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Novel Lipophilic Platinum(II) Compounds of Salicylate Derivatives

RESEARCH, DEVELOPMENT AND LIPOSOMAL FORMULATION

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A series of novel lipophilic platinum(II) compounds containing salicylate derivatives as the leaving group have been designed, synthesised and characterised. Most of the platinum compounds exhibit high solubility and have a partition coefficient suited to liposomal encapsulation. Some of the compounds are more pharmacologically active and/or less toxic than carboplatin and oxaliplatin. The liposomal formulation of the most promising compound has been successfully prepared with long stability and high encapsulation rate, showing great potential to be developed as a new tumour-target drug.

In developed countries, such as the U.S.A., Canada, Australia and European countries, about 25% of deaths are related to malignant diseases. Chemotherapy is a central component in the fight against cancer. It is based on various classes of compounds, among which platinum-based drugs are a unique class. *cis*-Diamminedichloroplatinum(II) (cisplatin), first approved for clinical use in 1978 in the U.S.A., is one of the most effective anticancer drugs currently available for the treatment of testicular, lung and bladder carcinomas. Driven by the impressive impact of cisplatin on cancer therapy, numerous analogues have been prepared and evaluated in a search for alternative active agents, leading to the discovery of another important Pt drug, carboplatin, *cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II) in 1986. Today, carboplatin has become one of the most successful anticancer drugs after cisplatin and has received worldwide approval for treating ovarian and small lung cancers (1, 2). Carboplatin shows a spectrum of activity identical with that of cisplatin, but is much less nephrotoxic and emetic. However carboplatin is not effective in treating cancer cells resistant to cisplatin, possibly due to the same diammine carrier, suggesting that cross-resistance exists between the two Pt drugs (3, 4). Therefore, the search for new potent Pt complexes possessing high antitumour activity and lack of cross-resistance continues. The so-called 'third generation' Pt drug, oxaliplatin, (*trans*-1*R*,2*R*-cyclohexane-1,2-diamine)oxalatoplatinum(II), was approved in 1999 as the first line therapy for metastatic colorectal cancer in combination with 5-fluoroural. Oxaliplatin has also shown potency in many cancer cell lines, including some cells resistant to cisplatin and carboplatin (5). Further Pt-based drugs, nedaplatin, lobaplatin and eptaplatin, have gained regionally limited approval, respectively, in Japan, China and South Korea, for the treatment of certain kinds of cancers (6). Pt-based drugs currently in clinical use are shown in Figure 1.

In the meantime, the rational design of Pt anticancer compounds with specific characteristics has led to the invention of the orally available drugs satraplatin (JM216) and picoplatin (AMD473, a sterically hindered complex), see

