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(54) Title: CYCLIC DINUCLEOTIDE STING AGONISTS FOR CANCER TREATMENT

(57) Abstract: Therapies comprising administering at least one cyclic dinucleotide compound that activates the Stimulator of Interferon Genes (STING) pathway, and the use of such therapies in the treatment of cell-proliferation disorders such as cancer, are disclosed herein.

TITLE OF THE APPLICATION

CYCLIC DINUCLEOTIDE STING AGONISTS FOR CANCER TREATMENT

FIELD OF THE INVENTION

[0001] The present disclosure relates to therapies that are useful to treat cancer. In particular, this disclosure relates to therapies comprising at least one cyclic dinucleotide compound (CDN) that is useful as a STING (Stimulator of Interferon Genes) agonist and activates the STING pathway.

BACKGROUND OF THE INVENTION

[0002] A potential immune therapy for cancers and for other cell-proliferation disorders is related to the immune system response to certain danger signals associated with cellular or tissue damage. The innate immune system has no antigen specificity but does respond to a variety of effector mechanisms, such as the damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), such as those associated with opsonization, phagocytosis, activation of the complement system, and production of soluble bioactive molecules such as cytokines or chemokines. These are all mechanisms by which the innate immune system mediates its response. In this way, the innate immune system is able to provide broad protection against a wide range of threats to the host.

[0003] Free cytosolic DNA and RNA are among these PAMPs and DAMPs. It has recently been demonstrated that the main sensor for cytosolic DNA is cGAS (cyclic GMP-AMP synthase). Upon recognition of cytosolic DNA, cGAS catalyzes the generation of the cyclic-dinucleotide 2'-3' cGAMP, an atypical second messenger that strongly binds to the ER-transmembrane adaptor protein STING. A conformational change is undergone by cGAMP-bound STING, which translocates to a perinuclear compartment and induces the activation of critical transcription factors IRF-3 and NF-κB. This leads to a strong induction of type I interferons and production of pro-inflammatory cytokines such as IL-6, TNF-α and IFN-γ.

[0004] The importance of type I interferons and pro-inflammatory cytokines on various cells of the immune system has been very well established. In particular, these molecules strongly potentiate T-cell activation by enhancing the ability of dendritic cells and macrophages to uptake, process, present and cross-present antigens to T-cells. The T-cell stimulatory capacity of these antigen-presenting cells is augmented by the up-regulation of critical co-stimulatory

molecules, such as CD80 or CD86. Finally, type I interferons can rapidly engage their cognate receptors and trigger the activation of interferon-responsive genes that can significantly contribute to adaptive immune cell activation.

[0005] From a therapeutic perspective, interferons, and compounds that can induce interferon production, have potential use in the treatment of human cancers. Such molecules are potentially useful as anti-cancer agents with multiple pathways of activity. Interferons can inhibit human tumor cell-proliferation directly and may be synergistic with various approved chemotherapeutic agents. Type I interferons can significantly enhance anti-tumor immune responses by inducing activation of both the adaptive and innate immune cells. Finally, tumor invasiveness may be inhibited by interferons by modulating enzyme expression related to tissue remodeling.

[0006] In view of the potential of type I interferons and type I interferon-inducing compounds as anti-viral and anti-cancer agents, there remains a need for new agents that can induce potent type I interferon production. With the growing body of data demonstrating that the cGAS-STING cytosolic DNA sensory pathway has a significant capacity to induce type I interferons, cyclic dinucleotide STING activating agents are rapidly taking an important place in today's anti-tumor therapy landscape.

SUMMARY OF THE INVENTION

[0007] Embodiments of the disclosure include therapies comprising at least one cyclic dinucleotide STING agonist.

[0008] Another embodiment includes a method of treating a cell-proliferation disorder in a subject in need thereof, comprising administering a therapy comprising at least cyclic dinucleotide STING agonist.

[0009] Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples, and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

ABBREVIATIONS

μg, ug	Microgram
BID	One dose twice daily

C57B1/6	Common inbred strain of laboratory mouse, also "C57 black 6", "C57", "black 6", or "B6"
CR	Complete regression
Ctrl	Control
DFS	Disease free survival
DLT	Dose limiting toxicity
FFPE	Formalin-fixed, paraffin-embedded
FR	Framework region
IgG	Immunoglobulin G
IgG1	Immunoglobulin G subclass 1
IHC	Immunohistochemistry or immunohistochemical
IP	Intraperitoneal
IT	Intratumoral
kg	Kilogram
mAb	Monoclonal antibody
MC38	Murine Carcinoma-38 Mouse colon adenocarcinoma cell line
mg	Milligram
mL	Milliliter
mm	Millimeter
mm^3	Cubic millimeter, 0.001 mL
MPK	Milligram per kilogram
MTD	Maximum tolerated dose
n	Number of subjects in a treatment group
NCI	National Cancer Institute
OR	Overall response
OS	Overall survival
PBS	Phosphate-buffered saline, vehicle control for cyclic dinucleotide STING agonists
PFS	Progression free survival
PR	Partial response
p-values	Calculated probability
QD	One dose per day

RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SEM	Standard error of the mean
TGI	Tumor growth inhibition
T/C	Median tumor volume of the treated animal/Median tumor volume of the control animal

[0010] Additional abbreviations may be defined throughout this disclosure.

DEFINITIONS

[0011] Certain technical and scientific terms are specifically defined below. Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this disclosure relates.

[0012] "About" when used to modify a numerically defined parameter (e.g., the dose of a CDN STING agonist, or the length of treatment time with a therapy described herein) means that the parameter may vary by as much as 10% below or above the stated numerical value for that parameter; where appropriate, the stated parameter may be rounded to the nearest whole number. For example, a dose of about 5mg/kg may vary between 4.5mg/kg and 5.5mg/kg.

[0013] As used herein, including the appended claims, the singular forms of words such as "a," "an," and "the," include their corresponding plural references unless the context clearly dictates otherwise.

[0014] The terms "administration of" and or "administering" a compound should be understood to include providing a compound described herein, or a pharmaceutically acceptable salt thereof, and compositions of the foregoing to a subject.

[0015] As used herein, the terms "at least one" item or "one or more" item each include a single item selected from the list as well as mixtures of two or more items selected from the list.

[0016] As used herein, the term "immune response" relates to any one or more of the following: specific immune response, non-specific immune response, both specific and non-specific response, innate response, primary immune response, adaptive immunity, secondary immune response, memory immune response, immune cell activation, immune cell-proliferation, immune cell differentiation, and cytokine expression.

[0017] The term "pharmaceutically acceptable carrier" refers to any inactive substance that is suitable for use in a formulation for the delivery of a therapeutic agent. A carrier may be an antiadherent, binder, coating, disintegrant, filler or diluent, preservative (such as antioxidant, antibacterial, or antifungal agent), sweetener, absorption delaying agent, wetting agent, emulsifying agent, buffer, and the like. Examples of suitable pharmaceutically acceptable carriers include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), dextrose, vegetable oils (such as olive oil), saline, buffer, buffered saline, and isotonic agents such as sugars, polyalcohols, sorbitol, and sodium chloride.

[0018] The term "subject" (alternatively "patient") as used herein refers to a mammal that has been the object of treatment, observation, or experiment. The mammal may be male or female. The mammal may be one or more selected from the group consisting of humans, bovine (e.g., cows), porcine (e.g., pigs), ovine (e.g., sheep), capra (e.g., goats), equine (e.g., horses), canine (e.g., domestic dogs), feline (e.g., house cats), Lagomorpha (rabbits), rodents (e.g., rats or mice), Procyon lotor (e.g., raccoons). In particular embodiments, the subject is human.

[0019] The term "subject in need thereof" as used herein refers to a subject diagnosed with, or suspected of having a diagnosis of a cell-proliferation disorder, such as a cancer, as defined herein.

[0020] As used herein, the terms "treatment" and "treating" refer to all processes in which there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of a disease or disorder described herein. The terms do not necessarily indicate a total elimination of all disease or disorder symptoms.

[0021] "Biotherapeutic agent" means a biological molecule, such as an antibody or fusion protein, that blocks ligand/receptor signaling in any biological pathway that supports tumor maintenance and/or growth or suppresses the anti-tumor immune response.

[0022] "Chemotherapeutic agent" refers to a chemical or biological substance that can cause death of cancer cells, or interfere with growth, division, repair, and/or function of cancer cells. Examples of chemotherapeutic agents include those that are disclosed in WO2006/129163, and US20060153808, the disclosures of which are incorporated herein by reference. Classes of chemotherapeutic agents include, but are not limited to: hypomethylating agents, alkylating agents, antimetabolites, spindle poison, plant alkaloids, cytoxic/antitumor antibiotics, topisomerase inhibitors, photosensitizers, hormonal therapies such as anti-estrogens and selective estrogen receptor modulators (SERMs), anti-progesterones, estrogen receptor down-regulators

(ERDs), estrogen receptor antagonists, leutinizing hormone-releasing hormone agonists, anti-androgens, aromatase inhibitors, and targeted therapies such as kinase inhibitors, EGFR inhibitors, VEGF inhibitors, and anti-sense oligonucleotides that inhibit expression of genes implicated in abnormal cell-proliferation or tumor growth. Chemotherapeutic agents useful in the treatment methods of the present disclosure include cytostatic and/or cytotoxic agents.

[0023] The therapeutic agents and compositions provided by the present disclosure can be administered via any suitable enteral route or parenteral route of administration. The term "enteral route" of administration refers to the administration via any part of the gastrointestinal tract. Examples of enteral routes include oral, mucosal, buccal, and rectal route, or intragastric route. "Parenteral route" of administration refers to a route of administration other than enteral route. Examples of parenteral routes of administration include intravenous, intramuscular, intradermal, intraperitoneal, intratumor, intravesical, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, transtracheal, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal, subcutaneous, or topical administration. The therapeutic agents and compositions of the disclosure can be administered using any suitable method, such as by oral ingestion, nasogastric tube, gastrostomy tube, injection, infusion, implantable infusion pump, and osmotic pump. The suitable route and method of administration may vary depending on a number of factors such as the specific therapeutic agent being used, the rate of absorption desired, specific formulation or dosage form used, type or severity of the disorder being treated, the specific site of action, and conditions of the patient, and can be readily selected by a person skilled in the art.

[0024] The term "simultaneous administration" as used herein in relation to the administration of medicaments refers to the administration of medicaments such that the individual medicaments are present within a subject at the same time. In addition to the concomitant administration of medicaments (via the same or alternative routes), simultaneous administration may include the administration of the medicaments (via the same or an alternative route) at different times.

[0025] "Consists essentially of," and variations such as "consist essentially of" or "consisting essentially of," as used throughout the specification and claims, indicate the inclusion of any recited elements or group of elements, and the optional inclusion of other elements, of similar or different nature than the recited elements, that do not materially change the basic or novel properties of the specified dosage regimen, method, or composition.

[0026] "RECIST 1.1 Response Criteria" as used herein means the definitions set forth in Eisenhauer, E.A. *et al.*, *Eur. J. Cancer* 45:228-247 (2009) for target lesions or nontarget lesions, as appropriate based on the context in which response is being measured.

[0027] "Sustained response" means a sustained therapeutic effect after cessation of treatment as described herein. In some embodiments, the sustained response has a duration that is at least the same as the treatment duration, or at least 1.5, 2.0, 2.5 or 3 times longer than the treatment duration.

[0028] "Tissue Section" refers to a single part or piece of a tissue, e.g., a thin slice of tissue cut from a sample of a normal tissue or of a tumor.

[0029] "Treat" or "treating" a cell-proliferation disorder as used herein means to administer a therapy of a CDN STING agonist to a subject having a cell-proliferation disorder, such as cancer, or diagnosed with a cell-proliferation disorder, such as cancer, to achieve at least one positive therapeutic effect, such as for example, reduced number of cancer cells, reduced tumor size, reduced rate of cancer cell infiltration into peripheral organs, or reduced rate of tumor metastasis or tumor growth. Such "treatment" may result in a slowing, interrupting, arresting, controlling, or stopping of the progression of a cell-proliferation disorder as described herein but does not necessarily indicate a total elimination of the cell-proliferation disorder or the symptoms of the cell-proliferation disorder. Positive therapeutic effects in cancer can be measured in a number of ways (*See*, W. A. Weber, *J. Nucl. Med.* 50:1S-10S (2009)). For example, with respect to tumor growth inhibition, according to NCI standards, a T/C $\leqq$ 42% is the minimum level of anti-tumor activity. A T/C < 10% is considered a high anti-tumor activity level, with T/C (%) = Median tumor volume of the treated/Median tumor volume of the control $\times$ 100. In some embodiments, the treatment achieved by a therapy of the disclosure is any of PR, CR, OR, PFS, DFS, and OS. PFS, also referred to as "Time to Tumor Progression" indicates the length of time during and after treatment that the cancer does not grow, and includes the amount of time patients have experienced a CR or PR, as well as the amount of time patients have experienced SD. DFS refers to the length of time during and after treatment that the patient remains free of disease. OS refers to a prolongation in life expectancy as compared to naive or untreated individuals or patients. In some embodiments, response to a therapy of the disclosure is any of PR, CR, OR, PFS, DFS, or OS that is assessed using RECIST 1.1 response criteria. The treatment regimen for a therapy of the disclosure that is effective to treat a cancer patient may vary according to factors such as the disease state, age, and weight of the patient, and the

ability of the therapy to elicit an anti-cancer response in the subject. While an embodiment of any of the aspects of the disclosure may not be effective in achieving a positive therapeutic effect in every subject, it should do so in a statistically significant number of subjects as determined by any statistical test known in the art such as the Student's t-test, the chi^2-test, the U-test according to Mann and Whitney, the Kruskal-Wallis test (H-test), Jonckheere-Terpstra-test and the Wilcoxon-test.

[0030] The terms "treatment regimen", "dosing protocol", and "dosing regimen" are used interchangeably to refer to the dose and timing of administration of a therapeutic agent in a a therapy of the disclosure.

[0031] "Tumor" as it applies to a subject diagnosed with, or suspected of having, a cancer refers to a malignant or potentially malignant neoplasm or tissue mass of any size, and includes primary tumors and secondary neoplasms. A solid tumor is an abnormal growth or mass of tissue that usually does not contain cysts or liquid areas. Different types of solid tumors are named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and lymphomas. Leukemias (cancers of the blood) generally do not form solid tumors (National Cancer Institute, Dictionary of Cancer Terms).

[0032] "Advanced solid tumor malignancy" and "advanced solid tumor" are used interchangeably to refer to a tumor for which curative resection is not possible. Advanced solid tumors include, but are not limited to, metastatic tumors in bone, brain, breast, liver, lungs, lymph node, pancreas, prostate, and soft tissue (sarcoma).

[0033] "Tumor burden" also referred to as "tumor load", refers to the total amount of tumor material distributed throughout the body. Tumor burden refers to the total number of cancer cells or the total size of tumor(s), throughout the body, including lymph nodes and bone narrow. Tumor burden can be determined by a variety of methods known in the art, such as, e.g., by measuring the dimensions of tumor(s) upon removal from the subject, e.g., using calipers, or while in the body using imaging techniques, e.g., ultrasound, bone scan, computed tomography (CT) or magnetic resonance imaging (MRI) scans.

[0034] The term "tumor size" refers to the total size of the tumor which can be measured as the length and width of a tumor. Tumor size may be determined by a variety of methods known in the art, such as, e.g. by measuring the dimensions of tumor(s) upon removal from the subject, e.g., using calipers, or while in the body using imaging techniques, e.g., bone scan, ultrasound, CT or MRI scans.

[0035] It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0036] The term "alkyl" refers to a monovalent straight or branched chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range. Thus, for example, "C_{1-6} alkyl" (or "C_1-C_6 alkyl") refers to any of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec-, and *tert*-butyl, n- and iso-propyl, ethyl, and methyl. As another example, "C_{1-4} alkyl" refers to n-, iso-, sec-, and *tert*-butyl, n- and isopropyl, ethyl, and methyl.

[0037] As used herein, the term "alkylene" refers to a bivalent straight chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range.

[0038] As used herein, the term "alkenyl" refers to a monovalent straight or branched chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more double bond.

[0039] As used herein, the term "alkenylene" refers to a bivalent straight chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more double bond.

[0040] As used herein, the term "alkynyl" refers to a monovalent straight or branched chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more triple bond.

[0041] As used herein, the term "alkynylene" refers to a bivalent straight chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more triple bond.

[0042] The term "halogen" (or "halo") refers to fluorine, chlorine, bromine, and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo or F, Cl, Br, and I).

[0043] The term "haloalkyl" refers to an alkyl group as defined above in which one or more of the hydrogen atoms have been replaced with a halogen. Thus, for example, "C_{1-6} haloalkyl" (or "C_1-C_6 haloalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "fluoroalkyl" has an analogous meaning except the halogen substituents are restricted to fluoro. Suitable fluoroalkyls include the series $(CH_2)_{0-4}CF_3$ (*i.e.*, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

[0044] As used herein, the term "haloalkenyl" refers to an alkenyl group as defined above in which one or more of the hydrogen atoms have been replaced with a halogen.

[0045] As used herein, the term "haloalkynyl" refers to an alkynyl group as defined above in which one or more of the hydrogen atoms have been replaced with a halogen.

[0046] As used herein, the term "alkoxy" as used herein, alone or in combination, includes an alkyl group connected to the oxy connecting atom. The term "alkoxy" also includes alkyl ether groups, where the term 'alkyl' is defined above, and 'ether' means two alkyl groups with an oxygen atom between them. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, methoxymethane (also referred to as 'dimethyl ether'), and methoxyethane (also referred to as 'ethyl methyl ether').

[0047] As used herein, the term "cycloalkyl" refers to a saturated hydrocarbon containing one ring having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0048] As used herein, the term "heterocycle", "heterocyclyl", or "heterocyclic", as used herein, represents a stable 3- to 6-membered monocyclic that is either saturated or unsaturated, and that consists of carbon atoms and from one to two heteroatoms selected from the group consisting of N, O, and S. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, triazolyl and thienyl.

[0049] As used herein, the term "fused ring" refers to a cyclic group formed by substituents on separate atoms in a straight or branched alkane or alkene, or to a cyclic group formed by substituents on separate atoms in another ring.

[0050] As used herein, the term "spirocycle" or "spirocyclic ring" refers to a pendant cyclic group formed by substituents on a single atom.

[0051] Unless expressly stated to the contrary, all ranges cited herein are inclusive; *i.e.*, the range includes the values for the upper and lower limits of the range as well as all values in between. As an example, temperature ranges, percentages, ranges of equivalents, and the like described herein include the upper and lower limits of the range and any value in the continuum there between. Numerical values provided herein, and the use of the term "about", may include variations of ± 1%, ± 2%, ±3%, ± 4%, ± 5%, ± 10%, ± 15%, and ± 20% and their numerical equivalents. All ranges also are intended to include all included sub-ranges, although not necessarily explicitly set forth. For example, a range of 3 to 7 days is intended to include 3, 4, 5, 6, and 7 days. In addition, the term "or," as used herein, denotes alternatives that may, where appropriate, be combined; that is, the term "or" includes each listed alternative separately as well as their combination.

[0052] Where aspects or embodiments of the disclosure are described in terms of a Markush group or other grouping of alternatives, the present disclosure encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group, but also the main group absent one or more of the group members. The present disclosure also envisages the explicit exclusion of one or more of any of the group members in the claims.

[0053] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure relates. In case of conflict, the present specification, including definitions, will control. Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Any example(s) following the term "e.g." or "for example" is not meant to be exhaustive or limiting.

[0054] Exemplary methods and materials are described herein, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure. The materials, methods, and examples are illustrative only and not intended to be limiting.

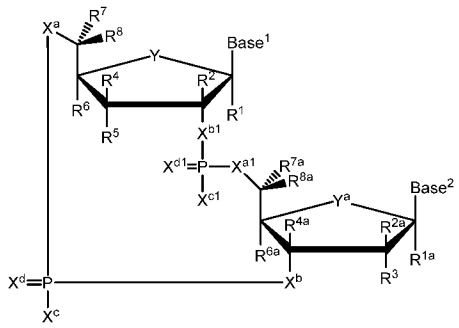
[0055] The present disclosure relates to methods of treating a cell-proliferation disorder as defined herein, wherein the method comprises administering to a subject in need thereof a therapy that comprises a cyclic dinucleotide STING agonist.

[0056] The present disclosure relates to methods of treating a cell-proliferation disorder, wherein the method comprises administering to a subject in need thereof a therapy that comprises a cyclic dinucleotide STING agonist; wherein the cell-proliferation disorder is selected from the group consisting of solid tumors and lymphomas.

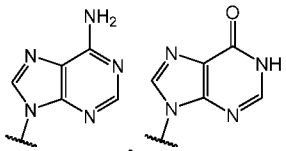
CYCLIC DINUCLEOTIDE STING AGONISTS

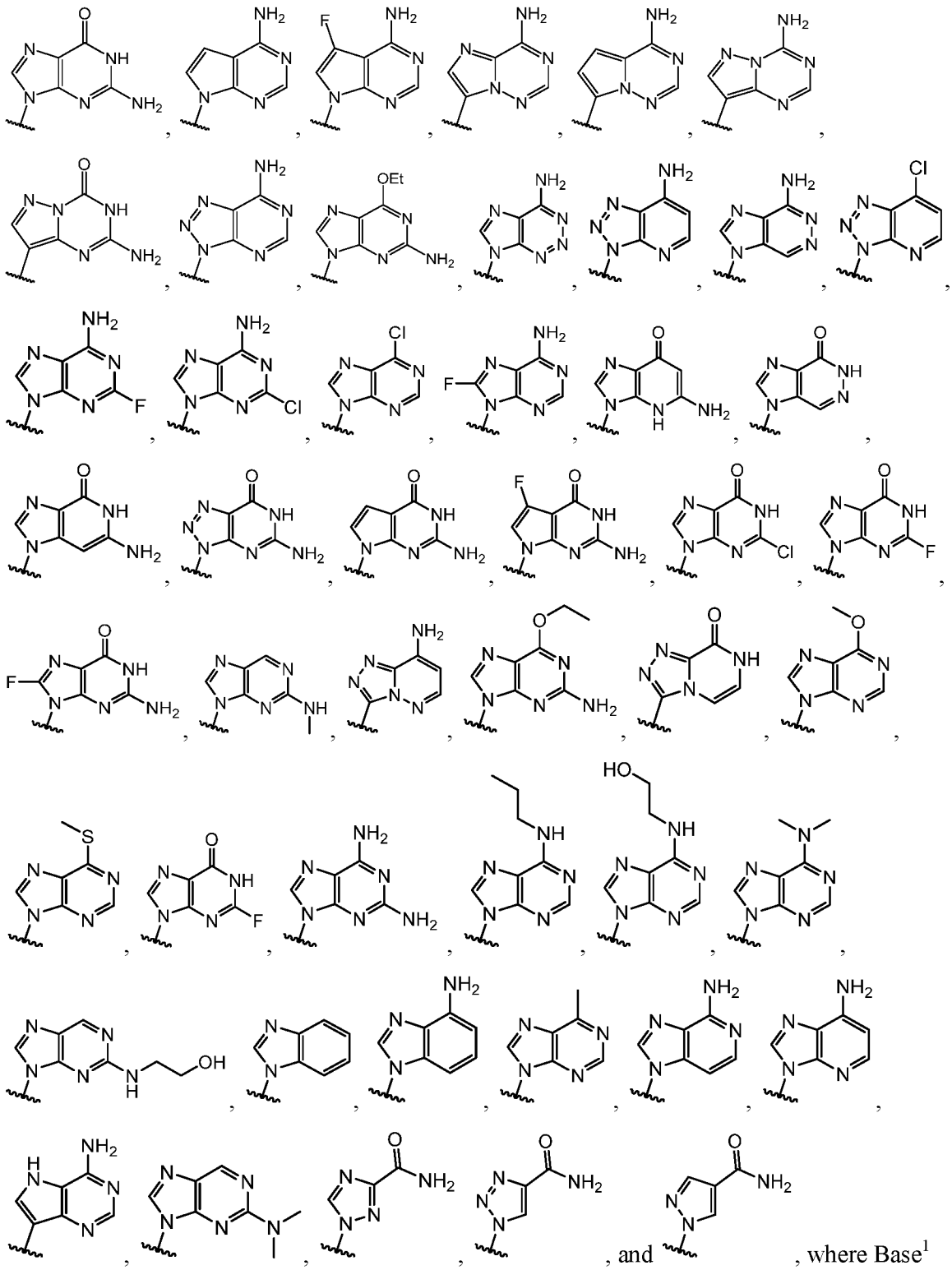
[0057] As used herein, "CDN STING agonist" means any cyclic dinucleotide STING agonist chemical compound that activates the STING pathway, and in particular, the cyclic dinucleotide STING agonists as disclosed in PCT International Patent Application No. PCT/US2016/046444, which published as PCT International Patent Application Publication No. WO2017/027646, and United States Patent Application No. 15/234,182, which published as U.S. Patent Application Publication No. US2017/0044206, both of which are incorporated herein in their entirety. CDN STING agonists, and particularly the compounds of formulas (I), (Ia), (Ib), (Ic), (I'), (I'a), (I'b), (I'c), (I"), (I"a), and (I"b) may be used in the therapeutic combinations of this disclosure.

[0058] In embodiments, the CDN STING agonist is selected from cyclic di-nucleotide compounds of formula (I):



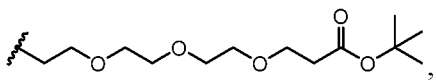
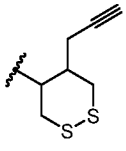
(I)

or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of  , ,

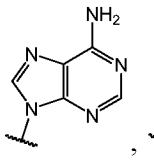
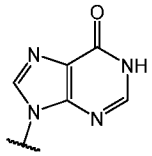
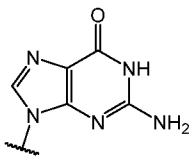
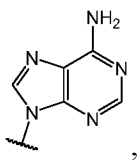
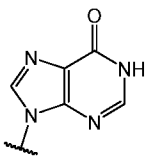
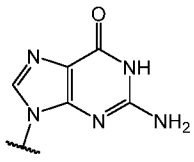


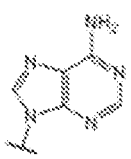
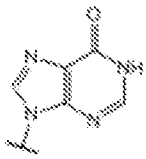
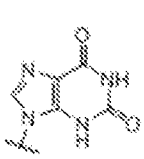
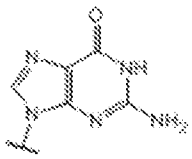
and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6}

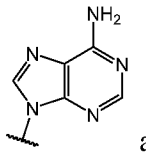
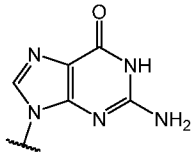
cycloalkyl, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl), S(C_{1-3} alkyl), S(C_{3-6} cycloalkyl), NH(C_{1-3} alkyl), NH(C_{3-6} cycloalkyl), N(C_{1-3} alkyl)$_2$, and N(C_{3-6} cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O-, -S-, -SO_2-, -CH_2-, and -CF_2-; X^a and X^{a1} are each independently selected from the group consisting of O, C, and S; X^b and X^{b1} are each independently selected from the group consisting of O, C, and S; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^1 and R^{1a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^2 and R^{2a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^3 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^4 and R^{4a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^5 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6

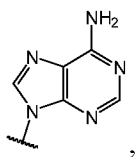
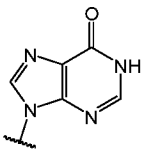
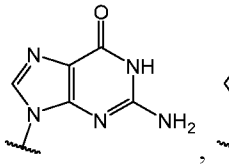
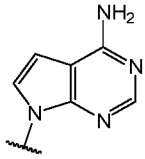
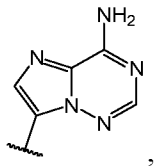
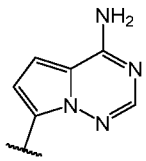
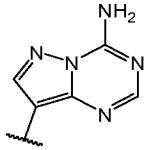
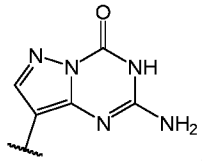
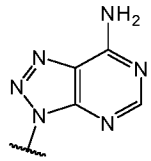
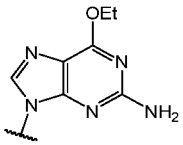
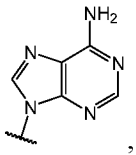
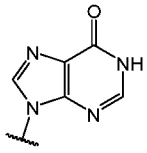
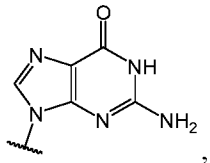
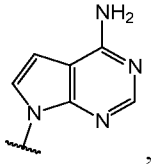
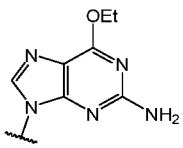
haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^6 and R^{6a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^7 and R^{7a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^7 and R^{7a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^8 and R^{8a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^8 and R^{8a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,  , and  , where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl; optionally R^{1a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^{1a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position; optionally R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^{2a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position; optionally R^3 and R^{6a} are connected to form

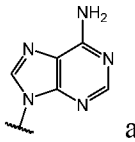
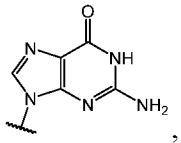
-O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position; optionally R^4 and R^5 are connected to form are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position; optionally R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position; optionally R^7 and R^8 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene; and optionally R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene.

[0059] In specific aspects of this embodiment, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, R^6 and R^{6a} are each H, R^7 and R^{7a} are each H, R^8 and R^{8a} are each H, and $Base^1$ and $Base^2$ are each selected from the group consisting of  ,  , and  , R^5 and R^3 are not both selected from the group consisting of H, F and OH. That is, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, R^6 and R^{6a} are each H, R^7 and R^{7a} are each H, R^8 and R^{8a} are each H, and $Base^1$ and $Base^2$ are each selected from the group consisting of  ,  , and  , either only one of R^5 and R^3 is selected from the group consisting of H, F, and OH, or neither R^5 and R^3 is selected from the group consisting of H, F, and OH. In specific instances of this aspect, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH, X^d and X^{d1} are each O or S, R^1 and R^{1a} are each H, R^2 is H, R^6 and R^{6a} are each H, R^7 and R^{7a} are each H, R^8 and R^{8a} are each H, and $Base^1$ and $Base^2$ are each selected from the group consisting of

 ,  ,  and  , R^5 and R^3 are not both selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where said C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I and OH.

[0060] In further specific aspects of this embodiment, when $Base^1$ and $Base^2$ are each selected from the group consisting of  and  , and R^{2a} is F and R^5 is F, at least one of X^c and X^{c1} is SR^9.

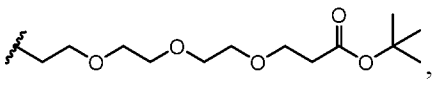
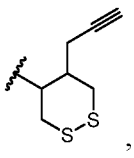
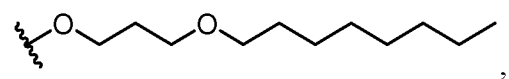
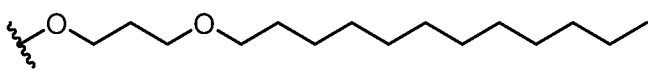
[0061] In aspects of this embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl$)_2$, and $N(C_{3-6}$ cycloalkyl$)_2$. In particular instances, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  ,  ,  , and  , where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from

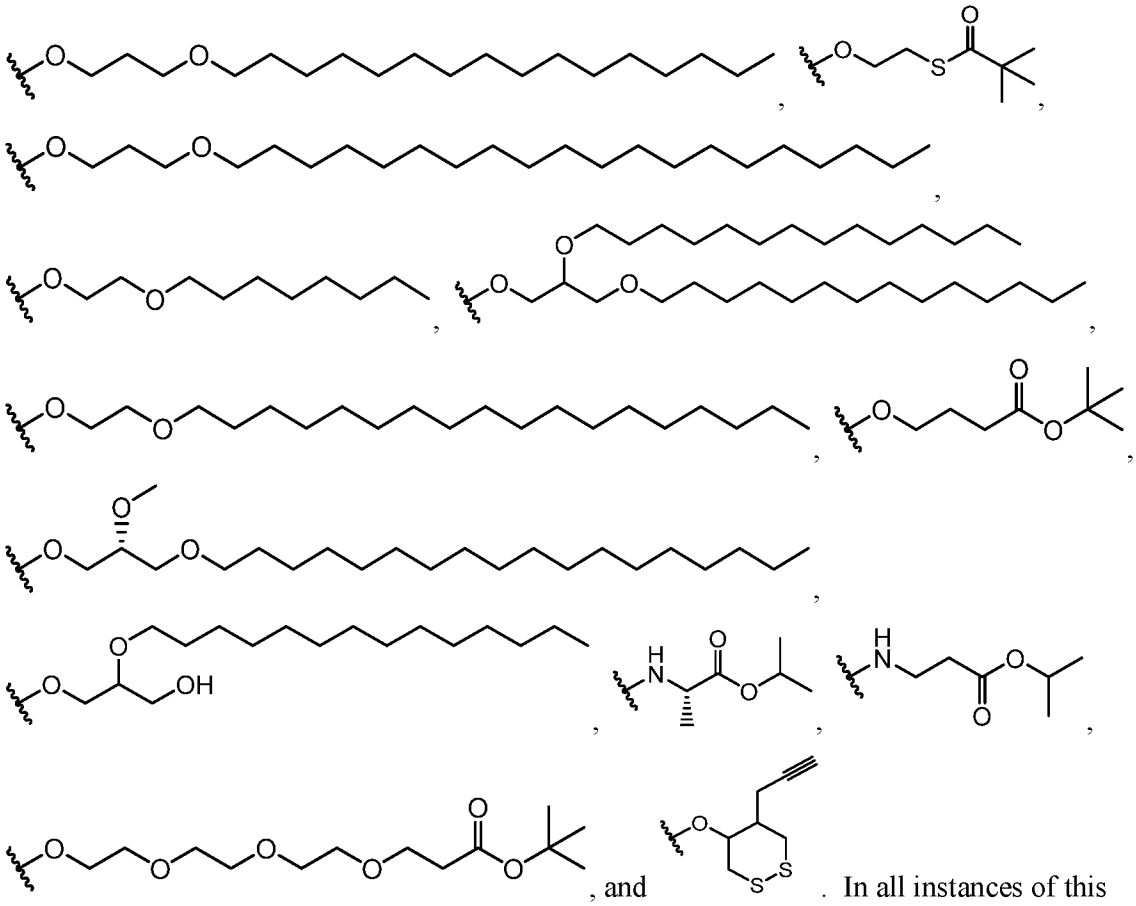
the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$. In even more particular instances, Base[1] and Base[2] are each independently selected from the group consisting of  and  , where Base[1] and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$. In this aspect, all other groups are as provided in the formula (I) above.

[0062] In aspects of this embodiment, Y and Y^a are each independently selected from the group consisting of -O- and -S-. In this aspect, all other groups are as provided in the formula (I) above or in the aspect described above.

[0063] In aspects of this embodiment, X^a and X^{a1} are each independently selected from the group consisting of O and S. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0064] In aspects of this embodiment, X^b and X^{b1} are each independently selected from the group consisting of O and S. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0065] In aspects of this embodiment, X^c and X^{c1} are each independently selected from the group consisting of O^-, S^-, OR^9, and NR^9R^9, where each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,  , and  , where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl. In particular instances, X^c and X^{c1} are each independently selected from the group consisting of O^-, S^-,  ,  ,



, and . In all instances of this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0066] In aspects of this embodiment, X^d and X^{d1} are each independently selected from the group consisting of O and S. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0067] In aspects of this embodiment, R^1 and R^{1a} are each H. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0068] In aspects of this embodiment, R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^2 and R^{2a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3. In particular instances, R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, CF_3, CH_3, CH_2OH, and CH_2CH_3. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0069] In aspects of this embodiment, R^3 is selected from the group consisting H, F, Cl, I, Br, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3. In particular instances, R^3 are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, CF_3, CH_3, CH_2OH, and CH_2CH_3. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0070] In aspects of this embodiment, R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^4 and R^{4a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3. In particular instances, R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, CF_3, CH_3, CH_2OH, and CH_2CH_3. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0071] In aspects of this embodiment, R^5 is selected from the group consisting of H, F, Cl, I, Br, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3. In particular instances, R^5 are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, CF_3, CH_3, CH_2OH, and CH_2CH_3. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0072] In aspects of this embodiment, R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0073] In aspects of this embodiment, R^7 and R^{7a} are each H. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0074] In aspects of this embodiment, R^8 and R^{8a} are each H. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0075] In aspects of this embodiment, R^{1a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^{1a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0076] In aspects of this embodiment, R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^{2a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

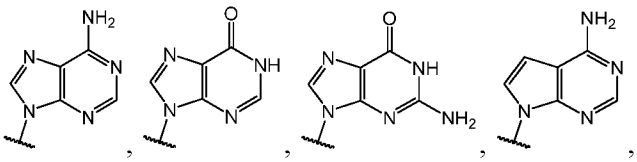
[0077] In aspects of this embodiment, R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, and -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

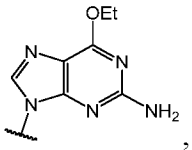
[0078] In aspects of this embodiment, R^4 and R^5 are connected by C_1-C_6 alkylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0079] In aspects of this embodiment, R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

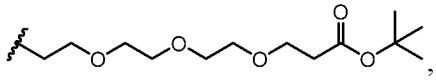
[0080] In aspects of this embodiment, R^7 and R^8 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

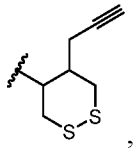
[0081] In aspects of this embodiment, R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene. In this aspect, all other groups are as provided in the formula (I) above or in the aspects described above.

[0082] In aspects of this embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  , and



, where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O-, -S-, $-SO_2-$, $-CH_2-$, and $-CF_2-$; X^a and X^{a1} are each independently selected from the group consisting of O and S; X^b and X^{b1} are each independently selected from the group consisting of O and S; X^c and X^{c1} are each independently selected from the group consisting of O^-, S^-, OR^9, and NR^9R^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each H; R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^2 and R^{2a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^3 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^4 and R^{4a} are each independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^4 and R^{4a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^5 is selected from the group consisting of H, F, Cl, I, Br, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, and C_1-C_6 haloalkyl, where said R^6 and R^{6a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^7 and R^{7a} are each H; R^8 and R^{8a} are each H; each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,

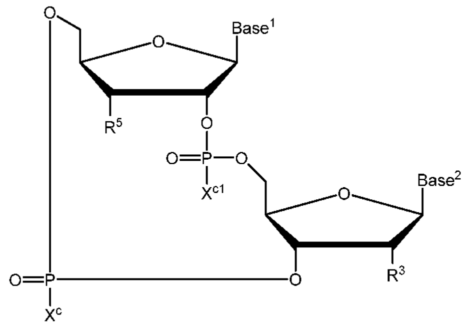


, and


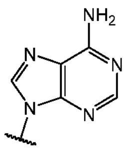
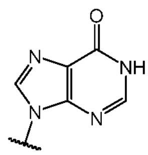
, where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl; optionally R^3 and R^{6a} are

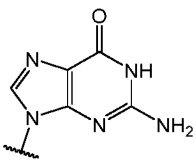
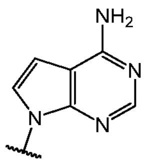
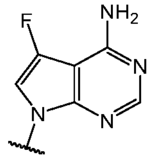
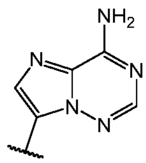
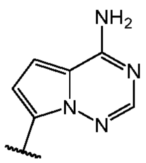
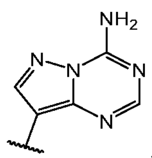
connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, and -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position or optionally R^4 and R^5 are connected by C_1-C_6 alkylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position. In this aspect, all other groups are as provided in the formula (I) above.

