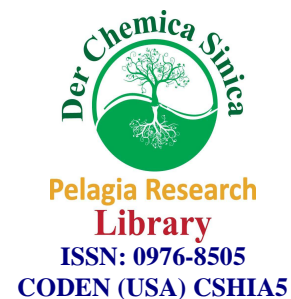




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### Synthesis and physico-chemical studies of newly formed complexes of transition and inner transition metals with (5-methoxy- 2- {(4-methoxy-3, 5-dimethyl- 1-pyridinyl) methyl} sulfinyl)-1H-benzimidazole)

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#### ABSTRACT

Few complexes of Transition and Inner transition metals have been synthesized by reacting their metal salts with (5-methoxy- 2- {(4-Methoxy-3, 5-dimethyl- 1-pyridinyl) methyl} sulfinyl)-1H-benzimidazole). All the complexes were synthesized in ethanolic medium and refluxed in reaction medium (1:1, M: L ratio). The yield percentage of formed complex is ranging from 80-90%. The complexes are colored solids and of the type (LOme.M.xH<sub>2</sub>O). They are characterized through elemental analyses, conductance measurements, spectroscopy (IR, mass, nmr and U.V). An IR spectrum indicates that the ligand behaves as bidentate ligand. Molar conductance studies indicates electrolytic behavior of these complexes. The metal complexes have been screened for their antifungal activity towards *Aspergillus niger* fungi. The result obtained is compared with that of parent drug. The result reveals that the metal chelates showed resistance as compared with parent drug.

**Keywords:** Spectroscopy, conductance measurements and antifungal activity.

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#### INTRODUCTION

Metal ions affect the well-being of human in various ways. Several of these elements are indispensable for life and nature governs their uptake, metabolism, and excretion consequently their concentrations in a human body are compartmentalized and well defined. The Transition and Inner transition metal ions are known to have the Small radii and variable coordination number ranging from 3 to 12, which make them excellent spacers in assembling fascinating metal organic frameworks. Mixed ligand complexes play an important role in biological process in which enzymes are known to be activated by metal ions [1, 2]. Transition and inner transition metal complexes are of continuing interest mainly due to their structural and catalytic

properties and their application in diagnostic pharmaceutical and laser technology [3 - 9]. They have been found to exhibit anticancer and fungicidal properties also [11-12].

Synthesis, characterization and antimicrobial studies of transition and inner transition metal complexes have been an active field of research (13-14) thus, in the present study a Proton Pump Inhibitor named Omeprazole (OME) is used as ligand for the formation of Binary complexes. Proton Pump Inhibitors are used for the treatment in acid induced inflammation conditions and ulcers of the stomach and duodenum, gastro esophageal reflux disease which are all caused by stomach acid [15-19]. It blocks the enzyme in the wall of the stomach that produces acid [20]. By blocking the enzyme, the production of acid is decreased and this allows the stomach and esophagus to heal.

Its chemical name is (5-methoxy-2-[(4-methoxy-3,5-dimethyl-1-pyridinyl)methyl]sulfinyl)-1H-benzimidazole [21-22]. It is an important anti-ulcer drug which is chiral since it has a stereogenic center, the sulphur atom.

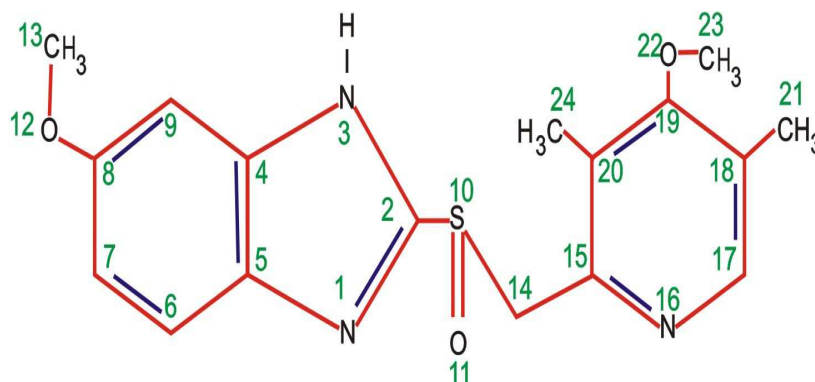


Fig.1 Omeprazole

## MATERIALS AND METHODS

### Experimental

All the chemicals used throughout the course of experimental were either BDH or E merck quality. Spectroscopic grade solvents were employed for recording the spectra.

### Preparation of the complexes

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 hours 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 desiccators containing dry calcium chloride.

### Physical measurement

Conductance measurement was done in DMF. The melting point was recorded on labotech instrument. The Mass spectra 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 u.v-vis spectra.

