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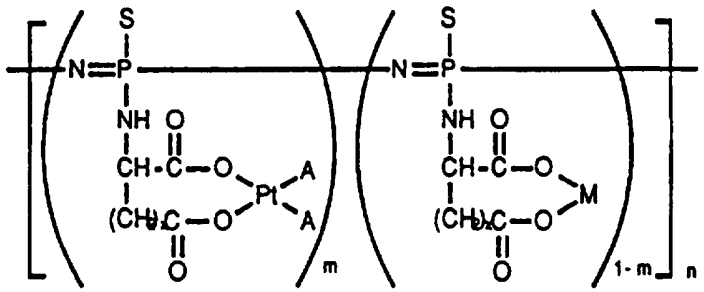
(57) Abstract

A novel polymeric platinum complex represented by formula (I), wherein S, A, x, m and n are defined as above, a process for prepartion thereof, and the use thereof as an anticancer agent.



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POLYMERIC PLATINUM COMPLEX, PREPARATION THEREOF, AND ANTICANCER AGENT COMPRISING THEREOF

TECHNICAL FIELD

The present invention relates to novel polymeric platinum complex derivatives, preparation thereof, and use thereof. More particularly, the present invention relates to controlled releasing platinum complex derivatives incorporated in polyphosphazene, preparation thereof, and use thereof as an anticancer agent.

Background of the Invention

Among the known anticancer agents, cisplatin [cis-$(NH_3)_2PtCl_2$], which was reported to exhibit high anticancer activity by Rogsenberg [B. Rosenberg, Nature 205, 698(1965)], was approved in 1979 by FDA of the United States as an anticancer agent, and has been used as one of the most effective chemotherapeutic agents against various cancers such as testicular cancer, ovarian cancer, bladder cancer, head and neck cancer or the like. However, the use of the drug is limited because of the high toxicity [LD_{50} = 13 mg/kg, M.J. Cleare, Biochimie 60, 835(1978)].

Meanwhile, carboplatin [cis-$(NH_3)_2Pt$(CBDCA), wherein CBDCA represents 1,1-dicyclobutanedicarboxylate], which was approved by FDA in 1989 and has been used as a second-generation anticancer agent, has much lower toxicity than that of cicplatin. However, it has lower and narrower anticancer activity as well as high price, so that it cannot be widely used either.

Therefore, extensive researches for developing a third-generation anticancer agent having higher anticancer activity and lower toxicity than those of cisplatin have been performed worldwide, but in spite of such a great deal of efforts, commercialization of a third generation anticancer drug has not been successful so far.

Requirements for the third-generation platinum anticancer agent are

excellent anticancer activity comparative to or higher than that of cisplatin and low toxicity comparative to that of carboplatin as well as wide therapeutic spectrum for the cancer treatment. In addition, it should have excellent activity to cancer cells resistant to cisplatin or carboplatin, showing no cross-resistance. Furthermore, the drug should have high water solubility and chemical stability. At present, ten or more candidate compounds are in clinical studies, but no drug has been successfully commercialized.

The anticancer activity and toxicity of the cisplatin analogs have not yet been clearly verified, but the research reports on this matter up to the present may be summarized as follows:

According to Pharmac. Ther. 25, 297 (1984) and Chem. Rev. 87, 1153 (1987), cisplatin administered into blood via intravenous injection or the like, exists mostly as neutral molecules without ionization because of the high chloride ion concentration (about 100 mM) in the blood plasma and easily diffuse through cell membrane. However, since the chloride ion concentration inside the cell is low(4 mM), the cisplatin molecules diffused into the cell are subjected to hydrolysis resulting in dissociation of chloride ions, and amine-platinum cations thus formed are combined with DNA in the cell mostly via intrastrand cross-linking mode to inhibit the replication of DNA, whereby kill the cell. Like other anticancer drugs, platinum complex cannot distinguish cancer cells from the normal cells, leading to cytotoxicity. The oligomers produced by hydrolysis of cisplatin are also understood to cause various toxicities in body. However, concrete relationship between the molecular structures of the neutral amine ligand and the anionic leaving group of cisplatin molecule and the anticancer activity or toxicity in body has not yet been clarified.

DISCLOSURE OF THE INVENTION

Accordingly, it is an object of the present invention to provide an anticancer agent having low toxicity and high anticancer activity, which can be released in a controlled manner.

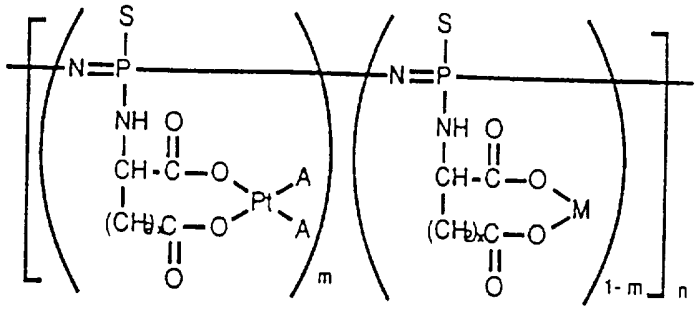
In accordance with the present invention, there is provided novel controlled releasing platinum complex derivatives incorporated in polyphosphazene.

In accordance with the present invention, there is also provided a method for prepartion of the above novel platinum complex derivatives incorporated in polyphosphazene and use thereof as an anticancer agent.

METHOD FOR CARRYING OUT THE INVENTION

The present inventors have intensively studied to develop a novel third-generation platinum anticancer agent having higher anticancer activity and lower toxicity than those of the conventional cisplatin, and, as a result, found that a polymeric platinum complex represented by the following formula (I), prepared by incorporating a solubilizing group and a dicarboxylic amino acid derivative in the polyphosphazene back-bone, a biodegradable inorganic polymer, and by combining diamineplatinum(II) moiety to the dicarboxylic amino acid, shows not only much higher anticancer activity than that of cisplatin and low toxicity comparable to carboplatin, but also excellent anticancer activity to cancer cells resistant to cisplatin and to the cells of lung cancer, gastric cancer or intestine cancer which cannot be well treated by conventional cisplatin. It is presumed that, when the drug of the present invention is administered to body, the bioactive diamineplatinum(II) moiety incorporated in the polyphosphazene back-bone is controlled-releasing from the polymer chain so as to maintain an optimal efficacious level of the active moiety in the blood for certain time, so that the drug can show low toxicity and excellent anticancer activity.

More specifically, the present invention relates to a novel platinum complex incorporated in polyphosphazene, represented by the following formula (I) which has excellent anticancer activity, and preparation thereof.



(I)

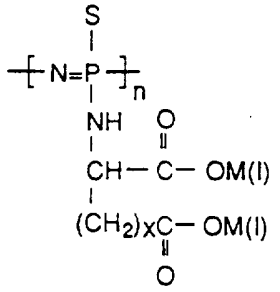
In the formula, polymeric backbone is polyphosphazene having P=N repeating unit; S represents hydroxy group, alkoxy group such as methoxy, ethoxy or (2-methoxy)ethoxy group, or alkylamine group such as methylamine or dimethylamine as solubilizing group: A represents ammonia, or C_1 - C_3 alkylamine such as methylamine, ethylamine or cyclopropylamine(CPA) as monodentate neutral ligand, or AA-type bidentate cheleting amine selected from the group consisting of ethylenediamine(en), propylenediamine(pn), 2-hydroxy-1,3-diaminopropane (HDAP), 2,2-dimethyl-1,3-diaminopropane (DMDAP), 1,1-diaminomethylcyclobutane(DAMCB), tetrahydro-4H-pyrane-4,4-dimethanamine (THPDMA), 2,2-bisaminomethyl-1,3-propandiol(BAMPDO) and trans(±)-1,2-diaminocyclohexane(DACH); x showing the type of dicarboxylic amino acid as anion group represents 0, 1 or 2, the type being aminomalonic acid (Am) derivatives when x=0, being aspartic acid derivatives (Asp) when x=1, and being glutamic acid derivatives (Glt) when x=2; M represents two alkaline metal ions such as sodium ion or potassium ion, or one alkaline earth metal ion such as calcium ion or barium ion; m showing the content of platinum complex is 0.2 to 1; and n showing degree of polymerization of polyphosphazene is 10 to 100.

The polymeric platinum complex represented by formula (I) above where a diamineplatinum(II) moiety is incorporated in the polyphosphazene back-bone is a novel compound which has never been reported, and proved to show excellent anticancer activity and superior physical properties.

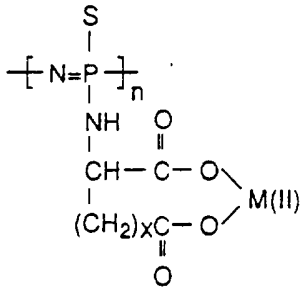
A process for preparation of the platinum complex incorporated in polyphosphazene, represented by formula (I) is briefly described here-in-

below.

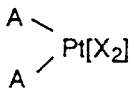
The polymeric platinum complex represented by general formula (I) can be obtained by reacting an alkaline metal salt of general formula (II) or alkaline earth metal salt of general formula (III) obtained by incorporating a solubilizing group and a dicarboxylic amino acid derivative as a spacer group for the platinum moiety to be covalently bonded, with a diamineplatinum (II) salt of general formula (IV) in a molar ratio 1:0.2 to 1:1 in an aqueous solution at room temperature.



