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Synthesis and Biological Evaluation of a Novel Schiff Base Ligand [(E)-2,4-Dichloro-6-(1-((4-Fluorophenyl) iminoethyl)phenol] and Its Metal Complexes

Priyanka Kashid[1*], Yogesh Pawar[2], Saroj Bembalkar3, Rajendra. Pawar[4]

Abstract

The study involved the synthesis and characterization of a novel bidentate Schiff base ligand, [(E)-2,4-dichloro-6-(1-((4-fluorophenyl) iminoethyl) phenol)], derived from 1-(3,5-dichloro-2-hydroxyphenyl) ethanone and 4-fluoroaniline. Transition metal salts (Co (II), Cu (II), Fe (II), Zn (II), Ni (II), Mn (II), Ag (II), Cd (II), Hg (II), and Pd (II)) were used to synthesize metal complexes. The chemicals used were of analytical grade, and solvents were distilled before use. Characterization involved UV, IR, and NMR spectroscopic techniques, alongside physical properties such as melting points. The ligand exhibited bidentate behavior with a ligand-to-metal ion stoichiometry of 2:1.UV-Visible spectrophotometry at 240 nm and FT-IR spectroscopy (400-4000 cm^-1) confirmed the successful synthesis of the ligand and metal complexes. NMR spectra recorded on a 500 MHz spectrophotometer further validated the structures. Thin layer chromatography (TLC) monitored reaction progress. The metal complexes exhibited characteristic bands indicating coordination between the metal ion and ligand atoms. Biological activity assays against various bacteria (Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis) revealed significant antimicrobial activity for Cu (II) and Ni (II) complexes, surpassing that of standard drugs. The metal complexes showed varying degrees of activity against different bacterial strains.The synthesized ligand and metal complexes displayed promising antimicrobial properties, particularly Cu (II) and Ni (II) complexes. This research contributes to the understanding of Schiff base complexes as potential antibacterial agents.

Keywords: Schiff Base, Metal Complexes, Spectroscopic Characterization, Antimicrobial Activity, Bidentate Behavior

INTRODUCTION

Schiff bases remained important ligands even a century after they were discovered in coordination chemistry [1]. Schiff base molecules are fundamental to coordination chemistry [2]. Schiff bases are created when amines and aromatic/aliphatic aldehydes/ketones condense [3]. Synthesised ligands that form stable complexes with different transition metal ions continue to be of great interest to inorganic chemistry [4]. Because of their excellent solubility in common solvents and extremely stable coordination molecules, Schiff's bases have found widespread usage as ligands [5]. Because coordinated metal ions operate as bidentate or tetradentate ligands in biological systems, which aids in our understanding of their structure and behavior in a variety of functions, these Schiff's base metal derivatives are incredibly fascinating [6]. Because of their excellent solubility in common

***Author for Correspondence**
Priyanka Kashid
E-mail: priyanka.y.pawar@gmail.com
[1]Ph D Scholar, Deogiri College, Chatrapati Sambhajinagar, Maharashtra Department of Chemistry
[2]Registrar, Sanjivani College of Engineering, Kopargaon
[3-4]Professor, Department of Chemistry, Deogiri College, Sambhajinagar, Maharashtra, India

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solvents and extremely stable coordination molecules, Schiff's bases have found widespread usage as ligands [7]. Because coordinated metal ions operate as bidentate or tetradentate ligands in biological systems, which aids in our understanding of their structure and behavior in a variety of functions, these Schiff's base metal derivatives are incredibly fascinating [89].

