

Synthesis of Mixed Ligand Complexes of M(II) Dithiocarbamato Derivative and 2,2'-bipyridyl and Study their Cytotoxic Effect Against HepG2 Cell Line *in vitro*

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Abstract:

Mixed ligand of Co and Ni (II) complexes were prepared from [5-(*p*-nitrophenyl)-4'-phenyl-1,2,4-triazole-3-dithiocarbamato hydrazide](TRZ.DTC) as primary ligand and 2,2'-bipyridyl (bipy) as a co-ligand with metal salts. These complexes were analytically and spectroscopically characterized in solid state by elemental analyses, flame atomic absorption, magnetic susceptibility and molar conductance measurements, as well as by UV-Vis and FTIR spectroscopy. Infrared, ultra violet spectra reveal a bidentate coordination of the two ligands with metal ions 1:1:1 mole ratio. Room temperature magnetic moments and solid reflectance spectra data indicate paramagnetic complexes with five-coordinate square pyramidal geometry for nickel (II) complex, while six-coordinate octahedral geometry for cobalt (II) complex in solid state. The mixed ligand and its respective complexes were screened for cytotoxicity assay on human HepG2 cell line using cis-Pt drug as a control positive following the cell culture method for 3 days after treatment with the tested compounds using eight different concentrations. The bioassay results showed good inhibition activity of these synthetic compounds especially Ni (II) complex on selected cell lines comparable with standard drug.

Key words: Mixed ligand , dithiocarbamato, HepG2, cytotoxicity assay, cis-Pt

Introduction:

Dithiocarbamates and their metal complexes have invited much research attention due to their diverse applications and interesting biological, structural, magnetic, electrochemical and thermal properties [1-3]. Dithiocarbamates comprise a group of ligands with great binding potential to metals and as such find wide use in coordination chemistry [4]. The strong metal binding properties of dithiocarbamates are directly related to their possession of two donor sulphur atoms [5]. Metal complexes of dithiocarbamates with nitrogenous bases such as pyridine, picoline, 1,10-phenanthroline and 2,2'-bipyridine,

phosphine and its derivatives have been reported [6,7]. Some metal complexes of DTC used in medical applications like in health care for the management of alcoholism [8], also dithiocarbamates have been applied to prevent arthrosclerosis [9]. Their antimicrobial activity, anti-inflammatory and metal transport in membranes have been reported [10]. Studies on sulfur-bonding chemo protective agents have suggested that dithiocarbamates are the best rescue agents in S-donor series of thiourea, thiosulfate and glutathione against cisplatin toxicity [11] because they have the ability to stabilize transition metals in a wide range of

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oxidation states [12]. In view of the wide range of applications of dithiocarbamates and various aspects of bioactivity of Schiff bases, we report in this paper the synthesis and characterization of nickel and cobalt (II) mixed ligand complexes of the type [Ni(TRZ.DTC) (bipy) ONO₂].H₂O and [Co(TRZ.DTC) (bipy)(H₂O) Cl]. EtOH where: TRZ.DTC=5-(*p*-nitrophenyl)-4'-phenyl-1,2,4-triazole -3-dithiocarbamato hydrazide] and bipy=2,2'-bipyridyl (Schiff base). Antitumor activities of this mixed ligand and their metal complexes were investigated *in vitro*.

Materials and Methods:

Instrumentations

All the reagents and the solvents except starting materials were purchased commercially and used without any further purification. The (CHNS) contents of the compounds were determined using elemental analyses by standard micro-methods with an Elemental EM-017 analyzer. The metal analysis of the separated solid chelates for metal content was performed by using AA-680 Shimadzu Atomic Absorption Spectrophotometer. Electronic spectra were recorded using dimethylformamide solutions in 1 cm cell with a Shimadzu UV-160 Spectrophotometer. FTIR spectra were scanned as a CsI and KBr discs using IR Prestige-21 spectrophotometer in the 4000-200 and 4000-400 cm⁻¹ region. Magnetic susceptibility measurements of the complexes in solid state were carried out at room temperature with Burkert BM6 instrumentation. The conductivity measurements were made

using WTW conductmeter type, using approximately 10⁻³ M solution of the complexes in DMF. Melting point apparatus of Gallen Kamp M. F. B-60 was used to measure melting points of all prepared compounds. Carbon dioxide incubator (SANYO, incubator Japan) was used to keep the cells used in this study as well as Inverted Microscope (MEJI, Japan), and Centrifuge (Eppendorf, Germany) were used in cytotoxicity part. Optical density of each well in cell culture plates was read by using micro ELISA reader (ASYS, Austria) at a transmitting wave length on 492nm.

Ligand synthesis

A reported method [13] was used to prepare the Sodium [5-(*p*-nitrophenyl)-4'-phenyl-1,2,4-triazole -3-dithiocarbamato hydrazide] (TRZ.DTC) as primary ligand.

Complexes synthesis

The Co and Ni(II) complexes were prepared from Sodium (TRZ.DTC 15 ml) and (bipy 5 ml) as mixed ligand dissolved in alcoholic media and added to (5 ml) of ethanolic solution of metal salts gradually in a molar ratio 1:1:1 (M: TRZ. DTC: bipy). Reaction mixture was heated under reflux for 45 minutes with stirring, then left to cool at room temperature. The resulting colored precipitate was separated by filtration, washed with water and recrystallized with small amount of ethanol, then collected and left to dry in air. Complete drying was done using an oven at 50 °C for 1 hr. Some physical properties are listed in (Table 1).

