JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A Comparative Study of Schiff Base Metal Complexes Based on Its Biological Application: A Review

[1]Dr. S. E. Bhandarkar, [2]P. P. Pathare, [3]B. P. Khobragade

[1]Professor, [2]Research Scholar, [3]Assistant Professor
[1]Department of Chemistry,
[1]Govt. Vidharbha Institute of Science and Humanities, Amravati, India

Abstract: The Schiff bases ligand has been found extensive use in the field of research and field of interest. The term Schiff base is normally applied to these compounds when they are being used as ligands to form coordination complexes with metal ions. Such complexes occur naturally, for instance in corrin, but the majority of Schiff bases are artificial and are used to form many important catalysts. Schiff bases are azomethine (-C=N-) linked compounds that are typically formed by the condensation of carbonyl compounds (aldehydes/ketones) with primary aliphatic / aromatic / hetroaromatic amines. Schiff bases are known for their antitumor, antifungal, antiviral, antibacterial and anticancer activities. The intermolecular hydrogen bonding ability and proton transfer equilibrium of Schiff bases offer them excellent bioactivity. The Schiff base complexes of transition metal have played prominent role in the developments of coordination chemistry. Insecticides, pesticides, bactericides, and fungicides have been developed using metal complexes derived from Schiff bases. Transition metal complexes of Schiff base ligands are a very interesting topic for young scientists to study because of the variety of possible structures for the ligand depending on the ketones/amines used and their specific industrial or biological applications. The present work focuses on comparative study of various Schiff base metal complexes based on its biological applications with the help of available research work.

Index Terms **- Schiff Bases, Metal Complexes, Biological Applications, Review**

I. INTRODUCTION

The Schiff bases which contain azomethine linkage are usually derived by the condensation of carbonyl compounds such as aldehydes and ketone with primary aliphatic/aromatic/heteroaromatic amines (Fig. 1.1). These Schiff bases are found more effective in various biological activities such as antitumor, antifungal, antiviral, antibacterial, anticancer and antioxidant [Vhanale B. T. et al. 2019]. Over the years, a lot of research work has been carried out on synthesis of Schiff base ligands to form metal complexes using metal ion which has wide use in medicinal chemistry. This results in need of comparative study of Schiff base metal complexes based on their biological application.

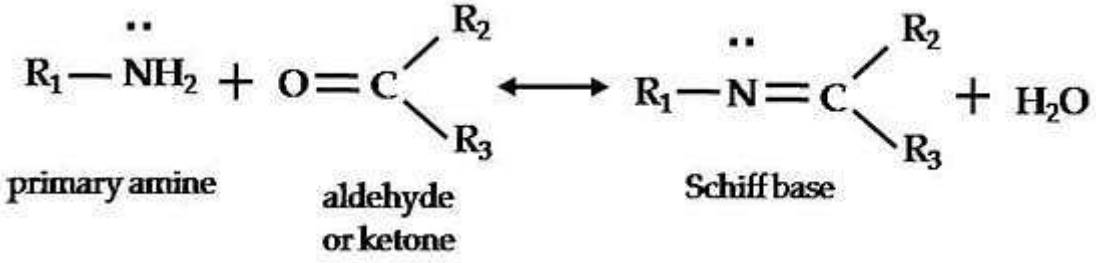

Figure 1.1: Mechanism of Synthesis of Schiff Base

II. LITERATURE REVIEW

The available studies on synthesis of Schiff base ligands to form metal complexes using various metal ions are reviewed based on their applications in biological activities such as anticancer and antiviral.

C. Elamathi *et al* [1] (2018) had carried out Anomalous coordination behavior of 6-methyl-2-oxo-1, 2-dihydroquinoline-3-carboxaldehyde-4(N)-substituted Schiff bases in Cu (II) complexes: Studies of structure, bimolecular interactions and cytotoxicity. Using various analytical and spectroscopic techniques, a series of Copper (II) complexes containing 6–methyl-2oxo-1, 2-dihydroquinoline-3-carboxaldehyde derived Schiff bases were synthesized and characterized. The complexes demonstrated

significant activity against the human skin cancer cell line (A431) while being less toxic to the human keratinocyte cell line (HaCaT). Complexes 1 and 4 had higher cytotoxicity y against cancerous cell lines and much lower toxicity against noncancerous cell lines. The results of the AO/PI dual staining strongly suggested that the induction of an apoptotic pathway for the anticancer activity of these complexes could be necrosis. Complex 4 demonstrated superior activities in all cases when compared to other complexes and ligands. This could be due to the complex's aromatic substitution on the N-terminal group, geometry, and ionic nature.

