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FULL PAPER

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Platinum (II) *N*-heterocyclic carbene complexes: Synthesis, characterization and cytotoxic properties

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Platinum (II) complexes bearing *N*-heterocyclic carbene (NHC) ligands have been widely used in catalytic chemistry, but there are very few reports of biological properties of this type of complexes. A series of $[PtCl_2(NHC)(PEt_3)]$ complexes were synthesized. The structures of all compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, IR and elemental analysis techniques, which supported the proposed structures. The single crystal structures of complexes **1a** and **1e** were determined. The title complexes show slightly distorted square-planar coordination around the platinum (II) metal center. The cytotoxic properties of the platinum (II)–NHC complexes have been assessed in various human cancer lines, including cisplatin-sensitive and resistant cells. IC_{50} values of these four complexes were determined by the MTS-based assay on three human cell lines—brain (SHSY5Y), colon (HTC116) and liver (HEP3B). These complexes have been highlighted cancer therapeutic agent with unique structures and functions.

KEYWORDS
antitumor activity, Imidazolidine-2-ylidene, *N*-heterocyclic carbene, platinum complexes

1 | INTRODUCTION

In recent years, medicinal inorganic chemistry has become a rapidly growing field with a broad range of medicinal applications for inorganic and metal-based compounds, including mineral supplements (Fe, Cu, Zn) and antimicrobial (Ag), anticancer (Pt), diagnostic (Ba, Mn, Gd, I), antiulcer (Bi) and antiarthritic (Au) agents, among others.[1,2] Cisplatin and other platinum (II) derivatives such as oxaliplatin play a key role as anticancer agents despite their dose-dependent toxicity and acquired or intrinsic drug resistance. These severe side effects are important factors motivating scientists to design new drugs that can overcome the limitations of the clinically used platinum compounds.[3] It is generally accepted that the mecanism of action of cisplatin involves adduct formation with DNA, which causes DNA damage and subsequently induces cell death.[4,5] Undoubtedly, these platinum (II) complexes can also interact with other cellular macromelecules and induce a parallel mode of action that is different from DNA damage.[4,6]

As potential anticancer drugs, metal-*N*-heterocyclic carbenes (NHCs) constitute a recent and very rapidly growing field of research. Metal complexes with *N*-heterocyclic carbene ligands were first reported by the group of Wanzlick[7] and Öfele[8] followed by Lappert and co-workers.[9,10] However, it was not until the isolation of a crystalline carbene by Arduengo *et al*. in 1991 that NHCs turned from mere curiosities into applicable chemical reagents.[11] Metal–NHC complexes have played a significant role in catalytic processes.[12–15] In recent years, a number of research groups have highlighted the potential of NHCs as new chemical structures for the development of metal-based drugs.[16–24] These highly σ-donating ligands form stable transition metal complexes, which might be a key requirement for biological applications.[25] Indeed, the lack of *in vivo* efficacy and the side effects of some metal-based anticancer drugs are strongly correlated with their instability under physiological conditions.[26] The benefits of the using NHC–metal complexes as anticancer agents lie in several aspects: (a) the NHC ligand can form strong bonds with different metal centers and the resulting complexes are more stable toward moisture, air and heat; (b) the large diversity of structures is easily accessible by some relatively simple synthetic pathways; and (c) the steric and electronic effects can contribute to the bonding formation between the metal centers and the NHC ligands. Moreover, the volume of the attached side chains can also influence the stabilty and reactivity of the complexes.[27] The cytotoxic activity of a variety of NHC-containing metal complexes (metal: Ag, Au, Cu, Pd and Pt) has been successfully studied on cancer cell lines.[18–22] Since the first report of platinum–NHC complexes as potential drug candidated by Marinetti and co-workers[26,28], several groups have confirmed *in vitro* the cytotoxic effect of such platinum complexes.[29–35]

In a recent study we have reported the synthesis of silver (I), gold and ruthenium complexes, which were tested as potential antimicrobial agents.[36–40] We report herein the synthesis and characterization of five imidazolidine-2-ylidene platinum (II) complexes of the general formula $[PtCl_2(NHC)(PEt_3)]$ **1a–e** (Figure 1). The anticancer activities of these new compounds were evaluated over several cancer cell lines—brain (SHSY5Y), colon (HTC116) and liver (HEP3B)—and these data confirmed the high level of cytotoxicity of Pt–NHC complexes.

