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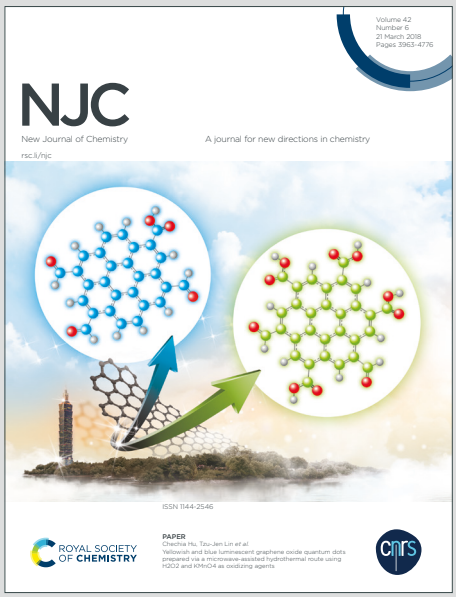

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ARTICLE

High cytotoxic and apoptotic effects of platinum(II) complexes bearing 4-acridinol ligand

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Here, two platinum(II) complexes, [Pt^{II}(Q)(DMSO)Cl] (**PtQ**) and [Pt^{II}(A)(DMSO)Cl] (**PtA**) bearing 8-hydroxyquinoline (HQ) and 4-acridinol (HA) ligands were first synthesized and fully characterized by elemental analysis, NMR, IR spectroscopies and X-ray crystallography. All this two 4-acridinol Pt complexes (**PtQ** and **PtA**) were active against cisplatin-resistant SK-OV-3/DDP cancer cells with lower IC_{50} values than cisplatin. Notably, complex **PtA** exhibited IC_{50} values (0.05±0.02 μM) that were an order of two and three magnitude lower than those of the 8-hydroxyquinoline Pt complex **PtQ** (5.08±0.47 μM) and clinical cisplatin (71.23±1.02 μM), respectively. Interestingly, complex **PtA** displayed potent cytotoxic activity especially in cisplatin-resistant SK-OV-3/DDP cells, but it was practically inactive against the human liver HL-7702 normal cells. Analyzing the uptake and distribution of complex **PtA** in the cisplatin-resistant SK-OV-3/DDP cells revealed that the **PtA** was mainly localized in the mitochondria. In addition, complex **PtA** significantly cause the loss of bcl-2 and mitochondrial membrane potential ($\Delta\Psi_m$), increase of [Ca^{2+}] and the reactive oxygen species (ROS) levels, cytochrome c (cyto C), apaf-1 and caspase-3/9 ratio in cisplatin-resistant SK-OV-3/DDP cells. Complex **PtA** may trigger the cell apoptosis *via* a mitochondrial dysfunction pathway whereas 8-hydroxyquinoline Pt complex **PtQ** does not. The better cytotoxicity and the more significant anticancer mechanism of complex **PtA** than 8-hydroxyquinoline Pt complex **PtQ**, which should be undoubtedly correlated with the key roles of the more extended planar 4-acridinol (HA) ligand.

Introduction

Despite their clinical efficacy, the therapeutic effect of cisplatin and its drugs were accompanied by acquired severe side effects and drug resistance.[1–7] Hence, there is an increased focus on developing alternative platinum-based chemotherapeutic agent with high efficacy, low toxicity, and that selectively target cancer cells.[6–8] These Pt complexes include substitution inert Pt agent [Pt(1S,2Sdiaminocyclohexane)(5,6-dimethyl-1,10-phenanthroline)]$^{2+}$ (56MeSS)[9], Rigosertib derivatives Pt(IV) complexes[10], 4'-substituted-2,2':6',2''-terpyridine binuclear Pt(II) complexes[11], quinoline-coumarin organoplatinum(II) complexes[12], neutral and cationic *cis*-[bis(1,3-dibenzylimidazol-2-ylidene)Cl(L)]Pt(II) complexes[13], rhein Pt^{IV} prodrugs[14], *etc*.

