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Original article

Synthesis, characterization of copper(II), cobalt(II), nickel(II), zinc(II) and cadmium(II) complexes of [7-hydroxy-4-methyl-8-coumarinyl]glycine and a comparitive study of their microbial activities

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Abstract

A new Mannich base, [7-hydroxy-4-methyl-8-coumarinyl]glycine [$MCGH_2$], has been prepared by the condensation of 7-hydroxy-4-methyl-coumarin with glycine and formaldehyde. Its conformational changes on complexation with transition metal ions [copper(II), cobalt(II), nickel(II), zinc(II) and cadmium(II)] have been studied on the basis of elemental analysis, conductivity measurements, spectral (infrared, ^{1}H NMR, electronic, EPR), magnetic and thermogravimetric studies. The infrared spectral studies of all the complexes reveal that the ligand has coordinated through −NH and two hydroxyl groups. The conductance data of the complexes suggest them to be non-electrolytes. Fluorescence property of the ligand and its metal complexes was studied and concluded that the ligand $MCGH_2$ can be a potential candidate for the determination of zinc(II) and cadmium(II) at room temperature by fluorimetric method. The antimicrobial activity of all the compounds was studied against Gram negative (*Escherichia coli*) and Gram positive (*Bacillus cirroflagellosus*) bacteria and fungi, *Aspergillus niger* and *Candida albicans*. It was observed that the coordination of metal ion has a pronounced effect on the microbial activities of the ligand. All the metal complexes have shown higher antimicrobial effect than the free ligand.

Keywords: Coumarin; Glycine; Transition metal complexes; Antimicrobial activity

1. Introduction

Coumarin (1,2-benzopyrone) is structurally the least complex member of a class of compounds known as benzopyrones [1]. Nowadays, natural and synthetic coumarin derivatives represent an important group of organic compounds that are used as antibiotics [2,3], fungicides [4], anti-inflammatory [5], anticoagulant [6] and antitumor agents [7–10]. Regarding their high fluorescence ability, they are widely used as optical whitening agents, brighteners, laser dyes and also as fluorescent probes [11] in biology and medicine [12]. More recently, coumarin derivatives have been evaluated in the treatment of human immunodeficiency virus, due to their ability to inhibit human immunodeficiency virus integrase [13,14]. Hydroxycinnamic acids, related to coumarins, seem to be inhibitory to Gram positive bacteria [15]. Also, phytoalexins, which are hydroxylated derivatives of coumarins, are produced in carrots in response to fungal infection and can be presumed to have antifungal activity [16]. General antimicrobial activity was documented in Woodruff (*Galium odoratum*) extracts [17].

Interest in metal–coumarin complexes has arisen from the search for novel lead compounds along with the desire to improve the pharmacological profile. Kokotos et al. [18] have synthesized a number of amino-coumarin–platinum(II) complexes and evaluated their in vitro anti-proliferative activity using a colonic carcinoma cell line (Caco-2). Creaven et al. have also studied metal complexes of coumarin derivatives as antimicrobial agents [19].

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Coumarins combined with amino acids have attracted significant attention as appropriate ligands for the synthesis of new coordination compounds. The coumarin derivatives have been the focus of our recent research concerning the design of new antimicrobial agents. In the present work, we have synthesized and characterized Cu(II), Ni(II), Co(II), Mn(II), Zn(II) and Cd(II) complexes of [7-hydroxy-4-methyl-8-coumarinyl]glycine. The antimicrobial activity of the free ligand, its metal complexes and the simple salts were screened against *Escherichia coli* (Gram negative) and *Bacillus cirroflagellosus* (Gram positive) bacteria and fungi, *Aspergillus niger* and *Candida albicans*.

2. Chemistry

2.1. Methods

2.1.1. Synthesis of the ligand

The preparation of [7-hydroxy-4-methyl-8-coumarinyl]glycine [$MCGH_2$] involves the following steps (Scheme 1).

