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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF SCHIFF BASE METAL COMPLEXES CONTAINIG QUINAZOLINE CORE UNIT

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ABSTRACT:
A new Schiff base is derived from 2,4-dichloroquinazoline, ammonia and benzophenone. The metal complexes of Schiff base were prepared from nitrate salt of Ni(II),Co(II), Cu(II) in alcoholic medium.The complexes were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, UV-visible spectroscopy and X-ray diffraction studies. The Schiff base ligand and complexes were tested for their antibacterial activity against Staphylococcus aureus, Escherichia coli and Proteus vulgaris to assess their inhibiting potential. In screening medium was nutrient agar and biological screening were performed by employing cup plate method. Antibacterial activity of the ligand and its metal complexes is compared with the standard drug ciprofloxacin. In this series Co (II) complexes showed high antibacterial activity and the other complexes showed moderate antibacterial activity against different bacterial activity than the respective free Schiff base.

KEYWORDS: Schiff base, Metal complexes, antibacterial activity, 2,4dichloroquinazoline.

INTRODUCTION:

Schiff base ligand are derived by the condensation of active carbonyl group with primary amine containing the azomethine (CH=N) group in which the carbonyl group of aldehyde or ketone is replaced by azomethine group under specific condition and it was named by Hugo Schiff (1864). Schiff base was invented by Hugo Schiff, which is named after him. Basicallythere are compounds with a functional group those possess a carbon-nitrogen double bond with the

nitrogen atom connected to an aryl or alkyl group, not with hydrogen. In general sense Schiff bases, could be represented as the general formula $R_1R_2C=NR_3$, where R is an organic side chain. Some of them are restricted to the secondary aldimines (like azo-methines as the carbon is attached with a hydrogen atom) with the general formula RCH=NR'[i-iii]. Carbon-nitrogen double bond provides a significant contribution in various progresses of chemical sciences. Schiff-base compounds have been potentially used as fine chemicals and medical substrates. Number of methods are been applied for synthesis of Schiff base. In traditional method of synthesis also known as organic synthesis, which commonly involve the removal solvents from the reaction mixture or liquid extraction especially in the case of aprotic dipolar solvent with high boiling point, or product isolation through liquid-liquid extraction [**iv**]. Microwave-assisted reactions have been intensively investigated as mentioned in previous study. Microwave methods have been popularly used in Schiff base synthesis by organic synthesis as it has several benefits like better atom economy, environmental friendly, less hazardous, etc**[v-viii].**

In general mechanism of synthesis of Schiff base, an aromatic amine reacts with a carbonyl compound by nucleophilic addition. This forms a hemiaminal, followed by a dehydration to produce imines. Schiff bases obtained from aromatic aldehydes and aromatic amines have a shown number of applications in many fields including pharmaceutical, life sciences and chemical science including inorganic and analytical chemistry **[ix-xii]**.

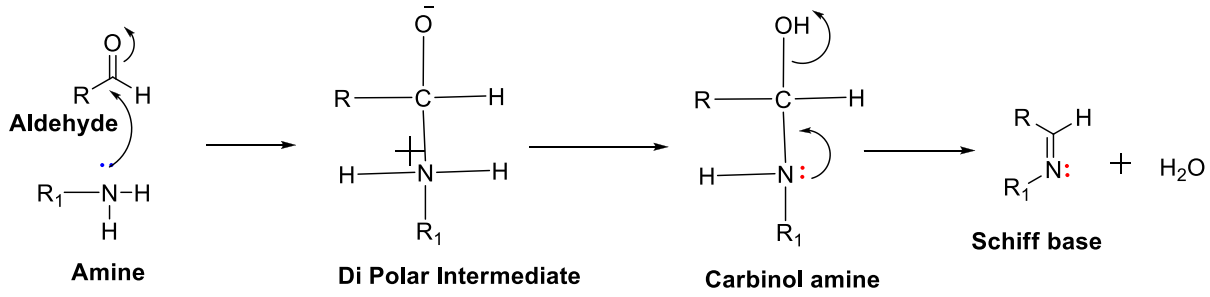


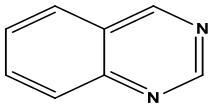
Figure-1 General reaction mechanism of Schiff base

