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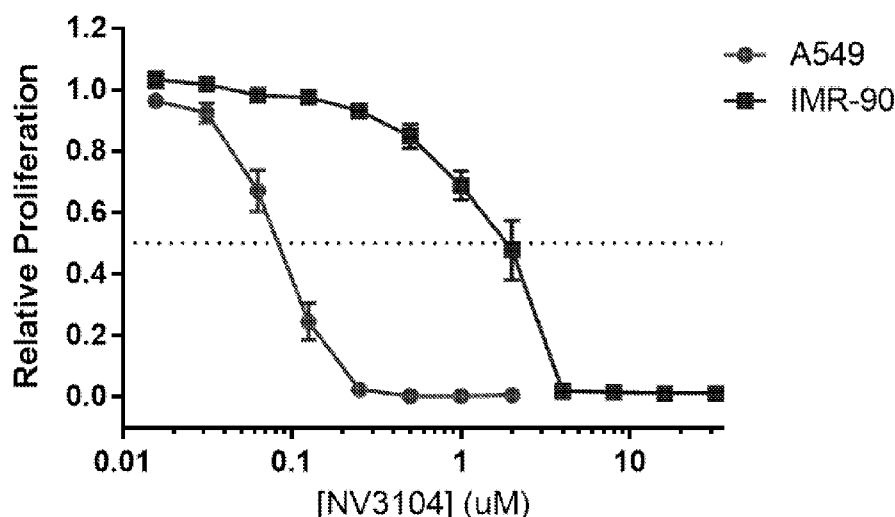
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(54) Title: THIOSEMICARBAZONE DERIVATIVES AS ANTI-CANCER AGENTS

FIG. 1

Anti-Proliferative Activity Assay – I-1



(57) Abstract: Some embodiments of the invention include inventive compounds (e.g., compounds of Formula (I) or (Ia)). Other embodiments include compositions (e.g., pharmaceutical compositions) comprising the inventive compound. Still other embodiments of the invention include compositions (e.g., pharmaceutical compositions) for treating, for example, certain diseases using the inventive compounds. Some embodiments include methods of using the inventive compound (e.g., in compositions or in pharmaceutical compositions) for administering and treating (e.g., diseases such as cancer). Further embodiments include methods for making the inventive compounds. Additional embodiments of the invention are also discussed herein.



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THIOSEMICARBAZONE DERIVATIVES AS ANTI-CANCER AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application
5 No. 62/501,553, filed May 4, 2017 entitled "THERAPEUTIC APPLICATIONS OF
VARIOUS METAL N₂S₂ COMPOUNDS" which is herein incorporated by reference
in its entirety.

GOVERNMENT RIGHTS

[0002] This invention was made with government support under
10 CHE-1361728 awarded by National Science Foundation. The government has certain
rights in the invention.

BACKGROUND

[0003] Several compounds are known to treat diseases, such as cancer, but do
so inadequately. For example, some platinum-containing drugs can be effective
15 anticancer therapies, but they can sometimes have side effects, such as toxicity.
Attempts to design compounds (e.g., compounds containing metals) have not yielded
effective anticancer agents and are not always as less toxic to non-cancer cells as
would be desired.

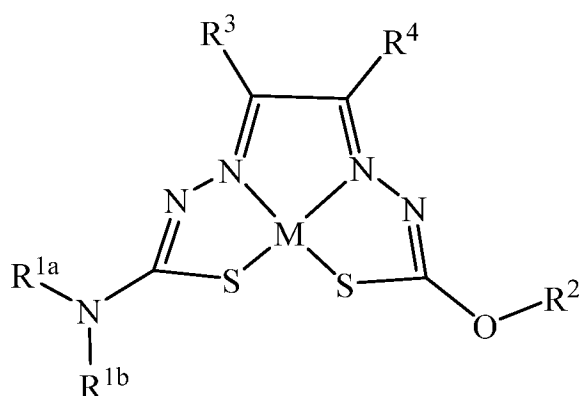
[0004] Certain embodiments of the invention address one or more of the
20 deficiencies described above. Some embodiments of the invention include inventive
compounds (e.g., compounds of Formula (I) or (Ia)). Other embodiments include
compositions (e.g., pharmaceutical compositions) comprising the inventive
compound. Still other embodiments of the invention include compositions (e.g.,
pharmaceutical compositions) for treating, for example, certain diseases using the

inventive compounds. Some embodiments include methods of using the inventive compound (e.g., in compositions or in pharmaceutical compositions) for administering and treating (e.g., diseases such as cancer). Further embodiments include methods for making the inventive compounds. Additional embodiments of the invention are also discussed herein.

SUMMARY

[0005] Some embodiments of the present invention include a compound selected from

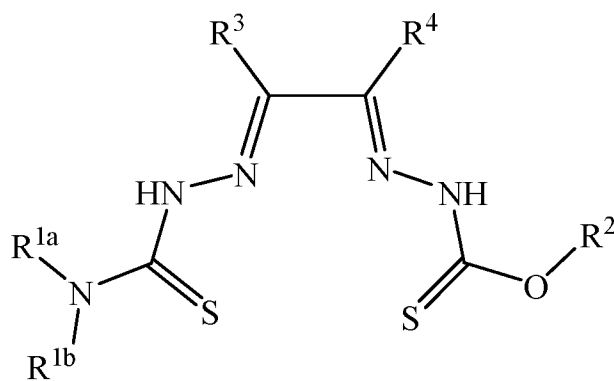
10 (a) Formula (Ia)



(Ia) and salts, optical isomers,

geometric isomers, salts of isomers, and derivatives thereof; and

(b) Formula (Ib)



optical isomers, geometric isomers, salts of isomers, and derivatives thereof. In some embodiments, R^{1a} is H, halogen, -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In other embodiments, R^{1b} is H, halogen, -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In yet other

embodiments, R^{1a} and R^{1b} are optionally bonded together with their attached nitrogen to form heterocyclyl or heteroaryl, which heterocyclyl or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy.

In certain embodiments, R² is H, halogen, -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In some embodiments, R³ is H, halogen, -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In other embodiments, R⁴ is H, halogen, -CN, hydroxy (-OH), methanoyl

(-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In some embodiments, R³ and R⁴ are optionally bonded together to form a ring with their attached carbons that is fused to the attached carbons of R³ and R⁴, where the ring that is fused is cycloalkyl, heterocyclyl, aryl, or heteroaryl, which cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In certain embodiments, M is a divalent cation.

[0007] In some embodiments, R^{1a} is H, methyl, ethyl, C₁₋₅ alkyl, C₃ alkyl, n-propyl, isopropyl, ethoxy, methoxy, 5-hydroxy pyridyl, indolyl, 1,2,3,4-tetrahydroisoquinolyl, furyl, 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy

phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In other
 5 embodiments, R^{1a} is H, methyl, ethyl, n-propyl, or phenyl. In yet other embodiments, R^{1a} is not H.

[0008] In some embodiments, R^{1b} is H, Cl, hydroxy (-OH), methyl, ethyl, C₁₋₅ alkyl, C₃ alkyl, C₄ alkyl, -CN, ethynyl, -CONH₂, -CON(CH₃)₂, 2-(morpholinyl)ethoxy, -CO-morpholin-4-yl, ethoxy, methoxy, 5-hydroxy pyridyl,
 10 indolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, furyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl,
 15 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated
 20 ethyl. In other embodiments, R^{1b} is H, methyl, ethyl, n-propyl, or phenyl. In still other embodiments, R^{1b} is not H.

[0009] In some embodiments, R² is methyl, ethyl, C₃ alkyl, n-propyl, isopropyl, ethoxy, methoxy, 5-hydroxy pyridyl, indolyl, 1,2,3,4-tetrahydroisoquinolyl, furyl, 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, 2-chlorophenyl, 3-

chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In other
 10 embodiments, R^2 is methyl, ethyl, n-propyl, or phenyl.

[0010] In some embodiments, R^3 is H, Cl, hydroxy (-OH), methyl, ethyl, C_{1-5} alkyl, C_3 alkyl, -CN, ethynyl, -CONH₂, -CON(CH₃)₂, 2-(morpholinyl)ethoxy, -CO-morpholin-4-yl, ethoxy, methoxy, 5-hydroxy pyridyl, indolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, furyl,
 15 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy
 20 phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In other
 embodiments, R^3 is H, methyl, ethyl, n-propyl, or phenyl.

[0011] In some embodiments, R⁴ is H, Cl, hydroxy (-OH), methyl, ethyl, C₁₋₅ alkyl, C₃ alkyl, -CN, ethynyl, -CONH₂, -CON(CH₃)₂, 2-(morpholinyl)ethoxy, -CO-morpholin-4-yl, ethoxy, methoxy, 5-hydroxy pyridyl, indolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, furyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In other embodiments, R⁴ is H, methyl, ethyl, n-propyl, or phenyl.

[0012] In some embodiments, M is iron (Fe), nickel (Ni), palladium (Pd), cadmium (Cd), manganese (Mn), cobalt (Co), copper (Cu), or zinc (Zn). In other embodiments, M is Cu, Ni, or Zn. In still other embodiments, M is Cu.

[0013] In some embodiments, the compound of Formula (I) is I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-10, I-11, I-12, I-13, I-14, I-15, I-16, I-17, I-18, I-19, I-20, I-21, I-22, I-23, I-24, I-25, I-26, I-27, I-28, I-29, I-30, I-31, I-32, I-33, I-34, I-35, I-36, I-37, I-38, I-39, I-40, I-41, I-42, I-43, I-44, I-45, I-46, I-47, I-48, I-49, I-50, I-51, I-52, I-53, I-54, I-55, I-56, I-57, I-58, I-59, I-60, I-61, I-62, I-63, I-64, I-65, I-66, I-67, I-68, I-69, I-70, or I-71. In other embodiments, the compound of Formula (I) is I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22. In still other embodiments, the compound of Formula

(I) is I-1 or I-5. In yet other embodiments, (a) R^{1a} is H, R^{1b} is methyl, R² is ethyl, R³ is methyl, R⁴ is methyl, M is Cu, or combinations thereof; (b) R^{1a} is methyl, R^{1b} is H, R² is ethyl, R³ is methyl, R⁴ is methyl, M is Cu, or combinations thereof; (c) R^{1a} is H, R^{1b} is methyl, R² is ethyl, R³ is methyl, R⁴ is methyl, M is Zn, or combinations thereof; or (d) R^{1a} is methyl, R^{1b} is H, R² is ethyl, R³ is methyl, R⁴ is methyl, M is Zn, or combinations thereof. In still other embodiments, R^{1a} is H or R^{1b} is H, but both R^{1a} and R^{1b} are not H.

[0014] Some embodiments of the invention include a composition comprising a compound, as disclosed herein (e.g., Formula (I)). In certain embodiments, the amount of the compound is from about 0.0001% (by weight total composition) to about 99%. In other embodiments, the composition further comprises a formulary ingredient, an adjuvant, or a carrier.

[0015] Some embodiments of the invention include a pharmaceutical composition comprising a compound, as disclosed herein (e.g., Formula (I)). In some embodiments, the amount of the compound is from about 0.0001% (by weight total composition) to about 50%. In other embodiments, the pharmaceutical composition further comprises a formulary ingredient, an adjuvant, or a carrier.

[0016] Some embodiments of the invention include a method for providing an animal with a compound comprising one or more administrations of one or more compositions comprising a compound as disclosed herein (e.g., Formula (I)), wherein the compositions may be the same or different if there is more than one administration. In other embodiments, at least one of the one or more compositions further comprises a formulary ingredient. In still other embodiments, at least one of the one or more compositions comprises a composition (e.g., as disclosed herein) or a

pharmaceutical composition (e.g., as disclosed herein). In certain embodiments, at least one of the one or more administrations comprises parenteral administration, a mucosal administration, intravenous administration, subcutaneous administration, topical administration, intradermal administration, oral administration, sublingual administration, intranasal administration, or intramuscular administration. In other embodiments, if there is more than one administration at least one composition used for at least one administration is different from the composition of at least one other administration. In still other embodiments, the compound of at least one of the one or more compositions is administered to the animal in an amount of from about 0.01 mg/kg animal body weight to about 15 mg/kg animal body weight. In yet other embodiments, the animal is a human, a rodent, or a primate.

[0017] Some embodiments of the invention include a method for treating an animal for a disease, comprising one or more administrations of one or more compositions comprising a compound as disclosed herein (e.g., Formula (I)), wherein the compositions may be the same or different if there is more than one administration. In some embodiments, at least one of the one or more compositions further comprises a formulary ingredient. In other embodiments, at least one of the one or more compositions comprises a composition (e.g., as disclosed herein) or a pharmaceutical composition (e.g., as disclosed herein). In yet other embodiments, at least one of the one or more administrations comprises parenteral administration, a mucosal administration, intravenous administration, subcutaneous administration, topical administration, intradermal administration, oral administration, sublingual administration, intranasal administration, or intramuscular administration. In still other embodiments, if there is more than one administration at least one composition

used for at least one administration is different from the composition of at least one other administration. In certain embodiments, the compound of at least one of the one or more compositions is administered to the animal in an amount of from about 0.005 mg/kg animal body weight to about 50 mg /kg animal body weight. In other

5 embodiments, the animal is a human, a rodent, or a primate. In some embodiments, the animal is in need of the treatment. In other embodiments, the method is for treating cancer. In still other embodiments, the method is for treating acute lymphoblastic leukemia, astrocytoma, basal cell carcinoma, bladder cancer, bone marrow cancer, breast cancer, chronic lymphocytic leukemia (CLL), CNS cancer,

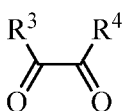
10 colon cancer, colorectal cancer, endometrial cancer, gastric cancer, glioblastoma, glioblastoma multiforme, glioma, gliosarcoma, hepatocellular carcinoma, kidney cancer, leukemia, liver cancer, lung cancer, lymphoma, melanoma, malignant nerve sheath tumors, medulloblastoma, meningioma, multiple myeloma, nasopharyngeal carcinoma, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral

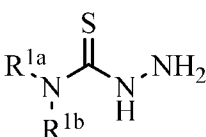
15 cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, renal cancer, renal cell carcinoma, rhabdomyosarcoma, squamous cell carcinoma, stomach cancer, thyroid cancer, uterine cancer, cancers that can result in metastasis, cancers resulting from metastasis, or cancerous tumors thereof. In some embodiments, the method is for treating leukemia, lung cancer, non-small cell lung cancer, colorectal cancer,

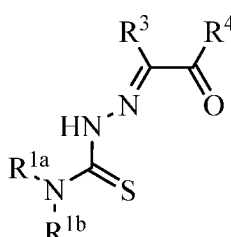
20 colon cancer, rectal cancer, CNS cancer, glioblastoma, glioblastoma multiforme, gliosarcoma, astrocytoma, melanoma, cutaneous malignant melanoma, melanoma tumorigenesis, ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof. In other embodiments, the method does not include treating leukemia. In yet other embodiments, the method is for treating lung cancer,

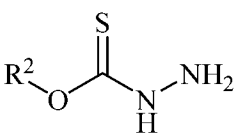
non-small cell lung cancer, colorectal cancer, colon cancer, rectal cancer, CNS cancer, glioblastoma, glioblastoma multiforme, gliosarcoma, astrocytoma, melanoma, cutaneous malignant melanoma, melanoma tumorigenesis, ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof. In other
 5 embodiments, the method is for treating cancerous tumors.

[0018] Some embodiments of the invention include a method for preparing a compound disclosed herein (e.g., Formula (I)) comprising (a) reacting a compound of Formula (II) with a compound of Formula (III) to result in a mixture comprising a compound of Formula (IV) and (b) reacting a compound of Formula (IV) with a
 10 compound of Formula (V) to result in a mixture comprising a compound of Formula (Ib). In other embodiments, the method further comprises recovering a compound of Formula (Ib). In some embodiments, the method further comprises (c) reacting a compound of Formula (Ib) with a compound of Formula (VI) and (d) recovering a

compound of Formula (Ia). In some embodiments, Formula (II) is  (II).

15 In other embodiments, Formula (III) is  (III). In other

embodiments, Formula (IV) is  (IV). In yet other embodiments,

Formula (V) is  (V). In still other embodiments, Formula (VI) is

M:anion (VI). In some embodiments, the anion is a weak base, acetate, acetate monohydrate, acetate dihydrate, or acetate tetrahydrate. In other embodiments, the Formula (VI) is copper (II) acetate monohydrate, nickel (II) acetate tetrahydrate, or zinc (II) acetate dihydrate.

5 [0019] Other embodiments of the invention are also discussed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The
10 invention may be better understood by reference to one or more of these drawings in combination with the description of specific embodiments presented herein.

[0021] **FIG. 1:** Anti-proliferative activity of compound I-1 (NV3104) using MTT assay.

[0022] **FIG. 2:** Anti-proliferative activity of compound I-3 (NV40109) using
15 MTT assay.

[0023] **FIG. 3:** Anti-proliferative activity of compound I-3 (NV40109) using MTT assay.

[0024] **FIG. 4:** Anti-proliferative activity of compound I-4 (NV40122) using MTT assay.

20 [0025] **FIG. 5:** Anti-proliferative activity of compound I-4 (NV40122) using MTT assay.

[0026] **FIG. 6:** Anti-proliferative activity of compound I-5 (NV30189) using MTT assay.

- [0027] **FIG. 7:** Anti-proliferative activity of compound I-6 (NV30169) using MTT assay.
- [0028] **FIG. 8:** Anti-proliferative activity of compound I-7 (NV40069) using MTT assay.
- 5 [0029] **FIG. 9:** Anti-proliferative activity of compound I-8 (NV30182) using MTT assay.
- [0030] **FIG. 10:** Anti-proliferative activity of compound I-8 (NV30182) using MTT assay.
- [0031] **FIG. 11:** Anti-proliferative activity of compound I-9 (NV30177)
- 10 using MTT assay.
- [0032] **FIG. 12:** Anti-proliferative activity of compound I-10 (NV30178) using MTT assay.
- [0033] **FIG. 13:** Anti-proliferative activity of compound I-11 (NV40110) using MTT assay.
- 15 [0034] **FIG. 14:** Anti-proliferative activity of compound I-11 (NV40110) using MTT assay.
- [0035] **FIG. 15:** Anti-proliferative activity of compound I-12 (NV30156) using MTT assay.
- [0036] **FIG. 16:** Anti-proliferative activity of compound I-12 (NV30156)
- 20 using MTT assay.
- [0037] **FIG. 17:** Anti-proliferative activity of compound I-14 (NV30164) using MTT assay.
- [0038] **FIG. 18:** Anti-proliferative activity of compound I-22 (MB10014) using MTT assay.

- [0039] **FIG. 19:** One-dose data for compound I-1 (NV3104). The compound is tested at a single high dose (10 μ M) in the panel's 60 cell lines.
- [0040] **FIG. 20:** One-dose data for compound I-5 (NV30189). The compound is tested at a single high dose (10 μ M) in the panel's 60 cell lines.
- 5 [0041] **FIG. 21:** Cell proliferation for several cell lines using MTT assays for compound I-1 (NV3104).
- [0042] **FIG. 22:** Cell survival assays of A549 lung cancer cells for compound I-1 (NV3104) at several concentrations.
- [0043] **FIG. 23:** Reactive Oxygen Species (ROS) production of A549 lung
10 cancer cells for several concentrations of compound I-1 (NV3104).
- [0044] **FIG. 24:** The ^1H NMR spectrum of the product of reaction A.
- [0045] **FIG. 25:** The ^{13}C NMR spectrum of the product of reaction A.
- [0046] **FIG. 26:** The ^1H NMR spectrum of the product of reaction B.
- [0047] **FIG. 27:** The ^{13}C NMR spectrum of the product of reaction B.
- 15 [0048] **FIG. 28:** The ^1H NMR spectrum of the product of reaction C (ethyl) which is compound I-4.
- [0049] **FIG. 29:** The ^{13}C NMR spectrum of the product of reaction C (ethyl) which is compound I-4.
- [0050] **FIG. 30:** The ^1H NMR spectrum of the product of reaction C (propyl)
20 which is compound I-12.
- [0051] **FIG. 31:** The ^{13}C NMR spectrum of the product of reaction C (propyl) which is compound I-12.
- [0052] **FIG. 32:** The ^1H NMR spectrum of the product of reaction D which is compound I-8.

[0053] **FIG. 33:** The ^{13}C NMR spectrum of the product of reaction D which is compound I-8.

[0054] **FIG. 34:** An ORTEP representation of the product of reaction E (ethyl) which is compound I-1.

5 [0055] **FIG. 35:** An ORTEP representation of the product of reaction F which is compound I-5.

DETAILED DESCRIPTION

[0056] While embodiments encompassing the general inventive concepts may
10 take diverse forms, various embodiments will be described herein, with the understanding that the present disclosure is to be considered merely exemplary, and the general inventive concepts are not intended to be limited to the disclosed embodiments.

[0057] Some embodiments of the invention include inventive compounds
15 (e.g., compounds of Formula (I) or (Ia)). Other embodiments include compositions (e.g., pharmaceutical compositions) comprising the inventive compound. Still other embodiments of the invention include compositions (e.g., pharmaceutical compositions) for treating, for example, certain diseases using the inventive compounds. Some embodiments include methods of using the inventive compound
20 (e.g., in compositions or in pharmaceutical compositions) for administering and treating (e.g., diseases such as cancer). Further embodiments include methods for making the inventive compounds. Additional embodiments of the invention are also discussed herein.

[0058] As used herein (unless otherwise specified), the term “alkyl” means a monovalent, straight or branched hydrocarbon chain. For example, the terms “C₁-C₇ alkyl” or “C₁-C₄ alkyl” refer to straight- or branched-chain saturated hydrocarbon groups having from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7), or 1 to 4 (e.g., 1, 2, 3, or 4),
5 carbon atoms, respectively. Examples of C₁-C₇ alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, n-hexyl, and n-septyl. Examples of C₁-C₄ alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, and t-butyl.

[0059] As used herein (unless otherwise specified), the term “alkenyl” means
10 a monovalent, straight or branched hydrocarbon chain that includes one or more (e.g., 1, 2, 3, or 4) double bonds. Examples of alkenyl groups include, but are not limited to, vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, and 5-hexenyl.

15 [0060] As used herein (unless otherwise specified), the term “alkoxy” means any of the above alkyl groups which is attached to the remainder of the molecule by an oxygen atom (alkyl-O-). Examples of alkoxy groups include, but are not limited to, methoxy (sometimes shown as MeO-), ethoxy, isopropoxy, propoxy, and butyloxy.

[0061] As used herein (unless otherwise specified), the term “alkynyl” means
20 a monovalent, straight or branched hydrocarbon chain that includes one or more (e.g., 1, 2, 3, or 4) triple bonds and that also may optionally include one or more (e.g. 1, 2, 3, or 4) double bonds in the chain. Examples of alkynyl groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-

pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, and 5-hexynyl.

[0062] As used herein (unless otherwise specified), the term “aryl” means a monovalent, monocyclic or bicyclic, 5, 6, 7, 8, 9, 10, 11, or 12 membered aromatic hydrocarbon group which, when unsubstituted. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, tolyl, and xylyl. For a bicyclic aryl that is designated as substituted, one or both rings can be substituted.

[0063] As used herein (unless otherwise specified), the term “cycloalkyl” means a monovalent, monocyclic or bicyclic, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 membered hydrocarbon group. The rings can be saturated or partially unsaturated. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and bicycloalkyls (e.g., bicyclooctanes such as [2.2.2]bicyclooctane or [3.3.0]bicyclooctane, bicyclononanes such as [4.3.0]bicyclononane, and bicyclodecanes such as [4.4.0]bicyclodecane (decalin), or spiro compounds). For a monocyclic cycloalkyl, the ring is not aromatic. For a bicyclic cycloalkyl, if one ring is aromatic, then the other is not aromatic. For a bicyclic cycloalkyl that is designated as substituted, one or both rings can be substituted.

[0064] As used herein (unless otherwise specified), the term “halogen” means monovalent Cl, F, Br, or I.

[0065] As used herein (unless otherwise specified), the term “heteroaryl” means a monovalent, monocyclic or bicyclic, 5, 6, 7, 8, 9, 10, 11, or 12 membered, hydrocarbon group, where 1, 2, 3, 4, 5, or 6 carbon atoms are replaced by a hetero atom independently selected from nitrogen, oxygen, or sulfur atom, and the

monocyclic or bicyclic ring system is aromatic. Examples of heteroaryl groups include, but are not limited to, thienyl (or thiophenyl), furyl, indolyl, pyrrolyl, pyridinyl, pyrazinyl, oxazolyl, thiazolyl, quinolinyl, pyrimidinyl, imidazolyl, triazolyl, tetrazolyl, 1H-pyrazol-4-yl, 1-Me-pyrazol-4-yl, pyridin-3-yl, pyridin-4-yl, 3,5-dimethylisoxazolyl, 1H-pyrrol-3-yl, 3,5-di-Me-pyrazolyl, and 1H-pyrazol-4-yl.

For a bicyclic heteroaryl, if one ring is aryl, then the other is heteroaryl. For a bicyclic heteroaryl, one or both rings can have one or more hetero atoms. For a bicyclic heteroaryl that is designated as substituted, one or both rings can be substituted.

[0066] As used herein (unless otherwise specified), the term “heterocyclyl” means a monovalent, monocyclic or bicyclic, 5, 6, 7, 8, 9, 10, 11, or 12 membered, hydrocarbon, where 1, 2, 3, 4, 5, or 6 carbon atoms are replaced by a hetero atom independently selected from nitrogen atom, oxygen atom, or sulfur atom, and the monocyclic or bicyclic ring system is not aromatic. Examples of heterocyclyl groups include, but are not limited to, tetrahydropyran, pyrrolidinyl (e.g., pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, or pyrrolidin-4-yl), piperazinyl (e.g., piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, or piperazin-4-yl), piperidinyl (e.g., piperadin-1-yl, piperadin-2-yl, piperadin-3-yl, or piperadin-4-yl), and morpholinyl (e.g., morpholin-1-yl, morpholin-2-yl, morpholin-3-yl, or morpholin-4-yl). For a bicyclic heterocyclyl, if one ring is aromatic (e.g., monocyclic aryl or heteroaryl), then the other ring is not aromatic. For a bicyclic heterocyclyl, one or both rings can have one or more hetero atoms. For a bicyclic heterocyclyl that is designated as substituted, one or both rings can be substituted.

[0067] As used herein (unless otherwise specified), the term “hetero atom” means an atom selected from nitrogen atom, oxygen atom, or sulfur atom.

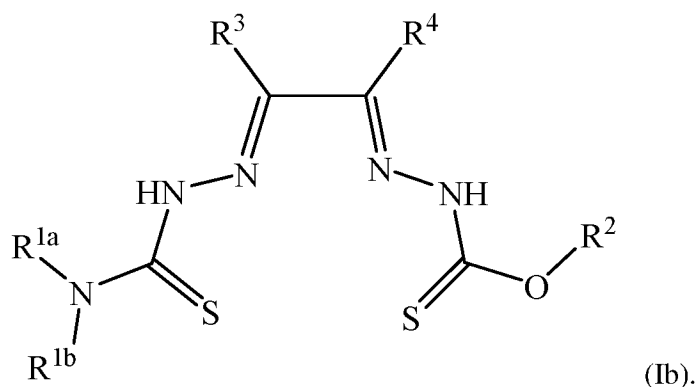
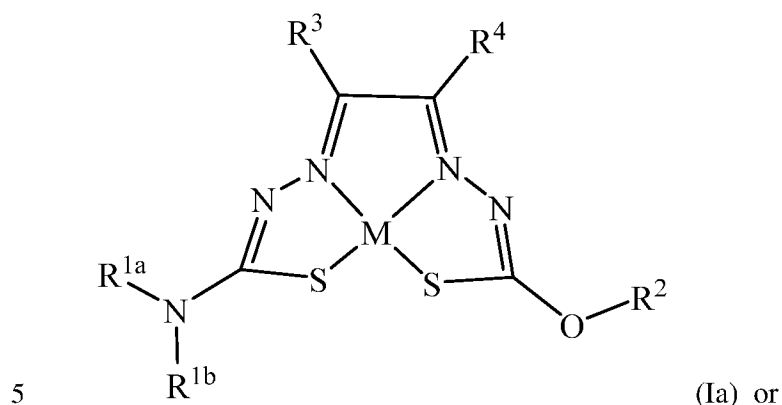
[0068] As used herein (unless otherwise specified), the terms “hydroxy” or “hydroxyl” indicates the presence of a monovalent -OH group.

5 [0069] As used herein (unless otherwise specified), the term “substituted” (e.g., as in substituted alkyl) means that one or more hydrogen atoms of a chemical group (with one or more hydrogen atoms) can be replaced by one or more non-hydrogen substituents selected from the specified options. The replacement can occur at one or more positions. The term “optionally substituted” means that one or more
10 hydrogen atoms of a chemical group (with one or more hydrogen atoms) can be, but is not required to be, substituted.

[0070] Some compounds of the invention can have one or more chiral centers and can exist in and be isolated in optically active and racemic forms, for any of the one or more chiral centers. Some compounds can exhibit polymorphism. The
15 compounds of the present invention (e.g., Formula I) encompass any optically active, racemate, stereoisomer form, polymorphism, or mixtures thereof. If a chiral center does not provide an indication of its configuration (i.e., R or S) in a chemical structure, it should be considered to represent R, S or a racemate.

[0071] Compounds and Compositions including Pharmaceutical Compositions

[0072] Some embodiments of the invention include compounds of Formula (Ia) and (Ib) (collectively Formula (Ia) and Formula (Ib) are referred to as Formula (I)):



[0073] In some embodiments, R^{1a} can be monovalent H, halogen (e.g., F, Cl, Br, or I), -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl (e.g., C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkyl), C₂-C₁₀ alkenyl (e.g., C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkenyl), C₂-C₁₀ alkynyl (e.g., C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkynyl), C₁-C₉ alkoxy (e.g., C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, or C₉ alkoxy), cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more (e.g.,

10

0, 1, 2, 3, 4, 5, or 6) of halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In other embodiments, R^{1a} can be monovalent H, halogen (e.g., F, Cl, Br, or I), -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl (e.g., C₁, C₂, C₃, C₄, C₅, C₆, or C₇ alkyl), C₁-C₆ alkoxy (e.g., C₁, C₂, C₃, C₄, C₅, or C₆ alkoxy), cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₁-C₆ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more (e.g., 0, 1, 2, 3, 4, 5, or 6) of halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In some embodiments, R^{1a} can be H, Cl, hydroxy (-OH), methyl, ethyl, C₁₋₅ alkyl, C₃ alkyl (e.g., n-propyl or isopropyl), -CN, ethynyl, -CONH₂, -CON(CH₃)₂, 2-(morpholinyl)ethoxy, -CO-morpholin-4-yl, ethoxy, methoxy, 5-hydroxy pyridyl (e.g., 5-hydroxy pyrid-3-yl), indolyl (e.g., 1-indolyl), 1,2,3,4-tetrahydroisoquinolyl (e.g., 2-1,2,3,4-tetrahydroisoquinolyl), 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, furyl (e.g., 2-furyl), 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-

trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In some embodiments, R^{1a} can be H, methyl, ethyl, C₃ alkyl, n-propyl, isopropyl, ethoxy, methoxy, 5-hydroxy pyridyl (e.g., 5-hydroxy pyrid-3-yl), indolyl (e.g., 1-indolyl), 1,2,3,4-tetrahydroisoquinolyl (e.g., 2-1,2,3,4-tetrahydroisoquinolyl), furyl (e.g., 2-furyl), 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In some embodiments, R^{1a} can be H, methyl, ethyl, n-propyl, or phenyl. In other embodiments, R^{1a} is not H.

[0074] In some embodiments, R^{1b} can be monovalent H, halogen (e.g., F, Cl, Br, or I), -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl (e.g., C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkyl), C₂-C₁₀ alkenyl (e.g., C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkenyl), C₂-C₁₀ alkynyl (e.g., C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkynyl), C₁-C₉ alkoxy (e.g., C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, or C₉ alkoxy),

cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more (e.g., 0, 1, 2, 3, 4, 5, or 6) of halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH),

5 methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In other embodiments, R^{1b} can be monovalent H, halogen (e.g., F, Cl, Br, or I), -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl (e.g.,

10 C₁, C₂, C₃, C₄, C₅, C₆, or C₇ alkyl), C₁-C₆ alkoxy (e.g., C₁, C₂, C₃, C₄, C₅, or C₆ alkoxy), cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₁-C₆ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more (e.g., 0, 1, 2, 3, 4, 5, or 6) of

15 halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In some

embodiments, R^{1b} can be H, Cl, hydroxy (-OH), methyl, ethyl, C₁₋₅ alkyl, C₃ alkyl (e.g., n-propyl or isopropyl), C₄ alkyl, -CN, ethynyl, -CONH₂, -CON(CH₃)₂,

20 2-(morpholinyl)ethoxy, -CO-morpholin-4-yl, ethoxy, methoxy, 5-hydroxy pyridyl (e.g., 5-hydroxy pyrid-3-yl), indolyl (e.g., 1-indolyl), 1,2,3,4-tetrahydroisoquinolyl (e.g., 2-1,2,3,4-tetrahydroisoquinolyl), 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, furyl (e.g., 2-furyl), 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-

methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In some embodiments, R^{1b} can be H, methyl, ethyl, C₃ alkyl, n-propyl, isopropyl, ethoxy, methoxy, 5-hydroxy pyridyl (e.g., 5-hydroxy pyrid-3-yl), indolyl (e.g., 1-indolyl), 1,2,3,4-tetrahydroisoquinolyl (e.g., 2-1,2,3,4-tetrahydroisoquinolyl), furyl (e.g., 2-furyl), 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In some embodiments, R^{1b} can be H, methyl, ethyl, n-propyl, or phenyl. In other embodiments, R^{1b} is not H.

[0075] In other embodiments, R^{1a} and R^{1b} can be bonded together (with their attached nitrogen) to form heterocyclyl or heteroaryl, which heterocyclyl or heteroaryl

can optionally be substituted with one or more (e.g., 0, 1, 2, 3, 4, 5, or 6) of halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In some embodiments, R^{1a} and R^{1b} can be bonded together to form pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, indolinyl, morpholinyl, pyrrolyl, pyrazolyl, isoxazolyl, pyrazinyl, pyridyl, 5-hydroxy pyridyl, indolyl, indazolyl, or 1,2,3,4-tetrahydroisoquinolyl. In some embodiments, R^{1a} and R^{1b} are not bonded together.

[0076] In some embodiments, R² can be monovalent H, halogen (e.g., F, Cl, Br, or I), -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl (e.g., C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkyl), C₂-C₁₀ alkenyl (e.g., C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkenyl), C₂-C₁₀ alkynyl (e.g., C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkynyl), C₁-C₉ alkoxy (e.g., C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, or C₉ alkoxy), cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more (e.g., 0, 1, 2, 3, 4, 5, or 6) of halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In other embodiments, R² can be monovalent H, halogen (e.g., F, Cl, Br, or I), -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl (e.g., C₁, C₂, C₃, C₄, C₅, C₆, or C₇ alkyl), C₁-C₆ alkoxy (e.g., C₁, C₂, C₃, C₄, C₅, or C₆

alkoxy), cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₁-C₆ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more (e.g., 0, 1, 2, 3, 4, 5, or 6) of halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In some embodiments, R² can be Cl, hydroxy (-OH), methyl, ethyl, C₁₋₅ alkyl, C₃ alkyl (e.g., n-propyl or isopropyl), -CN, ethynyl, -CONH₂, -CON(CH₃)₂, 2-(morpholinyl)ethoxy, -CO-morpholin-4-yl, ethoxy, methoxy, 5-hydroxy pyridyl (e.g., 5-hydroxy pyrid-3-yl), indolyl (e.g., 1-indolyl), 1,2,3,4-tetrahydroisoquinolyl (e.g., 2-1,2,3,4-tetrahydroisoquinolyl), 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, furyl (e.g., 2-furyl), 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In some embodiments, R² can be methyl, ethyl, C₃ alkyl, n-propyl, isopropyl, ethoxy, methoxy, 5-hydroxy pyridyl (e.g., 5-hydroxy pyrid-3-yl), indolyl (e.g., 1-indolyl), 1,2,3,4-tetrahydroisoquinolyl (e.g., 2-1,2,3,4-tetrahydroisoquinolyl), furyl (e.g., 2-

furyl), 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In some embodiments, R^2 can be methyl, ethyl, n-propyl, or phenyl. In other embodiments, R^2 is not H.

[0077] In some embodiments, R^3 can be monovalent H, halogen (e.g., F, Cl, Br, or I), -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl (e.g., C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkyl), C₂-C₁₀ alkenyl (e.g., C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkenyl), C₂-C₁₀ alkynyl (e.g., C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, or C₁₀ alkynyl), C₁-C₉ alkoxy (e.g., C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, or C₉ alkoxy), cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more (e.g., 0, 1, 2, 3, 4, 5, or 6) of halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-

C₃ alkoxy. In other embodiments, R³ can be monovalent H, halogen (e.g., F, Cl, Br, or I), -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl (e.g., C₁, C₂, C₃, C₄, C₅, C₆, or C₇ alkyl), C₁-C₆ alkoxy (e.g., C₁, C₂, C₃, C₄, C₅, or C₆ alkoxy), cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH),

5 carboxy (-CO₂H), C₁-C₇ alkyl, C₁-C₆ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more (e.g., 0, 1, 2, 3, 4, 5, or 6) of halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-

10 C₃ alkyl, C₁-C₃ perfluoronated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In some embodiments, R³ can be H, Cl, hydroxy (-OH), methyl, ethyl, C₁₋₅ alkyl, C₃ alkyl (e.g., n-propyl or isopropyl), -CN, ethynyl, -CONH₂, -CON(CH₃)₂, 2-(morpholinyl)ethoxy, -CO-morpholin-4-yl, ethoxy, methoxy, 5-hydroxy pyridyl (e.g., 5-hydroxy pyrid-3-yl), indolyl (e.g., 1-indolyl), 1,2,3,4-tetrahydroisoquinolyl (e.g., 2-1,2,3,4-

15 tetrahydroisoquinolyl), 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, furyl (e.g., 2-furyl), 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl

20 phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In some

embodiments, R^3 can be H, methyl, ethyl, C_3 alkyl, n-propyl, isopropyl, ethoxy, methoxy, 5-hydroxy pyridyl (e.g., 5-hydroxy pyrid-3-yl), indolyl (e.g., 1-indolyl), 1,2,3,4-tetrahydroisoquinolyl (e.g., 2-1,2,3,4-tetrahydroisoquinolyl), furyl (e.g., 2-furyl), 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In some embodiments, R^3 can be H, methyl, ethyl, n-propyl, or phenyl. In other embodiments, R^3 is not H.