2.1.1.1. Preparation of 7-hydroxy-4-methyl coumarin [HMC]. A mixture of polyphosphoric acid (160 g, obtained by dissolving 126 g of P_2O_5 in 70 g of orthophosphoric acid), resorcinol (11 g, 0.1 mol) and ethylacetoacetate (13 g, 0.1 mol) is stirred and heated at 75–80 °C for 20 min. It is poured into ice water, the solid separated is filtered, washed with cold water and recrystallised from dilute ethanol [20].

Yield: 97%. M.P.: 184 °C.

2.1.1.2. Preparation of $MCGH_2$. A mixture of HMC (17.6 g, 0.1 mol) and glycine (7.5 g, 0.1 mol) is taken in 100 ml of 80% ethanol and 3 ml formaldehyde is added. The resulting mixture is refluxed on a water bath for 3 h. The white solid separated is filtered and washed with ethanol. It is recrystallised from DMF [21].

Yield: 80%. M.P.: 250 °C.

2.1.2. Synthesis of metal(II) complexes of $MCGH_2$

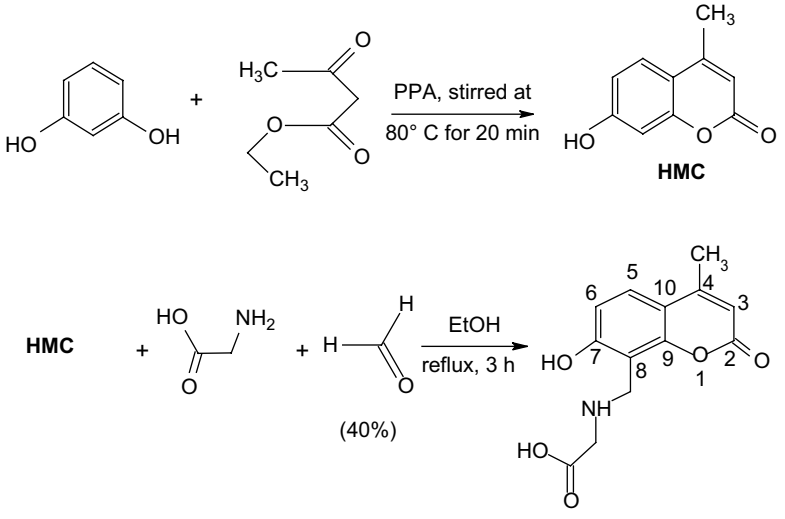
$MCGH_2$ (2.63 g, 0.01 mol) is dissolved in 20 ml of 10% aq. DMF and metal(II) chloride [0.01 mol, M = Cu(II), Ni(II), Co(II), Zn(II), Mn(II), Cd(II)] was added. The resulting mixture was refluxed for 4–5 h, the precipitate obtained was filtered, washed with aq. DMF and ethanol till it is free from any unreacted ligand and the metal salt.

3. Pharmacology

The antimicrobial activity of all the compounds was studied against Gram negative (*E. coli*) and Gram positive (*B. cirroflagellosus*) bacteria and fungi, *A. niger* and *C. albicans*. The nutrient broth was prepared by dissolving peptone (0.5%), yeast extract (0.15%), beef extract (0.15%), sodium chloride (0.36%) and monopotassium phosphate (0.13%) in distilled water (100 ml). The pH of the solution was adjusted to 7.2 by adding sodium hydroxide solution (4%) and the resulting solution was autoclaved for 20 min at 15 psi. Each test sample (5 mg) was dissolved in DMSO (1 ml) and 0.1 ml of this solution (50 μgm) was used for testing.

