International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Antimicrobial Studies of Schiff Base Ligands and their Transition Metal Complexes : A Review

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ABSTRACT

Schiff bases and their metal complexes are very important in medicinal and pharmaceutical fields because of their wide spectrum of biological activities. Most of them show biological activities such as antibacterial, antifungal as well as antitumor activity. This review summarizes the synthesis and biological activities of Schiff bases and their metal complexesand an appropriate balance between the broad spectrum pharmacological profile.This study is summarized, which gathers the most important techniques used over the past few years to design a promising antimicrobial transition complexes of Schiff's bases which may be useful for active scientists or researchers in the field of biology and are expected to hopefully produce analogues with better biological profiles.

Key words: Schiff base ligand, spectral studies, antimicrobial activity, transition metals

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known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (CO) has been replaced by an imine or azomethine group **(Fig. 1**).The azomethine group of Schiff's base play an important role for showing excellent biological activities **[1].**

Fig.1. Formation of Schiff's base ligand Where R = alkyl group or aryl group

The chemistry involved in the formation of Schiff's base complexes had been very well developed on account of the extensive diversity of feasible structure for the ligands and their complexes, depending upon the presence of donor atoms. A lot of Schiff's bases and their transition metal complexes had been synthesized due to their pharmaceutical and industrial applications **[2-4].** 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 **[5].**Recently, a number of researchers are expressing keen interest and are working in the field of functionalizing metal complexes with biomolecules and nanomaterials for therapeutic applications. The different routes have been used for attachment of metal complexes to different types of biomolecules and nanomaterials. The nano-functionalized metal complexes of Schiff's base ligands have been acted towards targeted delivery and are used to demonstrate the broad range of opportunities and challenges of this promising approach **[6].**Cu(II) and Zn(II) complexes of 5-aminobenzofuran-2-carboxylate Schiff base ligand were synthesized and characterized **[7].** The structure of synthesized compounds were elucidated using the various techniques i.e. ^{1}H NMR, ^{13}C-NMR, Mass, XRD, TGA, ESR. The Schiff base ligands and their metal complexes were screened for antibacterial activity against *S. Aureus, E. coli* and *B. Subtilis by* Disc diffusion method. The anti-tubercular activity of synthesized compounds was evaluated using Microplate Almar Blue assay against *M. Tuberculosis* The results revealed that Cu(II)complexes are more active as compared to Zn(II) complexes. The enhance activity of Cu(II) complexes is due to permeability through the cell membrane. In all the bacterial strain *M. Tuberculosis* were found to be more active against all the synthesized compounds.

The homo and hetero binuclear complexes**(Fig. 2)** were synthesized from the Schiff base ligand derived from 4-chloro-o-phenylenediamine and 3,5-

dichloro-2-hydroxyacetophenone **[8].**Cu(II) complexes were characterized with the support of more than a few standard physicochemical techniques such as elemental analysis, spectroscopic, thermal, cyclic voltammetry and magnetic moment studies. The Schiff base and their complexes have been screened for their anticancer activity using MCF7 cell line.

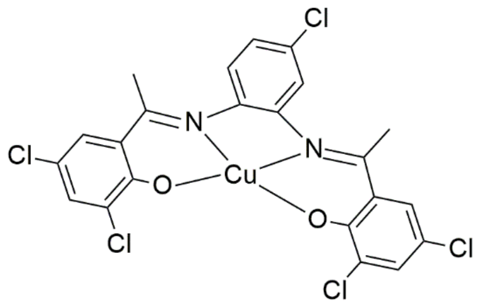

Fig. 2. Structure of mononuclear complex of Cu(II)

Schiff base ligand with condensation of *o*- hydroxy benzaldehyde and 2-amino pyridine has been synthesized. The ligand and its Cu(II) complex **(Fig. 3**) were characterized by elemental analysis, molar conductance, magnetic susceptibility, electronic spectra, IR and ESR spectroscopy. An octahedral geometry was proposed for the complexes on the basis of spectral studies.. The molar conductivity data of complex suggested non-electrolytic nature. The ligand and metal complexes had been screened for microbiological activity **[9].**

