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Antiproliferative activity and DNA binding studies of cyclometalated complexes of platinum(II) containing 2-vinylpyridine

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Abstract The cytotoxic activity of four cyclometalated platinum(II) complexes [PtMe(vpy)(L)], containing 2-vinylpyridine (vpy) and the phosphine ligands (L) PMe_2Ph (**1a**), PPh_3 (**1b**), $PMePh_2$ (**1c**), and $P(c\text{-}Hex)_3$ (**1d**), were evaluated against human breast cancer (MDA-MB-231), human lung cancer (A549), human colon cancer (SW1116), and non-tumor epithelial breast (MCF-10 A) cell lines. The highest activity was found for **1c** with IC_{50} values of 21.10 µM, 23.36 µM, and 12.96 µM, compared to cisplatin, which was 10.12 µM, 47.57 µM, and 19.50 µM against the A549, SW1116, and MDA-MB-231 cell lines, respectively. **1a–d** showed a higher selectivity index (SI) than cisplatin. Docking studies confirmed interaction to the DNA minor groove for all complexes. Genotoxicity studies on **1c** showed interactions with the genomic content of malignant cells. Compared with cisplatin as a positive control, a slight shift was found in the electrophoresis mobility, which was utilized further to study the direct interaction of **1c** with DNA.

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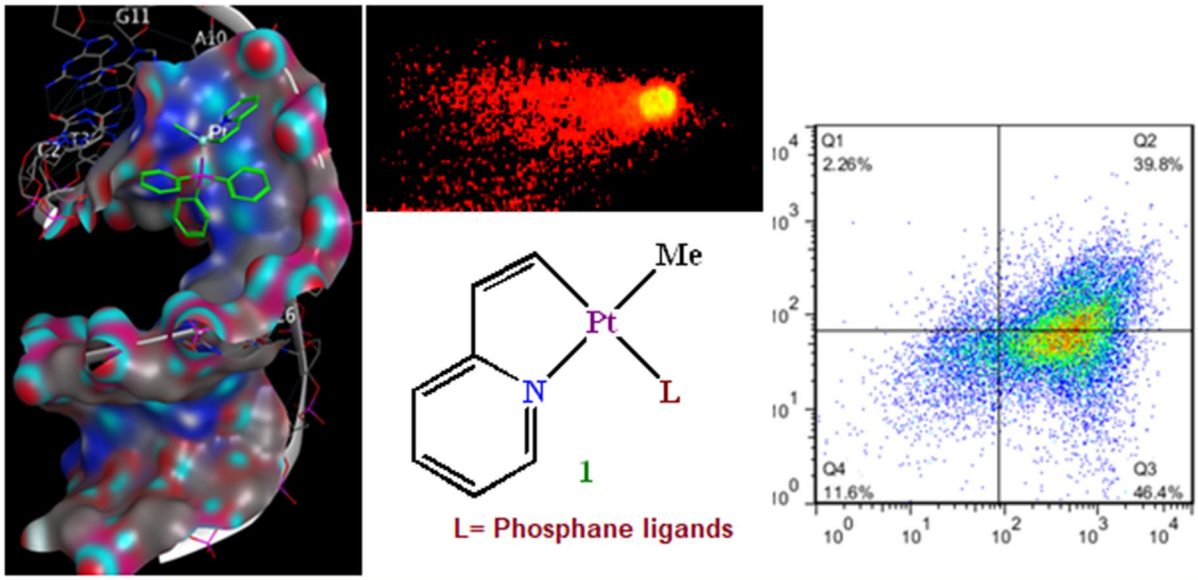
Graphical abstract



Complex	(IC_{50} ± SD) µM				Selectivity Index (SI)[1]
	A549	SW1116	MDA-MB-231	MCF-10A	
1a	24.94±1.84	27.96±0.09	21.96±0.32	42.36±0.87	1.92

Keywords Cyclometalated complexes of platinum (II) · Cytotoxic activity · Apoptosis · DNA binding

Introduction

Cisplatin, oxaliplatin, and carboplatin are the only FDA-approved platinum-based anticancer drugs (Farrell 2015; Johnstone et al. 2016; Kenny and Marmion 2019; Messori and Merlino 2016). These anticancer agents and other potential metallodrugs such as lobaplatin, heptaplatin, and nedaplatin are used to treat variety of tumors (Oun et al. 2018; Wang et al. 2015). However, these compounds have serious disadvantages, side effects, and toxicities for the healthy cells and organs in the patient's body (Oun et al. 2018). Furthermore, another main issue with the chemotherapy treatment is the resistance of cancer cell lines against antitumor drugs. Since the potency of these chemotherapeutic agents often decreases or is lost after a number of cycles of remedy (Burger et al. 2011; Oun et al. 2018; Wang and Guo 2011; Wang et al. 2015). To overcome these concerns, various methods and approaches have been recommended and developed by many research groups. Therefore, it is vital to improve the biological activity of these categories of anticancer agents or introduce new chemotherapeutic drugs with differences in their mechanisms of action or coordination properties to the current marketed antitumor agents (Bergamo and Sava 2015; Johnstone et al. 2016).

