

*Republic of Iraq
Ministry of High Education and
Scientific Research
Al-Qadisiyha University
College of Pharmacy*



Complexes of Ag (I), Cd (II) and Hg(II) with Imide Ligand Derived from Benzoxazole

A Research

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

فَتَعَالَى اللَّهُ الْمَلِكُ الْحَقُّ ۖ وَلَا

تَعْجَلُ بِالْقُرْآنِ مِنْ قَبْلِ أَنْ يُقْضَىٰ

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صدق الله العلي العظيم

من سورة طه الآية (114)

Abstract:

The work includes the synthesis of new ligand was synthesized in two steps, first step included a reaction of 2-mercaptobenzoxazole with 1,3-diamine Propane, while the other step included a reaction of product from first step with phthalic anhydride, by using reflux method. Three complexes were synthesized for this ligand by reacting with transition metals salt [AgNO_3 , $\text{CdCl}_2 \cdot 2\text{H}_2\text{O}$, HgCl_2] by refluxing in absolute ethanol as solvent. The ligand and its complexes were characterized by using FTIR, UV-VIS. spectra, melting points.

The biological activity showed the ability of the prepared ligand and its complexes to inhibit growth of *Escherichia Coli*. By using (250 ppm) of the ligand and its complexes. Most of the prepared complexes effective against both types of bacteria in varying degree, with the high activity for Hg(II) complexes.

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[1-1] Heterocyclic Compounds^[1-3]

Cyclic organic compounds containing only carbon atoms in their composition are called cyclic carbon compounds or homocyclic compounds such as benzene and its derivatives.

If one or more atoms inside the ring are different, such as nitrogen, oxygen and sulfur are called heterocyclic compounds such as pyrrole, furan and thiophene

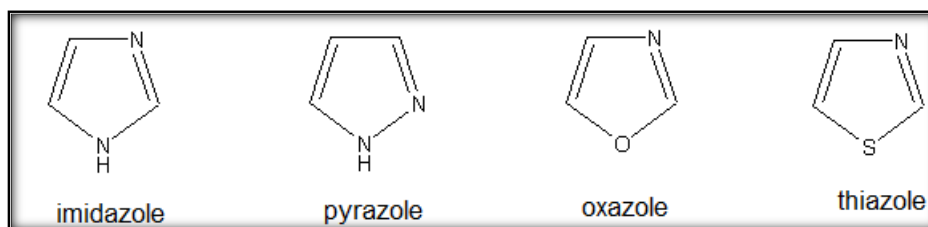
These compounds are widely found in many natural products, many of which are important in everyday life, such as alkaloids, amino acids, vitamins, hemoglobin and hormones. heterocyclic compounds are also involved in the synthesis of many drugs and antibiotics such as antibiotics, germs, infections, fungus, tumors and antioxidants. Great efficacy to inhibit growth of microorganisms.

There are many of heterocyclic compounds entering the industry, as well as the manufacture of dyes and polymers with wide use, as well as used as raw materials to prepare many other organic compounds and prevent corrosion.

There are many types of heterocyclic compounds. This difference depends on the type of hetero atoms found in the compound, as well as the size of the ring (three-membered , four-membered, five-membered). The most important of these compounds are pentagon rings such as furan, thiophene and pyrrole.



There are other types of five-ring compounds that contain similar hetero atoms such as imidazole and pyrazole or are different, such as oxazole and thiazole.



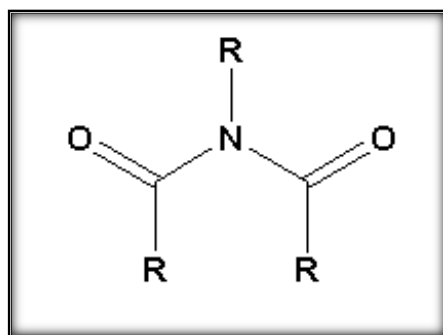
These types of compounds are present in the number of carbohydrates and hem in the blood as well as are important for the life of plants and animals, a large number of them present in the enzymatic reactions and the co-enzyme reactions, also represents a large part of the composition of amino acids in the composition of various heterocyclic compounds.

[1-2] imides^[4,5]

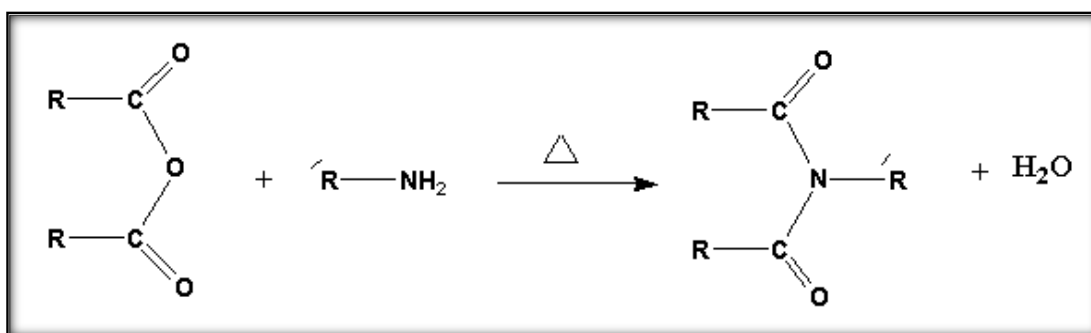
An **imide** is one of organic compounds which contains two acyl group as a functional group bound to nitrogen atom. These compounds

are derived from acid anhydrides, although imides are less reactive than anhydride .

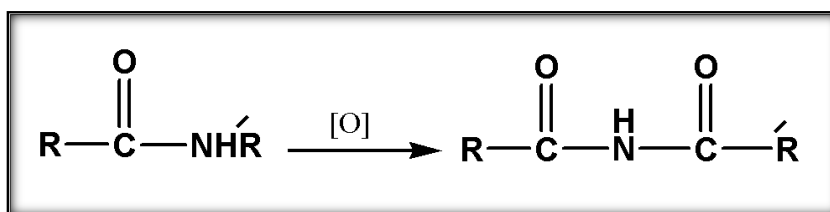
Imides are compounds that are derived from carboxylic acids , therefore their name is derived from it by replacing the imide section rather than oic acid, Such as succinimide, derived from succinic acid, and phthalimide, derived from phthalic acid.



Preparation of the most common amides of the reaction of bicarboxyl acids or anhydride with ammonia or primary amines by heating .



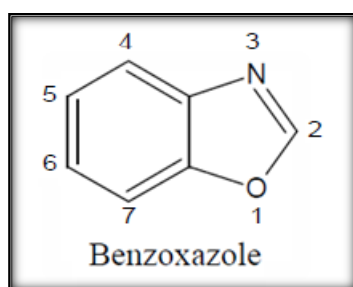
Imides can also be prepared from oxidation of amides.



