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Synthesis, Structures and Antimicrobial Activities of Novel Schiff Base Ligand and Its Metal Complexes

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ABSTRACT

A novel ligand (E)-7-hydroxy-4-methyl-8-(1-(naphthalen-1-ylimino) ethyl)-2H-chromen-2-one [HOMNIEC] was synthesized by condensation of 8-acetyl-7-hydroxy-4-methyl-2H-chromen-2-one and Naphthalen-1-amine by the reported method. The metal complexes with this ligand were synthesized by using a common new method. FTIR, ^{1}H NMR, Mass Spectrometry and TGA techniques were used to confirm their structures. The FTIR spectral data indicate that the ligand was coordinated with the metal ions through the phenolic oxygen on coumarin moiety and nitrogen of azomethine. The ligand and complexes were examined for *in vitro* antimicrobial activities using broth microdilution method in DMSO medium against *Escherichia coli* (MTCC 443) and *Pseudomonas aeruginosa* (MTCC 1688) a *Gram-negative* bacterial strain, *Staphylococcus aureus* (MTCC 96) and *Streptococcus pyogenes* (MTCC 442) a *Gram-positive* bacterial strain, and *Candida albicans* (MTCC 227), *Aspergillus clavatus* (MTCC 1323) and *Aspergillus niger* (MTCC 280) fungal strains. The metal complexes were found to have enhanced antimicrobial activities compare to the Schiff base [HOMNIEC] ligand. Especially, the antifungal activity of Cu(II) and Zn(II) ions complexes was found to be twofold more than the standard drug griseofulvin against *C. albicans*.

Keywords: Ligand, Complexes, Spectroscopy, Thermogravimetry, Broth Dilution Method.

INTRODUCTION

Ligands bearing oxygen and nitrogen donors play an important role in coordination chemistry where extensive literature is available for the synthesis, structural and biological studies of metal complexes of these ligands[1-14]. Apart from conventional donors, heterocyclic compounds played a major role as ligands in metal complexes synthesis. One of the major classes of heterocycles used for the same are coumarin derivatives due to their potential biological applications[2].

Coumarin derivatives are known for their anti-coagulant, bacteriostatic and antitumor activities and also play an important role in designing of new cytotoxic agents[3,4].

The metal complex formation with oxygen

and nitrogen donor ligands is feasible because of its chelating property and the bacteriostatic activities seem to be due to chelation. Also, their antimicrobial activities studies reveal that the metal complexes have more activities than the ligands[5,6].

Recently, few Schiff bases of coumarin derivatives, identified as potential scaffolds for synthesis of novel biological agents. Therefore, the synthesis of novel Schiff bases from coumarin derivatives and their transition metal complexes remains a main focus of chemical and medicinal research[7,8]. These properties of Schiff bases of coumarin derivatives are due to heterocyclic rings and substituted functional groups at appropriate positions. It has been observed that the properties of these compounds can be enhanced by complexation with suitable transition metal ions[9-15].

These facts encourage us to prepare a new Schiff base ligand from coumarin derivative with donor groups at appropriate positions and its transition metal complexes. Also, to evaluate their antimicrobial activities such as antibacterial and antifungal, as many of such metal complexes found antimicrobials.

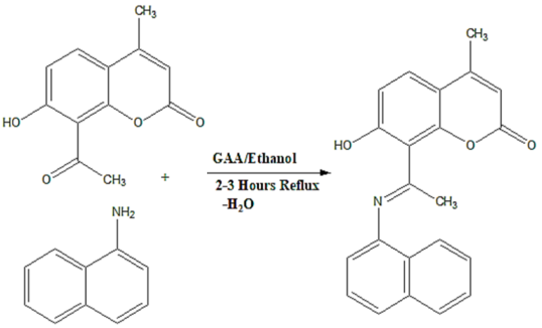
EXPERIMENTAL

All solvents and chemicals were obtained from TCI Chemicals, Loba Chemie, S.D. Fine Chem and were used without further purification. All solvents used were of analytical grade and dried as per the standard procedures[16]. All metal (II) chloride salts were used. Magnetic stirrer was used and the reactions were monitored by thin layer chromatography. Melting points or decomposition points were determined by an open capillary method. The metal (II) ions content and metal to ligand ratio of metal complexes were analysed volumetrically by the reported method[17].

