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Synthesis, anticancer activity and toxicity of a water-soluble *4S,5S*-derivative of heptaplatin, *cis*-{Pt(II)[(*4S,5S*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]·(3-hydroxyl-cyclobutane-1,1-dicarboxylate)}

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ABSTRACT

A water-soluble *4S,5S*-derivative of heptaplatin, *cis*-{Pt(II)[(*4S,5S*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]·(3-hydroxyl-cyclobutane-1,1-dicarboxylate)} was synthesized. The anticancer activity and toxicity were evaluated by comparing its interaction with DNA, cytotoxicity against four human cancer cell lines, antitumor efficiency in human gastric carcinoma NCI-N87 xenografts in nude mice, and preliminary side-effects in rats to those of its *4R,5R*-optical isomer which is under preclinical development. Both isomers induce condensation of DNA to the same extent and have similar cytotoxicity, but show different antitumor activity and toxicity, probably owing to the difference in respective pharmacokinetic profiles. *4S,5S*-Isomer seems to exhibit superior antitumor activity and less toxicity than *4R,5R*-optical isomer as well as the parent heptaplatin. These results imply that *4S,5S*-configuration as a new drug candidate may be better than *4R,5R*-counterpart.

1. Introduction

Platinum-based drugs, represented by cisplatin (DDP), carboplatin and oxaliplatin, have been key players in systemic anticancer chemotherapy since cisplatin was approved in 1978 by the Food and Drug Administration for clinical application [1–3]. In addition, three regionally approved platinum complexes, nedaplatin and heptaplatin and lobaplatin, are also available for clinical options [4–6]. However, the unfavorable toxicity and drug resistance associated with these drugs severely hamper their clinical use. Reducing toxicity and overcoming resistance of platinum chemotherapy are still the most important objectives in the drug development [7–12].

Heptaplatin was developed in 1999 by Sunkyong Industries Co., Ltd., Republic of Korea, and is used particularly in the clinical treatment of advanced gastric cancer [13–15]. It shows an altered antitumor profile in comparison with the cisplatin and is active in the cisplatin-resistant L1210 model due to its unique carrier (*4R,5R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane [16–18]. Hepatotoxicity and nephrotoxicity are two major dose-limiting side effects of heptaplatin [19,20], which is considered to be closely related to its low water solubility (4–5 mg/ml). In our previous studies, a new water-soluble analogue of heptaplatin, *cis*-{Pt(II)[(*4R,5R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]·(3-hydroxyl-cyclobutane-1,1-dicarboxylate)} was synthesized. It possesses greater antitumor activity and much lower nephrotoxicity than the parent heptaplatin, therefore has been selected for preclinical development [21,22].

Structurally, 4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane (A_2) has two asymmetric carbon centers, consequently platinum complexes of A_2 as a carrier group can exist as *4R,5R*- and *4S,5S*-optical isomers, as illustrated in Fig. 1. The importance of isometric configuration to antitumor activity of chiral platinum complexes was highlighted by many researchers [16,23–26]. From this point of view, a comparative study of two optical isomers is of great interest and is also a must in drug development. In the present study, we have synthesized **1a**-(*S,S*) and compared its anticancer activity and preliminary toxicity with those of **1b**-(*R,R*).

2. Experimental section

2.1. Chemistry

2.1.1. Materials and instrument

Potassium tetrachloroplatinate(II) and L-tartaric acid diethyl ester, two starting materials, were purchased from Alfa Aesar. All other chemicals obtained from commercial suppliers were of analytical grade and used as received. Water was distilled prior to use. The synthetic procedures were carried out in light protected environment

