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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 15 (2005) 4936–4943

Synthesis and in vitro cytotoxicity of novel hydrophilic chiral 2-alkoxy-1,4-butanediamine platinum (II) complexes

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Received 14 June 2005; revised 23 July 2005; accepted 6 August 2005
Available online 19 September 2005

Abstract—Twenty-six new hydrophilic chiral 2-alkoxy-1,4-butanediamine platinum (II) complexes having a seven-membered ring structure between a bidentate carrier ligand and a platinum atom have been synthesized and most of them were evaluated for their in vitro cytotoxicity toward A549 human non-small cell lung carcinoma and HCT-116 human colon cancer cell lines. The cytotoxicities of platinum complexes are related to the nature of the carrier ligand and leaving group. Complex 5′b, viz. *cis*-dichloro[(2*R*)-ethoxy-1,4-butanediamine] platinum (II), exhibits the greatest potency among those 21 tested platinum complexes in both cell lines.

Cisplatin, *cis*-[$Pt(NH_3)_2Cl_2$], is one of the most widely used clinical agents in the treatment of a variety of solid tumors.[1,2] However, the clinical usefulness of cisplatin has been frequently limited by its low aqueous solubility, serious toxicity, narrow range of activity, and, especially, by inherent and acquired tumor resistance.[3] In attempt to overcome these drawbacks of cisplatin, numerous analogues have been synthesized and evaluated in a search for alternative active agents.[4–8] Among them, carboplatin exhibited higher water solubility and reduced nephrotoxicity but failed to expand antitumor activity spectrum and overcome the tumor resistance, probably due to the fact that they have the same diamine carrier ligand.[9–12]

Platinum compounds are supposed to express their cytotoxic effects by loss of the leaving groups and subsequent binding of the platinum-AA′ moiety to DNA. The DNA double helix is per se a chiral structure, therefore, platinum complexes carrying enantiomeric amines are expected to produce different diastereoisomeric interactions with this helical arrangement. This point of view leads to the design of platinum antitumor drug focusing mainly on the chirality of the carrier ligand and various chiral diamine platinum complexes have been designed, synthesized, and evaluated for antitumor activity.[13–17] Among them, oxaliplatin, SKI-2053R, and lobaplatin have received limited approval for use in some countries. Oxaliplatin, (*trans*-1*R*,2*R*-diaminocyclohexane)(oxalato)platinum (II), having a five-membered ring structure between a bidentate carrier ligand and the metal atom, is the first clinically approved platinum compound which demonstrated lack of cross-resistance in some cisplatin-resistant cell lines. The lack of cross-resistance was attributed to the chiral 1,2-diaminocyclohexane carrier ligand.[18]

Most of the platinum complexes reported to date have five-membered or six-membered chelating rings between a bidentate carrier ligand and a platinum atom.[19] Recently, several research groups have reported the synthesis and antitumor activity evaluation of the platinum complexes with a seven-membered ring structure between a bidentate carrier ligand and a platinum atom such as ((*R*)-2-methyl-1,4-butanediamine) (1,1-cyclobutane dicarboxylato)platinum(II)(NK-121), *cis*-[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane](malonato)-platinum(II) (SKI-2053R), and *cis*-[*trans*-1,2-cyclobutanebis(methylamine)][(*S*)-lactato-O^1,O^2] platinum(II) (lobaplatin).[18] In addition, we have recently reported a series of D- and DL-camphorate platinum complexes which possess (4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane carrier ligand.[20a] These studies indicate that such a type of platinum complex displays desirable antitumor activity and sufficient stability in aqueous solution.[15,20–22]

On the basis of these findings, we have designed and synthesized a new series of chiral 2-alkoxy-1,4-butanedi-

Keywords: Platinum (II) complexes; Antitumor drugs; Chiral 2-alkoxy-1,4-butanediamine.
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doi:10.1016/j.bmcl.2005.08.025

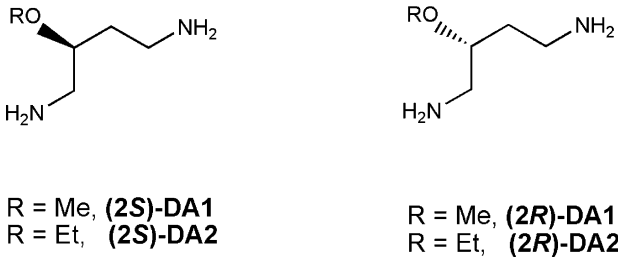


Figure 1. Structures of (2*S*)- and (2*R*)-2-alkoxyl-1,4-butanediamine (**DA1**, **DA2**).

amine compounds that are represented by the general structural formulas given below (Fig. 1). Then, these chiral 2-alkoxy-1,4-butanediamine compunds were applied to prepare target platinum (II) complexes.

This article describes synthesis and in vitro cytotoxicity evaluation together with their structure–activity relationships of a series of novel chiral 2-alkoxy-1, 4-butanediamine platinum (II) complexes which have a seven-membered ring structure between a bidentate carrier ligand and a platinum atom. All the target platinum compound structural formulas are represented in Figure 2. The result showed that the incorporation of oxygen in the diamino moiety of the platinum complexes enhances water solubility.

