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Microwave assisted synthesis, spectroscopic characterization and biological screening of macrocyclic metal (II) complexes of Malonic acid dihydrazide and 5-chloroisatin

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ABSTRACT

A series of macrocyclic metal (II) complexes were synthesized by template condensation of Malonic acid dihydrazide and 5-chloroisatin with Co (II), Ni (II), Cu (II) and Zn (II) salts in methanolic medium. Complexes have been characterized on the basis of various techniques like Elemental analysis, Molar Conductance, Magnetic susceptibility, Thermal gravimetric analysis, FTIR, ^{1}H-NMR, ESR and UV-Visible spectroscopy. Octahedral geometry is proposed for all the macrocyclic metal (II) complexes. These complexes have been tested for their in vitro antibacterial activities against bacterial strains Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli. Some of the complexes have exhibited good antibacterial activity. Complexes were also tested for their antioxidant property and found good results.

Key words: Microwave synthesis, macrocyclic metal complexes, antibacterial and antioxidant.

INTRODUCTION

Macrocyclic complexes of transition metals have received a great attention due to their biological activities like antibacterial, antifungal [1] antiviral, anticarcinogenic [2] and antifertile [3]. Synthetic macrocyclic complexes mimic with some natural macrocycles like porphyrins, metalloproteins and cobalamine [4][5]. Macrocyclic metal chelating agents e.g. DOTA have DNA nuclease activity [6] as well as useful for detection of tumor lesions [7]. The importance of transition metal aza-macrocyclic complexes is because of they used like models in biological systems for protein metal binding sites, electrocatalyst in fuel cells [8], synthetic ionophores [9], luminescent sensors [10], anticancer drugs [11], M.R.I contrast agents [12], and radio-immunotherapeutic agents [13]. These applications develop a need for the design of new macrocyclic ligand and their transition metal complexes for industrial and biological applications [14]. Isatin is a versatile molecule for designing various bioactive agents and its derivatives have been reported for broad spectrum of antiviral activities [15]. Schiff bases of isatin possess a wide range of pharmacological applications like antibacterial, antifungal [16][17], anticonvulsant [18] and anti-HIV [19] activities. Macrocyclic metal complexes derived from Isatin and Carbohydrazide effective against gram positive Bacteria [20]. Therefore the researchers have shown interest in isatin for different fields.

Metal reduce the polarity of the complexes and enhances the penetration into lipid membranes. The metal complex blocks metal binding sites in the enzymes of pathogens interfere in the cellular respiration and therefore inhibit the protein synthesis. This restricts growth of the pathogenic species[21].

The synthesis by microwave irradiation is a branch of green chemistry. The microwave-assisted synthesis in organometallic and coordination chemistry continues to become an astonishing pace and interesting because of shorter reaction times, low cost, less pollution, simple reaction conditions and high yields [22][23]. In continuation with our reported work synthesis and characterization of macrocyclic complexes of 5-chloroisatin and Malonic dihydrazide with Cr(III) and Fe(III)[24], we present here the synthesis and characterization of a new series of Co (II), Ni (II), Cu (II) and Zn (II) macrocyclic complexes of 5-chloroisatin and Malonic acid dihydrazide. All the complexes were studied for their in vitro antibacterial activity against two Gram positive and two Gram negative bacteria. Complexes were also screened for their antioxidant property.

MATERIALS AND METHODS

2.1 Materials

Analytical grade chemicals were used. Malonic acid dihydrazide and 5-chloroisatin were purchased from Sigma-Aldrich, metal salts and other chemicals were purchased from Himedia and HPLC.