[0078] In some embodiments, R^4 can be monovalent H, halogen (e.g., F, Cl, Br, or I), -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C_1 - C_{10} alkyl (e.g., C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , or C_{10} alkyl), C_2 - C_{10} alkenyl (e.g., C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , or C_{10} alkenyl), C_2 - C_{10} alkynyl (e.g., C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9 , or C_{10} alkynyl), C_1 - C_9 alkoxy (e.g., C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , or C_9 alkoxy), cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_9 alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more (e.g., 0, 1, 2, 3, 4, 5, or 6) of halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH),

methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In other embodiments, R⁴ can be monovalent H, halogen (e.g., F, Cl, Br, or I), -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl (e.g., C₁, C₂, C₃, C₄, C₅, C₆, or C₇ alkyl), C₁-C₆ alkoxy (e.g., C₁, C₂, C₃, C₄, C₅, or C₆ alkoxy), cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₁-C₆ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more (e.g., 0, 1, 2, 3, 4, 5, or 6) of halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy. In some embodiments, R⁴ can be H, Cl, hydroxy (-OH), methyl, ethyl, C₁₋₅ alkyl, C₃ alkyl (e.g., n-propyl or isopropyl), -CN, ethynyl, -CONH₂, -CON(CH₃)₂, 2-(morpholinyl)ethoxy, -CO-morpholin-4-yl, ethoxy, methoxy, 5-hydroxy pyridyl (e.g., 5-hydroxy pyrid-3-yl), indolyl (e.g., 1-indolyl), 1,2,3,4-tetrahydroisoquinolyl (e.g., 2-1,2,3,4-tetrahydroisoquinolyl), 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, furyl (e.g., 2-furyl), 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-

diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In some embodiments, R⁴ can be H, methyl, ethyl, C₃ alkyl, n-propyl, isopropyl, ethoxy, methoxy, 5-hydroxy pyridyl (e.g., 5-hydroxy pyrid-3-yl), indolyl (e.g., 1-indolyl), 1,2,3,4-tetrahydroisoquinolyl (e.g., 2-1,2,3,4-tetrahydroisoquinolyl), furyl (e.g., 2-furyl), 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl. In some embodiments, R⁴ can be H, methyl, ethyl, n-propyl, or phenyl. In other embodiments, R⁴ is not H.

[0079] In other embodiments, R³ and R⁴ can be bonded together (with their attached carbons) to form a ring that is fused to the attached carbons of R³ and R⁴, where the ring that is fused can be cycloalkyl, heterocyclyl, aryl, or heteroaryl, which cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more (e.g., 0, 1, 2, 3, 4, 5, or 6) of halogen (e.g., F, Cl, Br, or I), oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-

CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl,
 phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃,
 or C₁-C₃ alkoxy. In some embodiments, R³ and R⁴ can be bonded together to form a
 ring that is fused to the attachments of R³ and R⁴, where the ring that is fused can be
 5 cyclobutyl, cyclopentyl, cyclohexyl, chlorocyclohexyl, fluorocyclohexyl,
 methoxycyclohexyl, ethoxycyclohexyl, methylcyclohexyl, trifluoromethylcyclohexyl,
 cycloheptyl, cyclooctyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl,
 piperidyl, piperazinyl, indolinyl, morpholinyl, 5-hydroxy pyridyl, indolyl, 1,2,3,4-
 tetrahydroisoquinolyl, furyl, 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl,
 10 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-
 fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-
 methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-
 ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl
 phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy
 15 phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-
 diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-
 trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, or
 methylenedioxyphenyl. In some embodiments, R³ and R⁴ are not bonded together.

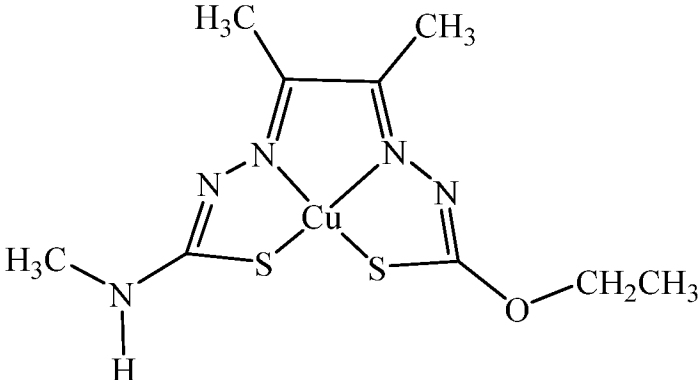
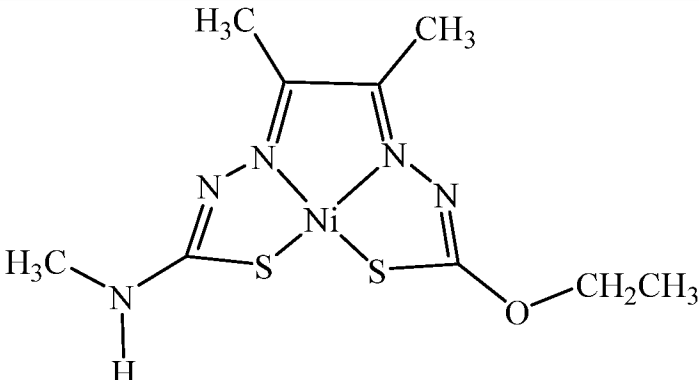
[0080] In other embodiments, M can be a divalent cation. In certain
 20 embodiments, M can be iron (Fe), nickel (Ni), palladium (Pd), cadmium (Cd),
 manganese (Mn), cobalt (Co), copper (Cu), or zinc (Zn). In some embodiments, M
 can be nickel (Ni), copper (Cu), or zinc (Zn). In other embodiments, M can be nickel
 (Ni). In some embodiments, M can be zinc (Zn). In some embodiments, M can be
 copper (Cu).

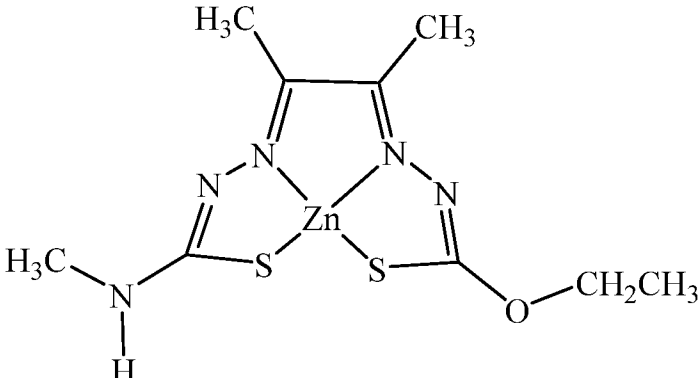
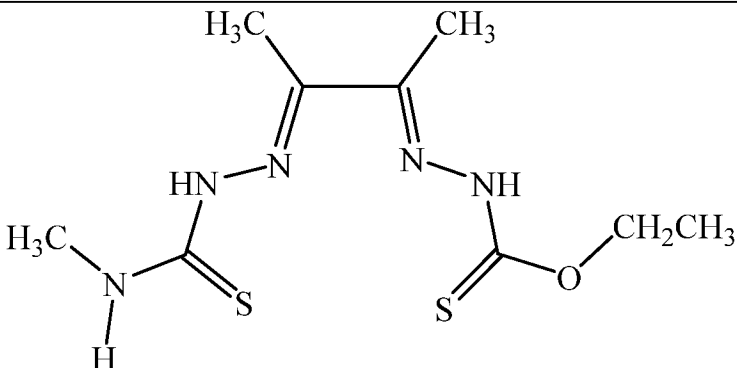
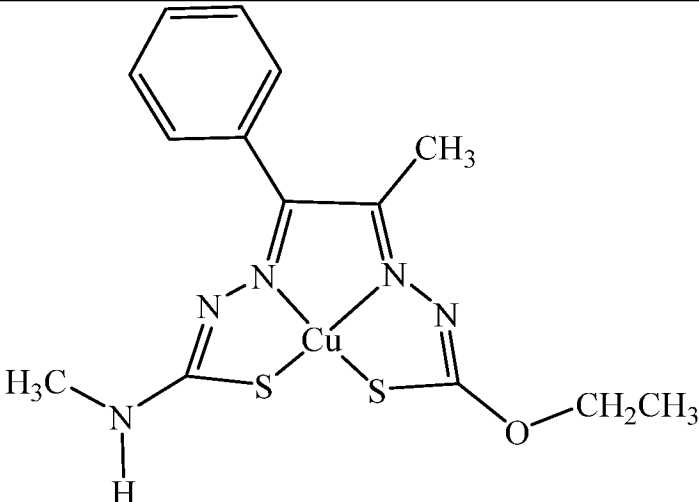
[0081] In certain embodiments, Formula (I) is only Formula (Ia) (i.e., Formula (Ib) is excluded from Formula (I)). In other embodiments, Formula (I) is only Formula (Ib) (i.e., Formula (Ia) is excluded from Formula (I)).

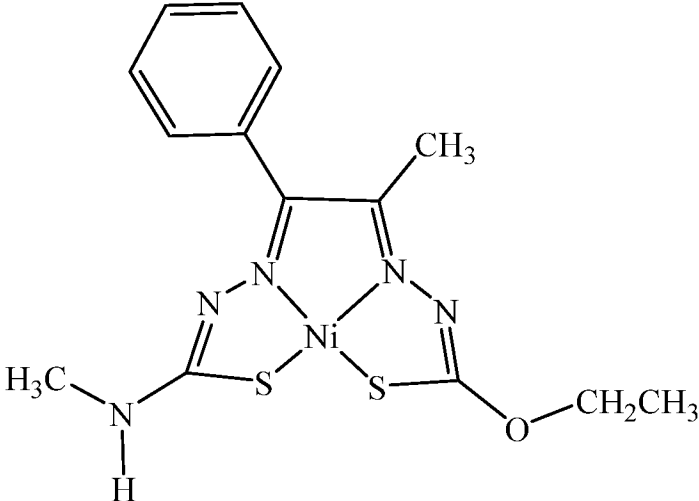
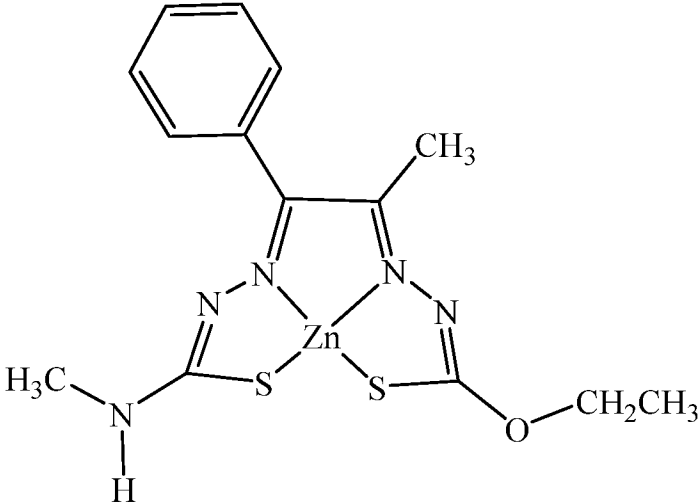
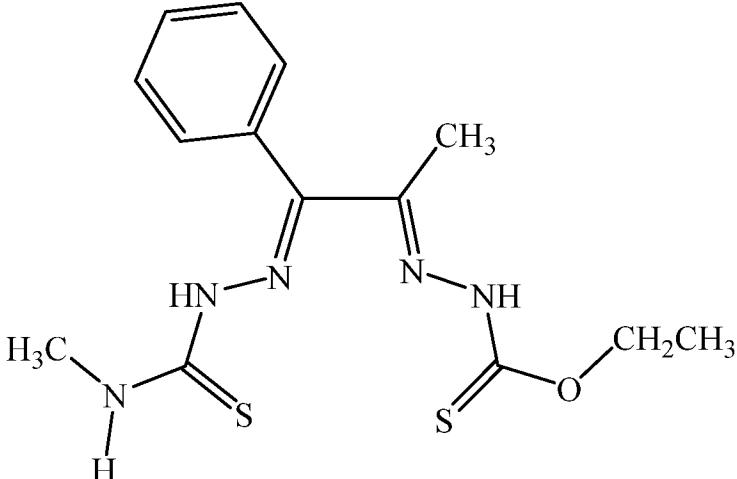
[0082] In some embodiments, the compounds of Formula (I) can be selected

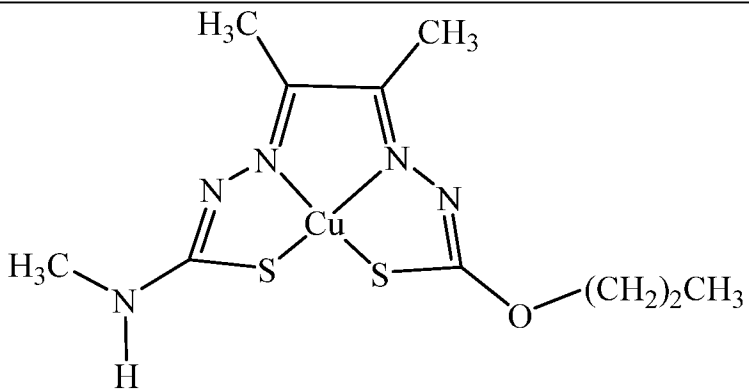
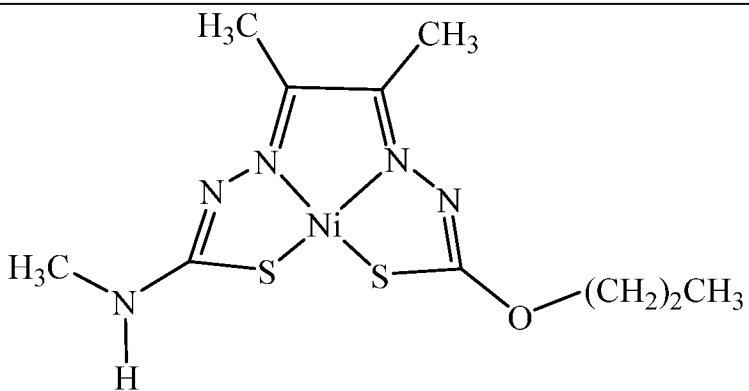
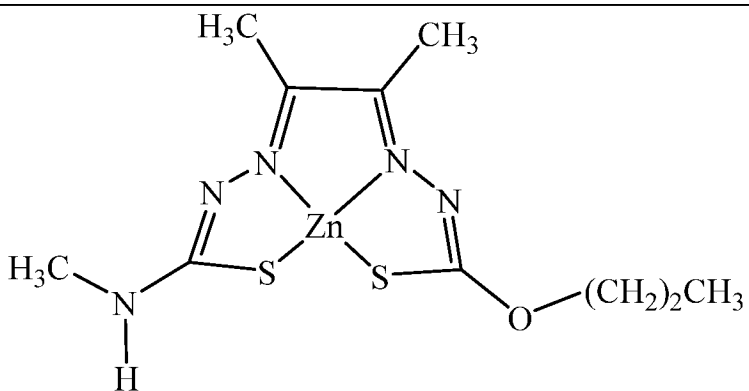
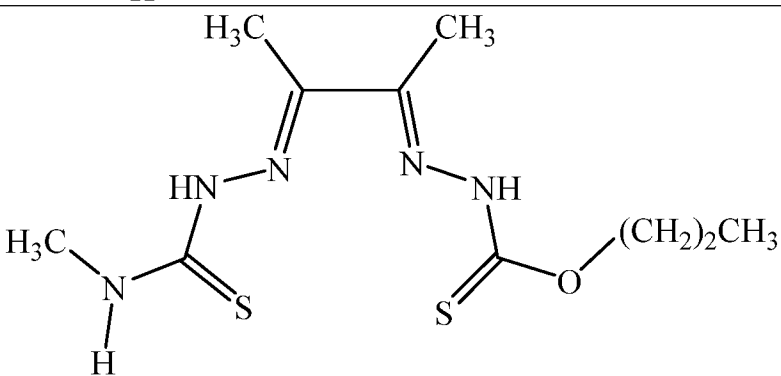
5 from those specified in Table 1.

Table 1

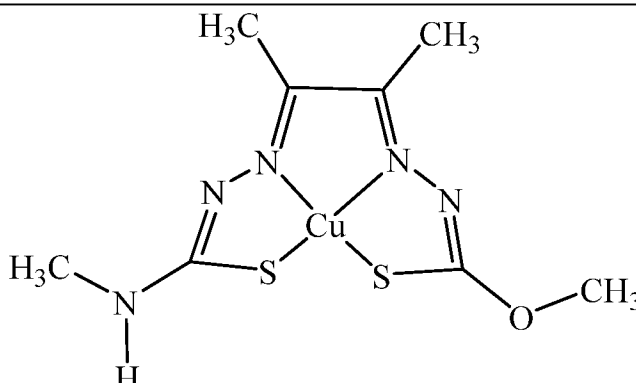
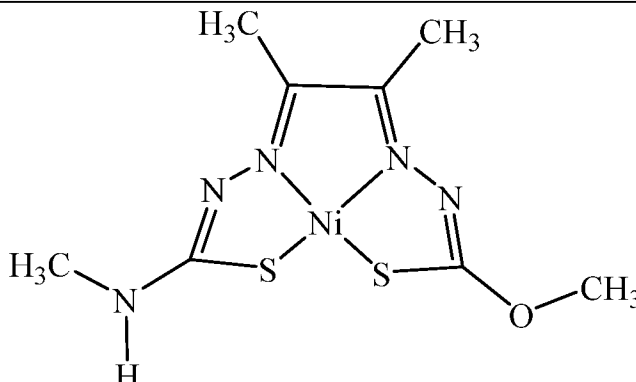
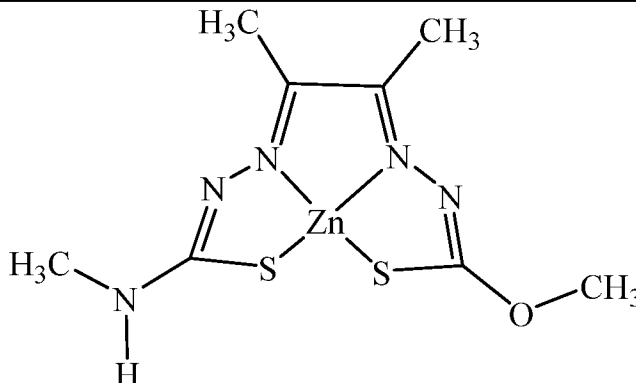
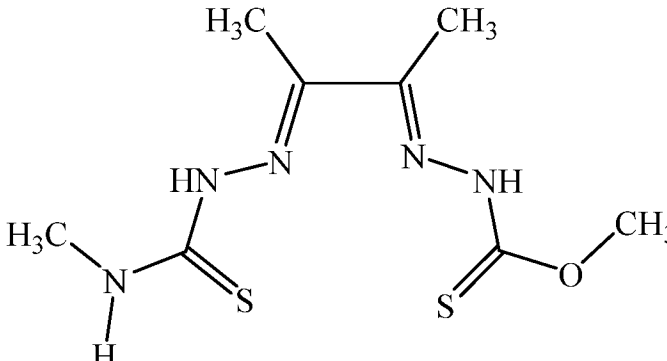
Compound Number (alternative designation)	Compound Structure
I-1 (NV3104)	
I-2	

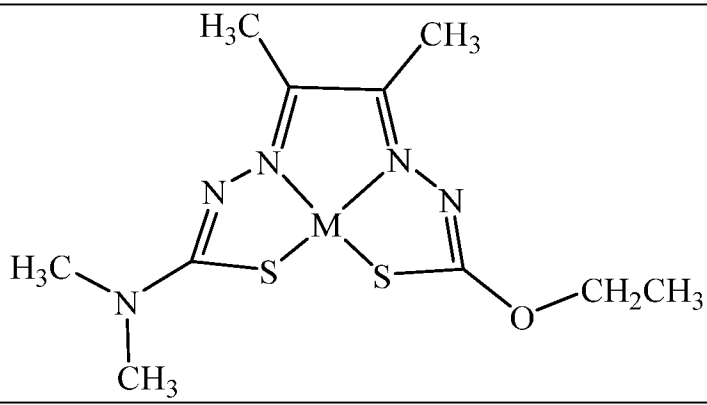
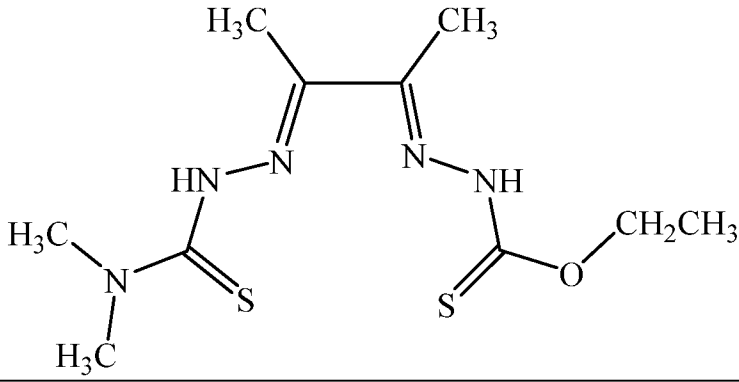
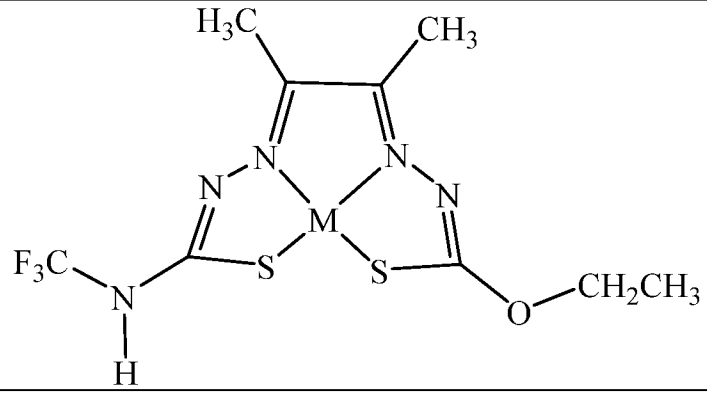
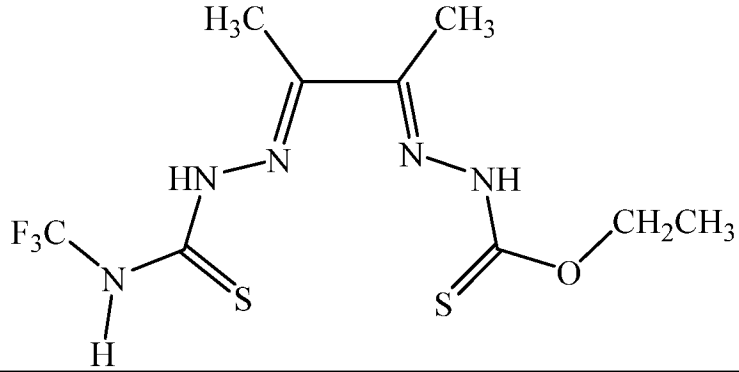
I-3 (NV40109)	
I-4 (NV40112)	
I-5 (NV30189)	

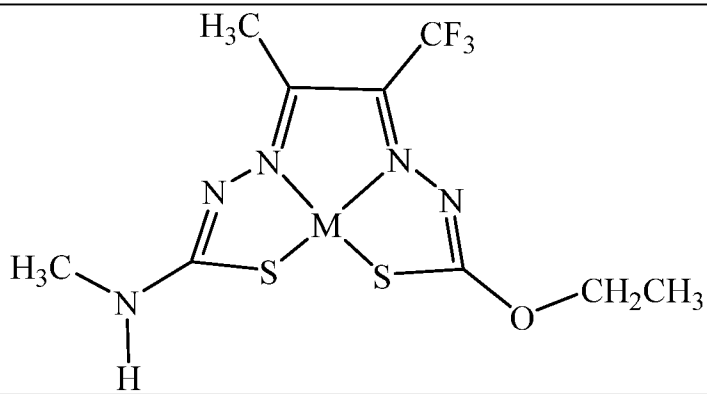
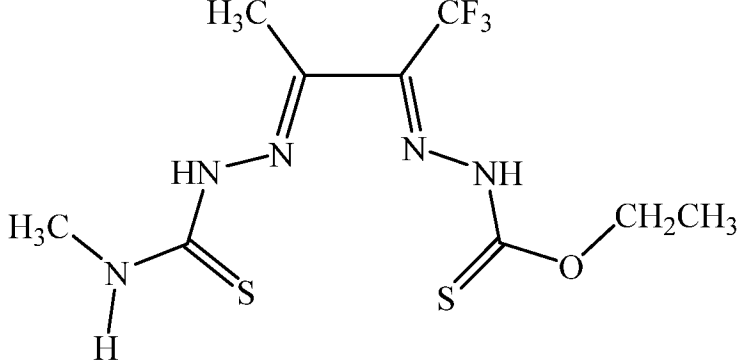
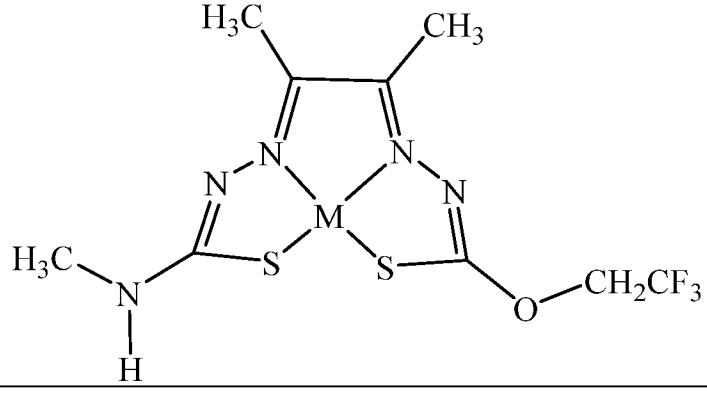
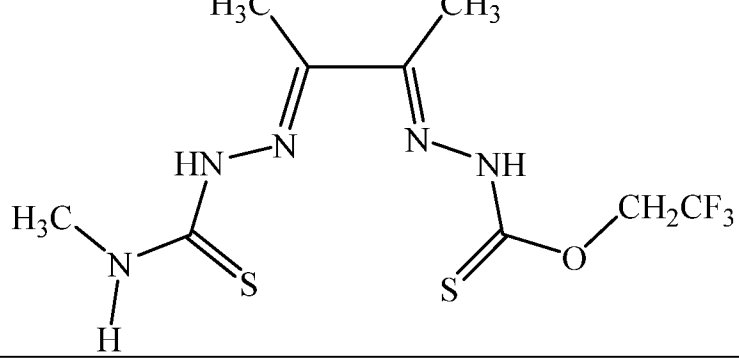
I-6 (NV30169)	
I-7 (NV40069)	
I-8 (NV30182)	

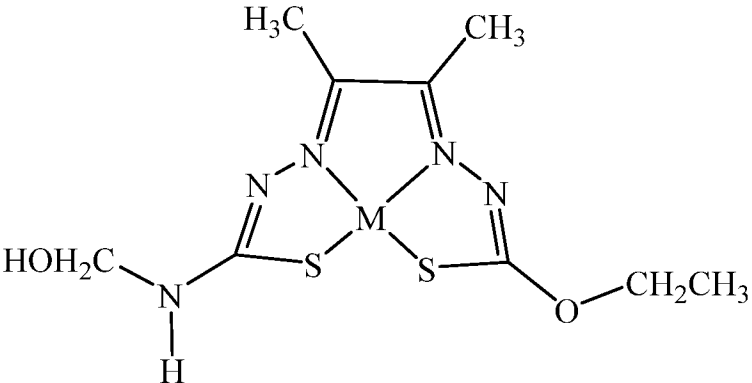
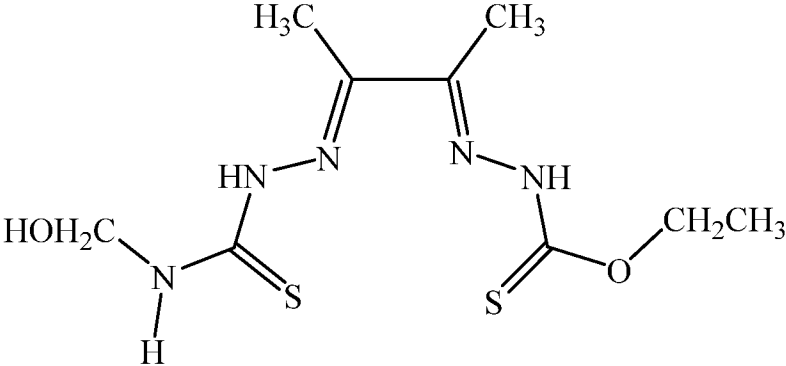
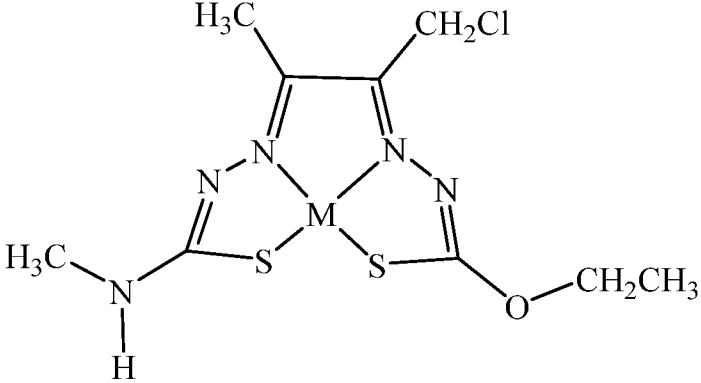
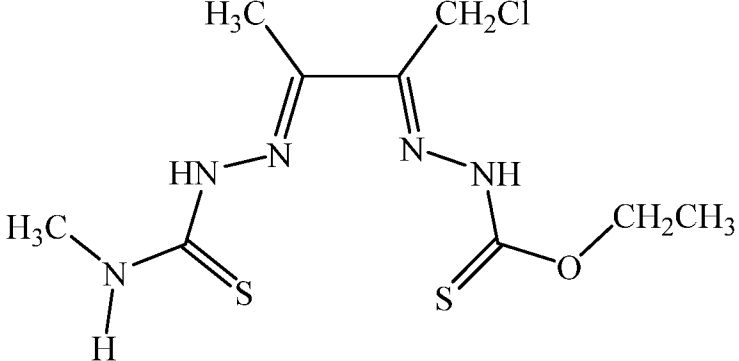
I-9 (NV30177)	
I-10 (NV30178)	
I-11 (NV40110)	
I-12 (NV30156)	

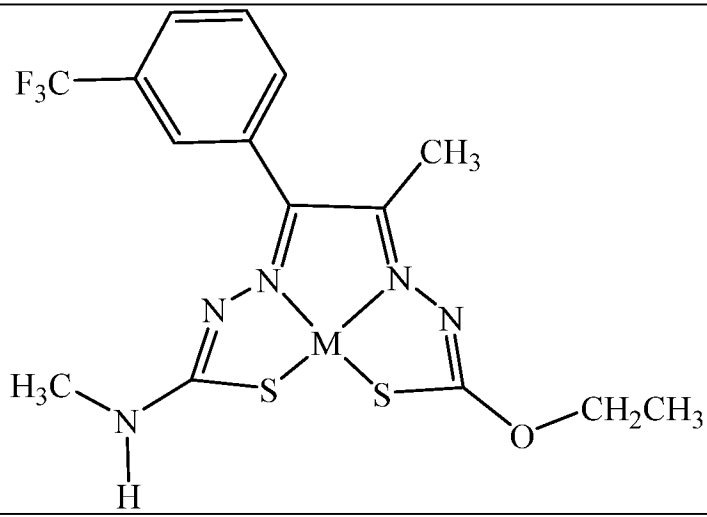
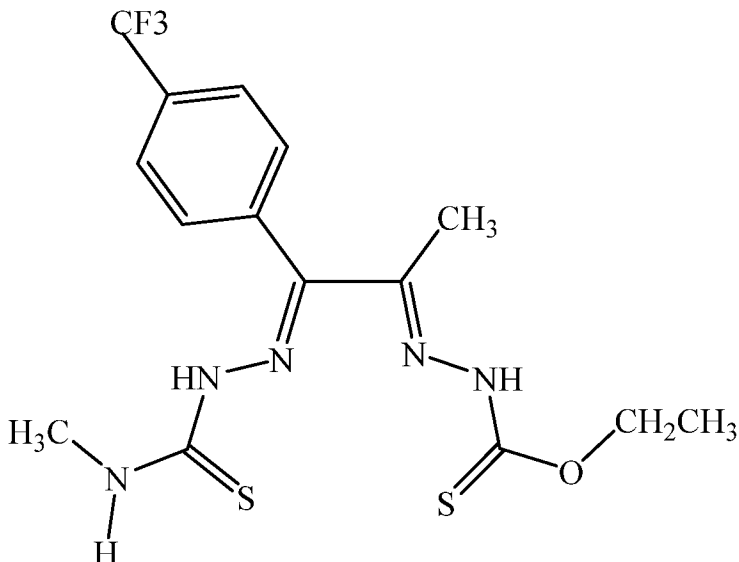
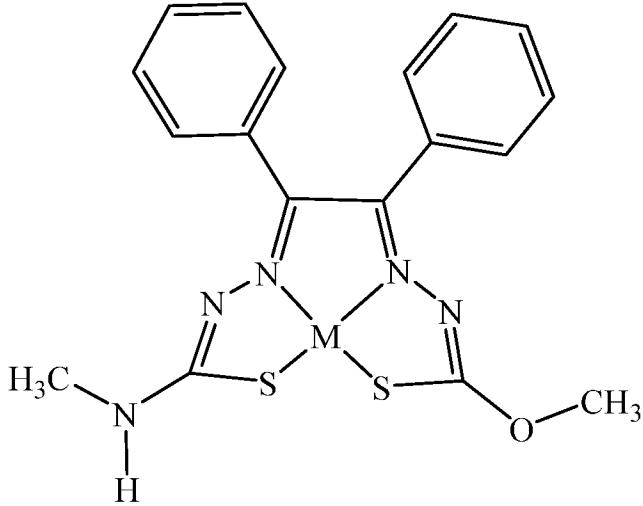
I-13	 <chem>CN(C)C1=NC2=C(C)N(C)C(S1)C2OCC</chem>
I-14 (NV30164)	 <chem>CN(C)C1=NC2=C(C)N(C)C(S1)C2OCC</chem>
I-15	 <chem>CN(C)C1=NC2=C(C)N(C)C(S1)C2OCC</chem>
I-16	 <chem>CN(C)C(=S)N=C(C)N(C)C(=S)N</chem>

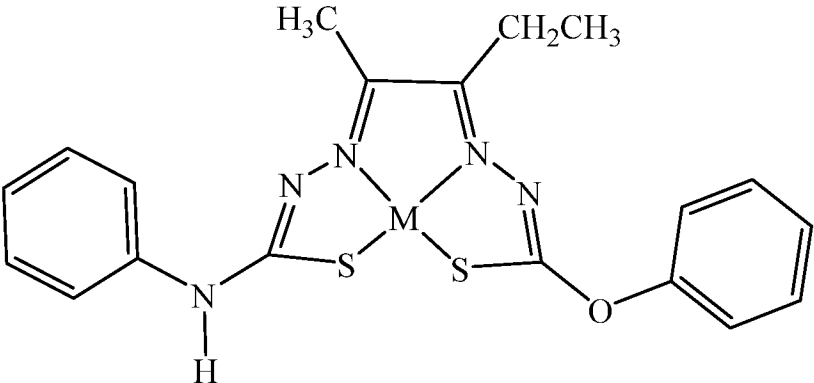
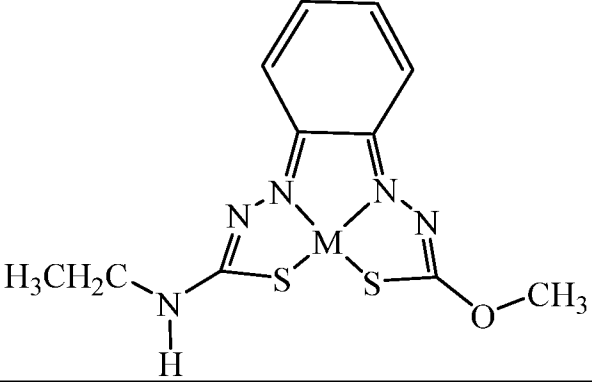
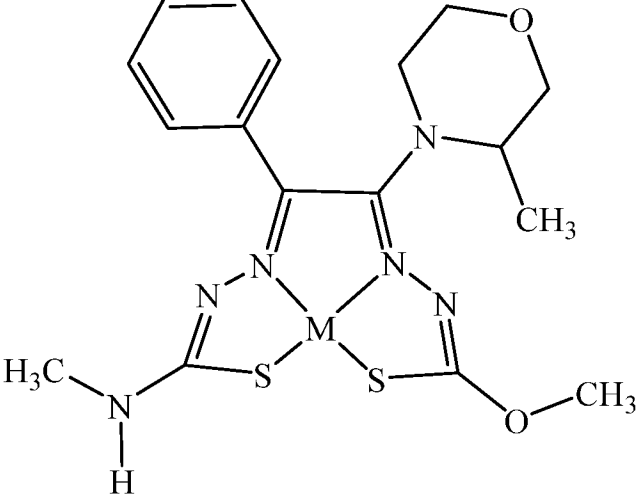
I-17	
I-18	
I-19	
I-20	