FT-IR spectrophotometer (KBr), Bruker Germany, Model No. 3000, Hyperion Microscope with Vertex 80 FTIR System was used to record the IR spectra. NMR spectrometer ($CDCl_3$) 600 MHz, JEOL, Japan, ECZR Series was used to record the 1H MR spectra. Waters Single COD, Model No. Waters-3100 was used to record mass spectrometry. Perkins Elmer, Model No. TGA-4000 was used to record the TGA thermogram. The *in vitro* antimicrobial activities examinations were performed by broth microdilution method and the bacterial and fungal strains are listed in Table 3 and Table 4.

Synthesis of (E)-7-hydroxy-4-methyl-8-(1-(naphthalen-1-ylimino) ethyl)-2H-chromen-2-one [HOMNIEC]

It was prepared by condensation of 8-acetyl-7-hydroxy-4-methyl-2H-chromen-2-one and Naphthalen-1-amine as per the reported method[8] (Scheme 1). Yield: 65%, pale yellow solid ($C_{22}H_{17}NO_3$), molecular weight 343.40 g/mol, melting point 203-205°C and found soluble in DMSO, DMF, and Chloroform. ^{1}HNMR: chemical shift (δ) in ppm: 1.60 (s, 3H, Ar-Methyl protons), 2.65 and 2.45 (s, 3H, -N=C-CH_3) and (s, 3H, -C=C-CH_3) isomers (azomethine -CH_3 protons), 6.20 (s, 1H, Ar-Hydroxyl proton), 7.26 (s, 1H), 7.63 (d, 1H), 7.92 (d, 1H) coumarin moiety C-H protons, 7.76-7.81 (m, broad, 2H), 7.50-7.58 (m, broad, 2H), 7.78-7.81 (m, broad, 2H), 7.0-7.1 (d, sharp, 1H) naphthalene ring C-H protons, 17.0 (s, small peak, 1H) for hydroxyl hydrogen (intramolecular hydrogen bond) tautomerism with nitrogen of (>C=N-) imino group[8] (Figs. 1a, 1b and 1c). FTIR: IR, ν(KBr, cm^{-1}): 1728 (lactonyl -O-C=O), 1597 (imino >C=N-), 1496 (aromatic -C=C-), 1253 (hydroxyl =C-O-), 1164 (-C-N), 1057 (=C-C-), 3425 (hydroxyl -O-H), 3060 (aromatic -C-H), 446-924 aromatic C-H bending vibration modes (Fig. 2). Mass: (m/z) 313.2, 344.1, (M+1) = 344.5, 344.8, and 597 (Figure 3).



