Preparation, characterization and cytotoxic evaluation of novel au(iii) complexes of thioglycolate and ٢-mercaptoglycolate ligands

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ABSTRACT

Objectives: One of the main goals of the present research is to establish whether any direct correlation exists between the nature of the gold(III) S-ligands and the cytotoxic properties of these compounds.

Methods: The gold(III) complexes $[Au(L)(L')_n]$; where L = SCH_2COO^-; L' = $HSCH_2COO^-$, were synthesized according to the reported procedure. The cytotoxic evaluation where done by the exposure of the synthesized compounds to HEP-٢ cell line.

Results: The cytotoxic evaluation revealed that the HEP-٢ cell line differ in its sensitivity toward the selected complexes compared to cisplatin.

Conclusion: Different arrangement of thioglycolate (L) and ٢-mercaptoglycolate (L') ligands around Au(III) metal core may not be responsible for such different affinities toward synthesized complexes. The increase in sensitivity to gold(III) may imply that these complexes either remain in part as gold(III) species or that one of their metabolites is highly cytotoxic.

الخلاصة

الهدف: احد أهداف البحث الرئيسية لإثبات إمكانية وجود علاقة مباشرة مابين طبيعة ليكاند Au(III) S– والصفات السمية لهذه المركبات .

طرائق: ان معقدات الذهب ذات الصيغة Au(L)(L')n عندما $L=SCH_2COO^-$ و $L'=HSCH_2COO^-$ ، حضرت اعتمادا على الطرق المعروفة وان التقييم السمي انجز بمعاملة خلية HEP-٢ الى المركبات المحضرة .**النتائج:** ان التقييم السمي يكشف بان خلية الـ HEP-٢ تختلف في حساسيتها باتجاه المعقدات المختارة مقارنة بالـCisplatin .

الاستنتاج: ان الترتيبات المختلفة للـيكاند ثايوكلايكوليت (L) و 2 – مركبتو كلايكوليت (L') حول نواة الفلزالمركزية قد لاتكون المسؤولة للتحسسات المختلفة تجاه المقعدات المحضرة . اما زيادة التحسس تجاه الذهب (III)؛ فقد تعزى الى ان هذه المعقدات اما تبقى كفلز ذهب او ان احد النتائج الايضية له؛ ذو سمية عالية.

According to the American Cancer Society, cancer was the second leading cause of death in ٢٠٠٦[١]. With cancer at the forefront of health concerns, it is vital that new and improved approaches to treatment are created to eradicate the cancerous cells ; one of the most common approaches is chemotherapy, which oftentimes utilizes bio-inorganic molecules. Medicinal inorganic chemistry is a thriving area of research[٢,٣], which was initially fueled by the discovery of the metallopharmaceutical cisplatin about ٤٠ years ago. It is widely used to treat testicular, ovarian, bladder and stomach cancers among many others[٤,٥]. The major limitations of cisplatin and other platinum anticancer drugs are related to drug resistance and their side

effects, including nephrotoxicity, neurotoxicity and emetogensis[٦]. Some cancer cell lines are inherently resistant to cisplatin[٧], whereas others develop resistance overtime[٨]. Given these limitations, the development of alternative therapeutics is warranted. Due to the success of cisplatin, much research has been conducted with metal complexes that are analogous to platinum(II).

The design and testing of gold complexes, especially gold(III) complexes with anticancer activity begin to be intensively pursued in the past few years. The potential use of gold(III) complexes as anticancer drugs were based on three rationables[٩,١٠]: (a)analogies between square planar complexes of both platinum(II) and gold(III) are d^8 ions ; (b) analogy to the immunomodulatory effects of gold(I) antiarthritic agents ; and (c) complexation of gold(I) and gold(III)with known anticancer agents to form new compounds with enhanced activity.