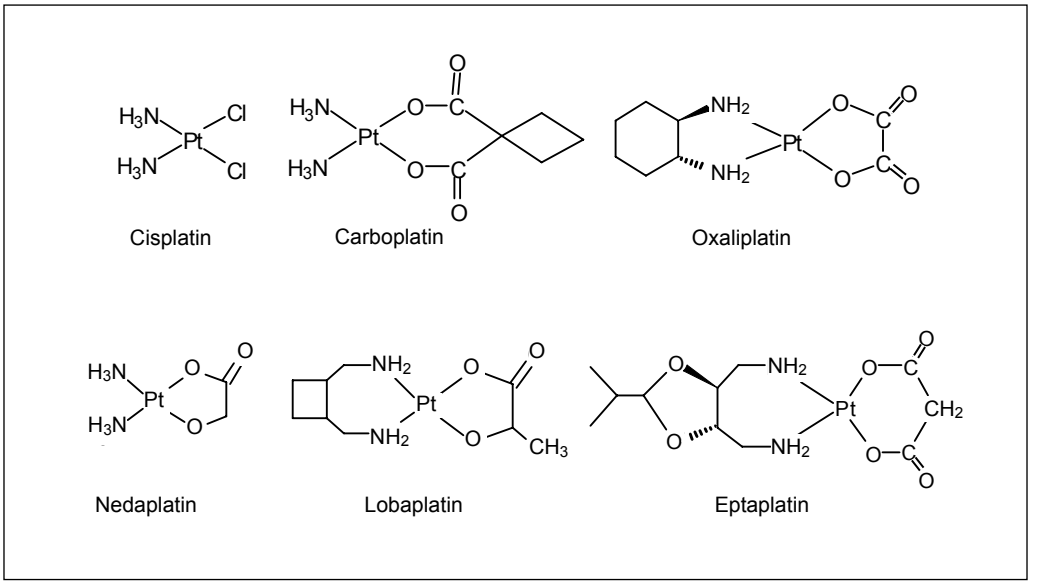


Fig. 1 Platinum-based drugs currently in clinical use

Figure 2. Satraplatin and picoplatin are able to circumvent some drug resistance. They have recently shown promising clinical activity, respectively, in hormone-refractory prostate cancer and in small-cell lung cancer, and are strongly anticipated to receive clinical approval (7, 8).

The clinical use of Pt-based drugs is frequently limited by severe toxic side effects such as nephrotoxicity, neurotoxicity and meylosuppression, as well as drug resistance. One of the most intriguing strategies to overcome these drawbacks is to encapsulate the agent in a liposome (9). Some anticancer drugs such as doxorubicin have been approved in their liposomal formulations (doxil in the case of doxorubicin) for the treatment of AIDS-related Kaposi's sarcoma (AIDS-KS) and relapsed ovarian cancer in the U.S.A. and Europe (10). Several different liposomal formulations of cisplatin have also been prepared and biologically evaluated. Among them, SPI-77 and lipoplatin are currently in Phase I and II clinical trials (11–14). To date, none of the liposomal formulations of cisplatin have been approved for clinical use. The key reasons for this are the poor water solubility and low lipophilicity of cisplatin (other Pt anticancer drugs show similarly poor lipophilicity), which makes it difficult to efficiently encapsulate the drug in a liposome. An alternative approach is to synthesise lipophilic Pt complexes. NDDP (*cis*-bis-neodecanoato-*trans*-*R*,*R*-1,2-diaminocyclohexane platinum(II)) is an example of such a complex, and its liposomal formulation L-NDDP (aroplatin) has entered Phase II clinical trials (15, 16). Unfortunately, NDDP is intraliposomally

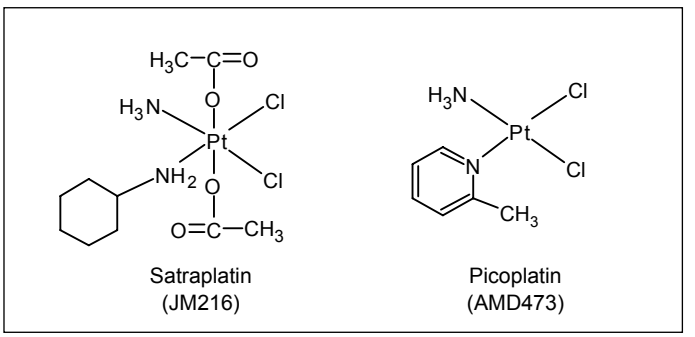


Fig. 2 Chemical structures of satraplatin (JM216) and picoplatin (AMD473)

unstable due to the presence of two monodentate carboxylate leaving groups (17, 18). Furthermore, in order to improve the liposolubility of NDDP, highly branched aliphatic carboxylate groups were used, greatly increasing the molecular weight and making passive diffusion through the cell membrane difficult. It is therefore important to identify lipophilic Pt complexes using chelating bidentate ligands of small molecular weight.

Design and Synthesis

On the basis of the above findings, we designed a series of novel lipophilic platinum(II) compounds of salicylate derivatives (19) including 3,5-diiodosalicylate (DISA), 3-isopropyl-6-methylsalicylate (*o*-thymotate) and 3,5-diisopropylsalicylate (DIPSA) as the leaving groups. DISA is a food additive used as an iodine source and *o*-thymotate is derived from plants of the genus *Thymus*. Salicylate and its derivatives are important non-steroidal anti-inflammatory agents. Their capacity to block metastasis of cancer cells by inhibiting synthesis of prostaglandin is well known, as well as their reduction of the ototoxic and nephrotoxic side effects caused by cisplatin (20). This is a further reason for selecting salicylate derivatives as leaving groups in the target Pt complexes.

