

Synthesis and Physico-Chemical Characterization and Biological Activity of Fe(II) and Zn(II) Complexes of Rabeprazole

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The template condensation between rabeprazole drug which is 2-([4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl)-1*H*-benzimidazole] and ferrous(II) sulphate and Zn(II) chloride in 1:2 ratio is described. Formation of new complex $[(C_{18}H_{21}N_3O_3S)_2Fe \cdot 2H_2O]$ and $[(C_{18}H_{21}N_3O_3S)_2Zn]$ have been supported by elemental analysis, conductivity measurements and spectral studies including IR, 1H NMR, UV and SEM studies. The molar conductance measurements of the complex in DMSO indicate that the complex is non-electrolytic in nature. The spectroscopic results show the involvement of C=N and S=O groups in coordination to the central metal ion. The magnetic moment value of ferrous(II) complex is 5.83 BM suggesting a high spin state of the metal ion in this complex. Based on spectral studies, octahedral geometry has been proposed for the Fe(II) complex and tetrahedral geometry for Zn(II) complex. The ligand and its complexes were tested for their antibacterial and antifungal activities against bacteria *Pseudomonas*, *Staphylococcus aureus* and fungi *Aspergillus niger*. It is observed that the complexes are better bactericidal agent than the parent drug.

Key Words: Complex, Rabeprazole, Template, Ligand, Antiulcerative.

INTRODUCTION

The literature reveals that the complexes of metallic salts are more potent and less toxic in many cases as compared to the parent drug¹. These metal complexes are found to be interesting due to their biological applications like antifungal², antibacterial³ and antitumor⁴ activity. A large number of drugs have been used to synthesize the complex with many metals with a view to enhance their therapeutic action⁵⁻⁷. We have recently reported isolation, characterization and antimicrobial activities of different metal complexes with benzimidazole derivatives⁸. As an extension of our previous studies, the objective of the present work is to synthesize and study physicochemical characteristics as well as antimicrobial activity of rabeprazole with metals. The present paper describes the synthesis and character-

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ization of Fe(II) and Zn(II) complexes with rabeprazole *i.e.*, 2-([4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl)-1*H*-benzimidazole] (L) which is an antiulcerative drug and contains benzimidazole ring (Fig.1).

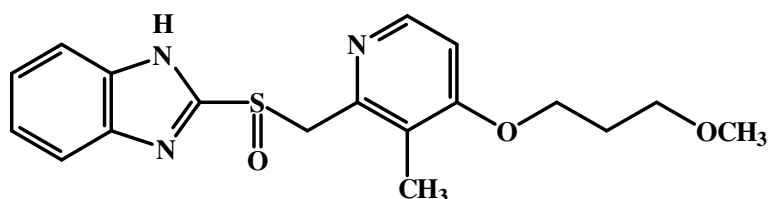


Fig. 1. Structure of rabeprazole

EXPERIMENTAL

All chemicals used were of analytical grade. Pure sample of rabeprazole (m.f. $C_{18}H_{21}N_3O_3S$ with m.w. 359.450) was obtained from Aristo Pharmaceuticals Ltd. Mandideep, Bhopal. Metal salts $FeSO_4 \cdot 7H_2O$ and $ZnCl_2$ were of Merck Chemicals. The solvents used were distilled water and methanol. Metal-ligand ratio was calculated using Systronics digital conductivity meter, IR spectra were obtained from CDRI Lucknow (Instrument used: Perkin Elmer FTIR spectrophotometer in the range of $4000-400\text{ cm}^{-1}$). Magnetic susceptibility measurements were received from CAT Indore (Instrument used-Vibrating Sample Magnetometer). Nitrogen was determined by the Dumas method and sulphur was estimated by the Messenger's method. The elemental micro-analyses of C, H and N for ligand were carried out with Thomas and Coleman Analyzer Carlo Erba 7106.

Ligand-metal ratio: To confirm the ligand-metal ratio, conductometric titrations using mono-variation method were carried out at $21\text{ }^\circ\text{C}$. 0.01 M solution of rabeprazole drug was prepared in 20:80 mixture of methanol and water. Similarly, 0.02 M solutions of metal salts $FeSO_4 \cdot 7H_2O$ and $ZnCl_2$ were prepared in the same solvent. The ligand was titrated against metal salt solutions using mono-variation 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). Stability constants and free energy changes were also calculated by using Job's method⁹ of continuous variation modified by Turner and Anderson¹⁰.

Synthesis of complexes: The complexes were synthesized by mixing the solutions of (20 % methanol) metal salts with that of ligand in 1:2 molar ratios, respectively and refluxing the mixtures at low temperature for 2 h. The reaction mixture was kept for few days. A reddish brown coloured crystalline complex of $(RAB)_2Fe \cdot 2H_2O$ and white crystalline complex of $(RAB)_2Zn$ formed were filtered, washed with mixture of methanol and distilled water (20:80) and dried. Carbon, hydrogen, nitrogen, metal and water were estimated micro analytically at CDRI, Lucknow.