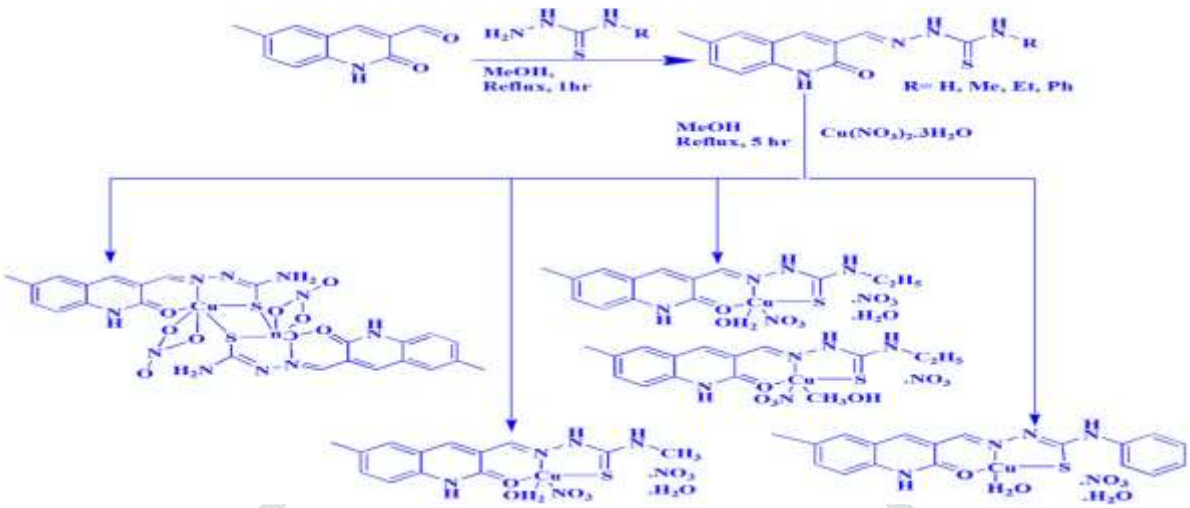

Figure 2.1: New Water-Soluble Copper (II) Complexes

P. Shamly *et al* [2] (2018) had carried out the condensation of salicylaldehyde with various amines, both aromatic and aliphatic and the Schiff bases formed were complexed with a transition metal Ni and an alkaline earth metal Mg. When this green synthetic approach was compared to the conventional procedure, it was discovered to have advantages such as high yield and reduced reaction time and byproducts. The antibacterial activity of complexed and uncomplexed Schiff bases against Escherichia coli was compared, and the Mg complex was found to be more effective than the corresponding Ni complex. The synthesized ligands were successfully complexed with the metal ions Mg (II) and Ni (II). FTIR Spectroscopic analysis have indicated the successful formation of salicylaldehyde based Schiff bases and their complexes. Based on antibacterial study, it was found that the metal complexes of Schiff bases are more efficient antimicrobial agents than its native form. Thus metal complexes of these Schiff bases could find potential applications in designing new therapeutic agents. However, the antimicrobial potentiality of metal complexes is highly dependent of the metal ions used for complex formation. Results of antimicrobial activity reflected that the Schiff base metal complex of Mg has more antimicrobial activity than Ni complex. They can also be used in water purification to kill or inhibit the growth of water borne bacteria.

Ravikant *et al* [3] (2018) had carried out synthesis, structural analysis and biological properties of Mn (II), Co (II), Ni (II) and Cu (II) complexes of schiff's base ligand. Ligand (L) is prepared from acetophenone and nicotinic hydrazide by following condensation reaction and its Mn (II), Co (II), Ni (II) and Cu (II) complexes also prepared and structural analysis carried out by elemental analyses, IR, UV-Vis., mass, 1H-NMR and EPR spectral studied The synthesized acyclic Schiff's base and its metal complexes have been screened for antifungal and antibacterial activities against some selective microorganisms. The experimental investigation showed that Schiff base was found potentially active towards microbial strains (bacteria and fungi).

P. Muhammad *et al* [4] (2018) synthesis spectral and microbial studies of amino acid derivative schiff base metal (Co, Mn, Cu and Cd) complexes. The experimental investigation that was conducted The Schiff base amino acid derivative was created by reacting leucine with salicyldehyde in basic medium. The Schiff base was used as a ligand in the reactions with Co, Mn, Cu, and Cd metals to form stable complexes. Different spectroscopic tools, such as FT-IR, mass spectrometry, and NMR, were used to characterize the synthesised ligand and metal complexes. All compounds, including ligands and complexes, were also tested against various bacterial and fungal strains (Escheria coli, Staphylococcus aureus, and Bacillus subbtilis) (Alternaria alternate, Aspergillus flavus and Aspergillus Niger). It was concluded that the structure of the ligand and complexes was practically determined, and the antimicrobial activity analysis data revealed that metal complexes have higher values of antibacterial and antifungal activities than parental synthesised ligands, and this would be part of future recommendations because these complexes can be used in the pharmaceutical sector due to their high ability to kill microbes.

M. Munjal [5] (2018) had carried out Synthesis, characterization and Antifungal activity of transition metal (II) complexes of Schiff base derived from p-amino acetanilide and salicylaldehyde. Tridentate Schiff base (L) was created by combining salicylaldehyde and p-amino acetanilide in ethanol and then treating it with copper, nickel, cobalt, and zinc chlorides to form metal complexes. Analytical and spectral methods are used to characterise the synthesised compounds.

N. Uddin *et al* [6] (2019) had carried out synthesis, characterization, and anticancer activity of Schiff bases. The experimental investigation was to synthesis of five Schiff bases, 2-((3-chlorophenylimino)methyl)-5-(diethylamino)phenol(L1),2-((2,dichlorophenylimino)methyl)-5-(diethylamino)phenol (L2), 5-(diethylamino)-2-((3,5-dimethylphenylimino)methyl)phenol (L3), 2-((2-chloro-4-methylphenylimino)methyl)-5-(diethylamino)phenol (L4), and 5-(diethylamino)-2-((2,6-diethylphenylimino)methyl)phenol(L5) were synthesized and characterized by elemental analysis. To evaluate the structural details of all the synthesized compounds, theoretical investigations were conducted. UV-Vis spectroscopy and electrochemistry studies of drug-DNA interactions show that the compounds bind to DNA via electrostatic interactions. The cytotoxicity of the

synthesized compounds was investigated using an MTT assay against cancer cell lines (HeLa and MCF-7) and a normal cell line (BHK-21), with IC50 values in the micro molar range. Fluorescence microscopy, cell cycle analysis, caspase-9 and -3 activity, reactive oxygen species production, and DNA binding studies were used to evaluate the active compound L5's pro-apoptotic mechanism, adding to the evidence that L5 is a powerful anti-cancer drug.

