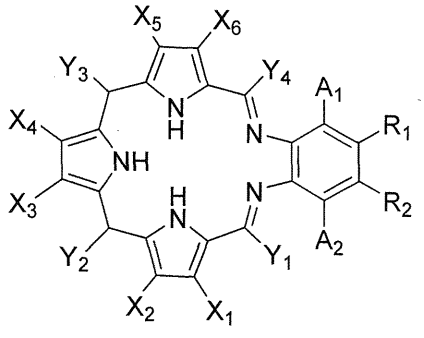
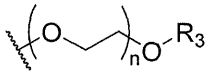
SUMMARY ~~OF THE INVENTION~~

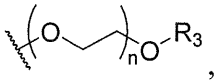
The present invention refers to subject matter as defined in the attached set of claims. In some ~~aspects~~examples, the present disclosure ~~provides~~ describes compounds of the formula:



(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$_{(C\leq12)}$;

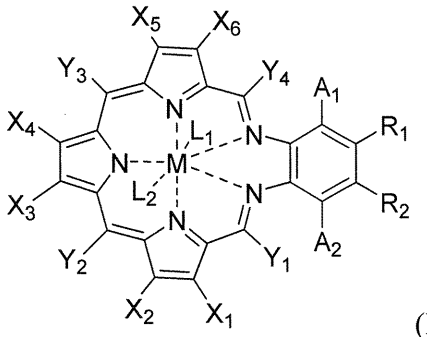
X_1, X_2, X_3, X_4, X_5, and X_6 are each independently selected from hydrogen, hydroxy, halo, amino, carboxy, nitro, or cyano,

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;

or an oxidized metal complex, a pharmaceutically acceptable salt, organometallic isomer, or tautomer thereof. In some ~~embodiments~~examples, the compound is further defined as an oxidized metal complex with the formula:



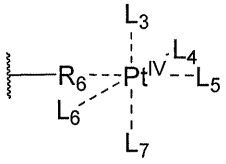
(II)

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. In some ~~embodiments~~examples, the platinum(IV) chelating group is $-A_3-X_7-A_4-R_4$, 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 amino, hydroxy, mercapto, carboxy, dicarboxy, or 

wherein:

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

L_3, L_4, L_5, and L_6 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, L_3, L_4, L_5, and L_6 are appropriately charged to obtain a neutral complex. In some ~~embodiments~~examples, the formula is further defined as:

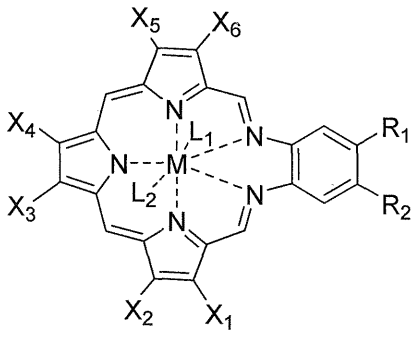
diaminoalkane$_{(C\leq12)}$, diaminocycloalkane$_{(C\leq12)}$, diaminoarene$_{(C\leq12)}$, alkyldicarboxylate$_{(C\leq18)}$, aryldicarboxylate$_{(C\leq18)}$, or a substituted version of any of these groups.

provided that 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

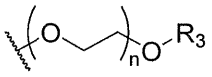
L_1 and L_2 are each anionic ligands independently selected from fluoride, chloride, bromide, perchlorate, nitrate, sulfate, trifluoromethylsulfonate, acetate, or trifluoroacetate;

or a pharmaceutically acceptable salt, organometallic isomer, or tautomer thereof. In some ~~embodiments~~examples, the formula is further defined as:

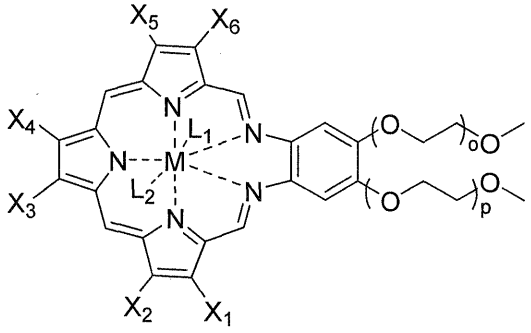


(III)

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. In some ~~embodiments~~examples, the formula is further defined as:



(IV)

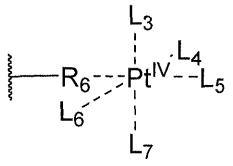
wherein:

o and p are each independently 1, 2, 3, 4, 5, or 6 or any range derivable therein;

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 carboxy or



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

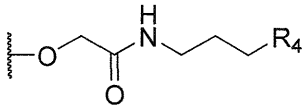
M is a trivalent lanthanide metal ion; and

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

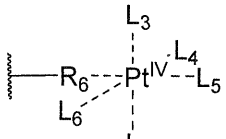
or a pharmaceutically acceptable salt, organometallic isomer, or tautomer thereof.

In some ~~embodiments~~examples, o is 2, 3, or 4. In some ~~embodiments~~examples, o is 3. In some examples~~embodiments~~, p is 2, 3, or 4. In some examples~~embodiments~~, p is 3.

In some examples~~embodiments~~, R_1 or R_2 is a platinum(IV) chelating group. In some examples~~embodiments~~, R_2 is a platinum(IV) chelating group of the formula:

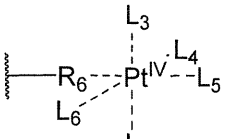


wherein: R_4 is as defined above. In some examples~~embodiments~~, X_1 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$. In some examples~~embodiments~~, X_1 is methyl. In some examples~~embodiments~~, X_2 is a platinum(IV) chelating group of the formula: $-A_3-X_7-A_4-R_4$, wherein A_3 and 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 carboxy, dicarboxy, or 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.

In some examples~~embodiments~~, A_3 is alkanediyl$_{(C\leq12)}$ or substituted alkanediyl$_{(C\leq12)}$. In some examples~~embodiments~~, A_3 is alkanediyl$_{(C\leq8)}$. In some examples~~embodiments~~, A_3 is $-CH_2CH_2CH_2-$. In some embodiments, X_7 is $-C(O)NH-$ or $-NHC(O)-$. In some examples~~embodiments~~, X_7 is $-NHC(O)-$. In some examples~~embodiments~~, A_4 is alkanediyl$_{(C\leq12)}$ or substituted alkanediyl$_{(C\leq12)}$. In some examples~~embodiments~~, A_4 is alkanediyl$_{(C\leq8)}$. In some