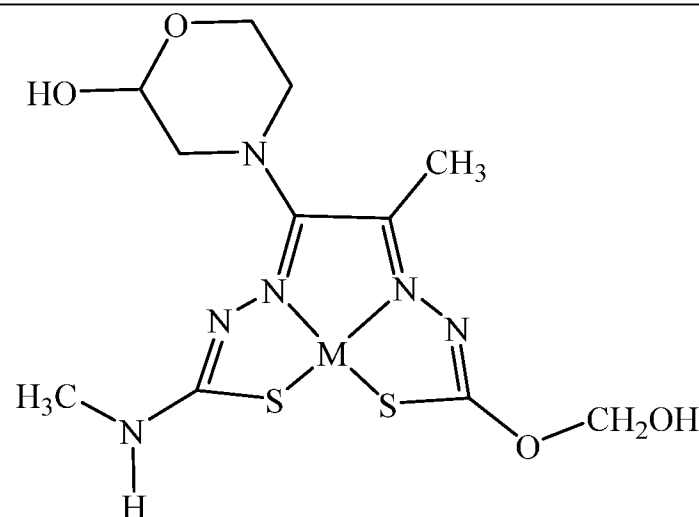
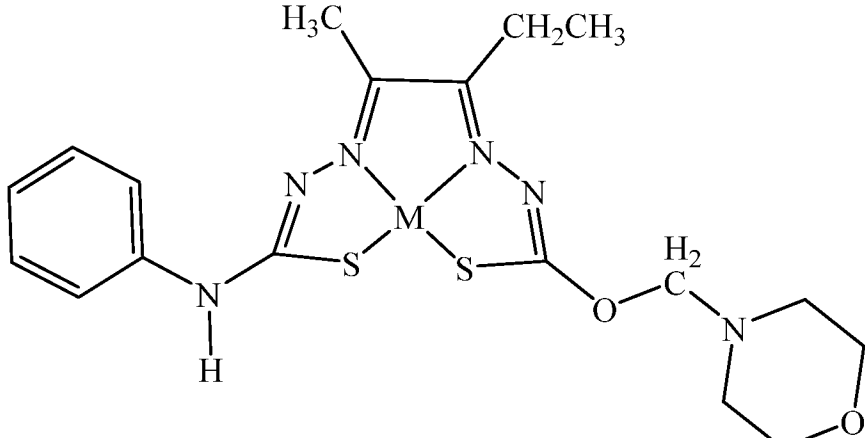
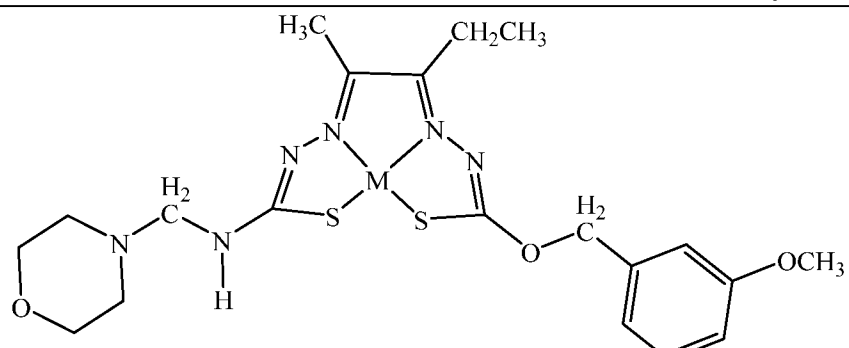
I-21	
I-22 (MB10014)	
I-23	
I-24	

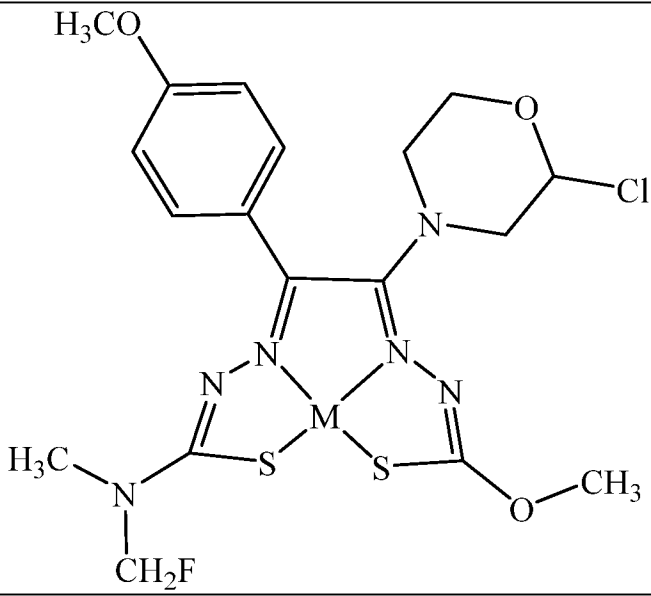
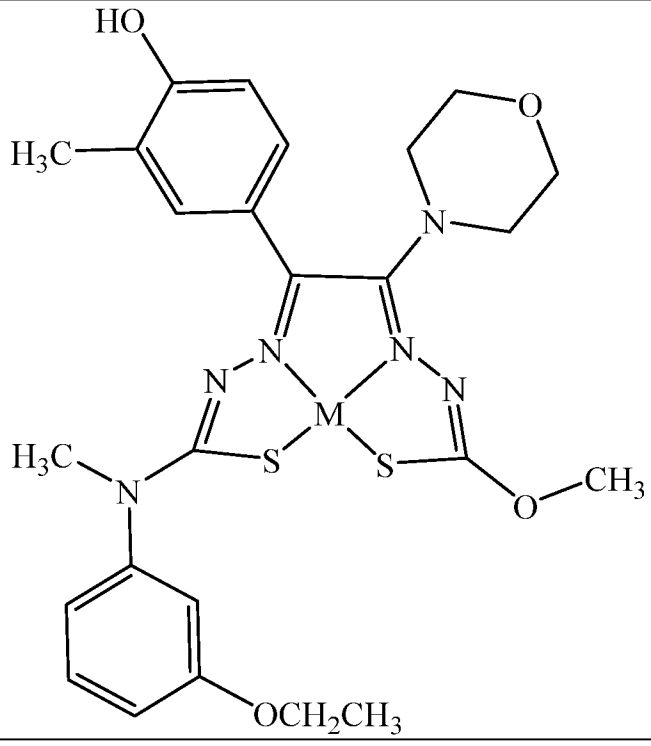
I-25	
I-26	
I-27	
I-28	

I-29	
I-30	
I-31	
I-32	

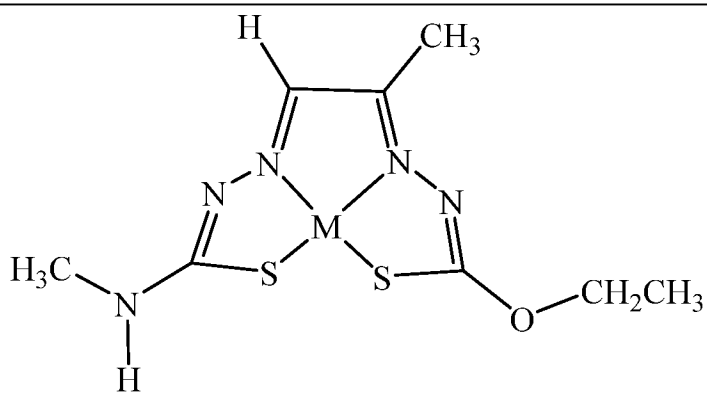
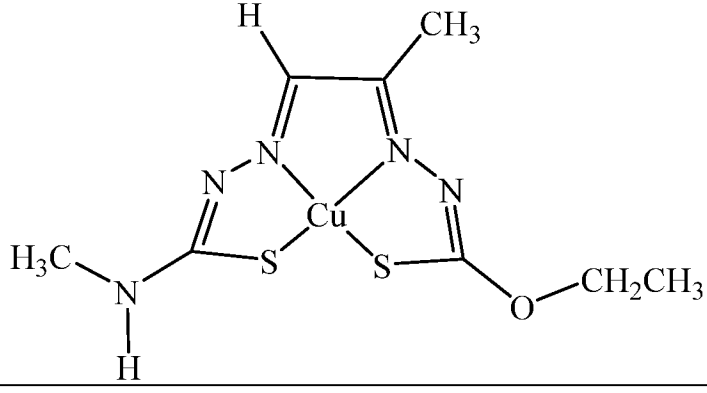
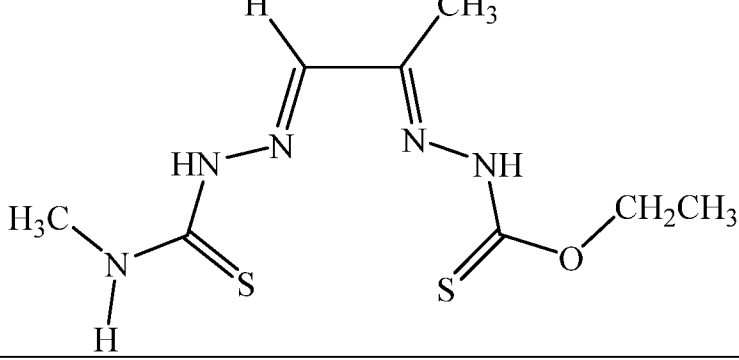
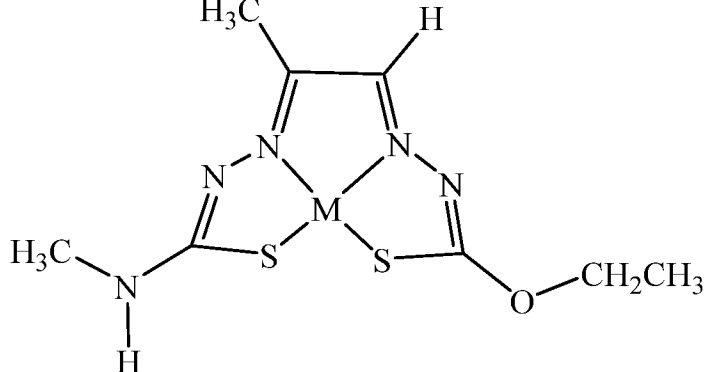
I-33	
I-34	
I-35	

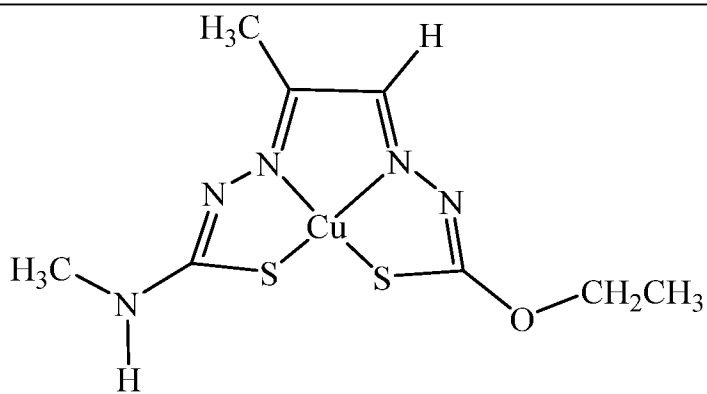
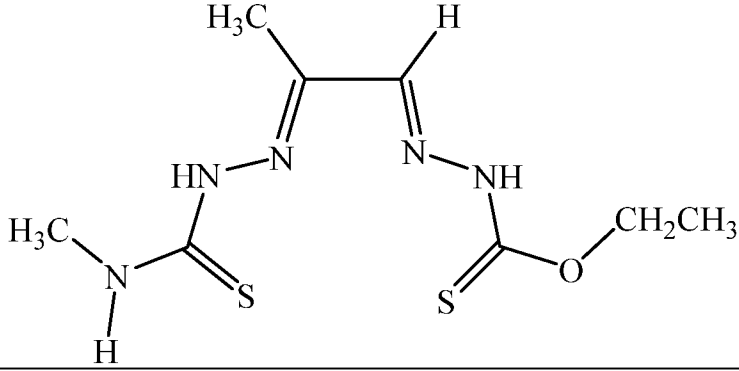
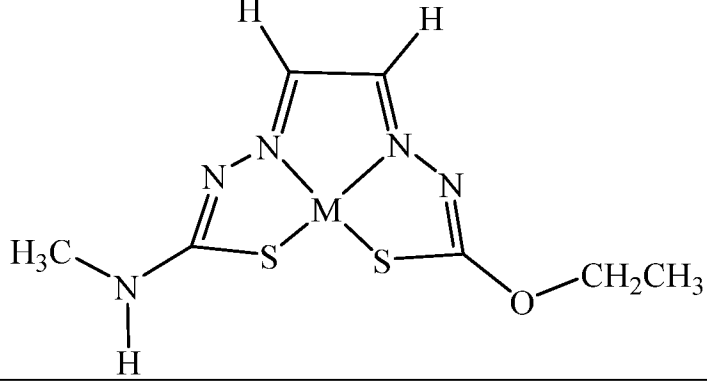
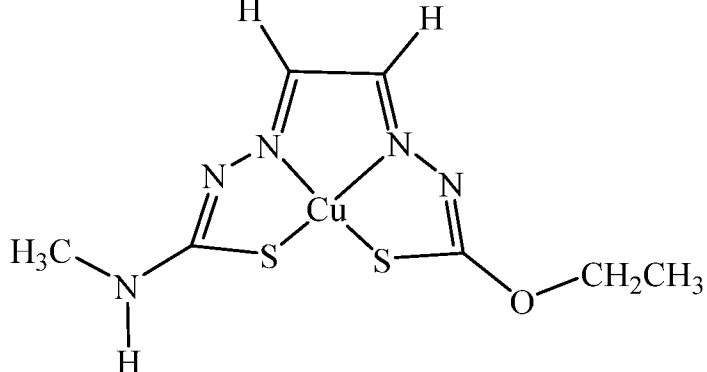
I-36	
I-37	
I-38	

I-39	
I-40	
I-41	

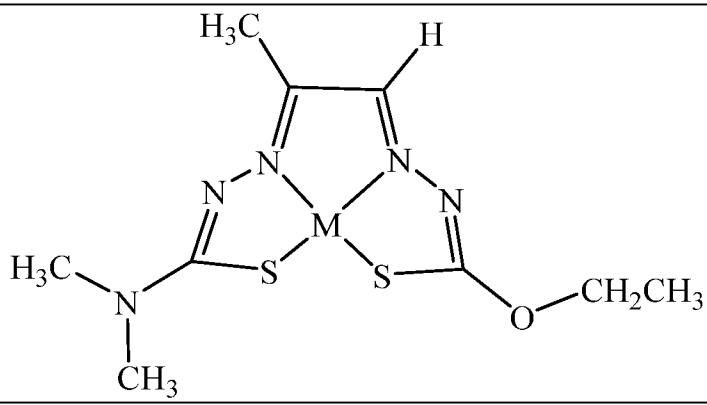
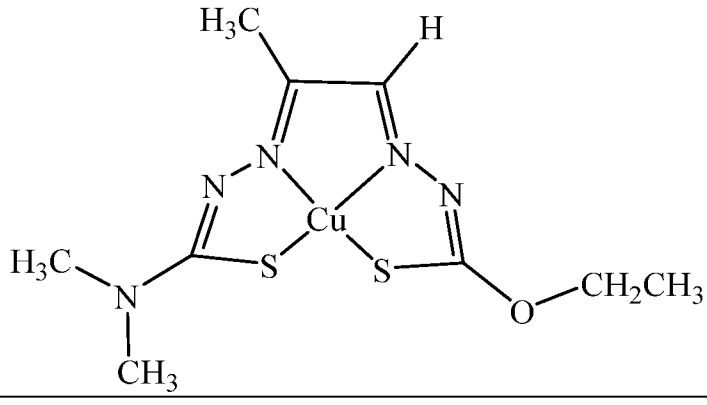
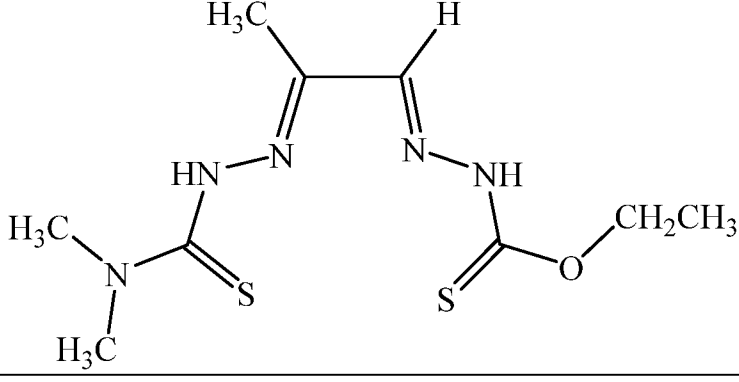
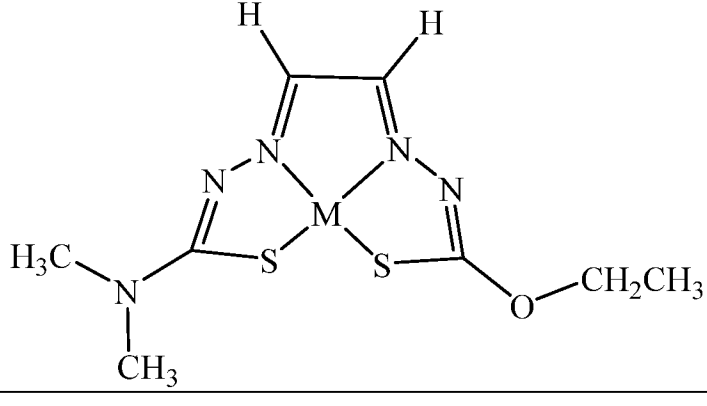
I-42	 Chemical structure of compound I-42: A central metal atom (M) is coordinated by two sulfur atoms (S) and two nitrogen atoms (N) in a porphyrin-like core. The core is substituted with a 4-methoxyphenyl group, a 2-chloroethoxy group, a 2-(dimethylamino)ethyl group, and a 2-methoxyethyl group.
I-43	 Chemical structure of compound I-43: A central metal atom (M) is coordinated by two sulfur atoms (S) and two nitrogen atoms (N) in a porphyrin-like core. The core is substituted with a 4-hydroxy-3-methylphenyl group, a 2-methoxyethyl group, a 2-(dimethylamino)ethyl group, and a 2-ethoxyethyl group.

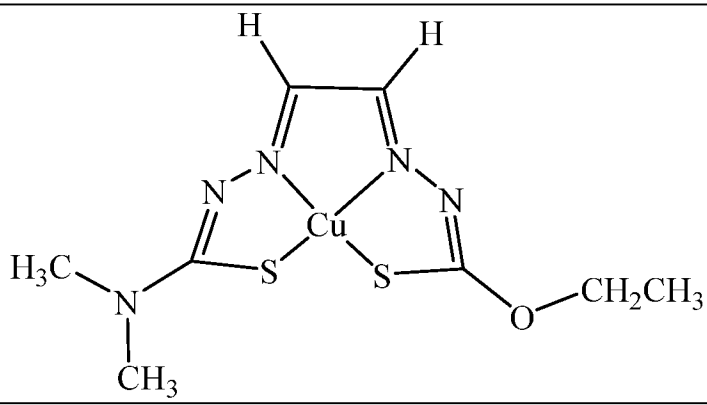
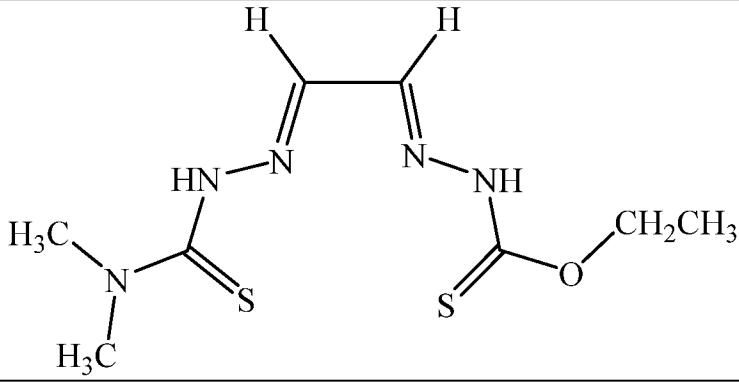
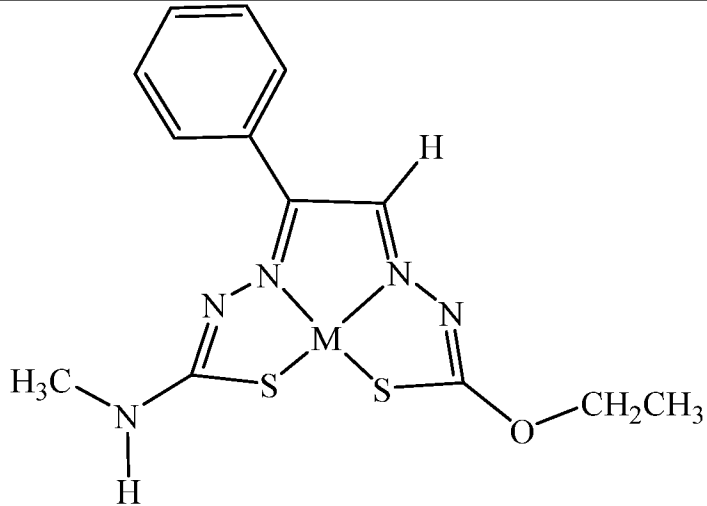
I-44	
I-45	
I-46	
I-47	

I-48	
I-49	
I-50	
I-51	

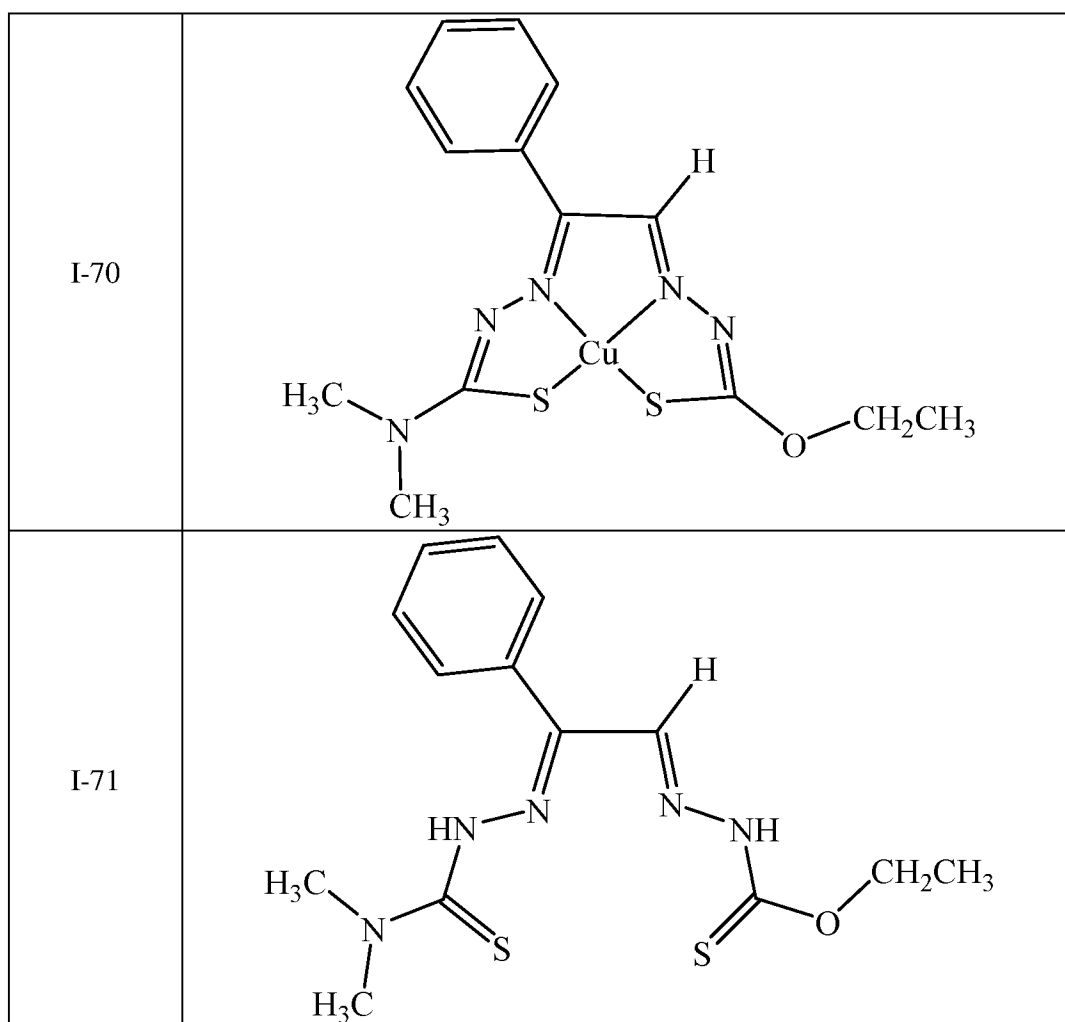
I-52	
I-53	
I-54	
I-55	

I-56	 <chem>CN(C)C(=S)N=Nc1cc2nnc(C(=S)NCC)nc2cc1</chem>
I-57	 <chem>CN(C)C(=S)N=Nc1cc2nnc(C(=S)NCC)nc2cc1</chem>
I-58	 <chem>CN(C)C(=S)N=Nc1cc2nnc(C(=S)NCC)nc2cc1</chem>
I-59	 <chem>CN(C)C(=S)N=Nc1cc2nnc(C(=S)NCC)nc2cc1</chem>

I-60	 Chemical structure of I-60: A macrocyclic complex with a central metal M coordinated by two sulfur atoms and two nitrogen atoms. The ring is substituted with a methyl group (H₃C), a hydrogen atom (H), a dimethylamino group (N(CH₃)₂), and an ethoxy group (OCH₂CH₃).
I-61	 Chemical structure of I-61: Similar to I-60, but the central metal is copper (Cu).
I-62	 Chemical structure of I-62: A macrocyclic complex with a central metal M coordinated by two sulfur atoms and two nitrogen atoms. The ring is substituted with a methyl group (H₃C), a hydrogen atom (H), a dimethylamino group (N(CH₃)₂), and an ethoxy group (OCH₂CH₃).
I-63	 Chemical structure of I-63: Similar to I-60, but the central metal is copper (Cu).

I-64	
I-65	
I-66	

I-67	 <chem>CCNc1nc2c(c1)nc3c2c(c1)nc4c3nc5c4cnc5c6c1ccccc16</chem>
I-68	 <chem>CCNc1nc2c(c1)nc3c2c(c1)nc4c3nc5c4cnc5c6c1ccccc16</chem>
I-69	 <chem>CCN(C)c1nc2c(c1)nc3c2c(c1)nc4c3nc5c4cnc5c6c1ccccc16</chem>



[0083] In some embodiments, one or more of compounds I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-10, I-11, I-12, I-13, I-14, I-15, I-16, I-17, I-18, I-19, I-20, I-21, I-22, I-23, I-24, I-25, I-26, I-27, I-28, I-29, I-30, I-31, I-32, I-33, I-34, I-35, I-36, I-37, I-38, I-39, I-40, I-41, I-42, I-43, I-44, I-45, I-46, I-47, I-48, I-49, I-50, I-51, I-52, I-53, I-54, I-55, I-56, I-57, I-58, I-59, I-60, I-61, I-62, I-63, I-64, I-65, I-66, I-67, I-68, I-69, I-70, or I-71 are excluded from the compounds of the invention (e.g., Formula (I)).

[0084] In some embodiments, the compounds of the invention include one or more of I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-10, I-11, I-12, I-13, I-14, I-15, I-16, I-17, I-18, I-19, I-20, I-21, I-22, I-23, I-24, I-25, I-26, I-27, I-28, I-29, I-30, I-31, I-32,

I-33, I-34, I-35, I-36, I-37, I-38, I-39, I-40, I-41, I-42, I-43, I-44, I-45, I-46, I-47, I-48, I-49, I-50, I-51, I-52, I-53, I-54, I-55, I-56, I-57, I-58, I-59, I-60, I-61, I-62, I-63, I-64, I-65, I-66, I-67, I-68, I-69, I-70, or I-71. In some embodiments, the compounds of the invention include one or more of I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22. In
5 some embodiments, the compounds of the invention include one or more of I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, I-22, I-49, I-52, I-55, I-58, I-61, I-64, I-67, or I-70. In some embodiments, the compounds of the invention include one or more of I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, I-22, I-49, or I-52. In some embodiments, the compounds of the invention include one or more of I-1 or I-5. In some embodiments,
10 the compounds of the invention include one or more of I-1, I-5, I-49, or I-52.

[0085] In some embodiments, the compounds of the invention include I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-10, I-11, I-12, I-13, I-14, I-15, I-16, I-17, I-18, I-19, I-20, I-21, I-22, I-23, I-24, I-25, I-26, I-27, I-28, I-29, I-30, I-31, I-32, I-33, I-34, I-35, I-36, I-37, I-38, I-39, I-40, I-41, I-42, I-43, I-44, I-45, I-46, I-47, I-48, I-49, I-50, I-51, I-52, I-53, I-54, I-55, I-56, I-57, I-58, I-59, I-60, I-61, I-62, I-63, I-64, I-65, I-66, I-67, I-68, I-69, I-70, and I-71. In some embodiments, the compounds of the invention include I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, and I-22. In some embodiments, the compounds of the invention include I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, I-22, I-49, I-52, I-55, I-58, I-61, I-64, I-67, and I-70. In some embodiments, the compounds of the invention include I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, I-22, I-49, and I-52. In some embodiments, the compounds of the invention include I-1 and I-5. In some embodiments, the compounds of the invention include I-1, I-5, I-49, and I-52.

[0086] In some embodiments, one or more (e.g., one, two, three, four, five, or six) of the following apply to Formula (I): R^{1a} is H, R^{1b} is methyl, R^2 is ethyl, R^3 is

methyl, R⁴ is methyl, or M is Cu. In some embodiments, one or more (e.g., one, two, three, four, five, or six) of the following apply to Formula (I): R^{1a} is methyl, R^{1b} is H, R² is ethyl, R³ is methyl, R⁴ is methyl, or M is Cu. In some embodiments, one or more (e.g., one, two, three, four, five, or six) of the following apply to Formula (I):

5 R^{1a} is H, R^{1b} is methyl, R² is ethyl, R³ is methyl, R⁴ is methyl, or M is Zn. In some embodiments, one or more (e.g., one, two, three, four, five, or six) of the following apply to Formula (I): R^{1a} is methyl, R^{1b} is H, R² is ethyl, R³ is methyl, R⁴ is methyl, or M is Zn.

[0087] In some embodiments, one or more (e.g., one, two, three, four, five, or
10 six) of the following apply to Formula (I): R^{1a} is H, R^{1b} is methyl, R² is ethyl, R³ is phenyl, R⁴ is methyl, or M is Cu. In some embodiments, one or more (e.g., one, two, three, four, five, or six) of the following apply to Formula (I): R^{1a} is methyl, R^{1b} is H, R² is ethyl, R³ is phenyl, R⁴ is methyl, or M is Cu. In some embodiments, one or more (e.g., one, two, three, four, five, or six) of the following apply to Formula (I):
15 R^{1a} is H, R^{1b} is methyl, R² is ethyl, R³ is phenyl, R⁴ is methyl, or M is Zn. In some embodiments, one or more (e.g., one, two, three, four, five, or six) of the following apply to Formula (I): R^{1a} is methyl, R^{1b} is H, R² is ethyl, R³ is phenyl, R⁴ is methyl, or M is Zn.

[0088] In some embodiments, R^{1a} is H, R^{1b} is H, or both. In other
20 embodiments, R^{1a} is H or R^{1b} is H, but both R^{1a} and R^{1b} are not H. In some embodiments, R^{1a} is H. In some embodiments, R^{1b} is H. In some embodiments, R^{1a} is H and R^{1b} is methyl. In some embodiments, R^{1a} is methyl and R^{1b} is H. In some embodiments, R^{1a} is methyl and R^{1b} is methyl. In some embodiments, R² is H, methyl, or ethyl. In some embodiments, R² is ethyl. In some embodiments, R³ is H,

methyl, or phenyl. In some embodiments, R^3 is methyl or phenyl. In some embodiments, R^3 is methyl. In some embodiments, R^3 is H. In some embodiments, R^4 is H, methyl, or phenyl. In some embodiments, R^4 is methyl or phenyl. In some embodiments, R^4 is methyl. In some embodiments, R^4 is H.

5 [0089] In some embodiments, the compounds of Formula (I) (e.g., (e.g., Formula (Ia), (Ib), I-1, I-2, I-3, I-4, I-5, I-6, I-7, or I-8)) can be in the form of salts, optical and geometric isomers, and salts of isomers. In other embodiments, the compounds can be in various forms, such as uncharged molecules, components of molecular complexes, or non-irritating pharmacologically acceptable salts, including
10 but not limited to hydrochloride, hydrobromide, sulphate, phosphate, nitrate, borate, acetate, maleate, tartrate, and salicylate. In some instances, for acidic compounds, salts can include metals, amines, or organic cations (e.g. quaternary ammonium). In yet other embodiments, derivatives of the compounds (e.g., ethers, esters, or amides) which have desirable retention and release characteristics, but which are hydrolyzed
15 (e.g., easily hydrolyzed) by body pH, enzymes, or other suitable means, can be employed.

[0090] In some embodiments, the compounds of the invention having a chiral center and can exist in and be isolated in optically active and racemic forms. In other embodiments, compounds may exhibit polymorphism. Some embodiments of the
20 present invention encompass any racemic, optically active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound described herein. The preparation of optically active forms can be accomplished by any suitable method, including but not limited to, resolution of the racemic form by recrystallization

techniques, synthesis from optically-active starting materials, chiral synthesis, or chromatographic separation using a chiral stationary phase.

[0091] In other embodiments, compounds of the invention encompass Formula (I) and salts, optical isomers, geometric isomers, salts of isomers, and derivatives thereof. In yet other embodiments, compounds of the invention encompass Formula (Ia) and salts, optical isomers, geometric isomers, salts of isomers, and derivatives thereof. In still other embodiments, compounds of the invention encompass Formula (Ib) and salts, optical isomers, geometric isomers, salts of isomers, and derivatives thereof.

[0092] In some embodiments, the compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) do not use cellular production of Reactive Oxygen Species (ROS) to kill the cell or decrease the cell viability. In some embodiments, the compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) use a mechanism to kill the cell or decrease the cell viability that is different than the mechanism for increasing production of ROS in the cells. In some embodiments, a compound from Formula (Ib) can combine with a divalent metal (e.g., Cu or Zn) (e.g., in the composition or the pharmaceutical composition) to form a compound from Formula (Ia). In some embodiments, a compound from Formula (Ib) can combine with a divalent metal (e.g., Cu or Zn) that is endogenous to an animal to form a compound from Formula (Ia). In certain embodiments, a compound from Formula (Ia) can switch divalent metals (e.g., transmetalation) in the composition or the pharmaceutical composition to form a compound from Formula (Ia) that has a different divalent metal. For example, in some embodiments, a Cu can replace the Zn in compound I-3, so that compound I-

3 becomes compound I-1. In other embodiments, a compound from Formula (Ia) can switch divalent metals (e.g., transmetalation) and the divalent metal that replaces the previous divalent metal is endogenous to the animal. In the example above, Cu would be endogenous to the animal.

5 [0093] In certain embodiments, one or more compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) can be part of a composition and can be in an amount (by weight of the total composition) of at least about 0.0001%, at least about 0.001%, at least about 0.10%, at least about 0.15%, at least about 0.20%, at least about 0.25%, at least about 0.50%, at least about 0.75%, at least about 1%, at least about 10%, at least about 25%, at least about 50%, at least about 75%, at least about 90%, at least about 95%, at least about 99%, at least about 99.99%, no more than about 75%, no more than about 90%, no more than about 95%, no more than about 99%, or no more than about 99.99%, from about 0.0001% to about 99%, from about 0.0001% to about 50%, from about 0.01% to about 95%, from about 1% to about 95%, from about 10% to about 90%, or from about 25% to about 75%.

[0094] In some embodiments, one or more compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) can be purified or isolated in an amount (by weight of the total composition) of at least about 0.0001%, at least about 0.001%, at least about 0.10%, at least about 0.15%, at least about 0.20%, at least about 0.25%, at least about 0.50%, at least about 0.75%, at least about 1%, at least about 10%, at least about 25%, at least about 50%, at least about 75%, at least about 90%, at least about 95%, at least about 99%, at least about 99.99%, no more than about 75%, no more than about 90%, no more than about

95%, no more than about 99%, no more than about 99.99%, from about 0.0001% to about 99%, from about 0.0001% to about 50%, from about 0.01% to about 95%, from about 1% to about 95%, from about 10% to about 90%, or from about 25% to about 75%.

5 [0095] Some embodiments of the present invention include compositions comprising one or more compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22). In certain embodiments, the composition is a pharmaceutical composition, such as compositions that are suitable for administration to animals (e.g., mammals, primates, monkeys, humans, canine, feline, 10 porcine, mice, rabbits, or rats). In some instances, the pharmaceutical composition is non-toxic, does not cause side effects, or both. In some embodiments, there may be inherent side effects (e.g., it may harm the patient or may be toxic or harmful to some degree in some patients).

[0096] “Therapeutically effective amount” means an amount effective to 15 achieve a desired and/or beneficial effect. An effective amount can be administered in one or more administrations. For some purposes of this invention, a therapeutically effective amount is an amount appropriate to treat an indication. By treating an indication is meant achieving any desirable effect, such as one or more of palliate, ameliorate, stabilize, reverse, slow, or delay disease progression, increase the quality 20 of life, or to prolong life. Such achievement can be measured by any suitable method, such as measurement of tumor size.