Cyclometalated platinum(II) complexes are a novel class of organometallic compounds with broad applications in the material (Berenguer et al. 2018; Chi and Chou 2010; Ezquerro et al. 2017; Murphy and Williams 2010), and medicinal (Lalinde et al. 2018; Millán et al. 2019) sciences. They have shown attractive luminescence and promising anticancer properties, while becoming good alternatives to the present platinum chemotherapy agents (Babak et al. 2018; Omae 2014; Zou et al. 2014). The propensity to the bioactive cycloplatinated(II) complexes is mainly related to the unrivaled structure of these compounds in biological

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conditions due to the existence of strong sigma bonds between the platinum center and the coordinated carbon of cyclometalated ligands. This feature enhances the stability of the cycloplatinated(II)complexes complexes in physiological media and excludes undesirable reactions (Bauer et al. 2017; Fereidoonnezhad et al. 2018a; Lalinde et al. 2018; Millán et al. 2019). These capabilities have allowed these compounds to demonstrate high cytotoxicity against resistant cancer cell lines. Also, the correct selection of the ancillary groups (phosphines) (Fereidoonnezhad et al. 2018a; Lalinde et al. 2018; Millán et al. 2019), and cyclometalated ligands (C^N) (Fereidoonnezhad et al. 2017a, b; Shahsavari et al. 2021) in the structure of the cycloplatinated(II) complexes has a vital role in the antiproliferative activity of these compounds. As a result, slight changes in the backbone of Pt(II) complexes can manifest different biological activities (Shahsavari et al. 2021).

Based on this perspective and our great interest in the evaluation of the anticancer activity of cycloplatinated(II) complexes (Fereidoonnezhad et al. 2017a, b, c, 2018a; Hajipour et al. 2021; Shahsavari et al. 2019, 2021), we decided to choose a less explored category of cycloplatinated(II)compounds i.e., 2-vinylpyridine (vpy) family (Dolatyari et al. 2021; Niazi and Shahsavari 2016a, b; Zucca et al. 2014). We synthesized four previously reported 2-vinylpyridinate Pt(II) complexes with different phosphine donor ligands. The kinetic, photophysical properties (Dolatyari et al. 2021; Niazi and Shahsavari 2016a), and electrochemical behavior (Zucca et al. 2014) of this class of complexes have been investigated, while in the present study, the *in vitro* cytotoxic activity of these compounds against several tumor cell lines such as lung (A549), invasive breast cancer (MDA-MB-231), and colon (SW1116), as well as normal breast (MCF-10 A) using MTT assay, has for the first time been reported by us. To understand the antiproliferative mechanism of these compounds, the interaction of these compounds with DNA using molecular docking studies, comet assay, and electrophoresis mobility shift assay was explored. The effect of **1c** on the induction of apoptosis against MDA-MB-231 has also been investigated.

Materials and methods

Chemistry

^{1}H NMR (400 MHz), and ^{31}P{^{1}H} NMR (162 MHz) spectra were recorded on a Bruker Avance III instrument and were referenced to SiMe4 (for ^{1}H and ^{13}C) and 85% H_3PO_4 (for ^{31}P). 2-Vinylpyridine (vpy), $PPhMe_2$, PPh_3, PPh_2Me, PCy_3 and the other chemicals were purchased from commercial sources. The complexes [PtMe(vpy)(dmso)], **A**, (Niazi and Shahsavari 2016a, b; Zucca et al. 2014) PtMe(vpy)($PPhMe_2$)], **1a**, (Dolatyari et al. 2021) [PtMe(vpy)(PPh_3)], **1b**, (Dolatyari et al. 2021; Zucca et al. 2014) [PtMe(vpy)(PPh_2Me)], **1c**, (Niazi and Shahsavari 2016a) and [PtMe(vpy)(PCy_3)], **1d**, (Zucca et al. 2014) were prepared according to the literature methods.

Cell culture and MTT assay

MDA-MB-231, A549, SW1116, and MCF-10 A were used alongside with a standard 3-(4,5-dimethylthiazol-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay as described in our previous work (Fereidoonnezhad et al. 2020). All experimental details were reported in the Supplementary Information.

Docking procedure

The complexes **1a–d** were studied on four different DNA structures, (PDB ID: 1BNA, 3CO3, 198D, and 1LU5), and human serum albumin (HSA, PDB ID: 4S1Y) using AutoDock 4.2 based on the Lamarckian genetic algorithm (Taheri et al. 2020). All the details were reported in the Supplementary Information.

