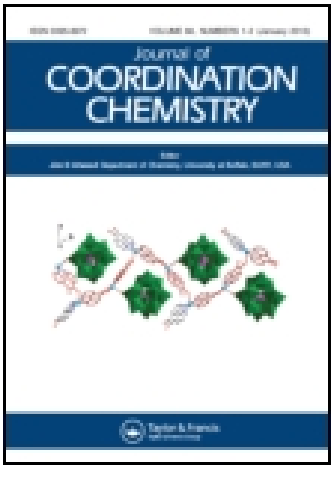

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Synthesis and antiproliferative activity of (1R,2R)-N^1-(2-butyl)-1,2-cyclohexanediamine platinum(II) complexes with malonate derivatives

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Synthesis and antiproliferative activity of (1*R*,2*R*)-N^1-(2-butyl)-1,2-cyclohexanediamine platinum(II) complexes with malonate derivatives

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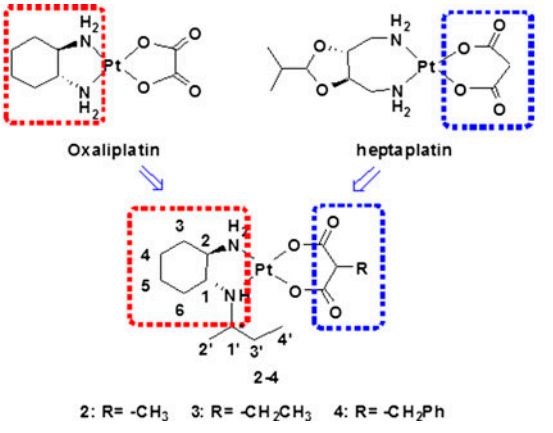

Three new platinum(II) complexes with 2-substituted malonate derivatives as leaving groups have been designed, synthesized, and spectrally characterized. They were tested *in vitro* against four human cancer cell lines. In addition, the DNA unwinding capability was also investigated.

Three new platinum(II) complexes of (1*R*,2*R*)-N^1-(2-butyl)-1,2-cyclohexanediamine with malonate derivatives as leaving groups have been synthesized and spectrally characterized. They were tested *in vitro* against four human cancer cell lines. [(1*R*,2*R*)-N^1-(2-butyl)-1,2-cyclohexanediamine-*N*,*N*′](2-ethylmalonato-*O*,*O*′)platinum(II) turned out to be more active (IC_{50} = 4.65 μM) than oxaliplatin (IC_{50} = 6.55 μM) against the MCF-7 cell line and is superior to its parent complex, [(1*R*,2*R*)-N^1-(2-butyl)-1,2-cyclohexanediamine-*N*,*N*′](malonato-*O*,*O*′)platinum(II). In addition, agarose gel electrophoresis study revealed that the interaction of the complex with pET22b plasmid DNA had a different behavior from that of cisplatin or oxaliplatin.

Keywords: Platinum(II) complexes; Malonate derivatives; Cytotoxicity; DNA binding; Antitumor

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1. Introduction

Since the serendipitous discovery of the cytotoxicity of cisplatin by Rosenberg and his team in the 1960s, success has been made in the development of platinum-based anticancer drugs, and many of them continue to be used in the frontline as antineoplastic drugs against a number of solid tumors [1, 2]. However, they have several limitations including drug resistance, side effects, etc., which significantly reduce the quality of life of cancer patients [3]. These drawbacks urge researchers to find novel platinum-based anticancer drugs to improve their chemotherapy [4–6]. Until now, three platinum drugs (cisplatin, carboplatin, and oxaliplatin) have been used worldwide [7–9], while five other platinum drugs (nedaplatin, lobaplatin, heptaplatin, miriplatin, and dicycloplatin) have been permitted for use only in a few countries [10–15]. Notably, all the platinum-based drugs available at present are the so-called "classical structure–activity-relationship platinum complexes" whose formula is abbreviated as *cis*-[PtA_2X_2], in which X_2 on the complex as the leaving group affects the biodistribution and side effects of the drug, and A_2 as the non-leaving group alters the therapy and forms structurally different DNA adducts. So far, it is still a reasonable way to design antitumor platinum complexes based on the classical structure–activity relationship summarized by Cleare and Hoeschele [16, 17].

