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Metal Anticancer Compounds

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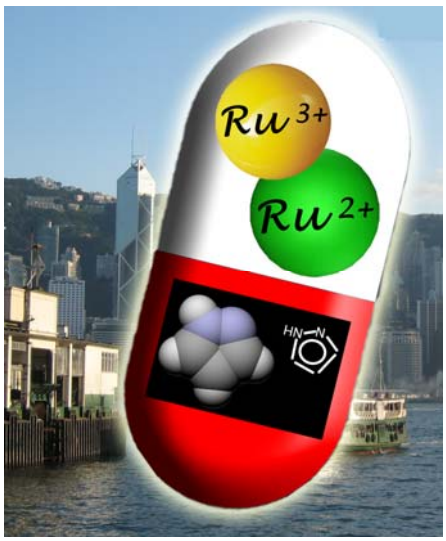

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Mono- and dinuclear platinum(II) compounds with 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine. Structure, cytotoxic activity and reaction with 5′-GMP†

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Mono- and dinuclear platinum(II) coordination compounds of formula *cis*-$[PtCl_2(NH_3)(dmtp)]$, **1**, *cis*-$[PtCl_2(dmtp)_2]$, **2** and $\{H^+[C_{28}H_{32}Cl_2N_{16}Pt_2]^{2+}(NO_3)_3(H_2O)_6\}$, **3**, in which dmtp is 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine have been synthesized and characterized by infrared and by ^1H, ^{13}C, ^{195}Pt NMR spectroscopy. The coordination units of the cationic species of formula $[Pt_2(\mu\text{-dmtp})_2Cl_2(dmtp)_2]^{2+}$ are built up by two platinum atoms in a square-planar environment. Two sites are occupied by two 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (dmtp) bridging ligands which are linked to both metal atoms through their nitrogen atoms in positions 3 and 4. The other two positions are occupied by one monodentate 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (dmtp) molecule and a coordinated chloride. This compound is the first in which the same triazolopyrimidine ligand (dmtp) coordinates to a metal ion in two different ways, *i.e.* bridging bidentate and non-bridging monodentate. In addition, the interaction of compounds **1** and **2** with 5′-GMP was investigated in solution by ^1H NMR spectroscopy. The cytotoxicity of all the new platinum(II) compounds were studied by using two different cell lines: T47D (breast cancer) and HCV29T (bladder cancer).

Introduction

Cisplatin is one of the most effective and commonly used agents used to treat various types of human cancer (bladder, testicular, ovarian and head and neck tumors),[1] but its clinical effectiveness has been limited by significant, undesirable side effects, such as dose–dependent nephrotoxicity and neurotoxicity. Also, the induced drug resistance to cells and its low aqueous solubility has restricted the application of this drug. These clinical inconveniences in cisplatin chemotherapy prompted the design and synthesis of more effective and less toxic platinum based anticancer drugs. Consequently, new platinum drugs with equal or improved antitumor activity, but lower toxicity, have been developed by modifying the pharmacokinetics of cisplatin by replacing the stable amine ligands with other non-leaving groups.[2] Some such mononuclear platinum(II) compounds display promising activity; however, those compounds often show cross-resistance to cisplatin, probably due to their similar mode of action.[3] In recent years, a number of polynuclear platinum(II) compounds with high antitumor activity in both cisplatin-sensitive and cisplatin-resistant cell lines have been discovered.[4] In contrast to cisplatin and its analogs, they are more water soluble, which is very convenient for clinical use. In addition, their DNA-binding mode is very different from that of cisplatin and the induced distortion upon DNA binding is less severe.[5]

