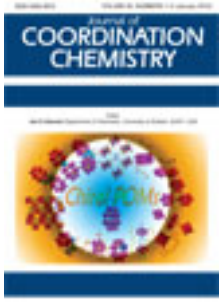

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# Synthesis, characterization, and biological activity of five new mixed-ligand palladium(II) complexes with ethylenediamine and 4-toluenesulfonyl-*L*-amino acid dianion

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Five new palladium(II) complexes with 4-toluenesulfonyl-*L*-amino acid dianion and en, [Pd(en)(TsserNO)] (**1**), [Pd(en)(TsglyNO)] (**2**), [Pd(en)(TsalaNO)]·1.5$H_2O$ (**3**), [Pd(en)(TsleuNO)]·$H_2O$ (**4**), and [Pd(en)(TspheNO)]·2$H_2O$ (**5**), have been synthesized and characterized by elemental analysis, IR, UV, $^1$H NMR, and mass spectrometry. Crystal structure of **1** has been determined by X-ray diffraction analysis. The cytotoxicity was tested by MTT and SRB assays. The results indicate **1**–**5** exert cytotoxic effects against HL-60, Bel-7402, BGC-823, and KB cell lines and **5** displays the best cytotoxicity. The structure–activity relationships suggest that both amino acid and N-containing ligands have important effects on cytotoxicity.

*Keywords*: Palladium(II) complexes; 4-Toluenesulfonyl-*L*-amino acid; Ethylenediamine; Cytotoxicity



## 1. Introduction

Cisplatin is one of the most successful antineoplastic drugs; carboplatin and oxaliplatin have also received worldwide approval. Nedaplatin, lobaplatin, and heptaplatin have gained regionally limited approval and a few platinum drugs continue to be evaluated in clinical trials. Regardless of the achievements of current platinum drugs, they have several major drawbacks, including cumulative toxicities of nephrotoxicity and ototoxicity [1–5]. Besides the serious side effects, the therapeutic efficacy is also limited by inherent or treatment-induced resistant tumor cells. These drawbacks have provided the motivation for alternative chemotherapeutic strategies [6, 7].

Due to the structural and thermodynamic similarity between platinum(II) and palladium(II) complexes, there is increased interest in palladium(II) derivatives as potential anticancer drugs [8–13]. Ligands like pyridine, quinoline, phenanthroline, and their derivatives have been widely used in metal-based anticancer drugs because they have the ability to participate as DNA intercalators. Numerous palladium complexes with aromatic N-containing ligands are effective against tumors. It was reported that

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three planar palladium complexes *trans*-[$PdCl_2L_2$] (where L = 3-hydroxypyridine, 2-hydroxypyridine and 4-hydroxypyridine) might be able to overcome resistance of cisplatin [14]. Owing to higher lability of palladium *versus* platinum analogs, amino acid ligands, which do not dissociate easily in aqueous solution, have been used to synthesize palladium anticancer complexes [15]. The synthesis and cytotoxicity of nine palladium(II) complexes $[Pd(phen)(AA)]^+$ (where AA is an anion of *L*-gly, ala, leu, phe, tyr, try, val, pro, or ser) were previously reported [16]. The palladium(II) complexes exhibit growth inhibition of P388 lymphocytic leukemic cells. The $IC_{50}$ values of the palladium(II) complexes with gly and val are comparable to that of cisplatin, whereas the other palladium(II) complexes show higher $IC_{50}$ values [16]. We previously reported the synthesis and cytotoxicity of eight palladium(II) complexes with 4-toluenesulfonyl-*L*-amino acid dianion and aromatic N-containing ligands. The complexes had cytotoxic effects and selectivity against BGC-823, Bel-7402, KB, and HL-60 cell lines [17]. Clinically used platinum-based anticancer drugs have aliphatic N-containing ligands as carrier groups, but the cytotoxicity of mixed-ligand palladium(II) complexes with aliphatic N-containing ligands and 4-toluenesulfonyl-*L*-amino acid dianions has not been reported. To further explore the structure–activity relationships and discover new metal-based anticancer drugs, the synthesis, characterization, and cytotoxicities of five new palladium(II) complexes (**1**–**5**) with 4-toluenesulfonyl-*L*-amino acid dianion and en are described in this work.



## 2. Experimental

### 2.1. *Materials*

4-Toluenesulfonyl chloride and $K_2[PdCl_4]$ were of chemical grade; en was of analytical grade. Commercially pure ser, gly, ala, leu, and phe were purchased from Sigma. RPMI-1640 medium, trypsin, and fetal bovine serum were purchased from Gibco. MTT, 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 an Elementar Vario EL III elemental analyzer. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Electronic spectra in DMF were measured on a UV-3400 Toshniwal spectrophotometer. IR spectra were recorded on a Perkin-Elmer Model-683 spectrophotometer using KBr pellets. $^1H$ NMR spectra were recorded on a Bruker AVIII 600 NMR spectrometer. Mass spectra were measured by LC-MS Agilent 1200–6310. The single-crystal X-ray structure was performed on a Bruker SMART APEX II CCD diffractometer. The OD was measured on a microplate spectrophotometer (Bio-Rad Model 680, USA).