Table (1): Some physical and analytical properties of ligands and its metal complexes

Comp.	Color	m.p °C	Yield %	M.Wt g/mole	Elemental and metal analysis found (Calc.)				
					C	H	N	S	M
(TRZ.DTC)	Light orange	66-68	88.5	394.4	45.84 (45.63)	3.05 (2.78)	21.99 (21.29)	16.80 (16.22)	----
(bipy)	White	70-72	----	156.19	----	----	----	----	----
Ni (TRZ.DTC) (bipy)	Dark orange	231d	88	639.77	45.93 (45.02)	3.69 (3.15)	18.55 (18.91)	10.24 (9.60)	9.23 (8.80)
Co (TRZ.DTC) (bipy)	Brown	254d	80	686.02	47.02 (47.22)	3.65 (3.64)	13.89 (13.99)	9.03 (9.32)	9.13 (8.60)

d= decomposition degree

Method of cytotoxicity assay

The human tumor cell line HepG2 used in the present study was obtained from Biotechnology Research Center Al-Nahrain University. The cells were maintained as attached type in DMEM supplemented with 10 % FBS, 50 mg/ml streptomycin and 1000U/L penicillin. Single cell suspension was prepared by treating 25 cm³ flask of tissue culture at passage 10 with 2 ml 25% trypsin solution incubated for 2 min at 37°C in an incubator, after detachment of the cells from the flask surface single cell suspension made by gently taping of the flask followed by addition of 20 ml of growth medium. Then, the viability and counting of the cells was made by using trypan blue dye which stains the dead cells. Cell suspension was well mixed followed by transferring 200 µl/well of the 96 well flat bottom plate using automatic micropipette containing (1x10⁴ cell/well). Plates were incubated at 37°C for 24 hrs in an incubator supplemented with (5%) CO₂ until 60-70% confluence of the internal surface

area of the well for HepG2 cell lines. The cells were then exposed to different concentrations (2000, 1000, 500, 250, 125, 62.5, 31.25 & 15.625 µg/ml) respectively of new synthesized compounds, each compound was added to the cells in triplicate form of each concentration, cisplatin added as a positive control; Only cells incubated with culture media represented the negative control, the plate incubated at 37°C for 72 hrs and checked daily for any changes in morphology. After elapsing the incubation period, the culture medium was discarded from micro titer plates, 50 µl/well of neutral red dye solution was added to wells and the plates were incubated for 2 hrs. Plates were washed gently with phosphate buffered saline (PBS) and 100 µl/well of elution buffer was added. Then plates were examined by ELISA reader at 492nm, only viable cells were able to take the stain while the dead cells were not. The inhibition percentage was measured according to Gao *et al* equation [14] as follows:-

$$\text{Inhibition rate\%} = \frac{\text{Absorbance of negative control} - \text{Absorbance of test}}{\text{Absorbance of negative control}} \times 100$$

Statistical analysis

Data were analyzed by 2-way analysis of variance with ANOVA- test, and presented as means \pm SD. The level of significance $P < 0.05$ was used for analysis of variance test (ANOVA).

Results and Discussion:

The microanalytical data listed in (Table 1) reveals that the experimental values are in approximate agreement with the theoretically calculated values correspond to the suggested compositions. The complexes are stable to moisture and heat for extended periods. The complexes are amorphous powders, soluble in organic solvents like (DMF and DMSO). The molar conductance of 10^{-3} M solutions of the complexes in DMF is indicated of their non-electrolytic nature of both complexes.

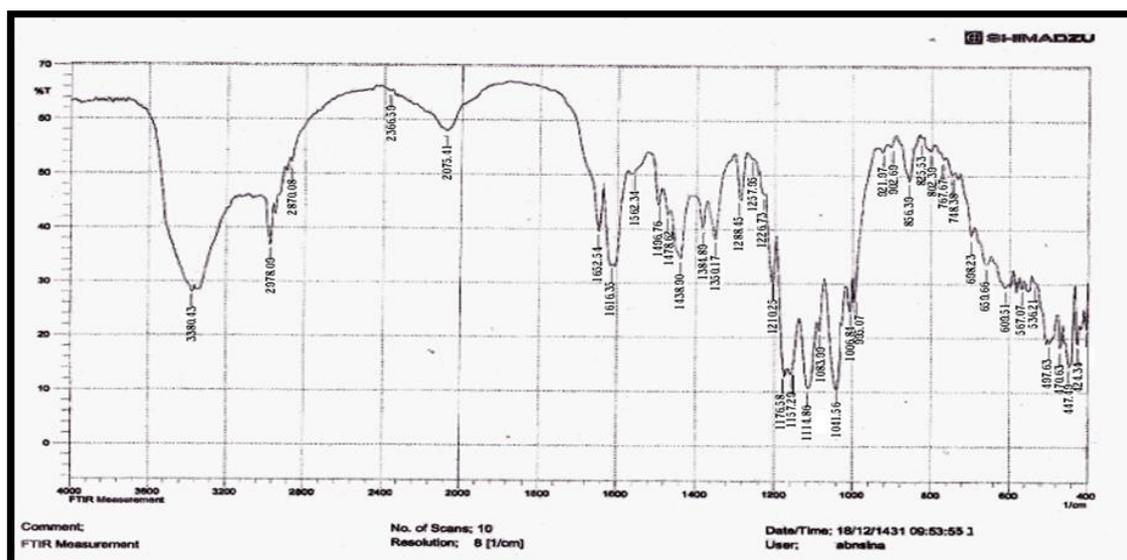
FTIR characterization

FTIR spectral data for free ligands as well as Co and Ni (II) complexes are reported in (Table 2), FTIR spectra of free ligands and their metal complexes were analyzed to get information of active coordination sites of ligands with metal ions. The region (950-1050) cm^{-1} is considered as a characteristic for the nature of binding of the dithiocarbamate moiety. According to the criterion of Bonati and Ugo [15], the presence of a solitary band in the above region is due to symmetrical bidentate coordination of the dithiocarbamate group while the splitting of this band within a narrow range of ± 20 cm^{-1} is due to the asymmetrical ambidentate or monodentate nature of the dithiocarbamate group in the metal complexes. The C-S stretching band at 995 cm^{-1} in the spectra of (TRZ.DTC) shows a negative shift ~ 25 cm^{-1} in the

