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Design, synthesis and anticancer activity of diam(m)ine platinum(II) complexes bearing a small-molecular cell apoptosis inducer dichloroacetate

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ABSTRACT

Four new diam(m)ine platinum complexes containing the dichloroacetate moiety in 3-dichoroacetoxylcyclobutane-1,1-dicarboxylate as the leaving group were synthesized, characterized by elemental analysis as well as by ESI^+-MS (electrospray ionization mass spectrometry in positive mode), FT-IR, ^1H- and ^{13}C-NMR, and evaluated for their *in vitro* anticancer activity against human lung cancer cell line (A549) and ovarian cancer cell lines (SK-OV-3, SK-OV-3/DDP). Diam(m)ines used in the present study belong to the carriers of six clinically approved platinum drugs. Among the complexes synthesized, complex **2**, *cis*-[Pt(II)(*1R,2R*-diaminocyclohexane)·(3-dichoroacetoxylcyclobutane-1,1-dicarboxylate)] is the most promising in terms of water solubility and potential of being totally devoid of cross-drug resistance with cisplatin. Therefore, complex **2** was selected for the dichloroacetate release test. The test shows dichloroacetate can be efficiently released from complex **2** under physiological conditions via the hydrolysis of an ester bond bridging the dichloroacetate moiety and platinum pharmacophores together. Our study supports the further evaluation of this complex as a drug candidate.

1. Introduction

In today's world malignant tumors have become one of the most common and serious diseases, and rank first in human disease-related lethality. Chemotherapy is a central component in the fight against malignant tumors, and it is based on different classes of anti-cancer drugs. Among them, platinum-based drugs represent an important class characterized by killing cancer cells primarily through cross-linking DNA and inhibiting transcription [1,2]. Platinum-based drugs now available for clinical options include cisplatin (DDP, *cis*-diamminedichloroplatinum(II)), carboplatin, oxaliplatin, nedaplatin, heptaplatin and lobaplatin, and they have been successfully used in the treatment of solid tumors [3–5]. However, like other chemotherapy agents, the clinical applications of platinum-based drugs are largely restricted by side-effects as well as by drug resistance [6–8]. Ovarian cancer is a typical example of drug resistance. Most women with ovarian cancer respond fully to the initial cisplatin-based chemotherapy, but as tumors recur, they develop resistance not only to cisplatin but also to other platinum drugs. Drug resistance leads to the failure of chemotherapy. As a result, ovarian cancer has the highest mortality among gynecological cancers, highlighting the need for the development of new strategies to overcome this drawback. One of the strategies involves the synthesis and evaluation of non-classical platinum compounds represented by picoplatin, polynuclear complexes, and trans-platinum complexes, however the outcomes of clinical trials remained below expectations and none of these compounds has been approved for clinical application [9].

Drug resistance can emerge from failure to execute apoptosis despite initiation of the apoptotic cascade caused by either the predominance of anti-apoptotic factors or defects in downstream effectors. It has been demonstrated that failure to achieve final cell death after the formation of platinum-DNA adduct might be an important factor contributing to the drug resistance mechanisms in platinum-based chemotherapy [10,11]. One innovative and efficient strategy for combating this drug resistance, as highlighted by Dhara, Xiao and Lippard [12,13], is to incorporate dichloroacetate groups into the existing platinum drugs to form a prodrug. Dichloroacetate is a small-molecular cell apoptosis inducer and can trigger apoptosis through selectively targeting the mitochondria of cancer cells resistant to the anticancer drugs [14–16]. The resulting complex molecules contain both the platinum pharmacophore and dichloroacetate moiety displaying a dual-functional profile. As a result, the enhanced drug sensitivity and decreased resistance of tumor cells via a synergistic effect between the two active components were verified. Furthermore, molecular hybridization is an important drug discovery strategy which involves the rational design of new chemical entities by the fusion of two drugs [17].

