Synthesis and spectroscopic characterization of transition metal complexes of a 14-membered tetraaza [N$_4$] macrocyclic ligand and their biological activity

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ABSTRACT

Macrocyclic ligand was derived from β-Diketone 1-(3-chlorophenyl)-3-(2-hydroxyphenyl) propane-1,3-dione, o-phenylene diamine and its metal complexes with Cr(II), Mn(II), Co(II), Ni(II), and Cu(II), have been synthesised with newly synthesised biologically active macrocyclic ligand and characterized by spectral and other physicochemical techniques such as elemental analysis, molar conductivity, magnetic susceptibility, thermal analysis, X-ray diffraction, IR, ^{1}H-NMR, UV-Vis spectroscopy and mass spectrometry. The synthesized complexes are stable powders insoluble in common organic solvents such as ethanol, benzene chloroform, carbon tetrachloride. From the analytical data, stiochiometry of the complexes was found to be 1:2 (metal: ligand). Thermal behavior (TG/DTA) and kinetic parameters calculated by Horowitz-Metzer and Coats-Redfern method suggest more ordered activated state in complex formation. All the complexes are of high spin type and six coordinated. On the basis of IR, electronic spectral studies and magnetic behavior, an octahedral geometry has been assigned to these complexes. The antibacterial and antifungal activities of the ligand and its metal complexes, as growth inhibiting agents, has been screened in vitro against Staphylococcus aureus, Escherichia coli and Aspergillus Niger, C.Albicans respectively.   © 2014 Trade Science Inc. - INDIA

INTRODUCTION

The field of macrocyclic chemistry of metals is developing very rapidly because of its importance in the area of coordination chemistry[1]. Macrocyclic compounds and their derivatives are interesting ligand-systems because they are good hosts for metal anions, neutral molecules and organic cation guests[2]. Synthetic tetraaza macrocycle (N$_4$) molecules are considered typi-cally good models for oxygen carrier due to the presence of four nitrogen donor sites confined to a single four-fold or a slightly four fold plane in a ring structure, appropriate for metal ligand binding. A survey of the tetraaza macrocyclic ligand systems reported so far by earlier workers indicates that the ring size of 12–16 is most common for molecular model studies[3,4]. The stability of macrocyclic metal complexes depends upon number of factors, including the number and type of

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donor atoms present in the ligand and their relative positions within the macrocyclic skeleton, as well as the number and size of the chelate rings formed on complexation. For transition metal ions, features such as the nature and magnitude of crystal-field effects also play an important role[5]. There is a continued interest in synthesizing different macrocyclic complexes because of their potential applications in fundamental and applied sciences and importance in the area of coordination chemistry[6].In the present paper we report comparative determination of structure, function, relationship underlying metal ion binding by the orthophenyl diamine containing nitrogen donor [N$_4$] macrocyclic ligand having 14-membered backbone with the Cr(II), Mn(II), Co(II), Ni(II), and Cu(II) metal ions.

EXPERIMENTAL

Material and measurements

All chemicals used were of the analytical grade (AR) and of highest purity. 3-chlorobenzoic acid, ortho-hydroxy acetophenone and o-phenylenediamine were used for synthesis of ligand. AR grade metal chlorides were used for complex preparation. Spectroscopic grade solvents were used for spectral measurements. The carbon, hydrogen, nitrogen contents were determined on Perkin Elmer (2400) CHNS analyzer. IR spectra in the range of 4000-400 cm^{-1} were recorded on Jasco FT-IR-4100 spectrometer using KBr pellets. ^{1}H-NMR spectra of the ligand was recorded in DMSO using TMS as an internal standard. The TG/DTA analysis was recorded on Perkin Elmer TA/SDT-2960 and XRD were recorded on Perkin Elmer employing CuKα radiation λ= 1.541A^0 in the rang 10-80^0. The UV-Vis spectra of the complexes were recorded on ShimadzuUV-1800 Spectrophotometer. Magnetic susceptibility measurements were done on Guoy balance at room temperature using Hg.[Co(SCN)$_4$] as calibrant. Molar conductance of complexes was measured on Elico CM-180 conductometer using 1mM solution in dimethyl sulphoxide.

