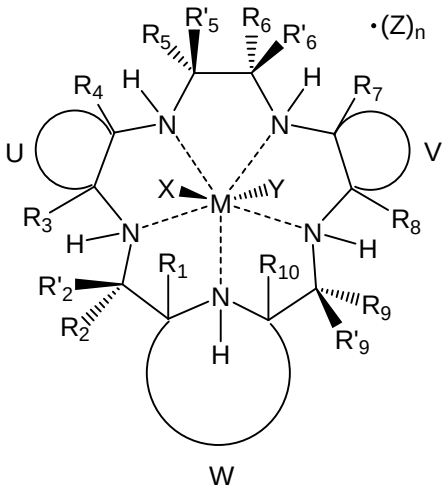
WHAT IS CLAIMED IS:

1. Use of at least one active agent comprising a thioredoxin reductase inhibitor, and a pentaaza macrocyclic ring complex in the manufacture of a medicament for treating a cancer in a mammalian subject afflicted with the cancer,

wherein the pentaaza macrocyclic ring complex corresponds to formula (I) below:



(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

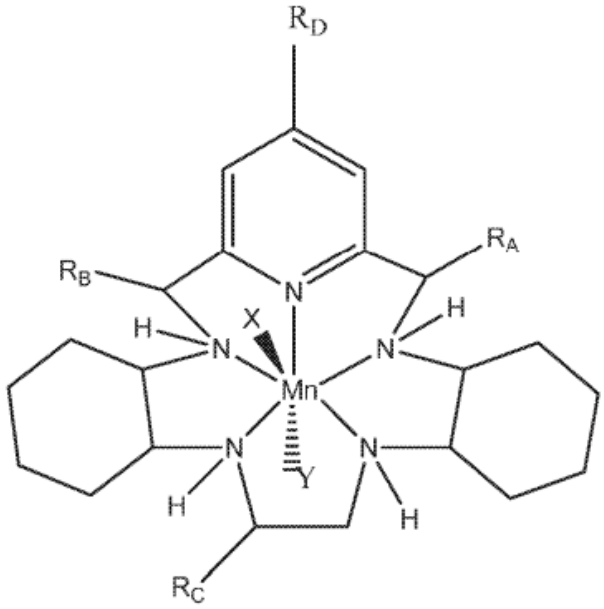
the dashed lines represent coordinating bonds between the nitrogen atoms of the macrocycle and the transition metal, manganese.

2. The use of claim 1, 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.

3. The use according to any preceding claim, wherein W is an unsubstituted pyridine moiety.

4. The use according to any preceding claim, wherein U and V are trans-cyclohexanyl fused rings.

5. The use according to any preceding claim, wherein the pentaaza macrocyclic ring complex is represented by formula (II):



(II)

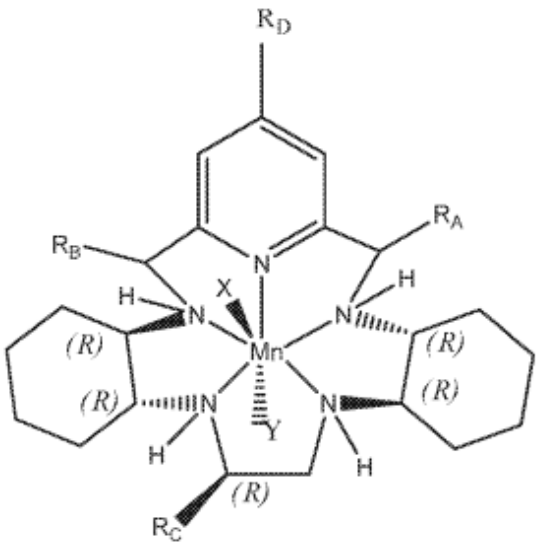
wherein

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

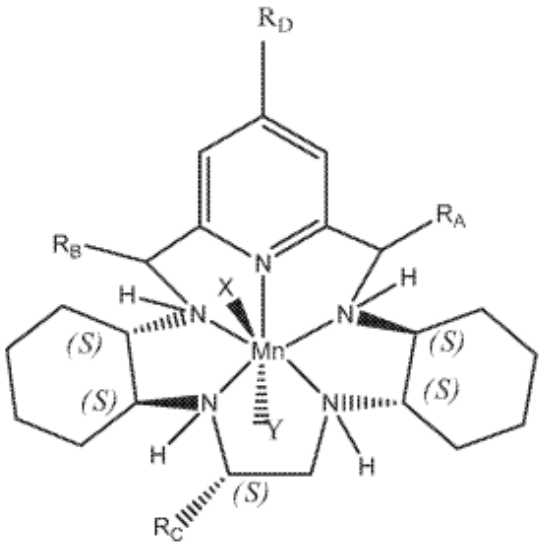
R_A, R_B, R_C, and R_D are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclyl, an amino acid side chain moiety, or a moiety selected from the group consisting

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.