Schiff bases are chelating that are used to complex metal ions [1011]. Schiff bases, which contain the C=N functional group, are an important class of compounds because they are used in the synthesis of biologically active heterocyclic compounds [12]. Complexes with metal ions can be formed by Schiff base ligands containing nitrogen and oxygen donor atoms [13]. Imines are essential due to their chemical stability and biological activity [14]. Schiff base ligands and their metal complexes exhibited antidepressant, antitubercular, anticonvulsant, antimicrobial, antimalarial, anti-inflammatory anti-fungal and anti-viral activities and antioxidant properties., [15] Cobalt (II) and iron (III) complexes of pyridine bisimine ligands were found to be active in ethylene polymerization.[16]. Bis-imines can be used to synthesize a wide range of bioactive compounds used in medicine [17], agriculture, materials science [18], and pharmaceuticals [19]. Some bis-imine metal complexes are used as catalysts in organic reactions [20].

As a continuation of our work on the synthesis and biological activity of Schiff base ligand and metal complexes [21], we report the synthesis of Schiff base (bis-imine) ligand from 1-(3,5-dichloro-2-hydroxyphenyl) ethanone and 4 fluoroaniline. Transition metal complexes were created using the newly synthesized Schiff base ligand. Different spectroscopic techniques were used to characterize the synthesized compound, and metal complexes were tested for antimicrobial activity. Antibacterial activity of metal complexes against Gram positive and Gram-negative bacteria.[22]

Experimental

Chemicals

Ammonia (AR), Ethanol (AR), Conc. Sulphuric acid, Acetone, Pet ether, Ethyl acetate Recrystallized 1-(3,5-dichloro-2-hydroxyphenyl) ethanone, 4-fluoro aniline Merck Chemicals in India supplied transition metal nitrate or chlorides salts of [Co (II), Cu (II), Fe (II), Zn (II), Ni (II), Mn (II), Ag (II), Cd (II), Hg (II), and Pd (II). All of the chemicals were used in the analytical grade synthesis. Purify The solvents used were distilled. Without further purification, metal salts were used. [23].

Instruments

UV- Visible Spectrophotometer

The UV detection at wavelength 240 nm was selected by using UV- Vis Spectrophotometer (UV-1650 PC) SHIMADZU INC.

FT-IR Spectrophotometer

The IR spectra were recorded by using Fourier Transform Infrared spectrophotometer with range 400- 4000 cm-1 by Perkin Elmer 10.4.2.

NMR Spectrophotometer

The NMR spectra were recorded by using BRUKER AVANCENEO 500 MHz NMR Spectrophotometer.

Thin layer Chromatography

The reaction's progress was monitored on a regular basis using the TLC method. A polar solvent system of Pet-ether and ethyl acetate (20%) was used, as well as an iodine developing tank. At the end of the reaction, a single spot appeared for all of the complexes, and the starting material vanished, confirming the completion of the reaction.[24]

Methods

Synthesis of [(E) -2,4 – dichloro – 6-(1-((4-fluorophenyl) imino ethyl) phenol]

1-(3,5-dichloro-2-hydroxyphenyl) ethanone. (1) (1 mmol) and 4 fluoroaniline (2) (0.6 mmol) were dissolved in ethanol as the solvent, and 1-2 drops of concentrated sulphuric acid were added as the catalyst. The resulting reaction mixture was refluxed for 4 hours at 80-90° C, and the reaction's progress was monitored using TLC. After the reaction was completed, the reaction mixture was cooled, and the product was precipitated by air contact. The product crystals are then filtered. [(E) -2,4 - dichloro - 6-(1-((4-fluorophenyl) imino ethyl) phenol] (3) was recrystallized from ethanol and confirmed by melting point, NMR, and IR spectra (Scheme 1). Melting point is 161° C, colour is yellow, and it is solid. IR spectra: 1646 (C=N), 3068 (FTIR-ATR, vmax cm-1) (NH). [25]

