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Synthesis, DFT calculations and cytotoxic investigation of platinum complexes with 3-thiolanespiro-5′-hydantoin and 4-thio-1H-tetrahydropyranespiro-5′-hydantoin

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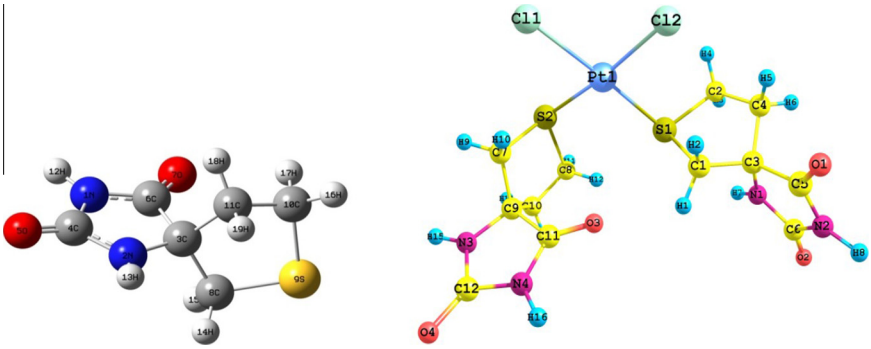
HIGHLIGHTS

- Pt(II) complexes with heterocyclic spiro hydantoins were synthesized and characterized.
- Pt(IV) complexes with heterocyclic spiro hydantoins were synthesized and characterized.
- New synthesized complexes were investigated by elemental analysis, IR, NMR spectra.
- DFT calculations of one organic ligand and its Pt(II) complex were made.
- Complexes were studied for cytotoxicity *in vitro* on panel of human tumor cell lines.

GRAPHICAL ABSTRACT

Two organic compounds and four new Pt(II) and Pt(IV) complexes with the same compounds as ligands were synthesized and investigated. They were characterized by elemental analysis, IR, ^{1}H and ^{13}C NMR spectroscopy. The coordination mode of the 3-thiolanespiro-5′-hydantoin and its Pt(II) complex **(1)** is confirmed by DFT calculations. All data showed that the carrier ligands coordinate to the platinum ion in a monodentate manner through the sulfur atom from the cyclic ring.
The complexes were tested for antiproliferative activity *in vitro* on panel of human tumor cell lines. The tested compounds exerted concentration-dependent cytotoxic effects against some of the tumor cell lines.



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ABSTRACT

Two organic compounds – 3-thiolanespiro-5′-hydantoin, 4-thio-1H-tetrahydropyranespiro-5′-hydantoin and four new Pt(II) and Pt(IV) complexes with general formulas *cis*-$[Pt(L)_2Cl_2]$ and *cis*-$[Pt(L)_2Cl_4]$ were synthesized. The obtained compounds were characterized by elemental analysis, IR, ^{1}H, ^{13}C NMR spectroscopy. The hybrid DFT calculations were used for optimization of the structure geometries of the ligand **(L1)** and its Pt(II) complex **(1)**. The calculated structural parameters such as bond lengths and angles are in good agreement with the experimental data for similar hydantoins and their platinum complexes. The obtained results showed that the geometry of the complex **(1)** is plane square and the bounding of the **L1** with platinum ion is realized by sulfur atom from thiolane ring. The complexes were tested for cytotoxicity *in vitro* on four human tumor cell lines. The tested compounds exerted concentration-dependent cytotoxic effects against some of the tumor cell lines.

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Introduction

All metal containing drugs used in clinics are Pt(II) compounds such as cisplatin, carboplatin, oxaliplatin, nedaplatin, lobaplatin and heptaplatin [1]. In the search for new platinum anticancer drugs, great efforts were devoted to the design of complexes more efficient and less toxic than drugs already in clinical use. Moreover in some cases, after the initial treatment, tumors become resistant [2,3] so an important objective, which is involving great research efforts is the development of new drugs without acquired resistance [4].

Over the last few decades, there has been considerable interest in the synthesis and characterization of hydantoin derivatives as an important class of heterocyclic compounds. Many of the hydantoins containing natural and synthetic products exhibit diverse biological activities, such as antitumor [5], antiarrhythmic [6], anticonvulsant [7], herbicidal [8], and others [9–11]. Although hydantoin compounds are studied extensively, there are not many studies about their anticancer properties. Recently, the cytotoxic activity of spirohydantoin derivatives was tested in ovarian and breast cancer cells [12]. It has been shown that a spirohydantoin derivative induces growth inhibition and apoptosis in leukemic cells [13].

The diversity associated with the biological activities of currently available hydantoin derivatives and further scope of development of new analogues of hydantoins prompted researchers to pay attention to the synthesis of new derivatives of hydantoin and screen its biological activities [12].

