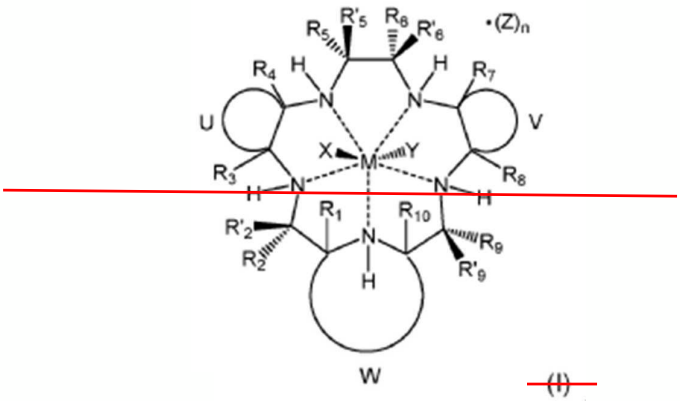
~~WHAT IS CLAIMED IS:~~

CLAIMS

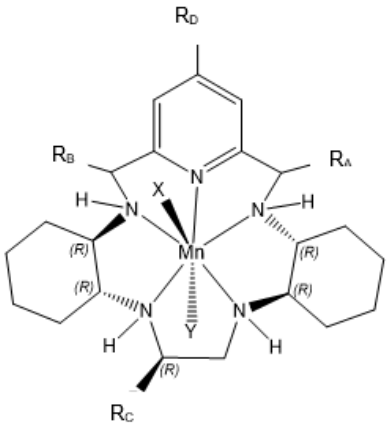
1. ~~A method~~ Use of a pentaaza macrocyclic ring complex corresponding to Formula (III) or (IV) in the manufacture of a medicament for treating a cancer~~ in a mammalian subject afflicted with the cancer~~, the ~~method~~medicament consisting essentially of:

~~administering to the subject~~ a therapeutically effective amount of a platinum-based anticancer agent;

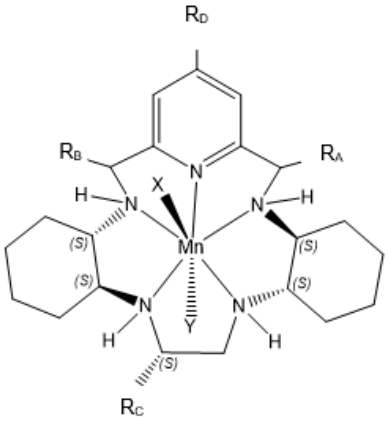
~~administering to the subject~~ a therapeutically effective amount of a pentaaza macrocyclic ring complex corresponding to the Formula (~~I) below~~III) or (IV) below, wherein the pentaaza macrocyclic ring complex is to be administered in a dose that is sufficient to increase response of the cancer to the platinum-based anticancer agent, and wherein the pentaaza macrocyclic ring complex is to be administered, prior to, concomitantly with, or after administration of the platinum-based anticancer agent~~, whereby response of the cancer to the platinum-based anticancer agent is increased~~:



~~(I)~~



(III)



(IV)

wherein

~~M is Mn^{2+} or Mn^{3+};~~

~~R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9~~ R_A, R_B, R_C, and ~~R_{10}~~ R_D are independently hydrogen~~,~~ or hydrocarbyl~~, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting of OR_{11}, $NR_{11}R_{12}$, COR_{11}, CO_2R_{11}, $CONR_{11}R_{12}$, SR_{11}, SOR_{11}, SO_2R_{11}, $SO_2NR_{11}R_{12}$, $N(OR_{11})(R_{12})$, $P(O)(OR_{11})(OR_{12})$, $P(O)(OR_{11})(R_{12})$,~~; and ~~$OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or alkyl;~~

~~U, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;~~

~~V, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;~~

~~W, together with the nitrogen of the macrocycle and the carbon atoms of the macrocycle to which it is attached, forms an aromatic or alicyclic, substituted or unsubstituted, saturated, partially saturated or unsaturated nitrogen-containing fused heterocycle having 2 to 20 ring carbon atoms, provided that when W is a fused aromatic heterocycle the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and R_1 and R_{10} attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent;~~

X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof~~;~~.

Z is a counterion;

n is an integer from 0 to 3; and

the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.

2. The method of use according to claim 1, comprising administeringwherein

i) therapeutically effective amounts of the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex are to be administered that reduce toxic effects of the platinum anti-cancer agent.; and/or

3. The method of claim 1 or 2, ii) wherein the pentaaza macrocyclic ring complex is to be administered in a therapeutically effective amount that results in an increase in cancer response corresponding to any selected from the group consisting of reduced tumor volume, reduced tumor growth rate, increased survival, reduced occurrence and/or extent of metastasis and reduced proliferation of cancer cells, and/or may decrease cancer complications.; and/or

4. The method of claim 1, 2 or 3, iii) wherein the pentaaza macrocyclic ring is administreredto be administered in a therapeutically effective amount that reduces levels of at least one of creatine and blood urea nitrogen (BUN).); and/or

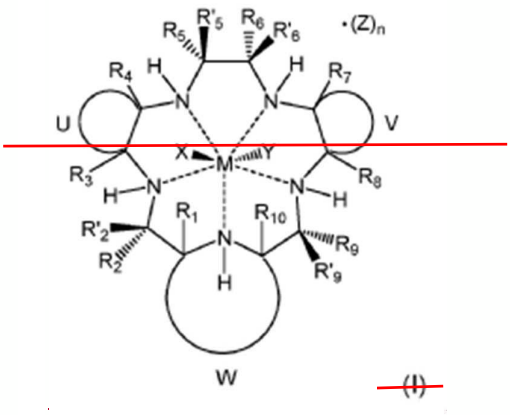
5. The method of claim 1, 2, 3 or 4, iv) wherein the pentaaza macrocyclic ring is to be administered in a therapeutically effective amount that reduces levels of markers for kidney damage selected from the group consisting of kidney injury molecule 1 (KIM1) and neutrophil gelatinase-associated lipocalin (NGAL).

