

## Synthesis, physico-chemical investigation, DFT calculations and cytotoxic activity of palladium complexes with 3'-amino-4-thio-1H-tetrahydropyranspiro-5'-hydantoin

E. Cherneva<sup>1\*</sup>, R. T. Buyukliev<sup>1</sup>, N. Burdzhiev<sup>2</sup>, R. Michailova<sup>3</sup>, A. G. Bakalova<sup>1</sup>

<sup>1</sup> Department of Chemistry, Faculty of Pharmacy, Medical University - Sofia, 2 Dunav Str., 1000 Sofia, Bulgaria

<sup>2</sup> Department of Organic Chemistry and Pharmacognosy, Faculty of Chemistry and Pharmacy, Sofia University, 1 James Bourchier Blvd., 1164 Sofia, Bulgaria

<sup>3</sup> Department of Pharmacology, Pharmacotherapy and Toxicology, Faculty of Pharmacy, Medical University - Sofia, 2 Dunav Str., 1000 Sofia, Bulgaria

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*Dedicated to Acad. Ivan Juchnovski on the occasion of his 80<sup>th</sup> birthday*

A new organic compound - 3'-amino-4-thio-1H-tetrahydropyranspiro-5'-hydantoin and two new Pd(II) and Pd(IV) complexes were prepared and investigated by elemental analyses, IR and NMR spectral analyses. The structure geometries of the ligand and its palladium complexes were obtained using the hybrid DFT method. 6-311++G\*\* set was used for the optimization of the geometry of the ligand, while for the Pd(II) and Pd(IV) complexes LANL2DZ basis set was utilized. According to the calculations data the geometry of the Pd(II) complex is square planar and of the Pd(IV) complex is distorted octahedral. The complexes were tested for cytotoxicity *in vitro* on five human tumor cell lines. The compounds tested exerted concentration dependent cytotoxic effects against the human tumor cell lines.

**Key words:** palladium complexes; amino-spiro-5'-hydantoins; DFT calculations; cytotoxic activity

### INTRODUCTION

Platinum complexes are the most widely used drugs for the treatment of cancer. Cisplatin together with the second generation drug carboplatin and with the third generation drug oxaliplatin are widely used in worldwide [1]. All other clinically used platinum drugs have limited use in the world. Pt<sup>2+</sup> and Pd<sup>2+</sup> ions have similar chemical properties and modes of coordination forming square planar complexes [2,3]. The palladium compounds are more labile from both a thermodynamic and a kinetic point of view with respect to corresponding platinum compounds [4]. Palladium-based drugs can undergo a rapid hydrolysis before they reach the DNA target; this results in both a low antitumor activity or even inactivity and toxicity [5]. But some palladium complexes show significant antitumor activity in normal tumor cells and lower resistance of tumor cells to clinical treatments as well as lower side effects. Mononuclear palladium complexes with aromatic N-containing ligands, amino acid ligands, S-donor ligands, and P-containing ligands have respective qualities and properties due to the different structures and properties of the ligands [6].

The aim of this article is to synthesis, spectroscopic and theoretical study of new palladium complexes with 3'-amino-4-thio-1H-tetrahydropyranspiro-5'-hydantoin as carrier ligand. The spectroscopic study includes IR and NMR spectral investigation. The theoretical study comprehends the using of DFT calculations employing the B3LYP hybrid functional and 6-311++G\*\* set for the ligand and LANL2DZ basis set for the palladium complexes. The ligand and the palladium complexes were investigated for cytotoxic activity on some human tumour cell lines.