Cyclic imides and their derivatives have great importance for their applications in biological and chemical fields. They are used as intermediates in the synthesis of drugs, dyes and polymers, and cyclic imides are generally synthesis from the dicarboxyl acid or anhydride with primary amines under severe conditions (250-380 °C) or by using microwave .

[1-3] Benzoxazoles^[6-8]

Benzoxazoles are an aromatic organic compounds with a molecular formula $\text{C}_7\text{H}_5\text{NO}$, consisting of a fused benzene ring with an oxazole ring at 4.5 positions and numbering as follows.



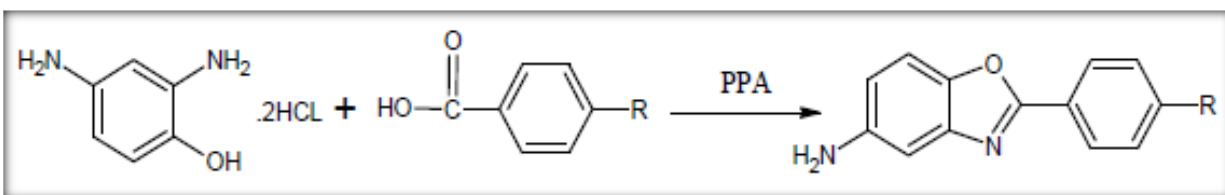
Benzoxazole compounds are particularly important in chemistry and biochemistry. These heterocyclic compounds show properties of various drugs such as antivirals, antibiotics, antimicrobials, antifungal

drugs , anti-inflammatory , and is used in the synthesis of drugs because of its therapeutic properties.

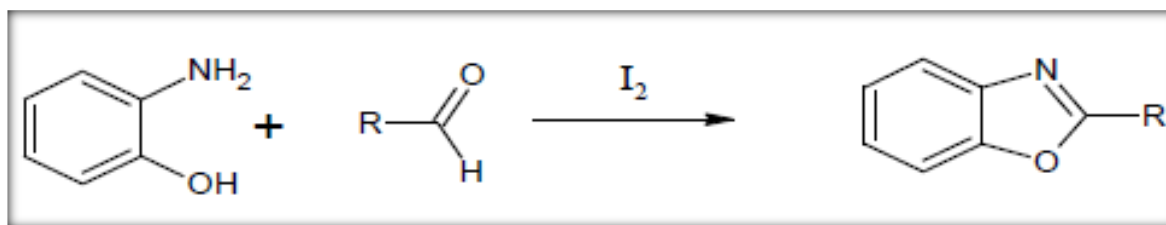
[1-4] Benzoxazole synthesis^[6,7]

Benzoxazole compounds and their derivatives have biological and pharmacological efficacy, they are well suited to play a major role in the fields of medicine, pharmacy as drugs and biochemistry. They also play an important role in the field of coordination chemistry as good ligand that can be consistent with the transitional elements to form complexes , as well as analytical chemistry, determine elements that have low concentration. Therefore, these compounds were synthesized in a different methods , which can be summarized as follows:

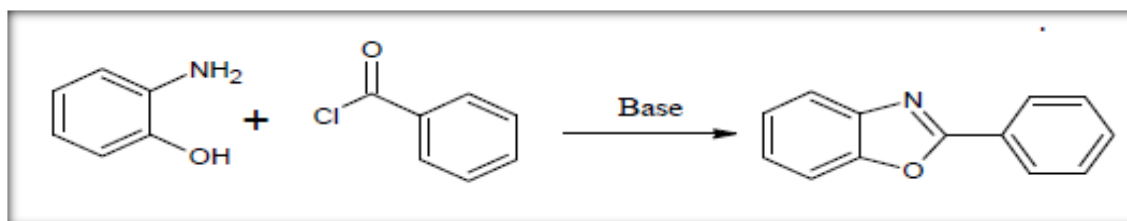
[1] **Reaction with Acid:** - 2 amino phenyl or 5-amino (p-substituted phenyl) benzoxazoles were obtained by heating substituted benzoic acid with 2-4-diamino phenol in PPA (polyphosphoric acid).



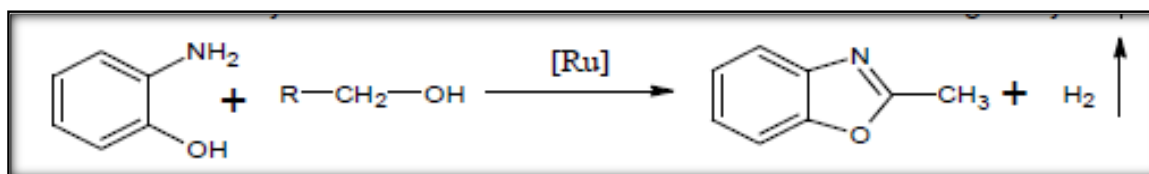
[2] Reaction of aldehydes:- condensation of 2-amino phenol with various aldehyde were carried out using I2 in solvent free



[3] Reaction with acid chloride:



[4] Reaction with alcohol: - 0-amino phenol reacts with alcohol in presence of amount of a ruthenium as a catalytic to lead 2-substituted Benzoxazole in good yield.



[1-6] Imide compounds^[4]

