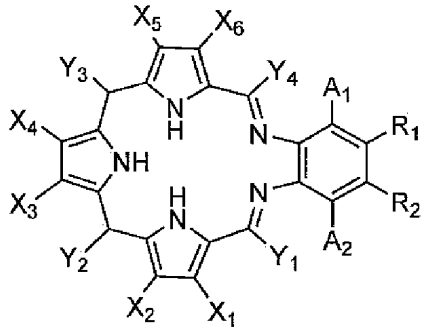
CLAIMS

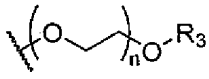
What is claimed is:

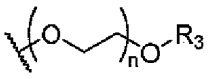
1. A compound of the formula:



(I)

wherein:

R_1 and R_2 are each independently selected from hydrogen, halo, hydroxy, amino, mercapto, $alkoxy_{(C\leq12)}$, substituted $alkoxy_{(C\leq12)}$, or , wherein n is 1-20 and R_3 is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$, or a platinum(IV) chelating group;

A_1 and A_2 are each independently selected from hydrogen, halo, hydroxy, $alkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, substituted $alkoxy_{(C\leq12)}$, or , wherein n is 1-20 and R_3 is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$, or a platinum(IV) chelating group;

Y_1, Y_2, Y_3, and Y_4 are each independently selected from hydrogen, halo, $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, or substituted $aryl_{(C\leq12)}$;

X_1, X_2, X_3, X_4, X_5, and X_6 are each independently selected from hydrogen, hydroxy, halo, amino, carboxy, nitro, or cyano,

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups, or

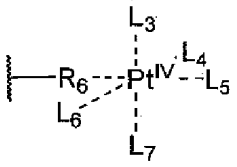
a platinum(IV) chelating group;

provided that at least one of X_1, X_2, X_3, X_4, X_5, and X_6 is a platinum(IV) chelating group;

wherein the platinum(IV) chelating group is further defined as:

$-A_3-X_7-A_4-R_4$, wherein A_3 and A_4 are each independently $alkanediyl_{(C\leq12)}$, $alkenediyl_{(C\leq12)}$, $arenediyl_{(C\leq12)}$,

alkoxydiyl$_{(C\leq12)}$, alkylaminodiyl$_{(C\leq12)}$, or a substituted version of any of these groups, X_7 is $-O-$, $-S-$, $-NR_5-$, $-C(O)NR_5-$, or $-NR_5C(O)-$, wherein R_5 is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$, and R_4 is



wherein:

R_6 is amino, hydroxy, mercapto, carboxy, or dicarboxy;

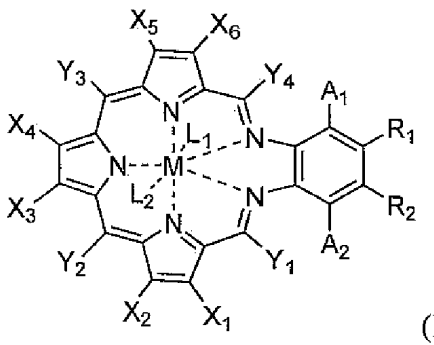
L_3-L_7 are each ligands independently selected from aqua, ammonia, nitrate, sulfate, halide, hydroxide, phosphate, or glucose-6-phosphate,

alkylamine$_{(C\leq12)}$, cycloalkylamine$_{(C\leq12)}$, dialkylamine$_{(C\leq18)}$, dicycloalkylamine$_{(C\leq18)}$, arylamine$_{(C\leq12)}$, diarylamine$_{(C\leq18)}$, diaminoalkane$_{(C\leq12)}$, diaminocycloalkane$_{(C\leq12)}$, diaminoarene$_{(C\leq12)}$, heteroarene$_{(C\leq12)}$, alkylcarboxylate$_{(C\leq12)}$, alkyldicarboxylate$_{(C\leq18)}$, arylcarboxylate$_{(C\leq12)}$, aryldicarboxylate$_{(C\leq18)}$, or a substituted version of any of these groups

provided that R_6 and L_3-L_7 are appropriately charged to obtain a neutral platinum(IV) chelating group;

or an oxidized metal complex, a pharmaceutically acceptable salt, organometallic isomer, or tautomer thereof.