2.2 Conventional method for the synthesis of metal (II) complexes

Metal complexes were synthesized by template method of synthesis. In a hot stirring 50 mL methanolic solution of Malonic acid dihydrazide (10 mmol), a 20 mL of methanolic solution of metal (II) salt (e.g. cobalt, nickel, copper or zinc) (10 mmol) was added and refluxed for 30 min. After that 20 mL methanolic solution of 5-chloroisatin (10 mmol) added and refluxed for 8-10 h. The mixture was evaporated to half of its volume and kept for overnight cooling. The dark coloured precipitate was filtered, washed with methanol, acetone, and diethyl ether and dried in vacuum desiccator; Yield ~ 55 %. All the complexes were found soluble in DMSO and DMF, but insoluble in water and common organic solvents. The syntheses of complexes may be represented as follows **(Figure 1):**

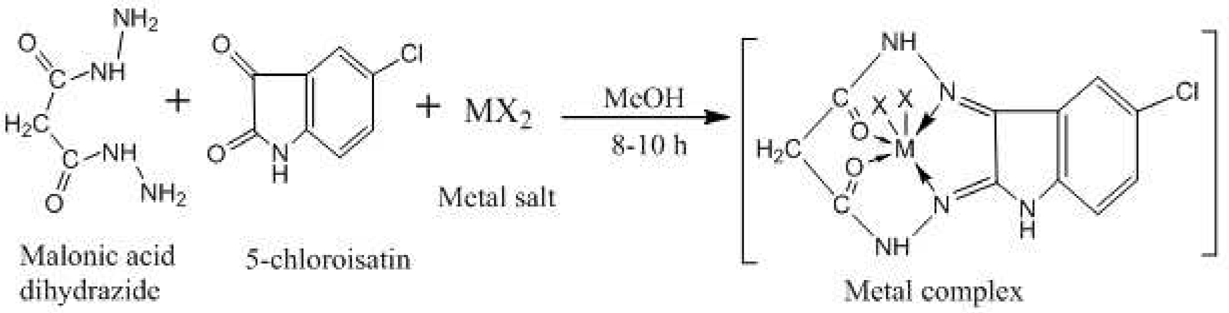

Figure 1 Synthesis of metal (II) complexes

Where M = Co (II), Ni (II), Cu (II) and Zn (II) and X = Cl^-, NO_3^- CH_3COO^-.

2.3 Microwave assisted synthesis of metal (II) complexes

Malonic acid dihydrazide, 5-chloroisatin and the metal salt were mixed in 1:1:1 ratio in a grinder. The reaction mixture was irradiated in UWave-1000, Sineo microwave synthesizer by taking 8-10 mL of methanol as a solvent. The reaction was completed in 8– 10 min with higher yields (74 – 80 %). The product was then recrystallized with methanol and dried in vacuum desiccator over anhydrous $CaCl_2$. The purity of the product was checked by TLC using silica gel G.

2.4 Analytical and physical measurements

The microanalyses of C, H and N were carried out by Euro EA, Elemental Analyzer. The metal contents were determined by Atomic absorption spectrophotometer, PG instruments. Electronic spectra were recorded on LAMBDA 25 PerkinElmer spectrophotometer. The magnetic susceptibility measurements of the complexes were carried out by Gouy balance. The FTIR spectra were recorded on Thermo Scientific Nicolet iS50 FTIR Spectrometer in the range 4000-400 cm^{-1} using ATR from Thermo Fisher Scientific Technical Centre, Mumbai. The ^1H NMR spectra were recorded on Bruker NMR spectrometer at 400 MHz. The molar conductivity (10^{-3}M) was measured on digital conductivity meter, Hach. X-band EPR spectra were recorded by ESR-JEOL spectrometer at room temperature from SAIF, IIT Bombay. Thermal study was done by Universal TA instruments.

2.5 In vitro antibacterial activity

The evaluation of in vitro antibacterial activity of all the complexes was carried out against two Gram positive (*B. subtilis and S. aureus) and two Gram negative (P. aeruginosa and E. coli*) bacteria by agar well diffusion method [25]. All bacterial cultures were adjusted to 0.5McFarland standard, approximately equal to 1.5 x 10^8 Cfu/mL. Plates were prepared by 20 ml Mueller Hinton agar media and spread 100 µL culture over it. After 10 min wells were bored with 8 mm sterile cork borer and filled with 100 µL test compound of 2mg/mL in DMSO. Plates were incubated for 24 h at 37 ºC. The DMSO used as negative control and Ciprofloxacin used as positive control. The zone of growth inhibition measured with zone reader.