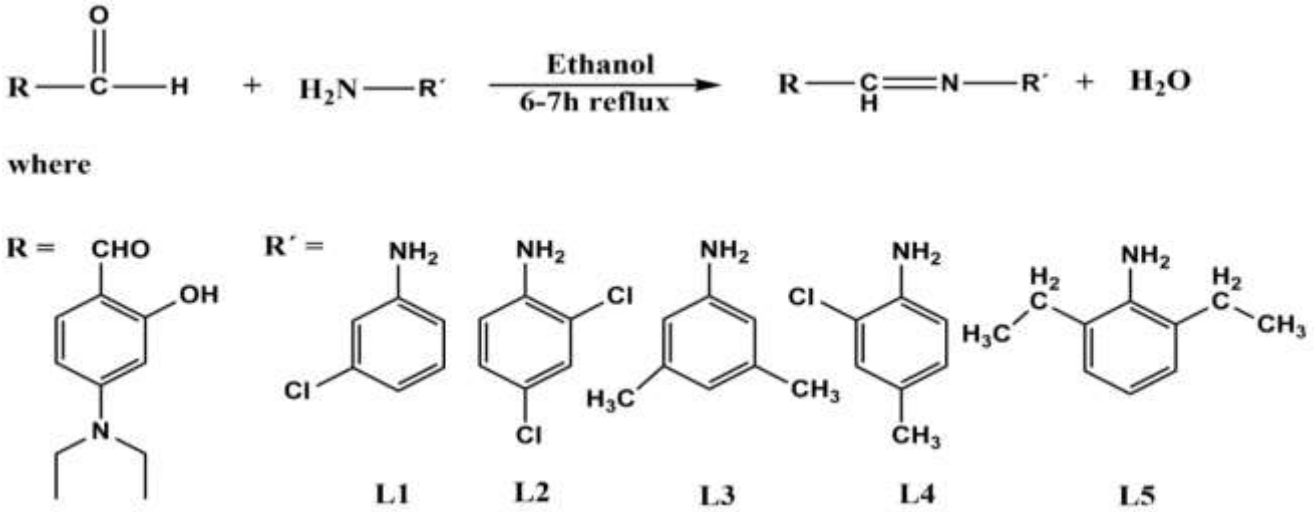

Figure 2.2: General Synthesis of Schiff Bases (L1-L5)

From the experimental evaluation, it was observed that synthesized azomethines were investigated for their antineoplastic effect on HeLa and MCF-7 cancer cell lines, while their cytotoxicity to normal cells was assessed using the MTT viability assay on a BHK-21 cell line. Fluorescence microscopy, cell cycle analysis, caspase 9 and 3 activity, reactive oxygen species (ROS) production, and DNA binding studies were used to investigate an active compound's pro-apoptotic mechanism. As a result, the researchers discovered that the potent compound L5 could be important for drug discovery and development in the future due to its anticancer properties.

B. Vhanale *et al* [7] (2019) had carried out Synthesis, characterization, spectroscopic studies and biological evaluation of Schiff bases derived from 1–hydroxy-2-acetonapthanone. The condensation reactions of 1(1-hydroxynaphthalen-2-yl) ethanone, 1-(4-chloro-1hydroxynaphthalen-2-yl) ethanone, and 1-(4-bromo-1-hydroxynaphthalen-2-yl) ethanone with propane-1,3-diamine and pentane-1,3-diamine resulted in the experimental investigation of four Schiff bases (I - IV). UVvis, FT-IR, 1H NMR, 13C NMR, LCMS, and elemental analyses are used for structural analysis. Antibacterial (Escherichia coli and Salmonella Typhi) and antioxidant (2, 2-Diphenyl-1-Picryl Hydrazyl (DPPH) and Hydroxyl radical scavenging method) activity were determined for these compounds.

Among all of these schiff bases, compound II and IV have stronger hydrogen bonding than compounds I and III, according to experimental results. It concludes that compound II has superior antibacterial activity against E. coli and Salmonella Typhi, while compound IV has superior radical scavenging activity using both the DPPH and hydroxyl radical methods. These studies show that Schiff bases of 1-hydroxyacetonaphthone have antibacterial and antioxidant properties.

