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# Synthesis, crystal structure and antimicrobial studies of a thione derivative of transplatin, *trans*- $[Pt(NH_3)_2(Diaz)_2]Cl_2 \cdot 2H_2O$ (Diaz = 1,3-diazinane-2-thione)



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## ABSTRACT

Platinum(II) complexes, *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(Diaz)<sub>2</sub>]Cl<sub>2</sub>·2H<sub>2</sub>O (**1**) and *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(Tu)<sub>2</sub>]Cl<sub>2</sub> (Diaz = 1,3-diazinane-2-thione, Tu = thiourea) were prepared and characterized by elemental analysis, IR and NMR spectros-copy. The crystal structure of compound **1** was determined by X-ray crystallography. The structure of **1** consists of *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(Diaz)<sub>2</sub>]<sup>2+</sup> cation, two chloride ions and two water molecules. In *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(Diaz)<sub>2</sub>]<sup>2+</sup>, the geometry at platinum is nearly regular square planar with the average *cis* and *trans* angles of 90° and 180° respectively. The <sup>1</sup>H and <sup>13</sup>C NMR spectral data indicated the coordination of both ligands to platinum(II). Antimicrobial activities of the complexes were evaluated by minimum inhibitory concentration and the results showed that the complexes exhibited significant activities against gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*). However, moderate activity was observed against molds (*Aspergillus niger, Penicillium citrinum*).

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Platinum based drugs are among the most successful and widely used anticancer therapeutic agents. Cisplatin and oxaliplatin are extremely effective against testicular and ovarian cancers [1-8]. The major disadvantages of platinum therapy are its significant toxicological profile and the occurrence of primary or acquired resistance [8–11]. In response to these limitations, efforts have been made to develop cisplatin analogues with improved efficacy and reduced toxicity [5.6.12–14]. Platinum complexes with distinctively different DNA binding modes from that of cisplatin may provide higher antitumor activity against cisplatin-resistant cancer cells. Such complexes include those with amine ligands having trans stereochemistry [15–19]. Systematic studies of the transplatin analogues containing heterocyclic and aliphatic amines as non-leaving spectator ligands have confirmed that these analogues of transplatin exhibit cytotoxic effects in a number of tumor cell lines including those resistant to cisplatin [15–19]. Several thione derivatives of transplatin are also known but their antimicrobial and antitumor activities have not been reported [20-23]. Structural studies on platinum(II) complexes with heterocyclic thiones/thionates describe a square-planar geometry around the metal center and the thione ligands coordinate in terminal S-bonded [22-29] and bidentate chelating [30,31] modes. The present report deals with the synthesis, crystal

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structure and antimicrobial properties of a new transplatin complex of a heterocyclic thione, 1,3-diazinane-2-thione (diaz), *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(-Diaz)<sub>2</sub>]Cl<sub>2</sub>·2H<sub>2</sub>O (**1**). The spectroscopic and biological properties of another complex, *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(Tu)<sub>2</sub>]Cl<sub>2</sub> (Tu = thiourea) are also described, the crystal structure of which has already been reported [23].

For the preparation of complexes, 0.15 g (0.5 mmol) transplatin (*trans*-diamminedichloridoplatinum(II)) was dissolved in a 20 mL 1:1 mixture of water and acetonitrile on heating (transplatin was obtained from Strem Chemical Company, USA and 1,3-diazinane-2-thione (Diaz) was prepared according to the method reported in the literature [32]). To the clear solution of transplatin, 0.120 g (1.0 mmol) 1,3-diazinane-2-thione (Diaz) or 0.076 g (1.0 mmol) thiourea in 20 mL acetonitrile was added. Upon mixing, a clear solution was obtained. The mixture was stirred for 1 h. Then it was filtered and the filtrate was kept in refrigerator for 3 days for crystallization on slow evaporation. As a result, light yellow crystals of *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(Tu)<sub>2</sub>]Cl<sub>2</sub> or colorless crystals of *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(Tu)<sub>2</sub>]Cl<sub>2</sub>: calc: C, 5.13%; H, 3.12%; N, 18.58%; S, 14.18%. Found: C, 4.96%; H, 3.30%; N, 18.26%; S, 13.72%.

Single crystal data collection was performed at 296 K on a Bruker Kappa APEXII CCD diffractometer equipped with a four-circle goniometer and using MoK $\alpha$  graphite mono-chromated radiation. The refinement and all further calculations were carried out using SHELX-97

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Table 1

Crystal, intensity collection and refinement data for compound 1.