[0097] In some embodiments, one or more compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) can be part of a pharmaceutical composition and can be in an amount of at least about 0.0001%, at

least about 0.001%, at least about 0.10%, at least about 0.15%, at least about 0.20%,
at least about 0.25%, at least about 0.50%, at least about 0.75%, at least about 1%, at
least about 10%, at least about 25%, at least about 50%, at least about 75%, at least
about 90%, at least about 95%, at least about 99%, at least about 99.99%, no more
5 than about 75%, no more than about 90%, no more than about 95%, no more than
about 99%, no more than about 99.99%, from about 0.001% to about 99%, from
about 0.001% to about 50%, from about 0.1% to about 99%, from about 1% to about
95%, from about 10% to about 90%, or from about 25% to about 75%. In some
embodiments, the pharmaceutical composition can be presented in a dosage form
10 which is suitable for the topical, subcutaneous, intrathecal, intraperitoneal, oral,
parenteral, rectal, cutaneous, nasal, vaginal, or ocular administration route. In other
embodiments, the pharmaceutical composition can be presented in a dosage form
which is suitable for parenteral administration, a mucosal administration, intravenous
administration, subcutaneous administration, topical administration, intradermal
15 administration, oral administration, sublingual administration, intranasal
administration, or intramuscular administration. The pharmaceutical composition can
be in the form of, for example, tablets, capsules, pills, powders granulates,
suspensions, emulsions, solutions, gels (including hydrogels), pastes, ointments,
creams, plasters, drenches, delivery devices, suppositories, enemas, injectables,
20 implants, sprays, aerosols or other suitable forms.

[0098] In some embodiments, the pharmaceutical composition can include
one or more formulary ingredients. A “formulary ingredient” can be any suitable
ingredient (e.g., suitable for the drug(s), for the dosage of the drug(s), for the timing
of release of the drugs(s), for the disease, for the disease state, or for the delivery

route) including, but not limited to, water (e.g., boiled water, distilled water, filtered water, pyrogen-free water, or water with chloroform), sugar (e.g., sucrose, glucose, mannitol, sorbitol, xylitol, or syrups made therefrom), ethanol, glycerol, glycols (e.g., propylene glycol), acetone, ethers, DMSO, surfactants (e.g., anionic surfactants, cationic surfactants, zwitterionic surfactants, or nonionic surfactants (e.g., polysorbates)), oils (e.g., animal oils, plant oils (e.g., coconut oil or arachis oil), or mineral oils), oil derivatives (e.g., ethyl oleate, glyceryl monostearate, or hydrogenated glycerides), excipients, preservatives (e.g., cysteine, methionine, antioxidants (e.g., vitamins (e.g., A, E, or C), selenium, retinyl palmitate, sodium citrate, citric acid, chloroform, or parabens, (e.g., methyl paraben or propyl paraben))), or combinations thereof.

[0099] In certain embodiments, pharmaceutical compositions can be formulated to release the active ingredient (e.g., one or more compounds of the invention such as Formula (I), (Ia), (Ib), I-1, I-2, I-3, I-4, I-5, I-6, I-7, or I-8) substantially immediately upon the administration or any substantially predetermined time or time after administration. Such formulations can include, for example, controlled release formulations such as various controlled release compositions and coatings.

[00100] Other formulations (e.g., formulations of a pharmaceutical composition) can, in certain embodiments, include those incorporating the drug (or control release formulation) into food, food stuffs, feed, or drink.

[00101] In some embodiments, a compound from Formula (Ib) can combine with a divalent metal (e.g., Cu or Zn) in the composition or the pharmaceutical composition to form a compound from Formula (Ia). In some embodiments, a

compound from Formula (Ib) can combine with a divalent metal (e.g., Cu or Zn) that is endogenous to the animal to form a compound from Formula (Ia).

[00102] In certain embodiments, a compound from Formula (Ia) can switch divalent metals (e.g., transmetalation) in the composition or the pharmaceutical composition to form a compound from Formula (Ia) that has a different divalent metal. For example, in some embodiments, a Cu can replace the Zn in compound I-3, so that compound I-3 becomes compound I-1. In other embodiments, a compound from Formula (Ia) can switch divalent metals (e.g., transmetalation) and the divalent metal that replaces the previous divalent metal is endogenous to the animal. In the example above, Cu would be endogenous to the animal.

[00103] Other embodiments of the invention can include methods of administering or treating an organism, which can involve treatment with an amount of at least one compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) that is effective to treat the disease, condition, or disorder that the organism has, or is suspected of having, or is susceptible to, or to bring about a desired physiological effect. In some embodiments, the composition or pharmaceutical composition comprises at least one compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) which can be administered to an animal (e.g., mammals, primates, monkeys, or humans) in an amount of about 0.005 to about 50 mg/kg body weight, about 0.01 to about 15 mg/kg body weight, about 0.1 to about 10 mg/kg body weight, about 0.5 to about 7 mg/kg body weight, about 0.005 mg/kg, about 0.01 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 3 mg/kg, about 5 mg/kg, about 5.5 mg/kg, about 6 mg/kg, about 6.5 mg/kg, about 7 mg/kg, about 7.5 mg/kg, about 8

mg/kg, about 10 mg/kg, about 12 mg/kg, or about 15 mg/kg. In regard to some conditions, the dosage can be about 0.5 mg/kg human body weight or about 6.5 mg/kg human body weight. In some instances, some animals (e.g., mammals, mice, rabbits, feline, porcine, or canine) can be administered a dosage of about 0.005 to about 50 mg/kg body weight, about 0.01 to about 15 mg/kg body weight, about 0.1 to about 10 mg/kg body weight, about 0.5 to about 7 mg/kg body weight, about 0.005 mg/kg, about 0.01 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 20 mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, about 80 mg/kg, about 100 mg/kg, or about 150 mg/kg. Of course, those skilled in the art will appreciate that it is possible to employ many concentrations in the methods of the present invention, and using, in part, the guidance provided herein, will be able to adjust and test any number of concentrations in order to find one that achieves the desired result in a given circumstance. In other embodiments, the compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) can be administered in combination with one or more other therapeutic agents for a given disease, condition, or disorder.

[00104] In some embodiments, the compositions can include a unit dose of one or more compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) in combination with a pharmaceutically acceptable carrier and, in addition, can include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, and excipients. In certain embodiments, the carrier, vehicle or excipient can facilitate administration, delivery and/or improve preservation of the composition. In other embodiments, the one or more carriers, include but are not limited to, saline solutions such as normal saline, Ringer's solution, PBS (phosphate-

buffered saline), and generally mixtures of various salts including potassium and phosphate salts with or without sugar additives such as glucose. Carriers can include aqueous and non-aqueous sterile injection solutions that can contain antioxidants, buffers, bacteriostats, bactericidal antibiotics, and solutes that render the formulation isotonic with the bodily fluids of the intended recipient; and aqueous and non-aqueous sterile suspensions, which can include suspending agents and thickening agents. In other embodiments, the one or more excipients can include, but are not limited to water, saline, dextrose, glycerol, ethanol, or the like, and combinations thereof. Nontoxic auxiliary substances, such as wetting agents, buffers, or emulsifiers may also be added to the composition. Oral formulations can include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, and magnesium carbonate.

[00105] Administration Routes and Treatments of Disease

[00106] The compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) can be administered to animals by any number of suitable administration routes or formulations. The compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) can also be used to treat animals for a variety of diseases. Animals include but are not limited to mammals, primates, monkeys (e.g., macaque, rhesus macaque, or pig tail macaque), humans, canine, feline, bovine, porcine, avian (e.g., chicken), mice, rabbits, and rats. As used herein, the term “subject” refers to both human and animal subjects.

[00107] The route of administration of the compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) can be of any suitable route. Administration routes can be, but are not limited to the oral route, the parenteral route, the cutaneous route, the nasal route, the rectal route, the vaginal route, and the ocular route. In other embodiments, administration routes can be parenteral administration, a mucosal administration, intravenous administration, subcutaneous administration, topical administration, intradermal administration, oral administration, sublingual administration, intranasal administration, or intramuscular administration. The choice of administration route can depend on the compound identity (e.g., the physical and chemical properties of the compound) as well as the age and weight of the animal, the particular disease (e.g., cancer), and the severity of the disease (e.g., stage or severity of cancer). Of course, combinations of administration routes can be administered, as desired.

[00108] Some embodiments of the invention include a method for providing a subject with a composition comprising one or more compounds of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) described herein (e.g., a pharmaceutical composition) which comprises one or more administrations of one or more such compositions; the compositions may be the same or different if there is more than one administration. In some embodiments, a compound from Formula (Ib) can combine with a divalent metal (e.g., Cu or Zn) to form a compound from Formula (Ia). In some embodiments, a compound from Formula (Ib) can combine with a divalent metal (e.g., Cu or Zn) that is endogenous to the animal to form a compound from Formula (Ia). In certain embodiments, a compound from Formula (Ia) can switch divalent metals (e.g., transmetalation) in the

composition or the pharmaceutical composition to form a compound from Formula (Ia) that has a different divalent metal. For example, in some embodiments, a Cu can replace the Zn in compound I-3, so that compound I-3 becomes compound I-1. In other embodiments, a compound from Formula (Ia) can switch divalent metals (e.g.,
5 transmetalation) and the divalent metal that replaces the previous divalent metal is endogenous to the animal. In the example above, Cu would be endogenous to the animal.

[00109] Diseases that can be treated in an animal (e.g., mammals, porcine, canine, avian (e.g., chicken), bovine, feline, primates, rodents, monkeys, rabbits,
10 mice, rats, and humans) using a compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) include, but are not limited to cancers.

[00110] In some embodiments, cancers that can be treated in an animal (e.g., mammals, porcine, canine, avian (e.g., chicken), bovine, feline, primates, rodents,
15 monkeys, rabbits, mice, rats, and humans) using a compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) include, but are not limited to, acute lymphoblastic leukemia, astrocytoma, basal cell carcinoma, bladder cancer, bone marrow cancer, breast cancer, chronic lymphocytic leukemia (CLL), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or
20 astrocytoma), colon cancer, colorectal cancer (e.g., colon cancer or rectal cancer), endometrial cancer, gastric cancer, glioblastoma, glioblastoma multiforme, glioma, gliosarcoma, hepatocellular carcinoma, kidney cancer (e.g., renal cancer), leukemia, liver cancer, lung cancer (e.g., non-small cell lung cancer), lymphoma, melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), malignant nerve

sheath tumors, medulloblastoma, meningioma, multiple myeloma, nasopharyngeal
 carcinoma, neuroblastoma, non-Hodgkin lymphoma (e.g., diffuse large B-cell
 lymphoma), non-small cell lung cancer, oral cancer, ovarian cancer, pancreatic cancer
 (e.g., pancreatic ductal adenocarcinoma), prostate cancer, rectal cancer, renal cancer,
 5 renal cell carcinoma, rhabdomyosarcoma, squamous cell carcinoma (e.g., head and
 neck squamous cell carcinoma), stomach cancer, thyroid cancer, uterine cancer,
 cancers that can result in metastasis, cancers resulting from metastasis, or cancerous
 tumors thereof. In some embodiments, cancers that can be treated do not include
 leukemia. In some embodiments, cancers that can be treated include, but are not
 10 limited to, basal cell carcinoma, bladder cancer, bone marrow cancer, breast cancer,
 CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or
 astrocytoma), colon cancer, colorectal cancer (e.g., colon cancer or rectal cancer),
 endometrial cancer, gastric cancer, glioblastoma, glioblastoma multiforme, glioma,
 gliosarcoma, hepatocellular carcinoma, kidney cancer (e.g., renal cancer), liver
 15 cancer, lung cancer (e.g., non-small cell lung cancer), lymphoma, melanoma (e.g.,
 cutaneous malignant melanoma or melanoma tumorigenesis), malignant nerve sheath
 tumors, medulloblastoma, meningioma, multiple myeloma, nasopharyngeal
 carcinoma, neuroblastoma, non-Hodgkin lymphoma (e.g., diffuse large B-cell
 lymphoma), non-small cell lung cancer, oral cancer, ovarian cancer, pancreatic cancer
 20 (e.g., pancreatic ductal adenocarcinoma), prostate cancer, rectal cancer, renal cell
 carcinoma, rhabdomyosarcoma, squamous cell carcinoma (e.g., head and neck
 squamous cell carcinoma), stomach cancer, thyroid cancer, uterine cancer, cancers
 that can result in metastasis, cancers resulting from metastasis, or cancerous tumors
 thereof. In some embodiments, cancers that can be treated include, but are not limited

to, leukemia, lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof. In some embodiments, cancers that can be treated include, but are not limited to, lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof. In some embodiments, cancers that can be treated include, but are not limited to, cancerous tumors. Animals that can be treated include but are not limited to mammals, rodents, primates, monkeys (e.g., macaque, rhesus macaque, pig tail macaque), humans, canine, feline, porcine, avian (e.g., chicken), bovine, mice, rabbits, and rats. As used herein, the term “subject” refers to both human and animal subjects. In some instances, the animal is in need of the treatment (e.g., by showing signs of disease or cancer, or by having a cancerous tumor).

[00111] In some embodiments, cancers that can be treated in an animal (e.g., mammals, porcine, canine, avian (e.g., chicken), bovine, feline, primates, rodents, monkeys, rabbits, mice, rats, and humans) using a compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) include, but are not limited to cancers that do not use an increase in reactive oxidative species as a mechanism to kill cancer cells.

[00112] As used herein, the term “treating” (and its variations, such as “treatment”) is to be considered in its broadest context. In particular, the term “treating” does not necessarily imply that an animal is treated until total recovery. Accordingly, “treating” includes amelioration of the symptoms, relief from the symptoms or effects associated with a condition, decrease in severity of a condition, or preventing, preventively ameliorating symptoms, or otherwise reducing the risk of developing a particular condition. As used herein, reference to “treating” an animal includes but is not limited to prophylactic treatment and therapeutic treatment. Any of the compositions (e.g., pharmaceutical compositions) described herein can be used to treat an animal.

[00113] As related to treating cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof), treating can include but is not limited to prophylactic treatment and therapeutic treatment. As such, treatment can include, but is not limited to: preventing cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof); reducing the risk of cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma),

melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof); ameliorating or relieving symptoms of cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof); eliciting a bodily response against cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof); inhibiting the development or progression of cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof); inhibiting or preventing the onset of symptoms associated with cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof); reducing the severity of cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer),

CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof); causing a regression of cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof) or one or more of the symptoms associated with cancer (e.g., a decrease in tumor size); causing remission of cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof); or preventing relapse of cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof). In some embodiments, treating does not include prophylactic treatment of cancer (e.g., preventing or ameliorating future cancer).

[00114] Treatment of an animal can occur using any suitable administration method (such as those disclosed herein) and using any suitable amount of a compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12,

or I-22). In some embodiments, methods of treatment comprise treating an animal for cancer (e.g., lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof). Some embodiments of the invention include a method for treating a subject (e.g., an animal such as a human or primate) with a composition comprising a compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) (e.g., a pharmaceutical composition) which comprises one or more administrations of one or more such compositions; the compositions may be the same or different if there is more than one administration.

[00115] In some embodiments, the method of treatment includes administering an effective amount of a composition comprising a compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22). As used herein, the term “effective amount” refers to a dosage or a series of dosages sufficient to affect treatment (e.g., to treat cancer, such as but not limited to lung cancer (e.g., non-small cell lung cancer), colorectal cancer (e.g., colon cancer or rectal cancer), CNS cancer (e.g., glioblastoma, glioblastoma multiforme, gliosarcoma, or astrocytoma), melanoma (e.g., cutaneous malignant melanoma or melanoma tumorigenesis), ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof) in an animal. In some embodiments, an effective amount can encompass a therapeutically effective amount, as disclosed herein. In certain embodiments, an effective amount can vary depending on the subject and the

particular treatment being affected. The exact amount that is required can, for example, vary from subject to subject, depending on the age and general condition of the subject, the particular adjuvant being used (if applicable), administration protocol, and the like. As such, the effective amount can, for example, vary based on the

5 particular circumstances, and an appropriate effective amount can be determined in a particular case. An effective amount can, for example, include any dosage or composition amount disclosed herein. In some embodiments, an effective amount of at least one compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) (which can be administered to an animal such as

10 mammals, primates, monkeys or humans) can be an amount of about 0.005 to about 50 mg/kg body weight, about 0.01 to about 15 mg/kg body weight, about 0.1 to about 10 mg/kg body weight, about 0.5 to about 7 mg/kg body weight, about 0.005 mg/kg, about 0.01 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 3 mg/kg, about 5 mg/kg, about 5.5 mg/kg, about 6 mg/kg, about 6.5

15 mg/kg, about 7 mg/kg, about 7.5 mg/kg, about 8 mg/kg, about 10 mg/kg, about 12 mg/kg, or about 15 mg/kg. In regard to some embodiments, the dosage can be about 0.5 mg/kg human body weight or about 6.5 mg/kg human body weight. In some instances, an effective amount of at least one compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) (which can be

20 administered to an animal such as mammals, rodents, mice, rabbits, feline, porcine, or canine) can be an amount of about 0.005 to about 50 mg/kg body weight, about 0.01 to about 15 mg/kg body weight, about 0.1 to about 10 mg/kg body weight, about 0.5 to about 7 mg/kg body weight, about 0.005 mg/kg, about 0.01 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 20

mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, about 80 mg/kg, about 100 mg/kg, or about 150 mg/kg. In some embodiments, an effective amount of at least one compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) (which can be administered to an animal such as mammals, primates, monkeys or humans) can be an amount of about 1 to about 1000 mg/kg body weight, about 5 to about 500 mg/kg body weight, about 10 to about 200 mg/kg body weight, about 25 to about 100 mg/kg body weight, about 1 mg/kg, about 2 mg/kg, about 5 mg/kg, about 10 mg/kg, about 25 mg/kg, about 50 mg/kg, about 100 mg/kg, about 150 mg/kg, about 200 mg/kg, about 300 mg/kg, about 400 mg/kg, about 500 mg/kg, about 600 mg/kg, about 700 mg/kg, about 800 mg/kg, about 900 mg/kg, or about 1000 mg/kg. In regard to some conditions, the dosage can be about 20 mg/kg human body weight or about 100 mg/kg human body weight. In some instances, an effective amount of at least one compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) (which can be administered to an animal such as mammals, rodents, mice, rabbits, feline, porcine, or canine) can be an amount of about 1 to about 1000 mg/kg body weight, about 5 to about 500 mg/kg body weight, about 10 to about 200 mg/kg body weight, about 25 to about 100 mg/kg body weight, about 1 mg/kg, about 2 mg/kg, about 5 mg/kg, about 10 mg/kg, about 25 mg/kg, about 50 mg/kg, about 100 mg/kg, about 150 mg/kg, about 200 mg/kg, about 300 mg/kg, about 400 mg/kg, about 500 mg/kg, about 600 mg/kg, about 700 mg/kg, about 800 mg/kg, about 900 mg/kg, or about 1000 mg/kg.

[00116] “Therapeutically effective amount” means an amount effective to achieve a desired and/or beneficial effect (e.g., decreasing tumor size). A therapeutically effective amount can be administered in one or more administrations.

For some purposes of this invention, a therapeutically effective amount is an amount appropriate to treat an indication (e.g., to treat cancer). By treating an indication is meant achieving any desirable effect, such as one or more of palliate, ameliorate, stabilize, reverse, slow, or delay disease (e.g., cancer) progression, increase the quality of life, or to prolong life. Such achievement can be measured by any suitable method, such as but not limited to measurement of tumor size.

[00117] In some embodiments, the treatments can also include one or more of surgical intervention, chemotherapy, radiation therapy, hormone therapies, immunotherapy, and adjuvant systematic therapies. Adjuvants may include but are not limited to chemotherapy (e.g., temozolomide), radiation therapy, antiangiogenic therapy (e.g., bevacizumab), and hormone therapies, such as administration of LHRH agonists; antiestrogens, such as tamoxifen; high-dose progestogens; aromatase inhibitors; and/or adrenalectomy. Chemotherapy can be used as a single-agent or as a combination with known or new therapies.

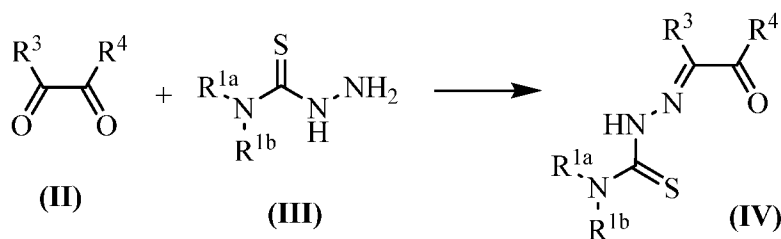
[00118] In some embodiments, the administration of at least one compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) is an adjuvant cancer therapy or part of an adjuvant cancer therapy. Adjuvant treatments include treatments by the mechanisms disclosed herein and of cancers as disclosed herein, including, but not limited to tumors. Corresponding primary therapies can include, but are not limited to, surgery, chemotherapy, or radiation therapy. In some instances, the adjuvant treatment can be a combination of chemokine receptor antagonists with traditional chemotoxic agents or with immunotherapy that increases the specificity of treatment to the cancer and potentially limits additional systemic side effects. In still other embodiments, a compound of the

invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) can be used as adjuvant with other chemotherapeutic agents. The use of a compound of the invention (e.g., Formula (I), (Ia), (Ib), I-1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22) can, in some instances, reduce the duration of the dose of both drugs and drug combinations reducing the side effects.

[00119] In some embodiments, the treatments disclosed herein can include use of other drugs (e.g., antibiotics) or therapies for treating disease. For example, antibiotics can be used to treat infections and can be combined with a compound of the invention to treat disease (e.g., infections associated with cancer). In other embodiments, intravenous immunoglobulin (IVIG) therapy can be used as part of the treatment regime (i.e., in addition to administration of the compound(s) of the invention).

[00120] Methods for Preparing Compounds of Formula (I)

[00121] Some embodiments of the present invention include methods for the preparation of compounds of Formula (I). The compounds of Formula (I) can be prepared using any suitable method. In certain embodiments, a compound of Formula (I) can be prepared comprising the step of reacting a compound of Formula (II) with a compound of Formula (III) to result in Formula (IV), which is later made into Formula (I) (e.g., using one or more synthetic steps).

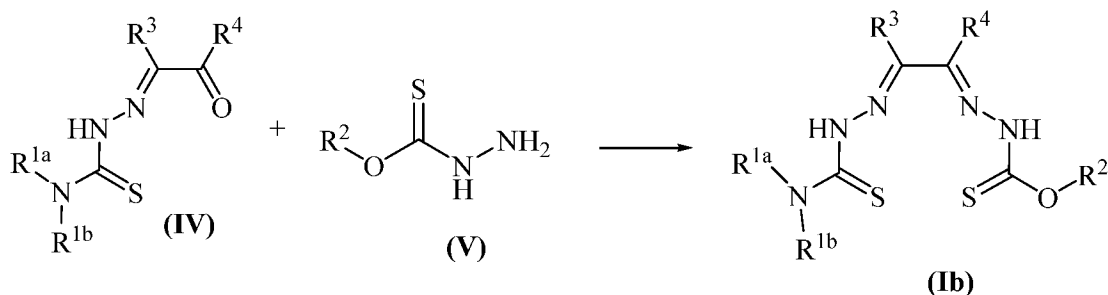


[00122] R^{1a} , R^{1b} , R^3 , and R^4 of Formulas (II), (III), and (IV) are the same as that defined in Formula (I). Formula (II) can be prepared using any suitable method or can be purchased if available. Formula (III) can be prepared using any suitable method or can be purchased where available.

5 [00123] In some embodiments, Formula (II) can be reacted with Formula (III) under the following conditions: Formula (II) can be mixed with an acid (e.g., sulfuric acid) and Formula (III) can be dissolved in a solvent (e.g., water). The mixtures can be added to one another (e.g., by dropwise addition). Formula (IV) can then optionally be recovered using any suitable method.

10 [00124] In some embodiments, Formula (II) (e.g., 2.5 mL, 0.0285 mol) is mixed with concentrated sulfuric acid (e.g., 6 drops) and Formula (III) (e.g., 1.0 g, 0.0095 mol) is dissolved in water (e.g., 6 mL). Formula (III) can be added dropwise to Formula (II) (e.g., at a drop rate of 1 drop per 3 seconds) with stirring (e.g., vigorous stirring). The solution can optionally be placed under vacuum. The solution
15 (e.g., after being placed in a vacuum) can optionally be placed in a freezer (e.g., overnight) which can in some instances result in a solid. Formula (IV) can be recovered (e.g., via filtration with an optional wash (e.g., washed one or more times with water, ethanol, or water/ethanol mixture)).

[00125] In some embodiments, Formula (IV) can be reacted with Formula (V)
20 to provide Formula (Ib).



[00126] R^{1a} , R^{1b} , R^2 , R^3 , and R^4 of Formulas (IV) and (V) are the same as that defined in Formula (I). Formula (IV) can be prepared using any suitable method (e.g., see above) or can be purchased if available. Formula (V) can be prepared using any suitable method or can be purchased if available.

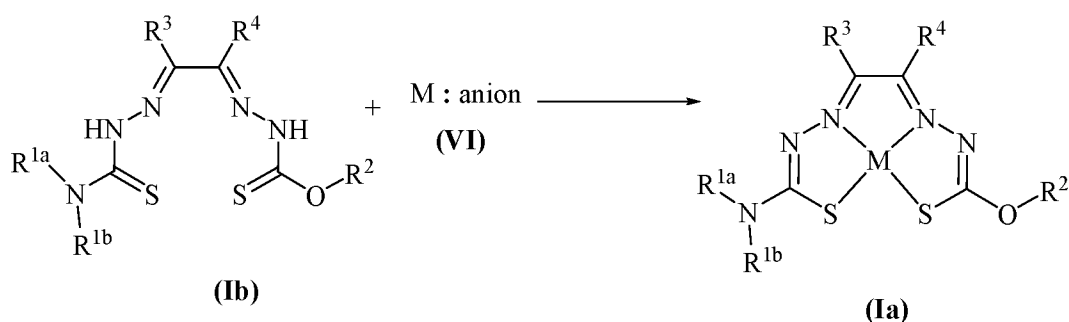
[00127] In some embodiments, Formula (IV) can be reacted with Formula (V) to provide Formula (Ib) under the following conditions: Formula (IV) can be suspended in a solvent (e.g., ethanol). Formula (V) can be added to the suspension. An acid can then be added to the suspension. Formula (Ib) can then optionally be recovered using any suitable method.

[00128] In some embodiments, Formula (IV) (e.g., 0.0063 mol, 0.011 mol, or 0.0036 mol) can be suspended in a solvent (e.g., 25 mL of ethanol). Formula (V) can then be added to the suspension (e.g., in equimolar amounts as Formula (IV), such as 0.0063 mol, 0.011 mol, or 0.0036 mol). An acid (e.g., concentrated sulfuric acid) can then be added (e.g., 6 drops) dropwise to the suspension (e.g., with stirring such as vigorous stirring) to form a precipitate. Formula (Ib) can be recovered (e.g., by filtration) which can optionally include washing the precipitate (e.g., with one or more washes of water, ethanol, or a water/ethanol mixture).

[00129] Formula (Ib) can be optionally or further recovered. Recovery can occur using any suitable method including but not limited to HPLC (e.g., reverse

phase), LC, filtration, precipitation, centrifugation, column chromatography (e.g., size exclusion chromatography or ion exchange chromatography), use of silica gel, washings (e.g., one or more time with one or more solvents or solvent mixtures), or combinations thereof.

- 5 [00130] In some embodiments, Formula (Ib) can be reacted with Formula (VI) to provide Formula (Ia).



- [00131] M of Formula (VI) is the same as that defined in Formula (I). The
 10 M:anion of Formula (VI) can be prepared using any suitable method or can be purchased if available. The term “anion” (i.e., from M:anion) can be any suitable anion including but not limited to any a non-basic anion (e.g., in the presence of a suitable base) or a suitable weak base (e.g., a weak base without any added water or a weak base with added water such as monohydrate, dihydrate, trihydrate, or
 15 tetrahydrate), acetate, acetate monohydrate, acetate dihydrate, or acetate tetrahydrate.

- [00132] In some embodiments, Formula (Ib) can be reacted with Formula (VI) to provide Formula (Ia) under the following conditions: Formula (Ib) can be suspended in a solvent (e.g., methanol). Formula (VI) can be added. The mixture can be heated. Formula (Ia) can then optionally be recovered using any suitable method.
 20 [00133] In some embodiments, Formula (Ib) (e.g., 0.00129 mol) can be suspended in about methanol. Formula (VI) (e.g., in a molar excess of Formula (Ib),

such as 0.00149 mol) can be added to the suspension. The suspension can be heated (e.g., refluxed for four hours) and then cooled (e.g., to room temperature) to produce a precipitate. Formula (Ia) can be optionally recovered (e.g., by filtration) which can optionally include washing the precipitate (e.g., with one or more washes of water, ethanol, or a water/ethanol mixture).

[00134] Formula (Ia) can be optionally or further recovered. Recovery can occur using any suitable method including but not limited to HPLC (e.g., reverse phase), LC, filtration, precipitation, centrifugation, column chromatography (e.g., size exclusion chromatography or ion exchange chromatography), use of silica gel, washings (e.g., one or more time with one or more solvents or solvent mixtures), or combinations thereof.

[00135] In some embodiments, a method for the preparation of a compound of Formula (I) can comprise one or more of the above-mentioned steps. In certain embodiments, a method for preparing a compound of Formula (I) comprises (a) reacting a compound of Formula (II) with a compound of Formula (III) to result in a mixture comprising a compound of Formula (IV) and (b) reacting a compound of Formula (IV) with a compound of Formula (V) to result in a mixture comprising a compound of Formula (Ib). In other embodiments, the method further comprises recovering Formula (Ib). In yet other embodiments, the method further comprises (c) reacting a compound of Formula (Ib) with a compound of Formula (VI) and (d) recovering Formula (Ia).

[00136] The presently-disclosed subject matter is further illustrated by the following specific but non-limiting examples. The following examples may include

compilations of data that are representative of data gathered at various times during the course of development and experimentation related to the present invention.

EXAMPLES

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Example Set A

[00137] Anti-proliferative activity of compounds using MTT assay - Methods

[00138] Anti-proliferative activity of the indicated compounds was evaluated for A549 (human lung adenocarcinoma) cells and IMR-90 (human non-malignant lung fibroblast) cells using a previously published 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay protocol (MORGAN, "Tetrazolium (MTT) Assay For Cellular Viability And Activity" Methods Mol. Biol. (1998) Vol. 79, pp. 179-183; BATES et al., "Antiproliferative Activity of G-rich Oligonucleotides Correlates with Protein Binding" J. Biol. Chem. (1999) Vol. 274, No. 37, pp. 26369-26377; SALIPUR et al., "A Novel Small Molecule That Induces Oxidative Stress And Selectively Kills Malignant Cells" Free Radical Biology and Medicine (2014) Vol. 68, pp. 110-121. Cells were seeded in quadruplicate wells in 96-well plates and allowed to adhere overnight. To account for intrinsic differences in growth rates, cells were plated at the following densities to achieve comparable MTT absorbance values (OD₅₇₀ between 0.5 and 1) for untreated cells: A549, 1000 cells/well; IMR-90, 5000 cells/well. After 72 hrs of treatment with test compounds, MTT (Sigma, St. Louis, MO) was added for 4 hrs prior to cell lysis. Each assay was performed in at least triplicate.

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[00139] Anti-proliferative activity of compounds using MTT assay - Results

[00140] Figs. 1-3, 6, 8, 11, 13, and 14 show that some compounds containing Cu appear to have a greater activity in cancer cells (A549) compared to some compounds containing Zn. Figs. 1-3, 6-8, 11-14, and 17 show that some compounds containing Ni did not appear to reduce cancer cell growth, as much as Cu or Zn containing compounds.

[00141] Figs. 4, 5, 9, 10, 15, 16, and 18 indicate that the ligands themselves appear to reduce cancer cell growth. Without being bound by theory, this could occur by self-assembling with trace metals (e.g., Cu) in the medium.

[00142] One Dose Data- Methods

[00143] The One-dose method can be found at <<https://dtp.cancer.gov/discovery_development/nci-60/methodology.htm>> which is herein incorporated by reference in its entirety. In general, compounds submitted to the NCI-60 human cancer cell line screen were tested initially at a single high dose (10 μ M) for a fixed period of time in the panel's 60 cell lines. The list of cell lines can be found at <<https://dtp.cancer.gov/discovery_development/nci-60/cell_list.htm>> which is herein incorporated by reference in its entirety and some characteristics of these cell lines can be found at <<<https://www.nature.com/articles/sdata2017157/tables/1>>> which is herein incorporated by reference in its entirety. The list of cell lines is also provided in Table 2, which are listed in the same order as that found in Figs. 19-20.

Table 2

Cell Line	Related Cancer
CCRF-CEM	Leukemia
HL-60(TB)	Leukemia
K-562	Leukemia
MOLT-4	Leukemia
RPMI-8226	Leukemia
SR	Leukemia
A549/ATCC	Non-Small Cell Lung
EKVX	Non-Small Cell Lung
HOP-62	Non-Small Cell Lung
HOP-92	Non-Small Cell Lung
NCI-H226	Non-Small Cell Lung
NCI-H23	Non-Small Cell Lung
NCI-H322M	Non-Small Cell Lung
NCI-H460	Non-Small Cell Lung
NCI-H522	Non-Small Cell Lung
COLO 205	Colon
HCC-2998	Colon
HCT-116	Colon
HCT-15	Colon
HT29	Colon
KM12	Colon
SW-620	Colon
SF-268	CNS
SF-295	CNS
SF-539	CNS
SNB-19	CNS
SNB-75	CNS
U251	CNS
LOX IMVI	Melanoma
MALME-3M	Melanoma
M14	Melanoma
MDA-MB-435	Melanoma

SK-MEL-2	Melanoma
SK-MEL-28	Melanoma
SK-MEL-5	Melanoma
UACC-257	Melanoma
UACC-62	Melanoma
IGR-OV1	Ovarian
OVCAR-3	Ovarian
OVCAR-4	Ovarian
OVCAR-5	Ovarian
OVCAR-8	Ovarian
NCI/ADR-RES	Ovarian
SK-OV-3	Ovarian
786-0	Renal
A498	Renal
ACHN	Renal
CAKI-1	Renal
RXF 393	Renal
SN12C	Renal
TK-10	Renal
UO-31	Renal
PC-3	Prostate
DU-145	Prostate
MCF7	Breast
MDA-MB-231/ATCC	Breast
HS 578T	Breast
BT-549	Breast
T-47D	Breast
MDA-MB-468	Breast

[00144] The One-dose data is reported as a mean graph of the percent growth of treated cells. The number reported for the One-dose assay is growth relative to the no-drug control, and relative to the time zero number of cells. This allows detection of both growth inhibition (values between 0 and 100) and lethality (values less than 0).

For example, a value of 100 means no growth inhibition. A value of 40 would mean 60% growth inhibition. A value of 0 means no net growth over the course of the experiment. A value of -40 would mean 40% lethality. A value of -100 means all cells are dead.

5

[00145] One Dose Data- Results

[00146] Figs. 19-20 indicate that the two compounds (I-1 and I-5) appear to have similar profiles; this could suggest they have the same mechanism of action. Figs. 19-20 indicate that the two compounds provide 100% growth inhibition or better at 10 μ M in most cell lines, and close to 100% cytotoxicity (all cells dead) in some cell lines. Figs. 19-20 also appear to indicate that the growth of leukemia cells is not as inhibited as other cell types.

10

[00147] Cell Proliferation and Reactive Oxygen Species (ROS) Production -
15 Methods

[00148] **A549** (human lung adenocarcinoma) cells and **MDA-MB-231** (human breast adenocarcinoma) cells were cultured in DMEM medium containing 10% FBS and 1% Penicillin/Streptomycin. **IMR-90** (human non-malignant lung fibroblast) cells were cultured in EMEM medium containing 10% FBS and 1% Penicillin/Streptomycin. **MCF10A** (human non-malignant breast epithelial) cells in MEBM containing 10% FBS. Cell viability after treatment was determined using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). After 72 h treatment with compound, a 5 mg/ml solution MTT of (Sigma, St. Louis, MO) was added in at 1/10 total sample volume. Cells were then incubated for 4 h. Lysis buffer

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(10% SDS in 0.01 N HCl) was added at half of the original sample volume and incubated overnight. Plates were read at 570 nm. Graphs indicate average of one or two experiments (performed in quadruplet wells) $\pm$ SEM. Cell death in A549 cells was assessed by trypan blue exclusion. Average of one or two experiments (each performed in triplicate) $\pm$ SEM displayed on graphs. ROS production in A549 lung cancer cells after 48 h treatment with the compounds was assayed using ROS-Glo™ H₂O₂ Assay Kit (Promega). Graph displays mean of three experiments performed $\pm$ SEM as percent of vehicle.

