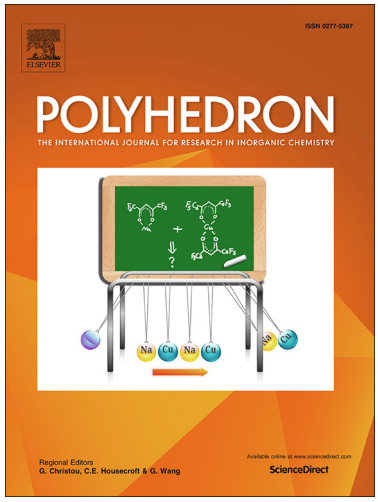

Multinuclear magnetic resonance characterization and antiproliferative studies of novel dichlorido platinum(II) complexes containing kinetin riboside and 1– β-D-ribofuranosyl-4-(2-pyridyl)-1*H*-1,2,3-triazole

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Multinuclear magnetic resonance characterization and antiproliferative studies of novel dichlorido platinum(II) complexes containing kinetin riboside and 1-β-D-ribofuranosyl-4-(2-pyridyl)-1*H*-1,2,3-triazole

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Abstract

The chemical reaction between *cis*-[$PtCl_2(dmso)_2$] and kinetin riboside (KR) or 1-β-D-ribofuranosyl-4-(2-pyridyl)-1*H*-1,2,3-triazole (PTR) has resulted in two novel platinum(II) complexes being obtained with different compositions of the coordination sphere: *cis*-[$PtCl_2$(PTR)] (**1**) and *cis*-[$PtCl_2$(dmso)(KR)] (**2**). Based on multinuclear NMR results (^{1}H, ^{13}C, ^{15}N, ^{195}Pt), we have demonstrated that the N-donor ligands PTR and KR are able to coordinate to the Pt(II) ion as bidentate via two nitrogen atoms (N(3) and N(7)) or monodentate via only one nitrogen atom (N(7)), respectively. On the other hand, biological

studies showed that the novel platinum(II) complexes exhibit different *in vitro* cytotoxicity towards A549 (lung carcinoma epithelial cells), T24 (urinary bladder cancer cells) and CRL1872 (malignant melanoma cells). The complex *cis*-[$PtCl_2$(dmso)(KR)] (**2**) shows in vitro cytotoxicity against T24 and CRL1872 cell lines (the IC_{50} parameters amount to 52.2 μM and 21.4 μM, respectively), whereas *cis*-[$PtCl_2$(PTR)] (**1**) is not able to inhibit a proliferation of these cells in the range of tested concentrations.

Introduction

From a biological as well as a chemical point of view, nucleosides an play important role in the cells of various organisms. They build genomic blocks and are able to interact with enzymes, proteins and nucleic acids, which are present in all living cells [1,2]. For that reason, nucleosides have been considered as model compounds with a wide range of activities. It has been observed that naturally occurring and synthetic nucleosides can exhibit antiviral and anti-inflammatory properties [1,3,4,5], and are able to inhibit the metabolic pathways of various cancer cells by blocking the biosynthesis of nucleic acids [6,7,8]. One of them is kinetin riboside (KR) which shows satisfactory *in vitro* cytotoxic activities towards HOS (bone osteosarcoma), HL-60 (promyelocytic leukemia), CEM (acute lymphoblastic leukemia), MCF-7 (breast adenocarcinoma) and K-562 (chronic myelogenous leukemia) cell lines [1,9].

On the other hand, the characterization of the interactions between nucleic acids components (e.g. nucleosides) and metal ions (e.g. Pt(II)) is the reason why nucleosides have been considered to be N-donor ligands in platinum(II/IV) complexes [10,11,12]. It is commonly known that the activity of metal complexes is modified by the application of the appropriate ligands. Therefore, the coordination of an active ligand to the platinum(II) ion may enable coordination compounds to be obtained which exhibit therapeutic properties.

Previous studies in this field have demonstrated that Pt(II) monoadducts with different ribosides present the ability to further interact with DNA and prompt cell death [6,7,13].

These encouraging results have motivated us to search for and obtain novel cisplatin derivatives with the use of 1-β-D-ribofuranosyl-4-(2-pyridyl)-1*H*-1,2,3-triazole (PTR) and kinetin riboside (KR) as N-donor ligands. As a part of our studies in this field, we have synthesized two novel complexes, i.e. *cis*-[$PtCl_2$(PTR)] (**1**) and *cis*-[$PtCl_2$(dmso)(KR)] (**2**) (Fig. 1). Our chemical studies were focused on multinuclear magnetic resonance measurements of the free ligands and their novel complexes. Moreover, in order to evaluate preliminary biological properties of these compounds, we have examined their lipophilicity with the use of the shake-flask method and their *in vitro* cytotoxicity towards the human cancer cell lines A549 (lung carcinoma epithelial cells), T24 (urinary bladder cancer cells) and CRL1872 (malignant melanoma cells), and normal human cell lines, such as CRL2522 (skin fibroblast cells). It was necessary to investigate the impact of KR or PTR insertion in the Pt(II) ion coordination sphere on the antiproliferative activity of these compounds.

