Synthesis and characterization of Copper (II), Cobalt (II) and Nickel (II) complexes of Knoevenagel Condensate with 2-Amino phenol and their Antifungal activity

Thesis submitted in
Partial fulfilment of the
Degree of Master of Philosophy (M.Phil.)

By
Ushanandhini.S
(19MPCHF004)

A Dissertation Submitted to
Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore-641043.

JUNE-2022

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Signature of the supervisor

22/6/2022

Signature of the Head Of the Department

CERTIFICATE FROM THE SUPERVISOR

This is to certify that the dissertation entitled **"Synthesis and Characterization of Copper (II), Cobalt (II) and Nickel (II) Complexes of Knoevenagel condensate with 2-Aminophenol and their Antifungal activity"** submitted by Ushanandhini S for the degree of Master of Philosophy (M.Phil.) is the record of work carried out by her during the period from under the guidance of **Dr. M. Gowri**, Assistant Professor (SG), Department of Chemistry and this work has not formed the basis for the award of any Degree, Diploma, Associate ship, Fellowship, Titles in this University or any other University or other similar institution of Higher learning.

22/06/2022

Signature of the Supervisor

DECLARATION

I declare that the dissertation entitled **"Synthesis and Characterization of Copper (II), Cobalt (II) and Nickel (II) Complexes of Knoevenagel condensate with 2-Amino phenol and their Antifungal activity"** submitted by Ushanandhini S for the degree of Master of Philosophy (M.Phil.) is the record of work carried out by her during the period under the guidance of **Dr. M. Gowri**, Assistant Professor (SG), Department of Chemistry and this work has not formed the basis for the award of any Degree, Diploma, Associate ship, Fellowship, Titles in this University or any other University or other similar institution of Higher learning.

Signature of the Student


Acknowledgment

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Ushanandhini . S

CONTENTS

INTRODUCTION

INTRODUCTION

Organometallic chemistry is the study of organometallic compounds. The field of organometallic chemistry combines aspects of traditional inorganic and organic chemistry. It joins the coordination complexes of inorganic chemistry with the synthetic methods of organic chemistry. Organometallic chemistry is used extensively in the modern world, from the construction of polymers, plastics, petrol, electronic circuitry and solar panel etc.

American organic Chemist, Henry Gilman (1893-1986) is the father of organometallic chemistry, who discovered the Gilman reagent which bears his name. A compound is regarded as organometallic if the compounds contain a covalent bond between a carbon atom and a metal, that is, there needs to be at least one metal- carbon (M-C) bond where the carbon is a part of an organic group. Organometallic compounds are particularly determined to have metallic single-bond of covalent radii with polar single bonded species. Organometallic compounds generally use the metal such as Alkali metals, alkaline earth metals, transition metals with a complete d or f shells in neutral or cationic states, and sometimes broadened to include Metalloids like Boron, Silicon and Tin.

Organometallic compounds coordinate with the elements in complex where the coordination complexes can be easily compared to other group of elements. The coordination complexes metals act as a Lewis acid and the coordination complexes ligands act as Lewis base to form Organometallic compounds, where, the ligands donates one or more electron pair to the metal ion. The properties depend upon the type of ligands used to prepare the coordination complexes and these complexes are nowadays growing in the technological field due to its varied applications. The catalytic applications in organometallic compound is performed by various transition metal and inner transition metals that form coordination complex with bi, tri and tetra dentate Schiff bases, which contains oxygen and nitrogen donor atoms. Schiff base usually formed in condensation of a ketone and aldehyde with a primary amine. A Schiff base is an analogue of a carbonyl groups which are replaced by C=N-R group.

Tri dentate Schiff bases in which the donor atoms are oxygen and nitrogen (ONO donor set) extensively investigated as ligands. The copper (II) complexes are known to be effective coordination complexes especially for its use against rheumatoid arthritis, gastrointestinal damage and anti- ulcer activities**.**

The compounds such as transitional metal hydrides and metal phosphine complexes are often included in organometallic compounds, even when they are not necessarily organometallic. There is an also distinct metal-organic compound that refers to the metal containing compounds which lack in the direct metal carbon bonds with organic ligands, metal β-diketonates, alkoxides, dialkylamides and metal phosphine complexes members of class**.**

Danish organic chemist William Christopher Zeise developed the first organometallic compound containing a transition metal was by placing platinum tetrachloride in boiling ethanol. The resulting ion formed was trichloro (ethane) palatinate (II) ion. When combined with a potassium counter ion, the Zeise's salt was formed (Fig.1).

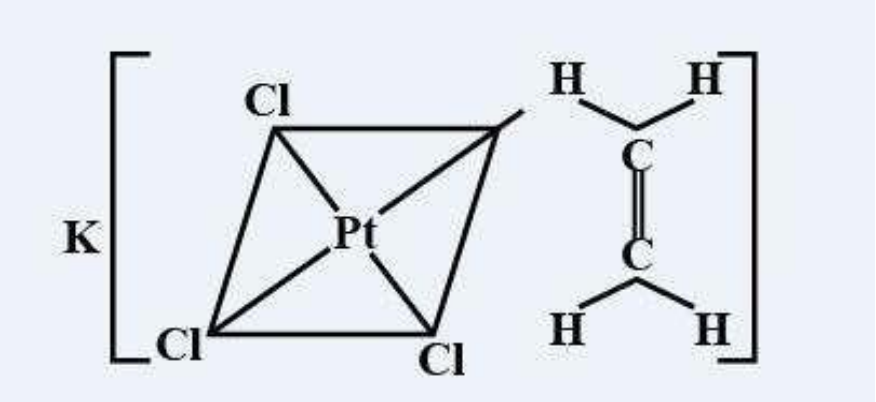


Fig.1. The structure of Zeise's salt

French chemist Victor Grignard discovered a new method of coupling carbon to the carbonyl group of a ketone or aldehyde by nucleophilic addition using an alkyl or aryl halide coupled to Magnesium metal**.** He was awarded the 1912 Nobel price of chemistry. The Grignard reagent finds uses in various applications of industry fields (Fig.2).

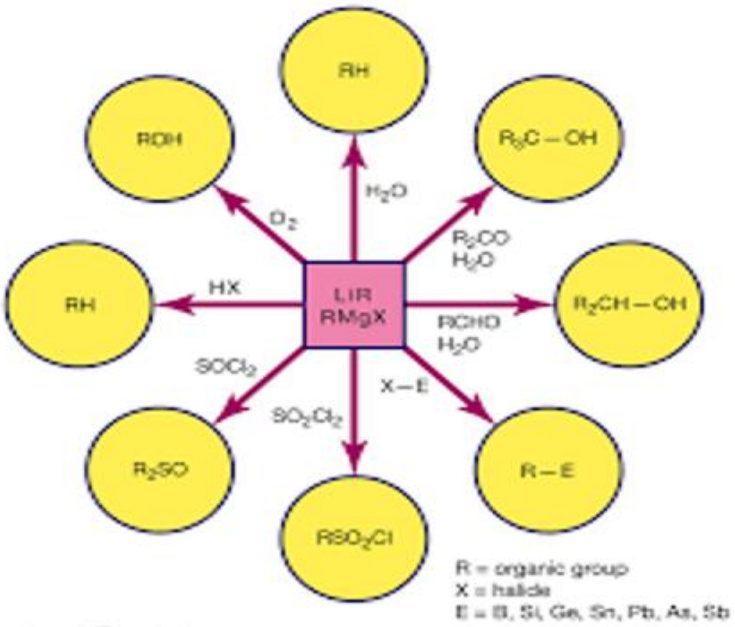


Fig.2. Applications of Grignard reagent

Alfred Werner (1866- 1919) is called as the father of modern Inorganic chemistry for his work involving the coordination chemistry of ligands to metals, especially for the structure of hexaaminecobalt (III) chloride $[Co(NH3)_6]Cl_3$. Werner's work in coordination chemistry proved to be vital in the understanding of organometallic coordination chemical reaction of the compounds. He won the Nobel Prize (1913) in chemistry for his work involving metal- ligand coordination.

Peter Pauson and Tom Kealy are American chemist who created ferrocene compounds in 1951 by reaction substrate of cyclopentadiene, $FeCl_3$ and MgBr to form of an orange powder known as ferrocene. This structure iron (Fe) act as bridge in between the first carbon of two cyclopentadiene molecules. General formula of the Ferrocene $[Fe(C_5H_5)_2]$ (Fig.3).

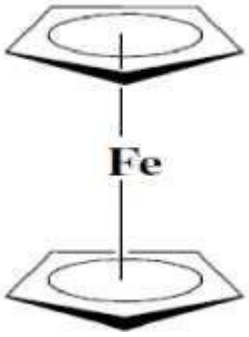


Fig.3. The structure of Ferrocene

Some important roles of Organometallic Compound :

The organomagnesium halides (Grignard reagents) are useful widely in synthetic organic chemistry, as are organo lithium and organo boron compounds.

- Alkyl aluminum (RLi) compounds are also employed in organic synthesis. Used with titanium salts, they are important catalysts in the polymerization of unsaturated hydrocarbons, such as ethylene and propylene. The mechanism of action of the titanium-aluminium alkyl catalysts probably involves interaction between the titanium atoms and the double bonds of the hydrocarbons.
- Organometallic compounds containing lead, tin, and mercury are commercially useful. A large number of organotin compounds are used as pharmaceuticals, pesticides, stabilizers for polyvinyl chloride, and fire retardants.
- Carbon monoxide react with many transition-metals to form metal carbonyls.One of the earliest to be discovered was tetracarbonylnickel, a volatile nickel compound that became the basis of a process for purifying nickel. Metal carbonyls are employed as catalysts in many reactions in the petrochemical industry.

Properties of Organometallic Compounds:

- The bond between the metal and the carbon atom is highly covalent in nature.
- Most of the organometallic compounds exist in solid states, especially the compounds in which the hydrocarbon groups are aromatic or have a ring structure.
- The compounds consisting of highly electropositive metals such as sodium or lithium are very volatile and can undergo spontaneous combustion.
- These compounds can act as reducing agents, especially the compounds formed by highly electropositive metals.

Applications:

Organometallic Compounds have a broad range of applications in various fields. Some of them are given below

- In some commercial chemical reactions, organometallic compounds are used as homogeneous catalysts.

- These compounds are used as stoichiometric reagents in both industrial and research-oriented chemical reactions.
- These compounds are also used in the manufacture of some semiconductors, which require the use of compounds such as trimethyl gallium, trimethyl aluminum, trimethyl indium, and trimethyl antimony.
- They are also used in the production of light emitting diodes.
- These compounds are employed in bulk hydrogenation processes such as the production of margarine.
- These compounds are used as catalysts and reagents during the synthesis of some organic compounds.
- The complexes formed from organometallic compounds are useful in the facilitationof the synthesis of many organic compounds.

SCHIFF BASES AND THEIR APPLICATIONS:

German chemist Hugo Schiff, who discovered Schiff bases in 1864. He discovered Schiff bases and their imines and was responsible for research into aldehyde, leading to the development of the Schiff test. He also worked in the field of amino acids and the Biuret reagent. Schiff bases are a functional group containing a C-N double bond with the nitrogen connected to an aryl and alkyl group. Schiff bases has a general formula $R^1R^2C=NR^3$ where, R is an organic side chain. Schiff base synonymouswith Azomethine and is also referred as Imines. Schiff bases have wide applications in many fields such as analytical chemistry, biological, inorganic, and electrochemical sensors, herbicidal activities**,** antibacterial, diuretic**,** anti-fungal, anti-arthritic drugs, Synthetic flexibility, agrochemical, biological fields, and sensitivity towards a variety of organisms, oxidation catalysis, food industry, pharmaceutical and biological fields, optical and electrochemical sensors, antiviral and antitumor activities, acidic anti- inflammatory agents, anticonvulsant, analgesic, non linear optics fluorescence, chemical industry, metallo-organic, electrochromism, magnetic, fascinating structural feature etc. The Schiff bases are used intermediates for the synthesis of amino acids or ligands having for preparation of metal. complexes series with different structures. Schiff base compounds and their metal complexes are very important as polymers, dyes, catalysis in various biological system, medical chemistry, birth control, food packages, oxygen detector.

The complex formation usually make Schiff bases effective stereo specific catalysts for oxidation, reduction, transformation of organic and inorganic chemistry, hydrolysis and agrochemical, photography, binder polymer possess hole transporting refining of metal, electroplating , material chemistry, photoreceptor of laser printers, horticultural insect pests, molecular sensors, luminescent probe, HIV protease inhibitors, anti tuberculosis, antiradical properties, application of analytical fields. Some Schiff base complexes are also used as model molecules for biological oxygen carrier system and exploitation of such activity is of considerable importance in the development of germicides, disinfectants, sanitizers, antiseptics, bactericides, vasodilator, trypanocidal activities, DNA- binding, stability, chelating properties. The metal complexes of Schiff bases are widely used as homogeneous and heterogeneous catalyst in reaction. In recent years development of efficient new catalysts for several reaction like reduction, hydroformylation, oxidation, epoxidation, carbonylation, hydrolysis considerable attention as well as for the use as corrosion inhibitors.

The large impact of the use of Schiff base ligands in metal complexes are evident from their advantage in various catalytic reactions such as, transfer of an amino group, carbonyl groups, hydrogenation of olefins, photo chromic properties, complexing ability toward some toxic metals, etc. The most active and selective hydrogen transfer catalysts are Ruthenium, Iridium, Rhodium complexes. The different Ruthenium compounds and arene - ruthenium compounds belong to a well- established family of metal – organic molecules that have played an important role in the development of organic chemistry.

Knoevenagel Condensation:

Knoevenagel condensation is a nucleophilic addition of an active methylene compound to a ketone or aldehyde using an amine base (e.g., piperidine, pyridine) as a catalysts that leads to dehydration reaction in which the molecular of water is eliminated (condensation reaction) finally forming often an α, β unsaturated carbonyl compound. German chemist, Emil Albert Knoevenagel first discovered, established this reaction between 1896 and 1898 , Knoevenagel condensation can be considered as a modification of the aldol condensation. Emil Knoevenagel demonstrated that primary and secondary amines and their respective salts, except tertiary amines are effective catalysts for the aldol condensation reaction of β- keto esters or malonate with either ketones or aldehydes. The generation of minimum type with the presence of basic catalysts such as intermediates (Schiff type) was proposed. Knoevenagel further investigates the result in the logical development of amino

catalysis. The reaction is usually preformed under mild reaction conditions. As a matter of fact, the Knoevenagel condensation reaction is in the presence of amine catalyst to give same bis-product. Knoevenagel himself was concerned with the condensation reaction of formaldehyde with ethyl benzoyl, diethyl malonate in the presence of ethylamine (primary aliphatic amine) as a catalyst, because it results in the same reaction with same bis-product 3 and 5 respectively. Different aldehydes were demonstrated to condense with diethyl malonate, acetylacetone, and ethyl benzoylacetate, ethyl benzoyl- pyruvate in the presence of primary and secondary amines. Knoevenagel in 1896 exhibited ethyl acetoacetate and benzaldehydes condensation at ambient temperature in the presence of piperidine to afford a bis-product. The active methylene groups are directly attached in moieties such as the acryl, nitro or cyano. Some disqualified methylene groups can undergo Knoevenagel condensations when the strong base is present, such as NaOH or quaternary ammonium hydroxides. Knoevenagel condensation reaction is a scalable, dependable, and effective approach for the construction of carbon-carbon bonds, thus, extensively is utilized in both industry and academia**.** Knoevanagel condensation is applied as intermediate in the construction of naturally occurring compounds, used in therapeutic agents, polymers containing different functional groups, pesticides and insecticides. Knoevenagel condensation reaction commonly performed in organic solvents and mediated by organic bases (e.g., piperidine and pyridine), with most of the used catalysts is non- recoverable.

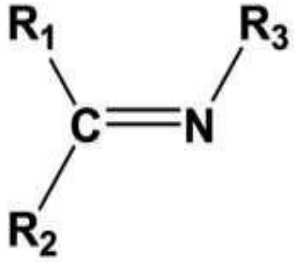
The application of this reaction is unlimited in chemical industry since they are associated with catalyst. In the last five decades, Knoevenagel condensation reaction is utilized in biologically activity with natural products, synthetic organic chemistry and nowadays overgrowing in the ground organic chemistry, new synthetic methods approaches have been effective construction of new complex molecules or hitherto structurally determined natural products that are prescribed in drugs and medications.

Notably, alkaloids are a group of natural products mostly containing basic nitrogen atom. Sometimes alkaloids results in the neutral products and even weakly acidic character. Mostly alkaloids include nitrogen, carbon and hydrogen, with some exceptional involvement of sulphur, oxygen and rarely other atoms such as Br, Cl, and P clinically (prescribed drugs). The naming reactions has replaced the local anaesthetic in the application like in the total synthesis of natural product, biological activity, anti-protozic properties, lymphatic leukaemia, tubulosine, inhibition of protein biosynthesis, HIV reverse transcriptase properties, cancer cell lines, hetero –Diels-Alder reaction ,asymmetric catalytic transfer hydrogenation reaction.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

. Schiff base (also known as imine or azomethine) is an analogue of a ketone or aldehyde in which the carbonyl group (C=O) has been replaced by an imine or azomethine group. A Schiff base or Schiff's base is a type of chemical compounds containing a carbon-nitrogen double bond as functional group, where the nitrogen atom connected to aryl group or alkyl group (R) but not hydrogen. The Schiff base is synonymous with an azomethine. These compounds were named after Hugo Schiff on have the following general structure (Fig.4).



R_1, R_2 and / or R_3=alkyl or aryl

Fig.4. Schiff base general structure

Where, R is a phenyl or alkyl group which makes the Schiff base a stable imine (Fig.5). This kind of ligands is able to coordinate metal ions through the imine nitrogen and another group,

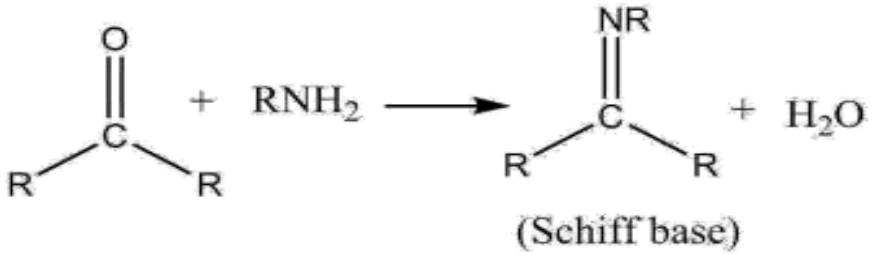


Fig.5. Formation of Schiff base by condensation reaction

Where R, may be an alkyl or an aryl group. Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable . While those of aromatic aldehydes having effective conjugation are more stable.

The formation of a Schiff base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis or upon heating (Fig.6).

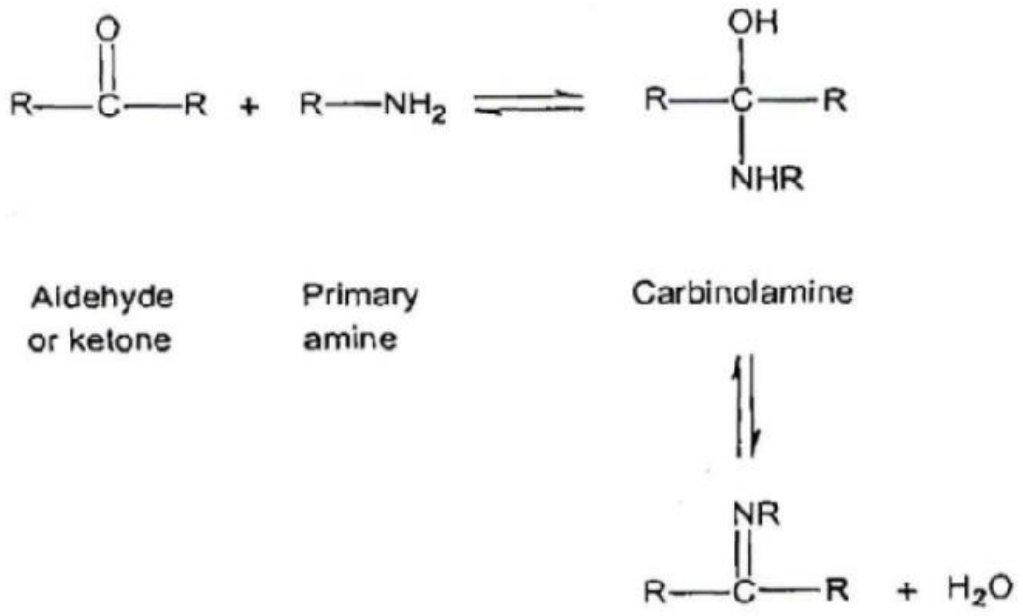


Fig.6. Reversible reaction of a Schiff base formed from an aldehydes or ketones

The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base. The mechanism of Schiff base formation (Fig.7) is another variation on the theme of neucleophilic addition to the carbonyl group. In this case, the neucleophile is the amine. In the first part of the mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine. The carbinolamine losses water by either acid or base catalyzed pathways. Since thecarbinolamine is an alcohol, it undergoes acid catalyzed dehydration

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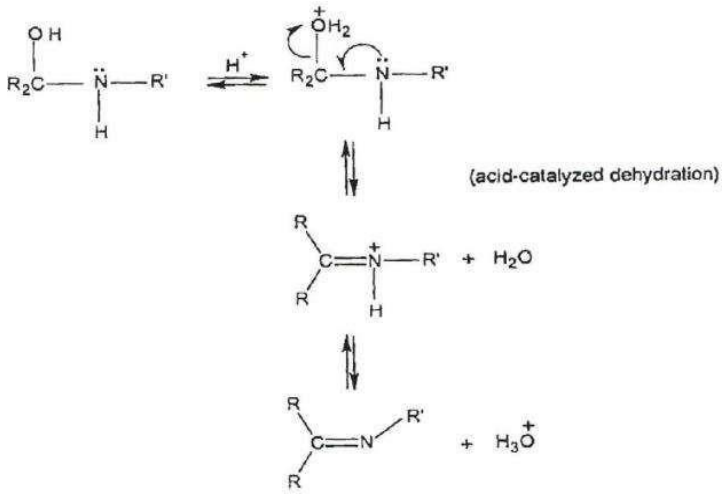

Fig.7. Mechanism of formation of Schiff base

A number of Schiff bases containing the imino functionality have been shown to have a wide range of biological activities, including antibacterial, antifungal, antidiabetic, antitumor, antiproliferative, anticancer, anticorrosive and anti- inflammatory activities. It is believed that the biological activity is related to the hydrogen bonding through the imino group of Schiff bases with the active centres of the cell constituents. Metal-imines complexes have been widely investigated due to catalytic and herbicidal utilization. Thiosemicarbazone are a class of compounds obtained by condensation of thiosemicarbazide with suitable aldehydes or ketones and they are also applicable in fields of inorganic chemistry. They are used as a chelating ligand for the formation of metal complexes because of variety of flexible donor sets of sulphur and nitrogen. People are working from last many years on the synthesis and characterization of transition metal complexes with thiosemicarbazone because of their wide range of medicinal applications and their abilities to coordinate with the transition metal ions which is highly desirable. The properties of thiosemicarbazone have received considerable attention because of their variable bonding modes, promising biological implications, structural diversity, and ion- sensing ability.

They have been used as drugs and are reported to show a wide variety of biological activities against bacteria, fungi, and certain type of tumours, and they are also a useful model for bioinorganic processes. A number of thiosemicarbazone are comparatively specific inhibitors of ribonucleotide, reductase, which is an important metabolic target for the development chemotherapeutic agents against tumor cells.

Like thiosemicarbazide and its derivatives as ligands with potential sulphur and nitrogen are fascinating and have achieved unique attention due to their importance in therapeutic and pharmaceutical field and also possess biological activities consisting of antibacterial, antifungal, anticancer, herbicidal, anticorrosion and anti-inflammatory activities. Thiosemicarbazone derivatives have found application in drug improvement for the treatment of central nervous system disorders, of bacterial infection, as well as analgesic and antiallergic agent.

Schiff bases played an important role as ligands even a century after their discovery in coordination chemistry. Schiff bases are derived from the condensation reaction of aromatic/aliphatic aldehydes and amines and form stable complexes with different transition metal ions are still relevant to be of great interest in inorganic chemistry. Schiff bases and their metal complexes have been shown to be promising leads for both synthetic and structural research due to their relatively simple synthesis and structural diversity and have been widely investigated, due to their incredible chemicalproperties and applications in various areas. The chelating ability and biological applications of metal complexes have attracted remarkable attention and they can work as models for biologically important species.

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Yue-PengCai et al.(2001) [1] Copper(II) complexes [Cu(acetylacetone)H_2O]$_2$ (**1**) and[Cu_2(acetylacetone)K_2ClO_4]$_2$ (**2**) (Fig.8), where H_2 acetylacetone is a tetradentate Schiff base bis(acetylacetone)trimethylenediimine, have been prepared and characterized by IR, CV and X-ray single crystal structure analyses. The ligand H_2acactn is strongly metallophilic to stabilize Cu(II) ion with a square planar N_2O_2 coordination environment. Complex **1** can be seen as a hydrogen-bonded dimer of building block Cu(acetylacetone) via bridging water molecules, while complex **2** is a tetra metric adduct of [Cu(acetylacetone)] moiety and $KClO_4$, in which K+ and ClO_4− are the bridging-groups. Electrochemical studies displayed that Cu(II)/Cu(I) is an irreversible one-electron reduction process.

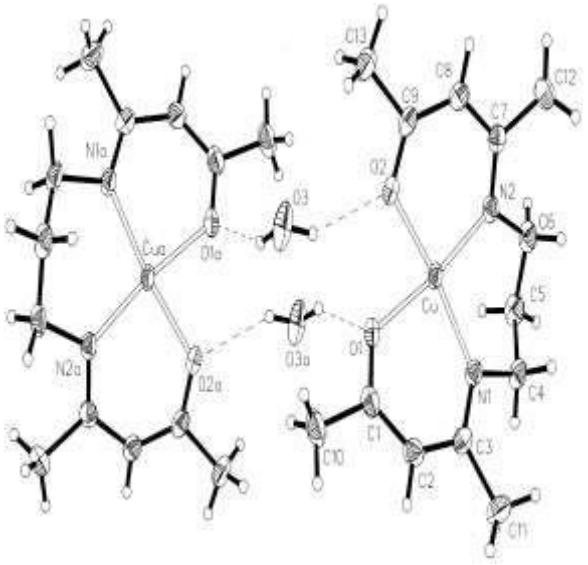


Fig.8. Molecular structure of the dimeric complex

Sushil K. Gupta et al., (2002) [2] The square-planar nickel (II) complex of composition [Ni(bae)] 1/2 H_2O (1) [where H_2bae is bis(acetylacetone)ethylenediamine] has been synthesized by [2+1] template condensation of acetylacetone and ethylenediamine in the presence of $NiCl_2$ .6H_2O and characterized. An X-ray structure determination of the complex has been completed. Average Ni–N and Ni–O distances are, respectively, 1.86(2)A ˚ and 1.849(14)A ˚. N. N bite distance and bite angle are 2.627(6) A^o and 87.2(2) A^o, respectively, for the five membered chelate rings. The water molecule forms hydrogen bonds with O atoms of two complex molecules.

Shehab A. Sallam et al.,(2002) [3] Complexes of Cu(II), Ni(II), Co(II) and Fe(III) with Schiff-bases derived by condensing o-aminophenol and ethanolamine with dibenzoylmethane, benzoylacetone, acetylacetone and thenoyltrifluoroacetone have been prepared and characterized by elemental analysis, electrical conductivity, magnetic moment, DTA and TGA measurements, IR, UV–vis., ESR, and Mossbauer spectra. All the complexes are non-electrolytes. Those with 1:2 (metal:ligand) ratios have an octahedral or distorted octahedral environment. Square-planar, Td or D2d structures have been proposed for the 1:1 complexes. The Mossbauer spectrum of the Fe (III) complex confirms its high-spin octahedral stereochemistry.

N Raman et al., (2003)[4] Neutral tetradentate N_2O_2 type complexes of Cu (II), Ni(II), Co(II) and Zn(II) have been synthesised using the Schiff base formed by the condensation of acetylacetone and *p*-anisidine. Microanalysis, molar conductance, magnetic susceptibility, IR, UV-Vis, 1H NMR, CV and EPR studies have been carried out to determinethe structure of the complexes. From the data, it is found that all the complexes possess square-planar geometry. The EPR spectrum of the copper complex in DMSO at 300 K and 77 K was recorded and its salient features are reported. All the title complexes were screened forantimicrobial activity by the well diffusion technique using DMSO as solvent. The minimum inhibitory concentration (MIC) values were calculated at 37°C for a period of 24 h. It hasbeen found that all the complexes are anti-microbial active and show higher activity than the free ligand.

M. Salavati- Niasari et al., (2003) [5] New Mn(II), Co(II), Ni(II) and Cu(II) complexes of a tetradentate Schiff base ligand [bis(2hydroxyanil)acetylacetone], “2[{1methyl3[(2hydroxyphenyl)imino]butylidene}amino] phenol”, H2haacac, have been prepared and characterized by elemental analyses, IR and conductometry. The results suggest that the Schiff base is a bivalent anion with tetradentate ONNO donors derived from the phenolic oxygen and azomethine nitrogen. The formulae was found to be [M(haacac)] for the 1:1 non-electrolytic complexes.

Alumina-supported [M(haacac)] complexes catalyze the oxidation of cyclohexene with *tert*-butylhydroperoxide (TBHP). The major products of the reaction were 2-cyclohexene-1-ol (–OH), 2-cyclohexene-1-one (C=O) and 2-cyclohexene-1-(*tert*- butylperoxy) (–OO*t* Bu). The influence of temperature, solvent and time for the oxidation reaction has been studied. The selectivity of 2-cyclohexene-1-(*tert*-butylperoxy) varied with reaction temperature. Mn(haacac)-alumina shows significantly higher catalytic activity than other alumina-supported complexes.

