International Research Journal in Global Engineering and Sciences. (IRJGES)
ISSN : 2456-172X | Vol. 3, No. 3, Sep. - Nov, 2018
Pages 26-36 | Cosmos Impact Factor (Germany): 5.195
Received: 05.10.2018 Published : 21.10.2018

DNA BINDING ACTIVITY OF MIXED LIGAND COPPER COMPLEXES OF POLYAZOLE LIGANDS WITH PENDANT ARMS AMIDE AND HYDRAZIDE

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ABSTRACT

New pyridyl tetrazole ligands 2-(5-(pyridin-2-yl)-1H-tetrazol-1-yl)acetamide (L1), 2-(5-(pyridin-2-yl)-2H-tetrazol-2-yl)acetamide (L2), 2-(5-(pyridin-2-yl)-1H-tetrazol-1-yl)acetohydrazide (L3), and 2-(5-(pyridin-2-yl)-2H-tetrazol-2-yl)acetohydrazide (L4) have been prepared. These ligands and phenanthroline have been coordinated with CuCl2.2H2O to furnish corresponding mixed complexes [Cu(L1)(Phen)]-[Cu(L4)(Phen)]. Electron paramagnetic resonance spectra of all the copper complexes are characteristic of square planar geometry, with nuclear hyperfine spin 3/2. DNA binding studies were carried using UV-Vis absorption spectroscopy. Viscosity and thermal denature studies revealed that each of these complexes is avid binders of calf thymus DNA.

Key words: Pyridyl-tetrazole, Pendant arm, Mixed ligand copper complexes, DNA binding properties

1. INTRODUCTION

Tetrazoles exhibit various biological activities and act as a pharmacophore for the carboxylate group [1]. Recently, there is a growing demand for the use of pyridyl tetrazoles to prepare metal–organic frameworks which have attracted remarkable attention in the past decade as a result of their amazing structural topographies as well as their excellent properties and applications, including storage of gases, catalysis, drug delivery, magnetism, and luminescence [2]. The metal complexes of tetrazoles find a wide range of biochemical and pharmaceutical applications with respect to high physiological activity and low toxicity of tetrazoles [3]. Tetrazoles are important tools in synthetic organic chemistry and also used as precursors of carbenes in flash pyrolysis [4]. The pharmacological applications of tetrazoles with glycosidase inhibitory, antihypertensive, anti-inflammatory, antibacterial, antifungal, analgesic, antinociceptive, anticancer, anticonvulsant, antidiabetic, antiulcer, and antitubercular activities are reported [5]. Tetrazoles play a significant role in coordination chemistry as ligands,

International Research Journal in Global Engineering and Sciences. (IRJGES)
ISSN : 2456-172X | Vol. 3, No. 1, March - May, 2018
Pages 26-36 | Cosmos Impact Factor (Germany): 5.195
Received: 05.03.2018 Published : 21.03.2018

metabolically stable surrogate for a carboxylic acid group in medical chemistry, and as special explosives in materials science [6]. Tetrazole closely resembles the carboxylic group in acidic characteristics and is metabolically stable [7]. Furthermore, the applications of 5-substituted-1H-tetrazoles as lipophilic spacers are reported [8]. In addition, pyridines are associated with diverse biological activities [9]. In continuation of our ongoing research [10], we altered the pendant arms with acetamide and acetohydrazide groups and prepared corresponding pyridyl tetrazole copper(II) complexes.

3. EXPERIMENT

2.1. Materials and Measurements

Picolinonitrile was purchased from Sigma-Aldrich. The solvents used in the synthesis of the ligands and metal complexes were distilled before use. All other chemicals were of AR grade and were used without further purification. Hydrazine hydrate is a hazardous compound, and MSDS data sheet was referred before using it. All melting points were obtained using Elico instrument, India (Model MP96), and are uncorrected. Mass spectra were obtained on a Pexciex API 2000 eV spectrometer, Q1MSQ1/autoinjection mass spectra. 1H and 13C NMR spectra were recorded on a Bruker TopSpin Instrument. Infrared (IR) spectra were recorded using Alpha T OPUS instrument. Elemental analysis (% of C, H, and N) was carried out using a PerkinElmer 2400 elemental analyzer. Magnetic moments were determined in the polycrystalline state on a PAR model-155 vibrating sample magnetometer operating at a field strength of 2–8 kG. High purity Ni metal (saturation moment 55 emug¢1) was used as standard. Electron paramagnetic resonance (EPR) spectra were recorded on Varian E-122 X-band spectrophotometers at liquid nitrogen temperature in DMF.