Following this research line, we report herein the synthesis, molecular structure and antitumor properties of mononuclear and dinuclear platinum(II) compounds containing 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine. Triazolopyrimidine derivatives are known to have coordination compounds similar in structure to that of purine, differing from it by the presence of a pyrimidine nitrogen atom in a bridgehead position.[6] In addition, triazolopyrimidine derivatives display a great versatility in their interaction with metal ions, because they can bind the metal ion through different sites. The chemistry of triazolopyrimidines, including their coordination to transition metals, has resulted in a significant number of new coordination compounds with interesting structural and biological properties.[6,7] Nevertheless, reported studies of 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine compounds with mononuclear and dinuclear structures have shown the influence of the central ion and inorganic anions on the complex geometry. Up until now, platinum(II) coordination compounds with triazolopyrimidines have been studied only on a small scale. The chemistry of platinum-group metals and 1,2,4-triazolo[1,5-*a*]pyrimidine ligands has so far been dominated by Pt(II),[7b,8] Pd(II)[9] and Ru(III)[10] compounds, because many of these compounds often show cytotoxicity; for example *cis*-$[PtCl_2(HmtpO)_2]\cdot 2H_2O$[8d] indicated a moderate activity against the cells of breast cancer, however *cis*-$[PtCl_2(dbtp)_2]$,[8e] *cis*-$[PtCl_2(dptp)_2]$,[7b,8e] *cis*-$[PtCl_2(NH_3)(dptp)]$[7b,8e] and $[PtCl_4(dbtp)_2]$[8f] compounds presented significant cytotoxicity against T47D (breast cancer) and SW707

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† Electronic supplementary information (ESI) available: NMR spectral details for all compounds and reaction products with 5′-GMP and the packing of the dimer compound in the crystal. CCDC reference numbers 728067, **2** and 728846, **3**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b912404g

(rectal adenocarcinoma) tumor cells. The cytotoxic values for those platinum(II) compounds were even higher than the clinically used cisplatin. Therefore, these compounds seem promising enough to be recommended for further *in vivo* studies.

Only the following coordination compounds of Pt(II), Pd(II) and Ru(III) with dmtp had been described earlier: $[Pt(dmtp)_4][Pt(SCN)_6]$,[8a] *trans*-$[PdBr_2(dmtp)_2]\cdot CH_3OH$,[9a] $[Pd_2(\mu\text{-}dmtp)_2Cl_2]\cdot H_2O$,[9b] *cis*-$[PdCl_2(dmtp)_2]$,[9a] $(dmtpH^+)_2[PtCl_6]$,[8c] *trans*-$[PtCl_2(dmso)(dmtp)]$,[8b] *mer*-$[RuCl_3(dmtp)_2(H_2O)]\cdot H_2O$.[10]

In this paper we present three new Pt compounds containing 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (dmtp), namely *cis*-$[PtCl_2(NH_3)(dmtp)]$, **1**, *cis*-$[PtCl_2(dmtp)_2]$, **2**, and $\{H^+[C_{28}H_{32}Cl_2N_{16}Pt_2]^{2+}(NO_3)_3(H_2O)_6\}$, **3**, and present the crystal structures of two of them, as well as their interaction with 5′-GMP and their cytotoxicity activity against tumor cell lines.

Results and discussion

Structure description of compound 2

The molecular structure of **2** is depicted in Fig. 1, and consists of molecular units of mononuclear *cis*-$[PtCl_2(dmtp)_2]$.

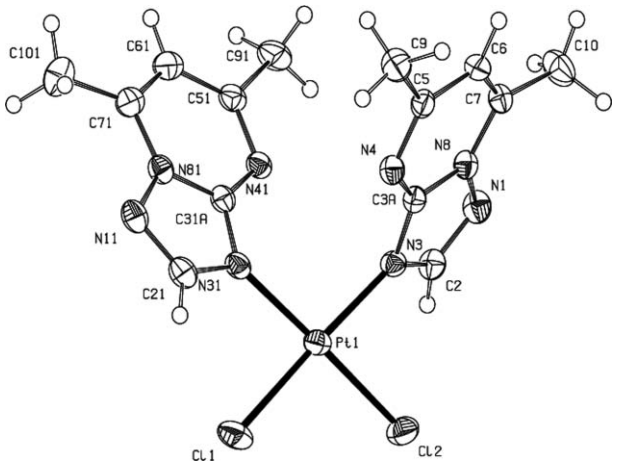

Fig. 1 Displacement ellipsoid plot for compound **2**, drawn at the 50% probability level with the labelling scheme for the non-hydrogen atoms.

The platinum(II) ion is four-coordinated by two triazolopyrimidine nitrogen atoms and two chloride ions in *cis* orientation. The two molecules of 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine ligands are coordinated to platinum(II) in a monodentate manner through the nitrogen atom in position 3, which is the most frequently occurring binding site for this type of heterocyclic ligand.[11]

The geometry of the PtN_2Cl_2 chromophore is characterized by a small distortion from a square-planar coordination. In the metal environment PtN_2Cl_2, the triazolopyrimidine ligands are bonded to Pt(II) *via* their nitrogen atoms N(3), the Pt1–N3 distance being 2.020(3) Å and Pt1–N31 2.024(3) Å. The chloride ions are in terminal *cis* positions, the Pt–Cl bond distances being 2.2916(12) Å and 2.2949(12) Å. Other relevant distances are given in Table 1. The packing of the compound in the crystal is unremarkable.