Synthesis of β-diketone step I

Equimolar amount of 3-chloro benzoic acid and ortho-hydroxy acetophenone were dissolved in 50 mL dry pyridine. The reaction mixture was then cooled to 0°C. To this, phosphorus oxychloride (0.06 mol) was added drop wise maintaining temperature below 10°C. The reaction mixture was kept overnight at room temperature. It was then poured on crushed ice with vigorous stirring. The crimson coloured solid (ester) was obtained which was filtered and washed several times with ice-cold water. Ester was then crystallized with distilled ethanol. Purity of the compound was checked by TLC. Ester was subjected to well known Baker-Venkatraman transformation. Ester (0.03 mol) was dissolved in 15 mL dry pyridine. To this mixture, powdered KOH (1gm) was added and the reaction mixture was stirred on magnetic stirrer at room temperature for 3 hours. Then it was poured over crushed ice and acidified with concentrated hydrochloric acid. Finally yellow coloured product was obtained which was recrystallized from ethanol (Yield 55-58%). Purity of all synthesized β-diketones were checked by TLC using silica gel G and melting points (Figure 1).

Step II synthesis of macrocyclic ligand

A hot ethanolic solution, 25 ml of orthophenylene diamine 0.02M and an ethanolic solution, 25 ml of β-
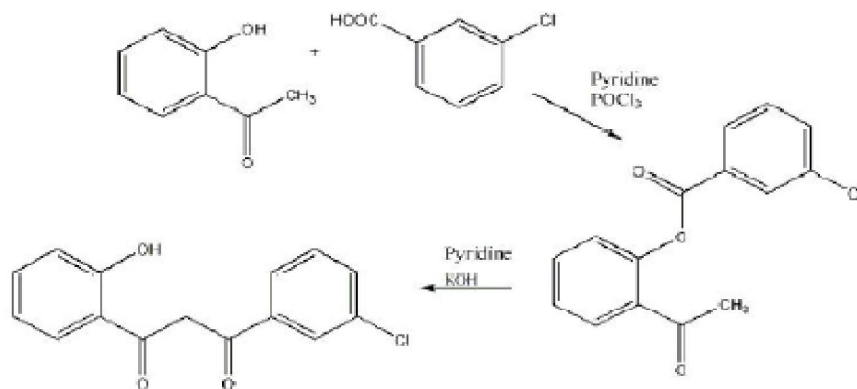

Figure 1: Synthesis of β-Diketone

Diketone 0.02M were mixed slowly under constant stirring. The resulting solution was refluxed for six hours in presence of 2-3 drops of concentrated HCl. On cooling, light yellowish crystals separated out. These were filtered washed with ethanol and dried under vacuum (Figure 2).

Synthesis of metal complexes

A hot ethanolic solution, 25 ml of ligand (0.002M) and a hot ethanolic solution, 25 ml of required metal salt (0.001M) were mixed together under constant stirring. The mixture was refluxed for 8-9 hours. On cooling, a coloured solid precipitate formed was filtered, washed with cold ethanol, chloroform and dried under vacuum (Figure 3).

RESULTS AND DISCUSSION

All the complexes are colored solids, air stable and soluble in polar solvents like DMF and DMSO. The elemental analysis show 1:2 (metal: ligand) stoichiometry for all the complexes. Micro analytical data and molar conductance values are given in TABLE 1. The metal contents in complexes were estimated by gravimetric analysis[9]. All the complexes show low conductance which indicates their non-electrolytic nature. The magnetic measurement studies suggest that the Mn(II),

Co(II), and Cu(II) complexes exhibit paramagnetic whereas the Ni(II) show diamagnetic behavior (TABLE 1).

¹H-NMR spectra of ligand

The ¹H NMR spectra of the ligand was recorded in DMSO. It shows following signals at 4.50δ, (s,4H - CH_2), 8.95 δ (s,2H,-OH),6.8-8.5δ corresponding to phenyl ring protons (m,24H).

Mass spectra of the ligand

Mass spectral data confirmed the structure of the ligand HL as indicated by the peaks corresponding to their molecular mass.