Based on the above findings, we previously synthesized two mixed-NH_3/amine (amine = cyclopentylamine, cyclohexylamine) platinum(II) complexes featuring a dichloroacetate moiety tethered to the leaving group via an ester bond [18]. They exhibited markedly cytotoxicity

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toward cancer cells by selectively inducing the apoptosis of cancer cells, resulting in the decreased resistance of SK-OV-3 cancer cells to cisplatin. Unfortunately, the two complexes appeared very insoluble in water (≈0.034 mg/ml), a physico-chemical character unfavorable as a drug candidate. In the continuation of our interest to develop more effective platinum anticancer drugs, a series of new platinum complexes, as shown in Fig. 1, were designed based on the same strategy, synthesized and biologically evaluated in the present studies. Four diam(m)ines of clinically approved platinum drugs were used as the carriers and dichloroacetate-containing 3-dichoroacetoxylcyclobutane-1,1-dicarboxylate as the leaving group, with the intention of optimizing the structures and improving the solubility of the resulting complexes.

2. Experimental section

2.1. Materials and instrument

Potassium tetrachloroplatinate(II) and *1R,2R*-diaminocyclohexane were purchased from Alfa Aesar, and *trans*-1.2-bis(methylamine)cyclobutane was kindly provided by Hainan Changan International Pharmaceutical Co., Ltd., China. 3-Dichoroacetoxylcyclobutane-1,1-dicarboxylic acid and (*4R,5R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane were prepared as previously described [18,19]. All other chemicals obtained from commercial suppliers were of analytical grade and used as received. Water was distilled prior to use. Composition analyses for C, H and N were performed with a Carlo-Ebra instrument, whereas the content of platinum was analyzed according to the method in EP6.5. FT-IR spectra were measured in KBr pellets with a Perkin Elmer 880 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO on Brucker AV-400 MHz relative to TMS (tetramethylsilane) as an external standard. Electrospray ionization mass spectra (ESI-MS) were recorded on Agilent G6230 TOF MS equipped with an electrospray ion source. A Waters Associates system equipped with a 1525 pump, a 717 automated injector, and a Model 2998 photodiode array detector was employed to determine the release of dichloroacetate from the complexes.

2.2. General procedures for the synthesis of complexes 1–4

The synthetic procedures were carried out in light protected environment when platinum complexes were involved. $K_2[PtCl_4]$ (10 g, 28 mmol) was dissolved in water (100 ml) and treated with KI (20.9 g, 126 mmol). After standing for 40 min at room temperature, a solution of NH_3 (34 mmol in 50 ml water) or diamine (28 mmol in 50 ml water) was added dropwise while stirring, yielding the corresponding intermediate *cis*-$[PtA_2I_2]$ ($A_2 = 2NH_3$ or diamine) and the intermediate was filtered off, washed with water and ethanol and dried in vacuo at 55 °C. To a suspension of *cis*-$[PtA_2I_2]$ (6.00 mmol) in 40 ml distilled water, 2.039 g (12.00 mol) $AgNO_3$ in 10 ml distilled water was added, and the reaction mixture was stirred for 24 h at 35 °C. After the precipitated AgI was filtrated off, the resulting filtrate containing *cis*-$[PtA_2(H_2O)_2]^{2+}$ species was cooled down to 10 °C and then mixed with a freshly prepared aqueous solution of potassium 3-dichoroacetoxylcyclobutane-1,1-dicarboxylate (6.6 mmol). A white product precipitated. It was collected immediately by filtration, washed with distilled icy water and ethanol, dried under vacuum at 45 °C. Yield: 45% for complex **1**, 60% for complex **2**, 64% for complex **3**, 55% for complex **4**. The solubility of the resulting complexes in different solvents was determined by AAS (atomic absorption spectroscopy).

Complex **1** found (% calculated for $C_8H_{12}N_2O_6Cl_2Pt$): Pt 38.9 (39.2), C 19.1 (19.3), H 2.45 (2.40) and N 5.57 (5.62). MS-ESI^{+} m/z: 521 ($[M + Na]^{+}$, 19%). IR (KBr, cm^{-1}): 3430 (s, ν_{O-H}), 3281 (s, ν_{N-H}), 2953, 2857 (w, ν_{C-H}), 1749 (s, $\nu_{C=O}$), 1631 (vs, $\nu_{as(COO)}$), 1383 (vs, $\nu_{a(COO)}$), 1175 (m), 1023 (m), 894 (m), 819 (s) and 672 (m). ^{1}H NMR (dmso, δ): 2.10, 2.22 (≈4H, $2CH_2$, C-2, cyclobutane), 4.65 (≈1H, CH, cyclobutane), 5.57 (≈6H, $2NH_3$), and 6.84 (≈1H, $COCHCl_2$). ^{13}C NMR (dmso, δ): 42.1 (C-2, cyclobutane), 48.1 (C-1, cyclobutane), 60.5 (C-4, dichloroacetoxyl), 71.0(C-3, cyclobutane), 164.8 (C = O), 177.3 and 177.6 ($2COO^{-}$).