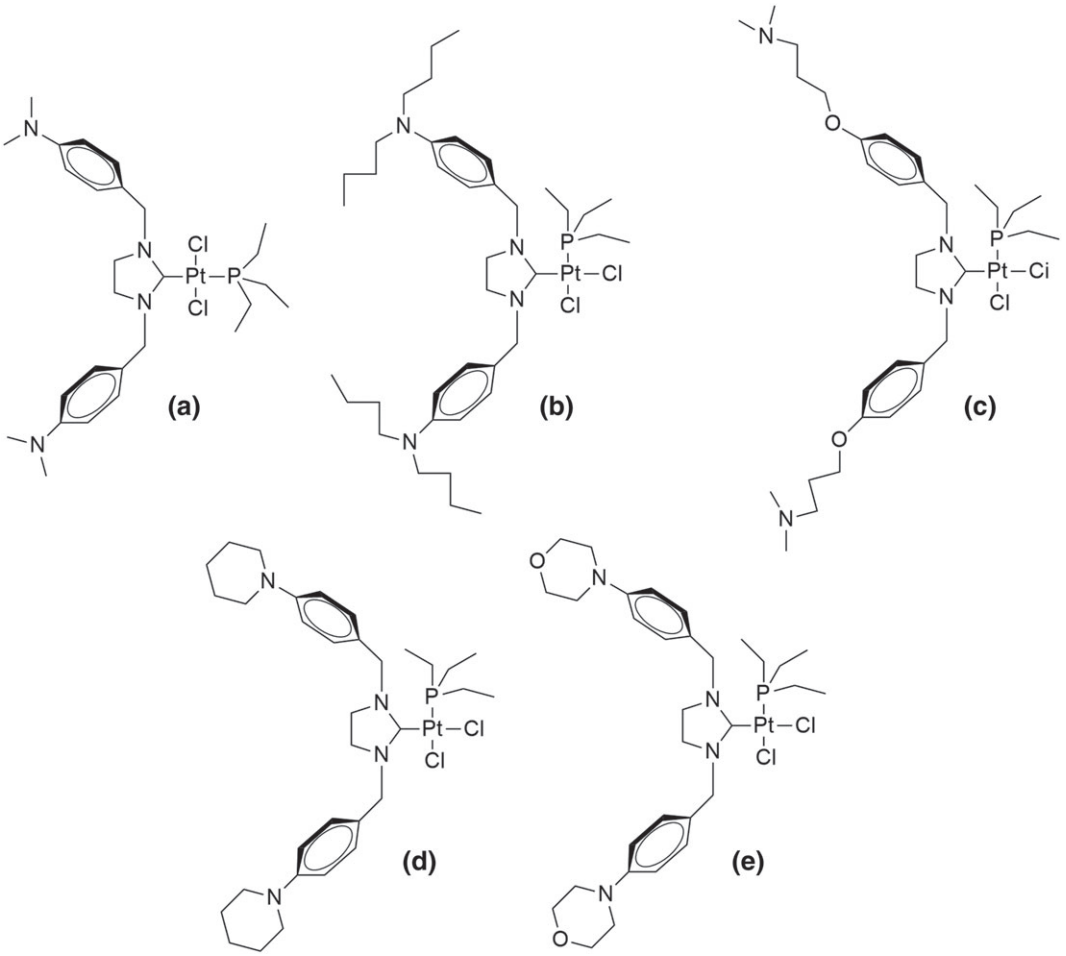


FIGURE 1 Platinum complexes **1a–e** synthesized and assessed in the present study

2 | EXPERIMENTAL SECTION

2.1 | General methods

All reactions for the preparation imidazolidine-2-ylidene and their complexes were carried out under argon in flame-dried glassware using standard Schlenk techniques. Chemicals and solvents were purchased from Sigma-Aldrich and Merck. Dichloromethane, dimethylformamide, toluene and diethyl ether were of anhydrous quality and were used as received. The solvents used were purified by distillation over the drying agents indicated and were transferred under argon. All reagents were purchased from commercial sources and used without further purification. Microanalyses were performed by İnönü University Scientific and Technological Research Center (Malatya, Turkey). IR spectra were recorded on an ATR unit in the range of 400–4000 cm^{-1} with a Perkin Elmer Spectrum 100 Spectrofotometer. Melting points were measured in open capillary tubes with a Stuart automatic point apparatus (SMP-40). Routine ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance AMX spectrometer operating at 400 MHz for ^1H NMR, and at 100 MHz for ^{13}C NMR in $CDCl_3$ with tetramethylsilane as an internal reference. The NMR studies were carried out in high-quality 5 mm NMR tubes. Chemical shifts (δ) and coupling constants (J) are reported in ppm and in Hz, respectively. ^1H NMR spectra are referenced to residual protiated solvents (δ = 7.26 ppm for $CDCl_3$), and ^{13}C chemical shifts are reported relative to deuteriated solvents (δ = 77.16 ppm for $CDCl_3$).

2.2 | General procedure for the preparation of the platinum–(NHC) complexes (1a–e)

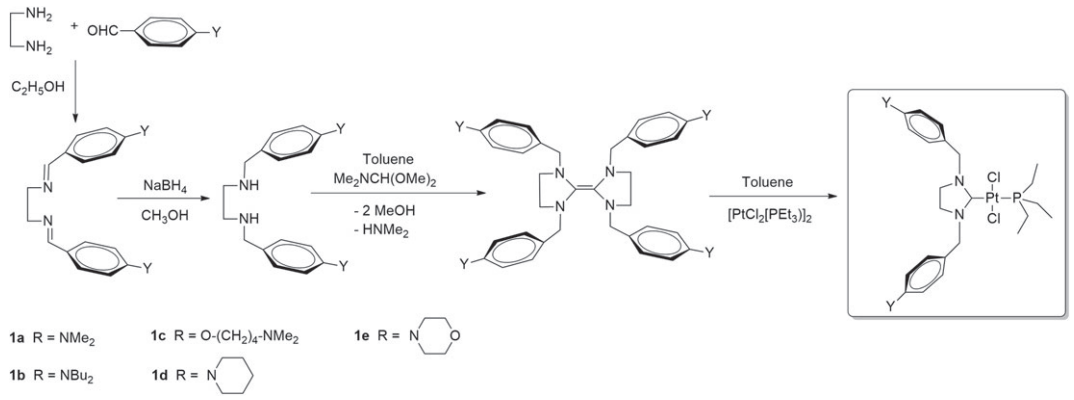
The aromatic aldehyde (20 mmol) and the ethylenediamine (10 mmol) were stirred overnight in methanol. The diimine was collected as a white solid, filtrated and recrystallized in an alcohol–ether mixture. The diimine (10 mmol) was subsequently reduced by $NaBH_4$ (30 mmol) in CH_3OH (30 mL). The solution was then treated with 1 M HCl, and the organic phase was extracted with CH_2Cl_2 (3 × 30 mL). After drying over $MgSO_4$ and evaporation, the 1,2-*bis*(benzylamino)ethane was isolated as a solid. 1,2-*Bis*(benzylamino)ethane (0.10 mol) was dissolved in toluene (15 mL) and *N*,*N*-dimethylformamide dimethylacetal (0.12 mol) was added. The solution was submitted to a water bath for 3 h in an inert atmosphere. At the end of this period, the mixture temperature was raised to 100 °C and allowed to stand for 1 h (Scheme 1). The toluene was removed in vacuum, and the product was used in the synthesis of the complex, which was very sensitive to air humidity and oxygen. The electron-rich olefin (0.1 mol) was dissolved in toluene and then $[PtCl_2(PEt_3)_2]_2$ (0.9 mol) was added and heated at 100 °C for 5 h. The solution was removed *in vacuo* to give a yellow solid. After washing with hexane, the product was crystallized in a dichloromethane–diethyl ether mixture (1:2).