(II)



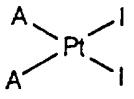
(III)



(IV)

In the formula, S, A, x, m and n are defined as above, M(I) is ammonium or alkaline metal ion such as sodium or potassium ion, M(II) is alkaline earth metal ion such as barium or calcium ion, and X_2 is anion(s) such as two nitrate ions or one sulfate ion.

Water soluble diamineplatinum(II) salts of general formula (IV) can be prepared by reacting a diamineplatinum(II) iodide of general formula (V) and a water soluble silver salt according to a method written in the literature [R.C. Harrison, Inorg. Chimica Acta 46, L15(1980)].



(V)

A of the general formula (V) is defined as that of general formula (I). Diamineplatinum (II) iodide of general formula (V) can be easily obtained by reacting potassium tetrachloroplatinate(II) with the corresponding amine in the presence of potassium iodide according to the literature [M.J. Cleare, Biochimie 60, 835(1978)].

The process for preparation of the polymeric platinum complex

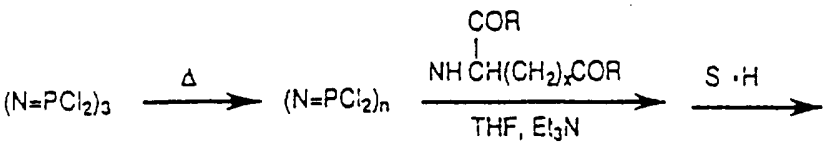
derivative represented by general formula(I) according to the present invention comprises three steps: synthesis of polyphosphazene which is the main polymeric backbone to incorporate platinum complexes, incorporation of solubilizing and spacer groups into the polymeric backbone, and final incorporation of diamineplatinum(II) moiety.

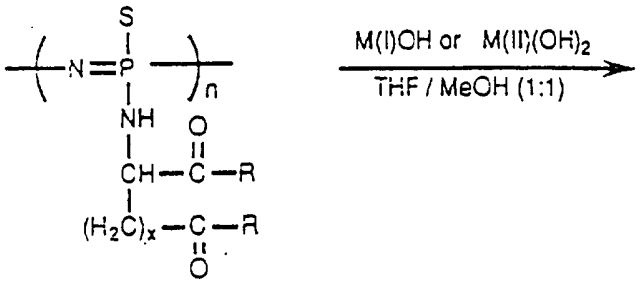
At first, synthesis of polyphosphazene comprises thermal polymerization from the trimer $(N=PCl_2)_3$ to provide a linear polymer of poly(dichlorophosphazene) $(N=PCl_2)_n$ in accordance with a conventional method [e.g. Macromolecule, 8, 36(1975)]. The resultant polymer is dissolved in a solvent such as dry benzene, toluene, tetrahydrofuran or dioxane, and is added thereto an excess amount of triethylamine as a remover of hydrogen chloride. The resultant solution is slowly added to a solution where methyl, ethyl or benzyl ester or alkyl amide of a dicarboxylic amino acid such as aminomalonic acid, aspartic acid or glutamic acid, is dissolved in the same solvent in the same molar ratio as the polymer unit, and the resultant reaction mixture is stirred at room temperature. After filtering triethylamine hydrochloride precipitated, water, water soluble alcohol such as methanol, ethanol or (2-methoxy)ethanol, or water soluble amine such as methylamine or dimethylamine as a solubilizing group is added together with equimolar triethylamine to the filtrate, which is further stirred for 2 - 10 hours, and, if required, refluxed. The resultant reaction mixture is poured into an excess amount of n-hexane, where most of the polymer is precipitated. The purification process comprising of dissolving the precipitated polymer obtained by filtering the hexane solution in a polar solvent such as tetrahydrofuran or dioxane, and pouring the solution into water to produce precipitate is repeated 2 - 3 times. The purified polymer is dissolved in a cosolvent of alcohol-tetrahydrofuran, and alkaline metal (Na or K) hydroxide, or alkaline earth metal (Ca or Ba) hydroxide corresponding to 1.0 - 1.5 equivalent to the substituted amino acid is dissolved therein. The solution mixture is stirred at room temperature for 2 - 10 hours for hydrolysis yielding a water soluble amino acid metal salt as precipitate. After filtering, thoroughly washing with alcohol or acetone,

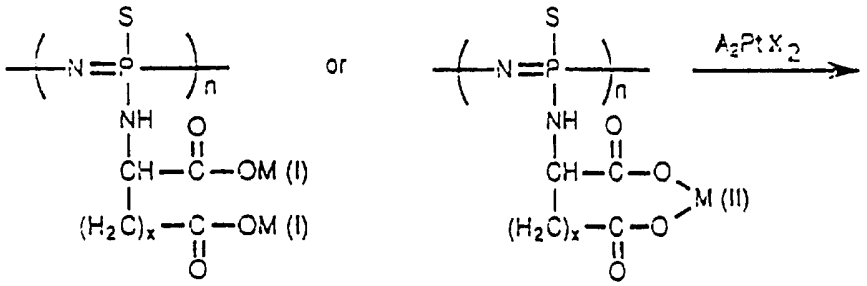
and drying, the precipitate is reacted with a diamineplatinum(II) intermediate as follows:

An aqueous solution of potassium tetrachloroplatinate(II) is reacted with an excess amount of potassium iodide, and then two equivalents of a desired amine(A) in an aqueous solution is added thereto to obtain diamineplatinum(II) iodide according to the method in the literature. A water soluble silver salt, e.g. silver nitrate or silver sulfate, is reacted with an equimolar diamineplatinum(II) iodide in water by stirring at room temperature for 2 - 10 hours. The precipitated silver iodide is filtered off to obtain water soluble diamineplatinum(II) salt of general formula(IV). The resultant aqueous solution of diamineplatinum(II) salt is finally reacted with an aqueous solution of the alkaline metal salt of amino acid incorporated in polyphohsphazene of general formula (II) or that of alkaline earth metal salt of general formula(III) in a molar ratio of 0.2:1 to 1:1 to obtain diamineplatinum(II) complex of polyphsphazene of general formula (I). In order to remove the byproduct, that is, alkaline or alkaline earth metal nitrate or sulfate, thus obtained, the reaction mixture is placed in a semipermeable membrane (m.w.cutoff: 1000) vessel and dialyzed with distilled water for 10 - 24 hours. Alternatively, the by-product may be separated using the difference of solubility between the polyphohsphazene platinum complex and the alkali metal or alkaline earth metal nitrate or sulfate. For example, where an alkaline earth metal salt of amino acid incorporated in polyphosphazene is reacted with diamineplatinum(II) sulfate, separation is performed by filtration of the alkaline earth metal sulfate which is insoluble in water. When an alkaline metal salt of amino acid incorporated in polyphosphazene is reacted with diamineplatinum(II) nitrate, potassium nitrate or sodium nitrate is produced as by-product which is very soluble in water so that it coexists with the platinum complex of polyphohsphazene in the reaction mixture. However, as sodium nitrate or potassium nitrate is soluble in alcohol whereas platinum complex is hardly soluble, it can be separated using a solvent pair of water and alcohol. When sodium or potassium salt of amino acid incorporated in

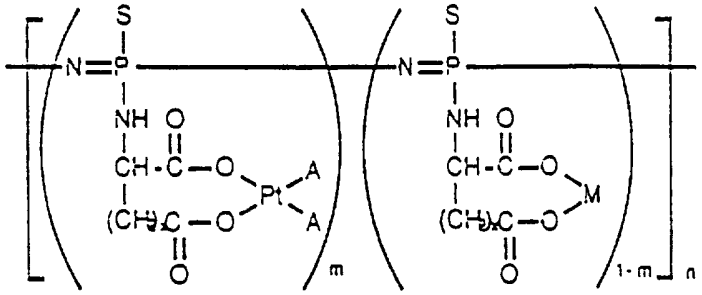
polyphosphazene is reacted with diamineplatinum(II) sulfate, the by-product, sodium sulfate or potassium sulfate which is water- soluble may be easily separated by the use of a solvent pair of water and acetone. The process for the preparation of the polymeric platinum complex of general formula (I) is illustrated by the scheme below:







(II) (III)



(I)

R : OMe, OEt, OCH_2Ph, NHMe, NHEt

S : OH, OMe, OEt, OCH_2CH_2OMe, NHMe, NHEt, NMe_2

M (I) : Na^+, K^+, NH_4^+

M (II) : Ca^{2+}, Ba^{2+}

x = 0, 1, 2 ; m = 0.2-1 ; n = 10-100

(Scheme)

Now, the present invention is further described by referring to the following examples. However, the present invention should not be understood to be limited to the examples.

Example 1 : Synthesis of $\{NP(OH)[Asp\cdot Pt(DACH)]_{0.9}\ (Asp\cdot K_2)_{0.1}\cdot 2H_2O\}_n$

Three(3.0) grams (8.63 mmol) of hexachlorocyclotriphosphazene $[(NPCl_2)_3]$ and 0.15 g (2.25 mmol) of anhydrous aluminum chloride were introduced to a 220mm x 23mm Pyrex ampoule. After sealing the ampoule, thermal polymerization reaction was performed at 250°C for 2 hours with rotating the ampoule at 1 rpm to produce poly(dichloro-phosphazene). The ampoule was cooled to room temperature and opened in a dry box under argon atmosphere. A solution obtained by dissolving the content in purified dry THF or benzene was directly used in the next substitution reaction.

