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Preparation, characterization, theoretical investigation and cytotoxic activity of new mixed ammine/amine platinum complexes with 3-amino-5-methyl-5-phenylhydantoin

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Dedicated to Acad. Bogdan Kurtev on the occasion of his 100th birth anniversary

New mixed ammine/amine Pt(II) and Pt(IV) complexes with 3-amino-5-methyl-5-phenylhydantoin (**L**) as carrier ligand were synthesized. The chemical formulas of the complexes *cis*-[$Pt(NH_3)LCl_2$] and *cis,cis,trans*-[$Pt(NH_3)LCl_2(OH)_2$] were proved by melting points, elemental analysis and IR spectra. For the prediction of the molecular structures of the ligand and its complexes DFT method was used. Theoretical analysis of the complexes showed the square planar coordination of Pt(II) complex and distorted octahedral coordination of Pt(IV) complex. The theoretical IR spectra were compared to the experimental and a good agreement was found. The cytotoxic activity of the organic compound and its complexes was determined *in vitro* by MTT assay against five human tumor cell lines - Hep-G2, MDA-MB-231, HT-29, HL-60 and REH. The IC_{50} values of the tested compounds showed that platinum complexes have higher cytotoxic activity than the organic compound.

Key words: Pt complexes; hydantoins; IR spectra; DFT calculations; cytotoxicity

INTRODUCTION

Because of the cisplatin (*cis*-[$Pt(NH_3)_2Cl_2$]) success in clinical therapy, various new *cis*-Pt(II) complexes have been synthesized and studied by substitution of either chlorine or ammonia ligands with different structures. A new classes of platinum compounds with general formulas *cis*-[Pt(L)(L')(L"$_2$)] and *cis*-[Pt(L)(L')(L"$_2$)(L'"$_2$)], where L and L' are different amines, L" is chloride ions, L'" is hydroxido or carboxylato ions in axial position have been reported to show cytotoxic activity against several tumor cell lines [1]. For example, Pt(II) complexes with chemical formula *cis*-[$PtL(NH_3)Cl_2$] (L=pyridine, pyrimidine, purine) [2] were reported to show promising antitumor activity. AMD473 (*cis*-[Pt(2-methylpyridine)(NH_3) Cl_2] was rationally designed in order to reduce the reactivity of glutathione which may be the key to improve responses in resistant tumors [3, 4]. It is active against acquired cisplatin- and oxaliplatin-resistant cell lines [5] and possesses a toxicity profile similar to carboplatin. This promising compound named also picoplatin has been introduced in the treatment of patients with solid tumors. Its clinical trials started in 1997 and investigations of the picoplatin derivatives continue [6, 7]. Recently new complexes of picoplatin with different organic molecules were prepared and studied for cytotoxicity on some cancer cell lines. The results showed that inclusion complexation may be a promising strategy to design a novel formulation of picoplatin as an anticancer therapy [8, 9].

Platinum(IV) complexes are known to be much more tolerant to ligand substitution reactions than their Pt(II) counterparts [10]. In order to rationally design of new Pt(IV) complexes, correlation between structure, reduction and activity were needed, since it is generally admitted that Pt(IV) compounds must be reduced to be activated [11]. Octahedral Pt(IV) complexes act as prodrugs of their Pt(II) counterparts and represent an important role of recent metal-based anticancer research [12]. Mixed ammine/amine Pt(IV) complexes with equatorial chloride and axial carboxylate or hydroxide ligands also demonstrate cytotoxic activity against cisplatin resistant cells *in vitro*. Some Pt(IV) complexes have shown promising results to enter in clinical trials: Iproplatin (*cis,trans,cis*-[Pt(isopropylamine)$Cl_2(OH)_2$] [13], Tetraplatin ([Pt(d,l-cyclohexane-1,2-diamine)Cl_4] [14] and Satraplatin (*cis,trans,cis*-[Pt(cyclohexyl-amine)(NH_3)$(OAc)_2Cl_2$]) [15]. Satraplatin showed

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higher activity compared to cisplatin against human cervical, small-cell lung and ovarian carcinoma cell lines [16]. In recent years, satraplatin has emerged as a novel oral platinum analogue with a better toxicity profile than cisplatin. Since satraplatin is more hydrophobic than cisplatin or oxaliplatin, it appears to demonstrate efficacy in cisplatin-resistant cell lines [17].