As for non-leaving groups, the diammines of cisplatin, oxaliplatin and eptaplatin were used. The design strategy in our research is to develop Pt complexes providing higher liposolubility and chemical stability, along with higher antitumour activities and lower systemic toxicity. The compounds we designed are illustrated in Figure 3.

All the compounds can be synthesised as precipitates from aqueous solution by the general method shown in Scheme I, owing to their low water solubility. Potassium tetrachloroplatinate (K_2PtCl_4) was first converted to potassium tetraiodoplatinate (K_2PtI_4) *in situ* by reaction with potassium iodide (KI). K_2PtI_4 was then treated with ammine/diamine ('A_2') to form diam(m)ine-diiodoplatinum(II) complexes, which were reacted with silver nitrate ($AgNO_3$), giving rise to $[PtA_2(H_2O)_2](NO_3)_2$. The addition of sodium salicylate derivatives ('Na_2X_2') to the solution of $[PtA_2(H_2O)_2](NO_3)_2$ precipitated the target compounds. Purification was carried out by re-precipitation from an ethanol or acetone solution of the compound after adding water.

Characterisation and Lipophilicity

The compounds were characterised by elemental analysis, Fourier transform infrared (FTIR) spectroscopy, ^{1}H nuclear magnetic resonance (NMR) spectroscopy and positive ion fast atom bombardment mass spectrometry (FAB^+-MS). The elemental analysis data for each compound were in good agreement with the empirical formula proposed. All the compounds developed $[M + H]^+$ peaks in the FAB^+-MS spectra, corresponding to their molecular weights. The binding of the salicylic acid derivatives to Pt(II) atoms as a bidentate ligand was confirmed by the shift of the C=O absorption frequency, $\nu_{C=O}$, to lower values and the absence of ν_{O-H} absorption in the IR spectra in the resulting compounds. ^{1}H NMR spectral peaks were compatible with the chemical

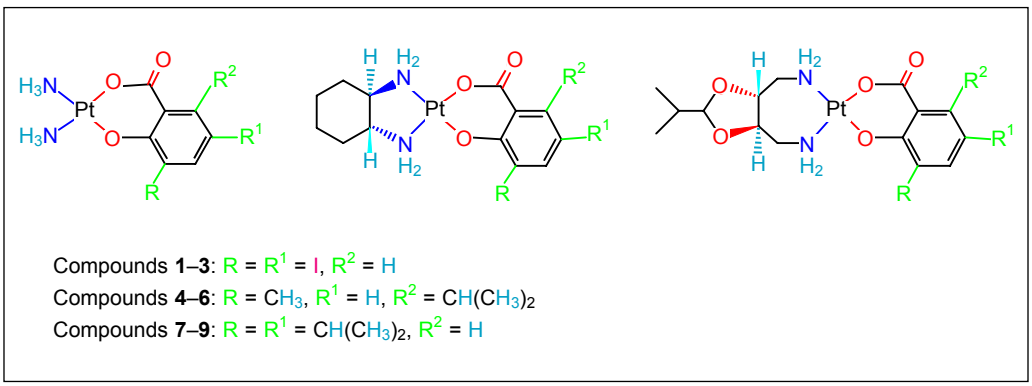
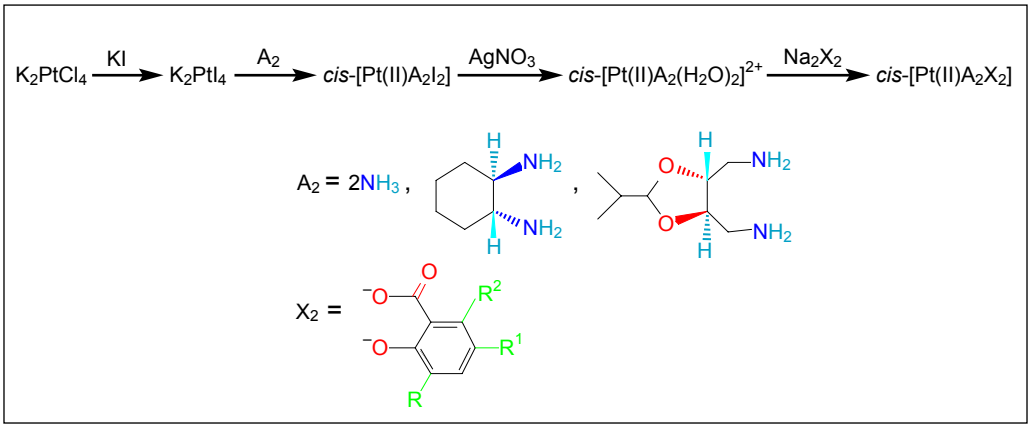


