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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL SCREENING OF NEW NICKEL (II) METAL COMPLEXES INCORPOATING SCHIFF BASES

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Abstract

In this, research four Schiff bases ligand (L_1-L_4) and its Ni (II) Complexes (CL_1-CL_4) synthesized and characterized. These complexes were synthesized using the ligands listed above and $NiCl_2.6H_2O$ in a 1:1 stoichiometric ratio. Synthesized ligands were characterized by using ^1H NMR, ^{13}C NMR, UV-Visible, FT-IR, and HRMS techniques. The Ni (II) complexes were characterized by using UV-Visible, FT-IR, and TGA techniques. These complexes and ligands exhibit significant antibacterial activity over four distinct human pathogenic bacterial strains such as gram-negative *Escherichia coli*, *Pseudomonas aeruginosa*, and gram-positive *Staphylococcus aureus* and *Bacillus substilis* whereas antifungal activity against *Candida albicans* and *Aspergillus niger* fungal strains.

Introduction

Currently, there has been an increase of drug-resistant in bacteria. This is directly linked to higher mortality rates from infectious illnesses. Therefore need of search of new drugs [1, 2]. Coordination complexes increasingly replace traditional organic drugs. Zinc, calcium, iron, and cobalt metals exhibit significant biological effects when combined with Schiff base ligand. Recently, Inorganic materials like metal and metal oxides have gained increased attention because they are typically safe for both humans and animals. Oxides of transition metals are made up of oxygen atoms attached to transition metals [3].

Schiff bases were used in a variety of fields like biology, medicine, and catalysis [4, 5]. Schiff base complexes contributed to significant developments in coordination and stereochemistry [6, 7]. From last 12 years, many advances and new techniques have been discovered for synthesis of Schiff base including solvent-free, clay, solid-state synthesis, K-10/microwave, BF_4/molecular sieves water

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suspension medium, microwave irradiation, infrared irradiation, microwave/solvent-free and silica/ultrasound irradiation [8-16].

Nickel complexes are highly studied in the field of coordination. These Complexes have high stability and diverse uses. Ni (II) ions form complexes with Schiff bases in several geometries, particularly tetrahedral, square planar, as well as octahedral. The square Planar, octahedral and geometries are the most common. The tetrahedral, trigonal, and square-based pyramidal geometries are rare [17]. The Nickel complexes plays important role in biochemistry. The tetradentate N_2O_2 Schiff base Ni (II) complexes formed from salicylaldehyde may be used as homogeneous and heterogeneous hydrogenation catalysts in the cages of zeolites Y and X [18-20]. When N-substituted heterocycles react with metal salts, they produce their corresponding coordination complexes, which have important pharmacological properties [21-23].

Taking into account what was said before and continuing on with our efforts to develop novel Antimicrobial drugs. We are presenting here the synthesis and characterization of Ni (II) complexes using a Schiff base ligand.

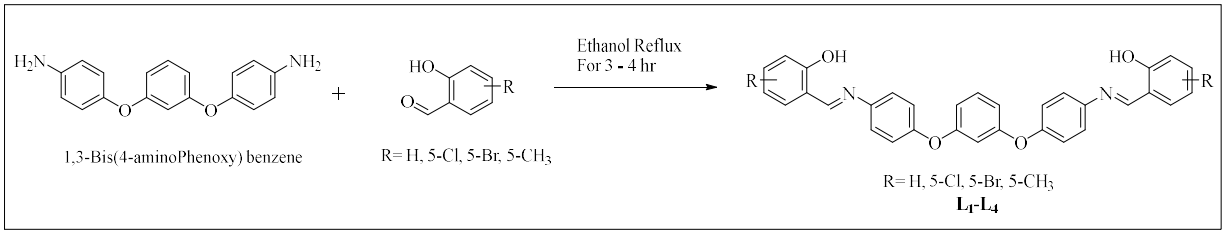
EXPERIMENTAL

Materials and Methods

All necessary chemicals and reagents were purchased from Merck chemicals. All commercially available chemicals and solvents were used exactly as they were supplied. All the chemical transformations were monitored by using Thin Layer Chromatography (TLC) on a 2–5 cm percolated E. Merck Silica Gel 60 F254 plates (0.25 mm) and spots were visualized using UV lamp. To find the chemical composition of produced compounds a Perkin-Elmer 1200 FT-IR spectrometer was used. All melting points were determined on a Biotechnic India capillary melting point apparatus and are uncorrected. NMR spectra were recorded with a Bruker AM-400 MHz spectrometer in $CDCl_3$; with $(CH_3)_4Si$ is an internal standard for ^{1} H NMR spectra and solvent signals as internal standard for ^{13}C NMR spectra at ambient temperature. Chemical shifts (δ) are reported in ppm. Coupling constants J were reported in Hz. NMR signal splitting patterns were designated as follows: s - singlet, d - doublet, dd -doublet of doublet, dt -doublet of triplet, td - triplet of doublet, t- triplet, q-quartet, p-pentet, bs-broad singlet, m-multiplet, br-broad The electronic absorption of synthesized compounds was examined with a UV-Visible spectrophotometer (Analyticjena, UV-1800).