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



(III)



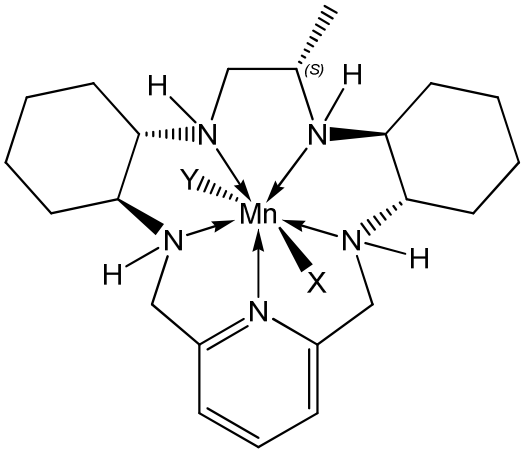
(IV)

wherein

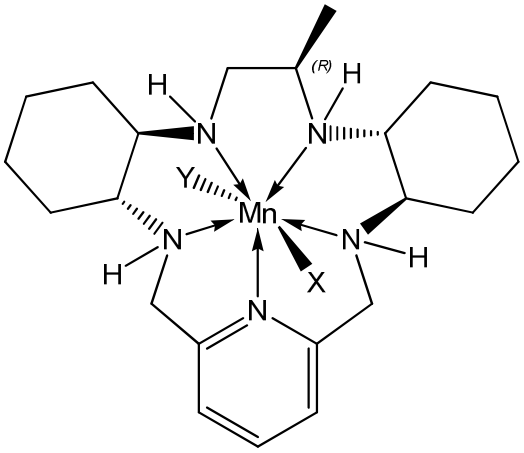
X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and

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.

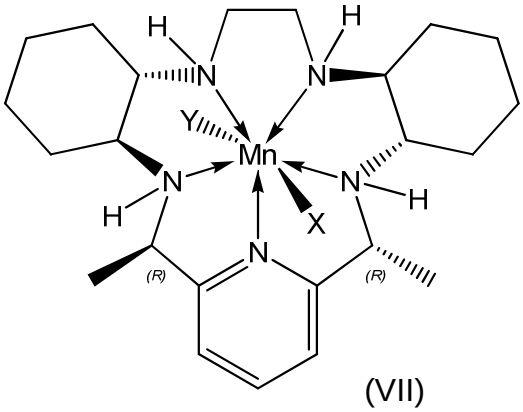
7. The use according to any preceding claim, wherein the pentaaza macrocyclic ring complex is a compound represented by a formula selected from the group consisting of the complexes of formula (V)-(XVI) below:



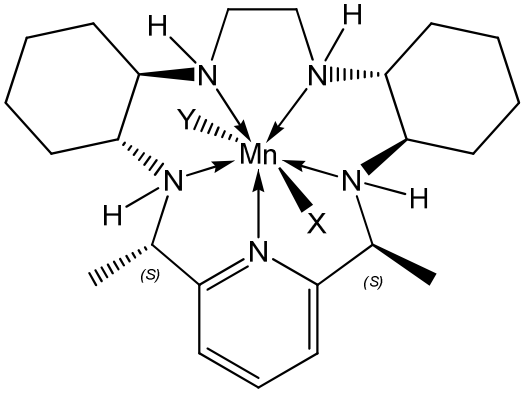
(V)



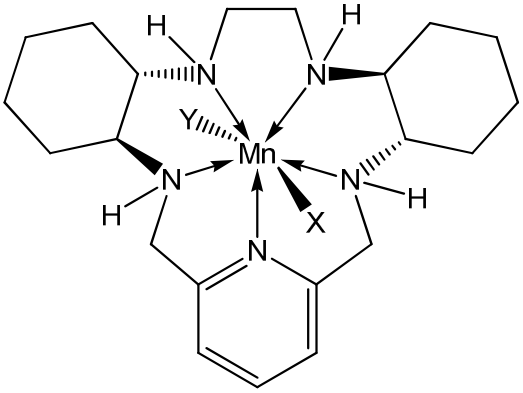
(VI)