In addition, a study of the long-term mortality of patients undergoing chrysotherapy, the use of gold(I) in medicine, suggested that cancer levels were no higher or even lower than for patients not undergoing chrysotherapy[١١,١٢]. Nevertheless, it really was only in the ١٩٨٠'s that reports of systematic investigations of the anticancer potential of gold compound started appearing. After a relatively slow start in comparison, investigations on gold(III) compounds have become increasingly important with time. Now, the greatest activity in the development of antitumor active gold compounds currently involves studies of gold in the higher oxidation state.

Although ligands having oxygen and nitrogen as donor atoms are by far the most extensively studied , interest in sulfur donor chelating agents has grow over the years and the number of chemical studies in this area has increased considerably[١٣-١٦] .Interest in complexes of these ligand system now covers several areas ,ranging from general considerations of the effect of sulfur and electron delocalization in transition metal complexes of potential biological activity and practical application[١٧-٢٠].

In this study, two S- ligands : thioglycolate [$–SCH_2COO^-$](L) and ٢-mercaptoacetic acid [$SHCH_2COO^-$] (L') were incorporated as ligands for three considerations :First the cyclic bidentate ligand was seen to reduce rapid detoxification[٢١]. Secondly, the use of monodentate and bidentate (L) and / or (L') ligands could lead to prevent translabilization and carrying the metal into its site of action .Thirdly the presence of ١H proton on (L) ligand is ideal for hydrogen bonding with DNA[٢١,٢٢], and because that Au (III) is isoelectrical to Pt (II); a gold based molecule with a flat planar ligand attached might allow for DNA interaction. (DNA dependent) . If so, this might be used as an alternative to cisplatin . Two ligands were incorporated into gold(III) metal center ; thioglycolate S-CH_2COOH(L) and ٢-mercapto acetate HSCHCOOH (L'), but with different distribution around central Au (III metal).

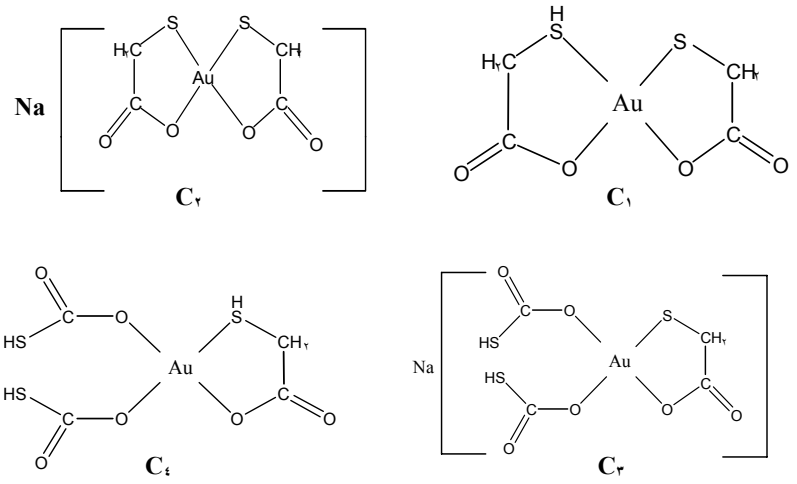

Figure ١: The Chemical structure of the synthesized complexes

Due to the previous literature survey ,it is suggested that the synthesized complexes C١ - C٤ (figure ١) may be acting by virtue of their chelating properties at the cellular level thereby exerting their anticancer activity .Hence , it was considered worthwhile to subject the presently studied complexes for evaluation of their anticancer activity using Hep-٢ cell line .

So, one of the main goals of the present research is to establish whether any direct correlation exists between the nature of the S-ligands (L) and (L') ligands and their different arrangements around Au(III) metal core.