General Procedure for the synthesis of Schiff base ligands (L_1 –L_4)

1,3-Bis(4-aminoPhenoxy) benzene was made to react with 2-hydroxy-benzaldehyde, 5-Chloro-2-hydroxybenzaldehyde,5-bromo-2-hydroxybenzaldehyde,2-hydroxy-5methylbenzaldehyde in 1:2 ratio in ethanol and the reaction mixture is refluxed for 3–4 h to yield Schiff bases L_1, L_2, L_3 and L_4 (**Fig-1**) respectively **(Scheme-I).** Prepared ligands are tetra dentate consisting of ONNO.



Scheme-I: General synthetic scheme for Schiff base Ligand (L_1 -L_4)

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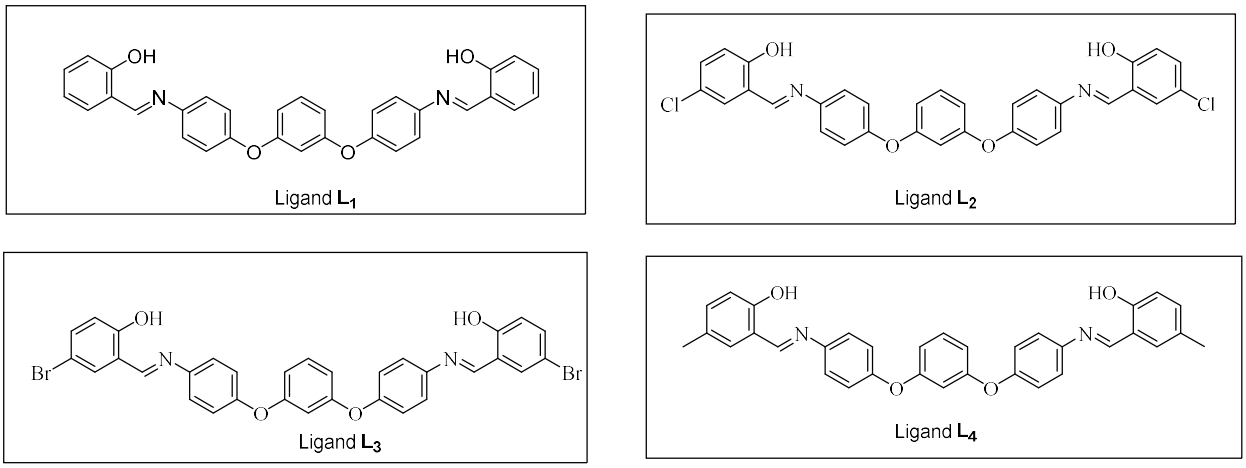

Figure1: Structure of Ligands **L_1-L_4**

Spectral data of Ligands

2,2'-((1E,1'E)-(((1,3-phenylenebis(oxy))bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene))diphenol (L_1)

Yield: 81 % %; mp: 106-108°C; FT-IR (KBr, ν/cm^{-1}): 3401 (OH), 3048 (Ar–C–H), 1618 (C=N), 1566 (C=C), 1584, (C-O) 1266,1209,1183,1127; ^{1}H NMR (400 MHz, $CDCl_3$) □ ppm: 13.25 (2H, s, Ar-OH 8.55 (2H, s, Azomethine)7.44 - 7.51 (d, 5 H) 7.33 - 7.35 (s, 1 H) 7.29 - 7.32 (m, 3 H) 7.28 (s, 1 H) 7.11 - 7.12 (t, 3 H) 7.08 - 7.10 (t, 2 H) 6.94 (s, 1 H) 6.92 (s, 1 H) 6.81 (d, *J*=2.25 Hz, 1 H) 6.79 (d, *J*=2.38 Hz, 1 H) 6.74 – 6.75 (t, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) □□ppm: 159.94 , 159.73, 158.09, 155.78, 143.14, 135.29, 133.81, 130.35, 122.32, 120.27, 119.59, 118.92, 113.34, 110.21, 109.26, 76.89, 76.68, 76.36; Mass (m/z): 501.18 [M+1].