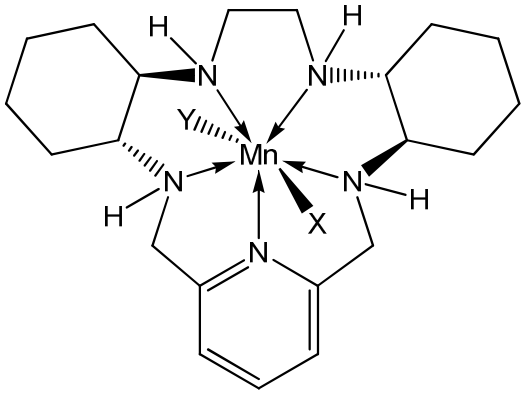
(VII)



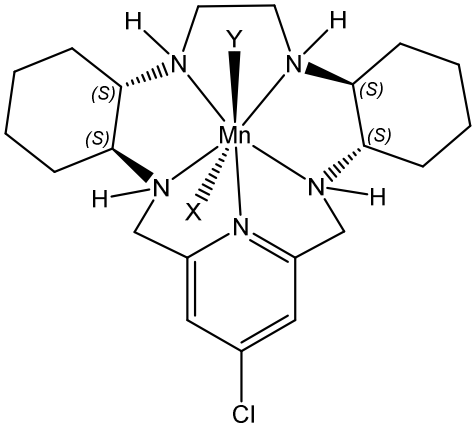
(VIII)



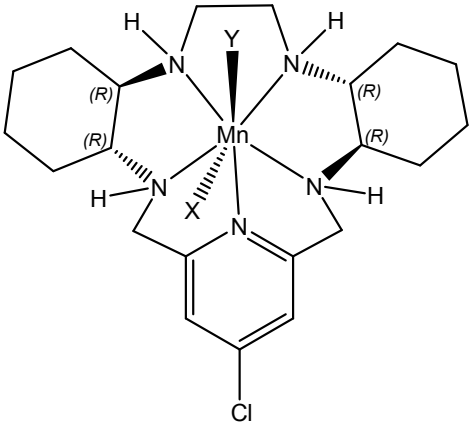
(IX)



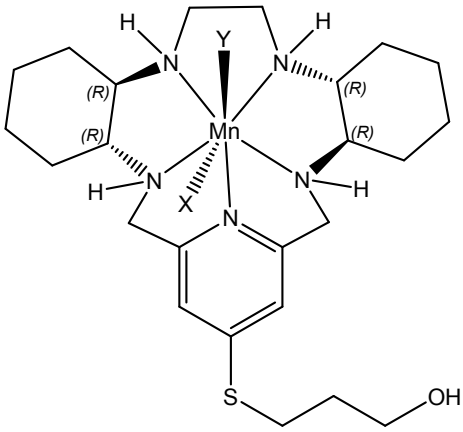
(X)



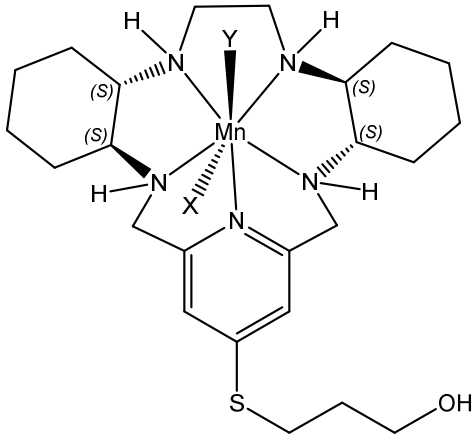
(XI)



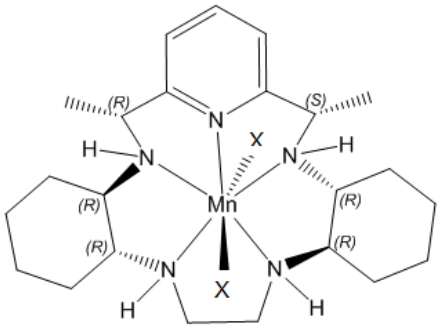
(XII)