Experimental

Chemistry

All chemicals were of reagent grade quality and were purchased from commercial sources (BDH and Fluka). They were used without further purification. IR spectra were recorded on Brucker Tensor ٢٧١٠ (FTIR) spectrophotometer in the ٤٠٠٠-٢٠٠ cm^{-1} range using CsI disc. Electronic spectra were recorded on Shimadzu UV ١٦٠ spectrophotometer for $١٠^{-٣}$ M solution of the complexes in dimethylformamide using ١ cm quartz cell. The ^{١}HNMR spectra were recorded on Brucker/ Hims University ,Syria. Spectrophotometer in DMSO-$d_٦$ at room temperature. Conductivity measurements were made on conductivity meter ٤٠٧٠ Jenway. The magnetic measurements were carried out at ٢٥^{o}C on the solid state by Faraday's method using Bruker BM٦ instrument. Metal content analyses were made on Shimadzu AA٦٧٠ atomic absorption spectrophotometer. Elemental Analysis (C H S) were carried out using Perkin Elmer ٢٤٠٠ in Al –Bait 's University /Jordan.

Preparation of disodium ٢-thioglycolate (L')

The ligand was prepared according to the following general method. The reaction of an equivalent amount of NaOH (٤.٠٠ g, ٠.٠١ mol) and mercaptoacetic acid sodium salt (١.١٢ g, ٠.٠١ mol) in ٣٠ ml ethanol. The mixture was boiled under reflux for ٣ h. The product was obtained through evaporation of the solvent , then the precipitate was washed and

diethylether , then dried under vacuum for ٤ hrs.

Preparation of [Au(SCH٢CO) (OC-CH٢SH] (C١)

A solution of H[AuCl٤] (٠.٣٤ g, ٠.٠٠١ mol.) in ١٥ ml., ethanol was added to a stirred solution of the ligand mercaptoacetic acid sodium salt (٠.١ g, ٠.٠٠١ ml.) and disodium thioglycolate (٠.١٤ g, ٠.٠٠١ mol.) in ١٠ ml ethanol. The reaction mixture was refluxed for ٣ h and then the mixture was left ٢٤ h at room temperature to give the precipitate which was filtered off, washed with ethanol and diethylether and then dried under vacuum for ٤ h.

Preparation of Na[Au SCH٢COO)٢] (C٢)

A solution of H[AuCl٤] (٠.٣٤ g ,٠.٠٠١ mol) in ١٥ ml ethanol was added to a stirred solution of the ligand disodium thioglycalate (٠.٢٨ g, ٠.٠٠٢ mol.) in ethanol (١٥ ml). The addition was continued for ٠.٥ h and the reaction mixture was refluxed for ٣ h; and then the mixture was left for ٢٤ h at room temperature to give the precipitate which was filtered off, washed with ethanol and diethylether then dried under vacuum for several hours.

Preparation of Na[Au (OCOCH٢SH)٢(OCOCH٢S)] (C٣)

A solution of H[AuCl٤] (٠.٣٤ g, ٠.٠٠١ mol.) in ١٥ ml ethanol was added to a solution of the ligands, mercaptoacetic acid sodium salt (٠.٢٣ g., ٠.٠٠٢mol.) and disodium thioglycolate (٠.١٤ g, ٠.٠٠١ mol.) in ٣٠ ml ethanol. The addition was continued for ٠.٥ h. and the reaction mixture was refluxed for ٣ h and then the mixture was left ٢٤ h at room temperature to give the precipitate which was filtered off, washed with ethanol and diethyl ether then dried under vacuum for several hours.

Preparation of [Au(OCOCH٢SH)٢] (C٤)

This complex was prepared as in above, except the use of ٣ moles of the ligand mercaptoacetic acid sodium salt.

Stability in Buffer

stability tests were run on compound C٢ & C٣ which were used as a representive compounds. A minimum amount of dimethyl sulfoxide (DMSO) was used to dissolve the complex, which was then diluted in phosphate buffer (pH ٧.٤), a solution of concentration ٥.٠* ١٠$^{-٥}$M was made and observed daily for a period of ٣ days. The sample was stored in a dark environment throughout the ٣-day period. There appears to be no significant shift in the absorption maxima at ٣٢٠ nm, which is the absorption that arises due to the gold(III) metal ion.