2,2'-((1E,1'E)-(((1,3-phenylenebis(oxy))bis(4,1 phenylene))bis(azanylylidene))bis(methanylylidene))bis(4-chlorophenol) (L_2)

Yield: 79 %; mp:174-176 ◦C; FT-IR (KBr, ν/cm^{-1}): 3418 (OH), 3071 (Ar–C–H), 1619 (C=N), 1506 (C=C), 1378,1358,1260,1240 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) □ ppm 13.20 (2H, s, Ar-OH 8.54 (2H, s, Azomethine) 7.35 (d, *J*=2.50 Hz, 2 H) 7.31 - 7.33 (m, 2 H) 7.29 (m, 3 H) 7.25 (s, 1 H) 7.09 - 7.10 (t, 3 H) 7.07 - 7.08 (t, 2 H) 6.97 (s, 1 H) 6.95 (s, 1 H) 6.79 (d, *J*=2.25 Hz, 1 H) 6.77 (d, *J*=2.38 Hz, 1 H) 6.72 - 6.73 (t, 1 H) ^{13}C NMR (101 MHz, $CDCl_3$) □ ppm 160.42, 159.61, 158.45, 156.11, 143.54 , 132.85, 131.15, 130.68, 123.72, 122.65, 119.95 ,118.83 , 113.68, 109.58, 77.34, 77.22, 77.02, 76.70. Mass (m/z): 569.10[M+1].

2,2'-((1E,1'E)-(((1,3-phenylenebis(oxy))bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene))bis(4-bromophenol) (L_3)

Yield: 80 %; mp:158-160◦C FT-IR (KBr, ν/cm^{-1}): 3423 (OH), 2978 (Ar–C–H), 1606 (C=N), 1504 (C=C), 1383, 1272, 1240, 1228 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) □□ppm 13.24 (2H, s, Ar-OH) 8.53 (2H, s, Azomethine) 7.49 -7.50 (d, *J*=2.50 Hz, 2 H) 7.44 – 7.45 (d, *J*=2.50 Hz, 1 H) 7.42 (d, *J*=2.38 Hz, 1 H) 7.28- 7.33 (m, 4 H) 7.25 (s, 1 H) 7.09 - 7.11 (t, 2 H) 7.07 - 7.08 (t, 2 H) 6.93 (s, 1 H) 6.90 (s, 1 H) 6.79 - 6.80 (d, *J*=2.25 Hz, 1 H) 6.77 (d, *J*=2.38 Hz, 1 H) 6.72 - 6.74 (t, 1 H) ; ^{13}C NMR (101 MHz,

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$CDCl_3$) □ ppm 161.88, 161.02, 158.58, 155.64, 144.13, 133.06, 132.18, 130.57, 122.54, 119.95, 119.18, 119.08, 117.22, 113.38, 109.32, 77.32, 76.68. 569. Mass (m/z): 658.99[M+1].

2,2'-((1E,1'E)-(((1,3-phenylenebis(oxy))bis(4,1-phenylene))bis(azanylylidene))bis(methanylylidene))bis(4-methylphenol) (L_4)

Yield: 78 % mp:138-140◦C FT-IR (KBr, ν/cm^{-1}): 3425(OH), 2925 (Ar–C–H), 1614 (C=N), 1497 (C=C), 1384,1288,1263,1225 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) □ ppm 12.99 (2H, s, Ar-OH) 8.57 (2H, s, Azomethine) 7.31 (s, 1 H) 7.29 (s, 1 H) 7.29 (s, 1 H) 7.28 (s, 1 H) 7.26 (s, 1 H) 7.20 (d, 1 H) 7.18 (s, 3 H) 7.10 - 7.11 (t, 2 H) 7.07 - 7.08 (t, 2 H) 6.94 (d, 1 H) 6.91 - 6.93 (d, 1 H) 6.78 – 6.79 (d, *J*=2.38 Hz, 1 H) 6.76 - 6.77 (d, 1 H) 6.72 - 6.75 (t, 1 H) 2.32 (s, 6 H) ^{13}C NMR (101 MHz, $CDCl_3$) □ ppm 161.70, 155.35, 144.09, 133.77, 131.95, 130.35, 122.30, 119.74, 116.77, 115.79, 113.14, 109.09, 20.14, 9.63. Mass (m/z): 529.21[M+1].

Synthesis of Ni (II) Complexes (CL_1–CL_4)

An ethanoic solution of 0.1 M (5.00 g in 25 mL of ethanol) of the Schiff base ligand L_1 was added to a Ni (II) chloride solution of 0.102 M (2.59 g in 10 mL of ethanol). The above reaction mixture was refluxed under continuous stirring for about 6 h. The progress of reaction was checked by TLC and spots were visualized under UV light. The precipitate obtained was then filtered, washed thoroughly with ethanol, and dried in desiccator over anhydrous $CaCl_2$. Ni (II) complexes with other Schiff bases L_2 (5.69 g), L_3 (6.55 g) and L_4 (5.28 g) were synthesized using the above procedure. The synthesized complexes are characterized using physio-chemical techniques. The tentative structures of the prepared complexes are depicted in Figure-2