Minimum inhibitory concentration (MIC) of the complexes was tested against bacterial strains by macrodilution tube method [26]. Mueller Hinton Broth medium was prepared and 100 μL was poured in each sterile tube no. 1-10. Serial dilutions of all the complexes were prepared to final concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2 and 1μg/mL in sterile test tubes. To each test tube 100μL of inoculum was added. Ciprofloxacin was used as positive control. All tubes were incubated for 24 h at 37 ºC. The MIC of all complexes was recorded as the lowest concentration of each in the test tubes with no growth of bacteria. Each assay was performed in duplicate.

2.6 Antioxidant Assay (DPPH, free radical scavenging activity)

Antioxidant assay was done by DPPH method [27]. Different concentrations 10, 50 and 100μg/100μL in DMF of complexes and butylated hydroxyl anisole (BHA) were taken in test tubes. To these test tubes 5 mL solution of 0.1mM methanolic DPPH was added and allow standing for 30 minutes at room temperature. The control was prepared without any complex or standard. The absorbance was measured by spectrophotometer at 517nm and radical scavenging activity was calculated using following formula:

% Radical scavenging activity = [(Control OD – Sample OD) / Control OD] x 100

RESULTS AND DISCUSSION

The microwave-assisted synthesis completed reaction in a short time and higher yields compared to the conventional method. The microwave irradiation technique improved the yields from 55–80%. Analytical and physical measurement data of macrocyclic metal (II) complexes shows that all the complexes may be represented by formula: [M ($C_{11}H_8N_5O_2Cl$) X_2] where M = Co (II), Ni (II), Cu (II), Zn (II) and X = Cl^-, $NO_3^{\,-}$, and $CH_3COO^{\,-}$. All the complexes are dark coloured powder and are soluble in DMSO and DMF. Molar Conductivity (10^{-3}M) measurement of complexes in DMSO indicated them to be non-electrolyte. All complexes were stable up to 250 ºC indicating their thermal stability.

3.1 Elemental Analysis

All complexes exhibit satisfactory elemental analyses results **(Table 1)**.

Table 1 Analytical and physical data of the macrocyclic metal (II) complexes

S. N.	Complexes	Elemental analysis, found (calcd.)%				Colour	Mol. wt.
		M	C	H	N		
1	[Co($C_{11}H_8N_5O_2Cl$)Cl_2]	14.39 (14.46)	32.71 (32.42)	1.92 (1.97)	17.45 (17.18)	Yellowish orange	407.50
2	[Co($C_{11}H_8N_5O_2Cl$)(NO_3)$_2$]	12.55 (12.79)	28.82 (28.68)	1.82 (1.75)	21.11 (21.28)	Dark yellow	460.60
3	[Co($C_{11}H_8N_5O_2Cl$)(OAc)$_2$]	12.88 (12.96)	39.73 (39.62)	3.26 (3.10)	15.62 (15.4)	Dark brown	454.68
4	[Ni($C_{11}H_8N_5O_2Cl$)Cl_2]	14.56 (14.41)	32.12 (32.44)	1.99 (1.97)	17.06 (17.19)	Yellow	407.26
5	[Ni($C_{11}H_8N_5O_2Cl$)(NO_3)$_2$]	12.68 (12.74)	28.48 (28.69)	1.81 (1.75)	21.33 (21.29)	Yellow	460.36
6	[Ni($C_{11}H_8N_5O_2Cl$)(OAc)$_2$]	12.87 (12.91)	39.70 (39.64)	3.21 (3.1)	15.62 (15.41)	Dark brown	454.44
7	[Cu($C_{11}H_8N_5O_2Cl$)Cl_2]	15.39 (15.41)	32.13 (32.05)	1.98 (1.95)	16.84 (16.99)	Brown	412.11
8	[Cu($C_{11}H_8N_5O_2Cl$)(NO_3)$_2$]	13.61 (13.65)	28.42 (28.39)	1.84 (1.73)	21.14 (21.07)	Brown	465.22
9	[Cu($C_{11}H_8N_5O_2Cl$)(OAc)$_2$]	13.78 (13.83)	39.20 (39.22)	3.10 (3.07)	15.29 (15.24)	Light brown	459.30
10	[Zn($C_{11}H_8N_5O_2Cl$)Cl_2]	14.12 (14.17)	39.10 (39.06)	3.04 (3.06)	15.23 (15.18)	Yellowish orange	461.13

