



RESEARCH ARTICLE

Novel (N₄) Macrocyclic Metal Complexes: Synthesis, Characterization, Spectral Studies and Anticancer Activity

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Abstract:**Introduction:**

A new series of mononuclear Fe(II), Co(II), Ni(II), Cu(II) and Pd(II) complexes correspond to tetradentate macrocyclic nitrogen ligand *i.e.* naphthyl-3,4:10,11-dibenzo,7-methylene,8-methyl,6-phenyl-1,5,9,13-tetraazacyclohexadecane-5,8-diene-2,12-dione metal(II) complexes, have been synthesized by the template condensation reaction.

Methods:

The complexes have been characterized by elemental analysis, spectral (IR, UV-Vis, and ESR, molar conductivity, and magnetic as well as thermal analysis measurements.

Results:

On the basis of above studies, an octahedral geometry has been proposed for all complexes except Cu(II) nitrate complex that adopt square pyramidal geometry, and square planar geometry for Pd(II) chloride complex, respectively.

Conclusion:

The thermal behavior and the kinetic parameters of degradation were determined using Coats-Redfern and Horowitz-Metzger methods. Moreover, the *in vitro* antitumor activity of the some synthesized complexes against human breast and human hepatocarcinoma cell lines (MCF-7) and (HePG2), respectively has been studied.

Keywords: Tetra-azamacrocyclic, Macrocyclic metal complexes, Monobenzoylacetone, Spectral studies, Antitumor activity, IC₅₀.

1. INTRODUCTION

The interest in the study of synthetic macrocyclic compounds is a very integral part of coordination chemistry due to their presence in many biological naturally occurring metal complexes. The field of macrocyclic metal chemistry is developing very rapidly because of its applications and the great importance in the coordination chemistry [1 - 12]. The importance of macrocyclic systems in chemistry is attributed to their many industrial applications and in a number of biological processes such as photosynthesis, catalytic properties, dioxygen transport and their potential application to extract specific metals [9, 10]. The selectivity of the macrocyclic ligands that contain combination of Oxo (O), Aza (N), Phospha (P) and Sulpha (S) for the extraction of metal ions depends on the ligand flexibility, nature of the ligand backbone, the cavity size of the macrocyclic core, nature and number of donor atoms in addition to their relative position in the macrocyclic ligands and the pendant coordinating arms attached to the ligand [8, 10]. Complexes with poly -azamacrocyclic ligands have attracted a focus of scientific attention [7, 13]. Recently, much attention has been

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paid to macrocyclic compounds containing amide groups [14, 15]. Macrocyclic amides have applications in elector fluorescence devices (EL) and homogeneous catalysis [16]. The template condensation for the preparation of the macrocyclic ligands often offers selective routes towards products that are not formed in the absence of metal ions [17]. The template condensation methods lie at the heart of macrocyclic chemistry [18]. Therefore, if the ligand yield is low, macrocyclic complexes have been widely isolated using the template reactions [19]. The transition metal ions are used as the templating agent [20]. The metal ions direct the reaction preferentially towards cyclic rather than oligomeric or polymeric products [21]. Recently, poly-azamacrocycles and its transition metal complexes have been synthesized and characterized. The *in vitro* antitumor activity against human breast cancer cell line and human hepatocarcinoma cell line has been studied [14, 15, 22]. Taking into consideration the above facts, we have reported the preparation, spectral and thermal studies of novel Fe(II), Co(II), Ni(II), Cu(II), Pd(II) complexes. The *in vitro* antitumor activity of the compounds against human breast (MCF-7) and human hepatocarcinoma cancer cell lines (HepG2) were done.

2. RESULTS AND DISCUSSION

2.1. Physical Properties

The condensation reaction of the starting material N,N'-(naphthalene-1,8-diyl)bis(2-aminobenzamide) and monobenzoylacetone in presence of different transition metal salts [Fe(II),Co(II), Ni (II), Cu(II), or Pd (II)] in 1:1:1 molar ratio gives the macrocyclic complexes i.e. naphthyl-3,4:10,11-dibenzo,7-methylene,8-methyl,6- phenyl-1,5,9,13-tetraazacyclohexadecane-5,8-diene-2,12-dione metal(II) complexes. All complexes are air stable, and insoluble in most common organic solvents. However, they are soluble in DMF or DMSO. The thermal analysis, spectral, magnetic, and elemental data (Tables 1-5) are agreed with their proposed structure. From elemental analyses, all complexes are formed in 1M:1L molar ratio. X-ray crystal determination is not possible for any of complexes due to the fact that crystals of these complexes could not be grown. The molar conductivities, recorded for 10^{-3} M solution of the metal complexes in DMF at room temperature are given in Table 1.

The molar conductance values of complexes (1-4,6-8) indicate their non-electrolytic nature [11, 23]. However, complexes (5,9-11) show molar conductivity value in the range 62– 66 $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$ in DMF 10^{-3} M confirming their 1:1 electrolytic nature [23, 24].

