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(54) Title: AROMATIC COMPOUNDS AND METAL COMPLEXES THEREOF

(57) Abstract: Provided are aromatic compounds and metal complexes thereof which may be useful treating various forms of proliferative diseases, such as cancer. In some instances, the metal complexes thereof are relatively stable, and may be suitable for oral administration. Also provided are methods of treatment, as well as methods of imaging or diagnosing a disease in a subject.



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AROMATIC COMPOUNDS AND METAL COMPLEXES THEREOF

BACKGROUND

1. Field

[0001] The present invention relates to aromatic compounds that can conjugate with metal ions to form metal complexes of the aromatic compounds, suitable for application in imaging, radiotherapy, medical therapy, and the treatment of cancer.

2. Description of Related Art

[0002] Metal complexes have been widely used for treating a variety of cancers, as well as for medical imaging and diagnosis, radiotherapy, and medical therapy. For example, platinum complexes, such as cisplatin and oxaliplatin, have been shown to exhibit anti-cancer activity (Kelland L. *Nature Reviews Cancer* **2007**, 7, 573-584). [Cis-1R,2R-(diaminocyclohexane)PtCl₂] was identified as having interesting activity and remarkable biological properties, but was precluded from therapeutic use due to its complete lack of solubility in water (Abu-Surrah, A.S.; Kettunen, M. *Current Medicinal Chemistry*, **2006**, 13, 1337-1357). Several derivatives of the dichloride complex have been made, but most have been abandoned during clinical trials due to moderate *in vivo* activity, side effects, chemical instability, and/or difficulties in synthesis.

[0003] Other platinum compounds, such as PtCl₃(NO₂)(NH₃)₂, have been described in, for example, (a) Chernyaev, I.I.; Muraveiskaya, G.S.; Korablina, L.S. *Russ. J. Inorg. Chem.* **1965**, 70, 158; (b) Chernyaev, I.I.; Muraveiskaya, G.S.; Korablina, L.S. *Russ. J. Inorg. Chem.* **1996**, 11, 728; (c) Chernyaev, I.I.; Leonova, T.N. *Russ. J. Inorg. Chem.* **1969**, 14, 307; (d) Turkon, J.; Zhang, S.; Palmer, J.; Kay, H.; Stanko, J.; Mora, L.B.; Sebti, S.; Yu, H.; Jove, R. *Molecular Cancer Therapeutics*, **2004**, 3, 1533; (e) US 2005/0288365; (f) US 2005/0080131; (g) US 2007/0161613; and (h) US 5,849,790. The synthesis of mononitro compounds of platinum (IV), however, has been problematic to synthesize due to side reactions resulting in numerous contaminants.

[0004] Metal complexes for biomedical imaging are widely used by physicians and

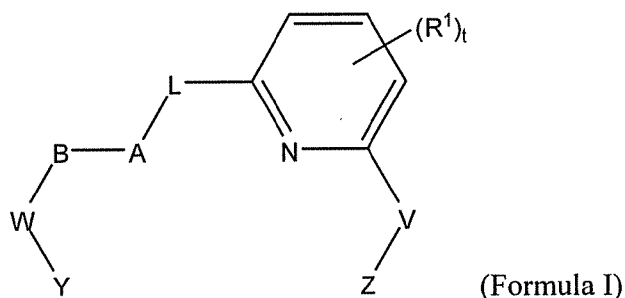
researchers to assist with the diagnosis of a disease in a subject. For example, ^{99m}Tc -EC-ESMOLOL has been used as a cardiac imaging agent (US2008/107598). Moreover, indium-labeled phospho-tyrosine antibodies (^{111}In -EC-P-Tyr) have been applied as a noninvasive functional imaging technique to assess therapeutic efficiency based on phospho-tyrosine activity in patients with a tumor (WO2008/064040).

[0005] There is a need for metal complexes that are therapeutically effective, with acceptably low toxicity that are readily synthesized, and relatively stable. There is also a need for metal complexes for use in medical imaging and diagnosis.

BRIEF SUMMARY

[0006] Provided are aromatic compounds and complexes thereof, including metal complexes that can be used in a variety of applications, such as imaging, radiotherapy, medical therapy, and the treatment of cancer.

[0007] In one embodiment, provided is an aromatic compound of Formula I:



wherein:

A is NR^f , wherein R^f is H, alkyl, or aryl;

B is a C_{1-2} alkylene substituted with at least one R^1 moiety, wherein the C_{1-2} alkylene is optionally further substituted;

L is an optionally substituted C_{1-2} alkylene; or

B and L taken together with A form an aromatic, 6-membered heterocycle substituted with at least one R^1 moiety;

each R^1 is independently $\text{XC}(=\text{O})\text{O}-\text{R}^a$, or $\text{XC}(=\text{O})\text{NR}^a\text{R}^b$;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C₁₋₃ alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

Y and Z are independently SR^c or NR^dR^e, wherein Y and Z are the same or different;

R^c is H or a C₁₋₃ alkyl;

R^d and R^e are independently H or a C₁₋₃ alkyl, wherein R^d and R^e are the same or different;

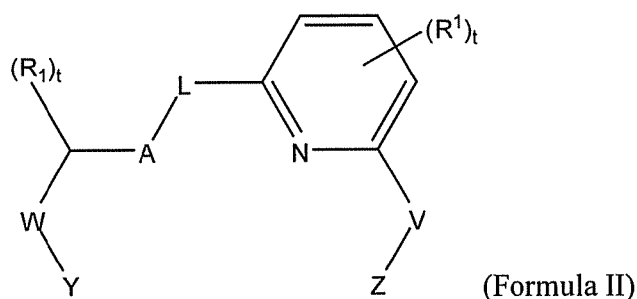
or a salt thereof or a metal complex thereof.

[0008] In some embodiments of the aromatic compound of Formula I, the targeting agent is a saccharide, lectin, receptor ligand, protein, antibody, polyether, or an amino acid polymer.

[0009] In other embodiments of the aromatic compound of Formula I, X is an optionally substituted alkyl or alkylene ether.

[0010] In other embodiments of the aromatic compound of Formula I, B and L are taken together with A to form a pyridyl substituted with at least one R¹ moiety

[0011] In another aspect, provided is an aromatic compound of Formula II:



wherein:

A is NR^f, wherein R^f is H, alkyl, or aryl;

L is an optionally substituted C₁₋₂ alkylene;

each R¹ is independently XC(=O)O-R^a, or XC(=O)NR^aR^b;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C₁₋₃ alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

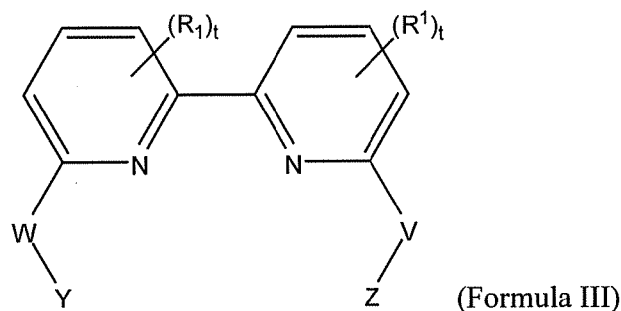
Y and Z are independently SR^c or NR^dR^e, wherein Y and Z are the same or different;

R^c is H or a C₁₋₃ alkyl;

R^d and R^e are independently H or a C₁₋₃ alkyl, wherein R^d and R^e are the same or different;

or a salt thereof or a metal complex thereof.

[0012] In yet another aspect, provided is an aromatic compound of Formula III:



wherein:

each R¹ is independently XC(=O)O-R^a, or XC(=O)NR^aR^b;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C₁₋₃ alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

Y and Z are independently SR^c or NR^dR^e, wherein Y and Z are the same or different;

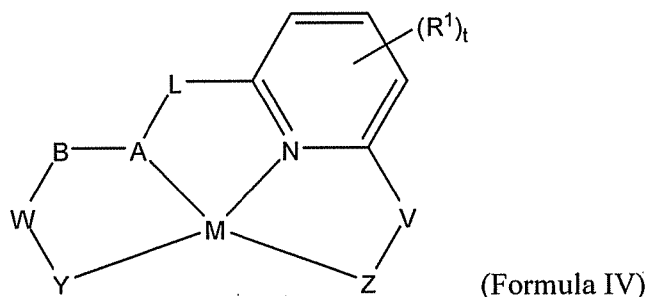
R^c is H or a C₁₋₃ alkyl;

R^d and R^e are independently H or a C₁₋₃ alkyl, wherein R^d and R^e are the same or different;

or a salt thereof or a metal complex thereof.

[0013] In another aspect, provided is a metal salt or a metal complex of a compound of Formula I, II, or III. In some embodiments of the metal complex of a compound of Formula I, II, or III, the metal complex is an oxo metal complex. For example, $^{99m}\text{Tc}=\text{O}$ may complex with the compounds of Formula I to form an oxo metal complex.

[0014] In yet another aspect, provided is a metal complex of Formula IV:



wherein:

A is N;

B is a C_{1-2} alkylene substituted with at least one R^1 moiety, wherein the C_{1-2} alkylene is optionally further substituted;

L is an optionally substituted C_{1-2} alkylene; or

B and L taken together with A form an aromatic, 6-membered heterocycle substituted with at least one R^1 moiety;

each R^1 is independently $\text{XC}(=\text{O})\text{O}-\text{R}^a$, or $\text{XC}(=\text{O})\text{NR}^a\text{R}^b$;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C_{1-3} alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are the same or different;

R^c is H or a C_{1-3} alkyl;

R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different; and

wherein M is a metal ion.

[0015] In some embodiments of the metal complex of Formula IV, the metal ion is an oxo metal ion. In some embodiments of the metal complex of Formula IV, the metal ion is a radionuclide. In other embodiments of the metal complex of Formula IV, the metal ion is a technetium ion, a copper ion, an indium ion, a thallium ion, a gallium ion, an arsenic ion, a rhenium ion, a holmium ion, a yttrium ion, a samarium ion, a selenium ion, a strontium ion, a gadolinium ion, a bismuth ion, an iron ion, a manganese ion, a lutecium ion, a cobalt ion, a platinum ion, a calcium ion, a palladium ion, or a rhodium ion. In yet other embodiments of the metal complex of Formula IV, the metal ion is a technetium ion, a platinum ion, and a palladium ion.

[0016] In yet another aspect, provided is a pharmaceutical composition including a compound of Formula I, II, or III, or the metal complex of Formula IV and a pharmaceutically acceptable excipient.

[0017] In other aspects, methods of treating a cancer in a subject are provided that include administering to a subject in need thereof an effective amount of a compound of any of Formula I, II, or III, or a metal complex of Formula IV. The cancer is, *e.g.*, breast cancer, lung cancer, prostate cancer, ovarian cancer, brain cancer, liver cancer, cervical cancer, colon cancer, renal cancer, skin cancer, head and neck cancer, bone cancer, esophageal cancer, bladder cancer, uterine cancer, lymphatic cancer, stomach cancer, pancreatic cancer, testicular cancer, lymphoma, or leukemia.

[0018] In yet other aspects, methods of imaging or diagnosing a disease in a subject are provided that include administering to a subject an effective amount of a compound of any of Formula I, II, or III, or a metal complex of Formula IV, and detecting a signal from the aromatic compound or metal complex thereof.

DESCRIPTION OF THE FIGURES

[0019] The present application can be understood by reference to the following description taken in conjunction with the accompanying figures, in which like parts may be referred to by like numerals:

[0020] FIG. 1 depicts an exemplary reaction scheme for producing a monopyridyl complex; and

[0021] FIG. 2 depicts an exemplary reaction scheme for producing a bipyridyl complex.

DETAILED DESCRIPTION

[0022] Provided are aromatic compounds and metal complexes thereof. The aromatic compounds may conjugate with suitable metal ions to form metal complexes with the aromatic compounds. In certain embodiments, the metal complexes of the aromatic compounds may exhibit some stability to de-complexation during biological processes such as the actions of enzymes or proteins, *e.g.*, transferrin. Such aromatic compounds and metal complexes thereof may be useful for cancer treatments, as well as medical therapy, imaging, and radiotherapy.

[0023] Also provided are pharmaceutical compositions comprising the aromatic compounds or metal complexes thereof, and optionally a pharmaceutically acceptable carrier. Also provided are methods of treating cancer by administering the aromatic compounds or the metal complexes thereof described herein. Also provided are methods of imaging or diagnosing a disease in a subject using the aromatic compounds or the metal complexes thereof described herein.

Abbreviations and Definitions

[0024] The term “alkyl,” by itself or as part of another substituent, means, unless otherwise stated, a fully saturated straight-chain (linear; unbranched) or branched chain, or combination thereof, having the number of carbon atoms specified, if designated (*i.e.* C₁-C₁₀ means one to ten carbons). Examples include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. If no size is designated, the alkyl groups mentioned herein may contain, for example, 1-20 carbon atoms, typically 1-10 carbon atoms, or 1-8 carbon atoms, or 1-6 carbon atoms, or 1-4 carbon atoms, or 1-3 carbon atoms.

[0025] The term “alkylene” is by itself or in combination with other terms, represents a divalent radical derived from an alkyl, as exemplified, but not limited, by -CH₂CH₂CH₂CH₂-. In some embodiments, the alkylene group is methylene or ethylene.

[0026] The term “alkenyl” refers to unsaturated aliphatic groups including straight-chain (linear; unbranched), branched-chain groups, and combinations thereof, having the number of carbon atoms specified, if designated, which contain at least one double bond (-C=C-). All double bonds may be independently either (*E*) or (*Z*) geometry, as well as mixtures thereof. Examples of alkenyl groups include, but are not limited to, $\text{-CH}_2\text{-CH=CH-CH}_3$; -CH=CH-CH=CH_2 and $\text{-CH}_2\text{-CH=CH-CH(CH}_3\text{)-CH}_2\text{-CH}_3$. If no size is designated, the alkenyl groups mentioned herein can contain, *e.g.*, 2-20 carbon atoms, typically 2-10 carbon atoms, or 2-8 carbon atoms, or 2-6 carbon atoms, or 2-4 carbon atoms. Alkenyl may be substituted or unsubstituted unless otherwise noted.

[0027] The term “alkynyl” refers to unsaturated aliphatic groups including straight-chain (linear; unbranched), branched-chain groups, and combinations thereof, having the number of carbon atoms specified, if designated, which contain at least one carbon-carbon triple bond ($\text{-C}\equiv\text{C-}$). Examples of alkynyl groups include, but are not limited to, $\text{-CH}_2\text{-C}\equiv\text{C-CH}_3$; $\text{-C}\equiv\text{C-C}\equiv\text{CH}$ and $\text{-CH}_2\text{-C}\equiv\text{C-CH(CH}_3\text{)-CH}_2\text{-CH}_3$. If no size is designated, the alkynyl groups mentioned herein can contain, *e.g.*, 2-20 carbon atoms, typically 2-10 carbon atoms, or 2-8 carbon atoms, or 2-6 carbon atoms, or 2-4 carbon atoms.

[0028] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent which can be a single ring or multiple rings (*e.g.*, from 1 to 3 rings) which are fused together or linked covalently. Additionally, aryl may contain fused rings, wherein one or more of the rings are optionally cycloalkyl or heterocycloalkyl. Examples of aryl groups include, but are not limited to, phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl.

[0029] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, *e.g.*, a fluorine, chlorine, bromine, or iodine atom.

[0030] The term “heteroalkyl” includes a branched or an unbranched hydrocarbon chain having one or more heteroatoms in between carbon atoms. Examples of heteroatoms include nitrogen, oxygen, and sulfur.

[0031] The term “heteroaryl” includes aryl groups (or rings) that contain from one to

four annular heteroatoms selected from nitrogen, oxygen, and sulfur. The nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule at an annular carbon or annular heteroatom. Additionally, heteroaryl may contain fused rings, wherein one or more of the rings are optionally cycloalkyl or heterocycloalkyl. Non-limiting examples of heteroaryl groups are 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 3-quinolyl, and 6-quinolyl.

[0032] The term “heterocycle” includes a hydrocarbon chain forming one or more rings and having one or more heteroatoms in the ring. Heteroalkyl and heterocyclic groups may be substituted for example as described for alkyl groups.

[0033] The term “heterocycloalkyl,” by itself or in combination with other terms, includes a saturated or unsaturated cyclic hydrocarbon radical containing at least one carbon atom and at least one annular heteroatom such as oxygen, nitrogen, phosphorus, silicon, and sulfur, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) oxygen, nitrogen, phosphorus, silicon, and sulfur may be placed, e.g., at any interior position of the heterocycloalkyl group or at the position at which the heterocycloalkyl group is attached to the remainder of the molecule. Examples of heterocycloalkyl include, but are not limited to, thiazolidinonyl, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0034] Each of the above terms (e.g., “alkyl,” “alkylene,” “alkenyl,” “alkynyl,” “aryl,” “cycloalkyl,” “heteroalkyl,” “heteroaryl,” “heterocycle,” and “heterocycloalkyl”) are meant to include, unless otherwise indicated, both substituted and unsubstituted forms of the stated radical.

[0035] “Optionally substituted” or “substituted” refers to the replacement of one or more hydrogen atoms with a monovalent or divalent radical. Suitable substituent groups include, for example, hydroxyl, nitro, amino, imino, cyano, halo (such as F, Cl, Br, I), haloalkyl (such as $-\text{CCl}_3$ or $-\text{CF}_3$), thio, sulfonyl, amido, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, alkoxy, alkoxy-alkyl, alkylcarbonyl, alkylcarbonyloxy ($-\text{OCOR}$), aminocarbonyl, arylcarbonyl, aralkylcarbonyl, carbonylamino, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, carbamoyl ($-\text{NHCOOR}-$ or $-\text{OCONHR}-$), urea ($-\text{NHCONHR}-$), aryl and the like.

[0036] A substituent group can itself be substituted. The group substituted onto the substitution group can be, for example, carboxyl, halo, nitro, amino, cyano, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, aminocarbonyl, $-\text{SR}$, thioamido, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{R}$ or cycloalkyl, where R is *e.g.*, a hydrogen or alkyl.

[0037] A “monodentate ligand” or variant thereof refers to a ligand which binds a metal at one site. A “bidentate ligand” or variant thereof refers to a ligand which binds a metal at two sites. A “tridentate ligand” or variant thereof refers to a ligand which binds a metal at three sites. It is understood that as used herein, a monodentate, bidentate, or tridentate ligand may contain additional atoms capable of binding the metal, but wherein the ligand binds the metal with only the indicated number of sites. For example, a ligand containing two nitrogens would be considered a monodentate ligand if only one nitrogen binds the metal, and would be considered a bidentate ligand if both nitrogens bind the metal.

[0038] As used herein, “treatment”, “treating”, or “treat” is an approach for obtaining beneficial or desired results, including clinical results. For purposes herein, beneficial or desired results include, but are not limited to, one or more of the following: decreasing one or more symptoms resulting from the disease (*e.g.*, cancer), diminishing the extent of the disease, stabilizing the disease (*e.g.*, preventing or delaying the worsening of the disease, such as cancer), delay or slowing the progression of the disease, ameliorating the disease state, decreasing the dose of one or more other medications required to treat the disease, increasing the quality of life of an individual who has been or is suspected of

having the disease, and/or prolonging survival (including overall survival and progression free survival). Also encompassed by “treatment” is a reduction of pathological consequence of cancer. The methods described herein contemplate any one or more of these aspects of treatment.

[0039] As used herein, “delaying” with respect to a condition means to defer, hinder, slow, retard, stabilize, and/or postpone development of, and/or one or more symptoms of the condition (*e.g.*, cancer). This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the condition (*e.g.*, cancer). A method that “delays” development of cancer is a method that reduces the probability of disease development in a given time frame and/or reduces the extent of the condition in a given time frame, when compared to not using the method. Such comparisons are typically based on clinical studies, using a statistically significant number of subjects. Cancer development can be detectable using standard methods, such as routine physical exams or x-ray. Development may also refer to disease progression that may be initially undetectable and includes occurrence and onset.

[0040] As used herein, an “at risk” individual with respect to a condition is an individual who is at risk of developing a condition (*e.g.*, cancer). An individual “at risk” may or may not have a detectable condition, and may or may not have displayed symptoms associated with a detectable condition prior to the treatment methods described herein. “At risk” denotes that an individual has one or more so-called risk factors, which are measurable parameters that correlate with development of the condition. An individual having one or more of these risk factors has a higher probability of developing the condition than an individual without these risk factor(s).

[0041] As used herein, “pharmaceutically acceptable” with respect to a material refers to a material that is not biologically or otherwise unsuitable, *e.g.*, the material may be incorporated (*e.g.*, at the time of manufacturing or administration) into a pharmaceutical composition administered to an individual without causing any significant undesirable biological effects or interacting in a deleterious manner with any

of the other components of the composition in which it is contained. As used herein, the term “pharmaceutically acceptable carrier,” refers to, for example, solvents, stabilizers, pH-modifiers, tonicity modifiers, adjuvants, binders, diluents, etc., known to the skilled artisan that are suitable for administration to an individual (*e.g.*, a human). Combinations of two or more carriers are also contemplated. The pharmaceutically acceptable carrier(s) and any additional components, as described herein, should be compatible for use in the intended route of administration (*e.g.*, oral, parenteral) for a particular dosage form. Such suitability will be easily recognized by the skilled artisan, particularly in view of the teaching provided herein. Pharmaceutically acceptable carriers or excipients have preferably met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug Administration.

