



3D-Metal Complexes Derived from Proton Pump Inhibitors-Synthesis, Characterization and Biological Studies

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Abstract: Complexes of lansoprazole 2[[[3-methyl, 4-(2,2,2-trifluoroethoxy)]-2-pyridinyl] methyl]sulfonyl]-1*H*-benzimidazole (LAN) with chlorides of Co(II), Ni(II), Cu(II), Mn(II) and Zn(II) were synthesized. LAN is a weak base and it can form several complexes with transition and non-transition metal ions. It should be noticed that the reaction of all the metal salts yielded bis(ligand) complexes of the general formula $[ML_2(H_2O)_2]$ and $[ML_2]$ (M = Co, Ni, Cu, Mn and Zn). The complexes were characterized by elemental analysis, molar conductivity, magnetic susceptibility measurements, IR, ¹H-NMR, UV-visible spectral studies, ESR, SEM, x-ray diffraction, TGA and mass spectra. In all the complexes ligand is coordinated by participation of the pyridine nitrogen of the benzimidazole ring and sulphonyl group. Electronic spectra and magnetic susceptibility reveal octahedral geometry for Mn(II), Co(II), Ni(II) and Cu(II) complexes and tetrahedral for Zn(II) complex. The antimicrobial activity of the ligand and its complexes against bacteria *Pseudomonas aeruginosa*, *Staphylococcus aureus* and fungi *Aspergillus niger* and *Aspergillus flavous* were investigated. The effect of metals on the antimicrobial activity of the ligand has been discussed.

Keywords: Complexes, Ligand, ESR, SEM, X-Ray diffraction.

Introduction

Proton pump inhibitors are highly effective in the management of acid-related diseases, including duodenal ulcer(DU), gastric ulcer(GU), gastroesophageal reflux disease(GERD), erosive oesophagitis, hypersecretory syndroms like Zollinger-Ellison and Helicobacter pylori (H.pylori) infections¹⁻⁴. There are currently five different proton pump inhibitors (PPIs) available, including esomeprazole, lansoprazole, omeprazole, pantoprazole and

rabeprazole⁵⁻¹⁰. These agents are all substituted benzimidazoles that inhibit the final common pathway of gastric acid secretion. The gastric H⁺K⁺ATPase or gastric acid pump is the molecular target for the proton-pump inhibitors. This H⁺K⁺ATPase pump is the final common pathway for acid secretion in the stomach. Inhibitors of this pump are the most effective antisecretory agents currently available. Proton pump inhibitors irreversibly inhibit the proton pump and acid production can only be restored through endogenous synthesis of new proton pumps. Metal complexes are gaining increasing importance in the design of respiratory, slow release and long acting drugs. Metal ions are therefore known to accelerate drug actions¹¹. The efficacies of some therapeutic agents are known to increase upon coordination¹². Some metal complexes are known to exhibit remarkable antitumor, antifungal, antiviral and special biological activities^{13,14}. Therefore, complexation of chemotherapeutic agents has been found to be applicably useful in medicine and pharmacy¹⁵. As a part of our continuing studies, the objective of the present work was to synthesize complexes of some transition metals with the well-known PPI Lansoprazole. The present paper reports the synthesis, characterization and antimicrobial activity of a very common PPI-Lansoprazole (Figure 1) with first row transition metals like Mn(II), Co(II), Ni(II), Cu(II) and Zn(II).

