Preparation and Characterization of Nickel (II), Copper (II), and Zinc (II)Ion Complexes Using a new Schiff Base Ligand and Study of their Biological Activity.

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Abstract

The synthesis of the novel ligands was disclosed in this study, (6-(((5-bromothiophen-2-yl) methylene) amino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo {3,2,0} heptane-2-carboxylic acid). These Schiff base type ligands were synthesized from react between the 5-Bromo-2-thiophene carboxaldehyde and 6-aminopenicilic acid by Schiff base reaction, respectively. The relevant Ni (II), Cu (II), and Zn (II) complexes were produced using a molar ratio of metal chloride to ligand [1:2] M: L. Spectroscopic data was used to establish the chemical identity of ligands and their corresponding complexes (FT-IR, UV-Vis,1HNMR,13CNMR) and elemental analysis studies (magnetic susceptibility, atomic absorption). The Schiff base ligand, (L) demonstrated coordination with the central metal ion via azomethine nitrogen and B-lactam ring oxygen in mixed-ligand complexes. Sp3d2hybridization results in an octahedral form. When the biological activity the ligand and their complexes tested against Pseudomonas and Sauers microorganisms, the synthesized ligands and complexes showed substantial antibacterial efficacy.

Keywords: Schiff bases, B-lactam, 6-aminopenicilic acid, Thiophenes, Biological activity.

1. Introduction

Schiff bases (imines), which have a high chemical reactivity, have been known since their discovery by German chemist Hugo Schiff [1]. The most diverse starting molecules in coordination chemistry, Schiff bases, have a wide range of biological applications, including antifungal properties [2], antibacterial [3], antiviral, anticancer, and antioxidant activities [4,5]. Carbapenems and monobactams, the other two groups of B-lactam antibiotics, were discovered more recently in an endeavor to find new members of this large set of compounds [6]. One of the first and most extensively used B-lactam antibiotics was penicillin [7]. Because of their importance in the treatment of bacterial illnesses, penicillin-based Schiff bases have seen a lot of usage in medicinal chemistry throughout the years [8]. Alexander Fleming is widely credited with the accidental discovery of penicillin G, the first member of this large group of compounds, in 1929 [9]. 6-aminopenicillin acid is the first beta-lactam antibiotic. The 6-aminopenicillanic acid (semisynthetic amino penicillin) is the most extensively used antibacterial agent. On a variety of bacterial strains, this acid has been demonstrated to have significant biological effects. This acid has significant biological implications [10]. In both humans and animals, it is effective against a wide range of illnesses caused by a wide range of Gram-positive and Gram-negative bacteria [22]. Figure (1) shows the 6-amino penicilic acid [11]. Continuing with the studies on novel antibiotic-based Schiff base metal complexes and to establish whether complexation affects the bactericidal properties, this paper was focused on the synthesis and characterization of transition metal-Schiff base complexes [23]. The 6-APA structure is shown in Figure (1).

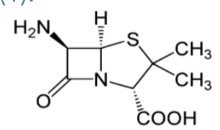


Figure (1). Structure of 6-amio panicillic acid (6-APA).

Recently, the field of Schiff bases has grown tremendously, now including their fascinating characteristics in coordination chemistry, with a focus on bioinorganic chemistry [12] and medicinal chemistry [13]. Heterocyclic compounds with an amide bond and a Schiff base have been shown to have a wide range of biological effects, including anti-inflammatory, anti-diabetic, and antibacterial properties. [14,15]. Many heterocycles such as arylated thiophenes have been synthesized using this as an Antioxidant, Antibacterial [16]. The 5-Bromo-2-thiophene carboxaldehyde is shown in Figure (2).

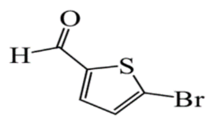


Fig (2). The 5-bromo-2-thiophene carboxaldehyde.

The coordination chemistry of Nickel (II) and copper (II) and zinc (II) attracts much attention because of its biological relevance and its interesting coordination chemistry such as geometry, and flexible redox properties [17]. The synthetic, spectroscopic, and antibacterial studies of Schiff's base and its nickel (II), copper (II), and zinc (II) complexes are discussed in this study. Metal complexes have been identified. The Schiff bases and their metal complexes have been tested and reported in vitro against Gram-positive and Gram-negative bacteria and fungi [12].