Fig. 3 Structures of platinum(II) complexes of salicylate derivatives



Scheme I General procedure for the synthesis of the platinum(II) compounds of salicylate derivatives

structures given in Figure 1. In order to further explore the chemical structures, we attempted to prepare single crystals suitable for X-ray crystallography, but failed. So we resorted to the "Gaussian 03" computer software (21, 22) and constructed the chemical structures of two representative Pt compounds **6** and **8**, as shown in Figure 4.

The Pt(II) compound had the expected square planar geometry exhibiting the usual structural parameters. Pt-N1, Pt-N2, Pt1-O1, and Pt1-O2 distances were in the normal range, and bond angles of O2-Pt1-O1, N1-Pt1-N2 were also within the normal values for other diaminedicarboxylatoplatinum(II) complexes (23–25).

The solubilities of the compounds **1**–**9** in both water and organic solvents such as ethanol, acetone and ether were determined. All the compounds except for compounds **1** and **4** had low solubility in water but high solubility in the organic solvents (> 20 mg cm^{-3}). Partition coefficients in an octanol/water system were measured for the lipophilic Pt compounds **2**, **3**, **5**, **6**, **7**, **8** and **9**. The partition coefficients and solubility in water are listed in Table I. The lipophilic complexes were stable in the organic solvents for five days at room temperature, as indicated by monitoring their ultraviolet (UV) spectra. Presumably this stability results from the chelation effect of the leaving groups.

From Table I it appears that both the carrier and leaving group influenced the lipophilicity of the compounds. For the same leaving group the order of lipophilicity was: DACH > BAMID > NH_3, and DIPSA > thymotate > DISA when the carrier is the same. (DACH = *trans*-1*R*,2*R*-

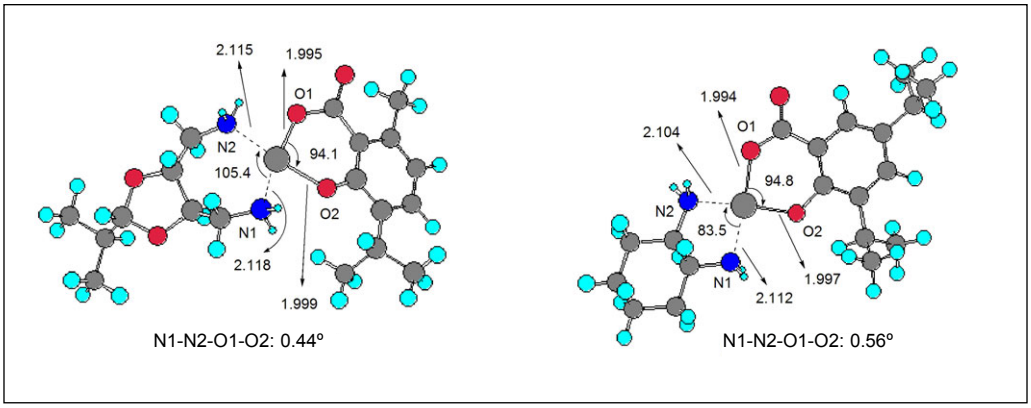


*Fig. 4 The steric structures of platinum compounds **6** and **8***

Table I

Partition Coefficients and Solubility of the Platinum Compounds

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	Cisplatin	Carboplatin
Solubility in water, μg cm^{-3}	300	12	25	250	12	7.3	5.9	5.7	3.5	1000	17,500
Partition coefficient, log *P*	–	3.3	3.1	–	3.4	4.3	4.1	4.4	4.3	–	–