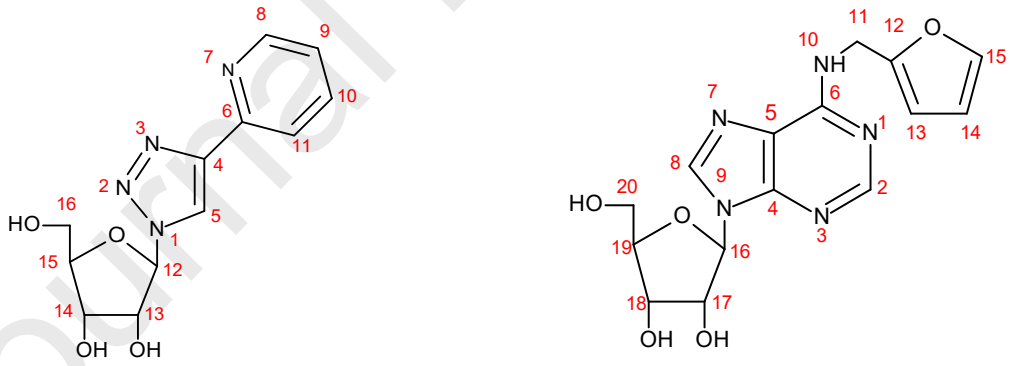

Fig. 1. 1-β-D-ribofuranosyl-4-(2-pyridyl)-1*H*-1,2,3-triazole (PTR), kinetin riboside (KR) and their ring-numbering systems.

Experimental

1. Starting materials

1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose was purchased from Carbosynth. K_2PtCl_4, thiazolyl blue tetrazolium bromide and other chemical reagents were purchased from Sigma-Aldrich. The analytical grade solvents were purchased from Avantor Performance Materials Poland S.A. Anhydrous CH_2Cl_2 was prepared by distillation with P_2O_5.

2. Instrumentation

The C, H and N contents were determined with an Elementar Analysensysteme GmbH Vario MACRO analyser. Analysis by thin layer chromatography (TLC) was carried out on Merck precoated 60 F_{254} silica gel plates, while column chromatography used Merck silica gel 60H (40-63 μm).

NMR spectra were recorded at 298 K in DMF-d_7 solutions with a Varian INOVA 500 spectrometer operating at 499.8, 125.7, 50.6 and 107.4 MHz for ^{1}H, ^{13}C, ^{15}N and ^{195}Pt, respectively. The NMR spectra for kinetin riboside (KR) were recorded at 343 K because the resonance signals for some nitrogen atoms were not observed at 298 K. The reference standards were TMS for ^{1}H and ^{13}C, CH_3NO_2 for ^{15}N, and H_2PtCl_6 for ^{195}Pt. Gradient-enhanced IMPACT-HMBC ^{1}H-{^{15}N} [14] correlation spectra were optimized for the coupling constant of 6 Hz under the following experimental conditions: 0.2 s acquisition time, 6000 (F2) and 10,000 (F1) Hz spectral windows, 1 K complex data points, 256 time increments, 30 ms WURST-2 mixing sequence centered within the 60 ms preparation interval (ASAP[2]) and the 150° Ernst angle as the excitation pulse [15].

The UV-Vis measurements performed for the lipophilicity determination were obtained with a HITACHI U-2900 UV-Vis spectrophotometer equipped with 1.0 cm path length quartz cuvettes (1.5 mL). IC_{50} values were calculated based on measurement of absorbance (MTT test) with the use of a Varioskan Lux spectrophotometer (Thermo Fisher Scientific).

3. Chemical part

3.1. Syntheses of the ligands (KR, PTR) and the starting complex *cis*-[$PtCl_2(dmso)_2$]

Kinetin riboside (KR) was prepared by N^6-alkylation of *N*^{6}-acetyl-2',3',5'-tri-*O*-acetyladenosine with furfuryl alcohol under Mitsunobu conditions, as previously described [16]. The *cis*-[$PtCl_2(dmso)_2$] complex was obtained by the reaction of 1 eq. K_2PtCl_4 and 2 eq. dmso in aqueous solution [17].