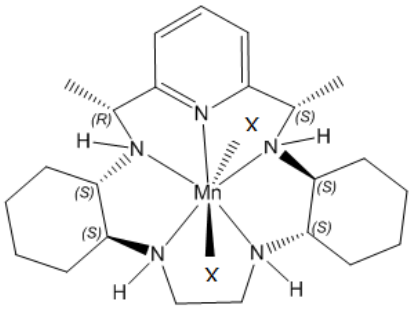
(XIII)



(XIV)



(XV)



(XVI)

8. The use 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}.

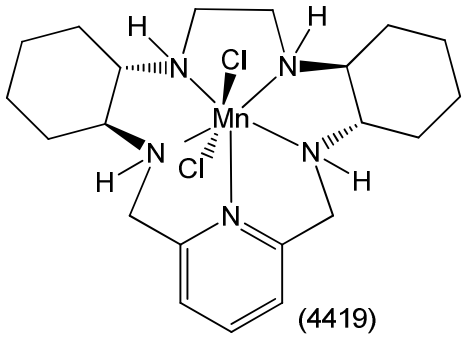
9. The use according to any preceding claim, wherein X and Y are independently selected from the group consisting of fluoro, chloro, bromo, and iodo anions.

10. The use according to any one of claims 1-8, wherein X and Y are independently selected from the group consisting of alkyl carboxylates, aryl

carboxylates and arylalkyl carboxylates.

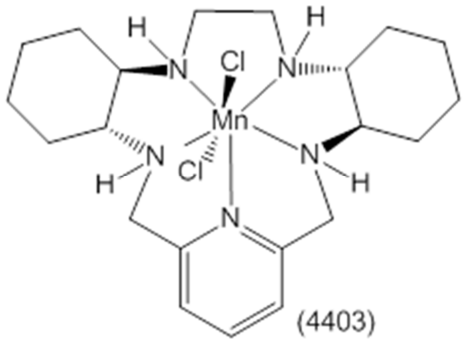
11. The use according to any one of claims 1-8, wherein X and Y are independently amino acids.

12. The use according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



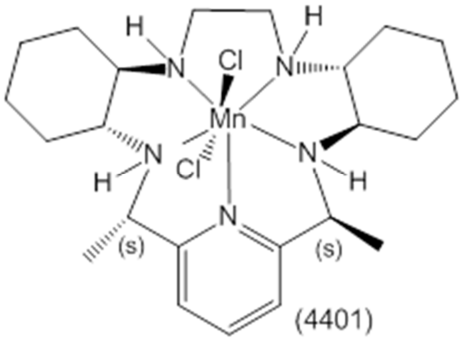
(4419) .

13. The use according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



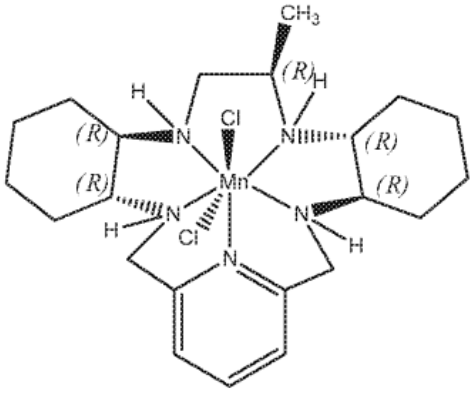
(4403) .

14. The use according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is a compound represented by the formula:



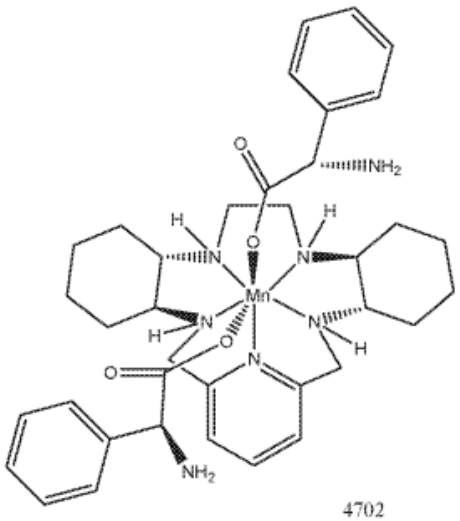
(4401)