Table 1. Analytical data and physical properties of the macrocyclic metal complexes

No	Compound	Color	Yield (%)	M.Wt	D.T/C	Analysis Calc. (F)%					$(\Lambda_m)^a$
						C	H	N	M	X	
1	[FeLCl ₂].½EtOH.½H ₂ O	Black	93	680.8	300	61.69(61.91)	4.4(4.51)	8.22(8.32)	8.19(7.44)	10.43(9.94)	23
2	[CoLCl(OH)].H ₂ O	Black	63	651.4	322	62.63 (62.06)	4.2 (3.53)	8.59(9.05)	9.04(8.83)	10.89(10.65)	16
3	[CoLNO ₃ (OH)].1½H ₂ O	Black	90	678.9	200	60.09 (59.24)	4.42 (3.51)	10.31(10.37)	8.67(8.84)	-	31
4	[CoL(OAc)OH].½EtOH	Black	100	698.9	230	65.24(66.56)	4.57 (4.37)	8.01 (8.2)	8.16(8.25)	-	2
5	[NiLCl ₂ .H ₂ O].½EtOH	Black	83	710.7	340	59.09 (60.03)	4.64 (3.72)	7.88(8.39)	8.47(7.82)	10.25(10.65)	66
6	[NiL(OAc)OH].½EtOH	Black	95	679.7	280	65.32 (65.69)	4.85 (4.44)	8.24 (8.16)	8.64(8.8)	-	16
7	[CuLCl ₂].2H ₂ O	Black	100	692.5	300	58.92 (59.68)	4.33(3.97)	8.08(8.02)	9.16(8.47)	10.25(9.47)	29
8	[CuLBr(OH)].½EtOH	Black	100	705.5	230	59.53(60.79)	4.25 (3.31)	7.94 (7.51)	11.26(11.5)	11.34(10.91)	35
9	[CuL(OH)]NO ₃ .H ₂ O	Black	92	683.5	154	59.69(60.03)	4.24(4.12)	8.19 (8.94)	9.29(8.89)	-	62
10	[CuL(OH)H ₂ O]ClO ₄ .½EtOH	Black	100	716.5	-	59.8(60.85)	4.33(4.06)	7.76(7.65)	9.4(10.58)	13.79(13.93)	63
11	[PdLCl ₂ .H ₂ O]Cl.2½H ₂ O	Black	100	762.4	220	53.51(54.48)	4.33(4.04)	7.34(7.75)	13.95(14.18)	9.31(9.46)	66

^a: $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$ DMF solutions (10^{-3} M), X: Halogen

2.2. FT-IR

The main bands and their assignments are listed in Table 2. In the IR spectra of all complexes, the presence of a single broad band in the region 3256-3176 cm^{-1} may be assigned to $\nu(\text{N-H})$ stretching vibration. The IR spectra of all complexes show the absence of carbonyl and amino groups, which showed no bands corresponding to these groups. The appearance of new strong intensity bands at 1609–1572, 1535-1504 and 1296-1277 cm^{-1} is assigned to amide-I $\nu(\text{C=O})$, amide-II $\nu(\text{C-N}) + \nu(\text{N-H})$ and amide-III $\nu(\text{N-H})$ stretching vibrations, indicating the formation of macrocyclic

framework. This is in consistence with the presence of a new medium band in the region 450- 410 cm⁻¹, assignable to ν (M-N) vibrational modes [13, 25]. It is worth to mention that, for most complexes, the region of ν (C=N) of azomethine overlapped with a strong broad peak of amide-I ν (C=O). The observed value of absorption band due to amide-I ν (C=O), azomethine ν (C=N) is lower than that that usually occur for these groups which supports the coordination of these groups to the metal atom [26, 27]. The small intensity bands present in the region 3061–2913 cm⁻¹ may be assigned to the ν (C–H) stretching vibrations of the aromatic and aliphatic group.

All complexes display a strong as well as broadband at 3429-3321 cm⁻¹ due to ν (OH) vibration. The appearance of new medium intensity band in the region 541-498 cm⁻¹, assigned to ν (M-O) [25]. The additional bands observed due to anions (Table 2). Complex (3) shows IR bands at 1383 (ν_3), 1296(ν_1), 1041(ν_2) cm⁻¹. The value of $\Delta(\nu_3-\nu_1)$, stretching vibration is, separated by 87 cm⁻¹ suggesting uncoordinated nitrate ion [28, 29], whereas complex (9) shows IR bands at 1370 and 1284 cm⁻¹ characterizing the ionic nitrate [13, 14]. These observations are further confirmed from molar conductivities (Table 1). Complexes (4,6) show two bands at 1586-1575 and 1330-1323 cm⁻¹. The energy separation between ν_{as} and ν_s is found to be >144 cm⁻¹ indicating the monodentate coordination of the acetate ion [14, 28]. The presence of uncoordinated perchlorate anion in the complex (10) is confirmed from the bands around 1114 and 629 cm⁻¹ [30]. On the basis of the IR spectra, it is concluded that the macrocyclic ligand behaves as a neutral quadridentate one, with the lone electron pairs of two amide nitrogen atoms and two azomethine nitrogen atoms, or as neutral bidentate one with the lone electron pairs of two azomethine nitrogen atoms only for Pd(II) complex (11).

Table 2. Important IR spectral bands (cm⁻¹)^a of the macrocyclic complexes.