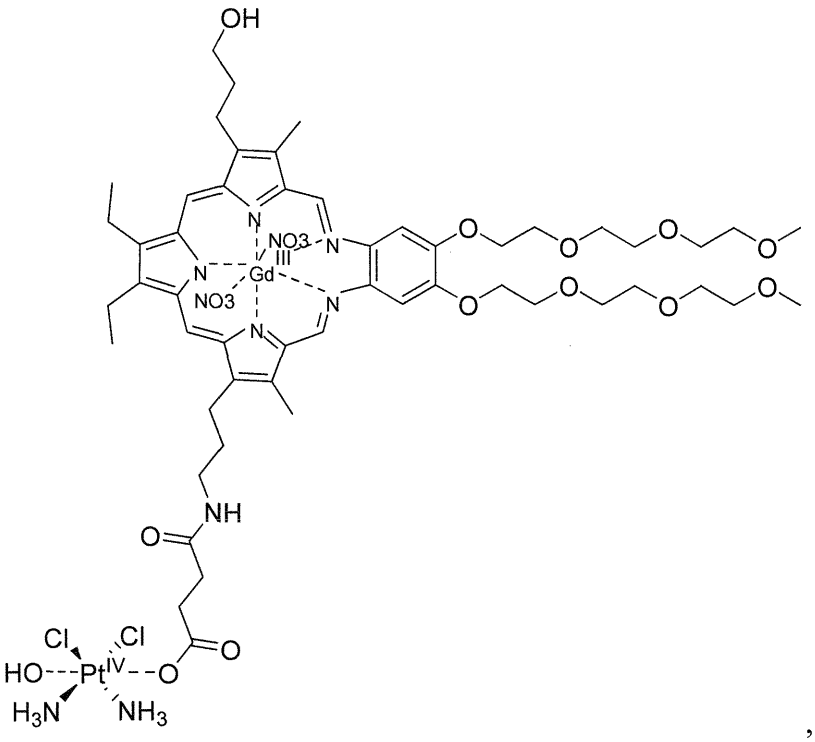
examples~~embodiments~~, A_4 is $-CH_2CH_2-$. In some embodiments, R_4 is . In some examples~~embodiments~~, R_6 is carboxy. In some examples~~embodiments~~, L_3 is halide, such as chloride. In some examples~~embodiments~~, L_4 is hydroxide. In some examples~~embodiments~~, L_5 is amino. In some examples~~embodiments~~, L_6 is halide, such as chloride. In some examples~~embodiments~~, L_3 and L_6 are taken together and are alkyldicarboxylate$_{(C\leq18)}$. In some examples~~embodiments~~, L_3 and L_6 are $^-O_2CCO_2^-$. In some examples~~embodiments~~, L_7 is amino. In some examples~~embodiments~~, L_5 and L_7 are taken together and are diaminocycloalkane$_{(C\leq12)}$. In some examples~~embodiments~~, L_5 and L_7 are each the amino group of 1,2-diaminocyclohexane.

In some examples~~embodiments~~, X_3 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$. In some examples~~embodiments~~, X_3 is alkyl$_{(C\leq8)}$. In some examples~~embodiments~~, X_3 is ethyl. In some examples~~embodiments~~, X_4 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$. In some examples~~embodiments~~, X_4 is alkyl$_{(C\leq8)}$. In some examples~~embodiments~~, X_4 is ethyl. In some examples~~embodiments~~, X_5 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$. In some examples~~embodiments~~, X_5 is substituted alkyl$_{(C\leq8)}$. In some examples~~embodiments~~, X_5 is $-CH_2CH_2CH_2OH$. In some examples~~embodiments~~, X_5 is a platinum(IV) chelating group. In some

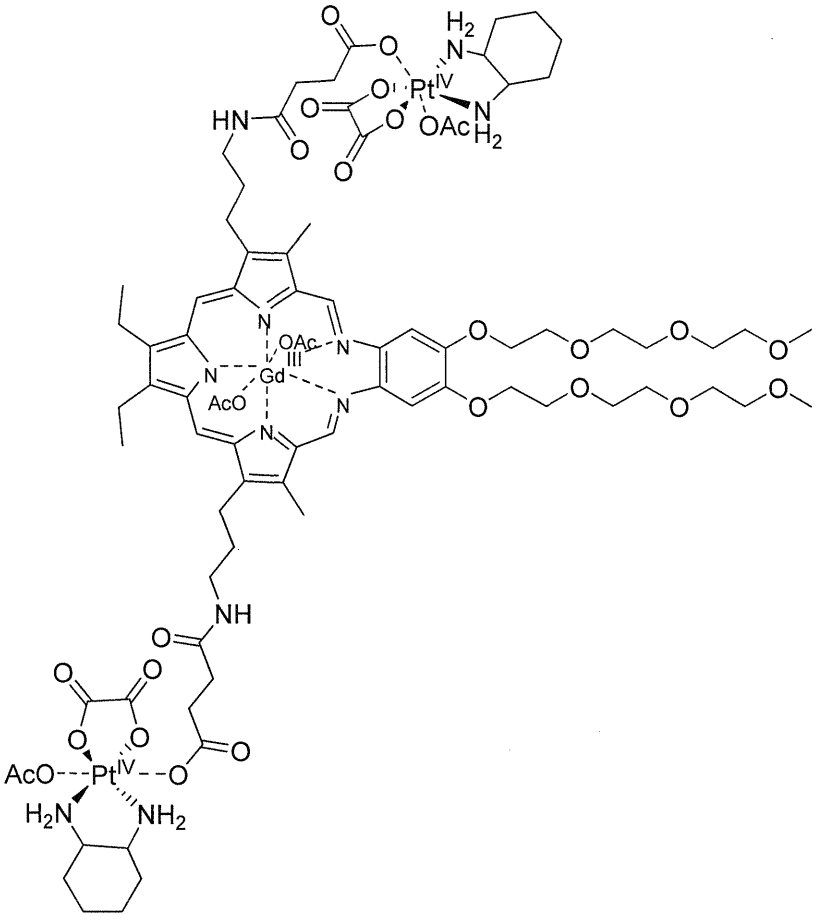
~~embodiments~~examples, X_6 is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$. In some examples~~embodiments~~, X_6 is $alkyl_{(C\leq8)}$. In some examples~~embodiments~~, X_6 is methyl.

In some examples~~embodiments~~, M is gadolinium such as Gd(III). In some examples~~embodiments~~, L_1 is acetate or nitrate. In some examples~~embodiments~~, L_2 is acetate or nitrate.

In some examples~~embodiments~~, the compound is further defined as:



,



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

In yet another exampleaspect, the present disclosure ~~provides~~ describes pharmaceutical compositions comprising:

(A) a pharmaceutically acceptable carrier; and

(B) a compound of the present disclosure.

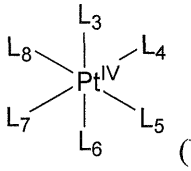
In still yet another ~~aspect~~example, the present disclosure ~~provides~~ describes pharmaceutical compositions comprising:

(A) a texaphyrin compound; and

(B) a high oxidation state metal-containing chemotherapeutic complex.

In some examples~~embodiments~~, the metal in the high oxidation state metal-containing chemotherapeutic complex is selected from: gold, platinum, osmium, ruthenium, titanium, iron, cobalt, copper, iridium, gallium, arsenic, molybdenum, tin, rhodium, and lanthanum. The metal may be gold, osmium, platinum, ruthenium, or titanium. In some examples~~embodiments~~, the metal is osmium, platinum, or ruthenium. In some examples~~embodiments~~, the metal is platinum.