2.2. General Procedure for the Synthesis of 3 and 4 Ligands

To a solution of tetrazole 2 (1 g, 6.8 mmol) in DMF (15 ml), ethylbromo acetate (0.75 ml, 6.8 mmol) was added. The mixture was allowed to stir for 8 h at 70°C. The reaction mixture was diluted with ethyl acetate (50 ml), and the organic layer was washed with saturated NaHCO3 (50 ml) and washed successively with water (40 ml 3 ml) followed by brine solution (40 ml). The organic layer was dried over MgSO4, filtered, and the solvent was evaporated under reduced pressure to afford a brown-colored gummy liquid, which was purified by column chromatography using 17% EtOAc in hexane (V/V) to afford the esters 3 and 4.

Ethyl 2-(5-(pyridin-2-yl)-1H-tetrazol-1-yl)acetate (3) [2] yellowish solid; yield: 0.45 g (28%). Yellow solid. M.p.54–57°C. Anal. Calc. for C10H11N5O2 (233.23): % of C, 51.50; H, 4.75; O, 13.72; N, 30.03. Found: % of C, 51.48; H, 4.74; O, 13.69; N, 30.01. 1H NMR (CDCl3, 300

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MHz): δ 8.66 (d, 1H, J=3.3 Hz), 8.43 (d, 1H, J=8.1 Hz), 7.92 (dt, 1H, J=7.8, 1.8Hz), 7.48–7.41 (m, 1H), 5.75 (s, 2H), 4.19 (q, 2H, 6.9 Hz), 1.21 (t, 3H, J=6.9 Hz) ppm.

Ethyl 2-(5-(pyridin-2-yl)-2H-tetrazol-2-yl)acetate (4) [2] yellowish solid yield: 0.80 g (50 %). White solid. M.p. 94–98°C. Anal. Calc. for C10H11N5O2 (233.23): % of C, 51.50; H, 4.75; O, 13.72; N, 30.03. Found: % of C, 51.47; H, 4.71; O, 13.71; N, 29.99. 1H NMR (CDCl3, 300 MHz): δ 8.79 (d, 1H, J=4.8 Hz), 8.28 (d, 1H, J=7.8 Hz), 7.88 (td, 1H, J=7.8, 1.8 Hz), 7.42 (m, 1H), 5.50 (s, 2H), 4.29 (q, 2H, J=7.2 Hz), 1.29 (t, 3H, J=7.2 Hz) ppm.

2.3. General Procedure for the Synthesis of 5 and 6 Ligands

To the methanolic (21 ml) solution of ester 3 or 4 (0.5 g, 2.14 mmol), 2 ml of aqueous NaOH (1N) was added and the resulting solution was stirred for 6 h at room temperature, and the formation of a white precipitate in the reaction mixture was observed. The reaction was quenched with 3–4 drops of acetic acid and 10 ml of ethyl acetate was added. Then, the mixture was filtered and the residue was washed with ethyl acetate (20 ml), and the colorless residue was collected and dried in air.

2-(5-(Pyridin-2-yl)-1H-tetrazole-1-yl)acetic acid (5): Color less solid; yield: 400 mg (91%). M.p.284-287oC. Anal. Calc. for C8H7N5O2 (205.17): % of C, 46.83; H, 3.44; O, 15.60; N, 34.13. Found: % of C, 46.80; H, 3.40; O, 15.57; N, 34.12. 1H NMR (CDCl3, 300 MHz): δ 8.72 (t, 1H, J=4.8,3.9 Hz), 8.12 (d, 1H, J=7.8 Hz), 8.03 (m, 1H), 7.58 (m, 1H), 5.45 (s, 2H) ppm. 13C NMR (CDCl3, 65 MHz): δ 172.5, 153.1, 149.9, 143.2, 138.4, 126.3, 124.4, 52.9. Electrospray ionization-mass spectrometry (ESI-MS): m/z 204 (M-1).