### MATERIALS AND METHODS

All chemicals were purchased from Fluka (UK) and Sigma-Aldrich. The newly synthesized Pd(II) and Pd(IV) complexes were characterized by elemental analyses, melting points, IR and NMR spectra. The elemental analyses were 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<sup>-1</sup> as Attenuated Total Reflection Fourier Transform Infrared Spectroscopy (ATR-FTIR). The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker WM 500 (500

\* To whom all correspondence should be sent:  
E-mail: e.d.cherneva@gmail.com

MHz) spectrometer. Because the solubility of the complexes (1) and (2) is highly insufficient in DMSO, only  $^1\text{H}$  NMR spectra of the palladium complexes were recorded. Intensities of reported IR bands are defined as br = broad, s = strong, m = medium, w = weak and sh- shoulder. The splitting of proton resonances in the  $^1\text{H}$  NMR spectra is defined as s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

#### *Synthesis of 3'-amino-4-thio-1H-tetrahydropyranspiro-5'-hydantoin*

The synthesis and structure of 4-thio-1H-tetrahydropyranspiro-5'-hydantoin were described in details in our previously published work [7]. 4-thio-1H-tetrahydropyranspiro-5'-hydantoin (1.86 g) is dissolved in 20 mL 96% hydrazine-hydrate. The solution was heated with reflux condenser 4 hours. After that the mixture was poured in 50 mL of water and cooled below  $0^\circ\text{C}$ . After 24 hours the resulting crystals were filtered off and recrystallized from ethanol. IR (ATR): 3335 w, 3287 br, 3224 sh, 1781 m, 1707 s, 1609 m, 1411 w, 623 w.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ ): 8.65 (s, 1H, NH); 4.66 (s, 2H,  $\text{NH}_2$ ); 2.82-2.76 (m, 2H,  $\text{CH}_2\text{-S(ax)}$ ); 2.62-2.59 (m, 2H,  $\text{CH}_2\text{-S(eq)}$ ); 1.92-1.88 (m, 2H,  $\text{CH}_2\text{-C(ax)}$ ); 1.75-1.72 (m, 2H,  $\text{CH}_2\text{-C(eq)}$ ).  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ ): 174.6 (CO-2'); 156.0 (CO-4'); 58.5 (C-5'); 34.6 (C-3 + C-5); 23.0 (C-2 + C-6).

#### *Synthesis of cis-bis(3'-amino-4-thio-1H-tetrahydropyranspiro-5'-hydantoin)-dichlorido palladium(II) – cis-[PdL<sub>2</sub>Cl<sub>2</sub>](1)*

Two solutions of  $\text{K}_2[\text{PdCl}_4]$  and 3'-amino-4-thio-1H-tetrahydropyranspiro-5'-hydantoin were prepared for the synthesis of the complex *cis*-[PdL<sub>2</sub>Cl<sub>2</sub>]. A 4 ml ethanol solution of the L (0.1344 g, 0.6137 mmol) was added dropwise to 5 ml aqueous solution of  $\text{K}_2[\text{PdCl}_4]$  (0.0998 g, 0.3058 mmol) at constant stirring. The homogenous solution was stirred for 6 hours. A light-yellow product was obtained, filtered off and dried in a vacuum desiccator. IR (ATR): 3325 w, 3250 br, 3220 sh, 1775 m, 1720 s, 1604 m, 1412 w, 647 w.  $^1\text{H}$ -NMR (500 MHz, DMSO- $d_6$ ): 8.65 (s, 1H, NH); 4.59 (bs, 2H,  $\text{NH}_2$ ); 2.98-2.89 (m, 2H,  $\text{CH}_2\text{-S(ax)}$ ); 2.76-2.70 (m, 2H,  $\text{CH}_2\text{-S(eq)}$ ); 2.02-1.98 (m, 2H,  $\text{CH}_2\text{-C(ax)}$ ); 1.83-1.79 (m, 2H,  $\text{CH}_2\text{-C(eq)}$ ).

