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SYNTHESES, CHARACTERISATION AND ANTIMICROBIAL STUDIES ON TRANSITION METAL COMPLEXES OF METHYLPHENYL-4-[PHENYL (PHENYLHYDRAZONO) METHYL]-3-PYRAZOLONE

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ABSTRACT

We aimed to synthesize the phenylhydrazone derivative of 4- benzoyl-3-methyl-1-phenyl-5-pyrazolone which is a novel Schiff base. The ligand was synthesized in three stages. 3-methyl-1-phenyl-5-pyrazolone was synthesized as reported in the literature. (Ref. Vogel). This was benzoylated at the 4- position to get 4- benzoyl-3-methyl-1-phenyl-5-pyrazolone (ref. Jesen's procedure). This was condensed with phenylhydrazine to get the novel Schiff base. Though there are four potential ligating sites, only two of the ligating sites are involved in coordination. The ligand was characterised by elemental analysis and IR spectrum. Co(II), Ni(II) and Cu(II) complexes of the neutral bidentate chelating Schiff base ligand were synthesized using acetates, chlorides and nitrates of the metals. They were characterised by elemental analysis, conductance and magnetic susceptibility measurements, UV, VIS and IR spectra. The ligand exhibited tautomerism and the complexes were found to have octahedral geometry. The in vitro antifungal activity against Aspergillus niger of the ligand and the complexes were investigated using nutrient agar medium.

KEY WORDS

Aspergillus niger, Metal complexes, IR spectral analysis, ^{1}H NMR spectral analysis, Schiff base.

INTRODUCTION

Metal complexes of Schiff bases have played a central role in the development of coordination chemistry. A class of cinnamoyl and thiopheneacryloyl chloride phenylhydrazones, which are new compounds to the organic chemical art, are effective in the treatment of helminthiasis in domestic and companion animals. The compounds may be substituted on either or both of their rings. The compounds are particularly effective against helminths of the economically-important ruminant animals. [1]

Hydrazones

Hydrazones and their derivatives are an important class of compound in organic chemistry and show interesting biological properties such as anti-convulsant, anti-tuberculosis, antitumor, anti-HIV, anti-inflammatory, and anti-microbial activity.[2-5] For example, nifuroxazide is a biologically active hydrazone, which shows an intestinal antiseptic activity and isoniazid displays very high activity against M. tuberculosis H37Rv.[2]

A perusal of the literature revealed that no work has been done on the transition metal complexes of the Schiff base derived from phenylhydrazine and 4-benzoyl-3-methyl-1-phenyl-5-pyrazolone. The present work involves the synthesis of a new type of bidentate/tetradentate ligand formed by the condensation of phenylhydrazine with 4-benzoyl-3-methyl-1- phenyl-5-pyrazolone. The ligand system has five sites which may offer

coordination, i.e., azomethine nitrogen, the pyrazolone ring oxygen atom, nitrogen atom of –N-H group, oxygen atom of carbonyl group and nitrogen atom of the pyridine moiety (**Fig.1**). Hence it was considered worthwhile to synthezise this ligand and to complex it with first row transition metal ions with a view to characterise them and also to study their biological activity.

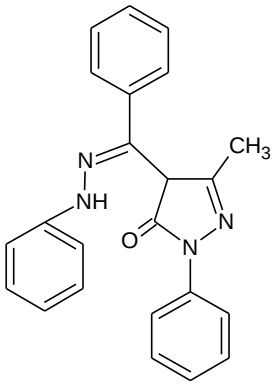

Fig. 1: Methylphenyl-4-[phenyl (phenylhydrazono) methyl]-3-pyrazolone)

MATERIALS AND METHODS

All chemicals used in the present work viz., benzoylchloride, ethylacetoacetate, phenylhydrazine, metal salts, solvents etc., were of AR grade. (BDH,Sarabhai, Qualigens, E. Merck, Loba Chemie or Glaxo). Carbon, hydrogen and nitrogen analyses were carried out by using VarioEL III CHNS analyser at SAIF, CUSAT,Kochi. The anions present in the complexes were estimated by standard methods. Infrared spectra were measured in the range 4000-400 cm^{-1} as KBr pellets on a Perkin-Elmer spectrophotometer. The solid-state electronic spectra of the complexes were recorded on a JASCO UV-Visible spectrophotometer. The magnetic measurements were made at room temperature by Evans method using $Hg[Co(CNS)_4]$ as calibrant**.**

