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Copper(II) Complexes Bearing Hydrazone Schiff Base Ligands: Synthesis, Structural Characterization and Biological Activity

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Abstract:
Five copper(II) complexes bearing aroylhydrazone Schiff base ligands were prepared and studied by spectroscopies which indicated that the ligands can act as dianionic tridentate chelates in enol forms. The obtained mass spectra data induced the hydrazone Schiff base copper(II) complexes as binuclear copper(II) complexes probably. The effective magnetic moments measured for these complexes are expected for one unpaired electron and distorted square-planar geometry around Cu(II) centers. The electrochemical properties of obtained complexes were conducted by cyclic voltammetric method. Their antibacterial and antifungal activity of all copper(II) complexes were examined on some Gram-positive strains, Gram-negative strains and a fungi. The obtained Cu(II) complexes were also tested for their anticancer activity against human breast cancer (MCF-7) and hepatocellular carcinoma (HepG-2).

Keywords. *Hydrazones, copper(II) complexes, spectroscopies, electrochemical property, biological activities*

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I. Introduction

Hydrazones are chemical compounds having a basic structure $R^1R^2C = NNR^3R^4$. The hydrazone group can be seen as resulting from the reaction of an aldehyde or a ketone with a hydrazine having a free NH_2- group [1]. Hydrazones, Schiff base-type compounds actually, containing an azomethine (C = N) constitute an important class of compounds which exhibit various pharmacological activities including antitumor, antiviral, antifungi, and antituberculosis properties [2,3]. Hydrazones with *ONO, ONO, or NO* coordination atoms that may coordinate metal ions, and making them potential chelating ligands [4, 5]. In addition, hydrazone compounds perform keto-enol tautomerism, and they have a variety of coordination numbers when they coordinate to metal ions in neutral, monoanionic or dianionic forms [6, 7]. Hydrazones can form mononuclear, binuclear and polynuclear metal complexes [8-10]. So hydrazones and their complexes have been attended by chemists extensively.

In previous research works, some transition metal complexes of hydrazones have taken an important place in medicinal chemistry. They have interesting bioactive properties such as enzyme inhibitors, antibacterial, antifungal, anti-inflammatory, antioxidant, anti-tubercular, anticoagulant, antitumor, anticonvulsant, antimalarial agents [11-15] and especially antiviral compounds [16]. Recently, their copper(II) complexes were also found having anti-cancer, antibacterial, antitubercular, antioxidant and anti-inflammatory activity [8,17-20]. They can play as potential urease inhibitory compounds [21,33]. The copper(II) complexes of hydrazones could be coordinated in the diversity of stereochemistry so their physicochemical and biological properties become especially interesting [7]. In this report, we continue to study on copper(II) complexes bearing some aroylhydrazone ligands about their preparation, structural characterization and biological properties.

II. Materials and Methods

Organic chemicals such as benzoylhydrazine, aromatic aldehydes were commercially obtained from Across Organics without further purification. The metal salts, anhydrous Na_2CO_3 98.5%, $CuCl_2.2H_2O$ 98.0% were purchased from Xilong Scientific Co. Ltd., China. All solvents were purified following laboratory processes.

The high resolution mass spectra (m/z) as +IDA-TOF-MS were measured on a Sciex X500 QTOF spectrometer for ligands. An Agilent 6310 Ion Trap spectrometer was used to record mass spectra (m/z) in electrospray ionization (ESI) mode of the obtained complexes. A Bruker Advance 500MHz NMR spectrometer was used to determine NMR spectra using DMSO-d_6 as the solvent. A Perkin Elmer Spectrum Two spectrophotometer was used to carry out FT-IR spectra measurements (KBr pellet, 400–4000 cm^{-1}). A Perkin Elmer Lambda UV-35 spectrophotometer was used to measure UV-Visible spectra of the hydrazone complexes (230 – 600 nm) in methanol solution (1.0×10^{-5} M). A Sherwood Scientific magnetic susceptibility balance (Mark 1, serial No. 25179) was used to identify magnetic susceptibility of the synthetic complexes as powder compounds at room temperature.