Table 1 Selected bond lengths [Å] and angles [deg] for *cis*-$[PtCl_2(dmtp)_2]$, **2**

Bond lengths		Angles	
Pt1–N3	2.020(3)	N3–Pt1–N31	92.16(13)
Pt1–N31	2.024(3)	N3–Pt1–Cl1	177.72(11)
Pt1–Cl1	2.2916(12)	N31–Pt1–Cl1	89.98(10)
Pt1–Cl2	2.2949(12)	N3–Pt1–Cl2	88.49(10)
N31–C31A	1.347(5)	N31–Pt1–Cl2	176.12(11)
N3–C3A	1.346(5)	Cl1–Pt1–Cl2	89.43(4)
N3–C2	1.351(5)	C31A–N31–Pt1	129.0(3)
N31–C21	1.368(5)	C3A–N3–Pt1	129.9(3)
		C21–N31–Pt1	126.9(3)
		C2–N3–Pt1	125.2(3)

Table 2 Selected bond lengths [Å] and angles [deg] for the cationic part of compound **3** $[Pt_2(\mu\text{-}dmtp)_2Cl_2(dmtp)_2]^{2+}$

Bond lengths		Bond lengths	
Pt1–Cl1	2.328(2)	Pt1–N3X	2.019(6)
Pt1–N3	2.005(6)	Pt1–N4X	2.046(6)
N3–C3A	1.339(9)	C3XA–N3X	1.342(9)
N3–C2	1.366(9)	C2X–N3X	1.373(8)
N4–C3A	1.328(9)	N4X–C3XA	1.354(9)

Angles		Angles	
Cl1–Pt1–Pt1	104.41(5)	N4X–Pt1–Pt1	84.11(16)
N3–Pt1–Pt1	96.66(17)	N3X–Pt1–Pt1	76.81(17)
N3–Pt1–Cl1	89.92(18)	N3X–Pt1–Cl1	178.70(18)
N3–Pt1–N3X	89.5(2)	N4X–Pt1–Cl1	92.10(17)
N3–Pt1–N4X	177.6(2)	N3X–Pt1–N4X	88.5(2)
C3A–N3–Pt1	127.3(6)	C5X–N4X–Pt1	124.0(5)
C2–N3–Pt1	127.7(5)	C3XA–N4X–Pt1	118.8(5)
C2X–N3X–Pt1	126.5(5)	C3XA–N3X–Pt1	129.4(5)
C3A–N3–C2	105.0(7)	C3XA–N3X–C2X	104.0(6)
C5–N4–C3A	115.7(8)	C5X–N4X–C3XA	117.0(7)
N3–C3A–N8	106.8(7)	N3X–C3XA–N8X	108.7(7)
N4–C3A–N8	124.3(7)	N4X–C3XA–N8X	122.0(7)
N3–C3A–N4	128.9(8)	N3X–C3XA–N4X	129.3(7)
N1–C2–N3	115.2(7)	N1X–C2X–N3X	114.3(7)

Structure description of compound 3

The cationic part of compound **3** is depicted in Fig. 2, while Table 2 lists relevant bond lengths and angles.

The dinuclear cationic part of the structure as depicted in Fig. 2 is built by two platinum atoms in a square-planar environment. The platinum atoms bind to two nitrogen-donor atoms (N3, N4) from two different dmtp entities, which bridge the two coordination planes, arranged in a head-to-tail fashion. The other two positions around each Pt atom are occupied by a nitrogen atom (N3) from another, monodentate 5,7-dimethyl-1,2,4-triazolo-[1,5-*a*]pyrimidine (dmtp) molecule and chloride ions. This compound appears to be the first one where the same triazolopyrimidine ligand binds to the same metal ion in two different ways, *i.e.* bridging and monodentate. Relevant bond lengths and angles are given in Table 2. The monodentate coordinating ligands are oriented in such a way that their repulsion is minimal.