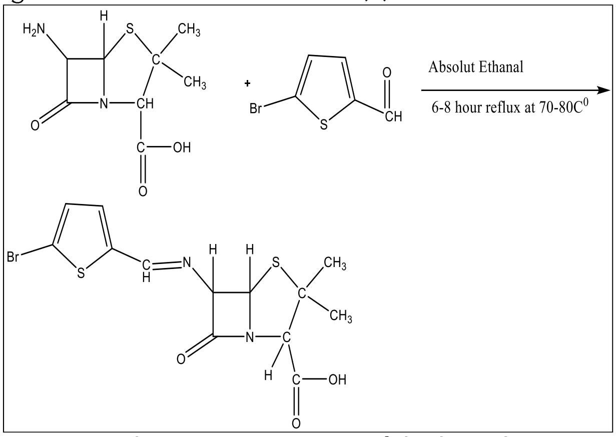
2. Methodology

Materials

All the chemicals were analytical grad and used as received. metal salts ($NiCl_2.6H_2O$, $CuCl_2.2H_2O$, $ZnCl_2$) 5-bromo-2-thiophene carboxaldehyde (98), pyridine (98%) and 6-aminopenicilic acid (98%), absolute ethanol (99.9%),distaled water,DMSO(98%).

Synthesis of ligand (L)

Synthesis of Unsymmetrical bidentate Schiff Base Ligands. Unsymmetrical bidentate Schiff base ligands were prepared by the condensation of 6-amino penicilic acid (0.01 mol,2.162g) with 5-Bromo-2-thiophene carboxaldehyde (0.01mol,1.188 ml), was mixed in absolute ethanol solution at 50ml. dissolved in absolute ethanol was added (1-3) drop from pyridine was reflex for 6-8 h with heat. dried and returned recrystallized from absolute ethanol the reaction follows illustrates this. the preparation of the ligand is shown in the scheme (1):

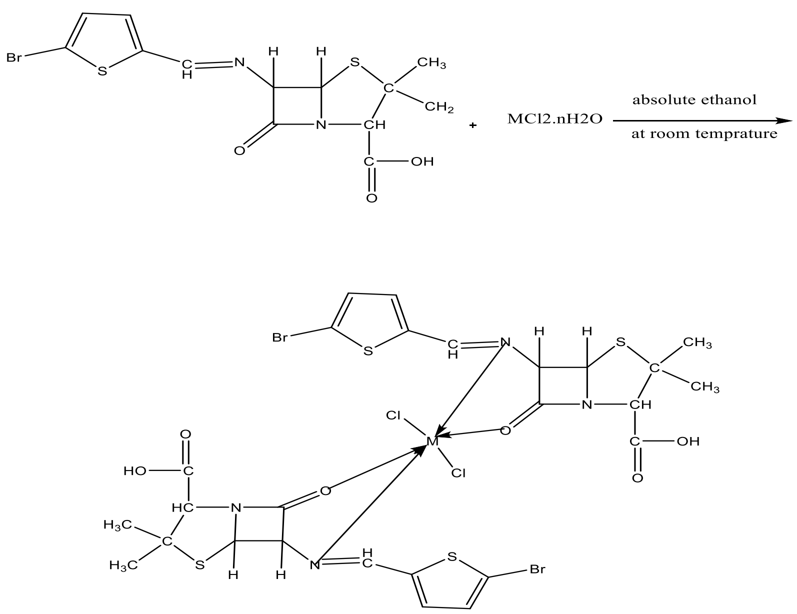


Scheme (1): Prepration of the ligand.

Synthesis of metal-ligand complexes

For the preparation of complexes, a ligand (0.688 g, 0.002 moles) solution was mixed with 0.001 moles of (0.170 g, 0.237 g, and 0.137 g) of $CuCl_2.\ 2H_2\ O$, $NiCl_2\ .6H_2\ O$, and $ZnCl_2$ respectively in 20 ml of absolute ethanol at a ratio [1:2]. The mixture was stile24-48 h at room temperature, then dried to room temperature, the colored complexes got precipitated slowly, which was filtered, and washed repeatedly with distilled water and ethanol in the preparation of the complex shown in scheme (2). Table (1) shows the physical properties of the free ligand and its complexes (in the table (1).