RESULTS AND DISCUSSION

The synthesized complexes are stable solids soluble in DMF and DMSO and insoluble in all other organic solvents. Analytical data and conductometric studies suggest 2:1 [L:M] ratio (Table-1). Measured conductance values of these complexes are too low to account for their electrolytic behaviour. The magnetic studies indicate that the ligand-Fe complex to be paramagnetic with magnetic moment of 5.83 BM while Zn complex found to be diamagnetic (Table-2).

TABLE-1
ANALYTICAL DATA OF COMPLEXES

Composition of complex (m.w.)	Colour	Yield (%)	m.p. (°C)	Elemental analysis (%): Found/(calcd.)			
				C	H	N	M
$C_{18}H_{21}N_3O_3S$ (359.45)	White	–	99	60.15	5.89	11.69	–
$(C_{18}H_{21}N_3O_3S)_2Zn$ (784.24)	White	45	110	55.13 (55.91)	5.39 (5.30)	10.71 (10.22)	8.17 (9.09)
$(C_{18}H_{21}N_3O_3S)_2Fe \cdot 2H_2O$ (813.606)	Reddish brown	52	119	53.33 (53.20)	5.22 (5.73)	10.36 (10.42)	6.88 (7.15)

TABLE-2
STABILITY CONSTANT, FREE ENERGY CHANGE, MOLAR CONDUCTANCE AND MAGNETIC-MOMENT DATA OF COMPLEXES

Composition of complex	Stability constant log K (L/mol)	Free energy change ($-\Delta F$) (Kcal/mol)	Molar conductance ($ohm^{-1} cm^2 mol^{-1}$)	Magnetic moment (BM)
$(C_{18}H_{21}N_3O_3S)_2Zn$	10.7471	15.9751	9.34	–
$(C_{18}H_{21}N_3O_3S)_2Fe \cdot 2H_2O$	11.4208	16.039	11.08	5.83

IR Spectra: The IR spectra¹¹⁻¹⁴ of ligand and its iron and zinc complexes have been recorded and the probable assignments are given in the Table-3. 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. The shift of the $\nu(C=N)$ and $\nu(S=O)$ by 10-15 cm^{-1} in the complexes indicating that these groups are involved in the complexation. In the ligand, band appearing at 3456 cm^{-1} due to NH stretching remains unaltered in the complexes. The band due to $\nu(C=N)$ in the ligand at 1585 cm^{-1} is shifted to lower wave number at 1585-1565 cm^{-1} in the complexes there by confirming the coordination through the azomethine nitrogen atom. The IR band at 1020 cm^{-1} in the ligand due to aromatic sulfoxide stretching in Fe-complex and Zn-complex shifted to 1028 and 1022 cm^{-1} , respectively which indicates the involvement of oxygen of sulfoxide in complex formation. In Fe(II) complex, band appearing at region 3565 cm^{-1} may be due to coordinated water molecule. The appearance of bands in the far IR region at 429-409 cm^{-1} in the complexes may be assignable to M-N frequency. Additional bands in the complex in the region 615-608 cm^{-1} compared with IR spectra of free ligand have tentatively been assigned to M-O frequency and

TABLE-3
IR ABSORPTION (cm^{-1}) frequencies OF THE LIGAND AND ITS METAL COMPLEXES

Ligand and complex	$\nu(\text{NH})$ (cm^{-1})	$\nu(\text{C}=\text{N})$ (cm^{-1})	$\nu(\text{S}=\text{O})$ (cm^{-1})	$\nu(\text{M}-\text{N})$ (cm^{-1})	$\nu(\text{M}-\text{O})$ (cm^{-1})	$\nu(\text{H}_2\text{O})$ (cm^{-1})
$\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$	3456	1585	1020	–	–	–
$(\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_3\text{S})_2\text{Fe}\cdot 2\text{H}_2\text{O}$	3453	1576	1028	415	610	3565
$(\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_3\text{S})_2\text{Zn}$	3455	1572	1022	426	615	–

new band appearing at $1380\text{--}1390\text{ cm}^{-1}$ in the complexes might be due to chelate ring formation in the complexes.

Electronic spectra and magnetic susceptibility data: The spectra of Fe(II) complex of rabeprazole shows two bands at 28160 and 21075 cm^{-1} . The first band is assigned to charge transfer while the second band would be due to the transitions ${}^5\text{E}_g \leftarrow {}^5\text{T}_{2g}$ indicating octahedral¹⁵ geometry of the complex. The proposed geometry is further confirmed by high μ_{eff} value at 5.83 BM ^{16,17}. As expected Zn(II) complex is diamagnetic in nature. The complex is suggested to be tetra coordinated probably having tetrahedral geometry based on analytical, IR and conductance data.