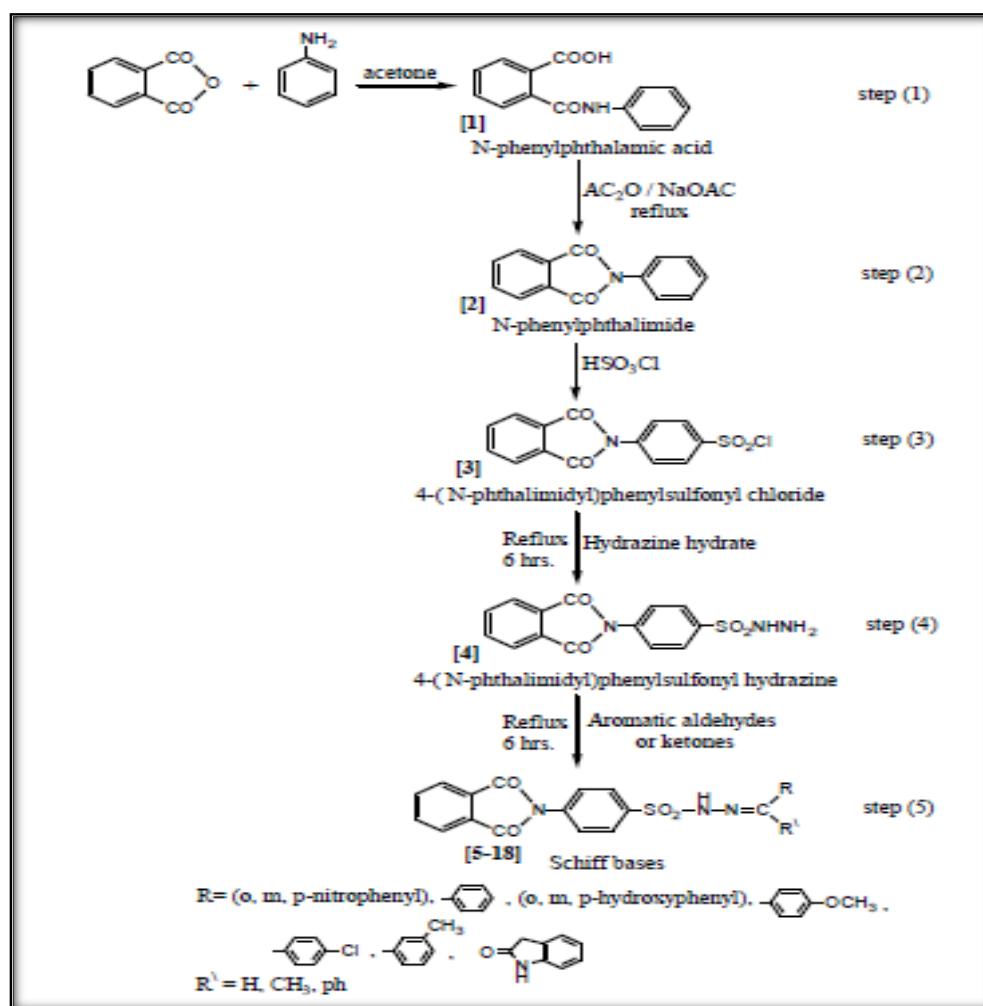
Imide compounds have great important by their high biological efficiency, as well as extensive uses in the fields of medical, pharmaceutical, inorganic and analytical chemistry, antioxidants and corrosion inhibitors.

A large number of organic compounds containing phthalamide rings were present in several steps. The first step involved the interaction of phthalic anhydride with aniline, which produces the phthalamine N-

phenyl acid, which loses a water molecule that is converted to N-phenyl, corresponding to the presence of anhydride and the anhydrous sodium hydroxide, and several steps to give compounds (Schiff bases) containing phthalimide rings.

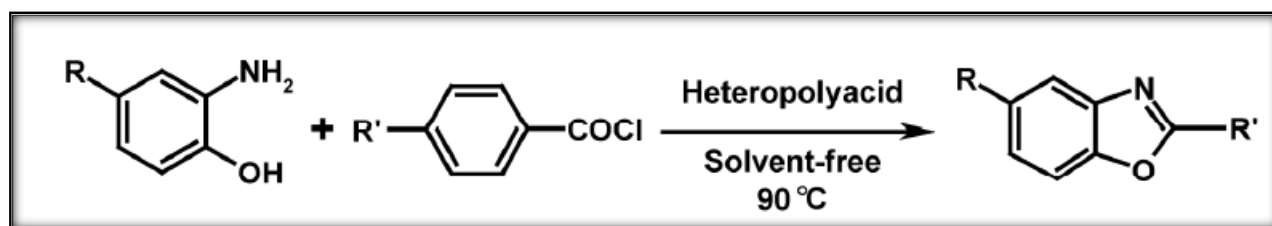
The structures of these compounds was confirmed by using FTIR, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra.

The evaluation of biological activities for these compounds against two microorganisms *Staphylococcus aureus* and *Escherichia coli* and found to be effective against these types of bacteria under study.



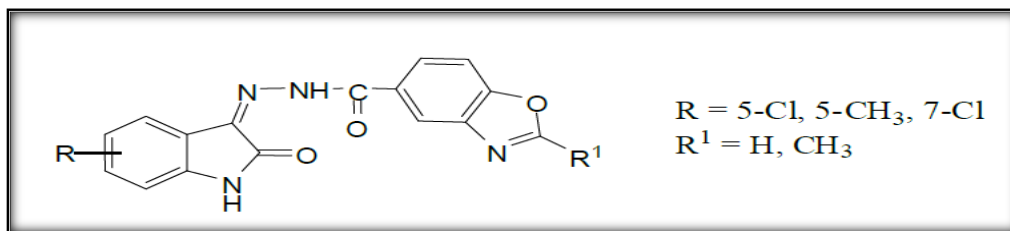
[1-7] Benzoxazole compounds^[9,10]

Benzoxazole is an organic compound and has many biological activity and medically activity. Many of these compounds were prepared using new methods, including 2-arylbenzoxazole compounds, by condensation o-aminophenols and benzoyl chloride derivatives without solvents with a quantity of acid as an adjuvant. These compounds were identified using spectral methods and these compounds were found to be highly effective against species of bacteria under study.



Benzoxazole derivatives play an important role in medical chemistry due to the great biological efficacy of these compounds. Many of the benzoxazole substitutions are characterized by their high ability to inhibit the growth of microbes and infections. They also have activities such as the central nervous system, control of tuberculosis, hypoglycemia, For fungus, anti-cancer, inhibitory protein kinase.

Sarangapani et al. In the preparation of hydrazine-derived compounds containing benzoxazole rings, these compounds showed anti-bacterial activity such as E.coli and P.vulgaris as well as anti-fungal activity against A. niger and C.verticulat.

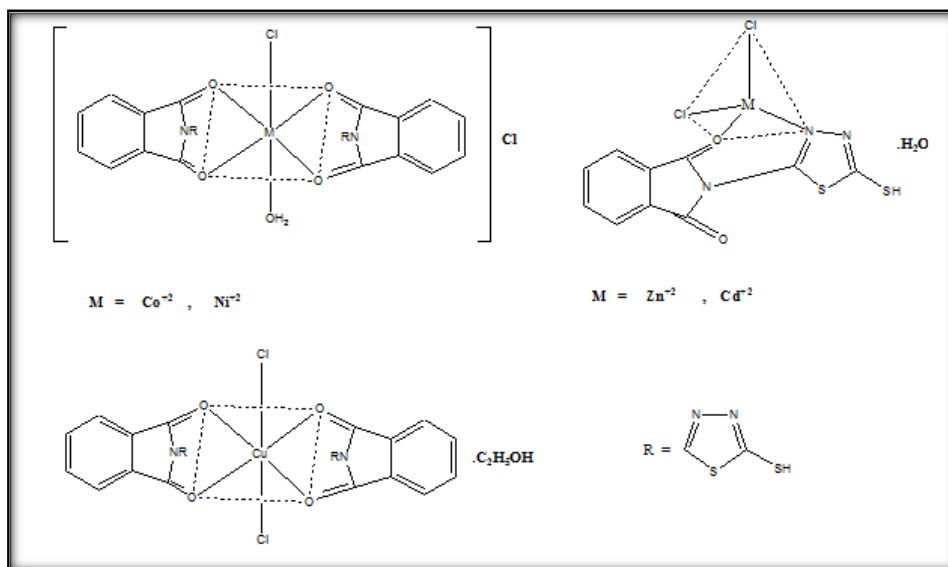


[1-8] Imide and benzoxazole complexes^[11,12]