The monoclinic unit cell contains four formula units of $\{H^+[C_{28}H_{32}Cl_2N_{16}Pt_2]^{2+}(NO_3)_3(H_2O)_6\}$. The cation and one of the NO_3^- anions is located on a crystallographic twofold axis. The other species are in general positions. The H^+ is likely to be

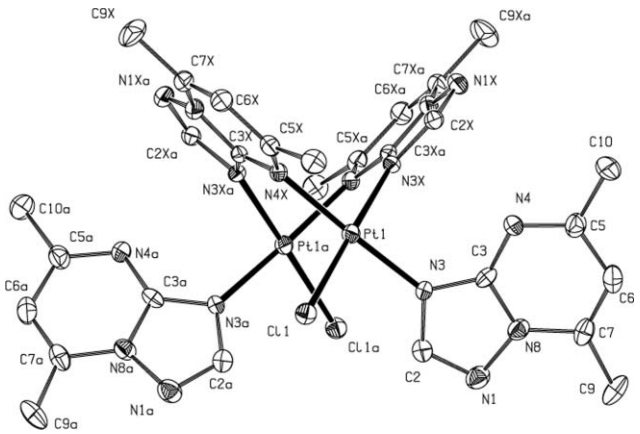

Fig. 2 Displacement ellipsoid plot for compound **3**, drawn at the 20% probability level with labelling. The nitrate anions and water molecules are not shown for clarity. Symmetry code a = −x, y, 1/2−z.

associated with the water molecules but could not be detected explicitly.

NMR spectroscopy

The ^{1}H and ^{13}C NMR spectra of compounds **1–3** confirmed the complexation of the ligand dmtp. Analysis of the ^{1}H NMR spectra revealed that binding of triazolopyrimidine to Pt(II) ions results in the deshielding of H2 and H6 resonances (Δ_{coord} = 0.13–0.50 ppm). However, detailed structural information deduced from ^{1}H NMR spectra can only be limited, since the deshieldings are in the same direction for all the protons present. Therefore such changes do not indicate unambiguously which of the heterocyclic nitrogen atoms is engaged in the formation of the platinum–nitrogen bond. This problem was solved by using ^{13}C NMR, as these spectra appear to be more sensitive to coordination. The coordination effect indeed has a clear impact on the C2 and C3a signals, which are shielded by some 1.2–4.3 ppm in relation to free dmtp, while C5, C6 and C7 resonances are detected 2.0–7.7 ppm towards the low field, which has been explained by the deshielding effect of metal, as a result of coordination at N3. The ^{13}C NMR resonances appear to be more sensitive to coordination, the N3, N4 bridging of the dmtp moieties appearing to be responsible for the great deshielding in C5, C6 and C7 resonance (3.8–7.7 ppm).

The ^{1}H NMR spectrum of **1**, as expected, also displays the broad signal from the NH_3 protons (δ = 4.38 ppm), which agrees with its coordination to the platinum ion.[11b,12]

Regarding compound **3**, the ^{1}H NMR spectrum displays two equivalent sets of signals assigned to H2 and H6. The most deshielded signal at δ 9.76 (H2) and 9.40 ppm (H6) was found related to the bidentate coordination of dmtp, therefore the signals at 9.32 (H2) and 9.56 ppm (H6) are considered as characteristics for a monodentate coordination of heterocyclic ligand. In this case monodentate coordination of dmtp *via* N3 can be proposed, because in the case of the bridging mode (N3, N4), the coordination shifts are known to be much larger.[13] The ^{13}C NMR spectrum of **3** is also indicative of a dinuclear platinum(II) species in solution. The characteristic signals for chelating dmtp are clearly more deshielded then signals for monodentate coordination of dmtp.

The ^{1}H and ^{13}C spectral data for all three compounds are given in the ESI.†

Reactions of compounds 1 and 2 with 5′-GMP

The reaction of compounds **1** and **2** with 5′-GMP indicated that both *cis*-[$PtCl_2(NH_3)$(dmtp)] and *cis*-[$PtCl_2$(dmtp)$_2$] are unable to react at pH = 7 and 37 °C; hence it was decided to study the reaction of 5′-GMP with monoaqua species of studied mononuclear platinum(II) compounds: [$PtCl(D_2O)$(dmtp)$_2$]$^+$ and [$PtCl(D_2O)(NH_3)$(dmtp)]$^+$. The monoaqua species were obtained from the reaction of *cis*-[$PtCl_2(NH_3)$(dmtp)] or *cis*-[$PtCl_2$(dmtp)$_2$] with $AgNO_3$ in D_2O. Both complexes were stirred for 24 hours at room temperature, followed by reaction with 5-GMP.

