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Preparation, Characterization of A New Cis – Iodoplatin and Cis - Carboplatin Complexes and Study There Spectral, Physical and Pharmaceutical Properties

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Abstract

This search includes preparation of new cis–platin, in the form of iodin, and new two cis - carboplatin complexes {cis [Pt(4-aminoantipyrine) $(NH_3)_2]I_2$ and cis[Pt (aminosalicylicacid) $(NH_3)_2]I$}, which used as anti - cancer drugs, they are prepared by using the organic ligands 4-amino salicylic acid and 4-amino anti pyrine. These complexes were characterized by using UV–Vis., FTIR, XRD and ^{1}HNMR spectroscopic techniques . The effect of the concentration and the temperature on the molar electrical conductivity of its solutions were studied. The expiry date (half-life) for the solutions of the complexes in the circumstances at the degrees (35^0C) and (20^0C) was determined.

Keyword: Cis-[Diaminodiiodoplatinum(II)], Carboplatin, XRD, ^{1}HNMR.

Abbreviations:

4 – aminoantipyrine: 4-AAP

4 – aminosalcylicacid: 4-ASA

Introduction

Cis – platin and cis - carboplatin complexes are coordination complexes of platin (II) and classify as anti - cancer drugs according to American drugs record[1]. The DNA nuclear acid in the cell is the target of the cis – platin [2],[3]. Cis - carboplatin is less toxic than cis - platin and more active against the same tumor[4]. Carboplatin had been using for long time for the treatment of many types of tumors such as lung tumors and contrast of cis-platin mechanism, carboplatin linked

covalently with the DNA nuclear acid and do not cause any kidney poisoning or nausea or puke and its poisoning is inhibition bone marrow, which leads to decrease the platelets, therefore, it is more used than cis – platin for the patients who suffer from toxic intolerances of cis – platin, also cis - carboplatin has more stability in blood plasma than cis - platin [5].The proposed mechanism for cis – platin to stop the cell division is: cis – platin can enter inside the cell easily and associated with the two sandwiches of the DNA at the same by hydrogen bonds during nitrogen, sulfur and oxygen atoms cause to kill the cancer cell[6].

Excremental

1-Prepration of cis – iodoplatin: $[Pt(NH_3)_2I_2]$ [7-10]:

In a small beaker (0.003mol ,1.25g) of (K_2PtCl_4) was put and (2ml) of distilled water was added. The solution was heated in a water bath at (40 °C) and KI solution ((0.015mol)(2.5g) in 5ml hot distilled water was added. The color of the resulting solution changed from red-brown to red- black. This solution was heated to (70 ^{0}C) with stirring after that add drop wise (5ml) of ammonia solution (2M) to control the Ph at 7, soon a fine yellow crystals of cis- [Pt (NH_3) $_2I_2$) precipitate was formed. To adjust the PH, add ammonium chloride (0.2g) as a buffer solution to prevent the formation of hydroxide complex. Heat the solution to a (60 ^{0}C) for one hour and take care of that the pH not raised above 7. Cool the solution by using ice bath, soon greenish – brown precipitate was formed. Filter and wash with 10ml of cool ethanol and with 30 ml of cool distilled water, product percentage was (85%) according to the following equations

$$K_2PtCl_4 + 4KI \rightarrow K_2PtI_4 + 3KCl$$
$$K_2PtI_4 + 2NH_4OH \rightarrow cis-[Pt(NH_3)_2I_2] + 2KI + 2H_2O$$

2-Preparation of cis - $[Pt(4\text{-aminoantipyrine})(NH_3)_2]I_2$:

In distilled flask (0.00083mol,0.4g) of cis- [Pt (NH_3) $_2I_2$] and (0.00083mol,0.17 g) of (4-amino anti pyrine) reagent were mixed and dissolved in (20ml) of absolute ethanol. By reflux process, at (80 ^{0}C) with stirring for three hours, the reaction was done. Brown precipitate was formed. The mixture was cooled in ice bath. Filtrated and washed with (10ml) of ethanol and (20 ml) of cooled water. The following equation to make clear this reaction:

$$cis-[Pt(NH_3)_2I_2] + 4-a\,\text{min}\,oantipyrine \rightarrow$$
$$cis-[Pt(4-a\,\text{min}\,oantipyrine)(NH_3)_2]I_2$$

3-Prepration of cis - $[Pt(4\text{-aminosalicylicacid})(NH_3)_2]I$:

In distilled flask (0.00083mol)(0.4g) of cis- [Pt (NH_3) $_2I_2$] and (0.00083mol)(0.122 g) of (4-amino salicylic acid) reagent were mixed and dissolved in (20ml) of

absolute ethanol. The pH of the solution was adjust between (8-7) so the solution become light basic by using very dilute potassium hydroxide solution. By reflux process, at (80 ^{0}C) with stirring for three hours, the reaction was done.. The mixture was cooled in ice bath. Filtrated and washed with (10ml) of ethanol and (20 ml) of cool water Black precipitate was formed. The following equation to make clear this reaction:

$$cis-[Pt(NH_3)_2I_2]+4-a\min osalicyli\text{-}acid \rightarrow$$
$$cis-[Pt(4-a\min osalicyli\text{-}acid)(NH_3)_2]I$$