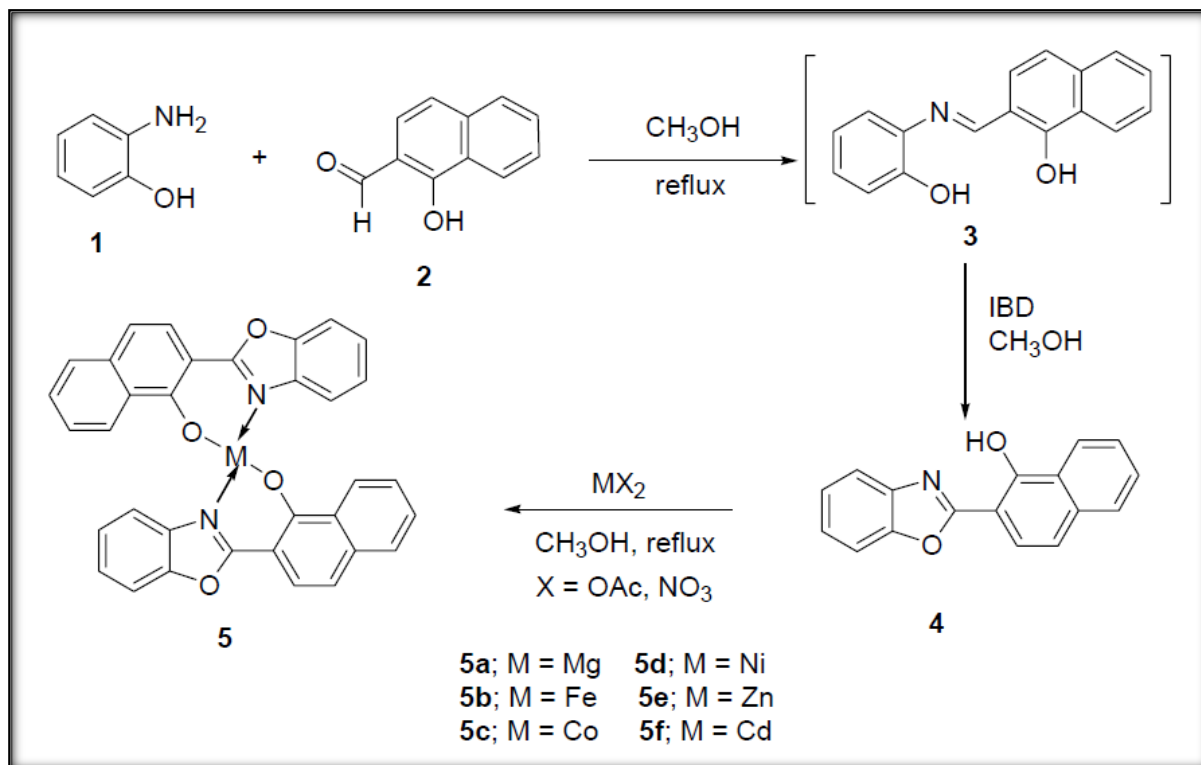
Applications of inorganic chemistry in the fast-spreading specialty have become rapid, and metal complexes are now very important in therapeutic and diagnostic fields. Significant advances in biochemistry are important. Many of these complexes have been used in the treatment of cancer.

In 2014, the ligand 2- (5-mercapto-4,3,1-thiadiazole-2-yl) isoindoline-3,1-dion was prepared from reaction 5-amino-4,3,1-thiadiazole-2-thiol with phthalic anhydride. The complexes of the ligand by reacting with the ionic chloride, cobalt, nickel, copper, zinc and cadmium chlorides .

The structures of the ligand and its complexities were determined by using spectral methods (infrared, visible-ultraviolet radiation, NMR spectrum), magnetic sensitivity measurements Molar, melting degrees and atomic absorption. The proposed structures of cobalt, nickel and copper complexes are octahedral geometry, while zinc and cadmium complexes are tetrahedral geometry.



The Mg (II), Fe (II), Co (II), Ni (II), Zn (II) and Cd (II) complexes were synthesized from reactions ligand 1-(2'-hydroxynaphthyl) benzoxazole with the metal ions above. They have been found to be effective against the types of bacteria.



[1-9] Aim of the work

The aim of the study is summarized in following :

- 1- Preparation of the imide ligand containing benzoxazole.
- 2- Preparation of [Cu(II), Cd(II) and Hg(II)] complexes with of the ligand (L) .
- 3- identification of the synthesized ligand and its complexes by using IR , UV-Vis. , melting points .
- 3- Evaluation of biological activity for the ligand and its complexes against selected types of bacteria [*Escherichia Coli* as gram negative] .

[2-1] Chemicals

Table (2-1): showed the used chemicals in the work .

Chemicals and their Sources :(1-Table (2

Chemicals	Purity (%)	Supplied from
2-Mercaptobenzoxazole	99	Aldrich
1,3-diamine Propane-	97	Aldrich
Phthalic anhydride	98	Aldrich
AgNO ₃	98	Merck
CdCl ₂ .2H ₂ O	99	BDH
HgCl ₂	99	Merck
Nutrient agar medium	-	BDH

[2-2] Physical Measurements

Table(2-2) explained devices which using to confirm ligand and its complexes .

Physical Measurements	device
Melting point	Stuart SMP3 melting point apparatus
UV-Visible spectroscopy	Shimadzu U.V-165PCS spectrophotometer
Infra-red spectroscopy	Shimadzu FT-IR 8400S spectrophotometer

2.3- Biological activity

Biological activity is evaluated by using Autoclave, Incubator and PH meter.

[2-4] Synthesis of the ligand

2.4.1- Synthesis of the compound (A)

The compound (A) was prepared from the reaction of the 2-mercaptobenzoxazole with -1.3 diamine Propane as follows:

A (1.5 g , 10 mmole) of 2-mercaptobenzoxazole dissolved in (25 mL) absolute ethanol and added to a solution consisting of (0.74 g ,10mmole) 1,3-diamine propane in (25 mL) of absolute ethanol, the mixture was refluxed for 4 hours. After the reflux, the reaction mixture was observed to be precipitate, it was collected and filtered, then dried, the precipitate recrystallized from absolute ethanol, filtered and dried (yield % = 73%, M.P.= 121-124 °C).