Recently, a series of 8-hydroxyquinoline derivatives metal complexes with high β-glusosidase activation and good antineoplastic ability have been reported[15–28]. Especially, the Pt(II,IV) complexes bearing 8-hydroxyquinoline and its derivatives showed the excitingly treated of various cancer cells, such as 8-hydroxyquinoline and 8-hydroxy-2-methylquinoline platinum(II) compounds[29], clioquinol platinum(II, IV) complexes[30,31], quinolines-aryl olefins organoplatinum(II) complexes[32], 2-methyl-8-quinolinol derivatives platinum(II) compounds[33], sixteen 8-quinolinethiol-1,3,5-triaza-7-phosphaadamantane platinum(II) complexes[34], 5,7-diiodo-8-hydroxyquinoline platinum(II) complex[35], quinoline–platinum complexes [$Pt(Cl)_2$(quinoline)(dmso)] and [PtCl(8-O-quinoline)(dmso)][36]. However, the cell apoptosis effects of 8-hydroxyquinoline Pt(II,IV) derivatives had limited and needed to be explored in depth. To date, the design of Pt(II) complexes with 4-acridinol (HA) has not been reported.

In the current study, we first synthesized one platinum(II) complexes [Pt^{II}(A)(DMSO)Cl] (**PtA**) with 4-acridinol (HA) ligand in comparison with 8-hydroxyquinoline platinum(II) complexes [Pt^{II}(Q)(DMSO)Cl] (**PtQ**). By characterizing their cytotoxicity against tumor cells SK-OV-3, cisplatin-resistant SK-OV-3/DDP cancer cells and normal HL-7702 cells, we proposed a possible antineoplastic mechanism in the cisplatin-resistant SK-OV-3/DDP cells.

Results and discussion

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† Electronic Supplementary Information (ESI) available: The CCDC number for **PtQ** and **PtA** were 2033526 and 2033527. The data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK (Fax: (+44) 1223-336-033; E-mail: deposit@ccdc.cam.ac.uk). See DOI: 10.1039/x0xx00000x

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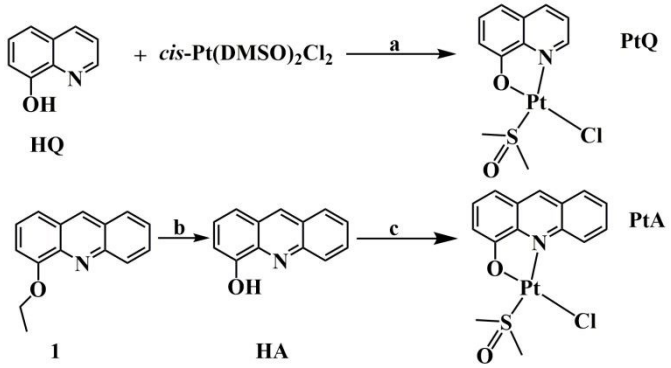
Synthesis and characterization of 4-acridinol (HA) ligand and its Pt complexes

The 4-ethoxyacridine (**1**) was synthesized according to the reported procedures[37]. In addition, compound **1** (0.2 mol) in concentrated HBr was refluxed for 4.0 h (Scheme 1). After 4.0 h of reflux the reaction mixture was carefully diluted with H_2O and made alkaline with NaOH. Following filtration and acidification with dilute HCl the resultant precipitate was dissolved in $CHCl_3$ and purified by column chromatography using silica gel and $CHCl_3$ as the solvent. The yield of yellow crystals of 4-acridinol (HA) ligand was 24.5%. Further, the reactions of 4-acridinol HQ and HA ligands with *cis*-$Pt(DMSO)_2Cl_2$ in presence of 0.1 mL DMSO and 3.5 mL CH_3OH at 90 °C for 3.0 days, gave rise to **PtQ** (yellow) and **PtA** (black) (Scheme 1). The structures of 4-acridinol (HA) ligand and its Pt complexes (**PtQ** and **PtA**) were determined by elemental analysis, NMR, ESI-MS, IR spectroscopies and X-ray crystallography (Tables S1−S6, Figs. 1, 2 and S1−S11).



Scheme 1. Synthesis of 4-acridinol (HA) ligand and its Pt complexes (**PtQ** and **PtA**). (a and c) *cis*-$Pt(DMSO)_2Cl_2$, 0.1 mL DMSO and 3.5 mL CH_3OH, 90.0 °C, 3.0days; (b) concentrated HBr, refluxed, 4.0h.

