

**SYNTHESES CHARACTERIZATION AND BIOLOGICAL ACTIVITY
OF MIXED LIGAND BASED METAL COMPLEXES OF 3D SERIES
WITH 2,3-DIHYDROXYPYRIDINE(DHP) AND AMINO ACIDS
GLYCINE(GLY), ALANINE(ALA), VALINE(VAL) AND
LEUCINE(LEU)**

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ABSTRACT

Mixed ligand metal complexes of Mn(II), Fe(II), Co(II) and Cu(II) with 2,3-dihydroxypyridine (DHP) and amino acids glycine(gly), alanine(ala), valine(val) and leucine(leu) have been synthesized. Chemical and structural composition of all synthesized complexes were characterized by analytical and spectral studies i.e. elemental analysis, magnetic moment, electronic, IR and EPR spectral studies. On the basis of characterization data Mn(II), Fe(II), Co(II) complexes possessed octahedral geometry while Cu(II) complexes possessed tetrahedral geometry. The *in vitro* biological activity of the complexes was examined against the bacteria and fungus.

KEYWORDS: Mixed ligand; amino acid; complex; IR; octahedral; tetrahedral; biological activity.

INTRODUCTION

In recent year, transition metal complexes of asymmetrical mixed ligands have attracted attention of chemists due to their diversity of molecular structure.^[1-4] The study of metal complexes of mixed ligands appears to be interesting in view of the possibility of obtaining coordinating compounds of scarce structure and stability. The formation of mixed ligand

complexes depends on the size of the ligand cavity, on the nature of donor atoms present in ligand moiety and on the complexing behavior of the anions involved in coordination mode.^[5-7] Asymmetrical mixed ligands are also of theoretical interest since they are capable of furnishing an environment of controlled geometry and ligand field strength.^[8] Mixed complexes have numerous biological activities, e.g. anticarcinogenic, antibacterial, anti-HIV^[9] anticancer,^[10] antiviral,^[11] antifungal,^[12] antitumor etc.^[13-15] First row of transition metal complexes with such ligands have a wide range of biological activities.^[16-18] In this papers the syntheses and structural aspects of a number of transition metal complexes of NO donor systems has been described. In view of the above applications it is highly desirable to synthesize and characterize transition metal complexes with such ligands. Here, we reported the synthesis, characterization and biological activity of mixed ligand based metal complexes of 3d series with 2,3-dihydroxypyridine and amino acids glycine(gly), alanine(ala), valine(val) and leucine(leu).

PHYSICAL METHODS

The metal contents in the complexes were determined following standards methods. C, H and N were estimated in RRL Bhopal. Nitrogen contents were determined by Kjeldahl's method. Electronic spectra of the complexes run on Beckman DU-64 spectrophotometer in the ranges 250-800 nm in CCl₄. IR spectra were recorded in the range 4000-200 cm⁻¹ on Perkin-Elmer, 621-spectrometer using KBr Pellets. EPR spectra were recorded using Varian EPR spectrometer.

EXPERIMENTAL DETAILS

Synthesis of mixed ligand metal complexes

The metallic salt, DHP and amino acids (gly/ala/val/leu) were taken in the stoichiometric ratio 1:2:1 in case of Mn(II), Fe(II) and Co(II) metal salt and 1:1:1 in case of Cu(II) metal salt. So, that the total weight was about 1-1.5 gm. The metallic salt was dissolved in 50 mL of distilled water; the ligands were added slowly into a solution of metallic salt with continuous stirring. The pH was maintained ~ 9.0 by adding ammonia solution. The reaction solution was refluxed for nearly 1.30 hours on a water bath. On concentrating and cooling the complex was separated out, which was filtered, washed and dried in desiccator.

RESULTS AND DISCUSSION**Elemental analysis**

On the basis of the elemental analysis, Mn(II), Fe(II), Co(II) and Cu(II) mixed ligands based metal complexes with DHP and amino acid (gly/ala/val/leu) have been assigned the composition as given in Table 1 to 4. The presence of ammonia NH_4^+ in the complexes was confirmed by the reaction of complexes with NaOH which gave the smell of ammonia.

