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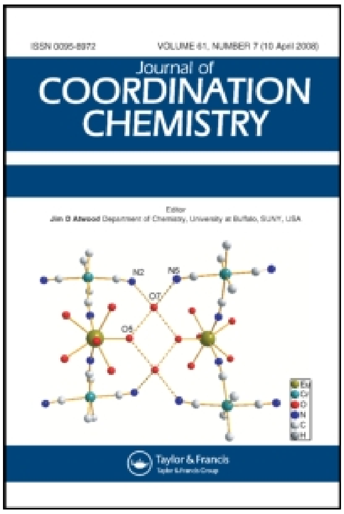

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Metal complexes of omeprazole. Preparation, spectroscopic and thermal characterization and biological activity

Gehad G. Mohamed[a]; F. A. Nour El-Dien[a]; Shaban M. Khalil[b]; Aliaa S. Mohammad[b]
[a] Faculty of Science, Chemistry Department, Cairo University, Giza, Egypt [b] National Organization for Drug Control and Research, Cairo, Egypt

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Metal complexes of omeprazole. Preparation, spectroscopic and thermal characterization and biological activity

GEHAD G. MOHAMED*†, F. A. NOUR EL-DIEN†, SHABAN M. KHALIL‡ and ALIAA S. MOHAMMAD‡

†Faculty of Science, Chemistry Department, Cairo University, Giza, Egypt
‡National Organization for Drug Control and Research, P.O. Box 29, Cairo, Egypt

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Metal complexes of omeprazole (OPZ) are prepared and characterized based on elemental analyses, IR, diffuse reflectance, magnetic moment, molar conductance and thermal analyses (TGA and DTA) techniques. From the elemental analyses, the complexes have the general formula $[M(L)_2]X_n$ [where $M = Cr(III)$ ($X = Cl$, $n = 3$), Ni(II) ($X = ClO_4$, $n = 2$) and Zn(II) ($X = Cl$, $n = 2$)], and $[M(L)_2(H_2O)_2]X_n \cdot yH_2O$ (where $M = Fe(III)$ ($X = Cl$, $n = 3$, $y = 0$), Co(II) ($X = Cl$ or ClO_4, $n = 2$, $y = 0$–4) and Ni(II) ($X = Cl$, $n = 2$, $y = 4$) and $[Cu(L)_2]Cl_2 \cdot H_2O$. The molar conductance data reveal that all the metal chelates are 3 : 1 electrolytes (for Cr(III) and Fe(III) complexes) and 2 : 1 (for the remaining complexes). IR spectra show that OPZ coordinates to the metal ions as neutral bidentate with ON donor sites of the pyridine–*N* and sulphone-*O*. The magnetic and solid reflectance spectra indicate octahedral ($FeCl_3$, $CoCl_2$, $CoClO_4$ and $NiCl_2$), square planar [Cu(II)] and tetrahedral [Mn(II), Cr(III), $NiClO_4$ and Zn(II)] structures. The thermal behavior of these chelates using thermogravimetric and differential thermal analyses (TGA and DTA) techniques indicate the hydrated complexes lose water of hydration followed immediately by decomposition of the anions and ligand molecules in the successive overlapping OPZ and its metal complexes are screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Aspergillus flavus* and fungi (*Candida albicans*). The activity data show the metal complexes to be more potent/antibacterial than the parent OPZ ligand against one or more bacterial species.

Keywords: Omeprazole; Metal complexes; IR; Molar conductance; Solid reflectance; Magnetic moment; Thermal analyses; Biological activity

1. Introduction

H^+/K^+ ATPase inhibitors, omeprazole (OPZ) and pantoprazole (PNZ) sodium, were effective in the treatment of gastric ulcers [1–3]. OPZ was also found to be unstable in neutral and weakly alkaline media with maximum stability at pH 11 [4, 5]. OPZ was used when inhibition of gastric acid secretion might be beneficial, including aspiration syndromes, dyspepsia, gastro-oesophagal reflux disease, peptic ulcer disease and Zollinger–Ellison syndrome [6].