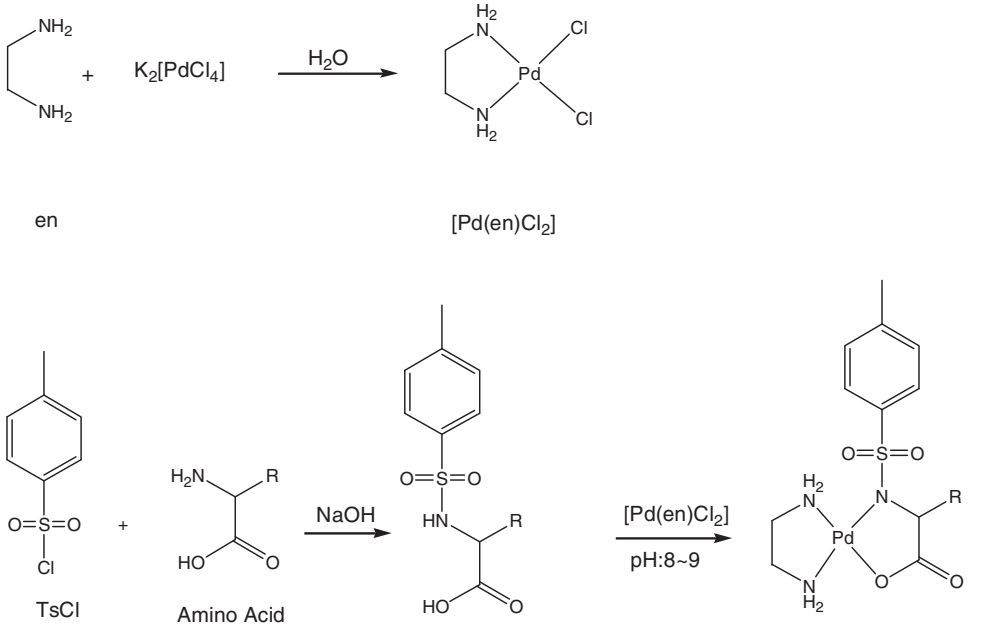


Figure 1. The synthetic routes of **1**–**5**.
**1**: R = –$CH_2OH$; **2**: R = –H; **3**: R = –$CH_3$; **4**: R = –$CH_2CH(CH_3)_2$; **5**: R = –$CH_2(C_6H_5)$.



### 2.3. *Synthesis of compounds*

[Pd(en)(TsserNO)] (**1**), [Pd(en)(TsglyNO)] (**2**), [Pd(en)(TsalaNO)] · 1.5$H_2O$ (**3**), [Pd(en)(TsleuNO)] · $H_2O$ (**4**), and [Pd(en)(TspheNO)] · 2$H_2O$ (**5**) have been prepared by the reaction of [Pd(en)$Cl_2$] with 4-toluenesulfonyl-*L*-amino acids: Tsser$H_2$, Tsgly$H_2$, Tsala$H_2$, Tsleu$H_2$, or Tsphe$H_2$ in a mixture of $CH_3OH/H_2O$ (figure 1).

**2.3.1. 4-Toluenesulfonyl-L-amino acids.** To a rapidly stirred solution of ser (273 mg, 2.6 mmol) in 5.0 mL · $H_2O$ was added 2.6 mL NaOH (1 mol $L^{-1}$). 4-Toluenesulfonyl chloride (500 mg, 2.6 mmol) was added to the solution and then 2.6 mL NaOH (1 mol $L^{-1}$) was added dropwise over 0.5 h. After further 8 h, the solution was cooled by ice and acidified to pH = 3–4 with HCl solution. The resulting white precipitate was collected by filtration, washed with cold $H_2O$ (50 mL), and dried to give Tsser$H_2$. Tsser$H_2$: m.p.: 223.9–224.9°C. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta_{(ppm)}$ 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), 3.80–3.69 (m, 1H, CH), 3.53–3.45 (m, 2H, $CH_2$), 2.37 (s, 3H, $CH_3$).

Tsgly$H_2$, Tsala$H_2$, Tsleu$H_2$, Tsphe$H_2$ were carried out in an identical manner. Tsgly$H_2$: m.p.: 149.2–150.8°C. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta_{(ppm)}$ 7.97 (t, $J$ = 6.1 Hz, 1H, NH), 7.68 (d, $J$ = 8.2 Hz, 2H, ArH), 7.38 (d, $J$ = 8.2 Hz, 2H, ArH), 3.55 (s, 2H, $CH_2$), 2.38 (s, 3H, $CH_3$). Tsala$H_2$: m.p.: 133.2–135.4°C. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta_{(ppm)}$ 8.04 (d, $J$ = 8.3 Hz, 1H, NH), 7.67 (d, $J$ = 7.9 Hz, 2H, ArH), 7.37 (d, $J$ = 8.1 Hz, 2H, ArH), 3.78–3.69 (m, 1H, CH), 2.37 (s, 3H, $CH_3$), 1.14 (d, $J$ = 7.2 Hz, 3H, $CH_3$). Tsleu$H_2$: m.p.: 119.4–120.7°C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta_{(ppm)}$ 7.73 (d, $J$ = 8.3 Hz, 2H, ArH), 7.28 (d, $J$ = 8.0 Hz, 2H, ArH), 5.33 (d, $J$ = 9.7 Hz,

1H, NH), 3.84–4.00 (m, 1H), 2.41 (s, 3H, $CH_3$), 1.68–1.83 (m, 1H, CH), 1.59–1.42 (m, 2H, $CH_2$), 0.89 (d, $J = 6.7$ Hz, 3H, $CH_3$), 0.81 (d, $J = 6.6$ Hz, 3H, $CH_3$). TspheH$_2$: m.p.: 150.4–152.9°C. $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta_{(ppm)}$ 8.18 (d, $J = 5.0$ Hz, 1H, NH), 7.15–7.05 (m, 2H, ArH), 7.36–7.16 (m, 5H, ArH), 7.12 (m, 2H, ArH), 3.82–3.92 (m, 1H, CH), 3.00–2.87 (m, 1H, $CH_2$), 2.83–2.66 (m, 1H, $CH_2$), 2.34 (s, 3H, $CH_3$).