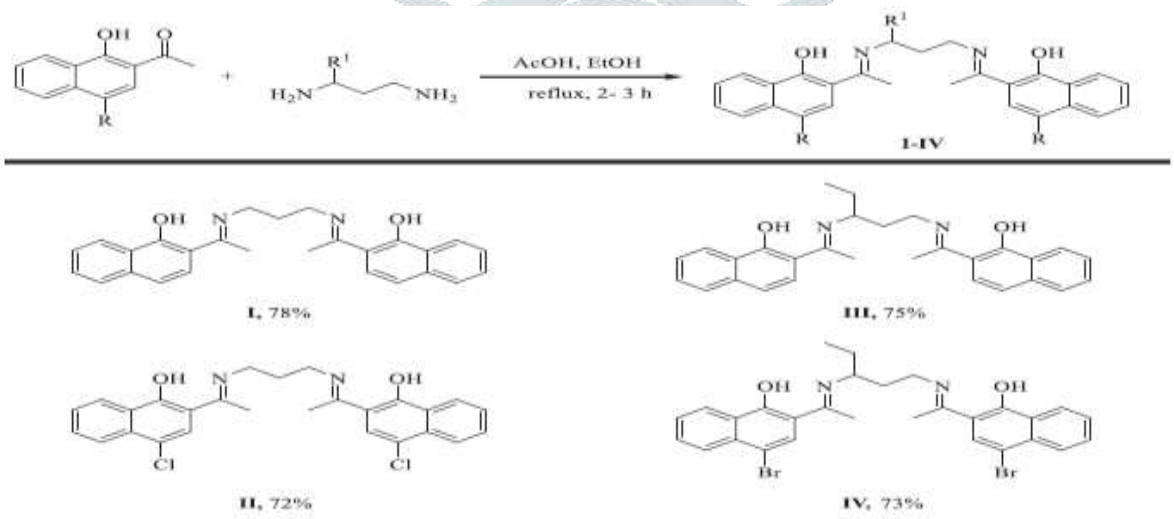

Figure 2.3: Synthesis and structure of Schiff bases (I-IV)

A. Bhowmick *et al* [8] (2019) had carried out study of highly reactive four dentate Schiff base ligand L-1 which has been prepared and used to synthesize a series of metal [Mg(II), Cu(II), Ni(II), Zn(II)] coordinating complexes 1-4 with the goal of investigating antibacterial activity. All compounds' structures were determined using spectroscopic and analytical techniques. E. Coli, Shigella Dysenteriae, and Shigella Sonnei gramme negative bacteria were used to investigate the complexes' antibacterial

activities, while streptomycin and ciprofloxacin antibiotics were used as controls. All complexes performed well as antibacterial agents, inhibiting bacterial growth.

A. Mumtaz *et al* [9] (2019) had carried out synthesis, characterization and in vitro biological studies of novel schiff base and its transition metal complexes derived from sulphadoxine. Synthesis of series of coordination transition metal complexes were prepared from Schiff base obtained from sulphadoxineandthiophene-2-carboxaldehyde. Antibacterial activity was increased against selected bacterial strains. The metal complexes also showed antifungal activity against Aspergillus Niger and Mucor, despite the fact that the parent drug and ligand had no antifungal activity. These findings were consistent with previous research that found metal-based drugs to have greater therapeutic potential.

A. Omanakuttan *et al* [10] (2019) had carried out the Synthesis Characterization and anti-microbial properties of two Salicylaldimine Schiff base complexes of transition metals. Two four coordinated copper (II) and zinc (II) complexes of bis orthophenylene diamine salicylaldehyde Schiff base were synthesized as part of the experimental investigation. Spectroscopic techniques such as FT-IR and UV-Visible spectrophotometers are used to characterise the complexes and the Schiff base. The complexes are being researched further for their anti-microbial activity against the bacteria Klebsiella pneumoniae, Salmonella typhi, Staphylococcus aureus, and Bacillus subtilis. The findings revealed that both metal complexes are more toxic to the gram-positive bacteria Staphylococcus Aureus than the Schiff base ligand.

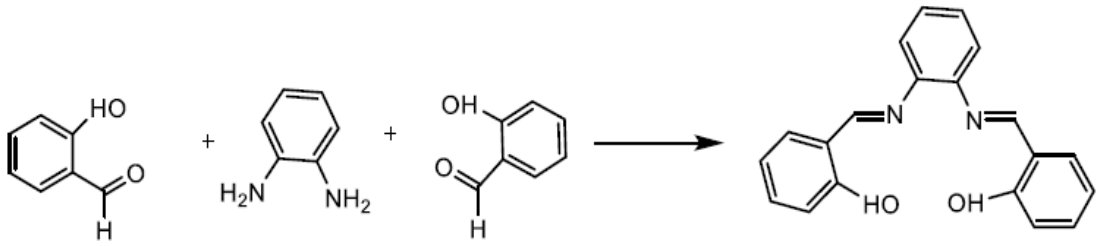

Figure 2.4: Schiff Base Complex of O-Phenylene Dimmine and Salicylaldehyde

R. Govindharaju *et al* [11] (2019) had carried out Using microwave irradiation, Cr (III) and Mn (II) metal complexes of Schiff base ligand derived from phenylacetylurea condensed with salicylaldehyde (SBPS) and thiocyanate (SCN-) ion were synthesized. Elemental analysis, metal estimation, electrical conductance, magnetic moment, electronic spectra, FT-IR, Far IR spectra, cyclic voltammetry, thermal analysis, and powder-XRD techniques were used to determine the molecular formulae and geometry of the complexes. According to the molar conductance values, the complexes are non-electrolyte (1:0). The FT-IR spectra show that the Schiff base and thiocyanate ion are monodentately coordinated to the metal ion. The electronic spectra and magnetic moment show that the complexes' geometry is octahedral.

The antimicrobial activities of ligands and their Cr (III) and Mn (II) complexes were investigated using the agar well diffusion method against microorganisms such as E. coli, Klebsiella Pneumonia, P. aeruginosa, S. aureus, Bacillus cereus, Aspergillus flavus, Aspergillus niger, Aspergillus oryzae, Aspergillus It was discovered that antimicrobial activities of synthesized complexes were tested. When compared to free ligands, the metal complexes had significant antimicrobial and antioxidant activities. In the case of emission spectral studies, the effectiveness of the complexes' DNA binding is confirmed by changes in emission intensity. The results suggest that the complexes strongly bind to DNA because of metal complexes are well-known to speed up the drug action and the ability of a therapeutic agent which can frequently be enhanced upon coordination with a metal ion.