Scheme 1. Reaction Scheme for Synthesis of Ligand

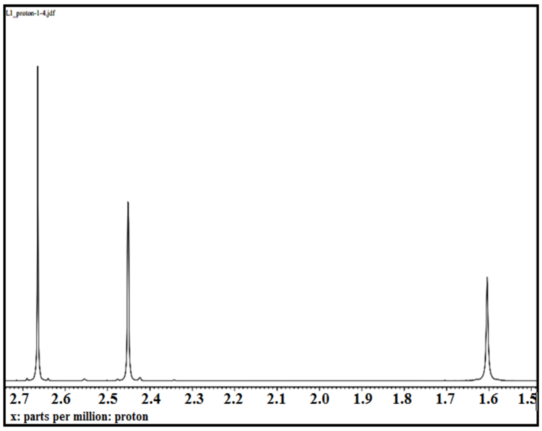


Fig. 1a. ^{1}HNMR Spectrum of Ligand

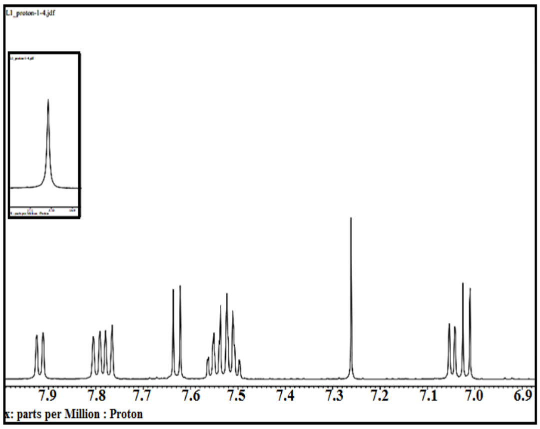


Fig. 1b. ^{1}HNMR Spectrum of Ligand

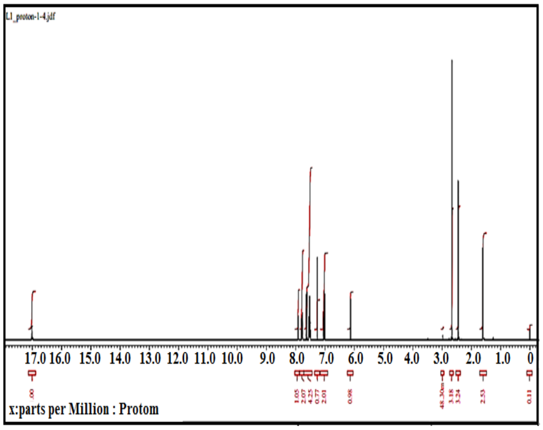


Fig. 1c. ^{1}HNMR Spectrum of Ligand

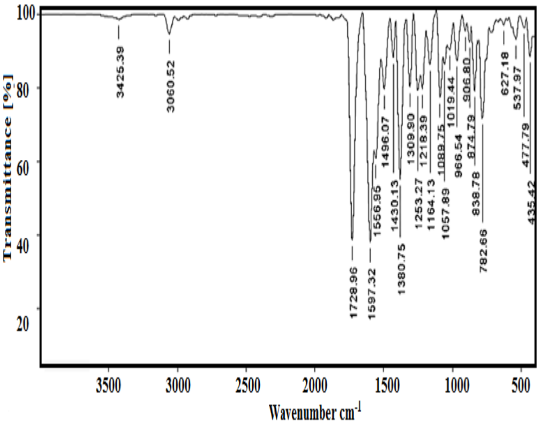


Fig. 2. IR Spectrum of Ligand

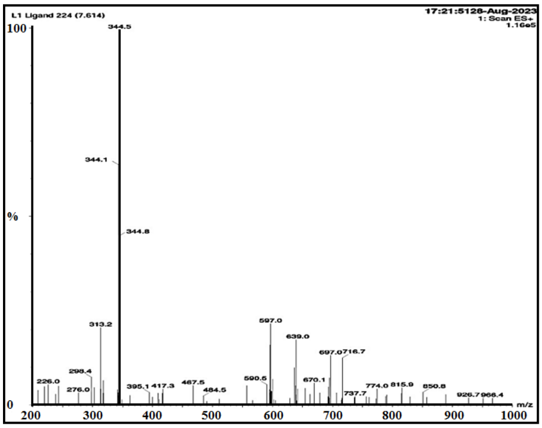
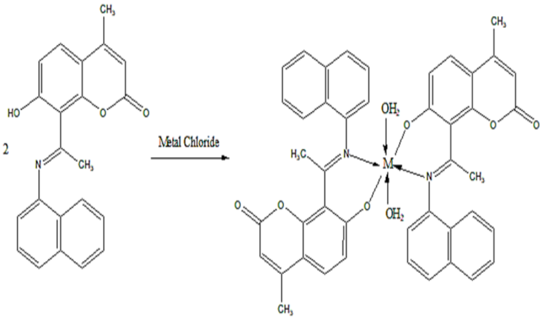


Fig. 3. Mass Spectrum of Ligand

Synthesis of metal complexes of (E)-7-hydroxy-4-methyl-8-(1-(naphthalen-1-ylimino) ethyl)-2H-chromen-2-one [HOMNIEC]

The metal complexes of [HOMNIEC] were prepared by a common new method (Scheme 2). To a clear solution of [HOMNIEC] (0.5 mmol) in 15 mL dimethylformamide (DMF) was added respective metal(II) chloride salts (1.0 mmol) with catalytic amount of aqueous ammonia (For the purpose to maintain basicity) at 0-5^{0}C. Then the resulting mixtures were moved to room temperature slowly and stirred for 2-3 hours. With the TLC monitoring the reaction progress was checked. TLC by 5% MDC/MeOH solvent mixture. On completion of reaction, the reaction mixtures were diluted by diethyl ether and stirred for 2 h to obtain the solid products. On Whatman filter paper the products were filtered and washed by diethyl ether and for 30 minutes dried under vacuum. The yields of the reactions were between 70% to 75% with respect to the Schiff base [HOMNIEC]. Coloured solid metal complexes soluble in DMF and DMSO were obtained with M.P./D.P. between 180°C to 190°C.



