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Feature article

Synthesis, characterization and antioxidant activity of new dibasic tridentate ligands: X-ray crystal structures of DMSO adducts of 1,3-dimethyl-5-acetyl-barbituric acid *o*-hydroxybenzoyl hydrazone copper(II) complex

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ABSTRACT

o-Hydroxybenzoyl hydrazine and *p*-hydroxybenzoyl hydrazine react with 1,3-dimethyl-5-acetyl-barbituric acid in ethanol to give H_2L^1 (85% yield) and H_2L^2 (91% yield) respectively. The copper(II) complexes with DMSO adducts, [Cu(L^1)(DMSO)] and [Cu(L^2)(DMSO)], were prepared by the stoichiometric reaction of the $CuCl_2 \cdot 5H_2O$ with the H_2L^1 and H_2L^2 in a molar ratio (M:L) of 1:1 in DMSO/water mixture. All compounds have been fully characterized using conventional spectroscopic techniques. X-ray structure analysis was carried out on the [Cu(L^1)(DMSO)] which crystallizes in the triclinic P-1 space group. In addition, both ligands were applied several antioxidant assays including total antioxidant activity by phosphomolybdate, ferric reducing antioxidant power (FRAP) and scavenging activity on 1,1-diphenyl-2-picrylhydrazyl (DPPH). The results from antioxidant assays have shown that both ligands have excellent activities.

Contents

Introduction. Aroylhydrazines and their hydrazone derivatives, an interesting class of chelating agents for transition metals and a number of studies of chelation with several such ligands, have been prepared [1–4]. These compounds have many applications especially as reagents for the determination of transition metal ions [5,6]. Also these ligands and their metal complexes are reported to possess antimicrobial, antitubercular, anticonvulsant and anti-inflammatory, and antiproliferative activities [7–11]. Another important group for contemporary medicinal chemistry is barbituric acid and its derivatives. The derivatives of barbituric acid were widely studied as bioactive compounds [12–15]. The barbituric acid derivatives are used extensively in therapy for many diseases. This is likely due to susceptibility to rapid metabolic attack and subsequent degradation of the compounds within the body, because of an acidic hydrogen at C-5 position [16,17].

The chemistry of metal complexes of biologically active compounds is very important for bioorganometallic chemistry. Therefore many studies on such complexes have been published so far [18–21]. Although several derivatives for both aroylhydrazone and barbituric acid derivatives are known, chelating ligands which are combined with them are very rare [22–26].

In this study, we synthesized new ONO pincer ligands by bringing together these two important chemical compounds as well as their copper(II) complexes with additional binding of DMSO. Ligands are fully characterized by MS, FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. Metal complexes are characterized by MS and FT-IR spectroscopy. We also described the X-ray crystal structures of 1,3-dimethyl-5-acetyl-barbituric acid *o*-hydroxybenzoyl hydrazone copper(II) complex, [Cu(L^1)(DMSO)], which crystallizes in the monoclinic P-1 space

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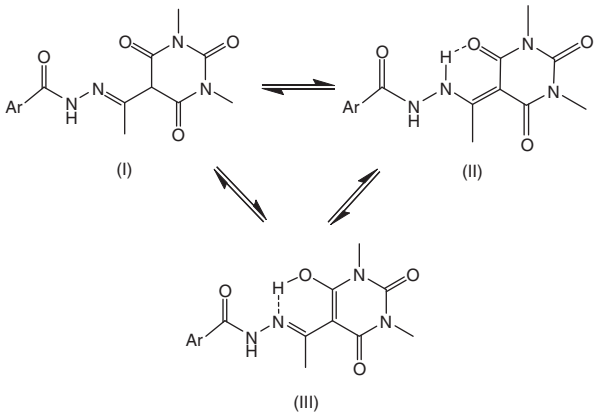

Ar = *o*-HOC_6H_4 for H_2L^1, *p*-HOC_6H_4 for H_2L^2

Fig. 1. Tautomeric forms of H_2L^1 and H_2L^2.

group. X-ray structural analyses and spectral data indicate that ligands which are synthesized in this study act as dibasic tridentate ligands. In addition, we investigated the antioxidant potential of ligands with three different test systems.

Experimental. *General.* Commercially available reagents were used without further purification. *o*-Hydroxybenzoyl hydrazine and *p*-hydroxybenzoyl hydrazine were prepared by refluxing ethyl *o*-hydroxybenzoate or ethyl *p*-hydroxybenzoate (1.48 mL, 10 mmol) with hydrazine hydrate (2.5 mL) for 4 h [27,28]. 1,3-Dimethyl-5-acetylbarbituric acid was prepared according to the reported procedures [29]. Melting points were measured with an Electro thermal 9200 melting point apparatus and the values are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus NMR spectrometer. Chemical shifts are reported in ppm downfield from Me_4Si and were referenced to solvent peaks. Mass spectra were recorded on Shimadzu LCMS-8030 Mass spectrometer. IR spectra were obtained on a Varian 900 FTIR spectrometer using KBr pellets.