**2.3.2. [Pd(en)Cl$_2$].** Precursor complex [Pd(en)Cl$_2$] was synthesized according to a published procedure [13]. Yield: 71.6%. Yellow solid. Anal. Calcd for $C_2H_8Cl_2N_2Pd$ (%): C, 10.12; H, 3.40; N, 11.80. Found (%): C, 10.20; H, 3.39; N, 11.64.



**2.3.3. [Pd(en)(TsserNO)] (1).** [Pd(en)Cl$_2$] (15 mg, 0.063 mmol) was added to a 6 mL $CH_3OH/H_2O$ (volume 1 : 1) solution of TsserH$_2$ (33 mg, 0.126 mmol), the mixture was adjusted to pH = 8–9 by NaOH solution, then heated to 48°C and stirred for 3 h. The solution was concentrated to about 80% of the original volume by reduced pressure distillation. By evaporating the concentrated solution at room temperature, yellow crystals suitable for X-ray diffraction were obtained after a few weeks and separated from the solution. Yield: 61.9%. Yellow solid. IR (KBr, cm$^{-1}$): 1623, 1361, 587, 477. $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta_{(ppm)}$ 8.02 (d, $J = 8.1$ Hz, 2H, ArH), 7.34 (d, $J = 8.1$ Hz, 2H, ArH), 5.10–4.80 (m, 2H, $NH_2$), 4.50–4.20 (m, 2H, $NH_2$), 3.74–3.68 (t, $J = 3.71$ Hz, 1H, OH), 3.65–3.57 (m, 1H, $CH_2$), 3.57–3.52 (m, 1H, $CH_2$), 3.30–3.15 (t, $J = 4.8$ Hz, 1H, CH), 2.23–2.45 (m, 2H, $CH_2$), 2.38 (s, 3H, $CH_3$). ESI-MS: major peak: 448.0 $[M + Na]^+$; the relative abundance of isotope peaks match the expected values, i.e., 447.1, 448.0, and 450.0. Anal. Calcd for $C_{12}H_{19}N_3O_5PdS$ (%): C, 34.01; H, 4.52; N, 9.92. Found: C, 34.25; H, 4.43; N, 10.21.

The other four complexes, [Pd(en)(TsglyNO)] (**2**), [Pd(en)(TsalaNO)] · 1.5H$_2$O (**3**), [Pd(en)(TsleuNO)] · H$_2$O (**4**), and [Pd(en)(TspheNO)] · 2H$_2$O (**5**), were prepared in an identical manner.

[Pd(en)(TsglyNO)] (**2**): Yield: 58.0%. Yellow solid. IR (KBr, cm$^{-1}$): 1641, 1394, 587, 450. $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta_{(ppm)}$ 7.84 (d, $J = 8.2$ Hz, 2H, ArH), 7.31 (d, $J = 7.8$ Hz, 2H, ArH), 4.97–4.92 (m, 2H, $NH_2$), 4.72–4.65 (m, 2H, $NH_2$), 3.24 (s, 2H, $CH_2$), 2.44–2.39 (m, 2H, $CH_2$), 2.39–2.34 (m, 2H, $CH_2$), 2.36 (s, 3H, $CH_3$). ESI-MS: major peak: 416.0 $[M + Na]^+$; the relative abundance of isotope peaks match the expected values, i.e., 415.1, 416.0, and 418.0. Anal. Calcd for $C_{11}H_{17}N_3O_4PdS$ (%): C, 33.55; H, 4.35; N, 10.67. Found: C, 33.61; H, 4.39; N, 10.64.

[Pd(en)(TsalaNO)] · 1.5H$_2$O (**3**): Yield: 65.5%. Yellow solid. IR (KBr, cm$^{-1}$): 1603, 1372, 573, 404. $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta_{(ppm)}$ 7.98 (d, $J = 8.1$ Hz, 2H, ArH), 7.32 (d, $J = 7.9$ Hz, 2H, ArH), 5.05–4.80 (m, 2H, $NH_2$), 4.45–4.30 (m, 2H, $NH_2$), 3.31 (q, $J = 7.0$ Hz, 1H, CH), 2.48–2.40 (m, 2H, $CH_2$), 2.40–2.33 (m, 2H, $CH_2$), 2.38 (s, 3H, $CH_3$), 1.25 (d, $J = 7.0$ Hz, 3H, $CH_3$). ESI-MS: major peak: 430.5 $[M + Na]^+$; the relative abundance of isotope peaks match the expected values, i.e., 429.9, 430.5, and 430.9. Anal. Calcd for $C_{12}H_{19}N_3O_4PdS$ (%): C, 33.15; H, 5.10; N, 9.66. Found: C, 33.16; H, 4.80; N, 9.49.

