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**Design, Preparation some transition metal complexes of Chalcone-Azo with Paracetamol ligand and Evaluation anti-biological activity of some complexes**

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**Abstract:**

This search designed new series complexes of (Mn , Fe, Co, Ni, Cu, and Pd)(II) ,which prepared from Chalcone - Azo derived contained Paracetamol . The results illustrate that, the mole ratio (ligand : metal) (2:1) for all complexes and the geometric shapes of complexes were an Octahedral except Pd(II) complex was Square planer. the complexes characterized by ( UV-Visible, FTIR, C.H.N, Electrical molar conductivity and Magnetic susceptibility). This ligand coordinated with metal ions via (N) atom of Azo group and (O) atom of OH group of Paracetamol , the biological examination tested Pd(II)complex as antitumor Thyroid cancer cells(FTC-133) and compered it with healthy cells to evaluate the possibility of using it as therapeutic method. In addition , it tested Cu(II) and Ni(II) complexes as antimicrobial activity towards two types of Gram negative and Gram positive bacteria .

**Keywords :** Chalcone-Azo, Paracetamol compound, Thyroid cancer, antimicrobial activity.

**Introduction:**

Recently, the attention of scientists has increased towards Chalcones and their derivatives , it may be because the successful biological activity of them which recorded as anti-cancer [1]anti-malarial [2]anti-oxidant [3]anti-viral[4], anti-microbial, anti-convulsant and anti-inflammatory[5] . In addition, the two position ( $\alpha$  and  $\beta$ ) as unsaturated keto-ethylenic group gave chalcone derivatives a vital role in Industry[6] and Inorganic chemistry to synthesis a plenty of heterocyclic compounds[7,8].

Modernly, number of researchers synthesized organic compounds contained both chalcone and azo groups , this is because azo compounds had an important effects as catalysts, anti-microbial , colorants , corrosion inhibitors and anti-cancer [9-11] .

It could be noticed that, Paracetamol attractive many chemists to use it in synthesis of organic compounds because it has wide medical applications as analgesic and anti-pyretic the same as aspirin in reducing body temperature and it is safe to the gastric mucosa [12] and it used as anti-oxidant of LDL and reduce the risk of heart [13].

This work focused on synthesized several of new complexes derivative from chalcone –azo with Paracetamol and study the biological activity of Pd(II) complex against Thyroid cancer (FTC-133) and antibacterial activity of both Ni(II) and Cu(II) complexes .

**Experimental part:**

**Materials and measurements:**

In this work all materials were provided by significant companies such as Fluka, BDH and Sigma Aldrich. In addition, all measurements have done by noticeable equipment. Elemental Analysis (C.H.N. and M) was obtained by Elemental Analysis system Instrument :Flash EA/1112-thermofinniganco and Shimadzu AA-66300/Atomic Absorption /Flame Emission spectrophotometer . Molar conductivity measurements have done by 470WTW apparatus in  $(1 \times 10^{-3})$ M DMSO at room temperature . Magnetic Susceptibility were carried by Faraday method by using Sherwood Scientific Balance apparatus. Melting point measurements were studied by Stuart Melting Point /Germany (SPM10) . FTIR spectra characterized by Shimadzu FTIR 8400 at  $(4000-400) \text{ cm}^{-1}$  and UV-Visible spectrophotometer considered by Shimadzu UV-Vis. 1700 double beam at  $(200-1100) \text{ nm}$  .

### Preparation of ligand complexes :

The ligand has been prepared previously[14]. The aqueous solutions of chloride salts (Mn, Co, Ni, Cu) (II) and aqueous solution of sulphate salt (Fe)(II) and  $(\text{CH}_3\text{CN})$  solution of chloride salt Pd(II) were added to the basic acetone solution of ligand (HL) in mole ratio (L:M)(2:1) with stirring and heating (30min.) the painted precipitations of complexes were dried and crystallized with hot acetone.

