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A Short Review on Antimicrobial Activity Study on Transition Metal Complexes of Ni Incorporating Schiff Bases

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Abstract:

Schiff bases and their complexes are flexible compounds synthesized from the condensation of an amino compound with carbonyl compounds and extensively used for industrial purposes and also show a broad range of biological activities including antibacterial, antifungal, antiviral, antimalarial, ant proliferative, anti-inflammatory, anticancer, anti-HIV, anthelminthic and antipyretic properties. Many Schiff base complexes show excellent catalytic activity in various reactions and in the presence of moisture. Over the past few years, there have been many reports on their applications in homogeneous and heterogeneous catalysis. The high thermal and moisture stabilities of many Schiff base complexes were useful attributes for their application as catalysts in reactions involving at high temperatures. The activity is usually increased by complexation therefore to understand the properties of both ligands and metal can lead to the synthesis of highly active compounds. The influence of certain metals on the biological activity of these compounds and their intrinsic chemical interest as multidentate ligands has prompted a considerable increase in the study of their coordination behavior. Development of a new chemotherapeutic Schiff bases and their metal complexes is now attracting the attention of medicinal chemists. This review compiles the antimicrobial activity of transition metal complexes of Ni over the few year decades.

Keywords:

Schiff Bases, Nickel Complexes, Antibacterial Activity, Antifungal Activity and Antiviral Activity

1. Introduction

Schiff bases are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (CO) has been replaced by an imine or azomethine group (Figure 1, Figure 2). Schiff base ligands are easily synthesized and form complexes with almost all metal ions. Metal ions are electron deficient, whereas most biological molecules such as proteins and DNA are electron rich. The attraction of these opposing charges leads to a general tendency for metal ions to bind and interact with biological molecules [1,2]. This same principle applies to the affinity of metal ions for many small molecules and ions crucial to life, such as oxygen. Given this wide scope for the interaction of metals in biology, it is not surprising that natural evolution has incorporated many metals into essential biological functions. Metals perform a wide variety of tasks such as carrying oxygen throughout the body and shuttling electrons. Hemoglobin, an iron-containing protein that binds to oxygen by which it carries this vital molecule to body tissues. Similarly, calcium-containing minerals are the basis of bones, the structural framework of the human body. 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. Metal complexes are already in clinical use, and encourage further studies for new metallo drugs such as metal mediated antibiotics, antibacterials, antivirals, antiparasitics, anti-HIV [3], anti-diabetes, radio-sensitizing agents and anticancer compounds. However, their mechanisms of action are often still unknown. Nowadays, the bioinorganic chemists target the heterocyclic ligands and their metal complexes to study their pharmacology as the main focus of research [4,5]. Over the past few years, there have been many reports on their applications in biology including antibacterial, antifungal, anticancer, antioxidant, anti-inflammatory, antimalarial, antiviral activity, cytotoxicity [6-23] and also as catalyst in several reactions such as polymerization reaction, reduction of thionyl chloride, oxidation of organic compounds, reduction reaction of ketones, aldol reaction, Henry reaction, epoxidation of alkenes, hydrosilylation of ketones, synthesis of bis(indolyl) methane and Diels Alder reaction hence the need for a review article highlighting the uses of Schiff base ligands and their complexes.