Table 1: Physical characteristic of mixed ligand based metal complexes

Complexes	Color	Yield (%)	Elemental Analysis (%)							
			Calculated				Found			
			M	C	N	H	M	C	N	H
$\text{NH}_4[\text{Mn}(\text{L})_2\text{L}_1]$	Brown	44.34	14.98	39.23	15.25	4.25	14.56	38.17	14.90	3.96
$\text{NH}_4[\text{Fe}(\text{L})_2\text{L}_1]$	Green	39.75	15.21	39.13	15.21	4.34	14.90	38.75	14.85	4.12
$\text{NH}_4[\text{Co}(\text{L})_2\text{L}_1]$	Pink	23.38	15.90	38.81	15.09	4.31	15.45	38.09	14.77	4.09
$[\text{Cu}(\text{L})\text{L}_1]$	Blue	33.59	25.65	33.93	11.31	3.23	26.00	34.07	11.92	3.37

L = DHP, L_1 = Glycine

Table 2: Physical characteristic of mixed ligand based metal complexes

Complexes	Color	Yield (%)	Elemental Analysis (%)							
			Calculated				Found			
			M	C	N	H	M	C	N	H
$\text{NH}_4[\text{Mn}(\text{L})_2\text{L}_2]$	Bright Brown	40.92	14.43	40.94	14.69	4.72	14.05	39.86	13.90	4.03
$\text{NH}_4[\text{Fe}(\text{L})_2\text{L}_2]$	Green Brown	51.42	14.65	40.83	14.55	4.71	14.13	39.75	13.79	4.02
$\text{NH}_4[\text{Co}(\text{L})_2\text{L}_2]$	Light Pink	20.65	15.32	40.51	14.54	4.67	14.95	39.96	13.96	4.11
$[\text{Cu}(\text{L})\text{L}_2]$	Blue Brown	31.28	24.28	36.71	10.70	3.82	24.75	36.96	11.15	4.15

L = DHP, L_2 = Alanine

Table 3: Physical characteristic of mixed ligand based metal complexes

Complexes	Color	Yield (%)	Elemental Analysis (%)							
			Calculated				Found			
			M	C	N	H	M	C	N	H
$\text{NH}_4[\text{Mn}(\text{L})_2\text{L}_3]$	Dark Brown	42.77	13.44	44.00	13.69	5.37	12.96	43.65	13.52	5.09
$\text{NH}_4[\text{Fe}(\text{L})_2\text{L}_3]$	Brownish Green	59.68	13.65	43.90	13.65	5.36	13.09	43.20	13.45	5.07
$\text{NH}_4[\text{Co}(\text{L})_2\text{L}_3]$	Pale Pink	20.20	14.28	43.58	13.55	5.32	13.75	43.08	13.28	5.05
$[\text{Cu}(\text{L})\text{L}_3]$	Bluish Black	33.49	21.93	41.45	09.67	4.83	22.07	42.00	09.96	5.00

L = DHP, L_3 = Valine

Table 4: Physical characteristic of mixed ligand based metal complexes

Complexes	Color	Yield (%)	Elemental Analysis (%)							
			Calculated				Found			
			M	C	N	H	M	C	N	H
NH ₄ [Mn(L) ₂ L ₄]	Light Brown	45.53	13.00	45.39	13.23	5.67	12.95	44.75	12.90	5.07
NH ₄ [Fe(L) ₂ L ₄]	Greenish Brown	37.90	13.20	45.28	13.20	5.66	12.80	44.64	12.87	5.05
NH ₄ [Co(L) ₂ L ₄]	Light Pink	25.97	13.81	44.96	13.11	5.62	13.45	44.49	12.98	5.02
[Cu(L)L ₄]	Blueish Brown	24.52	20.92	43.49	9.22	5.27	21.17	43.90	09.57	5.39