**Table (1) some of physical properties of complexes**

Compound	M.Wt g/mole	Colour	M.p. °C	Yield %	(Found) Calc. %			
					%C	%H	%N	%M
$[\text{Mn}(\text{C}_{32}\text{H}_{17}\text{N}_3\text{O}_3\text{Br})_2(\text{H}_2\text{O})_2]$	1017.53	Dark reddish-Brown	219-222	78	54.24 (54.12)	3.34 (3.29)	8.25 (7.22)	5.39 (5.22)
$[\text{Fe}(\text{C}_{32}\text{H}_{17}\text{N}_3\text{O}_3\text{Br})_2(\text{H}_2\text{O})_2]$	1018.44	Reddish brown	183-187	73	54.20 (54.13)	3.33 (3.13)	8.24 (7.72)	5.48 (5.23)
$[\text{Co}(\text{C}_{32}\text{H}_{17}\text{N}_3\text{O}_3\text{Br})_2(\text{H}_2\text{O})_2]$	1021.53	Dark Brown	147-151	80	54.03 (54.01)	3.32 (3.21)	8.22 (8.13)	5.76 (4.99)

[Ni(C <sub>32</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> Br) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	1021.29	Reddish Brown	196-199	72	54.04 (53.96)	3.32 (3.13)	8.22 (7.91)	5.74 (5.66)
[Cu(C <sub>32</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> Br) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	1026.14	Light reddish Brown	143-148	74	53.79 (52.98)	3.31 (3.22)	8.18 (8.10)	6.19 (5.98)
[Pd(C <sub>32</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> Br) <sub>2</sub> ]	1033.02	Dark brown	>237	80	53.43 (53.34)	3.29 (3.25)	8.13 (7.90)	10.30 (10.25)

### Cytotoxic Activity of [Pd(HL)<sub>2</sub>]:

This study focused on the cytotoxic effect of Pd(II) complex on Thyroid cancer cells line (FTC-133) compared with healthy cells line (WRL-68) by taking number of concentrations of Pd(II) complex (6.2-400) µg/ml and adding these concentrations to both cancer and healthy cells by using MTT method[15] , the result is shown that (25)µg/ml of Pd(II) complex is the best concentration to inhibit the tumor of cancer cells . However, it was less influence on healthy cells , which is approved that Pd(II) complex might be used as new medicine of Thyroid cancer line (FTC-133).

**Table (2):The Effect of [Pd(HL)<sub>2</sub>]on Thyroid cancerous cells (FTC-133) and healthy cells (WRL-86) at the same conc. Using 24 hrs. MTT test at 37<sup>o</sup>c.**

Con. (µg.mL <sup>-1</sup> )	Mean Percentage (%) for each cell line			
	(FTC-133)		(WRL-86)	
	Cancerous line cells of (FTC-133)		Normal line cells of (WRL-86)	
	Cell Viability	Cell Inhibition	Cell Viability	Cell Inhibition
6.25	95.50	6.40	98.04	4.98
12.5	95.33	5.66	97.80	4.94
25	94.19	5.85	95.07	4.83
50	94.82	5.16	94.40	5.60
100	91.88	8.17	85.66	14.33
200	84.02	15.98	75.85	24.19
400	74.83	25.18	72.66	27.32

### Anti-bacterial activity of [Ni(HL)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] and [Cu(HL)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]:

This method has been weighted (6000)mg of both complexes and dissolved in 1ml of DMSO , then 2ml of DW was added and mixed well to yield a crud solution of 2000mg/ml. A concentrated solutions (100%) was

prepared by mixing 1ml of crude solution in 19 ml of DW ( V/V) . A half dilution (50%) was prepared by diluted the concentrated solution (V/V).

Tested Bacteria: 3 isolates from each Gram negative bacteria and Gram positive bacteria were tested for antimicrobial activity. The Gram positive bacteria include *Enterococcus faecium* and *Staphylococcus saprophyticus* while Gram negative bacteria include *E. coli*, *Klebsiella pneumoniae* and *Salmonella typhimurium*.