3.1.1. The synthesis of 1-β-D-ribofuranosyl-4-(2-pyridyl)-1*H*-1,2,3-triazole (PTR)

The synthesis of 1-β-D-ribofuranosyl-4-(2-pyridyl)-1*H*-1,2,3-triazole (PTR), accomplished by a 1,3-dipolar cycloaddition between 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl azide (A) and 2-ethynylpyridine, followed by the removal of the acetyl protecting groups, was based on the reported procedure [18] with modifications (Fig. 2). 2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl azide was prepared from 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose [19].

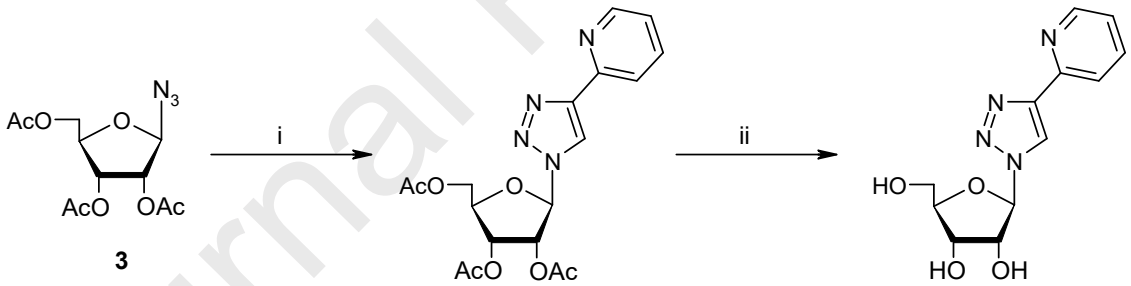

Fig. 2. Synthesis of PTR. Reagents and conditions: (i) 2-ethynylpyridine, CuI, DIEA, AcOH, anhydrous CH_2Cl_2, rt; (ii) NH_4OH-MeOH-CH_2Cl_2 1:1:1, rt.

2-Ethynylpyridine (268 mg, 2.60 mmol), copper iodide (826 mg, 4.34 mmol), diisopropylethylamine (1.4 g, 10.85 mmol) and acetic acid (0.5 mL) were added to a solution of 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl azide [19] (A; 653 mg, 2.17 mmol) in anhydrous CH_2Cl_2 (35 mL). The resulting suspension was stirred at room temperature overnight, then one more portion of 2-ethynylpyridine (45 mg, 0.43 mmol) was added and the reaction was

continued overnight. The mixture was filtered and the insoluble part was washed with CH_2Cl_2 several times. The filtrate was evaporated and co-evaporated with toluene twice. The residue was subject to chromatographic separation on a silica gel column with CH_2Cl_2-MeOH (100:0→98.5:1.5) to obtain pure the A' compound as a yellow oil (837 mg, 95% yield) (Fig. 2); ^{1}H NMR ($CDCl_3$) as in the literature [20]. Next, the A' compound was treated with NH_4OH-MeOH-CH_2Cl_2 (1:1:1, 60 mL) and stirred at room temperature overnight. The mixture was evaporated and co-evaporated twice with toluene. Chromatographic separation was carried out on a silica gel column with CH_2Cl_2-MeOH (95:5→92:8) to obtain PTR as a white powder (410 mg, 71% yield); ^{1}H NMR (dmso-d_6) as in the literature [21] (Fig. 2).

3.2. Syntheses of the novel platinum(II) complexes *cis*-[$PtCl_2$(PTR)] (1) and *cis*-[$PtCl_2$(dmso)(KR)] (2)

Both novel platinum(II) complexes, *cis*-[$PtCl_2$(PTR)] (**1**) and *cis*-[$PtCl_2$(dmso)(KR)] (**2**), with two different ribosides were obtained by the reaction between *cis*-[$PtCl_2(dmso)_2$] and the corresponding N-donor ligand, i.e. PTR or KR, in 1:1 molar ratios in ethanol. The reaction mixture was heated to 45 °C and stirred for 5 h. After that period, stirring was continued at r.t. for 24 h. Slow evaporation of the solvent resulted in the pale yellow *cis*-[$PtCl_2$(PTR)] precipitate being obtained, which was freeze-dried. However, the *cis*-[$PtCl_2$(dmso)(KR)]) precipitate was formed directly in the reaction mixture. The platinum(II) complex was isolated from the reaction mixture by filtration, washed with ethanol, then diethyl ether and finally dried under vacuum. An attempt to obtain the complex **1** by the direct reaction between K_2PtCl_4 and PTR turned out to be unsuccessful.