Shift mobility assay

The interaction of **1c** with the circular pGEM-FT plasmid was assessed using the electrophoresis mobility shift assay based on known methods (Sakamaki et al. 2019). All the experimental details have been reported in the Supplementary Information.

Comet assay

We also used the comet assay to determine the genotoxic potential of **1c**. To accomplish this, 5×10^5

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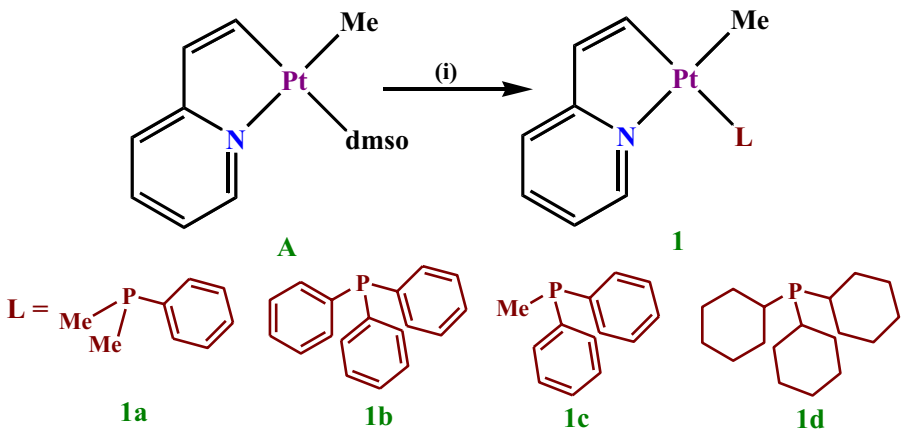

Scheme 1 Synthesis of cyclometalated 2-vinylpyridine Pt(II) complexes **1a–d**. (i): L, acetone, room temperature (Dolatyari et al. 2021; Niazi and Shahsavari 2016a, b; Zucca et al. 2014)

MCF7 cells were cultured in 2 ml complete culture media and treated with **1c** in a 13 µM. All the experimental details were reported in the Supplementary Information.

Cellular uptake

Inductively coupled plasma mass spectrometry (ICP-MS) were carried out to quantify the amount of Pt taken up by the cells based on known method (Nahaei et al. 2022). All the experimental details were reported in the Supplementary Information.

Statistical analysis

Figure 4b graph, calculations, and statistical analyses (Tables S1–S4) were performed using GraphPad Prism software version 8.0 (GraphPad Software, San Diego, CA, USA). The one-way ANOVA was used to compare the means of various numerical variables.

Results and discussion

Chemistry

Based on the previously reported methods, the synthesis of the cycloplatinated(II) complexes bearing various phosphines (L) is shown in Scheme 1. (Dolatyari et al. 2021; Niazi and Shahsavari 2016a, b; Zucca et al. 2014). The reaction of previously reported starting material complex [PtMe(vpy)(DMSO)], **A**,(Niazi and Shahsavari 2016a, b; Zucca et al. 2014) vpy = 2-vinylpyridine; DMSO = dimethyl sulfoxide, with one equivalent of different L ligands gave known product complexes [PtMe(vpy)

Table 1 Cytotoxic activity of the studied complexes against three cancerous cell lines (A549, SW1116, and MDA-MB-231) and non-tumorigenic breast cell line (MCF-10 A)

Complex	(IC_{50} ± SD) µM			MCF-10 A	Selectivity Index (SI)[1]
	A549	SW1116	MDA-MB-231		
1a	24.94 ± 1.84	27.96 ± 0.09	21.96 ± 0.32	42.36 ± 0.87	1.92
1b	49.48 ± 2.77	92.80 ± 0.81	36.18 ± 1.19	75.32 ± 1.54	2.08
1c	21.10 ± 2.53	23.36 ± 0.73	12.96 ± 0.90	29.84 ± 1.23	2.30
1d	91.89 ± 1.49	57.86 ± 0.75	44.08 ± 0.65	96.16 ± 1.49	2.18
Cisplatin	10.12 ± 1.52	47.57 ± 1.29	19.50 ± 1.30	28.73 ± 1.55	1.47

Incubation time: 72 h

[1]IC_{50} for MCF-10 A cell line/IC_{50} for MDA-MB-231 cell line

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(L)], **1**, L = dimethylphenylphosphine ($PPhMe_2$, **1a**); (Dolatyari et al. 2021) triphenylphosphine (PPh_3, **1b**); (Dolatyari et al. 2021; Zucca et al. 2014) methyldiphenylphosphine (PPh_2Me, **1c**); (Dolatyari et al. 2021; Niazi and Shahsavari 2016a) tricyclohexylphosphine (PCy_3, **1d**), (Zucca et al. 2014) in good yield. The successful preparation of these compounds was confirmed by (^1H and $^{31}P\{^1H\}$) NMR spectroscopy. The presence of the phosphine ligands can improve the anti-proliferative activity of the Pt(II) complexes. Therefore, we investigated the biological activity of our cycloplatinated(II) compounds **1a–d** on several tumor cell lines.