[0042] With respect to treatment, an “effective amount,” as used herein refers to an amount that results in a desired pharmacological and/or physiological effect for a specified disease (*e.g.*, cancer) or one or more of its symptoms and/or to completely or partially prevent the occurrence or recurrence of the disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for the condition and/or adverse effect attributable to the condition (*e.g.*, cancer). In reference to conditions described herein (*e.g.*, cancer), a pharmaceutically or therapeutically effective amount may comprise an amount sufficient to, among other things, reduce the number of cancer cells; reduce the tumor size; inhibit (*i.e.*, slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (*i.e.*, slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; prevent growth and/or kill existing cancer cells; be cytostatic and/or cytotoxic; restore or maintain vasculostasis or prevention of the compromise or loss of vasculostasis; reduction of tumor burden; reduction of morbidity and/or mortality; and/or relieve to some extent one or more of the symptoms associated with the cancer. The effective amount may extend progression free survival (*e.g.*, as measured by Response Evaluation Criteria for Solid Tumors, RECIST, or CA-125 changes), result in an objective response (including a partial response or a complete response), increase overall survival time, and/or improve one or more symptoms of cancer (*e.g.*, as assessed by FOSI). In certain embodiments, the

pharmaceutically effective amount is sufficient to prevent the condition, as in being administered to an individual prophylactically. Effective amount includes the eradication or amelioration of the underlying condition being treated and/or eradication or amelioration of one or more of the symptoms associated with the underlying condition such that the individual reports an improvement in feeling or condition (*e.g.*, decreased pain intensity and/or duration), notwithstanding that the individual may still be afflicted with the underlying disease. Effective amount also includes halting or slowing the progression of the disease (*e.g.*, cancer), regardless of whether improvement or the disease or condition is realized.

[0043] The “effective amount” may vary depending on the composition being administered, the condition being treated/prevented (*e.g.*, the type of cancer), the severity of the condition being treated or prevented, the age, body size, weight, and relative health of the individual, the route and form of administration, the judgment of the attending medical or veterinary practitioner (if applicable), and other factors appreciated by the skilled artisan in view of the teaching provided herein. An effective amount may be assessed, for example, by using data from one or more clinical, physiological, biochemical, histological, electrophysiological, and/or behavioral evaluations.

[0044] As is understood in the art, an “effective amount” may be in one or more doses, *i.e.*, a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more additional pharmaceutical agents, and an aromatic compound or a metal complex of an aromatic compound as described herein may be considered to be given in an effective amount if, in conjunction with one or more additional pharmaceutical agents, one or more desirable or beneficial result(s) may be or are achieved.

[0045] When used with respect to methods of treatment/prevention and the use of aromatic compounds or metal complexes thereof and compositions thereof described herein, an individual “in need thereof” may be an individual who has been diagnosed with, previously treated for, and/or suspected of having the disease to be treated (*e.g.*, a proliferative disease such as cancer). With respect to prevention, the individual in need

thereof may also be an individual who is at risk for a condition (*e.g.*, a family history of the condition, life-style factors indicative of risk for the condition, etc.).

[0046] In some embodiments, the individual is a mammal, including, but not limited to, bovine, horse, feline, rabbit, canine, rodent, or primate. In some embodiments, the mammal is a primate. In some embodiments, the primate is a human. In some embodiments, the individual is human, including adults, children, infants, and preemies. In some embodiments, the individual is a non-mammal. In some variations, the primate is a non-human primate such as chimpanzees and other apes and monkey species. In some embodiments, the mammal is a farm animal such as cattle, horses, sheep, goats, and swine; pets such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs; and the like. In some embodiments, the individual is a non-mammal, including, but not limited to, birds, and the like. The term “individual” does not denote a particular age or sex.

[0047] As used herein, “combination therapy” means a first therapy that includes an aromatic compound or a metal complex of an aromatic compound in conjunction with a second therapy (*e.g.*, surgery and/or an additional pharmaceutical agent) useful for treating, stabilizing, preventing, and/or delaying the disease or condition. Administration in “conjunction with” another compound includes administration in the same or different composition(s), either sequentially, simultaneously, or continuously, through the same or different routes. In some embodiments, the combination therapy optionally includes one or more pharmaceutically acceptable carriers or excipients, non-pharmaceutically active compounds, and/or inert substances.

[0048] As used herein, the term “additional pharmaceutical agent,” with respect to an aromatic compound or a metal complex of an aromatic compound refers to an active agent other than the aromatic compound or the metal complex of the aromatic compound (*e.g.*, a drug or a different aromatic compound or metal complex of an aromatic compound), which is administered to elicit a therapeutic effect. The pharmaceutical agent(s) may be directed to a therapeutic effect related to the condition that aromatic compounds or metal complexes thereof are intended to treat or prevent (*e.g.*, cancer), or the pharmaceutical agent may be intended to treat or prevent a symptom of the

underlying condition (*e.g.*, tumor growth, hemorrhage, ulceration, pain, enlarged lymph nodes, cough, jaundice, swelling, weight loss, cachexia, sweating, anemia, paraneoplastic phenomena, thrombosis, etc.) or to further reduce the appearance or severity of side effects of the aromatic compound or the metal complex thereof.

[0049] Reference to “about” a value or parameter herein includes (and describes) variations that are directed to that value or parameter per se. For example, a description referring to “about Y” includes the description of “Y”.

[0050] Where linking groups are specified by their conventional chemical formula herein, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, *e.g.*, -CH₂O- is intended to also refer to -OCH₂- for this purpose only.

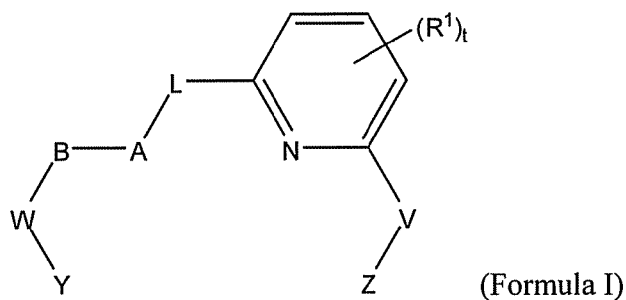
[0051] As used herein and in the appended claims, the singular forms “a,” “or,” and “the” include plural referents unless the context clearly dictates otherwise. It is understood that aspect and variations described herein include “consisting” and/or “consisting essentially of” aspects and variations.

[0052] Unless defined otherwise or clearly indicated by context, all technical and scientific terms and abbreviations used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

Aromatic Compounds

[0053] Provided are aromatic compounds which may be useful in the treatment of diseases (*e.g.*, cancer), as well as for imaging, radiotherapy, and medical therapy.

[0054] In one embodiment, provided is an aromatic compound of Formula I:



wherein:

A is NR^f , wherein R^f is H, alkyl, or aryl;
B is a C_{1-2} alkylene substituted with at least one R^1 moiety, wherein the C_{1-2} alkylene is optionally further substituted;
L is an optionally substituted C_{1-2} alkylene; or
B and L taken together with A form an aromatic, 6-membered heterocycle substituted with at least one R^1 moiety;
each R^1 is independently $\text{XC}(=\text{O})\text{O}-\text{R}^a$, or $\text{XC}(=\text{O})\text{NR}^a\text{R}^b$;
each R^a comprises a targeting agent;
each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;
X is or is not present, and if present, is a spacer group;
W and V are independently a C_{1-3} alkylene, a carbonyl, or a sulfonyl;
t is 0 to 3;
Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are the same or different;
 R^c is H or a C_{1-3} alkyl;
 R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;
or a salt thereof or a metal complex thereof.

[0055] In some embodiments of Formula I, A is NH.

[0056] In some embodiments of Formula I, B is methylene or ethylene substituted with at least one R^1 moiety. In other embodiments of Formula I, B is methylene substituted with one R^1 moiety.

[0057] In some embodiments of Formula I, L is an unsubstituted C_{1-2} alkylene, or a substituted C_{1-2} alkylene. In other embodiments of Formula I, L is an unsubstituted methylene.

[0058] In other embodiments of Formula I, B and L are taken together with A to form a pyridine substituted with at least one R^1 moiety. In yet other embodiments of Formula I, B and C are taken together with A to form a pyridine substituted with one R^1 moiety.

[0059] In some embodiments of Formula I, R^1 is $\text{XC}(=\text{O})\text{NHR}^a$.

[0060] In some embodiments of Formula I, R^a comprises a targeting agent selected from the group consisting of a saccharide, lectin, receptor ligand, protein, antibody, polyether, and an amino acid polymer. One skilled in the art would recognize that the targeting agent can be any moiety affording preferential uptake by, or localization to certain proteins, cells or organelles. In some embodiments of Formula I, R^a may be any carbohydrate that may enhance uptake by auto-proliferative cancer cells with up-regulated glycolysis. In other embodiments of Formula I, R^a is a monosaccharide.

[0061] In some embodiments of Formula I, R^b is H; an unsubstituted alkyl; a substituted alkyl; an unsubstituted aryl; a substituted aryl; an unsubstituted heteroalkyl; a substituted heteroalkyl; an unsubstituted heteroaryl; or a substituted heteroaryl.

[0062] In some embodiments of Formula I, X is an optionally substituted alkyl or alkylene ether; a substituted alkyl; a substituted alkylene ether; an unsubstituted alkyl; or an unsubstituted alkylene ether. In other embodiments of Formula I, X is not present.

[0063] In some embodiments of Formula I, W and V are independently a C_{1-3} alkylene. In other embodiments of Formula I, W and V are both methylene.

[0064] In some embodiments of Formula I, t is 0, 1, 2, or 3.

[0065] In some embodiments of Formula I, Y and Z are both SR^c , wherein R^c is H or a C_{1-3} alkyl. In other embodiments of Formula I, Y and Z are both NR^dR^e , wherein R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different. In yet other embodiments of Formula I, Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are different; R^c is H or a C_{1-3} alkyl; R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different.

[0066] In some embodiments of Formula I, the metal complex is an oxo metal complex. For example, $^{99m}\text{Tc}=\text{O}$ may complex with the compounds of Formula I to form an oxo metal complex.

[0067] In another embodiment, the compound is a compound of Formula I, wherein:

A is NH;

B is a C_{1-2} alkylene (e.g., methylene) substituted with at least one R^1 moiety; and

L is an unsubstituted C_{1-2} alkylene (e.g., methylene); or

B and L are taken together with A form an aromatic, 6-membered heterocycle (*e.g.*, pyridine) substituted with at least one R¹ moiety;
each R¹ is independently XC(=O)NR^aR^b;
each R^b is H;
X is not present;
W and V are both methylene;
t is 1;
Y and Z are SR^c;
R^c is H or a C₁₋₃ alkyl;
or a salt thereof or a metal complex thereof.

[0068] In another embodiment, the compound is a compound of Formula I, wherein:

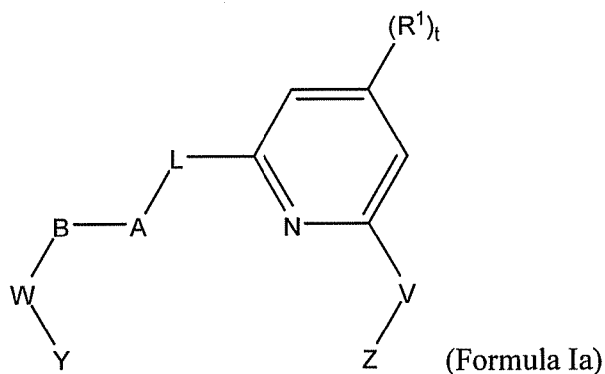
A is NH;
B is a C₁₋₂ alkylene (*e.g.*, methylene) substituted with at least one R¹ moiety; and
L is an unsubstituted C₁₋₂ alkylene (*e.g.*, methylene); or
B and L are taken together with A form an aromatic, 6-membered heterocycle (*e.g.*, pyridine) substituted with at least one R¹ moiety;
each R¹ is independently XC(=O)NR^aR^b;
each R^b is H;
X is not present;
W and V are both methylene;
t is 1;
Y and Z are NR^dR^e;
R^d and R^e are independently H or a C₁₋₃ alkyl, wherein R^d and R^e are the same or different;
or a salt thereof or a metal complex thereof.

[0069] In another embodiment, the compound is a compound of Formula I, wherein:

A is NH;
B is a C₁₋₂ alkylene (*e.g.*, methylene) substituted with at least one R¹ moiety; and
L is an unsubstituted C₁₋₂ alkylene (*e.g.*, methylene); or

B and L are taken together with A form an aromatic, 6-membered heterocycle
(*e.g.*, pyridine) substituted with at least one R^1 moiety;
each R^1 is independently $XC(=O)NR^aR^b$;
each R^b is H;
X is not present;
W and V are both methylene;
t is 1;
Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are different;
 R^c is H or a C_{1-3} alkyl;
 R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;
or a salt thereof or a metal complex thereof.

[0070] In another embodiment, provided is an aromatic compound of Formula Ia:



wherein:

A is NR^f , wherein R^f is H, alkyl, or aryl;
B is a C_{1-2} alkylene substituted with at least one R^1 moiety, wherein the C_{1-2} alkylene is optionally further substituted;
L is an optionally substituted C_{1-2} alkylene; or
B and L taken together with A form an aromatic, 6-membered heterocycle substituted with at least one R^1 moiety;
each R^1 is independently $XC(=O)O-R^a$, or $XC(=O)NR^aR^b$;
each R^a comprises a targeting agent;
each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C₁₋₃ alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

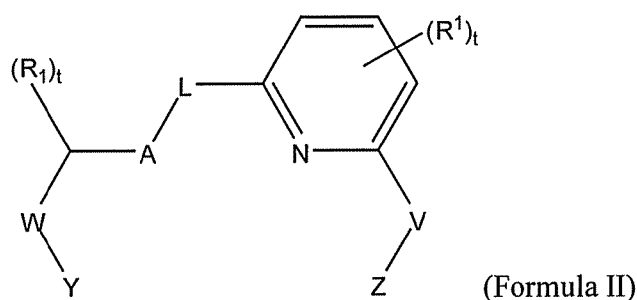
Y and Z are independently SR^c or NR^dR^e, wherein Y and Z are the same or different;

R^c is H or a C₁₋₃ alkyl;

R^d and R^e are independently H or a C₁₋₃ alkyl, wherein R^d and R^e are the same or different;

or a salt thereof or a metal complex thereof.

[0071] In another embodiment, provided is an aromatic compound of Formula II:



wherein:

A is NR^f, wherein R^f is H, alkyl, or aryl;

L is an optionally substituted C₁₋₂ alkylene;

each R¹ is independently XC(=O)O-R^a, or XC(=O)NR^aR^b;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C₁₋₃ alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

Y and Z are independently SR^c or NR^dR^e, wherein Y and Z are the same or different;

R^c is H or a C₁₋₃ alkyl;

R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;

or a salt thereof or a metal complex thereof.

[0072] In some embodiments of Formula II, A is NH.

[0073] In some embodiments of Formula II, L is an unsubstituted C_{1-2} alkylene, or a substituted C_{1-2} alkylene. In some embodiments, L is an unsubstituted methylene.

[0074] In some embodiments of Formula II, R^1 is $XC(=O)NHR^a$.

[0075] In some embodiments of Formula II, R^a comprises a targeting agent selected from the group consisting of a saccharide, lectin, receptor ligand, protein, antibody, polyether, and an amino acid polymer. In other embodiments of Formula II, R^a is a monosaccharide.

[0076] In some embodiments of Formula II, R^b is H; an unsubstituted alkyl; a substituted alkyl; an unsubstituted aryl; a substituted aryl; an unsubstituted heteroalkyl; a substituted heteroalkyl; an unsubstituted heteroaryl; or a substituted heteroaryl.

[0077] In some embodiments of Formula II, X is an optionally substituted alkyl or alkylene ether; a substituted alkyl; a substituted alkylene ether; an unsubstituted alkyl; or an unsubstituted alkylene ether. In other embodiments of Formula II, X is not present.

[0078] In some embodiments of Formula II, W and V are independently a C_{1-3} alkylene. In other embodiments of Formula II, W and V are both methylene.

[0079] In some embodiments of Formula II, t is 0, 1, 2, or 3.

[0080] In some embodiments of Formula II, Y and Z are both SR^c , wherein R^c is H or a C_{1-3} alkyl. In other embodiments of Formula II, Y and Z are both NR^dR^e , wherein R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different. In yet other embodiments of Formula II, Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are different; R^c is H or a C_{1-3} alkyl; R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different.

[0081] In some embodiments of Formula II, the metal complex is an oxo metal complex. For example, $^{99m}\text{Tc}=\text{O}$ may complex with the compounds of Formula I to form

an oxo metal complex.

[0082] In another embodiment, the compound is a compound of Formula II, wherein:

A is NH;

L is an unsubstituted C₁₋₂ alkylene (*e.g.*, methylene);

each R¹ is independently XC(=O)NR^aR^b;

each R^b is H;

X is not present;

W and V are both methylene;

t is 1;

Y and Z are SR^c;

R^c is H or a C₁₋₃ alkyl;

or a salt thereof or a metal complex thereof.

[0083] In another embodiment, the compound is a compound of Formula II, wherein:

A is NH;

L is an unsubstituted C₁₋₂ alkylene (*e.g.*, methylene);

each R¹ is independently XC(=O)NR^aR^b;

each R^b is H;

X is not present;

W and V are both methylene;

t is 1;

Y and Z are independently NR^dR^e;

R^d and R^e are independently H or a C₁₋₃ alkyl, wherein R^d and R^e are the same or different;

or a salt thereof or a metal complex thereof.

[0084] In another embodiment, the compound is a compound of Formula II, wherein:

A is NH;

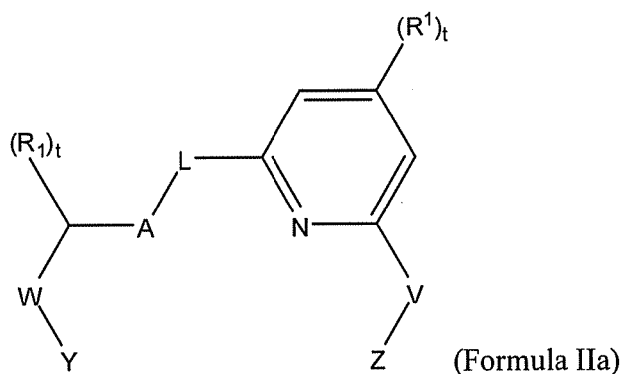
L is an unsubstituted C₁₋₂ alkylene (*e.g.*, methylene);

each R¹ is independently XC(=O)NR^aR^b;

each R^b is H;

X is not present;
 W and V are both methylene;
 t is 1;
 Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are different;
 R^c is H or a C_{1-3} alkyl;
 R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;
 or a salt thereof or a metal complex thereof.

[0085] In yet another embodiment, provided is an aromatic compound of Formula IIa:



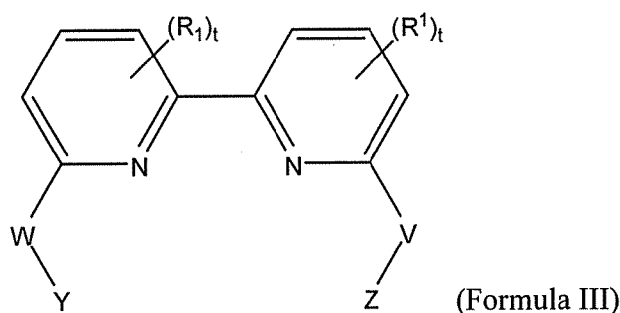
wherein:

A is NR^f , wherein R^f is H, alkyl, or aryl;
 L is an optionally substituted C_{1-2} alkylene;
 each R^1 is independently $\text{XC}(=\text{O})\text{O}-\text{R}^a$, or $\text{XC}(=\text{O})\text{NR}^a\text{R}^b$;
 each R^a comprises a targeting agent;
 each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;
 X is or is not present, and if present, is a spacer group;
 W and V are independently a C_{1-3} alkylene, a carbonyl, or a sulfonyl;
 t is 0 to 3;
 Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are the same or different;
 R^c is H or a C_{1-3} alkyl;

R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;

or a salt thereof or a metal complex thereof.

[0086] In another embodiment, provided is an aromatic compound of Formula III:



wherein:

each R^1 is independently $XC(=O)O-R^a$, or $XC(=O)NR^aR^b$;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C_{1-3} alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are the same or different;

R^c is H or a C_{1-3} alkyl;

R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;

or a salt thereof or a metal complex thereof.

[0087] In some embodiments of Formula III, R^1 is $XC(=O)NHR^a$.

[0088] In some embodiments of Formula III, R^a comprises a targeting agent selected from the group consisting of a saccharide, lectin, receptor ligand, protein, antibody, polyether, and an amino acid polymer. In other embodiments of Formula III, R^a is a monosaccharide.