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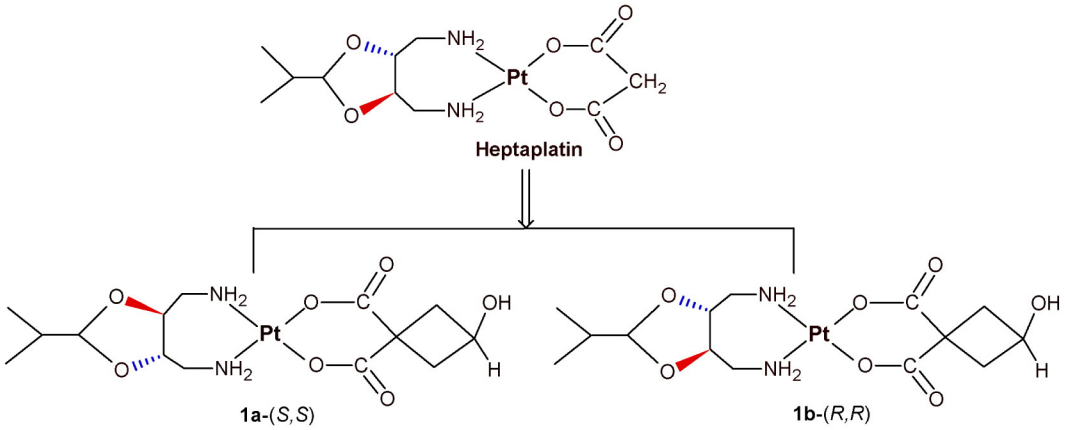


Fig. 1. Chemical structures of heptaplatin and two optical isomers.

when platinum complexes were involved. Composition analyses for C, H and N were performed with a Carlo-Erba 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 type.

The specific optical rotation was determined on an AP-300 Automatic Polarimeter. The purity was determined by analytical reverse-phase column chromatography (RP-HPLC) on a Waters Associates system (consisting of a 1525 pump, a 717 automated injector, and a Model 2998 photodiode array detector), using Kromasil-C_{18}, 5-μm particle size, 4.6 × 250 mm column. The mobile phase was a MeOH–H_2O (30:70) system, and the flow rate was 1.0 ml/min. The peak was monitoring at λ = 230 nm.

*2.1.2. Synthesis of **1a**-(S,S)*

1a-(*S,S*) was synthesized from L-tartaric acid diethyl ester and K_2PtCl_4(II) as the starting chemicals by following the same procedure as previously described for **1b**-(*R,R*) [21]. Briefly, K_2PtCl_4 (5 g, 12 mmol) was mixed at 45 °C with KI (12 g, 6 × 12 mmol) in 100 ml H_2O for 2 h, and then (*4S,5S*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane (2.09 g, 12 mol) was dropwise added with vigorous stirring. After standing for 4 h, the resulting yellow precipitate—diaminediiodoplatinum(II) was collected by filtration, washed with water and ethanol, and dried in vacuo at 65 °C. The yield was 93% (6.6 g). Freshly prepared disilver 3-hydroxyl-cyclobutane-1,1-dicarboxylate (3.60 g, 9.62 mmol) [27] was mixed with diaminediiodoplatinum(II) (6.01 g, 9.64 mmol) in 150 ml H_2O for 36 h with stirring at 37 °C. After AgI was filtrated off, the solution was condensed at 45 °C under reduced pressure to 20 ml to precipitate a white crystalline product — **1a**-(*S,S*). It was collected, washed successively with icy water and ethanol, and dried in vacuo at 45 °C. Yield: 73% (3.71 g). $[\alpha]_D^{25\,^{\circ}C} = +39.7°$ (*C* = 20.5 mg/ml in water). Found (% calculated for $C_{14}H_{24}N_2O_7Pt$): C 31.6(31.9), H 4.59(4.55), N 5.27(5.31), Pt 36.7(37.0); ESI^+-MS (m/z, RI): 550($[C_{14}H_{24}N_2O_7PtNa]^+$, 100%) 528($[M + 1]^+$,4%). EI-HRMS calcd. = 550.1129 for $C_{14}H_{24}N_2O_7PtNa$, Found = 550.1117; IR(KBr, cm^{-1}): 3416(s, ν_{O-H}), 3240, 3211(m, ν_{N-H}), 2966–2877(w, ν_{C-H}), 1595(vs, $\nu_{as(COO)}$), 1365(vs, $\nu_{a(COO)}$). ^{1}H NMR (dmso, δ): 0.84(6H, $2CH_3$), 1.72(1H, CH, isopropyl), 2.30, 2.57(4H, $2CH_2$, cyclobutane), 2.98, 3.07(4H, $2C\underline{H}_2NH_2$), 3.83(1H, CH, cyclobutane), 4.40, 4.47(2H, 2CH, 1,3-dioxolane), 4.78(1H, CH, 1,3-dioxolane), 4.97(1H, C–OH), 5.36, 5.46(4H, $2CH_2N\underline{H}_2$); ^{13}C NMR (dmso, δ): 16.5, 16.6($2CH_3$, isopropyl), 31.4(CH, isopropyl), 41.9, 42.2($2CH_2$, cyclobutane), 48.1(C-1, cyclobutane), 60.1(C-3, cyclobutane), 77.9, 78.0($2CH_2NH_2$), 79.5, 79.6(C-4, C-5, 1,3-dioxolane), 107.0(C-2, 1,3-dioxolane), 177.1, 177.5($2COO^-$).