6. A method

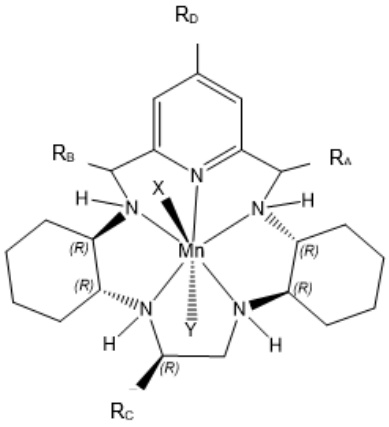
3. Use of a pentaaza macrocyclic ring complex corresponding to Formula (III) or (IV) in the manufacture of a medicament for increasing the sensitivity of a mammalian subject to treatment with a platinum-based anti-cancer agent in a subject in need thereof, the methodthe treatment of cancer, the medicament consisting essentially of:

administering to the subject a therapeutically effective amount of a pentaaza macrocyclic ring complex corresponding to the Formula (I) below,III) or (IV) below, wherein the pentaaza macrocyclic ring complex is to be administered in a dose that is sufficient to increase treatment response to the platinum-based anti-cancer agent; wherein the pentaaza macrocyclic ring complex is to be administered prior to,

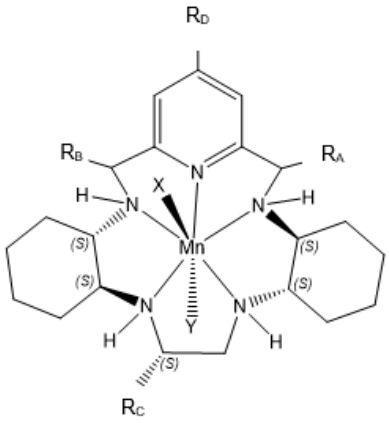
concomitantly with, or after administration of the platinum-based anticancer agent~~, whereby treatment response to the platinum-based anti-cancer agent is increased~~:



~~(I)~~



(III)



(IV)

wherein

~~M is Mn^{2+} or Mn^{3+};~~

~~R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9,~~

R_A, R_B, R_C, and ~~R_{10}~~ R_D are independently hydrogen~~,~~ or hydrocarbyl~~, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting of $-OR_{11}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{11}$, $-CONR_{11}R_{12}$, $-SR_{11}$, $-SOR_{11}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$, $-N(OR_{11})(R_{12})$, $-P(O)(OR_{11})(OR_{12})$, $-P(O)(OR_{11})(R_{12})$,~~; and ~~$-OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or alkyl;~~

~~U, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;~~

~~V, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;~~

~~W, together with the nitrogen of the macrocycle and the carbon atoms of the macrocycle to which it is attached, forms an aromatic or alicyclic, substituted or unsubstituted, saturated, partially saturated or unsaturated nitrogen-containing fused heterocycle having 2 to 20 ring carbon atoms, provided that when W is a fused aromatic heterocycle the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and R_1 and R_{10} attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent;~~

X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof~~;~~.

~~Z is a counterion;~~

~~n is an integer from 0 to 3; and~~

~~the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.~~

~~7.~~

4. The ~~method of~~ use according to claim ~~6,~~3:

i) wherein the subject is afflicted with cancer~~.~~; and/or

~~8. The method of claim 6 or 7, comprising administering~~ ii) wherein therapeutically effective amounts of the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex are to be administered that reduce toxic effects of the platinum anti-cancer agent~~.~~; and/or

~~9. The method of claim 6, 7 or 8,~~ iii) wherein the pentaaza macrocyclic ring complex is to be administered in a therapeutically effective amount that results in an increase in cancer response corresponding to any selected from the group consisting of reduced tumor volume, reduced tumor growth rate, increased survival, reduced occurrence and/or extent of metastasis, and reduced proliferation of cancer cells, and/or may decrease cancer complications~~.~~; and/or

~~10. The method of claim 6, 7, 8 or 9,~~ iv) wherein the pentaaza macrocyclic ring is

~~administrered~~to be administered in a therapeutically effective amount that reduces levels of at least one of creatine and blood urea nitrogen (BUN~~).~~); and/or

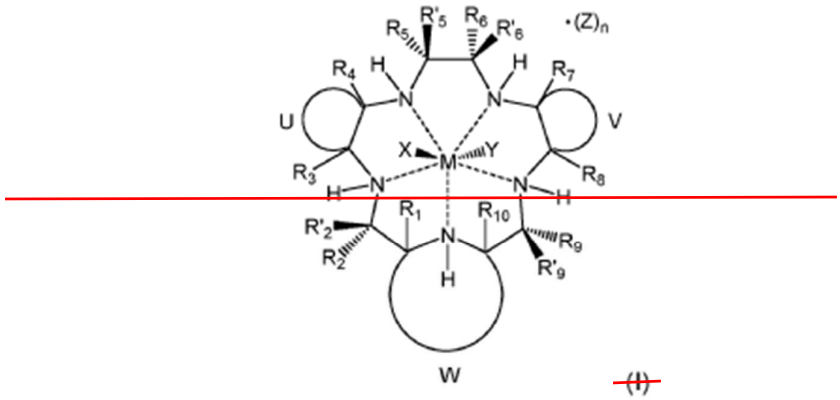
~~11. The method of any of claims 6-10,~~ v) wherein the pentaaza macrocyclic ring is ~~administrered~~to be administered in a therapeutically effective amount that reduces levels of markers for kidney damage selected from the group consisting of kidney injury molecule 1 (KIM1) and neutrophil gelatinase-associated lipocalin (NGAL).

~~12. A method of~~

5. Use of a pentaaza macrocyclic ring complex corresponding to Formula (III) or (IV) in the manufacture of a medicament for treating and/or reducing the risk of a toxic effect selected from the group consisting of nephrotoxicity and myelotoxicity associated with ~~treatment~~treatment with a platinum-based anti-cancer agent in a ~~mammalian~~ subject in need thereof, the ~~method~~medicament consisting essentially of:

~~administering to the subject~~ a therapeutically effective amount of a platinum-based anticancer agent; and

~~administering to the subject~~ a therapeutically effective amount of a pentaaza macrocyclic ring complex corresponding to the formula (~~I) below~~III) or (IV) below, wherein the pentaaza macrocyclic ring complex is to be administered in a dose that is sufficient to reduce toxic effects of the platinum-based anti-cancer agent, and wherein the pentaaza macrocyclic ring complex is to be administered, prior to, concomitantly with, or after administration of the platinum-based anticancer agent~~,~~ ~~whereby toxic effects of the platinum-based anti-cancer agent are reduced~~:

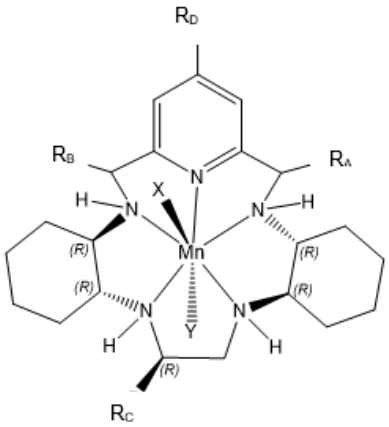


~~(I)~~

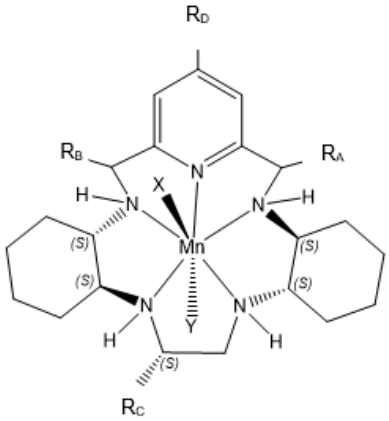
~~wherein~~

~~M is Mn^{2+} or Mn^{3+};~~

~~R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9~~



(III)



(IV)

wherein

R_A, R_B, R_C, and ~~R_{40}~~ R_D are independently hydrogen~~,~~ or hydrocarbyl~~, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting of OR_{41}, $NR_{41}R_{42}$, COR_{41}, CO_2R_{41}, $CONR_{41}R_{42}$, SR_{41}, SOR_{41}, SO_2R_{41}, $SO_2NR_{41}R_{42}$, $N(OR_{41})(R_{42})$, $P(O)(OR_{41})(OR_{42})$, $P(O)(OR_{41})(R_{42})$,~~; and ~~$OP(O)(OR_{41})(OR_{42})$,~~

~~wherein R_{41} and R_{42} are independently hydrogen or alkyl;~~

~~U, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;~~

~~V, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;~~

~~W, together with the nitrogen of the macrocycle and the carbon atoms of the macrocycle to which it is attached, forms an aromatic or alicyclic, substituted or unsubstituted, saturated, partially saturated or unsaturated nitrogen containing fused heterocycle having 2 to 20 ring carbon atoms, provided that when W is a fused aromatic heterocycle the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and R_1 and R_{40} attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent;~~

X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof~~;~~.

~~Z is a counterion;~~

n is an integer from 0 to 3; and

the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.

6.

13. The methoduse according to claim 12,5:

i) wherein the subject is afflicted with cancer.; and/or

ii)14. The method according to any one of claims 12-13, wherein the subject is suffering from nephrotoxicity and/or myelotoxicity associated with treatment with the platinum-based anti-cancer agent.; and/or

15. The method according to any one of claims 12-14, comprising administeringiii) wherein therapeutically effective amounts of the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex are to be administered that increase treatment response to the platinum-based anti-cancer agent.; and/or

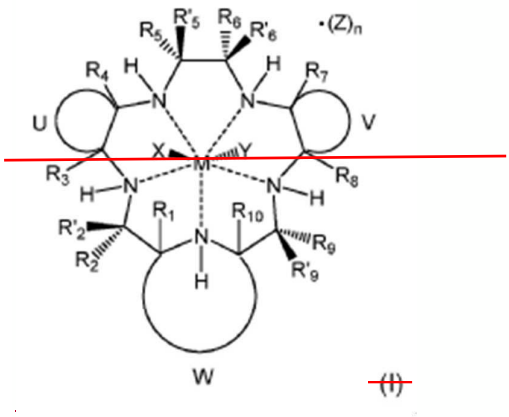
16. The method of any of claims 12-15, wherein the pentaaza macrocyclic ring complex is administered in a therapeutically effective amount that results in an increase in cancer response corresponding to any selected from the group consisting of reduced tumor volume, reduced tumor growth rate, increased survival, reduced occurrence and/or extent of metastasis, and reduced proliferation of cancer cells, and/or may decrease cancer complications

17. The method of any of claims 12-16, wherein the pentaaza macrocyclic ring is administrered in a therapeutically effective amount that reduces levels of at least one of creatine and blood urea nitrogen (BUN).

18. The method of any of claims 12-17, wherein the pentaaza macrocyclic ring is administrered in a therapeutically effective amount that reduces levels of markers for kidney damage selected from the group consisting of kidney injury molecule 1 (KIM1) and neutrophil gelatinase associated lipocalin (NGAL).

19. A method of treating and/or reducing the risk of a toxic effect selected from the group consisting of nephrotoxicity and myelotoxicity associated with treatment with a platinum based anti-cancer agent in a mammalian subject in need thereof, the method consisting essentially of:

administering to the subject a pentaaza macrocyclic ring complex corresponding to the Formula (I) below, prior to, concomitantly with, or after administration of the platinum based anticancer agent, whereby toxic effects of the platinum-based anti-cancer agent are reduced:



(I)

wherein

M is Mn^{2+} or Mn^{3+};

R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9, and R_{10} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting

of $-OR_{11}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{11}$, $-CONR_{11}R_{12}$, $-SR_{11}$, $-SOR_{11}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$, $-N(OR_{11})(R_{12})$, $P(O)(OR_{11})(OR_{12})$, $P(O)(OR_{11})(R_{12})$, and $OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or alkyl;

U, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;

V, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;

W, together with the nitrogen of the macrocycle and the carbon atoms of the macrocycle to which it is attached, forms an aromatic or alicyclic, substituted or unsubstituted, saturated, partially saturated or unsaturated nitrogen-containing fused heterocycle having 2 to 20 ring carbon atoms, provided that when W is a fused aromatic heterocycle the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and R_1 and R_{10} attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent;

X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof;

Z is a counterion;

n is an integer from 0 to 3; and

the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.

20. The method according to claim 10, wherein the subject is afflicted with cancer.

21. The method according to any one of claims 19-20, wherein the subject is suffering from nephrotoxicity and/or myelotoxicity associated with treatment with the platinum-based anti-cancer agent.

22. The method according to any one of claims 19-21, comprising administering therapeutically effective amounts of the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex that increase treatment response to the platinum based anti-cancer agent.

23. The method of any one of claims 19-22, wherein the pentaaza macrocyclic ring complex isiv) wherein the pentaaza macrocyclic ring complex is to be administered in a therapeutically effective amount that results in an increase in cancer response corresponding to any selected from the group consisting of reduced tumor volume, reduced tumor growth rate, increased survival, reduced occurrence and/or extent of metastasis, and reduced proliferation of cancer cells, and/or may decrease cancer complications.complication; and/or

24. The method of any one of claims 19-23,v) wherein the pentaaza macrocyclic ring is administreredto be administered in a therapeutically effective amount that reduces levels of at least one of creatine and blood urea nitrogen (BUN).); and/or

25. The method of any one of claims 19-24,vi) wherein the pentaaza macrocyclic ring is administreredto be administered in a therapeutically effective amount that reduces levels of markers for kidney damage selected from the group consisting of kidney injury molecule 1 (KIM1) and neutrophil gelatinase-associated lipocalin (NGAL).