**Antimicrobial activity:** A well diffusion methods was used to evaluate the antimicrobial activity as followed: Firstly, Mueller Hinton Agar ( MHA) plates were prepared and inoculated with 100µl of each fresh bacterial isolates ( the turbidity of inoculum equal to McFarland tube NO 0.5 ) by spreading methods and the plates left to dry for 10 min. Then, using cork porer (5mm), a 7 wells in each plates were done and Fifteen microliter of each chemical was filled in the well and DMSO alone was filled in the central well. Following that, All plated were incubated for 24hr. at 37°C. The antimicrobial activity was detected by measuring the inhibition zone that appeared around the well . Finally, The test was done in triplicate for each isolates and the mean of inhibition zone was calculated.

**Table (3):The Effect of [Ni(HL)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] and [Cu(HL)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]against Gram Negative bacteria**

Gram Negative Bacteria	Chemicals	Mean Inhibition zone* (mm) of a concentration(100%)	Mean Inhibition zone* (mm) of a concentration(50%)
<i>E. coli</i>	[Ni(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	18	12
	[Cu(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	-----	-----
<i>Klebsiella pneumoniae</i>	[Ni(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	15	12
	[Cu(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	-----	-----
<i>Salmonella typhimurium</i>	[Ni(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	12	-----
	[Cu(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	-----	-----

\* mean of triple measurements of inhibition zone

**Table (4):The Effect of [Ni(HL)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] and [Cu(HL)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]against Gram Positive bacteria**

Gram positive Bacteria	Chemicals	Mean Inhibition zone* (mm) of a concentration(100%)	Mean Inhibition zone* (mm) of a concentration(50%)
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<i>Enterococcus faecium</i>	[Ni(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	17	14
	[Cu(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	18	20
<i>Staphylococcus aureus</i>	[Ni(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	16	14
	[Cu(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	-----	-----

\* mean of triple measurements of inhibition zone

## Results and Discussion:

### FT-IR Spectra :

The FT-IR spectra are appeared an important information about functional groups of the complexes . The spectrum of ligand is given an absorption band at (3433)cm<sup>-1</sup> due to (OH)group of paracetamol[14], this band did not notice in spectra of complexes because of coordination [16] . Both bands at (1662 and 1597)cm<sup>-1</sup> attributed to (C=O) group at chalcone and amide[14] , which did not share of coordination[17] and absorption band at (1489)cm<sup>-1</sup> of (N=N) azo group[14] , which shifted towards lower frequencies in spectra of complexes [18] . In addition, there are new bands of (M-O) and (M-N) at spectra of complexes.

**Table (5): FTIR data of complexes**

Compound	$\nu$ (O-H) parace.	$\nu$ (H <sub>2</sub> O)	$\nu$ (C=O)chal. amide	$\nu$ (N=N)	$\nu$ (M-N)	$\nu$ (M-O)
[Mn(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	----	3406	1654 1597	1410	495	426
[Fe(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	-----	3414	1656 1593	1417	476	424
[Co(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	-----	3402	1653 1598	1409	497	430
[Ni(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	-----	3417	1654 1598	1408	482	428
[Cu(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	-----	3412	1658 1597	1411	443	422
[Pd(HL) <sub>2</sub> ]	-----	-----	1658 1598	1406	486	430