FTIR spectra

The IR spectra of ligand do not show any band at 1700 cm^{-1} (υ C=O), 3380 cm^{-1} (υas NH_2) and 3250 cm^{-1} (υs NH_2) corresponding to carbonyl groups and free amine[10]. There are two main features in the infrared spectrum of the macrocyclic ligand. The frist feature is the disappearance of the two characteristics between the primary amine group –NH_2 of the diamine and >C=O of diketone. It also confirmed the elimination of a water molecule and complete condensation[11]. A band corresponding to the (υ C=N) (azomethine linkage) appers at 1637 cm^{-1} in the spectra of ligand. The position of this band is shifted to lower frequency in the
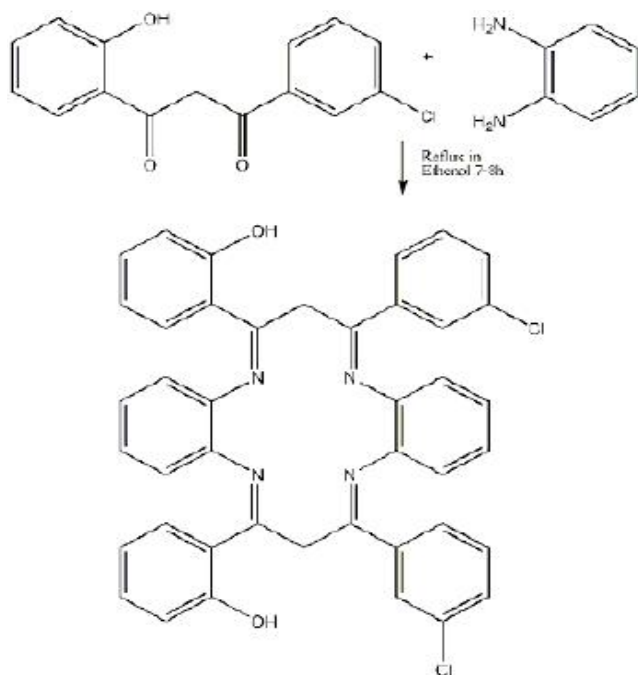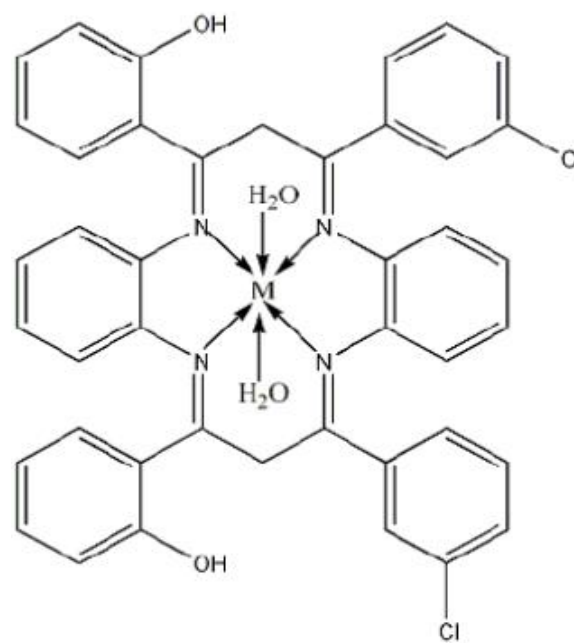

Figure 2: Synthesis of macrocyclic ligand

Where M = Cr (II), Mn (II), Co (II), Ni (II), Cu (II)

Figure 3 : Synthesis of metal complexes

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TABLE 1: Physical characterization, analytical and molar conductance data of ligand and its metal complexes

Ligand/Complexes	F. W.	M.P. / Decomp. Temp. ^{0}C	Magnetc moment μ_{eff} (B.M.)	Molar conduc. Mho cm^2 mol^{-1}	% Found (Calculated)			
					C	H	N	M
(HL)	693.63	193	----	----	72.19 (72.72)	4.88 (4.35)	7.91 (8.07)	_
[CrL (H2O)₂]	781.62	>300	Dia.	33.04	64.06 (64.53)	3.98 (4.38)	6.96 (7.16)	7.34 (7.14)
[MnL (H2O)₂]	784.56	>300	2.58	29.00	64.65 (64.29)	4.10 (4.36)	7.10 (7.14)	7.25 (7.00)
[CoL (H2O)₂]	788.56	>300	3.50	30.06	63.22 (63.97)	4.14 (4.34)	6.93 (7.10)	7.06 (7.47)
[NiL (H2O)₂]	788.32	>300	3.70	21.04	63.47 (63.99)	4.10 (4.34)	7.80 (7.10)	7.50 (7.44)
[CuL (H2O)₂]	793.17	>300	1.55	28.05	63.30 (63.60)	4.11 (4.32)	6.80 (7.06)	8.60 (8.01)

complexes as compared to free macrocyclic ligand suggesting that the coordination takes place through the nitrogen of (υ C=N) group[12].

