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Synthesis, characterization and antibacterial activity study of platinum(II) complex with quinoline ligand

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Abstrat :

Cis-dichloro(quinoline)$_2$Platinum(II)complex [(Qu.)$_2$PtCl$_2$] was prepared using quinoline as non-leaving ligand and chloride ion Cl^- as leaving group.

Platinum(II) complexes was characterized based on infrared spectral and UV-visible measurements, and screened in vitro for their biological activity (both antimicrobial and cytotoxicity). All results were compared with cisplatin and standard free ligand. The compound to be tested was dissolved in dimethylsulfoxide DMSO, thus solvent was used as negative control and cisplatin was analyzed as the positive control.

Antimicrobial activity against gram negative bacteria Escherichia coli and gram positive *Staphylococcus aureus*, show that *Cis*- [(Qu.)$_2$PtCl$_2$] complex exhibit strong antibacterial activity (27.5, 25, mm respectively) against both tested bacteria as compared with free ligand and cisplatin.

Finally, the effect of prepared complex on human red blood cells hemolysis was investigated, found that [(Qu.)$_2$PtCl$_2$] complex caused simple cells hemolysis in vitro about 2.597%) as compared with cisplatin (5.050 %) .

In the present investigation, all results obtained indicate that quinoline ligand plays an important role in the synthesis of new platinum complexes with high efficacy and low toxicity compared with cis-platin anticancer drug.

Key words: platinum (II) complex , Quinoline ligand, antibacterial activity, *in vitro* cytotoxicity.

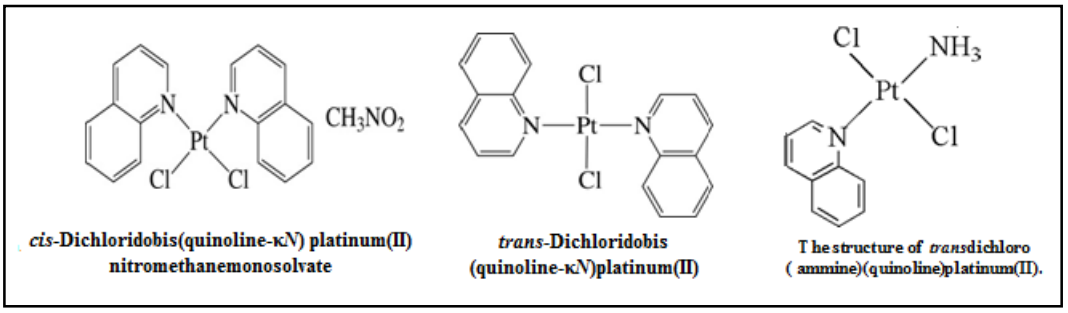
Chemistry classification : QD 146-197

Introduction

Platinum compounds are one of the most potent class antitumor drugs used in cancer chemotherapy (1). The role of metals in cancer therapy and biological chemistry has gained much interest since the discovery of the potent anticancer drug cisplatin. To date, cisplatin, and its second-generation analogue carboplatin are the most successful of the anticancer metal complexes and are currently widely used in the treatment of cancer (2). However, it has a number of side effects and also cancer cells can have intrinsic resistance to the drug or develop resistance due to the continued use of cisplatin, severe toxicity (3,4,5,6,7). In an effort to overcome the

drawbacks of cisplatin, many platinum (II) complexes have been synthesized and screened for anti-cancer activity. To reduce the toxic side effects of cisplatin and to widen the spectrum of activity, thousands of cisplatin analogues have been prepared during the last thirty years by varying the nature of leaving groups and the carrier ligands (8,9). The use of amines more compatible to the human system has been another important area. For this purpose, naturally occurring substances like amino acids, peptides,carbohydrates and glucosamines whose uptake is increased in malignant cells have been used as non-leaving ligands in some platinum complexes (10,11,12,13,14).