The goal of the study is to prepare new mixed ammine/amine Pt(II) and Pt(IV) complexes with ligand 3-amino-5-methyl-5-phenylhydantoin and general formulae *cis*-[$Pt(NH_3)LCl_2$] and *cis,cis,trans*-[$Pt(NH_3)LCl_2(OH)_2$]. The complexes were studied by melting points, elemental analysis and IR spectral method. For prediction of molecular structures of the organic compound and its platinum complexes hybrid DFT method was used. The investigated compounds were pharmacologically examined in comparison to clinically applied drug cisplatin.

EXPERIMENTAL

Chemistry

All chemicals were purchased from Fluka (UK) and Sigma-Aldrich. The newly mixed ammine/amine Pt(II) and Pt(IV) complexes were characterized by elemental analysis, melting points and IR spectra. The elemental analysis was carried out on a "EuroEA 3000 – Single", EuroVectorSpA apparatus (Milan, Italy). Corrected melting points were determined, using a Bushi 535 apparatus (BushiLabortechnik AG, Flawil, Switzerland). The IR spectra were recorded on Thermo Scientific Nicolet iS10 spectrophotometer (Thermo Scientific, USA) in the range of 4000-400 cm^{-1} as Attenuated Total Reflection Fourier Transform Infrared Spectroscopy (ATR-FTIR).

The new complexes *cis*-[$Pt(NH_3)LCl_2$] (**1**) and *cis,cis,trans*-[$Pt(NH_3)LCl_2(OH)_2$] (**2**), where **L** is 3-amino-5-methyl-5-phenylhydantoin (**L**) were prepared by using reported procedure with minor revisions [18, 19]. The synthesis and the structure of 3-amino-5-methyl-5-phenylhydantoin (**L**) were described in details in our previously published work [20].

Synthesis of new mixed Pt(II) and Pt(IV) complexes

*Synthesis of cis-3-amino-5-methyl-5-phenyl-hydantoin-ammine-dichlorido platinum(II) – cis-[$Pt(NH_3)LCl_2$] (**1**)*: An aqueous ethanol solution of (**L**) (0.3216 mmol) was added dropwise to an aqueous solution of K[$Pt(NH_3)Cl_3$] (0.5621 mmol) with constant stirring at ambient temperature. The solution was stirred for 5–6 h, concentrated and cooled to 4 °C. A light yellow precipitate was collected by filtration and dried in a vacuum desiccator. The purity was confirmed by TLC with eluent $CH_3COOC_2H_5/C_2H_5OH$ (2:1) and elemental analysis. Yield: 30%; m.p. (dec.) 221 °C.

*Synthesis of cis-3-amino-5-methyl-5-phenylhydantoin,ammine,cis-dichlorido,trans-dihydroxidoplatinum(IV) – cis,cis,trans-[$Pt(NH_3)LCl_2(OH)_2$] (**2**)*: 0.1926 mmol of the complex (**1**) and excess of 30% H_2O_2 were mixed. The suspension was stirred for 4-5 h at 50 °C. After 6-7 days from the solution whitish crystals were isolated and dried in vacuum desiccator under P_2O_5 and KOH. The purity was confirmed by TLC with eluent $CH_3COOC_2H_5/C_2H_5OH$ (2:1) and elemental analysis. Yield: 23%; m.p. (dec.) 218 °C.

Calculations

All theoretical calculations were performed using the Gaussian 09 package [21] of programs. Optimization of the structures of the ligand 3-amino-5-methyl-5-phenylhydantoin and possible conformers of Pt(II) and Pt(IV) complexes were carried out by DFT calculations, employing the B3LYP (Becke's three-parameter non-local exchange [22]) and Lee *et al.* correlation [23] hybrid functional and 6-311++G** set for the ligand and LANL2DZ basis set for the platinum complexes. The B3LYP hybrid functional [24, 25] was used because of its high accuracy. The basis set LANL2DZ was chosen to include the pseudopotential of the core electrons in atoms of heavy elements like platinum and it is compatible with all other organic elements (C, N, H, O, Hal).

Pharmacology

The present study describes a comparative evaluation of the cytotoxic effects of the ligand and two newly synthesized platinum complexes. The cytotoxicity of the complexes was compared to metal-free ligand **(L)** and the referent antineoplastic agent cisplatin.