2. The compound of claim 1, wherein the compound is further defined as an oxidized metal complex with the formula:



(II)

wherein: R_1, R_2, A_1, A_2, Y_1, Y_2, Y_3, Y_4, X_1, X_2, X_3, X_4, X_5, and X_6 are as defined above;

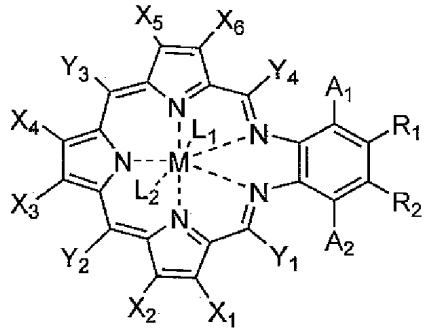
M is a monovalent metal ion, a divalent metal ion, or a trivalent metal ion; and

L_1 and L_2 are each absent or anionic ligands independently selected from fluoride, chloride, bromide, carbonate, hydroxide, perchlorate, nitrate, sulfate, trifluoromethylsulfonate, acetylacetonate, acetate, or trifluoroacetate;

provided that when M is a monovalent metal ion then L_1 and L_2 are absent, and when M is a divalent metal ion, then L_1 or L_2 is absent;

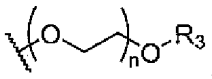
or a pharmaceutically acceptable salt, organometallic isomer, or tautomer thereof.

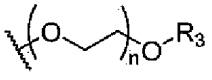
3. The compound of either claim 1 or claim 2, wherein the formula is further defined as:



(II)

wherein:

R_1 and R_2 are each independently selected from hydrogen, halo, hydroxy, amino, mercapto, $alkoxy_{(C\leq12)}$, substituted $alkoxy_{(C\leq12)}$, or , wherein n is 1-20 and R_3 is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

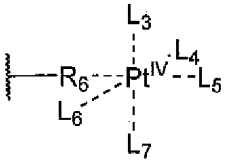
A_1 and A_2 are each independently selected from hydrogen, halo, hydroxy, $alkyl_{(C\leq12)}$, substituted $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, substituted $alkoxy_{(C\leq12)}$, or , wherein n is 1-20 and R_3 is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

Y_1, Y_2, Y_3, and Y_4 are each independently selected from hydrogen, halo, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$;

X_1, X_2, X_3, X_4, X_5, and X_6 are each independently selected from hydrogen, hydroxy, halo, amino, carboxy, nitro, or cyano,

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, or a substituted version of any of these groups, or

a platinum(IV) chelating group of the formula: $-A_3-X_7-A_4-R_4$, wherein A_3 and A_4 are each independently alkanediyl$_{(C\leq12)}$, alkoxydiyl$_{(C\leq12)}$, alkylaminodiyl$_{(C\leq12)}$, or a substituted version of any of these groups, X_7 is $-NR_5-$, $-C(O)NR_5-$, or $-NR_5C(O)-$, wherein R_5 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$, and R_4 is



wherein:

R_6 is amino, hydroxy, mercapto, carboxy, or dicarboxy;

L_3L_7 are each ligands independently selected from aqua, ammonia, halide, or hydroxide,

diaminoalkane$_{(C\leq12)}$, diaminocycloalkane$_{(C\leq12)}$, diaminoarene$_{(C\leq12)}$, alkyldicarboxylate$_{(C\leq18)}$, aryldicarboxylate$_{(C\leq18)}$, or a substituted version of any of these groups;

provided that R_6 and L_3-L_7 are appropriately charged to obtain a neutral platinum(IV) chelating group;

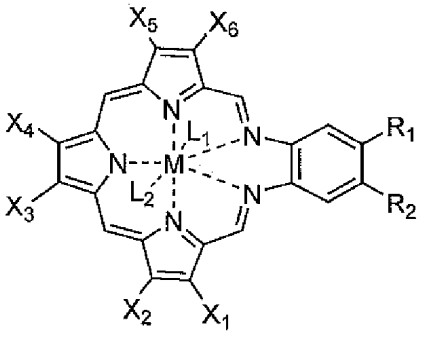
provided that at least one of X_1, X_2, X_3, X_4, X_5, and X_6 is a platinum(IV) chelating group;

M is a trivalent lanthanide metal ion; and

L_1 and L_2 are each anionic ligands independently selected from fluoride, chloride, bromide, perchlorate, nitrate, sulfate, trifluoromethylsulfonate, acetate, or trifluoroacetate;

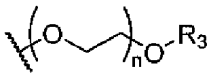
or a pharmaceutically acceptable salt, organometallic isomer, or tautomer thereof.

