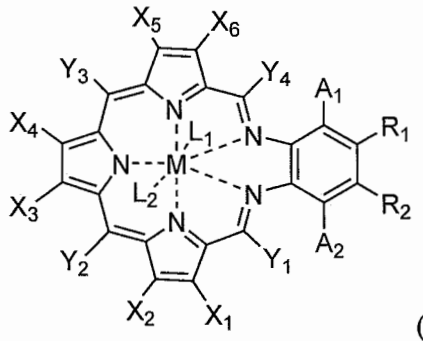
CLAIMS

What is claimed is:

1. A compound of 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;

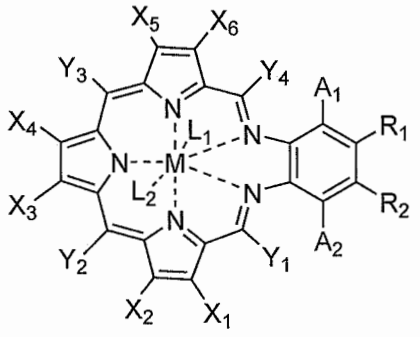
M is a monovalent metal ion, a divalent metal ion, or a trivalent metal ion; and

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.

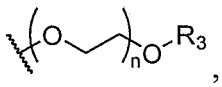
2. The compound of claim 1, wherein the formula is further defined as:

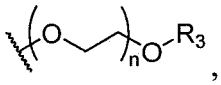


(II)

wherein:

R_1 and R_2 are each independently selected from hydrogen, halo, hydroxy, amino, mercapto, $alkoxy_{(C\leq12)}$, substituted $alkoxy_{(C\leq12)}$, or

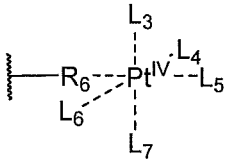
, wherein n is 1-20 and R_3 is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$;

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;

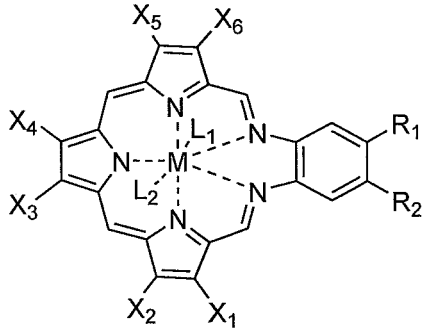
provided that at least one of X_1, X_2, X_3, X_4, X_5, and X_6 is a platinum(IV) chelating group;

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;

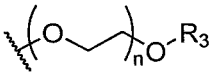
or a pharmaceutically acceptable salt, organometallic isomer, or tautomer thereof.

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



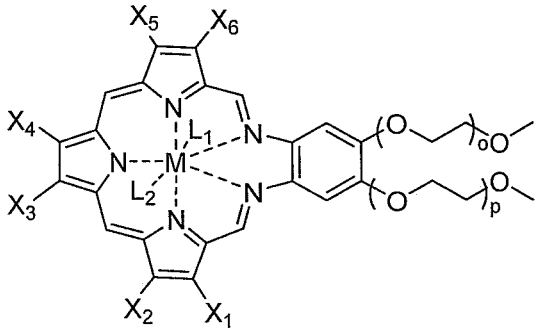
(III)

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.

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



(IV)

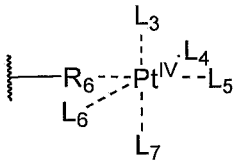
wherein:

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.

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

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

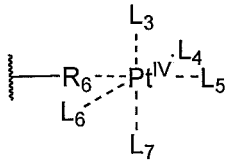
7. The compound according to any one of claims 4-6, wherein p is 2, 3, or 4.