[0089] In some embodiments of Formula III, R^b is H; an unsubstituted alkyl; a substituted alkyl; an unsubstituted aryl; a substituted aryl; an unsubstituted heteroalkyl; a substituted heteroalkyl; an unsubstituted heteroaryl; or a substituted heteroaryl.

[0090] In some embodiments of Formula III, X is an optionally substituted alkyl or alkylene ether; a substituted alkyl; a substituted alkylene ether; an unsubstituted alkyl; or an unsubstituted alkylene ether. In some embodiments of Formula III, X is not present.

[0091] In some embodiments of Formula III, W and V are independently a C_{1-3} alkylene. In other embodiments of Formula III, W and V are both methylene.

[0092] In some embodiments of Formula III, t is 0, 1, 2, or 3.

[0093] In some embodiments of Formula III, Y and Z are both SR^c , wherein R^c is H or a C_{1-3} alkyl. In other embodiments of Formula III, Y and Z are both NR^dR^e , wherein R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different. In yet other embodiments of Formula III, Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are different; R^c is H or a C_{1-3} alkyl; R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different.

[0094] In some embodiments of Formula III, the metal complex is an oxo metal complex. For example, $^{99m}\text{Tc}=\text{O}$ may complex with the compounds of Formula I to form an oxo metal complex.

[0095] In another embodiment, the compound is a compound of Formula III, wherein:

each R^1 is independently $\text{XC}(=\text{O})\text{NR}^a\text{R}^b$;

each R^b is H;

X is not present;

W and V are both methylene;

t is 1;

Y and Z are independently SR^c ;

R^c is H or a C_{1-3} alkyl;

or a salt thereof or a metal complex thereof.

[0096] In another embodiment, the compound is a compound of Formula III,

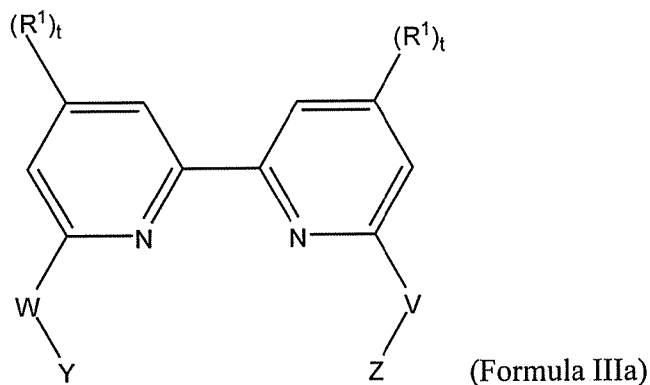
wherein:

each R^1 is independently $XC(=O)NR^aR^b$;
each R^b is H;
X is not present;
W and V are both methylene;
t is 1;
Y and Z are independently NR^dR^e ;
 R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;
or a salt thereof or a metal complex thereof.

[0097] In another embodiment, the compound is a compound of Formula III,
wherein:

each R^1 is independently $XC(=O)NR^aR^b$;
each R^b is H;
X is not present;
W and V are both methylene;
t is 1;
Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are different;
 R^c is H or a C_{1-3} alkyl;
 R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;
or a salt thereof or a metal complex thereof.

[0098] In another embodiment, provided is an aromatic compound of Formula IIIa:



wherein:

each R^1 is independently $XC(=O)O-R^a$, or $XC(=O)NR^aR^b$;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C_{1-3} alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

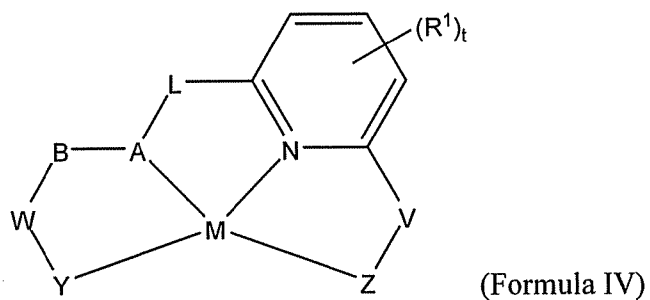
Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are the same or different;

R^c is H or a C_{1-3} alkyl;

R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;

or a salt thereof or a metal complex thereof.

[0099] Also provided is a metal complex of Formula IV:



wherein:

A is N;

B is a C₁₋₂ alkylene substituted with at least one R¹ moiety, wherein the C₁₋₂ alkylene is optionally further substituted;

L is an optionally substituted C₁₋₂alkylene; or

B and L taken together with A form an aromatic, 6-membered heterocycle substituted with at least one R¹ moiety;

each R¹ is independently XC(=O)O-R^a, or XC(=O)NR^aR^b;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C₁₋₃ alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

Y and Z are independently SR^c or NR^dR^e, wherein Y and Z are the same or different;

R^c is H or a C₁₋₃ alkyl;

R^d and R^e are independently H or a C₁₋₃ alkyl, wherein R^d and R^e are the same or different; and

wherein M is a metal ion.

[0100] In some embodiments of Formula IV, B is methylene or ethylene substituted with at least one R¹ moiety. In some embodiments of Formula IV, B is methylene substituted with one R¹ moiety.

[0101] In some embodiments of Formula IV, L is an unsubstituted C₁₋₂alkylene, or a substituted C₁₋₂alkylene. In other embodiments, L is an unsubstituted methylene.

[0102] In some embodiments of Formula IV, B and L are taken together with A to form a pyridine substituted with at least one R¹ moiety. In other embodiments of Formula IV, B and L are taken together with A to form a pyridine substituted with one R¹ moiety.

[0103] In some embodiments of Formula IV, R¹ is XC(=O)NHR^a.

[0104] In some embodiments of Formula IV, R^a comprises a targeting agent selected from the group consisting of a saccharide, lectin, receptor ligand, protein, antibody,

polyether, and an amino acid polymer. In other embodiments of Formula IV, R^a is a monosaccharide.

[0105] In some embodiments of Formula IV, R^b is H; an unsubstituted alkyl; a substituted alkyl; an unsubstituted aryl; a substituted aryl; an unsubstituted heteroalkyl; a substituted heteroalkyl; an unsubstituted heteroaryl; or a substituted heteroaryl.

[0106] In some embodiments of Formula IV, X is an optionally substituted alkyl or alkylene ether; a substituted alkyl; a substituted alkylene ether; an unsubstituted alkyl; or an unsubstituted alkylene ether. In other embodiments of Formula IV, X is not present.

[0107] In some embodiments of Formula IV, W and V are independently a C₁₋₃ alkylene. In other embodiments of Formula IV, W and V are both methylene.

[0108] In some embodiments of Formula IV, t is 0, 1, 2, or 3.

[0109] In some embodiments of Formula IV, Y and Z are both SR^c, wherein R^c is H or a C₁₋₃ alkyl. In other embodiments of Formula IV, Y and Z are both NR^dR^e, wherein R^d and R^e are independently H or a C₁₋₃ alkyl, wherein R^d and R^e are the same or different. In yet other embodiments of Formula IV, Y and Z are independently SR^c or NR^dR^e, wherein Y and Z are different; R^c is H or a C₁₋₃ alkyl; R^d and R^e are independently H or a C₁₋₃ alkyl, wherein R^d and R^e are the same or different.

[0110] In some embodiments of Formula IV, M is a technetium ion, a platinum ion, and a palladium ion. In other embodiments of Formula IV, M is an oxo metal ion. For example, M may be ^{99m}Tc=O that forms an oxo metal complex. It should be recognized that dative bonds may exist in forming the metal complex of Formula IV.

[0111] In another embodiment, the complex is a metal complex of Formula IV, wherein:

B is a C₁₋₂ alkylene (*e.g.*, methylene) substituted with at least one R¹ moiety; and

L is an unsubstituted C₁₋₂ alkylene (*e.g.*, methylene); or

B and L are taken together with A form an aromatic, 6-membered heterocycle (*e.g.*, pyridine) substituted with at least one R¹ moiety;

each R¹ is independently XC(=O)NR^aR^b;

each R^b is H;

X is not present;
W and V are both methylene;
t is 1;
Y and Z are independently SR^c ;
 R^c is H or a C_{1-3} alkyl;
wherein M is a metal ion.

[0112] In another embodiment, the complex is a metal complex of Formula IV, wherein:

B is a C_{1-2} alkylene (*e.g.*, methylene) substituted with at least one R^1 moiety; and
L is an unsubstituted C_{1-2} alkylene (*e.g.*, methylene); or
B and L are taken together with A form an aromatic, 6-membered heterocycle (*e.g.*, pyridine) substituted with at least one R^1 moiety;
each R^1 is independently $XC(=O)NR^aR^b$;
each R^b is H;
X is not present;
W and V are both methylene;
t is 1;
Y and Z are independently NR^dR^e ;
 R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different; and
wherein M is a metal ion.

[0113] In another embodiment, the complex is a metal complex of Formula IV, wherein:

B is a C_{1-2} alkylene (*e.g.*, methylene) substituted with at least one R^1 moiety; and
L is an unsubstituted C_{1-2} alkylene (*e.g.*, methylene); or
B and L are taken together with A form an aromatic, 6-membered heterocycle (*e.g.*, pyridine) substituted with at least one R^1 moiety;
each R^1 is independently $XC(=O)NR^aR^b$;
each R^b is H;
X is not present;

W and V are both methylene;

t is 1;

Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are different;

R^c is H or a C_{1-3} alkyl;

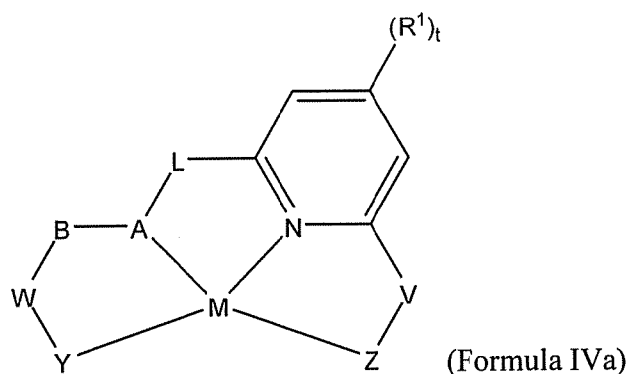
R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different; and

wherein M is a metal ion.

[0114] In some embodiments of Formula IV, M is selected from the group consisting of Tc, Re, Ga, In, Bi, Cu, Pd, and Pt. In other embodiments of Formula IV, M is selected from the group consisting of $^{99\text{m}}\text{Tc}$, ^{186}Re , ^{188}Re , ^{67}Ga , ^{68}Ga , ^{111}In , ^{212}Bi , ^{60}Cu , ^{61}Cu , ^{64}Cu , ^{62}Cu , ^{103}Pd , and $^{195\text{m}}\text{Pt}$. In a preferred embodiment, M is $^{99\text{m}}\text{Tc}$, ^{186}Re , ^{188}Re , ^{103}Pd or $^{195\text{m}}\text{Pt}$. In another preferred embodiment, M is $^{99\text{m}}\text{Tc}$, ^{103}Pd or $^{195\text{m}}\text{Pt}$. Without being bound by any theory, it is possible that the π covalent capability of the aromatic nitrogen donor atoms in contrast to the σ covalent character of the aliphatic nitrogen donor atoms of aliphatic amines (like ethylenediamine) are suitable for complexing with the higher oxidation states of 4d and 5d transition elements like technetium(V) and rhenium(V). In another preferred embodiment, M is ^{103}Pd or $^{195\text{m}}\text{Pt}$. Without being bound by any theory, it is possible that divalent palladium and platinum bonds strongly to the aromatic compounds described herein, in view of the enhanced covalent potential of the aromatic nitrogen atoms and the large nephelauxetic capability of these transition metal ions.

[0115] The metal ion may be any radionuclide. The radionuclides used herein may occur naturally, but can also be artificially produced. Radionuclides may be either therapeutic or diagnostic. Radionuclides for diagnostic imaging often include gamma emitters (e.g., $^{99\text{m}}\text{Tc}$), and radionuclides for therapeutic purposes often include alpha emitters (e.g., ^{225}Ac) and beta emitters (e.g., ^{90}Y). Examples of other radionuclides include, but are not limited to, ^{96}Tc , ^{95}Tc , ^{192}Ir , ^{225}Ac , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{149}Pm , ^{90}Y , ^{212}Bi , ^{109}Pd , ^{159}Gd , ^{140}La , ^{198}Au , ^{199}Au , ^{169}Yb , ^{175}Yb , ^{165}Dy , ^{166}Dy , ^{123}I , ^{131}I , ^{67}Cu , ^{105}Rh , ^{111}Ag , and ^{192}Ir .

[0116] Also provided is a metal complex of Formula IVa:



wherein:

A is N;

B is a C₁₋₂ alkylene substituted with at least one R¹ moiety, wherein the C₁₋₂ alkylene is optionally further substituted;

L is an optionally substituted C₁₋₂alkylene; or

B and L taken together with A form an aromatic, 6-membered heterocycle substituted with at least one R¹ moiety;

each R¹ is independently XC(=O)O-R^a, or XC(=O)NR^aR^b;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C₁₋₃ alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

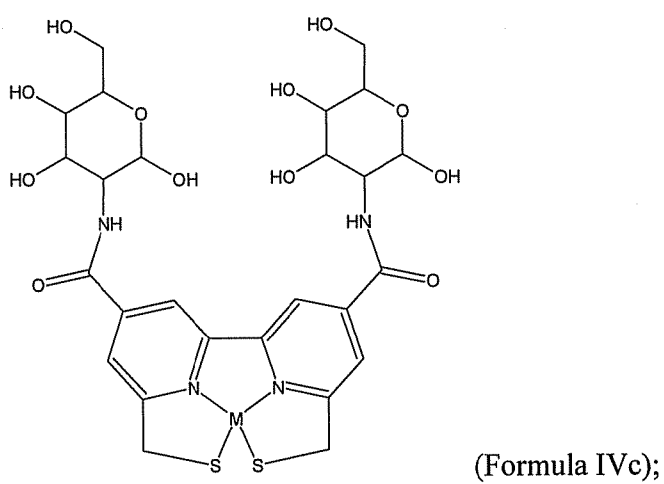
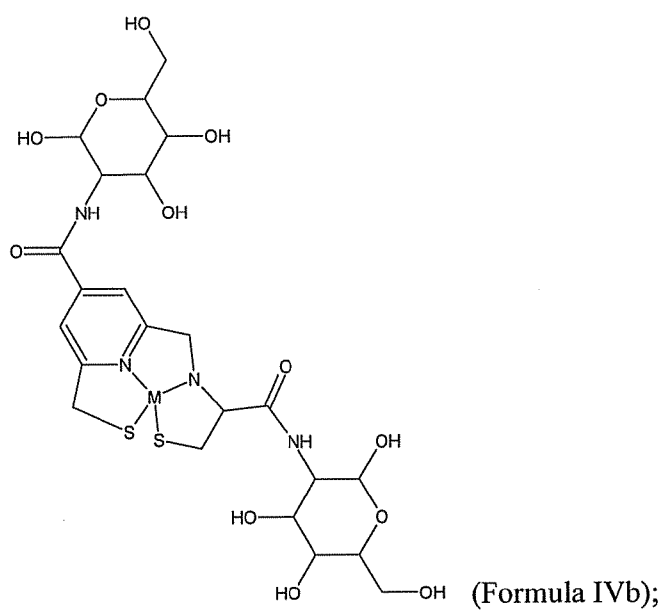
Y and Z are independently SR^c or NR^dR^e, wherein Y and Z are the same or different;

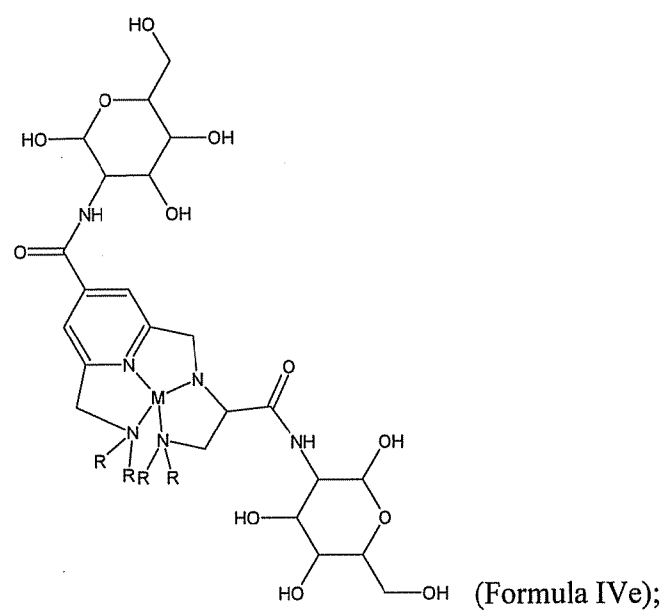
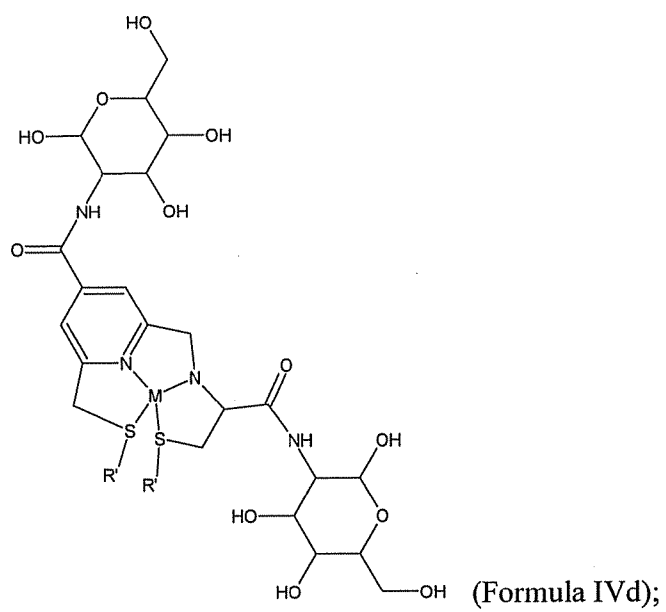
R^c is H or a C₁₋₃ alkyl;

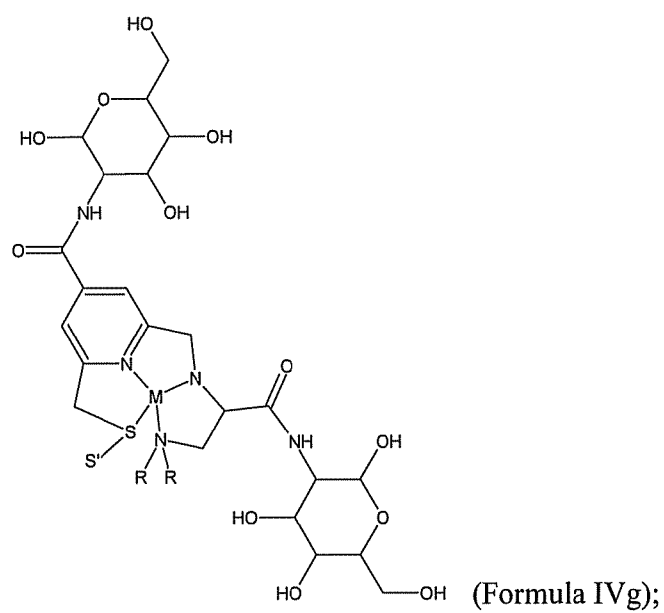
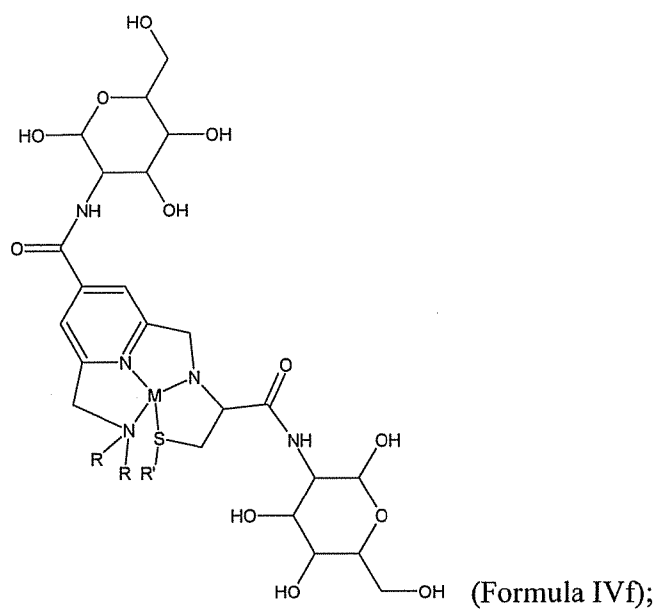
R^d and R^e are independently H or a C₁₋₃ alkyl, wherein R^d and R^e are the same or different; and

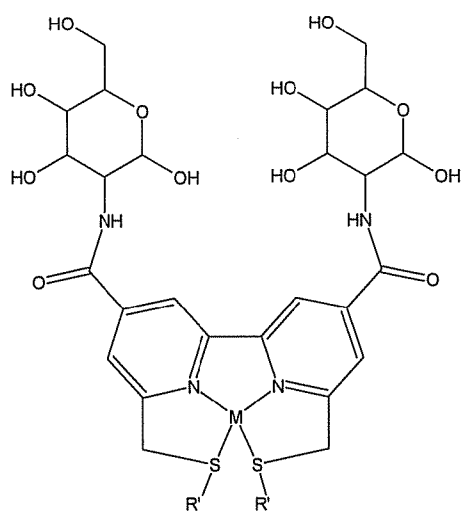
wherein M is a metal ion.

