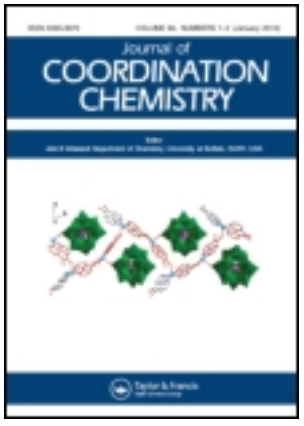

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Synthesis, characterization, and cytotoxicity of complexes of platinum(II) with 2,2′-bipyridine and *N*-benzoyl-*L*-amino acid dianion

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Four new platinum(II) complexes (**1**–**4**) with *N*-benzoyl-*L*-amino acid and bipy were synthesized and characterized by elemental analysis, IR, UV, ^{1}H NMR, and mass spectra. The crystal structure of **1** was determined by X-ray diffraction analysis. Cytotoxicities were measured by MTT and SRB assays. Complexes **1**–**4** exert cytotoxicity with selectivity against HL-60, Bel-7402, BGC-823, and KB cell lines. This suggests that amino acids and acylated groups have important effects on cytotoxicity; the cytotoxicity is also related to the species of tumor cells, but the IC_{50} values do not show definite correlation with the variation of amino acids and acylated groups.

Keywords: Mixed-ligand platinum(II) complexes; *N*-Benzoyl-*L*-amino acid dianion; 2,2′-Bipyridine; Synthesis; Cytotoxicity

1. Introduction

The landmark discovery of cisplatin by Rosenberg in 1965 heralded a new era of anticancer drug research based on metallopharmaceuticals [1]. Cisplatin is still one of the world's best-selling anticancer drugs with carboplatin and oxaliplatin also receiving worldwide approval. Nedaplatin, lobaplatin, and heptaplatin have gained regional approval and a few platinum drugs continue to be evaluated in clinical studies. There are some major drawbacks of current platinum drugs, including a limited range of cancers, acquired or intrinsic resistance, and severe side-effects [2–4]. These problems have prompted chemists to develop new platinum anticancer drugs.

It was reported that 2,2′-bipyridine (bipy), quinoline, 1,10-phenanthroline (phen), and their derivatives have ability to participate as DNA intercalators. Amino acids are the fundamental material of life and the basis of metabolism. Introducing amino

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acid into an antitumor drug can improve selectivity to tumor cells, enhance their liposolubility, and remit their toxicity to normal cells, thus widely used in platinum anticancer drugs as ligands. Jin and Ranford [5]. synthesized and characterized nine complexes of platinum(II) with phen and amino acids (where amino acids are glycine (Gly), *L*-histidine (His), *L*-cysteine (Cys), *L*-isoleucine (Ile), *L*-alanine (Ala), *L*-proline (Pro), *L*-serine (Ser), *L*-aspartic acid (Asp), and *L*-glutamic acid (Glu)). Most of the complexes were less cytotoxic than cisplatin. The IC_{50} of [Pt(phen)(Pro)]$Cl \cdot 2H_2O$ is similar to cisplatin. Mital and Srivastava [6] reported the cytotoxicities of some platinum(II) complexes with phen and amino acids (where amino acids are Gly, Ala, *L*-leucine (Leu), and *L*-tyrosine (Tyr)). These complexes exhibit a growth inhibition of P388 lymphocytic leukemic cells, but the IC_{50} values for the platinum(II) complexes are higher than cisplatin. Puthraya *et al.* [7] have tested several platinum(II) complexes with bipy and amino acids against tumor cells; the results indicated that some complexes had good cytotoxicity. Cytotoxicities of platinum(II) complexes with bipy and *N*-benzoyl-*L*-amino acid dianion has not been reported. In order to develop new platinum anticancer drugs, in this work, we present the synthesis, characterization, and cytotoxicity of four mixed-ligand platinum(II) complexes with *N*-benzoyl amino acid dianion and bipy.

2. Experimental

2.1. *Materials*

Benzoyl chloride and $K_2[PtCl_4]$ were of chemical grade and bipy was of analytical grade. Commercially pure *L*-tryptophan (Trp), *L*-valine (Val), Leu, and *L*-phenylalanine (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), benzyl penicillin, 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 an UV-3400 Toshniwal spectrophotometer. IR spectra were recorded using KBr pellets and a Perkin-Elmer Model-683 spectrophotometer. ^{1}H 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 optical density (OD) was measured on a microplate spectrophotometer (Bio-Rad Model 680, USA).