Cytotoxic study

Preliminary cytotoxic test

Cell line and growth conditions

Human Larynx epidermoid carcinoma (Hep-٢) was kindly provided by the Iraqi center for Cancer and Medical Genetics Research ICCMGR). This human cells grew rapidly ,doubling themselves in ٢-٣ days and were shown to be extremely resistant to ultraviolet rays [٢٣] & were grown in Rosswell Park Memorial Institute (RPMI) ١٦٤٠ Medium (Gibco ,USA) , which was prepared as follows

- RPMI ١٦٤٠ medium powder was dissolved in approximately ٦٠٠ ml of double distilled water

(DDW) and then the other components added :

- ٠.٥ ml ,Streptomycin (١ g/٥ ml)
- Sodium bicarbonate (٤.٤%) ١٥ ml to give the final pH of ٧.٢ Sodium bicarbonate solution was prepared by dissolving ٤.٤ g. in ١٠٠ ml D.W. The solution was autoclaved at ١٢١° for ١٥ minutes and stored at ٤ °C[٢٤].
- ٠.٥ ml Benzyl Penicillin G (٦٠٠ I U /٥ ml)
- ٢.٥ mg Amphotericin B .
- ١٠٠ml Fetal calf serum .

The volume was completed to one liter with DDW. Then the mixture was sterilized using Seitz filter and filtration repeated using ٠.٢ □m filter unit. The sterilization was done in a sterile environment , then stored at ٤ C for direct use . All antibiotics were freshly prepared .

The growth medium was decanted off and the cell sheet washed twice with phosphate buffered saline (PBS), composed of :

- Sodium chloride (NaCl) ٨ g.
- Disodium hydrogen phosphate (Na_2HPO_4) ٠.٩ g.
- Potassium dihydrogen phosphate (KH_2PO_4) ٠.٢ g.

After dissolving all components, the solution was autoclaved at ١٢١°C for ١٥ min and then stored at ٤°C prior to any usage, PBS was warmed to ٣٧°C.

Cells were regularly subcultured when monolayers were confluent. Two to three ml of warm trypsin-versene (prepared by mixing ٢٠ ml of trypsin solution, ١٠ ml of versene solution and ٣٧٠ ml PBS and stored at ٤°C). were added to the sheet and the flask rocked gently [٢٤].

Preparationof٣-(Dimethylthiazol-٢-yl)-٢,٥-Diphenyltetrazoliumbromid (MTT) solution (Sigma ,USA).

Fifty milligram per ml of MTT dye was used as a final concentration [٢٥] .The solution was filtered through ٠.٢٢ µ syringe filter to remove any blue formazan product [٢٦], and then stored in sterile , dark ,screw –capped bottles at ٤ °C.

The solution was used within no longer than ٢ weeks of preparation .

Cytotoxic Assay on Hep-٢ Cell Line

This step must be prepared under aseptic condition[٢٧,٢٨]. All complexes (C_1-C_4) were prepared for micotitration assay by dissolving ٢ mg. of each compound in ٢ ml of solvent (٠.٢ ml DMSO & ١.٨ ml DDW, the stock concentration is ١٠٠٠µg/ml)and filtered by ٠.٢٢ µ Millipore filter .Serial dilutions of each compound (٢.٥٠, ١.٢٥, ٠.٦٢٥ & ٠.٣٣١) µmol/ml under assay in SFM were added to the well. Three replicates were used for each concentration of either four tested complexes in addition to cisplatin (EBEWE, Austria Europe) as a reference (D:positive control)

When the cells are exactly in the exponential phase in the population doubling time (PDT) , then the cells in full of their activity , the cells were collected after adding trypsin/versin (٢-

٣ ml) not more than ١٠ min. ,then concentrated into known volume with SFM. Afterwards, ٠.٢ml of cells in growth medium were added to each well of sterile ٩٦-well micro titration plate. The plate were sealed with a self adhesive filer, placed on $CO_٢$ incubator at ٣٧ ^oC for not more than ٢٤ hrs. (for cell adherence) .After cells attachment, the plate was checked –out for contamination and the media were removed .Serial concentrations were added and three replicates were used to each concentration and negative control (cell with SFM only),the exposure time was ٧٢ hrs.