In some examples~~embodiments~~, the high oxidation state metal-containing chemotherapeutic complex is a platinum(IV) complex. The platinum(IV) complex may have a formula:



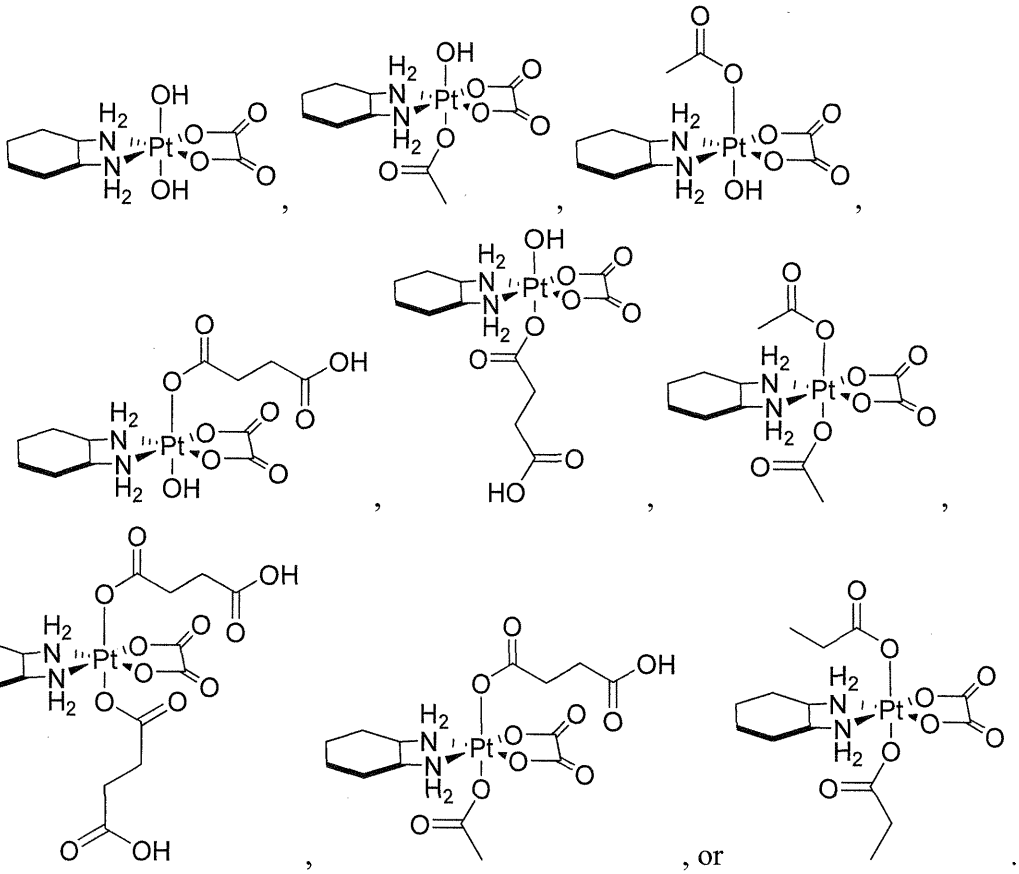
(VII)

wherein:

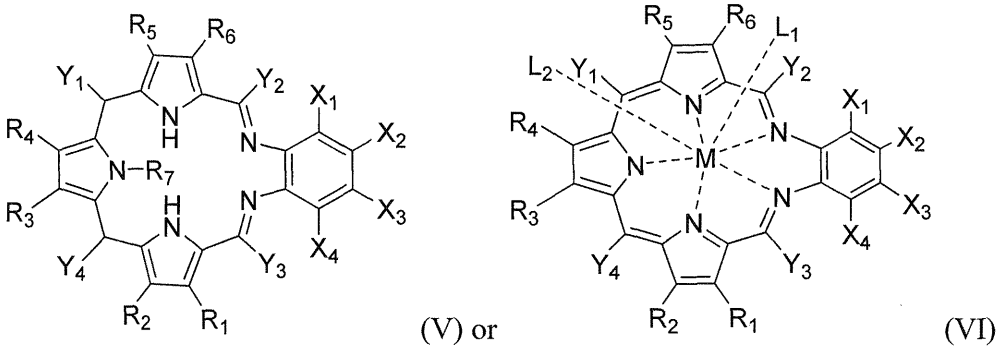
L_3-L_6 are each independently selected from: hydroxide, water, nitrate, carbonyl, phosphate, sulfate, amine, halide, phosphine$_{(C\leq24)}$, alkylcarboxylate$_{(C\leq12)}$, cycloalkylcarboxylate$_{(C\leq12)}$, alkylcarbamate$_{(C\leq12)}$, cycloalkylcarbamate$_{(C\leq12)}$, alkoxide$_{(C\leq12)}$, aryloxide$_{(C\leq12)}$, alkylamine$_{(C\leq12)}$, cycloalkylamine$_{(C\leq12)}$, dialkylamine$_{(C\leq12)}$, dicycloalkylamine$_{(C\leq12)}$, heterocycloalkane$_{(C\leq12)}$, heteroarene$_{(C\leq12)}$, or a substituted version of any of these groups; or

a divalent ligand wherein two or more of L_3-L_6 are taken together and wherein each L_3-L_6 variable is a chelating group selected from: hydroxide, amine, alkylcarboxylate$_{(C\leq12)}$, cycloalkylcarboxylate$_{(C\leq12)}$, alkylcarbamate$_{(C\leq12)}$, cycloalkylcarbamate$_{(C\leq12)}$, alkoxide$_{(C\leq12)}$, aryloxide$_{(C\leq12)}$, alkylamine$_{(C\leq12)}$, cycloalkylamine$_{(C\leq12)}$, dialkylamine$_{(C\leq12)}$, dicycloalkylamine$_{(C\leq12)}$, heterocycloalkane$_{(C\leq12)}$, or heteroarene$_{(C\leq12)}$, or a substituted version of any of these groups; and joined together to the one or more other L_3-L_6 variables by a linking group selected from: a covalent bond, an alkanediyl$_{(C\leq12)}$, an alkenediyl$_{(C\leq12)}$, an arenediyl$_{(C\leq12)}$, a heteroarenediyl$_{(C\leq12)}$, or a heterocycloalkanediyl$_{(C\leq12)}$ wherein the linking group replaces one or more hydrogens from the chelating group

provided that L_3-L_6 have a total charge of −4. In some examples~~embodiments~~, L_3 or L_6 is hydroxide, alkylcarboxylate$_{(C\leq8)}$ or substituted alkylcarboxylate$_{(C\leq8)}$. In other examples~~embodiments~~, L_3 or L_6 is hydroxide. In other examples~~embodiments~~, L_3 and L_6 are hydroxide. In some examples~~embodiments~~, the platinum(IV) complex is satraplatin or LA-12. In other examples~~embodiments~~, the platinum(IV) complex is a platinum(IV) analogue of cisplatin, carboplatin, oxaliplatin, lobaplatin, nedaplatin, heptaplatin, picoplatin, or BBR3464. In some examples~~embodiments~~, the platinum(IV) complex is a platinum(IV) analogue of cisplatin, carboplatin, or oxaliplatin. In some examples~~embodiments~~, the platinum(IV) complex is of the formula:



In some examplesembodiments, the texaphyrin compound is of the formula:



(V) or (VI)

wherein:

Y_1-Y_4 are each independently selected from: hydrogen, amino, cyano, halo, hydroxy, or hydroxyamino,

$alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $cycloalkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heterocycloalkoxy_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylthio_{(C\leq12)}$, $arylthio_{(C\leq12)}$, $alkylsulfinyl_{(C\leq12)}$, $arylsulfinyl_{(C\leq12)}$, $alkylsulfonyl_{(C\leq12)}$, $arylsulfonyl_{(C\leq12)}$, or a substituted version of any of these groups; or

R_1-R_6 are each independently selected from: hydrogen, amino, cyano, halo, hydroxy, hydroxyamino, or nitro,

$alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $cycloalkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heterocycloalkoxy_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, or a substituted version of any of these groups; or

a PEG moiety wherein the PEG moiety is of the formula: $-(OCH_2CH_2)_nOR_8$; wherein:

n is 1-20; and

R_8 is hydrogen, $alkyl_{(C\leq8)}$, or substituted $alkyl_{(C\leq8)}$;