2-(5-(Pyridin-2-yl)-2H-tetrazole-2-yl)acetic acid (6): Color less solid; Yield: 0.38 g (86%). M.p. 277–279°C. Anal. Calc. for C8H7N5O2 (205.17): % of C, 46.83; H, 3.44; O, 15.60; N, 34.13. Found: % of C, 46.79; H, 3.42; O, 15.55; N, 34.10. 1H NMR (CDCl3, 300 MHz): δ 8.73 (d, 1H, J=4.5 Hz), 8.11 (d, 1H, J=8.1 Hz), 7.98 (td, 1H, J=7.5, 1.5 Hz), 7.52 (m, 1H), 4.97 (s, 2H) ppm. 13C-NMR (CDCl3, 75 MHz): δ 172.19, 164.49, 150.15, 145.47, 139.25, 126.59, 123.58, 56.71 ppm. ESI-MS: m/z 204 (M-1).

2.4. General Procedure for the Synthesis of L1 and L2

To a solution of acid 5 or 6 (0.5 g, 2.44 mmol) in dioxane (30 ml), a mixture of BOC anhydride (0.85 ml, 3.7 mmol) and pyridine (0.24 ml, 2.93 mmol) was added at r.t. The mixture was stirred over a period of 0.5 h. Then, ammonium carbonate (281 mg, 2.93 mmol) was added and the resulting solution was stirred for 8 h. The reaction mixture was filtered, and the filtrate was extracted with ethyl acetate (30 ml). The organic layer was washed with water (30 ml × 3 ml) followed by brine solution to remove any impurities in the product. The organic layer was dried

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over Na2SO4, filtered, and the solvent was removed under reduced pressure to afford a crude product which was triturated with diethyl ether to furnish colorless solid.

Ethyl 2-(5-(pyridin-2-yl)-1H-tetrazol-1-yl)acetamide (L1): Colorless solid; yield: 0.25 g (50%). M.p. 97-99oC. Anal. Calc. for C8H8N6O (204.19): % of C, 47.06; H, 3.95; O, 7.84; N, 41.16. Found: % of C, 47.03; H, 3.92; O, 7.83; N, 41.14. 1H NMR (CDCl3, 300 MHz): δ 8.73 (t, 1H, J=4.2, 3.3 Hz), 8.16 (d, 1H, J=7.8 Hz), 8.05 (m, 1H), 8.01 (br. s, 1H), 7.59 (m, 2H), 6.14 (br. s, 1H), 6.13 (s, 2H) ppm. 13C-NMR (CDCl3, 75 MHz): δ 172.6, 153.3, 149.4, 143.6, 138.4, 126.3, 124.6, 53.1 ppm. ESI-MS: m/z 205 (M+1).
Ethyl 2-(5-(pyridin-2-yl)-2H-tetrazol-2-yl)acetamide (L2): Colorless solid; yield: 0.36 g, (72%). M.p. 98–103°C. Anal. Calc. for C8H8N6O (204.19): % of C, 47.06; H, 3.95; O, 7.84; N, 41.16. Found: % of C, 47.03; H, 3.92; O, 7.83; N, 41.14. 1H NMR (CDCl3, 300 MHz): δ 8.75 (t, 1H, J=4.2, 3.3 Hz), 8.15 (d, 1H, J=7.8 Hz), 8.02 (td, 1H, J=7.5, 1.5 Hz), 7.90 (br-s, 1H), 7.56 (m, 2H), 6.16 (br-s, 1H), 5.51 (s, 2H) ppm. 13C-NMR (CDCl3, 75 MHz): δ 172.2, 164.5, 150.2, 145.5, 139.3, 126.6, 123.6, 56.7 ppm; ESI-MS: m/z 205 (M+1).

3. RESULTS AND DISCUSSION

The synthetic route was started from picolinonitrile 1 by following the method available in the literature to form the tetrazole 2, and the structure was confirmed by comparing the analytical data of 2 with the reported data [13,14]. Tetrazole 2 on alkylation with ethyl bromoacetate in dry DMF at 70oC afforded regioisomers 3 and 4 by alkylation at N(1) or N(2) positions of tetrazole rings, respectively (Scheme 1). The acid derivatives are further confirmed by their mass spectra which showed M-1 (negative mode) peaks at 204. The acid derivatives 5 and 6 on treatment with ammonium carbonate, BOC anhydride, and pyridine in dry 1,4-dioxane afforded the respective acetamide ligands L1 and L2. The formation of L1 is confirmed by observing –CO-NH2 signals at δ 8.01 and 6.14 as broad singlets. The formation of L2 is confirmed by observing –CO-NH2 signals at δ 7.9 and 6.16 as broad singlets. Further, the mass spectra of both the ligands showed M+H peaks at 205.