After the exposure time was finished , the mixtures of analogues and media were removed and a fresh SFM was added to all wells ,and incubated for ٢٤ hrs at ٣٧ ^oC to give chance if the affected cells and not damaged being repaired by self repairing system .Then the media was removed from the plate and washed PBS .A ٠.٢ ml of MTT working solution dye was added to each well and incubated at ٣٧ ^oC for ٣ hrs.

At the end of last incubation period the dye was removed from the plate and the well washed with warm PBS twice , then ٠.٢ ml DMSO was added to each well to dissolve the MTT –formazan crystals ,during that we added ٢٥ µl of glycine buffer to each well containing DMSO.

Finally the plate became readily for reading by ELISA reader at ٥٧٠ nm.

Statistical Analysis

Experimental data were analyzed using statistical software SPSS ١٧.٠ for Windows. Significance between control and samples was determined using Students' t-test. A P value $\leq$ ٠.٠٥ was considered statistically significant.

The results were expressed as percentage of viability which was calculated as the percentage of the mean of absorbance compound to the control.

The $IC_{٥٠}$, which is the lowest concentration that kill ٥٠% of cells[٢٧] was calculated according to Wilson[٢٨].

Results and Discussion

Chemistry

The thioglycolate ligands form stable, colored solid and acts as monodentate (O) and bidentate (O/S) with Au(III) ion. All complexes are thermally stable and insoluble in organic solvents. However, fair solubility was attributed in DMF and DMSO. The $١٠^{-٣}$M solution in DMSO $C_٢$ and $C_٣$ display molar conductance equal to ٧٠ and ٨٠ $ohm^{-١}$ $cm^{-٢}$ $mol^{-١}$ indicating a ١:٢ electrolytic nature of the complexes , where as for the rest of the complexes the value ١٠-٢٠ $ohm^{-١}$ $cm^{-٢}$ $mol^{-١}$ indicating non electrolytic nature of the complexes[٢٩] .This is consistent with stoichiometry for the complexes on the basis of analytical data.

The most important diagnostic feature of IR spectra of the complexes were listed in Table ٢. The most significant information on the geometry of these complexes were came from the analysis of caboxylate and thioether absorption region. Stretching frequencies of these functional groups are closely related to the way in which they are coordinated to the metal ion[٣٠]. The IR spectra of the complexes showed broad and intense bands ranging between ١٥٨٠-

١٦٣٥ and ١٤١٥-١٤٧٥ cm^{-1} assigned for asym ν (COO^{-1}) and for sym. ν (COO^{-1}) respectively.(Table ٢).

The magnitude of Δ ν (Δν = ν asym COO - ν sym COO) were in the range ١٥٠-١٨٠ cm-١ suggested monodentate bonding of carboxylic group to metal ion[٣١].

Further support for this argument came from the IR of the complexes which showed a new band at ٤٦٩-٤٨٦ cm^{-1} attributable ν (Au-O).,The (C-S) band of the ligand was observed at ٨٦٠ cm^{-1}, upon coordination with metal ions in complexes it was shifted to lower frequency values (Table ٢).Further support for this coordination has provided from the appearance of new bands in the ٣٤٠-٣٦٠cm^{-1} ranges which are tentatively attributed to ν(Au-S)[٣٢] .

The ^{1}HNMR spectra of the complexes (١-٤) were recorded in DMSO d_6 and showed the signal of the coordinated ligands, NMR data are explained below. For **C**١ , Shows, broad band at ٣.٣١which can be attributed to each CH_2 proton in the S-CH_2CO moiety and a band at ١.٨ ppm which attributed to SH proton.

C٢ **,**shows only one band which can be attributed to each CH_2 proton in the S-CH_2CO group of each ligand at ٣.٢٥-٤.٠١ ppm . In complex (٣) two bands can be assigned to each CH_2 in the SCH_2CO at ٢-٢٥٨ ppm and the thiol protons of ١.٠٧ and ١.٢١ ppm, for complex ٤ same as ٣.