2.2. Interaction with λ-DNA

2.2.1. Magnetic tweezer apparatus

The magnetic tweezer setup was purchased from Pico Twist Company (France). In brief, it was made up of an inverted microscope objective, a microfluidics flow cell and a pair of permanent magnets. Under the flow cell, the microscope objective (Olympus 1006, numerical aperture [NA] = 1.2, oil immersion) was used to observe the beads in real time. In the flow cell, the DNA was bound to the bottom of the cell at one end. The other end was tethered to a super-paramagnetic bead (MyOne, Dynabeads, Invitrogen). Above the flow cell, there was a set of magnets producing a strong field gradient to exert a force on beads. The force was varied by changing the position of the magnets relative to the beads. The beads can be rotated through rotating the magnets.

2.2.2. λ-DNA preparation for magnetic tweezers study

The bacteriophage λ-DNA (New England Biolabs), which has two 12-nt cohesive termini, was separately annealed with two 12-nt labeled oligomers (labeled by biotin and digoxigenin, respectively). These oligomers have complementary sequences to the overhangs. The 12-nt oligomers were obtained from Sangon Biotech (Shanghai).

2.2.3. Single molecule measurement by magnetic tweezers

1a-(*S,S*) or **1b**-(*R,R*) at a concentration of 400 mM was injected into the flow cell and incubated with DNA while keeping DNA stretched by a large constant force (approximately 6 pN). The stretching force prevented the formation of micro-loops and long range cross-links. A changing curve of force-extension length of DNA with the incubation time was recorded for at least two times for each complex.

2.3. In vitro cytotoxicity

2.3.1. Cell culture

Human cancer cell lines NCI-N87, SK-OV-3 were purchased from the American Type Culture Collection (Manassas, VA, USA), and, SGC-7901 were 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.

2.3.2. MTT assay

Cytotoxicity was determined by MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide] assay. The tested compounds were dissolved in water and diluted in culture media at the indicated concentrations. A 100 μl of cell suspension was seeded in 96-well cell culture plates and allowed to adhere overnight. The cells were treated with drugs for 48 h, and then 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 a wavelength of 490 nm. Concentrations of 50% inhibition of growth (IC_{50}) were calculated on the basis of the relative survival curve.

2.4. In vivo tests

Animal experiments were conducted in accordance with the Institutional Animal Care and Use Committee guidelines of Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

2.4.1. Acute toxicity study in mice

Healthy ICR mice of both sexes, weighting 18–22 g, were divided into 5 groups of 10 animals matched for weight and size. The tested drug was i.v. injected into animals with a single dose ranging from 180 to 440 mg/kg (dissolved in 5% glucose). Dose increments confirmed to a geometric progression. The death was recorded within 14 days, and LD_{50} values as well as LD_{10} values were calculated using Probit method.