Cis-[$PtCl_2$(PTR)] (**1**). Yield: 65%. ^{1}H NMR (499.8 MHz, 298 K) δ, pm: 7.79 (H9), 8.30 (H11), 8.41 (H10), 9.48 (H5), 9.49 (H8); ^{13}C NMR (125.7 MHz, 298 K) δ, ppm: 61.3 (C16), 70.4 (C14), 76.4 (C13), 87.3 (C15), 95.8 (C12), 122.3 (C11), 124.4 (C5), 126.0 (C9), 140.7

(C10), 148.6 (C4), 148.7 (C8), 149.6 (C6); ^{15}N NMR (50.6 MHz, 298 K) δ, ppm: -175.5 (N7), -129.6 (N3), -121.9 (N1), -30.8 (N2); ^{195}Pt NMR (107.4 MHz, 298 K) δ, ppm: -2296. Analysis calc/found for $C_{12}Cl_2H_{14}N_4O_4Pt$: C, 26.5/26.7; H 2.6/3.0; N, 10.3/9.8%.

Cis-[$PtCl_2$(dmso)(KR)] (**2**). Yield: 60%. ^{1}H NMR (499.8 MHz, 298 K) δ, ppm: 4.93 (H11), 6.44 (H14), 6.50 (H13), 7.64 (H15), 8.12 (NH10), 8.48 (H2), 9.22 (H8); ^{13}C NMR (125.7 MHz, 298 K) δ, ppm: 3.50 (DMSO), 37.8 (C11), 61.6 (C20), 70.8 (C18), 75.1 (C17), 86.9 (C19), 89.9 (C16), 107.5 (C13), 110.6 (C14), 116.0 (C5), 142.5 (C8), 142.6 (C15), 148.2 (C4), 151.9 (C12), 152.4 (C6), 153.9 (C2); ^{15}N NMR (50.6 MHz, 298 K) δ, ppm: -289.2 (N10), -224.0 (N7), -203.5 (N9), -155.7 (N3), -145.1 (N1); ^{195}Pt NMR (107.4 MHz, 298 K) δ, ppm: -3031. Analysis calc/found for $C_{17}Cl_2H_{23}N_5O_6PtS$: C, 29.5/29.1; H, 3.4/3.4; N, 10.1/9.8%.

4. Biological part

4.1. Lipophilicity (logP)

The lipophilicities of the new platinum(II) complexes were determined using the standard shake-flask method, which is common for different types of coordination compounds [22,23]. First, aqueous sodium chloride (0.9% w/v) and organic (*n*-octanol) phases were saturated for 1 week. Complex **1** was dissolved in the saturated aqueous phase, but complex **2** was dissolved in *n*-octanol. Subsequently, based on UV-Vis measurements, the complexes' stability in the applied solvents was confirmed. All the solutions were at a concentration of 0.30 mg/mL in 4.0 mL. The same volume of the immiscible solvent was added to each sample. The obtained mixtures were stirred mechanically in plastic tubes for 30 minutes. The samples were centrifuged (6000 rpm, 15 min). After separation, the phases were analyzed by UV-Vis spectroscopy to determine the amount of the compound in each phase. The absorption values at λ_{max} before and after shaking were compared. In the next step, the partition coefficients in both phases for each compound were calculated according to the

Lambert–Beer Law to determine the logP values. For each complex, the procedure was repeated three times.

4.2. Cell culture

The cytotoxic activities of tested compounds *in vitro* were assessed against four human cell lines: normal fibroblast cells (CRL2522), lung carcinoma epithelial cells (A549), urinary bladder carcinoma cells (T24) and skin malignant melanoma cells (CRL1872). All the cell lines were cultured in Dulbecco's Modified Eagle Medium (DMEM)/Ham's F-12 medium (Corning, USA) supplemented with 10% fetal bovine serum (FBS; Biowest), 5 μg/mL amphotericin B, 100 μg/ml streptomycin and 100 U/mL penicillin (Corning). The cells were grown in 75 cm^2 cell culture flasks (Falcon) at 37 °C in a humidified atmosphere with 5% CO_2.

4.3. Preparation of compound dilutions

Stock solutions of the tested compounds (KR, PTR, **1** and **2**) at a concentration of 100 μg/ml were prepared by dissolving of 100 μg of each compound in 2 μL of DMSO or ethanol and adding Dulbecco's Modified Eagle Medium (DMEM)/Ham's F-12 medium (Corning, USA). Serial dilutions of the stock solution with DMEM/Ham's F-12 medium were prepared to obtain 10, 1 and 0.1 μg/mL solutions of the tested compounds. Culture medium with solvent was used as a control.

