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Study of Antifungal Activity of 2-Methoxy-6-{[2-(2-Methoxy-Phenoxy)-Ethylimino]- Methyl}-Phenol And Its Transition Metal Complexes on Asperligues Niger And Candida Albicuns

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Abstract

Coordination complexes of transition metals with Schiff base ligands were synthesized. The characterization of these compounds were carried out by physical parameters and spectral analysis namely color, melting point, IR, NMR, UV, Magnetic measurements, TGA,ESR, XRD and Conductivity studies. The spectral analyses are used for elucidating the structure of ligand and metal complexes. Biological activity of the compounds has been studied for fungi *Asperligues niger* and *Candida albicuns*

Keywords: Schiff bases, Metal Complexes**,** Spectral analysis, Antifungal activity

1. Introduction

The importance of metal complexes as drugs, their role in the biological systems and in the biological action of certain drugs has been realized. They are based upon the drug certain physical properties, e.g., low dissociation constants resulting in tightly metal ions, special oxidation-reduction potentials, solubility and electron distribution. The majority of the important metal complexes are chelates[1]. Studies on the relationship of metal complexes and biological response have been reported [2],[3]. The Schiff bases and their metal complexes are of biological importance. The Schiff bases possess various activities such as antibacterial activity, antifugal activity, anticancer activity, antitumor activity and antitubercular activity[4]. Metal complexes of the Schiff bases also show these activities. These complexes are often more active than the ligands due to complexation with less side effects.

Present work deals with synthesis of Schiff base ligand and its transition metal complexes by condensing with metal salts of Ni (II), Cu (II), Co (II), Mn (II) and Zn (II).

2. Materials and Methods

Chemicals and reagents: The chemicals used are 2-(2-Methoxy-phenoxy)-ethylamine (Merck ,AR grade) and o-Vanillin (Merck ,AR grade),Ethyl alcohol (Merck ,AR grade) , Cobalt (II) chloride dihydrate (Sigma Aldrich), Nickel(II) chloride hexahydrate (Sigma Aldrich), Copper(II) chloride dihydrate (Sigma Aldrich), Zinc (II) chloride (Sigma Aldrich) , Manganese (II) chloride tetrahydrate (Sigma Aldrich)

3. Synthesis of Ligand (MMPEMP): The Schiff Base ligand 2-Methoxy-6-{[2-(2-methoxy-phenoxy)-ethylimino]-methyl}-

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phenol (Fig 1) was synthesized by condensing amine 2-(2-Methoxy-phenoxy)-ethylamine with o- Vanillin in equimolar proportions. To an ethanolic solution (10 ml) of the amine (0.01 mole) was added o- Vanillin (0.01 mole) in ethanol (10 mL) with stirring. The mixture was then refluxed for 30 mins. The reaction mixture was then cooled which immediately gave a precipitated product. The product then obtained was filtered, washed with ethanol and then dried. The crude product was then crystallized from aqueous ethanol to give a yield of 86%.

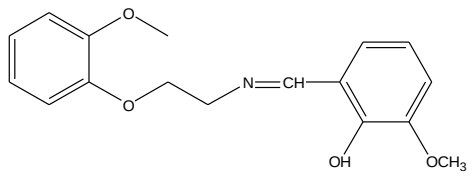

Fig 1. Structure of Ligand(MMPEMP): 2-Methoxy-6-{[2-(2-methoxy-phenoxy)-ethylimino]-methyl}-phenol

4. Synthesis of metal complexes: The ligand and metal salt in the molar ratio of 2:1 was dissolved in a ethanol and the reaction mixture was heated on water bath for about one hour. It was then cooled when colored solid separated out which was washed with ethanol and dried. This is the general method employed for the synthesis of metal complexes of ligand with metal chlorides viz Ni(II), Cu(II), Co(II), Mn(II) and Zn(II).

Antifungal studies: The various screening studies carried out include the in-vitro study against two fungi *Asperligues niger* and *Candida albicuns*

5. Results and Discussion

Formation of the complex was indicated by physical parameters color change and melting point[5].