diaminocyclohexane; BAMID = (4*R*,5*R*)-4,5-bis-(aminomethyl)-2-ispropyl-1,3-dioxolane.)

Biological Evaluation

The target Pt compounds **1**–**9** were assayed *in vitro* against several human cancer cell lines, including A549 (human lung carcinoma) and SGC-7901 (human gastric carcinoma). Cellular survival was evaluated by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) method (26). The median inhibitory concentration (IC_{50}) values were calculated from plots of cell survival (%) *versus* compound concentration (in μM).

Surprisingly, all the compounds were more active against A549 and SGC-7901 cell lines with lower IC_{50} values than the parent drugs carboplatin, oxaliplatin and SKI-2053R (*cis*-malonato(4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane)platinum(II)) (Table II). Among the lipophilic compounds **2**, **3** and **5**–**9**, compounds **6** and **8** were the most active. No clear structure-activity relationship could be established from *in vitro* activity.

Table II

In Vitro Cytotoxicity of the Platinum Compounds Against Selected Human Tumour Cell Lines

Compounds	Carriers (non-leaving groups)	Leaving groups	IC_{50}, μM	
			A549	SGC-7901
1	$2NH_3$	DISA	1.54 ± 0.08	2.65 ± 0.16
2	DACH	DISA	1.05 ± 0.05	2.93 ± 0.13
3	BAMID	DISA	2.16 ± 0.11	2.93 ± 0.15
4	$2NH_3$	thymotate	0.89 ± 0.03	1.83 ± 0.09
5	DACH	thymotate	1.49 ± 0.04	6.95 ± 0.62
6	BAMID	thymotate	1.27 ± 0.07	2.64 ± 0.06
7	$2NH_3$	DIPSA	0.33 ± 0.03	7.63 ± 0.82
8	DACH	DIPSA	0.28 ± 0.03	1.09 ± 0.06
9	BAMID	DIPSA	1.80 ± 0.07	2.54 ± 0.34
Carboplatin	$2NH_3$	CBDCA*	9.26 ± 0.25	16.34 ± 0.69
Oxaliplatin	DACH	oxalate	3.54 ± 0.18	7.77 ± 0.56
SKI-2053R	BAMID	malonate	3.56 ± 0.20	2.36 ± 0.07

**CBCDA = cyclobutane-1,1-dicarboxylate*

Compounds **6** and **8** were therefore evaluated for their *in vivo* antitumour activity using conventional methods (27). Sarcoma S180 tumour-bearing mice and NCI-H460 (human lung cancer) xenograft mice were established and used as the *in vivo* models, as described in previous studies (28, 29). The potency of the antitumour effects was measured in terms of the ratio of tumour weights for treated (T) and control (C) animal groups (T:C), expressed as a percentage. Tables III and IV show the antitumour activity of compound **6** in solid S180 tumour-bearing mice, and of compound **8** in mouse NCI-H460 xenograft following intraperitoneal (i.p.) administration. The results indicate that compound **6** exhibited *in vivo* activity comparable to carboplatin in treating animals with S180. However compound **6** was much more active *in vitro* than carboplatin, probably due to its different pharmacokinetic behaviour. Nevertheless compound **8** was more effective on mouse NCI-H460 xenograft than carboplatin and oxaliplatin. We also tested the preliminary toxicity of compound **8**. A range of doses (mg kg^{-1}) of the test compound were administered i.p. to healthy Institute of Cancer Research mice in volumes of 0.1 cm^3 per 10 g body weight (n = 10, 12–22 g, in standard environmental conditions).

