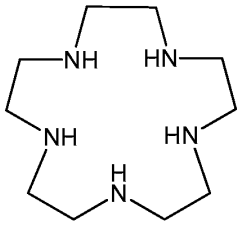
COMBINATION CANCER THERAPY WITH PENTAAZA MACROCYCLIC RING COMPLEX AND PLATINUM-BASED ANTICANCER AGENT

[0001] This application is an International PCT Patent Application which claims the benefit of priority from U.S. Patent Application No. 62/624,250 filed on 31 January 2018, all of which are hereby incorporated by reference herein in their entireties.

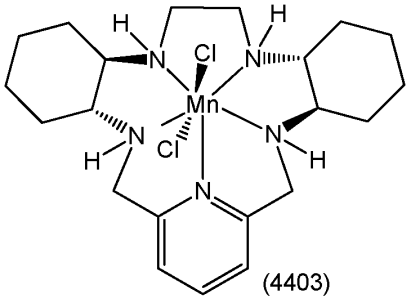
[0002] The present disclosure generally relates to combination therapies for cancer treatment, including administration of a pentaaza macrocyclic ring complex in combination with a platinum-based anticancer agent.

[0003] Transition metal-containing pentaaza macrocyclic ring complexes having the macrocyclic ring system corresponding to Formula A have been shown to be effective in a number of animal and cell models of human disease, as well as in treatment of conditions afflicting human patients.



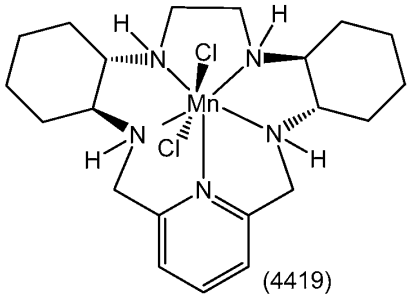
FORMULA A

For example, in a rodent model of colitis, one such compound, GC4403, has been reported to very significantly reduce the injury to the colon of rats subjected to an experimental model of colitis (see Cuzzocrea *et al.*, *Europ. J. Pharmacol., 432*, 79-89 (2001)).

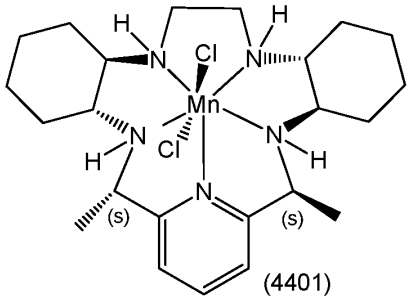


(4403)

GC4403 has also been reported to attenuate the radiation damage arising both in a clinically relevant hamster model of acute, radiation-induced oral mucositis (Murphy *et al.*, *Clin. Can. Res., 14*(13), 4292 (2008)), and lethal total body irradiation of adult mice (Thompson *et al.*, *Free Radical Res., 44*(5), 529-40 (2010)). Similarly, another such compound, GC4419, has been shown to attenuate VEGFr inhibitor-induced pulmonary disease in a rat model (Tuder, *et al.*, , *Am. J. Respir. Cell Mol. Biol.*, *29,* 88–97 (2003)). Additionally, another such compound, GC4401 has been shown to provide protective effects in animal models of septic shock (S. Cuzzocrea, et.al., *Crit. Care Med.,* 32(1), 157 (2004) and pancreatitis (S. Cuzzocrea, et.al., *Shock, 22*(3), 254-61 (2004)).



(4419)



(4401)

[0004] Certain of these compounds have also been shown to possess potent anti-inflammatory activity and prevent oxidative damage *in vivo*. For example, GC4403 has been reported to inhibit inflammation in a rat model of inflammation (Salvemini, et.al., *Science, 286,* 304 (1999)), and prevent joint disease in a rat model of collagen-induced arthritis (Salvemini *et al.*, *Arthritis & Rheumatism, 44*(12), 2009-2021 (2001)). Yet others of these compounds, MdPAM and MnBAM, have shown *in vivo* activity in the inhibition of colonic tissue injury and neutrophil accumulation into colonic tissue (Weiss *et al.*, *The Journal of Biological Chemistry*, 271(42), 26149-26156 (1996)). In addition, these compounds have been reported to possess analgesic activity and to reduce inflammation and edema in the rat-paw carrageenan hyperalgesia model, *see, e.g.*, U.S. Pat. No. 6,180,620.

[0005] Compounds of this class have also been shown to be safe and effective in the prevention and treatment of disease in human subjects. For example, GC4419 has been shown to reduce oral mucositis in head-and-neck cancer patients undergoing chemoradiation therapy (Anderson, C., *Phase 1 Trial of Superoxide Dismutase (SOD) Mimetic GC4419 to Reduce Chemoradiotherapy (CRT)-Induced Mucositis (OM) in Patients (pts) with Mouth or Oropharyngeal Carcinoma (OCC)*, Oral

Mucositis Research Workshop, MASCC/ISOO Annual Meeting on Supportive Care in Cancer, Copenhagen, Denmark (June 25, 2015)).

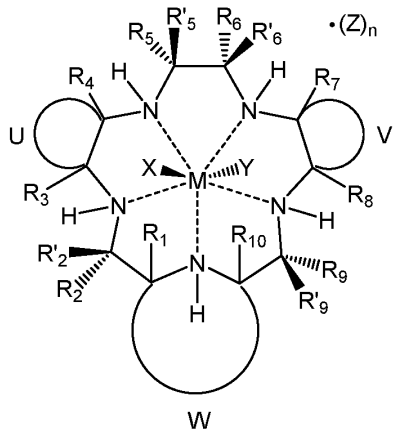
[0006] In addition, transition metal-containing pentaaza macrocyclic ring complexes corresponding to this class have shown efficacy in the treatment of various cancers. For example, certain compounds corresponding to this class have been provided in combination with agents such as paclitaxel and gemcitabine to enhance cancer therapies, such as in the treatment of colorectal cancer and lung cancer (non-small cell lung cancer) (*see, e.g.,* U.S. Patent No. 9,998,893) The 4403 compound above has also been used for treatment in *in vivo* models of Meth A spindle cell squamous carcinoma and RENCA renal carcinoma (Samlowski *et al.*, *Nature Medicine*, 9(6), 750-755 (2003), and has also been used for treatment in *in vivo* models of spindle-cell squamous carcinoma metastasis (Samlowski *et al.*, *Madame Curie Bioscience Database (Internet)*, 230-249 (2006)). The 4419 compound above has also been used in combination with cancer therapies, such as in combination with a therapy involving administration of cisplatin and radiation, to enhance treatment in *in vivo* models (Sishc *et al.*, poster for Radiation Research Society (2015)).

[0007] Platinum-based anticancer agents such as cisplatin and oxaliplatin act by induction of DNA damage in cancer cells (Cruet-Hennequart et al, *DNA Repair*, 7(4): 582-596 (2008)), and have proven to be highly effective in cancer treatment (Kellan et al, *J. Inorg Biochem*, 77(1-2); 121-124 (1999); Wang X, *Anticancer Agents Med Chem*, 10(5): 396-411 (2010); Dilruba et al, *Cancer Chemother Pharmacol*, 77(6): 1103-1124 (2016)). However, while platinum-based anticancer agents such as cisplatin are widely used as chemotherapeutic agents, such agents also frequently have toxicities associated with the administration thereof, such as nephrotoxicity, ototoxicity, gastrotoxicity, and myelotoxicity (Miller *et al.*, *Toxins (Basel),* 2(11): 2490-2518 (2010). Accordingly, the use of such platinum-based anticancer agents may be limited by the need to minimize toxic effects associated therewith.

[0008] Accordingly, a need remains for enhanced methods for cancer treatment that provide improved efficacy in the killing of cancer cells, while also providing good selectivity in the killing of cancer cells as compared to normal cells. There also remains a need for enhanced methods of treatment to improve outcomes for patients receiving these treatments. There also remains a need for methods of

treatment that reduce the toxic effects associated with platinum-based anti-cancer agents such as cisplatin.

[0009] Briefly, therefore, aspects of the present disclosure are directed to a method of treating a cancer in a mammalian subject afflicted with the cancer, the method comprising 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, prior to, concomitantly with, or after administration of the platinum-based anticancer agent, to increase the response of the cancer to the platinum-based anticancer agent:



(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;

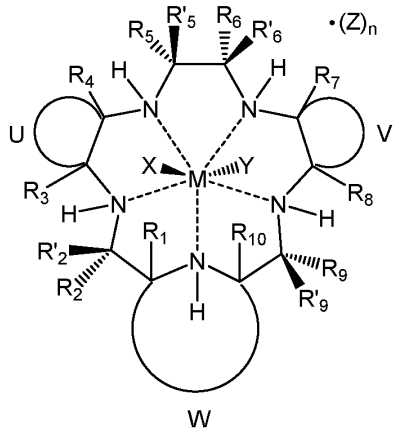
Z is a counterion;

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.

[0010] Another aspect of the present disclosure is directed to a method of increasing the sensitivity of a mammalian subject to treatment with a platinum-based anti-cancer agent in a subject in need thereof, the method comprising:

administering to the subject a therapeutically effective amount of a pentaaza macrocyclic ring complex corresponding to the Formula (I) below, prior to, concomitantly with, or after administration of the platinum-based anticancer agent, to increase the treatment response to the platinum-based anti-cancer agent:



(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;

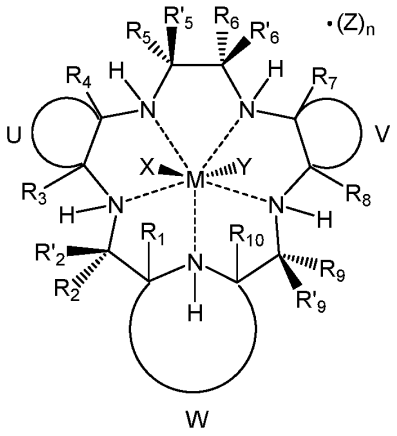
n is an integer from 0 to 3; and

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

[0011] Another aspect of the present disclosure is directed to a method of reducing toxic effects to a mammalian subject associated with treatment with a platinum-based anti-cancer agent in a subject in need thereof, the method comprising:

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, prior to, concomitantly with, or after administration of the platinum-based anticancer agent, to reduce toxic effects of the platinum-based anti-cancer agent:



(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;

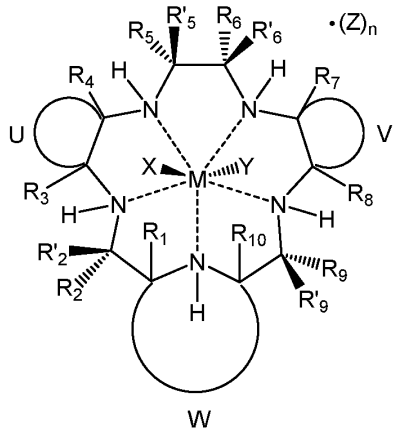
n is an integer from 0 to 3; and

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

[0012] Another aspect of the present disclosure is directed to a method of treating and/or reducing the risk for a toxic effect associated with treatment with a

platinum-based anti-cancer agent in a mammalian subject in need thereof, the method comprising:

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, to reduce toxic effects of the platinum-based anti-cancer agent:



(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.

[0013] Other objects and features will be in part apparent and in part pointed out hereinafter.

Brief Description of the Drawings

[0014] FIG. 1 shows an effect of GC4419 on survival of H460 cells in culture.

[0015] FIG. 2 shows an effect of GC4419, cisplatin and overexpressoinof catalase on survival of H1299CAT cells in culture.

[0016] FIG. 3 shows an effect of GC4419 and cisplatin on PARP activation in H460 cells.

[0017] FIG. 4 shows an effect of GC4419 and cisplatin on PARP activation H1299 cells.

[0018] FIG. 5 shows an effect of GC4419, cisplatin and radiation on PARP activation in H460 cells.

[0019] FIG. 6A shows an effect of GC4419, cisplatin and radiation on PARP activation in H1299 cells.

[0020] FIG. 6B shows treatment of H1299CAT cells with cisplatin and GC4419.

[0021] FIG. 6C shows treatment of H1299CAT cells with cisplatin, IR and GC4419.

[0022] FIGs. 7A-7D show total reactive oxygen species in cancer cell lines with treatment with cisplatin and GC4419.

[0023] FIGs. 8A-8D show mitochondrial superoxide in cancer cells with treatment with cisplatin and GC4419.

[0024] FIGs. 9A-9D show hydrogen peroxide in cancer cells with treatment with cisplatin and GC4419.

[0025] FIG. 10A shows BUN and creatinine Levels in cisplatin-treated mice.

[0026] FIG. 10B shows KIM1 and NGAL biomarkers in cisplatin-treated mice.

[0027] FIG. 10C shows cisplatin-induced weight loss.

[0028] FIG. 10D shows survival in cisplatin-treated mice.

[0029] FIG. 11A shows cisplatin-induced thrombocytopenia.

[0030] FIG. 11B shows GC4419 and white blood cell count.

[0031] FIG. 11C shows cisplatin-induced neutropenia.

[0032] FIG. 11D shows cisplatin-induced eospinophil increase.

Abbreviations and Definitions

[0033] The following definitions and methods are provided to better define the present invention and to guide those of ordinary skill in the art in the practice of the present invention. Unless otherwise noted, terms are to be understood according to conventional usage by those of ordinary skill in the relevant art.

[0034] "Acyl" means a -COR moiety where R is alkyl, haloalkyl, optionally substituted aryl, or optionally substituted heteroaryl as defined herein, *e.g.*, acetyl, trifluoroacetyl, benzoyl, and the like.

[0035] "Acyloxy" means a -OCOR moiety where R is alkyl, haloalkyl, optionally substituted aryl, or optionally substituted heteroaryl as defined herein, *e.g.*, acetyl, trifluoroacetyl, benzoyl, and the like.

[0036] "Alkoxy" means a -OR moiety where R is alkyl as defined above, *e.g.*, methoxy, ethoxy, propoxy, or 2-propoxy, n-, iso-, or tert-butoxy, and the like.

[0037] "Alkyl" means a linear saturated monovalent hydrocarbon moiety such as of one to six carbon atoms, or a branched saturated monovalent hydrocarbon moiety, such as of three to six carbon atoms, *e.g.*, C_1-C_6 alkyl groups such as methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), pentyl (including all isomeric forms), and the like.

[0038] Moreover, unless otherwise indicated, the term "alkyl" as used herein is intended to include both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Indeed, unless otherwise indicated, all groups recited herein are intended to include both substituted and unsubstituted options.

[0039] The term "C_{x-y}" when used in conjunction with a chemical moiety, such as alkyl and aralkyl, is meant to include groups that contain from x to y carbons in the chain. For example, the term C_{x-y} alkyl refers to substituted or unsubstituted saturated hydrocarbon groups, including straight chain alkyl and branched chain alkyl groups that contain from x to y carbon atoms in the chain.

[0040] "Alkylene" means a linear saturated divalent hydrocarbon moiety, such as of one to six carbon atoms, or a branched saturated divalent hydrocarbon moiety, such as of three to six carbon atoms, unless otherwise stated, *e.g.*, methylene, ethylene, propylene, 1-methylpropylene, 2-methylpropylene, butylene, pentylene, and the like.

[0041] "Alkenyl" a linear unsaturated monovalent hydrocarbon moiety, such as of two to six carbon atoms, or a branched saturated monovalent hydrocarbon moiety, such as of three to six carbon atoms, *e.g.*, ethenyl (vinyl), propenyl, 2-propenyl, butenyl (including all isomeric forms), pentenyl (including all isomeric forms), and the like.

[0042] "Alkaryl" means a monovalent moiety derived from an aryl moiety by replacing one or more hydrogen atoms with an alkyl group.

[0043] "Alkenylcycloalkenyl" means a monovalent moiety derived from an alkenyl moiety by replacing one or more hydrogen atoms with a cycloalkenyl group.

[0044] "Alkenylcycloalkyl" means a monovalent moiety derived from a cycloalkyl moiety by replacing one or more hydrogen atoms with an alkenyl group.

[0045] "Alkylcycloalkenyl" means a monovalent moiety derived from a cycloalkenyl moiety by replacing one or more hydrogen atoms with an alkyl group.

[0046] "Alkylcycloalkyl" means a monovalent moiety derived from a cycloalkyl moiety by replacing one or more hydrogen atoms with an alkyl group.

[0047] "Alkynyl" means a linear unsaturated monovalent hydrocarbon moiety, such of two to six carbon atoms, or a branched saturated monovalent hydrocarbon moiety, such as of three to six carbon atoms, *e.g.*, ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like.

[0048] "Alkoxy" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with a hydroxy group.

[0049] "Amino" means a $-NR^aR^b$ group where R^a and R^b are independently hydrogen, alkyl or aryl.

[0050] "Aralkyl" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with an aryl group.

[0051] "Aryl" means a monovalent monocyclic or bicyclic aromatic hydrocarbon moiety of 6 to 10 ring atoms *e.g.*, phenyl or naphthyl.

[0052] "Cycle" means a carbocyclic saturated monovalent hydrocarbon moiety of three to ten carbon atoms.

[0053] "Cycloalkyl" means a cyclic saturated monovalent hydrocarbon moiety of three to ten carbon atoms, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, and the like.

[0054] "Cycloalkylalkyl" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with a cycloalkyl group, *e.g.*, cyclopropylmethyl, cyclobutylmethyl, cyclopentylethyl, or cyclohexylethyl, and the like.

[0055] "Cycloalkylcycloalkyl" means a monovalent moiety derived from a cycloalkyl moiety by replacing one or more hydrogen atoms with a cycloalkyl group.

[0056] "Cycloalkenyl" means a cyclic monounsaturated monovalent hydrocarbon moiety of three to ten carbon atoms, *e.g.*, cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl, and the like.

[0057] "Cycloalkenylalkyl" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with a cycloalkenyl group, *e.g.*, cyclopropenylmethyl, cyclobutenylmethyl, cyclopentenylethyl, or cyclohexenylethyl, and the like.

[0058] "Ether" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with an alkoxy group.

[0059] "Halo" means fluoro, chloro, bromo, or iodo, preferably fluoro or chloro.

[0060] "Heterocycle" or "heterocyclyl" means a saturated or unsaturated monovalent monocyclic group of 4 to 8 ring atoms in which one or two ring atoms are heteroatom selected from N, O, or $S(O)_n$, where n is an integer from 0 to 2, the remaining ring atoms being C. The heterocyclyl ring is optionally fused to a (one) aryl or heteroaryl ring as defined herein provided the aryl and heteroaryl rings are monocyclic. The heterocyclyl ring fused to monocyclic aryl or heteroaryl ring is also referred to in this Application as "bicyclic heterocyclyl" ring. Additionally, one or two ring carbon atoms in the heterocyclyl ring can optionally be replaced by a –CO- group. More specifically the term heterocyclyl includes, but is not limited to, pyrrolidino, piperidino, homopiperidino, 2-oxopyrrolidinyl, 2-oxopiperidinyl, morpholino, piperazino, tetrahydropyranyl, thiomorpholino, and the like. When the heterocyclyl ring is unsaturated it can contain one or two ring double bonds provided that the ring is not aromatic. When the heterocyclyl group is a saturated ring and is not fused to aryl or heteroaryl ring as stated above, it is also referred to herein as saturated monocyclic heterocyclyl.

[0061] "Heteroaryl" means a monovalent monocyclic or bicyclic aromatic moiety of 5 to 10 ring atoms where one or more, preferably one, two, or three, ring atoms are heteroatom selected from N, O, or S, the remaining ring atoms being carbon. Representative examples include, but are not limited to, pyrrolyl, pyrazolyl, thienyl, thiazolyl, imidazolyl, furanyl, indolyl, isoindolyl, oxazolyl, isoxazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolinyl, isoquinolinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl, and the like.

[0062] "Nitro" means $–NO_2$.

[0063] "Organosulfur" means a monovalent moiety a –SR group where R is hydrogen, alkyl or aryl.

[0064] "Platinum based anticancer agent" refers to the class of compounds having anti-cancer effects that are coordination complexes of platinum, and that may also be referred to as platins, platinates, and platinum-based antineoplastic agents. Examples of platinum-based anticancer agents used in chemotherapy include cisplatin, oxaliplatin, carboplatin, nedaplatin, lobaplatin, heptaplatin, dicycloplation, lipoplatin, LA-12, phosphaplatin, phenanthriplatin, ProLindac, triplatin tetranitrate, picoplatin, satraplatin and/or pharmaceutically acceptable salts thereof.

[0065] "Substituted alkyl," "substituted cycle," "substituted phenyl," "substituted aryl," "substituted heterocycle," and "substituted nitrogen heterocycles" means an alkyl, cycle, aryl, phenyl, heterocycle or nitrogen-containing heterocycle, respectively, optionally substituted with one, two, or three substituents, such as those independently selected from alkyl, alkoxy, alkoxyalkyl, halo, hydroxy, hydroxyalkyl, or organosulfur. Generally, the term "substituted" includes groups that are substituted with any one or more of C_{1-4}alkyl, C_{2-4}alkenyl, halogen, alcohol and/or amine.

[0066] "Thioether" means a monovalent moiety derived from an alkyl moiety by replacing one or more hydrogen atoms with an –SR group wherein R is alkyl.

[0067] As used herein, (i) the compound referred to herein and in the Figures as compound 401, 4401 or GC4401 is a reference to the same compound, (ii) the compound referred to herein and in the Figures as compound 403, 4403 or GC4403 is a reference to the same compound, (iii) the compound referred to herein and in the Figures as compound 419, 4419 or GC4419 is a reference to the same compound, and (iv) the compound referred to herein and in the Figures as compound 444, 4444 or GC4444 is a reference to the same compound.

[0068] Furthermore, the use of the term "consisting essentially of," in referring to a method of treatment, means that the method substantially does not involve providing another therapy and/or another active agent in amounts and/or under conditions that would be sufficient to provide the treatment, and which are other than the therapies and/or active agents specifically recited in the claim. Similarly, the use of the term "consisting essentially of," in referring to a kit for treatment, means that the kit substantially does not include another therapy and/or another active agent provided in

amounts and/or under conditions that would be sufficient to provide the treatment, and which are other than the therapies and/or active agents specifically recited in the claim.

Detailed Description

[0069] In one embodiment, aspects of the present disclosure are directed to the treatment of cancer by administration of a therapeutically effective amount of a pentaaza macrocyclic ring complex according to Formula (I), described below, in combination with a therapeutically effective amount of a platinum-based anticancer agent, to a subject suffering from cancer, to provide treatment of the cancer. The pentaaza macrocyclic ring complexes may be administered prior to, concomitantly with, or after administration of the platinum-based anticancer agent, to increase response of the cancer to the platinum-based anti-cancer agent. In particular, it has unexpectedly been discovered that the pentaaza macrocyclic ring complex according to Formula (I) exhibits synergistic effects when administered in combination with the platinum-based anti-cancer agent, to produce a more-than-additive effect as compared to administration of either the platinum-based anti-cancer agent and/or pentaaza macrocyclic ring complex according to Formula (I) alone. Without being limited by any specific theory, it is believed that the pentaaza macrocyclic ring complex according to Formula (I) may act to sensitize cancer cells to treatment with the platinum-based anti-cancer agent, such that the cancer cells become highly responsive to the anti-cancer effects of the platinum-based anti-cancer agent. Furthermore, again without being limited by any particular theory, it has been discovered that the platinum-based anti-cancer agents may be capable of acting to kill cancer cells in combination with pentaaza macrocyclic ring complexes according to Formula (I) via a previously unknown mechanism of action involving hydrogen peroxide, which mechanism is synergistically enhanced by the combination. Further discussion of the synergy between the pentaaza macrocyclic ring complex according to Formula (I) and the platinum-based anti-cancer agents is provided in the Examples described herein.