In NMR spectra formation of ligand was confirmed by presence of CH=N peak at 8.4 δ and OH at 5.6 δ. In the present investigation the Infra red values for major peaks are assigned. The IR spectrum of ligand gave a strong band at 1642.09 cm-1 and 2901.27cm^{-1} which are attributed to the stretching frequencies of C=N (azomethine) and OH respectively. Complexes showed a lower shift of wave numbers for C=N. Also IR bands were observed for M-O and M-N. All complexes showed bands 3300 cm^{-1} to 3400 cm^{-1} indicating co-ordinated H_2O moiety in the complexes[5.] The electronic spectra the complexes exhibited energy peaks for d-d transitions which are attributed to well-defined octahedral geometry[5].

Magnetic susceptibility measurements

The effective magnetic moment values for the complexes were determined. The magnetic moment value 4.24 B.M for Co(II) complex suggests an octahedral environment[6],[7]. The magnetic moment value of the Cu (II) complexes of 1.63 B.M suggests distorted octahedral geometry[8],[9]. The magnetic moment value of the Ni(II) complexes 3.13 B.M suggests an octahedral geometry. Mn (II) complexes with the value of 5.64 B.M indicate octahedral geometry[10]. The Zn(II) complexes were found to be diamagnetic, as expected for d^{10} configuration.

Thermo Gravimetric Analysis

TGA analysis is carried out to explain the thermal stability of complexes. TGA study of complex showed weight loss in the temperature range of 110^{o}C-200 ^{o}C is due to elimination of coordinated water molecule. Also gradual decrease in mass is seen up to 300 ^{o}C due to loss of volatile matter. And a plateau observed above 350 ^{o}C respectively which corresponds to the formation of stable metal oxide.

ESR

The gll and g⊥ value for Copper complex is reported in the following Table 2. The spectrum showed asymmetric bands with two g values. The trend gll> g⊥> 2.00277, indicating that the unpaired electron lay predominately in the dx^2-y^2 orbital with possibly mixing of dz^2 orbital because of the low symmetry. The axial symmetry parameter

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'G' is determined as $G = \frac{(g\parallel - 2.00277)}{(g\perp - 2.00277)}$. G values found to be more than 4 suggesting very weak or no interaction in the solid state.

Conductivity measurements

The present solid complexes were dissolved in DMSO to perform conductivity experiments. The molar conductivity of 10^{-1} M concentration of these solutions was measured at room temperature. The conductance values for all the newly synthesized complexes were in the range 23 to 94 mhos cm^2 mol^{-1}, indicating very low conductance. These values indicate that the complexes are non electrolytic nature. The conductance values of the metal complexes were given in Table. 3.

X-ray diffraction studies of metal complex

The X- ray diffractogram of the complexes was measured in the range of 10^oC-80^oC, 2theta values. The interpretation of the spectra was carried out using Powder X software for assigning the cell parameters a, b and c and the crystal systems. XRD pattern indicates complexes have well defined crystalline patterns, with various degrees of crystallinity. The diffraction pattern obtained for the Ni (II) complex, Co (II) complex and Zn (II) complex shows orthorhombic crystal system whereas Cu (II) complex and Mn (II) complex shows rhombohedral crystal system.

Table 1: Thermogravimetry analysis of complexes

Complexes	Temperature Range (°C)	Calc (%)	Obs (%)	Mass loss
MMPEMP-Ni	110 - 200	5.18	5.0	Mass loss due to H_2O molecules
	250 - 320	13.34	14.0	Mass loss due to volatile matter
	Above 350	10.75	10.0	Mass of the metal oxide
MMPEMP-Cu	110 - 200	5.14	6.0	Mass loss due to H_2O molecules
	250 - 320	13.90	14.0	Mass loss due to volatile matter
	Above 350	11.37	10.0	Mass of the metal oxide
MMPEMP-Co	110 - 200	5.17	5.0	Mass loss due to H_2O molecules
	275 - 320	13.45	15.0	Mass loss due to volatile matter
	Above 350	10.77	10.0	Mass of the metal oxide
MMPEMP-Mn	110 - 200	5.20	6.0	Mass loss due to H_2O molecules
	200 - 300	12.95	14.0	Mass loss due to volatile matter
	Above 350	10.25	10.0	Mass of the metal oxide
MMPEMP-Zn	110 - 200	5.10	5.0	Mass loss due to H_2O molecules
	250 - 320	14.00	16.0	Mass loss due to volatile matter
	Above 350	11.62	11.0	Mass of the metal oxide