The reported methods for determination of OPZ and PNZ included HPLC [4, 5, 7–10], HPTLC [11, 12], polarography [13–15], electrophoresis [16],

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*Corresponding author. Email: ggenidy@hotmail.com

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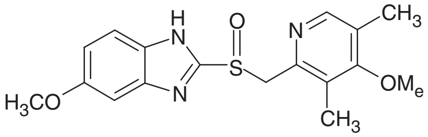


Figure 1. Structure of OPZ.

spectrophotometry [17–21], colourimetry [22, 23] and titrimetry [24, 25]. Very few methods using visible spectrophotometry have been reported [21] for determination of both drugs. Hence, sensitive and accurate visible spectrophotometric methods have been viewed as essential. The ability of both drugs to chelate certain metal ions, present in biological fluids, has not been previously studied except for the ternary complex formed between PNZ, Cu(II) and eosin [26]; a prospective work will be a bioavailability study using chelation procedures [27, 28].

However, in this work we prepare chelates of Mn(II), Cr(III), Fe(III), Co(II) (Cl and ClO_4), Ni(II) (Cl and ClO_4), Cu(II) and Zn(II) with OPZ. The solid chelates are characterized using physico-chemical methods such as elemental analyses (C, H, N, S and metal content), IR, magnetic moment and reflectance spectra, and thermal analyses (TGA and DTA). Biological activities of the complexes are studied. The structure of OPZ is given in figure 1.

2. Experimental

2.1. *Materials and reagents*

All chemicals were of analytical reagent grade (AR), including omeprazole (UniPharma), copper(II) chloride dihydrate (Prolabo), cobalt(II) and nickel(II) chloride hexahydrates (BDH), cobalt(II) and nickel(II) perchlorate hexahydrates (Sigma), zinc(II) chloride dihydrate (Ubichem), chromium(III) chloride hexahydrate (Sigma), manganese(II) chloride and ferric(III) chloride hexahydrate (Prolabo), zinc oxide, disodium salt of ethylenediaminetetraacetic acid; EDTA (Analar), ammonia solution (33% v/v) and ammonium chloride (El-Nasr Pharm. Chem. Co., Egypt). Solvents used include absolute ethyl alcohol, diethylether, and dimethylformamide (DMF). These solvents were spectroscopic pure from BDH and tested for their spectral purity. Hydrogen peroxide, hydrochloric and nitric acids (MERCK) were used. De-ionized water collected from all glass equipment was used in all preparations.

2.2. *Instruments*

The molar conductance of solid complexes in DMF was measured using a Sybron–Barnstead conductometer (Meter-PM.6, E = 3406). Microanalyses of the separated solid chelates for C, H, N and S were performed in the Microanalytical Center, Cairo University. The analyses were repeated twice to check the accuracy of the data. Infrared spectra were recorded on a Perkin–Elmer FT-IR type 1650 spectrophotometer in wavenumber region 4000–400 cm^{-1}. The spectra were recorded as KBr pellets. ^1H NMR spectra were recorded using 300 MHz Varian-Oxford Mercury. The solid reflectance spectra were measured on a Shimadzu 3101pc spectrophotometer.

The molar magnetic susceptibility was measured on powdered samples using the Faraday method; diamagnetic corrections were made by Pascal's constant and $Hg[Co(SCN)_4]$ was used as a calibrant. The thermogravimetric (TGA and DrTGA) and differential thermal (DTA) analyses were carried out in dynamic nitrogen atmosphere ($20\,mL\,min^{-1}$) with a heating rate of $10^\circ C\,min^{-1}$ using Shimadzu TGA-50H and DTA-50H thermal analyzers.

2.3. *Synthesis of metal complexes*

Metal complexes were prepared by the addition of hot solution (60°C) of the appropriate metal chloride or perchlorate salts (1 mmol) in an ethanol–water mixture (1 : 1, 25 mL) to hot solution (60°C) of OPZ (0.69 g, 2 mmol) in the same solvent (25 mL). The resulting mixture was stirred under reflux for one hour whereupon the complexes precipitated, were collected by filtration and washed with a 1 : 1 ethanol : water and diethyl ether. The analytical data for C, H, N and S were repeated twice.

2.4. *Biological activity*

A filter paper sterilized disc saturated with measured quantity of the sample is placed on a plate containing solid bacterial medium (nutrient agar broth) or fungal medium (Dox s medium) which has been heavily seeded with the spore suspension of the tested organism. After inoculation, the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism. 0.1 mL DMSO alone was used as a control under the same condition for each organism. The antibacterial activities can be calculated as a mean of three replicates [29, 30].

3. Results and discussion

Binary complexes of OPZ with metal ions have not been studied yet, but may affect the bioavailability of these drugs as certain metal ions are present in appreciable concentration in biological fluids [27].