SYNTHESIS OF THE COMPOUNDS:

The synthesis of the ligand consisted of three stages. First, 3-methyl-1-phenyl-5-pyrazolone was prepared and benzoylated to give 4-benzoyl-3-methyl-1-phenyl-5-pyrazolone[7]. The third stage involved phenylhydrazine to prepare the Schiff base ligand. Added an ethanolic solution of phenylhydrazine (5.0 mL 0.0507 mol) to the hot solution. Cooled and added 1 ml of concentrated sulphuric acid. A yellow-green solid was formed. Cooled and added some more of ethanol and refluxed for 0.5 h. On cooling, bright yellow coloured crystals were obtained. Filtered at the pump, washed with ethanol and dried. Yield: 12.3570 g, 66.2 %.

Complexes of Co (II) with this ligand were synthesized using nitrate salts of the metal. Complexes of Ni (II) with this ligand were synthesized using acetate and chloride salts of the metal. Complexes of Cu (II) of this ligand were synthesized using acetate, chloride and nitrate salts of the metal.

Nitrate salts of cobalt (II) and copper (II) and chloride salts of nickel (II) and copper (II) were prepared by adding an ethanolic solution of the salt hydrates to an ethanolic solution of the ligand it in 1:2 metal:ligand molar ratio, followed by the addition of sodium acetate-acetic acid buffer solution of pH=4 and heated for a few minutes. Filtered the solid at the pump, washed with ethanol and dried.

The acetate salts of nickel (II) and copper (II) were synthesized by adding an ethanolic solution of the metal salts to an ethanolic solution of the ligand in 1:2 metal:ligand molar ratio and heated on a water bath for 45 minutes. A green solid was formed at the bottom of the beaker. Cooled, filtered the solid at the pump, washed with ethanol and dried.

RESULTS AND DISCUSSION

Characterization of the ligand

The ligand was characterized by m.p., elemental analysis, IR spectral data and ^{1}H NMR spectral data. The 1H NMR spectrum of the ligand was recorded in DMSO-d_6 and it showed a number of characteristic signals of the compound. The singlet observed at 1.89 δ is assigned to the methyl protons at 3rd position of the pyrazolone ring. The multiplet observed in the range 6.8-7.9δ is assigned to the aromatic protons. A broad singlet centered at 11. δ is due to the N-H proton. The singlet at 9.54 ð was assigned to the proton at 4th position of the pyrazolone ring. The singlet observed at 3.3δ is due to DMSO. The infrared spectrum of the ligand showed a number of absorption bands which were characteristic of different groups present in the molecule (**Table 1**). Assignments have been made by reference to generalized charts of characteristic group frequencies and on the basis of analogous structures, known earlier.[8] The sharp band at 3325 cm^{-1} has been assigned to –NH group. A sharp band of medium intensity at 1632 cm^{-1} has been assigned to >C=O group. The sharp band at 1250 cm^{-1} has been assigned to C-N stretching vibration. The sharp band of medium intensity at 953 cm^{-1} has been assigned to υ(N-N)vibration of the hydrazono moiety. The appearance of the azomethine υ(C=N) vibration in the Schiff base, BMPPPH at lower frequency 1578 cm^{-1}, in comparison with the normal value (1675 cm^{-1}), indicated the involvement of the azomethine nitrogen atoms in hydrogen bonding. The sharp band at 3198 cm^{-1} was attributed to aromatic C-H stretching band. Strong and medium intense bands between 690 and 837 cm^{-1} resulted from the out-of-plane bending of the ring C-H bonds. In-plane bending bands appeared in the 1300-1000 cm^{-1} region. Skeletal vibrations, involving carbon-carbon stretching within the ring, were found in the 1600-1585 and 1500-1400 cm^{-1} regions.