However it was shown that Pt(IV) complexes also exhibit strong cytotoxic activity and can have some advantages in comparison to their Pt(II) analogues [14,15]. Significances of the higher oxidation state are the introduction of two additional ligands and the change from square planar to octahedral geometry. These characteristics together with their higher kinetic inertness compared to their Pt(II) counterparts opens up new possibilities in the design of new platinum-based drugs. The mechanism of action of the octahedral Pt(IV) complexes was similar with those of square planar Pt(II) complexes. They can act as prodrugs for Pt(II) agents (reduction *in vivo* to the corresponding Pt(II) counterparts).

Over the last few years we have been synthesized and studied for cytotoxicity *in vitro* some Pt(II) and Pt(IV) complexes with different hydantoin and spirohydantoin derivatives [16–18]. Some of them have similar cytotoxic activity to referent antitumor agent cisplatin.

The present study represents the synthesis, physicochemical evaluation and pharmacological investigation of new Pt(II) and Pt(IV) complexes with organic compounds 3-thiolanespiro-5′-hydantoin **(L1)** and 4-thio-1H-tetrahydropyranespiro-5′-hydantoin **(L2)** as carrier ligands.

Experimental

Materials and methods

Tetrahydrothiophene-3-one and tetrahydro-1H-thiopyran-4-one used for preparation of two new organic compounds were purchased from Aldrich – USA. Potassium tetrachloroplatinate(II) utilized for the synthetic procedures was purchased from Merck – Germany, platinum(IV) chloride was purchased from Heraeus GmbH. All other chemicals were of analytical grade.

The synthesized 3-thiolanespiro-5′-hydantoin, 4-thio-1H-tetrahydropyranespiro-5′-hydantoin and their Pt(II) and Pt(IV) complexes were characterized by elemental analysis, IR, ^{1}H, ^{13}C NMR spectra and mass spectrum.

The carbon, nitrogen and hydrogen contents of the compounds were determined by elemental analysis, carried out on a "EuroEA 3000 – Single, EuroVector SpA".

The IR spectra were recorded on Thermo Scientific Nicolet iS10 spectrophotometer in the range of 4000–400 as ATR and on IFS 113 v Bruker FTIR spectrophotometer in the range of 400–150 cm^{-1} in polyethylene. Intensities of reported IR bands are defined as br = broad, s = strong, m = medium, and w = weak. The ^{1}H and ^{13}C NMR spectra were registered on a Bruker WM 250 (250 MHz) spectrometer in DMSO-d_6 solutions. The splitting of proton resonances in the ^{1}H NMR spectra is defined as s = singlet, d = doublet, dd = doublet from doublets and m = multiplet (see Figs. 5 and 6 for NMR numbering scheme). Corrected melting points were determined, using a Buchi 535 apparatus.

Thermal analysis were performed on a C.MOM thermal analyzer (Budapest, Hungary) with a simultaneous DTA–TG module using the following conditions: sample mass 10 mg, heating range 20–900 °C (293–1173 K), heating rate 5 °C min^{-1}, air atmosphere.

*Synthesis of the ligands (**L1** and **L2**)*

To 5 mL (0.0490 mol) of thiolane-3-one in 50 mL water/ethanol or 5 g (0.043 mol) tetrahydro-1H-thiopyran-4-one dissolved in 60 mL water–ethanol (1:1) respectively, were added 2.94 g (0.0600 mol) NaCN or 9.6 g (0.1000 mol) $(NH_4)_2CO_3$. The resulting mixtures were stirred with magnetic stirrer and heated at 65 °C for 30 h. The obtained reaction mixtures were acidified in a strong ventilation hood with conc. HCl to pH = 5. The solid products were filtered off and recrystallized from 50% ethanol (Yields 53% and 75%, respectively) (see Fig. 1).

*Synthesis of the complexes **(1), (2), (3)** and **(4)***

Water/ethanol solutions of the ligand **(L1)** (0.0829 g, 0.4819 mmol) and (0.1021 g, 0.5936 mmol) were added dropwise to the water solutions of $K_2[PtCl_4]$ (0.1000 g, 0.2409 mmol) and $PtCl_4$ (0.1007 g, 0.2989 mmol) for the obtaining of the complexes **(1)** and **(2)** resp. To the ethanol solutions of the ligand **(L2)** (0.0913 g, 0.4909 mmol) and (0.1124 g, 0.6043 mmol) were added $K_2[PtCl_4]$ (0.1025 g, 0.2469 mmol) and $PtCl_4$ (0.1015 g, 0.3014 mmol) for the preparing of the complexes **(3)** and **(4)** resp. The obtained homogenous solutions were stirred for 4–8 h at room temperature. The solutions were concentrated and cooled to 4 °C. Yellow products were obtained and filtered off, washed several times with ethyl ether and dried in a vacuum desiccator. The compounds are soluble in DMSO, water and ethanol. The purity is checked up by thin layer chromatography with the eluent $CH_3COOC_2H_5/C_2H_5OH$ – 2:1 and elemental analysis (Yields 54–69%). The scheme of the synthesis of the new Pt(II) and Pt(IV) complexes was given in the Fig. 2. The analytical and physical data of the ligands and of their platinum complexes are given in Table 1.