[0070] Accordingly, in one aspect of the present disclosure, a method of increasing the sensitivity of a mammalian subject to treatment with a platinum-based anti-cancer agent in a subject in need thereof is provided. The method can comprise administering to the subject a therapeutically effective amount of a pentaaza macrocyclic ring complex corresponding to the Formula (I) below, prior to, concomitantly

with, or after administration of the platinum-based anticancer agent, to increase the treatment response to the platinum-based anticancer agent.

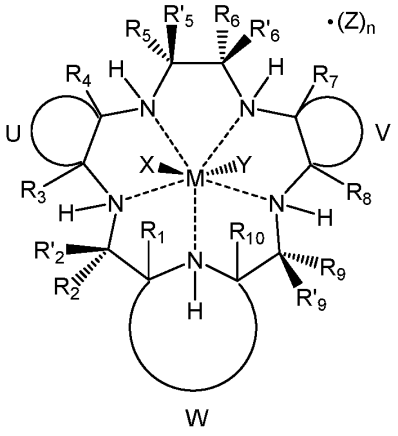
[0071] Yet another aspect of the present disclosure relates to the discovery that administration of the pentaaza macrocyclic ring complex corresponding to Formula (I) below can reduce the toxic effects of platinum-based anticancer agents, such as for example nephrotoxicity and myelotoxicity. Accordingly, in one embodiment a method of reducing toxic effects to a mammalian subject associated with treatment with a platinum-based anti-cancer agent in a subject in need thereof comprises 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, prior to, concomitantly with, or after administration of the platinum-based anticancer agent, to reduce toxic effects of the platinum-based anti-cancer agent. In yet another embodiment, a method of treating and/or reducing the risk for a toxic effect associated with treatment with a platinum-based anti-cancer agent in a mammalian subject in need thereof is provided that comprises 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, to reduce toxic effects of the platinum-based anti-cancer agent.

[0072] In one embodiment, the subject may be one that is at risk for a toxic effect associated with treatment with a platinum-based anti-cancer agent, by virtue of their receiving the platinum-based anti-cancer agent as a part of a treatment regimen. For example, the subject may be receiving the platinum-based anti-cancer agent as a part of a regimen for cancer treatment, and thus may be at risk for development of toxic effects associated with the platinum-based anti-cancer agent while receiving the cancer treatment. In another embodiment, the subject may be also and/or alternatively be one who is currently suffering from toxic effects associated with the platinum-based anti-cancer agents, such as nephrotoxicity, myelotoxicity and/or other toxicities. It has been discovered that, in certain embodiments, the administration of the pentaaza macrocyclic ring complex corresponding to Formula (I) can mitigate, alleviate and/or otherwise treat conditions associated with platinum-based anti-cancer agent toxicities, and may even be able to reduce the subject's risk of developing conditions associated with such toxicities. Accordingly, the pentaaza macrocyclic ring complex according to Formula (I)

below may, in certain embodiments, be capable of reducing the toxicity of platinum-based anti-cancer agents without substantially reducing the effectiveness of the platinum-based anticancer agents. Further, in certain embodiments, the reduced toxicity provided by the combination can even result simultaneously in an enhancement in treatment response of cancer to the platinum-based anti-cancer agent. That is, the combination may be capable of simultaneously and synergistically sensitizing cancer cells to killing with the platinum-based anti-cancer agent, while also reducing the toxic effects to normal (non-cancerous cells) of the platinum-based anti-cancer agent.

Transition Metal Pentaaza Macrocyclic Ring Complex

[0073] In one embodiment, the pentaaza macrocyclic ring complex corresponds to the complex of Formula (I):



(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.

[0074] As noted above in connection with the pentaaza macrocyclic ring complex of Formula (I), M is Mn^{2+} or Mn^{3+}. In one particular embodiment in which the pentaaza macrocyclic ring complex corresponds to Formula (I), M is Mn^{2+}. In another particular embodiment in which the pentaaza macrocyclic ring complex corresponds to Formula (I), M is Mn^{3+}.

[0075] In the embodiments in which 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} are hydrocarbyl, for example, suitable hydrocarbyl moieties include, but are not limited to alkenyl, alkenylcycloalkenyl, alkenylcycloalkyl, alkyl, alkylcycloalkenyl, alkylcycloalkyl, alkynyl, aralkyl, aryl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylcycloalkyl, cycloalkenylalkyl, and aralkyl. In one embodiment,

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, or heterocyclyl. More preferably in this embodiment, 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 or lower alkyl (*e.g.*, C_1-C_6 alkyl, more typically C_1-C_4 alkyl). Thus, for example, 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} may be independently hydrogen, methyl, ethyl, propyl, or butyl (straight, branched, or cyclic). In one preferred embodiment, 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 or methyl.

[0076] In one preferred embodiment in which the pentaaza macrocyclic ring complex corresponds to Formula (I), R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_7, R_8, R_9, R'_9, and R_{10} are each hydrogen and one of R_6 and R'_6 is hydrogen and the other of R_6 and R'_6 is methyl. In this embodiment, for example, R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R_7, R_8, R_9, R'_9, and R_{10} may each be hydrogen while R'_6 is methyl. Alternatively, for example, R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R'_6, R_7, R_8, R_9, R'_9, and R_{10} may each be hydrogen while R_6 is methyl. In another preferred embodiment in which the pentaaza macrocyclic ring complex corresponds to Formula (I), R_1, R_3, R_4, R_5, R'_5, R'_6, R_7, R_8, and R_{10} are each hydrogen, one of R_2 and R'_2 is hydrogen and the other of R_2 and R'_2 is methyl, and one of R_9 and R'_9 is hydrogen and the other of R_9 and R'_9 is methyl. In this embodiment, for example, R_1, R'_2, R_3, R_4, R_5, R'_5, R_7, R_8, R_9, and R_{10} may each be hydrogen while R_2 and R'_9 are methyl. Alternatively, for example, R_1, R_2, R_3, R_4, R_5, R'_5, R_7, R_8, R'_9, and R_{10} may each be hydrogen while R'_2 and R_9 are methyl. In another embodiment in which the pentaaza macrocyclic ring complex corresponds to Formula (I), 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.

[0077] In certain embodiments the U and V moieties are independently substituted or unsubstituted fused cycloalkyl moieties having 3 to 20 ring carbon atoms, more preferably 4 to 10 ring carbon atoms. In a particular embodiment, the U and V moieties are each trans-cyclohexanyl fused rings.

[0078] In certain embodiments the W moiety is a substituted or unsubstituted fused heteroaromatic moiety. In a particular embodiment, the W moiety is a substituted or unsubstituted fused pyridino moiety. Where W is a substituted fused pyridino moiety, for example, the W moiety is typically substituted with a hydrocarbyl or substituted hydrocarbyl moiety (*e.g.*, alkyl, substituted alkyl) at the ring carbon atom positioned para

to the nitrogen atom of the heterocycle. In a one preferred embodiment, the W moiety is an unsubstituted fused pyridino moiety.

[0079] As noted above, X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof (for example benzoic acid or benzoate anion, phenol or phenoxide anion, alcohol or alkoxide anion). For example, X and Y may be selected from the group consisting of halo, 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, among other possibilities. In one embodiment, X and Y if present, are independently selected from the group consisting of halo, nitrate, and bicarbonate ligands. For example, in this embodiment, X and Y, if present, are halo ligands, such as chloro ligands.

[0080] Furthermore, in one embodiment 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).

[0081] In yet another embodiment, 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}.

[0082] In the pentaaza macrocyclic ring complex corresponding to Formula (I), Z is a counterion (*e.g.*, a charge-neutralizing anion), wherein n is an integer from 0 to 3. In general, Z may correspond to counterions of the moieties recited above in connection for X and Y.

[0083] In combination, among certain preferred embodiments are pentaaza macrocyclic ring complexes corresponding to Formula (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 or lower alkyl;

U and V are each trans-cyclohexanyl fused rings;

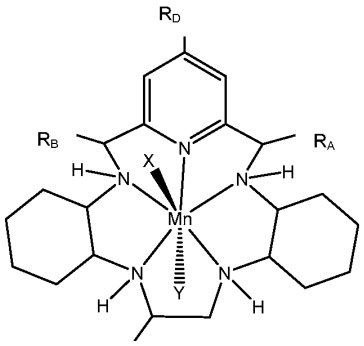
W is a substituted or unsubstituted fused pyridino moiety;

X and Y are ligands; and

Z, if present, is a charge-neutralizing anion.

[0084] More preferably in these embodiments, M is Mn^{2+}; 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 or methyl; U and V are each trans-cyclohexanyl fused rings; W is an unsubstituted fused pyridino moiety; and X and Y are independently halo ligands (*e.g.*, fluoro, chloro, bromo, iodo). Z, if present, may be a halide anion (*e.g.*, fluoride, chloride, bromide, iodide).

[0085] In yet another embodiment, the pentaaza macrocyclic ring complex is representd by Formula (II) below:



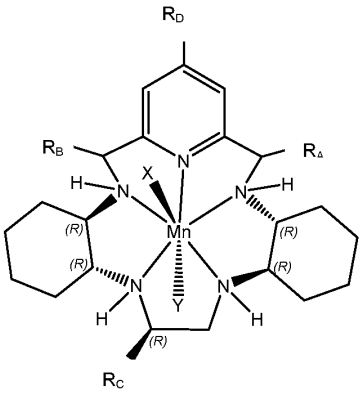
(II)

wherein

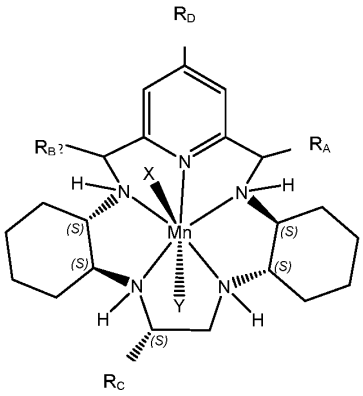
X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and

R_A, R_B, R_C, 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.

[0086] Furthermore, in one embodiment, the pentaaza macrocyclic ring complex is represented by Formula (III) or Formula (IV):



(III)



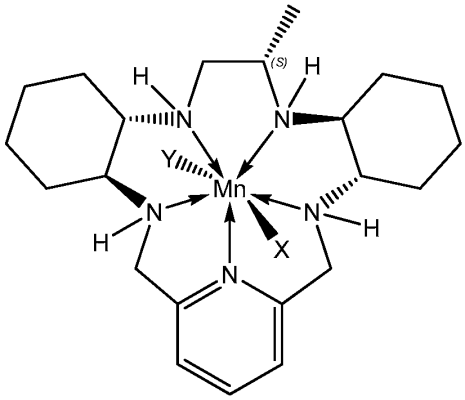
(IV)

wherein

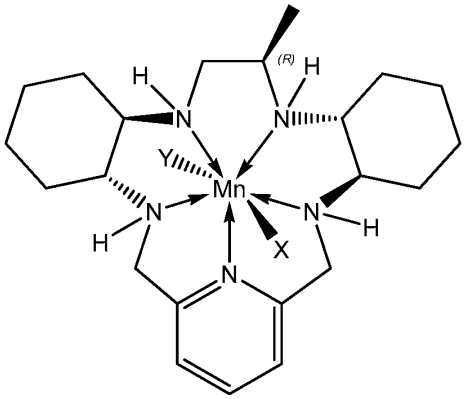
X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and

R_A, R_B, R_C, 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.

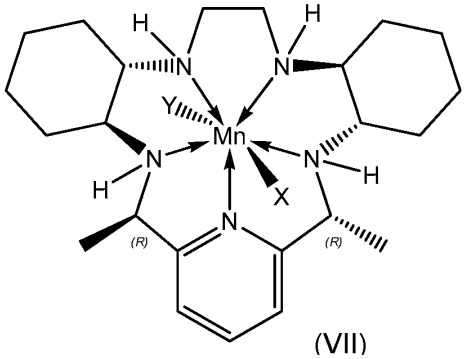
[0087] In yet another embodiment, the pentaaza macrocyclic ring complex is a compound represented by a formula selected from the group consisting of Formulae (V)-(XVI):



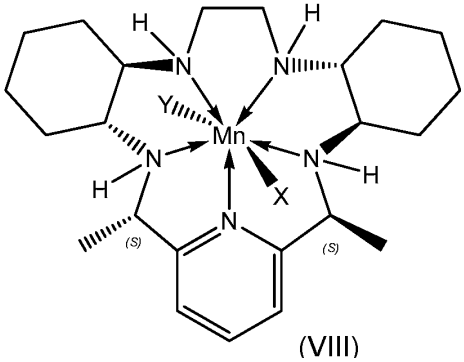
(V)



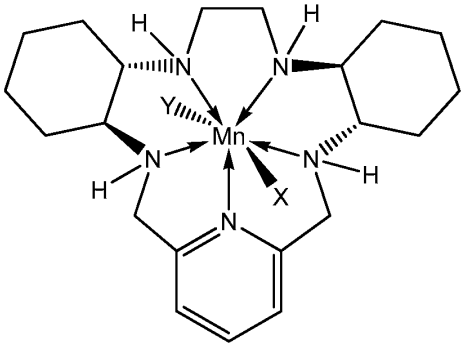
(VI)



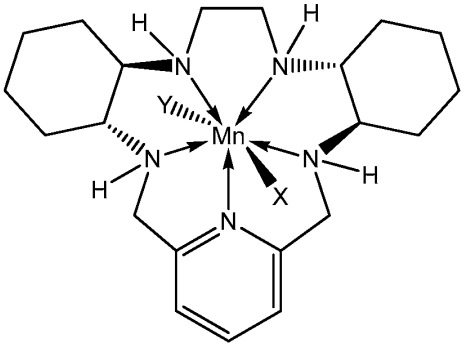
(VII)



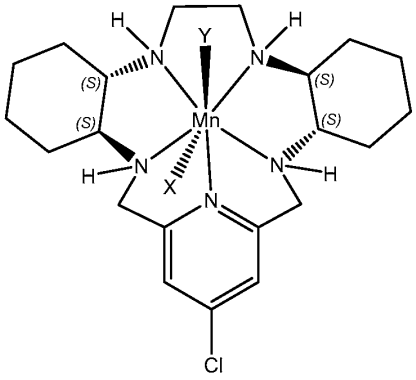
(VIII)



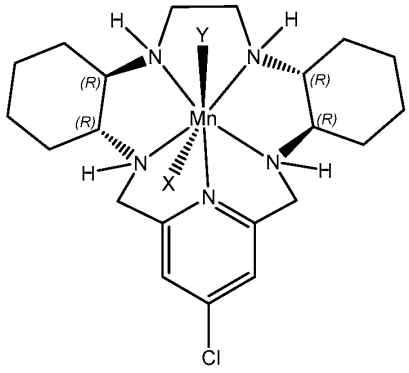
(IX)



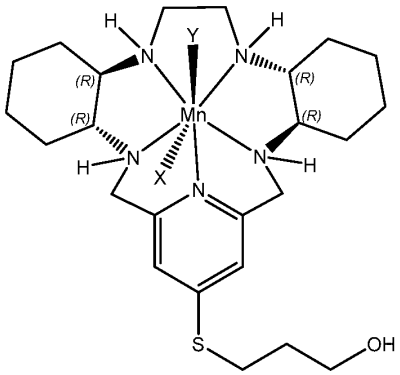
(X)



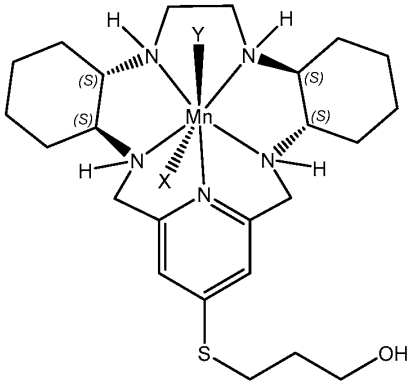
(XI)



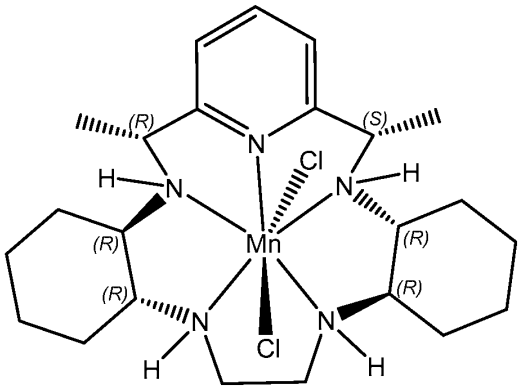
(XII)


H
N
Y
N
H
(R)
(R)
(R)
(R)
Mn
N
H
X
N
H
N
S
OH

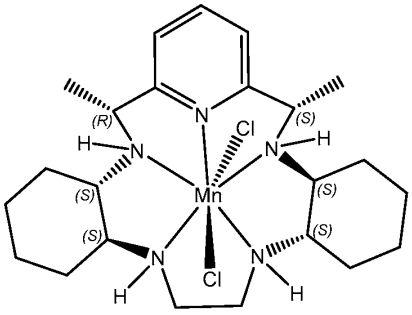
(XIII)


H
N
Y
N
H
(S)
(S)
(S)
(S)
Mn
N
H
X
N
H
N
S
OH

(XIV)


(R)
(S)
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N
N
Cl
H
H

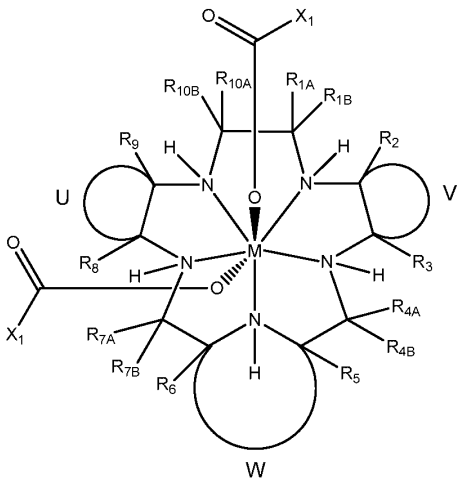
(XV)



(XVI)

[0088] In one embodiment, X and Y in any of the formulae herein are independently selected from the group consisting of fluoro, chloro, bromo and iodo anions. In yet another embodiment, X and Y in any of the formulae herein are independently selected from the group consisting of alkyl carboxylates, aryl carboxylates and arylalkyl carboxylates. In yet another embodiment, X and Y in any of the formulae herein are independently amino acids.

[0089] In one embodiment, the pentaaza macrocyclic ring complex has the following Formula (IA):



(IA)

wherein

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

R_{1A}, R_{1B}, R_2, R_3, R_{4A}, R_{4B}, R_5, R_6, R_{7A}, R_{7B}, R_8, R_9, R_{10A}, and R_{10B} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an

amino acid side chain moiety, or a moiety independently selected from the group consisting of -OR_{11}, -$NR_{11}R_{12}$, -COR_{11}, -CO_2R_{11}, -C(=O)$NR_{11}R_{12}$, -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_5 and R_6 attached to the carbon atoms which are both part of the heterocycle and the macrocycle are absent; wherein

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 or alkyl;

each X_3 is independently hydrogen, hydroxyl, alkyl, amino, -X_5C(=O)R_{13} where X_5 is NH or O, and R_{13} is C_1-C_{18} alkyl, substituted or unsubstituted aryl or C_1-C_{18} aralkyl, or -OR_{14}, where R_{14} is C_1-C_{18}alkyl, substituted or unsubstituted aryl or C_1-C_{18} aralkyl, or together with X_4 is (=O);

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

the bonds between the transition metal M and the macrocyclic nitrogen atoms and the bonds between the transition metal M and the oxygen atoms of the axial ligands –OC(=O)X_1 are coordinate covalent bonds.

[0090] In one embodiment, within Formula (IA), and groups contained therein, in one group of compounds X_1 is $–C(-X_2)(-X_3)(-X_4)$ and each X_2, X_3, and X_4, in combination, corresponds to any of the combinations identified in the following table:

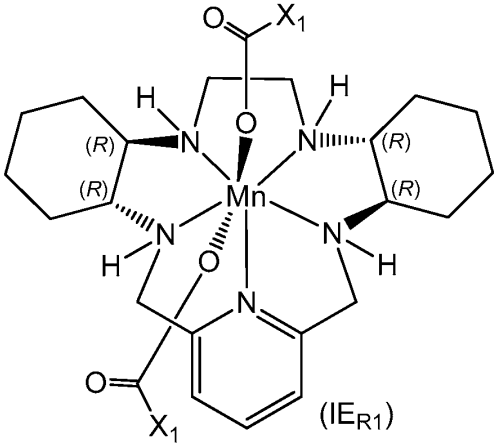
Combination	X_2	X_3	X_4
1	Ph	H	H
2	Ph	OH	H
3	Ph	NH_2	H
4	Ph	=O (X_3 and X_4 in combination)	
5	Ph	CH_3	H
6	CH_3	H	H
7	CH_3	OH	H
8	CH_3	NH_2	H
9	CH_3	=O (X_3 and X_4 in combination)	

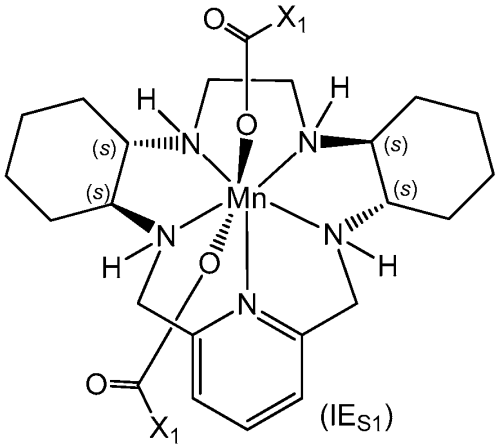
[0091] Furthermore, within embodiment (IA), and groups contained therein, in one group of compounds X_1 is $C(-X_2)(-X_3)(-X_4)$, and X_3 is $-X_5C(=O)R_{13}$, such that the combinations of X_2, X_3 and X_4 include any of the combinations identified in the following table:

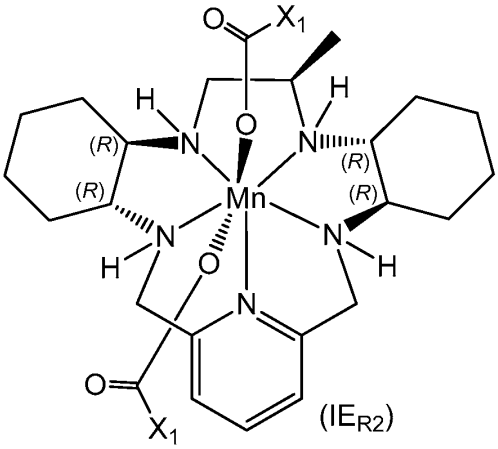
Combination	X_2	X_3	X_4
1	Ph	$NHC(=O)R_{13}$	H
2	Ph	$OC(=O)R_{13}$	H
3	CH_3	$NHC(=O)R_{13}$	H
4	CH_3	$OC(=O)R_{13}$	H

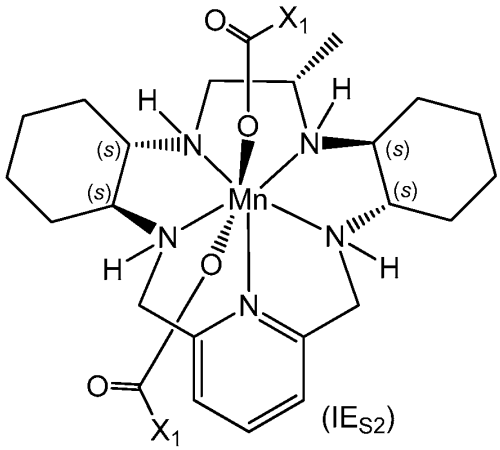
where R_{13} is C_1-C_{18} alkyl, substituted or unsubstituted aryl or C_1-C_{18} aralkyl, or $-OR_{14}$, where R_{14} is C_1-C_{18} alkyl, substituted or unsubstituted aryl or C_1-C_{18} aralkyl.