S. Mbugua *et al* [13] (2020) had carried out New Palladium (II) and Platinum (II) Complexes Based on Pyrrole Schiff Bases: Synthesis, Characterization, X-ray Structure, and Anticancer Activity the experimental investigation was to New palladium (Pd) II and platinum (Pt) II complexes (C1−C5) from the Schiff base ligands, R-(phenyl)methanamine (L1), R-(pyridin-2-yl)methanamine (L2), and R-(furan-2-yl) methanamine (L3) (R-(E)-N-((1H-pyrrol-2-yl) methylene)) are herein reported. The complexes (C1−C5) were characterized by spectroscopic technique. The two ligands (L1L2) and a Pt complex were studied using single-crystal X-ray crystallography. L1 and L2 are both part of the P21/n monoclinic and P-1 triclinic space systems, respectively. The complex C5 is a member of the P21/c monoclinic space group. Using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and Apopercentage assays, the complexes' anticancer activity and mechanism were investigated against various human cancerous (Caco-2, HeLa, HepG2, MCF-7, and PC-3) and noncancerous (MCF-12A) cell lines. With a binding constant of 8.049 104 M1, C5 demonstrated strong DNA-binding affinity for calf thymus DNA (CTDNA). C3 reduced the cell viability of all six cell lines, including five cancerous cell lines, by more than 80%. The C5 complex also showed remarkable selectivity, with no cytotoxic activity toward the noncancerous breast cell line but significantly reducing the viability of the five cancerous cell lines, one of which was a breast cancer cell line, by more than 60%. More research is needed to assess the selective toxicity of these two complexes and fully understand their mechanism of action.

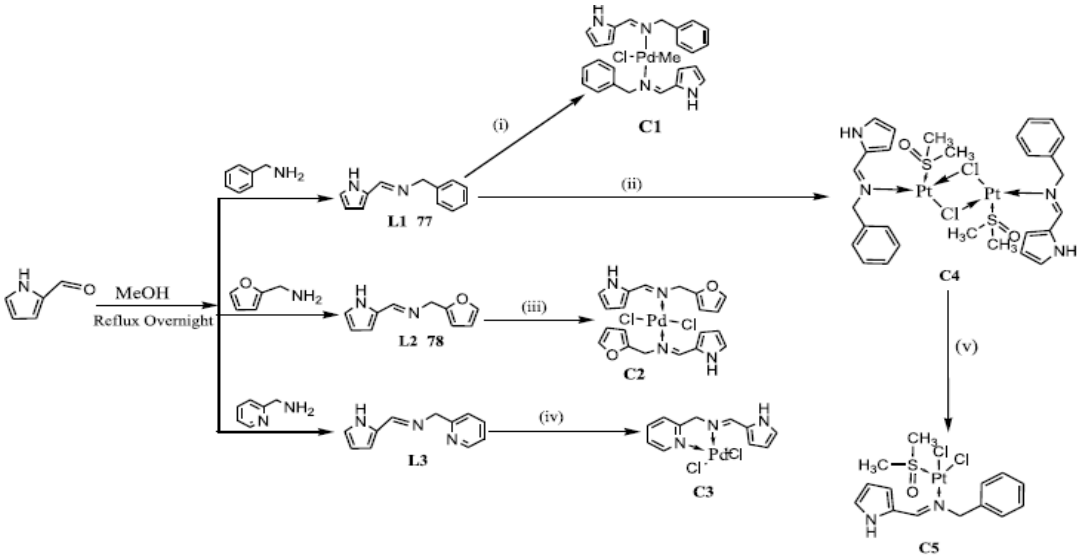

Figure 2.5: Synthetic Routes for the Ligands and Their Corresponding Complexes

From experimental investigation it was concluded that the bioactivity of C2 (trans-geometry with bulky ligands) compared to C3 (cis-geometry with unshielded metal centre). C2 showed selective cytotoxicity, while C3 displayed high cytotoxicity to all six cell lines tested in this study. The Pt complex (C5), also of cis-conformation, showed enhanced and selective cytotoxicity and selectivity to cancer cells. This compound also demonstrated strong DNA intercalation activity. This suggests that C5 can be a viable candidate for cancer treatment and requires further in vivo tests.

M. Mukhtar *et al* [14] (2020) had carried out synthesis, characterization and antibacterial screening of Schiff Base and It's Metal (II) Complexes Derived from 3-Aminophenol and Salicylaldehyde via a condensation of the ligands in methanol. The Schiff base were synthesized in 1:2 molar ratio reactions The complexes [Mn (HL1)2Cl, Cu(HL1)2 and Ni(HL1)2Cl] have been characterized on the basis of FTIR, electronic spectra, melting points/decomposition temperature, solubility and molar conductance. The in-vitro antibacterial activity of the complexes was tested using two gram-negative (Escherichia coli and Salmonella typhimurium) and two gram-positive (Staphylococcus pyogenes and Staphylococcus aureus) bacterial strains.

