

## Synthesis and Characterization of Cu(II), Zn(II), Cd(II) and Hg(II) Complexes of Rabeprazole

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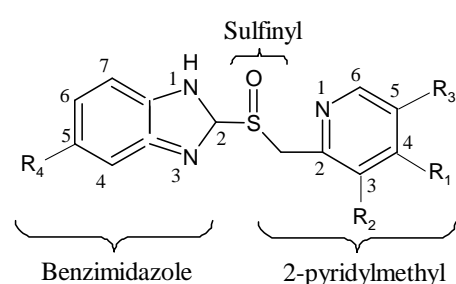
### Abstract

Rabeprazole (RPZH) (available as rabeprazole sodium, RPZNa) is a proton pump inhibitor (PPI), widely used for the treatment of acid-related diseases in the stomach and duodenum. It is a weak base with  $pK_a = 4.9$  and show a strong ability to form complexes with transition and non-transition metal ions. Its complexes with Cu(II), Zn(II), Cd(II) and Hg(II) have been synthesized and characterized by solubility, melting point, metal content estimation, IR and UV-Visible spectral analysis, magnetic measurement, thermogravimetric analysis, differential scanning calorimetry and X-ray powder diffraction studies. On the basis of metal contents, the complexes have been formulated as  $[Cu(RPZ)(H_2O)Cl]$ ,  $[Zn(RPZ)_2]$ ,  $[Cd(RPZ)_2] \cdot 2H_2O$  and  $[Hg(RPZ)_2] \cdot H_2O$ . Rabeprazole sodium (RPZNa) loses  $Na^+$  ion in solution yielding a monoanionic RPZ that behaves as a bidentate ligand and coordinates through C-N<sup>-</sup> and S=O groups with the divalent metal ion. Tetrahedral geometry of all complexes is proposed. Zn(II), Cd(II) and Hg(II) complexes have 1:2 metal to ligand stoichiometry while Cu(II) complex possesses ligand to metal ratio of 1:1. Cu(II) and Zn(II) complexes have also been screened for their antibacterial and antifungal activities against several bacteria and fungi.

**Key words:** Rabeprazole, infrared spectra, thermogravimetry, magnetic susceptibility.

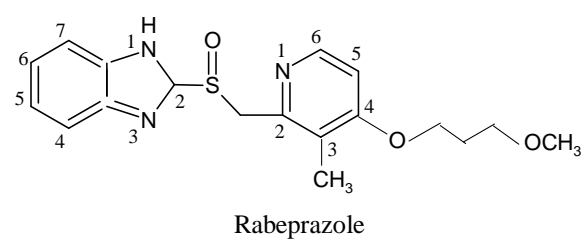
### I. Introduction

Proton pump inhibitors (PPIs) are substituted benzimidazoles and are lipophilic weak bases that cross the parietal cell membrane and enter the acidic parietal cell canaliculus<sup>1</sup>. All PPI compounds contain a basic structural framework and differ only in the nature of substituents placed on the pyridine and benzimidazole rings as shown by the following formula:

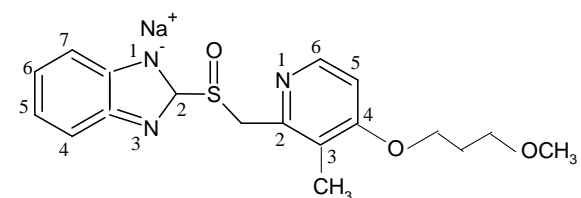


The PPI requires an acidic environment to undergo the rearrangement to the active form. In the acidic environment, the PPIs become protonated producing the activated sulphonamide form that binds covalently with the  $H^+/K^+$ -ATPase enzyme resulting in irreversible inhibition of acid secretion by the pump<sup>2-4</sup>. Thus these drugs are highly effective for the treatment in acid induced inflammation conditions and ulcers of the stomach and duodenum, gastroesophageal reflux disease, all caused by stomach acid<sup>5-8</sup>.