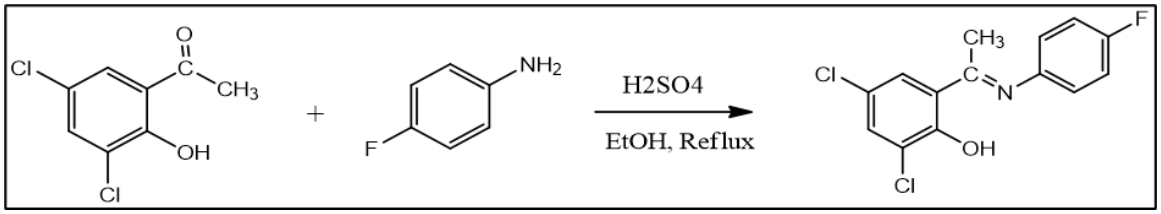

Figure 1. Synthesis of Schiff base ligand

Synthesis of Metal Complexes

In the ethanol-based solvent, a combination of the Schiff base ligand and transition metal salts (metal chlorides/metal nitrates) were dissolved. utilized a magnetic stirrer to agitate the reaction mixture. In molar, the metal to ligand ratio was 1:2. Ammonia was introduced to the mixture in small amounts. For 3–4 hours, the reaction mixture was refluxed. TLC kept track of the reaction's development. The items were poured into ice, where colored crystals developed, were filtered out, and were then dried. Its observed yield was good. All the newly synthesized metal complexes were confirmed by thin layer chromatography The goods' melting points were identified. [26] Figure 1

M=Co (II), Cu (II), Fe (II), Zn (II), Ni (II), Mn (II), Ag (II), Cd (II), Hg (II) and Pd (II).

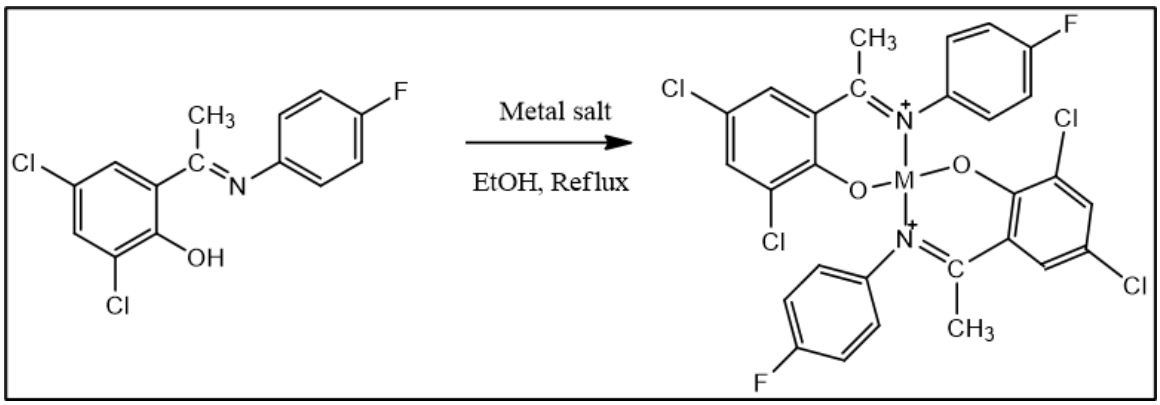

Figure 2. Synthesis of metal complexes.

The physical and analytical data of synthesized compounds are presented in Table 1.

Infrared Spectra of Metal Complexes

The IR spectra were recorded by using Fourier Transform Infrared spectrophotometer .The IR spectra of metal complexes were recorded in the wave number region of 400 cm-1- 4000 cm-1 [27]. The characteristic spectral band in the region 404- 440 cm-1 indicates the M-N band frequency i.e., the coordination of metal ion with the nitrogen atom of the ligand. The low-frequency band in the region 500-800cm-1 was characterized for metal complexes and indicates the coordination of oxygen atom of the ligand with metal, i.e., M-O frequency bands. The frequency bands at 1633-1648 cm-1 can be

recognized for C=N group. The stretching frequency bands at 2956-3072 cm-1 were assigned for C-H bond. IR spectra for metal complexes are reported in Table 2. IR spectra of Schiff base ligand shows in fig no.3.and Metal complex shows in fig no.4 respectively.[28] Figure2