Cell culture conditions

The following cell lines were used for the experiments: (i) Hep-G2(Human Caucasian hepatocyte carcinoma, isolated from a liver biopsy of a male Caucasian aged 15 years, with a well

differentiated hepatocellular carcinoma), (ii) MDA-MB-231 (human breast cancer cell line, established in 1973 from the pleural effusion of a 51-year-old woman with breast carcinoma), (iii) HT-29(colon adenocarcinoma, established from the primary tumor of a 44-year-old Caucasian woman with colon adenocarcinoma in 1964), (iv) HL-60 (acute myeloid leukemia, established from the peripheral blood of a patient with acute promyelocyte leukemia), (v) REH(acute lymphoblastic leukemia, established from the peripheral blood of a 15-year-old North African girl with acute lymphoblastic leukemia in 1973). The cell lines were obtained from DSMZ German Collection of Microorganisms and Cell Cultures and were well validated in our laboratory as a proper test system for metal complexes. Their DSMZ catalogue numbers are as follows: Hep-G2 (ACC 180), MDA-MB-231 (ACC 73), HT-29 (ACC 299), HL-60 (ACC 3) and REH (ACC 22).

Cytotoxicity assessment

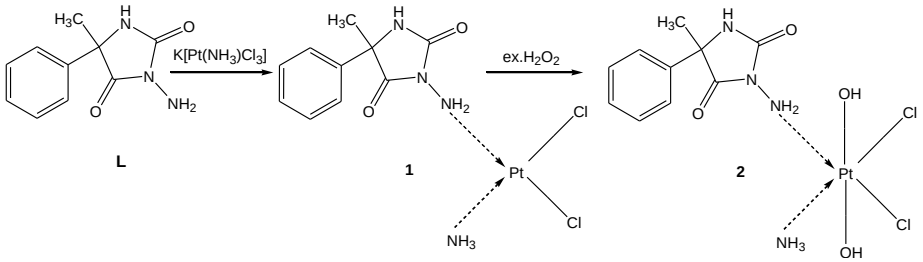
Cytotoxicity of the compounds was assessed using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] dye reduction assay as described by Mossman [26] with some modifications [27]. Exponentially growing cells were seeded in 96-well microplates (100 μL/well at a density of 3.5 x 10^5 cells/mL for the adherent and 1 x 10^5 cells/mL for the suspension cell lines) and allowed to grow for 24 h prior the exposure to the studied compounds. Stock solutions of the investigated Pt(II) and Pt(IV) complexes were freshly dissolved in DMSO and then promptly diluted in RMPI-1640 growth medium, immediately before treatment of cells. Our preceding experience with water-insoluble platinum agents, including cisplatin has indicated that the dose-response curves following dissolution in water or stock solution in DMSO (which is then promptly diluted in aqueous phase) overlap and there is no significant modulation of the individual cell lines chemosensitivity. At the final dilutions the solvent concentration never exceeded 0.5%. Cells were exposed to the tested compounds for 72 h, whereby for each concentration a set of 8 separate wells was used. Every test was run in triplicate, *i.e.* in three separate microplates. After incubation with the tested compounds MTT solution (10 mg/mL in PBS) aliquots were added to each well. The plates were further incubated for 4 h at 37 ºC and the formazan crystals formed were dissolved by adding 110 μL of 5% HCOOH in 2-propanol. Absorption of the samples was measured by an ELISA reader (UniscanTitertec) at 580 nm. Survival fraction was calculated as percentage of the untreated control. In addition IC_{50} values were calculated from the concentration-response curves. The experimental data was processed using GraphPadPrizm software and was fitted to sigmoidal concentration/response curves *via* non-linear regression.

RESULTS AND DISCUSSION

Calculations

The new platinum complexes were prepared according to the Scheme 1.

The elemental analyses of the complexes (**1**) and (**2**) were in good agreement with the corresponding chemical formulae – *cis*-[Pt($C_{10}H_{11}N_3O_2$)(NH_3)Cl_2]



Scheme 1. Synthesis of the complexes (**1**) and (**2**).

Table 1. Physico-chemical data of the newly prepared compounds.