Several researchers have designed novel platinum complexes that contain biologically active ligands, in the hope that these complexes would be more potent than the parent complex. Examples of some of the biologically active ligands in use was Quinoline**,** 1-azanaphthalene, is an aromatic nitrogen compound characterized by a solid-ring structure contains a benzene fused to pyridine at two adjacent carbon atoms. It can be obtained by the distillation of coal tar(15,16). Quinoline family compounds are widely used as a parent compound to make drugs (especially anti-malarial medicines), fungicides, biocides, alkaloids, dyes, rubber chemicals and flavoring agents. They have antiseptic, antipyretic, and antiperiodic properties. They are also used as catalyst, corrosion inhibitor, preservative, and as solvent for resins and terpenes (17,18)**.** Several compounds of this class have shown various biological activities, such as antimalarial, antitumor, anti-inflammatory, and antiparasitic. Substitution of an ammonia ligand of tranplatin with a planar amine such as quinoline or thiazole dramatically enhances the cytotoxicity of the *trans* geometry (15,18.19,20,21,22,23) (Fig 1).



cis-Dichloridobis(quinoline-κN) platinum(II) nitromethanemonosolvate

trans-Dichloridobis (quinoline-κN)platinum(II)

The structure of *trans*dichloro (ammine)(quinoline)platinum(II).

Figure (1): Chemical structure of some platinum(II) complexes with biologically active Quinoline ligand

Thus, the aims of the present study are:

[1] Prepare and characterize of new platinum (II) complex using quinoline amine (as non-leaving ligand) with the hope of obtaining compound which display less toxicity, broad activity, reduced development of drug-resistance, and reasonable water solubility.

[2] Study the antibacterial activity of the synthesized complex.

[3] Study the effect of complex on human red blood cells hemolysis *in vitro.*

Materials and methods

(1) Preparation of potassium tetrachloro- palatinate k_2PtCl_4

K_2PtCl_4 is prepared as described in the chemical literatures (14) as follow: A suspended solution of potassium hexachloro-platinate K_2PtCl_6 (2 mmole, 0.972 gm) in distilled water, and (4 mmole, 0.420 gm) hydrazine was added drop wise with continuous stirring at 50 ^{o} C. The solution was evaporated on rotary evaporator under reduced pressure, needles red- crystals were obtained, the precipitate was filtered off, washed with acetone, and dried over night at room temperature.

(2) Ligand used in the study:

Quinoline(Qu.)[Benzopyridine, C_9H_7N, 129.16 g/mol] drug was used in the platinum (II) complexes preparation as monodentate non-leaving group **.**

(3) Preparation of *Cis*-dichloro-platinum (II) complexes

[$(Qu.)_2$ Pt (Cl_2)] complex (in which Cl represents leaving group), was prepared as described in (24) as follow: Aqueous solution of K_2PtCl_4 (1 mmole, 0.418gm) was added to a solution of (0.26 gm, 2 mmole) for monodentate ligand (quinoline drug) in 50 ml-distilled water. The reaction mixture was stirred for (6 hours) at room temperature away from light. The precipitate of $[(Qu.)_2Pt\ Cl_2]$ was filtered , washed with ethanol and dried in room temperature.

(4) Chemical Identification:

All measurements were determined in Central Laboratory/Kufa University**.**

(i) - Ultra-violet and visible spectroscopy:

Each complex was dissolved DMSO to study the UV-visible in range of (200-600) nm, using a computerized thermospectronic (Model LR115161, Helios, England).

(ii)- Infrared spectroscopy:

Infrared spectra were recorded in KBr pellets using a Fourier Transform Infrared (FT.I.R) spectrophotometer (Model 8400S, SW shimadzu, Japan), in the range (4000-200) cm^{-1} to fined the functional groups of each prepared complex.

(iii) - Melting point measurement:

melting points were determined using electro- thermal® melting point apparatus (Gallenhamp, England).