15. The use according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is represented by the formula:



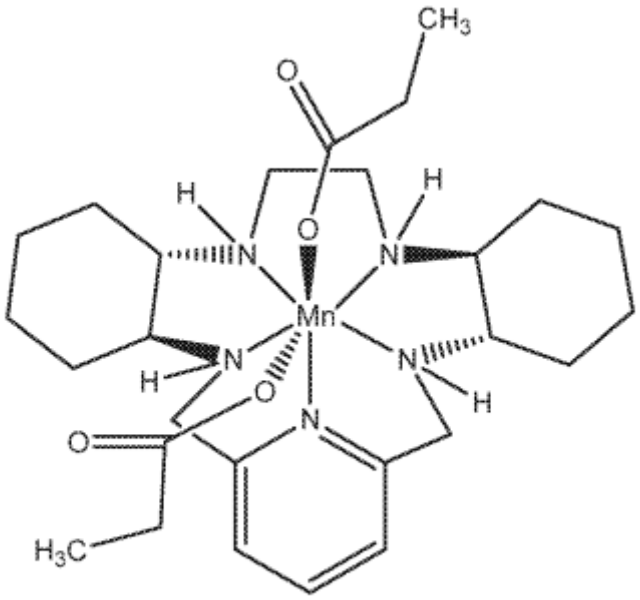
4444

16. The use according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is represented by the formula:



4702

17. The use according to any one of claims 1-8, wherein the pentaaza macrocyclic ring complex is represented by the formula:



4711

18. The use according to any preceding claim, wherein the at least one active agent is one that increases intracellular H_2O_2 levels in cancerous cells, when provided to such cancerous cells *in vitro* in combination with the pentaaza macrocyclic ring complex.

19. The use according to any preceding claim, wherein the combination of the at least one active agent and pentaaza macrocyclic ring complex selectively kills cancer cells over normal cells when administered for the cancer treatment.

20. The use according to any preceding claim, wherein the thioredoxin reductase inhibitor is at least one of auranofin, auro-thio-glucose, chloro(triethylphosphine)gold(I), aurothiomalate, gold sodium thiomalate, sodium aurothiosulfate, gold acetate, 1,2,5-selenadiazole and derivatives thereof, metal complexes with 2-acetylpyridine-N(4)-orthochlorophenylthiosemicarbazone and/or a pharmaceutically acceptable salt thereof.

21. The use of claim 20, wherein the thioredoxin reductase inhibitor is auranofin.

22. The use according to claim 25, wherein the glutathione depleting agent is at least one of a glutathione synthesis inhibitor, an inhibitor of x_c^- cysteine/glutamate antiporter, and a glutathione reductase inhibitor.

23. The use of claim 22, wherein the glutathione-depleting agent is at least one of buthionine sulfoximine (BSO), sulfasalazine, piperlongumine, N-ethylmaleimide, N-pyrenylmaleimide, 2-AAPA, erastin, sorafenib, 1S,3R-RSL3, DPI19, DPI18, DPI17, DPI13, DPI12, DPI10 (ML210), DPI7(ML162), and altretamine, and/or pharmaceutically acceptable salts thereof.

24. The use of claim 23, wherein the glutathione-depleting agent is at least one of buthionine sulfoximine and sulfasalazine.

25. The use according to any preceding claim, comprising administering both a thioredoxin reductase inhibitor and a glutathione depleting agent in combination with the pentaaza macrocyclic ring complex.

26. The use according to any preceding claim, wherein the mammal is a human patient.

27. The use according to any preceding claim, wherein the cancer is selected from the group consisting of cancer 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.

28. The use of claim 27, wherein the subject is afflicted with cancer selected from the group consisting of breast cancer, lung cancer, renal cell carcinoma, spindle cell carcinoma, colorectal cancer, and head and neck cancer.

29. The use of claim 28, wherein the subject is afflicted with cancer selected from the group consisting of breast cancer and lung cancer.

30. The use according to any preceding claim, wherein the active agent is

administered substantially simultaneously with the pentaaza macrocyclic ring complex.

31. The use according to any of claims 1-29, wherein the active agent is administered before the pentaaza macrocyclic ring complex.

32. The use according to any of claims 1-29, wherein the active agent is administered after the pentaaza macrocyclic ring complex.

33. The use according to any preceding claim, wherein the active agent and pentaaza macrocyclic ring complex are administered within 24 hours of each other.

34. The use according to any preceding claim, wherein the active agent and pentaaza macrocyclic ring complex are administered within 1 hour of each other.

35. The use according to any preceding claim, wherein the active agent and pentaaza macrocyclic ring complex are administered by an administration route selected from the group consisting of oral, parenteral, intravenous, intraarterial, subcutaneous, rectal, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intraperitoneal, 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.