Synthesis of hydrazone Schiff base ligands

Ligands H_2L1 - H_2L5 were synthesized according to the previously published procedure [22] by mixing equimolar amounts of benzoylhydrazine with the relative salicylaldehyde. The reaction was run in ethanol, stirred for about 5 hrs at room temperature and checked by TLC. The received precipitates were filtered and washed several times by cold ethanol, then dried in *vacuo*. The reaction yields and molecular weight of the obtained ligands are presented in **Table 1**.

Preparation of hydrazone copper(II) complexes

The hydrazone copper(II) complexes were prepared by following the known literature procedure [23] using $CuCl_2.2H_2O$ instead of $Cu(OAc)_2.H_2O$. The ethanol solution containing $CuCl_2.2H_2O$ (1 mmol) was added to the ethanol solution of respective ligand (1 mmol) at the presence of Na_2CO_3 (1 mmol) under magnetic stirring and then refluxed for 3 hrs. After the reaction mixture was cool to room temperature, the precipitated color complexes were filtered and washed with cold ethanol, finally dried in *vacuo*. The coordination yields, effective magnetic moments and molecular weight of the hydrazone Cu(II) complexes are presented in **Table 1**.

Electrochemical studies

A Zahner Elektrik IM6 instrument was used to study the electrochemical properties of synthetic complexes. The cyclic voltammograms were recorded using the complexes' concentration of 1.0×10^{-3} M in DMSO solution and $LiClO_4$ 0.1 M as supporting electrolyte. The electrochemical studies were carried out by using the reference electrode was Ag/AgCl/KCl, the counter electrode as a platinum wire and the working electrode was a platinum electrode. All experiments in standard cells at a scan rate of 100 mV s^{-1} at room temperature were performed within the potential window −4 V to +2 V *vs* the reference electrode.

Biological assay

Antibacterial assay

All the received complexes were screened for their antibacterial activity against the standard bacterial strains ofbothGram-positive bacteria, *Staphylococcus aureus* (ATCC 13709), *Bacillus subtilis* (ATCC 6633), *Lactobacillus fermentum* (N4), and Gram-negative bacteria, *Salmonella enterica*, *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 15442) and a fungi, *Candida albicans* (ATCC 10231) using the broth microdilution method [24, 25]. Ampicilline, cefotaxime and nystatin were tested as the reference antibacterial and antifungal agents. Bacterial and fungal strains were suspended in nutrient broth at a concentration of approximately 5.10^5 CFU/mL. The nutrient broths containing microorganisms were transferred by 200 µL into 96 well plates, and 10 µL of each solution with the different complexes' concentration of 128 – 0.015 µg/mL were added. All the tests were grown at 37 ºC in an incubator for 24 h. The minimum inhibitor concentration (MIC, µg/ml), at which no bacterial growth was determined, was represented for at least three observations. The received results were presented in **Table 6**.

Cytotoxicity assay

MTT reduction assay was used to determine anticancer activity of the hydrazone Cu(II) complexes against human cancer cell lines, MCF-7 and HepG-2according to Mosmann's modified method [26]. MCF-7and HepG-2 cells were grown in 96 well plates in standard condition of a humidified atmosphere containing 5% $CO_2$with 10% fetal bovine serum (FBS), 100 U/mL penicillin, 100 U/mL streptomycin, and incubated at 37 °C for 24 h. Then, each complexes were tested for cells with different concentrations, 128.0, 32.0, 8.0, 2.0 and 0.5 µg/ml in DMSO for 48 h more. Subsequently, 10 µL of freshly prepared MTT (5mM) solution were added to each well, and the plate was incubated for 4h at 37 ºC in the atmosphere of 5% CO_2. Formazan crystals formed in the wells were dissolved with 100 µL DMSO. The optical density (OD) of each well was measured at a wavelength of 560 nm in a Biotek Epoch 2 Microplate Spectrophotometer. Each experiment was carried out in triplicates for every tested complexes' concentration. The % cell inhibition were calculated from the obtained optical densities following the formulae (**1**) in the published article [27].