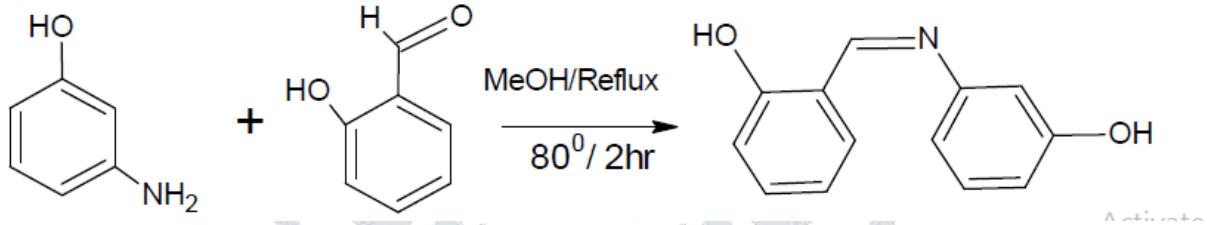

Figure 2.6: Synthetic Route for Target Ligand

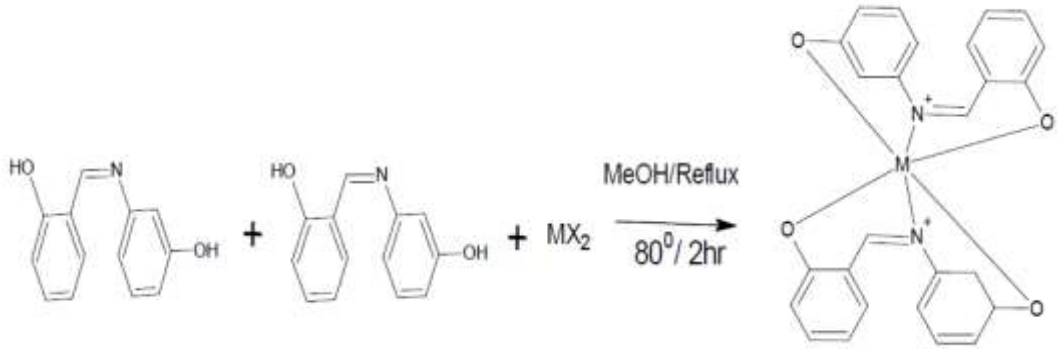

Figure 2.7: Metal (II) Complex Synthetic Route (M= FeSO4, NiCl2.6H2O, ZnCl2)

From experimental investigation it was observed that the synthesized metal complexes showed improved broad-spectrum antimicrobial activity against gram-positive and gram-negative bacteria better than the Schiff base.

Y. Bayeh *et al* [15] (2020) had carried out experimental investigation of three Schiff bases L1, L2 and L3 which were synthesized by condensing salicylaldehyde with 4-aminoantipyrine, ethylendiamine and 2-aminophenol respectively and subsequently characterized by various physicochemical investigations. By using the agar diffusion method, all three compounds were tested for in-vitro antibacterial activity against two gramme positive bacteria, Staphylococcus aureus (S.A), Staphylococcus epidermidis (S.E), and two gramme negative bacteria, Klebsiella pneumonia (K.P) and Pseudomonas aeruginosa (P.A). When compared to the activity of commercially available antibiotics like Ciprofloxacin and Chloramphenicol, the newly synthesised compounds demonstrated comparable antibacterial activity.