4 - Physical, spectral and pharmaceutical studies:

The prepared complex was characterized by UV. Vis., FTIR and HNMR spectra. XRD spectra for the cis – iodoplatinum complex was recorded by using X-ray diffraction technique. HNMR spectra for the complexes were measured. Molar conductivity was measured, for the prepared complexes with different concentrations, from 8x10^{-3} M to 1x10^{-4} M at 35 ^{0}C. The change in molar connectivity at different temperatures from 80 ^{0}C to 20 ^{0}C was measured. The effect of temperature of the prepared complexes (4x10^{-4}M) studied by using UV. Vis. technique at different temperatures (80-20 ^{0}C). The expiry date of the complex solutions (1x10^{-3}M) at two temperatures, 40 ^{0}C and 20^{0}C, was studied by using UV. Vis. Technique, in which the absorbance was measured at each (48) hour for 20 days.
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Results and Discussion

1-UV.Vis. spectra:

The electronic spectra of the complexes cis-[Pt(4-aminoantipyrine) $(NH_3)_2$] I_2 and cis-[Pt(4-aminosalicylicacid) $(NH_3)_2$]I, show that λ_{max} are (495 nm) (440 nm) respectively which belong to the transmission (M→L.C.T.) [11]. The λ_{max} (364nm) (330 nm) which belong to the transmission (n→π *)[12] and the λ_{max} (296 nm) (304 nm) which belong to the transmission (π-→π*) [13], while the complex cis-[Pt$(NH_3)_2I_2$)] shows a λ_{max} (302 nm) which belongs to the transmission (M→L.C.T.). table (1)and figures (1,2,3) show these results. The differences in λ_{max} between the primary material and the complexes is a good evidence for the formation the new complexes.

Table (1): UV.Visb. data for the prepared complexes

Compounds	λ (nm)	V(cm^{-1})	Type of transition
Cis-[$Pt(NH_3)_2I_2$)]	302	33112	M→L.C.T.
Cis-[Pt(4-AAP) $(NH_3)_2$] I_2	296 364 495	33783 27472 20202	π*→π n→π* M→L.C.T.
Cis-[Pt(4-ASA) $(NH_3)_2$]I	304 330 440	23894 30303 22727	π*→π n→π* M→L.C.T.

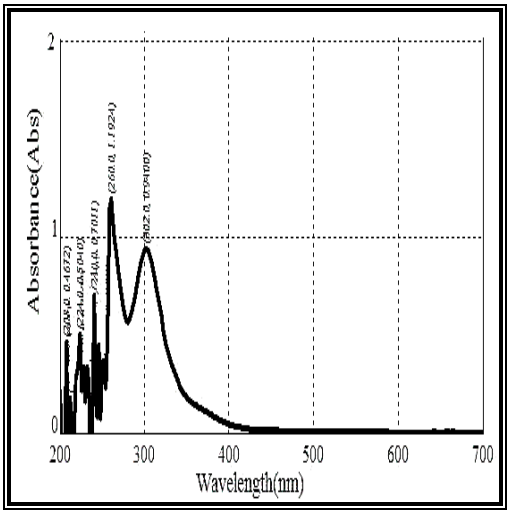

Figure (1): UV-Vis. spectrum for cis-[$Pt(NH_3)_2I_2$)]