In both cases, a typical deshielding of H8 of 5′-GMP (known 8.19 ppm for the H8 of free 5′-GMP;[14] at pH = 7) to a value of 8.5 ppm for H8 of bis-bound and 8.8–8.7 ppm for H8 of mono-bound 5′-GMP) was observed, indicating that the platination site is at the N7 position 5′-GMP for all the compounds.[15] Careful monitoring of the H(8) proton shift of 5′-GMP allowed the observation of the gradual appearance and disappearance of the different platinum-GMP species formed in the reaction as schematically presented in Fig. 3.

Cytotoxic activity

All 3 new platinum(II) compounds have been tested for their antiproliferative activity *in vitro* against the tumor cell lines.

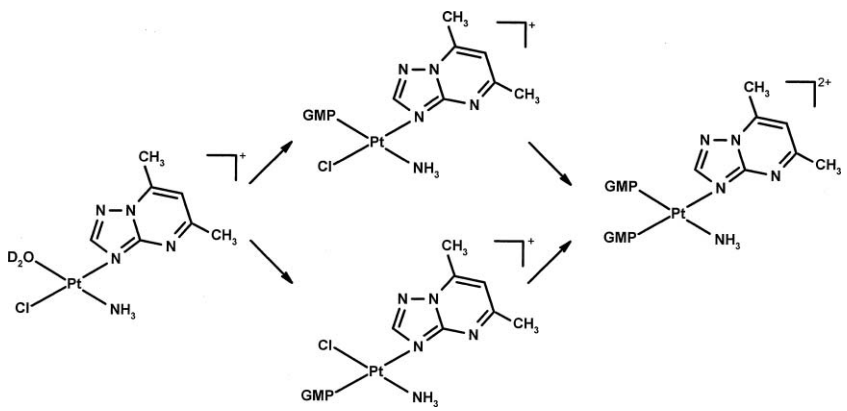

Fig. 3 The reaction of [$PtCl(D_2O)(NH_3)$(dmtp)]$^{2+}$ with 5′-GMP.

Table 3 IC_{50} values (μM) for compounds **1–3**, cisplatin in two different cell lines

	Compounds/IC_{50} [in μM]			
Cell lines	**1**	**2**	**3**	cisplatin
T47D	>180	>180	2.3	10.7
HCV29T	>180	>180	>82	7.9

The cytotoxic activity of all the new platinum(II) compounds in all the cells assayed was found to be lower (except for the dinuclear compound **3** against T47D) than that of cisplatin under the same conditions (Table 3). The activity of compound **3** against breast cancer (T47D) is in fact rather high (IC_{50} as low as 2.3 μM).

Experimental

Reactants and methods

Dipotassium tetrachloridoplatinum(II), potassium hexafluoridophosphate (98%), tetraethylammonium chloride hydrate, tetraphenylphosphanium chloride (98%) and 5,7-dimethyl-*s*-triazolo[1,5-*a*]pyrimidine (98%) were purchased from Aldrich, whereas the inorganic salts of analytical grade were obtained from POCh Gliwice (Poland).

Preparation of the compounds

The starting compound $K[PtCl_3(NH_3)]$ was prepared from K_2PtCl_4 by a published method[16]

***cis*-[PtCl$_2$(NH$_3$)(dmtp)], 1.** To a solution of $K[PtCl_3(NH_3)]$ (0.100 g, 0.28 mmol) in 10 cm^3 of water, a solution of dmtp (0.044 g, 0.30 mmol) in 10 cm^3 of water was added. The reaction mixture was stirred at room temperature for 24 hours. The light yellow precipitate was filtered, washed with water, acetone, diethyl ether and dried in vacuum. Yield 0.075 g (58%). Analysis: calcd/exp. for $C_7H_{11}Cl_2N_5Pt$: C 19.5/19.7; N 16.2/16.1; H, 2.6/2.1. ^{1}H NMR(DMSO-d_6) δ 8.86 (s, H2), δ 7.43 (s, H6), δ 2.75 (s, $5CH_3$), δ 2.68 (s, $7CH_3$) and δ 4.12 (s, NH_3); ^{1}H NMR (DMF-d_7): δ 8.92 (s, H2), δ 7.48 (s, H6), δ 2.84 (s, $5CH_3$), δ 2.73 (s, $7CH_3$) and δ 4.38 (s, NH_3); ^{13}C NMR (DMF-d_7) δ 154.7 (s, C2), δ 168.9 (s, C5), δ 114.0 (s, C6), δ 150.0 (s, C7), δ 16.4 (s, $7CH_3$), δ 24.8 (s, $5CH_3$); ^{195}Pt(DMSO-d_6) -2071. Crystals suitable for X-ray diffraction were not obtained.