[0117] In some embodiments, the metal complex is of one of the following formulas:

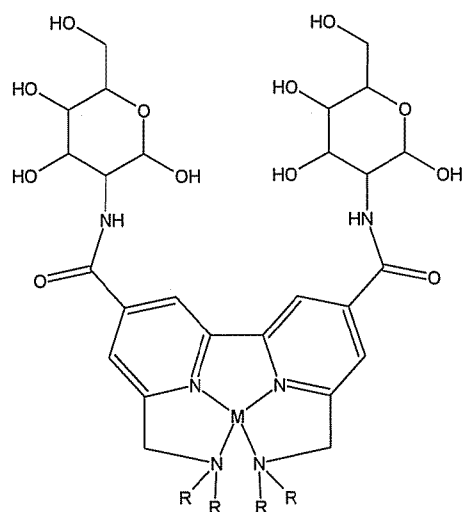




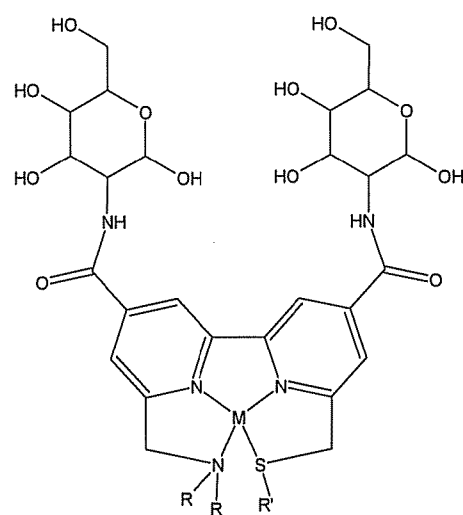




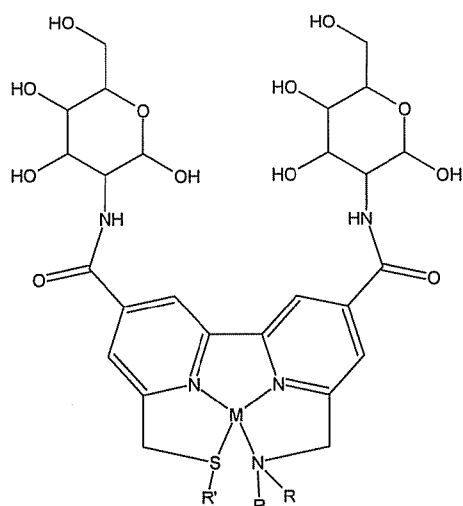
(Formula IVh);



(Formula IVi);



(Formula IVj); or

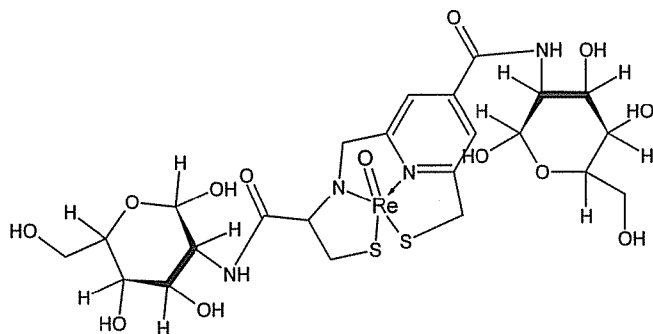


(Formula IVk),

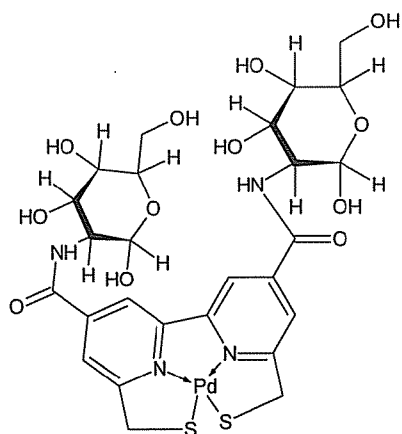
wherein M is a metal ion, such as ^{99m}Tc , ^{186}Re , ^{188}Re , ^{67}Ga , ^{68}Ga , ^{111}In , ^{212}Bi , ^{60}Cu , ^{61}Cu , ^{64}Cu , ^{62}Cu , ^{103}Pd , or ^{195}Pt .

[0118] Also included are aromatic compounds in uncomplexed form of Formulae IVa-k.

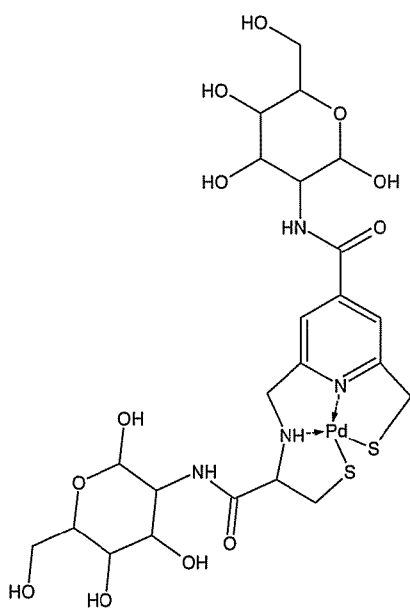
[0119] For example, the metal complexes are:



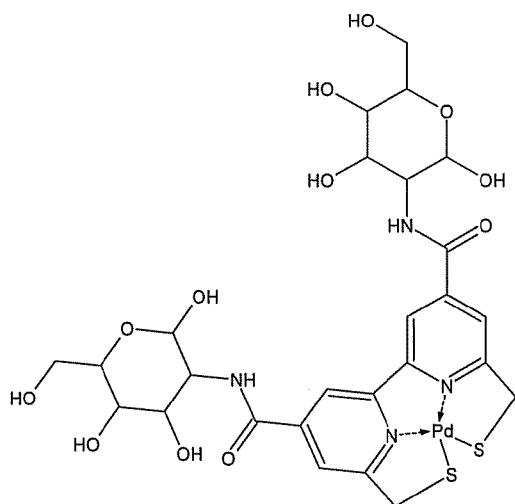
(1);



(2);



(3); or



(4).

[0120] Also included are aromatic compounds in uncomplexed form of Compounds (1)-(4).

Advantages and Properties of the Compounds

[0121] The aromatic compounds and metal complexes thereof provided herein offer in some embodiments advantages over metal complexes known in the art, for example in diagnostic and therapeutic applications. For example, aromatic compounds may be soluble in water, yet selective in their interactions. Without being bound by theory, aromatic interactions have been proposed to consist of Van der Waals, hydrophobic and electrostatic forces (Hunter CA, Lawson KR, Perkins J, Urch CJ: Aromatic interactions, *J. Chem Soc Perkin Trans*, 2001:651-669). The relative contribution and magnitude of each of these components are influenced by the fact that aromatic groups interact in one of several geometries, depending on the nature of the rings involved. As a result, aromatic interactions have the ability to be strong in water due to the hydrophobic component of the interaction, yet selective if the electrostatic component is significant (Waters, ML: Aromatic interactions in model systems, *Current Opinion in Chemical Biology*, 2002, 6:736-741).

[0122] The planar aromatic nature of these chelates and their associated capability to be involved in π/π interactions with the heteroaromatic nuclear bases of DNA contributes to their biocompatibility and selectivity. For example, the neutral planar N_2S_2 complexes

of Pd are thermodynamically and kinetically stable, thus making these metal complexes useful targeting chelate complexes for application with radio-active Pd(II) or Pt(II).

[0123] Furthermore, the aromatic compounds and salts thereof in some embodiments may be sufficiently stable when complexed with a metal ion to withstand de-complexation during biological processes, such as the actions of enzymes or proteins. Without wishing to be bound by theory, it is possible that the stability of these aromatic compounds is achieved when bonded to soft metal ions, such as the later 3d, 4d and 5d transition metal ions. This stability can result from the presence of the nitrogen and sulfur donor atoms on the aromatic rings, and the aliphatic substituents extending from aromatic rings. The advantageous properties of aromatic compounds coupled with the targeting potential of glucose derivatives contribute towards the usefulness of the metal complexes described herein for cancer imaging.

Method of Making Compounds and Complexes

[0124] The aromatic compounds and metal complexes provided herein can be made using methods known in the art and as described herein, *e.g.*, in the Examples. FIG. 1 depicts an exemplary embodiment of a method to make a monopyridyl Re complex, and FIG. 2 depicts an exemplary embodiment of a method to make a bipyridyl Pd complex. It should be recognized, however, that the substituents of the starting materials may vary depending on the aromatic compound to be synthesized. Moreover, the metal reagents may vary depending on the metal complex to be synthesized from the aromatic compounds.

Formulations

[0125] Provided are formulations including the aromatic compounds or metal complexes thereof described herein (*e.g.*, an aromatic compound of Formula I, II, or III, or metal complex of Formula IV), such as pharmaceutically acceptable formulations comprising a pharmaceutical acceptable carrier. The formulations may include, *e.g.*, excipients, stabilizing agents and/or other agents known in the art. These formulations may be used in a variety of therapeutic methods of administration, and dosage regimes such as those described herein.

[0126] The formulations may vary or be tailored according to the condition to be treated, the amount of compound or complex to be administered, the condition of the individual, and other variables that will readily be apparent to one of ordinary skill in the art in view of the teachings provided herein. The aromatic compounds or metal complexes thereof may be formulated, for example, as a solid, semi-solid, and liquid dosage forms, such as tablets, pills, powders, liquid solutions or suspensions, suppositories, injectable and infusible solutions, and sprays. The preferred form depends on the intended mode of administration and therapeutic application. The following formulations, additives, and methods are merely exemplary and are in no way limiting.

[0127] Additives include, for example, one or more excipients (*e.g.*, one or more excipients), antioxidants (*e.g.*, one or more antioxidants), stabilizers (*e.g.*, one or more stabilizers), preservatives (*e.g.*, one or more preservatives), pH adjusting and buffering agents (*e.g.*, one or more pH adjusting and/or buffering agents), tonicity adjusting agents (*e.g.*, one or more tonicity adjusting agents), thickening agents (*e.g.*, one or more thickening agents), suspending agents (*e.g.*, one or more suspending agents), binding agents (*e.g.*, one or more binding agents), viscosity-increasing agents (*e.g.*, one or more viscosity-increasing agents), and the like, either alone or together with one or more additional pharmaceutical agents, provided that the additional components are pharmaceutically acceptable for the particular disease to be treated (*e.g.*, cancer). In some embodiments, the formulation may include combinations of two or more of the additional components as described herein (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more additional components). In some embodiments, the additives include processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-*beta*-cyclodextrin, polyvinylpyrrolidinone, low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more thereof. Other suitable pharmaceutically acceptable excipients are described in REMINGTON'S PHARMACEUTICAL SCIENCES, Mack Pub. Co., New Jersey 18th edition (1996), and REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, Lippincott Williams & Wilkins, Philadelphia, 20th edition (2003) and 21st edition (2005).

[0128] Formulations suitable for oral administration may include, for example, (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice, (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as solids or granules, (c) suspensions in an appropriate liquid, (d) suitable emulsions, and (e) powders. Tablet forms can include one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible excipients. Lozenge forms may include the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles including the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such excipients as are known in the art.

[0129] The aromatic compounds or metal complexes thereof, or formulations thereof, can be enclosed in a hard or soft capsule, can be compressed into tablets, or can be incorporated with beverages or food or otherwise incorporated into the diet. Capsules can be formulated by mixing the aromatic compounds or metal complexes thereof with an inert pharmaceutical diluent and inserting the mixture into a hard gelatin capsule of the appropriate size. If soft capsules are desired, a slurry of the aromatic compound or metal complex thereof with an acceptable vegetable oil, light petroleum or other inert oil can be encapsulated by machine into a gelatin capsule.

[0130] Formulations suitable for parenteral administration include aqueous and nonaqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation compatible with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizing agents, and preservatives. The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient methods of treatment, methods of administration, and dosage regimes described herein (*i.e.*, water) for injection,

immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0131] Formulation in liquid form (for oral administration, parenteral administration, or otherwise) may have a pH in the range of about 4.5 to about 9.0, including for example pH ranges of any of about 5.0 to about 8.0, about 6.5 to about 7.5, and about 6.5 to about 7.0. In some embodiments, the pH of the composition is formulated to no less than about 6, including for example no less than about any of 6.5, 7, or 8 (*e.g.*, about 8). The formulation can also be made to be isotonic with blood by the addition of a suitable tonicity modifier, such as glycerol.

[0132] Also provided are unit dosage forms including the formulations described herein. These unit dosage forms can be stored in a suitable packaging in single or multiple unit dosages and may also be further sterilized and sealed. For example, the pharmaceutical formulation (*e.g.*, a dosage or unit dosage form of a pharmaceutical formulation) may include (i) an aromatic compound or a metal complex of an aromatic compound (*e.g.*, any aromatic compound of Formula I, II, or III, or any metal complex of Formula IV) and (ii) a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical formulation also includes one or more other compounds (or pharmaceutically acceptable salts thereof) that are useful for treating cancer. In various variations, the amount of aromatic compound or metal complex of the aromatic compound in the formulation is included in any of the following ranges; about 5 to about 50 mg, about 20 to about 50 mg, about 50 to about 100 mg, about 100 to about 125 mg, about 125 to about 150 mg, about 150 to about 175 mg, about 175 to about 200 mg, about 200 to about 225 mg, about 225 to about 250 mg, about 250 to about 300 mg, about 300 to about 350 mg, about 350 to about 400 mg, about 400 to about 450 mg, or about 450 to about 500 mg. In some embodiments, the amount of aromatic compound or metal complex of the aromatic compound in the formulation (*e.g.*, a dosage or unit dosage form) is in the range of about 5 mg to about 500 mg, such as about 30 mg to about 300 mg or about 50 mg to about 200 mg, of the aromatic compound or metal complex of the aromatic compound. In some embodiments, the carrier is suitable for parental administration (*e.g.*, intravenous administration). In some embodiments, the aromatic

compounds or metal complexes thereof described herein is the only pharmaceutically active agent for imaging or the treatment of cancer that is contained in the formulation.

[0133] Some embodiments provide dosage forms (*e.g.*, a unit dosage form) for imaging or the treatment of cancer including (i) an aromatic compound or a metal complex of an aromatic compound (*e.g.*, any aromatic compound of Formula I, II, or III, or any metal complex of Formula IV), wherein the amount of compound or metal complex in the unit dosage form is in the range of about 5 mg to about 500 mg, and (ii) a pharmaceutically acceptable carrier. In some embodiments, the amount of aromatic compound or metal complex of an aromatic compound in the unit dosage form includes about 30 mg to about 300 mg.

Kits

[0134] Also provided are kits containing materials useful for the treatment of a disease that is responsive to the aromatic compounds or metal complexes thereof (*e.g.*, cancer). The kits may contain an aromatic compound or a metal complex thereof (*e.g.*, any aromatic compound of Formula I, II, or III, or any metal complex of Formula IV) and optionally contain instructions for use (*e.g.*, instructions for preparation and/or administration of a formulation including an aromatic compound or a metal complex of an aromatic compound). Information detailing possible side effects of the formulation, and any other relevant information may also be enclosed. The instructions may be in any suitable format, including, but not limited to, printed matter, videotape, computer readable disk, optical disc or directions to internet-based instructions.

[0135] One aspect of the present disclosure provides a kit for treating an individual who suffers from or is susceptible to the disease or conditions described herein, including a first container including a dosage amount of a formulation as disclosed herein, and instructions for use. The container may be any of those known in the art and appropriate for storage and delivery of intravenous formulation. In certain embodiments the kit further includes a second container including a pharmaceutically acceptable carrier, diluent, adjuvant, etc. for preparation of the formulation to be administered to the individual.

[0136] In some embodiments, the kits include a container with a label. Suitable containers include, for example, bottles, vials, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The containers may hold an aromatic compound or a metal complex of an aromatic compound or a formulation of an aromatic compound or a metal complex of an aromatic compound (*e.g.*, a formulation including an aromatic compound or a metal complex of an aromatic compound, and further including one or more additional pharmaceutical agents). The label on the container may indicate that the aromatic compound or the metal complex of the aromatic compound or the formulation is used for treating or suppressing a condition that is responsive to the aromatic compound or metal complex of the aromatic compound (*e.g.*, cancer), and may also indicate directions for either *in vivo* or *in vitro* use, such as those described herein.

[0137] The kit may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for performing any methods described herein. In some embodiments, the kit includes the container described above and a second container including a buffer.

[0138] The kits may include additional pharmaceutical agents for use in conjunction with the formulation described herein. In some variations, the additional pharmaceutical agent(s) may be one or more anticancer drug(s). These agents may be provided in a separate form, or mixed with the aromatic compounds or metal complexes thereof described herein, provided such mixing does not reduce the effectiveness of either the pharmaceutical agent or formulation described herein and is compatible with the route of administration. Similarly the kits may include additional agents for adjunctive therapy or other agents known to the skilled artisan as effective in the treatment or prevention of the conditions described herein.

[0139] Kits may also be provided that contain sufficient dosages of the compounds described herein (including formulations thereof) to provide effective treatment for an individual for an extended period, such as 1-3 days, 1-5 days, a week, 2 weeks, 3, weeks,

4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months or more.

[0140] The kits may include the composition as described herein packaged in either a unit dosage form or in a multi-use form. The kits may also include multiple units of the unit dose form. The kits may be used for any of the methods described herein, including, for example, to treat an individual with cancer, or to delay cancer. In certain embodiments the kits may include a dosage amount of at least one formulation as disclosed herein. Kits may also include a means for the delivery of the formulation thereof.

Methods of Treatment

[0141] The aromatic compounds and metal complexes thereof described herein may be used to treat a variety of diseases, such as those associated with cellular proliferation or hyperproliferation (*e.g.*, cancer). Provided in one embodiment is a method of treating a cancer in a subject by administering to a subject in need thereof an effective amount of an aromatic compound or metal complex thereof (*e.g.*, an aromatic compound of Formula I, II, or III, or a metal complex of Formula IV), or pharmaceutically acceptable formulation thereof. In some embodiments are provided methods of delaying a proliferative disease (*e.g.*, cancer) in an individual, by administering to the individual an effective amount of the aromatic compounds or metal complex thereof described herein, or pharmaceutically acceptable formulation thereof.

[0142] The aromatic compounds or metal complexes thereof described herein may be used to inhibit and/or delay cell proliferation. In some embodiments, methods are provided of inhibiting and/or delaying cell proliferation (*e.g.* in an individual) by contacting the cells with an aromatic compound or a metal complex thereof (*e.g.*, any aromatic compound of Formula I, II, or III, or any metal complex of Formula IV). In some embodiments, the cell proliferation is undesirable cell proliferation (*e.g.*, cancer cell proliferation).

[0143] In some embodiments, the cancer includes one or more of breast cancer, lung cancer, prostate cancer, ovarian cancer, brain cancer, liver cancer, cervical cancer, colon cancer, renal cancer, skin cancer, head and neck cancer, bone cancer, esophageal cancer,

bladder cancer, uterine cancer, lymphatic cancer, stomach cancer, pancreatic cancer, testicular cancer, lymphoma, and leukemia. Other examples of cancers that may be treated, inhibited, and/or delayed by the methods described herein include, but are not limited to, multiple myeloma, melanoma, colorectal cancer, and gastric cancer.

[0144] In some variations, the individual being treated for a proliferative disease has been identified as having one or more of the conditions described herein. Identification of the conditions as described herein by a skilled physician is routine in the art (*e.g.*, via blood tests, X-rays, CT scans, endoscopy, biopsy, etc.) and may also be suspected by the individual or others, for example, due to tumor growth, hemorrhage, ulceration, pain, enlarged lymph nodes, cough, jaundice, swelling, weight loss, cachexia, sweating, anemia, paraneoplastic phenomena, thrombosis, etc. In some embodiments, the individual has been identified as susceptible to one or more of the conditions as described herein. The susceptibility of an individual may be based on any one or more of a number of risk factors and/or diagnostic approaches appreciated by the skilled artisan, including, but not limited to, genetic profiling, family history, medical history (*e.g.*, appearance of related conditions), lifestyle or habits.

[0145] In some embodiments, the methods and/or compositions used herein reduce the severity of one or more symptoms associated with proliferative disease (*e.g.*, cancer) by at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% compared to the corresponding symptom in the same individual prior to treatment or compared to the corresponding symptom in other individuals not receiving the methods and/or compositions.

