



## Synthesis and Spectroscopic Studies of Mixed Ligand Complexes of Transition Metals with a Proton Pump Inhibitor and RNA Bases†

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Few mixed ligand complexes of transition metals have been synthesized by reacting their metal salts with a proton pump inhibitor namely lansoprazole and RNA bases adenine. All the complexes were synthesized in ethanolic medium and refluxed in reaction medium (1:1:2, M:L:L2 ratio). The yield percentage ranging from 80-90%. The complexes are coloured solids and of the type  $(L_{\text{lanso}})_m \cdot M \cdot (L_{\text{Ade}})_2 \cdot xH_2O \cdot X \cdot nH_2O$  and X can be  $SO_4$ . They are characterized through elemental analyses, conductance measurements, spectroscopy (IR, Mass, <sup>1</sup>H NMR and UV). An IR spectrum indicates that all the ligands behave as bidentate ligand. Molar conductance studies indicate electrolytic behaviour of these complexes. Metal complexes have been screened for their antibacterial activity towards *P. aruginosa* bacteria. The result reveals that the metal chelates showed more resistance as compared with parent drug.

**Key Words:** Spectroscopy, Ligand, Lansoprazole, Adenine, Molar conductance, Antibacterial activity.

### INTRODUCTION

Mixed ligand complexes play an important role in biological process in which enzymes are known to be activated by metal ions. Transition metal complexes are of continuing interest mainly due to their structural and catalytic properties and their application in diagnostic pharmaceutical and laser technology<sup>1-6</sup>. They have been found to exhibit anticancer and antifungal properties<sup>7</sup>. Synthesis, characterization and antimicrobial studies of transition metal complexes have been an active field of research, thus in the present study proton pump inhibitor, lansoprazole is used as one of the ligands for the complex formation. It is an antiulcer drug having chemical formulae 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-pyridine-2-yl]methyl]sulfinyl]-1H-benzimidazole. This is a potent drug producing profound suppression of gastric acid secretion and is highly effective at treating acid related disorder<sup>8-11</sup>. As the interaction of metal ions with nucleobases is of great interest because of their relevance to the essential, medical or toxic bioactivity of metal, where nucleobase molecule can coordinate as exogenous ligands in metalloproteins, function as cofactors in the enzymatic systems<sup>12,13</sup>. Thus, the RNA bases namely adenine is selected as the secondary ligand for the formation of ternary complexes. Adenine is a 9H-purin-6-amine<sup>14-16</sup>.

### EXPERIMENTAL

All the chemicals used throughout the course of experimental were either BDH or E. merck quality. Lansoprazole was obtained from Nosh Lab Pvt. Hyderabad. Spectroscopic grade solvents were employed for recording the spectra.

**Preparation of the complexes:** For the formation of mixed ligand complexes sulphates of transition metals *i.e.*, Cu(II), Cr(II), Co(II), Cd(II), Mn(II) are used with primary ligand lansoprazole and secondary ligand adenine. The solid complexes were prepared by mixing the aqueous solution of metal salts with ethanolic solution of ligand in molar ratio 1:1. The resulting mixtures were then refluxed for 4-5 h to give the precipitate. After cooling at room temperature the solid complexes were filtered as fine precipitates. These precipitates were washed twice with water. Then they were dried and stored in a desiccator containing dry calcium chloride.

Conductance measurement was done in DMF. The melting point was recorded on labotech instrument. Elemental analysis was performed on a Carlo Erba mod 1108 elemental analyzer. The mass spectrum was done on a Jeol SX-102 spectrometer using argon as the FAB gas. Elico, SL191 double beam UV-VIS spectrophotometer is used for recording UV-VIS spectra. The IR spectrum was recorded on Varian 1000 FT IR using

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TABLE-1  
PHYSICAL CHARACTERISTICS OF MIXED LIGAND COMPLEXES OF M- LANSO- ADE

S no.	Complex	Yield (%)	Colour	m.p. (°C)	Solubility	Molar conductance ( $\nu$ S cm <sup>2</sup> mol <sup>-1</sup> )
1	[Cu(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	89	Light blue	300	Freely soluble in DMF, DMSO, ethanol. Insoluble in cold water, HCl, NaOH.	20.12
2	[Cr(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	87	Brown	310	Freely soluble in DMF, DMSO, ethanol. Insoluble in cold water, NaOH.	23.00
3	[Mn(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	82	Brown	340	Freely soluble in DMF, DMSO, ethanol. Insoluble in cold water, NaOH.	13.45
4	[Cd(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	80	Dark brown	350	Freely soluble in DMF, DMSO, ethanol. Insoluble in NaOH, HCl, water.	14.64
5	[Co(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	83	Brown	300	Freely soluble in DMF, DMSO, ethanol. Insoluble in cold water, NaOH.	21.11