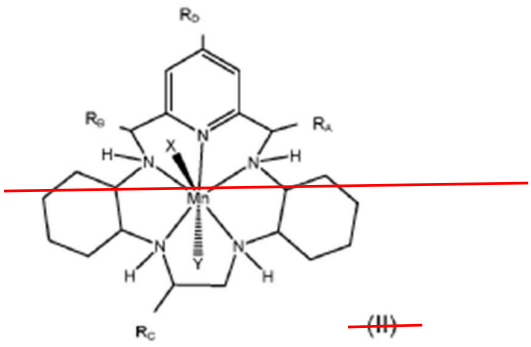
26. The method according to any preceding claim, wherein R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9, and R_{10} are each hydrogen.

27. The method according to any preceding claim,

7. Use of a wherein W is an unsubstituted pyridine moiety.

28. The method according to any preceding claim, wherein U and V are transcyclohexanyl fused rings.

~~29. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is represented by Formula (II):~~

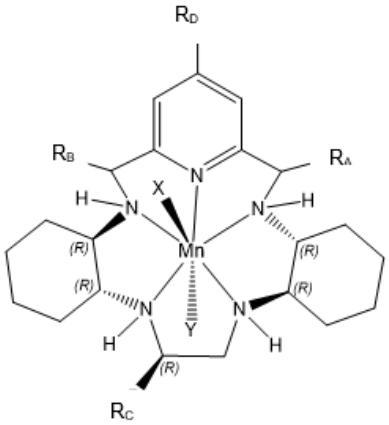


~~(II)~~

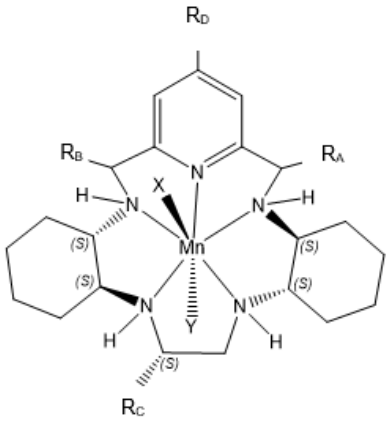
~~wherein~~

pentaaza macrocyclic ring complex corresponding to Formula (III) or (IV) in the manufacture of a medicament for treating and/or reducing the risk of a toxic effect selected from the group consisting of nephrotoxicity and myelotoxicity associated with treatment with a platinum-based anti-cancer agent in a subject in need thereof, the medicament consisting essentially of:

a pentaaza macrocyclic ring complex corresponding to the Formula (III) or (IV) below, the pentaaza macrocyclic ring complex is to be administered in a dose that is sufficient to reduce toxic effects of the platinum-based anti-cancer agent, and wherein the pentaaza macrocyclic ring complex is to be administered prior to, concomitantly with, or after administration of the platinum-based anticancer agent,:



(III)



(IV)

wherein

R_A, R_B, R_C, and R_D are independently hydrogen or hydrocarbyl; and

X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof~~; and~~.

~~R_A, R_B, R_C, and R_D are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting~~

~~of OR_{11}, $NR_{11}R_{12}$, COR_{11}, CO_2R_{11}, $CONR_{11}R_{12}$, SR_{11}, SOR_{11}, SO_2R_{11}, $SO_2NR_{11}R_{12}$, $N(OR_{11})(R_{12})$, $-P(O)(OR_{11})(OR_{12})$, $-P(O)(OR_{11})(R_{12})$,~~

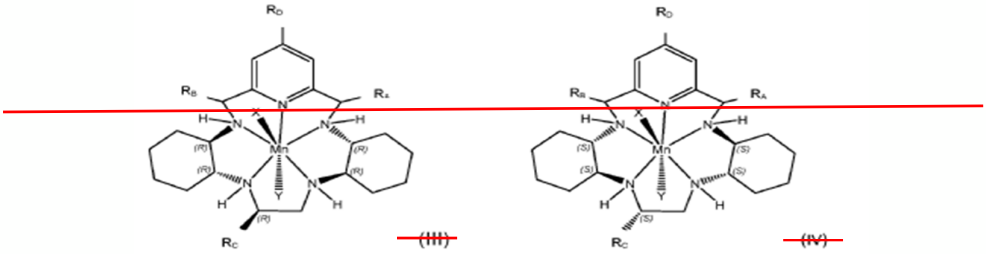
~~and $OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or alkyl.~~

~~30.~~

8. The ~~method~~use according to ~~any preceding~~ claim~~,~~ 7:

i) wherein the subject is afflicted with cancer; and/or

ii) wherein the ~~pentaaza macrocyclic ring complex is represented by Formula (III) or Formula (IV):~~



~~(III)~~ ~~(IV)~~

~~wherein~~

~~X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and~~

~~R_A, R_B, R_C,~~subject is suffering from nephrotoxicity and/or myelotoxicity associated with treatment with the platinum-based anti-cancer agent; and ~~R_D are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety~~ /or

iii) wherein therapeutically effective amounts of the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex are to be administered that increase treatment response to the platinum-based anti-cancer agent; and/or

iv) wherein the pentaaza macrocyclic ring complex is to be administered in a therapeutically effective amount that results in an increase in cancer response corresponding to any selected from the group consisting of reduced tumor volume,

reduced tumor growth rate, increased survival, reduced occurrence and/or extent of metastasis, and reduced proliferation of cancer cells, and/or may decrease cancer complications; and/or

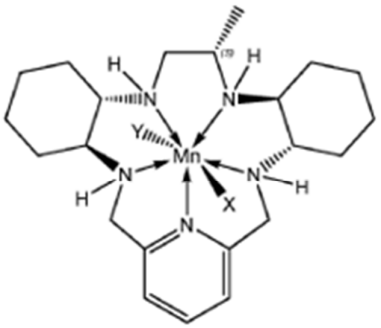
~~of OR_{11}, $NR_{11}R_{12}$, COR_{11}, CO_2R_{11}, $CONR_{11}R_{12}$, SR_{11}, SOR_{11}, SO_2R_{11}, $SO_2NR_{11}R_{12}$, $N(OR_{11})(R_{12})$, $-P(O)(OR_{11})(OR_{12})$, $-P(O)(OR_{11})(R_{12})$,~~

~~and $OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or alkyl.~~

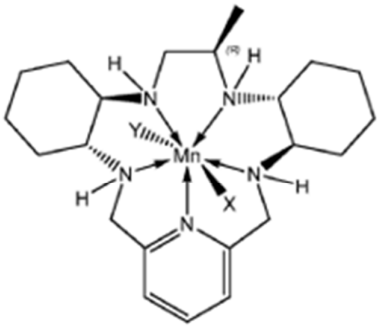
~~31.~~ v) wherein the pentaaza macrocyclic ring is to be administered in a therapeutically effective amount that reduces levels of at least one of creatine and blood urea nitrogen (BUN); and/or

vi) wherein the pentaaza macrocyclic ring is to be administered in a therapeutically effective amount that reduces levels of markers for kidney damage selected from the group consisting of kidney injury molecule 1 (KIM1) and neutrophil gelatinase-associated lipocalin (NGAL).