Compound	Molecular formula	MW	Yield[a] (%)	M.p.[b] (dec.) (°C)	Elemental analysis % Calc. (% Found)		
					C	H	N
1	$C_{10}H_{14}N_4O_2Cl_2Pt$	487.90	30	221	24.60 (24.72)	2.87 (3.29)	11.48 (11.46)
2	$C_{10}H_{16}N_4O_4Cl_2Pt$	521.90	23	218	22.99 (23.47)	3.07 (3.35)	10.73 (10.88)

[a]Yield of analytically pure product; [b]Mp of analytically pure product.

and *cis,cis,trans*-[Pt($C_{10}H_{11}N_3O_2$)(NH_3)Cl_2($OH)_2$]. The data from elemental analysis and some physical properties are summarized in Table 1.

IR spectra

In the vibrational spectrum of the ligand (**L**), the stretching vibrations of NH_2 and NH groups three bands in the region 3347-3197 cm^{-1} were observed. While in the spectra of the complexes all amino groups (NH_3, NH_2, NH) were characterized by a broad band appeared at 3400-3280 cm^{-1}. Their corresponding theoretical spectra were presented by several bands at 3560-3100 cm^{-1}. The difference between the experimental and theoretical results is probably due to the formation of some inter- and intra-molecular interactions as H-bonds in solid state.

The C-H stretching vibrations of the CH_3 group and C_6H_5 fragment (theoretical and experimental spectra) were appeared in their usual regions.

In the experimental IR spectra ν(C=O) vibrations of the (**L**), (**1**) and (**2**) were observed as two bands in the area 1787-1700 cm^{-1} (theoretical bands: 1790–1658 cm^{-1}).

The NH_2 deformation vibrations (theoretical and experimental spectra) were shifted to the lower frequencies with approximately 30 cm^{-1} in the complexes compared to the ligand. This indicated coordination through the N-atom from the amino group. The results showed a good correlation between theoretical and experimental data.

Geometry

The optimized geometry of the ligand with *R*-configuration and energetically preferred structures of the complexes (**1**), (**2**) and atom numbering were shown on Figs.1-3.

Evaluation of the molecular structures of the (**L**) and complexes (**1**) and (**2**) were carried out by DFT method. The ligand can exist in two stereo configurations – *R* and *S* according to the arrangement of substituents around C_1 atom. In order to establish the geometry of both stereoisomer, full optimization of the molecules was performed at the B3LYP/6-311++G^{**} level of theory. As a result, we found that the stereoisomers are characterized by similar geometry parameters and dipole moments. The hydantoin fragment showed a planar structure as expected. In both cases the molecules were stabilized by formation of a hydrogen bond between the NH_2- and C=O groups from the hydantoin moiety with identical geometry parameters: N-H…O bond length of 2.87 Å and N-H…O angle of 88.7° respectively.

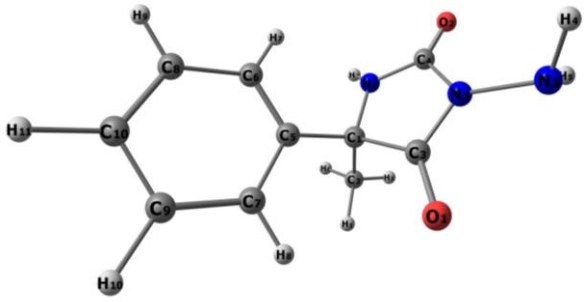


Fig. 1. Optimized structure of the ligand with *R*-configuration.

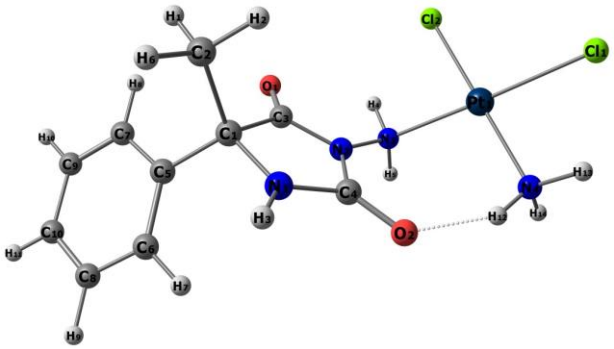


Fig. 2. Optimized structure of the *cis*-[Pt(NH_3)(L)Cl_2].

