Preparation, Characterization and *in Vitro* Anticancer Activity of Platinum(II) Complexes with *N*-Cyclohexyl-1,3-propanediamine as the Carrier

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New JM118 (active form of satraplatin) analogues with *N*-cyclohexyl-1,3-propanediamine (N-chpda) as the carrier, *cis*-[Pt(N-chpda)X_2] (X_2=2Cl^- (1), oxalate (2), malonate (3), 1,1-cyclobutanedicarboxylate (CBDCA) (3), and 3-hydroxy-1,1-cyclobutanedicarboxylate(HO-CBDCA) (4)), have been synthesized and characterized by elemental analysis and spectroscopic data along with X-ray crystal structure for a representative compound *cis*-[Pt(N-chpda)Cl_2].The complexes have also been evaluated for their *in vitro* anticancer activity. All these analytical data are in good agreement with the structures of the desired compounds. The Pt(II) is in a square planar environment and is coordinated by a chelating N-chpda ligand and 2Cl^- in *cis* position, and there are two crystallographically independent *cis*-[Pt(N-chpda)Cl_2] molecules linked together by intermolecular N–H···Cl hydrogen bonds. Compounds 1 and 2 are very active against human lung cancer cell line (AGZY) and human lymphocytic leukemia cell line (Raji), and are much more active than carboplatin. Platinum(II) complexes with *N*-cyclohexyl-1,3-propanediamine is an alternative choice for mixed ammine/aminoplatinum anticancer drugs.

Key words analogue; JM118; synthesis; structure; anticancer activity

Since the serendipitous discovery of anticancer activity of platinum compounds in 1965, more than 35 have entered clinical trials. Of these, cisplatin, carboplatin and oxaliplatin are in world-wide clinical use, whereas nedaplatin, lobaplatin and eptaplatin have gained limited regional approval in Japan, China and Korea, respectively, for the treatment of certain kinds of cancers (Fig. 1).[1)] However there are severe side-effects such as nephrotoxicity, myelosuppression, peripheral neuropathy, as well as acquired drug resistance.[2)] Therefore, the search for the new potent platinum complexes possessing high antitumour activity, low toxicity and lack of cross-resistance is continuing.[3)]

According to the structure–activity relationship,[4,5)] amine or ammine, the carrier of the platinum anticancer complexes, is known to play an important role not only in determining antitumor activity but also overcoming the cross-resistance of the complexes. Great efforts have been undertaken to modify the carrier. One strategy is to develop platinum complexes involving two different mixed ammine(NH_3)/amine(RNH_2) in *cis*-position.[6,7)] There are some reports that such platinum complexes showed more active against some tumors and less toxic than the corresponding diammine and diamine complexes.[8,9)] One important example is *cis*, *trans*, *cis*-ammine(cyclohexylamine)diacetatodichloroplatinum(IV) (satraplatin, JM 216, Fig. 2), which has recently entered III clinical trials.[10)] The active form of JM216 is generally believed to be its reduced product JM118 in cells.[11,12)] However the impediment to the development of this series of platinum complexes with two different mixed amine has been the diffi-

