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Correlations between the *in vitro* antiproliferative activity, structure and thermal stability of some macrocyclic dinuclear Cu(II) complexes

SLAĐANA B. TANASKOVIĆ[1#], MIRJANA ANTONIJEVIĆ-NIKOLIĆ[2#], BERTA BARTA HOLLÓ[3#], BRANKA DRAŽIĆ[1*#], TATJANA STANOJKOVIĆ[4], KATALIN MÉSZÁROS SZÉCSÉNYI[3#] and GORDANA VUČKOVIĆ[5#]

[1]*Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11000 Belgrade, Serbia,* [2]*Higher Technological School of Professional Studies 15000, Šabac, Serbia,* [3]*Faculty of Sciences, University of Novi Sad, Trg Dositeja Obradovića 3, 21000 Novi Sad, Serbia,* [4]*Institute for Oncology and Radiology of Serbia, Pasterova 14, 11000 Belgrade, Serbia and* [5]*Faculty of Chemistry, University of Belgrade, Studentski trg 16, 11158 Belgrade, Serbia*

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Abstract: Seven macrocyclic dinuclear Cu(II) complexes with tpmc = = *N*,*N'*,*N''*,*N'''*-tetrakis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane of coordination formulae $[Cu_2tpmc](ClO_4)_4$ (**1**), $[Cu_2(X)tpmc](ClO_4)_3 \cdot nH_2O$, X= F^-, *n* = 0 (**2**), X = Cl^-, *n* = 1 (**3**), X = Br^-, *n* = 0 (**4**), X= I^-, *n* = 1 (**5**), X = = NO_2^-, *n* = 0 (**6**), $[Cu_2(NCS)_2tpmc](ClO_4)_2$ (**7**) were evaluated for their cytotoxic activity against human cervix adenocarcinoma (HeLa), human melanoma (Fem-x) and human colon carcinoma (LS174) cell lines. The results were compared with the corresponding data for the *cis*-diamminedichloridoplatinum(II) (CDDP) as referent cytostatic, as well as with the free ligands and the solvent dimethyl sulfoxide (DMSO) as controls. The complexes showed considerable antiproliferative effect, although significantly less than CDDP. The thermal decomposition pattern of the complexes was determined by simultaneous TG/DSC measurements. The thermal stability of the compounds **2**–**7** followed the trend of their antiproliferative activity against the HeLa cell line, as well as their corresponding stability constants. The highest thermal stability and cytotoxicity belonged to complex $[Cu_2tpmc](ClO_4)_4$, with no anionic co-ligand. Complex $[Cu_2(NO_2)tpmc](ClO_4)_3$ exhibited a selective cytotoxicity against LS174 cells, at the level of the most active $[Cu_2tpmc](ClO_4)_4$.

Keywords: copper(II)complexes; octaazamacrocycle; antiproliferative activity; thermal analysis.

* Corresponding author. E-mail: bdrazic@pharmacy.bg.ac.rs
# Serbian Chemical Society member.
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INTRODUCTION

The coordination chemistry of macrocyclic ligands has attracted much attention.[1] Macrocyclic ligands coordinated with metal ions give stable complexes of different structures, and different catalytic, redox, *etc*. characteristics. They are applied as antitumor,[2] antiviral (including HIV activity),[3,4] antibacterial, antifungal or antimalarial agents.[5–10] The clinical success of cisplatin in the treatment of several human malignant tumors motivated major research efforts toward the discovery of alternative metal complexes with potential anticancer activity[11,12] but with fewer side effects. Copper is a physiologically important metal that plays a significant role in endogenous oxidative DNA damage associated with aging and cancer.[13] For the past several decades, great effort has been devoted to binding studies of copper complexes with DNA.[14–16] In particular, many studies were focused on binuclear copper complexes due to their presence in metalloproteinase as well as their affinity for DNA.[17–22]

The ligand *N*,*N*′,*N*″,*N*‴-tetrakis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane (tpmc) has four pendant arms that could participate in coordination with metal ions.[23] Depending on the metal centre, the structure and the number of co-ligand(s), it forms mono-, bi- or tetra-nuclear complexes. Metal centers linked to tpmc are either *exo* or *endo*, or may be bridged with additional ligands or bound in the *trans* position (one for each metal ion). Numerous complexes containing various co-ligands have been previously described.[24–29]