Biological activity

From the four Pt complexes (**1a–d**), **1c** showed the highest activity with IC_{50} values of 21.10 µM, 23.36 µM, and 12.96 µM, against the A549, SW1116, and MDA-MB-231 cell lines, respectively (Table 1), all of them lower than the values for cisplatin (10.12 µM, 47.57 µM, and 19.50 µM). One-way ANOVA statistical analysis showed that this difference is statistically significant. In addition, the MTT test against MCF-10 A, a non-tumorigenic epithelial breast cell line, revealed that the compounds could differentiate well between tumorigenic and non-tumorigenic cell lines. The selectivity index (IC_{50} for the MCF-10 A cell line/IC_{50} for the MDA-MB-231 cell line) for the four Pt(II) complexes was generally larger than 2, compared with the 1.47, calculated for cisplatin. The studied complexes were shown to have a good and acceptable selectivity index (SI) between the tumorigenic and non-tumorigenic cell lines. **1b** and **1c** have a higher selectivity for human breast cancer cells while causing less harm to normal epithelial breast cells.

The structure-activity relationship investigation revealed that **1c** and **1a**, which contain PPh_2Me and $PPhMe_2$ ligands, show significantly higher antitumor activity than the other compounds, while the presence of the PPh_3 and PCy_3 ligands in compounds **1b** and **1d** significantly reduced cytotoxic activity in these complexes. It seems that the presence of a small, non-cyclic group such as methyl attached to the phosphorus moiety can increase the anti-proliferative activity.

To compare the cytotoxic activity of the synthesized compounds in this study with that of other studies, we used papers whose MTT method was almost similar to ours, to make a more accurate comparison.

Table 2 Molecular docking binding energies (kcal/mol) of the complexes (**1a–d**) in binding to different DNA structures, as well as HSA (human serum albumin)

Name/receptor	1BNA[a]	198D[b]	3CO3[c]	1LU5[d]	4S1Y[e]
1a	− 8.95	− 8.51	− 6.92	− 6.10	− 6.04
1b	− 9.91	− 9.23	− 8.00	− 7.15	− 6.61
1c	− 10.06	− 8.71	− 8.08	− 7.35	− 7.17
1d	− 9.74	− 8.88	− 8.15	− 8.21	− 7.04
Cocrystal-Ligand	–	–	− 6.39	− 6.78	− 6.90

[a]Structure of a B-DNA dodecamer

[b]Trigonal form of the idarubicin-D(CGATCG) complex (DNA structure with intercalation site)

[c]*Cis*-Diammine(pyridine)chloroplatinum(II) Bound to Deoxyguanosine in a Dodecamer Duplex (a monofunctional platinum-DNA Adduct) (Lovejoy et al.)

[d]Asymmetric platinum complex $\{Pt(NH_3)(cyclohexylamine)\}^{2+}$ bound to a Dodecamer DNA Duplex. (Silverman et al.)

[e]X-ray structure of human serum albumin complexed with cisplatin

In this regard, the results obtained from the cytotoxic activity of the best compound studied by Mavroidi et al. showed that this compound had an IC_{50} of 26.7 µM on invasive breast cancer (MDA-MB-231), in contrast, **1c** in our study showed higher anti-proliferative activity with an IC_{50} of 12.96 µM on the same cancer cell line (Mavroidi et al. 2016). In another study based on the results of cytotoxic activity, [Pt(bzq)(SpyO)], had an IC_{50} of 59.1 µM on the A549 cell line, while **1c** in our study had an IC_{50} of 22.1 µM on the same cancer cells (Fereidoonnezhad et al. 2018b).

Molecular docking studies

To find the binding position and binding modes for DNA, molecular docking studies were performed on the Pt(II) complexes containing 2-vinylpyridine. The docking binding energies of complexes (**1a–d**) with various DNA structures and HSA are shown in Table 2. Negative binding free energy values indicate that these complexes are tightly linked to DNA. The ΔG_{bind} values of the best-docked poses of the Pt(II) complexes in binding to DNA (PDB ID: 1LU5) are within the range of − 6.10 to − 8.21 kcal mol^{-1}, in binding to 1BNA are within the range of − 8.95 to − 10.06 kcal mol^{-1}, in binding to 3CO3 are within the range of − 6.92 to − 8.15 kcal mol^{-1}, and in