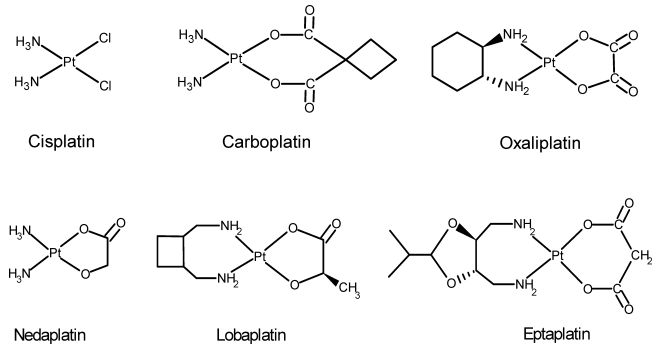

Fig. 1. Platinum-Based Drugs Currently in Clinical Use

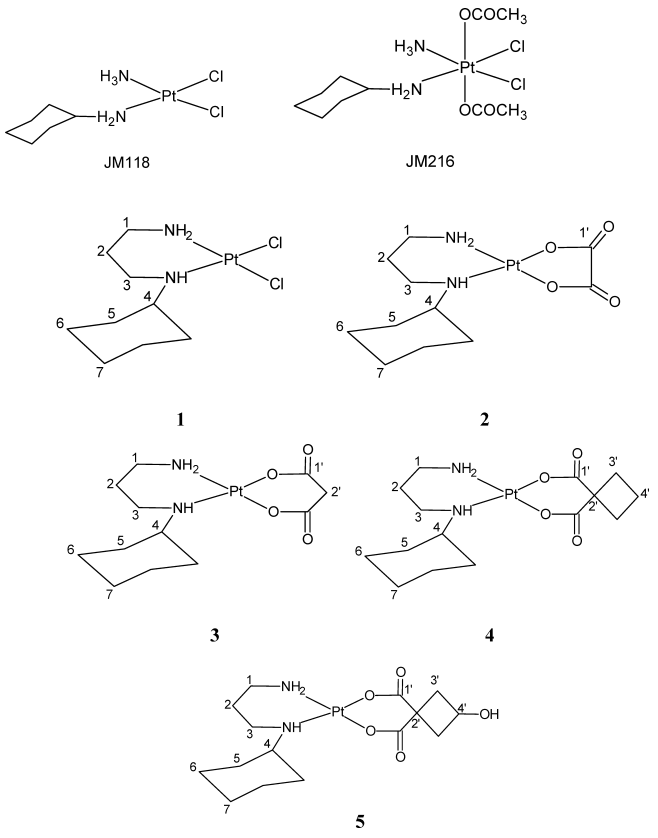

Fig. 2. Chemical Structure of JM118, JM216 and Compounds **1**—**5**

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cult access to the *cis*-Pt(II)$Cl_2(NH_3)$(amine) core because of extreme difficulty to prepare the Pt(II)$Cl_3(NH_3)^-$ anion.

One approach addressing this chemical problem in our laboratory has been to link ammine and amine together by alkyl group, forming novel platinum complexes containing an asymmetric chelating diamine. In the previous paper,[13] we described the synthesis and structure of such platinum compounds involving an asymmetric chelating diamine 2-morpholinoethylamine as the carrier. Here we report preparation, characterization and anticancer activity of platinum(II) complexes with *N*-cyclohexyl-1,3-propanediamine as a new asymmetric chelating diamine.

Experimental

General Commercially available substances *i.e.* potassium tetrachloroplatinate(II) (K_2PtCl_4), 1,1-cyclobutane dicarboxylic acid (CBDCA) and acrylonitrile were purchased from Aldrich. All reagents were of high purity and used without any further purification. 3-Hydroxy-1,1-cyclobutanedicarboxylic acid (HO-CBDCA) was prepared according to the reported method.[14] Chemical analyses for C, H and N were performed with a Carlo-Ebra Instrument, whereas platinum was determined according to the method in USP24. Mass spectrometry studies were carried out on a VG-Autospec Spectrometry in the FAB^+ mode using glycerine as matrix. FI-IR spectra were recorded in the 4000—400 cm^{-1} regions on a Perkin Elmer 880 spectrometer with KBr pellets. ^1H- and ^{13}C-NMR were obtained in DMSO, respectively, on Bruker DRX-500 (500.13 MHz) and on Brucker AV400 (100.62 MHz), relative to TMS as an external standard. The solubility of the platinum compounds in water was measured by AAS (GGS-6A Spectrometer), whereas the aqueous stability was monitored *via* conductivity (Mettler Toledo 326 Conductivity-Meter) or electronic spectrum(Shimadzu MPS-2000 Vis-UV Spectrometer).

The single crystal data (Tables 1, 2, 3) were collected on a SMART APEX II CCD diffractometer at room temperature. For extracting intensities from CCD images the program Nonius was used. The structures were solved by direct methods and refined by full-matrix least-squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. H atoms were calculated and allowed to ride. Computer programs: structure solution, SHELXS-97,[15] refinement, SHELXS-97,[16] molecular diagrams, ORTEP.[17]

Synthesis *N*-Cyclohexyl-1,3-propanediamine (N-chpda) was synthesized *via* the following procedures.[18] Freshly distilled acrylonitrile (10.6 g) was added dropwise with stirring to 30 g cyclohexylamine at a temperature below 20 °C. The reaction mixture was stirred overnight at room temperature and fractioned through a 20-cm Widmer column and elute was reduced by $LiAlH_4$ in air-dried THF (450 ml). The crude product was distilled at reduced pressure to give a colorless oily liquid. Yield: 40%.

