Monomeric and dimeric copper (II) complexes based on bidentate N'-(propan-2-ylidene) thiophene carbohydrazide Schiff base ligand: Synthesis, structure, magnetic properties, antioxidant and anti-Alzheimer activities

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Abstract

The present study deals with the synthesis and characterization by single-crystal X-ray analysis and IR spectroscopy of two new Copper (II) complexes with bidentate Schiff base ligand [N'-(propan-2-ylidene) thiophene-2-carbohydrazide] (HL). Depending on the copper salt used in the synthesis, a mononuclear or doubly chloro bridged dinuclear Copper (II) complexes of respective formula $[\text{Cu}(\text{L})_2]$ (**1**) and $[\text{Cu}_2(\mu\text{-Cl})_2(\text{HL})_2\text{Cl}_2]$ (**2**) have been obtained. Magnetic study of complex **2** indicates the presence of weak antiferromagnetic interactions between the metal centers. To determine the antioxidant properties of both complexes, the ABTS radical scavenging and the reduction of copper (II)-neocuproine [Cu(II)-Nc] (CUPRAC) methods were used; **1** was more efficient than **2**, for the two antioxidants assays. Lastly, Anti AChE activity method has been used to estimate *in vitro* anti-Alzheimer effect of **1** and **2** both of which show a potent AChE inhibition.

Keywords:

Cu(II) complexes / X-ray crystal structure / Chloro-bridge / Magnetic properties / Antioxidant / Anti-Alzheimer activities.

1. Introduction

Schiff bases are an interesting class of ligands which have played a key role in the development of coordination chemistry due to their synthetic flexibility, selectivity and sensitivity towards the central metal ion and their ability to form stable complexes.^[1-4] Metal complexes of Schiff bases have been widely investigated because of their applications in various fields. Such complexes have an important role in the bio-inorganic chemistry,^[5-8] molecular magnetism^[9, 10] or act as catalysts in different reactions such as selective insertion of oxygen into different organic molecules.^[11-15] Numerous studies have reported that this class of compounds containing various donor atoms (such as N, O and S) have exhibited excellent antioxidant, antitumor, anti-inflammatory, antimicrobial activities and are of special interest because of the variety of ways in which they are bonded to the transition metal ions.^[16-20] Especially, sulfur is an essential component in normal physiological function and incorporated into amino acids, including cysteine, methionine, taurine, glutathione (GSH), N-acetylcysteine (NAC), and other sulfur compounds. It is an essential part of many antioxidant molecules (glutathione, thioredoxin and glutaredoxin), some sulfur-containing compounds can efficiently form a line of defense against reactive oxygen and nitrogen species. Metal binding by sulfur antioxidants may also afford significant protection against cellular oxidative damage and prevent oxidative damage which is also very important for the reduction of metal toxicity, they are well known in the treatment of oxidative stress induced pathological disorders.^[21, 22] Furthermore, some dichloro bridged dinuclear Cu(II) complexes, based on a Schiff base ligand, have been investigated for their ability to act as anticancer agents.^[23-25] In addition to their various biological activities, polynuclear complexes of Schiff bases containing paramagnetic centers connected through various types of bridges (OH, OR, Cl) have attracted considerable interest because they possess the essential structural features for the study of magnetic interactions between the magnetic centers.^[26-31] Dimeric Cu (II) complexes with Cu(μ -Cl)₂Cu core, have aroused chemists' interests due to the potential applications in the field of magnetic materials,^[30, 32-36] this class of dinuclear compounds show a variety of structures ranging from square pyramid to trigonal bipyramid with diverse bond distances (Cu-Cl) and angles (Cu-Cl-Cu) depending on the nature of the coordinated ligands.^[37]

Here, we report the synthesis, crystal structures, magnetic properties, antioxidant and anti-alzheimer activities of two complexes with Cu (II) ions based on N'-(propan-2-ylidene) thiophene-2-carbohydrazide ligand.