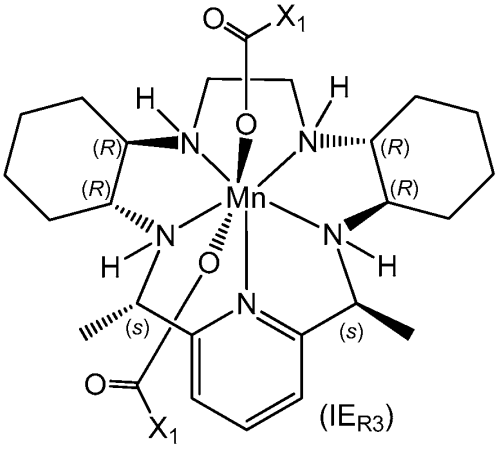
[0092] In one embodiment, the pentaaza macrocyclic ring complex corresponding to Formula (IA) is one of the complexes Formula (IE), such as (IE_{R1}), (IE_{S1}), (IE_{R2}), (IE_{S2}), (IE_{R3}), or (IE_{S3}):

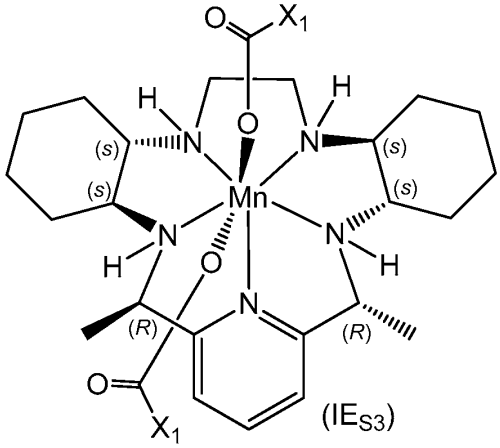

(IE_{R1})


(IE_{S1})


(IE_{R2})


(IE_{S2})


(IE_{R3})


(IE_{S3})

wherein

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

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, or together with X_4 is =O;

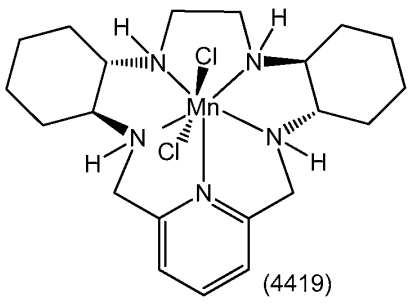
each X_4 is independently hydrogen or together with X_3 is =O; and

the bonds between the manganese and the macrocyclic nitrogen atoms and the bonds between the manganese and the oxygen atoms of the axial ligands $–OC(O)X_1$ are coordinate covalent bonds.

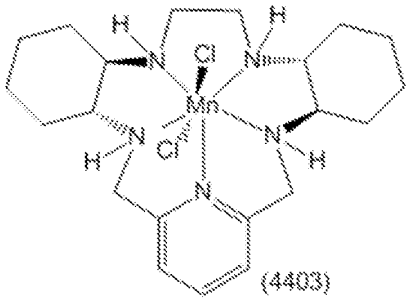
[0093] In one embodiment, each X_1 is $-C(X_2)(X_3)(X_4)$ and each $-C(X_2)(X_3)(X_4)$ corresponds to any of combinations 1 to 9 appearing in the table for Formula (IA) above.

[0094] In yet another embodiment, the X and Y in pentaaza macrocyclic ring complex of Formula (I) correspond to the ligands in Formulas (IA) or (IE). For example, X and Y in the complex of Formula (I) may correspond to $-O-C(O)-X_1$, where X_1 is as defined for the complex of Formula (IA) and (IE) above.

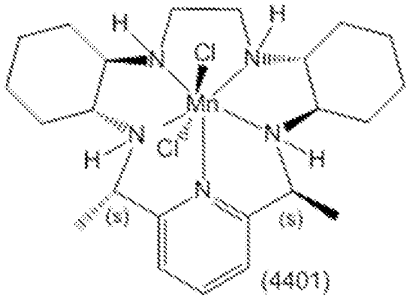
[0095] In one embodiment, the pentaaza macrocyclic ring complexes corresponding to Formula (I) (e.g., of Formula (I) or any of the subsets of Formula (I) corresponding to Formula (II)-(XIV), (IA) and (IE)), can comprise any of the following structures:



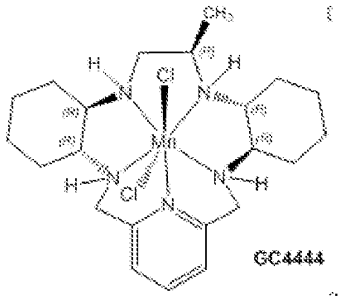
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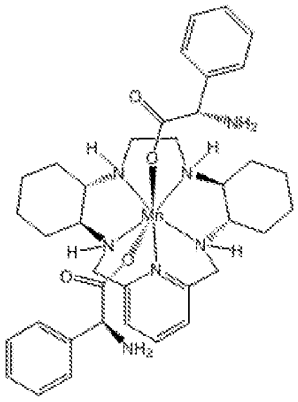


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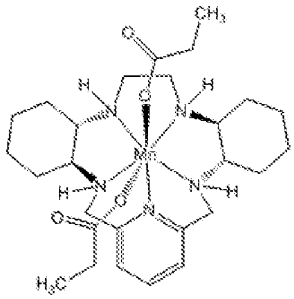
GC4444

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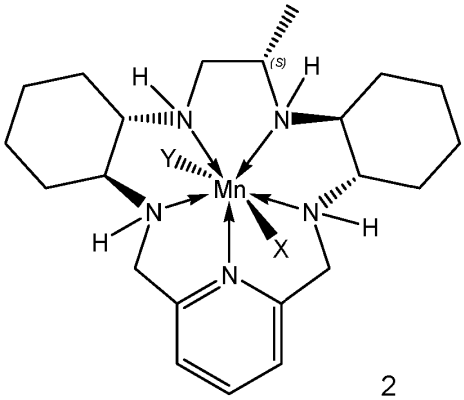
GC4702

I

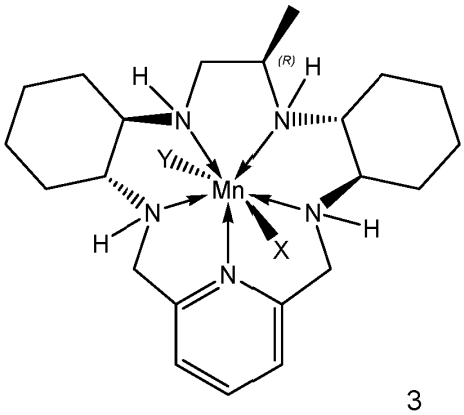


GC4711

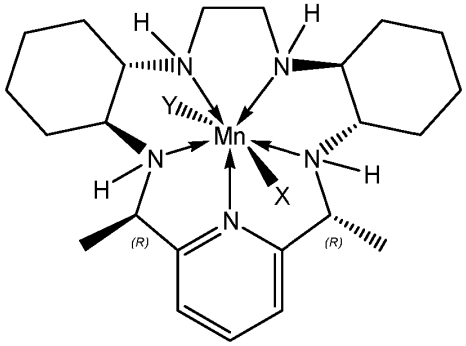
[0096] In one embodiment, the pentaaza macrocyclic ring complexes for use in the methods and compositions described herein include those corresponding to Formulae (2), (3), (4), (5), (6), and (7):



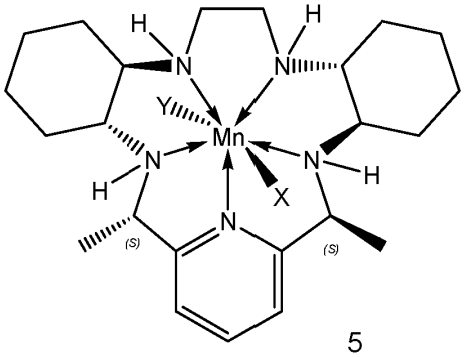
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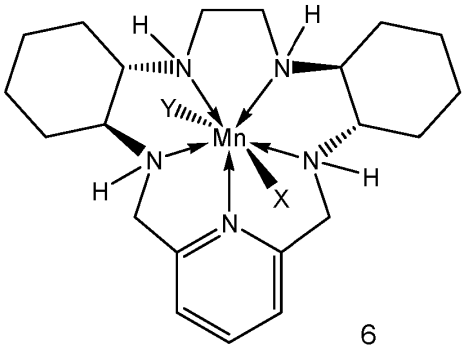
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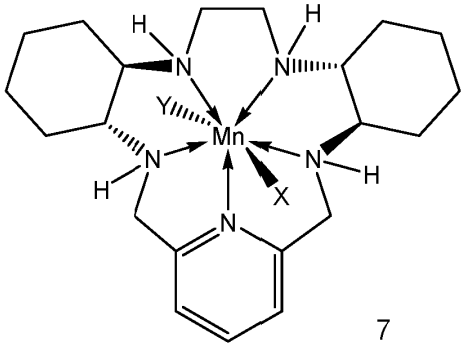
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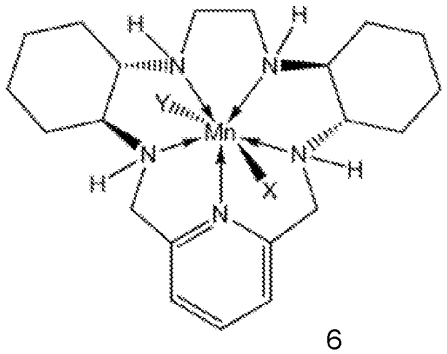
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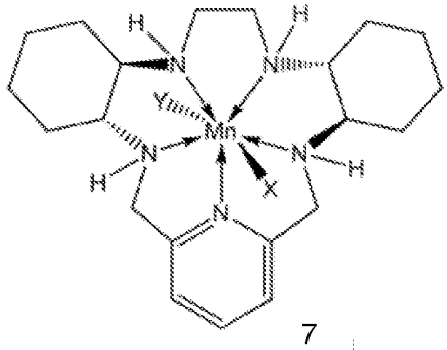
7

wherein X and Y in each of Formulae (2), (3), (4), (5), (6), and (7) are independently ligands. For example, according to one embodiment, the pentaaza macrocyclic ring complex for use in the methods and compositions described herein include those corresponding to Formulae (2), (3), (4), (5), (6), and (7) with X and Y in each of these formulae being halo, such as chloro. Alternatively, X and Y may be ligands other than chloro, such as any of the ligands described above.

[0097] In another embodiment, the pentaaza macrocyclic ring complex corresponds to Formula (6) or Formula (7):



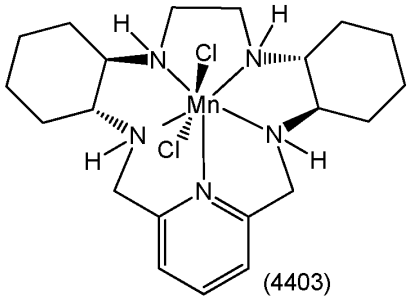
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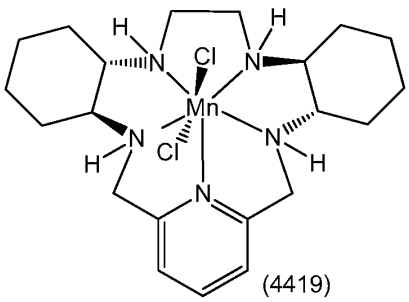
7

[0098] The chemical structures of 6 (such as the dichloro complex form described, for example, in Riley, D.P., Schall, O.F., 2007, Advances in Inorganic Chemistry, 59: 233-263) and of 7 herein (such as the dichloro complex form of 7), are identical except that they possess mirror image chirality; that is, the enantiomeric structures are non-superimposable.

[0099] For example, the pentaaza macrocyclic ring complex may correspond to at least one of the complexes below:

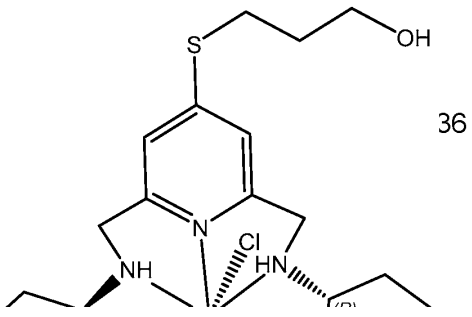


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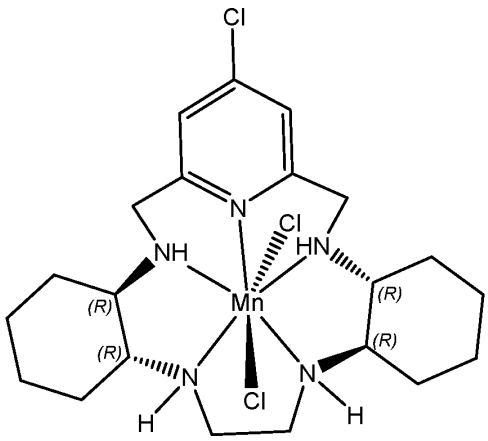
(4419)

[00100] In yet another embodiment, the pentaaza macrocyclic ring complex may correspond to at least one of the complexes below, and/or an enantiomer thereof:



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(4432)



[00101] In one embodiment, the enantiomeric purity of the pentaaza macrocyclic ring complex is greater than 95%, more preferably greater than 98%, more preferably greater than 99%, and most preferably greater than 99.5%. As used herein, the term "enantiomeric purity" refers to the amount of a compound having the depicted absolute stereochemistry, expressed as a percentage of the total amount of the depicted compound and its enantiomer. In one embodiment, the diastereomeric purity of the pentaaza macrocyclic ring complex is greater than 98%, more preferably greater than 99%, and most preferably greater than 99.5%. As used herein, the term "diastereomeric purity" refers to the amount of a compound having the depicted absolute stereochemistry, expressed as a percentage of the total amount of the depicted compound and its diastereomers. Methods for determining diastereomeric and enantiomeric purity are well-known in the art. Diastereomeric purity can be determined by any analytical method capable of quantitatively distinguishing between a compound

and its diastereomers, such as high performance liquid chromatography (HPLC). Similarly, enantiomeric purity can be determined by any analytical method capable of quantitatively distinguishing between a compound and its enantiomer. Examples of suitable analytical methods for determining enantiomeric purity include, without limitation, optical rotation of plane-polarized light using a polarimeter, and HPLC using a chiral column packing material.

[00102] In one embodiment, a therapeutically effective amount of the pentaaza macrocyclic ring complex may be an amount sufficient to provide a peak plasma concentration of at least 0.1 μM when administered to a patient. For example, in one embodiment, the pentaaza macrocyclic ring complex may be administered in an amount sufficient to provide a peak plasma concentration of at least 1 μM when administered to a patient. In yet another embodiment, the pentaaza macrocyclic ring complex may be administered in an amount sufficient to provide a peak plasma concentration of at least 10 μM when administered to a patient. Generally, the pentaaza macrocyclic ring complex will not be administered in an amount that would provide a peak plasma concentration greater than 40 μM when administered to a patient. For example, the pentaaza macrocyclic ring complex may be administered in an amount sufficient to provide a peak plasma concentration in the range of from 0.1 μM to 40 μM in a patient. As another example, the pentaaza macrocyclic ring complex may be administered in an amount sufficient to provide a peak plasma concentration in the range of from 0.5 μM to 20 μM in a patient. As another example, the pentaaza macrocyclic ring complex may be administered in an amount sufficient to provide a peak plasma concentration in the range of from 1 μM to 10 μM in a patient.

[00103] In yet another embodiment, a dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be at least 0.1 mg/kg, such as at least 0.2 mg/kg. For example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be at least 0.5 mg/kg. As another example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be at least 1 mg/kg. In another example, the pentaaza macrocyclic compound that is administered per kg body weight may be at least 2 mg/kg, such as at least 3 mg/kg, and even at least about 15 mg/kg, such as at least 24 mg/kg and even at least 40 mg/kg. Generally, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the

patient will not exceed 1000 mg/kg. For example the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be in the range of from 0.1 to 1000 mg/kg, such as from 0.2 mg/kg to 40 mg/kg, such as 0.2 mg/kg to 24 mg/kg, and even 0.2 mg/kg to 10 mg/kg. As another example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight may be in a range of from 1 mg/kg to 1000 mg/kg, such as from 3 mg/kg to 1000 mg/kg, and even from 5 mg/kg to 1000 mg/kg, such as 10 mg/kg to 1000 mg/kg. As another example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight may be in a range of from 2 mg/kg to 15 mg/kg. As yet another example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight may be in a range of from 3 mg/kg to 10 mg/kg. As another example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be in the range of from 0.5 to 5 mg/kg. As yet a further example, the dose of the pentaaza macrocyclic ring complex that is administered per kg body weight of the patient may be in the range of from 1 to 5 mg/kg.

[00104] In one embodiment, the dosages and/or plasma concentrations discussed above may be particularly suitable for the pentaaza macrocyclic ring complex corresponding to GC4419, although they may also be suitable for other pentaaza macrocyclic ring complexes. In addition, one or ordinary skill in the art would recognize how to adjust the dosages and/or plasma concentrations based on factors such as the molecular weight and/or activity of the particular compound being used. For example, for a pentaaza macrocyclic ring complex having an activity twice that of GC4419, the dosage and/or plasma concentration may be halved, or for a pentaaza macrocyclic ring complex having a higher molecular weight that GC4419, a correspondingly higher dosage may be used.

[00105] The dosing schedule of the pentaaza macrocyclic ring complex can similarly be selected according to the intended treatment. For example, in one embodiment, a suitable dosing schedule can comprise dosing a patient at least once per week, such as at least 2, 3, 4, 5, 6 or 7 days per week (*e.g.*, daily), during a course of treatment. As another example, in one embodiment, the dosing may be at least once a day (qd), or even at least twice a day (bid). In one embodiment, the course of treatment with the pentaaza macrocyclic ring complex may last at least as long as a course of treatment with a platinum-based anti-cancer agent, such as cisplatin, and may

even exceed the duration during which the platinum-based anticancer agent is provided. The course of therapy with the pentaaza macrocyclic ring complex may also start on the same date as treatment with the platinum-based anticancer agent, or may start sometime after initial dosing with the platinum-based anti-cancer agent, as is discussed in more detail below. For example, in one embodiment, for platinum-based anticancer agent that is administered for a course of therapy lasting at least a day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, a month, two months, three months, four months, five months, six months, the pentaaza macrocyclic ring complex may be administered for a course of therapy lasting at least at least a day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, a month, two months, three months, four months, five months, six months.

Platinum-Based Anti-Cancer Agent

[00106] According to one embodiment, a platinum-based anti-cancer agent is provided as a part of the treatment method(s) herein, in combination with the pentaaza macrocyclic compound. Platinum-based anti-cancer agents include the class of compounds that are coordination complexes of platinum, and that have anti-cancer effects. Platinum-based anticancer agents such as cisplatin and oxaliplatin have been understood to provide anti-cancer effects by induction of DNA damage in cancer cells (Cruet-Hennequart et al, *DNA Repair*, 7(4): 582-596 (2008)), and have proven to be highly effective in cancer treatment (Kelland et al, *J. Inorg Biochem*, 77(1-2); 121-124 (1999); Wang X, *Anticancer Agents Med Chem*, 10(5): 396-411 (2010); Dilruba et al, *Cancer Chemother Pharmacol*, 77(6): 1103-1124 (2016); Johnstone *et al.*, *Anticancer Res*, 34(1): 471-476 (2014)). The platinum-based anticancer compounds can comprise platinum(II) complexes such as cisplatin,carboplatin and oxaliplatin, and may also comprise platinum(IV) complexes such as satraplatin and LA-12 (*see, e.g.,* Bouchal *et al. Proteome Science*, 9:68 (2011). The platinum-based anticancer agent may be provided in various formulations, and may also be provided as a part of a delivery vesicle or other targeting moiety for targeting tumors and/or cancerous cells, such as for example with the platinum-based anticancer agent ProLindac (AP5346), which is a DACH (diaminocyclohexane) platinum polymer prodrug that uses a 25 kDa polymer delivery vehicle based on hydroxypropylmethacrylamide (HPMA) to target oxaliplatin to tumors (*see, e.g.,* Nowotnik *et al.*, *Advanced Drug Delivery Reviews*, 61(13): 1214-1219 (2009). Other targeting mechanisms for targeting and/or enhancing delivery of the

platinum-based anticancer agent to tumors and/or cancerous cells can include, for example, peptides, polymer carriers, micelles, radiation and/or photoactivated prodrugs, functionalized carbon nanotubes and/or nanorods, hollow Prussian Blue, magnetic iron oxide and/or gold nanoparticles, and nanogels (*see, e.g.,* Butler *et al.*, *Current Opinion in Chemical Biology,* 17(2): 175-188 (2013).

[00107] In one embodiment, suitable platinum-based anticancer agents can be selected from the group consisting of cisplatin, carboplatin, oxaliplatin, nedaplatin, lobaplatin, heptaplatin, dicycloplation, lipoplatin, LA-12 ((*OC*-6-43)-bis(acetato)(1-adamantylamine)amminedichloroplatinum (IV)), phosphaplatin, phenanthriplatin, ProLindac (AP5346), triplatin tetranitrate, picoplatin, satraplatin, pyriplatin and/or a pharmaceutically acceptable salt thereof.

[00108] The dose of the platinum-based anticancer agent can be selected according to the treatment to be provided and the particular platinum-based anticancer agent being used. For example, a suitable dose of a platinum-based anti-cancer agent such as cisplatin may be in a range from 10 mg/m^2 to 200 mg/m^2, such as 20 mg/m^2 to 100 mg/m^2.

[00109] The dosing schedule of the platinum-based anti-cancer agent can similarly be selected according to the intended treatment and the platinum-based anti-cancer agent being provided. For example, in one embodiment, a suitable dosing schedule can comprise dosing a patient at a frequency of once or twice per day, two days, three days, four days, five days, six days, per week, per two weeks, per three weeks or per month.

Timing of Administration

[00110] In one embodiment, a course of therapy with the platinum-based anti-cancer agent and pentaaza macrocyclic ring complex can comprise one or multiple doses of the agent and/or complex, according to the treatment to be provided. In one embodiment, a course of therapy comprising one or multiple doses can comprise administering a dose of the pentaaza macrocyclic complex a predetermined period of time before administration of the platinum-based anticancer agent. For example, the course of therapy can comprise administering an initial dose and optionally one or more subsequent doses of the platinum-based anticancer agent, with the onset of dosing with the pentaaza macrocyclic ring complex being performed a predetermined period of time

before the initial platinum-based anticancer agent dose. In another embodiment, a course of therapy comprising one or multiple doses can comprise administering a dose of the pentaaza macrocyclic complex after a predetermined period of time has elapsed since administration of an dose of a platinum-based anticancer agent. That is, the course of therapy can comprise administering an initial dose and optionally one or more subsequent doses of the platinum-based anticancer agent, with the onset of dosing with the pentaaza macrocyclic ring complex being delayed for a predetermined period of time after the initial platinum-based anticancer agent dose.