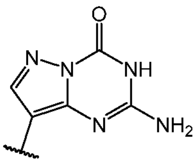
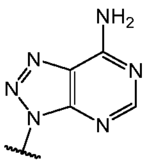
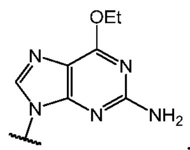
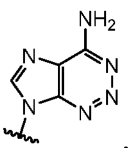
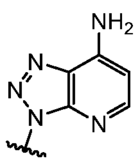
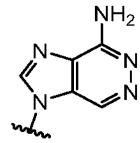
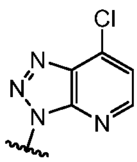
[0083] In aspects of this embodiment, the compound of formula (I) is a compound of formula (Ia):

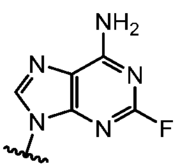
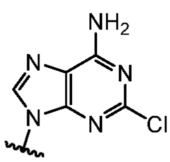
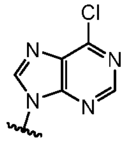
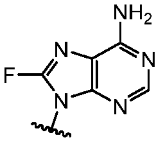
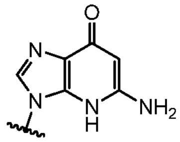
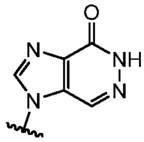


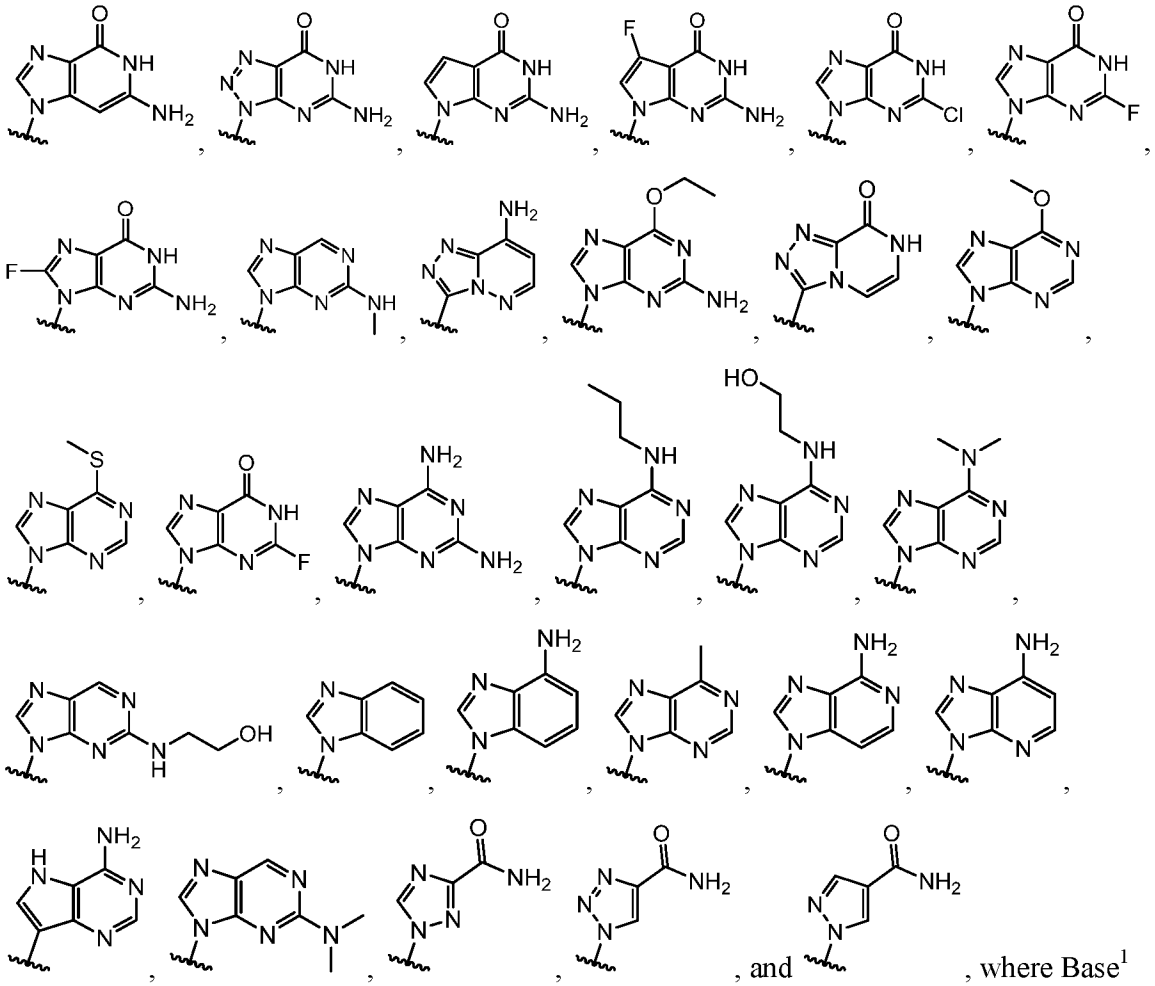
(Ia)

or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  ,

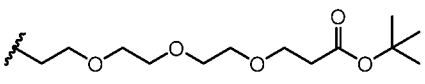
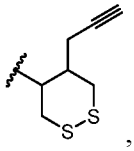
 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,

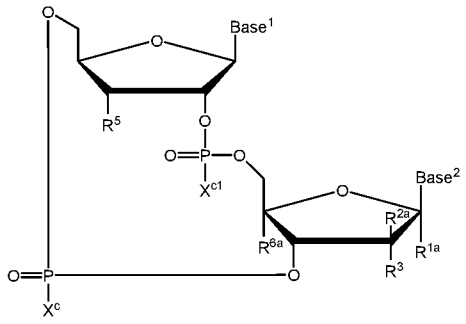
 ,  ,  ,  ,  ,  ,



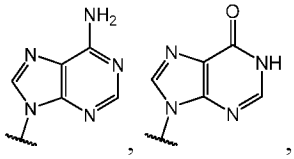
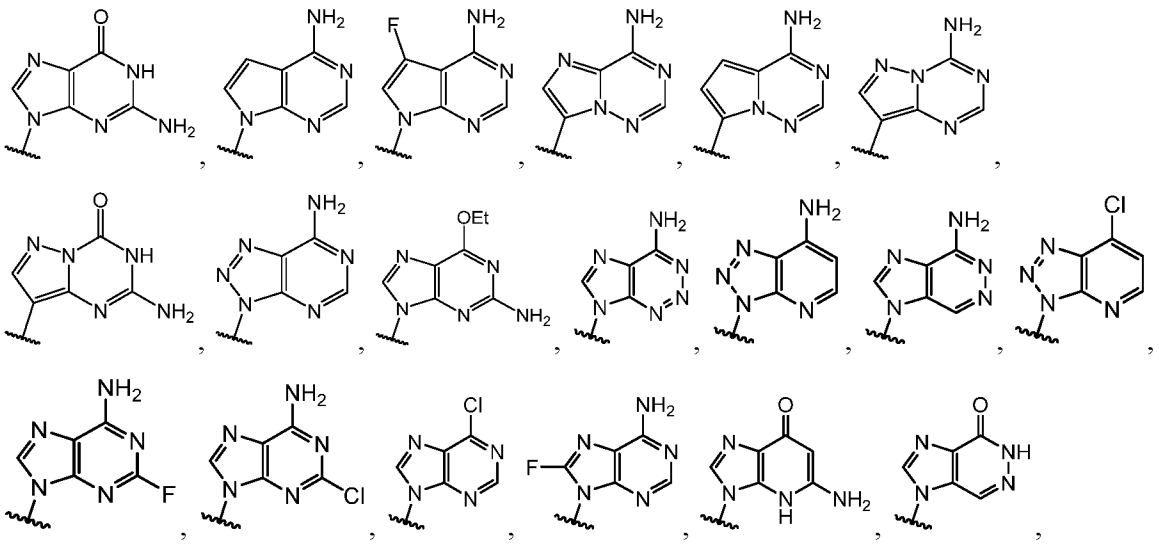
and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; X^c and X^{c1} are each independently selected from the group consisting of O^-, S^-, OR^9, and NR^9R^9; R^3 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, I, Br, and OH; R^5 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, I, Br, and OH; R^3 and R^5 are not both selected from the group consisting of OH, C_1-C_6 alkyl substituted with OH, and C_1-C_6 haloalkyl substituted with OH; and each R^9 is independently selected from the group consisting

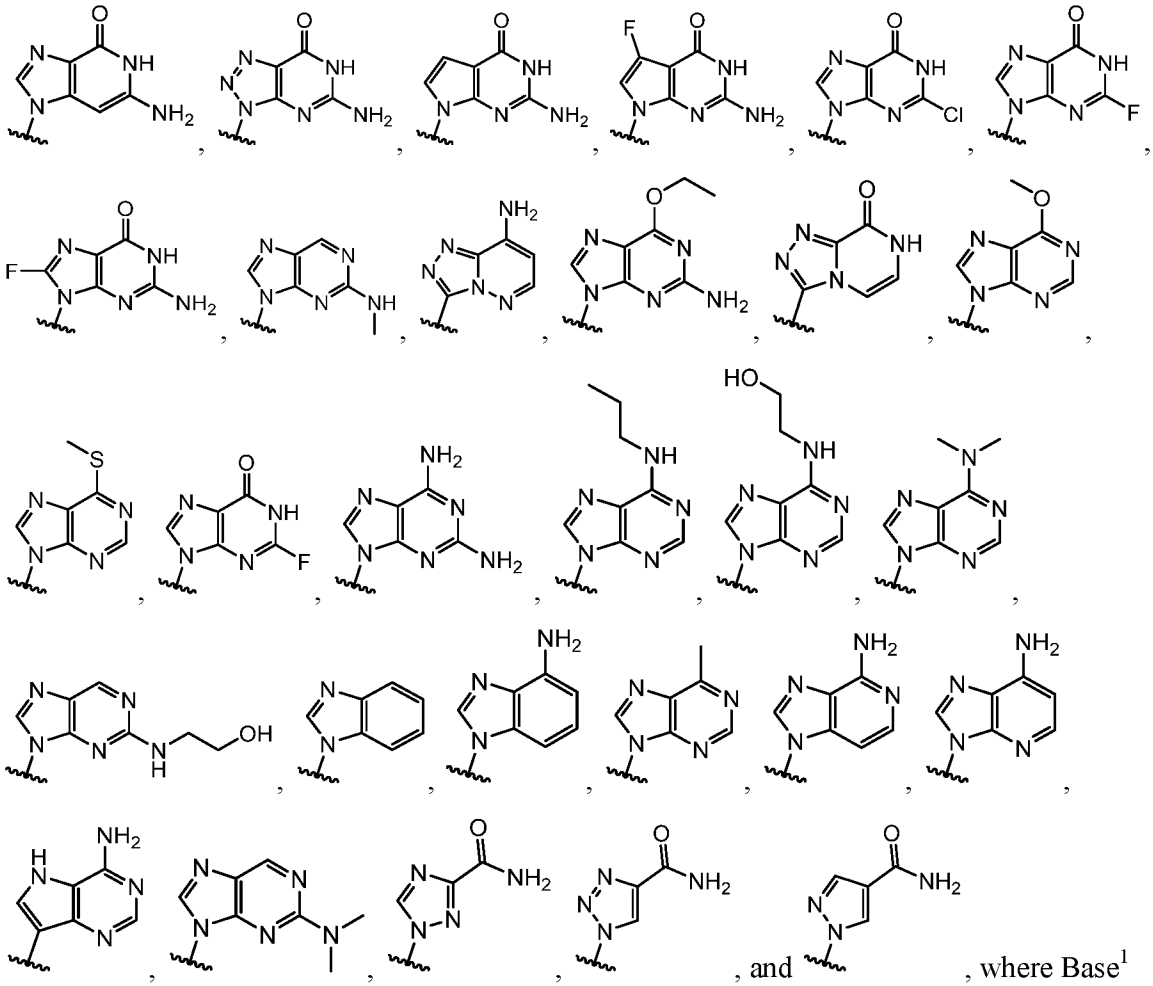
of H, C_2-C_3 alkyl,  , and  , where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl. In this aspect, all other groups are as provided in the formula (I) above.

[0084] In aspects of this embodiment, the compound of formula (I) is a compound of formula (Ib):

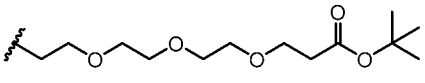
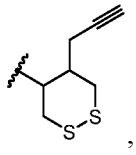


(Ib)

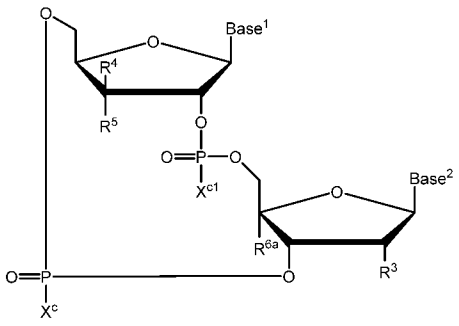
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  .



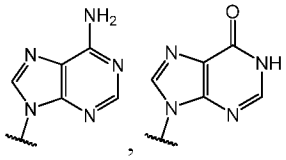
and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9; R^{1a} is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^{1a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^{2a} is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^{2a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, I, Br, and OH; R^3 is selected from the

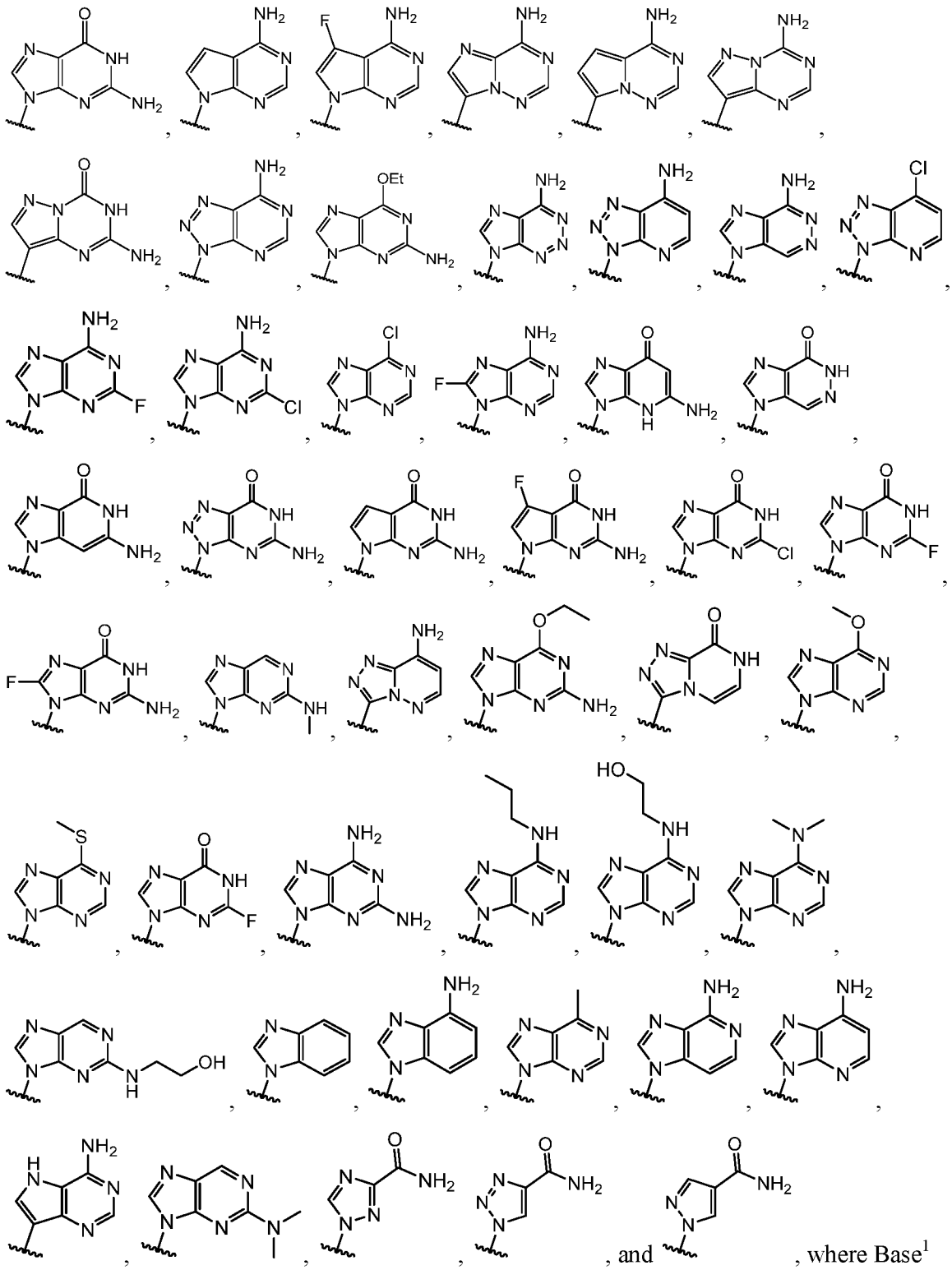
group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, I, Br, and OH; R^5 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, I, Br, and OH; R^3 and R^5 are not both selected from the group consisting of OH, C_1-C_6 alkyl substituted with OH, and C_1-C_6 haloalkyl substituted with OH; R^{6a} is selected from the group consisting of H, F, Cl, I, Br, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl; each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,  , and  , where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl; and optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, and -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position. In this aspect, all other groups are as provided in the formula (I) above.

[0085] In aspects of this embodiment, the compound of formula (I) is a compound of formula (Ic):

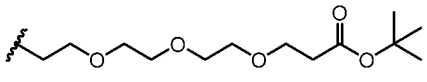
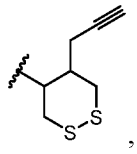


(Ic)

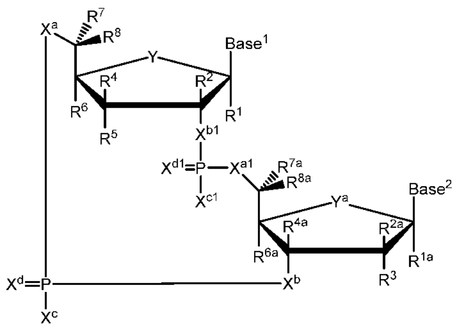
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,



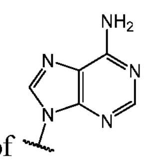
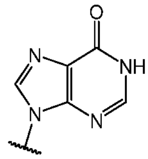
and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6}

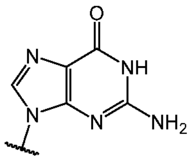
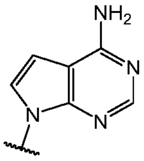
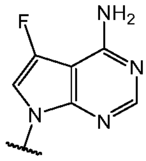
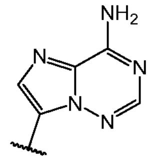
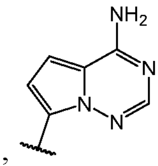
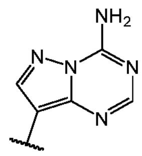
cycloalkyl, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl), S(C_{1-3} alkyl), S(C_{3-6} cycloalkyl), NH(C_{1-3} alkyl), NH(C_{3-6} cycloalkyl), N(C_{1-3} alkyl)$_2$, and N(C_{3-6} cycloalkyl)$_2$; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9; R^3 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, I, Br, and OH; R^4 is selected from the group consisting of H, F, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^4 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, I, Br, and OH; R^5 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, I, Br, and OH; R^3 and R^5 are not both selected from the group consisting of OH, C_1-C_6 alkyl substituted with OH, and C_1-C_6 haloalkyl substituted with OH; R^{6a} is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^{6a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, I, Br, and OH; each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,  , and  , where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl; and optionally R^4 and R^5 are connected by C_1-C_6 alkylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position. In this aspect, all other groups are as provided in the formula (I) above.

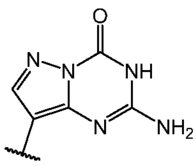
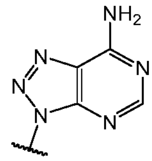
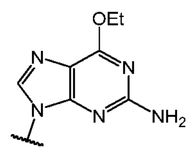
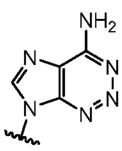
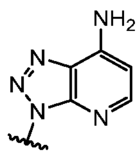
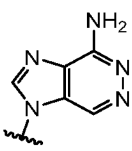
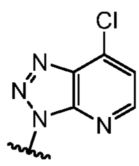
[0086] In an additional embodiment, the CDN STING agonist is selected from cyclic di-nucleotide compounds of formula (I'):

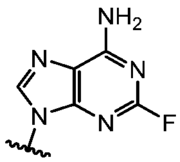
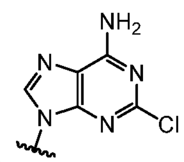
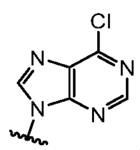
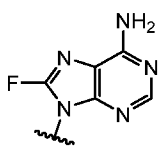
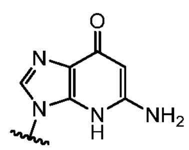
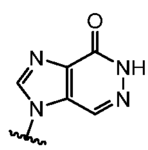


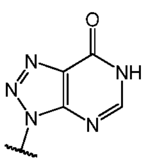
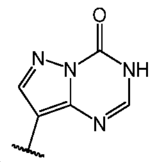
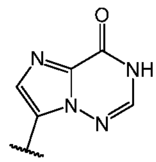
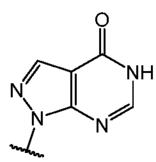
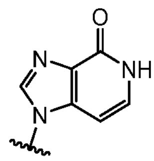
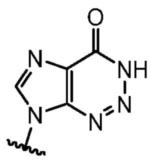
(I')

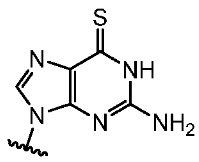
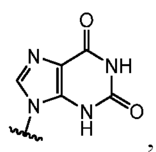
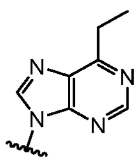
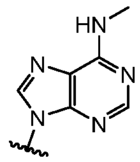
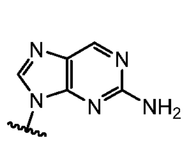
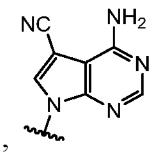
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  ,

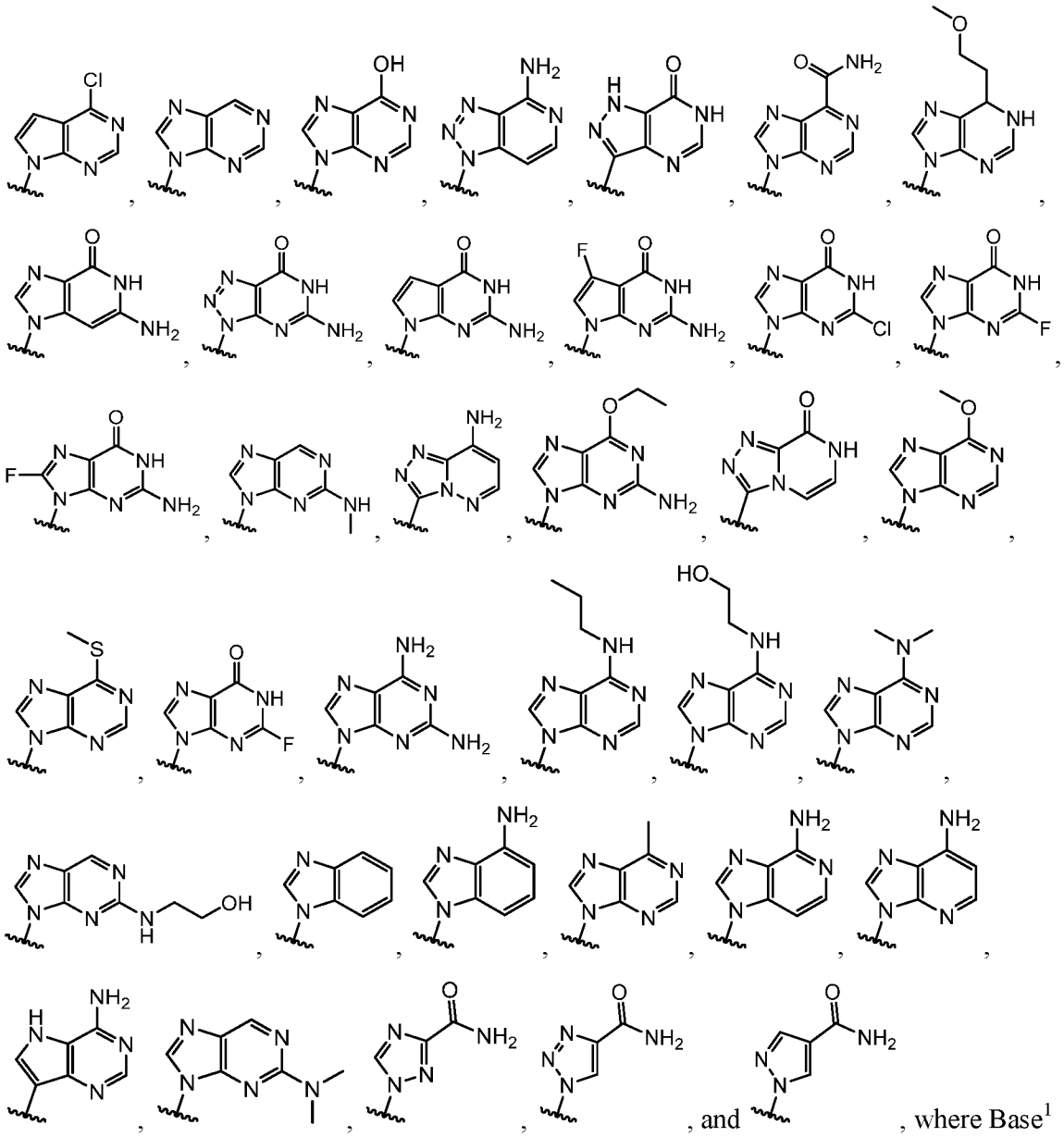
 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

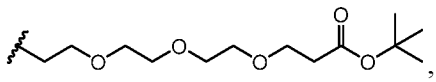
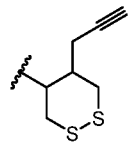
 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,

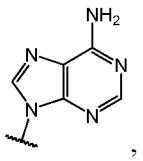
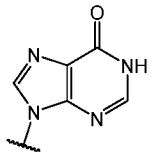
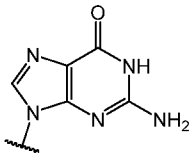
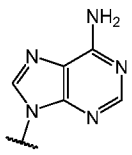
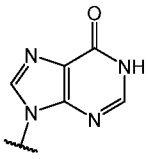
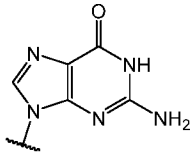
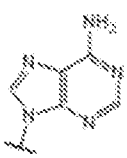
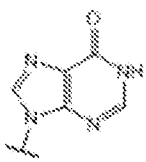
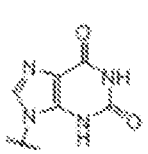
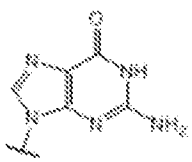


and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each independently selected from the group consisting of O, and S; X^b and X^{b1} are each independently selected from the group consisting of O, and S; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9; X^d and X^{d1} are each independently selected from the group

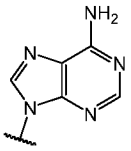
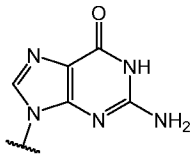
consisting of O and S; R^1 and R^{1a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^1 and R^{1a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^2 and R^{2a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^3 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^4 and R^{4a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^5 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, NR^9R^9, and N_3; R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^6 and R^{6a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6

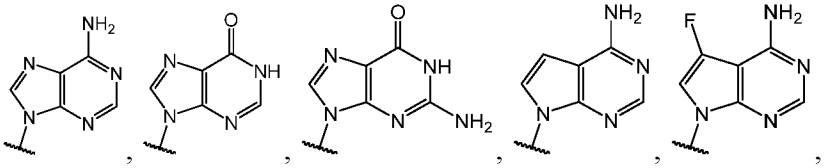
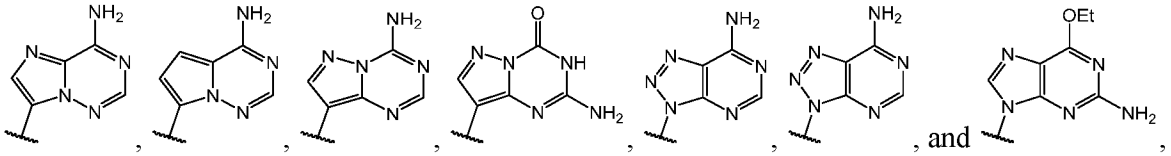
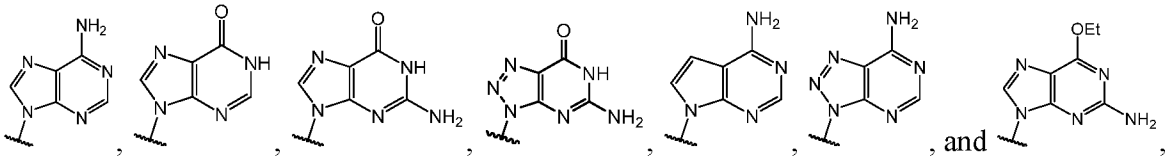
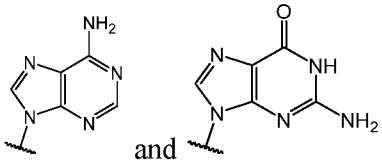
haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^7 and R^{7a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^7 and R^{7a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^8 and R^{8a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^8 and R^{8a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,  , and  , where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl; optionally R^{1a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^{1a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position; optionally R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^{2a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position; optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position; optionally R^4 and R^5 are connected to form are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position; optionally R^5

and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position; optionally R^7 and R^8 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene; and optionally R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene.

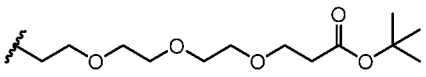
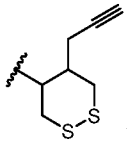
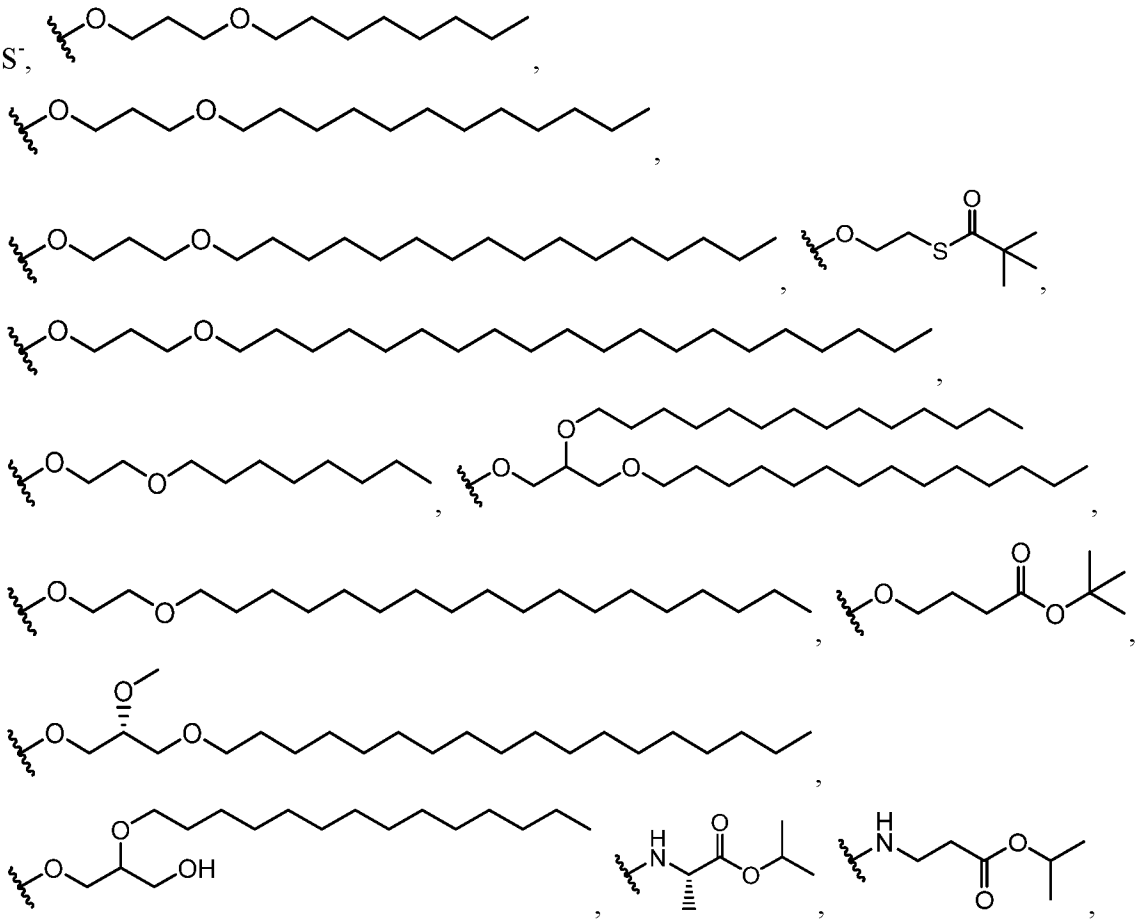
[0087] In specific aspects of this embodiment, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, R^6 and R^{6a} are each H, R^7 and R^{7a} are each H, R^8 and R^{8a} are each H, and $Base^1$ and $Base^2$ are each selected from the group consisting of  ,  , and  , R^5 and R^3 are not both selected from the group consisting of H, F and OH. That is, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, R^6 and R^{6a} are each H, R^7 and R^{7a} are each H, R^8 and R^{8a} are each H, and $Base^1$ and $Base^2$ are each selected from the group consisting of  ,  , and  , either only one of R^5 and R^3 is selected from the group consisting of H, F, and OH, or neither R^5 and R^3 is selected from the group consisting of H, F, and OH. In specific instances of this aspect, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH, X^d and X^{d1} are each O or S, R^1 and R^{1a} are each H, R^2 is H, R^6 and R^{6a} are each H, R^7 and R^{7a} are each H, R^8 and R^{8a} are each H, and $Base^1$ and $Base^2$ are each selected from the group consisting of  ,  ,  , and  , R^5 and R^3 are not both selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where said C_1-C_6 alkyl,

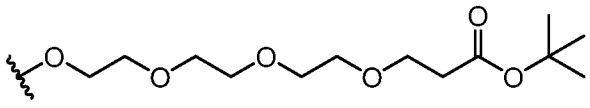
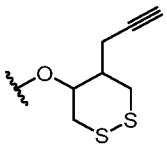
C_2-C_6 alkenyl and C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I and OH.

[0088] In further aspects of this embodiment, when $Base^1$ and $Base^2$ are each selected from the group consisting of  and  , and R^{2a} is F and R^5 is F, at least one of X^c and X^{c1} is SR^9.

[0089] In aspects of this embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  , and , where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$. In particular instances, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  , and , where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$. In more particular instances, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  and , where $Base^1$ and $Base^2$ each may be independently substituted

by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$. In this aspect, all other groups are as provided in the formula (I') above.

[0090] In aspects of this embodiment, X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9, where each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,  , and  where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl. In particular instances, X^c and X^{c1} are each independently selected from the group consisting of O^-, S^-, 

 , and  . In all instances of this aspect, all other groups are as provided in the formula (I') above or in the aspect described above.

[0091] In aspects of this embodiment, R^1 and R^{1a} are each H. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0092] In aspects of this embodiment, R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^2 and R^{2a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3. In particular instances, R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, CF_3, CH_3, CH_2OH, and CH_2CH_3. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0093] In aspects of this embodiment, R^3 is selected from the group consisting H, F, Cl, I, Br, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3. In particular instances, R^3 are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, CF_3, CH_3, CH_2OH, and CH_2CH_3. In more particular instances, R^3 is selected from NH_2 and N_3. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0094] In aspects of this embodiment, R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^4 and R^{4a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3. In particular instances, R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, CF_3, CH_3, CH_2OH, and CH_2CH_3. In more particular instances, R^4 and R^{4a} are each F. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0095] In aspects of this embodiment, R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, NR^9R^9, and N_3. In particular instances, R^5 are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, CF_3, CH_3, CH_2OH, and CH_2CH_3. In even more

particular instances, R^5 is selected from NH_2 and N_3. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0096] In aspects of this embodiment, R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0097] In aspects of this embodiment, R^7 and R^{7a} are each independently selected from the group consisting of H and C_1-C_6 alkyl. In particular instances, R^7 and R^{7a} are each independently selected from the group consisting of H and CH_3. In more particular instances, R^{7a} is CH_3. In additional instances, R^7 and R^{7a} are each H. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0098] In aspects of this embodiment, R^8 and R^{8a} are each independently selected from the group consisting of H and C_1-C_6 alkyl. In particular instances, R^8 and R^{8a} are each independently selected from the group consisting of H and CH_3. In more particular instances, R^{8a} is CH_3. In additional instances, R^8 and R^{8a} are each H. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0099] In aspects of this embodiment, R^{1a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^{1a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0100] In aspects of this embodiment, R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^{2a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

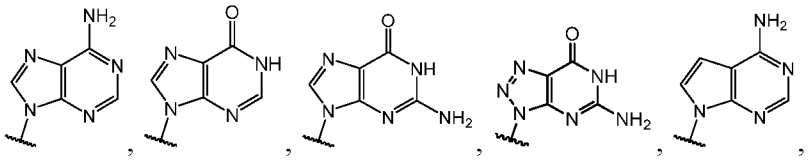
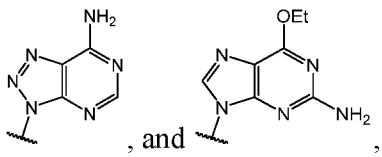
[0101] In aspects of this embodiment, R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, and -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0102] In aspects of this embodiment, R^4 and R^5 are connected by C_1-C_6 alkylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

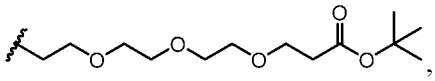
[0103] In aspects of this embodiment, R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0104] In aspects of this embodiment, R^7 and R^8 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

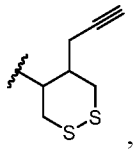
[0105] In aspects of this embodiment, R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene. In this aspect, all other groups are as provided in the formula (I') above or in the aspects described above.

[0106] In aspects of this embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  , and , where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl), S(C_{1-3} alkyl), S(C_{3-6} cycloalkyl), NH(C_{1-3} alkyl), NH(C_{3-6} cycloalkyl), N(C_{1-3} alkyl)$_2$, and N(C_{3-6} cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each independently selected from the group consisting of O and S; X^b and X^{b1} are each independently selected from the group consisting of O and S; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each H; R^2 and R^{2a} are each

independently selected from the group consisting of H, F, Cl, Br, I, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^2 and R^{2a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^4 and R^{4a} are each independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^4 and R^{4a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, NR^9R^9, and N_3; R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, and C_1-C_6 haloalkyl, where said R^6 and R^{6a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^7 and R^{7a} are each H; R^8 and R^{8a} are each H; each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,

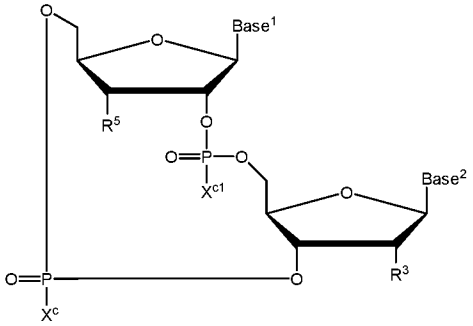


, and



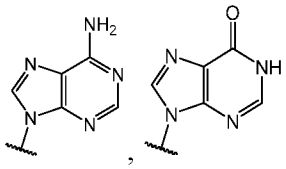
, where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl; optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, and -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position or optionally R^4 and R^5 are connected by C_1-C_6 alkylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position. In all instances of this aspect, all other groups are as provided in the formula (I') above.