(5) Biological Activity of Platinum (II) Complexes

(1) Stock solution of Platinum (II) complexes

For all biological experiment, stock solution of complex as well as standard drug (quinoline) [100 µg/ml] were prepared , dimethyl sulfoxide DMSO were used as solvent to prepare their stock solutions (the final concentration of the solvent should be 1 %), and standard cisplatin was dissolved in normal saline.

(2) Bacterial cultures

Gram positive bacteria(*Staphylococcus aureus* NCTC 25923) and Gram negative bacteria (*Escherichia coli* NCTC 25922**)** reference strains were obtained from Microbiology Laboratory, College of Pharmacy/ Kufa University for antibacterial activity evaluation.

(3) ***Screening for antibacterial activity***

The disc diffusion method was used to evaluate the antibacterial activity (25,26).

Nutrient agar was prepared in the plates as the media for the test microorganisms. Sterile filter paper discs (Whatman No. 1mm) were impregnated with 100 µl of each of the test compound and left to dry under the laminar flow cabinet overnight. The bacterial inoculum was spread evenly onto the surface of the nutrient agar plates using a sterile glass L-form rod before the extract discs were positioned on the inoculated agar surface. Each extract was assayed in triplicate. Dimethylsulfoxide served as negative control, whereas cisplatin drug present the positive control. All the plates were incubated for 24 hr at 37° C. The antibacterial activity was interpreted from the size of the diameter of zone inhibition measured to the nearest millimeter (mm) as observed from the clear zones surrounding the discs.

(4) Cytotoxicity assay:

(1) Blood sample

Heparinized peripheral normal blood sample from Al- Sader Hospital Al-Najaf City were tested *in vitro* for chemosensitivity of Pt (II) complexes using the cytotoxicity assay.

(2) Blood Hemolysis (*In Vitro* Cellular Toxicity)

The potential of platinum (II) complex solution at a concentration of [100 µg/ml] to cause hemolysis was examined using the static *in vitro* test models according to (27) as follow:

A 30-µl of test solution was added to 0.2-ml blood (from healthy non-smoker volunteer) resulting in a formulation: blood ratio of 0.15. The solutions were slowly whirl-mixed for 5 seconds and added to 20-ml normal saline to quench any hemolytic reaction. Subsequently, an aliquot of the diluted test solution was centrifuged at 3000 rpm for 10 minutes.

The absorption (A) of the resulting supernatant was measured at 540 nm with UV/VIS spectrophotometer. The baseline degree of hemolysis was measured using normal saline at the same formulation: blood ratios, with 30 µl of DMSO as a positive control. The 100% hemolysis level was determined by diluting the blood used with a 100- fold larger volume of distilled water instead of normal saline.

The percentage hemolysis induced by all solutions was calculated using equation:

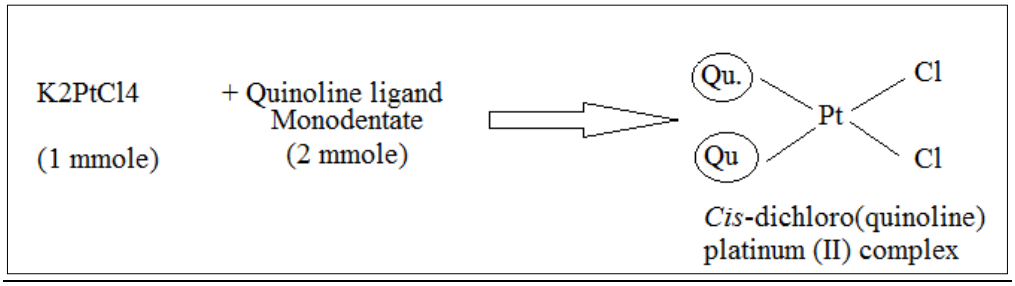
$$\textbf{Hemolysis \%} = (A_{\text{test solution}} - A_{\text{normal saline}}) / (A_{100\%} - A_{\text{normal saline}}) \times 100\%$$

Results And Discussion

(1) Preparation of Pt (II) complex with quinoline ligand :

In this study, Quinoline drug was utilized in complex preparation as a carrier Ligand.