cis-[Pt(N-chpda)I_2] (N-chpda=*N*-cyclohexyl-1,3-propanediamine), an intermediate, was prepared by using the conventional method.[19,20] Briefly, K_2PtCl_4 (2 mmol) was dissolved in water (20 ml) and treated with KI (12 mmol). After standing in dark for 40 min at room temperature, a solution of *N*-cyclohexyl-1,3-propanediamine (2 mmol in 10 ml water) was added dropwise. The mixture was stirred for 4 h at 30 °C and the yellow precipitate was filtrated off, washed with water and ethanol and dried *in vacuo* at 60 °C. Yield: 91%.

To prepare *cis*-[Pt(N-chpda)Cl_2] (**1**), 3.7 mmol silver nitrate was added to a suspension of *cis*-[PtA_2I_2] (1.86 mmol in 60 ml water) and the reaction mixture was stirred at 40 °C for 8 h. After AgI formed was filtrated off, 7.4 mmol potassium chloride was added to the filtrate giving yellow precipitate. A crystal suitable for X-Ray crystallography was collected, and then product was filtrated off, washed with water and ethanol and dried *in vacuo* at 60 °C. Yield: 75% (0.78 g). Found (Calcd for $C_9H_{20}Cl_2N_2Pt$): Pt 46.5 (46.3), C 25.4 (25.6), H 4.80 (4.75), N 6.59 (6.65). MS-FAB^+ *m/z*: 422 (M^+, rel. int.=60%), 157 (Nchdpa$^+$, 100%). IR (KBr): 3247—3148 (s, ν_{N-H}), 2929, 2852 (m, ν_{C-H}). ^1H-NMR (DMSO, ppm) δ: 1.02—1.95 (m, 12H, 6$\underline{CH_2}$), 2.58—3.15 (m, 5H, 1C$\underline{H}$NH, 2C$\underline{H_2}$$NH_2$), 4.75 (s, 1H, $\underline{NH}$), 5.10, 5.50 (s, 2H, $\underline{NH_2}$). ^{13}C-NMR (DMSO, ppm) δ: 57 (C-4), 45 (C-3), 43 (C-1), 36 (C-5), 33 (C-2), 27 (C-6), 25 (C-7).

For the preparation of more water-soluble compounds (**2**—**5**) with dicarboxylate as the leaving group, to a suspension of *cis*-[PtA_2I_2] (2.5 g, 4.4 mmol) in 100 ml water was added 1.54 g, 4.3 mmol disilver salt of dicarboxylic acid, and the reaction mixture was stirred at 40 °C for 36 h. After AgI formed was filtrated off, the filtrate was condensed at 40 °C under reduced pressure to 5 ml, a white crystalline product precipitated and then it was filtrated off, washed with water and ethanol and dried in a vacuum oven at 60 °C.

Table 1. Crystallographic Data for *cis*-[Pt(N-chpda)Cl_2]

Crystal data	
[$PtCl_2(C_9H_{18}N_2)$]	F_{000}=1600
M_r=422.26	D_X=2.166 Mg m^{-3}
Monoclinic, $P2_1/c$	Mo$K\alpha$ radiation
	λ=0.71073 Å
Hall symbol: −P 2ybc	Cell parameters from 4537 reflections
a=18.6553 (17) Å	θ=2.3—27.4°
b=12.2229 (11) Å	μ=11.22 mm^{-1}
c=11.7912 (10) Å	T=293 (2) K
β=105.620 (1)°	BLOCK, yellow
V=2589.4 (4) $Å^3$	0.27×0.25×0.18 mm
Z=8	
Data collection	
Bruker SMART APEXII CCD	6027 independent reflections
area-detector diffractometer	4679 reflections with $I>2\sigma(I)$
Radiation source: fine-focus	R_{int}=0.034
sealed tube	θ_{max}=28.3°
Monochromator: graphite	θ_{min}=2.0°
T=293(2) K	
Φ and ω scans	
Absorption correction: multi-scan	
(SADABS: Sheldrick, 2002)	$h=-23\rightarrow24$
T_{min}=0.068, T_{max}=0.133	$k=-14\rightarrow15$
16372 measured reflections	$l=-8\rightarrow15$
Refinement	
Refinement on F^2	Hydrogen site location: inferred from
Least-squares matrix: full	neighbouring site
	H-atom parameters constrained
$R[F^2>2\sigma(F^2)]$=0.035	$w=1/[\sigma^2(F_O^2)+(0.0458P)^2$
	$+1.8205P)$
	where $P=(F_O^2+2F_C^2)/3$
$wR(F^2)$=0.090	$(\Delta/\sigma)_{max}$=0.002
S=1.00	$\Delta\rho_{max}$=2.68 e $Å^{-3}$
6027 reflections	$\Delta\rho_{min}$=−1.16 e $Å^{-3}$
253 parameters	Extinction correction: SHELXL97
	Extinction coefficient: 0.00297 (8)
Primary atom site loction: structure-invariant direct methods	
Secondary atom site location: difference Fourier map	