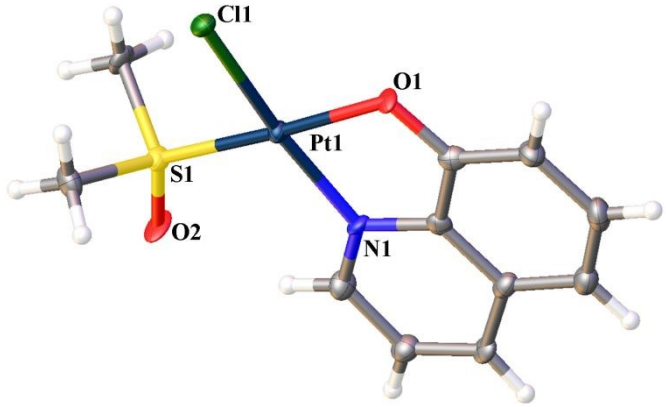


Fig. 1 The ORTEP drawings of **PtQ**.

Crystal structure of PtQ and PtA

The crystal structures of **PtQ** and **PtA** (Tables S1−S6, Figs. 1 and 2) were confirmed by X-ray single crystal diffraction analysis. In two 4-acridinol Pt complexes, the each Pt^{II} central was also four-coordinated by one deprotonated 8-hydroxyquinoline (HQ) and 4-acridinol (HA), one Cl atom and one DMSO, respectively (Figs. 1 and 2). The bite angles (°) of N(1)–Pt(1)–O(1), Cl(1)–Pt(1)–O(1) and Cl(1)–Pt(1)–N(1) were 82.5(2) and 80.6(3)°, 88.41(12) and 172.9(2)°, 170.36(16) and 104.4(2)°, respectively. The bond length of Pt–Cl (2.3013(14)–2.325(3) Å) was substantially longer than that of Pt–S (2.2032(14)–2.219(3)Å), Pt–O (1.984(8)–2.044(4) Å) and Pt–N (2.025(6)–2.072(8)Å) respectively, which are within the normal range.

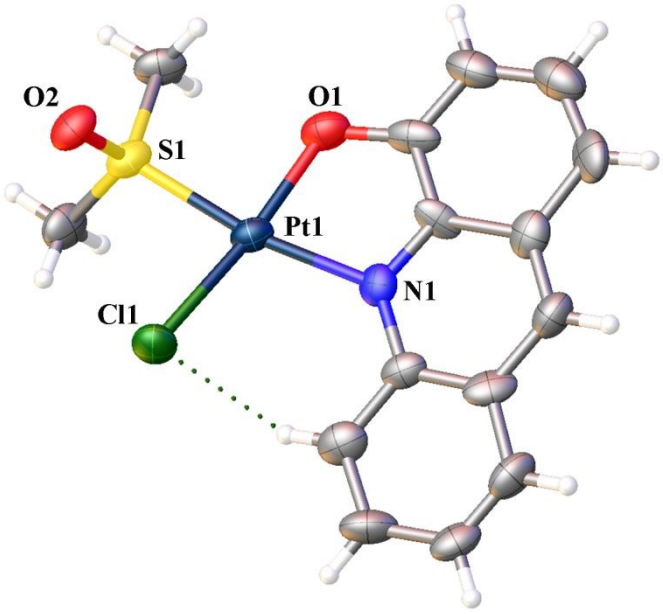


Fig. 2 The ORTEP drawings of **PtA**.

Table 1. In vitro cytotoxic activity (μM) against SK-OV-3, cisplatin-resistant SK-OV-3/DDP and HL-7702 cells for 24h.

compounds	SK-OV-3/DDP	SK-OV-3	HL-7702
HQ	98.34±1.69	53.42±0.47	>50
PtQ	5.08±0.47	15.67±1.23	>50
HA	80.01±1.00	45.63±0.75	>50
PtA	0.05±0.02	11.09±0.29	>50
cis-$Pt(DMSO)_2Cl_2$	>150	>150	>100
cisplatin	71.23±1.02	10.25±1.77	18.51±1.02