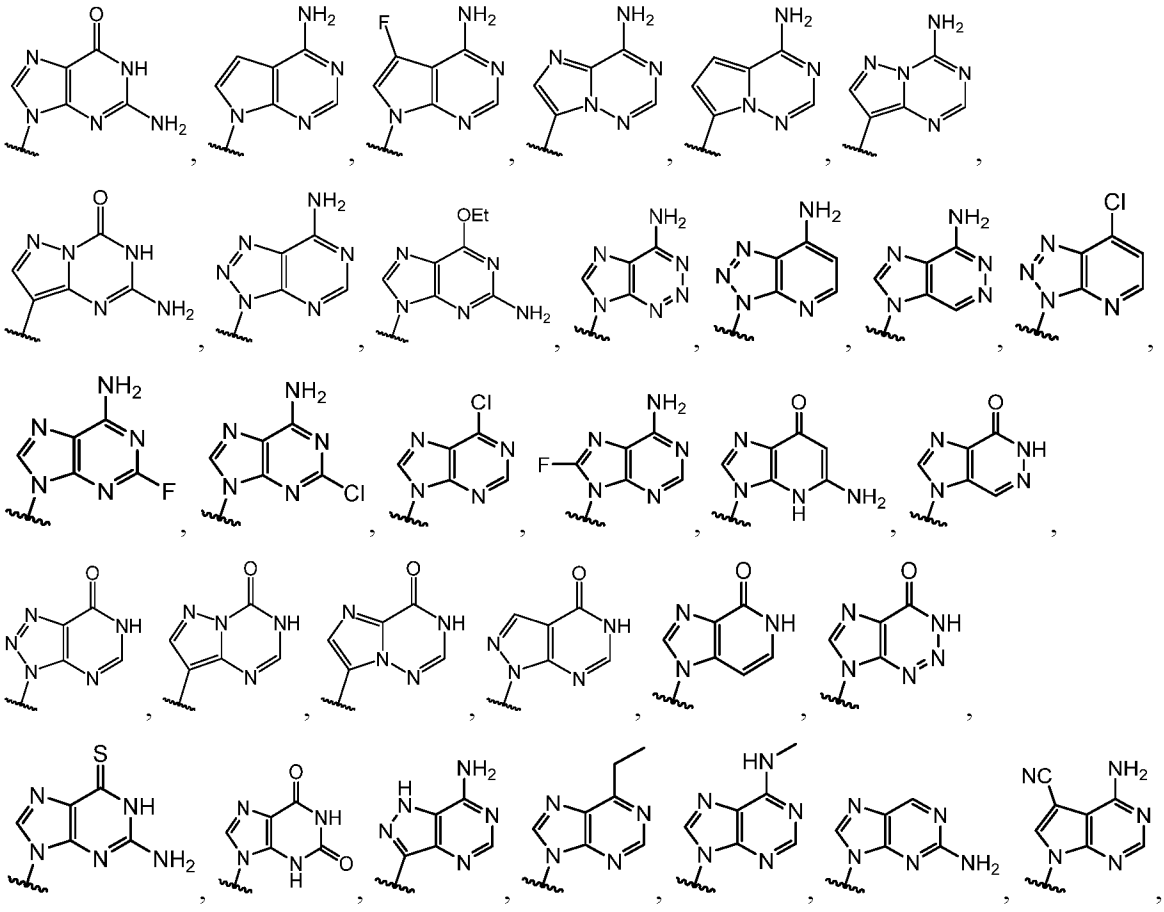
[0107] In aspects of this embodiment, the compound of formula (I') is a compound of formula (I'a):

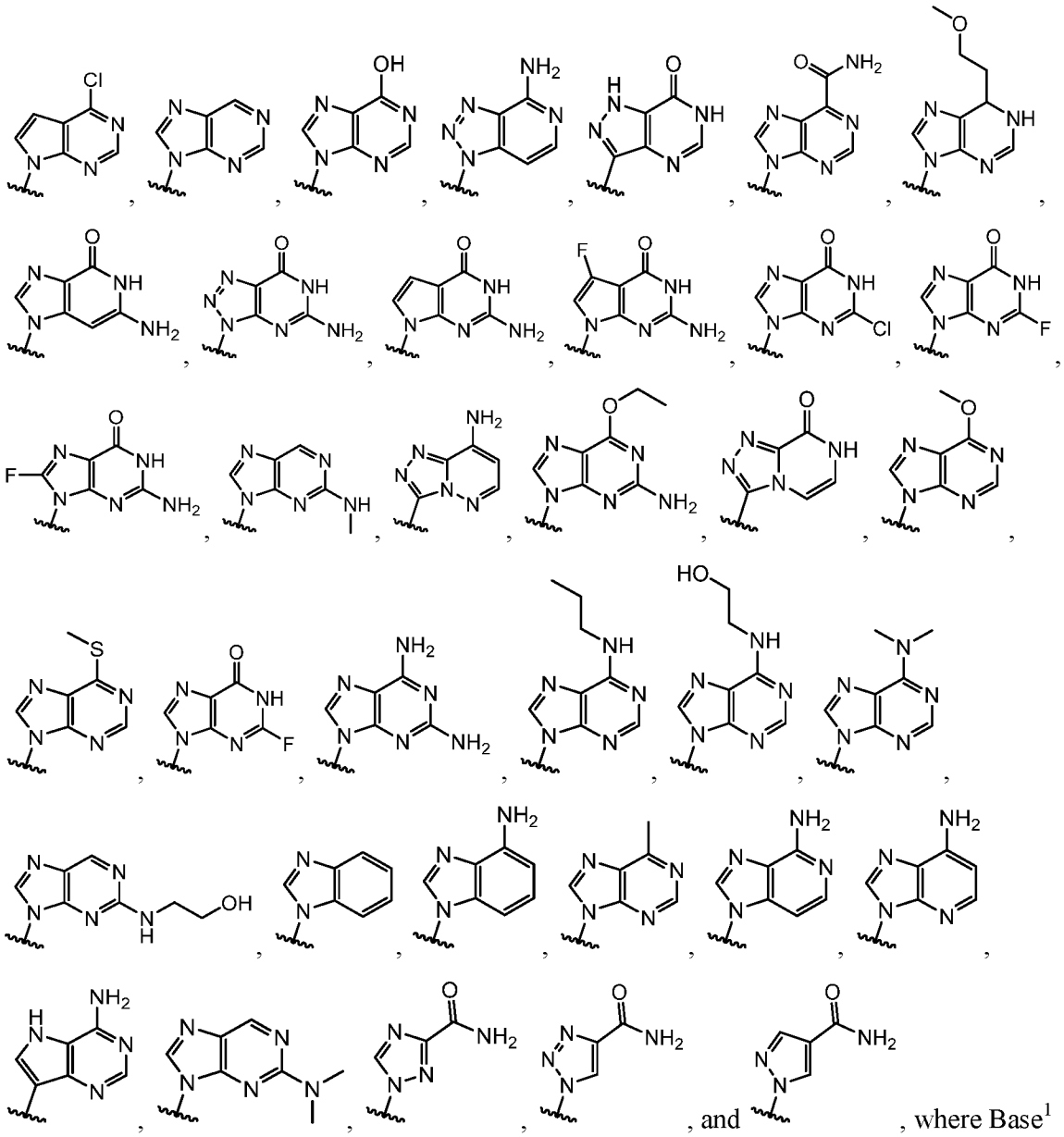


(I'a)

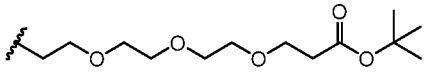
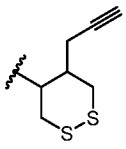
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of



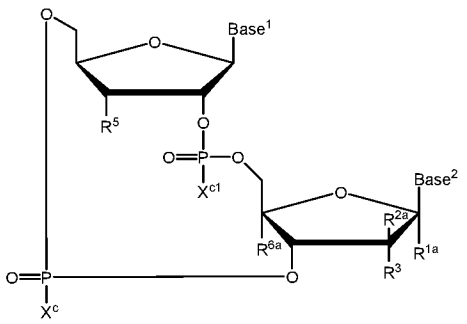




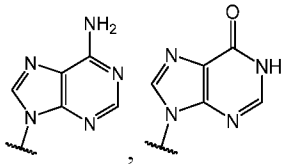
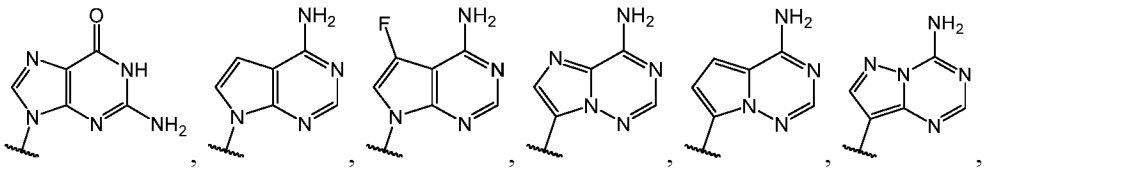
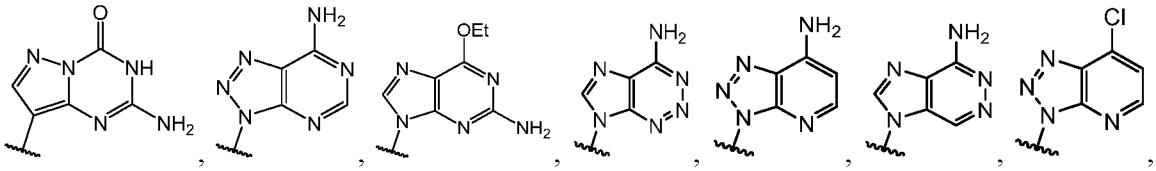
and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9; R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, and OH; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2,

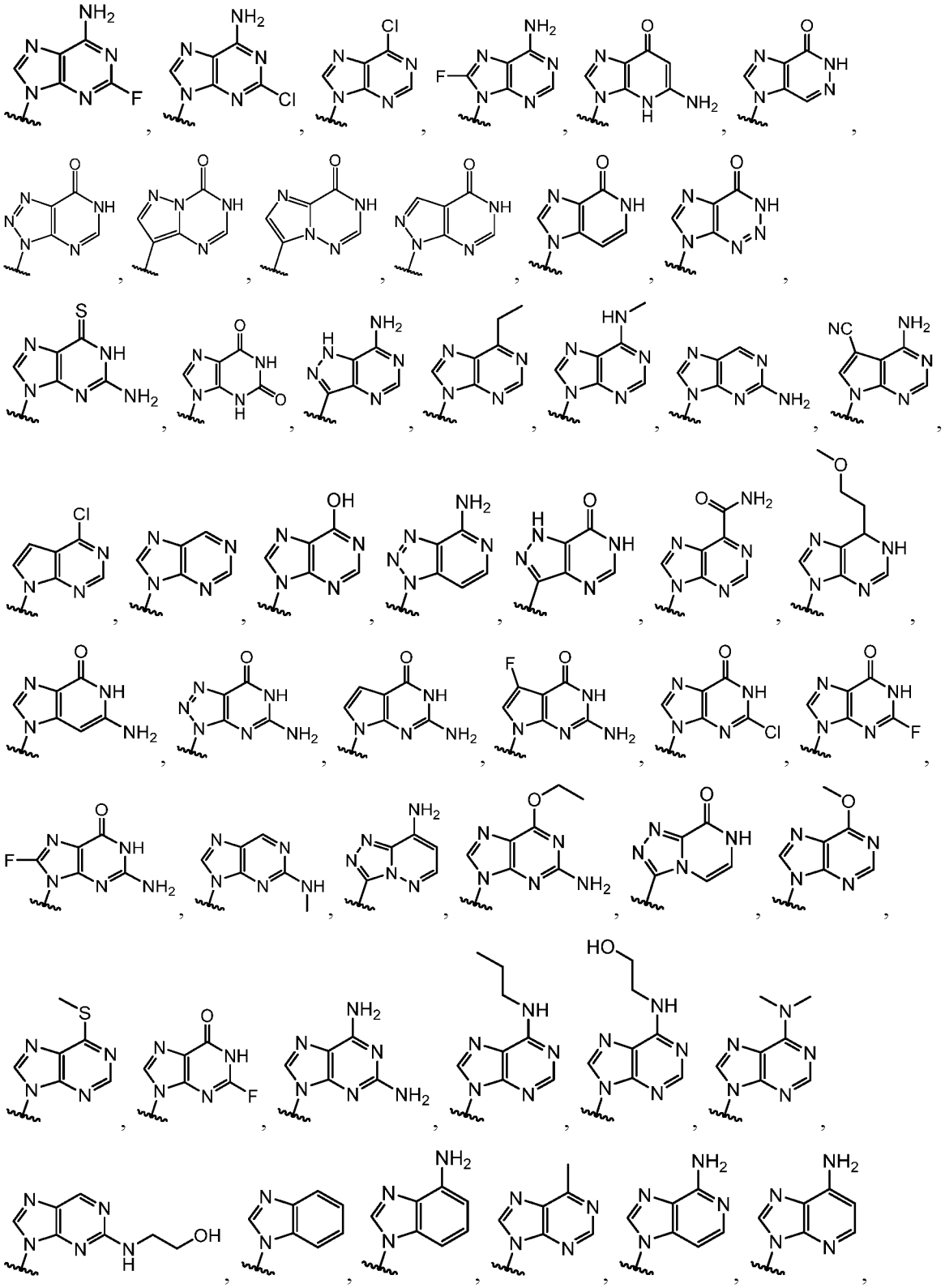
N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, and OH; R^3 and R^5 are not both selected from the group consisting of: OH, R^5 C_1-C_6 alkyl substituted with OH, or C_1-C_6 haloalkyl substituted with OH; and each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,  , and  , where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl. In all instances of this aspect, all other groups are as provided in the formula (I') above.

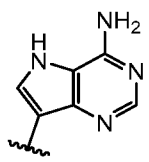
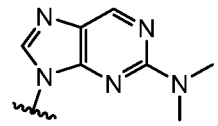
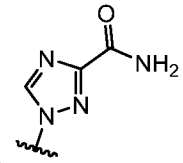
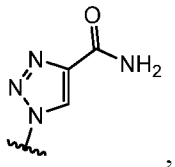
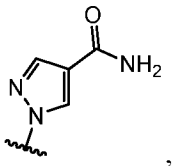
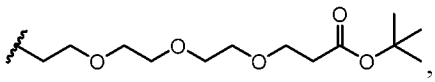
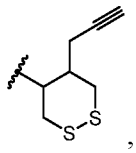
[0108] In aspects of this embodiment, the compound of formula (I') is a compound of formula (I'b):



(I'b)

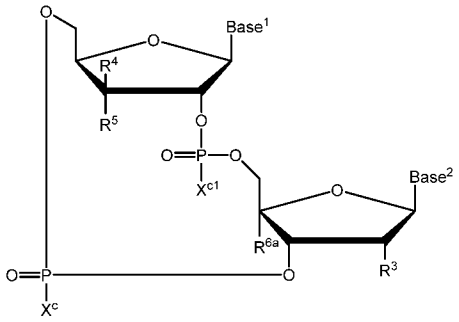
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  ,  ,








, and , where Base[1] and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9; R^{1a} is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^{1a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^{2a} is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^{2a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, and OH; R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, and OH; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, and OH; R^3 and R^5 are not both selected from the group consisting of OH, C_1-C_6 alkyl substituted with OH, and C_1-C_6 haloalkyl substituted with OH; R^{6a} is selected from the group consisting of H, F, Cl, Br, I, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl; each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,  , and  , where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl; and optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, and -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene,

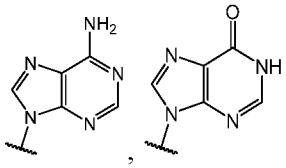
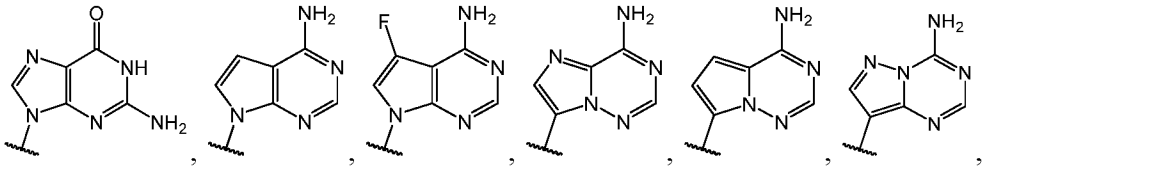
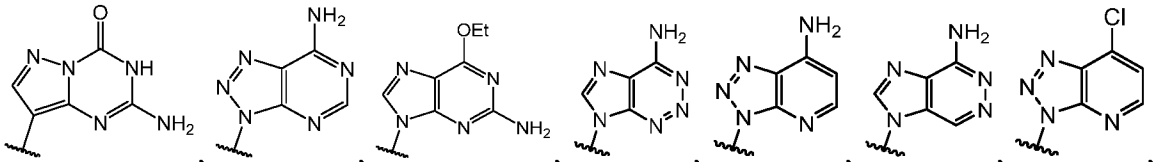
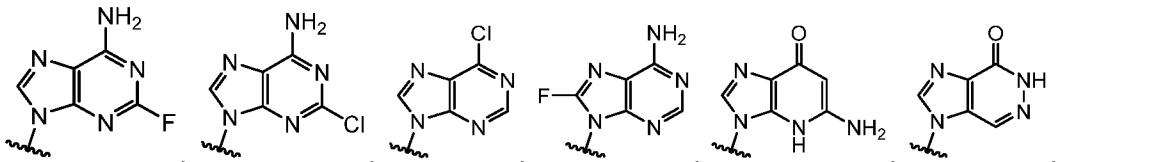
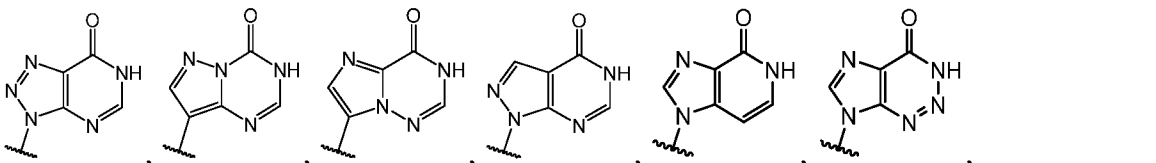
-O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position. In this aspect, all other groups are as provided in the formula (I') above.

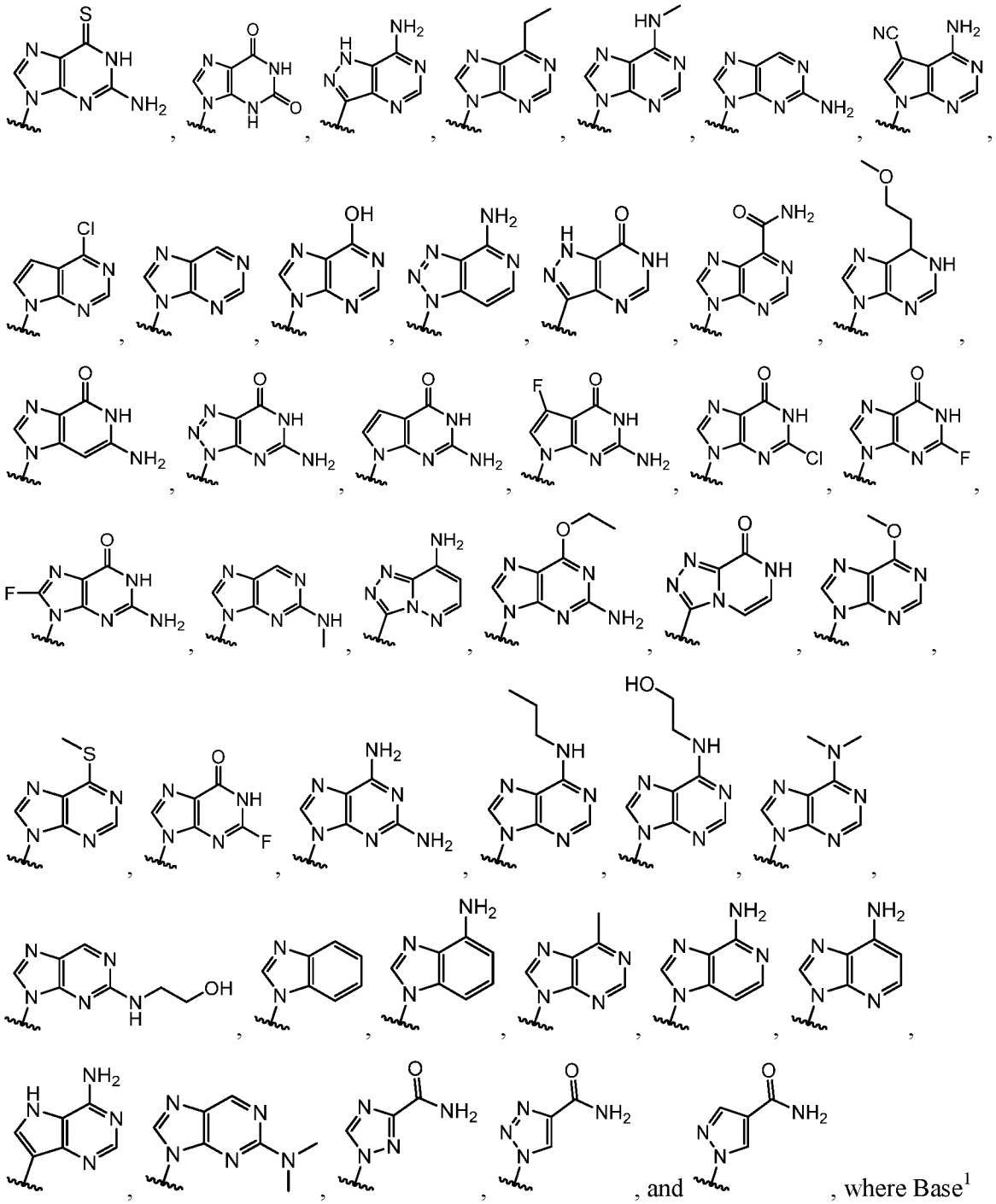
[0109] In aspects of this embodiment, the compound of formula (I') is a compound of formula (I'c):



(I'c)

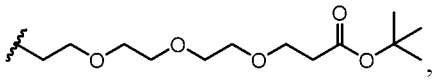
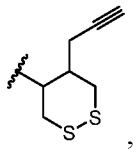
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of

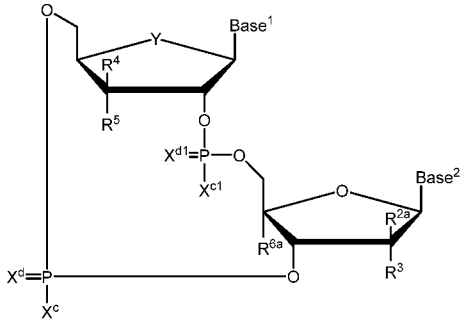


, and , where Base[1] and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9; R^3 is selected from the group

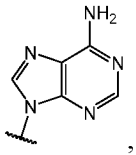
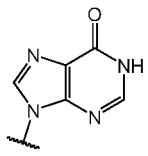
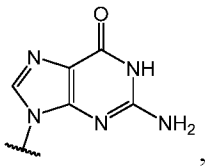
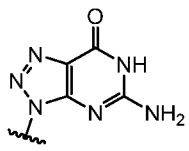
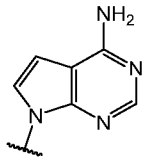
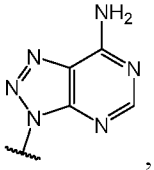
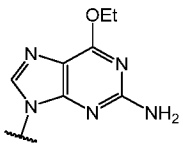
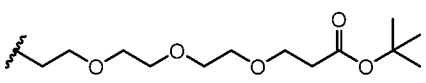
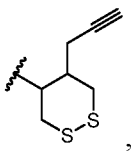
consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, and OH; R^4 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^4 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, and OH; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, and OH; R^{6a} is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^{6a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, and OH; each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,

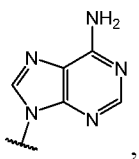
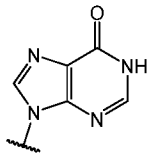
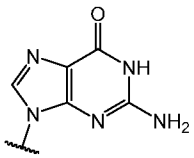
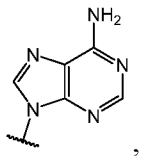
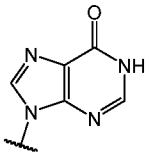
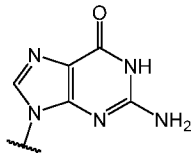
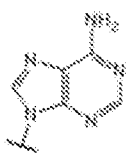
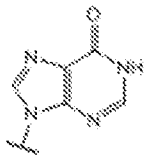
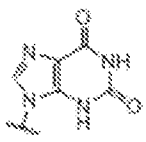
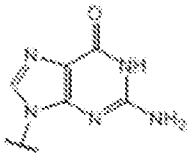

, and

, where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl; and optionally R^4 and R^5 are connected by C_1-C_6 alkylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position. In this aspect, all other groups are as provided in the formula (I') of the second embodiment above.

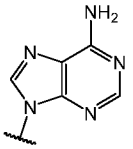
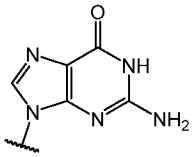
[0110] In another embodiment, the CDN STING agonist is selected from cyclic di-nucleotide compounds of formula (I"):



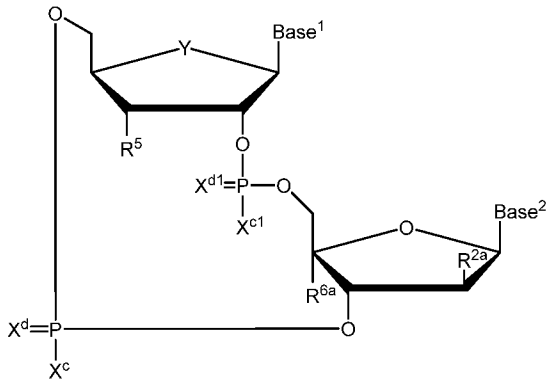
(I")

or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  ,  ,  ,  ,  , and  ; Y is selected from the group consisting of -O- and -S-; X^c and X^{c1} are each independently selected from the group consisting of OR^9 and SR^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^{2a} is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; R^4 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; R^{6a} is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,  , and  , where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl; and optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position.

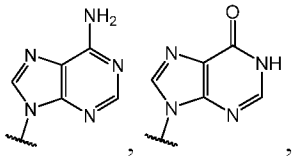
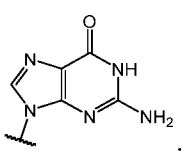
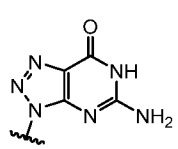
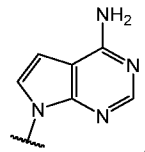
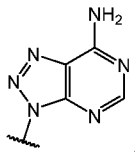
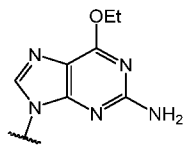
[0111] In specific aspects of this embodiment, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, R^6 and R^{6a} are each H, R^7 and R^{7a} are each H, R^8 and R^{8a} are each H, and $Base^1$ and $Base^2$ are each selected from the group consisting of  ,  , and  , R^5 and R^3 are not both selected from the group consisting of H, F and OH. That is, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, R^6 and R^{6a} are each H, R^7 and R^{7a} are each H, R^8 and R^{8a} are each H, and $Base^1$ and $Base^2$ are each selected from the group consisting of  ,  , and  , either only one of R^5 and R^3 is selected from the group consisting of H, F, and OH, or neither R^5 and R^3 is selected from the group consisting of H, F, and OH. In further specific instances of this aspect, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH, X^d and X^{d1} are each O or S, R^1 and R^{1a} are each H, R^2 is H, R^6 and R^{6a} are each H, R^7 and R^{7a} are each H, R^8 and R^{8a} are each H, and $Base^1$ and $Base^2$ are each selected from the group consisting of  ,  ,  , and  , R^5 and R^3 are not both selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where said C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I and OH.

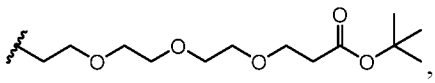
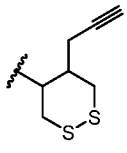
[0112] In further aspects of this embodiment, when $Base^1$ and $Base^2$ are each selected from the group consisting of  and  , and R^{2a} is F and R^5 is F, at least one of X^c and X^{c1} is SR^9.

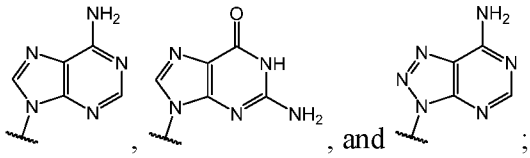
[0113] In aspects of this embodiment, the compound of formula (I") is a compound of formula (I"a):



(I"a)

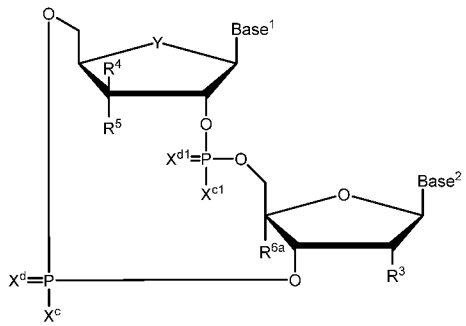
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  ,  ,  ,  , and  ; Y is selected from the group consisting of -O- and -S-; X^c and X^{c1} are each independently selected from the group consisting of OR^9 and SR^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^{2a} is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; R^{6a} is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl,

-O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; and each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,  , and  , where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl.

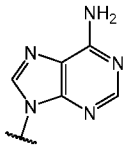
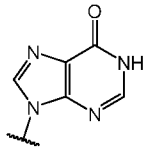
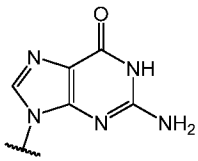
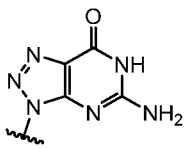
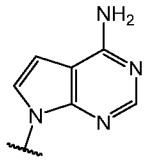
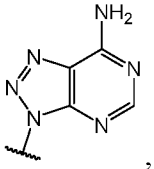
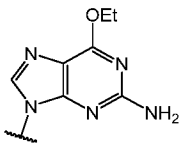
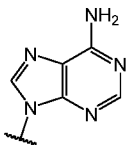
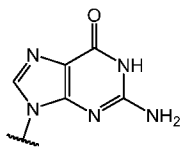
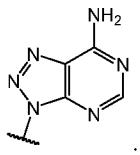
In instances of this aspect, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ; Y is selected from the group consisting of -O- and -S-; X^c and X^{c1} are each independently selected from the group consisting of OR^9 and SR^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^{2a} is F; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; R^{6a} is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; and each R^9 is independently H.

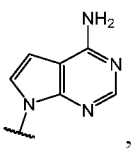
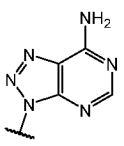
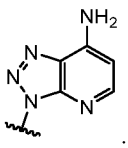
[0114] In aspects of this embodiment, the compound of formula (I") is a compound wherein R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position.

[0115] In aspects of this embodiment, the compound of formula (I") is a compound of formula (I"b):

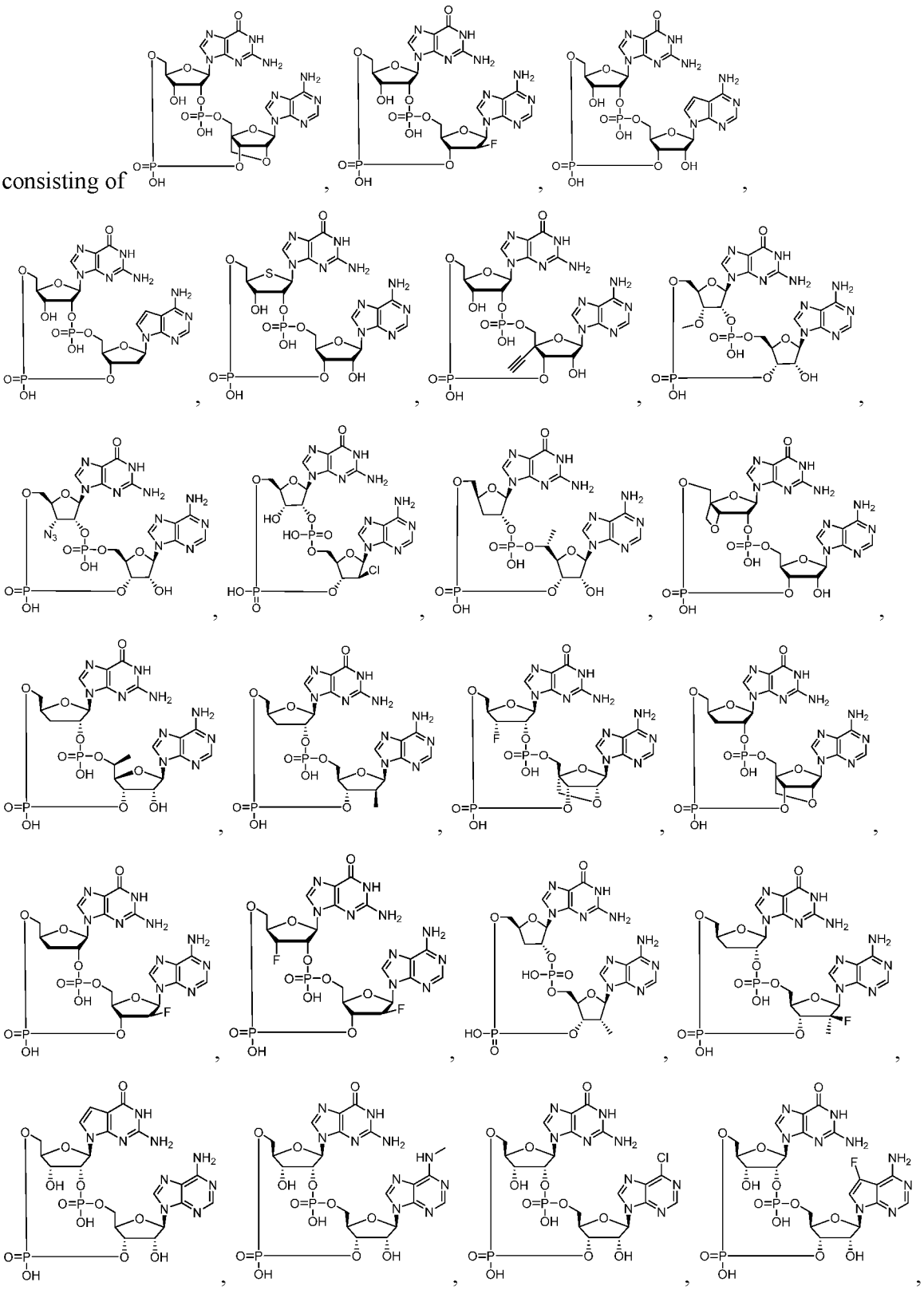


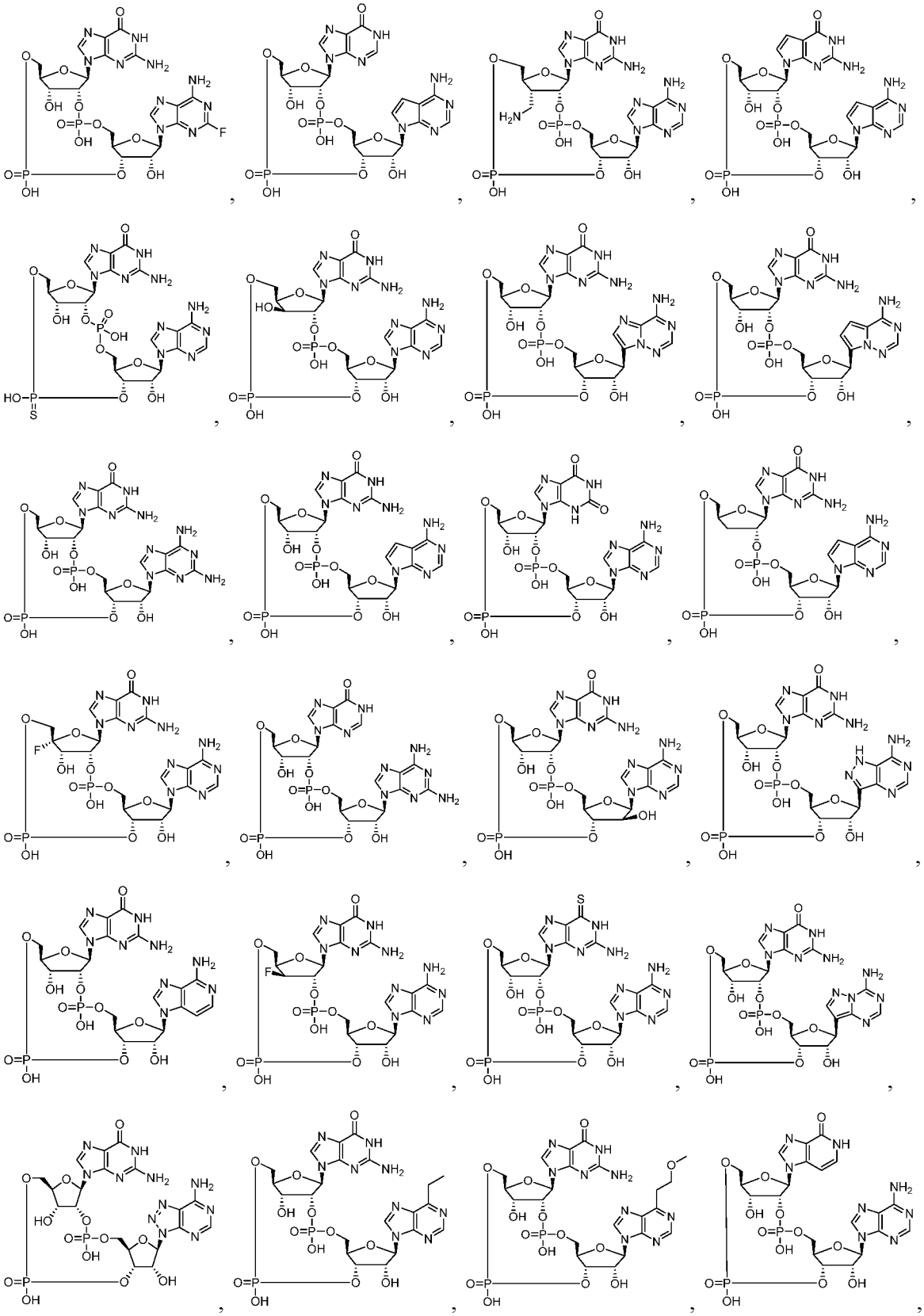
(I"b)

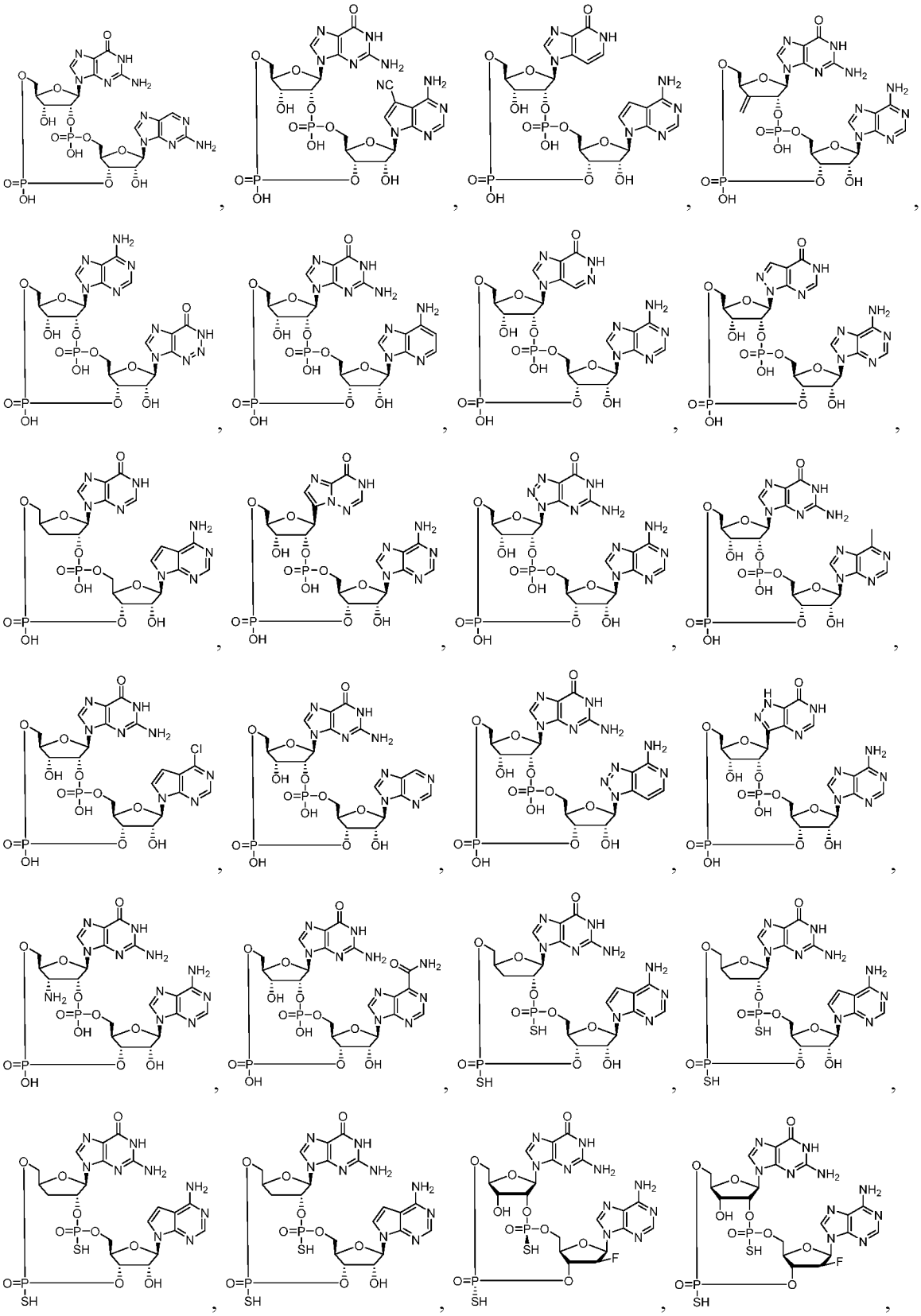
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  ,  ,  ,  ,  , and  ; Y is selected from the group consisting of -O- and -S-; X^c and X^{c1} are each independently selected from the group consisting of OR^9 and SR^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; R^4 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; R^{6a} is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl; each R^9 is independently H; and R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position. In instances of this aspect, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  , and  .

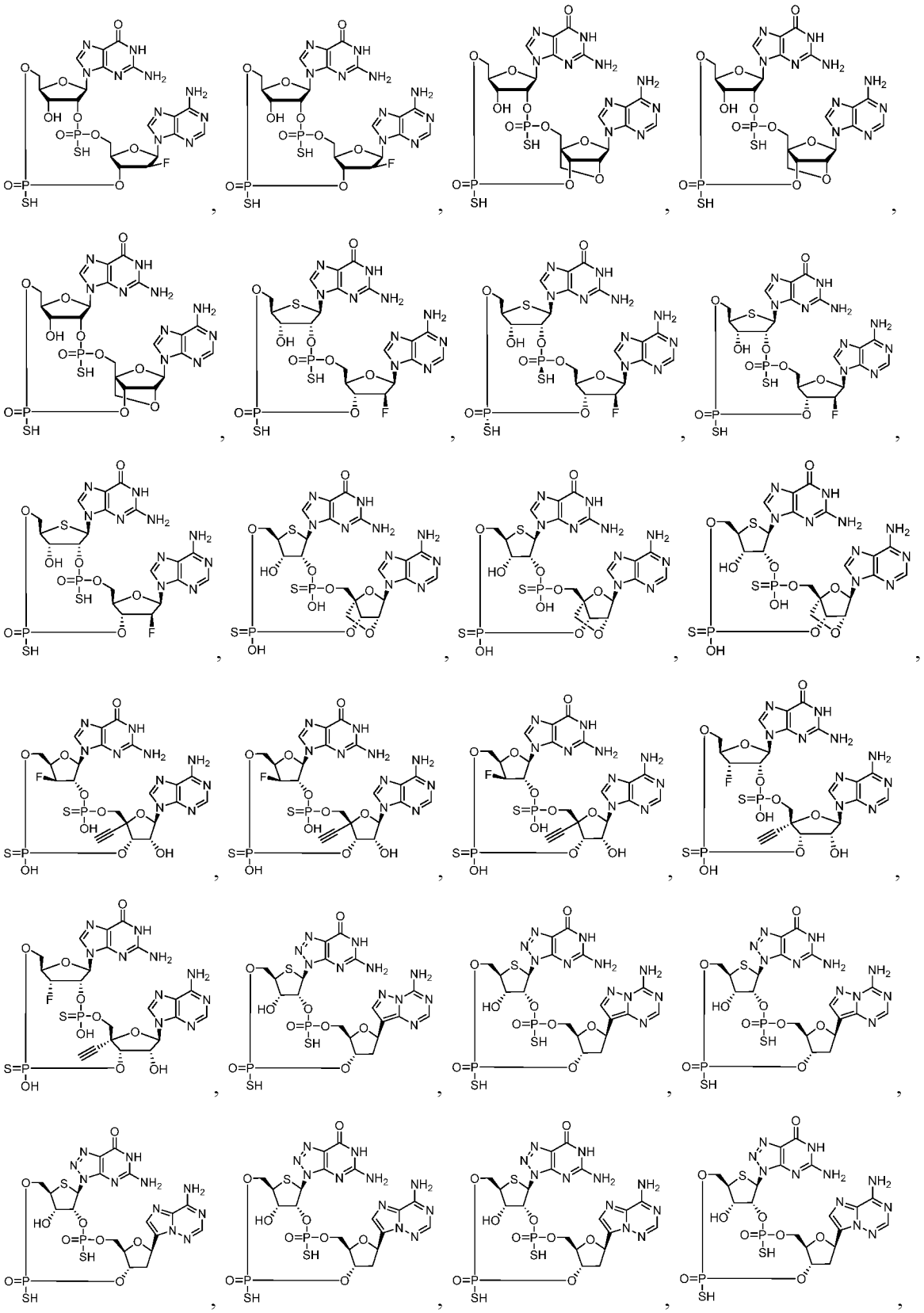
[0116] In aspects of this embodiment, the compound of formula (I") is a compound wherein at least one of $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  , and  .