3.2 Infrared Spectroscopy

The FTIR spectrum of Malonic acid dihydrazide shows a pair of bands at 3270 and 3304 cm^{-1} corresponding to starching vibrations of ν(NH_2), but absent in spectra of all the complexes. However, a single medium band at 3092 – 3241 cm^{-1} was observed in the spectra of complexes, which may be assigned to ν(NH) stretching vibrations[28]. A strong band at 1670 cm^{-1} assigned to ν(C=O) vibrations of the CONH moiety in the FTIR spectrum of Malonic acid dihydrazide. In the spectra of all the complexes this peak shifted to lower value 1607–1620 cm^{-1}, suggesting the coordination of oxygen with the metal.

The strong band of ν(C=O) vibrations at1730 - 1745 cm^{-1} of 5-chloroisatin were absent in metal complexes and appearance of new strong absorption band in the region 1542-1597 cm^{-1} assigned to the ν(C=N) vibrations [29]. This indicates the formation of macrocyclic frame by condensation of carbonyl groups and amino groups [28]. The lower values of ν(C=N) stretching vibration indicates the coordination of azomethine nitrogen towards metal atom [30]. The bands present at 3000-3050 cm^{-1} , 1470-1594 cm^{-1} and 1010-1340 cm^{-1} may be assigned to ν(C-H), ν(C=C) and ν(C-N) vibrations of 5-chloroisatin respectively[30][31].

The far infrared spectra show bands in the region 522–555 cm^{-1} corresponding to ν(M–O) vibrations and 447–498 cm^{-1} corresponding to ν(M–N) vibrations in all the complexes [32][33]**(Table 2)**.

Table 2 Infrared spectroscopic data of macrocyclic metal (II) complexes

S. N.	Complex	ν(NH) cm^{-1}	ν(C=O) cm^{-1}	ν(C=N) cm^{-1}	ν(M–O) cm^{-1}	ν(M–N) cm^{-1}
1	$[Co(C_{11}H_8N_5O_2Cl)Cl_2]$	3216	1607	1594	522	491
2	$[Co(C_{11}H_8N_5O_2Cl)(NO_3)_2]$	3212	1620	1592	526	498
3	$[Co(C_{11}H_8N_5O_2Cl)(OAc)_2]$	3092	1610	1557	526	483
4	$[Ni(C_{11}H_8N_5O_2Cl)Cl_2]$	3208	1618	1595	522	497
5	$[Ni(C_{11}H_8N_5O_2Cl)(NO_3)_2]$	3206	1618	1595	522	497
6	$[Ni(C_{11}H_8N_5O_2Cl)(OAc)_2]$	3195	1614	1597	531	455
7	$[Cu(C_{11}H_8N_5O_2Cl)Cl_2]$	3205	1617	1591	523	497
8	$[Cu(C_{11}H_8N_5O_2Cl)(NO_3)_2]$	3169	1619	1596	539	447
9	$[Cu(C_{11}H_8N_5O_2Cl)(OAc)_2]$	3241	1612	1542	555	498
10	$[Zn(C_{11}H_8N_5O_2Cl)Cl_2]$	3200	1617	1578	528	492

3.3 ^{1}H NMR spectroscopy

The ^{1}H NMR spectrum of Zinc(II) complex showed a singlet at 8.45 ppm due to protons of the –CONH moiety [34]. A singlet at 2.4 ppm may be due to $–CH_2$ proton [35]. The multiplets at 7.20 – 7.88 ppm may be assigned to hydrogens of aromatic rings [36]. A broad singlet at 10.80 ppm may be assigned to proton of the –NH group of 5-chloroisatin [37].

