Accepted Manuscript

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PII:	S1386-1425(14)00789-6
DOI:	http://dx.doi.org/10.1016/j.saa.2014.05.018
Reference:	SAA 12180
To appear in:	Spectrochimica Acta Part A: Molecular and Biomo- lecular Spectroscopy
Received Date:	5 March 2014
Revised Date:	1 May 2014
Accepted Date:	9 May 2014



Please cite this article as: H.A. El-Boraey, A.A. Serag El-Din, Transition metal complexes of a new 15-membered $[N_5]$ penta-azamacrocyclic ligand with their spectral and anticancer studies, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* (2014), doi: http://dx.doi.org/10.1016/j.saa.2014.05.018

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Transition metal complexes of a new 15-membered [N₅] penta-azamacrocyclic ligand with their spectral and anticancer studies

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ABSTRACT

Novel penta-azamacrocyclic 15-membered [N₅] ligand [L] i.e. 1,5,8,12- tetetraaza - 3,4 : 9,10-dibenzo-6- ethyl-7- methyl-1,12-(2,6-pyrido)cyclopentadecan-5,7 diene-2,11-dione and its transition metal complexes with Co(II), Ni(II), Cu(II), Ru(III) and Pd(II) have been synthesized and structurally characterized by elemental analysis, spectral, thermal as well as magnetic and molar conductivity measurements. On basis of IR, MS, UV-Vis ¹H NMR and EPR spectral studies an octahedral geometry has been proposed for all complexes except Co(II), Cu(II) nitrate complexes and Pd(II) chloride complex that adopt tetrahedral, square pyramidal and square planar geometries, respectively. The antitumor activity of the synthesized ligand and some complexes against human breast cancer cell lines (MCF-7) and human hepatocarcinoma cell lines (HepG2) has been studied. The complexes (IC₅₀=2.04-9.7, 2.5-3.7 μ g/mL) showed potent antitumor activity comparable with their ligand (IC₅₀= 11.7, 3.45 μ g/mL) against the above mentioned cell lines, respectively. The results evidently show that the activity of the ligand becomes more pronounced and significant when coordinated to the metal ion.

Keywords: penta-azamacrocyclic, macrocyclic metal complexes, Spectral studies, antitumor activity, IC₅₀

Introduction

Chemistry of macrocycles and their metal complexes has attracted much attention and has become a growing class of research [1-9], largely as a result of their remarkable applications in biology, supramolecular chemistry and new materials [2-9], etc. To some extent the interest in macrocyclic complexes especially those with polydentate ligands stems from the chemical properties that the macrocyclic ligands bring to the complexes as well as the variety of geometrical forms available and the possible encapsulation of the metal ion [10,11]. Complexes with aza-macrocyclic ligands have

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remained a focus of scientific attention [12-15]. Much attention has been paid to macrocyclic compounds containing amide groups [4,6,12,16]. These compounds not only can act as hydrogen bonding host molecules but also can form macrocyclic rotors [17]. The formation of macrocyclic complexes depends significantly on the dimension of internal cavity, rigidity of macrocycles, nature of its donor atoms, the selectivity of metal ions and the complexing properties of the anion involved in coordination, for transition metal ions, features such as the nature and magnitude of crystal-field effects play also an important role [18-20]. Moreover, macrocyclic Schiff bases have been widely studied due to their selective chelation to certain metal ions depending on the number, type and position of their donor atoms, the ionic radius of metal ion and coordinating properties of counter ions [21]. In view of the interest and importance of nitrogen macrocycles, we have reported the synthesis, spectroscopic characterization and anticancer activity of Co(II), Ni(II), Cu(II), Ru(III), Pd(II) complexes with new penta-azamacrocyclic 15-membered $[N_5]$ ligand i.e. 1,5,8,12tetraaza -3,4 :9,10-dibenzo-6- ethyl-7- methyl-1,12-(2,6-pyrido)cyclopentadecan-5,7 diene- 2,11-dione. These complexes have been characterized with the help of various physicochemical techniques. Furthermore, the *in vitro* antitumor activity against human breast cancer cell lines (MCF-7) and human hepatocarcinoma cell lines (HepG2) has been studied.

Experimental

Materials and methods

All the chemicals used were of AnalaR grade and procured from Sigma– Aldrich and Fluka. Metal salts (E. Merck) were commercially available as pure samples and solvents were used as received.

Synthesis of start material

The starting material (**A**) has been synthesized as previously reported for similar compounds [22, 23]. A mixture of 1H-benzo [d] [1,3]oxazine-2,4-dione (2.0 mmol, 2 gm) with 2,6 diaminopyridine (1.0 mmol, 0.66 gm) in distilled water was stirred at 60 °C for about 3 h, heating on water bath was continued till the effervescence of CO₂ gas ceased. The reaction mixture was allowed to stand over night. Light brown crystals were filtered off and washed several times with cold distilled water. Recrystallization from ethanol gave 2-amino-N-{2-[(2-amino-benzoylamino) pyridine]-benzamide (**A**) {Color: off white, Yield: 50 %, m.p. = 95 °C. Analysis Cal. (Found) for C₁₉H₁₇N₅O₂.2H₂O (MW: 383) C, 59.53 (59.52); H, 5.48 (5.34); N, 18.27

(18.53) %. IR (KBr, υ cm⁻¹): 3293 υ (NH₂); 1664 υ (C=O);1617 υ (C=N); 1509 [υ (C-N) + δ (N-H)].¹H NMR (DMSO-*d*₆, δ , ppm) δ = 4.00 (H₂O), δ = 6.54-8.08 (py, Ar, H), δ = 5.74-5.79 (Ar–NH₂), δ = 13.23 (NH- amide). MS (EI⁺, *m*/*z*): Calc. for C₁₉H₁₇N₅O₂ (M = 347 Found: 346 [M-H]⁺.