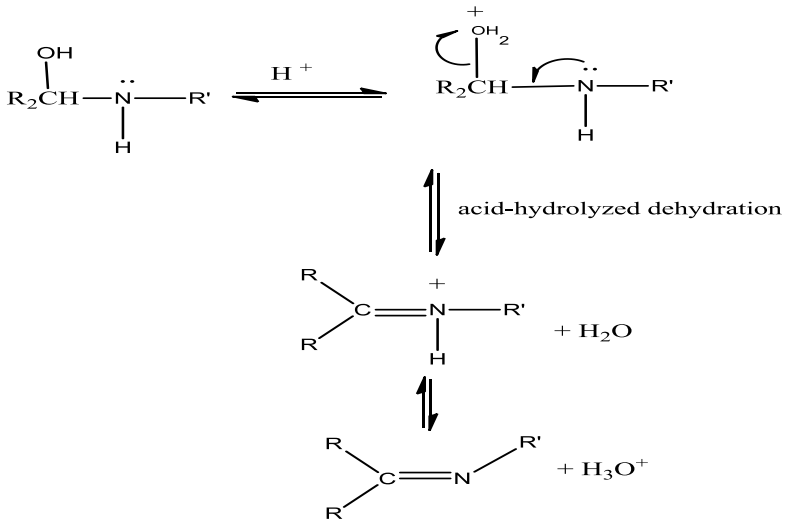


Figure 1. *General Scheme for the preparation of Schiff bases.*

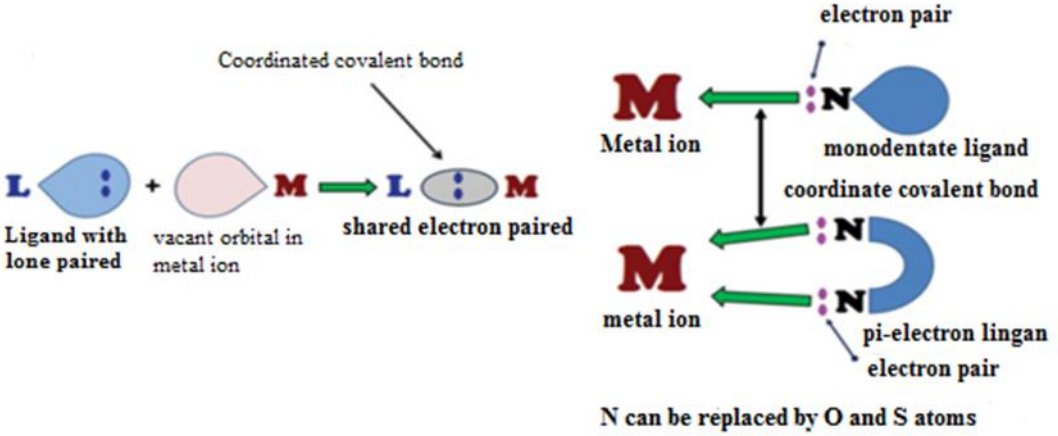


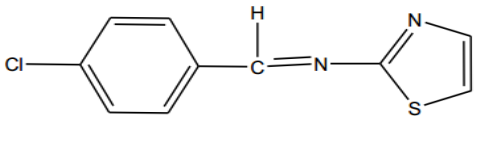
Figure 2. *Schematic representation behind the formation metal complexes.*

2. Biological Importance of Schiff Base Nickel Complexes

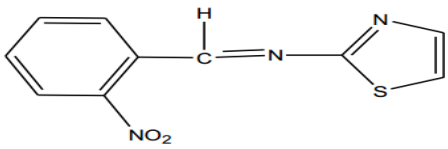
The development in the field of bio-inorganic chemistry has increased the interest in Schiff base complexes, since it has been recognized that many of these complexes may serve as models for biologically important species. Thus, we report them in the following:

2.1. Antimicrobial Activity of Schiff Base Metal Complexes

Schiff base metal complexes of Co(II), Ni(II) and Cu(II) derived from 4-chlorobenzylidene-2-aminothiazole (CAT) and 2- nitrobenzylidene-2-aminothiazole (NAT) have been synthesized by A.P. Mishra and *et al.* [24]. The Schiff base and metal complexes screened against the Gram-positive bacteria; *Staphylococcus aureus* and Gram-negative bacteria; *Escherichia coli* and fungi *Aspergillus niger* and *Candida albicans.* The antimicrobial data show that the metal complexes to be more biological active compared to those parents Schiff base ligand (Figure 3) against all phathogenic species. The compounds also inhibit the growth of fungi and bacteria to a greater extent as the concentration is increased.



4-chlorobenzylidene-2-aminothiazole (CAT)



2-nitrobenzylidene-2-aminothiazole (NAT)

Figure 3. *Structure of Schiff base ligand.*

Narendra Kumar Chaudhary and *et al.* were synthesized two new metal complexes (Figure 4, Figure 5) of general formula $M(Ha\alpha ft)_2$ [M = Ni^{II} and Cu^{II}] of asymmetrical Schiff base ligand (HL = $Ha\alpha ft)_2$ derived from amoxicillin andα-formylthiophene. The antibacterial sensitivity study suggests promising activities of Haαf (Ligand) and $M(Ha\alpha ft)_2$ complexes against four clinical pathogenic bacteria, namely, *E. coli*, *P. vulgaris, P. aeruginosa, and S. aureus*, though being less active than the standard drug amikacin [25].