The chemistry of coordination compounds with heterocyclic ligands containing oxygen and nitrogen as donor atoms has attracted the attention of chemists in recent years. It is well known that such ligands coordinate to metal atom in different ways in different media. Transition metal complexes with Schiff base have played an important role in much biological system in nature[**xiii-xv**]. The chelating properties of Schiff base display manifold applications in medicine and industry. Pyridine moieties have been reported to possess antimicrobial **[xvi]**, anti-inflammatory **[xvii]** and anticonvulsant **[xviii]** etc.

Schiff base metal complexes based research works have been widely carried out from 1930 because of their biological and industrial application **[xix-xxii]**, In organic chemistry Schiff bases are most widely used as pigments and dyes, catalysts, intermediate in organic synthesis, and as a polymer stabilizer **[xxiii]**. Schiff bases and their metal complexes are also well known to have pronounced biological activity **[xxiv-xxv]** and form an important class of compounds in medicine and pharmaceutical field also showed some degree of antibacterial ,antifungal, antitumor, anticancer and anti-inflammatory activity **[xxvi-xxxiv]** ,the azo-methine linkage are responsible for the biological activity of Schiff bases.

Quinazoline is a fused bicyclic compound and it is composedof six–membered benzene ring and apyrimidine ring. It was prepared in the laboratory in 1903 by Gabriel**[xxxv].**Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal

concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer **[xxxvi-xxxix]**, anti-inflammation **[xl]**, antibacterial **[xli]**, analgesia, anti-virus **[xlii]**, anti-cytotoxin **[xliii]**, anti-spasm **[xliv]**, anti-tuberculosis **[xlv]**, anti-oxidation **[xlvi]**, anti malarial**[xlvii],** anti-hypertension **[xlviii]**, anti-obesity **[xlix]**, anti-psychotic **[l]**, anti-diabetes **[li-liii],** etc. Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. And the potential applications of the quinazoline derivatives in fields of biology, pesticides and medicine have also been explored.



QUINAZOLINE

Table 1 BIOLOGICAL ACTIVITY OF QUINAZOLINE CORE UNIT

S.No	Quinazoline derivative	Use
1	Afatinib	Antifungal activity
2	Alfuzocin	Anticancer activity
3	Barasertib	Acute myloid leukemia
4	Cediranib	Heamatological
5	Letemovir	Human cytomegalovirus
6	Sotrastaurin	Psoriasis, Ulcerative Colitis
7	Tandutinib	Glioblstoma
8	Varlitinib	Anticancer drug
9	Verubulin	Anticancer drug
10	Dacomitinib	Antifungal
11	Alfuzosine	Anticancer
12	Prazosin	High blood pressure Treatment
13	Terazosine	Hyper tension

The aim of this study was to make Schiff bases of Metal complexes followed by characterization and antimicrobial activity determination of the Schiff bases and metal complexes. In view of these findings we have synthesized some metal complexes with a new Schiffbasebis((4phenylpyrimidin2yl)(((2thioxo1,2dihydroquinolin3yl)methylene)hydrazono) methoxy)which was prepared by the reaction between-4-phenylpyrimidine-2-carbohydrazide and 2thioxo-1,2-dihydroquinoline-3carbaldehyde.

Table-2 physical characterization, analytical and molar conductance of Schiff base and metal complex

Compound molecular formula	Mol.Wt	Melting point in ^{0}C	colour	Molecular conductivityin Mho.cm^2 mol^{-1}
$C_{21}H_{14}N_3Cl$	343.5	85	yellow	-
$C_{84}H_{60}N_{12}Cl_4Cu$	1473.5	256	Light green	28.45
$C_{84}H_{60}N_{12}Cl_4Ni$	1468.7	270	Brown	45.63
$C_{84}H_{60}N_{12}Cl_4Co$	1468.9	284	Dark brown	36.45