X-ray diffraction data of the complex were collected on a Xcalibur, Eos diffractometer using Mo-Kα radiation at room temperatures (293 K). The data were corrected for Lorentz, polarization and absorption effects using the analytical numeric absorption correction technique [30]. Using Olex2 [31], the structure was solved by direct methods using SHELXS [32] and refined by full-matrix least-squares based on $|F_{obs}|^2$ using SHELXL [33]. The non-hydrogen atoms were refined anisotropically, while the hydrogen atoms, generated using idealized geometry, were made to "ride" on their parent atoms and used in the structure factor calculations. Drawings of the molecule and crystal structure were performed using Ortep 3 [34] and Pluton [35] package. Details of the supramolecular pi-interactions were calculated with the program PLATON [36]. CCDC reference number for the title compound is 739392. These data can be obtained free of charge via www.ccdc.cam.ac.uk/datarequest/cif.

Synthesis. General procedure for the syntheses of H_2L^1 and H_2L^2. A solution of *o*-hydroxybenzoyl hydrazine or *p*-hydroxybenzoyl hydrazine (1.52 g, 10 mmol) in ethanol (50 mL) was added 1,3-dimethyl-5-acetylbarbituric acid (1.98 g,10 mmol) and two drops of glacial acetic acid. The reaction mixture was stirred while refluxing for 24 h. On standing overnight, the white crystalline product was separated, collected by filtration, washed with small quantities of cold ethanol and diethyl ether and then dried in vacuum.

1,3-Dimethyl-5-acetylbarbituric acid *o*-hydroxybenzoyl hydrazone, (H_2L^1). H_2L^1 was obtained as colorless crystals. Yield: 85%. m.p.: 266 °C, ^{1}H NMR (400 MHz, DMSO-d6): δ 13.77 (s, 1H); 11.26 (br, 2H); 7.82 (d, J_{HH} = 6.5 Hz, 1H); 7.46 (*t*, J_{HH} = 8.5 Hz, 1H); 6.95-7.02 (m, 2H); 3.19 (s, 6H); 2.69 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d6): δ = 171.7, 165.3, 157.6, 150.6, 134.1, 129.5, 119.3, 117.0, 115.9, 88.9, 27.5, and 16.6 ppm. FT-IR (KBr) υ: 3290–2580, 1687, 1647, 1642, 1612, 1582, 1310, and 1035 cm^{-1}. MS (m/z) 332 (M + 1).

1,3-Dimethyl-5-acetylbarbituric acid *p*-hydroxybenzoyl hydrazone, (H_2L^2). H_2L^2 was obtained as colorless crystals. Yield: 91%. m.p.: 273 °C, ^{1}H NMR (400 MHz, DMSO-d6): δ 13.72 (s, 1H); 11.18 (s, 1H); 10.29 (s, 1H); 7.82 (d, J_{HH} = 8.9Hz, 2H); 6.90 (d, J_{HH} = 8.9Hz, 2H); 3.17 (s, 6H); 2.68 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d6): δ = 171.8, 164.9, 161.4, 150.6, 129.9, 121.7, 115.2, 88.7, 27.5, and 16.7 ppm. FT-IR (KBr) υ: 3250, 2960, 1683, 1628, 1612, 1590, 1340, and 1028 cm^{-1}. MS (m/z) 332 (M + 1).