Parameter	Value
Formula	C <sub>8</sub> H <sub>26</sub> Cl <sub>2</sub> N <sub>6</sub> O <sub>2</sub> PtS <sub>2</sub>
Fw	568.46
Crystal system	Monoclinic
Space group	$P 2_1/n$
A, b, c (Å)	7.4601(4), 14.3133(9), 9.3198(6)
$\alpha, \beta, \gamma$ (deg)	90.00, 109.598(3), 90.00
V, Å <sup>3</sup>	937.51(10)
Ζ	2
$\rho_{calcd}$ , g cm <sup>-3</sup>	2.014
μ, mm <sup>-1</sup>	8.002
F(000)	552
Crystal size (mm)	$0.30\times0.25\times0.23$
Temperature (K)	296(2)
$\lambda$ (MoK $\alpha$ ) Å	0.71073
$\theta$ range, deg	2.72-28.28
Limiting indices	-9:9, -18:17, -11:12
Reflections: collected, unique	$8412,2330 \ (R_{\rm int} = 0.0431)$
Observed data ( $I > 2\sigma(I)$ )	2071
T <sub>min</sub> , T <sub>max</sub>	0.105, 0.160
Data, restraints, parameters	2330, 0, 99
$R_1$ , $wR_2$ , $S(I > 2\sigma(I))$	0.0211, 0.0541, 1.069
Largest diff. peak, hole, $e Å^{-3}$	1.681, -0.877

 $w = [\sigma^2(F_o^2) + (0.0224P)^2 + 0.2122P]^{-1}$ , where  $P = (F_o^2 + 2F_c^2) / 3$ .

[33]. For molecular graphics PLATON [34] was used. Crystal data and details of the data collection are summarized in Table 1.

The selected IR bands of the ligands and their platinum(II) complexes are given in Table S1 (Supplementary material). In IR spectra of these complexes, the presence of  $\nu$ (C=S),  $\nu$ (N–H) and  $\nu$ (C–N) bands are indicative of coordination of the ligands to the metal ion in the solid state [31,35,36]. The <sup>1</sup>H and <sup>13</sup>C NMR spectra in DMSO were obtained at the frequency of 125.65 MHz with <sup>1</sup>H broadband decoupling at 298 K. The chemical shifts were measured relative to TMS. The <sup>1</sup>H and <sup>13</sup>C chemical shifts of the complexes in DMSO-d6 are summarized in Table S1 (Supplementary material). In the <sup>1</sup>H NMR spectra of the complexes, downfield shifts in the N–H resonances were observed as compared to uncomplexed Tu and Diaz. The downfield shifts are related to an increase in  $\pi$  character of the C–N bond upon coordination of ligands to platinum. The ammonia protons were observed around 4 ppm.

In the <sup>13</sup>C NMR spectra of both complexes, the C=S resonances of Tu and Diaz were shifted upfield as compared to the free ligand's resonances in accordance with the data observed for other complexes [31,35,36]. Slight downfield shifts were observed in the N–C resonances. These shifts are consistent with a decrease in bond order of C=S bond and an increase in bond order of C–N bond.

The structure of compound **1** shown in Fig. 1, consists of a complex  $[Pt(NH_3)_2(Diaz)_2]^{2+}$  cation, two chloride counter ions and two water molecules as solvent. The selected geometrical parameters are given in Table 2. Within the complex the platinum atom is bound to two sulfur atoms of Diaz and two N atoms of ammonia in a *trans* fashion. The platinum atom adopts an essentially square-planar environment lying exactly within the plane defined by the two S and two N atoms. The entire  $[Pt(NH_3)_2(Diaz)_2]^{2+}$  cation lies at the center of symmetry and

#### Table 2

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Selected bond distances (Å	) and bond angles (°)	for compound 1.

Bond distances		Bond angles	
Pt1 – N1 Pt1 – S1 C1 – S1 C1 – N2 C1 – N3 C2 – N2	2.040(3) 2.3159(7) 1.741(2) 1.313(3) 1.316(3) 1.456(3)	$\begin{array}{c} N1 - Pt1 - N1^{i} \\ N1 - Pt1 - S1^{i} \\ N1 - Pt1 - S1 \\ N1^{i} - Pt1 - S1^{i} \\ N1^{i} - Pt1 - S1 \\ S1 - Pt1 - S1^{i} \\ Pt1 - S1 - C1 \\ N2 - C1 - N3 \end{array}$	180.0 90.86(9) 89.14(9) 90.86(9) 180.0 106.20(8) 120.6(2)
		N2-C1-S1	120.0(2)

i = 1 - x, -y, 1 - z.