The acetohydrazide ligands L3 and L4 were prepared by reacting the ethyl ester derivatives 3 and 4 with hydrazine hydrate in ethanol at 80°C (Scheme 1). The hydrazide L3 was confirmed by observing its 1H NMR which showed a characteristic peak of –CO-NH at δ 9.48 as broad singlet. The –NH2 peak of hydrazide appeared as a broad singlet at δ 4.29, which confirmed the formation of hydrazide ligand L3. The hydrazide L4 was confirmed by observing its 1H NMR which showed a characteristic peak of –CO-NH at δ 10.8 as broad singlet. The –NH2 peak of hydrazide appeared as broad singlet at δ 3.56, which confirmed the formation of hydrazide ligand L4. Further, the mass spectra of both the ligands L3 and L4 showed M+H peaks at 220.

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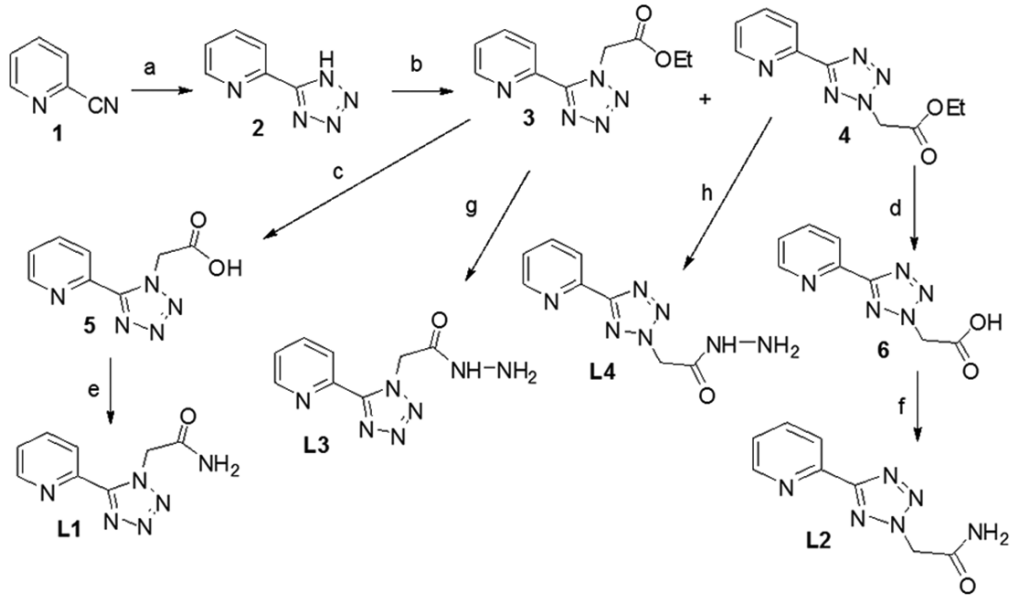

Scheme 1: Synthesis of L1-L4: Reagents and conditions: (a) NaN3, LiCl, NH4Cl, DMF, reflux, 10 h; (b) ethylbromo acetate, DMF, 70oC, 8 h; (c and d) aqueous NaOH (1N), MeOH, r.t., 6 h; (e and f) BOC anhydride, pyridine, (NH4)2CO3, dioxane, r.t., 8 h; (g and h) hyrazine hydrate, EtOH, 80oC, 10 h.

The 1H NMR spectra of all the compounds 3, 4, 5, 6, L1, L2, L3, and L4 showed separately four signals corresponding to pyridyl protons.

The ligands L1-L4 are treated with CuCl2.2H2O in methanol at reflux temperature under N2 atmosphere for 2 h. All the reactions were carried out using a 1:2 metal:ligand stoichiometry ratio to give corresponding complexes [Cu(L1)(Phen)]-[Cu(L4)(Phen)] (Scheme 2). The physical properties such as color, melting points, and magnetic moments of the complexes are shown in Table 1. The elemental analysis of the obtained complexes [Cu(L1)(Phen)]-[Cu(L4)(Phen)] showed that all are in 1:2 (metal: ligand) compositions. All copper complexes have magnetic moment values in the range of 1.84–1.92 BM, which is slightly higher than the spin only values (1.73 μeff) expected for a d 9 system

Electronic spectra of copper complexes [[**Cu(L1)(Phen)]-[Cu(L4)(Phen)]** recorded in DMF are shown in Table 2.