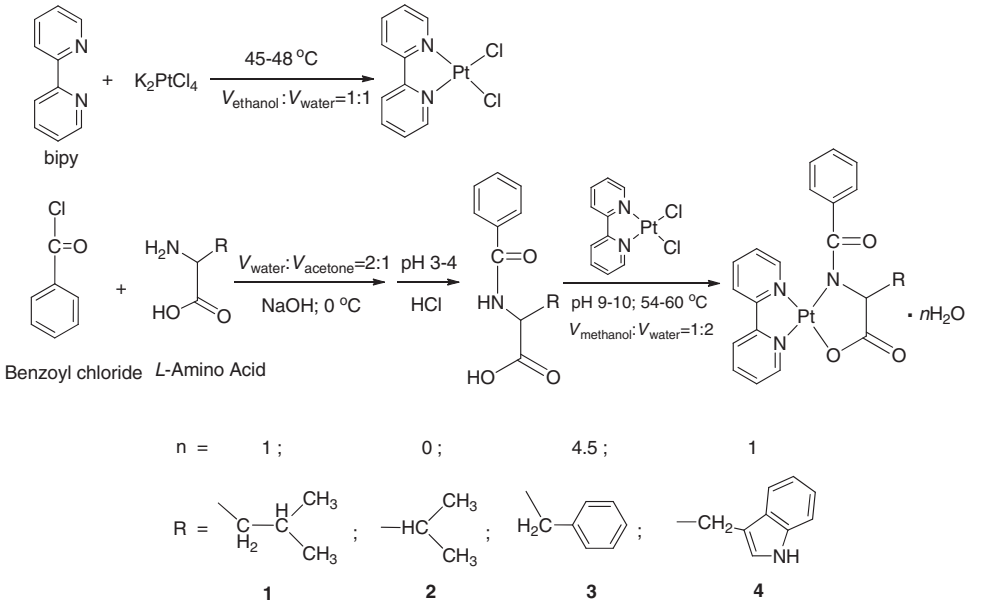

Figure 1. The synthetic routines of **1–4**.

2.3. *Synthesis of compounds*

[Pt(bipy)(Bzleu-N,O)]·H_2O (**1**), [Pt(bipy)(Bzval-N,O)] (**2**), [Pt(bipy)(Bzphe-N,O)]·$4.5H_2O$ (**3**), and [Pt(bipy)(Bztrp-N,O)]·H_2O (**4**) have been prepared by the reaction of [Pt(bipy)Cl_2] with *N*-benzoyl-*L*-amino acids: benzoyl-*L*-leucine ($BzleuH_2$), benzoyl-valine ($BzvalH_2$), benzoyl-*L*-phenylalanine ($BzpheH_2$), and benzoyl-*L*-tryptophan ($BztrpH_2$), in a mixed solution of CH_3OH/H_2O (figure 1) [8].

2.3.1. Benzoyl-*L*-amino acids. To a stirred solution of Leu (200 mg, 1.5 mmol) in 1.5 mL H_2O, 1.5 mL of NaOH aqueous solution (1 mol L^{-1}) was added. Benzoyl chloride (0.18 mL, 1.5 mmol) dissolved in 8 mL of $CHCl_3$ and 8 mL of NaOH (0.5 mol L^{-1}) aqueous solution were added slowly to the solution at the same time under ice bath. After the reaction was complete, the reaction mixture was acidified to pH = 3–4 with HCl (0.5 mol L^{-1}). The organic layer was separated and the aqueous layer was extracted with 8 mL $CHCl_3$. The combined organic layers were washed with water (2 × 5 mL), dried over $MgSO_4$, filtered, and concentrated to 3 mL by a rotary evaporator at 40°C; then white solid was precipitated. The collected solid was recrystallized twice from an ethanol–water mixture ($V/V = 1:1$) and dried to give $BzleuH_2$. m.p.: 135–137°C; IR (KBr, cm^{-1}): 3378, 1635, 1535, 1720, 1244. ^1H NMR (600 MHz, $CDCl_3$) δ ppm 7.81–7.79 (d, 2H, $J = 7.6$ Hz), 7.54–7.51 (t, 1H, $J = 7.8$ Hz), 7.45–7.43 (t, 2H, $J = 7.8$ Hz), 6.62–6.60 (d, 1H, $J = 7.8$ Hz), 4.85–4.82 (m, 1H), 1.85–1.78 (m, 2H), 1.74–1.69 (m, 1H), 1.00–0.98 (q, 6H, $J = 3.0$ Hz).

