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Synthesis, characterization, and cytotoxicity of platinum(II)/palladium(II) complexes with 4-toluenesulfonyl-L-amino acid dianion and diimine/diamine

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Eight new platinum(II)/palladium(II) complexes with 4-toluenesulfonyl-L-amino acid dianion and diimine/diamine ligands, [Pd(en)(Tsile)]·H_2O (**1**), [Pd(bipy)(Tsile)] (**2**), [Pd(bipy)(Tsthr)]·0.5H_2O (**3**), [Pd(phen)(Tsile)]·0.5H_2O (**4**), [Pd(phen)(Tsthr)]·H_2O (**5**), [Pd(bqu)(Tsthr)]·1.5H_2O (**6**), [Pt(en)(Tsser)] (**7**), and [Pt(en)(Tsphe)]·H_2O (**8**), have been synthesized and characterized by elemental analyses, ^{1}H NMR and mass spectrometry. The crystal structure of 7 has been determined by X-ray diffraction. Cytotoxicities were tested by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide and sulforhodamine B assays. The complexes exert cytotoxicity against HL-60, Bel-7402, BGC-823, and KB cell lines with 4 having the best cytotoxicity against HL-60, Bel-7402, and BGC-823 cell lines; the compounds are less cytotoxic than cisplatin.

Keywords: Platinum(II)/palladium(II); Synthesis; 4-Toluenesulfonyl-L-amino acids; Diimine/diamine; Cytotoxicity

1. Introduction

The landmark discovery of cisplatin by Rosenberg in 1965 heralded a new era of metal-based anticancer drugs [1]; cisplatin is one of the most effective drugs in treatment of testicular, ovarian, small cell lung, bladder, cervical, head and neck carcinomas [2–6]. Carboplatin and oxaliplatin have received worldwide approval, while nedaplatin, lobaplatin, and heptaplatin have gained regionally limited approval [7–9]. Regardless of the achievements of current platinum drugs, there are major drawbacks including effectiveness against a limited range of cancers, drug-resistance, and severe side effects [10, 11]. These problems provide incentive to discover new metal-based anticancer drugs.

Due to the structural and thermodynamic analogy between platinum(II) and palladium (II) complexes, there is also interest in palladium(II) derivatives as potential anticancer drugs [12–16]. Jin and Ranford have synthesized and characterized nine platinum(II) complexes with phen and amino acids (where amino acids are Gly, His, Cys, Ile, Ala, Pro,

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Ser, Asp, and Glu) as well as two palladium(II) complexes with phen and amino acids (where amino acids are Asp and Glu) [17]. These complexes were less cytotoxic than cisplatin. The IC_{50} values of $[Pt(phen)(Pro)]Cl{\cdot}2H_2O$ and $[Pd(phen)(Asp)]Cl{\cdot}1.5H_2O$ were similar to cisplatin [17]. Mital *et al.* reported synthesis and cytotoxicity of palladium(II) complexes, $[Pd(phen)(AA)]^+$ (where AA is an anion of Gly, Ala, Leu, Phe, Tyr, Trp, Val, Pro, or Ser) [18], with IC_{50} values of the palladium(II) complexes with Gly and Val comparable to that of cisplatin; the other palladium(II) complexes showed higher IC_{50} values. The IC_{50} values do not show definite correlation with variation of the amino acid side chains [17, 18]. Puthraya *et al.* reported synthesis and cytotoxicity of palladium(II) complexes, $[Pd(bipy)(AA)]^{n+}$ (where AA is an anion of Cys, Asp, Glu, Met, His, Arg, Phe, Tyr, or Trp, and $n = 0$ or 1) [19]. In the L1210 system, complexes with Asp, Glu, Met, and Arg have shown lower IC_{50} values than or comparable to cisplatin [19]. In the P388 system, complexes with Asp and Glu showed lower IC_{50} values than cisplatin [19]. In the Ehrlich ascites tumor system, complexes with Asp and Arg have lower IC_{50} values than cisplatin [19]. Recently, we reported synthesis and cytotoxicity of a series of platinum(II)/palladium(II) complexes with 4-toluenesulfonyl-L-amino acid dianion and diimine/diamine [20–23]. These complexes displayed cytotoxic effects against HL-60, Bel-7402, BGC-823, and KB cell lines with some complexes having better cytotoxicity than cisplatin. For example, cytotoxicity of $[Pd(phen)(Tsleu)]{\cdot}H_2O$ is better than that of cisplatin against BGC-823, Bel-7402, and KB cell lines. The cytotoxicity of [Pt(bipy)(Tsphe)] is comparable to that of cisplatin against BGC-823 and Bel-7402 cell lines. In order to further explore the structure–activity relationships and discover new metal-based anticancer drugs, in the present work, we present the synthesis, characterization, and cytotoxicity of eight new platinum(II)/palladium(II) complexes with 4-toluenesulfonyl-L-amino acid dianion and diimine/diamine (bpy, phen, and bqu/en) for the first time.