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Table 2: ESR values for Copper complex

Complex	gll value	g⊥ value	g_{avg}	G
MMPEMP-Cu complex	2.297	2.047	2.13033	6.65227

Fig 2: ESR spectra of Copper complex

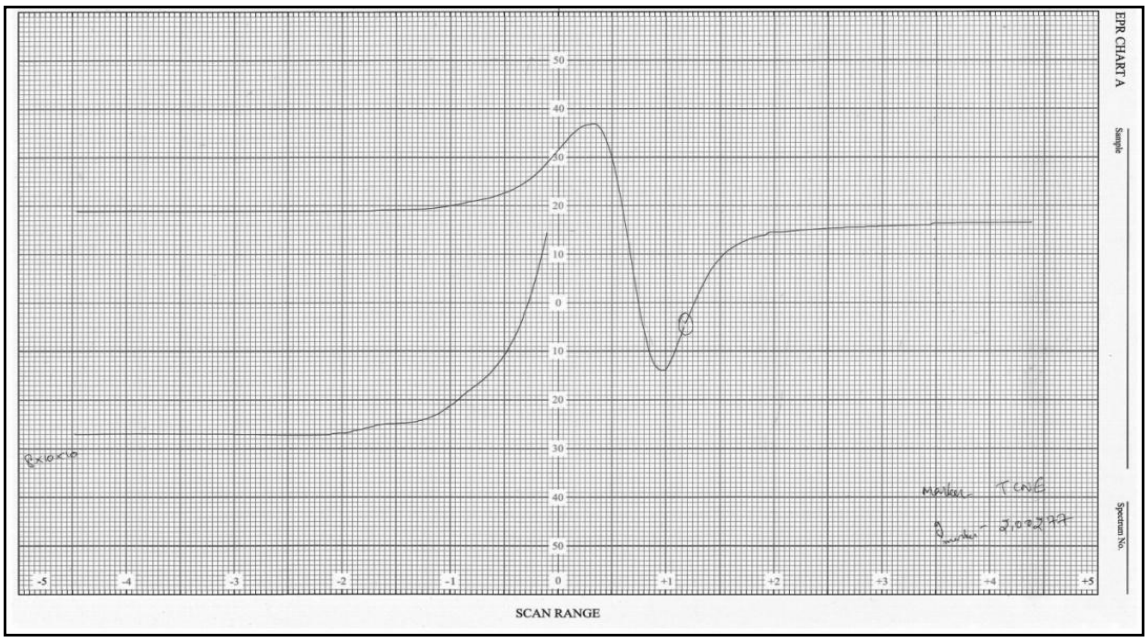

Table 3: Molar conductance of MMPEMP complexes

Complex	Conductance (mhos)	Specific conductance (mhos cm^{-1})	Molar conductance (mhos cm^2 mol^{-1})
MMPEMP- Ni	0.03	2.34 x 10 -3	23.40
MMPEMP- Cu	0.12	9.36 x 10 -3	93.60
MMPEMP- Co	0.06	4.68 x 10 -3	46.80
MMPEMP- Mn	0.11	8.58 x 10 -3	85.50
MMPEMP- Zn	0.12	9.36 x 10 -3	93.60