Rabeprazole (RPZH) is a rapid acting proton pump inhibitor frequently used to treat acid reflux and ulcers of the stomach and duodenum. It is a weak base composed of two moieties, a substituted pyridine with a primary  $pK_a$  of about 4.9, and a benzimidazole with a second  $pK_a$  of about 1.0. Because of the higher  $pK_a$  values, rabeprazole provides faster action compared to other PPIs (omeprazole, pantoprazole, lansoprazole, esomeprazole, etc.). For the same reason, rabeprazole is a better donor and can form complexes easily with dipositive metal ions at ambient condition. Moreover, biological science literature reveals that compare to the parent drugs; their complexes with metal salts are more potent and less toxic in many cases.



Rabeprazole



Rabeprazole sodium

Considering the importance of rabeprazole and its metal complexes, it is desirable to synthesize and characterize the complexes of rabeprazole with metal ions. In this paper, we are describing the synthesis and characterization of Cu(II), Zn(II), Cd(II) and Hg(II) complexes of RPZ in which RPZ acts as a bidentate O, N donor.

### II. Experimental

#### Chemicals

Rabeprazole sodium was collected from SK+F Pharmaceutical Ltd., Bangladesh.  $CuCl_2 \cdot 2H_2O$ ,  $ZnCl_2 \cdot nH_2O$ ,  $CdCl_2 \cdot H_2O$ ,  $HgCl_2$ , HCl,  $HNO_3$ , NaOH and organic solvents used in all synthetic and analytical work were analar grade, either Aldrich (USA), E. Merck (Germany) or E. Merck (India).

#### Methods and Equipments

Melting points of the complexes were taken in a melting point apparatus (Kruss, Germany), having the capacity of recording the temperature up to  $360^\circ C$ . The solubility of the complexes was determined qualitatively using different solvents in the usual manner. The solvents used were water, methanol, ethanol, acetone and dichloromethane in both room temperature and warm conditions. Zinc, cadmium and mercury contents of the complexes were determined by

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complexometric method using standard Na<sub>2</sub>EDTA solution as the titrating agent. Copper and chloride contents were determined using gravimetric method. The infrared spectra (IR) of the complexes were recorded on an Infrared Spectrometer of model IR-470 (Shimadzu, Japan) in the range of 4000-400 cm<sup>-1</sup> using KBr pallets. The UV-visible spectra (electronic spectra) of the complexes were recorded using a UV-Visible spectrometer Model UV-1800 (Shimadzu, Japan), in the wavelength range of 200-1100 nm using methanol as the reference solvent. The thermogravimetric analysis (TGA) of the complexes was carried out with TGA-50 thermogravimetric analyzer (Shimadzu, Japan), the quasi-static thermal analysis (QSTG) was carried out in a CARBOLITE calibrated muffle furnace of the type CWF11/5 and the differential scanning calorimetric (DSC) analysis was carried out with DSC-60 analyzer (Shimadzu, Japan). Magnetic susceptibility of the complexes was determined by the SHERWOOD SCIENTIFIC Magnetic Susceptibility Balance (M.S.B.) of model Magway MSB Mk1, Cambridge, England. X-ray Powder diffraction photograph of [Hg(RPZ)<sub>2</sub>].H<sub>2</sub>O complex

was recorded in a PHILIPS PW-1729 X-ray generator equipped with XDC-700 Gunier Hägg camera, using copper filtered CuK<sub>α1</sub> radiation ( $\lambda = 1.540981 \text{ \AA}$ ).

#### Synthesis

Rabeprazole containing metal complexes of Cu(II), Zn(II), and Hg(II) were synthesized in methanolic medium, whereas Cd(II) complex in a mixture of water and methanol (50:50, v/v) at room-temperature. Respective metal(II) salt and rabeprazole sodium in 1:2 molar ratio were dissolved in minimum volume of solvent separately. They were then mixed together and the resulting solution was kept at ambient condition for crystallization. For the copper complex, few drops of dilute NaOH was added to adjust the pH at about 10-11. The products formed were isolated by filtration, washed with methanol and dried in a desiccator over blue silica gel. All the complexes are air stable, insoluble in water but sparingly soluble in methanol. A summarized synthetic procedure is given in Table 1.