4. The compound according to any one of claims 1-3, wherein the formula is further defined as:



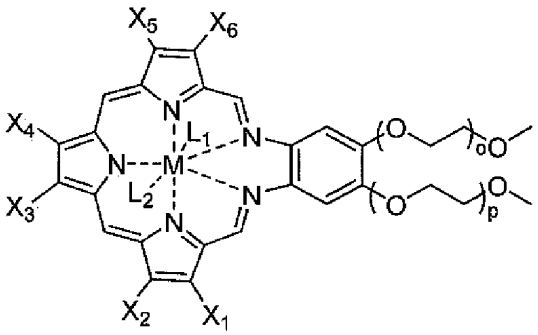
(III)

wherein:

R_1 and R_2 are each independently selected from hydroxy, $alkoxy_{(C\leq12)}$, substituted $alkoxy_{(C\leq12)}$, or  wherein n is 1-20 and R_3 is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

or a pharmaceutically acceptable salt, organometallic isomer, or tautomer thereof.

5. The compound according to any one of claims 1-4, wherein the formula is further defined as:



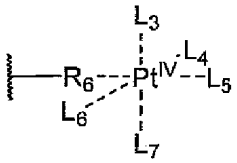
(IV)

wherein:

o and p are each independently 1, 2, 3, 4, 5, or 6;

X_1, X_2, X_3, X_4, X_5, and X_6 are each independently selected from hydrogen, hydroxy, or halo,

$alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$, or

a platinum chelating group of the formula: $-A_3-X_7-A_4-R_4$, wherein A_3 and A_4 are each independently $alkanediyl_{(C\leq12)}$, $alkoxydiyl_{(C\leq12)}$, or a substituted version of any of these groups, X_7 is $-C(O)NR_5-$, or $-NR_5C(O)-$, wherein R_5 is hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$, and R_4 is 

wherein:

R_6 is carboxy or dicarboxy;

L_3, L_4, L_5, and L_6 are each ligands independently selected from aqua, ammonia, halide, or hydroxide,

$diaminoalkane_{(C\leq12)}$, $diaminocycloalkane_{(C\leq12)}$, $alkyldicarboxylate_{(C\leq18)}$, or a substituted version of any of these groups;

provided that R_6 and L_3-L_7 are appropriately charged to obtain a neutral platinum(IV) chelating group;

provided that at least one of X_1, X_2, X_3, X_4, X_5, and X_6 is a platinum(IV) chelating group;

M is a trivalent lanthanide metal ion; and

L_1 and L_2 are each anionic ligands independently selected from nitrate, acetate, or trifluoroacetate;

or a pharmaceutically acceptable salt, organometallic isomer, or tautomer thereof.

6. The compound of claim 5, wherein o is 2, 3, or 4.

7. The compound of claim 6, wherein o is 3.

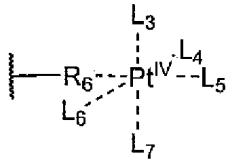
8. The compound according to any one of claims 5-7, wherein p is 2, 3, or 4.

9. The compound of claim 8, wherein p is 3.

10. The compound according to any one of claims 1-9, wherein X_1 is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$.

11. The compound of claim 10, wherein X_1 is methyl.

12. The compound according to any one of claims 1-11, wherein X_2 is a platinum(IV) chelating group of the formula: $-A_3-X_7-A_4-R_4$, wherein A_3 and A_4 are each independently $alkanediyl_{(C\leq12)}$, $alkoxydiyl_{(C\leq12)}$, or a substituted version of any of these groups, X_7 is $-C(O)NR_5-$ or $-NR_5C(O)-$, wherein R_5 is hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$, and R_4 is



wherein:

R_6 is carboxy or dicarboxy;

L_3, L_4, L_5, and L_6 are each ligands independently selected from aqua, ammonia, halide, or hydroxide,

diaminoalkane$_{(C\leq12)}$, diaminocycloalkane$_{(C\leq12)}$, alkyldicarboxylate$_{(C\leq18)}$, or a substituted version of any of these groups.

13. The compound of claim 12, wherein A_3 is alkanediyl$_{(C\leq12)}$ or substituted alkanediyl$_{(C\leq12)}$.

14. The compound of claim 13, wherein A_3 is alkanediyl$_{(C\leq8)}$.

15. The compound of claim 14, wherein A_3 is $-CH_2CH_2CH_2-$.

16. The compound according to any one of claims 1-15, wherein X_7 is $-C(O)NH-$ or $-NHC(O)-$.

17. The compound of claim 16, wherein X_7 is $-NHC(O)-$.

18. The compound according to any one of claims 12-17, wherein A_4 is alkanediyl$_{(C\leq12)}$ or substituted alkanediyl$_{(C\leq12)}$.