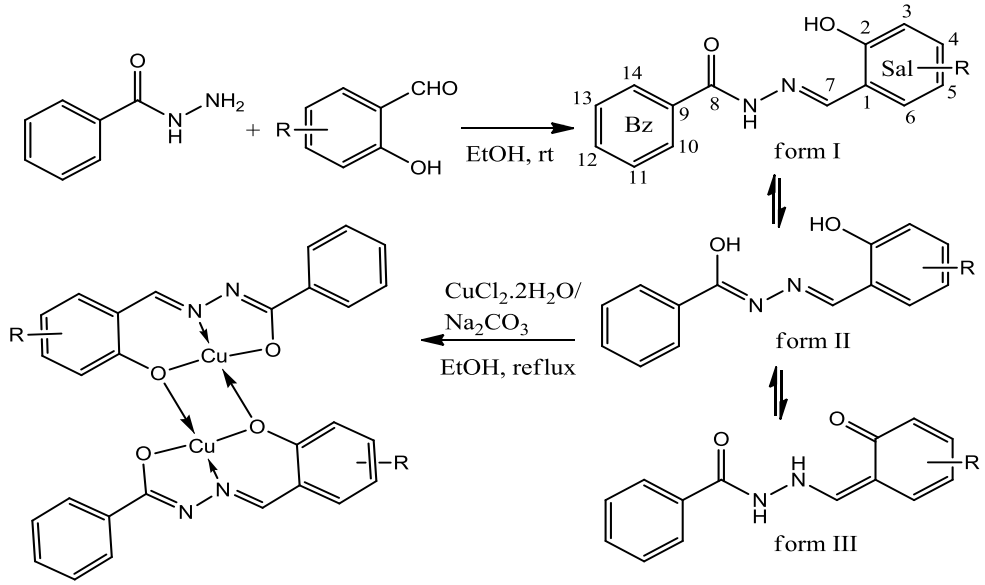
The IC_{50} values, at which the tested complex concentration has caused 50% inhibition of cell growth, were estimated from the plots performed % cell inhibitions based on tested complex concentrations and presented in **Table 7**.

III. Results and Discussion

Chemistry and Spectra

Studied aroylhydrazones (**Table 1**) were prepared by condensation of benzoylhydrazine and salisaldehydes in good yields (72.5 – 81.0%). The obtained ligands can be soluble in DMSO, dichloromethane, ethylacetate and methanol. These ligands were spectrally analyzed by ESI-MS, FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectrometries. The copper(II) complexes were coordinated between the obtained ligands with $CuCl_2.2H_2O$ in the mole ratio of 1:1 with the presence of Na_2CO_3 and in ethanol as solvent. The reaction yields were quite high (84.0 – 93.0%). The received copper(II) complexes (**Table 1**) are soluble in dichloromethane, methanol and DMSO. The synthetic complexes were studied by the analysis of ESI-MS, FTIR, UV-Vis spectra and effective magnetic moments (μ_{eff}).

The pseudo-molecular ion signals found in the high resolution mass spectra as $[M+H]^+$ of the obtained ligands clearly indicate molecular masses suitable for the suggested fomulae (**Table 1**). On ESI mass spectra of the received hydrazone copper(II) complexes, pseudo-molecular ion peaks are assigned to $[Cu(II)L]_2 + H]^+$ which probably induce that coordination compounds in binuclear complexes (**Scheme 1**) [23,28,29]. They are good compatible with the suggested formulae.



R = 5-F; 5-*t*-Bu; 3-*t*-Bu; 3,5-di-*t*-Bu

Scheme 1. Synthesis of hydrazone ligands and hydrazone Schiff base Cu(II) complexes