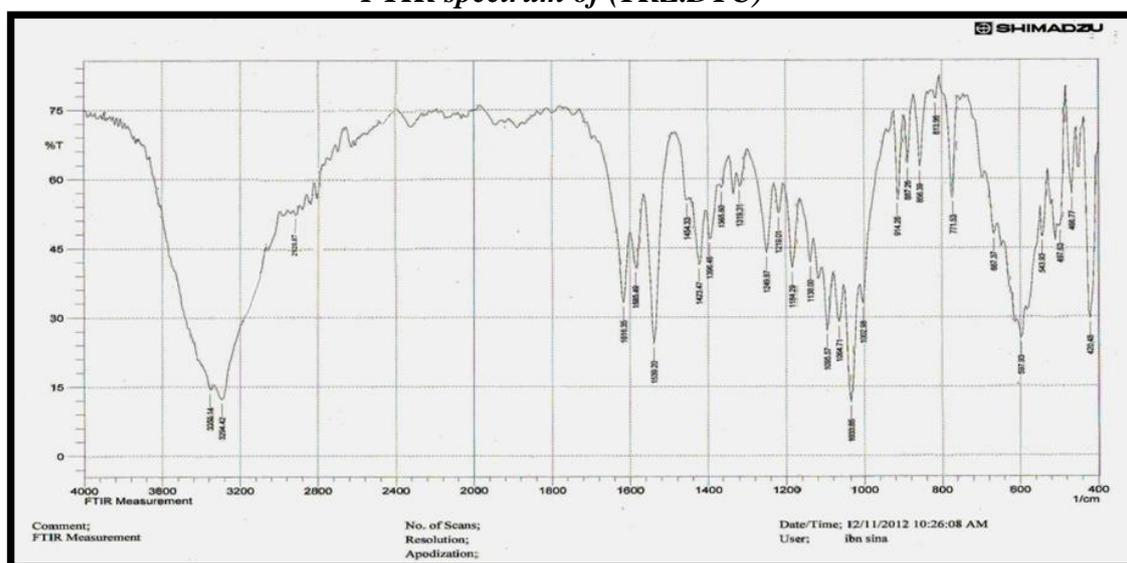
spectra of both complexes, another band appeared at 1041 cm^{-1} indicate to the stretching frequency of C=S band of the free ligand which also undergoes shift toward lower frequencies in all complexes between 23-39 cm^{-1} and these results refer to the involvement of the DTC group by two S atoms in coordination. The ν C-N appeared in the region (1450-1550) cm^{-1} as thioureide band [16], it can appear outside the region proposed in the literature at lower frequencies, especially when the S_2CN group attached to the N atom is an aryl or H [17]. A ν C=N band at (1438-1442) cm^{-1} region was observed [16], while the band at (1496) cm^{-1} of ν N-N mode remained unchanged in both complexes. The FTIR of (TRZ.DTC) ligand show stretching and bending bands of $\text{NH}_{(1,2)}$ at 3380 and 1652 cm^{-1} respectively, which undergoes a slight shift about (± 5) cm^{-1} in both complexes which did not support the coordination ligand with central metal ion by these groups. The position of the bands found in the spectrum of 2,2'-bipyridyl exhibit bands at 1604-1450 cm^{-1} region which due to stretching band of ν C=C + C=N has been completely changed in the spectra of the complexes where it is used as a co-ligand, an additional band at 265 and 270 cm^{-1} in the spectra of both complexes also confirms the coordination of bipyridyl- nitrogen with metal ion [18]. The presence of uncoordination EtOH or H_2O which supported by the observed a stretching band at (3421-3471) cm^{-1} in the spectra of metal complexes assigned to the ν -OH group. Some new non-ligand bands appeared in the far IR region around 524-265 cm^{-1} were noticed in the spectra of metal complexes, are assigned to $\nu(\text{M-O})$, $\nu(\text{M-S})$, $\nu(\text{M-Cl})$ and $\nu(\text{M-N})$ respectively [19].

Table (2): Main FTIR bands (cm⁻¹) of the mixed ligand and its complexes.

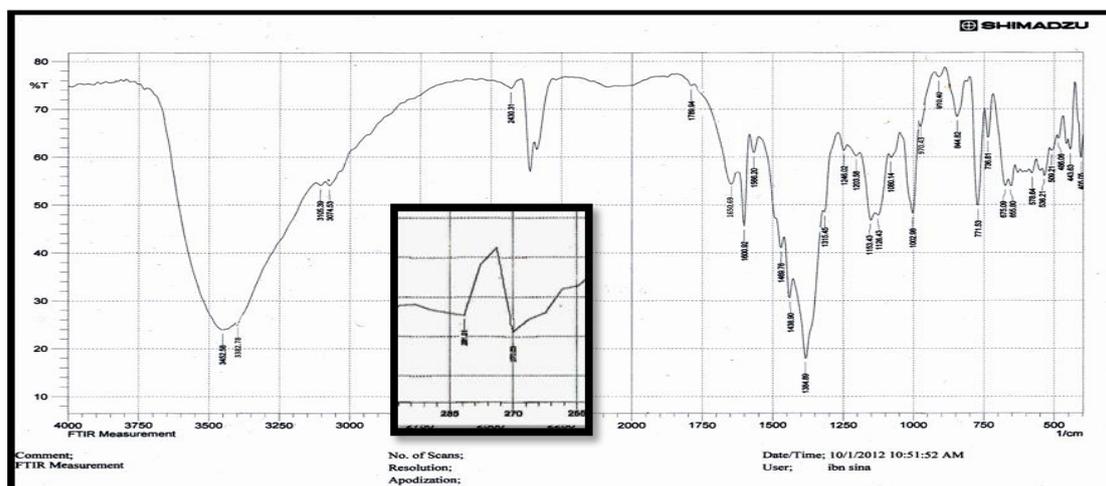
Comp.	$\nu\text{NH}_{(1,2)}$	$\delta\text{NH}_{(1,2)}$	$\nu\text{C}=\text{S}$	$\nu\text{C}-\text{S}$	$\nu\text{N}-\text{N}$	$\nu\text{C}-\text{N}$	$\nu\text{C}=\text{C}+\text{C}=\text{N}$ (bipy)	$\nu\text{M}-\text{S}$	$\nu\text{M}-\text{N}$	$\nu\text{M}-\text{O}$	Others
(TRZ.DTC)	3380 3380	1652 1652	1041	995	1496	1438	---	---	---	---	---
(bipy)	---	---	---	---	---	---	1604,1519, 1481, 1450	---	---	---	---
Ni (TRZ.DTC) (bipy)	3382 3382	1650 1650	1002	970	1496	1438	1600,1566, 1469, 1438	443	270	524	$\nu\text{OH}=\text{}$ 3452
Co (TRZ.DTC) (bipy)	3378 3378	1650 1650	1018	972	1496	1442	1608,1566, 1469, 1442	432	265	505	$\delta\text{H}_2\text{O}=\text{}$ 891 $\nu\text{OH}=\text{}$ 3471 $\nu\text{Co}-\text{Cl}=\text{}$ 324



