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# Mononuclear Cu(II) Complex of an Oxime Ligand Derived From N-Heterocyclic Hydrazide: Synthesis, Spectroscopy, Electrochemistry, DFT Calculations and Catecholase Activity

Ali Zengin<sup>a</sup>, Kaan Karaoğlu<sup>b</sup>, Mustafa Emirik<sup>c</sup>, Emre Menteşe<sup>c</sup>, and Kerim Serbest<sup>c,\*</sup> <sup>a</sup> Pazar Vocational School, Recep Tayyip Erdogan University, 53300 Pazar/Rize, Turkey <sup>b</sup> Vocational School of Technical Studies, Recep Tayyip Erdogan University, 53100 Rize, Turkey

<sup>c</sup> Department of Chemistry, Recep Tayyip Erdogan University, 53100 Rize, Turkey

# Abstract

A new oxime derivative N-heterocyclic hydrazide ligand, N'-[(1E,2E)-2-(hydroxyimino)-1methylpropylidene]-2-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-l)thio] acetohydrazide (1) and its mononuclear copper(II) complex (1a) have been synthesized and characterized by using IR, UV-Vis, NMR and MALDI-TOF mass spectrometry. DFT-based molecular orbital energy calculations and electrochemical behaviors of the compounds have been also studied to explain redox potential of the compounds. The catecholase-mimetic activity of the Cu(II) complex (1a) has been investigated by monitoring the formation of 3,5-di-tert-butylbenzoquinone from 3,5-di-tert-butylcatechol. Irreversible electrochemical ring-closing of the ligand by oxidation is proposed. Electrochemical ring-closing reaction is shielded by the coordination of Cu(II) to the oxime moiety of the ligand and the title complex undergoes quasi-reversible oxidation and irreversible reduction. Under aerobic conditions, the title copper(II) complex behaves as an effective catalyst towards oxidation of 3,5-di-tertbutylcatechol to its corresponding quinone derivative in MeOH. The turnover number was found as  $100.1 \text{ h}^{-1}$ .

Keywords: Catecholase; Triazole; Vibrational analyses; DFT; Electrochemistry.

\*Corresponding author. Department of Chemistry, Recep Tayyip Erdogan University, 53100, Rize, Turkey Tel.: +90 464 2236126.

E-mail address: kerimserbest@yahoo.com (K.Serbest).

# **1. Introduction**

Due to their bearing of hydroxyl (OH) and azomethine (C=N) group, the word "oxime" is derived from the combination of the words "oxy" and "imine". Oximes can form stable complexes by the coordination to the metal ion. The imine and oxyimine (oxime) ligands and their coordination compounds have been found interesting by researchers for their stability, biological activity [1–3], medicine [4], liquid crystals [5], electro optical sensors [6] trace metal analysis [7], and catalysis [8–10]. Transition metal complexes having different types of nuclearity have been investigated to obtain new more effective catalytic systems. Copper is defined to be active center in many metaloenzymes [11]. Industrially, inexpensive selective oxidation of alcohols to quinone is essential and the catechol oxidase as antiferromagnetically coupled dinuclear Cu(II) system catalyzes the oxidation of catechols to orthoquinones in aerobic condition. The copper complexes are good candidates and some dicopper(II) complexes with catecholase like activity have been described to model the dicopper active centre of catecholase [12–15], but only a few reported literature that uses monocopper(II) complexes of the oxime ligands as a catalyst for the oxidation of catechols to orthoquinones [10,16–18].

Our research group has investigated more effective catalysts for oxidation of 3,5ditertiarybutyl catechol to the corresponding quinone derivative. So, novel Cu(II) complexes

with new oxime ligands is needed for the advances in the development of effective catalysts. In this study, we report the synthesis and characterization of an oxime ligand derived from Nheterocyclic hydrazide and its copper(II) complex with catecholase mimetic activity.

# 2. Experimental

#### 2.1. Materials and Methods

The synthesis of N'-[(1E,2E)-2-(hydroxyimino)-1-methylpropylidene]-2-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)thio]acetohydrazide (**1**) was carried out under an atmosphere of dry, oxygen-free nitrogen, using standard Schlenk techniques. 2,3-Butanedione monoxime (Alfa Aesar), copper(II) acetate (Merck) and all the solvents were of reagent grade and used without any further purification. 2-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]acetohydrazide was synthesized in four steps by previously reported procedure [19].