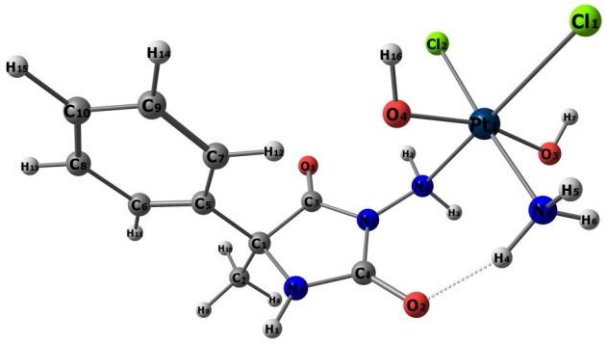


Fig. 3. Optimized structure of the *cis,cis,trans*-[Pt(NH_3)(L)Cl_2($OH)_2$].

Taking into account the possible existence of *R* and *S* enantiomers, we carried out analysis on the potential energy surface of all stereoisomer complexes at B3LYP/LAN2DZ level of theory. For each complex, the most probable conformations were constructed and optimized.

It has been found that the complex of Pt(II) with the *R* isomer of the ligand is the preferred structure to complex with the *S* isomer of the ligand with 1.81 kJ/mol.

The coordination around the Pt centre was square planar. In the case of Pt(IV), the complex

with *S* isomer was more favorable than those with *R*-configuration by 1.30 kJ/mol. The platinum centre in Pt(IV) complex was hexacoordinated in a distorted octahedral geometry. The octahedral coordination was formed by two chloride ions, two hydroxyl groups, ammonia and one molecule of the ligand. The complexes were stabilized by an intramolecular N-H…O hydrogen bond of 2.80 Å of Pt(II) and 2.76 Å of Pt(IV) complexes.

The N_2-N_3 bond in the complexes becomes lightly longer than those in the ligand. The coordination leads to small changes in the geometric parameters of the hydantoin fragment as well as of the complexes (Table 2).

The most significant geometric parameters of the ligand and platinum complexes were presented in Table 2.

Table 2. Calculated geometry parameters of the ligand and its complexes (**1**, **2**) using atom numbering in Figs. 1-3.

Parameters	**Ligand(L)*R***	**1**	**2**
μ(D)	2.74	13.66	9.68
Bond lengths (Å)			
Pt-Cl_1	-	2.42	2.40
Pt-Cl_2	-	2.39	2.42
Pt-N_3	-	2.12	2.11
Pt-N_4	-	2.09	2.08
N_2-N_3	1.39	1.43	1.41
Pt-O_4	-	-	2.04
Pt-O_3	-	-	2.05
Angles (°)			
N_1–C_4-N_2	106.0	105.5	105.5
N_1-C_1-C_3	101.2	100.6	100.3
C_4-N_2-N_3	123.4	123.4	123.9
N_2-N_3-Pt	-	119.9	121.0
N_3-Pt-Cl_2	-	81.1	83.4
N_4-Pt-Cl_1	-	83.6	84.8
N_3-Pt-N_4	-	98.6	97.7
Cl_1-Pt-Cl_2	-	96.4	93.7
O_3-Pt-Cl_1	-	-	97.2
O_3-Pt-Cl_2	-	-	94.4
O_3-Pt-N_3	-	-	79.8
O_3-Pt-N_4	-	-	82.3
O_4-Pt-Cl_1	-	-	92.3
O_4-Pt-Cl_2	-	-	93.2
O_4-Pt-N_3	-	-	90.9
O_4-Pt-N_4	-	-	90.2
Dihedral angles (°)			
C_4-N_2-C_3-C_1	-3.8	-0.2	-2.6
C_4-N_1-C_1-C_2	112.7	-114.3	115.4
N_1–C_4-N_2-C_3	5.7	0.7	3.3
O_{12}-C_4-N_2-N_3	0.8	-8.9	-11.0
C_4-N_2-N_3-Pt	-	-51.9	-57.0
C_3-N_2-N_3-Pt	-	119.0	109.4
N_2-N_3-Pt-Cl_2	-	105.6	-112.9
N_2-N_3-Pt-N_4	-	74.9	70.6
N_2-N_3-Pt-O_4	-	-	-19.7
N_2-N_3-Pt-O_3	-	-	151.3

