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Synthesis, Characterization and Anticancer Study of New3-[(2Z)-2(2-hydroxybenzylidene) hydrazinyl]-5-(2-hydroxyphenyl)-1, 3, 4-oxadiazol-3-ium and its Transition Metal Complexes

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***Abstract*— A new ligand 2-{5-[2-(2-hydroxybenzylidene)hydrazinyl]-1,3,4-oxadiazol-2-yl}phenol (L) was prepared and characterized by Infrared Spectra, H1 Nuclear magnetic resonance, C13 Nuclear magnetic resonance , and mass spectroscopy. Ligand was used as chelating ligand to prepare some of transition metal complexes with Ni(II), Co(II), and Cr(III). The prepared complexes were characterized by FTIR, mass spectroscopy and conductance measurement. The hyper chem. program 7.51 was used for theoretical study using PM3 methodor the purpose of this study,. Regarding the information obtained about the complexes, we can suggest the octahedral geometry for Cr (III) complex, tetrahedral geometry for Co(II) and square planer for Ni(II). The effectiveness of these ligands against the breast cancer was studied and showed excellent results. The most active derivatives of 1,3,4-oxadiazole exceeded the effect of reference drugs, so they may become the main new anti-cancer drugs in the future.**

Keywords*— *Transitions metal complexes, anticancer, 1.3.4-oxadiazole

I. INTRODUCTION

1,3,4- oxadiazole as simple heterocyclic molecule has two nitrogen in 3,4 position, one oxygen in 1 position, p and two carbon atoms [1]. The Oxadiazoles have different isomeric forms such as 1,3,4-oxadiazoles , 1,2,3-oxadiazoles,1,2,4-oxadiazoles and 1,2,5-oxadiazoles as showen in figure (1) [2]. They have been known for more than eighty years.

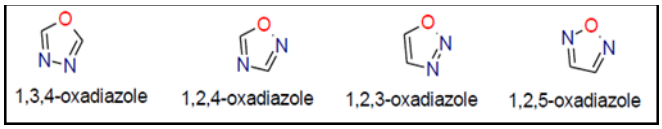

Figure 1: oxadiazole

1,3,4- oxadiazole is thermally stable and exists in two partially reduced form(2);2,3-dihydro 1,3,4- oxadiazole and (3) ;2,5 –dihydro 1,3,4-oxdiazole depending on the position of double bond. The completely reduced form of 1,3,4-oxadiazole as 2,3,4,5- tetrahydro 1,3,4-oxadiazole (4) as shown in figure (2) [3]

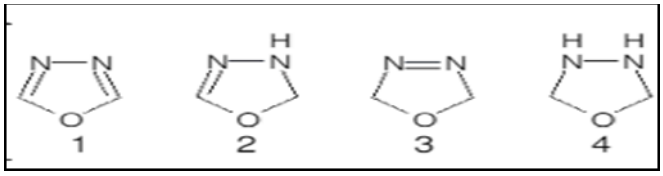

Figure 2: 1,3,4- oxadiazole

Because of the interesting activity of 2,5- disubstituted 1,3,4- oxadiazole biological agents focused on the current work. 1,3,4-oxadiazole moiety plays an important application in the field of biological activities as anticancer [4]. Cancer is one of the most difficult illnesses that affectspeople'life. Currently, there are no treatments or medications that are both practical and widely applicable. The world health organization (WHO) estimates that cancer is a significant health issue that affects more than 7 million people.The biological activities of 1,3,4- oxadiazole are , anti-inflammatory , antiviral antimicrobial , antineoplastic, and fungicidal . and tyrosine's inhibition [11,12]

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II. EXPREIMENTAL PART

All chemicals that were used in this study were supplied by Sigma Aldrich, TCI and Merck without additional purification. Also, some metal salts, like chloride, were used.

The ligand was prepared as follows:-

A. Synthesis of 2-hydroxybenzohydrazide (A)

A mixture of methyl 2-hydroxybenzoate(27.2ml-0,2mol) and hydrazine monohydrate (15ml-0,2mol) in absolute ethanol (100 ml) were refluxed for 6 hours, the mixture was evaporated to half volume, cooled, filtered and washed with absolute ethanol [13], the crystals (A) was lighting white.