$BzvalH_2$, $BzpheH_2$, and $BztrpH_2$ were carried out in an identical manner. $BzvalH_2$: m.p.: 129–130°C; IR (KBr, cm^{-1}): 3364, 1640, 1546, 1726, 1206. ^1H NMR (600 MHz, $CDCl_3$) δ ppm 7.80–7.78 (d, 2H, $J = 7.2$ Hz), 7.55–7.52 (t, 1H, $J = 7.8$ Hz), 7.46–7.44

(t, 2H, $J = 7.8$ Hz), 6.63–6.61 (d, 1H, $J = 7.8$ Hz), 4.62–4.60 (m, 1H), 2.37–2.25 (m, 1H), 1.07–1.02 (q, 6H, $J = 3.0$ Hz). $BzpheH_2$: m.p.: 184–186°C; IR (KBr, cm^{-1}): 3327, 1612, 1538, 1722, 1228. ^1H NMR (600 MHz, $CDCl_3$) δ ppm 7.78–7.70 (d, 2H, $J = 7.2$ Hz), 7.54–7.52 (t, 1H, $J = 7.8$ Hz), 7.47–7.45 (t, 2H, $J = 7.8$ Hz), 7.30–7.24 (m, 5H), 6.64–6.62 (d, 1H, $J = 7.8$ Hz), 4.61–4.58 (m, 1H), 3.24–3.20 (m, 2H). $BztrpH_2$: m.p.: 193–195°C; IR (KBr, cm^{-1}): 3396, 1624, 1543, 1724, 1234. ^1H NMR (600 MHz, $CDCl_3$) δ ppm 10.82–10.78 (s, 1H), 7.78–7.75 (d, 2H, $J = 7.2$ Hz), 7.54–7.52 (t, 1H, $J = 7.8$ Hz), 7.48–7.46 (t, 2H, $J = 7.8$ Hz), 7.20–7.10 (d, 2H, $J = 7.2$ Hz), 7.10–6.96 (d, 2H, $J = 7.8$ Hz), 6.96–6.80 (s, 2H), 6.64–6.62 (d, 1H, $J = 7.8$ Hz), 4.80–4.60 (m, 1H), 3.30–3.25 (m, 2H).

2.3.2. [Pt(bipy)Cl_2]. Precursor complex [Pt(bipy)Cl_2] was synthesized according to a published procedure [9]. Yield: 87.7%. Yellow solid. Anal. Calcd for $C_{10}H_8Cl_2N_2Pt$ (%): C, 28.45; H, 1.91; N, 6.64. Found (%): C, 28.56; H, 1.98; N, 6.80.

2.3.3. [Pt(bipy)(Bzleu-N,O)]·H_2O (1). $BzleuH_2$ (22 mg, 0.094 mmol) dissolved in 5.0 mL of NaOH (0.047 mmol) water solution was added to a suspension of [Pt(bipy)Cl_2] (20 mg, 0.047 mmol) in 6 mL mixture of CH_3OH/H_2O ($V/V = 1:2$). The reaction mixture was adjusted to pH = 9–10 with a NaOH solution and stirred for 6 h at 56°C until a clear solution was formed. The clear solution was filtered and concentrated to 2 mL at 40°C. By slowly evaporating the solution after several days at room temperature, a yellow crystalline solid was separated, and collected by filtration, washed with a small amount of cold methanol and diethyl ether, and dried under vacuum at 60°C. Yield: 70.2%. Yellow solid. IR (KBr, cm^{-1}): 3446, 1560, 1634, 1394, 556, 455. ^1H NMR (600 MHz, DMSO-d_6) $\delta_{(ppm)}$ 0.80 (d, $J = 6.59$ Hz, 3H, CH_3), 0.83 (d, $J = 6.48$ Hz, 3H, CH_3), 1.87–1.81 (m, 1H, CH), 2.06 (d, $J = 7.50$ Hz, 2H, CH_2), 4.25 (dd, $J = 8.97$, 5.79 Hz, 1H, CH), 7.00–9.33 (13H, Ar-H). ESI-MS: 584.53 $[M]^+$. Anal. Calcd for $C_{23}H_{25}N_3O_4Pt$ (%): C, 45.85; H, 4.18; N, 6.97. Found (%): C, 45.85; H, 3.94; N, 7.12.

