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SYNTHESIS AND ANTITUMOR ACTIVITY OF (2*R*,3*R*)-2,3-DIHYDROXY- AND -2,3-DIALKOXY-1,4-DIAMINOBUTANE PLATINUM(II) COMPLEXES

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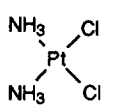
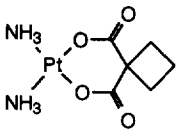
Abstract: The synthesis and antitumor activity of (2*R*,3*R*)-2,3-dihydroxy- and -2,3-dialkoxy-1,4-diaminobutane platinum(II) complexes **10–15** are described. *cis*-Dichloro[(2*R*,3*R*)-2,3-dimethoxy-1,4-diaminobutane]platinum(II) (**11**) and *cis*-(cyclobutane-1,1-dicarboxylato)[(2*R*,3*R*)-2,3-dihydroxy-1,4-diaminobutane]platinum(II) (**13**) showed the potent antitumor activity against L1210 leukemia in mice with % T/C values of around 200.

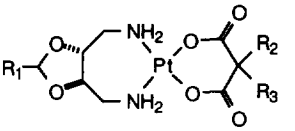
cis-Dichlorodiammineplatinum(II) (cisplatin)[1] is one of the most effective anticancer agents currently available for the treatment of testicular, ovarian, and bladder cancers.[2] In addition, cisplatin is widely used in combination with other anticancer agents in treating head and neck cancer, lung carcinoma, and stomach carcinoma.[3] However, the adverse effects that are observed in patients receiving cisplatin, such as nephrotoxicity, gastrointestinal toxicity, ototoxicity, and neurotoxicity[4] as well as the low activity for certain kinds of cancers, such as breast and colon cancers[2a] strongly limit its clinical use. Furthermore, the development of acquired resistance to cisplatin is frequently observed during chemotherapy.[5] In order to overcome these drawbacks of cisplatin, numerous analogues have been synthesized and evaluated to develop alternative active agent with equivalent or greater antitumor activity and lower toxicity than cisplatin.[6]



Cisplatin



Carboplatin



SKI 2053R : R_1 = *i*-Pr, R_2 = R_3 = H
SKI 2019R : R_1 = Et, R_2, R_3 = -$(CH_2)_3$-

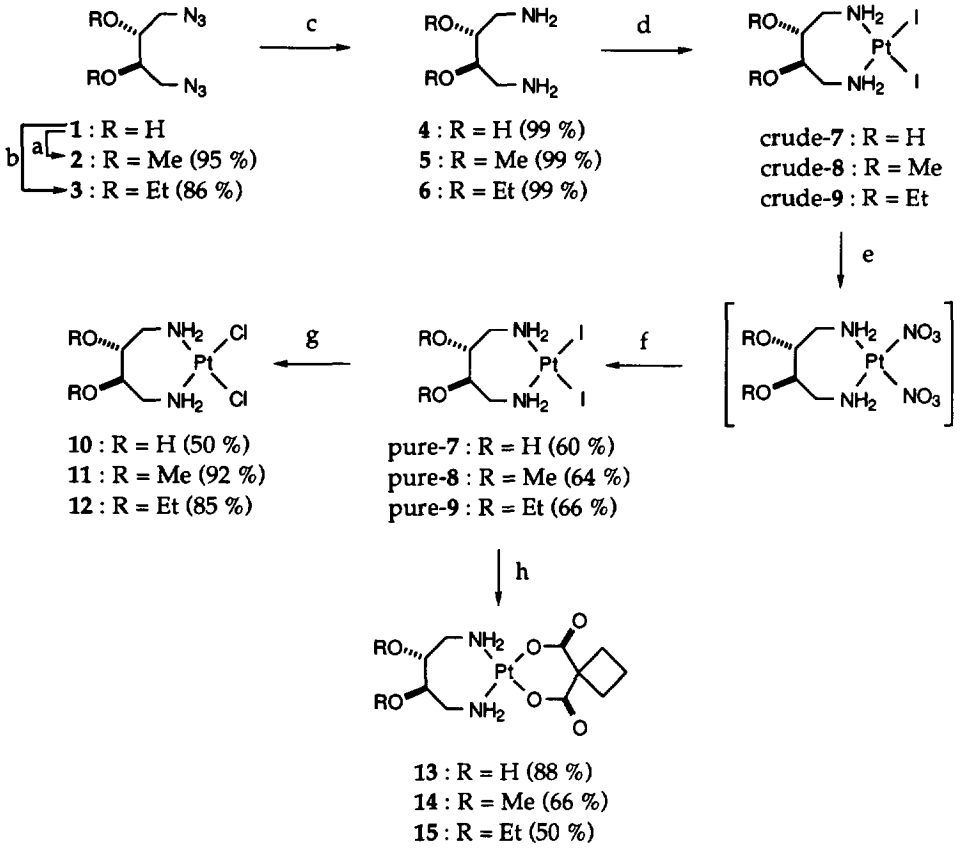
Among them, *cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II) (carboplatin) shows the same level of activity as cisplatin in treating some kinds of cancers, such as ovarian cancer and small-cell lung cancer, and is much less nephrotoxic and emetic than cisplatin.[6a] The spectrum of antitumor activity of carboplatin, however, does not seem to be expanded compared to that of cisplatin.