3.1. *Composition and structures of metal complexes*

The results of elemental analyses listed in table 1 suggest $[M(L)_2]X_n$ (where $M = Cr(III)$ $(X = Cl,\ n = 3)$, Ni(II) $(X = ClO_4,\ n = 2)$ and Zn(II) $(X = Cl,\ n = 2)$, and $[M(L)_2(H_2O)_2]X_n \cdot yH_2O$ (where $M = Fe(III)$ $(X = Cl,\ n = 3,\ y = 0)$, Co(II) ($X = Cl$ or ClO_4, $n = 2$, $y = 0$–4) and Ni(II) $(X = Cl,\ n = 2,\ y = 4)$ and $[Cu(L)_2]Cl_2 \cdot H_2O$.

3.2. *Molar conductivity measurements*

The molar conductivities of 10^{-3} M of chelate solutions in DMF at 25°C (table 1) show values of 150–320 $\Omega^{-1}\,mol^{-1}\,cm^2$ indicating that all the metal chelates are electrolytes, and of the type 3 : 1 (for Cr(III) and Fe(III) complexes) and 2 : 1 (for the remaining complexes).

Table 1. Analytical and physical data of omeprazole metal complexes.

Complex	Color (% yield)	M.p. (°C)	% Found (Calcd) C	H	N	S	M	μ_{eff} (B.M.)	Λ_m (Ω^2 mol^{-1}cm^{-1})
$[Cr(L)_2]Cl_3$	Red	>300	48.42	4.59	9.99	8.07	6.33		320.0
$C_{34}H_{38}Cl_3CrN_6O_6S_2$	(75)		(48.04)	(4.47)	(9.89)	(7.54)	(6.12)		
$[Mn(L)_2]Cl_2 \cdot H_2O$	Brown	>300	48.84	4.56	10.44	7.54	6.29	4.82	185.0
$C_{34}H_{40}Cl_2N_6MnO_7S_2$	(70)		(48.93)	(4.80)	(10.07)	(7.68)	(6.60)		
$[Fe(L)_2(H_2O)_2]Cl_3$	Red	>300	45.61	4.41	9.92	7.57	5.98	5.75	345.0
$C_{34}H_{42}Cl_3FeN_6O_8S_2$	(78)		(45.88)	(4.72)	(9.45)	(7.20)	(6.30)		
$[Co(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$	Red	>300	43.67	5.51	8.91	7.12	6.70	5.86	168.0
$C_{34}H_{50}Cl_2CoN_6O_{12}S_2$	(68)		(43.93)	(5.38)	(9.04)	(6.89)	(6.35)		
$[Co(L)_2(H_2O)_2](ClO_4)_2$	Brown	>300	41.42	4.45	9.03	6.33	6.09	5.74	198.0
$C_{34}H_{42}Cl_2CoN_6O_{16}S_2$	(77)		(41.43)	(4.26)	(8.53)	(6.50)	(5.99)		
$[Ni(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$	Red	>300	44.00	5.41	8.89	7.09	6.05	3.54	150.0
$C_{34}H_{50}Cl_2NiN_6O_{12}S_2$	(66)		(43.93)	(5.38)	(9.04)	(6.89)	(6.35)		
$[Ni(L)_2](ClO_4)_2$	Red	>300	42.78	3.96	9.25	9.05	6.53	2.42	205.0
$C_{34}H_{38}Cl_2NiN_6O_6S_2$	(69)		(43.00)	(4.01)	(8.85)	(8.85)	(6.22)		
$[Cu(L)_2]Cl_2 \cdot H_2O$	Brown	>300	48.22	4.72	9.85	7.93	7.85	1.92	178.0
$C_{34}H_{40}Cl_2CuN_6O_7S_2$	(72)		(48.38)	(4.74)	(9.96)	(7.59)	(7.53)		
$[Zn(L)_2]Cl_2$	Brown	>300	49.77	4.90	10.38	7.46	8.12	Diam.	166.0
$C_{34}H_{38}Cl_2N_6O_6S_2Zn$	(80)		(49.35)	(4.60)	(10.16)	(7.74)	(7.86)		

Table 2. IR spectra (4000-400 cm^{-1}) of the OPZ ligand and its metal complexes.

