting iron metabolism in bacteria. This mode is proposed due to the chemical similarity of gallium and iron. Technically, the gallium incorporates with the iron dependant enzymes, thereafter, the organism fails to reduce gallium (III) to gallium (II) which then inhibits that enzyme [88, 89]. Ruthenium complexes have also shown interesting bioactive properties, especially as potential anticancer agents. However, some studies have shown some interesting antibacterial properties of ruthenium. Such properties include the photodynamic antimicrobial chemotherapy

(PACT). This therapy uses photosensitive molecules like ruthenium complexes. The principle of this therapy is that a biological target is destructed by the use of molecular oxygen and a photosensitizer so as to induce oxidative damage to bacteria. Ruthenium polypyridyl complexes are good example of these complexes as shown to be potent by Donnely (2007) and associates [90]. Li and associates (2015) described flexible ruthenium polypyridyl complexes which showed more activity towards prokaryotic cells as opposed to the eukaryotic cells. This led to a study in degerming this difference, and a genomic binding study was carried on RNA-rich nucleus and chromosal DNA. From this study, they revealed that these complexes had better binding properties to the RNA than the DNA. This suggested the mode of action of these complexes to be through genomic material disruption with affinity to ribosomal DNA [91-92].

Copper complexes have been observed to have multiple modes of action towards bacteria, including damage to the cell membranes, oxidative damage, enzyme inhibition, DNA destruction [93]. Evangelinou *et al.* (2014) studied the toxicity of copper complexes in *E. coli*. They studied the light of formation of reactive oxygen species (ROS) through the measurement of malondialdehyde (MDA) equivalent. The principle of their assay was that the more inhibition of growth observed, the more ROS generation. And the more ROS are generated then there would be membrane lipid peroxidation [94]. Table 2 below summarizes some of the possible modes of actions of metal complexes against bacteria as described in literature. However, it should be noted that there are less to no literature on the modes of action of some metal-based compounds against bacteria. Literature mostly includes *in vitro* screening assays of the antibacterial activity of these metals.

Table 2: Some Examples of Metal Centre Biological Targets

Metal Center	Biological Target or Mode of Action	Reference
Silver	glyceraldehyde-3-phosphate dehydrogenase (GAPDH) binding,	[86]
Gold	thioredoxin reductase (Trx) targets,	[87]
Copper	Damage to the cell membranes, oxidative damage by producing reactive oxygen species, DNA damage, Enzyme inhibition, DNA intercalation	[93–96]
Palladium	bacterial disruption and leakage of intracellular component	[97]
Iron	Ferroptosis	[85]
Gallium	Iron metabolism,	[88-89]
Ruthenium	DNA Intercalation, Photodynamic therapy (PDT), RNA or DNA binding, and RNA-ribosome localized binding	[90–92], [98]

Conclusion

Transition metal compounds are promising potential drugs that may aid in the treatment of bacterial infections, especially in this era of antibiotic resistance. Because of their diverse and observed multiple modes of action, these compounds are a good step in fighting antibiotic resistance. These compounds combine the activity derived from the organic ligands bound to them and the central metal. Research has shown that these compounds can induce or increase the activity of free organic ligands when bound to metals.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to responsible for all the aspects of this work.

Conflict of Interest

The authors have no conflict of interest to declare.

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