Synthesis of ligand (L)

The (N₅) ligand has been synthesized by refluxing ethanolic (20 ml) of (**A**) (1.0 mmol, 1gm) with 2,3 pentandione (1.0 mmol, 0.29 gm) in the same solvent for 12 h, the brown precipitate obtained was filtered and washed several times with cold ethanol and dried over P_4O_{10} (m.p. 230 °C) (Scheme 1).

General procedure for synthesis of the macrocyclic complexes

All the complexes were prepared using the following general procedure. To a suspension of the macrocyclic ligand (L) (1.0 mmol, 0.5 gm) in ethanol (20 ml), a solution of hydrated metal salt (chloride, perchlorate, nitrate, acetate or bromide) in 20 ml ethanol was added gradually, in molar ratio 1:1 (L: M). The reaction mixture was heated under reflux for 10 h. The formed solid product was removed by filtration washed several times with cold ethanol and vacuuo dried over P_4O_{10} .

Physical measurements

The elemental analysis (C,H,N) were performed at Microanalytical Center, Cairo University, Giza, Egypt using CHNS-932 (LECO) Vario Elemental Analyzer. Metals and halide analyses were estimated using standard methods. The FTIR measurements were performed (4000-400 cm⁻¹) in KBr discs using Nenexeus-Nicolidite-640-MSA FT-IR, Thermo-Electronics Co. The UV-visible absorption spectra were measured 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 recorded using a Varian E-109C model X-band spectrometer. Molar conductivities were measured in DMSO solution (10⁻³ M) using a CON 6000 conductivity meter. Magnetic susceptibilities of the complexes were measured at room temperature by the modified Gouy method using magnetic susceptibility Johnson Matthey Balance. The effective magnetic moments were calculated using the relation $\mu_{eff} = 2.828 (\chi_m T)^{\frac{1}{2}}$ B.M., where χ_m is the molar susceptibility corrected for diamagnetism of all atoms in the compounds. Thermal analysis (TGA / DTG) was obtained out by using a Shimadzu DTA / TG -50 Thermal Analyzer with heating rate of 10 °C/ min in nitrogen atmosphere with a

following rate 20 ml /min in the temperature range 25-800 °C using platinum crucibles. Electrospray mass spectra (ESI) for the complexes were performed at the National Research Center, Egypt by the Thermo Electron Corporation. The electron impact (EI) mass spectrum for the ligand was run on Shimadzu-QP 2010 plus Mass Spectrometer, Microanalytical Laboratory, Faculty of Science, Cairo University, Egypt.

Biological tests

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.* [24]. Cells were plated in 96-multiwell plate (10^4 cells/well) for 24 h before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentration of the compound under test (0, 2.5, 5, 10, 20 µg/mL) were 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 °C and in atmosphere of 5% CO₂. 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 get the survival curve of each tumor cell line after the specified compound.

Results and discussion

Physical properties

The condensation of 2-amino-N-{2-[(2-amino-benzoylamino) pyridine] - benzamide (**A**) with 2, 3 pentanedione afford the macrocyclic ligand (L) (Scheme1). The reaction of (L) with different transition metal salts resulted in the formation of mononuclear macrocyclic complexes; the purity of the ligand and complexes has been checked by TLC. All the metals complexes are colored solids, stable towards air. Analytical data of the complexes (Table1) suggest that the metal to ligand ratio in all the complexes is 1M: 1L (Scheme 2). All complexes are slightly soluble in alcohols, insoluble in most common organic solvents, but soluble in DMF/DMSO. Crystals of these complexes could not be grown therefore X-ray crystal determination is not possible. The molar conductivity of complexes (2-5,8-10) in DMSO solutions (10^{-3} M) at room temperature indicates that they are non-electrolytes. Complexes (6,7) show molar

conductivity value (70, 68 Ω^{-1} cm² mol⁻¹) indicating that they are (1:1) electrolyte. However, complexes (1,11) show molar conductivity value (100, 87 Ω^{-1} cm² mol⁻¹) indicating their (1:2) electrolytic nature [8,25].

¹H NMR and mass spectral studies of ligand

The 'H NMR spectrum of the ligand (L) was recorded in DMSO- d_6 solution. The spectrum do not show any signal assignable to primary amino protons (at $\delta = 5.7$ ppm). This is strong evidence that proposed macrocyclic is formed by condensation reaction. The spectrum displays a singlet at ca. δ 1.05 ppm (s, 3H, N=C-CH₃) corresponding to the protons of one methyl group, another signal at ca. δ 2.14-2.46 ppm (m, 3H, – CH₂– CH₃) due to three protons of the second methyl group, signal at ca. δ 3.39 ppm (m, 2H, N=C-CH₂) due to two protons of one methylene group, signal at δ (6.50-8.61 ppm) assigned to aromatic and pyridine rings and signal at ca. δ 13.17 ppm (m, 2H, -NH-CO-) assigned to amide proton. Thus, the 'H NMR result supports the assigned geometry. The electron impact (EI) mass spectrum of the free ligand (Fig. 1S) confirms the proposed formula by showing a peak at 412 *amu* (M+1) corresponding to the macrocyclic moiety (C₂₄H₂₁N₅O₂, atomic mass *m/z* =411). The series of peaks in the range *m/z* = 65[C₄H₃N]⁺, 77[C₅H₃N]⁺, 92[C₅H₄N₂]⁺, 120 [C₆H₄N₂O]⁺, 255 [C₁₃H₉N₄O₂+2H]⁺ may be assigned to various fragments.



Scheme1.Synthetic route for the preparation of the macrocyclic ligand.