B. Synthesis of 2-(5-Sulfanyl-1, 3, 4-oxadizol-2-yl) phenol (B).

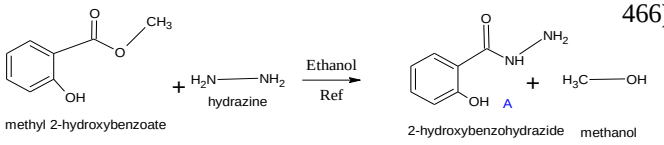
A mixture of 2-hydroxybenzohydrazide (A) (15.2gm, 0.1 mol), potassium hydroxide (5.6 gm., 0.1 mol) and carbon disulfide (6ml, 0.1 mol) were refluxed in absolute ethanol (100 ml). Then, the prepared solvent was evaporated and acidified with HCl (10%). The precipitate was filtered followed by recrystallization from ethanol absolute[14]. The solid (B) was white yellowish.

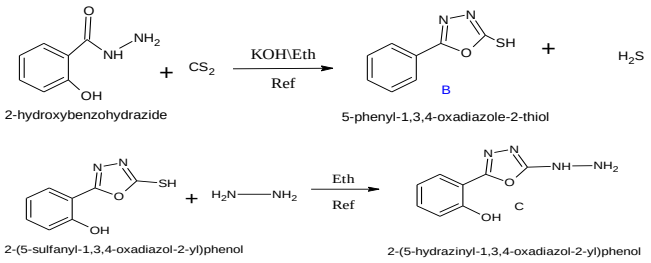
C. Synthesis of 2-(5-hydrazinyl -1,3,4-oxadiazol-2-yl) phenol (C)

2-(5-Sulfanyl-1, 3, 4-oxadizol-2-yl) phenol (B) (6.5gm, 0.028mol) and hydrazine monohydrate (5ml p, 0.057mol) in ethanol absolute as solvent (40ml) were refluxed for 36 hours. White precipitate was appeared [15, 16]. The precipitate was filtered and recrystallized from absolute ethanol.

D. Synthesis of3-[(2Z)-2(2-hydroxybenzylidene) hydrazine]-5-(2- hydroxyphenyl)-1, 3, 4-oxadiazol-3-ium (L) .

The ligand was synthesized by condensation of (2gm-0.01mole) of2-(5-hydrazinyl -1,3,4-oxadiazol-2-yl)phenol (C) and (1.26ml 0.01mol)2-hydroxybenzaldehyde in absolute ethanol (50 ml). Then, the mixture was refluxed for 10 hours. The ligand was precipitated, filtered and recrystallized from absolute ethanol to get yellow-.





E. Synthesis of complex

The complexes were synthesized by mixing of (0.0013 mol-2,6gm) from the ligand with salts (COCl2.6H2O, CrCl3.6H2O, and NiCl2.6H2O) in (5ml) absolute ethanol and refluxed for3hrs. The precipitate was filtered and washed several times with ethanol or aqueous ethanol to removed unreacted salts or ligand, then the precipitated complexes were dried.

III. ANALYSIS AND PHYSICAL MEASUREMENT

Table 1: physical properties of the ligand and its complexes

No	formula	Color	M.Wt	M.p °C
1	$C_{15}H_{12}N_4O_4$	white	296	230
2	[Cr(L)]Cl_3	green	453	323
3	[Co (L) Cl_2]H_{2O}	Black	426	215
4	[Ni(L)Cl_2]	Light green	425	220

IV. RESULT AND DISCUSSION

- FT-IR spectral

FT-IR spectroscopy is one of the important tool which was used for the -characterization of functional groups in the prepared ligand and was carried out using a KBr disc. The free ligand (L) exhibited nine major bands at (3417), (3200), (3095),(2933),(1622), (1582),(1599), (1271), and (1359) cm-1. Which are corresponding with (υO-H), (υN-H), (υC-H aro), (υC-H Elaf) (υC=N)oxo, (υC=N)endo,(υC=C), (υC-N-C)sym, (υ C-N-C)asy structure movement bands respectively, as shown in table (2) and figure(3). New bands were formed corresponding with the coordinated (M- N) and (M-O) bonds and shown at the region (476-561) cm-1, (463-466) cm-1respectively [17].