Table 1. Hydrazone Schiff base ligands and their Cu(II) complexes

R	Compound	Yield (%)	Mol. Weight (Cal.)	μ_{eff} (BM)	Geometry
H	H_2L1	79.5	241.0866 (241.2653)	-	-
	$[Cu(II)L1]_2$	92.5	602.9 (603.5)	2.04	Distorted square-planar
5-F	H_2L2	72.5	259.0885 (259.2257)	-	-
	$[Cu(II)L2]_2$	86.5	638.9 (639.5)	2.03	Distorted square-planar
5-*t*-bu	H_2L3	76.5	297.1605 (297.3716)	-	-
	$[Cu(II)L3]_2$	93.0	715.1 (715.8)	2.10	Distorted square-planar
3-*t*-bu	H_2L4	72.5	297.1600 (297.3716)	-	-
	$[Cu(II)L4]_2$	84.0	715.1 (715.8)	2.02	Distorted square-planar
3,5-di-*t*-bu	H_2L5	81.0	353.2229 (353.4779)	-	-
	$[Cu(II)L5]_2$	85.5	827.3 (828.0)	1.83	Distorted square-planar

In theory, obtained aroylhydrazones can be existed in three forms of keto-enol tautomeric interconversion [7]. In FT-IR spectra of the ligands, there were the absorptions at 3172 – 3268 cm^{-1} attributed to the ν (N−H) and at 1640 – 1672 cm^{-1} attributed to the ν (C=O) which indicate the obtained ligands in the forms I (**Scheme 1**). These received results were similar to published ones [30,31]. In IR spectra of the synthetic Cu(II) complexes, the disappearance of the bands of N−H vibrations, some movements of intense bands at 1608 − 1625 cm^{-1} from 1640 – 1672 cm^{-1} for C=O, at 1491– 1524 cm^{-1} from 1539 – 1565 cm^{-1} for C=N, at 1208 − 1250 cm^{-1} from 1271 – 1292 cm^{-1} for C−O vibrations and the appearance of the new bands at 525 – 573 cm^{-1} for Cu−O, and at 444 – 486 cm^{-1} for Cu−N vibrations (**Table 2**) indicated the coordination of Cu(II) with the ligands in O,N,O positions in enol forms (**Scheme 1**). These received results were similar to published ones [7,28,32].

Table 2. The typical IR data of hydrazone ligands and their Cu(II) complexes

Compound	ν_{N-H} (cm^{-1})	$\nu_{C=O}$ (cm^{-1})	$\nu_{C=N}$ (cm^{-1})	ν_{C-N} (cm^{-1})	ν_{C-O} (cm^{-1})	ν_{N-N} (cm^{-1})	ν_{Cu-O} (cm^{-1})	ν_{Cu-N} (cm^{-1})
H_2L1	3268	1672	1539	1488	1271	1079	-	-
$[Cu(II)L1]_2$	-	1624	1509	1479	1208	1041	533	456
H_2L2	3215	1640	1548	1486	1281	1069	-	-
$[Cu(II)L2]_2$	-	1623	1509	1480	1232	1047	545	453
H_2L3	3210	1641	1547	1491	1292	1089	-	-
$[Cu(II)L3]_2$	-	1625	1514	1484	1250	1048	525	444
H_2L4	3188	1644	1559	1429	1285	1081	-	-
$[Cu(II)L4]_2$	-	1610	1491	1416	1226	1027	573	464
H_2L5	3172	1654	1565	1435	1289	1089	-	-
$[Cu(II)L5]_2$	-	1608	1524	1402	1231	1027	546	486

Table 3. ^{1}H-NMR data of hydrazone ligands

Compound	δ (ppm), protons of					
	NH	OH	CH=N	Bz	Sal	t-Bu
H_2L1	12.09 (s, 1H)	11.29 (s,1H)	8.65 (s, 1H)	7.94 (d, 2H), 7.62 (t, 1H, 7.55 (m, 2H)	7.55 (m, 1H), 7.31 (t,1H), 6.91-6.95 (m, 2H)	-
H_2L2	12.14 (s, 1H)	11.01 (s, 1H)	8.64 (s, 1H)	7.94 (d, 2H), 7.62 (t, 1H), 7.55 (t, 2H)	7.43 (dd, 1H), 7.14 (dt, 1H), 6.94 (m, 2H)	
H_2L3	12.06 (s, 1H)	11.08 (s, 1H)	8.65 (s, 1H)	7.94 (d, 2H), 7.61 (t, 1H), 7.55 (t, 2H)	7.50 (d, 1H), 7.35 (dd, 1H), 6.87 (d, 1H)	1.28 (s, 9H)
H_2L4	12.45 (s, 1H)	12.20 (s, 1H)	8.58 (s, 1H)	7.95 (d, 2H), 7.62 (t, 1H), 7.56 (t, 2H)	7.28 (m, 2H), 6.89 (t, 1H)	1.41 (s, 9H)
H_2L5	12.28 (s, 1H)	12.18 (s, 1H)	8.58 (s, 1H)	7.94 (d, 2H), 7.63 (t, 1H), 7.56 (t, 2H)	7.32 (d, 1H), 7.22 (d, 1H)	1.42 (s, 9H), 1.29 (s, 9H)