Scheme 1. Schematic representation of N'-(propan-2-ylidene) thiophene-2-carbohydrazide ligand (HL)

2. Experimental

2.1. Materials

Thiophene-2-carboxylic hydrazide, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, were purchased from Alfa Aesar. All the reagents and solvents were used as received without further purification. EnSpire Multimode plate reader PerkinElmer was used for measuring the absorbance, procedures were carried out on 96-well microplate. Chemical products include: Methanol for analysis and Ethanol absolute purchased from EMSURE, ABTS 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt, Neocupronine, DTNB (6,6'-Dinitro-3,3'-dithiodibenzoic acid), Acetylcholinesterase from Electrophorus electricus (electric eel) AChE 500 UNITS, Butylated hydroxytoluene $\geq 99\%$, FCC, FG $(\text{CH}_3)_3\text{C}]_2\text{C}_6\text{H}_2(\text{CH}_3)\text{OH}$, Butylated hydroxyanisole $\geq 98.5\%$ $(\text{CH}_3)_3\text{CC}_6\text{H}_3(\text{OCH}_3)\text{OH}$, Sodium phosphate monobasic and NaH_2PO_4 Sodium phosphate dibasic Na_2HPO_4 were all purchased from Sigma-Aldrich, Persulfate de Potassium $\text{K}_2\text{S}_2\text{O}_8$ from Fluka, Copper chlorid II from VWR CHEMICALS, Ammonium acetate, extra pure $\text{CH}_3\text{COONH}_4$ from Scharlau, Acetylthiocholine iodide from AppliChem, Galantamine Hydrobromide USP.

2.2. Physical Measurements

Elemental analysis (C, H, N, S) was carried out with a Perkin-Elmer 2400 elemental analyzer. FT-IR spectra, in the region $400\text{--}4000\text{ cm}^{-1}$, were recorded on a Perkin-Elmer Spectrum Two on ATR mode. Magnetic susceptibility data were collected with a Quantum Design MPMS-XL SQUID magnetometer working in the $1.8\text{--}350\text{ K}$ temperature range with the applied magnetic field up to 7 Tesla. The data were corrected for the sample holder and the diamagnetic contributions calculated from Pascal's constants. Susceptibility was measured on heating in an applied field of 0.1 Tesla.

2.3. Antioxidant and neuroprotective in-vitro activities

Compound **1** and **2** were investigated for their antioxidant potential, by means of two distinct in vitro methods, and for their neuroprotective effect by means of an in vitro antialzheimer

assay (anti acetylcholinesterase (AChE) activity). The results were compared with those of standards (positive controls) including: Butylated Hydroxyl Anisole (BHA); Butylated HydroxylToluene (BHT) (for antioxidant assay) and Galantamine (for anti-alzheimer assay).

2.3.1. ABTS radical (ABTS•+) scavenging assay

The assay was performed according to the method of Re et al.^[38] with slight modifications. It consists to add 160 µL of ABTS•+ solution (7 mM ABTS dissolved in water and 2.45 mM potassium persulfate (K₂S₂O₈), stored in dark at room temperature for 16 hours. By diluting, the solution absorbance was adjusted to 0.700 ± 0.020 at 734 nm) to 40 µL of sample solution at different concentrations in methanol, then it was incubated for 10 minutes in a darkroom, the mixture absorbance was measured at 734 nm.

The scavenging potential of ABTS•+ was evaluated by calculating the inhibition percentage

(I %), following this formula : $I \% = \frac{(Ab-As)}{Ab} \times 100$

Ab absorbance of the blank (methanol instead of sample).

As absorbance of sample.

The sample concentration (µM) inhibiting 50% of ABTS•+ (IC₅₀) was estimated from the curve of ABTS•+ + I% correlated to the sample concentrations.

2.3.2. Cupric ion reducing antioxidant capacity (CUPRAC)

The CUPRAC (CUPric Reducing Antioxidant Capacity) was assessed by the method described previously with minor changes.^[39] A 40 µL of sample solution at different concentrations was added by 50 µL CuCl₂ (10 mM), 50 µL neocuproine in ethanol (7.5 mM), and 60 µL NH₄AC buffer (1 M, pH 7.0). The mixture was then left for 60 min before reading the absorbance at 450 nm. The concentration (µM) giving an absorbance of 0.5 (A_{0.5}) was determined from the absorbance curves.