In the present study, $[(Qu.)_2Pt\ Cl_2]$ complex has been synthesized (Fig 2). General synthetic methods have been used to prepare this complex: Quinoline ligand was bioactive molecules with reactive properties, can produce numerous derivatives having a wide range of uses, thus increased the chance of their coordination to the platinum metal center. The direct reaction of two moles of Quinoline with one mole of potassium tetrachloroplatinate (K_2PtCl_4) gives $[(Qu.)_2\ Pt\ Cl_2\ ]$ complex as below:



Figure(2): Synthesis of Cis- dichloro(quinoline)2 plsatinum (II) complex.

$[(Qu.)_2PtCl_2]$ complex was soluble in dimethylsulfoxide (DMSO) as well as in polar organic solvents such as methanol, dimethylformamide (DMF), and chloroform due to the polarity of the anionic drug ligand. Table (1) shows the physical properties of prepared complexes .

Table (1) : Some physical properties of the prepared complex

No.	*Compounds*	*Physical properties*		
		Color	*Melting point (dec)°C*	*Solubility*
1-	$[(Qu.)_2PtCl_2]$	Pale- yellow	290-300*	DMSO,DMF, ethanol
2-	Quinoline standard	Dark-brown	26-28	Alcohol,ether,carbone disulfide**
3-	Cisplatin standard	Deep-yellow	270	Water, DMF**

Dec.= decomposition

(2) Characterization of Pt(II) complexes :

(a) Infrared spectra (IR) :

All the prepared complex has been characterized by infrared spectroscopy. The wavenumbers (in cm^{-1}) of bands observed in the infrared spectra of this complex in the (4000-200) cm^{-1} region are listed in Table (2), and showed in Figure (2 a,b).

The interpretation of the observed bands has been based mainly on published spectra (28,29,30).

Of the various mode in the infrared spectra, particular attention is focussed on the stretching vibrations of the $–NH_2$ group (s), -OH, C=O of ligands and complexes ,these groups which are most likely to change as a consequence of complexation.