Recently, our group reported a series of platinum complexes of *trans*-1,2cyclohexyldiamine (DACH) derivatives [18–21], aiming to study the steric effect of *N*-alkyl groups on the antitumor activity of the resulting complexes. Based on our previous studies, platinum complexes with (1*R*,2*R*)-N^1-(2-butyl)-1,2-cyclohexanediamine (L) as a carrier ligand usually have enhanced cytotoxicity over those with other DACH derivatives [18, 19]. Meanwhile, the leaving ligand played an important role in the biological features of the metal complex. With the same carrier ligand (L), Pt(II) complexes of oxalate or 1,1-cyclobutanedicarboxylate were found to have superior cytotoxicity to those of malonate like **1** (see figure 1) [19]. However, it is noticed that heptaplatin, approved for the treatment of gastric cancer in South Korea in 2005, is a Pt(II) complex of malonate which is less nephrotoxic and more water soluble than its dichloro complex [22]. In order to promote the cytotoxicity of platinum(II) complexes of malonate as L, malonic acid was modified by introducing a substituent at the

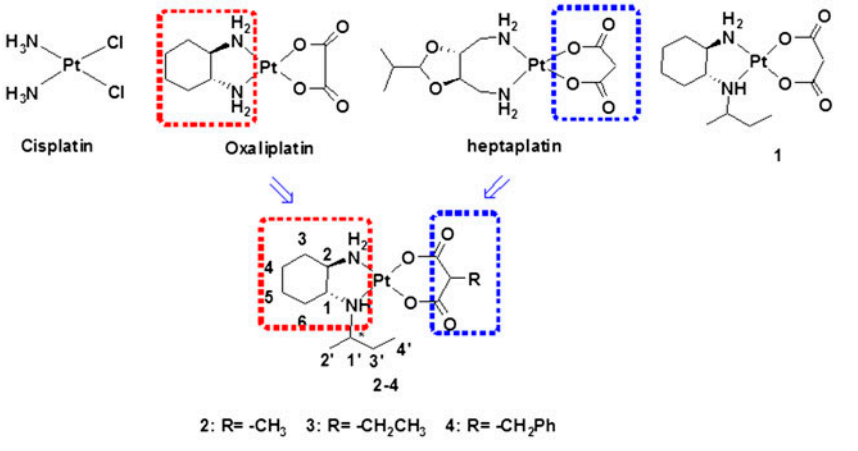


Figure 1. Chemical structures of cisplatin, oxaliplatin, heptaplatin and the target complexes.

C-2 position so that the antitumor features of the resulting complexes would be improved. Herein, we report three such platinum(II) complexes, shown in figure 1, which contain (1*R*,2*R*)-N^1-(2-butyl)-1,2-cyclohexanediamine as a carrier ligand and a 2-substituted malonate derivative as a leaving ligand (**L1**, **L2**, and **L3**).

2. Experimental

2.1. *Materials*

Potassium tetrachloroplatinate(II) and silver nitrate were purchased from a local chemical company. All reagents and chemicals were of analytical reagent grade and used without purification. (1*R*,2*R*)-N^1-(2-butyl)-1,2-cyclohexanediamine was prepared as described in our previous study [18, 19]. According to literature methods, 2-substituted malonate derivatives (**L1**, **L2**, and **L3**) were prepared [23–25].