Computational study

All calculations were performed with Gaussian 09 program using the hybrid DFT method B3LYP [20]. 6-31++G(d) basis set

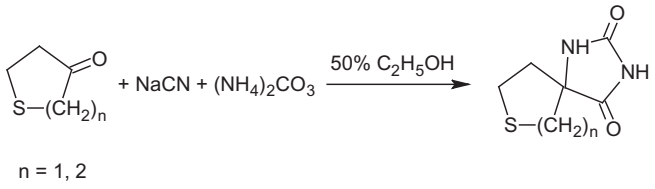

Fig. 1. Scheme of the synthesis of the organic compounds (**L1** and **L2**).

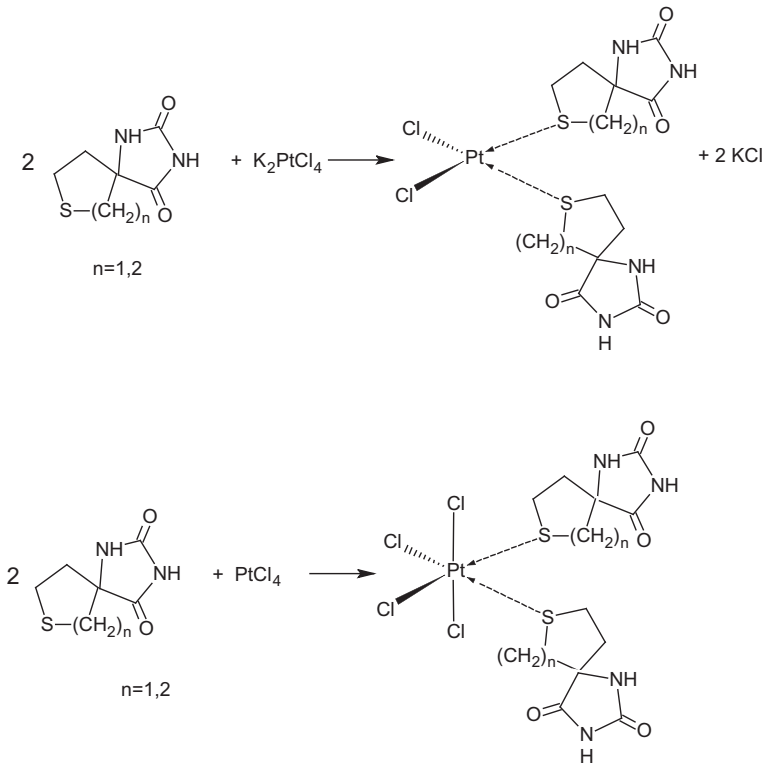

Fig. 2. Scheme of the synthesis of new Pt(II) **(1,3)** and Pt(IV) **(2,4)** complexes with organic ligands **(L1)** and **(L2)**.

Table 1
Analytical and physical data of organic ligands and their platinum complexes.

No.	Compound (empirical formula)	Color	m.p. (°C)	%Yield	M. Wt.	Elemental analysis found (calc.)		
						%C	%H	%N
L1	$C_6H_8N_2O_2S$	Pale-yellow	236–237	53	172			
1	$[Pt(C_6H_8N_2O_2S)_2Cl_2]$	Light-yellow	238(Dec.)	56	610	23.18 (23.61)	3.42 (2.62)	10.13 (9.18)
2	$[Pt(C_6H_8N_2O_2S)_2Cl_4]$	Lemon-yellow	209(Dec.)	54	681	21.37 (21.15)	2.62 (2.35)	8.05 (8.23)
L2	$[C_7H_{10}N_2O_2S]$	White	261–262	75	186			
3	$[Pt(C_7H_{10}N_2O_2S)_2Cl_2]\cdot 2H_2O$	Light-yellow	222(Dec.)	66	674	24.39 (24.93)	3.51 (3.56)	8.24 (8.31)
4	$[Pt(C_7H_{10}N_2O_2S)_2Cl_4]\cdot H_2O$	Light-yellow	210(Dec.)	69	727	22.93 (23.11)	2.93 (3.03)	7.58 (7.71)

was used for optimization the geometry of the **L1**, while for the Pt(II) complex **(1)** LANL2DZ basis set was utilized. We have to mention B3LYP [21–23] as a functional, which is used in the present investigation. It gives realistic results for molecules up to 60–70 atoms. The basis set involved are 6-31++G(d) for optimization, because its basic functions are applicable to the lighter elements, which are in composition in organic molecules. For the metal complexes we have to use heavier LANL2DZ basis set, which is relevant to heavier elements like platinum. This basis set was chosen in order to include the pseudo potential of the core electrons in atoms of heavy elements like platinum and it is compatible with all other organic elements (C, N, H, O, Cl, S).