Fig 1: Significant IR bands of ligand and their assignments

BAND FREQUENCY * (cm-1)	ASSIGNMENT
3325 (s)	-NH stretch
3198 (s)	Aromatic C-H stretch
1632 (s) (m)	>C=O stretch
1578 (s)	>C=N stretch
1300-1000 (s)	In-plane bending of aromatic ring protons
1250 (s)	C-N stretch
953 (s) (m)	N-N stretch
837 (s) (m)	Out-of-plane bending of the ring C-H
690 (s) (m)	Out-of-plane bending of the ring C-H

Formulae and general properties of the complexes

All the complexes were found to be coloured, stable to light, heat and moisture and non-hygroscopic solids. Some of them looked crystalline in nature. The solubility of these complexes in common organic solvents was very low, but they were soluble in DMF/DMSO. The

analytical data (**Table 2**) and the molar conductance values (**Table 3**) showed that the complexes had the formula $[ML_2X_2]$. The spectral and magnetic data also confirmed the suggested formulae.

The reaction of the ligand (L) with different salts of Co(II), Ni(II) and Cu(II) ions in 2:1 molar ratios gave metal complexes of the formula $[ML_2X_2]$, as evidenced by the microanalytical and spectral data. The suggested structure for $[ML_2X_2]$ is shown in **Fig.2**. The colours, magnetic susceptibilities, molar conductivities and melting points and the micro-analytical data of the complexes are listed in **Table 1**. These air-stable metal complexes were nonhygroscopic, partially soluble in most of the organic solvents but freely soluble in DMF and DMSO. The molar conductivities in DMF/DMSO (10^{-3}M) showed that the complexes had the formula $[ML_2X_2]$. The spectral and magnetic data also confirmed the suggested formulae.

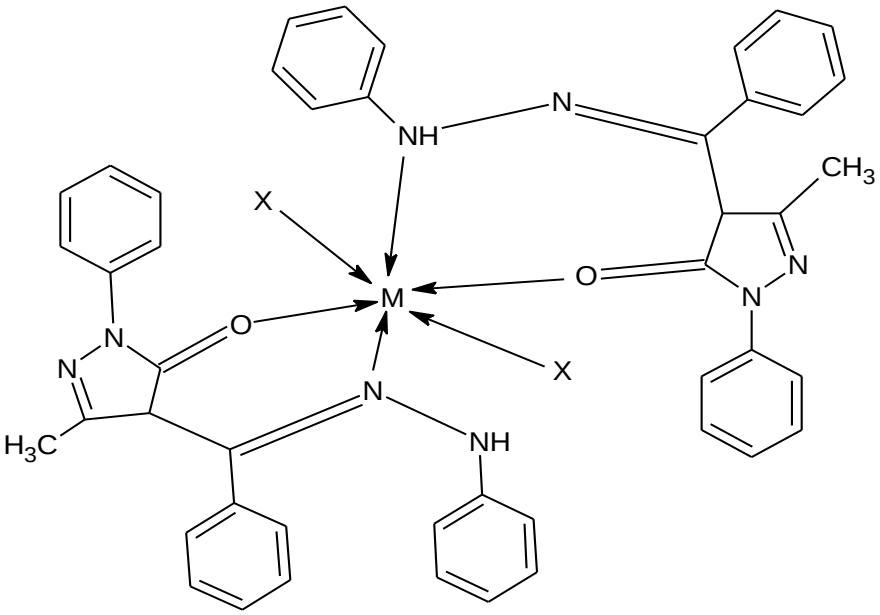

Fig.2: Suggested structure for $[ML_2X_2]$ where M=Co (II), Ni (II) or Cu (II) and X= CH_3COO^-, Cl^- or NO_3^-

TABLE 2: Formulae, general properties and micro analytical data of ligand and complexes

