3-Hydroxycarboplatin, a Simple Carboplatin Derivative Endowed with an Improved Toxicological Profile

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3-Hydroxycarboplatin, a simple carboplatin derivative, was synthesised using a novel method, characterised and evaluated for its anticancer activity in vitro and in vivo. It shows comparable antitumour activity to that of carboplatin but has much lower toxicity particularly with respect to myelosuppression, revealing great potential for development as a new antitumour platinum drug to replace carboplatin.

1. Introduction

cis-Diammine(1,1-cyclobutanedicarboxylato)platinum(II) (carboplatin) is a second generation Pt anticancer drug following *cis*-diamminedichloroplatinum(II) (cisplatin). It shows the same level of activity as cisplatin in treating some kinds of cancers, but is much less nephrotoxic and emetic than cisplatin (1, 2). Carboplatin has gained worldwide marketing approval and is currently used as standard therapy in ovarian cancer patients.

Compared with cisplatin, carboplatin causes substantial myelosuppression, principally thrombocytopenia – a dose-limiting side effect that has prompted a continuing search for new, potent Pt complexes possessing lower toxicity. Indeed, the past decade has witnessed a shift in focus toward nonclassical Pt compounds represented by picoplatin, polynuclear complexes, *trans*-Pt complexes and Pt(IV) complexes (3). Unfortunately, the outcomes of clinical trials of these complexes have failed to meet expectations, and none of these complexes has been approved for clinical application (4). However, direct modification of clinically established Pt drugs remains an effective way to create new derivatives with improved toxicological profiles (5, 6). 3-Hydroxycarboplatin (**Figure 1**), first reported in 2004 by G. Bernhardt *et al.* (7), is a direct and simple derivative of carboplatin in which the cyclobutane ring is substituted with OH at position 3. As part of a drug development programme beginning in 2001 aimed at improving the pharmacological profile of

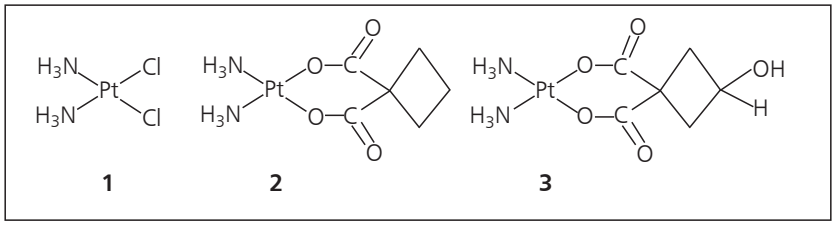


*Fig. 1. The chemical structures of cisplatin, **1**, carboplatin, **2**, and 3-hydroxycarboplatin, **3***

carboplatin, we designed and prepared a series of carboplatin derivatives, including 3-hydroxycarboplatin. Following extensive biological evaluation, we found that 3-hydroxycarboplatin showed anticancer activity similar to that of carboplatin, but exhibited an improved toxicological profile, suggesting great promise for further development. In the present article, we report the synthesis, characterisation and biological effects of 3-hydroxycarboplatin *in vitro* as well as *in vivo* using two animal models.

