Synthesis and Anticancer Effect for Cisplatin Like Pt(II) Complexes Involving Phosphonate Group

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Clinically used anticancer Pt(II) complexes such as cisplatin, carboplatin, oxaliplatin, nedaplatin are commonly found 2N and 2Cl or 2O(carboxylate and alchohol) as coordination atoms. These Cl and O containing groups called "Leaving Group" were less importance because these drugs have been believed to work (attack DNA) after dissociation of the leaving group. However, cisplatin and carboplatin are clinically difference. This means anticancer platinum drugs may also work before dissociation of the leaving group. Here we report the usefulness of the Pt(II) complexes involvingwith the bidentate chelate-type phosphonate ligand (Fig. 1).

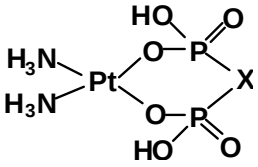

Fig. 1 New Pt(II) complex

Methylenediphosphonate (MDP) and pyrophophate (PP) are simple bidentate ligands involving two phosphonates and form stable 6-membered rings in *cis*-diammine Pt(II) complexes, $Pt(NH_3)_2$(MDP) and $Pt(NH_3)_2$(PP) which were prepared by Ag^+ method. *pKa* for $Pt(NH_3)_2$(MDP) at 25°C, I = 0.1(KNO_3) were determined as pKa_1 3.84, pKa_2 5.82. Half live time ($t_{1/2}$) of the Pt(II) complex in H_2O was evaluated: $Pt(NH_3)_2$(MDP), 193 hr; $Pt(NH_3)_2$(PP), 300 hr. This indicated Pt(II) complexes containing chelated phosphonates were stable for hydrolysis. IC_{50} in human cancer cell line showed the order : cisplatin > $Pt(NH_3)_2$(PP) > $Pt(NH_3)_2$(MDP) > carboplatin . These showed usefulness of these new Pt(II) complexes as an anticancer drug though these present a form of -2 anion in neutral solution.

Good assay of Pt(NH3)2L (L = MDP, PP) indicated (1) possible new anticancer mechanism of Pt(II) complex with biological target before hydrolysis, (2) possible active transport of the phosphonate anion. In addition good adsorption of Pt(NH3)2(MDP) to hydroxyapatite (inorganic component of bone) exhibited (3) possible candidate of bone cancer, as cisplatin and carboplatin showed low adsorption.

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