Pharmacology

The following cell lines were used for the experiments: (i) SKW-3 or a KE-37 derivative (human T-cell leukemia, established from peripheral blood of a 61-year-old man with T-cell lymphocytic leukemia); (ii) HL-60 (acute myeloid leukemia, established from the peripheral blood of a patient with acute promyelocyte leukemia); (iii) EJ (human urinary bladder carcinoma), (iv) LAMA-84 (human chronic myeloid leukemia, established from peripheral blood of a 29-year-old woman with chronic myeloid leukemia). EJ cells (also designated MGH-U1) were originally isolated from a high grade (G3) invasive bladder carcinoma. These cell lines have been well validated in our laboratory as a proper test system for platinum agents. The EJ cell line has been obtained from the unit of Toxicology and Chemotherapy at the Deutsches Krebsforschungszentrum. The other cell lines were obtained from DSMZ German Collection of Microorganisms and Cell Cultures. Their DSMZ catalogue numbers are as follows: HL-60 (ACC 3), SKW-3 (ACC 53) and LAMA-84 (ACC 168).

The cell culture flasks and the 96-well microplates were obtained from NUNCLON (Denmark). MTT, FCS and cisplatin were purchased from Sigma Co. The stock solutions of tested compounds (10 mM) were freshly prepared in DMSO. The serial dilutions of the tested compounds were prepared immediately before use. At the final dilutions obtained the concentrations of DMSO never exceeded 1%.

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 [24] with some

Table 2
IR spectral bands of the ligands and their platinum complexes.

Compound	ν(N—H)	ν^{as}(C=O)	ν^{s}(C=O)	ν(C—S)	ν(Pt—S)	ν(Pt—Cl)
L1	3172	1780	1738	1021		
	3077					
(1)	3242	1773	1729	1043	424	314
	3143					305
(2)	3310	1773	1713	1052	422	311
	3167					302
L2	3189	1772	1735	1013		
	3068					
(3)	3257	1769	1724	1064	421	315
	3136					308
(4)	3172	1769	1728	1066	418	312
	3060					306

modifications [25]. Exponentially growing cells were seeded in 96-well microplates (100 μL/well at a density of 3.5×10^5 cells/mL for the adherent and 1×10^5 cells/mL for the suspension cell lines) and allowed to grow for 24 h prior the exposure to the studied compounds. Cells were exposed to the tested agents for 72 h, whereby for each concentration a set of 8 separate wells was used. Every test was run in triplicate. 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 °C and the formazan crystals formed were dissolved by adding 110 μL of 5% HCOOH in 2-propanol. The MTT-formazan absorption was measured using a multimode microplate reader (Beckman Coulter DTX880) and the results were normalized as percentage of the untreated control (set as 100% viable). The data were fitted to sigmoidal dose-response curves and the IC_{50} values were calculated using non-linear regression analysis (Curve-fir; GraphPad Prism software for PC).

Results and discussion

Chemistry

The ligands 3-thiolanespiro-5′-hydantoin **(L1)** and 4-thio-1H-tetrahydropyranespiro-5′-hydantoin **(L2)** were prepared by the Bucherer–Berg method. Their Pt(II) and Pt(IV) complexes were synthesized using reported procedure with minor revisions [19].

The elemental analysis for the new Pt(II) and Pt(IV) complexes were in good agreement with the following chemical formulas: $[Pt(C_6H_8N_2O_2S)_2Cl_2]$ **(1)**, $[Pt(C_6H_8N_2O_2S)_2Cl_4]$ **(2)**, $[Pt(C_7H_{10}N_2O_2S)_2Cl_2]\cdot 2H_2O$ **(3)** and $[Pt(C_7H_{10}N_2O_2S)_2Cl_4]\cdot H_2O$ **(4)**. The determination of crystal water content in the complexes **(3)** and **(4)** was defined by DTA analysis. In order to evaluate the mode of coordination of the ligand to the metal ion, IR, ^1H and ^{13}C NMR spectra of the metal free ligands as well as of their Pt(II) and Pt(IV) complexes were recorded.