2.4.2. In vivo antitumor activity

Five- to six-week-old female Balb/cA-nude mice were purchased from Shanghai Laboratory Animal Center of Chinese Academy of Sciences, and were kept in a pathogen-free environment. Every procedure with animals was done in a laminar airflow cabinet. 5×10^6 NCI-N87 cells were implanted subcutaneously into the right axillary region of Balb/c mice. When tumor volumes reached 100–200 mm^3, the mice were randomly assigned to control and treatment groups and therapy was started. Animals were i.p. treated twice (on day 0 and day 4) with **1a**-(*S,S*), **1b**-(*R,R*) (120 mg/kg dissolved in 5% glucose) or heptaplatin (80 mg/kg in 5% glucose). Animals in the control group received the same amount of 5% glucose solution. Tumor size was assessed regularly by caliper measurement and tumor volume was expressed as (length × $width^2$)/2. Inhibition rates (%) of tumor growth were calculated from the formula [(mean tumor volume of the treated group) / (mean tumor volume of the control group) × 100]. Mouse body weight was determined at baseline before the drug administration and recorded regularly during the experiment which was terminated on day 21.

2.4.3. Preliminary toxicity

Forty healthy male SD rats weighting 180–220 g were divided into 3 treatment groups and one control group, each having 10 rats matched for weight. All the animals were raised in SPF environment during the experiment. A dose of 60 mg/kg **1a**-(*S,S*), **1b**-(*R,R*) and 40 mg/kg heptaplatin were, respectively, i.p. administrated on days 1, 5, 9, 14 to the animals in the respective treatment groups, whereas animals in the control group received the vehicle, a 5% solution of glucose. Rats were weighed regularly for the drug dosing during the experiment. On day 15, all animals were anesthetized after being weighed again and blood samples were collected for biochemical analysis. Blood cell counts and serum levels of CRE (creatinine), BUN (urea nitrogen), ALT (alanine transaminase) and AST (aspartate transaminase) were determined according to the standard procedures. All data are expressed as mean ± SD.

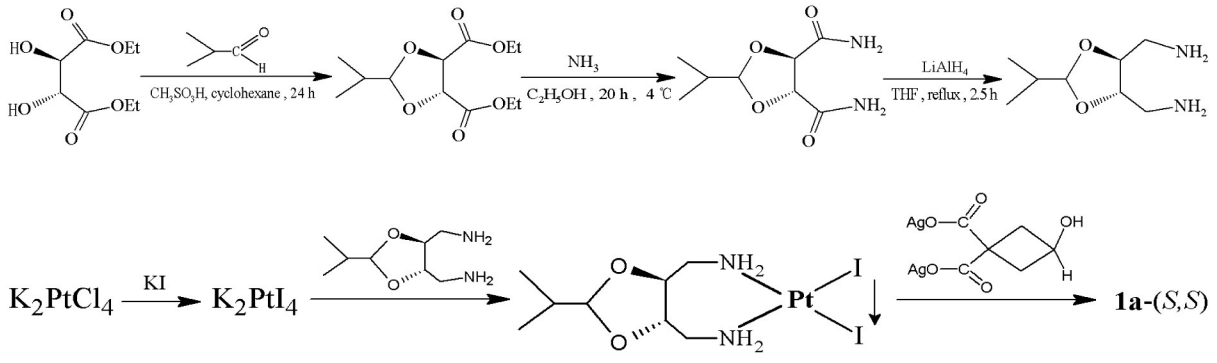
3. Results and discussion

3.1. Synthesis

For the synthesis of **1b**-(*R,R*), D-tartaric acid diethyl ester was employed as the starting chemical. **1a**-(*S,S*), the enantiomer of **1b**-(*R,R*), was synthesized from L-tartaric acid diethyl ester instead of D-configuration, by following the same procedure (see Scheme 1) as previously described for **1b**-(*R,R*) [16,22,27,28], The chemical structure was well confirmed by elemental analysis, FT-IR, NMR, ESI^+-MS spectroscopy (Supplementary Figs. S1–S5). As expected, **1a**-(*S,S*) had the same water solubility (≈25 mg/ml) as **1b**-(*R,R*) but opposite specific optical rotation (+39.7°). The specific optical rotation measurements were used to differentiate **1a**-(*S,S*) from **1b**-(*R,R*) ($[\alpha]_D^{25\,°C} = -40°$). The purity of **1a**-(*S,S*) was determined by HPLC to be >99.0% (Supplementary Fig. S6).