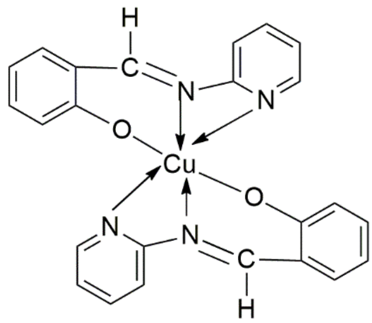

Fig. 3. Cu(II) complex of *o*-hydroxy benzaldehyde and 2- amino pyridine

Mononuclear Cu(II) complex**(Fig. 4)** was synthesized by bidentate Schiff base N_2O_2 donor ligand i.e. *(E)*-2-bromo-4-chloro-6-[(2,6-dimethylphenylimino)methyl]phenol (HL). The detailed studies of their photophysical properties such as UV-Vis and florescence were done and the x-ray diffraction pattern were investigated in the powder forms **[10].** The antibacterial activities of the synthesized compounds were studies against bacterial species *S. aureus, P. aeruginosa* and *E. coli*. The MIC valueof copper complex was found 1.25 mmol L^{-1} against *E. coli*

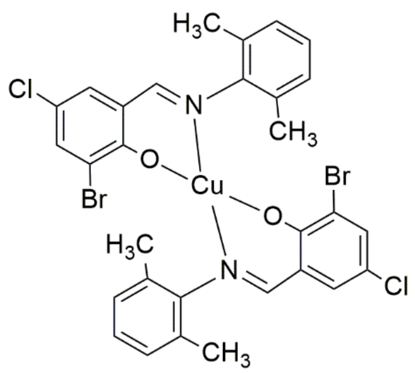

Fig. 4 Structure of Cu(II) complex of N_2O_2 donor ligand

The thiosemicarbazide based Schiff's base has been synthesized and its coordination behavior with Cu(II) metal ions has also been studied. On the basis of spectral studies complexes were found to have tetragonal geometry**(Fig. 5)** . The thermal studies suggested that the complexes are more stable as compared to ligand. Molecular modelling calculations results hold a good comparison between the theoretically predicted geometries and the experimental ones, which is clearly validating our methodology. In the biological environment, hydrogen bonding with the solvent is also expected to affect the relative energies and geometries, but the good correspondence between our calculations and experimental data suggest that crystal packing and hydrogen bonding effects are negligible. The metal complexes were found more active as compared to free ligand in fungicidal screening **[11].**

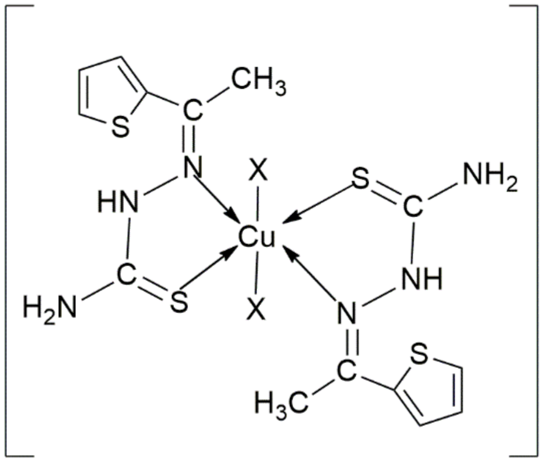

Fig.5. Suggested structure of Cu(II) complexes [X= Cl^-, NO_3^-]

Cu(II) metal complex **(Fig. 6)** was synthesized from a Schiff's base ligand derived by the condensation of 4-aminoantipyrine with furfural and amino acid. Structural features of ligand and metal complex were obtained from the analytical and spectral techniques. *In vitro* antibacterial and antifungal assay suggested that Cu(II) complex was good antimicrobial agents against tested pathogens **[12].**