Table-3 Elemental analysis of Schiff base and Cu(II),Ni(II),Co(II) complexes

compound	Found (calculated)				
	C	H	Cl	N	M
$C_{21}H_{14}N_3Cl$	73.43 (73.36)	4.1(4.07)	10.42(10.35)	12.5(12.24)	-----
$C_{84}H_{60}N_{12}Cl_4Cu$	68.12 (68.4)	4.03 (4.07)	9.52 (9.64)	11.2(11.4)	4.1(4.3)
$C_{84}H_{60}N_{12}Cl_4Ni$	67.86(68.63)	3.92(4.08)	9.56(9.7)	11.3(11.4)	3.89(4.01)
$C_{84}H_{60}N_{12}Cl_4Co$	67.89(68.62)	3.93(4.06)	9.58(9.68)	11.09(11.4)	3.92(4.01)

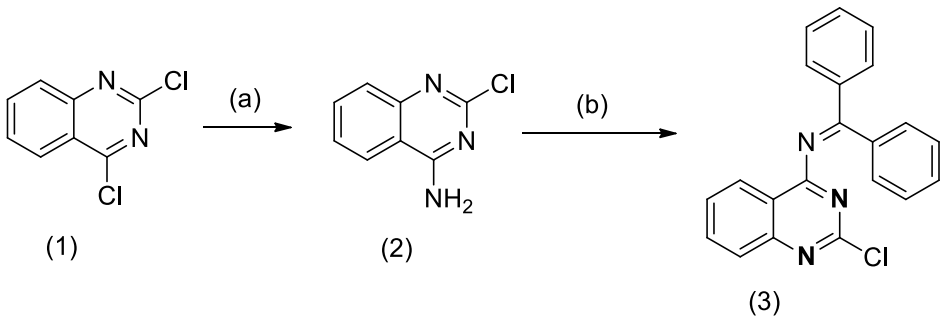
MATERIALS AND METHODS:

In this research all chemicals were purchased from SD fine chemicals Pvt.Ltd and used without further purification.

EXPERIMENTAL SECTION:

The reagents and solvents used in this work were analytical grade and used directly. The melting points were determined in open glass capillaries tubes. Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel G plates and spots were located byusing iodine chamber. The IR spectra were recorded on a Beckman Acculab-10 spectrometer (ν max in cm^{-1}) and the ^1H NMR spectra were recorded by Brucker DPX300 MHz using $CDCl_3$ as solvent.