The aim of this study was to investigate the potential antiproliferative activity of seven macrocyclic binuclear Cu(II) complexes with or without co-ligands with the formulas: $[Cu_2tpmc](ClO_4)_4$ (**1**), $[Cu_2(X)tpmc](ClO_4)_3{\cdot}nH_2O$, X = F^-, *n* = 0 (**2**), X = Cl^-, *n* = 1 (**3**), X = Br^-, *n* = 0 (**4**), X = I^-, *n* = 1 (**5**), X = NO_2^-, *n* = 0 (**6**), $[Cu_2(NCS)_2tpmc](ClO_4)_2$ (**7**), which were earlier described.[30]

Thermal stability may be crucial in assessing the applicability of new compounds. Due to this, the thermal behavior of the ligand and the complexes are discussed in details in this article.

EXPERIMENTAL

Chemicals and materials

Macrocyclic ligand (tpmc),[31] $Cu(ClO_4)_2{\cdot}6H_2O$,[32] complex **1** ($[Cu_2tpmc](ClO_4)_4$)[30a] and complexes **2**–**7** ($[Cu_2(X)tpmc](ClO_4)_3{\cdot}nH_2O$, X = F^-, *n* = 0 (**2**), X = Cl^-, *n* = 1 (**3**), X = Br^-, *n* = 0 (**4**), X = I^-, *n* = 1 (**5**), X = NO_2^-, *n* = 0 (**6**), $[Cu_2(NCS)_2tpmc](ClO_4)_2$ (**7**))[30b] were obtained and purified according to literature procedures*. All other chemicals were of p.a. grade and were used as supplied, except for recording electronic spectra, when acetonitrile (MeCN) for HPLC was used.

* Warning: perchlorate salts of metal complexes with organic ligands are potentially explosive and should be stored and handled with great caution!

Antiproliferative assay

Human cervix adenocarcinoma (HeLa), human melanoma (Fem-x) and human colon carcinoma (LS174) cell lines were obtained from the American Type Culture Collection (Manassas, VA, USA). All cancer cell lines were maintained in the recommended RPMI-1640 medium supplemented with 10 % heat-inactivated (56 °C) fetal bovine serum, L-glutamine (3 mM), streptomycin (100 mg mL^{-1}), penicillin (100 IU mL^{-1}), 25 mM HEPES and adjusted to pH 7.2 with bicarbonate solution. Cells were grown in a humidified atmosphere of 95 % air and 5 % CO_2 at 37 °C. Stock solutions (10 mM) of the compounds, made in DMSO, were dissolved in the corresponding medium to the required working concentrations. Neoplastic HeLa cells (2000 cells per well), Fem-x cells (5000 cells per well) and LS174 cells (7000 cells per well) were seeded into 96-well microtiter plates, and 24 h later, after cell adherence, five different, double diluted concentrations of the investigated compounds were added to the wells. The final concentrations applied to the target cells were: 200, 100, 50, 25 and 12.5 μM, except to the control wells, where only nutrient medium was added. The cultures were incubated for 72 h. The effect of compounds on cancer cell survival was determined by the MTT test according to Mosmann,[33] with modification by Ohno and Abe,[34] 72 h upon addition of the compounds, as was described earlier. Briefly, 20 μL of MTT solution (5 mg mL^{-1} PBS) were added to each well. The samples were incubated for a further 4 h at 37 °C in a 5 % CO_2 humidified air atmosphere. Then, 100 μL of 10 % SDS were added to extract the insoluble product formazan, resulting from the conversion of the MTT dye by viable cells. The number of viable cells in each well was proportional to the intensity of the absorbance of light, which was then read in an ELISA plate reader at 570 nm. Absorbance (A) at 570 nm was measured 24 h later. To obtain cell survival (%), the A of a sample with cells grown in the presence of various concentrations of the investigated extracts was divided by the control optical density (the A of control cells, grown only in nutrient medium), and multiplied by 100. Absorbance, of the blank, A_s, was subtracted from the absorbance of the treated cells, A_t, of the corresponding sample with target cells. Concentration IC_{50} was defined as the concentration of an agent inhibiting cell survival by 50 %, compared with a vehicle-treated control. All experiments were performed in triplicate. The cell survival (S) was calculated by the equation:

$$S\ (\%) = 100\frac{(A_t - A_s)}{(A_c - A_s)}$$

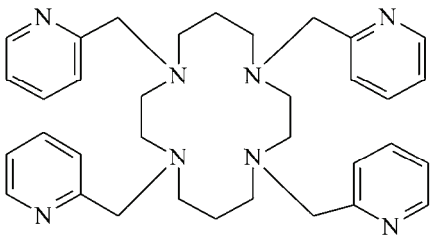
where A_c is the absorbance of the control.