L-Aspartoyl dibenzyl ester-p-toluenesulfonate(13.2 g, 27.2 mmol) was dissolved in 400 ml of THF, and the mixture was cooled to 0°C. Triethylamine(7.56 ml, 54.4 mmol) was added thereto and the resultant mixture was stirred for 30 minutes. A THF solution(150 ml) containing 3.0 g of poly(dichlorophosphazene) prepared above was added dropwise thereto over 1 hour, and the resultant mixture was stirred at room temperature for 20 hours. After the precipitates produced ($Et_3N.HCl$ and triethylammonium p-toluenesulfonate) were filtered off, triethylamine(3.78 ml, 27.2 mmol) and water(0.49 ml, 27.2 mmol) were added to the filtrate, and the resultant mixture was stirred at room temperature for 12 hours. The precipitate produced ($Et_3N.HCl$) was filtered off again, and the product obtained by distillation of the filtrate under reduced pressure at 30°C was dissolved again in THF. The THF solution was added dropwise to an excess amount of n-hexane yielding a white precipitate. The precipitate was dissolved again in THF, and the solution was added dropwise to an excess amount of water to obtain a white polymer $[NP(OH)(Asp\cdot CH_2Ph)_2]_n$, which was filtered and dried under reduced pressure(yield: 85%).

To a solution of the above polyphosphazene(4.0 g, 10.7 mmol) derivative dissolved in 80 ml of a THF-MeOH(1:1, vol %) mixed solvent

KOH(1.80 g, 32.1 mmol) or NaOH(1.28 g, 32.1 mmol) in 50 ml of the same mixed solvent was added slowly and the reaction mixture was stirred for 5 hours. The resultant precipitate was filtered and washed with a sufficient amount of the THF-MeOH mixed solvent and ethyl ether. This was dissolved in 40 ml of 2N KOH or 2N NaOH aqueous solution, and the solution was added dropwise to 500 ml of THF-MeOH(1:1,vol%) mixed solvent. The precipitate[NP(OH)(Asp·K_2)] or [NP(OH)(Asp·Na_2)]$_n$ thus obtained by hydrolysis was filtered and washed with methanol and ethyl ether, and then, dried under vacuum (yield: 90%).

Meanwhile, platinum intermediate (DACH)PtI_2(2.08 g, 3.70 mmol) and Ag_2SO_4(1.15 g, 3.70 mmol) were reacted in 100 ml of water at room temperature for 10 hours and the precipitated AgI was filtered off. The filtrate containing (DACH)$PtSO_4$ was added to 30 ml of aqueous solution of [NP(OH)(Asp·K_2)]$_n$ (1.0 g, 3.70 mmol) prepared above and the resultant reaction mixture was stirred for 1 hour under darkness. To remove the byproduct K_2SO_4, the reaction mixture was condensed to 30 ml under reduced pressure, and then acetone (400 ml) was added thereto. The precipitated solid product was filtered and washed with ethyl ether and then, dried under reduced pressure to obtain the desired polymeric platinum complex.

Elemental Analysis(%):

C,22.3; H,4.27; N,9.58; P,5.25; Pt,34.3

Calculated(%):

C,21.6; H,4.50; N,10.1; P,5.58; Pt,35.2

^{1}H NMR(D_2O, ppm):

1.2 - 1.3(4H), 1.6(2H), 2.1(2H), 2.4(2H), 2.7(2H), 3.8(1H)

IR (KBr cell, cm^{-1}):

516(m), 714(m), 816(m), 1034(m), 1065(m), 1172(m), 1248(m), 1384(s), 1450(m), 1618(s), 3213(s), 3428(s)

Example 2 : Synthesis of {NP(OH)[Asp··Pt(DACH)]$_{0.5}$(Asp·K_2)$_{0.5}$·3H_2O}$_n$

(DACH)PtI_2(1.04 g, 1.85 mmol), Ag_2SO_4(0.58 g, 1.85 mmol) and [NP(OH)(Asp·K_2)]$_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the

same procedure as Example 1 to obtain the title complex.

Elemental Analysis(%):

C,18.5; H,3.31; N,5.86; P,6.56; Pt,21.4

Calculated(%):

C,19.1; H,3.87; N,6.37; P,7.05; Pt,22.2

^{1}H NMR(D_2O, ppm):

1.2 - 1.3(4H), 1.6(2H), 2.1(2H), 2.4(2H), 2.7(2H), 3.8(1H)

IR (KBr cell, cm^{-1}):

518(m), 614(m), 1065(m), 1119(s), 1167(m), 1307(m), 1393(s), 1591(s), 1645(m), 2934(m), 3213(s), 3406(s)

Example 3 : Synthesis of $\{NP(OH)[Asp\cdot Pt(DACH)]_{0.2}\ (Asp\cdot K_2)_{0.8}\cdot 3H_2O\}_n$

(DACH)PtI_2(0.42 g, 0.74 mmol), Ag_2SO_4(0.23 g, 0.74 mmol) and $[NP(OH)(Asp\cdot K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the title complex.

Elemental Analysis(%):

C,15.9; H,3.14; N,8.25; P,7.38; Pt,9.77

Calculated(%):

C,16.9; H,3.76; N,9.08; P,8.36; Pt,10.54

^{1}H NMR(D_2O, ppm):

1.2 - 1.3(4H), 1.6(2H), 2.1(2H), 2.4(2H), 2.7(2H), 3.8(1H)

IR (KBr cell, cm^{-1}):

534(m), 620(m), 979(m), 1060(m), 1124(s), 1205(m), 1307(m), 1404(s), 1591(s), 2945(m), 3224(s), 3406(s)

Example 4 : Synthesis of $\{NP(OH)[Asp\cdot Pt(CPA)_2]_{0.9}(Asp\cdot K_2)_{0.1}\cdot 2H_2O\}_n$

$(CPA)_2PtI_2$(2.08 g, 3.70 mmol), Ag_2SO_4(1.15 g, 3.70 mmol) and $[NP(OH)(Asp\cdot K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the title complex.

Elemental Analysis(%):

C,21.7; H,3.82; N,9.33; P,5.18; Pt,34.7

Calculated(%):

C,21.9; H,4.23; N,10.35; P,6.02; Pt,34.1

^{1}H NMR(D_2O, ppm):

0.7(8H), 2.5(2H), 3.7(1H)

IR (KBr cell, cm^{-1}):

619(m), 827(m), 964(m), 1030(m), 1122(m), 1261(m), 1375(s), 1637(s), 3103(m), 3188(s), 3404(m)

Example 5 : Synthesis of $\{NP(OH)[Asp\cdot Pt(NH_3)_2]\cdot 3H_2O\}_n$

$(NH_3)_2PtI_2$(1.79 g, 3.70 mmol), Ag_2SO_4(1.15 g, 3.70 mmol) and $[NP(OH)(L\text{-}Asp\cdot K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the title complex.

Elemental Analysis(%):

C,10.4; H,2.88; N,9.54; P,5.98; Pt,40.4

Calculated(%):

C,10.1; H,3.37; N,8.84; P,6.52; Pt,41.1

^1H NMR(D_2O, ppm):

2.7(2H), 3.9(1H)

IR (KBr cell, cm^{-1}):

619(m), 1118(m), 1369(m), 1639(s), 3128(m), 3259(s), 3443(m)

Example 6 : Synthesis of $\{NP(OH)[Asp\cdot Pt(en)]_{0.85}\ (Asp\cdot K_2)_{0.15}\cdot 2H_2O\}_n$

(en)PtI_2(1.88 g, 3.70 mmol), Ag_2SO_4(1.15 g, 3.70 mmol) and $[NP(OH)(L\text{-}Asp\cdot K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the title complex.

Elemental Analysis(%):

C,15.8; H,4.54; N,10.7; P,6.11; Pt,36.4

Calculated(%):

C,15.0; H,3.55; N,11.4; P,6.78; Pt,36.3

^1H NMR(D_2O, ppm):

2.4 - 2.6(6H), 3.8(1H)

IR (KBr cell, cm^{-1}):

570(m), 765(m), 1049(m), 1128(m), 1291(m), 1400(s), 1638(s), 3267(m), 3450(m)

Example 7 : Synthesis of $\{NP(OH)[Asp\cdot Pt(pn)]_{0.85}(Asp\cdot K_2)_{0.15}\cdot 2H_2O\}_n$

(pn)PtI_2(1.94 g, 3.70 mmol), Ag_2SO_4(1.15 g, 3.70 mmol) and $[NP(OH)(L\text{-}Asp\cdot K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with

the same procedure as Example 1 to obtain the title complex.

Elemental Analysis(%):

C,16.5; H,4.43; N,10.7; P,6.14; Pt,35.4

Calculated(%):

C,16.7; H,3.81; N,11.0; P,6.58; Pt,35.2

^{1}H NMR(D_2O, ppm):

1.4(2H), 2.4 - 2.7(6H), 3.8(1H)

IR (KBr cell, cm^{-1}):

530(m), 936(m), 1108(m), 1196(m), 1291(m), 1402(s), 1634(s), 2932(m), 3224(m), 3428(m)

Example 8 : Synthesis of $\{NP(OH)[Asp{\cdot}Pt(NH_2CH_3)_2]_{0.85}(Asp{\cdot}K_2)_{0.15}{\cdot}2H_2O\}_n$

$(CH_3NH_2)_2PtI_2$(1.89 g, 3.70 mmol), Ag_2SO_4(1.15 g, 3.70 mmol) and $[NP(OH)(L\text{-}Asp{\cdot}K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the title complex.