Compound	ν(C=N)	ν(C=N) benzimidazole	ν(S=O)	δ(C=N)	ν(M–O)	ν(M–N)
OPZ	1626sh	1566m	1075sh	627m	–	–
$[Cr(L)_2]Cl_3$	1638m	1565m	1095m	625m	543s	497s
$[Mn(L)_2]Cl_2 \cdot H_2O$	1638sh	1560m	1077m	620m	542s	506w
$[Fe(L)_2(H_2O)_2]Cl_3$	1635sh	1563m	1069m	622m	544s	510s
$[Co(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$	1636sh	1562m	1089m	614sh	543s	498s
$[Co(L)_2(H_2O)_2](ClO_4)_2$	1633sh	1567br	1092br	624sh	542s	436s
$[Ni(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$	1635m	1565m	1080s	623m	546s	502s
$[Ni(L)_2](ClO_4)_2$	1639sh	1561m	1090s	621sh	540s	499s
$[Cu(L)_2]Cl_2 \cdot H_2O$	1636m	1564sh	1098m	621m	544w	496s
$[Zn(L)_2]Cl_2$	1638sh	1560sh	1087m	621sh	541s	502s

sh = sharp, m = medium, s = small, w = weak, br = broad.

3.3. *IR spectra and mode of bonding*

The IR data of the spectra of OPZ ligand and its complexes are listed in table 2. The band at 1626 cm^{-1} is assigned to ν(C=N) of pyridyl nitrogen and coordination is indicated by a 7–13 cm^{-1} shift to higher wavenumbers. The in-plane ring deformation is at 627 cm^{-1} in OPZ shifting to 614–625 cm^{-1} in the chelates [31]. Detecting the shift of the out-of-plane ρ(py) at 424 cm^{-1} is difficult because the spectra are rich for the complexes.

The υ(S=O) of the sulfone group is at 1075 cm^{-1} in the free ligand, shifting to lower wavenumbers (1069 cm^{-1}) or higher wavenumbers (1080–1095 cm^{-1}) in the complexes indicating participation of the sulfone oxygen in coordination (M–O) [32]. The υ(C=N) stretching vibration of the benzimidazole N3 is observed at 1566 cm^{-1} for OPZ and shifts to 1560–1567 cm^{-1} in the metal complexes may indicate a hydrogen bond [32]. The ligands under investigation have a band near 3050 cm^{-1} due to N–H stretching of the benzimidazole ring [33]. With a minor shift, this band remains in the same region in all the complexes, indicating its non-involvement in coordination [34, 35]. This band is masked with a very broad band in the region 3600–2600 cm^{-1} in the spectra of the complexes due to intermolecular hydrogen bonding in the solid state [33–35]. New bands are found in the spectra of the complexes in the regions 540–546 cm^{-1}, assigned to υ(M–O) and at 436–510 cm^{-1} assigned to υ(M–N).

OPZ and PNZ can form metal chelates between the imidazole-NH group, the oxygen of the sulfur dioxide side chain, or the N of the pyridine ring to yield six-membered ring chelates [27]. Our IR data indicate that OPZ is a neutral bidentate ligand coordinated to the metal ions via the pyridine N and sulfone O, while the small shift in IR bands due to NH is attributed to hydrogen bond formation rather than complex formation [33–35].

3.4. *^{1}H NMR spectra*

The ^{1}H NMR spectra of OPZ and its diamagnetic Zn(II) complex in DMSO-d_6 show the NH proton in OPZ at 8.30 ppm and in the Zn(II) complex at 8.355 ppm. The small shift means that the NH proton of OPZ ligand is not involved in chelation.

3.5. *Magnetic susceptibility and electronic spectra measurements*

From the diffuse reflectance spectrum it is observed that, the Fe(III) chelate exhibits a band at 21,290 cm^{-1}, assigned to the $^6A_{1g} \rightarrow T_{2g}$ (G) transition in octahedral geometry of the complex [36]. The $^6A_{1g} \rightarrow {}^5T_{1g}$ transition appears to be split into two bands at 17,540 and 14,998 cm^{-1}. The observed magnetic moment of Fe(III) complex is 5.75 B.M. These data are consistent with octahedral geometry [31, 37]. The spectrum also shows a band at 28,675 cm^{-1} attributed to ligand to metal charge transfer. The diffuse reflectance spectrum of the Mn(II) complex shows three bands at 16,445, 22,965 and 27,265 cm^{-1} assignable to $^6A_{1g} \rightarrow {}^4T_{1g}$, $^6A_{1g} \rightarrow {}^4T_{2g}$(G) and $^6A_{1g} \rightarrow {}^4T_{2g}$(D) respectively [37]. The magnetic moment value is 4.82 B.M., which indicates the presence of Mn(II) complex in tetrahedral structure.