In our efforts to develop a water-soluble new platinum complex that possesses a broader spectrum of antitumor activity, lower toxicity, and lack of cross-resistance to cisplatin, we have recently prepared a series of 2-substituted-4,5-bis(aminomethyl)-1,3-dioxolane platinum(II) complexes.[7] Of these complexes, *cis*-malonato[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (SKI 2053R) showed the excellent antitumor activity against a number of murine tumors including cisplatin-resistant L1210 leukemia and human tumor cell lines, reduced renal toxicity in rats and dogs compared to cisplatin, desirable pharmacokinetic and pharmacodynamic characteristics, and suitable physicochemical properties such as high solubility and stability in aqueous solution.[8] SKI 2053R is currently undergoing Phase II clinical trials against selected tumors, including stomach, lung, head and neck, and cervical cancers in Korea.

Since there is a possibility that the 1,3-dioxolane ring moiety in this series may be hydrolyzed chemically or enzymatically in biological fluids, we were interested in the examination of the antitumor activity of the possible metabolites. Therefore, in this report, we have synthesized and evaluated antitumor activity of (2*R*,3*R*)-2,3-dihydroxy- and -2,3-dialkoxy-1,4-diaminobutane platinum(II) complexes as potential metabolites of (4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane platinum(II) complexes.

The synthesis of the dichloro platinum(II) complexes **10**–**12** and the 1,1-cyclobutanedicarboxylato platinum(II) complexes **13**–**15** is outlined in Scheme 1. Treatment of (2*R*,3*R*)-2,3-dihydroxy-1,4-diazidobutane (**1**)[7] with sodium hydride in *N*,*N*-dimethylformamide followed by the reaction of the resulting disodium salt with either methyl iodide or ethyl bromide afforded the corresponding dialkylated products **2** and **3** in 95 % and 86 % yields, respectively. The diazido compounds **1**–**3** were reduced with hydrogen (50 psi) in the presence of 10 % palladium on activated carbon in ethanol at 50 °C for 3 h to give the diamino compounds **4**–**6** in almost quantitative yields. The compounds **4**–**6** were reacted with an equimolar amount of *in situ* generated potassium tetraiodoplatinate(II) from potassium tetrachloroplatinate(II) (1 equiv.) and potassium iodide (6 equiv.) to produce the crude diiodo platinum(II) complexes **7**–**9**, which were subsequently treated with an aqueous silver nitrate solution, followed by potassium iodide according to the published procedure[6f] to give the pure diiodo platinum(II) complexes in 60–66 % yields. Conversion of **7**–**9** into the corresponding *cis*-dichloro platinum(II) complexes **10**–**12** was accomplished in 50–92 % yields by the similar procedure described for the purification of the crude diiodo platinum(II) complexes. Treatment of **7**–**9** with the disilver salt of 1,1-cyclobutanedicarboxylic acid afforded the corresponding 1,1-cyclobutanedicarboxylato platinum(II) complexes **13**–**15** in 50–88 % yields. The compounds **10**–**15** were purified by preparative HPLC on Delta pak C_{18}-100-Å reversed-phase bonded silica cartridge with methanol-water system as the mobile phase, freeze-dried, and characterized by spectral data and elemental analysis.[9]

Scheme 1[a]