After fourteen days, the median lethal dose (LD_{50}) was calculated by the Bliss method (30). The data in Table V show the LD_{50} value to be 230 mg kg^{-1} (95% confidence limit 207 to 258 mg kg^{-1}) by i.p. administration to ICR mice, much larger than that of carboplatin (150 mg kg^{-1}) and oxaliplatin (19.8 mg kg^{-1}), indicating that compound **8** was less toxic. Antitumour activity of the two compounds on other animal models is being assayed at the Shanghai Institute of Materia Medica.

Table III

Antitumour Activity of Platinum Compound **6** in Mice with S180

Group	Dose, mg kg^{-1}	Treatment scheme	Number of mice	Tumour weight, g, $x \pm$ SD	T:C, %
Control	–	–	12	1.42 ± 0.25	–
Compound **6**	30	i.p., d 1, 4	6	1.26 ± 0.34	83.4
	60		6	0.74 ± 0.51	53.1*
	90	i.p., d 1	6	0.96 ± 0.29	67.6*
Carboplatin	60	i.p., d 1, 4	8	0.62 ± 0.29	43.7*

*Note: The compound was dissolved in arachis oil before administration; SD = standard deviation; d = day(s);*P < 0.01 vs. control*

Table IV

Antitumour Activity of Platinum Compound **8** in Mouse NCI-H460 Xenograft

Group	Dose, mg kg^{-1}	Scheme	Number of mice	RTV, $x \pm$ SD	T:C, %
Control	–	–	12	18.5 ± 5.4	–
Compound **8**	15	i.p., d 0, 4, 8	6	11.5 ± 3.8	62.2
	30		6	5.7 ± 2.0	38.8*
	60	i.p., d 0	6	7.1 ± 1.9	30.4*
Carboplatin	60	i.p., d 0, 4, 8	8	8.5 ± 4.1	45.9*
Oxaliplatin	9	i.p., d 0, 4, 8	6	11.2 ± 7.3	60.5*

*Note: The compound was dissolved in arachis oil before administration; *P < 0.01 vs. control; RTV = relative tumour volume*

Table V

Acute Toxicity of Platinum Compound **8** Following Intraperitoneal Administration in Mice

Group	Dose, mg kg^{-1}	Number of mice	Death number	LD_{50}, mg kg^{-1}
1	197.0	10	2	230.9
2	226.0	10	6	
3	260.0	10	7	
4	299.0	10	7	
5	344.0	10	10	

Liposomal Platinum Compound

A liposomal formulation of compound **8** has been successfully prepared in our laboratory by an evaporation-lypophilisation method. The compound, lipoid *Emblica officinalis* (Indian gooseberry) polyphenol fraction (EOP) and cholesterol were mixed and dissolved in chloroform. After removal of chloroform at 37°C in a rotary evaporator, *tert*-butanol was added to form a clear solution. The solution was freeze-dried, yielding lyophilised pre-liposomal powder from which the final liposomal Pt compound can be obtained by reconstitution in aqueous solution.

The liposomal entrapment efficiency (EE) was greatly influenced by pH, as shown in Table VI. EE exceeded 95% when pH was below 4.0, indicating good compatibility between compound **8** and the lipids used. The optimal pH was 3.4 to 4, since the compound would undergo dissociation under more acid conditions. The average size of the liposome reconstituted in saline varied from 100 to 300 nm with a distribution index of 0.1 to 0.2 (Figure 5). As observed by transmission electron microscopy (TEM), the particles were of elliptical or ellipsoidal form, containing about 5% of Pt compound (Figure 6). The liposomal formulation of compound **8** so prepared was determined by high-performance liquid chromatography (HPLC) to be stable for ninety days when kept at 4°C in a sealed, nitrogen-filled container.