Thermal analysis

Thermogravimetric (TG) measurements were performed on a simultaneous TGA/DSC thermal analyzer Q600 SDT (TA Instruments) using open alumina sample pans and the corresponding empty reference pan in a dynamic nitrogen atmosphere (flow rate: 100 cm^3 min^{-1}). Sample mass: ≈1 mg; heating rate: 20 °C min^{-1} and temperature range: up to 500 °C. For the evolved gas analysis (TGA/DTA–MS), an SDT 2960 Simultaneous TGA/DTA (TA Instruments Inc.) thermal analyzer and a Thermostar GSD 200 (Balzers Instruments) quadrupole mass spectrometer were coupled. Measurements data: open platinum crucible, $m \approx 2$ mg, heating rate: 10 °C min^{-1}, heated capillary connection (t = 200 °C, methyl deactivated fused silica capillary tube, ϕ = 0.15 mm).

RESULTS AND DISCUSSION

Binuclear Cu(II) complexes **1**–**7** were prepared and purified according to described procedures.[30] All the tested Cu(II) complexes are binuclear wherein the macrocycle is *exo*-bonded to the metal ions. The structure of the tpmc ligand is presented in Scheme 1 while the structures of selected complexes are presented in Scheme 2a–c. As can be seen, each Cu(II) is coordinated to two nitrogen atoms of the cyclam ring and to two nitrogens from the two 2-pyridylmethyl groups of the macrocyclic ligand. For complexes **1** and **7** (Scheme 2a and c), the chair conformation was found.[30] In **7**, an NCS^- ligand is bonded in the *trans* position to each copper(II) ion (Scheme 2c). In complexes **2**–**6**, only one monovalent anion is coordinated to the binuclear complex cations. Due to the coordinated co-ligand anions, the complex cations have different charges: 4+ in **1**, 3+ in complexes **2**–**6** and 2+ in **7**. For complexes with F^- (**2**) and Cl^- (**3**) co-ligands, X-ray analysis confirmed the bridged coordination of the fluoride and chloride with Cu(II) that is *exo*-coordinated with respect to the cyclam ring in the boat conformation (Scheme 2b).[30b] For the complexes containing Br^-, I^- and NO_2^-, the same coordination mode is proposed based on their analytic data, and physical and chemical properties.[30b]