#### 2.2. Measurements

Fourier transform infrared (FT-IR) spectra were recorded on a Perkin Elmer Spectrum 100 spectrometer equipped with an ATR apparatus. Elemental analyses were performed using a LECO truspect analyzer at the Central Research Laboratory of Recep Tayyip Erdogan (RTE) University. Mass spectra were recorded using Thermo Sci. TSQ Quantum Access MAX Triple Stage Quadrupole mass spectrometer equipped with heated electrospray ionization (H-ESI) probe at the Central Research Laboratory of RTE University for the ligand. MALDI-TOF mass spectroscopy in a DHB matrix was investigated on a Bruker microflex LT at the Gebze Institute of Technology for the complex. <sup>1</sup>H and <sup>13</sup>C NMR spectra

were recorded on an Agilent Technologies 400/54 spectrometer at the Central Research Laboratory of RTE University. UV–vis spectra were recorded on a SpectroScan 60DV UVvis. spectrophotometer.

# 2.3. Catecholase activity

The catalytic oxidation of 3,5-di-tert-butyl catechol (3,5-DTBC) to the corresponding oquinone (3,5-DTBQ) was selected as model reaction for screening catechol oxidase mimetic activity. Catecholase mimetic activity was monitored spectrophotometrically by following the absorbance increase of 3,5-di-tert-butylquinone at 400 nm under aerobic conditions. Because of the good solubility of the complex as well as the substrate and its product, the catalytic reactivity assays were performed in DMSO. In a typical experiment, 50 µL of a solution of copper complex was added to give a final concentration of  $5.1 \times 10^{-5}$  M in a quartz cuvette containing 900 µL of O<sub>2</sub>-saturated DMF solution of 3,5-DTBC (varying its concentration from  $1.67 \times 10^{-4}$  to  $8.63 \times 10^{-3}$ ) and 50 µL of aqueous TRIS pH 8.0 buffer (50 mM) at 24°C. The conversion of the reaction rate units from A/s to M/s was done using  $\varepsilon$ = 2818 M<sup>-1</sup> cm<sup>-1</sup> for 3,5-DTBQ in DMSO [20]. A kinetic treatment on the basis of the Michaelis-Menten approach was applied and the results were evaluated from Lineweaver-Burk double-reciprocal plots.

# 2.4. Electrochemisty

Cyclic voltammograms (CV) were recorded by using Gamry Reference 3000 potentiostat controlled by an external PC. A three electrode system [BAS model (Bioanalytical System Inc.) consisted of glassy carbon (GC) (3.0 mm diameter) disc electrode as working electrode, a platinum wire counter electrode, and a Ag/AgCl (3.5 M KCl) reference electrode solid cell stand] was used for CV measurements in DMSO. The

electrochemical cells were deoxygenated by a stream of high purity nitrogen for 15 min before running the experiment and the solution was protected from air by a blanket of nitrogen during the experiment.

#### **2.5. Computational Details**

Density functional theory (DFT) calculations, as implemented in Gaussian 03 [21], were used for all the theoretical calculations. The gas phase molecular structure and vibrational frequencies were calculated by using the lanL2DZ effective potential (ECP) set of Hay and Wadt [22] for copper atom and the standard 6–311 ++ G(d,p) basis set for C, H, N and O atoms, respectively [23,24]. The absence of the imaginary frequencies confirms that the optimized molecular structure is stable at a minimum on the potential energy surface. The electronic excitations of compounds were calculated at the same level of theory by using Time-Dependent Density Functional Theory (TDDFT) combined with conductor-like polarizable continuum model (CPCM) in implicit solvent of DMSO [25]. Gaussview program was used to visualize the geometric and electronic results of the computations [26]. GAUSSSUM 3.0 [27] was used to calculate the fractional contributions of ligand fragment and metal ion to each molecular orbital to describe the excitation energies of UV-vis bands.

# 2.6. Synthesis of the ligand, (1)

A solution of 99% 2,3-butanedione monoxime (0.22 g, 2.2 mmol) in 10 mL anhydrous ethanol was added dropwise to a solution of 2-[(4-methyl-5-phenyl-4H-1,2,4-triazol-3-yl)sulfanyl]acetohydrazide (0.52 g, 2 mmol) in 20 mL anhydrous ethanol. The mixture was stirred at 90 °C temperature under nitrogen atmosphere and the process was monitored by

TLC (ethylacetate:ethanol 1:1 as mobile phase). After being stirred four days, the precipitate was filtered, washed with ethanol, dried in oven at 50 °C.