The diamagnetic nature of the Au(III) complexes is consistent with normal square-planar geometry around Au(III) ion[٣٣].

Electronic absorption spectra of the complexes in DMF are listed in Table ٢ in the spectrum of the ligand the π-π* transition were observed at ٣٦٢٣٢ and ٣٣٢٠٠cm^{-1}.

The spectrum of the complexes show new bands at ٢٥٠٠٠-٢٦٦٦٦ and ٢٧٢٤٨-٣٢٨٤٥ cm^{-1} assigned to $^{1}A_{1g} \rightarrow {}^{1}A_{2g}$ and $^{1}A_{1g} \rightarrow {}^{1}E_g$ transition respectively[٣٤], these bands correspond fairly well to a square planar geometry around the Au(III) ion. Also the band at ٤٠٠٥٠ cm^{-1} is tentatively assigned as ligand charge transfer transition. Similar results were found in Pt(II) and Au(III) complexes of the [M(diimine)(dithiolate)] type[٣٥].

The ligands used in this study, coordinate to the Au(III) ions in monodentate or bidentate fashion from both oxygen and sulfur atom of thioglycolate group. The suggested structures of the prepared complexes were according to the reaction molar ratios and all physico-chemical properties as indicated in Figure ١.

Cytotoxic study

Gold(III) compounds are emerging as a new class of metal complexes with outstanding cytotoxic properties and are presently being evaluated as potential biologically active & specifically as antitumor agents[٣٦-٣٩].

Given the strict similarity to cisplatin, gold(III) complexes are of interest for two main reasons : on the one side, they may constitute a new class of anticancer compounds with a novel profile of antitumor activity ; on the other side, they represent a further attempt to elucidate the mechanism of action of antitumor d^8 square planar metal complexes, which still remains largely unknown[٤٠].

Methylthiazoletetrazolium (MTT) assay was employed to assess cell viability . MTT assay was based on the ability of the viable cells to reduce soluble yellow MTT to blue formazan crystals .In this assay ,optical density (OD) values represented the absorption of formazan dissolved by DMSO at ٥٧٠ nm[٢٦].

The evaluation of the cytotoxic properties of synthesized Au(III) complex (C_1-C_4) were tested against HEP-٢ cell line; well known resisted to cisplatin[٤١]. In most cases the investigated compounds showed relevant in vitro anticancer properties with IC_{50} values generally falling in the low μM concentration (~ ٠.٠١ μM) ,additionally , these compounds turned out to overcome largely resistance of HEP-٢ cell line to cisplatin (Figure ٢ and Figure ٣).

Concerning their physiological stability , the C_2 and C_3 Au (III) complexes bearing S- ligands motif , showed acceptable stability within physiological like environment , and important cytotoxic properties.

The application of T-test , show that the potency parameter (IC_{50})of the tested complexes (C_1-C_4) , although not significant , it represent high potency compared to the reference compound , the lack of cross-resistance suggests that gold (III) induce cytotoxicity through different mechanism .So ,S-ligands (L) and (L') are crucial both in stabilizing the Au (III) center and in carrying the metal to its cellular targets[٤٢] i.e. to pharmacokinetic.

It may be ruled out that there is no correlation between different arrangement of ligands (L) and (L') whether monodentate or bidentate, planar or pentacyclic , and neutral or charged around central metal,. Such a finding allows us to state that the presence of H in sulfur-donor ligand is not an essential requirement for cytotoxicity in gold(III) complexes, i.e. to pharmacodynemic.

Since , the cytotoxic profile of synthesized complexes is largely differ to cisplatin , it may come in agreement with many literatures stated that Au (III) were found to perturbs greatly the mitochondrial function [٤٣-٤٥].

This hypothesis is further reinforced by the observation that antiarthritis Au(I) compounds such as; Auranofin ,are known as potent inhibitors of thioredoxin reductase and as effective antimitochondrial agent[٤٦,٤٧].