No	Compound	ν OH	ν NH	Amide bands				ν (M-O)	ν (M-N)	(NO ₃ ⁻ , OAc ⁻ , ClO ₄ ⁻)
				I	II	III	(IV)			
1	[FeLCl ₂].½EtOH.½H ₂ O	3424(vb)	3176(vb)	1591(b)	1514(m)	1282(w)	757(s)	575(w)	411(m)	-
2	[CoLCl(OH)].H ₂ O	3354(b)	3200(vb)	1585(b)	1516(m)	1286(m)	758(s)	500(w)	425(w)	-
3	[CoLNO ₃ (OH)].½H ₂ O	3321(b)	3200(vb)	1584(m)	1518(b)	1297(m)	755(s)	498(w)	437(m)	1383(s),1296(b),876(w)
4	[CoL(OAc)OH].½EtOH	3416(b)	³ 3208(vb)	1586(b)	1518(w)	1281(m)	757(s)	508(w)	434(m)	1586(vb),1323(w),1166(m), 679(m)
5	[NiLCl ₂ .H ₂ O]Cl ₂ .H ₂ O.½EtOH	3322(b)	3190(w)	1584(b)	11522(b)	1291(b)	757(s)	500(m)	416(m)	-
6	[NiL(OAc)OH].½EtOH	3412(b)	3200(w)	1575 (b)	11535(w)	1288(w)	757(s)	524(w)	418(w)	1575(b),1330(w),680(m)
7	[CuLCl ₂].2H ₂ O	3418(b)	3192(b)	1609(m),1584(m)	1517(s)	1296(m)	755(s)	525(w)	416(vw)	-
8	[CuL Br(OH)].½EtOH	3415(s)	3216(w)	1600(m),1573(m)	1504(s)	1285(m)	745(s)	500(m)	450(m)	-
9	[CuL(OH)]NO ₃ .H ₂ O	3423(b)	3256(w)	1572(m)	1505(s)	1284(m)	745(s)	510(w)	440(w)	1370(s),838(m)
10	[CuL(OH)H ₂ O]ClO ₄ .½EtOH	3429(b)	3200(vb)	1608(b)	1509(b)	1295(m)	758(s)	541(w)	412(m)	1114(s),629(s)
11	[PdLClH ₂ O]Cl ₂ .½H ₂ O	3422(b)	3208(b)	1594(b)	1521(m)	1277(b)	759(s)	519(m)	410(m)	-

^a:vb, very broad s, strong; m, medium; w, weak; b, broad; v, stretching

2.3. Electronic Spectra and Magnetic Data

The electronic spectra of the macrocyclic complexes were measured in DMF solution. The absorption bands and the magnetic moment values at room temperature (μ_{eff} B.M.) are given in Table 3.

2.3.1. Iron(II) Complex

The electronic spectrum of Fe(II) complex (1) displays a broad peak at 525 nm, may be assigned to ⁵T_{2g}→⁵E_g transition indicating octahedral geometry around Fe(II) [31]. Its magnetic moment value is 4.9 B.M. indicating an octahedral geometry around Fe(II) ion [31, 32].

2.3.2. Cobalt(II) Complexes

The electronic spectra of Co(II) complexes (2-4) show a broadband in the range 520-510 nm corresponding to ⁴T_{1g}(F)→⁴A_{2g}(F) transition. It may be concluded that the complexes show octahedral geometry [33]. The magnetic moment value of the Co(II) complexes is in the range 4.6 5.05. 05 B.M., confirming the high-spin octahedral configuration [33, 34].

2.3.3. Nickel(II) Complexes

The electronic spectra of nickel(II) complexes (5,6) exhibit band in the ranges 520-510 nm which is assigned to

${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ transition. This band is a characteristic of the octahedral environment [35, 36]. The magnetic moment of the nickel complexes is in the range of 2.6 – 2.86 B.M. These values are in tune with the presence of an octahedral geometry around the nickel(II) ion [35].

2.3.4. Copper(II) Complexes

The electronic spectra of the copper(II) complexes (**7,8,10**) display one broad band centered at 528-520 nm. The 2E_g and ${}^2T_{2g}$ states of the octahedral Cu(II) ion (d^9) split under the effect of the tetragonal distortion and the distortion can be such as to cause the three transition ${}^2B_{1g} \rightarrow {}^2A_{1g}$, ${}^2B_{1g} \rightarrow {}^2B_{2g}$ and ${}^2B_{1g} \rightarrow {}^2E_g$ to remain unresolved in the spectra [35, 37]. It was concluded that all three transitions lie within the one broad envelope centered at the same range previously mentioned. The electronic spectrum of the copper(II) complex (**9**) showed an intensive band at 660 and 520 nm could be attributed to ${}^2B_{1g} \rightarrow {}^2A_{1g}$ and ${}^2B_{1g} \rightarrow {}^2E_g$ transitions, respectively [13, 38] suggesting distorted square pyramidal structure around Cu(II) ion. The magnetic moment of all the Cu(II) complexes is in the range of 2.12 - 1.8 B.M., these values correspond to one unpaired electron [33].

2.3.5. Palladium(II) Complex

The electronic absorption spectrum of Pd(II) complex (**11**) exhibits band at 500 nm, which may be assigned to ${}^1A_{1g} \rightarrow {}^1A_{2g}$ transitions [39, 40], indicating square-planar structure around the Pd(II) ion. The coordination of the chloride to the square-planar bivalent palladium centre is confirmed by its non-electrolytic nature in DMF solution. Pd(II) complex is diamagnetic confirming the square planar geometry.

Table 3. Electronic spectral data (nm) and magnetic moment (B.M.) of the macrocyclic metal complexes.

