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NICKEL COMPLEXES AND THEIR ANTIMICROBIAL ACTIVITIES: A REVIEW

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ABSTRACT

Nickel complexes plays important role in the development of bioinorganic chemistry. Divalent nickel ion interacts with a number of organic ligands and biomolecules to form stable complexes. The unique properties of nickel ions have been exploited in the field of medicinal inorganic chemistry for the design of new metal-based drugs. The use of nickel and its complexes for medicinal purposes has been present throughout history. This review focuses on antimicrobial activities of different nickel complexes, with varying geometrical structures, synthesized with different organic chelating agents. All synthesized nickel complexes reviewed showed great antimicrobial activity against human pathologic bacterial as well as human fungi. The inhibitive action of the nickel complexes could be explained on the basis of chelation theory. This review encourages further research in the field of bioinorganic chemistry.

Keywords: Nickel, complexes, antimicrobial, chelation, inhibition

INTRODUCTION

In man, the highest concentration of nickel is found in the nucleic acids, especially in the RNA and DNA, and is thought to be somehow involved in protein structure or function [1]. It activates enzymytic reactions that lead to the breakdown or utilization of glucose. Nickel improves prolactin production, hence, it aids human breast milk production. Nickel improves iron absorption andbone strength, enhances adrenaline, glucose metabolism, hormones, lipid, cell membrane and may also be involved in production of red blood cells [2]. It probably has a role in stabilizing RNA structure [3]. Divalent nickel coordinates with Glyoxalase I enzyme and assist in the breakdown of to methylglycol lactate and water [4]. Acireductone dioxygenase, an octahedral high spin Ni(II) complex catalyses the peroxo intermediate that decomposes to CO, formic acid and a carboxylic acid [5]. Nickel superoxide dismutase (Ni-SOD) is a

metalloenzyme that protects cells from oxidative damage by catalyzing the disproportionation of the cytotoxic superoxide radical to hydrogen peroxide and molecular oxygen [6].

Increase in death rate in Africa related to infectious diseases, is directly linked to the bacteria that have multiple resistances to antibiotics [7]. The shortage of efficient antimicrobial agents is the main cause of this problem. Recent research focuses more on the synthesis of complexes of nickel with ligands, as a result of the biological properties [7]. The synthesis of latest antibacterial agents, through various methods, is, for sure, an emergency medical issue [8, 9].The discovery of latest nickel based drugs has been largely supported on ability of nickel to increase inhibitory potential of chemotherapy agents. Efficacy of some therapeutic agents has been reported to have increased upon coordination [7]. The development of more potent nickel based drugs has been under investigations over the last three decades, and it has been discovered that chelates of nickel have enormous impart in medicine.

It becomes interesting to note that to the best of our knowledge that the review on antimicrobial potentials of nickel complexes is scanty. Therefore, this present review is aimed at discussing the antimicrobial potentials of different nickel complexes, with varying geometrical structures, synthesized with different organic chelating agents.

Antimicrobial activity of nickel complexes

Nickel complexes derived from diphenyl acetic acid (DiPhAc), Quinoline (Q), isoquinoline, α-picotine (pic), γ-picotine, 2-aminopyridine (py) and triethylamine (Figure 1) were synthesized by the reaction of diphenyl acetic acid, heterocylic amine bases (Quinoline, isoquinoline, α-picoting, γ-picoting, 2-aminopyridine), triethylamine with $NiCl_2.6H_2O/Zn(NO_3)_2.6H_2O$ [10].Their melting points were greater than 300 °C and their molar conductances were 4.8 cm^2mol^{-1}, 4.69 cm^2mol^{-1} and 13.6 cm^2mol^{-1}. Their colours were pest, green and pest for $[Ni(DiPhAc)(Q)(H_2O)]$, $[Ni(DiPhAc)(2\text{-}pic)(H_2O)]_2Cl_2$, and $[Ni(DiPhAc)(Py)(H_2O)]_2Cl_2$ respectively. Square planar geometery was suggested for the nickel complexes.

The antibacterial activities of the synthesized complexes were reported [10]. The results of antibacterial activity were measured in terms of zone of inhibition. The complexes, $[Ni(DiPhAc)(Q)(H_2O)]$, $[Ni(DiPhAc)(2\text{-}pic)(H_2O)]_2Cl_2$, and $[Ni(DiPhAc)(Py)(H_2O)]_2Cl_2$ showed maximum sensitivity against both Gram positive and Gram negative bacteria and on comparing the obtained nickel complexes with antibiotic *kanamycin.* The nickel complexes

showed relatively higher activity than *kanamycin*. It was deduced that nature of metal ion, the nature of ligand and orientation of the ligand around the metal ion was responsible for the increased antibacterial activity. It was also suggested that the higher activity of the nickel complexes were due to the effect of metal ions on the normal cell membrane. The variation in the activity of different complexes against different organisms depended either on the impermeability of cells of the microbes or differences in the ribosomes of microbial cells.

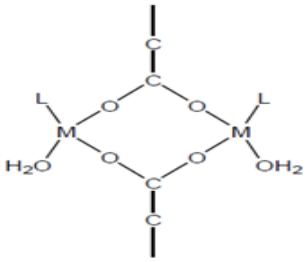

Figure 1: Square planar structure of [Ni(DiPhAc)(Q)(H_2O)], [Ni(DiPhAc)(2-pic)(H_2O)]$_2Cl_2$, and [Ni(DiPhAc)(Py)(H_2O)]$_2Cl_2$, where M = Ni, L = quinoline, isoquinoline, 2-amino pyridine, 2 picoline, pyridine.