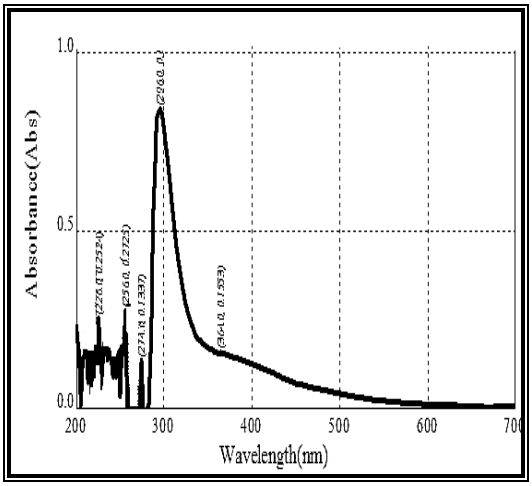

Figure (2): UV-Vis. spectrum for cis-[Pt(4-AAP) $(NH_3)_2$] I_2

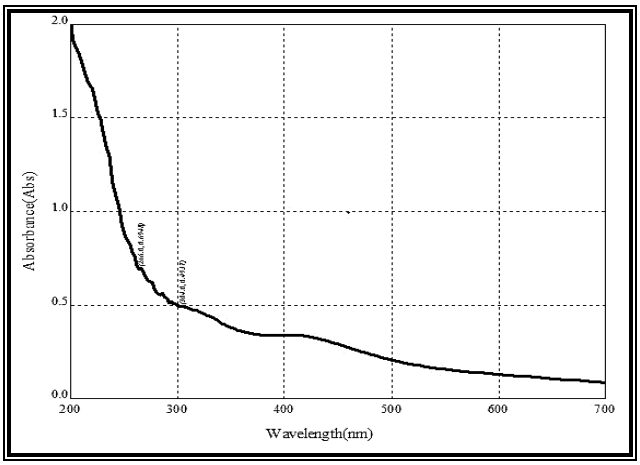

Figure (3): UV-Vis. spectrum for cis-[Pt(4-ASA) $(NH_3)_2$]I

FTIR spectra:

The FTIR spectra for the complexes cis-[$Pt(NH_3)_2I_2$)], cis-[Pt(4-AAP)$(NH_3)_2$] I_2 and cis-[Pt(4-ASA) $(NH_3)_2$]I show the frequencies ($595\,cm^{-1}$), ($586\,cm^{-1}$) and ($546\,cm^{-1}$) belong to the bond (M-N) respectively. The the frequencies ($498\,cm^{-1}$) and ($441\,cm^{-1}$) for the complexes Cis-[Pt(4-AAP)$(NH_3)_2$] I_2 and cis-[Pt(4-ASA) $(NH_3)_2$]I respectively belong to the transmission (M-O) respectively, and the frequency ($3251\,cm^{-1}$) belongs to the bond (O-H) of the complex cis-[Pt(4-ASA) $(NH_3)_2$]I [14], table (2) and figures (4,5,6) show these results. The shifting,

removing and appearing of some frequencies is an evidence of the formation of new complexes.

Table (2): Explain the frequencies FTIR spectra for the complexes

Compounds	(N-H)	(N-N), (N=N)	(C=O)	(M-N)	(M-O)	(O-H)
Cis-[Pt(NH_3)$_2$$I_2$)]	3272s 1290w			595 m		
Cis-[Pt(4-AAP)(NH_3)$_2$] I_2	3431s 1161w	1492s	1643s	586 m	498 m	
Cis-[Pt(4-ASA) (NH_3)$_2$]I	3461s 1028w		1608s	547 m	441 m	3251b

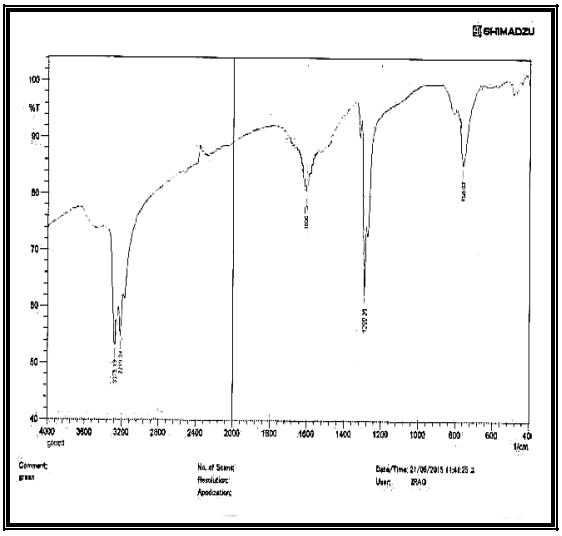

Figure (4): FTIR spectrum for Cis-[Pt(NH_3)$_2$$I_2$

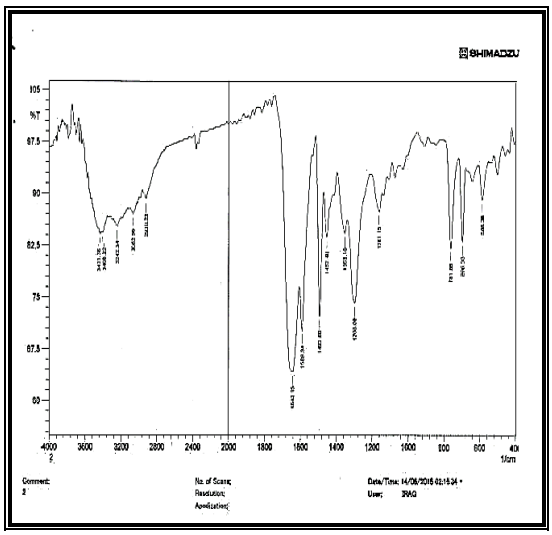

Figure (5): FTIR spectrum for Cis-[Pt(4-AAP) $(NH_3)_2$] I_2

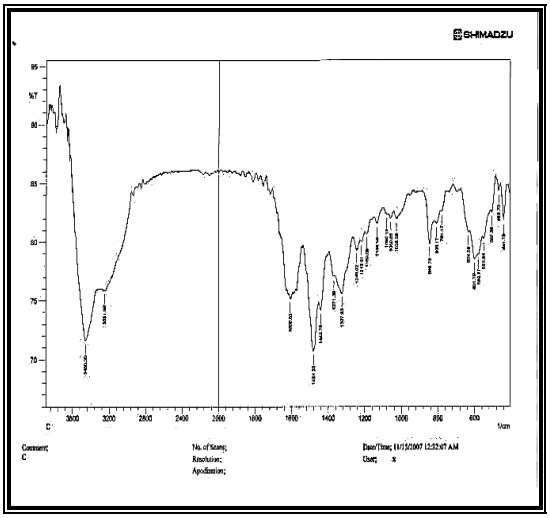

Figure (6): FTIR spectrum for Cis-[Pt(4-ASA) $(NH_3)_2$]I

XRD spectra:

X-ray diffraction angles(degree) for the complex cis-[$Pt(NH_3)_2I_2$)] are 12.68, 18.06 and 39.19, the first value belongs to Pt(ll), that ensures that the complex contains Pt(ll) rather than Pt(lV) ion, which ensures what we want. Table (3) and figure (7) show these results.

Table (3): XRD data for the cis – iodoplatin complex

Compounds	2 Theta (deg.)	I/I_2
(Cis-[$Pt(NH_3)_2I_2$)])	12.68	100
	18.06	15
	39.19	14

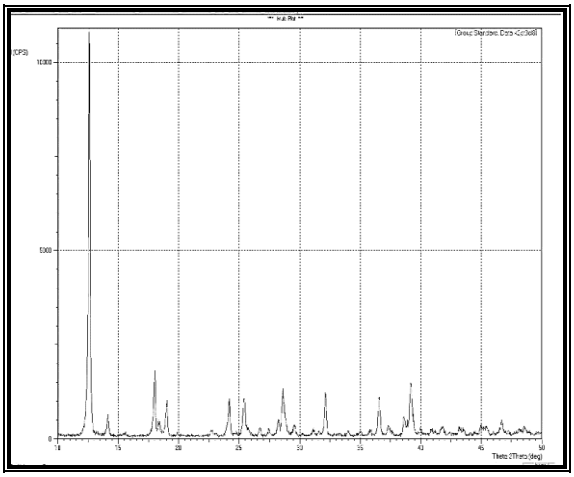

Figure (7): XRD spectrum for cis-[$Pt(NH_3)_2I_2$)] complex

^{1}HNMR Spectra

^{1}HNMR spectra of the complexes cis-[$Pt(NH_3)_2I_2$)], cis-[Pt(4-AAP) $(NH_3)_2$] I_2) and cis-[Pt(4-ASA) $(NH_3)_2$]I had been studied. ^{1}HNMR spectrum of the complex cis-[$Pt(NH_3)_2I_2$)] shows an appearance a single peak at 3.32 ppm which belongs to the six protons of the two groups of NH_3 as obvious in figure 8. ^{1}HNMR spectrum of the complex cis-[Pt(4-AAP) $(NH_3)_2$] I_2 shows an appearance of a single peak at 6.70 ppm which belongs to the benzene ring within the complex and two single peaks at 2.09 ppm and 2.70 ppm, the first belongs to CH_3 group that attached to carbon atom and the second belongs to CH_3 group that attached to nitrogen atom in pyrol ring, additionally, there is a single peak at 3.8 ppm belongs to NH_2 group, figure 9 shows all these peaks. ^{1}HNMR spectrum of the complex cis-[Pt(4-ASA) $(NH_3)_2$]I shows an appearance of a single peak at 7.10 ppm which belongs to the aromatic ring, also there is a single peak at 3.33 ppm which belongs to NH_2 group, additionally, there

are two peaks at 2.74 ppm and 2.09 ppm which belong to NH_3 group. All these peaks proved that the ligands and the ion metal joined together to form the complexes.