Elemental analysis was performed on a Carlo erba mod 1108 elemental analyzer. The IR spectrum was recorded on varian 1000 FTIR using KBR Pallets. The NMR spectra was recorded on bruker DRX-300.

The antifungal activity is studied by paper disk method and data was recorded after 48 hours of incubation.

## RESULTS AND DISCUSSION

The reaction of the Transition and Inner transition metal ions with OME afforded in good yield (80-90%) of stable solid compound. The compounds prepare were colourful, soluble in ethanol, 1, 4 dioxane, DMF, DMSO and insoluble in water. The characterization of their molecular structure was made by elemental analysers conductivity and spectroscopy studies. The studied complexes of transition and Inner transition metal showed 1:1 (M:OME) composition as it is indicated from elemental analyser and exhibit corresponding conductivities suggesting 1:1 electrolytic behaviour. The analytical data including yield percentage of the complexes are recorded in table 1

**Table – 1: Analytical data of synthesized binary complexes**

Sr.No.	complexes	Yield (%)	Colour	Melting point(°C)	Solubility	Molar Conductance ( $\wedge^{\wedge}/S\text{ cm}^2\text{ mol}^{-1}$ )
1	Cu-Ome	80	Blue	220	Freely soluble in DMF, DMSO, Ethanol. Insoluble in cold water, NaOH, HCl.	17.23
2	Cr-Ome	82	Reddish yellow	230	Freely soluble in DMF, DMSO, Ethanol. Insoluble in cold water, NaOH, HCl.	15.45
3	Cd-Ome	85	Brown	210	Freely soluble in DMF, DMSO, Ethanol. Insoluble in NaOH, HCl, cold water.	9.78
4	Mn-Ome	80	Pinkish White	240	Freely soluble in DMF, DMSO, Ethanol. Insoluble in cold water, NaOH, HCl.	11.23
5	Co-Ome	88	Pale Pink	205	Freely soluble in DMF, DMSO, Ethanol. Insoluble in cold HCl, water, NaOH.	20.13
6	Th- Ome	85	Brown	203	Freely soluble in DMF, DMSO, Ethanol, 1,4 Dioxane, Nitric acid Insoluble in cold water NaOH and partially in hot water, HCl	97.5
7	Ce- Ome	88	Light Brown	223	Freely soluble in DMF, DMSO, Ethanol, 1,4 Dioxane, Nitric acid, partially in hot water and Insoluble in cold water.	45.1
8	Gd - Ome	89	Brown	213	Freely soluble in DMF, DMSO, Ethanol, 1,4 Dioxane, Nitric acid Insoluble in cold water NaOH and partially in hot water, HCl.	70.3

### I.R spectra

The relevant vibration bands of the free ligand and the complexes are in the region  $4000-400\text{ cm}^{-1}$  [23-24]. The characteristics frequencies of the ligand and metal complexes are given in table 2. In case of OME molecule the N-H (aromatic sec. amine) stretching occurs at  $3050\text{ cm}^{-1}$ , where as sulfoxide (S=O) stretching occurs at  $1076\text{ cm}^{-1}$ . The aromatic tertiary amine (C=N) occurs at  $1660\text{ cm}^{-1}$  in OME [25].

In case of binary complexes of M-OME, all the complexes showed frequency of (N-H) at  $\sim 3050\text{ cm}^{-1}$  showing that there is no involvement (N-H) group in complex formation, where as sulfoxide stretching shifts to lower frequencies at  $\sim 50/60\text{ cm}^{-1}$  due to coordination of the sulfonyl

oxygen with metals in all the complexes. The frequency of (C=N) bands appears at different region in complexes i.e lowered by  $\sim 40 \text{ cm}^{-1}$  indicating the coordination of nitrogen atom of (C=N) with metal.

Thus, OME molecule chelates with metal ions using its(C=N) group and(S=O) group, acting as bidentate ligand. The M-O bond appears at  $\sim 720 \text{ cm}^{-1}$  in all the complexes

The appearance of strong band at  $\sim 820 \text{ cm}^{-1}$  and  $\sim 3380 \text{ cm}^{-1}$  in the spectra of all the binary complexes indicates the presence of coordinated water.