Scheme 2. Reaction Scheme for Synthesis of Metal Complexes Where, M is Ni(II), Co(II), Cu(II) and Zn(II)

Co(II) ion Complex with Schiff Base [HOMNIEC]: IR, ν(cm^{-1}): 1730 (lactonyl-C=O), 1577 (imino C=N-), 1519 (aromatic -C=C-), 1300 (phenolic -C-O-), 1091 (=C-C-), 3000 (aromatic C-H), 3168 (Broad) H_2O lattice/coordinated hydrogen bonded, 820 with shoulder peak (coordinated water molecules with metal ion) (Fig. 4). Mass of Complex: (m/z) (L+1) = 344.5, M$^+$ = 779.8, (M+1) = 780.6, (M+2) = 781.1 (Figure 5).

Ni(II) ion Complex with Schiff Base [HOMNIEC]: IR, ν(cm^{-1}): 1722 (lactonyl -C=O), 1592 (imino C=N-), 1519 (aromatic -C=C-), 1390 (phenolic -C-O-), 1087 (=C-C-), 2906-3043 (aliphatic/aromatic C-H), 3149-3322 (Broad) H_2O lattice/coordinated hydrogen bonded, 826 with small shoulder peak (coordinated water molecules with metal ion). Mass of Complex: (m/z) (L-1) = 342.3, (M-1) = 778.6, M$^+$ = 779.1.

Cu(II) ion Complex with Schiff Base [HOMNIEC]: IR, ν(cm^{-1}): 1730 (lactonyl -O-C=O), 1604 (imino C=N-), 1524 (aromatic -C=C-), 1387 (phenolic -C-O-), 1089 (=C-C-), 2900-3036 (aliphatic/aromatic C-H), 3221-3321 (Broad) H_2O lattice/coordinated hydrogen bonded, 815 & 838 (coordinated water molecules with metal ion). Mass of Complex: (m/z) (L+1) = 344.3, (M+1) = 785.4, 785.9, (M-1) = 783.1.