#### *Synthesis of cis-bis(3'-amino-4-thio-1H-tetrahydropyranspiro-5'-hydantoin) dichlorido palladium(IV) – cis-[PdL<sub>2</sub>Cl<sub>4</sub>](2)*

Two solutions of  $\text{K}_2[\text{PdCl}_6]$  and 3'-amino-4-thio-1H-tetrahydropyranspiro-5'-hydantoin were prepared for the synthesis of the complex *cis*-[PdL<sub>2</sub>Cl<sub>4</sub>]. A 5 ml ethanol solution of the L (0.1106 g, 0.5050 mmol) was added dropwise to 5 ml aqueous solution of  $\text{K}_2[\text{PdCl}_6]$  (0.1010 g, 0.2540 mmol) at constant stirring. The homogenous solution was stirred for 6 hours. A light-yellow product was obtained, filtered off, washed several times with water and dried in a vacuum desiccator. IR (ATR): 3331 w, 3251 br, 3220 sh, 1775 m, 1720 s, 1604 w, 1412 w, 648 w.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ ): 8.62 (s, 1H, NH); 4.60 (bs, 2H,  $\text{NH}_2$ ); 2.92-2.86 (m, 2H,  $\text{CH}_2\text{-S(ax)}$ ); 2.70-2.66 (m, 2H,  $\text{CH}_2\text{-S(eq)}$ ); 1.99-1.93 (m, 2H,  $\text{CH}_2\text{-C(ax)}$ ); 1.81-1.75 (m, 2H,  $\text{CH}_2\text{-C(eq)}$ ).

#### *Computational details*

All theoretical calculations were performed using the Gaussian 09 package [8] of programs. Optimization of the structures of the ligand 3'-amino-thio-1H-tetrahydropyranspiro-5'-hydantoin and possible conformers of Pd(II) and Pd(IV) complexes were carried out by DFT calculations, employing the B3LYP (Becke's three-parameter non-local exchange [9]) and Lee et al. correlation [10] hybrid functional and 6-311++G\*\* set for the ligand and LANL2DZ basis set for the palladium complexes. The B3LYP hybrid functional [11, 12] 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, palladium etc. and it is compatible with all other organic elements (C, N, H, O, Hal).

#### *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) REH(acute lymphoblastic leukemia, established from the peripheral blood of a 15-year-old North African girl with acute lymphoblastic leukemia in 1973); (iii) MDA-MB-231(human breast cancer cell line, established in 1973 from the pleural effusion of a 51-year-old woman with breast carcinoma); (iv) HL-60(acute myeloid leukemia,

established from the peripheral blood of a patient with acute promyelocyte leukemia); (v) EJ(human urinary bladder carcinoma). 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: Hep-G2 (ACC 180), REH (ACC 22), MDA-MB-231(ACC 73) and HL-60 (ACC 3).

#### 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 [13] with some modifications [14]. Exponentially growing cells were seeded in 96-well microplates (100  $\mu\text{L}$ /well at a density of  $3.5 \times 10^5$  cells/mL for the adherent and  $1 \times 10^5$  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 ligand and its Pd(II) and Pd(IV) complexes were freshly dissolved in DMSO and then promptly diluted in RMPI-1640 growth medium, immediately before