2.3 | *trans*-Dichloro-[1,3-*bis*(4-dimethylaminobenzyl)imidazolidine-2-ylidine]triethylphosphineplatinum (II), 1a

Yield: 0.25 g, 68%; m.p., 222.4 °C. IR: $\nu_{(CN)}$, 1510 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.16 and 1.20 (t, J = 8.0 Hz, 9H, PCH_2CH_3), 1.86 (p, J = 8.0 Hz, 6H, PCH_2CH_3), 2.90 [s, 12H, $CH_2C_6H_4N(CH_3)_2$ – 4], 3.33 (s, 4H, NCH_2CH_2N), 5.15 [s, 4H, $CH_2C_6H_4N(CH_3)_2$ – 4], 6.70 and 7.42 [d, J = 8.0 Hz, 8H, $CH_2C_6H_4N(CH_2CH_3)_2$ – 4] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 7.75 (PCH_2CH_3), 12.4 (d, J = 120 Hz, PCH_2CH_3), 44.3 [$CH_2C_6H_4N(CH_3)_2$ – 4], 47.6 (NCH_2CH_2N), 52.9 [$CH_2C_6H_4N(CH_3)_2$ – 4], 112.6, 123.7, 129.9, 150.3 [$CH_2C_6H_4N(CH_3)_2$ – 4], 193.4 (d, J = 300 Hz, Pt-C_{karb}) ppm. Elemental analysis for $C_{27}H_{43}Cl_2N_4PPt$: calcd, C 45.00, H 6.01, N 7.77; found, C 45.02, H 6.00, N 7.75.

2.4 | *cis*-Dichloro-[1,3-*bis*(4-dibutylaminobenzyl)imidazolidine-2-ylidene] triethylphosphineplatinum (II), 1b

Yield, 0.34 g, 76%; m.p., 110.9 °C. IR: $\nu_{(CN)}$, 1519 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.95 [t, J = 8.0 Hz, 12H, $CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4], 1.20 [p, J = 8.0 Hz, 8H, $CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4], 1.34 [p, J = 8.0 Hz, 8H, $CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4], 1.54 (t, J = 8.0 Hz, 9H, PCH_2CH_3), 1.95 (p, J = 8.0 Hz, 6H, PCH_2CH_3), 3.23 [t, J = 8.0 Hz, 8H, $CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4], 3.30 (t, J = 4.0 Hz, 4H, NCH_2CH_2N), 4.48 and 5.63 [d, J = 8.0 Hz, 4H, $CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4], 6.58 and 7.31 [d, J = 8.0 Hz, 8H, $CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4]. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 8.9 [$CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4], 14.0 [$CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4], 20.3 [$CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4], 29.4 (PCH_2CH_3), 15.9 (d, J = 152 Hz, 6H, PCH_2CH_3), 50.7 [$CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4], 50.8 (NCH_2CH_2N), 54.7 [$CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4], 111.8, 120.6, 130.1, 147.9 [$CH_2C_6H_4N(CH_2CH_2CH_2CH_3)_2$ – 4], 176.7 (d, J = 14 Hz, Pt-C_{karb}). Elemental analysis for $C_{39}H_{67}$



SCHEME 1 Synthesis of platinum complexes **1a–e**

Cl_2N_4PPt: calcd, C 52.69, H 7.60, N 6.30; found, C 52.68, H 7.59, N, 6.32.

2.5 | *cis*-Dichloro-[1,3-*bis*(4-diethylaminopropoxybenzyl)imidazolidine-2-ylidine]triethylphosphineplatinum (II), 1c

Yield: 0.29 g, 69%; m.p., 172.3 °C. IR: $\nu_{(CN)}$, 1510 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.19 (t, J = 8.0 Hz, 9H, PCH_2CH_3), 1.91–1.96 [m, 10H, PCH_2CH_3 and $CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4)], 2.23 [s, 12H, $CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4], 2.44 [t, J = 8.0 Hz, 4H, $CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4], 3.28–3.34 [m, 4H, $CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4], 3.99 (t, J = 8.0 Hz, 4H, NCH_2CH_2N), 4.51 and 5.77 [d, J = 12.0 Hz, 4H, $CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4], 6.87 and 7.43 [d, J = 4.0 Hz, 8H, $CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4]. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 8.22 (PCH_2CH_3), 27.6 and 15.9 [d, J = 156 Hz, PCH_2CH_3 and $CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4], 45.6 [$CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4], 47.3 [$CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4], 54.5 [$CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4], 56.4 (NCH_2CH_2N), 66.3 [$CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4], 114.7, 126.4, 130.2, 159.0 [$CH_2C_6H_4OCH_2CH_2CH_2N(CH_3)_2$ – 4], 177.8 (d, J = 12 Hz, Pt-C_{karb}). Elemental analysis for $C_{33}H_{55}Cl_2N_4O_2PPt$: calcd, C 47.37, H 6.63, N 6.70; found, C 47.35, H 6.61, N 6.72.