Elemental Analysis(%):

C,15.1; H,4.58; N,10.8; P,6.36; Pt,36.5

Calculated(%):

C,14.9; H,3.91; N,11.3; P,6.76; Pt,36.2

^{1}H NMR(D_2O, ppm):

2.4 - 2.7(8H), 3.8(1H)

IR (KBr cell, cm^{-1}):

582(m), 753(m), 1084(m), 1237(m), 1418(s), 1621(s), 2923(m), 3218(m), 3421(m)

Example 9 : Synthesis of $\{NP(OH)[Asp{\cdot}Pt(NH_2C_2H_5)_2]_{0.8}(Asp{\cdot}K_2)_{0.2}{\cdot}2H_2O\}_n$

$(NH_2C_2H_5)_2PtI_2$(1.99 g, 3.70 mmol), Ag_2SO_4(1.15 g, 3.70 mmol) and $[NP(OH)(L\text{-}Asp{\cdot}K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the title complex.

Elemental Analysis(%):

C,18.3; H,4.32; N,10.8; P,6.20; Pt,33.6

Calculated(%):

C,18.3; H,4.40; N,10.7; P,6.56; Pt,33.1

^{1}H NMR(D_2O, ppm):

1.1(6H), 2.5 - 2.8(6H), 3.8(1H)

IR (KBr cell, cm^{-1}):

603(m), 762(m), 1064(m), 1201(m), 1231(m), 1407(s), 1633(s), 2934(m), 3214(s), 3402(s)

Example 10 : Synthesis of $\{NP(OH)[Asp\cdot Pt(HDAP)]_{0.8}(Asp\cdot K_2)_{0.2}\cdot 2H_2O\}_n$

(HDAP)PtI_2(1.99 g, 3.70 mmol), Ag_2SO_4(1.15 g, 3.70 mmol) and $[NP(OH)(L\text{-}Asp\cdot K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the title complex.

Elemental Analysis(%):

C,15.9; H,4.42; N,10.2; P,6.13; Pt,33.1

Calculated(%):

C,16.3; H,3.20; N,10.7; P,6.56; Pt,33.1

^1H NMR(D_2O, ppm):

2.3 - 2.5(6H), 3.8(1H)

IR (KBr cell, cm^{-1}):

532(m), 851(m), 974(m), 1071(m), 1189(m), 1312(m), 1402(s), 1632(s), 3202(m), 3449(m)

Example 11 : Synthesis of $\{NP(OH)[Asp\cdot Pt(DMDAP)]_{0.8}(Asp\cdot K_2)_{0.2}\cdot 2H_2O\}_n$

(DMDAP)PtI_2(2.04 g, 3.70 mmol), Ag_2SO_4(1.15 g, 3.70 mmol) and $[NP(OH)(L\text{-}Asp\cdot K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the title complex.

Elemental Analysis(%):

C,21.4; H,5.26; N,9.52; P,6.23; Pt,32.8

Calculated(%):

C,20.0; H,4.31; N,10.5; P,6.43; Pt,32.4

^1H NMR(D_2O, ppm):

1.4(6H), 2.3 - 2.5(6H), 3.8(1H)

IR (KBr cell, cm^{-1}):

522(m), 700(m), 915(m), 1108(m), 1200(m), 1221(m), 1307(m), 1400(m), 1632(s), 2945(m), 3224(s), 3442(s)

Example 12 : Synthesis of $\{NP(OH)[Asp\cdot Pt(DAMCB)]_{0.8}(Asp\cdot K_2)_{0.2}\cdot 2H_2O\}_n$

(DAMCB)PtI_2(2.08 g, 3.70 mmol), Ag_2SO_4(1.15 g, 3.70 mmol) and

$[NP(OH)(L\text{-}Asp\cdot K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the title complex.

Elemental Analysis(%):

C,22.1; H,4.51; N,9.84; P,5.87; Pt,32.1

Calculated(%):

C,21.5; H,4.23; N,10.3; P,6.31; Pt,31.8

^1H NMR(D_2O, ppm):

0.8 - 1.1(6H), 2.2 - 2.4(6H), 3.8(1H)

IR (KBr cell, cm^{-1}):

530(m), 920(m), 1087(m), 1114(m), 1200(m), 1400(s), 1632(s), 2966(m), 3224(m), 3442(m)

Example 13 : Synthesis of $\{NP(OCH_3)[Asp\cdot Pt(DACH)]_{0.8}(Asp\cdot K_2)_{0.2}\cdot 2H_2O\}_n$

L-Aspartoyl dibenzyl ester-p-toluenesulfonate (13.2 g, 27.2 mmol) was dissolved in 400 ml of THF, and the mixture was cooled to 0°C. Triethylamine(7.56 ml, 54.4 mmol) was added thereto and the resultant mixture was stirred for 30 minutes. A THF solution(150 ml) containing 3.0 g of polydichlorophosphazene prepared according to Example 1 was added dropwise thereto and the resultant mixture was stirred at room temperature for 20 hours. Precipitates formed ($Et_3N.HCl$ and triethylammonium p-toluenesulfonate) were filtered off and then, the filtrate was condensed to 300 ml below 30 °C. To the filtrate, were added methanol(50ml) and triethylamine(3.78 ml, 27.7 mmol), and the resultant mixture was stirred at 60 - 70 °C for 14 hours. The precipitate formed ($Et_3N.HCl$) was filtered off, and the product obtained by evaporating the solvent of the filtrate below 30 °C was dissolved again in THF. The THF solution was added dropwise to an excess amount of n-hexane to produce a white precipitate. The precipitate was dissolved again in THF, and the solution was added dropwise to an excess amount of water to obtain a white polymer as precipitate. This procedure was repeated twice and then, the resultant polymer $[NP(OCH_3)(Asp\cdot(CH_2Ph)_2)]_n$ was dried under reduced pressure. After hydrolysing the synthesized polyphosphazene derivative (4.0 g, 10.7 mmol) as in Example 1, $(DACH)PtI_2$(1.98 g, 3.52 mmol), Ag_2SO_4(1.10 g,

3.52 mmol) and $[NP(OCH_3)(L\text{-}Asp.K_2)]_n$ (1.0 g, 3.52 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,23.4; H,4.45; N,9.67; P,5.88; Pt,31.8

Calculated(%):

C,23.3; H,4.51; N,9.98; P,6.13; Pt,30.9

^1H NMR(D_2O, ppm):

1.2 - 1.3(4H), 1.6(2H), 2.2(2H), 2.5(2H), 2.7(2H), 3.4(3H), 3.8(1H)

IR (KBr cell, cm^{-1}):

516(m), 613(m), 1110(m), 1034(m), 1172(m), 1253(m), 1398(s), 1594(s), 2940(m), 3218(s), 3426(m)

Example 14 : Synthesis of $\{NP(OCH_3)[Asp{\cdot}Pt(NH_3)_2]_{0.85}(Asp{\cdot}K_2)_{0.15}{\cdot}2H_2O\}_n$

$(NH_3)_2PtI_2$(1.78 g, 3.52 mmol), Ag_2SO_4(1.10 g, 3.52 mmol) and $[NP(OCH_3)(Asp{\cdot}K_2)]_n$ (1.0 g, 3.52 mmol) were reacted in accordance with the same procedure as Example 13 to obtain the title complex.

Elemental Analysis(%):

C,13.1; H,4.33; N,11.0; P,7.42; Pt,37.1

Calculated(%):

C,13.5; H,3.64; N,11.6; P,6.94; Pt,37.2

^1H NMR(D_2O, ppm):

2.5(2H), 3.3(3H), 3.8(1H)

IR (KBr cell, cm^{-1}):

520(m), 714(m), 1038(m), 1174(m), 1205(m), 1377(s), 1624(s), 2927(m), 3267(s), 3442(m)

Example 15 : Synthesis of $\{NP(OC_2H_5)[Asp{\cdot}Pt(DACH)]_{0.8}(Asp{\cdot}K_2)_{0.2}{\cdot}2H_2O\}_n$

Polydichlorophosphagen(3.0 g), L-aspartoyl dibenzyl ester-p-toluenesulfonate(13.2 g, 27.2 mmol), ethanol(50 ml), $(DACH)PtI_2$(1.88 g, 3.34 mmol), Ag_2SO_4(1.04 g, 3.34 mmol) and $[NP(OC_2H_5)(Asp{\cdot}K_2)]_n$ (1.0 g, 3.34 mmol) were reacted in accordance with the same procedure as Example 13 to obtain the title complex.