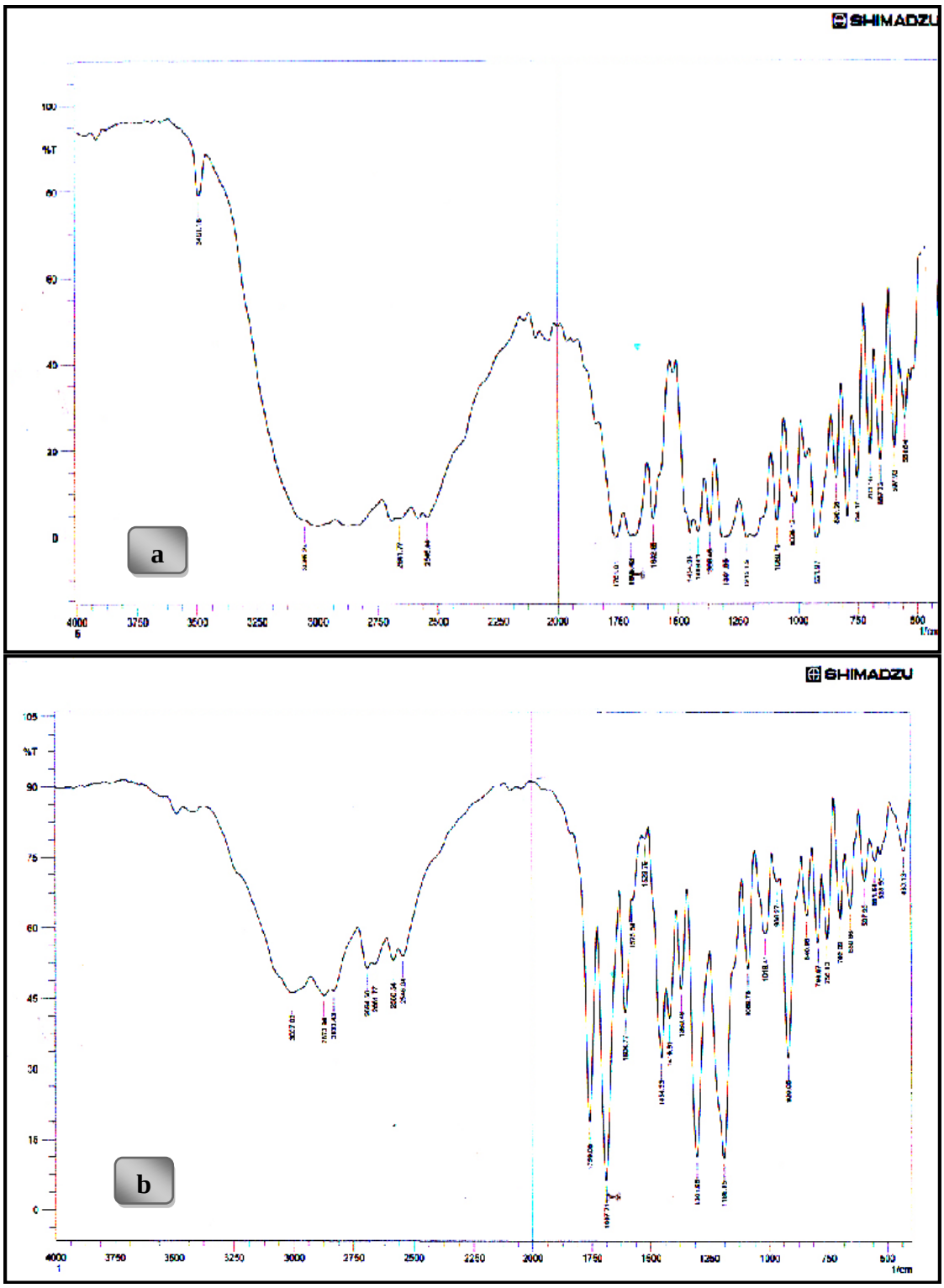
From the study of the IR spectra of the platinum (II) complex, we can see some important functional groups vibrations can be interpreted by using the group theory for molecular vibrations , namely two stretching bands between the platinum metal and oxygen or nitrogen or chloride appear in the "far infrared region". One of these represents the symmetrical vibration stretching to the cis-band, while the other represents the asymmetrical vibration stretching.

The characteristic vibrations and assignments of ligand quinoline (Qu.) and its complex was described in Table (2) and Figure (3).The IR -spectrum of the standard quinoline ligand (Fig. 3a) shows the widely braod band (3400-3049cm^{-1}) due to stretching vibration of C-H aromatic and another strong band appeared at (1581cm^{-1}) attributed to stretching vibration of C=N in the pyridine ring. Whereas in $[(Qu.)_2PtCl_2]$ IR-spectrum(Fig. 3b), the appearance of Pt-N stretching at 513 cm^{-1} refers to the interaction between N atom of the pyridine ring in the quinoline ligand and the Pt-ion, thus the interaction could be a monodentate between the lone pair electron of the nitrogen atom and the empty dxy orbital of platinum (II) ion.The shifting was (6 cm^{-1}) to the higher frequencies which indicated the coordination of ligands with metal. The band at 379 cm^{-1} is due to (Pt-Cl) stretching vibration.

Table(2): The characteristic bands of infrared spectra of The quinoline ligand and its complex.

Compounds	***V*(C-H)**	***V*(C-N)**	***V*(C=C)**	***V*(Pt-N)**	***V*(Pt-Cl)**
Free Quinoline	3400-3049 m.br	1581 W	1500 s.sh	-	-
$[(Qu.)_2Pt(Cl)_2]$ Complex	3421-3062 br	1587 m.sh	1506 s.sh	513	379

s= strong; m=medium; w=weak; v=very ;br=broad; sh=sharp



Figure(3): FT-IR spectra of free Quinoline (a) and $[(Qu.)_2PtCl_2]$ complex(b).