2. Experimental

2.1. *Materials*

4-Toluenesulfonyl chloride, $K_2[PdCl_4]$, and $K_2[PtCl_4]$ were of chemical grade; en, bipy, phen, and bqu were of analytical grade. Commercially pure Ile, Thr, Ser, and Phe were purchased from Sigma. RPMI-1640 medium, trypsin, and fetal bovine serum were purchased from Gibco. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), sulforhodamine B (SRB), benzylpenicillin, and streptomycin were from Sigma. Four different human carcinoma cell lines: HL-60 (immature granulocyte leukemia), Bel-7402 (liver carcinoma), BGC-823 (gastrocarcinoma), and KB (nasopharyngeal carcinoma) were obtained from American type culture collection.

2.2. *Instrumentation and measurement*

Elemental analyses were determined on a Elementar Vario EL III elemental analyzer. ^1H NMR spectra were recorded on a Bruker AVIII 600 NMR spectrometer. Mass spectra were measured by LC-MS apparatus Agilent 1200–6310. X-ray single crystal structure was

performed on a Bruker SMART APEX II CCD diffractometer. The OD was measured on a microplate spectrophotometer (Bio-Rad Model 680, USA).

2.3. *Synthesis of compounds*

The palladium(II)/platinum(II) complexes [Pd(en)(Tsile)]·H_2O (**1**), [Pd(bipy)(Tsile)] (**2**), [Pd(bipy)(Tsthr)]·0.5H_2O (**3**), [Pd(phen)(Tsile)]·0.5H_2O (**4**), [Pd(phen)(Tsthr)]·H_2O (**5**), [Pd(bqu)(Tsthr)]·1.5H_2O (**6**), [Pt(en)(Tsser)] (**7**), and [Pt(en)(Tsphe)]·H_2O (**8**) were prepared by reaction of [Pd(*NN*)Cl_2] (NN = en, bipy, phen or bqu) or [Pt(en)Cl_2] with 4-toluenesulfonyl-L-amino acids: $TsileH_2$, $TsthrH_2$, $TsserH_2$, or $TspheH_2$ in a mixture of CH_3OH/H_2O (see figure 1) [24].

2.3.1. 4-Toluenesulfonyl-L-amino acids. To a rapidly stirred solution of Ile (262 mg, 2.0 mM) in 5.0 mL H_2O was added 2.0 mL NaOH (1 M L^{-1}). 4-Toluenesulfonyl chloride (378 mg, 2.0 mM) was added to the solution. After that, 2.0 mL NaOH (1 M L^{-1}) was added dropwise over 0.5 h. After further 8 h, the solution was cooled by placing the flask on ice and acidified to pH = 3–4 with HCl monitored by universal pH test strips. The resulting white precipitate was filtered. The collected solid was washed with cold H_2O

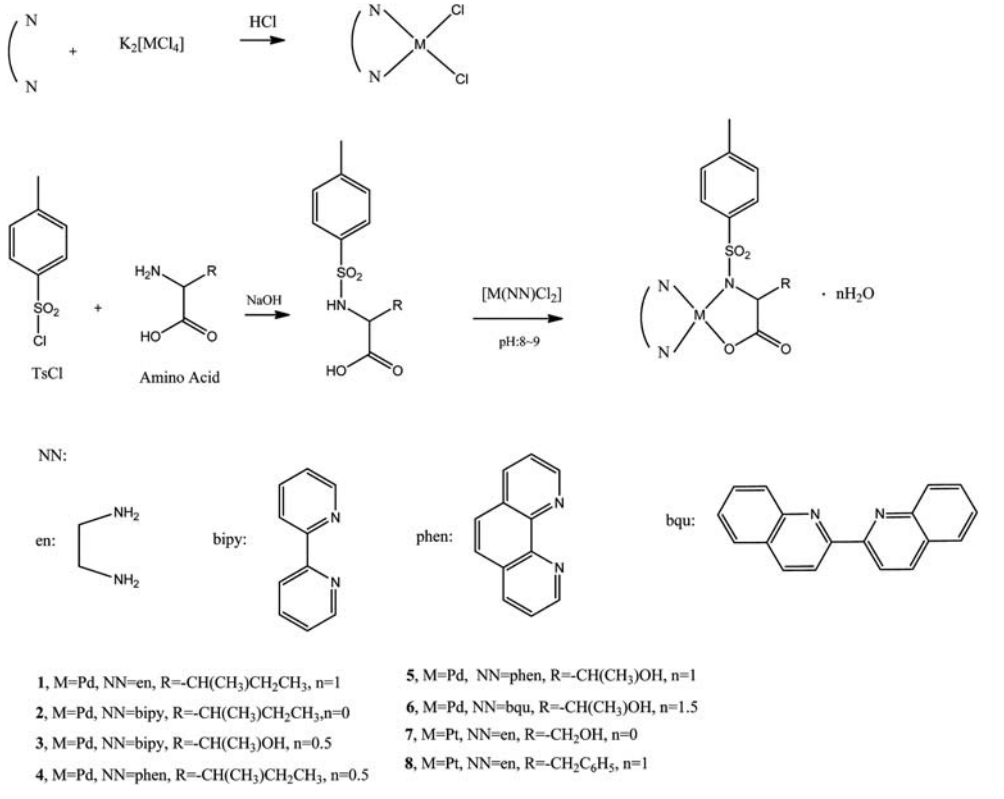

Figure 1. Synthetic schemes of **1–8**.