The procedure for synthesis of 2-alkoxy-1,4-butanediamine is outlined in Scheme 1. Starting from malic acid, malate (**I**) was prepared by refluxing with ethanol under acidic condition. Alkoxy substituted malate, **IIa** and **IIb**, were prepared according to the literature.[23] Key intermediate 1,4-diol, **IIIa** and **IIIb**, were conveniently obtained by $LiAlH_4$ reduction of **IIa** and **IIb** in THF[24] and then directly transformed by standard methods (tosylation and reaction with sodium azide in DMF) into diazide (**V**).[25,26] The diazide (**V**) was directly used to undergo catalytical hydrogenation in the presence of 10% Pd/C[27] to get the corresponding diamine (**VI**) without purification. Finally, **VI** was transformed to the corresponding salt of hydrochloric acid.[28] Recrystallization of the salt with ethanol afforded pure white

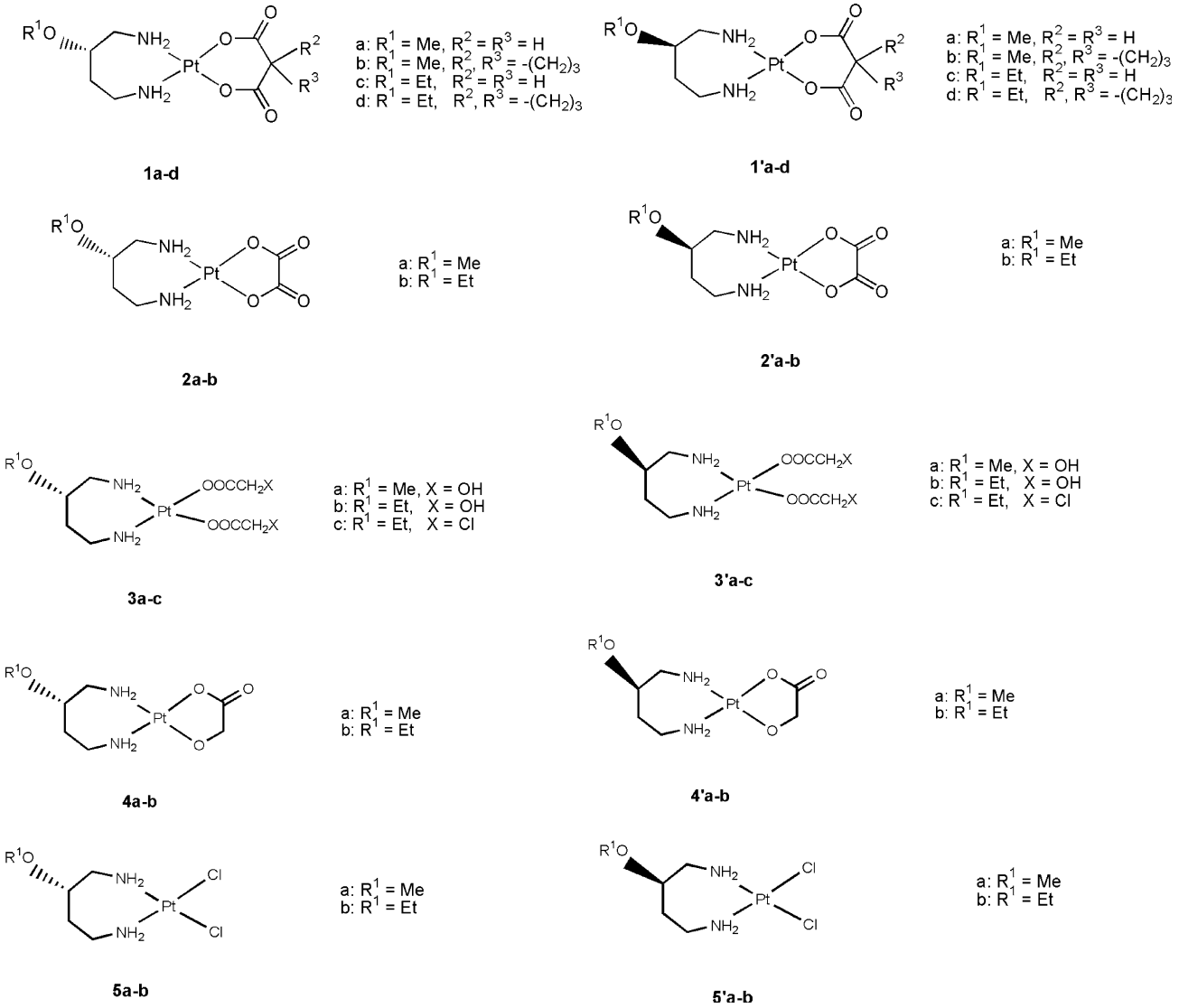
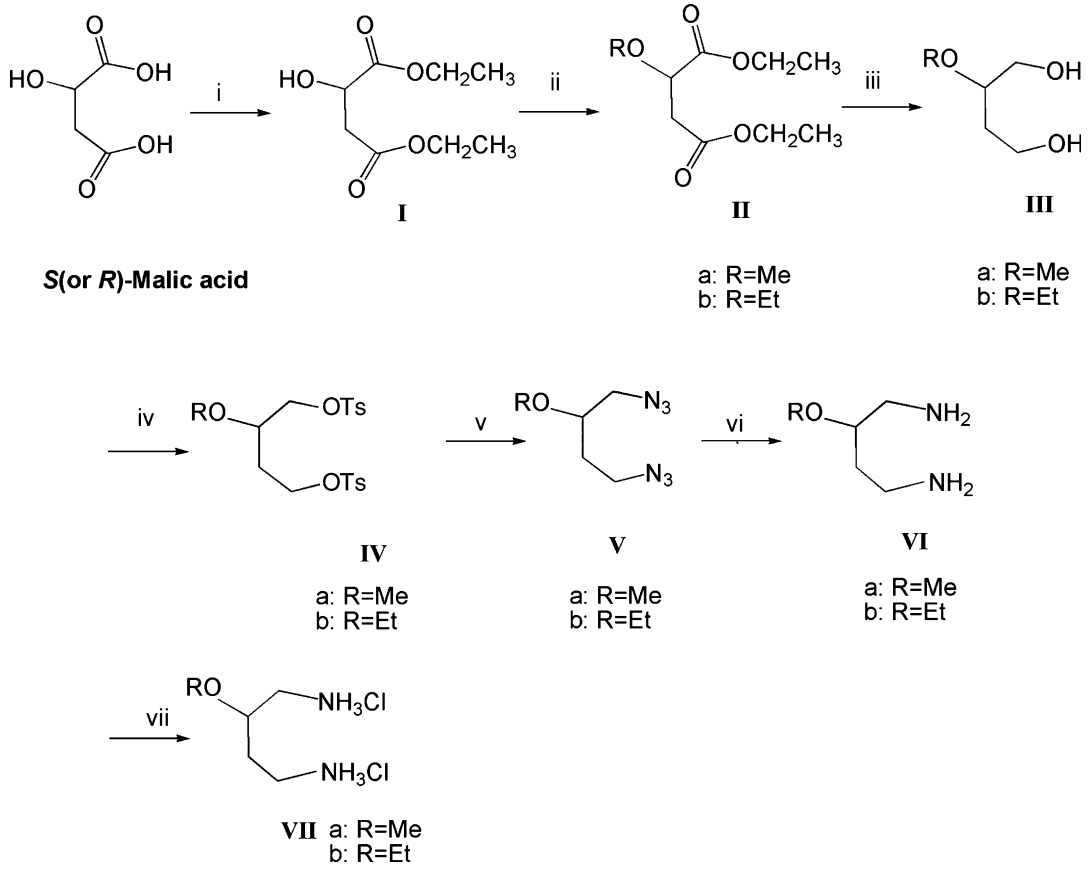