2. Synthesis and Characterisation

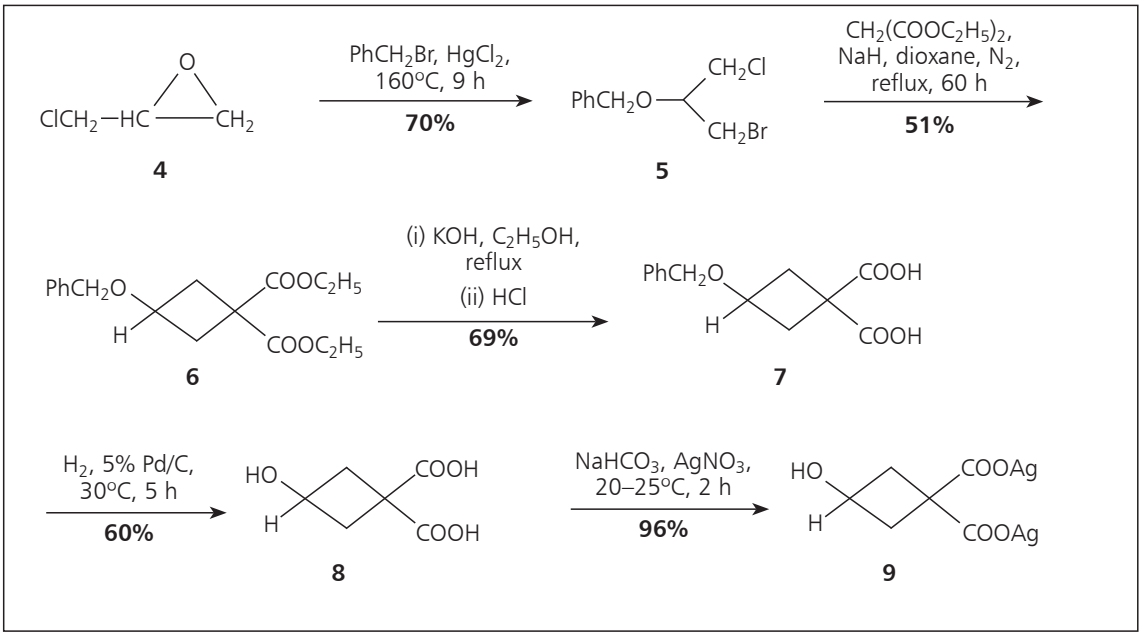
2.1 Preparation of 3-Hydroxy-1,1-cyclobutanedicarboxylic Acid

3-Hydroxy-1,1-cyclobutanedicarboxylic acid was prepared according to **Scheme I** in a similar method to that reported earlier (7) with epichlorohydrin as the starting chemical. First, epichlorohydrin was treated with benzyl bromide in the presence of mercuric chloride and heated at 160°C to give the benzyl ether **5** with a yield of 70%. Then, the addition of diethyl malonate on derivative **5** gave the cyclobutane **6** with 51% yield. The hydrolysis of **6** yielded the potassium salt **7** with 69% yield. Hydrogenolysis was then used for the cleavage of **7** forming the desired 3-hydroxy-1,1-cyclobutanedicarboxylic acid **8** in 60% yield. The overall yield for the formation of **8** was about 15% (melting point 156–158°C). The product **8** was characterised by elemental analysis and proton nuclear magnetic resonance spectroscopy (^{1}H-NMR), and the data are consistent with its composition and structure and are as reported in the literature (7).

Found (% calculated for $C_6H_8O_5$): C, 44.8 (45.0); H, 5.05 (5.00).

^{1}H-NMR (D_2O, 500.1 MHz, δ (ppm)): 4.27 (1H, *CH*OH), 2.77 (2H, C*H*$_2$), 2.37 (2H, C*H*$_2$).

In order to further characterise the product, single crystals suitable for X-ray analysis were selected from its zinc salt which was prepared in a two-step procedure. 3-Hydroxy-1,1-cyclobutanedicarboxylic acid was mixed



Scheme I. Preparation of the silver salt of 3-hydroxy-1,1-cyclobutanedicarboxylic acid

with an excess of zinc hydroxide ($Zn(OH)_2$) in water at 45°C for 2 h and then the remaining $Zn(OH)_2$ was removed by filtration. The resulting filtrate was evaporated under reduced pressure to give rise to the corresponding zinc salt in a white crystalline form. A molecular plot of the chemical structure determined by X-ray analysis, depicted in **Figure 2**, demonstrates that the anion is 3-hydroxy-1,1-cyclobutanedicarboxylate.

Treatment of 3-hydroxy-1,1-cyclobutanedicarboxylic acid with sodium hydrogen carbonate ($NaHCO_3$) in water provided the Na salt of 3-hydroxy-1,1-cyclobutanedicarboxylic acid, which was then reacted with silver nitrate ($AgNO_3$) to produce the insoluble Ag salt as an intermediate with a yield of 96% (**Scheme I**).

Found (% calculated for $Ag_2C_6H_6O_5$): C, 19.4 (19.2); H, 1.65 (1.60); Ag, 57.5 (57.8).