(b) Electronic spectra (UV-Visible):

In order to obtain some more information about the coordination behavior of the platinum (II) metal ion, the electronic spectra of the prepared complex has been recorded in the range of (200-600)nm or (25000-50000)cm^{-1}.

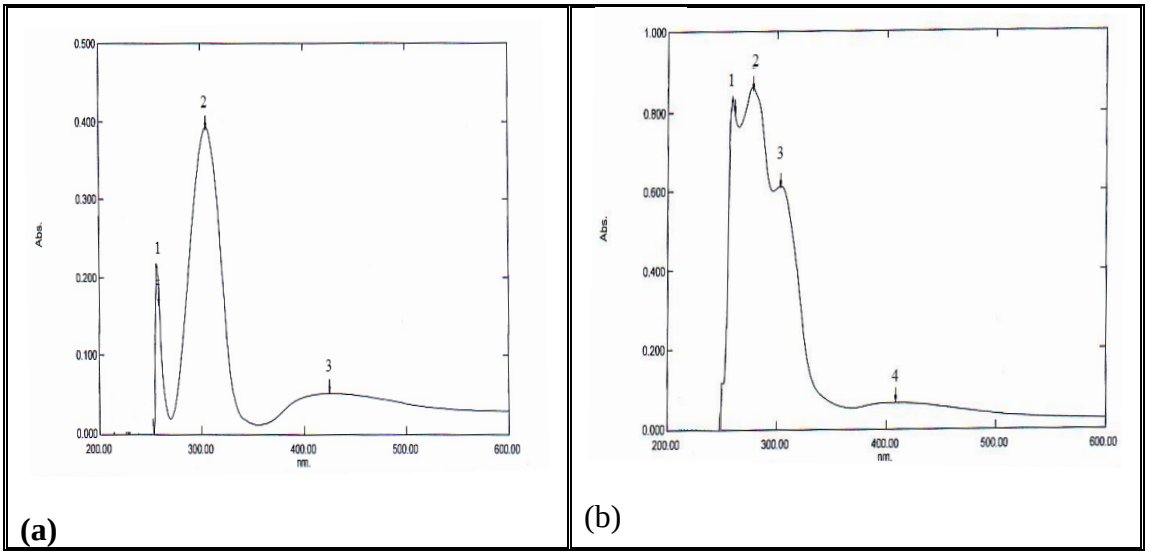
The absorption bands are listed in Table (3) and Figure (3 a & b)) shows the electronic spectra of platinum (II) complex $[(Qu.)_2Pt\ Cl_2]$ compared to standard ligand (30).

The extra bands appeared in the complexes spectra comparing to the drugs spectra refer to both charge transfer and d-d transitions, indicating that coordination between the drug and metal was certain. The spectrum of free ligand showed strong band at λmax 258nm attributed to (π-π*) and another at λmax (305-425nm) due to (n-π*). The pale –yellow complex showed strong bands at λmax (278, 303nm), these are attributed to charge transfer (CT) and the shoulder at λmax 409nm .Both LMCT(Ligand-Metal transfer) and MLCT(Metal-Ligand Charge Treansfer) transitions generally interfere with the observation of the weak d-d transitions 409 nm (28).

Table (3) :UV-Visible spectra of free quinoline ligand and its platinum complex in DMSO solvent.

Compounds	λ-max (nm)	Transition
$[(Qu.)_2\ PtCl_2]$	278 303, 409	π -π* CT, d-d
Quinoline standard	258 305, 425	π -π*

CT= Charge Transfer



(a) (b)

Figure(2): UV-visible of Quinoline ligand (a) and $[(Qu.)_2Pt\ Cl_2]$ complex(b).

(3) Biological activity study:

(a) Antibacterial activity :

In vitro antibacterial screening is generally performed by disc diffusion method against *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25922 bacteria for the primary selection of the compound as therapeutic agent.

