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Synthesis and biological evaluation of mixed ammine/amine platinum(II) complexes with dicarboxylate containing organic nitrate as ligand

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ABSTRACT

Two novel platinum(II) complexes cis-[Pt(L′)(NH_3)X] (where L′ = cyclopentylamine or cyclohexylamine, X = 3-(nitrooxy)cyclobutane-1,1-dicarboxylate) were synthesized and spectrally characterized in this study. The purity of complexes **1** and **2** were studied by HPLC–MS spectra, and the contents of complexes **1** and **2** were more than 98%. It was demonstrated that the newly synthesized compounds with dicarboxylate containing organic nitrate as ligand possessed DNA unwinding capability similar to cisplatin by the means of agarose gel electrophoresis. In addition, the antiproliferative study by WST-8 assay revealed that these platinum(II) complexes exhibited considerable cytotoxicity against tested cancer cell lines in vitro compared with positive agents (cisplatin, oxaliplatin and carboplatin), especially complex **1**, showing higher in vitro antitumoractivity than oxaliplatin and carboplatin in SGC7901 and A549 cell lines.

1. Introduction

The successful application of cisplatin as anticancer drugs in clinic has attracted much attention to designing new generation of platinum-based anticancer complexes that circumvent shortcomings of cisplatin [1,2]. For several decades, numerous platinum(II) complexes have been synthesized and screened as potential anticancer antitumor agents. However, only two cisplatin analogues, carboplatin and oxaliplatin, were worldwide approved for malignant tumor chemotherapy [3]. One of the reasons for this limited success in the anticancer research of platinum-based complexes is due to the relative lack in structural diversity [4]. Most of the reported platinum(II) complexes are so called classical ones which have been designed based on the structure–activity relationships summarized by Cleare and Hoeschele [5,6], and these platinum(II) complexes often contain two identical amines, which may show cross-resistance with cisplatin, such as carboplatin [4,7].

Satraplatin [bis-acetato-ammine-dichlorido-cyclohexylamine-platinum(IV), JM216, Fig. 1] with two different amines in the equatorial plane showed promise against second-line hormone refractory prostate cancer in clinical trials [8–10]. It exerted anticancer activity by losing its axial acetate groups to form a platinum(II) complex (JM118), an asymmetrical cisplatin analogue which binds to DNA via a similar mechanism to cisplatin [11–13]. JM118 is considerably more active than cisplatin in numerous cisplatin sensitive and resistant human tumor cells [14–17]. Hence, many mixed ammine/amine platinum(II) complexes analogous to JM118, have been synthesized and investigated for anticancer activity against various human solid tumor cell lines by other researchers. Zhang's group has reported that mixed ammine/cyclohexylamine platinum(II) complexes with carboxylates/dicarboxylate as leaving groups show activity in vitro against EJ (human bladder carcinoma), HCT-8 (human colon carcinoma), BGC-823 (human gastric carcinoma), HL-60(human immature granulocyte leukemia) and MCF-7 (human galactophore carcinoma) cell lines [17,18].

Carboplatin exhibits decreased side effects (nephrotoxicity and neurotoxicity) and higher aqueous solubility compared with cisplatin because of 1,1-cyclobutanedicarboxylate (CBDC) as ligand. Liu's research group has reported a series of mixed ammine/cyclohexylamineplatinum(II) complexes with CBDC derivatives as leaving groups showing cytotoxicity against SK-OV-3, SGC-7901, 22RV-1, A549 and Beas-2B cell lines [19]. In our previous study, we have synthesized cisplatin and oxaliplatin derivatives with 3-(nitrooxy)cyclobutane-1,1-dicarboxylate (L^{2-}) as leaving group (GSH-1, GSH-2, Fig. 1), which showed considerable antitumor activity against the tested cancer cell lines [20]. Organic nitrate, as one of the nitrogen oxide donors, is well known for

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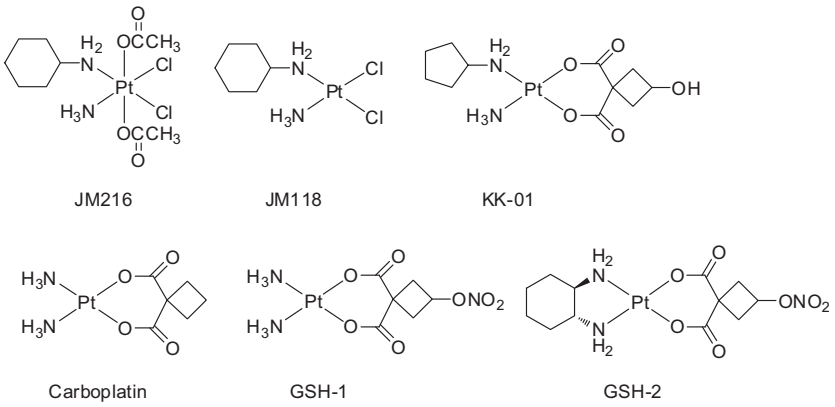
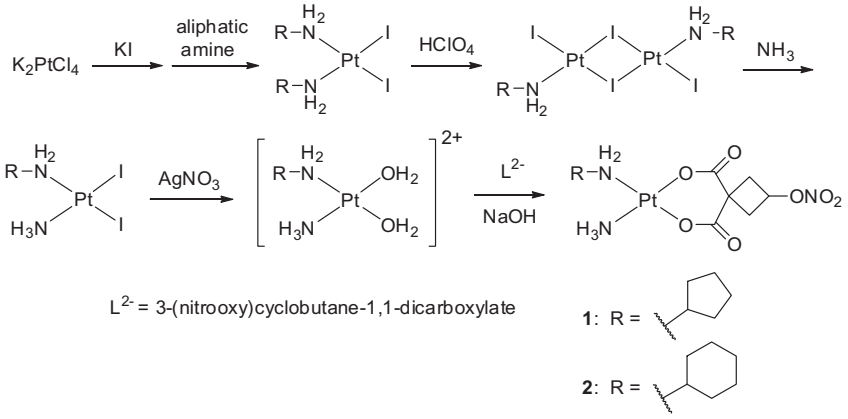