(50 mL) and dried to give $TsileH_2$. $TsileH_2$: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.95 (s, 1H, COOH), 7.72 (d, J = 8.1 Hz, 2H, ArH), 7.27 (d, J = 8.3 Hz, 2H, ArH), 5.32 (d, J = 9.7 Hz, 1H, NH), 3.82 (dd, J = 9.7, 4.9 Hz, 1H, NCH), 1.18 (m, 1H, CH), 1.39 (m, 1H, CH_2), 1.14 (m, 1H, CH_2), 0.90 (d, J = 6.8 Hz, 3H, CH_3), 0.86 (t, J = 7.4 Hz, 3H, CH_3).

$TsthrH_2$, $TsserH_2$, and $TspheH_2$ were carried out in a similar manner. $TsthrH_2$: ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.53 (s, 1H, COOH), 7.68 (d, J = 8.3 Hz, 2H, ArH), 7.53 (d, J = 9.2 Hz, 1H, NH), 7.34 (d, J = 8.4 Hz, 2H, ArH), 3.96 (qd, J = 6.3, 3.8 HZ, 1H, CH), 3.64 (m, 1H, CH), 2.37 (s, 3H, CH_3), 1.01 (d, J = 6.4 Hz, 3H, CH_3). $TsserH_2$: ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.89 (d, J = 8.6 Hz, 1H, NH), 7.68 (d, J = 7.9 Hz, 2H, ArH), 7.35 (d, J = 7.9 Hz, 2H, ArH), 3.73 (m, 1H, CH), 3.49 (m, 2H, CH_2), 2.37 (s, 3H, CH_3). $TspheH_2$: ^{1}H NMR (600 MHz, DMSO-d_6) δ *12*.67 (s, 1H, COOH), 8.18 (d, J = 5.0 Hz, 1H, NH), 7.09 (m, 2H, ArH), 7.19 (m, 5H, ArH), 7.12 (s, 2H, ArH), 3.86 (m, 1H, CH), 2.93 (m, 1H, CH_2), 2.72 (m, 1H, CH_2), 2.34 (s, 3H, CH_3).

2.3.2. Precursor complexes [M(*NN*)Cl_2]. Precursor complexes [Pd(en)Cl_2] (i), [Pd(bipy)Cl_2] (ii), [Pd(phen)Cl_2] (iii), [Pd(bqu)Cl_2] (iv), and [Pt(en)Cl_2] (v) were synthesized according to a published procedure [25].

2.3.3. [Pd(en)(Tsile)]·H_2O (1). A 3 mL CH_3OH/H_2O (volume 1:1) solution of $TsileH_2$ (34 mg, 0.12 mM) was heated to 48 °C, and then [Pd(en)Cl_2] (14 mg, 0.06 mM) was added to the solution. The mixture was adjusted to pH = 9 by NaOH solution monitored by universal pH test strips and stirred for 2 h. Then, the solution was transferred into a 10 mL test tube and the test tube was capped by polypropylene film with a few pierced holes. By evaporating the solution at room temperature, a yellow solid was obtained after a few weeks. Complex **1** was separated from the solution. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.01 (d, J = 8.1 Hz, 2H, ArH), 7.31 (d, J = 8.0 Hz, 2H, ArH), 4.99 (m, 1H, NH_2), 4.87 (m, 1H, NH_2), 4.77 (d, J = 4.8 Hz, 1H, NH_2), 4.26 (m, 1H, NH_2), 3.27 (d, J = 3.7 Hz, 1H, CH), 2.45 (m, 2H, CH_2), 2.36 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 1.65 (m, 2H, CH_2), 1.42 (m, 1H, CH), 1.11 (d, J = 6.6 Hz, 3H, CH_3), 0.85 (t, J = 7.2 Hz, 3H, CH_3). ESI-MS: 472.5[M + Na]$^+$. Anal. Calcd for $C_{15}H_{27}N_3O_5PdS$ (%): C, 38.51; H, 5.82; N, 8.98. Found (%): C, 38.20; H, 5.74; N, 9.15.

2.3.4. [Pd(bipy)(Tsile)] (2). The synthesis of **2** was carried out in a similar manner to **1** starting from [Pd(bipy)Cl_2] (20 mg, 0.06 mM) and $TsileH_2$ (34 mg, 0.12 mM). Yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.34 (d, J = 5.6 Hz, 1H, ArH), 8.59 (d, J = 5.4 Hz, 1H, ArH), 8.28 (t, J = 6.4 Hz, 1H, ArH), 8.26 (t, J = 7.5 HZ, 1H, ArH), 8.12 (d, J = 8.2 Hz, 2H, ArH), 8.07 (m, 2H, ArH), 7.64 (ddd, J = 7.2, 5.6, 1.3 Hz, 1H, ArH), 7.57 (ddd, J = 7.2, 5.5, 1.6 Hz, 1H, ArH), 7.26 (d, J = 7.9 Hz, 2H, ArH), 3.73 (d, J = 5.3 Hz, 1H, CH), 2.39 (s, 3H, CH_3), 2.08 (m, 2H, CH_2), 1.66 (m, 1H, CH), 1.15 (d, J = 6.7 Hz, 3H, CH_3), 0.92 (t, J = 7.3 Hz, 3H, CH_3). ESI-MS: 568.1[M + Na]$^+$. Anal. Calcd for $C_{23}H_{25}N_3O_4PdS$ (%): C, 50.60; H, 4.62; N, 7.70. Found (%): C, 50.68; H, 4.46; N, 7.79.