8. The compound of claim 7, wherein p is 3.

9. The compound according to any one of claims 1-8, wherein X_1 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$.

10. The compound of claim 9, wherein X_1 is methyl.

11. The compound according to any one of claims 1-10, 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.

12. The compound of claim 11, wherein A_3 is alkanediyl$_{(C\leq12)}$ or substituted alkanediyl$_{(C\leq12)}$.

13. The compound of claim 12, wherein A_3 is alkanediyl$_{(C\leq8)}$.

14. The compound of claim 13, wherein A_3 is $-CH_2CH_2CH_2-$.

15. The compound according to any one of claims 1-14, wherein X_7 is $-C(O)NH-$ or $-NHC(O)-$.

16. The compound of claim 15, wherein X_7 is $-NHC(O)-$.

17. The compound according to any one of claims 11-16, wherein A_4 is alkanediyl$_{(C\leq12)}$ or substituted alkanediyl$_{(C\leq12)}$.

18. The compound of claim 17, wherein A_4 is alkanediyl$_{(C\leq8)}$.

19. The compound of claim 18, wherein A_4 is $-CH_2CH_2-$.

20. The compound according to any one of claims 11 to 19, wherein R_6 is carboxy.

21. The compound according to any one of claims 11 to 20, wherein L_3 is halide.

22. The compound of claim 21, wherein L_3 is chloride.

23. The compound according to any one of claims 11-22, wherein L_4 is hydroxide.

24. The compound according to any one of claims 11-23, wherein L_5 is amino.

25. The compound according to any one of claims 11-24, wherein L_6 is halide.

26. The compound of claim 25, wherein L_6 is chloride.

27. The compound according to any one of claims 11 to 20, wherein L_3 and L_6 are taken together and are alkyldicarboxylate$_{(C\leq 18)}$.

28. The compound of claim 27, wherein L_3 and L_6 are $^{-}O_2CCO_2^{-}$.

29. The compound according to any one of claims 11-28, wherein L_7 is amino.

30. The compound according to any one of claims 11-23 and 25-28, wherein L_5 and L_7 are taken together and are diaminocycloalkane$_{(C\leq 12)}$.

31. The compound of claim 30, wherein L_5 and L_7 are each the amino group of 1,2-diaminocyclohexane.

32. The compound according to any one of claims 1-31, wherein X_3 is alkyl$_{(C\leq 12)}$ or substituted alkyl$_{(C\leq 12)}$.

33. The compound of claim 32, wherein X_3 is alkyl$_{(C\leq 8)}$.

34. The compound of claim 33, wherein X_3 is ethyl.

35. The compound according to any one of claims 1-34, wherein X_4 is alkyl$_{(C\leq 12)}$ or substituted alkyl$_{(C\leq 12)}$.

36. The compound of claim 35, wherein X_4 is alkyl$_{(C\leq 8)}$.

37. The compound of claim 36, wherein X_4 is ethyl.

38. The compound according to any one of claims 1-37, wherein X_5 is alkyl$_{(C\leq 12)}$ or substituted alkyl$_{(C\leq 12)}$.

39. The compound of claim 38, wherein X_5 is substituted alkyl$_{(C\leq 8)}$.

40. The compound of claim 39, wherein X_5 is $-CH_2CH_2CH_2OH$.

41. The compound according to any one of claims 1-37, wherein X_5 is a platinum(IV) chelating group.

42. The compound according to any one of claims 1-41, wherein X_6 is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$.

