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Original article

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

Yao Yu [a], Li-Guang Lou [b], Wei-Ping Liu [a,*], Hua-Jie Zhu [c], Qing-Song Ye [a], Xi-Zhu Chen [a], Wen-Gui Gao [a], Shu-Qian Hou [a]

[a] *Platinum-based Drug Laboratory, Kunming Institute of Precious Metals, Kunming 650221, PR China*
[b] *Shanghai Institute of Materia Medica, China Academy of Science, Shanghai 201203, PR China*
[c] *Kunming Institute of Botany, Chinese Academy of Science, Kunming 650204, PR China*

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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

* Corresponding author. Tel./fax: +86 871 5133648.
E-mail address: liuweiping0917@126.com (W.-P. Liu).

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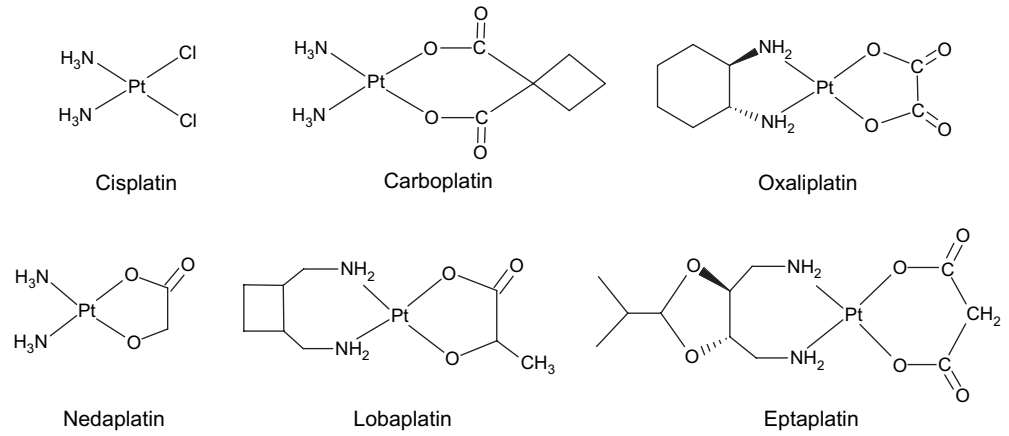

Fig. 1. Platinum-based drugs currently in clinical use.

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

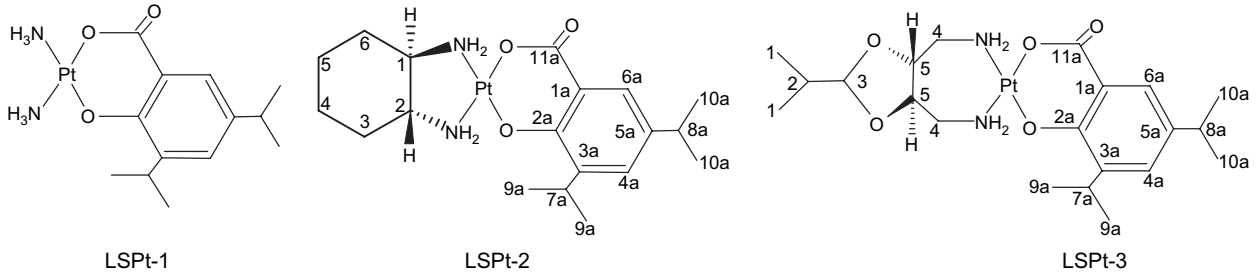

Fig. 2. Complexes of (3,5-diisopropylsalicylato)platinum(II) with diam(m)ine ligands.