***cis*-[PtCl$_2$(dmtp)$_2$], 2.** K_2PtCl_4 (0.100 g; 0.24 mmol) was dissolved in 10 cm^3 and treated with KI (0.199 g; 1.2 mmol) solved in the same solution. The solution was stirred for 15 min. Two equivalents of dmtp (0.071 g; 0.48 mmol) was added quickly to the resulting K_2PtI_4. The reaction mixture was further stirred for 3 hours. The dark yellow precipitate *cis*-$[PtI_2(dmtp)_2]$ was filtered, washed with water, acetone, diethyl ether and dried in vacuum. Yield 0.171 g (96%). Next a suspension of *cis*-$PtI_2(dmtp)_2$ (0.171 g, 0.23 mmol) in 20 cm^3 of water was treated with $AgNO_3$ (0.075 g, 0.44 mmol) in 5 cm^3 water. The suspension was stirred in the dark for 2 days. Precipitated AgI was filtered off and the filtrate was treated with KCl. After a few days, a yellow precipitate was formed and separated. Yield 0.059 g (44%). Analysis calcd/exp. for $C_{14}H_{16}Cl_2N_8Pt$: C 29.9/29.5; N 19.9/19.5; H 2.9/2.6. ^{1}H NMR (DMSO-d_6): δ 9.03 (s, H2), δ 7.27 (s, H6), δ 2.37 (s, $5CH_3$), δ 2.68 (s, $7CH_3$) ^{195}Pt(DMSO-d_6) –2034. Crystals suitable for X-ray diffraction were manually selected.

{H$^+$[C$_{28}$H$_{32}$Cl$_2$N$_{16}$Pt$_2$]$^{2+}$(NO$_3$)$_3$(H$_2$O)$_6$}, 3. *cis*-$[PtCl_2(dmtp)_2]$ (0.103 g; 0.72 mmol) was suspended in 30 cm^3 of water. The aqueous solution of $AgNO_3$ (0.120 g; 0.72 mmol) in 20 cm^3 was added. This solution was brought to pH = 1 by addition of 4 M HNO_3. The reaction mixture was stirred at 35 °C for 36 hours without light. The AgCl was filtered and a light yellow solution was obtained. The solution was evaporated to about 5 cm^3 and 20 cm^3 of 2-propanol was added. The reaction solution was kept at 4 °C. The crystalline product was precipitated after 1 month. (Yield ~20%, analysis calcd/exp. for $C_{28}H_{45}Cl_2N_{19}O_{15}Pt_2$: C 24.9/24.7; N 19.7/19.3; H 3.4/3.0). ^{1}H NMR (DMF-d_7) for monodentate dmtp: δ 9.32 (s,H2), δ 7.40 (H6); for bidentate dmtp: δ 9.76 (s,H2), δ 7.56 (H6); ^{13}C NMR (DMF-d_7) for monodentate dmtp: δ 153.8 (s, C2), δ 152.2 (s, C3a), δ 169.0 (s, C5), δ 114.0 (s, C6), δ 149.7 (s, C7); for bidentate dmtp: δ 154.3 (s, C2), δ 151.5 (s, C3a), δ 172.7 (s, C5), δ 115.3 (s, C6), δ 155.7 (s, C7). Crystals suitable for X-ray diffraction were manually selected.

Instrumentation and analyses

The C, H, N content was determined by elemental semi-microanalysis; IR spectra were measured with a Perkin-Elmer Spectrum-2000 FT–IR spectrometer, using KBr (400–4000 cm^{-1}) and polyethylene discs (100–400 cm^{-1}). The ^{1}H{^{13}C} HSQC, ^{1}H{^{13}C} HMBC and ^{1}H{^{15}N} HMQC spectra were performed with a Varian INOVA-500 NMR spectrometer equipped with an inverse Nalorac Z-gradient shielded probe. The solvent used was dmso-d_6, the concentrations of saturated solutions being *ca.* 0.01–0.05 M, at a temperature of 298 K. The reference standard was TMS for ^{1}H and ^{13}C and K_2PtCl_6 (external) for ^{195}Pt.