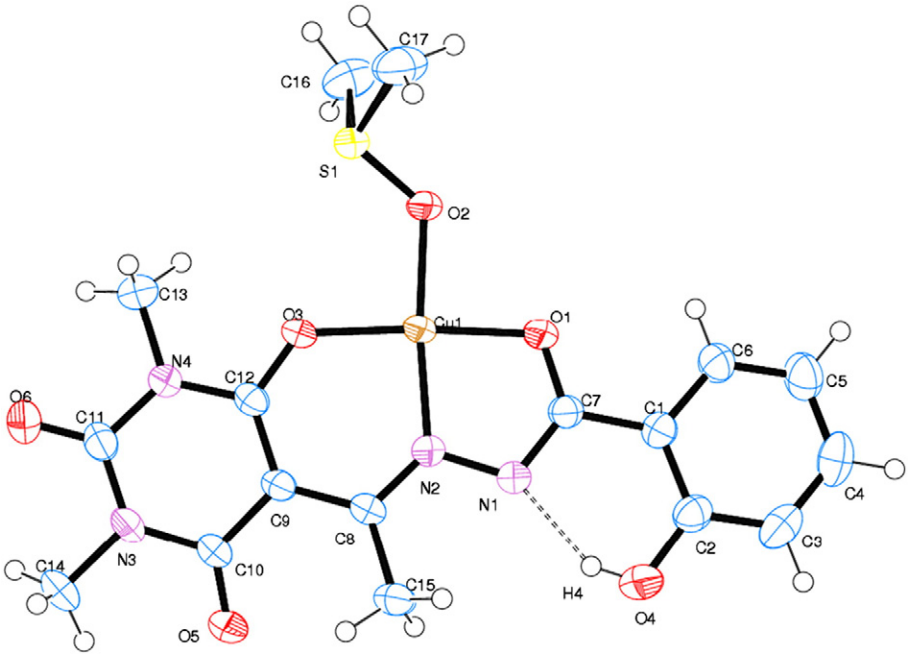

Fig. 2. The molecular structure of [Cu(L^1)(DMSO)] in the solid state, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed line indicates the intra-molecular hydrogen bond.

Table 1
Selected bond lengths (Å) and angles (deg) with esd's in parentheses, for [Cu(L[1])(DMSO)].

N(2) – C(8)	1.316(3)	C(8) – C(9)	1.440(3)
N(1) – N(2)	1.394(3)	C(9) – C(12)	1.404(3)
N(1) – C(7)	1.318(3)	O(1) – C(7)	1.286(3)
C(8) – N(2) – N(1)	117.9(2)	C(8) – N(2) – Cu(1)	129.9(2)
N(1) – N(2) – Cu(1)	111.6(1)	O(2) – C(7) – N(1)	124.1(2)

Table 2
Details related to both intra- and weak inter-molecular interactions.

D–H ….A	D–H (Å)	H···A (Å)	D···A(Å)	D–H···A(°)
O4–H4···N1	0.82	1.83	2.556(3)	147
C6–H6···O1	0.93	2.46	2.786(4)	100
C14–H14B···O5	0.96	2.28	2.668(4)	103
C15–H15B···O5	0.96	2.18	2.753(4)	117
C16–H16C···O5[a]	0.96	2.48	3.379(4)	156
C16–H16C···O6[b]	0.96	2.49	3.356(4)	149

D: donor, A: acceptor. Symmetry transformation used to generate equivalent atoms.
[a] : 1−x,1−y,1−z.
[b] : 2−x,1−y,1−z.

General procedure for the syntheses of [*Cu*(*L*[1])(*DMSO*)] *and* [*Cu*(*L*[2])(*DMSO*)]. A solution of H_2L^1 or H_2L^2 (1.66 g, 5 mmol) in hot ethanol (50 mL) was added by small portions with stirring to a solution of $CuCl_2 \cdot 2H_2O$ (0.85 g, 5 mmol) in water (15 mL), and DMSO (10 mL) was added to the mixture. The reaction mixture was heated about 2 h at 80 °C after adding an equivalent amount of ethanolic solution of KOH (0.56 g, 10 mmol). After this time the dark green solution filtered and stored in air at room temperature. The crystals which formed in two days were filtered, washed with water and dried at room temperature to give [Cu(L[1])(DMSO)] and [Cu(L[2])(DMSO)] as green crystals. Suitable crystal of [Cu(L[1])(DMSO)] for X-ray diffraction was obtained via re-crystallization from DMSO in two weeks.

Copper(II) complex of 1,3-dimethyl-5-acetylbarbituric acid *o*-hydroxybenzoyl hydrazone, [Cu(L[1])(DMSO)].