**Table 1. Nominal composition of reactants used for the preparation of complexes.**

Metal salts	Metal salts /g	RPZNa /g	Solvent	pH	Complexes
CuCl <sub>2</sub> .2H <sub>2</sub> O	0.0367	0.1645	methanol	10.5	[Cu(C <sub>18</sub> H <sub>20</sub> N <sub>3</sub> O <sub>3</sub> S)(H <sub>2</sub> O)Cl]
ZnCl <sub>2</sub>	0.1570	0.8226	methanol	7	[Zn(C <sub>18</sub> H <sub>20</sub> N <sub>3</sub> O <sub>3</sub> S) <sub>2</sub> ]
CdCl <sub>2</sub> .H <sub>2</sub> O	0.2003	0.7644	methanol + water (50:50, v/v)	7	[Cd(C <sub>18</sub> H <sub>20</sub> N <sub>3</sub> O <sub>3</sub> S) <sub>2</sub> ].2H <sub>2</sub> O
HgCl <sub>2</sub>	0.2787	0.7704	methanol	7	[Hg(C <sub>18</sub> H <sub>20</sub> N <sub>3</sub> O <sub>3</sub> S) <sub>2</sub> ].H <sub>2</sub> O

### III. Results and Discussion

Results of metal analysis of the complexes are in good agreement with the theoretically calculated values of the proposed formulae. The metal contents were estimated by both complexometric and/or gravimetric methods following the standard procedures. The water content was estimated by thermal analysis of the compounds. All the prepared complexes are powdered. The proposed empirical formulae

of the complexes are as follows:

- (i) [Cu(RPZ)(H<sub>2</sub>O)Cl]                      (ii) [Zn(RPZ)<sub>2</sub>]  
 (iii) [Cd(RPZ)<sub>2</sub>].2H<sub>2</sub>O                      (iv) [Hg(RPZ)<sub>2</sub>].H<sub>2</sub>O

Some of their physical properties e.g. metal content, yield, colour, melting point and solubility in water that have been studied, are tabulated in Table 2.

**Table 2. Metal contents and some physical properties of the complexes.**

Complexes	Metal /%			Yield */%	Colour	Decomp. Temp. /K	Melting Point /K	Solubility in Water
	Complexo- -metric	Gravimetric	Average					
[Cu(RPZ)(H <sub>2</sub> O)Cl]	-	11.04 (As oxide)	11.04 (13.37)	14.92	Green	-	426-429	Insoluble
[Zn(RPZ) <sub>2</sub> ]	9.98	9.65 (As oxide)	9.82 (8.36)	33.96	White	448-523	>623	Insoluble
[Cd(RPZ) <sub>2</sub> ].2H <sub>2</sub> O	14.09	13.19 (As oxide)	13.64 (12.99)	70.32	White	428-443	268-473	Insoluble
[Hg(RPZ) <sub>2</sub> ].H <sub>2</sub> O	23.80	21.99 (As sulfide)	22.89 (21.44)	85.54	White	423-443	448-450	Insoluble

The calculated metal contents are in parentheses. \*The percentage of yield was calculated on the basis of metal content.

It is seen from the Table 2, that the studied Zn(II), Cd(II) and Hg(II) compounds have incongruent melting points, i.e., they decompose at temperature before melting.

*IR Spectral analysis:* The infrared spectra of the complexes are collected by passing a beam of infrared light through them. Some important assigned IR peaks<sup>9-12</sup> of different titled complexes are shown in Table 3. All complexes show weak intensity absorption peaks in the region 400-550 cm<sup>-1</sup>

are due to M-O and M-N<sup>-</sup> stretching vibrations. The stretching frequency of characteristic sulfoxide group,  $\nu(\text{S}=\text{O})$  appeared at 990-1010 cm<sup>-1</sup> in complexes, while that of rabeprazole is at 1011 cm<sup>-1</sup>. This implies that the absorption peak originated from  $\nu(\text{S}=\text{O})$  are shifted to lower frequency region in complexes. The downward shifting of  $\nu(\text{S}=\text{O})$  can be explained on the basis of its participation in coordination with metal ions through O atom.