Table 1: Physical properties of pyridyl-tetrazole copper complexes **[Cu (L1)(Phen)]-[Cu (L4)(Phen)].**

S.No	Complex	Color	Melting Point (°C)	μeff (BM)
1	[Cu (L1)(Phen)]	Green	162–164	1.84

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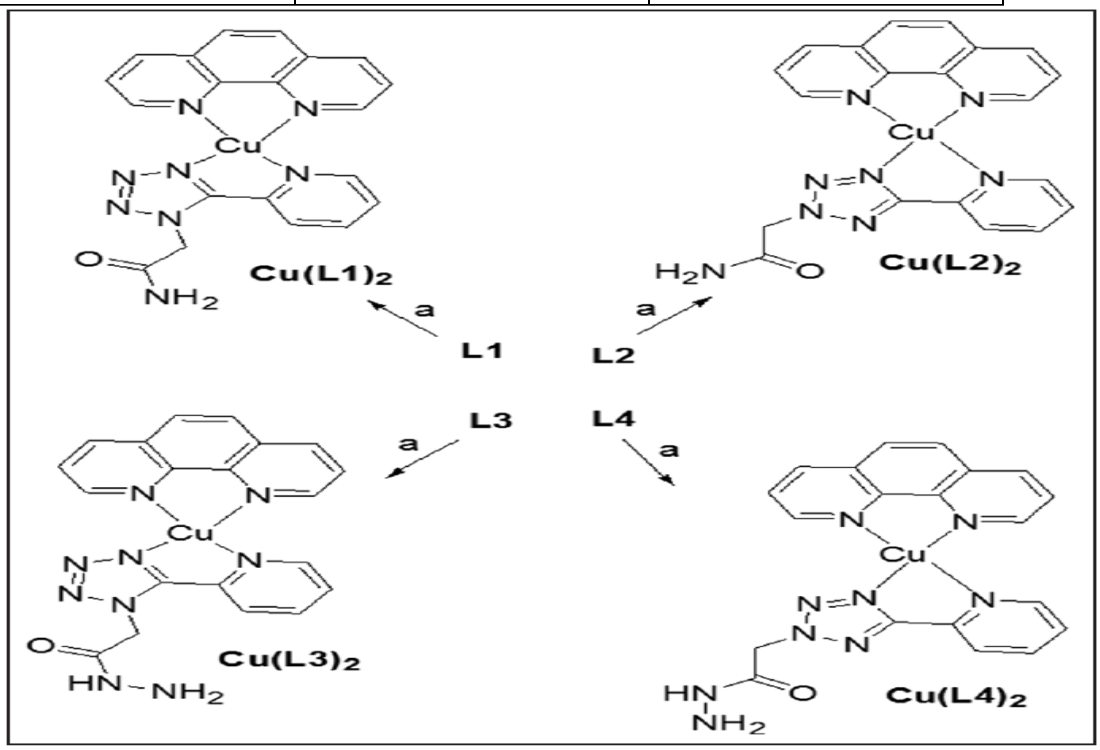
2	[Cu (L2) (Phen)]	Green	158–160	1.92
3	[Cu (L3) (Phen)]	Green	201–203	1.86
4	[Cu (L4) (Phen)]	Green	194–198	1.90

Table 2: Electronic spectral data λmax (nm) of the Cu (II) complexes.

Complexes	MLCT (nm)	d-d (nm)
[Cu (L1) (Phen)]	438	655
[Cu (L2) (Phen)]	430	652
[Cu (L3) (Phen)]	437	650
[Cu (L4) (Phen)]	445	654



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Scheme 2: Synthesis of [**Cu(L1)(Phen)]-[Cu(L4)(Phen)]**complexes**.** Reagents and conditions: (a) CuCl2.2H2O, methanol, 70°C, 2 h complexes showed bands in the region around 430–450 nm with high molar extinction coefficient in range 8300–7300 M− 1 cm− 1 which are assigned to the metal-to-ligand charge transfer (MLCT) transition (n – π*), while the single broadband observed in the region 655–650 nm is assigned to d-d transition. The electronic spectra of these complexes display weak d–d bands in the low intensity with molar extinction coefficients in between 130 and 95 M− 1 cm− 1 regions which are assigned to 2Eg → 2T2g electronic transition, and these assignments suggest a symmetrical square planar geometry for the copper(II) complexes [16,17].