[00111] In one embodiment, at least one of the doses of the pentaaza macrocyclic ring complex during the course of therapy, is administered at least one week, at least 5 days, at least 3 days, at least 2 days, at least 1 day at least 12 hours, at least 8 hours, at least 4 hours, at least 2 hours, at least 1 hour and/or at least 30 mins before administration of the platinum-based anticancer agent. In another embodiment, the at least one of the doses of the pentaaza macrocyclic ring complex during the course of therapy, is administered at least one week, at least 5 days, at least 3 days, at least 2 days, at least 1 day at least 12 hours, at least 8 hours, at least 4 hours, at least 2 hours, at least 1 hour and/or at least 30 mins after administration of the platinum-based anticancer agent. Furthermore, the timing of the at least one dose of the pentaaza macrocyclic ring complex may also apply to a plurality of doses provided during the course of therapy, such as at least 25%, at least 50%, at least 75%, at least 90%, and even substantially all of the doses provided during the course of therapy.

Other Cancer Therapies

[00112] In one embodiment, the treatment provided herein can further comprise treatment with another therapy other than those specifically described above, such as for example one or more of a radiation therapy and/or another chemotherapeutic treatment. As yet another example, the treatment could comprise administering another anti-cancer agent such as a PARP inhibitor (poly ADP ribose polymerase inhibitor), such as for example any one or more of olaparib, rucaparib, niraparib, iniparib, talazoparib, and veliparib, before, concomitantly with, or after administration of one or more of the platinum-based anti-cancer compound and pentaaza macrocyclic ring complex. Other anti-cancer agents could also be provided. For example, in one embodiment, a radiation therapy may be administered to the subject prior to, concomitantly with, or after administration of one or more of the

platinum-based anticancer agent and the pentaaza macrocyclic ring complex. Further detailed description of radiation therapies and other chemotherapies suitable for the treatment of cancer are provided below.

[00113] In one embodiment, a radiation therapy can be administered concomitantly with administration of one or more of the platinum-based anticancer agent and pentaaza macrocyclic ring complex. For example, one or more of the platinum-based anticancer agent and pentaaza macrocyclic ring complexes may be administered during a course of radiation therapy, such as in between, before or after, or on the same day as dosing with radiation, such that the subject is receiving radiation therapy concurrently with one or more of the platinum-based anticancer agent and pentaaza macrocyclic ring complex.

[00114] In yet another embodiment, the combination therapy of the pentaaza macrocyclic ring complex and platinum-based anticancer agent (*e.g.* cisplatin) and pentaaza macrocyclic ring complexes, can be administered in the absence of any other cancer treatment. As demonstrated further in the examples below, it has been unexpectedly discovered that the pentaaza macrocyclic ring complexes are capable of enhancing the response to and/or efficacy of platinum-based anticancer agents such as cisplatin, even when administered without radiation therapy. Accordingly, in one embodiment, the cancer treatment provided to the subject may consist essentially of the pentaaza macrocyclic ring complex and platinum-based anticancer agent, without radiation exposure (*i.e.* without administering a radiation dose or dose fraction). For example, the combination of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may be administered to a subject that is not receiving radiation therapy. That is, in one embodiment, the treatment comprises administering the pentaaza macrocyclic ring complex to a subject that is not receiving radiation therapy. In yet another embodiment, the treatment comprises administering the platinum-based anticancer agent and the pentaaza macrocyclic ring complex to a subject that is not receiving radiation therapy. In yet another embodiment, where a course of therapy comprises administration of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent, they are administered to a subject that does not receive radiation therapy during the course of therapy.

[00115] In one embodiment, the subject receiving the combination of pentaaza macrocyclic ring complex and platinum-based anticancer agent (*e.g.* cisplatin), may be

one that has not been exposed to radiation (*i.e.*, received a dose or dose fraction of radiation) for at least one day, such as at least one week, and even at least one month, and even at least 6 months, and/or that has not ever received such treatment at all before initial treatment with one or more of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent. In yet another embodiment, any radiation therapy that is administered to the subject after the combination treatment with the pentaaza macrocyclic ring complex and the platinum-based anticancer agent is delayed by at least one day, such as at least one week, and even at least one month, such as at least 6 months, after a final dose of one or more of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent provided during the course of the combination therapy treatment. That is, the combination therapy of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent can be administered to a subject that has never before received radiation therapy, or that has received such therapy only in the distant past. Furthermore, the combination therapy of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent can be administered to provide a course of treatment that does not include any exposure to radiation. As yet a further embodiment, the combination therapy of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent can be provided to form a course of treatment substantially without performing any radiation therapy during or after the course of treatment, or with such radiation treatment being performed only after a significant period of time has elapsed after the course of combination treatment has ended. In one embodiment, the treatment comprises administering one or more of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent to the subject on a day other than a day that the subject is receiving radiation therapy.

METHODS OF ADMINISTRATION

[00116] According to one embodiment, the platinum-based anticancer agent (e.g., cisplatin), is administered as a co-therapy or combination therapy with the pentaaza macrocyclic ring complex. Co-therapy or combination therapy according to the methods described herein is intended to embrace administration of each compound in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent, or single or

multiple parenteral administrations, or other routes of administration and dosage forms. When administered in combination, therefore, the therapeutic agents (*i.e.*, the pentaaza macrocyclic ring complex and/or the platinum-based anticancer agent) can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic agents can be given as a single composition. Pharmaceutical compositions and formulations are discussed elsewhere herein.

[00117] It is not necessary that the pentaaza macrocyclic ring complex and the platinum-based anticancer agent be administered simultaneously or essentially simultaneously; the agents and compounds may be administered in sequence. The advantage of a simultaneous or essentially simultaneous administration, or sequential administration, is well within the determination of the skilled clinician. For instance, while a pharmaceutical composition or formulation comprising platinum-based anticancer agent may be advantageous for administering first in the combination for one particular treatment, prior to administration of the pentaaza macrocyclic ring complex, prior administration of the pentaaza macrocyclic ring complex may be advantageous in another treatment. It is also understood that the instant combination of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may be used in conjunction with other methods of treating cancer (typically cancerous tumors) including, but not limited to, radiation therapy and surgery, or other chemotherapy. It is further understood that another active agent, such as a cytostatic or quiescent agent, or antiemetic agent, if any, may be administered sequentially or simultaneously with any or all of the other synergistic therapies.

[00118] Thus, embodiments of the therapeutic method include wherein a pentaaza macrocyclic ring complex and a platinum-based anticancer agent, and combinations thereof, are administered simultaneously or sequentially. For instance, aspects of the present disclosure encompass a method for the treatment of cancer wherein a pentaaza macrocyclic ring complex and a platinum-based anticancer agent are administered simultaneously or sequentially. Other active agents can also be administered simultaneously or sequentially with the pentaaza macrocyclic ring complex and the platinum-based anticancer agent.

[00119] As noted above, if the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are not administered simultaneously or essentially

simultaneously, then the initial order of administration of the components may be varied. Thus, for example, the platinum-based anticancer agent may be administered first, followed by the administration of the pentaaza macrocyclic ring complex; or the pentaaza macrocyclic ring complex may be administered first, followed by the administration of the platinum-based anticancer agent. This alternate administration may be repeated during a single treatment protocol. Other sequences of administration to exploit the effects described herein are contemplated, and other sequences of administration of other active agents can also be provided.

[00120] In one embodiment, the subject is pre-treated with the platinum-based anticancer agent, followed by administration of the pentaaza macrocyclic ring complex, or vice versa. In accordance with such embodiments, the pentaaza macrocyclic ring complex may be administered at least 1 hour, and even at least 3 days, after administration of the platinum-based anticancer agent, or vice versa. For example, in one embodiment, the pentaaza macrocyclic ring complex is administered between 1 hour and 3 days after administration of the platinum-based anticancer agent, or vice versa. In another embodiment, for example, the pentaaza macrocyclic ring complex is administered between 1 hour and 1 day after administration of the platinum-based anticancer agent, or vice versa. For example, the pentaaza macrocyclic ring complex may be administered within 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, one week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 9 weeks, 10 weeks or 12 weeks after administration of the platinum-based anticancer agent, or vice versa. In these and other embodiments, the platinum-based anticancer agent may be administered in multiple doses leading up to administration of the pentaaza macrocyclic ring complex, or vice versa.

[00121] Alternatively, the subject may be pre-treated with the pentaaza macrocyclic ring complex, followed by administration of the platinum-based anticancer agent, or vice versa. In accordance with such embodiments, the pentaaza macrocyclic ring complex may be administered within at least 1 plasma half-life of the platinum-based anticancer agent, such as within 4 plasma half-lives of the platinum-based anticancer agent, or vice versa. For example, the pentaaza macrocyclic ring complex may be administered within 1, 2, or 3 plasma half-lives of the other platinum-based anticancer agent, or vice versa.

[00122] In other alternative embodiments, the subject may be pre-treated with the platinum-based anticancer agent, followed by administration of the pentaaza macrocyclic ring complex, which is further followed by one or more additional administrations of the platinum-based anticancer agent, or vice versa. For example, the subject could be pre-treated with a dose of platinum-based anticancer agent, followed by administration of a dose of pentaaza macrocyclic ring complex, which is then followed by the administration of additional (or partial) dose of the same or different platinum-based anticancer agent, which may be further followed by another dose of pentaaza macrocyclic ring complex. Further, the subject could be pre-treated with a partial or full dose of pentaaza macrocyclic ring complex, followed by administration of a platinum-based anticancer agent, which is then followed by administration of an additional (or partial) dose of pentaaza macrocyclic complex.

[00123] As described in further detail below, the combinations of the disclosure may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. Combinations may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a multiple combination formulation is inappropriate.

[00124] In one embodiment, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent can generally be administered according to therapeutic protocols that may be known for these agents. For example, the administration of the various components can be varied depending on the disease being treated and the effects of pentaaza macrocyclic ring complex and platinum-based anticancer agent on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (*e.g.*, dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents (*i.e.*, pentaaza macrocyclic ring complex, platinum-based anticancer agent) on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

[00125] Also, in general, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, the pentaaza macrocyclic ring complex may be administered orally to generate and maintain good

blood levels thereof, while the platinum-based anticancer agent may be administered intravenously or via transfusion, or vice versa. The mode of administration may include, where possible, in the same pharmaceutical composition, or in separate pharmaceutical compositions (*e.g.*, two or three separate compositions). Furthermore, once the initial administration has been made, then based upon the observed effects, the dosage, modes of administration and times of administration can be modified.

[00126] The particular choice of pentaaza macrocyclic ring complex and the platinum-based anticancer agent, and other related therapies (such as radiation or other chemotherapies), will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

[00127] Thus, in accordance with experience and knowledge, the practicing physician may modify each protocol for the administration of a component (the pentaaza macrocyclic ring complex and the platinum-based anticancer agent of the treatment according to the individual patient's needs, as the treatment proceeds.

[00128] The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, *e.g.*, CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

[00129] The products of which the combination are composed may be administered simultaneously, separately or spaced out over a period of time so as to obtain the maximum efficacy of the combination; it being possible for each administration to vary in its duration from a rapid administration to a relatively continuous perfusion of either component (in separate formulations or in a single formulation). As a result, for the purposes of the present disclosure, the combinations are not exclusively limited to those which are obtained by physical association of the constituents, but also to those which permit a separate administration, which can be simultaneous or spaced out over a period of time.

[00130] Accordingly, administration of the components described herein can occur as a single event or over a time course of treatment. For example, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent can be administered (simultaneously or in sequence) hourly (*e.g.*, every hour, every two hours, every three hours, every four hours, every five hours, every six hours, and so on), daily, weekly, bi-weekly, or monthly. For treatment of acute conditions, the time course of treatment may be at least several hours or days. Certain conditions could extend treatment from several days to several weeks. For example, treatment could extend over one week, two weeks, or three weeks. For more chronic conditions, treatment could extend from several weeks to several months, a year or more, or the lifetime of the patient in need of such treatment. Alternatively, the compounds and agents can be administered hourly, daily, weekly, bi-weekly, or monthly, for a period of several weeks, months, years, or over the lifetime of the patient as a prophylactic measure.

[00131] The dose or amount of pharmaceutical compositions including the pentaaza macrocyclic ring complex and the platinum-based anticancer agent administered to the patient should be an effective amount for the intended purpose, *i.e.*, treatment or prophylaxis of one or more of the diseases, pathological disorders, and medical conditions discussed herein, particularly cancer. Generally speaking, the effective amount of the composition administered can vary according to a variety of factors such as, for example, the age, weight, sex, diet, route of administration, and the medical condition of the patient in need of the treatment. Specifically preferred doses are discussed more fully herein. It will be understood, however, that the total daily usage of the compositions described herein will be decided by the attending physician or veterinarian within the scope of sound medical judgment.

[00132] As noted above, the combinations can be co-administered (via a co-formulated dosage form or in separate dosage forms administered at about the same time). The combinations can also be administered separately, at different times, with each agent in a separate unit dosage form. Numerous approaches for administering the platinum-based anticancer agent and pentaaza macrocyclic ring complex can be readily adapted for use in the present disclosure. The pharmaceutical compositions may be delivered orally, *e.g.*, in a tablet or capsule unit dosage form, or parenterally, *e.g.*, in an

injectable unit dosage form, or by some other route. For systemic administration, for example, the drugs can be administered by, for example, intravenous infusion (continuous or bolus). The compositions can be used for any therapeutic or prophylactic treatment where the patient benefits from treatment with the combination.

[00133] The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound(s) employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound(s) employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound(s) employed and like factors well known in the medical and/or veterinary arts. For example, it is well within the skill of the art to start doses of the compound(s) at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily doses may be divided into multiple doses for purposes of administration. Consequently, single dose compositions may contain such amounts or submultiples to make up the daily dose.

[00134] In one embodiment, suitable or preferred doses for each of the components are employed in the methods or included in the compositions described herein. Preferred dosages for the pentaaza macrocyclic ring complex, for instance, may be within the range of 10 to 500 mg per patient per day. However, the dosage may vary depending on the dosing schedule, which can be adjusted as necessary to achieve the desired therapeutic effect. It should be noted that the ranges of effective doses provided herein are not intended to limit the disclosure and represent exemplary dose ranges. The most preferred dosage will be tailored to the individual subject, taking into account, among other things, the particular combinations employed, and the patient's age, sex, weight, physical condition, diet, *etc.*, as is understood and determinable by one of ordinary skill in the art without undue experimentation.

[00135] Treatment of cancer, or cancer therapies, described herein includes achieving a therapeutic benefit, however the therapy may also be administered to achieve a prophylactic benefit. Therapeutic benefits generally refer to at least a partial eradication or amelioration of the underlying disorder being treated. For example, in a

cancer patient, therapeutic benefit includes (partial or complete) eradication or amelioration of the underlying cancer. Also, a therapeutic benefit is achieved with at least partial, or complete, eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding the fact that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, a method of the disclosure may be performed on, or a composition of the invention administered to, a patient at risk of developing cancer, or to a patient reporting one or more of the physiological symptoms of such conditions, even though a diagnosis of the condition may not have been made.

[00136] Furthermore, treatment of toxic effects associated with administration of a platinum-based anticancer agent, and/or treatment of a condition resulting from administration of a platinum-based anticancer agent, includes achieving a therapeutic benefit, however the therapy may also be administered to achieve a prophylactic benefit. Therapeutic benefits generally refer to at least a partial eradication or amelioration of the underlying disorder being treated. For example, in a patient at risk for or suffering from the toxic effects associated with administration of a platinum-based anticancer agent, therapeutic benefit includes (partial or complete) eradication or amelioration of the underlying condition and/or symptoms thereof. Also, a therapeutic benefit is achieved with at least partial, or complete, eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding the fact that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, a method of the disclosure may be performed on, or a composition of the invention administered to, a patient at risk for toxicities associated with platinum-based anticancer agents (*e.g.*, a person that is receiving or has received a platinum-based anticancer agent, or that is scheduled to receive a platinum-based anticancer agent), or to a patient reporting and/or suffering from one or more of the physiological symptoms of such conditions, even though a diagnosis of the condition may not have been made.

Cancer Treatment Methods

[00137] In general, any subject having, or suspected of having, a cancer or other proliferative disorder may be treated using the compositions and methods of the

present disclosure. Subjects receiving treatment according to the methods described herein are mammalian subjects, and typically human patients. Other mammals that may be treated according to the present disclosure include companion animals such as dogs and cats, farm animals such as cows, horses, and swine, as well as birds and more exotic animals (*e.g.*, those found in zoos or nature preserves). In one embodiment of the disclosure, a method is provided for the treatment of cancerous tumors, particularly solid tumors. Advantageously, the methods described herein may reduce the development of tumors, reduce tumor burden, or produce tumor regression in a mammalian host. Cancer patients and individuals desiring cancer prophylaxis can be treated with the combinations described herein.

[00138] Cancer and tumors generally refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. By means of the pharmaceutical combinations, co-formulations, and combination therapies of the present disclosure, various tumors can be treated such as tumors of the breast, heart, lung, small intestine, colon, spleen, kidney, bladder, head and neck, ovary, prostate, brain, pancreas, skin, bone, bone marrow, blood, thymus, uterus, testicles, cervix, and liver.

[00139] In one embodiment, the tumor or cancer is chosen from adenoma, angio-sarcoma, astrocytoma, epithelial carcinoma, germinoma, glioblastoma, glioma, hamartoma, hemangioendothelioma, hemangiosarcoma, hematoma, hepato-blastoma, leukemia, lymphoma, medulloblastoma, melanoma, neuroblastoma, osteosarcoma, retinoblastoma, rhabdomyosarcoma, sarcoma, and teratoma. The tumor can be chosen from acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangio-carcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia,

interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic, papillary serous adeno-carcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudo-sarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

[00140] Thus, for example, the present disclosure provides methods for the treatment of a variety of cancers, including, but not limited to, the following: carcinoma including that of the bladder (including accelerated and metastatic bladder cancer), breast, colon (including colorectal cancer), kidney, liver, lung (including small and non-small cell lung cancer and lung adenocarcinoma), ovary, prostate, testes, genitourinary tract, lymphatic system, rectum, larynx, pancreas (including exocrine pancreatic carcinoma), esophagus, stomach, gall bladder, cervix, thyroid, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, histiocytic lymphoma, and Burketts lymphoma; hematopoietic tumors of myeloid lineage including acute and chronic myelogenous leukemias, myelodysplastic syndrome, myeloid leukemia, and promyelocytic leukemia; tumors of the central and peripheral nervous system including astrocytoma, neuroblastoma, glioma, and schwannomas; tumors of mesenchymal origin including fibrosarcoma, rhabdomyoscarcoma, and osteosarcoma; and other tumors including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer, and teratocarcinoma.

[00141] For example, particular leukemias that can be treated with the combinations and methods described herein include, but are not limited to, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia,

aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, and undifferentiated cell leukemia.

[00142] Lymphomas can also be treated with the combinations and methods described herein. Lymphomas are generally neoplastic transformations of cells that reside primarily in lymphoid tissue. Lymphomas are tumors of the immune system and generally are present as both T cell- and as B cell-associated disease. Among lymphomas, there are two major distinct groups: non-Hodgkin's lymphoma (NHL) and Hodgkin's disease. Bone marrow, lymph nodes, spleen and circulating cells, among others, may be involved. Treatment protocols include removal of bone marrow from the patient and purging it of tumor cells, often using antibodies directed against antigens present on the tumor cell type, followed by storage. The patient is then given a toxic dose of radiation or chemotherapy and the purged bone marrow is then re-infused in order to repopulate the patient's hematopoietic system.

[00143] Other hematological malignancies that can be treated with the combinations and methods described herein include myelodysplastic syndromes (MDS), myeloproliferative syndromes (MPS) and myelomas, such as solitary myeloma and multiple myeloma. Multiple myeloma (also called plasma cell myeloma) involves the skeletal system and is characterized by multiple tumorous masses of neoplastic plasma cells scattered throughout that system. It may also spread to lymph nodes and other sites such as the skin. Solitary myeloma involves solitary lesions that tend to occur in the same locations as multiple myeloma.

[00144] In one embodiment, the methods and pharmaceutical compositions described herein are used to treat a cancer that is any of breast cancer, melanoma,

oral squamous cell carcinoma, lung cancer including non-small cell lung cancer, renal cell carcinoma, colorectal cancer, prostate cancer, brain cancer, spindle cell carcinoma, urothelial cancer, bladder cancer, colorectal cancer, head and neck cancers such as squamous cell carcinoma, and pancreatic cancer. In yet another embodiment, the methods and pharmaceutical compositions described herein are used to treat a cancer that is any of head and neck cancer and lung cancer.

Methods for Treatment of Toxicities Associated with Platinum-Based Anticancer Agents

[00145] In general, any subject having, or suspected of having, a condition resulting from the toxic effects of administration of a platinum-based anticancer agent (*e.g.*, cisplatin) may be treated using the compositions and methods of the present disclosure. Subjects receiving treatment according to the methods described herein are mammalian subjects, and typically human patients. Other mammals that may be treated according to the present disclosure include companion animals such as dogs and cats, farm animals such as cows, horses, and swine, as well as birds and more exotic animals (*e.g.*, those found in zoos or nature preserves). In one embodiment of the disclosure, a method is provided for the treatment of a condition associated with the toxicity of platinum-based anticancer agents, such as a condition from which a subject is suffering following administration to the subject of a platinum-based anticancer agent, for example as provided during cancer treatment, to alleviate the condition. In another emboidment, the treatment is provided to reduce and/or inhibit the toxicity of a platinum-based anticancer agent, for example when the platinum-based anticancer agent is provided during cancer treatment, to reduce the risk of developing a condition associated with the toxicity of the platinum-based anticancer agent. Advantageously, the methods described herein may reduce the toxic effects and/or alleviate toxic condition while simultaneously allowing for cancer treatment with the platinum-based anti-cancer agent, so example to reduce the development of tumors, reduce tumor burden, or produce tumor regression in a mammalian host. Cancer patients and individuals desiring cancer prophylaxis can be treated with the combinations described herein.

[00146] In one embodiment, the toxicity and/or toxic condition associated with administration of the platinum-based anticancer agent, and which may be treated with the method(s) described herein (and/or the risk of developing such a condition can be

reduced), includes at least one of nephrotoxicity, myelotoxicity, ototoxicity and neurotoxicity, and conditions associated therewith. For example, in one embodiment the administration of the pentaaza macrocyclic ring complex may be capable of reducing nephrotoxic effects associated with the administration of a platinum-based anticancer agent. Nephrotoxicity refers to toxicity to the kidneys, and can result in reduced renal function, and acute kidney injury, and even renal failure, among other conditions and is commonly associated with the administration of anti-cancer drugs (*see, e.g.,* Lameire N., *Clin Kidney J*, 7(1): 11-22 (2014); Zhu et al, *Arch Toxicol*, 89(12): 2197-2205 (2015)). Whole blood blood urea nitrogen (BUN) levels and creatinine levels may be measured to provide an indication of an extent of kidney injury, with increased levels indicating reduced kidney function. Other markers of kidney injury include kidney injury molecule 1 (KIM1) and neutrophil gelatinase-associated lipocalin (NGAL). As another example, in one embodiment the administration of the pentaaza macrocyclic ring complex may be capable of reducing myelotoxic effects associated with the administration of a platinum-based anticancer agent. Myelotoxicity, also referred to as myelosuppression and/or bone marrow suppression, refers to the decrease in the production of cells such as leukocytes, erythrocytes and thrombocytes, and can result in conditions such as neutropenia, thrombocytopenia, and anemia, among other conditions, and is commonly associated with the administration of anti-cancer drugs (*see, e.g.,* Kurtin S., *J Adv Pract Oncol*, 3(4): Jul-Aug (2012); Son *et al.*, *Hum Exp Toxicol,* 30(7): 649-655 (2011)). Neutrophils and white blood cell counts may also be decreased. In yet another embodiment, the administration of the pentaaza macrocyclic ring complex may be capable of reducing ototoxic effects associated with the administration of a platinum-based anticancer agent, which are toxicities to the each such as the cochlea, auditory nerve and/or vestibular system. Accordingly, in one embodiment, the treatment methods herein can comprise treating a subject who is afflicted with and/or at risk for a toxicity resulting from platinum-based anticancer treatment, such as a subject afflicted with and/or at risk for one or more of nephrotoxicity and myelotoxicity, due to administration of a platinum-based anticancer agent.