Compound 2 Yield: 64% (1.24 g). Found (Calcd for $C_{11}H_{20}N_2O_4Pt$) C 29.7 (30.0), H 4.58 (4.56), N 6.33 (6.37), Pt 43.0 (43.3). MS-FAB^+ *m/z*: 624 (M^++2Gly, 7%), 532 (M^++Gly, 10%), 440 (M^+, 100%), 350 (M^+-C_2O_4, 35%), 157 (Nchdpa$^+$, 17%). IR (KBr): 3262—3143 (m, ν_{N-H}), 2938, 2855 (w, ν_{C-H}), 1704 (s, $\nu_{a(COO)}$), 1384 (s, $\nu_{s(COO)}$). ^1H-NMR (DMSO, ppm) δ: 1.01—2.01 (m, 12H, 6$\underline{CH_2}$), 2.75—2.84 (m, 5H, 1C$\underline{H}$NH, 2$\underline{CH_2}$$NH_2$), 5.10 (s, 1H, $\underline{NH}$), 5.74, 6.32 (s, 2H, $\underline{NH_2}$). ^{13}C-NMR (DMSO, ppm) δ: 168 (C-1′), 57 (C-4), 45 (C-3), 43 (C-1), 36 (C-5), 33 (C-2), 27 (C-6), 25 (C-7).

Compound 3 Yield: 60% (1.20 g). Found (Calcd for $C_{12}H_{22}N_2O_4Pt$) C 31.4 (31.8), H 4.88 (4.85), N 6.20 (6.18), Pt 42.6 (43.0). MS-FAB^+ *m/z*: 454 (M^+, 100%), 350 (M^+-malonate, 75%), 157 (Nchdpa$^+$, 87%). IR (KBr): 3172, 3091 (m, ν_{N-H}), 2926, 2858 (w, ν_{C-H}), 1667 (s, $\nu_{a(COO)}$), 1387 (s, $\nu_{s(COO)}$). ^1H-NMR (DMSO, ppm) δ: 1.02—1.98 (m, 12H, 6C$\underline{H_2}$), 2.75—3.27 (m, 7H, C$\underline{H}$NH, 2C$\underline{H_2}$$NH_2$ C$\underline{H_2}$(COO)), 4.95 (s, 1H, N$\underline{H}$), 5.52, 6.02 (s, 2H, N$\underline{H_2}$). ^{13}C-NMR (DMSO, ppm) δ: 174 (C-1′), 57 (C-4), 50 (C-2′), 45 (C-3), 43 (C-1), 36 (C-5), 33 (C-2), 27 (C-6), 25 (C-7).

Compound 4 Yield: 55% (1.20 g). Found (Calcd for $C_{15}H_{26}N_2O_4Pt$) C 36.4 (36.5), H 5.30 (5.27), N 5.70 (5.68), Pt 39.2 (39.6). MS-FAB^+ *m/z*: 493 (M^+, 40%), 349 (M^+-CBDCA, 100%), 157 (Nchdpa$^+$, 77%). IR (KBr): 3217, 3138 (m, ν_{N-H}), 2937, 2857 (w, ν_{C-H}), 1630 (s, $\nu_{a(COO)}$), 1373 (s, $\nu_{s(COO)}$). ^1H-NMR (DMSO, ppm) δ: 1.02—2.27 (m, 18H, 9$\underline{CH_2}$), 2.71—2.90 (m, 5H, C$\underline{H}$NH, 2$\underline{CH_2}$$NH_2$ 4.94 (s, 1H, $\underline{NH}$), 5.47, 6.02 (s, 2H, $\underline{NH_2}$), ^{13}C-NMR (DMSO, ppm) δ: 178 (C-1′), 57 (C-4), 55 (C-2′), 45 (C-3), 43 (C-1), 36 (C-5), 33 (C-2), 30 (C-3′), 27 (C-6), 25 (C-7), 16 (C-4′).