Mehmet Tunc et al., (2003) [6] New Schiff bases have been synthesised by the condensation of 4-amino-5-hydroxynaphthalene-2,7-disulfonic acid mono sodium salt with ovanillin (H2L1) and salicylaldehyde (H2L2), and their complexes with copper(II), cobalt(II) and nickel(II) have been prepared. All compounds were characterized by elemental analyses, FT-IR, electronic spectral data, magnetic moments, mass spectroscopy and molar conductance. The 13CNMR and 1H NMR spectra of the Schiff base ligands have been recorded.

S.M. El-Medani et al.,(2004) [7] The interaction of salicylaldehyde hydrazone (shH) with $Cr(CO)_6$ in the absence of oxygen resulted in the formation of the tris derivative $Cr(sh)_3$, 1. Reactions of $M(CO)_6$, M ¼ Cr, Mo in air gave the oxo derivatives $M(O)(sh)_2$, 2 and 3, with the metal atom in þ4 formal oxidation state. Prolonged heating of a mixture $Mo(CO)_6$ and shH in air resulted in the formation of the dinuclear complex $Mo_2(O)_6(shH)$, 4. Structures for the complexes were proposed based on the spectroscopic studies. Reactions of $W(CO)_6$ with shH in air or under reduced pressure lead to the formation of the salicylaldehyde azine dimer via elimination of a hydrazine molecule. The structure of the dimer was confirmed by crystal structure determination and by FTIR and FT-Raman spectroscopy.

The binuclear copper, nickel and cobalt complexes of the Schiff-bases obtained by condensation of glycylglycine with acetylacetone, benzoylacetone, dibenzoylmethane and thenoyltrifluoroacetone were prepared by template synthesis. The complexes were characterized by elemental analysis, conductivity measurements, magnetic moments, IR, UV-vis.spectra, ESR, X-ray diffraction, TGA, DTA and DSC thermal analysis. All the complexes are nonelectrolytes with low magnetic moments that indicate spin-spin or antiferromagnetic exchange interactions. Spectral properties support square planar and square pyramidal or trigonal bipyramidal structure provided by the N_2O_2 chromophores. ESR spectra of thecopper complex confirm the binuclear structure and the presence of magnetic interaction.

Shehab A. Sallam et al., (2006) [8] Thermal studies supported the chemical formulation of these complexes and showed that they decompose in three to four steps depending on the type of ligand. Activation energies Ea and enthalpies DH, associated with the thermal decomposition of the complexes were calculated and correlated with the type of complexed metal. A mechanism for thermal decomposition is proposed for the complexes.

P.P Hankare et al., (2003) [9] The Schiff base ligand 2-[2‟‟-hydroxysalicylidene-5‟‟- (2‟‟-thiazolylazo)]- phenol was prepared and characterized. The ligand yields binuclearcomplexes of the type $[ML(H2O)_2]_2$ [H2L =2-[2‟‟-hydroxysalicylidene-5‟‟-(2‟‟-thiazolylazo]phenol, M= Mn (II), Co(II), Ni(II), Cu(II) and Zn(II)] have been synthesized and characterized byelemental analyses, magnetic susceptibility, molar conductance, IR,electronic spectra and thermal analysis (TGA). The ESR spectra of the Cu(II) complex were Studied resulting in g > g> 2.0023. The N_2O_2 environment of the metal ion is realized in thecomplexes by involvement of the -N=N- group in coordination. The magnetic moments and electronic spectra indicate octahedral geometry for the Mn(II), Co(II), Ni(II) and Zn(II)complexes and distorted octahedral geometry for the Cu(II) complex.

Mannar R. Maurya et al., (2004) [10] Interaction of ammonium salt of N-isonicotinamidosalicylaldimine (H_2sal-inh) and N-(2-hydroxyphenyl)salicylideneamine (H_2sal-oap) with NH_4VO_3 inserted in Na–Y zeolite in aqueous solution at pH ca. 7.5 leads to the formation of dioxovanadium(V) complexes in the super cages of the zeolite–Y. These encapsulated complexes exhibit good catalytic activity towards the oxidative bromination of salicylaldehyde using H_2O_2 as an oxidant in presence of KBr a reaction similar to that exhibited by vanadate-dependent haloperoxidases (V-HalPO). Under the reaction conditions the percent formation of a major product 5-bromosalicylaldehyde follows the order: NH_4 $[VO_2$(sal-inh)]–Y (34%) > $NH_4[VO_2$(sal-oap)]–Y (26.8%) > Na/NH_4VO_3–Y (22%) with ca. 87% selectivity after 4 h of reaction time. These encapsulated complexes do not leach or decompose during catalytic activity study, showing their practical utility over free complexes.

Anindita Sarkaret al., (2006) [11] The reactions of one equivalent each of $[VO(acac)_2]$ and N-(2-pyridyl)-NO-(5-R-salicylidene) hydrazines (HphsalR) (derived from 2-hydrazinopyridine and 5-substituted salicylaldehydes) in boiling acetonitrile under aerobic conditions provide ternary complexes of oxovanadium(IV) having the general formula [VO(phsalR)(acac)]. The complexes have been characterized by analytical, magnetic and spectroscopic measurements. The structures of two representative complexes have been determined by X-ray crystallography. In each structure, the metal centre is in a distorted octahedral N2O4 coordination sphere. The tridentate coordinates the metal ion via the pyridine-N, the imine-N and the phenolate-O atoms in a meridional fashion. The remaining three coordinations sites are occupied by the bidentate O, O-donor acetylacetonate (acac) and the oxo group. In the crystal lattice, the molecules of each of the two complexes assemble to form one-dimensional supramolecular structure via intermolecular N–H....O=V hydrogenbond interaction. Electronic spectra collected using dimethylsulfoxide solutions of the complexes display a weak absorption within 643–720 nm due to d–d transition and some strong absorption in the range 510–262 nm due to ligand-to-metal charge transfer and ligand centred transitions. The room temperature (298 K) effective magnetic moments of the complexes in the solid state are consistent with an S = 1/2 ground state of the metal ion in each complex. All the complexes display axial EPR spectra with well-resolved 51V hyperfine structure characteristic of an axially compressed octahedral coordination geometry around the metal centre.

Qi-Long Zhang et al., (**2008) [12]** The synthesis and X-ray structure of a dinuclear nickel(II) complex (Fig.9) of the triply deprotonated pentadentate Schiff base, N,N0-(2-hydroxypropane-1,3diyl)bis(acetylacetoneimine) (apacaH3), are reported. The complex, which was obtained by reaction of apacaH3 with nickel acetate in ethanol, has a binuclear structure of type [Ni2 (apaca)(OAc)] in which each metal centre is bound to a deprotonated enolic oxygen and an imine nitrogen from an acetylacetoneimine „arm" of apaca. The nickel centres are bridged by both analkoxide oxygen derived from the 2-hydroxypropane unit in apaca and an acetato group. Each metal centre has a distorted square-planar geometry, with the overall configuration being non-planar. This complex is isostructural with a previously- reported, copper(II) complex of similar stoichiometry, prepared by an analogous procedure from copper(II) acetate. The present result contrasts with a previous report in which apacaH3 was claimed to interact with Nickel(II) acetate in ethanol in the presence of potassiumethoxide to yield a square-planar complex of the corresponding doubly deprotonated Schiff base ligand.

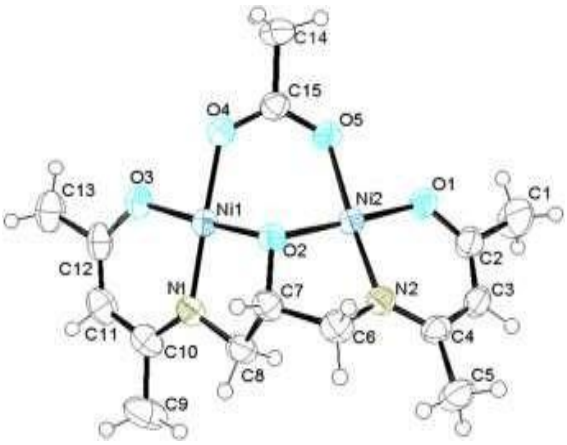


Fig.9. X-Ray structure of dinuclear Nickel(II) complex

Two new symmetrical acetylacetone-based Schiff bases, here in called LA and LB, have been synthesized.The complexes formed by their association with Mn(II) have been evaluated for catalytic alkene epoxidationwith H_2O_2. **Ag. Stamatis et al., (2009) [13].** The catalytic efficiency of Mn(II)/LA and Mn(II)/LB systems were shown to be switched on by ammonium acetate with remarkable effectiveness and selectivity towards epoxides. EPR spectroscopy for Mn(II)/LA shows that the catalytic centre is a mononuclear Mn complex. Additives that allow easier oxidation of Mn(II) to higher oxidation states,such as acetate and bicarbonate, can promote decisively the catalytic function. Additives that do not allow oxidation of Mn(II) to higher oxidation states, such as formate and oxalate, inhibit severely the catalytic function. Monocarboxylate ions, acetate, bicarbonate and formate do not disturb considerably the first coordination sphere of Mn(II). Dicarboxylate additives, such as oxalate, form strong complex with the Mn(II). Based on the catalytic and EPR data, a double role is suggested for ammonium acetate. This is to promote Mn(II) oxidation, and to function as a dual acid-base system, participating into the catalytic cycle.

P. **Mayer et al., (2009) [14]** The oxo-bridged dinuclear Rhenium(V) complex (Fig.10) [(μ- O)(Re OCl(amp))$_2$] (1) was prepared by the reaction of trans-[ReOCl$_3$(PPh$_3$)$_2$] and 6-amino- 3-methyl-1-phenyl-4-azahept-2-ene-1-one (Hamp) in acetone. The characterization of 1 by elemental analysis, infrared and 1H NMR spectroscopy and X-ray crystallography shows that amp is coordinated as a monoanionic NNO-donor chelate as an amino-amido ketone. However, the reaction of the similar ligand 7-amino-4,7-dimethyl-5-aza-3-octen-2-one (Hada) with [Re(CO)$_5$Br] produced fac-[Re(CO)$_3$Br(Hada)], with Hada coordinated as a neutral bidentate N,N-donor amino-imino-ketone.

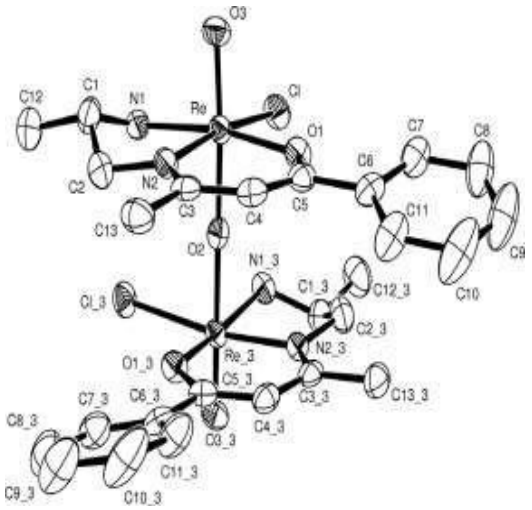


Fig.10. Oxo-bridged dinuclear Rhenium(V) complex

Aurkie Ray et al., (2009) [15] A new tridentate N_2O donor Schiffbase ligand [$(C_6H_5C(OH)=CHC(CH_3)=NCH_2C_5H_4N)$=LH] was obtained by 1:1 condensation of benzoylacetone with 2-picolylamine and has been used to synthesise a mononuclear [CuLCl] (1) and an end-to-end dicyanamide bridged polynuclear $\{[Cu_2(\mu\text{-}L)2(\mu\text{ -}1,5\text{-}(CN)_2N)]ClO_4\}_n$ copper(II) complexes (Fig.11). The ligand, 1 and 2 were clearly characterised by elemental analysis, FT-IR, 1H NMR, UV–Vis spectral studies, electrochemical studies and in addition single crystal X-ray diffraction studies were performed for 1 and 2. The Schiff base ligand [LH] shows a significant variation in its coordination behaviour with copper(II) ion inabsence and in presence of dicyanamide ion in 1 and 2 respectively.In absence ofdicyanamide the deprotonated enolato oxygen of the tridentate Schiff base ligand $[L]^-$ coordinates the copper(II) ion in a monodentate fashion generating a mononuclear species Where as in presence of the dicyanamide ion, the deprotonated enolato oxygen of $[L]^-$ bridges two adjacent [Cu $L(CN)_2N$] units through μ-OL bridges, forming dimers. The dimeric units are further linked to adjacent dimeric units through μ_2-1,5-dicyanamide bridges to produce 1D polymeric chains in 2. Variable temperature magnetic susceptibility measurements for 2 in the temperature range 2-300 K reveal the presence of weak antiferromagnetic exchange interactions in the polymeric chain**.**

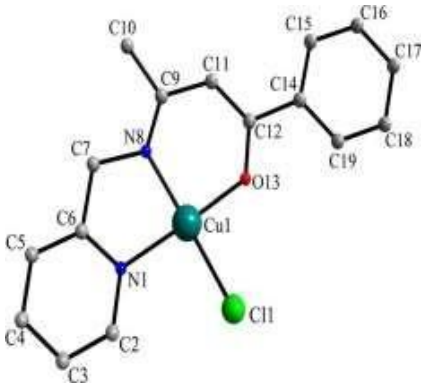


Fig.11. Schiff base Copper(II) complex

Perumal Subramani et al., (2009) [17] Novel complexes of the type [Ni(TAA-sal)(H_2O)]X (TAA-sal = Schiff base derived from tris(2-aminoethyl)amine –TAA and salicylaldehyde–sal, X= Cl) or [Ni(TAA-acac)(H2O)]BPh4 (TAA-acac=Schiff base derived from TAA and acetylacetone-acac) have been prepared and studied by elemental analysis, IR and magnetic measurements. Physicochemical studies account for the deformed octahedral coordination mode.

Apurba Biswas et al., (2010) [18] Two new reduced Schiff base ligands, [HL^1 = 4-{2-[(pyridin-2-ylmethyl)-amino]-ethylimino}-pentan-2-one and HL^2 = 4-[2-(1-pyridin-2-yl-ethylamino)-ethylimino]-pentan-2-one] have been prepared by reduction of the corresponding tetra dentate unsymmetrical Schiff bases derived from 1:1: 1 condensation of 1,2-ethanediamine, acetylacetone and pyridine-2-carboxaldehyde/2-acetyl pyridine. Newly synthesized Four complexes of [Ni(L1)]ClO_4 (complex1), [Cu(L1)]ClO_4 (complex 2), [Ni(L2)]ClO_4 (complex 3), and [Cu(L2)]ClO_4 (4) with these two reduced Schiff base ligands have been synthesized and structurally characterized by X-ray crystallography. The mono-negative ligands L1 and L2 are chelated in all four complexes through the four donor atoms to form square planar Nickel (II) and Copper(II) complexes. Structures of 3 and 4 reveal that enantiomeric pairs are crystallized together with opposite chirality in the nitrogen and carbon atoms. The two Cu(II) complexes (2 and 4) exhibit both irreversible reductive (Cu(II)/Cu(I) Epc, 1.00 and -1.04 V) and oxidative (Cu(II)/Cu(III), Epa, +1.22 and +1.17V, respectively)negative ligands L1 and L2 are chelated in all four complexes through the four donor atomsto form square planar Nickel (II) and Copper(II) complexes. Structures of 3 and 4 reveal that enantiomeric pairs are crystallized together with opposite chirality in the nitrogen and carbon atoms. The two Cu(II) complexes (2 and 4) exhibit both irreversible reductive

(Cu(II)/Cu(I) Epc, 1.00 and -1.04 V) and oxidative (Cu(II)/Cu(III), Epa, +1.22 and +1.17V, respectively) responses in cyclic voltammetry. The electrochemically generated Cu(I) species for both the complexes are unstable and undergo disproportionation.

Belkasem et al., (2010) [19] Schiff bases are highly important in industrial and biological fields. The present study has been carried out to investigate the geometrical structure of complexes with M(II) and M(III) ions. The complexes were prepared by condensation of acetyl acetone with benzidine (L), P–phenylene diamine (L1), P- toluidine (L2), and aniline (L3) using different techniques such as elemental analysis, molar conductivity, thermal analysis, IR spectra and magnetic properties. Some neutral tetradentate N2O2 type complexes of Co(II) have been synthesized using Schiff bases formed by condensation of 5-nitro-salicylaldehyde with various diamines in alcohol.

Hossein Naeimi et al., (2010) [20]. The nature of the ligands and complexes was established by spectroscopic techniques. The Schiff bases are bivalent anions with tetradentate ONNO donors derived from phenolic oxygen and azomethine nitrogen. IR and UV-Vis spectral data suggest that all the complexes are square-planar.

V. Koteswara Rao et al., (2010) [21] Schiff bases constitute a class of pharmaceutical and medicinally important molecules. The conventional methods for the synthesis of Schiff‟s bases require long reaction times and use of organic solvents. We report a novel and eco-friendly condensation reaction method permitting the „„„green synthesis‟‟‟ of various Schiff‟s bases by stirring 1,2diaminobenzene with various aromatic aldehydes in water as solvent. This method is experimentally simple, clean, high yielding, green, and with reduced reaction times. The product is purified by simple filtration followed by washing with water and drying processes.

Halime Guzin Aslan et al., (2011) [22] In this study Benzenesulfonicacid-1-methylhydrazide (bsmh) derivatives (Fig.12) such as salicylaldehyde benzenesulfonylhydrazone (Hsalbsmh) and its Ni(II), Pd(II), Pt(II), Cu(II), Co(II) complexes (Fig.12) were synthesized for the first time. The structure of these complexes was investigated by using elemental analyses, the FT-IR, LC–MS and UV–VIS spectrophotometric methods, magnetic susceptibility and conductivity measurement techniques. The complexes were found to have general compositions [ML2]. Using disk diffusion methods all the synthesized complexes were evaluated in vitro as antimicrobial agents against representative strains of grampositive (Staphylococcus aureus ATCC 25923, Bacillus cereus ATCC 11778, Enterococcus faecalis ATCC 29212, Bacillus subtilis ATCC 6633, Staphylococcus

epidermidis ATCC 12228, Enterobacter aerogenes ATCC 13048) and gram-negative bacteria (Pseudomonas fluorescens ATCC 49838, Klebsiella pneumoniae ATCC 13883, Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853) and as an antifungal agent against Candida albicans (ATCC 90028). All the bacteria and fungus studied were screened against some antibiotics to compare with our chemical zone diameters.

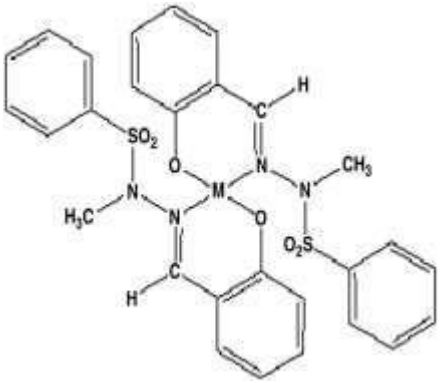


Fig.12. Metal (II) complexes of Hsalbsmh

Gabrieli L. Parrilha et al.,(2011)[23] The Complexes $[Zn_2(HL1)_2(CH_3COO)_2]$ (1) and $[Zn2(L^2)_2]$ (2) were synthesized with salicylaldehyde semicarbazone (H_2L^1) and salicylaldehyde-4-chlorobenzoyl hydrazone (H2LASSBio-1064, H_2L^2), respectively. The crystal structure of (1) was determined. Upon recrystallization of previously prepared $[Zn_2(HL^2)_2(Cl)_2]$ (3) in 1:9 DMSO:acetone crystals of $[Zn_2(L^2)_2(H_2O)_2]$_$[Zn_2(L^2)_2(DMSO)_4]$ (3a) were obtained. The crystal structure of 3a was also determined. All crystal structures revealed the presence of phenoxo-bridged binuclear zinc(II) complexes.

Ziyad A. Taha et al.,(2011) [24] Eight new lanthanide metal complexes $[Ln\mathbf{L}(NO_3)_2]NO_3$ {Ln(III) = Nd, Dy, Sm, Pr, Gd, Tb, La and Er, L = bis-(salicyladehyde)- 1,3-propylenediimine Schiff base ligand} were prepared. These complexes were characterized by elemental analysis, thermogravimetric analysis (TGA), molar conductivity measurements and spectral studies (^{1}H NMR, FT-IR, UV–vis, and luminescence). The Schiff base ligand coordinates to Ln(III) ion in a tetra-dentate manner through the phenolic oxygen and azomethine nitrogen atoms. The coordination number of eight is achieved by involving two bi-dentate nitrate groups in the coordination sphere. Sm, Tb and Dy complexes exhibit the characteristic luminescence emissions of the central metal ions attributed to efficient energy transfer from the ligand to the metal center. Most of the complexes exhibit antibacterial activity against a number of pathogenic bacteria.

Hui-Jun Zhang and Carsten Bolm et al., (2011) [25] Highly region selective intermolecular hydroacylations of enamides under rhodium catalysis with monodentate phosphane ligands are reported for the first time. The presence of MeCN facilitates this novel C-C bond formation, and the electron-deficient phosphine P $(p\text{-}F\text{-}Ph)_3$ has proven most effective for the direct hydroacylation of 1-vinyl-2-pyrrolidinone. Accordingly, an atom-economic synthetic route to R-amido ketones from readily available substrates has been developed.

Q. **Zaky et al.,(2013) [26]** The o-Hydroxy acetophenone [N-(3-hydroxy-2- naphthoyl)] hydrazone (H2O-HAHNH) has been prepared and its structure is confirmed by elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectroscopy. It has been used to produce diverse complexes with Co(II), Cd(II), Hg(II) and $U(VI)O_2$ ions. The isolated complexes have been investigated by elemental analysis, magnetic measurements, molar conductivity, thermal (TG, DTG) and spectral (^{1}H NMR, 13C NMR, IR, UV–visible, MS) studies. Infrared spectra suggested H_2O-HAHNH acts as a bidentate and/or tridentate ligand. The electronic spectrum of $[Co(Ho\text{-}HAHNH)_2]$ complex as well as its magnetic moments suggesting octahedral geometry around Co(II) center. The TG analyses suggest high stability for most complexes followed by thermal decomposition in different steps. Moreover, the kinetic and thermodynamic parameters (Ea, A, DH*, DS*and DG* for the different decomposition steps of the $[Co(Ho\text{-}HAHNH)_2]$ and $[Cd(Ho\text{-}HAHNH)_2]$ complexes were calculated using the Coats–Red fern and Horowitz–Metzger methods. Moreover, the antibacterial and antifungal activities of the isolated compounds were studied using a wide spectrum of bacterial and fungal strains.

Khosro Mohammadi et al.(2012) [27] A series of new VO(IV) complexes with two new tetradentate Schiff base of 4,40-(2,2-dimethylpropane -1,3-diyl)-bis(azan-1-yl-1-yldene)dipent-2-en-2-ol) $[H2L^1]$ and 3,30-(2,2-dimethylpropane-1,3-diyl)azan-1-yl-1-ylidene)-bis(1-phenylbut-1-en-1-ol) $[H2L^2]$ (which have been derived from2,2-dimethyl-1,3-diaminopropan,and diketones of acetylacetone and benzoylacetone) were synthesized and characterized by ^{1}H NMR, ^{13}C NMR, FT–IR, mass and UV–Visible spectrophotometry. The electrochemical properties of the vanadyl complexes were investigated by means of cyclic voltammetry. The oxidation potentials are increased by increasing the electron-withdrawing properties of functional groups of the Schiff base ligands according to the trend of Me < Ph. The thermogravimetry (TG) and differential thermoanalysis (DTA) of the VO (IV) complexes were carried out in the range of 20–700^{o}C. The complexes were decomposed in two stages.

Also, decomposition of the synthesized complexes is related to the Schiff base characteristics. The thermal decomposition of the studied reactions was first order. Thekinetic parameters for the decomposition steps in vanadyl complexes thermograms have beencalculated.

A series of novel amino acid derived Schiff-bases and their Oxovanadium(IV) complexes (Fig.13) were synthesized and well characterized by elemental analyses, spectral studies, conductivity and magnetic measurements. **Misbah ur Rehman et al.,(2013)[28]** Physical and analytical data suggest that the Schiff bases act as tridentate ligands towards metal ion via azomethine-N, deprotonated-O of carboxylic group and enolic-O group of acetylacetone. All the complexes have lower molar conductance values, indicating their non-electrolytic nature. The synthesized ligands, along with their metal complexes were screened for their in- vitro antibacterial activity against two Gram-negative (Escherichia coli, Salmonella typhi) and two Gram-positive (Bacillussubtilis, Staphylococcus aureus) bacterial strains and for in vitro antifungal activity against Trichophyton longifusus, Candidaalbicans, Aspergillus flavus, and Candida glaberata species. The results of these studies revealed that all the compounds and their metal complexes showed significant antibacterial and antifungal potency. Brine shrimp bioassay was also carried out for in vitro cytotoxic properties against Artemia salina.

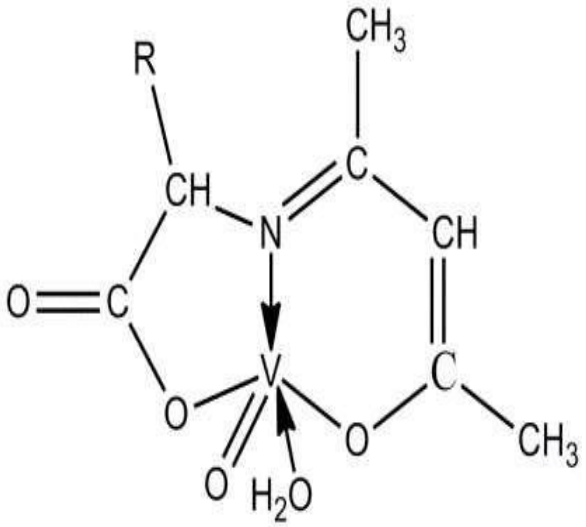


Fig.13. Oxovanadium (IV) complex of Schiff base

Sunita Bhagat et al.,(2013) [29] A new efficient and environmental friendly procedure for the synthesis of a series of Salicylaldehyde-based schiff bases under microwave irradiation is described. The method is compared with the conventional method also. The present work involves Condensation of Salicylaldehyde with various aromatic amines in

water under microwave irradiation. A judicious choice of the solvent and reaction conditions allowed the final products to be generated in excellent yields in a one-step procedure,whereas experiments under thermal conditions led to lower yields with tedious work-up. Microwave irradiation method gives advantages like reduction in reaction time, increase in conversion, reduced wastes, and good yields. The structures of synthesized compounds were confirmed by IR, ^{1}H-NMR, and Mass Spectra data.

T. I. Kashar et al.,(2014)[30] have synthesized some schiff bases Mn(II),Co(II),Ni(II) and Zn(II) complexes with N-Anilinoacetohydrazobenzoylacetone (H2L). The newly synthesized complexes were investigated using several spectral techniques. The binuclear complexes with molar ratios of M: L = 2:1 are formed. Newly synthesized binuclear Schiff base complexes of manganese (II), Cobalt (II), Zinc(II), Nickel(II) complexes synthesized and characterized. Newly synthesized complexes were investigated using several spectral techniques. The spectral technique of UV spectroscopy and magnetic susceptibility shows that all complexes have octahedral structure. Antibacterial activity of the Schiff base and its metal complexes were tested some Gram-positive and Gram-negative strains. Antifungal activity higher shows Manganese(II)complex than the free ligand. And other Cu(II) complexes shows higher antibacterial activity of G+ bacteria Bacillus subtilis.

Cristina Rimbu et al.,(2014) [31] Palladium(II) complexes with Schiff bases ligands derived from salicylaldehyde and amino acids (Ala, Gly, Met, Ser, Val) have been synthesized and characterized by Fourier transform (FT)-IR, UV-Vis and 1H-NMR spectroscopy. The electrospray mass spectrometry (ES-MS) spectrometry confirms the formation of palladium(II) complexes in 1/2 (M/L) molar ratio. All the Pd(II) complexes $[Pd(SalAla)_2]Cl_2$, $[Pd(SalGly)_2]Cl_2$, $[Pd(SalMet)_2]Cl_2$, $[Pd(SalSer)_2]Cl_2$, $[Pd(SalVal)_2]Cl_2$, have shown antibacterial activity against Gram-positive bacteria Staphylococcus aureus and Gram-negative bacteria Escherichia coli.

Nasser Mohammed Hosny et al.,(2014)[32] Four new metal complexes derived from the reaction of Cu(II), Co(II), Ni(II) and Zn(II) acetates with the Schiff-base ligand (H3L) resulted from the condensation of the amino acid 2-amino-3-hydroxyprobanoic acid (serine) and acetylacetone have been synthesized and characterized by, elemental analyses, ES-MS, IR, UV-Vis., 1H-NMR, 13C-NMR, ESR, thermal analyses (TGA and DTG) and magnetic measurements. The results showed that the Schiff-base ligand acts as bi-negative tridentate through the azomethine nitrogen, the deprotonated carboxyl ate oxygen and the enolic carbonyl oxygen. The optical band gaps measurements indicated the semiconducting nature of

these complexes. Molecular docking was used to predict the binding between the Schiff base ligand with the receptor of prostate cancer mutant H874Y. The interactions between the Cu (II) complex and calf thymus DNA (CT-DNA) have been studied by UV spectra. The results confirm that the Cu(II) complex binds to CT-DNA in an intercalative mode.

Xavier et al.,(2014) [33] The new Schiff bases are synthesis from various and aldehyde and amine under magnetic stirrer method .The synthesized Schiff base were characterized by spectral techniques (UV-Spectra & IR-Spectra). And the Schiff bases are yellow colour solid and having sharp melting point and insoluble in organic solvents.