4.4. Cell viability determination by an MTT assay

The cytotoxic activities of the compounds *in vitro* were evaluated using an MTT assay with thiazolyl blue tetrazolium bromide. For this purpose, cells were seeded into 24-well plates at a density of 2 x 10^4 cells/cm^2 and cultured for 24 h. Subsequently, the culture medium was removed, the tested compounds at their final concentrations (0.1, 1, 10 and 100 μg/mL) were added and incubated for another 24 h. The next day, the tested compound

solutions were removed, the wells were washed with phosphate-buffered saline and filled with MTT solution (500 μL) at a concentration of 1 mg/mL. After 2 h incubation, the remaining MTT solution was carefully removed and 1 mL of DMSO was added to the wells. The absorbance of the resulting solutions was measured at 570 nm wavelength and 655 nm as a reference in the spectrophotometer. The results were compared to the control (untreated cells) and expressed as an IC_{50} value.

Results and discussion

1. NMR spectroscopy

Multinuclear magnetic resonance spectroscopy (^{1}H, ^{13}C, ^{15}N, ^{195}Pt) was applied in order to determine the central atom environment and the ligand binding mode in the both platinum(II) complexes (**1** and **2**). A comparison of the location of the appropriate resonance signals for each complex ($\delta_{complex}$) and the free ligands (δ_{ligand}) allows the calculation of the coordination shifts ($\Delta_{coord.} = \delta_{complex} - \delta_{ligand}$), which can be used to suggest the structure of the platinum(II) complexes in solution.

The obtained results, such as chemical shifts characteristics for all the atoms of the N-donor ligands and their platinum(II) complexes, are summarized in the supplementary materials (Tab.S1-S2, Fig.S1-S13).

The ^{1}H NMR spectra of **1** and **2** in the aromatic range of chemical shifts exhibit the strongest resonance signals at δ 7.36-8.89 ppm for PTR and δ 8.20-8.39 ppm for KR (Table 1). The coordination shifts calculated in comparison to the spectra of the free ligands vary between +0.19 and +0.86 ppm for **1**, and -0.08 and +0.83 ppm for **2**. Slightly stronger effects were observed for H(8) which suggests the coordination of PTR by the N(7) atom of the pyridyl ring and via the N(7) or N(9) atom in the 5-membered purine ring of KR. By extension, a comparison of the spectra of the free ligands and complexes **1** and **2** clearly confirms the coordination of the N-donor ligands to the platinum(II) ions. Additionally, the

singlet at δ 3.50 ppm in the ^{1}H NMR spectrum and the resonance signal at δ 42.8 ppm in the ^{13}C NMR spectrum confirm the presence of the S-bonded molecule of dmso in the coordination sphere of *cis*-[$PtCl_2$(dmso)(KR)] [24].

Similar changes in the chemical shifts were observed in the ^{13}C NMR spectra. The signals which belong to the C(4)-C(16) atoms in *cis*-[$PtCl_2$(PTR)] (**1**) and to the C(2)-C(20) atoms in *cis*-[$PtCl_2$(dmso)(KR)] (**2**) were found in the ranges δ 61.3-149.6 and 37.8-153.9 ppm, respectively. The coordination shifts calculated in comparison to the spectra of the free ligands vary between -1.10 and +3.6 ppm for **1** and between -4.6 and +2.1 ppm for **2**.

Table 1. ^{1}H NMR chemical shifts for the ligands and complexes **1** and **2** in DMF-d_7 at 298 K (coordination shifts in parentheses)

Hydrogen atom	PTR	*cis*-[$PtCl_2$(PTR)] (**1**)
H(5)	8.89	9.48 (+0.59)
H(8)	8.63	9.49 (+0.86)
H(9)	7.36	7.79 (+0.43)
H(10)	7.93	8.41 (+0.48)
H(11)	8.11	8.30 (+0.19)
Hydrogen atom	KR	*cis*-[$PtCl_2$(dmso)(KR)] (**2**)
H(2)	8.27	8.48 (+0.21)
H(8)	8.39	9.22 (+0.83)
H(10)	8.20	8.12 (-0.08)