3.4 Electronic spectral and Magnetic studies

The electronic spectra of metal complexes were recorded in DMSO **(Table 3)**. Three absorption bands for octahedral Cobalt (II) complex at 8100-9100 (ν_1), 12550-15750 (ν_2) and 18700-20250 cm^{-1} (ν_3) assigned to $^4T_{1g}$ (F) → $^4T_{2g}$ (F), $^4T_{1g}$ (F) → $^4A_{2g}$ (F) and $^4T_{1g}$ (F) → $^4T_{1g}$ (P) respectively have been reported [25]. In the Co (II) complexes the first band appeared usually in infrared region, so ν_1 transition could not be observed. The two bands appeared at 14593 - 14871(ν_2) and 20187 – 20208 cm^{-1} (ν_3) assigned to $^4T_{1g}$ (F) → $^4A_{2g}$ (F) and $^4T_{1g}$ (F) → $^4T_{1g}$ (P) transitions respectively in an octahedral environment. The magnetic moments of the Co (II) complexes at room temperature found 4.84–4.91 BM in agreement with the octahedral geometry and correspond to three unpaired electrons. The electronic spectra of Ni (II) complexes exhibit three absorption bands at 12210–12290 cm^{-1}(ν_1), 15860–16824 cm^{-1}(ν_2), and 26910–27680 cm^{-1}(ν_3) assignable to $^3A_{2g}$ (F) → $^3T_{2g}$ (F), $^3A_{2g}$ (F) → $^3T_{1g}$ (F) and $^3A_{2g}$ (F) → $^3T_{1g}$ (P) respectively. The magnetic moment of Ni (II) complexes at room temperature lie at 2.95-3.12 BM in agreement with the octahedral geometry and corresponds to two unpaired electrons. The spectra are consistent with octahedral nature of these complexes [38]. The electronic spectra of Cu (II) complexes show a single broad absorption bands at 15465–19100 cm^{-1} due to the mixing of all transitions $^2B_{1g}$ → $^2A_{2g}$ (ν_1), $^2B_{1g}$ → $^2B_{2g}$ (ν_2), and $^2B_{1g}$ → $^2E_{1g}$ (ν_3). The broadness of the absorption band may be due to John Teller distortion. The magnetic moment of Cu (II) complexes at room temperature lie at 1.80-1.86 BM in agreement with the octahedral geometry [39]. The Zn (II) complex exhibit a single band at 32550 cm^{-1} assignable to charge transfer from ligand to metal. Zn (II) complex is diamagnetic due to complete d-orbital and geometry may be octahedral [40].

Table 3 Electronic spectrum and magnetic moments data of macrocyclic metal (II) complexes

Complex	Electronic spectral bands (cm^{-1})	Assignment	Magnetic moment	Molar conductance (ohm^{-1} cm^2 $mole^{-1}$)	Geometry
Co(II) complexes	14593 – 14871, 20187 - 20208	$^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)$, $^4T_{1g}(F)\rightarrow{}^4T_{1g}(P)$,	4.84 – 4.91	6.48 – 7.28	Octahedral
Ni(II) complexes	12210–12290 15860–16824, and 26910–27680	$^3A_{2g}(F)\rightarrow{}^3T_{2g}(F)$, $^3A_{2g}(F)\rightarrow{}^3T_{1g}(F)$, $^3A_{2g}(F)\rightarrow{}^3T_{1g}(P)$,	2.95 - 312	7.91 – 8.36	Octahedral
Cu(II) complexes	15465–19100	$^2B_{1g}\rightarrow{}^2A_{2g}$, $^2B_{1g}\rightarrow{}^2B_{2g}$, $^2B_{1g}\rightarrow{}^2E_{1g}$,	1.80 – 1.86	12.08 – 14.27	Octahedral
Zn(II) complexes	32550	LMCT	Diamagnetic	8.02	Octahedral

3.5 Thermal study

TGA study carried out for $[Cu (C_{11}H_8N_5O_2Cl) Cl_2]$ complex. The TGA curve of complex indicates that weight loss occurred in a single stage 300-450 ºC and loss is 86.73%, the remaining residue about 13.27% may be metal oxide. The weight loss may be due to decomposition of chloride ions and ligand. The metal content determination in the complex done by Atomic absorption spectrophotometer agrees well with the thermal studies.