COMPOUND	EMPIRICAL FORMULA	F.WT. *	YIELD %	FOUND (CALCULATED) %				
				METAL	C	H	N	ANION
BMPPPH (L)	$C_{23}H_{20}N_4O$	368	66	-	75.12 (75.00)	5.40 (5.44)	15.20 (15.22)	-
$[Co(L)_2(NO_3)_2]$	$CoC_{46}H_{40}N_{10}O_8$	918.93	42	6.40 (6.41)	61.01 (60.07)	4.70 (4.35)	15.60 (15.24)	-
$[Ni(L)_2(CH_3COO)_2]$	$NiC_{50}H_{46}N_8O_6$	912.71	44	6.39 (.6.43)	65.90 (65.74)	5.07 (5.04)	12.32 (12.27)	-
$[Ni(L)_2Cl_2]$	$NiC_{46}H_{40}N_8O_2Cl_2$	865.71	45	6.70 (6.78)	64.00 (63.76)	4.62 (4.62)	13.00 (12.94)	8.14 (8.20)
$[Cu(L)_2(CH_3COO)_2]$	$CuC_{50}H_{46}N_8O_6$	917.54	43	6.89 (6.93)	65.94 (65.39)	4.97 (5.01)	12.32 (12.21)	-
$[Cu(L)_2Cl_2]$	$CuC_{46}H_{40}N_8O_2Cl_2$	870.54	43	7.25 (7.30)	63.56 (63.41)	4.64 (4.59)	12.80 (12.87)	8.09 (8.16)
$[Cu(L)_2(NO_3)_2]$	$CuC_{46}H_{40}N_{10}O_8$	923.54	43	6.79 (6.88)	59.68 (59.77)	4.30 (4.33)	15.12 (15.16)	-

*** F.WT. = FORMULA WEIGHT**

TABLE 3: Molar conductances of Co (II), Ni (II) and Cu (II) complexes of ligand

COMPLEX	Ω_m ohm^{-1} cm^2 mol^{-1}	SOLVENT
$[Co(L)_2(NO_3)_2]$	10.75	DMF
$[Ni(L)_2(CH_3COO)_2]$	0.0	DMSO
$[Ni(L)_2Cl_2]$	0.0	DMSO
$[Cu(L)_2(CH_3COO)_2]$	10.75	DMSO
$[Cu(L)_2Cl_2]$	20.15	DMSO
$[Cu(L)_2(NO_3)_2]$	0.0	DMSO

Table 4: Significant bands in the ir spectra of the Co (II), Ni(II) and Cu(II) complexes of ligand and their assignments

COMPOUNDS	ASSIGNMENTS AND BAND FREQUENCIES * (cm^{-1})									
	υ N-H	υ C =N	υ C= O (cm^{-1})	δ N-N-H	υ M-N	υ M-O	υ M-X	υ COO- asym	υ COO- sym	υ NO_3^- coordinated
BMPPPH (I)	3325 m,sh	1578 s,sh	1632 s	1539s,sh	-			-		-
$[Co(L)_2(NO_3)_2]$	3269 m,sh	1554 s,sh	1612 s,sh	1533s,sh	470 w,sh	619 m,sh	-	-	-	1437 s,sh 1157 m,sh 1020 m,sh
$[Ni(L)_2(CH_3COO)_2]$	3292 m,sh	1554s,sh	1612 s,sh	1533 s,sh	360 w,sh	619 m,sh	-	1500 sh	1369 sh	-
$[Ni(L)_2Cl_2]$	3323 m	1562 s,sh	1612 s,sh	1529 m,sh	439 m,sh	603 w,sh	~400 w	-	-	-
$[Cu(L)_2(CH_3COO)_2]$	33210 m	1568 s,sh	1620 s,sh	1529 m,sh	470 w	619 w,sh	-	1599 s,sh	1381 s,sh	
$[Cu(L)_2Cl_2]$	3020 m	1550 s,sh	1575 s,sh	1530 m,sh	490 w	611 w	~455`	-	-	
$[Cu(L)_2(NO_3)_2]$	3338 m,sh	1560 s,sh	1599 s,sh	1535 s,sh	462 w,sh	615 s,sh	-	-	-	1440 m,sh 1280 w,sh 1020 w,sh

*** s = sharp; m = medium; w = weak; sh = sharp**

Table 5: Magnetic susceptibility data of Co(II), Ni(II) and Cu(II) complexes of ligand

COMPLEX	χ_g x10^{-6}	χ_m x 10^{-6}	$\chi_{m\ corr}$ x 10^{-6}	μ_{eff}	T(K)
$[Co(L)_2(NO_3)_2]$	14.62	13436.62	13651.79	5.68	296.1
$[Ni(L)_2(CH_3COO)_2]$	1.49	1359.83	1575.02	1.93	295.7
$[Ni(L)_2Cl_2]$	2.54	2201.60	2416.79	2.40	296.1
$[Cu(L)_2(CH_3COO)_2]$	1.88	1722.04	1937.22	2.14	295.9
$[Cu(L)_2Cl_2]$	1.70	1476.11	1691.30	2.00	295.7
$[Cu(L)_2(NO_3)_2]$	2.00	1845.37	2060.56	2.21	295.7