In ^{1}H-NMR spectra, there were typical singlets at 12.06 – 12.45 and 11.01 – 12.20 ppm for the protons of NH and OH groups of the synthetic hydrazone ligands in forms I. There was a singlet at 8.58 – 8.65 ppm for the proton signal of CH=N groups probably. The aromatic proton signals of benzyl and salicyl groups were found at 6.87 – 7.95 ppm. The 5-F group of H_2L2 induced the aromatic protons of salicyl ring in multilets as usual. The protons of *t*-butyl groups were singlets at 1.28 – 1.29 ppm for 5-*t*-butyl and 1.41 – 1.42 ppm for 3-*t*-butyl (**Table 3**).

In ^{13}C-NMR spectra, all the received signals of the ligands were well suitable to the suggested formulae. The typical signals were at 162.75 – 162.87 ppm attributable to the carbon of C_8=O groups, 154.67 – 157.44 ppm assigned to the carbon of C=N groups, 146.25 – 151.26 ppm to the carbon of C_2−O groups. The double signal at 154.34 and 153.55 ppm was associated to the carbon of C_5−F of H_2L2. The signals at 135.62 – 141.46 ppm belonged to the carbons of C−t-Bu of H_2L3 –H_2L5. Other carbon signals of benzyl and salicyl rings were at 132.87 – 113.78 ppm. The salicyl containing fluoro group (H_2L2) showed the typical carbon signals in doublets as usual [27]. The carbon signals of *t*-butyl (H_2L3 –H_2L5) were observed at 34.59 – 29.21 ppm (**Table 4**).

Table 4. ^{13}C-NMR data of hydrazone ligands

Compound	δ (ppm), carbons of				
	C=O	CH=N	Bz	Sal	t-Bu
H2L1	162.80	157.44	132.77, 131.34, 128.50 (2C), 127.58 (2C)	148.35 (C−OH), 131.92, 129.52, 119.30. 118.62, 116.38	-
H2L2	162.87	156.21	132.74, 131.93, 128.47 (2C), 127.60 (2C)	146.25 (C−OH), 154.34 and 153.55 (C−F), 119.73 and 119.67, 118.01 and 117.83, 117.59 and 117.52, 113.97 and 113.78	-
H2L3	162.83	155.26	132.87, 131.88, 128.49 (2C), 127.58 (2C)	148.73 (C−OH), 141.46 (C−t-Bu), 128.54, 125.58, 117.87, 116.02	33.72, 31.20 (3C)
H2L4	162.77	156.93	132.52, 132.08, 128.58 (2C), 127.60 (2C)	150.86 (C−OH), 136.37 (C−t-Bu), 129.50, 128.51, 118.74, 117.64	34.45, 29.21 (3C)
H2L5	162.75	154.67	132.60, 131.99, 128.53 (2C), 127.58 (2C)	151.26 (C−OH), 140.37 (C−t-Bu), 135.62 (C−t-Bu), 125.66, 125.52, 116.93	34.59, 33.81, 31.23 (3C), 29.24 (3C)