**Table 3. Tentative assignments of IR bands of rabeprazole sodium and rabeprazole-metal complexes.**

Compounds	$\nu(\text{M-O})$ /cm <sup>-1</sup>	$\nu(\text{M-N})$ /cm <sup>-1</sup>	$\nu(\text{S}=\text{O})$ /cm <sup>-1</sup>	$\nu(\text{C-N})$ /cm <sup>-1</sup>	$\nu(\text{C=N})$ /cm <sup>-1</sup>	$\nu(\text{C=C})$ /cm <sup>-1</sup>	$\nu(\text{C-H})_{\text{arom}}$ /cm <sup>-1</sup>	$\nu(\text{O-H})$ /cm <sup>-1</sup>
(RPZ)Na.1.5H <sub>2</sub> O	-	-	1011	1464	1585	1681	2904	3411
[Cu(RPZ)(H <sub>2</sub> O)Cl]	438	523	1000	1461	1585	1405	3047	3392
[Zn(RPZ) <sub>2</sub> ]	445	-	992	1460	1585	1690	3032	-
[Cd(RPZ) <sub>2</sub> ].2H <sub>2</sub> O	441	520	1004	1460	1585	-	2935	3384
[Hg(RPZ) <sub>2</sub> ].H <sub>2</sub> O	430	535	1007	1457	1577	-	2984	3422

Vibrations of  $\nu(\text{C-N}^-)$  in benzimidazole ring appear at 1457-1461 cm<sup>-1</sup> in the complexes, while that of 1465 cm<sup>-1</sup> in rabeprazole. Shifting of these frequencies to the lower wavenumber also indicates the contribution of this group in bond formation with the metal ions.

The -C=N- group stretches at 1577-1585 cm<sup>-1</sup> and its position remains unchanged in complexes as observed in free ligand. Cu(II), Cd(II) and Hg(II) complexes show broad band of medium intensity at about 3384-3422 cm<sup>-1</sup> due to stretching vibration of O-H bond. The broadening of  $\nu(\text{O-H})$  peak indicates that the complexes have either coordinated or crystalline water molecules. The zinc compound does not show any absorption frequency in that region. So zinc compound has no water molecule.

*UV-visible spectral analysis:* The electronic spectra of the metal complexes were recorded and the data obtained from the spectral investigations are tabulated in Table 4.

**Table 4. Electronic spectral data of the complexes.**

Complexes	$\lambda$ /nm
[Cu(RPZ)(H <sub>2</sub> O)Cl]	885, 284, 207
[Zn(RPZ) <sub>2</sub> ]	285
[Cd(RPZ) <sub>2</sub> ].2H <sub>2</sub> O	286, 205
[Hg(RPZ) <sub>2</sub> ].H <sub>2</sub> O	285, 206

The Cu(II) complex show a strong absorption band at 885 nm (11299 cm<sup>-1</sup>) in the visible region of the spectrum. This single absorption band indicates one allowed transition  $^2\text{T}_{2g} \leftarrow ^2\text{E}_g$ . The crystal field splitting,  $\Delta$  value associated with this electronic transition is 135.28 kJ mol<sup>-1</sup>. The low  $\Delta$

value suggests that copper compound has a tetrahedral geometry. All complexes show absorption bands in the UV region at 205-210 nm and 280-290 nm respectively. These bands suggest the presence of rabeprazole in the complexes. The shorter wavelengths are associated with  $\pi \rightarrow \pi^*$  transition in which electronic transition occur from filled  $\pi$  to empty  $\pi^*$  orbital of (>C=C<). The higher wavelength corresponds to  $n \rightarrow \pi^*$  transition where the electronic transition occur from filled nonbonding n to empty  $\pi^*$  orbital of (-C=N-).

*Thermal analysis:* The thermograms obtained from the thermogravimetric analysis of the complexes are plotted in Fig. 1 for comparative study. Cu(II), Cd(II) and Hg(II) complexes loss their weight at relatively low temperature. This accounts for the loss of water molecule(s). Except the copper complex, all other complexes melt with decomposition below 300°C. The decomposition process at higher temperature is rapid and continuous, and within the temperature range of 600-700°C the Cu(II) and Zn(II) complexes are converted to their corresponding metal oxides. There remains no end product in the case of the Hg(II) complex due to sublimation and volatilization of the decomposed products. The metal contents calculated from the end product are consistent with the formulae of the compounds. The differential scanning calorimetric studies (Fig. 2-5) show that the decomposition processes occur below 300°C are endothermic in nature.