TABLE-2  
IR DATA OF MIXED LIGAND COMPLEXES OF M- LANSO- ADE

S. no.	Ligands and metal complexes	$\nu$ (S=O) cm <sup>-1</sup>	$\nu$ (C=N) cm <sup>-1</sup>		$\nu$ (C=N) cm <sup>-1</sup>	$\nu$ (C-N) cm <sup>-1</sup>	$\nu$ (M-O) cm <sup>-1</sup>	$\nu$ (Coordinated H <sub>2</sub> O) cm <sup>-1</sup>	
			Stretching	Bending				Stretching	Bending
1	LANSOPRAZOLE	1090	1590	547	-	-	-	-	-
2	ADENINE	-	-	-	1672	1356	-	-	-
3	[Cu(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	1068	1582	520	1640	1338	758	3402	844
4	[Cr(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	1022	1572	532	1642	1341	755	3311	856
5	[Co(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	1042	1521	564	1640	1338	746	3201	859
6	[Cd(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	1050	1510	580	1635	1332	743	3262	862
7	[Mn(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	1056	1584	540	1645	1340	784	3217	843

KBR Pallets. The <sup>1</sup>H NMR spectrum was recorded on bruker DRX-300. The antibacterial activity is studied by paper disk method and data was recorded after 48 h of incubation.

## RESULTS AND DISCUSSION

The reaction of the transition metal ions with lansoprazole and adenine afforded in good yield (80-90 %) of stable solid compound. The characterization of their molecular structure was made by elemental analyser's, conductivity and spectroscopy studies. The compounds prepare were of blue or brown colour and soluble in ethanol, DMF, 1,4 dioxane, DMSO and insoluble in water. The analytical data including yield percentage of the complexes are recorded in Table-1.

**IR spectra:** The characteristics frequencies of the ligands and mixed ligand complexes of the metals are given in Table- 2. The relevant vibration bands of the free ligand and their mixed ligand complexes are in the region 4000-400 cm<sup>-1</sup><sup>17-20</sup>. In case of lansoprazole molecule the N-H (aromatic sec. amine) stretching occurs at 3447 cm<sup>-1</sup>, where as sulfoxide (S=O) stretching occurs at 1090 cm<sup>-1</sup>. The aromatic tertiary amine (C=N) occurs at 1590 cm<sup>-1</sup> in lansoprazole. In free ligand adenine molecule the (N-H) and (C-N) frequency is located in 1600-1300 cm<sup>-1</sup> region. The bending vibration of N(9)-H is at 1418 cm<sup>-1</sup> and (C-N) band is at 1366 cm<sup>-1</sup>. The spectrum of adenine shows strong bands at 1672 and 1356 cm<sup>-1</sup> may be attributed to the C=N and C-N stretching frequencies respectively.

In case of ternary complexes of M-lanso-ade, all the complexes showed frequency of (N-H) at *ca.* 3050 cm<sup>-1</sup> showing that there is no involvement (N-H) group in complex formation, where as sulfoxide stretching shifts to lower frequencies at 50-60 cm<sup>-1</sup> due to coordination of the sulfonyl oxygen with lanthanides in all the complexes. The frequency of (C=N) bands appears at different region lowered by 40 cm<sup>-1</sup> indicating

the coordination of nitrogen atom of (C=N) with metal. Thus, lansoprazole molecule chelates with metal ions using its (C=N) group and (S=O) group, acting as bidentate ligand. There is a considerable shifts in the frequencies of the nitrogen atom in (C=N) and (C-N) groups of adenine molecule. Thus, in the complexes adenine acts as a chelating ligand binding through nitrogen atom in (C=N) and (C-N) groups. Additional bands in the complexes in the region 765-725 cm<sup>-1</sup> compared with IR spectra of free ligand have tentatively been assigned to M-O frequency and new band appeared at 1390-1380 cm<sup>-1</sup> in complexes might be due to chelate ring formation in the complex. The appearance of strong band at *ca.* 820 cm<sup>-1</sup> and *ca.* 3380 cm<sup>-1</sup> in the spectra of all the mixed ligand complexes indicates the presence of coordinated water.