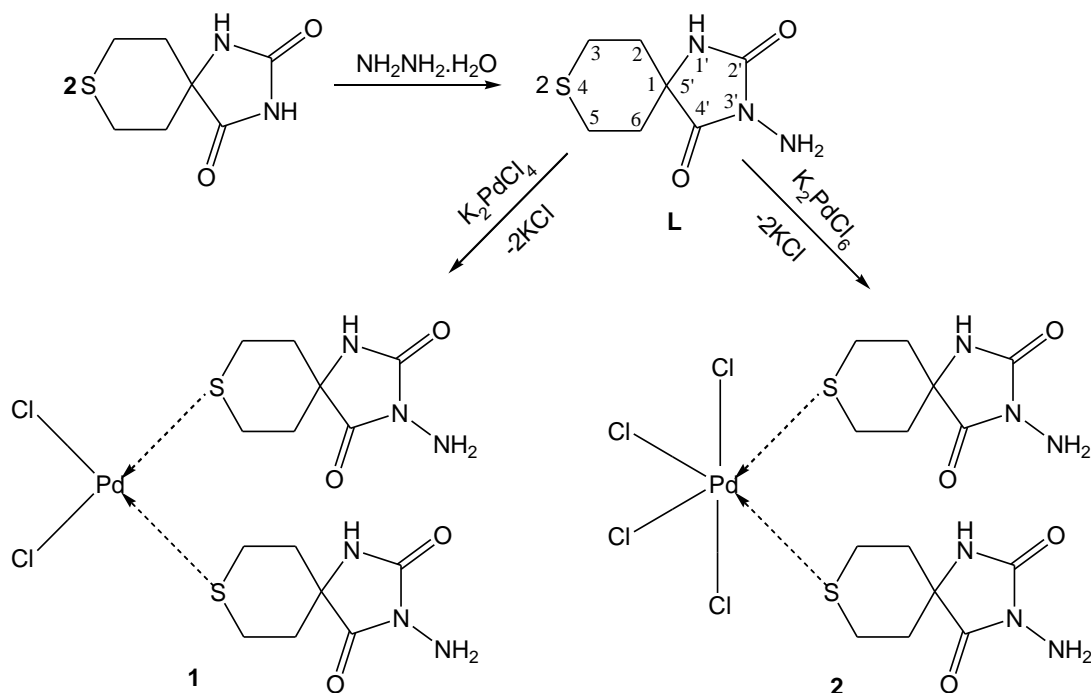
treatment of cells. At the final dilutions the solvent concentration never exceeded 0.5%. Cells were exposed to the tested compounds for 72 h, whereby for each concentration a set of 8 separate wells was used. Every test was run in triplicate, i.e. in three separate microplates. After incubation with 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°C and the formazan crystals formed were dissolved by adding 110  $\mu\text{L}$  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<sub>50</sub> 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

### Synthesis

The ligand and its new palladium 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 formulas – *cis*-[Pd(C<sub>7</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>S)<sub>2</sub>Cl<sub>2</sub>] and *cis*-[Pd(C<sub>7</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>S)<sub>2</sub>Cl<sub>4</sub>]. The data from elemental analyses and some physical properties are summarized in Table 1.



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

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

Compound	Molecular formula	MW	Yield <sup>a</sup> (%)	M.p. <sup>b</sup> (dec.) (°C)	Elemental analysis		
					% Calc. (% Found)		
					C	H	N
<b>Ligand</b>	C <sub>7</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S	201	55	236	41.79 (42.00)	5.47 (5.81)	20.89 (21.03)
<b>(1)</b>	C <sub>14</sub> H <sub>22</sub> N <sub>6</sub> O <sub>4</sub> S <sub>2</sub> Cl <sub>2</sub> Pd	579.30	87	265	29.00 (30.38)	3.80 (4.16)	14.50 (14.49)
<b>(2)</b>	C <sub>14</sub> H <sub>22</sub> N <sub>6</sub> O <sub>4</sub> S <sub>2</sub> Cl <sub>4</sub> Pd	650.20	65	218	25.84 (26.05)	3.38 (3.68)	12.92 (12.70)

<sup>a</sup>Yield of analytically pure product; <sup>b</sup>Mp of analytically pure product

### IR spectral analysis

Due to the intermolecular hydrogen bonds of the ligand, the stretching vibrations of  $\nu(\text{NH})$  and  $\nu(\text{NH}_2)$  appear at the broad absorption band in the range of 3300 - 3150  $\text{cm}^{-1}$ . The bands are slightly shifted to higher frequencies in the palladium complexes. Deformation vibrations of  $\text{NH}_2$  and  $\text{NH}$  groups in the ligand at 1609 and 1411  $\text{cm}^{-1}$  are not affected in the complexes (1604  $\text{cm}^{-1}$  and 1412  $\text{cm}^{-1}$  resp.) It proves that nitrogen atom from the  $\text{NH}_2$  group is not participated in the coordination with metal ions. Upon the coordination of the sulphur atom to the metal ions the stretching vibration of the C-S bond is shifted from 623  $\text{cm}^{-1}$  to 647 and 648  $\text{cm}^{-1}$  respectively.