No	Compound	$\lambda_{max}(nm)$	(μ_{eff} B.M.)
1	[FeLCl ₂].½EtOH.½H ₂ O	525 ^a ,385 ^b ,360 ^c ,266 ^d	4.9
2	[CoLCl(OH)].H ₂ O	518 ^a ,385 ^b ,360 ^c ,265 ^d	4.8
3	[CoLNO ₃ (OH)].1½H ₂ O	520 ^a ,380 ^b ,330 ^c ,270 ^d	5.05
4	[CoL(OAc)OH].½EtOH	510 ^a ,385 ^b ,350 ^c ,266 ^d	4.6
5	[[NiLCl H ₂ O]Cl.H ₂ O.½EtOH	520 ^a ,385 ^b ,345 ^c ,268 ^d	2.6
6	[NiL(OAc)OH].½EtOH	510 ^a ,345 ^c ,260 ^d	2.86
7	[CuLCl ₂].2H ₂ O	520 ^a ,386 ^b ,360 ^c ,265 ^d	2.1
8	[CuLBr(OH)].½EtOH	528 ^a ,335 ^c ,260 ^d	2.12
9	[CuL(OH)]NO ₃ .H ₂ O	660 ^a ,520 ^a ,385 ^b ,360 ^c ,266 ^d	1.8
10	[CuL(OH)H ₂ O]ClO ₄ .½EtOH	525 ^a ,385 ^b ,360 ^c ,270 ^d	2.07
11	[PdLCl H ₂ O]Cl.2½H ₂ O	500 ^a ,388 ^b ,362 ^c ,266 ^d	Dia

^a: d-d transition. ^b: LMCT. ^c: $n \rightarrow \pi^*$. ^d: $\pi \rightarrow \pi^*$

2.4. EPR Spectroscopic Studies

The powder ESR spectra were carried out for the 16-membered N₄ macrocyclic copper(II) complexes (**7, 9**) at room temperature on the X-band frequency 9.719 GHz. The EPR parameters are tabulated in Table 4. The complexes give axial spectra (Fig. 1). Analysis of spectra gives $g_{||} = 2.16$ and $g_{\perp} = 2.039 - 2.033$. The trend $g_{||} > g_{\perp} > 2.0023$ suggests $d_{x^2-y^2}$ ground state for the Cu(II) ion, indicating that the unpaired electron is in the $d_{x^2-y^2}$ orbital of the Cu(II) ion [14, 15, 35]. The greater value of $g_{||}$ compared to g_{\perp} indicates a tetragonal distortion around the Cu(II) ions [41, 42]. Moreover, the observed $g_{||}$ values < 2.3 revealing an appreciable covalent nature for Cu-L bond [43]. The exchange interaction between the copper centers in polycrystalline sample is explained by Hathaway expression $G = g_{||} - 2.0023 / g_{\perp} - 2.0023$ [44]. The calculated G value for complexes is higher than 4 indicating no exchange interaction between copper centers.

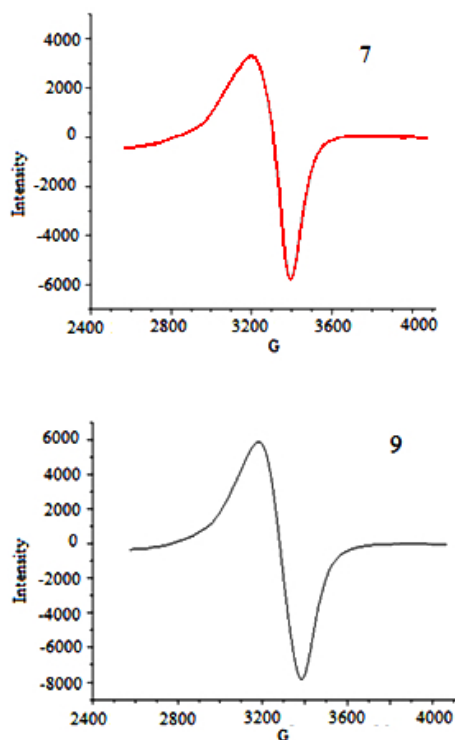


Fig. (1). EPR spectra for Cu(II) complexes (7,9).

Table 4. : EPR spectral data of Cu(II) complexes.

No	Complex	g_{\parallel}	g_{\perp}	g_{av}	G
7	[CuLCl ₂].2H ₂ O	2.160	2.033	2.087	4.8
9	[CuL(OH)]NO ₃ .H ₂ O	2.160	2.039	2.081	4.1

2.5. Thermogravimetric Studies

The thermal properties of the 16-membered N₄ macrocyclic metal(II) complexes were carried out by thermogravimetric analysis (TGA/DTG) in N₂ atmosphere from 25 to 800 °C, at a rate of 10 °C min⁻¹. The obtained data are represented in Table 5.

2.5.1. Iron(II) Complex

The TG curve iron (II) complex (**1**) exhibits a weight loss in the temperature range of 30-80 °C associated with one endothermic DTG peak at 48 °C which is assigned to loss of solvent of crystallization. The TG/DTG curves display gradual decomposition at 272–460 °C, leaving Fe₂O₃, as the final product.

2.5.2. Cobalt (II) Complexes

In TG curves cobalt(II) complexes (**2-4**), mass loss within the temperature range 30– 97 °C, corresponding to one endothermic DTG peak at 44– 47°C, that is attributed to the loss of solvent of crystallization. The TG curves show gradual decomposition at a temperature range of 200-508 °C, remaining Co for complexes (**2,3**) and CoO for complex (**4**) as final residue.

