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SYNTHESIS AND *IN VITRO* CYTOTOXICITY OF *CIS*-(GLYCOLATO-*O,O'*)-[2-SUBSTITUTED-(4*R*,5*R*)-4,5-BIS(AMINOMETHYL)-1,3-DIOXOLANE]PLATINUM(II)

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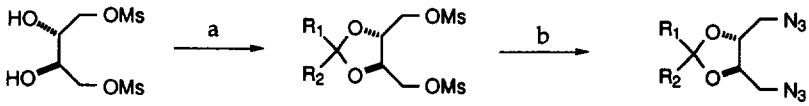
Abstract : The synthesis and *in vitro* cytotoxicity of *cis*-(glycolato-*O,O'*)[2-substituted-(4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane]platinum(II) are described. Among them, *cis*-(glycolato-*O,O'*)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2,2-diethyl-1,3-dioxolane]platinum(II) (**26**) was found to be almost equally cytotoxic to cisplatin against two human non-small cell lung cancer cell lines, PC-9 and PC-14, and two human stomach cancer cell lines, MKN-45 and KATO III.

Since the discovery of the antitumor properties of platinum compounds by Rosenberg *et al.*[1], *cis*-dichlorodiammineplatinum(II) (cisplatin) has demonstrated a remarkable chemotherapeutic potential in treating testicular, ovarian, bladder, head and neck, lung, and stomach cancers.[2] However, the adverse effects that are observed in patients receiving cisplatin, such as nephrotoxicity, severe nausea and vomiting, ototoxicity, and neurotoxicity[3] as well as the low activity for some kinds of cancers, such as breast and colon cancers[2a] have stimulated the search for new platinum-based anticancer agents that will display reduced toxicity and different spectrum of antitumor activity.[4]

In an attempt to develop a new water-soluble antitumor platinum drug, we have recently prepared a series of 2-substituted-4,5-bis(aminomethyl)-1,3-dioxolane platinum(II) complexes with malonate, dimethylmalonate, ethylmalonate, 1,1-cyclobutanedicarboxylate, glycolate, or L-lactate as a leaving ligand.[5] Of these complexes, *cis*-malonato[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (SKI 2053R) and *cis*-(glycolato-*O,O'*)[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (SKI 2034R) 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 animals compared to cisplatin, desirable pharmacokinetic characteristics, and suitable physicochemical properties such as high solubility and stability in aqueous solution.[5,6] SKI 2053R is currently undergoing Phase II clinical trials in Korea and SKI 2034R has been selected as a clinical candidate. It has been previously shown that the glycolato platinum(II) complexes in an above-mentioned series were the most potent and highly water-soluble and the substitution of a hydrogen at the 2-position of the 1,3-dioxolane ring moiety by the isopropyl group remarkably increased the cytotoxicity against a number of human tumor cell lines.[5] On the basis of the previous structure-activity relationships, we decided to synthesize the additional glycolato platinum(II) complexes with a C_{3-4} alkyl group or C_{1-2} dialkyl groups at the 2-position of the (4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolane carrier ligand for the refinement of 2-substituents. These complexes are expected to be not only more active but also more lipophilic than those with unsubtituted or a lower C_{1-2} alkyl group at the 2-position of the 1,3-dioxolane ring, thus, penetrating into the tissues of solid tumors more efficiently.

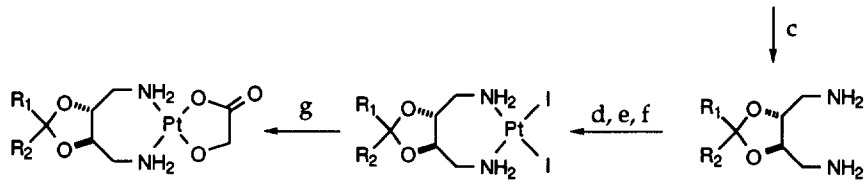
Scheme 1[a]



1

2 : R_1 = *n*-Pr, R_2 = H (95 %)
3 : R_1 = *i*-Bu, R_2 = H (92 %)
4 : R_1 = *tert*-Bu, R_2 = H (88 %)
5 : R_1 = Et, R_2 = Me (90 %)
6 : R_1 = R_2 = Et (86 %)

7 : R_1 = *n*-Pr, R_2 = H (96 %)
8 : R_1 = *i*-Bu, R_2 = H (95 %)
9 : R_1 = *tert*-Bu, R_2 = H (97 %)
10 : R_1 = Et, R_2 = Me (95 %)
11 : R_1 = R_2 = Et (98 %)