3.6 ESR Spectra

ESR spectra of the Cu (II) complexes were recorded at room temperature on X-band at a frequency of 9.4 GHz under the magnetic field of 5000 G. in present study the Cu (II) complexes exhibited $g_{\|} = 2.270$ and $g_{\perp} = 2.141$. The value of $g_{\|}$ (2.270) > $g_{\perp}$ (2.141)> 2.0023 indicating that the unpaired electron localized in dx^2-y^2 ground state characteristic of octahedral geometry with distortion in complexes. The complexes have $g_{\|}$ value less than 2.3, indicating covalent character of the metal ligand bond. The geometric parameter (G) is calculated by the expression

$G = g_{\parallel}-2.0023/g_{\perp}-2.0023$. The calculated G value for Cu (II) complexes is 1.9, which is less than 4, indicating exchange interaction in solid complexes.[41]

3.7 Antibacterial activity results and discussions

All the synthesized macrocyclic metal (II) complexes were tested for their in vitro antibacterial activity by agar well diffusion method **(Table 4)** and MIC by macrodilution tube method **(Table 5)**. Some of the complexes show good antibacterial activity. The complex 4, 10 and 6 show good antibacterial activity against *B. subtilis* and *S. aureus*. Complex 4, 6 and 10 possessed good antibacterial activity against *P. aeruginosa*. Complex 6 (MIC 8 and 16 µg/mL) among all the complexes found most effective against Gram positive and Gram negative bacteria.

Table 4 Antibacterial activities of macrocyclic metal (II) complexes by agar well diffusion method

S. N.	Compounds	Zone of inhibition, diameter (mm)			
		B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*
1	$[Co(C_{11}H_8N_5O_2Cl)Cl_2]$	22.2	19.8	17.4	11.8
2	$[Co(C_{11}H_8N_5O_2Cl)(NO_3)_2]$	16.9	17.1	16.8	10.4
3	$[Co(C_{11}H_8N_5O_2Cl)(OAc)_2]$	17.0	16.4	13.8	17.3
4	$[Ni(C_{11}H_8N_5O_2Cl)Cl_2]$	24.2	22.0	23.8	18.2
5	$[Ni(C_{11}H_8N_5O_2Cl)(NO_3)_2]$	19.4	18.5	16.5	11.2
6	$[Ni(C_{11}H_8N_5O_2Cl)(OAc)_2]$	24.0	25.1	24.2	10.2
7	$[Cu(C_{11}H_8N_5O_2Cl)Cl_2]$	21.6	22.4	19.2	10.8
8	$[Cu(C_{11}H_8N_5O_2Cl)(NO_3)_2]$	18.2	17.9	16.1	9.0
9	$[Cu(C_{11}H_8N_5O_2Cl)(OAc)_2]$	22.4	21.3	21.3	9.9
10	$[Zn(C_{11}H_8N_5O_2Cl)Cl_2]$	23.1	24.2	23.6	10.0
	Ciprofloxacin	26.2	26.1	25.6	25.4