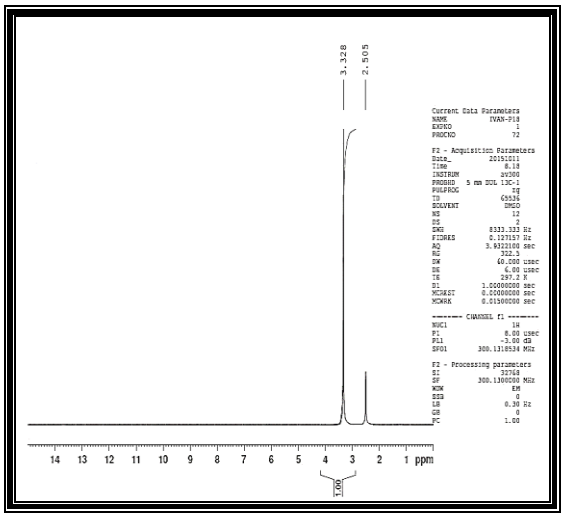

Figure (8): ^{1}HNMR spectra for cis-[Pt$(NH_3)_2I_2$)] complex

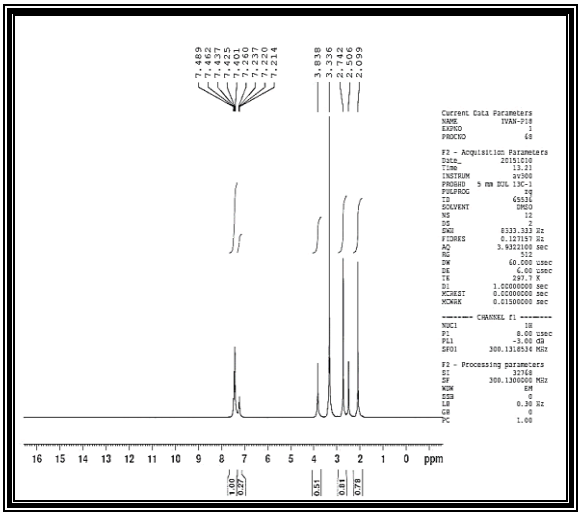

Figure (9): ^{1}HNMR spectra for cis-[Pt(4-AAP) $(NH_3)_2$] I_2 complex

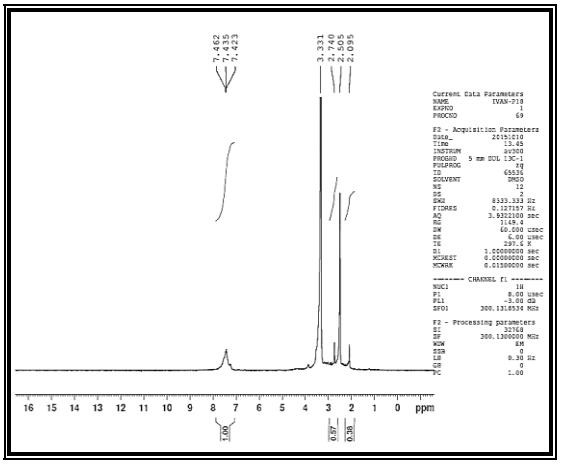

Figure (10): ^{1}HNMR spectrum for cis-[Pt(4-ASA) $(NH_3)_2$]I complex

The effect of concentration on molar conductivity:

The effect of concentration on the molar conductivity was studded for the solutions of the complexes. This study shows that the complexes cis-[Pt(4-AAP) $(NH_3)_2$] I_2 and cis-[Pt(4-ASA) $(NH_3)_2$]I have an increase in the molar conductivity with the increasing in the concentration of the complexes. Table (4) and figures (11,12) show the data of this study.

Table (4): the effect of conc. on molar conductivity for the complexes.

Con. (M)	Cond. Mc/cm Cis-[Pt(4-AAP)$(NH_3)_2$] I_2	Cond. Mc/cm Cis-[Pt(4-ASA) $(NH_3)_2$]I
0.0001	2.24	38.8
0.0005	4.76	156.0
0.0010	8.45	278.0
0.0020	13.79	502.0
0.0030	18.82	722.0
0.0040	23.20	903.0
0.0050	27.60	1105.0
0.0060	32.00	1243.0
0.0070	36.30	1481.0
0.0080	39.50	1591.0

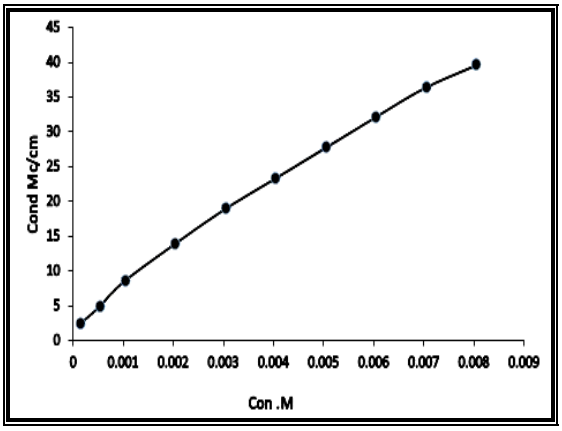

Figure (11): The effect of con. on the cond. for the complex cis-[Pt(4-AAP) $(NH_3)_2$] I_2

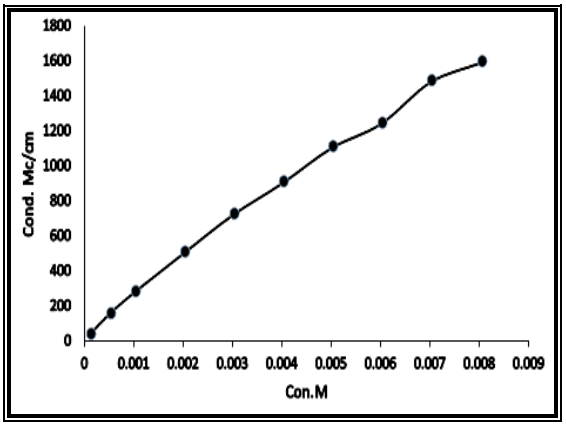

Figure (11): The effect of con. on the cond. for the complex cis-[Pt(4-ASA) $(NH_3)_2$]I_2

The effect of temperature on molar conductivity:

The effect of temperature on the molar conductivity of the complexes ($1x10^{-3}$M) has been studied. The complexes cis-[Pt(4-AAP)$(NH_3)_2$] I_2 and cis-[Pt(4-ASA) $(NH_3)_2$]I had shown that there is an increase in the molar conductivity with an increase the temperature. Table (5)and figures (13,14) show the results of this study.