Unfortunately, we were unable to indicate expressly which nitrogen atoms are engaged in the formation of the platinum-nitrogen bond using the shifts values obtained from the ^{1}H and ^{13}C NMR spectra only. In order to solve this problem, heterocorrelation ^{15}N-^{1}H NMR spectra were recorded. It was observed that the resonance signals for the N(1) and (N2) atoms in the PTR spectrum show a relatively small amount of shielding after coordination to the Pt(II) ion ($\Delta_{coord.}$= -2.4 and -13.6 ppm, respectively) when compared to the shielding characteristic for the N(3) and N(7) atoms ($\Delta_{coord.}$= -98.4 and -101.7 ppm relatively) (Fig. 3A). A similar

dependence was observed for the ^{1}H-^{15}N NMR experiments for **2**. The coordination shifts calculated for the N(1), N(3), N(9) and N(10) atoms ($\Delta_{coord.}$= +2.3, +0.8, +7.1 and +6.2 ppm respectively) were definitely smaller that the value characteristic of the N(7) atom ($\Delta_{coord.}$= 84.1 ppm) (Fig. 3B). It should be noted that the unambiguous assignment of resonance signals for the N(1) and N(3) atoms in free KR was only possible with the use of literature data [25]. The above-mentioned dependences verify the fact that the N(3) and N(7) atoms in PTR and the N(7) atom in KR are the coordination site of these ligands. It confirms that PTR and KR are bidentate and the monodentate N-donor ligands, respectively. Additionally, the range of chemical and coordination shifts is in good agreement with these characteristic parameters of other compounds with similar coordination but other N-donor ligands [26].

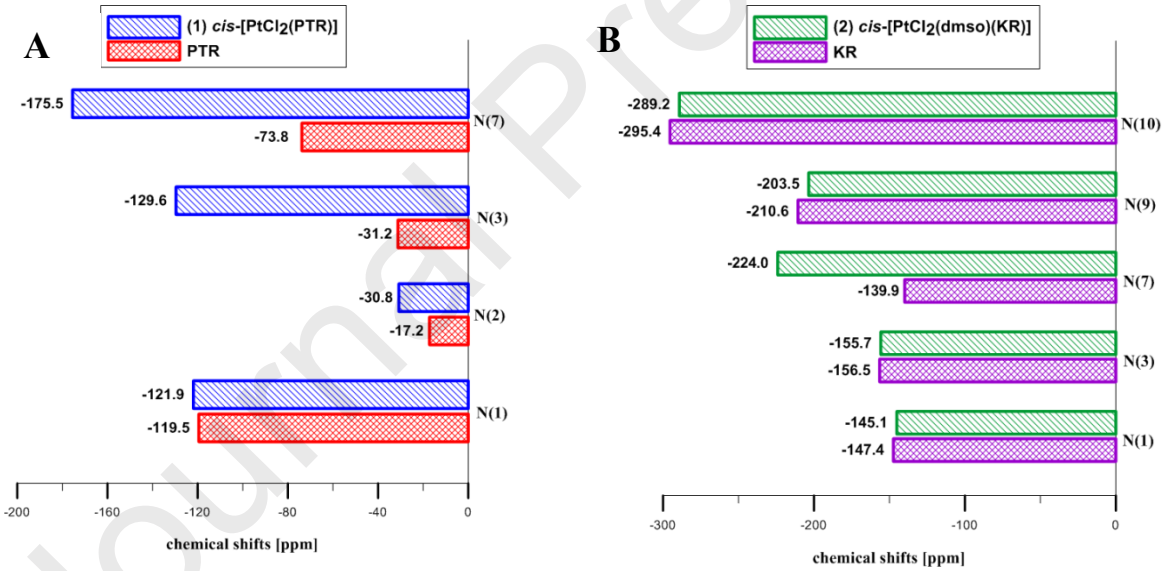

Fig. 3. ^{15}N chemical shifts for PTR and *cis*-[$PtCl_2$(PTR)] (**1**) (A), and for KR and *cis*-[$PtCl_2$(dmso)(KR)] (**2**) (B). The spectra were recorded in DMF-d_7 at 298 K for PTR, **1** and **2**, and at 343 K for KR.

Additionally, the type of the chromophore system present in the coordination spheres of **1** and **2** was assayed based on their ^{195}Pt NMR spectra. First, it was observed that resonance signals of the complexes were definitely shielded in comparison to K_2PtCl_4 and absolutely

deshielded compared to *cis*-[$PtCl_2(dmso)_2$], both of which were used as substrates in our synthesis pathways (Fig. 4). Moreover, the ^{195}Pt NMR spectra of **1** and **2** displayed only one signal at δ -2296 ppm (which can be assigned to a $PtCl_2N_2$ complex) and at δ -3031 ppm (which can be assigned to a $PtCl_2NS$ complex), respectively [27,28]. The singlets for both complexes are in the range typical for dichlorido platinum(II) complexes. Indeed, a change in the coordination sphere composition, which consists of exchanging the N-donor atom by the S-donor molecule of dimethyl sulfoxide, causes a distinct shielding of the resonance signal (Fig. 4).