[Pd(en)(TsleuNO)] · H$_2$O (**4**): Yield: 63.8%. Yellow solid. IR (KBr, cm$^{-1}$): 1641, 1368, 587, 442. $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta_{(ppm)}$ 8.00 (d, $J = 8.1$ Hz, 2H, ArH), 7.31 (d, $J = 7.9$ Hz, 2H, ArH), 5.04–4.85 (m, 2H, $NH_2$), 4.85–4.75 (m, 1H, $NH_2$), 4.35–4.22 (m, 1H, $NH_2$), 3.31 (dd, $J = 7.6$, 5.7 Hz, 1H, CH), 2.48–2.42 (m, 2H, $CH_2$), 2.42–2.32 (m, 2H, $CH_2$), 2.37 (s, 3H, $CH_3$), 1.99–1.90 (m, 1H, $CH_2$), 1.66–1.59 (m, 1H,

$CH_2$), 1.55–1.45 (m, 1 H, CH), 0.89 (d, $J = 6.7$ Hz, 3H, $CH_3$), 0.85 (d, $J = 6.6$ Hz, 3H, $CH_3$). ESI-MS: major peak: 472.1 $[M + Na]^+$; the relative abundance of isotope peaks match the expected values, i.e., 471.1, 472.1, and 474.1. Anal. Calcd for $C_{15}H_{27}N_3O_5PdS$ (%): C, 38.51; H, 5.82; N, 8.98. Found: C, 38.53; H, 5.73; N, 8.74.

[Pd(en)(TspheNO)] · $2H_2O$ (**5**): Yield: 71.4%. Yellow solid. IR (KBr, $cm^{-1}$): 1582, 1380, 567, 497. $^1H$ NMR (600 MHz, DMSO-$d_6$) $\delta_{(ppm)}$ 7.97 (d, $J = 8.1$ Hz, 2H, ArH), 7.54–7.09 (m, 7H, ArH), 4.90–4.70 (m, 2H, $NH_2$), 4.60–4.40 (m, 1H, $NH_2$), 4.40–4.20 (m, 1H, $NH_2$), 3.54 (t, $J = 5.4$ Hz, 1H, CH), 3.00–2.90 (m, 2H, $CH_2$), 2.45–2.33 (m, 2H, $CH_2$), 2.33–2.23 (m, 2H, $CH_2$), 2.34 (s, 3H, $CH_3$). ESI-MS: major peak: 506.0 $[M + Na]^+$, the relative abundance of isotope peaks match the expected values, i.e., 505.1, 506.0, and 508.0. Anal. Calcd for $C_{18}H_{27}N_3O_6PdS$ (%): C, 41.58; H, 5. 23; N, 8.08. Found: C, 41.75; H, 5.02; N, 7.86.

### 2.4. *X-ray structure determination of 1*

The data collection of **1** was performed on a Bruker SMART APEX II CCD diffractometer equipped with graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) at 296(2) K. Multi-scan absorption corrections were applied using SADABS. The structure was solved by direct methods using SHELXS-97. Refinements on $F^2$ were performed using SHELXL-97 by full-matrix least-squares with anisotropic thermal parameters for all non-hydrogen atoms. Table 1 lists crystallographic details.

### 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 per mL of penicillin and 100 μg · $mL^{-1}$ of streptomycin. Cells were maintained at 37°C in a humidified atmosphere of 5% $CO_2$ in air.

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

| | [Pd(en)TsserNO] |
|---|---|
| Empirical formula | $C_{12}H_{19}N_3O_5PdS$ |
| Formula weight | 423.76 |
| Temperature (K) | 296(2) |
| Crystal system | Orthorhombic |
| Space group | P2(1)2(1)2(1) |
| Unit cell dimension (Å) | |
| *a* | 7.9394(9) |
| *b* | 10.7939(13) |
| *c* | 17.753(2) |
| Volume ($nm^3$), *Z* | 1521.3(3), 4 |
| Calculated density (Mg $m^{-3}$) | 1.850 |
| *F*(000) | 856 |
| Crystal size ($mm^3$) | 0.55 × 0.46 × 0.35 |
| $\theta$ range for data collection (°) | 2.21–28.28 |
| *hkl* ranges | $-10 < h < 5$; $-14 < k < 14$; $-23 < l < 23$ |
| Data/parameters | 3715/202 |
| Goodness-of-fit on $F^2$ | 1.082 |
| Final *R* indices [$I > 2\sigma(I)$] | $R_1 = 0.0197$; $wR_2 = 0.0532$ |

### 2.6. *Solutions*

The complexes were dissolved in DMSO at a concentration of $5\,mmol \cdot L^{-1}$ as stock solution and diluted in culture medium at concentrations of 1.0, 10, 100, and $500\,\mu mol \cdot L^{-1}$ as working solutions. To avoid the cytotoxicity of DMSO, the concentration of DMSO was less than 0.1% (v/v) in all experiments.