The electronic spectrum of the Co(II) complexes with the general formula $[Co(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$ and $[Co(L)_2(H_2O)_2](ClO_4)_2$ give three bands at 15,696–15.360, 17,467–18.023 and 21,930–22.125 cm^{-1}, assigned to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (ν_1), $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ (ν_2) and $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$ (ν_3), respectively, suggesting octahedral Co(II) ion [31, 37]. The complexes have magnetic susceptibility values of 5.86 and 5.74 B.M. (table 1), respectively, consistent with octahedral geometry. The region at 24,560–24,625 cm^{-1} is a charge transfer band.

The Ni(II) complex, $[Ni(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$, has a room temperature magnetic moment value of 3.54 B.M. in the normal range for octahedral Ni(II) complexes [31, 37]. The electronic spectrum, in addition to π–π^* and n–π^* bands of ligand, displays three bands at ν_1, 16,090 cm^{-1}, $^3A_{2g} \rightarrow {}^3T_{2g}$, ν_2, 18,224 cm^{-1}, $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ and ν_3, 21,402 cm^{-1}, $^3A_{2g} \rightarrow {}^3T_{1g}(P)$. The spectrum also shows a band at 24,555 cm^{-1} from ligand to metal charge transfer. $[Ni(L)_2](ClO_4)_2$ has a lower magnetic susceptibility than expected for a tetrahedral complex [38, 39] due to the tetradentate H_2L causing planar distortion. The diffused reflectance spectrum shows bands at 6860 and

Table 3. Thermal analyses (TGA and DTA) data of OPZ and its metal complexes.

Compound	TG range (°C)	$n^{\#}$	% Found (Calcd) Mass loss	Total mass loss	Assignment	Metallic residue	DTA (°C)$^{\$}$
1	120–450	2	42.83 (42.56)		–Loss of $C_8H_7N_2O$	–	158(+), 175(−), 359(−), 430(+), 620(+)
	450–800	2	57.32 (57.17)	100 (99.88)	–Loss of $C_9H_{12}NO_2S$		
2	30–210	2	8.20 (8.60)		–Loss of 2HCl	1/2Cr_2O_3	50(+), 110(−), 209(−), 284(−), 503(−), 558(+), 590(+), 625(−)
	210–800	3	83.01 (82.43)	91.21 (91.03)	–Loss of HCl and 2L		
3	30–110	1	11.27 (10.91)		–Loss of 2HCl and H_2O	MnO	77(+), 110(+), 170(−), 220(−), 290(−), 450(+), 600(−), 657(−)
	110–800	2	80.91 (80.69)	92.18 (91.60)	–Loss of 2L		
4	30–200	2	15.97 (16.02)		–Loss of 3HCl and $2H_2O$	1/2Fe_2O_3	60(+), 270(−), 310(+), 504(−)
	200–700	2	75.53 (75.88)	91.50 (91.90)	–Loss of 2L		
5	30–115	1	7.49 (7.75)		–Loss of $4H_2O$	CoO	77(+), 122(+), 136(−), 475(+), 517(−), 583(−), 761(−)
	115–325	2	11.24 (11.52)		–Loss of $2H_2O$ and 2HCl		
	325–800	3	72.13 (72.65)	91.86 (91.92)	–Loss of 2L		
6	25–300	2	24.53 (24.07)		–Loss of $2HClO_4$ and $2H_2O$	CoO	50(−), 248(−), 310(+), 376(−), 470(+), 592
	300–900	2	68.20 (68.52)	92.73 (92.59)	–Loss of 2L		
7	25–230	2	20.08 (19.27)		–Loss of $4H_2O$, $2H_2O$ and 2HCl	NiO	86(+), 171(+), 297(−), 489(+), 547(−), 598(−)
	230–1000	3	72.28 (72.65)	92.36 (91.92)	–Loss of 2L		
8	30–300	2	21.50 (21.18)		–Loss of $2HClO_4$	NiO	42(−), 60(+), 155(−), 263(−), 430(+), 506(−), 565(−)
	300–700	2	71.43 (71.12)	92.93 (92.30)	–Loss of 2L		
9	25–110	1	2.38 (2.13)		–Loss of H_2O	CuO	60(+), 150(−), 200(−), 220(−), 330(−), 466(−)
	110–200	1	8.38 (8.42)		–Loss of 2HCl		
	200–800	3	79.78 (80.02)	90.75 (90.21)	–Loss of 2L		
10	30–200	2	9.05 (8.59)		–Loss of 2HCl	ZnO	80(+), 270(+), 310(−), 500(+), 578(−), 670(−)
	200–800	3	81.62 (81.70)	90.75 (90.21)	–Loss of 2L		