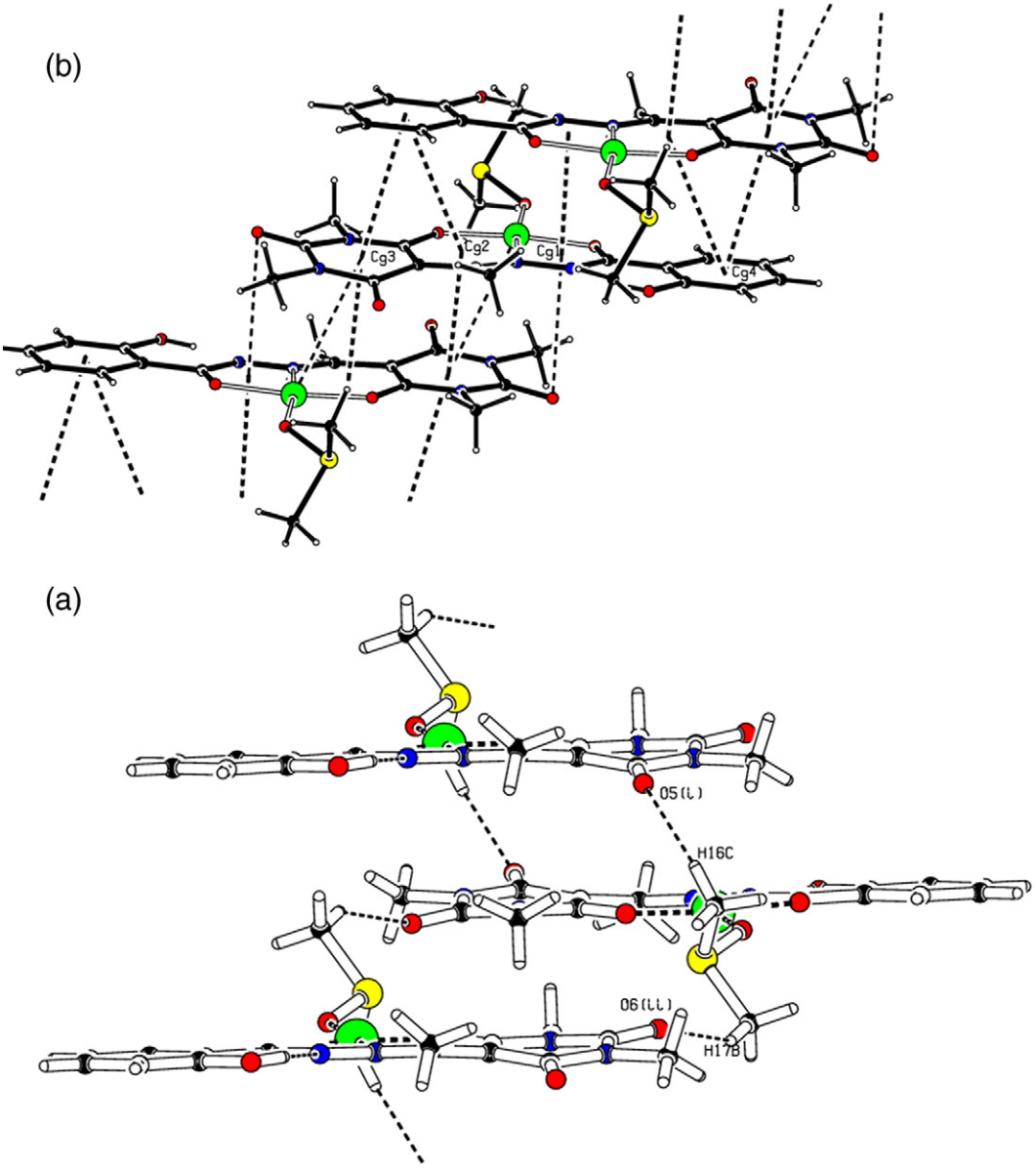

Fig. 3. Packing diagram of [Cu(L[1])(DMSO)] (a) with two centrosymmetric hydrogen-bonded chains and (b) with π–π stacking, C – O…π–ring and Cu… π–ring interactions (see Table 2 and Table 3 for further details.).

Table 3
Intermolecular π–π interactions (dist. centroids <4.0 Å), ring — metal interactions (Cg–Me <4.0 Å) and Y–X…Cg interactions (X..Cg < 4.0 Å) parameters of [Cu(L^1)(DMSO)].

Cg(I)–Cg(J)	Dist. centroids (Å)	Dihedral angle (°)	CgI_Perp (Å)	CgJ_Perp (Å)
Cg1–Cg1[iii]	3.4616(13)	0	−3.3143(9)	−3.3144(9)
Cg2–Cg3[i]	3.3927(15)	3.72(11)	3.3413(10)	3.2978(11)
Cg2–Cg4[iii]	3.6504(15)	3.13(12)	−3.3190(9)	−3.3573(13)
Cg3–Cg4[iii]	3.5858(15)	5.93(14)	−3.4365(11)	−3.3669(13)
Y–X…Cg(π–ring) interactions				
Y–X…Cg	Y–X(Å)	X…Cg(Å)	Y…Cg(Å)	Y–X..Cg(°)
C11 – O6…Cg1[i]	1.217(3)	3.563(2)	3.605(3)	82.21(18)
Ring–metal interactions				
	Dist. centroids (Å)	MeJ_Perp(Å)	β(°)	
Cg3–Cu1[i]	3.687	3.315	25.97	

[Cg(1):Cu1/O1/C7/N1/N2, Cg(2):Cu1/O3/C12/C9/C8/N2, Cg(3): N3/C10/C9/C12/N4/C11, Cg(4):C1/C2/C3/C4/C5/C6; Cg(I) = plane number I, dihedral angle = dihedral angle between planes I and J (°), dist. centroids = distance between ring centroids (Å), CgI_Perp = perpendicular distance of Cg(I) on ring J (Å), CgJ_Perp = perpendicular distance of Cg(J) on ring I (Å), β = angle Cg(I) – Me vector and normal to plane I (°)].
[i] = 1−X,1−Y,1−Z.
[iii] = 1−X,−Y,1−Z.

Table 4
Crystal data and structure refinement for [Cu(L^1)(DMSO)].