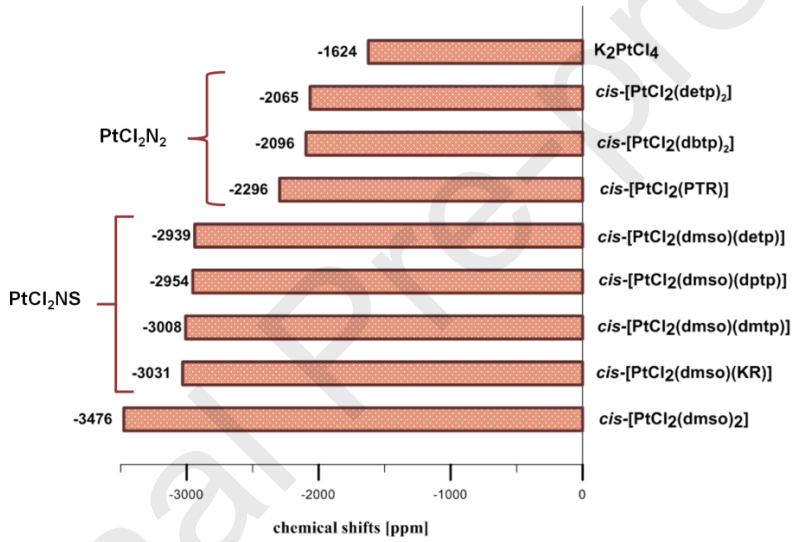

Fig. 4. ^{195}Pt chemical shifts for different types of platinum(II) complexes in DMF-d_7 at 298 K

2. Lipophilicity and *in vitro* antiproliferative activity of the novel complexes

In the first step of the biological studies we determined the partition coefficients for the platinum(II) compounds **1** and **2** between aqueous sodium chloride and organic phases. It is obvious that a drug's permeability across cell membranes, which has an impact on absorption efficiency, depends on its lipophilicity [29,30]. The literature data suggest that the best logP value varies between 0 and 3 [29,31]. Drugs showing a greater lipophilic character are poorly soluble in water and they are absorbed by the digestive tract to a smaller extent [29,32].

The logP values for *cis*-[$PtCl_2$(PTR)] and *cis*-[$PtCl_2$(dmso)(KR)] are -1.33 ± 0.04 and +1.09 ± 0.05, respectively. Therefore, it is noticeable that our two complexes exhibit definitely different characters. The positive logP value for complex **2** confirms that it presents a lipophilic property absolutely higher than that of complex **1**. Hence, we can suppose that lipophilic *cis*-[$PtCl_2$(dmso)(KR)] (**2**) is able to be transported and absorbed more efficiently than *cis*-[$PtCl_2$(PTR)] (**1**) [29]. Additionally, the difference between the lipophilicities of these complexes may result from the different N-donor ligand properties and also the presence of dimethyl sulfoxide in the coordination sphere of compound **2**.

In the next step, the *in vitro* cytotoxic activities of the PTR and KR ligands, the platinum(II) compounds (**1** and **2**) and cisplatin were determined against A549 (non-small cell lung carcinoma), T24 (urinary bladder cancer), CRL1872 (malignant melanoma) and a normal human cell line, namely CRL2522 (skin fibroblast cells). Unfortunately, only kinetin riboside (KR) and the dichlordo platinum(II) complex containing KR (**2**) were able to inhibit the grow of these cells in the range of tested concentrations (Fig. 5). It suggests that the lipophilic complex **2** is more cytotoxic in comparison with hydrophilic complex **1**. Obviously, the inactivity of **1** results from the inactivity of the free ligand PTR.