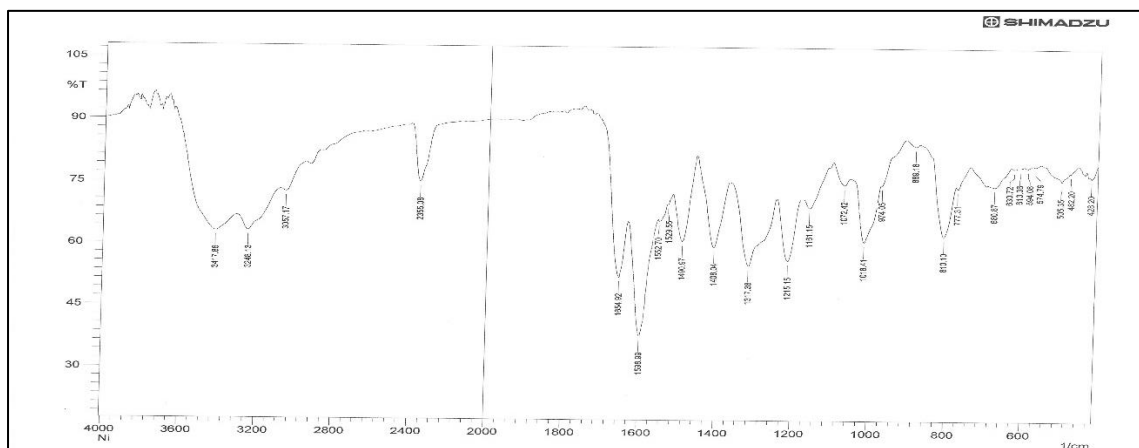


Fig. (1) FT-IR spectrum of  $[\text{Ni}(\text{HL})_2(\text{H}_2\text{O})]$

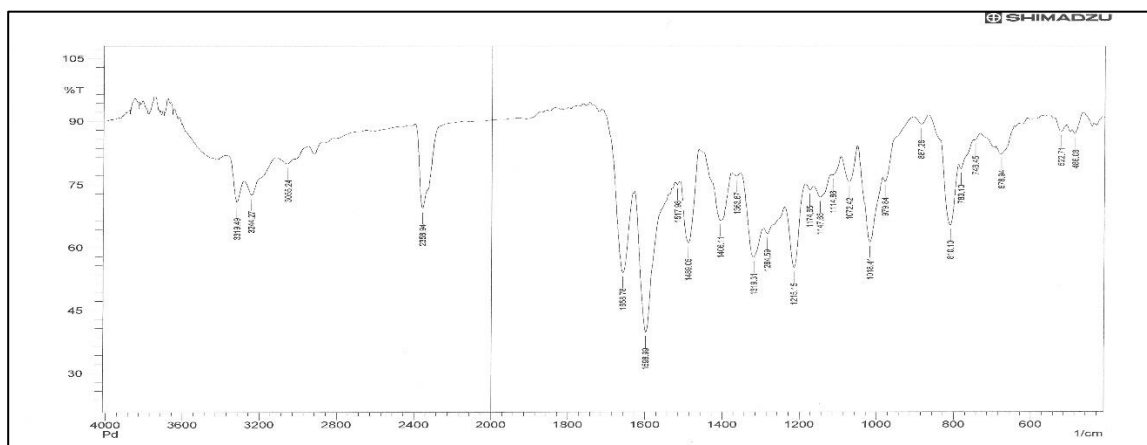


Fig. (2) FT-IR spectrum of  $[\text{Pd}(\text{HL})_2]$

### Electronic Spectra:

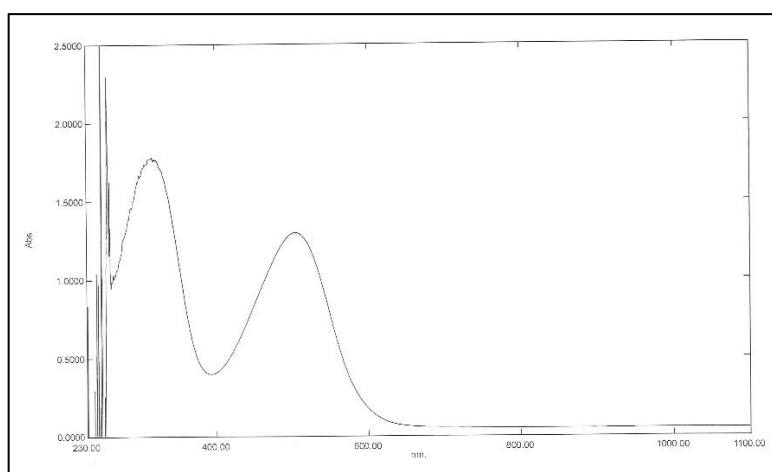
this study appears the main bands of complexes which shifted to higher wavelength compared with free ligand [14] for the reason of coordination [19] the table (6) shows this result.