2.4.1- Synthesis of the ligand (L)

To a compound solution (A) consisting of (1.9 g , 0.01 mmole) in (25 ml) ethanol added to (1.42 g ,0.01 mole) solution of the phthalicanhydride. The mixture refluxed four hours. A precipitation formed and dried and then recrystallized from absolute ethanol, and given yield % = 84%, M.P.= 143-145°C).

[2-4] Synthesis of the Complexes

The ligand (L) (0.001mol , 0.3gm) was dissolved in 20 ml ethanol in a 100 ml round-bottom flask. A solution of (0.001mol) of the metal

chloride Ag(I) , Cd(II) and Hg(II), respectively in 20 ml ethanol was added dropwise , with continuous stirring at room temperature. Reflux for 1hr . The resulting precipitates were filtered off, washed with ethanol , dried and recrystallized from ethanol .

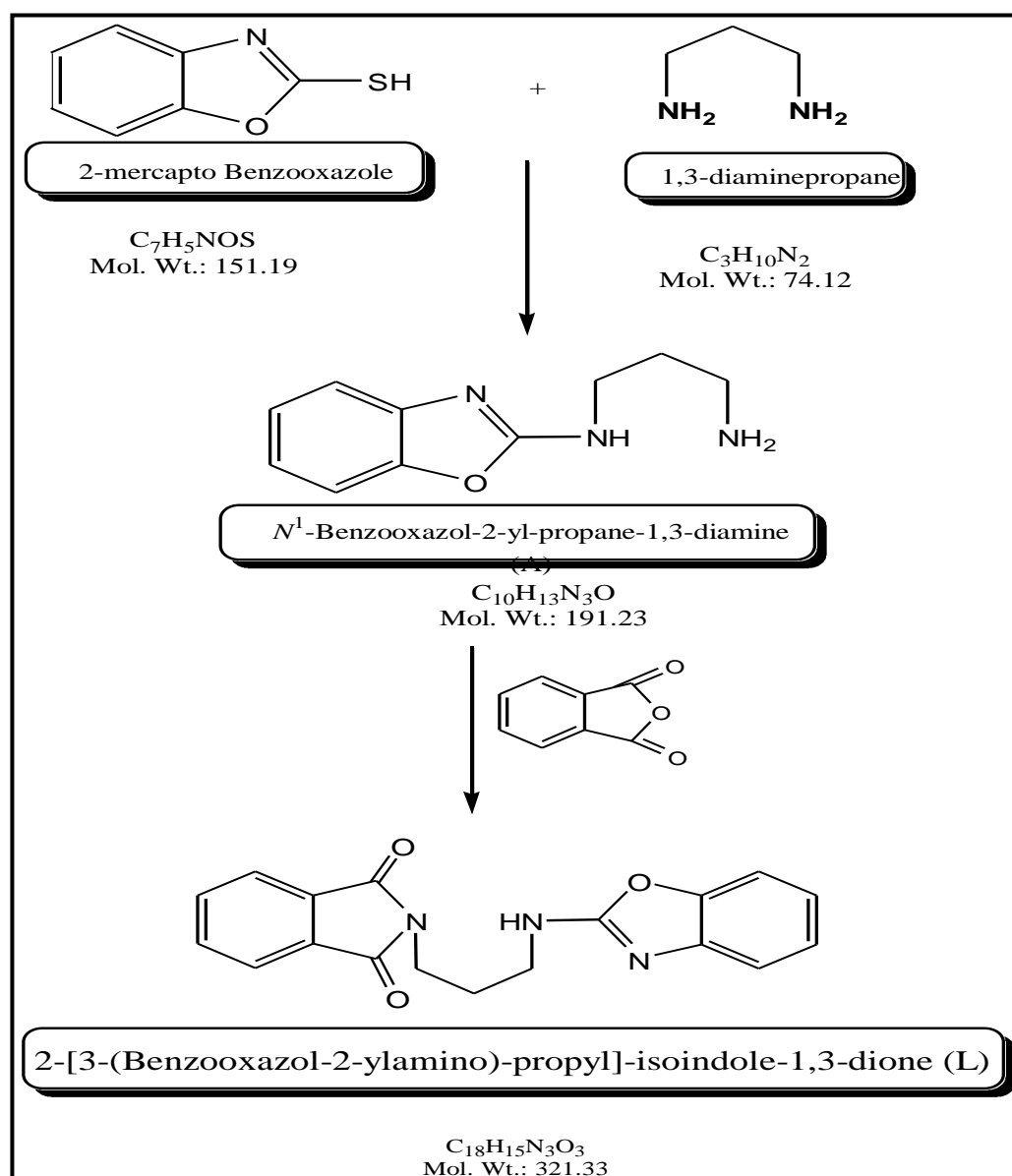


Figure (2-1) Preparation of the ligand

[2-5] Biological Activity

2.5.1 – Preparation of Agricultural Medium

Agricultural Medium was prepared, according to the providing company, by adding (28 gm) dry Nutrient agar to (1L) distilled water in volumetric flask with the adjustment of the (pH=7.4), then mixed and dissolved by heating, then the nozzle of volumetric flask was closed by cotton and sterilized with autoclave in 121°C for 20 minutes ; after that cooling, to the medium temperature of (45⁰C), and poured into Petri dishes about (25ml)for a dish then left to cool and solidifies so that the medium became ready to transplant bacteria.

2.5.2 – Preparation of Solutions

The solutions of ligands and metal complexes under study were prepared with concentration (250 ppm) in ethanol as solvent.

atment MethodTre – 2.5.3

The bacteria was spread out in the dishes and on the surface of Nutrient agar . In the Petri dish holes were put in a diameter (5mm) after hardening the medium by using a cork - borer, about 4 holes in dishes, taken (5ml) from these solutions on the dishes (inside the holes) then, these dishes were kept in the refrigerator for (4hr) to ensure better spread in the medium.

The Petri dishes were put in the incubator for (24hr) at 37°C. After that, the inhibition zone was measured for the compounds by the use of the millimeter ruler.

Table (2-3): Physical properties of the synthesized ligand and its complexes

No	compounds	colour	(C°)M.P	(%)Yield
1	L	Brown	143-145	84
2	[Ag(L)NO ₃]	Light brown	162-164	76
3	[Cd(L)Cl]Cl	Light brown	181-184	72
4	[Hg(L)Cl]Cl	Light brown	201-203	87

[3-1]Synthesis of the ligand(L)

The ligand (L) was prepared in two steps, first step included a reaction of 2-mercaptobenzoxazole with 1,3-diamine Propane, while the other step included a reaction of product from first step with phthalicanhydride, by using reflux method.