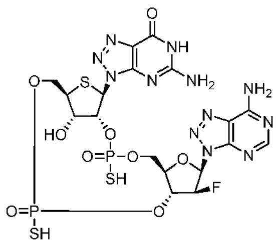
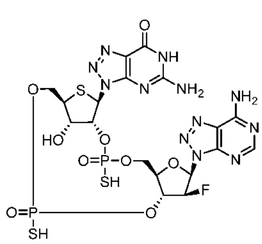
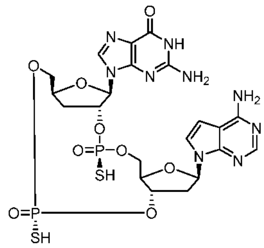
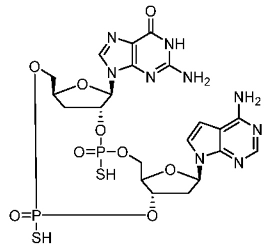
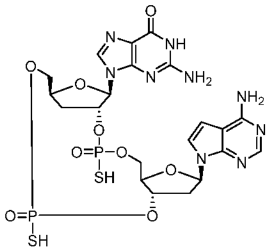
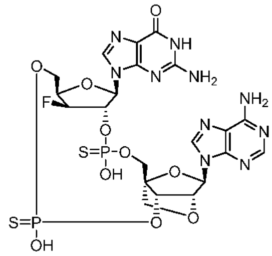
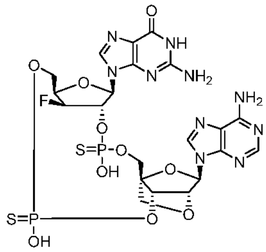
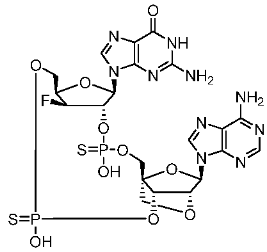
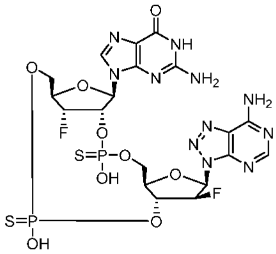
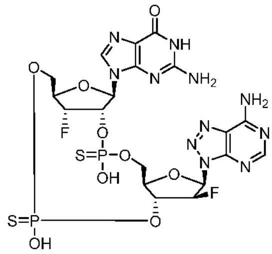
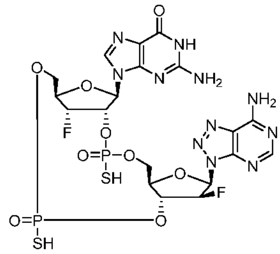
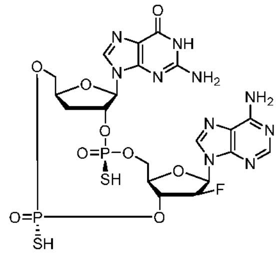
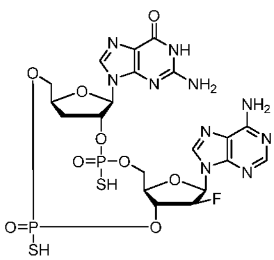
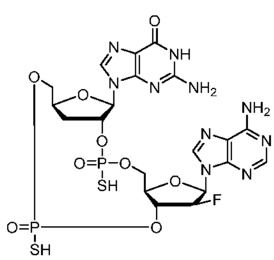
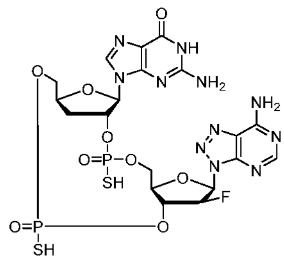
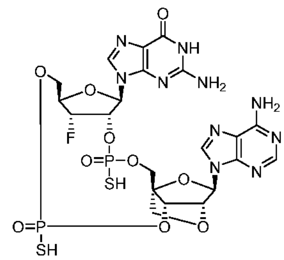
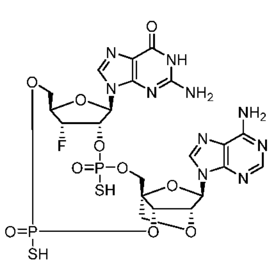
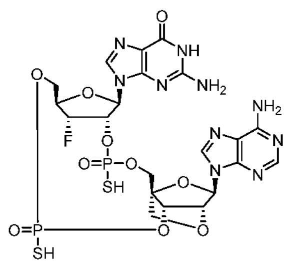
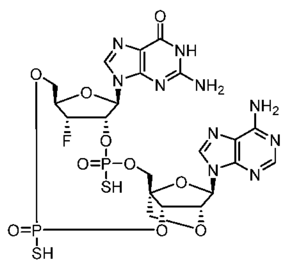
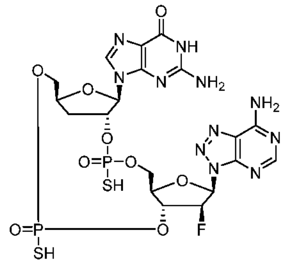
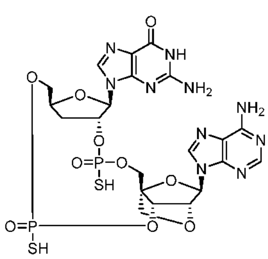
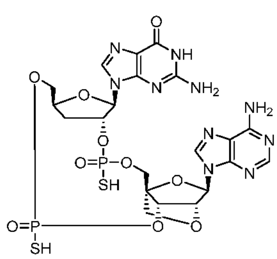
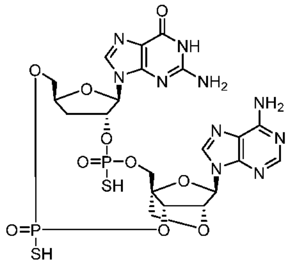
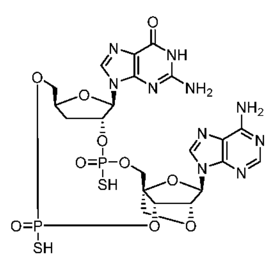
[0117] In an additional embodiment, the CDN STING agonist is selected from the group consisting of

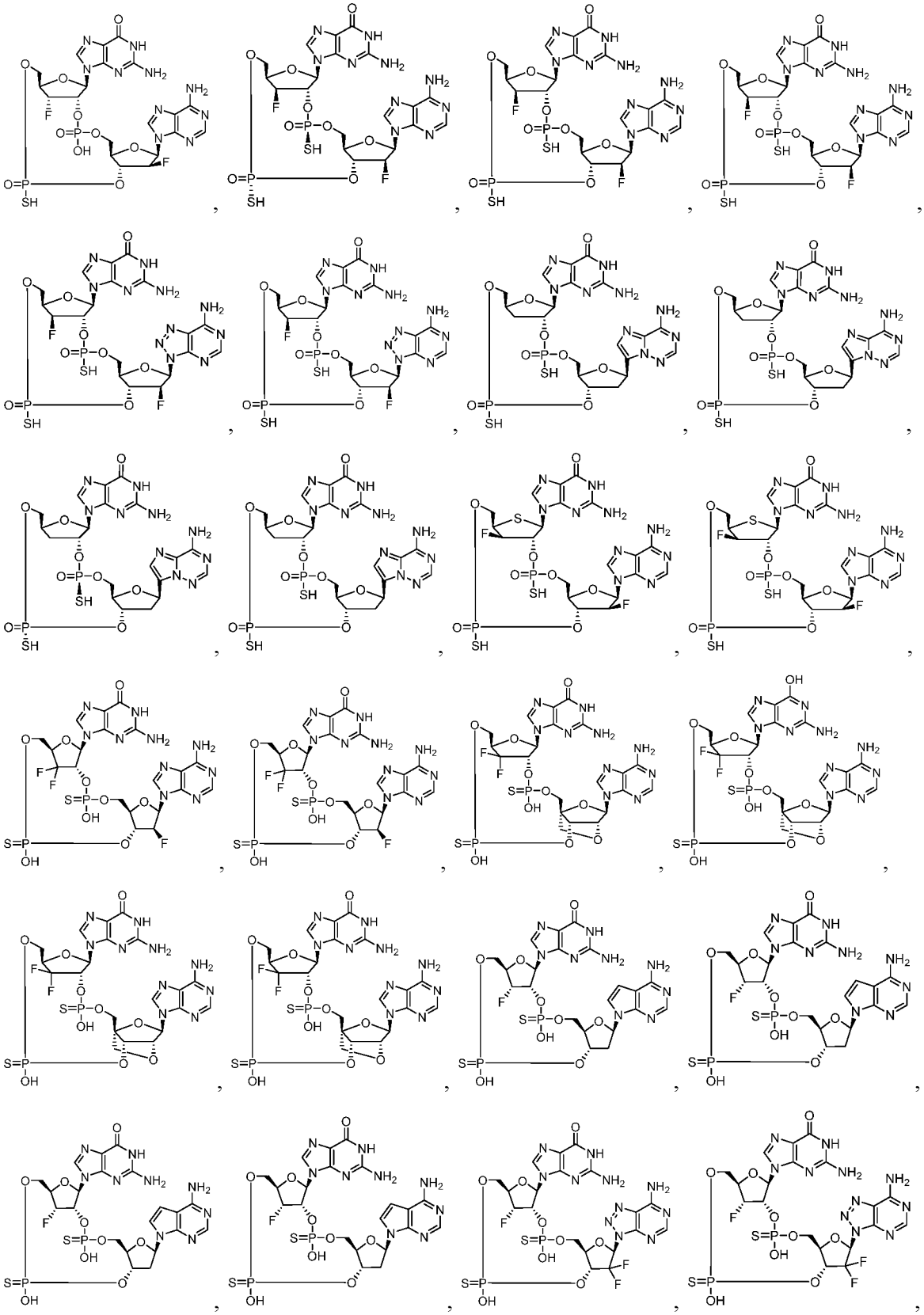


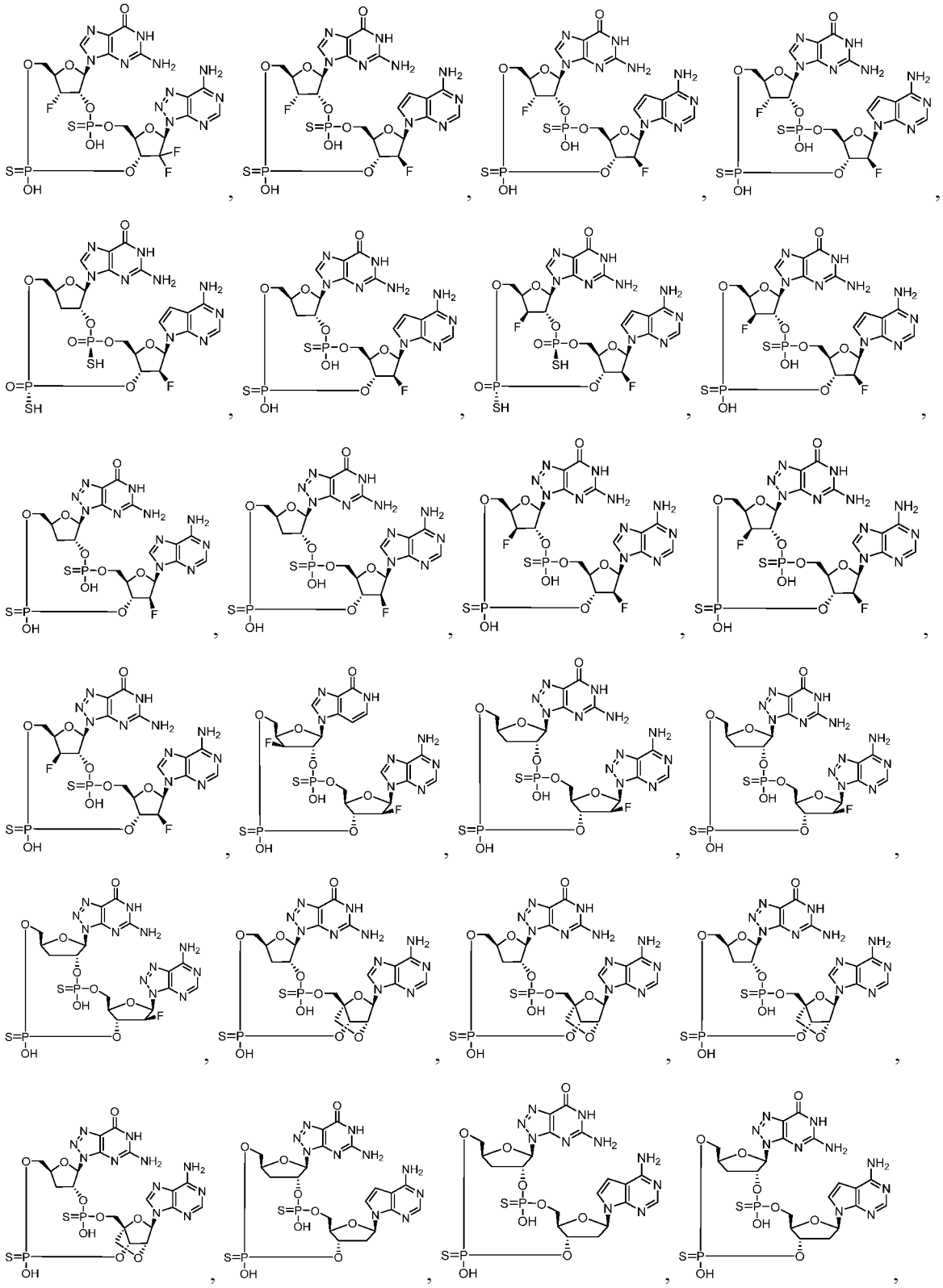


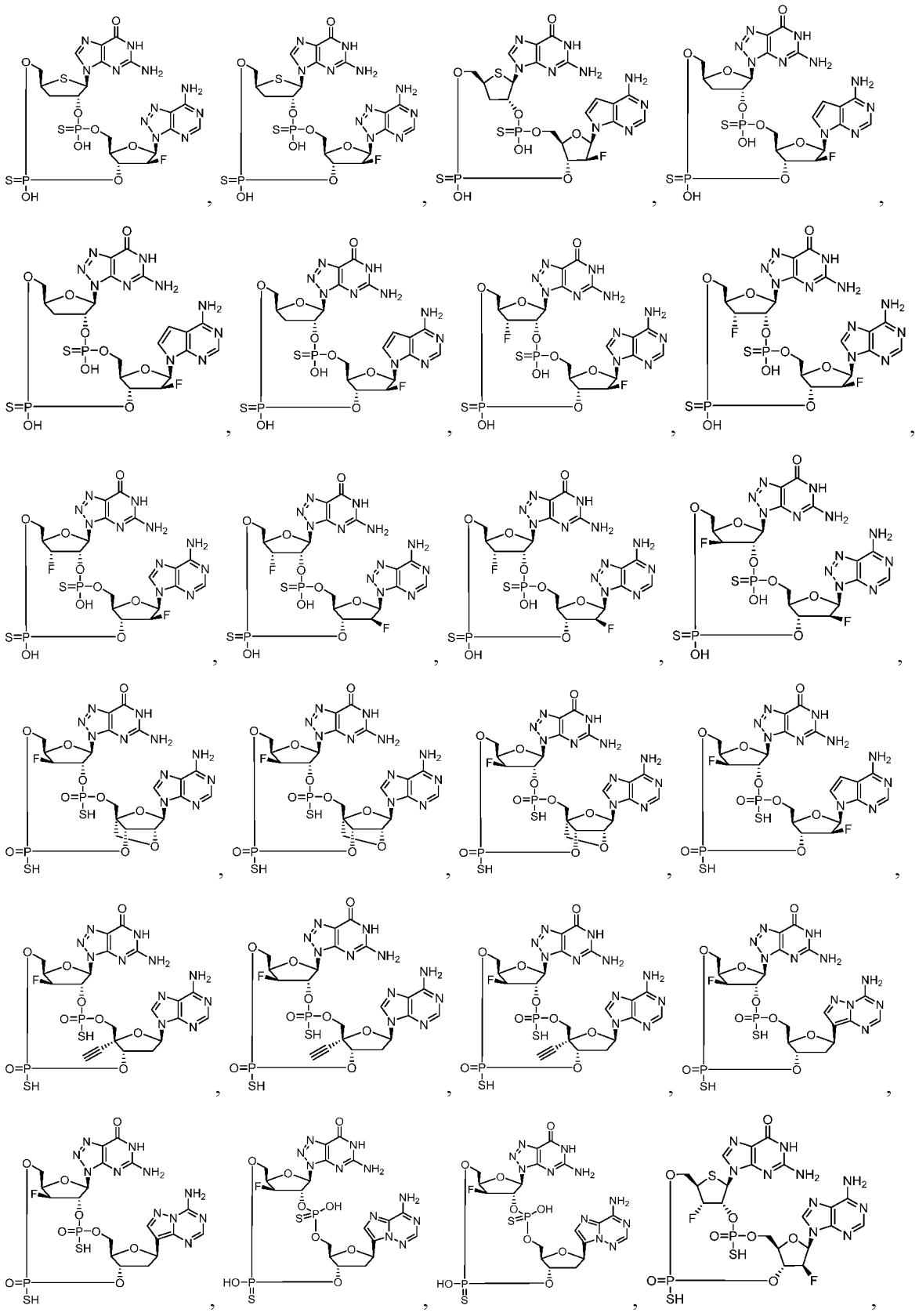


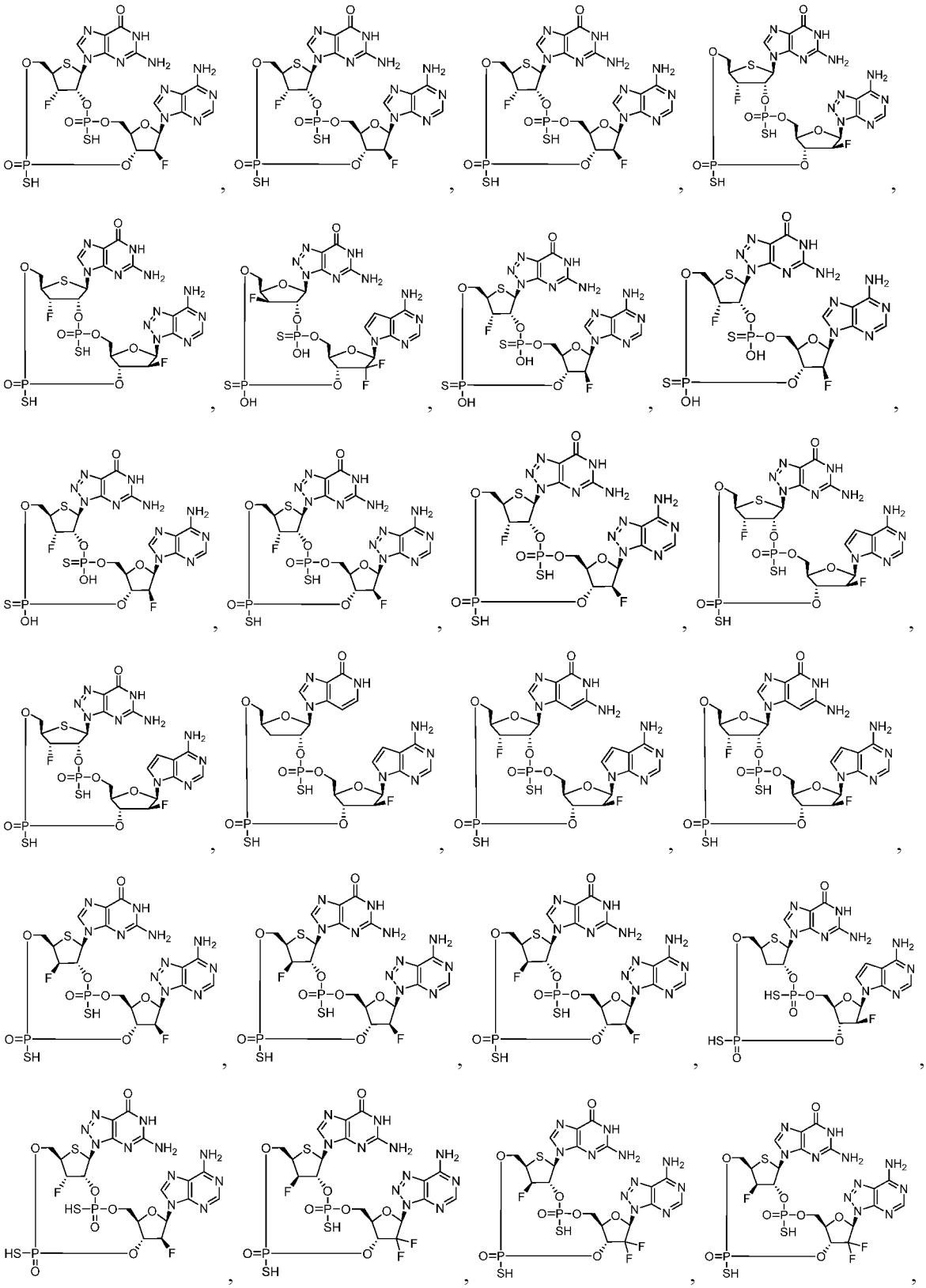


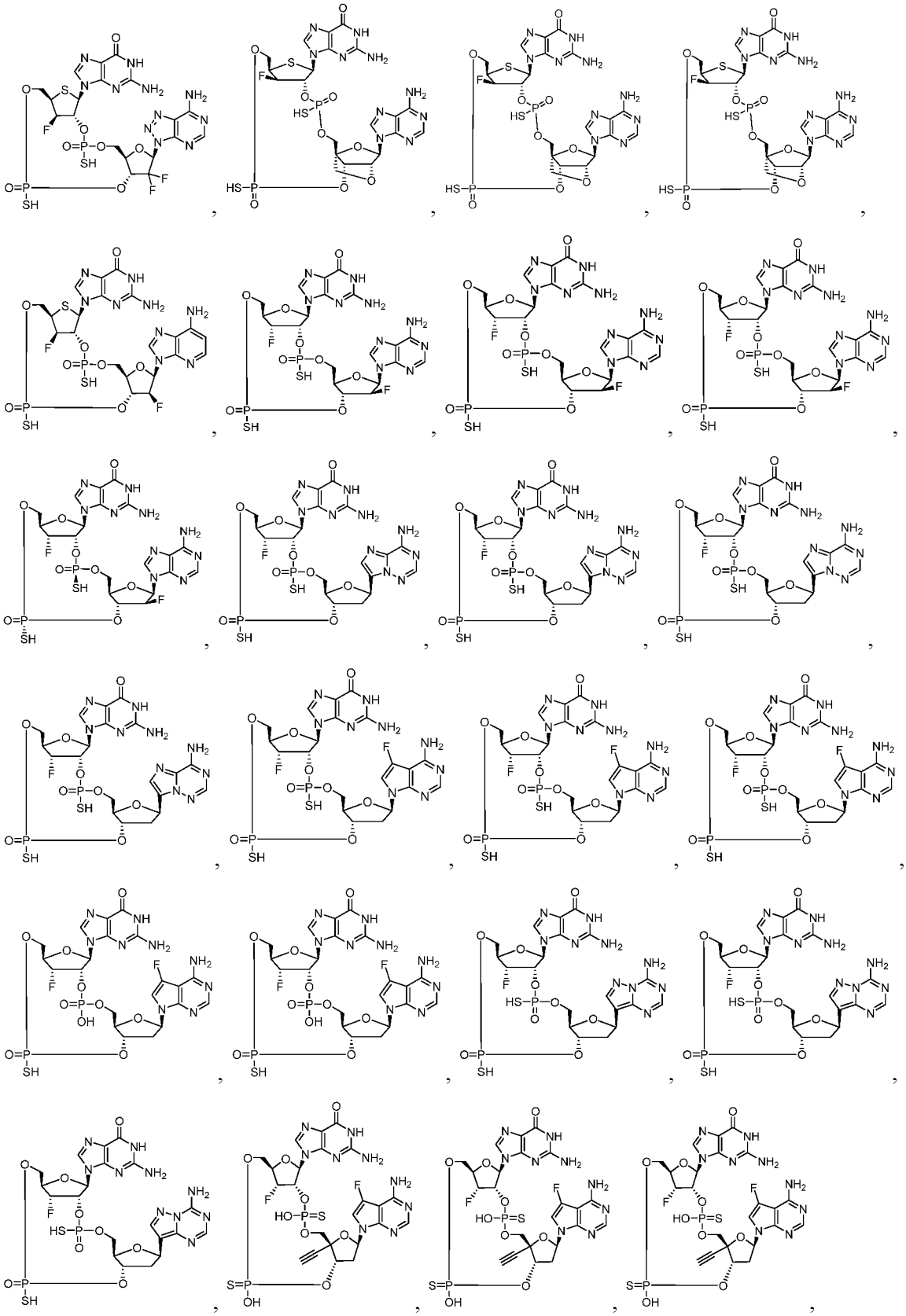
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,

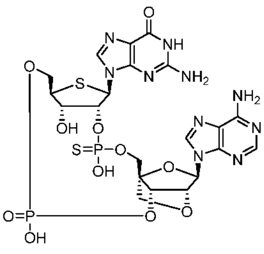
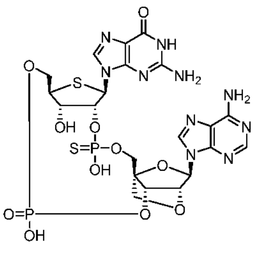
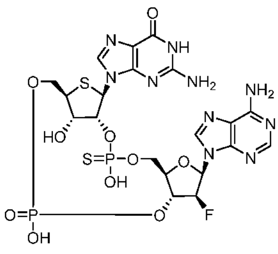
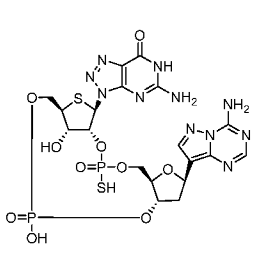


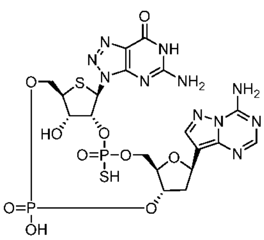
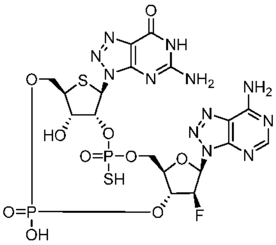
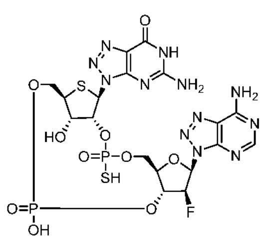
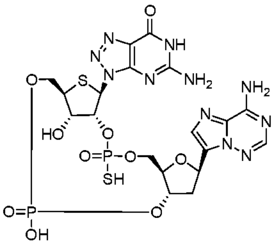


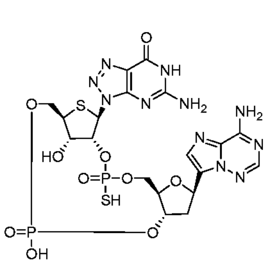
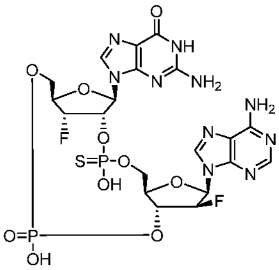
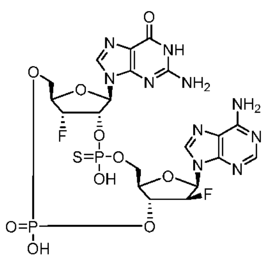
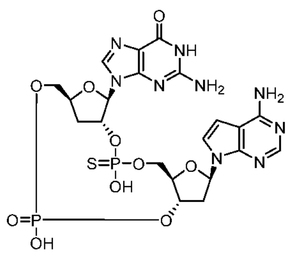


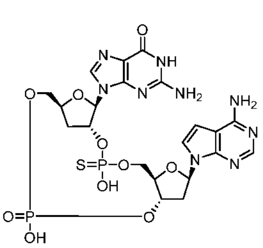
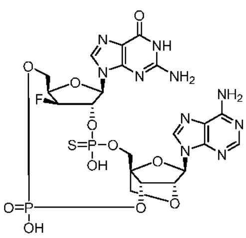
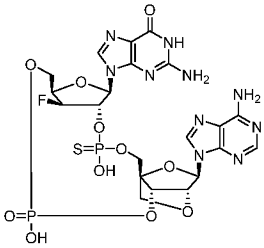
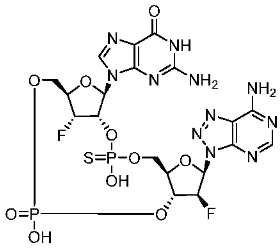


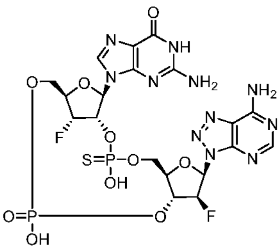
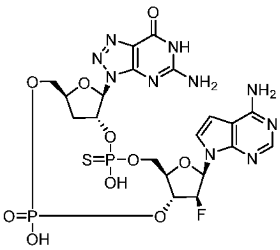
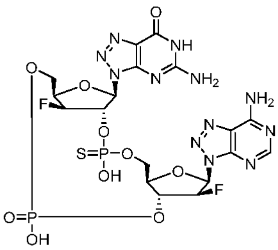
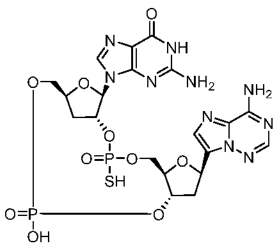


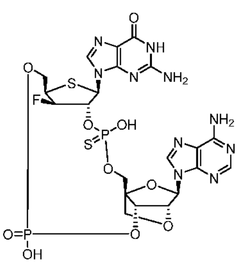
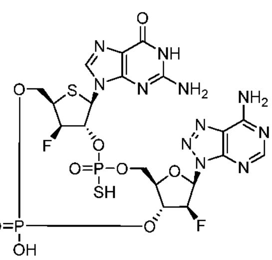
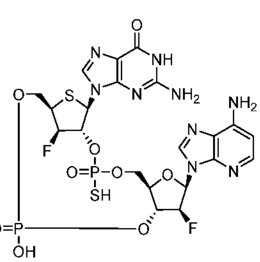
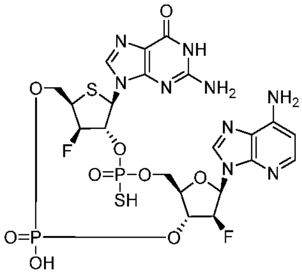
 ,
 ,
 ,
 ,

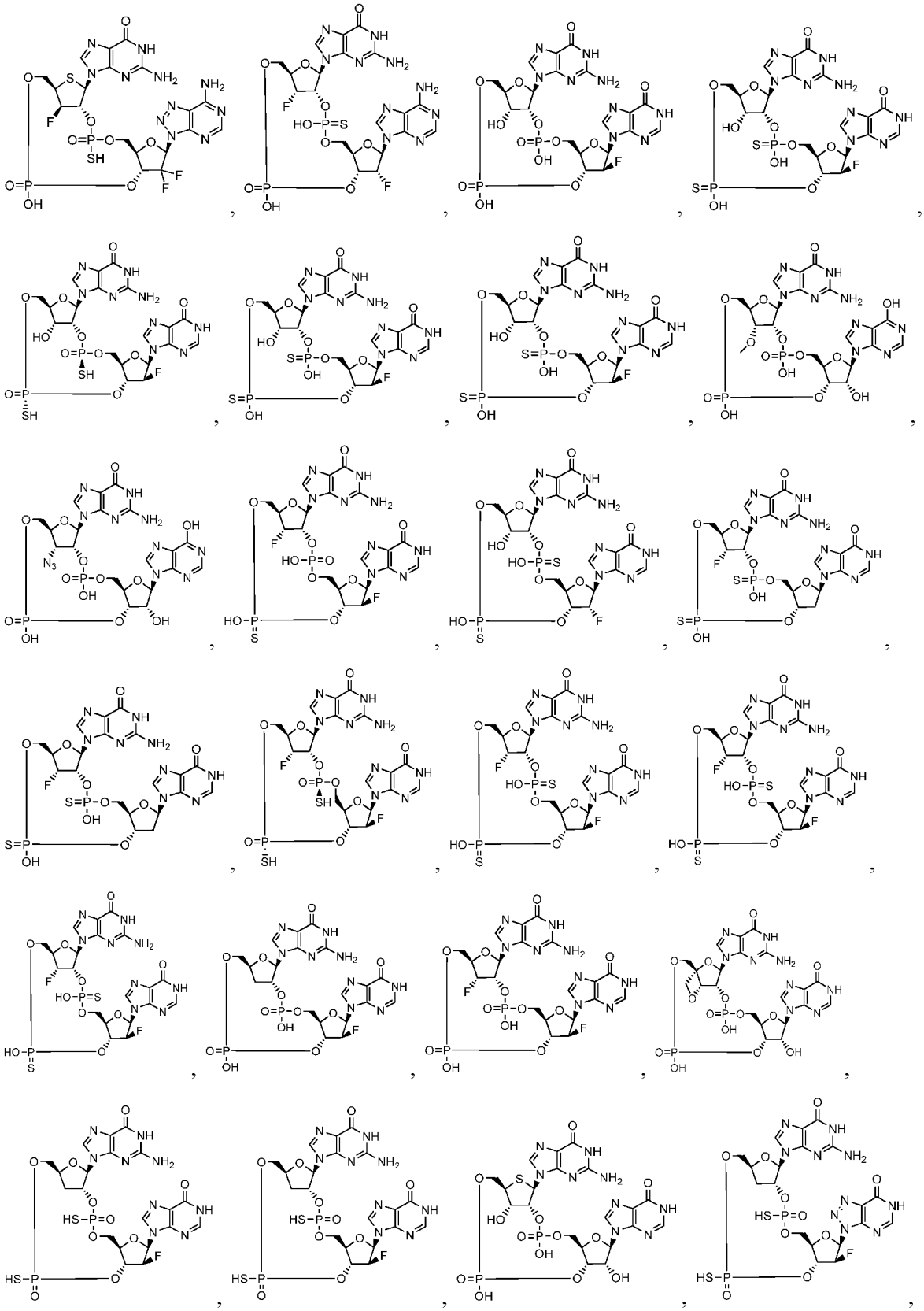
 ,
 ,
 ,
 ,

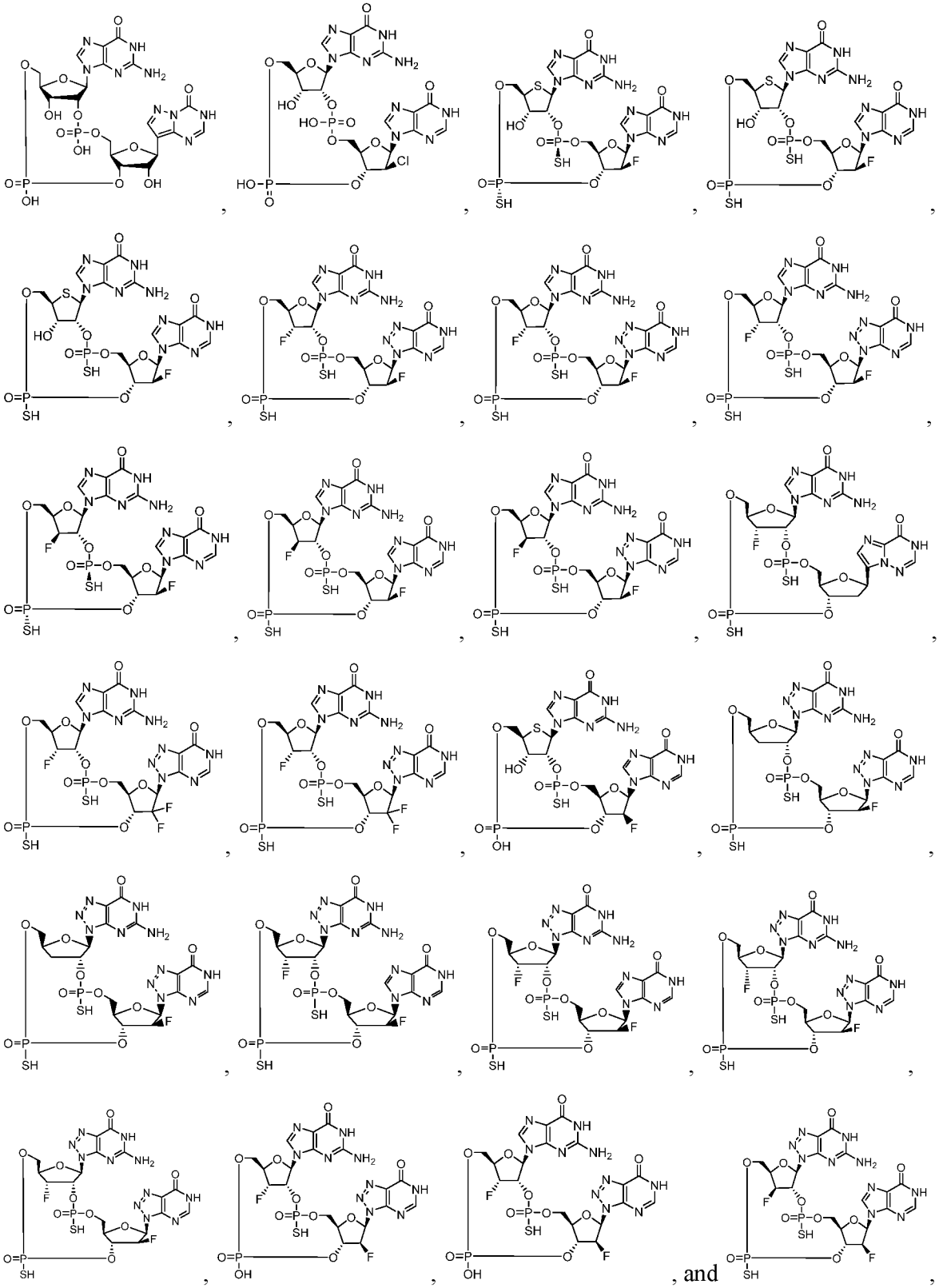
 ,
 ,
 ,
 ,

 ,
 ,
 ,
 ,

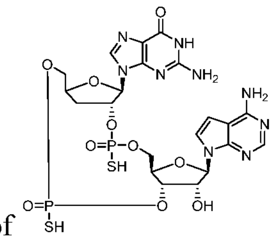
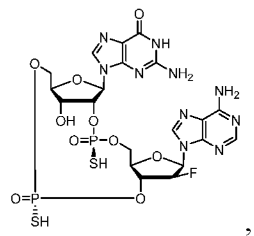
 ,
 ,
 ,
 ,

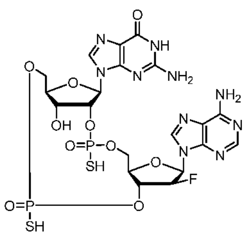
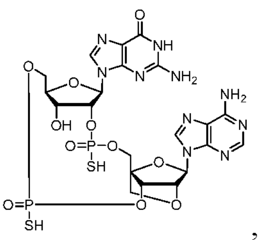
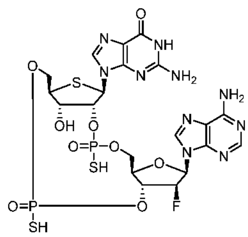
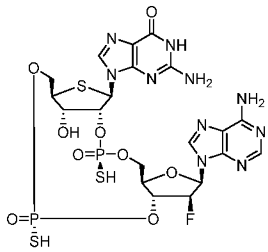
 ,
 ,
 ,
 ,

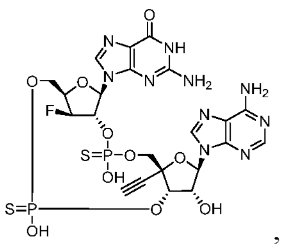
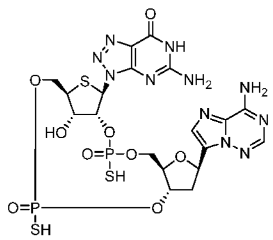
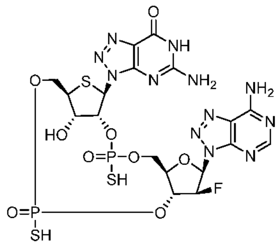
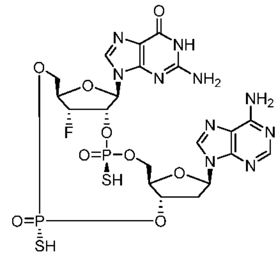


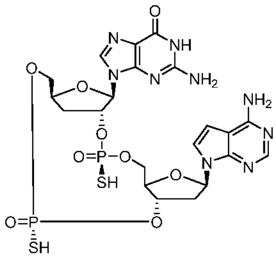
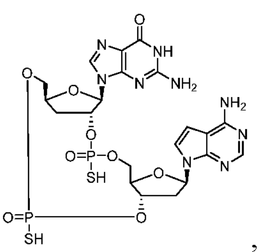
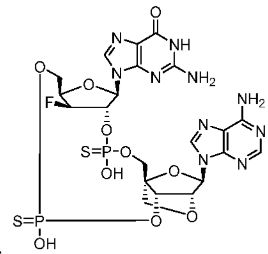
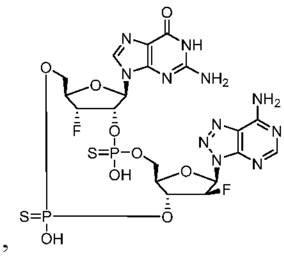


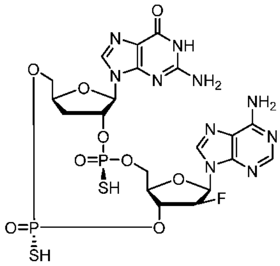
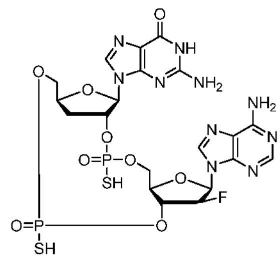
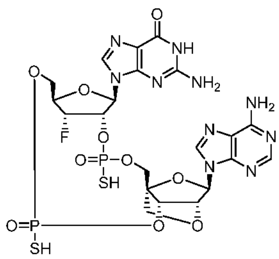
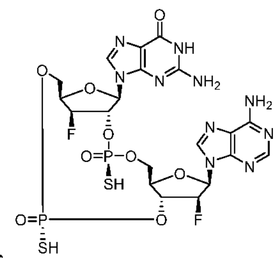
and pharmaceutically acceptable salts thereof. In particular aspects of this embodiment, the

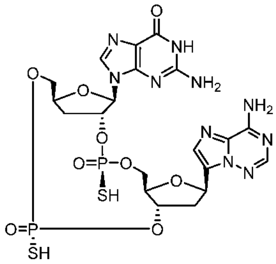
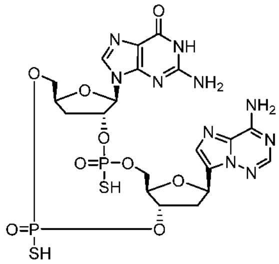
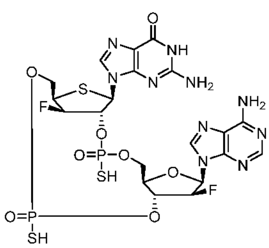
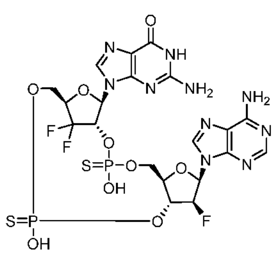
compound is selected from the group consisting of  ,  ,