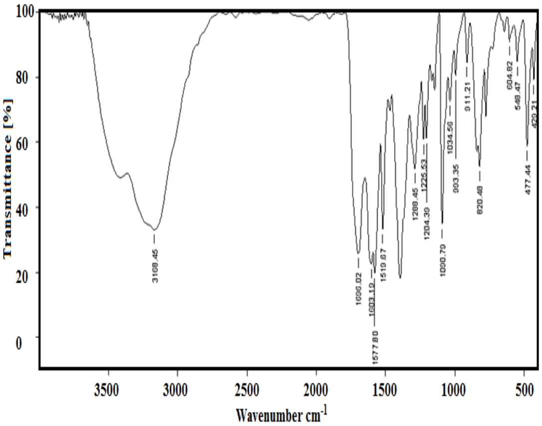


Fig. 4. FTIR Spectrum of Co(II) ion complex

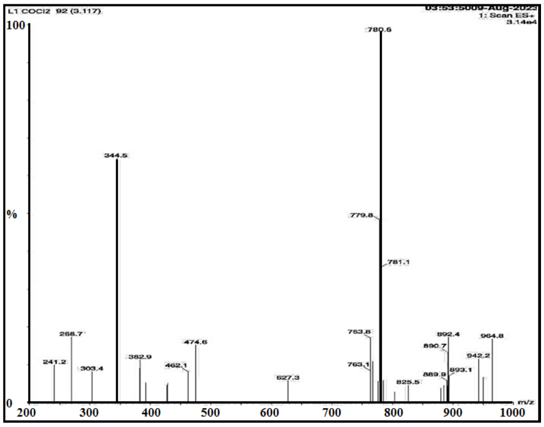


Fig. 5. Mass Spectrum of Co(II) ion complex

Table 1: Physical Analysis of Ligand and Metal Complexes

Ligand/Complexes	Mol. Wt./For. Wt.	Colour	%Yield (Isolated)	M.P./D.P.°C	At. Wt. of Metal ions	% of Metal ions Observed (Calculated)
HL1:$C_{22}H_{17}NO_3$	343.40	Pale Yellow	65	205	-	-
$[Co(C_{22}H_{16}NO_3)_2(H_2O)_2]$	779.73	Black	70	182	58.93	7.400 (7.557)
$[Ni(C_{22}H_{16}NO_3)_2(H_2O)_2]$	779.49	Brick Red	75	183	58.69	7.300 (7.529)
$[Cu(C_{22}H_{16}NO_3)_2(H_2O)_2]$	784.34	Violet	70	186	63.54	8.000 (8.100)
$[Zn(C_{22}H_{16}NO_3)_2(H_2O)_2]$	786.19	Light Green	70	188	65.39	8.200 (8.317)

Mol. Wt.-Molecular Weight, For. Wt.-Formula Weight, M.P.-Melting point, D.P.-Decomposition point, At. Wt.-Atomic Weight

Table 2: TGA Data of Complexes

Complexes	% of Metal ion Observed (Calculated)	% of H_2O Observed (Calculated)	M.W./F.W.g/mol	Wt. of Sample (mg)	% Wt. Loss 30-105°C	105-800°C	Residue (Oxides)
$[Co(C_{22}H_{16}NO_3)_2(H_2O)_2]$	6.774 (7.557)	6.281 (4.617)	779.73	4.257	6.281	84.492	9.227
$[Ni(C_{22}H_{16}NO_3)_2(H_2O)_2]$	6.704 (7.529)	5.651 (4.618)	779.49	4.206	5.651	82.925	11.424
$[Cu(C_{22}H_{16}NO_3)_2(H_2O)_2]$	7.996 (8.100)	5.880 (4.589)	784.34	4.843	5.880	83.103	11.017
$[Zn(C_{22}H_{16}NO_3)_2(H_2O)_2]$	7.802 (8.317)	6.187 (4.579)	786.19	4.422	6.187	84.101	9.712

Mol. Wt.-Molecular Weight, For. Wt.-Formula Weight, Wt.-Weight

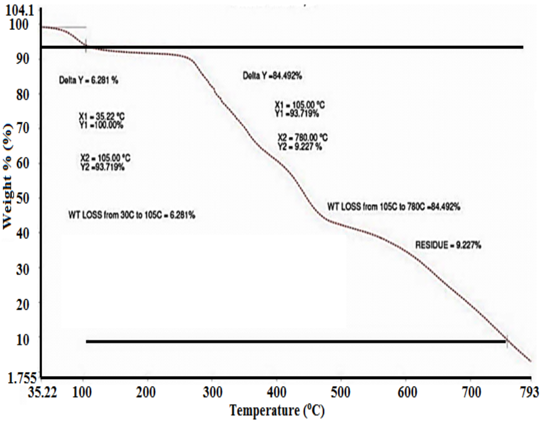


Fig. 6. TGA Thermogram of Co(II) ion complex

Zn(II) ion Complex with Schiff Base [HOMNIEC]: IR, ν(cm^{-1}): 1730 (lactonyl -O-C=O), 1594 (imino C=N-), 1504 (aromatic -C=C-), 1392 (phenolic -C-O-), 1088 (=C-C-), 2900-3000 (aliphatic/aromatic C-H), 3254-3329 (Broad) H_2O lattice/coordinated hydrogen bonded, 837 with small shoulder peak (coordinated water molecules with metal ion). mass of complex: (m/z) (L+1) = 344.4, (M+1) = 787.1, 680.1. Where L and M represented ligand and metal complexes respectively.