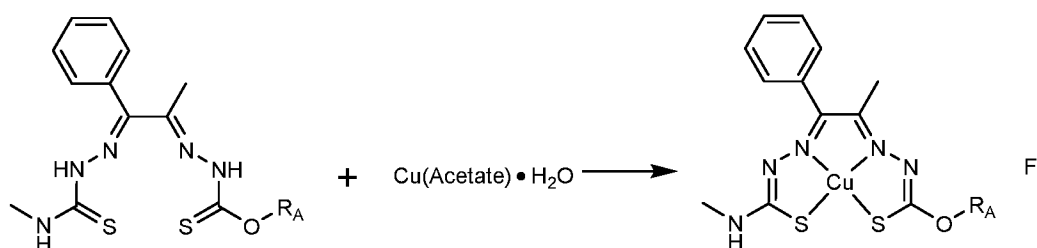
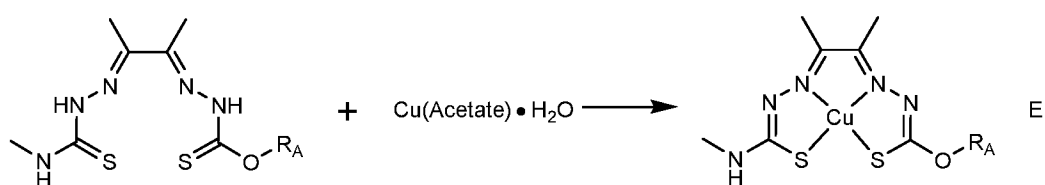
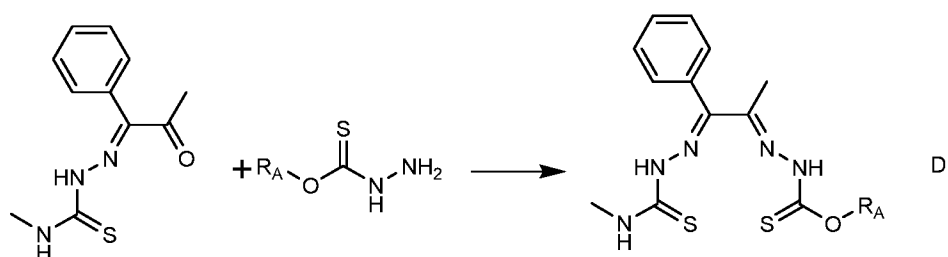
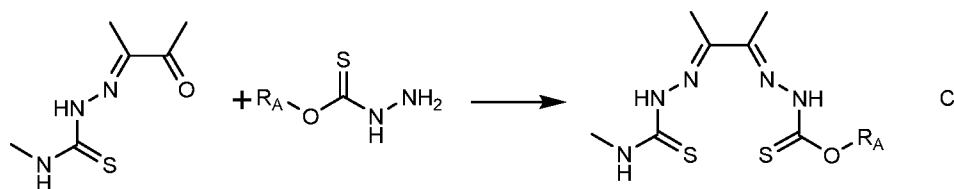
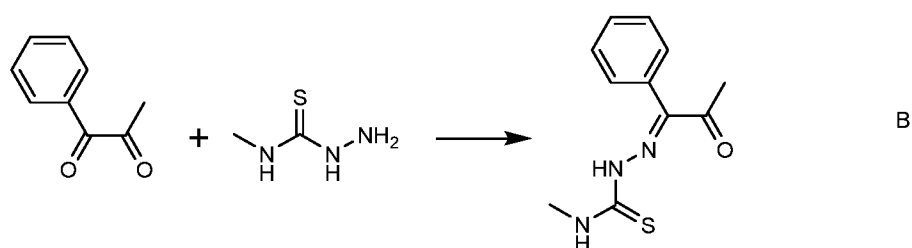
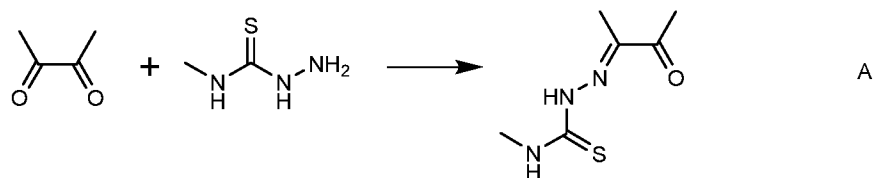
10 [00149] Cell Proliferation and Reactive Oxygen Species (ROS) Production - Results

[00150] Figs. 21-22 indicate that compound I-1 was able to inhibit proliferation of cancer cells at lower concentrations than in non-malignant cells. The GI₅₀ values (concentration needed to inhibit cell proliferation by 50%) for compound I-1 for each cell line are: A549 (0.13 μ M); MDA-MB-231 (0.34 μ M); IMR-90 (0.98 μ M); MCF 15 10A (>2 μ M). These results suggest that compound I-1 is selectively toxic to cancer cells.

[00151] Fig. 23 shows that compound I-1 does not produce a significant increase in ROS. This suggests that the mechanism for the toxicity of compound I-1 does not involve increasing ROS within cancer cells; a different mechanism could be 20 implicated.

Example Set B - Synthetic Methods and Compound Characterization

[00152] The following reactions (A-F) are referenced in Example Set B.



[00153] All starting materials were purchased from a commercial vendor, synthesized according to literature procedures, or otherwise described herein. The hydrazinecarbothioc acid O-alkyl esters were synthesized according to Reüfenacht 1972 (REÜFENACHT, "Arbetien über Phosphosäure- und Thiosphosphorsäureester mit einem Heterocyclischen Substituenten Thiadiazol-Ringschluss und eine Dabei Auftretende Methylübertragung" *Helv. Chim. Acta* (1972) Vol. 55, Issue 4, pp. 1178-1187). The reactions A and B are modified from Bocokic et al. 2012 (BOCOKIC et al., "Bis-(thiosemicarbazonato) Zn(ii) complexes as building blocks for construction of supramolecular catalysts" *Dalton Trans.* (2012) Vol. 41, Issue 13, pp. 3740-3750).

10 The 4-methyl-3-thiosemicarbazide was purchased from Alfa Aesar, the 2,3-butane dione and 1-phenyl-1,2-propane dione were purchased from Sigma Aldrich, and the copper acetate was purchased from Lancaster.

[00154] Reaction A

15 [00155] In 25 mL of water 2,3-butane dione (2.5 mL, 0.0285 mol) was mixed with 6 drops of concentrated sulfuric acid. In 100 mL of water the 4-methyl-3-thiosemicarbazide (1.0 g, 0.0095 mol) was dissolved. The solution of the 4-methyl-3-thiosemicarbazide was added to the dione solution at a drop rate of 1 drop per 3 seconds with vigorous stirring. A white precipitate formed and was isolated via

20 filtration with a water wash. 1.55 g (95%) yield. The ¹H NMR spectrum of the product of reaction A is shown in Fig. 24 and the ¹³C NMR spectrum of the product is shown in Fig. 25.

[00156] Reaction B

[00157] In 25 mL of ethanol 1-phenyl-2,3-propane dione (3.8 mL, 0.0285 mol) was mixed with 6 drops of concentrated sulfuric acid. In 100 mL of ethanol (1.0 g 0.0095 mol) the 4-methyl-3-thiosemicarbazide was dissolved. The solution of the 4-methyl-3-thiosemicarbazide was added to the dione solution at a drop rate of 1 drop per 3 seconds with vigorous stirring. The solution was then concentrated under vacuum and then stored in a freezer overnight. A yellow solid formed after being placed in the freezer. This yellow solid was then filtered and washed with ethanol. 1.55 g (70%) yield. The ^1H NMR spectrum of the product of reaction B is shown in Fig. 26 and the ^{13}C NMR spectrum of the product of reaction B is shown in Fig. 27.

[00158] Reaction C - Generic procedure

[00159] In 25 mL of ethanol, the compound isolated from reaction A was suspended. The appropriate hydrazinecarbothioc acid O-alkyl esters (R_A = ethyl or propyl) was added to this suspension, followed by 6 drops of concentrated sulfuric acid. A white/creme precipitate formed and was isolated via filtration with an ethanol and water wash.

[00160] Reaction C - R_A = Ethyl

[00161] In 25 mL of ethanol, the compound isolated from reaction A was suspended (0.894 g, 0.0063 mol). The hydrazinecarbothioc acid O-ethyl ester (0.760 g, 0.0063 mol) was added to this suspension, followed by 6 drops of concentrated sulfuric acid. A white/creme precipitate formed and was isolated via filtration with an ethanol and water wash. 1.32 g (76%) yield. Elemental analysis calculated: C: 39.25 H: 6.22 N: 25.43. Found: C: 39.12 H: 6.16 N: 25.54. The ^1H NMR spectrum of the

product of reaction C (ethyl) (compound I-4) is shown in Fig. 28 and the ^{13}C NMR spectrum of the product of reaction C (ethyl) (compound I-4) is shown in Fig. 29.

[00162] Reaction C - R_A = Propyl

[00163] In 25 mL of ethanol, the compound isolated from reaction A was
5 suspended (1.58 g, 0.011 mol). The hydrazinecarbothioc acid O-propyl ester (0.145 g, 0.011 mol) was added to this suspension, followed by 6 drops of concentrated sulfuric acid. A white/creme precipitate formed and was isolated via filtration with an ethanol and water wash. 1.32 g (75%) yield. Elemental analysis calculated: C: 41.50 H: 6.62 N: 24.20. Found: C: 41.31 H: 6.46 N: 24.02. The ^1H NMR spectrum of the
10 product of reaction C (propyl) (compound I-12) is shown in Fig. 30 and the ^{13}C NMR spectrum of the product of reaction C (propyl) (compound I-12) is shown in Fig. 31.

[00164] Reaction D

[00165] In 25 mL of ethanol, the compound isolated from reaction B (0.840 g, 0.0036 mol) was suspended. The hydrazinecarbothioc acid O-ethyl ester (0.43 g, 0.0036 mol) was added to this suspension, followed by 6 drops of concentrated
15 sulfuric acid. A white/creme precipitate formed and was isolated via filtration with an ethanol and water wash. 0.871 g (72%) yield. Elemental analysis calculated: C: 49.83 H: 5.67 N 20.75. Found: C: 49.14 H: 5.60 N: 20.18. The ^1H NMR spectrum of the product of reaction D is shown in Fig. 32 and the ^{13}C NMR spectrum of the product of
20 reaction D (compound I-8) is shown in Fig. 33.

[00166] Reaction E - Generic Procedure

[00167] The ligand was suspended in methanol (0.00129 mol). To this suspension copper (II) acetate monohydrate (0.00149 mol) was added which caused an immediate color change of the suspension to red-brown. The suspension was

refluxed for 4 hours then cooled to room temperature then filtered and washed with methanol.

[00168] Reaction E – R_A = Ethyl

[00169] The ligand was suspended in methanol (0.354 g, 0.00129 mol). To this
5 suspension copper (II) acetate monohydrate (0.285 g, 0.00149 mol) was added which caused an immediate color change of the suspension to red-brown. The suspension was refluxed for 4 hours then cooled to room temperature then filtered and washed with methanol. 0.220 g (51%) yield. Elemental analysis calculated: C: 32.08 H: 4.49 N: 20.79. Found: C: 31.53 H: 4.34 N: 20.26 Mass spec. calculated for R_A = -CH₂CH₃:
10 336.00141 found: 337.0080 (it appears to have picked up a proton in the mass spec). An ORTEP representation of the product of reaction E (ethyl) (compound I-1) is shown in Fig. 34.

[00170] Reaction E - R_A = Propyl

[00171] The ligand was suspended in methanol (0.373 g, 0.00129 mol). To this
15 suspension copper (II) acetate monohydrate (0.285 g, 0.00149 mol) was added which caused an immediate color change of the suspension to red-brown. The suspension was refluxed for 4 hours then cooled to room temperature then filtered and washed with methanol. 0.200 g (44%) yield Calculated for R_A = -CH₂CH₂CH₃: C: 34.22 H: 4.88 N: 19.96. Found: C: 34.17 H: 4.83 N: 20.01. Mass spec. calculated: 350.01706
20 found: 351.0239 (it appears to have picked up a proton in the mass spec). This is compound I-9.

[00172] Reaction F

[00173] The ligand was suspended in methanol. To this suspension copper (II) acetate monohydrate was added which caused an immediate color change of the

suspension to red-brown. The suspension was refluxed for 4 hours then cooled to room temperature then filtered and washed with methanol. 0.146 g (29%) yield.

Elemental Analysis calculated: C: 42.14 H: 4.29 N: 17.55. Found: C:41.84 H: 4.22 N: 17.53. Mass spec. calculated: 398.01706 found: 339.0238. (it appears to have picked up a proton in the mass spec). An ORTEP representation of the product of reaction F (compound I-5) is shown in Fig. 35.

[00174] Reaction G – Generic preparation of Ni compounds

[00175] The ligand was suspended in methanol (0.00129 mol). To this suspension nickel (II) acetate tetrahydrate (0.00149 mol) (Lancaster) was added which caused an immediate color change of the suspension to dark brown color. The suspension was refluxed for 4 hours then cooled to room temperature then stored in a freezer overnight. The following day the suspension was filtered cold and washed with methanol.

[00176] Characterization of compound I-6 prepared using Reaction G: Mass spec calculated 393.02281. Found 394.0295 (picked up a proton). Elemental analysis calculated C: 42.66 H: 4.35 N: 17.77 Found C: 42.85 H: 4.46 N: 17.57

[00177] Reaction H – Generic preparation of Zn compounds

[00178] The ligand was suspended in methanol (0.00129 mol). To this suspension zinc (II) acetate dihydrate (0.00149 mol) (Fischer) was added which caused an immediate color change of the suspension to yellow-orange. The suspension was refluxed for 4 hours then cooled to room temperature then filtered and washed with methanol.

[00179] Characterization of compound I-3 prepared using Reaction H: Mass spec calculated 337.00096 Found 338.2153 (picked up a proton). Elemental analysis calculated C: 31.91 H: 4.46 N: 20.67. Found C: 31.92 H: 4.45 N: 20.67.

[00180] Characterization of compound I-7 prepared using Reaction H: Mass spec calculated 399.01661. Found 400.3753 (picked up a proton). Elemental analysis calculated: C: 41.95 H: 4.27 N: 17.47. Found: C: 40.65 H: 4.08 N: 19.97.

[00181] The headings used in the disclosure are not meant to suggest that all disclosure relating to the heading is found within the section that starts with that heading. Disclosure for any subject may be found throughout the specification.

[00182] It is noted that terms like “preferably,” “commonly,” and “typically” are not used herein to limit the scope of the claimed invention or to imply that certain features are critical, essential, or even important to the structure or function of the claimed invention. Rather, these terms are merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment of the present invention.

[00183] As used in the disclosure, “a” or “an” means one or more than one, unless otherwise specified. As used in the claims, when used in conjunction with the word “comprising” the words “a” or “an” means one or more than one, unless otherwise specified. As used in the disclosure or claims, “another” means at least a second or more, unless otherwise specified. As used in the disclosure, the phrases “such as”, “for example”, and “e.g.” mean “for example, but not limited to” in that the list following the term (“such as”, “for example”, or “e.g.”) provides some examples but the list is not necessarily a fully inclusive list. The word “comprising” means that

the items following the word “comprising” may include additional unrecited elements or steps; that is, “comprising” does not exclude additional unrecited steps or elements.

[00184] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about”. Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and claims are approximations that can vary depending upon the desired properties sought to be obtained by the presently-disclosed subject matter.

10 [00185] As used herein, the term “about,” when referring to a value or to an amount of mass, weight, time, volume, concentration or percentage is meant to encompass variations of in some embodiments $\pm 20\%$, in some embodiments $\pm 10\%$, in some embodiments $\pm 5\%$, in some embodiments $\pm 1\%$, in some embodiments $\pm 0.5\%$, and in some embodiments $\pm 0.1\%$ from the specified amount, as such variations are
15 appropriate to perform the disclosed method.

[00186] Detailed descriptions of one or more embodiments are provided herein. It is to be understood, however, that the present invention may be embodied in various forms. Therefore, specific details disclosed herein (even if designated as preferred or advantageous) are not to be interpreted as limiting, but rather are to be used as an
20 illustrative basis for the claims and as a representative basis for teaching one skilled in the art to employ the present invention in any appropriate manner. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the

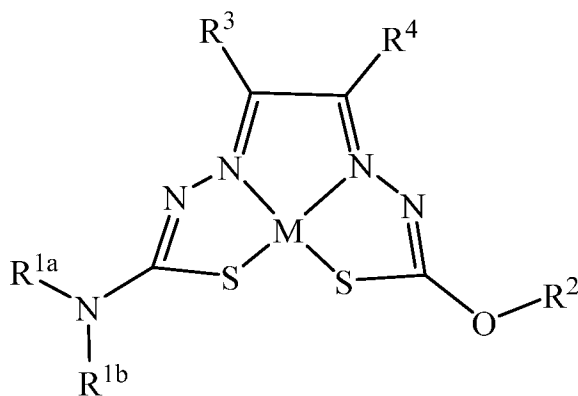
accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[00187] What is claimed is:

CLAIMS

1. A compound selected from

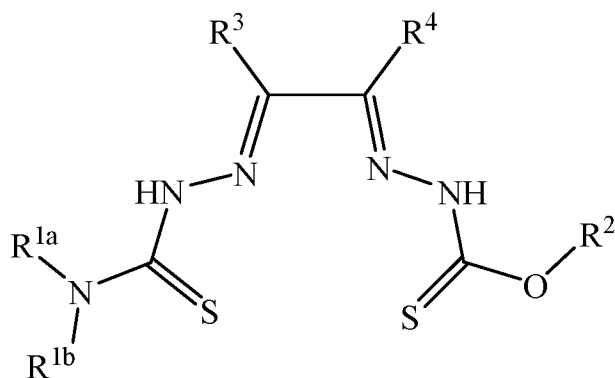
(a) Formula (Ia)



(Ia) and salts, optical isomers,

5 geometric isomers, salts of isomers, and derivatives thereof; and

(b) Formula (Ib)



(Ib), and salts, optical isomers,

geometric isomers, salts of isomers, and derivatives thereof;

wherein

10 - R^{1a} is H, halogen, -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O),

hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy;

5 - R^{1b} is H, halogen, -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O),
 10 hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy;

 - R^{1a} and R^{1b} are optionally bonded together with their attached
 15 nitrogen to form heterocyclyl or heteroaryl, which heterocyclyl or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-
 20 C₃ alkoxy;

 - R² is H, halogen, -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or

heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy;

- R³ is H, halogen, -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy;

- R⁴ is H, halogen, -CN, hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₉ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy;

- R³ and R⁴ are optionally bonded together to form a ring with their attached carbons that is fused to the attached carbons of R³ and R⁴, where the ring that is fused is cycloalkyl, heterocyclyl, aryl, or heteroaryl, which cycloalkyl, heterocyclyl, aryl, or heteroaryl can optionally be substituted with one or more of halogen, oxo (=O), hydroxy (-OH), methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), morpholinyl, -CO-morpholin-4-yl, phenyl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, -CF₃, -OCF₃, or C₁-C₃ alkoxy; and

- M is a divalent cation.

10

2. The compound of claim 1, wherein R^{1a} is H, methyl, ethyl, C₁₋₅ alkyl, C₃ alkyl, n-propyl, isopropyl, ethoxy, methoxy, 5-hydroxy pyridyl, indolyl, 1,2,3,4-tetrahydroisoquinolyl, furyl, 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl.

20

3. The compound of claim 1 or claim 2, wherein R^{1a} is H, methyl, ethyl, n-propyl, or phenyl.

4. The compound of any of claims 1-3, wherein R^{1a} is not H.

5

5. The compound of any of claims 1-4, wherein R^{1b} is H, Cl, hydroxy (-OH), methyl, ethyl, C₁₋₅ alkyl, C₃ alkyl, C₄ alkyl, -CN, ethynyl, -CONH₂, -CON(CH₃)₂,

2-(morpholinyl)ethoxy, -CO-morpholin-4-yl, ethoxy, methoxy, 5-hydroxy pyridyl, indolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2-methylenedioxyphenyl, 2,3-

10 methylenedioxyphenyl, furyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-

15 trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl.

20

6. The compound of any of claims 1-5, wherein R^{1b} is H, methyl, ethyl, n-propyl, or phenyl.

7. The compound of any of claims 1-6, wherein R^{1b} is not H.

8. The compound of any of claims 1-7, wherein R² is methyl, ethyl, C₃ alkyl, n-propyl, isopropyl, ethoxy, methoxy, 5-hydroxy pyridyl, indolyl, 1,2,3,4-tetrahydroisoquinolyl, furyl, 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl, 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl, pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl.
9. The compound of any of claims 1-8, wherein R² is methyl, ethyl, n-propyl, or phenyl.
10. The compound of any of claims 1-9, wherein R³ is H, Cl, hydroxy (-OH), methyl, ethyl, C₁₋₅ alkyl, C₃ alkyl, -CN, ethynyl, -CONH₂, -CON(CH₃)₂, 2-(morpholinyl)ethoxy, -CO-morpholin-4-yl, ethoxy, methoxy, 5-hydroxy pyridyl, indolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2-methylenedioxyphenyl, 2,3-methylenedioxyphenyl, furyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl,

3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl,
4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-
trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-
dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-
5 dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl,
pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated
ethyl.

11. The compound of any of claims 1-10, wherein R^3 is H, methyl, ethyl, n-propyl, or
10 phenyl.

12. The compound of any of claims 1-11, wherein R^4 is H, Cl, hydroxy (-OH),
methyl, ethyl, C_{1-5} alkyl, C_3 alkyl, -CN, ethynyl, -CONH₂, -CON(CH₃)₂,
2-(morpholinyl)ethoxy, -CO-morpholin-4-yl, ethoxy, methoxy, 5-hydroxy pyridyl,
15 indolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2-methylenedioxyphenyl, 2,3-
methylenedioxyphenyl, furyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-
fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-
methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethoxyphenyl,
3-ethoxyphenyl, 4-ethoxyphenyl, 2-trifluoromethyl phenyl, 3-trifluoromethyl phenyl,
20 4-trifluoromethyl phenyl, 2-trifluoromethoxy phenyl, 3-trifluoromethoxy phenyl, 4-
trifluoromethoxy phenyl, 3,5-dimethoxyphenyl, 3,5-diethoxyphenyl, 3,5-
dimethylphenyl, 3,5-diethylphenyl, 3,5-dihydroxyphenyl, 3,5-difluorophenyl, 3,5-
dichlorophenyl, 3,5-bis-trifluoromethyl phenyl, phenyl, naphthyl, tolyl, xylyl, benzyl,

pyridyl, 3-pyridyl, methylenedioxyphenyl, perfluorinated methyl, or perfluorinated ethyl.

13. The compound of any of claims 1-12, wherein R⁴ is H, methyl, ethyl, n-propyl, or
5 phenyl.

14. The compound of any of claims 1-13, wherein M is iron (Fe), nickel (Ni),
palladium (Pd), cadmium (Cd), manganese (Mn), cobalt (Co), copper (Cu), or zinc
(Zn).

10

15. The compound of any of claims 1-14, wherein M is Cu, Ni, or Zn.

16. The compound of any of claims 1-15, wherein M is Cu.

15 17. The compound of any of claims 1-16, wherein the compound of Formula (I) is I-
1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-10, I-11, I-12, I-13, I-14, I-15, I-16, I-17, I-18, I-
19, I-20, I-21, I-22, I-23, I-24, I-25, I-26, I-27, I-28, I-29, I-30, I-31, I-32, I-33, I-34,
I-35, I-36, I-37, I-38, I-39, I-40, I-41, I-42, I-43, I-44, I-45, I-46, I-47, I-48, I-49, I-50,
I-51, I-52, I-53, I-54, I-55, I-56, I-57, I-58, I-59, I-60, I-61, I-62, I-63, I-64, I-65, I-66,
20 I-67, I-68, I-69, I-70, or I-71.

18. The compound of any of claims 1-17, wherein the compound of Formula (I) is I-
1, I-3, I-4, I-5, I-7, I-8, I-9, I-11, I-12, or I-22.

19. The compound of any of claims 1-18, wherein the compound of Formula (I) is I-1 or I-5.

20. The compound of any of claims 1-19, wherein (a) R^{1a} is H, R^{1b} is methyl, R^2 is ethyl, R^3 is methyl, R^4 is methyl, M is Cu, or combinations thereof; (b) R^{1a} is methyl, R^{1b} is H, R^2 is ethyl, R^3 is methyl, R^4 is methyl, M is Cu, or combinations thereof; (c) R^{1a} is H, R^{1b} is methyl, R^2 is ethyl, R^3 is methyl, R^4 is methyl, M is Zn, or combinations thereof; or (d) R^{1a} is methyl, R^{1b} is H, R^2 is ethyl, R^3 is methyl, R^4 is methyl, M is Zn, or combinations thereof.

10

21. The compound of any of claims 1-20, wherein R^{1a} is H or R^{1b} is H, but both R^{1a} and R^{1b} are not H.

22. A composition comprising a compound of any of claims 1-21.

15

23. The composition of claim 22, wherein the amount of the compound is from about 0.0001% (by weight total composition) to about 99%.

24. The composition of claim 22 or claim 23, further comprising a formulary ingredient, an adjuvant, or a carrier.

20

25. A pharmaceutical composition comprising a compound of any of claims 1-21.

26. The pharmaceutical composition of claim 25, wherein the amount of the compound is from about 0.0001% (by weight total composition) to about 50%.

27. The pharmaceutical composition of claim 25 or claim 26, further comprising a
5 formulary ingredient, an adjuvant, or a carrier.

28. A method for providing an animal with a compound comprising one or more administrations of one or more compositions comprising the compound of any of claims 1-21, wherein the compositions may be the same or different if there is more
10 than one administration.

29. The method of claim 28, wherein at least one of the one or more compositions further comprises a formulary ingredient.

15 30. The method of claim 28 or claim 29, wherein at least one of the one or more compositions comprises the composition of any of claims 22-24 or the pharmaceutical composition of any of claims 25-27.

31. The method of any of claims 28-30, wherein at least one of the one or more
20 administrations comprises parenteral administration, a mucosal administration, intravenous administration, subcutaneous administration, topical administration, intradermal administration, oral administration, sublingual administration, intranasal administration, or intramuscular administration.

32. The method of any of claims 28-31, wherein if there is more than one administration at least one composition used for at least one administration is different from the composition of at least one other administration.

5 33. The method of any of claims 28-32, wherein the compound of at least one of the one or more compositions is administered to the animal in an amount of from about 0.01 mg/kg animal body weight to about 15 mg/kg animal body weight.

34. The method of any of claims 28-33, wherein the animal is a human, a rodent, or a
10 primate.

35. A method for treating an animal for a disease, comprising one or more administrations of one or more compositions comprising the compound of any of claims 1-21, wherein the compositions may be the same or different if there is more
15 than one administration.

36. The method of claim 35, wherein at least one of the one or more compositions further comprises a formulary ingredient.

20 37. The method of claim 35 or claim 36, wherein at least one of the one or more compositions comprises the composition of any of claims 22-24 or the pharmaceutical composition of any of claims 25-27.

38. The method of any of claims 35-37, wherein at least one of the one or more administrations comprises parenteral administration, a mucosal administration, intravenous administration, subcutaneous administration, topical administration, intradermal administration, oral administration, sublingual administration, intranasal administration, or intramuscular administration.
39. The method of any of claims 35-38, wherein if there is more than one administration at least one composition used for at least one administration is different from the composition of at least one other administration.
40. The method of any of claims 35-39, wherein the compound of at least one of the one or more compositions is administered to the animal in an amount of from about 0.005 mg/kg animal body weight to about 50 mg /kg animal body weight.
41. The method of any of claims 35-40, wherein the animal is a human, a rodent, or a primate.
42. The method of any of claims 35-41, wherein the animal is in need of the treatment.
43. The method of any of claims 35-42, wherein the method is for treating cancer.
44. The method of any of claims 35-43, wherein the method is for treating acute lymphoblastic leukemia, astrocytoma, basal cell carcinoma, bladder cancer, bone

marrow cancer, breast cancer, chronic lymphocytic leukemia (CLL), CNS cancer, colon cancer, colorectal cancer, endometrial cancer, gastric cancer, glioblastoma, glioblastoma multiforme, glioma, gliosarcoma, hepatocellular carcinoma, kidney cancer, leukemia, liver cancer, lung cancer, lymphoma, melanoma, malignant nerve sheath tumors, medulloblastoma, meningioma, multiple myeloma, nasopharyngeal carcinoma, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, renal cancer, renal cell carcinoma, rhabdomyosarcoma, squamous cell carcinoma, stomach cancer, thyroid cancer, uterine cancer, cancers that can result in metastasis, cancers resulting from metastasis, or cancerous tumors thereof.

45. The method of any of claims 35-44, wherein the method is for treating leukemia, lung cancer, non-small cell lung cancer, colorectal cancer, colon cancer, rectal cancer, CNS cancer, glioblastoma, glioblastoma multiforme, gliosarcoma, astrocytoma, melanoma, cutaneous malignant melanoma, melanoma tumorigenesis, ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof.

46. The method of any of claims 35-45, wherein the method does not include treating leukemia.

47. The method of any of claims 35-46, wherein the method is for treating lung cancer, non-small cell lung cancer, colorectal cancer, colon cancer, rectal cancer, CNS cancer, glioblastoma, glioblastoma multiforme, gliosarcoma, astrocytoma, melanoma,

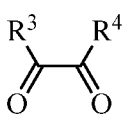
cutaneous malignant melanoma, melanoma tumorigenesis, ovarian cancer, kidney cancer, prostate cancer, breast cancer, or cancerous tumors thereof.

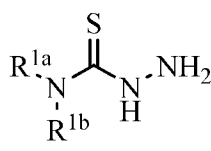
48. The method of any of claims 35-47, wherein the method is for treating cancerous tumors.

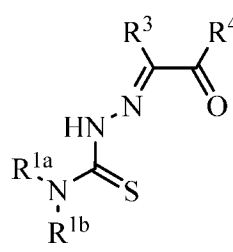
49. A method for preparing a compound of any of claims 1-21 comprising,

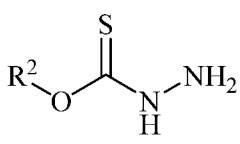
(a) reacting a compound of Formula (II) with a compound of Formula (III) to result in a mixture comprising a compound of Formula (IV) and

(b) reacting a compound of Formula (IV) with a compound of Formula (V) to result in a mixture comprising a compound of Formula (Ib),

wherein Formula (II) is  (II);

Formula (III) is  (III);

Formula (IV) is  (IV); and

Formula (V) is  (V).

50. The method of claim 49, wherein the method further comprises recovering the compound of Formula (Ib).

51. The method of claim 49 or claim 50, wherein the method further comprises

5 (c) reacting the compound of Formula (Ib) with a compound of Formula (VI)

and

(d) recovering a compound of Formula (Ia), wherein

Formula (VI) is M:anion **(VI)**.

10 52. The method of claim 51, wherein the anion is a weak base, acetate, acetate monohydrate, acetate dihydrate, or acetate tetrahydrate.

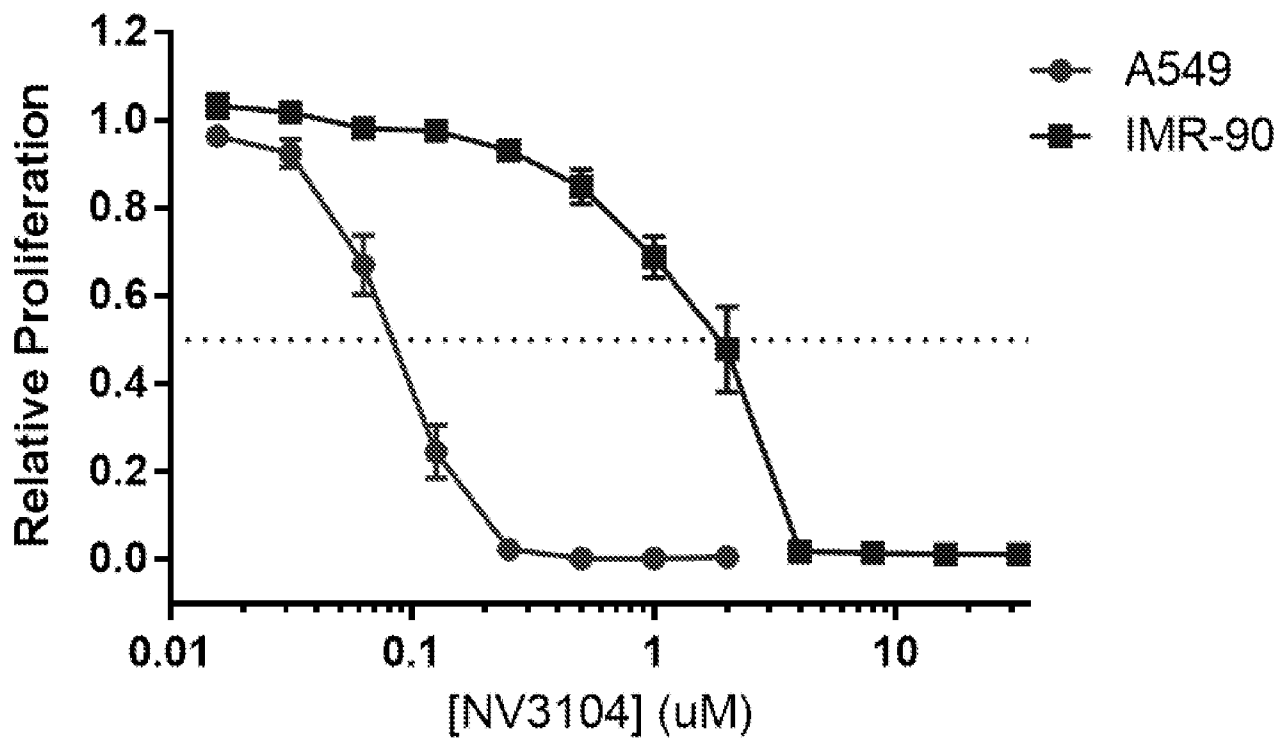
53. The method of claim 51 or claim 52, wherein the compound of Formula (VI) is copper (II) acetate monohydrate, nickel (II) acetate tetrahydrate, or zinc (II) acetate

15 dihydrate.