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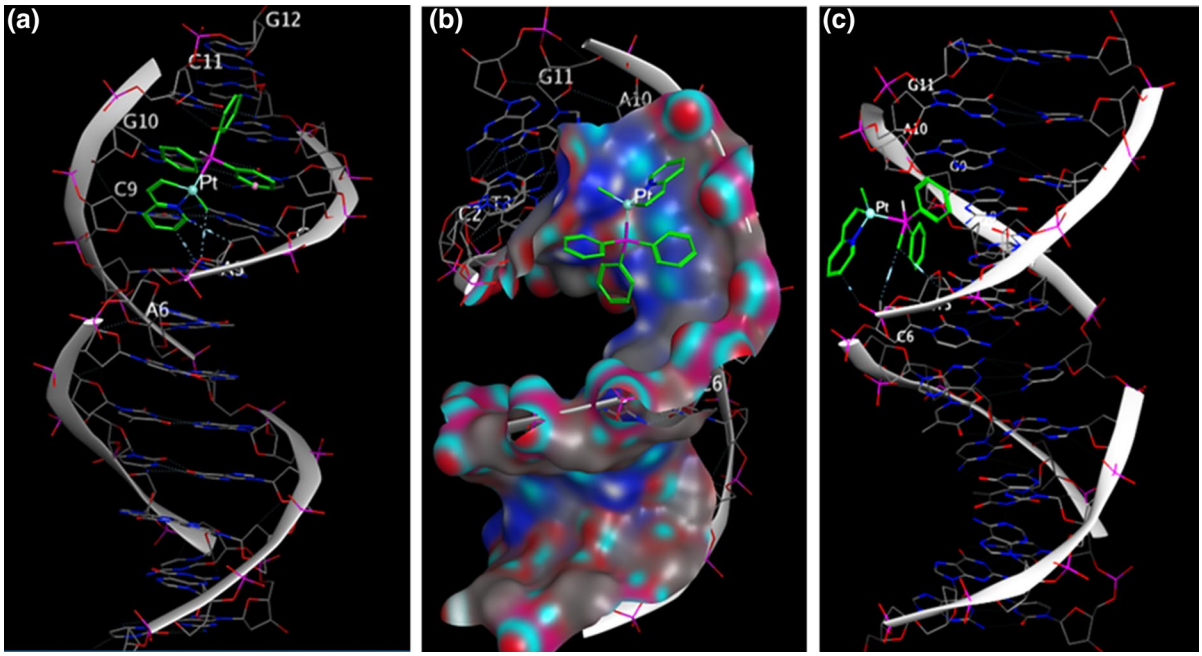

Fig. 1 Studies of the interaction between compounds and DNA using molecular docking simulations. **a 1a** with PDB ID: 1BNA, **b 1b** with 1LU5, **c 1c** with 3CO3

binding to 198D are within the range of − 8.51 to − 9.23 kcal mol^{-1}.

As shown in Table 2, compound **1d** has the best (most negative) binding energy to different DNA structures. This compound performs better in binding to DNA due to its platinum nucleus containing the vinylpyridine-2 ligand. However, better binding to DNA does not indicate better cytotoxic activity of this compound. The order of the docking energy of the compounds on the four DNA structures is as follows: in binding to 1BNA: **1c > 1b > 1d > 1a**, in binding to 1LU5: **1d > 1c > 1b > 1a**, in binding to 3CO3: **1d > 1c > 1b > 1a**, in binding to 198D: **1b > 1d > 1c > 1a**.

Re-docking of the co-crystallized conformation of ligands (as shown in Table 2 for 3CO3, 1LU5, and 4S1Y) into the 3D structure of the receptors was also studied as part of the docking validation stage. For the studied targets, the RMSD was less than 2 Å.

As shown in Fig. 1a, compound **1a** is located in the minor groove of DNA (1BNA), so the key connections of this compound are with the bases in the minor groove of DNA. It has shown interaction via hydrophobic interaction with bases G4, G10, and C11 through its two methyl groups. The compound also forms a π–π interaction with the G10 base through the pyridine ring. As shown in Fig. 1b, compound **1b** is also oriented in the minor groove of DNA (1LU5). It binds to the G5 base through carbon number 2 of the pyridine ring and its phosphine group. The key junctions of compound **1c** with the bases in the minor groove of DNA (3CO3) are shown in Fig. 1c. It binds to the T5 base through its methyl group via hydrophobic interaction. It has also interacted through the methyl group and carbon number 5 of the pyridine ring with the C6 base.