3.2. Interaction with λ-DNA

It is generally believed that the cytotoxicity of platinum anticancer complexes derives mainly from their adducts with DNA [29]. The formation of the adducts will bend and condense DNA, leading to the shortening of DNA extension length [30] which can be measured under a stretching force by magnetic tweezers [31,32]. As illustrated in Fig. 2. DNA extension length gradually shortened with the incubation time following treatment with **1a**-(*S,S*) and **1b**-(*R,R*), implying that both isomers are able to bind to DNA, forming A_2Pt/DNA adducts. However, it is of note that the changes in DNA extension length induced by **1a**-(*S,S*) were nearly the same as those by **1b**-(*R,R*), suggesting that both isomers have similar effect on DNA. This finding is very different from the result observed between oxaliplatin and its enantiomer [32] which showed oxaliplatin had greater shortening effect on DNA than its enantiomer. The chiral centers of **1a**-(*S,S*) and **1b**-(*R,R*) lie at position 4 and 5 of dioxolane ring, relatively far away from the binding site with DNA, as compared to the situations in oxaliplatin and its *1S,2S*-counterpart where the chiral centers are located right at position 1 and 2 of cyclohexane ring. Based on this fact, it seems to be reasonable to explain the



Scheme 1. Synthetic route for **1a**-(*S,S*).

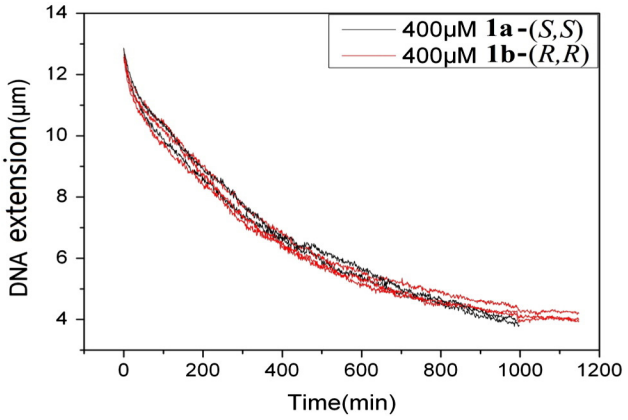


Fig. 2. DNA extension versus time of λ-DNA treated with 400 μM **1a**-(*S,S*) or **1b**-(*R,R*).

similar shortening effect of DNA length induced by these two isomers **1a**-(*S,S*) and **1b**-(*R,R*).

3.3. In vitro cytotoxic activity

The cytotoxicity of **1a**-(*S,S*) and **1b**-(*R,R*) along with the parent compound was tested by means of MTT assay [33] in four human cancer cell lines representing two tumor entities: gastric carcinoma (NCI-87, SGC-7901) and ovarian carcinoma (SK-OV-3, SK-OV-3/DDP). Among them, SK-OV-3/DDP is resistant to cisplatin with a resistance index of 6.3 fold. The data in Table 1 show that all three compounds yielded IC_{50} values in the micro-molar range, displaying considerable anticancer activity. Moreover they had some potential (<2 fold) to overcome the resistance of SK-OV-3 cells to cisplatin. In addition, **1a**-(*S,S*) and **1b**-(*R,R*) exhibited nearly equal potency against the four cell lines, in well agreement with above finding that the shortening effect of DNA induced by both isomers was very similar. The overall cytotoxicity of **1a**-(*S,S*) and **1b**-(*R,R*) was slightly less than that of heptaplatin, being in the opposite order of water solubility: **1a**-(*S,S*) = **1b**-(*R,R*) (25 mg/ml) > heptaplatin (5 mg/ml). These results are in accordance with the observation made by a previous study that an increase in water solubility will lead to a decrease in cytotoxicity of heptaplatin-like complexes [22]. (See Table 2.)