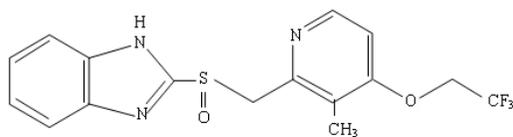


Figure 1. Structure of Lansoprazole

Experimental

All chemicals used were of analytical grade. Pure sample of Lansoprazole having molecular formula C₁₆H₁₄F₃N₃O₂S and molecular weight 369.363 was obtained from Cipla Pharmaceuticals Limited Mumbai. All metal salts CuCl₂·2H₂O, NiCl₂·6H₂O, CoCl₂·6H₂O, MnCl₂·4H₂O and ZnCl₂ were of Merck Chemicals. The solvents used were distilled water and methanol. Metal/ligand ratio was calculated using Systronics digital conductivitymeter, IR spectra were obtained from CDRI Lucknow (Instrument used PerkinElmer FTIR spectrophotometer) in the range of 4000-400 cm⁻¹. ¹H-NMR spectra were recorded on a Bruker DRX-300 spectrometer using TMS as an internal standard and DMSO-*d*₆ as solvent. The electronic spectra were recorded on PerkinElmer Lambda-25UV spectrometer. The FAB mass spectrum was recorded at room temperature on Jeol SX-102 FAB mass spectrometer at CDRI Lucknow. Magnetic susceptibility measurements were received from CAT Indore (Instrument used-Vibrating Sample Magnetometer).

X-band ESR spectra was recorded at IIT Mumbai on E-112 ESR spectrometer with specification of X-band microwave frequency (9.5 GHz). Nitrogen was determined by Dumas method and sulphur was estimated by the Messenger's method. The analysis of carbon, hydrogen and nitrogen was performed on a CarloErba 7106 analyzer. Thermograms (TGA and DTA curves) of complexes were recorded at IIT, Roorkee on Exstar TG/DTA 6300.

Ligand / metal ratio

To confirm the ligand/metal ratio, conductometric titrations using monovariation method were carried out at 21 °C. 0.01 M solution of Lansoprazole drug was prepared in 70% of methanol. Similarly, 0.02 M solutions of metal salts were prepared in the same solvent. The ligand solution was titrated against the metal salt solutions using monovariation method. Conductance was recorded after each addition. From the equivalence point in the graph, it has been concluded that the complex formation has taken place in the ratio of 2:1 (L:M).

Synthesis of complexes

The complexes were synthesized by mixing the solutions (70% methanol) of metal salt with that of ligand in 1:2 molar ratio respectively. The thick precipitates of different colors for different metal salts were observed by adjusting the pH with the addition of dilute NaOH solution and refluxing the mixtures for three and a half hours. Colored crystalline complexes were obtained. The complexes were filtered, washed with (70:30) mixture of methanol-water and dried. Carbon, hydrogen, nitrogen, metal and water were estimated microanalytically at CDRI, Lucknow.

Results and Discussion

The synthesized complexes are stable solids. They are soluble in DMF and DMSO and insoluble in all other organic solvents. Analytical data (Table 1) and conductometric studies suggest 2:1 (L:M) ratio. Stability constants (Table 2) and free energy changes were also calculated by using Job's method¹⁶ of continuous variation modified by Turner and Anderson¹⁷. Measured conductance values of these complexes suggests a 1:2 electrolyte behavior. The magnetic studies indicate the Mn(II), Co(II), Ni(II) and Cu(II) complexes to be paramagnetic while the Zn(II) complex to be diamagnetic.

Table 1. Analytical data of complexes.

Compound (m.wt.)	Colour	Yield, %	M.p., °C	Elemental Analyses: Found (Calcd.), %			
				C	H	N	M
C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S-LAN (369.36)	White	—	177	51.82 (51.98)	3.61 (3.79)	11.21 (11.37)	—
[C ₃₂ H ₃₂ F ₆ N ₆ O ₆ S ₂ Mn] (829.69)	Buff	79	260	46.11 (46.28)	3.67 (3.85)	9.95 (10.12)	6.44 (6.62)
[C ₃₂ H ₃₂ F ₆ N ₆ O ₆ S ₂ Co] (833.68)	Pale Pink	56	180	45.88 (46.06)	3.66 (3.83)	9.89 (10.07)	6.87 (7.06)
[C ₃₂ H ₃₂ F ₆ N ₆ O ₆ S ₂ Ni] (833.43)	Green	78	195	45.89 (46.07)	3.67 (3.84)	9.92 (10.08)	6.89 (7.04)
[C ₃₂ H ₃₂ F ₆ N ₆ O ₆ S ₂ Cu] (838.26)	Brown	44	208	45.63 (45.81)	3.62 (3.81)	9.83 (10.02)	7.39 (7.57)
[C ₃₂ H ₂₈ F ₆ N ₆ O ₄ S ₂ Zn] (804.09)	Yellow	34	210	47.57 (47.75)	3.31 (3.48)	10.26 (10.44)	7.95 (8.13)

Table 2. Stability constant, free energy change, molar conductance and magnetic moment data of complexes.