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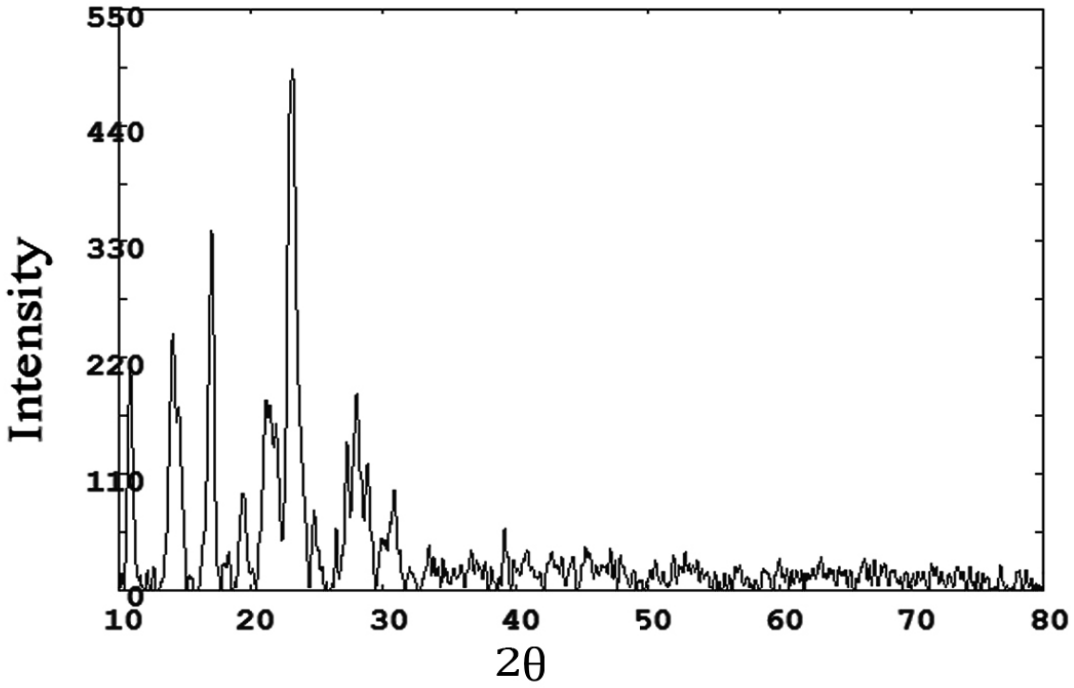
1. XRD of MMPEMP- Ni



2.

Fig 3: XRD of MMPEMP- Ni

Table 4: XRD values of MMPEMP- Ni

h k l	2θ (Exp.)	2θ (calc.)	d (Exp.)	d (calc.)	Intensity (Exp.)
0 2 0	10.872	10.854	8.13082	8.1387	209.77
0 0 1	14.096	14.020	6.27776	6.3117	241.61
1 2 0	14.523	14.632	6.09414	6.0520	173.46
-1 1 1	17.040	16.994	5.19930	5.2041	339.79
-1 3 1	22.998	22.992	3.86396	3.8612	462.55
-2 1 1	23.145	23.388	3.83986	3.8087	492.72
2 2 1	27.993	27.889	3.18481	3.1972	186.25

Cubic system, Lattice Parameter: a= 4.9168 b= 4.9168 c= 5.4089; $\alpha =$ 89.99990, $\beta =$ 100.99990, $\gamma =$ 89.99997