Table (1): physical properties of the free ligand and its complexes				
compounds	M.p (C0)	M.wt (g/mol)	Color	Yield%
L	93C0	389.177	brawn-red bright	93%
Ni(L)2 Cl2	110 C0	909.044	brawn bright	80%
Cu(L)2 Cl2	100 C0	913.904	brawn –black	42%
Zn(L)2Cl2	129 C0	915.734	brawn-orangy	44%



Scheme (2). Preparation the complexes (M=Ni (II), Cu (II), Zn (II)), n=2,6

3. Resulted and Discussion

FT-IR spectra

The IR spectrum of 6-amino penicillic acid exhibited a band at 1299.6 cm-1 referring to the υ(O-H) group [17], 18] whereas the band at 2991.6 cm−1[17]. was ascribed to the stretching vibrations υ(-NH2). In addition, the presence of a band at 1624.64 cm−1 was assigned to υ(C=O) of the B-lactam group [17].

The band at 1772.64 cm-1 was due to ʋ(C=O) stretching vibration of the –COOH group [17, 18]. The IR spectrum for the ligand, (L) displayed a broad band at around 3270 cm−1 ascribed to the stretching vibration of ʋ(O-H). However, the display of a new band at 1618.1 cm−1 assigned to ʋ(C=N-) for the Schiff base ligand, (L), and the absence of the band due to ʋ(-NH2) suggested the occurrence of the condensation [16]. The band at 1734.06 cm−1 was due to the ʋ(C=O) stretching vibration of the –COOH group whereas the band at 1338.64 cm−1 was assigned to the stretching vibration of ʋ(C–N) [17, 19]. The band at 1670 cm−1 was attributed to the stretching vibration ʋ(C=O) of a B-lactam group [19]. However, the band due to the azomethine group was shifted to a lower frequency in all the complexes (Supporting Information Table (2), Show (in the table (2)) and appeared in the range of 1635-1560 cm 1, indicating its participation in complexation [20]. The stretching vibrations at 1668.48 -1664.62 cm−1 due to ʋ(C=O) of the β-lactam group were shifted to a lower frequency in the metal complexes showing its coordination through the oxygen atom of the B-lactam group. Furthermore, the weak bands observed at 500-532 cm−1 and 474-470 cm−1 were assigned to ʋ(M–N) and ʋ(M–O) [19]. shownin figure (3) of ligand and figures (4,5,6) for its complexes:

Compound	OH	S-	HO-C=O	C=O B- Lactam	HC=N	C-N	C-O	C-S	M-N	M-O
L	3270	2650	1734.06	1670	1618.33	1369.9	1222.91	1130.32		
[Ni(L)2Cl2]	3269.45	2600.13	1734.06	1668.48	1635.69	1375.23	1220.91	1130.32	590	520
[Cu(L)2Cl2]	3147.34	2650	1734.04	1668.48	1590	1373.36	1220.98	1116.82	590	550
[Zn(L)2Cl2]	3228.95	2600	1732.31	1664.62	1560	1390.72	1222.91	1130.32	550	518

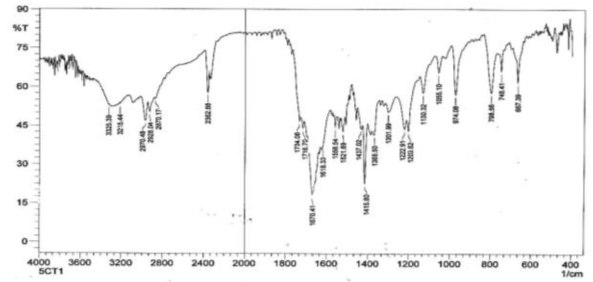


Fig (3).IR spectra of(6-(((5-bromothiophen-2-yl) methylene) amino)-3,3- dimethyl-7-oxo-4-thia-1-azabicyclo {3,2,0} heptane-2-carboxylic acid)) ligand

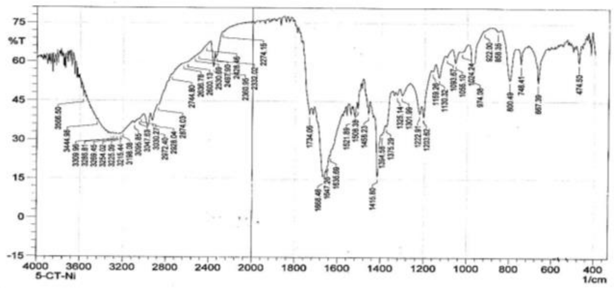


Fig (4). IR spectra of di(6-(((5-bromothiophen-2-yl) methylene) amino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo {3,2,0} heptane-2-carboxylic acid)), dichloro nickel (II)complex