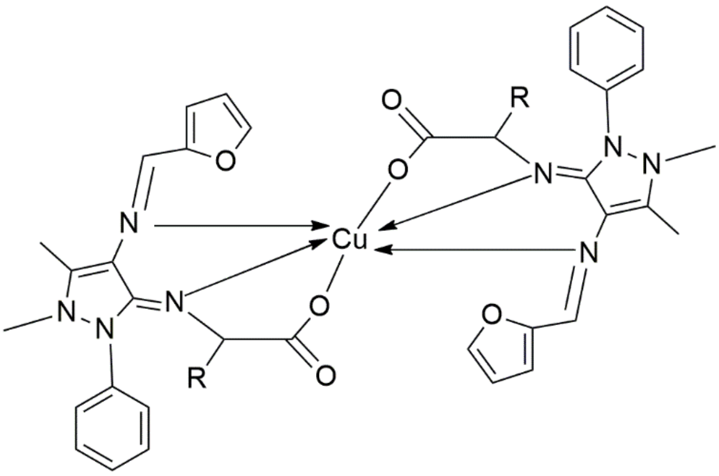

Fig. 6. Cu(II) complex of 4-aminoantipyrine with furfural and amino acid

Ni(II) complex with novel ligand i.e. N,N′-bis(4-chlorobenzylidene)benzene-1,2-diamine **(Fig.7.)** having general formula $[NiL(ox)]Cl_2$ (where ox = $C_2O_4^{2-}$) had been synthesized. The ligand and its metal complexes were analyzed by micro-analytical data, magnetic moment, molar conductance, ^{1}H-NMR, UV-Visible, FT-IR, ^{13}C-NMR and EPR spectroscopic studies. The synthesized compounds were tested for their antimicrobial activity and their MIC values suggested that the complex had better activity as compared to novel ligand **[13].**

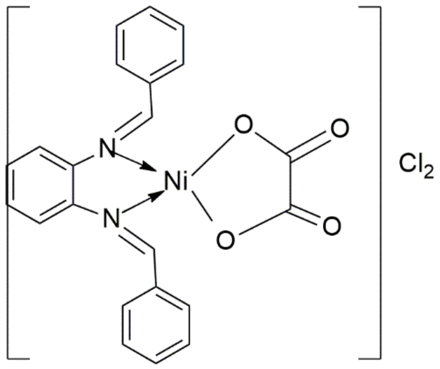

Fig.7. Ni(II) complex of N,N′-bis(4-chlorobenzylidene)benzene-1,2-diamine

Coordination behavior of square planar Ni(II) complex **[14]**of pyridine was investigated and characterized using various techniques like elemental analyses, electronic, infrared, ^{1}H NMR, ^{13}C NMR spectra, magnetic susceptibility and also aid of molar conductivity measurement. Conductivity measurement reveals non-electrolytic nature of the complex. IR and ^{13}C NMR spectra revealed the presence of *cis*- and *trans*-structure **(Fig.8).** The new nickel(II) complex has also been screened for antibacterial and antifungal activities against various pathogenic bacteria and fungi.

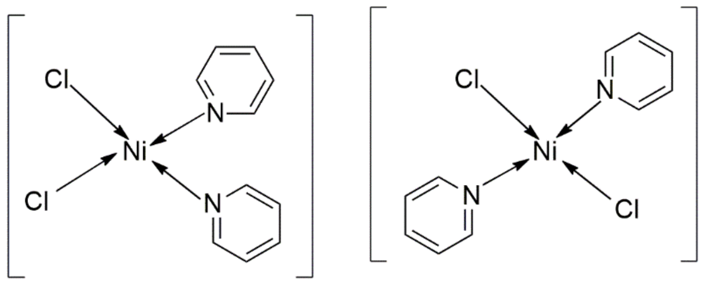

Fig.8.*cis* and *trans* structure of Ni(II) complex with pyridine

Ni(II) complexes **(Fig. 9)** of Schiff's base ligand i.e. 4-hydroxy-3-(1-(arylimino)ethyl)chromen-2-one were synthesized by condensation. The ligand and the complexes were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral analysis. In vitro biological screening effects of the synthesized compounds were tested by Agar cup method against the bacterial species *S.aureus,E.coli, S.typhi* and *B.subtilis*. The poison food method had been employed to check antifungal activities against the fungal species *A.niger, P.chrysogenum, F.moneliforme* and *A.flavus*. The experimental studies indicated that the Ni(II) complexes exhibit higher antimicrobial activity than the free ligand **[15].**