Yield 0.25 g (37%). mp 210 °C (dec.). Color: Brooken white. Anal. Calc. for  $C_{15}H_{18}N_6O_2S$  (M = 346.41): C, 52.01; H, 5.24; N, 24.26; Found: C, 52.12; H, 5.18; N, 24.08%. ESI-MS, m/z (%): 368.91 (100) [M+Na-H]<sup>+</sup>. FT-IR (cm<sup>-1</sup>): 3242 v(-OH), 3164 v(-NH), 2960, 2880 v<sub>as/s</sub>(CH<sub>3</sub>), 1663 v(C=O), 1606 v(C=N), 1554 v(-C=C-)/ β(-NH)/, 974 v(N-O), 700,783 (mono subs.). <sup>1</sup>H NMR δ (ppm): 11.61, 11.56 (s., 1H, -OH); 10.88,10.81 (s., 1H, -NH); 7.66 (s., 2H, Ar); 7.54 (s., 3H, Ar); 4.36, 4.09 (s., 2H, H<sub>2</sub>C-S); 3.61 (s., 3H, H<sub>3</sub>C-N); 2.04, 1.94 (s., 6H, -CH<sub>3</sub>). UV-Vis. nm (ε, M<sup>-1</sup> cm<sup>-1</sup>) in DMSO: 270 (433).

# 2.7. Synthesis of the Cu(II) complex, (1a)

A hot solution of copper(II) acetate (0.05 g; 0.3 mmol) in 10 mL anhydrous ethanol was added to the hot suspension of the ligand (0.10 g; 0.3 mmol) in 20 mL anhydrous ethanol. The mixture was stirred at 60 °C for 8 hours and then filtered to afford a green crude product, washed with ethanol, and dried in oven 50 °C.

Yield 87 mg (62%), m.p.=220 °C (dec). Anal. Calc. for C<sub>17</sub>H<sub>20</sub>CuN<sub>6</sub>O<sub>4</sub>S (M=468.0): C, 43.63; H, 4.31; N, 17.96; Cu, 13.58. Found: C, 43.46; H, 4.19; N, 18.11%. MALDI-TOF MS, m/z (%): 409.828 (69.85 a.u.) [M-CH<sub>3</sub>COO]<sup>+</sup>. FT-IR (cm<sup>-1</sup>): 3242 v(-OH), 1622 v<sub>asym</sub>(COO<sup>-</sup>), 1498 v(-C=C-)/ β(-NH)/, 1376 v<sub>sym</sub>(COO<sup>-</sup>), 987 v(N-O), 700,783 (mono subs.). UV-Vis. nm ( $\epsilon$ , M<sup>-1</sup> cm<sup>-1</sup>) in DMSO: 280 (24500), 402 (2430), 624 (232).  $\mu_{eff}$  (B.M.) = 1.62.  $\Lambda$  ( $\Omega^{-1}$  cm<sup>2</sup> mol<sup>-1</sup>) = 0.01.

# 3. Results and Discussion

# 3.1. Structural characterizations

Theoretical calculations have been executed using GAMESS software in order to produce structural parameters of the investigated compounds because crystals suitable for X-ray diffraction were not be obtained. DFT optimized molecular structures are presented in Figure 1. DFT calculations showed that oxime group of the free ligand (1) has E-isomer form and coordination of the donor atoms of group leads transformation to the Z-form as expected.

7



Figure 1. DFT optimized molecular structures of **1** (up) and **1a** (down).

According to DFT calculations, Cu(II) complex prefers a distorted square pyramidal geometry wherein one of the oxygen atoms from acetate ion lies in the square plane and the other oxygen is at the apical position. Some selected bond length (Å) dihedral angles (°) around Cu(II) center were tabulated in Table 1.

Bond	Length (Å)	Dihedral angle	Degree (°)
O <sub>1</sub> —Cu	2.019	O <sub>1</sub> -Cu-N <sub>3</sub> -N <sub>2</sub>	0.432
O <sub>2</sub> —Cu	1.999	$O_4$ – $N_1$ – $Cu$ – $O_2$	1.661
O <sub>3</sub> —Cu	2.450	O <sub>4</sub> -N <sub>1</sub> -Cu-O <sub>3</sub>	55.701
N <sub>1</sub> —Cu	2.031	N <sub>2</sub> -C <sub>2</sub> -C <sub>3</sub> -N <sub>1</sub>	1.454
N <sub>2</sub> —Cu	1.923	S	7

Table 1. The selected bond lengths and dihedral angles 1a.