χ_g = mass susceptibility

χ_m = molar susceptibility

$\chi_{m\ corr}$ = corrected molar susceptibility

μ_{eff} = effective magnetic moment

T=Temperature in Kelvin

Table 6:Electronic spectral bands of Co(II), Ni(II) and Cu(II) complexes of ligand and their assignments

COMPLEX	BANDS(nm)	ASSIGNMENT	GEOMETRY
$[Co(L)_2(NO_3)_2]$	~ 565 448	$^4T_{1g}\rightarrow{}^4T_{2g}(P)$ $^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$	Octahedral
$[Ni(L)_2(CH_3COO)_2]$	~742 440	$^3A_{2g}(F)\rightarrow{}^3T_{2g}(F)$ $^3A_{2g}(F)\rightarrow{}^3T_{1g}(P)$	Octahedral
$[Ni(L)_2Cl_2]$	~800	$^3A_{2g}(F)\rightarrow{}^3T_{2g}(F)$	Octahedral
$[Cu(L)_2(CH_3COO)_2]$	~ 602	$^2E_g\rightarrow{}^2T_{2g}$	Distorted octahedral
$[Cu(L)_2Cl_2]$	~526	$^2E_g\rightarrow{}^2T_{2g}$	Distorted octahedral

Table 7: Antifungal activity study on Aspergillus niger

COMPLEX	ZONE OF INHIBITION (mm)
BMPPPH (L_3)	13
$[Ni(L_3)_2Cl_2]$	10
$[Ni(L_3)_2(NO_3)_2]$	17
$[Cu(L_3)_2(CH_3COO)_2]$	8
$[Cu(L_3)_2Cl_2]$	8
$[Cu(L_3)_2(NO_3)_2]$	19

Coordinated anions

The infrared spectrum of the acetato complex of copper(II) showed two sharp bands at 1599 and 1381 cm^{-1} assigned to $\upsilon_a(COO^-)$ and $\upsilon_s(COO^-)$ vibrations respectively (**Table 4**). The former was greater and the latter was at a lower frequency than that of the free acetate ion i.e., 1560 and 1416 cm^{-1}.[9] Hence, the separation between the two υ (CO) was very large, suggesting unidentate coordination of the acetate ion to the copper (II) ion.

The band at ~ 400 cm^{-1} in the infrared spectrum of the chloro complex of nickel (II) has been assigned to Ni-Cl bond, i.e., the chlorine atom present was terminal and not bridging.

The infrared spectrum of the nitrato complex of copper (II) complex showed bands at 1440, 1280 and 1020 cm^{-1} which were assigned, respectively,

to υ_4, υ_1 and υ_2 modes of coordinated nitrate ion. Since the magnitude of separation of υ_4 and υ_1 modes was 160 cm^{-1}, it was ascertained that the nitrate ions are coordinated unidentatively.[10]

Magnetic and electronic spectral studies

Co (II) complexes:

The mass susceptibility, molar susceptibility, corrected molar susceptibility and the effective magnetic moment values for the cobalt (II), nickel (II) and copper (II) complexes are tabulated in **Table 5**. The value of 5.68 B.M. calculated for the nitrato complex of Co(II) suggested high-spin octahedral geometry with very high contributions attributable to the three-fold degeneracy of $^4T_{1g}(F)$ ground term.[11,12] The observed high value of μ_{eff} may be due to the mixing of the ground state with the excited state. A broad band between 525 and 650 nm, centered at 565 nm was observed which has been assigned to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$ transition(**Table 6**). This suggested an octahedral environment around cobalt (II) ion. The shoulder at 448 nm may be assigned to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ transition. The position, intensity considerations, the magnetic moment values and analytical data favoured octahedral geometry[13-15].