IR spectral studies

In the IR spectra of the platinum compounds shifting of the signals corresponding to C—S bond is observed: ν(C—S) in a metal free ligand **(L1)** is at 1030 cm^{-1}, while in the complexes **(1)** and **(2)** frequency arises at 1050 and 1052 cm^{-1}, respectively. In the case of **L2** this values are as follows: 1013 cm^{-1} for **L2** and 1040 and 1066 cm^{-1} for the complexes **(3)** and **(4)**, respectively. In the IR spectra of the complexes **(1–4)** the new bands at 424, 422, 421 and 418 cm^{-1} are appeared. These stretching vibrations can be attached to the ν(Pt—S) coordinative bonds. New bands at 315–302 cm^{-1} were assigned to the ν(Pt—Cl) stretching vibrations. Two bands for ν(Pt—Cl) stretching vibrations were observed,

Table 3
^1H spectral data of the ligands and their platinum complexes.

Compound	^1H NMR spectra (ppm)									
	δ(NH-3)	δ(NH-1)	δ(CH_2)-2-S(a)	δ(CH_2)-5(a)	δ(CH_2)-5(e)	δ(CH_2)-2-S(e)	δ(CH_2)-4	δ[CH_2-2 + CH_2-6-(a)]	δ[CH_2-2 + CH_2-6-(e)]	δ[CH_2-3 + CH_2-5-(a)]	δ[CH_2-3 + CH_2-5-(e)]
L1	10.78	8.38	3.22	3.11	3.06	2.93	2.28–2.17				
(1)	10.75	8.44	3.06	3.02	2.97	2.87	2.17–2.04				
(2)	11.15	8.78	3.25	3.09	2.99	2.97	2.31–2.21				
L2	10.65	8.47						2.85–2.74	2.63–2.55	1.94–1.87	1.84–1.74
(3)	10.63	8.90						2.88–2.78	2.66–2.57	1.99–1.89	1.90–1.79
(4)	10.66	9.00						2.84–2.74	2.62–2.56	2.32–2.16	1.90–1.75

Table 4
^{13}C spectral data of the ligands and their platinum complexes.

Compound	^{13}C NMR spectra (ppm)							
	δ(CO-4′)	δ(CO-2′)	δ(C-5′)	δ(C-2)	δ(C-5)	δ(C-4)	δ(C-2 + C-6)	δ(C-3 + C-5)
L1	176.5	156.7	71.6	41.2	40.3	30.0		
(1)	176.0	156.2	70.6	39.8	39.5	29.5		
(2)	177.0	156.5	71.1	40.8	40.3	30.3		
L2	177.7	156.2	60.9				34.1	22.7
(3)	177.4	156.1	60.1				33.6	21.5
(4)	175.8	154.7	59.0				32.2	20.9

implying *cis*-location of chloride ligands according to Nakamoto [26].

The bands related to the stretching vibrations of the two carbonyl groups in the metal-free ligands did not shift upon coordination of **L1** and **L2** to Pt(II) and Pt(IV) ions, indicating that the C=O groups were not involved in binding to the metals (Table 2).

^{1}H and ^{13}C NMR spectra of the complexes

In the ^{1}H NMR spectra of freshly prepared DMSO-d_6 solutions of the Pt(II) and Pt(IV) complexes with 3-thiolanespiro-5′-hydantoin **(1,2)**, the signals of the protons for CH_2(2) and CH_2(5) are in relatively wide range – 3.25 and 2.85 ppm. This is due to the fact that S-containing ring is fixed and sulfur atom is bonding with platinum ions; axial and equatorial hydrogens are easily discernment.

In the ^{1}H NMR spectra of the Pt(II) and Pt(IV) complexes with 4-thio-1H-tetrahydropyranespiro-5′-hydantoin **(3,4)** the signals of the protons for CH_2(2) and CH_2(6) are not in such wide range in comparison with previous compounds – 2.88 and 2.56 ppm. This is due to the symmetry of the studied compounds with tetrahydropyran ring. In this case the ring is fixed because sulfur is bonded with platinum ions; axial and equatorial hydrogens are easily discernment (Table 3).

In the ^{13}C NMR spectra of the Pt(II) and Pt(IV) complexes with 3-thiolanespiro-5′-hydantoin **(1,2)** the signals of the carbon atoms C(2) and C(4), directly connected to the sulfur are weakly