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FIG. 1

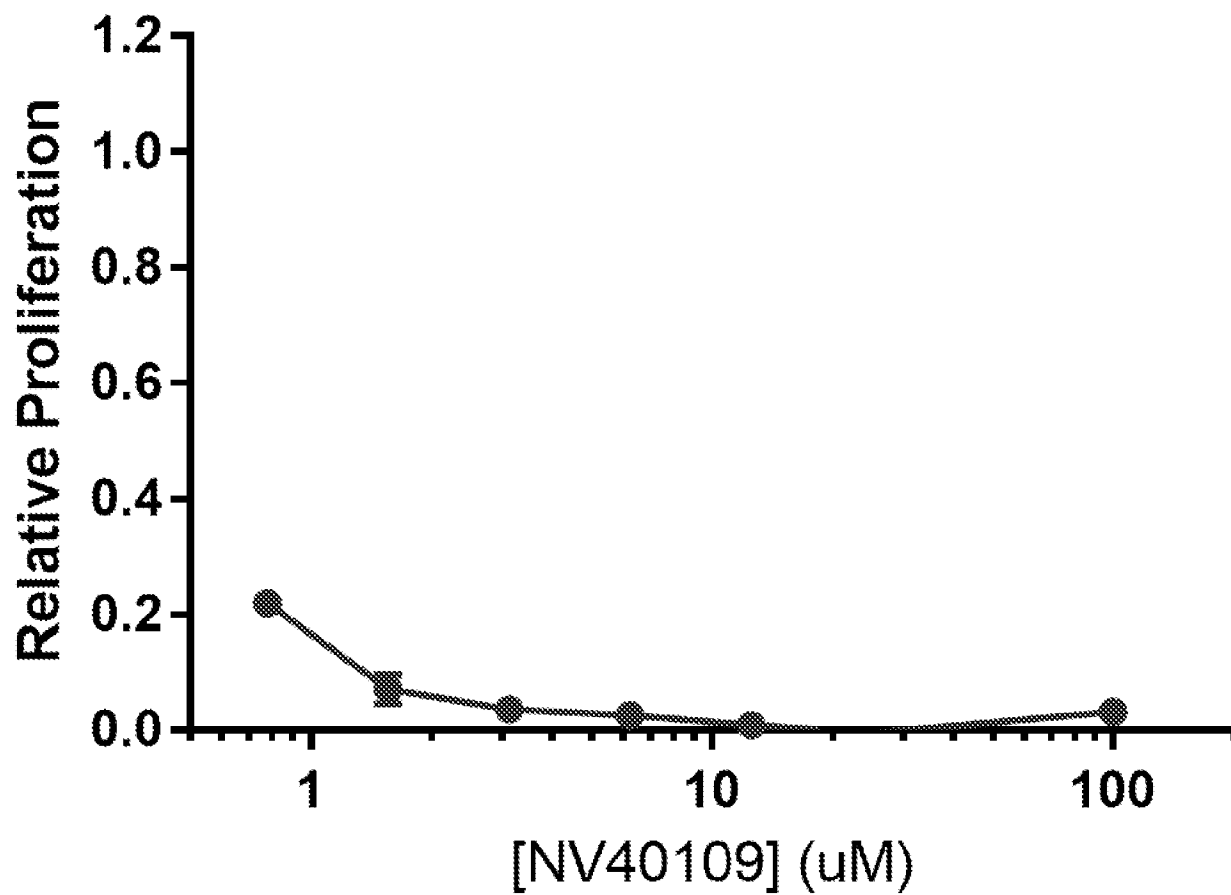
Anti-Proliferative Activity Assay – I-1



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FIG. 2

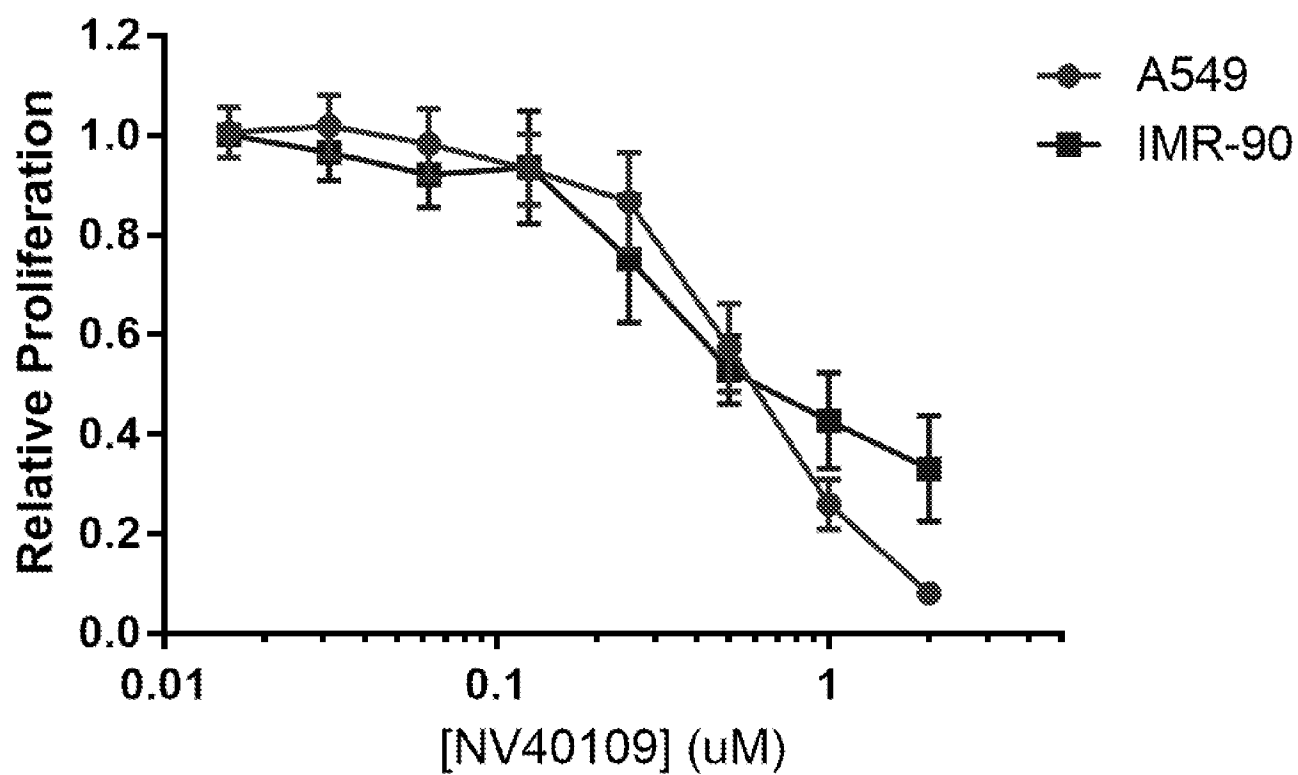
Anti-Proliferative Activity Assay – I-3



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FIG. 3

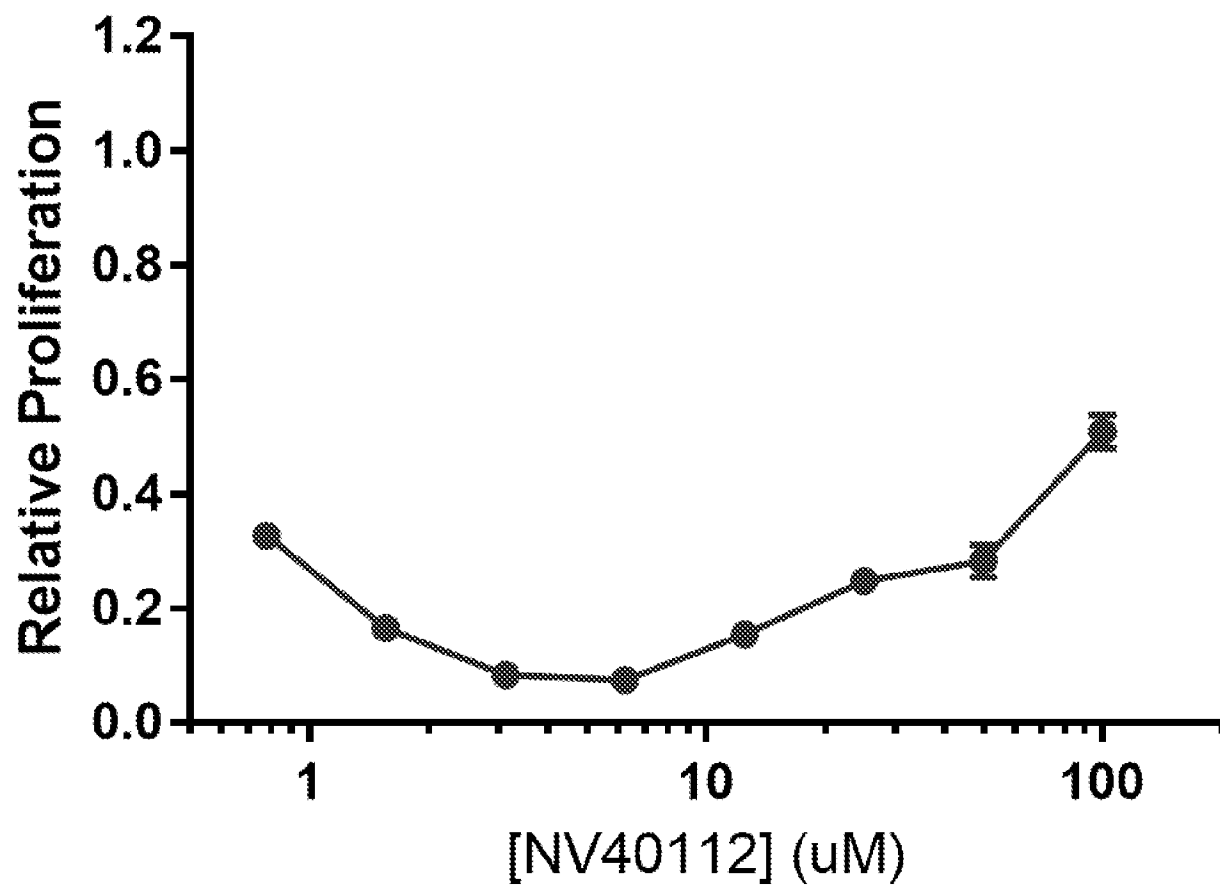
Anti-Proliferative Activity Assay – I-3



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FIG. 4

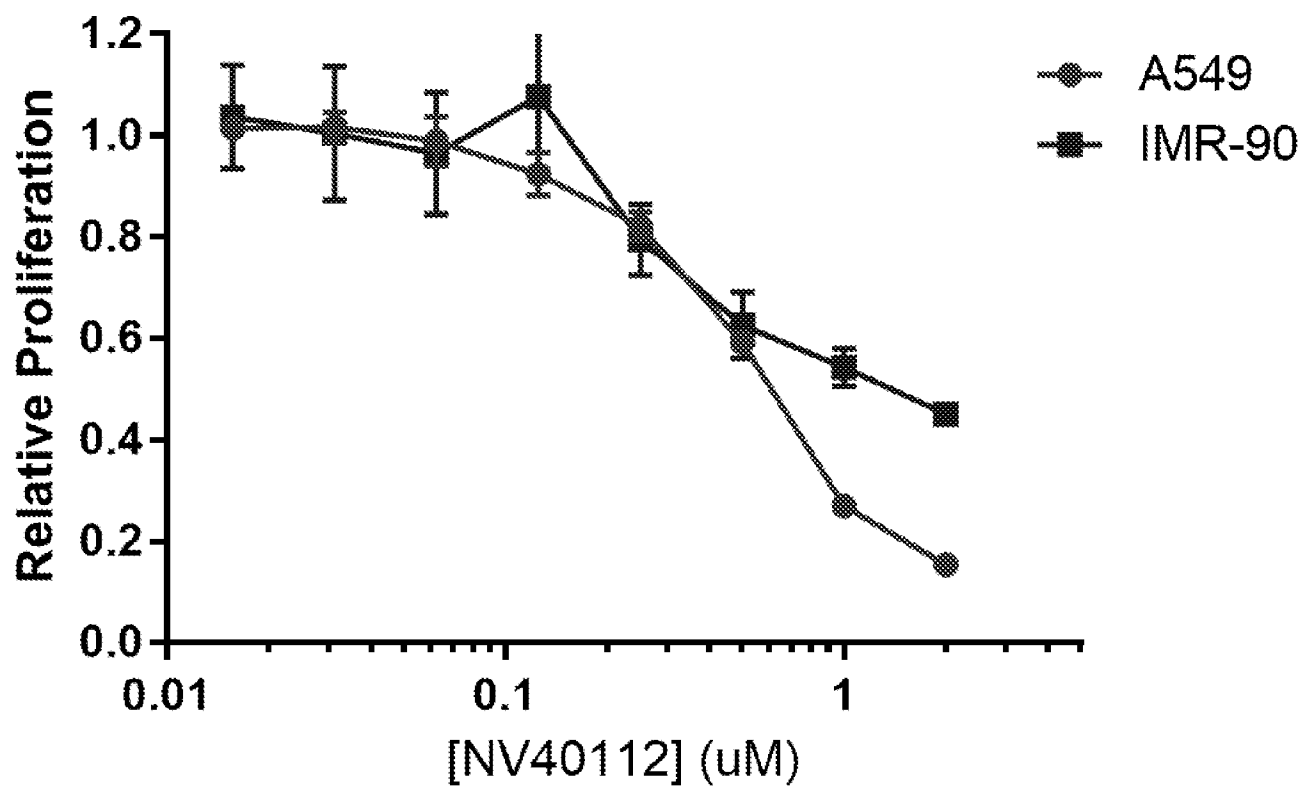
Anti-Proliferative Activity Assay – I-4



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FIG. 5

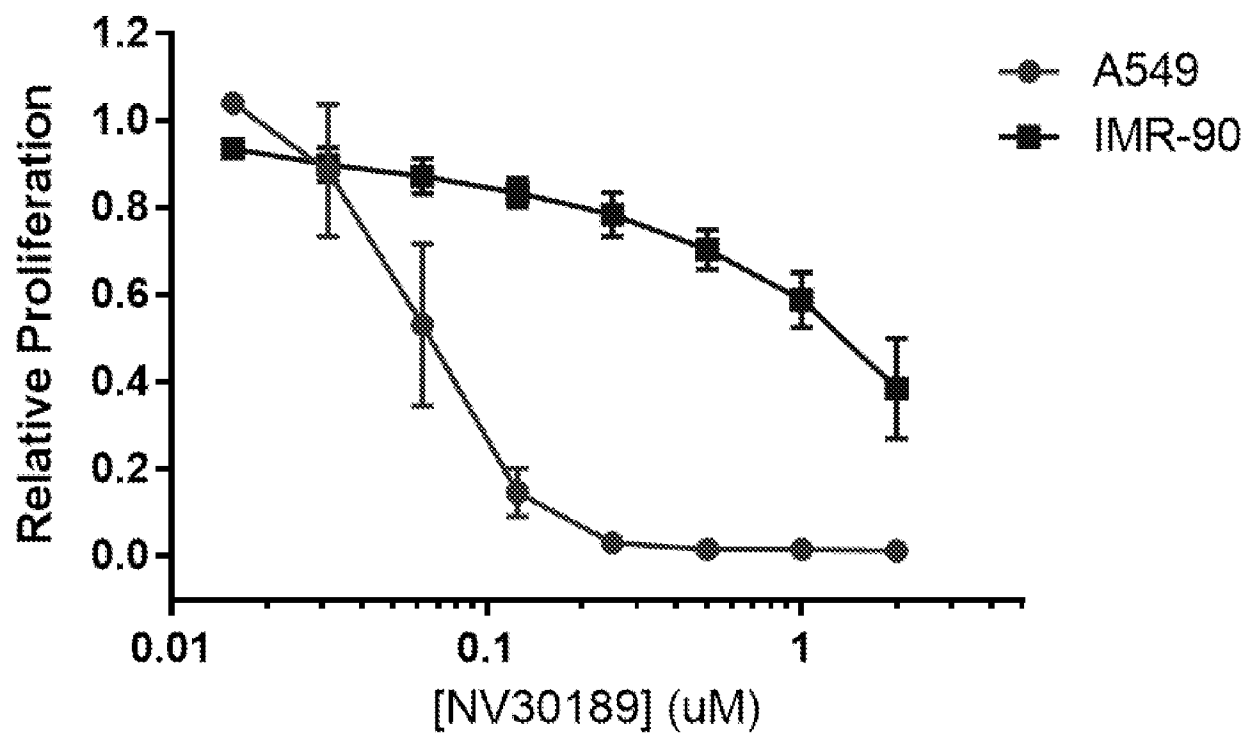
Anti-Proliferative Activity Assay – I-4



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FIG. 6

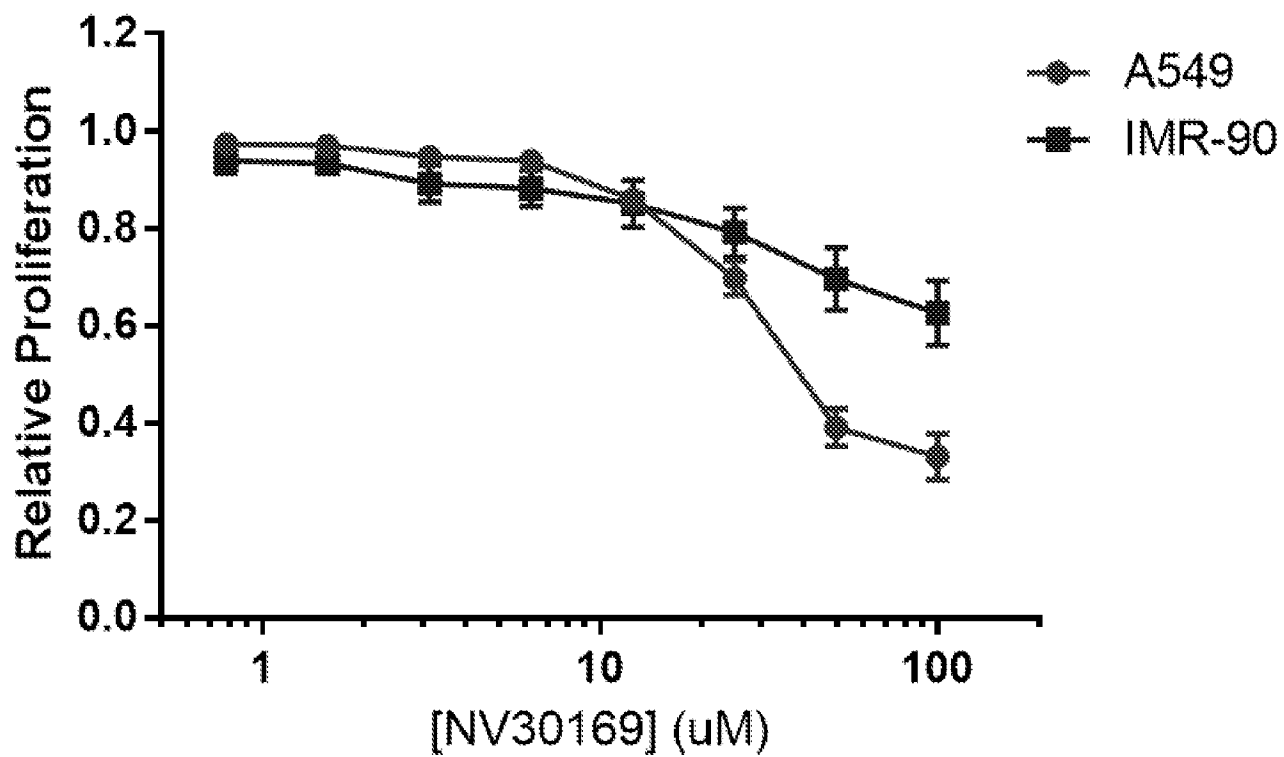
Anti-Proliferative Activity Assay – I-5



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FIG. 7

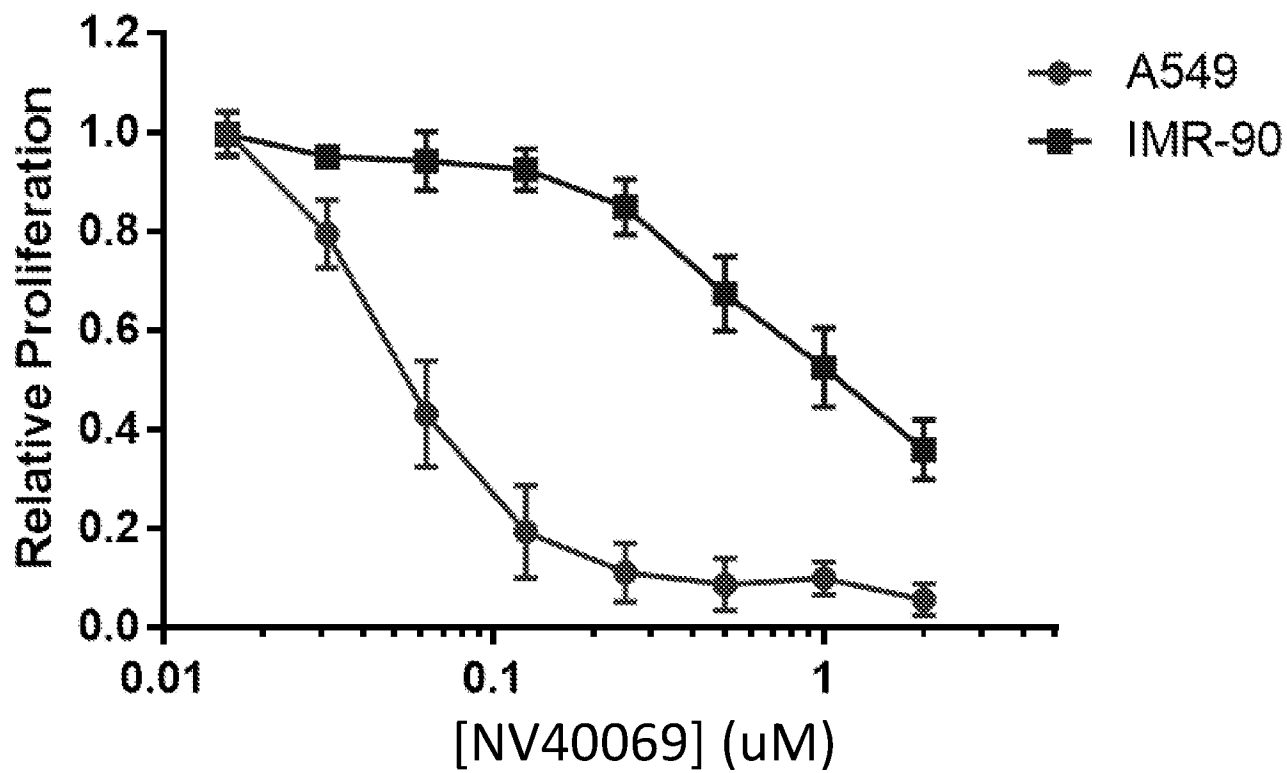
Anti-Proliferative Activity Assay – I-6



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FIG. 8

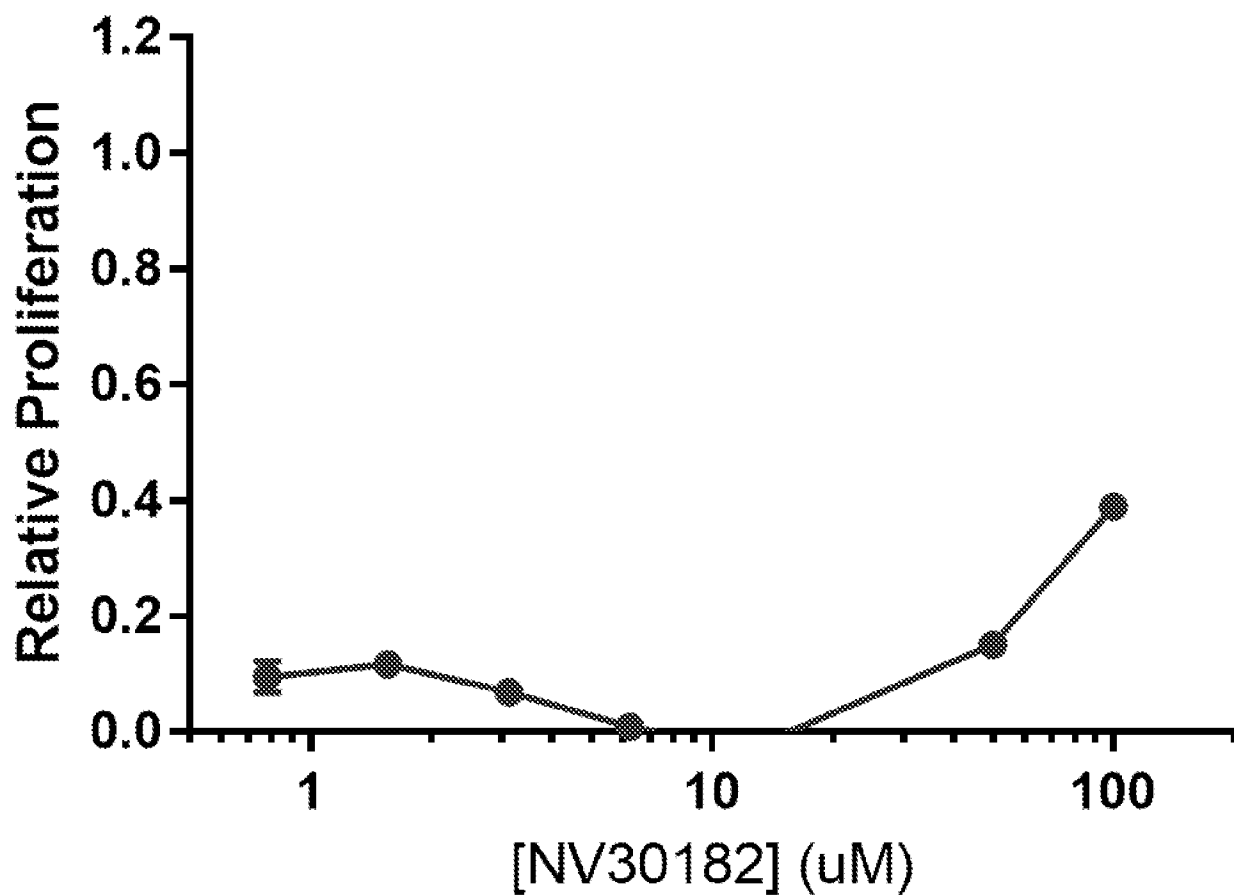
Anti-Proliferative Activity Assay – I-7



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FIG. 9

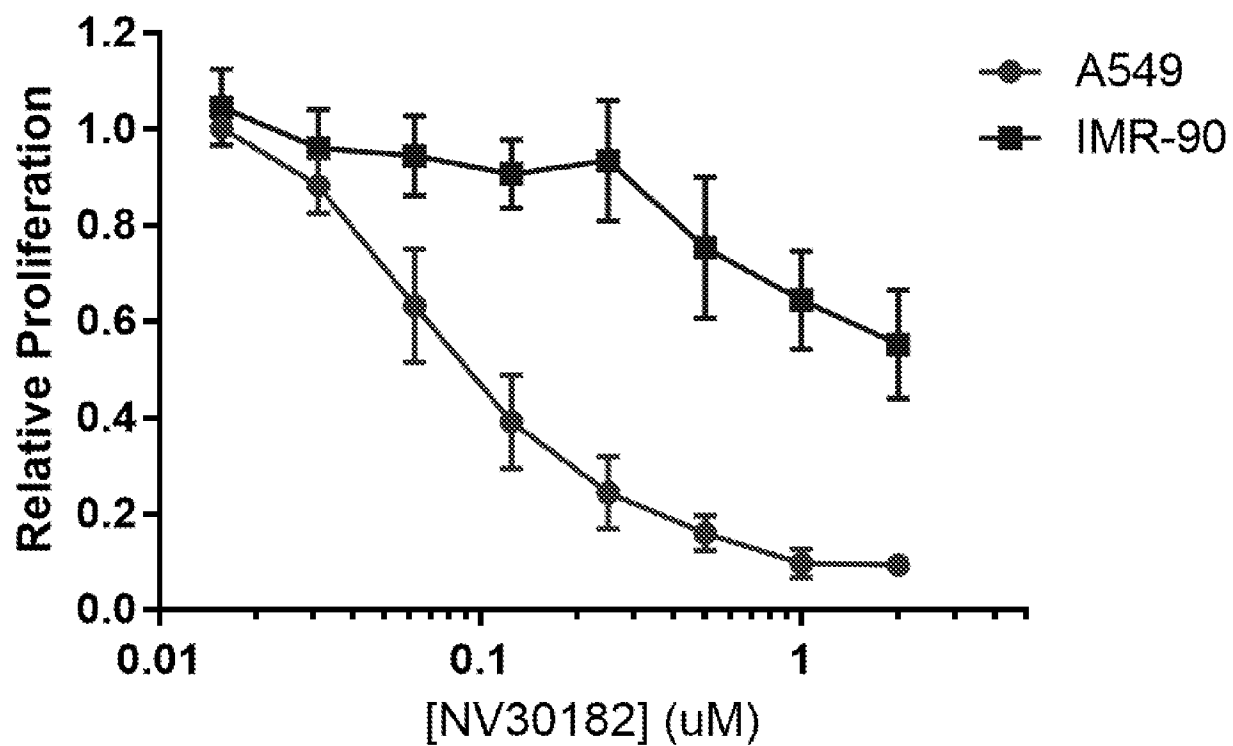
Anti-Proliferative Activity Assay – I-8



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FIG. 10

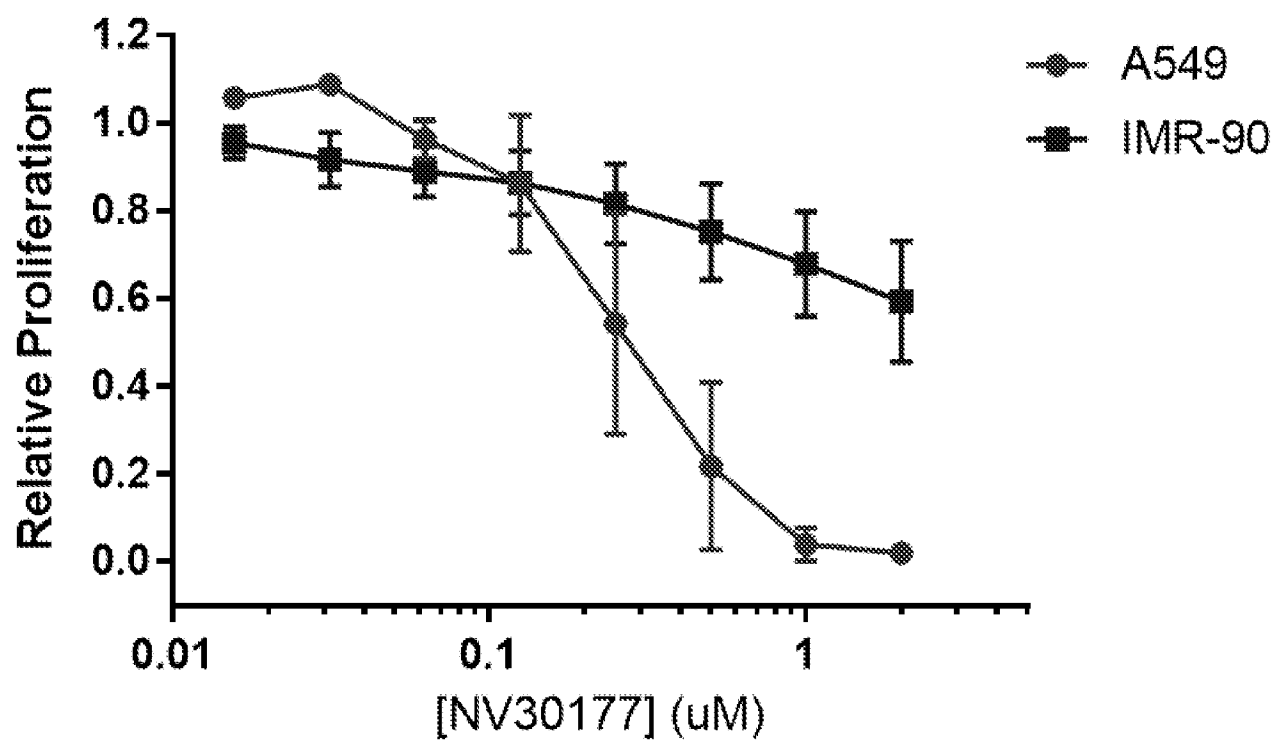
Anti-Proliferative Activity Assay – I-8



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FIG. 11

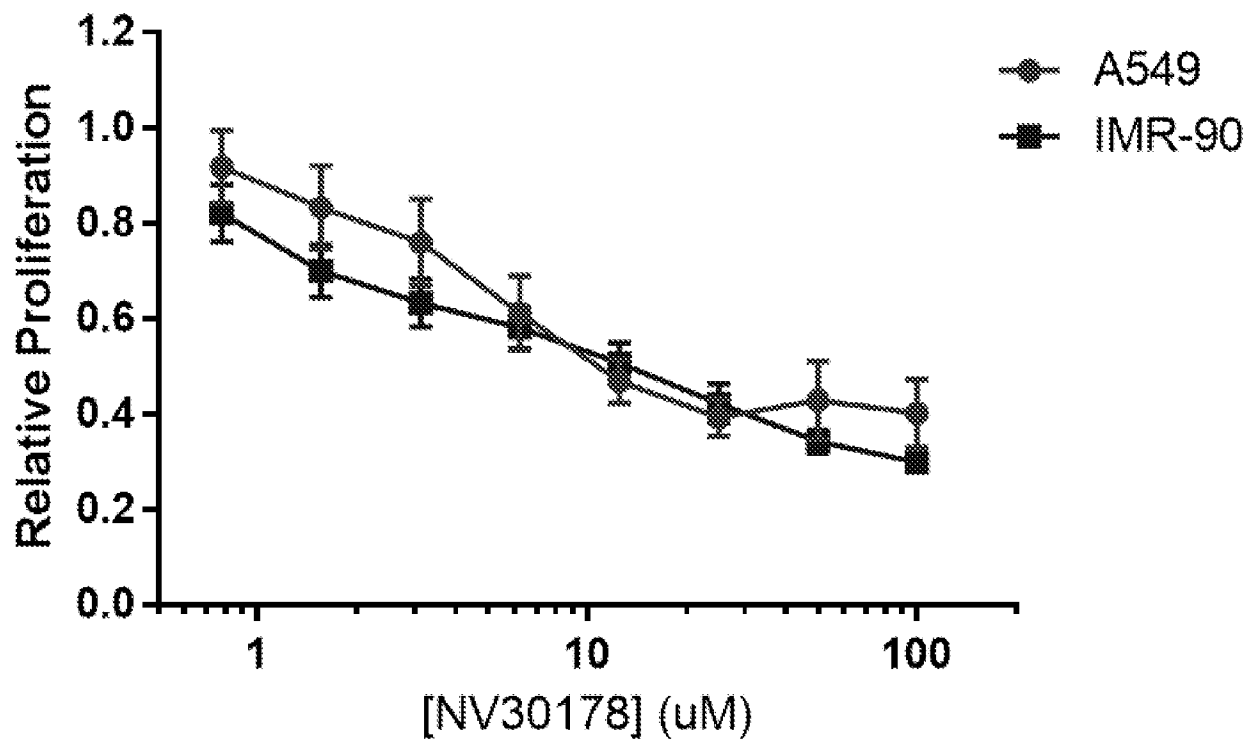
Anti-Proliferative Activity Assay – I-9



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FIG. 12

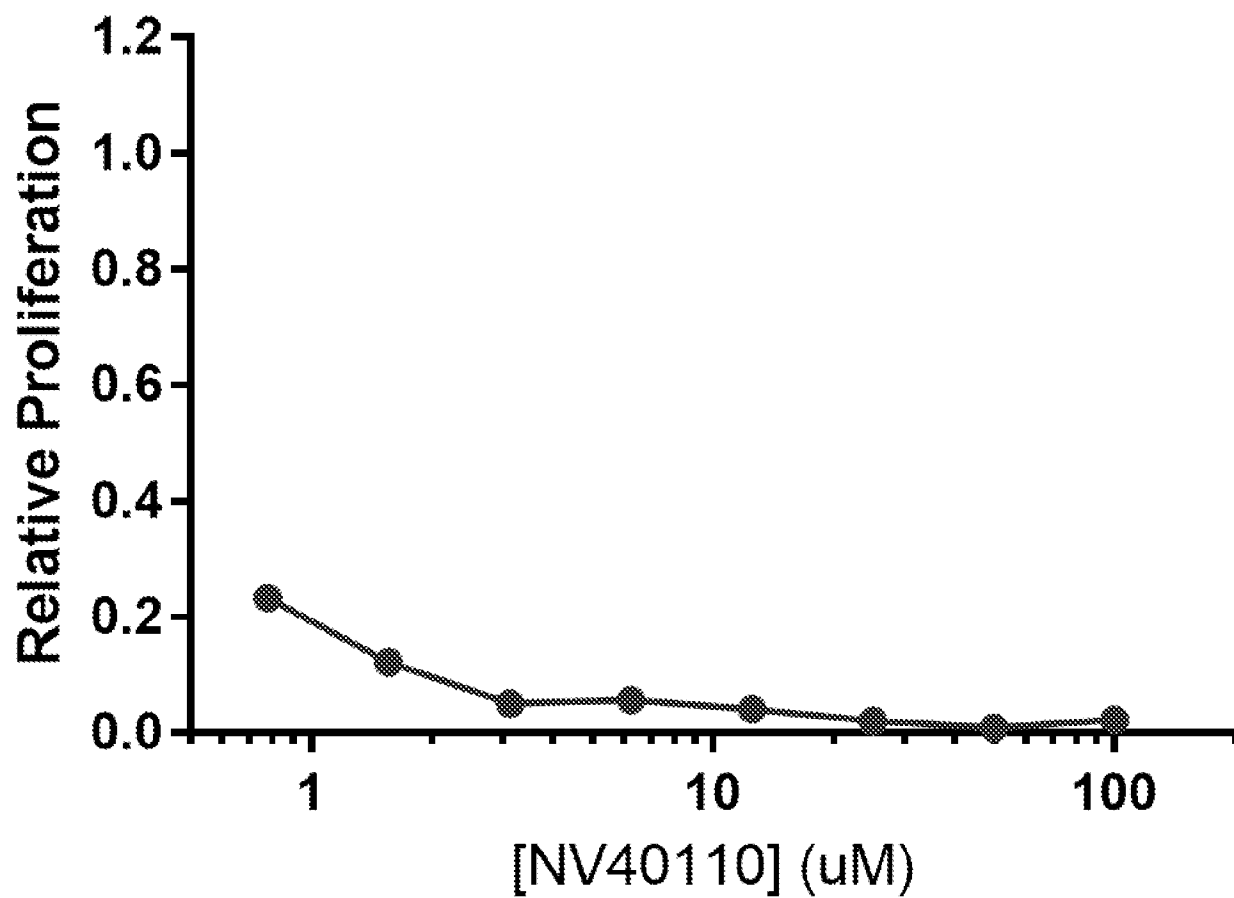
Anti-Proliferative Activity Assay – I-10



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FIG. 13

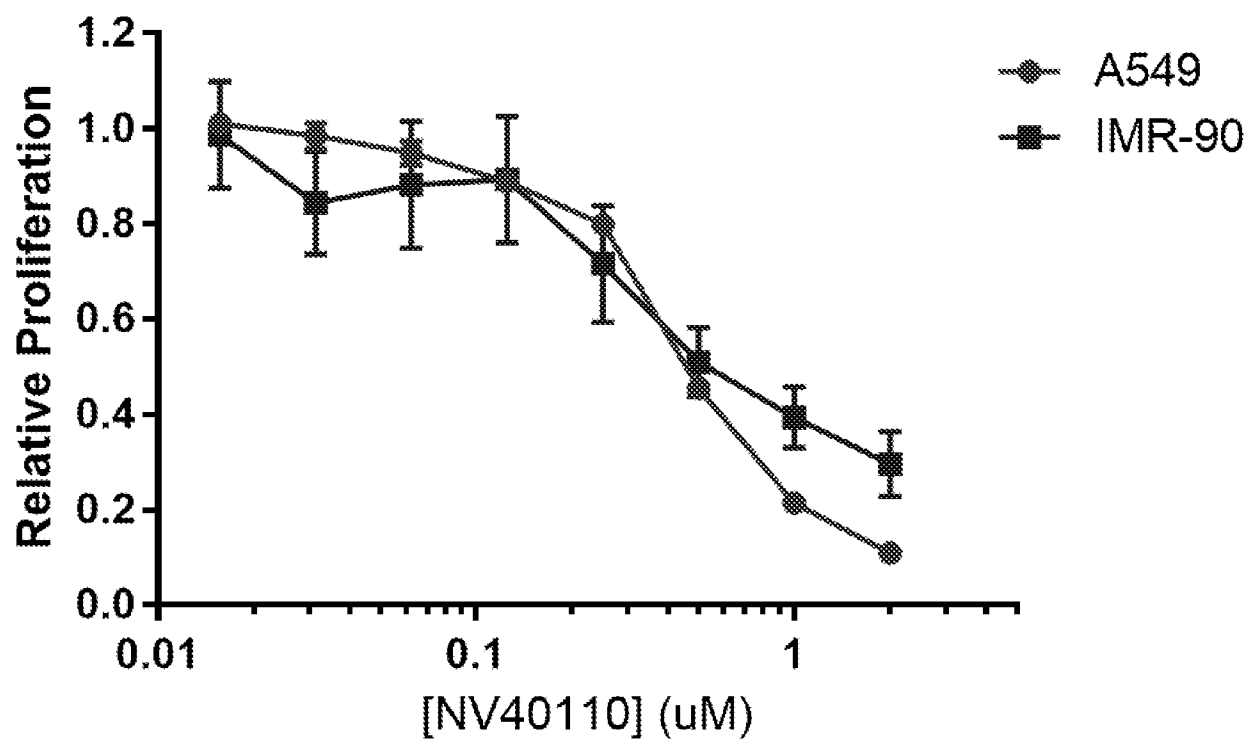
Anti-Proliferative Activity Assay – I-11