Combination Therapy

[0146] The aromatic compounds or metal complexes thereof described herein (*e.g.*, any aromatic compound of Formula I, II, or III, or any metal complex of Formula IV) may be formulated and/or administered in conjunction with one or more additional pharmaceutical agents, as described herein and as known in the art, including one or more additional pharmaceutical agents to further reduce the occurrence and/or severity of symptoms and/or clinical manifestations thereof, as well as additional pharmaceutical agents that treat or prevent the underlying conditions, and/or in conjunction with (*e.g.*,

prior to, concurrently with, or after) additional treatment modalities. As used herein, the term “additional treatment modality” refers to treatment/prevention of the conditions described herein without the use of a pharmaceutical agent (*e.g.*, surgery, radiotherapy, etc.). Where combinations of pharmaceutical agent(s) and/or additional treatment modality(ies) are used, they may be, independently, administered prior to, concurrently with, or after administration of one or more of the aromatic compounds or metal complexes thereof (or formulation(s) thereof) as described herein.

[0147] In some embodiments, the aromatic compounds or metal complexes thereof described herein (*e.g.*, any aromatic compound of Formula I, II, or III, or any metal complex of Formula IV) may be used in combination with one or more additional pharmaceutical agents. The aromatic compound or metal complex thereof may also be administered in conjunction with (*e.g.*, prior to, concurrently with, or after) agents to alleviate the symptoms associated with either the disease or the treatment regimen. Representative additional pharmaceutical agents include anticancer agents, pre-medication (*e.g.*, corticosteroids, such as dexamethasone, prednisone, prednisolone, etc.), anti-emetics (*e.g.*, antihistamines, such as diphenhydramine), selective 5HT₃ receptor antagonists (*e.g.* ondansetron), and H₂-receptor antagonists (*e.g.*, cimetidine, ranitidine). Examples of anticancer agents contemplated for combination with the aromatic compounds or metal complexes thereof include, but are not limited to, other platinum-based anti-cancer compounds (*e.g.*, cisplatin, oxaliplatin, carboplatin); vinblastine and/or bleomycin (with or without cisplatin); pemetrexed (as pemetrexed disodium; with or without cisplatin); topotecan (as hydrochloride; with or without cisplatin); paclitaxel (with or without cisplatin); docetaxel (with or without cisplatin); docetaxel (with or without cisplatin); 5-fluorouracil (with or without cisplatin); and capecitabine (with or without another platinum-based regimen, such as cisplatin).

[0148] The above additional pharmaceutical agents (*e.g.*, anticancer agents) administered with one or more of the aromatic compounds or metal complexes thereof described herein (*e.g.*, any aromatic compound of Formula I, II, or III, or any metal complex of Formula IV) can be administered at the recommended maximum clinical dosage or at lower doses, such as those indicated in the Physicians' Desk Reference (PDR) 53rd Edition (1999), or at such therapeutically useful amounts as would be known

to one of ordinary skill in the art. Dosage levels of the additional pharmaceutical agents in the formulations may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the characteristics and response of the patient. When administered as a combination, the aromatic compounds or metal complexes thereof can be formulated as separate formulations, which are given at the same time or different times, or the aromatic compounds or metal complexes thereof can be given with the additional pharmaceutical agent as a single formulation.

[0149] In some embodiments, are provided methods of treating cancer in an individual by administering to the individual an effective amount of a combination of a) a first therapy that comprises an aromatic compound or a metal complex of an aromatic compound described herein, and b) a second therapy useful for treating cancer. In some embodiments, the second therapy includes surgery, radiation, gene therapy, immunotherapy, bone marrow transplantation, stem cell transplantation, hormone therapy, targeted therapy, cryotherapy, ultrasound therapy, and/or photodynamic therapy. It is understood that reference to and description of methods of treating cancer herein is exemplary and that this description applies equally to and includes methods of treating cancer using combination therapy.

[0150] The optimal combination of one or more additional pharmaceutical agents and/or one or more additional treatment modalities in conjunction with administration of the aromatic compounds or metal complexes thereof described herein can be determined by an attending physician or veterinarian based on the individual and taking into consideration the various factors effecting the particular individual, including those described herein.

Dosing and Methods of Administration

[0151] The amount of the aromatic compound or metal complex of the aromatic compound administered to an individual (such as a human) may vary with the particular formulation, the method of administration, and the particular type of recurrent cancer being treated, and should be sufficient to produce a desirable beneficial effect. The amount administered in order to achieve an effective amount will depend upon a variety

of factors, including, for example, the particular condition being treated, the frequency of administration, the particular formulation being administered, the severity of the condition being treated and the age, weight and general health of the individual, the adverse effects experienced by the individual being treated, etc. A pharmaceutical unit dosage chosen may be fabricated and administered to provide a defined final concentration of drug in the blood, tissues, organs, or other targeted region of the body. Determination of an effective amount for a given situation can be readily determined by routine experimentation (*e.g.*, using *in vivo* animal models) and is within the skill and judgment of the ordinary clinician, particularly in view of the teachings provided herein.

[0152] In some embodiments, the amount of the aromatic compound or metal complex of the aromatic compound is effective to result in an objective response (such as a partial response or a complete response). In some embodiments, the amount of the aromatic compound or metal complex of the aromatic compound is sufficient to result in a complete response in the individual. In some embodiments, the amount of the aromatic compound or metal complex of the aromatic compound is sufficient to result in a partial response in the individual. In some embodiments, the amount of the aromatic compound or metal complex of the aromatic compound administered alone is sufficient to produce an overall response rate of more than about any of about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95% among a population of individuals treated with the aromatic compound or metal complex of the aromatic compound. Responses of an individual to the treatment of the methods described herein can be determined, for example, based on RECIST or CA-125 level. For example, when CA-125 is used, a complete response can be defined as a return to a normal range value of at least 28 days from the pretreatment value. A partial response can be defined as a sustained over 50% reduction from the pretreatment value.

[0153] In some embodiments, the amount of the aromatic compound or complex thereof is sufficient to prolong progress-free survival of the individual (for example as measured by RECIST or CA-125 changes). In some embodiments, the amount of the aromatic compound or metal complex thereof is sufficient to prolong overall survival of the individual. In some embodiments, the amount of the aromatic compound or metal complex of the aromatic compound is sufficient to produce clinical benefit of more than

about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95% among a population of individuals treated with the aromatic compound or metal complex of the aromatic compound.

[0154] In some embodiments, the amount of the aromatic compound or metal complex thereof is below the level that induces a toxicological effect (*i.e.*, an effect above a clinically acceptable level of toxicity) or is at a level where a potential side effect can be controlled or tolerated when the aromatic compound or metal complex thereof is administered to the individual. In some embodiments, the amount of the aromatic compound or metal complex thereof is close to a maximum tolerated dose (MTD) of the aromatic compound or metal complex thereof following the same dosing regime. In some embodiments, the amount of the aromatic compound or metal complex thereof is more than about any of 80%, 90%, 95%, or 98% of the MTD.

[0155] In some embodiments, the amount of the aromatic compound or metal complex thereof is an amount sufficient to decrease the size of a tumor, decrease the number of cancer cells, or decrease the growth rate of a tumor by at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 100% compared to the corresponding tumor size, number of cancer cells, or tumor growth rate in the same subject prior to treatment or compared to the corresponding activity in other subjects not receiving the treatment. Standard methods can be used to measure the magnitude of this effect, such as *in vitro* assays with purified enzyme, cell-based assays, animal models, or human testing.

[0156] In some embodiments, the aromatic compound or metal complex of the aromatic compound (*e.g.*, the aromatic compound or metal complex of the aromatic compound in a formulation) is included in any of the following ranges: about 0.5 to about 5 mg, about 5 to about 10 mg, about 10 to about 15 mg, about 15 to about 20 mg, about 20 to about 25 mg, about 20 to about 50 mg, about 25 to about 50 mg, about 50 to about 75 mg, about 50 to about 100 mg, about 75 to about 100 mg, about 100 to about 125 mg, about 125 to about 150 mg, about 150 to about 175 mg, about 175 to about 200 mg, about 200 to about 225 mg, about 225 to about 250 mg, about 250 to about 300 mg, about 300 to about 350 mg, about 350 to about 400 mg, about 400 to about 450 mg, or about 450 to

about 500 mg. In some embodiments, the aromatic compound or metal complex of the aromatic compound in the effective amount of the formulation (*e.g.*, a unit dosage form) is in the range of about 5 mg to about 500 mg, such as about 30 mg to about 300 mg or about 50 mg to about 200 mg. In some embodiments, the concentration of the aromatic compound or metal complex of the aromatic compound in the formulation is dilute (about 0.1 mg/ml) or concentrated (about 100 mg/ml), including for example any of about 0.1 to about 50 mg/ml, about 0.1 to about 20 mg/ml, about 1 to about 10 mg/ml, about 2 mg/ml to about 8 mg/ml, about 4 to about 6 mg/ml, about 5 mg/ml. In some embodiments, the concentration of the aromatic compound or metal complex of the aromatic compound is at least about any of 0.5 mg/ml, 1.3 mg/ml, 1.5 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml, 5 mg/ml, 6 mg/ml, 7 mg/ml, 8 mg/ml, 9 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 40 mg/ml, or 50 mg/ml.

[0157] Exemplary effective amounts of the aromatic compound or metal complex of the aromatic compound include, but are not limited to, about any of 25 mg/m², 30 mg/m², 50 mg/m², 60 mg/m², 75 mg/m², 80 mg/m², 90 mg/m², 100 mg/m², 120 mg/m², 160 mg/m², 175 mg/m², 180 mg/m², 200 mg/m², 210 mg/m², 220 mg/m², 250 mg/m², 260 mg/m², 300 mg/m², 350 mg/m², 400 mg/m², 500 mg/m², 540 mg/m², 750 mg/m², 1000 mg/m², or 1080 mg/m² of an aromatic compound or a metal complex thereof. In various variations, the composition includes less than about any of 350 mg/m², 300 mg/m², 250 mg/m², 200 mg/m², 150 mg/m², 120 mg/m², 100 mg/m², 90 mg/m², 50 mg/m², or 30 mg/m² of an aromatic compound or a metal complex thereof. In some embodiments, the amount of the aromatic compound or metal complex of the aromatic compound per administration is less than about any of 25 mg/m², 22 mg/m², 20 mg/m², 18 mg/m², 15 mg/m², 14 mg/m², 13 mg/m², 12 mg/m², 11 mg/m², 10 mg/m², 9 mg/m², 8 mg/m², 7 mg/m², 6 mg/m², 5 mg/m², 4 mg/m², 3 mg/m², 2 mg/m², or 1 mg/m². In some embodiments, the effective amount of an aromatic compound or a metal complex of an aromatic compound is included in any of the following ranges: about 1 to about 5 mg/m², about 5 to about 10 mg/m², about 10 to about 25 mg/m², about 25 to about 50 mg/m², about 50 to about 75 mg/m², about 75 to about 100 mg/m², about 100 to about 125 mg/m², about 125 to about 150 mg/m², about 150 to about 175 mg/m², about 175 to about

200 mg/m², about 200 to about 225 mg/m², about 225 to about 250 mg/m², about 250 to about 300 mg/m², about 300 to about 350 mg/m², or about 350 to about 400 mg/m².

[0158] In some embodiments of any of the above aspects, the effective amount of an aromatic compound or a metal complex of an aromatic compound includes at least about any of 1 mg/kg, 2.5 mg/kg, 3.5 mg/kg, 5 mg/kg, 6.5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg. In various variations, the effective amount of an aromatic compound or a metal complex of an aromatic compound includes less than about any of 350 mg/kg, 300 mg/kg, 250 mg/kg, 200 mg/kg, 150 mg/kg, 100 mg/kg, 50 mg/kg, 25 mg/kg, 20 mg/kg, 10 mg/kg, 7.5 mg/kg, 6.5 mg/kg, 5 mg/kg, 3.5 mg/kg, 2.5 mg/kg, or 1 mg/kg of an aromatic compound or a metal complex of an aromatic compound.

[0159] Exemplary dosing frequencies include, but are not limited to, weekly without break; weekly, three out of four weeks; once every three weeks; once every two weeks; weekly, two out of three weeks. In some embodiments, the composition is administered about once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 6 weeks, or once every 8 weeks. In some embodiments, the composition is administered at least about any of 1x, 2x, 3x, 4x, 5x, 6x, or 7x (i.e., daily) a week. In some embodiments, the intervals between each administration are less than about any of 6 months, 3 months, 1 month, 20 days, 15 days, 12 days, 10 days, 9 days, 8 days, 7 days, 6 days, 5 days, 4 days, 3 days, 2 days, or 1 day. In some embodiments, the intervals between each administration are more than about any of 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 8 months, or 12 months. In some embodiments, there is no break in the dosing schedule. In some embodiments, the interval between each administration is no more than about a week.

[0160] The administration of the aromatic compound or metal complex thereof can be extended over an extended period of time, such as from about a month up to about seven years. In some embodiments, the composition is administered over a period of at least about any of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 30, 36, 48, 60, 72, or 84 months. In some embodiments, the aromatic compound or metal complex thereof is administered over a period of at least one month, wherein the interval between each administration is no more than about a week, and wherein the dose of the aromatic compound or metal

complex thereof at each administration is about 0.5 mg/m^2 to about 250 mg/m^2 , such as about 25 mg/m^2 to about 150 mg/m^2 or about 50 mg/m^2 to about 100 mg/m^2 .

[0161] Other exemplary dosing schedules for the administration of the aromatic compound or metal complex thereof include, but are not limited to, 100 mg/m^2 , weekly, without break; 75 mg/m^2 weekly, 3 out of four weeks; 100 mg/m^2 , weekly, 3 out of 4 weeks; 125 mg/m^2 , weekly, 3 out of 4 weeks; 125 mg/m^2 , weekly, 2 out of 3 weeks; 130 mg/m^2 , weekly, without break; 175 mg/m^2 , once every 2 weeks; 260 mg/m^2 , once every 2 weeks; 260 mg/m^2 , once every 3 weeks; $180\text{-}300 \text{ mg/m}^2$, every three weeks; $60\text{-}175 \text{ mg/m}^2$, weekly, without break; $20\text{-}150 \text{ mg/m}^2$ twice a week; and $150\text{-}250 \text{ mg/m}^2$ twice a week. The dosing frequency of the aromatic compound or metal complex thereof may be adjusted over the course of the treatment based on the judgment of the administering physician.

[0162] Also contemplated is infusion of the aromatic compound or metal complex thereof to an individual over an infusion time that is, e.g., shorter than about 24 hours. For example, in some embodiments, the aromatic compound or metal complex of the aromatic compound is administered over an infusion period of less than about any of 24 hours, 12 hours, 8 hours, 5 hours, 3 hours, 2 hours, 1 hour, 30 minutes, 20 minutes, or 10 minutes. In some embodiments, the aromatic compound or metal complex thereof is administered over an infusion period of about 30 minutes.

[0163] Any of the aromatic compounds or metal complexes thereof described herein can be administered to an individual (such as human) via various routes, including, for example, intravenous, intra-arterial, intraperitoneal, intrapulmonary, oral, inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, intraocular, intrathecal, transmucosal, and transdermal. In some preferred embodiments, the aromatic compounds or metal complexes thereof described herein can be administered to an individual (such as human) intravenously. In some embodiments, sustained continuous release formulation of the composition may be used. In one variation, the aromatic compounds or metal complex thereof described herein can be administered by any acceptable route including, but not limited to, orally, intramuscularly, transdermally, intravenously, through an inhaler or other air borne delivery systems and the like.

Additional methods of administration are known in the art. The physiochemical properties (such as stability *in vivo*) of the aromatic compounds or metal complexes described herein may allow for oral administration.

[0164] As described herein, the aromatic compounds or metal complexes thereof may be administered with an additional therapeutic agent and/or an additional treatment modality. The dosing frequency of the aromatic compound or metal complex of the aromatic compound and the additional therapeutic agent may be adjusted over the course of the treatment based on the judgment of the administering physician. In some embodiments, the aromatic compound or metal complex of the aromatic compound and the additional therapeutic agent are administered simultaneously, sequentially, or concurrently. When administered separately, the aromatic compound or metal complex of the aromatic compound and the additional therapeutic agent can be administered at different dosing frequency or intervals. For example, the aromatic compound or metal complex of the aromatic compound can be administered weekly, while the additional therapeutic agent can be administered more or less frequently. In some embodiments, sustained continuous release formulation of the aromatic compound or metal complex of the aromatic compound and/or the additional therapeutic agent may be used. Various formulations and devices for achieving sustained release are known in the art. A combination of the administration configurations described herein can be used.

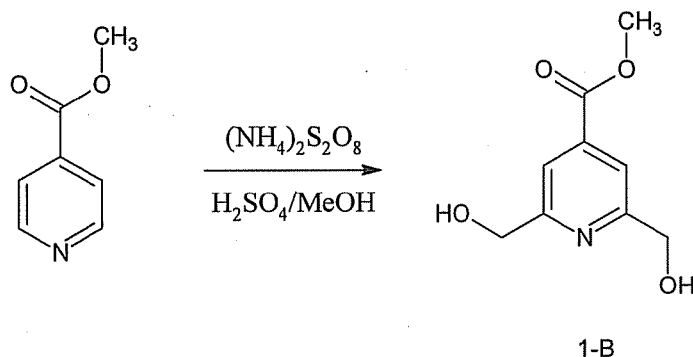
Methods of Imaging or Diagnosing a Disease

[0165] The aromatic compounds and metal complexes thereof described herein may be used to image or diagnose diseases such as those associated with cellular proliferation or hyperproliferation (*e.g.*, cancer) in a subject. Some embodiments provide methods of imaging a cancer disease in a subject by administering to a subject an effective amount of an aromatic compound or a metal complex thereof, optionally in a pharmaceutically acceptable formulation, to detect a signal from the compound or salt. Other embodiments provide methods of diagnosing a proliferative disease (*e.g.*, cancer) in an individual, by administering to the individual an effective amount of the aromatic compound or metal complex, each optionally in a pharmaceutically acceptable formulation, to detect a signal from the compound, metal or complex.

[0166] The aromatic compounds and metal complexes thereof described herein may be used with a variety of biomedical imaging modalities, including positron emission tomography (PET), single photon emission computed tomography (SPECT), gamma camera imaging, computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound, dual imaging, and optical imaging. In some preferred embodiments, the aromatic compounds and metal complexes thereof described herein may be used for PET and gamma camera imaging.

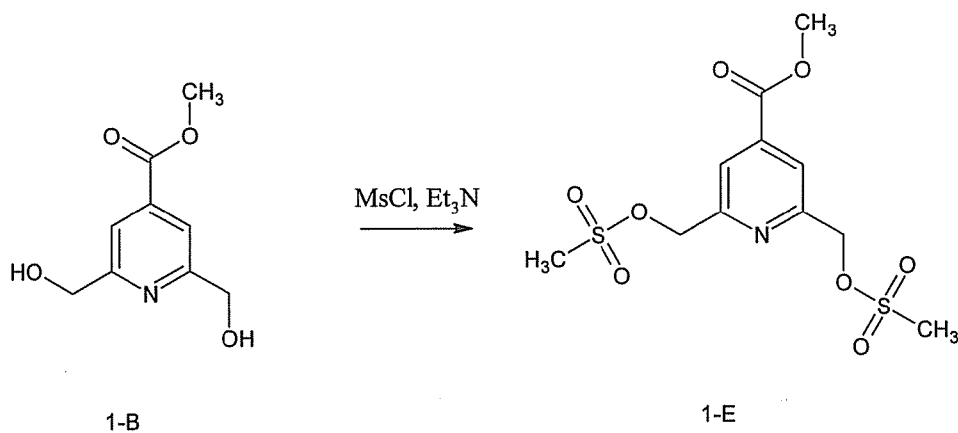
[0167] The present invention will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

Example 1: Synthesis of PCCM**Synthesis of 2,6 bis(hydroxymethyl)-methyl-iso-nicotinate**

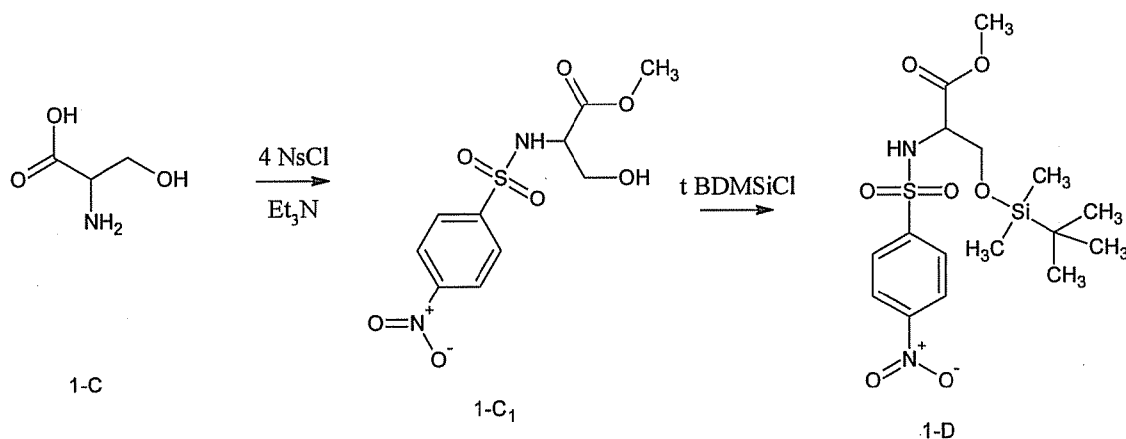
[0168] Methyl-iso-nicotinate (15.0g; 109.489 mmol) was added to methanol (200 mL) in a 2-necked 500 mL flask and stirred. Sulphuric acid (95%; 3.0 mL; 54.744 mmol) was added drop-wise and the solution was heated to a gentle reflux. Ammonium persulfate (99.65g; 7.95 mmol) was dissolved in distilled water (150 mL), and transferred to a dropping funnel and added dropwise over 1 hr to the refluxing iso-nicotinate solution. After complete addition, reflux was maintained for 2 hrs, and the yellow solution was cooled to room temperature. Excess methanol was removed under reduced pressure to yield a dark yellow oily residue. Ethyl Acetate (150 mL) was added, and the aqueous layer was neutralized with the addition of solid Na_2CO_3 . The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (50 mL portions) until colourless. The organic layers were combined, dried with anhydrous sodium sulfate and evaporated to yield a dark brown oil. The desired compound was isolated via column purification to yield 9.5g (44.94%) of an off white solid (Chloroform: Ethyl Acetate: Methanol 60:30:10). The identity of the product was confirmed by ESI MS $\text{C}_9\text{H}_{11}\text{NO}_4$ (MW = 197.187 g/mol). $\text{M}+\text{H} = 198.04$.