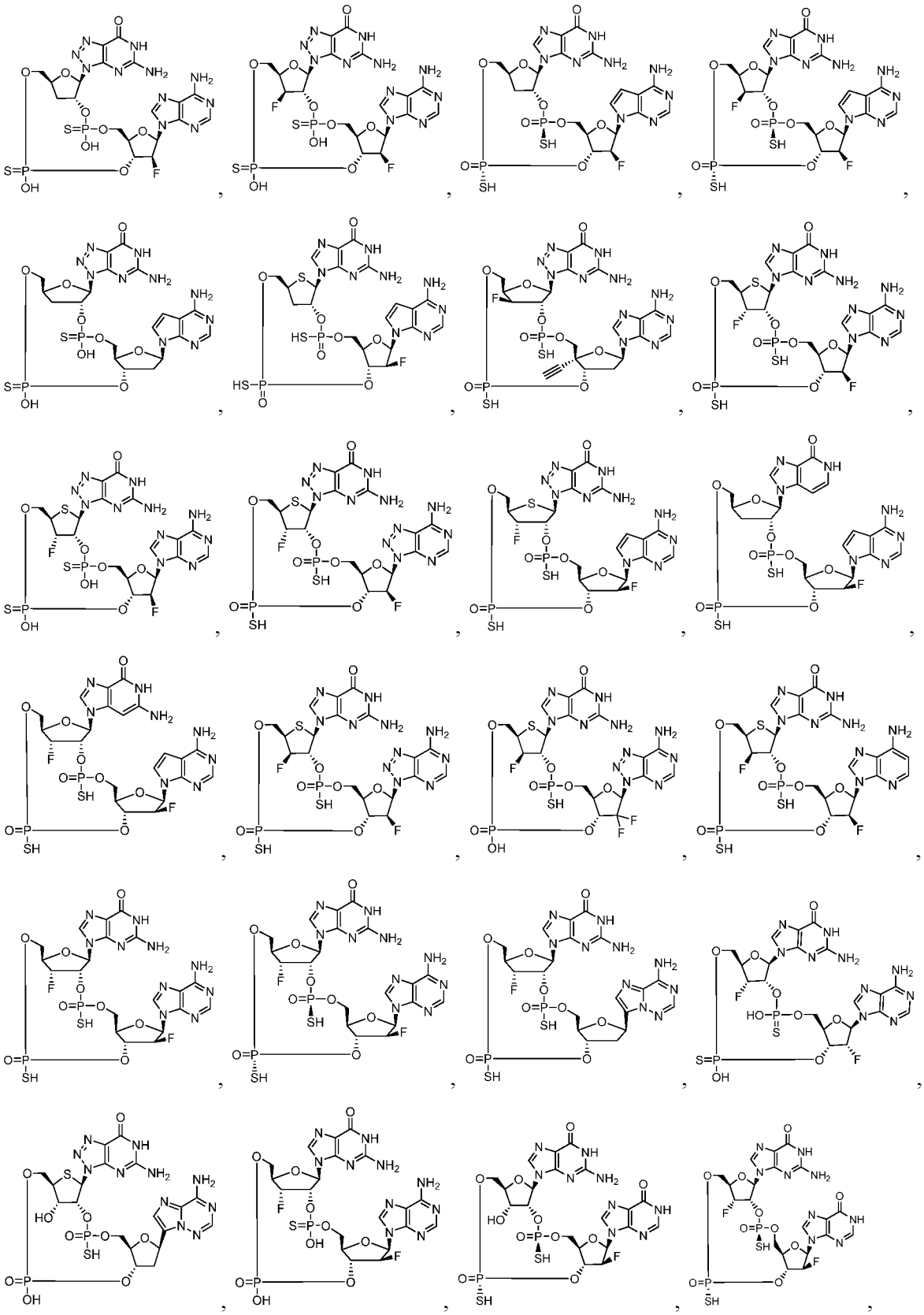
 ,  ,  ,  ,

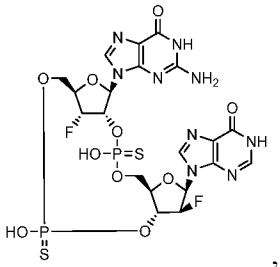
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

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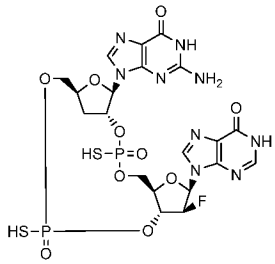
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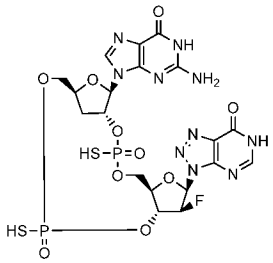
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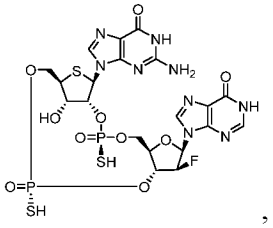
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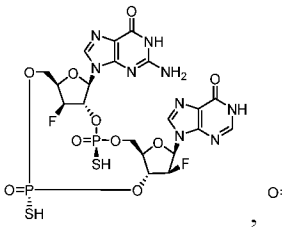
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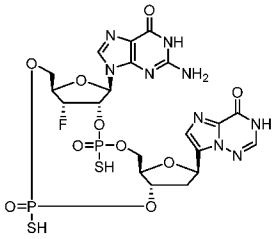
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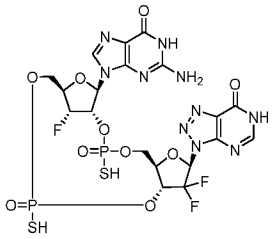
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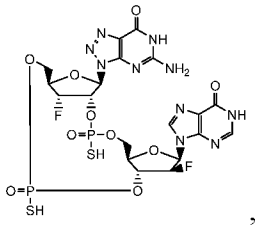
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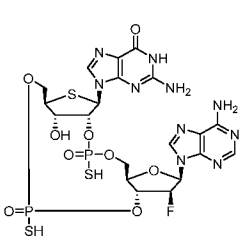
and pharmaceutically acceptable salts thereof. In more particular aspects of this embodiment, the compound is selected from the group consisting of

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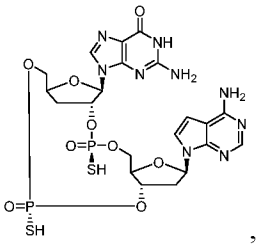
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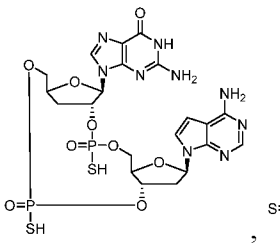
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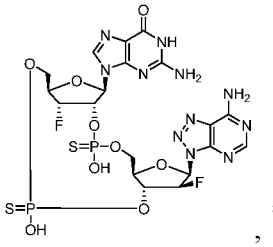
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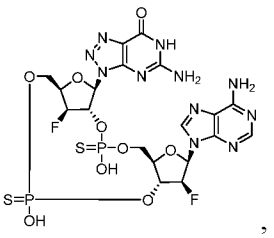
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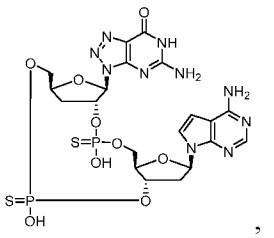
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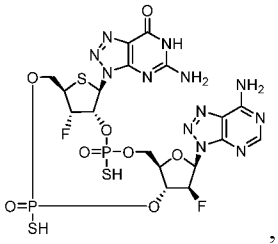
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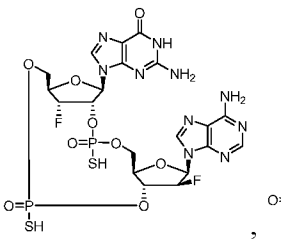
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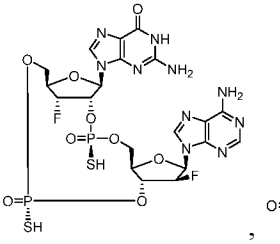
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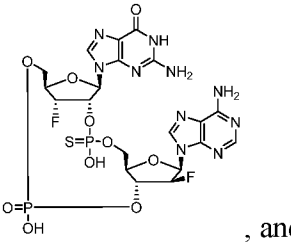
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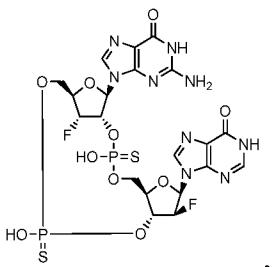

, and pharmaceutically acceptable salts thereof.

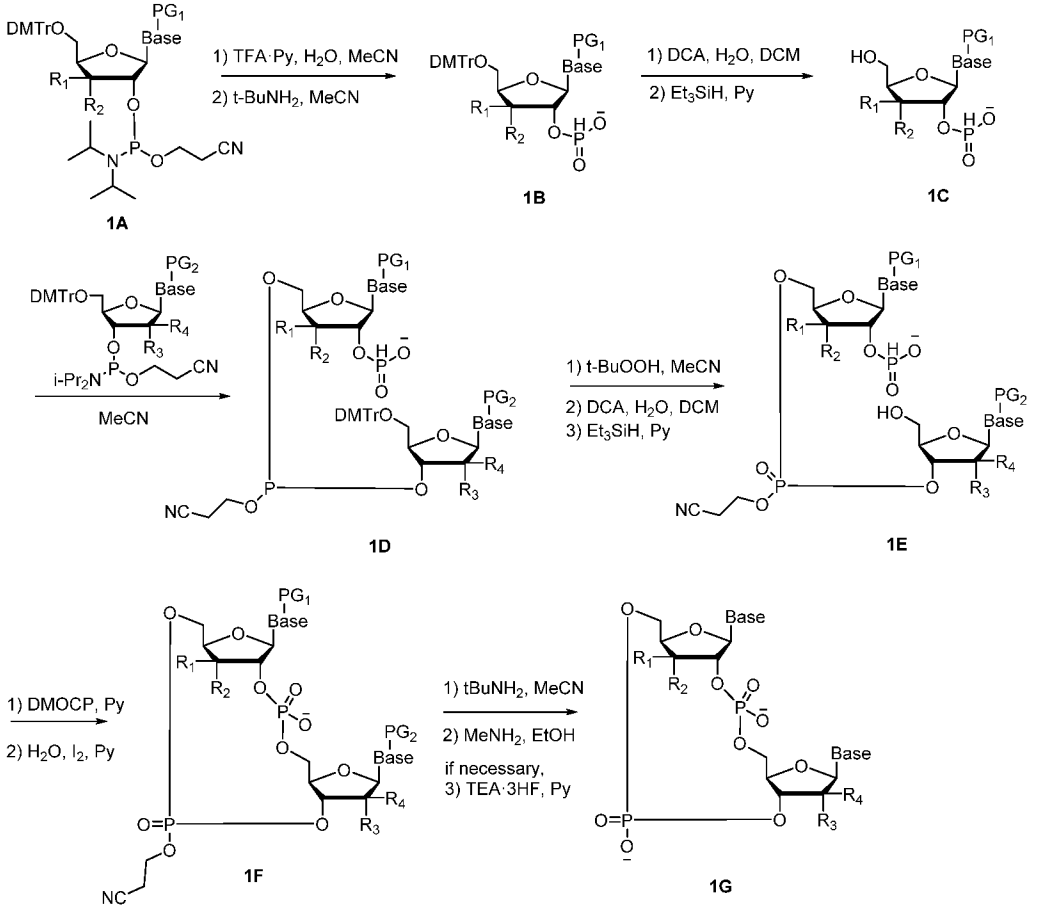
Methods of Preparing Compounds

[0118] The CDN STING agonists of the disclosure may be prepared according to the methods disclosed in PCT International Patent Application No. PCT/US2016/046444, which published as PCT International Patent Application Publication No. WO2017/027646, and United States Patent Application No. 15/234,182, which published as U.S. Patent Application Publication No. US2017/0044206. In particular, several methods for preparing the compounds of general formula (I), compounds of general formula (I'), and compounds of general formula (I"), or pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof, are described in the following Schemes. Starting materials and intermediates are purchased from commercial sources, made from known procedures, or are otherwise illustrated. In some cases the order of carrying out the steps of the reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

Method 1

[0119] One method for the preparation of examples of the disclosure is detailed in Scheme 1. This procedure was adequately modified from the previously reported procedure for cyclic dinucleotide synthesis (Barbara L. Gaffney *et al.*, *One-Flask Syntheses of c-di-GMP and the [Rp,Rp] and [Rp,Sp] Thiophosphate Analogues*, 12 ORG. LETT. 3269-3271 (2010)). The sequence starts with modified ribo-nucleoside with a nucleobase of which amino group was appropriately protected with an alkyl or phenyl carbonyl group, a phosphoramidite functionality at 2'-O position, and DMTr ether at 5'-O position. It was treated with aqueous TFA/pyridine condition and subsequently t-butylamine to convert the 2'-phosphoramidite moiety to an H-phosphonate. Then, DMTr ether was removed under acidic condition. The resulting 5'-hydroxyl group was reacted with 3'-phosphoramidites of fully protected second modified ribo-nucleoside to give a cyclized compound. It was immediately oxidized with t-butyl hydroperoxide. Then, the 5'-hydroxyl group of the second ribo-nucleoside was deprotected with dichloroacetic acid. Using 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide as a coupling reagent, the H-phosphonate at 2'-O of the first ribo-nucleoside was reacted with 5'-OH of the second ribo-nucleoside to give a cyclic product. It was immediately oxidized with aqueous iodine. Treatment with t-butylamine and methylamine plus fluoride anion in case silyl protection was used provided the desired cyclic dinucleotide 1G.

SCHEME 1

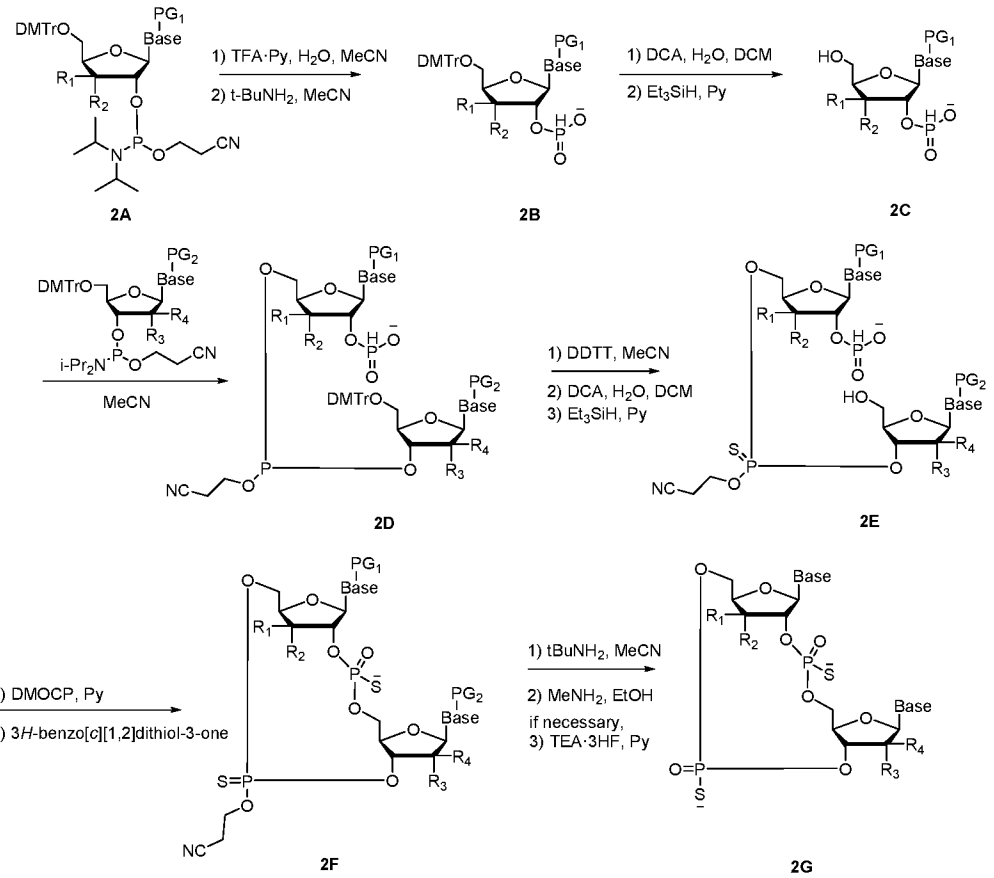


Method 2

[0120] Another method for the preparation of examples of the disclosure is detailed in Scheme 2. This procedure was modified from Scheme 1. The sequence starts with modified ribo-nucleoside with a nucleobase of which amino group was appropriately protected with an alkyl or phenyl carbonyl group, a phosphoramidite functionality at 2'-O position, and DMTr ether at 5'-O position. It was treated with aqueous TFA/pyridine condition and subsequently t-butylamine to convert the 2'-phosphoramidite moiety to an H-phosphonate. Then, DMTr ether was removed under acidic condition. The resulting 5'-hydroxyl group was reacted with 3'-phosphoramidites of fully protected second modified ribo-nucleoside to give a cyclized compound. It was immediately thioated with (E)-N,N-dimethyl-N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)formimidamide. Then, the 5'-hydroxyl group of the second ribo-nucleoside was deprotected with dichloroacetic acid. Using 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide as a coupling reagent, the H-phosphonate at 2'-O of the first ribo-nucleoside was reacted

with 5'-OH of the second ribo-nucleoside to give a cyclic product. It was immediately thioated with 3H-benzo[c][1,2]dithiol-3-one. Treatment with t-butylamine and methylamine plus fluoride anion in case silyl protection was used provided the desired cyclic dinucleotide diphosphorothioate 2G.

SCHEME 2



[0121] The CDN STING agonists and a pharmaceutically acceptable carrier or excipient(s) will typically be formulated into a dosage form adapted for administration to a subject by a desired route of administration. For example, dosage forms include those adapted for (1) oral administration, such as tablets, capsules, caplets, pills, troches, powders, syrups, elixirs, suspensions, solutions, emulsions, sachets, and cachets; and (2) parenteral administration, such as sterile solutions, suspensions, and powders for reconstitution. Suitable pharmaceutically acceptable carriers or excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically acceptable carriers or excipients may be chosen for a particular function that they may serve in the composition. In embodiments, the CDN STING

agonist may be formulated into a dosage form that allows for systemic use, i.e., distribution of the CDN STING agonist throughout the body of the subject; examples of such systemic administration include oral administration and intravenous administration. In additional embodiments, the CDN STING agonist may be formulated into a dosage form that allows for targeted or isolated use, i.e., administration of the CDN STING agonist only to the portion of the subject's body to be treated; examples of such targetted administration include intratumoral injection.

[0122] The cyclic dinucleotide STING agonist is administered once every 1 to 30 days. In embodiments, the cyclic dinucleotide STING agonist is administered once every 3 to 28 days. In particular embodiments, the cyclic dinucleotide STING agonist is administered once every 3, 7, 14, 21, or 28 days.

[0123] In embodiments of such methods, the cyclic dinucleotide STING agonist is administered for from 2 to 36 months. In specific embodiments, the cyclic dinucleotide STING agonist is administered for up to 3 months.

[0124] In additional embodiments of such methods, the cyclic dinucleotide STING agonist is administered once every 3, 7, 14, 21, or 28 days for from 2 to 36 months. In further embodiments, the cyclic dinucleotide STING agonist is administered once every 3, 7, 14, 21, or 28 days for up to 3 months. In specific embodiments, the cyclic dinucleotide STING agonist is administered once every 3, 7, 14, 21, or 28 days for up to 3 months, followed by a period, lasting at least 2 months, in which the time interval between doses is increased by at least two-fold. In more specific embodiments, the cyclic dinucleotide STING agonist is administered once every 3, 7, 14, 21, or 28 days for up to 3 months, followed by a period, lasting at least 2 months, in which the time interval between doses is increased by at least three-fold. For example, if the cyclic dinucleotide STING agonist is administered once every 7 days for up to 3 months, it may be followed by a period in which the cyclic dinucleotide STING agonist is administered once every 14 or 21 days for up to two years.

[0125] A therapy of the invention may be used prior to or following surgery to remove a tumor and may be used prior to, during, or after radiation treatment.

[0126] In some embodiments, a therapy of the invention is administered to a patient who has not previously been treated with a biotherapeutic or chemotherapeutic agent, targeted therapy, or hormonal therapy, i.e., is treatment-naïve. In other embodiments, the therapy is

administered to a patient who failed to achieve a sustained response after prior therapy with the biotherapeutic or chemotherapeutic agent, i.e., is treatment-experienced.

[0127] In specific embodiments, the cyclic dinucleotide STING agonist is administered once every 3 to 30 days for 9 to 90 days, then optionally once every 3 to 30 days for up to 1050 days. In specific embodiments, the cyclic dinucleotide STING agonist is administered once every 3 to 21 days for 9 to 63 days, then optionally once every 3 to 21 days for up to 735 days. In further specific embodiments, the cyclic dinucleotide STING agonist is administered once every 7 to 21 days for 21 to 63 days, then optionally once every 7 to 21 days for up to 735 days. In still further embodiments, the cyclic dinucleotide STING agonist is administered once every 7 to 10 days for 21 to 30 days, then optionally once every 21 days for up to 735 days. In still further embodiments, the cyclic dinucleotide STING agonist is administered once every 7 days for 21 days, then optionally once every 21 days for up to 735 days. In additional embodiments, the cyclic dinucleotide STING agonist is administered once every 21 days for 63 days, then optionally once every 21 days for up to 735 days. In specific embodiments of the foregoing, the cyclic dinucleotide STING agonist is administered at least three times.

[0128] In some embodiments, one or more optional "rest" periods, during which the CDN STING agonist is not administered, may be included in the treatment period. In specific embodiments, the optional rest period may be for from 3 to 30 days, from 7 to 21 days, or from 7 to 14 days. Following the rest period, dosing of the CDN STING agonist may be resumed as described above.

CELL-PROLIFERATION DISORDERS

[0129] The therapies disclosed herein are potentially useful in treating diseases or disorders including, but not limited to, cell-proliferation disorders. Cell-proliferation disorders include, but are not limited to, cancers, benign papillomatosis, gestational trophoblastic diseases, and benign neoplastic diseases, such as skin papilloma (warts) and genital papilloma. The terms "cancer", "cancerous", or "malignant" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth.

[0130] In specific embodiments, the disease or disorder to be treated is a cell-proliferation disorder. In certain embodiments, the cell-proliferation disorder is cancer. In particular embodiments, the cancer is selected from brain and spinal cancers, cancers of the head and neck, leukemia and cancers of the blood, skin cancers, cancers of the reproductive system, cancers of the gastrointestinal system, liver and bile duct cancers, kidney and bladder cancers,

bone cancers, lung cancers, malignant mesothelioma, sarcomas, lymphomas, glandular cancers, thyroid cancers, heart tumors, germ cell tumors, malignant neuroendocrine (carcinoid) tumors, midline tract cancers, and cancers of unknown primary (*i.e.*, cancers in which a metastasized cancer is found but the original cancer site is not known). In particular embodiments, the cancer is present in an adult patient; in additional embodiments, the cancer is present in a pediatric patient. In particular embodiments, the cancer is AIDS-related.

[0131] In specific embodiments, the cancer is selected from brain and spinal cancers. In particular embodiments, the brain and spinal cancer is selected from the group consisting of anaplastic astrocytomas, glioblastomas, astrocytomas, and estheosioneuroblastomas (also known as olfactory blastomas). In particular embodiments, the brain cancer is selected from the group consisting of astrocytic tumor (e.g., pilocytic astrocytoma, subependymal giant-cell astrocytoma, diffuse astrocytoma, pleomorphic xanthoastrocytoma, anaplastic astrocytoma, astrocytoma, giant cell glioblastoma, glioblastoma, secondary glioblastoma, primary adult glioblastoma, and primary pediatric glioblastoma), oligodendroglial tumor (e.g., oligodendroglioma, and anaplastic oligodendroglioma), oligoastrocytic tumor (e.g., oligoastrocytoma, and anaplastic oligoastrocytoma), ependymoma (e.g., myxopapillary ependymoma, and anaplastic ependymoma); medulloblastoma, primitive neuroectodermal tumor, schwannoma, meningioma, atypical meningioma, anaplastic meningioma, pituitary adenoma, brain stem glioma, cerebellar astrocytoma, cerebral astorcytoma/malignant glioma, visual pathway and hypothalmic glioma, and primary central nervous system lymphoma. In specific instances of these embodiments, the brain cancer is selected from the group consisting of glioma, glioblastoma multiforme, paraganglioma, and suprantentorial primordial neuroectodermal tumors (sPNET).

[0132] In specific embodiments, the cancer is selected from cancers of the head and neck, including recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), nasopharyngeal cancers, nasal cavity and paranasal sinus cancers, hypopharyngeal cancers, oral cavity cancers (e.g., squamous cell carcinomas, lymphomas, and sarcomas), lip cancers, oropharyngeal cancers, salivary gland tumors, cancers of the larynx (e.g., laryngeal squamous cell carcinomas, rhabdomyosarcomas), and cancers of the eye or ocular cancers. In particular embodiments, the ocular cancer is selected from the group consisting of intraocular melanoma and retinoblastoma.

[0133] In specific embodiments, the cancer is selected from leukemia and cancers of the blood. In particular embodiments, the cancer is selected from the group consisting of

myeloproliferative neoplasms, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML), myeloproliferative neoplasm (MPN), post-MPN AML, post-MDS AML, del(5q)-associated high risk MDS or AML, blast-phase chronic myelogenous leukemia, angioimmunoblastic lymphoma, acute lymphoblastic leukemia, Langerans cell histiocytosis, hairy cell leukemia, and plasma cell neoplasms including plasmacytomas and multiple myelomas. Leukemias referenced herein may be acute or chronic.

[0134] In specific embodiments, the cancer is selected from skin cancers. In particular embodiments, the skin cancer is selected from the group consisting of melanoma, squamous cell cancers, and basal cell cancers. In specific embodiments, the skin cancer is unresectable or metastatic melanoma.

[0135] In specific embodiments, the cancer is selected from cancers of the reproductive system. In particular embodiments, the cancer is selected from the group consisting of breast cancers, cervical cancers, vaginal cancers, ovarian cancers, endometrial cancers, prostate cancers, penile cancers, and testicular cancers. In specific instances of these embodiments, the cancer is a breast cancer selected from the group consisting of ductal carcinomas and phyllodes tumors. In specific instances of these embodiments, the breast cancer may be male breast cancer or female breast cancer. In more specific instances of these embodiments, the breast cancer is triple-negative breast cancer. In specific instances of these embodiments, the cancer is a cervical cancer selected from the group consisting of squamous cell carcinomas and adenocarcinomas. In specific instances of these embodiments, the cancer is an ovarian cancer selected from the group consisting of epithelial cancers.

[0136] In specific embodiments, the cancer is selected from cancers of the gastrointestinal system. In particular embodiments, the cancer is selected from the group consisting of esophageal cancers, gastric cancers (also known as stomach cancers), gastrointestinal carcinoid tumors, pancreatic cancers, gallbladder cancers, colorectal cancers, and anal cancer. In instances of these embodiments, the cancer is selected from the group consisting of esophageal squamous cell carcinomas, esophageal adenocarcinomas, gastric adenocarcinomas, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, gastric lymphomas, gastrointestinal lymphomas, solid pseudopapillary tumors of the pancreas, pancreatoblastoma, islet cell tumors, pancreatic carcinomas including acinar cell carcinomas and

ductal adenocarcinomas, gallbladder adenocarcinomas, colorectal adenocarcinomas, and anal squamous cell carcinomas.

[0137] In specific embodiments, the cancer is selected from liver and bile duct cancers. In particular embodiments, the cancer is liver cancer (also known as hepatocellular carcinoma). In particular embodiments, the cancer is bile duct cancer (also known as cholangiocarcinoma); in instances of these embodiments, the bile duct cancer is selected from the group consisting of intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma.

[0138] In specific embodiments, the cancer is selected from kidney and bladder cancers. In particular embodiments, the cancer is a kidney cancer selected from the group consisting of renal cell cancer, Wilms tumors, and transitional cell cancers. In particular embodiments, the cancer is a bladder cancer selected from the group consisting of urothelial carcinoma (a transitional cell carcinoma), squamous cell carcinomas, and adenocarcinomas.

[0139] In specific embodiments, the cancer is selected from bone cancers. In particular embodiments, the bone cancer is selected from the group consisting of osteosarcoma, malignant fibrous histiocytoma of bone, Ewing sarcoma, chordoma (cancer of the bone along the spine).

[0140] In specific embodiments, the cancer is selected from lung cancers. In particular embodiments, the lung cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancers, bronchial tumors, and pleuropulmonary blastomas.

[0141] In specific embodiments, the cancer is selected from malignant mesothelioma. In particular embodiments, the cancer is selected from the group consisting of epithelial mesothelioma and sarcomatoids.

[0142] In specific embodiments, the cancer is selected from sarcomas. In particular embodiments, the sarcoma is selected from the group consisting of central chondrosarcoma, central and periosteal chondroma, fibrosarcoma, clear cell sarcoma of tendon sheaths, and Kaposi's sarcoma.

[0143] In specific embodiments, the cancer is selected from lymphomas. In particular embodiments, the cancer is selected from the group consisting of Hodgkin lymphoma (e.g., Reed-Sternberg cells), non-Hodgkin lymphoma (e.g., diffuse large B-cell lymphoma, follicular lymphoma, mycosis fungoides, Sezary syndrome, primary central nervous system lymphoma), cutaneous T-cell lymphomas, primary central nervous system lymphomas.

[0144] In specific embodiments, the cancer is selected from glandular cancers. In particular embodiments, the cancer is selected from the group consisting of adrenocortical cancer

(also known as adrenocortical carcinoma or adrenal cortical carcinoma), pheochromocytomas, paragangliomas, pituitary tumors, thymoma, and thymic carcinomas.

[0145] In specific embodiments, the cancer is selected from thyroid cancers. In particular embodiments, the thyroid cancer is selected from the group consisting of medullary thyroid carcinomas, papillary thyroid carcinomas, and follicular thyroid carcinomas.

[0146] In specific embodiments, the cancer is selected from germ cell tumors. In particular embodiments, the cancer is selected from the group consisting of malignant extracranial germ cell tumors and malignant extragonadal germ cell tumors. In specific instances of these embodiments, the malignant extragonadal germ cell tumors are selected from the group consisting of nonseminomas and seminomas.

[0147] In specific embodiments, the cancer is selected from heart tumors. In particular embodiments, the heart tumor is selected from the group consisting of malignant teratoma, lymphoma, rhabdomyosacroma, angiosarcoma, chondrosarcoma, infantile fibrosarcoma, and synovial sarcoma.

[0148] In specific embodiments, the cell-proliferation disorder is selected from benign papillomatosis, benign neoplastic diseases and gestational trophoblastic diseases. In particular embodiments, the benign neoplastic disease is selected from skin papilloma (warts) and genital papilloma. In particular embodiments, the gestational trophoblastic disease is selected from the group consisting of hydatidiform moles, and gestational trophoblastic neoplasia (*e.g.*, invasive moles, choriocarcinomas, placental-site trophoblastic tumors, and epithelioid trophoblastic tumors).

[0149] In embodiments, the cell-proliferation disorder is a cancer that has metastasized, for example, a liver metastases from colorectal cancer.

[0150] In embodiments, the cell-proliferation disorder is selected from the group consisting of solid tumors and lymphomas. In particular embodiments, the cell-proliferation disorder is selected from the group consisting of advanced or metastatic solid tumors and lymphomas. In more particular embodiments, the cell-proliferation disorder is selected from the group consisting of malignant melanoma, head and neck squamous cell carcminoma, breast adenocarcinoma, and lymphomas. In aspects of such embodiments, the lymphomas are selected from the group consisting of diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, small lymphocytic lymphoma, mediastinal large B-cell lymphoma, splenic marginal zone B-cell lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated

lymphoid tissue (malt), nodal marginal zone B-cell lymphoma, lymphoplasmacytic lymphoma, primary effusion lymphoma, Burkitt lymphoma, anaplastic large cell lymphoma (primary cutaneous type), anaplastic large cell lymphoma (systemic type), peripheral T-cell lymphoma, angioimmunoblastic T-cell lymphoma, adult T-cell lymphoma/leukemia, nasal type extranodal NK/T-cell lymphoma, enteropathy-associated T-cell lymphoma, gamma/delta hepatosplenic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, mycosis fungoides, and Hodgkin lymphoma.

[0151] In particular embodiments, the cell-proliferation disorder is classified as stage III cancer or stage IV cancer. In instances of these embodiments, the cancer is not surgically resectable.

METHODS, USES, AND MEDICAMENTS

[0152] Products provided as therapies may include a composition comprising a CDN STING agonist in a composition.

[0153] The therapy may also comprise one or more additional therapeutic agents. The additional therapeutic agent may be, e.g., a chemotherapeutic, a biotherapeutic agent (including but not limited to antibodies to VEGF, VEGFR, EGFR, Her2/neu, other growth factor receptors, CD20, CD40, CD-40L, CTLA-4, OX-40, 4-1BB, and ICOS), an immunogenic agent (for example, attenuated cancerous cells, tumor antigens, antigen presenting cells such as dendritic cells pulsed with tumor derived antigen or nucleic acids, immune stimulating cytokines (for example, IL-2, IFNα2, GM-CSF), and cells transfected with genes encoding immune stimulating cytokines such as but not limited to GM-CSF). The one or more additional active agents may be administered either with the CDN STING agonist (co-administered) or administered separately from the CDN STING agonist, in a different dosage form. That is, the additional active agent(s) may be administered in a single dosage form with the CDN STING agonist, or the additional active agent(s) may be administered in separate dosage form(s) from the dosage form containing the CDN STING agonist.

[0154] The therapies disclosed herein may be used in combination with one or more other active agents, including but not limited to, other anti-cancer agents that are used in the prevention, treatment, control, amelioration, or reduction of risk of a particular disease or condition (e.g., cell-proliferation disorders). In one embodiment, a compound disclosed herein is combined with one or more other anti-cancer agents for use in the prevention, treatment, control amelioration, or reduction of risk of a particular disease or condition for which the compounds

disclosed herein are useful. Such other active agents may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present disclosure.

[0155] The additional active agent(s) may be one or more agents selected from the group consisting of STING agonists, anti-viral compounds, antigens, adjuvants, anti-cancer agents, CTLA-4, LAG-3, and PD-1 pathway antagonists, lipids, liposomes, peptides, cytotoxic agents, chemotherapeutic agents, immunomodulatory cell lines, checkpoint inhibitors, vascular endothelial growth factor (VEGF) receptor inhibitors, topoisomerase II inhibitors, smoothen inhibitors, alkylating agents, anti-tumor antibiotics, anti-metabolites, retinoids, and immunomodulatory agents including but not limited to anti-cancer vaccines. It will be understood the descriptions of the above additional active agents may be overlapping. It will also be understood that the treatment combinations are subject to optimization, and it is understood that the best combination to use of the CDN STING agonist, and one or more additional active agents will be determined based on the individual patient needs.

[0156] When the therapies disclosed herein are used contemporaneously with one or more other active agents, the CDN STING agonist may be administered either simultaneously with, or before or after, one or more other active agent(s). The CDN STING agonist may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agent(s).

[0157] The dosage amount of the CDN STING agonist may be varied and will depend upon the therapeutically effective dose of each agent. Generally, a therapeutically effective dose of each will be used. Combinations including at least one CDN STING agonist, and other active agents will generally include a therapeutically effective dose of each active agent. In such combinations, the CDN STING agonist disclosed herein and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent with, or subsequent to the administration of other agent(s).

[0158] In one embodiment, this disclosure provides a CDN STING agonist, and at least one other active agent as a combined preparation, for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a cell-proliferation disorder, such as cancer.

[0159] In one embodiment, the disclosure provides a kit comprising two or more separate pharmaceutical compositions, one of which contains a CDN STING agonist. In one

embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. A kit of this disclosure may be used for administration of different dosage forms, for example, oral and parenteral, for administration of the separate compositions at different dosage intervals, or for titration of the separate compositions against one another. To assist with compliance, a kit of the disclosure typically comprises directions for administration.

[0160] The disclosure also provides the use of a CDN STING agonist for treating a cell-proliferation disorder, where the patient has previously (e.g., within 24 hours) been treated with another agent.

[0161] Anti-viral compounds that may be used in combination with the therapies disclosed herein include hepatitis B virus (HBV) inhibitors, hepatitis C virus (HCV) protease inhibitors, HCV polymerase inhibitors, HCV NS4A inhibitors, HCV NS5A inhibitors, HCV NS5b inhibitors, and human immunodeficiency virus (HIV) inhibitors.

[0162] Antigens and adjuvants that may be used in combination with the therapies disclosed herein include B7 costimulatory molecule, interleukin-2, interferon-γ, GM-CSF, CTLA-4 antagonists, OX-40/0X-40 ligand, CD40/CD40 ligand, sargramostim, levamisol, vaccinia virus, Bacille Calmette-Guerin (BCG), liposomes, alum, Freund's complete or incomplete adjuvant, detoxified endotoxins, mineral oils, surface active substances such as lipolecithin, pluronic polyols, polyanions, peptides, and oil or hydrocarbon emulsions. Adjuvants, such as aluminum hydroxide or aluminum phosphate, can be added to increase the ability of the vaccine to trigger, enhance, or prolong an immune response. Additional materials, such as cytokines, chemokines, and bacterial nucleic acid sequences, like CpG, a toll-like receptor (TLR) 9 agonist as well as additional agonists for TLR 2, TLR 4, TLR 5, TLR 7, TLR 8, TLR9, including lipoprotein, lipopolysaccharide (LPS), monophosphoryllipid A, lipoteichoic acid, imiquimod, resiquimod, and in addition retinoic acid-inducible gene I (RIG-I) agonists such as poly I:C, used separately or in combination are also potential adjuvants.

[0163] Examples of cytotoxic agents that may be used in combination with the therapies disclosed herein include, but are not limited to, arsenic trioxide (sold under the tradename TRISENOX®), asparaginase (also known as L-asparaginase, and Erwinia L-asparaginase, sold under the tradenames ELSPAR® and KIDROLASE®).

[0164] Chemotherapeutic agents that may be used in combination with the therapies disclosed herein include abiraterone acetate, altretamine, anhydrovinblastine, auristatin,

bexarotene, bicalutamide, BMS 184476, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzene sulfonamide, bleomycin, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl- 1-Lproline-t-butylamide, cachectin, cemadotin, chlorambucil, cyclophosphamide, 3',4'-didehydro-4'deoxy-8'-norvin-caleukoblastine, docetaxol, doxetaxel, cyclophosphamide, carboplatin, carmustine, cisplatin, cryptophycin, cyclophosphamide, cytarabine, dacarbazine (DTIC), dactinomycin, daunorubicin, decitabine dolastatin, doxorubicin (adriamycin), etoposide, 5-fluorouracil, finasteride, flutamide, hydroxyurea and hydroxyurea and taxanes, ifosfamide, liarozole, lonidamine, lomustine (CCNU), MDV3100, mechlorethamine (nitrogen mustard), melphalan, mivobulin isethionate, rhizoxin, sertenef, streptozocin, mitomycin, methotrexate, taxanes, nilutamide, nivolumab, onapristone, paclitaxel, pembrolizumab, prednimustine, procarbazine, RPR109881, stramustine phosphate, tamoxifen, tasonermin, taxol, tretinoin, vinblastine, vincristine, vindesine sulfate, and vinflunine, and pharmaceutically acceptable salts thereof.

[0165] Examples of vascular endothelial growth factor (VEGF) receptor inhibitors include, but are not limited to, bevacizumab (sold under the trademark AVASTIN by Genentech/Roche), axitinib (described in PCT International Patent Publication No. WO01/002369), Brivanib Alaninate ((S)-((R)-1-(4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate, also known as BMS-582664), motesanib (N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide. and described in PCT International Patent Application Publication No. WO02/068470), pasireotide (also known as SO 230, and described in PCT International Patent Publication No. WO02/010192), and sorafenib (sold under the tradename NEXAVAR).

[0166] Examples of topoisomerase II inhibitors, include but are not limited to, etoposide (also known as VP-16 and Etoposide phosphate, sold under the tradenames TOPOSAR, VEPESID, and ETOPOPHOS), and teniposide (also known as VM-26, sold under the tradename VUMON).

[0167] Examples of hypomethylating agents and alkylating agents, include but are not limited to, 5-azacytidine (sold under the trade name VIDAZA), decitabine (sold under the trade name of DECOGEN), temozolomide (sold under the trade names TEMODAR and TEMODAL), dactinomycin (also known as actinomycin-D and sold under the tradename COSMEGEN), melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, sold under the tradename ALKERAN), altretamine (also known as hexamethylmelamine (HMM), sold under

the tradename HEXALEN), carmustine (sold under the tradename BCNU), bendamustine (sold under the tradename TREANDA), busulfan (sold under the tradenames BUSULFEX® and MYLERAN®), carboplatin (sold under the tradename PARAPLATIN®), lomustine (also known as CCNU, sold under the tradename CEENU®), cisplatin (also known as CDDP, sold under the tradenames PLATINOL® and PLATINOL®-AQ), chlorambucil (sold under the tradename LEUKERAN®), cyclophosphamide (sold under the tradenames CYTOXAN® and NEOSAR®), dacarbazine (also known as DTIC, DIC and imidazole carboxamide, sold under the tradename DTIC-DOME®), altretamine (also known as hexamethylmelamine (HMM) sold under the tradename HEXALEN®), ifosfamide (sold under the tradename IFEX®), procarbazine (sold under the tradename MATULANE®), mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, sold under the tradename MUSTARGEN®), streptozocin (sold under the tradename ZANOSAR®), thiotepa (also known as thiophosphoamide, TESPA and TSPA, and sold under the tradename THIOPLEX®, and pharmaceutically acceptable salts thereof.