2.3.5. [Pd(bipy)(Tsthr)]·0.5H_2O (3). The synthesis of **3** was carried out in a similar manner to **1** starting from [Pd(bipy)Cl_2] (20 mg, 0.06 mM) and $TsthrH_2$ (33 mg, 0.12 mM).

Yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.08 (dd, J = 5.6, 1.2 Hz, 1H, ArH), 8.60 (d, J = 8.1 Hz, 1H, ArH), 8.54 (d, J = 8.0 Hz, 1H, ArH), 8.36 (m, 2H, ArH), 8.29 (d, J = 5.4 Hz, 1H, ArH), 7.94 (d, J = 8.2 Hz, 2H, ArH), 7.86 (ddd, J = 7.2, 5.7, 1.1 Hz, 1H, ArH), 7.79 (ddd, J = 6.9, 3.3, 1.0 Hz, 1H ArH), 7.27 (d, J = 8.0 Hz, 2H, ArH), 4.79 (d, J = 5.5 Hz, 1H, OH), 3.99 (m, 1H, CH), 2.35 (s, 3H, CH_3), 1.11 (d, J = 6.3 Hz, 3H, CH_3). ESI-MS: 556.0$[M+Na]^+$. Anal. Calcd for $C_{21}H_{22}N_3O_{5.5}PdS$ (%): C, 46.46; H, 4.08; N, 7.74. Found (%): C, 46.80; H, 3.81; N, 7.51.

2.3.6. [Pd(phen)(Tsile)]·0.5H_2O (4). The synthesis of **4** was carried out in a similar manner to 1 starting from [Pd(phen)Cl_2] (21 mg, 0.06 mM) and TsileH_2 (34 mg, 0.12 mM). Yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.71 (d, J = 5.1 Hz, 1H, ArH), 8.93 (d, J = 4.9 Hz, 1H, ArH), 8.63 (dd, J = 15.0, 8.2 Hz, 2H, ArH), 8.17 (d, J = 7.9 Hz, 2H, ArH), 8.06 (m, 2H, ArH), 7.98 (dd, J = 8.0, 5.4 Hz, 1H, ArH), 7.88 (dd, J = 8.1, 5.1 Hz, 1H, ArH), 7.23 (d, J = 7.9 Hz, 2H, ArH), 3.87 (d, J = 5.1 Hz, 1H, CH), 2.36 (s, 3H, CH_3), 2.15 (m, 2H, CH_2), 1.77 (m, 1H, CH), 1.25 (d, J = 6.5 Hz, 3H, CH_3), 0.95 (t, J = 7.2 Hz, 3H, CH_3). ESI-MS: 592.1$[M+Na]^+$. Anal. Calcd for $C_{25}H_{26}N_3O_{4.5}PdS$ (%): C, 51.86; H, 4.53; N, 7.26. Found (%): C, 51.67; H, 4.41; N, 7.36.

2.3.7. [Pd(phen)(Tsthr)]·H_2O (5). The synthesis of **5** was carried out in a similar manner to **1** starting from [Pd(phen)Cl_2] (21 mg, 0.06 mM) and TsthrH_2 (33 mg, 0.12 mM). Yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.40 (m, 1H, ArH), 8.95 (m, 2H, ArH), 8.62 (m, 1H, ArH), 8.23 (m, 3H, ArH), 8.08 (m, 1H, ArH), 8.00 (d, J = 8.1 Hz, 2H, ArH), 7.28 (d, J = 8.1 Hz, 2H, ArH), 4.83 (s, 1H, OH), 4.00 (m, 1H, CH), 3.45 (d, J = 3.5 Hz, 1H, CH), 2.35 (s, 3H, CH_3), 1.18 (d, J = 6.3 Hz, 3H, CH_3). ESI-MS: 582.2$[M+Na]^+$. Anal. Calcd for $C_{23}H_{23}N_3O_6PdS$ (%): C, 47.97; H, 4.03; N, 7.30. Found (%): C, 47.86; H, 3.83; N, 6.89.