Compound	Stability constant, logK (L/mol)	Free energy change, ΔF(Kcal/mol)	Molar conductance, (Ω ⁻¹ .cm ² .mol ⁻¹)	Magnetic moment, (B.M.)
[(C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S) ₂ Zn]	10.747	15.975	137	—
[(C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S) ₂ Mn(H ₂ O) ₂]	12.088	17.032	130	5.92
[(C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S) ₂ Cu(H ₂ O) ₂]	11.170	15.590	140	1.91
[(C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S) ₂ Ni(H ₂ O) ₂]	11.420	16.174	124	3.12
[(C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S) ₂ Co(H ₂ O) ₂]	11.420	16.039	123	4.92

Infrared spectra

The vibrational spectra¹⁸⁻²¹ for the free ligand Lansoprazole, when compared with those of its complexes, provided meaningful information regarding the bonding sites of the ligand (Table 3).

Table 3. IR absorption data of the complexes (cm⁻¹).

Compound	$\nu(\text{NH})$	$\nu(\text{C}=\text{N})$	$\nu(\text{S}=\text{O})$	$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{O})$	$\nu(\text{H}_2\text{O})$
C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S-LAN	3416	1585	1038	–	–	–
[(C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S) ₂ Mn(H ₂ O) ₂]	3420	1579	1025	443	583	3551
[(C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S) ₂ Ni(H ₂ O) ₂]	3418	1575	1022	415	536	3535
[(C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S) ₂ Co(H ₂ O) ₂]	3424	1573	1020	423	575	3575
[(C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S) ₂ Cu(H ₂ O) ₂]	3417	1569	1018	465	576	3557
[(C ₁₆ H ₁₄ F ₃ N ₃ O ₂ S) ₂ Zn]	3422	1570	1008	433	573	–

The IR spectra of the complexes indicate that the ligand behaves as bidentate and coordinate to the metal via C=N and sulphonic acid group. In the IR spectrum of Lansoprazole, strong band at 3416 cm⁻¹ is assigned to secondary νNH stretching vibrations. This band remains unaltered or shifted to the higher wave number in the complexes suggesting non-involvement of secondary NH group in coordination with metal ions. The medium to strong bands appearing at 1585 cm⁻¹ in the free ligand are assigned to $\nu\text{C}=\text{N}$ stretching vibration of the azomethine group based on the available reports. This band shifts to lower wavenumber in all the complexes by about 10-15 cm⁻¹ indicating involvement of the azomethine nitrogen in bonding. The shifting of $\nu\text{S}=\text{O}$ stretching vibration to the lower wave number as compared to the free ligand is indicative of participation of sulphonic acid group in coordination. The weak intensity non-ligand bands observed in the complexes in the regions 583-535 cm⁻¹ and 465-410 cm⁻¹ are assigned to $\nu(\text{M}-\text{N})$ and $\nu(\text{M}-\text{O})$ stretching vibrations, respectively. Bands appearing at region 3675-3630 cm⁻¹ may be due to coordinated water molecules and new band at 1390-1380 cm⁻¹ in complexes might be due to chelate ring formation in them.