2.3.4. [Pt(bipy)(Bzval-N,O)] (2). The synthesis of **2** was carried out similar to **1,** starting from [Pt(bipy)Cl_2] (19 mg, 0.045 mmol) and $BzvalH_2$ (23 mg, 0.090 m mol). Yield: 68.4%. Yellow green solid. IR (KBr, cm^{-1}): 3427, 1587, 1645, 1384, 562, 447. ^1H NMR (600 MHz, DMSO-d_6) $\delta_{(ppm)}$ 1.10 (d, $J = 6.97$ Hz, 3H, CH_3), 1.20 (d, $J = 6.68$ Hz, 3H, CH_3), 3.99 (d, $J = 6.56$ Hz, 1H, CH), 5.26 (d, $J = 6.53$ Hz, 1H, CH), 6.99–8.20 (13H, Ar-H). ESI-MS: 593.50 $[M+Na]^+$. Anal. Calcd for $C_{22}H_{21}N_3O_3Pt$ (%): C, 46.32; H, 3.71; N, 7.37. Found (%): C, 46.31; H, 3.62; N, 7.43.

2.3.5. [Pt(bipy)(Bzphe-N,O)]·4.5H_2O (3). The synthesis of **3** was carried out similar to **1,** starting from [Pt(bipy)Cl_2] (19 mg, 0.045 mmol) and $BzpheH_2$ (25 mg, 0.094 m mol). Yield: 65.6%. Red brown solid. IR (KBr, cm^{-1}): 3427, 1597, 1645, 1384, 570, 463. ^1H NMR (600 MHz, DMSO-d_6) $\delta_{(ppm)}$ 3.19 (d, $J = 5.88$ Hz, 1H, CH_2), 3.22 (d, $J = 4.49$ Hz, 1H, CH_2), 5.32–5.28 (m, 1H, CH), 7.18–8.74 (18 H, Ar-H). ESI-MS: 641.54 $[M+Na]^+$. Anal. Calcd for $C_{26}H_{30}N_3O_{7.5}Pt$ (%): C, 44.64; H, 4.32; N, 6.01. Found (%): C, 44.60; H, 3.98; N, 6.43.

2.3.6. [Pt(bipy)(Bztrp-N, O)]·H_2O (4). The synthesis of **4** was carried out similar to **1,** starting from [Pt(bipy)Cl_2] (19 mg, 0.045 mmol) and BztrpH_2 (29 mg, 0.094 m mol). Yield: 74.2%. Deep green solid. IR: 3460, 1550, 1670, 1397, 555, 471. ^{1}H NMR (600 MHz, DMSO-d_6) $\delta_{(ppm)}$ 3.16–3.14 (m, 1H, CH_2), 3.18–3.16 (m, 1H, CH_2), 5.77–5.75 (m, 1H, CH), 7.04–8.64 (18H, Ar-H), 10.45–10.41 (m, 1H, indole-NH). ESI-MS: 696.56 $[M+K]^+$. Anal. Calcd for $C_{28}H_{24}N_4O_4Pt$ (%): C, 49.77; H, 3.55; N, 8.29. Found (%): C, 49.73; H, 3.41; N, 7.93.

2.4. *X-ray structure determination of [Pt(bipy)(Bzleu-N, O)]·H_2O (1)*

Data collection for **1** 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 and the structure was solved by direct methods using the SHELXS-97 program. 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 an RPMI-1640 medium supplemented with 10% fetal bovine serum, 100 unit mL^{-1} 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**.

	1
Empirical formula	$C_{92}H_{105}N_{12}O_{18}Pt_4$
Formula weight	2435.10
Temperature (K)	296(2)
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions (Å)	
a	10.1503(9)
b	21.152(2)
c	21.974(2)
Volume (nm^3), *Z*	4.6362(7), 8
Calculated density ($Mg\,m^{-3}$)	1.753
F(000)	2394
Crystal size (mm^3)	0.55 × 0.33 × 0.09
θ range for data collection (°)	0.94–28.38
Limiting indices	$-10 \le h \le 13$; $-28 \le k \le 27$; $-29 \le l \le 28$
Data/parameters	22,952/1144
Goodness-of-fit on F^2	0.966
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0458$, $wR_2 = 0.1082$

2.6. *Solutions*

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

2.7. *Cytotoxicity analysis*

The cells harvested from the 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 was performed as described by Mosmann for HL-60 [10]. Upon completion of the incubation for 44 h, stock MTT dye solution (20 mL, 5 mg 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 assay was performed as previously described for Bel-7402, BGC-823, and KB [11]. 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 mM unbuffered Tris base (100 mL) and OD was measured at 540 nm as mentioned above. The IC_{50} value was determined from the plot of % viability against dose of compounds added.