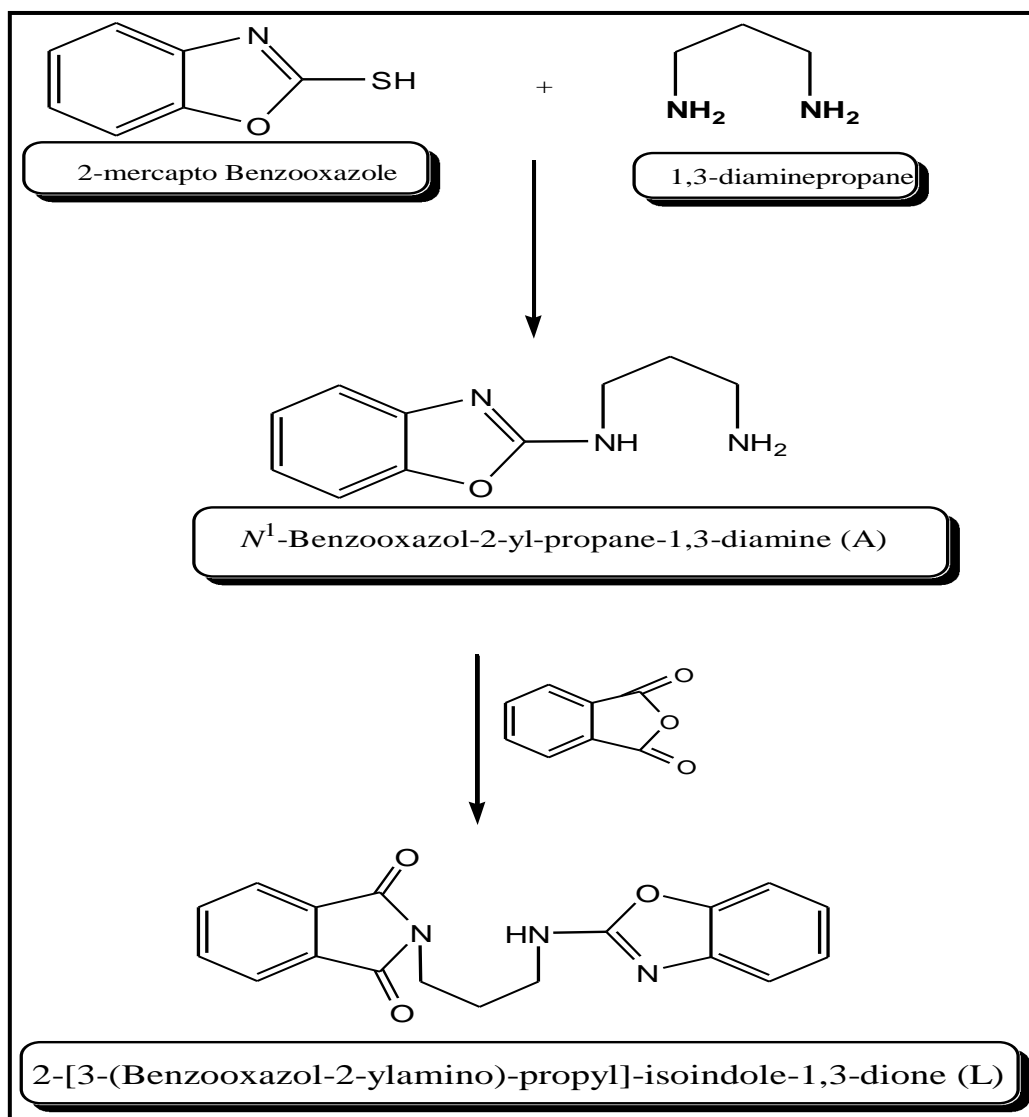


Figure (3–1) The synthesis of the ligand (L)

Three complexes were synthesized for this ligand by reacting with transition metals salt [AgNO₃, CdCl₂.2H₂O, HgCl₂] by refluxing in

absolute ethanol as solvent . the ligand and its complexes were characterized by using FTIR , UV-VIS. spectra , melting points .

[3-2] The FTIR Spectra of the ligand (L) and its complexes

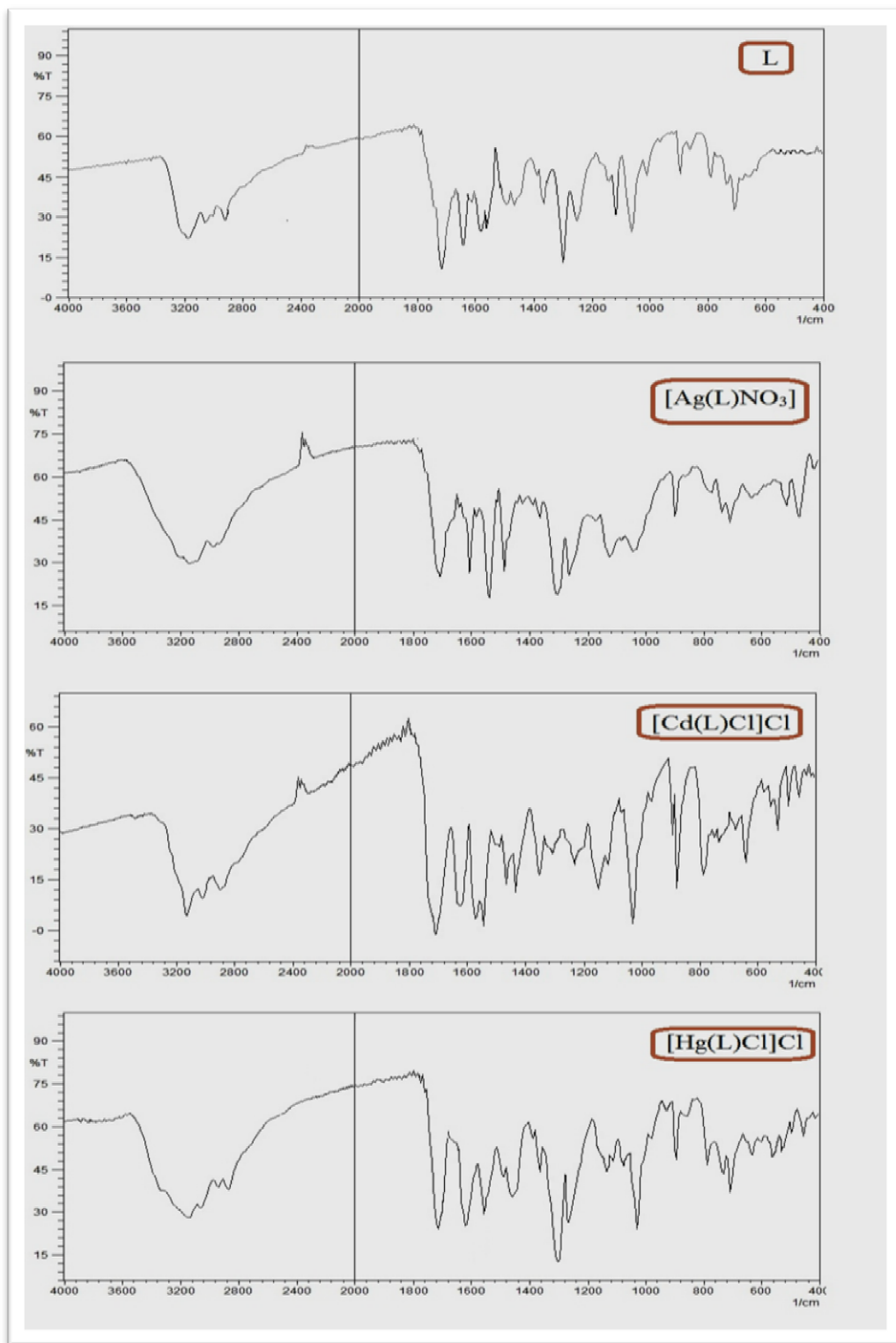
The FTIR spectrum of the free ligand (L), Figure (3-2) showed two bands at (3182) and (2916) cm^{-1} assigned for $\nu(\text{N-H})$ and $\nu(\text{C-H}_{\text{aliphatic}})$, respectively, and the bands at (1641 and 1714) cm^{-1} , which due to $\nu(\text{C=N})$ of the benzoxazole ring and $\nu(\text{C=O})$ group of imide , respectively. The bands at (1578, 1559) and (3046,3006) cm^{-1} were assigned to $\nu(\text{C=C})$ and $\nu(\text{C-H})$ aromatic, respectively. Also the spectrum shows bands at (1121 and 1067) cm^{-1} attributed to the $\nu(\text{C-O})$ and $\nu(\text{C-N})$ groups, respectively.