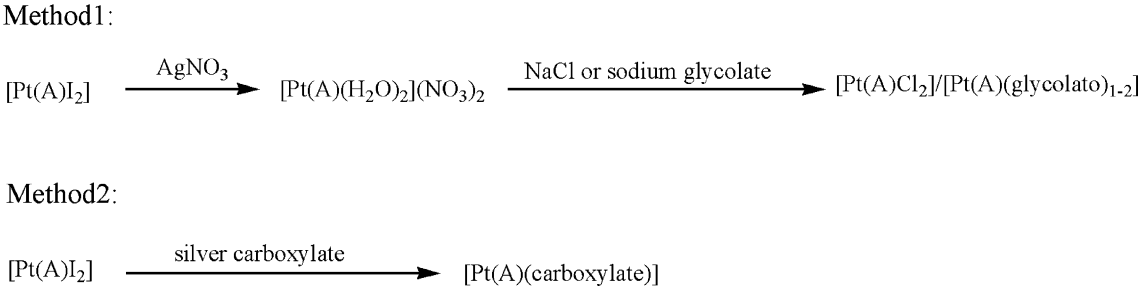
Figure 2. Structures of platinum (II) complexes **1a**–**5′b**.



Scheme 1. Synthesis of 2-methoxy-1,4-butanediamine (**VIIa**) and 2-ethoxy-1,4-butanediamine (**VIIb**) from *R* (or *S*)-malic acid. Reagents and conditions: (i) 98% H_2SO_4, reflux 20 h, 80%; (ii) (a) Ag_2O, MeI, reflux 6 h, 87%; (b) Ag_2O, EtI, reflux 6 h, 83%; (iii) $LiAlH_4$, THF; (iv) (a) *p*-toluenesulfonyl, pyridine, 0 °C, 50%; (b) *p*-toluenesulfonyl, pyridine, 0 °C, 56%; (v) NaN_3, DMF, reflux 8 h; (vi) 5% Pd/C, 76 atm H_2, EtOH; (vii) (a) HCl, acetone, 54%.

crystalline powders. Transformation of **IV** to **VII** was achieved in 54% (for **VIIa**) and 60% (for **VIIb**) overall yields, without purification of intermediate **V**. All key compounds were characterized by means of IR, ^1H NMR, and ESI mass spectra as well as elemental analyses. As expected, all intermediates derived from the starting material of (*R*)-malic acid have the same physical properties as those from (*S*)-malic acid, except for a nearly opposite optical rotation.

The general procedure for preparation of chiral 2-alkoxy-1,4-butanediamine platinum (II) complexes is shown in Scheme 2. First, potassium tetrachloroplatinate (II) was converted to potassium tetraiodoplatinate (II), which was subsequently treated with diamine to form a diamine–diiodoplatinum (II) complex[Pt(A)I_2] according to the literature method.[29] Then, two kinds of general methods have been applied to prepare the target platinum complexes containing 2-alkoxy-1,4-butanediamine, which are described in Scheme 2. One is involved in the treatment of [Pt(A)$(H_2O)_2$]$(NO_3)_2$ with sodium glycolate or sodium chloride,[29] the other is concerned with the reaction of [Pt(A) I_2] with silver carboxylate.[30,31] Complexes **3a–b**, **3′a–b**, **4a–b**, **4′a–b**, **5a–b**, and **5′a–b** with lower water solubility have been prepared in better yield by using method 1.[32] On the other hand, complexes **1a–d**, **1′a–d**, **2a–b**, **2′a–b**, **3c**, and **3′c** with higher water solubility have been got in



Scheme 2. General method for the synthesis of the platinum (II) complexes.