Biological activity studies

The in vitro cytotoxicity of 4-acridinol derivatives (HQ and HA) ligand and their Pt complexes (**PtQ** and **PtA**) were assessed by MTT assay.[38,39] The IC_{50} of 4-acridinol derivatives (HQ and HA) ligand and their Pt complexes (**PtQ** and **PtA**) against SK-OV-3, cisplatin-resistant SK-OV-3/DDP tumor cells and HL-7702 normal cells were presented in Table 1. Compound **PtA** showed greater anti-proliferative activity than HQ, HA, **PtQ** and cisplatin against the cisplatin-resistant SK-OV-3/DDP tumor cells, with the IC_{50} value as low as 0.05±0.02 μM (nanomole IC_{50} concentrations). However in the case of the SK-OV-3 cells, 4-acridinol derivatives (HQ and HA) ligand and their Pt complexes (**PtQ** and **PtA**) displayed lower in vitro cytotoxicity in comparison to cisplatin. The better cytotoxicity and the more significant anticancer mechanism of complex **PtA**

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than 8-hydroxyquinoline Pt complex **PtQ**, which should be undoubtedly correlated with the key roles of the more extended planar 4-acridinol (HA) ligand. Regarding the HL-7702 normal cells, the 4-acridinol derivatives Pt complexes **PtQ** and **PtA** were not toxicity, suggesting that the selectivity of **PtQ** and **PtA** on cisplatin-resistant SK-OV-3/DDP tumor cells.

The uptake assay

The cellular uptake and distribution of metal anti-cancer complexes in tumor cells is the key to the anticancer activity of this class of drugs.[40–44] Thus, the uptake of 4-acridinol derivatives Pt complexes **PtQ** (5.08μM) and **PtA** (0.05μM) in cisplatin-resistant SK-OV-3/DDP tumor cells was studied by ICP-MS analysis. As shown in Table 2, **PtA** ((22.03±0.09) $\mu g \cdot L^{-1}$ per 10^6 cells) was taken up by the tumor cells by approximately 1.84- and 2.76-times efficiently than **PtQ** ((12.00±0.18) $\mu g \cdot L^{-1}$ per 10^6 cells) and cisplatin ((7.98±0.55) $\mu g \cdot L^{-1}$ per 10^6 cells). In addition, **PtA** (0.05μM) accumulated to a higher extent in mitochondria fraction, while **PtQ** and cisplatin accumulated in the nuclear. The differences in cell distribution of Pt^{II} can be attributed to the different cellular pathways involved in both the uptake and efflux of the 4-acridinol derivatives Pt complexes **PtQ** (5.08μM) and **PtA** (0.05μM), which, in turn, may be highly associated with its ability to activate cell death pathways.[45]

Table 2. The uptake ($\mu g \cdot L^{-1}$ per 10^6 cells) of **PtQ** (5.08μM), cisplatin (71.23μM) and **PtA** (0.05μM) in cisplatin-resistant SK-OV-3/DDP tumor cells for 24h.

organelles	PtQ	PtA	cisplatin
Total	12.00±0.18	22.03±0.09	7.98±0.55
Mitochondria	2.84±0.76	11.67±0.25	1.13±0.02
Nuclei	3.55±0.11	1.94±0.04	3.99±0.18

PtA induced intracellular [Ca^{2+}] release

Metal-based anti-cancer compounds induced Ca^{2+} signaling by the intracellular release of the [Ca^{2+}] ion pool.[46,47] After 24h incubation, **PtA** (0.05μM) significantly increased the release of intracellular calcium level (Fig. 3). Intracellular [Ca^{2+}] level was 20.24% relative to the control after 4-acridinol Pt complex **PtA** (0.05μM)-treatment. In addition, 8-hydroxyquinoline Pt complex **PtQ** (5.08μM) was less effective in cisplatin-resistant SK-OV-3/DDP tumor cells for inducing intracellular [Ca^{2+}] release. This phenomenon was well agreed with the results with the ICP-MS analysis and MTT assay.

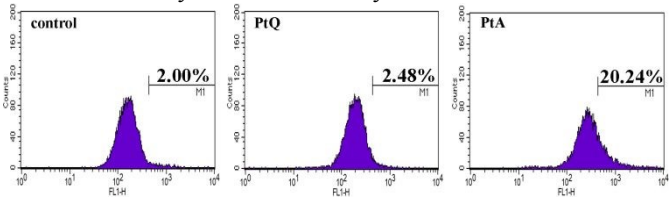

Fig. 3 4-acridinol derivatives Pt complexes **PtQ** (5.08μM) and **PtA** (0.05μM) induced intracellular release of [Ca^{2+}] in cisplatin-resistant SK-OV-3/DDP tumor cells.