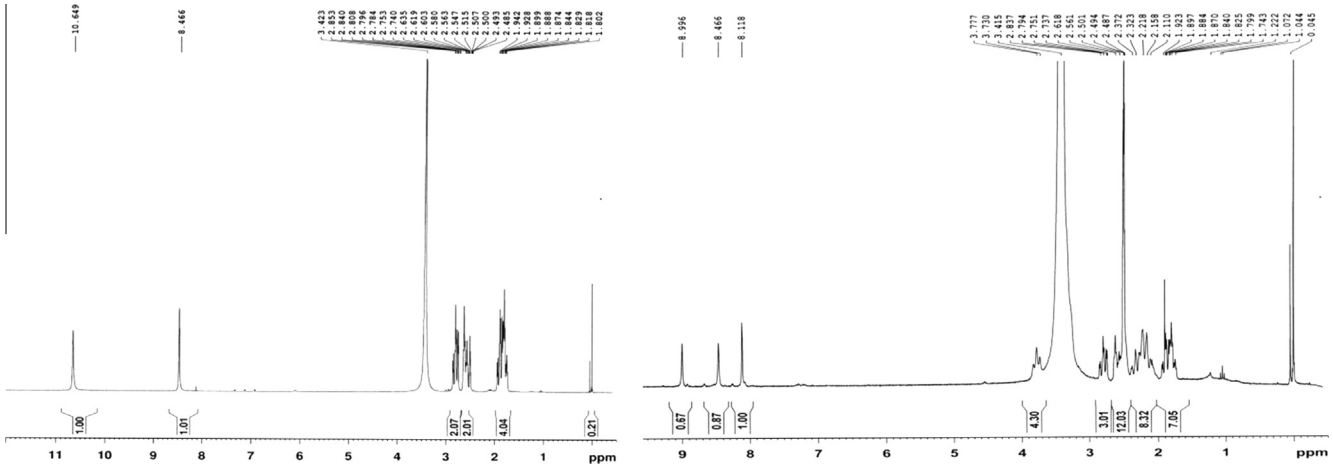

Fig. 3. ^{1}H NMR spectra of the ligand **L2** and its Pt(IV) complex **(4)**.

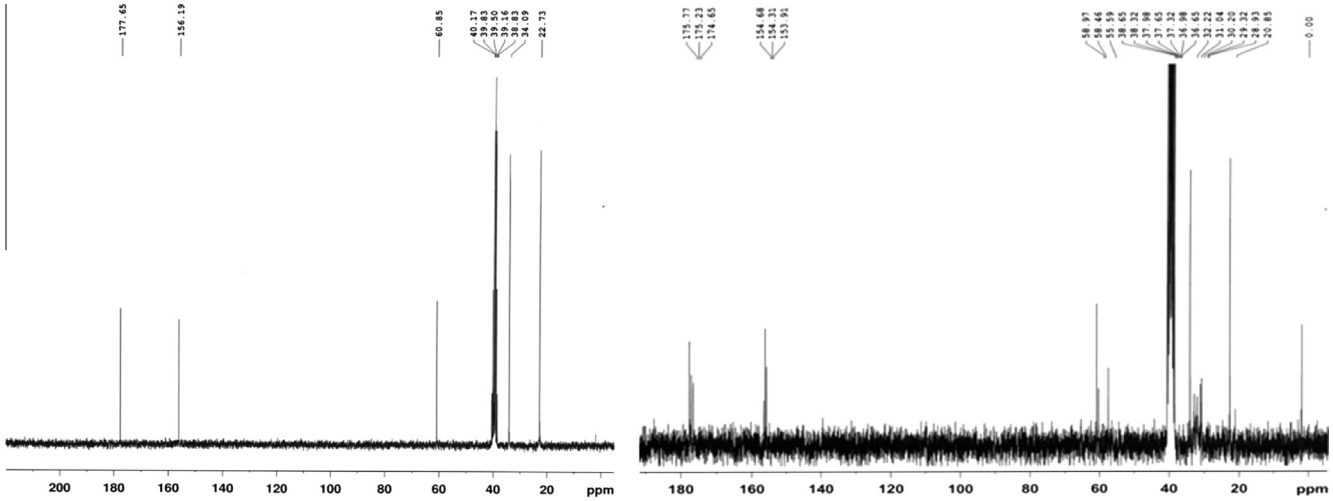

Fig. 4. ^{13}C NMR spectra of the ligand **L2** and its Pt(IV) complex **(4)**.

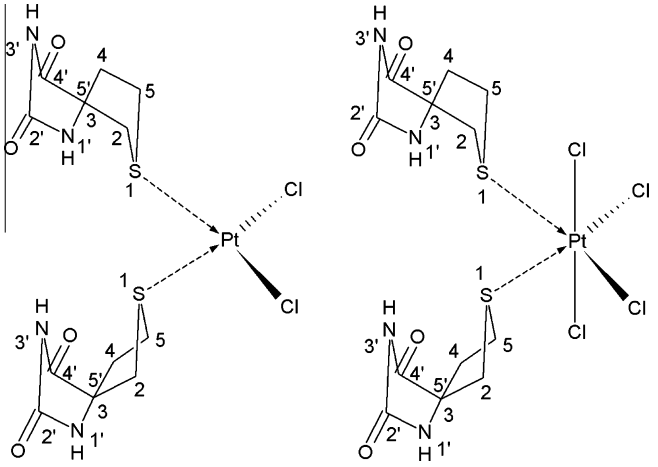

Fig. 5. Chemical formulas of the Pt(II) and Pt(IV) complexes with 3-thiolanespiro-5′-hydantoin.