### 2.7. *Cytotoxicity analysis*

Cells harvested from exponential phase were seeded equivalently into a 96-well plate, and then the complexes were added to the wells to achieve final concentrations. Control wells were prepared by the addition of culture medium. Wells containing culture medium without cells were used as blanks. All experiments were performed in quintuplicate. The MTT assay for HL-60 cell line was performed as described by Mosmann [18]. Upon completion of the incubation for 44 h, stock MTT dye solution (20 mL, $5\,mg \cdot mL^{-1}$) 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 assays for Bel-7402, BGC-823, and KB cell lines were performed as previously described [19]. Upon completion of the incubation for 44 h, the cells were fixed in 10% trichloroacetic acid (100 mL) for 30 min at 4°C, washed five times and stained with 0.1% SRB in 1% 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 $10\,mmol \cdot L^{-1}$ unbuffered Tris base (100 mL) and OD was measured at 540 nm as above. The $IC_{50}$ value was determined from plot of % viability against dose of the complexes added.

## 3. Results and discussion

### 3.1. *Characterization of the complexes*

Complex **1** was observed in the ESI-MS as singly charged $[M + Na]^+$ ion of $m/z$ 448.0. The experimental isotope patterns for this ion matches theoretical predictions (figure 2). ESI-MS of **2**–**5** are similar to that of **1**. These results provide evidence for the formation of **1**–**5**. In addition, there is good agreement between calculated and measured values for elemental analyses of **1**–**5**.

UV-Vis spectroscopy shows that 4-toluenesulfonyl-*L*-amino acids have shoulders at 267 and 273 nm. After formation of the complexes, the shoulders turn into a single peak at 267 nm. In addition, there is also a broad LMCT peak at 303–400 nm for the complexes, which further confirms the coordination of palladium(II) with en.

IR spectroscopy shows that the sulfonamide groups of $TsserH_2$, $TsglyH_2$, $TsalaH_2$, $TsleuH_2$, and $TspheH_2$ have a strong and sharp $\upsilon_{NH}$ at 3273–3280 $cm^{-1}$. These bands disappear for **1**–**5**, indicating that the sulfonamide groups have been deprotonated. This is further confirmed by the sulfonamide (I) shifting from ~1630 $cm^{-1}$ to ~1550 $cm^{-1}$ and the disappearance of the sulfonamide (II). New bands appear at 440–470 $cm^{-1}$ and 560–585 $cm^{-1}$, which are assigned to $\upsilon_{Pd-N}$ and $\upsilon_{Pd-NAr}$, respectively. The carboxylates of **1**–**5** show two bands, an intense antisymmetric carboxylate stretch

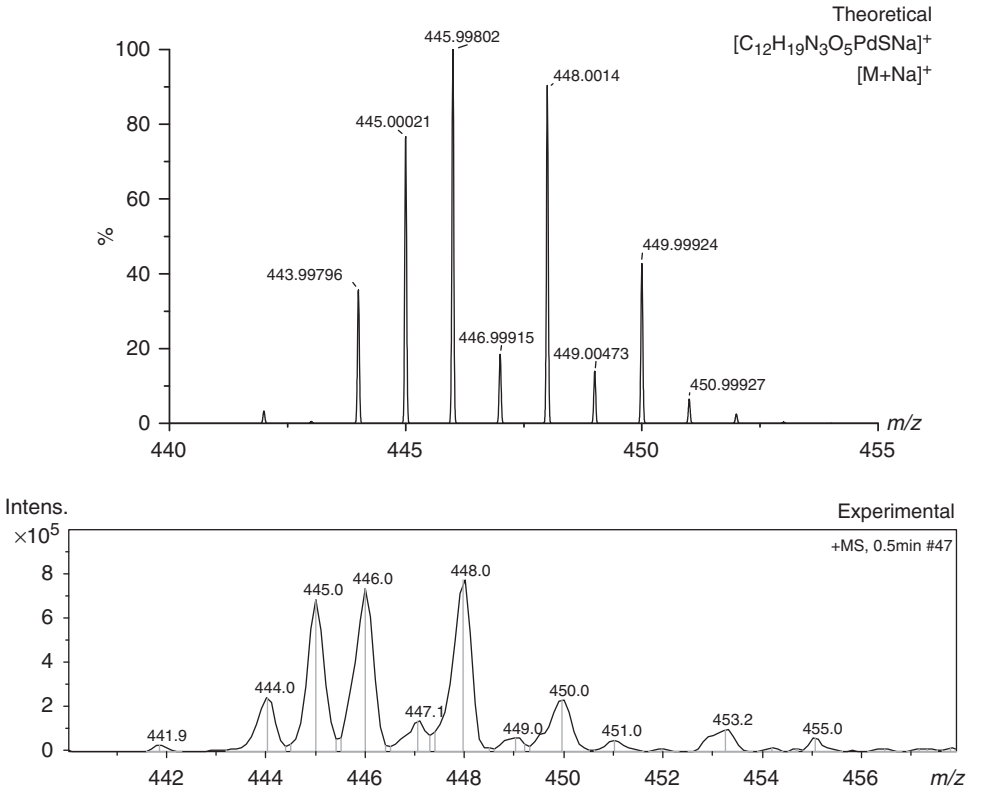


Figure 2. Experimental and theoretical isotope patterns of ESI-MS for **1**.

