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SYNTHESIS, CHARACTERIZATION AND BIOACTIVE EVALUATION OF COBALT(II) AND COPPER(II) COMPLEXES OF {4-[5-(5-SULFANYLIDENE-2,5-DIHYDRO-1H-1,2,4-TRIAZOL-3-YL) FURAN-2-YL] PHENYL} ACETIC ACID

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ABSTRACT. A new triazole derivative was synthesized by three steps. The first step involve adding 2-carboxyaledhyed furan to the 4-amino phenyl acetic acid after converting the substituted aromatic amine to the diazanium salt. In the first stage, [4-(5-formylfuran-2-yl) phenyl] acetic acid is the title of product. The second step is adding the thiosemicarbazide to the [4-(5-formylfuran-2-yl) phenyl] acetic acid which it gives the (4-{5-[(2-carbamothioylhydrazinylidene) methyl] furan-2-yl} phenyl) acetic acid. A final compound with the title {4-[5-(15-sulfanylidene-2,5-dihydro-1H-1,32,4-triazol-3-yl) furan-22-yl] phenyl} acetic acid was produced as a result of adding sodium acetate and chloro ethyl acetate to the product from the second step in the presence of triethyl amine which is used as a ligand to prepare cobalt(II) and copper(II) complexes. The structures of synthesized compounds were identified through the utilization of diverse measures, these measurements were (UV-Vis spectrum, LC-MS technique, FT-IR spectrophotometer, conductivity measurements, GC-mass spectra and atomic absorption) and melting point measurement. The results confirmed that the complexes have octahedral geometry. The biological activity data for the synthesized compounds revealed that the ligand and its complexes had antibacterial activity.

KEY WORDS: Synthesis, Triazole derivatives, Cobalt(II) complex, Copper(II) complex, Biological evaluation

INTRODUCTION

Heterocyclic compounds have diverse and endless applications in areas of interest in our daily lives. Therefore, they are considered the center of research in our current day. There is a system of heterocyclic compounds called the triazole system, which has received wide attention in the medical field because it possesses wide-ranging biological activities and has multifunctional clinical applications, as there are a number of triazole derivatives that are biologically active and useful in the pharmaceutical field as medicines, of high quality and these activities include antibacterial [1], anti-inflammatory [2], antifungal [3], antipyretic [4], anticancer [5], antitumor [6], and it may also be included as one of the components of the treatment of COVID-19 [7]. The specific absorption rate (SAR) report of the triazole compounds reveals that the replacement at the third, fourth, and fifth positions of the triazole ring can vary significantly, and the extreme change in physicochemical properties and biological appearance occurs due to the groups connected to the nitrogen atom at the fourth place. It also has the advantage of forming hydrogen bonds, and these hydrogen bonds formed by these compounds, whether these are between themselves or between them and other molecules, give them an advantage as compounds that are stable upon metabolic decomposition and have a high solubility, which facilitates their absorption and passage into human body. New triazole drugs found and created by applying bioreplacement technique with expanded biological activities have attracted particular interest in medicinal chemistry. Among the well-known and common medications available that contain the triazole molecule on the market are: antifungal - myclobutanil, tebuconazole, posaconazole, itraconazole, fluconazole, anticancer - litrozole, antimigraine rizatriptan, and antiviral - ribavirin, which are shown in the Figure 1 [8].

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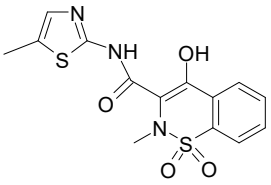
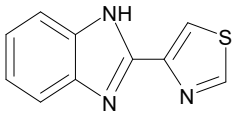


4-hydroxy-2-methyl-*N*-(5-methylthiazol-2-yl)-2*H*-benzo[*e*][1,2]thiazine-3-carboxamide 1,1-dioxide

Meloxicam



4-(1*H*-benzo[*d*]imidazol-2-yl)thiazole

Tiabendazole

Meloxicam and Tiabendazole are Commercial drugs containing a thiazole moiety

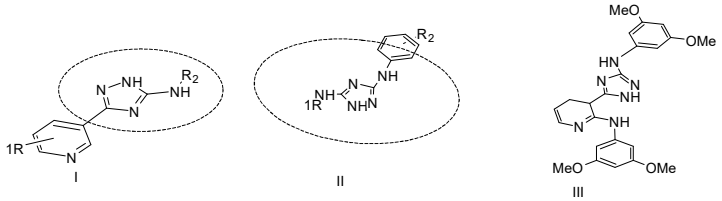


Figure 1. News types of triazole drugs.

Therefore, it is essential to develop powerful, highly selective anticancer drugs that cause little to no harm to healthy cells. Thiazole compounds have a variety of pharmacological activities. Thiazole rings are found in a wide range of well-known drugs, such as the anti-inflammatory non-steroidal drug meloxicam, the anti-ulcer drug famotidine, the antibacterial drug sulfathiazole, the antiviral drug ritonavir, the antiphrastic drug thiabendazole, and several anticancer drugs like dasatinib, dabrafenib, and epothilones (Figure 1) [9].

In 2011, a research effort was carried out that involved the synthesis of triazole derivatives as Schiff bases. Thiadiazole, thiadiazepine, and thiadiazine were among these derivatives that were tested against *P. aeruginosa*, *E. aerogenes*, and gram-negative bacteria as well as gram-positive bacteria *B. megaterium* and *S. aureus*.