22 : R_1 = *n*-Pr, R_2 = H (64 %)
23 : R_1 = *i*-Bu, R_2 = H (52 %)
24 : R_1 = *tert*-Bu, R_2 = H (61 %)
25 : R_1 = Et, R_2 = Me (70 %)
26 : R_1 = R_2 = Et (68 %)

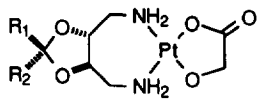
17 : R_1 = *n*-Pr, R_2 = H (62 %)
18 : R_1 = *i*-Bu, R_2 = H (66 %)
19 : R_1 = *tert*-Bu, R_2 = H (65 %)
20 : R_1 = Et, R_2 = Me (71 %)
21 : R_1 = R_2 = Et (74 %)

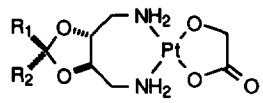
12 : R_1 = *n*-Pr, R_2 = H (99 %)
13 : R_1 = *i*-Bu, R_2 = H (99 %)
14 : R_1 = *tert*-Bu, R_2 = H (99 %)
15 : R_1 = Et, R_2 = Me (99 %)
16 : R_1 = R_2 = Et (99 %)

[a](a) R_1COR_2 (1.1 equiv. for **2**–**4** or 2.0 equiv. for **5** and **6**), anhydrous $CuSO_4$ (1.5 equiv.), MsOH (cat.), benzene, rt (for **2**–**4**) or reflux (for **5** and **6**), 16 h, then K_2CO_3, rt, 20 min; (b) NaN_3 (4 equiv.), DMF, 100 °C, 16 h; (c) 10 % pd/C, H_2 (50 psi), EtOH, 40 °C, 2 h; (d) K_2PtCl_4 (1 equiv.), KI (6 equiv.), H_2O, 60 °C, 1 h, N_2 atmosphere; (e) $AgNO_3$ (2 equiv. based on the crude diiodo platinum complex), H_2O, 60 °C, 2 h; (f) KI (10 equiv.), 0 °C, 1 h; (g) glycolic acid (2 equiv.), Ag_2O (2 equiv.), H_2O–MeOH (9:1), 60 °C, 16 h.

The synthesis of the glycolato platinum(II) complexes **22**–**26** is outlined in Scheme 1. Reaction of D-threitol 1,4-bis(methanesulfonate) (**1**)[5] with an appropriate aldehyde or ketone in the presence of anhydrous $CuSO_4$ and an acid catalyst gave (4*R*,5*R*)-4,5-bis[(methylsulfonyloxy)-methyl]-1,3-dioxolanes **2**–**6** in 86–95 % yields. These were then reacted with NaN_3 in DMF to give (4*R*,5*R*)-4,5-bis(azidomethyl)-1,3-dioxolanes **7**–**11** in 95–98 % yields. Hydrogenation of the diazides **7**–**11** at 50 psi in the presence of 10 % pd/C in EtOH afforded (4*R*,5*R*)-4,5-bis(aminomethyl)-1,3-dioxolanes **12**–**16** in almost quantitative yields. The diamino compounds **12**–**16** were reacted with an equimolar amount of *in situ* generated K_2PtI_4 from K_2PtCl_4 (1 equiv.) and KI (6 equiv.) to produce the crude diiodo platinum(II) complexes **17**–**21**, which were subsequently treated with an aqueous silver nitrate solution, followed by KI to give the pure diiodo platinum(II) complexes in 62–74 % yields. Treatment of the complexes **17**–**21** with glycolic acid in the presence of silver(I) oxide in a mixture of H_2O-MeOH (9:1) produced the glycolato platinum(II) complexes **22**–**26** in 52–70 % yields. Most of the glycolato platinum(II) complexes were sufficiently water-soluble (**22**, >30; **23**, 4.6; **24**, 2.1; **25**, 11.6; **26**, 30.0 mg/mL); therefore, they were purified by preparative HPLC on Delta pak C_{18}-100-Å reversed-phase bonded silica cartridge with MeOH-H_2O system as the mobile phase, freeze-dried, and characterized by spectral data and elemental

analysis.[7] As previously observed,[5] complexes **22–25** were present as a mixture of two geometrical isomers, which were not readily distinguishable each other in their ^{1}H NMR spectra but confirmed by their ^{13}C NMR spectra. For example, the ^{13}C NMR spectrum of **22** in D_2O showed a pair of C-5 and C-5' resonances at 48.62, 48.71, 48.89, and 49.01 ppm. A recent study of Miyamoto *et al.*[8] with the four optical isomers of (mandelato)(*trans*-1,2-diaminocyclohexane)platinum(II) showed that the chirality of both carrier ligands and leaving ligands influenced the antitumor activity of platinum complexes. Thus, it seems necessary to separate afore-mentioned geometrical isomers before biological evaluation. However, since the separation of those isomers was practically difficult even by using HPLC, they were tested without further separation.