**Table 2 IR bands ( $\text{cm}^{-1}$ ) of binary complexes of OME**

Sr. No.	Name of complex	S=O	C-N		M-O	H <sub>2</sub> O	
			Stretching	Bending		Stretching	Bending
1	Omeprazole	1076	1660	547	-	-	-
2	Cu- Ome	1114	1620	502	718	3403	822
3	Cd- Ome	1028	1600	575	722	3392	831
4	Mn- Ome	1026	1590	578	740	3390	873
5	Cr- Ome	1030	1610	512	712	3390	862
6	Co- Ome	1048	1580	575	752	3392	831
7	Th- Ome	1028(m)	1624	528	744	3330	811
8	Ce- Ome	1034(m)	1637(s)	511	750	3375	819
9	Gd- Ome	1030	1635(s)	511	772	3370	814

### <sup>1</sup>H NMR SPECTRA

To confirm the coordination of the ligand to the metal ion in the complexes, NMR spectra was recorded for the ligand and its Transition and Inner transition metal complexes. The important chemical shifts for the ligands and the complexes are given in the table 3. Chemical shift of ArNH in pure drug OME and the binary complex is same.

In case of binary complexes of OME, 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. Rest of the chemical shift is more or less same in the ligand and the complexes. Thus nmr studies confirms the structure of metal complexes. The integrated proton ratio also corresponds to the proposed structure.

Table – 3 <sup>1</sup>H NMR signals of the ligand and the binary complexes

Sr.No	Kind Of Proton	Atom no.	Ome	Cu- Ome	Cr- Ome	Mn- Ome	Th- Ome	Ce- Ome	Gd- Ome
1	Aromatic Benzimidazole	6,7,9	6.8 - 7.8	7.61,7.62	6.8- 7.8	6.5-7.8	6.8-7.8	6.84-7.9	6.9-7.8
2(a)	Aromatic Pyridine	17	8.22	8	8.06	8.1	8.2	8.2	8.2
3	-CH <sub>2</sub>	14	4.71- 4.75	4.2	4.2	4.2	4.5 (weak)	4.2 (weak)	4.2-4.5 (sharp)
4(a)	O-CH <sub>3</sub>	13	3.87	3.57	3.8	3.8	3.78	3.78	3.75
(b)	O-CH <sub>3</sub>	23	3.69	3.67	3.7	3.5	3.67	3.4	3.4
5(a)	-CH <sub>3</sub>	24	2.16	2.15	2.16	2	2.18	2	2.21
(b)	-CH <sub>3</sub>	21	2.5	2.5	2.5	2.5	2.46	2.46	2.48

### MASS SPECTRA

In the present investigations, the mass spectrum of the omeprazole shows the formation of molecular ion peak at M/Z 344 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 669 and 761 respectively supporting the composition of the complexes. Cu(II), Cr(II), Co(II), Cd(II) and Mn(II) shows the molecular ion peak at M/Z 680, M/Z 807, M/Z 693, M/Z 689 respectively supporting the composition of the complexes. Data on the molecular weight of complexes are present in table along with the values calculated on the basis of established molecular formulae of the complexes as shown in table 4.

Table – 4 molecular mass C, H, N values of omeprazole and its binary complexes

Sr.no.	Name of complex	cal. Mass	spec. mass	Base peak	C	H	N	O
1	Omeprazole	345	344	330	59.1	5.5	12.17	13.9
2	Mn-ome	481	491	330	41.7	15.5	8.5	9.8
3	Cu -ome	408	394	330	50	4.6	10.2	11.7
4	Cr-ome	435	422	330	46.8	8.7	9.6	11
5	Co-ome	493	492	330	41.3	15.4	8.5	9.7
6	Cd-ome	492	480	330	41.4	7.7	8.5	9
7	Th-ome	631	630	332	32.38	3.01	6.66	15.23
8	Ce-ome	557	551	331	37.02	4.9	7.62	20.32
9	Gd-ome	574	579	331	35.23	4.66	7.25	19.34

### Electronic Spectra

Typical spectral data of the metal salts, ligand and binary complexes of Transition and Inner transition metal complexes have been investigated in alcohol and is shown in table 5. The electronic spectra of the OME displays absorption bands at 219, 301 which is assigned to n-  $\pi^*$  and  $\pi - \pi^*$  transition respectively. The electronic spectra of the complexes are similar to that of the ligand expect for a very slight shift towards lower frequency. This slight shift was attributed to the effects of the crystal field upon the inter electronic 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[26- 27]. 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 ( $\beta$ ) in these chelate complexes. From the  $\beta$  values the covalence factors ( $b^{1/2}$ ), Sinha parameter ( $\delta$  %) (metal- ligand covalency percent) and the covalency angular overlap parameter ( $\eta$ ) have been calculated using the expressions[ 28] 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  $(1 - \beta)$  and  $\delta\%$  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 ( $b^{1/2}$ ) and angular overlap parameter ( $\eta$ ) were found to be positive, indicating covalent bonding.