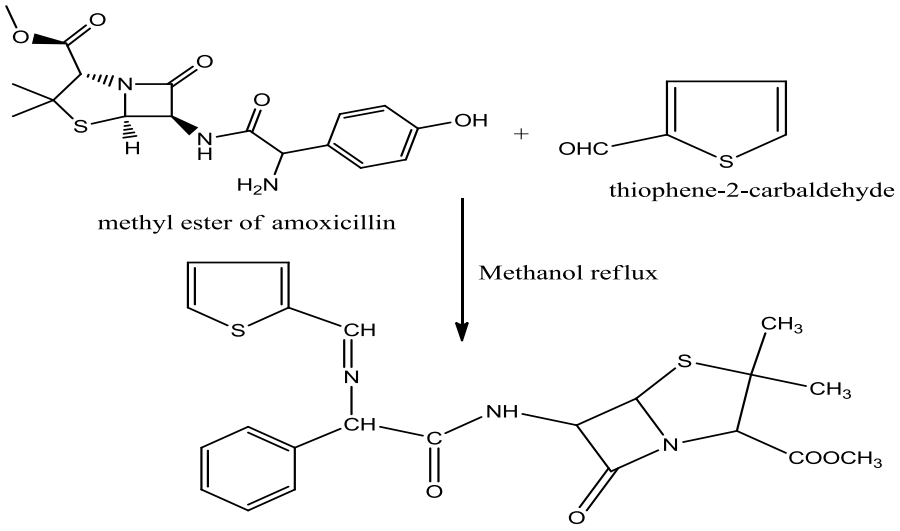


Figure 4. *Proposed route for the synthesis of ligand (HL).*

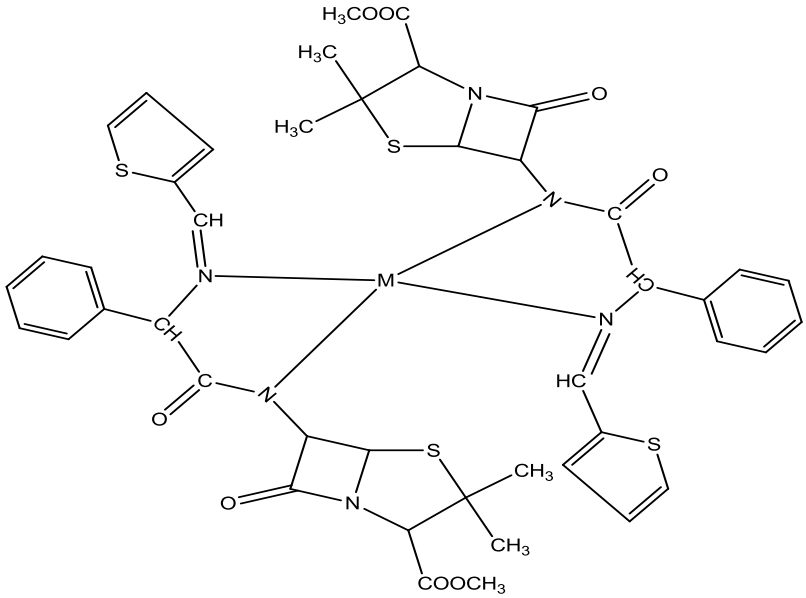


Figure 5. *Structure of metal complex (M = Ni & Cu).*

The Schiff base 4-Acyl-1-phenyl-3-methyl-2-pyrazolin-5-ones condensed with 2-amino-4(4'-methylphenyl)-thiazole. These Schiff bases form complexes (Figure 6) of type $ML_2.2H_2O$ (M=Mn, Fe, Co, Ni and Cu). The compounds were tested in vitro for the Antibacterial activity against *Escherichia coli* gram negative bacteria (responsible for diarrhea) (I), *Bacillus subtillis*-gram positive rods (general contaminant)(II) and *Staphylococcus aureus* gram positive spore forming rods (causative agent for wound infection) (III) using Agar cup assay method [27].

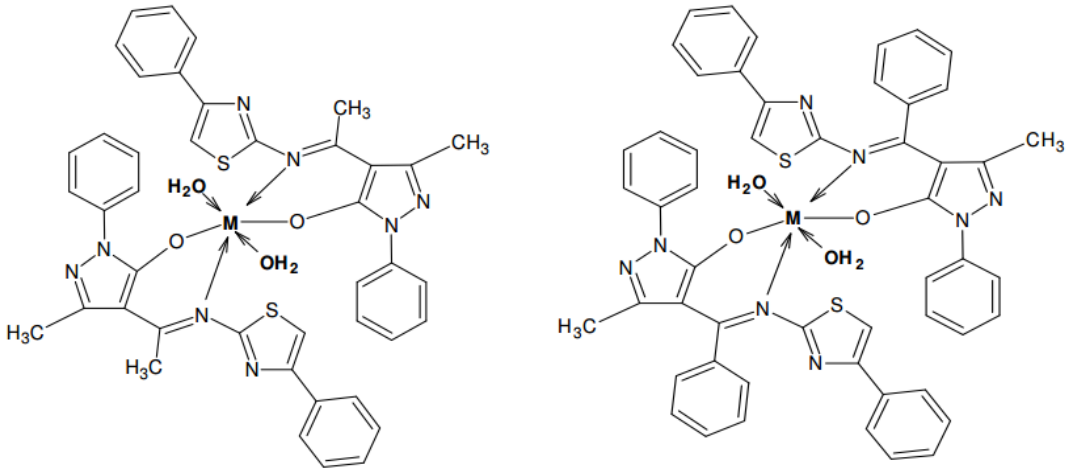


Figure 6. *Structure of Schiff base metal complexes.*

The Co, Ni and Cu complexes have been prepared by reacting metal chloride with 4-chlorobenzaldehyde oxime, 4-methylbenzaldehyde oxime, 4-nitrobenzaldehyde oxime, 4-chlorobenzaldehyde semicarbazone, 4-methylbenzaldehyde semicarbazone, 4-nitrobenzaldehyde semicarbazone, 4-chloro benzaldehyde phenylhydrazone, 4-methylbenzaldehyde phenyl hydrazone and 4-nitrobenzaldehyde phenylhydrazone by Mazed H. Hania [28]. The antibacterial activity of the ligand and the complexes have been studied and compared with their ligands against *E. coli* which gave significant results of activity. A new series of Cu, Ni, Co, Zn complexes have been synthesized from the Schiff base derived from 4-hydroxy 3-methoxy benzylidine-4-aminoantipyrine and 2-amino phenol. The biological activities of the synthesized compounds were tested against the bacterial species *E. coli, P. vulgaris, P. aeruginosa, and S. aureus* [29]. Mn(II), Fe(II), Ni(II), and Cu(II) complexes of N-benzoyl -N-2-thiophenethiocarbohydrazide (H2 BTTH) have been synthesized by Mahendra Yadav [30]. The antibacterial activity of H_2 BTTH and its complexes has been tested against *S. aureus*, *E. coli*, and *P. aeruginosa*. H_2 BTTH, [Mn (H NTTH)$_2$] and [Cu(BTTH)] show antibacterial activity starting from 62.5 to 2000 μg cm-3 against *S. aureus* and the activity increases with an increase in the concentration. The ligand is found to be active at a concentration of 1000 μg cm-3 against *E. coli*. [Mn (H NTTH)$_2$] and [Cu(BTTH)] also show activity against *E. coli* at 500 and 250 μg cm-3, respectively. Only [Cu(BTTH)] has been found active against *P. aeruginosa* at 250 μg cm^{-3}.Transition metal complexes of Cr(III), Mn(II), Fe(II), Co(II), Ni(II) and Cu(II) metal ions with general stoichiometry [$ML_2.2H_2O$] and [ML_3], where M= Mn(II), Cr(III), Fe(II), Co(II), Ni(II) and Cu(II), L= Schiff base derived from the condensation of 2-amino-4(4'-phenyl/methylphenyl)-5- methyl-thiazole with 4-acetyl-1(3-chloro phenyl)-3-methyl-2-pyrazoline-5- ones, have been synthesized by Ambit Thakar and *et al.*[31]. A new macrocyclic multidentate Schiff-base ligand Na4L consisting of two submacrocyclic units (10,21- bis-iminomethyl-3,6,14,17 tricyclo [17.3.1.18,12] tetracosa 1(23),2,6,8,10,12(24),13,17,19,21, decaene-23,24-disodium) and its tetranuclear metal complexes with Mn(II), Co(II), Ni(II), Cu(II), and Zn(II)were reported by Riyadh M. Ahmed and *et al.*[32]. Biological activity of the ligand and its metal complexes against Gram positive bacterial strain Staphylococcus aureus and Gram negative bacteria Escherichia coli revealed that the metal complexes become more potentially resistive to the microbial activities as compared to the free ligand. However, these metal complexes do not exhibit any effects on the activity of Pseudomonas aeruginosa bacteria. A novel Schiff base ligand (Figure 7) N-(4-