4. Results and discussions

The complexes were characterized by elemental analysis. All the complexes were stable in air, insoluble in methanol, ethanol, benzene, chloroform and DMF but soluble in DMSO. The water content in the complexes was determined by TGA. The formation of complexes was confirmed by IR-spectroscopy, ^{1}H NMR-spectroscopy and TGA. Table 1 shows the analytical data of the complexes, serving as a basis for the determination of their empirical formula. The results thus obtained are in agreement with metal/ligand ratio 1:1 in the investigated complexes. The data of thermogravimetric analysis of all the complexes are presented in Table 2. The mass spectrum (Fig. 2) of [Co(MCG)(H_2O)$_3$] shows the



Scheme 1.

Table 1
Analytical, conductance and magnetic moment data of $MCGH_2$ and its complexes

Compound	MF	FW	Found (Calcd.) %				Λ_M (mho cm^2 mol^{-1})	BM (μ_{eff})
			C	H	N	M		
$MCGH_2$	$C_{13}H_{13}O_5N$	263	59.20 (59.31)	4.90 (4.94)	5.28 (5.32)	–	–	–
$[Cu(MCG)(H_2O)_3]$	$CuC_{13}H_{17}O_8N$	378.5	41.00 (41.21)	4.32 (4.49)	3.60 (3.69)	16.70 (16.77)	8.61	1.78
$[Co(MCG)(H_2O)_3]$	$CoC_{13}H_{17}O_8N$	373.9	41.30 (41.72)	4.25 (4.54)	3.68 (3.74)	15.62 (15.75)	10.56	4.87
$[Ni(MCG)(H_2O)_3]$	$NiC_{13}H_{17}O_8N$	373.6	41.60 (41.75)	4.43 (4.55)	3.60 (3.74)	15.58 (15.68)	11.72	2.23
$[Mn(MCG)(H_2O)_3]$	$MnC_{13}H_{17}O_8N$	368.9	42.18 (42.28)	4.32 (4.60)	3.70 (3.79)	14.60 (14.88)	10.87	4.20
$[Zn(MCG)(H_2O)_3]$	$ZnC_{13}H_{17}O_8N$	379.3	41.00 (41.12)	4.40 (4.48)	3.59 (3.69)	17.19 (17.21)	14.45	Diamag.
$[Cd(MCG)(H_2O)_3]$	$CdC_{13}H_{17}O_8N$	426.4	36.33 (36.58)	3.97 (3.98)	3.13 (3.28)	26.29 (26.36)	5.45	Diamag.

Values in the parentheses are calculated, Diamag. = diamagnetic, MF = molecular formula, FW = formula weight.

molecular ion peak at 374, which supplements the proposed composition for the complex.

The important infrared frequencies along with the tentative assignments of the ligand and its respective complexes are presented in Table 3.

A broad band, characteristic of ν(OH) of coordinated water, was observed in the range 3400–3550 cm^{-1} followed by another band at 803–810 cm^{-1} in the spectra of the complexes. A comparison of the infrared spectra of the ligand and the respective complexes reveals the disappearance of absorption bands associated with the stretching OH of the phenolic group, indicating the loss of phenolic proton on complexation, forming metal–oxygen bond. This was further supported by the increase in ν(C–O) frequency by 60–96 cm^{-1} [22]. The ν(NH) group exhibits shift towards lower wavenumber values on complexation which may be taken as suggestion for the participation of the NH group in coordination. The bands observed at 1574–1597 and 1389–1394 cm^{-1} were assigned to $\nu(COO^-)_{asym}$ and $\nu(COO^-)_{sym}$ of carboxylate group, respectively. The magnitude of separation between these two vibrations (200–347 cm^{-1}) suggests the coordination of carboxylate group in unidentate fashion [23]. This suggests that the hydroxyl group of –COOH has involved in coordination via deprotonation. In all the complexes, the lactone carbonyl has shifted to lower energy (25–60 cm^{-1}), due to the strong intermolecular association between the lactone carbonyl and –NH in the solid state.