Table 2: IR spectra of L and its metal complexes

	OH	NH	C-H Ar	C=N exo	C=C Ar	C=N HETRO	C-O-C ASY	C-O-C SY		M-N	M-O
L	3417	3200	3095	1622	1599	1582	1359	1271	1153		
LCr	3400	3295	3089	1615	1582	1537	1379	1247	1062	476	466
LCo	3413	3200	3099	1600	1582	1504	1310	1245	1075	537	463
LNi	3414	3239	3099	1599	1561	1536	1311	1293	1034	561	464

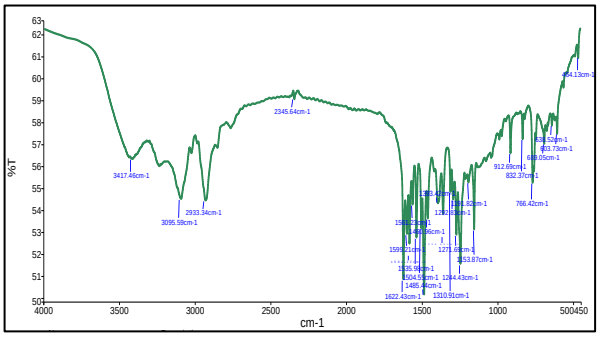


Figure 3: IR Spectra of the ligand

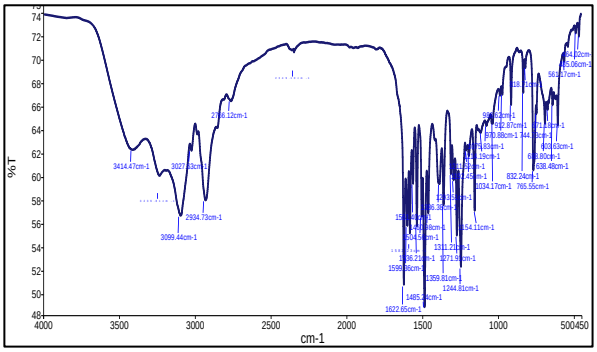


Figure 4: IR Spectra of the Cr Complex

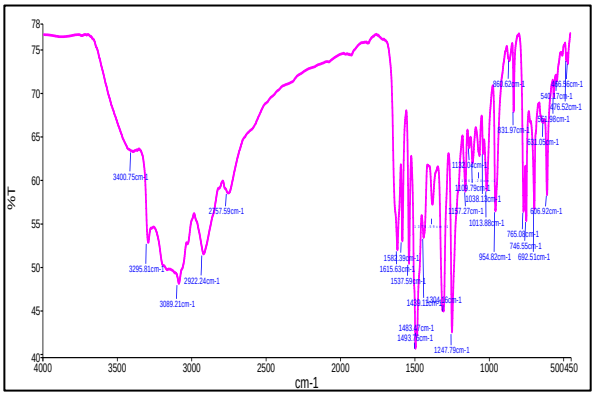


Figure 5: IR Spectra of the CO Complex

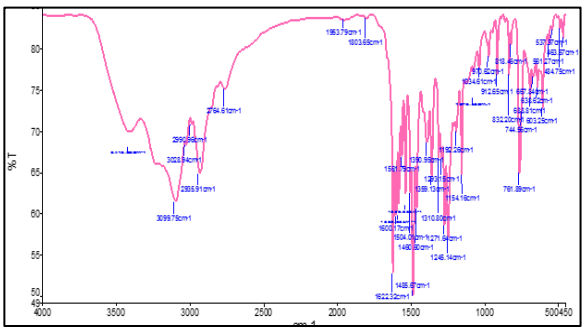


Figure 6: IR Spectra of the Ni Complex Nuclear

- Magnetic Resonance

The H1-NMR spectra of the ligand showed signals

- at (14.1ppm,S, H)due to N-Hproton,(9.79ppm,S,1H) due to the role of proton of azo methanegroup (-N=CH-),(10.45ppm,S,1H)(10.14,S,1H) due to Tow OH
- groups ,(6.87-7.64ppm,8H)due to protons of aromatic ring

As showing in the figure below [figure 7][18]