Elemental Analysis(%):

C,28.7; H,5.10; N,9.01; P,5.58; Pt,29.1

Calculated(%):

C,28.6; H,4.69; N,9.69; P,5.95; Pt,30.0

^{1}H NMR(D_2O, ppm):

1.1 - 1.3(4H), 1.4 - 1.6(6H), 2.2(2H), 2.4(2H), 2.8(2H), 3.4(2H), 3.8(1H)

IR (KBr cell, cm^{-1}):

516(m), 614(m), 963(m), 1032(m), 1122(m), 1173(m), 1248(m), 1302(m), 1390(s), 1624(s), 2923(m), 3212(s), 3426(s)

Example 16 : Synthesis of $\{NP(OC_2H_5)[Asp{\cdot}Pt(NH_3)_2]_{0.85}(Asp{\cdot}K_2)_{0.15}{\cdot}2H_2O\}_n$

$(NH_3)_2PtI_2$(1.61 g, 3.34 mmol), Ag_2SO_4(1.04 g, 3.34 mmol) and $[NP(OC_2H_5)(Asp{\cdot}K_2)]_n$ (1.0 g, 3.34 mmol) were reacted in accordance with the same procedure as Example 13 to obtain the title complex.

Elemental Analysis(%):

C,19.8; H,4.46; N,10.9; P,6.01; Pt,35.8

Calculated(%):

C,20.1; H,3.96; N,11.2; P,6.72; Pt,36.0

^{1}H NMR(D_2O, ppm):

1.3(3H), 2.6(2H), 3.3(2H), 3.8(1H)

IR (KBr cell, cm^{-1}):

601(m), 889(m), 1043(m), 1218(m), 1382(s), 1630(s), 2936(m), 3213(s), 3426(s)

Example 17 : Synthesis of $\{NP(OC_2H_4OCH_3)[Asp{\cdot}Pt(DACH)]_{0.8}(Asp{\cdot}K_2)_{0.2}{\cdot}2H_2O\}_n$

Polydichlorophosphazene(3.0 g), L-aspartoyl dibenzyl ester-p-toluenesulfonate (13.2 g, 27.2 mmol), $CH_3OCH_2CH_2ONa$ (2.70 g, 27.2 mmol), $(DACH)PtI_2$(1.71 g, 3.04 mmol), Ag_2SO_4(0.95 g, 3.04 mmol) and $[NP(OCH_2CH_2OCH_3)(Asp{\cdot}K_2)]_n$ (1.0 g, 3.04 mmol) were reacted in accordance with the same procedure as Example 13 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,25.7; H,5.38; N,8.76; P,5.10; Pt,28.9

Calculated(%):

C,25.8; H,4.81; N,9.18; P,5.64; Pt,28.4

^{1}H NMR(D_2O, ppm):

1.2 - 1.4(6H), 1.6(2H), 2.1(2H), 2.4(2H), 2.7(2H), 3.2 - 3.4(5H), 3.8(1H)

IR (KBr cell, cm^{-1}):

516(m), 840(m), 969(m), 1044(m), 1124(m), 1162(m), 1205(m), 1253(m), 1398(s), 1624(m), 2940(m), 3234(s), 3440(s)

Example 18 : Synthesis of $\{NP(NHCH_3)[Asp{\cdot}Pt(DACH)]_{0.8}(Asp{\cdot}K_2)_{0.2}{\cdot}2H_2O\}_n$

L-Aspartoyl dibenzyl ester p-toluenesulfonate (13.2 g, 27.2 mmol) was dissolved in 400 ml of THF, and the mixture was cooled to 0 °C. Triethylamine(7.56 ml, 54.4 mmol) was added thereto and the resultant mixture was stirred for 30 minutes. A THF solution(150 ml) containing 3.0 g of polydichlorophosphazene prepared according to Example 1 was added dropwise thereto and the resultant mixture was stirred at room temperature for 20 hours. After filtering the precipitates produced ($Et_3N.HCl$ and triethylammonium p-toluenesulfonate), the filtrate was cooled to 0 °C. Methylamine(54.4 mmol, liquified using dry ice - acetone mixed coolant) was added thereto and the resultant mixture was stirred for 10 hours. The solvent of the reaction mixture was removed and the product obtained was dissolved in 50 ml of methanol. This solution was dialyzed using dialysis membrane(mw. cutoff: 1000) for 48 hours and then reduced to 30 ml. The solution was added dropwise to an excess amount of acetone to obtain a white polymer as precipitate. After hydrolysing the synthesized polyphosphazene derivative(4.0 g, 9.89 mmol) prepared above as in Example 1, $(DACH)PtI_2$(2.08 g, 3.70 mmol), Ag_2SO_4(1.15 g, 3.70 mmol) and $[NP(NHCH_3)(Asp.K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,24.8; H,4.62; N,12.4; P,5.92; Pt,30.8

Calculated(%):

C,24.3; H,4.64; N,12.8; P,6.14; Pt,31.0

^{1}H NMR(D_2O, ppm):

1.2 - 1.4(4H), 1.6(2H), 2.1(2H), 2.4 - 2.6(7H), 3.8(1H)

IR (KBr cell, cm^{-1}):

518(m), 614(m), 716(m), 904(m), 1060(m), 1114(m), 1248(m), 1307(m), 1162(m), 1387(s), 1586(s), 1645(s), 2923(m), 3245(s), 3385(s)

Example 19 : Synthesis of $\{NP(NHCH_3)[Asp{\cdot}Pt(NH_3)]_{0.85}(Asp{\cdot}K_2)_{0.15}{\cdot}2H_2O\}_n$

$(NH_3)_2PtI_2$(1.79 g, 3.70 mmol), Ag_2SO_4(1.15 g, 3.70 mmol) and $[NP(NHCH_3)(L\text{-}Asp{\cdot}K_2)]_n$ (1.0 g, 3.70 mmol) were reacted in accordance with the same procedure as Example 18 to obtain the title complex.

Elemental Analysis(%):

C,13.3; H,4.28; N,14.7; P,6.89; Pt,37.4

Calculated(%):

C,13.5; H,3.87; N,14.8; P,6.96; Pt,37.3

^{1}H NMR(D_2O, ppm):

2.5(3H), 2.7(2H), 3.9(1H)

IR (KBr cell, cm^{-1}):

518(m), 963(m), 1114(m), 1162(m), 1231(m), 1253(m), 1302(m), 1401(s), 1639(s), 2945(m), 3245(s), 3421(s)

Example 20 : Synthesis of $\{NP[N(CH_3)_2])[Asp{\cdot}Pt(DACH)]_{0.8}(Asp{\cdot}K_2)_{0.2}{\cdot}2H_2O\}_n$

Poly(dichlorophosphazene)(3.0 g), L-aspartoyl dibenzyl ester-p-toluenesulfonate(13.2 g, 27.2 mmol), dimethylamine hydrochloride(2.22 g, 27.2 mmol), $(DACH)PtI_2$(1.89 g, 3.36 mmol), Ag_2SO_4(1.05 g, 3.36 mmol) and $[NP(N(CH_3)_2)(Asp{\cdot}K_2)]_n$ (1.0 g, 3.36 mmol) were reacted in accordance with the same procedure as Example 18 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,23.6; H,4.98; N,11.9; P,5.83; Pt,30.7

Calculated(%):

C,23.6; H,4.90; N,12.4; P,5.98; Pt,30.1

^{1}H NMR(D_2O, ppm):

1.1 - 1.3(4H), 1.5(2H), 2.1(2H), 2.3 - 2.5(8H), 3.9(1H)

IR (KBr cell, cm^{-1}):

502(m), 625(m), 985(m), 1065(m), 1151(m), 1237(m), 1291(m), 1392(s), 1632(s), 2923(m), 3191(s), 3442(s)

Example 21 : Synthesis of $\{NP(OH)[Glt{\cdot}Pt(DACH)]_{0.9}(Glt{\cdot}K_2)_{0.1}{\cdot}2H_2O\}_n$

Poly(dichlorophosphazene)(3.0 g), L-glutamoyl dibenzyl ester-p-toluenesulfonate(13.6 g, 27.2 mmol), triethylamine(7.57 ml, 54.4 mmol), H_2O (0.49 ml, 27.2 mmol), $[NP(OH)(Glt{\cdot}K_2)]_n$ (1.0 g, 3.52 mmol), $(DACH)PtI_2$ (1.98 g, 3.52 mmol) and Ag_2SO_4(1.10 g, 3.52 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the reaction mixture containing the polymeric platinum complex, which was subjected to dialysis for 15 hours using a semipermeable membrane (m.w. cutoff:1000) to remove the byproduct K_2SO_4. The purified solution was then freeze-dried under vacuum to obtain the title complex.

Elemental Analysis(%):

C,23.6; H,4.21; N,9.59; P,6.08; Pt,34.0

Calculated(%):

C,23.6; H,4.50; N,10.1; P,5.86; Pt,33.2

^1H NMR(D_2O, ppm):

1.1 - 1.3(4H), 1.5(2H), 2.0(4H), 2.3(4H), 3.7(1H)

IR (KBr cell, cm^{-1}):

518(m), 615(m), 829(m), 1033(m), 1064(m), 1170(m), 1345(m), 1400(s), 1447(m), 1634(s), 2937(m), 3234(s), 3422(s)

Example 22 : Synthesis of $\{NP(OH)[Glt{\cdot}Pt(CPA)_2]_{0.9}(Glt{\cdot}K_2)_{0.1}{\cdot}2H_2O\}_n$

$(CPA)_2PtI_2$(1.98 g, 3.52 mmol), Ag_2SO_4(1.10 g, 3.52 mmol) and $[NP(OH)(Glt{\cdot}K_2)]_n$ (1.0 g, 3.52 mmol) were reacted in accordance with the same procedure as Example 21 to obtain the title complex.