The electronic spectrum of the present Cu(II) complex in DMSO shows a lower energy band at 14,577 cm^{-1} and is assigned to $^2E_g \rightarrow {}^2T_{2g}$. The band at 24,570 cm^{-1} can be attributed to ligand–metal charge transfer transition. Another band observed at 27,322 cm^{-1} is due to the symmetry forbidden charge transfer transition [24,25]. From these observations one can conclude that the Cu(II) complex has a distorted octahedral geometry [24,25]. The electronic spectrum of Ni(II) complex shows the bands at 16,583 and 26,315 cm^{-1} assigned to $^3A_{2g} \rightarrow {}^3T_{1g}$ (F) and $^3A_{2g} \rightarrow {}^3T_{1g}$ (P), respectively, for an octahedral geometry [24,25] around Ni(II) ion. The Co(II) complex exhibits two bands at 10,111 and 15,060 cm^{-1} assigned to $^4T_{1g} \rightarrow {}^4T_{2g}$ and $^4T_{1g} \rightarrow {}^4A_{2g}$, respectively, which suggests an octahedral geometry [24,25] for the complex.

The room temperature magnetic moment values are summarized in Table 1. The Cu(II) complex exhibits an effective magnetic moment of 1.75 BM, expected for $S = 1/2$ system. A magnetic moment value of 4.87 BM for Co(II) complex and 2.23 BM for Ni(II) complex is typical of octahedral environments around the metal centers [26]. The Mn(II) complex has a magnetic moment of 4.20 BM which suggests a spin free complex.

The ^{1}H NMR spectrum of the ligand shows a doublet at 2.4 ppm due to $-CH_3$ group. The aromatic protons of C6 and C5 showed a pair of doublets at 6.80, 6.90 and 7.50, 7.60 ppm, respectively [27]. The singlet at 6.20 ppm is due to the aromatic C3 proton (Fig. 1a). Signals at 4.20 and 3.20 ppm were attributed to two methylene groups.

Table 2
Thermogravimetric characteristics of the complexes under study

Compound	Process	Temp. (°C)	Product	Mass %		No. of moles	Residue %	
				Calcd.	Exptl.		Calcd.	Exptl.
$[Co(MCG)(H_2O)_3]$	Decomposition of coordination sphere	160–260	H_2O	14.44	14.12	3	20.03	20.00
		260–530	L	69.80	69.77	1		
$[Cu(MCG)(H_2O)_3]$	Decomposition of coordination sphere	180–280	H_2O	14.26	14.15	3	21.00	20.95
		280–550	L	68.95	68.88	1		
$[Ni(MCG)(H_2O)_3]$	Decomposition of coordination sphere	170–260	H_2O	14.45	14.25	3	19.99	19.50
		260–600	L	69.86	69.68	1		
$[Mn(MCG)(H_2O)_3]$	Decomposition of coordination sphere	190–280	H_2O	14.63	14.60	3	19.24	19.10
		280–580	L	70.75	70.63	1		
$[Zn(MCG)(H_2O)_3]$	Decomposition of coordination sphere	170–250	H_2O	14.23	14.19	3	21.45	21.20
		250–520	L	68.81	68.70	1		
$[Cd(MCG)(H_2O)_3]$	Decomposition of coordination sphere	190–300	H_2O	12.66	12.50	3	30.11	30.00
		300–650	L	61.21	61.12	1		