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FIG. 14

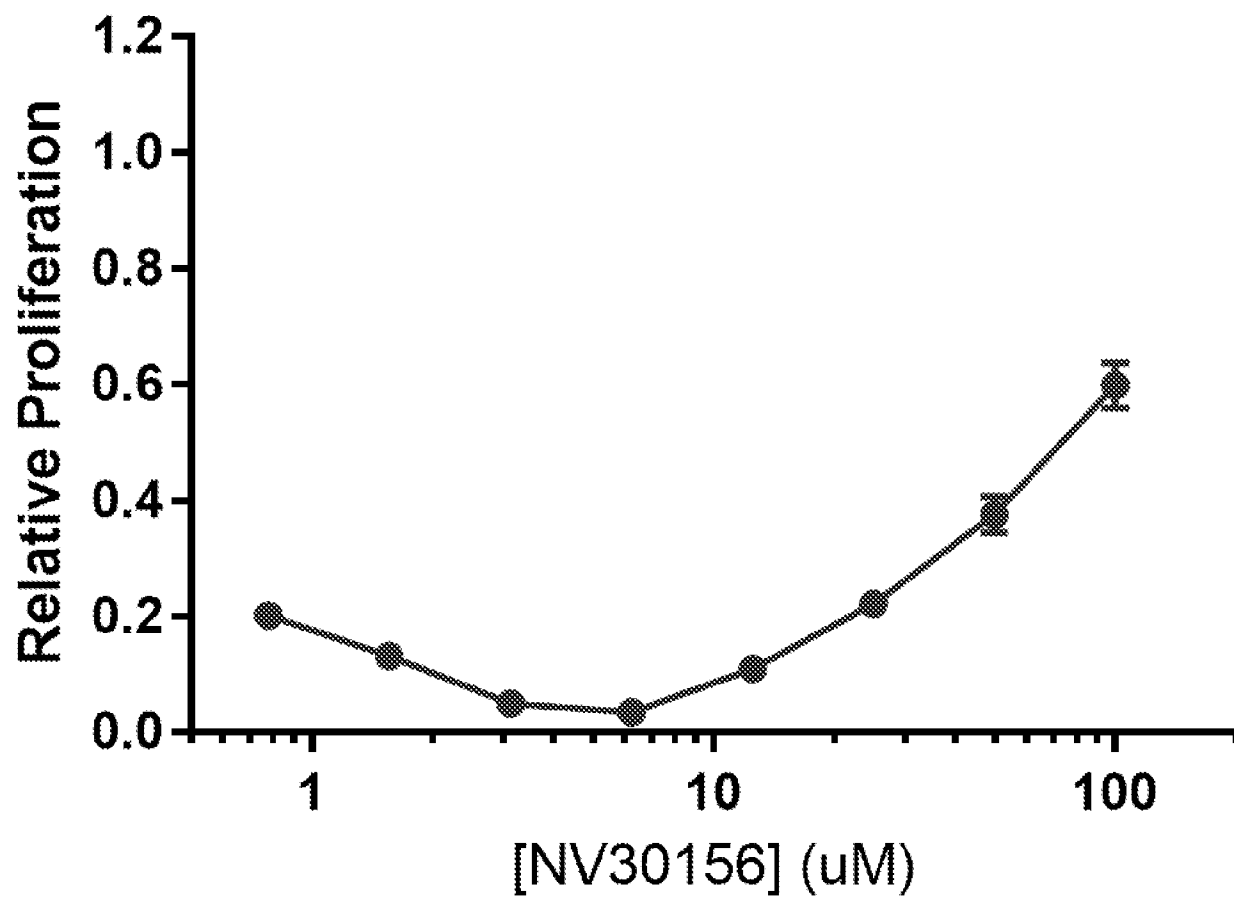
Anti-Proliferative Activity Assay – I-11



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FIG. 15

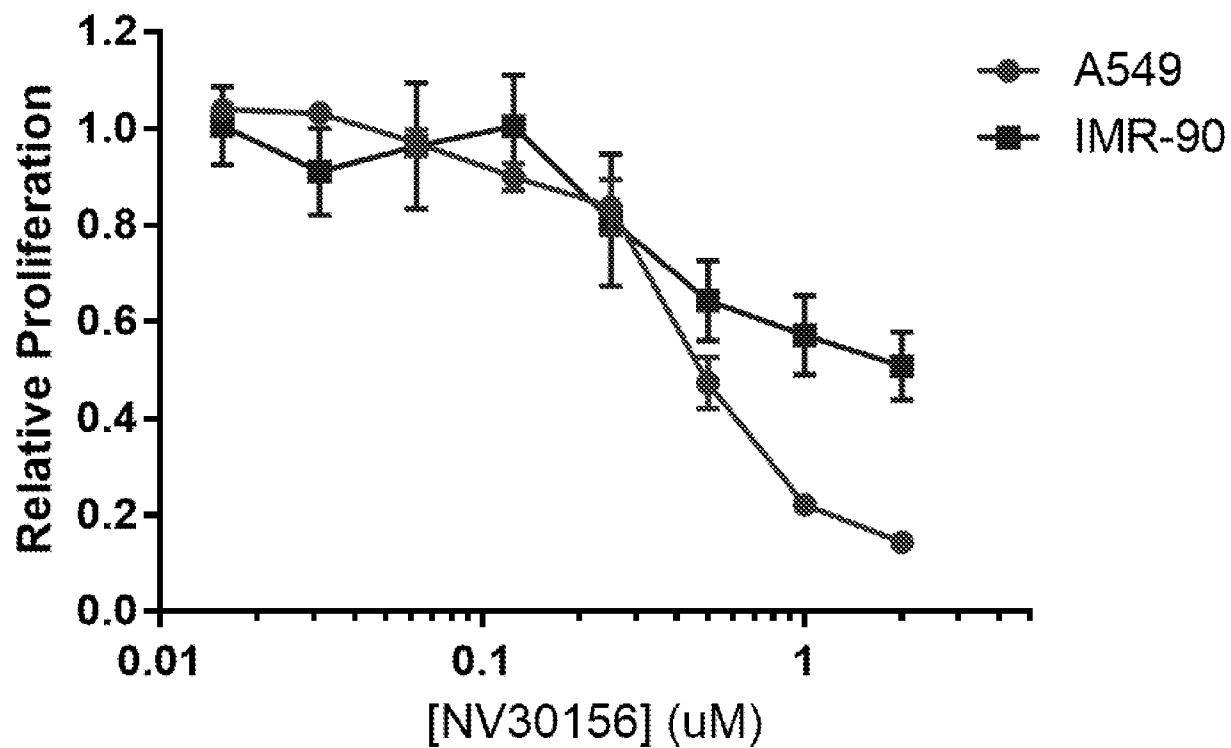
Anti-Proliferative Activity Assay – I-12



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FIG. 16

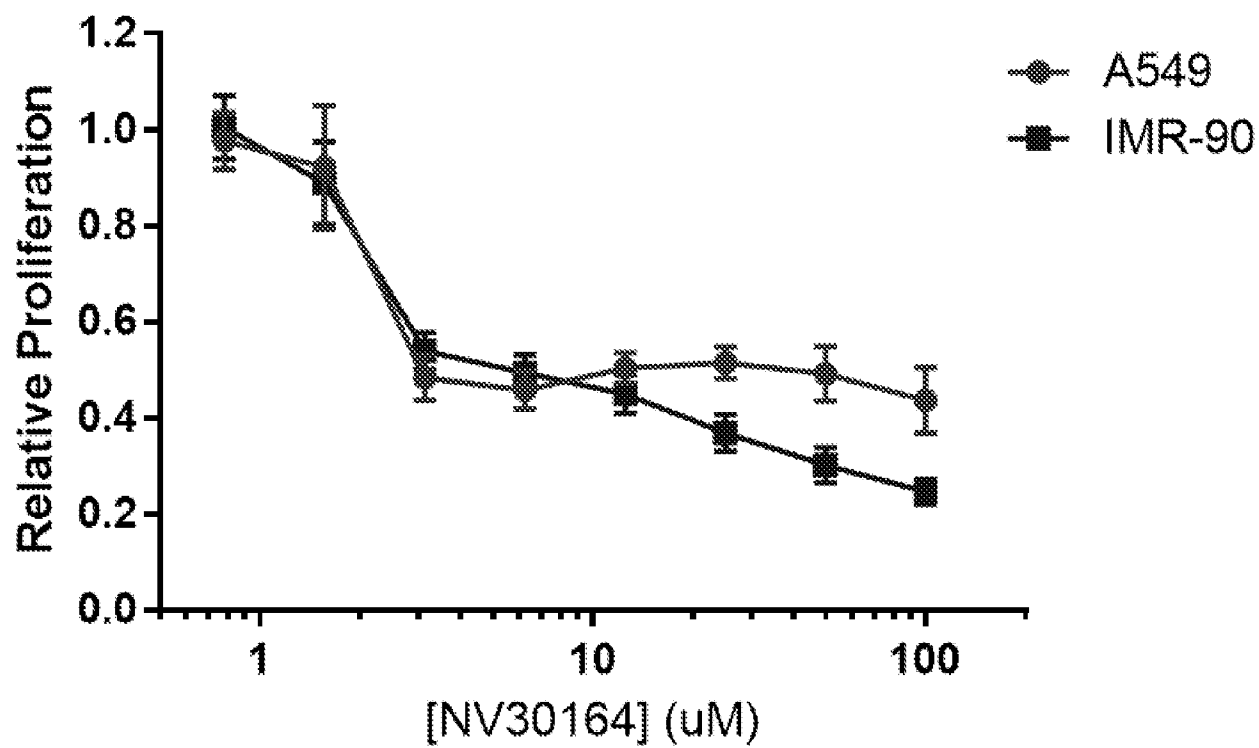
Anti-Proliferative Activity Assay – I-12



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FIG. 17

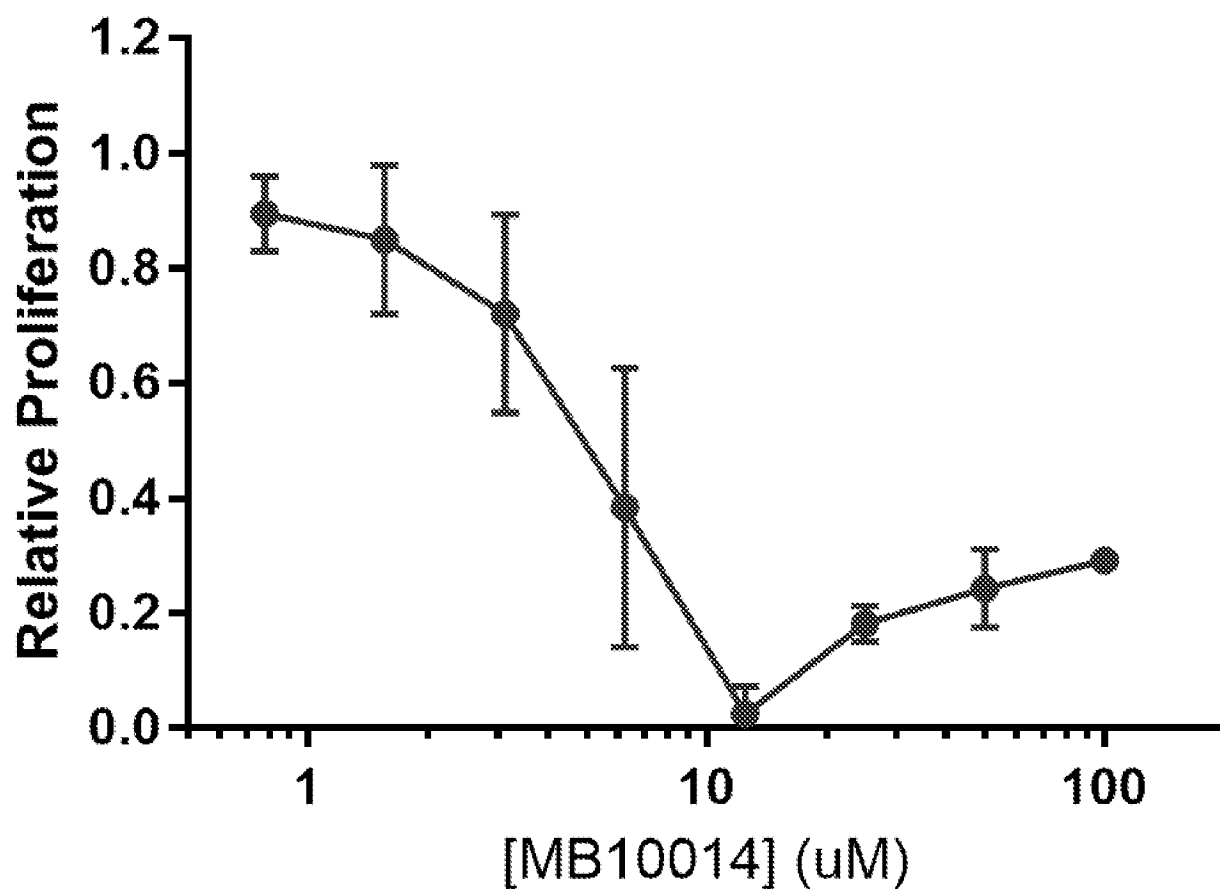
Anti-Proliferative Activity Assay – I-14



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FIG. 18

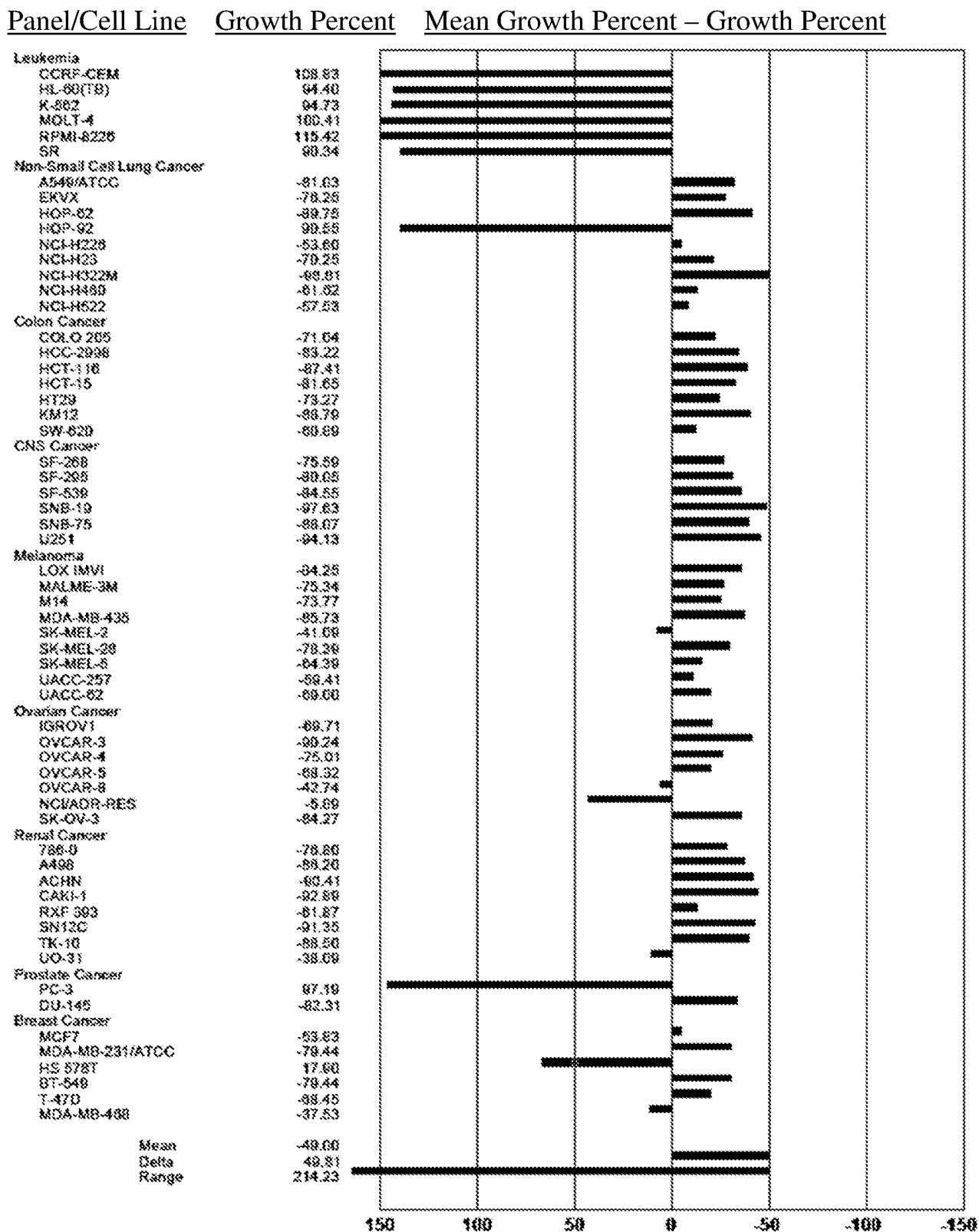
Anti-Proliferative Activity Assay – I-22



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FIG. 19

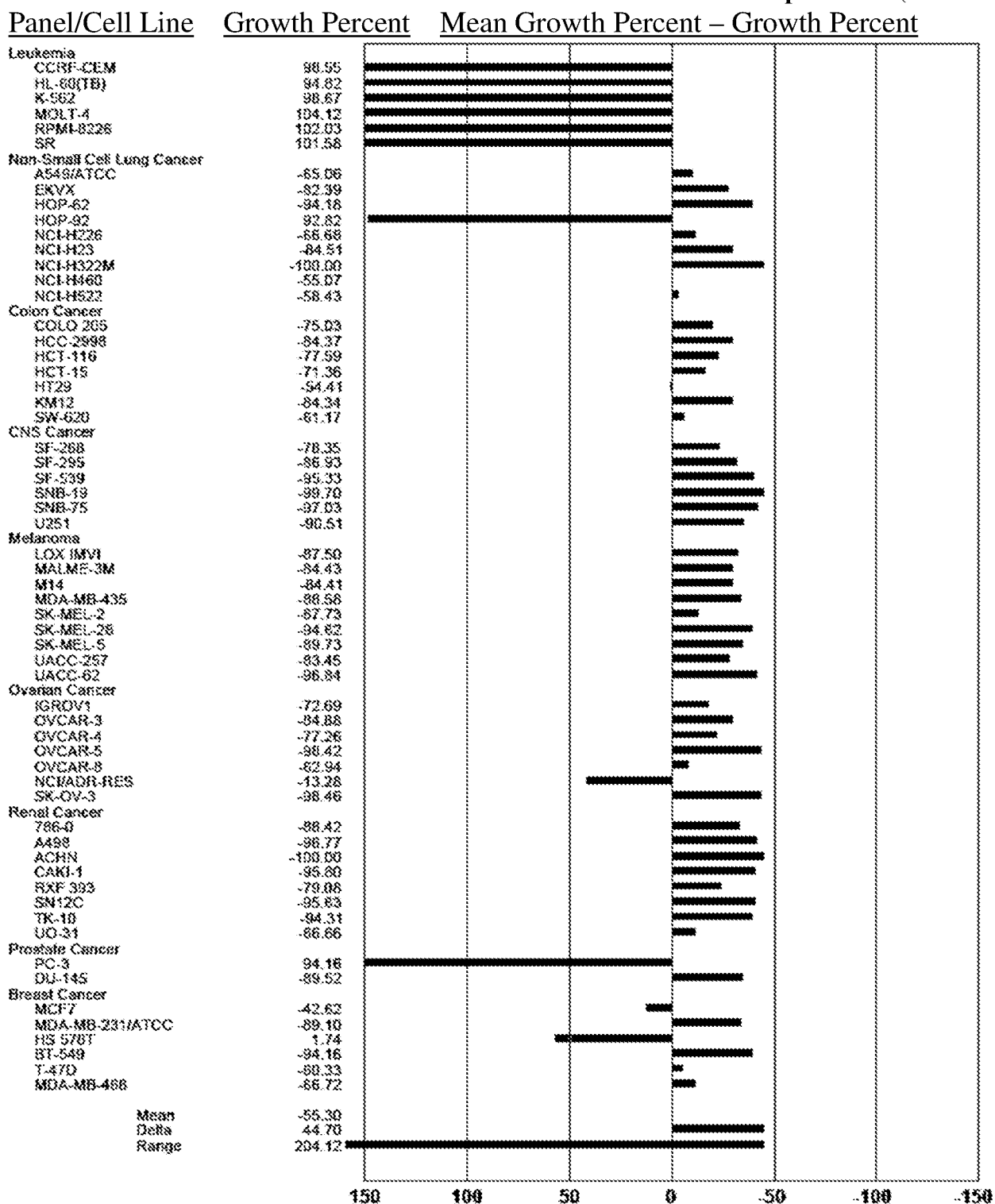
Compound I-1 (NV3104)



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FIG. 20

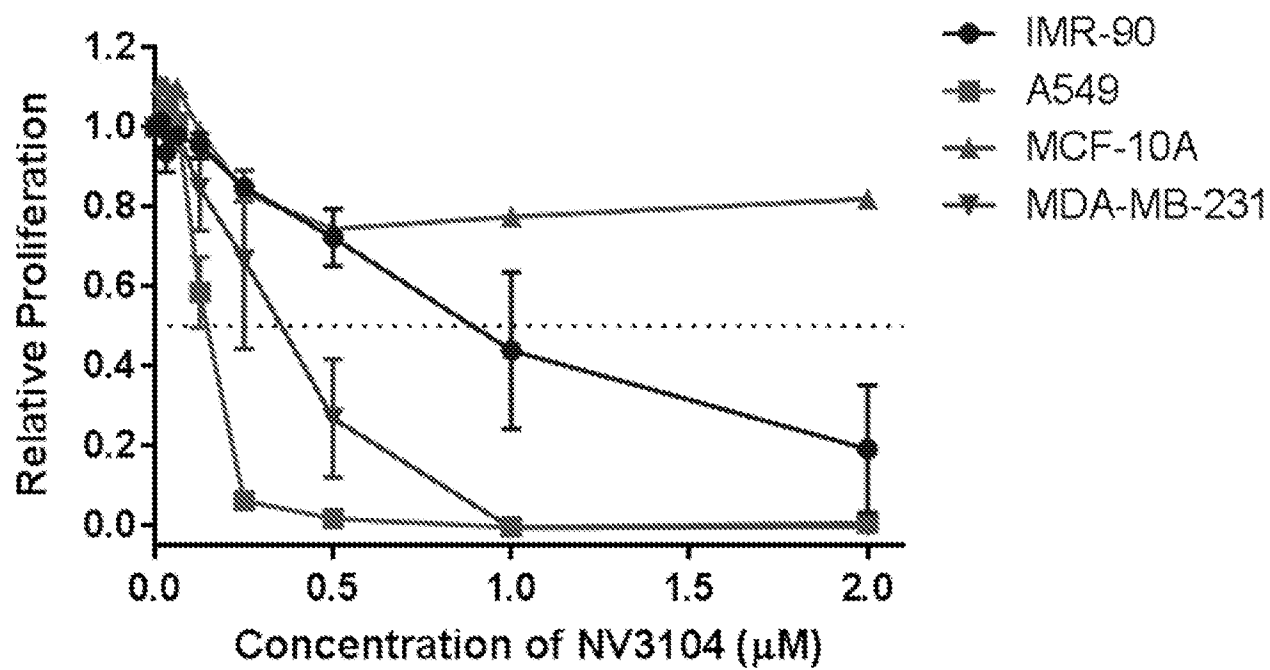
Compound I-5 (NV30189)



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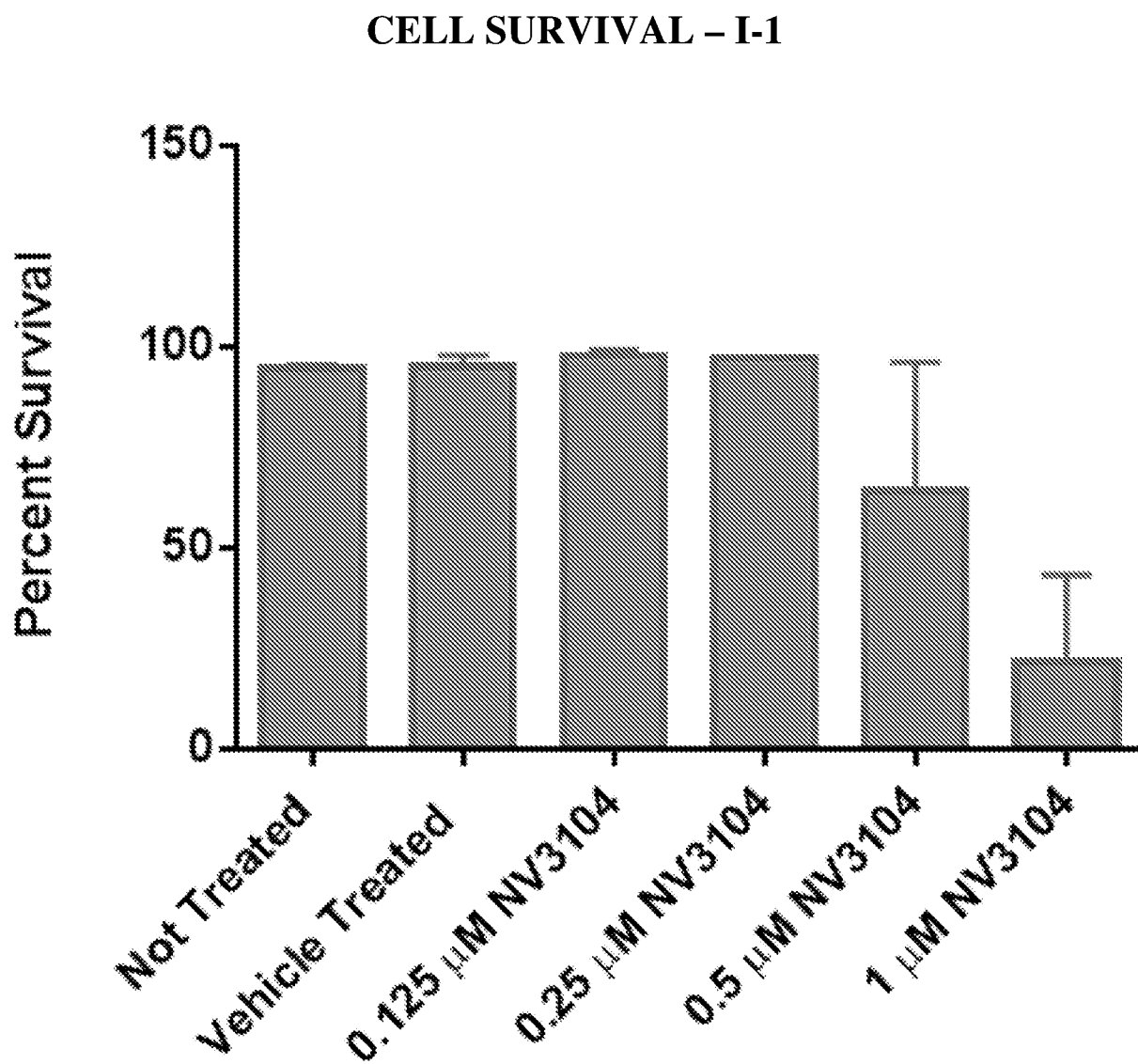
FIG. 21

CELL PROLIFERATION – I-1



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FIG. 22



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FIG. 23

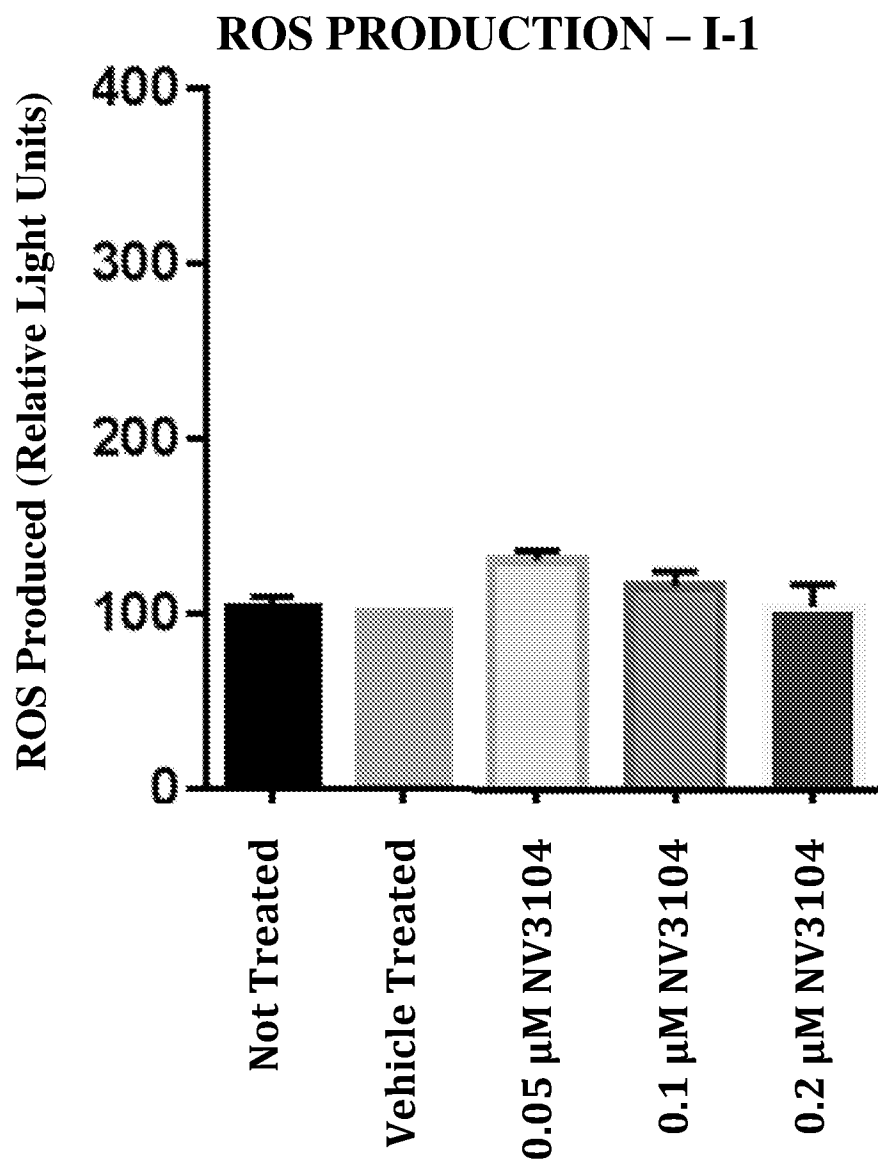
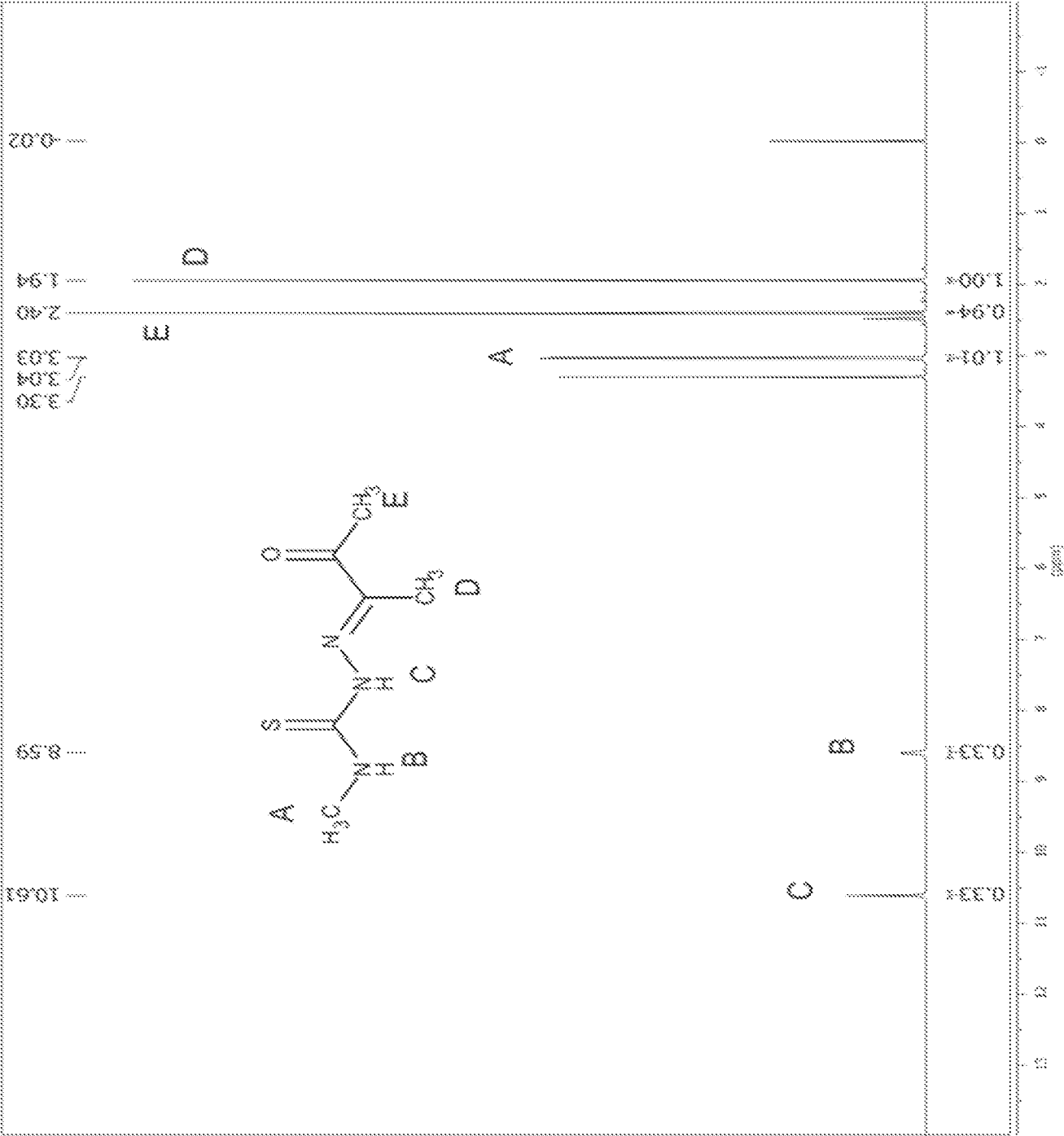
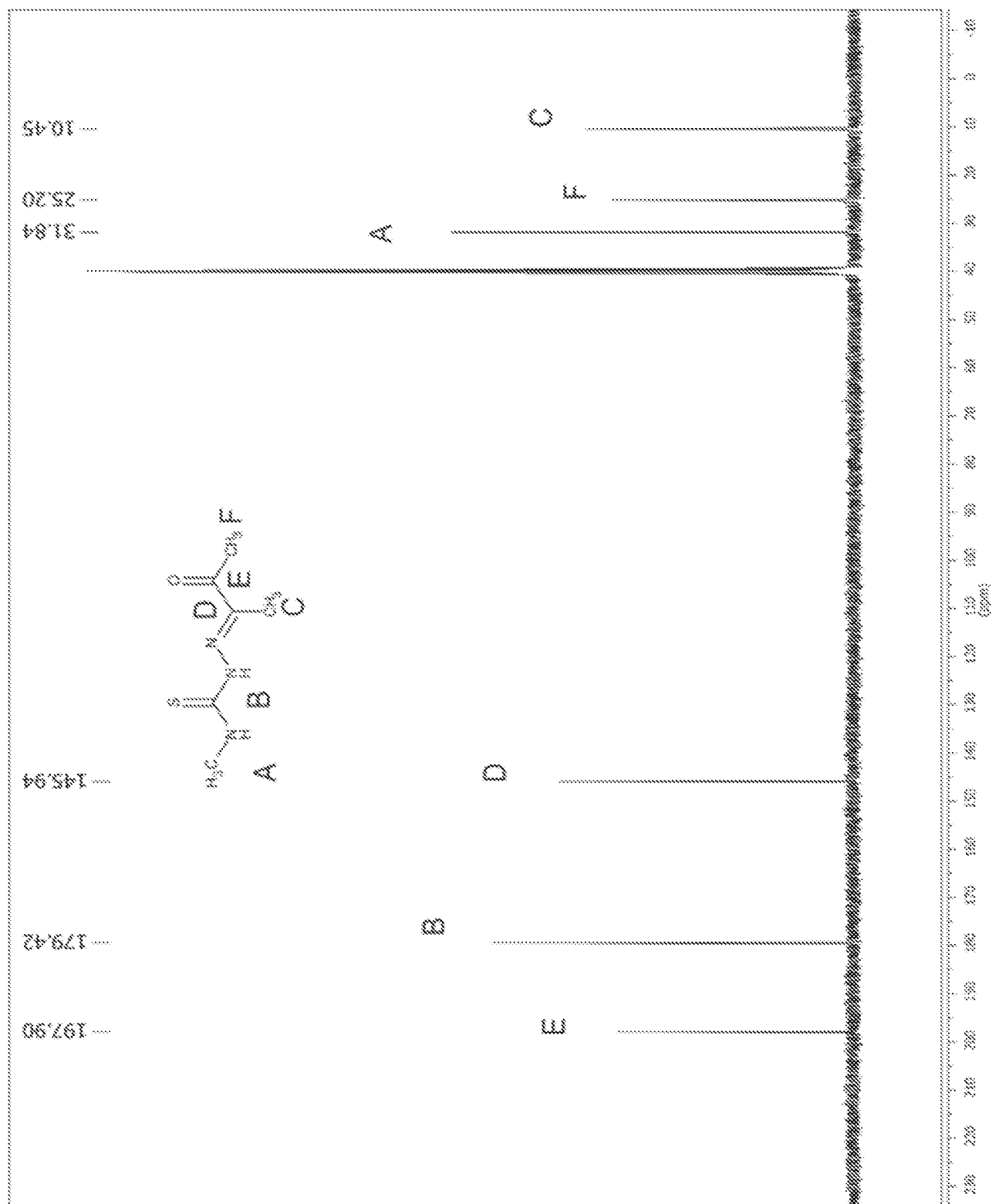