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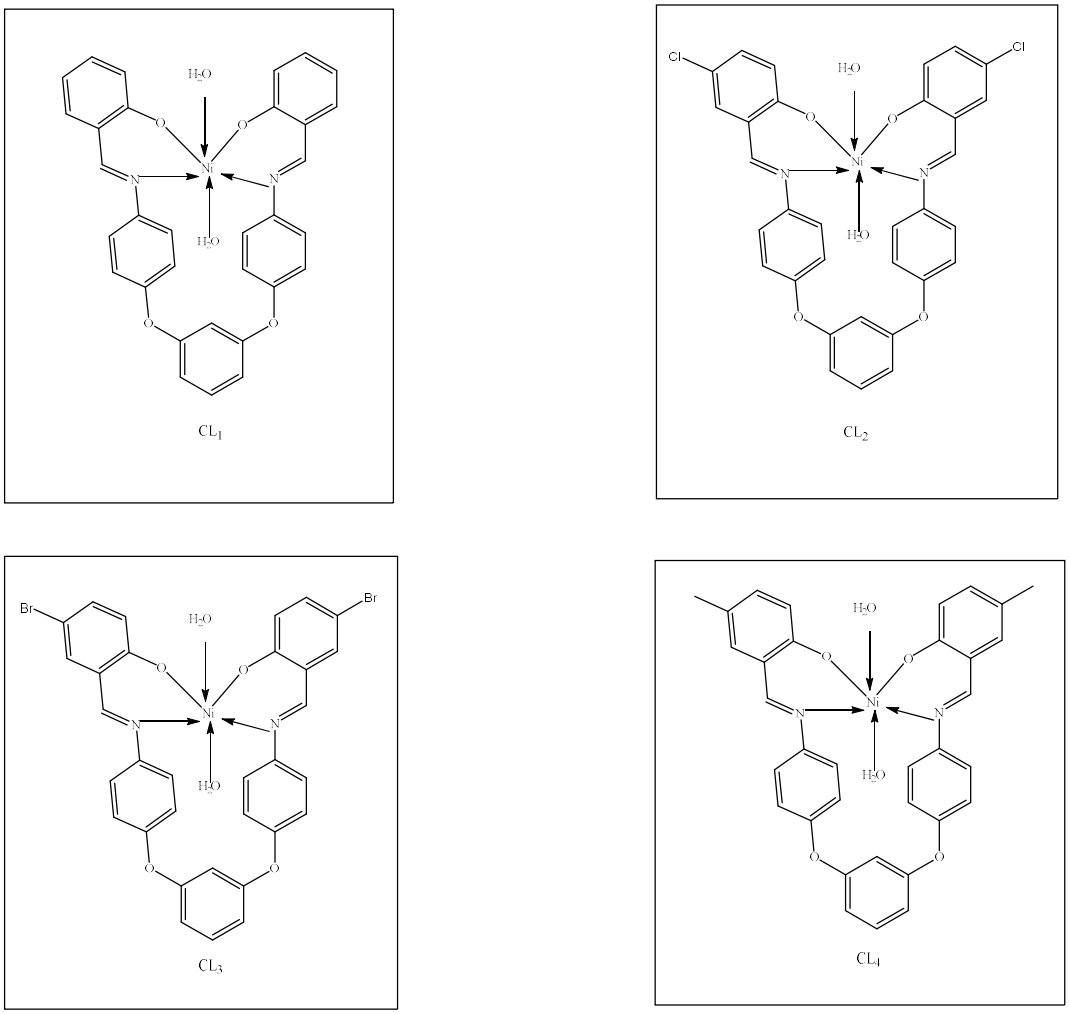

Figure-2: Structure of Complexes (CL_1 to CL_4).

Antibacterial activity

The antibacterial activity of the compounds was performed by enumerating the viable number of cells upon in the nutrient broth containing various concentrations of compounds. The viable number is represented by colony count method. The test organisms used on which the antibacterial activity was performed were *Escherichia coli* (NCIM2256), *Pseudomonas aeruginosa* (NCIM-2036), *Bacillus subtilis* (NCIM2063) and *Staphylococcus aureus* (NCIM-2901). In this method, the cells of test organisms were grown in nutrient broth till mid log phase and used as an inoculums for performing antimicrobial test. An approximately, 1×10^5 cells/mL test organisms were each inoculated with 0 to 500 ug/mL concentration of different compounds, separately, and each incubated for 16 to 18 h at 37 °C. During this incubation, cells tend to grow and multiply in number. However, if the compounds interfere with growth of cells, the numbers of cells decrease. After 16 to 18 h, viable numbers of cells were recorded by spreading an aliquot from the broth inoculated with test organisms and compounds as colony forming units per milliliter (CFU/mL). Minimum inhibitory concentration (MIC) was determined Ampicillin was used as standards for the comparison of antibacterial activity.