43. The compound of claim 42, wherein X_6 is $alkyl_{(C\leq8)}$.

44. The compound of claim 43, wherein X_6 is methyl.

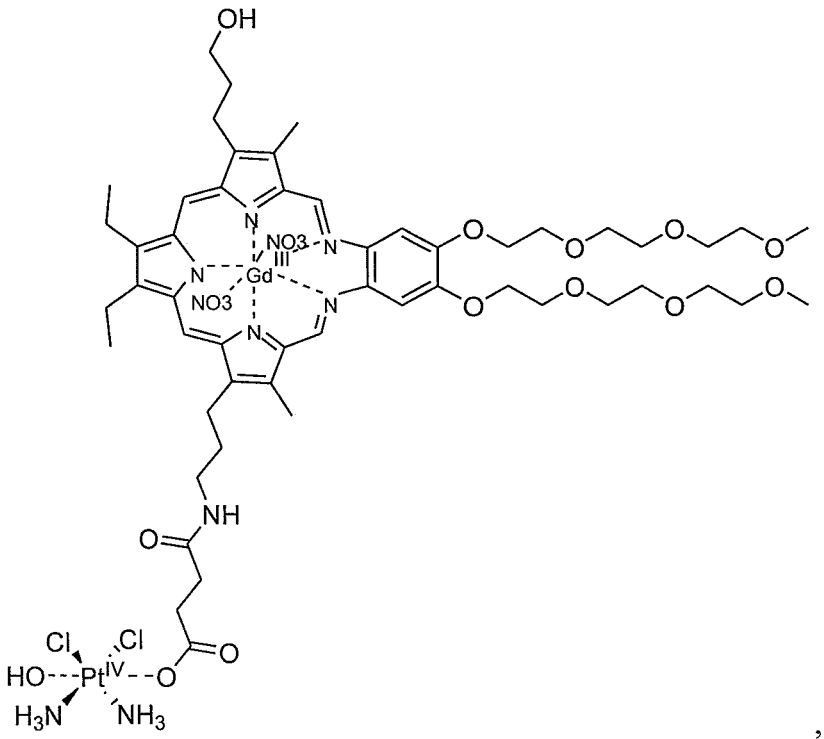
45. The compound according to any one of claims 1-44, wherein M is gadolinium.

46. The compound of claim 45, wherein M is Gd(III).

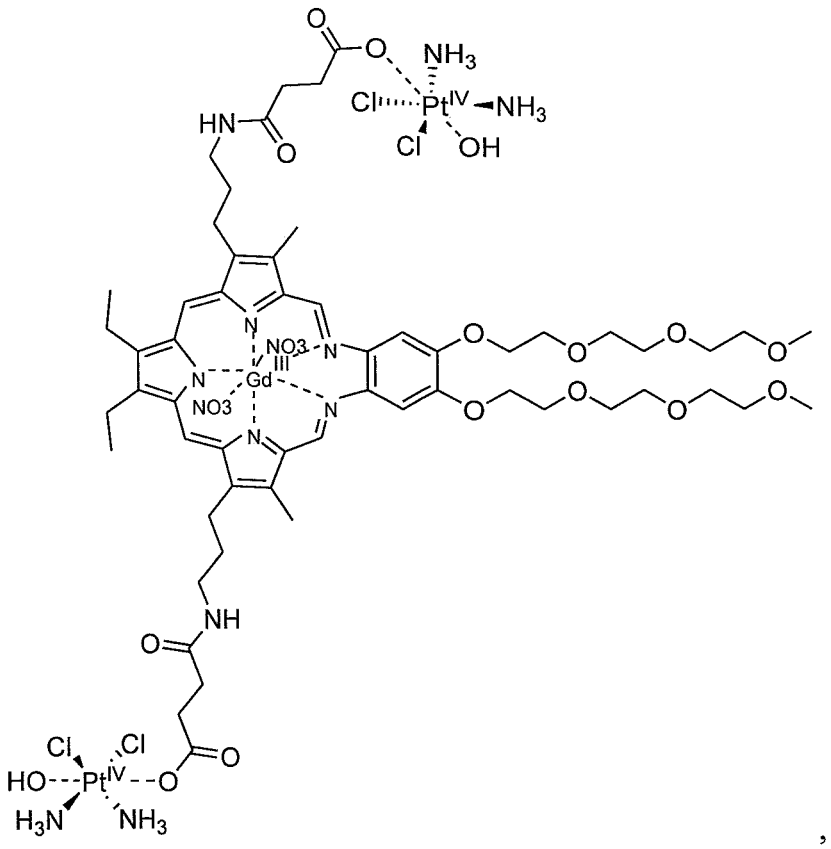
47. The compound according to any one of claims 1-46, wherein L_1 is acetate or nitrate.