Characteristics	[Cu(L^1)(DMSO)]
Empirical formula	$C_{17}H_{20}N_4O_6SCu$
Formula weight	471.97
Temperature	293(2) K
Crystal system	Triclinic
Space group	P-1
a, Å	9.8191(6)
b, Å	9.9857(6)
c, Å	10.7053(6)
α, deg	114.855(6)
β, deg	95.999(5)
γ, deg	91.912(5)
V, $Å^3$	943.74(10)
Z	2
d calc $Mg.m^{-3}$	1.661
μ, mm^{-1}	1.313
Reflections collected	7559
[R_{int}]	[0.0218]
Final R indices [I > 2sigma(I)]	R1 = 0.0337, wR2 = 0.0776
R indices (all data)	R1 = 0.0474, wR2 = 0.0847
Goodness –of-fit on F^2	1.034
Largest diff. peak and hole [e. $Å^{-3}$]	0.29–0.34

Yield: 78%. m.p.: >350 °C FT-IR (KBr) for [Cu(L^1)(DMSO)] υ: 3110, 3065, 2948, 1694, 1634, 1593, 1569, 1245, 1152, 1090, and 1042 cm^{-1}. MS (m/z) 472 (M + 1).

Copper(II) complex of 1,3-dimethyl-5-acetylbarbituric acid *p*-hydroxybenzoyl hydrazone, [Cu(L^2)(DMSO)].

Yield: 65%. m.p.: >350 °C FT-IR (KBr) for [Cu(L^2)(DMSO)] υ: 3143, 3053, 2950, 1686, 1615, 1573, 1560, 1234, 1148, 1094, and 1050 cm^{-1}. MS (m/z) 472 (M + 1).

Antioxidant activity. Evaluation of total antioxidant activity by phosphomolybdate assay. The total antioxidant capacities of ligands were evaluated by the phosphomolybdenum method according to Prieto et al. [37]. 0.1 mL of ligands solution in DMSO (2 mg/mL) was combined with 3 mL reagent solution (0. 6 M sulfuric acid, 28 mM sodium phosphate and 4 mM ammonium molybdate). The tubes containing the reaction solution were incubated at 95 °C for 90 min. Then the absorbance of the solution was measured at 695 nm against a blank. The antioxidant activity of sample was expressed as equivalents of

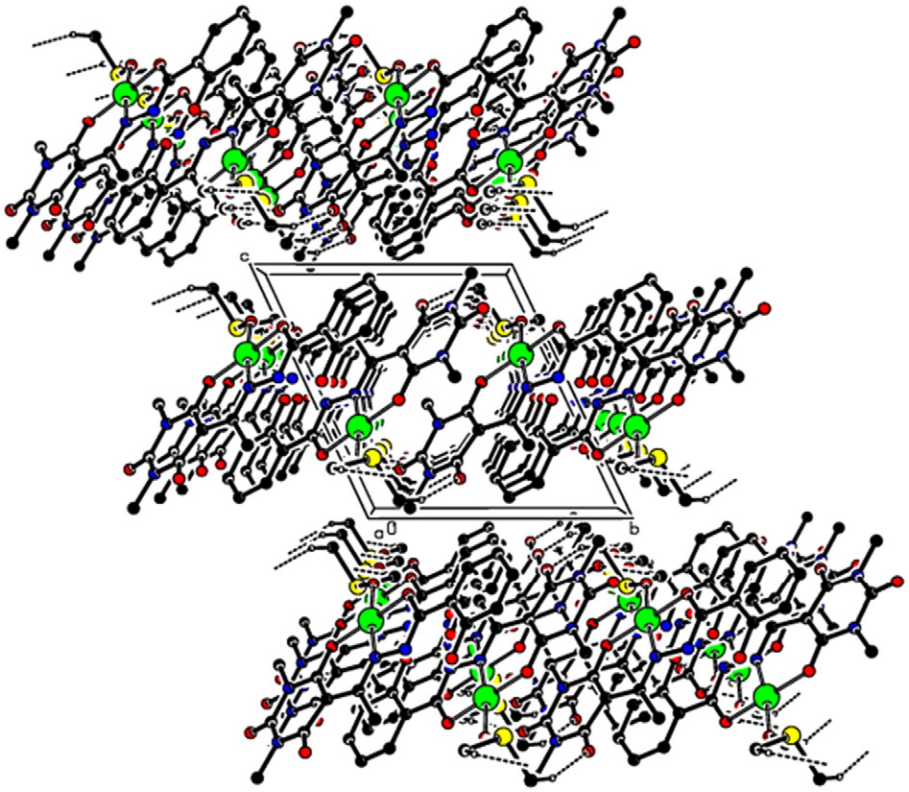

Fig. 4. Packing diagram in the unit cell of title complex perspective viewed along the a-axis, showing the formation of 2D supramolecular structure with weak intermolecular C – H…O hydrogen bonds, π–π stacking, C – O…π–ring and Cu… π–ring interactions. For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