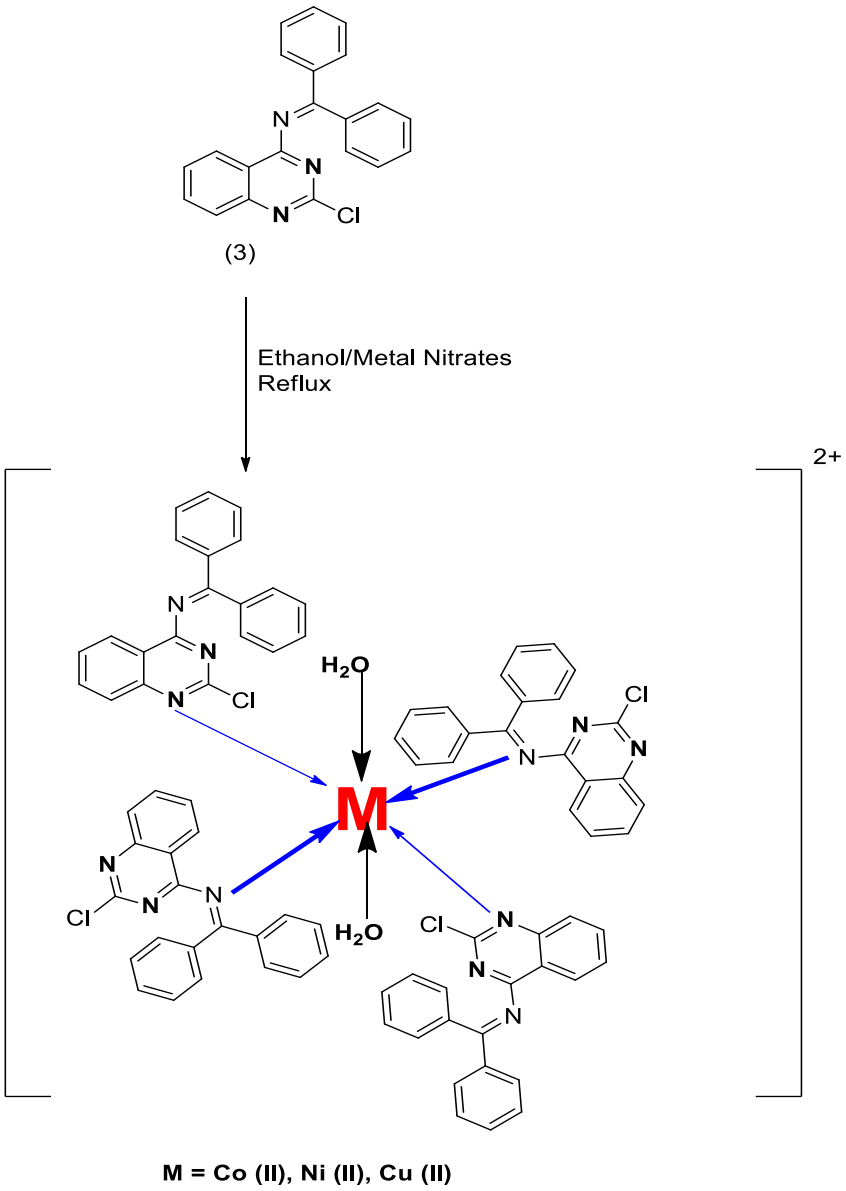
Scheme I Synthesis of Ligand



(1) (2) (3)

Reagents and Reaction conditions: (a) *Aqueous Ammonia, THF, RT, 3hrs (b) Ethanol, Acetic acid(catalytic),Benzophenone, reflux, 04 hrs*

Scheme II Synthesis of Metal Complexes



Reagents and Reaction conditions: *Ethanol, reflux, 04 hrs*

SYNTHESIS:

Synthesis of 2-chloroquinazolin-4-amine from 2,4-dichloroquinazoline

A mixture of 0.1 mole of 2,4-dichloroquinazoline in THF and water (2:1) were taken and cooled in an ice bath at 0-5^{O}C. 0.3 mole of Na_2CO_3 and then 20mL of ammonia solution (25%) was slowly added at 5-10^{0}C. The reaction mixture was allowed to stir at room temperature for 3 hour. Then THF was concentrated under reduced pressure then diluted with water. The solid was dried under vacuum over anhydrous $CaCl_2$. Total yield 75% of 2-chloroquinazolin-4-amine. Its M.P was determined as 2-315^{0}C.

Synthesis of Schiff base from 2-chloroquinazolin-4-amine

0.02mole of 2-chloroquinazolin-4-amine was dissolved in 10mL ethanol and 0.02mole of benzophenone were mixed in a 100mL round bottom (RB) flask. The mixture was stirred for

4 hours at 60^{o}C. The ethanol solution was evaporated under vacuum till the solvent is completely evaporated then filtered and washed several times with ethanol. It was re-crystallized with hot ethanol and dried. A yellow precipitate was obtained. The purity of the obtained product was checked by TLC.

Synthesis of metal complex

The ethanol solution of 0.005moles of Schiff base and mixed with ethanol solution of 0.005moles of metal solution. The mixture was refluxed for 4-6 hours at 75-80^{0}C. The color complex formed have been filtered and dried in vacuum. The synthesis of metal complexes is given in scheme 2 and Schiff bases and Schiff base metal complex physical and analytical analysis in the table 2 and table 3

RESULTS AND DISCUSSION:

Synthesis

2-chloroquinazolin-4-amine (2) was synthesized according to the reported procedure . The reaction of 2-chloroquinazolin-4-amine with Benzophenone to afford the corresponding Schiff base (3) as per the reported procedure**[liv],** which was reacted with Metal nitrates as per the reported procedure[**lv**] to afford Metal complexes.