Pharmaceutical Formulations

[00147] Another aspect of the present disclosure relates to the pharmaceutical compositions comprising the combinations described herein, together with a

pharmaceutically acceptable excipient. The pharmaceutical compositions include the pentaaza macrocyclic ring complex (*e.g.*, those corresponding to Formula (I)), and at least one platinum-based anticancer agent, and combinations thereof, as discussed above, typically formulated as a pharmaceutical dosage form, optionally in combination with a pharmaceutically acceptable carrier, additive or excipient. In one embodiment, for example, the pharmaceutical composition comprises a pentaaza macrocyclic ring complex, a platinum-based anticancer agent and a pharmaceutically acceptable excipient. Pharmaceutical compositions according to the present disclosure may be used in the treatment of cancer.

[00148] The pharmaceutical compositions described herein are products that result from the mixing or combining of more than one active ingredient and include both fixed and non-fixed combinations of the active ingredients. Fixed combinations are those in which the active ingredients, *e.g.*, a pentaaza macrocyclic ring complex and a platinum-based anticancer agent, are administered to a patient simultaneously in the form of a single entity or dosage. Other active agents may also be administered as a part of the single entity or dosage, or may be separately administered Non-fixed combinations are those in which the active ingredients, *e.g.*, a pentaaza macrocyclic ring complex and a platinum-based anticancer agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the compounds in the body of the patient. The latter also applies to cocktail therapy, *e.g.*, the administration of three or more active ingredients.

[00149] The above-described pentaaza macrocyclic ring complex and the platinum-based anticancer agent may be dispersed in a pharmaceutically acceptable carrier prior to administration to the mammal; *i.e.*, the components described herein are preferably co-formulated. The carrier, also known in the art as an excipient, vehicle, auxiliary, adjuvant, or diluent, is typically a substance which is pharmaceutically inert, confers a suitable consistency or form to the composition, and does not diminish the efficacy of the compound. The carrier is generally considered to be "pharmaceutically or pharmacologically acceptable" if it does not produce an unacceptably adverse, allergic or other untoward reaction when administered to a mammal, especially a human.

[00150] The selection of a pharmaceutically acceptable carrier will also, in part, be a function of the route of administration. In general, the compositions of the

described herein can be formulated for any route of administration so long as the blood circulation system is available via that route, and in accordance with the conventional route of administration. For example, suitable routes of administration include, but are not limited to, oral, parenteral (*e.g.*, intravenous, intraarterial, subcutaneous, rectal, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intraperitoneal, or intrasternal), topical (nasal, transdermal, intraocular), intravesical, intrathecal, enteral, pulmonary, intralymphatic, intracavital, vaginal, transurethral, intradermal, aural, intramammary, buccal, orthotopic, intratracheal, intralesional, percutaneous, endoscopical, transmucosal, sublingual and intestinal administration.

[00151] Pharmaceutically acceptable carriers for use in combination with the compositions of the present disclosure are well known to those of ordinary skill in the art and are selected based upon a number of factors: the particular compound(s) and agent(s) used, and its/their concentration, stability and intended bioavailability; the subject, its age, size and general condition; and the route of administration. Suitable nonaqueous, pharmaceutically-acceptable polar solvents include, but are not limited to, alcohols (*e.g.*, a-glycerol formal, 6-glycerol formal, 1,3-butyleneglycol, aliphatic or aromatic alcohols having 2 to 30 carbon atoms such as methanol, ethanol, propanol, isopropanol, butanol, t-butanol, hexanol, octanol, amylene hydrate, benzyl alcohol, glycerin (glycerol), glycol, hexylene glycol, tetrahydrofurfuryl alcohol, lauryl alcohol, cetyl alcohol, or stearyl alcohol, fatty acid esters of fatty alcohols such as polyalkylene glycols (*e.g.*, polypropylene glycol, polyethylene glycol), sorbitan, sucrose and cholesterol); amides (*e.g.*, dimethylacetamide (DMA), benzyl benzoate DMA, dimethylformamide, N-(6-hydroxyethyl)-lactamide, N,N-dimethylacetamide amides, 2-pyrrolidinone, 1-methyl-2-pyrrolidinone, or polyvinylpyrrolidone); esters (*e.g.*, 1-methyl-2-pyrrolidinone, 2-pyrrolidinone, acetate esters such as monoacetin, diacetin, and triacetin, aliphatic or aromatic esters such as ethyl caprylate or octanoate, alkyl oleate, benzyl benzoate, benzyl acetate, dimethylsulfoxide (DMSO), esters of glycerin such as mono, di-, or tri-glyceryl citrates or tartrates, ethyl benzoate, ethyl acetate, ethyl carbonate, ethyl lactate, ethyl oleate, fatty acid esters of sorbitan, fatty acid derived PEG esters, glyceryl monostearate, glyceride esters such as mono, di-, or tri-glycerides, fatty acid esters such as isopropyl myristrate, fatty acid derived PEG esters such as PEG-hydroxyoleate and PEG-hydroxystearate, N-methyl pyrrolidinone, pluronic 60, polyoxyethylene sorbitol oleic polyester,polyoxyethylene sorbitan esters such as polyoxyethylene-sorbitan

monooleate, polyoxyethylene-sorbitan monopalmitate, polyoxyethylene-sorbitan monolaurate, polyoxyethylene-sorbitan monostearate, and Polysorbate® 20, 40, 60 or 80 from ICI Americas, Wilmington, DE, polyvinylpyrrolidone, alkyleneoxy modified fatty acid esters such as polyoxyl 40 hydrogenated castor oil and polyoxyethylated castor oils (*e.g.*, Cremophor® EL solution or Cremophor® RH 40 solution), saccharide fatty acid esters (*i.e.*, the condensation product of a monosaccharide (*e.g.*, pentoses such as ribose, ribulose, arabinose, xylose, lyxose and xylulose, hexoses such as glucose, fructose, galactose, mannose and sorbose, trioses, tetroses, heptoses, and octoses), disaccharide (*e.g.*, sucrose, maltose, lactose and trehalose) or oligosaccharide or mixture thereof with a C_4 to C_{22} fatty acid(s) (*e.g.*, saturated fatty acids such as caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid and stearic acid, and unsaturated fatty acids such as palmitoleic acid, oleic acid, elaidic acid, erucic acid and linoleic acid)), or steroidal esters); alkyl, aryl, or cyclic ethers having 2 to 30 carbon atoms (*e.g.*, diethyl ether, tetrahydrofuran, dimethyl isosorbide, diethylene glycol monoethyl ether); glycofurol (tetrahydrofurfuryl alcohol polyethylene glycol ether); ketones having 3 to 30 carbon atoms (*e.g.*, acetone, methyl ethyl ketone, methyl isobutyl ketone); aliphatic, cycloaliphatic or aromatic hydrocarbons having 4 to 30 carbon atoms (*e.g.*, benzene, cyclohexane, dichloromethane, dioxolanes, hexane, n-decane, n-dodecane, n-hexane, sulfolane, tetramethylenesulfon, tetramethylenesulfoxide, toluene, di methylsulfoxide (DMSO), or tetramethylenesulfoxide); oils of mineral, vegetable, animal, essential or synthetic origin (*e.g.*, mineral oils such as aliphatic or wax-based hydrocarbons, aromatic hydrocarbons, mixed aliphatic and aromatic based hydrocarbons, and refined paraffin oil, vegetable oils such as linseed, tung, safflower, soybean, castor, cottonseed, groundnut, rapeseed, coconut, palm, olive, corn, corn germ, sesame, persic and peanut oil and glycerides such as mono-, di- or triglycerides, animal oils such as fish, marine, sperm, cod-liver, haliver, squalene, squalane, and shark liver oil, oleic oils, and polyoxyethylated castor oil); alkyl or aryl halides having 1 to 30 carbon atoms and optionally more than one halogen substituent; methylene chloride; monoethanolamine; petroleum benzin; trolamine; omega-3 polyunsaturated fatty acids (*e.g.*, alpha-linolenic acid, eicosapentaenoic acid, docosapentaenoic acid, or docosahexaenoic acid); polyglycol ester of 12-hydroxystearic acid and polyethylene glycol (Solutol® HS-15, from BASF, Ludwigshafen, Germany); polyoxyethylene glycerol; sodium laurate; sodium oleate; or sorbitan monooleate.

[00152] In some embodiments, oils or non-aqueous solvents may be employed in the formulations, *e.g.*, to bring one or more of the compounds into solution, due to, for example, the presence of large lipophilic moieties. Alternatively, emulsions, suspensions, or other preparations, for example, liposomal preparations, may be used. With respect to liposomal preparations, for example, any known methods for preparing liposomes may be used. See, for example, Bangham *et al.*, J. Mol. Biol, 23: 238-252 (1965) and Szoka *et al.*, Proc. Natl Acad. Sci 75: 4194-4198 (1978), incorporated herein by reference. Thus, in one embodiment, one or more of the compounds are administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phophatidylcholines. Ligands may also be attached to the liposomes, for instance, to direct these compositions to particular sites of action.

[00153] Other pharmaceutically acceptable solvents for use in the pharmaceutical compositions described herein are well known to those of ordinary skill in the art, and are identified in The Chemotherapy Source Book (Williams & Wilkens Publishing), The Handbook of Pharmaceutical Excipients, (American Pharmaceutical Association, Washington, D.C., and The Pharmaceutical Society of Great Britain, London, England, 1968), Modern Pharmaceutics, (G. Banker *et al.*, eds., 3d ed.) (Marcel Dekker, Inc., New York, New York, 1995), The Pharmacological Basis of Therapeutics, (Goodman & Gilman, McGraw Hill Publishing), Pharmaceutical Dosage Forms, (H. Lieberman *et al.*, eds.) (Marcel Dekker, Inc., New York, New York, 1980), Remington's Pharmaceutical Sciences (A. Gennaro, ed., 19th ed.) (Mack Publishing, Easton, PA, 1995), The United States Pharmacopeia 24, The National Formulary 19, (National Publishing, Philadelphia, PA, 2000), and A.J. Spiegel *et al.*, Use of Nonaqueous Solvents in Parenteral Products, Journal of Pharmaceutical Sciences, Vol. 52, No. 10, pp. 917-927 (1963).

[00154] Formulations containing the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms such as, for instance, aerosols, capsules, creams, emulsions, foams, gels/jellies, lotions, ointments, pastes, powders, soaps, solutions, sprays, suppositories, suspensions, sustained-release formulations, tablets, tinctures, transdermal patches, and the like, preferably in unit dosage forms suitable for simple

administration of precise dosages. If formulated as a fixed dose, such pharmaceutical compositions or formulation products employ the pentaaza macrocyclic ring complex and the platinum-based anticancer agent within accepted dosage ranges.

[00155] In one embodiment, a formulation is provided that contains the platinum-based anticancer agent as a part of liquid dosage form, such as a sterile liquid dosage form suitable for injection. For example, the liquid form containing the platinum-based anticancer agent in combination with one or more further ingredients, such as edetate disodium (EDTA). In one embodiment, the liquid form can comprise EDTA in an amount suitable to act as a preservative and/or metal-chelating agent, such as an amount of about 0.025%. The liquid form can further comprise water, and may also comprise a pH adjuster, such as sodium bicarbonate, for pH adjustment in the range of pH 5.5 to 7.0. In one embodiment, the pentaaza macrocyclic ring complex can also be provided as a part of a sterile liquid dosage form suitable for injection, either in the same liquid dosage form with the platinum-based anticancer agent or as a separate dosage form.

[00156] Formulations for certain pentaaza macrocyclic ring complexes are also described in, for example, in U.S. Patent Nos. 5,610,293, 5,637,578, 5,874,421, 5,976,498, 6,084,093, 6,180,620, 6,204,259, 6,214,817, 6,245,758, 6,395,725, and 6,525,041 (each of which is hereby incorporated herein by reference in its entirety).

[00157] It is contemplated that co-formulations of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may employ conventional formulation techniques for these components individually, or alternative formulation routes, subject to compatibility and efficacy of the various components, in combination.

[00158] The above-described pharmaceutical compositions including the pentaaza macrocyclic compound and the platinum-based anticancer agent may additionally include one or more additional pharmaceutically active components. Suitable pharmaceutically active agents that may be included in the compositions according to aspects of the present invention include, for instance, antiemetics, anesthetics, antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatory agents, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune

disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's Disease agents, antibiotics, anti-depressants, and antiviral agents. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

[00159] In yet another embodiment, a kit may be provided that includes both a pentaaza macrocyclic ring complex and a platinum-based anticancer agent, for treatment of a condition such as cancer, and/or to treat and/or reduce the risk of toxicities associated with administration of a platinum-based anticancer agent. For example, the kit may comprise a first vessel or container having therein a formulation comprising the pentaaza macrocyclic ring complex, such as an oral or injectable formulation of the pentaaza macrocyclic ring complex, and a second vessel or container having therein a formulation comprising the platinum-based anticancer agent, such as an injectable formulation of platinum-based anticancer agent. The kit may further comprise a label or other instructions for administration of the active agents, recommended dosage amounts, durations and administration regimens, warnings, listing of possible drug-drug interactions, and other relevant instructions, such as a label instructing therapeutic regimens (*e.g.*, dosing, frequency of dosing, *etc.*) corresponding to any of those described herein.

Combination Treatment with Cancer Therapy

[00160] In one embodiment, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent can be administered in combination with another cancer therapy, to provide therapeutic treatment. For example, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may be administered as a part of a radiation therapy.

[00161] In general, the temporal aspects of the administration of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may depend for example, on the particular radiation therapy that is selected, or the type, nature, and/or duration of the radiation exposure. Other considerations may include the disease or disorder being treated and the severity of the disease or disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration,

and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors. For example, the compounds may be administered in various embodiments before, during, and/or after the administration of the radiation therapy (*e.g.*, before, during or after exposure to and/or before, during or after a course of radiation therapy comprising multiple exposures and/or doses). By way of another example, the compounds may be administered in various embodiments before, during, and/or after an exposure to radiation.

[00162] If desired, the effective dose can be divided into multiple doses for purposes of administration; consequently, single dose compositions may contain such amounts or submultiples thereof to make up the dose.

[00163] In one embodiment, for example, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered to the patient prior to or simultaneous with the radiation exposure. In another embodiment, for example, the components are administered to the patient prior to, but not after, the radiation exposure. In yet another embodiment, one or more of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered to the patient at least 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 180 minutes, 0.5 days, 1 day, 3 days, 5 days, one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, ten weeks, eleven weeks, twelve weeks, or longer, prior to the radiation exposure, such as an initial radiation exposure in a course of radiation treatment, or prior to another dose or dose fraction of radiation that is one of the doses or dose fractions of radiation in the course of treatment. In still other embodiments, for example, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered to the patient after the radiation exposure; thus, for example, the compound may be administered up to 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, or 180 minutes, 0.5 days, 1 day, 3 days, 5 days, one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, ten weeks, eleven weeks, twelve weeks, or longer, after the radiation exposure, which may be a dose or dose fraction of radiation in a multi-dose course of radiation therapy, or may be the single or final dose or dose fraction of radiation in the radiation therapy.

[00164] In one embodiment, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered as a part of a course of therapy that includes the radiation therapy. In radiation therapy, a patient receives a dose or dose fraction of ionizing radiation to kill or control the growth of cancerous cells. The dose or dose fraction of radiation may be directed at a specific part of the body, and the beam of radiation may also be shaped according to a predetermined treatment regimen, to reduce deleterious effects on parts of the body not afflicted with cancer. A typical course of radiation therapy may include one or a plurality of doses or dose fractions of radiation, which can be administered over the course of days, weeks and even months. A total "dose" of radiation given during a course of radiation therapy typically refers to the amount of radiation a patient receives during the entire course of radiation therapy, which doses may be administered as dose "fractions" corresponding to multiple radiation exposures in the case where the total dose is administered over several sessions, with the sum of the fractions administered corresponding to the overall dose.

[00165] In one embodiment, at least one of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered within a predetermined time period before or after a radiation exposure, such as a before or after a radiation dose or dose fraction. For example, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may be administered within 1 week, 48 hours, 24 hours, 12 hours, 6, hours, 2 hours, 1 hour or even within 30 minutes of the patient receiving the radiation exposure, such as the dose or dose fraction (either before or after the radiation exposure corresponding to the radiation dose or dose fraction). Other durations between the radiation exposure and administration of the compound that result in the enhanced the killing of cancer cells may also be suitable. In one embodiment, one or more of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may be administered before the radiation exposure, and the remaining one or more of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent can be administered after the radiation exposure. One or more of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may also be administered both before and after administration of a radiation exposure.

[00166] In one embodiment, a course of radiation therapy includes a plurality of radiation doses or dose fractions given over a predetermined period of time, such as over the course of hours, weeks, days and even months, with the plural doses or dose

fractions being either of the same magnitude or varying. That is, a course of radiation therapy can comprise the administration of a series of multiple doses or dose fractions of radiation. In one embodiment, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent can be administered before one or more radiation doses or dose fractions in the series, such as before each radiation dose or dose fraction, or before some number of the radiation doses or dose fractions. Furthermore, the administration of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent during the course of radiation therapy can be selected to enhance the cancer treating effects of the radiation therapy, such as by sensitizing cancer cells to the radiation therapy. In one embodiment, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered within a predetermined duration before or after of each dose or dose fraction, such as the predetermined duration discussed above. In another embodiment, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered within a predetermined duration of time before or after only select doses or dose fractions. In yet another embodiment, at least one of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent is administered within a predetermined duration of time before the doses, while another of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent is administered within a predetermined duration of time after the doses or dose fraction. In a further embodiment, at least one of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent is administered only within the predetermined duration before or after select doses or dose fractions, while another of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent is administered only within the predetermined duration before or after doses or dose fractions other than the select doses or dose fractions.

[00167] A suitable overall dose to provide during a course of therapy can be determined according to the type of treatment to be provided, the physical characteristics of the patient and other factors, and the dose fractions that are to be provided can be similarly determined. In one embodiment , a dose fraction of radiation that is administered to a patient may be at least 1.8 Gy, such as at least 2 Gy, and even at least 3 Gy, such as at least 5 Gy, and even at least 6 Gy. In yet another embodiment, a dose fraction of radiation that is administered to a patient may be at least 10 Gy, such as at least 12 Gy, and even at least 15 Gy, such as at least 18 Gy,

and even at least 20 Gy, such as at least 24 Gy. In general, a dose fraction of radiation administered to a patient will not exceed 54 Gy. Furthermore, it should be noted that, in one embodiment, a dose fraction delivered to a subject may refer to an amount delivered to a specific target region of a subject, such as a target region of a tumor, whereas other regions of the tumor or surrounding tissue may be exposed to more or less radiation than that specified by the nominal dose fraction amount.

[00168] In yet another embodiment, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered as a part of a course of therapy that includes administration of an additional chemotherapeutic agent. In chemotherapy, chemotherapeutic agents are administered to a patient to kill or control the growth of cancerous cells. A typical course of chemotherapy may include one or a plurality of doses of one or more chemotherapeutic agents, which can be administered over the course of days, weeks and even months. Chemotherapeutic agents can include at least one of: alkylating antineoplastic agents such as nitrogen mustards (*e.g.* cyclophosphamide, chlorambucil), nitrosoureas (*e.g.* n-nitroso-n-methylurea, carmustine, semustine), tetrazines (*e.g.* dacarbazine, mitozolimide), aziridines (*e.g.* thiotepa, mytomycin); anti-metabolites such as anti-folates (*e.g.* methotrexate and pemetrexed), fluoropyrimidines (*e.g.*, fluorouracil, capecitabine), anthracyclines (*e.g.* doxorubicin, daunorubicin, epirubicin), deoxynucleoside analogs (*e.g.* cytarabine, gemcitabine, decitabine) and thiopurines (e.g., thioguanine, mercaptopurine); anti microtubule agents such as taxanes (*e.g.* paclitaxel, docetaxel); topoisomerase inhibitors (*e.g.* etoposide, doxorubicin, mitoxantrone, teniposide); and antitumor antibiotics (*e.g.* bleomycin, mitomycin). For example, the chemotherapeutic agent may be selected from the group consisting of all-trans retinoic acid, arsenic trioxide, azacitidine, azathioprine, bleomycin, carboplatin, capecitabine, cisplatin, chlorambucil, cyclophosphamide, cytarabine, daunorubicin, docetaxel, doxifluridine, doxorubicin, epirubicin, epothilone, etoposide, fluorouracil, gemcitabine, hydroxyurea, idarubicin, imatinib, mechlorethamine, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, pemetrexed, teniposide, tiguanine, valrubicin, vinblastine, vincristine, vindesine, and vinorelbine. The administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), *e.g.*, 1996 edition (Medical Economics Company, Montvale, N.J. 07645-1742, USA).

[00169] In one embodiment, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered as a part of a course of therapy that includes an additional chemotherapeutic agent selected from the group consisting of doxorubicin, bleomycin, and paclitaxel. Furthermore, in one embodiment, the additional chemotherapeutic agent may be selected from the group consisting of a taxane, an anticancer antibiotic, and an anthracycline. Other chemotherapeutic agents can include arsenic trioxide and 5-FU, which agents can also be used in the methods and compositions described herein. (Alexandre *et al.*, Cancer Res. 67: (8), 3512-3517 (2007); Yen *et al.*, J. Clin. Invest. 98 (5), 1253-1260 (1996); Masuda *et al.*, Cancer Chemother. Pharmacol. 47(2), 155-160 (2001)).

[00170] According to yet another embodiment, the additional chemotherapeutic agent can include at least one of an antimetabolite anti-cancer agents and antimitotic anti-cancer agents, and combinations thereof, which may include some of the agents described above and well as other agents described further herein. Various antimetabolite and antimitotic agents may be employed in the methods and compositions described herein.

[00171] Antimetabolic agents typically structurally resemble natural metabolites, which are involved in normal metabolic processes of cancer cells such as the synthesis of nucleic acids and proteins. The antimetabolites, however, differ enough from the natural metabolites such that they interfere with the metabolic processes of cancer cells. In the cell, antimetabolites are mistaken for the metabolites they resemble, and are processed by the cell in a manner analogous to the normal compounds. The presence of the “decoy” metabolites prevents the cells from carrying out vital functions and the cells are unable to grow and survive. For example, antimetabolites may exert cytotoxic activity by substituting these fraudulent nucleotides into cellular DNA, thereby disrupting cellular division, or by inhibition of critical cellular enzymes, which prevents replication of DNA.

[00172] In one embodiment, therefore, the antimetabolite agent is a nucleotide or a nucleotide analog. In certain embodiments, for example, the antimetabolite agent may comprise purine (*e.g.*, guanine or adenosine) or analogs thereof, or pyrimidine (cytidine or thymidine) or analogs thereof, with or without an attached sugar moiety.

[00173] Suitable antimetabolite agents for use in the present disclosure may be generally classified according to the metabolic process they affect, and can include, but are not limited to, analogues and derivatives of folic acid, pyrimidines, purines, and cytidine. Thus, in one embodiment, the antimetabolite agent(s) is selected from the group consisting of cytidine analogs, folic acid analogs, purine analogs, pyrimidine analogs, and combinations thereof.