The IR spectral data of the metal complexes are given in Table 3. IR spectra of the ligands (L1 and L2) show a broadband in range 3550–3100 cm− 1 corresponding to –NH2 of amide/hydrazine, and the peaks 1681 and 1685 cm− 1 in amide ligands (L1 and L2) and the peaks at 1622 and 1642 cm− 1 in hydrazine ligands (L3 and L4) are shifted to lower frequencies, suggesting the coordination of ligands to form copper complexes. The peaks at 1626–1534 cm− 1 corresponding to pyridyl tetrazole group are shifted to lower frequency in copper(II) complexes confirming the formation of coordination of pyridyl tetrazole ring with copper [18]. Additional peaks around 1395–1250 cm− 1 and 800–600 cm− 1 have appeared due to the coordination of pyridine ring with copper(II) atom. All spectra of copper complexes showed a lower number of frequencies, suggesting that the complexes are symmetric in nature [19].

The solid-state EPR spectra of copper(II) complexes [Cu(L1)(Phen)] and [Cu(L3) (Phen)] were recorded in the X-band region at room temperature (25°C), and the data are summarized in Table 4. Complexes [Cu(L1)(Phen)] and [Cu(L3)(Phen)] exhibit $g_{\parallel}$ values of 2.16 and 2.18 and $g^{\perp}$ values of 2.05 and 2.06, respectively. From the observed values of complexes [Cu(L1)(Phen) and Cu(L3)(Phen), predominantly in the dx2-y2 orbital. This is characteristic of copper(II) complexes with square planar geometry.

3.1. DNA Binding Studies

The binding interactions of copper(II) complexes with CT-DNA were monitored by UV–Vis spectroscopy. The complexes showed stability in the Tris-buffer solution and bound effectively with CT-DNA instead of Tris-buffer solution [21]. The absorption spectra of the copper complexes were compared with and without CT DNA at around 440 nm peak (Figure 1). The data of UV absorption spectra on the addition of CT-DNA and the binding constants of these complexes are given in Table 5. On addition of increasing amounts of CT-DNA, the UV–Visible absorption spectra of complexes [Cu(L1) (Phen)]-[Cu(L4) (Phen)] showed an increase in absorbance, exhibiting bathochromic shift (~ 0.5 nm) with hyperchromism with respect to control (0 µl DNA).

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Table 3: Selective I.R. bands cm ‘ of Cu (II) complexes with tentative assignments.

Vibration	L1	[Cu (L1) (Phen)]	L2	[Cu (L2) (Phen)]	L3	[Cu (L3) (Phen)]	L4	[Cu (L4) (Phen)]
Amide/	1681	1636	1685	1635	-	-	-	-
hydrazine	-	-	-	-	1622	1618	1642	1628
C=N (tetrazole)	1617	1575	1606	1568	1534	1455	1626	1592
C=C (tetrazole)	1498	1400	1486	1397	1471	1309	1508	1438
Py/M-Py	1392	1316	1334	1252	1433	1294	1443	1395

Table 4: EPR spectral assignments for complexes **[Cu (L1)(Phen)]** and **[Cu (L3)(Phen)]** at room temperature.

Complexes	**g∥**	**g⊥**	**gav**	**G**
[Cu (L1) (Phen)]	2.16	2.05	2.10	3.306
[Cu (L3) (Phen)]	2.14	2.04	2.09	3.652
EPR: Electron paramagnetic resonance				

4. CONCLUSIONS

Novel pyridyl tetrazole ligands with pendant arm of acetamide and acetohydrazide and their copper complexes were synthesized and characterized. Physicochemical and spectral studies revealed that the symmetric mononuclear complexes exhibit square planar geometry. All copper complexes are avid binders of CT-DNA and showed good antioxidant properties. The highlights of the present investigations are as follows:

(i) Mixed ligand complexes of pyridyl tetrazole with amide and hydrazide pendant arms with 1,10-phenanthroline were synthesized.

(ii) The regioisomeric and symmetric nature of synthesized copper complexes is attractive feature to develop chemotherapeutic drugs.

(iii) The present study showed that the synthesized compounds can be used as a template for future development through modification and derivatization to design more potent and selective antioxidant agents.

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