2.5.3. Nickel (II) Complexes

For Ni(II) complexes (**5,6**), the TG curves show that mass loss occurs at 30– 80 °C, associated with one endothermic DTG peak at 48–56 °C, is corresponding to release of the solvent of crystallization in one step (Table 5). On further heating, the organic part is lost in one or more stages, with the formation of Ni for complex (**5**), and NiO for complex (**6**) as final residue.

2.5.4. Copper(II) Complexes

TG thermograms of copper(II) complexes (**7-9**) show a mass loss from room temperature up to 97 °C, associated with one endothermic DTG peak, that is attributed to the loss of solvent molecules (Table 5). The TG/ DTG curves also show that complexes (**7,8**) decomposed at 300,230 °C, respectively. The thermogram of complex (**9**) displayed two degradation stages. The first stage at 97-297 °C is corresponding to the loss of (NO₃+OH) (weight loss; Calc./Found%; 11.47/11.8%). The next stage at 297-408 °C is attributed to the completion of the decomposition process. The final decomposition products can be CuO for complexes (**7-8**) and Cu for complex (**9**).

Table 5. Thermal data of the macrocyclic metal complexes.

No.	Compound	Temp/°C		Wt loss %.		Reaction	Leaving species
		DTG	TGA	Calc.	(F)		
1	[FeLCl ₂].½EtOH.½H ₂ O	48 334, 382	30-80 272-460 at 460	4.7 83.57 11.73	(4.65) (82.85) (12.6) ^c	(i) ^b (ii) ^d	- ½EtOH - Decomp. ≡Fe ₂ O ₃
2	[CoLCl(OH)].H ₂ O	42 341,531	30-70 341-675 at 675	2.76 88.2 9.04	(2.57) 88.43 (9) ^c	(i) ^a (ii) ^d	-H ₂ O - Decomp. ≡Co
3	[CoL NO ₃ (OH)].1½H ₂ O	47 142,234,437	30-70 200-508 at 508	3.93 87.57 8.5	(4.03) (87.56) (8.41) ^c	(i) ^a (ii) ^d	- 1½H ₂ O - Decomp. ≡Co
4	[CoL(OAc)OH].½EtOH	44 280,338,381	30-97 211-459 at 459	3.38 85.61 11.01	(3.55) (85.55) (10.9) ^c	(i) ^b (ii) ^d	- ½EtOH - Decomp. ≡CoO
5	[NiLCl H ₂ O]Cl.H ₂ O.½EtOH	56 422,450	30-80 340-527 at 527	5.92 85.61 8.47	(6.04) (85.96) (8) ^c	(i) ^{a+b} (ii) ^d	- H ₂ O + ½EtOH - Decomp. ≡Ni
6	[NiL(OAc)OH].½EtOH	48 285,490	30-63 280-544 at 544	3.38 85.72 10.9	(3.37) (85.16) (11.47) ^c	(i) ^b (ii) ^d	- ½ EtOH - Decomp. ≡NiO
7	[CuLCl ₂].2H ₂ O	46 316,369,484	30-80 300-468 at 468	5.19 83.33 11.48	(5.2) (83.27) (11.53) ^c	(i) ^a (ii) ^d	- 2H ₂ O - Decomp. ≡CuO
8	[CuLBr(OH)].½EtOH	47 296,419	30-77 230-508 at 508	3.26 85.48 11.26	(3.23) (85.69) (11.08) ^c	(i) ^b (ii) ^d	- ½ EtOH - Decomp. ≡CuO
9	[CuL(OH)]NO ₃ .H ₂ O	53 196, 358	30-97 97-297 297-408 at 408	3.34 11.47 75.99 9.2	(3.83) (11.8) (74.77) (9.6) ^c	(i) ^a (ii) ^d (ii) ^d	- H ₂ O -(NO ₃ +OH) - Completion of decomp. ≡Cu

^a: Dehydration ^b: Desolvation ^c: Final product percent ^d: Decomposition

2.6. Kinetic Data for the Macrocyclic Complexes

The kinetic and thermodynamic parameters of the decomposition stages of the complexes (**1, 4-7**) were calculated from TGA thermogram using the Coats–Redfern equation [45]. The Horowitz and Metzger [46] equation:

$$C_s = (n)^{1-n} \quad \text{was used for the evaluation of the value of the reaction order, and given by: } C_s = \frac{m_s - m_\infty}{m_0 - m_\infty} \quad \text{where}$$

is the weight fraction of the substance present at DTG peak temperature T_s, is the remaining weight at T_s, and are the initial and final weights of the substance, respectively. The estimated values of for the thermal decomposition of the desolvated complexes were found in the range of 0.28-0.35 (Table 6 and Fig. 2), indicating that the degradation suggests first order reaction [14, 15]. Thermodynamic parameters such as the activation energy E*, Arrhenius constant A, the activation entropy S*, the activation enthalpy H* and the free energy of activation G* were calculated using Coats–Redfern equation for n = 1:

$$\log \left[\frac{-\log(1-x)}{T^2} \right] = \log \frac{AR}{\theta E^*} \left(1 - \frac{2RT}{E^*} \right) - \frac{E^*}{2.303RT} \quad (1)$$