[00174] In one particular embodiment, for example, the antimetabolite agent is a cytidine analog. According to this embodiment, for example, the cytidine analog may be selected from the group consisting of cytarabine (cytosine arabinodside), azacitidine (5-azacytidine), and salts, analogs, and derivatives thereof.

[00175] In another particular embodiment, for example, the antimetabolite agent is a folic acid analog. Folic acid analogs or antifolates generally function by inhibiting dihydrofolate reductase (DHFR), an enzyme involved in the formation of nucleotides; when this enzyme is blocked, nucleotides are not formed, disrupting DNA replication and cell division. According to certain embodiments, for example, the folic acid analog may be selected from the group consisting of denopterin, methotrexate (amethopterin), pemetrexed, pteropterin, raltitrexed, trimetrexate, and salts, analogs, and derivatives thereof.

[00176] In another particular embodiment, for example, the antimetabolite agent is a purine analog. Purine-based antimetabolite agents function by inhibiting DNA synthesis, for example, by interfering with the production of purine containing nucleotides, adenine and guanine which halts DNA synthesis and thereby cell division. Purine analogs can also be incorporated into the DNA molecule itself during DNA synthesis, which can interfere with cell division. According to certain embodiments, for example, the purine analog may be selected from the group consisting of acyclovir, allopurinol, 2-aminoadenosine, arabinosyl adenine (ara-A), azacitidine, azathiprine, 8-aza-adenosine, 8-fluoro-adenosine, 8-methoxy-adenosine, 8-oxo-adenosine, cladribine, deoxycoformycin, fludarabine, gancylovir, 8-aza-guanosine, 8-fluoro-guanosine, 8-methoxy-guanosine, 8-oxo-guanosine, guanosine diphosphate, guanosine diphosphate-beta-L-2-aminofucose, guanosine diphosphate-D-arabinose, guanosine diphosphate-2-fluorofucose, guanosine diphosphate fucose, mercaptopurine (6-MP), pentostatin, thiamiprine, thioguanine (6-TG), and salts, analogs, and derivatives thereof.

[00177] In yet another particular embodiment, for example, the antimetabolite agent is a pyrimidine analog. Similar to the purine analogs discussed above, pyrimidine-based antimetabolite agents block the synthesis of pyrimidine-containing nucleotides (cytosine and thymine in DNA; cytosine and uracil in RNA). By acting as "decoys," the pyrimidine-based compounds can prevent the production of nucleotides, and/or can be incorporated into a growing DNA chain and lead to its termination. According to certain embodiments, for example, the pyrimidine analog may be selected from the group consisting of ancitabine, azacitidine, 6-azauridine, bromouracil (*e.g.*, 5-bromouracil), capecitabine, carmofur, chlorouracil (*e.g.* 5-chlorouracil), cytarabine (cytosine arabinoside), cytosine, dideoxyuridine, 3'-azido-3'-deoxythymidine, 3'-dideoxycytidin-2'-ene, 3'-deoxy-3'-deoxythymidin-2'-ene, dihydrouracil, doxifluridine, enocitabine, floxuridine, 5-fluorocytosine, 2-fluorodeoxycytidine, 3-fluoro-3'-deoxythymidine, fluorouracil (*e.g.*, 5-fluorouracil (also known as 5-FU), gemcitabine, 5-methylcytosine, 5-propynylcytosine, 5-propynylthymine, 5-propynyluracil, thymine, uracil, uridine, and salts, analogs, and derivatives thereof. In one embodiment, the pyrimidine analog is other than 5-fluorouracil. In another embodiment, the pyrimidine analog is gemcitabine or a salt thereof.

[00178] In certain embodiments, the antimetabolite agent is selected from the group consisting of 5-fluorouracil, capecitabine, 6-mercaptopurine, methotrexate, gemcitabine, cytarabine, fludarabine, pemetrexed, and salts, analogs, derivatives, and combinations thereof. In other embodiments, the antimetabolite agent is selected from the group consisting of capecitabine, 6-mercaptopurine, methotrexate, gemcitabine, cytarabine, fludarabine, pemetrexed, and salts, analogs, derivatives, and combinations thereof. In one particular embodiment, the antimetabolite agent is other than 5-fluorouracil. In a particularly preferred embodiment, the antimetabolite agent is gemcitabine or a salt or thereof (*e.g.*, gemcitabine HCl (Gemzar®)).

[00179] Other antimetabolite agents may be selected from, but are not limited to, the group consisting of acanthifolic acid, aminothiadiazole, brequinar sodium, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, Wellcome EHNA, Merck & Co. EX-015, fazarabine, fludarabine phosphate, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, 5-FU-fibrinogen, isopropyl pyrrolizine, Lilly LY-188011; Lilly LY-264618,

methobenzaprim, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, tiazofurin, Erbamont TIF, tyrosine kinase inhibitors, Taiho UFT and uricytin, among others.

[00180] In one embodiment, the chemotherapeutic agent comprises an antimitotic agent that is a microtubule inhibitor or a mictrotubule stabilizer. In general, microtubule stabilizers, such as taxanes (some of which are also described above) and epothilones, bind to the interior surface of the beta-microtubule chain and enhance microtubule assembly by promoting the nucleation and elongation phases of the polymerization reaction and by reducing the critical tubulin subunit concentration required for microtubules to assemble. Unlike mictrotubule inhibitors, such as the vinca alkaloids, which prevent microtubule assembly, the microtubule stabilizers, such as taxanes, decrease the lag time and dramatically shift the dynamic equilibrium between tubulin dimers and microtubule polymers towards polymerization. In one embodiment, therefore, the microtubule stabilizer is a taxane or an epothilone. In another embodiment, the microtubule inhibitor is a vinca alkaloid.

[00181] One element of the therapy described herein may include the use of a taxane or derivative or analog thereof, some of which have also been discussed above. In one embodiment, the taxane may be a naturally derived compound or a related form, or may be a chemically synthesized compound or a derivative thereof, with antineoplastic properties. The taxanes are a family of terpenes, including, but not limited to paclitaxel (Taxol®) and docetaxel (Taxotere®), which are derived primarily from the Pacific yew tree, Taxus brevifolia, and which have activity against certain tumors, particularly breast and ovarian tumors. In one embodiment, the taxane is docetaxel or paclitaxel. Paclitaxel is a preferred taxane and is considered an antimitotic agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

[00182] Also included are a variety of known taxane derivatives, including both hydrophilic derivatives, and hydrophobic derivatives. Taxane derivatives include, but are not limited to, galactose and mannose derivatives described in International Patent Application No. WO 99/18113; piperazino and other derivatives described in WO

99/14209; taxane derivatives described in WO 99/09021, WO 98/22451, and U.S. Patent No. 5,869,680; 6-thio derivatives described in WO 98/28288; sulfenamide derivatives described in U.S. Patent No. 5,821,263; deoxygenated paclitaxel compounds such as those described in U.S. Patent No. 5,440,056; and taxol derivatives described in U.S. Patent No. 5,415,869. As noted above, it further includes prodrugs of paclitaxel including, but not limited to, those described in WO 98/58927; WO 98/13059; and U.S. Patent No. 5,824,701. The taxane may also be a taxane conjugate such as, for example, paclitaxel-PEG, paclitaxel-dextran, paclitaxel-xylose, docetaxel-PEG, docetaxel-dextran, docetaxel-xylose, and the like. Other derivatives are mentioned in "Synthesis and Anticancer Activity of Taxol Derivatives," D. G. I. Kingston *et al.*, Studies in Organic Chemistry, vol. 26, entitled "New Trends in Natural Products Chemistry" (1986), Atta-ur-Rabman, P. W. le Quesne, Eds. (Elsevier, Amsterdam 1986), among other references. Each of these references is hereby incorporated by reference herein in its entirety.

[00183] Various taxanes may be readily prepared utilizing techniques known to those skilled in the art (see also WO 94/07882, WO 94/07881, WO 94/07880, WO 94/07876, WO 93/23555, WO 93/10076; U.S. Pat. Nos. 5,294,637; 5,283,253; 5,279,949; 5,274,137; 5,202,448; 5,200,534; 5,229,529; and EP 590,267) (each of which is hereby incorporated by reference herein in its entirety), or obtained from a variety of commercial sources, including for example, Sigma-Aldrich Co., St. Louis, MO.

[00184] Alternatively, the antimitotic agent can be a microtubule inhibitor; in one preferred embodiment, the microtubule inhibitor is a vinca alkaloid. In general, the vinca alkaloids are mitotic spindle poisons. The vinca alkaloid agents act during mitosis when chromosomes are split and begin to migrate along the tubules of the mitosis spindle towards one of its poles, prior to cell separation. Under the action of these spindle poisons, the spindle becomes disorganized by the dispersion of chromosomes during mitosis, affecting cellular reproduction. According to certain embodiments, for example, the vinca alkaloid is selected from the group consisting of vinblastine, vincristine, vindesine, vinorelbine, and salts, analogs, and derivatives thereof.

[00185] The antimitotic agent can also be an epothilone. In general, members of the epothilone class of compounds stabilize microtubule function according to mechanisms similar to those of the taxanes. Epothilones can also cause cell cycle arrest at the G2-M transition phase, leading to cytotoxicity and eventually apoptosis.

Suitable epithiolones include epothilone A, epothilone B, epothilone C, epothilone D, epothilone E, and epothilone F, and salts, analogs, and derivatives thereof. One particular epothilone analog is an epothilone B analog, ixabepilone (Ixempra™).

[00186] In certain embodiments, the antimitotic anti-cancer agent is selected from the group consisting of taxanes, epothilones, vinca alkaloids, and salts and combinations thereof. Thus, for example, in one embodiment the antimitotic agent is a taxane. More preferably in this embodiment the antimitotic agent is paclitaxel or docetaxel, still more preferably paclitaxel. In another embodiment, the antimitotic agent is an epothilone (*e.g.*, an epothilone B analog). In another embodiment, the antimitotic agent is a vinca alkaloid.

[00187] In one embodiment, at least one of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered within a predetermined time period before or after a dose of an additional chemotherapeutic agent is administered. For example, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may be administered within 1 week, 48 hours, 24 hours, 12 hours, 6, hours, 2 hours, 1 hour or even within 30 minutes of the patient receiving the dose of the additional chemotherapeutic agent (either before or after the dose of chemotherapeutic agent). Other durations between the additional chemotherapeutic agent dose and administration of the components that result in the enhanced the killing of cancer cells may also be suitable. In one embodiment, one or more of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may be administered before the dose of the additional chemotherapeutic agent, and the remaining one or more of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent can be administered after the dose of the additional chemotherapeutic agent. One or more of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent may also be administered both before and after administration of the dose of additional chemotherapeutic agent.

[00188] In one embodiment, a course of chemotherapy includes a singular dose of the additional chemotherapeutic agent. In another embodiment, a course of chemotherapy includes a plurality of doses of the additional chemotherapeutic agent given over a predetermined period of time, such as over the course of hours, weeks, days and even months. The plural doses may be either of the same magnitude or varying, and can include doses of the same or different chemotherapeutic agents and/or

a combination of chemotherapeutic agents. The administration of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent during the course of chemotherapy can be selected to enhance the cancer treating effects of the chemotherapy, such as by increasing intracellular levels of hydrogen peroxide to promote oxidative stress in the cancer cells. In one embodiment, the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered within a predetermined duration before or after each dose, such as the predetermined duration discussed above. In another embodiment, the pentaaza macrocyclic ring complex and platinum-based anticancer agent are administered within a predetermined duration of time before or after only select doses. In yet another embodiment, at least one of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered within a predetermined duration of time before the doses, while another of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent are administered within a predetermined duration of time after the doses. In a further embodiment, at least one of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent is administered only within the predetermined duration before or after select doses, while another of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent is administered only within the predetermined duration before or after doses other than the select doses.

[00189] In yet another embodiment, at least one of the pentaaza macrocyclic ring complex and the platinum-based anticancer agent is administered in combination with both a radiation therapy and a chemotherapy involving administration of an additional chemotherapeutic agent.

Examples

[00190] The following non-limiting examples are provided to further illustrate aspects of the present invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent approaches the inventors have found function well in the practice of the invention, and thus can be considered to constitute examples of modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Synergistic Effects of Anticancer Treatment

Example 1

[00191] **Effect of GC4419 and Cisplatin on Survival of Cancer Cells in Culture.** H460 human non-small cell lung carcinoma (NSCLC) cells in culture were treated with 24 μM GC4419 (+GC) or Media (-GC) and the indicated concentrations of cisplatin. After 120 hrs the surviving fraction of cells was determined. The addition of GC4419 to cisplatin treatment decreased the surviving fraction of H460 cells compared to cells treated with cisplatin alone. GC4419 signficantly sensitized H460 lung carcinoma cells to the cisplatin (*see* Figure 1: Effect of GC4419 and Cisplatin on Survival of H460 Cells in Culture).

Example 2

[00192] **Effect of GC4419, Cisplatin and Overexpression of Catalase on Survival of Cancer Cells in Culture.** H1299 human NSCLC cells, modified to inducibly overexpress catalase (CAT), an enzyme that removes hydrogen peroxide (H_2O_2) were treated in cell culture with 24 μM GC4419 (+GC) or Media (-GC) and the indicated concentrations of cisplatin. CAT overexpression in this line (H1299CAT) was induced by administration of doxycycline, which turned on transcription of the inserted catalase genes. 120 hrs after treatment with cisplatin with or without GC4419. the surviving fraction of H1299CAT cells was determined, both with and without CAT overexpression. Without CAT overexpression ("wt"), the addition of GC4419 to cisplatin treatment decreased the surviving fraction of H460 cells compared to cells treated with cisplatin alone. similarly to H460 cells when treated with both GC4419 and cisplatin. In contrast, the overexpression of CAT ("CAT", removing H_2O_2 generated from superoxide by GC4419) abrogated the GC4419 contribution to cisplatin response, demonstrating that GC4419 signficantly sensitized H460 lung carcinoma cells to the cisplatin and that the enhanced response was H_2O_2 dependent (*see,* Figure 2: Effect of GC4419, Cisplatin and Overexpression of Catalase on Survival of H1299CAT Cells in Culture).

Example 3

[00193] **Effect of GC4419 and Cisplatin on PARP Activation in Cancer Cells.** H460 NSCLC cells in culture were treated with 24 μM GC4419 and 1 μM cisplatin for 24 hr. At this time cells were solubilized and PARP (poly (ADP ribosyl)

polymerase) activity was measured by Western blot as the ratio of the 89 kd active form to the 116 kd inactive form. PARP is a nuclear enzyme involved in DNA repair of single strand breaks and is activated following cell stress including chemotherapy and irradiation. As shown in Figure 3, cisplatin increased PARP activity compared to untreated cells or GC4419 treatment alone. The addition of GC4419 to cisplatin further and significantly ($p<0.01$) increased PARP activity, suggesting that GC4419 increased the cancer cell damage caused by cisplatin (*see,* Figure 3: Effect of GC4419 and Cisplatin on PARP Activation in H460 Cells).

[00194] H1299 (wild type) NSCLC cells in culture were also treated with 24 μM GC4419 and 10 μM cisplatin for 24 hr. At this time cells were solubilized and PARP activity was measured by Western blot as the ratio of the 89 kd active form to the 116 kd inactive form. As shown in Figure 4 and consistent with the effects seen in H460 lung carcinoma cells, cisplatin increased PARP activity compared to untreated cells or GC4419 treatment alone. The addition of GC4419 to cisplatin further and significantly $p<0.01$) increased PARP activity, suggesting that GC4419 increased the cancer cell damage caused by cisplatin (*see* Figure 4: Effect of GC4419 and Cisplatin on PARP Activation in H1299 Cells).

[00195] H460 cells in culture were further exposed to 6 Gy irradiation (IR), and either 24 μM GC4419, 1 μM cisplatin, or GC4419 and cisplatin for 24 hr. At this time cells were solubilized and PARP activity was measured by Western blot as the ratio of the 89 kd active form to the 116 kd inactive form. As shown in Figure 5, radiation (IR) alone increased PARP activity significantly ($p<0.05$) over background. The addition of GC4419 to IR significantly increased PARP activity over that seen with radiation alone. Cisplatin added to IR caused a larger increase in PARP activity and GC4419 added to this combination significantly increased ($p<0.01$) this, suggesting that GC4419 increased the cancer cell damage caused by radiation and cisplatin (*see,* Figure 5: Effect of GC4419, Cisplatin and Radiation on PARP Activation in H460 Cells).

[00196] H1299 (wild type) cells in culture were also exposed to 6 Gy irradiation (IR), and either 24 μM GC4419, 1 μM cisplatin, or GC4419 and cisplatin for 24 hr. At this time cells were solubilized and PARP activity was measured by Western blot as the ratio of the 89 kd active form to the 116 kd inactive form. As shown in Figure 6A and consistent with the effects seen in H460 lung carcinoma cells, radiation (IR) alone

increased PARP activity slightly over background. The addition of GC4419 to IR significantly increased PARP activity over that seen with radiation alone. Cisplatin added to IR caused a larger increase in PARP activity and GC4419 added to this combination significantly increased ($p<.0.05$) this, suggesting that GC4419 increased the cancer cell damage caused by radiation and cisplatin (*see*, Figure 6A: Effects of GC4419, Cisplatin and Radiation on PARP Activation in H1299 Cells).

[00197] H1299CAT cells were also exposed to 6 Gy irradiation (IR), 24 μM GC4419, and/or 1 μM cisplatin for 24 hr. When treated with doxcycline, H1299CAT cells express greater levels of human catalase (CAT) than the "parent" cells, H1299 (wild type), eliminating all or part of the H2O2 generated from superoxide by GC4419 or other Mn pentaazamacrocyclic dismutase mimetcs. PARP activation in H1299CAT cells not exposed to doxycycline (data not shown) responded to cisplatin, IR and GC4419 treatments comparably to H1299 wild type cells (see Figure 5). But when CAT expression was induced in H1299CAT with doxycycline treatment, GC4419 significantly ($p<0.05$) reduced the PARP activation response to cisplatin ($p<0.01$, Figure 6B), IR ($p<0.05$, Figure 6C) and to IR + cisplatin ($p<0.001$, Figure 6C). These results strongly suggest that superoxide generated by cisplatin causes cellular damage, and that GC4419 removal of this superoxide can reduce cellular damage, consistent with the results reported in Example 5 below for reduction of cisplatin nephrotoxicity and hematotoxicity. However, since GC4419 increased PARP response to cisplatin in cancer cells, except when H_2O_2 when was removed by CAT overexpression, these results further support that GC4419-generated H_2O_2 (unless removed by CAT) was responsible for greater enhancement of cisplatin cellular damage and PARP activation than the superoxide it replaced (*see,* Figure 6B: Treatment of H1299CAT cells (with doxycycline induction of CAT overexpression) with Cisplatin and GC4419; and Figure 6C: Treatment of H1299CAT cells (with doxycycline induction of CAT overexpression) with cisplatin, IR and GC4419).

Example 4

[00198] **Cisplatin Treatment Increases Total Reactive Oxygen Species (ROS) Levels in Cancer Cells While GC4419 Selectively Decreases Superoxide and Increases H_2O_2 Levels.** H460 and H1299 (wild type) cells were exposed to 6 Gy

irradiation (IR), and either 24 μM GC4419, 1 μM cisplatin, or GC4419 and cisplatin. After the treatments and incubations CellROX fluorogenic probes for total ROS were added for 30 minutes continued incubation and the CellROX signal was measured using a flow cytometer. Figures 7A-7D show that GC4419 had little effect on total ROS when used alone on either cancer cell line, while cisplatin or cisplatin plus IR increased total ROS. GC4419 appeared to have a synergistic effect on total ROS when added to cisplatin therapy (*see,* Figures 7A-7D: Total Reactive Oxygen Species).

[00199] If instead, after the treatments and initial incubations, MitoSOX fluorogenic probe for mitochondrial superoxide was added for 10 minutes continued incubation and the MitoSOX signal was measured using a flow cytometer, Figures 8A-8D show that GC4419 significantly reduced the basal levels of mitochondrial superoxide in both cancer cell lines. In addition, GC4419 significantly reduced the increase in mitochondrial superoxide induced by cisplatin or cisplatin plus IR (*see,* Figures 8A-8D: Mitochondrial Superoxide)

[00200] In addition, if instead, after the treatments and initial incubations, PO-1 probe for H_2O_2 was added, Figures 9A-9D show that GC4419 significantly increases both the basal levels of H_2O_2, and significantly further increases the increase in H_2O_2 induced by cisplatin or cisplatin plus IR, in both cancer cell lines (*see,* Figures 9A-9D: Hydrogen Peroxide).

Reduced Toxicity of Platinum-Based Anticancer Agents

Example 5

[00201] **Effect of GC4419 on Cisplatin-induced Nephrotoxicity in Mice**. 4 month old male C57BL/6J mice (young) were purchased from Jackson Laboratories and 18 month old mice (old) were obtained as collaboration with Dr. Amy Sindler (University of Iowa) from the National institute of Aging. All mice were maintained in accordance with ACURF approval #4121235 at the University of Iowa Animal Care facility. Mice were maintained on normal diets and water *ad libitum* through the course of the experiment. Animals were randomly assigned to experimental groups which included vehicle control, cisplatin only, GC4419 and cisplatin+GC4419.

[00202] A cisplatin-induced acute kidney injury (AKI) model was as follows: Male C57BL/6J mice, either 4 months or 18 months of age were administered a single dose of 10mg/kg cisplatin or 0.9% saline by i.p, injection. Animals were sacrificed 72

hours following cisplatin treatment. Animals in GC4419 only and cisplatin+GC4419 groups were treated with 10mg/kg GC4419 daily starting 4 days prior to the cisplatin dose and until the day of euthanasia. Animals in the cisplatin only group were also given a bolus dose of saline every day following cisplatin treatment to avoid dehydration.

[00203] Whole blood blood urea nitrogen (BUN) and creatinine levels were measured using an *i-STAT* handheld clinical analyzer purchased from Abbott-Point of Care (Princeton, NJ) using single-use *i-STAT* test cartridges (Chem8+) prior to the start of treatment with GC4419 and 72 hours following cisplatin treatment. Animals were weighed every other day following the start of treatment with GC4419.

[00204] As seen in Figure 10A, cisplatin increased BUN and and creatinine levels three days after administration, both in young, and more dramatically in old, mice, indicating significant impairment of kidney function. GC4419 completely prevented these increases in BUN and creatinine, suggesting that it prevented acute kidney injury (*see* Figure 10A: BUN and Creatinine Levels in Cisplatin-treated Mice).

[00205] Two specific biomarkers of kidney injury, kidney injury molecule 1 (KIM1) and neutrophil gelatinase-associated lipocalin (NGAL) were also assessed. As seen in Figure 10B, these biomarkers are consistent with the BUN and creatinine levels, demonstrating that cisplatin caused nephrotoxicity and GC4419 prevented that injury (*see,* Figure 10B: KIM1 and NGAL biomarkers in Cisplatin-treated Mice).

[00206] Further consistent with these kidney injury and function results, cisplatin caused significant weight loss in both young and old mice (Figure 10C) and decreased survival in the more sensitive old mice (Figure 10D). GC4419 reduced the amount of weight loss in both sets of mice and prevented cisplatin mortality in the old mice (*see*, Figure 10C: Cisplatin-induced Weight Loss; and Figure 10D: Survival in Cisplatin-treated Mice).

[00207] Further consistent with these kidney injury and function results, cisplatin caused significant weight loss in both young and old mice (Figure 10C) and decreased survival in the more sensitive old mice (Figure 10D). GC4419 reduced the amount of weight loss in both sets of mice and prevented cisplatin mortality in the old mice.