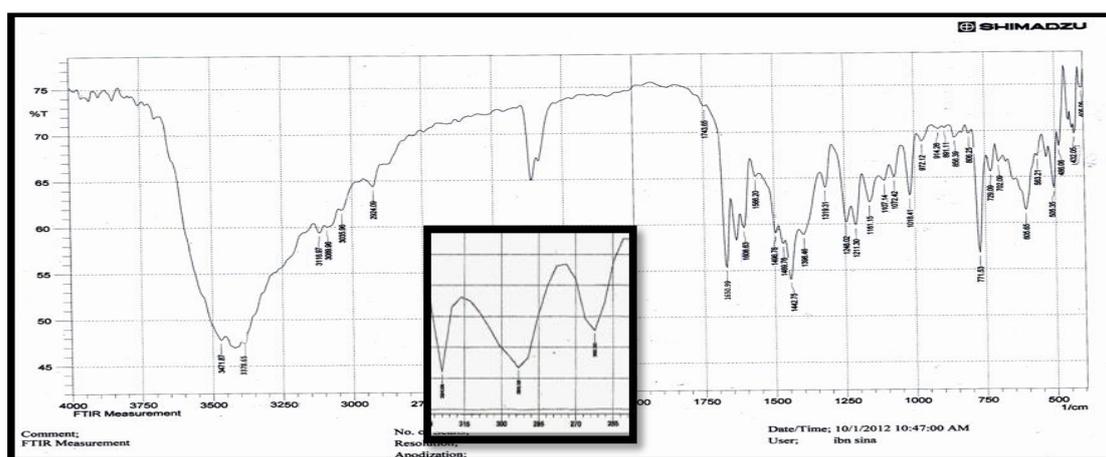
FTIR spectrum of (TRZ.DTC)



FTIR spectrum of (bipy)



FTIR spectrum of Ni(II) Complex



FTIR spectrum of Co(II) Complex

Magnetic susceptibility and conductivity measurement

The experimentally determined value of magnetic moment for each complex is listed in (Table 3). Magnetic measurements are widely used in studying transition metal complexes. The magnetic properties are due to the presence of unpaired electrons in partially filled d-orbital in outer shell of the metal ion in the complex. The magnetic moment for Co (II) complex is approximately 4.84 B.M. higher than spin value of cobalt (II) ion only, this result indicates a higher orbital contribution octahedral structure [20], while the value of Ni (II) is approximately 3.52 B.M. led to suggest the square pyramidal structure of this complex in solid state [21].

Electronic characterization

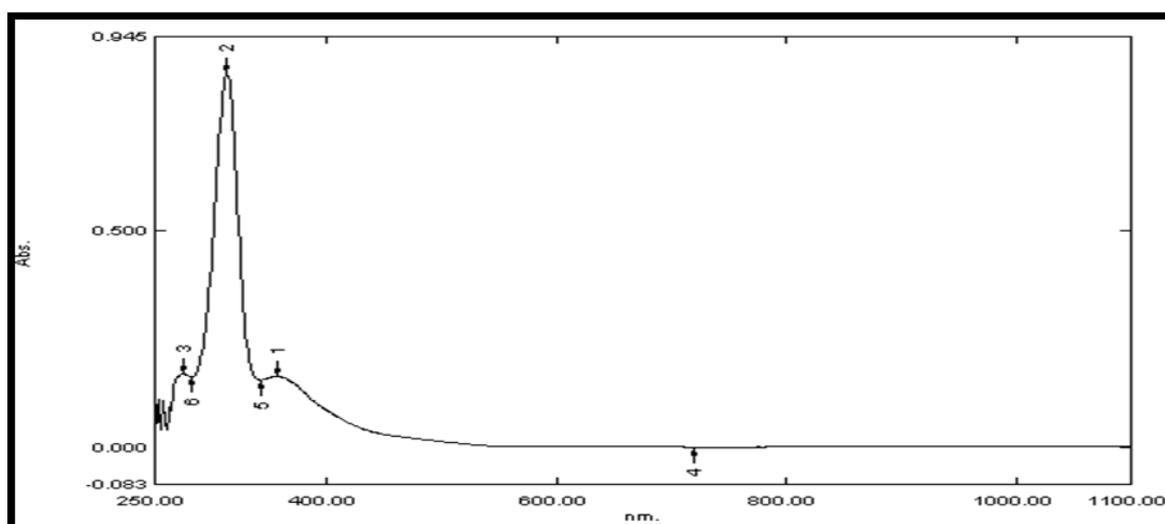
The electronic spectra of compounds as solution were recorded in DMF solvent. The electronic spectrum of primary free ligand (TRZ.DTC) exhibited three main bands. These absorption bands appeared at 266, 312, and 353 nm due to interligand ($\pi \rightarrow \pi^*$), ($\pi \rightarrow \pi^*$) and ($n \rightarrow \pi^*$) transition located on the $\text{N}=\text{C}=\text{S}$, and sulphur atoms respectively [22, 23]. While the electronic spectra of co-ligand (bipy) showed two main bands, the first appeared at 243 nm indicating to interligand ($\pi \rightarrow \pi^*$) transition located on $-\text{N}=\text{C}-$ group. The second absorption band appeared at 397 nm arises from ($n \rightarrow \pi^*$) refers to nitrogen of $-\text{N}=\text{C}-$ group [24]. The Cobalt (II) complex

exhibited two distinct bands at 1033 and 462 nm corresponding to ${}^4T_{1g} \rightarrow {}^4T_{2g}$ (ν_1) and ${}^4T_{1g} \rightarrow {}^4T_{1g(P)}$ (ν_3) transitions respectively, which suggests an octahedral geometry around the cobalt (II) ion [20, 25]. The ν_2 band that involves two-electron transitions did not observed in spectrum because of its approximately to strong ν_3 transition [25], ligand field parameter can be shown in (Table 3). The electronic spectrum of nickel (II) complex showed d-d bands in the region 915, 608, and 377 nm respectively. These are interpreted to the ${}^3A_{2g} \rightarrow {}^3T_{2g}$ (ν_1),