48. The compound according to any one of claims 1-47, wherein L_2 is acetate or nitrate.

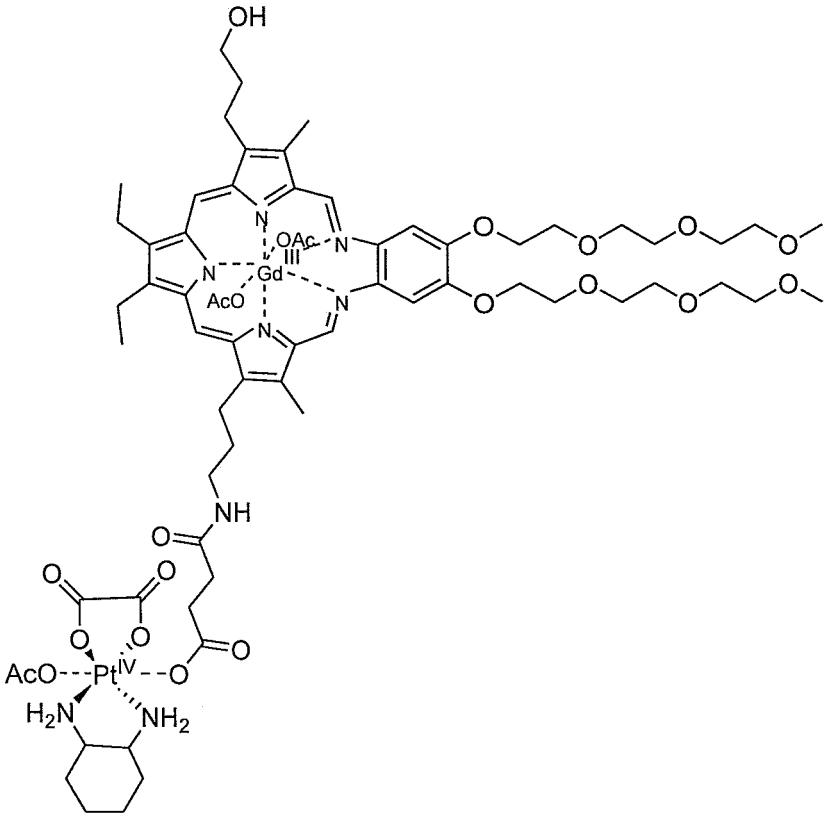
49. The compound of claim 1 further defined as:



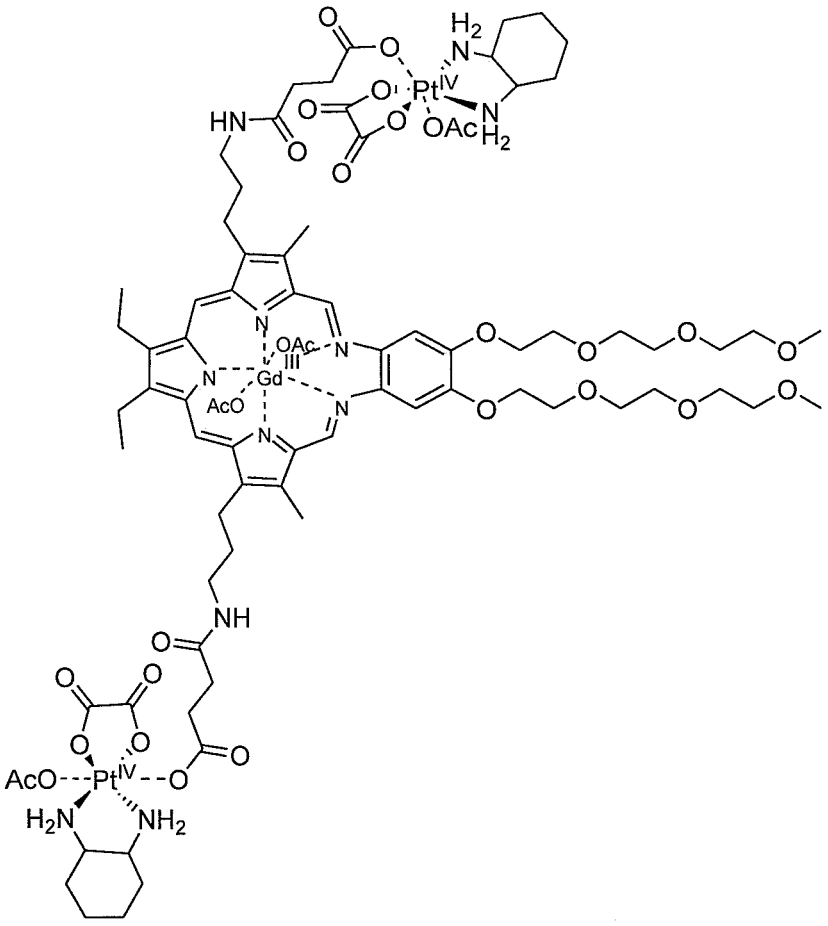
,



,



, or



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

50. A pharmaceutical composition comprising:

(A) a pharmaceutically acceptable carrier; and

(B) a compound according to any one of claims 1-49.

51. The pharmaceutical composition according to claim 50, 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.

52. The pharmaceutical composition of claim 51, wherein the pharmaceutical composition is formulated to be administered orally or intravenously.

53. The pharmaceutical composition according to any one of claims 50-52, wherein the composition is formulated as a unit dose.

54. Use of a compound or pharmaceutical composition according to claims 1 to 53 in the manufacture of a medicament for treating cancer in a patient.

55. The use of claim 54, wherein the cancer is a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma.

56. The use of claim 54, 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.

57. The use of claim 56, wherein the cancer is ovarian cancer, testicular cancer, or bladder cancer.

58. The use of claim 57, wherein the ovarian cancer is ovarian carcinoma.

59. The use of claim 56, wherein the cancer is colon cancer or colorectal cancer.

60. The use according to any one of claims 54-59, wherein the cancer is resistant to a metal chemotherapeutic.

61. The use of claim 60, wherein the cancer is resistant to a platinum chemotherapeutic.

62. The use of claim 61, wherein the cancer is resistant to cisplatin, carboplatin, or oxaliplatin.

63. The use according to any one of claims 54-62, wherein the use comprises a compound or composition according to any one of claims 1-53 to be administered.

64. The use of claim 63, wherein the compound localizes to a tumor before the reduction of the platinum(IV) chelating group.

65. The use according to any one of claims 54-64, wherein the compound of formula II is to be administered once.

66. The use according to any one of claims 54-64, wherein the compound of formula II is to be administered two or more times.

67. The use according to any one of claims 54-66, wherein the use further comprises a reducing agent to be administered.

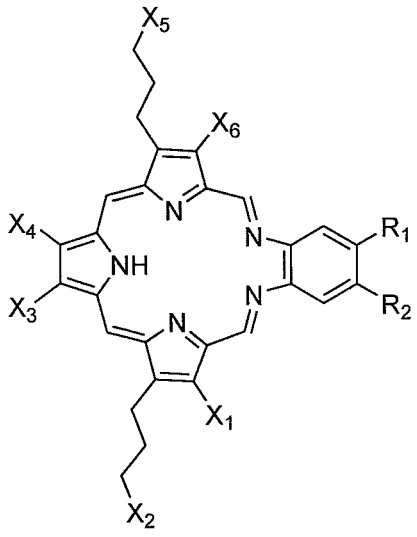
68. The use according to any one of claims 54-67, wherein the use is to be administered in conjunction with a second therapy.

69. The use of claim 68, wherein the second therapy is a second chemotherapeutic drug, surgery, radiotherapy, photodynamic therapy, sonodynamic therapy, cryotherapy, or immunotherapy.