L = DHP, L₄ = Leucine

IR SPECTRA

IR spectra of DHP and some representative mixed ligands metal complexes are given in Fig. 1-3. Important IR bands of the ligand and complexes are given in Table 5 to 8. A broad band of free DHP at 3200-3600 cm⁻¹ corresponding to phenolic OH disappeared in all metal complexes showing simultaneous deprotonation and formation of M-O bond. A strong band at 1625 cm⁻¹ (C=O) shifted to lower side (1616-1652 cm⁻¹) suggesting that DHP coordinated to metal through oxygen of carbonyl group.^[20] A relatively weak band at 3400 cm⁻¹ observed in free DHP and attributed to ν_{N-H} of α -pyridone like structure of DHP remained unchanged in complexes suggesting its non-involvement in coordination.^[21] In the IR spectra of each amino acid three bands around 3260 cm⁻¹, 3100 cm⁻¹ and 1500 cm⁻¹ were assigned to $\nu_{asym}(NH_2)$, $\nu_{sym}(NH_2)$ and $\delta(NH_2)$ in the mixed ligand complexes ν_{N-H} absorption band were observed in the form of broad bands in the range 3100-3233 cm⁻¹ which might be resulting from the shifting (due to complex formation) of ν_{N-H} bands of amino acids.^[22-23] The band due to $\nu_{as}(COO)$, $\nu_s(COO)$ of carboxylic group was observed in the region 1620 cm⁻¹ and 1400 cm⁻¹ in the free ligands. Bathochromic shift of these bands to in all the case showed the coordination of oxygen with the metal ion.^[24] The absence of $\nu_{(OH)}$ of the carboxylic group appeared at 2600 cm⁻¹ in free ligands, which confirms the deprotonation of OH bond by coordination.

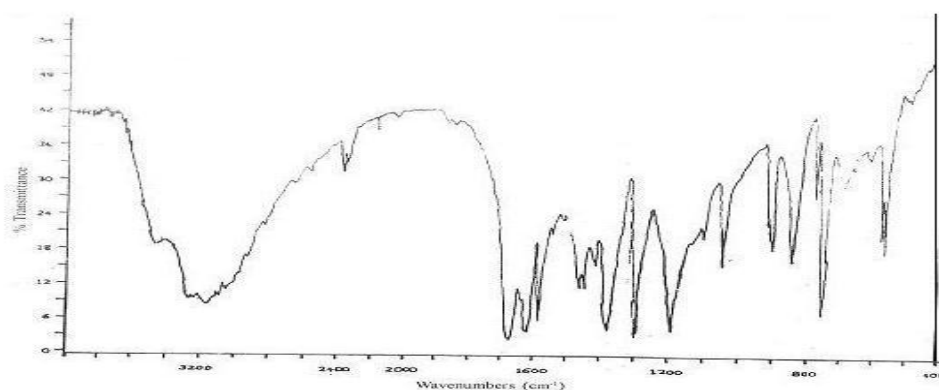


Fig. 1: IR Spectrum of 2, 3-Dihydroxypyridine (DHP)