The bands at (3182, 1641 and 1067) cm^{-1} , due to $\nu(\text{N-H})$ amine group , $\nu(\text{C=N})$ of benzoxazole ring and $\nu(\text{C-N})$ of imide , respectively , in the free ligand, these bands shifted to a lower wave number after complexation in the region (3122-3143) , (1608-1624) , (1037-1042) cm^{-1} for Ag(I), Cd(II)and Hg(II) complexes respectively , the shifted toward lower wave number due to coordinate nitrogen atom of these groups with metal ion .

The new bands at the range (422-537) cm^{-1} are due to the $\nu(\text{M-N})$ for synthesized complexes, respectively . The FTIR data for free ligand and its complexes were summarized in Table (3-2) .

Table (3-1): The infrared spectral bands for the ligand (L) and its synthesized complexes

Symbol of compound	$\nu(\text{H-N})$	$\nu(\text{C=N})$	$\nu(\text{C-N})$	$\nu(\text{N-M})$
L	3182	1641	1067	—
[Ag(L)NO ₃]	3143	1608	1042	514 , 471, 422
[Cd(L)Cl]Cl	3122	162	1037	529 , 487 , 451
[Hg(L)Cl]Cl	3143	1617	1038	537 , 494, 453



Figure(3-2): The FTIR spectra of the ligand (L) and its complexes

[3-3] The Electronic Spectra

The electronic spectrum of the ligand (L), Figure (3-3) , showed two peaks at () nm which are due to π - π^* and n- π^* transitions , respectively.

The electronic spectra of [Ag(I) , Cd(II) and Hg(II)] complexes, showed peaks at () nm , which due to charge transfer .The UV-Vis data for free ligand and its complexes are shown in Table (3-3).

Table (3-2): The UV-Vis spectral peaks for the ligand (L) and its synthesized complexes

Symbol of compound	(nm) _{max} λ	transitions
L	221	π - π^*
	259	n- π^*
[Ag(L)NO₃]	481	Charge transfer
[Cd(L)Cl]Cl	402	Charge transfer
[Hg(L)Cl]Cl	397	Charge transfer

