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Original article

Synthesis and anticancer activity of lipophilic platinum(II) complexes of 3,5-diisopropylsalicylate

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Abstract

Novel lipophilic platinum(II) complexes (LSPt-1−3), containing 3,5-diisopropylsalicylate (DIPS) as a leaving group and $2NH_3$ or 1*R*,2*R*-diaminocyclohexane or (4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane as the carrier, have been synthesized, characterized and evaluated in vitro and in vivo. The octanol/water distribution coefficient of the complexes has also been measured. The results showed that the complexes achieved a typical square planar and the octanol/water distribution coefficient log *P* was 4.27, 4.37 and 4.31. The complexes were tested by SRB method to be more cytotoxic than Carboplatin, Oxaliplatin and Eptaplatin against 3AO, A549, NCI-H460 and SGC-7901 human cancer cell lines. Among complexes, LSPt-2 was much more effective than Carboplatin and Oxaliplatin in treating the NCI-H460 non-small-cell lung tumor-bearing mice. Its optimal activity was 38.8% (*T*/*C*) at a dose of 30 mg/kg following i.p. administration. LD_{50} for the complex was found to be 230.9 mg/kg. LSPt-2 exhibited great anticancer activity, good lipophilic ability and low toxicity and therefore, it is a promising candidate for effective and stable pharmaceutical liposomal platinum anticancer drug.

Keywords: Lipophilic; Platinum(II) complexes; 3,5-Diisopropylsalicylic acid; Antitumor activity

1. Introduction

Cisplatin, *cis*-diamminedichloroplatinum(II), is one of the most widely used and most effective antitumor drugs in the treatment of various types of human cancers, especially testicular and ovarian cancers [1]. However, its continued clinical use is impeded by the severe cumulative toxicities such as nephrotoxicity, ototoxicity, peripheral neuropathy, as well as acquired drug resistance [2]. Therefore, much attention has been focused on designing Cisplatin analogues with reduced toxicity and/or broader antitumor spectrum, leading to successful development of several new anticancer platinum drugs including Carboplatin, Nedaplatin, Lobaplatin, Oxaliplatin and Eptaplatin (Fig. 1). However, it has been evident that they will not offer any clinical advantages over the existing Cisplatin [3–6]. Another effective way to address the problems associated with the lack of tumor selectivity and severe adverse reactions is to deliver the drug to tumor cells or tumor site by new drug delivery systems. A variety of novel drug delivery systems have been developed. Of these, the liposomal drug carrier system represents an advanced, matured and versatile technology. Several liposomal formulations of antitumor drugs have been approved for cancer chemotherapy, such as Doxil and Myocet [7]. Up to now, a few different liposomal formulations of Cisplatin and some lipophilic platinum complexes have also been prepared and biologically evaluated. Among them, Lipoplatin (liposomal Cisplatin formulation) and L-NDDP (the liposomal form of (*trans*-*R*,*R*-cyclohexane-1,2-diamine)-bis-neodecanoatoplatinum(II)) are currently in Phases II and

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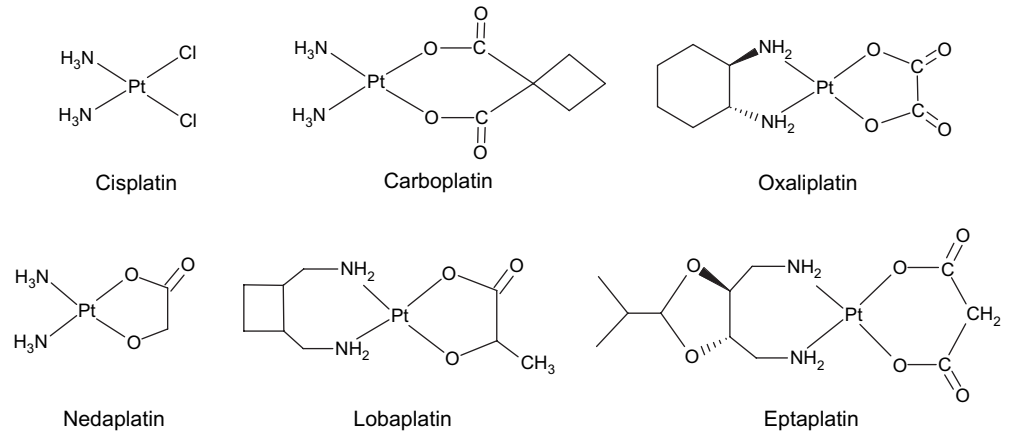

Fig. 1. Platinum-based drugs currently in clinical use.