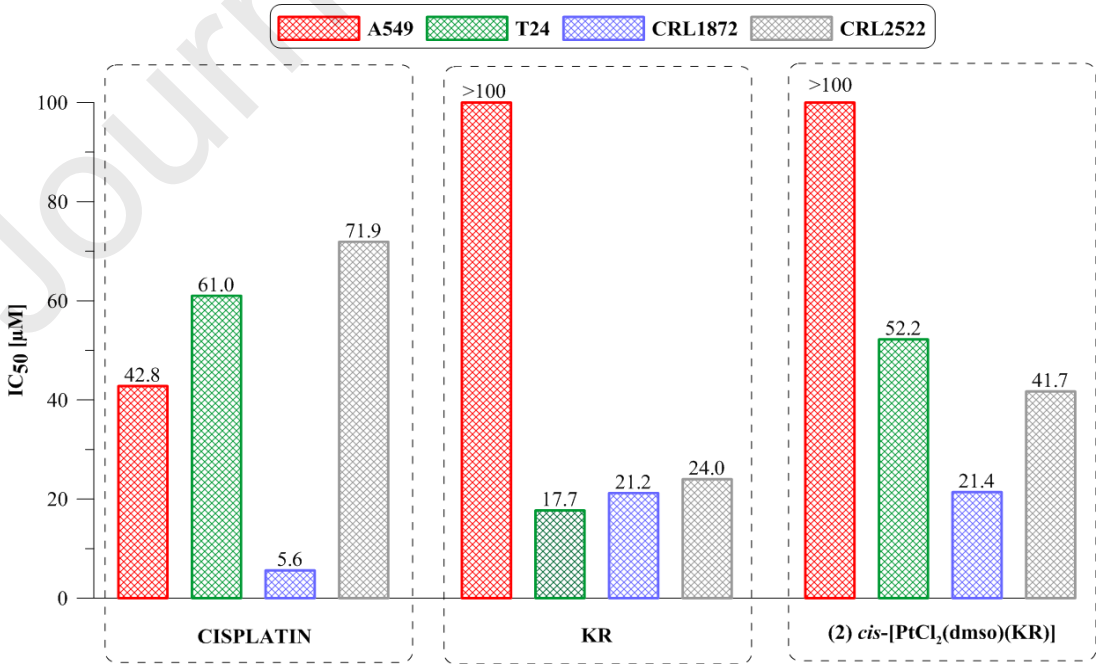

Fig. 5. *In vitro* antiproliferative activity of kinetin ryboside (KR) and complex **2**

On the other hand, free PTR presents more than 3 times higher *in vitro* cytotoxicity (IC_{50} = 17.7 μM) against the non-small cell lung cancer (A549) on comparison with cisplatin (IC_{50} = 61.0 μM). Moreover, after complexation with the platinum(II) ion, its activity did not change for A549 and CRL1872 cell lines, but it decreased for the T24 cell (Fig. 5). There are also differences in the toxicity of the free ligand KR and complex **2** towards the CRL2522 normal cell line. The platinum(II) complex with kinetin riboside is more toxic than the free kinetin riboside, with IC_{50} parameters amounting to 24.0 and 41.7 μM, respectively. However, both are more toxic than cisplatin (IC_{50} = 71.9 μM) (Fig. 5).

Conclusions

In conclusion, for the first time platinum(II) coordination compounds with ribosides have been designed and synthesized. During our research, we have successfully obtained and thoroughly characterized two novel platinum(II) complexes, *cis*-[$PtCl_2$(PTR)] (**1**) and *cis*-[$PtCl_2$(dmso)(KR)] (**2**), with the different N-donor ligands kinetin riboside (KR) and 1-β-D-ribofuranosyl-4-(2-pyridyl)-1*H*-1,2,3-triazole (PTR).

According to the data gained from multinuclear magnetic resonance spectra (^{1}H, ^{13}C, ^{15}N and ^{195}Pt), we were able to conclude that KR and PTR are monodentate (via the N(7) atom) and bidentate (via the N(3) and N(7) atoms) N-donor ligands, respectively. Additionally, it was observed that the biological properties, including the cytotoxic effect mechanism of the novel complexes, depend on the type of riboside. Finally, it was possible to suggest that the lipophilic complex **2** exhibits higher antiproliferative activities towards A549, T24 and CRL1872 cancer cell lines than complex **1**. For the above-mentioned reasons, we can suppose that the use of KR as the N-donor ligand in platinum(II) complexes is more promising than PTR insertion into the coordination sphere of the Pt(II) ion.

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References

Highlights:

- influence of different binding modes and environment around the platinum(II) on liphophilicity;
- role of N-donor ligands in creation of chemotherapeutic prodrugs;
- influence of type of riboside on lipophilicity, and in vitro activity;

By the reaction between *cis*-[$PtCl_2(dmso)_2$] and kinetin riboside (KR) or 1-β-D-ribofuranosyl-4-(2-pyridyl)-1*H*-1,2,3-triazole (PTR) in the M:L molar ratio of 1:1, two novel platinum(II) complexes with different compositions of the coordination sphere have been isolated. Biological studies showed that the lipophilic complex *cis*-[$PtCl_2$(dmso)(KR)] (**2**) exhibits higher antiproliferative activity towards A549, T24 and CRL1872 cancer cell lines than the complex *cis*-[$PtCl_2$(PTR)] (**1**).

CRediT author statement

Mateusz Jakubowski: Methodology and Formal analysis (synthesis of platinum(II) complexes), methodology for structural characterization, lipophilicity study, visualization; Writing - Original Draft;

Iwona Łakomska: Conceptualization; Formal analysis; management and coordination responsibility for the research activity planning and execution; Writing- Reviewing and Editing, supervision.

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