### Molar Conductivity and Magnetic Measurement:

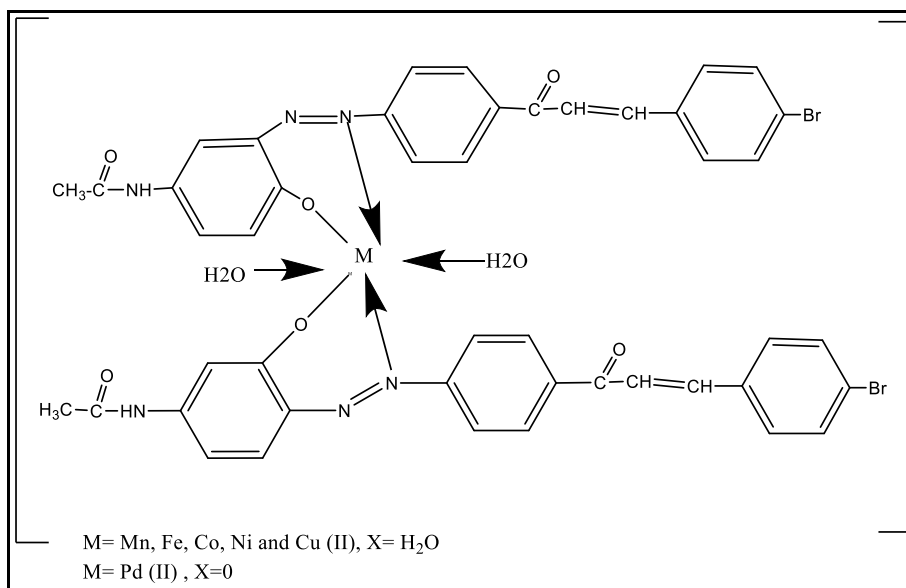
All complexes are solved in DMSO at ( $1 \times 10^{-3}$ )M and room temperature . The results indicated that, all complexes are non-electrolytic nature . In addition, the results appeared high spin with Para magnetic properties for Mn(II), Fe(II), Co(II), Ni(II) and Cu(II) complexes [20 ] . However, low spin with diamagnetic for Pd(II) complex , the table ( 6 ) recorded these results.

**Table (6): Electronic data (nm,  $\text{cm}^{-1}$ )Magnetic measurements, Geometry , Hybridization and Conductivity .**

Compounds	$\lambda_{\text{max}}$ (nm)	Absorption bands( $\text{cm}^{-1}$ )	Transitions	$\mu_{\text{eff}}$ (B.M)	Geometry	Hybridization	Conductivity $\text{S.mol}^{-1} . \text{cm}^2$
[Mn(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	508 396	19685 25252	M.L.C.T I.L.C.T.	5.32	Octahedral	Sp <sup>3</sup> d <sup>2</sup>	15.3
[Fe(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	529 324	18903 30864	M.L.C.T. I.L.C.T.	4.75	Octahedral	Sp <sup>3</sup> d <sup>2</sup>	16.8
[Co(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	504 343	19841 29154	M.L.C.T I.L.C.T.	3.73	Octahedral	Sp <sup>3</sup> d <sup>2</sup>	17.8
[Ni(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	507	19723	M.L.C.T.	2.73	Octahedral	Sp <sup>3</sup> d <sup>2</sup>	10.8
[Cu(HL) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	539	18552	M.L.C.T	1.82	Octahedral	Sp <sup>3</sup> d <sup>2</sup>	13.4
[Pd(HL) <sub>2</sub> ]	577	17331	<sup>1</sup> A <sub>1g</sub> → <sup>1</sup> B <sub>1g</sub>	Dia	Square planer	dsp <sup>2</sup>	12.3