Antifungal Activity

Antifungal activity was determined by dilution method as per CLSI (formerly, NCCLS)

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guidelines. The synthesized compounds and standard miconazole were dissolved in DMSO solvent. The medium yeast nitrogen base was dissolved in phosphate buffer pH 7 and it was autoclaved at 110 ˚C for 10 min.With each set a growth control without the antifungal agent and solvent control DMSO were included. The fungal strains were freshly subcultured onto Sabouraud dextrose agar (SDA) and incubated at 25 ˚C for 72 h.The fungal cells were suspended in sterile distilled water and diluted to get 10^3 cells/mL. Ten microliters of standardized suspension was inoculated onto the control plates and the media incorporated with the antifungal agents. The inoculated plates were incubated at 25 ˚C for 48 h. The readings were taken at the end of 48 and 72 h. The MIC was the lowest concentration of drug preventing growth of macroscopically visible colonies on drug containing plates when there was visible growth on the drug free control plates.

RESULTS AND DISCUSSION

The synthesized Schiff bases were found to be similar to the predicted results. Chemical and physical properties for every synthesized Schiff bases (L_1 to L_4) and Complexes (CL_1 to CL_4) are shown in Table 1. The molecular formula and compound values predicted theoretically and those observed from experimentation match very well.

Electronic Spectral Studies

Two bands might be seen in the UV–visible spectrum of the Schiff bases (L_1–L_4). (Fig. 3). Due to the azomethine group n → π* transition observed and a bright band in the 350–360 nm region [24, 25]. Three bands of absorption were seen in every complex. The first two were in 324 and 343 nm corresponding to the aromatic ring's π→π∗ transition, while the third one was between 413 and 424 nm, corresponding to the azomethine group's (C=N) n → π* transition [26].

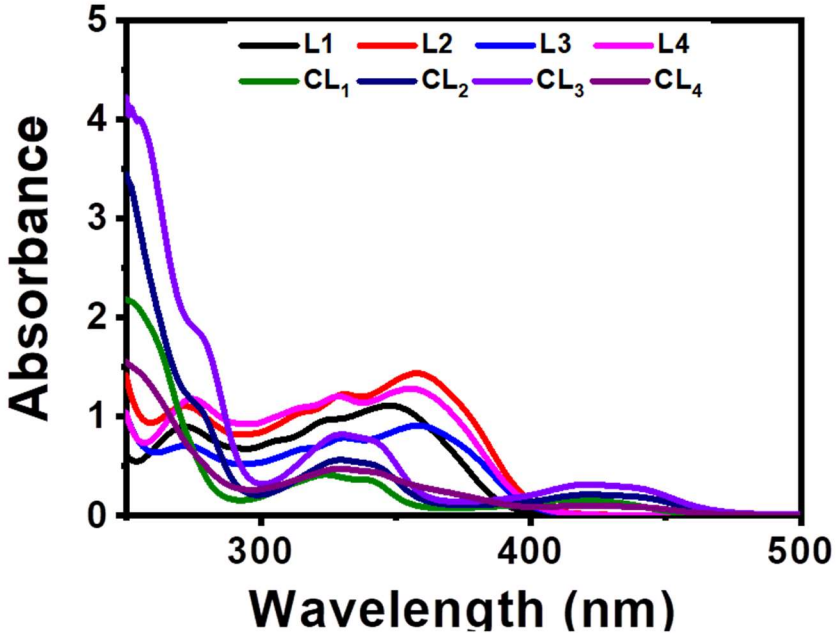

Fig. 3- UV of Schiff base Ligand and Complexes

Table -1 Analytical and Physical data of Compound studied

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Sr. No.	Compound	Molecular Formula	Color	Melting Point
1.	L_1	$C_{32}H_{24}N_2O_4$	Light Yellow	106 -108
2.	L_2	$C_{32}H_{22}Cl_2N_2O_4$	Pale Yellow	174 –176
3.	L_3	$C_{32}H_{22}Br_2N_2O_4$	Orange	158 - 160
4.	L_4	$C_{34}H_{28}N_2O_4$	Orange (Shining with Crystal)	138 - 142
5.	CL_1	$C_{32}H_{26}N_2O_6Ni$	Brown	> 250
6.	CL_2	$C_{32}H_{24}Cl_2N_2O_6Ni$	Brown	> 250
7.	CL_3	$C_{32}H_{24}Br_2N_2O_6Ni$	Brown	> 250
8.	CL_4	$C_{34}H_{30}N_2O_6Ni$	Brown	> 250

FT-IR spectral studies

The FT-IR spectra showed the significant stretching frequencies associated with groups such as enolic –OH, azomethine C=N-, aromatic C= C, -CO-, etc. In the range of 3401–3426 cm^{-1} phenolic–OH stretching vibrations are seen likewise, azomethine stretching, shown in the range of 1594–1624 cm^{-1}. It is a significant functional group [27]. Interestingly, all of the Ni (II) complexes showed a decrease in this frequency at about 1618–1624 cm^{-1}, suggesting that the imine nitrogen atom was involved in coordination with the metal ion [28]. The substituted salicylaldehyde's -OH stretching and bending vibrational frequencies were observed in the 3401–3425 cm^{-1} range. The coordination occurs through the enolic–OH group, as seen by the absence of these peaks in the spectra of all the nickel complexes. Additionally, the Ni (II) complexes show broad band at around 3412–3432 cm^{-1}indicates the presence of coordinate water molecules to the core metal ion [29, 30]. The existence of v (M-N) bands in the 556–573 cm^{-1}frequency range provides additional confirmation that the azomethine nitrogen is coordinated [31, 32]. Significant characteristic band in the FT - IR spectra of prepared Schiff bases ligand and its complexes were shown in **Table – 2**