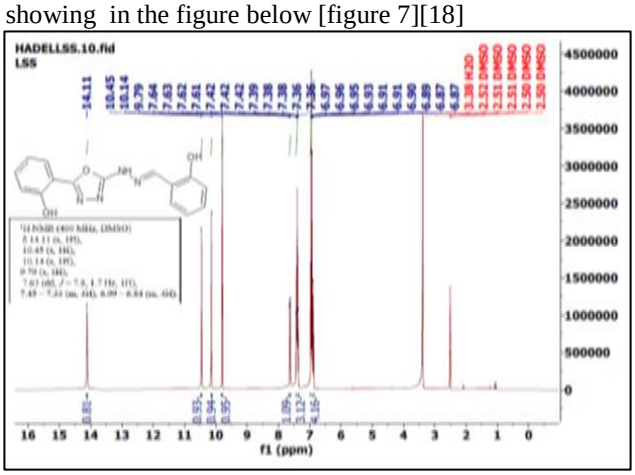


Figure7: 1HNMR Spectra of the ligand

- C13 –NMR

The C13 –NMR of the ligand gave recognizable signals at(122-113) ppm due to carbon atoms (C3-5, C11-13) which returns to Aromatic ring. another two chemical shift values observed at (132, 134) are assigned for (C6 ,C14) respectively. The spectra showed important signals at 147, 148 and 149 ppm attributed to C2, C1 and C10 respectively. In additional, three chemical shift observed at 158 , 163 and 165 ppm due to C7 ,C9 and C8.the signal at 193 ppm It may return to the C8 as a result of totumerism process nitrogen atoms as showmen in figures (8) [19].

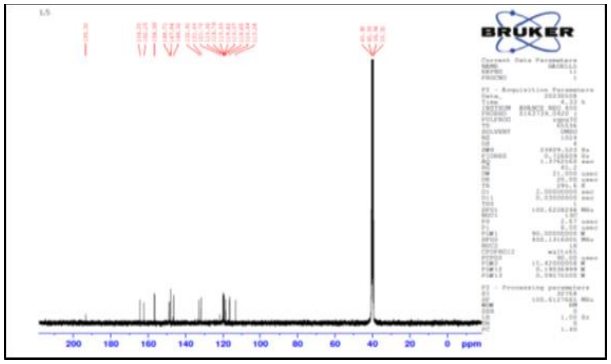


Figure8: C^{13}-NMR Spectra of the ligand

- Mass spectra

Mass spectra of the prepared ligand and its transition metal Complex were recorded at room temperature , the Mass spectra of the ligand showed a molecular ion peak At 296 m/z which is its molecular formula [C15H12N4O3] +. the spectra showed anther beak at) 203 m/z,191 m/z,177 m/, 145 m/z, 135 m/z, 93m/z (due to[C9H7N4O2]+C8H7N4O2]+,[C8H7N3O2]+,[C8H5 N2O] + [C7H8N2O]+,[C6H6O]+.respectively.[20]

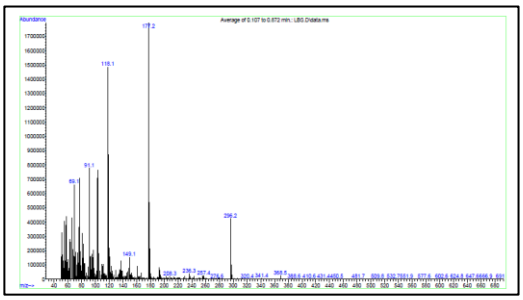


Figure 9: MASS Spectra of the Ligand

Figure 10 illustrates the mass spectrum of the Ni(II) complex [Ni (L) Cl2] .The complex was identified by a peak at 425 m/z .

Other distinctive peaks at 390 and 354 m/z which indicates loss the chloride ion the spectra shown a peak at 296m/z that is equivalent to the molecular mass of the ligand.

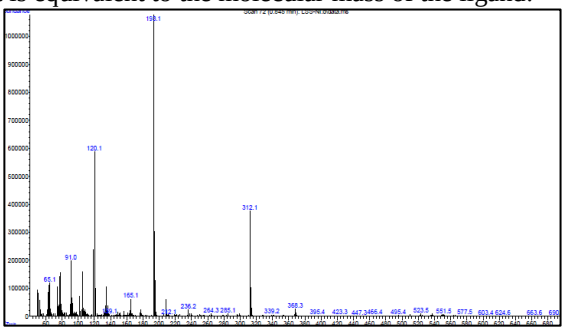


Figure 10:MASS Spectra of the Ni Complex

Figure 11 depicts the mass spectrum of the [Co (L) Cl2] complex [. The complex was identified by a peak at 426 m/z .