phenylthiazol-2yl)-2-((2-thiaxo-1,2-dihydroquinolin-3yl)methylene) hydrazinecarboxamide (L) obtained by the condensation of N-(4-phenylthiazol-2-yl) hydrazinecarboxamide with 2-thioxo-1,2-dihydroquinoline-3- carbaldehyde. The Cu(II), Co(II), Ni(II), and Zn(II) complexes with synthesized Schiff bases were prepared by Nagesh Gunvanthrao Yernale and his coworker Mruthyunjayaswamy Bennikallu Hire Mathada [33]. The brine shrimp bioassay was also carried out to study the in vitro cytotoxicity properties for the ligand and its metal complexes against *Artemia salina*. The results showed that the biological activities of the ligand were found to be increased on complexation.

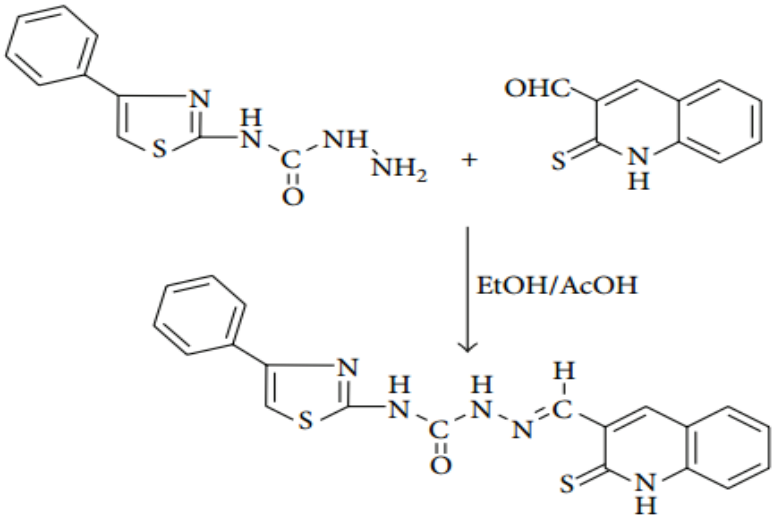


Figure 7. *Synthesis route of Schiff base ligand.*

Two bidentate Schiff base ligands having nitrogen sulphur donor sequence were derived from the condensation of S-benzyldithiocarbazate (SBDTC) with 2-chloroacetophenone and 4-chloroacetophenone to give S-benzyl-β-N-(2-chlorophenyl) methylenedithiocarbazate (NS2) and S-benzyl--N-(4-chlorophenyl) methylenedithiocarbazate (NS4) isomers. Each of the ligands was then chelated with Cd^{2+}, Zn^{2+}, Cu^{2+}, and Ni^{2+}. The ligand and the metal complexes were screened against gram positive and gram negative bacterial species [34]. New complexes of 2,3-bis(5-(4-chlorophenyl)diazenyl)-2 hydroxybenzylideneamino) maleonitrile (CDHBDMN) with VO(II), Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) were synthesized by C. Anitha and et al. [35]. The metal complexes (Figure 8) were also tested for their antibacterial and antifungal activities to assess their inhibiting potential.