[a](a) NaH (2 equiv.), DMF, rt, 1 h, then MeI (6 equiv.) rt, 2 h; (b) NaH (2 equiv.), DMF, rt, 1 h, then EtBr (5 equiv.) rt, 2 h; (c) 10 % pd/C, H_2 (50 psi), EtOH, 50 °C, 3 h; (d) K_2PtCl_4 (1 equiv.), KI (6 equiv.), H_2O, 60 °C, 1 h, N_2 atmosphere; (e) $AgNO_3$ (2 equiv.), H_2O, 60 °C, 2 h; (f) KI (10 equiv.), 0 °C, 1 h; (g) $AgNO_3$ (2 equiv.), H_2O, 60 °C, 2 h, then NaCl (10 equiv.), 40 °C, 1 h; (h) 1,1-cyclobutanedicarboxylic acid disilver salt, H_2O, 60 °C, 16 h.

The antitumor activity of the platinum(II) complexes **10–15** against L1210 leukemia (ip-ip system) in mice was evaluated in comparison with those of their corresponding dioxolanes (SKI 2053R and SKI 2019R), cisplatin, and carboplatin. In general, the antitumor activity of these (2*R*,3*R*)-2,3-dihydroxy- and -2,3-dialkoxy-1,4-diaminobutane platinum(II) complexes was lower than that of 2-substituted-(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane platinum(II) complexes, SKI 2053R and SKI 2019R. This result is in good agreement with the previous finding[10] that carrier ligands with polar substituents reduce the activity of an analogue. However, *cis*-dichloro[(2*R*,3*R*)-2,3-dimethoxy-1,4-diaminobutane]platinum(II) (**11**) and *cis*-(cyclobutane-1,1-dicarboxylato)- [(2*R*,3*R*)-2,3-dihydroxy-1,4-diaminobutane]platinum(II) (**13**) showed the potent antitumor activity with % T/C values of around 200, comparable or superior to either carboplatin or cisplatin.

Table 1. Antitumor Activity of Platinum(II) Complexes against L1210 Leukemia in Mice[a]

compound	% T/C[b] at dose (mg/kg, ip, days 1, 5, 9)						
	100	50	25	12.5	6.25	3.1	1.5
10		toxic	toxic	118	125	162	
11		toxic	toxic	75	119	201	
12			toxic	toxic	toxic	90	137
13	195		148	131	135	113	
14	132	125	104	115	105		
15	161	124	113	113	104		
SKI 2053R		220[c]	148	123			
SKI 2019R	391[c]	208	193	130	122		
cisplatin			toxic	toxic	82	167	142
carboplatin	197	196	148	125	107		

[a]Male BDF_1 mice (6 mice/treated group and 15 mice/control group) were implanted ip with 1×10^6 cells of L1210 on day 0. Compounds were given ip on a q4d × 3 schedule. [b]Antitumor activity was evaluated by comparing the mean survival time (MST) of treated groups (T) with that of control group (C) and was expressed as % T/C (the percentage of the MST of T relative to the MST of C). [c]Adapted from reference 7.

In conclusion, it has been shown that the possible metabolites of (4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane platinum(II) complexes, (2*R*,3*R*)-2,3-dihydroxy-1,4-diaminobutane platinum(II) complexes and their dialkylated analogues also possess moderate to high level of antitumor activity.