Infrared (IR) (KBr, cm^{-1}): 1720 (s, $\nu_{as}COO^-$), 1357 (s, ν_sCOO^-).

2.2 Preparation of 3-Hydroxycarboplatin

3-Hydroxycarboplatin was synthesised in a three-step reaction route (**Scheme II**) starting from commercially available potassium tetrachloroplatinate (K_2PtCl_4). K_2PtCl_4 was first converted *in situ* to potassium tetraiodoplatinate (K_2PtI_4), followed by addition of ammonia to produce insoluble *cis*-diamminediiodoplatinum(II) (*cis*-$[Pt(NH_3)_2I_2]$). The quantitative reaction in water with the Ag salt of 3-hydroxy-1,1-cyclobutanedicarboxylic acid yielded the target complex (**Scheme II**). Recrystallisation from a solution of water and ethanol (1:1) was required to obtain samples for structural characterisation and biological tests. The overall yield was about 76% and the purity, determined by an established reversed-phase high-performance liquid chromatography (RP-HPLC) method (8), was >98.5%.

The target complex was structurally characterised by elemental analysis, Fourier transform infrared (FTIR) spectroscopy, ^{1}H-/carbon nuclear magnetic resonance (^{13}C-NMR) spectroscopy, fast atomic bombardment mass spectrometry (FAB$^+$-MS) (**Table I**) and X-ray crystallography. The results agree well with the literature (7).

The elemental analysis data are in good agreement with the calculated values of 3-hydroxycarboplatin. It exhibited three typical protonated molecular ion peaks reflecting the platinum isotopes: ^{194}Pt (33%), ^{195}Pt (34%) and ^{196}Pt (25%) (9). A strong peak with a

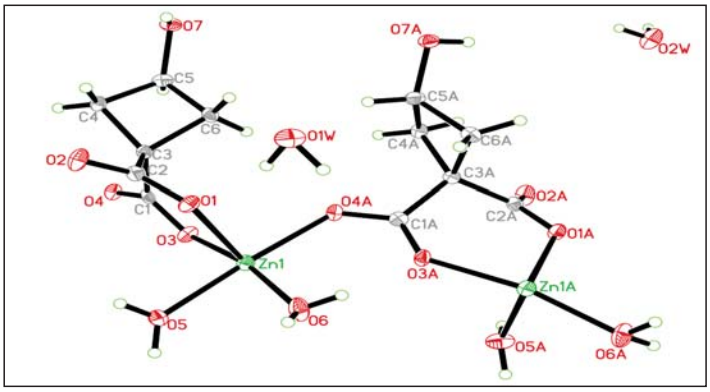
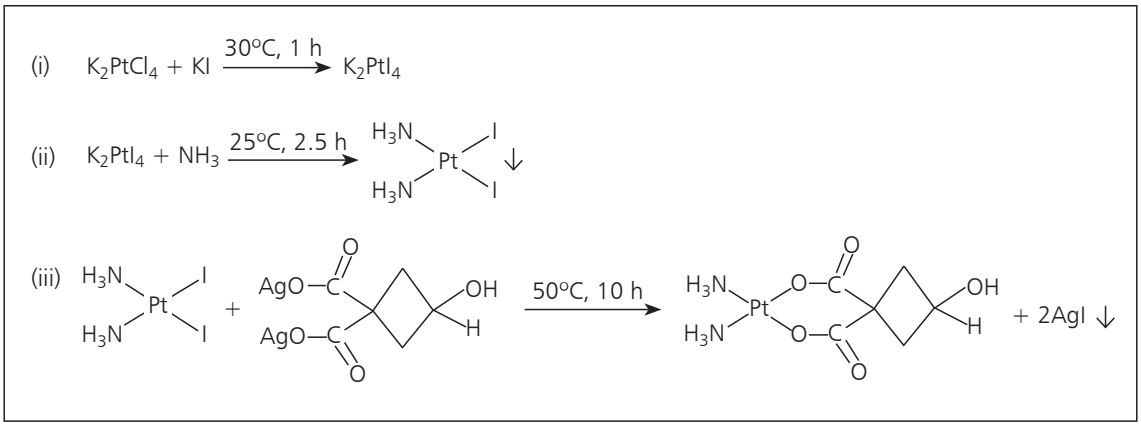