Elemental Analysis(%):

C,24.1; H,3.98; N,9.10; P,4.97; Pt,34.0

Calculated:

C,23.6; H,4.50; N,10.1; P,5.86; Pt,33.2

^1H NMR(D_2O, ppm)

0.7(8H), 2.1 - 2.4(6H), 3.8(1H)

IR (KBr cell, cm^{-1})

1124(m), 1388(s), 1631(s), 3086(s), 3184(s)

Example 23 : Synthesis of $\{NP(OH)[Glt{\cdot}Pt(NH_3)_2]{\cdot}3H_2O\}_n$

$(NH_3)_2PtI_2$(1.70 g, 3.52 mmol), Ag_2SO_4(1.10 g, 3.52 mmol) and $[NP(OH)(Glt{\cdot}K_2)]_n$ (1.0 g, 3.52 mmol) were reacted in accordance with the same procedure as Example 21 to obtain the title complex.

Elemental Analysis(%):

C,12.0; H,3.21; N,10.1; P,5.83; Pt,38.4

Calculated:

C,12.3; H,3.88; N,11.5; P,6.33; Pt,39.9

^1H NMR(D_2O, ppm)

2.2(2H), 2.5(2H), 3.8(1H)

IR (KBr cell, cm^{-1})

526(m), 617(m), 857(m), 1111(m), 1344(m), 1386(s), 1628(s), 2960(m), 3092(s), 3250(s), 3460(s)

Example 24 : Synthesis of $\{NP(OH)\ [Glt{\cdot}Pt(THPDMA)]_{0.8}\ (Glt{\cdot}K_2)_{0.2}{\cdot}2H_2O\}_n$

(THPDMA)PtI_2 (2.09 g, 3.52 mmol), Ag_2SO_4(1.10 g, 3.52 mmol) and $[NP(OH)(Glt{\cdot}K_2)]_n$ (1.0 g, 3.52 mmol) were reacted in accordance with the same procedure as Example 21 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,23.8; H,4.33; N,10.7; P,5.45; Pt,31.5

Calculated:

C,24.1; H,4.53; N,9.53; P,5.85; Pt,29.5

^1H NMR(D_2O, ppm)

1.5(4H), 2.4 - 2.6(8H), 3.7(5H)

IR (KBr cell, cm^{-1})

518(m), 620(m), 1116(m), 1167(m), 1384(s), 1638(s), 2945(m), 3234(s), 3446(s)

Example 25 : Synthesis of $\{NP(OH)[Glt{\cdot}Pt(BAMPDO)]_{0.8}(Glt{\cdot}K_2)_{0.2}{\cdot}2H_2O\}_n$

(BAMPDO)PtI_2 (2.05 g, 3.52 mmol), Ag_2SO_4(1.10 g, 3.52 mmol) and $[NP(OH)(Glt{\cdot}K_2)]_n$ (1.0 g, 3.52 mmol) were reacted in accordance with the same procedure as Example 21 to obtain the title complex.

Elemental Analysis(%):

C,22.4; H,5.62; N,11.6; P,6.12; Pt,34.2

Calculated:

C,22.3; H,4.61; N,10.4; P,6.38; Pt,32.2

^{1}H NMR(D_2O, ppm)

2.0 - 2.6(12H), 3.6(1H)

IR (KBr cell, cm^{-1})

526(m), 1044(m), 1228(m), 1275(m), 1384(s), 1457(m), 1618(s), 2925(m), 3202(s), 3404(s)

Example 26 : Synthesis of $\{NP(OCH_3)\ [Glt{\cdot}Pt(DACH)]_{0.8}(Glt{\cdot}K_2)_{0.2}{\cdot}2H_2O\}_n$

Poly(dichlorophosphazene)(3.0 g), L-glutamoyl dibenzyl ester p-toluenesulfonate (13.6 g, 27.2 mmol), methanol(50 ml), $(DACH)PtI_2$ (1.89 g, 3.35 mmol), Ag_2SO_4(1.04 g, 3.35 mmol) and $[NP(OCH_3)(Glt{\cdot}K_2)]_n$ (1.0 g, 3.35 mmol) were reacted in accordance with the same procedure as Example 13 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,25.0; H,4.66; N,9.26; P,5.90; Pt,29.4

Calculated:

C,25.0; H,4.70; N,9.71; P,5.97; Pt,30.1

^{1}H NMR(D_2O, ppm)

1.1 - 1.3(4H), 1.5(2H), 2.1(4H), 2.4(4H), 3.3(3H), 3.8(1H)

IR (KBr cell, cm^{-1})

514(m), 609(m), 813(m), 1052(m), 1170(m), 1213(m), 1240(m), 1387(s), 1618(s), 2940(m), 3254(s), 3420(s)

Example 27 : Synthesis of $\{NP(OCH_3)[Glt{\cdot}Pt(NH_3)_2]_{0.85}(Glt{\cdot}K_2)_{0.15}{\cdot}2H_2O\}_n$

$(NH_3)_2PtI_2$ (1.62 g, 3.35 mmol), Ag_2SO_4(1.04 g, 3.69 mmol) and $[NP(OCH_3)(Glt{\cdot}K_2)]_n$ (1.0 g, 3.35 mmol) were reacted in accordance with the same procedure as Example 26 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,15.8; H,4.78; N,10.6; P,6.36; Pt,35.1

Calculated:

C,15.7; H,3.97; N,11.3; P,6.73; Pt,36.0

^{1}H NMR(D_2O, ppm)

2.2(2H), 2.5(2H), 3.4(3H), 3.8(1H)

IR (KBr cell, cm^{-1})

528(m), 619(m), 889(m), 1112(m), 1245(m), 1337(m), 1389(s), 1621(s), 2948(m), 3241(s), 3354(s)

Example 28 : Synthesis of $\{NP(OC_2H_5)\ [Glt{\cdot}Pt(DACH)]_{0.8}(Glt{\cdot}K_2)_{0.2}{\cdot}2H_2O\}_n$

Poly(dichlorophosphazene) (3.0 g), L-glutamoyl dibenzyl ester p-toluenesulfonate (13.6 g, 27.2 mmol), ethanol(50 ml), $(DACH)PtI_2$ (1.80 g, 3.19 mmol), Ag_2SO_4(0.99 g, 3.19 mmol) and $[NP(OCH_2CH_3)(Glt{\cdot}K_2)]_n$ (1.0 g, 3.19 mmol) were reacted in accordance with the same procedure as Example 26 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,27.7; H,5.42; N,9.01; P,5.31; Pt,29.4

Calculated:

C,26.5; H,4.94; N,9.44; P,5.80; Pt,29.2

^{1}H NMR(D_2O, ppm)

1.1 - 1.3(7H), 1.6(2H), 2.0(4H), 2.4(4H), 3.4(2H), 3.8(1H)

IR (KBr cell, cm^{-1})

518(m), 874(m), 964(m), 1033(m), 1065(m), 1124(m), 1173(m), 1245(m), 1302(m), 1387(s), 2925(m), 3234(s), 3438(s)

Example 29 : Synthesis of $\{NP(NHCH_3)\ [Glt{\cdot}Pt(DACH)]_{0.8}\ (Glt{\cdot}K_2)_{0.2}{\cdot}2H_2O\}_n$

Poly(dichlorophosphazene) (3.0 g), L-glutamoyl dibenzyl ester p-toluenesulfonate (13.6 g, 27.2 mmol), methyl amine(54.4 mmol), $(DACH)PtI_2$ (1.89 g, 3.36 mmol), Ag_2SO_4(1.05 g, 3.36 mmol) and $[NP(NHCH_3)(Glt{\cdot}K_2)]_n$ (1.0 g, 3.36 mmol) were reacted in accordance with the same procedure as Example 18 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,25.3; H,5.53; N,12.0; P,5.76; Pt,30.1

Calculated:

C,25.0; H,4.90; N,12.4; P,5.98; Pt,30.1

^{1}H NMR(D_2O, ppm)

1.1 - 1.3(4H), 1.6(2H), 2.0(2H), 2.5(5H), 3.8(1H),

IR (KBr cell, cm^{-1})

518(m), 614(m), 904(m), 1060(m), 1082(m), 1201(m), 1248(m), 1307(m), 1403(s), 2938(m), 3194(s), 3418(s)

Example 30 : Synthesis of $\{NP(N(CH_3)_2[Glt{\cdot}Pt(DACH)]_{0.8}(Glt{\cdot}K_2)_{0.2}{\cdot}2H_2O\}_n$

Poly(dichlorophosphazene) (3.0 g), L-glutamoyl dibenzyl ester p-toluenesulfonate (13.6 g, 27.2 mmol), dimethylamine hydrochloride (2.22 g, 27.2 mmol), $(DACH)PtI_2$ (1.81 g, 3.21 mmol), Ag_2SO_4(1.0 g, 3.21 mmol) and $[NP(N(CH_3)_2)(Glt{\cdot}K_2)]_n$ (1.0 g, 3.21 mmol) were reacted in accordance with the same procedure as Example 29 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,27.4; H,5.80; N,11.8; P,5.12; Pt,29.0

Calculated:

C,26.6; H,5.15; N,12.1; P,5.82; Pt,29.3

^1H NMR(D_2O, ppm)

1.1 - 1.3(4H), 1.6(2H), 2.0(4H), 2.4 - 2.6(10H), 3.8(1H)