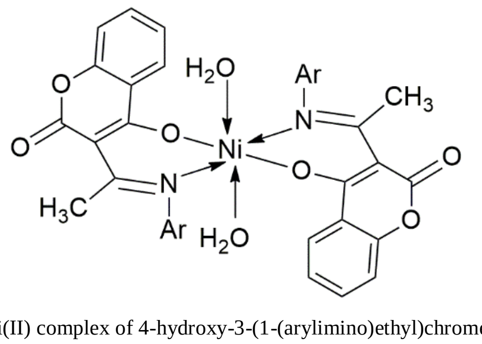

Fig. 9. Ni(II) complex of 4-hydroxy-3-(1-(arylimino)ethyl)chromen-2-one

The nickel(II) complexes of the dibasic tridentate Schiff bases *viz.* Sal-Anthra$\underline{H}_2$, HNP-Anthra$\underline{H}_2$, HAP-Anthra$\underline{H}_2$, HPP-Anthra$\underline{H}_2$, Acac-Anthra$\underline{H}_2$, Etac-Anthra$\underline{H}_2$, and Bzac-Anthra$\underline{H}_2$, have been synthesized and characterized by IR, ^{1}H NMR, mass and electronic spectra, and magnetic and conductance studies. On the basis of analytical data , four-coordinate geometry was proposed for the prepared nickel(II) complexes. The bio-efficacy of the prepared complexes has been examined against the growth of bacteria and fungi *in vitro* to evaluate their antimicrobial potential**[16].**

Ni(II) complexes with Schiff base ligands i.e. (L_1 = 2,3-bis(2-hydroxybenzylideneimino)-2,3-butenedinitrile,L_2 = 2,3-bis(2-hydroxy-3-methoxybenzylideneimino)-2,3-butenedinitrile) were synthesized in DMSO by one-pot syntheses. The complexes were characterized by physicochemical and spectroscopic methods. Also, their solid-state structures were determined by single-crystal X-ray diffraction. On the basis of spectral studies the complexes were found four coordinated **(Fig. 10)**square planar geometry. The complexes were screened *in vitro* against a fungal species and eight species of bacteria, revealing their antimicrobial activity **[17].**

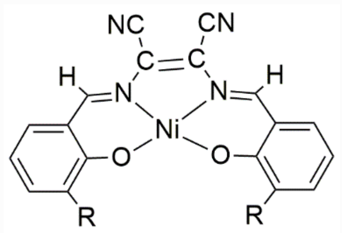

Fig.10. Structure of Ni(II) complexes [R = H [Ni(L_1)] [R = OCH_3[Ni(L_1)]

A novel macrocyclic tetradentate ligand 1,5,8,12-tetraaza-2,4,9,11-tetraphenyl-6,7:13,14-dibenzocyclohexadeca-1,4,8,11-tetraene (L) has been synthesized with condensation of dibenzoylmethane and *o*-phenylenediamine. Ni(II) complexes**(Fig. 11)** of this ligand have been prepared and characterized by elemental analysis, molar conductance measurements, magnetic susceptibitity measurements, and mass, IR, electronic, and ESR spectral studies. An octahedral geometry was assigned for the complexes using various spectral techniques. The investigated compounds and uncomplexed metal salts were tested against bacterial species like *Sarcinalutea, Escherchia coli,* and *Staphylococus aureus* **[18].**

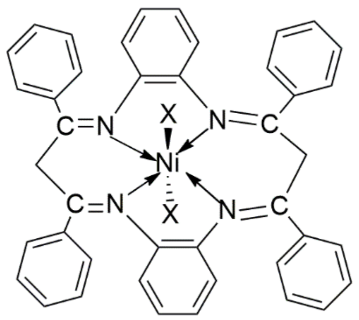

Fig.11. Ni(II) Complexes of Macrocyclic ligand derived from dibenzoylmethane and *o*-phenylenediamine[X = Cl^- , NO_3^-]

A new Schiff base and its Ni(II) complex [Ni(PTBS)] **(Fig.12)** were synthesized using benzaldehyde and sulphathiazole. They were characterized using elemental analyser, UV-visible spectrophotometer, FTIR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. Based on the continuous variation method, metal: ligand ratio of 1:1 was proposed. Elemental analysis and spectroscopic studies suggested that the Schiff base behaved as a tridentate ligand towards nickel ion **[19].** Antibacterial sensitivity of the ligand and its Ni (II) complex were assayed in vitro against *Staphylococcus aureus*, *Echerichia coli,Pseudomonas aeruginosa* and *Salmonella typhi*. Ni(II) complex was found more potent than the Schiff base against the bacterial strains used.