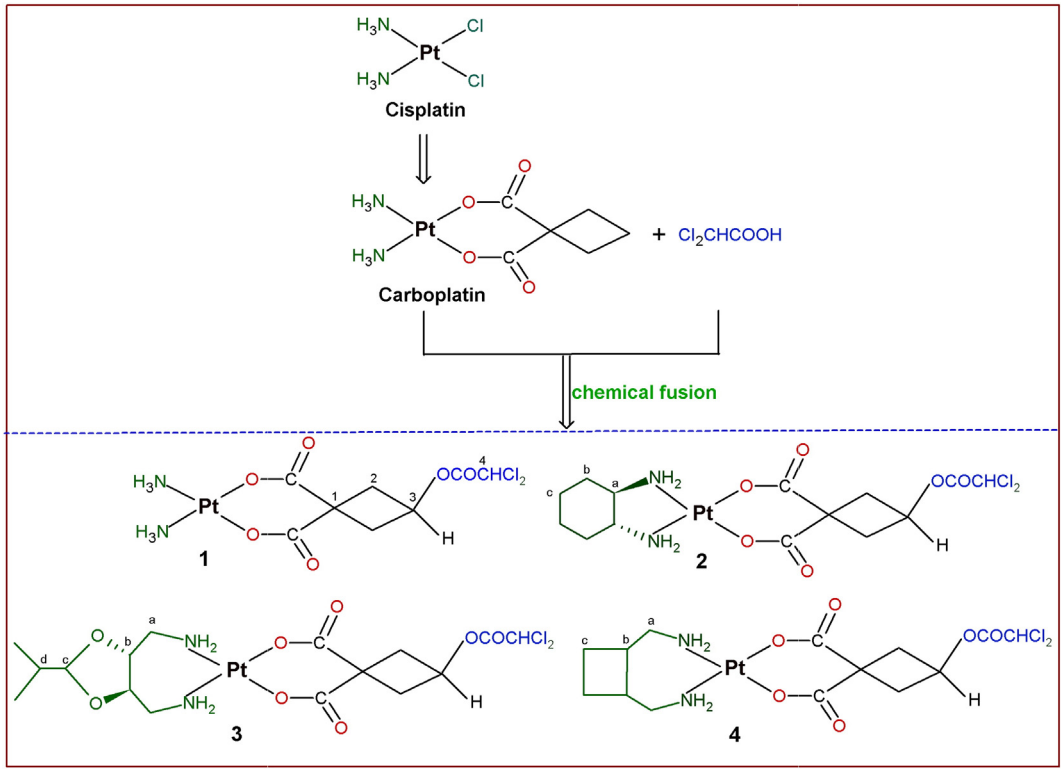


Fig. 1. Chemical structures of the designed platinum complexes.

Complex **2** found (% calculated for $C_{14}H_{20}N_2O_6Cl_2Pt$): Pt 33.4 (33.8), C 29.4 (29.0), H 3.50 (3.46) and N 4.87 (4.84). MS-ESI$^+$ m/z: 601 ($[M + Na]^+$, 100%). IR (KBr, cm^{-1}): 3441 (s, ν_{O-H}), 3246 (s, ν_{N-H}), 2940, 2863 (w, ν_{C-H}), 1748 (s, $\nu_{C=O}$), 1628 (vs, $\nu_{as(COO)}$), 1378 (vs, $\nu_{a(COO)}$), 1299 (m), 1176 (m), 1031 (m), 902 (w) and 819 (w). ^{1}H NMR (dmso, δ): 0.98, 1.18 (≈4H, $2CH_2$, C-c, cyclohexane), 1.43, 1.79 (≈4H, $2CH_2$, C-b, cyclohexane), 1.97, 2.03 (≈4H, $2CH_2$, C-2, cyclobutane), 2.61, 2.65 (≈2H, $2CHNH_2$, cyclohexane), 4.85 (≈1H, CH, cyclobutane), 5.92, 5.20 (≈4H, $2CH_2NH_2$), and 6.87 (≈1H, $COCHCl_2$). ^{13}C NMR (dmso, δ): 24.0, 24.1 (C-c, cyclohexane), 31.4, 31.5 (C-b, cyclohexane), 37.7, 37.8 (C-2, cyclobutane), 48.9 (C-1, cyclobutane), 62.0, 62.2 (C-a, cyclohexane), 64.8 (C-4, dichloroacetoxyl), 67.3 (C-3, cyclobutane), 163.9 (C = O), 175.8 and 176.1 ($2COO^-$).