IR (KBr cell, cm^{-1})

510(m), 625(m), 980(m), 1056(m), 1151(m), 1162(m), 1240(m), 1293(m), 1397(s), 1628(s), 2923(m), 3198(s), 3432(s)

Example 31 : Synthesis of $\{NP(OH)\ [Am{\cdot}Pt(DACH)]_{0.9}(Am{\cdot}Na_2)_{0.1}{\cdot}2H_2O\}_n$

Poly(dichlorophosphazene) (3.0 g), diethylaminomalonate hydrochloride (5.76 g, 27.2 mmol), water(0.49 ml, 27.2 mmol), $(DACH)PtI_2$ (2.50 g, 4.44 mmol), Ag_2SO_4(1.38 g, 4.44 mmol) and $[NP(OH)(Am{\cdot}Na_2)]_n$ (1.0 g, 4.44 mmol) were reacted in accordance with the same procedure as Example 1 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,19.4; H,4.01; N,9.82; P,5.88; Pt,34.5

Calculated:

C,20.3; H,3.91; N,10.7; P,6.23; Pt,35.3

^1H NMR(D_2O, ppm)

1.1 - 1.3(4H), 1.5(2H), 2.0(2H), 2.3(2H), 3.9(1H),

IR (KBr cell, cm^{-1})

503(m), 775(m), 931(m), 1034(m), 1108(m), 1173(m), 1243(m), 1342(s), 1453(m), 1641(s), 2923(m), 3208(s), 3414(s)

Example 32 : Synthesis of $\{NP(OH)[Am{\cdot}Pt(CPA)_2]_{0.9}\ (Am.Na_2)_{0.1}{\cdot}2H_2O\}_n$

$(CPA)_2PtI_2$ (2.50 g, 4.44 mmol), Ag_2SO_4 (1.38 g, 4.44 mmol) and $[NP(OH)(Am{\cdot}Na_2)]_n$ (1.0 g, 4.44 mmol) were reacted in accordance with the same procedure as Example 31 to obtain the title complex.

Elemental Analysis(%):

C,20.8; H,4.31; N,10.2; P,6.23; Pt,33.9

Calculated:

C,20.3; H,3.97; N,10.7; P,6.23; Pt,35.3

^1H NMR(D_2O, ppm)

0.8(8H), 2.3(2H), 3.8(1H)

IR (KBr cell, cm^{-1})

534(m), 754(m), 931(m), 1043(m), 1182(m), 1210(m), 1394(s), 1654(s), 2915(m), 3212(s), 3429(s)

Example 33 : Synthesis of $\{NP(OH)[Am{\cdot}Pt(NH_3)_2]{\cdot}2H_2O\}_n$

$(NH_3)_2PtI_2$ (2.14 g, 4.44 mmol), Ag_2SO_4(1.38 g, 4.44 mmol) and $[NP(OH)(Am{\cdot}Na_2)]_n$ (1.0 g, 4.44 mmol) were reacted in accordance with the same procedure as Example 31 to obtain the title complex.

Elemental Analysis(%):

C,8.81; H,3.31; N,11.9; P,7.57; Pt,43.1

Calculated:

C,8.63; H,2.96; N,12.6; P,6.99; Pt,44.0

^1H NMR(D_2O, ppm)

3.8(1H)

IR (KBr cell, cm^{-1})

518(m), 619(m), 976(m), 1072(m), 1176(m), 1334(m), 1386(s), 1632(s), 2923(m), 3219(s), 3415(s)

Example 34 : Synthesis of $\{NP(OCH_3)[Am{\cdot}Pt(DACH)]_{0.8}(Am.Na_2)_{0.2}{\cdot}2H_2O\}_n$

Poly(dichlorophosphazene) (3.0 g), diethyl aminomalonate hydrochloride (5.76 g, 27.2 mmol), methanol (50 ml), $(DACH)PtI_2$ (2.35 g,

4.18 mmol), Ag_2SO_4 (1.30 g, 4.18 mmol) and $[NP(OCH_3)(Am{\cdot}Na_2)]_n$ (1.0 g, 4.18 mmol) were reacted in accordance with the same procedure as Example 13 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,21.5; H,4.31; N,9.72; P,5.90; Pt,31.6

Calculated:

C,21.8; H,4.20; N,10.4; P,6.39; Pt,32.2

^1H NMR(D_2O, ppm)

1.1 - 1.3(4H), 1.5(2H), 2.0(2H), 2.3(2H), 3.4(3H), 3.8(1H)

IR (KBr cell, cm^{-1})

507(m), 775(m), 931(m), 1071(m), 1033(m), 1162(m), 1248(m), 1323(s), 1651(s), 2930(m), 3202(s), 3428(s)

Example 35 : Synthesis of $\{NP(OCH_3)[Am{\cdot}Pt(NH_3)_2]_{0.85}\ (Am{\cdot}Na_2)_{0.15}{\cdot}2H_2O\}_n$

$(NH_3)_2PtI_2$ (2.02 g, 4.18 mmol), Ag_2SO_4(1.30 g, 4.18 mmol) and $[NP(OCH_3)(Am{\cdot}Na_2)]_n$ (1.0 g, 4.18 mmol) were reacted in accordance with the same procedure as Example 26 to obtain the title complex.

Elemental Analysis(%):

C,12.0; H,3.81; N,11.5; P,6.69; Pt,37.9

Calculated:

C,11.2; H,3.33; N,12.1; P,7.25; Pt,38.8

^1H NMR(D_2O, ppm)

3.3(3H), 3.8(1H)

IR (KBr cell, cm^{-1})

507(m), 614(m), 714(m), 920(m), 1032(m), 1074(m), 1186(m), 1234(m), 1387(s), 1443(m), 1636(s), 2932(m), 3251(s), 3421(s)

Example 36 : Synthesis of $\{NP(NHCH_3)[Am{\cdot}Pt(DACH)]_{0.8}(Am{\cdot}Na_2)_{0.2}{\cdot}2H_2O\}_n$

Poly(dichlorophosphazene) (3.0 g), diethyl aminomalonate hydrochloride (5.76 g, 27.2 mmol), methylamine (54.4 ml), $(DACH)PtI_2$ (2.36 g, 4.20 mmol), Ag_2SO_4 (1.31 g, 4.20 mmol) and $[NP(NHCH_3)(Am{\cdot}Na_2)]_n$ (1.0 g, 4.20 mmol) were reacted in accordance with the same procedure as Example 18 to obtain the polymeric platinum complex.

Elemental Analysis(%):

C,23.1; H,4.31; N,12.6; P,5.83; Pt,31.9

Calculated:

C,21.8; H,4.42; N,13.3; P,6.40; Pt,32.3

^{1}H NMR(D_2O, ppm)

1.1 - 1.3(4H), 1.5(2H), 2.0(2H), 2.3(2H), 2.6(3H), 3.8(1H)

IR (KBr cell, cm^{-1})

518(m), 609(m), 765(m), 1119(m), 1259(m), 1318(m), 1323(s), 1447(m), 1661(m), 2912(m), 3224(s), 3396(s)

Anticancer activity

Assays to evaluate the anticancer activity of the present polymeric platinum complexes were performed according to a standard method [Goldin et al., Europ. J. Cancer, 17, 129(1981)].

Mouce leukemia cells L1210 (10^6 cells / mouce) were transplanted to each six to eight-week-old BDFI mouce (eight animals for 1 group), and a solution of the platinum complex according to the present invention dissolved in 0.9% physiological saline was then administered at doses of 30 - 60 mg/kg by intra peritoneal injection at 1st, 5th and 9th day. Mean value of the increased life span (ILS, %) and number of the animals survived after 60 days were examined. For comparison, cisplatin and carboplatin were used.

The results are shown in Table 1. It is found that the anticancer activity of the complexes of the present invention is much higher than that of cisplatin or carboplatin.

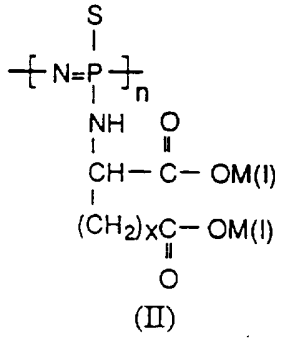
In addition, acute toxicity of some representative complexes of the present invention (LD_{50} = 160 mg/kg in Example 1; LD_{50} = 130 mg/kg in Example 21) is much lower than that of cisplatin (LD_{50} = 13 mg/kg) and comparative to that of carboplatin (LD_{50} = 180 mg/kg). Thus, the complexes of the present invention are highly promising to be developed as the third-generation anticancer agent.