2.3.8. [Pd(bqu)(Tsthr)]·1.5H_2O (6). The synthesis of **6** was carried out in a similar manner to **1** starting from [Pd(bqu)Cl_2] (26 mg, 0.06 mM) and TsthrH_2 (33 mg, 0.12 mM). Yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.66 (d, J = 8.4 Hz, 1H, ArH), 9.05 (d, J = 8.7 Hz, 1H, ArH), 8.99 (d, J = 8.6 Hz, 1H, ArH), 8.90 (d, J = 8.7 Hz, 1H, ArH), 8.82 (d, J = 8.6 Hz, 1H, ArH), 8.65 (d, J = 8.8 Hz, 1H, ArH), 8.19 (dd, J = 15.0, 8.0 Hz, 2H, ArH), 7.86 (m, 4H, ArH), 7.38 (d, J = 8.1 Hz, 2H, ArH), 7.06 (d, J = 8.1 Hz, 2H, ArH), 5.71 (d, J = 3.0 Hz, 1H, OH), 4.25 (m, 1H, CH), 3.31 (d, J = 1.5 Hz, 1H, CH), 2.21 (s, 3H, CH_3), 1.22 (d, J = 6.3 Hz, 3H, CH_3). ESI-MS: 632.1$[M+Na]^+$. Anal. Calcd for $C_{29}H_{28}N_3O_{6.5}PdS$ (%): C, 52.69; H, 4.27; N, 6.36. Found (%): C, 52.59; H, 3.96; N, 6.38.

2.3.9. [Pt(en)(Tsser)] (7). The synthesis of **7** was carried out in a similar manner to **1** starting from [Pt(en)Cl_2] (19 mg, 0.06 mM) and TsserH_2 (31 mg, 0.12 mM). White solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.04 (d, J = 8.2 Hz, 2H, ArH), 7.31 (d, J = 7.9 Hz, 2H, ArH), 5.58 (m, 2H, NH_2), 5.43 (m, 1H, NH_2), 4.98 (m, 1H, NH_2), 4.11 (m, 1H, OH), 3.66 (m, 1H, CH_2), 3.57 (m, 1H, CH_2), 3.42 (m, 1H, CH), 2.36 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.29 (m, 2H, CH_2). ESI-MS: 511.5$[M+Na]^+$. Anal. Calcd for $C_{12}H_{19}N_3O_5PtS$ (%): C, 28.13; H, 3.74; N, 8.20. Found (%): C, 28.32; H, 3.65; N, 8.11.

2.3.10. [Pt(en)(Tsphe)]·H_2O (8). The synthesis of **8** was carried out in a similar manner to **1** starting from [Pt(en)Cl_2] (19 mg, 0.06 mM) and TspheH_2 (38 mg, 0.12 mM). White solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.01 (d, J = 8.2 Hz, 2H, ArH), 7.26 (m, 6H, ArH), 7.17 (m, 1H, ArH), 5.51 (m, 2H, NH_2), 5.26 (m, 1H, NH_2), 4.94 (m, 1H, NH_2), 3.62 (dd, J = 6.4, 5.1 Hz, 1H, CH), 2.99 (qd, J = 13.2, 5.8 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.30 (m, 2H, CH_2), 2.22 (m, 2H, CH_2). ESI-MS: 572.5[M + Na]$^+$. Anal. Calcd for $C_{18}H_{25}N_3O_5PtS$ (%): C, 36.61; H, 4.27; N, 7.12. Found (%): C, 36.90; H, 4.44; N, 7.09.

2.4. *Data collection and structural refinement of 7*

Data collection for **7** was performed on a Bruker SMART APEX II CCD diffractometer equipped with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at 296(2) K. Multi-scan absorption corrections were applied using SADABS. The structure was solved by the direct method using SHELX-97. Full-matrix least-squares refinement on F^2 was performed using SHELXL-97 with anisotropic thermal parameters for all nonhydrogen atoms. Table 1 lists the crystallographic details. Crystallographic data for structural analysis of 7 have been deposited with the Cambridge Crystallographic Data Center, CCDC – 838,825. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax:+44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

2.5. *Cell culture*

Four different human carcinoma cell lines: HL-60, Bel-7402, BGC-823, and KB were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum, 100 units/mL of

Table 1. Crystallographic data for **7**.

Formula	$C_{12}H_{19}N_3O_5PtS$
Fw	512.45
T(K)	296(2)
Cryst. syst.	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	7.900(3)
b (Å)	10.788(4)
c (Å)	17.561(7)
V (Å^3)	1496.6(1)
Z	4
Dc (Mg m^{-3})	2.275
F(000)	984
Cryst. dimens. (mm)	0.56 × 0.45 × 0.41
θ Range (°)	2.22–28.48
	$-10 < h < 9$
	$-13 < k < 14$
hkl Ranges	$-23 < l < 22$
Data/parameters	3759/202
Goodness-of-fit on F^2	1.121
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0319; wR_2 = 0.0849

penicillin, and 100 µg/mL of streptomycin. Cells were maintained at 37 °C in a humidified atmosphere of 5% CO_2 in air.

2.6. *Solutions*

The complexes were dissolved in DMSO at 5 mM and diluted in culture medium at 1.0, 10, 100, and 500 µM as working-solutions. To avoid DMSO toxicity, the concentration of DMSO was less than 0.1% (v/v) in all experiments.