Assessment of total ROS generation

A high level of ROS is closely related to the oxidative damage and activation of cell death processes.[48–52] Further, The release of intracellular [Ca^{2+}] level induced the production of ROS in tumor cells.[46–52] Thus, to determine oxidative stress after treated with 4-acridinol derivatives Pt complexes **PtQ** (5.08μM) and **PtA** (0.05μM), we estimated the total ROS content *via* DCF-DA using a flow cytometry. This study suggested that the ROS level was a rapid increase (*ca*. 29.72%) during 24 h of **PtA** (0.05μM) treatment (Fig. 4). However, 8-hydroxyquinoline Pt complex **PtQ** (5.08μM) did not display such obvious effects on the total ROS generation of cisplatin-resistant SK-OV-3/DDP tumor cells.

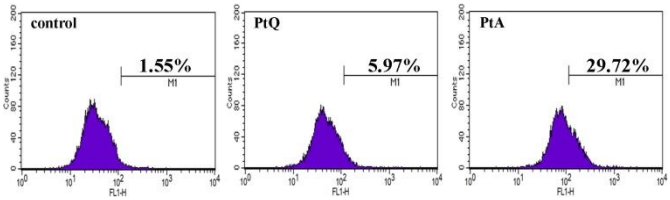

Fig. 4 Effect of 4-acridinol derivatives Pt complexes **PtQ** (5.08μM) and **PtA** (0.05μM) induced ROS generation.

Measured of $\Delta\Psi_m$ level

The activation of intracellular ROS level in tumor cells was an important factor affecting the $\Delta\Psi_m$ level, and finally leading the activation of mitochondrial dependent cell death signaling pathways.[46,53–57] The color of the $\Delta\Psi_m$ changed from red to green when the $\Delta\Psi_m$ decreased and was assayed by flow cytometry using a dye JC-1.[46,53–57] As shown in Fig. 5, the percentage of cells emitting green fluorescence increased (*ca.* 45.73%) after treated with 4-acridinol Pt complex **PtA** (0.05μM) for 24h, indicating the loss of $\Delta\Psi_m$ level in the early phases of apoptosis. Thus, 4-acridinol Pt complex **PtA** may induce apoptosis in the cisplatin-resistant SK-OV-3/DDP tumor cells possibly *via* the intrinsic signaling pathway. However, 8-hydroxyquinoline Pt complex **PtQ** (5.08μM) was less effective in the cisplatin-resistant SK-OV-3/DDP tumor cells for inducing cell apoptosis.[46,53–57]

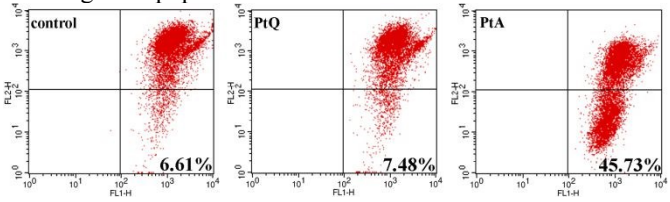

Fig. 5 Analysis of $\Delta\Psi_m$ level in cisplatin-resistant SK-OV-3/DDP tumor cells after treated with 4-acridinol derivatives Pt complexes **PtQ** (5.08μM) and **PtA** (0.05μM), and these cells were stained with JC-1.

Expression of apoptosis-related proteins

The change of apoptosis-related proteins were plays an important role in the tumor cell apoptosis.[46,53–59] To further study the death mechanism, western blot assay was carried out. As shown in Fig. 6, we can see significantly decreased bcl-2

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expression, and increased cyto c, caspase-3/-9 and apaf-1 levels when the cisplatin-resistant SK-OV-3/DDP tumor cells were treated with doses of 4-acridinol Pt complex **PtA** (0.05μM). In contrast, 8-hydroxyquinoline Pt complex **PtQ** (5.08μM) did not significantly inhibit the change of the apoptosis-related proteins in the cisplatin-resistant SK-OV-3/DDP tumor cells. These results suggested that the apoptosis of 4-acridinol Pt complex **PtA** (0.05μM) could be attributed to the apoptosis-related proteins correlated pathway in the cisplatin-resistant SK-OV-3/DDP tumor cells, which was different from 8-hydroxyquinoline Pt complex **PtQ** (5.08μM).