3.4. In vivo acute toxicity

Acute toxicity of two isomers was evaluated in healthy ICR mice by following the standard procedure [34]. The death was recorded within two weeks after a single i.v. injection of the tested compounds, and LD_{10} and LD_{50} were calculated using the Probit method. The LD_{10} and LD_{50} of **1a**-(*S,S*) were found to be 199.9 and 344.7 mg/kg, respectively, slightly larger than the corresponding values (LD_{10} = 187.6 and LD_{50} = 306.6 mg/kg) of **1b**-(*R,R*), indicating that **1a**-(*S,S*) appears to be less toxic than its *R,R*-configuration.

Table 1
Cytotoxicity of **1b**-(*R,R*), **1a**-(*S,S*) and heptaplatin in four human cancer cell lines.

Compd	IC_{50} (μM)[a]				
	NCI-N87	SGC-7901	SK-OV-3	SK-OV-3/DDP	Fold resistance
1a-(*S,S*)	31.2 ± 3.1	22.1 ± 2.0	23.3 ± 2.6	39.9 ± 3.2	≈1.7
1b-(*R,R*)	34.6 ± 2.4	22.3 ± 1.7	20.7 ± 1.5	32.9 ± 2.9	≈1.6
Heptaplatin	27.3 ± 3.4	14.9 ± 1.4	10.7 ± 3.1	20.5 ± 2.2	≈1.9
Cisplatin	n.d.	n.d.	3.00 ± 0.4	18.7 ± 1.8	≈6.3

n.d. = not determined.
[a] 50% inhibitory concentration in the MTT assay after 48 h drug exposure. Values are means ± standard deviation obtained from three independent experiments.

Table 2
Acute toxicity of **1a**-(*S,S*) and 1b-(R,R) in ICR mice by i.v. injection.

	Lethal dose (mg/kg)	
	LD_{10}	LD_{50}
1b-(*R,R*)	187.6 175.3–235.5 (With 95% confidence)	306.6 266.0–353.6 (With 95% confidence)
1a-(*S,S*)	199.9 185.2–254.1 (With 95% confidence)	344.7 299.5–398.1 (With 95% confidence)

3.5. In vivo antitumor activity

In vivo antitumor activity of **1a**-(*S,S*), **1b**-(*R,R*) and heptaplatin was analyzed in the human NCI-N87 gastric carcinoma where heptaplatin is prescribed as the first indication. Tumor-bearing mice were treated i.p. twice with vehicle (5% glucose solution) or the tested complexes at a dose of respective 1/2 LD_{10}, when the tumor was palpable. The results are presented in Fig. 3 and Supplemental Table S1. Although three tested compounds produced significant inhibition of the tumor growth ($p < 0.05$), among them **1a**-(*S,S*) was the most effective, resulting in a inhibition rate of 51%, greater than 31% produced by *R,R*-isomer and heptaplatin. It is interesting to note that the in vivo and in vitro activity order among these platinum complexes do not parallel each other. Given the similar interaction with DNA and cytotoxicity of **1a**-(*S,S*) and **1b**-(*R,R*), the superior antitumor activity of **1a**-(*S,S*) over R,R-enantiomer may be owing to the difference in their pharmacokinetic profiles. Surprisingly, the change in murine body weights monitored during the treatment reveals that **1a**-(*S,S*) did not retard, on the contrary, promoted growth of the animal, obviously different from **1b**-(*R,R*) and heptaplatin which caused body weight loss of the treated animals. This implies that the toxicity induced by **1a**-(*S,S*) is less than that by **1b**-(*R,R*).