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2. XRD of MMPEMP- Cu

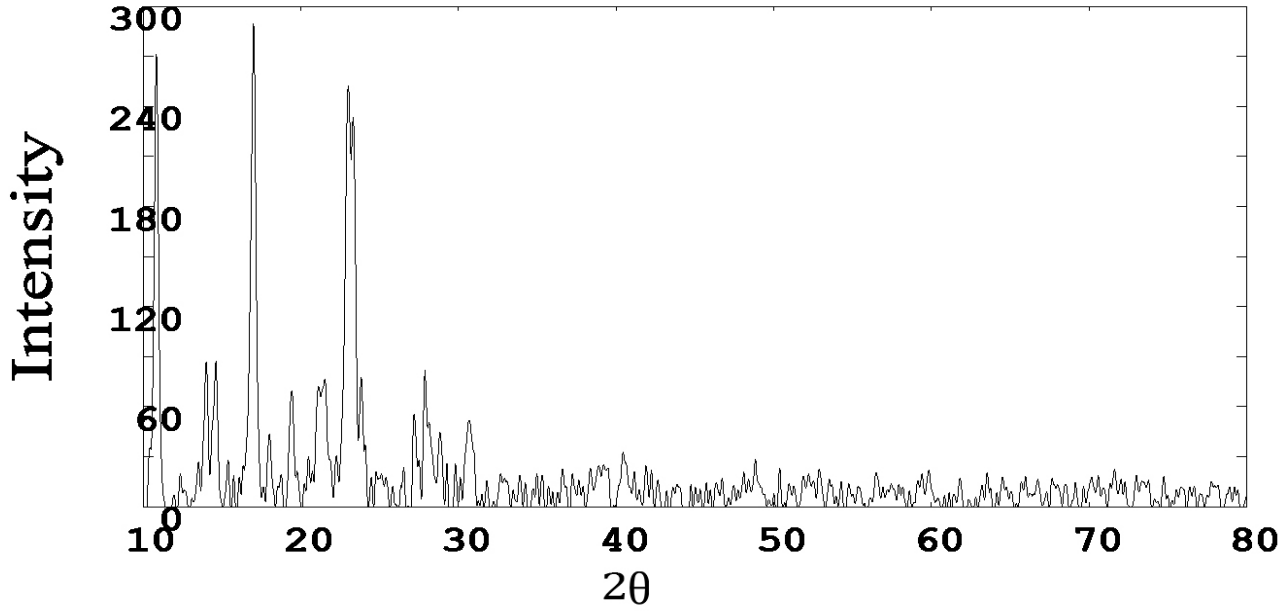

Fig 4: XRD of MMPEMP- Cu

h k l	2θ (Exp.)	2θ (calc.)	d (Exp.)	d (calc.)	Intensity (Exp.)
0 0 1	16.319	16.375	5.20558	5.40890	277.52
1 0 0	18.021	18.027	4.91844	4.91680	40.74
1 0 1	24.325	24.447	3.81053	3.63827	226.93
1 1 0	26.001	25.601	3.27419	3.47670	52.01

Table 5: XRD of MMPEMP- Cu

Tetragonal system, Lattice Parameter: a= 4.9168 b= 4.9168 c= 5.4089; $\alpha = 89.99995$, $\beta = 89.99996$, $\gamma = 89.99997$