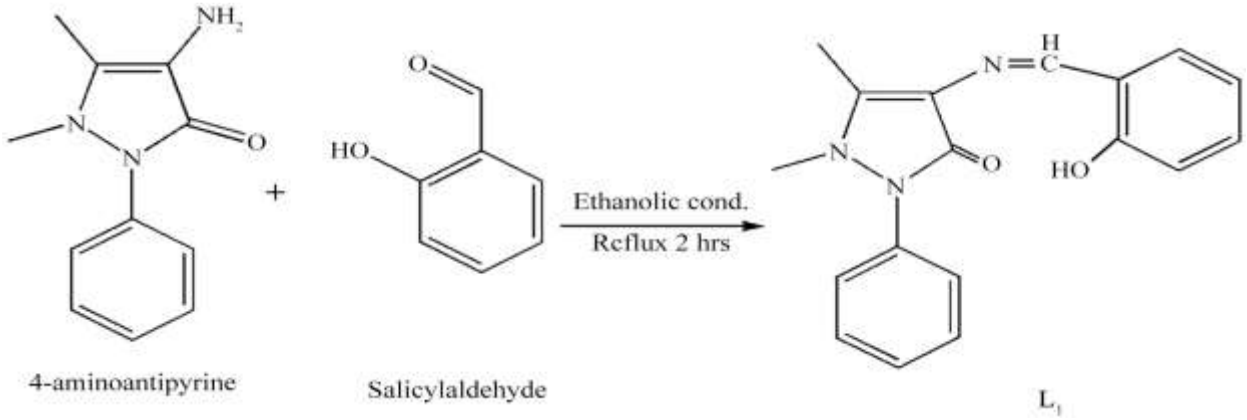

Figure 2.8: Synthetic Route of L1

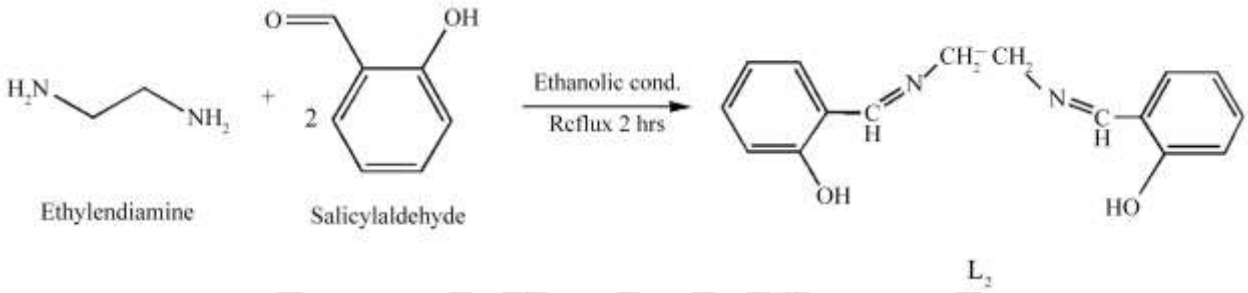

Figure 2.9: Synthetic Route of L2

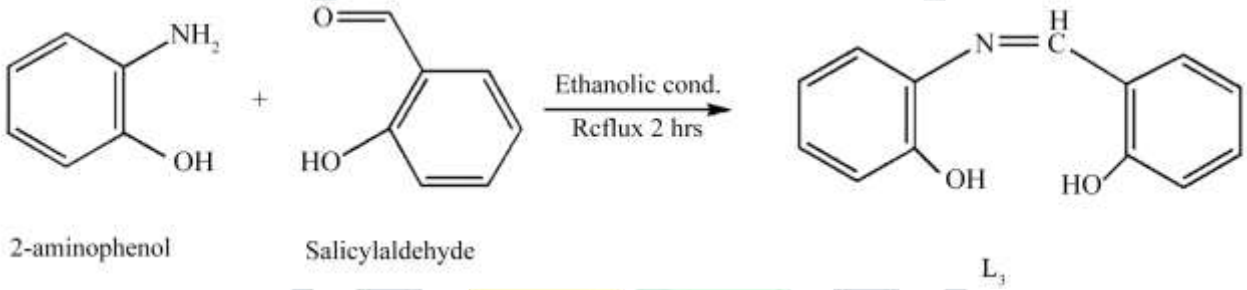

Figure 2.10: Synthetic Route of L3

The antibacterial activities of these compounds were tested using various bacteria cultures, and the results revealed that all of the Schiff bases studied in this study demonstrated appreciable activity. L3 demonstrated superior antibacterial activity against both types of bacteria (gram-positive and gram-negative) when compared to the reference antibiotics Ciprofloxacin and Chloramphenicol. This approach has the potential to open up new avenues in the treatment of infectious diseases.

B. Naureen *et al* [17] (2021) had carried out Synthesis, characterisation and biological activities of Iron (III) and zinc (II) monodentate Schiff base metal complexes. Two Schiff base ligands (L1, L2) were metal complexed to form iron (III) and zinc (II) metal complexes, respectively. Ligands and their metal complexes were physically and spectrally characterized using techniques such as ultraviolet-visible spectroscopy (UV-Vis), fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), and mass spectrometry (MS). Pharmacological activities such as antibacterial, antifungal, antioxidant, and antitumor assays were carried out.