2.6 | *cis*-Dichloro-[1,3-*bis*(4-piperidinylbenzyl)imidazolidine-2-ylidine] triethylphosphineplatinum (II), 1d

Yield: 0.30 g, 75%; m.p., 151.2 °C. IR: $\nu_{(CN)}$, 1515 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.19 (t, J = 8.0 Hz, 9H, PCH_2CH_3), 1.93 (p, J = 8.0 Hz, 6H, PCH_2CH_3), 1.57, 1.71 and 3.16 [p, J = 8.0 Hz, 20H, $CH_2C_6H_4(NC_5H_{10}O)$-4], 3.29 (s, 4H, NCH_2CH_2N), 4.55 and 5.65 [d, J = 8.0 Hz, 4H, $CH_2C_6H_4(NC_5H_{10})$ – 4], 6.89 and 7.36 [d, J = 4.0 Hz, 8H, $CH_2C_6H_4(NC_5H_{10})$ – 4]. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 7.7 (PCH_2CH_3), 8.3 (d, J = 152 Hz, PCH_2CH_3), 25.7, 47.4 and 50.5 [$CH_2C_6H_4(NC_5H_{10}O)$ – 4], 47.4 (s, 4H, NCH_2CH_2N), 54.7 [$CH_2C_6H_4(NC_5H_{10})$ – 4], 116.3, 129.7, 137.9 and 151.9 [d, J = 4.0 Hz, 8H, $CH_2C_6H_4(NC_5H_{10})$ – 4], 177.5 (d, J = 12 Pt-C_{karb}). Elemental analysis for $C_{33}H_{51}Cl_2N_4PPt$: calcd, C 49.50, H 6.42, N 7.00; found, C 49.53, H 6.40, N 7.02.

2.7 | *cis*-Dichloro-[1,3-*bis*(4-morpholinylbenzyl)imidazolidine-2-ylidine] triethylphosphineplatinum (II), 1e

Yield: 0.26 g, 65%; m.p., 192.9 °C. IR: $\nu_{(CN)}$, 1515 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.20 (h, J = 8.0 Hz, 9H, PCH_2CH_3), 1.95 (p, J = 8.0 Hz, 6H, PCH_2CH_3), 3.13 and 3.84 [t, J = 4.0 Hz, 16H, $CH_2C_6H_4(NC_4H_8O)$ – 4], 3.25–3.40 (m, 4H, NCH_2CH_2N), 4.48 and 5.77 [d, J = 8.0 Hz, 4H, $CH_2C_6H_4(NC_4H_8O)$ – 4], 6.87 and 7.43 [d, J = 4.0 Hz, 8H, $CH_2C_6H_4(NC_4H_8O)$ – 4]. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 8.2 (PCH_2CH_3), 15.7 (d, J = 152 Hz, PCH_2CH_3), 47.4, 48.8, 49.0, 51.7 [$CH_2C_6H_4(NC_4H_8O)$ – 4], 53.4 and 54.5 (NCH_2CH_2N), 66.8 [$CH_2C_6H_4(NC_4H_8O)$ – 4], 115.6, 123.4, 125.6, 129.9, 151.1, 158.1 [$CH_2C_6H_4(NC_4H_8O)$ – 4], 177.2 (d, J = 12 Hz, Pt-C_{karb}). Elemental analysis for $C_{31}H_{47}Cl_2N_4O_2PPt$: calcd, C 46.27, H 5.89, N 6.96; found, C 46.25, H 5.88, N, 6.94.

2.8 | X-ray crystallographic data

Single crystals of complexes **1a** and **1e** suitable for X-ray analysis were obtained by slow diffusion of diethyl ether into a dichloromethane solution of the complexes. Single crystal X-ray diffraction data of *trans*-dichloro-[1,3-

bis(4-dimethyllaminobenzyl)imidazolidine-2-ylidene]triethylphosphineplatinum (II) **1a** and c*is*-dichloro-[1,3-*bis*(4-morpholinilbenzyl)imidazolidine-2-ylidene]triethylphosphineplatinum (II) **1e** were collected at room temperature on an Rigaku-Oxford Xcalibur diffractometer with an Eos-CCD detector, operated at 50 kV and 40 mA using graphite monochromated Mo–Kα (λ = 0.71073 Å) radiation. Data collections and reductions along with absorption corrections were performed using CrysAlis^{Pro} software package.[41] Structure solutions were performed using SHELXT[42] embedded in the Olex2.[43] Refinement of coordinates and anisotropic thermal parameters of non-hydrogen atoms were carried out by the full-matrix least-squares method in SHELXL.[44]

2.9 | Cytotoxic activity

2.9.1 | Cell culture and incubation

Neuroblastoma (SHSY5Y), adenocarcinoma (HEP3B), colon carcinoma (HTC116) and human fibroblast (HF) cells were obtained from the American Type culture collection and maintained at 37 °C in a humidified incubator under 5% CO_2 conditions.[45] Cells were cultured in DMEM containing 10% fetal bovine serum and 1% antibiotics (100 μg/mL streptomycin and 10000 U/mL penicillin). Media were changed twice a week until cells reached 70–80% confluency.