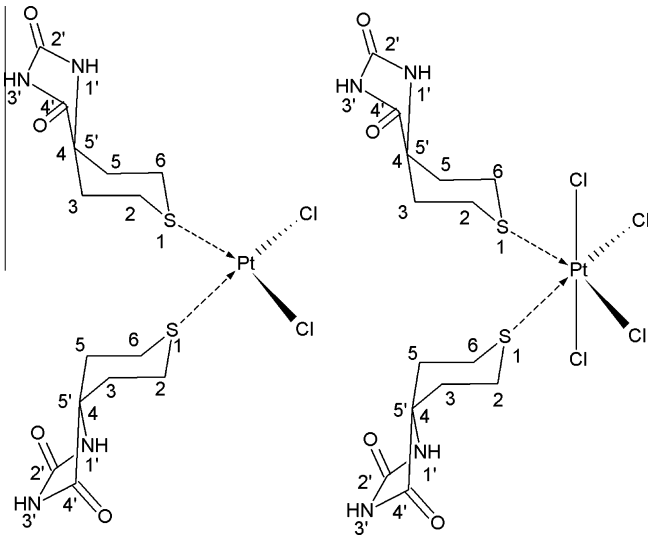

Fig. 6. Chemical formulas of the Pt(II) and Pt(IV) complexes with 4-thio-1H-tetrahydropyranespiro-5′-hydantoin.

influenced from the bonding with platinum ions – 39.2–40.8 ppm. In the case of the Pt(II) and Pt(IV) complexes with 4-thio-1H-tetrahydropyranespiro-5′-hydantoin **(3,4)**, carbon atoms directly connected to the sulfur are C(2) and C(6). They give only one signal due to the symmetry of the cyclic ring. This signal is at 33.6 ppm for complex **(3)** and 32.2 ppm for complex **(4)** (Table 4).

^{1}H and ^{13}C NMR spectra of the complexes show little differences between metal free ligands and newly synthesized Pt(II) and Pt(IV) complexes. These results show that sulfur atom has relatively low polarization when is included in the complex. Pt(IV) complexes with the N-, S-, O-containing heterocyclic organic ligands are diamagnetic and NMR spectra would be recorded [27]. Exemplary the ^{1}H and ^{13}C NMR spectra of the ligand **(L2)** and its Pt(IV) complex **(4)** were presented in Figs. 3 and 4.

General schemes of the investigated compounds are shown in Figs. 5 and 6.

Thermogravimetric study

In the temperature range 150–280 °C (in complex **(3)**) the TG changes its course after 170 °C. At 190 °C a mass loss Δm = 5. 68%. ($\Delta m_{calc.}$ = 5.34%) is registered, which corresponds to the

Table 5
Selected calculated parameters of **L1** and its Pt(II) complex **(1)**.

Parameters	Ligand(**L1**)	*cis*-[Pt(L1)$_2$Cl$_2$] **(1)**
μ (D)	2.06	10.20
Bond lengths (Å)		
Pt—S1	–	2.43
Pt—S2	–	2.46
Pt—Cl1	–	2.39
Pt—Cl2	–	2.41
Angles (°)		
C—S—C	93.35	–
C1—N2—C3	113.32	–
N1—C2—N3	105.22	–
N1—C2—C3	100.75	–
Cl—Pt—Cl	–	99.22
S—Pt—S	–	96.41
S—Pt—Cl		180.00

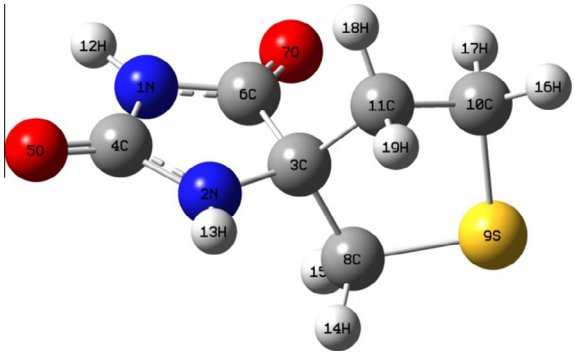

Fig. 7. Optimized geometry for 3-thiolanespiro-5′-hydantoin **(L1)**.