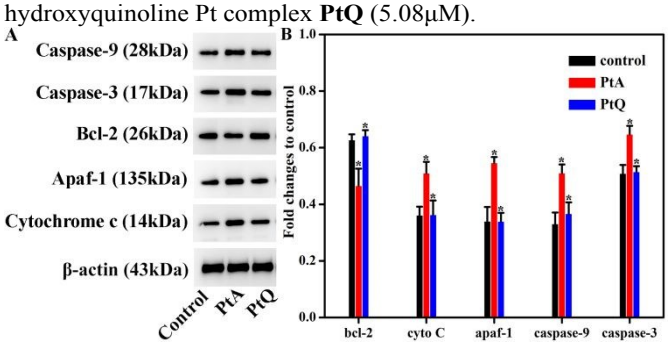

Fig. 6 Western blot analysis of the five apoptosis-related proteins in the cisplatin-resistant SK-OV-3/DDP tumor cells treated with 4-acridinol derivatives Pt complexes **PtQ** (5.08μM) and **PtA** (0.05μM) for 24h. (*) $P < 0.05$, *p* vs the vehicle control.

Cell apoptosis

Based on the above results, the antitumor activity of 4-acridinol derivatives Pt complexes **PtQ** (5.08μM) and **PtA** (0.05μM) has aroused our interest. The percentages of the SK-OV-3/DDP cells where 4-acridinol Pt complex **PtA** (0.05μM) promoted early apoptosis was 16.90%, in contrast, 8-hydroxyquinoline Pt complex **PtQ** (5.08μM) did not significantly induce the cisplatin-resistant SK-OV-3/DDP tumor cells apoptosis. The results clearly confirmed that the cell apoptosis induced by 4-acridinol Pt complex **PtA** could be different from 8-hydroxyquinoline Pt complex **PtQ**.

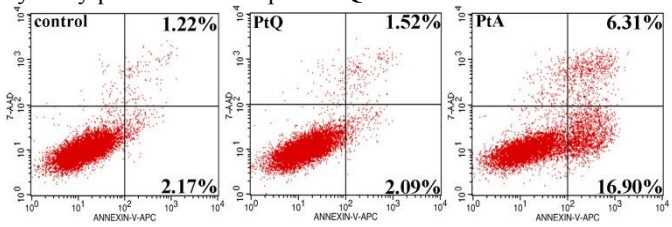

Fig. 7 The apoptosis analysis of the cisplatin-resistant SK-OV-3/DDP tumor cells treated by 4-acridinol derivatives Pt complexes **PtQ** (5.08μM) and **PtA** (0.05μM) for 24 h, and stained with 7-AAD and Annexin V.

Conclusions

In conclusion, two 4-acridinol Pt complexes **PtQ** and **PtA** with 8-hydroxyquinoline (HQ) and 4-acridinol (HA) ligands were synthesized and fully characterized. They exhibited significantly enhanced cytotoxicity against the cisplatin-resistant SK-OV-3/DDP cancer cells, with the IC_{50} values were 5.08±0.47 μM and 0.05±0.02 μM), and low cytotoxicity toward HL-7702 normal cells. 4-acridinol Pt complex **PtA** caused cell apoptosis *via* a mitochondrial dysfunction pathway on cisplatin-resistant SK-OV-3/DDP tumor cells whereas 8-hydroxyquinoline Pt complex **PtQ** does not. These studies suggested that the more extended planar ligand might promote its effect on the cell intake, which had also been proven in our study by examining the Pt^{II} intake and distribution of each compound using the ICP-MS method. This may be the most rational explanation for the better antiproliferative effect of 4-acridinol Pt complex **PtA** compared to 8-hydroxyquinoline Pt complex **PtQ** till now based on the present results. Thus, the antitumor mechanism of 4-acridinol Pt complex **PtA** was distinguished from 8-hydroxyquinoline Pt complex **PtQ**, which should be undoubtedly correlated with the key roles of the more extended planar 4-acridinol (HA) ligand. These results may contribute to the development of novel 4-acridinol Pt(II) anti-cancer agents.