Antimicrobial activities

The ligand [HOMNIEC]/HL1 and its complexes were examined for their *in vitro* antimicrobial activities in DMSO medium. The broth microdilution method[19-21] was employed to get the MIC values for the synthesized ligand and its complexes against *Escherichia coli* and *Pseudomonas aeruginosa* a *gram-negative* bacterial strain, *Staphylococcus aureus* and *Streptococcus pyogenes* a *gram-positive* bacterial strain, and *Candida albicans*, *Aspergillus clavatus* and *Aspergillus niger* fungal strains shown in the Table 3 and Table 4 and presented graphically in Fig. 7 and Fig. 8 respectively. Chloramphenicol and griseofulvin were used as reference drugs for this antimicrobial examination.

Table 3: The MIC Values of Ligand [HOMNIEC]/HL1 and Its Complexes

Test Compounds/ Complexes	Test Organisms Minimal Inhibitory Concentration [MIC in µg/mL]			
	Gram-negative		*Gram-positive*	
	E. coli (MTCC 443)	*P. Aeruginosa* (MTCC 1688)	*S. aureus* (MTCC 96)	*S. pyogenes* (MTCC 442)
$HL1=C_{22}H_{17}NO_3$	125	200	250	100
$[Co(C_{22}H_{16}NO_3)_2(H_2O)_2]$	100	200	100	125
$[Ni(C_{22}H_{16}NO_3)_2(H_2O)_2]$	125	125	200	100
$[Cu(C_{22}H_{16}NO_3)_2(H_2O)_2]$	62.5	100	250	200
$[Zn(C_{22}H_{16}NO_3)_2(H_2O)_2]$	100	125	200	125
CHLORAMPHENICOL	50	50	50	50

Table 4: MIC Values of Ligand [HOMNIEC]/HL1 and Its Complexes

Test Compounds/Complexes	Test Organisms Minimal Inhibitory Concentration [MIC in µg/mL]		
	C. albicans (MTCC 227)	*A. clavatus* (MTCC 1323)	*A. niger* (MTCC 282)
$HL1=C_{22}H_{17}NO_3$	1000	500	500
$[Co(C_{22}H_{16}NO_3)_2(H_2O)_2]$	>1000	500	500
$[Ni(C_{22}H_{16}NO_3)_2(H_2O)_2]$	1000	1000	1000
$[Cu(C_{22}H_{16}NO_3)_2(H_2O)_2]$	250	500	500
$[Zn(C_{22}H_{16}NO_3)_2(H_2O)_2]$	250	1000	1000
GRISEOFULVIN	500	100	100