Table 5 MIC of macrocyclic metal (II) complexes by macrodilution tube method

S.N.	Compounds	MIC (µg/mL)			
		B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*
1	$[Co(C_{11}H_8N_5O_2Cl)Cl_2]$	32	64	128	>128
2	$[Co(C_{11}H_8N_5O_2Cl)(NO_3)_2]$	128	128	>128	>128
3	$[Co(C_{11}H_8N_5O_2Cl)(OAc)_2]$	128	>128	>128	128
4	$[Ni(C_{11}H_8N_5O_2Cl)Cl_2]$	16	32	16	128
5	$[Ni(C_{11}H_8N_5O_2Cl)(NO_3)_2]$	64	128	>128	>128
6	$[Ni(C_{11}H_8N_5O_2Cl)(OAc)_2]$	32	8	16	>128
7	$[Cu(C_{11}H_8N_5O_2Cl)Cl_2]$	32	32	64	>128
8	$[Cu(C_{11}H_8N_5O_2Cl)(NO_3)_2]$	128	128	>128	>128
9	$[Cu(C_{11}H_8N_5O_2Cl)(OAc)_2]$	32	32	32	>128
10	$[Zn(C_{11}H_8N_5O_2Cl)Cl_2]$	16	16	16	>128
	Ciprofloxacin	5	5	5	5

3.8 Antioxidant Assay (DPPH, free radical scavenging activity)

All the metal (II) complexes were screened for free radical scavenging activity by DPPH method. The complex no.5 $[Ni(C_{11}H_8N_5O_2Cl)(NO_3)_2]$, no.6 $[Ni(C_{11}H_8N_5O_2Cl)(OAc)_2]$, no.9 $[Cu(C_{11}H_8N_5O_2Cl)(OAc)_2]$ and no.10 $[Zn(C_{11}H_8N_5O_2Cl)Cl_2]$ exhibited good free radical scavenging activity. BHA used as standard. The presented results are in percentage of free radical scavenging activity **(Figure 2)**.

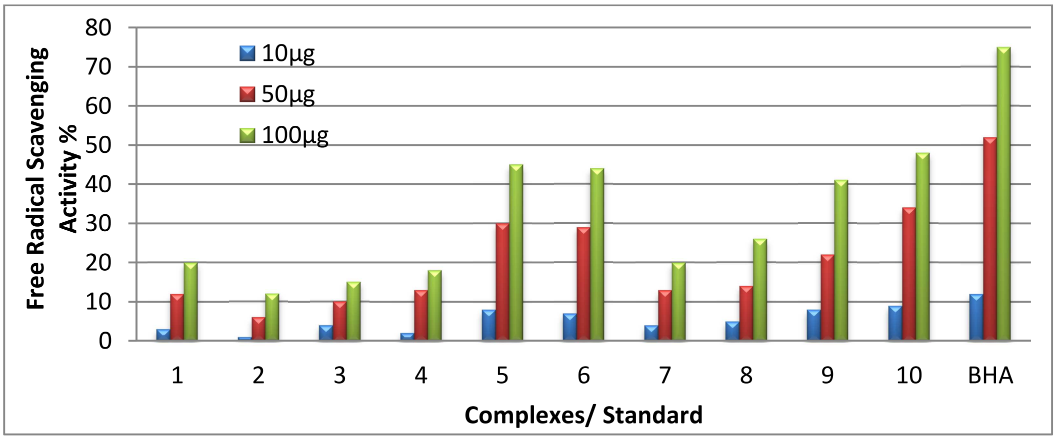

Figure 2 Antioxidant activities (1-10, metal complex and BHA as a standard)

CONCLUSION

The macrocyclic metal (II) complexes were synthesized by conventional as well as microwave method and characterized by various physical and spectral studies and investigated for antibacterial and antioxidant activity. The results are in agreement with coordination of metal ions with azomethine nitrogen and carbonyl oxygen donor atoms towards octahedral geometry for all metal (II) complexes **(Figure 1)**. The thermal study provides information about thermal stability of the complexes. Among the series some complexes have good antibacterial and antioxidant property.

Although, it has been suggested that coordination reduce the polarity of the metal complexes and enhances the penetration into lipid membranes. The metal complex blocks metal binding sites in the enzymes of pathogens interfere in the cellular respiration and inhibit the protein synthesis. This restricts growth of the pathogenic species[21].However further studies on the mechanism of antibacterial activity may required for better understanding.

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