Fig. 2. The X-ray structure of zinc 3-hydroxy-1,1-cyclobutanedicarboxylate



Scheme II. Preparation of target complex 3-hydroxycarboplatin via a three-step reaction route

Table I

The Elemental Analytical and Spectroscopic Data of 3-Hydroxycarboplatin

Composition, %	Found: C, 18.4; N, 7.14; H, 3.17; Pt, 50.2 Calculated for $C_6H_{12}N_2O_5Pt$: C, 18.6; N, 7.23; H, 3.10; Pt, 50.4
FTIR[a], KBr, cm^{-1}	3296 (s, νN–H), 3118–2953 (w, νC–H), 1641–1609 (s, $\nu_{as}COO^-$), 1391–1354 (s, ν_sCOO^-), 1103–1049 (m, νC–O), 449 (w, νPt–N)
FAB^+-MS[b, c] *m/z*, intensity	110 (100%) $[C_6H_5O_2]^+$, 202 (35%) $[C_6H_5O_2$ + gly$]^+$, 230 (12%) $[Pt(NH_3)_2]^+$, 355 (8%) $[C_6H_6O_5Pt]^+$, 388 (92%) M^+, 480 (28%) [M + gly]$^+$
^{1}H-NMR[d, e], DMSO-d_6, δ ppm	4.15 (qi, 1H, *CH*, *J* = 7.2 Hz), 3.27 (t, 2H, CH_2, *J* = 2.6 Hz), 2.55 (t, 2H, CH_2, *J* = 2.6 Hz)
^{13}C-NMR, DMSO-d_6, δ ppm	182.1 (C-1), 181.8 (C-3), 61.6 (C-6), 42.2 (C-2), 17.5 (C-4,5)

[a]*Vibration modes:* ν = *stretching,* ν_s = *symmetric stretching,* ν_{as} = *asymmetric stretching.*

Intensities: m = medium, s = strong, w = weak

[b]*some m/z values are plus hydrogen*

[c]*gly = glycol*

[d]*qi = quintet, t = triplet*

[e]*DMSO = dimethyl sulfoxide*

relative intensity of 92% at *m/z* 388, corresponding to M^+, was observed in its mass spectrum. The IR spectrum showed the characteristic absorption for stretching bands of N–H near 3296 cm^{-1}, C–H around 2900 cm^{-1} and Pt–N at 449 cm^{-1}. The $\nu_{as(COO)}$-$\nu_{s(COO)}$ value was larger than 200 cm^{-1}, suggesting that COO^- acts as a monodentate ligand (10). The ^{1}H-NMR spectra are all consistent with the corresponding protons both in the chemical shifts and the number of hydrogens. Two protons of CH_2 split into two bands near 3.27 ppm and 2.55 ppm, probably due to different spatial orientations in a chair configuration of the cyclobutane ring after the introduction of OH at position 3 (11). The ^{13}C-NMR spectra conform to the expected carbon chemical shifts in the 3-hydroxycarboplatin molecule.

The Oak Ridge Thermal Ellipsoid Plot (ORTEP) drawing of the complex depicted along with its atomic numbering scheme is shown in **Figure 3** and the selected bond distances and bond angles are listed in **Table II**. The Pt(II) centre has the expected square planar geometry exhibiting the usual structure parameters. The basal square plane is constituted by two NH_3 and two COO^- moieties of 3-hydroxy-1,1-cyclobutanedicarboxylate. As shown in **Table II**, Pt–N and Pt–O distances and coordinate bond angles of N–Pt–N and O–Pt–O are in the normal range. Similar to the carboplatin molecule (12), the cyclobutane ring adopts a chair configuration and is nearly perpendicular to the Pt(II) coordination plane.