Compound 5 Yield: 53% (1.20 g). Found (Calcd for $C_{15}H_{26}N_2O_5Pt$) C 35.1 (35.3), H 5.07 (5.10), N 5.46 (5.50), Pt 38.1 (38.3). MS-FAB^+ *m/z*: 510 (M^+, 90%), 349 (M^+-(HO-CBDCA), 45%), 157 (Nchdpa$^+$, 100%). IR (KBr): 32267, 3140 (m, ν_{N-H}), 2934, 2856 (w, ν_{C-H}), 1637 (s, $\nu_{a(COO)}$), 1374 (s, $\nu_{s(COO)}$). ^1H-NMR (DMSO, ppm) δ: 1.02—2.27 (m, 16H, 8$\underline{CH_2}$), 2.75—

3.13 (m, 5H, CHNH, $2CH_2NH_2$), 3.82 (1H, CHOH), 4.26 (1H, OH), 4.93 (s, 1H, NH), 5.50, 6.03 (s, 2H, NH_2). ^{13}C-NMR (DMSO, ppm) δ: 177 (C-1′), 62 (C-4′), 57 (C-4), 52 (C-2′), 45 (C-3), 43 (C-1), 36 (C-5), 33 (C-2, C-3′), 27 (C-6), 25 (C-7).

***In Vitro* Anticancer Tests** The cellular survival was evaluated by the MTT method.[13] Cells were plated onto 96-well sterile plates in 100 μl of medium at a density of 2×10^3 cells per well and incubated for 48 h at 37 °C in a 7% CO_2 containing incubator. The title complexes, cisplatin and carboplatin were added in final concentrations ranging from 0 to 100 μM. After 72 h, 50 μl MTT in PBS (5 mg/ml) was added to each well and the plates were incubated for 2—3 h at 37 °C. The solution was carefully removed and the remaining crystals dissolved in 100 μl of DMSO. Cell survival was evaluated by measuring the absorbance at 590 nm. All cytotoxicity tests were performed three times in quadruplicate. The IC_{50} values were calculated from curves constructed by plotting cell survival (%) *versus* compound concentration (in μM).

Results and Discussion

N-chpda, the new asymmetric chelating diamine, was synthesized by a two-step process (Chart 1) from acrylonitrile as the starting material. Michael addition of cyclohexylamine to acrylonitrile was achieved in about high yield. Reduction of the addition product with lithium aluminium hydride followed by distillation gave the desired compound in oily liquid state.

All platinum(II) compounds were prepared by using an extension of Dhara's method or by the direct reaction between *cis*-[Pt(N-chpda)I_2] and the disilver salt of corresponding dicarboxylic acid. The synthetic route is shown in Chart 2. Potassium tetrachloroplatinate(II), K_2PtCl_4, was converted *in situ* to the corresponding tetraiodoplatinate(II) by treatment with KI. After addition of the asymmetric chelating diamine (N-chpda)diiodoplatinum(II) was formed. Conversion of the diiodo to dicarboxylatoplatinum(II) complexes was performed by the quantitative reaction with the disilver salt of dicarboxylic acid, which offered the final product. The dichloroplatinum(II) complex was obtained by the reaction of the diiodoplatinum(II) complex with silver nitrate, followed by addition of potassium chloride.

All these platinum compounds were characterized by chemical analysis and spectroscopic data along with X-ray crystal structure for a representative compound (**1**). The elemental analysis data were in good agreement with the calculated values. The mass spectra of the compounds exhibited typical three protonated molecular ion peaks because of the isotopes ^{194}Pt (33%),^{195}Pt (34%) and ^{196}Pt (25%). There were also two intensive peaks at *m*/*z* 348—350 and 157, corresponding to Pt(N-chpda) and N-chpda ions, respectively.