III clinical trials [8–11]. Unfortunately, these liposomal formulations of platinum-based drug and complexes fail to meet the requirements for a pharmaceutical product in physical and chemical stabilities [12–14], and no liposomal formulations of Cisplatin or lipophilic platinum-based complexes have been obtained clinical approval in the world. One of the reasons is the poor hydrophilicity and lipophilicity of Cisplatin, which makes it difficult to be efficiently encapsulated in a liposome. Furthermore, lipophilic platinum complexes under development are intraliposomally unstable due to the two monodentatecarboxylates as the leaving groups. Therefore, it is important to design and synthesize lipophilic platinum complexes using chelating bidentate ligands with a small molecular weight.

One of the design strategies in our research is to develop platinum complexes with the expectation of higher liposolubility and chemical stability, along with higher antitumor activities and lower systemic toxicity. In our previous report, we described a series of novel lipophilic platinum(II) complexes containing two salicylate derivatives, 3,5-diiodosalicylate and 3-isopropyl-6-methylsalicylate, as leaving groups. Although they all showed greater cytotoxicity and lipophilicity [15], further in vivo assay has indicated that they were not superior to Carboplatin in treating mouse S180 tumor. Based on these findings, we have prepared and evaluated three novel lipophilic platinum(II) complexes (LSPt-1–3). These complexes contain more lipophilic 3,5-diisopropylsalicylate (DIPS) as a leaving group and $2NH_3$ or 1*R*,2*R*-diaminocyclohexane or (4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane as the carrier. We have filed a patent on these compounds (Fig. 2) [16]. Salicylate and its derivatives are selected in the present studies because they have been demonstrated to possess the ability to block metastasis of cancer cells by inhibiting synthesis of prostaglandin, as well as to reduce the ototoxic and nephrotoxic side effects caused by Cisplatin [17]. Herein, we report the synthesis, characterization and antitumor activity of the complexes.

2. Results and discussion

2.1. Chemistry

LSPt-1–3 could be synthesized by using an extension of Dhara's method [18]. Three platinum complexes were characterized by chemical analysis and spectroscopic determination. The elemental analysis data for each complex were in good agreement with the calculated values. The complexes showed $[M+1]^+$, $[M-L]^+$ and $[M-DIPS]^+$ corresponding to their molecular ion and relative fragmental peaks. The mass spectra also exhibited typical three protonated molecular ion peaks because of the isotopes ^{194}Pt (33%), ^{195}Pt (34%) and ^{196}Pt (25%). The characteristic bands of the complexes developed in the IR spectra. The binding of 3,5-diisopropylsalicylic acid to platinum(II) atoms as a chelating ligand was confirmed by the shift of ν(C=O) (1656 cm^{-1}) of free DIPS to lower frequencies (1620 cm^{-1}) of the coordinated DIPS and the absence of δ(O–H) (1433 cm^{-1}) of free DIPS after combination with platinum. The ^1H NMR spectra of the complexes were all consistent with their corresponding protons both in

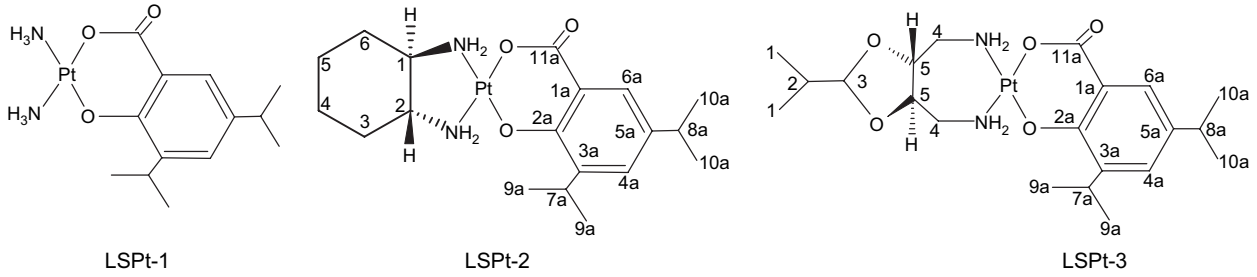

Fig. 2. Complexes of (3,5-diisopropylsalicylato)platinum(II) with diam(m)ine ligands.