[0168] Examples of anti-tumor antibiotics include, but are not limited to, doxorubicin (sold under the tradenames ADRIAMYCIN® and RUBEX®), bleomycin (sold under the tradename LENOXANE®), daunorubicin (also known as dauorubicin hydrochloride, daunomycin, and rubidomycin hydrochloride, sold under the tradename CERUBIDINE®), daunorubicin liposomal (daunorubicin citrate liposome, sold under the tradename DAUNOXOME®), mitoxantrone (also known as DHAD, sold under the tradename NOVANTRONE®), epirubicin (sold under the tradename ELLENCE™), idarubicin (sold under the tradenames IDAMYCIN®, IDAMYCIN PFS®), and mitomycin C (sold under the tradename MUTAMYCIN®).

[0169] Examples of anti-metabolites include, but are not limited to, claribine (2-chlorodeoxyadenosine, sold under the tradename LEUSTATIN®), 5-fluorouracil (sold under the tradename ADRUCIL®), 6-thioguanine (sold under the tradename PURINETHOL®), pemetrexed (sold under the tradename ALIMTA®), cytarabine (also known as arabinosylcytosine (Ara-C), sold under the tradename CYTOSAR-U®), cytarabine liposomal (also known as Liposomal Ara-C, sold under the tradename DEPOCYT™), decitabine (sold under the tradename DACOGEN®), hydroxyurea and (sold under the tradenames HYDREA®, DROXIA™ and MYLOCEL™), fludarabine (sold under the tradename FLUDARA®), floxuridine (sold under the tradename FUDR®), cladribine (also known as 2-chlorodeoxyadenosine (2-CdA) sold under the tradename LEUSTATIN™), methotrexate (also known as amethopterin, methotrexate sodium (MTX), sold

under the tradenames RHEUMATREX® and TREXALL™), and pentostatin (sold under the tradename NIPENT®).

[0170] Examples of retinoids include, but are not limited to, alitretinoin (sold under the tradename PANRETIN®), tretinoin (all-trans retinoic acid, also known as ATRA, sold under the tradename VESANOID®), Isotretinoin (13-c/s-retinoic acid, sold under the tradenames ACCUTANE®, AMNESTEEM®, CLARAVIS®, CLARUS®, DECUTAN®, ISOTANE®, IZOTECH®, ORATANE®, ISOTRET®, and SOTRET®), and bexarotene (sold under the tradename TARGRETIN®).

ADDITIONAL EMBODIMENTS

[0171] The present disclosure further relates to methods of treating a cell-proliferation disorder, said method comprising administering to a subject in need thereof a therapy that comprises a cyclic dinucleotide STING agonist compound; wherein the cyclic dinucleotide STING agonist is administered once every 1 to 30 days. In embodiments, the cyclic dinucleotide STING agonist is administered once every 3 to 28 days. In particular embodiments, the cyclic dinucleotide STING agonist is administered once every 3, 7, 14, 21, or 28 days.

[0172] In embodiments of such methods, the cyclic dinucleotide STING agonist is administered for from 2 to 36 months. In specific embodiments, the cyclic dinucleotide STING agonist is administered for up to 3 months.

[0173] In additional embodiments of such methods, the cyclic dinucleotide STING agonist is administered once every 3, 7, 14, 21, or 28 days for from 2 to 36 months. In further embodiments, the cyclic dinucleotide STING agonist is administered once every 3, 7, 14, 21, or 28 days for up to 3 months. In specific embodiments, the cyclic dinucleotide STING agonist is administered once every 3, 7, 14, 21, or 28 days for up to 3 months, followed by a period, lasting at least 2 months, in which the time interval between doses is increased by at least two-fold. In more specific embodiments, the cyclic dinucleotide STING agonist is administered once every 3, 7, 14, 21, or 28 days for up to 3 months, followed by a period, lasting at least 2 months, in which the time interval between doses is increased by at least three-fold. For example, if the cyclic dinucleotide STING agonist is administered once every 7 days for up to 3 months, it may be followed by a period in which the cyclic dinucleotide STING agonist is administered once every 14 or 21 days for up to two years.

[0174] The present disclosure further relates to methods of treating a cell-proliferation disorder, said method comprising administering to a subject in need thereof a therapy that comprises a cyclic dinucleotide STING agonist compound; wherein the cyclic dinucleotide

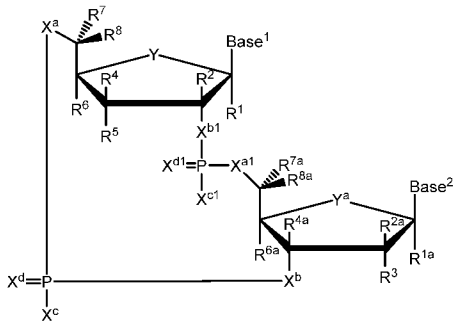
STING agonist is administered once every 1 to 30 days for 3 to 90 days, then optionally once every 1 to 30 days for up to 1050 days. In embodiments, the CDN STING agonist is administered at least three times.

[0175] In specific embodiments, the cyclic dinucleotide STING agonist is administered once every 3 to 30 days for 9 to 90 days, then optionally once every 3 to 30 days for up to 1050 days. In specific embodiments, the cyclic dinucleotide STING agonist is administered once every 3 to 21 days for 9 to 63 days, then optionally once every 3 to 21 days for up to 735 days. In further specific embodiments, the cyclic dinucleotide STING agonist is administered once every 7 to 21 days for 21 to 63 days, then optionally once every 7 to 21 days for up to 735 days. In still further embodiments, the cyclic dinucleotide STING agonist is administered once every 7 to 10 days for 21 to 30 days, then optionally once every 21 days for up to 735 days. In still further embodiments, the cyclic dinucleotide STING agonist is administered once every 7 days for 21 days, then optionally once every 21 days for up to 735 days. In additional embodiments, the cyclic dinucleotide STING agonist is administered once every 21 days for 63 days, then optionally once every 21 days for up to 735 days. In specific embodiments of the foregoing, the CDN STING agonist is administered at least three times.

[0176] Additionally, the present disclosure relates to methods of treating a cell-proliferation disorder, said method comprising administering to a subject in need thereof a therapy that comprises a cyclic dinucleotide STING agonist; wherein the cell-proliferation disorder is cancer. In specific embodiments, the cancer occurs as one or more solid tumors or lymphomas. In further specific embodiments, the cancer is selected from the group consisting of advanced or metastatic solid tumors and lymphomas. In still further specific embodiments, the cancer is selected from the group consisting of malignant melanoma, head and neck squamous cell carcinoma, breast adenocarcinoma, and lymphomas. In additional embodiments, the lymphoma is selected from the group consisting of diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, small lymphocytic lymphoma, mediastinal large B-cell lymphoma, splenic marginal zone B-cell lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (malt), nodal marginal zone B-cell lymphoma, lymphoplasmacytic lymphoma, primary effusion lymphoma, Burkitt lymphoma, anaplastic large cell lymphoma (primary cutaneous type), anaplastic large cell lymphoma (systemic type), peripheral T-cell lymphoma, angioimmunoblastic T-cell lymphoma, adult T-cell lymphoma/leukemia, nasal type extranodal NK/T-cell lymphoma, enteropathy-associated T-cell

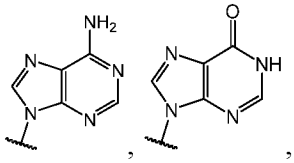
lymphoma, gamma/delta hepatosplenic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, mycosis fungoides, and Hodgkin lymphoma. In particular embodiments, the cell-proliferation disorder is a cancer that has metastasized, for example, a liver metastases from colorectal cancer. In additional embodiments, the cell-proliferation disorder is a cancer is classified as stage III cancer or stage IV cancer. In instances of these embodiments, the cancer is not surgically resectable.

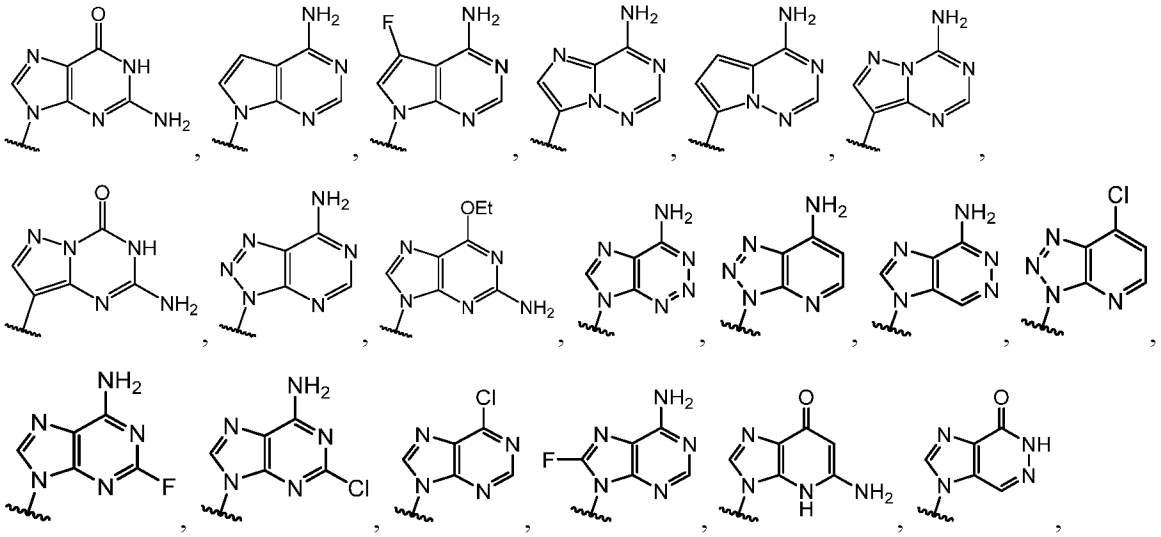
[0177] In embodiments of the methods disclosed herein, the cyclic dinucleotide STING agonist is selected from compounds of formula (I'):

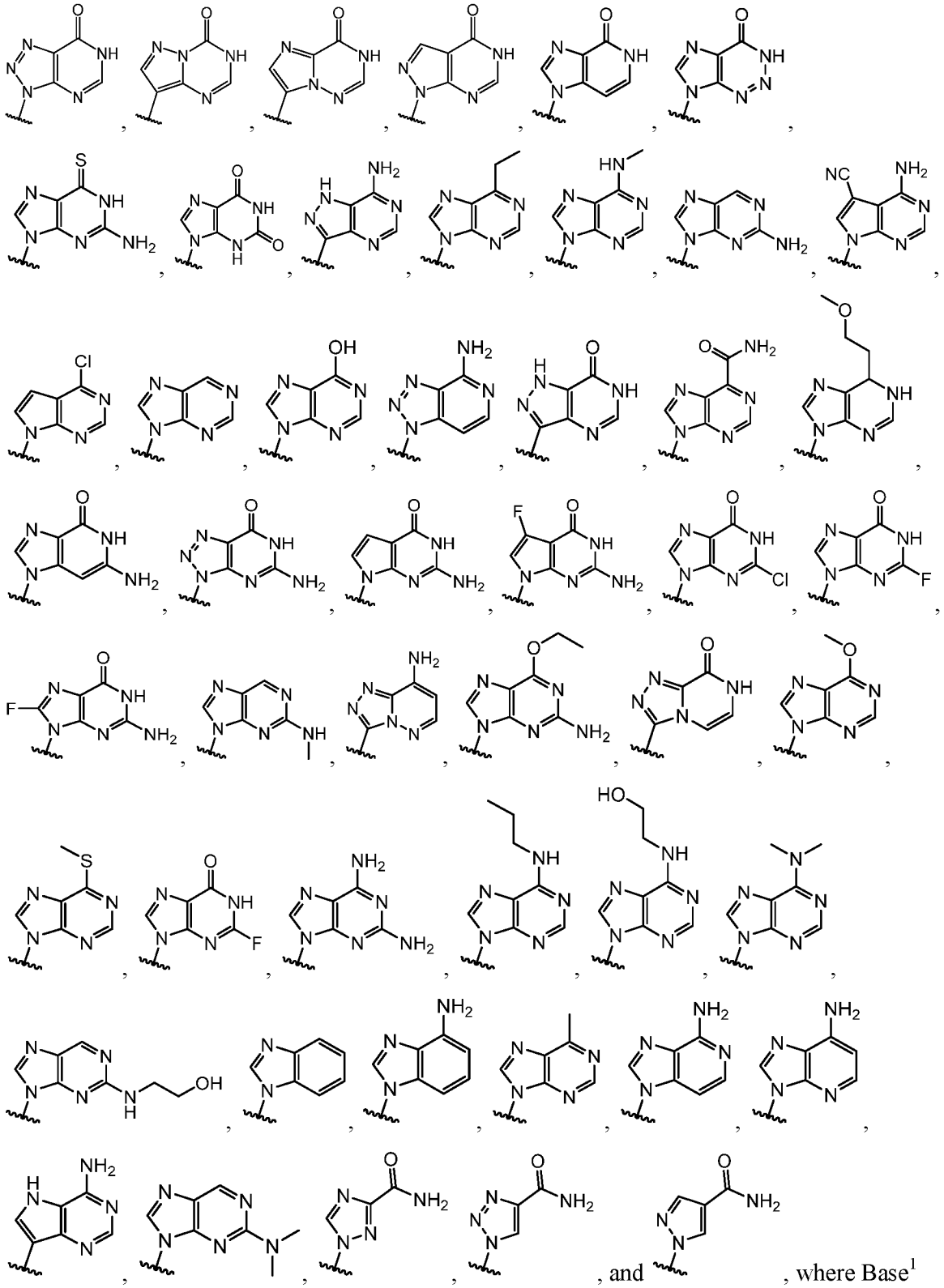


(I')

or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of

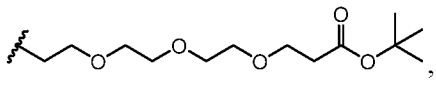
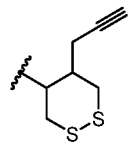






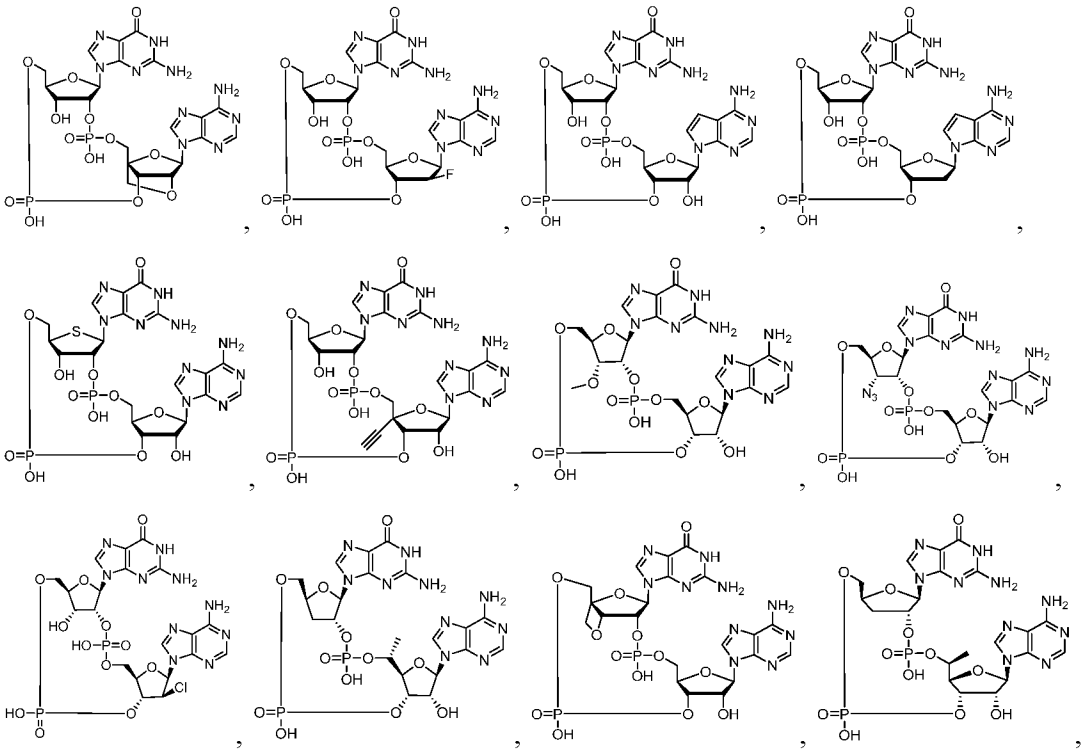
and Base^2 each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is

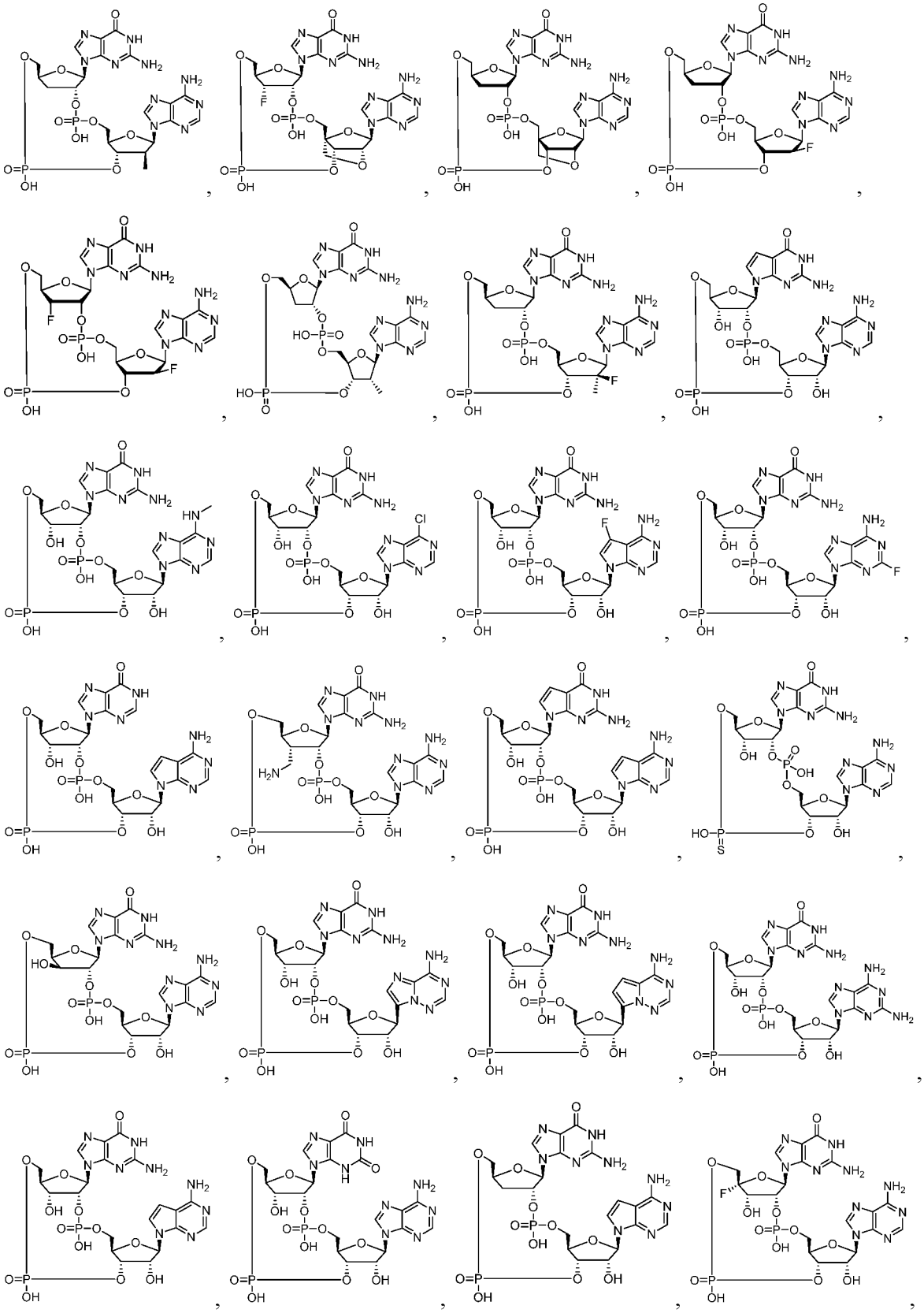
independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each independently selected from the group consisting of O, and S; X^b and X^{b1} are each independently selected from the group consisting of O, and S; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^1 and R^{1a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^2 and R^{2a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^3 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^4 and R^{4a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6

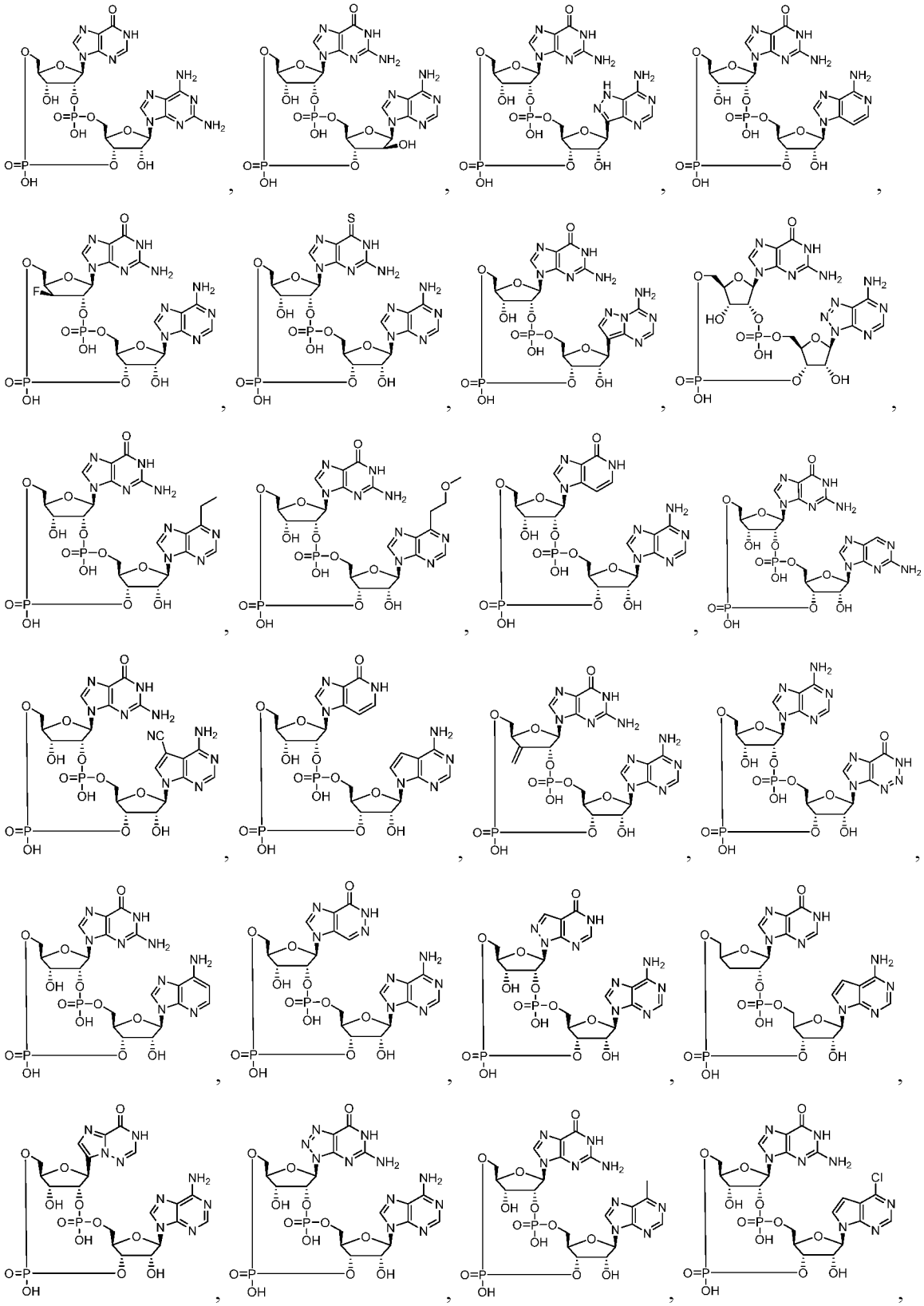
alkenyl, and -O-C_2-C_6 alkynyl, where said R^5 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, NR^9R^9, and N_3; R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^6 and R^{6a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^7 and R^{7a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^7 and R^{7a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^8 and R^{8a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^8 and R^{8a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,  , and  , where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl; optionally R^{1a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^{1a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position; optionally R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^{2a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or

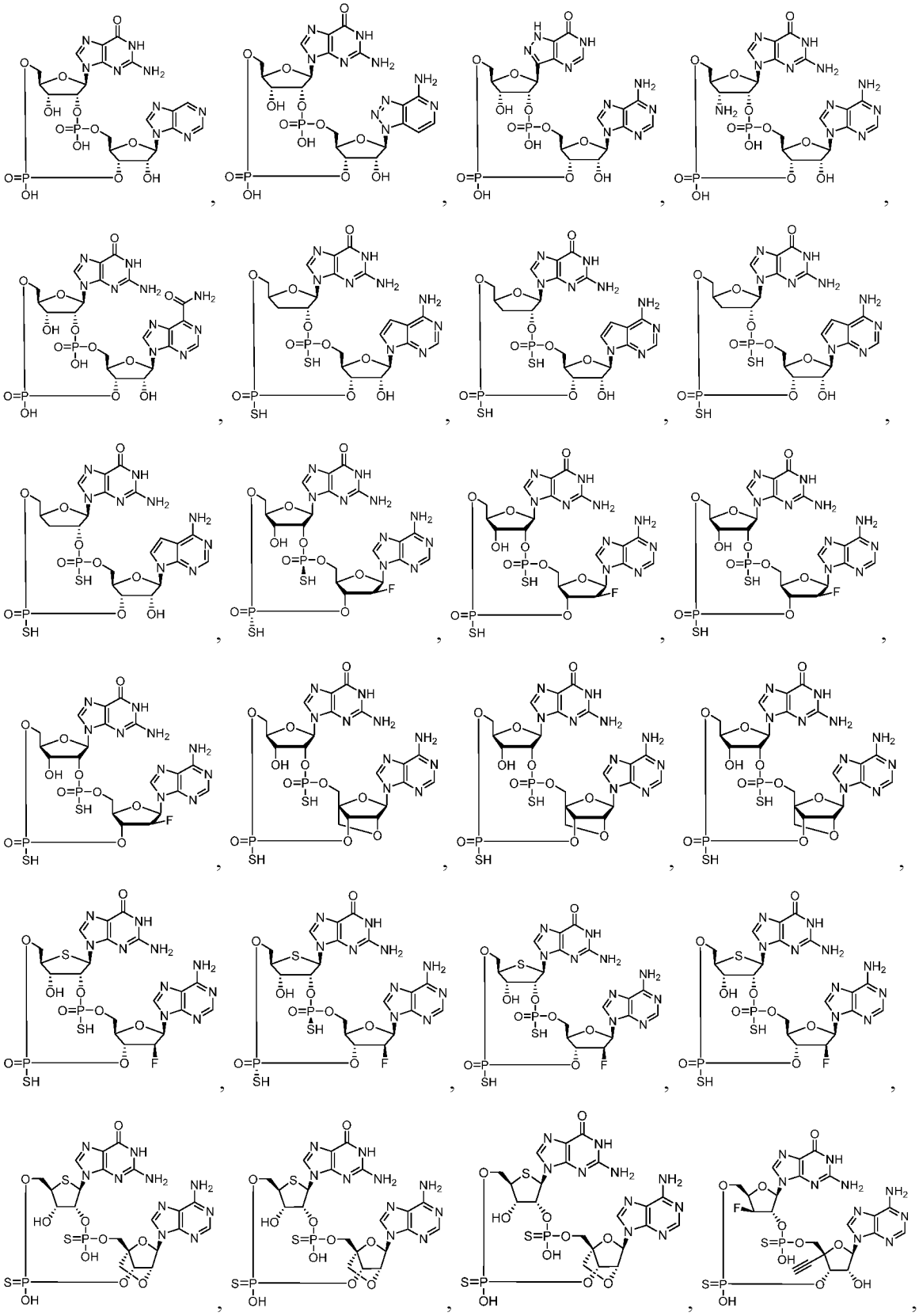
-O-C_2-C_6 alkynylene, said O is bound at the R^3 position; optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position; optionally R^4 and R^5 are connected to form are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position; optionally R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position; optionally R^7 and R^8 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene; and optionally R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene.

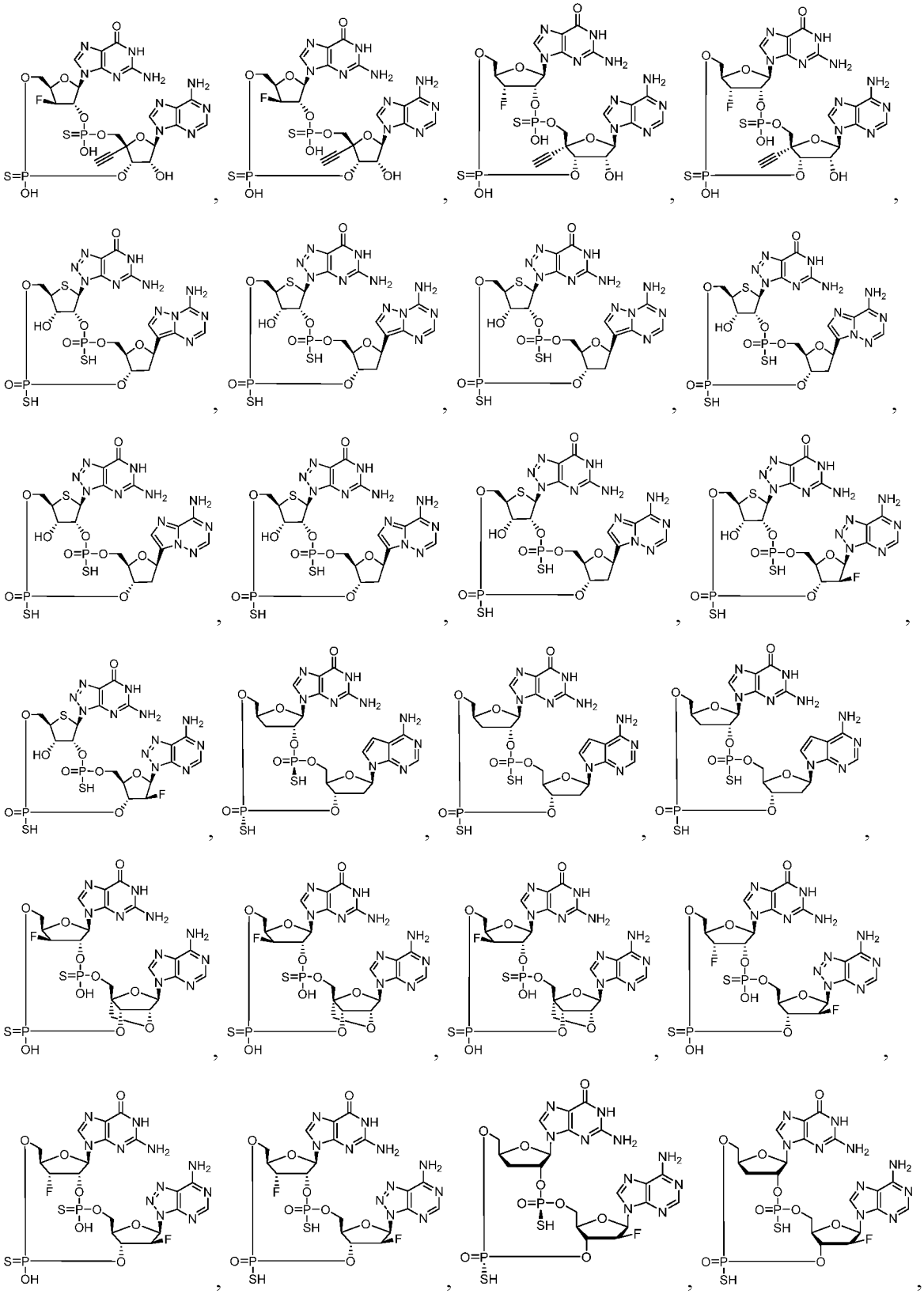
[0178] In instances of these embodiments, the cyclic dinucleotide STING agonist is selected from the group consisting of:

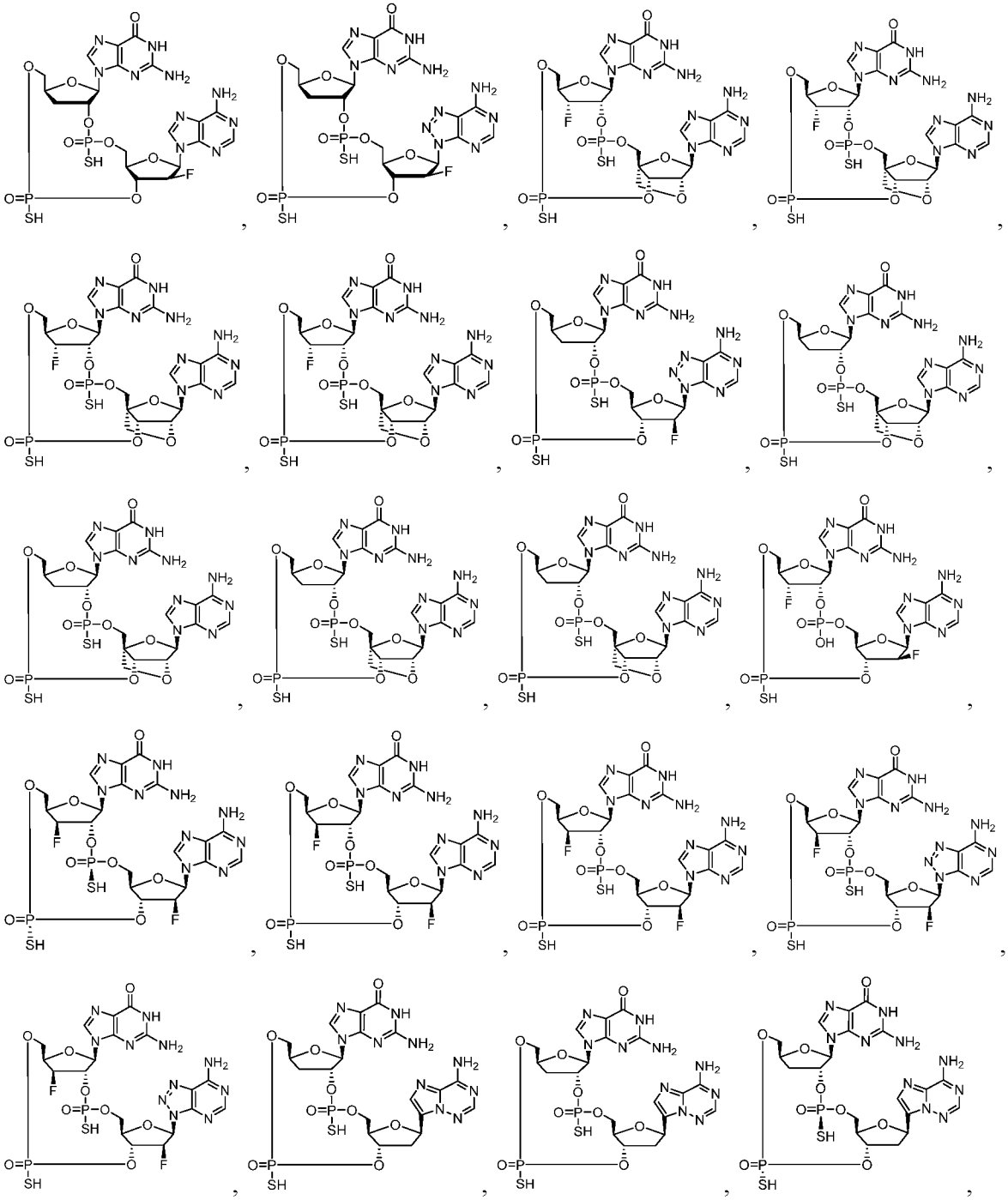


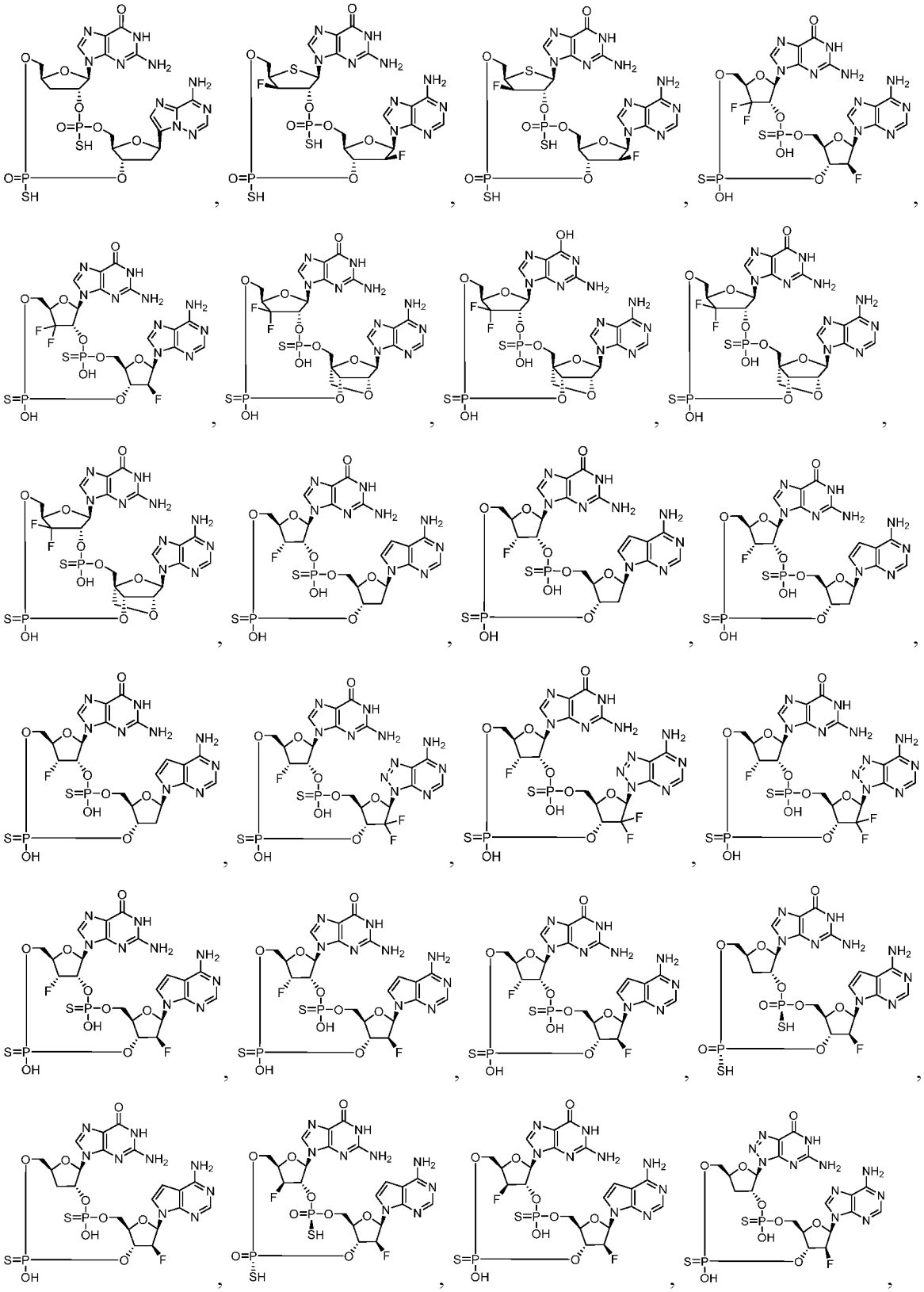


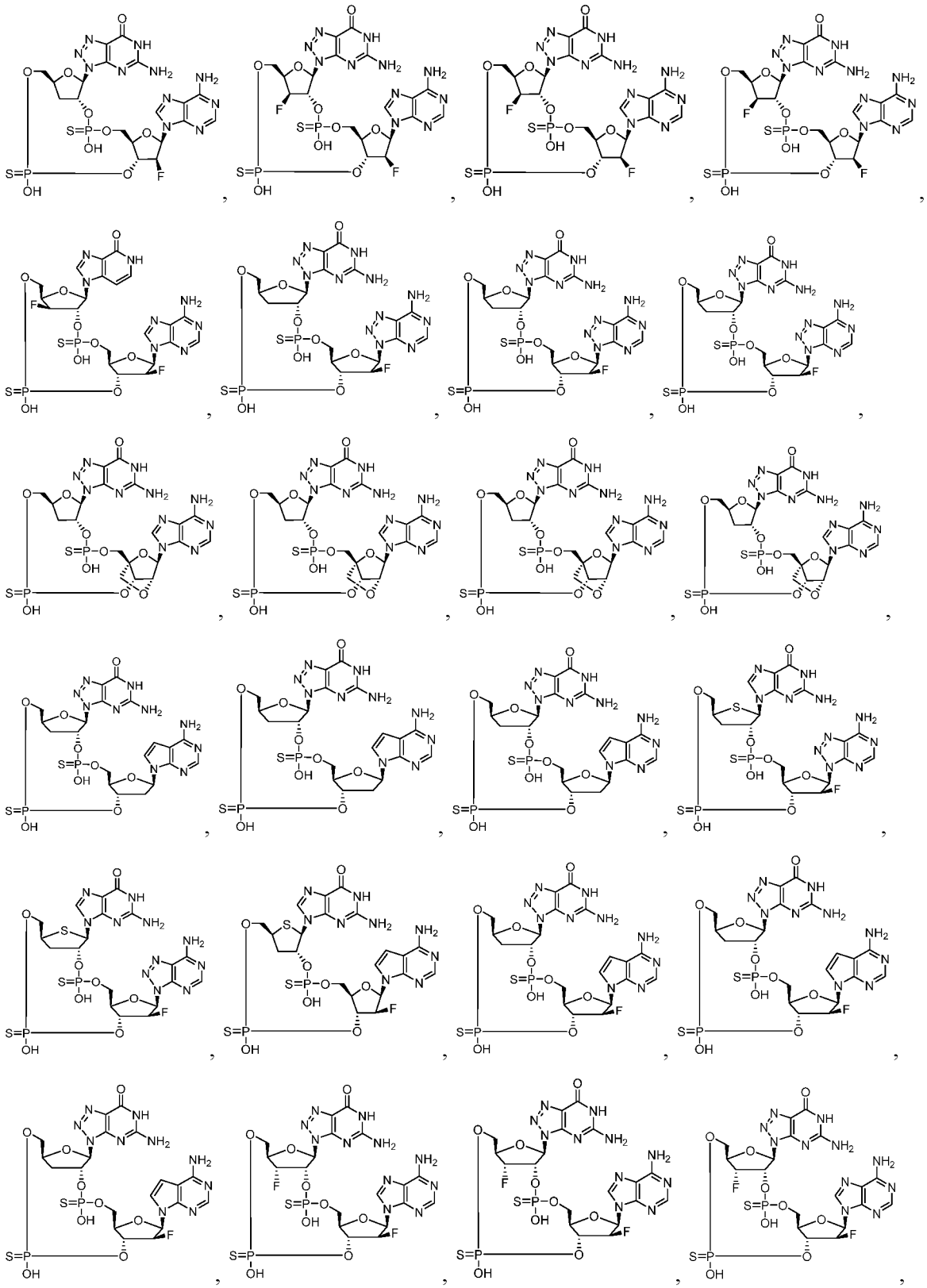


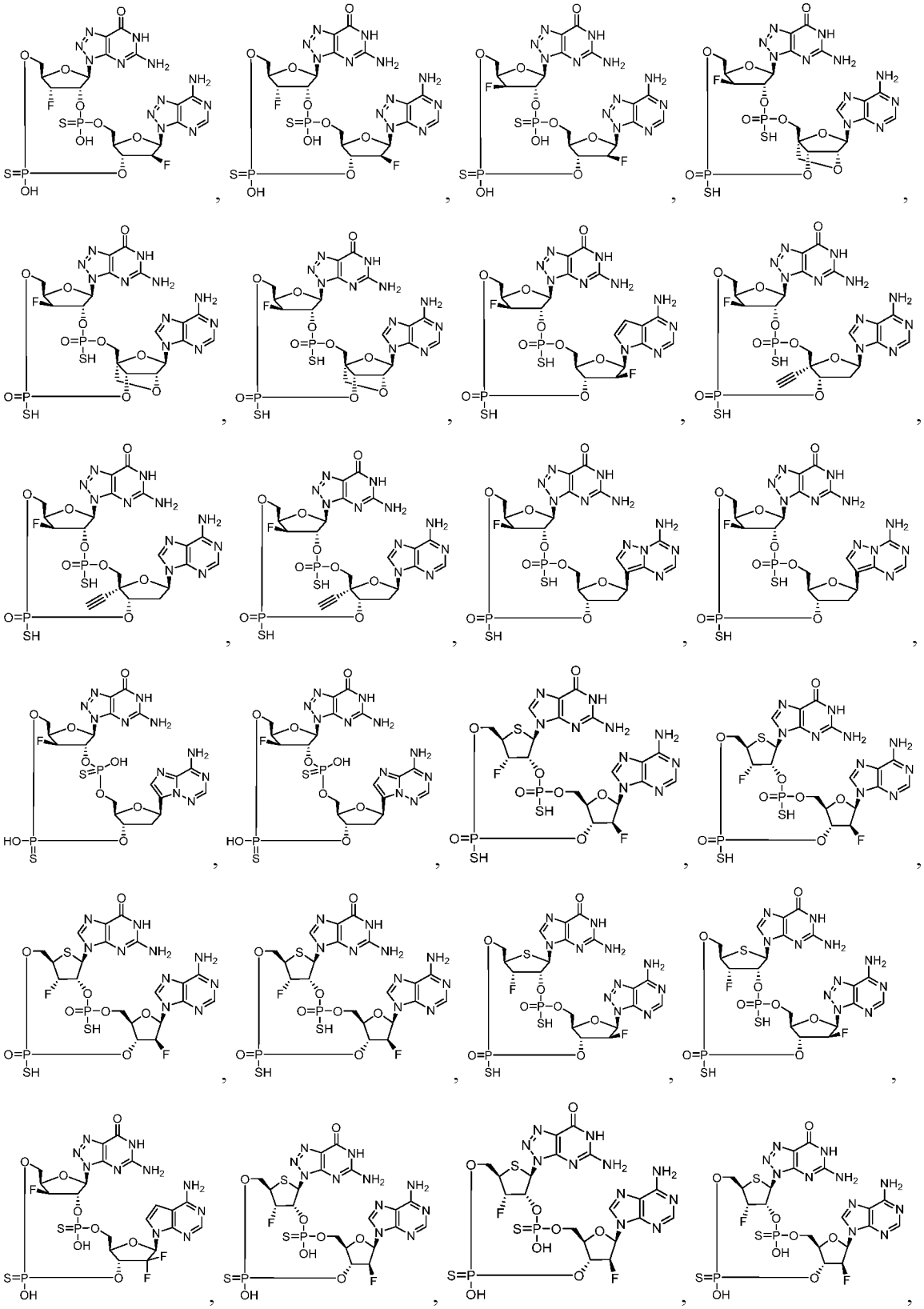


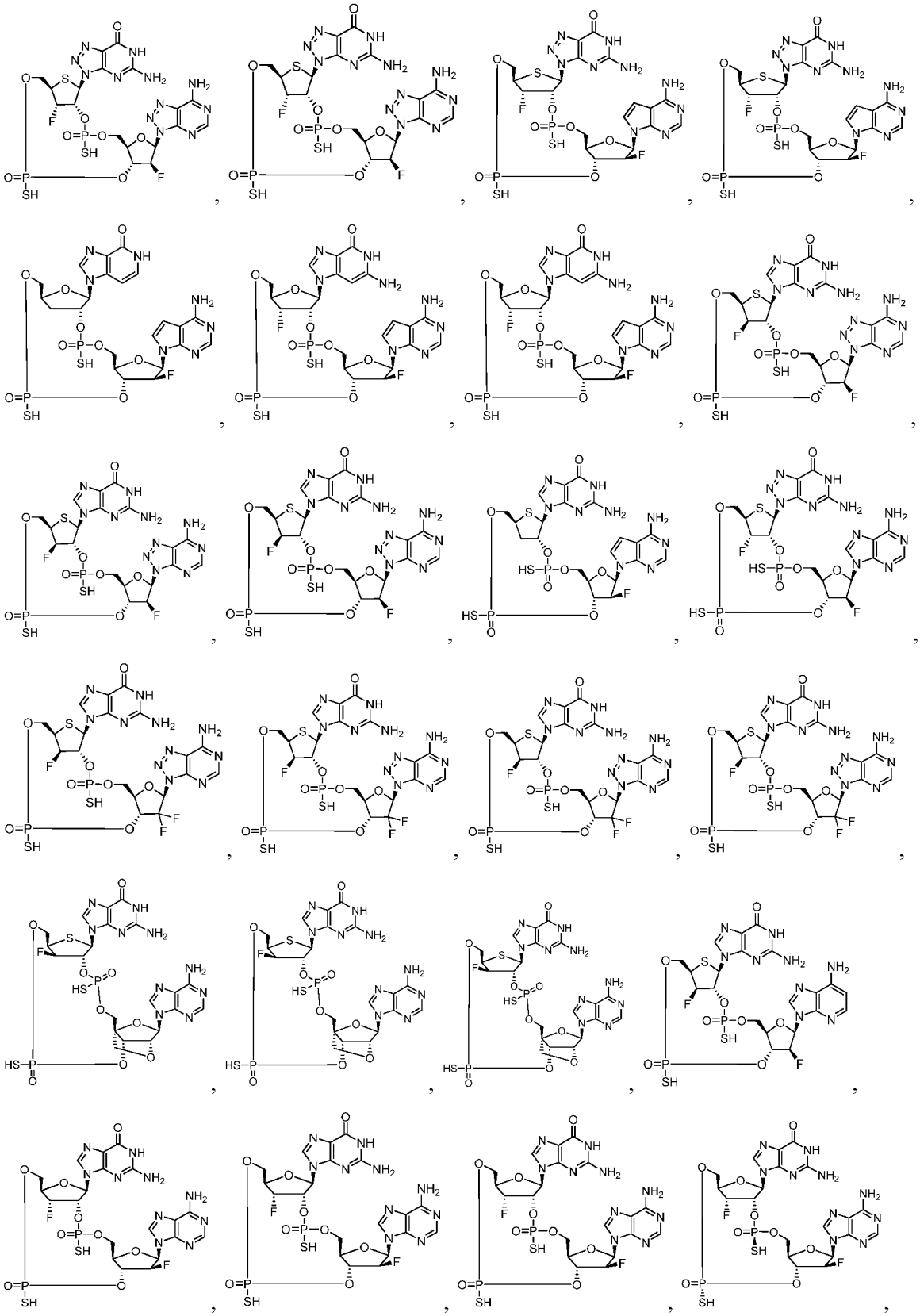


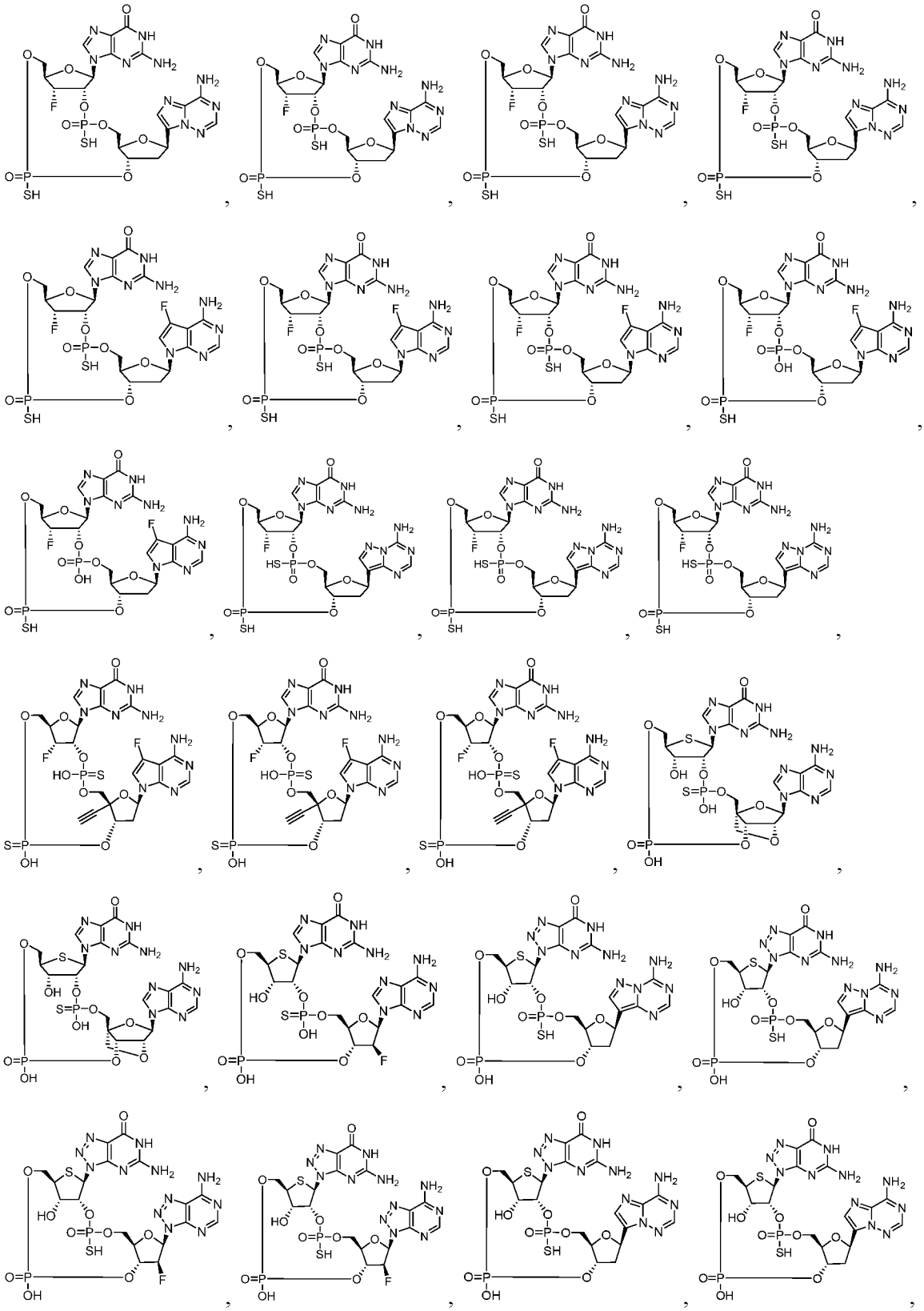


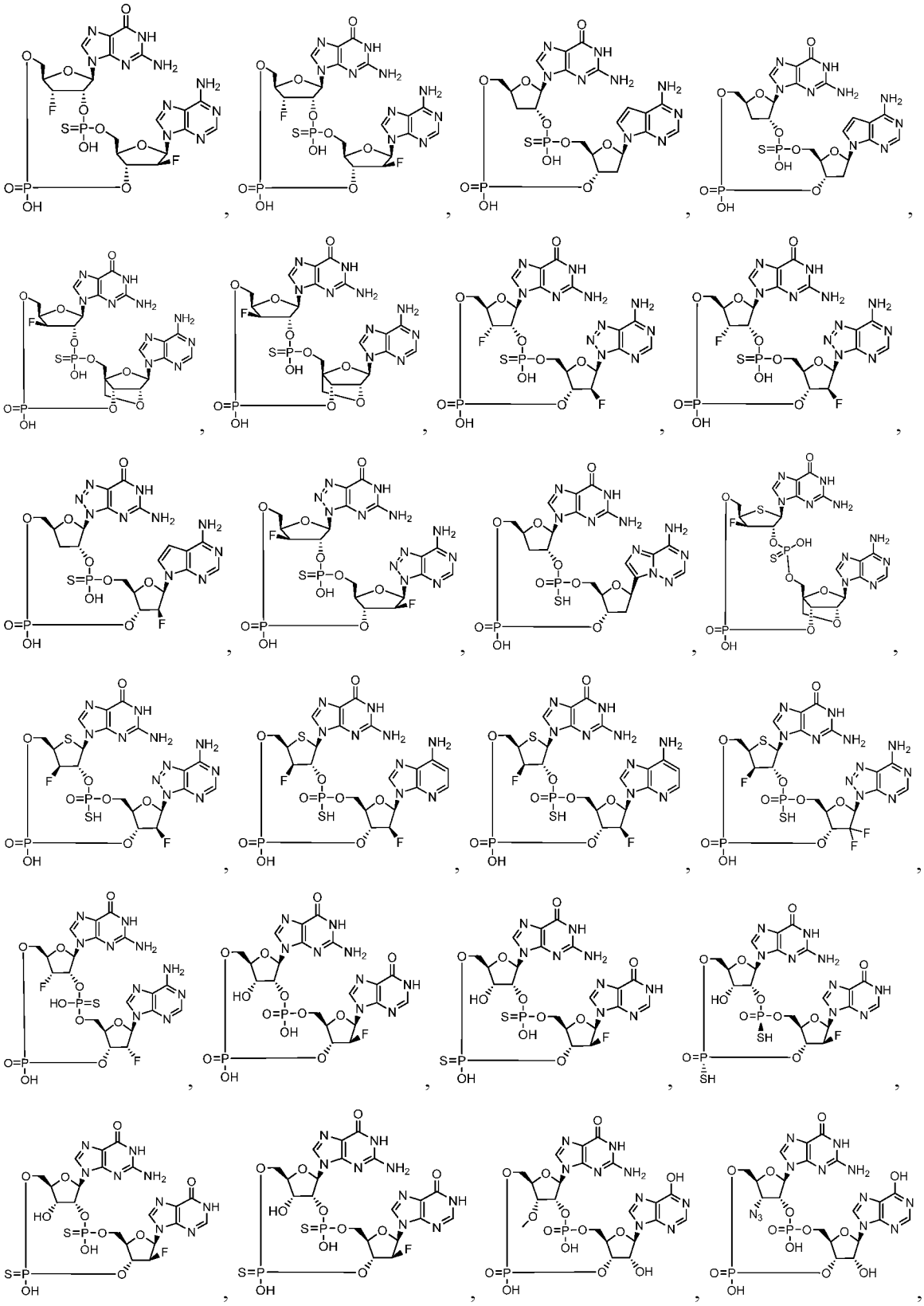


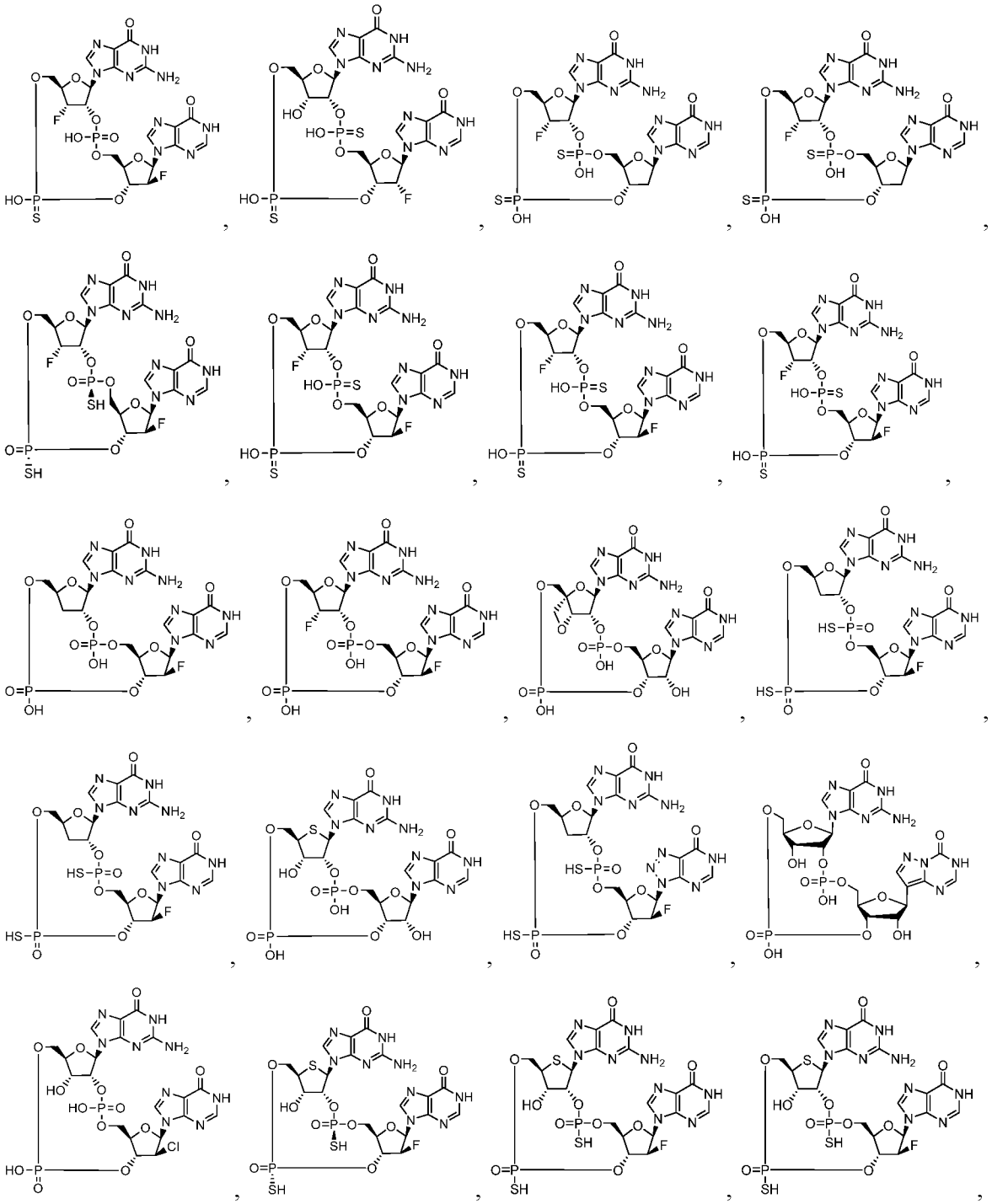


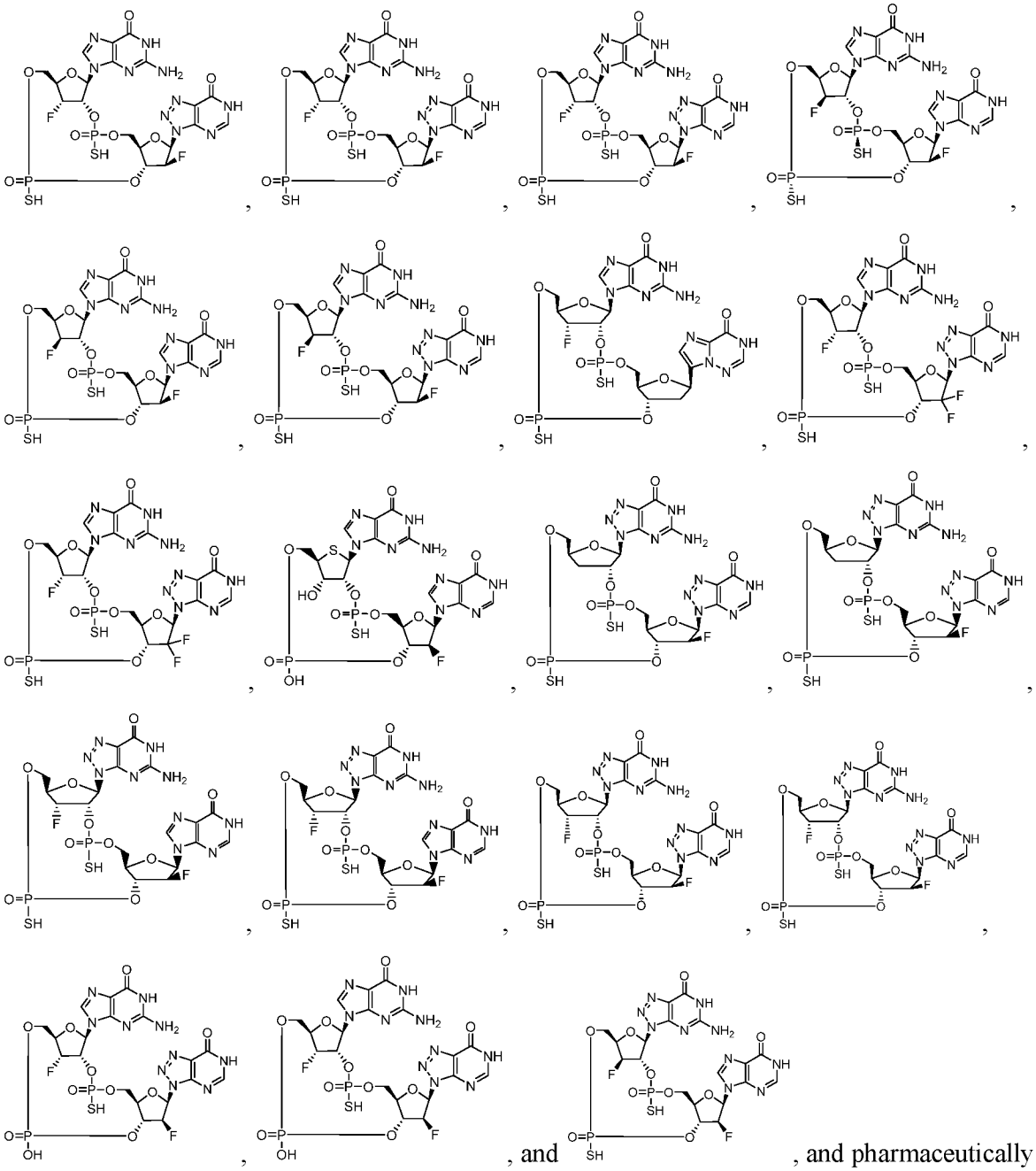












acceptable salts thereof.

[0179] In embodiments of the methods disclosed herein, the cyclic dinucleotide STING agonist is orally, by intravenous infusion, by intertumoral injection or by subcutaneous injection.

[0180] In embodiments of the methods disclosed herein, the cyclic dinucleotide STING agonist is administered at a dose of from 10μg to 3000μg. In aspects of such embodiments, the cyclic dinucleotide STING agonist is administered at a dose of from 10μg to 270μg.

[0181] Additional embodiments of the disclosure include the pharmaceutical compositions, combinations, uses and methods set forth in above, wherein it is to be understood that each embodiment may be combined with one or more other embodiments, to the extent that such a combination is consistent with the description of the embodiments. It is further to be understood that the embodiments provided above are understood to include all embodiments, including such embodiments as result from combinations of embodiments.

GENERAL METHODS

[0182] Standard methods in molecular biology are described Sambrook, Fritsch and Maniatis (1982 & 1989 2nd Edition, 2001 3rd Edition) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Sambrook and Russell (2001) *Molecular Cloning, 3rd ed.*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Wu (1993) *Recombinant DNA*, Vol. 217, Academic Press, San Diego, CA). Standard methods also appear in Ausbel, *et al.* (2001) *Current Protocols in Molecular Biology, Vols.1-4*, John Wiley and Sons, Inc. New York, NY, which describes cloning in bacterial cells and DNA mutagenesis (Vol. 1), cloning in mammalian cells and yeast (Vol. 2), glycoconjugates and protein expression (Vol. 3), and bioinformatics (Vol. 4).

[0183] Methods for protein purification including immunoprecipitation, chromatography, electrophoresis, centrifugation, and crystallization are described (Coligan, *et al.* (2000) *Current Protocols in Protein Science, Vol. 1*, John Wiley and Sons, Inc., New York). Chemical analysis, chemical modification, post-translational modification, production of fusion proteins, glycosylation of proteins are described (*see*, e.g., Coligan, *et al.* (2000) *Current Protocols in Protein Science, Vol. 2*, John Wiley and Sons, Inc., New York; Ausubel, *et al.* (2001) *Current Protocols in Molecular Biology, Vol. 3*, John Wiley and Sons, Inc., NY, NY, pp. 16.0.5-16.22.17; Sigma-Aldrich, Co. (2001) *Products for Life Science Research*, St. Louis, MO; pp. 45-89; Amersham Pharmacia Biotech (2001) *BioDirectory*, Piscataway, N.J., pp. 384-391). Production, purification, and fragmentation of polyclonal and monoclonal antibodies are described (Coligan, *et al.* (2001) *Current Protocols in Immunology, Vol. 1*, John Wiley and Sons, Inc., New York; Harlow and Lane (1999) *Using Antibodies*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Harlow and Lane, *supra*). Standard techniques for characterizing ligand/receptor interactions are available (*see*, e.g., Coligan, *et al.* (2001) *Current Protocols in Immunology, Vol. 4*, John Wiley, Inc., New York).

[0184] Monoclonal, polyclonal, and humanized antibodies can be prepared (*see*, e.g., Sheperd and Dean (eds.) (2000) *Monoclonal Antibodies*, Oxford Univ. Press, New York, NY; Kontermann and Dubel (eds.) (2001) *Antibody Engineering*, Springer-Verlag, New York; Harlow and Lane (1988) *Antibodies A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 139-243; Carpenter, *et al.* (2000) *J. Immunol.* 165:6205; He, *et al.* (1998) *J. Immunol.* 160:1029; Tang *et al.* (1999) J. Biol. Chem. 274:27371-27378; Baca *et al.* (1997) *J. Biol. Chem.* 272:10678-10684; Chothia *et al.* (1989) *Nature* 342:877-883; Foote and Winter (1992) *J. Mol. Biol.* 224:487-499; U.S. Pat.6,329,511).

[0185] An alternative to humanization is to use human antibody libraries displayed on phage or human antibody libraries in transgenic mice (Vaughan *et al.* (1996) *Nature* Biotechnol. 14:309-314; Barbas (1995) *Nature Medicine* 1:837-839; Mendez *et al.* (1997) *Nature Genetics* 15:146-156; Hoogenboom and Chames (2000) *Immunol. Today* 21:371-377; Barbas *et al.* (2001) *Phage Display: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; Kay *et al.* (1996) *Phage Display of Peptides and Proteins: A Laboratory Manual*, Academic Press, San Diego, CA; de Bruin *et al.* (1999) *Nature Biotechnol.* 17:397-399). Purification of antigen is not necessary for the generation of antibodies. Animals can be immunized with cells bearing the antigen of interest. Splenocytes can then be isolated from the immunized animals, and the splenocytes can be fused with a myeloma cell line to produce a hybridoma (*see*, e.g., Meyaard *et al.* (1997) *Immunity* 7:283-290; Wright *et al.* (2000) *Immunity* 13:233-242; Preston *et al.*, *supra*; Kaithamana *et al.* (1999) *J. Immunol.* 163:5157-5164).

[0186] Methods for flow cytometry, including fluorescence activated cell sorting (FACS), are available (*see*, e.g., Owens, *et al.* (1994) *Flow Cytometry Principles for Clinical Laboratory Practice*, John Wiley and Sons, Hoboken, NJ; Givan (2001) *Flow Cytometry, 2nd ed.*; Wiley-Liss, Hoboken, NJ; Shapiro (2003) *Practical Flow Cytometry*, John Wiley and Sons, Hoboken, NJ). Fluorescent reagents suitable for modifying nucleic acids, including nucleic acid primers and probes, polypeptides, and antibodies, for use, e.g., as diagnostic reagents, are available (Molecular Probesy (2003) *Catalogue*, Molecular Probes, Inc., Eugene, OR; Sigma-Aldrich (2003) *Catalogue*, St. Louis, MO).

[0187] Standard methods of histology of the immune system are described (*see*, e.g., Muller-Harmelink (ed.) (1986) *Human Thymus: Histopathology and Pathology*, Springer Verlag,

New York, NY; Hiatt, *et al.* (2000) *Color Atlas of Histology*, Lippincott, Williams, and Wilkins, Phila, PA; Louis, *et al.* (2002) *Basic Histology: Text and Atlas*, McGraw-Hill, New York, NY).

[0188] Software packages and databases for determining, e.g., antigenic fragments, leader sequences, protein folding, functional domains, glycosylation sites, and sequence alignments, are available (*see*, e.g., GenBank, Vector NTI® Suite (Informax, Inc., Bethesda, MD); GCG Wisconsin Package (Accelrys, Inc., San Diego, CA); DeCypher® (TimeLogic Corp., Crystal Bay, Nevada); Menne, *et al.* (2000) *Bioinformatics* 16: 741-742; Menne, *et al.* (2000) *Bioinformatics Applications Note* 16:741-742; Wren, *et al.* (2002) *Comput. Methods Programs Biomed.* 68:177-181; von Heijne (1983) *Eur. J. Biochem.* 133:17-21; von Heijne (1986) *Nucleic Acids Res.* 14:4683-4690).

Advanced MC38 Mouse Syngenic Tumor Model

[0189] Synergistic tumor models are recognized to be appropriate models to evaluate anti-tumor efficiacy of agents that target specific molecules, pathways, or cell types and to provide mechanistic rationale that targeting similar specific molecules, pathways, or cell types in human tumors will lead to favorable clinical outcomes. The mouse syngeneic MC38 tumor model is a mouse colon adenocarcinoma cell line that was established by carcinogenic induction of tumors in the C57BL/6 background. This cell line is considered immunogenic and is responsive to immune modulation. It is generally injected subcutaneously (SC) to evaluate tumor growth and response to treatment. Specifically, each animal is inoculated in the right lower flank with a SC dose of 1×10^6 MC38 colon adenocarcinoma cells in 100µL of serum-free Dulbecco's modified Eagle's medium. Tumor progression is monitored by measuring tumor volume using Vernier calipers. *See* T.H. Corbett *et al.*, *Tumor Induction Relationships in Development of Transplantable Cancers of the Colon in Mice for Chemotherapy Assays, with a Note on Carcinogen Structure*, 35(9) Cancer Res. 2434-2439 (September 1, 1975).

EXAMPLES

Example 1: Anti-Tumor Efficacy of a CDN STING Agonist Alone in Advanced MC38 Mouse Syngenic Tumor Model

[0190] To assess the anti-tumor efficacy of a CDN STING agonist in the advanced MC38 mouse syngeneic tumor model, a cohort of 8-12 week old female C57Bl/6 mice are implanted with $1x10^6$ MC38 cells. When the tumors reach a median size of approximately $350mm^3$, the animals are randomized into 6 treatment groups of 10 mice per group:

Treatment Group A: PBS and mIgG1 (5mg/kg)

Treatment Group B: CDN STING agonist (5μg) and mIgG1 (5mg/kg)

[0191] CDN STING agonist is administered intratumorally on every 3 to 7 days for up to 30 days. The study period will be 30 days post initiation of the dosing regimens.

[0192] Tumors on animals in Treatment Group A are anticipated to progress rapidly. Treatment Group B will be observed for tumor regression and number of CRs. It is anticipated that CDN STING agonist will demonstrate superior efficacy.

[0193] Where the foregoing experiment was conducted with select CDN STING agonists described herein, significant anti-tumor activity was noted in Treatment Group B relative to Treatment Group A.

Example 2: Clinical Study Evaluating a CDN STING Agonist in Treatment of Patients with Advanced/Metastatic Solid Tumors or Lymphomas

[0194] A Phase I clinical study will be conducted to evaluate, in part, the effects of a CDN STING agonist as described above delivered via intratumoral injection, on advanced or metastatic solid tumors or lymphomas. The study is a non-randomized, 2-arm, multi-site, open-label trial of CDN STING agonist monotherapy in subjects with advanced/metastatic solid tumors or lymphomas. CDN STING agonist will be administered intratumorally (IT).

[0195] Unless deemed medically unsafe by the Investigator, all subjects will be required to provide a sample of the tumor to be injected and a sample from a distant site prior to CDN STING agonist administration during screening, as well as on Cycle 3, Day 15. Subjects with amenable lesions at both injected and non-injected sites may undergo an additional optional tumor biopsy on Cycle 6, Day 15 of both the injected lesion and the non-injected lesion. Subjects will undergo a 24-hour observation period following the first dose administration on Cycle 1, Day 1. Each cycle within the trial is a 21-day cycle. Dosing in the first 3 cycles is once a week (Q1W) and dosing in cycles 4 and beyond is once every 3 weeks (Q3W).

[0196] Dose escalation will proceed based on emerging safety and tolerability data of CDN STING agonist. For each dose level, an assessment will be made of the safety and tolerability data in order to define the next dose level to be tested. The treatment will start with an accelerated titration design (ATD) followed by the modified toxicity probability interval (mTPI) method to identify a maximum tolerated dose (MTD) or maximum administered dose (MAD) of CDN STING agonist. Starting with a dose of 10μg of CDN STING agonist in single

patient cohorts (Part A), the trial will proceed in an ATD up to a dose that meets at least 1 of the following 3 criteria: 1) The 270μg cohort is completed, 2) ≥ Grade 2 non-disease-related toxicity at any dose level, or 3) Elevation of systemic TNF-α in blood above baseline levels by ≥ 3 fold increase for a given subject at any time during the first cycle of CDN STING agonist. Upon completion of the ADT phase by reaching at least one of the above triggering criteria, the study will proceed to a dose escalation and confirmation phase (Part B), using an mTPI design.

[0197] Intra-subject dose escalation of CDN STING agonist to the next dose level is permitted in Parts A and B. Intrasubject dose escalation will be at the discretion of the Investigator, provided that the subject remains on study after receiving 3 cycles of treatment without ≥ Grade 2 toxicity, and provided that the dose escalation has proceeded beyond the next dose level.

[0198] During CDN STING agonist dose escalation, at least 7 days of observation will occur between each of the first 2 subjects at each dose level. Over-enrollment in ATD up to 3 subjects per cohort is permitted, provided that the first 2 subjects will receive CDN STING agonist treatment at least 7 days apart. Dose escalation of CDN STING agonist to determine the MTD/MAD will be guided by the mTPI design, targeting a DLT rate of 30%.

[0199] A minimum of 3 subjects are required at each dose level during mTPI. The mTPI phase will have up to 3 to 6 subjects per cohort, and based on the occurrence of DLTs, up to 14 subjects may enroll per dose level. Therefore, during mTPI, up to 14 subjects may be enrolled per dose level, depending on the occurrence of a dose-limiting toxicity (DLT). Subjects may continue on their assigned treatment for up to 35 cycles (approximately 2 years) from the start of treatment. Treatment may continue until one of the following occurs: disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, Investigator decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trials treatment or procedure requirements, or administrative reasons requiring cessation of treatment.

[0200] The final number of subjects enrolled in the dose escalation and confirmation parts of the study will depend on the empirical safety data (DLT observations, in particular, at which dose the mTPI design is triggered and at which dose the preliminary recommended Phase 2 dose is identified). For example, in a scenario where CDN STING agonist starts at 10μg and continues to the highest dose, the sample size across Parts A and B may be approximately 40 subjects. An administrative analysis may be conducted to enable future trial planning at the

Sponsor's discretion, and data will be examined on a continuous basis to allow for dose escalation and confirmation decisions.

[0201] The trial will be conducted in conformance with Good Clinical Practices.

[0202] Adverse Experiences (AEs) will be evaluated according to criteria outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.

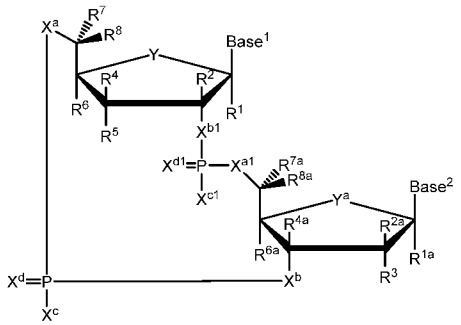
[0203] It will be appreciated that various of the above-discussed and other features and functions, or alternatives thereof, may be desirably combined into many other different systems or applications. Also that various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art which are also intended to be encompassed by the following claims.

WHAT IS CLAIMED IS:

1. A method of treating a cell-proliferation disorder, said method comprising administering to a subject in need thereof a cyclic dinucleotide STING agonist; wherein

the cyclic dinucleotide STING agonist is administered once every 3 to 28 days; and

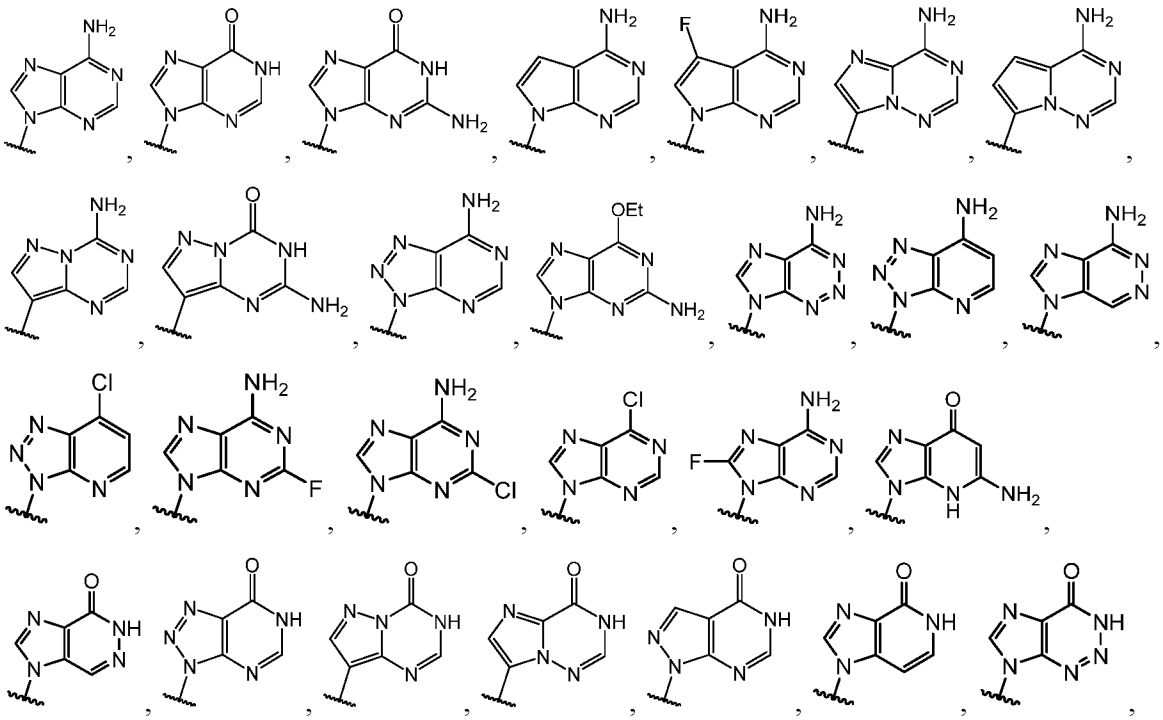
the cyclic dinucleotide STING agonist is selected from compounds of formula (I'):

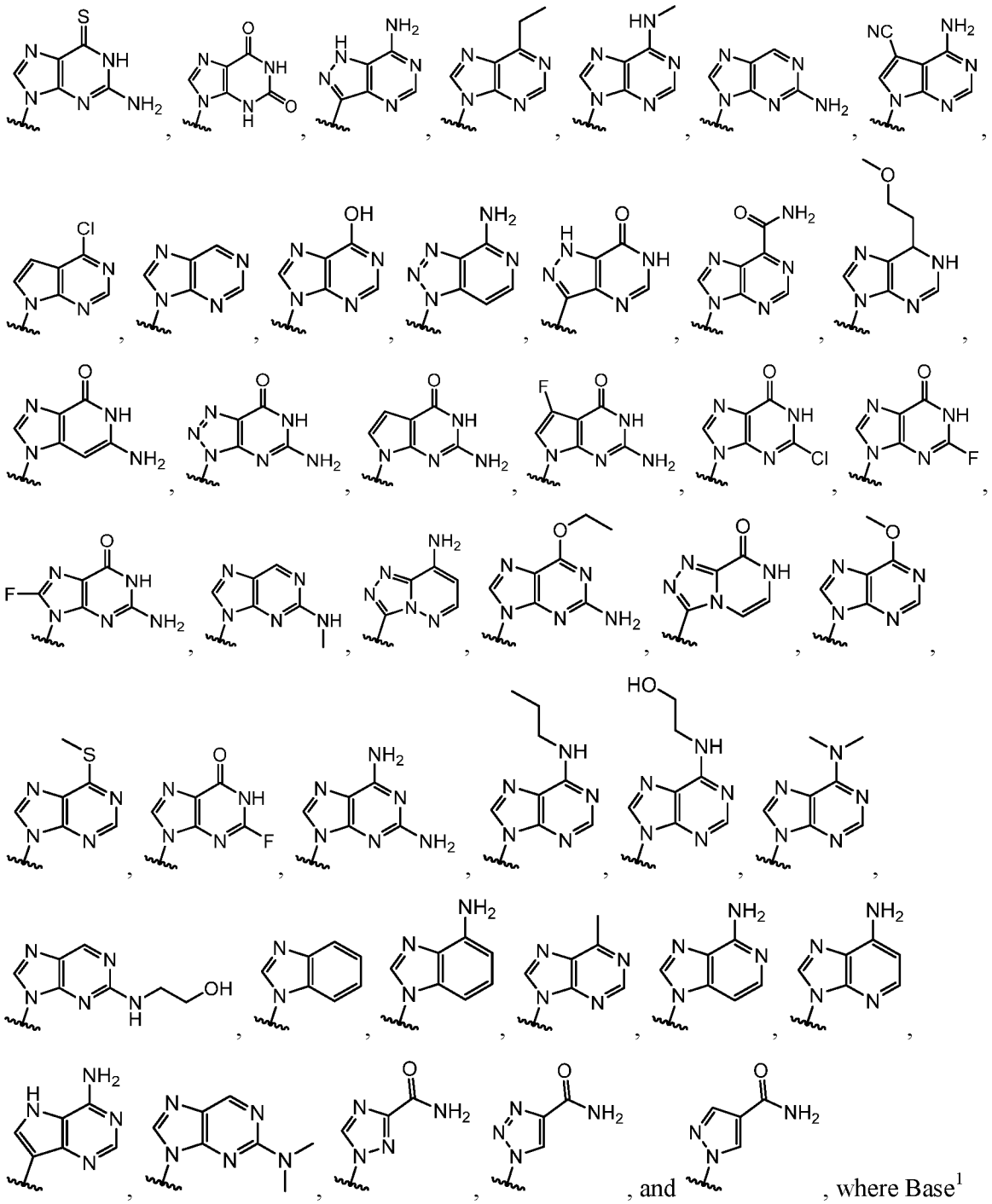


(I')

or a pharmaceutically acceptable salt thereof, wherein

$Base^1$ and $Base^2$ are each independently selected from the group consisting of





and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$;

Y and Y^a are each independently selected from the group consisting of -O- and -S-;

X^a and X^{a1} are each independently selected from the group consisting of O, and S;

X^b and X^{b1} are each independently selected from the group consisting of O, and S;

X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9;

X^d and X^{d1} are each independently selected from the group consisting of O and S;

R^1 and R^{1a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^1 and R^{1a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^2 and R^{2a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^3 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

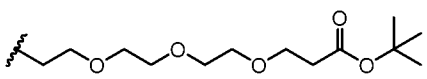
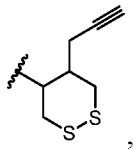
R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^4 and R^{4a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^5 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, NR^9R^9, and N_3;

R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^6 and R^{6a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^7 and R^{7a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^7 and R^{7a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^8 and R^{8a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^8 and R^{8a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,  , and  , where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl;

optionally R^{1a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that

where R^{1a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position;

optionally R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^{2a} and R^3 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position;

optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^3 position;

optionally R^4 and R^5 are connected to form are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position;

optionally R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position;

optionally R^7 and R^8 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene; and

optionally R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene.