2.3.3. Anti acetylcholinesterase activity

Anti AChE activity is the standard method used to estimate the in vitro anti-Alzheimer effect, the procedure that was used followed method of Ellman,^[40] with a few modifications. several concentrations of product solutions (10 µL) were added to 150 µL of sodium phosphate buffer (100 mM, pH 8.0), then 20 µL AChE (5.32×10^{-3} U) solution was mixed and incubated for 15 minutes at 25 °C, after that a 10 µL of 0.5 mM DTNB was added. The reaction was then initiated by the addition of 10 µL of acetylthiocholine iodide (0.71 mM). The formation of the yellow 5-thio-2-nitrobenzoate anion as a result of the reaction was monitored spectrophotometrically at 412 nm. % of AChE inhibition was calculated using this equation:

$I \% = \frac{(E-S)}{E} \times 100$, where E is the activity of the enzyme without test sample, and S is the activity of the enzyme with test sample. IC₅₀ (μM) values were determined by plotting the inhibition percentage versus extract solution concentrations.

2.3.4. Statistical analysis

All experiments were performed in triplicate (n = 3) and data are presented as mean ± standard deviation (SD). The concentration giving 50% inhibition (IC₅₀) was calculated with Excel Microsoft Office Professional Plus 2013.

2.4. Synthesis of the complexes [Cu^{II}L₂] (1) and [Cu^{II}(μ-Cl)(Cl)(L)]₂ (2)

Thiophene-2-carboxylic hydrazide (0.0284 g, 0.2 mmol) and sodium hydroxide (0.008 g, 0.2 mmol) were dissolved in a mixture of ethanol-acetone (3:1) 30 mL. After 30 minutes of stirring Cu(OAc)₂·H₂O (0.018 g, 0.1 mmol) and CuCl₂·2H₂O (0.017 g, 0.1 mmol) were added respectively for the complex **1** and **2**, the solutions were kept under stirring for 30 extra minutes. The resulting solutions affords upon slow evaporation the formation of green crystals suitable for X-ray analyses in (0.022 g, 52%) and (0.012 g, 38%) yield respectively for complexes **1** and **2** on the basis of Cu(OAc)₂·H₂O for **1** and CuCl₂·2H₂O for **2**. The antisymmetric ν_{as} (C-S) and symmetric stretching frequency ν_s (C-S) for both complexes are observed at: 550, 570, 700 and 710 and for (C=N) around 1670 cm⁻¹. Elemental Anal. Calcd. C₁₆H₁₈CuN₄O₂S₂, C: 45.10; H: 4.26; N: 13.15; S: 15.05%. Found: C: 44.92; H: 4.10; N: 13.45; S: 42.5% for **1**. Calcd. C₁₆H₂₀Cl₄Cu₂N₄O₂S₂, C: 30.34; H: 3.18; N: 8.84; S: 10.12%. Found: C: 30.02; H: 3.38; N: 9.03; S: 10.31% For **2**.

2.5. X-ray crystallography

Diffraction intensities for complexes **1** and **2** were collected on a Bruker-AXS APEX II CCD diffractometer at 296(2) K. The crystallographic data, details of the intensity data collections and structure refinements are listed in Table 1. The intensities were collected with Mo Kα radiation (λ = 0.71073 Å). Data processing, Lorentz-polarization were performed using APEX.^[41] The structures were solved by direct methods and refined by full-matrix least-squares methods on F², using the SHELXL-2018 program package.^[42] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms in **1–2** were placed in calculated positions and were refined in the “riding” model with $U(H)_{iso} = 1.2U_{eq}$ of their parent atoms ($U(H)_{iso} = 1.5U_{eq}$ for methyl groups). Molecular plots were performed with the CrystalMaker and Mercury programs.^[43, 44] Geometrical calculations were carried out with PLATON.^[45] CCDC– 1959149 (**1**) and 1959150 (**2**)

contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre: ccdc.cam.ac.uk/structures.

Table 1: Crystal data and structure refinement for **1** and **2**.