9. The ~~method~~use according to any preceding claim, wherein the pentaaza macrocyclic ring complex is a compound represented by a formula selected from the group consisting of Formulae (V)-(XVI):



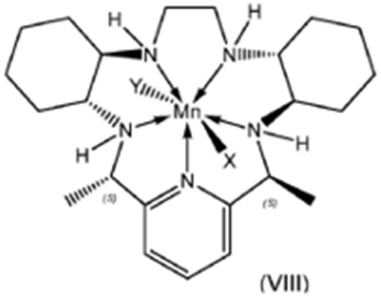
(V)



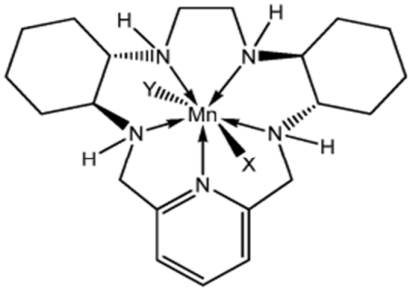
(VI)



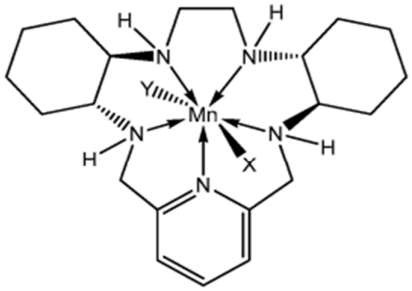
(VII)



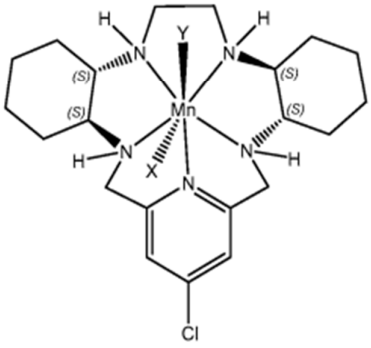
(VIII)



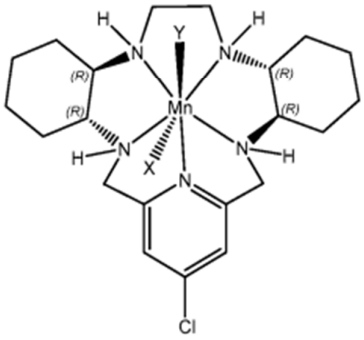
(IX)



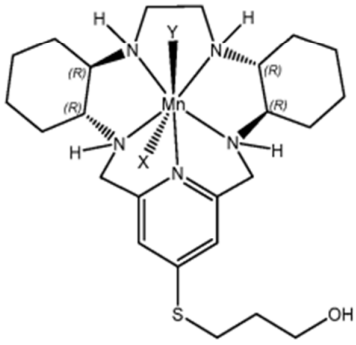
(X)



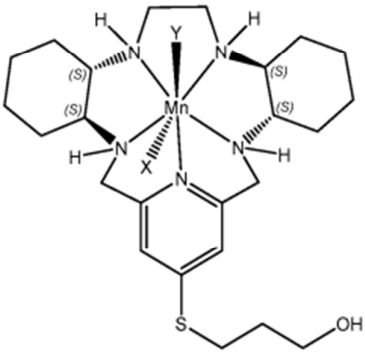
(XI)



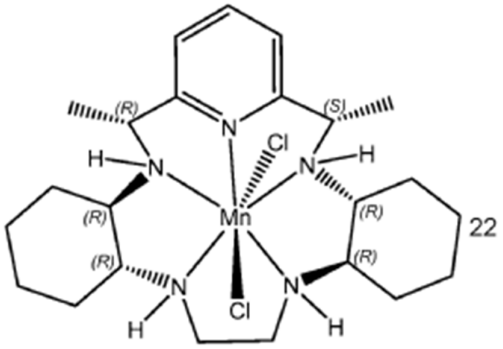
(XII)



(XIII)

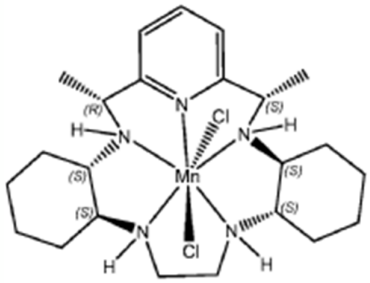


(XIV)



22

(XV)



(XVI)

10. The ~~method~~use according to any preceding claim, wherein

i) X and Y are independently selected from substituted or unsubstituted moieties of the group consisting of halide, oxo, aquo, hydroxo, alcohol, phenol, dioxygen, peroxo, hydroperoxo, alkylperoxo, arylperoxo, ammonia, alkylamino, arylamino, heterocycloalkyl amino, heterocycloaryl amino, amine oxides, hydrazine, alkyl hydrazine, aryl hydrazine, nitric oxide, cyanide, cyanate, thiocyanate, isocyanate, isothiocyanate, alkyl nitrile, aryl nitrile, alkyl isonitrile, aryl isonitrile, nitrate, nitrite, azido, alkyl sulfonic acid, aryl sulfonic acid, alkyl sulfoxide, aryl sulfoxide, alkyl aryl sulfoxide, alkyl sulfenic acid, aryl sulfenic acid, alkyl sulfinic acid, aryl sulfinic acid, alkyl thiol carboxylic acid, aryl thiol carboxylic acid, alkyl thiol thiocarboxylic acid, aryl thiol thiocarboxylic acid, alkyl carboxylic acid, aryl carboxylic acid, urea, alkyl urea, aryl urea, alkyl aryl urea, thiourea, alkyl thiourea, aryl thiourea, alkyl aryl thiourea, sulfate, sulfite, bisulfate, bisulfite, thiosulfate, thiosulfite, hydrosulfite, alkyl phosphine, aryl phosphine, alkyl phosphine oxide, aryl phosphine oxide, alkyl aryl phosphine oxide, alkyl phosphine sulfide, aryl phosphine sulfide, alkyl aryl phosphine sulfide, alkyl phosphonic acid, aryl phosphonic acid, alkyl phosphinic acid, aryl phosphinic acid, alkyl phosphinous acid, aryl phosphinous acid, phosphate, thiophosphate, phosphite, pyrophosphite, triphosphate, hydrogen phosphate, dihydrogen phosphate, alkyl guanidino, aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate, aryl thiocarbamate, alkylaryl thiocarbamate, alkyl dithiocarbamate, aryl dithiocarbamate, alkylaryl dithiocarbamate, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluoroantimonate, hypophosphite, iodate,