the chemical shifts and in the number of hydrogens. ^{13}C NMR spectra of the complexes LSPt-2 and LSPt-3 were recorded and the chemical shifts observed corresponded well to the carbon atoms of the complexes. The mass spectra and ^{1}H NMR spectra of representative complex are illustrated in Figs. 3 and 4. The maximum absorption bands of the three complexes appeared near 210 nm and 310 nm. The bands were assigned, respectively, to n–π* and π–π* excitations in DIPS molecule. The solubility of the complexes both in water and in organic solvents such as ethanol, acetone and ether was determined. The complexes had low solubility in water but were soluble in organic solvents (>20 mg/mL). The octanol/water distribution coefficients for the complexes were measured in an octanol/water system according to the literature method [19,20]. The distribution coefficients and solubility in water and octanol are listed in Table 1. LSPt-1–3 had desirable liposolubility.

LSPt-1–3 were stable in ethanol for 24 h and in dimethyl sulphoxide (DMSO) for 72 h at room temperature, as indicated by no changes of both λ_{max} and absorbance in UV spectra, presumably as a result of the chelation effect of the leaving groups.

We made several attempts to grow single crystal of LSPt-1–3 in order to obtain more information about the molecular structure of the complexes, but failed. So we resorted to simulation. The structural parameters of the LSPt-2 were optimized using B3LYP theory at the basis of SDDALL (Fig. 5) [22,23]. From Fig. 5, we can see that the platinum atom was coordinated by two nitrogen atoms from 1*R*,2*R*-diaminocyclohexane and two oxygen atoms from 3,5-diisopropylsalicylate in *cis*-configuration. Pt(II) had the expected square planar geometry exhibiting the usual structure parameters of ammine(amine)-carboxylatoplatinum(II) complexes [24–26]. The dihedral angle of N1–N2–O1–O2 was 0.56°. Bond lengths of Pt–N1, Pt–N2, Pt–O1 and Pt–O2 were 2.112 Å, 2.104 Å, 1.994 Å and 1.997 Å, respectively. The angles of N1–Pt–N2 and O1–Pt–O2 were 83.5° and 94.8°, respectively.

2.2. In vitro cytotoxic activity

The cytotoxic activity of LSPt-1–3 was evaluated against four human cancer cell lines consisting of A549 (a human non-small-cell lung cancer line), NCI-H460 (a human non-small-cell lung cancer line), 3AO (a human ovarian carcinoma cell line) and SGC-7901 (a human gastric adenocarcinoma cell line), and the results are listed in Table 2. As shown in Table 2, LSPt-1–3 had better cytotoxicity against the four cancer cell lines with lower IC_{50} values than that of Carboplatin, Oxaliplatin and Eptaplatin. However, LSPt-3 did not show activity against 3AO. Among the complexes, LSPt-2 was the most active. There is no close structure–activity relationship among these complexes with different ammine/amine. Nevertheless, it is very interesting that the three platinum(II) complexes with α-hydroxyl-carboxylate as leaving groups had high in vitro cytotoxic activity and lipophilicity compared with the parent drugs Carboplatin, Oxaliplatin and Eptaplatin.

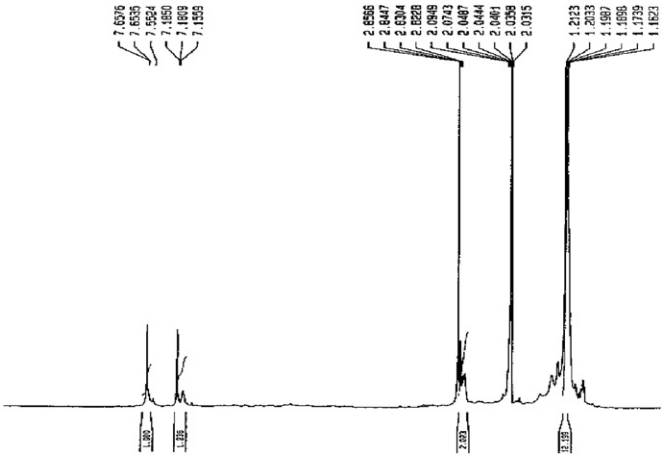

Fig. 3. The ^{1}H NMR spectra of LSPt-2.