2.7. *Cytotoxicity analysis*

The cells harvested from exponential phase were seeded equivalently into a 96-well plate, and then, the complexes were added to the wells to achieve the final concentrations. Control wells were prepared by addition of culture medium. Wells containing culture medium without cells were used as blanks. All experiments were performed in quintuplicate. The MTT assay was performed as described by Mosmann for HL-60 [26]. Upon completion of the incubation for 44 h, stock MTT dye solution (20 mL, 5 mg/mL) was added to each well. After 4 h incubation, 2-propanol (100 mL) was added to solubilize the MTT formazan. The OD of each well was measured on a microplate spectrophotometer at 570 nm. The SRB assay was performed as previously described for Bel-7402, BGC-823, and KB [27]. Upon completion of the incubation for 44 h, the cells were fixed in 10% aqueous trichloroacetic acid (100 mL) for 30 min at 4 °C, washed five times with water and stained with 0.1% aqueous SRB in 1% aqueous acetic acid (100 mL) for 15 min. The cells were washed four times in 1% acetic acid and air-dried. The stain was solubilized in 10 mM of unbuffered Tris base (100 mL) and OD was measured at 540 nm as above. The IC_{50} value was determined from a plot of % viability against dose of compounds added.

3. Results and discussion

3.1. *Synthesis and characterization*

Elemental analysis data of **1–8** are in agreement with calculated values. Mass spectra of **1–8** have molecular ion peaks. These experimental results provide support for the suggested composition and structures of the complexes.

Although the overall patterns of the ^{1}H NMR spectra of **1–8** resemble the free ligands, the signals shift upon coordination. TsileH$_2$ shows a doublet at $\delta = 5.32$, which is associated with the proton of the sulfonamide group, but this peak disappears for **4**, which shows that the sulfonamide group has been deprotonated. The methylene ^{1}H resonances (amino acid) shift downfield as a result of deprotonated sulfonamide nitrogen coordinating to Pd(II). The α-hydrogen of TsileH$_2$ appears as a *dd*, but this proton appears as a doublet in **4**, which also shows deprotonation of sulfonamide (figures 2 and 3). ^{1}H NMR spectra of **1**, **2**, **3**, **5**, **6**, **7**, and **8** are similar to that of **4**. These observations further confirm that the sulfonamide group coordinates to platinum(II)/palladium(II) through deprotonated sulfonamide nitrogen.

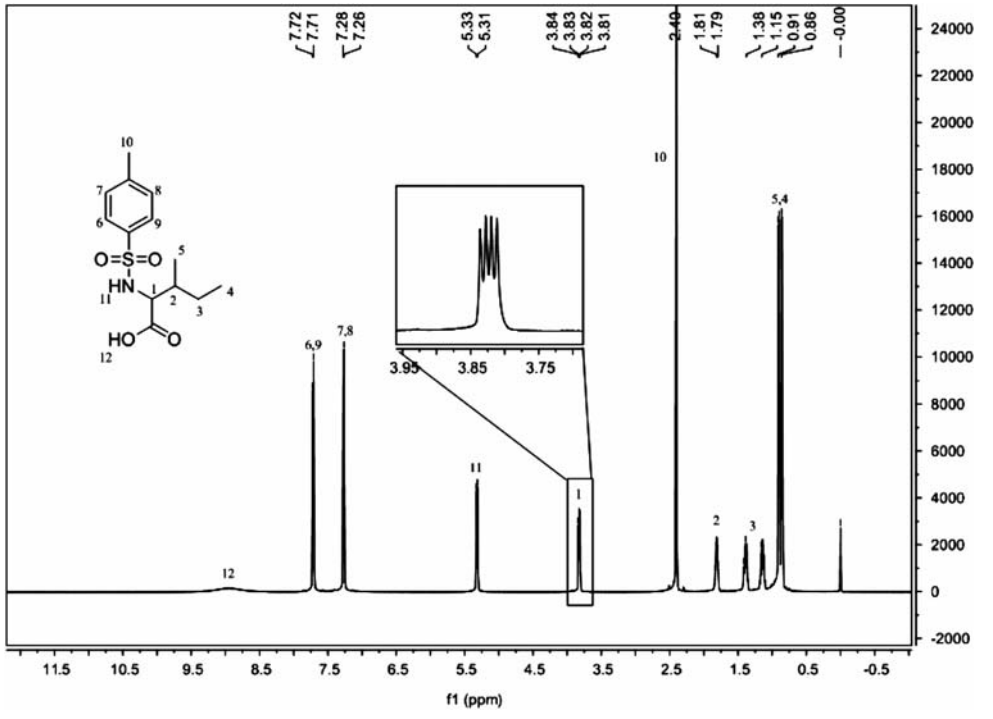

Figure 2. ^{1}H NMR spectrum of $TsileH_2$ in $CDCl_3$.