Table – 2 FT- IR spectra of ligand L_1 & Complex CL_1

Sr. No	Compound	ν (OH/ H_2O/CH)	ν (C=N)	ν (M-O)	ν (M-N)
1.	L_1	3401	1618	-	-
2.	L_2	3418	1610	-	-
3.	L_3	3423	1606	-	-
4.	L_4	3425	1594	-	-

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5.	CL_1	3432	1620	437	496
6.	CL_2	3384	1619	457	512
7.	CL_3	3426	1618	412	503
8.	CL_4	3412	1624	443	532

^{1}H NMR spectral studies

For all synthesized Schiff base ligand, the ^{1}H NMR spectra were recorded in $CDCl_3$ solvent and expressed in parts per million. The synthesized Schiff base ligand show ^{1}H NMR spectra signals at 6.72–7.50 ppm that are produced by aromatic protons. A singlet that was detected downfield at 12.99–13.25 ppm in the ^{1}H NMR spectra of the Schiff base ligands and that integrated for two proton is attributed to –OH [33]. Similarly, there is a singlet signal at 8.53–8.57 ppm that is the result of the azomethine proton, which is attached to the carbon nearby the nitrogen atom [34].

Mass spectral analysis

The mass spectra of all the Schiff base ligands exhibit parent ion peaks, due to their respective molecular ion (M+1), corresponding to the molecular weight and confirming their molecular composition. The proposed molecular formula of these compounds was confirmed by comparing their molecular formula weights with the *m*/*z* values

Mass spectra of the Schiff base ligand L_1 are depicted in Fig. 4

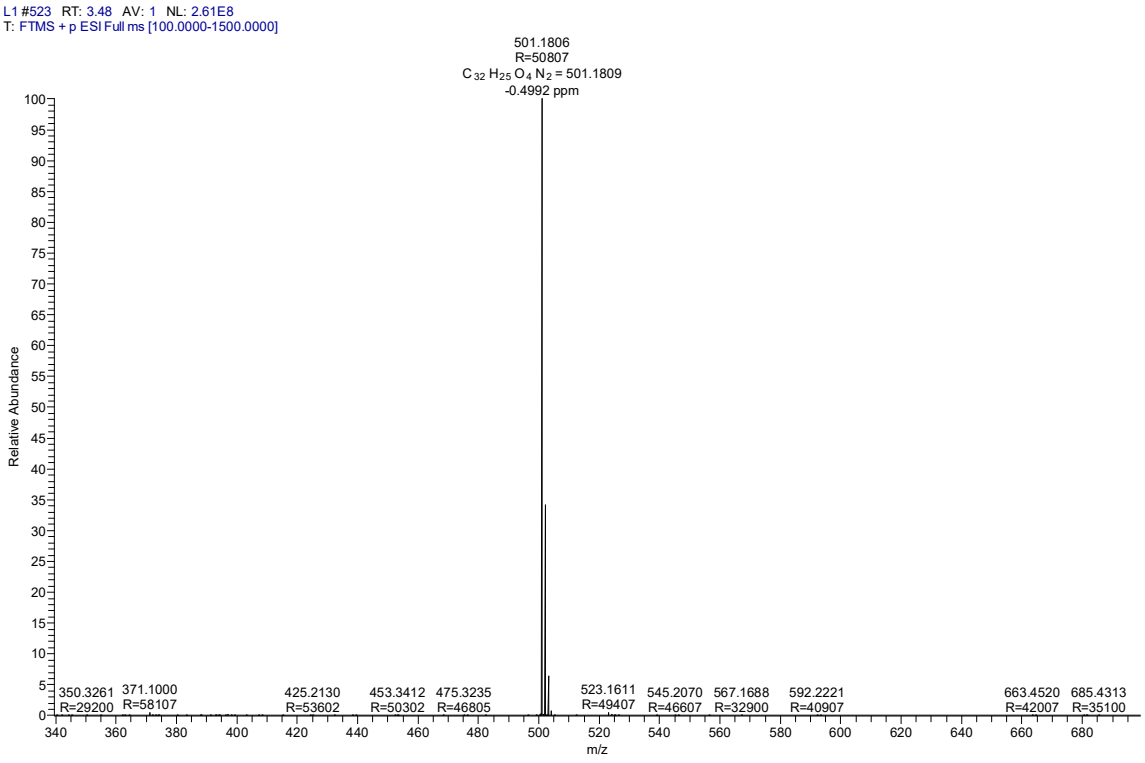

Fig. 4 - Mass spectra of the Schiff base ligand L_1

Antimicrobial and antifungal activity

The in vitro antimicrobial activity i.e. Antibacterial and antifungal activities of each produced four ligands (L_1, L_2, L_3 and L_4) and four Complexes (CL_1, CL_2, CL_3 and CL_4 have been investigated and the results are collectively shown in Table 3 below. The dilution method has been employed in this