Example 6

[00208] **Effect of GC4419 on Cisplatin-induced Hematotoxicity in Mice.** 7 week old athymic female Nu/Nu (nude) mice were implanted in a hind leg with SQ20B human head and neck squamous cell carcinoma cells. After tumors had been allowed to form and grow for 4 days, the mice received either no treatment or 2.7 mg/kg cisplatin and 2 Gy radiation (IR) every second or third day for five times. In addition, one group that received cisplatin and IR treatement also received 10 mg/kg GC4419 every day during the treatment period and for two days following. Mice were assessed for blood counts by tail vein blood collection either 2 days or 2 weeks after the treatment period.

[00209] As seen in Figure 11A, cisplatin+IR treatment resulted in a decrease in platelets (thrombocytopenia) measured two days after the end of treatments and GC4419 significantly restored platelet levels (*see,* Figure 11A: Cisplatin-induced Thrombocytopenia).

[00210] As seen in Figure 11B GC4419 treatment stimulated leukocyte (WBC) and proportionally lymphocyte subset production in mice treated with the combination of cisplatin and radiation at both 2 days and 2 weeks after the end of treatment (*see,* Figure 11B: GC4419 and WBC Count).

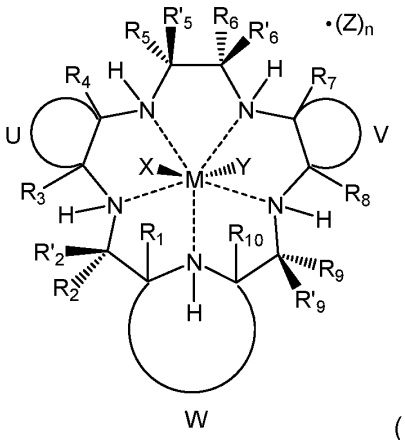
[00211] As seen in Figure 11C, cisplatin+IR treatment resulted in a decrease in neutrophil count and percentage (neutropenia), measured two days or two weeks after the end of treatments and GC4419 maintained neutrophil percentage at apparently normal levels (*see,* Figure 11C: Cisplatin-induced Neutropenia).

[00212] Conversely, as seen in Figure 11D, cisplatin+IR treatment resulted in an increase in eosinophil percentage, measured two days or two weeks after the end of treatments and GC4419 maintained eosinophil percentage at apparently normal levels (*see,* Figure 11D: Cisplatin-induced Eospinophil Increase).

[00213] The following are exemplary embodiments of aspects of the disclosure, but are not intended to be limiting, and the disclosure may encompass further aspects.

[00214] Embodiment 1. A method of treating and/or reducing the reducing toxic effects to a mammalian subject associated with treatment with a platinum-based anti-cancer agent in a subject in need thereof, the method comprising 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, prior to, concomitantly

with, or after administration of the platinum-based anticancer agent, to reduce toxic effects of the platinum-based anti-cancer agent:



(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.

[00215] Embodiment 2. The method according to Embodiment 1, wherein the subject is afflicted with cancer.

[00216] Embodiment 3. The method according to Embdiment 1 or 2, wherein the subject is afflicted with and/or at risk for a toxicity induced by treatment with the platinum-based anti-cancer agent, that is a toxicity selected from the group consisting of nephrotoxicity, myelotoxicity, and ototoxicity

[00217] Embodiment 4. The method according to any one of Embodiments 1-3, wherein the subject is afflicted with and/or at risk for one or more of nephrotoxicity and myelotoxicity.

[00218] Embodiment 5. The method according to any one of Embodiments 1-4, wherein the subject is suffering from nephrotoxicity and/or myelotoxicity associated with treatment with the platinum-based anti-cancer agent.

[00219] Embodiment 6. The method according to any one of Embodiments 1-5, 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.

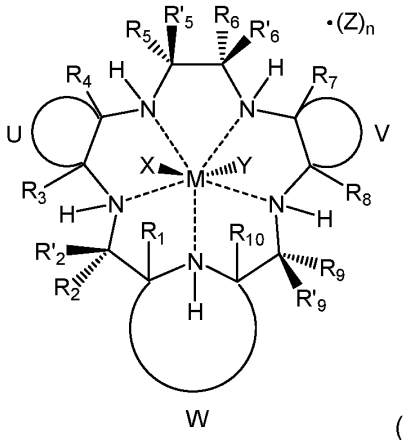
[00220] Embodiment 7. The method of any of Embodiments 1-6, wherein the pentaaza macrocyclic ring complex is administered in a therapeutically effective amount that results in an increase in cancer response corresponding to any selected from the

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.

[00221] Embodiment 8. The method of any of Embodiments 1-7, 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).

[00222] Embodiment 9. The method of any of Embodiments 1-8, 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)

[00223] Embodiment 10. A method of treating and/or reducing the risk for a toxic effect associated with treatment with a platinum-based anti-cancer agent in a mammalian subject in need thereof, the method comprising: 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, to reduce toxic effects of the platinum-based anti-cancer agent:



(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.

[00224] Embodiment 11. The method according to Embodiment 10, wherein the subject is afflicted with cancer.

[00225] Embodiment 12. The method according to Embodiment 10 or 11, wherein the subject is afflicted with and/or at risk for a toxicity induced by treatment with

the platinum-based anti-cancer agent, that is a toxicity selected from the group consisting of nephrotoxicity, myelotoxicity, and ototoxicity.

[00226] Embodiment 13. The method according to any one of Embodiments 10-12, wherein the subject is afflicted with and/or at risk for one or more of nephrotoxicity and myelotoxicity.

[00227] Embodiment 14. The method according to any one of Embodiments 10-13, wherein the subject is suffering from nephrotoxicity and/or myelotoxicity associated with treatment with the platinum-based anti-cancer agent.

[00228] Embodiment 15. The method according to any one of Embodiments 10-14, 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.

[00229] Embodiment 16. The method of any one of Embodiments 10-15, 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.

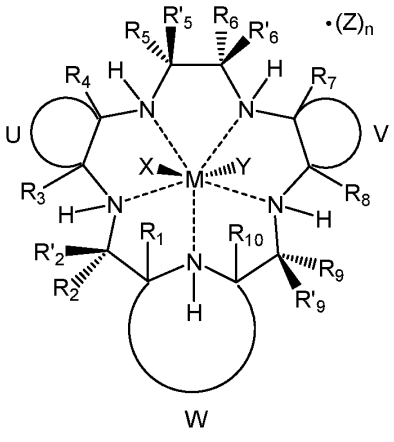
[00230] Embodiment 17. The method of any one of Embodiments 10-16, wherein the pentaaza macrocyclic ring is administrered in a therapeutically effective amount that reduces levels of at least one of creatine and blood urea nitrogen (BUN).

[00231] Embodiment 18. The method of any one of Embodiments 10-17, 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).

[00232] Embodiment 19. A method of treating a cancer in a mammalian subject afflicted with the cancer, the method comprising:

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, 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)

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.

[00233] Embodiment 20. The method of Embodiment 19, comprising administering therapeutically effective amounts of the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex that reduce toxic effects of the platinum anti-cancer agent.

[00234] Embodiment 21. The method of Embodiment 19 or 20, 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.

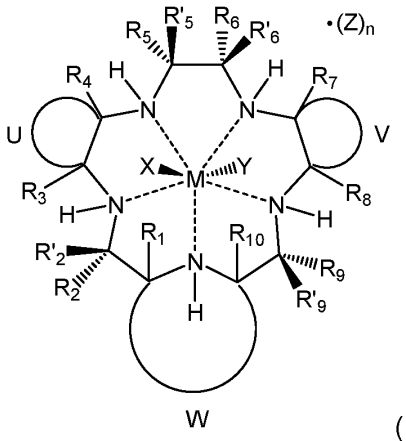
[00235] Embodiment 22. The method of Embodiment 19, 20 or 21, wherein the pentaaza macrocyclic ring is administrered in a therapeutically effective amount that reduces levels of at least one of creatine and blood urea nitrogen (BUN).

[00236] Embodiment 23. The method of Embodiment 19, 20, 21 or 22, wherein the pentaaza macrocyclic ring is 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).

[00237] Embodiment 24. A method of increasing the sensitivity of a mammalian subject to treatment with a platinum-based anti-cancer agent in a subject in need thereof, the method comprising:

administering to the subject a therapeutically effective amount of 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 treatment response to the platinum-based anti-cancer agent is increased:



(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.

[00238] Embodiment 25. The method of Embodiment 24, wherein the subject is afflicted with cancer.

[00239] Embodiment 26. The method of Embodiment 24 or 25, comprising administering therapeutically effective amounts of the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex that reduce toxic effects of the platinum anti-cancer agent.

[00240] Embodiment 27. The method of Embodiment 24, 25 or 26, 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.

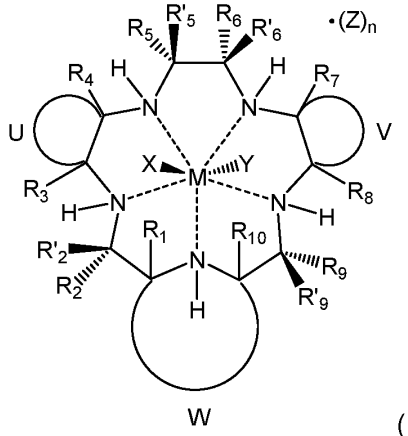
[00241] Embodiment 28. The method of Embodiment 24, 25, 26 or 27, wherein the pentaaza macrocyclic ring is administrered in a therapeutically effective amount that reduces levels of at least one of creatine and blood urea nitrogen (BUN).

[00242] Embodiment 29. The method of any of Embodiments 24-28, 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).

[00243] Embodiment 30. 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 comprising:

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, 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.

[00244] Embodiment 31. The method according to Embodiment 30, wherein the subject is afflicted with cancer.

[00245] Embodiment 32. The method according to any one of Embodiments 30-31, wherein the subject is suffering from nephrotoxicity and/or myelotoxicity associated with treatment with the platinum-based anti-cancer agent.

[00246] Embodiment 33. The method according to any one of Embodiments 30-32, 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.

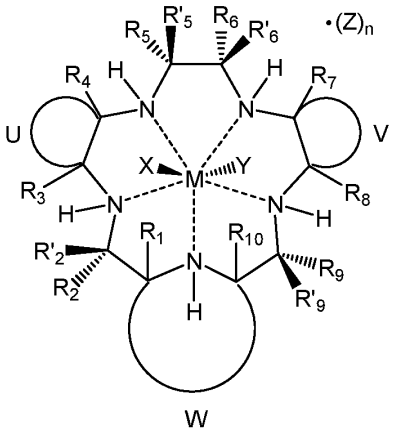
[00247] Embodiment 34. The method of any of Embodiments 30-33, wherein the pentaaza macrocyclic ring complex is administered in a therapeutically effective amount that results in an increase in cancer response corresponding to any selected from the group consisting of reduced tumor volume, reduced tumor growth rate, increased survival, reduced occurrence and/or extent of metastasis, and reduced proliferation of cancer cells, and/or may decrease cancer complications

[00248] Embodiment 35. The method of any of Embodiments 30-34, 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).

[00249] Embodiment 36. The method of any of Embodiments 30-35, 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).

[00250] Embodiment 37. 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 comprising:

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.

[00251] Embodiment 38. The method according to Embodiment 37, wherein the subject is afflicted with cancer.

[00252] Embodiment 39. The method according to any one of Embodiments 37-38, wherein the subject is suffering from nephrotoxicity and/or myelotoxicity associated with treatment with the platinum-based anti-cancer agent.

[00253] Embodiment 40. The method according to any one of Embodiments 37-39, 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.

[00254] Embodiment 41. The method of any one of Embodiments 37-40, 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.

[00255] Embodiment 42. The method of any one of Embodiments 37-41, 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).

[00256] Embodiment 43. The method of any one of Embodiments 37-42, wherein the pentaaza macrocyclic ring is administrered in a therapeutically effective amount that reduces levels of markers for kidney damage selected from the group

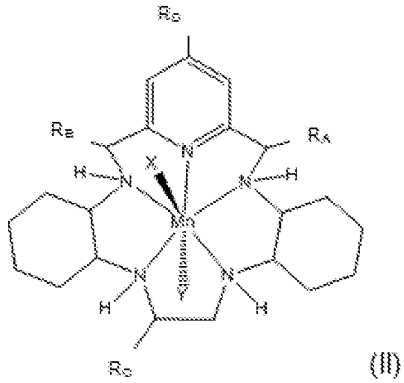
consisting of kidney injury molecule 1 (KIM1) and neutrophil gelatinase-associated lipocalin (NGAL).

[00257] Embodiment 44. The method according to any preceding Embodiment, 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.

[00258] Embodiment 45. The method according to any preceding Embodiment, wherein W is an unsubstituted pyridine moiety.

[00259] Embodiment 46. The method according to any preceding Embodiment, wherein U and V are transcyclohexanyl fused rings.

[00260] Embodiment 47. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is represented by Formula (II):



(II)

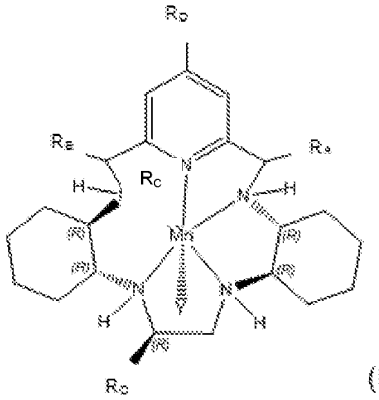
wherein

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

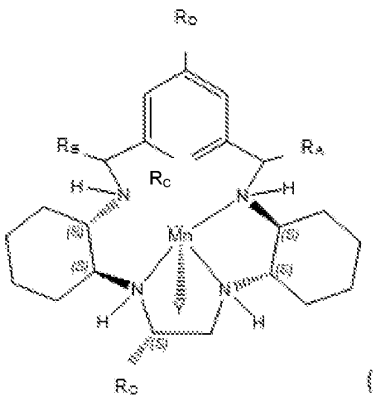
R_A, R_B, R_C, and R_D are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting of $-OR_{11}$, $-NR_{11}R_{12}$, $-COR_{11}$, $-CO_2R_{11}$, $-CONR_{11}R_{12}$, $-SR_{11}$, $-SOR_{11}$, $-SO_2R_{11}$,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

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

[00261] Embodiment 48. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is represented by Formula (III) or Formula (IV):



(III)



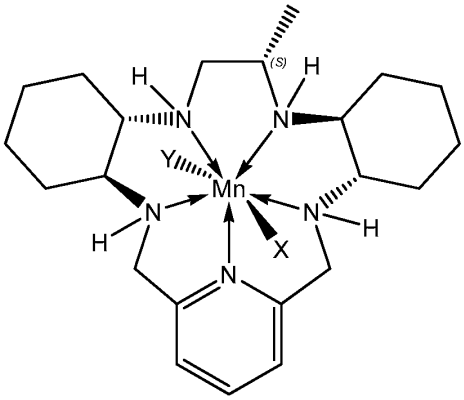
(IV)

wherein

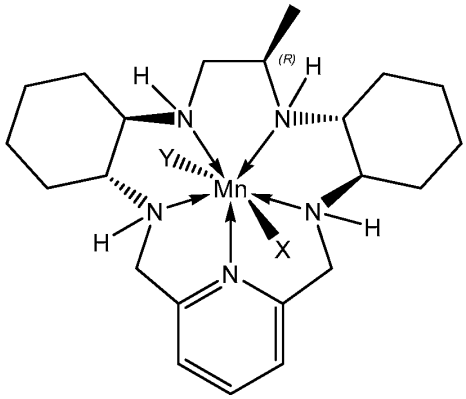
X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and

R_A, R_B, R_C, 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.

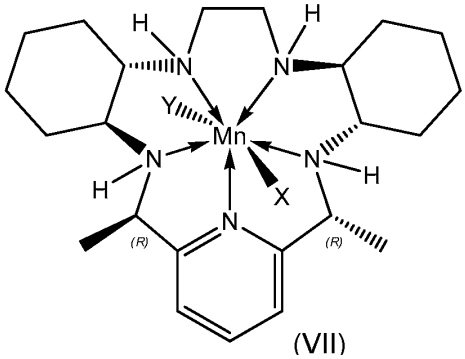
[00262] Embodiment 49. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is a compound represented by a formula selected from the group consisting of Formulae (V)-(XVI):



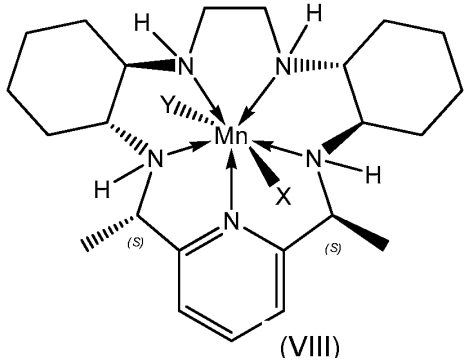
(V) 459)



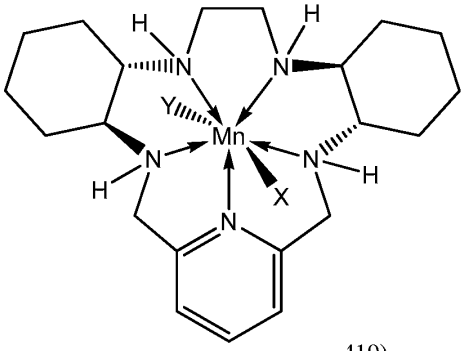
(VI) 444)



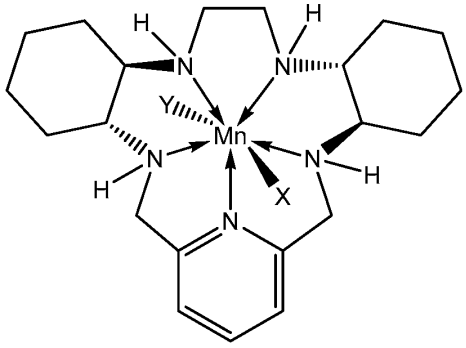
(VII)



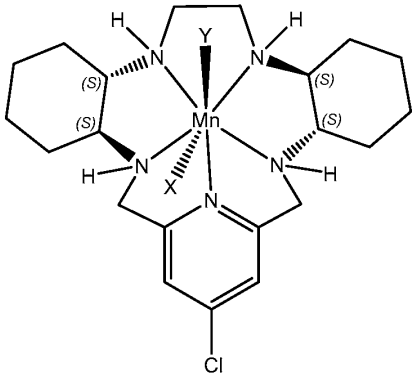
(VIII)



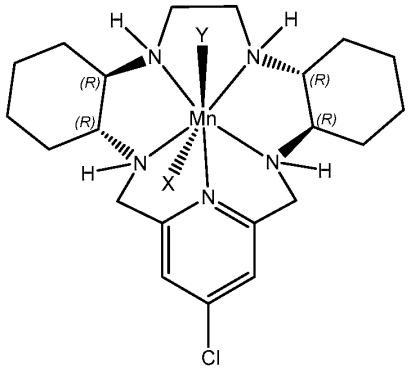
(IX) 419)



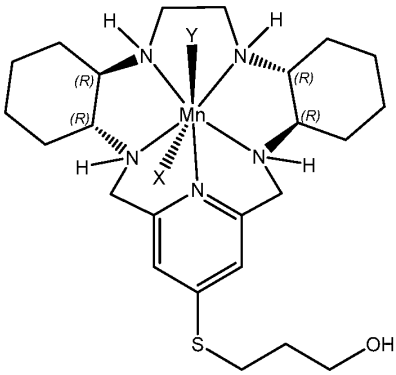
(X) 03)



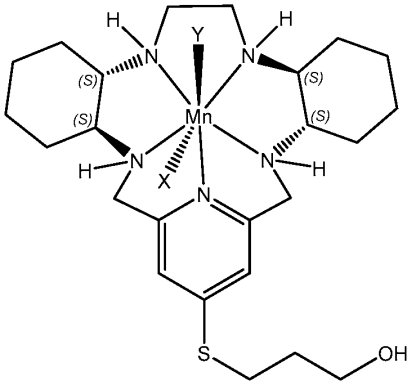
(XI)



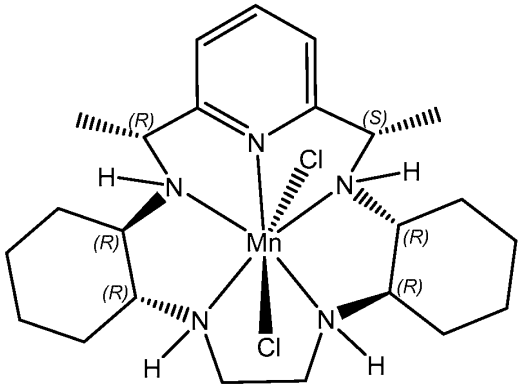
(XII)


H
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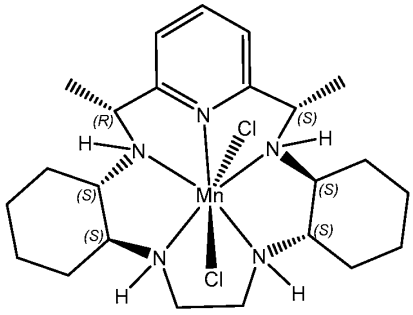
(XIII)


H
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S
OH

(XIV)


(R)
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H
(R)
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(R)
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Cl
H
H

(XV)



(XVI)

[00263] Emodiment 50. The method according to any preceding Embodiment, wherein 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;

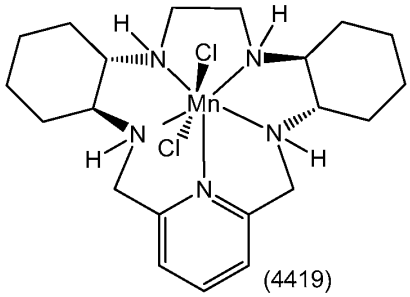
or X and Y are independently attached to one or more of R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9, and R_{10}.

[00264] Embodiment 51. The method according to any preceding Embodiment, wherein X and Y are independently selected from the group consisting of fluoro, chloro, bromo, and iodo anions.

[00265] Embodiment 52. The method according to any preceding Embodiment, wherein X and Y are independently selected from the group consisting of alkyl carboxylates, aryl carboxylates and arylalkyl carboxylates.

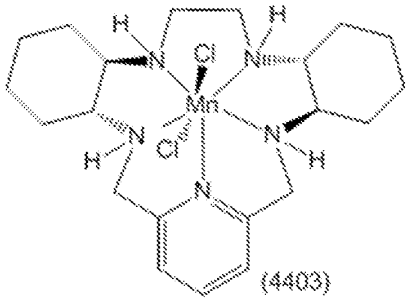
[00266] Embodiment 53. The method according to any preceding Embodiment, wherein X and Y are independently amino acids.