Electronic spectra and magnetic susceptibility data

The electronic spectra of the Ni(II), Co(II), Mn(II) and Cu(II) complexes of lansoprazole were taken in DMSO (10⁻³M) solution. The Co(II) complex exhibits two bands at 18520cm⁻¹ and at 21714cm⁻¹ respectively, assignable to ${}^4\text{A}_{2g}(\text{F})\leftarrow{}^4\text{T}_{1g}(\text{F})(\nu_2)$ and ${}^4\text{T}_{1g}(\text{P})\leftarrow{}^4\text{T}_{1g}(\text{F})(\nu_3)$ transitions which indicate octahedral²² geometry of the complex. The proposed geometry is further confirmed by high μ_{eff} value in the range^{23,24} 4.89-5.24 BM. The Ni(II) complex exhibits two bands at 13510cm⁻¹ and 23750cm⁻¹ which are assigned to ${}^3\text{T}_{1g}(\text{F})\leftarrow{}^3\text{A}_{2g}(\text{F})(\nu_2)$ and ${}^3\text{T}_{1g}(\text{P})\leftarrow{}^3\text{A}_{2g}(\text{F})(\nu_3)$ transitions indicating octahedral²² geometry of the complex. The geometry of Ni(II) complex is further confirmed^{23,24} by the high μ_{eff} value in the range 3.09-3.20 BM. The electronic spectrum of the paramagnetic Mn(II) complex displays three absorption bands at 24500cm⁻¹, 22670cm⁻¹ and 16666cm⁻¹ which can be assigned to ${}^4\text{E}_g(\text{G})\leftarrow{}^6\text{A}_{1g}$, ${}^4\text{T}_{2g}(\text{G})\leftarrow{}^6\text{A}_{1g}$ and ${}^4\text{T}_{1g}(\text{G})\leftarrow{}^6\text{A}_{1g}$ transitions respectively indicating octahedral²² geometry of the complex. The geometry of Mn(II) complex is further confirmed^{23,24} by the high μ_{eff} value in the range 5.85-5.98 BM. The Cu(II) complex exhibits a single broad, asymmetric band in region 12820 cm⁻¹ which may be assigned to ${}^2\text{B}_{2g}\leftarrow{}^2\text{B}_{1g}$ transition which is in analogy with expected tetragonally distorted octahedral geometry. The broadness of the band may be due to dynamic and Jahn-Teller distortion. It is further supported by μ_{eff} value in the range 1.89-1.92 BM. As expected Zn(II) complex is diamagnetic. The complex is suggested to be tetraordinated probably having tetrahedral geometry based on analytical, IR and conductance data.

NMR spectra

The $^1\text{H-NMR}^{25,26}$ spectrum of the ligand has the expected characteristic signals. The CH_3 protons shows singlet at δ 2.2 ppm and $\text{O-CH}_2\text{CF}_3$ protons at δ 3.5 ppm. The doublet peak observed at δ 4.36 ppm and 4.66ppm is attributed to CH_2 protons. In addition, a multiplet peak at δ 6.9-8.3 ppm may be due to aromatic protons and peak at δ 13.2 ppm may be due to NH proton of benzimidazole ring. Signals observed in the Zn(II) complex at region of δ 8.18-8.23 ppm due to the azomethine proton either remained unaffected or shifted slightly downfield with reference to those of the parent ligand and the position of signal due to NH proton remains unaffected in the complex. The aromatic protons show downfield shifts in the Zn(II) complex. These observations support the assigned structure to the complex.

ESR spectra

ESR spectra of powdered samples of $[\text{Cu}(\text{LAN})_2(\text{H}_2\text{O})_2]$ complex was recorded at room temperature. When the monomeric species change into dimeric species having axial symmetry and identical sites, the “g” values also change due to the change in symmetry. The spectra have asymmetric bands with two “g” values g_{\parallel} and g_{\perp} . The trend $g_{\parallel} > g_{\perp} > g$ (2.002), indicates that unpaired electron lies predominantly in the $d_{z^2-y^2}$ orbital of Cu(II) ion, these spectral features being characteristic of axial symmetry²⁷⁻³⁰. The values of the σ bonding parameter (α^2), show appreciable covalence character in the metal-ligand bonds. Similar spectral observations have been observed by many workers for Cu(II) mononuclear complexes³¹⁻³³. Based on these observations Cu(II) complex may have octahedral geometry. The g_{\parallel} or g_{av} values of the complex is found to be less than 2.3 indicating considerable covalent character to the Cu-L bonds³⁴. This value is in consistent with Cu-O and Cu-N bonded copper complexes in substituted imidazole and benzimidazole systems.