The <sup>1</sup>H NMR spectra of the ligand (1) was taken in  $d_6$ -dimethylsulfoxide (DMSO) and the obtained data revealed that the free ligand in solution undergoes to tautomerisation (see supplementary Fig. S1, 2). The NH and OH proton signal were split due to the tautomerism and observed at 11.607, 11.564 ppm and 10.878, 10.813 ppm, respectively. The tautomeric effect is stronger on the S-CH<sub>2</sub> protons and they are observed at 4.36, 4.09 ppm as singlets. All the integrating signal intensities are suitable with the structure of the ligand.

The experimental FT IR spectra of the ligand (1) and its Cu(II) complex (1a) have been elucidated by means of theoretical calculations. Theoretical vibrational analysis have been performed 6-311G(d, p) basis set and harmonic vibrational frequencies scaled by the factor 0.9688 [28]. Experimental and theoretical IR spectra of the compounds given in Figure 2. The theoretically calculations were used for bands assignments of the experimental vibrational spectra. In the experimental spectra of the ligand (1), the characteristic O–H, N–H, C=O and C=N bands were observed at 3242, 3164, 1663, and 1606 cm<sup>-1</sup>, respectively [8–10]. Theoretical frequency calculations were in accordance with the experimental data (Table 2), except for O–H stretching vibration because of effect of intermolecular hydrogen bonding in

solid state. For the Cu(II) complex (**1a**), O–H and C=N bands were only observed at 3408 and 1580 cm<sup>-1</sup>, respectively due to the fact that weak and sharp NH and very strong C=O bands were disappeared.

In the IR spectrum of the Cu(II) complex, the carbonyl and NH vibrations were disappeared. These signals disappeared confirmed that the ligand is coordinated to Cu(II) as enolate form. The magnitude of  $\Delta [v_{as} (CO_2^{-}) - v_s (CO_2^{-})]$  in the complex is used as constituting a diagnosis for probable binding mode of the acetate ion. The title Cu(II) complex shows a  $\Delta v$  value of is 100 cm<sup>-1</sup>, which is quite similar to the corresponding bidentate values of acetates [29]. So, bidentate coordination of acetate ion is tentatively assigned to this complex. This suggestion is also good agreement in theoretically calculated value of acetate ion (Table S1).



Figure 2. Experimental and theoretical IR spectra of 1 and 1a.

In order to obtain information about the fundamental spectroscopic properties, TD-DFT calculations have been performed in DMSO using CPCM. Experimental absorption band, theoretical electronic transitions and their characters of **1** and **1a** were tabulated in Table 2. The experimental electronic spectrum of **1** showed an absorption bands at 258 nm ( $\varepsilon$ =90948 M<sup>-1</sup> cm<sup>-1</sup>) an attributed as  $\pi \rightarrow \pi^*$  transition character. The band at 270 nm is theoretically assigned as the following excitations at 270 nm due to contribution of HOMO  $\rightarrow$  L+1 (94%), at 274 nm due to contributions of H-1  $\rightarrow$  LUMO (62%), H-1  $\rightarrow$  LUMO (20%) transitions.

Complex **1a** shows absorption band for ligand based  $\pi$ - $\pi^*$ ,  $\pi$  -d and d-d transitions around 280 nm, 402 nm and 624 nm, respectively. The band at 280 nm is theoretically assigned as the excitations at 277 nm due to contributions of HOMO(B)  $\rightarrow$  L+2(B) (32%), HOMO(A)  $\rightarrow$  L+1(A) (31%) and the excitations at 306 nm due to contributions of H-9(B)  $\rightarrow$ LUMO(B) (25%), H-7(B)  $\rightarrow$  LUMO(B) (15%) and interpreted as  $\pi \rightarrow \pi^*$  transitions. The peak observed at 402 nm (calculated as 377, 402 and 415 nm) corresponds to HOMO(A)  $\rightarrow$ LUMO(A) and HOMO(B) $\rightarrow$ L+1(B) transitions. Considering that the HOMO(A) and HOMO(B) are delocalized on the benzotriazole moiety and LUMO(A) and LUMO(B)+1 are delocalized on the oxime moiety of the ligand, the band at 402 nm represents an interligand charge transfer from benzotriazole group to oxime moiety of **1a**. The weak peak observed at 624 nm can be separate two groups. The first one calculated as 567 and 590 nm corresponds to HOMO(B)  $\rightarrow$ LUMO(B) and is interpreted as  $\pi \rightarrow$ d transition according to frontier orbital analyses. The second one calculated as 726 nm is responsible for H-3(B), H-4(B)  $\rightarrow$ LUMO(B) transitions and can be attributed as d $\rightarrow$ d transition.