R_7 is hydrogen,

$alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $cycloalkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, or a substituted version of any of these groups, or

an amino protecting group;

X_1-X_4 are each independently selected from: hydrogen, amino, cyano, halo, hydroxy, hydroxyamino, or nitro,

$alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $cycloalkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heterocycloalkoxy_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, or a substituted version of any of these groups; or

a PEG moiety wherein the PEG moiety is of the formula: $-(OCH_2CH_2)_nOR_8$; wherein:

n is 1-20; and

R_8 is hydrogen, $alkyl_{(C\leq8)}$, or substituted $alkyl_{(C\leq8)}$;

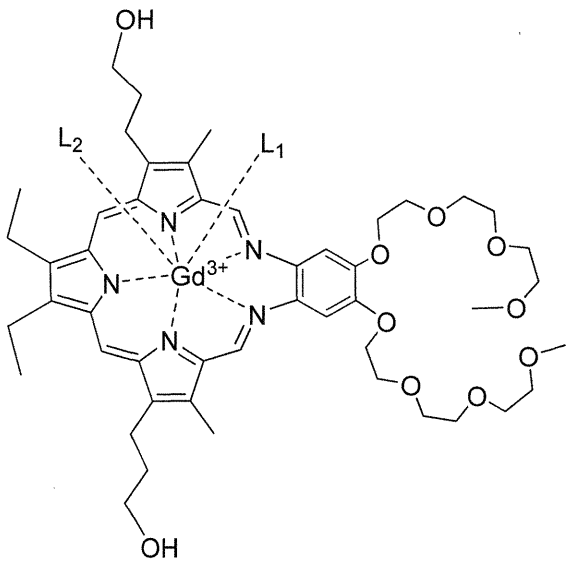
L_1 and L_2 are each independently absent, a neutral ligand, or an anionic ligand; and

M is a metal ion;

provided that L_1 and L_2 are present or absent as appropriate to balance the charge on the metal ion;

or a pharmaceutically acceptable salt or tautomer thereof. In other examples~~embodiments~~, the texaphyrin is a compound of formula VB. In some examples~~embodiments~~, M is a transition metal in the +2 oxidation state or +3 oxidation state such as gadolinium(III). In some examples~~embodiments~~, the texaphyrin compound wherein at least two of X_1-X_4 are a PEG moiety wherein the PEG

moiety is of the formula: $-(OCH_2CH_2)_nOR_8$; wherein: n is 1-20; and R_8 is hydrogen, $alkyl_{(C\leq 8)}$, or substituted $alkyl_{(C\leq 8)}$. In some examples~~embodiments~~, the texaphyrin compound has the following formula:



,

wherein:

L_1 and L_2 are each independently an anionic ligand; and

or a pharmaceutically acceptable salt or tautomer thereof. In some examples~~embodiments~~, the texaphyrin compound is motexafin gadolinium. In some examples~~embodiments~~, the texaphyrin compound is a compound of formula I or formula II. In some examples~~embodiments~~, the texaphyrin and the high oxidation state metal-containing chemotherapeutic complex are administered in a ratio from about 10:1 to about 1:10. In some examples~~embodiments~~, the ratio is from about 3:1 to about 1:3. In some examples~~embodiments~~, the ratio is about 1:2.

In some examples~~embodiments~~, the pharmaceutical composition further comprises a reducing agent. The reducing agent may be sodium ascorbate, thioredoxin reductase, a biological thiol, a platinum(II) complex, or light. In some examples~~embodiments~~, the biological thiol is cysteine, homocysteine, or glutathione. In some examples~~embodiments~~, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier. In some examples~~embodiments~~, the pharmaceutical composition is formulated for administration: 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. In some examples~~embodiments~~, the pharmaceutical composition is formulated for oral or intravenous administration. In some examples~~embodiments~~, the composition is formulated as a unit dose.

In still yet another ~~aspect~~example, the present disclosure ~~provides~~ describes methods of treating a disease in a patient comprising administering to the patient in need thereof a therapeutically effective amount of:

(A) a compound or pharmaceutical composition of the present disclosure;

(B) a pharmaceutical composition of the present disclosure; or

(C) a first agent selected from a texaphyrin compound and a second agent selected from a high oxidation state metal-containing chemotherapeutic complex.

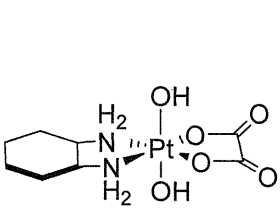
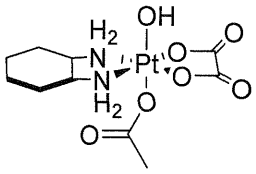
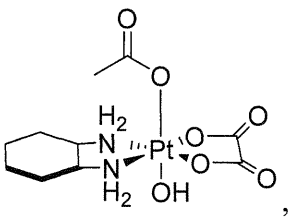
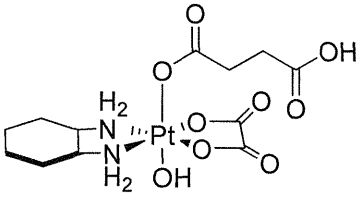
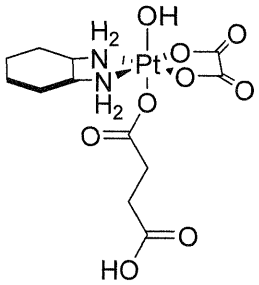
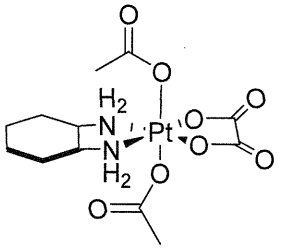
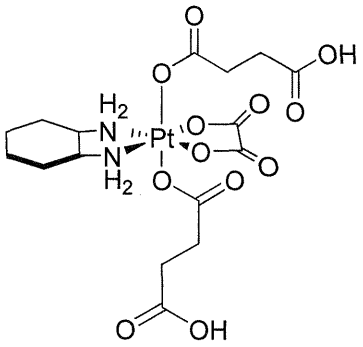
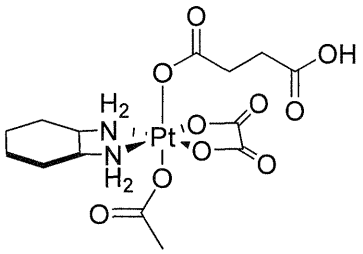
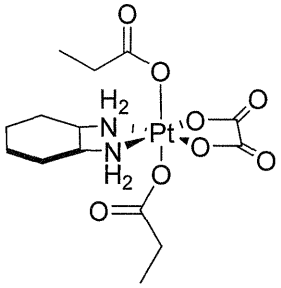
In some examples~~embodiments~~, the disease is cancer, such as a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma or the cancer is of the bladder, blood, bone, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder, genitalia, 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. In some examples~~embodiments~~, the cancer is ovarian cancer, testicular cancer, or bladder cancer. The ovarian cancer may be ovarian carcinoma. The cancer may be colon cancer or colorectal cancer. In some examples~~embodiments~~, the cancer is resistant to a metal chemotherapeutic. The cancer may be resistant to a platinum chemotherapeutic. In some examples~~embodiments~~, the cancer is resistant to cisplatin, carboplatin, or oxaliplatin.