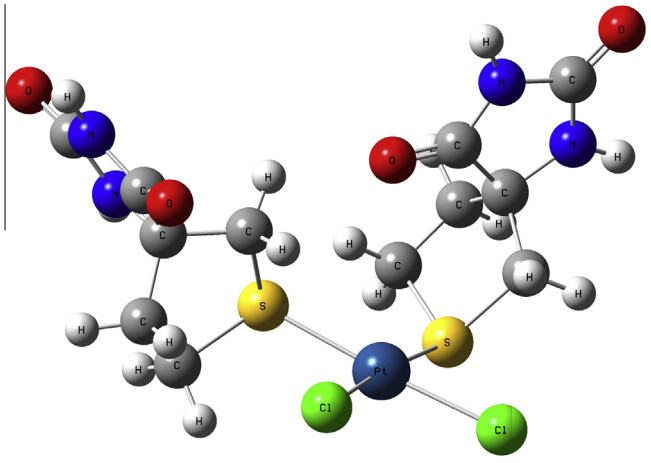

Fig. 8. Optimized geometry for *cis*-[Pt(L1)$_2$Cl$_2$] **(1)**.

disconnection of two molecules of crystal water. This fact is confirmed by the endothermic effect at T_{max} = 190 °C in the DTA curve.

Geometry optimization

The calculated structural parameters for **L1** and its Pt(II) complex **(1)** are in good agreement with experimental data for similar hydantoins and their platinum complexes [15,28]. The obtained results confirm the square-planar geometry of complex **(1)** with valent angles S–Pt–Cl close to 90° or 180°, depending on their position. Selected calculated parameters (i.e. bond lengths, angles, dipole moments) are shown in Table 5.

Based on the data, obtained from the spectroscopic analysis and the DFT calculations for **(L1)** and complex **(1)**, it can be concluded,

Table 6
Cytotoxicity of the Pt(II) and Pt(IV) complexes with 3-thiolanespiro-5′-hydantoin and 4-thio-1H-tetrahydropyranespiro-5′-hydantoin**(1–4)** in comparison to cisplatin in four human tumor cell lines.

Cell line compound	IC_{50} values (μM)			
	SKW-3[a]	HL-60[b]	EJ[c]	LAMA-84[d]
L1	114.0	202.8	115.2	174.5
1	142.3	147.2	>200	197.5
2	147.1	195.0	112.8	194.2
L2	92.6	180.9	143.5	101.1
3	109.4	127.7	144.6	129.8
4	154.5	167.7	165.8	186.4
Cisplatin	11.4	8.7	10.2	16.9

[a] T-cell leukemia.
[b] Acute myeloid leukemia.
[c] Urinary bladder carcinoma.
[d] Human chronic myeloid.

that the most probable bounding of the organic ligands with the metal ions in all complexes reported herein was realized through the sulfur atom from the cyclic ring. IR spectra of the **(L1)** and complex **(1)** were calculated and compared with the experimental IR spectra of the same compounds. The data showed that there was very good correlation between experimental and theoretical data of the IR spectra. The optimized structures of 3-thiolanespiro-5′-hydantoin **(L1)** and its Pt(II) complex **(1)** are presented in Figs. 7 and 8.

In vitro studies

The present study describes a comparative evaluation of the cytotoxic effects of four newly synthesized Pt(II) and Pt(IV) complexes with 3-thiolanespiro-5′-hydantoin and 4-thio-1H-tetrahydropyranespiro-5′-hydantoin vs. the referent antineoplastic agent cisplatin on a panel of human tumor cell lines, using the standard MTT-dye reduction assay for cell viability. The complexes exerted cytotoxic effects after 72 h continuous exposure, whereby the individual chemosensitivity varied among the different cell lines, as evidenced by the IC_{50} values, summarized in Table 6. The complex **(1)** proved to be more active as compared to the ligand **L1** on HL-60 cell line. This is due to the fact that maybe complex **(1)** has the similar action mechanism to the referent cisplatin. The cytotoxicity of the complex **(2)** was comparable to that of the ligand **L1** on EJ cell line. The cytotoxicity of the ligand **L2** was comparable to these complexes **(3)** and **(4)** on EJ cell line. The cytotoxic effects of the ligands **L1** and **L2** were similar to the effects of the complexes **(1)**, **(2)**, **(3)** and **(4)**, respectively. The tested platinum compounds displayed cytotoxic effects in a concentration dependent manner. As a result the ligands and the new synthesized platinum complexes are less active than the referent cisplatin.

Conclusion

Two organic compounds 3-thiolanespiro-5′-hydantoin and 4-thio-1H-tetrahydropyranespiro-5′-hydantoin were synthesized and used as carrier ligands for preparation of four Pt(II) and Pt(IV) complexes. The molecular formulae of the platinum complexes were determined by elemental analysis, IR, ^{1}H and ^{13}C NMR spectra. The coordination mode of the 3-thiolanespiro-5′-hydantoin and its Pt(II) complex **(1)** is confirmed by DFT calculations. Because the very close chemical structures of the **L1** and **L2** the mode of coordination of the ligands to the metal ions in all four complexes is realized through the sulfur atom from the cyclic ring. The complexes were tested for antiproliferative activity *in vitro* on panel of human tumor cell lines. The tested compounds exerted concentration-dependent cytotoxic effects against some of the tumor cell lines.

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