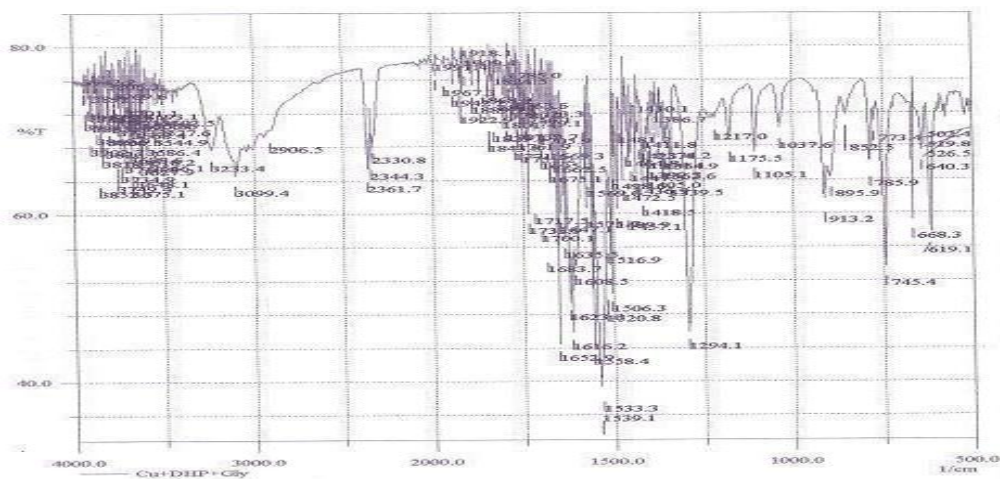


Fig. 2: IR Spectra of $[Cu(L)L_1]$ complex, L = DHP, L_1 = Glycine

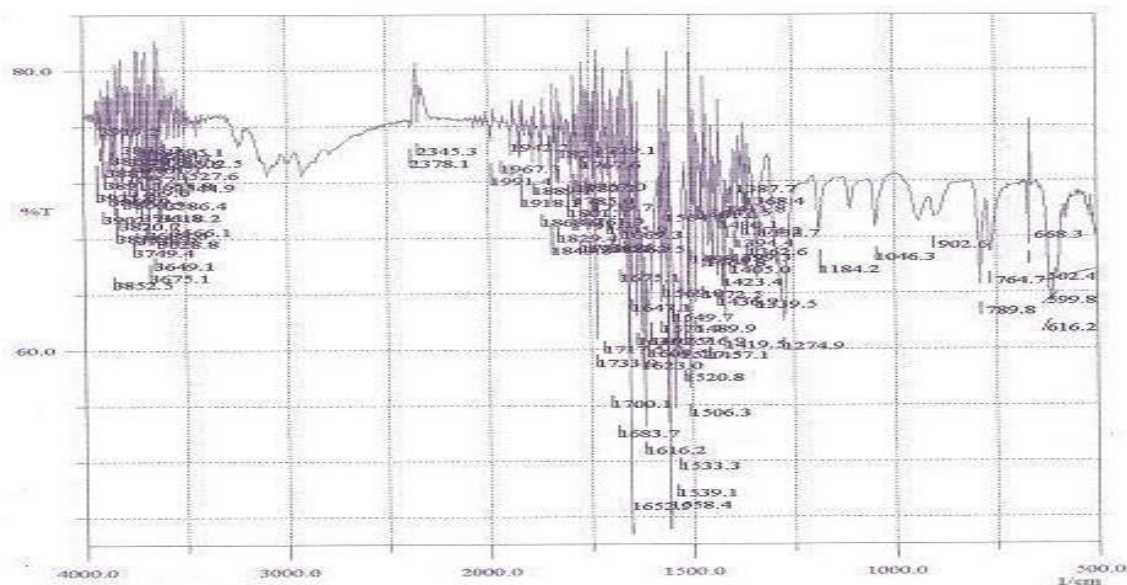


Fig. 3: IR Spectra of $NH_4[Co(L)_2L_2]$ Complex, L = DHP, L_2 = Alanine

Table 5: Important IR bands (cm^{-1}) of mixed ligand metal complexes of DHP and glycine

Compound	ν_{O-H}	$\nu_{C=O}$	ν_{N-H} (pyridine)	ν_{N-H} (amino acid)	ν_{COO} (asy)	ν_{COO} (sym)	ν_{O-H} (COOH)
DHP	3200-3600	1625	3400	-	-	-	-
Glycine	-	-	-	3100	1620	1400	2600
$NH_4[Mn(L)_2L_1]$	-	1620	-	3090	1610	1410	-
$NH_4[Fe(L)_2L_1]$	-	1615	-	3085	1607	1415	-
$NH_4[Co(L)_2L_1]$	-	1610	-	3078	1605	1416	-
$[Cu(L)L_1]$	-	1604	-	3070	1601	1420	-

L = DHP, L_1 = Glycine

Table 6: Important IR bands (cm⁻¹) of mixed ligand metal complexes of DHP and alanine

Compound	$\nu_{\text{O-H}}$	$\nu_{\text{C=O}}$	$\nu_{\text{N-H}}$ (pyridine)	$\nu_{\text{N-H}}$ (amino acid)	ν_{COO} (asy)	ν_{COO} (sym)	$\nu_{\text{O-H}}$ (COOH)
DHP	3200-3600	1625	3400	-	-	-	-
Alanine	-	-	-	3100	1620	1400	2600
NH ₄ [Mn(L) ₂ L ₂]	-	1605	-	3090	1609	1413	-
NH ₄ [Fe(L) ₂ L ₂]	-	1602	-	3082	1606	1418	-
NH ₄ [Co(L) ₂ L ₂]	-	1600	-	3075	1604	1423	-
[Cu(L)L ₂]	-	1590	-	3068	1600	1428	-