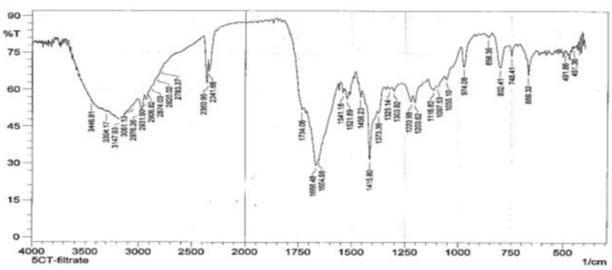


Fig (6). IR spectra of di(6-(((5-bromothiophen-2-yl) methylene) amino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo {3,2,0} heptane-2-carboxylic acid)), dichloro copper (II)complex.

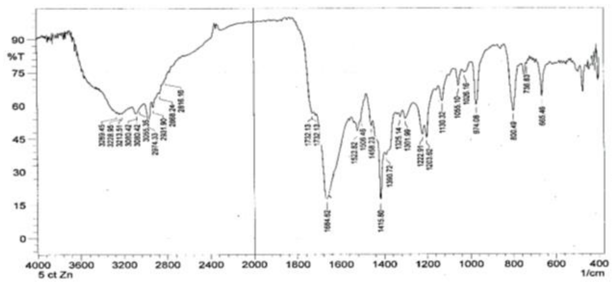


Fig (5). IR spectra of di(6-(((5-bromothiophen-2-yl) methylene) amino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo {3,2,0} heptane-2-carboxylic acid)), dichloro zinc (II)complex

HNMR-spectra

The HNMR spectrum of the ligand (L) in DMSO-d6 using. show the protons signal at δ 1.17,1.22,1.39 ppm(s) and δ 1.42,1.46,1.526(s) ppm for –CH3a and –CH3b, respectively [18,20] (Figure 2) The signals at δ 9.26 (s) δ9.827 ppm was observed due to azomethine protons in the spectra [16] [20]and COOH, respectively [20]. The(L) speaks at δ7.043-7.17 deplete ascribed to *B-lactam* ring proton [22] the peaks at δ 7.49-7.50 and δ 7.88-7.89 ppm deplete that ascribed to protons for thiophene ring [16, 18] [22]. shown in figure (7):

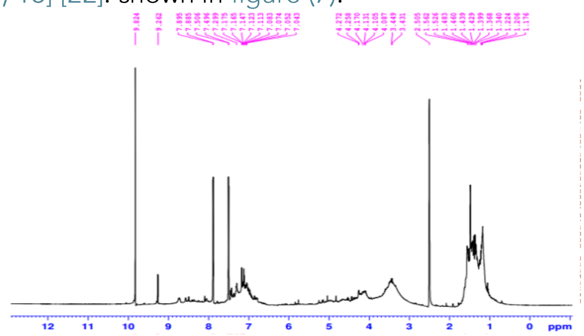


Fig (7). Proton NMR spectra for (L).

CNMR-spectra

The CNMR(400MHz,DMSO-d⁶) for ligand(L):(δ,ppm) spectrum asignal at 152.19 ppm to (C=N) and signal 27.05-27.5 for (CH3) and signal 28.94 and 39.32-

39.53 ppm and 39.74-40.1 and 40.53 ppm for (C-S),CH-COOH,CR4,C-Br respectively and the signal 124.09 ppm for (C=C)[19, 20]. The signals 128.99,133.09,139.18 ppm for B-lactam ring [22]. The signal 145ppm for (N-C=O)[19, 20].the signal 152.19ppm for (RC=N) [7,17] and the 184.02 ppm (HO-C=O)[19, 20] .shown in Figure(8).

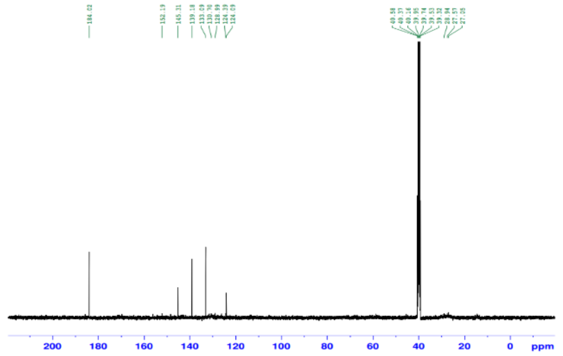


Fig (8). Carbon 13 NMR spectra for (L).