Mass spectra

The FAB Mass spectrum³⁴ of $[\text{Mn}(\text{LAN})_2(\text{H}_2\text{O})_2]$ showed an important molecular ion peak at m/z 828, which corresponds to molecular weight of the complex supported for the dimeric structure. Beside this peak, the complex showed the fragment ion peak at m/z 368, indicating fragmentation of dimer molecule to monomer. The intensity of peaks gives an idea about the abundance and stability of fragments. Other important peaks were observed at m/z 182,224,352,368,388,430, 587 and 669 as a result of fragmentation of ligand from the complex by the formation of radical cations such as the peak observed at m/z 352 corresponds to $[\text{C}_{15}\text{H}_{11}\text{F}_3\text{N}_3\text{O}_2\text{S}]^+$.

Thermal analysis

The thermal decomposition of the Co(II) complex was studied using the TG and DSC techniques (Figure 2). The thermogravimetric studies³⁵ of the complex were carried out in the temperature range 30-700 °C with a sample heating rate of 10 °C/min in air atmosphere. The weight-loss step between 175-200 °C may correspond the elimination of coordinated water molecules and step between 250-450 °C may be attributed to the loss of organic moiety of the complex molecule. The decomposition continues up to 700 °C and on further increasing the temperature no weight loss is observed which may be attributed to formation of stable metal oxide.

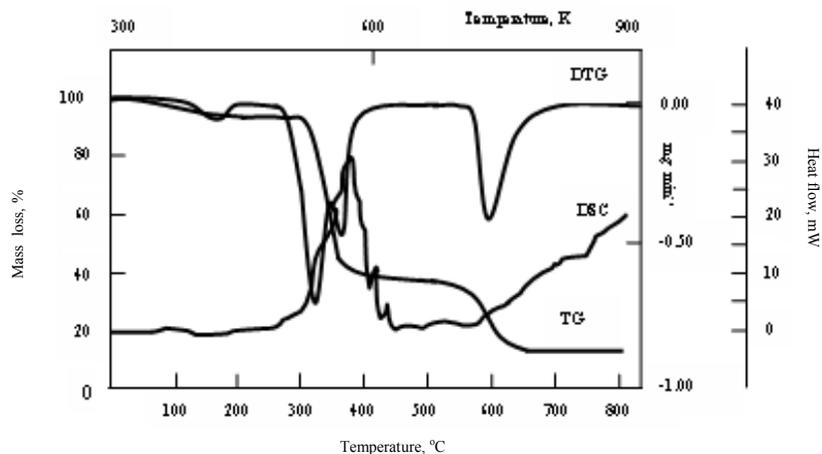


Figure 2. TGA/DTG and DSC curves of $[\text{Co}(\text{LAN})_2(\text{H}_2\text{O})_2]$ complex.

X-ray diffraction

The crystallinity of the material was analyzed with XRD with K- α radiation. The x-ray diffraction of Ni(II) complex of Lansoprazole (Figure 3) is studied as a representative system. The observed 2θ values with relative intensity more than 10% have been indexed and used for evaluation. The x-ray diffraction pattern of the complex with respect to their prominent peaks has been indexed by using computer software³⁶. The observed values fit well with orthorhombic system. The lattice constants for the complex were found to be to $a = 14.42857$, $b = 10.25224$, $c = 5.43030$ Å with a unit cell dimensions $\alpha=90$, $\beta=90$ and $\gamma=90^\circ$. Its Lattice type is P.