$\upsilon_{(as,\ coo-)}$ at 1620 $cm^{-1}$ and a symmetric carboxylate stretch $\upsilon_{(s,\ coo-)}$ at 1380 $cm^{-1}$. The values of $_{\Delta}\upsilon_{(coo-)}(\upsilon_{(as,\ coo-)}-\upsilon_{(s,\ coo-)})$ of **1**–**5** are in the range 210–260 $cm^{-1}$, which are greater than that of $_{\Delta}\upsilon_{(coo-)}$ of the corresponding sodium carboxylates, so the carboxylate group is monodentate [20]. This is further confirmed by the appearance of $\upsilon_{Pd-O}$. All the results are in agreement with the results revealed by X-ray crystal analysis.

$^1$H NMR spectra of the 4-toluenesulfonyl-*L*-amino acids are similar, $TsserH_2$, $TsglyH_2$, $TsalaH_2$, $TsleuH_2$, and $TspheH_2$ show a doublet at $\delta = 7.89$ ppm, a triplet at $\delta = 7.97$ ppm, a doublet at $\delta = 8.04$ ppm, a doublet at $\delta = 5.33$ ppm, and a doublet at $\delta = 8.18$ ppm, respectively, which are assigned to the proton of the sulfonamide. The protons of the aromatic ring appear at $\delta = 7.17$–$7.90$ ppm. Although the overall patterns of the $^1$H NMR spectra of **1**–**5** resemble very closely those of the free ligands, the signals shift upon coordination. For example, the proton of sulfonamide of $TsalaH_2$ shows a doublet at $\delta = 8.04$ ppm, while it disappears for **3**, showing deprotonation of the sulfonamide. The $\alpha$-hydrogen of $TsalaH_2$ is a multiplet, but this proton is a quartet in **3**, also supporting deprotonation of sulfonamide (figures 3 and 4). $^1$H NMR spectra of **1**, **2**, **4**, and **5** are similar to that of **3**. This provides further evidence that the sulfonamide coordinates to palladium(II) through deprotonated sulfonamide nitrogen.

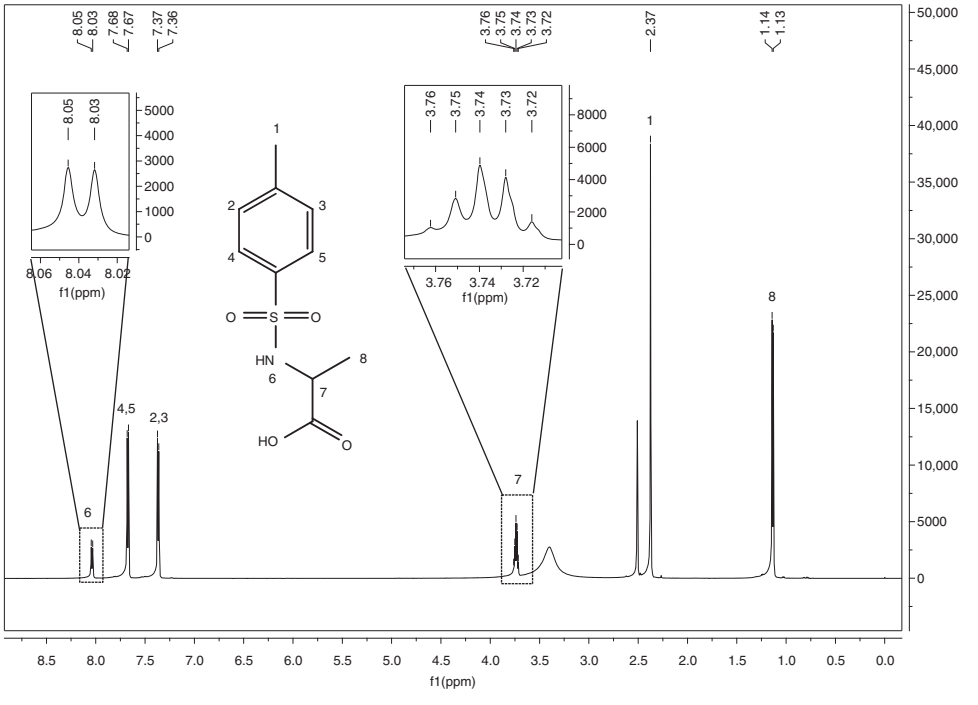


Figure 3. $^{1}$H NMR spectra of TsalaH$_2$ in DMSO-d$_6$.

### 3.2. *Structural studies*

A view of the molecular structure of [Pd(en)(TsserNO)] (**1**) is shown in figure 5. The selected bond lengths and angles are given in table 2. Palladium shows square-planar coordination by two nitrogen atoms of en, one deprotonated sulfonamide nitrogen atom, and one carboxylate oxygen atom in each molecule. The angle between planar N(1)–Pd(1)–N(2) and planar O(1) –Pd(1) –N(3) is 4.143(62)°, which indicates that the Pd(1)–O(1)–N(1)–N(2)–N(3) plane is slightly distorted. The Pd–N (deprotonated sulfonamide) length (2.029(2) Å) is similar to the lengths (2.0355(19) Å and 2.035(2) Å) of Pd–N (en) bonds and longer than (1.9989(17) Å) Pd–O (carboxylic oxygen). Sigel *et al*. reported that the coordination qualities of the deprotonated amide were "O-like" as the deprotonated amide group was isoelectronic with carboxylate; this has been confirmed by stability constants of some complexes [21]. Gong *et al*. also reported such coordination of deprotonated amide nitrogen [22]. According to our experimental results, the coordinating qualities of the deprotonated sulfonamide nitrogen might also be "O-like".