N.Aliyu et al., (2014) [34] A tetradentate Schiff base ligand was prepared by a 2:1 molar condensation of 4 (Benzeneazo) Salicylaldehyde with o-phenylenediamine. The Copper (II) chelate was synthesized by refluxing ethanolic solutions of the schiff base ligand and Copper (II) chloride. The ligand and the copper (II) complex were characterized by melting point, decomposition temperature, molar conductance, infrared, elemental analysis, antibacterial, antifungal and potentiometry. The ligand is orange, has a melting point temperature of 193^{o}C, and percentage yield of 70%. The copper (II) complex is red, has decomposition temperature of 286^{o}C and percentage yields of 62%. The ligand and its copper(II) complex are not soluble in water and most common organic solvents except DMSO and DMF. The molar conductance of the complex determined is 7.9 ohm-1cm2mol-1. The band at 1590cm-1 in the infrared spectral data of the ligand is assigned to *v*(C=N) stretching vibrations, which undergoes a shift to lower wave numbers at 1538cm-1 on coordination to the metal ions. The band at 586 and 511cm-1 are attributable to *v*(Cu-N) and *v*(Cu-O) vibration modes. The elemental analysis of the complex established 1:1 copper ligand ratio. The antifungal and antibacterial tests carried out on the ligand and its copper (II) copper showed moderate activity. The dissociation constant of the ligand determined is 11.67, indicating a week acid. The ratio of metal to ligand determined potentiometrically suggested 1:1. The stability constant and the Gibb‟s free energy of copper (II) complex determined are 3.16X1011 and 4.15 KJmol-1, respectively, establishing that the complex is very stable.

Chandini R. Nayaret al.,(2014) [35] Current trends suggest that light, rather than electricity, will increasingly be used in the area of information technology, with potential in optical communications, data storage and computer systems. Therefore there has been a growth of interest in development of molecular second order non-linear materials. In the last few years, organometallic and coordination complexes have emerged as interesting chromophores for producing NLO materials due to the large variety of structures and diversity of electronic properties tunable by metal centre. N_2O_2 Schiff base complexes are a promising class of efficient chromophores exhibiting large NLO responses. This reviewsummarizes second order NLO ligands and metal complexes of Schiff bases derived from Salicylaldehyde.

R. Venkatesh et al.,(2015) [36] The pentadentate Schiff base ligand prepared from 1,3-diamino-2-propanol and acetylacetone forms dinuclear complexes with Nickel(II). The ligand was characterized by 1H NMR, UV-Visible and FT-IR spectral studies and its complexes were characterized by UV-Visible, FT-IR, HRLCMS and molar conductance. Conductance measurements indicate that the above complexes are non electrolyte.

Sunkari Jyothi et al.,(2015) [37] Four new tetradentate amine-N donor ligands have been prepared by reducing Schiff bases derived from the condensation of 2-aminonicotinaldehyde with 1,2-diaminoethane (APMED)/ 1,2-diaminopropane (APMPD)/1,3-diaminopropane (APMP'D)/trans-cyclohexane-1,2-diamine (APMCD). The ligands react with transition metal [Co(II)/Ni(II)/Cu(II)/Zn(II)] salts to give microcrystalline solid complexes of 1 : 1 (M : L) composition. The ligands and the metal complexes have been characterized with analyses, molar conductance measurements, magnetic susceptibility measurements and spectroscopic investigations like mass, IR, electronic, NMR and ESR. All the complexes were found to have octahedral geometry holding 0-6 water molecules in the lattice with a general molecular formula $[MLCl_2].n\ H_2O$.

Antony et al.,(2016) [38] Metal chelates of Schiff base prepared by combining Salicylaldehyde and amino acids could be effectively used in understanding the mechanism of transamination reaction. They can act as biomimetic species. The current article focusedon the syntheses, characterization, complexation behaviour and antimicrobial studies of some novel Schiff bases formed from salicylaldehyde with 3-amino benzoic acid and Glycine and Alanine using sodium hydroxide as a catalyst. The synthesized Schiff base ligands have been successfully complexed with the metal Zn (II) and studied by their spectral data.

Morphological studies were carried out using SEM. The impact of complexation on the antimicrobial activity of Schiff bases and its Zn (II) complexes has also been studied.

Jessica K. Bilyj et al.,(2018) [39] The complexation reaction mechanism of acetylacetone bis-thiosemicarbazone ligands (H2acetylacetoneR) with Cu (II) is explored using a variety of physical methods. The complexes form via a complicated multistep mechanism that is initiated by ring opening of the pyrazoline form of the ligand and leads, ultimately in air, to an oxidised ketone form of the ligand. Tetra dentate N_2S_2 coordinated forms of the intermediate [Cu (acacR)] are stable only under anaerobic conditions. Upon exposure to air these complexes are cleanly oxidized to the ketone complex [Cu (acetylacetoneRO)] as shown by X-ray crystallography, electrochemistry, UV-Vis and EPR spectroscopy. The behaviour of these complexes contrasts with those of closely related bis-dithiocarbazate Schiff bases which stabilize Cu (III).

Mohammad Nasir Uddin et al.,(2018) [40] number of oxotitanium(IV) complexes of the type TiOL with bis-unsymmetric dibasic tetradentate Schiff base (LH2) containingONNO donor atoms have been synthesized. Mono-Schiff base (OPD-HNP) was prepared by the condensation of 1:3 molar ratio of 2-hydroxy-1-naphthaldehyde (HNP)with *o*-phenylenediamine (OPD). Dibasic unsymmetric tetradentate diamines Schiff bases were prepared by the reaction of OPD-HNP with 2-hydroxyacetophenone, 2-hydroxypropeophenone, benzoylacetone, acetylacetone and ethylacetoacetate. Further, titanylacetylacetonate was reacted with these ligands to obtain their metal complexes. On the basis of analytical and physiochemical data, the formation of complexes as TiOL was suggested having square pyramidal geometry. Quantum mechanical approach also confirmed this geometry. The assessment of the synthesized ligands and their complexes showed that some behave as good inhibitors of mycelia growth against selected phytopathogic fungi but weak inhibitors against some selected bacteria. A few of them also showed antioxidant properties.

Shamly P. et al.(2018) [41] A new, efficient and environmental friendly procedure for the synthesis of a series of Salicylaldehyde-based Schiff bases and their metal complexes in aqueous media were conducted. The work involved the condensation of Salicylaldehyde with various amines, both aromatic and aliphatic and the Schiff bases formed were complexeswith a transition metal Ni and an alkaline earth metal Mg. This green synthetic approach was compared with conventional procedure and found to have advantages like good yield and

reduction in reaction time and by products. The synthesized Schiff bases and their complexes were characterized by FTIR. The antibacterial activity of complexes and uncomplexed Schiff bases were compared against Escherichia coli and the Mg complex is found to have better antibacterial activity than the corresponding Ni (II) complex.

Bushra Iftikhar et al., (2018) [42] Three new Schiff base ligands were synthesized by the reaction of Salicylaldehyde with semi-aromatic diamines, prepared by the reduction of corresponding dinitro-compounds, and were further used for the formation of complexes with Cu(II) metal ion. The structural features of the synthesized compounds were confirmed by their physical properties and infrared, electronic and NMR spectroscopic techniques. The studies revealed that the synthesized Schiff bases existed as tetradentate ligands and bonded to the metal ion through the phenolic oxygen and azomethine nitrogen. One of the dinitro precursors was also analyzed by single crystal X-ray crystallography, which showed that it crystallizes in monoclinic system with space group P2/n. The thermal behaviour of the Cu(II) complexes was determined by thermo gravimetric analysis (TGA) and kinetic parameters were evaluated from the data. Schiff base ligands, their precursors and metal complexes were also screened for antibacterial, antifungal, antitumor, Brine shrimp lethality, DPPH free radical scavenging and DNA damage assays. The results of these analyses indicated the substantial potential of the synthesized Schiff bases, their precursors and Cu (II) complexes in biological field as future drugs (Fig.14).

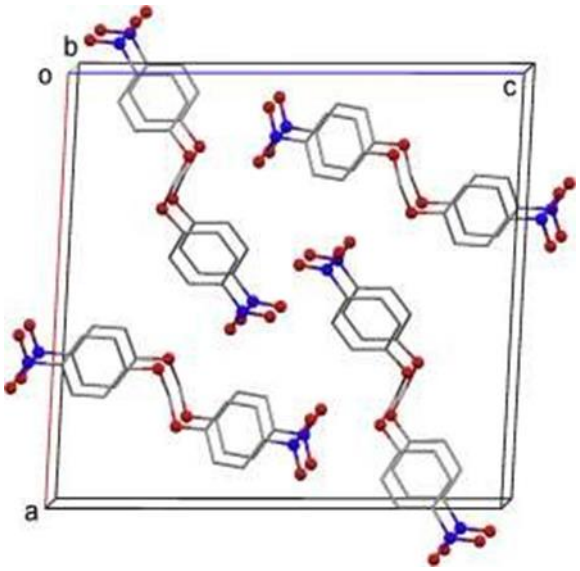


Fig.14. Structure of the Schiff base ligand

Joginder Kumar et al.,(2017) [43] The chemistry of Schiff base containing, compounds have been an interesting field of study from ancient years. Subsequently, Schiff base constitutes a significant class of compounds for new drug development. Recently,various Schiff base containing derivatives (Fig.15) have been synthesized and evaluated for their biological activities including as antimicrobial, anti-tuberculosis, antioxidant, anti-inflammatory, anticonvulsants, antidepressant and anxiolytic, antihypertensive, anticancerand antifungal activity. The search for Schiff base containing compounds with more selective activity and lower side effect continues to be an active area of argument examination in medicinal chemistry. This review is ornately pronounced the medicinal chemistry, their biological properties.

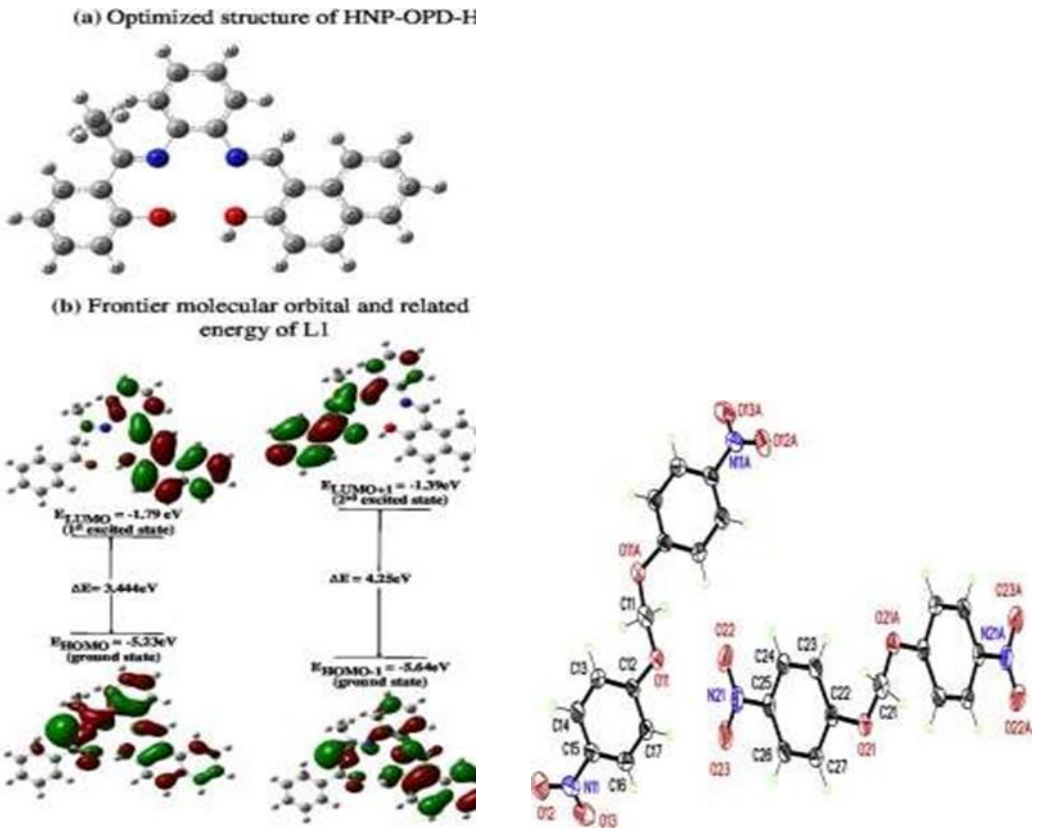


Fig.15. The crystal structure and the Frontier Molecular Orbital of the Schiff base

Ammavasi Gubendran et al.,(2017) [44] New Schiff base complexes [Cu(L^1)Cl] , [Ni(L^1)Cl],[Zn(L^1)Cl]and[Fe(L^2)H2OCl]{L^1=(4E)-3-(2-hydroxybenzylidene)-4-(2-hydroxyphenylimino)pentan-2-one, L^2=2,2′-(1E,1′E)-(3-(2-hydroxybenzylidene)-pentane-2,4-diylidene)bis(azan-1-yl-1idene)diphenol} have been synthesized and characterized by elemental analysis, UV–Vis, IR, FAB-mass, EPR, spectral studies and electrochemical studies, the ligands L^1 & L^2 were characterized by ^{1}H and ^{13}C NMR spectra. Complex 1 show a visible spectral d-d band near 600 nm and display cyclic voltammetric quasi reversible

response for the Cu(II)/Cu(I) couple vs Ag/AgCl in DMSO. The EPR spectrum of 1 shows g∥ N g⊥ suggesting a square planar geometry around copper with dx^2-y^2 as the ground state. The mass spectral results have confirmed the proposed structure for complexes 1–4. DNA binding properties of these complexes 1–4 have been investigated by absorption titrations, cyclic voltammetric studies and circular dichroism studies.On titration with DNA, the complexes 1–4 show hypochromism at the MLCT band (13–31%) with a red shift of 1–8 nm in the electronic spectrum and positive shift of voltammetric E1/2 in the CV studies are in favour of intercalative binding. CD spectra of 1 showed an increase in molar ellipticity (θ278) of the positive band with a minor red shift indicating the transition of B-form of DNA to A like form. DNA cleavage studies of complexes 1 and 4 with pUC18 DNA were studied by gel electrophoresis and complex 4 cleaves super coiled pUC18 DNA in an oxidative manner in the presence of H_2O_2 and on photo irradiation at 312 nm.

Kenan Buldurun et al.,(2018) [45] In this study, two novel Schiff base ligands (L1 and L2) derived from condensation of methyl 2-amino-6-methyl-4,5,6,7- tetrahydrothieno[2,3-c]pyridine-3-carboxylate and methyl 2-amino-6-phenyl-4,5,6,7- tetrahydrobenzo[b]thiophene-3-carboxylate both starting matter with 5-bromo- salicylaldehyde, and their Zn(II) and Ni(II) metal complexes have been prepared using a molar ratio of ligand:metal as 1:1 except the Ru(II) complexes 1:0.5. The structures of the obtained ligands and their metal complexes were characterized by elemental analysis, FT-IR, ^{1}H NMR, ^{13}CNMR, UV–vis, thermal analysis methods, mass spectrometry, and magnetic susceptibility measurements. Antioxidant and antiradical activity of Schiff base ligands and their metal complexes were been evaluated in vitro tests. Antioxidant activities of metal complexes generally were more effectives than free Schiff bases. 1c and 2c were used as catalysts for the transfer hydrogenation (TH) of ketones.1c, 2c complexes were found to be efficient catalyst for transfer hydrogenation reactions.

Z. Umar et al.,(2018)[46] The new Schiff base ligand, Sal-leucine (L) has been synthesized by the reaction of ethanolic solution of Salicylaldehyde with leucine. The corresponding metal complexes were obtained by refluxing the chlorides of manganese (II) and nickel (II) with the prepared Schiff base in an ethanolic medium. The chemical structures of the synthesized ligand and its corresponding complexes were established by IR, EI-mass spectra, elemental analysis, solubility, molar conductance measurement and melting point/decomposition temperature. The conductivity measurement indicated the complexes to be non electrolyte. The solubility tests carried out showed that the complexes are soluble in

most common organic solvents but insoluble in water, indicating that the compounds are not ionic. The antibacterial test of the ligand and the complexes showed that the complexes were found to be more active than the ligand against the organisms used.

M. M. El-ajaily et al.,(2018) [47] Schiff bases are organic compounds, considered to be a subclass of imines, which may be secondary aldimines or ketimines depending on the nature of the parent carbonyl compounds, which are synthesized by nucleophilic addition of aliphatic or aromatic amines with carbonyl compounds forming intermediate hemiaminals followed by elimination of water, the reaction often being catalyzed in acid medium. They have the general formula R-CH=NR' where R' ≠ H. The presence of the azomethine function in the Schiff base compounds renders them as potential candidates for forming a wide range of complex compounds with both transition and non transition metal ions. This class of compound has been found to exhibit a broad range of biological activities including antibacterial and antifungal properties. This article presents a short overview of the synthetic design and biological activities of a host of mixed ligand complexes containing Schiff base moieties.

Ranjan K. Mohapatra et al.,(2018)[48] Schiff bases are stable imines containing C=N, where N is bonded to an alkyl or aryl group, but not with hydrogen and are prepared by condensation of aliphatic or aromatic primary amine with carbonyl compounds. They have the general formula $R_1R_2C= NR_3$, where $R_3 \neq H$. The presence of the basic donor N atom andthe stability of the imines function render Schiff bases as the most favoured ligands that have the ability to stabilize metal ions in different oxidation states. The chelating environment in a Schiff base profoundly influences the electron distribution in the coordination sphere of metal in a complex and thereby regulates the property of the compounds in a big way. The structural diversity in some of the metal complexes with multidentate Schiff baseligands has triggered a wide range of applications of this class of compounds in sensors, catalysis, biology, medicines, and photonics. This review compiles the synthesis and biological activities (antimicrobial, antioxidant, anticancer, antitubercular, DNA interaction studies) of benzaldehydes-based Schiff bases and their metal complexes.

Sadia Afrin Dalia et al.,(2018)[49] 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, antiproliferative, 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 various synthesis procedures and application of Schiff bases and their metal complexes.

Mohammad Muzammil Y et al.,(2018) [50] A series of transition metal complexes of Cu (II), Co (II), Mn(II), Fe (II), Ni (II) and V (II) were prepared from bidentate schiff base. The Schiff base ligand synthesized from the condensation of 5- Bromo 2-Hydroxy Benzaldehydes (Neelima, D, Kulkarni; P, K, Bhattacharya. Can. J. Chem. 1987, 65, 348) and Aniline in an alcohol medium. These metal complexes were characterized on the basis of their analytical data like IR, NMR. The ligand and their metal complexes were screened antibacterial activity against various bacteria like Escherichia coli, B. subtilis. The result indicated that the complexes exhibited good antibacterial activities. By keeping the above mentioned knowledge of Schiff bases and Organometallic complexes, We would like to carry out the Synthesis of Schiff base from o-vannilin, Acetylacetone and 2- amino phenol and its Copper, Cobalt and Nickel complexes. As a part of application oriented studies, We would like to carry out the antifungal studies.

MATERIALS AND METHODS

MATERIALS AND METHODS

Materials

All the chemicals were purchased from Sigma Aldrich in analytical grade. DIGITAL MELTING POINT APPARATUS (SAFIRE) was used to determine the melting point of the synthesized Schiff base ligand and its metal complexes with the help of an open capillary tube with the heating rate of 10^{o} C/min. An elemental analysis (CHN) was performed using Thermal Finnegan Elemental Micro Analyzer. The infrared spectra of the samples were recorded in JASCO FT/IR-4700 spectrometer. BRUKER ADVANCE III HD NANOBAY 400MHZ FT-NMR Spectrometer is used to record ^{1}H (400MHz) and ^{13}C (100MHz) NMR spectra in $CDCl_3$ using TMS as an internal standard and the chemical shift values were recorded in parts per million (ppm). ESR spectra of resulted Schiff base complexes were recorded in the JEOL spectrometer. The reactions were monitored by thin layer chromatography coated with silica gel.

The Schiff base compound and its Copper, Cobalt and Nickel complexes were tested for antifungal activity against three representative fungal strains *Aspergillus niger*, *Aspergillus flavus*, and *Aspergillus terrus* at three different concentrations (10, 30, 50µl) by well diffusion method. Fluconazole was used as a reference drug in terms of minimum inhibitory concentration (MIC).

Methods:

Synthesis of the Schiff base ligand: (4E)-3-(2-hydroxy-3-methoxybenzylidene)-4-((2-hydroxyphenyl)imino)pentan-2-one

The Schiff base ligand has been synthesized in two steps, the first step is Knoevenagel condensation, and the final step to prepare the Schiff base ligand. In the first step, a mixture of o-Vanillin (1.521g, 10mmol) and acetyl acetone (1.002g, 10mmol) additionally adding few drops of piperidine as a catalyst, this mixture is refluxed with ethanol over a water bath for about 3 hours. Shiny yellow crystals appeared in the reaction mixture on cooling. The resulting Knoevenagel product (1.17g, 5mmol) is further condensed with 2-aminophenol (545mg, 5mmol) in a 1:1 ratio in ethanolic medium. Finally, the reddish orange color shiny solid Schiff base product appeared. The resulted Schiff base ligand was separated and dried under vacuum.

Colour : Reddish Orange

Melting Point : 160^0C

Yield : 91.6 %

Synthesis of Schiff base Copper complex

A hot ethanolic solution of $[CuCl_2(PPh_3)_2]$ (330mg, 0.5mmol) was gradually added to a hot ethanolic solution of the Schiff base ligand in a 1:1 ratio(208mg, 0.5mmol) and the solution mixture was refluxed for about 6-8 hours over a water bath. The reaction was monitored by TLC. The resulted product was separated, washed with petroleum ether, and dried under vacuum.

Colour : Green

Melting Point : 182^0C

Yield : 63.2%

Synthesis of Schiff base Cobalt complex

A hot ethanolic solution of $[CoCl_2(PPh_3)_2]$ (328mg, 0.5mmol) was gradually added to a hot ethanolic solution of the Schiff base ligand in a 1:1 ratio(208mg, 0.5mmol) and the solution mixture was refluxed for about 6-8 hours over a water bath. The reaction was monitored by TLC. The resulted product was separated, washed with petroleum ether, and dried under vacuum.

Colour : Brown

Melting Point : 173^0C

Yield : 71.08%

Synthesis of Schiff base Nickel complex

A hot ethanolic solution of $[NiCl_2(PPh_3)_2]$ (326mg, 0.5mmol) was gradually added to a hot ethanolic solution of the Schiff base ligand in a 1:1 ratio(208mg, 0.5mmol) and the solution mixture was refluxed for about 6-8 hours over a water bath. The reaction was monitored by TLC. The resulted product was separated, washed with petroleum ether, and dried under vacuum.

Colour : Yellow

Melting Point : 129^0C

Yield : 78.04%

Antifungal Activity

The newly synthesized Schiff base and Cu(II),Co(II) and Ni(II) complexes were subjected to the antifungal activity against *Aspergillus niger, Aspergillus flavus and Aspergillus terreus* .

Agar well diffusion method

Agar well diffusion method is widely used to evaluate the antimicrobial activity of plants or microbial extracts. The agar plate surface is inoculated by spreading a volume of the microbial inoculums over the entire agar surface. Then, a hole with a diameter of 6 to 8 mm is punched aseptically with a sterile cork borer or a tip, and a volume (20–100 µL) of the antimicrobial agent or extract solution at desired concentration is introduced into the well. Then, agar plates are incubated under suitable conditions depending upon the test microorganism. The antimicrobial agent diffuses in the agar medium and inhibits the growth of the microbial strain tested. Antimicrobial susceptibility testing can be used for drug discovery, epidemiology and prediction of therapeutic outcome.

Procedure

The antifungal study potato dextrose agar was prepared (39gm in 1000ml of distilled water, followed by autoclaving) and poured to petri plate. After solidification 80 µl of fungal spores of *Aspergillus niger, Aspergillus flavus* and *Aspergillus terreus* were added and spread, using above said method sample also added and incubated 3-5 days at 30^0C. 5 µl of Fluconazole was used as a standard drug (10mg/ml), after incubation zone of inhibition was measured in mm.

The various concentrations (10µL, 30µL, 50µL) of sample solution, solvent and standard drug of Flucanaazole 5 µL (10mg/ml), are placed in Petri dishes and kept the sterile forceps. The Petri discs are placed in refrigerator at 4^oC or room temperature for one hour for diffusion. Incubate at 30 ^{o}C for 3 to 5 days. Zone of inhibition is calculated for all the samples along with the solvent and standard drug Flucozanole [51].

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

In the present study, the synthesis of Schiff base ligand involves two steps. The first step is the Knoevenagal condensation of o-vanillin and Acetyl acetone of 1:1 molar ratio. The second step is the synthesis of the Schiff base ligand which involves the condensation between the Knoevenagal condensate and 2- amino phenol of 1:1 molar ratio. The new metal complexes were synthesized from the resultant product the Schiff base and the precursor metal complexes $[MCl_2(PPh_3)_2]$ in 1:1 molar ratio in absolute ethanol. The Schiff base and new complexes were subjected to various characterization studies and antifungal activity against *Aspergillus niger, Aspergillus flavus and Aspergillus terreus* .

Elemental analysis

The new series of the Schiff base (4E)-3-(2-hydroxy-3-methoxybenzylidene)-4-((2-hydroxyphenyl)imino)pentan-2-one and its metal complexes Cu(II), Co(II), and Ni(II)) are soluble in chloroform, ethanol, methanol and acetone. The Schiff base ligand and its metal complexes are stable at room temperature, melting points from 150^{o}C to 200^{o}C. The physical parameters and elemental analysis results are shown in Table 1.

Table 1 : The physical parameters and elemental analysis of Schiff base ligand and its metal complexes

Compound	Mol.wt	Elemental analysis found (calc.)			Melting point (^{o}C)	Colour	Yield %
		% C	% H	%N			
OVAAA ($C_{19}H_{19}NO_4$)	325.36	70.16 (70.14)	5.35 (5.89)	5.68 (5.31)	160	Reddish orange	91.6
OVAAACu ($C_{37}H_{33}ClCuNO_4P$)	685.64	64.00 (64.82)	4.11 (4.85)	1.925 (2.04)	182	Green	63.2
OVAAACo ($C_{37}H_{33}ClCoNO_4P$)	681.03	65.348 (65.26)	4.763 (4.88)	3.040 (2.06)	173	Deep green	71.08
OVAAANi ($C_{37}H_{33}ClNiNO_4P$)	680.79	60.604 (65.28)	4.718 (4.89)	2.420 (2.06)	129	Yellow	70.43

FT-IR Spectra of the Schiff base Ligand

FTIR (Fig.16) Spectra of the Schiff base ligand shows the carbonyl and azomethine peaks at 1685 cm^{-1} and 1616 cm^{-1}. In the experimental IR spectra, the C-N band was observed at 1171 cm^{-1}. Experimental infrared spectra observed the C-O of methoxy group (-OCH_3) and C-O of C-OH at 1242 cm^{-1} and 1103 cm^{-1} respectively. The experimental IR spectra show the –OH groups at 3432 (o-Vanillin) and 2950 cm^{-1}(2- amino phenol). The weak and broad peak at 2950 cm^{-1} has been assigned to intramolecular hydrogen bonding between the phenolic –OH and the enolizable carbonyl group of the Schiff base [52].

FT-IR Spectra of the Schiff base Copper complex

The FTIR spectra (Fig.17) of the Schiff base Copper complex show azomethine group at 1581 cm^{-1} and the carbonyl peak at 1670 cm^{-1}. The decrease in the absorption values for azomethine and carbonyl groups compared to the Schiff base ligand may be attributed to their strong coordination with the central metal atom. The covalent metal-oxygen bond appeared in experimental infrared at 499cm^{-1} and the C-N bond of 2-aminophenol appeared in experimental spectra at 1155cm^{-1}. The experimental infrared spectra of the Schiff base Copper complex observed aromatic C-O and aliphatic C-O at 1116 cm^{-1} and 1242 cm^{-1}. The –OH of the o-Vanillin ring observed the peak at 3433 cm^{-1} in the experimental infrared spectra [53]. In addition to the above peaks, there is the existence of peak at 1433cm^{-1} in the experimental and theoretical spectra authenticates the coordination of triphenylphosphine to the central metal atom (M-P bond) [54] .

FT-IR Spectra of the Schiff base Cobalt complex

The experimental FT-IR spectra (Fig.18) of the Cobalt complex show azomethine group at 1590 cm^{-1} and the carbonyl peak appeared at 1668 cm^{-1}. The decrease in the absorption values for azomethine and carbonyl groups compared to the Schiff base ligand may be attributed to their strong coordination with the central metal atom. The appearance of a peakat 1434 cm^{-1} may be attributed to forming a metal-phosphorous bond [54]. The experimental infrared spectra of the Schiff base Cobalt complex show the covalent metal-oxygen bond appeared at 451 cm^{-1}. The C-N bond appeared in the spectra at 1150 cm^{-1}. The aliphatic C-O and aromatic C-O bond appeared in experimental infrared at 1110 and 1240 cm^{-1}. The phenolic –OH of the o-Vanillin ring appeared at the peak at 3431 cm^{-1} in the experimental infrared spectra. [53].