UV-Visible spectra of the synthetic complexes (230 – 600 nm) in methanol solution (1.0×10^{-5} M) were measured at room temperature using a Perkin Elmer Lambda UV-35 spectrophotometer. The received results were presented in **Figure 1**. The maximum absorption bands with wavelengths at 232 - 238 nm and 264 – 268 nm may be assigned to π→π* electronic transition of aromatic rings. The absorption bands at 298 – 302 nm, 312 – 318 and 326 – 333 nm could confirm for n→π* electronic transitions of free electrons on O and N of C−O and C=N groups. A strong band found at 388 - 405 nm can be attributed to LMCT transitions [6,33]. The *d-d* bands seem to be not appreared at this low concentration (1.0×10^{-5} M) of the solutions. There are some small shifts to longer wavelength in UV-Vis spectra of hydrazone Schiff base Cu(II) complexes containing ligands with different substituted groups compared to $[Cu(II)L1]_2$. The copper(II) complexes in this report show the μ_{eff} values of 1.83 – 2.10 B.M. in good agreement with one unpaired electron d^9 and distorted square-planar geometry around Cu(II) centers [17,24,34].

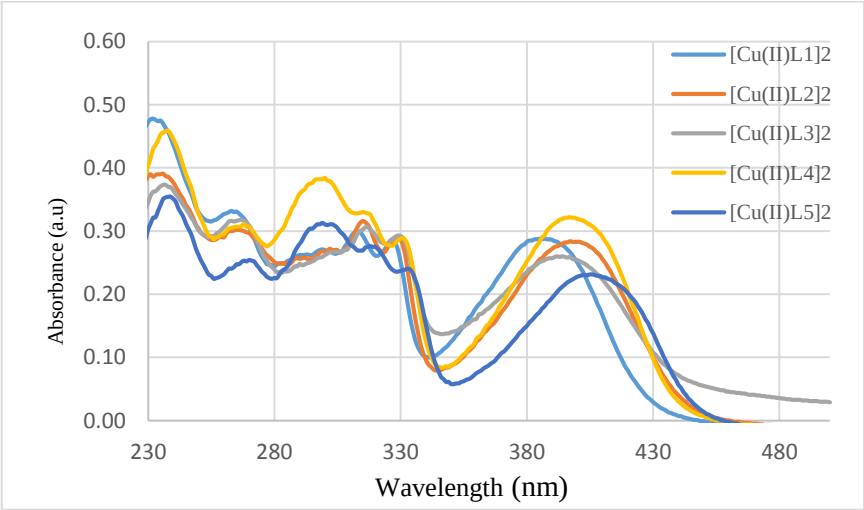


Figure 1. UV-Vis spectra of hydrazone Cu (II) complexes

Electrochemical studies

The cyclic voltammetry (CV) was used to study the electrochemical behaviors of the synthetic complexes. The cyclic voltammograms of synthetic Cu (II) complexes are received in **Figure 2**. The received cyclic voltammograms of synthetic hydrazone Cu(II) complexes performed well-defined cathodic peaks at (−) 2.302 – (−) 2.161 V for the reduction of Cu(II)→ Cu(I) probably. The similar signals were observed in the reported Cu(II) complexes [15,35]. Some shifts in the reduction potentials of the Cu(II) complexes bearing substituted groups to higher field compared with the reduction potential of $[Cu(II)L1]_2$ must be from the electronic and stereochemical behaviours of the substituted groups to the ligands as coordination (**Table 5**).

Table 5. Reduction potentials of hydrazone Cu(II) complexes

Complex	*E*pc (V)
$[Cu(II)L1]_2$	−2.302
$[Cu(II)L2]_2$	−2.255
$[Cu(II)L3]_2$	−2.161
$[Cu(II)L4]_2$	−2.161
$[Cu(II)L5]_2$	−2.161