Numerous investigations and reports have demonstrated that combining 1,2,4-triazole and 1,3-thiazole in a fused ring structure can produce novel compounds with improved pharmacological characteristics, due to thiazolo-triazole condensed ring system and mutual influence between the two heterocyclic rings [10]. In modern coordination chemistry, compounds containing cyclic imines are essential for producing stable complexes with specific transition metal ions. Triazole compounds containing specific transition metals are powerful antiviral medications and exhibit strong antibacterial, anticancer, and antifungal properties. It was found that the metal complexes of ligands which have S,N-heterocyclic promising for enhanced biological activities compared to the native ligand. Triazole medicines have been the subject of significant research during the past few decades. Among these, derivatives of 3-amino-1,2,4-triazoles have drawn particular interest due to their wide range of bioactivities, which include possible uses against thrombotic diseases, fibrotic [11], and auto-immune diseases, central nervous system disorders [12], obesity, diabetes, Alzheimer's disease [11], microbial infections or cancer [13]. Adding aryl groups to 3-amino-1,2,4-triazole produces anticancer scaffolds that show great promise. For example, a number of antiangiogenic substances include the 3-pyridotriazole core I, as well as the phenyl amino triazoles derivatives, A representative example of aryl-substituted 3-amino-1,2,4-triazole is compound III (Figure 1) that shows potent anti-proliferative and anti-tubulin polymerization activities [14].

It has been found in recent years, that the metal complexes with 1,2,4-triazole ligands has good application. A lot of transition metal complexes of 1,2,4-triazoles substituted can be prepared [15]. It has been discovered that the first row transition metal complexes including Co(II), Ni(II), Cu(II) complexes have fungicidal, bactericidal, and antiviral properties. Copper is an element that a vital to life and biological activity of more than a dozen enzymes (metallo enzymes) depend on copper [16]. Copper complexes are currently of interest due to their prospective applications as enzyme inhibitors, antibacterial, antifungal, antiviral, and anticancer drugs. The synthesis copper(II) complexes of physiologically active ligands has been a standard procedure to increase this biological activity. Numerous Schiff base copper complexes are utilized as biological system models due to their biological interest [14, 15]. The aim of this work is to synthesize a novel triazole derivative and investigate the biological activity of the new derivative as well as its complexes, which are expected to be hazardous agents. This research is regarded as a novel contribution to the earlier publications.

EXPERIMENTAL

All the chemicals and solvents used for this work were obtained from Merck (Germany) and Aldrich Chemical Company. The materials that used in this research were 4-amino phenyl acetic acid and 2-carboxy aldehyde-furan. Melting points was measured by fusion degree measuring devices Metlertolido (2013) Swiss and SMP-30. Shimadzu 8400S spectrophotometer was used to record the infrared spectra in the range (4000–200) cm^{-1} using (CsI) disc, also BRUKER ALPHA II between (4000-400) cm^{-1}. UV-Vis ultraviolet spectrophotometer model Shimadzu is used to measure the UV-Visible spectra at R.T. using 10 mm quartz cell, JASCO V-650, Japan and examined between 200-900 nm, at 10^{-3} M in DMSO.

Molar conductivity ($S.cm^2.mol^{-1}$) of the complexes were recorded at 25 °C for solution of the samples (1×10^{-3} M) in (DMSO) using a (BP3001) Professional Benchtop pH Meter. ^{1}H-NMR and ^{13}C spectra of ligand and complexes were recorded in DMSO-d_6 as a solvent at Bucker Bio Spin GmbH (400.13 MHz) with a tetramethylsilane (TMS) as an internal standard. Mass spectra was recorded by electron impact mass spectrometry (EIMS) using A direct Injection Probe Shimadzu GCMS – QP 2010 Spectrometer. Atomic absorption flame for the complexes were carried out by using Analytical Jena AA 350 NOV Germany 2012. LC-mass measurement for the complexes carried out by An Ic/ms_msab sciex model q_trap3200 made in the U.S.A.

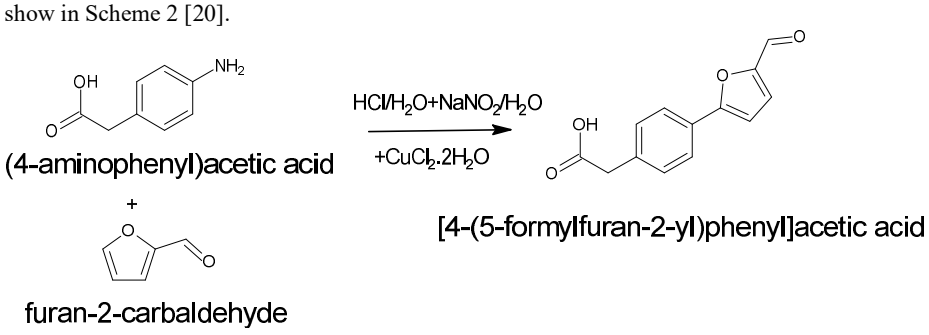
Pathways synthesis

Synthesis of the {4-[5-(5-sulfanylidene-2,5-dihydro-1H-1,2,4-triazol-3-yl) furan-2-yl] phenyl} acetic acid [L]