NMR Spectra: The ${}^1\text{H}$ NMR spectra of the ligand was the expected characteristic signals. The CH_3 proton shows singlet at δ 2.2 and $\text{O}-\text{CH}_2\text{CH}_3$ proton at δ 3.5. The doublet peak observed at δ 4.36 and 4.66 ppm is attributed to CH_2 protons. In addition a multiple peak at δ 6.9–8.3 may be due to aromatic protons and peak at δ 13.2 may be due to NH proton of benzimidazole ring. Signals observed in the complexes at region of δ 8.18–8.23 due to the azomethine proton 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 remains unaffected in the complexes. The aromatic protons show downfield shifts in the complexes. These observations support the assigned structure to the complexes.

Scanning electron micrographs [SEM]: Scanning electron micrographs of metal complexes indicate the presence of well defined crystals free from any shadow of the metal ion on their external surface. The representative micrographs of (a) ligand; (b) $[\text{ZnL}_2]$; (c) $[\text{FeL}_2(\text{H}_2\text{O})_2]$ are shown in Fig. 2.

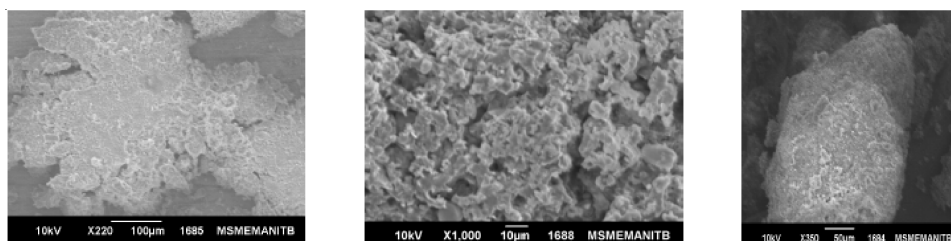


Fig. 2. Scanning electron micrograph of ligand and its complexes

Antimicrobial activity: The antimicrobial activity of the ligand and the complexes were determined by the disc diffusion technique¹⁸. The compounds were screened *in vitro* against *Pseudomonas*, *Staphylococcus aureus* and one strain of fungi, *Aspergillus niger*. A 1 mg/mL solution in DMF was used. The standard used was gentamycin sulphate 1 mg/mL and solvent control was used to know the activity of the solvent. The bacterium was maintained on nutrient agar and the agar media were incubated for different microorganism 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 were measured accurately. The Fe(II) and Zn(II) complexes show significant activity against bacteria *Pseudomonas* and *Staphylococcus aureus* and fungi *Aspergillus niger* compared to ligand. These preliminary results show that the activity of the ligand is enhanced when it is presented in the form of metal complex. In view of the foregoing discussions, the high melting points and insolubility in common organic solvents we have assigned following probable structures to the Fe(II) and Zn(II) complexes of rabeprazole (Figs. 3 and 4).

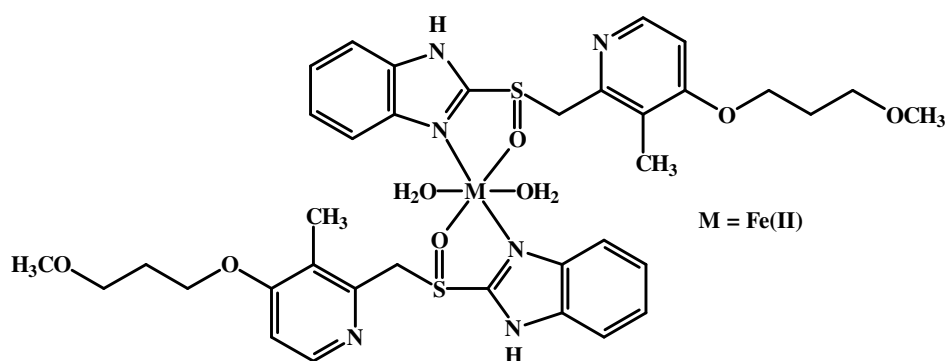


Fig. 3. Suggested structure for Fe(II) complex of rabeprazole

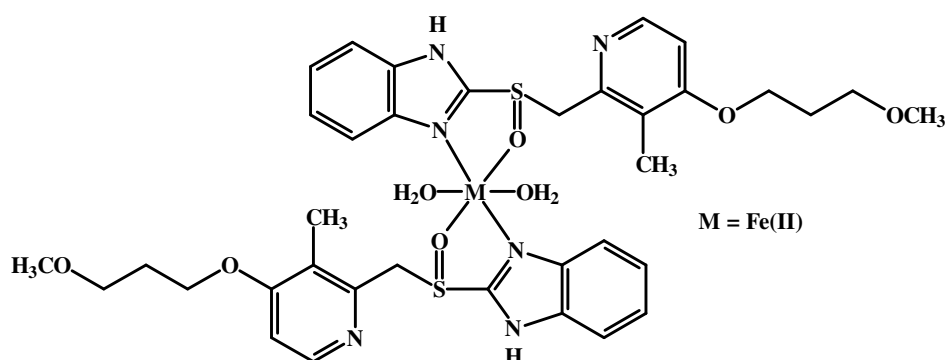


Fig. 4. Suggested structure for Zn(II) complex of rabeprazole

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