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3. XRD of MMPEMP-SB4 Co

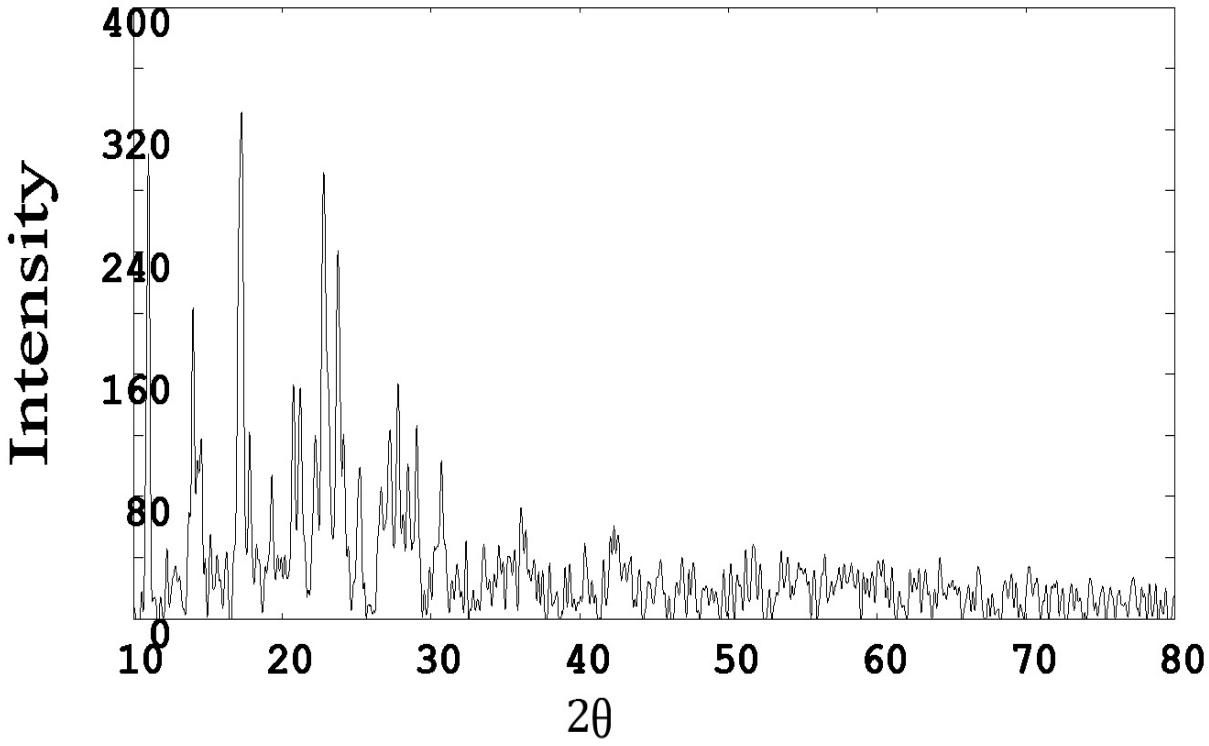

Fig 5: XRD of MMPEMP- Co

h k l	2θ (Exp.)	2θ (calc.)	d (Exp.)	d (calc.)	Intensity (Exp.)
0 0 1	16.273	16.375	5.12954	5.40890	332.02
1 0 0	18.293	18.027	5.12392	4.91680	319.61
1 0 1	23.748	24.447	3.74362	3.63827	241.01
1 0 1	26.660	26.622	3.34100	3.34573	85.92
1 1 1	30.505	30.542	2.90948	2.92464	103.67

Table 6: XRD of MMPEMP-Co

Tetragonal system, Lattice Parameter: a= 4.9168, b= 4.9168, c= 5.4089; $\alpha =$ 89.99990, $\beta =$ 89.99990, $\gamma =$ 89.99997