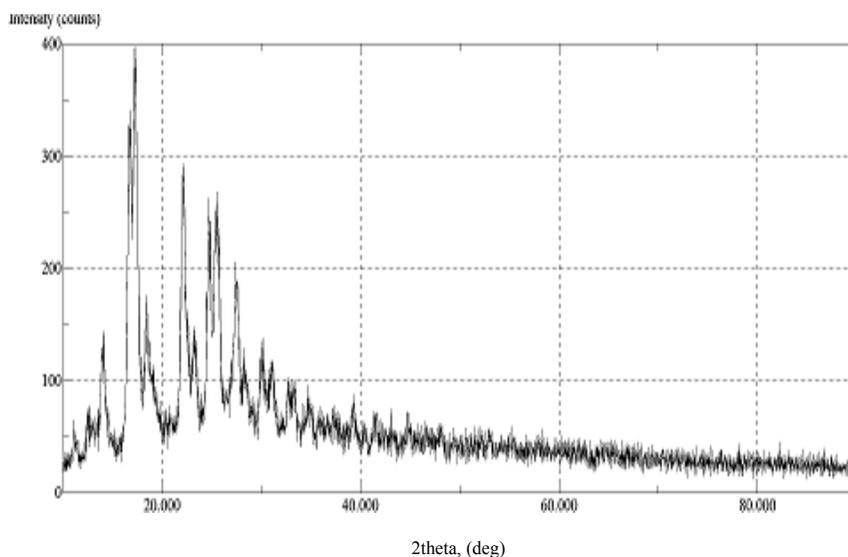


Figure 3. XRD graph for $[\text{Ni}(\text{LAN})_2(\text{H}_2\text{O})_2]$ complex.

Scanning Electron Micrographs [SEM]

SEM of metal complexes indicates the presence of well defined crystals free from any shadow of the metal ion on their external surface. The representative micrographs of a) Ligand (L) $[C_{16}H_{14}F_3N_3O_2S]$ and b) $[CoL_2(H_2O)_2]$ are shown in Figure 4. These results reveal that after complexation, the size of the complex gets reduced to much extent than their parent drug. To find out the maximum efficiency of the drugs and their metal complexes, studies on the particle size analysis are being considered very helpful³⁷. The bioavailability of low solubility drug is often intrinsically related to the drug particle size. By reducing particle size, the increased surface area may improve the dissolution rate of the drug to allow a wider range of formulation approaches and delivery technologies³⁸. Particle size and rate of dissolution not only affect the peak time and level but it may also affect the apparent pattern of drug pharmacokinetics³⁹.

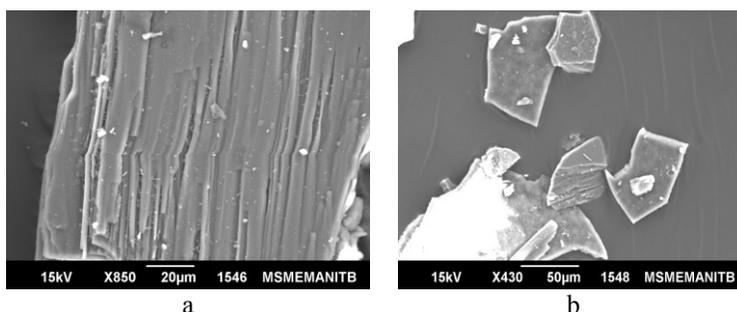


Figure 4. Scanning electron micrograph of ligand (a) and its Co(II) complex (b).

Antimicrobial activity

It is found that the use of complexes metal ions with antibiotics or other therapeutic agents represent an effective therapeutic method for the eradication of gastrointestinal microbes, for example for infections caused by *Helicobacter Pylori* the dietary metal complexes can be used in conjunction with antibiotics or agents such as proton pump inhibitors e.g. Omeprazole⁴⁰. If metal complexes of PPIs exhibit antimicrobial activity than there is no need of additional antibiotics with PPIs. With this view, in this study, some metal complexes of Lansoprazole were tested for their *in vitro* antimicrobial activities towards gram-positive(+) and gram-negative(-) bacteria viz, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and two stains of fungi *Aspergillus niger* and *Aspergillus flavus* (Table 4).

Table 4. Antibacterial activity-zone of inhibition, mm.