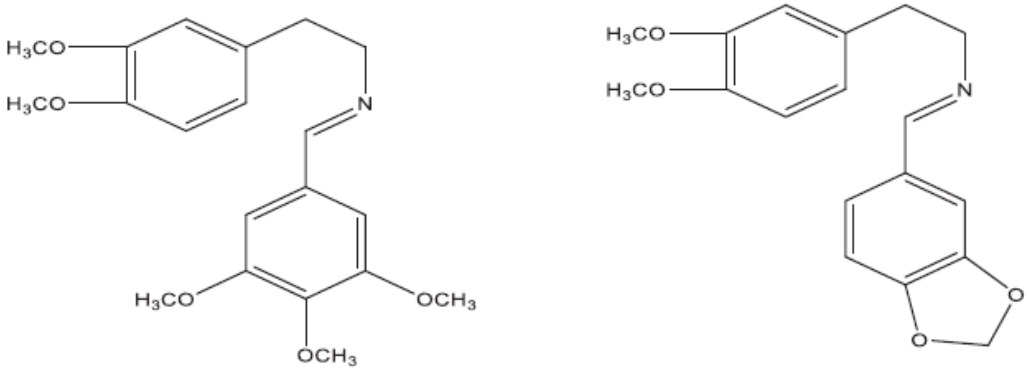

Figure 2.11: Structure of Schiff Base Ligand 1 and Ligand 2

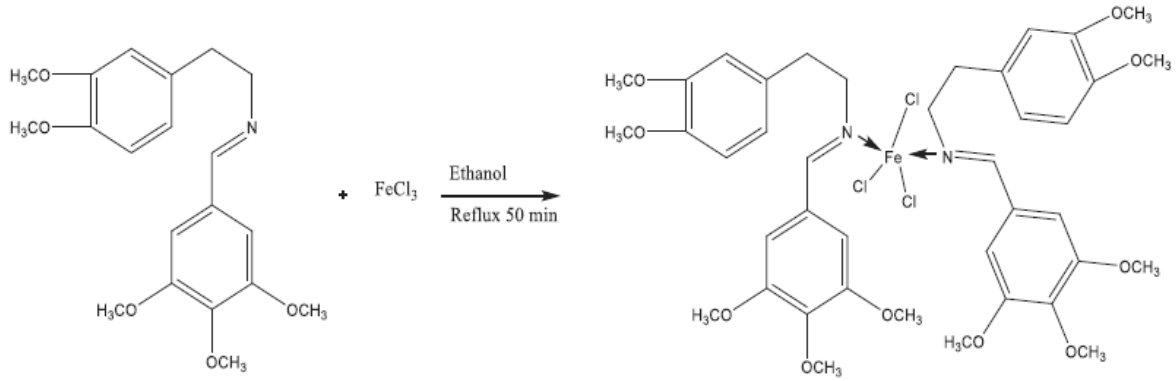

Figure 2.12: Synthesis of Iron (III) Complex of Ligand 1

The proposed structures of the ligands and their respective iron (III) and zinc (II) metal complexes were supported by all spectral characterisation techniques. Both ligands demonstrated antimicrobial activity, but their respective metal complexes demonstrated enhanced antimicrobial activity, particularly iron (III) complexes (especially the iron (III) complex of lig- and 2). When compared to Candida glabrata, all of the compounds demonstrated superior antifungal activity against Candida albican. All of the compounds, particularly the free ligands, demonstrated antioxidant activity as well as toxicity for brine shrimp eggs and antitumor activity against Agrobacterium tumefaciens strains, indicating that they have the potential to act as antitumor agents. To summarize, Schiff base ligands and their iron (III) and zinc (II) metal complexes are pharmacologically active. Thus, more research into Schiff bases, their derivatives, and metal complexes is needed. The zinc (II) complex of ligand 2 (L2) 2 Zn (Ac) 2 exhibits good antibacterial activity against all gram-positive and gram-negative bacterial strains, as well as exceptional activity against Candida albican strain.

H. Hashem *et al* [18] (2021) had carried out synthesis of a new series of heterocyclic Schiff base complexes derived from the condensation of nicotinohydrazide with different heterocyclic aldehyde, followed by metalation with Co (II) and Cu (II) metal ions. The chemical structures of the synthesized compounds have been characterized by elemental analysis. Thermo gravimetric analysis revealed the upgrading of the thermal stability of metal complexes compared to their Schiff base ligands. Antimicrobial efficacies of the Schiff base ligands and their corresponded metal complexes were screened against Staphylococcus aureus and Bacillus subtilis as Gram-positive bacteria, Escherichia coli, and Proteus vulgaris as Gram-negative bacteria, and fungi Aspergillus flavus, Candida albicans.

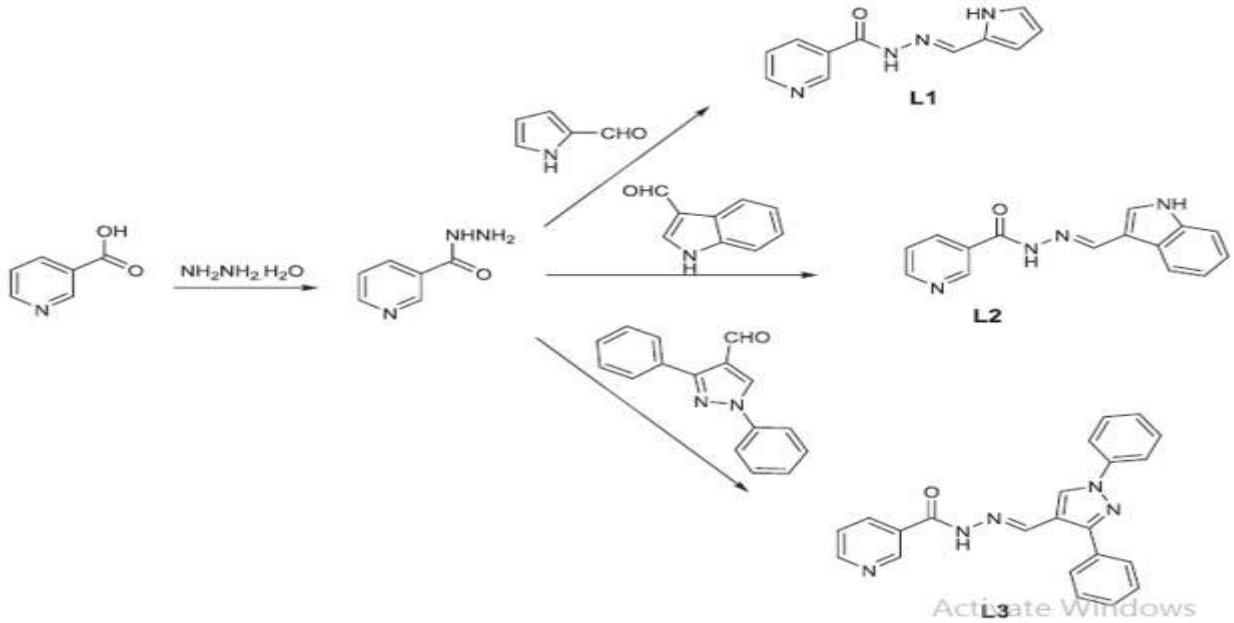

Figure 2.13: Synthesis of Schiff Base

The experimental investigation observed that In vitro antibacterial activities were studied and demonstrate that the Complexes formation increased their antimicrobial activities toward gram-positive and gram-negative bacteria.

III. CONCLUDING REMARKS

The various studies have been carried out on synthesis and characterization of Schiff base metal complexes using different approach by researchers. The concluding remarks based on their studies will be as follows:

- The study shows the variety of possible structure of metal complexes of Schiff base ligands depends upon the ketones/aldehydes and amines used.
- The specific industrial and biological application of metal complexes depends upon the orientation of Schiff base metal complexes.
- The study can be extended with the use of different aldehydes and amines to evaluate the biological application of Schiff base metal complexes.

- The synthesized Schiff base metal complex will be widely used in field of medicine and pharmacy.
- The synthesized Schiff base metal complex may have great application in chemical analysis and also be helpful in agriculture purpose.
- Schiff base metal complex have found to be more effective in various biological application (antimicrobial activity) such as antibacterial, anticancer and antitumor.
- The metals formed can undergo reaction with number of molecules for example imine ligand. This will help in synthesis of new drugs.

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