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

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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-

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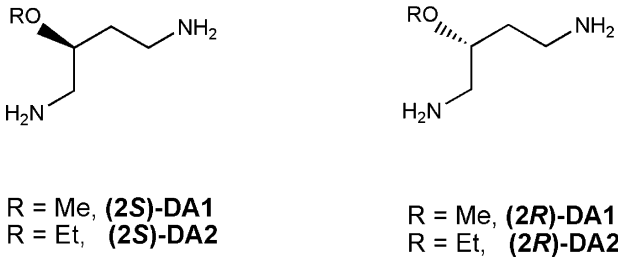

Figure 1. Structures of (2*S*)- and (2*R*)-2-alkoxyl-1,4-butanediamine (**DA1**, **DA2**).

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

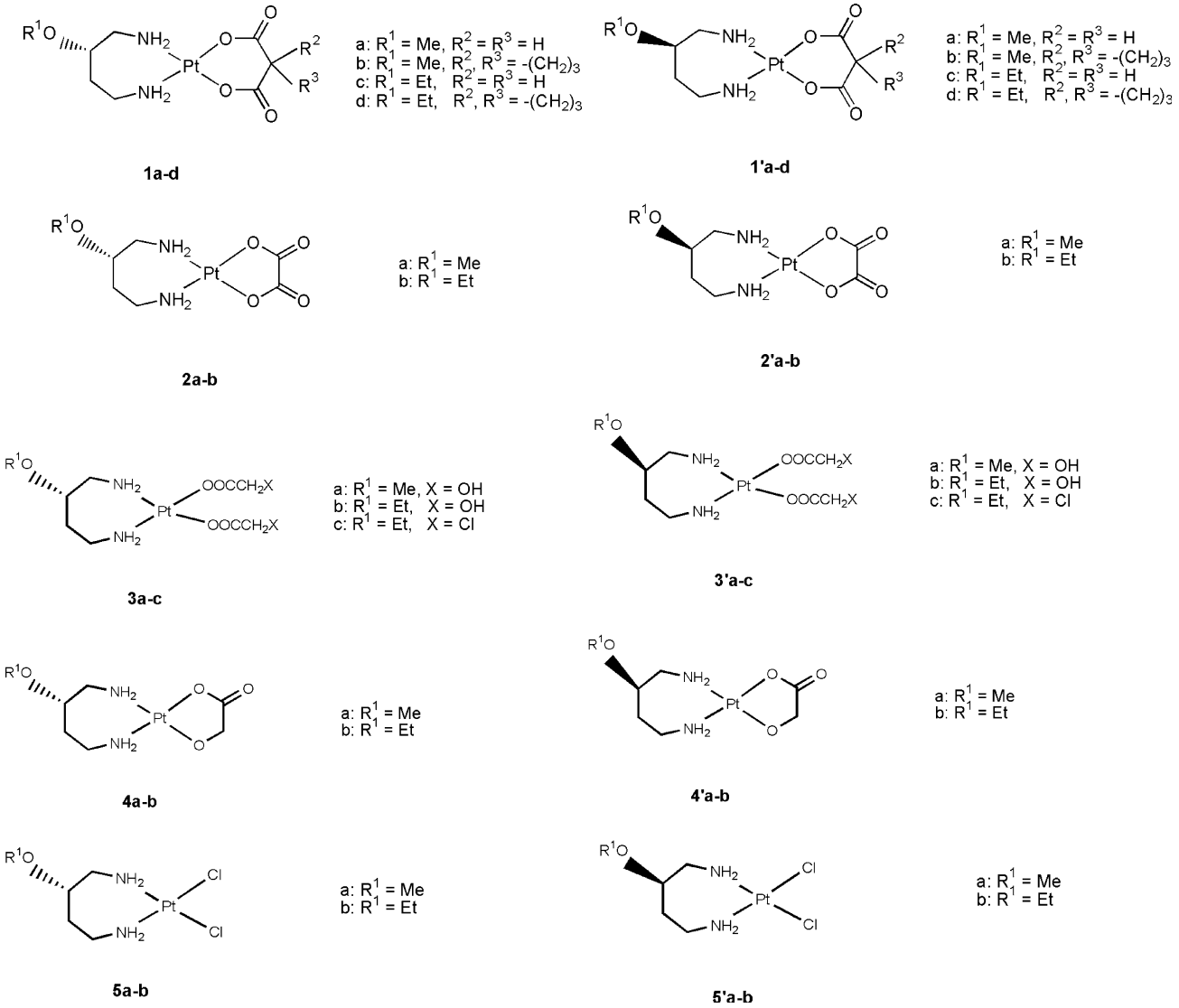

Figure 2. Structures of platinum (II) complexes **1a**–**5′b**.