The synthesized complex [Ni(Clazpy)$_2$(NCS)$_2$] [11] (Figure 2) was characterized on the basis of elemental analysis, nuclear magnetic resonance, infrared and electronic absorption spectroscopy. Minimal inhibitory concentrations (MIC), minimal bactericidal concentrations and minimal fungicidal concentrations (MFC) of all tested compounds were determined against human pathogens by a colorimetric microdilution method. All compounds were dissolved in dimethyl sulphoxide and were tested against *Staphylococcus aureus* ATCC25923, a clinical isolate of methicillin-resistant *S. aureus* (MRSA) SK1, *Escherichia coli* ATCC25922 and *Pseudomonas* aeruginosa ATCC27853. The [Ni(Clazpy)$_2$(NCS)$_2$] complex exhibited higher antimicrobial activities against fungal strains of *Microsporum gypseum* (MIC/MFC 64/128 µg/ml) than the [Zn(Clazpy)$_2$(NCS)$_2$] complex.

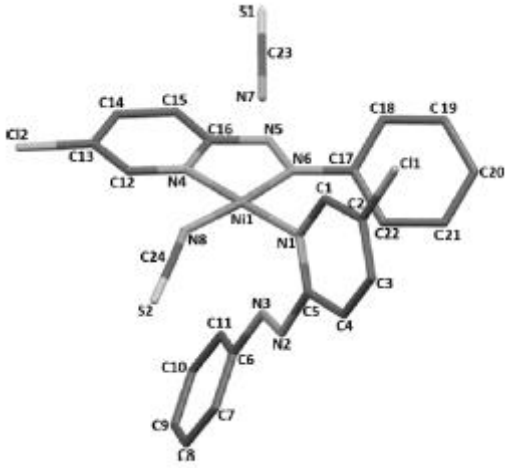

Figure 2: The optimized structure of $[Ni(Clazpy)_2(NCS)_2]$

Nickel complex of hexamethylenetetramine and ammoniumthiocyanate $[Ni(HMTA)_2(NCS)_2(H_2O)_2]\cdot H_2O$. (Figure 3) was prepared by the reaction of hexamethylenetetramine, $NiSO_4\cdot 6H_2O$ and ammoniumthiocyanate [12]. The nickel complex was deduced to have bluish-green colour. Slightly distorted octchedron was proposed for the complex. *In vitro* antimicrobial activity test against four strains of bacteria (*Salmonella enteric*, *Shigella flexneri*, *Escherichia coli* and *Staphylococcus aureus*) and four strains of fungi (*Candida albicans*, *Candida krusei*, *Candida parapsilosis* and *Candida neoforman* inferred that the nickel complex showed increased antimicrobial activity compared to the parent ligand. The highest activity of the complex was shown against *E. coli* and *S. flexneri*.

It was concluded that the antimicrobial activity of the nickel complex $[Ni(HMTA)_2(NCS)_2(H_2O)_2]\cdot H_2O$.could be due to the reduction of the polarity of the metal ion by partial sharing of the positive charge with the ligand's donor atoms so that there is electron delocalisation within the metal complex. This may increase the lipophilic character of the metal complex, enabling it to permeate the lipid layer of the organism killing them more effectively.

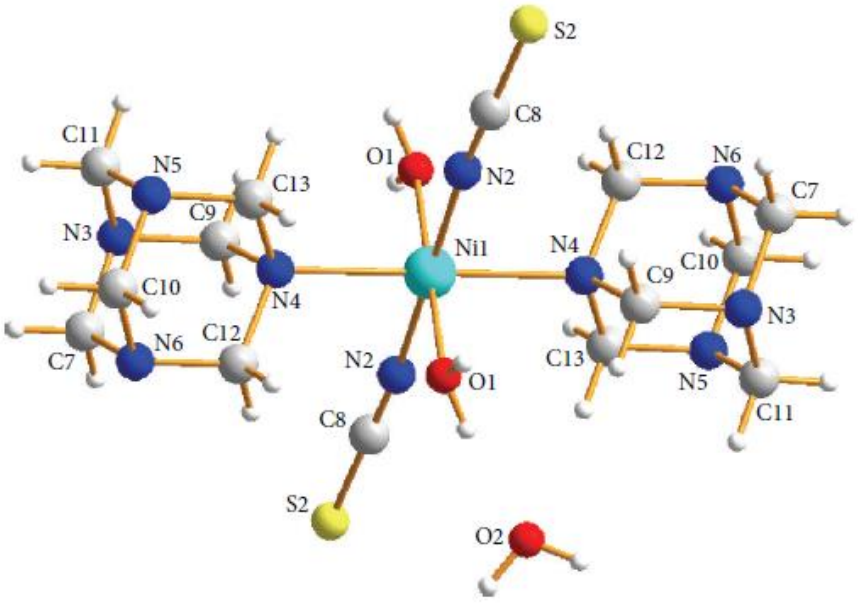

Figure 3: ORTEP view of $[Ni(HMTA)_2(NCS)_2(H_2O)_2]\cdot H_2O$

The complex, $[Ni(5\text{-}BSA)_2]$, was synthesized by reaction 5-bromosalicylaldehyde (5-BSA) and nickel perchlorate [13]. The magnetic moment suggested octahedral structure for $[Ni(5\text{-}BSA)_2]$. The antibacterial studies of $[Ni(5\text{-}BSA)_2]$ against Gram positive (*Bacillus subtilis, B. cereus*) and Gram negative (*Escherichia Coli, Pseudomonas aeruginosa*) bacterial species were reported [13], ciprofloxacin, a broad-spectrum antibacterial drug as a standard. It was deduced that the free ligand (5-BSA) possessed moderate antibacterial activity. $[Ni(5\text{-}BSA)_2]$ exhibited higher antibacterial activity . The antibacterial activity increased with the enhancement in the concentration of nickel chelate. The study revealed that $[Ni(5\text{-}BSA)_2]$ exhibited good antibacterial activity compared to 5-BSA against Gram positive and Gram negative bacterial species. It was concluded that the nickel-(II) complex showed a greater antibacterial activity than the uncomplexed ligand.