FT-IR Spectra of the Schiff base Nickel complex

The azomethine group of the Schiff base Nickel complex appeared at 1595 cm^{-1} and the C=O peak at 1668 cm^{-1}. The decrease in the absorption values for azomethine and carbonyl groups compared to the Schiff base ligand may be attributed to their strong coordination with the central metal atom. The existence of peak at 1434 cm^{-1} in the experimental IR confirms the coordination of the central nickel with the phosphorous of the triphenylphosphine ligand [54]. The covalent M-O bond observed at 496 cm^{-1} in experimental IR spectra. The experimental spectra observed the peak of C-N at 1152 cm^{-1}. In experimental infrared spectra, the aliphatic C-O and aromatic C-O of the Schiff base nickel complex were obtained at 1112 and 1234 cm^{-1}. The phenolic –OH of o-Vanillin appeared at 3366 cm^{-1} in the experimental IR spectra [53].(Fig.19)

NMR Spectral Study

Experimental ^{1}H and ^{13}C NMR Spectra of the Schiff base Ligand

Experimental NMR chemical shift values of aromatic protons were observed at 6.87 to 7.37 ppm. The NMR spectra observed the methyl protons of the Schiff base ligand at 2.46 (C-CH_3), and at 5.77 ppm (O-CH_3). The phenolic –OH appears at 11.81 ppm and 12.54 ppm in the experimental spectra. Experimental ^{1}H NMR spectra of the Schiff base are shown in (Fig.20)

The chemical shifts at 163.25 ppm (C=O) and 163.14 ppm (C=N) indicates carbonyl and azomethine groups of the Schiff base ligand in experimental ^{13}C NMR spectra (Fig.24) The experimental ^{13}C NMR spectra observed the aromatic carbon chemical shift value at 115.13 to 128.85 ppm. The simulated ^{13}C NMR spectra observed the aromatic carbon at 115.41 to 128.00 ppm. The chemical shift values for the methyl carbon appeared at 19.60 ppm (C-CH_3) and 56.20 ppm (O-CH_3) in the experimental ^{13}C NMR [55].

Experimental ^{1}H and ^{13}C NMR Spectra of the Schiff base Copper complex

The experimental ^{1}H NMR spectra of the Schiff base Copper complex shows aromatic proton chemical shift from 7.05 to 7.44 ppm . An experimental proton nuclear magnetic spectrum shows the chemical shift value of methyl protons at 2.17 ppm (C-CH_3), 5.93 ppm (O-CH_3). The phenolic –OH of experimental spectra shows at 11.87 ppm. The disappearance of the –OH peak at 12.54 confirms its deprotonation and bonding with the central metal atom copper. Experimental proton NMR spectra are shown in (Fig.21)

The experimental ^{13}CNMR spectra of the synthesized Schiff base Copper complex show carbonyl and azomethine peaks at 158.60 (C=O), 158.30 ppm (C=N). Experimental ^{13}C NMR spectra (Fig.25) observed the chemical shift value from 125.41 to 129.48 ppm indicates the aromatic carbons. The methyl carbon chemical shift values appear at 18.73 ppm (C-CH_3) and 56.20 ppm (O-CH_3) in the experimental ^{13}C NMR[55].

Experimental ^{1}H and ^{13}C NMR Spectra of the Schiff base Cobalt complex

The recorded ^{1}H NMR spectra of the Schiff base Cobalt complex show the aromatic proton chemical shift from 6.91 to 7.67 ppm. An experimental ^{1}H NMR spectrum(Fig.22) shows the chemical shift value of methyl protons at 2.17 ppm (C-CH_3) and 5.47 ppm (O-CH_3). The phenolic –OH of the o-Vanillin appeared at 11.13 ppm and the disappearance of the –OH peak at 12.54 confirms its deprotonation and bonding with the central metal atom cobalt

The experimental NMR spectra of the Schiff base Cobalt complex show the carbonyl and azomethine carbon at 158.60 (C=O), 158.30 ppm (C=N). The experimental ^{13}C NMR spectra (Fig.26) observed the chemical shift value from 125.41 to 129.48 ppm indicates the aromatic carbons. The chemical shift values of methyl carbon appear at 18.73 ppm (C-CH_3) and 55.47ppm (O-CH_3) in the experimental ^{13}C NMR [55].

Experimental ^{1}H and ^{13}C NMR Spectra of Schiff base Nickel complex

The experimental ^{1}H NMR spectra of the Schiff base Nickel complex show the aromatic proton chemical shift from 6.73-7.66 ppm. An experimental proton NMR spectrum (Fig.23)

shows the chemical shift value of methyl proton peaks at 2.06 ppm (C-CH_3), 5.73 ppm (O-CH_3). The phenolic –OH of experimental spectra shows the prak 11.17 ppm. The disappearance of the –OH group at 12.54 confirms its deprotonation and bonding with the central metal atom Nickel.

The experimental ^{13}C NMR spectra of the Schiff base Nickel complex show the azomethine and carbonyl carbon appeared at 158.00 (C=N), 158.37 ppm (C=O). Experimental ^{13}C NMR spectra (Fig.27) observed the chemical shift value from 129.49 ppm to 137.30 ppm indicates the aromatic carbons. The chemical shift values of methyl carbons have appeared at 18.74 ppm (C-CH_3) and 55.17 ppm (O-CH_3) in the experimental ^{13}C NMR. [55].

ESR Spectra

In the electron spin resonance spectra (ESR) of the Cobalt and Nickel complexes, the g factor value shows that $g_{\parallel}$ is greater than $g_{\perp}$ (Cobalt complex: $g_{\perp}$ = 2.006744, $g_{\parallel}$ = 2.006763, Nickel complex: $g_{\perp}$ = 7.778975, $g_{\parallel}$ = 7.779655). Usually, $g_{\parallel} > g_{\perp}$ indicates the trigonal bipyramidal structure Fig.(28, 29) [56, 57]. Thus, the above result confirms the trigonal bipyramidalgeometry for the Cobalt and Nickel complexes.