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9. **10**: IR (KBr) 3436, 3224 (NH) cm^{-1}; ^{13}C NMR (DMSO-d_6) δ 45.96, 47.36, 68.84, 69.03; FAB-MS *m/z* 386 (M^+); *Anal.* Calcd for $C_{14}H_{12}Cl_2N_2O_2Pt$: C, 12.44; H, 3.13; N, 7.25. Found: C, 12.32; H, 3.20; N, 7.18. **11**: IR (KBr) 3496, 3217 (NH) cm^{-1}; ^1H NMR (DMSO-d_6/TMS) δ 2.92 (m, 2 H, 2 C*H*NH_2), 3.04 (m, 2 H, 2 C*H*NH_2), 3.38 (s, 3 H, CH_3O), 3.39 (s, 3 H, CH_3O), 3.73 (m, 1 H, CH), 3.84 (m, 1 H, CH), 5.21 (br s, 1 H, NH), 5.42 (m, 1 H, NH), 5.50 (br s, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 41.34, 42.69, 56.88, 57.36, 76.86; FAB-MS *m/z* 415 (M^+ + H); *Anal.* Calcd for $C_6H_{16}Cl_2N_2O_2Pt$: C, 17.40; H, 3.89; N, 6.76. Found: C, 17.66; H, 3.69; N, 6.91. **12**: IR (KBr) 3457, 3230 (NH) cm^{-1}; ^1H NMR (DMSO-d_6/TMS) δ 1.18 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.19 (t, *J* = 6.9 Hz, 3 H, CH_3), 2.90 (m, 2 H, 2 C*H*NH_2), 3.02 (m, 2 H, 2 C*H*NH_2), 3.52 (m, 2 H, CH_2O), 3.67 (m, 2 H, CH_2O), 3.81 (m, 1 H, CH), 3.92 (m, 1 H, CH), 5.18 (m, 1 H, NH), 5.36 (m, 1 H, NH), 5.48 (m, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 15.23, 15.25, 42.30, 43.93, 64.64, 64.91, 75.14; FAB-MS *m/z* 442 (M^+); *Anal.* Calcd for $C_8H_{20}Cl_2N_2O_2Pt$: C, 21.73; H, 4.56; N, 6.33. Found: C, 21.60; H, 4.60; N, 6.35. **13**: IR (KBr) 3378, 3212 (NH, OH), 1635(C=O) cm^{-1}; ^1H NMR (DMSO-d_6/TMS) δ 1.65 (quintet, *J* = 7.8 Hz, 2 H, $CH_2CH_2CH_2$), 2.59 (m, 2 H, 2 C*H*NH_2), 2.67 (t, *J* = 7.8 Hz, 4 H, $CH_2CH_2CH_2$), 2.77 (m, 2 H, 2 C*H*NH_2), 3.79 (br s, 2 H, 2 CH), 4.66 (m, 2 H, 2 NH), 5.10 (br s, 2 H, 2 OH), 5.36 (m, 2 H, 2 NH); FAB-MS *m/z* 458 (M^+ + H); *Anal.* Calcd for $C_{10}H_{18}N_2O_6Pt$: C, 26.26; H, 3.97; N, 6.13. Found: C, 26.32; H, 3.80; N, 6.25. **14**: IR (KBr) 3441, 3243, 3221, 3182, 3103 (NH), 1657, 1628, 1599 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6/TMS) δ 1.65 (quintet, *J* = 7.8 Hz, 2 H, $CH_2CH_2CH_2$), 2.67 (t, *J* = 7.8 Hz, 4 H, $CH_2CH_2CH_2$), 2.72 (br s, 4 H, 2 CH_2NH_2, overlapped with $CH_2CH_2CH_2$), 3.34 (s, 6 H, 2 CH_3O), 3.66 (br s, 2 H, 2 CH), 4.67 (br s, 2 H, 2 NH), 5.42 (m, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 14.85, 30.25, 42.95, 55.53, 57.26, 79.68, 177.21; FAB-MS *m/z* 486 (M^++ H); *Anal.* Calcd for $C_{12}H_{22}N_2O_6Pt$: C, 29.69; H, 4.57; N, 5.77. Found: C, 29.86; H, 4.32; N, 5.70. **15**: IR (KBr) 3447, 3242, 3190, 3105 (NH), 1657, 1628, 1597 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6/TMS) δ 1.14 (t, *J* = 6.9 Hz, 6 H, 2 CH_3), 1.66 (quintet, *J* = 7.8 Hz, 2 H, $CH_2CH_2CH_2$), 2.68 (t, *J* = 7.8 Hz, 4 H, $CH_2CH_2CH_2$), 2.73 (br s, 4 H, 2 CH_2NH_2), 3.51 (m, 2 H, CH_2O), 3.62 (m, 2 H, CH_2O), 3.73 (br s, 2 H, 2 CH), 4.52 (m, 2 H, 2 NH), 5.35 (m, 2 H, 2 NH); ^{13}C NMR (DMSO-d_6) δ 14.86, 15.31, 30.27, 44.02, 55.54, 64.92, 77.79, 177.22; FAB-MS *m/z* 514 (M^++ H); *Anal.* Calcd for $C_{14}H_{26}N_2O_6Pt$: C, 32.75; H, 5.10; N, 5.46. Found: C, 32.90; H, 5.21; N, 5.25.

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