22 : R_1 = *n*-Pr, R_2 = H
23 : R_1 = *i*-Bu, R_2 = H
24 : R_1 = *tert*-Bu, R_2 = H
25 : R_1 = Et, R_2 = Me

The cytotoxicity of the glycolato platinum(II) complexes **22–26** along with SKI 2034R, cisplatin, and *cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II) (carboplatin) were tested against two human non-small cell lung cancer cell lines, PC-9 and PC-14, and two human stomach cancer cell lines, MKN-45 and KATO III,[9] by MTT assay[10] (Table 1).

Table 1. Cytotoxicity of Platinum(II) Complexes against Human Lung and Stomach Cancer Cell Lines *in Vitro*[a]

	IC_{50} (μM)[b]			
compound	PC-9[c]	PC-14[c]	MKN-45[d]	KATO III[d]
22	7.1	2.8	5.3	7.0
23	7.0	2.1	8.1	6.1
24	6.9	5.0	7.2	6.5
25	8.4	1.9	5.8	4.6
26	6.4	1.8	3.8	4.4
SKI 2034R	9.7	1.1	4.1	6.1
cisplatin	5.0	1.5	3.7	5.2
carboplatin	60.5	9.7	32.4	49.7

[a]Tested by MTT assay. [b]Mean value of 3 experiments. [c]Non-small cell lung cancer cell line. [d]Stomach cancer cell line.

All of the tested compounds **22-26** exhibited high cytotoxicity against these four human cancer cell lines, and among them, the compound **26** was almost equally cytotoxic to SKI 2034R and cisplatin. On the basis of this pronounced *in vitro* cytotoxicity and high solubility in aqueous solution, extensive *in vivo* studies of **26** to demonstrate its antitumor activity and target organ toxicity profiles are currently under way.