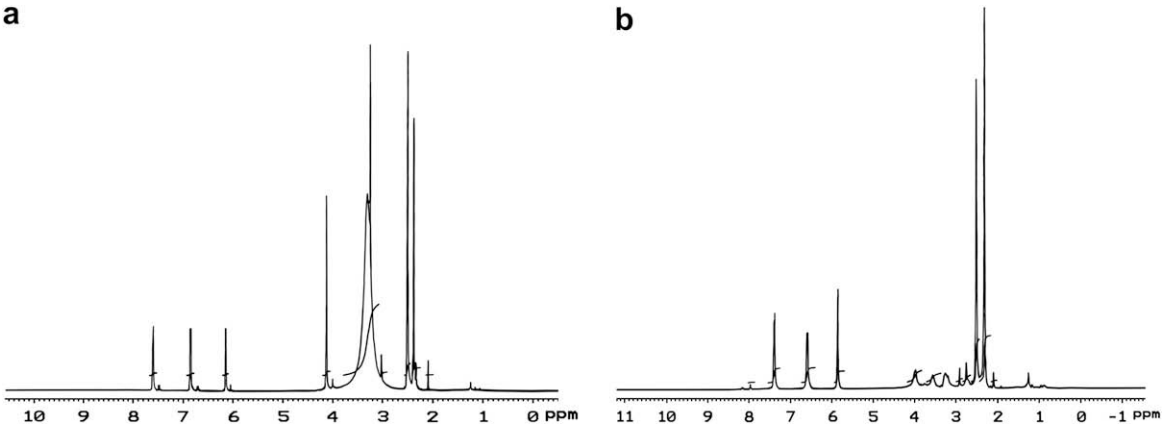


Fig. 1. ^{1}H NMR spectra of ligand (a) and its Zn(II) complex (b).

In the ^{1}H NMR spectrum of Zn(II) complex, a signal at 2.40 ppm due to $-CH_3$ group remained unaltered. The aromatic protons C6, C5 and C3 were observed at 6.60, 7.40 and 5.85 ppm, respectively. The signal due to methylene protons (NH$-CH_2-$C$=$O) shifted from 4.2 to 4.00 ppm (Fig. 1b).

The ESR spectra of the Cu(II) complex both at 300 and 77 K show an intense absorption band at high field, which is isotropic due to the tumbling motion of the molecules. The 'g_{iso}' values at 300 and 77 K are 2.11 and 2.12, respectively. Mononuclear nature of the complex was evident from the absence of a half field signal due to the $m_s = \pm 2$ transitions, ruling out any Cu–Cu interaction [28]. The ESR spectrum of the Mn(II) complex shows a broad isotropic signal with g_{iso} values of 2.04 and 2.00 at room temperature and liquid nitrogen temperature, respectively.

The origin of line broadening in Mn(II) complexes is attributed to forbidden transitions and also due to spin relaxation [29,30].

The fluorescence properties of the ligand, $MCGH_2$ and its complexes of Zn(II), Cd(II), Cu(II), Co(II), Ni(II) and Mn(II) have been investigated at the concentrations of 10^{-3}, 10^{-4} and 10^{-5} M. The fluorescence intensity of the ligand is quenched upon complexation with metal ions such as Cu(II), Co(II), Ni(II) and Mn(II) but enhanced four fold on complexation with Zn(II) and Cd(II) in DMSO. These properties could be exploited for the detection and spectrofluorimetric determination of Zn(II) and Cd(II) in real, environmental, biological and pharmaceutical formulations.

From the antimicrobial screening results (Table 4), it was seen that the ligand is moderately active against bacteria, *E. coli*, *B. cirroflagellosus* and fungi, *A. niger*, *C. albicans*. All the complexes have shown higher activity against both bacteria and fungi. The activity of the ligand as well as that of metal salts has increased on complexation. Among the complexes, the antifungal activity of Zn(II) and Cd(II) complexes is greater than that of the Greseofulvin, the antifungal drug in use. The antibacterial activity of Ni(II) complex is equal to that of Norfloxacin, the antibacterial drug in use, while the activity of Co(II) complex is more than the standard itself.

5. Conclusions

The ligand $MCGH_2$ was obtained by coupling 7-hydroxy-4-methyl coumarin with glycine and 40% formaldehyde. The ligand forms complexes with metal chlorides of 1:1 (M:L) stoichiometry with empirical formula $[M^I(MCG)(H_2O)_3]$ where M^I = Cu(II), Co(II), Ni(II), Mn(II), Zn(II) and Cd(II). The ligand behaves in a tridentate fashion with deprotonated OH, COOH groups along with NH group as the ligating sites (Fig. 3). All the complexes are having octahedral geometries. As a synergic effect, the metal complexes have shown enhanced activity against both the bacteria and fungi used.