The dicarboxylatoplatinum(II) compounds showed that their $\nu_{as(COO)}-\nu_{s(COO)}$ values in the infrared spectra were larger than 200 cm^{-1}, suggesting that carboxylate groups act as monodentate ligands.[21] The ^{1}H-NMR spectra of the compounds were all consistent with their corresponding protons both in the chemical shifts and the number of hydrogen. The NH_2 and NH protons resonated at 4.7—6.1 ppm as a singlet in DMSO, as listed in Table 1, and two protons of NH_2 split, probably due to different spatial orientation on six-membered chelating ring formed between platinum and N-chpda. CH_2 and CH protons developed two separate overlapping peaks at 1.0—2.3 and 2.5—3.1 ppm because of no apparent difference among their chemical shifts.

The dicarboxylatoplatinum(II) complexes were quite soluble in water, and also stable for there is no apparent change in conductivity of their aqueous solutions within 72 h. However, *cis*-[Pt(N-chpda)Cl_2], similar to cisplatin, is unstable in water, but very stable in saline solution, which was indicated by the change of electronic spectra with standing time. The solubility of the compounds in water at room temperature was related to the nature of leaving groups. The order of water solubility was compound **5** (10 mg/ml)≈**4**>**3** (4 mg/ml)>**2** (2.5 mg/ml)>**1** (1.5 mg/ml).

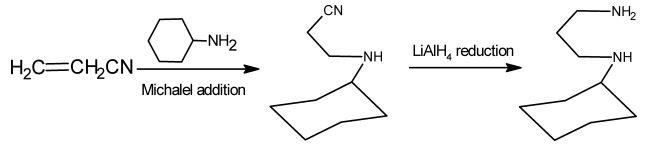

Chart 1

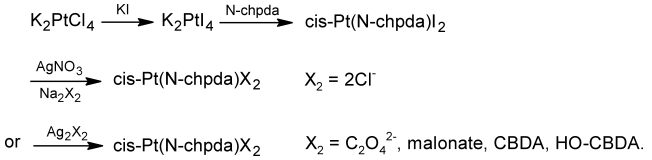

Chart 2

Table 2. Selected Bond Lengths [Å] and Angles [°] for *cis*-[Pt(N-chpda)Cl_2]

Pt(1)–N1	2.031 (5)	N(1)–Pt(1)–N(2)	90.6 (2)
Pt(1)–N2	2.067 (5)	Cl(1)–Pt(1)–Cl(2)	91.1 (7)
Pt(1)–Cl(1)	2.030 (5)	N(1)–Pt(1)–Cl(1)	86.5 (3)
Pt(1)–Cl(2)	2.031 (8)	N(2)–Pt(1)–Cl(2)	90.8 (7)°

cis-[Pt(N-chpda)Cl_2], one of the complexes, consisted of discrete monomeric molecules. The Pt(II) had the expected square planar geometry exhibiting the usual structure parameters. The basal square plane was constituted by N-chpda molecule which acted as a bidentate ligand through its two N atoms and two chloride atoms (Fig. 3). As shown in Table 3, Pt(1)–N1 [2.031(5) Å], Pt(1)–N2 [2.067(5) Å], Pt(1)–Cl(1) [2.030(5) Å] and Pt(1)–Cl(2) [2.031(8) Å] distances were in the normal range, and bond angles of N(1)–Pt(1)–N(2), Cl(1)–Pt(1)–Cl(2), N(1)–Pt(1)–Cl(1) and N(2)–Pt(1)–Cl(2) were determined to be 90.6(2)°, 91.1(7)°, 86.5(3)° and 90.8(7)°, respectively. The average Pt–N and Pt–Cl bond lengths were also within the normal range for other diamine platinum (II) complexes.[22—24] But Pt–N2 was longer than Pt–N1, indicating the different coordinate ability with Pt(II) between these two N atoms of the asymmetric chelating diamine. The six-membered chelate ring adopted the chair conformation.

In the asymmetric uint there were two crystallographically independent *cis*-[Pt(N-chpda)Cl_2] molecules where N–H$\cdots$Cl hydrogen bonds between the molecules formed a three-dimentional network in the crystal structure.