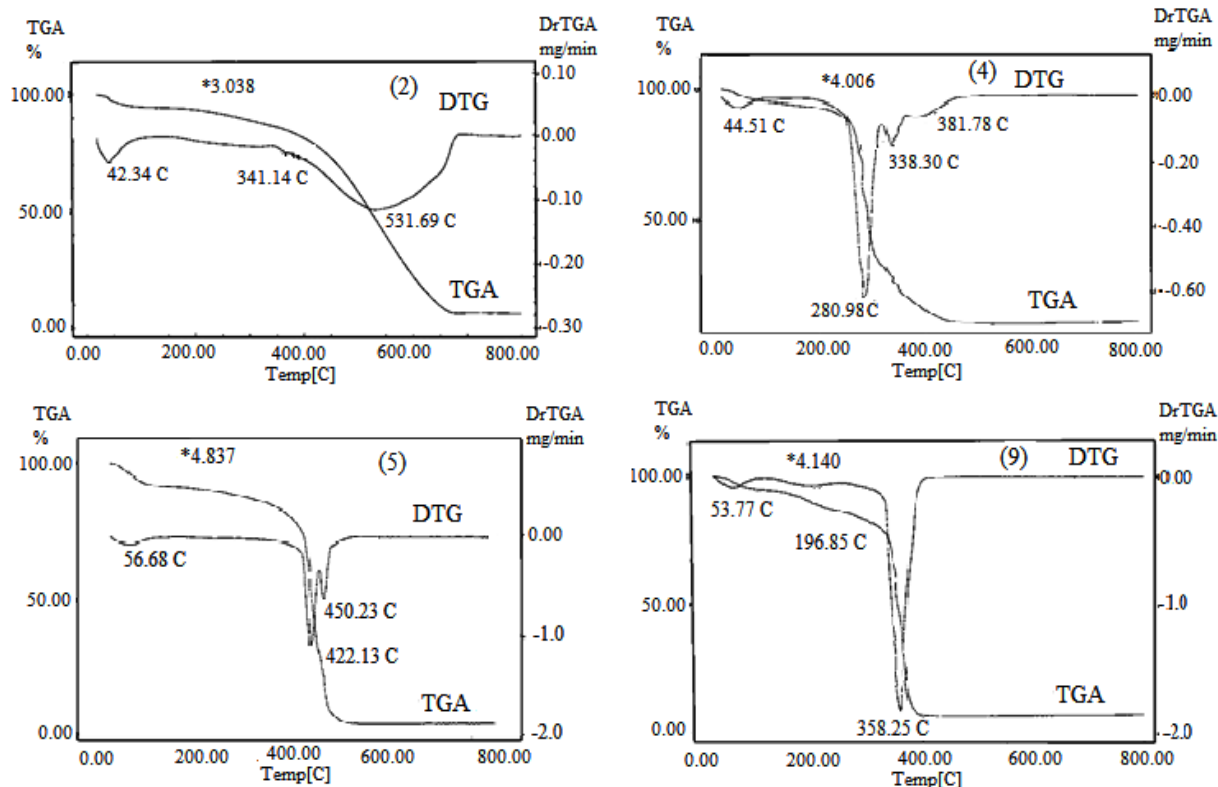


Fig. (2). TG/DTA curves of complexes (2,4, 5,9).

Where: x is the fraction decomposed, R : is the gas constant and θ is the heating rate. Since $(1-2RT/E^*) \approx 1$, a plot of the left-hand side of Eq. (1) against $1/T$ gives a straight line from its slope and intercept, E^* and A were determined. The entropy of activation S^* , enthalpy of activation H^* and Gibbs free energy G^* were calculated by applying the following equations: $\Delta S^* = [\ln(Ah/kT) - 1]R$, $\Delta H^* = \Delta E^* - RT$ and $\Delta G^* = \Delta H^* - T\Delta S^*$.

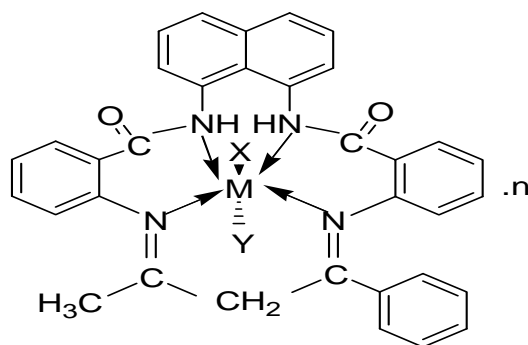
The calculated kinetic and thermodynamic values are listed in Table 6. From the results, the values reveal high stability of the complexes. Since the positive sign indicates that decomposition stages are endothermic processes. The reaction for which is positive and is negative reveals that the free energy of the final residue is higher than that of the initial compound, and all decomposition steps are non-spontaneous processes. On the other hand, the negative values of indicate more ordered activated complex than the corresponding reactants and that the reaction is slow [47]. The correlation coefficients of the Arrhenius plots of the thermal decomposition steps were found to lie in the range 0.97 to 0.95 showing the best fit with a linear function.