IR, ^{1}HNMR Spectra of Ligand

The IR spectrum of ligand showed peak at 1635 cm^{-1} due to imine group. The ^{1}HNMR spectra of the Schiff base in d_6 DMSO at room temperature showed signal at δ 7.40-7.94 (m, 10H, Ar-H) due to protons of benzene ring aromatic protons, 8.4(1H,d),8.86(1H,d)due to protons of Pyrimidine ring protons, 6.92-7.16(8H,m) due to protons of quinoline ring protons respectively.

IR Spectral data of the complexes of ligand

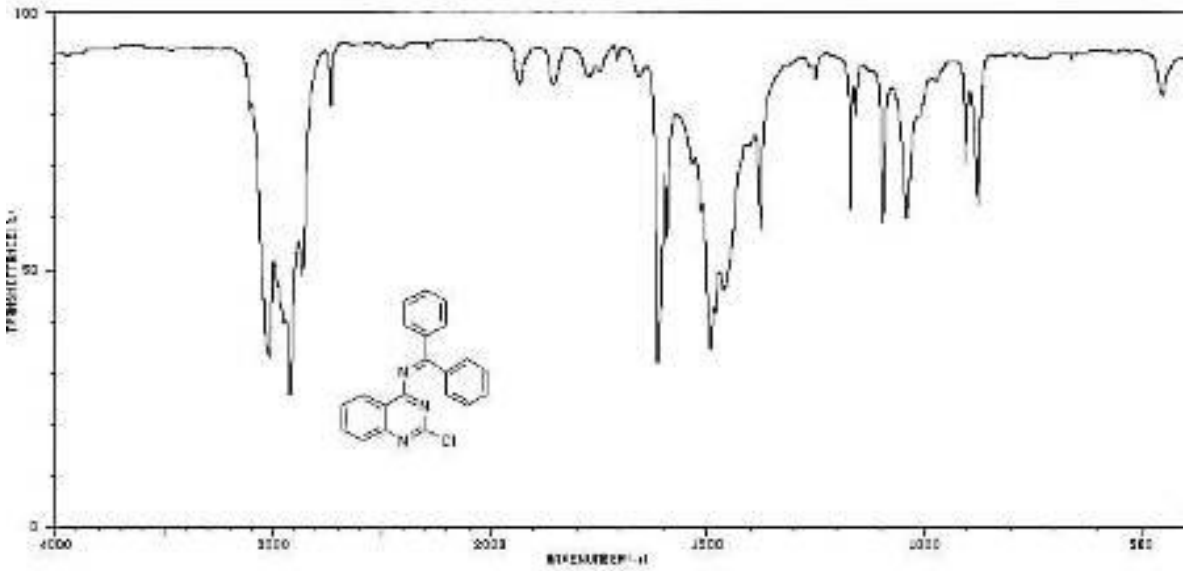
IR spectral data of ligand and its complexes are given in table 2. The IR spectrum of ligand was compared with those of the complexes of metal ions Co (II), Ni (II) and Cu (II) in order to study the binding mode of Schiff base to the metal ions.