2.3. In vivo antitumor activity of LSPt-2

Since the complex LSPt-2 was relatively more cytotoxic than the complexes LSPt-1 and LSPt-3, and was more sensitive to NCI-H460 than other human cancer cell lines, LSPt-2 was selected for further in vivo evaluation against NCI-H460 non-small-cell lung cancer in mice. The results are presented in Table 3 from which it can be seen that LSPt-2 showed greater inhibition rate of tumor growth than Carboplatin and Oxaliplatin in NCI-H460-bearing mice following the same administration scheme.

2.4. Acute toxicity studies in mice

The acute toxicity investigation showed that there was a regular dose-dependent increase in mortality in both sexes of mice after administration and death occurred after 48 h. In addition to death, the toxicities included anorexia, inactivity and loss of weight. The histological examination of the dead mice indicated that the reason of death was closely related to myelosuppression. The LD_{50} of LSPt-2 was calculated to be 230.9 mg/kg (95% confidence limits = 207.0–257.6 mg/kg), larger than the values of Carboplatin (LD_{50} = 150 mg/kg by i.p.) and Oxaliplatin (LD_{50} = 19.8 mg/kg by i.p.), indicating LSPt-2 was less toxic than Carboplatin and Oxaliplatin.

3. Conclusion

Three novel platinum(II) complexes involving 3,5-diisopropylsalicylate as the leaving ligand achieved a typical square planar arrangement with two nitrogen and two oxygen atoms. LSPt-1–3 were stable in ethanol solution. The values of log *P* for LSPt-1–3 were 4.27, 4.37 and 4.31, respectively. They all showed greater cytotoxicity against the four cancer cell lines than Carboplatin, Oxaliplatin and Eptaplatin. One of the complexes, LSPt-2, was more active against NCI-H460 non-small-cell lung cancer in mice and less toxic than Carboplatin and Oxaliplatin. LSPt-2, therefore, is a promising candidate for effective and stable pharmaceutical liposomal platinum anticancer drug. Further research to prepare the liposomal formulations of LSPt-2 is in progress in our laboratory.

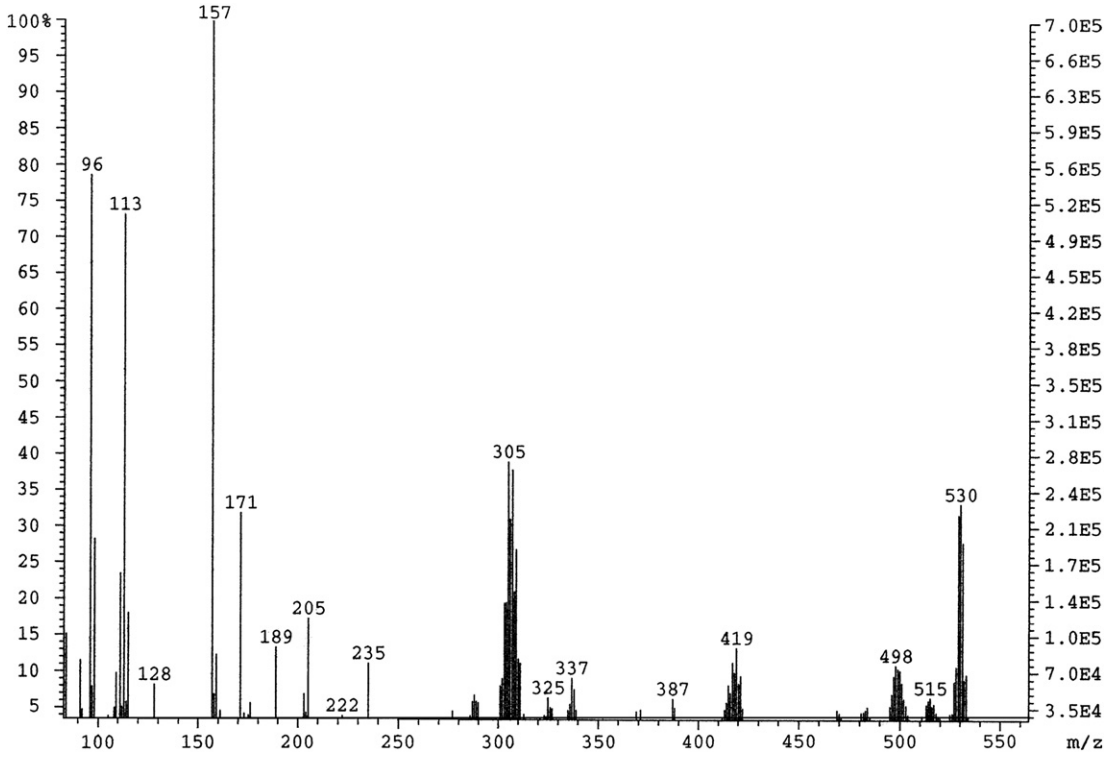

Fig. 4. The mass spectra of LSPt-2.