Table (5): The effect of temp. on the molar conductivity of the complexes.

Temp. C°	Cond. Mc/cm Cis-[Pt(4-AAP)$(NH_3)_2$] I_2	Cond. Mc/cm Cis-[Pt(4-ASA) $(NH_3)_2$]I
20	1.76	97.0
25	2.00	98.4
30	2.19	99.3
35	2.50	99.9
40	3.00	101.1
45	3.34	101.2
50	3.36	101.6
55	3.40	102.0
60	3.80	102.2
65	4.32	102.3
70	4.68	102.3
75	5.13	102.4
80	5.65	102.4

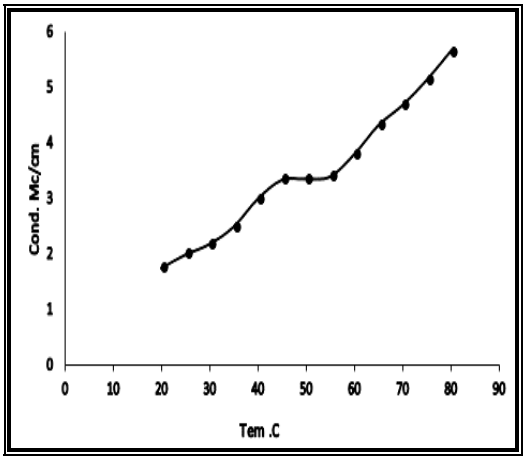

Figure (13): Effect of temp. on cond. cis-[Pt(4-AAP) $(NH_3)_2$] I_2

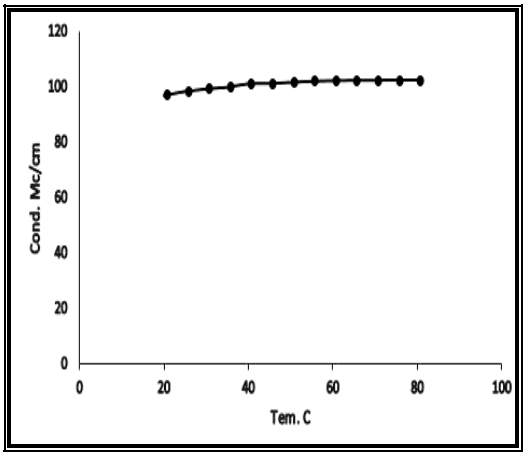

Figure (14): Effect of temp. on cond. cis [Pt(4-ASA) $(NH_3)_2$]I

The effect of temperature on the stability of the complexes:

The effect of temperature on the stability of the complexes had been studied by using UV.Vis. spectroscopy in which the absorbance of the solutions were measured. This study shows that the complex cis-[Pt(4 ASA) $(NH_3)_2$]I is stable until 50 ^{0}C and above this degree begins to break part, while the complex cis-[Pt(4AAP)$(NH_3)_2$] I_2 stable until 80 ^{0}C, that may be because of the composition structure of the ligands. Table (6) and figures (15, 16) show this study.

Table (6): the effect of temperature on the complexes stability

Tem.^{0} C	**Abs. Cis-[Pt(4AAP)$(NH_3)_2$] I_2**	**Abs. Cis-[Pt(4 ASA) $(NH_3)_2$]I**
20	1.6121	0.1320
25	1.6443	0.0999
30	1.6578	0.0961
35	1.6649	0.0960
40	1.6767	0.0538
45	1.6852	0.0445

50	1.6960	0.0405
55	1.7130	0.0237
60	1.7812	0.0166
65	1.8144	0.0136
70	1.9256	0.0030
75	1.9783	0.0010
80	1.9970	0.0005

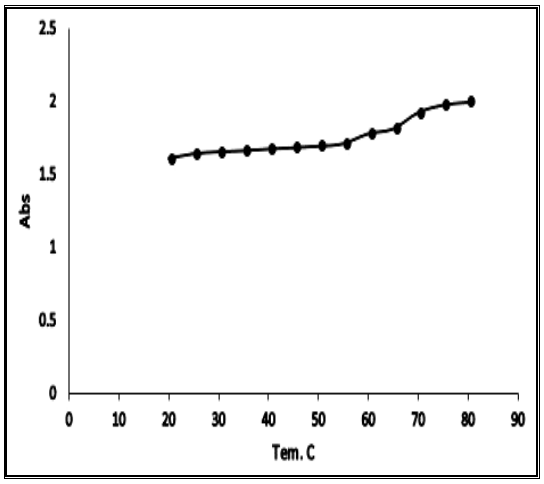

Figure (15): The effect of temp. on the stability of cis-[Pt(4AAP) $(NH_3)_2$] I_2 complex