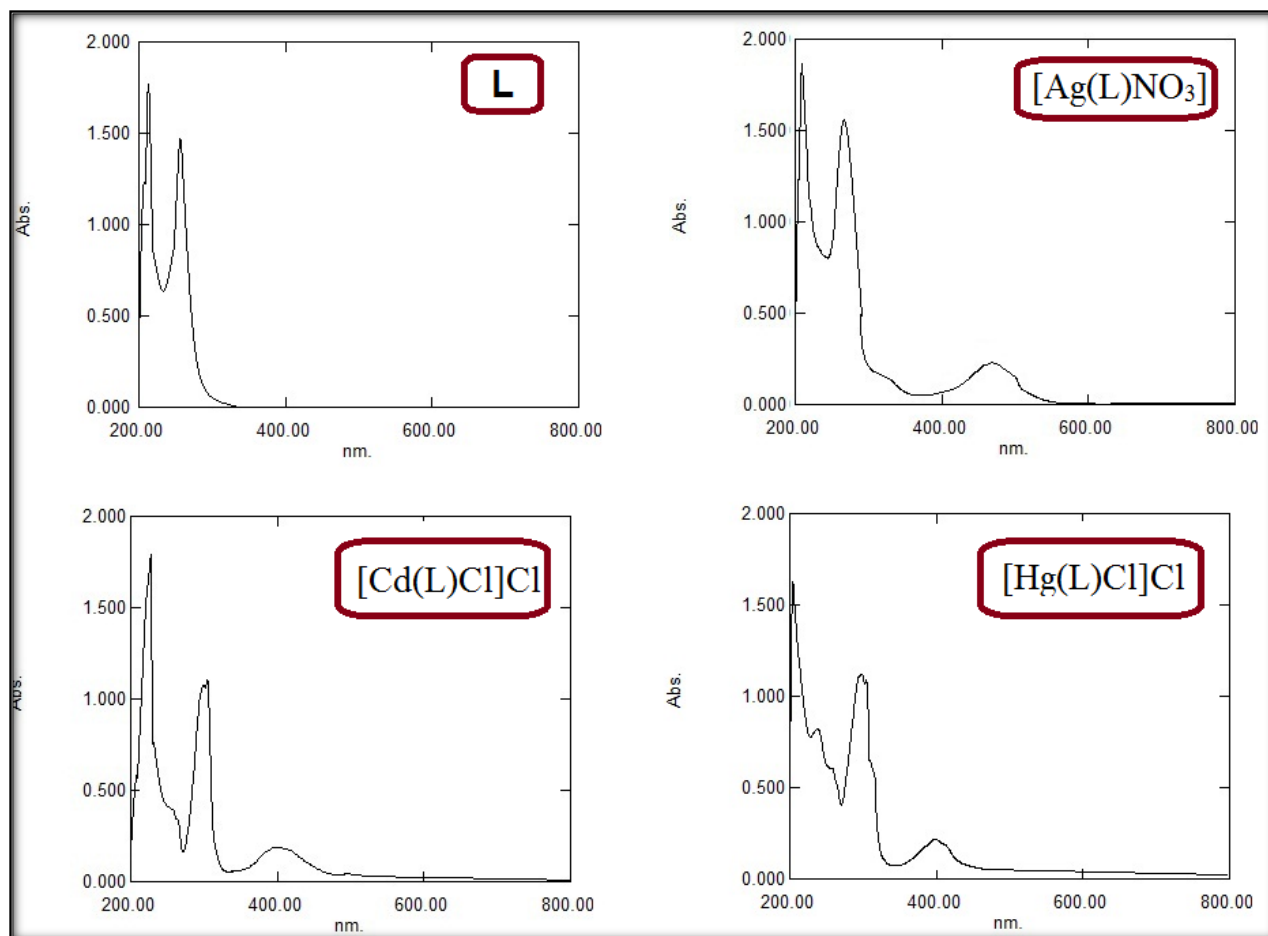


Figure (3-3) : The UV-Vis. spectrum of the ligand and its complex

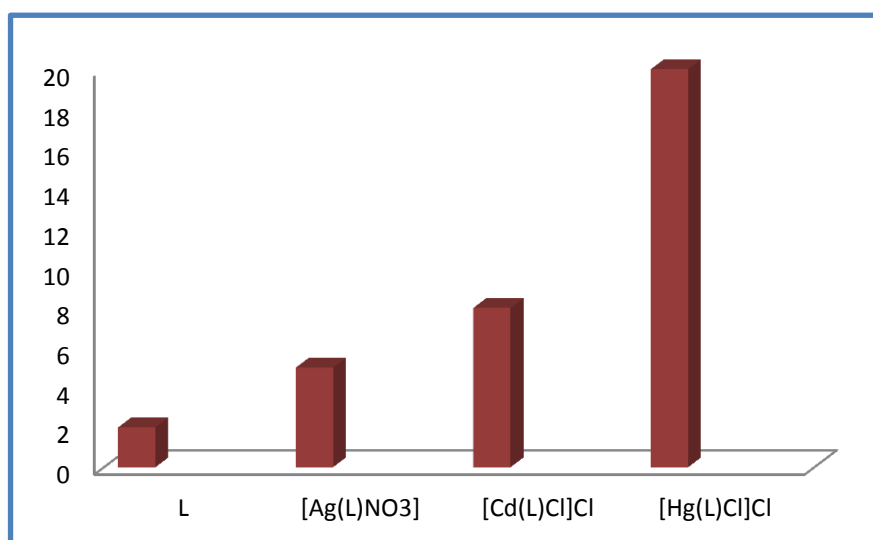
[3-4] Biological activity for the synthesized ligand and its complexes

The biological activity of the synthesized ligand and its complexes were studied against selected types of bacteria which include [*Staphylococcus aureus* as gram positive] and [*Escherichia Coli* as gram negative] .They were cultivated in Nutrient agar medium in concentration (250ppm) by plate agar method to determine the inhibitory effect for these ligands and their complexes on the growth of these bacteria.

Table (3-3) showed the results of activity for the ligand and its complexes which were studied against bacteria. Most of the prepared complexes were observed to have ability to inhibition and to possibility of existence of two groups active in ligands structures ((=N-C-S and azomethine) at the same time .

Table(3-3):-Biological activity data (zone of inhibition in mm) of ligand (L)and its metal complexes

<i>Compound</i>	<i>Zone of Inhibition</i>
	<i>E. Coli</i>
L	2
[Ag(L)NO ₃]	5
[Cd(L)Cl]Cl	8
[Hg(L)Cl]Cl	20



Figure(3-4) : Statistical representation for biological activity of the synthesized ligand and its metal complexes

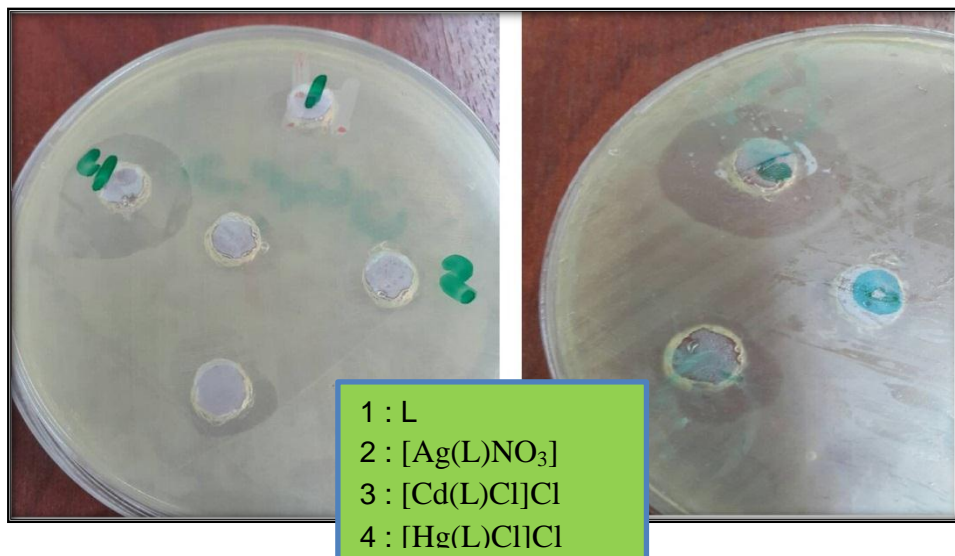


Figure (3-5) : The biological activity of the ligand (L) and its complexes against E. Coli

[3-5] Conclusions

According to the results, the ligand (L) behaves as tridentate ligand. The ligand (L) coordinates with metals ions through nitrogen atom of azomethine , amine groups in the complexes of Ag(I), Cd(II) and Hg(II).

The prepared ligands showed the ability to inhibition of growth toward *Escherichia Coli*. At prepared concentration. Most of the complexes prepared effectiveness against both types of bacteria and varying degree, where the complex of Hg(II) with the ligand showed high activity toward types of these bacteria.

[3-6] Recommendations

1. Preparation of new ligands derivatives from 2-mercaptobenzoxazol.
2. Preparation of new complexes for these ligands with metal ions of second and third series, also, metal ions of lanthanides and actinides.
3. Characterization these ligands and their complexes by the elemental analysis, Infrared and electronic spectra, magnetic susceptibility measurements, flame atomic absorption spectroscopy and molar conductivity.
4. Evaluation of biological activity for all ligand and their complexes.

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