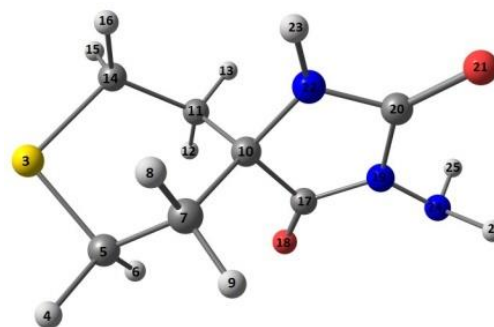
### NMR spectral analysis

It is not possible to record  $^{13}\text{C}$  NMR spectra of Pd (II) and Pd (IV) complexes due to their very poor solubility in DMSO- $d_6$ . In their proton NMR spectra, there is not visible shifting of N-NH<sub>2</sub> protons, which is proof for lack of complexation between metal cation and nitrogen from  $\text{NH}_2$  group. NH-(1') chemical shift is not influenced. There is a shifting of CH<sub>2</sub> groups in the complexes in comparison with the metal-free ligand. Thus, in Pd(II) complex, chemical shifts of axial S-CH<sub>2</sub> protons are moved with approximately 0.15 ppm and equatorial ones are moved with 0.13 ppm. In CH<sub>2</sub>-C(1) protons this difference is similar: 0.10 ppm for axial and 0.08 ppm for equatorial protons. In the Pd(IV) complex, the differences of chemical shifts of S-CH<sub>2</sub> protons are respectively 0.10 ppm for axial and 0.08 ppm for equatorial. For CH<sub>2</sub>-C(1) protons the differences are 0.08 ppm for axial and 0.05 ppm for equatorial protons. Atom numbering is in accordance with Scheme 1.

### Theoretical analysis

The optimized geometry of the ligand and the complexes **(1)**, **(2)** and atom numbering were shown on Figs.1-3.

Gas phase optimized geometry of the compounds were obtained at B3LYP hybrid functional and 6-311++G\*\*set for ligand and LANL2DZ basis set for the Pd complexes. The theoretical calculations showed that the atoms in the ligand are lying in two planes oriented perpendicularly to each other as expected. The first one comprises the hydantoin fragment together with  $\text{NH}_2$  group and the other – the tetrahydrothiopyran ring (Fig. 1). The angles around the Pd center suggest square planar coordination environment in the complex **(1)** and a distorted octahedral geometry in the complex **(2)** (Figs. 2, 3). Each complex has two molecules of the ligand bonded to the metal center through the sulfur atom. In both complexes ligand (**L**) is stretched above the plane formed by the metal ion, Cl<sub>1</sub>, Cl<sub>2</sub>, S<sub>3</sub>, S<sub>27</sub> while the second one is beneath the plane.



**Fig. 1.** Optimized geometry of the ligand, performed at B3LYP/6-311++G\*\*set.

The coordination leads to small changes in geometry parameters (Table 2).

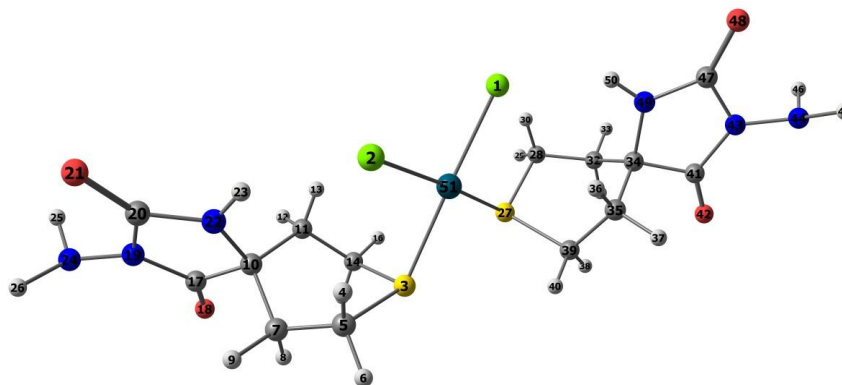


Fig. 2. Optimized geometry of the complex (1), performed at B3LYP/LANL2DZ basis set.