In some examples~~embodiments~~, the methods comprise administering a compound or composition of the present disclosure. In some examples~~embodiments~~, the platinum complex is reduced *in vivo* to form an active complex. The compound may be localized to a tumor before the reduction of the platinum complex.

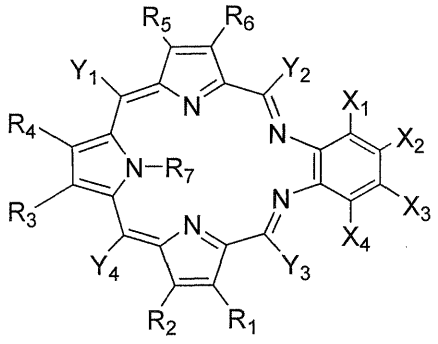
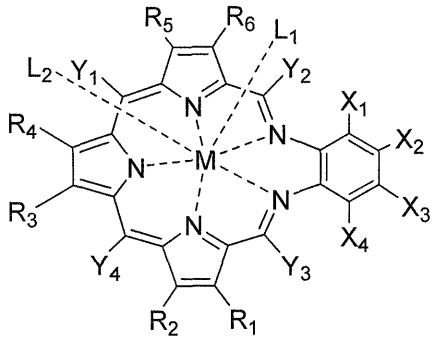
In some examples~~embodiments~~, the methods comprise administering a composition comprising a texaphyrin compound and high oxidation state metal-containing chemotherapeutic complex. The methods comprise administering a first agent selected from a texaphyrin compound and a

second agent selected from a high oxidation state metal-containing chemotherapeutic complex. In some examplesembodiments, the high oxidation state metal-containing chemotherapeutic complex is a metal-containing chemotherapeutic complex that is capable of undergoing reduction. The high oxidation state metal-containing chemotherapeutic complex may be in a pro-drug form. In some examplesembodiments, the high oxidation state metal-containing chemotherapeutic complex is in an oxidized form and is reduced *in vivo* to form a chemotherapeutically more active species. In some examplesembodiments, the high oxidation state metal-containing chemotherapeutic complex is activated in the presence of the texaphyrin compound. In some embodiments, the high oxidation state metal-containing chemotherapeutic complex is activated by a reduced form of the texaphyrin compound. In some examplesembodiments, the reduced form of the texaphyrin compound is produced *in vivo* by one or more reducing species. The high oxidation state metal-containing chemotherapeutic complex may be preferentially activated in a cancer cell. The high oxidation state metal-containing chemotherapeutic complex may be preferentially activated in the presence of a cancer cell. In some examplesembodiments, the texaphyrin compound localizes to a cancer cell and the high oxidation state metal-containing chemotherapeutic complex is preferentially activated by the texaphyrin compound in the cancer cell. In some examplesembodiments, the texaphyrin compound localizes to the extracellular matrix around a cancer cell and the high oxidation state metal-containing chemotherapeutic complex is preferentially activated by the texaphyrin compound in the presence of the cancer cell. The high oxidation state metal-containing chemotherapeutic complex may be selectively activated in the cancer cell. The high oxidation state metal-containing chemotherapeutic complex may be selectively activated in the presence of the cancer cell.

In some examplesembodiments, the metal in the high oxidation state metal-containing chemotherapeutic complex is selected from: gold, platinum, osmium, ruthenium, titanium, iron, cobalt, copper, iridium, gallium, arsenic, molybdenum, tin, rhodium, and lanthanum. In some examplesembodiments, the metal is platinum. In some examplesembodiments, the high oxidation state metal-containing chemotherapeutic complex is a platinum(IV) complex. The platinum(IV) complex may comprise one or more hydroxide ligands. The platinum(IV) complex may comprise two axial hydroxide ligands. In some examplesembodiments, the platinum(IV) complex is of the formula:


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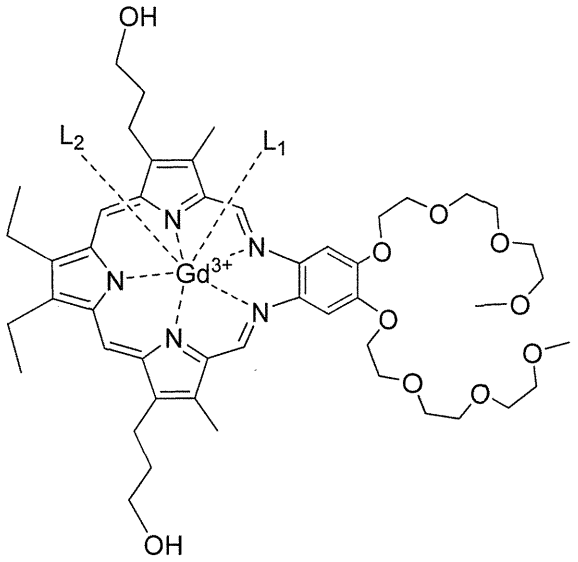
In some examples~~embodiments~~, the texaphyrin compound is of the formula:


(V) or

(VI)

wherein:

Y_1-Y_4 are each independently selected from: hydrogen, amino, cyano, halo, hydroxy, or hydroxyamino,

or a pharmaceutically acceptable salt or tautomer thereof. In some examplesembodiments, the texaphyrin compound is of the formula:



,

wherein:

L_1 and L_2 are each independently an anionic ligand; and

or a pharmaceutically acceptable salt or tautomer thereof. In some examplesembodiments, the texaphyrin compound is motexafin gadolinium.

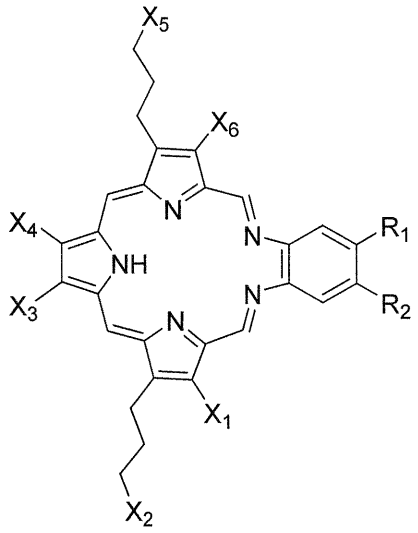
In some examplesembodiments, the texaphyrin and the high oxidation state metal-containing chemotherapeutic complex are administered in a ratio from about 10:1 to about 1:10. In some examplesembodiments, the texaphyrin and the high oxidation state metal-containing chemotherapeutic complex are administered together. In some examplesembodiments, the texaphyrin or the high oxidation state metal-containing chemotherapeutic complex is administered and then the other is administered within a time period of 1 week, or the time period is 24 hours., or the time period is 12 hours.

In other examplesembodiments, the texaphyrin is administered first and then the high oxidation state metal-containing chemotherapeutic complex is administered. In other examplesembodiments, the high oxidation state metal-containing chemotherapeutic complex is administered first and then the texaphyrin is administered. In some examplesembodiments, the texaphyrin is administered once. In other examplesembodiments, the texaphyrin is administered two or more times. In some examplesembodiments, the high oxidation state metal-containing chemotherapeutic complex is

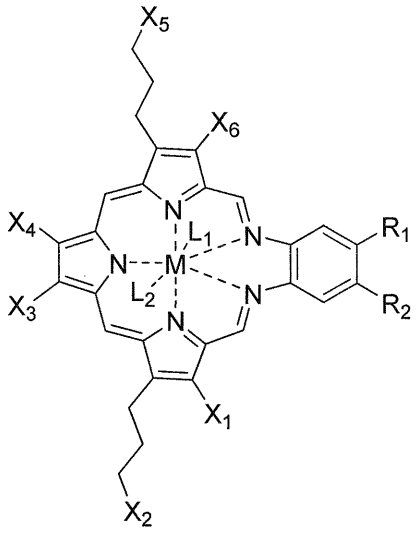
administered once. In other ~~embodiments~~examples, the high oxidation state metal-containing chemotherapeutic complex is administered two or more times.