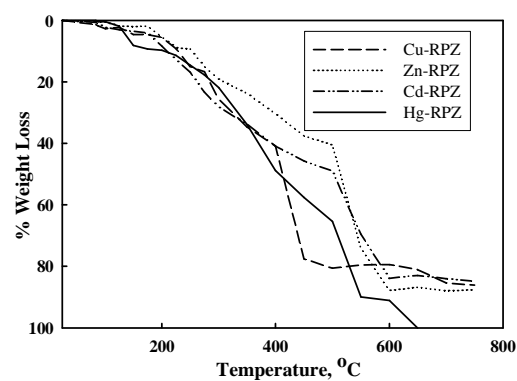


Fig. 1. QSTG graphs of Cu(II), Zn(II), Cd(II) and Hg(II) complexes of rabeprazole.

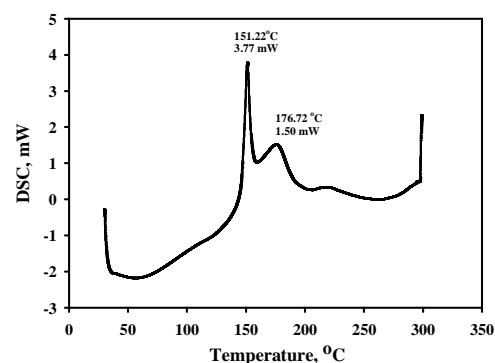


Fig. 2. DSC graph of  $[\text{Cu}(\text{RPZ})(\text{H}_2\text{O})\text{Cl}]$ .

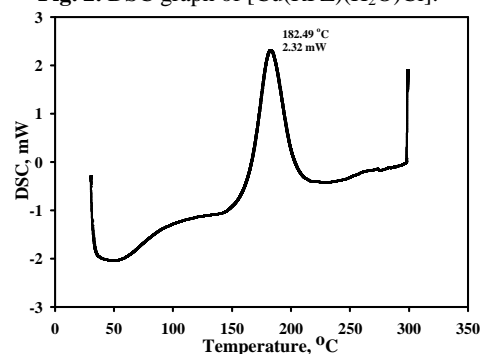


Fig. 3. DSC graph of  $[\text{Zn}(\text{RPZ})_2]$ .

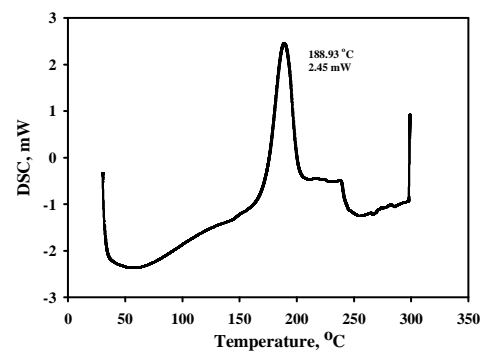


Fig. 4. DSC graph of  $[\text{Cd}(\text{RPZ})_2] \cdot 2\text{H}_2\text{O}$ .

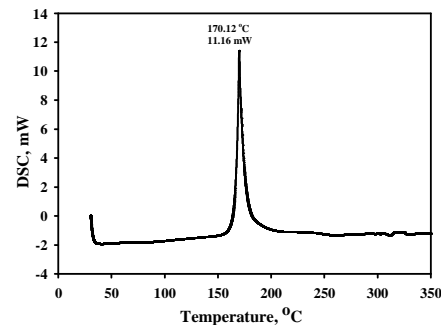


Fig. 5. DSC graph of  $[\text{Hg}(\text{RPZ})_2] \cdot \text{H}_2\text{O}$ .

**Magnetic measurement:** The magnetic susceptibilities of the prepared complexes were measured and the results are shown in Table 5. Cu(II) is a  $d^9$  ion with one unpaired electron either in  $e_g$  or  $t_{2g}$  level depending upon the geometry of the complex. The spin only value ( $\mu_{\text{eff}}$ ) calculated for a metal ion possessing one unpaired electron is 1.73 BM. However, the observed  $\mu_{\text{eff}}$  for the  $[\text{Cu}(\text{RPZ})(\text{H}_2\text{O})\text{Cl}]$  complex is 1.09 BM, significantly lower than the calculated value, the reason is not apparent. The magnetic measurements of zinc, cadmium and mercury complexes were also carried out. However, their observed magnetic moments are either negative or zero, indicating that they are diamagnetic with a +2 oxidation state of the metal ions. This is expected, because divalent Zn, Cd and Hg ions are all  $d^{10}$  system with paired up electrons.