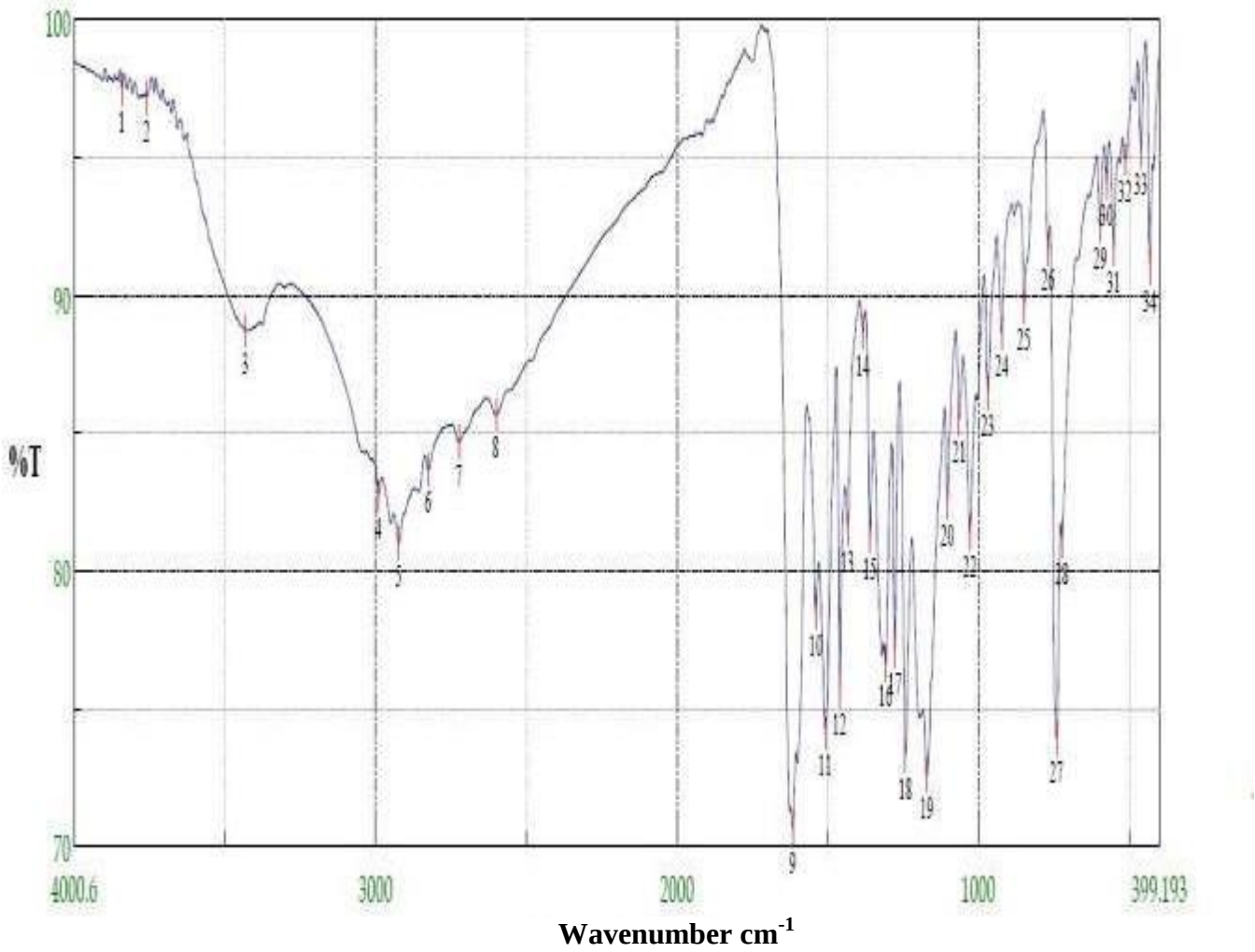


Fig.16- FTIR Spectrum of the Schiff base Ligand

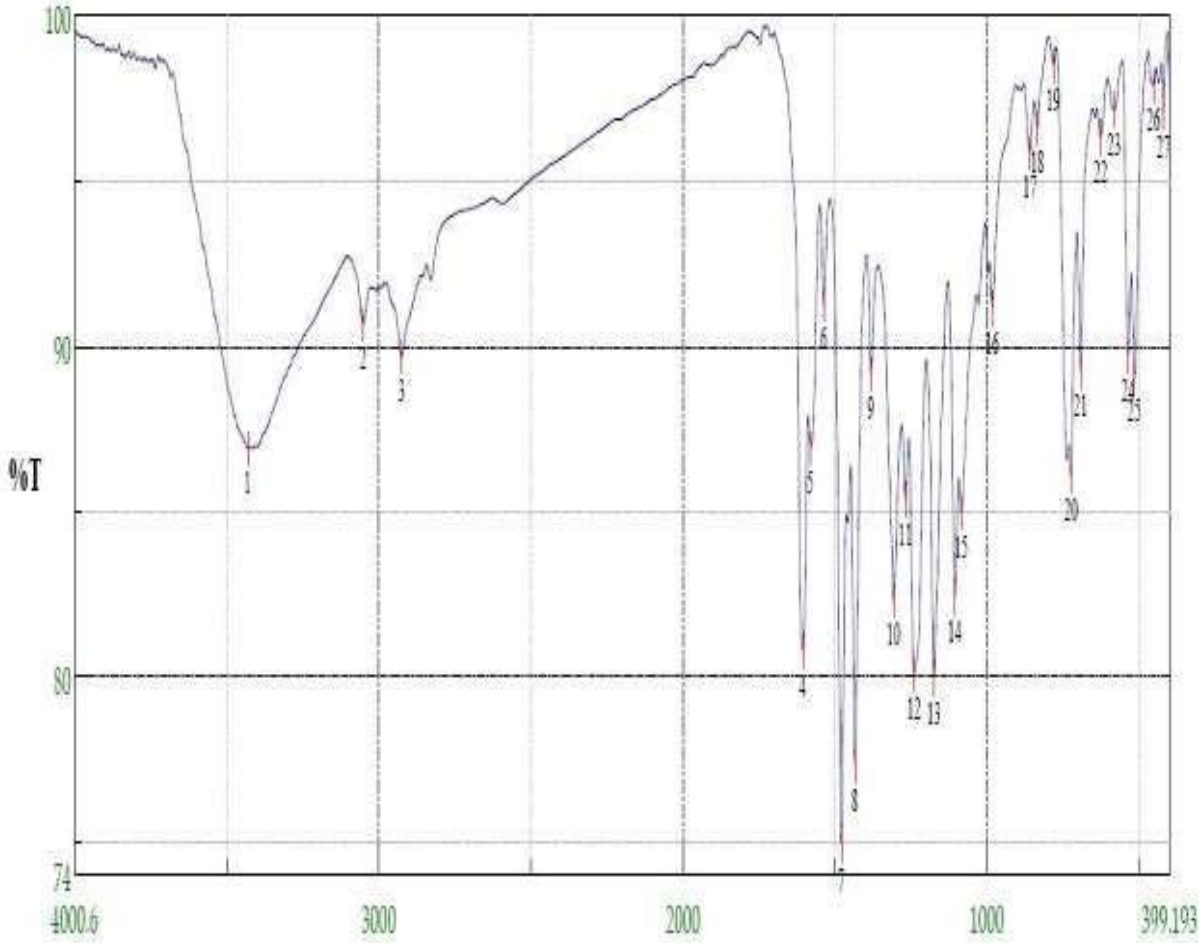


Fig.17- FTIR Spectrum of the Schiff base Cu (II) complex

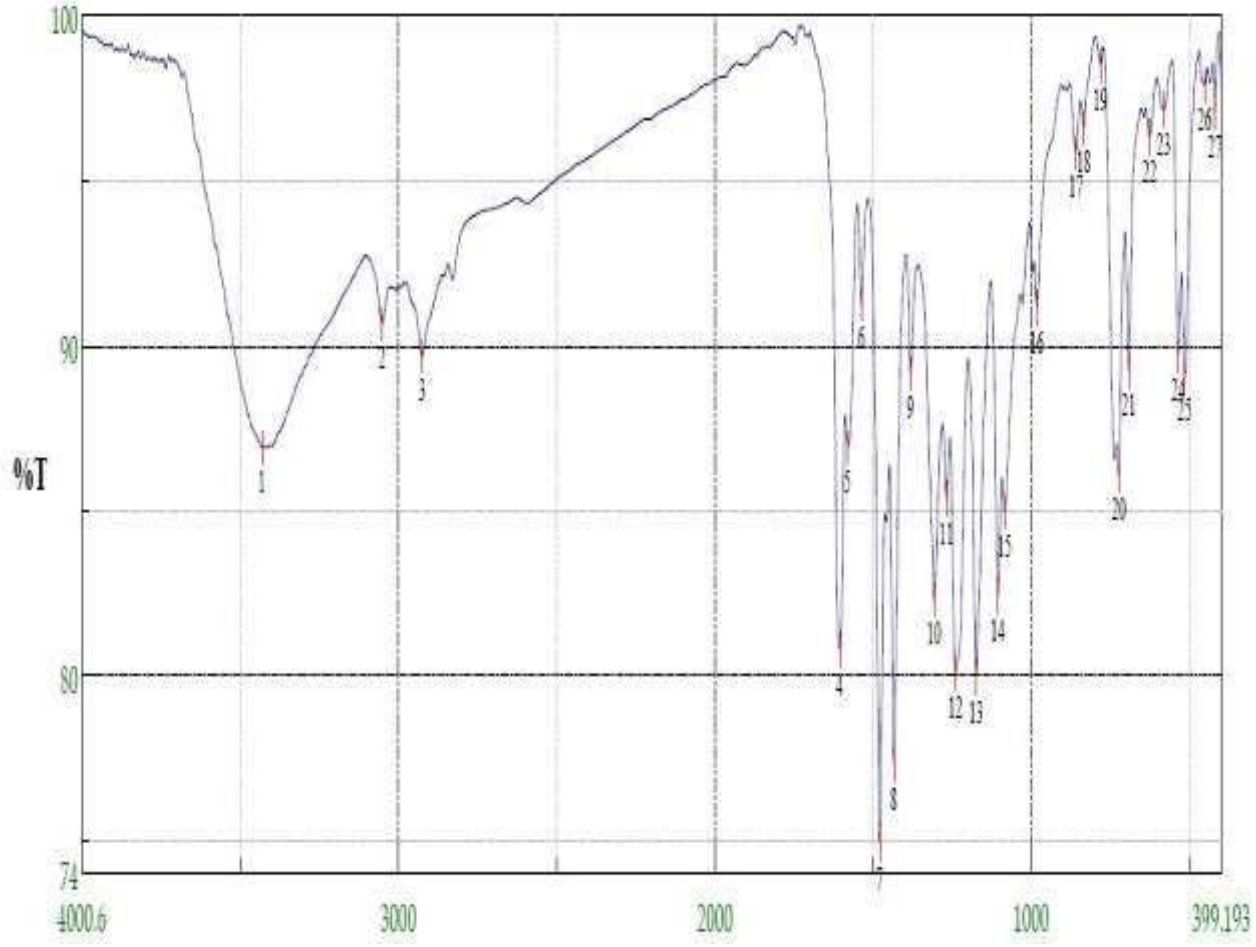


Fig.18- FTIR Spectrum of the Schiff base Co (II) complex

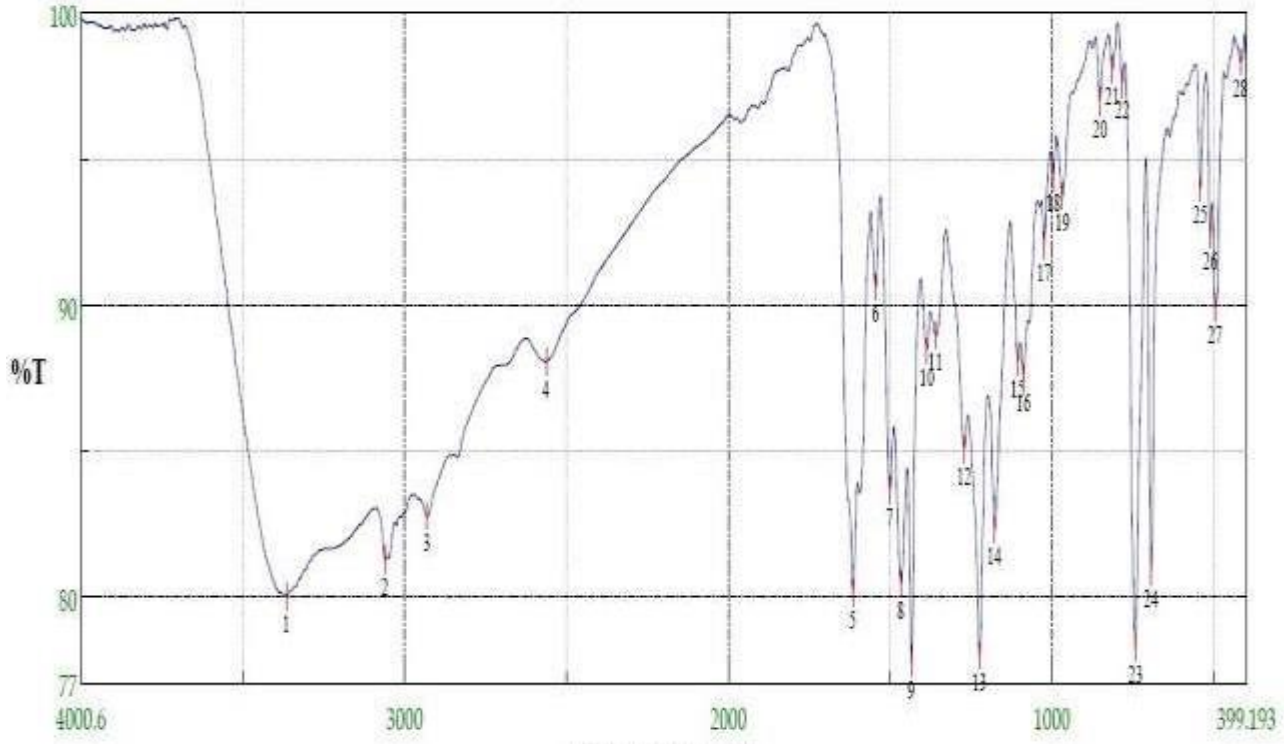


Fig.19- FTIR Spectrum of the Schiff base Ni (II) complex

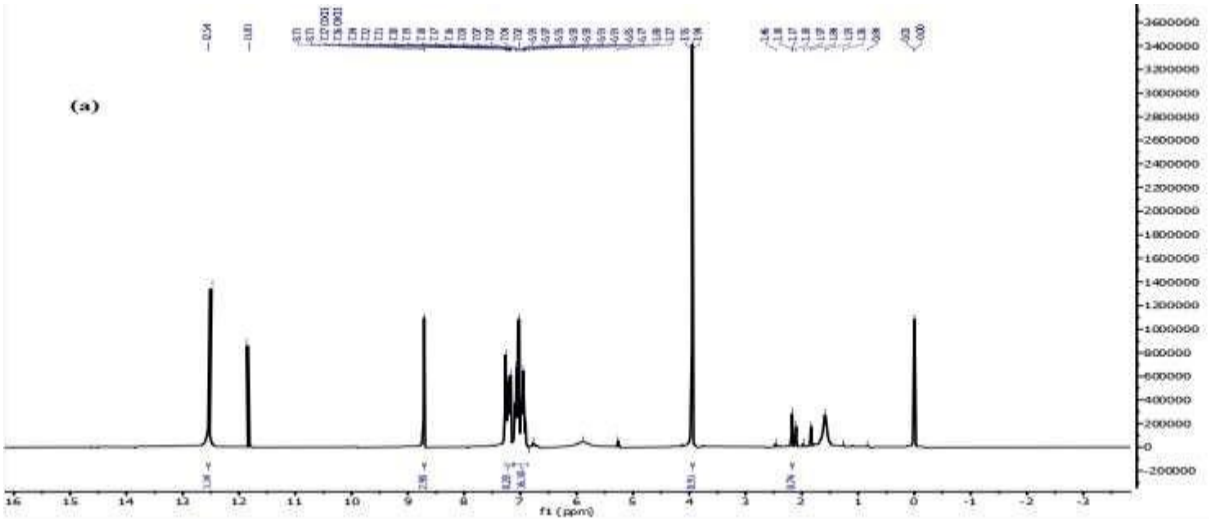


Fig.20- ^{1}H NMR spectra of the Schiff base ligand

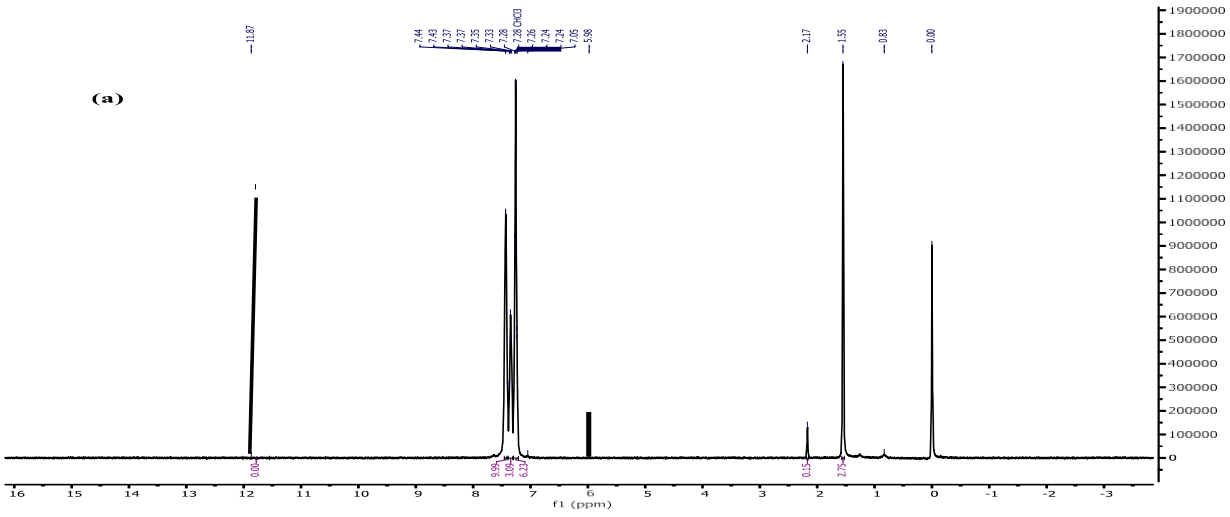


Fig.21- ^{1}H NMR spectra of the Schiff base Copper complex

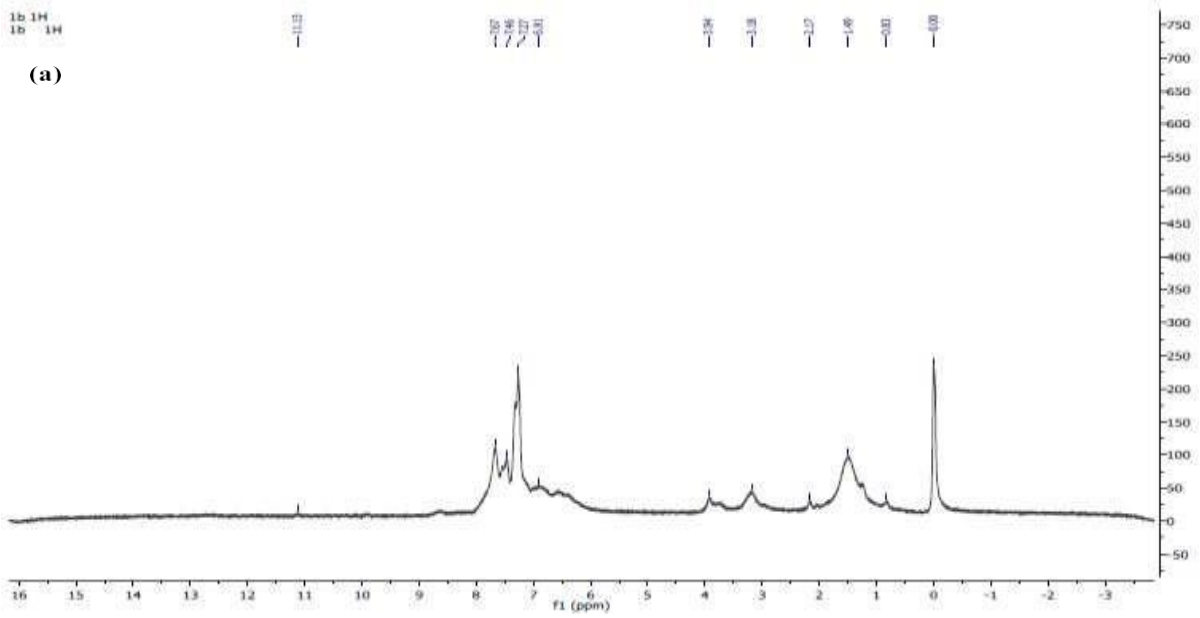


Fig.22- ^{1}H NMR spectra of the Schiff base Cobalt complex

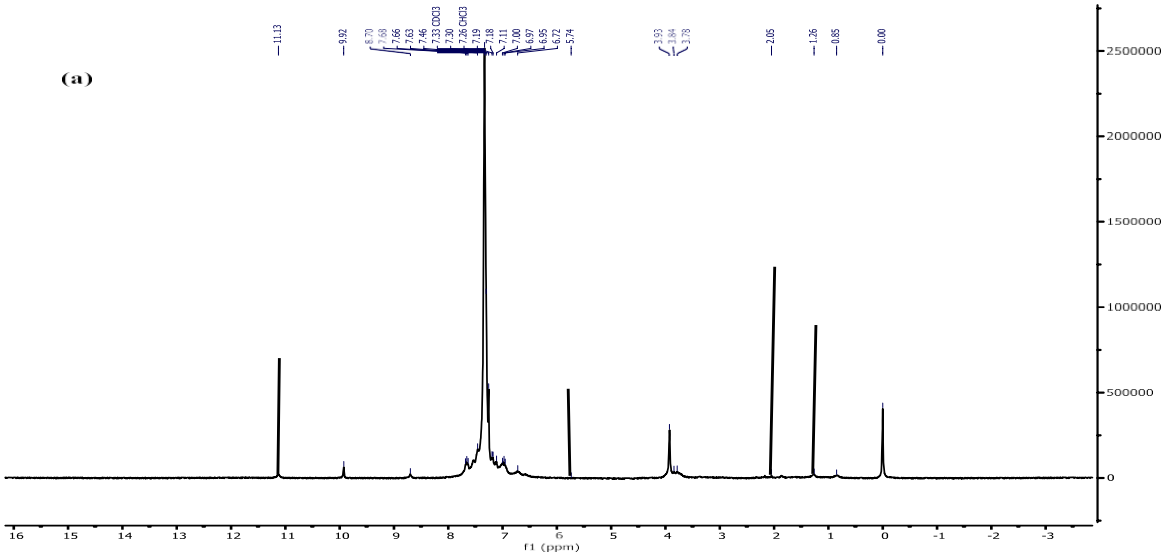


Fig.23- ^{1}H NMR spectra of the Schiff base Nickel complex

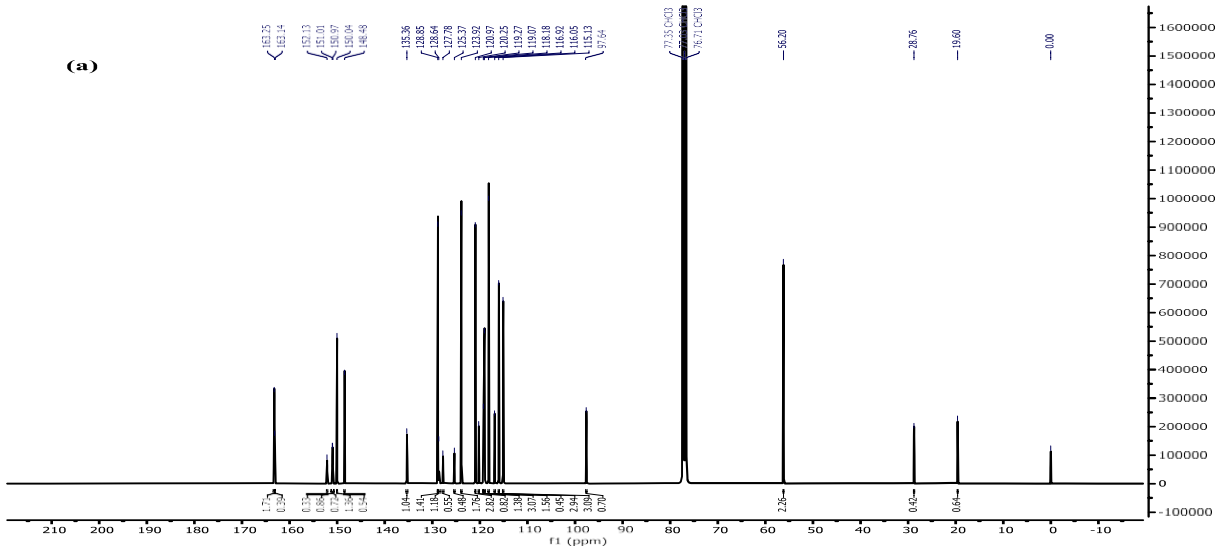


Fig.24- ^{13}C NMR of the Synthesized Schiff base ligand

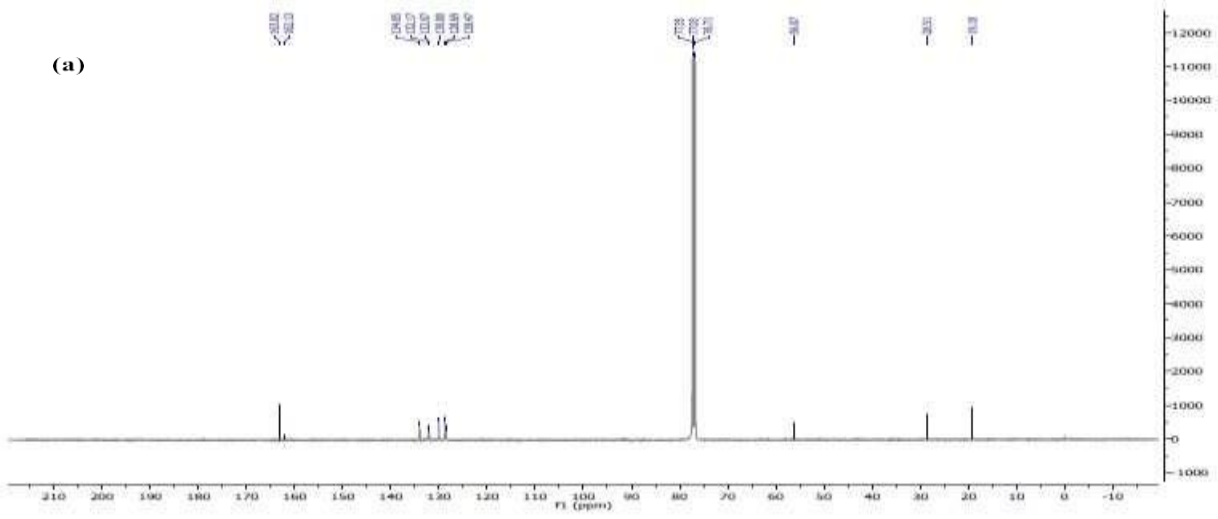


Fig.25- ^{13}C NMR spectra of the Schiff base Copper complex

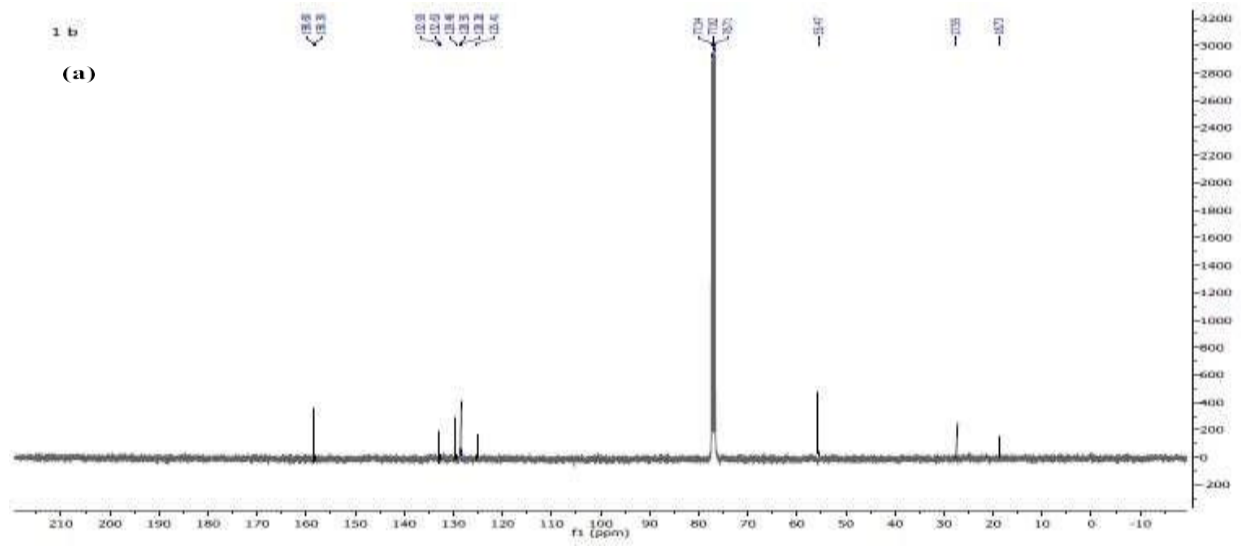


Fig.26- ^{13}C NMR spectra of the Schiff base Cobalt complex

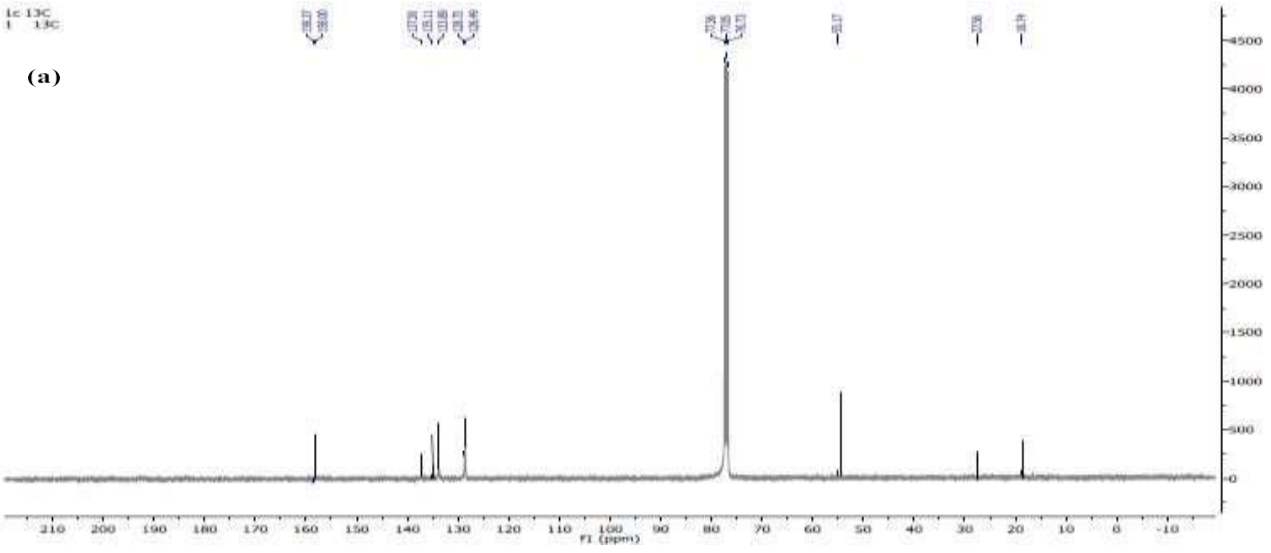


Fig.27- ^{13}C NMR spectra of the Schiff base Nickel complex

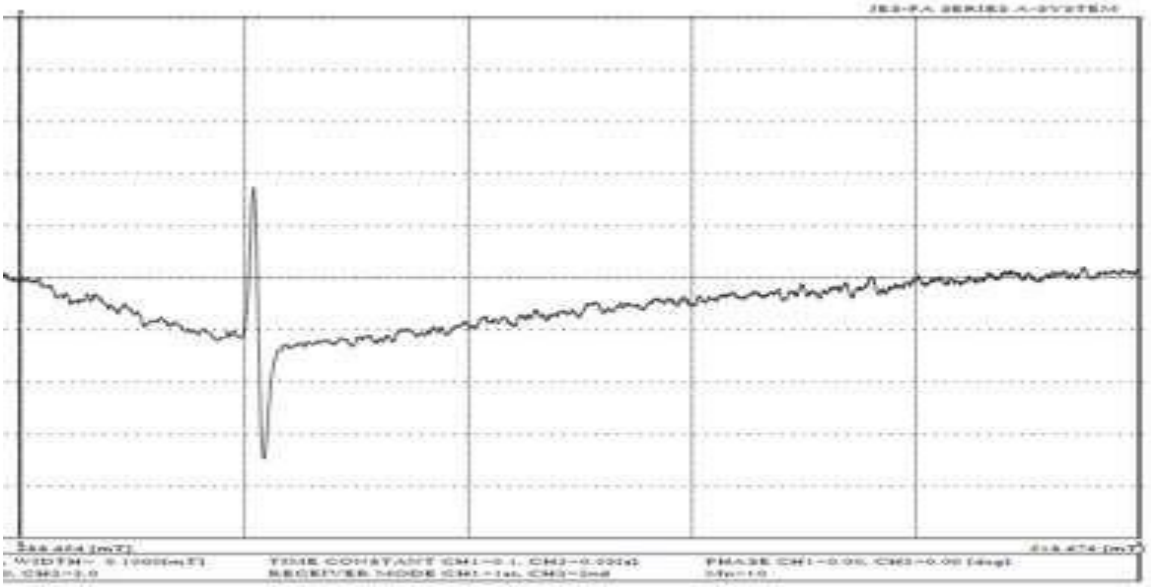


Fig.28- ESR spectra of the Schiff base Cobalt complex

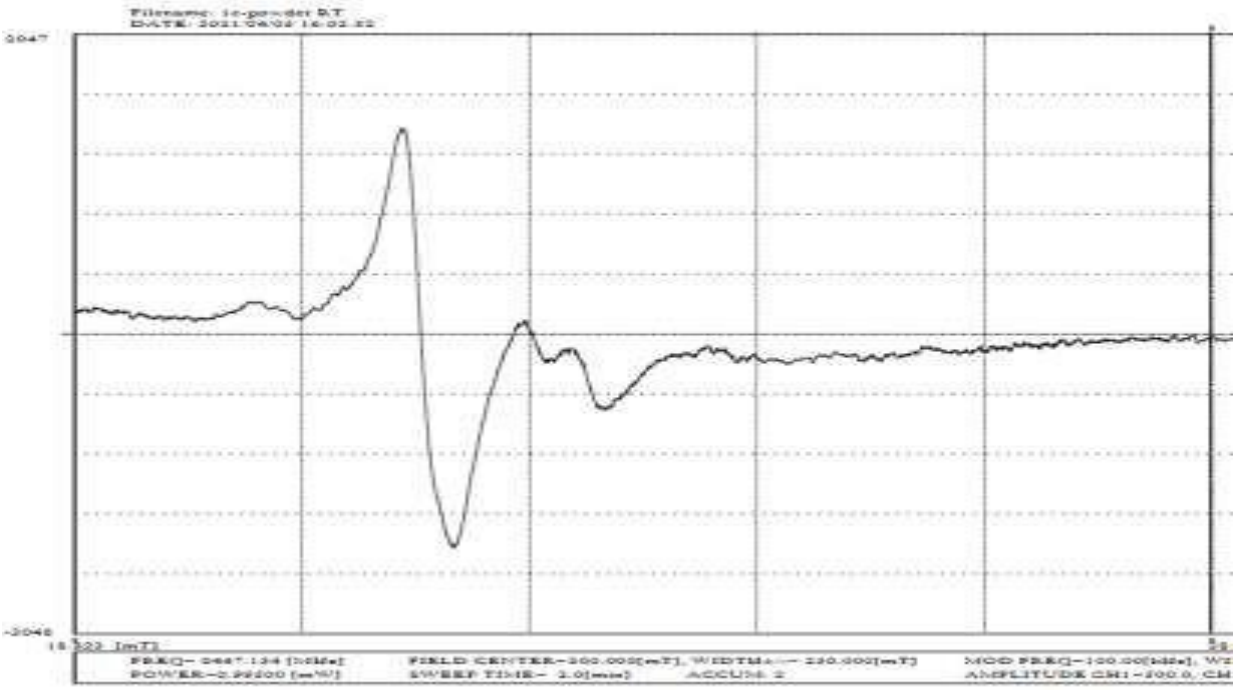
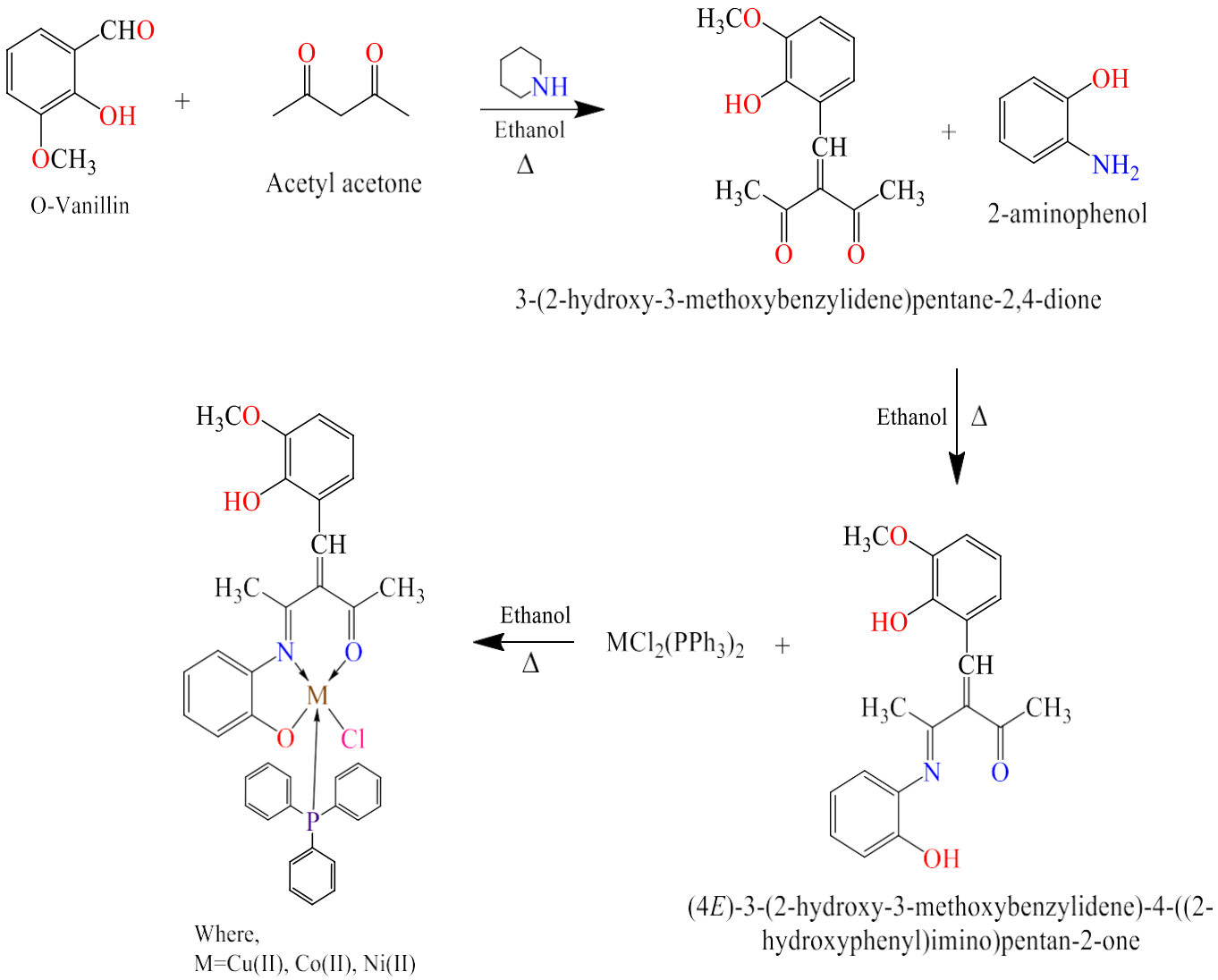


Fig.29- ESR spectra of the Schiff base Nickel complex

Based on the spectral characterization, the following scheme 1 and structure can be proposedfor the Schiff base and their Copper, Cobalt and Nickel Complexes

Scheme 1. Syntheses of the Schiff base ligand and its metal complexes



Antifungal Activity

Standard fungal cultures *Aspergillus niger, Aspergillus flavus* and *Aspergillus terreus* were used for antifungal studies. The fungal stock cultures were maintained on potato dextrose agar. The following tables (2, 3,4 and 5) show the comparison of zone of inhibition of the Schiff base ligand and its Copper, Cobalt and Nickel complexes(Fig.30-33) with the solvent (Chloroform) and the standard antifungal drug Flucozanole.

Table 2: Antifungal Activity of Schiff Base Ligand

S. No.	Organisms	10 µL	30 µL	50 µL	Chloroform	Standard
1.	*Aspergillus flavus*	3	4	4	Nil	4
2.	*Aspergillus niger*	2	3	5	Nil	4
3.	*Aspergillus terreus*	2	4	5	Nil	3

Table 3: Antifungal Activity of Schiff Base Copper Complex

S. No.	Organisms	10 µL	30 µL	50 µL	Chloroform	Standard
1.	*Aspergillus flavus*	3	4	6	Nil	4
2.	*Aspergillus niger*	2	2	3	Nil	4
3.	*Aspergillus terreus*	2	2	4	Nil	3

Table 4: Antifungal Activity of Schiff Base Cobalt Complex

S. No.	Organisms	10 µL	30 µL	50 µL	Chloroform	Standard
1.	*Aspergillus flavus*	Nil	2	3	Nil	5
2.	*Aspergillus niger*	2	2	2	Nil	4
3.	*Aspergillus terreus*	1	2	2	Nil	3

Table 5: Antifungal Activity of Schiff Base Nickel Complex

S. No.	Organisms	10 µL	30 µL	50 µL	Chloroform	Standard
1.	*Aspergillus flavus*	Nil	Nil	3	Nil	5
2.	*Aspergillus niger*	2	2	3	Nil	5
3.	*Aspergillus terreus*	1	2	2	Nil	4

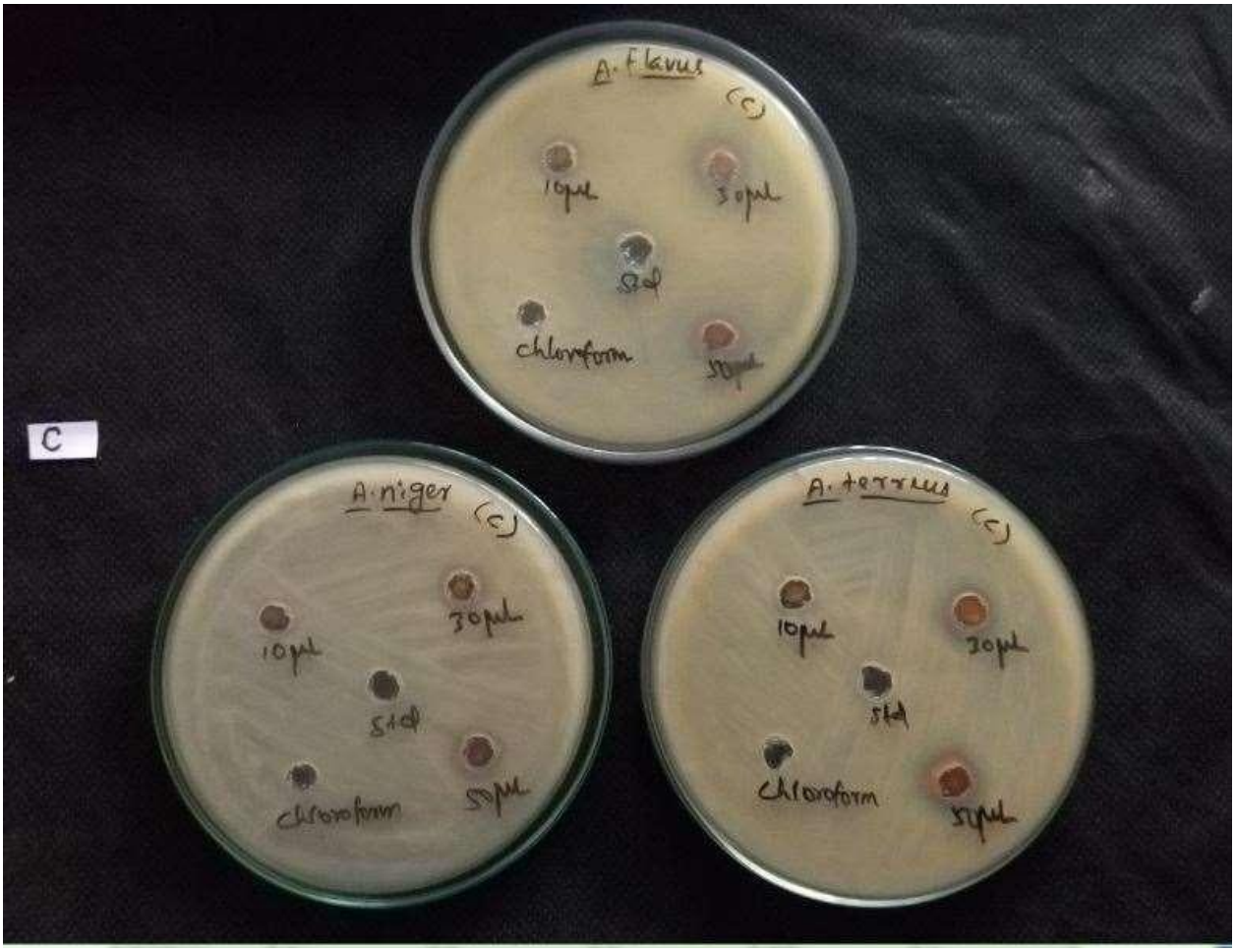


Fig.30- Antifungal Activity of Schiff base Ligand

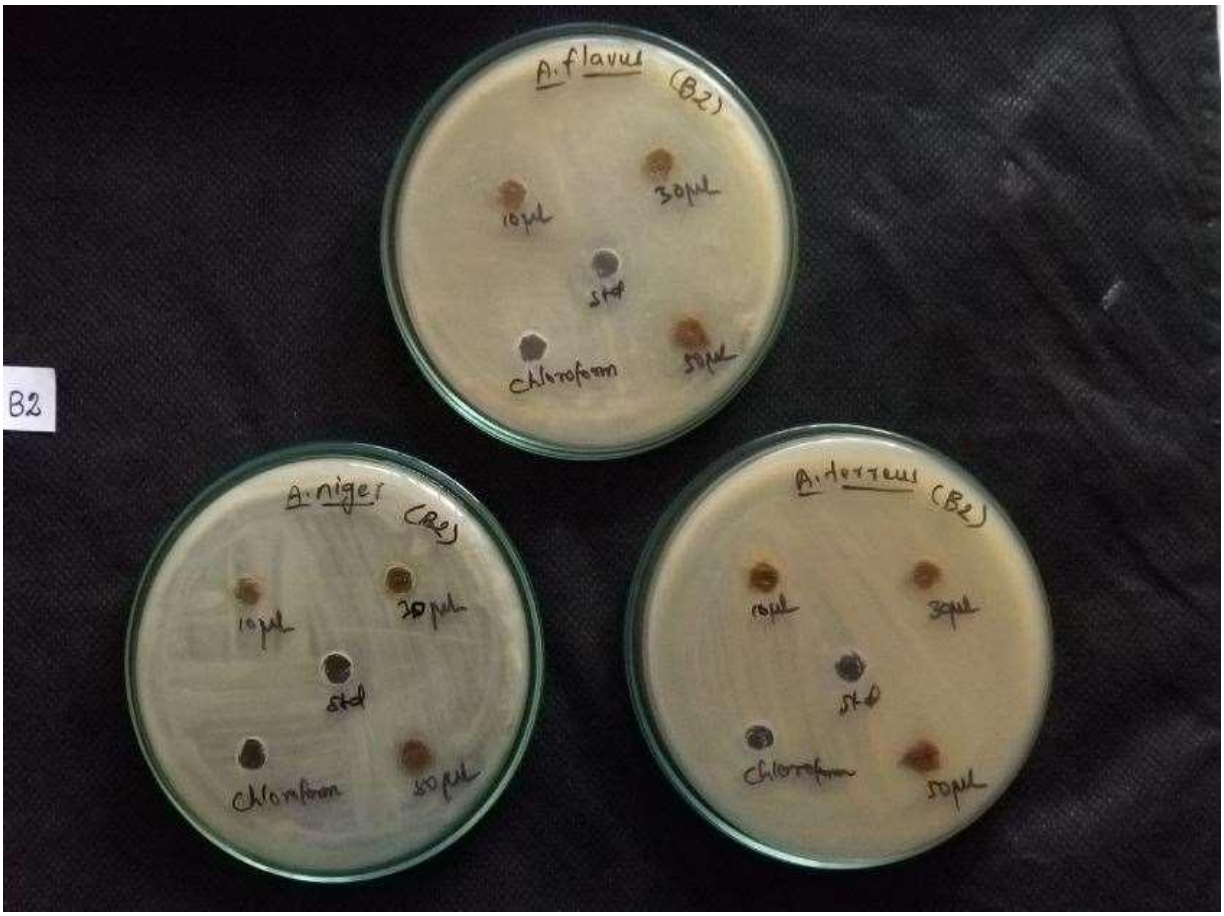


Fig.31- Antifungal Activity of Schiff base Cu(II) complex

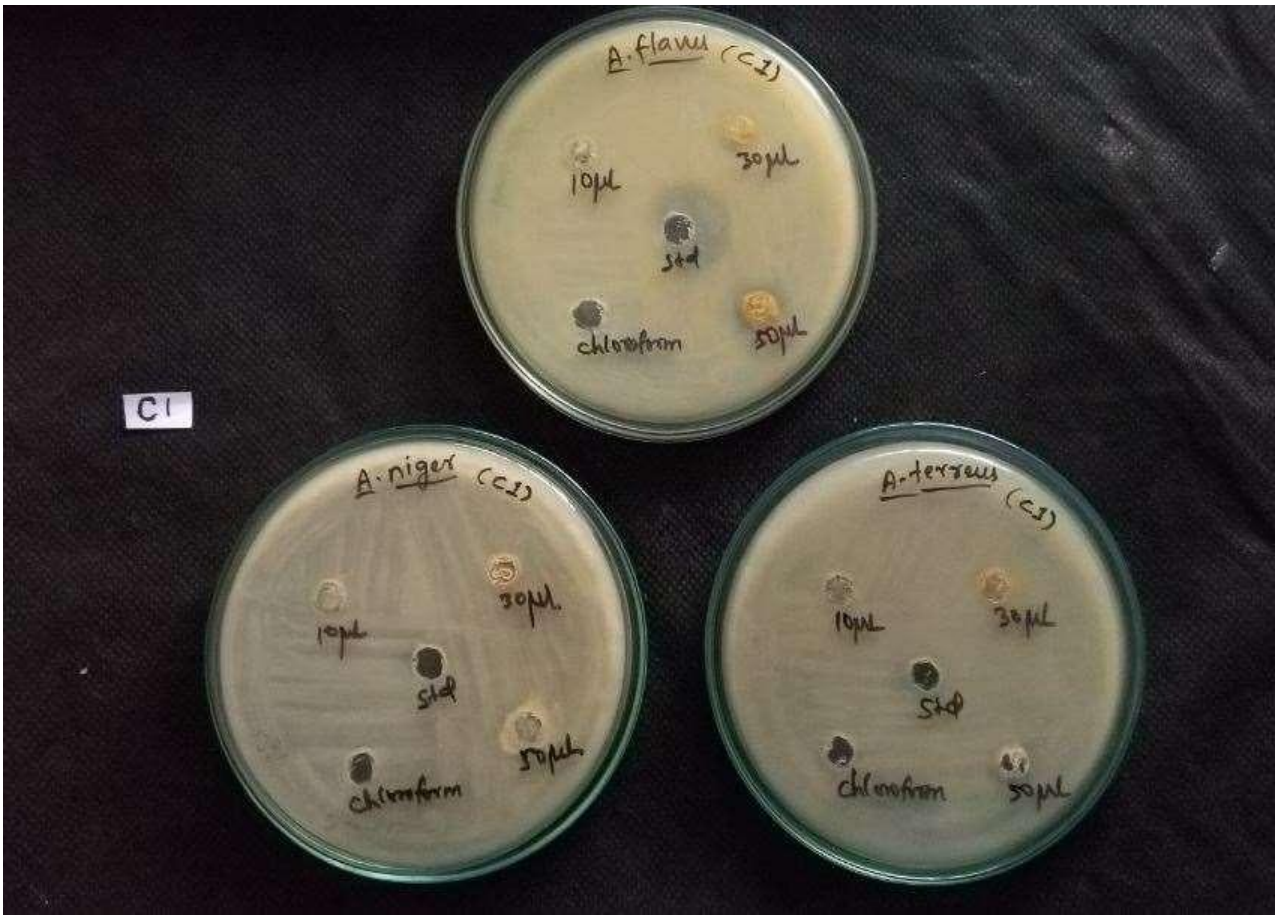


Fig.32- Antifungal Activity of Schiff base Co(II) complex

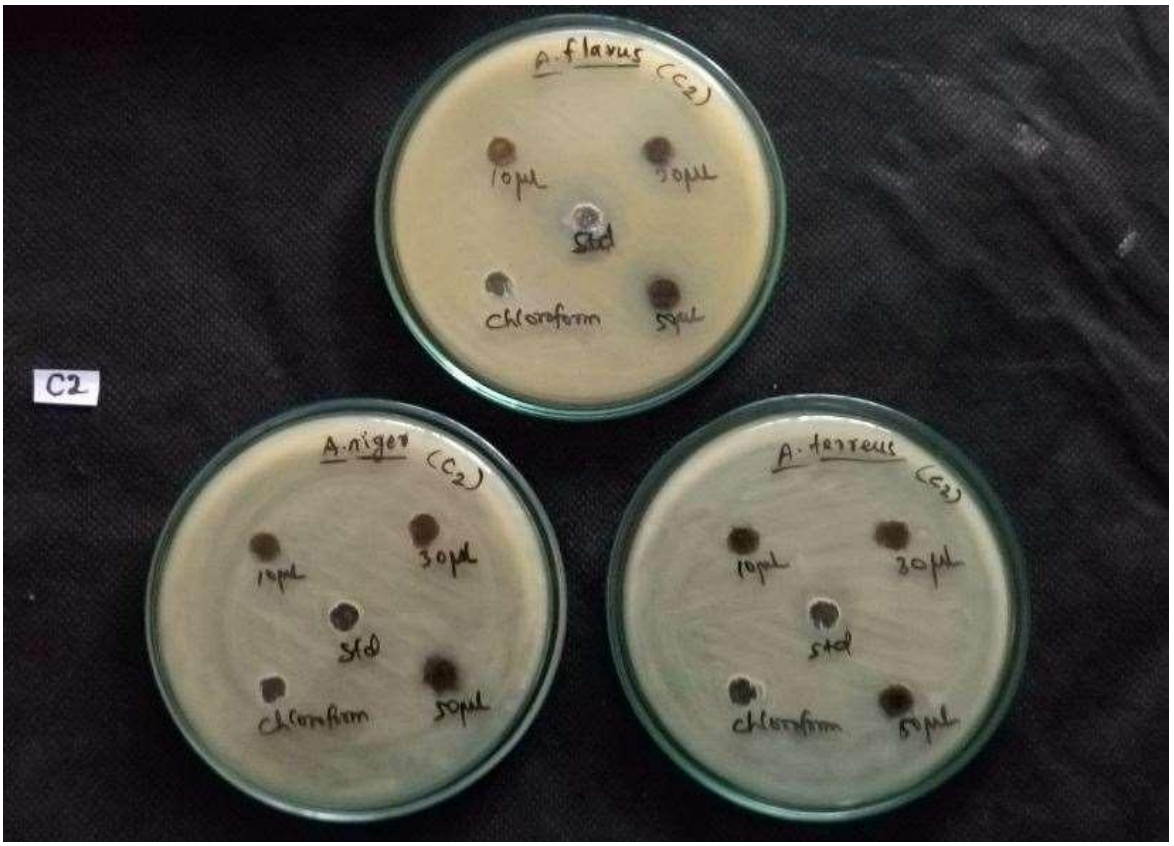


Fig.33- Antifungal Activity of Schiff base Ni(II) comlex

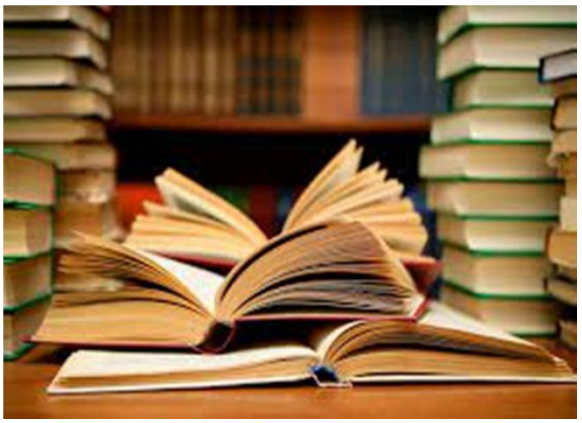
SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