2.4. UV -Visible spectra of metal complexes.

UV spectra of synthesized metal complexes was recorded in DMSO solvent. The wavelength of maximum absorbance (λmax) for metal complexes is reported in Table 3. UV spectra of metal complex shows in fig.5 and 6.[29]

Biological Activity

Resazurin-based 96-well plate microdilution method for the determination of minimum inhibitory concentration of various plant extracts was used. Testing Reagents were Nutrient broth, Resazurin, Plant extracts, Amphotericin B. Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis these Test Organism were used. Add 50µl of sterilized nutrient broth in each well of the 96-well plates. Then add 50µl of plant extract solution and antibiotic in the first column of the plate. Dilute the plant extract by transferring 50µl of extract from columns 1-10. That results in each well-containing 50µl of plant extract Add 50µl bacterial suspension in column 11 containing the nutrient broth for negative control. Column 12 contains only the 100µl of nutrient broth for sterilization control / positive control. Then add 50µl of the bacterial suspension in the wells containing plant extract and standard antibiotic. The time taken to prepare and dispense the OD-adjusted bacteria did not exceed 15min incubate the plate for 18-24 hrs at 37°C.After the incubation adds 30µl of the prepared resazurin solution in all wells of the microplate. After the addition of resazurin solution, incubate the plate for 2-4 hrs for observation of colour change. then observed that on completion of incubation, columns with no colour change (blue resazurin colour remain unchanged) were reported as above the MIC value.[30].

Results and Discussion

Physical and Analytical Data

The synthesised Schiff base ligand was prepared by the reaction of 1-(3,5-dichloro-2-hydroxyphenyl) ethanone and 4 fluoroaniline. Metal complexes were synthesized from Schiff base ligand and transition metal ions. Synthesized ligand and metal complexes were characterized by different spectroscopic techniques such as thin layer chromatography IR Spectroscopy NMR spectroscopy UV spectroscopy and by taking physical constant (melting points). The synthesised ligand and their complexes shows the good results. They are showing in table no. 1.

Table 1. Physical and analytical data of the synthesized compounds.

Sr. No.	Compound	Code	Molecular formula	M.P. (°C)	Colour of the ML	Percent Yield (%)
1.	Ligand(L)	PL	$C_{14}H_{10}NOFCl_2$	161	Yellow	81.52
2	CoL1	ML1	$C_{28}H_{18}N_2O_2F_2Cl_4Co$	244	Greenish Yellow	74.43
3	CuL2	ML2	$C_{28}H_{18}N_2O_2F_2Cl_4Cu$	>300	Faint Green	67.16
4	FeL3	ML3	$C_{28}H_{18}N_2O_2F_2Cl_4Fe$	>300	Brown	65.83
5	ZnL4	ML4	$C_{28}H_{18}N_2O_2F_2Cl_4Zn$	>300	Lemon yellow	68.83
6	NiL5	ML5	$C_{28}H_{18}N_2O_2F_2Cl_4Ni$	>300	Yellow	66.47
7	MnL6	ML6	$C_{28}H_{18}N_2O_2F_2Cl_4Mn$	>300	Greenish Yellow	57.67
8	AgL7	ML7	$C_{28}H_{18}N_2O_2F_2Cl_4Ag$	>300	Green	68.83
9	CdL8	ML8	$C_{28}H_{18}N_2O_2F_2Cl_4Cd$	>300	Pale Yellow	72.50
10	HgL9	ML9	$C_{28}H_{18}N_2O_2F_2Cl_4Hg$	>300	Yellow	85.24
11	PdL10	ML10	$C_{28}H_{18}N_2O_2F_2Cl_4Pd$	>300	Brown	63.31