19. The compound of claim 18, wherein A_4 is alkanediyl$_{(C\leq8)}$.

20. The compound of claim 19, wherein A_4 is $-CH_2CH_2-$.

21. The compound of claim according to any one of claims 12 to 20, wherein R_6 is carboxy.

22. The compound according to an one of claims 12 to 21, wherein L_3 is halide.

23. The compound of claim 22, wherein L_3 is chloride.

24. The compound according to any one of claims 12-23, wherein L_4 is hydroxide.

25. The compound according to any one of claims 12-24, wherein L_5 is amino.

26. The compound according to any one of claims 12-25, wherein L_6 is halide.

27. The compound of claim 26, wherein L_6 is chloride.

28. The compound according to any one of claims12 to 21, wherein L_3 and L_6 are taken together and are alkyldicarboxylate$_{(C\leq18)}$.

29. The compound of claim 28, wherein L_3 and L_6 are $^-O_2CCO_2^-$.

30. The compound according to any one of claims 12-29, wherein L_7 is amino.

31. The compound according to any one of claims 12-24 and 26-29, wherein L_5 and L_7 are taken together and are diaminocycloalkane$_{(C\leq12)}$.

32. The compound of claim 31, wherein L_5 and L_7 are each the amino group of 1,2-diaminocyclohexane.

33. The compound according to any one of claims 1-32, wherein X_3 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$.

34. The compound of claim 33, wherein X_3 is alkyl$_{(C\leq8)}$.

35. The compound of claim 34, wherein X_3 is ethyl.

36. The compound according to any one of claims 1-35, wherein X_4 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$.

37. The compound of claim 36, wherein X_4 is alkyl$_{(C\leq8)}$.

38. The compound of claim 37, wherein X_4 is ethyl.

39. The compound according to any one of claims 1-38, wherein X_5 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$.

40. The compound of claim 39, wherein X_5 is substituted alkyl$_{(C\leq8)}$.

41. The compound of claim 40, wherein X_5 is $-CH_2CH_2CH_2OH$.

42. The compound according to any one of claims 1-38, wherein X_5 is a platinum(IV) chelating group.

43. The compound according to any one of claims 1-42, wherein X_6 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$.

44. The compound of claim 43, wherein X_6 is alkyl$_{(C\leq8)}$.

45. The compound of claim 44, wherein X_6 is methyl.

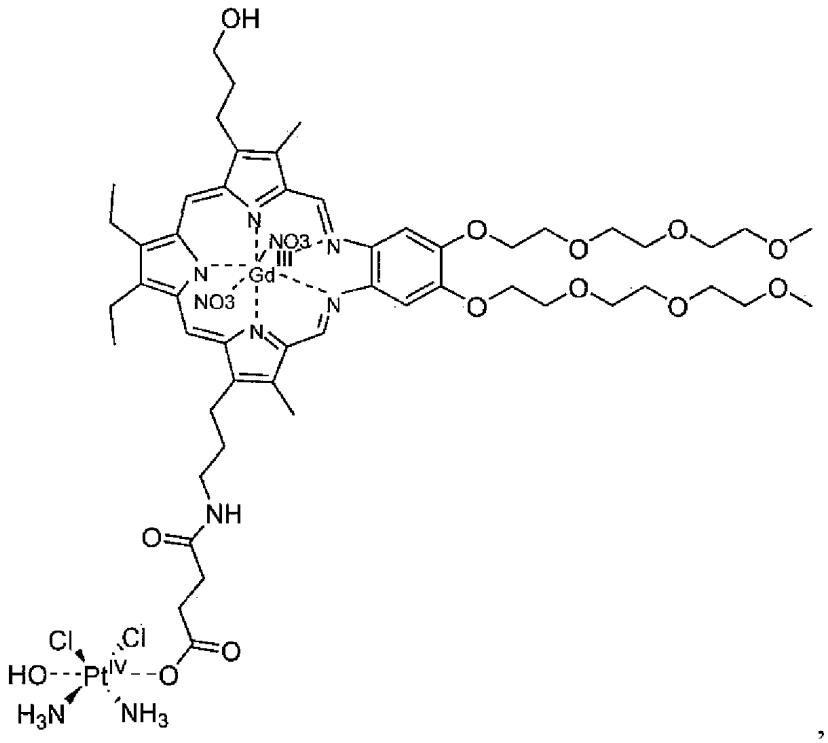
46. The compound according to any one of claims 1-45, wherein M is gadolinium.