Table 1. Analytical data of all platinum (II) complexes

Platinum (II) complexes	Results and analytical data
cis-(Malonato)[(2*S*)-methoxy-1,4-butanediamine] platinum (II) (**1a**) *cis*-(Malonato)[(2*R*)-methoxy-1,4-butanediamine] platinum (II) (**1′a**)	**1a**: Yield 12.0%; white powder; IR (KBr) 3441 (m, br), 3219 (m), 3128 (m), 3155 (m), 2947 (w), 1627 (vs), 1387 (s), 1288 (w), 1240 (m), 1227 (m), 1094 (m) cm^{-1}. ^1H NMR (500 MHz, D_2O): δ 3.93 (m, 1H, 1H of CH of 1,4-diamines), 3.59 (m, 2H, 2H of CH_2 of malonato), 3.26 (m, 3H, 3H of CH_3 of 1,4-diamines), 2.85 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 2.73–2.67 (m, 2H, 2H of $CHCH_2NH_2$ of 1, 4-diamines), 2.15 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines). ESI-MS *m/z* $[M+Na]^+$ = 438 (100%). Anal. Calcd for $C_8H_{16}N_2O_5Pt$: C, 23.14; H, 3.88; N, 6.75. Found: C, 23.32; H, 3.76; N, 6.68. **1′a**: Yield 24.1%; white powder; spectral data were identical with that of **1a**.
cis-(Cyclobutane-1,1-dicarboxylato)[(2*S*)-methoxy-1,4-butanediamine]platinum (II) (**1′b**) *cis*-(Cyclobutane-1,1-dicarboxylato)[(2*R*)-methoxy-1,4-butanediamine]platinum (II) (**1′b**)	**1b**: Yield 32.5%; white powder; IR (KBr) 3445 (m, br), 3229 (s), 3138 (m), 2947 (w), 1627 (vs), 1459 (w), 1384 (vs), 1252 (w), 1221 (m), 1115 (m), 1096 (m) cm^{-1}. ^1H NMR (500 MHz, D_2O): δ 3.82 (m, 1H, 1H of CH of 1,4-diamines), 3.27 (m, 3H, 3H of CH_3 of 1,4-diamines), 2.87 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 2.82–2.71 (m, 6H, 2H of $CHCH_2NH_2$ of 1,4-diamines overlapped with 4H of $CH_2CH_2CH_2$ of cyclobutane-1,1-dicarboxylato), 2.15 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 1.77 (m, 2H, 2H of $CH_2CH_2CH_2$ of cyclobutane-1,1-dicarboxylato). ESI-MS *m/z* $[M+Na]^+$ = 478 (100%). Anal. Calcd for $C_{11}H_{20}N_2O_5Pt$: C, 29.01; H, 4.43; N, 6.15. Found: C, 29.35; H, 4.31; N, 6.04. **1′b**: Yield 28.6%; white powder; spectral data were identical with that of **1b**.
cis-(Malonato)[(2*S*)-ethoxy-1,4-butanediamine] platinum (II) (**1c**) *cis*-(Malonato)[(2*R*)-ethoxy-1,4-butanediamine] platinum (II) (**1′c**)	**1c**: Yield 31.5%; white powder; IR (KBr) 3441 (m, br), 3219 (m), 3128 (m), 3155 (m), 2947 (w), 1627 (vs), 1387 (s), 1288 (w), 1240 (m), 1227 (m), 1094 (m) cm^{-1}. ^1H NMR (500 MHz, D_2O): δ 3.95 (m, 1H, 1H of CH of 1,4-diamines), 3.56–3.49 (m, 4H, 2H of CH_2CH_3 of 1, 4-diamines overlapped with 2H of CH_2 of malonate), 2.85–2.68 (m, 4H, 4H of $2CH_2NH_2$ of 1,4-diamines), 2.12 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 1.07 (m, 3H, 3H of CH_2CH_3 of 1,4-diamines). ESI-MS *m/z* $[M+H]^+$ = 430 (100%). Anal. Calcd for $C_9H_{18}N_2O_5Pt$: C, 25.18; H, 4.23; N, 6.52. Found: C, 25.37; H, 4.01; N, 6.39. **1′c**: Yield 24.5%; white powder; spectral data were identical with that of **1c**.
cis-(Cyclobutane-1,1-dicarboxylato)[(2*S*)-ethoxy-1,4-butanediamine]platinum (II) (**1d**) *cis*-(Cyclobutane-1,1-dicarboxylato)[(2*R*)-ethoxy-1,4-butanediamine]platinum(II) (**1′d**)	**1d**: Yield 23.4%; white powder; IR (KBr) 3454 (br), 3237 (sharp), 3109 (m), 2967 (w), 1654 (vs), 1614 (vs), 1374 (vs), 1225 (w), 1112 (m), 1098 (m) cm^{-1}. ^1H NMR (500 MHz, D_2O): δ 3.94 (m, 1H, 1H of CH of 1,4-diamines), 3.46 (m, 2H, 2H of CH_2CH_3 of 1,4-diamines), 2.86–2.66 (m, 8H, 4H of $2CH_2NH_2$ of 1,4-diamines overlapped with 4H of $CH_2CH_2CH_2$ of cyclobutane-1,1-dicarboxylato), 2.07–2.02 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 1.73 (m, 2H, 2H of $CH_2CH_2CH_2$ of cyclobutane-1,1-dicarboxylato), 1.02 (m, 3H, 3H of CH_2CH_3 of 1,4-diamines). ESI-MS *m/z* $[M+Na]^+$ = 492 (100%). Anal. Calcd for $C_{12}H_{22}N_2O_5Pt$: C, 30.71; H, 4.72; N, 5.97. Found: C, 30.92; H, 4.65; N, 5.91. **1′d**: Yield 23.4%; white powder; spectral data were identical with that of **1d**.