2.2. *Instrumentation and measurement*

IR spectra were recorded as KBr pellets with a Nicolet IR200 FT-IR spectrometer from 4000 to 400 cm^{-1} and ^{1}H NMR spectra were measured in DMSO-d_6 with a Bruker 500 MHz spectrometer. Mass spectra were measured on an Agilent 6224 TOF LC/MS instrument. Elemental analyses for C, H, and N were performed on a Vario MICRO CHNOS elemental analyzer.

2.3. *Preparation of 2–4*

Synthesis of *cis*-dichloro[(1*R*,2*R*)-N^1-(2-butyl)-1,2-diaminocyclohexane-*N*,*N*′]platinum(II): Under nitrogen and protection from light, an aqueous solution (20 mL) of K_2PtCl_4 (2.07 g, 5 mM) was added to (1*R*,2*R*)-N^1-(2-butyl)-1,2-diaminocyclohexane (0.85 g, 5 mM) in water (6 mL). The reaction mixture was then stirred at room temperature for 9 h and yellow solids were deposited. The product was filtered off, washed with distilled water and ethanol, and then dried in vacuum (yield 89%) [18].

General synthesis of ***2–4***: A mixture of *cis*-dichloro[(1*R*,2*R*)-N^1-(2-butyl)-1,2diaminocyclohexane-*N*,*N*′]platinum(II) (2 mM) and silver dicarboxylate (2 mM) in distilled water (150 mL) was heated to 50 °C and stirred for 24 h under nitrogen with protection from light. After completion of the reaction, the mixture was cooled to room temperature, and the precipitated white solid (AgCl) was removed by filtration. The filtrate was concentrated to 10 mL by a rotatory evaporator at 45 °C and then kept cool at 4 °C for 4 h. White crystals were filtered off, washed with a small quantity of chilled water, and then dried at 40 °C in vacuum.

2.3.1. [(1*R*,2*R*)-N^1-(2-butyl)-1,2-cyclohexanediamine-*N*,*N*′](2-methylmalonato-*O*,*O*′) platinum(II) (2). White solid. Yield: 0.63 g (65.2%). ^{1}H NMR (DMSO-d_6, ppm): δ 0.84 (t, J = 7.5 Hz, 3H, $CH_3CHCH_2CH_3$), 0.94–1.07 (m, 6H, *CH* of DACH and $CHCH_3$), 1.22 (d, J = 5.0 Hz, 3H, $CH_3CHCH_2CH_3$), 1.35–1.87 (m, 6H, $CH_3CHCH_2CH_3$ and CH_2 of DACH), 1.87–2.01 (m, 1H, *CH* of DACH), 2.10–2.28 (m, 3H, NH*CH* and 2×NH*CH*), 3.50

(q, J = 7.0 Hz, 1H, *CH*CH_3), 5.13–5.99 (m, 3H, CH*NH* and 2×CHNH_2). IR (KBr): 3442, 3163, 2936, 2863, 1652, 1491, 1372, 1260, 1168, 1066, and 1017 cm^{-1}. ESI-MS: *m/z* (%): 481(83), 482(100), 483(78) $[M + H]^+$; Anal. Calcd for $C_{14}H_{26}N_2O_4Pt$: C, 34.93; H, 5.44; N, 5.82. Found: C, 34.98; H, 5.51; N, 5.79.