3.2. *Structural studies*

A view of the molecular structure of [Pt(en)(Tsser)] (**7**) is shown in figure 4. Selected bond lengths and angles are given in table 2. The platinum shows square-planar coordination by two nitrogens of en, one deprotonated sulfonamide nitrogen, and one carboxylic oxygen. The angle between planar O(1)–Pt(1)–N(1) and planar N(2)–Pt(1)–N(3) is 3.0(2)°, which indicates that the Pt(1)–O(1)–N(1)–N(2)–N(3) plane is slightly distorted. The Pt–N (deprotonated sulfonamide) bond length (2.027(6) Å) is similar to the Pt–N (en) bond lengths (2.034(6) and 2.030(6) Å), while it is longer than Pt–O (carboxylic oxygen) bond length (1.999(5) Å). Examination of the crystallographic packing diagram revealed several hydrogen bonds. To depict hydrogen bonds clearer, only a portion of the complex molecule is shown in figure 5. Hydrogens bound to $N3^{i}$ hydrogen bond to noncoordinated oxygen ($O2^{ii}$) of a neighboring unit (ii = $x+1/2$, $-y+1/2$, $-z$) and to the hydroxyl oxygen ($O2^{iii}$) of a different neighboring unit (iii = $-x$, $y+1/2$, $-z+1/2$). Hydrogen bound to $N2^{iv}$ of the neighboring unit (iv = $x+1/2$, y, z) hydrogen bond to noncoordinated $O2^{i}$. An intramolecular hydrogen bond with a length 2.2 Å was also observed between $O4^{i}$ and hydrogen from amine $N2^{i}$, and another intramolecular hydrogen bond is observed between $O3^{i}$ and the hydrogen from hydroxyl $O5^{i}$ at 2.3 Å. No π–π stacking was observed between the phenyl rings of the complex, which indicates that hydrogen bonds play an important role in crystal formation.

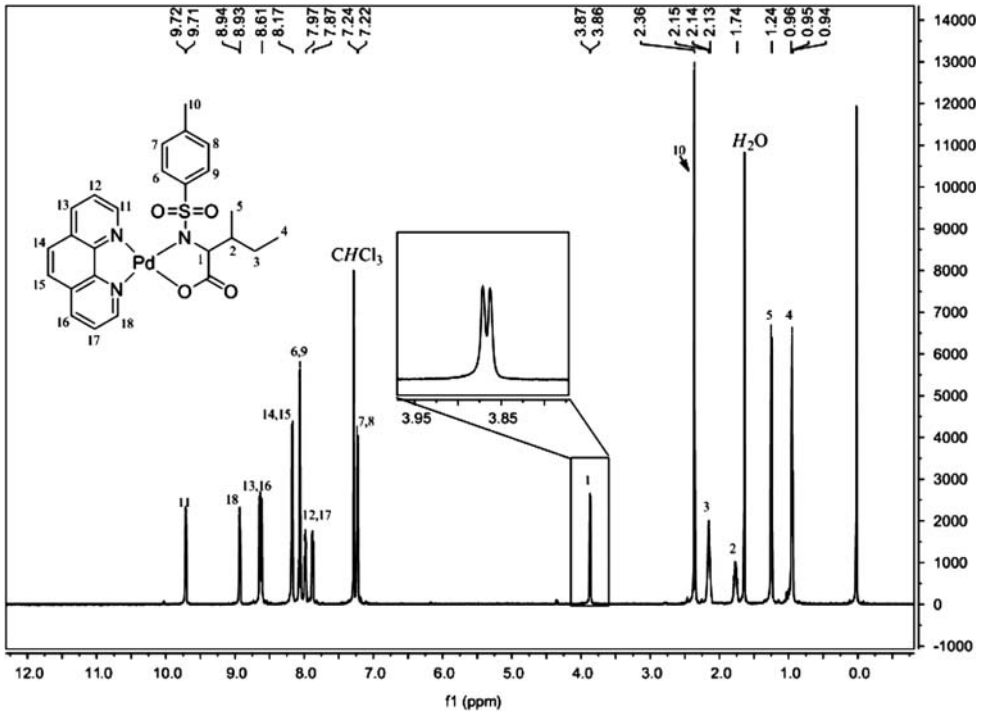

Figure 3. ^{1}H NMR spectrum of **4** in $CDCl_3$.

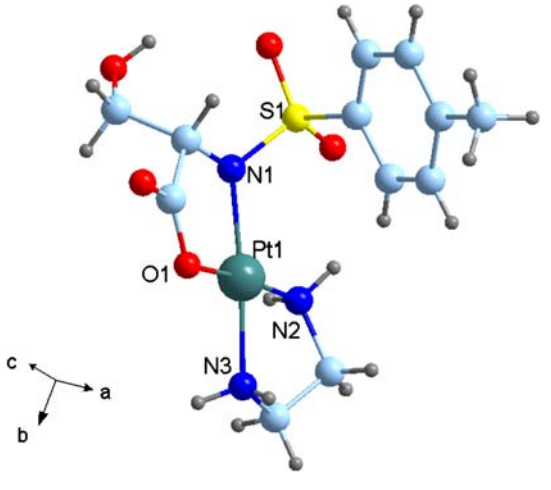

Figure 4. Molecular structure and partial atom-labeling scheme for 7.