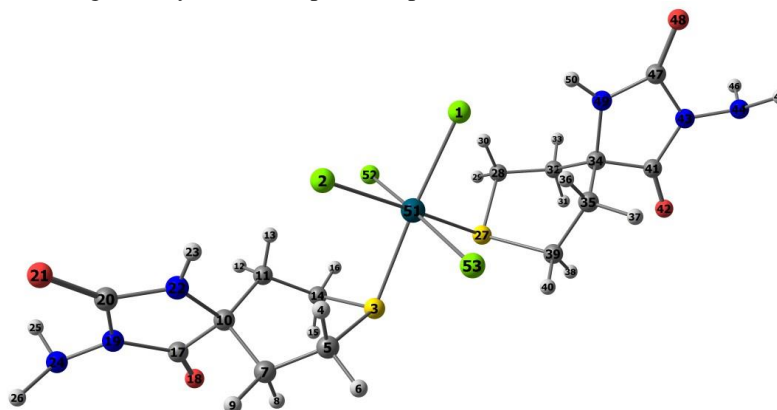


Fig. 3. Optimized geometry of the complex (2), performed at B3LYP/LANL2DZ basis set.

Table 2. Selected calculated geometry parameters.

Parameters	Ligand(L)	Complex (1)	Complex (2)
$\mu$ (D)	1.94	7.52	6.56
<b>Bond lengths (Å)</b>			
Pd-Cl <sub>1</sub>	-	2.39	2.41
Pd-Cl <sub>2</sub>	-	2.39	2.41
Pd-S <sub>3</sub>	-	2.48	2.52
Pd-S <sub>27</sub>	-	2.48	2.52
C <sub>5</sub> -S <sub>3</sub>	1.84	1.92	1.92
C <sub>14</sub> -S <sub>3</sub>	1.84	1.91	1.91
C <sub>28</sub> -S <sub>27</sub>	-	1.92	1.92
C <sub>39</sub> -S <sub>27</sub>	-	1.91	1.91
<b>Angles (°)</b>			
Cl <sub>1</sub> -Pd-Cl <sub>2</sub>	-	89.8	88.4
S <sub>3</sub> -Pd-Cl <sub>2</sub>	-	93.2	93.4
S <sub>27</sub> -Pd-Cl <sub>1</sub>	-	93.2	93.4
S <sub>3</sub> -Pd-S <sub>27</sub>	-	83.7	84.9
<b>Dihedral angles (°)</b>			
C <sub>5</sub> -S <sub>3</sub> -Pd-Cl <sub>2</sub>	-	-13.6	-33.0
C <sub>5</sub> -S <sub>3</sub> -Pd-S <sub>27</sub>	-	165.9	150.7
C <sub>14</sub> -S <sub>3</sub> -Pd-S <sub>27</sub>	-	-89.2	-103.2
C <sub>28</sub> -S <sub>27</sub> -Pd-Cl <sub>1</sub>	-	-13.6	-33.0
C <sub>39</sub> -S <sub>27</sub> -Pd-Cl <sub>1</sub>	-	91.1	72.9

In the complexes S-C bonds length increase than those in the ligand by 0.08 Å. For the Pd(II)

complex the two Pd-Cl bonds are equal, but they are slightly shorter than those calculated for Pd(IV) complex by 0.02 Å. It is similar for the Pd-S bonds, in complex (2) they are longer, which could be explained with the different coordination number. Bonds lengths are in agreement with those reported for the analogous complexes [15].

#### Pharmacological screening

The ligand (L) and the complexes (1,2) were tested for cytotoxic activity on five human tumor cell lines. 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 complex (1) showed higher cytotoxic activity than the ligand (L) and complex (2) on REH cell line. The complex (2) presented better cytotoxic activity than the ligand and complex (1) on MDA-MB-231 and EJ cell lines. This can be explained by the fact that palladium complexes have a similar mechanism of action as platinum complexes. 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 two human tumour cell lines.