2.3.2. [(1*R*,2*R*)-N^1-(2-butyl)-1,2-cyclohexanediamine-*N*,*N*′](2-ethylmalonato-*O*,*O*′) platinum(II) (3). White solid. Yield: 0.66 g (67.4%). ^{1}H NMR (DMSO-d_6, ppm): δ 0.85 (t, J = 7.5 Hz, 3H, $CH_3CHCH_2CH_3$), 0.93–1.07 (m, 6H, *CH* of DACH and CH_2CH_3), 1.22 (d, J = 5.0 Hz, 3H, $CH_3CHCH_2CH_3$), 1.37–1.57 (m, 4H, CH_2 of DACH and $CH_3CHCH_2CH_3$), 1.79–2.12 (m, 5H, *CH* of DACH and $CHCH_2CH_3$), 2.21–2.78 (m, 3H, NH*CH* and 2×NH*CH*), 3.48 (t, J = 7.3 Hz, 1H, $CH(COO)_2$), 5.18–5.94 (m, 3H, CH*NH* and 2×CHNH_2). IR (KBr): 3443, 3164, 2937, 2875, 1636, 1457, 1389, 1374, 1334, 1230, and 969 cm^{-1}. ESI-MS: *m/z* (%): 495(83), 496(100), 497(80) $[M + H]^+$, Anal. Calcd for $C_{15}H_{28}N_2O_4Pt$: C, 36.36; H, 5.70; N, 5.65. Found: C, 36.31; H, 5.73; N, 5.56.

2.3.3. [(1*R*,2*R*)-N^1-(2-butyl)-1,2-cyclohexanediamine-*N*,*N*′](2-benzylmalonato-*O*,*O*′) platinum(II) (4). White solid. Yield: 0.77 g (68.7%). ^{1}H NMR (DMSO-d_6, ppm): δ 0.82 (t, J = 7.5 Hz, 3H, $CH_3CHCH_2CH_3$), 0.95–1.05 (m, 3H, *CH* of DACH), 1.17 (d, J = 5.0 Hz, 3H, $CH_3CHCH_2CH_3$) 1.32–1.46 (m, 1H, *CH* of DACH), 1.46–1.52 (m, 2H, $CH_3CHCH_2CH_3$), 1.54–1.75 (m, 2H, CH_2 of DACH), 1.80–1.98 (m, 2H, CH_2 of DACH), 2.22–2.72 (m, 3H, NH*CH* and 2 × NH*CH*), 3.00 (d, J = 5.0 Hz, 2H, $CHCH_2Ph$), 4.10 (t, J = 6.5 Hz, 1H, *CH*CH_2Ph), 5.13–5.90 (m, 3H, CH*NH* and 2 × CHNH_2), 7.10–7.14 (m, 1H, *Ph*CH_2), 7.20–7.24 (m, 4H, *Ph*CH_2). IR (KBr): 3445, 3164, 2937, 2868, 1655, 1496, 1377, 1267, 1172, 1072, and 1030 cm^{-1}. ESI-MS: *m/z* (%): 579(79), 580(100), 581(82) $[M + Na]^+$. Anal. Calcd for $C_{20}H_{30}N_2O_4Pt$: C, 43.08; H, 5.42; N, 5.02. Found: C, 43.02; H, 5.45; N, 4.96.

2.4. *Cell culture*

Four human solid tumor cell lines, which are human hepatocellular carcinoma cell line (HepG-2), human breast carcinoma cell line (MCF-7), human non-small cell lung cancer cell line (A549), and human colorectal carcinoma cell line (HCT-116), were used in the cytotoxicity test for all platinum complexes. The cell lines were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum, 100 μg mL^{-1} of streptomycin, and 100 μg mL^{-1} of ampicillin sodium in an atmosphere of 5% CO_2 at 37 °C.

2.5. In vitro *cytotoxicity assay*

The *in vitro* cytotoxicities of **2**, **3**, and **4** (IC_{50} values) were determined by MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; MTT, Sigma). Briefly, the suspension of 1000 cells $well^{-1}$ was plated in 96-well culture plates with culture medium, which was incubated for 24 h at 37 °C in a water atmosphere (5% CO_2). First, the complexes were dissolved in water and diluted to the required concentration with culture medium. Second, the diluted solution of complexes was added to the wells, and the cells were incubated for 72 h (37 °C, 5% CO_2). Third, the cells were treated with 10 μL MTT dye solution (5 mg mL^{-1}) for 4 h cultivation. The media with MTT solution were removed with

DMSO solution (100 μL). The absorbance was measured at 540 nm with an automatic microplate ELISA reader. The IC_{50} value was determined from the chart of cell viability (%) against dose of complex added (μM).