Table	2.	The	experimental	and	theoretical	electronic	transitions	with	their	possible
assign	men	ts for	<b>1</b> and <b>1a</b> .							

Comp.	Wave	length (nm)		
	Exp.	Theo.	Major contribution	Character
		270	$HOMO \rightarrow L+1 (94\%)$	$\pi \rightarrow \pi^*$
1	270	274	H-1 $\rightarrow$ LUMO (62%), HOMO $\rightarrow$ LUMO (20%)	$\pi \rightarrow \pi^*$
		280	HOMO $\rightarrow$ LUMO (62%), H-1 $\rightarrow$ LUMO (20%)	$\pi { ightarrow} \pi^*$
	280	277	HOMO(B) $\rightarrow$ L+2(B) (32%), HOMO(A) $\rightarrow$ L+1(A) (31%)	$\pi \rightarrow \pi^*$
		306	H-9(B) → LUMO(B) (25%), H-7(B) → LUMO(B) (15%)	$\pi \rightarrow \pi^*$
	402	399	$HOMO(A) \rightarrow LUMO(A) (30\%)$	$\pi \rightarrow \pi^*$
		402	HOMO(B) $\rightarrow$ L+1(B) (89%)	$\pi { ightarrow} \pi^*$
1a		415	HOMO(A) $\rightarrow$ LUMO(A) (68%)	$\pi { ightarrow} \pi^*$
	624	567	HOMO(B) $\rightarrow$ LUMO(B) (71%)	$\pi \rightarrow d$
		590	HOMO(B) $\rightarrow$ LUMO(B) (26%), H-7(B) $\rightarrow$ LUMO(B) (22%)	$\pi \rightarrow d$
		726	H-3(B) →LUMO(B) (33%), H-4(B) →LUMO(B) (20%)	$d \rightarrow d$

# **3.2. Electrochemical studies**

Cyclic voltammetry is used to investigate electrochemical properties of the compounds in dichloromethane solution ( $5 \times 10^{-3}$  M) containing 0.1 M tetra-n-butylammonium perchlorate (TBAP, n-Bu<sub>4</sub>NClO<sub>4</sub>) in the potential range +1.5 to -2.5 V vs. Ag/AgCl reference electrode. The electrochemical data were tabulated in Table 3 and voltammograms of compounds were

given in Figure 3. Cyclic voltammograms (CVs) of ferrocene were recorded to establish electrochemical stability and reversibility criteria in the same experimental conditions. The formal standard potential ( $E^{0}$ ) of Fc<sup>+</sup>/Fc under experimental conditions was calculated as 0.518 V vs. Ag/AgCl [ $\Delta$ Ep (the anodic to cathodic peak-to-peak separation) = 0.087 V, I<sub>pc</sub>/I<sub>pa</sub> (the cathodic-anodic peak ratio) = 1.07].



Figure 3. Cyclic voltammogram of **1** and **1a** in DMSO containing 0.1 M n-Bu<sub>4</sub>NClO<sub>4</sub> at 100 mV s<sup>-1</sup> scan rate,  $c:5 \times 10^{-3}$  M.



Figure 4. Proposed electrochemical ring-closing reaction of the 1 by oxidation.

As seen in surface plots of the HOMO and LUMO (Figure 5), the HOMO of the 1 is mainly constituted by oxime part and the LUMO is constituted mainly by  $\pi$ -electron system of the phenyl part. Removal of an electron from HOMO in highly polar aprotic medium such as DMSO could cause polarization of the hydroxyl group of the oxime moiety and the hydroxyl group leads ring-closing reaction as proposed in Figure 4 [30,31]. This radical then undergoes further radical-molecule reactions. Because of weaker  $\pi^*$ -acceptor properties of the triazoles [32], additional electron to LUMO probably could not be transferred through triazole to the structure. Because the oxidized and reduced species are unstable in the DMSO medium on the cyclic voltammetry time scale, oxime ligand shows irreversible oxidation and reduction electron transfer reactions.