Compound	<i>Pseudomonas Aeruginosa</i> Gram(-)	<i>Staphylococcus Aureus</i> Gram(+)	<i>Aspergillus niger</i>	<i>Aspergillus flavus</i>
LAN (L)	13.10	11.20	8.01	7.13
[ZnL ₂]	12.30	13.10	12.80	11.00
[CuL ₂ (H ₂ O) ₂]	15.40	14.60	9.65	9.87
[NiL ₂ (H ₂ O) ₂]	–	6.80	6.12	3.45
[CoL ₂ (H ₂ O) ₂]	14.30	–	–	2.01
[MnL ₂ (H ₂ O) ₂]	13.20	12.60	4.60	–
Std.I-Gentamycin	21.40	19.20	12.71	11.02
Std.II-Grisofulvin	10.00	8.00	8.21	5.52

The antimicrobial activity of the ligand and its complexes was determined by the disc diffusion technique⁴¹. A 1 mg/mL solution in DMF was used. The standard used was gentamycin sulphate. The bacterium was maintained on nutrient agar and the agar media were incubated for different microorganisms culture tests. After 24 h of incubation at 37 °C for bacteria and 72 h of incubation at 25 °C for fungi, the diameter of zone of inhibition (mm) thus formed around each disc containing the test compound was measured accurately. All complexes showed significant activity against bacteria *Pseudomonas aeruginosa*, *Staphylococcus aureus* and fungi *Aspergillus niger* and *Aspergillus flavus* as compared to ligand. Some complexes like, Co(II) were found to be less active than the ligand in bacteria *Staphylococcus aureus* and fungi *Aspergillus niger*, Mn(II) complex in fungi *Aspergillus flavus* and Ni(II) complex in bacteria *Pseudomonas aeruginosa*. These preliminary results show that the activity of the ligand is enhanced when it is presented in the form of metal complex. Better activities of some metal complexes as compared to the ligand can be explained by chelation theory. The theory explains that decrease in polarizability of the metal could enhance the lipophilicity of the complexes which leads to the break-down of permeability of the cells resulting in interference with normal cell processes. In view of the foregoing discussions, following probable structures have been assigned to the complexes of Lansoprazole (Figure 5).

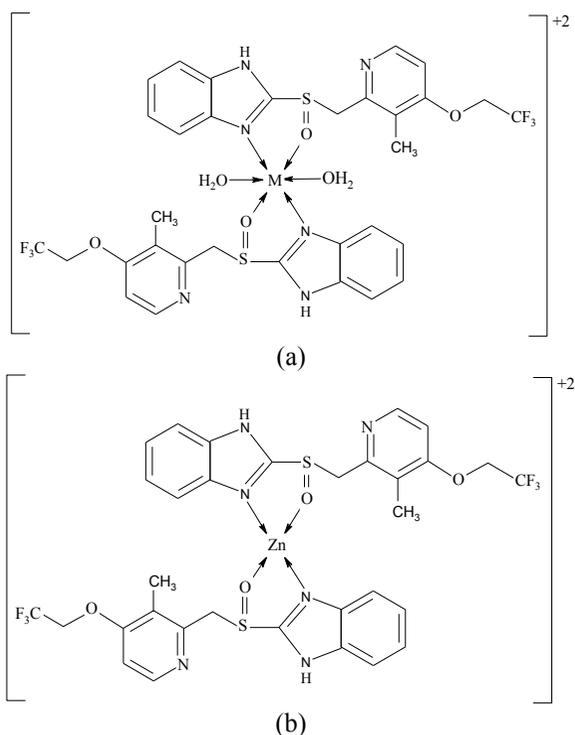


Figure 5. Structure of LAN complexes with: a) Mn(II), Cu(II), Co(II), Ni(II); b) Zn(II).

Conclusion

The ligand molecule acts as a bidentate ligand. The spectroscopic results show the involvement of C=N and S=O groups in coordination to the central metal ion. Spectral studies suggests that Ni(II), Co(II), Mn(II) and Cu(II) complexes possess octahedral geometry

and Zn(II) complex possesses tetrahedral geometry. It is observed that the formed complexes are better antibacterial agents in comparison to ligand.

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