4. Experimental

4.1. Materials and physical measurements

3,5-Diisopropylsalicylic acid and 1*R*,2*R*-diaminocyclohexane were purchased from Aldrich companies. All the reagents and solvents were used as-received. Elemental analysis for C, H and N was performed with a Perkin–Elmer 240 Instrument, whereas platinum was determined according to the method in USP24. Mass spectral studies were carried out on a VG-AutoSpec3000 spectrometer in the FAB^+ mode using glycerine as matrix. IR spectra were recorded in the 4000–400 cm^{-1} regions on a Perkin–Elmer 880 spectrometer with KBr pellets. ^1H NMR spectroscopy was performed on Brucker DRX-500 (500.13 MHz) in MeOD or DMSO. ^{13}C NMR spectroscopy was performed on Brucker AV400 (100.62 MHz) in acetone or DMSO. Electronic spectra were scanned in EtOH Shimadzu UV-2401PC. The specific rotation was measured using a HORIBA SEPA-300 apparatus. Molecular structure of the complexes was optimized using B3LYP method [22,23] at the basis set of SDDALL via Gaussian 03 package [27].

4.2. Preparation of complexes LSPt-1–3

A solution of K_2PtI_4 was obtained by mixing K_2PtCl_4 (2.41 mmol in 5 mL H_2O) and KI (9.75 mmol in 5 mL H_2O) for 10 min. *cis*-$[Pt(L)_2I_2]$ (L = $2NH_3$ or 1*R*,2*R*-diaminocyclohexane or (4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane) was synthesized according to Dhara's method [18] from the aqueous reaction of K_2PtI_4 and L. *cis*-$[Pt(L)_2I_2]$ (1.75 mmol) was reacted with $AgNO_3$ (3.37 mmol) in 20 mL water overnight to produce *cis*-$[Pt(L)_2(H_2O)_2](NO_3)_2$. After AgI was filtrated off, the filtrate was mixed with 2.10 mmol disodium salt of 3,5-diisopropylsalicylic acid and then the white product precipitated from the mixture solution. The white product was collected, washed with water and then dried under vacuum (LSPt-1: 0.35 g, LSPt-2: 0.62 g, LSPt-3: 0.71 g).

4.2.1. LSPt-1

Yield: 45%. Anal. Calc. for $C_{13}H_{22}N_2O_3Pt$ (%): C 34.74, H 4.93, N 6.23, Pt 43.40; found: C 34.85, H 5.01, N 6.17, Pt 43.55. UV–vis (EtOH) λ_{max} nm: 209, 312. ^1H NMR (CD_3OD,

Table 1
The octanol/water distribution coefficient and solubility of LSPt-1–3

	LSPt-1	LSPt-2	LSPt-3	Carboplatin	Oxaliplatin	Eptaplatin
Water (mmol/L)	0.013	0.005	0.006	45.787	12.585	9.546
Octanol (mmol/L)	251.66	111.13	122.54	0.22	0.28	0.47
log *P*	4.27	4.37	4.31	−2.30 [21]	−1.65 [21]	−1.29

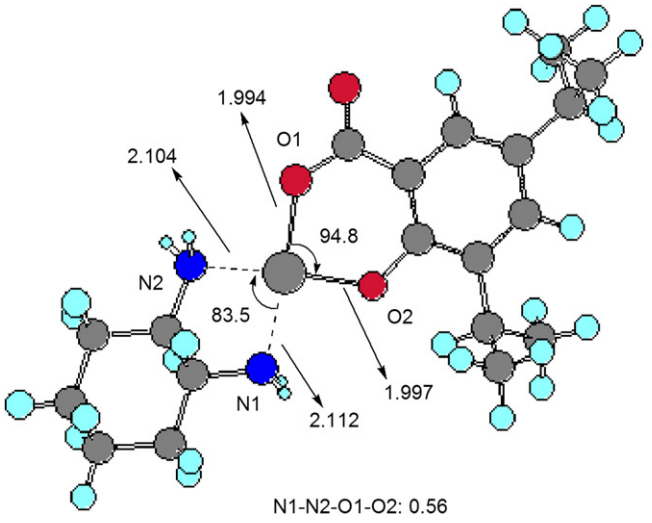

Fig. 5. The stereo-drawing of structure of LSPt-2.