Table 5. Magnetic susceptibility measurement data of copper complex.

Complex	$C_{\text{Bal}}$	l/cm	m/g	R	$R_o$	$\chi_g/\text{C.G.S. unit}$	T/K	$\mu_{\text{eff}}/\text{BM}$
$[\text{Cu}(\text{RPZ})(\text{H}_2\text{O})\text{Cl}]$	0.985	2.2	0.0895	9	-33	$1.058 \times 10^{-6}$	294	1.09

**X-ray Powder diffraction study:** X-ray powder diffraction photograph of  $[\text{Hg}(\text{RPZ})_2] \cdot \text{H}_2\text{O}$  complex was taken and d-values were measured. The d-values of  $[\text{Hg}(\text{RPZ})_2] \cdot \text{H}_2\text{O}$  are shown in Table 6. X-ray powder diffraction photograph of  $[\text{Cd}(\text{RPZ})_2] \cdot 2\text{H}_2\text{O}$  complex shows no line, rather a hump (Fig. 6). Copper and zinc complexes of rabeprazole show the similar type of X-ray powder photograph. This implies that the Cu(II), Zn(II) and Cd(II) complexes are very poorly crystalline substances.

Table 6. The d-values of  $[\text{Hg}(\text{RPZ})_2] \cdot \text{H}_2\text{O}$  complex.

Relative Intensity	$\sin\theta$	d values / $\text{\AA}$
Strong	0.0905	0.0697
Strong	0.1092	0.0841
Medium	0.1407	0.1084
Weak	0.1580	0.1217
Weak	0.1681	0.1295
Medium	0.1977	0.1523
Weak	0.2364	0.1821
Weak	0.2818	0.2170

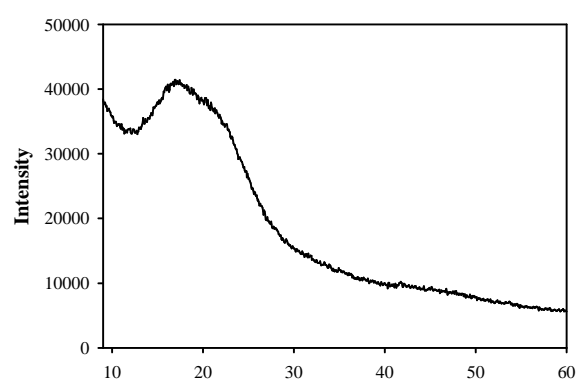


Fig. 6. X-ray powder photograph of  $[\text{Cd}(\text{RPZ})_2] \cdot 2\text{H}_2\text{O}$

**Antimicrobial activity:** In vitro antimicrobial activity of the Cu(II) and Zn(II) complexes of rabeprazole was tested against *Staphylococcus aureus*, *Escherichia coli*, *Shigelladysenteriae*, *Pseudomonas aureus*, *Shigellaboydii* and *Saccharomyces cerevaca*e in the Department of Pharmacy, University of Dhaka. The results (Table 7) show

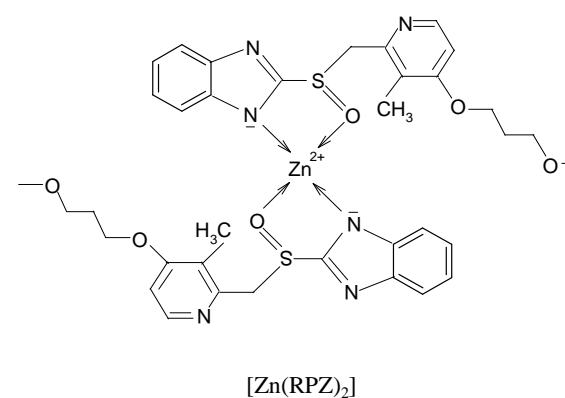
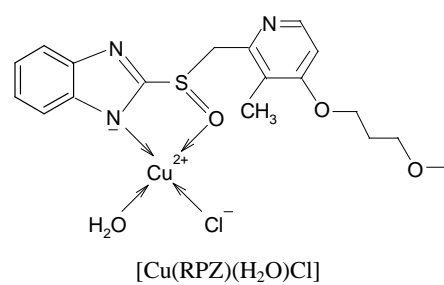
that the ligand itself some cases exhibit antimicrobial activity, but between Cu(II) and Zn(II) complexes of rabeprazole only the  $[\text{Zn}(\text{RPZ})_2]$  complex shows antimicrobial activity. This may be due to different degrees of chelation of RPZ with the metal ions.  $[\text{Cu}(\text{RPZ})(\text{H}_2\text{O})\text{Cl}]$  has a monoanionic RPZ which chelates with the Cu(II) ion whereas in  $[\text{Zn}(\text{RPZ})_2]$  there are two monoanionic RPZ chelates with Zn(II) ion. Upon chelation, the polarity of the Zn(II) ion is reduced due to the overlap of the ligand orbitals and partial sharing of the positive charge of the metal ion with donor groups. Chelation also allows the delocalization of  $\pi$ -electrons over the entire chelate ring and thus enhances the lipophilicity of the complex. The increased lipophilicity favours the permeation of the complex through the lipid layer of the cell and restricting proliferation of the microorganisms<sup>13</sup>. Cd(II) and Hg(II) are essentially toxic towards microbes. The toxicity of Cd(II) and Hg(II) ions are high, so that the quantification of their antimicrobial activities of RPZ complexes is not practicable.