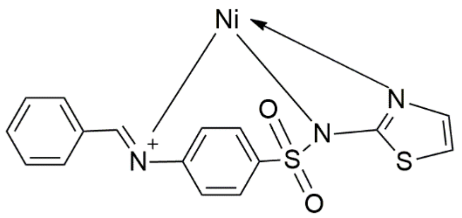

Fig.12. Structure of [Ni(PTBS)] complex

Schiff's base metal complexes of Co(II) had been synthesized from 2-[(5-bromo2-hydroxybenzylidene)amino]pyridin-3-ol,{5-chloro-2-[(2-hydroxynaphthylidene)amino]phenyl}-phenyl -methanone. All the synthesized compounds were characterized by various elemental and spectral analysis i.e., FT-IR, FAB-mass, molar conductivity, electronic spectra, ESR, thermal, magnetic susceptibility, cyclic voltammetry, electrical conductivity and XRD analyses .All the synthesized compounds were screened for antibacterial and antifungal activity against the different strains of bacteria and fungi. Antimicrobial data showed that the metal complexes displayed better antimicrobial activity as compared to the free ligand **[20].**

A series of Schiff base ligands and their Co(II) complexes from condensation of Terephthalaldehyde with ortho-anilines were synthesized. The structures of the synthesized compounds were proposed by FTIR, ^{1}H-NMR, UV-Vis and mass spectroscopy studies. The molar conductivity measurements showed that all the complexes were non-electrolyte. Antibacterial activities of the ligands and their metal complexes were examined against gram-positive and gram-negative bacteria strains. In general, metal complexes showed much higher antibacterial activities and better inhibitory effects than that of the ligands**[21].**

A Schiff base ligand i.e. 4-chloro-2-{(E)-[(4-fluorophenyl)imino]methyl}phenol was derived from the condensation reaction of 5-chlorosalicylaldehyde and 4-fluoroaniline at room temperature. Co(II) complex **(Fig. 13)**of this ligand was synthesized and characterized. Elemental analysis, FT-IR, UV-Vis, and NMR spectral data, molar conductance measurements, and melting points were used to characterize the Schiff base and the metal complexe. The Schiff base ligand and its metal complex were tested *in vitro* to evaluate their bactericidal activity against Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus typhi*) using the disc diffusion method**[22].**

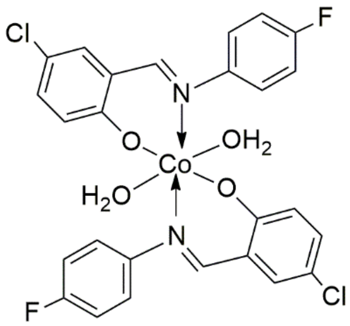

Fig.13. Structure of Co(II) complex of Schiff base ligand 4-chloro-2-{(E)-[(4-fluorophenyl)imino]methyl}phenol

Antimicrobial activities of cobalt(II) complexe with Schiff base ligand derived from the condensation of citral with valine (amino acid) was carried out on agar plate method **[23].** The antibacterial activity of Schiff base and its cobalt(II) complex were evaluated against two bacterial strains *Staphylococcus aureus* (Gram-positive), *Escherichia coli* (Gram-negative) and fungus *Candida albicans*.. The antimicrobial results revealed that cobalt(II) complex has a considerable antibacterial activity than antifungal activity and suggest their potential application as antibacterial agent.

Two biologically active Schiff bases were synthesized in equimolar reaction of 3-aminopyridine with *o*-vanillin and *p*-vanillin **(Fig. 14).** The synthesized Schiff bases were reacted with cobalt acetate, cobalt chloride or cobalt chloride with trimethylamine by using a molar ratio of Schiff base: cobalt salt as 2:1. The characterization of Schiff bases and cobalt complexes was done by UV–visible in methanol, diffused reflectance, FTIR , mass spectrometry studies while ^{1}H NMR and ^{13}C NMR were used to further characterize the Schiff bases. The FTIR results confirmed the bidentate binding of the Schiff bases with cobalt center after the formation of the complexes. On the basis of the spectral studies, distorted tetrahedral geometry has been assigned for the Co(II) complexes. The antimicrobial activities of the two Schiff bases and their cobalt(II) complexes were tested against laboratory isolated *Staphylococcus aureus*,*Pseudomonas aeruginosa*, *Escherichia coli* and one fungus strain, *Aspergillus niger*. The studies showed the complexes were higher in biological activity than the corresponding Schiff bases **[24].**

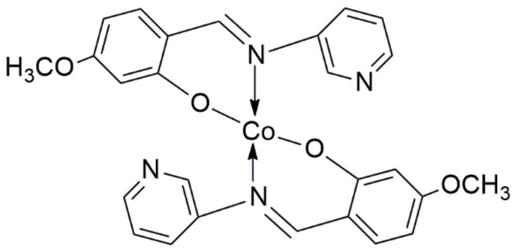

Fig.14. Cobalt(II) complex of Schiff base derived from *p-vanillin* and 3-aminopyridine