3. Results and discussion

3.1. *Characterization of the complexes*

The elemental analysis data of **1**–**4** are in agreement with the calculated values. Mass spectra of **1**–**4** also provide support for the suggested composition and structures of the complexes. Bipy has a maximum absorption at 282 nm, assigned to π–π^* transition. After the formation of the complexes, the absorption red shifts by 23–42 nm for **1**–**4** compared with bipy, caused by charge transfer transition (metal-ligand) from platinum d-orbital to a π^*-orbital of bipy.

The amide groups of $BzleuH_2$, $BzvalH_2$, $BzpheH_2$, and $BztrpH_2$ have strong and sharp ν_{NH} at 3327–3396 cm^{-1}, which disappears for the complexes, showing that the amide groups have been deprotonated. This is further confirmed by both the amide (I) shifting from 1612–1640 cm^{-1} to 1550–1597 cm^{-1} and the disappearance of the amide (II) from ~1540 cm^{-1}. A new band assigned to ν_{Pt-N} appears at 560 cm^{-1}. The carboxylates of **1**–**4** show two bands, an intense antisymmetric $\nu_{(as,\ coo^-)}$ and a symmetric $\nu_{(s,\ coo^-)}$ at 1720 and 1230 cm^{-1}, respectively. The values of $\Delta\nu_{(coo^-)}\nu_{(as,\ coo^-)} - \nu_{(s,\ coo^-)}$ of **1**–**4** are 240–270 cm^{-1}, greater than $\Delta\nu_{(coo^-)}$ of the corresponding sodium carboxylate, so the carboxylate is monodentate, coordinated with Pt(II) through oxygen [12]. This is further

confirmed by the appearance of ν_{Pt-O} (Supplementary material). These results are in agreement with the results revealed by the X-ray crystal analysis.

$BzLeuH_2$, $BzvalH_2$, $BzpheH_2$, and $BztrpH_2$ shows a doublet at $\delta = 7.8$–8.1, which is associated with a proton of the amide, however this peak disappeared for **1**–**4**, showing that the amide groups have been deprotonated. The methylene ^1H resonances (amino acid) for **1**–**4** shifted downfield as a result of deprotonated benzoylamide nitrogen coordinating to Pt(II).

3.2. *Structural studies*

A view of the molecular structure of $[Pt(bipy)(Bzleu\text{-}N,O)] \cdot H_2O$ (**1**) is shown in figure 2. Selected bond lengths and angles of **1** are given in table 2. The Pt–N bond length varies from 1.992(5) to 2.012(5) Å. The bond angles of O(1)–Pt(1)–N(1), O(1)–Pt(1)–N(2), N(1)–Pt(1)–N(2), N(1)–Pt(1)–N(3), N(2)–Pt(1)–N(3), and N(1)–Pt(1)–N(2) are 80.32(19)°, 95.03(18)°, 175.3(2)°, 104.4(2)°, 80.2(2)°, and 175.3(2)°, respectively. The platinum is square-planar from two nitrogen atoms of bipy, one deprotonated amide nitrogen, and one carboxylate oxygen. The torsion angles of Pt(1)–N(1)–C(2)–C(1) and Pt(1)–O(1)–C(1)–C(2) are 40.108(552)° and 6.642(747)°, indicating that *N*-benzoyl-*L*-leuline coordinates to Pt(II) in a distorted five-membered ring. The bond length

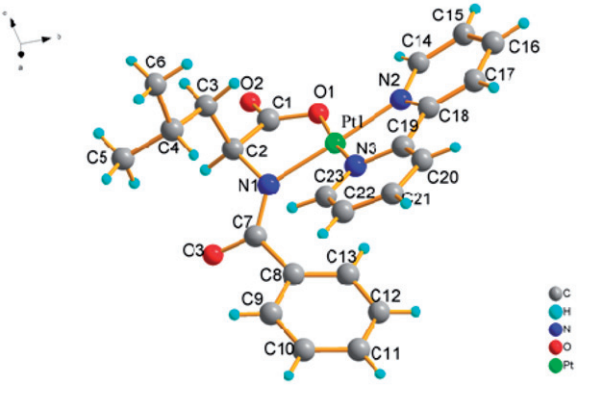

Figure 2. Molecular structure and atom-labeling scheme for **1** (H_2O is omitted for clarity).