Conclusion

The three principal Pt drugs, cisplatin, carboplatin and oxaliplatin, along with other Pt drugs including nedaplatin, lobaplatin and eptaplatin, continue to have a major role in contemporary medical oncology. Should other Pt drugs such as satraplatin and picoplatin receive approval for clinical use, they would further broaden the applicability of Pt compounds to prostate cancer and small-cell lung cancer. However, reducing toxicity and increasing activity are still the most important goals for Pt drug development. These will be achieved only by targeting tumours or tumour cells either *via* liposomal formulations or with new tumour-specific Pt compounds. Therefore an effective liposomal formulation affording antitumour activity must be developed, while preserving the chemical stability of Pt compounds within the liposomes up to the point of administration to cancer patients. Lipophilic Pt complexes with chelating bidentate ligands as the leaving group are required for such a liposomal formulation.

Our studies show that the Pt(II) compounds with salicylate derivatives as the leaving group are

Table VI

Effect of pH on Liposomal Entrapment Efficiency (EE)

pH	2.6–3.0	3.5	4.0	4.5	5.0	6.0–7.0
EE, %	99	95–97	93–95	90	85	80

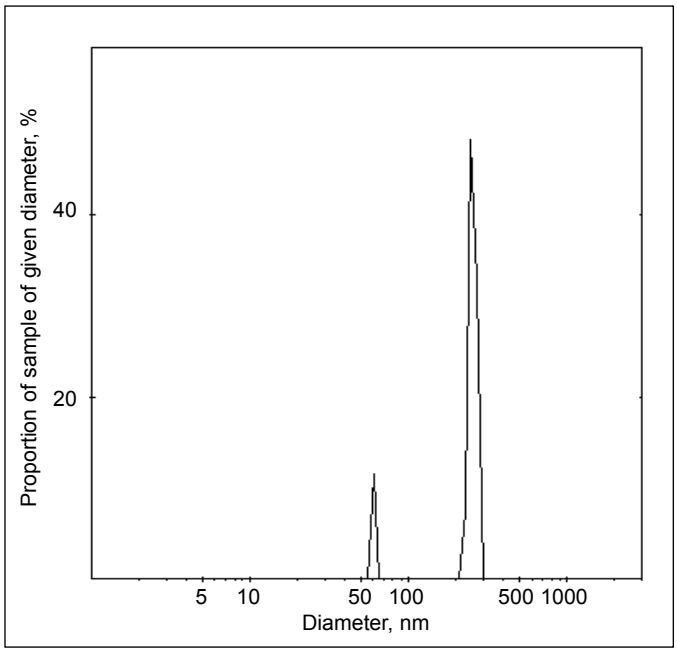


*Fig. 5 The size distribution of the liposomal formulation of platinum compound **8***

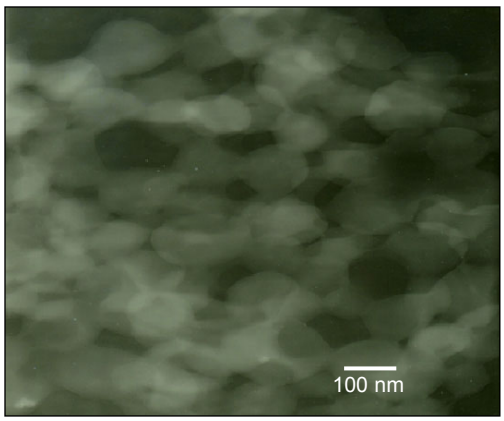


Fig. 6 Transmission electron microscope image of the liposome

lipophilic with partition coefficients of 3 to 4, and are stable as a result of the chelation effect of the leaving groups. Among them, Pt compound **8** shows greater antitumour activity and less toxicity than carboplatin and oxaliplatin. Its liposomal formulation has the advantages of high liposomal entrapment efficiency, high drug content and long stability, showing great potential for further development as a novel liposomal Pt drug which will directly target tumours. Further biological evaluation for compound **8** and its liposomal formulation including antitumour activity, toxicities and drug distribution are being carried out in our laboratories. Of course, there are many hurdles to be overcome and much research to be done before clinical testing can begin.

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