FT-IR

Fundamental IR spectral bands for the ligand and its complexes are given in Table 2. The IR spectrum of the free ligand is characterized mainly by the strong bands at 3206, 1644, 1618, 1499, 1289, and 754 cm⁻¹ are attributed to the stretching frequencies of secondary amide v(NH), amide-I [v(C=O)], azomethine v(C=N) group, amide-II $[v(C-N)+\delta(N-H)]$, amide-III $\delta(N-H)$ and amide-IV $[\phi(C=O)]$ wagging vibrations, respectively [16, 26-28]. This supports the macrocyclic nature of the ligand. The alkyl groups show characteristic stretching absorption bands in the region 2952- 2925 cm⁻¹, deformation band at 1432, 1367 cm⁻¹ and rocking at 695 cm⁻¹. respectively. The broad band at 3347 cm⁻¹ is assigned to the stretching frequency v(OH) of water molecules, which is also confirmed from elemental and thermal analysis. On complexation, the lowering of v(C=N) frequency values in all complexes (1611-1583 cm⁻¹) indicating the coordination of azomethine nitrogen to the metal center [26,27]. This is consistence with the presence of a new band at $(463-400 \text{ cm}^{-1})$ assignable to v (M-N) vibration [2,29]. The binding of secondary amide nitrogen in complexes (3-8,11) is indicated by a shift of amide-I vibration from 1644 cm⁻¹ in the free ligand to $(1626-1607 \text{ cm}^{-1})$ in the complexes [16]. Moreover, the shift to lower or higher frequencies at (3386-3174 cm⁻¹) of v(NH) of secondary amide group also confirms the involvement of amide nitrogen in metal coordination [16]. In case of complexes (1,2,9,10), the amide-I and $\nu(NH)$ of secondary amide group appears almost at nearly the same frequency, hence the mode of coordination is through (C=N) of azomethine only. Aquo and hydroxo complexes exhibit a strong as well as broad band at $(3444 - 3317 \text{ cm}^{-1})$ due to v(OH) vibration. This observation has been further confirmed by the appearance of new medium intensity band in the (625-529 cm^{-1}) region, assignable to v(M-O) [27,14]. The IR spectra of the complexes clearly demonstrate that the amide-II and amide-III are altered compare to the ligand due to complex formation. The strong band corresponding to the pyridine ring vibration, do not exhibit a shift in the all complexes [14]. Further, the complexes show the additional band due to anions (Table 2). Complexes (2,7) show IR bands at (1412-1380 (v_5), 1301-1269 (v_1), 1046-1041(v_2) cm⁻¹), (v_5-v_1) stretching vibration are separated by 111 cm⁻¹ suggesting unicoordinated nitrate ion [16,30]. Complex (7) also shows IR bands at (1380, 708 cm⁻¹) characterizing the ionic nitrate ion; the presence of ionic nitrate is also supported by conductance measurements (Table 1) [16,31,32]. The acetato complexes display bands at (1587-1583) and $(1379-1376 \text{ cm}^{-1})$ due to unidentate coordination of acetate ions [12,33,34]. It is worth to mention that, the

region of $v_{asym}(COO^-)$ overlapped with v(C=N) [35]. The presence of uncoordinated perchlorate anion in complex (6) is inferred from the bands around 1087 and 630 cm⁻¹ [15,36,37]. Therefore, and according to the IR spectra, it is concluded that the ligand behaves as neutral quatridentate one in complexes (3-8,11) with the lone electron pairs of two amide nitrogen atoms and the lone electron pairs of two azomethine groups. While in complexes (1,2,9,10) the ligand behaves as neutral bidentate one with the lone electron pairs of azomethine groups.

Mass spectra of complexes

Mass spectra provided additional structural information about the analyzed species. ESI-MS of the [Cu(L)Cl₂].5½H₂O complex (**5**) (Fig.1) and [Ru(L)(H₂O)Cl₃].5H₂O complex (**10**) show a molecular ions peak at *m/z* 642, 725 amu (calculated M=644.5, 726.5 amu, respectively) which coincide with their formulae weight. The spectra of the complexes also show structurally important fragment ion at *m/z* 52 [C₄H₄]⁺, 67 [C₅H₆+H]⁺, 76 [C₆H₄]⁺, 119 [C₇H₅NO]⁺, 238 [M-(C₁₁H₂₃N₂O_{5.5}+CuCl₂+H)]⁺, 370.5 [M-(C₁₁H₂₃N₂O_{5.5}+3H)]⁺, 516.5 [M-C₂H₁₆O_{5.5}]⁺ for complex (**5**) and fragment ion at *m/z* 52 [C₄H₄]⁺, 76 [C₆H₄]⁺, 119 [C₇H₅NO]⁺, 196 [C₁₂H₈N₂O]⁺, 239 [M-(C₁₁H₂₄N₂O₆+RuCl₃)]⁺, 315 [M-(C₅H₂₀N₂O₆+RuCl₃)]⁺, 502 [M-C₅H₁₉NO₆Cl]⁺ for complex (**10**). The observed data confirmed the proposed formulae for the complexes.

Electronic spectra and magnetic measurements

Nujol mull electronic absorption spectral data (λ_{max} , nm), room temperature effective magnetic moment values (μ_{eff} B.M.) are given in Table 3. The ligand and its complexes show the high energy bands in the range 250-224, 326-270 and 393-347 nm due to $\pi \rightarrow \pi^*$ transitions within the aromatic and pyridine rings, $n \rightarrow \pi^*$ transition of chromophore moieties present in the ligand, and CT transitions, respectively.