cis-(Oxalato)[(2*S*)-methoxy-1,4-butanediamine] platinum (II) (**2a**) *cis*-(Oxalato)[(2*R*)-methoxy-1,4-butanediamine] platinum (II) (**2′a**)	**2a**: Yield 24.9%; white powder; IR (KBr) 3451 (m, br), 3238 (m), 3193 (m), 3155 (m), 2977 (w), 1692 (s), 1668 (vs), 1388 (s), 1095 (m) cm^{-1}. ^1H NMR (500 MHz, D_2O): δ 3.83 (m, 1H, 1H of CH of 1,4-diamines), 3.24 (m, 3H, 3H of CH_3 of 1,4-diamines), 2.84 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 2.75–2.67 (m, 2H, 2H of $CHCH_2NH_2$ of 1,4-diamines), 2.17–2.10 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1, -diamines). ESI-MS *m/z* $[M+Na]^+$ = 424 (100%). Anal. Calcd for $C_7H_{14}N_2O_5Pt$: C, 20.95; H, 3.52; N, 6.98. Found: C, 21.09; H, 3.48; N, 6.82. **2′a**: Yield 33.7%; white powder; spectral data were identical with that of **2a**.
cis-(Oxalato)[(2*S*)-ethoxy-1,4-butanediamine] platinum (II) (**2b**) *cis*-(Oxalato)[(2*R*)-ethoxy-1,4-butanediamine] platinum (II) (**2′b**)	**2b**: Yield 31.3%; white powder; IR (KBr) 3411 (m, br), 3208 (s), 3112 (m), 3155 (m), 2965 (w), 2921 (w), 1694 (s), 1672 (vs), 1398 (s), 1189 (m), 1098 (m) cm^{-1}. ^1H NMR (500 MHz, D_2O): δ 3.96 (m, 1H, 1H of CH of 1,4-diamines), 3.45 (m, 2H, 2H of CH_2CH_3 of 1, 4-diamines), 2.85–2.64 (m, 4H, 4H of $2CH_2NH_2$ of 1,4-diamines), 2.17–2.03 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 1.03 (m, 3H, 3H of CH_2CH_3 of 1,4-diamines). ESI-MS *m/z* $[M+Na]^+$ = 38 (100%). Anal. Calcd for $C_8H_{16}N_2O_5Pt$: C, 23.14; H, 3.88; N, 6.75. Found: C, 23.30; H, 3.79; N, 6.71. **2′b**: Yield 18.1%; white powder; spectral data were identical with that of **2b**.
cis-di(Glycolato)[(2*S*)-methoxy-1,4-butanediamine] platinum (II) (**3a**) *cis*-di(Glycolato)[(2*R*)-methoxy-1,4-butanediamine] platinum (II) (**3′a**)	**3a**: Yield 38.9%. ^1H NMR (500 MHz, D_2O): δ 4.00–3.94 (m, 4H, 4H of $2CH_2$ of glycolato), 3.88 (m, 1H, 1H of CH of 1,4-diamines), 3.28 (m, 3H, 3H of CH_3 of 1,4-diamines), 2.88–2.86 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 2.78–2.66 (m, 2H, 2H of $CHCH_2NH_2$ of 1, 4-diamines), 2.26–2.18 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines). ESI-MS *m/z* $[M+Na]^+$ = 486 (100%);$[M-OCOCH_2OH+H_2O]^+$ = 406 (80%). Anal. Calcd for $C_9H_{20}N_2O_7Pt$: C, 23.33; H, 4.35; N, 6.05. Found: C, 23.47; H, 4.29; N, 5.98. **3′a**: Yield 34.6%; spectral data were identical with that of **3a**.
cis-di(Glycolato)[(2*S*)-ethoxy-1,4-butanediamine] platinum (II) (**3b**) *cis*-di(Glycolato)[(2*R*)-ethoxy-1, 4-butanediamine] platinum (II) (**3′b**)	**3b**: Yield 25.1%. ^1H NMR (500 MHz, D_2O): δ 4.12–3.93 (m, 5H, 1H of CH of 1,4-diamines overlapped with 4H of $2CH_2$ of glycolato), 3.57–3.45 (m, 2H, 2H of CH_2CH_3 of 1,4-diamines), 2.89–2.81 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 2.72–2.68 (m, 2H, 2H of $CHCH_2NH_2$ of 1,4-diamines), 2.25–2.15 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 1.11–1.08 (m, 3H, 3H of CH_2CH_3 of 1,4-diamines). ESI-MS *m/z* $[M-OCOCH_2OH+H_2O]^+$ = 420 (10%); $[M+Na]^+$ = 500 (80%). Anal. Calcd for $C_{10}H_{22}N_2O_7Pt$: C, 25.16; H, 4.65; N, 5.87. Found: C, 25.29; H, 4.60; N, 5.82. **3′b**: Yield 30.1%; spectral data were identical with that of **3b**.