In some examples~~embodiments~~, the method further comprises administering a reducing agent. In some examples~~embodiments~~, the method is administered in conjunction with a second therapy, wherein the second therapy is a third chemotherapeutic drug, surgery, radiotherapy, photodynamic therapy, sonodynamic therapy, cryotherapy, or immunotherapy. In some examples~~embodiments~~, the third chemotherapeutic drug is bleomycin, doxorubicin, taxol, taxotere, etoposide, 4-OH cyclophosphamide, or 5-fluorouracil or the third chemotherapeutic drug is cisplatin, carboplatin, oxaliplatin, or a Pt(IV) complex.

In yet another ~~aspect~~example, the present disclosure ~~provides~~ describes methods of preparing a platinum-texaphyrin complex of the formula:

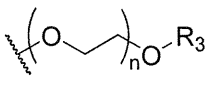


(VII) or



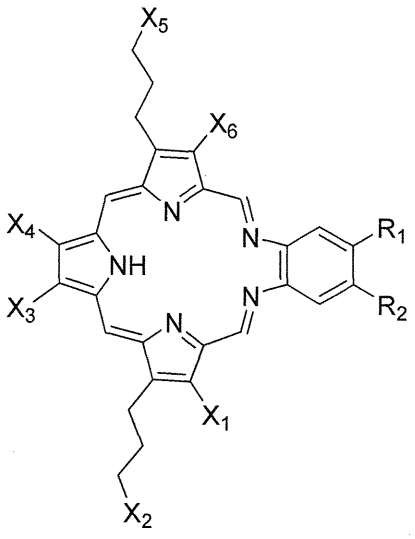
(VIII)

wherein:

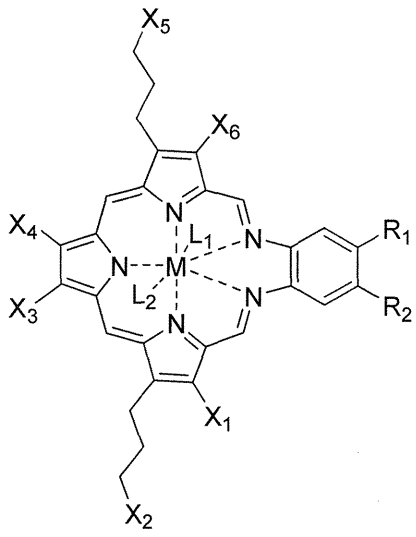
R_1 and R_2 are each independently selected from hydrogen, halo, hydroxy, amino, mercapto, $alkoxy_{(C\leq12)}$, substituted $alkoxy_{(C\leq12)}$, or  wherein n is 1-8 and R_3 is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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,



(VII) or



(VIII)

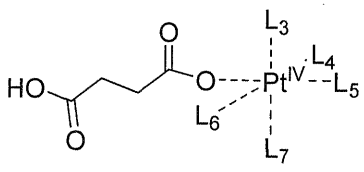
wherein:

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. In some examples~~embodiments~~, the solvent is an aqueous organic mixture, such as a water and acetonitrile mixture. In some examples~~embodiments~~, 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). In some examples~~embodiments~~, the activating agent is a N-hydroxysuccinimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein.

The terms "comprise" (and any form of comprise, such as "comprises" and "comprising"), "have" (and any form of have, such as "has" and "having"), "contain" (and any form of contain, such as "contains" and "containing"), and "include" (and any form of

or a pharmaceutically acceptable salt or tautomer thereof.

76. The pharmaceutical composition of claim 75, wherein the texaphyrin compound is motexafin gadolinium.

77. The pharmaceutical composition according to any one of claims 56-69, wherein the texaphyrin compound is a compound of formula I or formula II.

78. The pharmaceutical composition according to any one of claims 56-76, wherein the texaphyrin and the high oxidation state metal-containing chemotherapeutic complex are administered in a ratio from about 10:1 to about 1:10.

79. The pharmaceutical composition of claim 78, wherein the ratio is from about 3:1 to about 1:3.

80. The pharmaceutical composition of claim 79, wherein the ratio is about 1:2.

81. The pharmaceutical composition according to any one of claims 56-80, wherein the pharmaceutical composition further comprises a reducing agent.

82. The pharmaceutical composition of claim 81, wherein the reducing agent is sodium ascorbate, thioredoxin reductase, a biological thiol, a platinum(II) complex, or light.

83. The pharmaceutical composition of claim 82, wherein the biological thiol is cysteine, homocysteine, or glutathione.

84. The composition according to any one of claims 56-83, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

85. The pharmaceutical composition according to any one of claims 55-84, wherein the pharmaceutical composition is formulated for administration: 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.

86. The pharmaceutical composition of claim 85, wherein the pharmaceutical composition is formulated for oral or intravenous administration.

87. The pharmaceutical composition according to any one of claims 55-86, wherein the composition is formulated as a unit dose.

88. Use of~~A method of treating a disease in a patient comprising administering to the patient in need thereof a therapeutically effective amount of~~:

(A) a compound or pharmaceutical composition according to claims 1-55 or 85-87;

(B) a pharmaceutical composition according to any one of claims 56-87; or

(C) a first agent selected from a texaphyrin compound and a second agent selected from a high oxidation state metal-containing chemotherapeutic complex,

in the manufacture of a medicament for treating a disease in a patient.

89. The ~~method~~ use of claim 88, wherein the disease is cancer.

90. The use ~~method~~ of claim 89, wherein the cancer is a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma.

91. The use ~~method~~ of claim 89, 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.

92. The use ~~method~~ of claim 91, wherein the cancer is ovarian cancer, testicular cancer, or bladder cancer.

93. The use ~~method~~ of claim 92, wherein the ovarian cancer is ovarian carcinoma.

94. The use ~~method~~ of claim 91, wherein the cancer is colon cancer or colorectal cancer.

95. The use ~~method~~ according to any one of claims 88-94, wherein the cancer is resistant to a metal chemotherapeutic.

96. The use ~~method~~ of claim 95, wherein the cancer is resistant to a platinum chemotherapeutic.

97. The use ~~method~~ of claim 96, wherein the cancer is resistant to cisplatin, carboplatin, or oxaliplatin.

98. The use ~~method~~ according to any one of claims 88-97, wherein the use ~~method~~ comprises ~~administering~~ a compound or composition according to any one of claims 1-55 or 85-87 to be administered.

99. The use ~~method~~ of claim 98, wherein the platinum complex is reduced *in vivo* to form an active complex.

100. The use ~~method~~ of either claim 98 or claim 99, wherein the compound localizes to a tumor before the reduction of the platinum complex.

101. The use ~~method~~ according to any one of claims 88-97, wherein the use ~~method~~ comprises ~~administering~~ a composition according to any one of claims 56-87 to be administered.