Cobalt (II) complexes

The electronic spectrum of the Co(II) complex (1) exhibits three d-d transition bands at 700, 640 and 450 nm, respectively. These bands can be assigned to ${}^{4}T_{1g}(F) \rightarrow {}^{4}T_{2g}(F)(v_{1})$; ${}^{4}T_{1g}(F) \rightarrow {}^{4}E_{2g}(F)(v_{2})$; ${}^{4}T_{1g}(F) \rightarrow {}^{4}T_{2g}(P)(v_{3})$ transition, respectively suggesting an octahedral geometry around Co(II) ion [38,39]. The electronic spectrum of Co(II) complex (2) displays only one band in the visible region at 648 nm due to ${}^{4}A_{2}(F) \rightarrow {}^{4}T_{1}(P)$ transition, which indicates tetrahedral geometry [40,41]. The value of the room temperature magnetic moment of complex (1) is 5.12 B.M., is well within the

range usually observed for high-spin octahedral Co(II) (4.8-5.6 B.M.) with ${}^{4}T_{1g}$ (F) ground state. The magnetic moment of complex (**2**) is 4.51 B.M., is well within the reported range (4.2–4.7 B.M.) for tetrahedral complexes of cobalt(II) [41,42].

Nickel complexes

The electronic absorption spectra of Ni(II) complexes (3,4) display three d-d transition bands at 633-632, 535-495, 427-420 nm, are attributable to the ${}^{3}A_{2g} \rightarrow {}^{3}T_{2g}(v_{I}); {}^{3}A_{2g} \rightarrow {}^{3}T_{1g}(v_{2}); {}^{3}A_{2g} \rightarrow {}^{3}T_{1g}$ (P)(v₃) transitions, respectively. These observations together with the magnetic moment value of the nickel(II) complexes (Table 3) give adequate support to an octahedral environment around the Ni(II) ions [42-44].

Copper (II) complexes

The electronic absorption spectra of all Cu(II) complexes (except 7) show three d-d transition bands at 644 - 632, 532-500 and 476-400 nm assigned to ${}^{2}B_{1g} \rightarrow {}^{2}A_{1g}(v_{I})$; ${}^{2}B_{1g} \rightarrow {}^{2}B_{2g}(v_{2})$; ${}^{2}B_{1g} \rightarrow {}^{2}E_{g}(v_{3})$ transitions, respectively. Suggesting tetragonally distorted octahedral geometry around Cu(II) ions [45,46]. Complex (7) shows bands around 770, 600 nm which are indicative of tetragonally distorted square pyramidal geometry. These bands may be assigned to transitions ${}^{2}B_{1g} \rightarrow {}^{2}A_{1g}$; ${}^{2}B_{1g} \rightarrow {}^{2}E_{g}$ [47]. Their room temperature magnetic moment is in the range 2.49-1.80 BM, corresponding to one unpaired electron. These values clearly support the monomeric nature of the complexes and also show the absence of metal-metal interaction.

Ruthenium(III) complex

Electronic spectra of Ru(III) complex (**10**) in Nujol mulls shows moderately intense band in the visible region at 632 nm due to d–d transition and an absorption band at 490 nm probably due to MLCT transition [48,49]. Its magnetic moment at room temperature is 2.21 B.M., corresponding to one unpaired electron.

Palladium(II) complex.

The electronic spectrum of Pd(II) complex (**11**) displays three d-d transition bands at 640, 520 and 420 nm which may be assigned to ${}^{1}A_{1g} \rightarrow {}^{1}A_{2g}$, ${}^{1}A_{1g} \rightarrow {}^{1}B_{1g}$ and ${}^{1}A_{1g} \rightarrow {}^{1}E_{g}$ transitions, respectively indicating square-planar geometry around the Pd(II) ion [16,50]. The magnetic susceptibility studies show that Pd(II) complex (**11**) is diamagnetic with spin-paired d⁸ system. Electrolytic nature of the complex indicates that, the chloride ion does not take part in coordination.

EPR spectroscopic studies

The solid state EPR spectra of the copper(II) complexes (5-9) were recorded at room temperature on the X-band frequency 9.719 GHz. The EPR parameters are listed in (Table 4). All complexes (except 7) give axial spectra. Analysis of spectra gives $g_{\parallel} = 2.20 - 2.15$ and $g_{\perp} = 2.06 - 2.03$. The trend $g_{\parallel} > g_{\perp} > 2.0023$ suggests $d_{x^2y^2}$ ground state for the Cu(II) ion and also indicates that the unpaired electron is localized in the d_{x^2,y^2} orbital of the Cu(II) ion [51-53]. The greater value of g_{\parallel} compared to g_{\perp} indicates a tetragonal distortion around the Cu(II) ions [54,55]. Also the observed g_{\parallel} values are less than 2.3 provide evidence for appreciable covalent character for Cu-L bond [56]. The exchange interaction between the copper centers in polycrystalline sample is explained by Hathaway expression $G = g_{\parallel} - 2.0023 / g_{\perp} - 2.0023$ [57]. The exchange interaction is negligible if G > 4, whereas a considerable interaction occurs for G < 4. As shown in (Table 4), the calculated G value for complex (5) (Fig. 2) is less than 4 suggesting some interaction between Cu(II) ions in the solid state. For complexes (6,8,9) G value is higher than 4 indicating no exchange interaction. The EPR of complex (7) (Fig. 2) displays rhombic features with three g-values ($g_1 = 2.048$, $g_2 = 2.087$, $g_3 =$ 2.161) the lowest g_1 value is > 2.04 indicating a rhombic distorted square based pyramidal geometry in the spectra with $g_3 > g_2 > g_1$ the rhombic spectral parameter $R = (g_2 - g_1)/(g_3 - g_2)$ may be significant, if R > 1, a predominant dz^2 ground state is present. If R<1, a predominant $d_{x^2y^2}$ ground state. Here R <1=0.524. Also for rhombic spectra G =($g_3 - 2.0023$)/($g_{\perp} - 2.0023$) where $g_{\perp} =$ $(g_1 + g_2)/2 = 2.45$. In view of the fact that G < 4.4 and R < 1, $d_{x^2y^2}$ ground state is assigned to this complex.