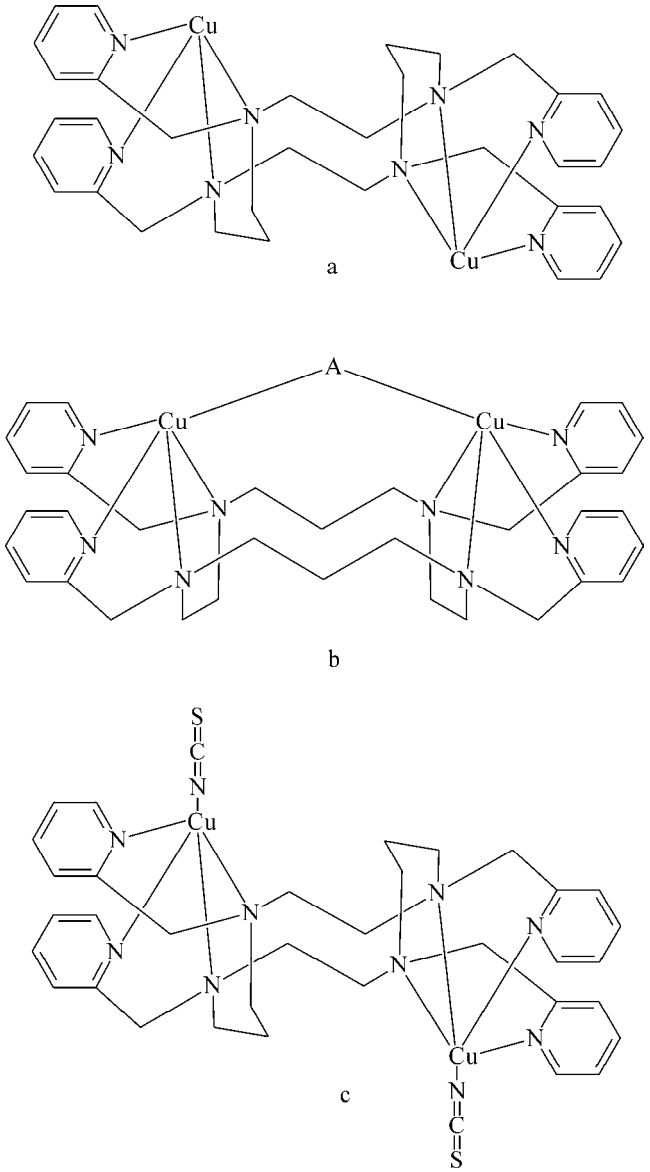


Scheme 1. Ligand *N*,*N*',*N*'',*N*'''-tetrakis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane (tpmc).

The *in vitro* antiproliferative activity of the compounds **1**–**7**, tpmc**,** $Cu(ClO_4)_2 \cdot 6H_2O$, co-ligands **2a**–**7a** and DMSO was tested against HeLa, Fem-x and LS174 cell lines and with *cis*-diamminedichloridoplatinum(II) (CDDP) as the referent cytostatic by the MTT colorimetric assay method. The IC_{50} values of the complexes were in the range 17.7–133.4 μM for the Cu(II) complexes against all the tested cell lines, while they were in the range 2.1–7.8 μM for CDDP. The tpmc ligand, $Cu(ClO_4)_2 \cdot 6H_2O$ and the free co-ligands showed significantly lower activity (IC_{50} > 200 μM).

The order of sensitivity of various cell lines to antiproliferative action of the complexes was cervix adenocarcinoma HeLa > colon carcinoma LS174 > melanoma Fem-x. In contrast, ligands used in doses from 0–200 μM were ineffective (IC_{50} > 200 μM) against the same cell lines. Only **2a** showed a moderate antiproliferative activity against all the tested lines, while **3a**, **4a** and **7a** exhibited very weak activity against HeLa cells. Generally, complexes **1**–**7** showed marked

effects compared to those of the ligands. Complex **1** showed remarkable cytotoxicity towards all three cell lines (Table I). The cytotoxic curves from the MTT assay showing the survival of HeLa, Fem-x and LS174 cells grown for 72 h in the presence of increasing concentrations of complexes **1** and **2** are depicted in Fig. 1a and b, respectively.



Scheme 2. Structure of the complex cation in the Cu(II) complexes: **1** (a), **2**–**6**, X = F^-, Cl^-, Br^-, I^- or NO_2^- (b) and **7** (c).

TABLE I. Results of the MTT (IC_{50} / μM) analysis for Cu(II) tpmc complexes (**1**–**7**), $Cu(ClO_4)_3 \cdot 6H_2O$, free ligand (tpmc), compounds **2a**–**7a** and CDDP; tpmc = *N*,*N'*,*N''*,*N'''*--tetrakis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane; CDDP = *cis*-diammine-dichloridoplatinum(II)

Compound	HeLa	Fem-X	LS174
$[Cu_2tpmc](ClO_4)_4$ (**1**)	19.0±0.3	17.7±2.3	22.0±0.5
$[Cu_2(F)tpmc](ClO_4)_3$ (**2**)	35.9±3.0	66.8±2.4	79.2±0.4
$[Cu_2(Cl)tpmc](ClO_4)_3 \cdot H_2O$ (**3**)	46.9±0.4	104.5±2.4	86.0±1.6
$[Cu_2(Br)tpmc](ClO_4)_3$ (**4**)	48.3±2.9	72.9±3.9	75.5±1.4
$[Cu_2(I)tpmc](ClO_4)_3$ (**5**)	45.0±3.4	79.0±1.9	57.9±0.2
$[Cu_2(NO_2)tpmc](ClO_4)_3$ (**6**)	51.4±4.1	133.4±4.0	22.1±0.2
$[Cu_2(NCS)_2tpmc](ClO_4)_2$ (**7**)	61.0±0.9	103.5±0.6	51.8±0.1
$Cu(ClO_4)_2 \cdot 6H_2O$, tpmc	>200	>200	>200
NaF (**2a**)	91.5±1.0	76.5±4.1	148.3±6.1
NaCl (**3a**)	186.2±3.8	>200	>200
KBr (**4a**)	186.9±1.3	>200	>200
KI (**5a**) $NaNO_2$ (**6a**)	>200	>200	>200
KSCN (**7a**)	108.5±4.0	>200	>200
CDDP	2.1±0.2	3.2±0.4	7.8±0.3