**<sup>1</sup>H NMR Spectra:** To confirm the coordination of the ligands to the metal ion the complexes, <sup>1</sup>H NMR spectra was recorded for the ligands and its transition metal complexes. The important chemical shifts for the ligands and the complexes are given in the Table-3.

The <sup>1</sup>H NMR spectra of the ligand has the expected characteristic signals. The CH<sub>3</sub> proton shows singlet at  $\delta$  2.16 and O-CH<sub>3</sub> proton at  $\delta$  3.69 ppm the peak observed at  $\delta$  4.71 is attributed to CH<sub>2</sub> protons. In addition multiplet peak at  $\delta$  6.8-8.2 may be due to aromatic protons and peak at  $\delta$  13.2 is observed due to NH proton of benzimidazole ring. In case of ternary complexes of lansoprazole-adenine, the chemical shifts occurs at low field *i.e.* deshielding of proton occurs in methylene group proving the involvement of electron of S=O in bonding. Signals observed in the complexes at region of  $\delta$  8.18-8 due to the azomethine proton are either remained unaffected or shifted slightly to higher field with reference to those of the parent ligand and the position of signal due to NH proton remain unaffected in the complexes. Rest of the chemical shift is more or less same in the ligands and their complexes.

TABLE-3  
<sup>1</sup>H SIGNALS OF MIXED LIGAND COMPLEXES OF M- LANSO-ADE

S. No.	Kind of proton	Atom no.	Lansoprazole	[Cu(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	[Cr(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	[Mn(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O
1	Aromatic Benzimidazole	6, 7, 8, 9	7.35-7.63	7.2-7.8	7.0-7.8	7.1-7.7
2	Aromatic Pyridine	15	8.18	8.1	8.19	8.2
3	Aromatic Pyridine	16	6.98	6.9	6.8	6.4
4	Methylene -CH <sub>2</sub> -	12	4.81	4.61	4.9	4.5
5	Methyl -CH <sub>3</sub> -	24	2.2	2.2	2.5	2.2-2.5
6	ADENINE					
7	NH <sub>2</sub>	3	7.09	7	7.1	7

TABLE-4  
 MOLECULAR MASS AND ELEMENTAL DATA OF MIXED LIGAND COMPLEXES OF M- LANSO- ADE

Sr. no.	Name of complex	Mol. Mass (calculated)	Mol. Mass (spectral)	C	H	N	F
1	[Mn(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	785	789	24.4	1.7	5.3	7.29
2	[Cu(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	704	687	27.2	1.9	5.9	8.09
3	[Co(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	789	789	24.3	1.7	5.3	7.22
4	[Cd(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	824	820	23.3	1.6	5.09	6.9
5	[Cr(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	712	713	26.9	1.9	5.0	8.0

TABLE - 5  
 ELECTRONIC SPECTRAL DATA AND BONDING PARAMETERS OF MIXED LIGAND COMPLEXES OF M- LANSO- ADE

S. no.	Compounds	Complex band (cm <sup>-1</sup> )	B	1 - β	b <sup>1/2</sup>	δ (%)	H
1	[Cr(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	418400	0.45	0.55	0.35014	0.0624	49.6
		42370	0.46	0.54	0.3514	0.0629	49
2	[Co(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	34480	0.35	0.65	0.4	0.05718	64.5
		33900	0.34	0.66	0.40336	0.05697	65
3	[Mn(Lanso)(Ade) <sub>2</sub> .2H <sub>2</sub> O]SO <sub>4</sub> .nH <sub>2</sub> O	41670	0.43	0.57	0.3763	0.06138	56.6
		41320	0.43	0.57	0.3774	0.06128	56.9

The <sup>1</sup>H NMR spectrum of the adenine was showed δ 7.09 (2H, s, NH<sub>2</sub>), 7.70 (1H, s, C8-H), 8.12 (1H, s, C2-H) and 13.6 (1H, s, NH). In the <sup>1</sup>H NMR spectra of complexes, there is no shift of the NH<sub>2</sub> and NH. Nevertheless, the C2-H and C8-H were deshielded to the lower field. This fact could probably be explained that the adenine is coordinated with the metal ions through N3 and N9 and the new bond of M-N have been made in complexes. Thus NMR studies confirms the structure of metal complexes. The integrated proton ratio also corresponds to the proposed structure.