Synthesis of dimethanesulfonate ester derivative



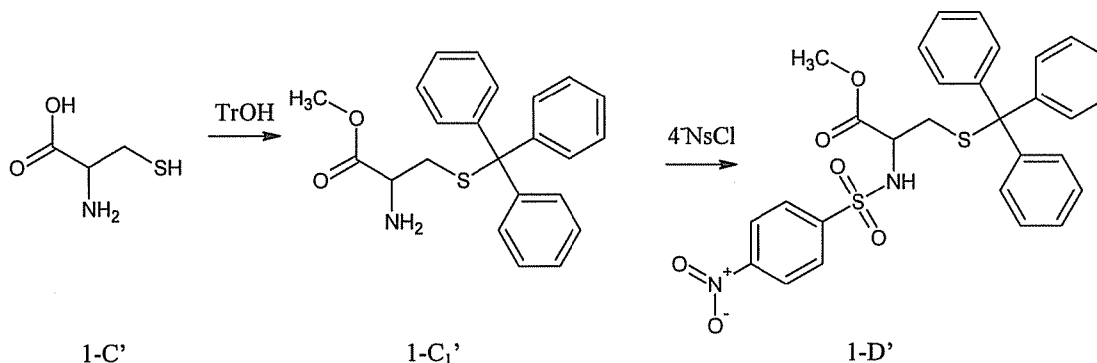
[0169] 2,6 bis(hydroxymethyl)-methyl-iso-nicotinate (1.5g; 7.61 mmol) was added to dichloromethane (30 mL) and triethylamine (2.83 mL; 22.83 mmol) was added. The yellow solution was cooled to 0 °C by placing the flask in an ice bath and stirring was started. Methanesulfonyl chloride, MsCl, (1.57 mL; 22.83 mmol) was added to this solution and the reaction was stirred at 0 °C until completion of the reaction was determined by TLC (Chloroform: Ethyl Acetate: Methanol 60:30:10). At this point, the reaction was quenched by the addition of distilled water (50 mL) and allowed to reach room temperature. The organic layer was isolated and washed with brine (50 mL), dried with anhydrous sodium sulphate and evaporated to yield 2.53 g (94.3%) of a light yellow semi solid. The identity of the product was confirmed by ESI MS $\text{C}_{11}\text{H}_{15}\text{NO}_8\text{S}_2$ (MW = 353.368 g/mol) $\text{M}+\text{H} = 354.01$.

Synthesis of protected amino acid 1-D



[0170] Serine-methyl ester (2.0g; 16.79 mmol) was dissolved in dried dichloromethane (75 mL) and cooled to 0 °C. Triethylamine (4.7 mL; 2 eq) was added as well as 4-nitrophenylsulfonyl chloride (3.71g; 1 eq), and the solution was stirred overnight at room temperature. After aqueous work-up, the dried solid was dissolved in DMF, combined with imidazole (2 eq) as well as t-butyldimethylsilyl chloride (1.5 eq) and stirred overnight at room temperature. The reaction was quenched by the addition of water. The solvent was removed under reduced pressure and purified by column chromatography (100% CHCl₃) to yield pure Compound 1-D (6.15 g) in 87% yield. The identity of the product was confirmed by ESI MS C₁₆H₂₆N₂O₇SSi (MW = 418.537 g/mol.) M-H = 417.19.

Synthesis of protected amino acid 1-D'

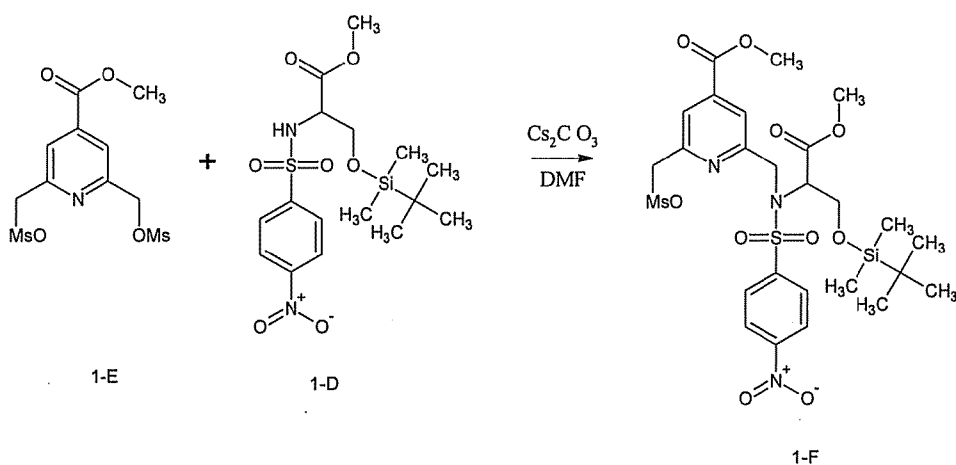


[0171] *O*-methyl-*S*-trityl-*L*-cysteine hydrochloride (Compound 1-C₁'): *L*-Cysteine hydrochloride monohydrate was dehydrated azeotropically. To the anhydrous *L*-cysteine hydrochloride (7.0 g) were added successively trityl alcohol (10.4 g, 40 mmol), freshly distilled acetic acid (40 mL), and boron trifluoride etherate (5.6 mL). The orange mixture was then placed in a preheated oil bath (40°C) and heated with stirring to 100 °C over a period of 25 min. During this time most of the trityl alcohol dissolved and, after a further 15 min at 100 °C a clear amber-coloured solution resulted. Heating was discontinued and the solution was allowed to cool to room temperature (45 min), during which time a white precipitate formed. The reaction was quenched by addition of ethanol (60 mL), which discharged the amber colour, and the solid dissolved. Water (40 mL) was added, followed by anhydrous sodium acetate (12 g). The mixture was stirred until all of the solid had dissolved and was then diluted with water (140 mL). The product precipitated as colourless oil, which rapidly crystallized as a fluffy white solid. This was collected the next day, washed well with water and acetone, and dried, finally under high vacuum to give a white amorphous solid, 13.06g (90% yield) which was characterized by ESI MS C₂₂H₂₁NO₂S (MW = 362.472 g/mol) M+H = 363.18.

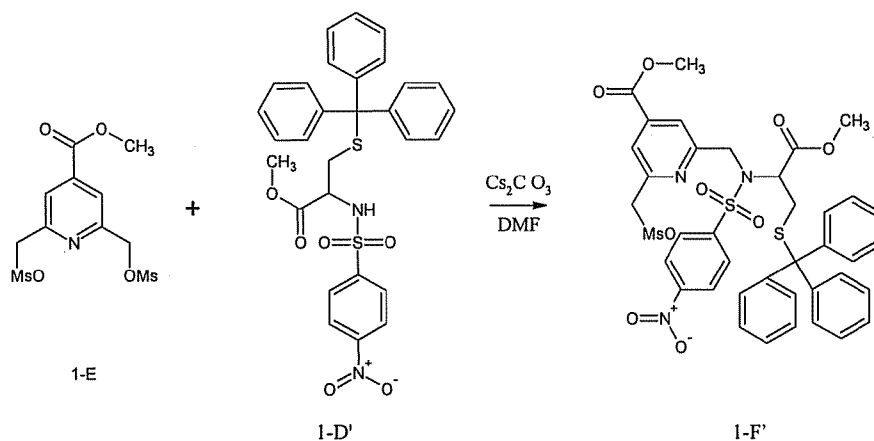
[0172] *O*-methyl-*S*-trityl-*L*-cysteine hydrochloride (Compound 1-D'): *S*-Trityl-*L*-cysteine (1.975 g, 5.434 mmol) was dissolved in 100 mL of anhydrous MeOH and was cooled to 0°C. After 20 minutes, thionyl chloride (3.2 mL, 43.6 mmol) was added and the resulting solution was stirred at 0°C for 1 hr. The solution was allowed to warm to

room temperature over 2 h and was then heated to reflux for 18 h. The reaction was cooled to room temperature, concentrated *in vacuo*, and co-stripped with anhydrous THF (5 x 20 mL) to yield Compound 1-D' as an off-white hydrochloride salt in quantitative yield. ESI-MS $C_{23}H_{23}NO_2S$ (MW = 377.499 g/mole) $M+H = 378.92$.

Synthesis of alkylated protected amino acid (1-F or 1-F')



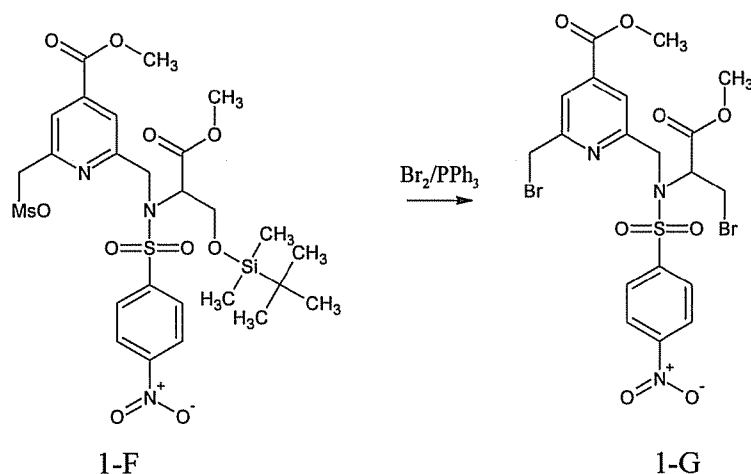
or



[0173] Compound 1-E (500 mg; 1.42 mmol) was dissolved in dried DMF (10 mL). In a separate 2-necked flask, 1 eq of protected amino acid (1-D or 1-D') was combined with 1.5 eq of Cs_2CO_3 , 500 mg powdered-dried 4A molecular sieves, and dried DMF (10

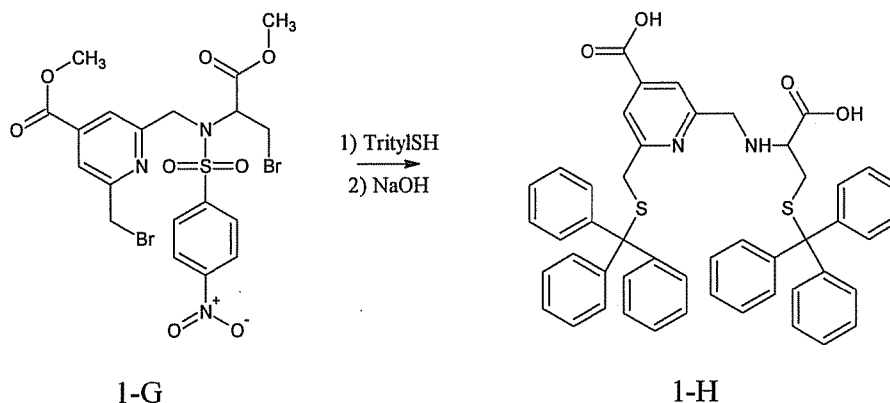
mL) under inert atmosphere. The contents of this second flask was stirred for 15 mins under nitrogen followed by the addition of the Compound 1-E solution, and stirring continued at room temperature for 5 hrs. Acetic acid (500 μ l) was added to neutralize excess base and the solvent was removed under reduced pressure until dry. The oily residue was partitioned between ethyl acetate (25 mL) and distilled water (25 mL). The organic layer was isolated, washed with brine, dried with anhydrous sodium sulphate and evaporated. The compound of interest was isolated by column chromatography. Yield of 1F = 31%; 1F' = 27%.

Synthesis of 1-G



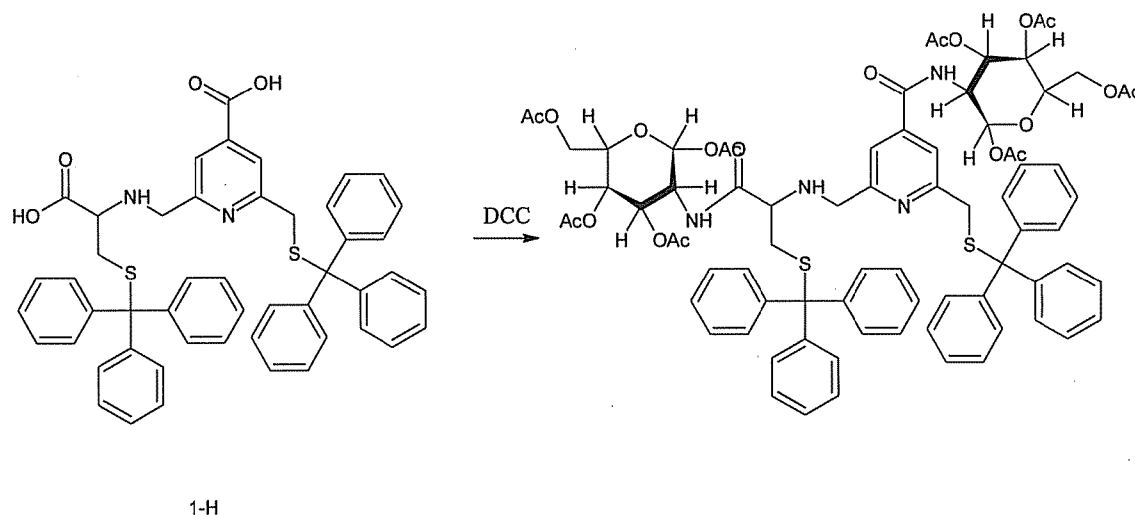
[0174] The pyridyl-serine derivative (1-F; 500 mg; 1 eq) is dissolved in dried THF (10 mL). Imidazole (2.5 eq) and triphenylphosphine (2.3 eq) are added, and the solution is immersed in an ice bath and stirred for 15 mins at this temperature. Bromine (Br_2 ; 2.1 eq) is slowly added in 5 equal portion over a period of minutes. The suspension is stirred at room temperature for 1 hour, poured into distilled water (50 mL) and extracted with dichloromethane (3×25 mL). The solvent is dried, evaporated and the solid residue purified by column chromatography.

Synthesis of 1-H (introduction of protected thiols)



[0175] Compound 1-G (1 eq) is dissolved in dried acetonitrile (30 mL) under inert atmosphere, to which triphenylmethylmercaptan (3 eq) and diisopropylethylamine (DIPEA, 6 eq) are added. The solution is stirred overnight at room temperature. Once the endpoint of the reaction is determined, the solution is evaporated, dissolved in methanol and 1N NaOH (2.5 eq) is added. The solution is stirred at 50 °C for 3 hrs until hydrolysis of the methyl esters is complete. Aqueous workup yields Compound 1-H in sufficient purity.

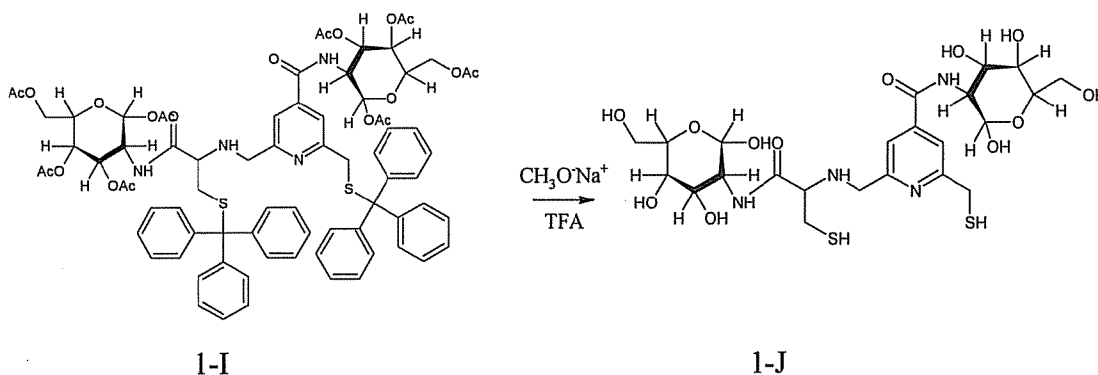
Carbodiimide mediated amide formation – Coupling of protected amino acid



[0176] Compound 1-H (1 eq) is dissolved in dried dichloromethane (50 mL). This mixture is immersed in an ice bath, and combined with tetra-acetyl glucosamine (2.2 eq)

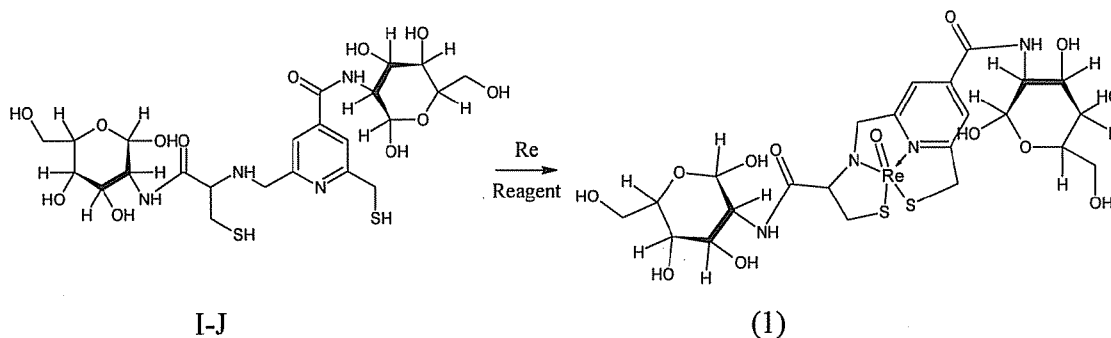
and DCC (2.0 eq), and stirred at 0°C for 1 hr. The solution is stirred at room temperature overnight. The following day the insoluble urea side product is removed via filtration and washed with cold dichloromethane (50 mL). The filtrate is washed successively with 0.5 N HCl (2 × 25 ml), saturated NaHCO₃ (2 × 25 mL), and distilled water (2 × 25 mL), and then dried and evaporated to yield Compound 1-I.

Deprotection of acetate groups of the glucosamine



[0177] Compound 1-I (1.00 g) is dissolved in anhydrous, degassed 6:1 dichloromethane : methanol, and stirred at 0 °C under inert atmosphere. Catalytic sodium methoxide is added and the solution stirred at 0 °C for 1 hr, and then at room temperature until completion of reaction as indicated by ESI-MS. At this point, acetic acid (500 µl) is added to quench the reaction, the solution is filtered, and the filtrate dried and evaporated. The dried solid (desiccator, 24 hrs) is dissolved in 30% TFA in dried dichloromethane, and 4 eq of Et₃SiH is added. After 1 hr at room temperature, the volatiles are removed under reduced pressure, the residue are washed with diethyl ether (50 mL), and then are filtered and dried in a desiccator to obtain Compound 1-J.

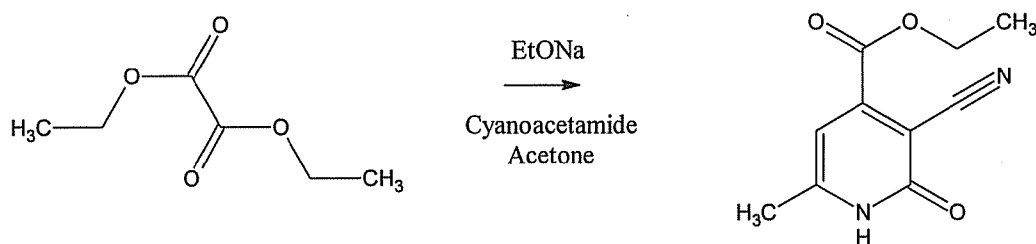
Rhenium complexation



[0178] $\text{ReOCl}_3(\text{PPh}_3)_2$ (0.328 g; 1.2 mmol) is dissolved in dried DMF (15 mL). Compound I-J (1.0 eq) is dissolved in 2 mL distilled water is added to the reaction mixture, and stirred at room temperature for 1 hr. Upon addition of distilled water (30 mL), a brown precipitate is produced which was removed by filtration. The filtrate is evaporated and DMF (10 mL) is added. Precipitated salts are removed with filtration. The filtrate is again evaporated to dryness and redissolved in acetone upon which the compound of interest precipitated. The precipitate is isolated by filtration, dried and characterized by LC/MS.