Complex **2** had the highest activity against the HeLa cell line. Complexes **3**–**6** showed decreasing activity in the series $I^- > Cl^- > Br^- > NO_2^-$. The order of the cytotoxicity of the complexes in the case of the HeLa cell line could be related to the corresponding stability constants.[30b] The lowest stability constants exhibited **5** (with I^-, log K = 2.76) and **2** (with F^-, log K = 3.03), in agreement with the Pearson Theory.[35,36] Copper(II), as a transition acid, forms stable complexes with transition bases, in the present case with Br^-, Cl^- and NO_2^- (log K = 3.77, 4.80, 4.20, respectively). When comparing the IC_{50} values for the HeLa cell line, it is clear that the least stable complexes had the highest activity, *i.e.*, the complexes with the hardest (F^-) and softest (I^-) bases acting as co-ligands. The cytotoxic effects of the complexes towards Fem-x and LS174 (IC_{50} 55–135 μM) were significantly lower than towards the HeLa cell line. An increasing order of cytotoxicity was observed with increasing ionic radii going from Cl^- to I^- in the case of LS174 cell line. However, complex **6** with an NO_2^- co-ligand showed a significantly higher activity against LS174 compared to the other complexes in all other cell lines. While complex **1** exhibited a rather high cytotoxicity against all three cell lines (IC_{50} 18–22 μM), complex **6** had a selective cytotoxicity towards the LS174 cell line, comparable with that of **1**.

The cytotoxic effect of the complexes partly originates from their amphiphilic nature, which bestows on them the capacity to penetrate easily the cell membrane. However, the mechanism of the cytotoxicity of the complexes in the different cell lines is obviously different and might involve changes in the energy or hypoxic status[37] in the microenvironment of cancer cell and other factors.

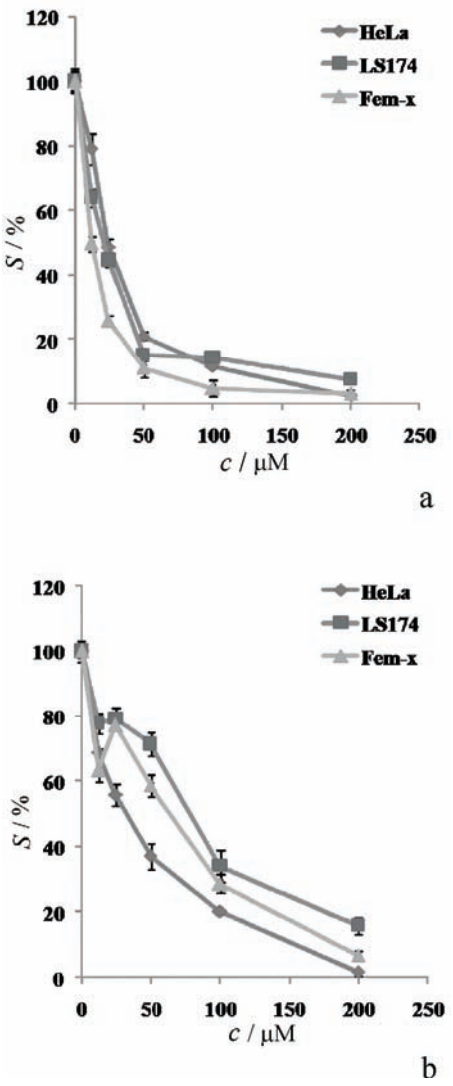


Fig. 1. Representative graph showing survival of HeLa, LS174 and Fem-x cells grown for 72 h in the presence of increasing concentrations of complexes: a) **1** and b) **2**.

Thermal methods have a special place in the characterization of samples with biological activity.[38–41] Namely, some of these compounds may be the active ingredients of newly developed drugs. Therefore, much attention has been paid to the thermal properties of these compounds.

The thermal decomposition of all the complexes was continuous. As complex **3** is a crystal hydrate, the first change in the TG curve resulted from loss of the crystal water. The water evaporation occurred at a steady rate up to the onset of complex decomposition at 264 °C. The amount of water lost was more than that calculated based on the stoichiometric composition (exp.: ≈3 %, calcd.: 1.73 %).