Antibacterial activity of lignad and complexes

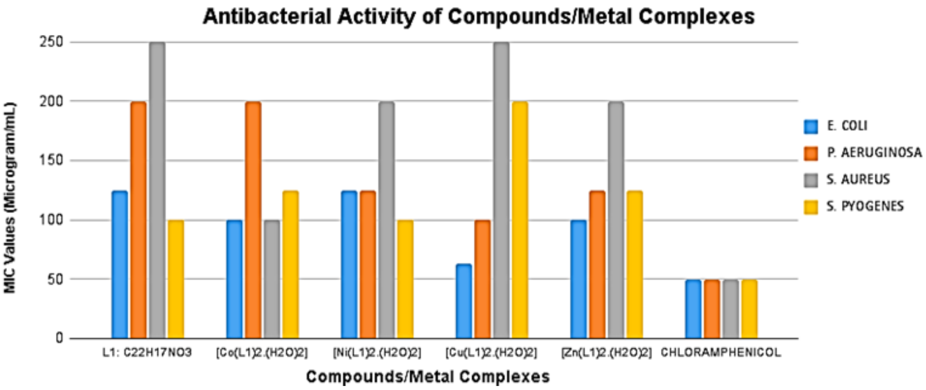


Fig. 7. Antibacterial Activity of [HOMNIEC]/HL1 and Metal Complexes

Antifungal activity of ligand and complexes

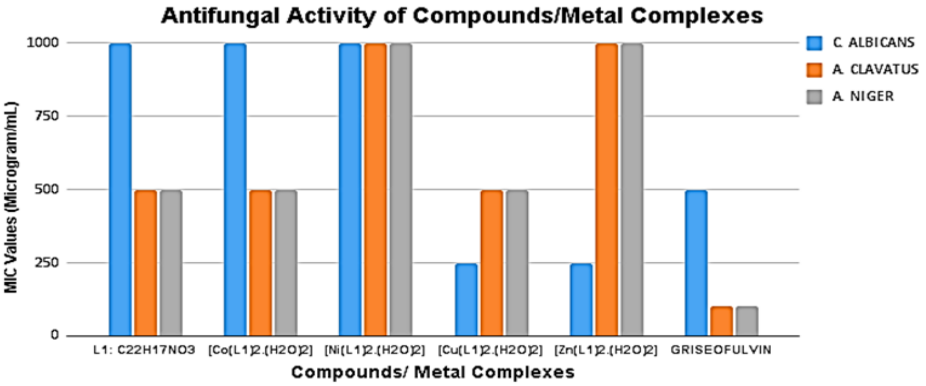


Fig. 8. Antifungal Activity of [HOMNIEC]/HL1 and Metal Complexes

RESULTS and DISCUSSION

Synthesis: A novel Schiff base ligand (E)-7-hydroxy-4-methyl-8-(1-(naphthalen-1-ylimino) ethyl)-2H-chromen-2-one was synthesized by condensation of 8-acetyl-7-hydroxy-4-methyl-2H-chromen-2-one and Naphthalen-1-amine (Scheme 1). The complexes were prepared by metal (II) chlorides reactions with the Schiff base ligand (Scheme 2).

FTIR Spectra: The FTIR spectra of ligand consists bands for carbonyl, imino and hydroxyl groups. However, the band for amino group (-NH_2) did not appear indicating the formation of imino/azomethine (>C=N-) group (Fig. 2). The characteristic peak for the hydroxyl group did not appear in the IR spectra of metal complexes. It confirms that the hydrogen removed from oxygen and metal ligand coordinate bond formation takes place through oxygen. Also, the presence of metal-oxygen and metal-nitrogen bands between 400-600 cm^{-1} in IR spectra of complexes indicate the formation of coordinate bonds through oxygen and nitrogen[8,22]. The broad peak between 3200-3600 cm^{-1} confirms the coordinated/lattice water molecules in the complexes. Also, the peaks between 820-840 cm^{-1} indicate the coordinated water molecules with the metal ions (Figure 4).

Mass Spectrometry: Mass spectrum m/z values confirm the molecular weight of Schiff base ligand (Fig. 3) and the mass spectra of complexes confirms the molecular weights/formula weights of metal complexes (Figure 5).

TGA: As per the TGA thermogram data interpretation the percentage (%) of metal ions observed and calculated were found nearly equal (Table 2). Also, the TGA thermograms of the complexes indicate the lattice or coordinated water molecules present in the complexes (Fig. 6). The slightly higher observed values may be indicating the removal of -CH_3 group[23] from ligand along with H_2O. From the TGA thermogram it can be seen that the decomposition of metal complexes starts from 180°C onwards and a sharp loss in mass was observed about 400°C. It suggested that the complexes are thermally stable.

Antimicrobial activities: *In vitro* antibacterial activity (Fig. 7) and *in vitro* antifungal activity (Fig. 8) of the ligand and its complexes show that the complexes have better antimicrobial activities than the ligand (Table 3 and Table 4). The MIC value for Cu(II) ion complex against *E. coli* is 62.5 µg/mL. This value is nearer to the MIC value for the standard drug Chloramphenicol (50 µg/mL). The MIC values for complexes of Cu(II) and Zn(II) ions against *C. albicans* is 250 µg/mL, which is lower than the MIC value for the standard drug Griseofulvin (500 µg/mL). So, the antifungal activity of these complexes is twofold more than Griseofulvin against *C. albicans*.

CONCLUSION

A novel ligand and its complexes were synthesized and their structures were confirmed by using FTIR, 1H MNR, Mass spectrometry, TGA techniques. The ligand is coordinated with phenolic oxygen (on coumarin moiety) and nitrogen of azomethine (>C=N-) group forming stable complexes with metal to ligand ratio 1:2. Also, the metal complexes were found to be thermally stable. All of these experimental results concluded that this oxygen and nitrogen donor Schiff base ligand formed stable metal complexes and the complexes would have potential to be useful as antimicrobial agents.

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Conflict of interest

Authors have no conflict of interest.

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