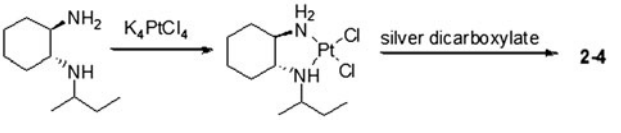
2.6. *Gel electrophoresis experiment*

According to the reported method [18], interaction of platinum(II) complexes (**3**, cisplatin, and oxaliplatin) with pET22b plasmid DNA was tested by agarose gel electrophoresis. Cisplatin and oxaliplatin were used as positive control, and pET22b plasmid DNA of 50 ng μL^{-1} was used as the target in the experiment. After preparing appropriate dilutions of tested compounds, prepared complex solutions were mixed with pET22b plasmid DNA (0.25 g, 5 μL) to achieve different concentrations of compounds (50, 100, 200, 300, 400, and 500 μM). Then the tested complexes were incubated with pET22b plasmid DNA at 37 °C for 24 h. Afterward, the agarose gel (made up to 1% w/v) containing ethidium bromide (1 μg mL^{-1}) was prepared by TA buffer (50 mM tris–acetate, pH 7.5). In agarose gel in TA buffer at 90 V, the mixtures with loading buffer (1 μL) underwent electrophoresis for 70 min. The gel was visualized under UV light and photographed using a gel image system (Tanon, China).

3. Results and discussion

3.1. *Synthesis and characterization*

Platinum(II) complexes were synthesized in two steps following the procedures shown in scheme 1. The intermediate dichloro((1*R*, 2*R*)-N^1-(2-butyl)-1,2-diaminocyclohexane)platinum(II) was prepared by our previous method [18, 19]. Reaction of silver dicarboxylate with dichloro-((1*R*,2*R*)-N^1-(2-butyl)-1,2-diaminocyclohexane)platinum(II) in water resulted in formation of the target complex (scheme 1). The synthesized compounds were characterized by ESI-MS, IR, ^{1}H NMR spectroscopy, and elemental analysis. IR spectra of the platinum complexes showed N–H stretching vibrations at 3163–3164 cm^{-1}, which moved to higher wavenumbers in contrast to the single amino group (comparable to 3428 cm^{-1} for L) [26], due to the amino group coordination with Pt(II). The presence of C–H bonds is confirmed by the presence of stretches between 2868 and 2937 cm^{-1}. The ν_{as}(C–O) vibration of complexes is at 1636–1655 cm^{-1}, characteristic of coordinated carboxylate, while the ν_s(C–O) vibration was at 1374–1389 cm^{-1} [19]. All ^{1}H NMR spectral data of the platinum(II) complexes are reasonably attributed to the proposed structures. The proton signals of N^1-(2-butyl)-1,2-cyclohexanediamine moieties in the complexes overlapped at 0.81–1.98 ppm, while the proton signals attributed to C–H groups connecting to the amino



Scheme 1. Synthetic route of the target complexes.

groups occurred as a multiplet between 2.05 and 2.78 ppm. Two amino group protons appeared at 5.13–5.99 ppm. Characteristic substituted proton signals of methyl, ethyl, and benzyl groups in **1–3** were also observed in their corresponding ^{1}H NMR spectra. The ESI-MS showed $[M + H]^+$ or $[M + Na]^+$ peaks which were in agreement with the proposed molecular formulas of the metal complexes.

As we described in our former studies, the chiral *N*-monoalkyl nitrogen of DACH adopts an S configuration after coordination, confirmed by theoretical calculations and X-ray crystallography with the analogous platinum complexes [18–21]. A stereogenic carbon center was introduced in **2**, **3**, and **4** in the presence of an asymmetric 2-butyl group; however, no attempt was made to resolve these enantiomers.