According to the stepwise isothermal (SWI) curve, this mass loss involves at least three steps referring to the different characters of the interactions of water or to solvent residue (MeCN) within the crystal of **3**. Except for **1**, the TG curves show a small mass loss up to the decomposition temperature in all complexes. The mass loss in these compounds may be related to strongly bonded water (< 2 %) or the consequence of residual solvent. When the samples were kept in a desiccator, the hygroscopic water could be partially eliminated. However, in **2**, **3** and **5** some mass loss (< 2 %) was detected even after drying over anhydrous $CaCl_2$. By coupled TG–MS measurements, no traces of MeCN were found and the mass loss belonged exclusively to water evaporation. It is important to note that SWI curves show that on isothermal heating at around 120 °C, all the compounds lost moisture completely.

The thermal stability of the compounds increased in order of **7** < **6** ≈ **5** < **4** < < **3** ≈ **2** < **1** from 203 °C in **7** to 282 °C onset in **1**. The decomposition is presented in Figs. 2 and 3 by the corresponding DTG curves. For all the complexes, the decomposition was accompanied by a highly exothermic effect, which was expected and is primarily due to the presence of the perchlorate ion. As the course of the DSC curves agreed with the course of the corresponding DTG curves, only the DTG curves are presented. In compounds with halide ligands, the rate of decomposition decreases with decreasing electronegativity of the halide. The exothermic effect of the reactions decreased in the same order. The decomposition of complexes **2** and **3** (with F^- and Cl^- co-ligands) is seemingly a one-step process. Starting from the bromide complex, fragmentation of the ligand

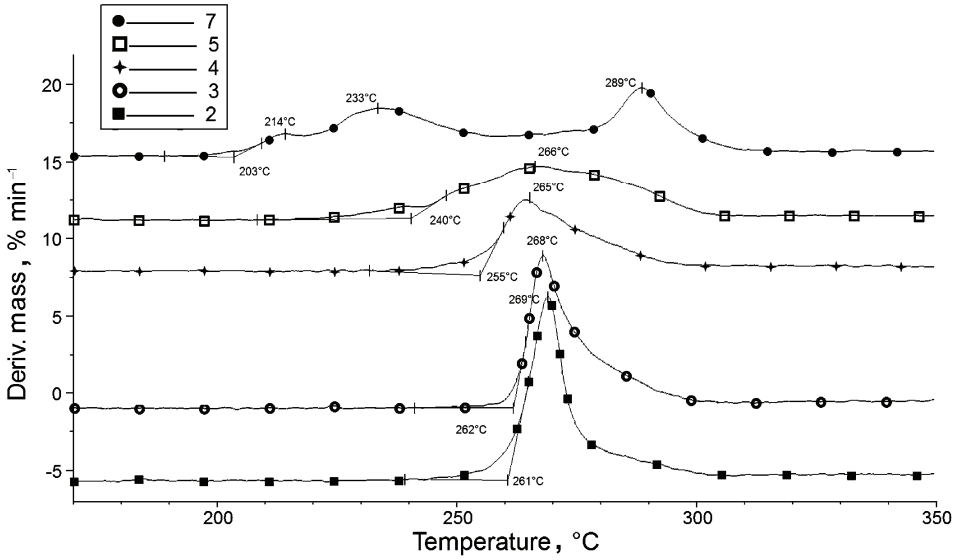


Fig. 2. DTG curves of compounds **2**–**5** and **7**.

is observable. In the complex with the two NCS^- (**7**), the decomposition steps are clearly separated (see Fig. 2).

In Fig. 3, the DTG curves of compound without a co-ligand (**1**) and with a coordinated oxoanion (NO_2^-, **6**) are presented together with the corresponding curves of the most and the least stable (pseudo)halido complexes (**2** and **7**). As can be seen in Fig. 2, the thermal stability of **1** is by far the highest. The enthalpy of its decomposition is about the same as that for **2**. The thermal stability and the decomposition pattern of **6** with nitrito ligand are similar to the corresponding ones in **5**. These facts refer to the role of the coordinated anion in decreasing thermal stability of the complexes. Moreover, the thermal stability can be related to the stability constants of the compounds and is in accordance with the Pearson Hard and Soft Acids and Bases (HSAB) principle.[35,36]