Electronic spectra

The electronic spectrum of the ligand and complexes have been measured in ethanol absolute solution between 200-1100 nm at room temperature. The UV-Visible spectra of ligand include absorption peaks at wavelengths 297 nm, and 220 nm which are assigned to n-π* transition for nonbonding pair of electrons of nitrogen azomethine group and π- π * transition for the unsaturated bonding [21,22], respectively. The UV-Vis spectrum of complexes exhibits two peaks, due to the (C.T) The UV-Vis data of ligand and complexes are reported in (Table 3). and Uv-Vis's spectrum of the Schiff base ligand (Figure (9) and the complex in figure (10,11,12):

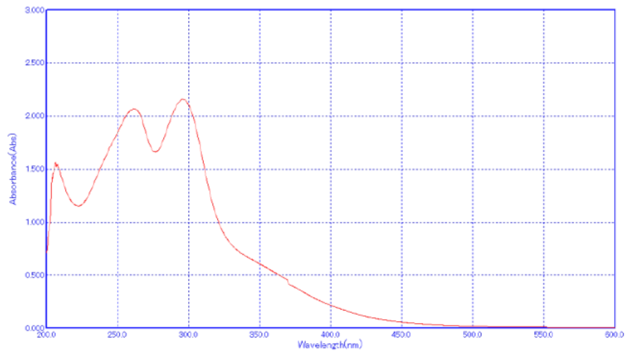


Fig (9). UV-Vi's spectrum of [L].

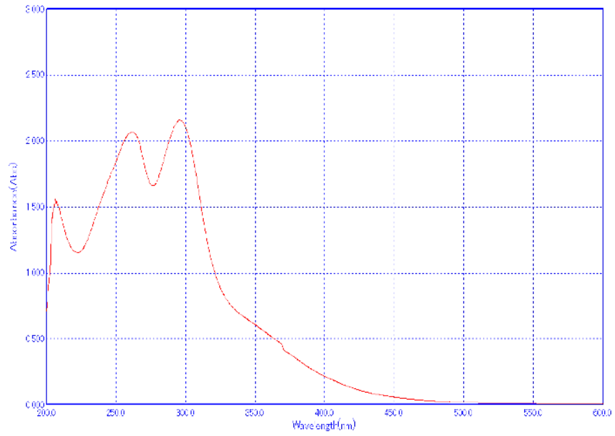


Fig (10). UV-Vi's spectrum of [Zn(L)2 Cl2].

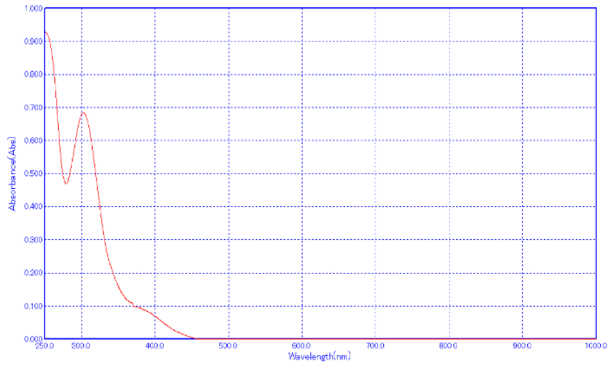


Fig (11). UV-Vi's spectrum of [Ni(L)$_2$Cl$_2$].

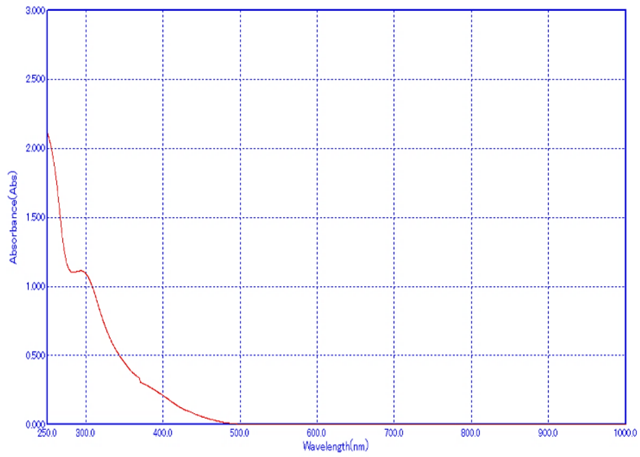


Fig (12). UV-Vi's spectrum of [Cu(L)2Cl2].