Co(II) complex with a tetradentate nitrogen donor [N_4] macrocyclic ligand i.e. 6,15-dimethyl-8,17diphenyl-7,16-dihydrodibenzo[b,i][1.4.8.11]tetraazacyclotetradecine, was synthesized. Their structures were determined based on elemental analyses, molar conductance and magnetic susceptibility measurements, and IR, ^{1}H-NMR (ligand) and electronic spectral studies. On the basis of spectral studies the complex **(Fig.15)** was found non-electrolyte. The ligand and its complex were evaluated for fungicidal activity against two pathogenic fungi to assess their growth inhibiting potential **[25].**

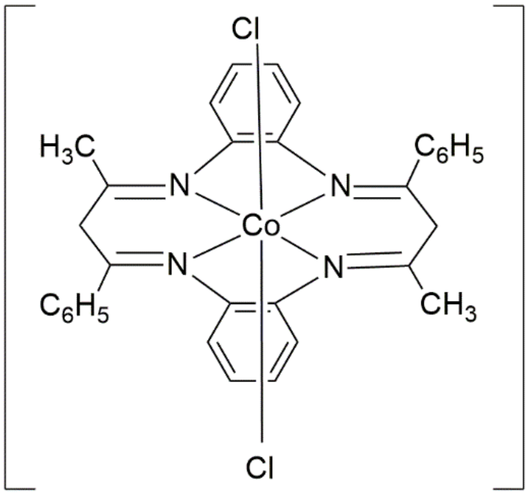

Fig.15. Co(II) complex of tetradenate macrocyclic ligand

Schiff base ligand i.e. benzilbis(carbohydarzone) and its Co(II) complex were synthesized. The synthesized compounds were characterized and analyzed by different spectral studies like elemental analysis like elemental analyses, molar conductance, and magnetic susceptibility, NMR, IR, UV-Visible, ESI mass and EPR. *In* vitroantifungal activity of the complex was examined againstplant pathogenic fungi i.e. *A.niger*,*A.brassicae* and *F.oxysporum* .The result of biological activity showed that metal free ligand had better growth inhibition power and this efficiency was positively affected by the Co(II) complex **[26].**

Co(II) complexes**(Fig. 16)** having the general composition $M(L)_2X_2$ [where L = 2-pyridinecarboxaldehyde semicarbazone, X = Cl^- and NO_3^-] have been synthesized. All the synthesized compounds were identified and confirmed by elemental analysis, molar conductance, magnetic susceptibility measurements, mass, IR, EPR, electronic spectral studies and thermogravimetric analysis (TG). On the basis of spectral studies an octahedral geometry has been assigned for Co(II) complexes. The thermal studies suggested that the complexes are more stable compared with free ligand. Antimicrobial screening of the free ligand and its Co(II) complexes were evaluated against the growth of fungi and bacteria *in vitro***[27].**

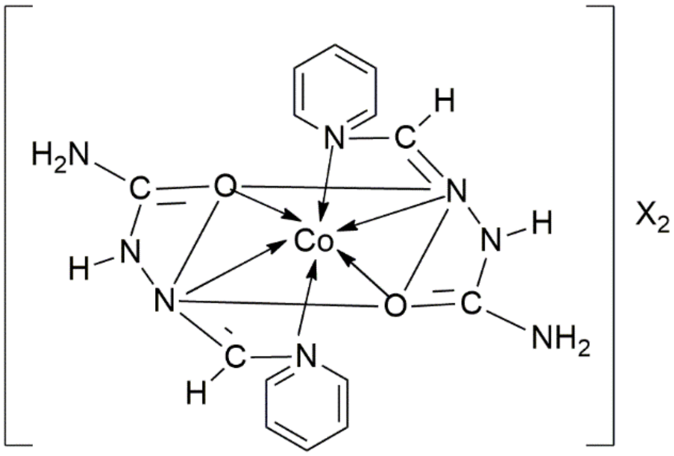

Fig. 16 Suggested structure of Co(II) complexes of 2-pyridinecarboxaldehye semicarbazone

Conclusion

Schiff bases are one of the most important chemical classes of compounds having a common integral feature of a variety of medicinal agents.This review reflects the contribution of Schiff bases to the design and development of novel lead having potential biological activities with fewer side effects. 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 biological importance from last decades. The present paper is an attempt to review all the biological activities reported for Schiff bases in the current literature with an update of recent research findings.

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