Electronic absorption spectra and magnetic measurements

Electronic spectra of Cr (II) complex in DMSO solution display three high intensity absorption bands (TABLE 2) in the 13,605–13623 cm^{-1}, 18,621 cm^{-1}, 31,150–32,362 cm^{-1} regions. First two bands may be assigned to the transitions, $^4A_{2g}$ (F) $\rightarrow$ $^4T_{2g}$ (F) and $^4A_{2g}$ (F) $\rightarrow$ $^4T_{1g}$ (F), respectively and the third band may be due to charge transfer. The magnetic moment recorded at room temperature is 3.74 B.M.[13].

Electronic spectra of Mn (II) complexes show three weak intensity absorption bands (TABLE 2) in the region of 19,120–20,325 cm^{-1}, 22,210–23,427 cm^{-1} and 26,000–28,241 cm^{-1}. These bands may be assigned to the transitions, $^6A_{1g} \rightarrow$ $^4T_{1g}$ (^4G), $^6A_{1g} \rightarrow$ ^4E_g, $^4A_{1g}$ (^4G) and $^6A_{1g} \rightarrow$ ^4E_g (^4D) respectively. The magnetic moment recorded at room temperature is 5.84 B.M. corresponding to five unpaired electrons[14,15].

The Co(II) complex shows three bands 10260-11521 cm^{-1}, 18691-18855 cm^{-1} and 28248-29325 cm^{-1} regions which may be assigned to the transitions $^4T_{1g}$ (F) $\rightarrow$ $^4T_{2g}$ (F), $^4T_{1g} \rightarrow$ $^4A_{2g}$ and $^4T_{1g}$ (F) $\rightarrow$ T$_{2g}$ (P) respectively. These electronic transitions and observed magnetic moment of 4.7 B.M. indicated high spin octa-

TABLE 2 : The kinetic parameters of metal complexes calculated by Horowitz-Metzger (HM) and Coats-Redfern (CM) methods

Complex	Step	n	Method	E_a (kJmol^{-1})	A (S^{-1})	$\Delta S\#$ JK^{-1}mol^{-1}	$\Delta G\#$ (kJmol^{-1})	Corelation coefficient (r)
Cr (II)	I	0.35	HM	22.33	5.326	-158.723	35.36	0.9985
			CR	27.02	1.344	-129.952	32.96	0.9981
	II	0.35	HM	20.89	0.251	-161.839	42.94	0.9987
			CR	10.16	4.418	-150.581	41.41	0.9975
Mn (II)	I	0.3	HM	17.86	1.72	-160.579	31.05	0.9976
			CR	26.67	21.19	-138.789	29.26	0.9985
	II	0.3	HM	19.66	0.203	-169.792	42.80	0.9955
			CR	9.49	3.14	-152.334	40.42	0.9968
Co (II)	I	0.4	HM	6.58	0.090	-174.312	19.53	0.9969
			CR	21.1	3.328	-164.116	18.78	0.9954
	II	0.4	HM	17.47	0.098	-167.249	42.26	0.9991
			CR	21.83	9.05	-157.073	40.85	0.9965
Ni (II)	I	0.35	HM	14.70	1.22	-168.442	27.17	0.9919
			CR	14.84	9.97	-143.552	25.28	0.9998
	II	0.35	HM	20.38	0.158	-160.568	44.18	0.9997
			CR	14.93	7.60	-153.696	43.17	0.9953

hedral geometry[16].