Genotoxicity and DNA interaction studies of 1c

In the present study, to evaluate the genotoxic effect of compound **1c** (as the most effective cytotoxic compound) against the MDA-MB-231 cells, the comet assay method was applied. Figure 2 shows that treatment with low-concentration MDA-MB-231 cells and 13 µM of **1c** results in a relatively long tail followed by electrophoresis cells, demonstrating that **1c** has a strong genotoxicity capability. It should be mentioned that in some parts, no nucleus remains and only a blunt sequence of degraded DNA is visible. Untreated cells (Fig. 2a) and cisplatin's (Fig. 2b)

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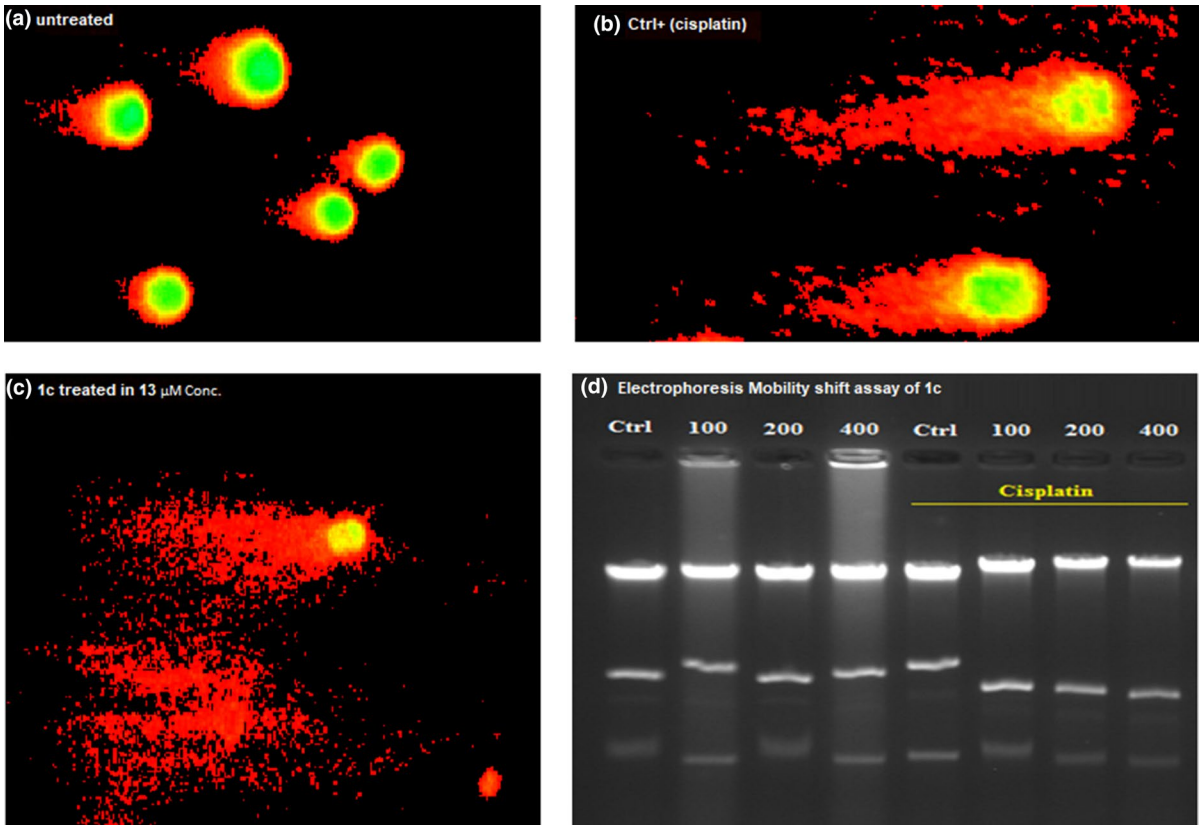

Fig. 2 Genotoxic effect of **1c** on the MDA-MB-231 cell line. In comparison to the untreated cells as negative control (**a**), the percentage of damaged DNA in the tail increased dramatically after treatment with cisplatin as positive control (**b**), and compound **1c** (**c**). A circular pGEM-FT plasmid was treated with various doses of cisplatin (positive controls) and compound 1c (**d**)

genotoxicity behavior was also determined as negative and positive control, respectively. The findings revealed that compound **1c** has a remarkable affinity for the cancer cell genome. Although the effect of genotoxicity in the comet assay clearly showed that the effective mechanism of **1c** is more related to direct interaction with DNA. Possibly other mechanisms are also involved in this process.

In order to check the DNA binding activity of compound **1c**, the electrophoretic mobility shift was also measured. As shown in Fig. 2d, cisplatin created a shift in plasmid mobility relative to untreated DNA, indicating its interaction with DNA. On the other hand, **1c** can lead to a significant change in plasmid motility compared to untreated DNA at higher concentrations (400 μM). Although these changes are less than cisplatin, they indicate **1c** interactions with DNA. Therefore, our results showed that at least part of the cytotoxic effect of **1c** is exerted through direct interaction with DNA.