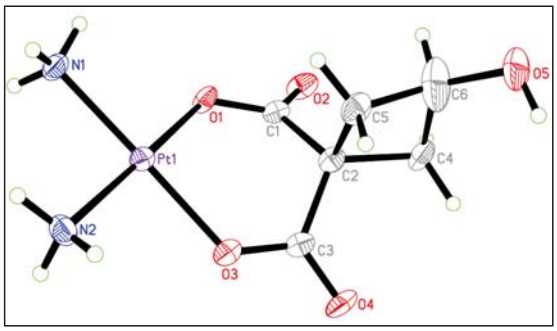


Fig. 3. The X-ray structure of 3-hydroxycarboplatin (see also (7))

2.3 Physicochemical Properties of 3-Hydroxycarboplatin

The solubility of 3-hydroxycarboplatin and carboplatin in water and in octanol was measured at 25°C (**Table III**). As expected, 3-hydroxycarboplatin

Table II

Selected Bond Lengths and Angles for 3-Hydroxycarboplatin

Bond lengths, Å		Bond angles, °	
Pt(1)-O(1)	2.012(5)	O(1)-Pt(1)-O(3)	92.2(2)
Pt(1)-O(3)	2.015(5)	O(1)-Pt(1)-N(1)	87.3(2)
Pt(1)-N(1)	2.016(6)	O(3)-Pt(1)-N(1)	178.1(2)
Pt(1)-N(2)	2.024(6)	O(1)-Pt(1)-N(2)	174.6(3)
		O(3)-Pt(1)-N(2)	88.7(3)
		N(1)-Pt(1)-N(2)	91.6(3)

is nearly twice as soluble in water as carboplatin. Surprisingly, it is also much more soluble in octanol than carboplatin, probably because the lattice energy is decreased with the reduction in symmetry from C_{2v} of carboplatin to C_s of 3-hydroxycarboplatin (13). Therefore, 3-hydroxycarboplatin has a more favourable oil/water partition coefficient (logP).

The aquation rate constant, which is an important parameter in judging the stability of Pt anticancer compounds, was determined by using a previously reported conductivity method (14). The observed aquation rate constant (k_{obs}) of 3-hydroxycarboplatin at 25°C under an N_2 atmosphere was 2.9×10^{-6} min^{-1}, less than k_{obs} of carboplatin (3.8×10^{-6} min^{-1}) under the same conditions, suggesting that 3-hydroxycarboplatin is slightly more stable in water than carboplatin itself.

3. Biological Evaluation

3.1 *In Vitro* Anticancer Activity

3-Hydroxycarboplatin and carboplatin were assayed *in vitro* against carboplatin-sensitive human cancer cell lines including the non-small cell lung cancer cell line A549 and the ovarian cancer cell lines SK-OV-3 and COCI. Cellular survival was evaluated by the 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method (15, 16). Fifty percent inhibitory concentration (IC_{50}) values were calculated from curves constructed by plotting cell survival (%) *versus* compound concentration (in μg ml^{-1}).

As shown in **Table IV**, the activity of 3-hydroxycarboplatin against A549, SK-OV-3 and COCI cancer cells was comparable to that of carboplatin. This indicates that introduction of the OH group into carboplatin does not reduce cytotoxicity.

Table III

Solubility and Partition Coefficient

Compound	Solubility at 25°C, mg ml^{-1}		Partition coefficient, logP
	In water	In octanol	
3-Hydroxycarboplatin	35.0	0.153	2.5
Carboplatin	17.0	0.015	3.2

Table IV

***In Vitro* Cytotoxicity Against Selected Human Tumour Cell Lines**

Compound	IC_{50}, μg ml^{-1}		
	A549	SK-OV-3	COCI
3-Hydroxycarboplatin	2.00 ± 0.34	14.4 ± 2.1	4.57 ± 1.13
Carboplatin	2.91 ± 0.20	25.9 ± 3.8	5.62 ± 2.06

3.2 Acute Toxicity

Acute toxicity is an adverse, non-specific effect that occurs in a healthy animal within 2 weeks of intravenous (iv) injection of a single dose of the drug. Acute toxicity tests of 3-hydroxycarboplatin and carboplatin were carried out in healthy Institute of Cancer Research (ICR) mice according to standard procedures (16). Toxicity, measured as the LD_{50} value (i.e., the dose that causes the death of 50% of tested animals), was 275 mg kg^{-1} for 3-hydroxycarboplatin and 148 mg kg^{-1} for carboplatin, indicating that 3-hydroxycarboplatin is less toxic than carboplatin in animals following iv administration. Histological postmortem examinations of the mice suggested that these Pt complexes caused death primarily through myelosuppression.