**Mass spectra:** In the present investigations, the mass spectrum of the Lansoprazole shows the formation of molecular ion peak at *m/z* 369, corresponds to the total molecular weight of the ligand. The mass spectra of the cerium and thorium shows the molecular ion peaks at *m/z* 829 and 902 respectively and mass spectra of Cu(II), Cr(II), Co(II), Cd(II), Mn (II) shows the molecular ion peak at *m/z* 704, *m/z* 712, *m/z* 789, *m/z* 824, *m/z* 784 supporting the composition of the complexes. The molecular weight of all the complexes and elemental analysis is also reported in Table-4.

**Electronic spectra:** Typical spectral data of the metal salts, ligands and ternary complexes of transition metal complexes have been investigated in alcohol and shown in Table- 5. The electronic spectra of the Lansoprazole displays absorption bands at 224, 285 which is assigned to n-π\* and π-π\* transition respectively. The electronic spectra of the complexes shows a shift towards lower frequency than that of the ligands. This slight shift was attributed to the effects of the crystal field upon the interelectronic repulsion between the 4f electrons. Some red shift or nephelauxetic effect is observed in the alcohol

solutions of these complexes. This red shift is usually accepted as evidence of a higher degree of covalency than the presence of aqua compounds<sup>21,22</sup>. In all the complexes, marked enhancement in the intensity of the bond has been observed. This red shift of the hyper sensitive bands has been utilized to calculate the nephelauxetic effect (β) in these chelate complexes. From the β values the covalence factors (b<sup>1/2</sup>), Sinha parameter (δ %) (metal-ligand covalency percent) and the covalency angular overlap parameter (η) have been calculated using the expressions<sup>23</sup> below:

$$b^{1/2} = \frac{1}{2}[(1-\beta)^{-1/2}], \delta (\%) = [(1-\beta)/\beta] \times 100, \eta = [(1-\beta)^{1/2}/\beta^{1/2}]$$

The positive values for (1-β) and δ % in these coordination compounds suggest that the bonding between metal and ligand is covalent compared with the bonding between the metal and an aqua ion. The values of parameter of bonding (b<sup>1/2</sup>) and angular overlap parameter (η) were found to be positive, indicating covalent bonding.

**Antibacterial activity:** The antibacterial activity of the ligand, metal salts and the corresponding complexes were assayed simultaneously against *P. aruginosa* culture by paper disk method at room temperature. The zones of inhibition against microorganism were measured (cm) after 48 h of incubation as shown in Table-6. In *P. aruginosa* culture the ternary complex of transition metals shows higher antibacterial activity as compared to parent drug Lansoprazole. The order of inhibition zone of these mixed ligand complexes are Cd > Cr = Co > Cu > Mn. The result indicates that the complexes are more active than free ligand. Increased activity of the complexes can be explained on the basis of chelation theory.

TABLE-6  
SENSITIVITY TEST OF LANSOPRAZOLE AND THEIR  
COMPLEXES AGAINST *P. aruginosa* CULTURE

S. no.	Metal ion	Inhibition diameter (cm)		
		lanso	[M(lanso)(ade) <sub>2</sub> ·2H <sub>2</sub> O]SO <sub>4</sub> ·nH <sub>2</sub> O	
1	Cu	1.5	0.7	1.8
2	Co	1.7	0.7	1.9
3	Cr	1.2	0.7	1.9
4	Mn	1.1	0.7	1.5
5	Cd	1.9	0.7	2.1

### Conclusion

The studied ternary complexes of transition metal showed 1:1:2 ( M:lanso:ade) composition as it is indicated from elemental analyser and exhibit corresponding conductivities suggesting 1:1 electrolytic behaviour. The electronic spectra data indicates the stereochemistry of formed complexes. The FT IR data reveals that the all the ligand function as bidentate ligands. The results of the study thus indicate the possibility of formation of metal-bridged drug receptor complex during antiulcer activity of the drug. The complexes may be formulated as (L<sub>lanso</sub>·M·(L<sub>ade</sub>)<sub>2</sub>·2H<sub>2</sub>O)X·nH<sub>2</sub>O and X can be SO<sub>4</sub><sup>2-</sup>.

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