1: OPZ; **2**: $[Cr(L)_2]Cl_3$; **3**: $[Mn(L)_2]Cl_2 \cdot H_2O$; **4**: $[Fe(L)_2(H_2O)_2]Cl_3$; **5**: $[Co(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$; **6**: $[Co(L)_2(H_2O)_2](ClO_4)_2$; **7**: $[Ni(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$; **8**: $[Ni(L)_2](ClO_4)_2$; **9**: $[Cu(L)_2]Cl_2 \cdot H_2O$; **10**: $[Zn(L)_2]Cl_2$.

$^{\#}n$ = number of decomposition steps.

$^{\$}$(+) = endothermic, (−) = exothermic.

17,230 cm^{-1} assigned to $^3T_1 \rightarrow {}^3A_1$ and $^3T_1 \rightarrow {}^3T_1(p)$ transitions, respectively, confirming tetrahedral Ni complex [37, 38].

The μ_{eff} value of the Cu complex is 1.92 B.M., indicative of square-planar geometry, confirmed by only one band in the spectrum at 13,889 with two shoulders on either side at 18,868 and 11,905 cm^{-1}. These are assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$, $^2B_{1g} \rightarrow {}^2B_{2g}$ and $^2B_{1g} \rightarrow {}^2E_{2g}$ transitions, respectively [39].

The Zn(II) complex is diamagnetic and tetrahedral geometry was proposed for this complex.

3.6. *Thermal analyses (TGA, DrTG and DTA)*

In the present investigation, heating rates are suitably controlled at 10°C min^{-1} under nitrogen atmosphere and the weight loss is measured from the ambient temperature up to ≅1000°C. The data are listed and assigned in table 3. The weight losses for each chelate are calculated within the corresponding temperature ranges. The different thermodynamic parameters are listed in Supplementary Material with discussions of each complex.

The data present in table 3 show the differential thermal analysis (DTA) of the complexes. It is shown from these data that the loss of hydrated and coordinated water molecules, anions and ligand molecules are accompanied by endothermic or exothermic processes within the temperature ranges given in table 3.

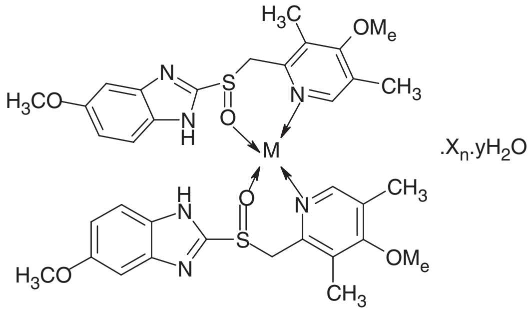
3.7. *Structural interpretation*

The structures of the complexes of OPZ with Cr(III), Mn(II), Fe(III), Co(II) (Cl and ClO_4), Ni(II) (Cl and ClO_4), Cu(II) and Zn(II) ions are confirmed by the elemental analyses, IR, molar conductance, magnetic, solid reflectance, 1H NMR and thermal analyses (TGA and DTA) data. OPZ is a neutral bidentate ligand coordinated to the metal ions via the pyridine-N and sulfone-O. The molar conductance data indicate that the complexes are electrolytes. The structures are shown in figure 2.

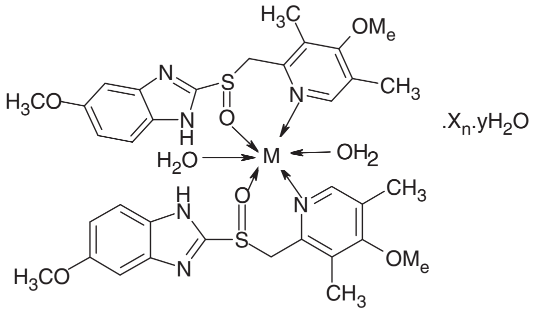
3.8. *Biological activity*

Interest in transition metal complexes containing N-donor ligands has increased to obtain metal-based drugs exhibiting a high biological activity with reduced toxicity [36]; benzimidazole derivatives of transition metal complexes have been extensively investigated [40]. One of the most attractive features of these ligands is their structural similarity with pyrimidine and purine type nucleobases. The data show that OPZ and its metal complexes have the capacity of inhibiting the metabolic growth of bacteria and fungi to different extents. The activities of all the tested complexes may be explained on the basis of chelation theory [41].