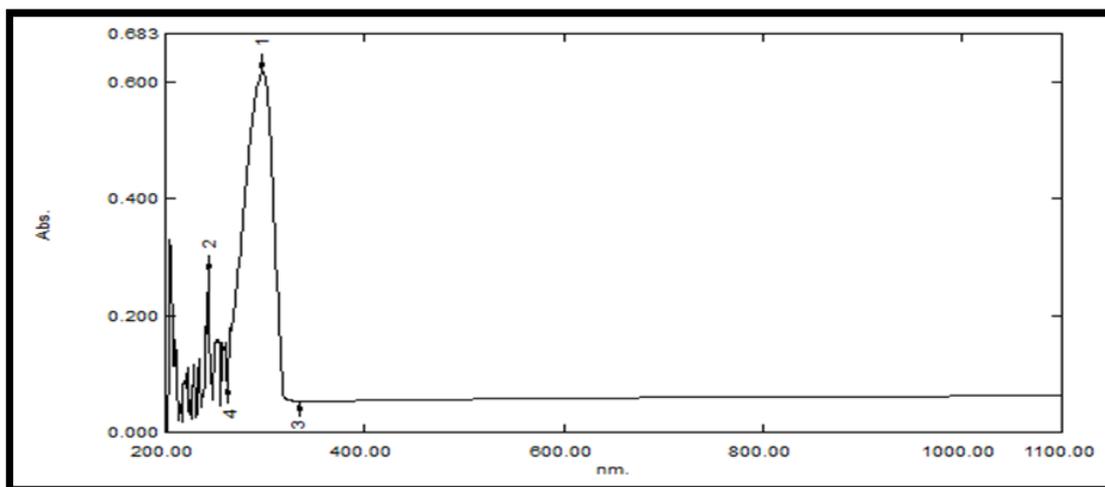
${}^3A_{2g} \rightarrow {}^3T_{1g}$ (ν_2), and ${}^3A_{2g} \rightarrow {}^3T_{1g(P)}$ (ν_3) transition respectively, which indicate an octahedral geometry around Ni (II) ion in solution state only furthermore the change of colour from dark orange to dark brown is support the change in geometry from square pyramidal in solid state to octahedral geometry in solution state [21]. The value of (ν_2 / ν_1) is found to be around 1.53 refers that the complex having distorted octahedral geometry [21]. The value of nephelauxetic factor β indicates the covalent character of the metal- ligand bond [25] (Table 3).

Table (3): Electronic spectra, Conductance in DMF solvent and magnetic moment (B.M.) for the prepared metal complexes

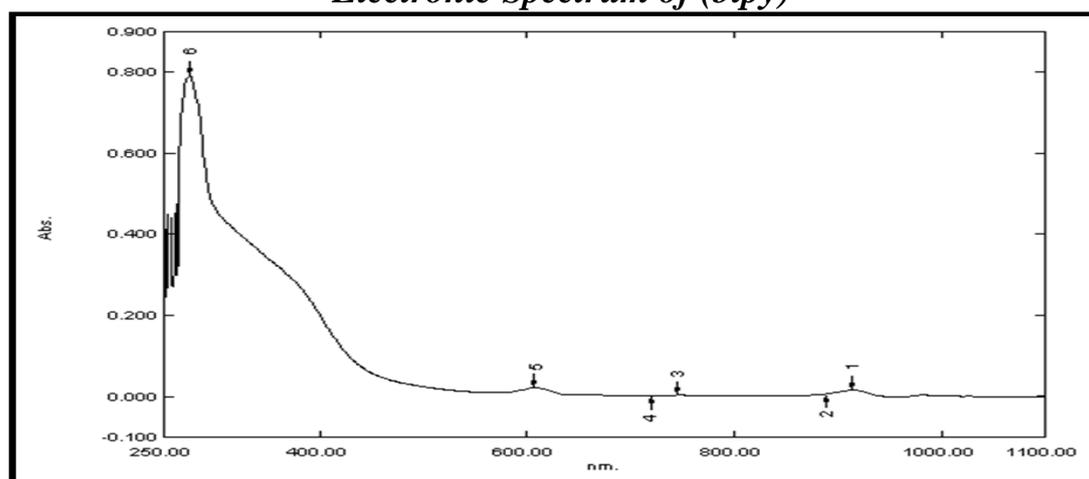
Comp.	Absorption Bands(cm^{-1})	Assignments	B^*	B'	β	Dq/B'	$10Dq$	$15B'/$ Separation term	μ_{eff} B.M.	$Ohm^{-1} cm^2 mol^{-1}$	Suggested geometry
(TRZ.DTC)	28328 32051 37593	$n \rightarrow \pi^*$ $\pi \rightarrow \pi^*$ $\pi \rightarrow \pi^*$	----	----	----	----	----	----	----	----	----
(bipy)	41152 25188	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	----	----	----	----	----	----	----	----	----
Ni TRZ.DTC (bipy)	10920 16431 26500	${}^3A_{2g} \rightarrow {}^3T_{2g}$ ${}^3A_{2g} \rightarrow {}^3T_{1g(F)}$ ${}^3A_{2g} \rightarrow {}^3T_{1g(P)}$	1035	678	0.655	1.6	10920	10170	3.52	30.99	Oh
Co TRZ.DTC (bipy)	9680 21600	${}^4T_{1g} \rightarrow {}^4T_{2g}$ ${}^4T_{1g} \rightarrow {}^4T_{1g(P)}$	971	851	0.87	1.14	9680	12765	4.48	36.5	Oh



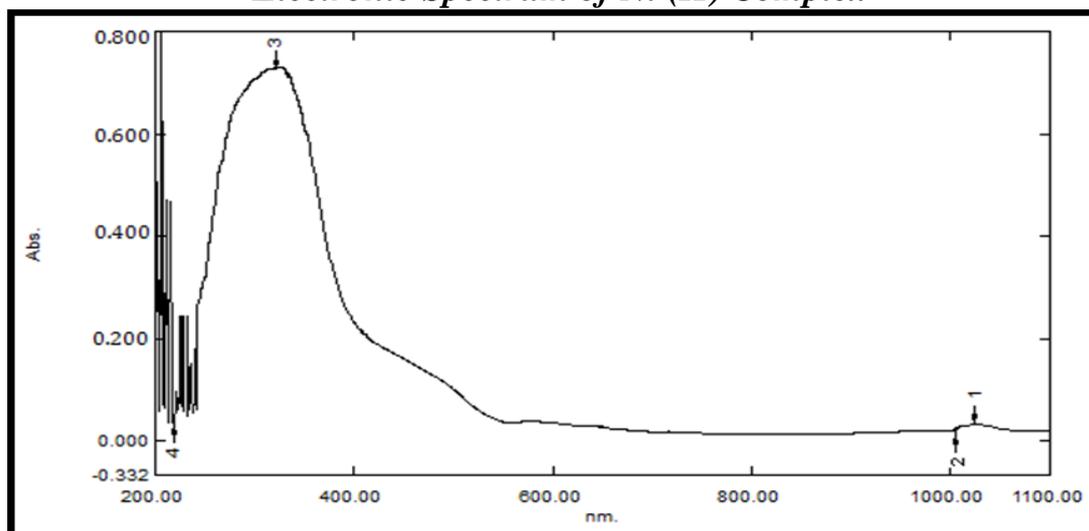
Electronic Spectrum of (TRZ.DTC)