3.3. *Cytotoxic studies*

Complexes 1–8 exert cytotoxicity against HL-60, Bel-7402, BGC-823, and KB cell lines (table 3) with 4 having the best cytotoxicity against HL-60, Bel-7402, and BGC-823 cell

Table 2. Selected bond lengths (Å) and angles (°) for **7**.

Bond length (Å)	Angles (°)
Pt(1)–N(1)	2.027(6)
Pt(1)–N(2)	2.034(6)
Pt(1)–N(3)	2.030(6)
Pt(1)–O(1)	1.999(5)
N(1)–Pt(1)–N(2)	102.3(2)
N(2)–Pt(1)–N(3)	82.2(2)
N(3)–Pt(1)–O(1)	92.3(2)
O(1)–Pt(1)–N(1)	83.3(2)
O(1)–Pt(1)–N(2)	174.2(2)
N(1)–Pt(1)–N(3)	174.9(2)

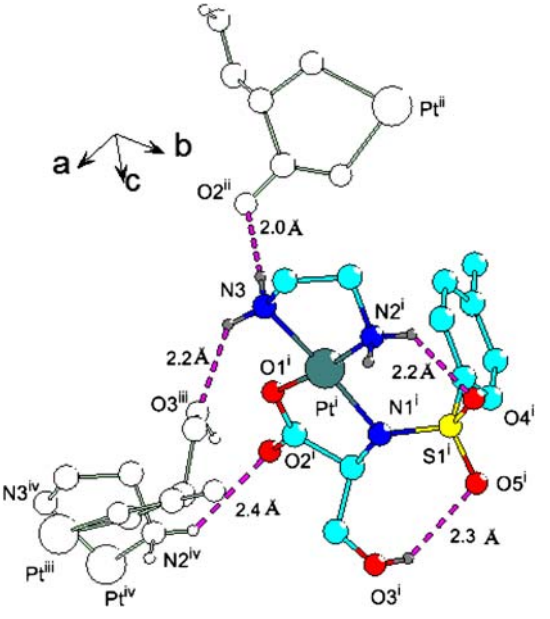

Figure 5. Inter and intra molecular hydrogen bonds in 7.

Table 3. The cytotoxicities of the complexes *in vitro* ($n = 5$).

	$IC_{50} \pm SD$ (μM)			
Complexes	HL-60	BGC-823	Bel-7402	KB
[Pd(en)(Tsile)]·H_2O (**1**)	15.89 ± 1.21	30.12 ± 2.08	29.76 ± 1.65	10.78 ± 1.06
[Pd(bipy)(Tsile)] (**2**)	18.66 ± 1.07	23.74 ± 1.23	44.52 ± 1.43	9.28 ± 1.07
[Pd(bipy)(Tsthr)]·0.5H_2O (**3**)	16.76 ± 1.08	25.78 ± 1.11	40.76 ± 1.45	6.54 ± 0.97
[Pd(phen)(Tsile)]·0.5H_2O (**4**)	9.20 ± 0.97	21.70 ± 2.08	18.01 ± 1.32	6.08 ± 0.87
[Pd(phen)(Tsthr)]·H_2O (**5**)	12.46 ± 1.05	23.45 ± 1.32	38.98 ± 2.08	5.98 ± 0.65
[Pd(bqu)(Tsthr)]·1.5H_2O (**6**)	16.54 ± 1.21	30.89 ± 1.34	30.76 ± 2.07	22.54 ± 1.23
[Pt(en)(Tsser)] (**7**)	13.43 ± 0.97	38.76 ± 2.43	31.56 ± 1.56	10.43 ± 1.34
[Pt(en)(Tsphe)]·H_2O (**8**)	12.43 ± 1.09	35.67 ± 1.43	30.21 ± 1.02	8.98 ± 0.96
Cisplatin[a]	2.89 ± 0.34	6.48 ± 0.81	8.12 ± 0.97	2.65 ± 0.33

[a]The IC_{50} (μM) values of Cisplatin were cited from our previous work [21].

lines, but the compounds are less cytotoxic than cisplatin. Recently, we reported cytotoxicities of a series of platinum(II)/palladium(II) complexes with 4-toluenesulfonyl-L-amino acid dianion and diimine/diamine [20–23]. These various studies indicate that amino acid side chain, the chelating diimine/diamine, and the central metal ion affect cytotoxicity, but the IC_{50} values do not show a definite correlation with variation of these parameters. In the present work, although we might expect to see cytotoxic dependencies on the nature of the amino acid side chain, the chelating diimine/diamine, and the central metal ion, no obvious trends are observed.

4. Conclusions

We have synthesized and characterized eight new palladium(II)/platinum(II) complexes with 4-toluenesulfonyl-L-amino acid dianions and diimine/diamine. Of these complexes, 4 have the best cytotoxicity against HL-60, Bel-7402, and BGC-823 cell lines, but none of the eight complexes are more cytotoxic than cisplatin. While one might expect to see cytotoxic dependencies on the nature of the amino acid side chain, the chelating diimine/diamine, and the central metal ion, no obvious trends are observed.

Acknowledgements

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