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instance for calculating the Minimum Inhibitory Concentration (MIC) [35 - 37]. To study the in vitro antibacterial activity of ligands and Complexes we have screened all the synthesized ligands against four different human pathogenic bacterial strains namely gram negative *Escherichia coli*, *Pseudomonas aeruginosa* and gram positive *Staphylococcus aureus*, *Bacillus subtilis*. To study the in vitro antifungal activity of ligands and complexes, we have screened all the synthesized ligands against two different human pathogenic fungal strains namely *Candida albicans* and *aspergillus Niger*. Here, we have used *Ampicillin* as standard antibacterial activity and *Miconazole* as standard for an antifungal activity to compare the biological activity results of screened ligands and complexes. The bioactivity results showed that most of the synthesized complexes possess better antibacterial activity against the tested bacterial strains as compared to Ampicillin. The Complex of CL_3 act as the most active antibacterial agent and show better antibacterial activity with MIC 109 ± 0.21, 278 ± 0.47, 106± 0.34 and 111± 0.66, respectively against all four different tested human pathogenic bacterial strains used in this study. The other synthesized Complexes were also shows a better antibacterial activity with MIC value CL_1 115 ± 0.94, 121± 0.74, 209±0.37 and 244±0.12 , CL_2 131 ± 0.99, 103± 0.92 and 279 ± 0.52 against all four human pathogens The bioactivity results also shows that the ligand L_3 also possess a better antibacterial activity against the tested bacterial strains as compared to Ampicillin. The ligands of L_3 acts as most active antibacterial agent among the all ligands and show better antibacterial activity with MIC 135 ± 0.39, 122 ± 0.12, and 130± 0.54, respectively against all four different tested human pathogenic bacterial strains used in this study. All the synthesized ligands were also observed active against *S. Aureus* with MIC ranging from 287 ± to 166 ± 0.29. Whereas, L_1, L_2, L_3, L_4 ligands show better antibacterial activity against *B. Subtilis* with MIC 296 ± 0.34, 157 ± 0.15,130 ± 0.54, and 166 ± 0.29 respectively. Ligand L_3 Contain Br and showing high antibacterial activity. It was observed that the antibacterial activity was seen in both gram positive and gram negative bacteria.

In the antifungal activity all four ligands shows a better antifungal activity against all two human pathogens compared to *Miconazole*. The ligand L_2 shows better antifungal activity with MIC 76 ± 0.05 and 56 ± 0.72 respectively. The other ligands L_1, L_3 and L_4 also shows a better antifungal 95±0.89, 79±0.11,81±0.38, 85±0.23, 101±0.34, 61±0.90

In the antifungal activity all four Complexes shows a better antifungal activity against all two human pathogens compared to *Miconazole* .The CL_3 complex shows better antifungal activity with MIC 65± 0.17 and 61± 0.23 against the fungi respectively. The other Complexes CL_2 ,CL_1 and CL_4 also shows better antifungal activity with MIC 69 ± 0.81,44 ± 0.57,78 ± 0.62,62 ± 0.90 and 89 ± 0.16 ,65 ± 0.76 against all the fungi.

The Ni (II) complex CL_3 contains Br hence it shows more antibacterial and antifungal activity and any other complexes.

The results from the current study are compared to previous reports [38, 39]. From the results of biological activity included in Table 3, it was concluded that almost all the synthesized ligands show good antibacterial activity against at least one of the tested strains whereas most.

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Table – 3

Compound	**MIC Values in µg/mL***					
	Antibacterial Activity				**Antifungal Actvity**	
	E.coli	***P.aerugino sa***	***S.aureus***	***B.subtilis***	***C.Albica ns***	***A.Niger***
L_1	156± 0.38	138 ± 0.25	287± 0.13	296± 0.34	95±0.89	79±0.11
L_2	194± 0.22	124± 0.47	*	157± 0.15	76± 0.05	56±0.72
L_3	135± 0.39	*	122± 0.12	130± 0.54	81±0.38	85±0.23
L_4	187± 0.62	191± 0.54	188± 0.16	166± 0.29	101±0.34	61±0.90
CL_1	115± 0.94	121± 0.74	209± 0.37	244± 0.12	78±0.62	62±0.90
CL_2	131± 0.99	103± 0.92	279± 0.52	*	69±0.81	44±0.57
CL_3	109± 0.21	278± 0.47	106± 0.34	111± 0.66	65±0.17	61±0.23
CL_4	146± 0.09	159± 0.314	155± 0.84	129± 0.72	89±0.16	65±0.76
Ampicillin	100± 0.56	100± 0.08	250± 2.29	250± 0.55		
Miconazole	*	*	*	*	25±0.97	25±0.58