¹H NMR spectra of Palladium(II) chelate

The $[Pd(L)]Cl_2.5H_2O$ complex (11) was selected as it is diamagnetic. Its ¹H NMR spectrum was recorded in DMSO- d_6 (Fig.2S). ¹H NMR spectrum showed similar signals as for the ligand, but the position of the amide proton signal in the complex is downfield (11.97 ppm) in comparison with the free ligand (13.17 ppm), indicating the involvement of the amide group in chelation [58]. This observation furthermore confirmed the conclusion drawn on the basis of infrared spectra regarding the coordination of amide nitrogen atom.

Thermal studies

TG/DTG measurements have yielded much insight in the composition and the thermal stability of compounds. The thermal properties of ligand and its metal complexes were investigated by thermogravimetric analysis (TG/DTG), under nitrogen atmosphere from 25 to 800 °C; important data are summarized in Table 1S. The results obtained from thermogravimetric analysis [59-61] were in agreement with the suggested theoretical formulae from the elemental analyses. *Ligand*

The TGA curve of the ligand shows weight loss of 8.04% (calc. 8.06%) in the temperature range of 28-253 °C. The DTG peaks recorded at 56,182°C reflect the loss of two water molecules (in two separate steps) per ligand molecule. Also the TG curve shows two decomposition steps (Fig.3) in the temperature range 253-676 °C, with total weight loss of 100% (Found 100%).

Cobalt(II) chelates

The TG curves of cobalt(II) complexes (1,2) show weight loss in the temperature range 28-221°C (Calc./Found% 10.5 /10.46; 10.42/10.43%), respectively associated with DTG peaks at 55, 114 and 48, 172 °C, that are assigned to release of four water molecules (complex 1, Fig. 3), one molecule of water of crystallization along with one ethanol molecule (complex 2). The TG thermograms also show that the complexes gradually decomposed at 235 and 221°C, ended with formation of metal oxide or metal for complexes 1,2, respectively.

Nickel(II) chelates

The TG curves of nickel(II) complexes (**3**,**4**) show weight loss in the temperature range 33-164 °C (Calc./Found % 14.22/14.27; 9.00/8.98 %), respectively associated with two DTG peak at 32, 156 and at 54, 151°C, that are assigned to release of solvent of crystallization in two steps. The TG thermograms also show that the complexes gradually decomposed at 254 and at 265°C ended with formation of metal or metal oxide, respectively.

Copper(II) chelates

The TG curves of copper(II) complexes (5, 7 -9) show weight loss in the temperature range 25-226 °C (Calc./Found% 15.35/15.37; 5.67/5.66; 9.68/9.67; 11.83/11.85%), respectively associated with two endothermic DTG peak at 42,59 °C, that are assigned to release of five and half water molecules (complex 5), peak at 53 °C, that is assigned

to release of two water molecules (complex 7, Fig. 3), peaks at 56, 156 °C that are assigned to release of half ethanol together with two water molecules in two steps (complex 8) and peak at 61 °C that is assigned to release of five water molecules (complex 9) (Table 1S). The TG thermograms also show that the complexes gradually decomposed in more than one stage, ended with the formation of CuO for all complexes [39]. It is worth to note that, the higher temperature of dehydration of the ligand, complexes (2,5,9,11) may be due to strong interaction of water molecules in the crystal lattice [62]. Due to the explosive nature of perchlorate complexes, the thermal behavior of copper perchlorate complex (6) has not been investigated.

Ruthenium(III) chelate

The TG curve of ruthenium(III) complex (10) shows weight loss in the temperature range 25-157 °C (Calc./Found% 12.38 /12.39) associated with a broad DTG peak at 61 °C, that is assigned to release of five molecules of water crystallization in one step (Fig. 3). The TG thermogram also shows that the complex starts decomposition at 157 °C ended with the formation of RuO₂ as final decomposition product.

Palladium(II) chelate

The TG curve of Palladium(II) complex (11) shows weight loss in the temperature range 26-95 °C (Calc./Found %7.96/7.98) associated with one endothermic DTG peak at 55 °C, that is assigned to release of three molecules of water crystallization. The TG thermogram also shows that the complex starts decomposition at 246 °C given Palladium(II) oxide as final decomposition product [63]. The slight higher value found for the percentage of the residue when compared with the theoretical value for pure metal oxides shows that the residue is contaminated with carbon [64]. The nature of the remaining residues was reported and identified by IR spectroscopy.

Kinetic and thermodynamic parameters for complexes (1,2,4,7)

The kinetic and thermodynamic parameters of the decomposition stages of the desolvated complexes (1,2,4,7) were determined from TGA thermogram using the Coats-Redfern equation [65]. The Horowitz and Metzger [66] equation $C_s = (n)^{\frac{1}{1-n}}$ was used for the determination of the value of the reaction order, and given by $C_s = \frac{m_s - m_{\infty}}{m_0 - m_{\infty}}$, where C_s is the weight fraction of the substance present

at DTG peak temperature T_s , m_s is the remaining weight at T_s , m_0 and m_{∞} are the initial and final weights of the substance, respectively. The estimated values of C_s for the thermal decomposition of the desolvated complexes were found in the range of 0.30–0.34 (Table 5). This indicated that the decomposition follows first order kinetic [67]. So the values of the activation energy E^* , Arrhenius constant A, the activation entropy S^* , the activation enthalpy H^* and the free energy of activation G^* are calculated by applying Coats–Redfern equation for n = 1

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

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. (I) against 1/T gives a straight line from its slope and intercept, E^* and A were calculated (Table. 5). The entropy of activation S^* , enthalpy of activation H^* and the free energy change of activation G^* were calculated using the following equations. $S^* = R[\ln(Ah/kT)]R, H^* = E^* - RT$ and $G^* = H^* - TS^*$. The calculated kinetic and thermodynamic values are summarized in Table 5. The High values of E reveals high stabilities of the chelates. Since $H^* \succ o$ the reactions are endothermic. The reaction for which G^* is positive and S^* is negative considered as non-spontaneous reactions. The entropy of activation was found to have negative values in the complexes, which indicates that the activated complex has a more ordered structure than the corresponding reactant [59]. The correlation coefficients of the Arrhenius plots of the thermal decomposition steps were found to lie in the range 0.9987 to 0.9988 showing a good fit with linear function.