L = DHP, L₂ = Alanine**Table 7: Important IR bands (cm⁻¹) of mixed ligand metal complexes of DHP and valine**

Compound	$\nu_{\text{O-H}}$	$\nu_{\text{C=O}}$	$\nu_{\text{N-H}}$ (pyridine)	$\nu_{\text{N-H}}$ (amino acid)	ν_{COO} (asy)	ν_{COO} (sym)	$\nu_{\text{O-H}}$ (COOH)
DHP	3200-3600	1625	3400	-	-	-	-
Valine	-	-	-	3100	1620	1400	2600
NH ₄ [Mn(L) ₂ L ₃]	-	1602	-	3085	1607	1415	-
NH ₄ [Fe(L) ₂ L ₃]	-	1598	-	3078	1605	1426	-
NH ₄ [Co(L) ₂ L ₃]	-	1690	-	3065	1601	1436	-
[Cu(L)L ₃]	-	1585	-	3055	1598	1445	-

L = DHP, L₃ = Valine**Table 8: Important IR bands (cm⁻¹) of mixed ligand metal complexes of DHP and leucine**

Compound	$\nu_{\text{O-H}}$	$\nu_{\text{C=O}}$	$\nu_{\text{N-H}}$ (pyridine)	$\nu_{\text{N-H}}$ (amino acid)	ν_{COO} (asy)	ν_{COO} (sym)	$\nu_{\text{O-H}}$ (COOH)
DHP	3200-3600	1625	3400	-	-	-	-
Leucine	-	-	-	3100	1620	1400	2600
NH ₄ [Mn(L) ₂ L ₄]	-	1602	-	3078	1606	1418	-
NH ₄ [Fe(L) ₂ L ₄]	-	1595	-	3075	1603	1430	-
NH ₄ [Co(L) ₂ L ₄]	-	1588	-	3068	1602	1438	-
[Cu(L)L ₄]	-	1580	-	3057	1588	1447	-

L = DHP, L₄ = Leucine**ELECTRONIC SPECTRA**

The magnetic measurement of the Mn(II) complexes lie in the range of 4.9 to 5.0 BM corresponds to four unpaired electron. Electronic spectra of Mn(II) and Fe(II) complexes displayed weak absorption bands at 17900-18100(ν_1), 24600-24700(ν_2), 29400-29600(ν_3) and 31700-31800(ν_4) cm⁻¹ characteristic of the octahedral geometry, in these complexes.^[25]

These bands may be assigned to ${}^6A_{1g} \rightarrow {}^4T_{1g}$, (4G) (10B+5C), ${}^6A_{1g} \rightarrow {}^4E_g$, ${}^4A_{1g}$ (4G) (10B+5C), ${}^6A_{1g} \rightarrow {}^4E_g$, (4D) (17B+5C) and ${}^6A_{1g} \rightarrow {}^4T_g$ (4P) (7B+7C) transition, respectively Table 9.