Table 2. Selected bond lengths and angles for **1**.

Pt(1)–N(1)	2.012(5)
Pt(1)–N(2)	1.992(5)
Pt(1)–N(3)	1.999(5)
Pt(1)–O(1)	2.004(4)
N(1)–Pt(1)–N(2)	175.3(2)
N(2)–Pt(1)–N(3)	80.2(2)
N(3)–Pt(1)–O(1)	174.60(19)
O(1)–Pt(1)–N(1)	80.32(19)
O(1)–Pt(1)–N(2)	95.03(18)
N(1)–Pt(1)–N(3)	104.4(2)

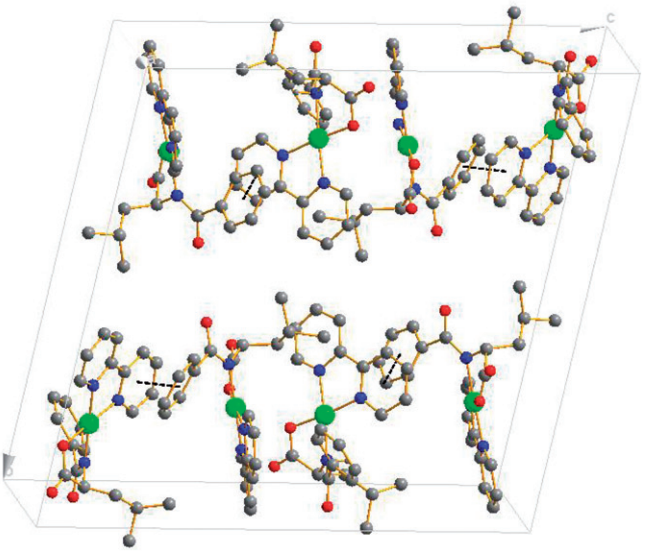

Figure 3. View showing the weak interactions of **1**.

(2.012(5) Å) of Pt–N (deprotonated amide) is longer than the bond lengths of Pt–N (bipy) (1.992(5) and 1.999(5) Å) and close to the bond length (2.004(4) Å) of Pt–O (carboxylate), in good agreement with Sigel's report [13].

There are some intramolecular interactions between phenyl and bipy rings in **1**. The edge of N3–C23–C22 on bipy is close to the edge of C9–C8–C13 on phenyl ring, causing the ligand to twist at nitrogen of the *N*-benzoyl amino acid. This weak interaction also exists intermolecularly. There are weak $\pi\cdots\pi$ stacking interactions between the benzene rings of one molecular and pyridyl rings of another, with an average interplanar separation and dihedral angle of 4.672 Å and 23.485° (figure 3). The water in the crystal cell does not form hydrogen bonds, hence we omit it for clarity.

3.3. *Cytotoxic studies*

In this work, as shown in table 3 and figure 4, compounds **1**–**4** exert cytotoxic effects with a low IC_{50} value ($<40\,\mu M$), have selectivity against tested carcinoma cell lines, but none showed higher cytotoxicity than cisplatin. The structure–activity relationships are summarized as follows: (1) the amino acids have important effect on the cytotoxicity. For **1**–**4**, the cytotoxicity against KB cell line decreases in the sequence: Phe > Val > Trp ≈ Leu, the cytotoxicity against BGC-823 cell line decreases in the sequence: Trp > Val > Leu > Phe, the cytotoxicity against Bel-7402 cell line decreases in the sequence: Trp > Leu > Val > Phe, the cytotoxicity against HL-60 cell line decreases in the sequence: Val > Trp > Leu > Phe. For platinum(II) complexes (**5**–**7**) with 4-toluenesulfonyl-*L*-amino acid dianion and bipy, the cytotoxicity against KB and BGC-823 cell lines decreases in the sequence: Phe > Leu > Val, the cytotoxicity against Bel-7402 cell line decreases in the sequence: Phe > Val > Leu, the cytotoxicity against HL-60 cell line decreases in the sequence: Val > Leu > Phe. (2) The acylated groups

Table 3. The cytotoxicities of **1–7** *in vitro* ($n = 5$).