Ni (II) complexes:

The magnetic moment values of 1.93 and 2.40 B.M. for the acetato and chloro complexes of nickel (II) also deviated significantly from the value expected for metal ion in the d^8 configuration. In a large number of tridentate ONO donor metal complexes, lower magnetic moment have been reported[16] which had been attributed to antiferromagnetic interactions as a consequence of dimeric or polymeric structural arrangements. But in the present work, the lower value than the one expected is due to metal-metal interaction.[11]

The solid reflectance spectrum of the acetato complex of nickel (II) showed a broad band between 700 and 800 nm centered at 742 nm and a shoulder at 440 nm. The former has been assigned to $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)(\upsilon_2)$ transition and the latter to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)(\upsilon_3)$ transition. A broad band between 750 and 850 m centered at ~800 nm has been observed in the spectra of the has been observed in the spectra of the chloro complex of nickel (II) and has been assigned to $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)(\upsilon_2)$ transition. The positions and assignments of these bands suggested octahedral environment around nickel (II) ion in the complexes.[17]

The magnetic moment values 2.14, 2.00 and 2.21 B.M. calculated for the acetato, chloro and nitrato complexes of copper (II) indicated that they were in the required range for complexes with D_{4h} symmetry.[18]

The solid reflectance spectra of the acetato and chloro complexes of copper (II) showed broad bands around 602, 526 and 547 nm in the acetato, chloro and nitrato complexes, respectively. They have been assigned to $^2E_g \rightarrow {}^2T_{2g}$ transition in an octahedral field. The broadening of the band may be due to Jahn-Teller effect[28] and suggested a distorted octahedral geometry around copper (II) ion.

Antimicrobial activity

The biological activity of the ligand and five of its complexes was investigated. The ligand and the acetato, chloro and nitrate complexes of Ni(II) and the acetate, chloro and nitrate complexes of Cu(II) were evaluated for in vitro antifungal activity against Aspergillus niger. Potato agar medium[19] was employed for the fungal growth. The zones of inhibition determined in the antifungal activity on Aspergillus niger are presented in **Table 7 and Figs.3 (A-F)**. The ligand as well as the complexes showed antifungal activity. The acetate complex of Cu (II) and the chloro complexes of Ni (II) and Cu (II) showed lesser antifungal activity than the ligand. But the nitrate complexes of Ni (II) and Cu (II) showed better antifungal activity than the ligand.

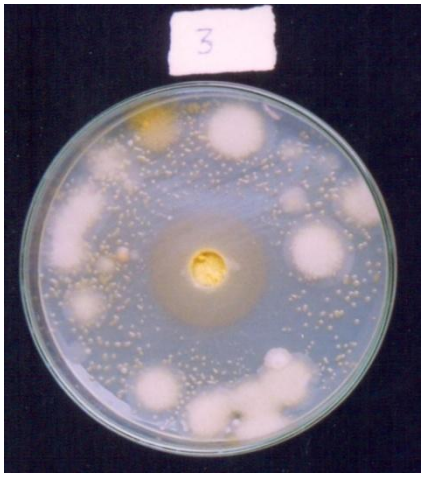

Fig.3 (A) Zone of inhibition (15 mm) observed in the antifungal activity of ligand on A. niger

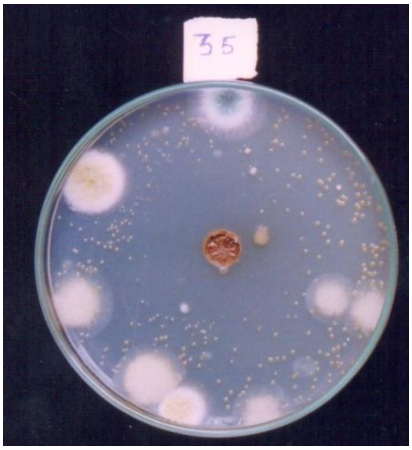

Fig. 3 (D) Zone of inhibition (8 mm) observed in the antifungal activity of [Cu $(L_3)_2(CH_3COO)_2$] on A. niger