References and Notes

1. Rosenberg, B.; VanCamp, L.; Trosko, J. E.; Mansour, V. H. *Nature* **1969**, *222*, 385.
2. (a) Carter, S. K. *Platinum Coordination Complexes in Cancer Chemotherapy*; Hacker, M. P., Douple, E. B., Krakoff, I. H., Eds.; Martinus Nijhoff Publishing: Boston, 1984; pp. 359; (b) Durant, J. R. *Cisplatin Current Status and New Developments*; Prestayko, A. W., Crooke, S. T., Carter, S. K., Eds.; Academic Press, Inc.: New York, 1980; pp. 317; (c) Loehrer, P. J.; Einhorn, L. H. *Ann. Intern. Med.* **1984**, *100*, 704; (d) Einhorn, L. H.; Donohue, J. *Ann. Intern. Med.* **1977**, *87*, 293; (e) Ozols, R. F.; Young, R. C. *Semin. Oncol.* **1984**, *11*, 251; (f) Soloway, M. S. *J. Urol.* **1978**, *120*, 716; (g) Choksi, A.; Hong, W. K. *Platinum and Other Metal Coordination Complexes in Cancer Chemotherapy*; Nicolini, M., Ed.; Martinus Nijhoff Publishing: Boston, 1988; pp. 375; (h) Paccagnella, A.; Favaretto, G.; Fiorentino, M. V. In ref 2g, pp. 394; (i) Wagener, D. J.; Yap, S. H.; Wobbes, T.; Burghouts, J. T.; van Dam, F. E.; Hillen, H. F.; Hoogendoorn, G. J.; Scheerder, H.; van der Vegt, S. G. *Cancer Chemother. Pharmacol.* **1985**, *15*, 86.
3. von Hoff, D. D.; Schilsky, R.; Reichert, C. M.; Reddick, R. L.; Rozencweig, M.; Young, R. C.; Muggia, F. M. *Cancer Treat. Rep.* **1979**, *63*, 1527.
4. (a) Kim, D.-K.; Gam, J.; Kim, K. H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 911; (b) Carter, S. K.; Canetta, R.; Rozencweig, M. *Cancer Treat. Rev.* **1985**, *12 (Suppl. A)*, 145; (c) Akamatsu, K.; Endo, K.; Matsumoto, T.; Kamisango, K.; Morikawa, K.; Koizumi, M.; Koizumi, K. *Br. J. Cancer* **1992**, *66*, 827; (d) Akaza, H.; Togashi, M.; Nishio, Y.; Miki, T.; Kotake, T.; Matsumura, Y.; Yoshida, O.; Aso, Y. *Cancer Chemother. Pharmacol.* **1992**, *31*, 187; (e) Kraker, A. J.; Hoeschele, J. D.; Elliott, W. L.; Showalter, H. D. H.; Sercel, A. D. *J. Med. Chem.* **1992**, *35*, 4526; (f) Mellish, K. J.; Kelland, L. R.; Harrap, K. R. *Br. J. Cancer* **1993**, *68*, 240.
5. Kim, D.-K.; Kim, G.; Gam, J.; Cho, Y.-B.; Kim, H.-T.; Tai, J.-H.; Kim, K. H.; Hong, W.-S.; Park, J.-G. *J. Med. Chem.* **1994**, *37*, 1471.
6. (a) Kim, D.-K. *Drugs Future* (in press); (b) Cho, Y.-B.; Kim, D.-K.; Kim, K. H.; Miyamoto, G. *Arzneim.-Forsch./Drug Res.* (in press); (c) Cho, Y.-B.; Kim, K. H.; Kim, D.-K.; Miyamoto, G. *Arzneim.-Forsch./Drug Res.* (in press);(d) Kim, D.-K.; Kim, H.-T.; Tai, J. H.; Cho, Y.-B.; Kim, T.-S.; Kim, K. H.; Park, J.-G.; Hong, W.-S. *Cancer Chemother. Pharmacol.* **1995**, *37*, 1; (e) Kim, D.-K.; Kim, H.-T.; Cho, Y.-B.; Tai, J. H.; Ahn, J. S.; Kim, T.-S.; Kim, K. H.; Hong, W.-S. *Cancer Chemother. Pharmacol.* **1995**, *35*, 441; (f) Hong, W.-S.; Kim, H.-T.; Kim, K. H.; Kim, D.-K. *Anticancer Res.* **1995**, *15*, 51; (g) Cho, Y.-B.; Kim, K. H.; Kim, D.-K. *Drug Metab. Dispos.* **1995**, *23*, 1280; (h) Hong, W.-S.; Min, Y. I.; Kim, H.-T.; Cho, Y.-B.; Kim, K. H.; Kim, D.-K. *J. Korean Med. Sci.* **1995**, *10*, 269; (i) Kim, D.-K.; Ahn, J. S.; Ryu, G.; Kim, K. H.; Park, C. W.; Kim, M. S.; Chung, M. H.; Shin, S. K.; Seo, Y. H.; Kim, Y. S.; Son, Y. S. *Arzneim.-Forsch./Drug Res.* **1994**, *44(II)*, 1080; (j) Kim, D.-K.; Kim, Y.; Rim, J.; Kim, G.; Gam, J.; Song, S.; Yoo, K.; Kim, K. H. *J. Labelled Compd Radiopharm.* **1994**,*34*, 157.
7. **26**: IR (KBr) 3422, 3208 (NH), 1640 (C=O) cm^{-1}; ^1H NMR (D_2O/DSS) δ 0.89 (t, J = 7.2 Hz, 6 H, 2 CH_3), 1.71 (q, J = 7.2 Hz, 4 H, 2 CH_2), 2.78–2.94 (m, 2 H, 2 $CHNH_2$), 3.27–3.40 (m, 2 H, 2 $CHNH_2$), 4.08 (s, 2 H, CH_2), 4.69 (m, 2 H, 2 CH, overlapped with HOD); ^{13}C NMR (D_2O/DSS) δ 8.10, 30.64, 49.29, 49.57, 69.25, 79.65, 115.53, 195.46; FAB-MS m/z 458 (M^+ + H); *Anal.* Calcd for $C_{11}H_{22}N_2O_5Pt$: C, 28.89; H, 4.85; N, 6.12. Found: C, 29.02; H, 4.92; N, 5.87.
8. Miyamoto, T. K.; Okude, K.; Maeda, K.; Ichida, H.; Sasaki, Y.; Tashiro, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3239.
9. PC-9, PC-14, MKN-45, and KATO III were kindly provided by Professor W.-S. Hong, Asan Medical Center, College of Medicine, Ulsan University, Korea.
10. (a) Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55; (b) Carmichael, J.; De Graff, W. G.; Gazdar, A. F.; Minna, J. D.; Mitchell, J. B. *Cancer Res.* **1987**, *47*, 936.

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