Complex **3** found (% calculated for $C_{16}H_{24}N_2O_8Cl_2Pt$): Pt 30.8 (30.6), C 29.7 (30.1), H 3.77 (3.76) and N 4.35 (4.39). MS-ESI$^+$ m/z: 639 ($[M + H]^+$, 10%), and 368 ([M + H-leaving group]$^+$, 70%). IR (KBr, cm^{-1}): 3445 (s, ν_{O-H}), 3227 (s, ν_{N-H}), 2967, 2878 (w, ν_{C-H}), 1758 (s, $\nu_{C=O}$), 1631 (vs, $\nu_{as(COO)}$), 1359 (vs, $\nu_{a(COO)}$), 1301 (m), 1169 (m), 1095 (s), 1009 (m) and 819 (m). ^{1}H NMR (dmso, δ): 0.89 (6H, $2CH_3$), 1.73 (1H, CH, isopropyl), 2.54, 2.62 (4H, $2CH_2$, cyclobutane), 4.20, 4.37 (4H, $2CH_2NH_2$), 4.47 (2H, 2CH, 1,3-dioxolane), 4.78 (≈1H, CH, cyclobutane), 5.27, 5.53 (≈4H, $2NH_2$), 5.88 (1H, CH, 1,3-dioxolane), and 6.84 (≈1H, $COCHCl_2$). ^{13}C NMR (dmso, δ): 16.4, 16.5 ($2CH_3$, isopropyl), 31.3 (C-d, isopropyl), 37.9 (C-2, cyclobutane), 48.0 (C-1, cyclobutane), 64.8 (C-4, dichloroacetoxyl), 67.1, 68.3 ($2CH_2NH_2$), 70.7 (C-3, cyclobutane), 79.5, 77.9 (C-b, 1,3-dioxolane), 106.9 (C-c, 1,3-dioxolane), 163.8 (C = O), 175.9 and 176.2 ($2COO^-$).

Complex **4** found (% calculated for $C_{14}H_{20}N_2O_6Cl_2Pt$): Pt 33.7 (33.8), C 28.6 (29.0), H 3.49 (3.46) and N 4.81 (4.84). MS-ESI$^+$ m/z: 601 ($[M + Na]^+$, 50%). IR (KBr, cm^{-1}): 3431 (s, ν_{O-H}), 3228(s, ν_{N-H}), 2944, 2873 (w, ν_{C-H}), 1746 (s, $\nu_{C=O}$), 1626 (vs, $\nu_{as(COO)}$), 1357 (vs, $\nu_{a(COO)}$), 1276 (s), 1212 (s), 1022 (m), 899 (m) and 817 (m). ^{1}H NMR (dmso, δ): 1.61, 1.85 (4H, $2CH_2$), 2.29 (2H, 2CH), 2.51, 2.67 (4H, $2CH_2$, cyclobutane), 4.31, 4.57 (4H, $2CH_2NH_2$), 4.85 (≈1H, CH, cyclobutane), 5.01, 5.30 (4H, $2NH_2$), and 6.87 (≈1H, $COCHCl_2$). ^{13}C NMR (dmso, δ): 22.3 (C-c), 37.7 (C-2), 49.0, 50.0 (C-b), 50.4 (C-1), 64.9 (C-a), 67.2 (C-4, dichloroacetoxyl), 71.0 (C-3), 163.9 (C = O), 176.5 and 177.5 ($2COO^-$).