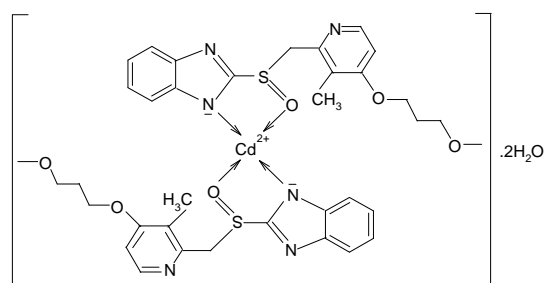
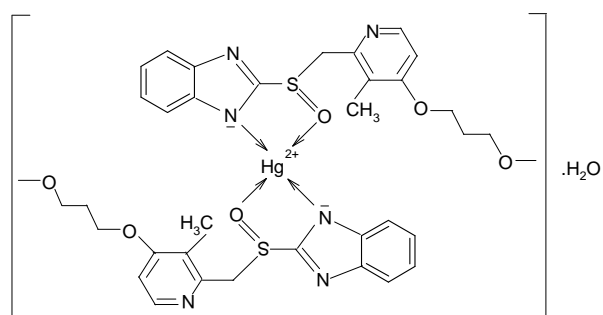
Table 7. Antimicrobial activity of rabeprazole and its copper and zinc complexes.

Microbiological Antibiotic Sensitivity Test	Standard Disc, Ciprofloxacin, 5 $\mu\text{g}/\text{disc}$	RPZ	$[\text{Cu}(\text{RPZ})(\text{H}_2\text{O})\text{Cl}]$	$[\text{Zn}(\text{RPZ})_2]$
<i>Bacillus cereus</i>	40	-	-	7
<i>Bacillus megaterium</i>	41	-	-	7
<i>Bacillus subtilis</i>	42	-	-	7
<i>Salmonella paratyphi</i>	42	-	-	7
<i>Salmonella typhi</i>	40	-	-	-
<i>Vibrio parahemolyticus</i>	40	-	-	8
<i>Vibrio mimicus</i>	40	-	-	8
<i>Staphylococcus aureus</i>	40	8	-	7
<i>Escherichia coli</i>	41	9	-	-
<i>Shigelladysenteriae</i>	41	8	-	-
<i>Pseudomonas aureus</i>	41	8	-	-
<i>Sarcinalutea</i>	40	-	-	-
<i>Shigellaboydii</i>	40	9	-	7
<i>Saccharomyces cerevaca</i> e	40	10	-	8
<i>Candida albicans</i>	40	-	-	8
<i>Aspergillusniger</i>	40	-	-	7

From the above discussions it can be concluded that the geometries of the studied compounds are tetrahedral around the central metal ion because PPIs,  $\text{H}_2\text{O}$  and  $\text{Cl}^-$  are all weak field ligands.

However, the structures of the compounds presented below are in square planar form for the clarity of the picture. The structural formulae of the studied complexes of rabeprazole are:



[Cd(RPZ)<sub>2</sub>].2H<sub>2</sub>O[Hg(RPZ)<sub>2</sub>].H<sub>2</sub>O

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