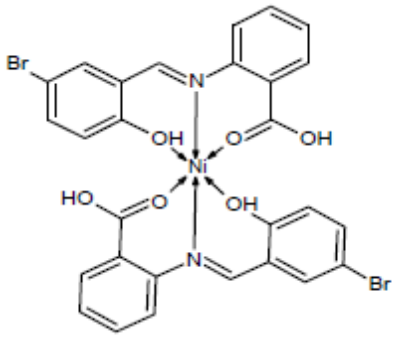

Figure 4: Possible geometry for $[Ni(5\text{-}BSA)_2]$

The nickel complex, $[NiL_2(NO_3)_2]$ (L = $C_{10}H_8ON_2$), (Figure 5) was prepared by the reaction of aqueous solution of Ni(II) nitrate with $C_{10}H_8ON_2$[14]. The analytical data suggested that all the complexes were mononuclear with the ligand coordinated to the central metal atom. From the magnetic susceptibility measurement it was deduced that $[NiL_2(NO_3)_2]$ exhibited octahedral coordination. It was deduced that $[NiL_2(NO_3)_2]$ showed greater activity compared to ligand.

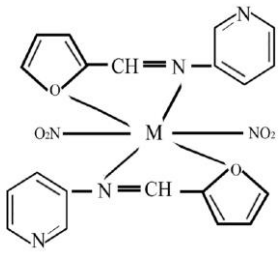

Figure 5: Suggested structure of $[NiL_2(NO_3)_2]$ (M=Ni, L = $C_{10}H_8ON_2$)

Nickel complex, $[NiL_2].zH_2O$ was synthesized by the reaction of nickel chloride and ligand (*E*)-1-(4-((E)-(4-(diethylamino)-2-hydroxybenzylidene)amino)phenyl)ethanoneoxime[15]. The chelated nickel complex, $[NiL_2].zH_2O$ is shown in Figure 6. The thermal stability study revealed that the nickel complex was stable. It was deduced that Ni(II) complex has a square planar geometry. The biological screening of the Ni(II) complex against two Gram-positive bacteria (*Staphylococcus aureus and Staphylococcus epidermidis*), four Gram-negative bacteria (*Salmonella spp, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella spp.*), and one fungus (*Candida albicans*) showed greater activity compared to the ligand. The nickel complex revealed nearly the same activity over gram-positive (*S. epidermidis*) and two gram-negative

(*Klebsiella spp*. and *Pseudomonas aeruginosa*).It was concluded that the inhibitory effect of the nickel complex solutions depended on the concentration of the solutions.

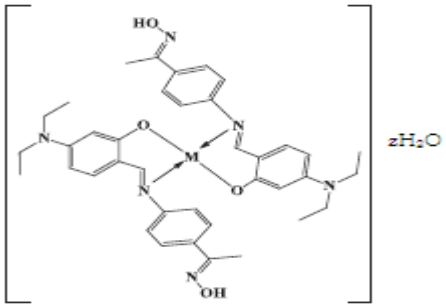

Figure 6: Proposed structures of $[NiL_2].zH_2O$ where M = Ni(II), z = 0 , where L = (E)-1-(4-((E)-(4-(diethylamino)-2-hydroxybenzylidene)amino) phenyl)ethanone oxime

The nickel complex of N, N'bis(salicylidene) ethylenediamine was prepared by the reaction of $NiSO_4.6H_2O$ and N,N'-bis(salicylidene) ethylenediamine (Figure 7) [16]. The synthesized ligand and metal complex were air stable. Complex was reddish in colour and crystalline. Antibacterial activity of the Schiff base ligand (N, N'-bis(salicylidene) ethlenediamine) and its nickel complex against *E. coli*, *Shigella dysenteriae* and *Shigella sonnei* Gram negative bacteria showed that the Schiff base and nickel complex individually exhibited varying degrees of inhibitory effects on the growth of tested bacterial species. The complex showed more antibacterial activity than Schiff base ligand N, N'-bis(salicylidene) ethlenediamine.