Table 6. Kinetic and thermodynamic parameters for macrocyclic metal complexes (1,4-7)

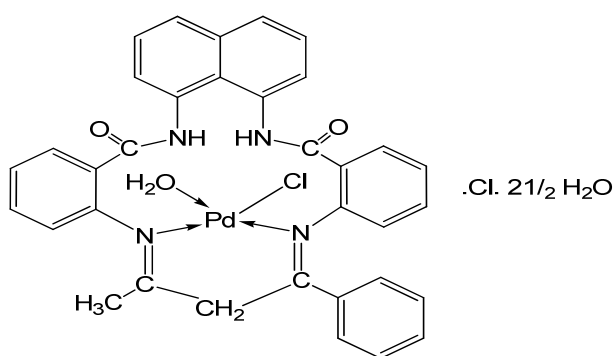
No	Complex	D.T. (K)	A	S^*	E^*	H^*	G^*	C_s	$^aR^2$
			(S^{-1})	($J mol^{-1}K^{-1}$)	(kJ mol $^{-1}$)				
1	[FeLCl $_2$]. $\frac{1}{2}$ EtOH. $\frac{1}{2}$ H $_2$ O	493-823	5.88E 7	-12.308	85.17	79.933	87.453	0.31	0.96
4	[CoL(OAc)OH]. $\frac{1}{2}$ EtOH	523-850	8.208E 7	-11.885	82.10	77.378	84.129	0.35	0.95
5	[NiLCl H $_2$ O]Cl.H $_2$ O. $\frac{1}{2}$ EtOH	503-673	7.749E 6	-14.461	102.18	96.336	106.502	0.28	0.95
6	[NiL(OAc)OH]. $\frac{1}{2}$ EtOH	553-817	6.848E 6	-14.508	36.78	31.36	21.918	0.336	0.97
7	[CuLCl $_2$].2H $_2$ O	573-741	2.943E 5	-17.646	33.03	27.65	39.067	0.286	0.95

$^aR^2$: Correlation coefficient

From the interpretation of elemental analyses, molar conductivity, magnetic susceptibilities, spectral and thermal studies, suggested structures for the complexes (1–11) are given in Fig. (3).



No	M	X	Y	n
(1)	Fe(II)	Cl	Cl	($\frac{1}{2}$ EtOH. $\frac{1}{2}$ H ₂ O)
(2)	Co(II)	Cl	OH	H ₂ O
(3)	Co(II)	NO ₃	OH	1 $\frac{1}{2}$ H ₂ O
(4)	Co(II)	OAc	OH	$\frac{1}{2}$ EtOH
(5)	Ni(II)	Cl	H ₂ O	(Cl.H ₂ O. $\frac{1}{2}$ EtOH)
(6)	Ni(II)	OAc	OH	$\frac{1}{2}$ EtOH
(7)	Cu(II)	Cl	Cl	2H ₂ O
(8)	Cu(II)	Br	OH	$\frac{1}{2}$ EtOH
(9)	Cu(II)	OH	nil	NO ₃ .H ₂ O
(10)	Cu(II)	OH	H ₂ O	(ClO ₄ . $\frac{1}{2}$ EtOH)



(11)

Fig. (3). Suggested structure of the macrocyclic complexes (1-11).

2.7. Biological Results

The anticancer activity of the 16-membered N₄ macrocyclic metal complexes (1,2,5,7,9) was detected *in vitro* against human breast cancer cell (MCF-7) and human hepatocarcinoma cell (Hep-G2) by SRB assay. The results of the

cytotoxic activity *in vitro* expressed as IC_{50} are given in Table 7 and plotted in (Fig. 4). The tested complexes show IC_{50} value in the range of 3.2-1.6 and 3.7-1.7 $\mu\text{g/mL}$ towards human breast cancer cell lines (MCF-7) and human hepatocarcinoma cells (Hep- G2), respectively. According to Sheir [48], these complexes are considered to be very active towards the two cell lines. The results indicate that Ni(II) complex (5) showed highest cytotoxic activity on both human breast cancer cell line and hepatocarcinoma cell (IC_{50} value = 1.6 and 1.7 $\mu\text{g/mL}$, respectively). The enhanced activity of the investigated complexes agrees well with and better than the documented activity of similar metal complexes as antitumor agents [13 - 15, 30, 49]. The macrocycle, as well as the type of metal ions, may be the reason for their different anticancer activity. These compounds seem to be promising as an anticancer agent because of their high cytotoxic activity. The active sequence of the complexes follows the trend:

Ni(II) > Co(II) = Cu(II) NO_3 > Fe(II) > Cu(II) Cl_2 for MCF-7 cells;

Ni(II) > Cu(II) NO_3 > Co(III) > Fe(II) > Cu(II) Cl_2 for Hep-G2 cells

Table 7. Lethal concentration (IC_{50}) of the macrocyclic metal complexes on MCF-7 and Hep-G2 cell lines.

No	Compound	$IC_{50}(\mu\text{g/mL})^a$	
		MCF-7	Hep-G2
1	[FeLCl ₂].1/2EtOH.1/2H ₂ O	2.5	3.0
2	[CoLCl(OH)]. H ₂ O	2.2	2.7
5	[NiLCl.H ₂ O] Cl.H ₂ O.1/2EtOH	1.6	1.7
7	[CuLCl ₂].2H ₂ O	3.2	3.7
9	[CuL(OH)]NO ₃ .H ₂ O	2.2	2.5

^a IC_{50} is the concentration of compound (in $\mu\text{g/mL}$) that inhibits a proliferation rate of the tumor cells by 50% as compared to control untreated cells.