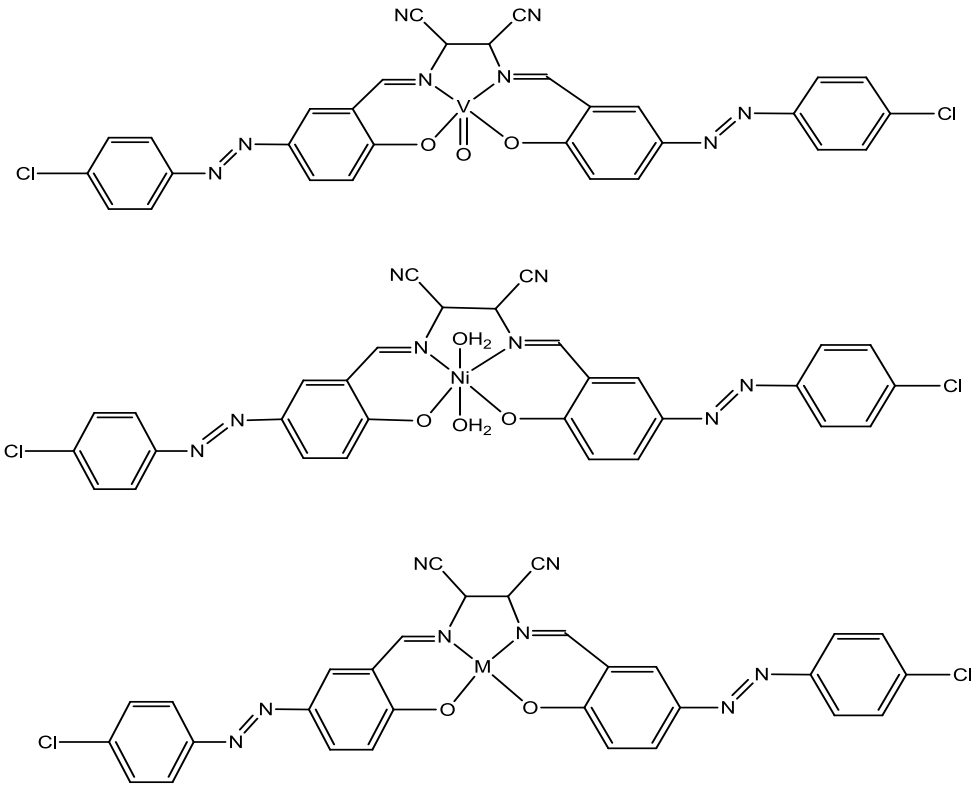


Figure 8. *Structure of Schiff base metal complexes.*

A series of new copper(II), cobalt(II), nickel(II), manganese(II), iron(III), and uranyl(VI) complexes of the Schiff base hydrazone 7-chloro-4-(benzylidenehydrazo) quinoline (HL) were prepared by Nora H. Al-Sha'alan [36]. The Schiff base ligand, HL, and its complexes were tested against one strain Gram (+ve) bacteria (Staphylococcus aureus), Gram (-ve) bacteria (Escherichia coli), and Fungi (Candida albicans). The prepared metal complexes exhibited higher antibacterial activities than the parent ligand. Transition metal complexes of Co(II), Ni(II) and Cu(II) metal ions with general stoichiometry [M(L)X]X and [M(L)SO_4], where M = Co(II), Ni(II) and Cu(II), L = 3,3'- thiodipropionic acid bis(4-amino-5-ethylimino-2,3-dimethyl-1-phenyl-3-pyrazoline) and X = NO^{3-}, Cl^- and OAc^-, have been synthesized by Sulekh Chandra and et al.[37]. The ligand and its complexes (Figure 8) have been screened for their antifungal and antibacterial activities against three fungi, i.e. *Alternaria brassicae*, *Aspergillus niger* and *Fusarium oxysporum* and two bacteria, i.e. *Xanthomonas compestris* and *Pseudomonas aeruginosa*.

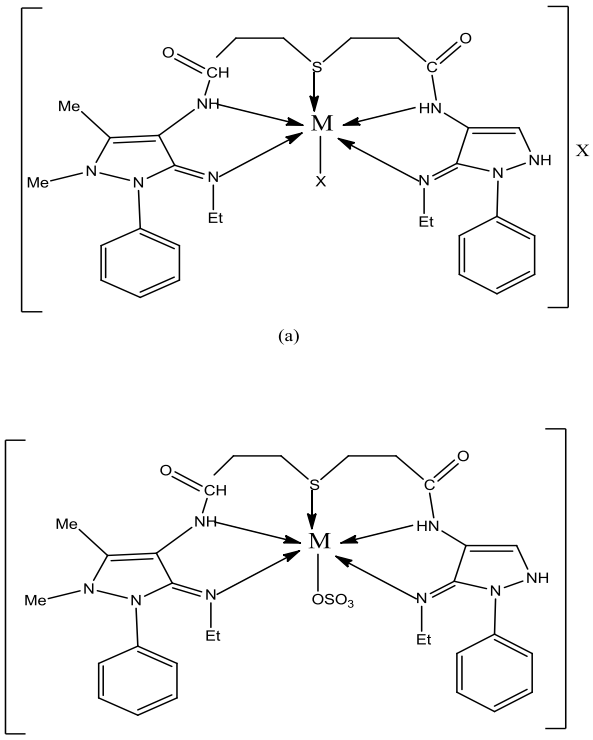


Figure 9. *Structure of complexes (a) [M(L)X]X, (b) [M(L)SO4], where M =Co(II), Ni(II) and Cu(II), L = ligand and X = NO3-, Cl- and OAc-.*

Yu-Ye Yu and *et al.*[38] were synthesized five transition metal(II) complexes of general formula MCl_2 ·nH_2O (M = Mn, Co, Ni, Cu, Cd) with the Schiff base ligand 2-[(4-methylphenylimino)methyl]-6-methoxyphenol ($C_{15}H_{15}NO_2$, **L**). The ligand was obtained by condensation of o-vanillin (2-hydroxy-3-methoxybenzaldehyde) with p-toluidine (Figure 10). The Schiff base ligand and its complexes have been tested *in vitro* to evaluate their antibacterial activity against bacteria, viz., *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*. It has been found that the complexes have higher activity than the corresponding free Schiff base ligand against the same bacteria.