All the studied compounds are soluble in DMSO and absolute ethanol and insoluble in water. The molar conductance values confirmed the non-electrolytic nature of the compounds. The examination for chloride ion with silver nitrate (AgNO3) solution indicated that chloride ion is present inside of the coordination sphere.

Table (3). The UV-Vis data of ligand and complexes				
Compounds	ʎmax	υ cm 1	Assignment	shifted
L3	297nm 220nm	3367cm-1 4545.4cm-1	n-π* π- π*	-
[Ni(L)2Cl2]	303.4nm	3295.9cm-1	L.F	Red shift
[Cu(L)2Cl2]	300nm	3333.3 cm 1	2Eg-2T2g	Red shift
[Zn(L)2Cl2]	370nm 295nm 261.7nm 206nm	2702.7cm-1 3389.8cm-1 3821.1cm-1 4854cm-	C.T C.T L.F L.F	Blue shift

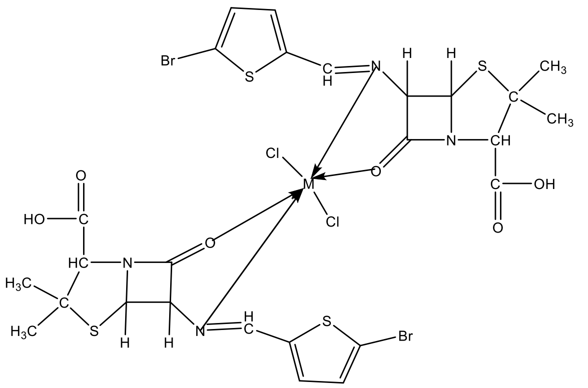
Magnetic Susceptibility for Coordination Complexes

Magnetic Susceptibility properties of the complexes [Ni(L)2 Cl2], [Cu(L)2Cl2], and [Zn(L)2Cl2] measured are (0.17,1.66,0) M.B respectively compared with the literature [7] which showed that forming these complexes was found to be the octahedral shape. The results of analyses and measurements of organic compounds used as a ligand can coordinate with metal ions through the oxygen atoms of carbonyl group, and the nitrogen atom of the azomethine group, where the ligand (L) acts as a bidentate ligand to form the octahedral shape shown in the table (4) (in the table) (4):

The ligand (L) acts as a bidentate ligand to form the octahedral shape with Sp3d2hybridization shown at the structure (3):

Table (4). Magnetic susceptibility and conductivity at the molar level for coordination complexes

Complexes	μeff (B.M)		Molar conductance (Ω−1 cm2 mol−1)	Shape
	Cal.	Exp.		
[Ni(L3)2Cl2]	2.82	0.17	0	Oct
[Cu(L3)2Cl2]	1.73	1.66	0	Oct
[Zn(L3)2Cl2]	0	0	0	Oct



structure (3): The suggested prepared complexes of (L).

Micro elemental analysis

Micro elemental analysis (C.H.N.S.) is Instruments are available that allow automated analysis of C, H, N, O, and S. and that analyses for C, H, and N, sometimes referred to as CHN analysis. The sample is heated to 900°C in oxygen and a mixture of carbon dioxide, carbon monoxide, water, nitrogen, and nitrogen oxides is produced. The atomic absorption spectroscopy that the absorbing species are free atoms or ions. Table (5) shows that calculated experimental values will be found as extremely theoretical values.