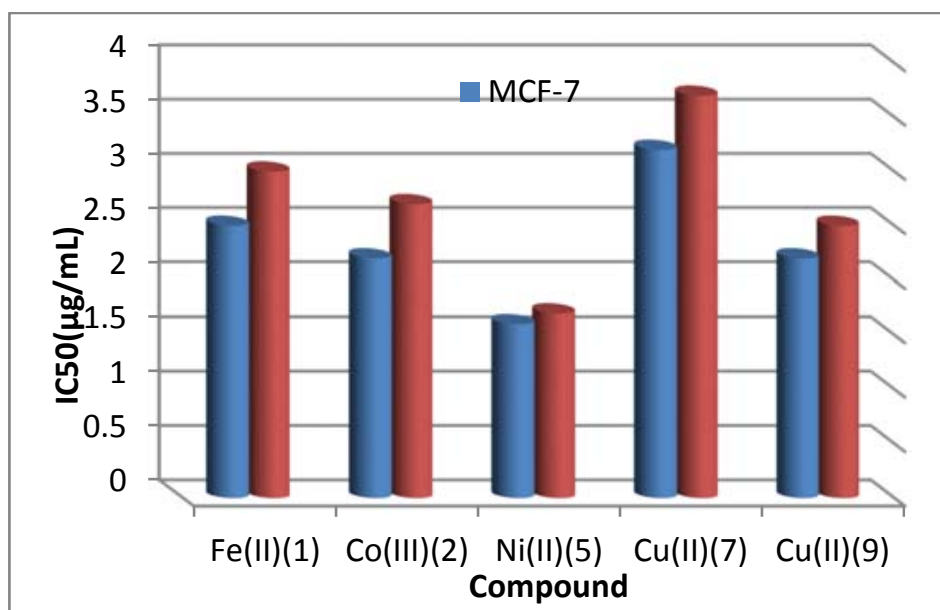


Fig. (4). Lethal concentration (IC_{50}) of the macrocyclic metal complexes on MCF-7 and Hep-G2 cell lines.

CONCLUSION

In the present study, a new Tetraaza (N_4) macrocyclic metal complexes obtained by template condensation reaction were synthesized. The structure of macrocyclic metal complexes have been proposed on the basis of the analytical data as elemental analyses, conductivity, magnetic, spectral as electronic, EPR and IR and thermal studies. The results revealed the formation of monomeric macrocyclic metal complexes. A distorted octahedral, distorted square pyramidal or square planar geometry may be proposed for these complexes. All the complexes of the tested series were potent anticancer agents.

5. EXPERIMENTAL

5.1. Materials

The metal salts (E.Merck) were commercially available as pure samples. All the chemicals used in this study were of AnalaR grade and procured from Sigma, Aldrich and Fluka. All solvents were used as received. All reactions were carried out under normal atmospheric conditions.

5.1.1. Synthesis of the Macrocyclic Complexes

The starting material, N,N'-(naphthalene-1,8-diyl)bis(2-aminobenzamide) has been synthesized and characterized as previously reported [15]. The macrocyclic metal complexes were synthesized by template condensation reaction as follows: 0.5 g (1mmol) of N,N'-(naphthalene-1,8-diyl)bis(2-aminobenzamide) in ethanol was refluxed with 0.2 g of 1-benzoylacetone in ethanol (1:1) molar ratio. To the above solution, 20 mL ethanolic solution of different metal salt was added. The reaction mixture was stirred under reflux whereupon the complexes precipitated. The brownish black solid precipitate formed was collected by filtration and washed several times with cold ethanol and dried under vacuum.

5.2. Physical Methods

Microanalyses (C,H and N) of these complexes were carried out at Cairo University, Giza, Egypt using CHNS- 932 (LECO) Vario Elemental Analyzer. Metal contents were estimated using standard methods [50]. The Fourier Transform Infrared (FT-IR) measurements in the range of 4000– 400 cm^{-1} were recorded in KBr discs using Neneus-Nicolidite-640-MSA FT-IR. Thermo-Electronics Co. Electronic spectra were determined in Nujol mull using 4802 UV/vis double beam spectrophotometer. The ^1H NMR spectrum was recorded in DMSO- d_6 using Varian Gemini 200 NMR spectrophotometer at 300 MHz. The EPR spectra were measured using a Varian E-109C model X-band spectrometer. The molar conductance was measured at 30 $^\circ\text{C}$ in DMSO solution (10^{-3} M) using a CON 6000 conductivity meter. Magnetic measurements (Gouy balance) were carried out at room temperature. The effective magnetic moments were calculated using the relation $\mu_{\text{eff}}=2.828 (\chi_m T)^{1/2}$ B.M., where χ_m is the molar susceptibility corrected for diamagnetism of all atoms in the compounds. The complexes were studied by thermogravimetry (TG /DTG) in a static nitrogen atmosphere with a sample heating rate of 10 $^\circ\text{C}/\text{min}$, using a Shimadzu DTA/TG-50 Thermal Analyzer.

5.3. Anticancer Activity

The cytotoxicity of the compounds was tested at the National Cancer Institute, Cairo University Egypt by SRB assay using the method of Skehan et al. [51]. Cells were plated in 96- multiwell plate (104 cells/ well) for 24 h before treatment with the compounds to allow attachment of a cell to the wall of the plate. Different concentrations of the compound under test (0, 2.5, 5, 10, 20 $\mu\text{g}/\text{mL}$) added to the cell monolayer triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37 $^\circ\text{C}$ and an atmosphere of 5% CO_2 . After 48 h, cells were fixed, washed and stained with Sulfo-Rhoda- mine-B stain. Excess stain was washed with acetic acid and attached stain was recovered with Tris EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to obtain the survival curve of each tumor cell line after the specified compound.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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