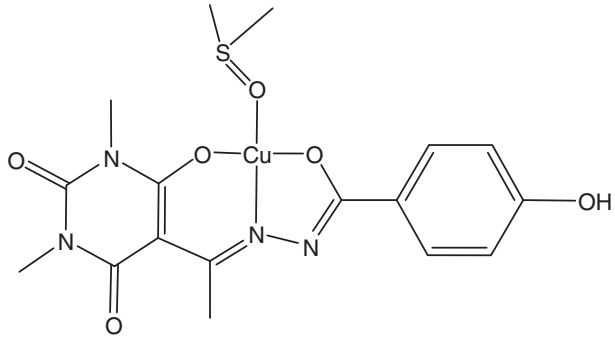

Fig. 5. The proposed structure of the [Cu(L^2)(DMSO)].

ascorbic acid (μg AAEs/mg ligand) according to the following equation obtained from the standard ascorbic acid graph:

$$\text{Absorbance} = 0.0088 \text{ ascorbic acid } (\mu g) + 0.0022. \quad (R2 : 0.9991)$$

Ferric reducing antioxidant power (*FRAP*) *assay*. The FRAP assay was determined through a method described by Benzie and Strain [38] with slight modifications. The FRAP reagent was prepared freshly by mixing 300 mM acetate buffer (pH 3.6), 10 mM TPTZ and 20 mM ferric chloride in a ratio of 10:1:1 (v/v/v). Then, 2 mL reagent and 0.1 mL of sample solution in DMSO (2 mg/mL) were added to test tubes and incubated at 30 °C for 30 min. Absorbance was measured at 593 nm. Trolox was used as standard and results were reported as equivalents of trolox (μg TEs/mg ligand) according to the following equation obtained from the standard trolox graph:

$$\text{Absorbance} = 0.0816 \text{ trolox } (\mu g) - 0.0373. \quad (R2 : 0.9977)$$

Scavenging activity on 1,1-diphenyl-2-picrylhydrazyl (*DPPH*). The hydrogen atoms or electron donation ability of some compounds were measured from the bleaching of purple colored methanol solution of DPPH. The effect of the H_2L^1 and H_2L^2 on DPPH radical was estimated according to Sarikurkcu et al. [39]. 1 mL of ligands solution in DMSO (0.2-2.0 mg/mL) was added to 1 mL of DPPH radical solution in methanol (final concentration of DPPH was 0.2 mM). After a 30 min incubation period at room temperature the absorbance was read against a blank at 517 nm. Inhibition of free-radical DPPH in percent (*I*%) was calculated in following way:

$$I\% = 100x(A_{Control} - A_{Sample})/A_{Control}$$

where, $A_{Control}$ is the absorbance of the control reaction (containing all reagents except the test compound), and A_{Sample} is the absorbance of the compound tested. BHT and BHA were used as a control.

Results and discussion. *Characterization*. The barbituric acid hydrazone ligands were synthesized by refluxing *o*-hydroxybenzoyl hydrazine or *p*-hydroxybenzoyl hydrazine with 1,3-dimethyl-5-acetylbarbituric acid in the presence of absolute ethanol along with catalytic amount of glacial acetic acid. The reaction proceeded smoothly and produced the corresponding ligands in good yields. All these ligands are air stable, nonhydroscopic and characterized by MS, FT-IR, ^{1}H, and ^{13}C spectroscopy. Ligands prepared in this study may exist in three tautomeric forms as shown in Fig. 1.

When we started structural analysis, we have checked two dimensional ^{1}H–^{13}C HETCOR spectrum to decide which tautomeric form exist in the solution. According to two dimensional ^{1}H–^{13}C HETCOR in DMSO-d6 solution spectra of H_2L^2 display two peaks with proton shifts in the signal range *ca* 2.7 and 3.2 ppm that correlate with carbon shifts in the range *ca* 17 and 28 ppm that are typical of aliphatic –CH_3 groups. Another group of peaks with proton shifts in the signal range *ca* 6.9 and 7.8 ppm that correlate with carbon shifts around *ca* 115 and 130 ppm that are typical of aromatic groups. If the resonance structure (I) were to exist in the solution, proton on the barbituric acid ring would have been in the two dimensional ^{1}H–^{13}C HETCOR spectrum. On the other hand, in the regular ^{13}C NMR spectra of H_2L^2 in DMSO-d6 solution, two peaks at 88.7 and 115. 2 ppm for H_2L^2 are attributed to NH – C – C carbons respectively. Therefore, on the basis of NMR data we can conclude that the ligands exist in tautomeric form (II) in the solution [40–42]. Another important peaks in the ^{1}H NMR spectrums of H_2L^1 and H_2L^2 in DMSO-d6 solution appear at 11.26 and 10.29 ppm for the phenolic OH resonance respectively. As expected, OH proton for H_2L^1 was shifted to low fields owing to the formation of strong intramolecular hydrogen bonding. The ^{1}H NMR spectra of ligands display a singlet belonging to NH (amide) proton for H_2L^1 at 11.26 (overlapped with OH proton) and H_2L^2 at 11.18 ppm.