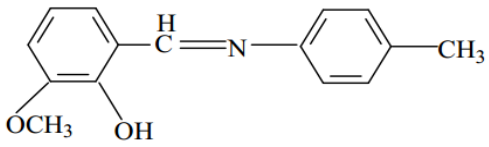


Figure 10. *Structure of Schiff base ligand.*

Mohamed Mustafa Ibrahim and *et al.* were investigated the gastroprotective activity of Schiff base ligand derived from the condensation reaction of tryptamine (an indole derivative) and 5-nitrosalicylaldehyde (TNS) and its nickel (II) complex (Figure 11) against ethanol-induced gastric ulcer in rats[39]. The compounds were orally administered with low (30 mg/kg) and high (60 mg/kg) doses to ulcer-induced Sprague-Dawley rats. Macroscopically, the ulcer control group exhibited severe mucosal injury, whereas pre-treatment with either cimetidine or TNS and its nickel (II) complex each resulted in significant protection against gastric mucosal injury. Flattening of gastric mucosal folds was also observed in rats pretreated with TNS and its nickel complex. Histological studies of the gastric wall of ulcer control group revealed severe damage of gastric mucosa, along with edema and leucocytes infiltration of the submucosal layer compared to rats pre-treated with either cimetidine or TNS and its nickel (II) compound, where there was marked gastric protection along with reduction of edema and leucocytes infiltration of the submucosal layer. Acute

toxicity study done on mice with a higher dose of 5 g/kg of TNS and its nickel (II) complex did not manifest any toxicological signs.

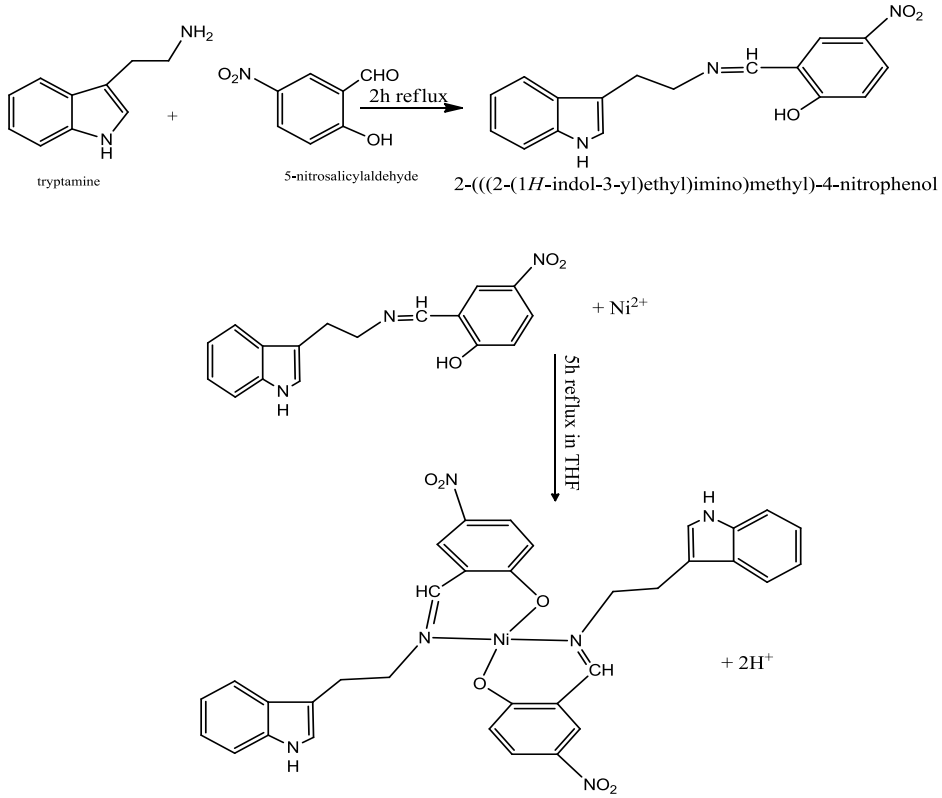


Figure 11. *Synthesis route of Schiff base ligand and its Ni complexes.*

The Co(II), Ni(II), Zn(II) and Cu(II) complexes of (3*E*)-3-[(2-{(*E*)-[1-(2,4 dihydrox yphenyl)ethylidene]amino}ethyl)imino]-1-phenylbutan-1-one (DEPH2) derived from ethylenediamine, 2′,4′-dihydroxyacetophenone and 1-phenylbutane-1,3-dione have be en synthesized by P. Ikechukwu and *et al.*[40]. The ligand and their metal complexes were screened for antibacterial activity against Gram (+) and Gram (-) bacteria by the agar well diffusion method. In addition, the antioxidant activities of the complexes we re also investigated through their scavenging effect on DPPH and ABTS radicals. The obtained IC50 value of the DPPH activity for the copper complex (2.08 ± 0.47 μM) a nd that of the ABTS activity for the copper complex (IC50 = 2.11 + 1.69 μM) were hi gher than the values obtained for the other compounds. Three new metal (II) complex es (copper(II)/nickel(II)) with N'-(pyridine-2-ylmethylene) acetohydrazide have been synthesized form N'-(pyridine-2-ylmethylene) acetohydrazide (HL/L) by Ram N. Pate l and *et al.*[41]. The biological activities of the synthesized compounds (Figure 12) we re calculated theoretically.