The *in vitro* anticancer activity of the complexes were assessed by MTT colorimetric assay as described in the literature[25,26] and each experiment was repeated three times. The results are given in Table 4. From the values of IC_{50}, it can been seen that compounds **3**—**5** do not show any significant *in vitro* anticancer activity against human lung cancer cell line (AGZY) and human lymphocytic leukemia cell line (Raji) whereas compounds **1** and **2** are very active and much more active than carboplatin. The order of activity is cis-

Table 3. Hydrogen Bonds for *cis*-[Pt(N-chpda)Cl_2] [Å]

D–H···A	D–H	H···A	D···A	D–H···A
N3–H3B···Cl3^{i}	0.90	2.68	3.377 (6)	1.35
N3–H3A···Cl1^{ii}	0.90	2.66	3.374 (6)	1.37
N2–H2A···Cl4^{i}	0.91	2.81	3.622 (6)	1.50
N1–H1B···Cl3^{iii}	0.90	2.66	3.439 (6)	1.46
N1–H1A···Cl2^{iv}	0.90	2.75	3.605 (6)	1.60

Symmetry codes: (i) x, $-y+3/2$, $z+1/2$; (ii) $-x+1$, $-y+1$, $-z+1$; (iii) $-x+1$, $y-1/2$, $-z-+1/2$; (iv) x, $-y+1/2$, $z-1/2$.

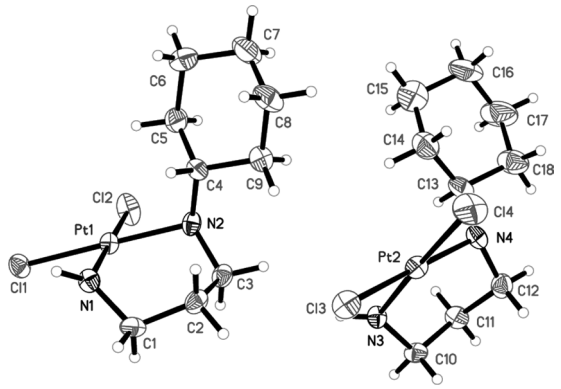

Fig. 3. ORTEP Diagram of *cis*-[Pt(N-chpda)Cl_2] Displaying Thermal Ellipsoids at 30% Probability

Table 4. *In Vitro* Anticancer Activity of Complexes **1**—**5** against Two Selected Human Tumor Cell Lines

Complexes	IC_{50} (μg/ml)	
	AGZY	Raji
1	1.03±0.05	4.39±0.57
2	10.2±0.11	8.50±0.01
3	33.8±3.0	>100
4	>100	>100
5	>100	>100
Cisplatin	0.38±0.02	3.10±0.03
Carboplatin	14.7±0.9	>100

platin>**1**>**2**>carboplatin>**3**—**5**.

Conclusion

Platinum(II) complexes involving two different mixed ammine(NH_3)/amine(RNH_2) in *cis*-position represent a very important class of anticancer platinum compounds. However, the difficulty in preparation has been limited further research and development of such compounds. Instead, their analogues, a series of novel platinum(II) compounds involving an asymmetric chelating diamine *N*-cyclohexyl-1,3-propanediamine as the carrier ligand, can be more easily synthesized by using an extension of Dhara's method or by the direct reaction between *cis*-[Pt(N-chpda)I_2] and the disilver salt of corresponding dicarboxylic acid, and the elemental analytical values, FAB^+-MS, FT-IR and ^{1}H-NMR spectroscopic data show they are in good agreement with the structures of the desired compounds. The crystal structure of *cis*-[Pt(N-chpd)Cl_2] exhibits that the platinum atom achieves a typical square planar arrangement with two nitrogen from N-chpda and two oxygen atoms in *cis* position. There are two crystallographically independent *cis*-[Pt(N-chpda)Cl_2] molecules linked together by intermolecule N–H···Cl hydrogen bonds. The dicarboxylate compounds are fairly soluble and stable in water, whereas *cis*-[Pt(N-chpd)Cl_2] is very stable in saline solution. The order of water solubility is Compound **5** (10 mg/ml)≈**4**>**3** (4 mg/ml)>**2** (2.5 mg/ml)>**1** (1.5 mg/ml). Compounds **3**—**5** do not show any significant *in vitro* anticancer activity against human lung cancer cell line (AGZY) and human lymphocytic leukemia cell line (Raji) whereas compounds **1** and **2** are very active and much more active than carboplatin. The order of activity is **1**>**2**>**3**>**4**, **5**. The results suggested that platinum(II) complexes with *N*-cyclohexyl-1,3-propanediamine should be an alternative choice for mixed ammine/amino platinum anticancer drugs, since they can easily be prepared.

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