### 3.3. *Cytotoxic studies*

As listed in table 3, **1**–**5** display cytotoxic effects against tested carcinoma cell lines with a low $IC_{50}$ value ($< 50\,\mu mol \cdot L^{-1}$). Moreover, they have selectivity against tested carcinoma cell lines, but none of the complexes show higher cytotoxicity than cisplatin. The structure–activity relationships are summarized as follows: (1) the amino acids have

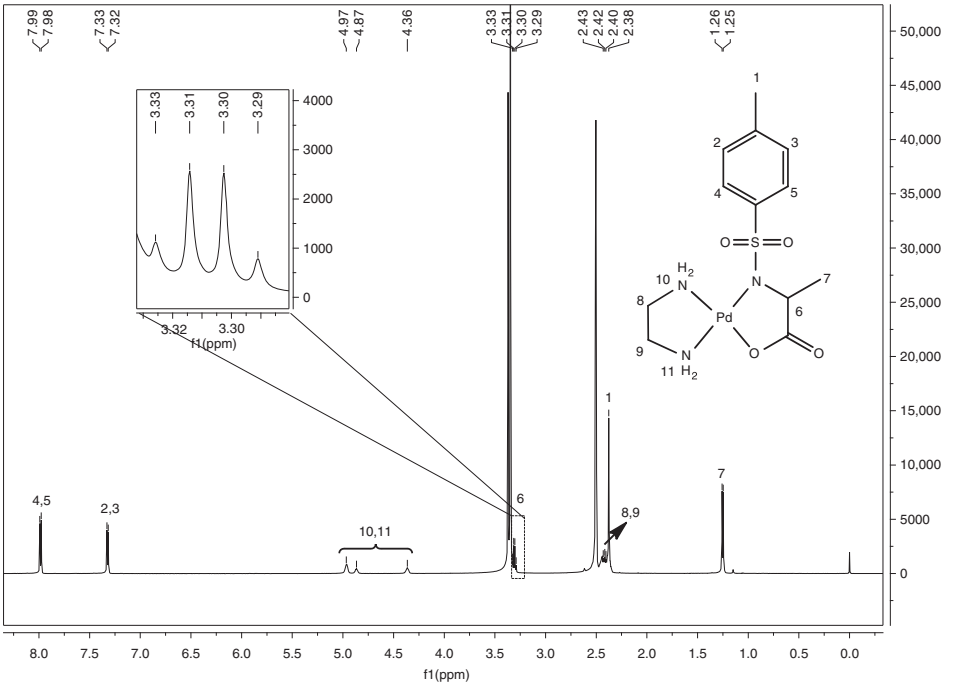


Figure 4. $^{1}$H NMR spectra of **3** in DMSO-$d_6$.

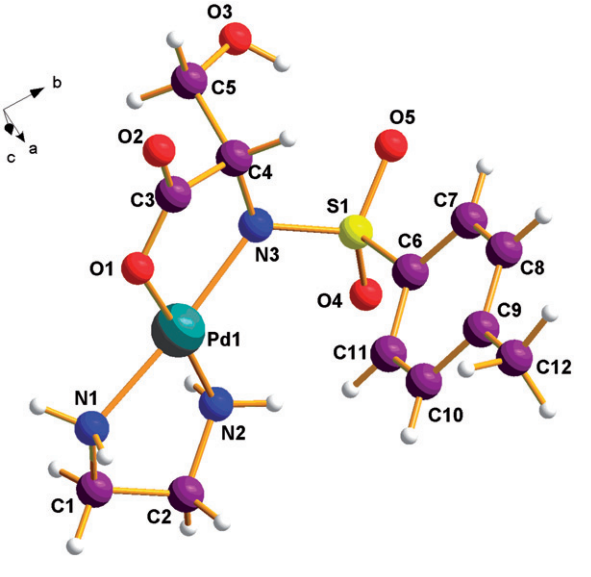


Figure 5. Molecular structure and atom-labeling scheme for **1**.

important effect on cytotoxicity; when the amino acid is phe, the complex has the best cytotoxicity. For **1**–**5** with en and different amino acids, the cytotoxicity against HL-60, BGC-823, Bel-7402, and KB cell lines decreases in the sequence: phe > leu > ala > gly > ser; phe > leu > gly > ala > ser; phe > leu > ala > gly > ser;

Table 2. Selected bond lengths (Å) and angles (°) for **1**.

| [Pd(en)TsserNO] | |
|---|---|
| Pd(1)–N(1) | 2.0355(19) |
| Pd(1)–N(2) | 2.035(2) |
| Pd(1)–N(3) | 2.029(2) |
| Pd(1)–O(1) | 1.9989(17) |
| N(2)–Pd(1)–N(1) | 83.39(9) |
| O(1)–Pd(1)–N(3) | 83.85(8) |
| N(3)–Pd(1)–N(2) | 101.08(8) |
| O(1)–Pd(1)–N(1) | 91.80(8) |
| N(3)–Pd(1)–N(1) | 174.67(9) |
| O(1)–Pd(1)–N(2) | 174.51(8) |