Identification code	1	2
Empirical formula	C ₁₆ H ₁₈ CuN ₄ O ₂ S ₂	C ₁₆ H ₂₀ Cl ₄ Cu ₂ N ₄ O ₂ S ₂
Formula weight	426.00	633.36
Temperature/K	296	296
Crystal system	monoclinic	monoclinic
Space group	P2 ₁ /n	C2/c
a/Å	7.1221(10)	10.9490(3)
b/Å	11.9489(16)	17.8037(5)
c/Å	10.8718(15)	13.1661(4)
α/°	90	90
β/°	101.612(3)	109.1420(10)
γ/°	90	90
Volume/Å ³ ; Z	906.3(2) ; 2	2424.60(12) ; 4
ρ _{calc} /g/cm ³	1.561	1.735
μ/mm ⁻¹	1.453	2.388
F(000)	438.0	1272.0
Crystal size/mm ³	0.14 × 0.13 × 0.11	0.17 × 0.15 × 0.12
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	7.168 to 60.054	5.628 to 61.054
Index ranges	-10 ≤ h ≤ 10, -16 ≤ k ≤ 16, -15 ≤ l ≤ 15	-15 ≤ h ≤ 15, -25 ≤ k ≤ 25, -17 ≤ l ≤ 18
Reflections collected	8839	15050
Independent reflections	2628 [R _{int} = 0.0301, R _{sigma} = 0.0374]	3695 [R _{int} = 0.0262, R _{sigma} = 0.0242]
Data/restraints/parameters	2628/0/117	3695/0/132
Goodness-of-fit on F ²	1.025	1.051
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0552, wR ₂ = 0.1507	R ₁ = 0.0322, wR ₂ = 0.0792
Final R indexes [all data]	R ₁ = 0.0884, wR ₂ = 0.1733	R ₁ = 0.0493, wR ₂ = 0.0875
Largest diff. peak/hole / e Å ⁻³	0.93/-0.55	0.80/-0.49

3. Results and discussion

3.1. Description of the molecular structures

The reaction of thiophene-2-carboxylic hydrazide with Cu(OAc)₂·H₂O with 2:1 molar ratio in the presence of sodium hydroxide in a mixture of ethanol-acetone (3:1) affords green crystals of [Cu(L)₂] (**1**). The use of CuCl₂·2H₂O affords a different di-μ-chloro bridged Cu (II) complex [Cu₂(μ-Cl)₂(HL)₂Cl₂] (**2**). Single crystal X-ray diffraction analyses reveal that the two compounds crystallize in the monoclinic space groups *P*2₁/*n* and *C*2/*c* for **1** and **2**

respectively. The crystallographic data of the two complexes are given in Table 1 and selected bond lengths and angles are given in Table 2.

Table 2: Bond Lengths and Bond Angles for **1** and **2**.

1						
Atom	Atom	Length/Å	Atom	Atom	Atom	Angle/°
Cu1	O1	1.890(2)	O1	Cu1	O1 ⁱ	180.0
Cu1	O1 ⁱ	1.890(2)	O1	Cu1	N1	81.02(11)
Cu1	N1	2.051(3)	O1	Cu1	N1 ⁱ	98.98(11)
Cu1	N1 ⁱ	2.051(3)	O1 ⁱ	Cu1	N1 ⁱ	81.02(11)
S1	C2	1.714(3)	O1 ⁱ	Cu1	N1	98.98(11)
S1	C5	1.684(4)	N1 ⁱ	Cu1	N1	180.00(14)
N1	N2	1.416(3)				
N1	C6	1.299(5)				
N2	C1	1.292(4)				
Symmetry code: (i) -X,1-Y,1-Z						
2						
Atom	Atom	Length/Å	Atom	Atom	Atom	Angle/°
Cu1	Cl1	2.3612(6)	Cl1 ⁱ	Cu1	Cl1	85.12(2)
Cu1	Cl1 ⁱ	2.2587(6)	Cl1 ⁱ	Cu1	Cl2	94.09(2)
Cu1	Cl2	2.2780(6)	Cl2	Cu1	Cl1	154.37(3)
Cu1	O1	2.1927(15)	O1	Cu1	Cl1 ⁱ	102.64(4)
Cu1	N1	2.0075(18)	O1	Cu1	Cl1	103.12(5)
S1	C2	1.715(2)	O1	Cu1	Cl2	102.04(5)
S1	C5	1.695(3)	N1	Cu1	Cl1	88.49(5)
N1	N2	1.390(2)	N1	Cu1	Cl1 ⁱ	173.40(5)
N1	C6	1.284(3)	N1	Cu1	Cl2	92.37(5)
N2	C1	1.359(3)	N1	Cu1	O1	77.22(6)
			Cu1 ⁱ	Cl1	Cu1	93.39(2)
Symmetry code: (i) -X,+Y, ¹ / ₂ -Z						