Experimental methods

Synthesis of 4-acridinol (HA) ligand

The 4-ethoxyacridine (**1**) was synthesized according to the reported procedures[37]. In addition, compound **1** (0.2 mol) were added to 300.0 mL concentrated HBr. After 4.0 h of reflux the reaction mixture was carefully diluted with 1000.0 mL H_2O and made alkaline with NaOH (pH=10.0) (Scheme 1). Following filtration and acidification with dilute HCl the resultant precipitate was dissolved in $CHCl_3$ and purified by column chromatography using silica gel and $CHCl_3$ as the solvent. The yield of yellow crystals of 4-acridinol (HA) ligand was 24.5%. IR (KBr): 3933, 3902, 3856, 3854, 3839, 3822, 3803, 3750, 3672, 3649, 3610, 3589, 3567, 3344, 3118, 3081, 3056, 3036, 3010, 2917, 2302, 2163, 2102, 1981, 1908, 1832, 1734, 1717, 1700, 1622, 1608, 1562, 1520, 1479, 1465, 1441, 1425, 1399, 1369, 1321, 1282, 1265, 1227, 1211, 1141, 1130, 1088, 1019, 1005, 980, 956, 941, 919, 893, 883, 866, 854, 813, 788, 759, 730, 720, 690, 674, 647, 636, 621, 612, 583, 562, 540, 490, 474, 454, 429, 413 cm^{-1}. Elemental analysis: calcd (%) for $C_{13}H_9NO$: C 79.98, H 4.65, N 7.17; found: C 79.97, H 4.67, N 7.16. ESI-MS: m/z = 196.25 for $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 9.07 (s, 1H), 8.20 (dd, J = 18.8, 8.6 Hz, 2H), 7.86 (ddd, J = 8.6, 6.7, 1.3 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.51 – 7.44 (m, 1H), 7.15 (dd, J = 7.3, 1.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.19, 147.21, 141.07, 136.49, 130.80, 129.30, 128.95, 127.41, 127.20, 127.00, 126.45, 118.69, 110.32, 40.64, 40.43, 40.22, 40.01, 39.80, 39.60, 39.39.

Synthesis of PtQ and PtA

0.1 mmol 4-acridinol HQ (or HA) ligand, 0.1 mmol *cis*-$Pt(DMSO)_2Cl_2$, 0.1 mL DMSO and 3.5 mL CH_3OH were placed into a thick Pyrex tube (*ca.* 25 cm long) that was then

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and sealed. The mixture was heated 90 °C for 3.0 days, gave rise to **PtQ** (yellow) and **PtA** (black) (Scheme 1).

Data for **PtQ**. Yield: 73.2%. IR (KBr): 947, 3902, 3852, 3818, 3749, 3672, 3649, 3629, 3610, 3568, 3199, 3158, 3096, 3066, 3047, 3024, 3003, 2915, 2855, 2793, 2705, 2665, 2643, 2506, 2563, 2526, 2397, 2324, 2299, 2229, 2185, 2163, 2141, 2101, 2037, 2016, 2002, 1981, 1955, 1936, 1905, 1870, 1804, 1777, 1758, 1732, 1711, 1678, 1611, 1592, 1577, 1505, 1471, 1444, 1431, 1418, 1407, 1398, 1383, 1321, 1302, 1293, 1282, 1242, 1218, 1175, 1151, 1122, 1065, 1034, 978, 955, 939, 928, 856, 819, 804, 777, 755, 747, 699, 648, 632, 586, 529, 508, 470, 450, 418 cm^{-1}. Elemental analysis: calcd (%) for $C_{11}H_{12}ClNO_2PtS$: C 29.18, H 2.67, N 3.09; found: C 29.16, H 2.70, N 3.08. ESI-MS: m/z = 495.25 for $[M\text{-}Cl+(DMSO)]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.39 (dd, J = 5.4, 1.1 Hz, 1H), 8.69 – 8.64 (m, 1H), 7.71 (dd, J = 8.3, 5.4 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 7.06 – 7.02 (m, 1H), 2.55 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.69, 148.39, 143.99, 140.71, 131.11, 130.74, 122.35, 114.68, 114.38, 40.90, 40.61, 40.40, 40.20, 39.98, 39.77, 39.57, 39.36.