Electronic Spectrum of (bipy)

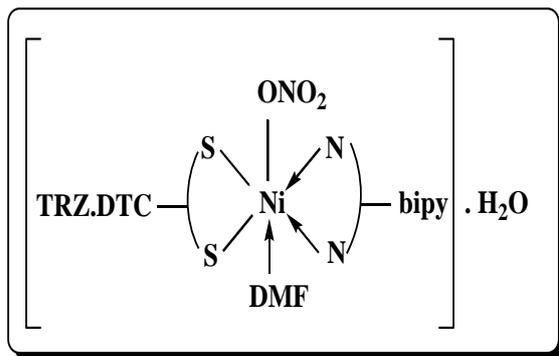


Electronic Spectrum of Ni (II) Complex

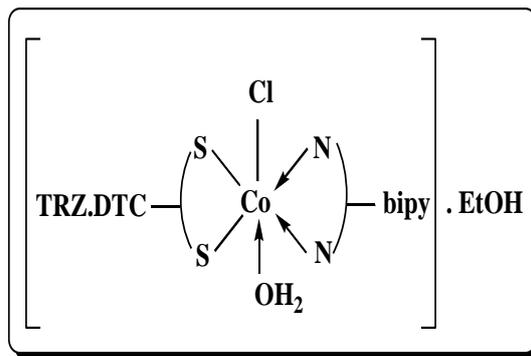


Electronic Spectrum of Co (II) Complex

The results obtained from CHNS, A.A., UV-Vis, FTIR spectrum as well as conductivity and magnetic susceptibility measurements led to suggest the following structural geometries of the new prepared complexes:-



$[Ni(TRZ.DTC)(bipy)ONO_2].H_2O$



$[Co(TRZ.DTC)(bipy)(H_2O)Cl].EtOH$

Cytotoxicity activity

The results of the *in vitro* cytotoxicity test of mixed ligand and its metal complexes were given in (Table 4). The data showed that all of these prepared compounds may be potent as anticancer activities against human HepG2 cell line in time of exposure 72 hrs comparable with standard drug cis-Pt as control positive. The mixed ligand exhibited cytotoxicity activity against selected cell line and in inhibition rates fairly high comparable with standard drug in the first five concentrations and this may be due to presence of CS₂ group of dithiocarbamate as well as the two nitrogen atoms of co-ligand 2,2'-bipyridyl, while the results down suddenly in three low concentrations i.e. 62.5, 31.25 and 15.625 µg/ml (Fig 1). The Ni (II) complex has the best activity among the prepared compounds and exceeding the cis-Pt in some concentrations i.e. 1000, 500, 250 and 125 µg/ml and without significant difference $P < 0.05$ at 250 and 125 µg/ml while exhibit significant difference $P < 0.05$ among these concentrations 1000, 500 and 250 µg/ml, while the same complex is recorded inhibition rates more than free ligand in all used concentrations and in significant difference $P < 0.05$ in all concentrations except at 125 µg/ml the result refer did not record any significant difference comparable with

standard drug and free mixed ligand. As for the Co (II) complex the statistical data indicated that the complex is less cytotoxicity against HepG2 comparable with control positive and free mixed ligand as well as Ni (II) complex and the highest inhibition rate exhibit at 125 µg/ml concentration and though another concentration are also recorded good inhibition rates almost from results of cis-Pt like in 2000, 1000, 250 and 62.5 µg/ml. Thus, in both cases chelation enhances the antiproliferative activity of the new complexes.

The results obtained in the present work, showed the cytotoxic effect of new dithiocarbamate ligand and its complexes on HepG2 cell line (*in vitro*). They may lead to a suggested mechanism of action for this new ligand according to the reported in literature; dithiocarbamates can form coordination complex with metal ions in which the two adjoining sulfur atoms are bound to the same metal ion including common transition metal ions. Without a reduced sulphhydryl, dithiocarbamate disulfides, thiolate anions, and coordination complexes are believed to have no antiproliferative activity against cancer due probably to their incapability to function as antioxidants. On the other hand, the dithiocarbamate anti-neoplastic activity suggested that the anti-neoplastic was

attributed to pro-apoptotic redox-related mitochondrial membrane permeabilization [26], as well as and from inorganic side many factors may be responsible in the activity of these prepared complexes in pharmacological composition field like size of metal, charge distribution, geometry shape, and polarity [13], and this elucidation the more activity of Ni (II) than Co(II) where the size of metal is larger than

Co(II), covalent bond between metal-ligand in this complex make them easy to inter to the cell as well as the square pyramidal geometry having the empty site which make them easy to coordinat with nitrogen bases of DNA, but the mechanism of action of this complexes remained

unclear because our study focused at the cell inhibition rates only not DNA, RNA and protein level.