periodate, metaborate, tetraaryl borate, tetra alkyl borate, tartrate, salicylate, succinate, citrate, ascorbate, saccharinate, amino acid, hydroxamic acid, thiotosylate, and anions of ion exchange resins, or the corresponding anions thereof;

or X and Y correspond to -O-C(O)-X_1, where each X_1 is -C(X_2)(X_3)(X_4), and

each X_1 is independently substituted or unsubstituted phenyl or -C(X_2)(X_3)(X_4);

each X_2 is independently substituted or unsubstituted phenyl, methyl, ethyl or propyl;

each X_3 is independently hydrogen, hydroxyl, methyl, ethyl, propyl, amino, -X_5C(=O)R_{13} where X_5 is NH or O, and R_{13} is C1-C18 alkyl, substituted or unsubstituted aryl or C1-C18 aralkyl, or -OR_{14}, where R_{14} is C1-C18 alkyl, substituted or unsubstituted aryl or C1-C18 aralkyl, or together with X_4 is (=O); and

each X_4 is independently hydrogen or together with X_3 is (=O);

or X and Y are independently selected from the group consisting of charge-neutralizing anions which are derived from any monodentate or polydentate coordinating ligand and a ligand system and the corresponding anion thereof;

or X and Y are independently attached to one or more of R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9, and R_{10}; and/or

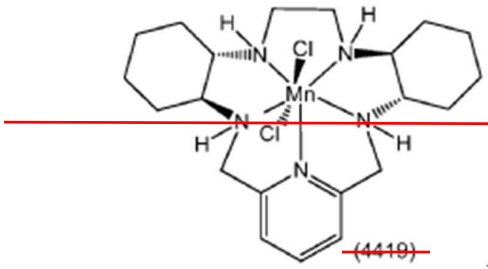
~~33. The method according to any preceding claim, wherein~~ i) X and Y are independently selected from the group consisting of fluoro, chloro, bromo, and iodo anions; and/or

~~34. The method according to any preceding claim, wherein~~ ii) X and Y are independently selected from the group consisting of alkyl carboxylates, aryl carboxylates and arylalkyl carboxylates; and/or

~~35. The method according to any preceding claim, wherein~~ iii) X and Y are independently

amino acids; and/or

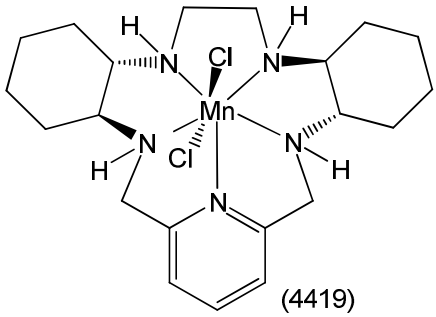
~~36. The method according to any preceding claim, wherein~~ iv) the pentaaza macrocyclic ring complex is a compound represented by the formula:



(4419)

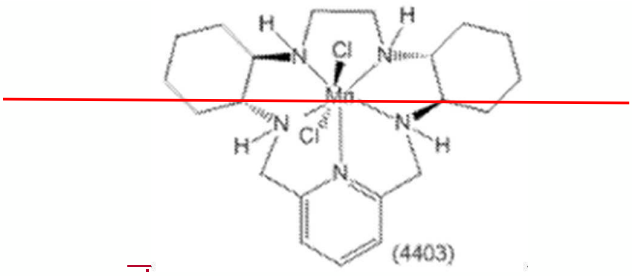
.

37. The method according to any preceding claim, wherein



(4419) ; and/or

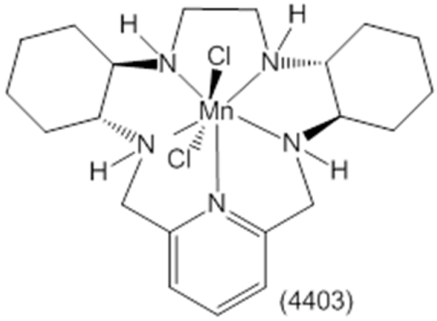
v) the pentaaza macrocyclic ring complex is a compound represented by the formula:



(4403)

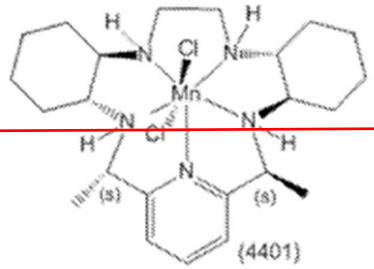
.

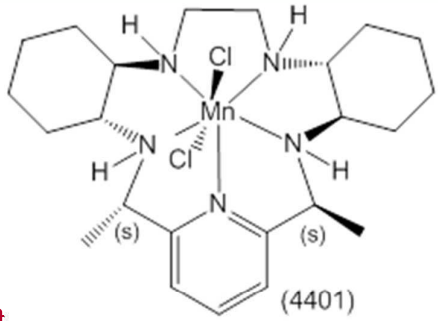
38. The method according to any preceding claim, wherein



(4403) ; and/or

vi) the pentaaza macrocyclic ring complex is a compound represented by the formula:

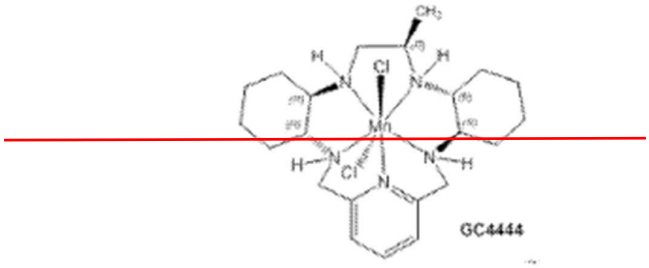




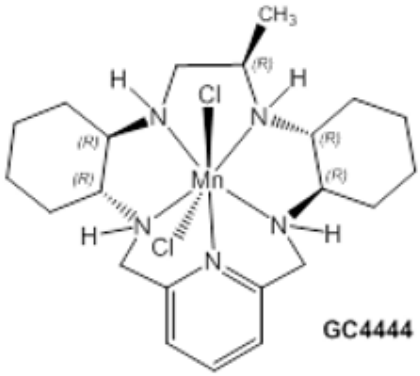
~~39. The method according to any preceding claim, wherein~~ ;

and/or

vii) the pentaaza macrocyclic ring complex is represented by the formula:

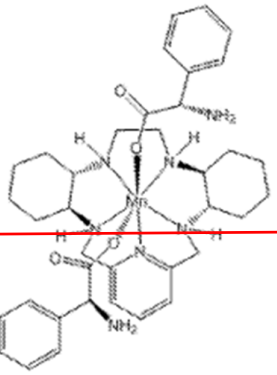


~~40. The method according to any preceding claim, wherein~~



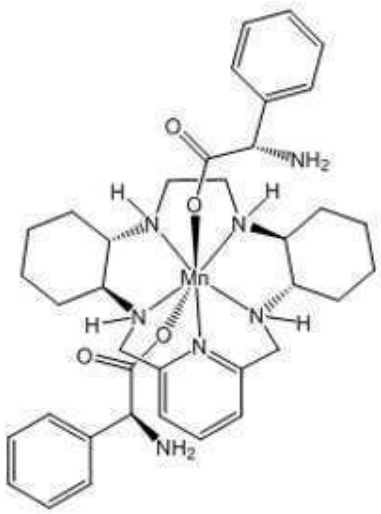
; and/or

viii) the pentaaza macrocyclic ring complex is represented by the formula:



~~GC4702~~

~~41. The method according to any preceding claim, wherein~~

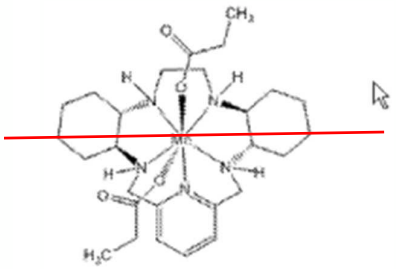


GC4702

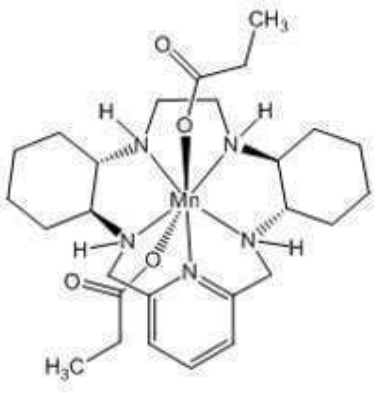
;

and/or

ix) the pentaaza macrocyclic ring complex is represented by the formula:



GC4711



GC4711

42.

11. The ~~method~~use according to any preceding claim, wherein:

i) the platinum-based anticancer agent is one selected from the group consisting of cisplatin, carboplatin, oxaliplatin, nedaplatin, lobaplatin, heptaplatin, dicycloplation, lipoplatin, LA-12, phosphaplatin, phenanthriplatin, ProLindac, triplatin tetranitrate, picoplatin, satraplatin, pyriplantin, and/or a pharmaceutically acceptable salt thereof.; and/or

~~43. The method according to any preceding claim, wherein~~ii) the platinum-based anti-cancer agent comprises cisplatin.; and/or

~~44. The method according to any preceding claim, wherein~~iii) the platinum-based anticancer agent is to be administered at a dosage in the range of 20 mg/m^2 to 200 mg/m^2.; and/or

45. The method according to any preceding claim, wherein administration ofiv) the pentaaza macrocyclic ring complex in a course of therapy is to be administered a predetermined period of time before administration of the platinum-based anti-cancer agent.; and/or

46. The method according to any preceding claim, wherein administration ofv) the pentaaza macrocyclic ring complex in a course of therapy is to be administered at least one week, one day or one hour before administration of the platinum-based anti-cancer agent.; and/or

47. The method according to any preceding claim, wherein administration ofvi) the pentaaza macrocyclic ring complex in a course of therapy is to be administered no more than 1 hour before, and/or simultaneously with, administration of the platinum-based anti-cancer agent.; and/or

48. The method according to any preceding claim, wherein administration of vii) the pentaaza macrocyclic ring complex in a course of therapy is to be administered no more than 1 hour, 1 day or 1 week after administration of the platinum-based anti-cancer agent.

49.

12. The methoduse according to any preceding claim, comprising administering wherein the platinum based anti-cancer agent is to be administered to a subject that is concurrently receiving radiation therapy.

13.50. The methoduse according to any one of claims 1-48, comprising administering11:

i) wherein the platinum based anti-cancer agent and the pentaaza macrocyclic ring complex are to be administered to a subject that is not receiving radiation therapy.; or

51. The method according to any one of claims 1-48, ii) wherein a course of therapy comprising administration of the pentaaza macrocyclic ring complex and the platinum-based anti-cancer agent, is to be administered to a subject that does not receive radiation therapy during the course of therapy.; or

52. The method according to any one of claims 1-48, comprising administeringiii) wherein one or more of the pentaaza macrocyclic ring complex and the platinum-based anti-cancer agent are to be administered to the subject on a day other than a day that the subject is receiving radiation therapy.; or

53. The method according to any one of claims 1-48, comprising administeringiv) wherein a course of therapy comprising administration of the platinum-based anti-

cancer agent and the pentaaza macrocyclic ring complex are to be administered to a subject that has not received radiation therapy for at least a day., at least a week, at least a month, or at least six months; or

54. The method according to any one of claims 1-48, comprising

administering a course of therapy comprising administration ofv) wherein the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex to a subject that has not received radiation therapy for at least a week.

55. The method according are to any one of claims 1-48, comprising administering a course of therapy comprising administration of the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex to a subject that has not received radiation therapy for at least a month.

56. The method according to any one of claims 1-48, comprising administering a course of therapy comprising administration of the platinum based anti cancer agent and the pentaaza macrocyclic ring complex to a subject that has not received radiation therapy for at least six months.

57. The method according to any one of claims 1-48, comprising administering the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complexbe administered to a subject, and delaying any radiation therapy optionally administered to the subject thereafter by at least one day after a final administration of the pentaaza macrocyclic ring complex.; or

58. The method according to any one of claims 1-48, comprising administeringvi) the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex are to be administered to a subject, and delaying any radiation therapy optionally administered to the subject

thereafter by at least one week after a final administration of the pentaaza macrocyclic ring complex.; or

59. The method according to any one of claims 1-48, comprising administeringvii) the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex are to be administered to a subject, and delaying any radiation therapy optionally administered to the subject thereafter by at least one month after a final administration of the pentaaza macrocyclic ring complex.; or

60. The method according to any one of claims 1-48, comprising administeringviii) the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex are to

be administered to a subject, and delaying any radiation therapy optionally administered ~~to the subject~~ thereafter by at least six months after a final administration of the pentaaza macrocyclic ring complex.