36. The use according to any preceding claim, wherein the use further comprises use of at least one of a radiation therapy and a chemotherapeutic therapy in the manufacture of a medicament for a cancer therapy to the subject.

37. The use of claim 36, wherein the active agent and pentaaza macrocyclic ring complex are administered prior to the cancer therapy.

38. The use according to any of claims 36-37, wherein the active agent and pentaaza macrocyclic ring complex are administered within 24 hours of the cancer therapy.

39. The use according to any of claims 36-38, wherein the active agent and pentaaza macrocyclic ring complex are administered within 1 hour of the cancer therapy.

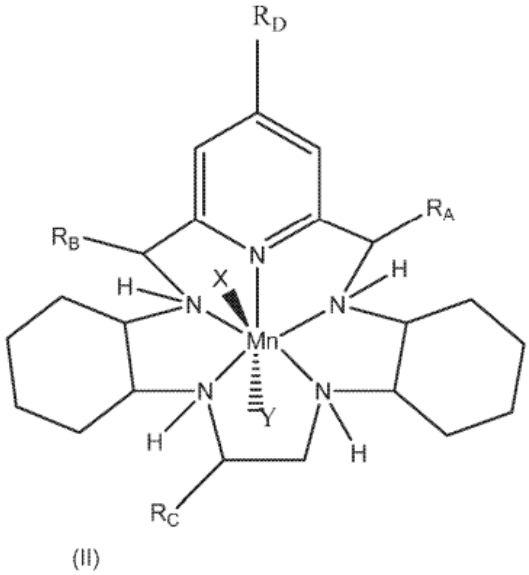
40. The use of claim 36, wherein at least one of the active agent and pentaaza macrocyclic ring complex are administered after the cancer therapy.

41. The use according to any of claims 36-40, wherein the cancer therapy comprises the administration of a series of multiple doses of radiation, and wherein the active agent and pentaaza macrocyclic ring complex are administered before one or more radiation dose in the series.

42. The use according to any of claims 36-40, wherein the chemotherapy dose comprises administration of a chemotherapeutic agent selected from the group consisting of all-trans retinoic acid, 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.

43. The use according to any of claims 1-42, wherein the pentaaza macrocyclic ring complex is a compound which can be represented by the following formulas:

a) formula (II):



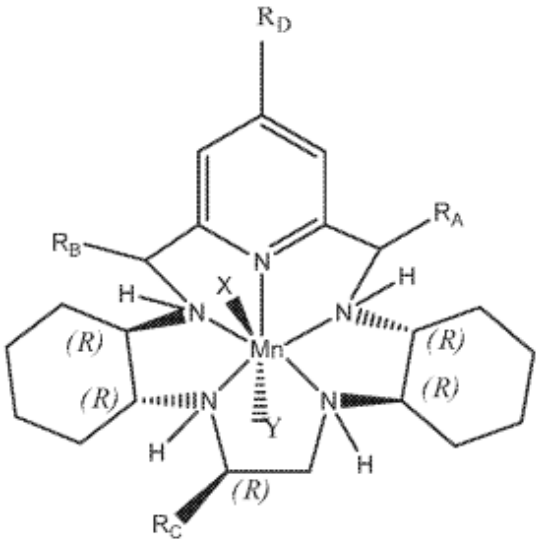
(II)

wherein

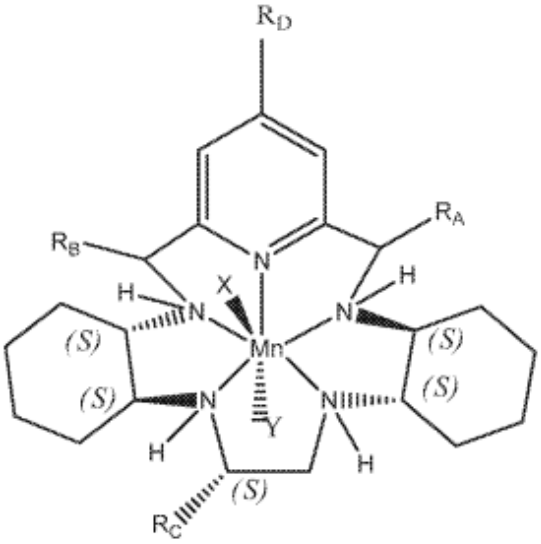
X and Y represent suitable ligands which are derived from any monodentate or polydentate coordinating ligand or ligand system or the corresponding anion thereof; and

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; or

b) 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.