2.9.2 | Cell viability assay

The MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4sulfophenyl)-2H-tetrazolium] assay was performed to identify the viable cell ratio according to the manufacturer's instructions (Promega). Briefly cells were seeded in 96-well flat-bottomed tissue culture plates at a concentration of 5×10^3 cells/well. After 24 h, the cells were treated with DMEM medium containing different concentrations (15, 25, 50 and 100 μM) of the test compounds for different incubation periods of 24, 48 and 72 h). At the end of each time point, fresh complete medium containing 10 μL of MTS solution was added and further incubated for 2 h in the incubator. Cell proliferation was assessed by measuring the absorbance with an ELISA microplate reader (Weida). Each experiment was performed in quadruplicate and results are expressed as the percentage growth inhibition with respect to the untreated cells. Statistical deviations for the viability were calculated automatically using Excel 2007 (SE $\leq$ 5%) and for the IC_{50} using "Origin Pro 7.5" and "Origin 6.1" (for 7Crf) PC.

3 | RESULTS AND DISCUSSION

3.1 | Preparation of platinum (II) complexes

4,5-Dihydroimidazol-2-ylidenes containing an unhindered R group[46,47] readily dimerize to give tetraaminoethene derivativea (L_2^R), which behave as carbene precursors under relatively mild conditions. The synthesis of the tetraaminoethene was accomplished in a three-step procedure as described in Scheme 1. The Schiff base was synthesized using a method similar to that reported by Billman et al.[48] The 1,2-disubstituted ethylendiamine was prepared successfully and subsequently reduced by $NaBH_4$ in CH_3OH. The tetraaminoethene (L_2^R) was synthesized by formylation of the NH bonds in an excess of $Me_2NCH(OMe)_2$ according to the literatüre.[49] The functional tetraaminoethenes readily reacted with the $[PtCl_2(PEt_3)]_2$ to afford $[PtCl_2(NHC)(PEt_3)]$ (**1a–e**) via a cleavage C=C bond. Each of the complexes (**1a–e**) was obtained in high yield as air-stable crystals, which where characterized by elemental anaysis, IR, ^{1}H and ^{13}C-NMR spectra. Their ^{13}C NMR spectra compare well with those of analogous complexes described in the literature. The characteristic peak of the platinum (II)–carbene resonance for compounds **1a–e** displays as a singlet at 193.4 176.7, 177.8, 177.5 and 177.2 ppm, respectively, in the ^{13}C NMR spectra. The chemical shift is consistent with those of the known platinum (II)–NHC complexes in the range of 173–195 ppm.[50] Platinum (II)–NHC complexes (**1a–e**) exhibit a characteristic $\nu_{(CN)}$ band typically at 1510, 1519, 1510, 1515 and 1515 cm^{-1}, respectively. Additional elemental analyses of these complexes are in agreement with the molecular formula proposed (Table 1).

3.2 | Single crystal X-ray diffraction and structure analysis of platinum complexes (1a, 1e)

All non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms of the title compounds on their respective parent carbon atoms were generated geometrically: C–H = 0.96 Å for methyl groups, C–H = 0.93 Å for methylene groups and C–H = 0.93 Å for aromatic groups. In **1e**, the H atoms bounded to C4 atom appeared in two positions with equal s.o.f. values because of the symmetrical disorder. Equal U_{ij} constraints (EADP) were used for the C atoms of phenyl and morpholinylbenzyl rings in **1e**, but for the C atoms of only one phenyl ring in **1a**. A summary of crystallographic data, experimental details and refinement

TABLE 1 Physical and spectroscopic properties of new compounds

Compound	Formula	Isolated yield (%)	m.p. (°C)	ν(CN) (cm^{-1})	C(2) ^{13}C NMR (ppm)	*J* (Hz)
1a	$C_{27}H_{43}Cl_2N_4PPt$	68	222.4	1510	193.4	300
1b	$C_{39}H_{67}Cl_2N_4PPt$	76	110.9	1519	176.7	14
1c	$C_{33}H_{55}Cl_2N_4O_2PPt$	69	172.3	1510	177.8	12
1d	$C_{33}H_{51}Cl_2N_4PPt$	75	151.2	1515	177.5	12
1e	$C_{31}H_{47}Cl_2N_4O_2PPt$	65	192.9	1515	177.2	12

results for the compounds is given in the Supporting Information. Further details concerning data collection and refinements are given in the Supporting Information.

A coordination of the *N*-heterocyclic carbene group (*trans* for **1a** and *cis* for **1e**) and phosphine group to Pt (II) atom is observed in the single crystal X-ray analysis of the complexes. The Pt (II) atom in **1e** lies on a twofold reflection plane. The asymmetric unit of the **1a** contains one molecule whereas the asymmetric unit of the **1e** contains half of a molecule (Figure 2). The other half of the molecule is generated with an $x, 1/2 - y, z$ symmetry operator. The dihedral angle between the two morpholinylbenzyl ring is 70.2(4)° in **1a**. The Pt1/Cl1/Cl2/P1/C1 coordination plane of the complexes is formed