The fact that measured cytotoxicity is nevertheless relevant, may imply that these complexes either remain in part as a gold(III) species and is quickly taken up by cells as such or that one of its metabolites is highly cytotoxic, this may come with agreement that Au(III) complexes may exerts their cytotoxic activity in different way to its isoelectronic and isostructural to Pt(II), hence, the nuclear DNA is not their ultimate target (DNA independent)[٤٤].

Conclusion

The cytotoxicity of the synthesized gold (III) is strictly related to the presence of the gold (III) center , and that C_1-C_4 are significantly more cytotoxic than cisplatin.

- Using different arrangement of S-ligand around central Au(III) atom appear to have no significant role in cytotoxic activity (non essential

modifications) of these complexes.

- Thiol-ligand is no more being neglected in Au(III) complexes, although Au(III) isoelectrical with Pt(II), suggests that the binding occurs with the gold(III) metal center or one of it metabolite (DNA independent).
- Different arrangement of thioglycolic molecule around Au(III) metal core may or may not be responsible for such different affinities toward synthesized compared to positive control (cisplatin).
- The amount of gold (III) that enters in the cells is roughly proportional to the exposure time , at least during the first hours.

It is clear , after all these evidences , that Au(III) complexes represent an interesting family of cytotoxic agents due to the peculiar chemical and biological properties and further researches have to be developed.

Table ١. Physical Properties of the C١ –C٤ complexes:

No.	Complex	Color	m.p. (^oC)	Yield %	Elemental analysis % Found (calc.) C	H	Au	S	$\Lambda_{ohm^{-1}}$	μ_{eff} (B.M)
١	[Au(SCH٢COO)(HSCH٢COO)]	Dark green	٣٤٦d	٦٥	١٢.٦١ (١٢.٦٩)	١.٣٠ (١.٣٢)	١٦.٨٩ (١٦.٩٣)	٥٠.٧٢ (٥٠.٧٩)	١٠	Dia
٢	Na[Au(SCH٢COO)٢]	Dark brown	>٣٧٥	٧٢	١١.٩٥ (١٢.٠٠)	١.٠٠ (١.٠٠)	١٥.٩٣ (١٦.٠٠)	٤٩.١٩ ٤٩.٢٥	١٩	Dia
٣	Na[Au(HSCH٢COO)٢(SCH٢COO)]	Pale brown	٢١٠d	٧٠	١٤.٦٠ (١٤.٦٣)	١.٦١ (١.٦٣)	١٩.٤٩ (١٩.٥١)	٤٠.٠٠ (٤٠.٠٤)	١٢	Dia
٤	[Au(SHCH٢COO)٢]	Brown	٢٠٠d	٦٩	١٤.٧١ (١٤.٧٨)	١.٢٠ (١.٢٣)	١٩.٦٩ (١٩.٧١)	٤٠.٣٥ (٤٠.٤٥)	١٨	Dia

d = decomposition, Dia = Diamagnetic.

Table ٢. Electronic and Infrared Specification of the complexes

No.	UV. VIS λ_{max} Cm^{-1})	IR bands (cm^{-1})						
		ν asy.(Coo)	ν sym.(Coo)	Δν (ν asy- ν sym)	ν (c-s)	ν(Au-o)	ν (Au-s)	ν (Au-d)
١	٣٢٠٠٠,٢٧٢٤٨١, ٤٤٠٥٠	١٦١٥ vs	١٤٦٥s	١٥٠	٨٤٢s	٤٦٩m	٣٤٥m	---
٢	٣٠١١٠, ٢٨٠٠٠, ٢٥٠٠٠	١٦١٠s	١٤٥٠s	١٦٠	٨٥٠s	٤٨٠m	٣٥٥w	---
٣	٢٦٦٦٦,٢٥٠٠٠	١٦٣٥s	١٤٧٠s	١٥٥	٨٣٩s	٤٧٠s	٣٦٠w	---
٤	٢٩٥٠٠, ٢٥٠٠٠	١٦٣٠s	١٤٦٠s	١٧٠	٨٤٢s	٤٨٥m	٣٥٠m	---