The oxime displayed a oxidation peak without the corresponding cathodic waves on the reverse scan, whereas Cu(II) complex gave a couple. Theoretical calculations showed that the LUMO of **1a** is mainly contributed by d-electrons of the Cu(II) center. Coordination of the Cu(II) center to the oxime moiety acts as shield to the ring-closing reactions and molecule gains quasi-reversible electrochemical properties. The voltammogram exhibits a redox couple whose oxidation occurs at  $E_{pa} = 0.707$  V and reduction at  $E_{pc} = 0.375$  V. Copper complex also shows an irreversible reduction wave at  $E_{pc} = -2.335$  V.



Figure 5. Surface plots of HOMO and LUMO's of the 1 and 1a.

Table 3. Electrochemical data for compounds.

Compound	$E_{pa}\left(V ight)^{a}$	$E_{pc}\left(V ight)^{a}$	$E^{0'}(V)^b$	$\Delta E (V)^{c}$	$I_c/I_a$
1	0.685	_	—	-	—
<b>V</b>	_	-0.646	_	_	_
<b>1</b> a	0.707	0.375	0.541	0.332	0.27
	-2.335	—	_	_	-

#### 3.3. Kinetic Study

The catalytic oxidation of 3,5-DTBC has been studied as a model reaction for the catecholase activity of catechol oxidase. Catalytic activity was monitored by following the absorbance increase at 400 nm for 60 minutes in methanol media, adjusted to pH 8 with Tris-HCl buffer (50 mM). Under aerobic conditions, saturation kinetics were found for the initial rates versus the 3,5-DTBC concentrations Figure 6.



Figure 6. Plot of rate vs. [3,5-DTBC] in presence of **1a** in methanol; inset: Lineweaver-Burk plot.

Michaelis-Menten model, originally developed for enzyme kinetics, was applied for kinetic experiments. The kinetic parameters calculated by linear regression using the

Lineweaver–Burk plot, gave reasonable straight lines, from which the parameters such as maximum velocity ( $V_{max}$ ), rate constant for the dissociation of the complex–substrate intermediate (the turnover number), and Michaelis binding constant (KM). As given in Equation 1, the y-intercept of such a graph is equivalent to the inverse of  $V_{max}$ ; the x-intercept of the graph represents  $-1/K_m$  [33].

$$\frac{1}{V} = \frac{K_m + [S]}{V_{max}[S]} = \frac{K_m}{V_{max}} \frac{1}{[S]} + \frac{1}{V_{max}}$$

Results were obtained from Lineweaver–Burk plot as  $v_{max} = 8.74 \times 10^{-5}$  mol dm<sup>3</sup> s<sup>-1</sup> and  $K_M = 2.47 \times 10^{-3}$  mol dm<sup>-3</sup>. The turnover number of 100.1 h<sup>-1</sup> was compared with literature data and as seen in Table 4, **1a** has comparable higher turnover number than some reported mononuclear copper(II) complexes.

Table 4. Some reported turnover numbers of catecholase mimetic activities for mono- and dinuclear copper(II) complexes.

Complex	Turnover number (h <sup>-1</sup> )	Reference
	6.00	[16]
mono-nuclear copper(II)	11.16	[17]
	13.32	[18]
	1.97	[13]
	15.84	[12]
di-nuclear copper(II)	28.50	[12]
	5470	[14]
	1.56×10 <sup>4</sup>	[15]

## 4. Conclusion

Previously, we reported catecholase mimics which are dinuclear Cu(II) complexes of ferrocenyl substituted heterocyclic ligands or mononouclear Cu(II) complex of oxime derivative unsymmetrical azine ligand [10,34]. In this paper, we have reported a new oxime derivative N-heterocyclic hydrazide ligand and its mononuclear Cu(II) complex and their applications in catalytical field. The results of catalytic activity studies show that the Cu(II) complex (1a) is an effective catalyst having turnover numbers (kcat) 100.1 h<sup>-1</sup>. The obtained turnover number in this study is lower than our previously reported study, but higher than some related oxime complexes [35].

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# Highlights

- An oxime derivative hydrazide ligand and its Cu(II) complex have been synthesized.
- DFT calculations were performed for vibrational assignments and electronic transitions.
- The Cu(II) complex shows catecholase mimetic activity.
- Electrochemical properties of compounds were investigated by CV.