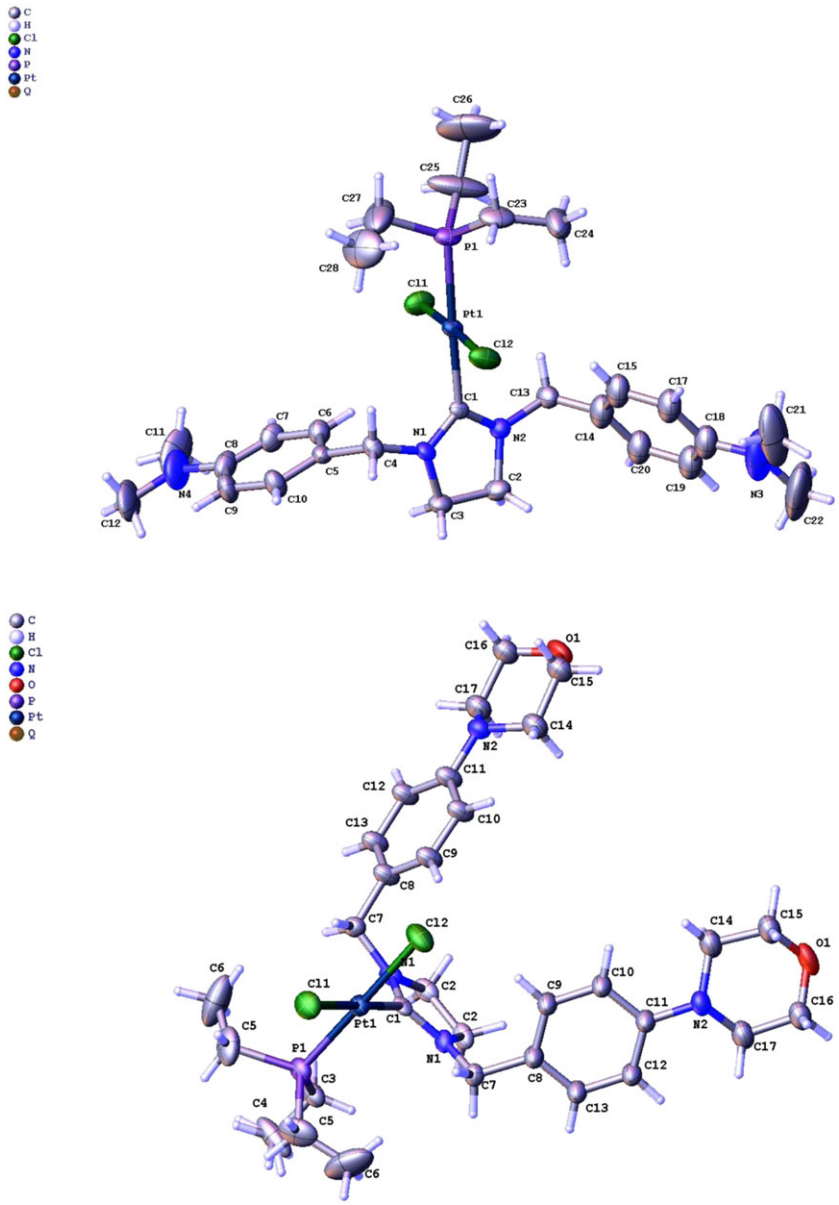


FIGURE 2 The molecular structure of 1a and 1e with atom numbering scheme and 75% probability displacement ellipsoids

by the slightly distorted square-planar coordination of the platinum (II) metal as reported for similar *N*-heterocyclic carbene complexes.[51] This coordination plane of **1a** and **1e** is nearly perpendicular to the plane of the imidazolidine ring, making a dihedral angle of 78.2 (3)° and 85.7 (6)°, respectively. The Pt–C bond lengths [1.977(10), 2.047 (6) Å] are compatible with those of many other Pt (II) complexes.[52] However, the value in **1e** is shorter than that in **1a.** These results show that the *N*-heterocyclic carbene ligands are more weakly bound to the Pt center in the *trans* form.[53] The Pt–P bond distances [2.231(4), 2.295(18) Å] are similar to those reported previously.[54–56] The bond angles at the Pt atom involving *trans* pairs of substituents deviating from the expexted values of 180° and 90° are Cl2–Pt1–P1 [91.78(6)° in **1a**; 177.99° (12) in **1e**] and Cl1–Pt1–C1 [89.40(8)° in **1a**; 180.00°(3) in **1e**]. The small difference between these angles confirms the distorted square planar geometry. These can be taken as a larger proportion of the σ-donor character in the Pt–P bonds, which results in a greater strict effect.[57] All of the bond lengths and bond angles (Table 2) are approximately within the normal range compared with other similar complexes (Figure 3).[58,59]

The bonding within the NHC ring demonstrates a pattern of delocalization in which the N1–C1 = 1.325(8) Å is significantly shorter than N1–C2 = 1.477(10) Å in **1**, and N1–C1 = 1.309(7) Å and N2–C1 = 1.334(4) Å are shorter than the N1–C3 = 1.466(8) Å and N2–C2 = 1.466(8) Å in **1a** in accordance with a previous study.[58] This is possibly indicative of a greater partial double bond character owing to partial electron donation by nitrogen to the carbene C-atom donor.[60]

Molecular packing in the crystal structure of the compound **1e** is stabilized by the intermolecular C–H···O interactions with the following dimensions C13–H13 = 0.929(15) Å, H13···O1 = 2.438 Å, C13···O1 = 3.336(13) Å, C13–H13···O1 = 162.6(12) Å along the *c*-axis (Figure 4) whereas molecular packing in the crystal structure of the compound **1a** is stabilized by the intermolecular C–H···Cl interactions which are formed with an R_2^2 (12) ringmotif[61] with the following dimensions: C2–H2A = 0.97(10) Å, H2A···Cl1 = 2.783(7) Å, C2···Cl1 = 3.677(7) Å, C2–H2A···Cl1 = 153.6(7) Å along the *abc* plane (Figure 3).