Complexes	IC_{50} (μM)			
	KB	BGC-823	Bel-7402	HL-60
Cisplatin	2.6 ± 0.3	6.5 ± 0.8	8 ± 1	2.9 ± 0.3
[Pt(bipy)Cl_2]	85 ± 2	43 ± 1	44 ± 2	32 ± 2
1	20 ± 1	34 ± 3	29 ± 2	25 ± 2
2	18 ± 1	25 ± 2	30 ± 3	20 ± 2
3	12 ± 1	39 ± 2	33 ± 3	26 ± 3
4	19 ± 1	11.9 ± 0.6	26 ± 2	23 ± 2
5	14 ± 1	22 ± 2	26 ± 2	26 ± 2
6	16 ± 1	27 ± 2	24 ± 2	18 ± 2
7	7 ± 1	10 ± 2	14 ± 1	28 ± 2

The IC_{50} (μM) values of [Pt(bipy)(Tsleu-N, O)] (**5**), [Pt(bipy)(Tsval-N, O)] (**6**), and [Pt(bipy)(Tsphe-N, O)] (**7**) were cited from our previous work [14].

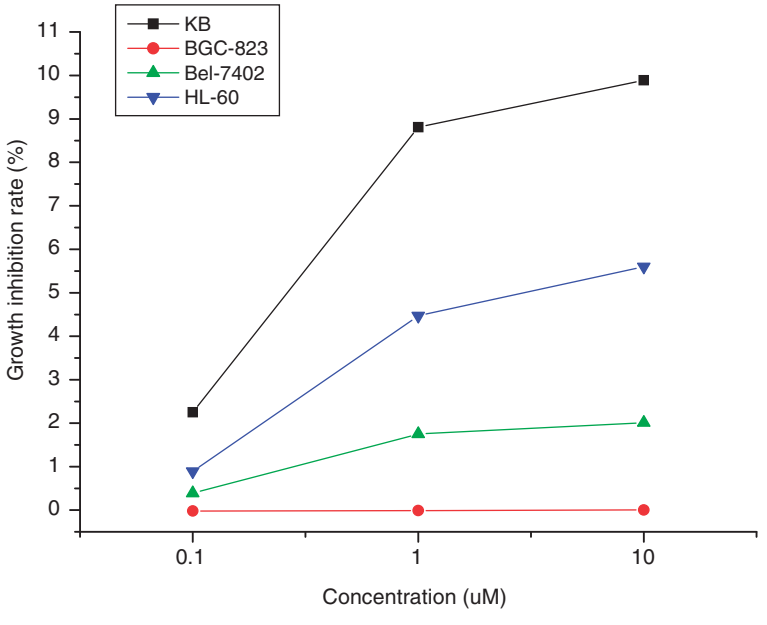

Figure 4. The dose–response curve for **1** against HL-60, Bel-7402, BGC-823, and KB cell lines.

have important impact on the cytotoxicity of complexes. For **1** and **5**, the cytotoxicities against KB, BGC-823 and Bel-7402 cell lines decrease in the sequence: Ts > Bz; the cytotoxicity against HL-60 cell line decreases in the sequence: Bz > Ts. For **2** and **6**, the cytotoxicity against KB, HL-60, and Bel-7402 cell lines decreases in the sequence: Ts > Bz; the cytotoxicity against BGC-823 cell line decreases in the sequence: Bz > Ts. For **3** and **7**, the cytotoxicity against KB, BGC-823 and Bel-7402 cell lines decreases in the sequence: Ts > Bz; the cytotoxicity against HL-60 cell line decreases in the sequence: Bz > Ts. In summary, both amino acids and acylated groups have important effects on cytotoxicity, but the IC_{50} values do not show definite correlation with the

variation of amino acids and acylated groups; the cytotoxicity of complexes is also related to tumor cell species.

4. Conclusions

Four new platinum(II) complexes with *N*-benzoyl-*L*-amino acid and bipy 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 acylated groups have important effect on cytotoxicity, but none of the complexes is more active than cisplatin. The platinum(II) complexes with *N*-benzoyl-*L*-amino acid and bipy may be a promising source of 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-780368. 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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