47. The compound of claim 46, wherein M is Gd(III).

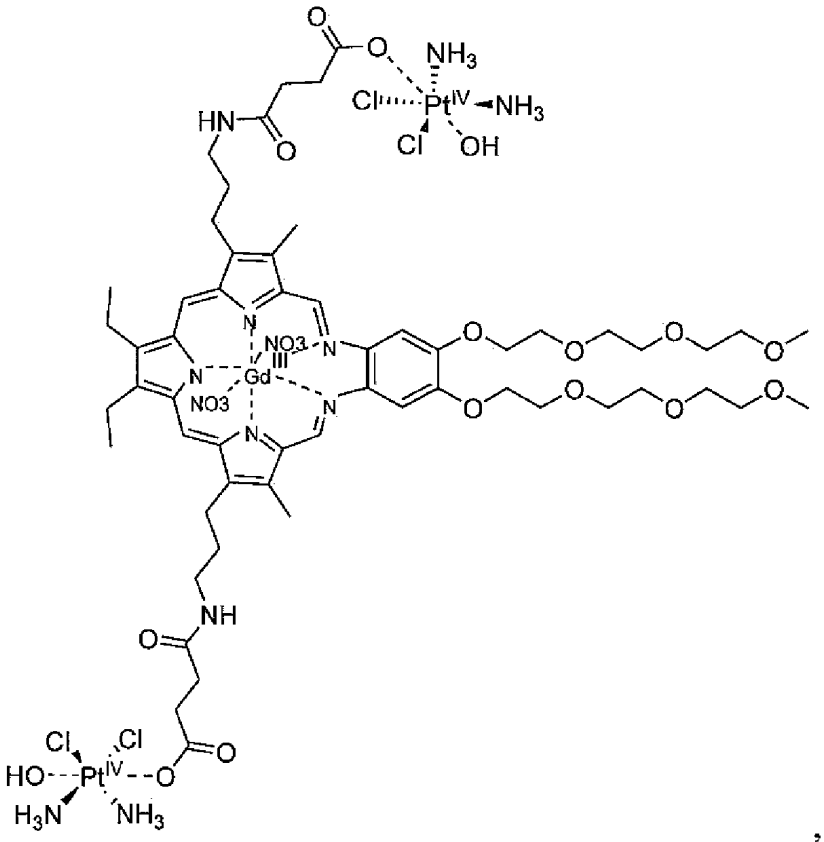
48. The compound according to any one of claims 1-47, wherein L_1 is acetate or nitrate.

49. The compound according to any one of claims 1-48, wherein L_2 is acetate or nitrate.

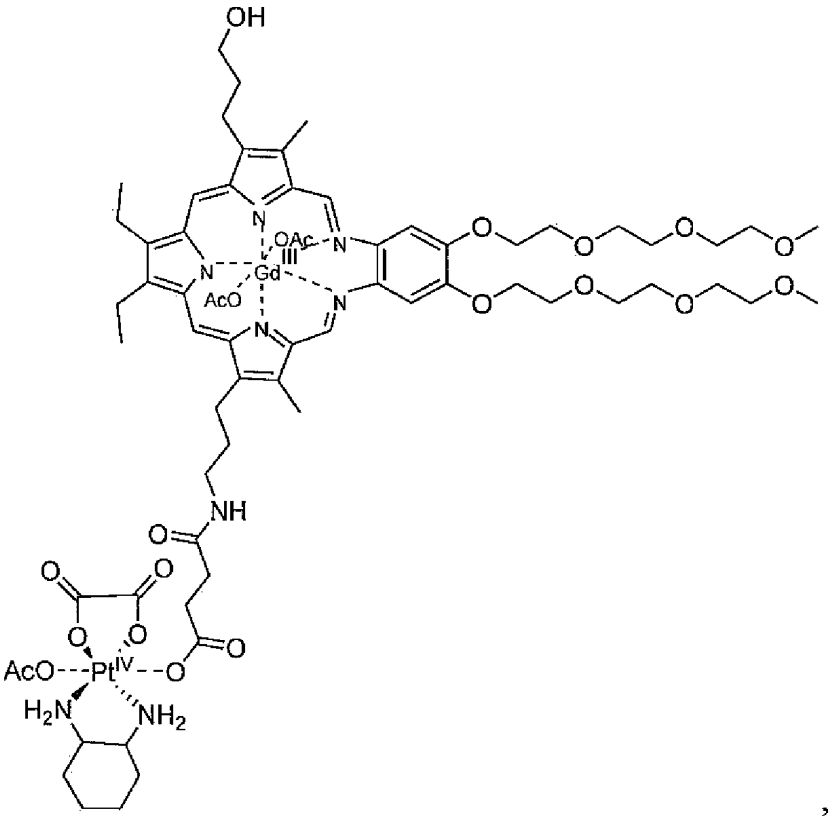
50. The compound of claim 1 further defined as:



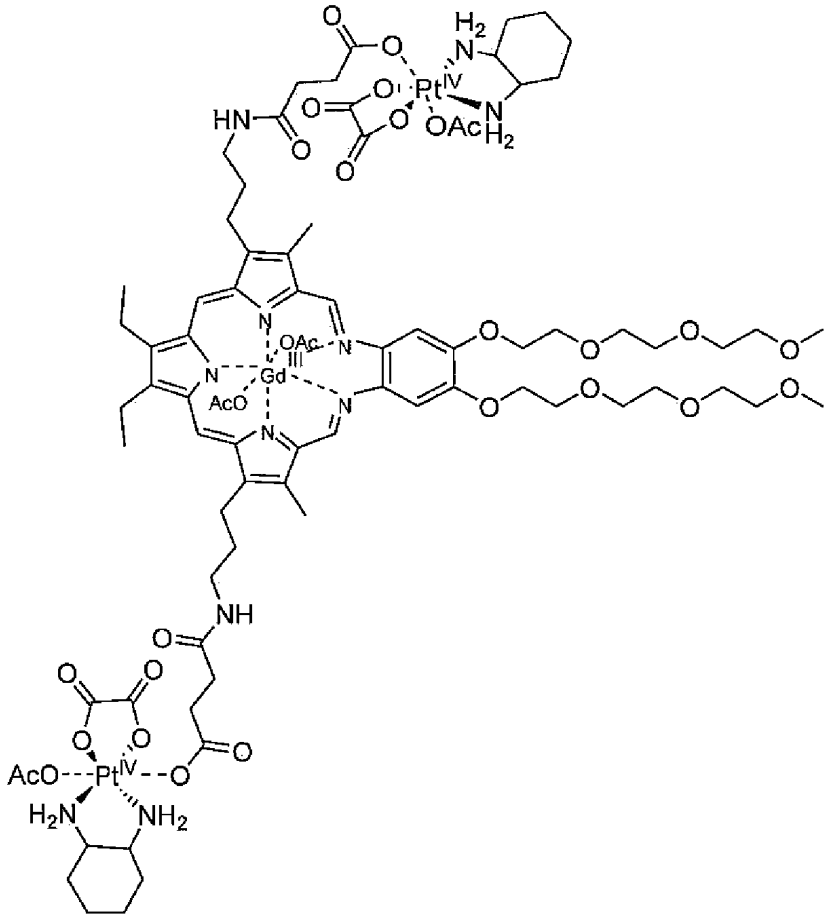
,



,



, or



or a pharmaceutically acceptable salt, organometallic isomer, or tautomer thereof.

51. A pharmaceutical composition comprising:

(A) a pharmaceutically acceptable carrier; and

(B) a compound according to any one of claims 1-50.

52. The pharmaceutical composition according to claim 51, wherein the pharmaceutical composition is formulated to be administered: orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularlly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctivally, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion.

53. The pharmaceutical composition of claim 52, wherein the pharmaceutical composition is formulated to be administered orally or intravenously.

54. The pharmaceutical composition according to any one of claims 51-53, wherein the composition is formulated as a unit dose.

55. Use of a compound or pharmaceutical composition according to claims 1 to 54 in the manufacture of a medicament for treating cancer in a patient.

56. The use of claim 55, wherein the cancer is a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma.

57. The use of claim 55, wherein the cancer is of the bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder, genitalia, genitourinary tract, head, kidney, larynx, liver, lung, muscle tissue, neck, oral or nasal mucosa, ovary, pancreas, prostate, skin, spleen, small intestine, large intestine, stomach, testicle, or thyroid.