Determining the apoptotic effect of 1c on MDA-MB-231 cell line

As shown in Fig. 3, increasing the concentration of **1c** from 10 to 40 μM considerably increases the proportion of cells in the apoptotic phase from 20.2 to 56.5% and 86.2% in the treated cells, respectively. The apoptosis results indicated that **1c** could actively induce apoptosis in the MDA-MB-231 cell line, and that the apoptosis increases with an increasing concentration of **1c**. By increasing the concentration of **1c**, the cancer cells entered the apoptotic phase and underwent a small amount of necrosis. Thus, **1c** can cause apoptosis in tumor cells in a dose-dependent way. It can be concluded that the anti-proliferative activity of

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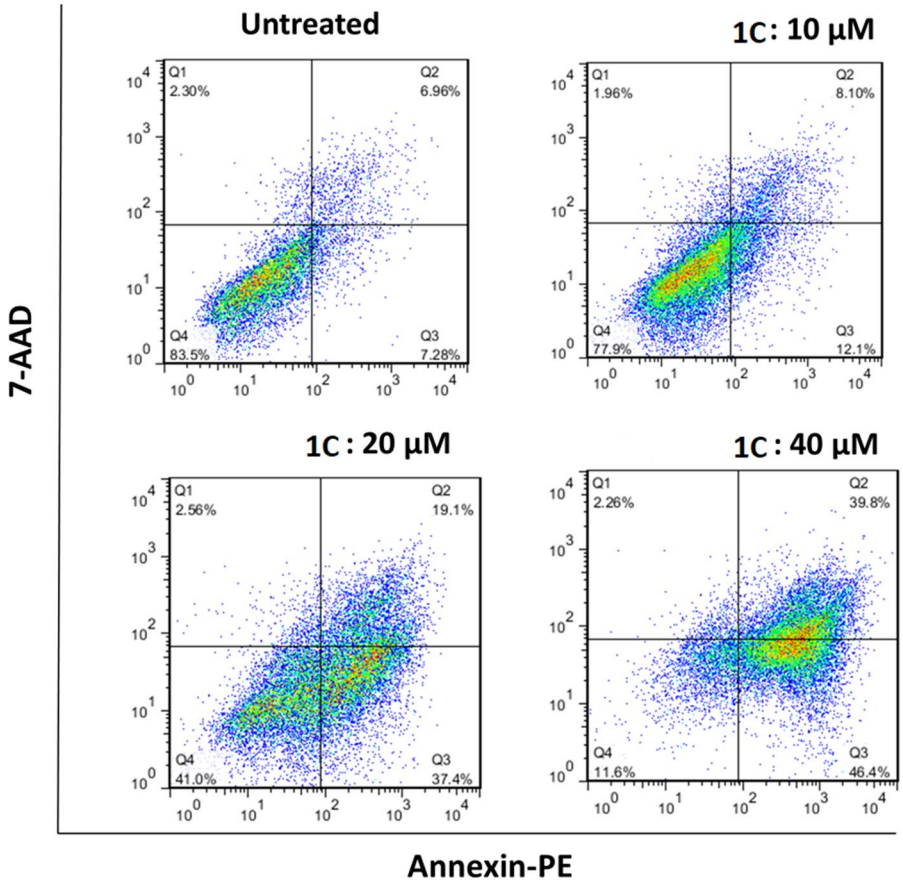

Fig. 3 Analyzing the apoptotic properties of **1c** in the MDA-MB-231 cell line using flow cytometry

Conc. (µM)	MDA-MB-231			
	1c			
	Necrotic cells: Q1 (%)	Early apoptotic cells: **Q2 (%)**	late apoptotic cells: **Q3 (%)**	vital cells: Q4 (%)
Untreated	2.3	6.9	7.3	83.5
10	1.8	8.1	12.1	60.6
20	2.6	19.1	37.4	41.0
40	2.3	39.8	46.4	11.6

1c in a cytotoxic assay may be mediated in part by inducing apoptosis in cancer cells. Furthermore, the entry of cells into the process of programmed cell death is much more desirable because the apoptotic cells are removed by the xenophagous cells, including the macrophages in the liver and spleen, without inflammation and damage to the normal surrounding tissues.

Intracellular ROS generation in MDA-MB-231 cells exposed to 1c

To investigate the effects of **1c** on ROS (Reactive Oxygen Species) generation in the MDA-MB-231 cells, 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) was used. An analysis of the mitochondrial membrane potential and intracellular ROS generation in the MDA-MB-231 cells exposed to **1c** (13, 26 and 39 µM) for 4 h is shown in Fig. 4. In our study, we found that **1c** induces ROS production in