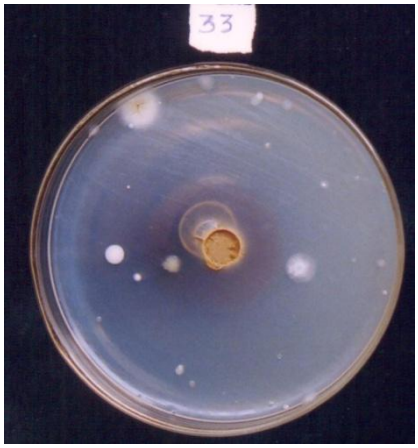

Fig. 3 (B) Zone of inhibition (10 mm) observed in the antifungal activity of [$Ni(L_3)_2Cl_2$] on A. niger

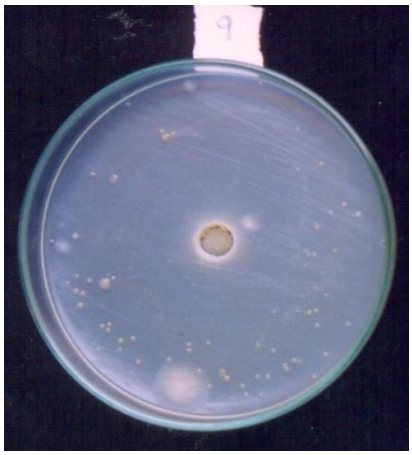

Fig. 3(E) Zone of inhibition (8 mm) observed in the antifungal activity of [Cu $(L_3)_2(Cl)_2$] on A. niger

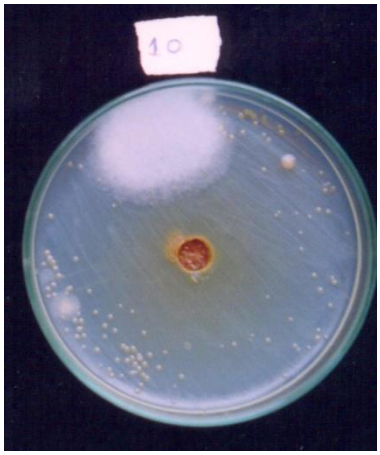

Fig: 3(C) Zone of inhibition (17 mm) observed in the antifungal activity of [$Ni(L_3)_2(NO_3)_2$] on A. niger

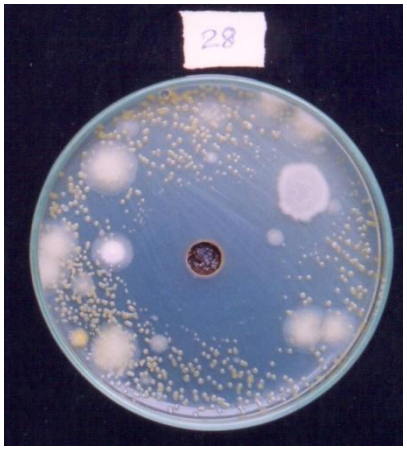

Fig. 3(F) Zone of inhibition (8 mm) observed in the antifungal activity of [Cu $(L_3)_2(NO_3)_2$] on A. niger

CONCLUSIONS

We have synthesized a novel Schiff base and also its metal complexes. The metal salts chosen are of biological importance, i.e., cobalt, nickel and copper. We have characterized the ligand and the metal complexes. The metal complexes are found to have octahedral geometry. Moreover the ligand and the metal complexes are found to be biologically active as evidenced by the antifungal activity against Aspergillus niger. By discovering and structurally characterizing compounds with medicinal activity, chemists are able to design new drugs[20] with enhanced potency and decreased adverse side effects. Lead compounds are molecules that have some biological activity with respect to the condition under investigation. However, the lead compound may not be effective in combating the disease, or it may produce undesirable side effects. Lead optimization involves chemical modifications to the lead compound to produce a more potent drug, or one with fewer or decreased adverse effects. Pharmaceutical chemists try to understand the biological mechanism responsible for a specific disease. If the biochemical pathways leading up to the diseases are understood, scientists can attempt to design drugs that will block one or several of the steps of the disease's progress. Pharmaceutical specialists use the findings from the preclinical stage to establish what form the drug should take for patient use.

For example, in a sublingual spray or a tablet, Governing agencies[21] who monitor drug development demand documentation of the chemical characteristics, including structure, quality, potency and purity of the active ingredient and of the final form of the drug. We hope that this work will help the pharmaceutical chemists to develop lead compounds.

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