Table (4): Statistical data of mixed ligand and its metal complex comparable with control positive cis-Pt on HepG2 cell line

<i>Treatment</i> <i>Concentrations</i> <i>µg/ml</i>	<i>Inhibition rate%(means ±standard deviation SD)</i>			
	cis-Pt Control positive	Mixed ligand (TZA.DTC)(bipy)	Ni (TRZ.DTC)(bipy)	Co (TRZ.DTC)(bipy)
2000	70.248 ± 0.626 A, a	59.928 ± 0.409 A, b	64.600 ± 0.172 A, c	62.843 ± 0.023 A, d
1000	73.764 ± 0.733 B, a	69.721 ± 0.091 B, b	74.663 ± 0.021 B, a	71.891 ± 0.015 B, d
500	75.022 ± 0.031 C, a	76.460 ± 0.213 C, b	78.167 ± 0.092 C, c	60.377 ± 0.978 C, d
250	75.202 ± 0.129 C, a	75.561 ± 0.931 C, a	80.592 ± 0.355 D, b	70.889 ± 0.831 B, c
125	77.890 ± 0.836 D, a	77.268 ± 0.822 C, a	79.964 ± 0.125 D, b	73.674 ± 0.361 D, c
62.5	67.115 ± 0.701 E, a	37.106 ± 0.539 D, b	61.904 ± 0.989 E, c	71.159 ± 0.335 B, d
31.25	66.037 ± 0.501 E, a	25.696 ± 0.129 E, b	62.533 ± 0.422 E, c	28.750 ± 0.775 E, d
15.625	52.740 ± 0.282 F, a	15.241 ± 0.395 F, b	30.368 ± 0.875 F, c	19.750 ± 0.939 F, d
<i>Differences A,B,C,D, E, F, G are significant (P<0.05) to compression column</i> <i>Differences a, b, c, d are significant (P<0.05) to compression row</i>				

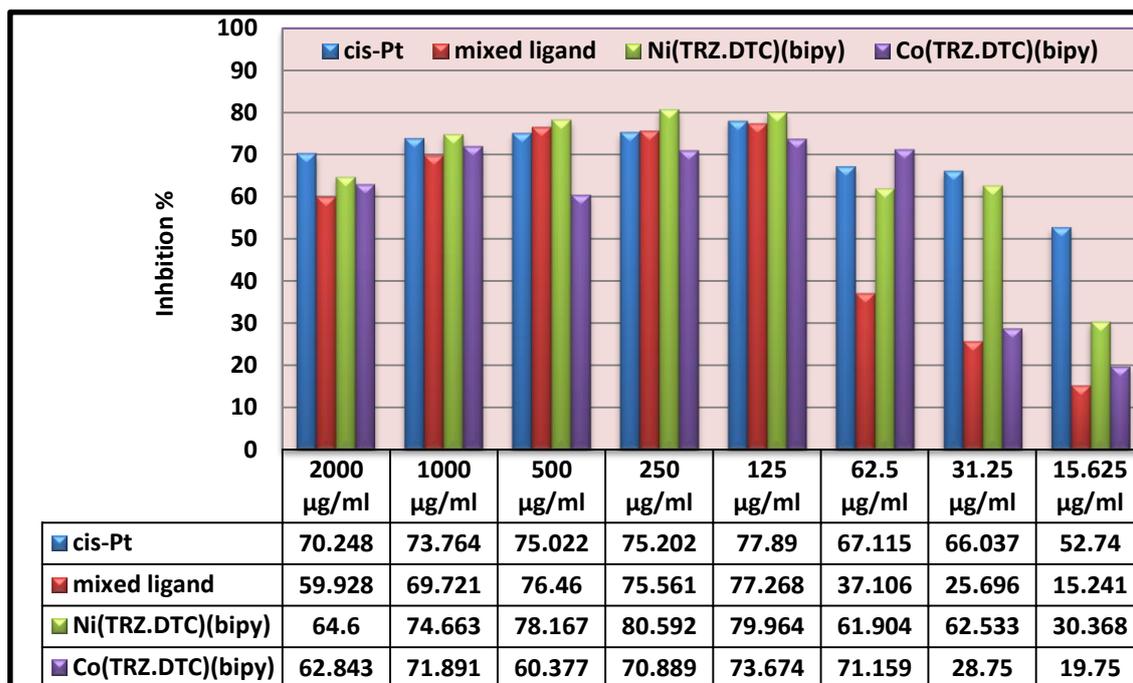


Fig (1): Shows the percentage inhibition rate on HpeG2 cell lines after exposure to mixed ligand and their metal complexes.

References:

1. Breviglieri ST; Cavalheiro ET; and Chierice GO. 2000. Correlation between ionic radius and thermal decomposition of Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) diethanoldithiocarbamates. *Thermochim. Acta*, 356, 79–84.
2. Cavalheiro ETG; Ionashiro M; Marion GS; Breviglieri T; and Chierice GO. 2000. Correlation between IR spectra and thermal decomposition of cobalt (II), nickel (II), copper (II) and mercury (II) complexes with piperidinedithiocarbamate and pyrrolidinedithiocarbamate. *Transition Met. Chem.*, 25(1) 69–72.
3. Faraglia G; Fregona D; Sitran S; Giovagnini L; Marzano C; Baccichetti F; Casellato U; and Graziani R. 2001. Platinum (II) and palladium (II) complexes with dithiocarbamates and amines: synthesis, characterization and cell assay. *J. Inorg. Biochem.*, 83, 31–40.
4. Dick de V; Soo Yei H; and Edward RTT. 2004. Cytotoxicity Profiles for a Series of Triorganophosphine-gold(I) Dithiocarbamates and Triorganophosphinegold (I) Xanthates. *J. Bioinor. Chem. Appli.*, 2(1-2), 141-154.
5. Awang N; Baba I; Yamin BM; Othman MS; and Kamaludin NF. 2011. Synthesis, Characterization and Biological Activities of Organotin (IV) Methylcyclohexyldithiocarbamate Compounds. *Amer. J. Appl. Sci.*, 8 (4): 310-317.
6. Giovagnini L; Marzano C; Bettio F; and Fregona D. 2005. Mixed Complexes of Pt(II) and Pd(II) with Ethylsarcosinedithiocarbamate and 2-/3-Picoline as Antitumor Agents. *J. Inorg. Biochem.*, 99: 2139-2150.
7. Baseer MA; Jadhav VD; Phule RM; Archana YV and Vibhute YB. 2000. Synthesis and Antimicrobial Activity of Some New Schiff Bases. *Orient. J. Chem.*, 16, 553-556.
8. Hacker MP; Douple EP; and Krakoff IH. 1984. Platinum Coordination Complexes in Cancer