500.13 MHz) δ ppm: 1.11–1.20 (m, 12H, $4CH_3$), 2.78–2.84 (m, 2H, $CH(CH_3)_2$), 7.15 (s, 1H, C_4–H), 7.63 (s, 1H, C_6–H). IR (KBr) cm^{-1}: 2960 ($\nu_{as}(CH_3)$, m), 2870 ($\nu_s(CH_3)$, m), 1623 ($\nu_{as}(COO^-)$, m), 1445 ($\nu_s(COO^-)$, m), 1392 ($\delta(CH(CH_3)_2)$, s), 1363 ($\delta(CH(CH_3)_2)$, m). MS-FAB$^+$ *m/z* (%): 450 ($(M+1)^+$, 100), 414 ($M^+ - 2(NH_3)$, 27), 230 ($M^+ - C_{13}H_{16}O_3$, 14).

4.2.2. LSPt-2

Yield: 67%. Anal. Calc. for $C_{19}H_{30}N_2O_3Pt$ (%): C 43.10, H 5.71, N 5.29, Pt 36.84; found: C 43.22, H 5.67, N 5.20, Pt 36.91. $[\alpha]_D^{20}$ +53.6 (EtOH). UV–vis (EtOH) λ_{max} nm: 207, 311. ^{1}H NMR (CD_3OD, 500.13 MHz) δ ppm: 1.16–1.21 (m, 12H, $4CH_3$), 2.82–2.85 (m, 2H, $CH(CH_3)_2$), 7.15 (s, 1H, C_{4a}–H), 7.65 (s, 1H, C_{6a}–H). ^{13}C NMR (DMSO-d_6, 100.62 MHz) δ ppm: 22.38 (C-9a), 24.04 (C-10a), 24.32 (C-4, C-5), 26.33 (C-7a), 32.91 (C-3, C-6 or C-8a), 62.49 (C-1, C-2), 114.5 (C-1a), 126.20 (C-6a), 133.96 (C-4a), 135.47 (C-3a), 137.51 (C-5a), 157.63 (C-2a), 172.99 (C-11a). IR (KBr) cm^{-1}: 2958 ($\nu_{as}(CH_3)$, m), 2866 ($\nu_s(CH_3)$, m), 1620 ($\nu_{as}(COO^-)$, m), 1446 ($\nu_s(COO^-)$, s), 1392 ($\delta(CH(CH_3)_2)$, s), 1361 ($\delta(CH(CH_3)_2)$, m). MS-FAB$^+$ *m/z* (%): 530 ($(M+1)^+$, 35), 419 ($M^+ - C_6H_{14}N_2$, 15), 309 ($M^+ - C_{13}H_{16}O_3$, 27).

4.2.3. LSPt-3

Yield: 69%. Anal. Calc. for $C_{21}H_{34}N_2O_5Pt$ (%): C 42.77, H 5.82, N 4.75, Pt 33.08; found: C 42.71, H 5.89, N 4.79, Pt 33.10. $[\alpha]_D^{20}$ −30.9 (EtOH). UV–vis (EtOH) λ_{max} nm: 210, 314. ^{1}H NMR (DMSO-d_6, 500.13 MHz) δ ppm: 0.84 (d, $J = 6.7$ Hz, 6H, $2CH_3$), 0.99 (m, 1H, $CH(CH_3)_2$), 1.08–1.21 (m, 12H, $4CH_3$), 2.72–2.75 (m, 2H, CH_2NH_2), 3.13–3.17 (m, 2H, CH_2NH_2), 6.92 (s, 1H, C_{4a}–H), 7.40 (s, 1H, C_{6a}–H). ^{13}C NMR (acetone-d_6, 100.62 MHz) δ ppm: 16.88 (C-1), 22.92 (C-9a), 24.77 (C-10a), 26.70 (C-7a), 32.55 (C-2), 34.16 (C-8a), 49.59 (C-4), 80.97 (C-5), 108.17 (C-3), 119.22 (C-1a), 126.36 (C-6a), 128.48 (C-4a), 135.31 (C-3a), 137.17 (C-5a), 158.64 (C-2a), 176.27 (C-11a). IR (KBr) cm^{-1}: 2961 ($\nu_{as}(CH_3)$, m), 2874 ($\nu_s(CH_3)$, m), 1620 ($\nu_{as}(COO^-)$, m), 1445 ($\nu_s(COO^-)$, s), 1391 ($\delta(CH(CH_3)_2)$, s), 1361 ($\delta(CH(CH_3)_2)$, m), 1123 (ν(C–O), m), 1097 (ν(C–O), m). MS-FAB$^+$ *m/z* (%): 590 (M^+, 15), 369 ($M^+ - C_{13}H_{16}O_3$, 12).