Other distinctive peaks at 390 and 355 m/z which indicates lose the chloride ione. The spectra shown a peak at 296m/z that is equivalent to the molecular mass of the ligand.

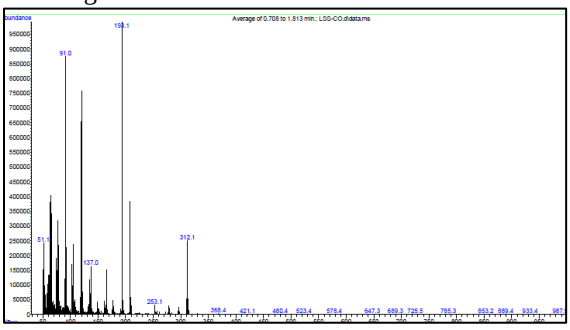


Figure 11: MASS Spectra of the CO Complex

Figure 12 depicts the electron impact mass spectrum of the [Cr (L) Cl3] complex. The complex was identified by peaks at 419, 383 and 348 m/z which indicates loss the free chloride ion. The spectra shown peak at 296m/z that is equivalent to the molecular mass of the free ligand.

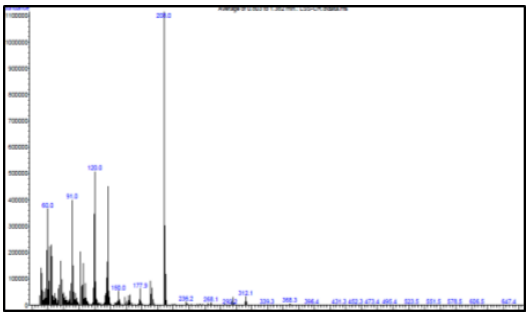


Figure 12:MASS Spectra of the Cr Complex

- Molar Conductivity

The molar conductance for all complexes have been measured. All of them showed. a low molar conductance (18-25) ohm-1 .cm^2. $mole^{-1}$ because there is no chloride ion of the coordination ball as explained. in table (3).

Table (3) Molar Conductivity values

complexes	Λ_M ohm^{-1} .cm^2. $mole^{-1}$
$[CrL_1Cl_3]$	20
$[NiL_1Cl_2]$	22
$[CoL_1Cl_2]$	18

- Anti-cancer activity

Molecules that contain 1,3,4- oxadiazole derivatives in their structure can be diagnosed by multidirectional biological activity.

The anti- Reproduction effects of oxadiazole derivatives are associated with different mechanics, such as inhibition of growth factors, enzymes and others. The activities of these compounds were tested on cell lines of various cancers. In most publications, the most active derivatives of 1,3,4-oxadiazole exceeded the effect of reference drugs, so they may become the main new anti-cancer drugs in the future. The new ligand has a high anti- cancer activity. Breast cancer (MCF-7) was tested for the prepared sample. We found the prepared compound has high effect on the cancer cells and a mild effect on normal cells, as shown in table (4) and figure (13).

Table (4): The cytotoxic effect of L on WRL68 and MCF-7 cell line

Concentration µg mL^{-1}	Mean viability(%)±SD	
	HdFn	MCF-7
400	51.50±4.68	54.784±2.43
200	70.13±4.51	61.92±2.02
100	75.46±1.00	75.8±3.64
50	91.85±5.68	82.98±10.74
25	95.21±0.82	85.031±1.98

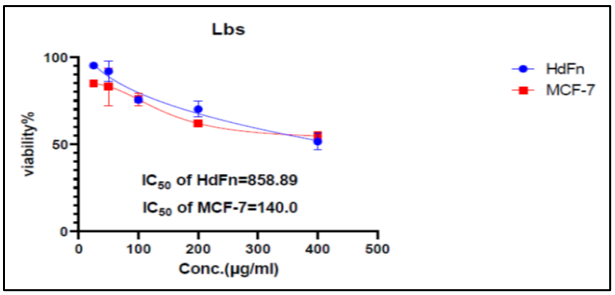


Fig 13: The cytotoxic effect of L on WRL68 and MCF-7 cell line.