3.3 | Antitumor activities of platinum–NHC complexes

The IC_{50} values of all complexes against three human cancer cell lines (SHSY5Y, HTC116, HEP3B) and healthy cell line (HF) were measured and are listed in Table 3. It was determined that the complexes **1a**–**e** have lower

TABLE 2 Selected experimental parameters of the compounds

Compound 1a		**Compound 1e**	
	Bond lengths (Å)		***Bond lengths (Å)***
Pt1–Cl1	2.2979(19)	Pt1–Cl1	2.351(3)
Pt1–Cl2	2.2926(18)	Pt1–Cl2	2.355(4)
Pt1–P1	2.2950(18)	Pt1–P1	2.231(4)
Pt1–C1	2.047(6)	Pt1–C1	1.977(10)
Pt1–C23	1.777(8)	P1–C3	1.817(12)
	Bond angles (deg)		***Bond angles (deg)***
Cl1–Pt1–Cl2	176.78(6)	Cl1–Pt1–Cl2	89.93(12)
Cl1–Pt1–P1	91.18(7)	Cl1–Pt1–P1	88.06(12)
Cl1–Pt1–C1	89.40(18)	Cl1–Pt1–C1	180.0(3)
Cl2–Pt1–P1	91.97(6)	Cl2–Pt1–P1	177.99(12)
Cl2–Pt1–C1	87.47(18)	Cl2–Pt1–C1	90.1(3)
P1–Pt1–C1	178.7(2)	P1–Pt1–C1	91.9(3)
Pt1–P1–C23	115.4(3)	Pt1–P1–C3	116.1(4)
Pt1–P1–C25	111.8(3)	Pt1–P1–C5	113.1(5)
Pt1–P1–C27	113.8(4)	Pt1–C1–N1	124.4(5)
Pt1–C1–N1	125.9(5)		
Pt1–C1–N2	124.0(4)		

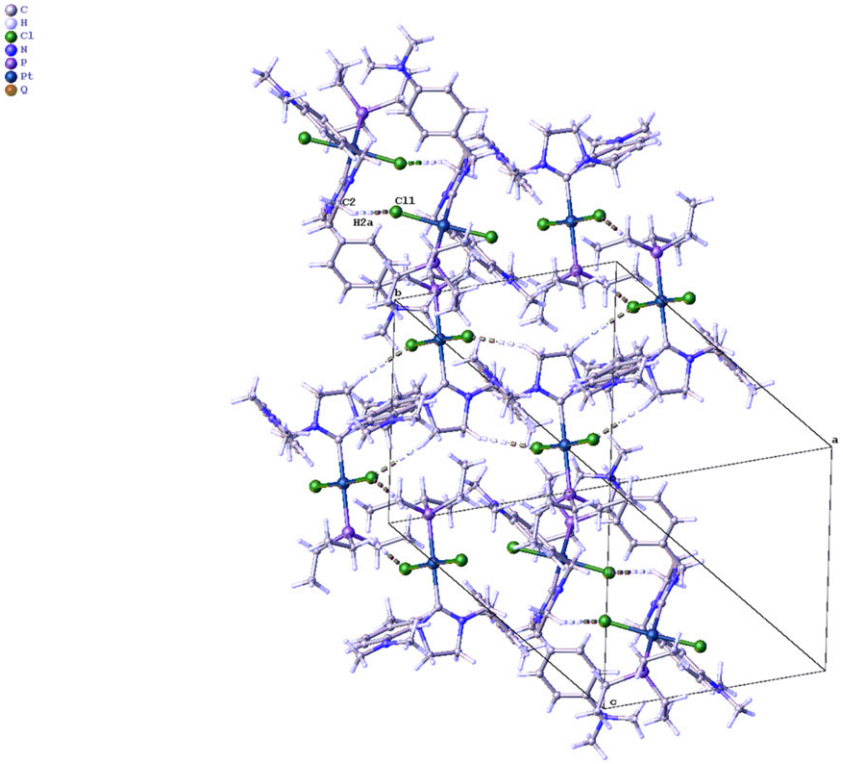


FIGURE 3 The packing diagram of the compound **1a** by C–H···Cl hydrogen bonds along the *(abc)* plane

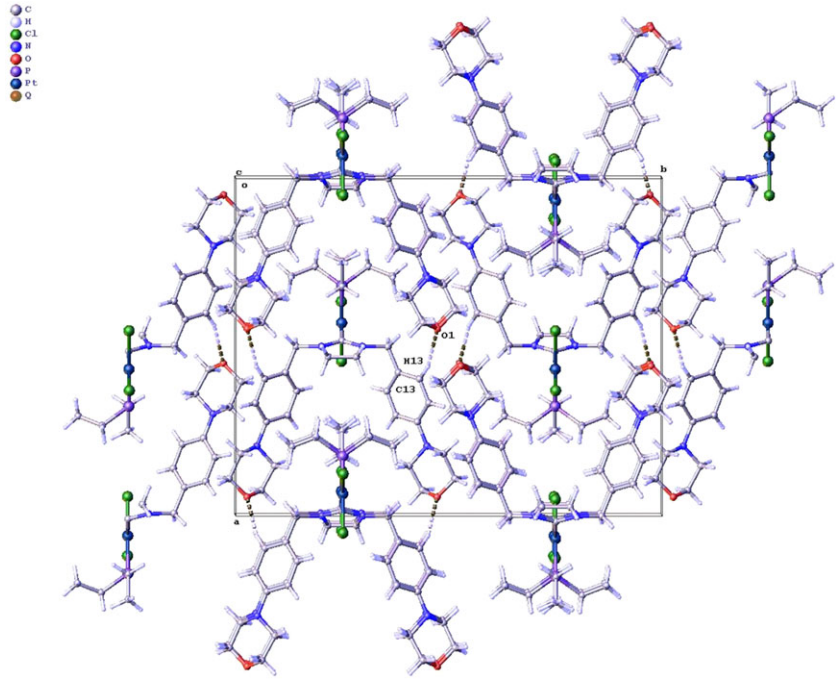


FIGURE 4 The packing diagram of the compound **1e** by C–H···O hydrogen bonds along the *c*-axis

cytotoxic activity against both cancer cell lines and healthy cell line compared with the cispaltin group. On the other hand, compound **1b** showed significant cytotoxicity in three cancer cell lines, but did not cause a cytotoxic effect in HF cells. Cisplatin caused more severe cytotoxic effects in HF compared with **1b**. In this context we determined that 1b is safer compared to cisplatin. In addition, the IC_{50} values of **1b** (1.629±) were lower than those for cisplatin (11.28) in SHSY5Y cell lines. Therefore we claimed that **1b** was more effective and more cytotoxic for the SHSY5Y cell line compared with cisplatin. Furthermore, **1b** exhibits cytotoxic activity in all cancer cell lines in which IC_{50} values below 50 μM are observed (Table 3). In addition, cytotoxic activities of **1a–e** were weaker as they had higher IC_{50} values when compared with cisplatin. Therefore, cisplatin has been