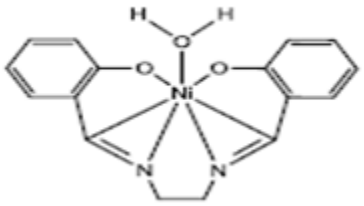

Figure 7: Proposed Ni(II) chelate of N, N'-bis(salicylidene) ethlenediamine

Mixed nickel complex derived from the reaction of 4- aminoantipyrine, furfuraldehyde, 2-aminobenzothiazole and 3- nitrobenzaldehyde has been reported (Figure 8) [17]. The complex was reported to be soluble in chloroform, dimethylformide, tetrahydrofuran and dimethylsulphoxide. The Ni(II) complex was square planar and diamagnetic. The *in vitro*

evaluation of the ligands and its nickel complex against bacterial species *Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia, Salmonella typhi, and Pseudomonas aeruginosa and* fungi species *Aspergillus niger, Rhizoctonia bataicoli and Candida albicans* revealed that the lowest concentration (l μg/ml) of complex, inhibited the growth of bacteria after 24 hr incubation at 37 ^{o}C and the fungi after 72 hr incubation at 37 ^{o}C. The DNA- binding properties of the mixed ligand complex studied by electronic absorption spectra and cyclic voltammetry suggested interaction of the complex with DNA through the interchelation binding mode. It was concluded from the antimicrobial activity studies that the nickel complex possessed better biological activity as compared to free ligand. The mixed ligand complex showed the greater bonding activity due to the presence of electron donating methyl group in the 4- aminoantipyrine.

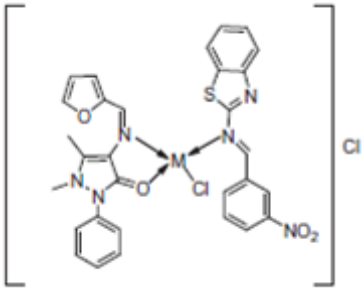

Figure 8: Proposed mixed nickel complex derived from the reaction of reaction of 4-aminoantipyrine, furfuraldehyde, 2- aminobenzothiazole and 3- nitrobenzaldehyde, M = Ni(II)

Mixed-ligand nickel(II) complexes [Ni(INAP)(Aa)] were prepared by the reaction of nickel(II) chloride, isonitrosoacetophenone (HINAP) and various chiral amino acids such as histidine, phenylalanine and tryptophan [18].It was suggested that the ligand isonitrosoacetophenonei coordinated in depronated form through oxygen and nitrogen atoms leading to neutral complexes .The nickel complexes were reported to be octahedral with two coordinated water molecules probably in *cis* position (Figure 9). The Nickel complexes [Ni(INAP)(Hist)$(H_2O)_2$], [Ni(INAP)(Phen)$(H_2O)_2$], [Ni(INAP)(Tryp)$(H_2O)_2$] were orange, orange and green in colour, respectively. The antibacterial screening against six bacteria [*Escherichia coli* (ATCC 4157), *Staphylococcus aureus* (ATCC 6538), *Streptococcus pyogenes* (ATCC 12358), *Proteus mirabilis* (ATCC 49565), *Pseudomonas aeruginosa* (ATCC 9027), *Bacillus subtilis* (ATCC 9372)] and one yeast *Candida albicans* (ATCC 24433) deduced that the complexes exhibit antimicrobial

properties and it was noted that the metal chelates exhibited more inhibitory effects than the free ligand. The increased activity of the metal chelates can be explained on the basis of chelation theory. Chelation considerably reduced the polarity of the metal ion because of the positive charge of the metal is partially shared with the donor atoms present in the ligand, and there may be electron delocalization over the whole chelating space. This increases the lipophilic character of the metal chelate and favors its permeation through the lipoid layer of the bacterial membranes. The antioxidant power of Ni(II) complexes increases in the order of the amino acids, from histidine to tryptophan. This order satisfactorily correlates with the cathodic potentials which shift towards more negative values on going from histidine to tryptophan. Ni(II) complexes with tryptophan had the higher antioxidant power. It can be explained on the basis of the indole, the aromatic heterocycle that terminates the tryptophan side chain, which is both electron rich and possesses H-bond donor. It was concluded that complexation increases the antimicrobial activity.

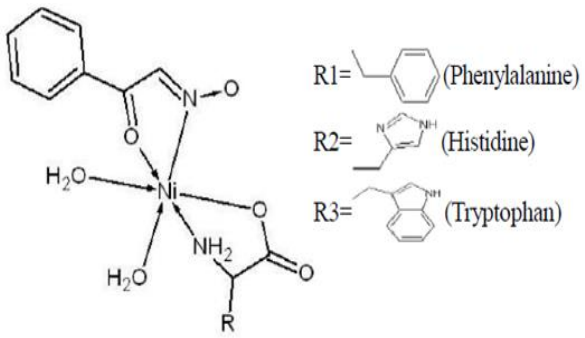

Figure 9: Proposed structure of mixed Ni(ll) complexes of isonitrosoacetophenone and amino acids

Ni(II) complexes derived from (a) 5-methylsalicylaldehyde, ethylenediamine and salicylaldehyde (b) 5-methylsalicylaldehyde, diaminomaleonitrile and salicylaldehyde have been reported [19] (Figure 10). The complexes were characterized based on elemental analysis, ^{1}H NMR, FT IR, and mass spectroscopy. From electronic spectra of the complexes, nickel(II) complexes exhibit four bands in their electronic spectra with the band at 460 nm attributed to the d–d transition. Antibacterial activities of the complexes tested against *Staphylococcus aureus (*ATCC 12600), *Bacillus subtilis* (ATCC 6633), *Klebsiella pneumonia* (ATCC 13883),

Pseudomonas aeruginosa (ATCC 10145), *Escherichia coli* (ATCC 11775), and *Candida albicans*. It was inferred that the metal complexes [Ni(II)L_1] and [Ni(II)L_2] showed greater inhibitory effect compared to ligands (L_1/L_2) and complexes of L_2 showed higher activity than complexes of L_1. The complexes showed higher activities against *S. aureus*, *P. aeroginosa*, *K. pneumonia*, *B. cearus*, and *E. coli*. It was concluded that the observed variation inhibition activity of the metal complexes and their corresponding ligands across the various classes of organisms studied may be attributed to the differences in cell wall and/or membrane.