Determination of the expiry date of the complexes:

The expiry date of the complexes were determined in 35°C and 20^0C for the solutions of the complexes ($1x10^{-3}$M). This study shows that the expiry date at 35^0C of the complex cis-[Pt(4AAP) $(NH_3)_2$] I_2 is 270 hours, while it is for the complex cis-[Pt(4 ASA) $(NH_3)_2$]I is 420 hours and at 20^0C the expiry date is between 410-435 hours for both complexes. Table (7,8,9) and figures (17,18,19,20) show this study.

Table (7): Expiry date data at 35^0C of the complexes

Tim. hour	Abs. Cis-[Pt(4AAP) $(NH_3)_2$] I_2	Abs. Cis-[Pt(4 ASA) $(NH_3)_2$]I
0	2.5970	2.6032
48	2.5600	2.2898
96	2.1970	2.0759
144	2.1430	2.0495
192	1.9660	2.0162
240	1.8760	1.8987
288	1.8320	1.6981
336	1.5390	1.5723
384	1.2530	1.3259
432	1.0100	1.1216

Table (8): Expiry date data at 20^0C of the complexes

Tim. hour	Abs. Cis-[Pt(4AAP) $(NH_3)_2$] I_2	Abs. Cis-[Pt(4 ASA) $(NH_3)_2$]I
0	2.4700	3.1169
48	2.2350	2.5199
96	2.1600	2.3489
144	1.9020	2.1471
192	1.8990	2.0467
240	1.8110	2.0348
288	1.7380	2.0322
336	1.4000	2.0283
384	1.2200	1.8633
432	0.9620	1.2434