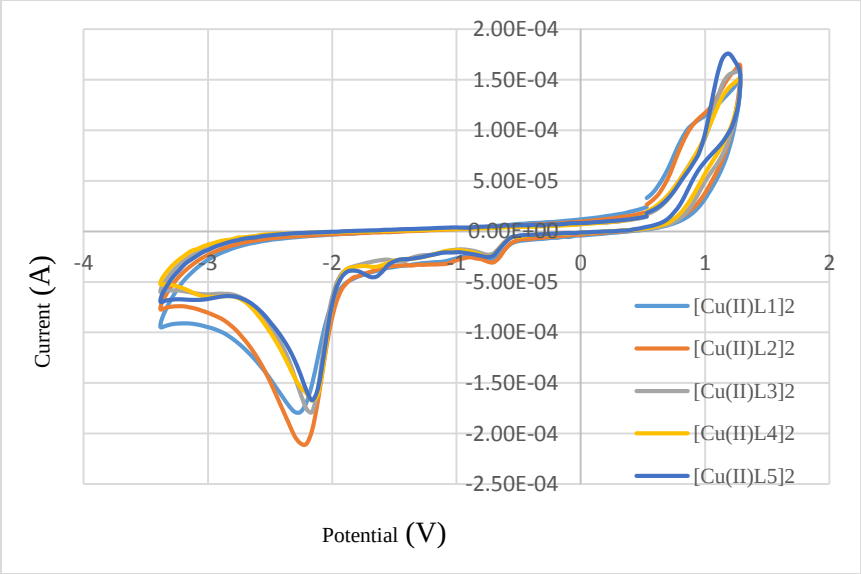


Figure 2. Cyclic voltammograms of hydrazone Cu(II) complexes

Biological activity of the hydrazone Cu(II) complexes

The antibacterial activities of complexes were evaluated against Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis* and *Lactobacillus fermentum*) and Gram-negative bacteria (*Salmonella enterica*, *Escherichia coli*, *Pseudomonas aeruginosa*) and fungi (*Candida albicans*) by using the minimal inhibitory concentration (MIC) method. The received results were performed in **Table 6**.

Table 6. Biological activity of the hydrazone Schiff base Cu(II) complexes

Compound	MIC (μg/ml)						
	Gram positive Bacteria			Gram negative Bacteria			Fungi
	Staphylococcus aureus	*Bacillus subtilis*	*Lactobacillus fermentum*	*Salmonella enterica*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*
$[Cu(II)L1]_2$	128 ± 0.0	> 128	> 128	> 128	> 128	> 128	> 128
$[Cu(II)L2]_2$	32.0 ± 0.0	128 ± 0.0	128 ± 0.0	> 128	> 128	> 128	32.0 ± 0.0
$[Cu(II)L3]_2$	> 128	> 128	> 128	> 128	> 128	> 128	> 128
$[Cu(II)L4]_2$	> 128	> 128	> 128	> 128	> 128	> 128	> 128
$[Cu(II)L5]_2$	> 128	> 128	> 128	> 128	> 128	> 128	> 128
Ampicilline	0.125 ± 0.0	32.0 ± 0.0	32.0 ± 0.0	-	-	-	-
Cefotaxime	-	-	-	32.0 ± 0.0	0.5 ± 0.0	8.0 ± 0.0	-
Nystatin	-	-	-	-	-	-	8.0 ± 0.0

$[Cu(II)L1]_2$ have antibacterial activity against a Gram-positive bacterium*Staphylococcus aureus* with MIC = 128 µg/ml), however it showed the no activity against Gram-negative bacteria and fungi. $[Cu(II)L2]_2$ containing F substituted group at 5-position in salicyl ring exhibited the activity to all Gram-positive bacteria with MICs ≤ 128 µg/ml and the best activity to the bacterium *Staphylococcus aureus* with MIC = 32 µg/ml. $[Cu(II)L2]_2$ also performed a good activity against fungi (*Candida albicans)* with MIC = 32 µg/mL which is quite close to the activity of standard compound, nystatin, with MIC= 8 µg/mL. The other complexes bearing *t*-butyl groups at 3 or/and 5-positions in salicyl ring showed inactive against these bacterial strains and fungi.

The anticancer activity of the obtained Cu(II) complexes was estimated against human cancer cell lines, MCF-7 (breast cancer) and HepG-2 (hepatocellular carcinoma), by using MTT assays and *cis*platin as a standard drug. **Table 7** represents the IC_{50} values for tested compounds which revealed that all synthetic hydrazone Schiff base copper(II) complexes exhibited good activity for both human cancer cell lines, MCF-7 and HepG-2, much better than the standard compound, *cis*platin.