3.3 Antitumour Activity

The antitumour activity of 3-hydroxycarboplatin and carboplatin was compared in mouse Lewis lung tumour and human ovarian carcinoma (3AO cell line) xenograft models, using well-established methods (15–19). Based on previous studies, the maximum tolerated dose (MTD) is 90 mg kg^{-1} for 3-hydroxycarboplatin and 60 mg kg^{-1} for carboplatin in mice treated with drugs every three days (Q3D) three times each. Tumour-bearing mice were intravenously given 3-hydroxycarboplatin and carboplatin at the MTD. As shown in **Table V**, treatment with 3-hydroxcarboplatin following tumour implantation caused a dose-dependent reduction of tumour weight in both Lewis lung tumour and 3AO xenograft mice. Notably, the potency of 3-hydroxcarboplatin with respect to inhibition of tumour growth was comparable or superior to that of carboplatin, consistent with the results observed in *in vitro* cytotoxicity tests.

3.4 Myelosuppression Toxicity

To further explore the potential advantage of 3-hydroxycarboplatin over carboplatin, a repeated-dosing toxicity study was conducted (20). ICR mice were iv administered either 3-hydroxycarboplatin or carboplatin on days 1, 3, 5, and 7. On day 8, all mice were anesthetised and blood samples were collected for blood cell analysis; bone marrow cells were also extracted for proliferation tests. Blood cell counts are a good indicator of bone marrow cell proliferation, and thus myelosuppression, a major side effect of carboplatin. The decrease in blood cell counts associated with this myelosuppression is especially prominent for white blood cell and platelet numbers. As shown in **Figures 4–6**, both 3-hydroxycarboplatin and carboplatin exerted myelosuppressive effects, as evidenced by lower blood cell counts compared with the control group. However, the effects were much more pronounced with carboplatin, which caused very severe thrombocytopenia.

Consistent with the results of peripheral blood cell counts, mouse bone marrow cell proliferation was suppressed to a much lesser extent by 3-hydroxycarboplatin than by carboplatin (**Table VI**). 3-Hydroxycarboplatin at a dose of 60 mg kg^{-1} did not significantly suppress bone marrow cell proliferation, with myeloproliferation ranging from extremely to moderately active. However, the degree of myeloproliferation was low or extremely low in bone marrow from mice treated with the same dose of carboplatin (60 mg kg^{-1}). Collectively, these data

Table V

Antitumour Activity of 3-Hydroxycarboplatin in Mouse Tumour Models

Compound	Dose, mg kg^{-1}	Dosing scheme	Tumour growth inhibition, %	
			Lewis lung	3AO
3-Hydroxycarboplatin	30	iv, Q3D × 3	40.7[a]	14.9
	60	"	65.0[a]	33.5[a]
	90	"	87.9[a]	–
Carboplatin	60	"	60.7[a]	28.4[a]

[a] $p < 0.05$ *vs. control* ($n = 7$)