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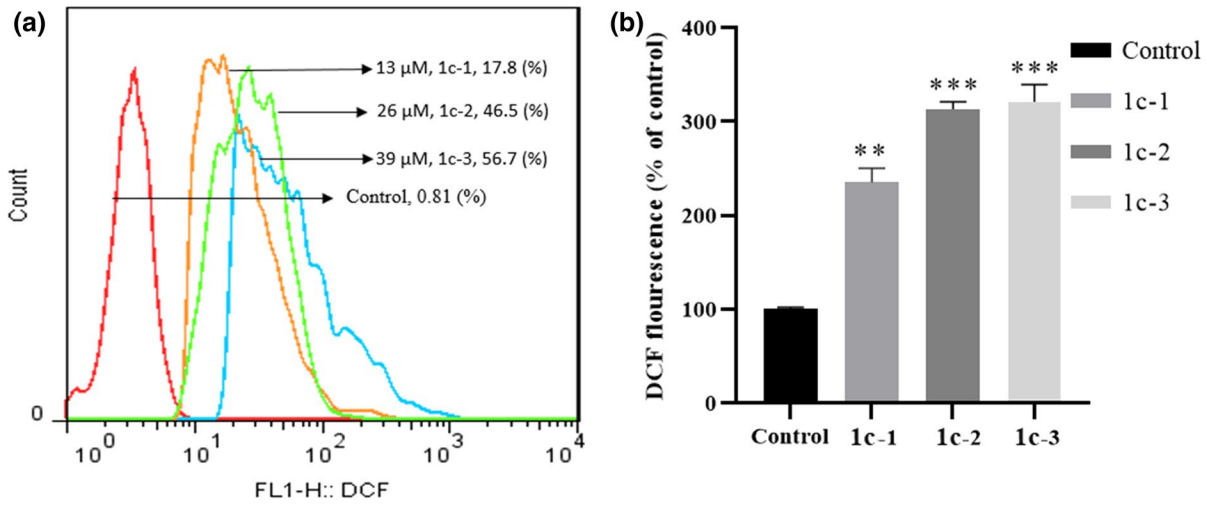

Fig. 4 Flow cytometric analysis of ROS generated within the MDA-MB-231 cells for 4 h after exposure to **1c** (13, 26 and 39 M µM). **a** Representative spectra of fluorescent DCF as a function of **1c** concentration. Control (red line), **1c** at 13 µM (orange line), 26 µM (green line), and 39 µM (blue line). **b** An analysis of the fluorescence enhancement of DCF by increasing the concentration of **1c**. Each histogram represents the mean ± S.D. values of DCF fluorescence obtained from three independent experiments. The ** represented the $pv < 0.01$, and the *** represented the $pv < 0.001$ versus control. (Color figure online)

the MDA-MB-231 cells when it is treated with DCF (2′–7′-dichlorofluorescein). As the concentration of the compound is increased from 13 µM to 39 µM, the amount of produced ROS is increased.

Cellular uptake

Using ICP-MS the amount of Pt taken in by the cells were calculated. After 12 h of exposure to 50 µM of **1c**, the Pt content was determined. ICP-MS results revealed 150 µg/µg protein. The complex is expected to be uniformly distributed throughout the cell, despite the fact that the average cell volume is anticipated to be 1.3 pL. The Pt concentration in the cell is around 0.97 µM.

Conclusions

In the present work, the cytotoxic activity of a series of Pt(II) complexes [PtMe(vpy)(L)], **1**, 2-vinylpyridine (vpy), and different phosphine (L) ligands were evaluated against human breast cancer (MDA-MB-231), human lung cancer (A549), human colon cancer (SW1116), and non-tumorigenic epithelial breast (MCF-10 A) cell lines. The most cytotoxic compound, [PtMe(vpy)(PPh_2Me)], **1c**, PPh_2Me = methyldiphenylphosphine, effectively causes cell death in the MDA-MB-231 cancer cell line by inducing apoptosis. It has a strong anti-proliferative effect on the A549, SW1116, and MDA-MB-231 cell lines, with the IC_{50} values of 21.10 µM, 23.36 µM, and 12.96 µM, respectively. One-way ANOVA statistical analysis revealed that it shows higher antiproliferative activity than cisplatin against the SW1116 and MDA-MB-231 cell lines with a better selectivity index against MCF-10a cells. To understand the antiproliferative mechanism of these compounds, the interaction of these compounds with DNA was explored using molecular docking studies, comet assay, and electrophoresis mobility shift assay. **1c** intensely targets the genome content of cancerous cells. However, in electrophoresis mobility shift assay, a very small shift was observed compared to cisplatin. The effect of **1c** on the induction of apoptosis against MDA-MB-231 has also been investigated, which showed that it could induce apoptosis in MDA-MB-231 cells on a concentration-dependent basis. These compounds, especially **1c**, have the potential to enter further clinical stages to introduce a suitable

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anticancer agent with lower toxicity properties in comparison to cisplatin.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethics: IR.AJUMS.REC.1397.198.

Research involving human and animal rights Not applicable.

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