Pharmacological screening

The ligand (**L**) and the complexes (**1**, **2**) were tested for cytotoxic activity on a panel of human tumor cell lines - hepatocyte carcinoma Hep-G2, human breast cancer cell line MDA-MB-231, colon adenocarcinoma HT-29, acute myeloid leukemia HL-60 and acute lymphoblastic leukemia REH. The tested organic compound (**L**) and complexes (**1**, **2**) exerted cytotoxic effect after 72 h continuous exposure, whereby the individual chemosensitivity varied among the different cell lines. The complexes (**1**) and (**2**) showed higher cytotoxic activity on HT-29, MDA-MB-231 and HL-60 cell lines than the ligand (**L**). Complex (**2**) manifested higher cytotoxic activity than the complex (**1**) and reference cisplatin on the colon adenocarcinoma HT-29 cell line. The results are summarized in Table 3.

Table 3. Cytotoxicity of the ligand (**L**) and complexes (**1**, **2**) in comparison with referent drug cisplatin in five human tumour cell lines.

	IC_{50} values/(μM)				
Cell line	**Hep-G2[a]**	**HT-29[b]**	**REH[c]**	**MDA-MB-231[d]**	**HL-60[e]**
Compound					
Ligand	> 200	> 200	> 200	> 200	> 200
Complex (1)	> 200	> 200	> 200	143.0	155.7
Complex (2)	-	145.5	> 200	-	> 200
Cisplatin	12.0	170.0	1.07	31.6	8.7

[a]human hepatocyte carcinoma; [b]colon adenocarcinoma; [c]acute lymphoblastic leukemia; [d]human breast cancer cell line; [e]acute myeloid leukaemia

CONCLUSION

Two new mixed ammine/amine Pt(II) and Pt(IV) complexes with 3-amino-5-methyl-5-phenyl-hydantoin were synthesized and studied. The geometry of the ligand and its platinum complexes were optimized, using the DFT method, employing the B3LYP with 6-311++G** basis set for the ligand and LANL2DZ basis set for the complexes. The metal–ligand binding mode in the new complexes was confirmed by the DFT calculations. In the complexes, platinum ion coordinates in a monodentate manner through the nitrogen atom from the NH_2 group of the hydantoin ring. The computed vibrational frequencies were used for determination of the molecular motions associated with each of observed experimental bands. Experimental frequencies were well reproduced by the theoretical method. The compounds tested exerted concentration-dependent cytotoxicity on a HT-29, MDA-MB-231 and HL-60 human tumor cell lines. The new Pt(IV) complex *cis,cis,trans*-$[Pt(NH_3)LCl_2(OH)_2]$ exhibited higher cytotoxic activity than the Pt(II) complex - *cis*-$[PtNH_3(L)Cl_2]$ and referent drug cisplatin on the colon adenocarcinoma HT-29 cell line.

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ПОЛУЧАВАНЕ, ОХАРАКТЕРИЗИРАНЕ, ТЕОРЕТИЧНО ИЗСЛЕДВАНЕ И ЦИТОТОКСИЧНА АКТИВНОСТ НА НОВИ СМЕСЕНИ ПЛАТИНОВИ КОМПЛЕКСИ С 3-АМИНО-5-МЕТИЛ-5-ФЕНИЛХИДАНТОИН

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(Резюме)

Синтезирани са нови смесени комплекси на Pt(II) и Pt(IV) с 3-амино-5-метил-5-фенилхидантоин, използван като носещ лиганд. Химичните формули на комплексите *cis*-[Pt(NH_3)LCl_2] и *cis,cis,trans*-[Pt(NH_3)LCl_2($OH)_2$] са доказани чрез точка на топене, елементен анализ и ИЧ спектроскопия. За предсказване на молекулната структура на лиганда и неговите комплекси е използван ДФТ метод. Теоретичният анализ на комплексите показва плоско-квадратна координация на комплекса на Pt(II) и деформирана октаедрична координация на комплекса на Pt(IV). Установено е добро съответствие между теоретичните и експерименталните данни за ИЧ спектрите. Лигандът и неговите комплекси бяха изследвани за цитотоксична активност *in vitro* с помощта на MTT тест върху пет човешки туморни клетъчни линии: Hep-G2, MDA-MB-231, HT-29, HL-60 and REH. IC_{50} стойностите на изследваните съединения показват, че платиновите комплекси проявяват по-висока цитотоксична активност в сравнение с органичното съединение.