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4. XRD of MMPEMP- Mn

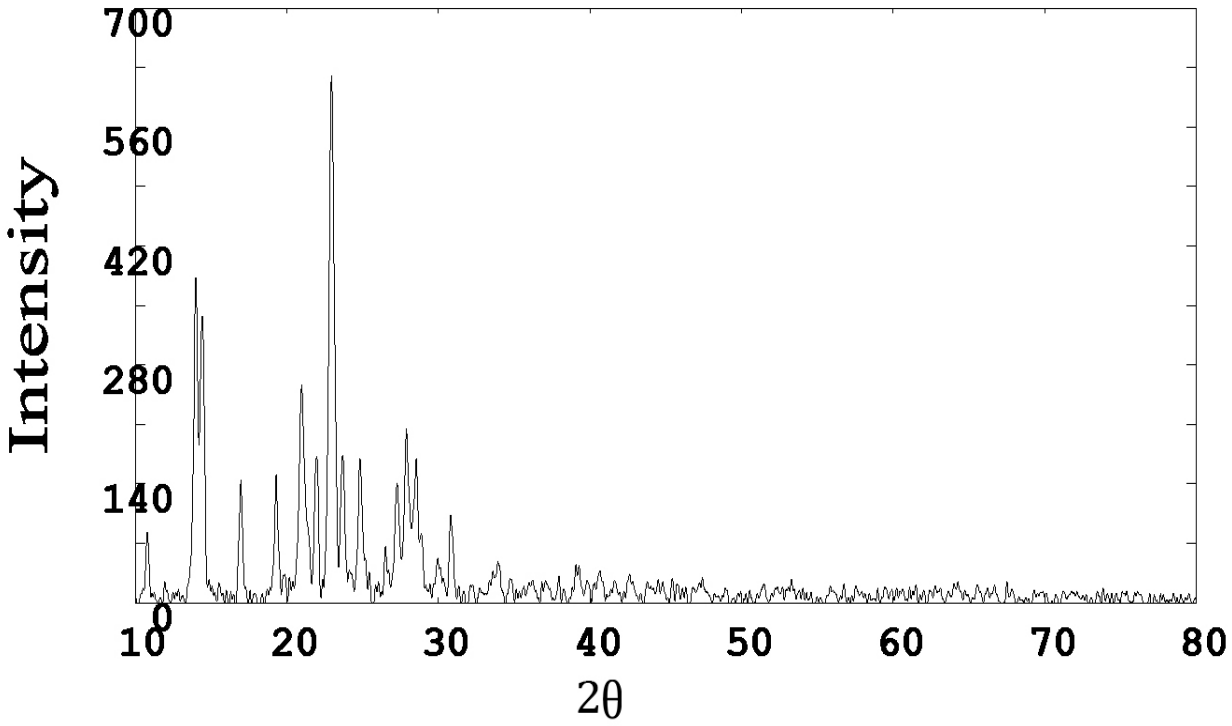

Fig 6: XRD of MMPEMP- Mn

h k l	2θ (Exp.)	2θ (calc.)	d (Exp.)	d (calc.)	Intensity (Exp.)
-2 0 0	14.014	14.014	6.31446	6.31441	358.64
-1 0 2	14.422	14.422	6.13660	6.13668	322.68
2 0 1	16.976	16.976	5.21879	5.21875	132.00
-1 1 0	19.304	19.304	4.59436	4.59431	136.14
-1 0 3	20.991	20.977	4.22869	4.23149	243.51
2 0 2	21.971	21.957	4.04233	4.04484	164.64
-2 0 3	22.956	22.964	3.87108	3.86969	592.38
2 1 1	24.844	24.818	3.58096	3.58464	158.73
-1 0 4	27.899	27.895	3.19535	3.19582	192.91
2 1 2	28.530	28.516	3.12614	3.12763	156.12
1 0 4	30.825	30.810	2.89842	2.89981	94.39

Table 7: XRD of MMPEMP- Mn

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Monoclinic system; a= 12.90994 b= 4.932281 c= 12.79410; α= 89.99996 β= 101.9786 γ=89.99996

5. XRD of MMPEMP- Zn

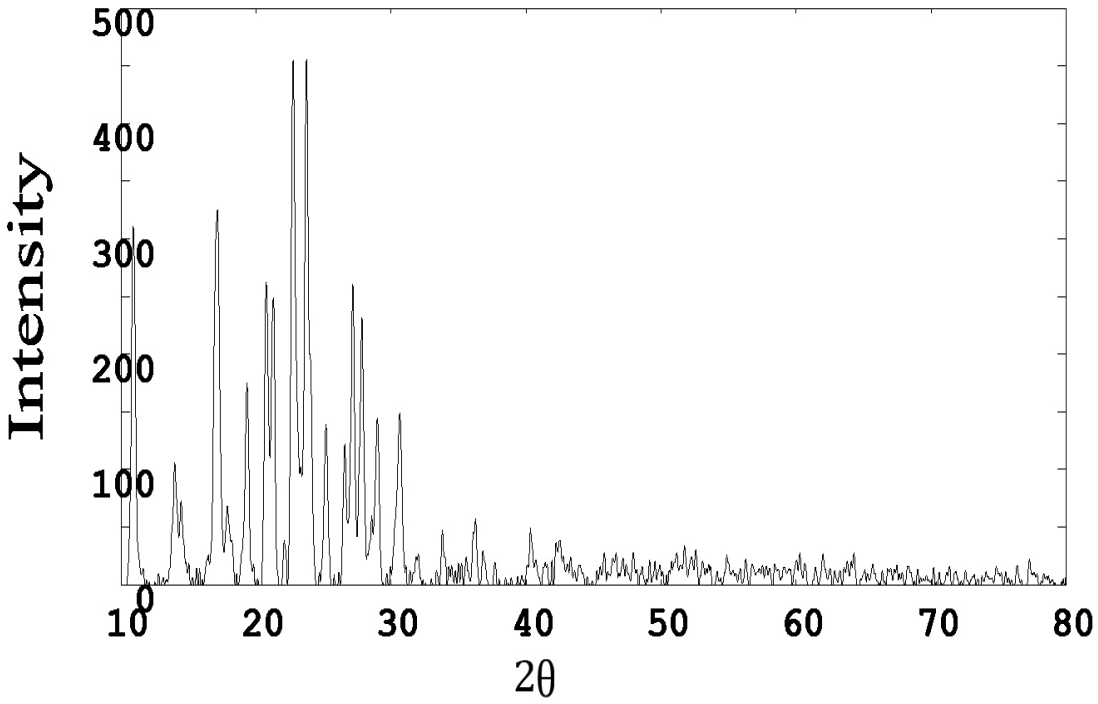

Fig 7 XRD of MMPEMP- Zn

h k l	2θ (Exp.)	2θ (calc.)	d (Exp.)	d (calc.)	Intensity (Exp.)
-1 0 2	14.452	14.422	6.12411	6.13668	73.17
2 0 1	17.684	17.976	5.01128	5.01875	348.22
0 0 1	16.896	16.375	5.24312	5.40890	298.59
-1 1 0	20.753	20.845	4.27663	4.25807	262.33
-2 0 3	22.753	22.964	3.90515	3.86969	455.34
1 0 1	26.585	26.622	3.35021	3.34573	121.78
1 0 4	30.753	30.810	2.91427	2.89981	149.45