Table 7. Cytotoxic activity of hydrazone Schiff base Cu(II) complexes

	IC_{50} (μM)	
Compound	MCF-7	HepG-2
$[Cu(II)L1]_2$	2.02 ± 0.03	0.75 ± 0.07
$[Cu(II)L2]_2$	1.78 ± 0.02	0.48 ± 0.03
$[Cu(II)L3]_2$	1.65 ± 0.05	1.24 ± 0.07
$[Cu(II)L4]_2$	1.27 ± 0.03	1.26 ± 0.04
$[Cu(II)L5]_2$	1.32 ± 0.06	1.20 ± 0.02
*Cis*platin	32.65 ± 0.78	18.60 ± 0.20

$[Cu(II)L2]_2$ containing electron withdrawing group at 5-postion in salicyl ring, flouro, performed the best anticancer activity for HepG-2 cells with IC_{50} = 0.48 µM, and 38.75-fold lower than *cis*platin with IC_{50} = 18.60 µM. $[Cu(II)L4]_2$ containing electron donating group at 3-postion in salicyl ring, *t*-butyl, showed the best antitumor activity against MCF-7 with IC_{50} = 1.27 µM, about 25.71-fold lower than *cis*platin with IC_{50} = 32.65 µM. It is notable that the activity of the obtained copper(II) complexes to kill MCF-7 human cancer cells followed the order $[Cu(II)L4]_2 \sim [Cu(II)L5]_2 > [Cu(II)L3]_2 > [Cu(II)L2]_2 > [Cu(II)L1]_2$ while the potency of the copper(II) complexes to inhibit HepG-2 cancer cells in the order $[Cu(II)L2]_2 > [Cu(II)L1]_2 > [Cu(II)L3]_2 \sim [Cu(II)L4]_2 \sim [Cu(II)L5]_2$. The results can be explained by the fact that different cancer cell lines have the different interaction to the copper(II) complexes. The bulkier substituted groups in salicyl ring may increase the activity of the synthetic complexes against MCF-7 while electron withdrawing group, fluoro, can raise the potency of copper(II) complex, $[Cu(II)L2]_2$, against HepG-2.

IV. Conclusion

Five copper(II) complexes were synthesized by coordination of $CuCl_2.H_2O$ and aroylhydrazones in the presence of Na_2CO_3. The physico-chemical data indicated that the obtained copper(II) complexes must be binuclear. Synthetic hydrazone Schiff base ligands act as tridentate dianionic ligands in the enol tautomeric form as coordination. The obtained copper(II) complexes in this study have the μ_{eff} values of 1.83 – 2.10 B.M. in accordance with one unpaired electron and distorted square-planar geometry. The electrochemical property of the hydrazone Cu(II) complexes were studied by cyclic voltammetry method. In the received cyclic voltammograms well-defined cathodic peaks at (−) 2.302 – (−) 2.161 V must indicate the reduction of Cu(II)→ Cu(I) probably. Due to the electronic and stereochemical effects of the substituted groups to the ligands coordinated with Cu(II) center, there are some shifts in the reduction potentials of the Cu(II) complexes bearing substituted groups to higher field compared with the reduction potential of $[Cu(II)L1]_2$ possibly.

The hydrazone copper(II) complexes were evaluated for their antimicrobial activity against some Gram-possitive and Gram-negative bacteria, as well as a fungi *Candida albicans*. The complexes were also tested against human cancer cell lines, MCF-7 and HepG-2. All studied hydrazone copper(II) complexes exhibit excellent anticancer activity much better than the standard drug, *cis*platin. $[Cu(II)L2]_2$ containing electron withdrawing group, flouro, at 5-postion in salicyl ring performed the best anticancer activity for HepG-2 cells with 38.75-fold

lower than *cis*platin and $[Cu(II)L4]_2$ containing electron donating group at 3-postion in salicyl ring, *t*-butyl, showed the best antitumor activity against MCF-7 about 25.71-fold lower than *cis*platin.

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Conflicts of interest

There are no conflicts of interest regarding to this article contents to declare.

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