**Table 5 electronic spectral data and related bonding parameter of binary complexes of OME**

Sr. No	Name Of Complex	Band position (nm)	Band position( $\text{cm}^{-1}$ )	B	1 - $\beta$	$b^{1/2}$	$\delta\%$	$\eta$
1	Cu-OME	237	42190	-	-	-	-	-
		242	41320	-	-	-	-	-
2	Cr-OME	223	44840	0.53	0.47	0.3392	46.03	0.0621
		226	44260	0.53	0.47	0.3418	46.75	0.06223
3	Co-OME	295	33780	0.34	0.66	0.404	65.3	0.0566
		293	34130	0.41	0.59	0.4027	64.89	0.0569
4	Cd-OME	239	41840	-	-	-	-	-
		236	42370	-	-	-	-	--
5	Mn-OME	250	40000	0.41	0.59	0.3834	58.81	0.0605
		244	44640	0.45	0.55	0.3676	54.07	0.062
6	Th-OME	217.	46082	0.9677	0.0323	0.08986	3.3378	0.01602
		283	34129	0.78838	0.21162	0.23001	26.842	0.09953
7	Ce-OME	217	46083	0.97697	0.02302	0.07586	2.35665	0.01144
		296	33784	0.77028	0.22971	0.23964	29.8219	0.10737
8	Gd-OME	221	45248	0.9457	0.0543	0.11651	5.7417	0.0543
		295	33898	0.85763	0.14237	0.18865	16.6003	0.14237

### Antifungal Activity

The antifungal activity of the ligand, metal salts and the corresponding complexes were assayed simultaneously against *Aspergillus niger* fungus by paper disk method [29] at room temperature. The pure metal salt and OME drug showed activity in *Aspergillus niger*. The zones of inhibition against microorganism were measured (in cm) after 48 hours of incubation as shown in table 6 and figure 2 and 3.

In *Aspergillus niger* culture the binary complex of OME with transition metals namely Cd (II), Cr (II), Cu (II), Mn shows higher Antifungal activity as compared to parent drug OME. The binary complexes of Th, Gd, Ce with OME also showed higher inhibition zone as compare to OME.

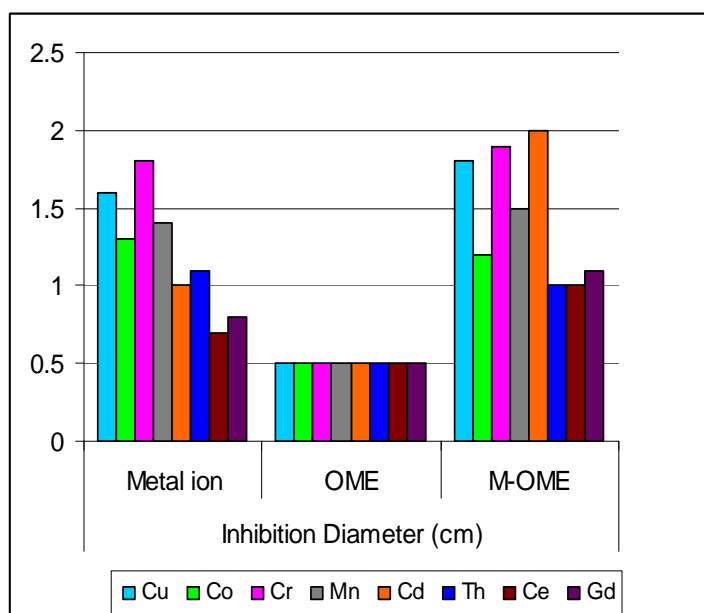
The order of inhibition zone of binary complexes are