Table 8: XRD of MMPEMP- Zn

Hexagonal system; Lattice Parameter a= 4.9168 b= 4.9168 c= 5.4089; α= 89.99990, β= 89.99996, γ=119.99990

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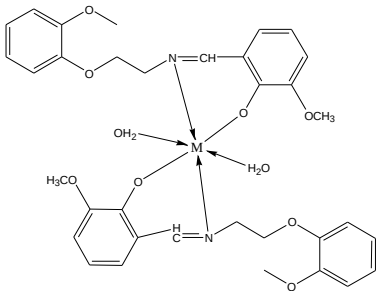

Fig : 8 Structure of complex (M= Ni, Cu, Co, Mn, Zn)

From the discussion of the results of various physico-chemical studies presented above, it may be concluded that the most probable geometry for the transition metal complexes with general formula $ML_2.2H_2O$ is octahedral and the bonding in the complexes can be represented in Fig 2.

Antifungal activity

In the present work the Schiff bases have been screened for their antifungal activity. The test compounds have been subjected to in vitro screening against two fungi *Aspergillus niger* and *Candida albicans* using Nutrient broth as the culture medium by agar cup diffusion method. The results of the studies for Schiff base and its complexes are summarized in Table 8 and Table 9 below.

1. Antifungal activity for *Candida albicuns*

Sample	Concn.	Zone of Inhibition in mm	Sample	Concn.	Zone of Inhibition in mm
MMPEMP-SB4	20	12	MMPEMP -Ni	20	-
	40	-		40	-
	60	-		60	-
	80	-		80	10
	100	10		100	09
	Control	0		Control	0
MMPEMP - Cu	20	-	MMPEMP -Co	20	-
	40	-		40	-
	60	-		60	-
	80	-		80	10
	100	-		100	-
	Control	0		Control	0
MMPEMP - Mn	20	-	MMPEMP -Zn	20	-
	40	-		40	-
	60	-		60	10
	80	11		80	08
	100	-		100	-
	Control	0		Control	0

Table 8

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2. Antifungal activity for A*sperligues niger*

Sample	Concn.	Zone of Inhibition in mm	Sample	Concn.	Zone of Inhibition in mm
MMPEMP-SB4	20	-	**MMPEMP-Ni**	20	-
	40	-		40	-
	60	-		60	-
	80	10		80	-
	100	11		100	10
	Control	0		Control	0
MMPEMP-Cu	20	-	**MMPEMP-Co**	20	-
	40	-		40	-
	60	-		60	11
	80	08		80	-
	100	10		100	-
	Control	0		Control	0
MMPEMP-Mn	20	-	**MMPEMP-Zn**	20	-
	40	-		40	-
	60	-		60	-
	80	-		80	10
	100	-		100	-
	Control	0		Control	0

Table 9: Activity of compounds for A*sperligues nige*

The evaluation of the antimicrobial activity was carried out after the incubation period by the measurement of the diameter of the inhibition zones. The different concentrations of ligand and metal complexes were found to inhibit the *Aspergillus niger* and *Candida albicans* which can be seen from zone of inhibition in the above tables. However the activity of complexes was found to be less than that of the ligand. All the above results were compared with two standard antibiotics Amphotericin B and Itraconazole. Amphotericin B showed a zone of inhibition of 17mm (intermediate range) and 15mm (intermediate range) for *Aspergillus niger* and *Candida albicans* respectively. Similarly Itraconazole showed a zone of inhibition of 16mm (intermediate range) and 14mm (intermediate range) for *Aspergillus niger* and *Candida albicans* respectively. Hence it was concluded that the synthesized compounds exhibited weak antimicrobial activity on the microbes under study. The order of the activity can be summarized as follows: Standard > Ligands > Complexes.

6.Acknowledgement:
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