IR Data

Metal complexes were screened for antimicrobial activities. IR spectra of Schiff base ligand (PL) showed a strong band at 1646 cm-1 corresponding to the stretching frequency of the C=N group. IR spectra of Schiff base ligand (PL) showed a strong band at 3060 cm-1for (-OH) hydroxyl stretching. The IR spectra of metal complexes show stretching frequency bands in the region 404-440 cm-1 can be recognized for coordination of metal ion and the nitrogen atom of ligand i.e., M-N bands. The IR stretching frequency bands at 500-840 cm-1 were characterized for metal ion, and the oxygen atom of ligand was coordinated (M-O). Frequency bands at 1633-1648 cm-1 indicate the C=N group. Frequency bands at 2918-3056cm-1 can be assigned to C-H bonds. The Schiff base ligand bis-imine is coordinated with metal ion through phenolic oxygen and azomethine nitrogen. Thus, the ligand behaves as bidentate.

Table 2. Infrared spectra data of metal complexeS.

Sample code	Compound	ν cm-1 (M-N)	ν cm-1 (M-O)	ν cm-1 (C=N)	ν cm-1 (C-H)
ML1	CoL1	413	507	1633	3068
ML2	CuL2	419	655	1585	2921
ML3	FeL3	407	555	1642	3066
ML4	ZnL4	434	500	1648	3072
ML5	NiL5	422	581	1648	3066
ML6	MnL6	459	646	1618	3074
ML7	AgL7	405	527	1612	2939
ML8	CdL8	457	648	1618	2968
ML9	HgL9	422	518	1639	3078
ML10	PdL10	434	537	1608	2937

1H NMR

1H NMR Spectra of (Schiff base ligand PL) [(E) -2,4 – dichloro – 6-(1-((4-fluorophenyl) imino ethyl) phenol] 1H NMR: d 0.77 (6H, q, J = 8.1 Hz), 2.33-2.43 (3H, 2.38 (s), 2.38 (s), 2.38 (s)), 7.02-7.14 (2H, 7.08 (dtd, J = 8.1, 1.3, 0.5 Hz), 7.08 (dtd, J = 8.1, 1.3, 0.5 Hz)), 7.31-7.65 (4H, 7.38 (dddd, J = 7.6, 4.7, 4.4, 0.9 Hz), 7.50 (dddd, J = 8.1, 7.6, 1.3, 0.5 Hz), 7.60 (d, J = 1.4 Hz)), 8.04 (1H, d, J = 1.4 Hz). Shows in fig no. 4