Cd>Cr>Cu>Mn>Co>Gd>Th>Ce

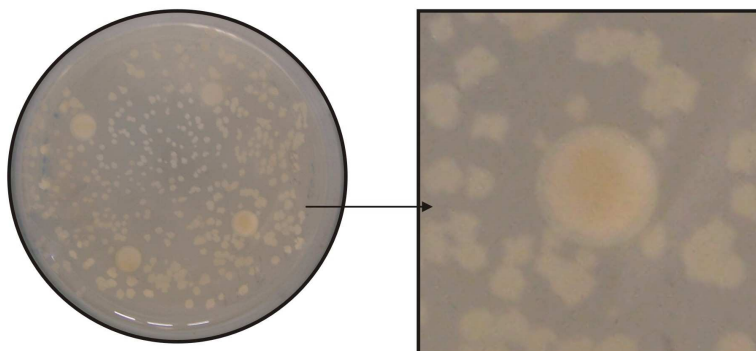
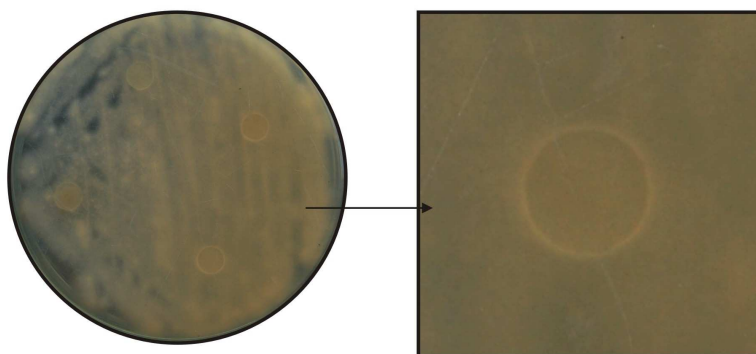
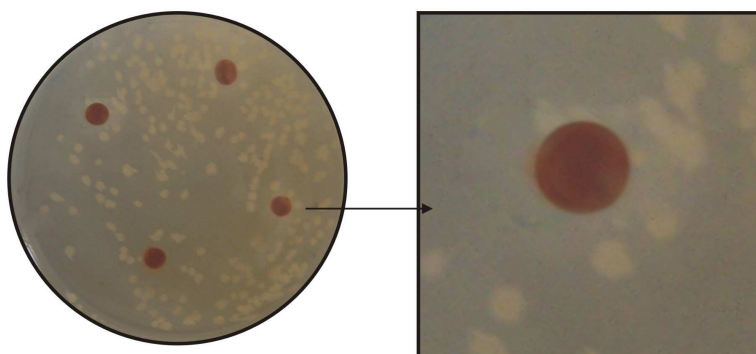
The result indicates that the complexes are more active than free ligand. Increased activity of the complexes can be explained on the basis of chelation theory. If the orbital of each metal ion overlaps the ligand orbital increases which enhances the lipophilicity of complexes due to delocalization of electron in the chelate.

**Table – 6 Sensitivity test of omeprazole & their complexes against A. Niger culture**

Sr.No.		Inhibition Diameter (cm)		
		Metal ion	OME	M-OME
1	Cu	1.6	0.5	1.8
2	Co	1.3	0.5	1.2
3	Cr	1.8	0.5	1.9
4	Mn	1.4	0.5	1.5
5	Cd	1	0.5	2
6	Th	1.1	0.5	1
7	Ce	0.7	0.5	1
8	Gd	0.8	0.5	1.1



**Fig .2. Comprision of Sensitivity Test of Omeprazole & their Complexes against A. niger Culture**

Fig. 3.1 Effect of Gd on *A. niger*Fig 3.2 Effect of OME on *A. niger*Fig. 3.3 Effect of Gd-OME on *A. niger***Fig. 3 Effect of *A. niger* Culture on ligand, metal salt and their complex**

### CONCLUSION

The characterization of the newly synthesized transition and inner transition metals with omeperazole was made by stoichiometric analysis, molar conductivity and spectroscopic studies. The electronic spectra data indicates the stereochemistry of formed complexes. The I.R. data



reveals that the ligand function as bidentate ligands. OME molecules chelates with the metal ions using its C=N group and S=O group. The  $^1\text{H-NMR}$  spectra of non-equivalent proton of OME in complex exhibit chemical shift towards lower field due to complexation with metals.

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  $(\text{L}_{\text{Ome}}\cdot\text{M}\cdot x\text{H}_2\text{O})\cdot\text{X}\cdot n\text{H}_2\text{O}$ . X can be  $\text{SO}_4$  or  $\text{NO}_3$ . The possible general structure of these coordination compounds can be shown in figure 4

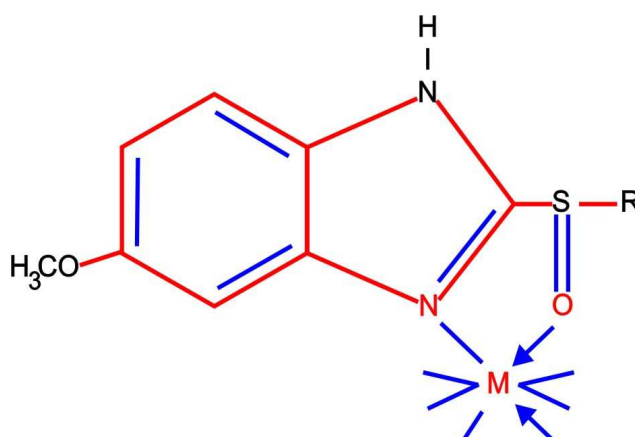


Fig 4. Proposed structure of representative binary complex

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