102. The use ~~method~~ according to any one of claims 88-97, wherein the use ~~method~~ comprises ~~administering~~ a first agent to be administered selected from a texaphyrin compound and a second agent to be administered selected from a high oxidation state metal-containing chemotherapeutic complex.

103. The use ~~method~~ of either claim 101 or claim 102, wherein the high oxidation state metal-containing chemotherapeutic complex is a metal-containing chemotherapeutic complex that is capable of undergoing reduction.

104. The use ~~method~~ according to any one of claims 101-103, wherein the high oxidation state metal-containing chemotherapeutic complex is in a pro-drug form.

105. The use ~~method~~ according to any one of claims 101-104, wherein the high oxidation state metal-containing chemotherapeutic complex is in an oxidized form and is reduced *in vivo* to form a chemotherapeutically more active species.

106. The use ~~method~~ according to any one of claims 101-105, wherein the high oxidation state metal-containing chemotherapeutic complex is activated in the presence of the texaphyrin compound.

107. The use ~~method~~ of claim 106, wherein the high oxidation state metal-containing chemotherapeutic complex is activated by a reduced form of the texaphyrin compound.

108. The use ~~method~~ of claim 107, wherein the reduced form of the texaphyrin compound is produced *in vivo* by one or more reducing species.

109. The use ~~method~~ of claim 106, wherein the high oxidation state metal-containing chemotherapeutic complex is preferentially activated in a cancer cell.

110. The use ~~method~~ of claim 106, wherein the high oxidation state metal-containing chemotherapeutic complex is preferentially activated in the presence of a cancer cell.

111. The use ~~method~~ according to any one of claims 101-109, wherein the texaphyrin compound localizes to a cancer cell and the high oxidation state metal-containing chemotherapeutic complex is preferentially activated by the texaphyrin compound in the cancer cell.

112. The use ~~method~~ according to any one of claims 101-109, wherein the texaphyrin compound localizes to the extracellular matrix around a cancer cell and the high oxidation state metal-containing chemotherapeutic complex is preferentially activated by the texaphyrin compound in the presence of the cancer cell.

113. The use ~~method~~ of claim 111, wherein the high oxidation state metal-containing chemotherapeutic complex is selectively activated in the cancer cell.

114. The use ~~method~~ of claim 111, wherein the high oxidation state metal-containing chemotherapeutic complex is selectively activated in the presence of the cancer cell.

115. The use ~~method~~ according to any one of claims 101-113, wherein the metal in the high oxidation state metal-containing chemotherapeutic complex is selected from: gold, platinum, osmium, ruthenium, titanium, iron, cobalt, copper, iridium, gallium, arsenic, molybdenum, tin, rhodium, and lanthanum.

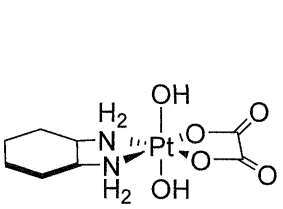
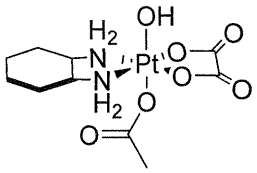
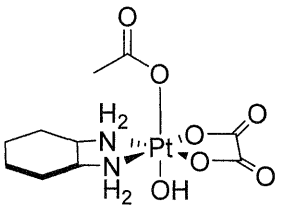
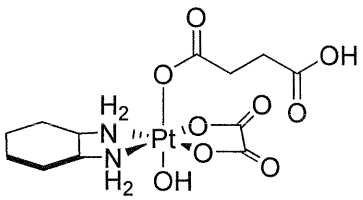
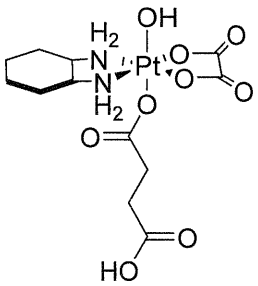
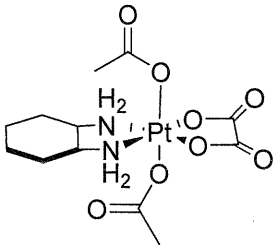
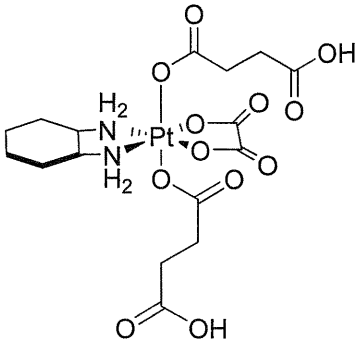
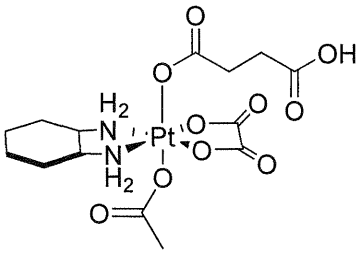
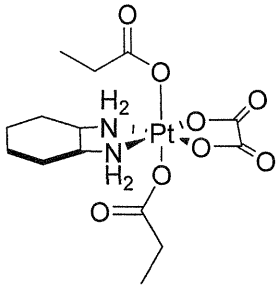
116. The use ~~method~~ of claim 115, wherein the metal is platinum.

117. The use ~~method~~ according to any one of claims 101-116, wherein the high oxidation state metal-containing chemotherapeutic complex is a platinum(IV) complex.

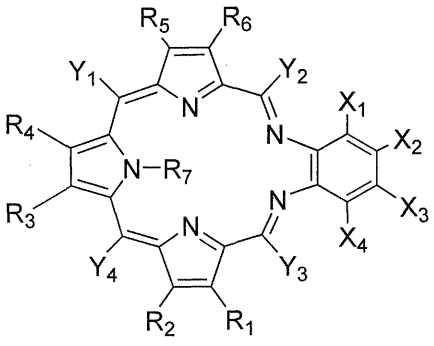
118. The use ~~method~~ of claim 117, wherein the platinum(IV) complex comprises one or more hydroxide ligands.

119. The use ~~method~~ of claim 118, wherein the platinum(IV) complex comprises two axial hydroxide ligands.

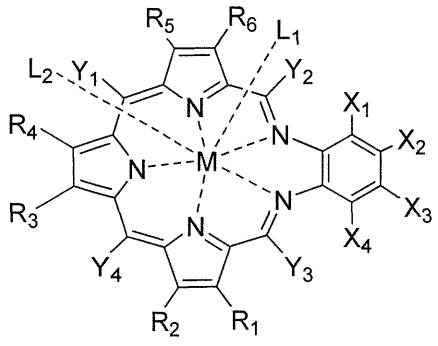
120. The use ~~method~~ of claim 117, wherein the platinum(IV) complex is of the formula:


,

,

,

,

,

,

,

, or

.