Example 2: Synthesis of DDDP

Synthesis of ethyl-3-cyano-6-methyl-2-oxo-1,2-dihydro-pyridine-4-carboxylate (2B)

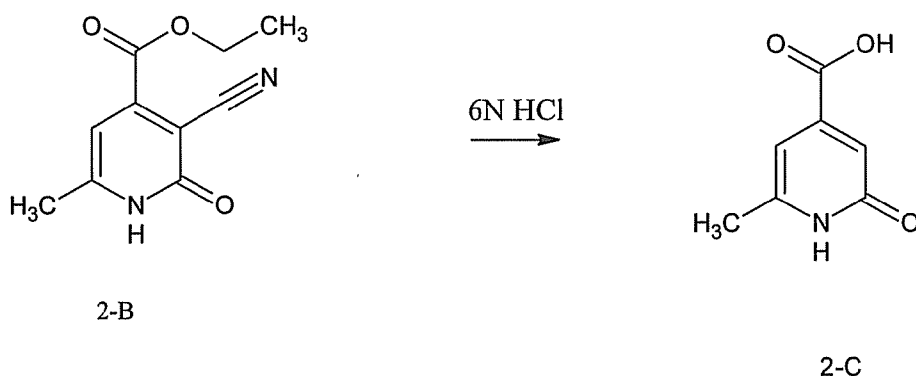


2-B

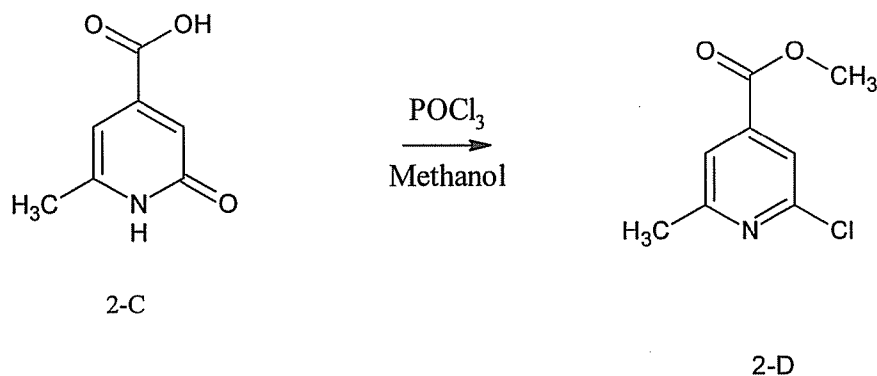
[0179] Dried ethanol (300 mL) was transferred to a two-necked flask, fitted with a CaCl_2 drying tube and flushed with dry N_2 . Over a period of 3 hrs, sodium metal (6.75 g

0.285 mol) was added in small portions while stirring magnetically and maintaining an inert atmosphere in the flask. Diethyl oxalate (34 mL, 0.25 mol) mixed with dry acetone (18.5 mL, 0.25 mol) was added drop-wise to the sodium ethoxide solution while stirring vigorously. The thick slurry was stirred for 3 hrs under nitrogen at room temperature. Cyanoacetamide (21.0 g; 0.25 mol) was then added, and the slurry was stirred at 80°C for 6 hrs. The mixture was observed to turn from yellow to bright orange to red. The excess ethanol was removed, and the dried orange-brown solid was dissolved in a 75 mL of boiling distilled water and glacial acetic acid was added to a pH of 4.7-4.9. The hot solution was covered and placed in a refrigerator. The orange precipitate was isolated by filtration, washed with ice water and vacuum dried. Yield: 33.4 g (66 %). The identity of the product was confirmed by ESI-MS. $C_{10}H_{10}N_2O_3$ (MW 206.198 g/mol.) $M+H = 207.16$.

Synthesis of 6-methyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (2C)



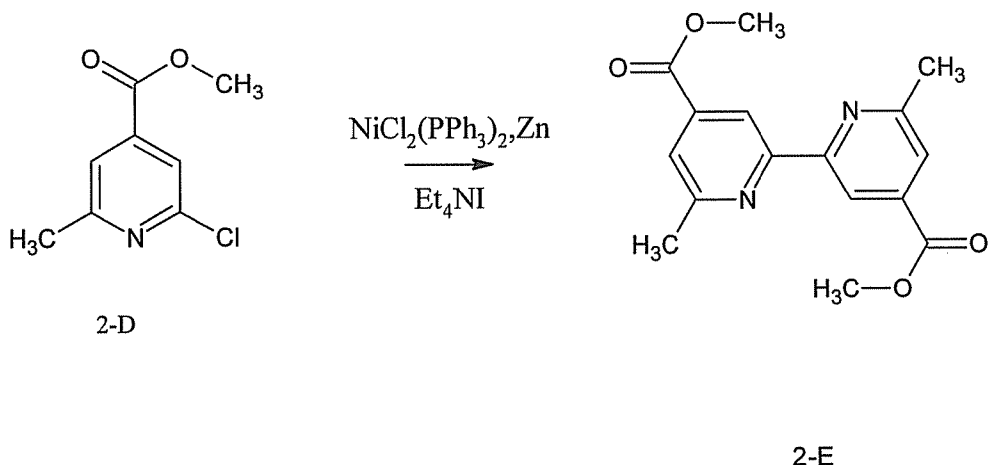
[0180] The cyanoester prepared in the previous step (15.0 g, 72.8 mmol) was added to a 250 mL flask fitted with magnetic stirring and 140 mL of 6 N HCl was added. The solution was stirred under gentle reflux for 24 hrs. The next day, the hot solution was poured onto 250 g crushed ice and placed in a refrigerator. The beige solid that precipitated was isolated by filtration, washed with ice water, and dried under vacuum. The identity of the product was confirmed by ESI-MS $C_7H_7NO_3$ (MW = 153.135 g/mol.). $M+H = 154.19$

Synthesis of methyl 2-chloro-6-methylpyridine-4-carboxylate (2D)

[0181] To a stirred solution of POCl₃ (30 ml, 321 mmol) was added 7.0 g of the carboxylic acid prepared in the previous step, and the solution was stirred at reflux for 18 hrs. Thereafter, the excess POCl₃ was removed under reduced pressure and the black oily residue placed in a crushed ice bath. Dried methanol (60 mL) was added slowly with vigorous swirling of the flask in the bath. A vigorous exothermic reaction was observed upon addition of the methanol. After complete addition of the methanol, the flask was sealed and stirred at room temperature for 24 hrs. The next day, the contents of the flask was neutralized by the addition of solid NaHCO₃ and partitioned between ethyl acetate and water (100 ml each). The organic layer was removed, and the aqueous layer was extracted with another portion of ethyl acetate (50 mL).

[0182] The organic layers were combined, and treated with activated carbon and stirred for 1 hr at room temperature. The carbon was removed by filtering the black solution through Celite. The clear solution was dried and evaporated to yield a light brown semi-solid which was purified by dissolution in hot petroleum ether, decanting the petroleum ether from the brown oily residue that forms and evaporating the ether to yield a white solid. The identity of the product was confirmed by ESI-MS. C₈H₈ClNO₂ (MW = 185.608 g/mol). M+H=186.24 ¹H NMR (300 MHz, CDCl₃) δ 7.4-7.8 (m, 3H, 5H) 4.0 (s, 10CH₃) 2.5 (s, 11CH₃)

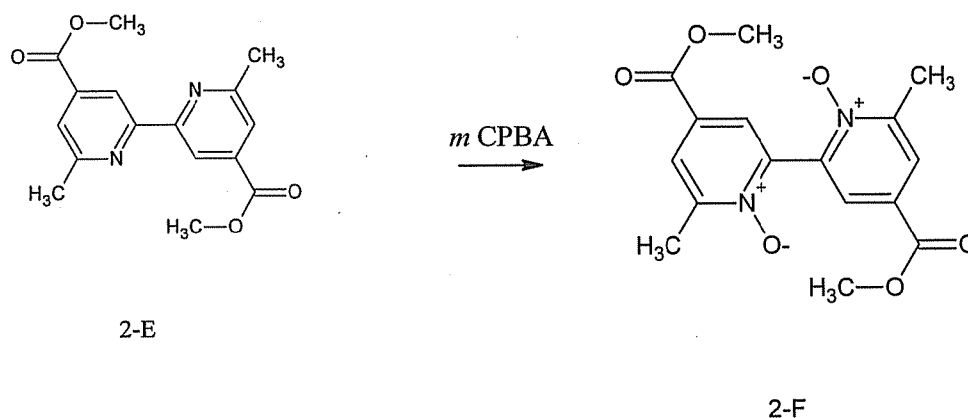
Synthesis of dimethyl-6, 6-dimethyl-2,2'-bipyridine-4,4'-carboxylate (2E)



[0183] Into a 250 mL oven dried 2-necked flask, $\text{NiCl}_2(\text{PPh}_3)_2$ (4.70 g; 6.486 mmol), activated Zn dust (2.12 g; 32.43 mmol), and tetra-ethyl ammonium iodide (5.56 g; 21.62 mmol) was added. N_2 was introduced into the flask. While maintaining the N_2 atmosphere in the flask, a pressure equalizing dropping funnel was connected to the flask and degassed and dried acetonitrile (50 mL) was added to the contents of the flask through the dropping funnel. The flask was placed into a waterbath set at 50 °C and stirred for 30 min. Dimethyl-6, 6-dimethyl-2,2'-bipyridine-4,4'-carboxylate (4.0 g; 21.62 mmol) was dissolved in degassed, dried acetonitrile (50 mL) and transferred to the dropping funnel, ensuring the presence of an inert atmosphere through the entire experimental setup. This solution was then added quickly to the stirring metal catalyst suspension at 50°C and stirred for 24 hrs. The next day, the black suspension was cooled to room temperature, filtered through a Celite bed and added to an aqueous solution of disodium EDTA (2 eq; 150 mL) and stirred. To this aqueous solution, chloroform (150 mL) was added and the suspension was vigorously stirred for 30 min, before stirring was stopped and the suspension allowed to separate into a blue aqueous layer, containing the EDTA-Ni complex and a red organic layer, containing the crude target bipyridine compound. The organic layer was isolated and the aqueous layer extracted with another 50 mL portion of chloroform. The organic layers were combined, dried with anhydrous sodium sulphate and evaporated, yielding a dark red solid. Triphenylphosphine was

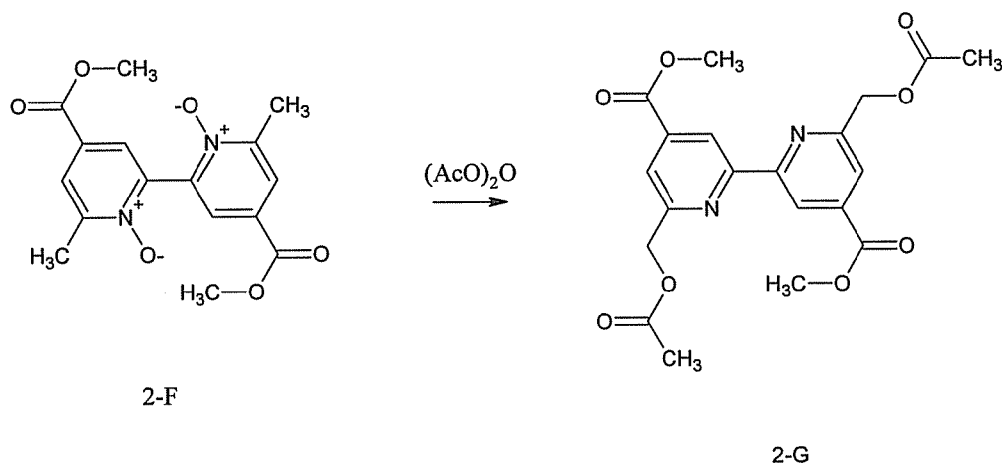
removed from this crude product by washing with two volumes of hexane (75 mL). The solid was isolated by filtration and finally purified by washing with three 50 mL portions of 2-methyl-3-pentanone to remove triphenylphosphine oxide, yielding a light orange solid (1.8g; 57.8%). Purity and identity was confirmed by GC-MS analysis $C_{16}H_{16}N_2O_4$ (MW of 300.309 g/mole) $m/z = 299.73$

Synthesis of dimethyl-6, 6-dimethyl-2,2'-bipyridine-4,4'-carboxylate-*N,N'*-dioxide (2F)



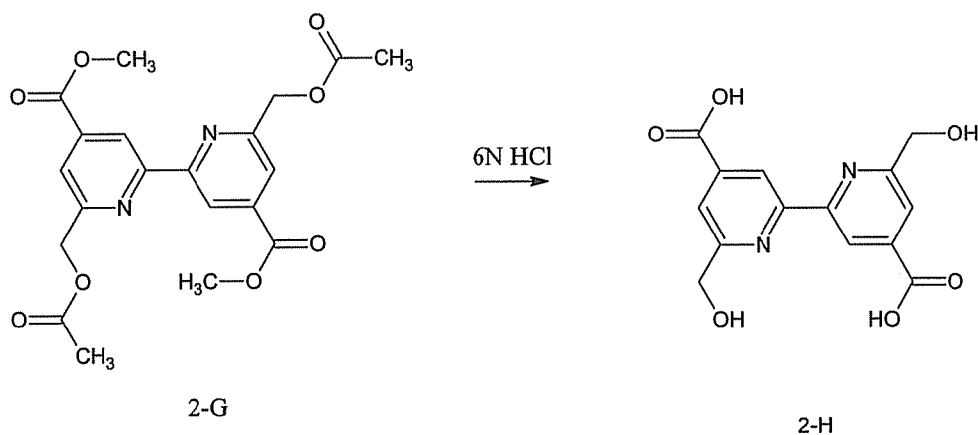
[0184] Dimethyl-6, 6-dimethyl-2,2'-bipyridine-4,4'-carboxylate (1.2 g; 4.0 mmol) was dissolved in chloroform (25 mL) and stirred. *m*-Chloroperbenzoic acid (3.52 g; 12.0 mmol) was dissolved in chloroform (75 mL), and added to the stirring bipyridine solution. The green solution was stirred at room temperature for 24 hrs. The next day the chloroform solution was washed with saturated $NaHCO_3$ (3×50 mL). The organic layer was dried with anhydrous sodium sulphate and concentrated to yield a crude yellow solid. This crude mixture was stirred in diethyl ether (100 mL) for 30 mins to remove unreacted starting material and some of the mono oxide impurity and then filtered to yield 1.3 g of an off-white solid containing the desired *N,N*-dioxide, contaminated with some mono oxide impurity. The crude mixture was dried in a desiccator for 24 hrs, and used for the next step without further purification. $C_{16}H_{16}N_2O_6$, MW = 332.126 g/mol ESI-MS ($M+H = 333.46$).

Synthesis of Dimethyl-6, 6'-diacetoxymethyl-2,2'-bipyridine-4, 4'-carboxylate (2G)



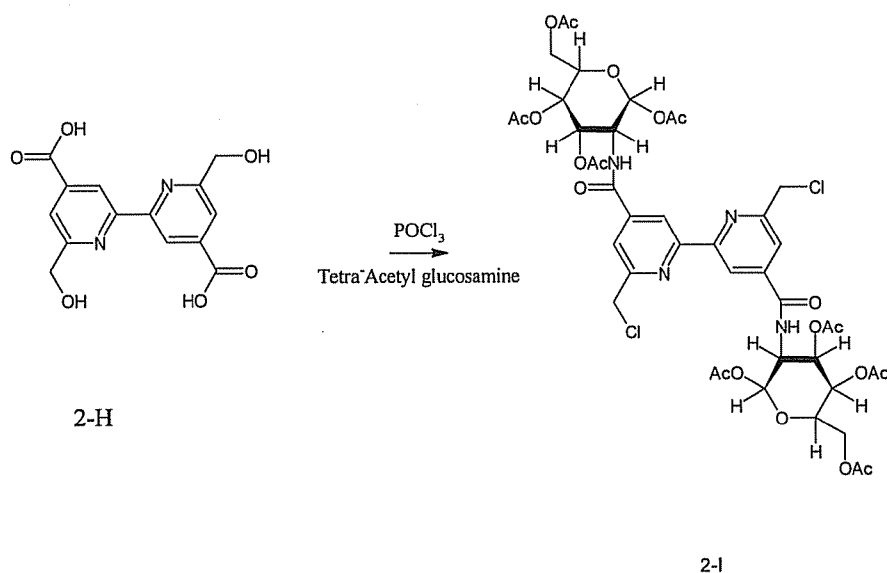
[0185] The dried crude N,N'-dioxide mixture (2.0 g) was added to freshly distilled acetic anhydride (25 mL) and the suspension was refluxed for 3 hrs. After 3 hrs, the dark solution was cooled to room temperature and evaporated. The residue was dissolved in dichloromethane (50 mL) and washed with 10% NaHCO₃ (50 mL). The organic layer was separated and dried with anhydrous sodium sulphate, and concentrated to yield an off-white solid. The crude product was purified by column using Silica Gel 60 in a solvent system of 97:3 CH₂Cl₂:MeOH (97:3). The column yielded 1.6 g of a light brown solid. The identity of the product was confirmed by NMR and MS. ¹H-NMR (300 MHz, CDCl₃) δ 9.05 (m, 3H, 12H) 7.9 (m, 5H, 10H), 5.13 (dd, 16C₂, 20CH₂) 4.00 (s, 15CH₃, 26CH₃) 2.4 (s, 28CH₃, 29CH₃). ESI-MS C₂₁H₂₁N₂O₈ (MW = 416.381 g/mol) M+H = 417.13.

Synthesis of 6,6'-bis(hydroxymethyl)-2,2'-bipyridine-4,4'-dicarboxylic acid (2H)



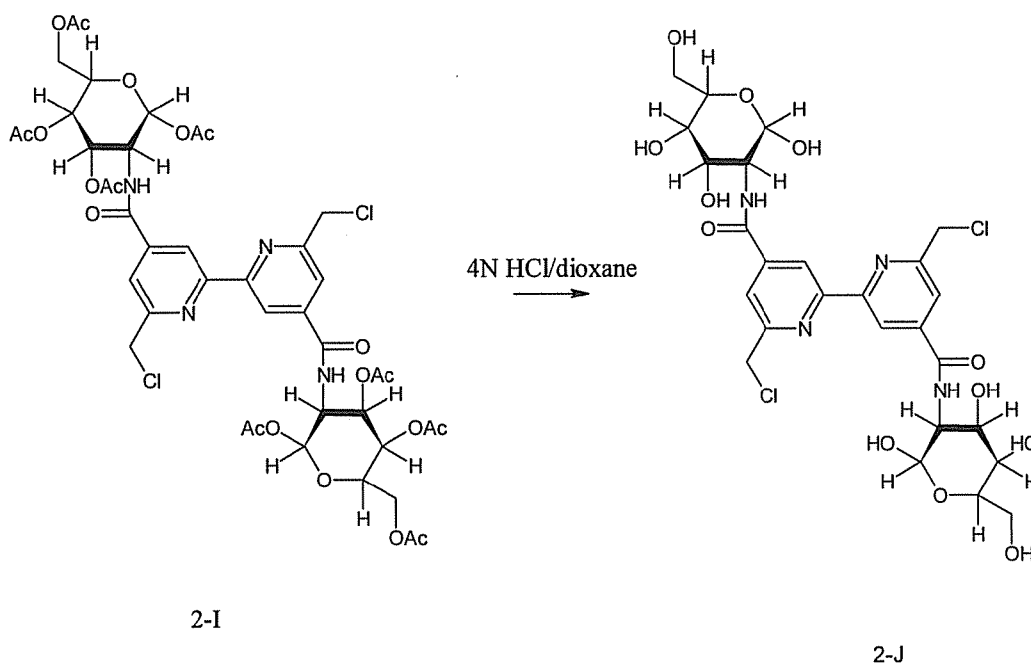
[0186] Dimethyl-6, 6'-diacetoxymethyl-2,2'-bipyridine-4, 4'-carboxylate (2.0 g; 4.79mmol) was added to 6N HCl (30 mL). The light brown solution was gently refluxed for 12 hrs. The next day the solvent was removed under reduced pressure to yield a very hygroscopic brown solid which was dried in a desiccator for 24 hrs. The identity of the product was confirmed by ESI-MS $C_{15}H_{13}NO_6$, MW = 303.267 g/mol. $M+H = 305.26$.