The electronic spectra of Ni(II) complex exhibit three bands in the range 13333–14390, 18587–18621, and26385–27700 cm^{-1}. which may be assigned to the transitions $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_g(F)$, and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$, respectively. Magnetic moment of Ni (II) complex at room temperature is 2.92 BM. These values are in tune with a high spin configuration and show the presence of an octahedral environment[17].

The electronic spectra of Cu (II) complex was recorded in DMSO show three bands at 10032-10253 cm^{-1}, 16845-18581 cm^{-1}, and 25098-28365 cm^{-1}. The bands were assigned to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow T_{1g}(P)$, respectively. The position of bands indicated that Cu(II) complex have octahedral geometry. Electronic spectral data coupled with observed magnetic moment 1.94 B. M. suggest the octahedral geometry[18].

Thermal analysis

The simultaneous TG/DT analysis of some representative metal complexes was studied from ambient temperature to 1000 ºC in nitrogen atmosphere using α-Al$_2$O$_3$ as reference. In the thermogram of Cu(II) complex, the first step shows a steep slope between 140–230 °C with a mass loss of 5.78 %(calculated 5.92%), indicating the removal of two molecules of coordinated water[12,14]. An endothermic peak in the range 140–200 °C (ΔTmax = 187°C) on the DTA curve corresponds to the dehydration step. The anhydrous complex first show slow decomposition from 200-300°C with 16.35% (calcd. 15.19%) mass loss. A broad exotherm (ΔTmax = 239°C) in DTA may be attributed to removal of noncoordinate part of the ligand. The second step decomposition is from 400 to 600°C with 13.78% (calcd 13.39%) mass loss corresponds to decomposition of coordinated part of ligand. A broad endotherm in DTA is observed for this. The mass of final residue corresponds to stable MnO, 28.04 %. In thermogram curve of Ni(II) complex, the first step shows a steep slope between 140–230 °C with a mass loss of 7.43 %(calculated 7.79%), indicating the removal of two molecules of coordinated water. An endothermic peak in the range 140–230 °C (ΔTmax = 217°C) on the DTA curve corresponds to the dehydration step. The anhydrous complex first show slow decomposition from

200-300°C with 11.20% (calcd. 12.73%) mass loss. A broad exotherm (ΔTmax = 232°C) in DTA may be attributed to removal of noncoordinated part of the ligand. The second step decomposition is from 400 to 600°C with 19.92% (calcd 19.21%) mass loss corresponds to decomposition of coordinated part of ligand. A broad endotherm in DTA is observed for this. The mass of final residue corresponds to stable NiO, 37.21 %

Kinetic calculations

The kinetic and thermodynamic parameters *viz* order of reaction (n), energy of activation (E$_a$), pre-exponential factor (z), entropy of activation (ΔS) and free energy change (ΔG) together with correlation coefficient (r) for non-isothermal decomposition of metal complexes have been determined by Horowitz-Metzer (HM) approximation method and Coats-Redfern integral method[19,20].

Horowitz-Metzer (HM) approximation method

$$\log\left(\frac{1-(1-\alpha)^{1-n}}{(1-n)}\right) = \frac{E_a\theta}{2.303RT_s^2} + \log\frac{ZRT_s^2}{E\beta} - \frac{E}{2.303RT_s^2}$$

Where α = Fraction decomposed.β = heating rate (10ºC/min.), n = order of reaction.R = Molar gas constant, T$_s$ = Temperature at half Wt. Loss. k = Boltzman constant, Z = Frequency factor.h = Plank's constant.

The equation used for calculating entropy change (ΔS) is given below.

$$\Delta S = 2.303R\log\frac{Z\,h}{k\,T_s}$$

Where, k - Boltzman constant, h- Planck's constant, β – Rate of heating 10ºC/min., R- Molar gas constant and T$_s$ -Peak temperature.