Fig. 1. Related antitumor platinum complexes in this paper.



Scheme 1. Preparation of platinum(II) complexes **1**–**2**.

its biological functions in vasodilation, neurotransmission, immune system, and cell apoptosis. Therefore, in this paper, 3-(nitrooxy)cyclobutane-1,1-dicarboxylate as a CBDC derivative, was introduced as a leaving group in the mixed ammine/amine platinum(II) complexes in order to adjust the antitumor activity (Scheme 1).

2. Experimental

2.1. Materials and instruments

All reagents and chemicals were of analytical reagent grade and used without further purification. Potassium tetrachloroplatinate(II), potassium iodide, cyclopentylamine, cyclohexylamine and silver nitrate were purchased from a local chemical company (Shandong Boyuan Chemical Co., Ltd., China). ^{1}H NMR spectra were measured in $D_2O$with a Bruker 300 MHz spectrometer. Mass spectra and HPLC were tested on an Agilent 6224 TOF LC/MS instrument. Elemental analyses for C, H and N were performed on a Vario MICRO CHNOS Elemental Analyzer. Elemental analyses for platinum were carried out on a J-A1100 inductively coupled plasma (ICP) spectrometer. Infrared spectra were recorded in the range 400–4000 cm^{-1} and measured in KBr pellets on a Nicolet IR200 FT-IR spectrometer.

2.2. Preparation of target complexes *1*–*2*

A mixture of cis-[Pt(L′)(NH_3)I_2] (1 mmol) and silver nitrate (2 mmol) in distilled water (40 mL) was stirred for 24 h at 40 °C, and then the depositing AgI was filtered off. To the filtrate was added 3-(nitrooxy)cyclobutane-1,1-dicarboxylic acid (1 mmol) mixed with NaOH (2 mmol) in 10 mL water. After the mixture was stirred for 24 h at room temperature, it was concentrated to 10 mL and the precipitate was filtered, yielding white solid. The product was dried at 35 °C in vacuo and kept in the dark. Complex **1**: Yield 0.31 g (62.3%). Whitesolid ^{1}H NMR (D_2O): δ 5.12 (quint, 1H, *CH*ONO_2), 3.06–3.34 (m, 5H, *CH*NH_2 and CH_2 of cyclobutyl), 1.96–2.78 (m, 4H, *CH_2*CH of cyclopentyl), 1.49–1.64 ppm (m, 4H, *CH_2*CH_2 of cyclopentyl); IR (KBr): 3222, 3125, 1635, 1384, 1283, 859 cm^{-1}; ESI-MS: *m*/*z* (%): 561 (89), 562 (100), 563 (82) $[M+NO_3^-]^-$; *Anal.* Calc. for $C_{11}H_{19}N_3O_7Pt$: C, 26.40; H, 3.83; N, 8.40; Pt, 38.99. Found: C, 26.31; H, 3.75; N, 8.59; Pt, 38.45%. The preparation of complex **2** was similar to that of complex **1** described above by applying the corresponding intermediate.

Complex **2**: Yield 0.33 g (64.4%). White solid ^{1}H NMR (D_2O): δ 5.11 (quint, 1H, *CH*ONO_2), 2.95–3.36 (m, 5H, *CH*NH_2 and CH_2 of cyclobutyl), 2.24–2.75 (m, 4H, *CH_2*CH of cyclopentyl), 1.04–1.68 ppm (m, 6H, *CH_2*CH_2 of cyclopentyl); IR (KBr): 3226, 3129, 1634, 1384, 1283, 860 cm^{-1}; ESI-MS: *m*/*z* (%): 575 (85), 576 (100), 577 (78) $[M+NO_3^-]^-$; *Anal.* Calc. for $C_{12}H_{21}N_3O_7Pt$: C, 28.02; H, 4.11; N, 8.17; Pt, 37.92. Found: C, 27.87; H, 4.32; N, 8.32; Pt, 37.56%.

2.3. Cell culture

Five human solid tumor cell lines including HCT-116 (human colorectal carcinoma), HepG-2 (human hepatocellular carcinoma), A549 (human non-small cell lung cancer), SGC7901 (human gastric cancer) and COC1 (human ovarian carcinoma) were used in the cytotoxicity test for the platinum complexes. They were cultured