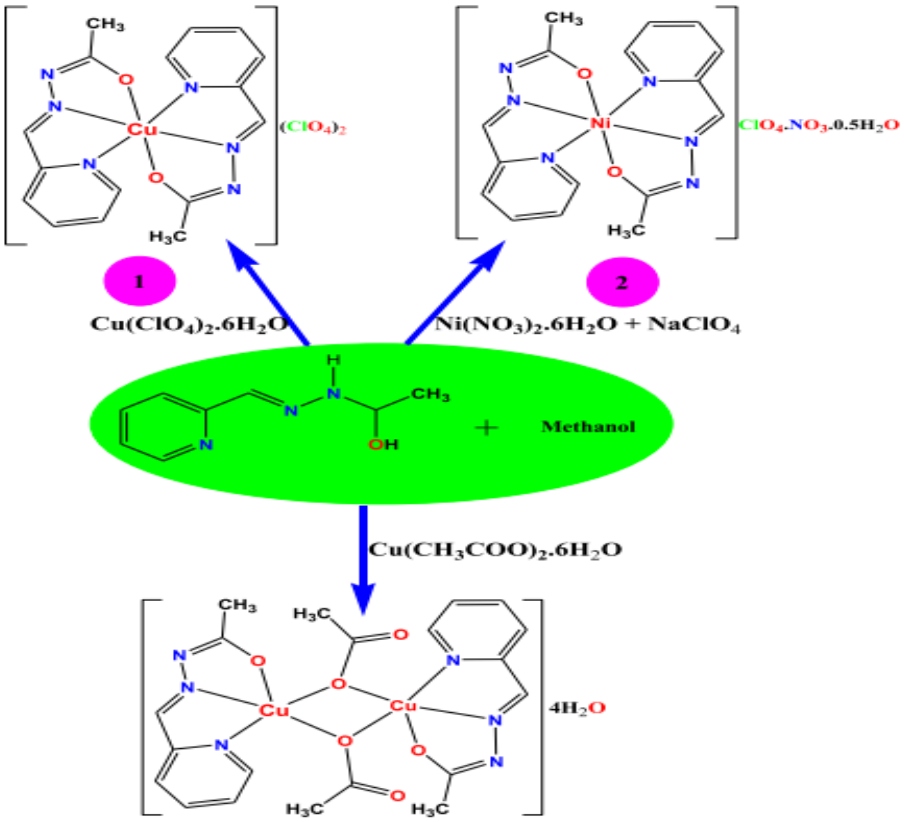


Figure 12. *Synthesis route of Metal complexes.*

Transition coordination compounds with a Schiff base (HL) derived from the conde nsation of cephalexin antibiotic with sulphathiazole were synthesized by J.R. Anacona and *et al.* [42]. The Schiff base (HL) derived from the condensation of cephalexin ant ibiotic with sulphathiazole (Figure 13). The antibacterial activity of Schiff base ligand and metal complexes was tested against Staphylococcus aureus as a Gram-positive ba cterium, and Escherichia coli as a Gram-negative bacterium according to a modified Kirby–Bauer disc diffusion method under standard conditions using Mueller–Hinton a gar medium.

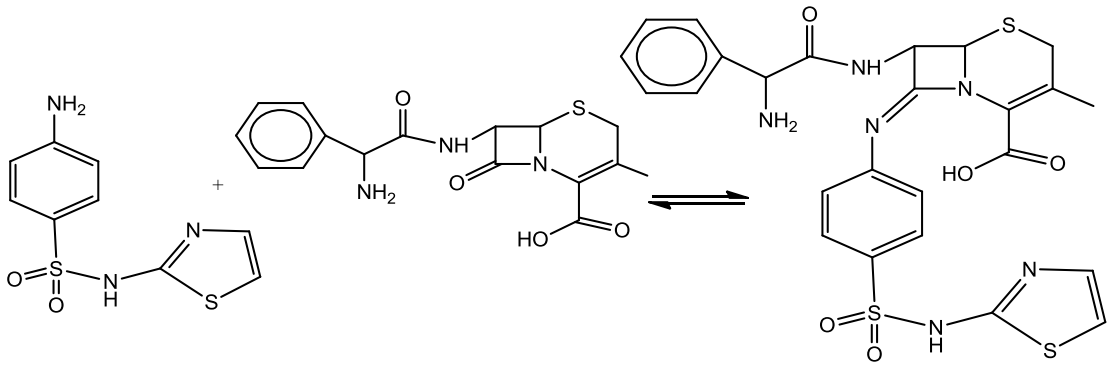


Figure 13. *The synthesis route of Schiff base ligand.*

Two Ni(II) xanthate complexes of composition $[Ni(S_2COR)_2(tmeda)]$ (R=Me (1), Et (2); tmeda = N,N,N',N'-tetramethylethylenediamine) have been synthesized by A M Qadir [43]. Both complexes were evaluated for their in vitro antibacterial activities against one Gram-positive bacterium, *B. cereus* and two Gram-negative bacteria, *E. coli* and *P. aeruginosa*, by the disk diffusion method. A mononuclear Ni(II)

compound $[Ni(L)(H_2O)_2](NO_3)_2$ [L= N,N'-bis((pyridine-2-yl)phenylidene)-1,3-diaminopropan-2-ol] was reported by Sarat Chandra Kumar and *et al.*[44]. The synthesized compounds showed excellent DNA cleavage activity. The Complexes of the type [Ni (L) (H_2O)] $Cl_2.nH_2O$, where L = [(pyridine-2-carboxaldhyde)-3-isatin] bishydrazone (cpish), [(2-acetyl pyridine)-3-isatin]-bishydrazone (apish) and [(2-benzoyl pyridine)-3-isatin]-bishydrazone (bpish) have been synthesized and characterized by Mostafa K. Rabia and *et al.*[45]. The bioefficacy of the ligands and their complexes have been examined for their in vitro antibacterial and antifungal activity against many types of bacteria and anti-fungal cultures, which are common contaminants of the environment in Egypt, and the results, indicate that the ligands and their metal complexes (Figure 14) possess notable antimicrobial activity.