**Fig.(3) UV-Vis. of [Co(HL)<sub>2</sub>(H<sub>2</sub>O)]**

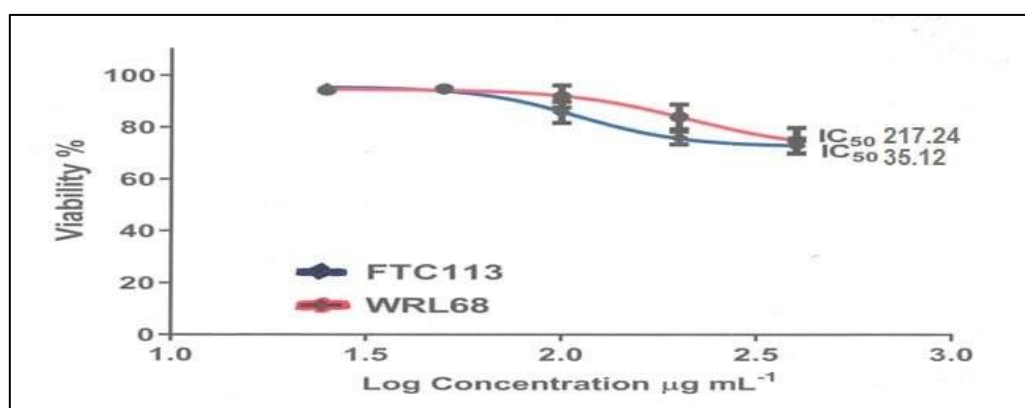


**Fig. (4): Suggestion geometry of complexes**

**Anti-biological studies:**

The results of anticancer demonstrated that, IC<sub>50</sub>= 35.12µg/ml for Thyroid cancer cells line (FTC113) . However, IC<sub>50</sub>= 217.24µg/ml for healthy cells line (WRL68) , which indicated that Pd(II)complex could be used as new medicine for this type of cancer .

In addition, Ni(II)complex was found to be active against *E. coli*, *Klebsiella pneumonia*, *Salmonella typhimurium* and *Staphylococcus aureus* . while, Cu (II)complex was active against *Enterococcus faecium* .



**Fig. (5):Anticancer activity data**

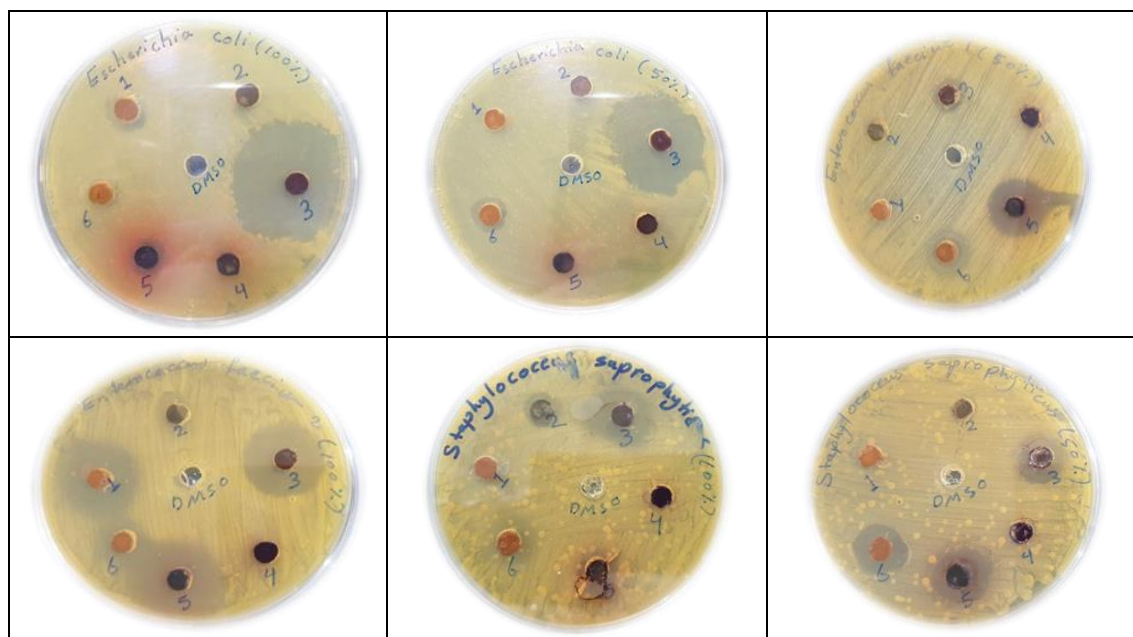


Fig. (6):Biological activity of Ni(II) and Cu(II) complexes against different types of Gram Negative and positive bacteria

### Conclusion:

From the above results , it could be concluded that, new complexes of (HL) ligand have been synthesized and characterized to suggest an Octahedral except Pd(II) complex was Square planer, which appears high activity against thyroid cancer cells line (FTC113) . However, Ni(II) complex and Cu(II) complex show antibacterial activity against different types of Gram Negative and positive bacteria .

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