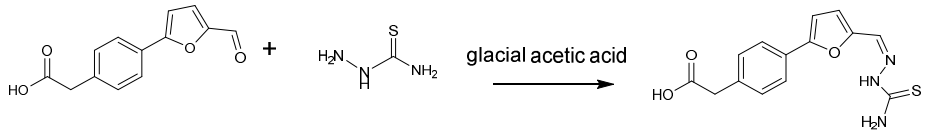
Synthesis [4-(5-formylfuran-2-yl) phenyl] acetic acid. (4-Aminophenyl)acetic acid (10.27 g, 0.068 mol) was added to a mixture of (16.85 mL) HCl conc. and (11.25 mL) distilled water (H_2O) then the mixture was diazotized with (4.75 g, 0.0688 mol) sodium nitrite at 0-5 ºC with stirring for 10 min. After that the mixture was filtered and (7.7 g, 0.08 mol) solution of furan-2-carboxaldehyde was added along with a solution of $CuCl_2.2H_2O$ (2.5 g, 0.0146 mol) at temperature 10-15 ºC then warmed slowly up to 40 ºC and stirred the mixture at this temperature for 4 h. The crude of product was filtered with suction, then sodium hydrogen carbonate (5%) is used for washing the precipitate. The products had been dried at room temperature and recrystallized from ethanol. The color of new compound was brown [19] as shown in Scheme 1.

Synthesis (4-{5-[(Z)-(2-carbamothioylhydrazinylidene) methyl] furan-2-yl} phenyl) acetic acid. 4-Amino phenyl acetic acid (10 g, 0.033 mol) are dissolved in 25 mL of ethanol in a round flask, then the solution was added 3 drops of glacial acetic acid and refluxed for half hour until all the

4-amino-phenyl acetic acid dissolved completely. Then thiosemicarbazide (3 g, 0.033 mol) was added to the solution of 4-amino phenyl acetic while, the refluxes had been continued for 6 h. After that mixture reaction was cooled, filtered and dried, and then recrystallized by ethanol as a show in Scheme 2 [20].

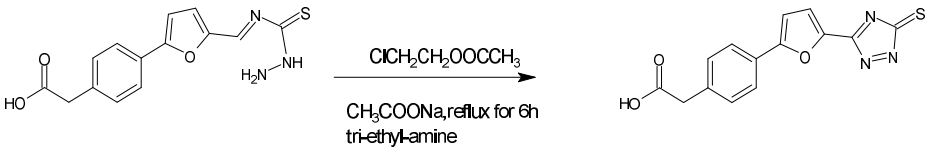


Scheme 1. Synthesis of [4-(5-formylfuran-2-yl) phenyl] acetic acid.



Scheme 2. Synthesis 4-{5-[(Z)-(2-carbamothioylhydrazinylidene) methyl] furan-2-yl} phenyl) acetic acid.

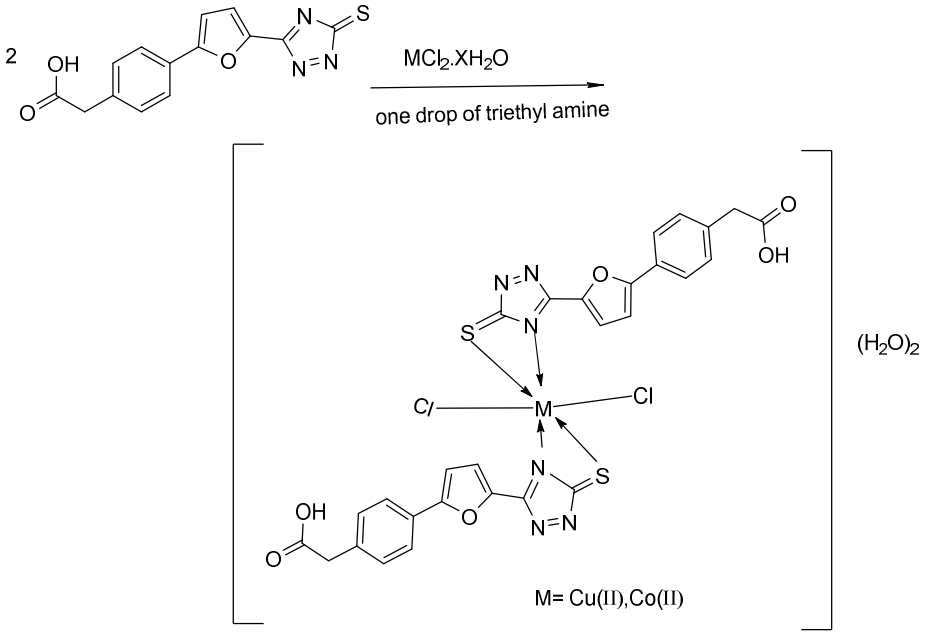
Synthesis of the {4-[5-(5-sulfanylidene-2,5-dihydro-1H-1,2,4-triazol-3-yl)furan-2-yl]phenyl} acetic acid [L]. A compound of 4-{5-[(Z)-(2-carbamothioylhydrazinylidene) methyl] furan-2-yl}phenyl)acetic acid (9 g, 0.029 mol) placed in a round flask then (3.6 g, 0.029 mol) of chloro ethyl acetate with (2.4 g, 0.029 mol) of sodium acetate were added to the mixture of the reaction in presence of triethyl amine and then refluxed for 6 h. After that the reaction mixture was cooled, filtered and dried the precipitate. The product was obtained was purified by recrystallized from ethanol. The Scheme 3 shows the synthesis of the {4-[5-(5-sulfanylidene-2,5-dihydro-1H-1,2,4-triazol-3-yl) furan-2-yl] phenyl} acetic acid [L].