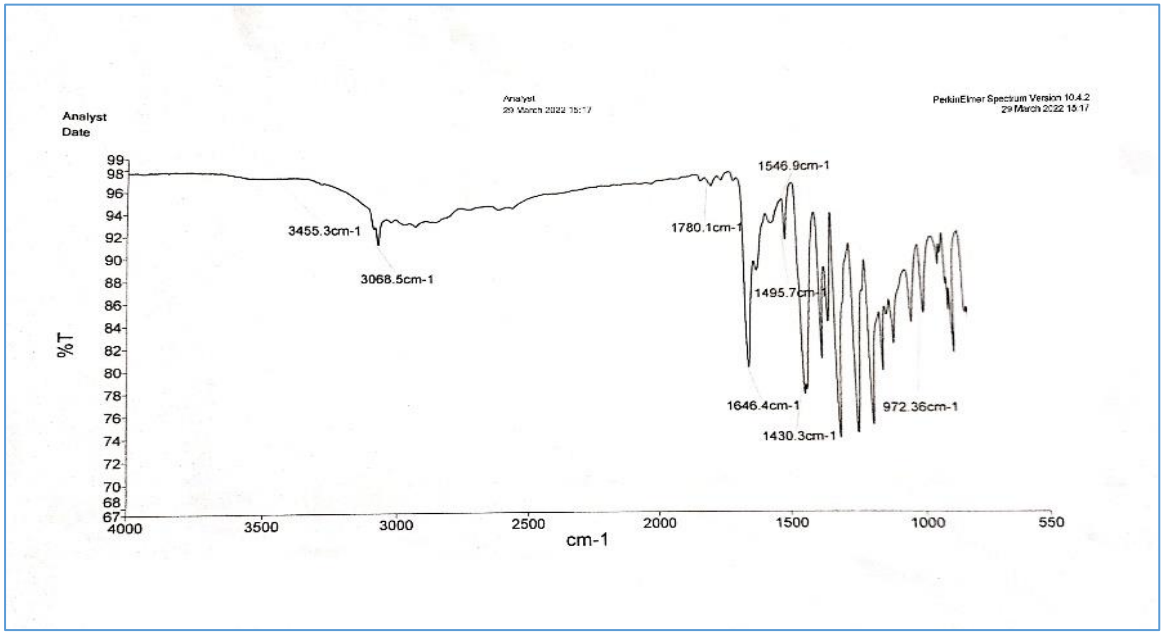

Fig 3: IR Spectra of (Schiff base ligand PL) [(E) -2,4 – dichloro – 6-(1-((4-fluorophenyl) imino ethyl) phenol]