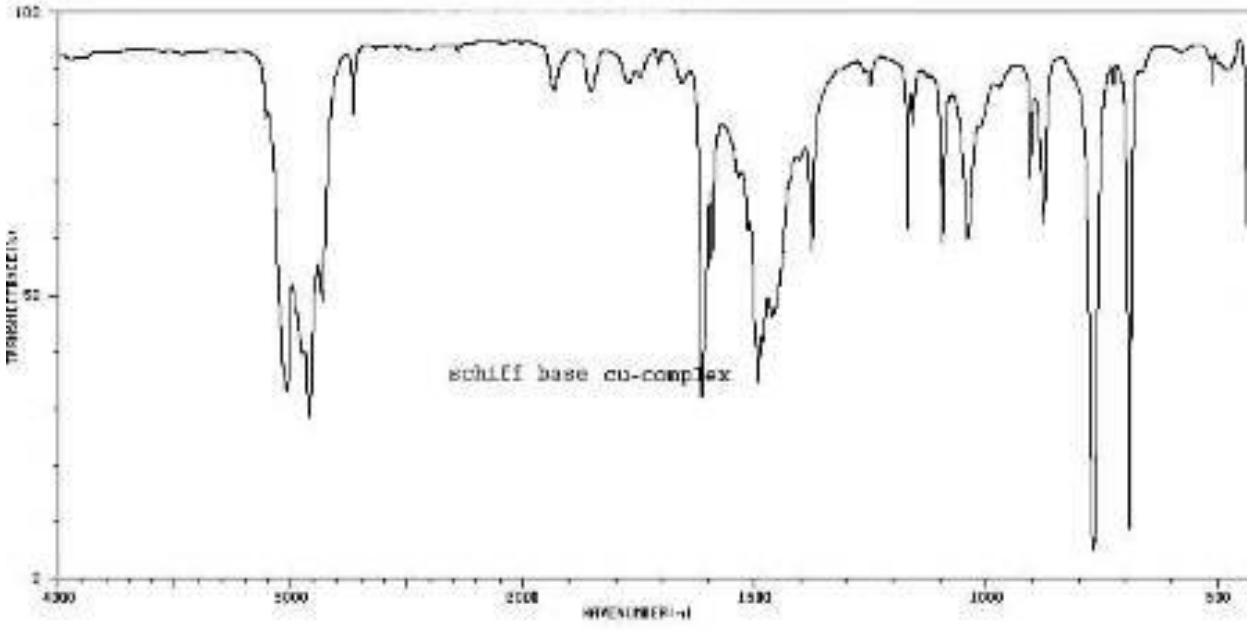
INFRARED SPECTRAL ANALYSIS:

Infrared spectra were recorded with a Perkin Elmer FTIR-4700 spectrometer (4000-400cm^{-1}) using Kbr pellets. FTIR is one the important analytical techniques which is the available to the chemistry based on the interaction of electromagnetic radiation with the matter. On the basis of this , the presence of important functional groups in the compound can be identified. The ligand was compared with the spectra of Cu(II), Ni(II) and Co(II) complexes.The IR spectrum of the ligand show at 1650cm^{-1}, which was assigned due to ν(C=N) stretching azomethine group[lvi]. The wave number of azomethine in the ligand (1650cm^{-1}) shifted to lower wave number 1630cm^{-1}, 1623cm^{-1} and 1635cm^{-1} after formation of Co(II), Ni(II) and Cu(II)complexes respectively[lvii]. It was suggested that the formation of co-ordination of nitrogen to metal ion in the complex due to reduce the electron density nitrogen in azomthine. The IR spectrum of Cu(II),Ni(II) and Co(II) metal complexes exhibits a broad and strong absorption band in the region 3500-3150cm^{-1} confirms the presence of ν(O-H) absorption for water[lviii-lx]. The bands between 500-440cm^{-1} were assigned to stretching wave number due to ν(M-N), the band between 640-620cm^{-1} have been assigned to the stretching wave number ν(M-N) respectively[lxi-lxii].

Table -4

Compound	**v(O-H)**	**v(C=N)**	**v(C-H)**	**v(M-N)**	**v(M-O)**
Schiffbase(L)	3400	1650	1057	--	….
Co-complex	3310	1630	1045	638	490
Ni-complex	3190	1623	1080	540	498
Cu-complex	3167	1635	1092	615	445





ELECTRONIC SPECTRA:

Electronic spectra of ligand and it's metal complexes was displayed in DMF solution.

Electronic spectra of ligand shows absorption in UV and visible region two high intensity bands at 39,780cm^{-1} and 41,650cm^{-1} which indicate $\pi\rightarrow\pi^*$and $n\rightarrow\pi^*$ transition of azomethine group ligand[63].