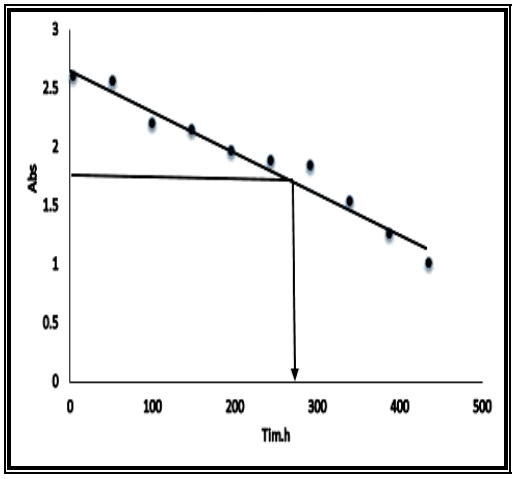

Figure (17): Expiry date for cis-[Pt(4-AAP) $(NH_3)_2$] I_2 at 35 °C

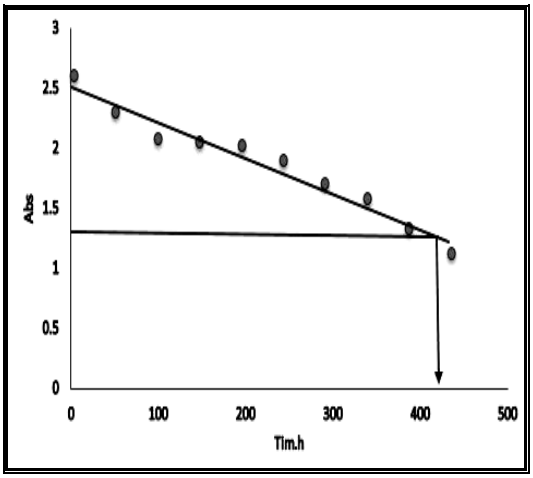

Figure (18):): Expiry date for cis-[Pt(4-ASA) $(NH_3)_2$]I at 35 °C

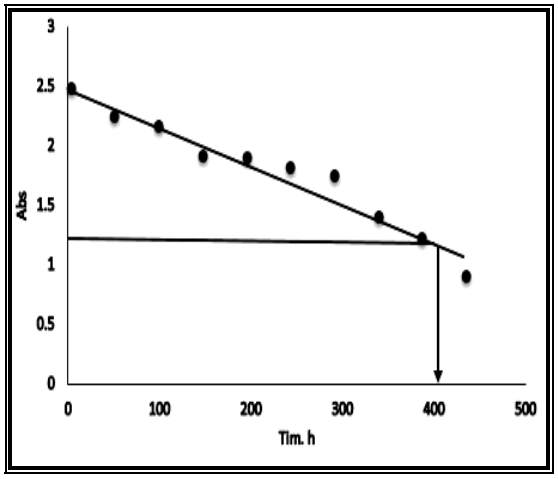

Figure (19): Expiry date for cis-[Pt(4-AAP) $(NH_3)_2$] I_2 at 20 °C

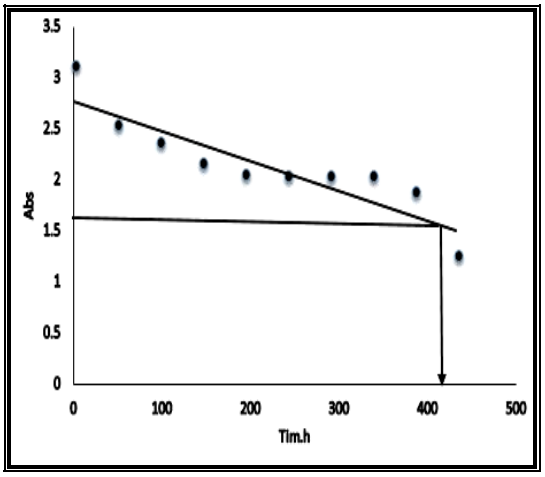

Figure (20): Expiry date for cis-[Pt(4-ASA) $(NH_3)_2$]I at 20 °C

Table (9): Expiry date of the complexes in hours

Complexes	**($t_{1/2}$) in 35-40 °C**	**($t_{1/2}$) in 20 °C**
Cis-[Pt(4-AAP) $(NH_3)_2$] I_2	270 h	410 h
Cis-[Pt(4-ASA) $(NH_3)_2$] I	420 h	435 h

CONFLICT OF INTERESTS.
There are non-conflicts of interest.

References

[1] Molina Dula Options Cal Medi Connect Plan Medicare – Medicade Plan H8677 – 14 – 15103 – 0004 – MMPCARX Ar Approved HPMS Approved Formulary File Submission 00014303, Version 12, 2014.

[2] Jamison E. R. and Lippard S., Structure, Recognition and Processing of Cis – Platin DNA Adducts, J. Chem. Rev., vol 99,2467 – 2498, 1999.

[3] Turek J. J., Leamon C. P. and Low P. S., Endocytosis of Flate – Protein Conjugates, Vltra – Structural Localization in KB Cells, J. Cell Sci., vol 106, 423 – 430, 1993.

[4] Bueno R, Appasani K, Mercer H, Laster S, Sugrbaker D, J. Thorac. Cardiovasc. Sury. ,vol 121, 225-233, 2001.

[5] Yuichi A, Tomoyo S, Yoshinari Y, Yoshinari H, J. Medi. Sci., vol76, 1-9, 2014.

[6] Robert R. C., Frederic L., Loanna S. M. P. and Roberta J. W., Biological Inorganic Chemistry An Introduction, Oxford OX5 IGB, UK,1st Edition, 2008.

[7] Kauffman GB, Cowan DO, Inorg. Synth. , vol 5, 239-245, 1963.

[8] Dhara SC, Indian J. Chem.vol 8, 1338-1346, 1970.

[9] Rhoda RN, Suffern NY, Crosby JN, U. S. Patent, 4, 273, 755, Jun. 16, 1981.

[10] Rebecca AA, Matthew DH, Trevor WH, J. of Chem., vol 83, 728-734, 2006.

[11] Al- Mukhtar, Mustafa IA, Arabic Version, Mosul University Press, 469, 64,618,647,669, 1988.

[12] Jian-ning L, Bo-Wan W, Bing Z, Yongchum L, Turk J. Chem., vol 30, 41-48, 2006.

[13] Hashem EY, J. AOAC Intr., 84, 2, 537-545, 2001.

[14] Al –Hamadan UJ, Gassim TH, Radhy TE, Molecules, vol 15, 5620-5628, 2010.

[15] Rajasekar K., Ramachandramoorthy T. and Paulraj A., Microwave Assisted Synthesis, Structural Characterization and Biological Activities of 4 – Amino anti pyridine and Thiocynate Mixed Ligand Complexes, Res. J. Pharmaceutical Sci.,vol 1, no.14, 22 – 27, 2012.

الخلاصة

يتضمن هذا البحث تحضير معقد جديد للسز – بلاتين بصيغة الآيودين (Cis – Iodoplatin) وكذلك معقدين جديدين للسز – كاربوبلاتين وهما : cis [Pt(aminosalicylicacid)$(NH_3)_2$] I و cis [Pt (4– aminoantipyrine) $(NH_3)_2]I_2$ واللذان يمكن ان يستخدما كعقاقير ضد السرطان، وقد حضرا باستخدام الليكاندات العضوية : 4–amino salicylic acid و4–amino antipyrine . شخصت هذه المعقدات باستخدام التقنيات الطيفية : UV–Vis و FTIR و XRD و ^{1}HNMR . وقد درست تأثير التركيز ودرجة الحرارة على التوصيلية الكهربائية لمحاليل هذه المعقدات. وقد حدد تاريخ انتهاء الصلاحية (عمر النصف) لمحاليل هذه المعقدات في ظروف درجة الحرارة 35 و20 درجة مئوية.