6. Experimental protocols

6.1. Chemistry

Reagents used: all the solvents used in the present investigation are of Anala'R' grade and were used without further

Table 3
IR spectral data of $MCGH_2$ and its metal complexes

Compound	ν(OH) (H_2O)	ν(OH) (phenol)	ν(OH) (acid)	ν(NH)	$\nu(COO^-)$ (asym)	$\nu(COO^-)$ (sym)	Δ	δ(C–O)	δ(OH) (H_2O)
$MCGH_2$	–	3344	obsc.	obsc.	–	–	–	1227	–
$[Cu(MCG)(H_2O)_3]$	3543	–	–	3246	1593	1276	317	1276	810
$[Co(MCG)(H_2O)_3]$	3434	–	–	3248	1574	1227	347	1313	817
$[Ni(MCG)(H_2O)_3]$	3411	–	–	3240	1592	1283	309	1283	807
$[Mn(MCG)(H_2O)_3]$	3598	–	–	3252	1597	1295	296	1288	806
$[Zn(MCG)(H_2O)_3]$	3431	–	–	3246	1591	1289	302	1289	807
$[Cd(MCG)(H_2O)_3]$	3434	–	–	3250	1589	1290	200	1290	803

obsc. = obscured; [ν(OH) (acidic) and ν(NH) groups have obscured with ν(OH) of phenolic group].

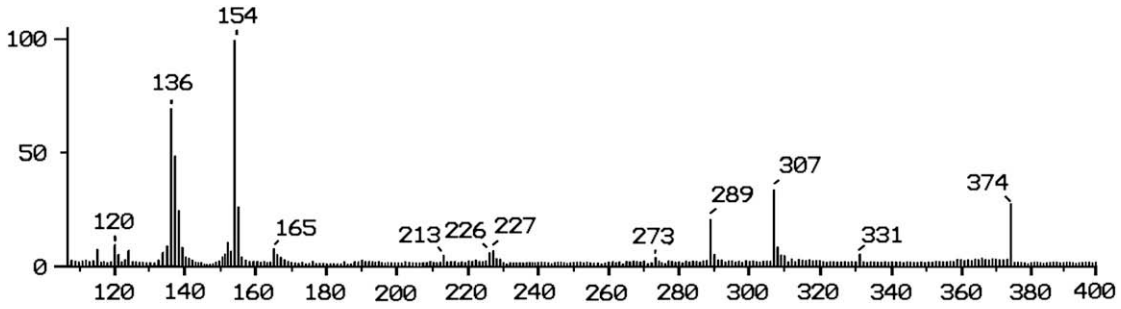


Fig. 2. Mass spectrum of $[Co(MCG)(H_2O)_3]$.

purification, while resorcinol, ethylacetoacetate and glycine were procured from s.d. Fine-chem Ltd, India.