14. ~~61.~~ The ~~method~~use according to any preceding claim, wherein:

i) the cancer is selected from the group consisting of breast cancer, non-small-cell lung cancer, melanoma, renal cell carcinoma, urothelial carcinoma, bladder cancer, pancreatic cancer, head and neck cancers, colorectal cancer, prostate cancer, brain cancer, spindle cell carcinoma, and oral squamous cell carcinoma~~.~~; and/or

~~62. The method according to any preceding claim, wherein~~ ii) the cancer is selected from the group consisting of breast cancer, lung cancer, renal cell carcinoma, spindle cell carcinoma, colorectal cancer, oral squamous cell carcinoma, and head and neck cancer~~.~~; and/or

~~63. The method according to any preceding claim, wherein~~ iii) the cancer is at least one of lung cancer and head and neck cancer~~.~~; and/or

~~64. The method according to any preceding claim, wherein~~iv) the pentaaza macrocyclic ring complex is to be administered ~~to the subject~~ in a dose in a range of from 0.2 mg/kg to 40 mg/kg~~.~~; and/or

~~65. The method according to any preceding claim, wherein~~v) the pentaaza macrocyclic ring complex is to be administered ~~to the subject~~ in a dose in a range of from 0.2 mg/kg to 24 mg/kg~~.~~; and/or

~~66. The method according to any preceding claim, wherein~~vi) the pentaaza macrocyclic ring complex is to be administered ~~to the subject~~ in a dose in a range of from 0.2 mg/kg to 10 mg/kg~~.~~; and/or

~~67. The method according to any preceding claim, wherein~~vii) the pentaaza macrocyclic ring complex is to be administered via at least one of parenteral route and oral route~~.~~; and/or

~~68. The method according to any preceding claim, wherein~~viii) the pentaaza macrocyclic ring complex is to be administered intraperitoneally or intravenously~~.~~; and/or

~~69. The method according to any preceding claim, wherein~~ix) the subject is a human.

~~70.~~

15. A kit for use in treating cancer and/or reducing the toxic effects of a platinum-based anti-cancer agent ~~in a mammalian subject in need thereof~~, the kit consisting essentially of:

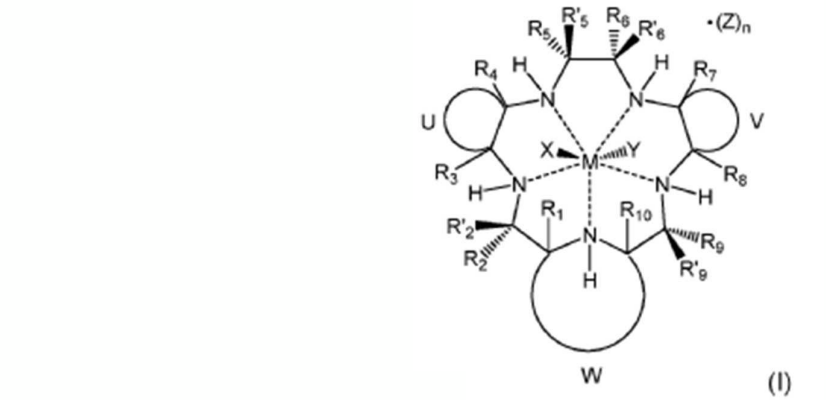
a platinum-based anti-cancer agent;

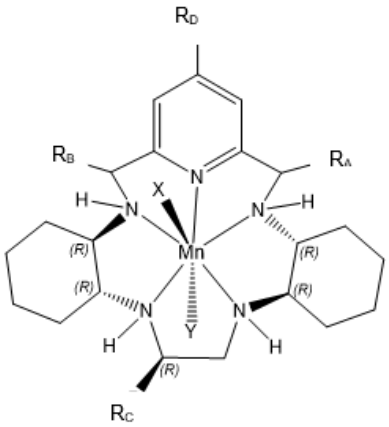
a pentaaza macrocyclic ring complex corresponding to Formula (~~I~~III) or (IV) below: and

instructions for administering a therapeutically effective amount of the platinum anti-cancer agent and a therapeutically effective amount of the pentaaza macrocyclic ring complex ~~to perform a method~~ according to any of the preceding claims,

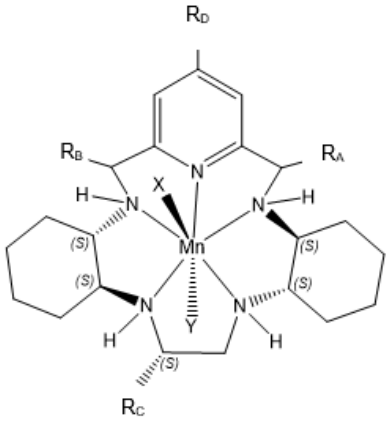
wherein the pentaaza macrocyclic ring complex according to Formula (I) is as follows:

~~wherein the pentaaza macrocyclic ring complex according to Formula (I) is as follows:~~





(III)



(IV)

wherein

~~M is Mn^{2+} or Mn^{3+};~~

~~R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9~~ R_A, R_B, R_C, and ~~R_{10}~~ R_D are independently hydrogen~~,~~ or hydrocarbyl~~, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting of OR_{11}, $NR_{11}R_{12}$, COR_{11}, CO_2R_{11}, $CONR_{11}R_{12}$, SR_{11}, SOR_{11}, SO_2R_{11}, $SO_2NR_{11}R_{12}$, $N(OR_{11})(R_{12})$, $P(O)(OR_{11})(OR_{12})$, $P(O)(OR_{11})(R_{12})$,~~; and ~~$OP(O)(OR_{11})(OR_{12})$, wherein R_{11} and R_{12} are independently hydrogen or alkyl;~~

~~U, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;~~

~~V, together with the adjacent carbon atoms of the macrocycle, forms a fused substituted or unsubstituted, saturated, partially saturated or unsaturated, cycle or heterocycle having 3 to 20 ring carbon atoms;~~

~~W, together with the nitrogen of the macrocycle and the carbon atoms of the macrocycle to which it is attached, forms an aromatic or alicyclic, substituted or unsubstituted, saturated, partially saturated or unsaturated nitrogen-containing fused heterocycle having 2 to 20 ring carbon atoms, provided that when W is a fused aromatic heterocycle the hydrogen attached to the nitrogen which is both part of the heterocycle and the macrocycle and R_1 and R_{10} attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent;~~

X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof~~;~~.

~~Z is a counterion;~~

~~n is an integer from 0 to 3; and~~

~~the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.~~