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

| | $IC_{50} \pm SD$ ($\mu mol \cdot L^{-1}$) | | | |
|---|---|---|---|---|
| Complexes | HL-60 | BGC-823 | Bel-7402 | KB |
| **1** | $26 \pm 1$ | $48 \pm 2$ | $45 \pm 1$ | $32 \pm 2$ |
| **2** | $23 \pm 1$ | $38 \pm 2$ | $35.8 \pm 0.9$ | $37 \pm 2$ |
| **3** | $15.9 \pm 0.5$ | $41 \pm 1$ | $33.9 \pm 0.6$ | $12 \pm 1$ |
| **4** | $12.9 \pm 0.9$ | $35.8 \pm 0.8$ | $33 \pm 2$ | $15.6 \pm 0.9$ |
| **5** | $12 \pm 1$ | $34 \pm 2$ | $28 \pm 1$ | $11.8 \pm 0.5$ |
| **6** | $19 \pm 2$ | $21 \pm 1$ | $36 \pm 3$ | $36 \pm 3$ |
| **7** | $30 \pm 2$ | $7.5 \pm 0.9$ | $23 \pm 2$ | $28 \pm 3$ |
| **8** | $18 \pm 2$ | $22 \pm 1$ | $38 \pm 3$ | $5.4 \pm 0.8$ |
| **9** | $14 \pm 1$ | $23 \pm 2$ | $22 \pm 1$ | $37 \pm 3$ |
| **10** | $5.5 \pm 0.3$ | $4.5 \pm 0.3$ | $2.9 \pm 0.2$ | $2.1 \pm 0.4$ |
| **11** | $7.2 \pm 0.6$ | $16 \pm 2$ | $15 \pm 2$ | $26 \pm 2$ |
| Cisplatin | $2.9 \pm 0.3$ | $6.5 \pm 0.8$ | $8 \pm 1$ | $2.6 \pm 0.3$ |

[a]The $IC_{50}$ ($\mu mol \cdot L^{-1}$) values of complexes [Pd(bipy)(TsalaNO)] · $H_2O$ (**6**), [Pd(bipy)(TsleuNO)] · $1.5H_2O$ (**7**), [Pd(bipy)(TspheNO)] (**8**), [Pd(phen(TsalaNO)] · $2.5H_2O$ (**9**), [Pd(phen)(TsleuNO)] · $H_2O$ (**10**), and [Pd(phen)(TspheNO)] · $2H_2O$ (**11**) were cited from [17].

and phe > ala > leu > ser > gly, respectively. (2) N-containing ligands also have important effect on cytotoxicity, dependent on cell type. For **3**, **6**, and **9** with ala and different N-containing ligands, the cytotoxicity against HL-60 and Bel-7402 cell lines decreases in the sequence: phen > en > bipy, while the cytotoxicity against BGC-823 cell line decreases in the sequence: bipy > phen > en. For **4**, **7**, and **10** with leu and different N-containing ligands, the cytotoxicity against HL-60 and KB cell lines decreases in the sequence: phen > en > bipy, while the cytotoxicity against BGC-823 and Bel-7402 cell lines decreases in the sequence: phen > bipy > en. For **5**, **8**, and **11** with phe and different N-containing ligands, the cytotoxicity against HL-60 and Bel-7402 cell lines decreases in the sequence: phen > en > bipy, while the cytotoxicity against KB cell line decreases in the sequence: bipy > en > phen.

We previously reported the synthesis and cytotoxicity of five platinum(II) complexes with 4-toluenesulfonyl-*L*-amino acid dianion and bipy. The results indicate that both amino acids and N-containing ligands have important effects on cytotoxicity and cytotoxicity is also related to cell type. [Pt(bipy)(TspheNO)] displays the best

cytotoxicity against BGC-823, Bel-7402, and KB cell lines, while [Pt(bipy)(TsglyNO)] has the best cytotoxicity against KB cell line. The cytotoxicity of these complexes with bipy and different N-containing ligands against HL-60, BGC-823, Bel-7402, and KB cell lines decreases in the sequence: gly ≈ val > ser > leu > phe; phe > leu > ser ≈ val > gly; phe > val > leu > ser > gly; and gly > phe > leu > val > ser, respectively [23]. For palladium(II)/platinum(II) complexes with 4-toluenesulfonyl-*L*-amino acid dianion and N-containing ligands, both amino acids and N-containing ligands have important effects on cytotoxicity, moreover, the effects on cytotoxicity are related to tumor cell type. Although the $IC_{50}$ values do not show definite correlation with variation of the amino acid and N-containing ligands, the palladium(II)/platinum(II) complexes with phe display better cytotoxicities.



## 4. Conclusion

Five new palladium(II) complexes with 4-toluenesulfonyl-*L*-amino acid dianion and en were synthesized and characterized. The cytotoxic experiment indicates that the complexes display cytotoxic effects against HL-60, Bel-7402, BGC-823, and KB cell lines; both amino acids and N-containing ligands have important effects on cytotoxicity. When the amino acid is phe, the complex has better cytotoxicity, but none of the complexes is more active than cisplatin. The palladium(II) complexes with 4-toluenesulfonyl-*L*-amino acid dianions and en may be promising metal-based antitumor agents. Current studies are ongoing in our laboratory to gain insight in the mechanism of action of these complexes, which may be helpful for the design of new metal-based antitumor agents.

## Supplementary material

Crystallographic data for the structural analysis of **1** have been deposited with the Cambridge Crystallographic Data Centre, CCDC – 760941. 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).

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