Based on analyses and spectral, thermal studies, tentative structures of the complexes are shown in Scheme 2.





(2)

Scheme 2. Suggested structures of complexes (1-11).

Biological activity

The results of the cytotoxic activity *in vitro* were expressed as IC_{50} (the concentration of the compound in µg/mL that inhibits proliferation of the cells by 50% as compared to the untreated control cells) are given in Table 6. The ligand shows IC_{50} value of 11.7 and 3.45 µg/mL toward human breast cancer cell lines (MCF-7) and human hepatocarcinoma cells (HepG2), respectively and that for some selected complexes (1,3,5,10,11) were in the range of 2.04 - 9.7 µg/mL toward the former cells and 2.5-3.7 µg/mL toward the latter one, respectively. Shier [68] suggested that compounds exhibiting IC_{50} values more than 10–25 µg/mL indicate weak cytotoxic activities while compounds

with IC_{50} values less than 5µg/mL are considered to be very active. Those having intermediate values ranging from 5 to 10 µg/mL are classified as moderately active. Accordingly, the tested complexes ($IC_{50} = 2.04 - 2.7 µg/mL$) (except L, complex **3**) are consider to be very active toward human breast cancer cell lines. Also the ligand and its tested compounds ($IC_{50} = 2.5 - 3.7 µg/mL$) are considered to be very active toward hepatocarcinoma cells. The results also show that Co(II) complex (**1**) showed highest cytotoxic activity on human breast cancer cell lines, IC_{50} value = 2.04 µg/mL. Whereas Cu(II), Ni(II) and Ru(III) complexes (**5**,**3**,**10**) showed highest cytotoxic activity of the investigated complexes agrees well with and better than the documented activity of similar metal complexes as antitumor agents [12,16,69-71].The enhanced activity may be attributed to the increase in conjugation in the ligand moiety on complexation [72]. The type of metal ions may be another reason for their different anticancer activity. The active sequence of the ligand and its complexes follows the trend:

Co(II) > Ru(III) > Pd(II) > Cu(II) > Ni(II) > L for MCF-7cells, Cu(II) Ni(II) > Ru(III) > Pd(II) > L > Co(II) for HepG2 cells

These compounds seem to be promising as an anticancer agent because of their high cytotoxic activity.

Acknowledgements

The authors would like to thank Dr. Mahmoud Moawad, Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt, for his help with the *in vitro* anticancer activity.

Conclusion

In this work the synthesis and spectroscopic characterization and anticancer activity of new eleven new transition metal complexes of (N_5) ligand, are reported. The analytical and physicochemical data confirmed the composition and structure of the newly obtained compounds. The results obtained can be summarized as follows:

- 1. The ligand shows interesting coordinating ability to metal ions, behaves as neutral quatridentate or bidentate one.
- 2. All the metal complexes are mononuclear, adopt octahedral geometry except, cobalt(II)(2), copper(II) (7) and palladium(II) (11) complexes in which the

metal ions prefer tetrahedral, square pyramidal or square planar geometry, respectively.

3. *In vitro* antitumor activity of the synthesized compounds suggests that the ligand and its tested complexes are potent anticancer agents. Besides, the complexes are more active as compared to their free ligand. This implies an increase in the antitumor activity with coordination.

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Fig.2. EPR spectra of complexes (5,7) as polycrystalline sample at RT.



ACCEPTED MANUSCRIPT Table 1 Analytical and physical data for the ligand and its complexes.