3.6. Preliminary toxicity

The preliminary toxicity of **1a**-(*S,S*) was further compared to those of **1b**-(*R,R*) and heptaplatin in healthy Sprague–Dawley rats. The grouping, dosage and scheme are given in Supplemental Table S2. The doses used, in terms of mg/m^2 unit, were equal to 1/2 LD_{10} in mice. All rats were anesthetized and blood samples were collected for biochemical analysis until termination of the experiment.

All animals in drug-treated groups survived and experienced a lower weight gain compared to the control group, but only **1a**-(*S,S*)-treated group exhibiting no significant difference. Myelosuppression is a major side-effect of cytotoxic anticancer drugs including heptaplatin and will lead to a decrease of blood cell counts, especially white blood cell and platelet numbers. All three platinum complexes had myelosuppressive effect causing a decrease of blood cell counts in animals, but the decrease induced by heptaplatin was the most pronounced with thrombocytopenia being most severe. By comparison, **1a**-(*S,S*) had only minor negative effect. Serum urea nitrogen and creatinine levels are an important measure of nephrotoxicity. Both **1a**-(*S,S*) and **1b**-(*R,R*) did not elevate serum urea or creatinine levels, whereas heptaplatin induced a significant increase in serum urea nitrogen and creatinine, indicating that **1a**-(*S,S*) and **1b**-(*R,R*) are less nephrotoxic than heptaplatin, probably due to their great water solubility. In addition, a marked increase of serum alanine transaminase level in aminals after treatment with heptaplatin was observed, reflecting damaged hepatic in these rats. Both **1a**-(*S,S*) and **1b**-(*R,R*) had an tendency to increase ALP, but without a statistical difference. In general, the order of preliminary toxicity for these complexes is: heptaplatin > **1b**-(*R,R*) > **1a**-(*S,S*).

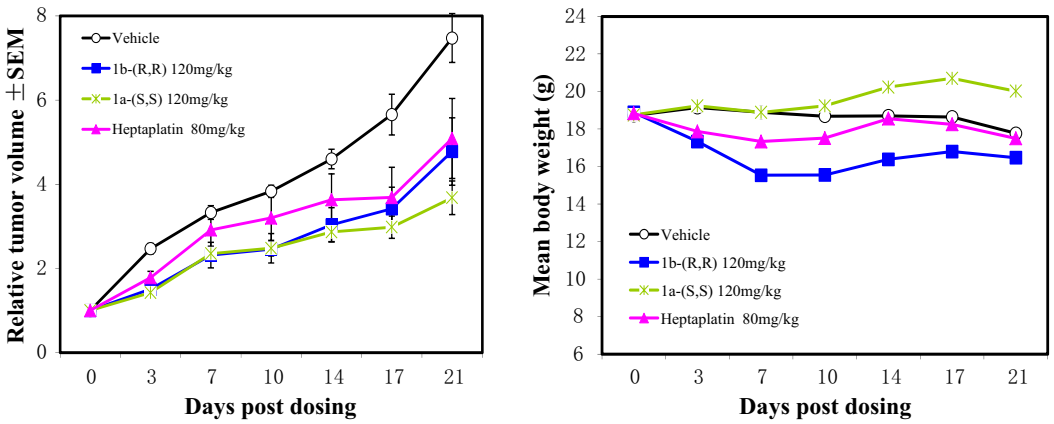


Fig. 3. The changes in tumor size (left) and in animal body weight (right) after mice xenografted with human gastric carcinoma NCI-N87 were treated with **1a**-(*S,S*), **1b**-(*R,R*) or heptaplatin. n = 6–10.

4. Conclusion

In this study, we have successfully developed a heptaplatin derivative, **1a**-(*S,S*), with enhanced antitumor activity and reduced toxicity compared to its *4R,5R*-isomer as well as to its parent heptaplatin. The advantages of *4S,5S*- over *4R,5R*-configuration may be due to the difference in respective pharmacokinetic profiles. Considering that nephrotoxicity and hepatotoxicity are a central problem of clinical heptaplatin application, further evaluation of this new derivative as a drug candidate is highly desirable.

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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.2014.07.013. This data include MOL files and InChiKeys of the most important compounds described in this article.

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