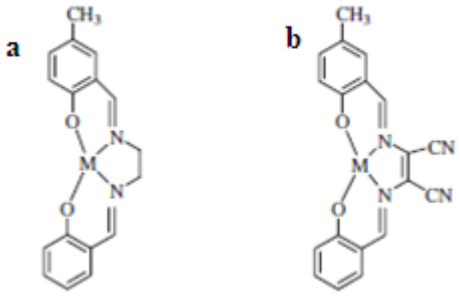

Figure 10: Ni(II) complexes derived from (a) 5-methylsalicylaldehyde, ethylenediamine and salicylaldehyde (b) 5-methylsalicylaldehyde, diaminomaleonitrile and salicylaldehyde

The complex, [Ni(C_5H_5N)$_2$$Cl_2$] (Figure 11) was synthesized by the reaction Ni(II) chloride and pyridine (C_5H_5N) [20]. The complex obtained was a yellow colored microcrystalline powder, soluble in water and chloroform. From IR and ^{13}C NMR spectra, a square planar geometry was confirmed for [Ni(C_5H_5N)$_2$$Cl_2$]. The antimicrobial studies against human pathogenic bacteria such *as Salmonella typhi*, *Shigella dysenteriae*, *Escherichia coli*, *Bacillus cereus* and phytopathogenic fungi such as *Macrophomina phaseolina,*, *Alternaria alternata*, *Fusarium equiseti*, *Colletotrichums corcolei* and *Botryodiplodia theobromae*. It was observed that the complex was more effective against bacteria than its ligand and the data show that *E. coli* was inhibited to the greatest degree by the prepared complex. The ligand and complexes were found to show higher inhibition on the growth of *Macrophomina phaseolina* in comparison with other fungi. Measurements of inhibition zones of ligand and complex showed that the prepared complex had greater antibacterial activity more than ligand. It was concluded that the nature of ligands and metals plays a significant role in the inhibition of mycelial growth, as such, could reasonably be used for the treatment of some common diseases.

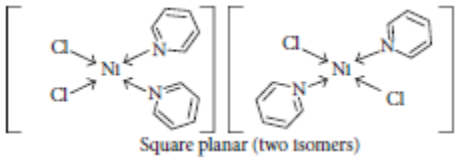

Figure 11: Square planar complexes of $[Ni(C_5H_5N)_2Cl_2]$

The complex, $[Ni(C_{22}H_20N_4O_2)]$, (Figure 12) was synthesized by the reaction of nickel chlorides and the ligand 3,3'-(Cyclohexane-1,2-Diylbis(azanylylidene))Bis(Indolin-2-One)[21]. The magnetic susceptibility of synthesized complex, $[Ni(C_{22}H_{20}N_4O_2)]$ suggested square-planar geometry arrangement.. Antibacterial screening of the ligand and complex against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* using ciprofloxacin as the standard antibacterial agents was reported. It was deduced that $[Ni(C_{22}H_{20}N_4O_2)]$ showed greater activity than the free ligand. Fairly moderate effectivenes was recorded for Ni(II) complex towards *Escherichia coli*. The differences in the activity against different organisms depends either on the impermeability of cells of the microbes or differences in the ribosomes of microbial cells. The higher antibacterial activity of $[Ni(C_{22}H_{20}N_4O_2)]$ than the free Schiff base ligand can be explained by chelation of the ligand with metal ions as metal chelates display both polar and nonpolar properties. This makes them suitable for permeation into cells and tissues. Chelation increases the delocalization of π-electrons over the entire chelate ring and enhances the penetration of the complexes into lipid membranes. However, it also increases the hydrophilic and lipophilic nature of the central metal ions, probably leading to lipo-solubility and permeability through the lipid layer of cell membranes. Further, lipophilicity, which controls the rate of entry of molecules into the cell, is modified by coordination, so the metal complex can become more active than the free ligand. It was concluded that the antimicrobial activity of metal complex depended more on the metal center itself than on the geometry around the metal ion.