Scheme 3. Synthesis of {4-[5-(5-sulfanylidene-2,5-dihydro-1H-1,2,4-triazol-3-yl) furan-2-yl] phenyl} acetic acid [L].

Synthesis of the cobalt(II) and copper(II) complexes. The ligand (L) (3 g, 0.01 mol) was placed in a round flask after dissolved in 50 mL of ethanol then (1.18 g, 0.05 mol) of cobalt salt ($CoCl_2.6H_2O$) or (0.85 g, 0.005 mol) of copper salt(II) ($CuCl_2.2H_2O$) was added to the solution of the ligand and refluxed for 30 min. During the reaction, a drop of triethyl amine was added and then the mixture reaction was continued refluxed for an additional hour. The mixture was left to

be cool. The formed complex was filtered and dried. The Scheme 4 shows that the synthesis of the complexes.



Scheme 4. Synthesis of the complexes.

RESULTS AND DISSECTION

FT-IR spectra of ligand (L) and its complexes

In FT-IR spectrum of free ligand exhibited a peak at (3426.95 cm^{-1}) which indicated to (OH) group, while the peaks of (CH) group was observed at (3000.7, 2985 and 2925 cm^{-1}) either the peak of the carbonyl group which belong to the acetic acid was appeared at 1701 cm^{-1}. The peaks at (1640, 1548 cm^{-1}) were peaks of the (C=O) and (C=N) groups respectively either the others were observed at (1463.81, 1442 cm^{-1}) assigned to the peaks of the (C=C) and (N-N) groups. The peak of the (C-S) group appeared at (1090.9 cm^{-1}) as shown in the Figure 2 [10, 11]. The data of the FT-IR spectra are shown in Table 1.

Table 1. FT-IR data of ligand (L) and its complex.

The compounds	V(NH)	V(CH)	V(C=O)	V(C=N)	V(N-N)	V(C-S)	C=C	M-N	M-Cl
$C_{14}H_9N_3O_3S$	3341 3262	2985 2925 2854	1701	1619 1545	1398	1090	1421	-	-
$[Co(C_{14}H_9N_3O_3S)_2Cl_2].(H_2O)_2$	3282.9	3051.10 2998.01 2983.27	1740	1645.28 1598.2	1317	1022.27	1400.2	480.98	337.54
$[Cu(C_{14}H_9N_3O_3S)_2Cl_2].(H_2O)_2$	3386.78	3036.78 2981.8	1730.79	1631.77 1589.3	1379.10	1026.13	1419.6	547.74	310.54