The metal content of the complexes was determined by EDTA titration after wet ashing with a mixture of HCl and $HClO_4$. The chloride content of the complexes was determined as AgCl gravimetrically [31]. The carbon, hydrogen and nitrogen contents of each sample were determined using a Heraus CHN rapid analyzer. IR spectra in the 4000–400 cm^{-1} range were measured with Thermo Nicolet 320 FT-IR spectrometer using KBr discs. ^1H NMR spectra were recorded in DMSO-d_6 as the solvent at 400 MHz with a BRUKER AMX 400 spectrometer using tetramethylsilane (TMS) as an internal reference. UV–vis spectra of the complexes were recorded on a Varian CARY 50 Bio UV–vis spectrophotometer. The magnetic susceptibility measurements were carried out on a Faraday balance using $Hg[Co(NCS)_4]$ as the calibrant and diamagnetic corrections were made by direct weighing of the ligand for diamagnetic pull. Conductance measurements were recorded in DMSO (10^{-3} M) using Elico conductivity bridge type CM-82, provided with a dip type conductivity cell fitted with platinum electrodes. EPR spectra were recorded on Varian E-4 X-band spectrometer using tetracyanoethylene (TCNE) as 'g' ($g = 2.0027$) marker at room temperature and also at liquid nitrogen temperature. The thermal studies of the complexes were carried on Mettler Toledo TGA/SDTA851[e] with star[e] software, under nitrogen atmosphere with a heating rate of 10 °C/min in the temperature range of 50–1000 °C. FAB mass was obtained on a Thermofinnigan1020 automated GCMS. The fluorescence spectra of the compounds were recorded in DMF and DMSO at different temperatures (16, 26, 36 °C), and different concentrations (10^{-3}, 10^{-4}, 10^{-5} M) on Hitachi spectrometer model F-2000 equipped with a 150 W xenon lamp with a slit width of 10 mm.

Table 4
Antibacterial and antifungal activities of $MCGH_2$ and its metal complexes

Compound	(Zone of inhibition in mm)			
	Antibacterial		Antifungal	
	B. C.	E. C.	A. N.	C. A.
$CuCl_2 \cdot 2H_2O$	16	21	28	27
$CoCl_2 \cdot 4H_2O$	28	28	28	28
$NiCl_2 \cdot 6H_2O$	26	26	22	22
$MnCl_2 \cdot 6H_2O$	20	20	21	21
$ZnCl_2 \cdot 2H_2O$	22	25	32	35
$CdCl_2 \cdot 2H_2O$	25	21	36	36
$MCGH_2$	18	18	17	17
$[Cu(MCG)(H_2O)_3]$	25	25	30	30
$[Co(MCG)(H_2O)_3]$	32	32	30	30
$[Ni(MCG)(H_2O)_3]$	29	29	25	24
$[Mn(MCG)(H_2O)_3]$	22	21	22	22
$[Zn(MCG)(H_2O)_3]$	24	26	40	40
$[Cd(MCG)(H_2O)_3]$	25	25	36	37
Norfloxacin	29	29	–	–
Griseofulvin	–	–	30	30

E. C. = *Escherichia coli*, B. C. = *Bacillus cirroflagellosus*, A. N. = *Aspergillus niger*, C. A. = *Candida albicans*.
Key to interpretation: less than 10 mm = inactive, 10–15 mm = weakly active, 15–20 mm = moderately active; more than 20 mm = highly active.

6.2. Biological evaluation

One day prior to the experiment, the bacterial and fungal cultures were inoculated in nutrient broth (inoculation medium) and incubated overnight at 37 °C. Inoculation medium containing 24 h grown culture was added aseptically to the nutrient medium and mixed thoroughly to get the uniform distribution. This solution was poured (25 ml in each dish) into petri dishes and then allowed to attain room temperature. Thereafter, punching the set of agar with a sterile cork borer and scooping out the punched part made the cups. The diameter of each cup was 5 mm. Norfloxacin and Greseofulvin were used as the standards for antibacterial and antifungal tests, respectively. DMSO was used as the solvent control.

The entire test samples and the standards were tested at a concentration of 50 μgm. The plates were allowed to stand for an hour in order to facilitate the diffusion of the drug solution. Then the plates were incubated at 37 °C for 48 h.

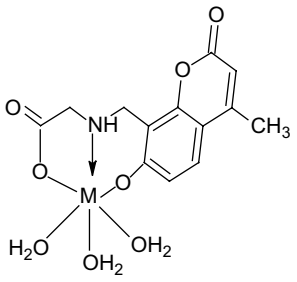


Fig. 3. The tentative structure of all metal complexes.

The zones of inhibition against all the microorganisms were measured in millimeters.

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