2.3. In vitro release studies of dichloroacetate from complex 2

A HPLC (high performance liquid chromatography) was established to determine the degradation of complex **2** or formation of *cis*-[Pt(II)(*1R,2R*-diaminocyclohexane)·(3-hydroxylcyclobutane-1,1-dicarboxylate)] (namely complex **5** in Fig. 2). It was prepared according to the reported method [20] and used as a reference for HPLC identification. We found that complex **5** was very stable in water and did not undergo apparent degradation within 72 h. Therefore it was also applied to HPLC quantitative analysis as the reference in our measurements. The HPLC was carried out on a Xterra C18 column (4.6 × 250 mm, 5 μm) at 40 °C using a MeOH–H_2O (29:71) system as the mobile phase. The flow rate was 1.0 ml/min, and the peak was monitoring at λ = 215 nm. Under these optimized chromatographic conditions, the peaks of two complexes suitable for quantitative analysis developed, and were effectively separated from each other with Rs > 2.5.

A solution of complex **2** was prepared by simply dissolving 10 mg complex 2 in 10 ml mixture solvent of water and methanol (50:50, v:v), and kept in dark place at 22 °C or 37 °C. A 10 μL solution was taken at different time points for HPLC measurement. Comparing the peak area of the degradation product from complex **2** to that of the reference at a known concentration would offer the amount of complex 5. Based on the degradation equation, the amount of complex 5 formed in the solution is equal to the amount of dichloroactetate released from complex **2**. The release percentage of dichloroacetate was calculated from the degree of formation of complex **5**.

2.4. In vitro anticancer activity

Human cancer cell lines A549, SK-OV-3 were purchased from the American Type Culture Collection (Manassas, VA, USA), and SGC-7901 was obtained from the Cell Bank of the Shanghai Institute for Biological Sciences, Chinese Academy of Science (Shanghai, China), whereas cisplatin-resistant SK-OV-3 cell line (SK-OV-3/DDP) was kindly provided by Chinese Academy of Medical Sciences (Beijing, China). Cells were grown in DMEM or RPMI-1640 medium containing 10% fetal bovine serum and supplemented with 100 units/mL of penicillin and 100 μg/mL of streptomycin. Cells were maintained at 37 °C in a humidified incubator with an atmosphere of 5% CO_2.

In vitro anticancer activity was determined by MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5 diphenyl-2-H-tetrazolium bromide] assay. A 100 μL of cell suspension was seeded in 96-well cell culture plates and allowed to adhere overnight. The tested compounds were dissolved in DMSO just before the incubation with cancer cells, and diluted in culture media at the indicated concentrations. The cells were incubated with drugs for 72 h, and then a 20 μL of CellTiter 96® AQ_{ueous} One Solution Reagent (Promega, Madison, USA) was added and the cells were further incubated at 37 °C for 1–2 h. Cell viability was measured by reading the absorbance at the wavelength of 490 nm. Concentrations of 50% inhibition of growth (IC_{50}) were calculated on the basis of the relative survival curve.

3. Results and discussion

3.1. Synthesis and characterization

Four designed complexes **1**–**4** containing a dichloroacetate moiety in the leaving group and with $2NH_3$ or diamines as the carriers were synthesized as white precipitates in aqueous solution by the general procedures (see Scheme 1) owing to their low water solubility. Introduction of a dichloroacetate moiety into cyclobutane-1,1-dicarboxylic acid had been previously described in our report [18]. Shortly, K_2PtCl_4 was first converted to K_2PtI_4 in situ by the treatment with KI, followed by addition of $2NH_3$ or diamines, forming an insoluble diam(m)inediiodoplatinum(II) intermediate. The quantitative reaction of the intermediate with silver nitrate in water offered a solution of *cis*-$[PtA_2(H_2O)_2](NO_3)_2$ which was finally transformed at a low temperature to the target products by mixing with potassium 3-dichoroacetoxylcyclobutane-1,1-dicarboxylate. The resulting platinum complexes were characterized by elemental analysis as well as by ESI$^+$-MS, FT-IR, ^{1}H–, and ^{13}C-NMR (Supplementary Fig. S1–S5), and gave satisfactory analytical and spectroscopic data, which are in