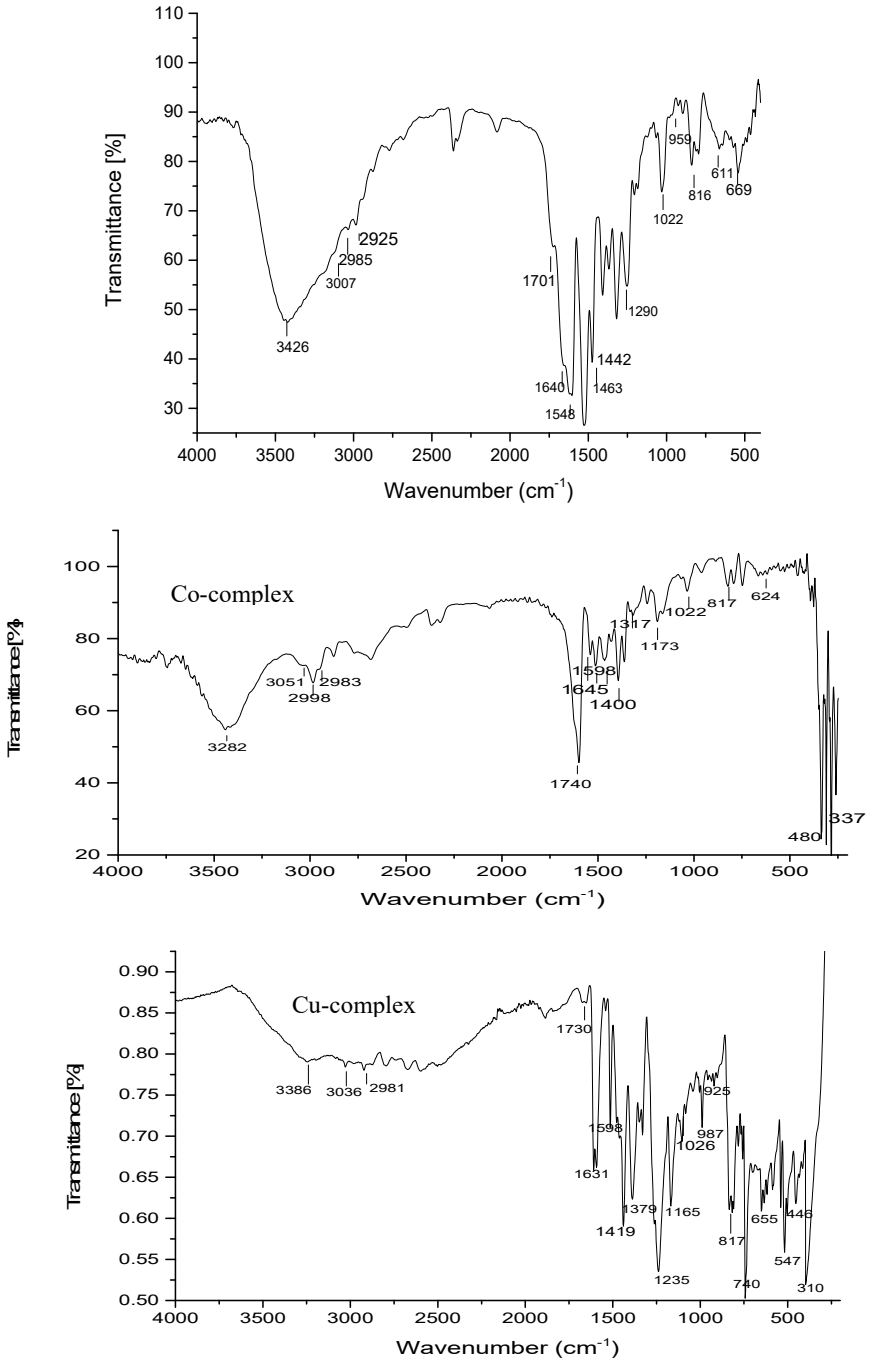


Figure 2. The spectra of FT-IR of the ligand (L) and complexes of cobalt(II) and copper(II).

According to the values of the appearance peaks in Figure 2 confirmed the formation of complexes. The coordination between the metals ions and nitrogen atoms of the triazole ring can be confirmed by the displacement the stretching vibration of C=N groups in the triazole spectrum which observed at (1598 and 1583 cm^{-1}) in addition, the Co(II) and Cu(II) complexes spectrum respectively exhibit peaks at (480.9 and 574.74 cm^{-1}) which indicated to M-N. While the coordination chlorine atoms with metal ions shows peaks at (337 and 310.54 cm^{-1}) which attributed to the M-Cl [12, 13]. Table 1 illustrates the results of FT-IR spectra for free ligand and their complexes.

The ^{1}H NMR of ligand (L)

In Figure 3 shows that the most important bands that appeared in ^{1}H NMR spectrum as follow: 1.77-1.94 ppm are attributed to the (CH) groups, (11.94 ppm) is assigned to (OH) group, also the peaks that observed at 7.34, 7.32, 7.07 and 4.39 ppm are indicted to furan ring, while the peaks at 8.09, 7.96, 7.76 and 7.74 ppm attributed to the benzene ring group [11].

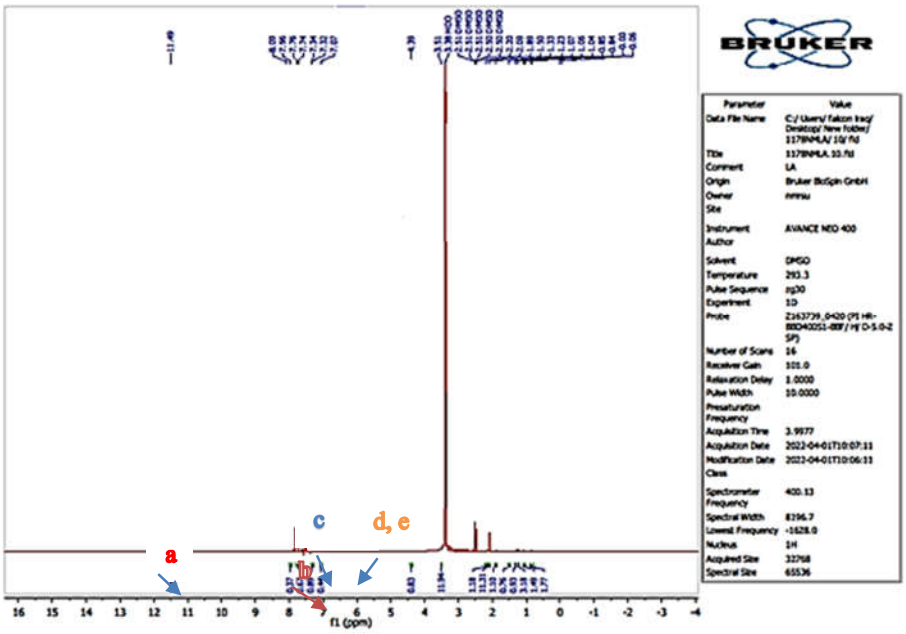


Figure 3. The ^{1}H NMR spectra of the ligand (L).

Mass spectra of ligand (L) and its complexes

Figure 4 shows the positive ions mass spectrum for ligand at m/z = 299 g/mol which indicated a molecular weight peak that agrees well with the theoretical calculation of the M.W. formula of the ligand which equal to the 299 g/mol, and confirmed the molecular formula of ligand L ($C_{14}H_9N_3O_3S$).