- Electrostatic potential (MEP) Molecular:

The hyper-chem. program drew the optimization structure of the ligand and found the electrostatic potential, which is considered important to find the active site in the free ligand as shown in the figure

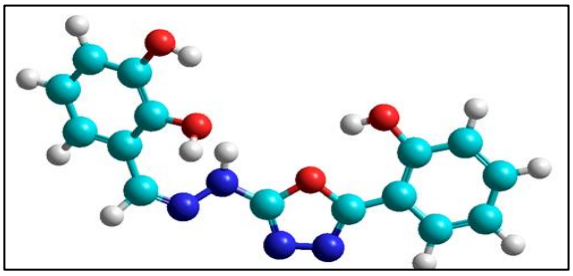


Figure (14). Graphical presentation of the stereochemistry of the Ligand

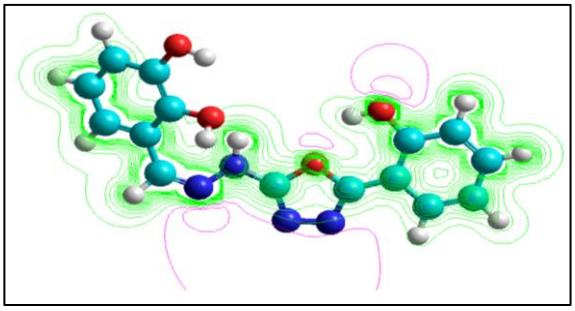


Figure (15). Electrostatic potential 2D counter of ligand

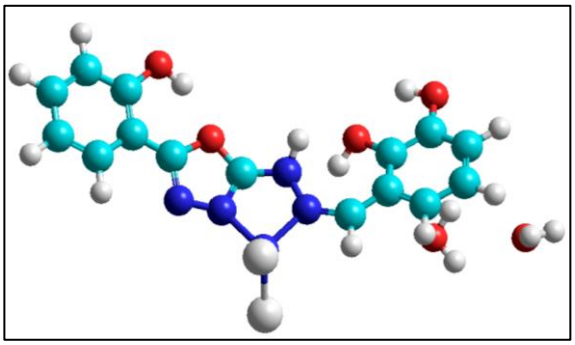


Figure (16). Graphical presentation of the stereochemistry of the [CO L Cl_2]

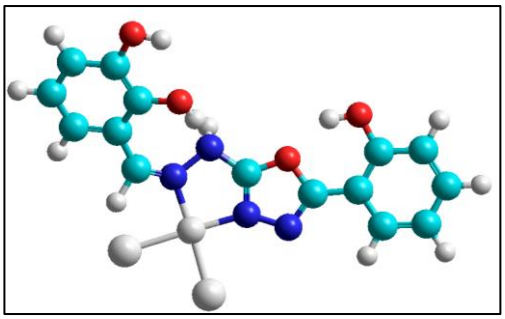


Figure (17). Graphical presentation of the stereochemistry of the [Ni) L (Cl2]

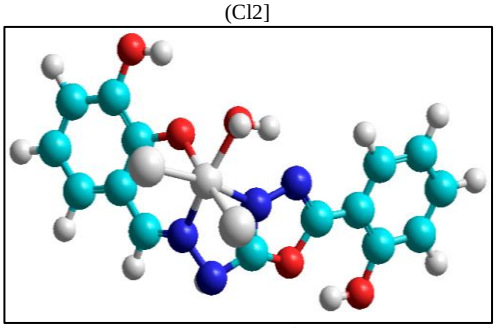


Figure (18). Graphical presentation of the stereochemistry of the [Cr) L (Cl3]

Note:: Ni: White color, Co: blue color , Cr: White color , Cl: White color

V. CONCLUSION

Many research is interested in synthesis 2-{5-[2-(2-hydroxybenzylidene)hydrazinyl]-1,3,4-oxadiazol-2-yl}phenol and its some transition metal complexes . In this study, We were able to synthesize a new 1.3.4-oxdiazole as ligand. Three complexes with transition elements (Cr3+, CO2+ ,Ni2+) were also prepared. The ligands and their complexes were identified using spectroscopic methods, This characterization confirmed the validity of the proposed structures. The Hypercom program through the use of the PM3 method, gave the ideal form and the electronic density of the atoms was drawn to know which of the atoms is ready for complexes. A study of the anti-cancer activity of the ligand was conducted. our study showed good efficacy of our results against cancer cells. It was noted that the amount of toxicity was low.

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