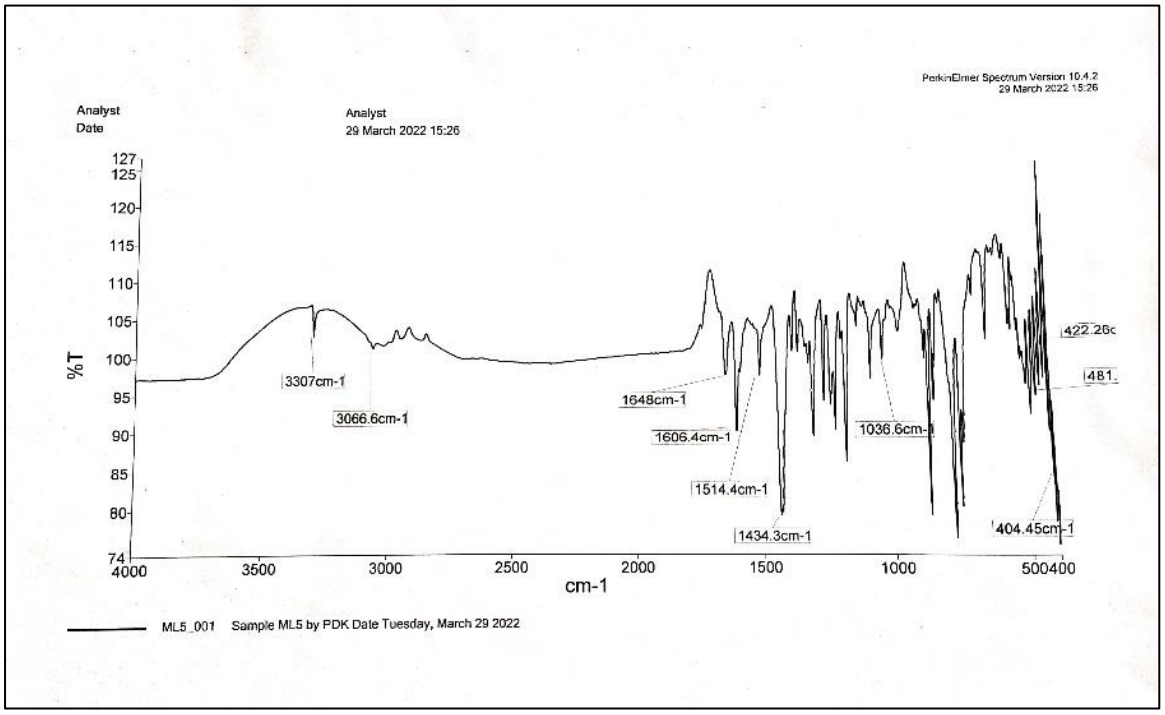

Fig 4: IR Spectra of Metal complex

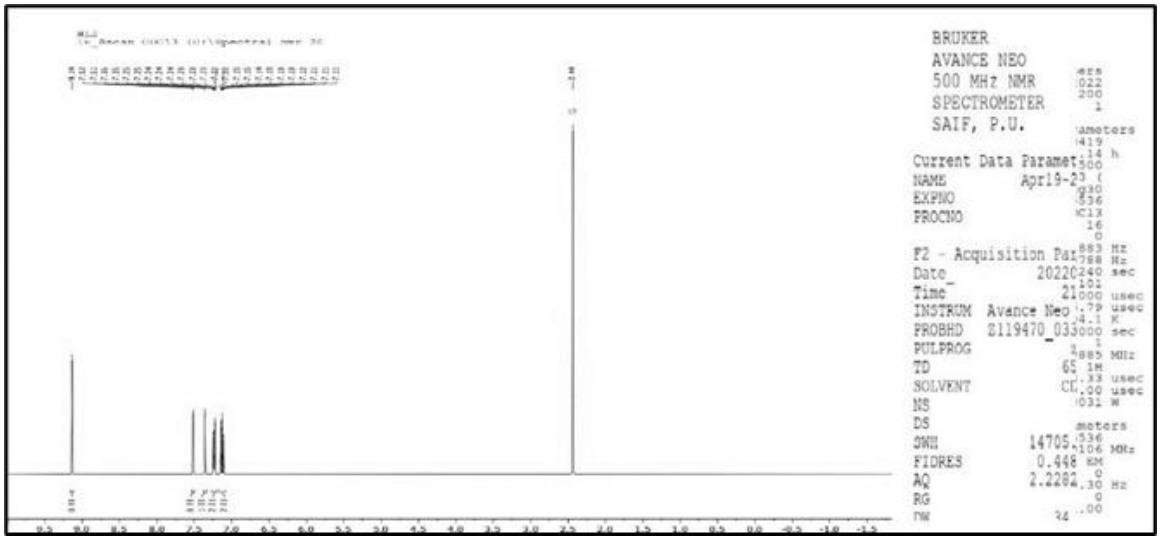

Fig 5. 1H NMR Schiff base ligand

UV Data

In the UV spectra of metal complexes, the wavelength of maximum absorbance (λmax) ranges from 275-300 nm. The λmax value of Ni (II) is high at higher absorption. The metal complexes were formed in a ligand to metal ratio of 2:1.

Table 3. λmax Value of synthesized metal complexes.

Sr. No.	Compound	Sample code	Wavelength (λmax)
1	CoL1	ML1	281.8
2	CuL2	ML2	279.60
3	FeL3	ML3	284.95
4	ZnL4	ML4	276.45
5	NiL5	ML5	292.86

6	MnL6	ML6	277.53
7	AgL7	ML7	282.20
8	CdL8	ML8	280.60
9	HgL9	ML9	281.45
10	PdL10	ML10	282.68

Antımıcrobıal Actıvıty Data

Cu (II), Zn (II), Fe (II), Ni (II), and Cd (II) metal complexes showed excellent activity against bacteria Bacillus subtilis (Gram+Ve. Zn (II), and Fe (II) showed remarkable activity against Staphylococcus aureus (Gram+Ve) Cu (II), Zn (II), Ni (II), Co (II), Mn (II), and Ag (II) showed moderate to excellent activity against Escherichia coli (Gram-Ve). Cu (II), Ni (II), and Zn (II) showed excellent activity against Pseudomonas aeruginosa (Gram-Ve)) bacteria species as compared to standard drug. The all-antibacterial activity shown in table no. 4

Table 4. Antimicrobial activity of the synthesized metal complexes

Compound	Standard conc. (ug/ml)	Bacteria	MIC (ug/ml)	Bacteria	MIC (ug/ml)	Bacteria	MIC (ug/ml)	Bacteria	MIC (ug/ml)
Amphotericin B (STD)	100	Bacillus subtilis (Gram+Ve)	100	Staphylococcus aureus (Gram+Ve)	25	Escherichia coli (Gram-Ve)	12.5	Pseudomonas aeruginosa (Gram-Ve)	11.1
ML1	1000		250		62.5		62.5		250
ML2	1000		62.5		62.5		15.62		31.5
ML3	1000		125		3.9		62.5		12.65
ML4	1000		125		7.5		11.25		12.65
ML5	1000		62.5		62.5		11.25		125
ML6	1000		62.5		62.5		11.25		31.5
ML7	1000		125		31.25		11.25		62.5
ML8	1000		62.5		62.5		15.62		125
ML9	1000		125		62.5		15.62		125
ML10	1000		500		125		62.5		500