Synthesis of diglycosylated bipyridine derivative (2I)



[0187] 6,6'-bis(hydroxymethyl)-2,2'-bipyridine-4,4'-dicarboxylic acid (1.00g; 2.65 mmol) was added to a 100 mL round bottom flask and excess POCl₃ (40 mL) was added. The mixture was refluxed in an oil bath for 5 hours and cooled down to room temperature. Excess POCl₃ was removed under vacuum and the oily residue was immersed in an ice bath. Tetra-Acetyl Glucosamine (2.76 g; 7.95 mmol) was dissolved in dried THF (40 mL) and triethylamine (3.32 mL) was added. This glucosamine solution was added dropwise to the acid chloride residue in the ice bath and stirred at 0 °C for 5 minutes. The ice bath was removed and the suspension was stirred for 1 hr at room temperature and filtered. The precipitate was isolated and characterized by ESI MS. Furthermore, the THF was evaporated and the residue was dissolved in ethyl acetate. Upon cooling the ethyl acetate layer, a further quantity of the product precipitated and was isolated. ESI –MS C₄₂H₄₈Cl₂N₄O₂₈ (MW = 999.751 g/mole) M+H = 1000.189.

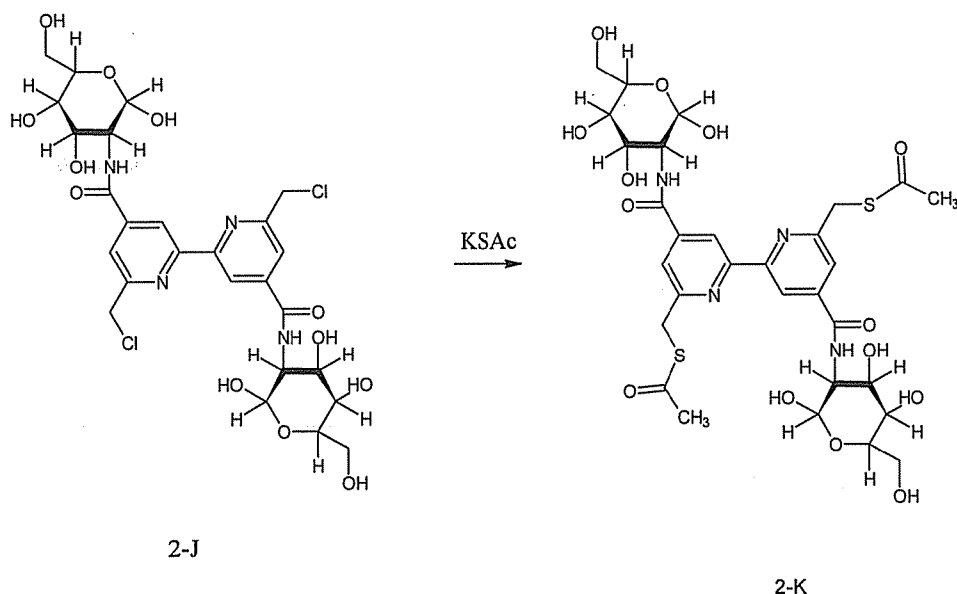
Deprotection of glucose moieties



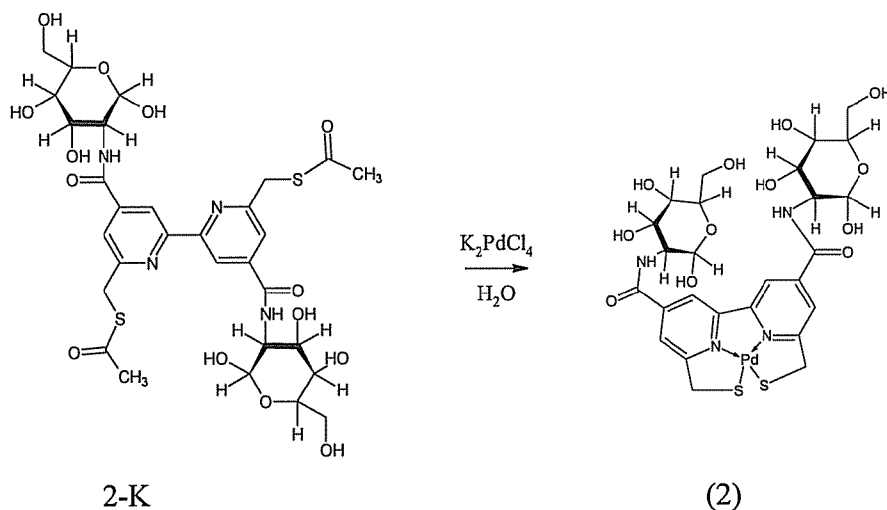
[0188] Compound 2-I (500 mg; 0.5 mmol) was dissolved in 10 mL 4N HCl in dioxane and stirred at room temperature for 24 hours. The next morning, the solvent was

removed to yield 280 mg of Compound 2-J. The identity of the product was confirmed by ESI-MS $C_{27}H_{33}N_3Cl_2O_{12}$, MW = 662.469 g/mol. M+H = 663.71

Introduction of protected thiol (thioacetylation)



[0189] Compound 2-K (500 mg; 0.754 mmol) was dissolved in dried DMF (10mL) and stirred. Triethylamine (4 eq) was added. In a separate vial, potassium thioacetate (KSAC; 2.1 eq) was dissolved in dried DMF (2 mL), and added in one portion. The suspension was stirred for 30 mins at room temperature. At this point, a sample analyzed by LC-MS confirmed the endpoint of the reaction. The solvent was evaporated and the residue partitioned between ethyl acetate (30 mL) and distilled water (30 mL). The organic layer was isolated, dried and removed under reduced pressure to yield 492 mg of Compound 2-K as confirmed by ESI-MS: $C_{31}H_{39}N_3O_{14}S_2$ (MW = 662.469 g/mol) M+H = 663.22.

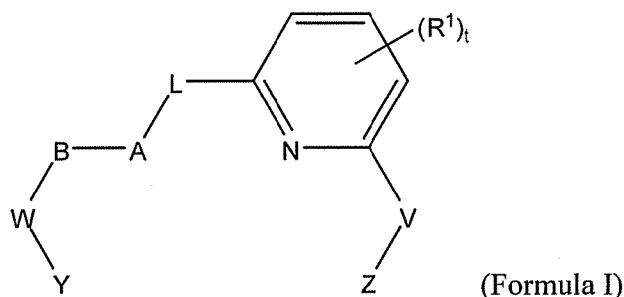
Preparation of N₂S₂-Pd complex

[0190] Compound 2-K (1 eq) is dissolved in DMF and stirred under a N₂ atmosphere. K₂PdCl₄ (1eq) is added to the reaction mixture as a solid. The mixture is stirred at room temperature under inert atmosphere. The end point of the reaction is determined by ESI-MS.

CLAIMS

What is claimed is:

1. An aromatic compound of Formula I:



wherein:

A is NR^f , wherein R^f is H, alkyl, or aryl;

B is a C_{1-2} alkylene substituted with at least one R^1 moiety, wherein the C_{1-2} alkylene is optionally further substituted;

L is an optionally substituted C_{1-2} alkylene; or

B and L taken together with A form an aromatic, 6-membered heterocycle substituted with at least one R^1 moiety;

each R^1 is independently $\text{XC}(=\text{O})\text{O}-\text{R}^a$, or $\text{XC}(=\text{O})\text{NR}^a\text{R}^b$;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C_{1-3} alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

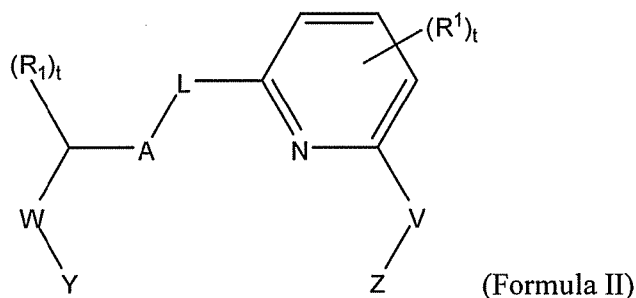
Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are the same or different;

R^c is H or a C_{1-3} alkyl;

R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;

or a salt thereof or a metal complex thereof.

2. The compound of claim 1, wherein the targeting agent is selected from the group consisting of a saccharide, lectin, receptor ligand, protein, antibody, polyether, and an amino acid polymer.
3. The compound of claim 1, wherein X is an optionally substituted alkyl or alkylene ether.
4. The compound of claim 1, wherein B and L are taken together with A to form a pyridyl substituted with at least one R^1 moiety.
5. The compound according to claim 1, of Formula II:



wherein:

A is NR^f , wherein R^f is H, alkyl, or aryl;

L is an optionally substituted C_{1-2} alkylene;

each R^1 is independently $XC(=O)O-R^a$, or $XC(=O)NR^aR^b$;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C_{1-3} alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

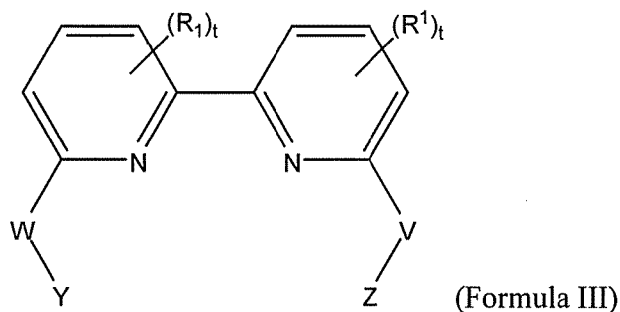
Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are the same or different;

R^c is H or a C_{1-3} alkyl;

R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;

or a salt thereof or a metal complex thereof.

6. The compound according to claim 1, of Formula III:



wherein:

each R^1 is independently $XC(=O)O-R^a$, or $XC(=O)NR^aR^b$;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C_{1-3} alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

Y and Z are independently SR^c or NR^dR^e , wherein Y and Z are the same or different;

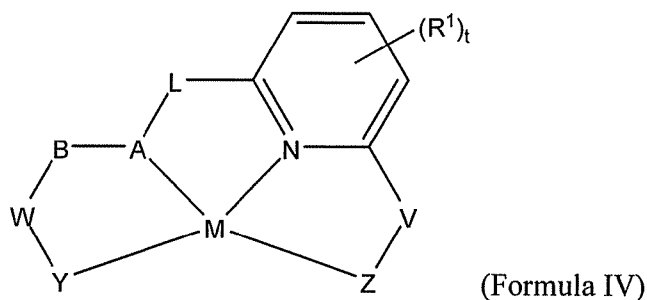
R^c is H or a C_{1-3} alkyl;

R^d and R^e are independently H or a C_{1-3} alkyl, wherein R^d and R^e are the same or different;

or a salt thereof or a metal complex thereof.

7. A metal salt or a metal complex of a compound of any of claims 1-6.
8. The metal complex of claim 7, wherein the metal complex is an oxo metal complex.

9. The metal complex of claim 1, of Formula IV:



wherein:

A is N;

B is a C₁₋₂ alkylene substituted with at least one R¹ moiety, wherein the C₁₋₂ alkylene is optionally further substituted;

L is an optionally substituted C₁₋₂alkylene; or

B and L taken together with A form an aromatic, 6-membered heterocycle substituted with at least one R¹ moiety;

each R¹ is independently XC(=O)O-R^a, or XC(=O)NR^aR^b;

each R^a comprises a targeting agent;

each R^b is H or optionally substituted alkyl, aryl, heteroalkyl, or heteroaryl;

X is or is not present, and if present, is a spacer group;

W and V are independently a C₁₋₃ alkylene, a carbonyl, or a sulfonyl;

t is 0 to 3;

Y and Z are independently SR^c or NR^dR^e, wherein Y and Z are the same or different;

R^c is H or a C₁₋₃ alkyl;

R^d and R^e are independently H or a C₁₋₃ alkyl, wherein R^d and R^e are the same or different; and

wherein M is a metal ion.

10. The metal complex of claim 7, 8 or 9, wherein the metal ion is an oxo metal ion.

11. The metal complex of claim 7, 8 or 9, wherein the metal ion is a radionuclide.
12. The metal complex of claim 7, 8 or 9, wherein the metal ion is selected from the group consisting of a technetium ion, a platinum ion, and a palladium ion.
13. A pharmaceutical composition comprising the aromatic compound or metal complex of any one of claims 1-12 and a pharmaceutically acceptable excipient.
14. A method of treating a cancer in a subject comprising administering to a subject in need thereof an effective amount of the aromatic compound or metal complex of any one of claims 1-12.
15. The method according to claim 14, wherein the cancer is selected from the group consisting of breast cancer, lung cancer, prostate cancer, ovarian cancer, brain cancer, liver cancer, cervical cancer, colon cancer, renal cancer, skin cancer, head and neck cancer, bone cancer, esophageal cancer, bladder cancer, uterine cancer, lymphatic cancer, stomach cancer, pancreatic cancer, testicular cancer, lymphoma, and leukemia.
16. A method of imaging or diagnosing a disease in a subject comprising administering to a subject an effective amount of the compound or metal complex of any of claims 1-12, and detecting a signal from the aromatic compound or metal complex.
17. The aromatic compound or metal complex of any one of claims 1-12, for use in a method of treating a cancer in a subject.
18. The use of an aromatic compound or metal complex of any one of claims 1-12, in a method of manufacturing a medicament for use in a method of treating a cancer in a subject.
19. The aromatic compound or metal complex of any one of claims 1-12, for use in a method of imaging or diagnosing a disease in a subject comprising administering to a subject an effective amount said compound

or metal complex, and detecting a signal from the aromatic compound or metal complex.

20. The use of an aromatic compound or metal complex of any one of claims 1-12, in a method of manufacturing a composition for use in a method of imaging or diagnosing a disease in a subject comprising administering said composition to a subject, and detecting a signal from the aromatic compound or metal complex.

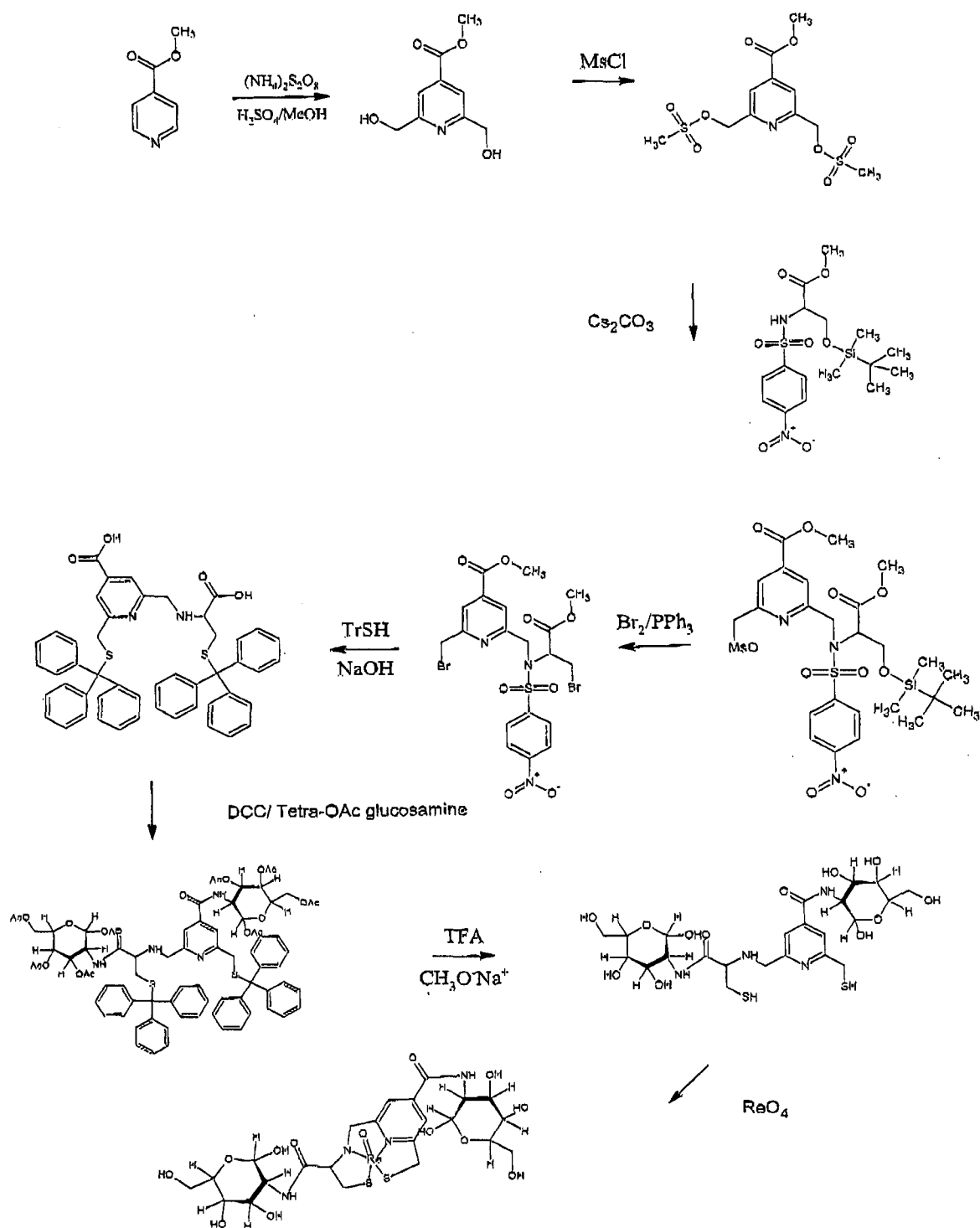


Figure 1

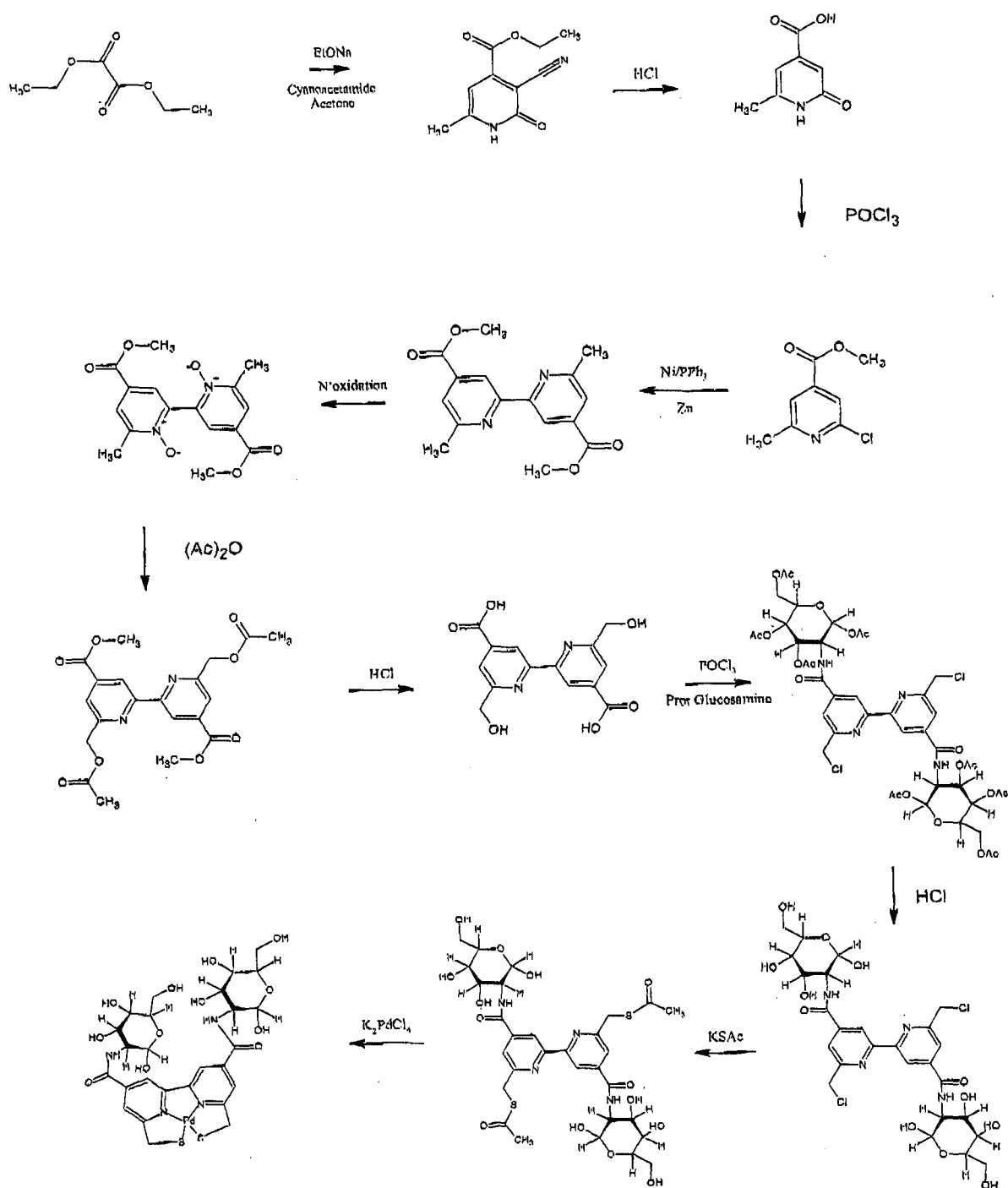


Figure 2