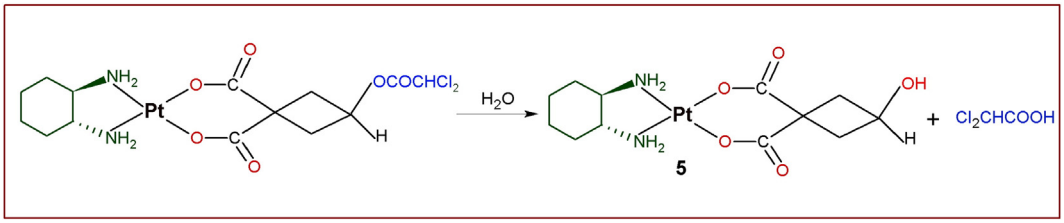
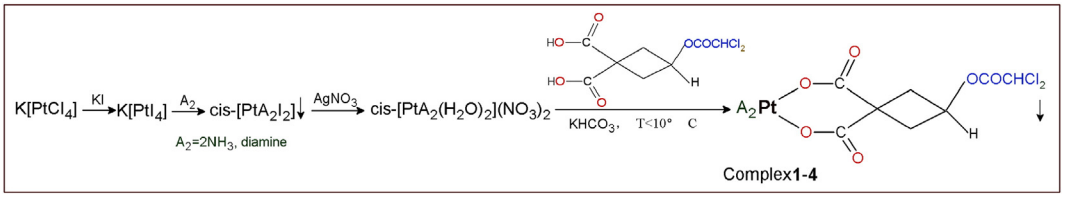


Fig. 2. The release reaction of dichloroacetate from complex **2** in water.



Scheme 1. Synthetic routes of the target complexes.

accordance with their proposed structures (Fig. 1). The fusion of dichloroacetate moiety was verified both by the development of a strong C = O vibration band approximately at 1750 cm^{-1} and by appearance of a distinct carbon resonance at 164 ppm belonging to C = O of $-OCOCHCl_2$ group.

The solubility of four complexes in water was found to be 0.40, 0.48, 0.083, 0.24 mg/ml at room temperature, respectively for complex **1**, **2**, **3** and **4**, much more soluble than corresponding mixed-NH_3/amine complexes (0.034 mg/ml). All complexes are fairly soluble in methanol (≈5 mg/ml) and DMSO (10 mg/ml), and also have a good solubility in polyethyleneglycol 400 (>5 mg/ml), a solvent which is frequently used in the *in vivo* test. For these complexes no close relationship could be deducted between the structure and solubility.

3.2. In vitro release of dichloroacetate

As complex **2** has the greatest water-solubility among the complexes we synthesized, it was selected for *in vitro* release studies of dichloroacetate. The ester bond bridging dichloroacetate moiety and the platinum pharmacophores together is weakened by the inductive effects of two chlorines, making it relatively easy to be hydrolyzed in water. The hydrolysis will result in the release of dichloroacetate. The release percentages from complex **2** in the mixture solvent of water and methanol (1:1, v:v) was monitored in our studies by an established HPLC, and complex **5**, one of the degradation products, was used as a reference (Supplementary Fig. S1–S5). The release percentages with the time at 22 and 37 °C are depicted in Fig. 3. The release profile is mainly dependent on the temperature. The release was mild at room temperature (22 °C), but much faster at physiological temperature (37 °C) and the release percentage was 100% within 48 h, indicating that dichloroacetate can be efficiently released from complex **2** under physiological conditions.

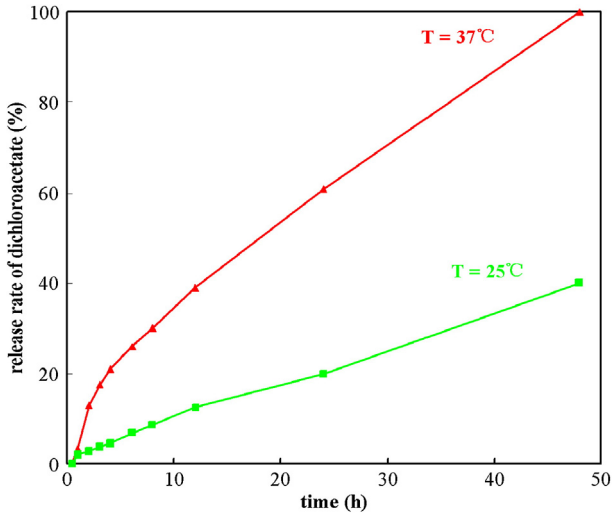


Fig. 3. The release percentage of dichloroacetate from complex **2** (C_0 = 1.73 mM) in 50% aqueous solution of methanol (v:v).