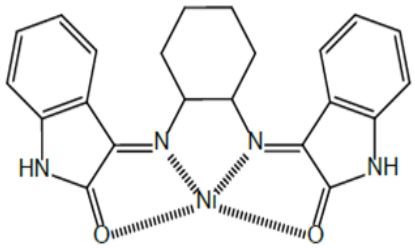

Figure 12: Proposed geometrical structure of $[Ni(C_{22}H_{20}N_4O_2)]$

The nickel complexes of dihydrazone ligands {$[Ni(L_1)(OAc)_2].2H_2O$, $[Ni_2(L_2–2H)(H_2O)_2].3H_2O$, $[Ni(L_3–2H)].CH_3OH$ and $[Ni(L_4–H)(OAc)].5H_2O$ (Figure 13) were prepared by the reaction of dihydrazone ligand and Ni(II) acetate [22]. It was reported that the complexes were air stable for long time, insoluble in MeOH/EtOH, Et_2O, $CHCl_3$, acetone, CCl_4 as well as benzene. Complexes were soluble in DMF and DMSO and existed either in the trans (staggered) configuration or cis-configuration. Electronic spectra suggested a tetrahedral geometry around the Ni(II) ion. Magnetic studies suggested that Ni(II) oxaloyldihydrazones -complexes had high spin but the presence of two metals near to each other in the same molecule may cause partial quenching of the spin moments of the metal ions (spin coupling) decreasing the magnetism. The antimicrobial activity screening of ligands and their nickel complexes against fungi *Aspergillus fumigatus*, *Synccephalastrum racemosum* using amphotericin B as standard were studied. The antibacterial screening against Gram-positive bacteria such as *Streptococcus pneumoniae*, *Bacillis subtilis* using ampicillin as standard were reported. The antibacterial screening against Gram-negative bacteria Escherichia *coli using* gentamicin as standard were also reported. It was deduced that all tested compounds have an appropriate activity against all the tested micro-organisms, bis(2-hydroxy-1naphthaldehyde)oxaloyldihydrazone, exhibited the highest activity against all the tested micro-organisms, fungi, Gram-positive bacteria and Gram-negative bacteria. $[Ni(L3–2H)].CH_3OH$, showed higher inhibition zones against *B. subtilis* and *S. pneumoniae* as well as *E. coli*. The metal complex $[Ni_2(L2–2H)(H_2O)_2].3H_2O$, exhibited the highest inhibition zone against *S. racemosum* and *Aspergillus fumumoniae* as well as *S. racemosum* (fungi). The dihydrazone ligand bis(salicylaldehyde)oxaloyldihydrazone showed lower inhibition zones against *S. pneumoniae* and S. *racemosum* (fungi). The enhancement in antibacterial activity of the nickel(II) complexes ($[Ni_2(L2–2H)(H_2O)_2].3H_2O$, $[Ni(L3–2H)].CH_3OH$) can be explained based on the chelation theory where the activity of hydrazone increases upon coordination. Chelation reduces the polarity of the metal ion because of partial sharing of its positive charge with the donor groups and possibly the π-electron delocalization within the completely chelate ring system that formed during coordination. These factors increase the lypophilic nature of the central metal atom and hence increase the hydrophobic character and liposolubility of the molecule favoring its permeation through the lipid layer of the bacterial membrane. Consequently, the metal complexes can easily penetrate into the lipid membranes and block the metal-binding sites of enzymes of the micro-organisms, thus

destroying them more aggressively. These metal complexes also affect the respiration process of the cell and thus block the synthesis of proteins, which restrict further growth of the organism.

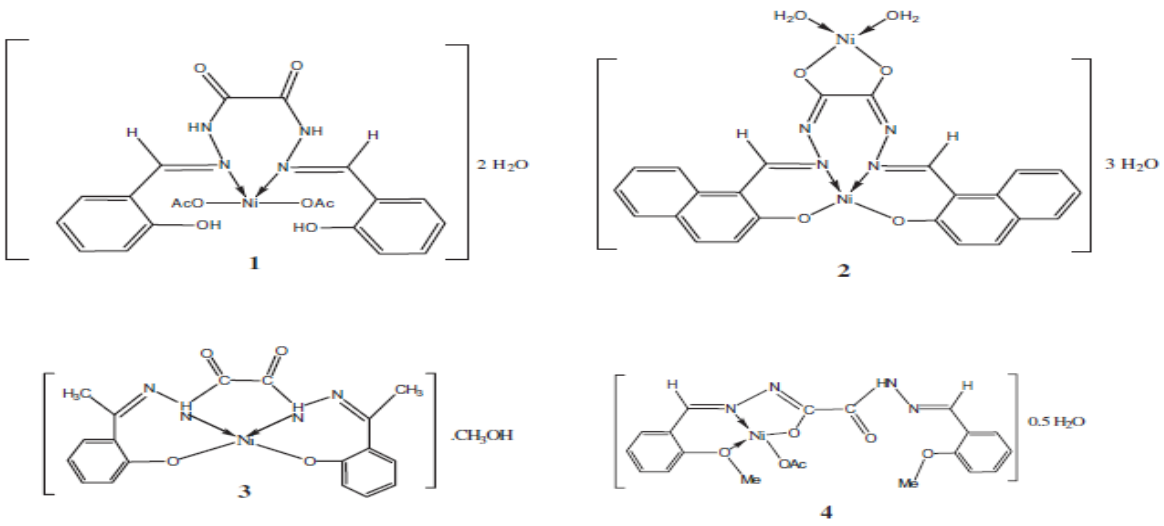

Figure 13: Suggested structures of the Ni(II)-oxaloyldihydrazone complexes

The complex [Ni(II)(SD)PhDTC] (Figure 14) was synthesized by the reaction of sulfadiazine ligand (SD), $Ni(NO_3)_2{\cdot}2½H_2O$ and aniline dithiocarbamate (PhDTC) [23]. Dark brown colour was reported for [Ni(II)(SD)PhDTC]. Antimicrobial activities of ligand and [Ni(II)(SD)PhDTC] were tested against *Proteus valgaris, Salmonella typhii, Shigella flexneri, Staphylococcus aureus, Bacillus subtilis, Streptococcus pneumonia, Psendomonas aeruginosa, Vibro chlolerae and Klebseilla pneumonia.* It was reported that both the ligand and the metal complex showed inhibitory activity. It was concluded that the complex showed bacterial and fungal growth inhibition in the order: control > metal complex > parent ligands

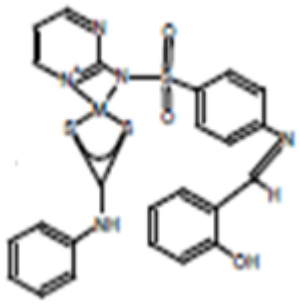

Figure 14: Proposed nickel complex of sulfadiazine and N-phenyl DTC Schiff base, where M = Ni(II)