The infrared spectra of H_2L^1 and H_2L^2 show four intense carbonyl bands appearing at 1687, 1642, 1612 and 1582 cm^{-1} for H_2L^1 and at 1683, 1628, 1612 and 1590 cm^{-1} for H_2L^2. The characteristic amide I band appears at ~1647 cm^{-1} for H_2L^1, but it doesn't appear for H_2L^2 probably because of overlapping carbonyl stretching frequency. In the case of H_2L^1 a very broad peak is observed in the ~3290–2580 cm^{-1} region which is assigned to the intramolecular H-bonding vibration (O – H….O) [43,44]. In case of H_2L^2 the broad medium intensity band appearing ~3250 cm^{-1} is assigned to the υ(O – H) vibration. Also the amide II υ(N – H) stretching band of these compounds are not observed in the FT-IR spectra probably because of overlapping with broad medium intensity of OH stretching frequency.

The most significant changes between the IR spectra of the ligands and their copper complexes were strong υ(S = O) bands at 1090 cm^{-1} for [Cu(L^1)(DMSO)] and 1094 cm^{-1} for [Cu(L^2)(DMSO)], indicating the presence of the DMSO molecule that coordinates from the oxygen to the metal [45,46].

Some of carbonyl absorption band which are appearing in the spectra of metal free ligand, changed to the lower frequency because of the coordination to the metal. But they could not be assigned since the spectra were complicated with overlaps in the 1500–1700 cm^{-1} region. On the other hand, a new band due to C – O vibration appears around 1245 cm^{-1} for [Cu(L^1)(DMSO)] and 1234 cm^{-1} for [Cu(L^2)(DMSO)] confirm that both complexes are enolate form [47,48].

Dark green crystals of [Cu(L^1)(DMSO)] suitable for an X-ray diffraction study were obtained by slow evaporation of a saturated DMSO solution at room temperature about two weeks. The X-ray structure analysis shows that [Cu(L^1)(DMSO)] crystallizes in the triclinic space group P-1. An ORTEP diagram giving the unique atom labeling is shown in Fig. 2 and selected bond distance and angle data are given in Table 1.

The single crystal X-ray diffraction analysis unambiguously demonstrates the H_2L^1 that coordinates to the metal center through ONO donor system. H_2L^1 acts as dibasic pincer type ligand. The copper(II) is coordinated in a slightly distorted square planar geometry with the DMSO which is coordinated over the oxygen atom to the metal center. All the data for the copper complex are in agreement with those reported for similar complexes [49,50]. The Cu1 – O1, Cu1 – O2, Cu1 – O3 and Cu1 – N2 bond distances are 1.8984(17) Å, 1.9312(17) Å, 1.8779(17) Å,

Table 5
Antioxidant activity of the ligands by phosphomolybdate and FRAP assays[a].

Sample	Phosphomolybdate assay (μg AAEs/mg ligand)[b]	FRAP assay (μg TEs/mg ligand)[c]
H_2L^1	270.65 ± 0.01	41.43 ± 1.17
H_2L^2	401.99 ± 13.61	170.35 ± 0.39

[a] Values expressed are means ± S.D. of three parallel measurements.
[b] AAEs, ascorbic acid equivalents.
[c] TEs, trolox equivalents.

Table 6
Scavenging effect (%) on 1,1-diphenyl-2-picrylhydrazyl of the ligands at different concentrations.
Ar = *o*-HOC_6H_4 for H_2L^1, *p*-HOC_6H_4 for H_2L^2.

Sample	Sample concentration (mg/mL)				Logarithm equation (r^2)
	0.2	0.5	1.0	2.0	
H_2L^1	42.06 ± 1.01[a]	49.67 ± 0.49	55.77 ± 2.32	61.33 ± 1.56	y = 8.4091 ln(x) + 55.593 (r^2 = 0.9998)
H_2L^2	39.61 ± 0.88	53.61 ± 0.66	60.90 ± 0.01	73.46 ± 1.32	y = 14.321 ln(x) + 62.66 (r^2 = 0.9923)

[a] Values expressed are means ± S.D. of three parallel measurements.

and 1.9084(19) Å, while the O1 – Cu1 – N2, O3 – Cu1 – N2, O1 – Cu1 – O2 and O3 – Cu1 – O2 angles are 83.71(8), 92.17(8), 90.28(7) and 94.17(7) respectively.