Crystallography

Crystallographic data and details of the refinement for compounds **2** and **3** are presented in Table 4. X-ray data for **2** and **3** were collected on a Nonius KappaCCD diffractometer on a rotating anode (MoKα, graphite monochromated, λ = 0.71073 Å, T = 150 K for **2** and 293 K for **3**. The structure for **2** was solved with Patterson methods (SHELXS-86). Refinement with SHELXL-97.[17] Hydrogen atoms were introduced at calculated positions and refined riding on their carrier atoms. The ORTEP illustration (Fig 1) and structure validation were performed with PLATON.[18] However, the structure for **3** was solved by Patterson methods and refined with the full-matrix least-squares method on F^2 with the use of the SHELXL-97 program package.[17] The fractional coordinates of **2** and **3** and selected bond lengths and angles are presented respectively in Tables 1 and 2.

No reliable hydrogen atom positions on the water molecules could be established for compound **3**. One of the two water molecules is disordered over two locations in a 60:40 ratio, and no exact location of the acidic hydrogen on one of the water molecules could be determined.

Table 4 Crystallographic data and details of refinement for compounds **2** and **3**

Compound	**2**	**3**
Formula	$C_{14}H_{16}Cl_2N_8Pt$	$C_{28}H_{45}Cl_2N_{19}O_{15}Pt_2$
Formula weight (g mol^{-1})	562.33	1348.91
Crystal system	Triclinic	Monoclinic
Space group	*P*-1	*C*2/*c*
a (Å)	8.2733(12)	26.974(5)
b (Å)	9.3493(12)	11.294(2)
c (Å)	12.7502(12)	20.317(4)
α (°)	78.721(10)	90
β (°)	75.241(10)	130.84(3)
γ (°)	72.229(10)	90
Z	2	4
V (Å^3)	900.7(2)	4682(4)
ρ_{calc}(g cm^{-1})	2.0734(5)	1.913
μ (Mo Kα) (mm^{-1})	8.10	6.165
F(000)	536	2624
θ range (°)	2.0-20.0	2.06-25.33
No. reflections collected	4100	4235
No. reflections observed	3840	2397
No. parameters refined	230	303
R_1	0.0256	0.0337
wR_2	0.0651	0.0758
Goodness-of-fit, S	1.021	0.888
Residual ρ_{max}, ρ_{min} (e Å^{-3})	1.03, –1.96	1.25, –0.82

Cytotoxic activity

The antiproliferative activity *in vitro* against two human tumor cell lines: T47D (breast cancer) and HCV29T (bladder cancer) were performed by using the microculture sulforhodamine B SRB.[19]

Cells were patted in 96-well sterile plates (Sarstedt, Costar) at a density of 10^4 cells per well (in 100 μL of culture medium) and incubated for 24 hours. The tested compounds **1–3** were added to give final concentrations ranging from 0.1 to 100 μg/cm^3 and the incubation continued for an additional 72 hours. The results of the cytotoxic activity *in vitro* were expressed as an IC_{50}—the dose of compound (in μM) that inhibits the proliferation rate of the tumors cells by 50% as compared to the control untreated cells. All experiments were carried out in triplicate.

Reaction with 5′-GMP

Reaction of compounds **1** and **2** and their monoaqua species with an excess (1:4) of 5′-GMP in D_2O (used ratio Pt–5′-GMP = 1:4) was carried out in an NMR tube. ^{1}H NMR spectra were measured at different time intervals (30 min) at 310 K and recorded on a Bruker DPX300 spectrometer.

Conclusion

We have reported for the first time the formation of a dinuclear platinum(II) complex in which the same triazolopyrimidine ligand (5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine) binds to a metal ion in two different ways, *i.e.* bridging bidentate (N3, N4) and non-bridging monodentate (N3). In addition the molecular structures of two new monuclear platinum complexes are described with the same heterocycle ligand (5,7-dimethyl-1,2,4-triazolo-[1,5-*a*]pyrimidine). The NMR results confirm, that the coordination mode *via* N3 in the mononuclear compounds has not been changed in solution. Dinuclear compound, **3**, exhibited higher toxicity *in vitro* against T47D than mononuclear compound **2** and cisplatin.

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