(*continued on next page*)

Table 1 (*continued*)

Platinum (II) complexes	Results and analytical data
cis-di(Chloroacetate)[(2*S*)-ethoxy-1,4-butanediamine] platinum (II) (**3c**) *cis*-di(Chloroacetate)[(2*R*)-ethoxy-1,4-butanediamine] platinum (II) (**3′c**)	**3c**: Yield 11.6%. ^{1}H NMR (500 MHz, D_2O): δ 4.11–3.90 (m, 5H, 1H of CH of 1,4-diamines overlapped with 4H of $2CH_2$ of chloroacetate), 3.51–3.44 (m, 2H, 2H of CH_2CH_3 of 1,4-diamines), 2.86–2.77 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 2.69–2.67 (m, 2H, 2H of $CHCH_2NH_2$ of 1,4-diamines), 2.26–2.10 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 1.08–1.04 (m, 3H, 3H of CH_2CH_3 of 1,4-diamines). ESI-MS *m*/*z* $[M-OCOCH_2Cl+H_2O]^+$ = 438 (100%). Anal. Calcd for $C_{10}H_{20}Cl_2N_2O_5Pt$: C, 23.36; H, 3.92; N, 5.45. Found: C, 23.50; H, 3.89; N, 5.41. **3′c**: Yield 16.5%; spectral data were identical with that of **3c**.
cis-(Glycolato)[(2*S*)-methoxy-1,4-butanediamine] platinum (II) (**4a**) *cis*-(Glycolato)[(2*R*)-methoxy-1,4-butanediamine] platinum (II) (**4′a**)	**4a**: Yield 34.9%. ^{1}H NMR (500 MHz, D_2O): δ 4.11–4.10 (m, 2H, 2H of CH_2 of glycolato), 3.94 (m, 1H, 1H of CH of 1,4-diamines), 3.39 (m, 3H, 3H of CH_3 of 1,4-diamines), 3.02–2.95 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 2.91–2.79 (m, 2H, 2H of $CHCH_2NH_2$ of 1,4-diamines), 2.35–2.20 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines). ESI-MS *m*/*z* $[M+Na]^+$ = 410 (100%). Anal. Calcd for $C_7H_{16}N_2O_4Pt$: C, 21.71; H, 4.16; N, 7.23. Found: C, 21.87; H, 4.02; N, 7.12. **4′a**: Yield 20.7%; spectral data were identical with that of **4a**.
cis-(Glycolato)[(2*S*)-ethoxy-1,4-butanediamine] platinum (II) (**4b**) *cis*-(Glycolato)[(2*R*)-ethoxy-1, 4-butanediamine] platinum (II) (**4′b**)	**4b**: Yield 21.2%. ^{1}H NMR (500 MHz, D_2O): δ 4.05–3.96 (m, 3H, 2H of CH_2 of glycolato overlapped with 1H of CH of 1,4-diamines), 3.51–3.47 (m, 2H, 2H of CH_2CH_3 of 1,4-diamines), 2.83–2.76 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 2.67–2.66 (m, 2H, 2H of $CHCH_2NH_2$ of 1,4-diamines), 2.18–2.17 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 1.06–1.03 (m, 3H, 3H of CH_2CH_3 of 1,4-diamines). ESI-MS *m*/*z* $[M+H]^+$ = 402 (100%). Anal. Calcd for $C_8H_{18}N_2O_4Pt$: C, 23.94; H, 4.52; N, 6.98. Found: C, 24.11; H, 4.37; N, 6.85. **4′b**: Yield 31.2%; spectral data were identical with that of **4b**.
cis-Dichloro[(2*S*)-methoxy-1,4-butanediamine] platinum (II) (**5a**) *cis*-Dichloro[(2*R*)-methoxy-1, 4-butanediamine] platinum (II) (**5′a**)	**5a**: Yield 26.0%; IR (KBr) 3448 (m, br), 3229 (s), 3202 (s), 3131 (m), 3061 (m), 2931 (m), 1595 (m), 1561 (m), 1461 (w), 1330 (m), 1227 (s), 1212 (s), 1107 (s), 1095 (s) cm^{-1}. ^{1}H NMR (500 MHz, D_2O): δ 3.91 (m, 1H, 1H of CH of 1,4-diamines), 3.25 (m, 3H, 3H of CH_3 of 1, -diamines), 2.85 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 2.77–2.68 (m, 2H, 2H of $CHCH_2NH_2$ of 1,4-diamines), 2.25–2.22 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines). ESI-MS *m*/*z* $[M-Cl^-+H_2O]^+$ = 366 (100%). Anal. Calcd for $C_5H_{14}Cl_2N_2OPt$: C, 15.63; H, 3.67; N, 7.29. Found: C, 15.78; H, 3.59; N, 7.21. **5′a**: Yield 27.3%; spectral data were identical with that of **5a**.
cis-Dichloro[(2*S*)-ethoxy-1,4-butanediamine] platinum (II) (**5b**) *cis*-Dichloro[(2*R*)-ethoxy-1,4-butanediamine] platinum (II) (**5′b**)	**5b**: Yield 25.1%; IR (KBr) 3444 (m, br), 3255 (s), 3220 (s), 3177 (m), 2971 (w), 1601 (m), 1449 (w), 1384 (vs), 1210 (m), 1184 (m), 1094 (m). ^{1}H NMR (500 MHz, D_2O): δ 4.04 (m, 1H, 1H of CH of 1,4-diamines), 3.48 (m, 2H, 2H of CH_2CH_3 of 1,4-diamines), 2.83 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1,4-diamines), 2.76–2.64 (m, 2H, 2H of $CHCH_2NH_2$ of 1,4-diamines), 2.22–2.06 (m, 2H, 2H of $CH_2CH_2NH_2$ of 1, 4-diamines), 1.10 (m, 3H, 3H of CH_2CH_3 of 1,4-diamines). ESI-MS *m*/*z* $[M-Cl^-+H_2O]^+$ = 381 (100%). Anal. Calcd for $C_6H_{16}Cl_2N_2OPt$: C, 18.10; H, 4.05; N, 7.04. Found: C, 18.23; H, 3.98; N, 6.95. **5′b**: Yield 27.6%; spectral data were identical with that of **5b**.