Data for **PtA**. Yield: 68.4%. IR (KBr): 3947, 3902, 3866, 3822, 3750, 3672, 3649, 3610, 3444, 3118, 3080, 3036, 3010, 2917, 2663, 2350, 2324, 2241, 2190, 2164, 2143, 2102, 2079, 2051, 1981, 1919, 1839, 1716, 1698, 1625, 1608, 1560, 1520, 1481, 1465, 1424, 1398, 1373, 1330, 1294, 1282, 1265, 1184, 1147, 1133, 1089, 1052, 1018, 980, 940, 919, 893, 850, 813, 798, 758, 727, 689, 675, 635, 620, 598, 582, 536, 528, 497, 429 cm^{-1}. Elemental analysis: calcd (%) for $C_{15}H_{14}ClNO_2PtS$: C 35.83, H 2.81, N 2.79; found: C 35.81, H 2.83, N 2.76. ESI-MS: m/z = 1027.0 for $[2M+Na]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.58 (d, J = 8.8 Hz, 1H), 8.43 (d, J = 8.3 Hz, 1H), 8.23 – 8.14 (m, 1H), 7.91 – 7.82 (m, 2H), 7.70 (t, J = 7.9 Hz, 1H), 7.56 (d, J = 7.3 Hz, 1H), 2.55 (s, 6H).

The other materials and methods

The materials and anticancer activities of 4-acridinol derivatives Pt complexes **PtQ** (5.08μM) and **PtA** (0.05μM) were studied according to our previously reported procedures.[3,27,35,60] Furthermore, the detailed procedures for the experimental methods and anticancer activities of 4-acridinol derivatives Pt complexes **PtQ** (5.08μM) and **PtA** (0.05μM) were described in the ESI.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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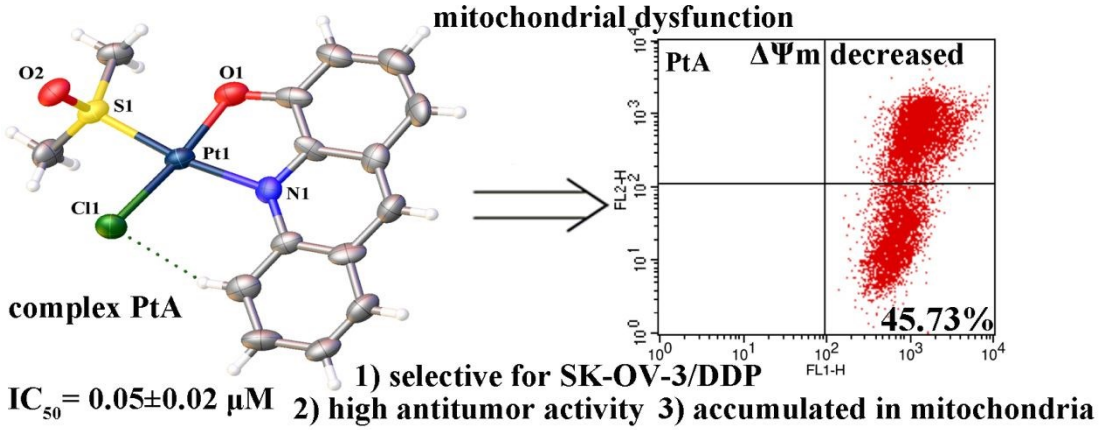
Graphical abstract

High cytotoxic and apoptotic effects of platinum(II) complexes bearing 4-acridinol ligand

Tai-Ming Shao,‡[a] Zu-Zhuang Wei,‡[c] Xiao-Ling Luo,[a] Qi-Pin Qin,*[ab] Ming-Xiong Tan,*[a] Jia-Jing Zeng,[a] Chun-Jie Liang,*[a] and Hong Liang[b]*



4-acridinol platinum(II) complex **PtA** induce SK-OV-3/DDP cell apoptosis was mediated by dysfunction of mitochondria.

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