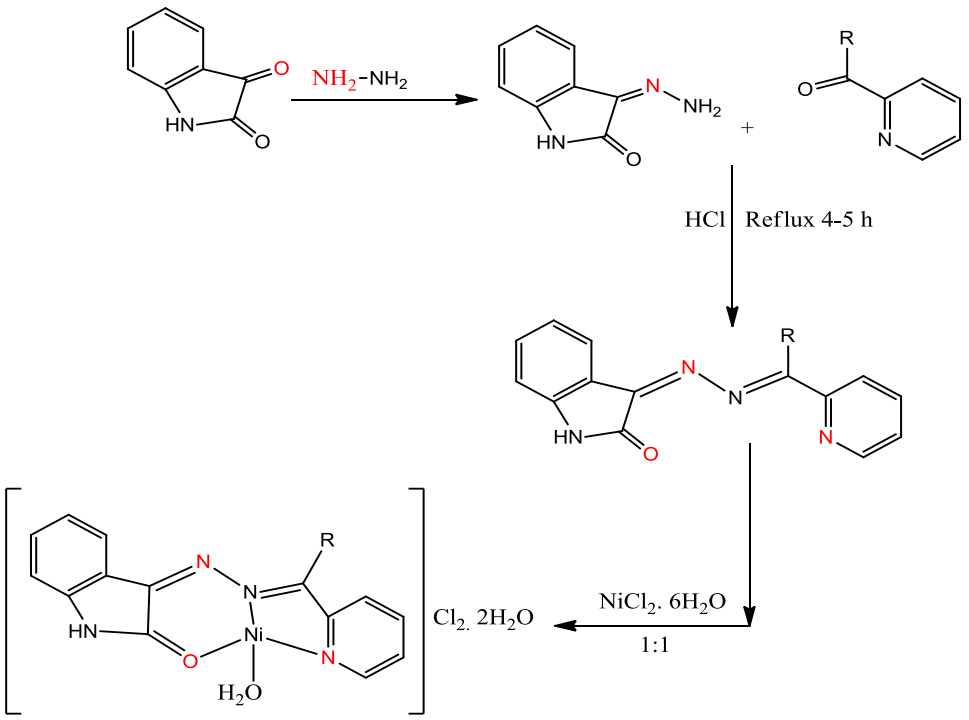


Figure 14. *Synthesis route of Schiff base and Ni complex.*

The potassium salt of salicylidene-DL-alanine (KHL), bis(benzylidene)ethylenedia mine (A1), thiophene-*o*-carboxaldene-*p*-toluidine (A2), and its metal complexes of the formula [(MII(L)(A)(H_2O)] (M = Mn(II), Co(II), Ni(II), Cu(II), Zn(II), and Cd(II); A = A1 or A2) was reported by H. M. Parekh and *et al.*[46]. All of these complexes, met al nitrates, fungicides (bavistin and emcarb), and ligands are screened for their antifun gal activity against *Aspergillus niger*, *Fusarium oxysporum*, and *Aspergillus flavus* usi ng a plate poison technique. The complexes show higher activity than those of the free ligands, metal nitrate, and the control (DMSO) and moderate activity against bavistin and emcarb. The ligands, 1-acetylferrocenehydrazinecarboxamide (HL^1) and acetyl fe rrocenehydrazine carbothioamide (HL^2), and their Ni(II) and Co(II) complexes were s ynthesized The ligands and their Co(II) and Ni(II) complexes were screened for antiba cterial and antifungal activities. The Co(II) and Ni(II) complexes show enhanced inhi bitory activity as compared to their parent ligands. The DNA cleavage activity of the Co(II) and Ni(II) complexes was determined by gel electrophoresis [48. It was shown that the complexes have better cleavage activity than the ligands. The antioxidant acti vity of the complexes was also evaluated and used to examine their scavenging ability on hydrogen peroxide. M(II) coordination compounds of Mn, Fe, Co and Ni with a S

chiff base (HL) (Figure 15) derived from the condensation of cephaclor antibiotic wit h 1,2-diaminobenzene were synthesized and characterized by Juan Anacona and *et al.* [49].

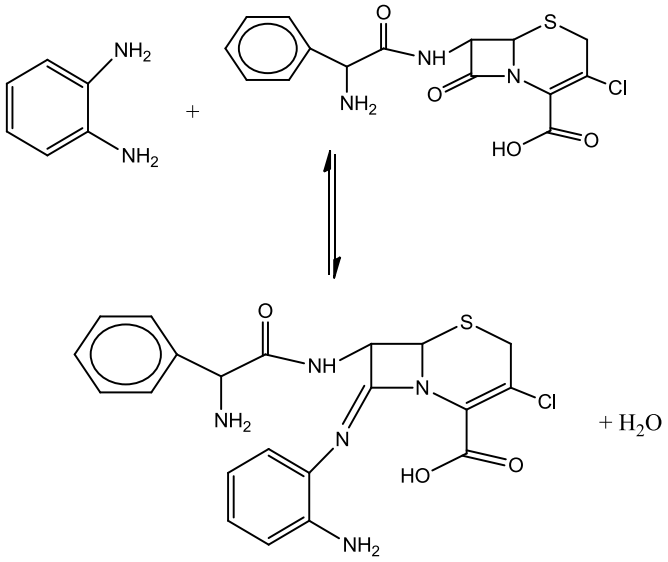


Figure 15. *Synthesis route of Schiff base.*

3. Conclusions

Schiff bases and their metal complexes are one of the most important chemical classes of compounds having a common integral feature of a variety structural diversity and of active medicinal agents. This review reflects the contribution of Schiff bases to the design and development of novel lead having potential biological activities. This bioactive core has maintained the interest of researchers in gaining the most suggestive and conclusive access in the field of various Schiff bases of medicinal importance from last decades. The present paper is an attempt to review the antimicrobial activities reported for Schiff bases and their Nickel complexes.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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