The strong intramolecular hydrogen bonding interaction between the donor O4 and acceptor N1 atoms gives rise to the formation of a six membered ring motif which can be represented mathematically as S(6) [51]. In the crystal packing there are weak intermolecular hydrogen-bonded chains (Fig. 3a), π–π stacking, C – O…π–ring and Cu…π–ring interactions (Fig. 3b). All details of interactions are given in Table 2. and Table 3. From these intermolecular contacts arise two dimensional supramolecular layers parallel to the ab-plane of the unit cell. Unit cell packing diagram shown in Fig. 4 and the relevant crystal data and experimental details along with the final parameters are summarized in Table 4.

Unfortunately, all attempts to produce suitable crystals of [Cu(L^2)(DMSO)] for X-ray analysis have failed. But comparison of the MS, FT-IR data and structural similarity of H_2L^1 with H_2L^2 confirmed the proposed structure of the [Cu(L^2)(DMSO)] in Fig. 5.

Antioxidant activity. Several assays are used for the evaluation of the antioxidant activities of pure or synthesized compounds. However, the assessment of antioxidant potentials of these compounds cannot be applied accurately by any single universal method. Thus, we carried out several antioxidant assays including total antioxidant activity by phosphomolybdate, ferric reducing antioxidant power (FRAP) and scavenging activity on 1,1-diphenyl-2-picrylhydrazyl (DPPH). Due to solubility problems of copper(II) complexes of H_2L^1 and H_2L^2, antioxidant tests were performed only for ligands.

Total antioxidant activities reflect the capacity of a nonenzymatic, antioxidant defense system. The phosphomolybdenum assay is a quantitative method to evaluate total antioxidant capacity. In the phosphomolybdenum method, molybdenum VI (Mo^{6+}) is reduced to form a green phosphate/Mo^{5+} complex at acidic pHs. High absorbance values indicate that the sample possesses significant antioxidant activity. The results reveal that the H_2L^2 was 1.5-fold higher as compared to the H_2L^1respectively with 401.99 and 270.65 μg AAEs/mg ligand (Table 5).

FRAP assay measures the reduction of ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) in the presence of antioxidants, which are reductants with half-reaction reduction potentials above Fe^{3+}/Fe^{2+}. This assay is also commonly used for the routine analysis of single antioxidants and total antioxidant activity of plant extracts. As shown in Table 5, H_2L^2 revealed the good ability to reduce Fe^{3+} to Fe^{2+} and its activity was about 4-fold higher than that of H_2L^1 with 170.35 and 41.43 μg TEs/mg ligand, respectively.

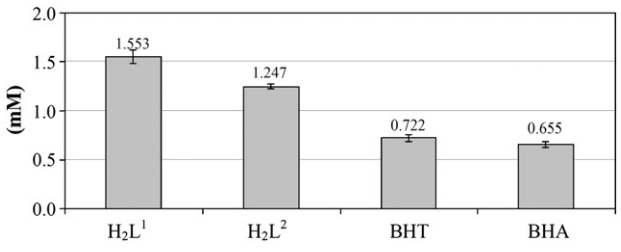

Fig. 6. EC_{50} values (mM, effective concentration at which 50% of DPPH radicals are scavenged) of ligands and standards on 1,1-diphenyl-2-picrylhydrazyl (DPPH). Values expressed are means ± S.D. of three parallel measurements. BHT, Butylated hydroxytoluene; BHA, Butylated hydroxyanisole.

Free radical scavenging is one of the best known mechanisms by which antioxidants inhibit lipid oxidation. DPPH radical scavenging activity evaluation is a standard assay in antioxidant activity studies and offers a rapid technique for screening the radical scavenging activity of specific compounds or extracts [52]. The free radical-scavenging activity for both ligands was evaluated using DPPH model system and the results are presented in Table 6.

The scavenging activity of both ligands increased with increasing amounts of ligands. From the result it is clear that the free radical-scavenging activities of H_2L^1 and H_2L^2 with their EC_{50} values 1.553 and 1.247 mM are slightly lower than those of BHT (0.722 mM) and BHA (0.655 mM) as shown in Fig. 6, indicating their abilities to act as radical scavengers.

Conclusion. This paper reports on the synthesis and characterization of two dibasic tridentate ligands as well as their copper(II) complexes. They were characterized by various spectroscopic techniques, which include MS, FT-IR, ^1H and ^{13}C NMR spectroscopy. The crystal structures of 1,3-dimethyl-5-acetylbarbituric acid *o*-hydroxybenzoyl hydrazone copper(II) complex have also been determined by the single crystal X-ray diffraction technique. In addition, data from pre-antioxidant assays have shown that both ligands have excellent activities. These ligands are taught new examples of biologically active compounds due to aroylhydrazone and barbituric acid moiety. Therefore, other potent biological activities and synthesis of their soluble metal complexes are under active investigation.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.inoche.2013.09.013.

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