The Schiff base (4E)-3-(2-hydroxy-3-methoxybenzylidene)-4-((2-hydroxyphenyl) imino)pentan-2-one (OVAAA) was synthesized and converted into Cu, Co and Ni complexes on treatment with the metal precursors $[MCl_2(PPh_3)_2]$ (where, M= Cu(II), Co(II) and Ni(II)). The reported Schiff base ligand and its metal complexes are characterized by elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR, and ESR spectroscopy. The electron spin resonance spectrum (ESR) recorded for the Cobalt and Nickel complexes conclude the trigonal bipyramidal structure for Cobalt and Nickel complexes.

The Schiff base compound and its Copper, Cobalt and Nickel complexes were tested for antifungal activity against three representative fungal strains *Aspergillus niger*, *Aspergillus flavus*, and *Aspergillus terrus* at three different concentrations (10, 30, 50µl) by well diffusion method. Fluconazole was used as a reference drug in terms of minimum inhibitory concentration (MIC).

Antifungal Activity of Schiff base ligand against *Aspergillus niger, Aspergillus flavus and Aspergillus terreus* more active on comparison with the standard drug Fluconazole. Antifungal activity of the Cu (II) complex against *Aspergillus flavus* is more active than Fluconazole and have comparable activity against the other fungi. Cobalt and Nickel complexes show lesser activity when compare drug flucozanole.



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Evaluation of Anticancer Activity of Schiff bases Derived from Pyridine and their Metal Complexes (A Review)

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ABSTRACT

Cancer is a deadly disease; many treatment strategies are available to cure/treat cancer. After the metal-based anticancer drug (Cisplatin), metal complexes play a vital role in pharmaceutical science. We aimed to analyze the anticancer activity of pyridine Schiff base complexes. This review article searched the anticancer studies of pyridine Schiff base metal complexes from 2015 to 2021. Information was gathered from the selected studies to analyze and highlight the importance of anticancer agents. A total of sixty six full-length articles were collected and evaluated. On the critical assessment, we found that compared to Schiff base ligand, the metal complexes exhibited excellent activity towards various cancer cell lines (including MCF-7, HeLa, HCT-116, Hepa-2).We identified more complexes that exhibited promising activity against various cell lines and revealed IC_{50} values equal to or even lower than the reference drug used.

Keywords: Pyridine, Metal complexes, Anti cancer activity, Cell viability, IC_{50}.

INTRODUCTION

Cancer is a fatal disease characterized by abnormal cell development in a specific section of the body and can destroy normal body tissues. The formed mass of tissues is called a tumor. These tumors can be malignant or benign. This benign tumor is not life threatening, while a malignant tumor is cancerous[1]. According to the Indian Council of Medical Research (ICMR) data from 2018, 2.25 million Indians are affected by cancer. Every year, there are 11, 57, 294 new cases and 7, 84, 821 deaths. In India, 9.81% of males and 9.42% of females are at the risk of developing cancer before 75 years.

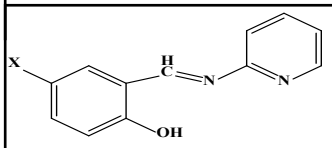
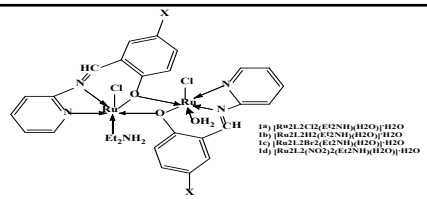
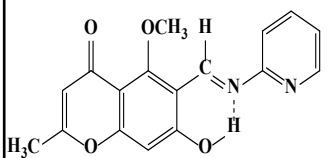
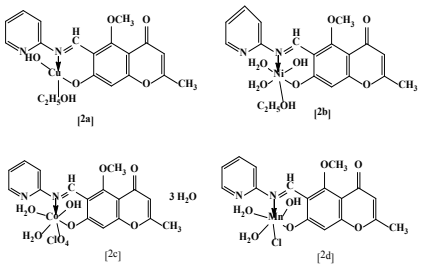
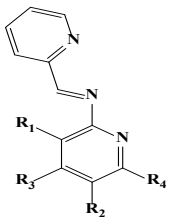
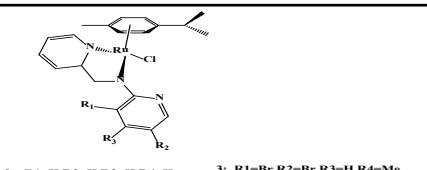
According to the National center for health statistics (2021), 18, 98, 160 new cancer cases and 6, 08, 570 cancer deaths occur in the united states[2]. Early diagnosis and immediate medical treatment are of utmost essential in cancer. The existing treatments such as radiotherapy, surgery, endocrine therapy has serious obstacles, with multidrug resistance (MDR) being the major challenge[3,4]. Scientists are curious to develop new effective anticancer

drugs to treat life-threatening cancer without acute side effects. Schiff base metal complexes are active in the medicinal and pharmaceutical fields because of their anticancer, antibacterial, anti-malarial, antifungal, antiviral, anti-inflammatory, anti-tuberculosis, insecticidal, anti-HIV activities. Schiff bases (R1R2C=NR3) (R-represent alkyl or aryl substituent) are an organic compound that contains the imine group (-C=N-) or azomethine (-CH=N-) [5]. Schiff base ligands are defined as "Privileged ligands" due to their affordability, easiness to synthesis, exhibiting various biological activities, and ability to form complexes with almost all metals such as transition metals, lanthanides, actinides, and more[1]. In this review, we mainly focused on Schiff base metal complexes containing pyridine moiety in their structure. Pyridine is a heterocyclic moiety containing a six-membered ring with one nitrogen atom. The presence of pyridine ring in Schiff base metal complex had a considerable interest in the medicinal field due to their structural modification property to target a particular disease by achieving the desired molecular structure. Although numerous reviews on Schiff bases and their metal complexes have been published, there is no systematic assessment of the anticancer activity of pyridine-based Schiff bases and their metal complexes in the literature[1,5-8]. The excellent therapeutic capabilities of Schiff base and pyridine drew the attention of scientists. In the coming years, we anticipate that this review paper will serve as a valuable resource for designing and synthesizing benign anticancer medicines based on pyridine-based Schiff bases and their metal complexes.

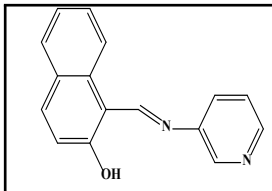
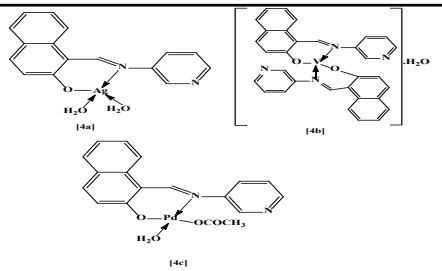
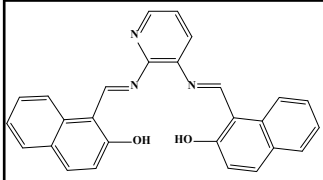
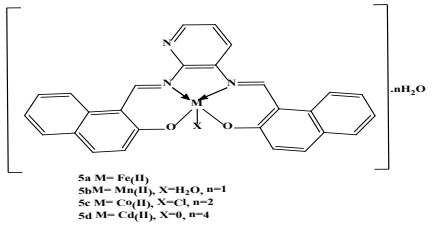
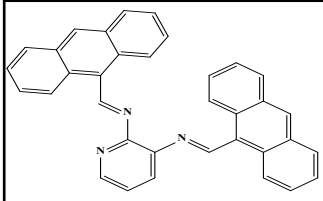
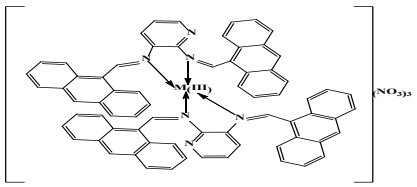
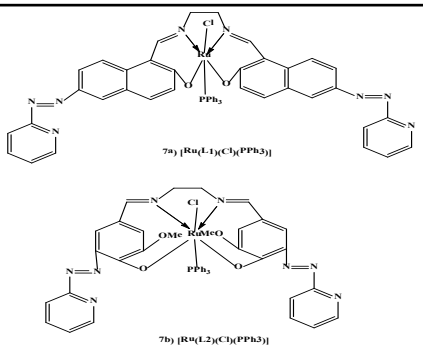
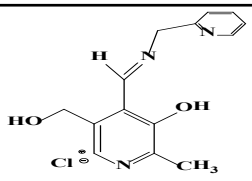
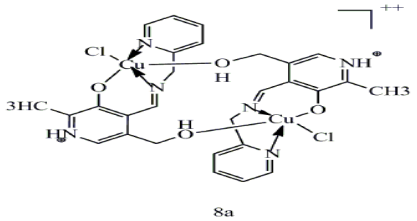
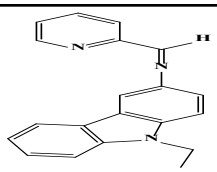
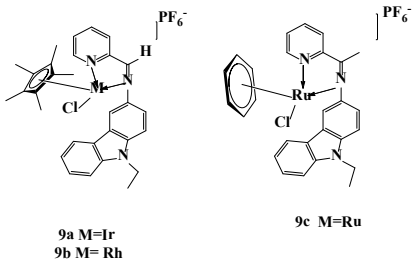
A systematic review of databases related to the anticancer activity of pyridine Schiff base metal complexes was conducted, with additional searches on Google scholar and Sci-Finder using a combination of subject headings and keywords: Schiff bases, pyridine, Schiff base metal complexes, Anticancer activity.

A total of sixty six full-length articles on the subject were examined, the results were summarized, and the activity against different cell types was given as IC_{50} values or inhibition percentages shown in Table 1.

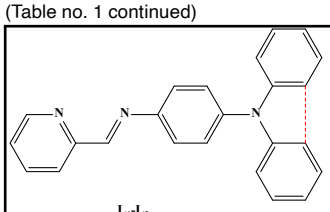
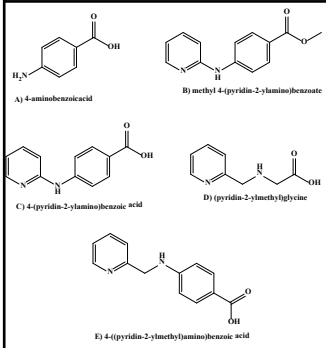
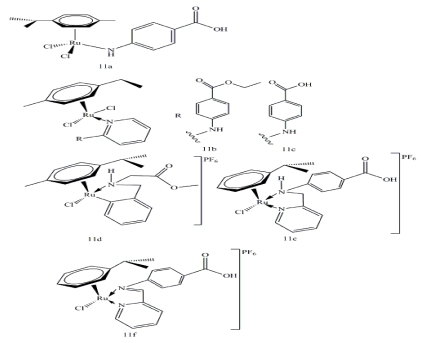
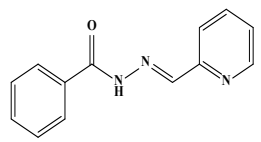
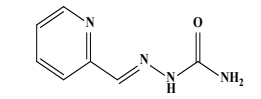
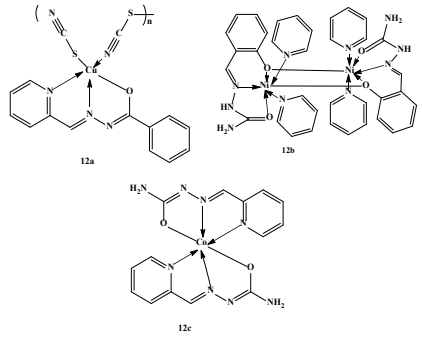
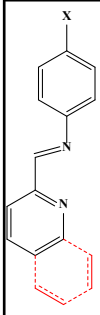
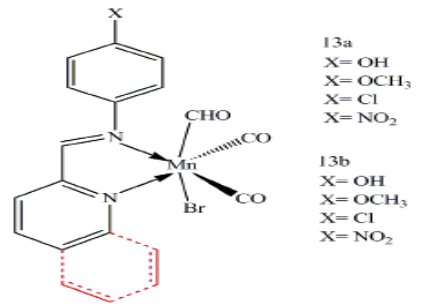
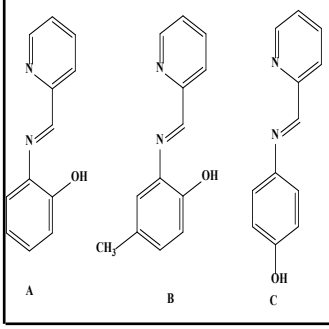
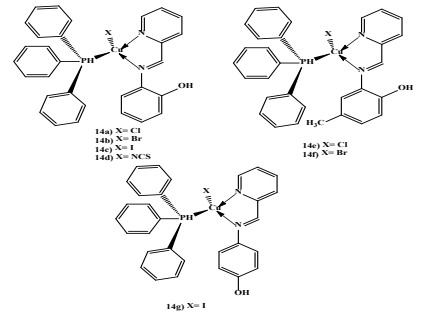
Table 1: Cytotoxic activity of metal complexes

Ligand	Metal Atom	Metal complex	Cytotoxic activity[IC_{50} (μM)]
 N-(2-Pyridyl)-5-X-salicylideneimine X= H, Cl, Br, NO2	Ru(II)	 1a) [Ru2L2Cl2(Et2NH)(H2O)]·H2O 1b) [Ru2L2H2(Et2NH)(H2O)]·H2O 1c) [Ru2L2Br2(Et2NH)(H2O)]·H2O 1d) [Ru2L2(NO2)2(Et2NH)(H2O)]·H2O	HeLa :1b (1.16±0.48μM) SW620 : 1b(1.99±0.56μM) A549: 1b(0.68±0.88μM) MCF-7: 1b(4.09±0.78μM) WI-38: 1b(2.51±98.88μM)
	Cu(II) Co(II) Mn(II) Ni(II)	 [2a] [2b] [2c] [2d]	Inhibition %: Mn-L: HeLa-FAS(80%) HeLa(53%) Huh-7(43%) HepG2(20%)
	Ru(II)	 3a. R1=H,R2=H,R3=H,R4=H 3b. R1=Br,R2=Me,R3=H,R4=H 3c. R1=Br,R2=Br,R3=H,R4=H 3d. R1=H,R2=Br,R3=H,R4=H 3e. R1=Me,R2=H,R3=H,R4=H 3f. R1=H,R2=H,R3=,MeR4=H 3g. R1=OH,R2=H,R3=H,R4=H 3h. R1=H,R2=Me,R3=H,R4=H 3i. R1=H,R2=Cl,R3=H,R4=H 3j. R1=Br,R2=Br,R3=H,R4=Me 3k. R1=Cl,R2=Cl,R3=H,R4=H 3l. R1=H,R2=I,R3=H,R4=H 3m. R1=NO2,R2=Br,R3=Me,R4=H 3n. R1=H,R2=Br,R3=Me,R4=H 3o. R1=NO2,R2=NO2,R3=H,R4=H 3p. R1=H,R2=NO2,R3=H,R4=H 3q. R1=NO2,R2=Br,R3=H,R4=H 3r. R1=H,R2=h,R3=H,R4=Me	MCF-7:3o(07.76±0.88(μM)[2]) HeLa:3o(07.10±1.28(μM)[2])

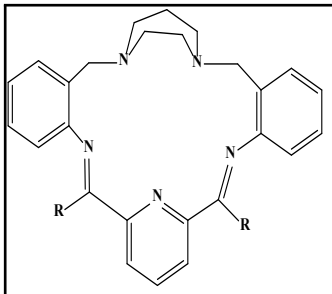
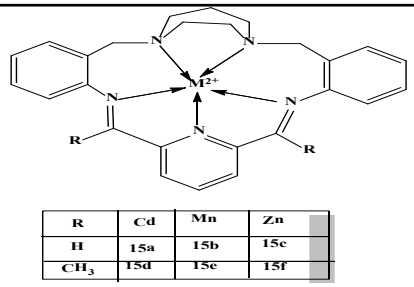
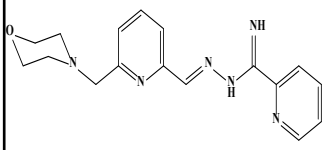
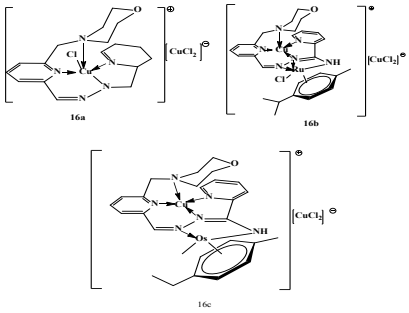
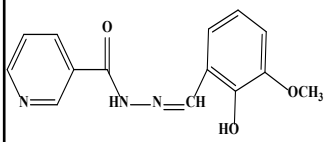
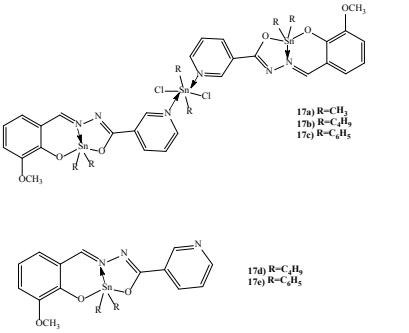
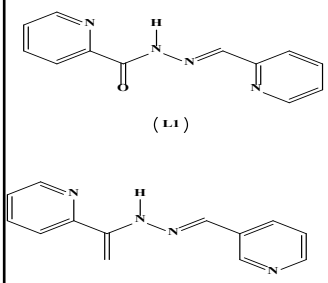
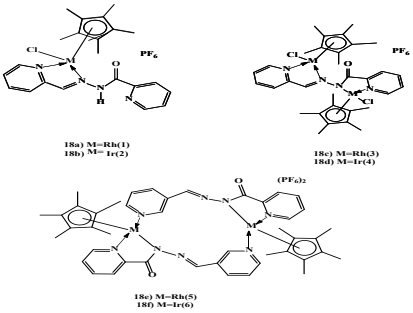
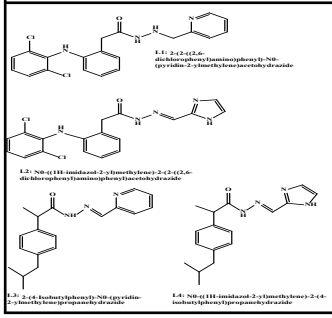
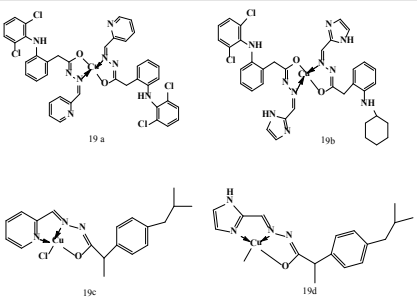
(Table no. 1 continued)

 [1(pyridine-3-yl-iminomethyl) naphthalene-2-ol] (HNAP)	Ag(I) Pd(II) VO(II)	 [4a] [4b] [4c]	HepG-2: 4c (7.90µg/µL) MCF-7 4c (10.60µg/µL)
 1,1'-(pyridine-2,3-dimethyliminomethyl)naphalene-2,2'-diol (HNDAP)	Mn(II) Fe(II) Co(II) Cd(II)	 5a M= Fe(II) 5bM= Mn(II), X=H_2O, n=1 5c M= Co(II), X=Cl, n=2 5d M= Cd(II), X=0, n=4	HepG-2: 5c (~11-18µg/mL) HCT-116: 5b (~10-18µg/mL)
 N,N bis (anthracen-9-ylmethylene) pyridine-2, 3-diamine	Er Pr Yb	 6a M= Er, 6b M=Pr 6c M= Yb	At 25µg/mL: In MCF-7, Vero, HeLa cell lines: 6b(~49-50%)
2-aminopyridine, 2-hydroxy napthaldehye/ vanillin and ethylene diamine	Ru(III)	 7a) $[Ru(L1)(Cl)(PPh3)]$ 7b) $[Ru(L2)(Cl)(PPh3)]$	MCF-7 7a : 25.85µg/mL NH3T3 7a:102.2µg/mL
	Cu(II)	 8a	HeLa HCT
	Ir(III) Rh(III) Ru(II)	 9a M=Ir 9b M= Rh 9c M=Ru	MCF-7 9a (5 µM)

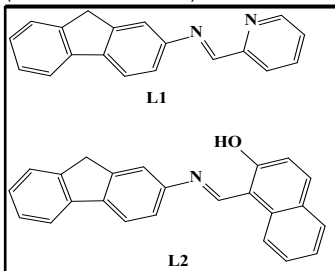
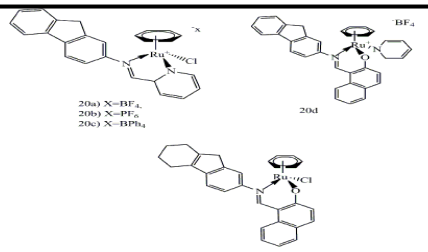
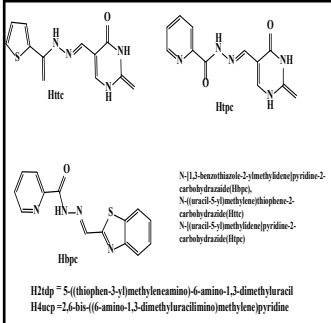
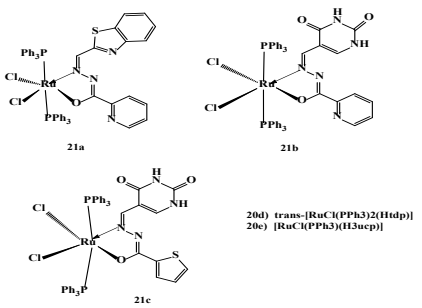
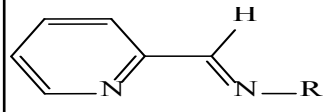
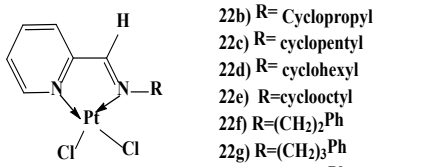
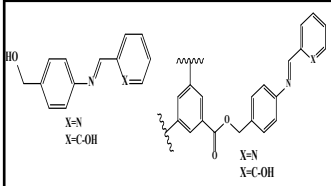
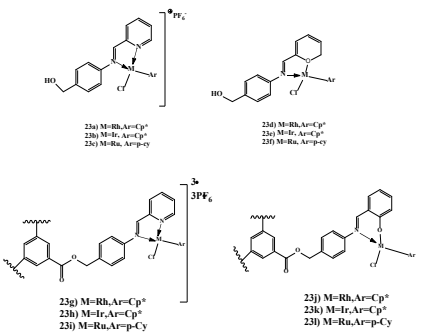
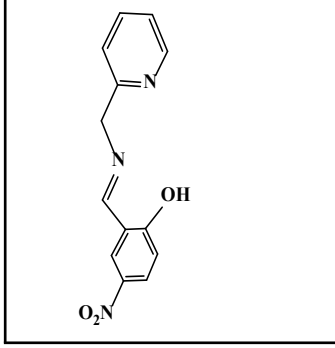
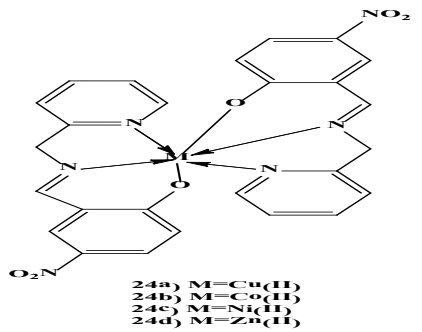
(Table no. 1 continued)

 L_1-L_2 2-formylpyridine and amino substituted triphenylamine	Ir(III)	10a)$[(\eta^5\text{-}C_5Me_5)Ir(L_1)Cl]PF^6$ 10b)$[(\eta^5\text{-}C_5Me_4C_6H_5)Ir(L_1)Cl]PF^6$ 10c) $[(\eta^5\text{-}C_5Me_5)Ir(L_2)Cl]PF^6$ 10d)$[(\eta^5\text{-}C_5Me_4C_6H_5)Ir(L_2)Cl]PF_6$	A549: 10d (2.9±0.2μM) HeLa: 8505C:
 A) 4-aminobenzoicacid B) methyl 4-(pyridin-2-ylamino)benzoate C) 4-(pyridin-2-ylamino)benzoic acid D) (pyridin-2-ylmethyl)glycine E) 4-((pyridin-2-ylmethyl)amino)benzoic acid (A, B, C, D, E = Ligands)	Ru(II)	 11a 11b 11c 11d 11e 11f	D(58.2±11.6μM), 11a(69.1±2.5μM) MCF-7: A(20.2±3.5μM), 11a(36.3±2.6μM) SW-480: D(44.1±5.1μM),
 A) (E)-N'-(pyridine-2-ylmethylene)benzohydrazide  B) (E)-2-(pyridine-2-ylmethylene)hydrazine-1-carboxamide	Cu(II) Ni(II) Co(II)	 12a 12b 12c	AGS &SW742: (12a-12c) > A&B
 pyridine-2-carboxaldehyde or quinoline-2-carboxaldehyde and para substituted aniline derivatives	Mn(I)	 13a X= OH X= OCH_3 X= Cl X= NO_2 13b X= OH X= OCH_3 X= Cl X= NO_2	HepG-2: 13b>13a
 A B C	Cu(I)	 14a) X= Cl 14b) X= Br 14c) X= I 14d) X= NCS 14e) X= Cl 14f) X= Br 14g) X= I	U87: 14c (20 ± 1.5μM)