As shown in Figure 1, compound **1** is square-planar copper (II) complex with two chelating L⁻¹ ligand. The asymmetric unit consist in a half molecule with 50% occupancy of metal ion and one L⁻¹ ligand, the coordination sphere is formed by two carbonyl oxygen atoms O1, O1-i and two imine nitrogen atoms N1, N1-i, from two chelating bidentate ligands species. The Cu–O and Cu–N distances of bidentate ligand are respectively 1.890(2) and 2.051(3). The values of O1–Cu–N1 and O1–Cu–N1-i angles are respectively 81.02(11)° and 98.98 (11)°.

Figure 1. Molecular structure of $[\text{Cu}(\text{L})_2]$ (1).

Symmetry operators for generating equivalent positions: (i) : $-x, -y+1, -z+1$.

The structure of **2** consists of a centrosymmetric dinuclear complex in which each Cu (II) ion is coordinated to one chelating HL ligand, through carbonyl oxygen O1 and imine nitrogen N1 with elongated $\text{Cu1-O1} = 2.1927(15)$ Å and $\text{Cu1-N1} = 2.0075(18)$ Å. Both Cu (II) ions are linked to each other by asymmetric double chloro bridge ($\mu\text{-Cl}$) [$\text{Cu1-Cl1} = 2.3612(6)$ Å and $\text{Cu1-Cl1-i} = 2.2587(6)$ Å], forming a Cu_2Cl_2 rectangular core with an intermetallic Cu...Cu distance of $3.363(2)$. The fifth coordination site around each copper is occupied by a terminal chloride Cl2 with $\text{Cu1-Cl2} = 2.278(6)$ Å. (Figure 2) Each Cu (II) ion is in highly distorted square-pyramidal coordination environment with trigonality index parameter $\tau = 0.317$. The parameter τ is determined by the relation $\tau = (\beta - \alpha)/60$ (where α and β are the larger basal angles with $\beta > \alpha$) and its value may vary from 0, representing ideal square-pyramidal geometry to 1, denoting ideal trigonal bipyramid geometry.^[46] This distortion has been observed for similar compounds.^[30, 47] In addition, the SHAPE analysis^[48] that has been carried out to ascertain the coordination geometry adopted by the Cu(II) centers reveals that it can be best described as distorted vacant octahedron (minimum CShM value of 2.283, Table 3) when compared to the square pyramidal geometry (minimum CShM value of 2.524, Table 3). The large values point out however a distorted geometry.

Table 3: SHAPE analysis for **2**

Structure [CuCl ₃ NO] (Cu1)	PP-5	vOC-5	TBPY-5	SPY-5
	28.286	2.283	3.844	2.524

PP-5 : Pentagon**SPY-5** : Spherical square pyramid**vOC-5** : Vacant octahedron**TBPY-5** : Trigonal bipyramid

Around each Cu (II) center, imine N1(/1-i), bridging chloride Cl1(/1-i), Cl1-i(/1) and terminal chloride Cl2(2-i) form the basal plane in the square pyramid. Each copper ion is 0.256 Å lifted towards the apical position occupied by O1(1-i). The Cu–Cl–Cu bridging angle is equal to 93.39(2)°.

Figure 2. Molecular structure of [Cu₂(μ-Cl)₂(HL)₂Cl₂] (**2**).

Symmetry operators for generating equivalent positions: (i) : x, -y+2, z+1/2.

The three-dimensional network of the structures is assured by weak hydrogen bond C–H...O and Van der Waals interactions for compound **1** (Figure 3, Table 4-1), and weak hydrogen bonds N–H...Cl and C–H...N for **2** (Figure 4, Table 4-2).

Figure 3: Projection of the crystal structure along the *a* crystallographic axis showing the packing for **1**. The hydrogen bonding is indicated by green dashed lines.

Figure 4: Perspective view of the crystal structure of **2** showing the two-dimensional network connected through the hydrogen bonds in dashed green lines

Table 4: Hydrogen-bond geometry (Å, °) for **1–2**

1				
<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
C8—H8C...O1 ⁱ	0.960	2.100	2.981 (4)	152.00
Symmetry code: (i) $-x, -y+1, -z+1$.				
2				
<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N2—H2...Cl2 ⁱ	0.860	2.700	3.350 (2)	133.00
C7—H7C...N2	0.960	2.460	2.798 (3)	101.00
Symmetry code: (i) $x, -y+2, z+1/2$.				