The complex $[C_{30}H_{30}NiN_4O_{10}S_2]$ (Figure 15), was synthesized by the reaction of the ligand (E)-N-(4-(2-Hydroxybenzylideneamino) phenylsulfonyl) and $NiSO_4{\cdot}6H_2O$ [24]. The IR spectra study of the ligand [(E)-N-(4-(2-Hydroxybenzylideneamino)phenylsulfonyl)] showed five potential donor sites, oxygen of the phenolic group (OH), nitrogen of the azomethine group (C=N), sulfonamide oxygen (SO_2), nitrogen of secondary amine (NH) and O acetamido (carbonyl group) (C=O). Octahedral geometry was suggested for $[C_{30}H_{30}NiN_4O_{10}S_2]$. The antifungi activity of complex was tested against Fungi (*Aspergillus fumigates*, *Candida albicans*) using Amphotericin B as standard. The antibacterial activity of the complex was also tested against Gram positive bacteria *(Sterptococcus pneumonie*, *Bacillus subtilis*) using Ampicillin as standard, Gram negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*) using Gentamicin as standard. It was inferred that both the ligand and the metal complex showed greater inhibitory activity against *Escherichia coli*. It was concluded that the complex could be used for the treatment of some common diseases caused by *E. coli*, e.g., septicemia, gastroenteritis, urinary tract infections, and hospital-acquired infections.

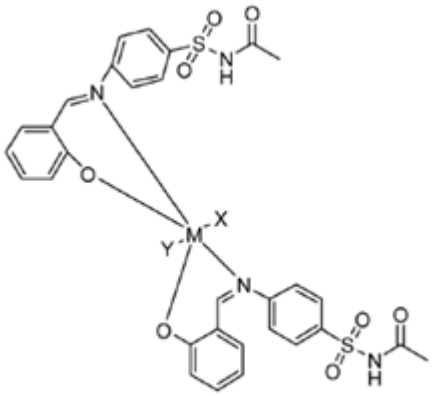

Figure 15: Proposed structure of $[C_{30}H_{30}NiN_4O_{10}S_2]$ where M = Ni (X = Y= H_2O)

The nickel complexes, $[C_{28}H_{18}N_2O_4Cl_2Ni]$ and $[C_{28}H_{18}N_2O_4F_6Ni]$ (Figure 16) have been reported [25]. FT- IR spectrum of the complexes indicated that ligands behaved in bidentate manner coordinating via the nitrogen and oxygen. ^{1}H-NMR and ^{13}C-NMR data of the ligands and complexes confirmed the formation of the coordination compounds. Other analytical techniques demonstrated that $[C_{28}H_{18}N_2O_4Cl_2Ni]$ and $[C_{28}H_{18}N_2O_4F_6Ni]$ are four coordinated.

The antibacterial activity of Schiff base and its nickel complexes against *Staphylococcus aureus* indicated that both Schiff base and its nickel complex showed significant antibacterial activity.

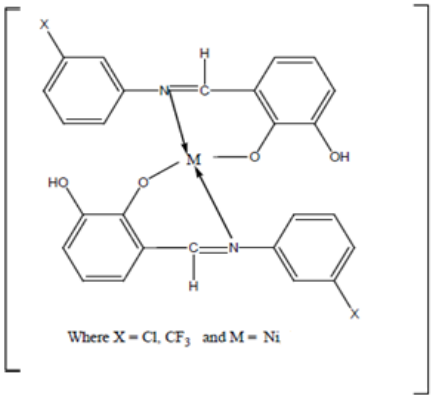

Figure 16: Proposed structures of $[C_{28}H_{18}N_2O_4Cl_2Ni]$ and $[C_{28}H_{18}N_2O_4F_6Ni]$

Ni(II) complex of 3-chloro-4-methyl-N-[(1E)-1-phenylethylidene]aniline was synthesized, characterized and the antifungicidal properties were evaluated [26]. The spectral data of the nickel complex was interpreted on the basis of comparison with that of the free ligand. The analysis showed that the ligand coordinated to the nickel ion through the azomethine nitrogen, the chloride and two aqua molecules. An octahedral geometry was suggested for the nickel complex (Figure 17). The compounds were screened against *Aspergillus niger, Macrophomina phaseolina, Fusarium oxysporum and Alternaria alternate.* Their potency have been discussed. It has been found that the nickel complexes are active and showed higher activity than the free ligand. Metal chelation affected the bioactive behavior of the organic ligand.

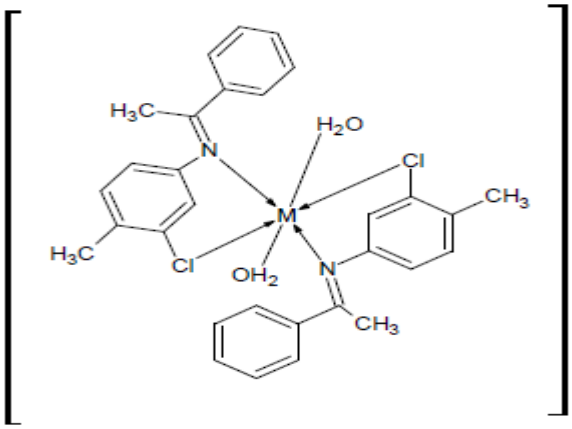

Figure 17: Proposed structure of Ni(II) complex of 3-chloro-4-methyl-N-[(1E)-1-phenylethylidene] aniline (M = Ni(II)