Electronic spectra of the complexes under study display two well defined spectral bands at 8700-8900 cm^{-1} and 20500-20800 cm^{-1} and a shoulder at 14000-14800 cm^{-1} to ${}^4T_{1g} \rightarrow {}^4T_{2g}(F)(v_1)$, ${}^4T_{1g} \rightarrow {}^4T_{1g}(P)(v_3)$ and ${}^4T_{1g} \rightarrow {}^4T_{1g}(F)(v_2)$ transitions respectively, characteristic of octahedral geometry of Co(II) complexes.^[26] The electronic spectra of six coordinated Cu(II) complexes had either D_{4h} or C_{4v} symmetry, and the E_g and T_{2g} level of the 2D free ion term will split into B_{1g} , A_{1g} , B_{2g} and E_g levels respectively.^[27] Thus three spins allowed transitions were expected in the visible and near IR region. But only a few complexes are known, in which such bands are resolved either by "Gaussian Analysis" or by "single crystal polarization" studies. These bands have been assigned to the following transitions in order of increasing energy ${}^2B_{1g} \rightarrow {}^2A_{1g}$ ($d_{x^2-y^2} - d_z^2$), ${}^2B_{1g} \rightarrow {}^2B_{2g}$ ($d_{x^2-y^2} - d_{xy}$) and ${}^2B_{1g} \rightarrow {}^2E_g$ ($d_{x^2-y^2} \rightarrow d_{xz}, d_{yz}$). The energy level sequence will depend on the amount of tetragonal distribution due to ligand-field and the John-Teller effect. The electronic spectra of complexes reported here showed two characteristic bands at 13400-13750 and 18500-18900 cm^{-1} . These may be assigned to the ${}^2B_{1g} \rightarrow {}^2A_{1g}$ and ${}^2B_{1g} \rightarrow {}^2E_g$ transitions respectively, and corresponding to the tetrahedral geometry of Cu(II) complexes. ${}^2B_{1g} \rightarrow {}^2B_{2g}$ transition is usually not observed as a separate band in the tetragonal field.

LIGAND FIELD PARAMETERS

By using the experimentally observed transition energies various ligand field parameters B, C, Dq & β for Cu(II) complexes had been calculated and values listed in Table 9. Various ligand field parameters Dq, B and β for Cu(II) complexes had been calculated and given in Table 10. Dq values have been evaluated by using Orgel energy level diagram.^[28] Nephelauxetic parameters β have been calculated by using the following expression.

$$\beta = B_{(\text{complex})} / B_{(\text{free ion})}$$

The value of β in the present study indicates appreciable covalent character in metal complexes.

Table 9: Ligand Field parameters of mixed ligand complexes of Mn(II) with DHP (L) and amino acids [glycine (L₁) /alanine(L₂) /valine (L₃) /leucine(L₄)]

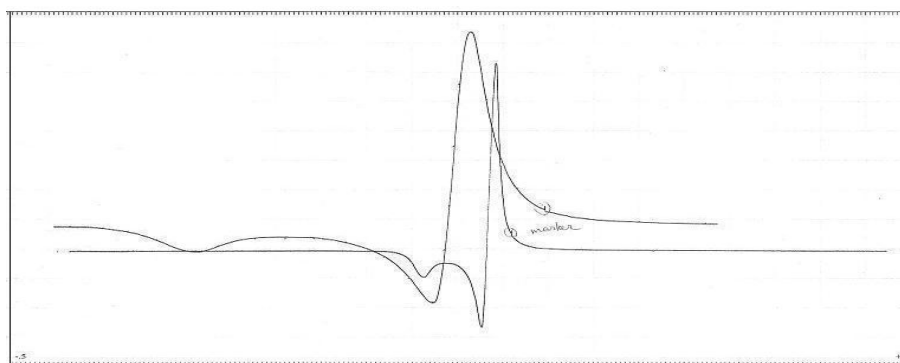
Complex	Dq(cm ⁻¹)	B(cm ⁻¹)	C(cm ⁻¹)	β(cm ⁻¹)
NH ₄ [Mn(L) ₂ L ₁]	1790	686	3548	0.87
NH ₄ [Mn(L) ₂ L ₂]	1815	700	3540	0.89
NH ₄ [Mn(L) ₂ L ₃]	1800	679	3592	0.86
NH ₄ [Mn(L) ₂ L ₄]	1805	700	3530	0.89

Table 10: Ligand Field parameters of mixed ligand complexes of Co(II) with DHP (L) and amino acids [glycine (L₁) /alanine(L₂) /valine (L₃) /leucine(L₄)]

Complex	Dq(cm ⁻¹)	B(cm ⁻¹)	β(cm ⁻¹)
NH ₄ [Co(L) ₂ L ₁]	1036	1079	0.96
NH ₄ [Co(L) ₂ L ₂]	1030	1073	0.95
NH ₄ [Co(L) ₂ L ₃]	1036	1079	0.96
NH ₄ [Co(L) ₂ L ₄]	1024	1067	0.95