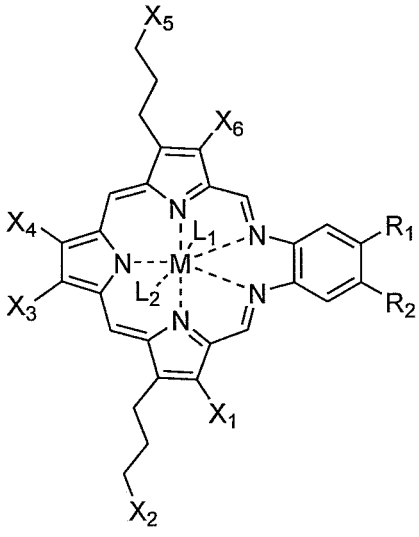
70. The use of claim 69, wherein the second chemotherapeutic drug is bleomycin, doxorubicin, taxol, taxotere, etoposide, 4-OH cyclophosphamide, or 5-fluorouracil.

71. The use of claim 69, wherein the second chemotherapeutic drug is cisplatin, carboplatin, oxaliplatin, or a Pt(IV) complex.

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

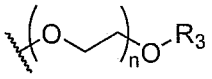


(VII) or



(VIII)

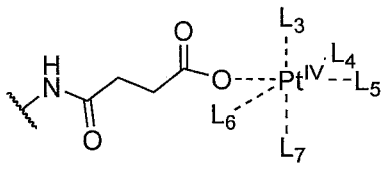
R_1 and R_2 are each independently selected from hydrogen, halo, hydroxy, amino, mercapto, $alkoxy_{(C\leq12)}$, substituted $alkoxy_{(C\leq12)}$, or



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,

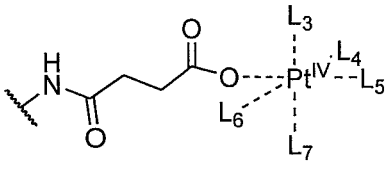
X_2 is  ;

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

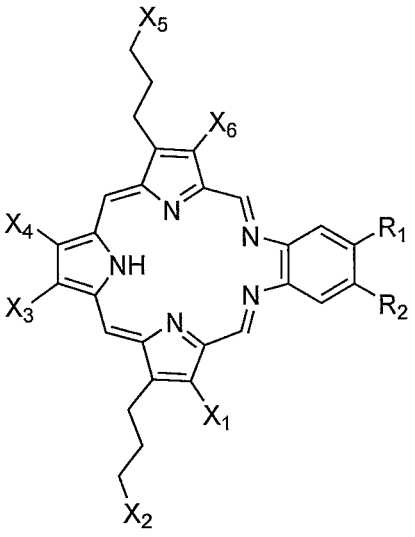
 ;

M is a metal ion; and

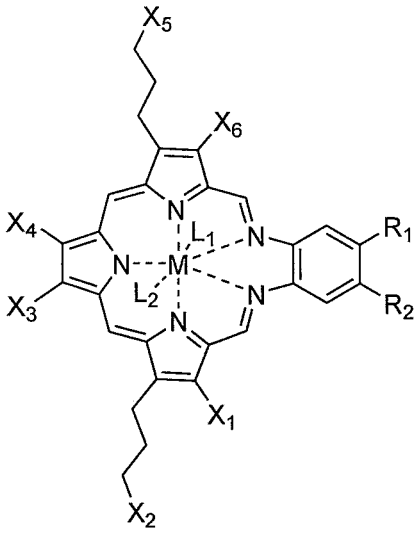
L_1 and L_2 are each anionic ligands independently selected from fluoride, chloride, bromide, carbonate, hydroxide, perchlorate, nitrate, sulfate, trifluoromethylsulfonate, acetylacetonate, acetate, or trifluoroacetate;

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)

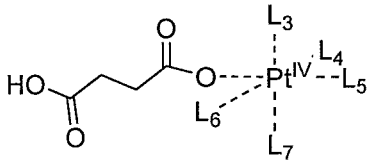
wherein:

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.

73. The method of claim 72, wherein the solvent is an aqueous organic mixture.

74. The method of claim 73, wherein the solvent is a water and acetonitrile mixture.

75. The method according to any one of claims 72-74, 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).

76. The method of claim 75, wherein the activating agent is a N-hydroxysuccinimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.