Table 1

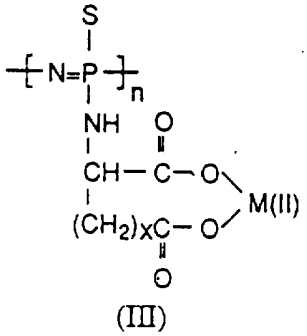
Compound	Dose(mg/kg)	ILS(%)	No. of survived animals after 60 days
Example 1	60	>542	8/8
	30	>288	3/8
Example 11	30	>279	3/8
Example 12	30	>460	6/8
Example 13	30	>142	1/8
Example 15	30	>143	1/8
Example 17	30	>385	5/8
Example 18	30	>195	1/8
Example 20	30	103	0
Example 21	60	>435	6/8
	30	>157	1/8
Example 36	30	123	0
Cisplatin	4	80	0
Carboplatin	40	60	0

CLAIMS

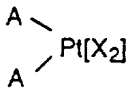
1. A polymeric platinum complex represented by following formula (I) :



(II)



(III)



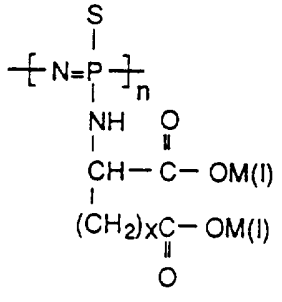
(IV)

wherein, polymeric backbone is a polyphosphazene having P=N repeating unit; S represents hydroxy group, alkoxy group such as methoxy, ethoxy or (2-methoxy)ethoxy group, or alkylamine group such as methylamine or dimethylamine group as solubilizing group: A represents ammonia, or C_1 - C_3 alkylamine such as methylamine, ethylamine or cyclopropylamine(CPA) as monodentate neutral ligand, or AA-type bidentate chelete amine selected from the group consisting of ethylenediamine(en), propylenediamine(pn), 2-hydroxy-1,3-diaminopropane (HDAP), 2,2-dimethyl-1,3-diaminopropane (DMDAP), 1,1-diaminomethyl-cyclobutane(DAMCB), tetrahydro-4H-pyrane-4,4-dimethanamine (THPDMA), 2,2-bisaminomethyl-1,3-propandiol(BAMPDO) and trans(±)-1,2-diaminocyclohexane(DACH); x showing the type of dicarboxylic amino acid as anion group represents 0, 1 or 2, the type being aminomalonic acid (Am) derivatives when x=0, being aspartic acid derivatives (Asp) when x=1, and being glutamic acid derivatives (Glt) when x=2; M represents two alkaline metal ions such as sodium ion or potassium ion, or one alkaline earth ion such as calcium ion or barium ion; m showing the content of platinum complex is 0.2 to 1; and n showing degree of polymerization of polyphosphazene is 10 to 100.

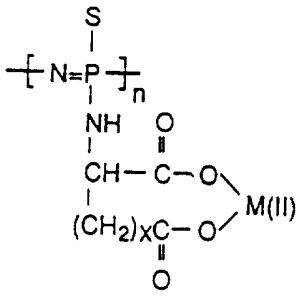
2. A polymeric platinum complex according to claim 1, wherein

m is 1.

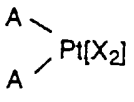
3. A process for preparation of the polymeric platinum complex represented by general formula (I) as defined in claim 1, comprising the steps of reacting an alkaline metal salt of general formula (II) or alkaline earth metal salt of general formula (III) obtained by incorporating a solubilizing group and a dicarboxylic amino acid derivative as a spacer group for the diamineplatinum(II) moiety and hydrolyzing the derivative, with a diamineplatinum(II) salt of general formula (IV) in a molar ratio 1:0.2 to 1:1 in an aqueous solution at room temperature.



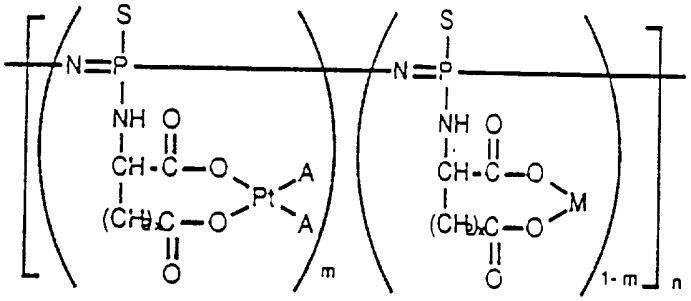
(II)



(III)



(IV)



(I)

wherein, S, A, x, m and n are defined as above, M(I) is ammonium or alkaline metal ion, M(II) is alkaline earth metal ion, X_2 is anion(s) such as two nitrate ions or one sulfate ion.

4. A process according to claim 3, wherein alkaline metal salt of general formula(II) or alkaline earth metal salt of general formula (III) is reacted with diamineplatinum(II) salt of general formula(IV) in a molar ratio

of 1:1.

5. A process according to claim 3, wherein dicarboxylic amino acid is selected form the group consisting of methyl ester, ethyl ester, benzyl ester and alkylamide of aminomalonic acid, aspartic acid or glutamic acid, and the solubilizing group is selected from the group consisting of hydroxy group, alkoxy group selected from methoxy group, ethoxy group or (2-methoxy)ethoxy group, or water soluble amine selected from methylamine or dimethylamine.

6. A process according to claim 3, wherein the alkaline metal is sodium or potassium, the alkaline earth metal is barium or calcium, and the diamineplatinum(II) salt of general formula (IV) is diamineplatinum(II) sulfate or diamineplatinum(II) nitrate.

7. A process according to claim 6, wherein alkaline metal salt of general formula (II) and diamineplatinum(II) sulfate or diamineplatinum(II) nitrate of general formula (IV) are reacted in an aqueous solution at room temperature in a molar ratio of 1:0.2 to 1:1; the reaction mixture is concentrated; and then organic solvent is added thereto.

8. A process according to claim 7, wherein the organic solvent is a single solvent or a mixed solvent selected from acetone, ethanol, methanol and ethyl ether.

9. A process according to claim 6, wherein alkaline metal salt of general formula (II) and diamineplatinum(II) nitrate of general formula (IV) are reacted in an aqueous solution at room temperature in a molar ratio of 1:0.2 to 1:1; and then the reaction mixture is dialyzed using a semipermeable membrane which transits molecules of molecular weight 1000 or less.

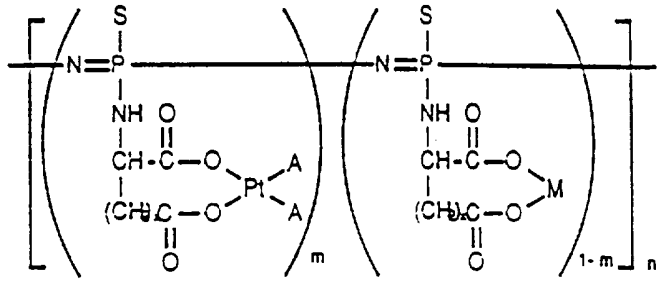
10. A process according to claim 6, calcium or barium salt of general formula(III) and diamineplatinum(II) sulfate of general formula(IV) are reacted in an aqueous solution at room temperature in a molar ratio of 1:0.2 to 1:1, and calcium or barium sulfate is removed by precipitation.

11. An anticancer agent comprising polymeric platinum complex of general formula(I) defined in claim 1 or 2 as an active component.

AMENDED CLAIMS

[received by the International Bureau on 20 January 1997 (20.01.97); original claim 1 amended; remaining claims unchanged (1 page)]

1. A polymeric platinum complex represented by following formula (I) :



(I)

wherein, polymeric backbone is a polyphosphazene having P=N repeating unit; S represents hydroxy group, alkoxy group such as methoxy, ethoxy or (2-methoxy)ethoxy group, or alkylamine group such as methylamine or dimethylamine group as solubilizing group: A represents ammonia, or C_1 - C_3 alkylamine such as methylamine, ethylamine or cyclopropylamine(CPA) as monodentate neutral ligand, or AA-type bidentate chelete amine selected from the group consisting of ethylenediamine(en), propylenediamine(pn), 2-hydroxy-1,3-diaminopropane (HDAP), 2,2-dimethyl-1,3-diaminopropane (DMDAP), 1,1-diaminomethyl-cyclobutane(DAMCB), tetrahydro-4H-pyrane-4,4-dimethanamine (THPDMA), 2,2-bisaminomethyl-1,3-propandiol(BAMPDO) and trans(±)-1,2-diaminocyclohexane(DACH); x showing the type of dicarboxylic amino acid as anion group represents 0, 1 or 2, the type being aminomalonic acid (Am) derivatives when x=0, being aspartic acid derivatives (Asp) when x=1, and being glutamic acid derivatives (Glt) when x=2; M represents two alkaline metal ions such as sodium ion or potassium ion, or one alkaline earth ion such as calcium ion or barium ion; m showing the content of platinum complex is 0.2 to 1; and n showing degree of polymerization of polyphosphazene is 10 to 100.

2. A polymeric platinum complex according to claim 1, wherein

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 95/00172

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 F 15/00; A 61 K 31/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 F; C 08 G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DARC CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 290 280 A2 (SANKYA COMPANY) 09 November 1988 (09.11.88), claims 1,34,35.	1,3,11
A	EP 0 284 197 A1 (TANABE SEIYAKA) 28 September 1988 (28.09.88), claims 1,12,13..	1,3,11
A	WO 81/00 256 A1 (UNITED STATES GOVERNMENT) 05 February 1981 (05.02.81), claim 1.	1
A	US 5 104 947 A (ETIENNE SCHACHT et al.) 14 April 1992 (14.04.92), abstract.	1
A	US 4 151 185 A (HARRY R. ALLCOCK et al.) 24 April 1979 (24.04.79), claims 1,5-7; abstract.	1,11

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 February 1996 (23.02.96)	14 May 1996 (14.05.96)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Reif Telephone No. 1/5337058/27

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 95/00172

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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		AU B2 617314	28-11-91
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		CN B 1017803	12-08-92
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