The electronic spectra of Co(II) complex shows two energy bands at 10,234cm^{-1} and 17,410cm^{-1}. This is due to $^2B_{1g}\rightarrow {}^2A_{1g}$and $^2B_{1g}\rightarrow {}^2B_{2g}$ transition respectively. The Co(II) complex show magnetic moment of 4.23BM. The high magnetic moment Co(II) suggested that octahedral geometry of around Co(II) ion[lxiv]. The electronic spectra of Cu(II) complex shows two energy bands at 10,868cm^{-1} and 14,970cm^{-1} is due to $^4T_{1g}(F)\rightarrow {}^4T_{2g}(F)$ and $^4T_{1g}(F)\rightarrow {}^4A_{2g}(F)$. The Cu(II) complex show magnetic moment of 1.96BM which is suggested that octahedral geometry[lxv]. The electronic spectra of Ni(II) shows absorption band at 16,110cm^{-1} and 23,210cm^{-1} assigned to $^3A_{2g}(F)\rightarrow {}^3T_{2g}(F)$ transition. The Ni(II) complex show magnetic moment 3.42BM, which is indicate the octahedral geometry[lxvi].

Table-5 Electronic spectrum of metal complexes

Complex	λ_{max}	Wave number (cm^{-1})	Electron transition	Magnetic momentum (BM)	Geometry
Schiff base	310nm 390nm	39,780cm^{-1} 41,650cm^{-1}	$\pi\rightarrow\pi^*$ $n\rightarrow\pi^*$	-	-
Cu(II) complex	396nm 438nm	10,868cm^{-1} 14,970cm^{-1}	$^4T_{1g}(F)\rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F)\rightarrow {}^4A_{2g}(F)$.	1.96	Octahedral
Co(II) complex	390nm 440nm	10,234cm^{-1} 17,410cm^{-1}	$^2B_{1g}\rightarrow {}^2A_{1g}$ $^2B_{1g}\rightarrow {}^2B_{2g}$	4.23	Octahedral
Ni(II) complex	410nm 450nm	16,110cm^{-1} 23,210cm^{-1}	$^3A_{2g}\rightarrow {}^3T_{1g}$ (F) $^3A_{2g}\rightarrow {}^3T_{2g}$ (F)	3.42	Octahedral

PHARMACOLOGICAL STUDIES:

Antibacterial Activity

All the newly synthesized metal complexes were tested for their antibacterial activity. Antibacterial activity was determined by agar cup plate method against the following organism- Staphylococcus aureus, Escherichia coli and Proteus vulgaris. The zone of inhibition of each strain was recorded. Antibacterial activity of the ligand and its metal complexes was compared with the standard drug ciprofloxacin. The variation in the activity of different metal complexes against different micro-organism depends on their impermeability of the cell or the differences in ribosomes in microbial cell. The lipid membrane surrounding the cell favours the passage of any lipid soluble materials and it is Known that lipo solubility is an important factor controlling antibacterial activity [lxvii-lxix].

Table 6: Antibacterial activity of ligand and its complexes:

Compounds	**Bacterial inhibition zone/mm**		
	S. aureus	**E. coli**	**P. vulgaris**
Ligand	13	16	14
Co- complex	19	20	19
Ni- complex	14	13	18
Cu- complex	12	18	19
Ciprofloxacin	20	22	20

The results showed (table-3) that ligand exhibits moderate activity against all tested bacteria. Co (II) complex showed high antibacterial activity against S. aureus, E. coli and P. vulgaris. Ni complex exhibited moderate activity against S. aureus and E. coli but highly effective against P. vulgaris. Zn complex exhibited moderate activity against S. aureus but showed good activity against E. coli and P. vulgaris microorganism. Antibacterial activity of the ligand and its metal complexes is compared with the standard drug ciprofloxacin. The variation in the activity of different metal complexes against different micro-organism depends on their impermeability of the cell [lxx-lxxiii].

CONCLUSION:

Based on overall study it was concluded that metal complexes of Schiff bases are more efficient antimicrobial agent than its native form. However the antimicrobial potentiality is of metal complex is highly dependent in the metal ion used for formation of metal complex.

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