3.2. In vitro *antitumor activity*

The cytotoxicities of positive controls and **2**, **3**, and **4** were tested by means of MTT assay against four human cancer cell lines, including HepG-2, MCF-7, A549, and HCT-116, with IC_{50} values presented in table 1. Cisplatin and oxaliplatin were used as positive controls.

According to the IC_{50} values of **2–4** and reference compounds, these three complexes showed high cytotoxic potency against HepG-2 and MCF-7, where the IC_{50} values were 3.74–14.36 and 4.65–16.84 μM, respectively. HepG-2 was the most sensitive cell line to these three complexes. It is noted that **3** is the most effective agent among the synthesized complexes, which has greater cytotoxic activity than oxaliplatin against MCF-7 cell (IC_{50} = 4.65 μM vs IC_{50} = 6.55 μM), while showing comparable cytotoxicity against HepG-2 (IC_{50} = 4.04 μM) to that of cisplatin (IC_{50} = 4.00 μM). However, it is 1.83-fold and 1.69-fold less potent against A549 and HCT-116 than cisplatin. The activity of **2** is similar to oxaliplatin and greater than cisplatin against HepG-2 cell, but 4.29-fold, 3.52-fold, and 12.5-fold less potent against MCF-7, A549, and HCT-116, respectively. Complex **4** was significantly less active than cisplatin and oxaliplatin. In general, the sequence of the cytotoxicities of the three complexes was **3** (R = Et) > **2** (R = Me) > **4** (R = Bz) according to the IC_{50} data.

Comparing tables 1 and 2, **3** showed more effective *in vitro* cytotoxicity than its precursor complex **1**, which was 158-fold and 29.2-fold less potent than cisplatin on HepG-2 and A549, respectively. However, **3** has greater cytotoxic activity than oxaliplatin against MCF-7 cell (IC_{50} = 4.65 μM *versus* IC_{50} = 6.55 μM), suggesting the substituted group on

Table 1. *In vitro* cytotoxicity (IC_{50} μM) of all complexes against human tumor cell lines.

	IC_{50} (μM)[a]			
Compound	HepG-2[b]	MCF-7[c]	A549[d]	HCT-116[e]
Cisplatin	4.00 ± 0.09	3.92 ± 0.08	12.16 ± 0.24	5.66 ± 0.17
Oxaliplatin	3.57 ± 0.10	6.55 ± 0.18	10.02 ± 0.22	5.54 ± 0.15
2	3.74 ± 0.08	16.84 ± 0.44	42.82 ± 1.14	70.89 ± 3.25
3	4.04 ± 0.11	4.65 ± 0.10	22.26 ± 0.48	9.57 ± 0.39
4	14.36 ± 0.41	9.33 ± 0.34	70.00 ± 3.13	>100

[a]IC_{50} is the drug concentration effective in inhibiting 50% of the cell growth measured by the MTT assay after 72 h drug exposure.
[b]HepG-2: human hepatocellular carcinoma cell line.
[c]MCF-7: human breast carcinoma cell line.
[d]A549: human non-small cell lung cancer cell line.
[e]HCT-116: human colorectal cancer cell line.

Table 2. IC_{50} values of the precursor complex **1** by MTT method.

Compound	IC_{50} (μM)[a]			
	HepG-2	MCF-7	A549	HCT-116
Cisplatin	0.10	5.52	2.49	n.d.
Oxaliplatin	1.70	n.d.	n.d.	1.28
1	15.80	15.80	72.60	8.52

[a]Data cited from Ref. [12].

the 2-position of malonic acid with different alkyl groups can improve the *in vitro* antitumor activity of the resulting Pt(II) complex.

3.3. *Interaction with pET22b plasmid DNA*

Agarose gel electrophoresis is useful for testing the interaction of platinum(II) compounds with pET22b plasmid DNA. The reaction of different concentrations of cisplatin, oxaliplatin, and **3** on plasmid DNA was monitored by agarose gel electrophoresis as shown in figure 2. In the electrophoretogram, the untreated plasmid DNA was used as negative control including the open circular form (Form I, oc) and the covalently closed circular form (Form II, ccc) that presented two bands.