58. The use of claim 57, wherein the cancer is ovarian cancer, testicular cancer, or bladder cancer.

59. The use of claim 58, wherein the ovarian cancer is ovarian carcinoma.

60. The use of claim 57, wherein the cancer is colon cancer or colorectal cancer.

61. The use according to any one of claims 55-60, wherein the cancer is resistant to a metal chemotherapeutic.

62. The use of claim 61, wherein the cancer is resistant to a platinum chemotherapeutic.

63. The use of claim 62, wherein the cancer is resistant to cisplatin, carboplatin, or oxaliplatin.

64. The use according to any one of claims 55-63, wherein the use comprises a compound or composition according to any one of claims 1-54to be administered.

65. The use of claim 64, wherein the platinum(IV) chelating group is reduced *in vivo* to form an active complex.

66. The use of either claim 64 or claim 65, wherein the compound localizes to a tumor before the reduction of the platinum(IV) chelating group.

67. The use according to any one of claims 55-66, wherein the texaphyrin is to be administered once.

68. The use according to any one of claims 55-66, wherein the texaphyrin is to be administered two or more times.

69. The use according to any one of claims 55-68, wherein the use further comprises a reducing agent to be administered.

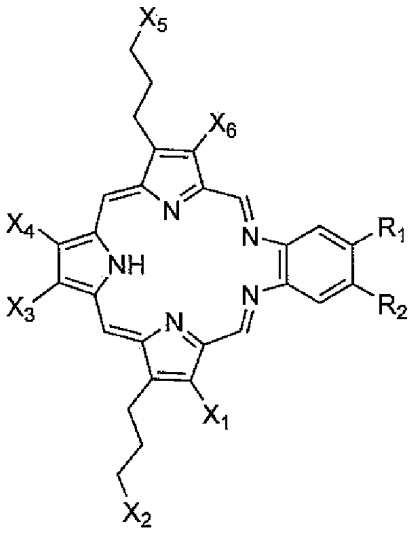
70. The use according to any one of claims 55-68, wherein the use is to be administered in conjunction with a second therapy.

71. The use of claim 70, wherein the second therapy is a second chemotherapeutic drug, surgery, radiotherapy, photodynamic therapy, sonodynamic therapy, cryotherapy, or immunotherapy.

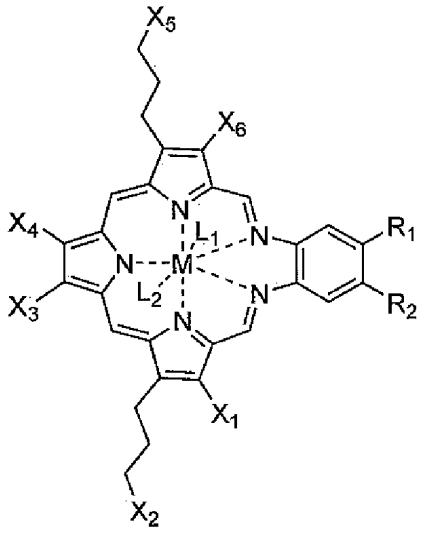
72. The use of claim 70, wherein the second chemotherapeutic drug is bleomycin, doxorubicin, taxol, taxotere, etoposide, 4-OH cyclophosphamide, or 5-fluorouracil.

73. The use of claim 70, wherein the second chemotherapeutic drug is cisplatin, carboplatin, oxaliplatin, or a Pt(IV) complex.

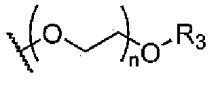
74. A method of preparing a platinum-texaphyrin complex of the formula:



(VII) or

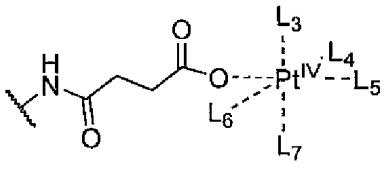


(VIII)

R_1 and R_2 are each independently selected from hydrogen, halo, hydroxy, amino, mercapto, $alkoxy_{(C\leq12)}$, substituted $alkoxy_{(C\leq12)}$, or  wherein n is 1-8 and R_3 is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

X_1, X_3, X_4, and X_6 are each independently selected from hydrogen, hydroxy, halo, amino, carboxy, nitro, or cyano,