FIG. 24



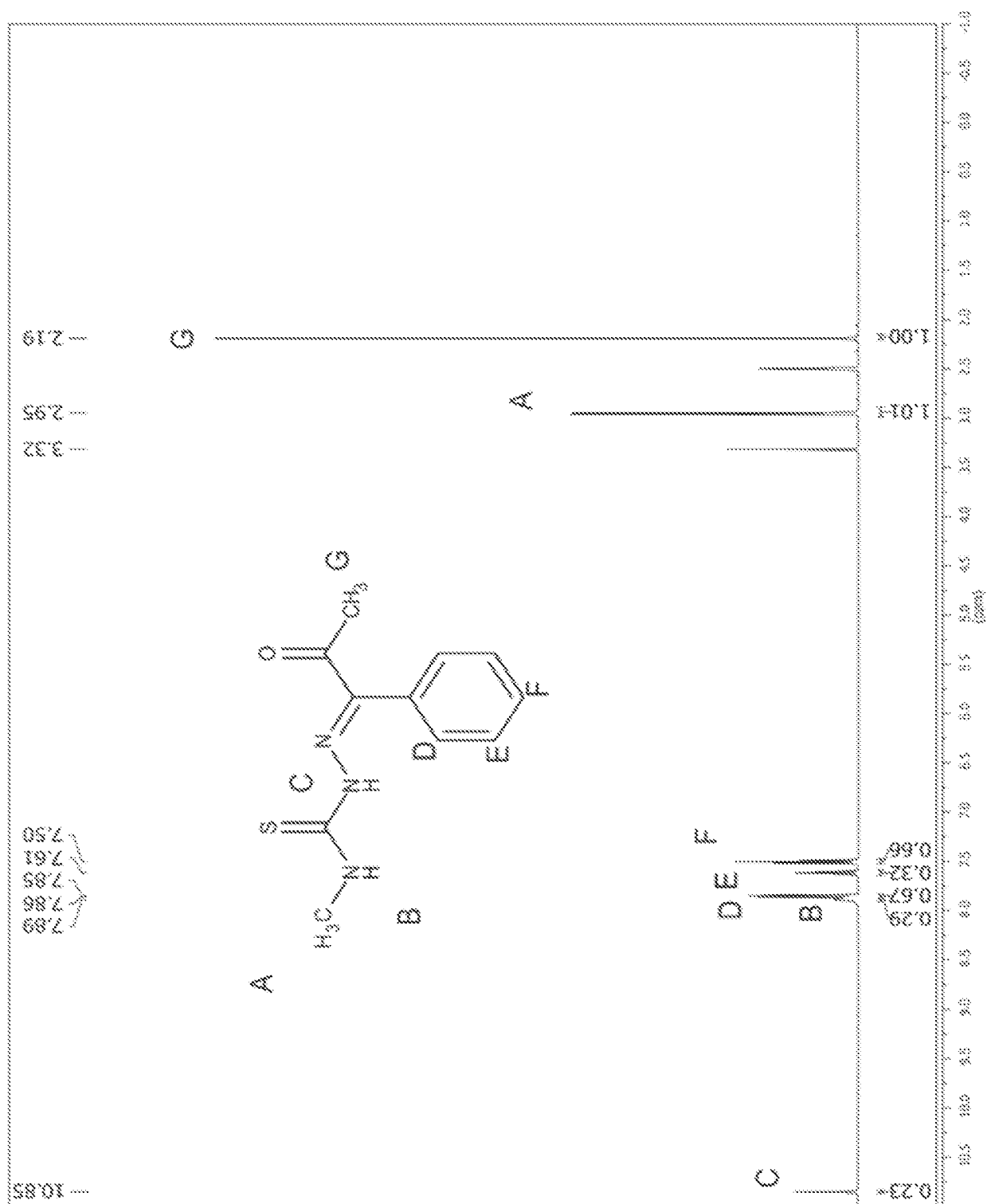
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FIG. 25



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FIG. 26



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FIG. 27

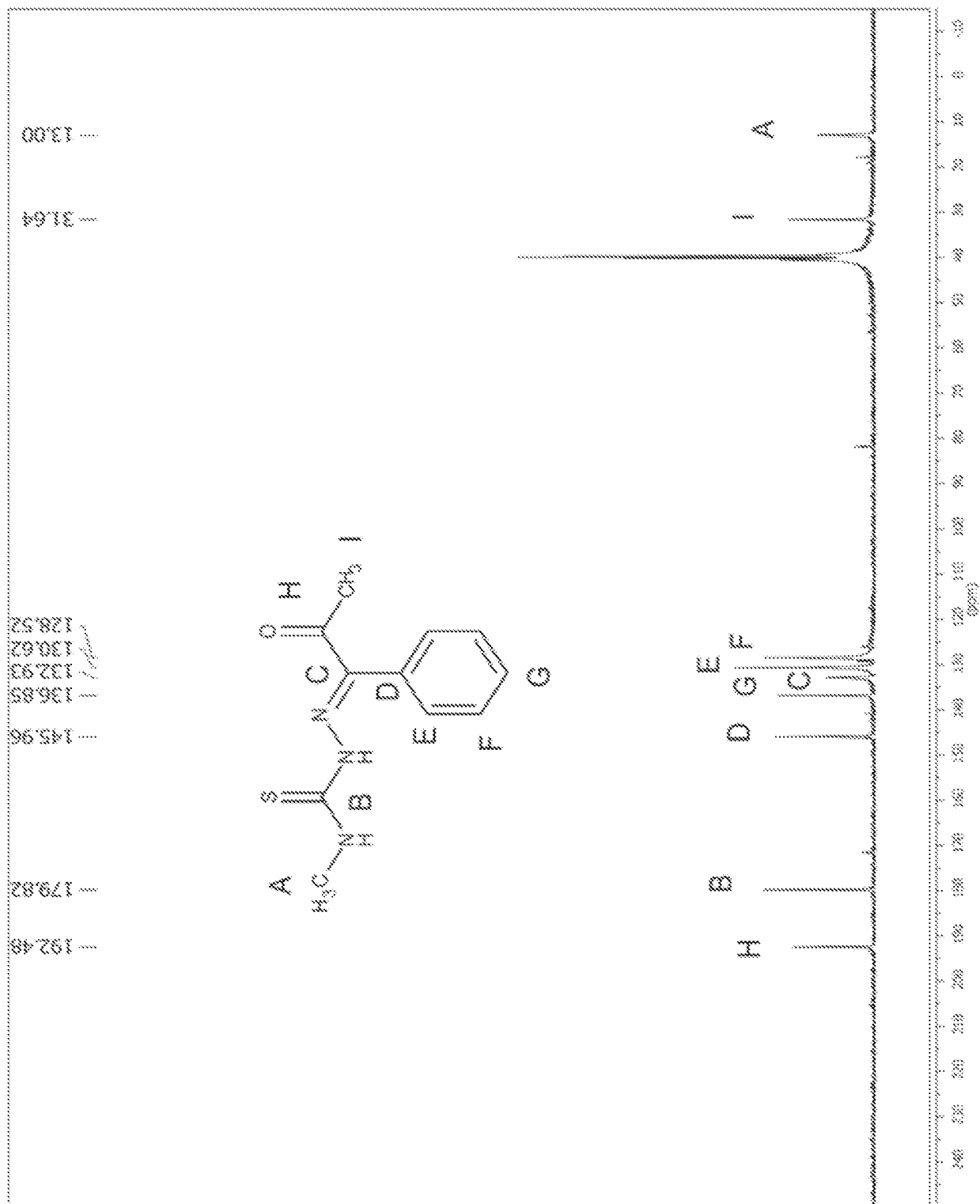
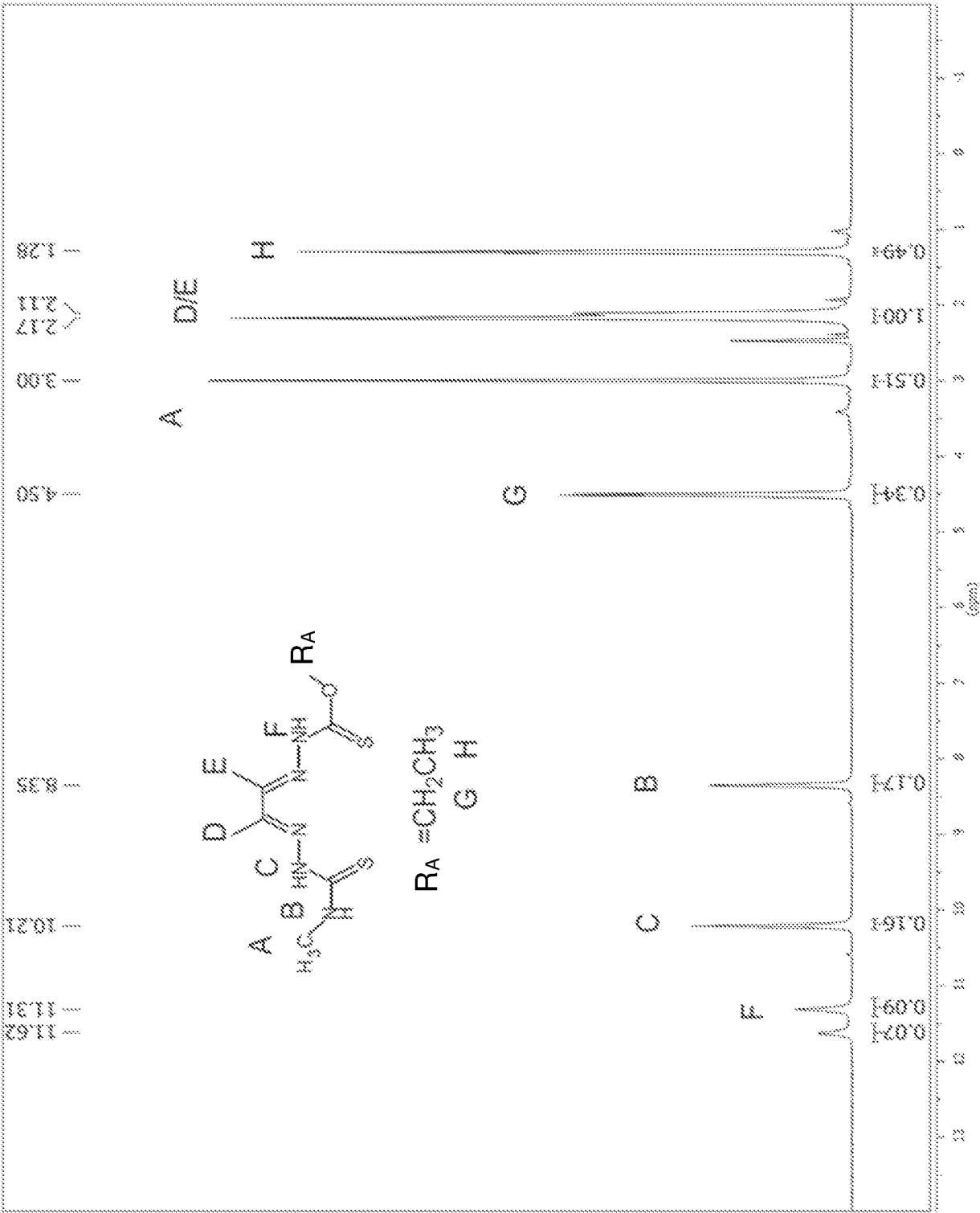


FIG. 28



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FIG. 29

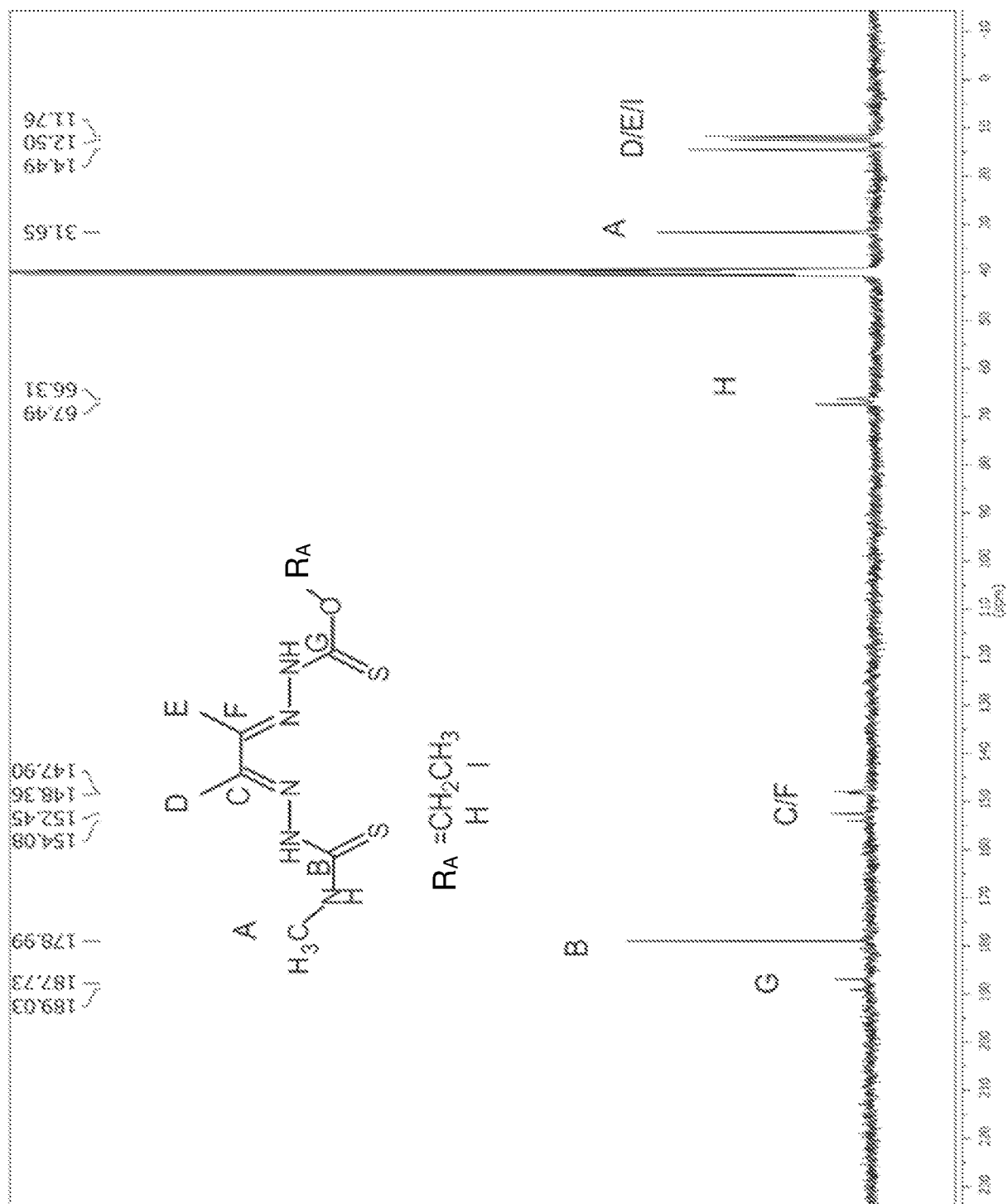
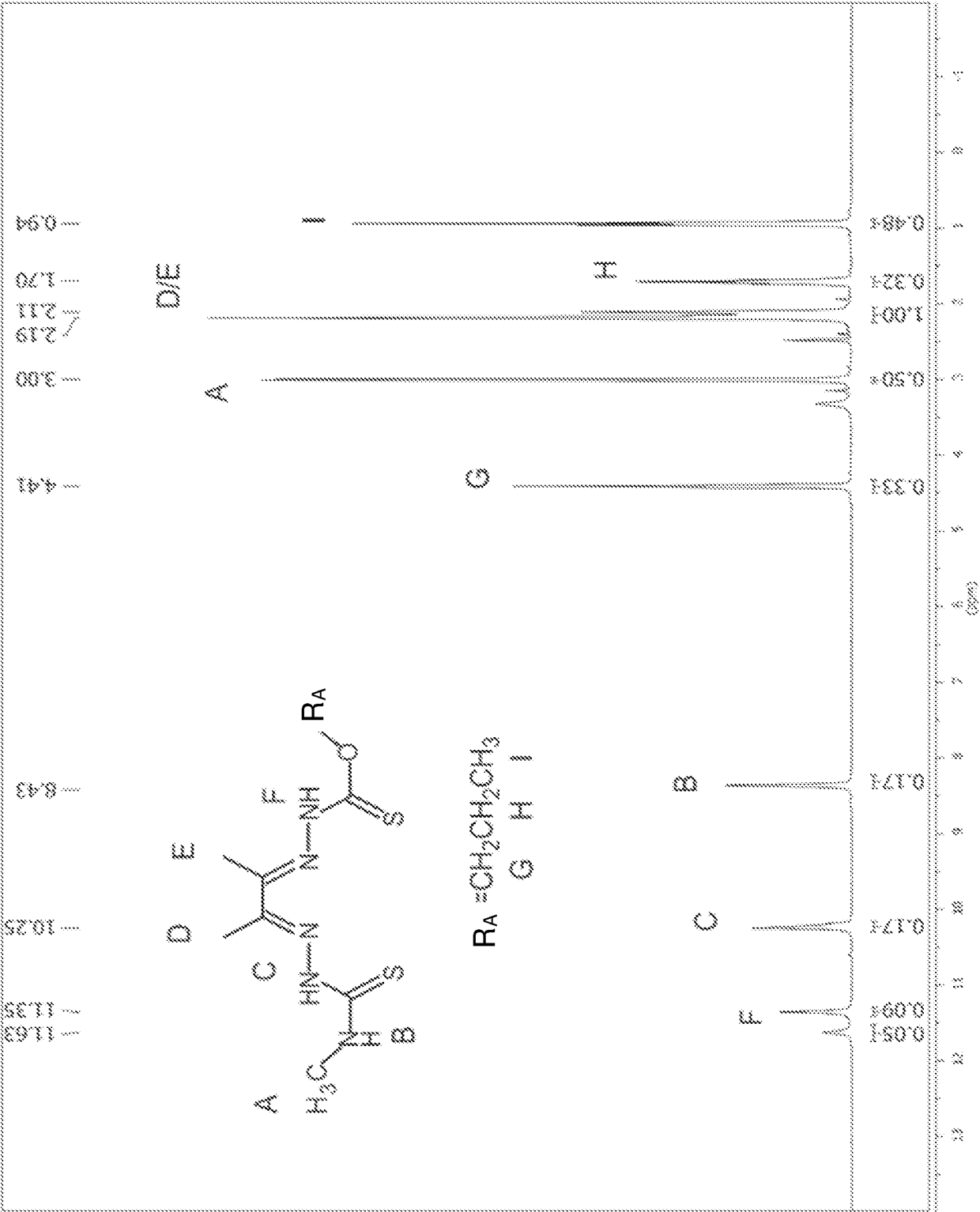
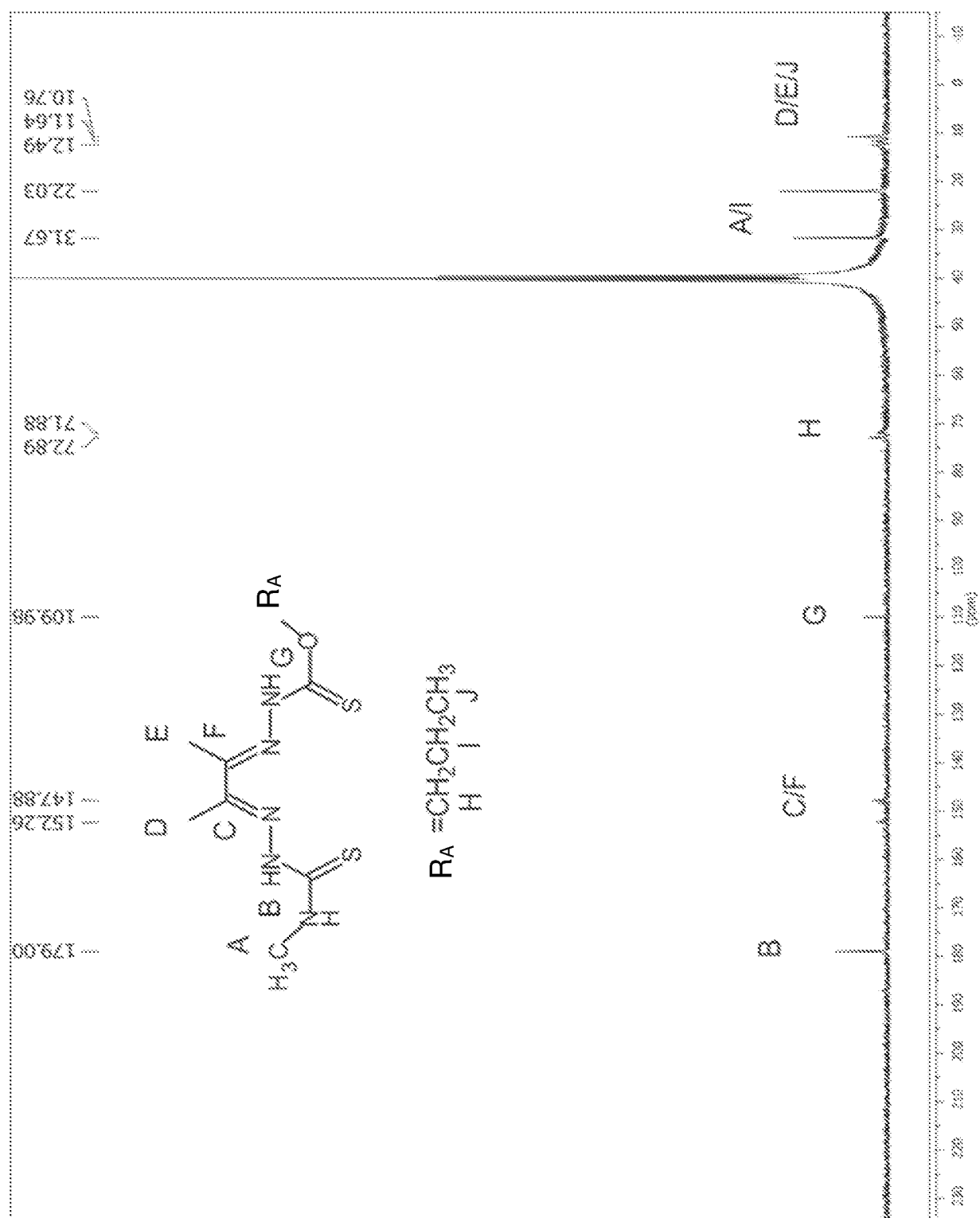


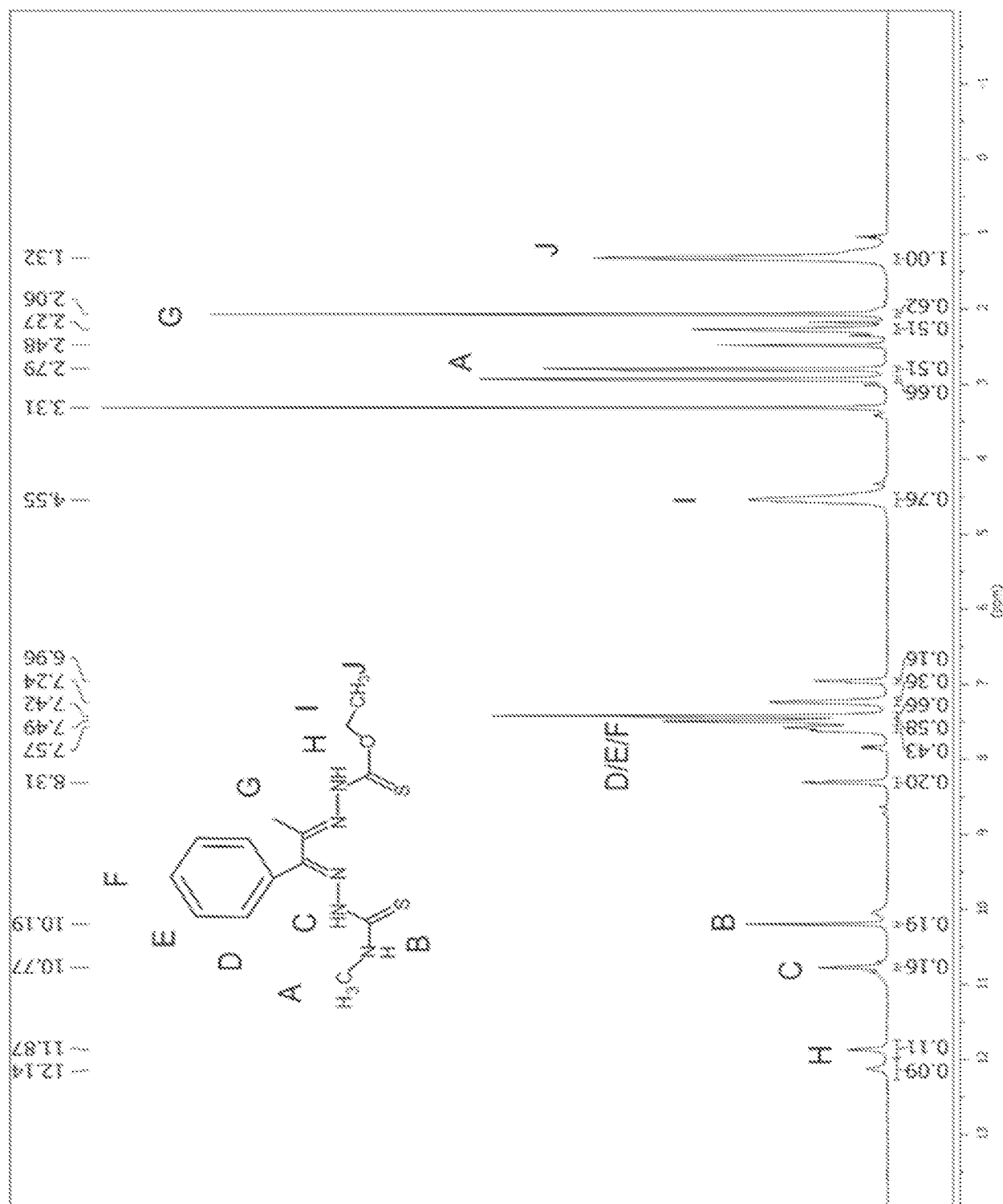
FIG. 30





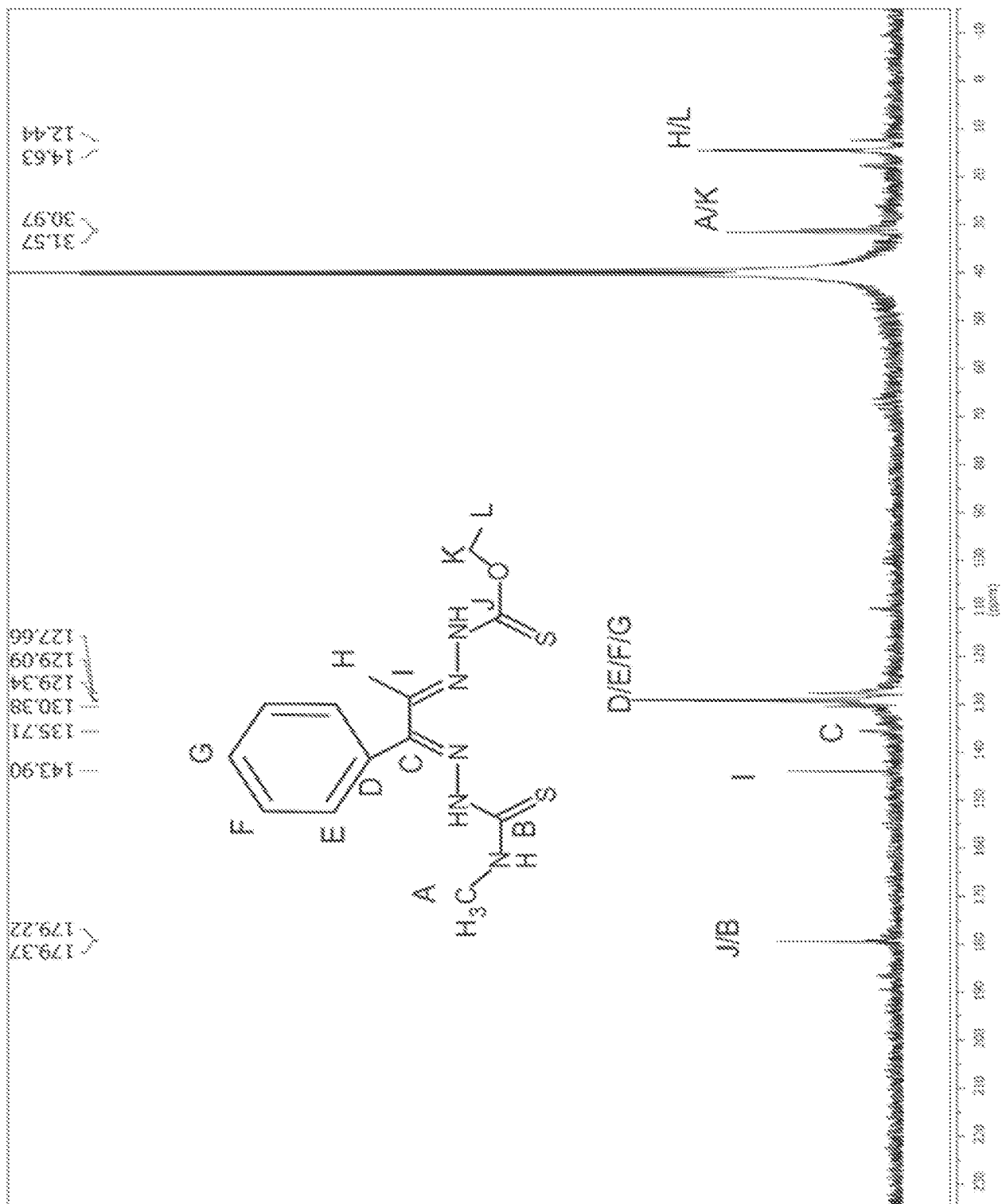
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FIG. 32



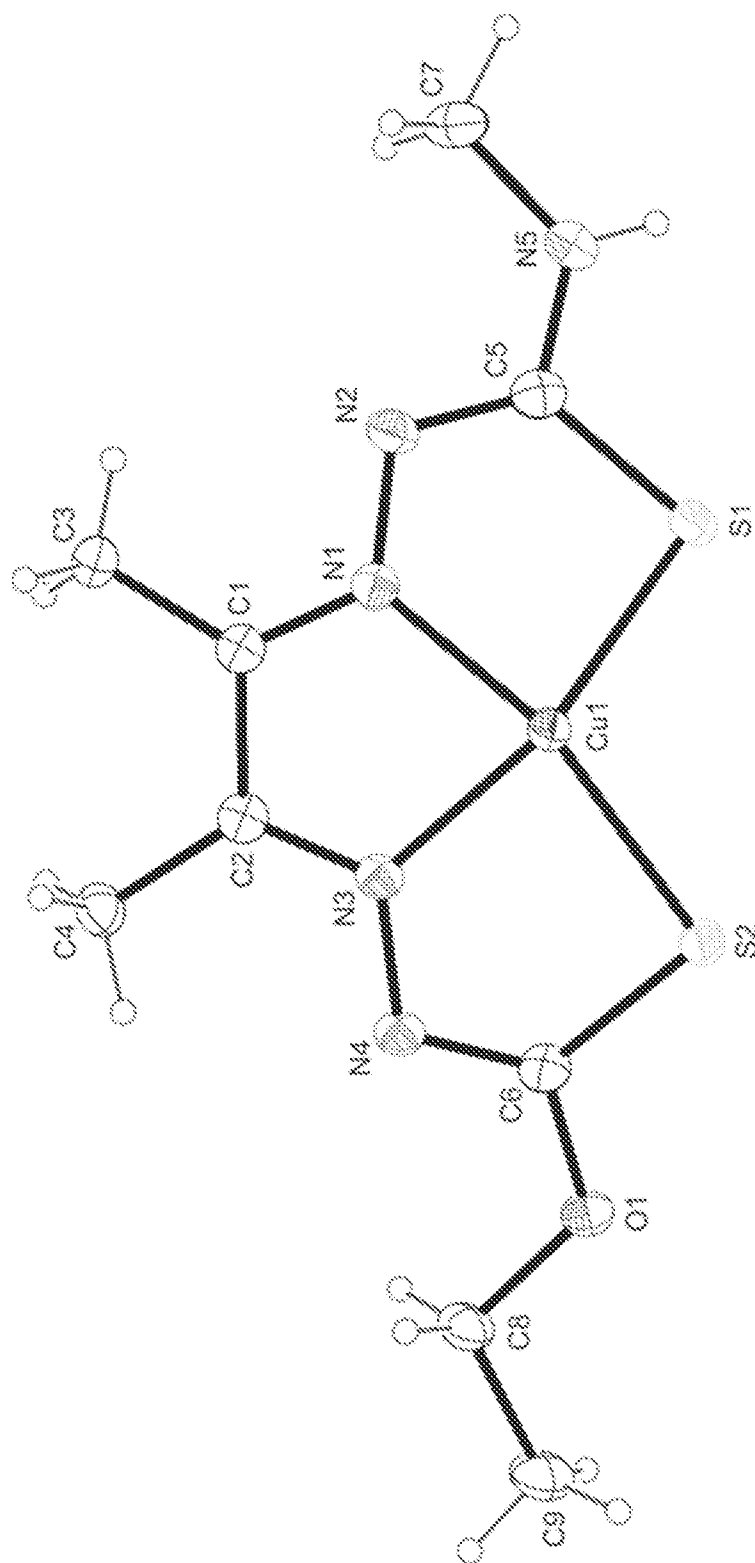
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FIG. 33



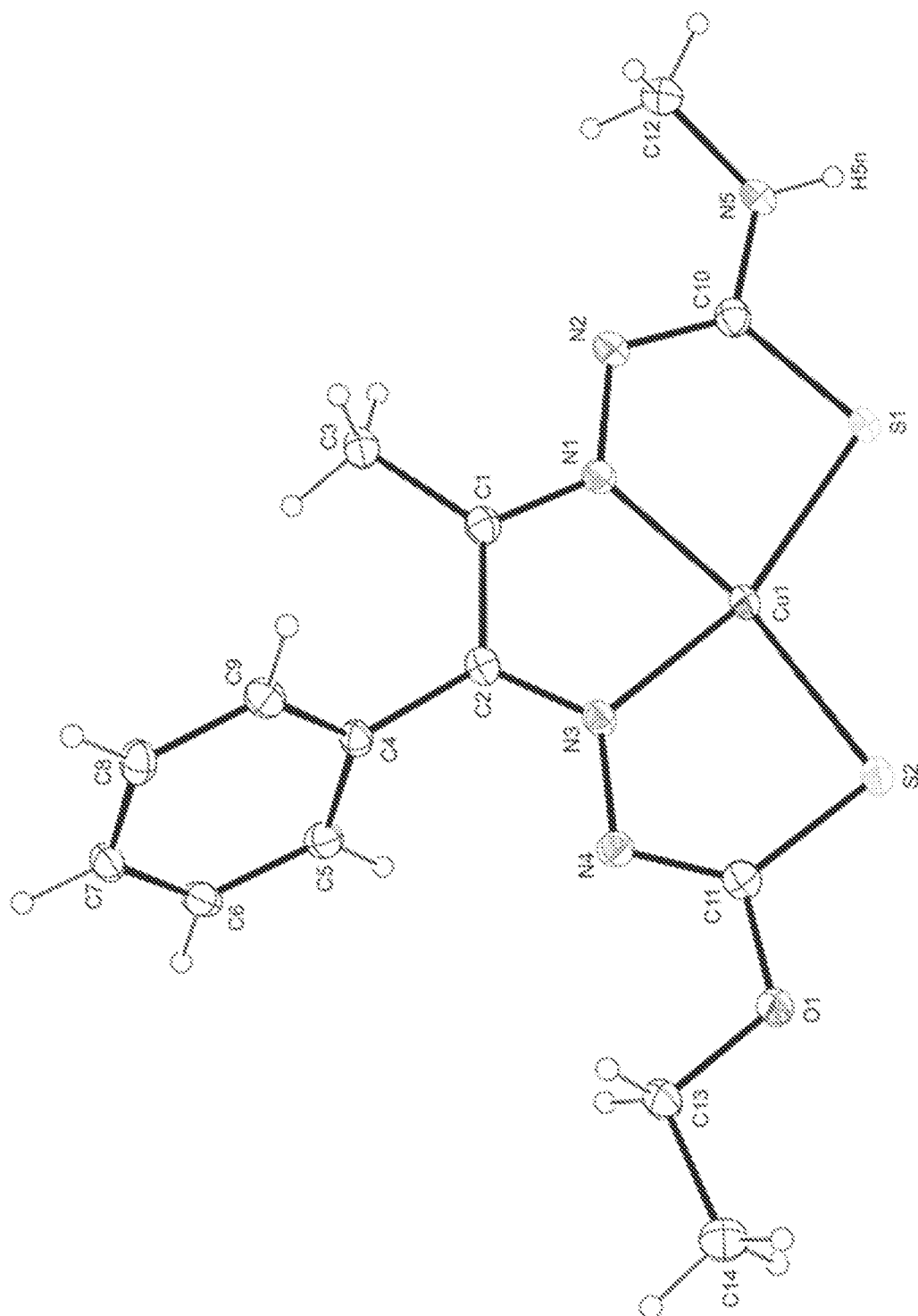
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FIG. 34



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FIG. 35



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/030765

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C337/08 A61K31/175 A61K31/30 A61K31/315 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2017/214546 A1 (UNIV OF LOUISVILLE RESEARCH FOUNDATION INC [US]) 14 December 2017 (2017-12-14)	1-24, 49-53
Y,P	Abstract; claims 1, 11; pages 109-110, paragraphs 363-365: compounds 5-8; pages 110-111, paragraphs 366-367: compounds 9a-c and 10a-c.	25-48
X	----- PALANIMUTHU ET AL.: "In Vitro and in Vivo Anticancer Activity of Copper Bis(thiosemicarbazone) Complexes", J. MED. CHEM., vol. 56, no. 3, 30 January 2013 (2013-01-30), pages 722-734, XP055492413, ISSN: 0022-2623, DOI: 10.1021/jm300938r	1-53
Y	the whole document ----- -/--	25-48



Further documents are listed in the continuation of Box C.



See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

13 July 2018

Date of mailing of the international search report

24/07/2018

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Authorized officer

Weisbrod, Thomas

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2018/030765

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STEFANI ET AL.: "Identification of differential anti-neoplastic activity of copper bis(thiosemicarbazones) that is mediated by intracellular reactive oxygen species generation and lysosomal membrane permeabilization", J. INORG. BIOCHEM., vol. 152, 2015, pages 20-37, XP029338706, ISSN: 0162-0134, DOI: 10.1016/J.JINORGBIO.2015.08.010 the whole document -----	1-53

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2018/030765

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017214546	A1	14-12-2017	NONE