EPR SPECTRA

In polycrystalline samples of Mn(II) complexes usually give broad signals attributed to forbidden transitions where ($M = \pm 1$) ($M =$ electron spin quantum number) and $\Delta m \neq 0$ (where $m =$ nuclear spin quantum number). The broadening of the spectrum in powder sample is analogous to that observed in Mn(II) complexes of conconavallin.^[29] Broadening due to immobilization of Mn(II) ion in the ligand results because the rotational motion of Mn(II) is highly restricted. Another origin of line broadening is spin relation, which is temperature dependent. EPR spectrum of NH₄[Mn(L)₂L₁] complex is shown in Fig. 4. The calculated g - values lies in the range of 1.9928-2.000, these values proposed octahedral geometry for the Mn(II) complexes.^[30] Complexes showed isotopic ESR spectra Fig. 5. Characteristic of tetrahedral Cu(II), g -values are given in the Table 12. The stronger interaction along the axis is to be accompanied by an increase in the value of g_{\parallel} . The stronger axial bonding leads to an increase in length of the bond in the xy plane, which results in a decrease of both the in plane covalency and energy of the $d_{x^2-y^2} - d_{xy}$ transition. Both these factors lead to increase the value of g_{\parallel} .

**Fig. 4: EPR Spectrum of NH₄[Mn(L)₂L₁] complex, L=DHP, L₁= Glycine**

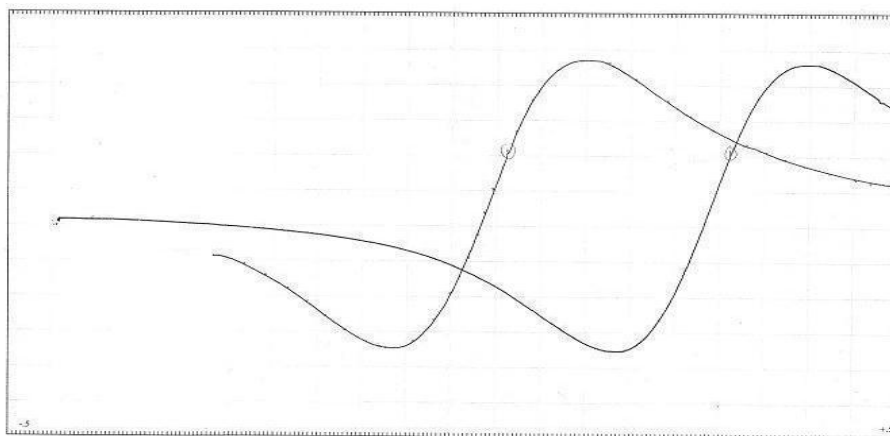


Fig. 5: EPR Spectra of $[\text{Cu}(\text{L})\text{L}_1]$ complex, $\text{L} = \text{DHP}$, $\text{L}_1 = \text{Glycine}$

Table 11: EPR spectral data of mixed ligand complexes of Mn(II) with DHP (L) and amino acids [glycine (L_1) /alanine(L_2) /valine (L_3) /leucine(L_4)]

Complex	F_4	F_2	hx	g
$\text{NH}_4[\text{Mn}(\text{L})_2\text{L}_1]$	101	1193	1.86	1.991
$\text{NH}_4[\text{Mn}(\text{L})_2\text{L}_2]$	101	1206	1.57	1.861
$\text{NH}_4[\text{Mn}(\text{L})_2\text{L}_3]$	103	1192	2.00	1.899
$\text{NH}_4[\text{Mn}(\text{L})_2\text{L}_4]$	101	1205	1.57	1.999

Table 12: EPR spectral data of mixed ligand complexes of Cu(II) with DHP (L) and amino acids [glycine (L_1) /alanine(L_2) /valine (L_3) /leucine(L_4)]

Complex	g_{\parallel}	g_{\perp}	g_{iso}	G
$[\text{Cu}(\text{L})\text{L}_1]$	2.268	2.056	2.127	4.79
$[\text{Cu}(\text{L})\text{L}_2]$	2.260	2.050	2.120	5.15
$[\text{Cu}(\text{L})\text{L}_3]$	2.261	2.055	2.124	4.75
$[\text{Cu}(\text{L})\text{L}_4]$	2.267	2.056	2.126	4.76

BIOLOGICAL STUDY

2,3-dihydroxypyridine(DHP) and amino acids glycine(gly), alanine(ala), valine(val), leucine(leu) and all complexes were evaluated against different species of bacteria and fungi by using disc diffusion method and food poisoning method, respectively.^[31-32] The results obtained from biological activity were compared with standard antibiotic and antifungal drug Streptomycin and Amphotericin, respectively.