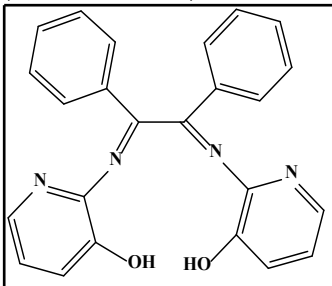
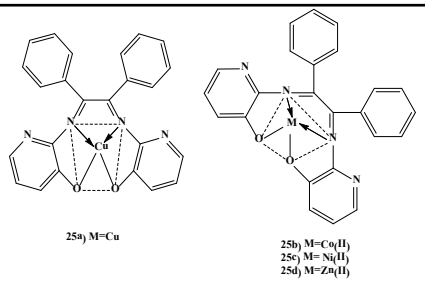
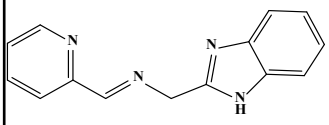
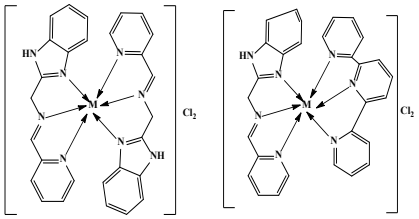
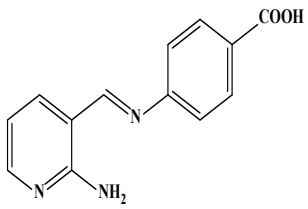
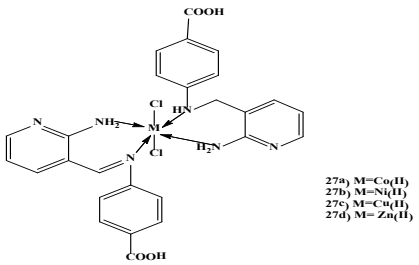
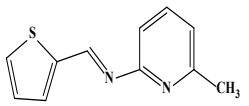
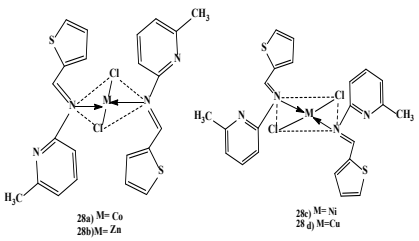
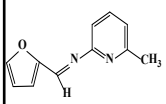
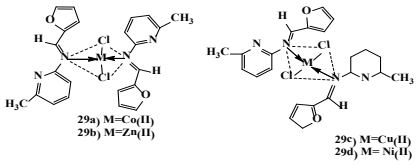
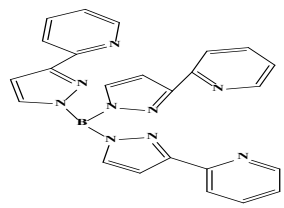
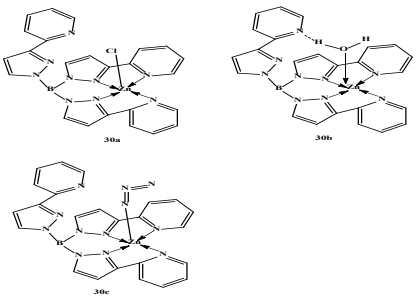
(Table no. 1 continued)

	Cd(II) Mn(II) Zn(II)	 **R** / **Cd** / **Mn** / **Zn** H / 15a / 15b / 15c CH_3 / 15d / 15e / 15f	A2780:15b(25.41±1.3μM) H1299:15b(25.41±1.3μM) U37 MG:15b(20.73±1.5μM)
	Cu(II) Ru(II) Os(II)	 16a 16b 16c	A2780: 16a(15±3μM) A2780cisR:16a(23±5μM) HeLa:16a(32±7μM) HEK293:16c(70±15μM)
	Sn	 17a) R=CH_3 17b) R=C_4H_9 17c) R=C_6H_5 17d) R=C_4H_9 17e) R=C_6H_5	A549: 17b (0.583 ± 0.245μg/mL) MCF-7: 17b (0.459 ± 0.185μg/mL) HeLa: 17b (0.399 ± 0.142μg/mL)
 (L1) (L2)	Rh Ir	 18a) M=Rh(1) 18b) M=Ir(2) 18c) M=Rh(3) 18d) M=Ir(4) 18e) M=Rh(5) 18f) M=Ir(6)	DL tumor cells
 L1: 2-(2-((2,6-dichlorophenyl)amino)phenyl)-N0-(pyridin-2-ylmethylene)acetohydrazide L2: N0-((1H-imidazol-2-yl)methylene)-2-(2-((2,6-dichlorophenyl)amino)phenyl)acetohydrazide L3: 2-(4-Isobutylphenyl)-N0-(pyridin-2-ylmethylene)propanehydrazide L4: N0-((1H-imidazol-2-yl)methylene)-2-(4-Isobutylphenyl)propanehydrazide	Cu(II)	 19 a 19b 19c 19d	A549: 19a (18.36 ± 1.26μM) HCT116: 19d (45.10 ± 3.24μM) MDA MB-231: L4 (2.26 ± 0.35μM)

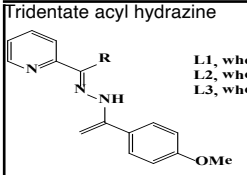
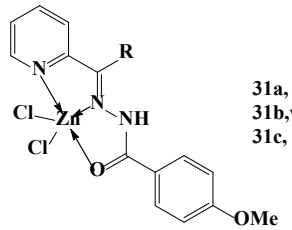
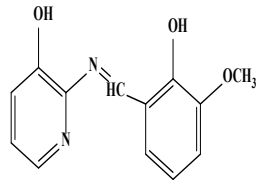
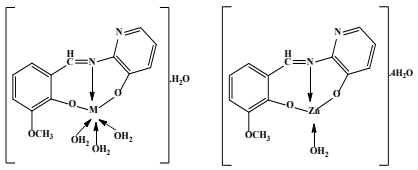
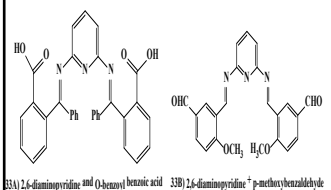
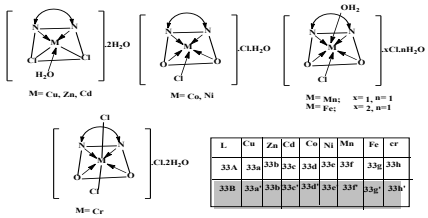
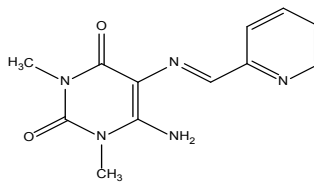
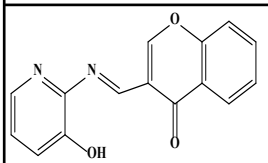
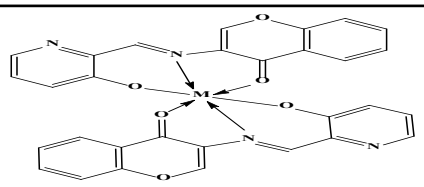
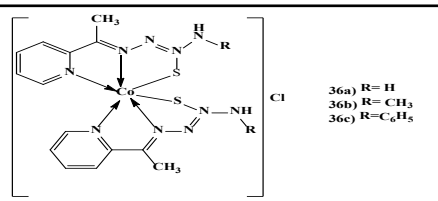
(Table no. 1 continued)

	Ru		MCF-7: 20e (14.7 (±1.4)μM) T47D: 20e (6.2 (±0.6)μM)
	Rh(II)		HCC-70: 21d (3.4 ± 0.010μM)
Pyridin-2-ylcarboxaldimine 	Pt(II)		LN405: 22i(3±4μM) LN18: 22e(11±1μM)
	Rh(II) Ir(II) Ru(II)		A2780: 23h (11.58±4.35μM) A2780cisR: 23g (10.61±0.40μM) KMST-6: 23g (43.39±3.72μM)
	Cu(II) Co(II) Ni(II) Zn(II)		HeLa: 24a(44.02±2μM) HepG-2: 24d (42.09 ±2μM) MCF-7: 24c(49.75±2μM) NHDF: 24a(88.76±2μM)

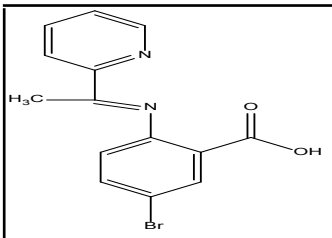
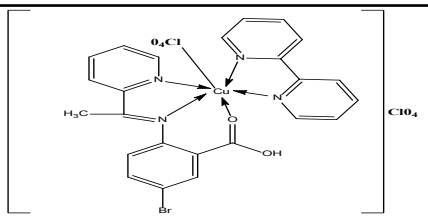
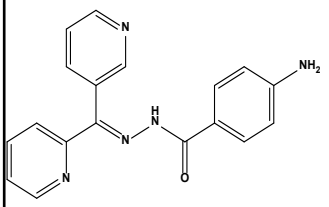
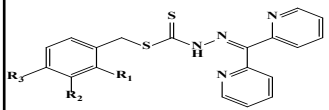
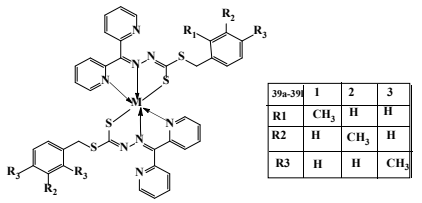
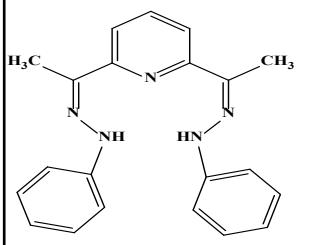
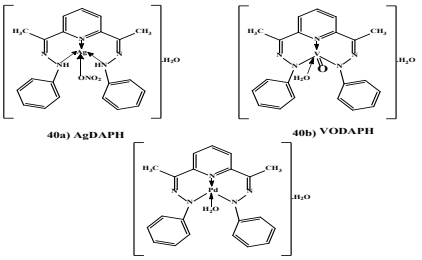
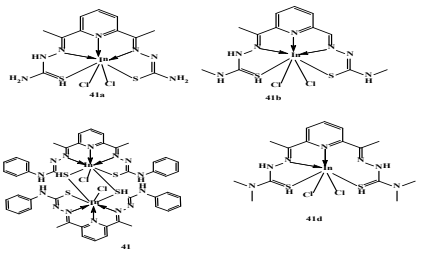
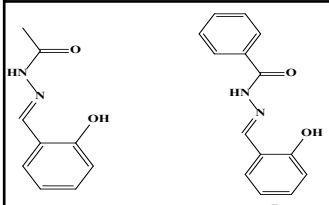
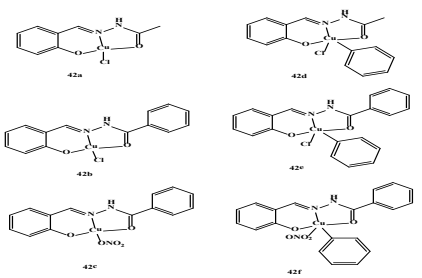
(Table no. 1 continued)

	Co(II) Ni(II) Zn(II)	 25a) M=Cu 25b) M=Co(II) 25c) M= Ni(II) 25d) M=Zn(II)	MCF-7: 25a (20±0.8μM) HepG-2: 25a (18±0.8μM) HBL100: 25a (78±0.8μM)
	Cu(II) Ni(II) Zn(II)	 26a) M=Cu(II) 26b) M=Co(II) 26c) M=Ni(II) 26d) M=Zn(II) 26e) M=Cu(II) 26f) M=Co(II) 26g) M=Ni(II) 26h) M=Zn(II)	HeLa: 26a (~53 mg/mL) MCF-7: 26e (~34 mg/mL) HepG-2:26h (~49 mg/mL)
4-aminobenzoic acid with 2-aminoicotinaldehye 	Co(II) Ni(II) Cu(II) Zn(II)	 27a) M=Co(II) 27b) M=Ni(II) 27c) M=Cu(II) 27d) M= Zn(II)	IMR-32: 27d (7.81±0.52μM) HeLa: 27a (5.94±1.13μM) MCF-7: 27d (7.41±0.32μM) HepG-2:27d(15.28±1.26μM) A549: 27d (6.18±1.15μM)
 (*E*)-*N*-(6-methylpyridin-2-yl)-1-(thiophen-2-yl)methanimine	Co(II)	 28a) M= Co 28b)M= Zn 28c) M= Ni 28 d) M=Cu	L929 28d (LC_{50}=30μg/mL)
Furfural–MAP 	Co(II) Zn(II) Cu(II) Ni(II)	 29a) M=Co(II) 29b) M=Zn(II) 29c) M=Cu(II) 29d) M= Ni(II)	PA1 L929: 29c(> 51% viable)
 tris(3-(pyridin-2-yl)-1*H*-pyrazol-1-yl)borane	Zn(II)	 30a 30b 30c	MDA-MB-231: 30a(6.81 ± 0.98μM) MDA-MB-468: 30b(10.85 ± 1.72μM) HCC1937: 30b(10.60 ± 1.04μM) HS578T: 30b(6.68 ± 1.16μM)

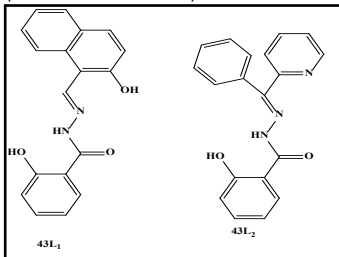
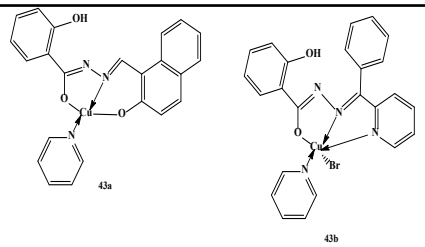
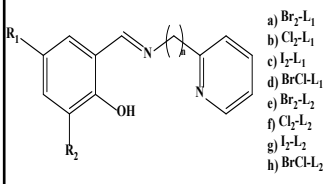
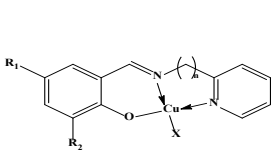
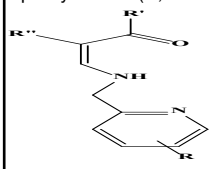
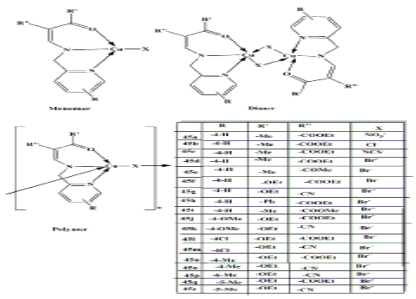
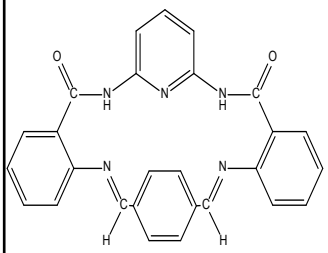
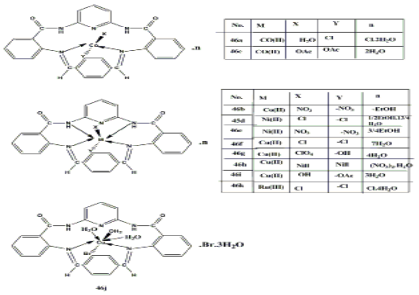
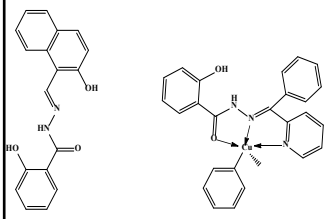
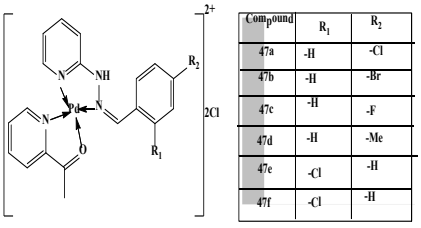
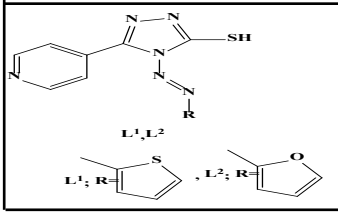
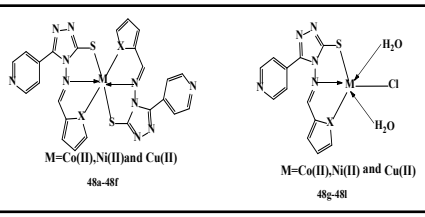
(Table no. 1 continued)

Tridentate acyl hydrazine 	Zn(II)		HCT116:31b(38.66±0.91µM) HepG2:31b(19.83±1.6µM) A549: 31b(41.85±0.57µM)
 2-[(2-hydroxy-3-methoxy-benzylidinr)-amino]-pyridin-3-ol	Cu(II) Co(II) Ni(II) Fe(II) Zn(II) Cd(II)	 32a) M= Cu 32b) M=Co 32c) M=Ni 32d) M= Fe 32e)M= Cd 32f) M=Zn	HCT-116: 32b (3.30µg/µL) MCF-7: 32a (3.26 µg/µL) HepG-2: 32e (3.26 µg/µL)
 33A) 2,6-diaminopyridine and O-benzoyl benzoic acid 33B) 2,6-diaminopyridine + p-methoxybenzaldehyde	Cr(III) Mn(II) Fe(III) Co(II) Ni(II) Cu(II) Zn(II) Cd(II)	 M= Cu, Zn, Cd M= Co, Ni M= Mn; M= Fe; x= 1, n= 1 x= 2, n=1 M= Cr L: 33A 33a 33b 33c 33d 33e 33f 33g 33h; 33B 33a' 33b 33c' 33d' 33e' 33f' 33g' 33h'	MCF-7: 33a (19.7µg/µL) 33d' (3.50µg/mL)
 (^{E})-6-amino-1,3-dimethyl-5-((pyridin-2-ylmethylene)amino)pyrimidine-2,4(1^{H},3^{H})-dic	Ni(II) Zn(II) Cd(II) Cu(II)	34a)[Cu(DAAUPicH–$_1$)(phen)]ClO_4 34b)[Cu(DAAUPicH–$_1$)(phen)]Br 34c){[Cu(DAAUPicH–$_1$)(H_2O)]ClO_4}n 34d)[Cu(NO_3)(DAAUPicH–$_1$)(H_2O)]·H_2O 34e) [CuBr(DAAUPicH–$_1$)]$_2$ 34f) [CuBr(DAAUPicH–$_1$)] 34g) [CuI(DAAUPicH–$_1$)]$_2$ 34h) [CuI(DAAUPicH–$_1$)] 34i) [Ni(DAAUPic)$_2$](NO_3)2·H_2O 34j)[Ni($SCN)_2$(DAAUPic)(H_2O)]·1.5H_2O 34k) Ni(AcO)(DAAUPicH-$_1$) 34l) [Ni(DAAUPicH-$_1$)$_2$]·H_2O 34m) [Zn(AcO)(DAAUPicH-$_1$)]$_2$ 34n)[Zn(DAAUPic)$_2$](ClO_4)$_2$·½H_2O 34o)[Zn(DAAUPicH-$_1$)$_2$]·H_2O·CH_3OH 34p)[Cd(NO_3)(DAAUPicH$_1$)(H_2O)]$_2$·2H_2O 34q)[Cd(NO_3)(DAAUPicH$_1$)(H_2O)]$_2$·2H_2O 34r) [CdI_2(DAAUPic)]	C6 glioma cell line 34a-34h: 330-400nM MCF-7: 34i-34r (5µM) MDA-MB-231: 34i-34r (4µM)
 3-(3-hydroxypyridin-2-yl)imino)methyl)-4H-chromen-4-one	Cu(II) Zn(II)	 35a) M= Cu(II) 35b) M=Zn(II)	PA-1 Cell Viability: 35a= 30.12%
2-acetylpyridine- N-substituted thiosemicarbozone	Cu(II)	 36a) R= H 36b) R= CH_3 36c) R=C_6H_5	A431:36c(9.3±0.03µM) MCF-7: 36c(1.99±0.13µM)

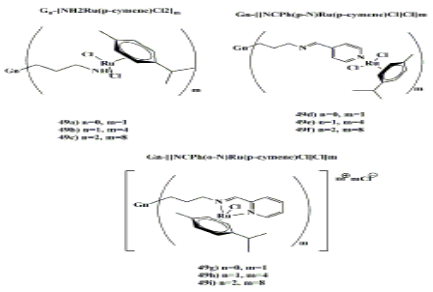
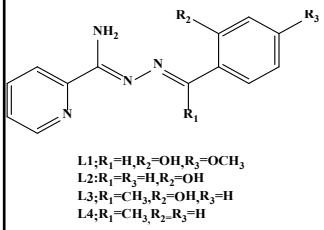
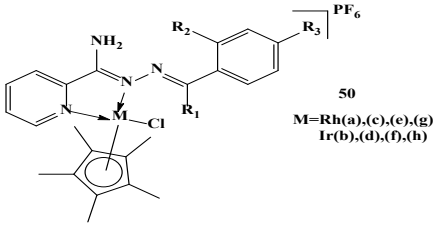
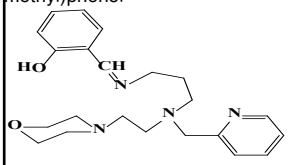
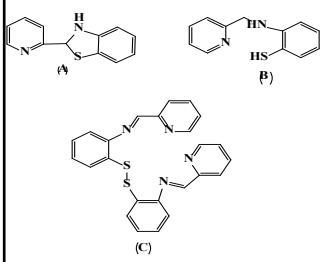
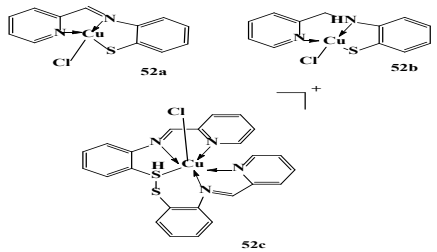
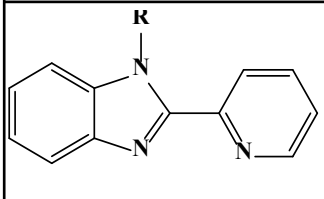
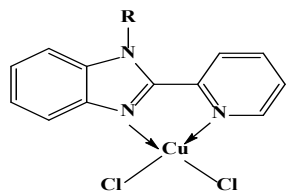
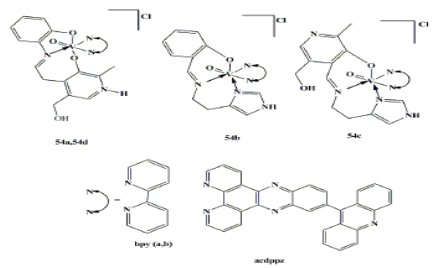
(Table no. 1 continued)

	Cu(II)	 37	MCF-7: (5.95μM)
 di-2-pyridylketone with isonicotinicacid hydrazide	Cu(II)	{[Cu(L)(H_2O)]·H_2O·NO_3}n	Bel-7402:38(4.12 ± 0.36μM) HeLa:38(2.37± 0.21μM) MCF-7: 38(1.47 ± 0.09μM) MCF-7/ADR:38(1.52±0.12μM) WI – 38: 38(6.28 ± 0.58μM)
S-n-β-N–(di-2-pyridine) methylene dithiocarbazate  Where n= 2methyl/3-meth -yl/4-methyl benzyl	Cu(II) Ni(II) Cd(II)	 M=Cu(II),Ni(II),Cd(II)and Zn(II)	MCF-7: 39f(0.4 μg/mL) MDA-MB-231: Zn(II) 39g(0.4μg/mL)
 Diacetyl Pyridine phenylhydrazone (DAP	Pd(II) V(IV) Ag(I)	 40a) AgDAPH 40b) VODAPH 40c) PdDAPH	HepG-2 40c(6.50±0.09 μM) HCT-116 40c(14.00±0.05 μM) MCF-7 40c(9.50±0.09 μM)
2,6-diacetylpyridinebis (thiosemicarbozide)	In(II)	 41a 41b 41c 41d	H460:41d(20.25 ± 1.33μM) SKOV-3:41d(19.11±1.07μM) MGC-803: 41d(11.77±0.88 μM) HeLa: 41d(15.22 ± 1.02 μM) t24: 41d (8.65 ± 0.68μM) HL-7702: 41d(21.09±1.01μM)
 A B	Cu(II)	 42a 42b 42c 42d 42e 42f	Bel-7402: 42f (2.27±0.21μM) MCF-7: 42f (1.12±0.23μM) A549: 42f (3.65±0.47μM) A549cisR: 42f (3.77±0.34μM) WI-38: 42f

(Table no. 1 continued)

	Cu(II)		(5.59±0.53μM) HepG2:43b(1.57±0.08 μM) Bel-7402:43b(1.86±0.09μM) MCF-7:43b(1.69±0.18 μM) A549: 43b (2.86±0.21 μM) A549cisR:42b(2.91±0.17μM) WI–38: 42b (4.19±0.32 μM)
 a) Br_2-L_1 b) Cl_2-L_1 c) I_2-L_1 d) BrCl-L_1 e) Br_2-L_2 f) Cl_2-L_2 g) I_2-L_2 h) BrCl-L_2 2-hydroxy-3,5 halogen-substituted salicylaldehyde + 2-(2-pyridyl)ethylamine and 2-picolylamine	Cu(II)	 44a) Cu(Cl_2-L_1)Cl 44b) Cu(Br_2-L_1)Cl 44c) Cu(BrCl-L_1)Cl 44d) Cu(Cl_2-L_1)NO_3 44e) Cu(Br_2-L_1)NO_3 44f) Cu(I_2-L_1)Cl 44g) Cu(I_2-L_1)NO_3 44h) Cu(BrCl-L_1)NO_3 44i) Cu(Br2-L2)Cl 44j) Cu(Cl2-L2)Cl 44k) Cu(I2-L2)Cl 44l) Cu(BrCl-L2)Cl 44m) Cu(Br2-L2)NO3 44n) Cu(Cl2-L2)NO3 44o) Cu(I2-L2)NO3 44p) Cu(BrCl-L2)NO3	HCT-116: 44d (18.1±1.78μM) A2780: 44d (4.2±2.2μM) MCF-7:44d (29.9±6.86μM)
NNO β-acylenamine ligand from 2-picolyl-amine (R,R′ and R″) 	Cu(II)		HCT-116wt: 45j (4.7 ± 0.1μM) 518A2: 45j (5.9 ± 0.4μM) HT-29: 45j (2.2 ± 0.3μM) HCT-116p53-/-: 45j (2.2 ± 0.3μM) HeLa: 45n(9.0 ± 0.8μM)
	Co(II) Ni(II) Cu(II) Ru(III)		MCF-7: 46a(1.33μg/mL) HepG-2: 46a(1.5μg/mL)
	Pd(II)	 Compound R_1 R_2 47a -H -Cl 47b -H -Br 47c -H -F 47d -H -Me 47e -Cl -H 47f -Cl -H	HCT-116: 47d (51 μg/mL)
 L^1, L^2 L^1; R= , L^2; R=	Co(II) Cu(II) Ni(II)	 M=Co(II),Ni(II)and Cu(II) 48a-48f M=Co(II),Ni(II) and Cu(II) 48g-48l	Inhibition(%) at 10 μM HepG-2: 48i (49%) MCF-7: 48j (38%)

(Table no. 1 continued)

Carbosilane metallo dentrimers with three different aldehydes (4-pyridinecarboxal -dehyde, 2-pyridine -carboxaldehyde and salicylaldehyde)	Ru(II)		HeLa: 49e (4.4±0.1μM) MCF-7: 49e (2.5±0.1μM) HT-29: 49e (3.3±0.2μM) MDA-MB-231: 49b (4.5±0.4 μM)
 L1:R_1=H,R_2=OH,R_3=OCH_3 L2:R_1=R_3=H,R_2=OH L3:R_1=CH_3,R_2=OH,R_3=H L4:R_1=CH_3,R_2=R_3=H	Rh(II) Ir(II)	 50 M=Rh(a),(c),(e),(g) Ir(b),(d),(f),(h)	HT-29: 50e(46.17 ± 12.78μM) ARPE-19: 50e(97.39 ± 4.53 μM)
Synthesis of 2-({3-[2-morpholinoe -thylamino] -N3-([pyridine-2-yl] methyl)phenol 	Cu(II) Co(II) Zn(II) Ni(II) Cd(II) Mn(II) Ag(I) Fe(III)	51a) $[ZnL](ClO_4)$ 51b) $[CdL](ClO_4)$ 51c) $[MnL](ClO_4)$ 51d) $[NiL](ClO_4)$ 51e) $[CuL](ClO_4)$ 51f) $[AgHL(NO_3)]$ 51g) $[FeLCl_2]$ 51h) $[CoL](ClO_4)$	MCF-7: 51f (10.9 ± 0.03μM) MDA-MB-231: 51f (10.2 ± 0.06μM) PC-3: 51f (28.5 ± 0.30μM) WI-38: 51e (15.45 ± 0.03μM)
	Cu(II)		Cellviability(%) at 5μM: HeLa: 51c(34.5%) HEK293: 51c(84%)
 pbzX	Cu(II)	 53a)pbzH 53b) pbzMe 53c) pbzBz 53d) pbzF 53e) $pbzF_2$ 53f) $pbzF_5$ 53	A549: 53b (5.5 ± 0.4 μM)
Vitamin-B6 Schiff base	V(IV)		In visible light: HeLa: 54d (0.24 ± 0.02μM) MCF-7: 54d (0.53 ± 0.03 μM) MCF-10A: 54a (85± 2μM)

DISCUSSION

Anti-proliferative activity of pyridine Schiff base complexes

A series of transition metal complexes of Schiff bases, derived from the condensation reaction of 2-amino pyridine with different aldehydes (5-substituted salicylaldehyde.[8] 6-formyl-7-hydroxy-hyphen-5methoxy benzo *puran*-4-one[9] and pyridine-2-carboxaldehyde[10]) were prepared.