The results of antibacterial activity of Pt (II) complex in concentration [100 μg/ml] was given in Table (4) and Figure(4).

The results of primary screening show that the synthesized Pt(II) complex has good antibacterial activity against both gram negative (-ve) *E. coli* (27.5mm) and gram positive(+ve)*S. aureus* bacteria (25mm) compared with standard ligand and cisplatin (Table 4& Fig. 4). it has better activity against *S. aureus* than *E. coli*. Antibacterial activity of prepared complex may be due to the increased in electronic density resulted from the presence of N=C, NH_2, and active groups, electronic density increased bond strength leading to enhanced inhibition activity of complexes (31).

Coordination complexes of transition metals have been widely studied for antibacterial activities (32,33,34). In this study, the quinoline ligand utilized in Pt (II) complex preparation initially has potent antibacterial activity against wide range of gram positive and gram negative bacteria through different mechanisms of action, whereas after complexation with platinum metal, they showed pronounced alteration in their activity resulted from changes in their chemical structure leading to change their biological activities (i.e. by bonding through the active group responsible for antibacterial activity). Thus, variations in antibacterial activity of Pt-complex against gram (-ve) and gram (+ve) bacteria compared with standard ligand may be due to the coordination of platinum metal away from active group responsible for antibacterial activity, which explain antibacterial activity of the resultant complex.

On the Other hand, antimicrobial agents with positively charged molecular structures may be electrostatically bound to acid or sulphate groups of the agar, and consequently the rate of diffusion through the agar gel falls off, such as amino glycosides seem to have a tendency for electrostatic binding to active groups on the agar (35). As well as molecular weight of Pt (II) complexes may affect the degree of compound distribution within agar as compared with free ligands. All these factors play an important role in the complexes activity as compared with standard ligand and cisplatin (25,36).

Table (4) : *In vitro* Antibacterial activity values of the [(Qu.)$_2$PtCl$_2$]complex against gram negative bacteria *Escherichia coli* and gram positive bacteria *Staphylococcus aureus* compared cisplatin and free quinoline.

Compounds	*E.coli* [ATCC 25922]	*S. aureus* [ATCC 25923]
	Concentration (100µg/ml)	
[(Qu.)$_2$ Pt Cl$_2$]	27.5	25
Quinoline standard	13.5	13
Cisplatin(+ve control)	15.5	12
DMSO(-ve control)	NI	NI

NI= No inhibition

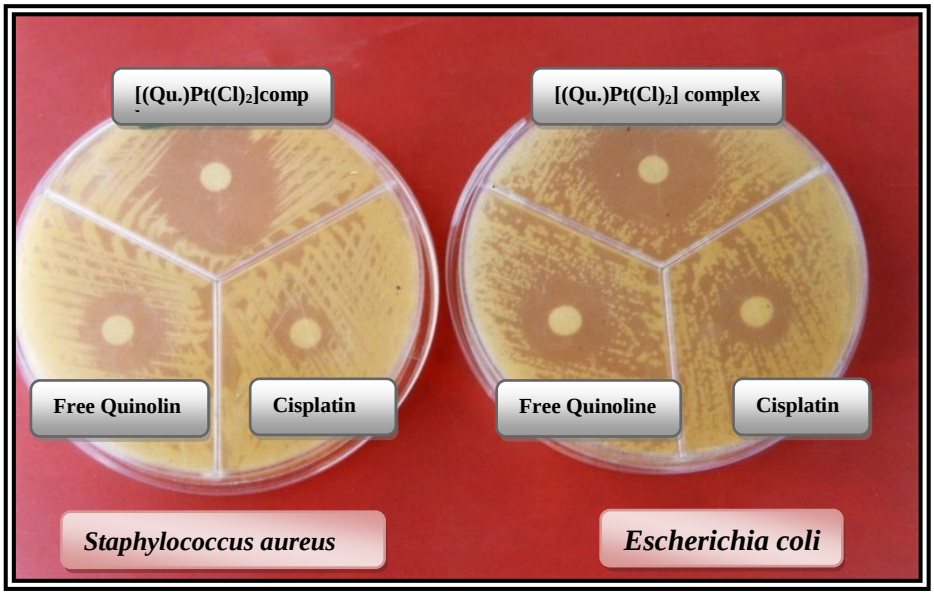


Figure (4) : Antibacterial activity of [(Qu.)$_2$ PtCl$_2$] complex in mm against *E.coli* and *S.aureus* compared to free ligand and cisplatin