better crop by using method 2.[33] Most of the complexes described in our paper have good aqueous solubility, except for **5a**, **5b**, **5′a**, and **5′b**. In particular, complexes **3a–3c**, **3′a–3′c**, **4a–4b**, and **4′a–4′b** were too hygroscopic to be characterized by infrared spectra. All the resulting complexes were confirmed by ^{1}H NMR and ESI mass spectra data listed in Table 1. It is noted that all the mass spectra of the platinum complexes showed three protonated molecular ion peaks because of the isotopes ^{194}Pt(33%,), ^{195}Pt(34%), and ^{196}Pt(25%). All spectral data are compatible to the chemical structures given in Figure 2.

The in vitro cytotoxicities of 21 novel platinum complexes such as **1a**, **1′a**, **1b**, **1′b**, **1c**, **1′c**, **1d**, **1′d**, **2a**, **2′a**, **2b**, **2′b**, **3a**, **3′a**, **3′b**, **3′c**, **4b**, **5a**, **5′a**, **5b**, and **5′b** toward A549 human non-small cell lung carcinoma and HCT-116 human colon cancer cell lines were performed by the National Center for Drug Screening.[34–36] Complexes **3a–c**, **3′a–3′c**, **4a–b**, and **4′a–4′b** were so strongly hygroscopic and unstable that only part of them was selected to evaluate. The references were cisplatin and carboplatin in A549, and oxaliplatin in HCT-116, respectively. The results are summarized in Tables 2 and 3.

The order of the cytotoxicities in A549 is cisplatin > **5′b > 5b > 2b > 3′c > 5a>4b > 5′a > 2′b > 3a > 2a > 1c > 1′a > 2′a** > carboplatin > **3′b > 1a > 1′c > 1′b > 1d > 1′d > 3′a > 1b**. The order of the cytotoxicities in HCT116 is oxaliplatin > **5′b > 5a > 5b > 2b > 5′a > 2′b > 3′c > 4b > 1c > 2a > 2′a > 3′b > 1a > 1′a > 1′c > 3a > 1′d > 1d > 1′b > 3′a > 1b**.

In general, the complexes with diamines of *R* or *RR* absolute configuration are slightly more active than the complexes with the corresponding diamines owning *S*, *SS* or *RS* configuration.[37] But in this series, most platinum complexes having a chiral (2*S*)-methoxy or (2*S*)-ethoxy bidentate diamine moiety are more active than those with (2*R*)-methoxy or (2*R*)-ethoxy diamine counterparts, such as **1c > 1′c**, **1d > 1′d**, **2a > 2′a**, **2b > 2′b**, **3a > 3′a**, and **5a > 5′a** in A549, and **1a > 1′a**, **1c > 1′c**, **2a > 2′a**, **2b > 2′b**, **3a > 3′a**, and **5a > 5′a** in HCT116. However, among these compounds, there are some exceptions, for example **1a < 1′a**, **1b < 1′b**, and **5b < 5′b** in A549, and **1b < 1′b**, **1d < 1′d**, and **5b < 5′b** in HCT116.

From the biological results, it is showed that most of platinum complexes with (2*S*)-ethoxy or (2*R*)-ethoxy diamine carrier ligand generally have higher cytotoxicity than those with the corresponding (2*S*)-methoxy or (2*R*)-methoxy carrier ligand, such as **1c > 1a**, **1d > 1b**, **2b > 2a**, **5b > 5a**, **2′b > 2′a**, **3′b > 3′a**, and **5′b > 5′a** in A549, and **1c > 1a**, **1d > 1b**, **2b > 2a**, **1′d > 1′b**, **2′b > 2′a**, **3′b > 3′a**, and **5′b > 5′a** in HCT116. But there are some exceptions, for example **1′c < 1′a**, **1′d < 1′b** in A549, and **1′c < 1′a**, **5b < 5a** in HCT116.