Thermogravimetric Analysis

Thermogram of the Ni (II) complexes of ligands (L_1, L_2, L_3, and L_4) confirmed four decomposition steps within 100°C and 985°C. The first step in the decomposition takes place after two water molecules are lost, and this occurs within 50°C and 250°C. Steps 1 to 3 in the following sequence: in the range of 200–400°C, 400–600°C, and 600 –985°C respectively. Metal oxide remaining as a residue after decomposition takes place. These temperatures correlate to the gradual decomposition of the ligand's organic moiety. Within the temperature range of 40 to 985 °C, the thermogram of the Ni (II) CL_1 complexes exhibited four decomposition phases (Fig.-5). An analytical metal content measurement was used to compare the metal percentages that from metal oxide or metal residues [40].

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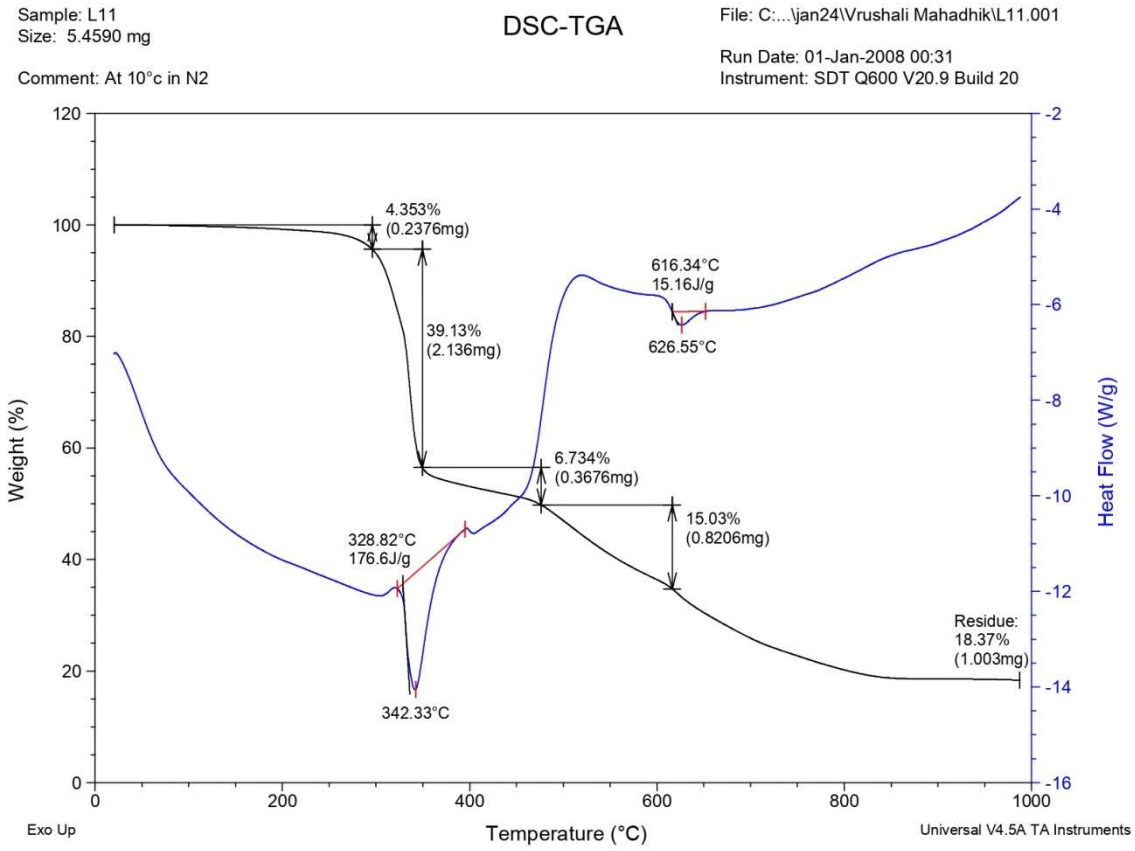

(Fig.-5) - The thermogram of the Ni (II) CL_1 complexes

Conclusion

In conclusion, the produced Schiff bases were coordinate to the Ni (II) ion through phenolic oxygen atoms and imine nitrogen, acting as a tetradentate ligand. spectrum analysis (FT-IR and UV-visible) TGA measurements are used to confirm that a ligand is attached to a metal ion.In bioactivity the Ni (II) complex CL_1, CL_2, CL_3 and CL_4 shows more better antibacterial and antifungal activity against all human pathogens than the ligand L_1, L_2, L_3 and L_4, because Ni (II) complexes shows bioactivity against all pathogens as compared to ligands. In the above bioactivity the Ni (II) complexes CL_3 is acts as better antimicrobial agent than ligand L_3. Hence Ni (II) Complexes would act as better antimicrobial agent.

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