Coats redfern method

The thermodynamic activation parameters of decomposition processes of complexes were calculated by this method. The activation energy (E$_a$), enthalpy (ΔH*), entropy (ΔS*) and Gibbs free energy change of the decomposition (ΔG*) were evaluated by employing the Coats –Redfern relation

$$\log\left[\frac{\log\{W_f/W_f-W\}}{T^2}\right] = \log\left[\frac{ZR}{\theta E^*}\left(1-\frac{2RT}{E^*}\right)\right] - \frac{E^*}{2.303RT}$$

Where W$_f$ -is the mass loss at the completion of the reaction, W is the mass loss up to temperature T, R- Gas constant, E*- Activation energy in KJ/mol, θ-is the

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heating rate, $(1-(2RT/E^*) \cong 1$

A plot of L.H.S. of equation against $1/T$ gave a slope from which E^* was calculated

$$\Delta H^* = E^* - RT$$

$$\Delta S^* = 2.303R[(\log \frac{Zh}{KT})]$$

$$\Delta G^* = \Delta H^* - T\Delta S^*$$

The data is given in (TABLE 2). The results show that the values obtained by two methods are comparable. The calculated value of energy of activation of the Mn(II), Co(II), Ni(II) and Cu(II) complex is relatively low indicating the autocatalytic effect of metal ion on thermal decomposition of the metal complex[20,21]. The negative value of entropy of activation indicates that the activated complex is more ordered than the reactant and that the reaction is slow. The more ordered nature may be due to the polarization of bonds in activated state which might happen through charge transfer electronic transition. The kinetic parameters of metal complexes calculated by Horowitz-Metzger (HM) and Coats-Redfern (CM) methods.

Antimicrobial activity

The antimicrobial activity of ligand and its metal complexes were tested in vitro against bacteria such as Staphylococcus aureus and Escherichia coli by paper disc plate method[22]. The compounds were tested at the concentration 250 and 500 µg cm^{-3} in DMSO and compared with known antibiotics viz Rifampicin (TABLE 3). For fungicidal activity, compounds were screened in vitro against Aspergillus Niger and Trichoderma by mycelia dry weight method[23] with glucose nitrate media. The compounds were tested at the con-

TABLE 3 : Antibacterial activity of HL and its metal complexes

| | inhibition Zone diameter (mm) | | | |
| | E.Coli | | Staphylococcus aures | |
Ligand/Complexes	250ppm	500ppm	250ppm	500ppm
Rifampicin	40	40	42	42
(HL)	10	14	13	15
[CrL(H$_2$O)$_2$]	12	18	09	30
[MnL(H$_2$O)$_2$]	9	19	10	25
[CoL(H$_2$O)$_2$]	10	17	11	18
[NiL(H$_2$O)$_2$]	11	23	16	31
[CuL(H$_2$O)$_2$]	13	20	12	22

TABLE 4 : Antifungal activity of compounds yield of mycelial dry weight in mg (%inhibition)

| | Aspergillus Niger | | C.albicans | |
Ligand/Complexes	250ppm	500ppm	250ppm	500ppm
Control	40	40	40	40
(HL)	14(65)	11(72)	12(70)	09(78)
[CrL(H$_2$O)$_2$]	22(45)	13(68)	16(60)	10(75)
[MnL(H$_2$O)$_2$]	38(05)	25(38)	19(53)	11(73)
[CoL(H$_2$O)$_2$]	30(25)	28(30)	21(48)	13(68)
[NiL(H$_2$O)$_2$]	27(33)	25(38)	15(63)	12(70)
[CuL(H$_2$O)$_2$]	31(22)	25(38)	23(43)	15(63)

centration 250and 500 µg cm^{-3} in DMSO and compared with control (TABLE 4). From TABLE 5 and 6, it is clear that the inhibition by metal chelates is higher than that of a parent ligand and metal salts. The results are in good agreement with previous findings with respect to comparative activity of free ligand and its complexes[22,23]. The metal chelates have higher antibacterial activity than the corresponding free ligand and control against the same microorganism under identical experimental conditions. Such enhanced activity of metal chelates is due to increased lipophilic nature of the metal ions in complexes[24]. The increase in activity with concentration is due to the effect of metal ions on the normal process. The microbial results are presented in TABLES 3 and 4. In case of antibacterial studies it was observed that, the ligand is moderately active towards Stapylococcus and less active towards E.Coli. Comparison of activities of the ligand and its metal chelates.

The ligand and metal complexes show fungal growth inhibition in the following order Mn(II) > Cu(II) > Co(II) > Ni(II) > Cr(II) > HL. The antibacterial capacity of the ligand and its metal complexes show following order Ni(II) > Cu(II) > Cr(II) > HL > Mn(II) > Co(II).

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