The anticancer activity of complexes (1a-1d) was investigated against HeLa, SW620, A549, MCF-7, and WI-38 cell lines. All tested complexes showed a strong anti-proliferative effect even in the meager μM range (IC_{50}=half maximal inhibitory concentration). Complex 1b had the highest proliferative activity against the A-549 cell line. The synthesized complexes (1a-1d) had high cytotoxicity against control cell lines, which was the major drawback[8].

Complexes (2a-2d) were tested against normal 3T3 cells with different concentrations (10-70μML-1). Mn(II) complex was less toxic than Schiff base up to 30μML^{-1}. The cytotoxicity was screened against cancerous cell lines at this concentration, and the result indicated promising activity. The Mn(II) complex inhibited HeLa-Fas cells (80%), HeLa cells (53%), Huh-7 cells (43%), and HepG-2 cells (20%)[9]. The cytotoxic effect of 3a-3r was screened against MCF-7 and HeLa cell lines and compared to standard drugs (Cisplatin and doxorubicin). The IC_{50} values for these complexes ranged from 7-25μM (MCF-7) and 7-29 μM (HeLa). The complexes 3o, 3c, 3j, and 3b were remarkably active against both the cell lines than Cisplatin[10].

A novel azomethine ligand [1(pyridine-3-yl-imino methyl) naphthalene-2-ol] and its Ag(I), Pd(II), and VO(II) complexes (4a-4c) have been prepared and investigated against various carcinoma cell lines, including HCT-116, MCF-7, and HepG-2. The calculated IC_{50} values showed that complex (4b) has the highest ability to inhibit the growth of both MCF-7 (IC_{50}=10.60μM) and HepG-2 (IC50=10.60μM) cells when compared to vinblastine. It may be considered a promising pharmaceutical drug for liver tumors[11].

The Schiff base synthesized from 2, 3-diamino pyridine and 2-hydroxy-1-naphthaldehyde and its metal complexes (5a-5d) were prepared with Mn(II), Fe(II), Co(II), and Cd(II) metals. Schiff base and its metal complexes were tested against two cancer cell lines, namely (HCT-116) and (HepG-2) cell lines. Complexes 5c and 5a were more potent against HepG-2 and HCT-116 cell lines[12].

A series of lanthanide complexes (6a-6c) was obtained from Schiff base ligand named N,N-bis (anthracen-9-yl methylene)pyridine-2, 3-diamine. The synthesized metal complexes were elaborately tested for cytotoxic activity against various cancer cell lines such as Vero, MCF-7, and HeLa. The synthesized complexes efficiently induced apoptosis in a dosage-dependent manner among these three cell lines. The test results on Vero cells depicted that the biocompatibility of Pr complex was more effective than the Er complex. The cytotoxic behavior of Pr and Er complexes against MCF-7 and HeLa cell lines exhibited cell death up to ~49% and ~42-51%, respectively[13].

Azo Schiff base ligands obtained from 2-aminopyridine and 2-hydroxy naphthaldehyde(L1) vanillin and ethylenediamine(L2) are converted into Ru(III) complexes (7a-7b). These complexes were screened for anticancer activity against MCF-7 and normal NH3T3 cell lines. The obtained results confirmed that Ru complexes were much less toxic towards NH3T3 (IC_{50}=102.2 μg/mL). The number of cells decreased with an increase in the concentration of complexes[14].

The cytotoxic activity of binuclear Cu(II) complex (8a) with tridentate ligand, prepared by the condensation reaction of 2-aminomethyl pyridine and pyridoxal, was evaluated against HeLa and HCT cells through MTT assay. The results showed that the complex would be mildly cytotoxic towards HCT and HeLa cell lines, and it could be used for biological imaging in very low dose[15].

The anti-proliferative activity of a series of transition metal complexes with Schiff base (derived from pyridine carboxaldehyde and 9-ethyl-9H-carbazole-3-amine) were tested against various cancer cell lines and reported. The anticancer study demonstrated that the new half-sandwich Ir(III), Rh(III), and Ru(II) complexes (9a-9c) potent against MCF-7 at low concentrations. The complexes 9a and 9b were found to be more potent than 9c[16].

Antitumor of half-sandwiched Ir(III) complexes (10a-10d) was tested against A549 and HepG-2. The results revealed that all these compounds exhibited IC_{50} value in the range of 1.4±0.1μM to 11.5±0.5μM which confirms that the synthesized complexes were effective antitumor agents[17].

Antitumor studies were done on several human cell lines (8505C, MCF-7, SW-480, and 518A2) with a series of Ru(II) arene complexes (11a-11f) of mono and bidentate N-donor ligands (A-D). The result revealed that the MCF-7 cell line was the most sensitive cancer cell, while others were almost resistant to the synthesized complexes. 11a and 11b show the highest cytotoxic activity against MCF-7 cells among all tested complexes[18].

The Schiff bases (E)-N′-(pyridine-2-yl-methylene)benzo hydrazide and (E)-2-(pyridine-2-yl-methylene)hydrazine-1-carboxamide were complexed with Cu and then the complexes (12a-12c) were screened for cytotoxic activity against AGS and SW742. It is interesting to note that all the complexes have higher activity than the free ligand. This might be due to the presence of the chelation in the complexes[19].

Synthesized photo-induced tricarbonyl manganese(I) compounds (13a-13b) were prepared and evaluated against HepG-2 with and without illumination. In comparison, complex 13b with methoxy supplements revealed higher cytotoxicity among the investigated compounds in a dose-dependent manner with an IC_{50} value of 7.1 μM[20].

A Series of complexes (14a-14g) were synthesized by interacting Cu(I) metal cation with imine ligand, and the potential anticancer effect was assessed for U87. All complexes exhibited dose-dependent cytotoxicity towards U87 cells. The 14c complex had the intensified anticancer activity[21].

Schiff base complexes (15a-15f) were synthesized by the condensation between 2,6-diacetyl pyridine and 2-((4-(2-amino benzyl)-1,4-diazepan-1-yl)methyl)benzenamine in the presence of Cd(II), Mn(II) and Zn(II) ions. The potency of complexes was evaluated on A2780, U-37MG, and H1299 cell lines using the MTT method. The investigated compounds 15b showed an excellent inhibitory effect on U37MG cells. The inhibitory effect of complex 15a showed a potent effect in U37MG cells and moderate potency against H1299 and A2780 cell lines[22].

Cu(II)-Ru(II) and Cu(II)-Os(II) complexes (16a-16c) have been synthesized by using Schiff base derived from 2-pyridin amidraone and 6-(morpholino ethyl)-pyridine-2-carboxaldehyde. The anti-proliferative activity of synthesized complexes and ligands was evaluated against A2780 and A2780cisR, HeLa, and human embryonic kidney cell line HEK293. All the tested complexes displayed more significant cytotoxicity than the ligand, and complexes 16a and 16b had the high selectivity to cancer cell lines over non-cancerous HEK293 cells, which might be helpful in their further clinical development[23].

A series of organotin(IV) hydrazine compounds (17a-17e) synthesized by using the ligand N′-[(1E)-(2-hyroxyl-3-methoxyphenyl) methylidene]pyridine-3-carbohydrazone. The cytotoxicity of the 17a-17e was assessed on A549, HeLa, and MCF-7 cell lines. All the compounds showed prominent antitumor activity towards cancer cell lines. Among all, Compound 17b and 17c were more suitable anticancer drugs[24].

The half sandwiched organometallic Rh and Ir complexes (18a-18f) with ligands (pyridine-2-yl-methylene picolinic hydrazine(L1) and pyridine-3-yl-methylene picolinic hydrazine (L2)) were synthesized. The in vitro antitumor activity of the complexes 18a and 18b by fluorescence-based apoptosis was evaluated against DL cells at different concentrations. In higher doses (60-100μg/mL), 18a and 18b exhibited moderate apoptotic effect with ~22% and~30% apoptotic cell death. The cytotoxicity of 18a and 18b on normal cells has been noticed as half of their activity on the DL tumor cells[25].

In vitro anti proliferative activity of Cu(II) complexes (19a-19d) of hydrazones with ligands (2-(2-((2,6-dichloro phenyl)amino)phenyl)-N0-(pyridin-2-yl-methylene)aceto hydrazide (L1), N0-((1H-imidazol-2-yl)methylene)-2-(2-((2,6-dichloro phenyl)amino) phenyl) aceto hydrazide(L2), 2-(4-Isobutylphenyl)-N0-(pyridin-2-yl methylene)propane hydrazide (L3), and N0-((1H-imidazol-2-yl)methylene)-2-(4-isobutyl phenyl)propane hydrazide) (L4) were tested against A549, HCT-116 and MDA MB-23 cell lines by MTT

assay. L1-L4 are active against these cell lines, and they exhibited better activity against MDA MB-231 cell lines. As compared to Cisplatin 19a-19d possess excellent potency as an anticancer drug with lower IC_{50} values (3.38-6.62 μM)[26].

Ruthenium arene complexes (20a-20e) with fluorene bearing Schiff base ligand prepared. Furthermore, the ligand is obtained by the condensation reaction of 2-amino fluorene with an aldehyde (2-formyl pyridine or 2-hydroxy naphaldehyde). The complexes 20a-20e were tested on MCF-7 and T47D cell lines. 20a and 20b did not influence the viability of MCF-7 and T47D cells. The activity of 20c was found to be slightly lower than Cisplatin against MCF-7 but more active against T47D, and complexes 20d and 20e were found to be more active than Cisplatin[27].

The metal complexes (21a-21e) were synthesized by the reactions of trans-[$RuCl_2(PPh3)_2$] with N-[1,3-benzothiozole-2-ylmethylidene]pyridine-2-carbohydrazide, N-[(uracil-5-yl)methylene] thiophene-2-carbohydrazide, N-[(uracil-5-yl) methylene]pyridine-2-carbohydrazide, 5-((thiophen-3-yl)methylene amino)-6-amino-1,3-dimethyluracil and 2,6-bis-((6-amino-1,3-dimethyl uracil imino) methylene)pyridine. These compounds were screened against HCC-70 cell line and the result showed that 21a and 21b were not toxic below 100μM. Among the 20a-20e complexes 20d showed more cytotoxicity with IC_{50} value of 3.4μM[28].

Eleven pyridine carbo aldimines were prepared from the condensation reaction of 2-pyridine carboxaldehyde and the corresponding lipophilic primary amines and its Pt(II) complexes (22a-22k). The cytotoxicity of seven novel Pt complexes was tested against LN18 and LN405 using Cisplatin as a control. Complex 22i displayed the lowest IC_{50} value against LN405, and 22e displayed the lowest IC_{50} value against LN18[29].

The Schiff base ligand was prepared from the condensation reaction of 4-amino phenyl methanol/2-pyridine carboxaldehyde of salicylaldehyde. These ligands were used to synthesize a series of trinuclear half-sandwich Ru(II), Rh(III), and Ir(II) polyester organometallic complexes (23a-23l). The anti-proliferative activity of 23a-23l was evaluated against A2780, A2780cisR, and non-tumorous cells KMST-6. The result showed that trimeric complexes 23g-23l had higher activity towards A2780 and A2780cisR than the free ligand and monomeric complexes. In the A2780 cell line, complex 23 h showed the highest activity with the IC_{50} of 11.58μM, while in the A2780cisR cell line, complex 23 g showed the highest activity with 10.61μM[30].

The cytotoxic nature of non platinated transition metal (II) complexes (Cu(II), Co(II), Zn(II) & Ni(II)) were evaluated against different cancer cell lines. The different Schiff bases were prepared as follows: the condensation reaction of 2-hydroxy-4-nitrobenzaldehyde with pyridine-2-yl-methamine,[31] benzyl with 2-amino-3-hydroxy pyridine,[32] 2-(aminomethyl)benz imidazol dihydrochloride with pyridine 2-carboxaldehyde,[33] 2-aminobenzoic acids with 2-amino nicotinaldehyde,[34] thiophene-2-carboxaldehyde with 2-amino-6-picoline[35], and furfural with 6-methyl-2-aminopyridine[36]. The prepared complexes with these Schiff bases are (24a-24d), (26a-26h), (27a-27d), (28a-28d) and (29a-29d) respectively. The complexes (24a-24d) showed cytotoxic behavior against human cancer cell lines (HeLa, MCF-7, and HepG-2). The toxicity of these compounds was less on the normal cell line (NHDF). The 24a complex showed slightly higher activity than the rest of the complexes[31]. The In vitro cytotoxic activity of synthesized complexes (25a-25d) was evaluated against MCF-7, HepG-2, and non-cancer cell line from human breast milk HBL100 by MTT assay, and Cisplatin acts as a standard drug. The IC_{50} values reduce with rising the concentration of metal complexes, and all the metal complexes showed good anticancer activity. Among all the tested complexes, 25a showed greater anticancer activity[32]. The antitumor activity of 26a-26d complexes evaluated against a selected human cancer cell line HeLa, MCF-7, and HepG-2 along with NHDF by colorimetric (MTT) assay. It was shown that the complexes with terpyridine (26e-26h) as co-ligand exhibited a better cytotoxic effect than the other complexes 26a-26d[33]. The anti-proliferative activity of complexes 27a-27d assessed against different human cancer cell lines IMR-32, MCF-7, COLO-205, A549, HeLa, and HEK293 which revealed that complex 27d showed excellent anti-proliferative activity against IMR-32, A549, and HepG-2 with an IC_{50} value 7.81±0.52 μM, 6.18±1.15μM and 15.28±1.26μM respectively. Similarly, complex 27a showed potent

activity against HeLa, HepG-2, A549, and MCF-7. The potent compounds 27a & 27d were tested against normal cancer cell line HEK293. The results indicated that none of the complexes interrupted the viability of the cell line[34]. Synthesized complexes (28a-28d) were tested against L929 fibroblast. The cytotoxicity of [CoL2Cl2] (28a) and [CuL2Cl2] (28d) showed the LC_{50} values 40μg/mL and 30μg/mL respectively in lethal concentration[35].

In anticancer activity evaluation, the Cu(II) complex showed better activity than other synthesized complexes (29a-29d) when investigated against PA1 and L929 cell lines at different concentrations. The cell viability of L929 cells was greater than 51%, indicating that 29c can be used as a safe compound for therapeutic biomedical application[36].

Three differently coordinated Tris-(2-pyridine)-pyrazolyl borate zinc(II) complexes (30a-30c) were synthesized and tested for in vitro cytotoxic ability on four triple-negative breast cancer cells lines (MDA-MB-231, MDA-MB-468, HCC1937 & HS578T). The results conclude that all the complexes were potent anticancer agents exhibiting excellent activity on all the four cancer cell lines with IC_{50} values ranging from 6.72 to 16.87μM owing to the presence of the pyrazole and pyridine units in the synthesized complexes. In comparison with the clinical drug Cisplatin (IC_{50}=32.38μM), the synthesized complexes exhibited better activity[37].

Zinc(II) complexes of a tridentate Schiff base ligand N,N′-bis(1-(2-pyridine)ethylidene)-2,2-dimethylpropane-1,3-diamine) were screened for their cytotoxic activity against MCF-7 cell line. The cell inhibition of Zinc complex was recorded as 8%, 39% and 62% at 5,10 and 20μg/mL concentrations respectively[38].

The Schiff base ligands were synthesized via condensation of 4-methoxy benzo hydrazide with picolinaldehyde, 1-(pyridine-2-yl)ethanone, and phenyl(pyridine-2-yl)methanone. The Zinc(II) complexes (31a-31c) were prepared by treatment of zinc(II) chloride with corresponding ligands, and the complexes were investigated against HCT-116, HepG-2, and A529 cells. All the complexes showed IC_{50} values greater than Cisplatin. Among all the complexes, complex 32b exhibited better activity[39].

The new nano-sized complexes of Cu(II), Co(II), Ni(II), Fe(II), Cd(II), and Zn(II) (32a-32f) with Schiff base derived from the condensation of 2-amino-3-hydroxy pyridine and 3-methoxy salicylaldehyde and these complexes were screened against various cancer cell lines. Complexes 32a-32d were investigated against HCT-116, and MCF-7, and complexes 32d-32f were screened against HCT-116 and HepG-2. Cytotoxic conclusions indicated that all the tested complexes (32a-32f) were demonstrated potent activity against HCT-116 cell lines. In HCT-116, the cobalt complex (32b) showed the highest cytotoxic effect (IC_{50}=3.30μg/μL) and in MCF-7, copper complex (32a) showed highest cytotoxic effect (IC_{50}=3.26 μg/μL). In HepG-2, the Cd complex (32e) had the highest cytotoxicity (IC_{50}=1.45μg/μL)[40,41].

Two different Schiff bases (33A, 33B) were prepared by the condensation reaction of 2,6-diamino pyridine with o-benzoyl benzoic acid[42] and 2,6-diamino pyridine with p-methoxy benzaldehyde, respectively.[43] The transition metals [Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II)] complexed with 33A and 33B to form 33a-33h and 33a′-33h′ complexes respectively. The IC_{50} value of complexes 33a-33h was found to be 19.7- 45.2 μM, and 33a exhibited the higher anti-cancer activity among all. The IC_{50} value of complexes 33a′-33h′ showed in the range of 3.5 to 41.9μg/mL, which are lower than lomefloxacin drug (11.2 to 43.1μg/mL), which indicates the effective anticancer activity of the prepared complexes[42,43].

The Schiff base (E)6-amino-1,3-dimethyl-5-((pyridine-2-yl-methylene)amino)pyrimidine-2,4(1H,3H)-dione prepared and its metal complexes (34a-34r) prepared with Cu(II), Ni(II), Zn(II), and Cd(II) metal ions. The Cytotoxic assay was performed for Copper complexes (34a-34h) to assess the anti-proliferative potential complexes using the C6 glioma cell line. The tested complexes showed a similar cytotoxic effect on C6 cell growth in higher doses (330-400nM). The percentage of apoptotic cells increased steadily in a dose-dependent manner, in which 34a, 34c, 34e and 34h had the highest cell death percentage[44]. The anticancer activity of Ni(II), Zn(II), and Cd(II) complexes (34i-34r) were explored and their effects on renin-angiotensin system (RAS) regulating amino-peptidases on estrogen dependent and MCF-7, MDA-MB-231breast cancer cell line reported effective anticancer activity[45].

A Copper and Zinc chelates with Schiff base 3-(3-hydroxy pyridin-2-yl)imino)methyl)-4H-chromen-4-one were tested against the cytotoxicity on human ovarian teratocarcinoma cell line (PA-1) evaluated by the MTT assay. It is interesting to note that 35a exhibits a higher cytotoxic effect than 35b[46]. Two different Schiff bases derived from condensation reaction of 2-acetyl pyridine with N-substituted thiosemicarbozone(L1)[47] and 2-acetyl pyridine with 2-amino-5-bromobenzoic acid(L2)[48]. The Co(III) complexes (36a-36c) from L1 were tested against A431 and MCF-7 cell lines which completely removed the cancer cells even at low concentrations. The complexes 36a-36c showed higher activity than that of Cisplatin[47]. The Cu(II) complex (37) from L2 showed promising anti breast cancer activity with the IC_{50} value of 5.95μM against MCF-7 cell line[48].

The Cu complex containing Schiff base was prepared by the condensation reaction of di-2-pyridine ketone with iso nicotinic acid hydrazide and evaluated against various cancer cell lines Bel-7402, HeLa, MCF-7 and MCF-7/ADR. The MTT assay revealed that the free ligand and Cu(II) salt had low activity against the cancer cells, while complex 38 exhibited better inhibition on cancer cells with lower IC_{50} values (1.47-4.12μM) than Cisplatin. And complex 38 has less toxicity towards the normal WI-38 cell line with an IC_{50} value of 6.28μM[49].

The complexes 39a-39l were synthesized with the ligand S-n-β-N–(di-2-pyridine)methylene dithiocarbazate (n=2-methyl benzyl/3-methyl benzyl/4-methyl benzyl) and these complexes were examined against two breast cancer cell lines MCF-7 and MDA-MB-231. Among all the complexes, 39f active against MCF-7 and 39g, 39j were active against MDA-MB-231 cell line[50].

The N3 tridentate imine ligand 2, 6-diacetyl pyridine diphenyl hydrazone and its Pd(II), V(IV) and Ag(I) complexes (40a-40c) were prepared and cytotoxic activity estimated via three human cancer cell lines HepG-2, MCF-7 and HCT-116. Among all the tested complexes Pd (40a) complex had the highest cytotoxicity on HepG-2 cancer cells with IC_{50} value of 6.50 μM[51].

Four different novel In(III) 2,6-diacetylpyridine bis(thiosemicarbazide) complexes (41a-41d) synthesized and the cytotoxicity were calculated at five tumor cell lines H460, SKOV-3, MGC-803, HeLa, t24 and non-tumor cell HL-7702. The complexes 41a-41c showed no cytotoxicity against these cell lines. 41d showed good cytotoxicity on cancer cell lines but lower activity in normal cells. Therefore 41d could be promising multi-target anticancer metal lead drug[52].

A new Schiff base synthesized from 3-pyridine carboxaldehyde with benzene sulfono hydrazide and in silico anticancer studies done which showed that the compound is similar to drug and it made favorable binding interaction with selected anticancer drug target[53].

A series of 1:1 Cu(II) complexes (42a-42c) and 1:1:1 Cu(II) complexes (42d-42f) were prepared and tested for anticancer activity against Bel-7402, MEF-7, A549, and A549cisR cancer cell lines. As a result, the 1:1:1 mixed ligand Cu(II) complexes exhibited two to eightfold better activity than the 1:1 Cu(II) complexes. The introduction of the co-ligand pyridine moiety increases the anticancer activity of compounds[54].

Two mixed ligands, which contained different aryl hydrazone as ligands and pyridine as a co-ligand, were prepared. Its Cu(II) complexes (43a-43b) anticancer activity was evaluated against humans cancer cells using MTT assay. The result displayed that the ligands and Cu^{2+} had low activity against cancer cells, but 43a & 43b exhibited high cytotoxicity. Both synthesized Cu(II) complexes showed a broad spectrum of inhibition with IC_{50} values ranging from 1.57 to 5.23μM, which were lower than those of Cisplatin (A549cisR). The 43b complex displayed higher cytotoxicity than the 43a complex. Both the complexes were less potent towards WI-38 and had great potential to display anti-metastatic activity via the inhibition of cancer cell migration[55].

A series of sixteen Cu(II) complexes (44a-44p) using eight ligands (a-h) were prepared by the condensation of 2-amino methyl pyridine and 2-hydroxy-3,5-halogen-substituted salicylaldehyde. The anti-proliferative effect of synthesized Cu(II) complexes was evaluated in three human cancer cell lines, A2780, HCT-116, and MCF-7. The 44a-44d complexes {Cu(Cl2-L1)Cl, Cu(Br2-L1)Cl, Cu(BrCl-L1)Cl and Cu(Cl2-L1)NO3}demonstrated the greatest antiproliferative activity in A2780 cell compared to HCT-116 cells. In vitro selectivity of

complexes in A2780 tumor cells compared to normal cells 44d was the most promising with a higher therapeutic window[56].

A series of eighteen Cu(II) complexes (45a-45r) with tridentate NNO β-acyl enamine ligand is prepared, which is derived from 2-picolin amine and bearing different substituents (R, R′, and R″) on the pyridine ring and the chelate cycle. All compounds cytotoxic activity was evaluated against human cell line 518A2, HT-29, HCT-116wt, HCT-116p53 and HeLa using the standard MTT assay. Complex 45j and 45n showed the highest activity among all the investigated compounds, including the clinical standard drug Cisplatin against all cancer cell lines. Complexes with a cyanide side chain (45k & 45º) were inactive (IC_{50}>50μM)[57].

A novel series of transition metal complexes (46a-46k) with a 19 membered pyridine base macrocyclic ligand (1, 5, 12, 16-tetraaza-3, 4:7, 10:13, 14-tribenzol 1,16 (2, 6-pyrido) cyclonadecan-5, 11diene 2, 15diene) has been prepared and investigated against the cancer cell lines MCF-7 and HepG-2. Except for Ru(III) complex, the ligand and all complexes showed great activity towards MCF-7 and HepG-2 cells. These complexes are considered as a promising anticancer agent[58].

A series of substituted hydrazilyl pyridine-based Schiff base ligand and corresponding palladium(II) complexes (47a-47f) were synthesized. The synthesized complexes were tested for In vitro anticancer activity against the HCT-116 cancer cell line with Cisplatin as the positive control. The IC_{50} values of the mixed ligand palladium(II) complex 47d are lower than carboplatin(64.97μM). The anticancer activity of palladium complexes found in decreasing order of 47d(51μM)>47e(132μM)>47b(138μM)> 47a(165μM)>47f(272μM)>47c(238μM)[59].

Two biologically active Schiff base ligands were prepared from the condensation reaction of 2-amino-5-(pyridine-4-yl)-4H-1,2,4-triazole-3-thiol with thiophene-2-carbaldehyde and furan-2-carbaldehyde. The prepared Schiff base was used for complexation with different metal ions [Co(II), Ni(II), and Cu(II)], and the cytotoxic effect of these complexes on cancer cell line MCF-7 and HepG-2 were investigated. All the complexes (48a-48l) showed moderate to significant %inhibition on HepG-2 and MCF-7 cells. The cell proliferation of the complexes 48f & 48i showed 38% and 49% inhibition on HepG-2, respectively. 48i, 48j and 48k showed 34%, 38% and 33% inhibition on MCF-7 cell line respectively[60].

The Schiff base ligands were synthesized using three different aldehydes (4-pyridine carboxaldehyde, 2-pyridine carboxaldehyde, and salicylaldehyde) and coordinated with ruthenium metal ion. These organo ruthenium complexes (49a-49i) were evaluated against HeLa, MCF-7, Ht-29, and MDA-MB-231 cell lines and non-cancerous HEK-293T cells. Complex 49a and 49f were selective towards HeLa, MCF-7, Ht-29 cell lines but less active on MDA-MB-231 cells[61].

Schiff base ligands, namely (2-hydroxy-4-methoxy benzylidene)2-pyridine amidrazone (L1), (2-hydroxy benzylidene)2-pyridine amidrazone (L2), (1-(2-hydroxy phenyl)ethylidene)2-pyridine amidrazone (L3), (1-phenyl ethylidene), 2-pyridine amidrazone (L4), and its corresponding rhodium and iridium half sandwiched metal complexes (50a-50h) were synthesized. The complexes (50a-50h) were evaluated against HT-29 and non-cancer cell line ARPE-19. All the complexes were found to be active against the HT-29 cell line, and 50e showed more activity[62].

A new Schiff base ligand was prepared from N1-(2-morpholino ethyl)-N1-([pyridine-2-yl]methyl)propane-1,3diamine and hydroxyl benzaldehyde, then its metal complexes (51a-51h) were synthesized. The cytotoxic effect of each compound against MCF-7, MDA-MB-231, PC-3, and WI-38 was examined using an MTT assay. All the complexes except 51h had higher potency towards MCF-7 and MDA-MB-231, and complex 51f had higher potency towards PC-3 (IC_{50}=28.5±0.30) compared to Cisplatin[63].

The three Cu(II) chloro complexes (52a-52c) containing N-(2-pyridine methyl)-2-mercapto aniline and (2,2′-di(pyridine-2-ethyleneimine)diphenyl disulfide) were prepared, and their biological activity was evaluated. The MTT assay showed that all complexes exhibited appreciable toxicity at 5μM dose on HeLa cell line with IC_{50} values of 1.27, 4.13, and 3.92 μM, respectively. The anti-proliferative activity of these complexes tested against normal HEK293 cells and 52c showed the minor activity in 5μM and

10μM concentrations. But the complex 51c at five μM concentration exhibited significant toxicity of 34.5% at HeLa and 84% in normal HEK293 cell lines[64].

The anticancer activity of Cu(II) complexes (53a-53f) developed by $CuCl_2$ and 2-(2-pyridinyl) benzimidazole were evaluated against A549 cells. The IC_{50} values of these complexes ranged from 5.5-12μM and showed promising cytotoxic activity. As compared to all the synthesized Cu(II) complexes, 53b showed the most potent activity[65].

Oxovanadium(IV) complexes of the new Schiff base ligands ((acridinyl)dipyrido-phenazine (acdppz) and vitamin B6) were synthesized, and the cytotoxicity of the complexes (54a-54d) were evaluated in the dark and visible light against HeLa, MCF-7, and normal MCF-10A cell lines. The MTT assay showed complexes 54c and 54d were photo-cytotoxic to the cancerous cells and non-toxic to MCF-10A cells. In visible light irradiation, the IC_{50} values of the complexes 54c and 54d in HeLa cells were 0.36±0.04μM and 0.24±0.02μM and in MCF-7 cells were 0.91±0.05μM and 0.53±0.03μM. In the dark, these complexes were non-toxic against the tested cell lines[66].

CONCLUSION

Cancer is a complex disease; there are numerous therapeutic options available. The success of platinum-based anticancer medications has paved the way for developing new metal-based cancer treatments that are free of side effects. Schiff bases are a well-known ligand that has gained much interest in several fields because of their biological actions. This review gathered all contemporary research findings on pyridine Schiff base complexes and their anticancer potential against various cancer cell lines. The majority of the complexes showed good activity against various cell lines, with IC_{50} values equal to or even lower than the reference drug. This review discovered that the metal complexes were more potent than the Schiff base ligands. We conclude that this review article will aid researchers in developing new Schiff base complexes with pyridine moiety as anticancer agents.

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Conflict of Interest

There is no conflict of interest among the authors.

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Certificate of Presentation

This is to certify that Ushanandhini.S, Mphil Scholar presented the paper on Comparative Study on Antifungal Activities of Knoevenagel Condensate Appended Schiff bases in the International Web Conference on "Food Technology and Nutrition-Prospects for Health" organised by Department of Food Science and Nutrition and Nutrition Society of India, Coimbatore Chapter on 28th & 29th January 2021.

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