3.3. In vitro anticancer activity

In vitro anticancer activity of the newly synthesized complexes **1**–**4** was determined by means of MTT assay [21] in the present work against three human cancer cell lines representing two tumor entities: lung carcinoma (A549) and ovarian carcinoma (SK-OV-3, SK-OV-3/DDP) in comparison to cisplatin and carboplatin. Dichloroacetic acid was also used as a reference. SK-OV-3/DDP is a cell line resistant to cisplatin with a resistance index of 5-fold. The IC_{50} values, defined as the concentrations corresponding to 50% growth inhibition, are presented in Table 1. Dichloroacetic acid alone had negligible *in vitro* anticancer activity with IC_{50} value up to 200 μM. This value is in accordance with the literature that dichloroacetic acid needs millimolar doses to elicit cytotoxicity [12, 13]. In contrast, all the complexes bearing a dichloroacetate moiety yielded IC_{50} values in the micro-molar range, displaying greater anticancer activity. Among them, complex **2** is the most active, only less in SK-OV-3, but greater in A549 and SK-OV-3/DDP than cisplatin. The overall activity order is complex **2** > cisplatin > **1** > **3** > **4** > carboplatin, suggesting that both the ligation of dichloroacetate and carriers have an obvious influence on anticancer activity of the complexes. Complex 1 was established to have greater activity than its direct parent carboplatin. This enhanced activity is attributed to the ligation of dichloroacetate. For the four complexes with the same leaving group (3-dichoroacetoxylcyclobutane-1,1- dicarboxylate) but different carriers, the activity order is **2** > **1** > **3** > **4**. This implies that when *1R,1R*-diaminocyclohexane (the carrier of oxaliplatin) is used as a carrier, it can render platinum drugs the best anticancer potency due to its unique structure [22]. More significantly, All four complexes had some potential (<2-fold) to overcome the resistance of SK-OV-3 cells to cisplatin, and again complex **2** was found to be the most potent one. These results reveal that the fusion of dichloroacetate moiety endows platinum drugs with ability to surmount drug resistance.

4. Conclusion

In our present study to develop new dichloroacetate moiety-bearing platinum-based drugs, four diam(m)ine complexes of 3-dichoroacetoxylcyclobutane-1,1-dicarboxylate as the leaving group were synthesized. All are more water-soluble than the corresponding mixed-NH_3/amine and exhibit some ability to overcome the resistance of cancer cells to cisplatin. Among them, complex **2**, an oxaliplatin-analogue, is most promising as a drug candidate, supported by its high

Table 1
In vitro anticancer activity of the tested compounds (t = 72 h, n = 3).

Compounds	IC_{50} (mean ± SD, μM)			Resistance index[a]
	A549	SK-OV-3	SK-OV-3/DDP	
Complex **1**	6.65 ± 0.52	7.69 ± 1.03	16.2 ± 1.9	≈2
Complex **2**	0.61 ± 0.10	6.84 ± 0.92	6.57 ± 0.88	≈1
Complex **3**	4.46 ± 0.51	13.5 ± 1.8	17.9 ± 1.9	≈1.3
Complex **4**	7.14 ± 0.80	15.2 ± 2.0	22.0 ± 2.8	≈1.5
Carboplatin	35.9 ± 2.3	42.0 ± 3.9	>100	>2.5
Cisplatin	1.76 ± 0.13	3.61 ± 0.44	17.4 ± 2.3	≈5
$Cl_2CHCOOH$	>200	>200	>200	

[a] Resistance index is the ratio of IC_{50} value of resistant cells to that of sensitive cells.

anticancer activity as well as its potential of being totally devoid of cross-drug resistance with cisplatin. Considering that drug resistance is a central problem of chemotherapy, further evaluation of this complex is going on in our laboratory.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jinorgbio.2015.02.002.

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