New Schiff base and its Ni(II) complex were synthesized using benzaldehyde and sulphathiazole [27]. They were characterized using elemental analyser, UV-visible spectrophotometer, FTIR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. IR spectral data suggested that the ligand coordinated to nickel ions through two azomethine nitrogen, and one amine nitrogen. Electronic spectral measurement indicated the occurrence of ligand to metal charge transfer. Based on the continuous variation method, metal: ligand ratio of 1:1 was proposed. Elemental analysis and spectroscopic studies suggested that the Schiff base, 4-{[(E)-phenylmethylidene] amino}-N-(1,3-thiazol-2-yl)benzenesulfonamide behaved as a tridentate ligand towards nickel ion (Figure 18). Antibacterial sensitivity of the ligand and its Ni-(II) complex were assayed *in vitro* against *Staphylococcus aureus, Echerichia coli, Pseudomonas aeruginosa and Salmonella typhi*. It was observed that the Ni(II) complex was more potent than the Schiff base against the bacterial strains used. Therefore, the Schiff base and its Ni(II) complex may inhibit bacterial infections caused by *E.coli, P.aeruginosa,S. typhi and S.aureus.* The Ni(II) complex showed enhanced antibacterial activity when compared with the pure the Schiff base.

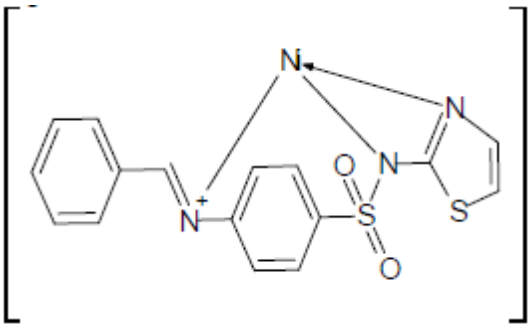

Figure 18: Proposed Ni(II) complex of 4-{[(E)-phenylmethylidene]amino}-N-(1,3-thiazol-2-yl)benzeneesulfonamide

Ni(II) complex of (3,3-dimethyl-7-oxo-6-(2-Phenylacetamido)-4-thia-1-Azabicyclo[3.2.0]heptane-2-carboxylic acid [Ni(DPTA)] was reported [28]. The complex was synthesized, characterized and the antibacterial activities were studied. Physical properties such as solubility, colour and melting point were determined for the ligand, DPTA and the synthesized complex, [Ni(DPTA)]. The complex was found to be light green in colour. The ligand and the complex are ionic in nature with molar conductivity values of 218.2 and 126.0 $Sm^{2}mol^{-1}$ respectively. The complex was characterized based on elemental analysis, UV-Visible, infrared,

1H NMR and 13C NMR spectroscopy. Spectroscopic data suggested that the DPTA coordinated to Ni ion through OH, C=O of amide, C=O of carboxylic acid, C=O of β-lactam and NH functional groups. Also since DPTA was coordinated to nickel centre through five sites it was also proposed that it acted as a pentadentate ligand around the nickel centre (Figure 19). The antibacterial studies of the ligand and its nickel complex were carried out against four-gram negative bacterial strains (*Escherichia coli, Enterobacter cloacae, Pneumonia aeruginosa and Campylobacter fetus*) and four-gram positive bacterial strains (*Staphylococcus aureus, Bacillus substilis, Bacillus cereus and Enterococcus faecalis*). The results showed that [Ni(DPTA)] exhibited better antibacterial activity than DPTA. Its study concluded that the process of chelation affected the biological behavior of the compound which in turn increase the inhibitory potential against the bacterial strains [29, 30].

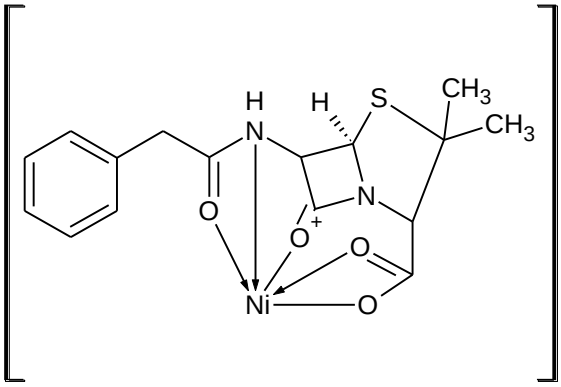

Figure 19: Proposed Ni(II) complex of (3,3-dimethyl-7-oxo-6-(2-Phenylacetamido)-4-thia-1-Azabicyclo[3.2.0] heptane-2-carboxylic acid

CONCLUSION

Since nickel possesses unique biological properties, its complexes can be synthesized for the design of new metallopharmaceuticals. The antimicrobial activity of nickel complexes is still an unexplored area of research and may be useful to develop novel antimicrobial agents. The exploration, targeting and activation strategies of nickel complexes should lead to future generations of drugs which can overcome some of the disadvantages associated with present antimicrobials such as elimination of side-effects, broadening of the activity spectrum and resistance. The field of biocoordination chemistry and interdisciplinary researches related to metal based drugs should, therefore, be exploited to solve the biological, pharmacological profiles and molecular activity mechanisms of metallopharmaceuticals in the complex living

systems. Thus, nickel based drugs will certainly take a vital part of drug development to enhance the quality of life of patients.

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