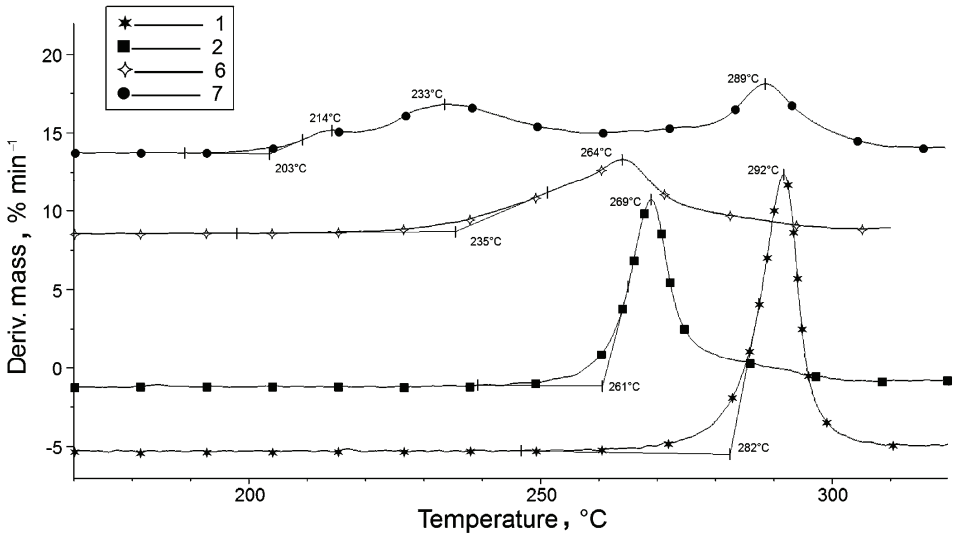


Fig. 3. Comparison of the DTG curves for compounds **1** and **6** with those for compounds **2** and **7**.

The thermal stability of the compounds and the corresponding IC_{50} values against HeLa cell line are presented in Fig. 4. As can be seen, the course of the curves is very similar and with decreasing thermal stability, the antiproliferative activity of the complexes decreases. When comparing the cytotoxic activity of the compounds against HeLa cells, it seems as if the dissociation of the molecule plays an important role in cytotoxicity. Namely, by dissociation of the co-ligand of the compounds **2**–**7**, complex **1** with the highest cytotoxicity is formed. The easier is the dissociation, the higher is the activity of the compound. In addition, on dissociation a conversion from the boat to the chair conformation is expected. As the thermal stability of the compounds depends on the least stable bond in the

molecule, it could be assumed that the thermal decomposition in complexes **2**–**7** starts with the loss of the co-ligand/s*. It could be expected, therefore, that with decreasing thermal stability, the cytotoxicity would increase. However, experimental data confirmed just the opposite, *i.e.*, with decreasing thermal stability, the cytotoxicity also decreased. This seemingly contradictory observation could be explained by changes in the rigidity[30b] of the complex molecules and/or to reduced possibility of H-bond formation by the coordination of the co-ligands. Therefore, the conformation of the molecule may significantly affect the interactions of the complexes with HeLa cells.

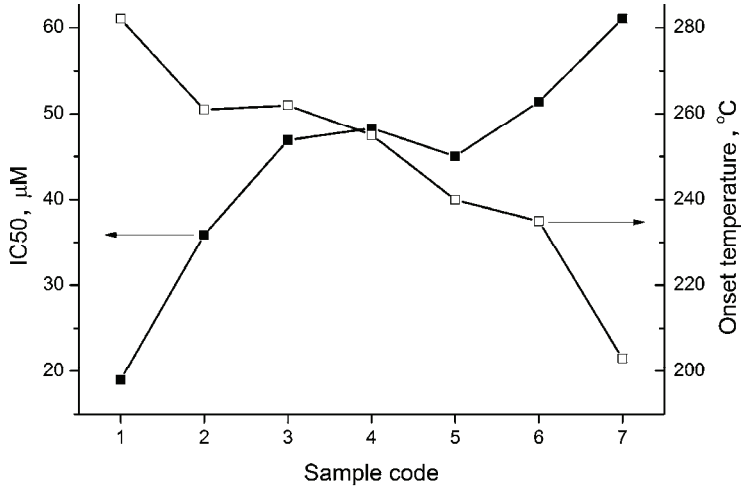


Fig. 4. Comparison of the thermal stability and the antiproliferative activity of compounds **1**–**7**.