Table (5). the data of micro elemental analysis of theoretical values values

compounds	C%		H%		N%		S%			M%
	Cal	Exp	Cal	Exp	Cal	Exp	Cal	Exp	Cal	Exp
L	40.12	39.066	3.34	3.72	7.19	7.076	16.478	16.85		
$[Ni(L)_2Cl_2]$									64.5	62.5
$[Cu(L)_2Cl_2]$									69.5	50.1
$[Zn(L)_2Cl_2]$									71.3	81

Antibacterial activity

The antibacterial activities of newly synthesized compounds. According to this method, an increase in the growth of microbial cells increases the microbial number [22,25,26,27] The prepared complexes of the ligand with Ni (II), Cu (II), Zn (II) were studied against the biological activity of four different types of bacteria (*Staphylococcus aureus* and *Pseudomonas*), at the concentration of 1 × 10-3 M and compare to the inhibitory effect of the original ligand (L) toward same types of bacteria. The four complexes recorded an elevation in the inhibition ability in comparison to the original ligand which was the precursor of these complexes studied at the concentration (1×10-3) when the ligand and its complexes were applied on the plantation of *pseudomonas* as shown in Figure (13) and *Staphylococcus aureus* in figure (14). (In the table (5). The complex of nickel illustrated the highest inhibitory effect among the two complexes, on the other hand, the complex of zinc showed approximate inhibitory effects at the concentration (1 × 10^{-3} M) than the complex of copper at the concentration ((1 × 10^{-3} M) Table (6). Minimum inhibitory concentration (MIC) in g/mL of the ligands and their metal complexes

compound	pseudomonas	Staphylococcus
11-L	**15**	**0**
13-[Ni(L)2 Cl2]	17	12
10- [Cu(L)2Cl2]	13	12
12-[Zn(L)2Cl2]	16	15

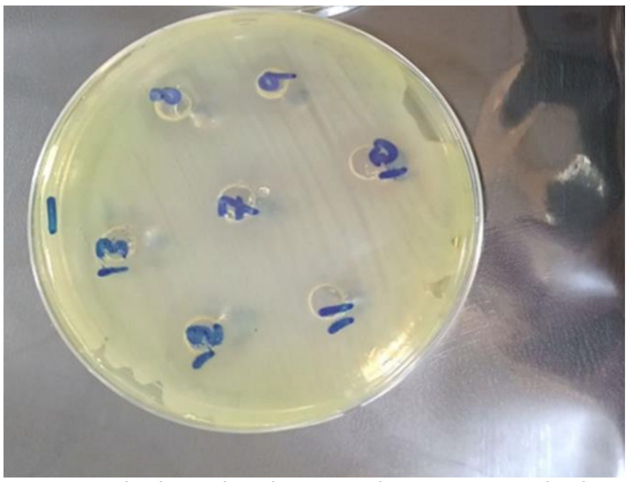


Fig (13). The ligand and its complexes were applied on *the plantation of pseudomonas*

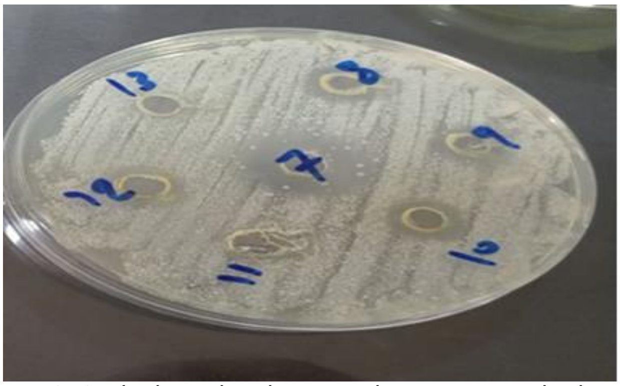


Fig (14). The ligand and its complexes were applied on the plantation of Staphylococcus aureus.

4. Conclusion

The core *B-lactam* compound of penicillins, 6-aminopenicillanic acid (6-APA), is an important active pharmaceutical intermediate that can be integrated and repurposed into semisynthetic antibiotics [28]. The ligand will be synthesized by Schiff base reaction between6-aminopenicillin acid and 5-Bromo-2-thiophene carboxaldehyde and three new metal (II) complexes with the Schiff base derived from this ligand. were obtained in a molar ratio [M(II): L] of [1:2]. IR data showed that the Schiff base behaved as a bidentate, monoanionic NO-chelating agent with azomethine-N, carbonyl(B-lactam) -O atoms. The metal complexes were found to be non- electrolytes with a molar conductivity in the range of 0–10 Ω^{-1} cm^2 mol^{-1}. Electronic spectra indicated octahedral geometry for the Ni (II), Cu (II), and Zn (II) complexes. The Schiff base and its metal complexes were tested against the *pseudomonas*, *staphylococcus*, and their inhibitory effects on the growth of bacteria.

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