Table 2
In vitro cytotoxic activity IC_{50} of LSPt-1–3

Complexes	IC_{50} (μM)			
	A549	NCI-H460	SGC-7901	3AO
LSPt-1	0.33	0.84	7.63	4.00
LSPt-2	0.28	0.15	1.09	1.23
LSPt-3	1.80	3.31	2.54	>100
Carboplatin	14.20	10.70	16.34	14.28
Oxaliplatin	3.54	5.47	7.77	>100
Eptaplatin	3.56	4.62	2.36	>100

Table 3
In vivo antitumor activity of LSPt-2 in mouse NCI-H460 xenograft

Complexes	Dose (mg/kg)	Administration schedule[a]	*T/C* (%)[b]
LSPt-2[c]	9	1, 4, 8	85.4
LSPt-2[c]	15	1, 4, 8	62.2
LSPt-2[c]	30	1, 4, 8	38.8[d]
Carboplatin	60	1, 4, 8	45.9[d]
Oxaliplatin	9	1, 4, 8	60.5[d]

[a] The dose was i.p. administered to mice on the 1st, 4th and 8th day after tumor transplantation, respectively.
[b] (Mean tumor volume of the treated group/mean tumor volume of the control group) × 100.
[c] Compound was dissolved in arachis oil before administration.
[d] $P < 0.01$ *vs* control.

4.3. In vitro cytotoxicity

Potential cytotoxicity was evaluated against an in vitro panel of four human cancer cell lines including A549 lung carcinomas, NCI-H460 lung carcinomas, 3AO ovarian carcinomas and SGC-7901 stomach carcinomas. The compound was predissolved in DMSO (20 mM) and diluted with cell culture medium to six required concentrations (20 μM, 10 μM, 2 μM, 1 μM, 0.2 μM, and 0.1 μM). The content of DMSO in the final concentrations did not exceed 0.1%. At this concentration, DMSO was found to be nontoxic to the cells tested. All cells were cultured in RPMI 1640 supplemented with 10% fetal bovine serum, 100 IU/mL penicilin and 100 μg/mL streptomycin, at 37 °C in a humidified atmosphere of 5% CO_2. The cells were seeded at a density of 5×10^4 cells per well in 96-well microplates. After 24 h, the cells were treated with a serial concentration of the test compound. The cells were exposed to drugs for 72 h. Cell growth was assayed using Sulforhodamine B (SRB). The optical density (OD) was read at 490 nm. All cytotoxicity tests were performed three times in quadruplicate. The IC_{50} values were calculated from the curves constructed by plotting cell survival (%) versus compound concentration (μM).

4.4. Antitumor activity

NCI-H460 non-small-cell lung carcinomas tumor cells (about 5×10^8 per mouse) were routinely implanted s.c. in

the right axillary region of BALB/cA-nude mice (20 ± 3 g body weight, 8 animals per group). After 48 h of tumor transplantation, the platinum complexes (i.p. administration), Carboplatin (i.p. administration) and Oxaliplatin (i.v. administration) were administered at several dosages for 1, 4, and 8 days. At day 14 the animals were sacrificed, the tumors removed and their volumes determined. The control received the same amount of vehicle solution. Data were expressed as *T/C* (%), where the *T/C* value has been calculated as follows: (mean tumor volume of the treated group/mean tumor volume of the control group) $\times$ 100.

4.5. Acute toxicity study in mice

Healthy ICR mice of both sexes, weighting 18–22 g, were divided into 5 groups of 10 animals matched for weight and size. The platinum complexes were i.p. administered at the dose of 197.0, 226.0, 260.0, 299.0 and 344.0 mg/kg body weight. Behavior and changes in the weight of mice were monitored and death was recorded within 14 days. The LD_{50} values were calculated using Bliss method.

Acknowledgements

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