3.2. Magnetic properties

Magnetic measurement of **2** (shown in Figure 5) was carried out on a powdered sample with a magnetic field of 1000 Oe in the temperature range of 1.8–300 K. The room temperature χT value of $0.82 \text{ cm}^3 \cdot \text{K} \cdot \text{mol}^{-1}$ is in perfect agreement with the expected value for two uncoupled copper (II) ions ($S = 1/2$, $g = 2.1$). Upon cooling a decrease of χT could be observed and suggest the occurrence of antiferromagnetic interactions between the spin carriers to reach the value of $0.07 \text{ cm}^3 \cdot \text{K} \cdot \text{mol}^{-1}$ at 1.8 K.

Figure 5. Temperature dependence of χT under an applied magnetic field of 1000 Oe for **2**. The blue solid line corresponds to the fit of the data.

The experimental magnetic data could be fitted using the PHI software.^[49] based derived equation of Bleaney–Bower expression for two interacting Cu (II) ions ($S = 1/2$) with the Hamiltonian in the form $H = -2JS_1 \cdot S_2$ ^[23, 50] with an additional intermolecular interaction zJ term.

The best fit parameters were found for $J = -2.99 \pm 0.03 \text{ cm}^{-1}$, $g = 2.106 \pm 0.002$, $zJ = -0.94 \pm 0.03$. In chloro-bridged dinuclear complexes, the sign and magnitude of the exchange interaction is known to depend on numerous parameters such as the coordination geometry of the copper ion, the nature of the terminal ligands, the Cu-Cl-Cu bridging angle and intramolecular Cu-Cu distance.^[27] In the absence of others related complexes with similar ligands, it is difficult to identify what are the key parameters that affect the exchange interaction.

Magneto-structural correlations in dinuclear copper (II) complexes have been largely studied in order to explain and predict the magnetic properties of these compounds. It has been shown that exchange interaction is affected by several structural parameters such as the identity of the bridging atoms (X), the Cu–Cu' distances, the bridging angles Cu–X–Cu' (α) and the coordination geometries around the copper ions.^[31, 34, 51-54] For instance, coupling constant ranging from -132 to 45.1 cm^{-1} have been reported.^[27] In generally, the magnetic coupling between the two pentacoordinated Cu ions through chloro bridges is expected to be weaker than that observed in analogous systems with oxo or hydroxo ligands. This could be ascribed to the Cu–Cl distances that are larger, reducing the efficiency of the coupling.^[30, 55, 56] For doubly chloro-bridged Cu(II) complexes, some works have related the exchange coupling with the bridging angle (Cu–Cl–Cu) (ϕ) and the Cu–Cl_{bridge} distance (R) particularly expressed by ϕ/R ratio.^[57-59] In a similar manner that for oxo or hydroxo systems, a switch in the sign of the magnetic interactions could be observed depending on the bridging angle. In the present case, the relatively small antiferromagnetic coupling constant of about -3 cm^{-1} suggests that the bridging angle of 93.39° is close to this threshold. In other works,^[34, 36, 60, 61] the sign and magnitude of coupling constant J are also related with geometry around the paramagnetic centers. Moreover, in pentacoordinated Cu(μ -Cl)₂Cu dinuclear complexes, the distortion of the coordination geometry constitutes also an important factor that may affect the the magnetic coupling.

3.3. *Antioxidant activity*

Previous research has revealed that sulfur-containing amino acids have valuable antioxidant activities based on in vitro assays, including DPPH, ABTS, superoxide radical scavenging activities, ferric reducing antioxidant power, hydrogen peroxide scavenging, and metal chelating activities.^[62] Both of our Schiff base complexes have demonstrated a moderate antioxidant effect; compound **1** was more efficient than compound **2**, whether for the inhibition of free radical ABTS, or the reduction of copper (II)-neocuproine [Cu(II)-Nc] formed during the reaction of CUPRAC. Table 4 shows that **1** has lower IC₅₀ and A_{0.5} values compared with **2** but are modestly higher than those of the reference compounds (BHA, BHT) which indicates both compounds have moderate antioxidant activity. It has been proved that Schiff base ligands and their copper complexes showed a significant free radical scavenging action. This may be due to the presence of -NH groups which may donate an electron or hydrogen atom and form a stable free radical.^[63] On the grounds of our products structure and supporting on others studies results and analysis, we strongly suggest that there

was a powerful synergic antioxidant effect of the sulfur coupled and incorporated atom within the current products molecular structure.