The activity of the compounds against the human melanoma (Fem-x) and human colon carcinoma (LS174) cell lines indicate different reaction routes and compound **6** with nitrito co-ligand showed a high selectivity toward LS174 cells.

CONCLUSIONS

The significantly higher thermal stability of **1** and its significantly higher cytotoxicity could be related to both the electronic and steric factors. Additional coordination of the co-ligands decreases the charge on the complex cation. The charge distribution in the molecule depends on the co-ligand, and may have a role in decreasing antiproliferative activity. In addition, the bridging of the two metal centers by one co-ligand modifies the geometry of the entire molecule, and the chair conformation of **1** is converted to the boat conformation in the other complexes, except in **7** in which the two NCS^- ligands are bonded in the *trans* configuration. The decrease in the thermal stability and stability constants of

*Unfortunately, due to the presence of perchlorates, the rate of the decomposition was too high, so the detection of the fragments belonging to the co-ligands was not possible.

compounds **2**–**7** is in accordance with the HSAB principle. However, the cytotoxicity of the compounds against the HeLa cell line with decreasing thermal stability also decreased, inferring the importance of the steric factors in the interaction of the complexes with the target cells. With the other two cell lines, the antiproliferative activities of the complexes were lower than that observed for **1**, except for **6** with a coordinated nitrite ion that exhibits a selective cytotoxicity against LS174 cell line that is comparable with the cytotoxicity observed for **1**.

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ИЗВОД

КОРЕЛАЦИЈА ИЗМЕЂУ *IN VITRO* АНТИПРОЛИФЕРАТИВНЕ АКТИВНОСТИ, СТРУКТУРЕ И ТЕРМИЧКЕ СТАБИЛНОСТИ НЕКИХ МАКРОЦИКЛИЧНИХ ДИНУКЛЕАРНИХ Cu(II) КОМПЛЕКСА

СЛАЂАНА Б. ТАНАСКОВИЋ[1], МИРЈАНА АНТОНИЈЕВИЋ-НИКОЛИЋ[2], BERTA BARTA HOLLÓ[3], БРАНКА ДРАЖИЋ[1], ТАТЈАНА СТАНОЈКОВИЋ[4], KATALIN MÉSZÁROS SZÉCSÉNYI и ГОРДАНА ВУЧКОВИЋ[5]

[1]*Фармацеутски факултет, Универзитет у Београду, Војводе Степе 450, 11000 Београд,* [2]*Висока школа струковних студија, Хајдук Вељкова 10, 15000 Шабац,* [3]*Природно–математички факултет, Универзитет у Новом Саду, Трг Доситеја Обрадовића 3, 21000 Нови Сад,* [4]*Институт за онкологију и радиологију Србије, Пастерова 14, 11000 Београд,* [5]*Хемијски факултет, Универзитет у Београду, Студентски трг 16, 11158 Београд*

За седам макроцикличних динуклеарних Cu(II) комплекса са *N,N′,N″,N‴*-тетракис(2-пиридилметил)-1,4,8,11-тетраазациклотетрадеканом (tpmc) формуле $[Cu_2tpmc](ClO_4)_4$ (**1**), $[Cu_2(X)tpmc](ClO_4)_3{\cdot}nH_2O$, X= F^-, n = 0 (**2**), X = Cl^-, n = 1 (**3**), X = Br^-, n = 0 (**4**), X= I^-, n = 1 (**5**), X = NO_2^-, n = 0 (**6**), $[Cu_2(NCS)_2tpmc](ClO_4)_2$ (**7**) испитивана је њихова цитотоксичност на хуманим малигним ћелијским линијама: цервикалног аденокарцинома (HeLa), меланома (Fem-x) и хуманог карцинома дебелог црева (LS174). Резултати су упоређени са одговарајућим подацима за *cis*-диамминдицхлоридоплатину (II) (CDDP) као референтним цитостатиком (слободни лиганди и растварач DMSO су били контролни). Комплекси су показали значајно антипролиферативно дејство, иако знатно мање него CDDP. Термичка разградња комплекса је одређена TG/DSC мерењем. Термичка стабилност једињења **2**–**7** прати тренд њихове антипролиферативне активности према HeLa ћелијској линији, као и њихове одговарајуће константе стабилности. Највећу термичку стабилност и цитотоксичност има комплекс **1** без анјонског колиганда.

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