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups,

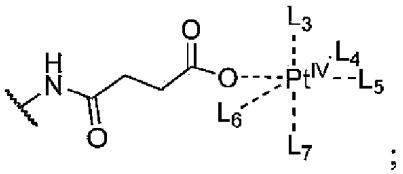
X_2 is  ;

wherein:

L_3, L_4, L_5, L_6, and L_7 are each ligands independently selected from aqua, ammonia, nitrate, sulfate, halide, hydroxide, phosphate, or glucose-6-phosphate,

$alkylamine_{(C\leq12)}$, $cycloalkylamine_{(C\leq12)}$, $dialkylamine_{(C\leq18)}$, $dicycloalkylamine_{(C\leq18)}$, $arylamine_{(C\leq12)}$, $diarylamine_{(C\leq18)}$, $diaminoalkane_{(C\leq12)}$, $diaminocycloalkane_{(C\leq12)}$, $diaminoarene_{(C\leq12)}$, $heteroarene_{(C\leq12)}$, $alkylcarboxylate_{(C\leq12)}$, $alkyldicarboxylate_{(C\leq18)}$, $arylcarboxylate_{(C\leq12)}$, $aryldicarboxylate_{(C\leq18)}$, or a substituted version of any of these groups;

X_5 are each independently selected from amino, hydroxy, $alkoxy_{(C\leq12)}$, substituted $alkoxy_{(C\leq12)}$, $aralkoxy_{(C\leq24)}$, or substituted $aralkoxy_{(C\leq24)}$, or

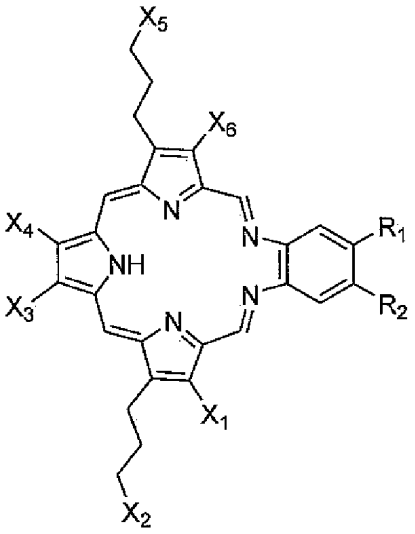
 ;

M is a metal ion; and

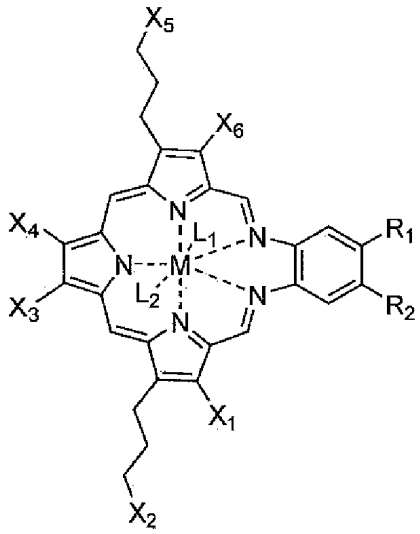
L_1 and L_2 are each anionic ligands independently selected from fluoride, chloride, bromide, carbonate, hydroxide, perchlorate, nitrate, sulfate, trifluoromethylsulfonate, acetylacetonate, acetate, or trifluoroacetate;

provided that L_1 and L_2 are present or absent as necessary to balance the charge on M;

comprising reacting a compound of the formula



(IX) or



(X)

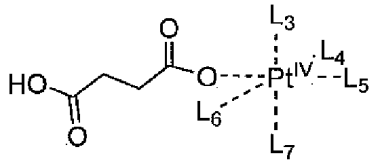
wherein:

X_2 is amino;

X_5 is amino, hydroxy, alkoxy$_{(C\leq12)}$, substituted alkoxy$_{(C\leq12)}$, aralkoxy$_{(C\leq24)}$, or substituted aralkoxy$_{(C\leq24)}$; and

R_1, R_2, X_1, X_3, X_4, and X_6 are as defined above;

with a compound of the formula:



(VIII)

in a solvent and in the presence of an activating agent.

75. The method of claim 74, wherein the solvent is an aqueous organic mixture.

76. The method of claim 75, wherein the solvent is a water and acetonitrile mixture.

77. The method according to any one of claims 74-76, wherein the activating agent is N-hydroxysuccinimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), PyBOP, BOP, HOBT, or N,N'-carbonyldiimidazole (CDI).

78. The method of claim 77, wherein the activating agent is a N-hydroxysuccinimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.