[00267] Embodiment 54. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



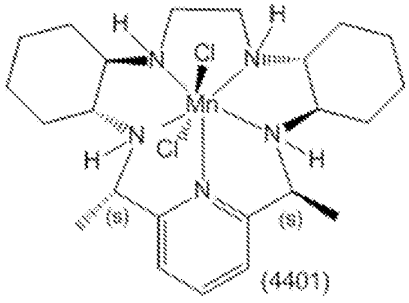
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[00268] Embodiment 55. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



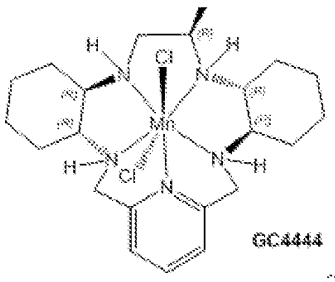
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[00269] Embodiment 56. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:

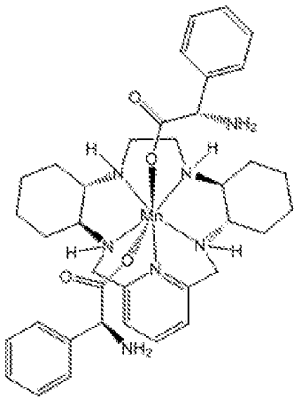


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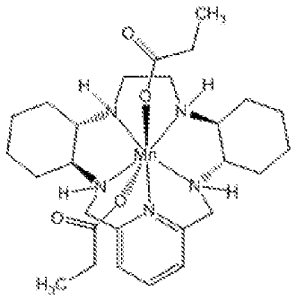
[00270] Embodiment 57. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is represented by the formula:



[00271] Embodiment 58. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is represented by the formula:



[00272] Embodiment 59. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is represented by the formula:



GC4711

[00273] Embodiment 60. The method according to any preceding Embodiment, wherein 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.

[00274] Embodiment 61. The method according to any preceding Embodiment, wherein the platinum-based anti-cancer agent comprises cisplatin.

[00275] Embodiment 62. The method according to any preceding Embodiment, wherein the platinum-based anticancer agent is administered at a dosage in the range of 20 mg/m^2 to 200 mg/m^2.

[00276] Embodiment 63. The method according to any preceding Embodiment, wherein administration of the pentaaza macrocyclic ring complex in a course of therapy is administered a predetermined period of time before administration of the platinum-based anti-cancer agent.

[00277] Embodiment 64. The method according to any preceding Embodiment, wherein administration of the pentaaza macrocyclic ring complex in a course of therapy is administered at least one week, one day or one hour before administration of the platinum-based anti-cancer agent.

[00278] Embodiment 65. The method according to any preceding Embodiment, wherein administration of the pentaaza macrocyclic ring complex in a course of therapy is administered no more than 1 hour before, and/or simultaneously with, administration of the platinum-based anti-cancer agent.

[00279] Embodiment 66. The method according to any preceding Embodiment, wherein administration of the pentaaza macrocyclic ring complex in a course of therapy is administered no more than 1 hour, 1 day or 1 week after administration of the platinum-based anti-cancer agent.

[00280] Embodiment 67. The method according to any preceding Embodiment, comprising administering the platinum based anti-cancer agent to a subject that is concurrently receiving radiation therapy.

[00281] Embodiment 68. The method according to any one of Embodiments 1-66, comprising administering the platinum based anti-cancer agent and pentaaza macrocyclic ring complex to a subject that is not receiving radiation therapy.

[00282] Embodiment 69. The method according to any one of Embodiments 1-66, wherein a course of therapy comprising administration of the pentaaza macrocyclic ring complex and the platinum-based anti-cancer agent, is administered to a subject that does not receive radiation therapy during the course of therapy.

[00283] Embodiment 70. The method according to any one of Embodiments 1-66, comprising administering one or more of the pentaaza macrocyclic ring complex and the platinum-based anti-cancer agent to the subject on a day other than a day that the subject is receiving radiation therapy.

[00284] Embodiment 71. The method according to any one of Embodiments 1-66, 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 day.

[00285] Embodiment 72. The method according to any one of Embodiments 1-66, 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 week.

[00286] Embodiment 73. The method according to any one of Embodiments 1-66, 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.

[00287] Embodiment 74. The method according to any one of Embodiment s 1-66, 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.

[00288] Embodiment 75. The method according to any one of Embodiments 1-66, comprising administering the platinum-based anti-cancer agent and pentaaza macrocyclic ring complex 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.

[00289] Embodiment 76. The method according to any one of Embodiments 1-66, comprising administering the platinum-based anti-cancer agent and pentaaza macrocyclic ring complex 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.

[00290] Embodiment 77. The method according to any one of Embodiments 1-66, comprising administering the platinum-based anti-cancer agent and pentaaza macrocyclic ring complex 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.

[00291] Embodiment 78. The method according to any one of Embodiments 1-66, comprising administering the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex 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.

[00292] Embodiment 79. The method according to any preceding claim, wherein 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.

[00293] Embodiment 80. The method according to any preceding Embodiment, wherein 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.

[00294] Embodiment 81. The method according to any preceding Embodiment, wherein the cancer is at least one of lung cancer and head and neck cancer.

[00295] Embodiment 82. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered to the subject in a dose in a range of from 0.2 mg/kg to 40 mg/kg.

[00296] Embodiment 83. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered to the subject in a dose in a range of from 0.2 mg/kg to 24 mg/kg.

[00297] Embodiment 84. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered to the subject in a dose in a range of from 0.2 mg/kg to 10 mg/kg.

[00298] Embodiment 85. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered via at least one of parenteral route and oral route.

[00299] Embodiment 86. The method according to any preceding Embodiment, wherein the pentaaza macrocyclic ring complex is administered intraperitoneally or intravenously.

[00300] Embodiment 87. The method according to any preceding Embodiment, wherein the subject is a human.

[00301] Embodiment 88. A kit for treating cancer and/or reducing the toxic effects of a platinum-based anti-cancer agent in a mammalian subject in need thereof, the kit comprising:

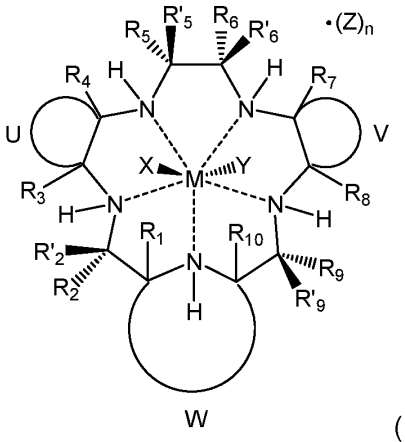
a platinum-based anti-cancer agent;

a pentaaza macrocyclic ring complex corresponding to Formula (I) 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:



(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

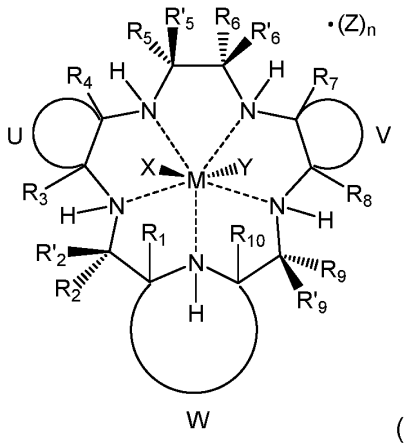
the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.

WHAT IS CLAIMED IS:

1. A method of treating a cancer in a mammalian subject afflicted with the cancer, the method 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, 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)

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.

2. The method of claim 1, comprising administering therapeutically effective amounts of the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex that reduce toxic effects of the platinum anti-cancer agent.

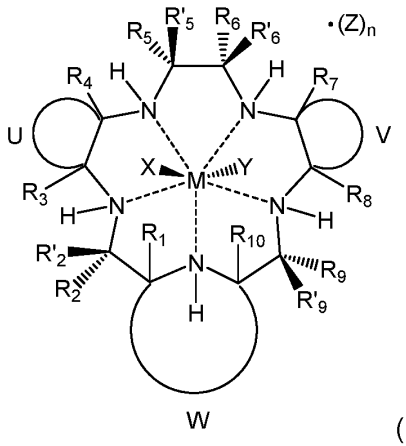
3. The method of claim 1 or 2, wherein the pentaaza macrocyclic ring complex is administered in a therapeutically effective amount that results in an increase in cancer response corresponding to any selected from the group consisting of reduced tumor volume, reduced tumor growth rate, increased survival,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

4. The method of claim 1, 2 or 3, 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).

5. The method of claim 1, 2, 3 or 4, wherein the pentaaza macrocyclic ring is 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 of increasing the sensitivity of a mammalian subject to treatment with a platinum-based anti-cancer agent in a subject in need thereof, the method consisting essentially of:

administering to the subject a therapeutically effective amount of 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 treatment response to the platinum-based anti-cancer agent is increased:



(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.

7. The method of claim 6, wherein the subject is afflicted with cancer.

8. The method of claim 6 or 7, comprising administering therapeutically effective amounts of the platinum-based anti-cancer agent and the pentaaza macrocyclic ring complex that reduce toxic effects of the platinum anti-cancer agent.

9. The method of claim 6, 7 or 8, 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.

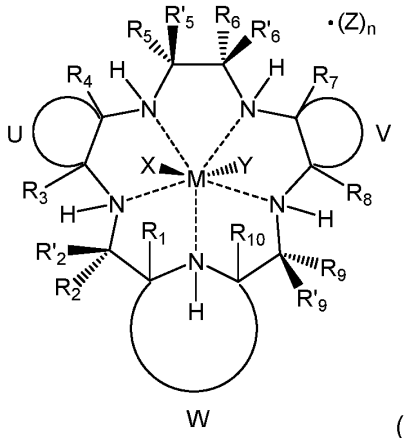
10. The method of claim 6, 7, 8 or 9, wherein the pentaaza macrocyclic ring is administrered in a therapeutically effective amount that reduces levels of at least one of creatine and blood urea nitrogen (BUN).

11. The method of any of claims 6-10, 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).

12. 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 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, 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.

13. The method according to claim 12, wherein the subject is afflicted with cancer.

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.

15. The method according to any one of claims 12-14, 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.

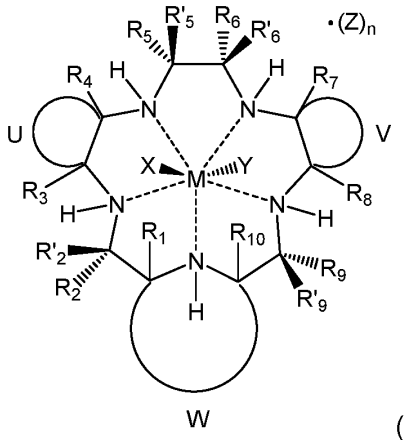
16. The method of any of claims 12-15, wherein the pentaaza macrocyclic ring complex is administered in a therapeutically effective amount that results in an increase in cancer response corresponding to any selected from the group consisting of reduced tumor volume, reduced tumor growth rate, increased 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 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.

24. The method of any one of claims 19-23, 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).

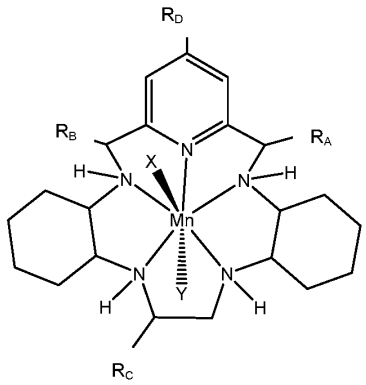
25. The method of any one of claims 19-24, wherein the pentaaza macrocyclic ring is administrered in a therapeutically effective amount that reduces levels of markers for kidney damage selected from the group consisting of kidney injury molecule 1 (KIM1) and neutrophil gelatinase-associated lipocalin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

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, 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):



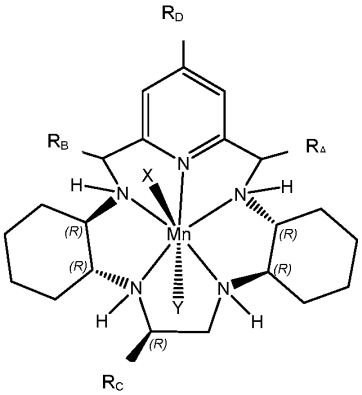
(II)

wherein

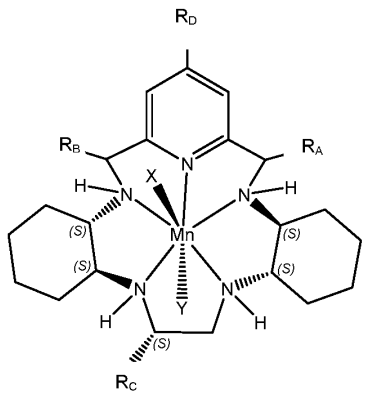
X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and

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. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is represented by Formula (III) or Formula (IV):



(III)



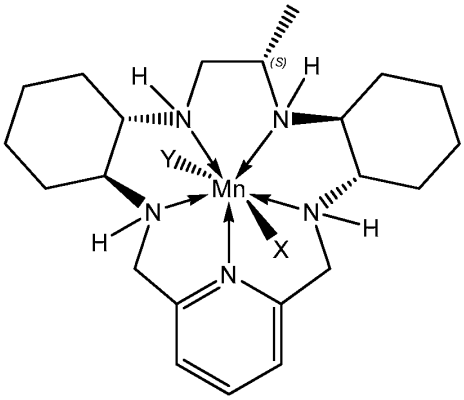
(IV)

wherein

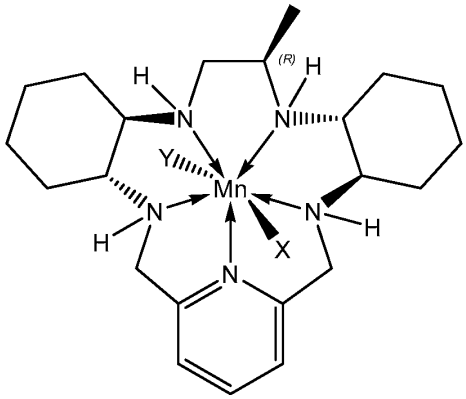
X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and

R_A, R_B, R_C, 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.

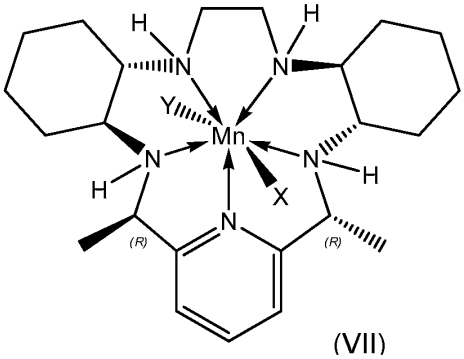
31. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is a compound represented by a formula selected from the group consisting of Formulae (V)-(XVI):



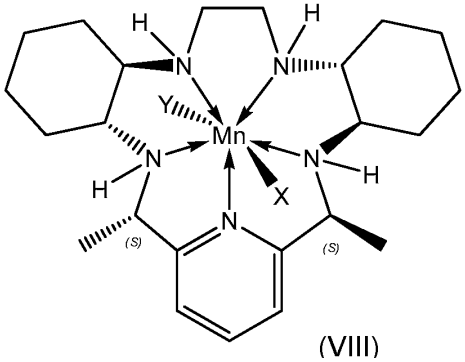
(V)



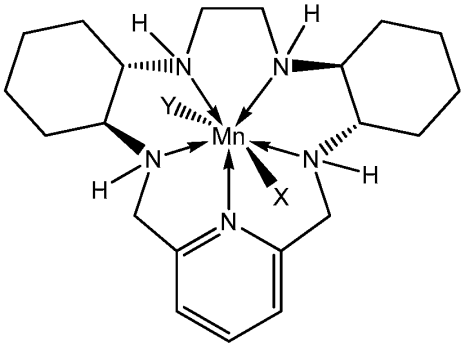
(VI)



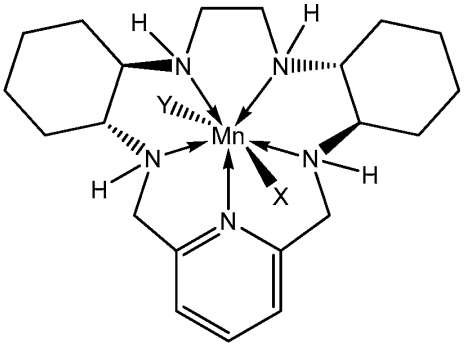
(VII)



(VIII)

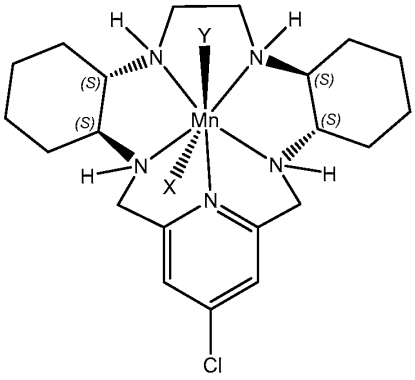


(IX)

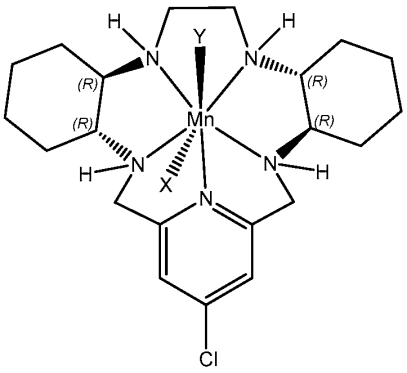


(X)

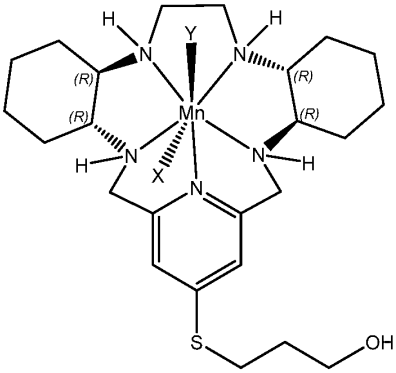
5



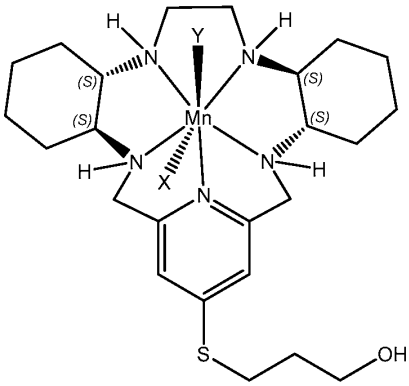
(XI)



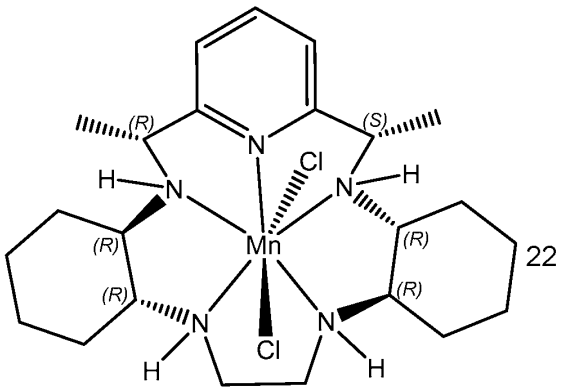
(XII)



(XIII)

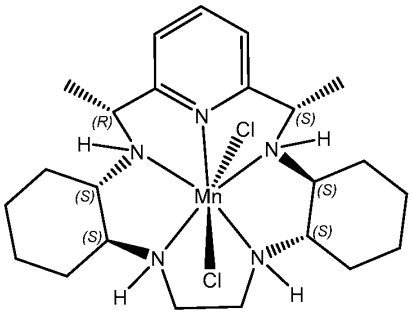


(XIV)



22

(XV)



(XVI)

32. The method according to any preceding claim, wherein 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;

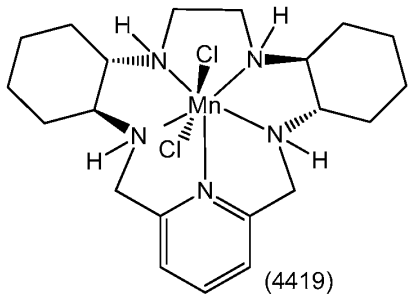
or X and Y are independently attached to one or more of R_1, R_2, R'_2, R_3, R_4, R_5, R'_5, R_6, R'_6, R_7, R_8, R_9, R'_9, and R_{10}.

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

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

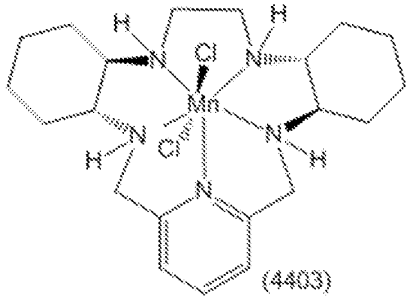
35. The method according to any preceding claim, wherein X and Y are independently amino acids.

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



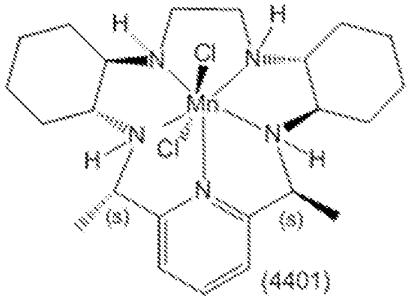
(4419)

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



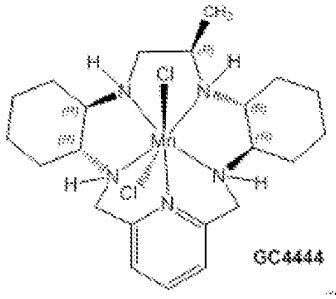
(4403)

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



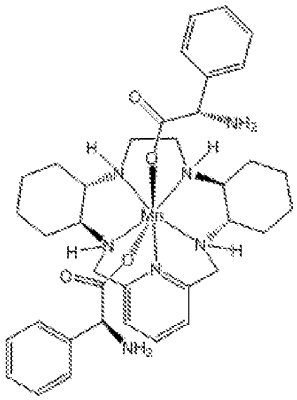
(4401)

39. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is represented by the formula:



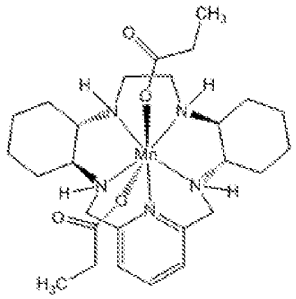
GC4444

40. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is represented by the formula:



GC4702

41. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is represented by the formula:



GC4711

42. The method according to any preceding claim, wherein 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.

43. The method according to any preceding claim, wherein the platinum-based anti-cancer agent comprises cisplatin.

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

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

46. The method according to any preceding claim, wherein administration of the pentaaza macrocyclic ring complex in a course of therapy is administered at least

one week, one day or one hour before administration of the platinum-based anti-cancer agent.

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

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

49. The method according to any preceding claim, comprising administering the platinum based anti-cancer agent to a subject that is concurrently receiving radiation therapy.

50. The method according to any one of claims 1-48, comprising administering the platinum based anti-cancer agent and the pentaaza macrocyclic ring complex to a subject that is not receiving radiation therapy.

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

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

53. 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 a day.

54. 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 a week.

55. 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 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 complex 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.

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

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

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

61. The method according to any preceding claim, wherein 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.

62. The method according to any preceding claim, wherein 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.

63. The method according to any preceding claim, wherein the cancer is at least one of lung cancer and head and neck cancer.

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

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

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

67. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered via at least one of parenteral route and oral route.

68. The method according to any preceding claim, wherein the pentaaza macrocyclic ring complex is administered intraperitoneally or intravenously.

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

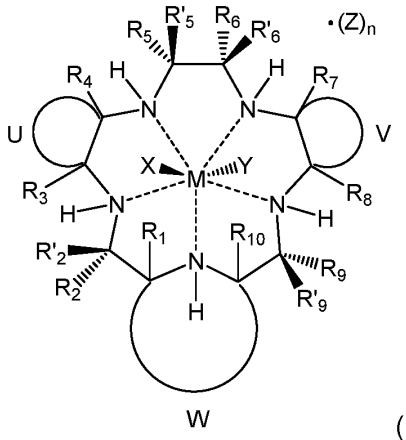
70. A kit for treating cancer and/or reducing the toxic effects of a platinum-based anti-cancer agent in a mammalian subject in need thereof, the kit consisting essentially of:

a platinum-based anti-cancer agent;

a pentaaza macrocyclic ring complex corresponding to Formula (I) 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:



(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.

5