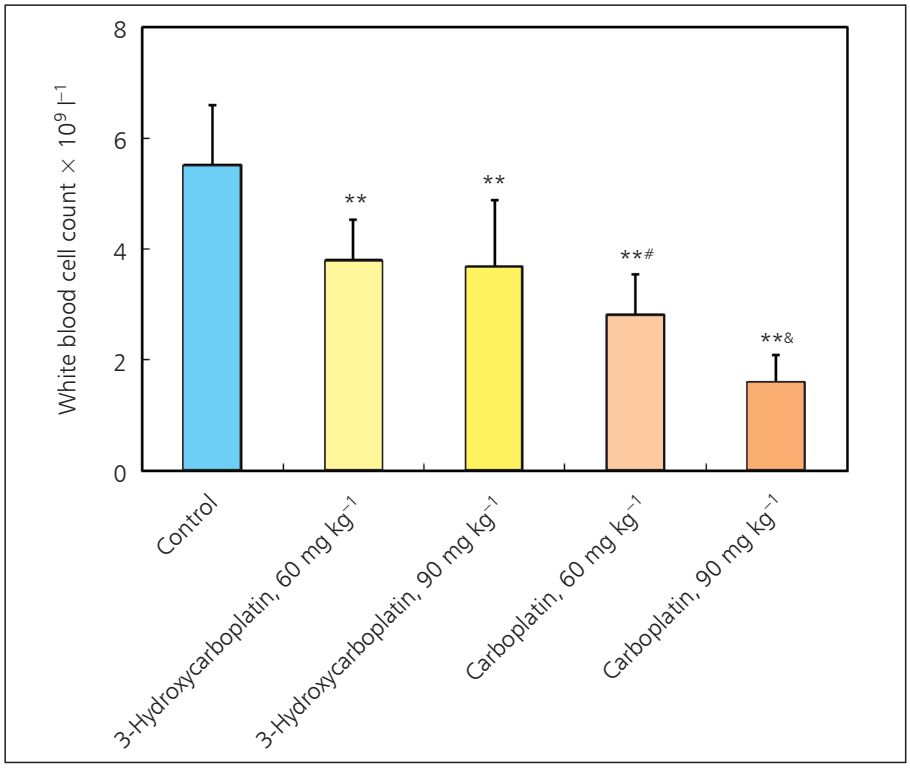


*Fig. 4. White blood cell counts in mouse peripheral blood following repeated dosing with 3-hydroxycarboplatin or carboplatin (n = 10). **P < 0.01 versus control; #P < 0.01 versus 3-hydroxycarboplatin 60 mg kg^{-1}; &P < 0.01 versus 3-hydroxycarboplatin 90 mg kg^{-1}*

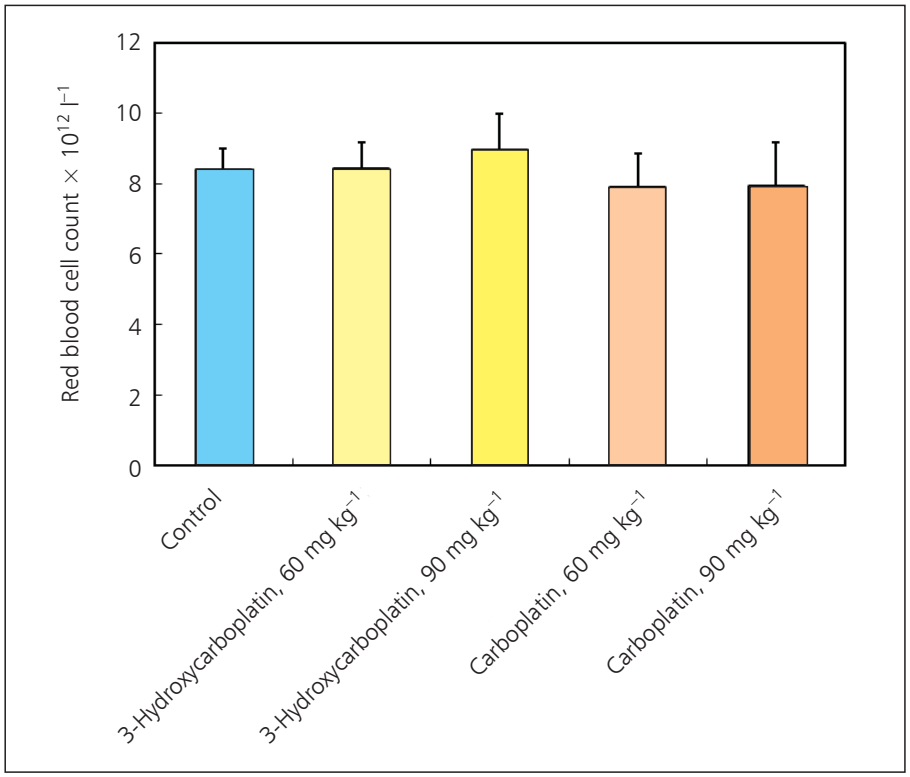


Fig. 5. Red blood cell counts in mouse peripheral blood following repeated dosing with 3-hydroxycarboplatin or carboplatin (n = 10)