- Chemotherapy. Boston, M.A: Nijhoff Publisher.
- Somers PK; Modford RM; and Saxena U. 2000. [Dithiocarbamates: effects on lipid hydroperoxides and vascular inflammatory gene expression.](#) *Free Radic. Biol. Med.* 15; 28(1) 1532-1537.
 - Messori L; Abbate F; Marcon G; Orioli P; Fontani M; Mini E; Mazzei T; Garotti S; Conell TO; and Zanello P. 2000. Gold(III) complexes as potential antitumor agents: solution chemistry and cytotoxic properties of some selected gold(III) compounds. *J. Med. Chem.* 43, 3541-3548.
 - Lemma K; Elmroth SKC; and Elding LI. 2002. Substitution reactions of $[\text{Pt}(\text{dien})\text{Cl}]^+$, $[\text{Pt}(\text{dien})(\text{GSMe})]^{2+}$, *cis*- $[\text{PtCl}_2(\text{NH}_3)_2]$ and *cis*- $[\text{Pt}(\text{NH}_3)_2(\text{GSMe})_2]^{2+}$ (GSMe = *S*-methylglutathione) with some sulfur-bonding chemoprotective agents. *J. Chem. Soc. Dalton trans.*, 1281-1286.
 - Manav N; Mishra AK; and Kaushik NK. 2006. *In vitro* antitumour and antibacterial studies of some Pt(IV) dithiocarbamate complexes. *Spectrochim. Acta.*, 65(1) 32-35.
 - Carolin S. 2012. Synthesis and Studying New Complexes of Some Transition Metals Ions on RD Cell Line. Thesis, M.Sc. Baghdad University.
 - Gao X; Xu X; Janak iraman N; and Gautam S. 2002. Disparate *in vivo* antileukemic effect of reseedatol a natural polyphenolic compound found in Grapes. *Nutv.* 132, 2076- 2081.
 - Bonati F; and Ugo R. 1967 Organotin IV N, N-disubstituted dithiocarbamates. *J. Organomet. Chem.* 10, 257-268.
 - Rayag I; Baba I; and Yamin BM. 2006. New mixed ligands complexes of samarium (III) with dithiocarbamates and 1,10-Phenanthroline. *Malaysia. J. Analy. Scien*, 10(1) :93-98.
 - Awang N; Baba I; Yousof N; and Kamaludin, NF. 2010. Synthesis and characterization of organotin(IV)*N*-Benzyl-*N*-Isopropyl dithiocarbamate compound: cytotoxic assay on human hepatocarcinoma cells (HepG2). *Amer. J. Appl. Scien.*, 7 (8) : 1024-1052.
 - Chaudhary R; and Shelly. 2012. Synthesis and Spectral Characterization of Mn(II), Zn(II) and Cd(II) Complexes with Thiosemicarbazone as Primary Ligand and 2,2'-Bipyridyl as Secondary Ligand, *J. Chem, Biolog. Phys. Scien*, 2(1), 1-5.
 - Nakamoto N. 2009. Infrared and Raman Spectra of Inorganic and Coordination Compounds. John Wiley & Sons, Inc., 6th Ed., New Jersey.
 - Zeena UJ. 2011. Synthesis and Characterization of New Mn(II), Co(II), Ni(II) and Cu(II) Complexes with [α -methyl-*N*-(3-methylidene indol)-2-amino anthraquinone] Ligand. *J. Colle. Basic. Educ. Rese.*, 10 (4), 570-581.
 - Nicholls D. 1973. The Chemistry of Iron, Cobalt and Nickel. 1st Ed., Pergman Press, Oxford.
 - Islamic-Moghaddam M; Mansouri-Torshizi H; Divsalar A; and Saboury AA. 2009. Synthesis, Characterization, Cytotoxic and DNA Binding Studies of Diimine Platinum (II) and Palladium (II) Complexes of Short Hydrocarbon Chain Ethyldithiocarbamate Ligand. *J. Iran. Chem. Soc.*, 6(3):552-569.
 - Leka Z; Grujic SA; Tesic Z; Lukic S; Skuban S; and Trifunovic S. 2004. The synthesis and characterization of complexes of Zinc (II), Cadmium (II), Platinum (II) and Palladium (II) with

- potassium 3-dithiocarboxy-3-aza-5-aminopentanoate. *J. Serb. Chem. Soc.*, 69(2):137-143.
24. Masaki Y; Koji A; and Shinsaku S. 1988. The electronic Spectra of 6,6'-Diamino-2,2'-bipyridine. *Bull. Chem. Soc. Jpn.*, 61(6), 2208-2210.
25. Lever ABP; 1984, Inorganic Electronic Spectroscopy, Elsevier, New York.
26. Klatt P; and Sies H. 1999. Glutathione and its Role in Cellular Functions. *Free. Rad. Biol. Med*; 27: 916-921.

تحضير معقدات من مزيج ليكاندات لفلزات ثنائية التعويض لمشتقات الدايثايوكاربميتو و 2,2'-بابيردال ودراسة تأثيرها السمي الخلوي ضد الخط الخلوي HepG2 خارج الجسم

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الخلاصة:

تم تحضير مزيج من الليكاندات لمعدي النيكل والكوبلت الثنائية باستخدام [5-(بارا نايترو فنيل)-4-فنيل-4,2,1-ترايزول-3-ثنائي ثايوكاربميت هيدرازيد] كليكاند أولي و 2,2'-بابيردال كليكاند مشارك مع املاح الفلزات. هذه المعقدات شخّصت تحليلياً و طيفياً في الحالة الصلبة بواسطة التحليل الدقيق للعناصر، الامتصاص الذري اللهي، الحساسية المغناطيسية و قياسات التوصيلية المولارية بالإضافة الى اطياف الاشعة تحت الحمراء و فوق البنفسجية. اطياف تحت الحمراء و فوق البنفسجية كشفت عن سلوك ثنائي السن لكلا الليكاندين المستخدمين مع ايونات الفلزات وبنسبة 1:1:1. قياسات الحساسية المغناطيسية و الأطياف في الحالة الصلبة أشارت الى شكل هرم مربع القاعدة خماسي التناسق لمعقد النيكل (II) بينما لمعقد الكوبلت (II) شكل ثماني السطوح سداسي التناسق. مزيج الليكاندات و معقداتها أختبرت لفحص السمية الخلوية على الخط الخلوي البشري من نوع HepG2 باستخدام عقار السيزبلاتين كسيطرة موجبة باتباع طريقة الزرع النسيجي و لمدة ثلاثة أيام بعد المعاملة مع المركبات المحضرة و باستخدام ثمان تراكيز مختلفة نتائج الأختبار الأحيائي أظهرت فعالية تثبيطية جيدة لهذه المركبات المحضرة خصوصاً معقد النيكل الثنائي على الخط الخلوي المختار مقارنة بالعقار القياسي.