vs = very strong s = strong m = medium w = weak

Table ٣. $IC_{٥٠}$ of $C_١ - C_٤$ compared to cisplatin

$C_١$	$C_٢$	$C_٣$	$C_٤$	D (cisplatin)
٠.٣٩	٠.٤٥	٠. ٤٥	٠.٣٢٥	٠.٣٦

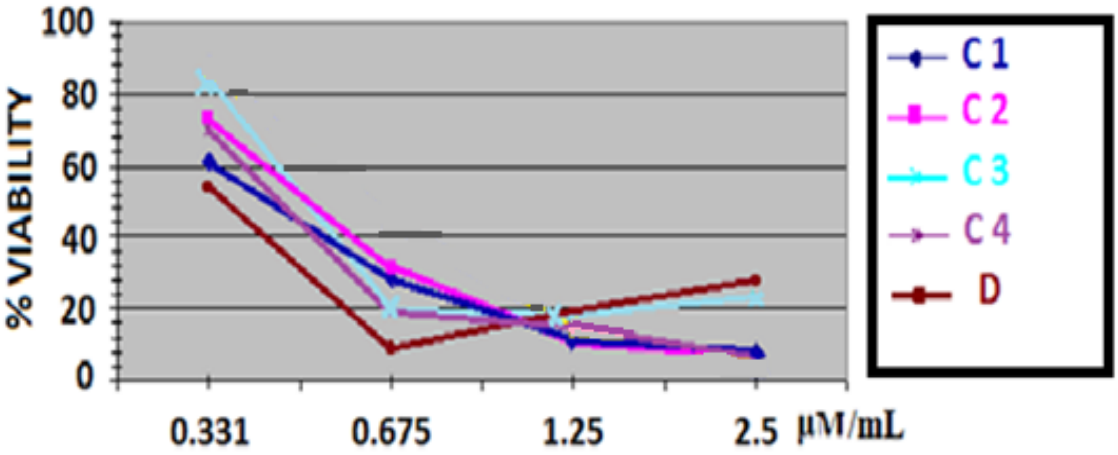

Figure ٢. Different % viability of the synthesized complexes

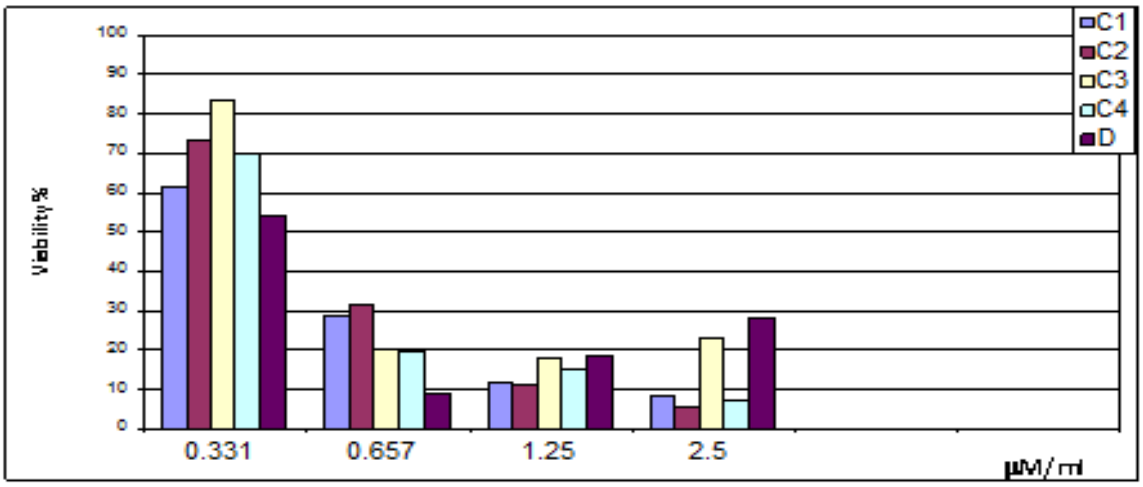

Figure ٣. Histogram of the synthesized complexes

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