Table 4: Antioxidant activity for **1** and **2**

A. ABTS radical scavenging potential of **1** and **2**

% Inhibition in ABTS assay ^a				
Products	1	2	BHA ^b	BHT ^b
IC 50 μ M	73.57 $\pm$ 2.52	109.73 $\pm$ 2.41	20.02 $\pm$ 0.77	6.79 $\pm$ 1.0

B. Cupric ion reducing antioxidant capacity for **1** and **2**

Absorbances in CUPRAC assay ^a				
Products	1	2	BHA ^b	BHT ^b
A 0.5 μ M	254.44 $\pm$ 1.73	256.24 $\pm$ 0.93	16.82 $\pm$ 2.34	7.67 $\pm$ 1.37

3.4. *Anti acetylcholinesterase activity*

A potent AChE inhibition was asserted by **1** and **2**, as indicated by their IC₅₀ values (the quantity that was sufficient to hinder 50% of the AChE enzyme in the reaction), which are as low as Galantamine (Table 5). While the in vitro neuroprotective potential of **2** was greater than for **1**, it is important to note that **2** was more effective than the reference compound Galantamine. A previous study reported that all of the Schiff bases showed high AChE inhibition, however none of them was more potent than Galanthamine.^[64] Regarding structures of **1** and **2**, the main difference between them is that there are two copper atoms in each molecule of **2** while there is only a single copper atom in **1**, so we believe that the response against AChE is proportional to the amount of copper; the activity of **2** is twice as effective as **1**. Other researchers have shown that the presence of heavy metals, such as chromium, copper, and mercury, strongly inhibited the activity of *P. javanicus* AChE to below 50%, while several pairwise combinations of different metals exhibited synergistic inhibiting effects on the enzyme, greater than was found for the individual metals; this was especially true for chromium, copper, and mercury.^[65] On the other hand, we suspect that the presence of the sulfur atom in our two compounds has not only shown antioxidant activities, but also plays a considerable effect on AChE inhibition, as a previous study reported the binding of the sulfur atom to the anionic site of cholinesterase was the major factor in cholinesterase inhibition by thioether carbamates.^[66]

4. **Table 5:** Anti-acetylcholinesterase activity for **1** and **2**

Acetylcholinesterase inhibitory activity			
Products	1	2	Galantamine ^b
IC 50 μ M	22.46 $\pm$ 0.37	10.23 $\pm$ 0.37	11.33 $\pm$ 1.01

^a Values expressed are means $\pm$ S.D. of three parallel measurements.

^b Reference compounds.

5. Conclusion

In conclusion, two new complexes of Cu (II) based on N'-(propan-2-ylidene) thiophene-2-carbohydrazide ligand were synthesized and structurally characterized, by using single crystal X-ray crystallographic tools. The two complexes exhibit different mono and dinuclear structures with square planar geometry around the Cu(II) for **1** and square pyramidal geometry for **2**. The magnetic properties of di- μ -chloro bridged Cu(II) complex indicate antiferromagnetic intra dimer coupling with $J = -2.99 \text{ cm}^{-1}$. This value agrees with the magnetic behaviour expected by such type of compounds with close values of Cu-Cu and Cu-Cl distances and Cu-Cl-Cu angle. Due to the presence of -NH groups and sulfur in the structure of **1** and **2**, these compounds have a noticeable effect on the inhibition of free radical ABTS or the reduction of copper(II)-neocuproine [Cu(II)-Nc] CUPRAC, compound **1** was more active than **2** for the two methods. However, for AChE inhibition, compound **2** with di- μ -chloro bridged Cu(II) was more effective than the reference compound Galantamine; this phenomenal finding requires supplement studies concerning *in vivo* evaluation, to strengthen the current result as to list this product among the panel of the most powerful antialzheimer standards.

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