Cell line	IC <sub>50</sub> values(μM)				
	Hep-G2 <sup>a</sup>	REH <sup>b</sup>	MDA-MB- 231 <sup>c</sup>	HL-60 <sup>d</sup>	EJ <sup>e</sup>
Compound					
Ligand	> 200	> 200	> 200	> 200	> 200
Complex ( <b>1</b> )	> 200	137.5	> 200	> 200	196.3
Complex ( <b>2</b> )	> 200	> 200	188.7	> 200	144.1
Cisplatin	12.0	1.07	31.6	8.7	10.2

<sup>a</sup>human hepatocyte carcinoma; <sup>b</sup>acute lymphoblastic leukemia; <sup>c</sup>human breast cancer; <sup>d</sup>acute myeloid leukemia;

<sup>e</sup>human urinary bladder carcinoma

## CONCLUSION

A new organic compound - 3'-amino-4-thio-1H-tetrahydropyranspiro-5'-hydantoin and two new Pd(II) and Pd(IV) complexes were synthesized. The chemical formulas were investigated by elemental analyses, IR and NMR spectral analyses. The geometry of the ligand and its palladium 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. From the results obtained the coordination mode of the ligand with the palladium ions is realized by the sulphur atom from the tetrahydrothiopyran ring. The compounds were tested for cytotoxic activity on five human tumour cell lines. According to the IC<sub>50</sub> values of the compounds, palladium complexes are more active than the ligand. Complex (**1**) is more active than complex (**2**) on REH tumour cell line, but complex (**2**) is more active than the complex (**1**) on MDA-MB-231 and EJ cell lines.

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СИНТЕЗ, ФИЗИКО-ХИМИЧНО ОХАРАКТЕРИЗИРАНЕ, ТЕОРЕТИЧНО ИЗСЛЕДВАНЕ И ЦИТОТОКСИЧНА АКТИВНОСТ НА ПАЛАДИЕВИ КОМПЛЕКСИ С 3'-АМИНО-4-ТИО-1Н-ТЕТРАХИДРОПИРАНСПИРО-5'-ХИДАНТОИН

Е. Чернева<sup>1\*</sup>, Р. Т. Буюклиев<sup>1</sup>, Н. Бурджиев<sup>2</sup>, Р. Михайлова<sup>3</sup>, А. Г. Бакалова<sup>1</sup>

<sup>1</sup> Катедра "Химия", Фармацевтичен факултет, Медицински университет - София,  
ул. „Дунав“ 2, 1000 София, България

<sup>2</sup> Катедра "Химия и фармакогнозия", Факултет по химия и фармация, Софийски Университет, бул. „Джеймс Баучер“ 1, 1164 София, България

<sup>3</sup> Катедра по фармакология, фармакотерапия и токсикология, Фармацевтичен факултет, Медицински университет - София, ул. „Дунав“ 2, 1000 София, България

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(Резюме)

Синтезирани и изследвани са едно ново органично съединение - 3'-амино-4-тио-1Н-тетрахиdropиранспиро-5'-хидантоин и два нови комплекса на Pd(II) и Pd(IV) чрез елементарен анализ, ИЧ и ЯМР спектрални методи. Геометрията на лиганда и на неговите паладиеви комплекси е изследвана с помощта на хибриден DFT метод. Използван е 6-311++G\*\* базисен сет за оптимизиране геометрията на лиганда, докато за комплексите на Pd(II) и Pd(IV) е използван LANL2DZ базисен сет. Според изчислените данни, геометрията на комплекса на Pd(II) е квадратно планарна, а на комплекса на Pd(IV) е деформиран октаедър. Комплексите бяха тествани *in vitro* за цитотоксичност върху пет човешки туморни клетъчни линии. Новосинтезираните съединения проявяват концентрационно зависима цитотоксична активност върху изследваните човешки туморни клетъчни линии.