In testing the antibacterial activity of OPZ and its metal complexes, we used more than one test organism to increase the chance of detecting antibiotic principles in tested materials. The sensitivity of a microorganism to antibiotics and other antimicrobial agents is determined by assay plates incubated at 28°C for two days for yeasts and at



M = Cr(III); X = Cl, n = 3, y = 0,
Mn(II); X = Cl, n = 2, y = 1,
Cu(II); X = Cl, n = 2, y = 1,
Ni(II); X = ClO_4, n = 2, y = 0,
Zn(II); X = Cl, n = 2, y = 0,



M = Fe(III); X = Cl, n = 3, y = 0,
Co(II); X = Cl, n = 2, y = 4,
Co(II); X = ClO_4, n = 2, y = 0,
Ni(II); X = Cl, n = 2, y = 4,
Zn(II); X = Cl, n = 2, y = 0,

Figure 2. Structure of metal complexes of OPZ.

Table 4. Antibacterial and antifungal activity of OPZ and its metal complexes.

	Inhibition zone diameter (mm mg^{-1} sample)			
Sample	*E. coli*	*S. aureus*	*A. flavus*	*C. albicans*
OPZ	16	14	0.0	0.0
$[Cr(L)_2]Cl_3$	15	14	0.0	13
$[Mn(L)_2]Cl_2 \cdot H_2O$	13	13	0.0	13
$[Fe(L)_2(H_2O)_2]Cl_3$	15	13	13	14
$[Co(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$	14	14	13	13
$[Co(L)_2(H_2O)_2](ClO_4)_2$	15	15	11	14
$[Ni(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$	16	15	0.0	13
$[Ni(L)_2](ClO_4)_2$	13	12	0.0	14
$[Cu(L)_2]Cl_2 \cdot H_2O$	15	13	12	12
$[Zn(L)_2]Cl_2$	16	13	0.0	0.0
Tetracycline (antibacterial agent)	32	34	0.0	0.0
Amphotricine B (antifungal agent)	0.0	0.0	17	21

37°C for one day for bacteria. All of the tested compounds show biological activity against different types of Gram-positive and Gram-negative bacteria. The data are listed in table 4 showing:

1. Biological activity against gram positive bacteria follow the order: OPZ = $[Ni(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O = [Zn(L)_2]Cl_2 > [Cr(L)_2]Cl_3 = [Fe(L)_2(H_2O)_2]Cl_3 = [Co(L)_2(H_2O)_2](ClO_4)_2 = [Cu(L)_2]Cl_2 \cdot H_2O > [Co(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O > [Mn(L)_2]Cl_2 \cdot H_2O = [Ni(L)_2](ClO_4)_2$. The biological activity of the metal complexes are comparable with the parent OPZ drug, which means that the complexes can have the same action as the parent drug.
2. Biological activity against gram negative bacteria follow the order: $[Co(L)_2(H_2O)_2](ClO_4)_2 = [Ni(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O >$ OPZ $= [Cr(L)_2]Cl_3 = [Co(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O > [Mn(L)_2]Cl_2 \cdot H_2O = [Fe(L)_2(H_2O)_2]Cl_3 = [Cu(L)_2]Cl_2 \cdot H_2O = [Zn(L)_2]Cl_2 > [Ni(L)_2](ClO_4)_2$.
3. $[Fe(L)_2(H_2O)_2]Cl_3$, $[Co(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$, $[Co(L)_2(H_2O)_2](ClO_4)_2$, $[Cu(L)_2]Cl_2 \cdot H_2O$, $[Cr(L)_2]Cl_3$, $[Mn(L)_2]Cl_2 \cdot H_2O$, $[Ni(L)_2(H_2O)_2]Cl_2 \cdot 4H_2O$ and $[Ni(L)_2](ClO_4)_2$ show antifungal activity comparable to the standard test sample. The parent OPZ does not show antifungal activity which make these complexes of interest.

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