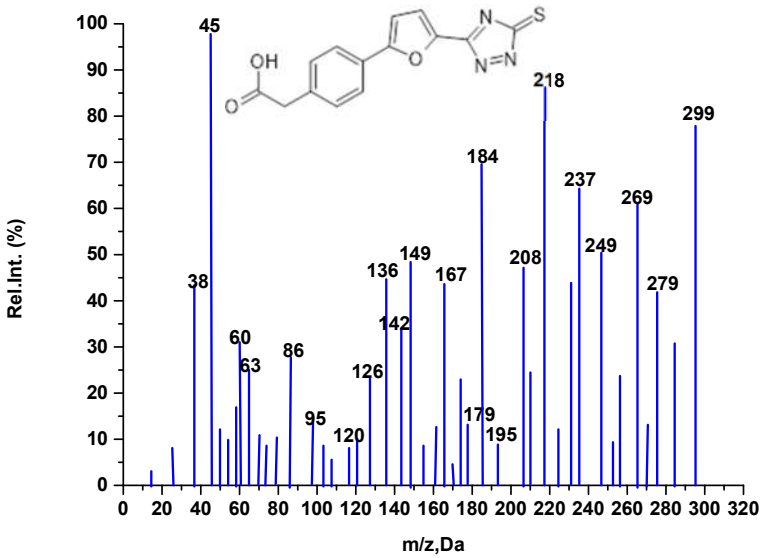
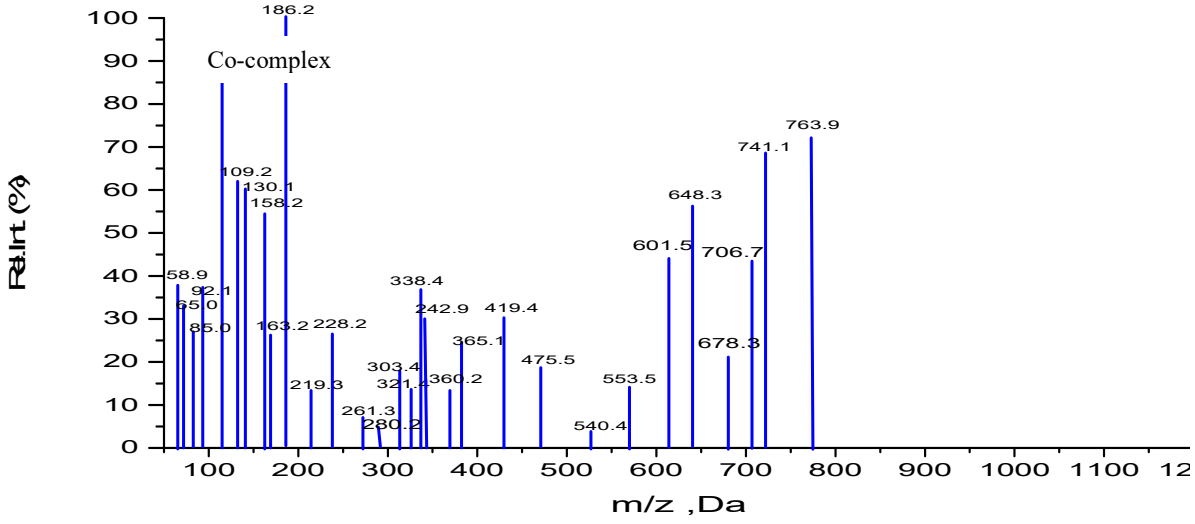


Figure 4. The electronic mass spectra of the ligand (L).

The LC-MS of complexes spectra showed main peaks at (m/z = 763.9, and 768.7) g m/mol Figure 5, that assigned to the molecular complexes of $[Co(C_{14}H_9N_3O_3S)_2Cl_2](H_2O)_2$, and $[Cu(C_{14}H_9N_3O_3)_2Cl_2](H_2O)_2$, respectively and which confirmed the suggested structure, and agree with the theoretical calculation (763.933 g/mol) for Co-complex and Cu-complexes is 768.5 g/mol approximately.



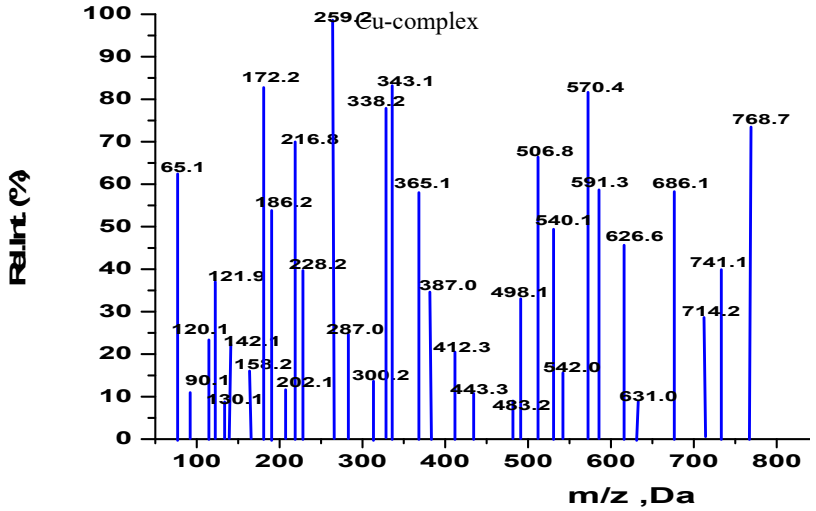


Figure 5. The LC-MS spectra of cobalt(II) and copper(II) complex.