possesses approximate C<sub>2</sub>h symmetry. The *cis* angles around platinum vary between  $89.14(9)^{\circ}$  and  $90.86(9)^{\circ}$ , while the *trans* angles are 180°. The Pt-N and Pt-S bond distances are 2.040(3) and 2.3159(7) Å respectively, and are in agreement with the average values reported for similar complexes such as [Pt(NH<sub>3</sub>)<sub>4</sub>][PtI<sub>4</sub>] [37], cis-[PtCl<sub>2</sub>(cyclobutylamine)(NH<sub>3</sub>)] [2.053(14) Å and 2067(13) Å] [38], [Pt(Imt)<sub>4</sub>]I<sub>2</sub> [2.328(2) Å] [24], [Pt(Hmimt)<sub>4</sub>]Cl<sub>2</sub> [2.324 Å] [25], [Pt(Mpy)4]Cl<sub>2</sub> [2.3439(7) Å] [27] and trans-[Pt(NH<sub>3</sub>)<sub>2</sub>(thiourea)<sub>2</sub>]Cl<sub>2</sub> [Pt-N = 2.054(6) Å, Pt-S = 2.307(2) Å] [23]. In  $[Pt(Imt)_4]I_2$  [24] and  $[Pt(Hmimt)_4]Cl_2$  [25], the four Pt – S distances are completely different from one another and vary from 2.291(5) Å to 2.357(5) Å. The sixmembered ring of Diaz in 1 has a puckered orientation as can be seen in Fig. 1. The carbon atoms in N – C=S moieties of the ligands are  $sp^2$  hybridized. The SCN<sub>2</sub> fragment of Diaz is essentially planar with the C-N and C-S bond length values intermediate between single and double bonds. The angles around S lie in the range expected for tetrahedral environment (Table 2). The complex cation,  $[Pt(NH_3)_2(Diaz)_2]^{2+}$  and chloride ions are associated to each other through electrostatic interactions.

Hydrogen bonding involving the N–H groups of Diaz or NH<sub>3</sub> ligands and chloride or water molecules plays an important role in stabilizing the crystal structure. A view of the crystal packing of the complex showing hydrogen bonds is given in Fig. 2. The details of the hydrogen bond geometry are given in Table S2 (Supplementary material). It appears from the table that the order of their strength on the basis of the lengths and polarities is NH-O > OH-Cl > NH-Cl > CH-S.

Antimicrobial activities of the title complex were estimated by minimum inhibitory concentration (MIC;  $\mu$ g mL<sup>-1</sup>) as described earlier [35]. Standard culture media of bacteria, *Escherichia coli* (ATCC 13706) & *Pseudomonas aeruginosa* (MTCC 424), molds, *Aspergillus niger* (MTCC 1349) & *Penicillium citrinum* (MTCC 5215) and yeasts, *Candida albicans* (MTCC 183) and *Saccharomyces cerevisiae* (MTCC 463) were obtained from Qingdao Yijia Huuyi Co. China. Amoxil (an antibiotic), prepared by SmithKline Beecham Pharmaceuticals, Worthing, United Kingdom, was purchased from Market in the form of capsules. Each capsule contains 500 mg amoxicillin as a trihydrate. The antimicrobial activities (average of three measurements) of free ligands, their platinum(II) complexes and Amoxil (as a standard drug) estimated by minimum inhibitory concentrations (MIC;  $\mu$ g mL<sup>-1</sup>) are listed in Table 3.

It can be seen from Table 3 that the tested complexes especially **1** showed remarkable activity against two gram-negative bacteria (*E. coli, P. aeruginosa*). Moderate activity was observed against the studied molds (*A. niger, P. citrinum*). The title complex also showed moderate activity against yeasts (*C. albicans, S. serevisaiae*), while the activity of *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(Tu)<sub>2</sub>]Cl<sub>2</sub> for yeasts was poor. The commercially available antibiotic, Amoxil is highly effective against the studied bacteria. A comparative study of the ligands and complexes shows that the complex **1** is more effective than the uncoordinated ligand, while *trans*-[Pt(NH<sub>3</sub>)<sub>2</sub>(Tu)<sub>2</sub>]Cl<sub>2</sub> is less effective than Tu. The biological activity of the complexes could be attributed to whether or not they possess the tendency of further ligand replacement with the biological ligands such as proteins and DNA. This suggests that Pt in these complexes is labile with replacement by biological ligands being possible [39,40].

In summary, in this study a new derivative of transplatin with diazinane-2-thione was prepared in 1:2 molar ratio in wateracetonitrile solution. The X-ray structure of the complex shows that the platinum atom adopts a square planar coordination environment and Diaz ligands coordinate in the thione form. The title complex exhibits significant biological activity showing the potential for its use as antibacterial agent.

### Appendix A. Supplementary data

Crystallographic data has been deposited with the Cambridge Crystallographic Data Center. CCDC No. 949124. Copies of the data can be obtained, free of charge, on application to The Director, CCDC, Union Road 12, Cambridge CB2 1EZ, UK (fax:b44 1223/336 033 or e-mail: Download English Version:

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