			Yield Decomp.	Decomp.	Elemental analysis Calc. (F) (%)					$\left(\Lambda_{\mathrm{m}} ight)^{\mathrm{a}}$	
No.	Compound	Color	Empirical formula	(%)	Temp./°C	С	Н	Ν	М	halogen	_
	$L \!\!=\!\! (C_{24}H_{21}N_5O_2.2H_2O)$	Brown	$C_{24}H_{25}N_5O_4$	65	253	64.42(63.69)	5.59(5.69)	15.65(15.12)	-	-	-
1	$[Co(L)(H_2O)_4]Cl_2.4H_2O$	Green	$C_{24}H_{37}N_5O_{10}Cl_2Co$	64	235	42.01(41.58)	5.39(5.18)	10.21(10.19)	8.67(9.15)	10.35(9.93)	100
2	[Co(L)OH(NO ₃)].EtOH.H ₂ O	Brown	$C_{26}H_{30}N_6O_8Co$	76	221	50.85(50.14)	4.88(4.53)	13.69(13.42)	9.69(10.9)	-	39
3	[Ni(L)(OH)Cl]1½EtOH.H2O	Pale grey	C ₂₇ H ₃₃ N ₅ O _{5.5} ClNi	60	254	53.15(54.54)	5.41(5.44)	11.48(11.59)	9.68(10.8)	5.82(5.80)	25
4	[Ni(L)OH(OAc)].3H ₂ O	Pale brown	$C_{26}H_{31}N_5O_8Ni$	90	265	52.0(51.6)	5.16(4.91)	11.66(11.73)	9.83(10.3)	-	20
5	[Cu(L)Cl ₂].5½H ₂ O	Dark brown	C ₂₄ H ₃₂ N ₅ O _{7.5} Cl ₂ Cu	60	226	44.68(44.14)	4.96(4.99)	10.86(10.83)	9.85(10.7)	11.01(10.65)	10
6	[Cu(L)OH(H ₂ O)]ClO ₄ ,4H ₂ O	Dark brown	$C_{24}H_{32}N_5O_{12}ClCu$	76	250	42.29(41.27)	4.69(4.69)	10.27(10.5)	9.32(10.5)	5.21(5.5)	70
7	[Cu(L)NO ₃]NO ₃ .2H ₂ O	Dark Green	$C_{24}H_{25}N_7O_{10}Cu$	74	153	45.39(45.51)	3.94(4.34)	15.44(15.45)	10.0(109)	-	68
8	[Cu(L)OH(OAc)].1/2EtOH.2H2O	Dark Green	$C_{27}H_{32}N_5O_{7.5}Cu$	98	180	53.15(53.97)	5.25(4.49)	11.48(11.89)	10.41(10.70)	-	2
9	$[Cu(L)(H_2O)_2Br_2].5H_2O$	Dark brown	$C_{24}H_{35}N_5O_9Br_2Cu$	77	202	37.86 (37.48)	4.6 (4.77)	9.2(10.0)	8.35(8.3)	21.03(21.4)	22
10	$[Ru(L)(H_2O)Cl_3].5H_2O$	Black	C ₂₄ H ₃₃ N ₅ O ₈ Cl ₃ Ru	98	157	39.64 (39.25)	4.54 (4.03)	9.63 (9.98)	13.90(13.71)	14.65(14.65)	12
11	[Pd(L)]Cl ₂ .5H ₂ O	Pale brown	$C_{24}H_{31}N_5O_7Cl_2Pd$	90	246	42.47(42.55)	4.57(4.52)	10.32 (10.03)	15.63(15.50)	10.47(10.50)	87
Ω ⁻¹ c1	m ² mol ⁻¹ DMSO solutions (10 ⁻¹	⁻³ M)	C	•							

^a: $\overline{\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1} \text{ DMSO solutions (10}^{-3}\text{M})}$

Table 2 Fundamental IR spectral bands $(cm^{-1})^a$ of Ligand and its metal complexes.

No.	Compound	$\nu(OH/H_2O)$	v(NH)	v(C=N)	Amide bands		v(M-O)	v(M- N)	Anion (NO ₃ ⁻ ,OAc ⁻ ,ClO ₄ ⁻)		
				Azomethi -ne	Ι	II	III	IV	_		
	L.2H ₂ O	3347(b)	3206(b)	1618(b)	1644(w)	1499(sh)	1289(m)	754(sh)	-		-
1	$[Co(L)(H_2O)_4]Cl_2.4H_2O$	3334-3365(b)	3206(m)	1587(m)	1640(b)	1505(sh)	1295(m)	758(m)	593(w)	418(sh)	-
2	[Co(L)OH(NO ₃)].EtOH.H ₂ O	3422-3331(m)	3206(b)	1590(w)	1639(b)	1505(sh)	1303(w)	757(m)	594(w)	400(m)	1380(sh),1269(w) ^b ,1046(m)
3	[Ni(L)(OH)Cl]1 ¹ / ₂ EtOH.H ₂ O	3413-3335(m)	3269(w)	1591(m)	1612(b)	1508(sh)	1301(w)	753(w)	606(w)	400(m)	
4	[Ni(L)OH(OAc)].3H ₂ O	3444-3331(m)	3262(w)	1583(m)	1626(b)	1506(sh)	1306(m)	754(m)	598(w)	424(w)	$\{1583 (sh)1379(sh)\}^{b}$
5	[Cu(L)Cl ₂].5 ¹ / ₂ H ₂ O	3331(b)	3174(w)	1607(b)	1607(b)	1505(m)	1301(w)	764(m)	-	463(w)	-
6	[Cu(L)OH(H ₂ O)]ClO ₄ .4H ₂ O	3386(b)	3386(b)	1590(b)	1626(b)	1503(w)	1301(w)	760(w)	533(w)	462(w)	{1087(sh),630(sh) ^c
7	[Cu(L)NO ₃]NO ₃ .2H ₂ O	3333(b)	3190(b)	1587(b)	1617(b)	1504(m)	1301(w)	762(w)	576(w)	416(w)	{1412(w),1301(w),1041(w)] ^b ,1380(sh),708(w)} ^c
8	[Cu(L)OH(OAc)] ½EtOH.2H ₂ O	3409(b)	3222(b)	1587(b)	1619(b)	1505(sh)	1297(m)	756(sh)	597(w)	424(w)	{1587 (b),1376(m)} ^b
9	$[Cu(L)(H_2O)_2Br_2].5H_2O$	3393(b)	3206(b)	1611(b)	1611(b)	1504(m)	1293(w)	764(m)	564(w)	459(w)	-
10	[Ru(L)(H ₂ O)Cl ₃].5H ₂ O	3396(b),3343(m)	3202(b)	1603(b)	1644(b)	1505(m)	1295(m)	766(m)	625(w)	438(m)	-
11	[Pd(L)]Cl ₂ .5H ₂ O	3317(b),3246(b)	3205(b)	1611(sh)	1626(b)	1525(m)	1309(sh)	759(sh)	529(sh	419(sh)	-

^a: s, strong; sh, shoulder; m, medium; w, weak; b, broad; v, stretching

^b:Monodentate ion, ^c:ionic

Table 3 Nujol mull electronic absorption spectra λ_{max} (nm), room temperature effective magnetic moment values (μ_{eff} , B.M.) of complexes.