(b) Blood Hemolysis (*In Vitro* RBCs toxicity) :

The synthesized Pt (II) complex with quinoline ligand was tested for its toxicity against human red blood cells (RBCs) using a dynamic in vitro test method. Table (5) show the values of absorbance at 540 nm and hemolysis percent for the complex at concentration of [100 µg/ml]. From the results shown in Table (5) ,the Pt(II) complex cause simple RBCs hemolysis at the tested concentration (2.597 %).

In general, [(Qu.)$_2$PtCl$_2$]complex with chloride represent leaving group, show low RBCs hemolysis percent (2.597 %) compared cisplatin (5.050%). Quinoline ligand used in complex preparation as non- leaving group show little toxic effect on the RBCs. When the nature of the leaving groups was modified, it was possible to make

change in toxicity profile of the compounds but no changes in the spectrum of activity could be achieved (37). Based on these results, intravenous infusion of Pt(II) complex solution is not expected to cause severe hemolysis.

Table (5): Hemolysis (%) of platinum (II) complex compared with cisplatin.

Compounds	Absorbance (540 nm)	Hemolysis (%)
[Qu.)$_2$pt Cl$_2$]	0.025	2.597
Cisplatin	0.042	5.050
Normal saline	**0.007**	
A 100%	**0.700**	

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تحضير وتشخيص ودراسة الفعالية البايولوجية لمعقد بلاتيني ثنائي مع أمين الكوينولين

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رجاء علي حسين

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الخلاصة :

تضمنت الدراسة الحالية تحضير المعقد البلاتني *Cis*-dichloro(Quinoline) platinum(II) [$(Qu.)_2PtCl_2$] باستخدام أمين الكوينولين(Quinoline) كمجموعة غير مغادرة في حين مثل ايون الكلورايد (Cl^-) المجموعة المغادرة .

شخص المعقد البلاتيني المحضر باستخدام طيف الأشعة تحت الحمراء وفوق البنفسجية Infrared and Ultra-Violet spectroscopy و درست فعاليته البايولوجية(و شملت الفعالية المضادة للجراثيم والسمية الخلوية) وقورنت جميع النتائج مع الدواء القياسي الـ Cisplatin والليكند الحر ، إذ حضرت تراكيز المعقد بإذابته في المذيب Dimethylsulfoxide (DMSO) .

أظهرت الفعالية البيولوجية للمعقد [$Pt(Qu.)_2\ Cl_2$] باستخدام العزلات القياسية الموجبة والسالبة لصبغة كرام(*Escherichia coli* و *Staphylococcus aureus*) ان للمعقد فعالية مضادة للبكتريا وبلغت (5.27 و 25 ملم على التوالي) مقارنة مع الكوينولين القياسي والسزبلاتين .

اختبر تأثير المعقد المحضر على تحلل كريات الدم الحمر في الإنسان ، و أظهرت النتائج تأثيرا بسيطا على تحلل كريات الدم (2.597 %) للمعقد[$(Qu.)_2PtCl_2$] مقارنة مع عقار Cisplatin (5.050%).

أكدت جميع نتائج الدراسة الحالية أن الليكند الكوينولين من أفضل الأمينات المستخدمة لتحضير معقدات بلاتين فعالة بيولوجيا وقليلة السمية مقارنة مع السزبلاتين .

الكلمات المفتاحية: معقد البلاتين الثنائي، أمين الكوينولين، الفعالية المضادة للجراثيم، السمية الخلوية .

Chemistry classification : QD 146-197