The cytotoxicities of platinum complexes are also related to the nature of the leaving group. It is showed that the same rule in HCT116 is dichloro > oxalato > malonato > cyclobutane-1,1-dicarboxylato when the carrier ligand was the same. It is also showed that the same rule in A549 is dichloro >

Table 2. In vitro cytotoxicity against A549 human non-small cell lung carcinoma cell lines of selected platinum complexes[a]

Complex	Carrier ligand (diamino)	Leaving group	IC_{50} (μM)
1a	*S*-meo[b]	Malonato	8.74
1′a	*R*-meo[c]	Malonato	5.59
1b	*S*-meo[b]	Cyclobutane-1,1-dicarboxylato	64.12
1′b	*R*-meo[c]	Cyclobutane-1,1-dicarboxylato	12.87
1c	*S*-eto[d]	Malonato	4.40
1′c	*R*-eto[e]	Malonato	9.76
1d	*S*-eto[d]	Cyclobutane-1,1-dicarboxylato	24.18
1′d	*R*-eto[e]	Cyclobutane-1,1-dicarboxylato	26.42
2a	*S*-meo[b]	Oxalato	3.79
2′a	*R*-meo[c]	Oxalato	5.81
2b	*S*-eto[d]	Oxalato	1.71
2′b	*R*-eto[e]	Oxalato	3.08
3a	*S*-meo[b]	Di(glycolato)	3.37
3′a	*R*-meo[c]	Di(glycolato)	34.32
3′b	*R*-eto[e]	Di(glycolato)	7.60
3′c	*R*-eto[e]	Di(chloroacetato)	1.73
4b	*S*-eto[d]	Glycolato	2.14
5a	*S*-meo[b]	Dichloro	1.80
5′a	*R*-meo[c]	Dichloro	2.63
5b	*S*-eto[d]	Dichloro	0.90
5′b	*R*-eto[e]	Dichloro	0.83
Cisplatin			0.30
Carboplatin			6.95

[a] All IC_{50} values calculated based on the Pt-content are means ± SD < ±3.0 ~10 from at least three separate experiments.
[b] *S*-meo: (2*S*)-methoxy-1,4-butanediamine.
[c] *R*-meo: (2*R*)-methoxy-1,4-butanediamine.
[d] *S*-eto: (2*S*)-ethoxy-1,4-butanediamine.
[e] *R*-eto: (2*R*)-ethoxy-1,4-butanediamine.

Table 3. In vitro cytotoxicity against HCT-116 human colon cancer cell lines of selected platinum complexes[a]

Complex	Carrier ligand (diamino)	Leaving group	IC_{50} (μM)
1a	*S*-meo[b]	Malonato	25.04
1′a	*R*-meo[c]	Malonato	28.00
1b	*S*-meo[b]	Cyclobutane-1,1-dicarboxylato	219.61
1′b	*R*-meo[c]	Cyclobutane-1,1-dicarboxylato	168.88
1c	*S*-eto[d]	Malonato	12.65
1′c	*R*-eto[e]	Malonato	30.75
1d	*S*-eto[d]	Cyclobutane-1,1-dicarboxylato	115.26
1′d	*R*-eto[e]	Cyclobutane-1,1-dicarboxylato	109.29
2a	*S*-meo[b]	Oxalato	15.62
2′a	*R*-meo[c]	Oxalato	15.90
2b	*S*-eto[d]	Oxalato	6.33
2′b	*R*-eto[e]	Oxalato	7.42
3a	*S*-meo[b]	Di(glycolato)	55.90
3′a	*R*-meo[c]	Di(glycolato)	215.82
3′b	*R*-eto[e]	Di(glycolato)	23.67
3′c	*R*-eto[e]	Di(chloroacetato)	8.69
4b	*S*-eto[d]	Glycolato	11.04
5a	*S*-meo[b]	Dichloro	2.03
5′a	*R*-meo[c]	Dichloro	6.87
5b	*S*-eto[d]	Dichloro	2.69
5′b	*R*-eto[e]	Dichloro	1.78
Oxaliplatin			1.28

[a] All IC_{50} values calculated based on the Pt-content are means ± SD < ±3.0 ~10 from at least three separate experiments.
[b] *S*-meo: (2*S*)-methoxy-1,4-butanediamine.
[c] *R*-meo: (2*R*)-methoxy-1,4-butanediamine.
[d] *S*-eto: (2*S*)-ethoxy-1,4-butanediamine.
[e] *R*-eto: (2*R*)-ethoxy-1,4-butanediamine.

oxalato > malonato > cyclobutane-1,1-dicarboxylato when the carrier ligand was the same such as (2*S*)-ethoxy, (2*R*)-ethoxy, and (2*S*)-methoxy bidentate diamine. One exception in A549 was dichloro > malonato > oxalato > cyclobutane-1,1-dicarboxylato for platinum complex with (2*R*)-methoxy bidentate diamine.

Complex **5′b** exhibits the greatest potency among these 21 tested platinum complexes in both two cell lines. Considering its good cytotoxicity and high stability in aqueous solution, complex **5′b** will be selected as a promising candidate for further development.

Acknowledgments

The authors are grateful to the National Natural Science Foundation of China (projects: 20471027 and 20391001) and Jiangsu Province Science and Technology Department (projects: BK2004413 and BE2004614) for financial supports.

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33. General procedure (method 1) for the synthesis of complexes **3a–b**, **3′a–b**, **4a–b**, **4′a–b**, **5a–b**, and **5′a–b**. To a stirred suspension of diiodoplatinum (II) complex (2.0 mmol) in H_2O (30 ml) was added a solution of $AgNO_3$ (4.0 mmol) in H_2O (20 ml). Under the nitrogen atmosphere the mixture was heated at 40 °C for 24 h in the dark and filtered though a pad of Celite. Then disodium glycolate (2.0 mmol), sodium chloride (4.0 mmol) or sodium glycolate (4.0 mmol) aqueous solution was added to the above filtration. The resultant solution was then mixed with the above filtration and stirred at 40 °C for 24 h. The reaction mixture was concentrated and ethanol was added before filtration. The filtrate was concentrated to afford yellow syrup, which gave a precipitate after addition of ether. The resulting precipitate was then filtered quickly to give a very hygroscopic solid.
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