Electronic UV-Vis spectra of ligand and its complexes

The electronic of the UV-Vis spectrum of the ligand and its complexes were measured in DMSO as illustrated in Figures 6. The UV-Vis spectrum of ligand (Figure 6) shows that two maximum absorption bands. The first absorption band appeared at (283.4 nm, 35285.815 cm^{-1}) due to ($\pi \rightarrow \pi^*$). The second high intensity peak appeared in the UV region at (398.4 nm, 25100.402 cm^{-1}) which assigned to ($n \rightarrow \pi^*$) transitions [14]. Whereas the UV-Vis spectrum for the prepared Co-complex and Cu-complex in Figures 5 show absorption peak at 400-900 nm and noticeable and significant changes in the peaks positions compared to that of free ligand.

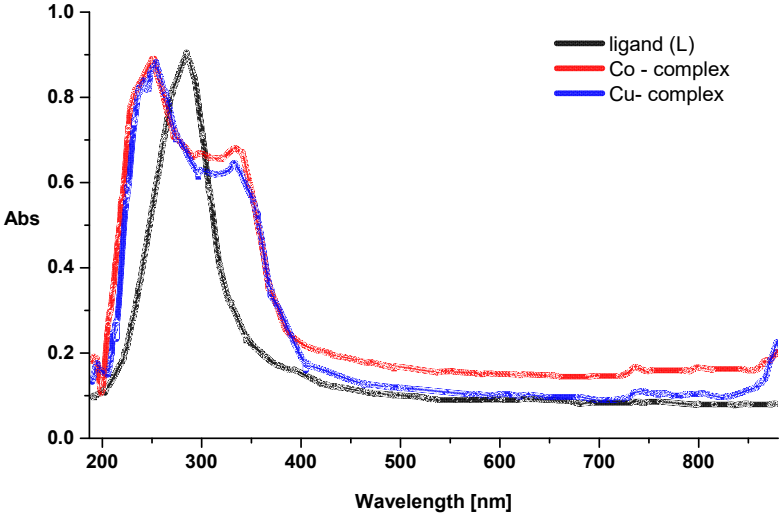


Figure 6. UV-Vis spectra of ligand and the complexes of cobalt(II) and copper(II).

The evidence that confirmed the coordination between metals ions and ligand is appeared bands at (196.6 nm = 50864.7 cm^{-1}, 257 nm = 38910.506 cm^{-1}) attributed to the ($\pi \rightarrow \pi^*$) and peak at (303 nm = 33003.3 cm^{-1}) assigned to the ($n \rightarrow \pi^*$), respectively. While the charge transfer peak is observed at (336.8 nm = 29691.211 cm^{-1}) either the peaks of the $^4T_1g \rightarrow {}^4T_1g$ (p), ($^4T_1g \rightarrow {}^4A_2g$ (F), $^4T_1g \rightarrow {}^4T_2g$ (F) were appeared at (505.2 nm = 19794.14 cm^{-1}, 740 nm = 13513.514 cm^{-1}, 810 nm = 12345.679 cm^{-1}), respectively. Whereas Cu-complex shows another bands which illustrated in Table 2 [15, 16].

Table 2. UV-Vis of the ligand and its complex.

The compounds	λ_{max} (nm)	V (cm^{-1})	Assignment	μeff. B.M.	Suggested geometry complexes	Molar conductance $\Lambda m^1.cm^2.mole^{-1}$
$C_{14}H_9N_3O_3S$	283.4	35285.815	$\pi \rightarrow \pi^*$	-	-	-
	398.4	25100.402	$n \rightarrow \pi^*$			
$[Co(C_{14}H_9N_3O_3S)_2Cl_2](H_2O)_2$	196.6	50864.7	$\pi \rightarrow \pi^*$	3.02	Oh	5.59
	257	38910.506	$\pi \rightarrow \pi^*$			
	303	33003.3	$n \rightarrow \pi^*$			
	336.8	29691.211	C.T			
	505.2	19794.141	$^4T_1g \rightarrow {}^4T_1g(p)$			
	740	13513.514	$^4T_1g \rightarrow {}^4A_1g$			
	810	12345.679	$^4T_1g \rightarrow {}^4T_1g(F)$			
$[Cu(C_{14}H_9N_3O_3S)_2Cl_2](H_2O)_2$	192.2	1922000000	$\pi \rightarrow \pi^*$	1.017	Oh	26.35
	241.2	41459.37	$\pi \rightarrow \pi^*$			
	253	39525.692	$\pi \rightarrow \pi^*$			
	303	33003.3	$n \rightarrow \pi^*$			
	363.2	2753.304	C.T			
	741.4	13487.996	$^2Eg \rightarrow {}^2T_2g$			

The magnetic moment (μeff = 3.021 and 1.017 B.M.) for cobalt(II) and copper(II) complexes, respectively, referring to paramagnetic properties and confirmed an octahedral geometry and the complexes have high spin. The molar conductance of all synthesized complexes were measured in dimethyl sulfoxide solvent at r.t. and the data were obtained indicates that the complexes synthesized were non-ionic. Magnetic susceptibility, and molar conductance values of all synthesized complexes were listed in Table 2.

Antibacterial activity for ligand and its complexes

Five types of bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella spp* and *Candida albicans*) had been selected to be tested against ligand and its metal complexes in concentration (0.0 1 M) at the time of exposure 24 h. The function of DMSO in the biological screening was clarified by separate studies adopted with the solutions of DMSO alone, which exhibited no activity toward any microbial strain. The results of biological activity for the ligand and Cu(II) complex have been shown to be effective against four types of *Bacteria* (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Klebsiella spp* and *Candida albicans*). While Co(II) complex exhibited activity against three kinds of bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis* and *Candida albicans*). According to the obtained results that shown in Figure 7 and Table 3, it can summarized as following: (i) Ligand L has low activity against all kinds of bacteria compared with corresponding complexes. (ii) Ligand has high activity against *Klebsiella spp and Candida albicans while* the activity of ligand against *Staphylococcus aureus, Staphylococcus epidermidis* exhibited low activity. (iii) The activity of complexes exhibited high activity compare with activity of ligand.