No. Complexes	plexes λ_{max} (Nujol mulls, nm)		$\mu_{eff}(B.M.)$
	(d-d)Transition	Intraligand and charge transfer bands	_
Ligand.2H ₂ O	-	353,270 ,224	-
[Co(L)(H ₂ O) ₄]Cl ₂ .4H ₂ O	700,640,450	380 ,326 ,230	5.12
[Co(L)OH(NO ₃)].EtOH.H ₂ O	648	385 ,323 ,240	4.51
[Ni(L)(OH)Cl]1 ¹ / ₂ EtOH.H ₂ O	632 ,495,427	398 ,323 ,229	3.78
[Ni(L)OH(OAc)].3H ₂ O	633 ,535 ,420	380 ,323 ,250	3.5
[Cu(L)Cl ₂].5½H ₂ O	644,512,400	356 ,290,240	1.95
[Cu(L)OH(H ₂ O)]ClO ₄ .4H ₂ O	632,520,420	380,323,240	2.49
[Cu(L)NO ₃]NO ₃ .2H ₂ O	770,600	380,323,240	1.97
[Cu(L)OH(OAc)].1/2EtOH.2H	I ₂ O 640,500,400	347,293,240	2.3
$[Cu(L)(H_2O)_2Br_2].5H_2O$	632,532, 476	365 ,300,240	1.8
$[Ru(L)(H_2O)Cl_3].5H_2O$	632, 490	393,323,240	2.21
$[Pd(L)]Cl_2.5H_2O$	640,520,420	380 ,326,250	(Dia) ^a
amagnetic			
	0		

No.	Compound	8 //	g $_{\perp}$	<i>g</i> _{av}	G
5	[Cu(L)Cl ₂].5 ¹ / ₂ H ₂ O	2.19	2.06	2.10	3.25
6	$[Cu(L)OH(H_2O)]ClO_4.4H_2O$	2.16	2.04	2.08	4.02
7	[Cu(L)NO ₃]NO ₃ .2H ₂ O	<i>g</i> ₁ =2.048	g ₂ =2.087	<i>g</i> ₃ =2.161	<i>R</i> =0.524<1
8	[Cu(L)OH(OAc)]. ¹ / ₂ EtOH.2H ₂ O	2.15	2.03	2.07	4.02
9	$[Cu(L)(H_2O)_2Br_2].5H_2O$	2.20	2.04	2.10	4.93

Table 4 EPR parameters for the Cu(II) complexes as polycrystalline sample at RT.

6 7 8	[Cu(L)OH(H ₂ O)]ClO ₄ .4H ₂ O [Cu(L)NO ₃]NO ₃ .2H ₂ O [Cu(L)OH(OAc)]. ¹ / ₂ EtOH.2H ₂ O	2.16 g 1 =2.048 2.15	2.04 g ₂ =2.0 2.03	2.08 87 g ₃ =2.1 2.07	4.02 61 <i>R</i> =0.52 4.02	24<1				8
9	$[Cu(L)(H_2O)_2Br_2].5H_2O$	2.20	2.04	2.10	4.93				5	
Table	e 5 Kinetic and thermodynam	ic data of the	complexes	s (1,2,4,7).		-	5	0		
No.	Complex D	ecomposition Temp. (K)	A (S ⁻¹)	s^{*} (J mol ⁻¹ K ⁻¹)	E [*] (kJ n	H^* nol ⁻¹)	G [*]	C_s	$^{a}R^{2}$	
1	$[Co(L)(H_2O)_4]Cl_2.4H_2O$	508-658	11.456E ⁵	-16.45	42.575	36.23	48.76	0.33	0.9987	
2	[Co(L)OH(NO ₃)].EtOH.H ₂ O	494-726	6.713E ⁵	-16.837	33.646	28.168	39.36	0.34	0.9987	
4	[Ni(L)OH(OAc)].3H ₂ O	538-665	2.798E ¹¹	-3.837	146.88	146.87	149.24	0.32	0.9988	
7	[Cu(L)(NO ₃)]NO ₃ .2H ₂ O	426-647	2.7785E ⁵	-17.459	14.926	10.724	23.82	0.30	0.9988	

^a R^2 : correlation coefficient

Table 6 Lethal concentration (IC₅₀) of the ligand and its metal complexes on MCF-7 and HepG2.

No.	Compound	IC ₅₀ (µ	$IC_{50} (\mu g/mL)^a$			
		MCF-7	HepG2			
	L.2H ₂ O	11.7	3.45			
1	$[Co(L)(H_2O)_4]Cl_2.4H_2O$	2.04	3.7			
3	[Ni(L)(OH)Cl].1 ¹ / ₂ EtOH.H ₂ O	9.7	2.7			
5	$[Cu(L)Cl_2].5\frac{1}{2}H_2O$	2.7	2.5			
10 11	$[Ru(L)(H_2O)Cl_3].5H_2O$ $[Pd(L)]Cl_2.5H_2O$	2.2 2.39	2.73 3.4			

^a: (IC₅₀) is the concentration of compound (μ g/mL) that inhibits a proliferation rate of the tumor cells by 50% as compared to control untreated cells.

	11.7	3.45	
	2.04	3.7	
$_{2}O$	9.7	2.7	
	2.7	2.5	
	2.2 2.39	2.73 3.4	
	2.07		
g/mL) ntrol ı) that inhibits a intreated cells.	proliferation rate	
	6		

Transition metal complexes of a new 15-membered [N5] penta-azamacrocyclic ligand with their spectral and anticancer studies

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2-amino-N-{2-[(2-amino-benzoylamino) pyridine]- benzamide

2,3 pentanedione

(L)

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HIGHLIGHTS

• Novel [N₅] quatridentate, bis-amide bis -imine macrocyclic ligand and its transition metal complexes have been synthesized and characterized. • Analytical, spectral and thermal data confirm the structure of the compounds. • The ligand shows interesting coordinating ability to metal ions. • In vitro antitumor activity of the synthesized compounds shows that the obtained complexes are potent anticancer agents.