Antibacterial Screening

Complexes were screened against *S.lutea* (gram-positive) and *E.coli* (gram-negative) bacteria, as growth inhibitor by using disc diffusion method. The results of the antibacterial screening showed the maximum inhibition by the $[\text{Cu}(\text{L})\text{L}_1]$, $[\text{Cu}(\text{L})\text{L}_4]$ complexes. But these complexes showed lesser activity than the standard drug (Streptomycin).

Antifungal Screening

A.niger and *A.glaucus* fungi were used as the tested microorganism for all the newly synthesized complexes for the purpose of antifungal screening by food poisoning method. All the complexes show nearly the same inhibition except the $\text{NH}_4[\text{Co}(\text{L})_2\text{L}_3]$ complex, which showed comparatively higher activity and all complexes exhibited lesser inhibition zone than used standard drug (Amphotericin).

CONCLUSION

In the light of above discussed studies, octahedral geometry is proposed for Mn(II), Fe(II), Co(II) complexes while tetrahedral geometry for Cu(II) Fig. 6-7. Among all metal complexes, $[\text{Cu}(\text{L})\text{L}_1]$, $[\text{Cu}(\text{L})\text{L}_4]$ complex showed an excellent inhibition potential against used bacteria and $\text{NH}_4[\text{Co}(\text{L})_2\text{L}_3]$ complex exhibited higher antifungal activity than other tested complexes. All

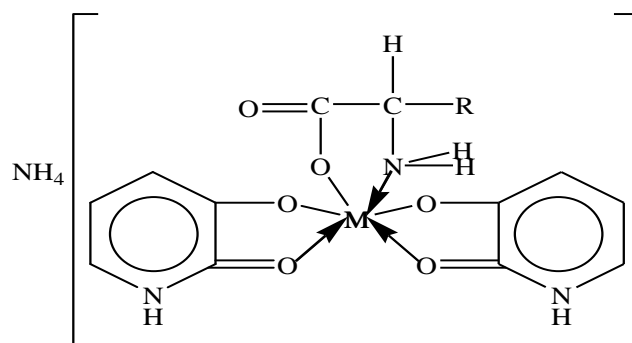


Fig 6: Octahedral structure of complex $\text{NH}_4[\text{M}(\text{L})_2\text{L}_{1-4}]$

Where H = DHP, L_{1-4} = Amino acid

R = -H, Glycine (L_1)

R = - CH_3 , Alanine (L_2)

R = - $\text{CH}(\text{CH}_3)_2$, Valine (L_3)

R = - $\text{CH}_2\text{-CH}(\text{CH}_3)_2$, Leucine (L_4)

M = Mn(II), Fe(II) and Co(II)

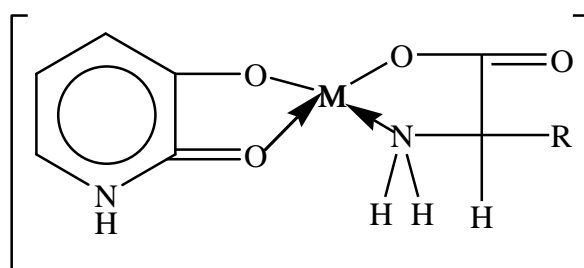


Fig 7: Tetrahedral structure of complex $[\text{M}(\text{L})\text{L}_{1-4}]$

Where L = DHP, L₁₋₄ = Amino acid

R = -H, Glycine (L₁)

R = -CH₃, Alanine (L₂)

R = -CH (CH₃)₂, Valine (L₃)

R = -CH₂-CH (CH₃)₂, Leucine (L₄)

M = Cu(II)

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