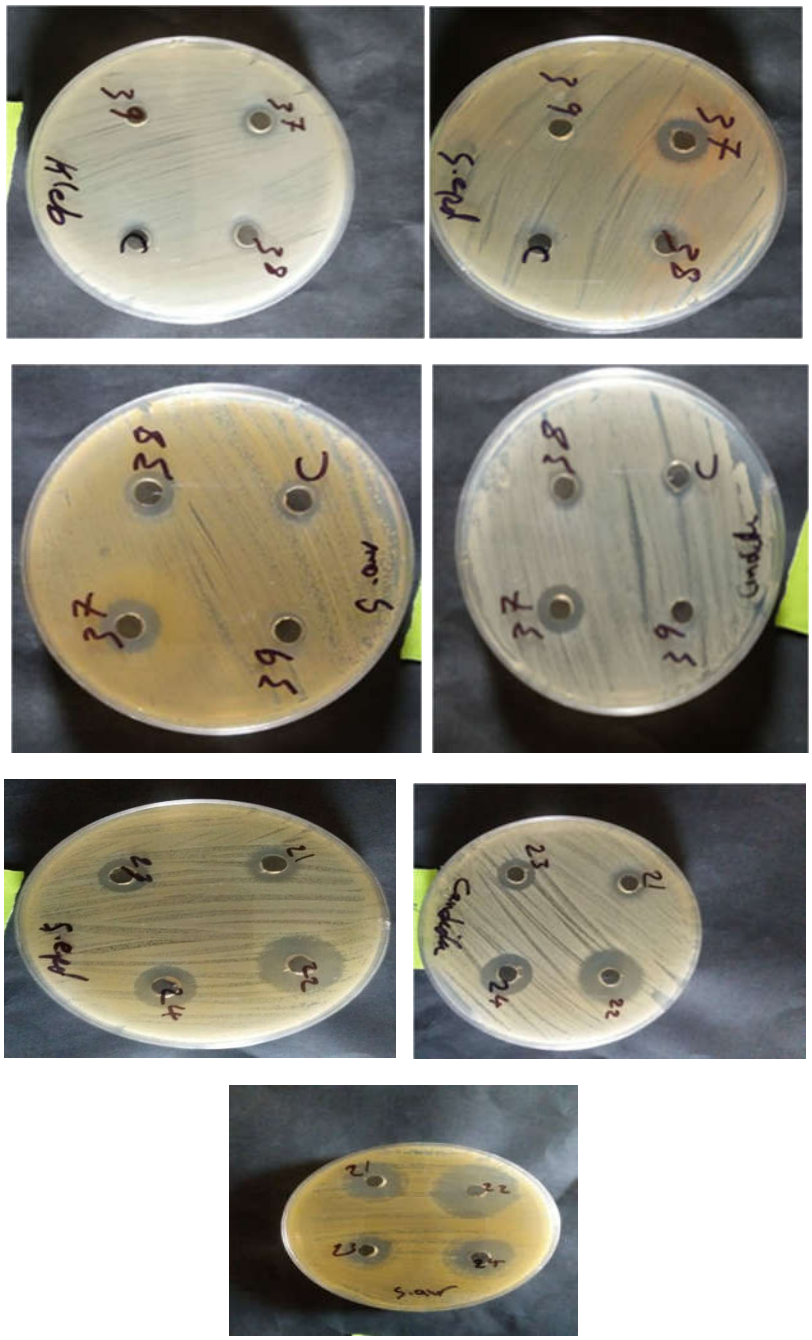


Figure 7. Antibacterial activity for ligand L and its complexes.

(iv) Cu-complex exhibited high activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Klebsiella spp* and *Candida albicans* compare with Co-complex due to these complexes of copper has a higher redox potential than cobalt, copper readily forms stable complexes with various ligands, including proteins and enzymes and copper is readily absorbed by cells, whereas cobalt uptake is often limited [21, 22]. (v) Activity of ligand and its complexes did not show any activity against *Escherichia coli*.

Table 3. Biological activity of ligand and its complexes with 0.01 M.

No. of sample	The compounds	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*Escherichia coli*	*Klebsiella. spp*	*Candida albicans*
37	$C_{14}H_9N_3O_3S$	12	12	-	13	13
22	Co-complex	17	9	-		10
38	Cu-complex	18	12	-	13	13

CONCLUSION

Through the results of ^{1}H NMR, LC-MS, UV-Vis, magnetic moment, molar conductivity and evaluation of biological activity for the Ligand and its complexes, had been confirmed the structure of ligand {4-[5-(5-sulfanylidene-2,5-dihydro-1H-1,2,4-triazol-3-yl)furan-2-yl]phenyl} acetic acid acetic acid and suggested geometry for complexes are octahedral, non-electrolyte, and all the creative compounds have biological activity against most selected bacteria. The synthesized triazole derivatives could be candidate as anti-cancer activity drugs.

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