From the electrophoretogram of cisplatin, oxaliplatin, and **3**, lanes 1–7 correspond to the DNA distort pattern produced by the tested compounds with concentration gradients of 0, 50, 100, 200, 300, 400, and 500 μM, respectively. When plasmid DNA was incubated with platinum complexes at 37 °C for 24 h, the agarose gel relative electrophoretic mobility (REM) of DNA molecules showed different changes (figure 2).

As for cisplatin and oxaliplatin, after 24-h incubation with plasmid DNA, open circular form (Form I) DNA increased with increased concentration of the complexes from 50 to 500 μM. However, as for complex **3** incubation with plasmid DNA on the same condition, it was observed that the REM of open circular (form I) DNA only slightly change even at the concent ration of 500 μM.

According to our former studies and the structure of our complexes [18–21], we assumed that the hindrance of N^1-alkyl group could protect the active platinum species from detoxification reactions by biological nucleophiles, which might increase the concentration of platinum complexes in cell plasma before reaching the cancer cells and reduce toxicity for the patient.

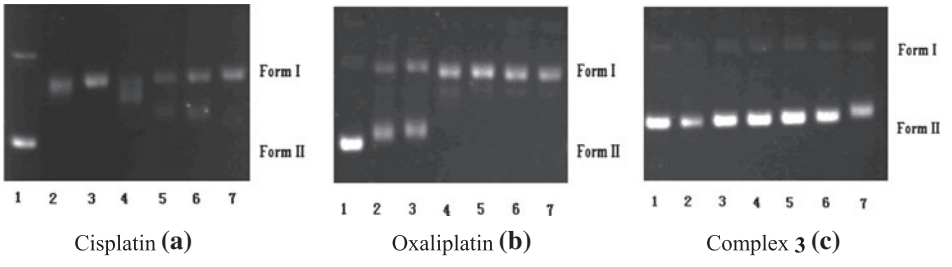


Figure 2. Gel electrophoretic mobility pattern of pET22b plasmid DNA incubated at 37 °C with various concentrations of tested compounds for 24 h. The lanes correspond to untreated plasmid DNA (lane 1), concentrations of 50, 100, 200, 300, 400, and 500 μM of cisplatin (a), oxaliplatin (b) and **3** (c) (lanes 2–7), respectively, incubated with DNA.

4. Conclusion

In this study, three platinum(II) complexes were synthesized with (1*R*,2*R*)-N^1-(2-butyl)-1,2-diaminocyclohexane and malonate derivatives as ligands. *In vitro* cytotoxicity revealed that **2** and **3** showed similar cytotoxicity to the positive controls (cisplatin and oxaliplatin). Notably, **3** is the most effective agent among the synthesized complexes and even has greater cytotoxicity than oxaliplatin against MCF-7 cell line. The result indicated that a substituted group at the C-2 position of malonic acid has a significant impact on the antitumor activity of the resulting platinum complexes with malonate derivatives as a leaving group. The gel electrophoresis study demonstrated that **3** can bind DNA via a different behavior from cisplatin and oxaliplatin. Through the comparison between the IC_{50} values and gel electrophoresis of complexes, we think that **3** has remarkable cytotoxic activity and relative stability by the steric hindrance effect of 2-butyl group in the 1*R*, 2*R*-DACH skeleton, which might extend the exposure time of the drug in the body. Further studies are ongoing in our laboratory to clarify the mechanism of action of these complexes.

A series of metal complexes have recently been reported which had the ability to participate as DNA intercalator by using amino acids as leaving groups [27, 28]. Consequently, it is still a reasonable way to design antitumor platinum complexes based on the classical structure–activity relationship when we adopt new findings and technology [29].

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