121. The use ~~method~~ according to any one of claims 101-120, wherein the texaphyrin compound is of the formula:



(V) or



(VI)

wherein:

Y_1-Y_4 are each independently selected from: hydrogen, amino, cyano, halo, hydroxy, or hydroxyamino,

$alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $cycloalkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heterocycloalkoxy_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylthio_{(C\leq12)}$, $arylthio_{(C\leq12)}$, $alkylsulfinyl_{(C\leq12)}$, $arylsulfinyl_{(C\leq12)}$, $alkylsulfonyl_{(C\leq12)}$, $arylsulfonyl_{(C\leq12)}$, or a substituted version of any of these groups; or

R_1-R_6 are each independently selected from: hydrogen, amino, cyano, halo, hydroxy, hydroxyamino, or nitro,

$alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $cycloalkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heterocycloalkoxy_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, or a substituted version of any of these groups; or

a PEG moiety wherein the PEG moiety is of the formula: $-(OCH_2CH_2)_nOR_8$; wherein:

n is 1-20; and

R_8 is hydrogen, $alkyl_{(C\leq8)}$, or substituted $alkyl_{(C\leq8)}$;

R_7 is hydrogen,

$alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $cycloalkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, or a substituted version of any of these groups, or

an amino protecting group;

X_1-X_4 are each independently selected from: hydrogen, amino, cyano, halo, hydroxy, hydroxyamino, or nitro,

$alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $cycloalkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heterocycloalkoxy_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, or a substituted version of any of these groups; or

a PEG moiety wherein the PEG moiety is of the formula: $-(OCH_2CH_2)_nOR_8$; wherein:

n is 1-20; and

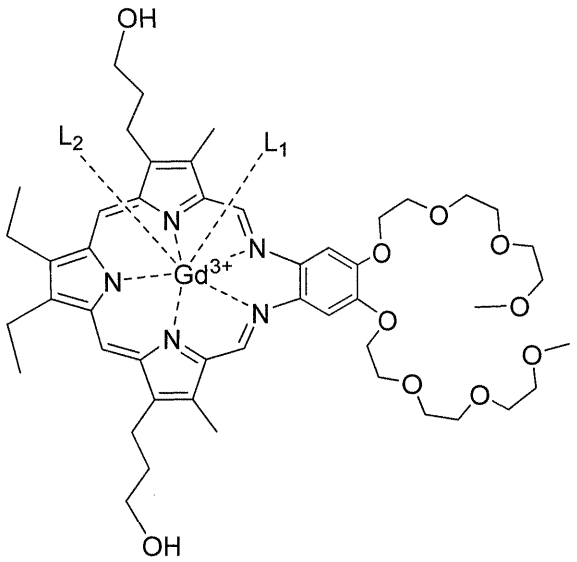
R_8 is hydrogen, $alkyl_{(C\leq8)}$, or substituted $alkyl_{(C\leq8)}$;

L_1 and L_2 are each independently absent, a neutral ligand, or an anionic ligand; and

M is a metal ion, provided that L_1 and L_2 are absent or a neutral ligand as needed to balance the charge on the metal ion;

or a pharmaceutically acceptable salt or tautomer thereof.

122. The use ~~method~~ according to any one of claims 101-121, wherein the texaphyrin compound is of the formula:



,

wherein:

L_1 and L_2 are each independently an anionic ligand; and

or a pharmaceutically acceptable salt or tautomer thereof.

123. The use ~~method~~ of claim 122, wherein the texaphyrin compound is motexafin gadolinium.

124. The use ~~method~~ according to any one of claims 101-123, wherein the texaphyrin and the high oxidation state metal-containing chemotherapeutic complex are to be administered in a ratio from about 10:1 to about 1:10.

125. The use ~~method~~ according to any one of claims 101-124, wherein the texaphyrin and the high oxidation state metal-containing chemotherapeutic complex are to be administered together.

126. The use ~~method~~ according to any one of claims 102-124, wherein the texaphyrin or the high oxidation state metal-containing chemotherapeutic complex is to be administered and then the other is to be administered within a time period of 1 week.

127. The use ~~method~~ of claim 126, wherein the time period is 24 hours.

128. The use ~~method~~ of claim 127, wherein the time period is 12 hours.

129. The use ~~method~~ according to any one of claims 126-128, wherein the texaphyrin is to be administered first and then the high oxidation state metal-containing chemotherapeutic complex is to be administered.

130. The use ~~method~~ according to any one of claims 126-128, wherein the high oxidation state metal-containing chemotherapeutic complex is to be administered first and then the texaphyrin is to be administered.

131. The use ~~method~~ according to any one of claims 88-130, wherein the texaphyrin is to be administered once.

132. The use ~~method~~ according to any one of claims 88-130, wherein the texaphyrin is to be administered two or more times.

133. The use ~~method~~ according to any one of claims 102-132, wherein the high oxidation state metal-containing chemotherapeutic complex is to be administered once.

134. The use ~~method~~ according to any one of claims 102-132, wherein the high oxidation state metal-containing chemotherapeutic complex is to be administered two or more times.

135. The use ~~method~~ according to any one of claims 88-134, wherein the use ~~method~~ further comprises ~~administering~~ a reducing agent to be administered.

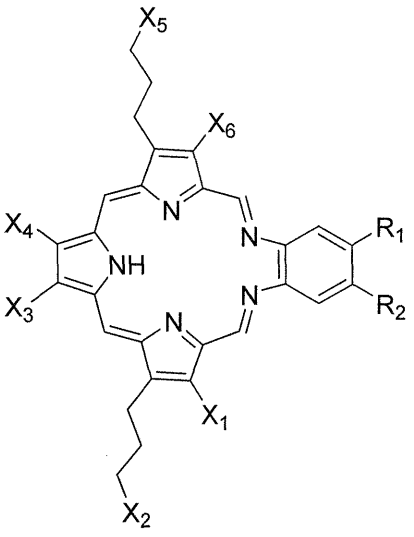
136. The use ~~method~~ according to any one of claims 88-134, wherein the use ~~method~~ is to be administered in conjunction with a second therapy.

137. The use ~~method~~ of claim 136, wherein the second therapy is a third chemotherapeutic drug, surgery, radiotherapy, photodynamic therapy, sonodynamic therapy, cryotherapy, or immunotherapy.

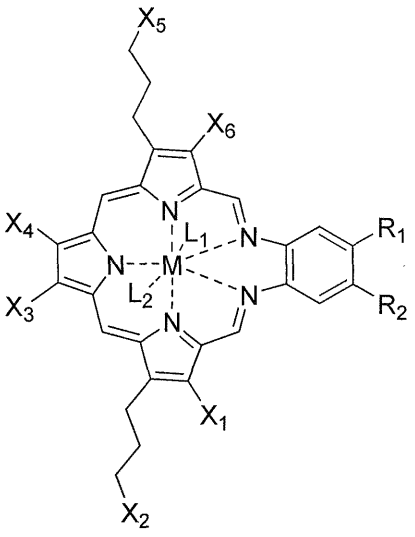
138. The use ~~method~~ of claim 137, wherein the third chemotherapeutic drug is bleomycin, doxorubicin, taxol, taxotere, etoposide, 4-OH cyclophosphamide, or 5-fluorouracil.

139. The use ~~method~~ of claim 137, wherein the third chemotherapeutic drug is cisplatin, carboplatin, oxaliplatin, or a Pt(IV) complex.

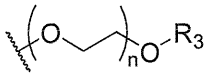
140. A method of preparing a platinum-texaphyrin complex of the formula:



(VII) or

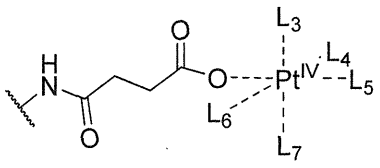


(VIII)

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

$alkylamine_{(C\leq12)}$, $cycloalkylamine_{(C\leq12)}$, $dialkylamine_{(C\leq18)}$, $dicycloalkylamine_{(C\leq18)}$, $arylamine_{(C\leq12)}$, $diarylamine_{(C\leq18)}$, $diaminoalkane_{(C\leq12)}$, $diaminocycloalkane_{(C\leq12)}$, $diaminoarene_{(C\leq12)}$,