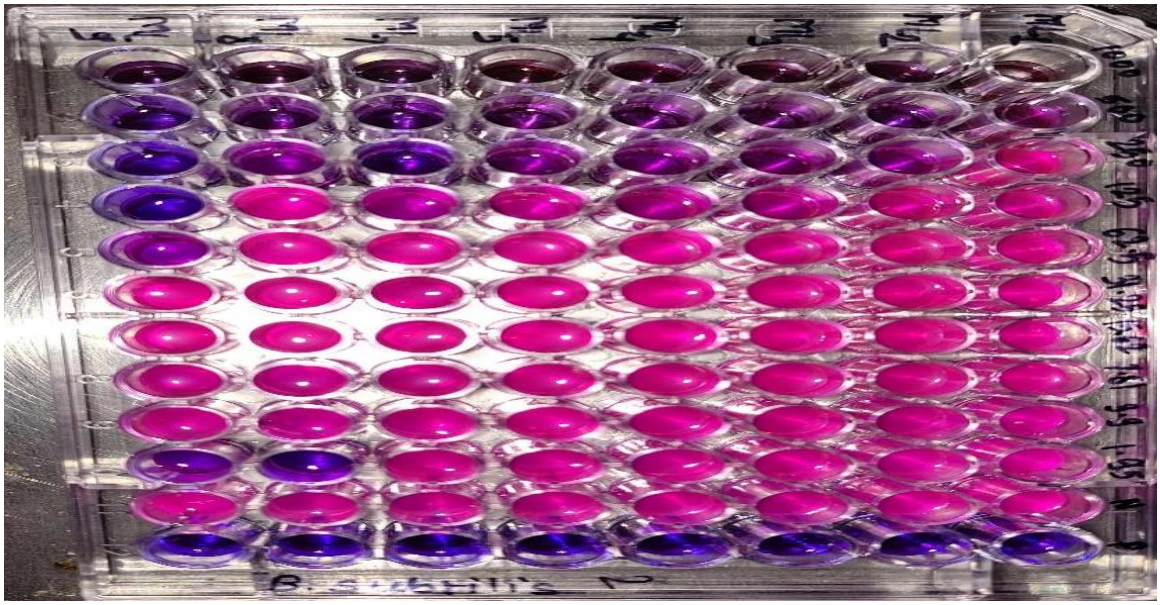

Fig 6: Biological Activity of metal complexes

CONCLUSION

In the present work, a new bidentate Schiff base ligand [(E) -2,4 – dichloro – 6-(1-((4-fluorophenyl) imino ethyl) phenol] was synthesized with1-(3,5-dichloro-2-hydroxyphenyl) ethanone and 4 fluoroaniline.It was yellow solid in nature.it shows the excellent characterization in IR NMR spectroscopy. The new schiff base ligand was used for the synthesis of metal complexes with transition metals salts of nitrates or chlorides Co (II), Cu (II), Fe (II), Zn (II), Ni (II), Mn (II), Ag (II), Cd (II), Hg (II) and Pd (II). The synthesized ligand and metal complexes were characterized by different spectroscopic methods. And they show the excellent results. The synthesized metal complexes were analyzed for antimicrobial activities aganst Bacillus subtilis (Gram+Ve), Staphylococcus aureus (Gram+Ve) and Escherichia coli (Gram-Ve) Pseudomonas aeruginosa (Gram-Ve) Cu (II), Ni (II), Fe (II) and Zn (II) showed excellent activity

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