TABLE 3 IC_{50} values for NHC complexes (μM), (mean ± SEM)

		IC_{50}		
Complex	**Hep3B**	**SHSY5Y**	**HTC116**	**HF**
Cisplatin	13.29 ± 1.16	11.28 ± 0.98	14.32 ± 1.67	0.012 ± 0.0001
1a	453.8 ± 44.65	66.23 ± 6.13	170.9 ± 16.5	1298 ± 117
1b	49.60 ± 6.75	1.629 ± 0.098	31,62 ± 2.96	114.6 ± 10.87
1c	867.8 ± 74.5	118.1 ± 9.65	2190 ± 198	2945 ± 280
1d	546.3 ± 48.7	95.34 ± 8.64	354.1 ± 29.6	459.6 ± 39.3
1e	837.5 ± 78.1	78.21 ± 8.01	1464 ± 154	1478 ± 125

shown to have more effective cytotoxic activity. All of these data show that the most potent cytotoxic compound is **1b**, and that some cell lines (SHSY5Y) may be more effective and safe than cisplatin in terms of IC_{50} values.

The cell viability of complexes and cisplatin against cancer cell lines and healthy cell line is given in Figures S5–S9 (see Supporting Information). The compound **1a** partially affected the SHSY5Y cells on 100 μM concetration in third day, but no effect was observed at the other cancer cells on determined concentrations. Similarly, compound **1d** affected only SHSY5Y cells on 50 μM concentration but it did not effect other cell lines (Figure S9). In terms of **1c** and **1e**, no cytotoxic activity was seen at 15–100 μM concentration on the first, second and third days in all cancer and healthy cell lines.

The NHC complexes have been important for selective and effective cancer therapy in recent years. The interest in the development of gold-based anticancer drugs is generally related to the treatment of rheumatoid arthritis, whereas the use of platinum-based anticancer drugs suggests that NHC platinum derivatives may have the same effect.[62] Until now, many reports on NHC complexes have shown that many derivatives, such as gold, silver and platinium in micromolar or submicromolar concentrations, have cytotoxicity.[63,64]

After the discovery of cisplatin, platinum complexes have begun to play an important role in anticancer therapy and are now the strongest metal-based drug type. We determined that the **1b** complexes have greater antiproliferative activity than cisplatin in three cancer cell lines (SHSY5Y, HTC116, HEP3B). In addition, they were safer than cisplatin in HF cells, with low IC_{50} values. On the other hand **1a**, **c–e** complexes did not have significant antiproliferative activity compared with cispaltin. These results agree well with a general feature reported in the literature. Similar to this paper, many biological studies on platinum NHC complexes have shown that different kinds of NHC ligands (e.g. xanthine, benzimidazole or imidazole derivatives) have antiproliferative activity in cancer cell lines.[65] Chtchigrovsky determined that new mono- and bimetallic (NHC)PtX_2(amine) complexes induce cell death by cellular pathways in various cancer cell lines such as nasopharyngeal epidermis carcinoma, ovarian carcinoma and myelomonocytic leukemia.[66] Additionally, Bippus et al. reported that some cationic platinum phosphine complexes containing thiocarbamate ligands show *in vitro* cytotoxicity in three human cancer cell lines (A549, CH1, SW480), particularly in the ovarian carcinoma cell line (CH1).[67] Also Marzano et al determined that a series of new platinum (II) amidine derivatives were active against a panel of human tumor cell lines containing examples of cervix (HeLa), breast (MCF7), lung (A549) and colon (HCT-15) cancer.[68a, b]

A genereal feature of structure–activity correlations for such complexes is unfolding, allowing a predection of the influence of the central metal, the NHC substituents, the charge, the lipophilicity and the sterical encumbrance around the metal center on their biological properties.[68a,b,69] The reason for the high cytotoxic activity of **1b** complex would be the well governed steric bulk and the chemical environment around the platinium center by the NHC ligand. In the case of other complexes, which are sterically less bulky than **1b**, weak governed steric and electronic properties by NHC ligands may lead to lesser cyctotoxic activity. These observations point out that the steric and electronic properties of NHCs have a major influence on the cyctotoxic activity of the platinium center and complexes can show different activities against various cancer cell lines. Amongst the generally bigger and more lipophilic monophosphine complexes, the *N*-4-dibutylaminobenzyl substituted **1b** was more active than other complexes. The complex *cis*-[Pt (PEt_3)(NHC)Cl_2], which bear an accesible chlorido leaving group ligand, although to a lesser extent, bound coordinatively to DNA but also initiated some DNA aggregation.[69]

4 | CONCLUSIONS

In summary, in this study, a series of functionalized imidazolidine-2-ylidine platinum (II) complexes (**1a–e**) are accessible from appropriately *N*-substituted

tetraaminoalkene, L_2^R. All of these compounds were characterized by spectroscopic and analytic techniques. A preliminary anticancer study of these compounds was evaluated against the three human cell lines brain (SHSY5Y), colon (HTC116), and liver (HEP3B). The platinum complexes were found to be active against the tested cell lines, showing comparable activity with examples in the literature. An important effort is currently being made in our laboratories to develop the potential of these complexes for biological or catalytic applications.

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