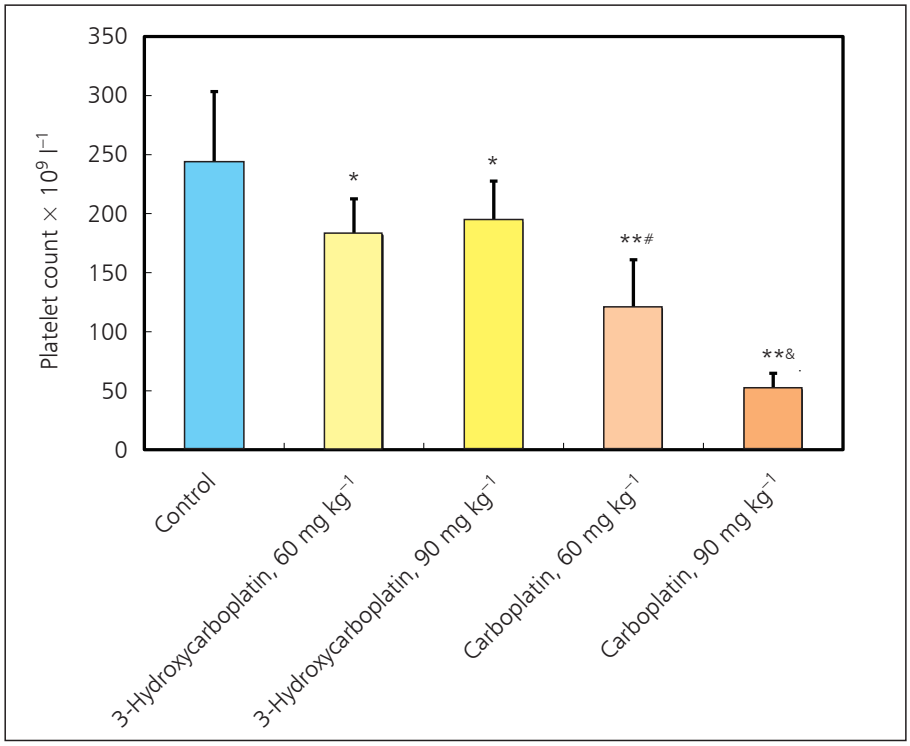


*Fig. 6. Platelet counts in mouse peripheral blood following repeated dosing with 3-hydroxycarboplatin or carboplatin (n = 10). *P < 0.05, **P < 0.01 versus control; #P < 0.01 versus 3-hydroxycarboplatin 60 mg kg^{-1}; &P < 0.01 versus 3-hydroxycarboplatin 90 mg kg^{-1}*

Table VI

Effect of Repeated Dosing with 3-Hydroxycarboplatin or Carboplatin on the Proliferation of Bone Marrow Cells in Mice

		Relative myeloproliferative index[a]				
		I	II	III	IV	V
Control		4/10	4/10	2/10	0/10	0/10
3-Hydroxycarboplatin	60 mg kg^{-1}	2/10	7/10	1/10	0/10	0/10
	90 mg kg^{-1}	0	6/10	2/10	2/10	0/10
Carboplatin	60 mg kg^{-1}	0/10	1/10	2/10	4/10	3/10
	90 mg kg^{-1}	0/9	0/9	0/9	1/9	8/9

[a]*Number of mice in each myeloproliferative class: I, extremely active; II, active; III, moderate; IV, low; V, extremely low*

indicate that the myelosuppressive side effects of 3-hydroxycarboplatin are much lower than those of carboplatin.

4. Conclusion

3-Hydroxycarboplatin, a simple carboplatin derivative, shows antitumour activity comparable to that of carboplatin but has much lower toxicity, particularly with respect to myelosuppression, reflecting an improved toxicological profile. It also exhibits desirable physicochemical properties. Therefore, 3-hydroxycarboplatin has extremely high potential for development as a clinically useful anticancer agent to replace carboplatin.

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