2. The method according to claim 1, wherein the cell-proliferation disorder is cancer.

3. The method according to claim 2, wherein the cancer occurs as one or more solid tumors or lymphomas.

4. The method according to claim 2, wherein the cancer is selected from the group consisting of advanced or metastatic solid tumors and lymphomas.

5. The method according to claim 2, wherein the cancer is selected from the group consisting of malignant melanoma, head and neck squamous cell carcinoma, breast adenocarcinoma, and lymphoma.

6. The method according to any one of claims 3 to 5, wherein the lymphoma is selected from the group consisting of diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, small lymphocytic lymphoma, mediastinal large B-cell lymphoma, splenic marginal zone B-cell lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (malt), nodal marginal zone B-cell lymphoma, lymphoplasmacytic lymphoma, primary effusion lymphoma, Burkitt lymphoma, anaplastic large cell lymphoma (primary cutaneous type), anaplastic large cell lymphoma (systemic type), peripheral T-cell lymphoma, angioimmunoblastic T-cell lymphoma, adult T-cell lymphoma, nasal type extranodal NK/T-cell lymphoma, enteropathy-associated T-cell lymphoma, gamma/delta hepatosplenic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, mycosis fungoides, and Hodgkin lymphoma.

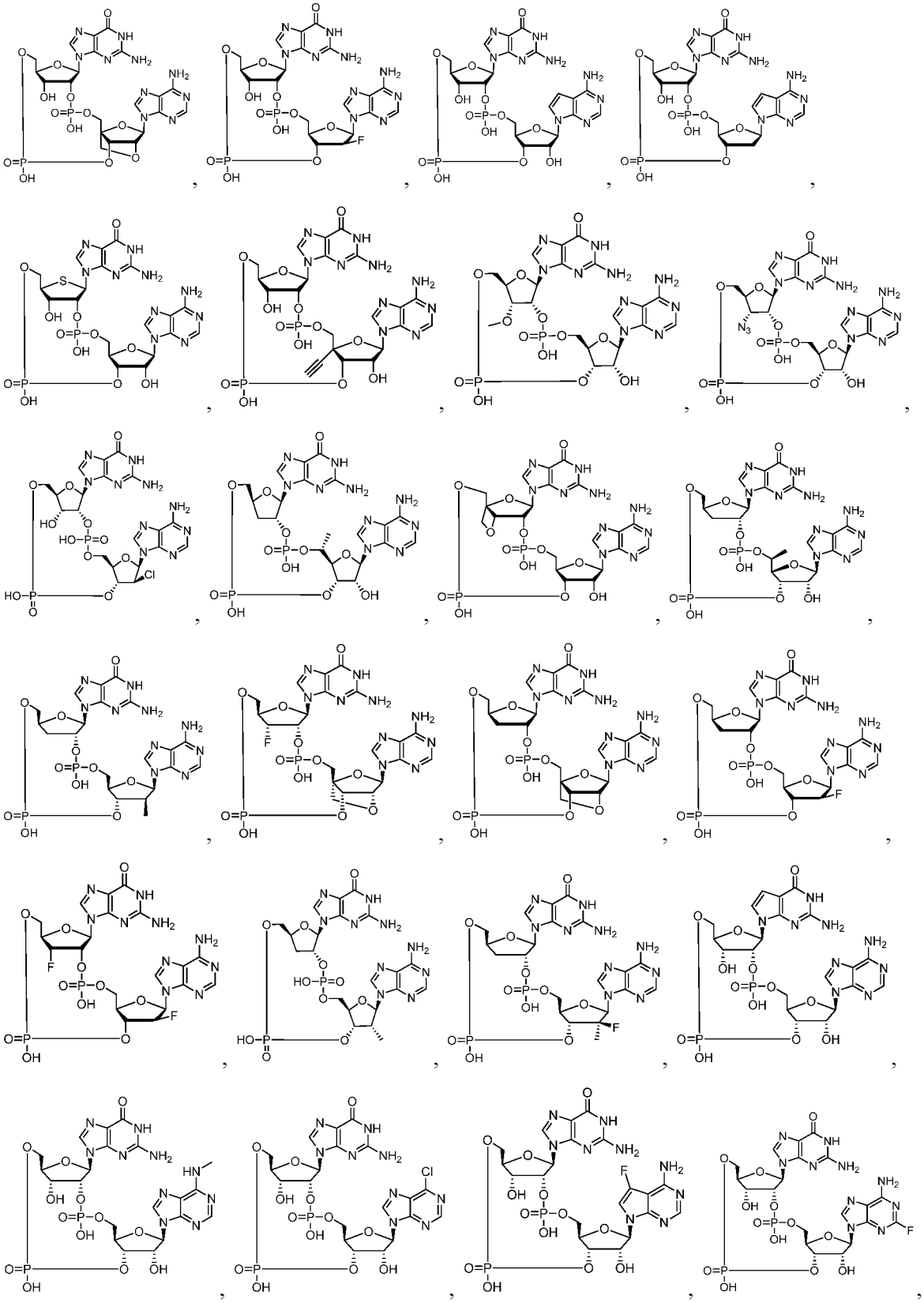
7. The method according to claim 2, wherein the cell-proliferation disorder is a cancer that has metastasized.

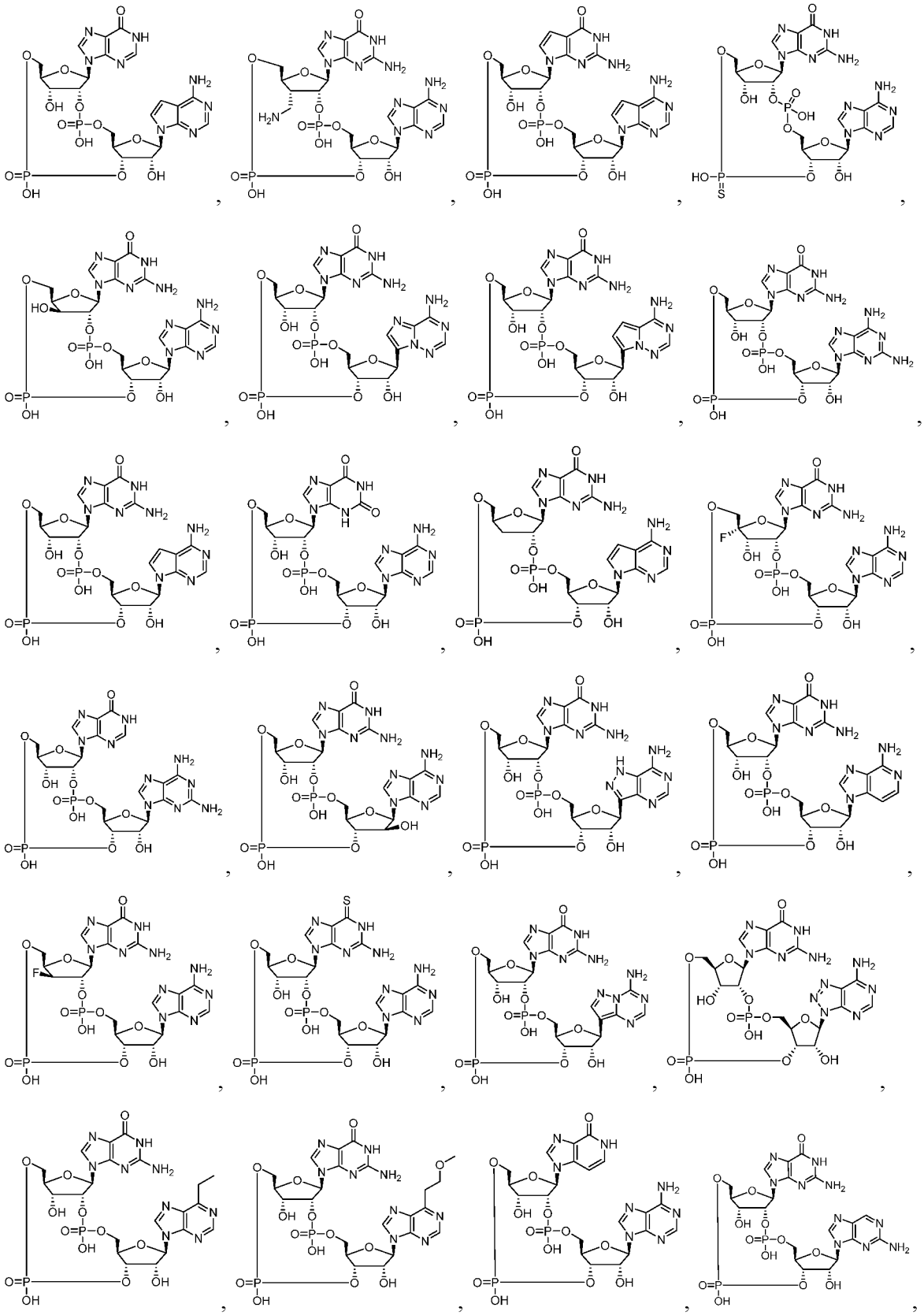
8. The method according to any one of claims 1 to 7, wherein the cyclic dinucleotide STING agonist is administered orally, by intravenous infusion, by intertumoral injection or by subcutaneous injection.

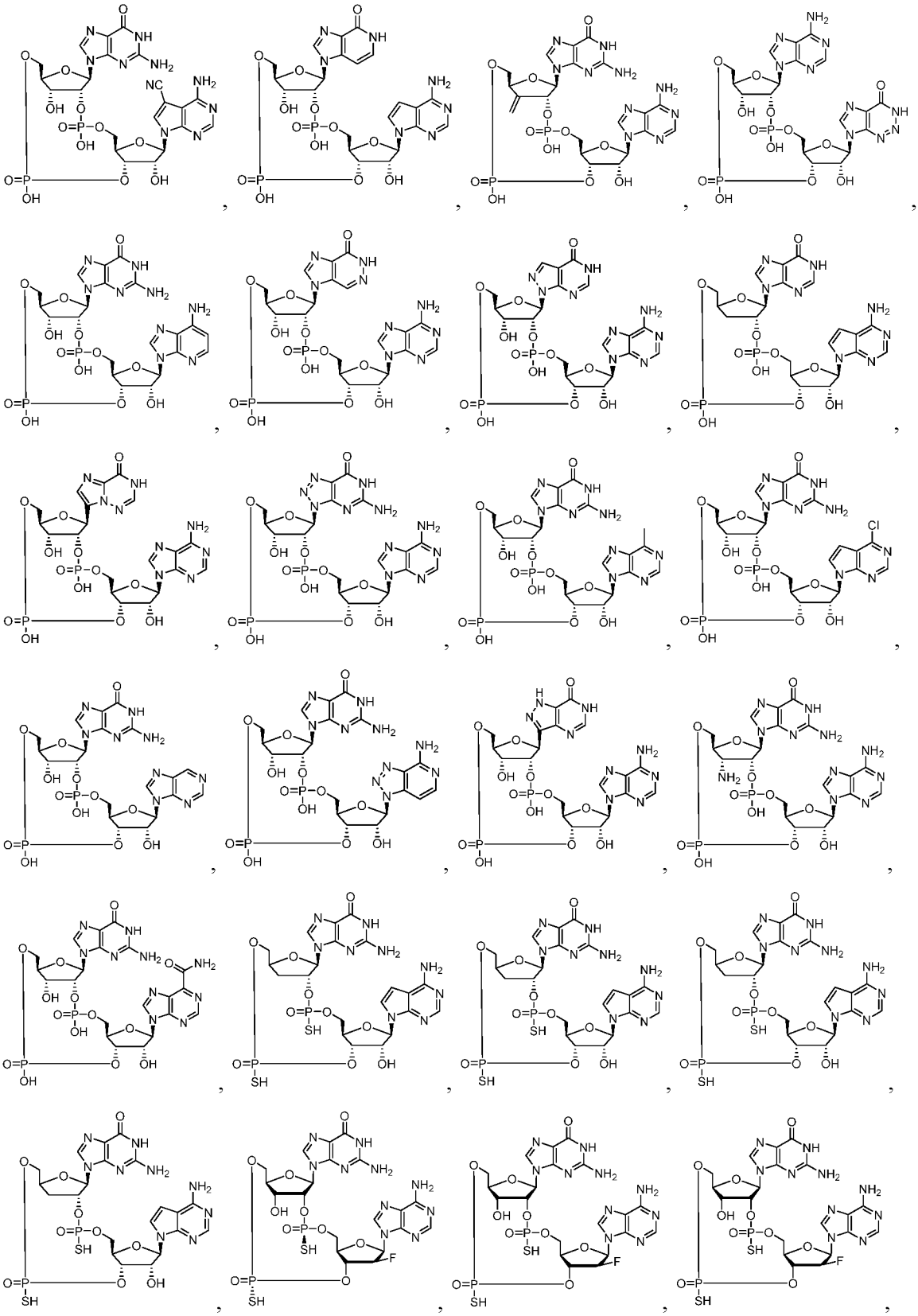
9. A method of treating a cell-proliferation disorder, said method comprising administering to a subject in need thereof a cyclic dinucleotide STING agonist; wherein

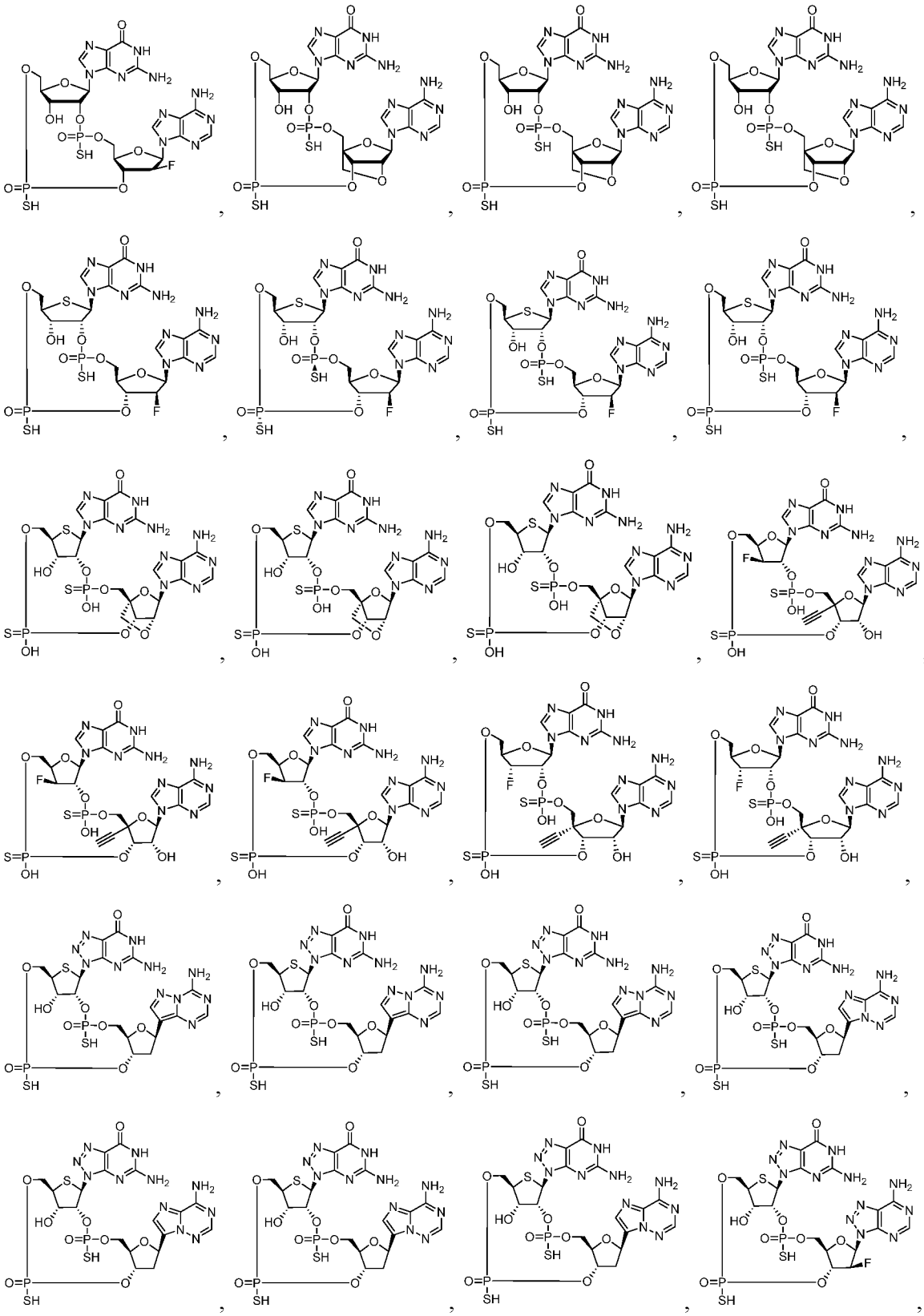
the cyclic dinucleotide STING agonist is administered once every 3 to 28 days; and

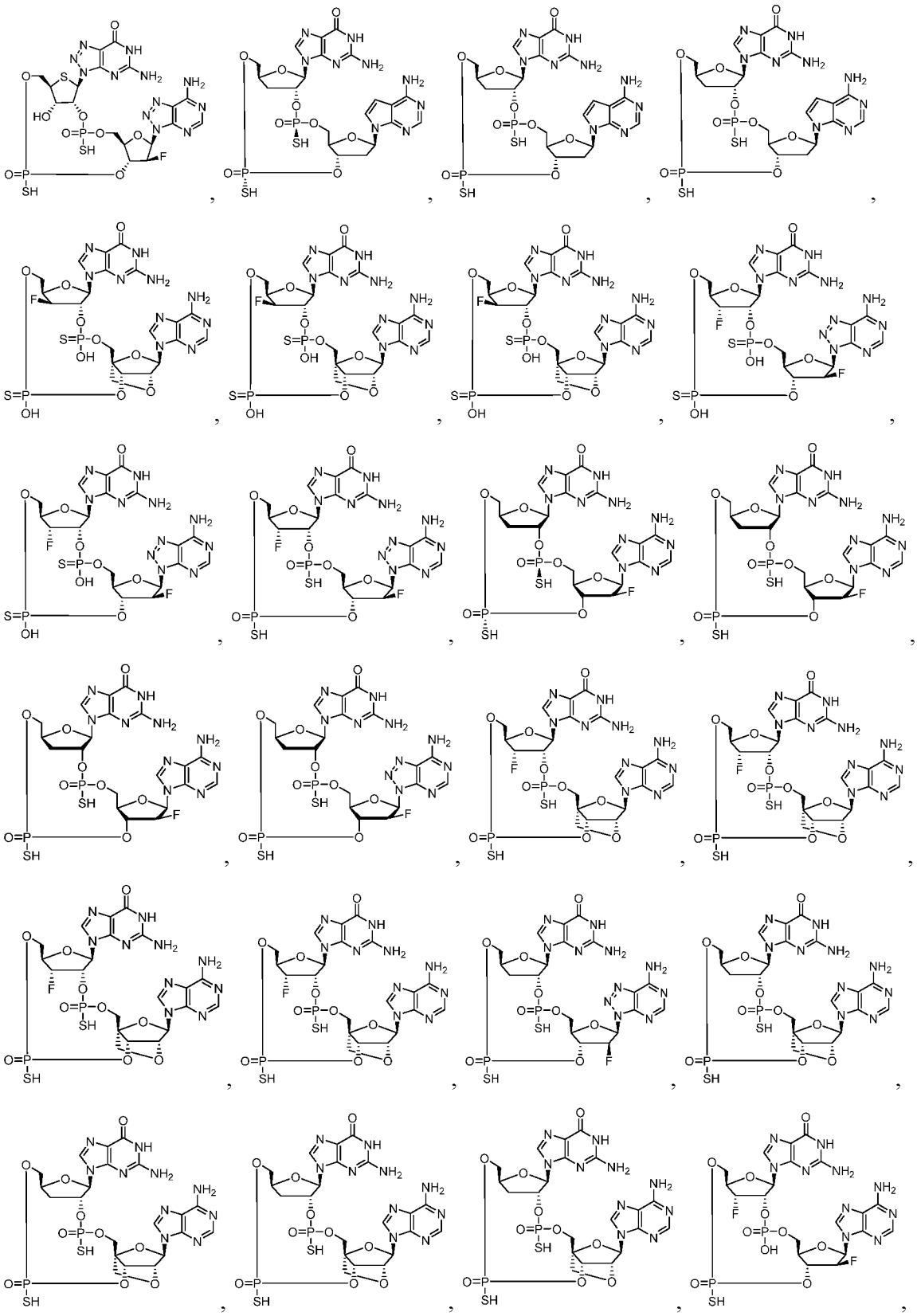
the cyclic dinucleotide STING agonist is selected from the group consisting of:

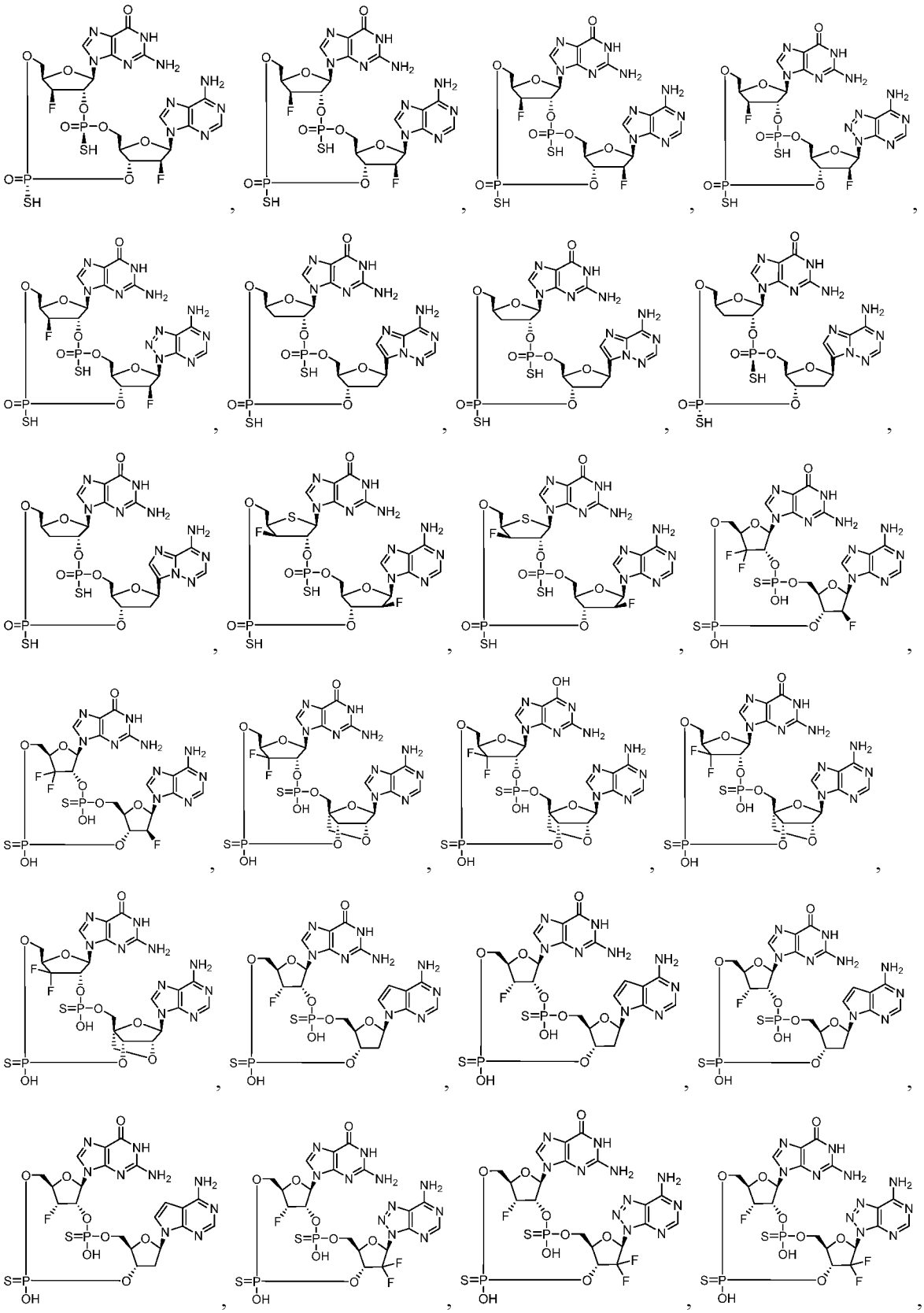


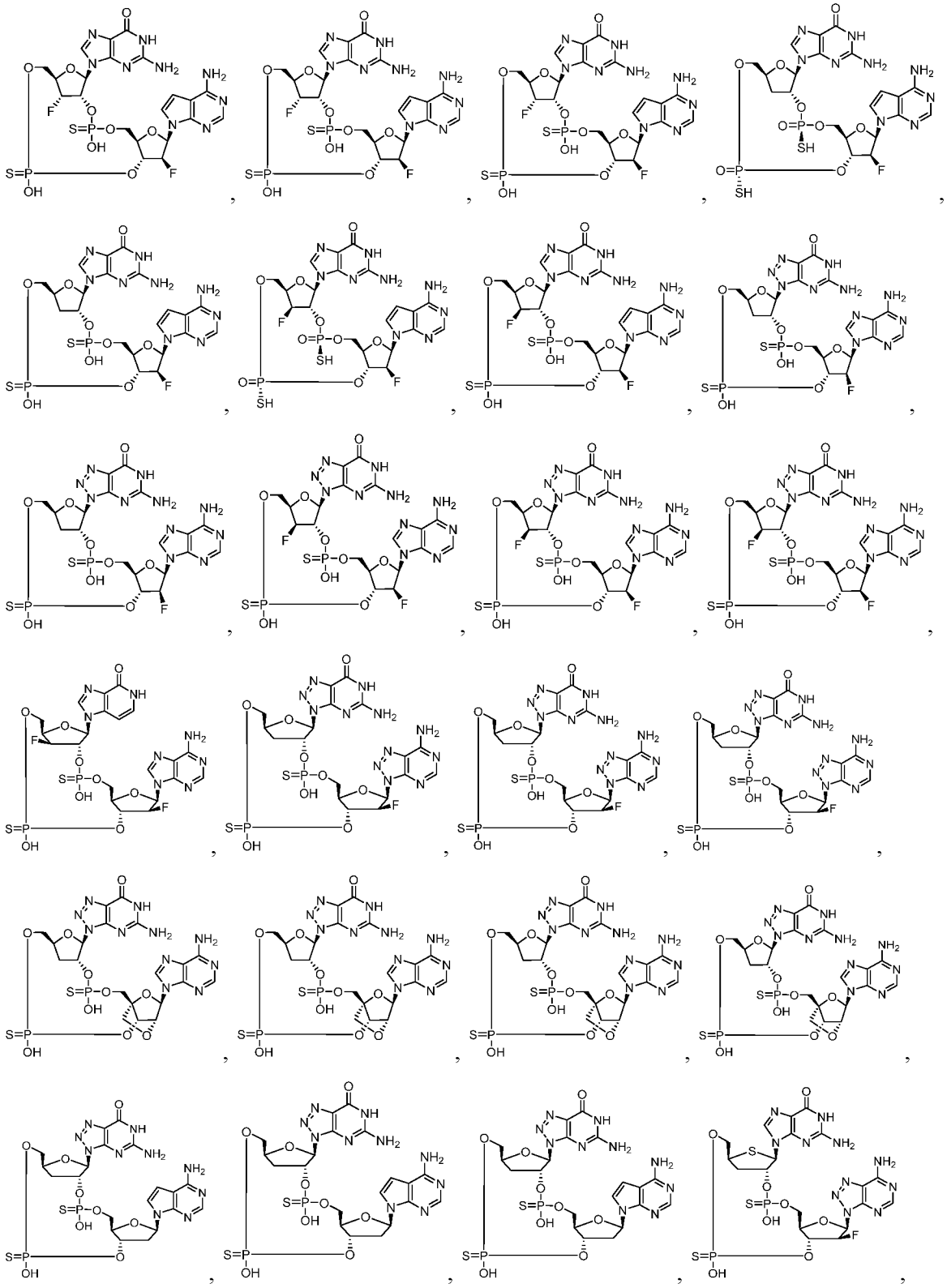


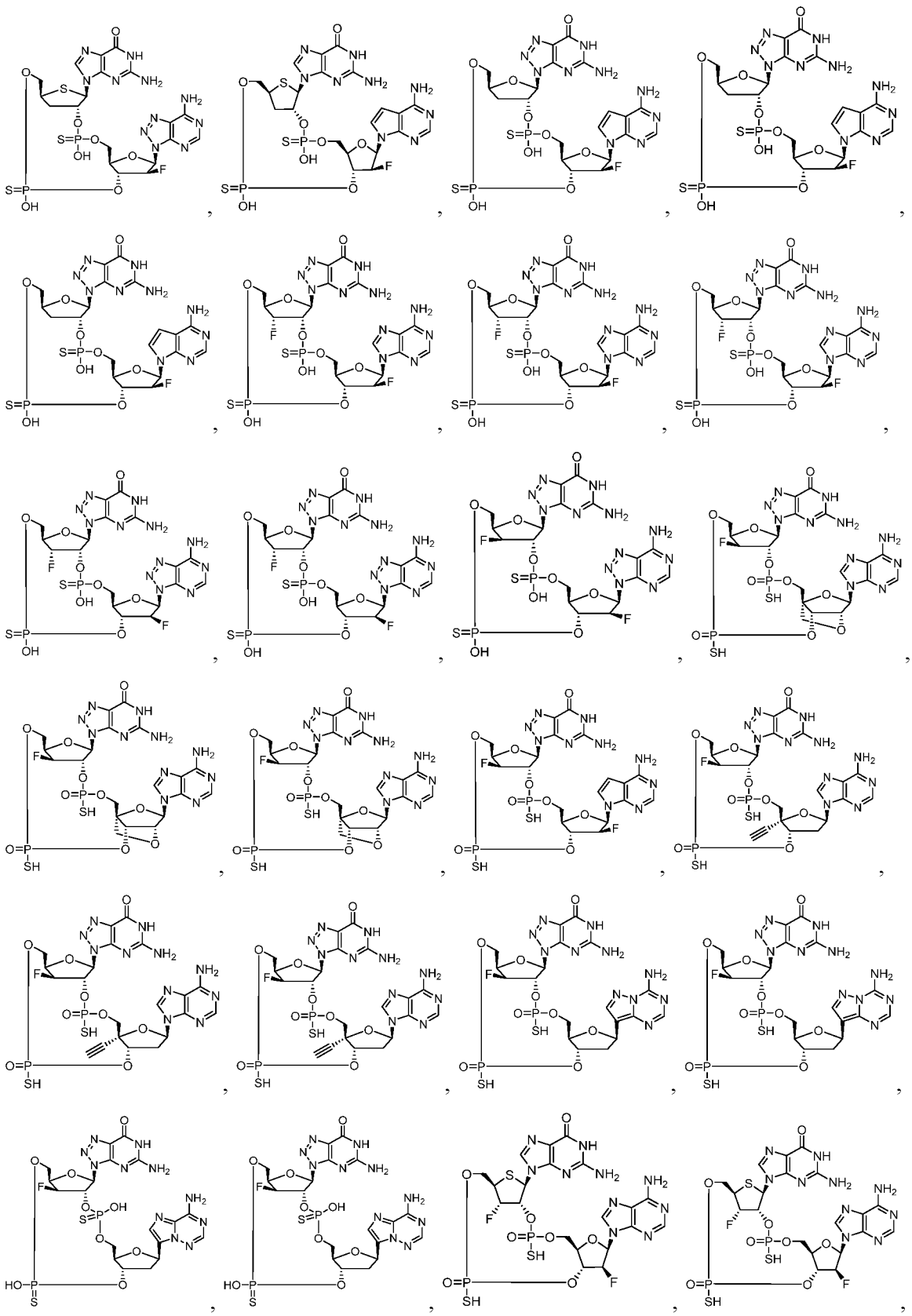


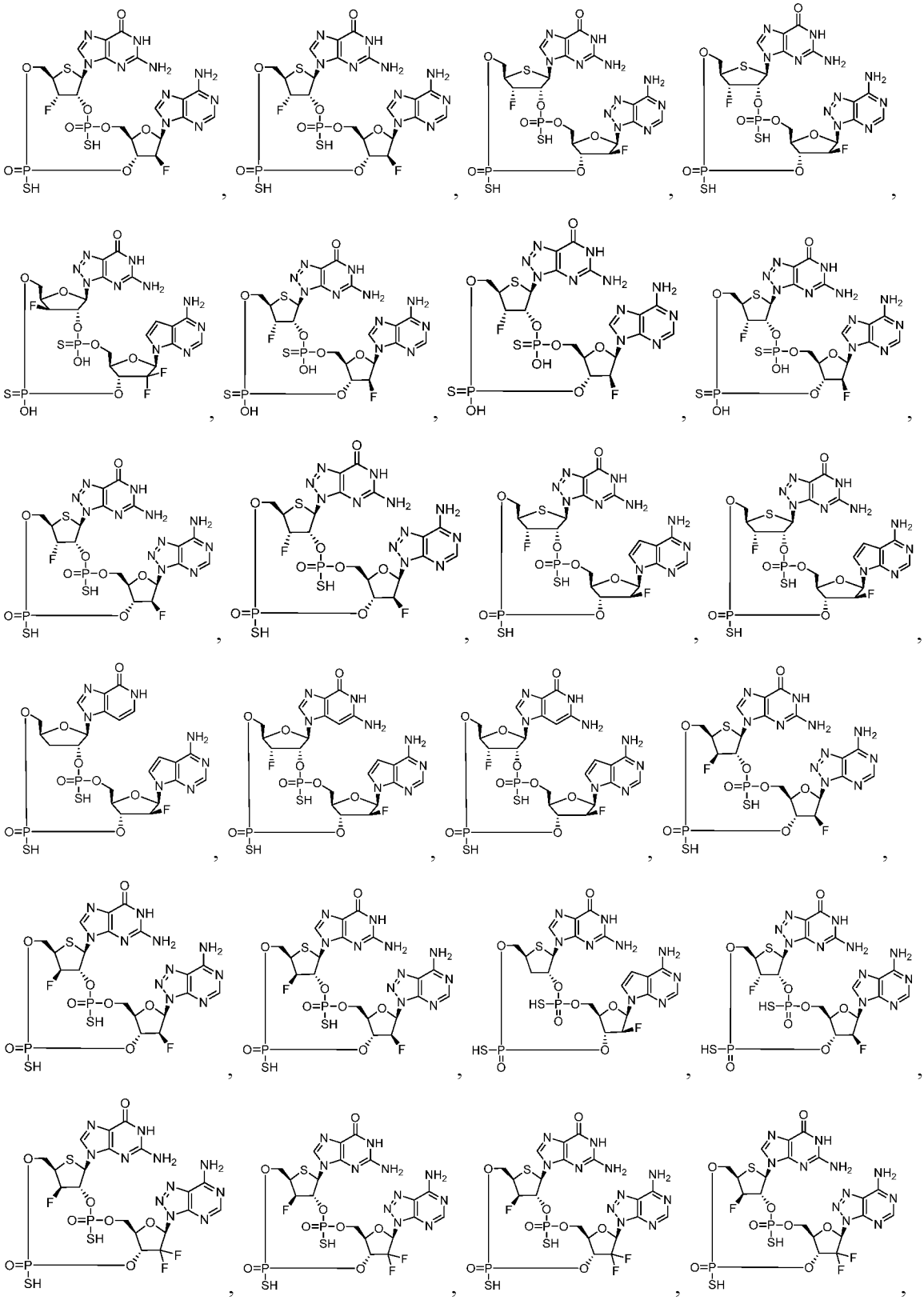


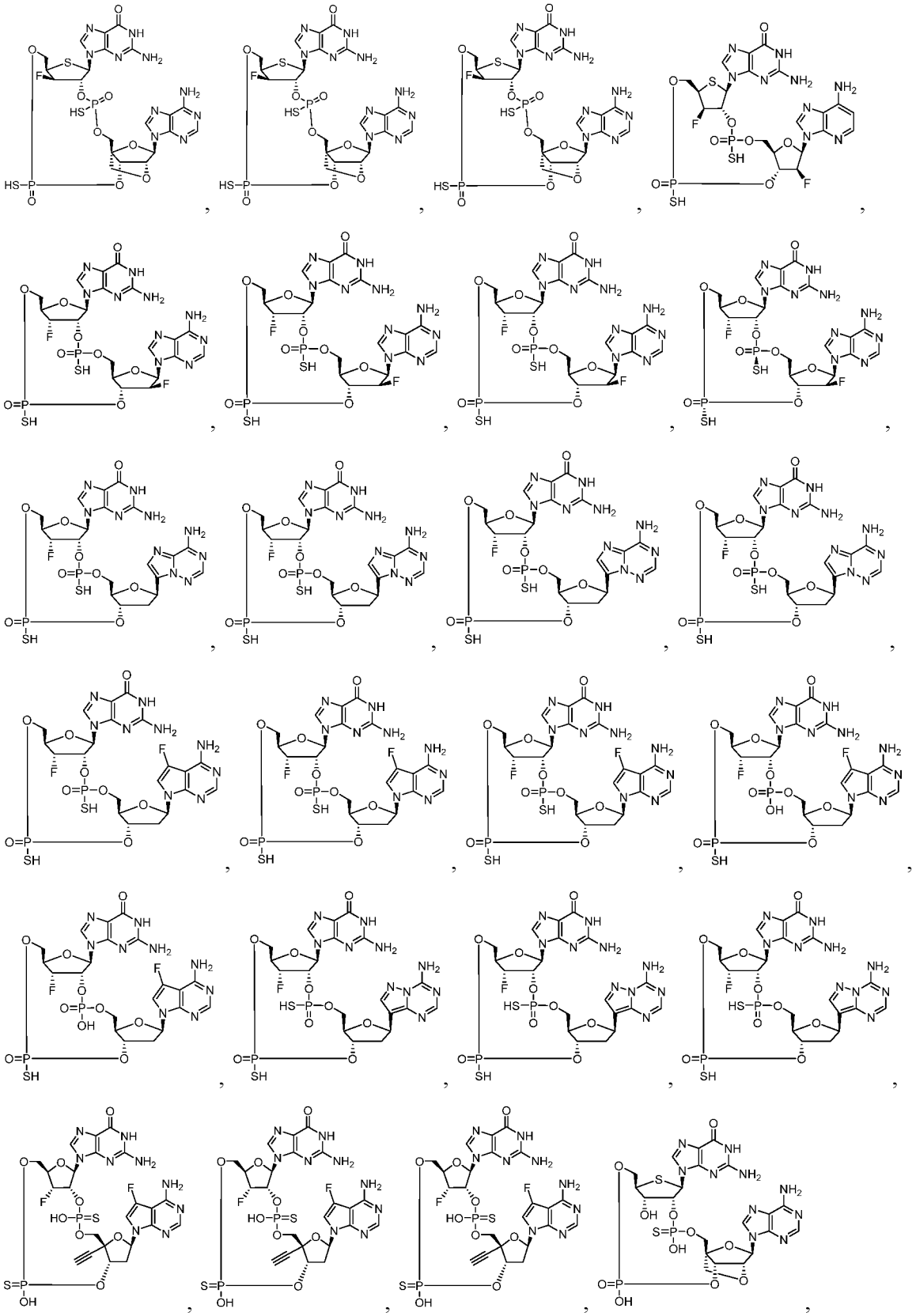


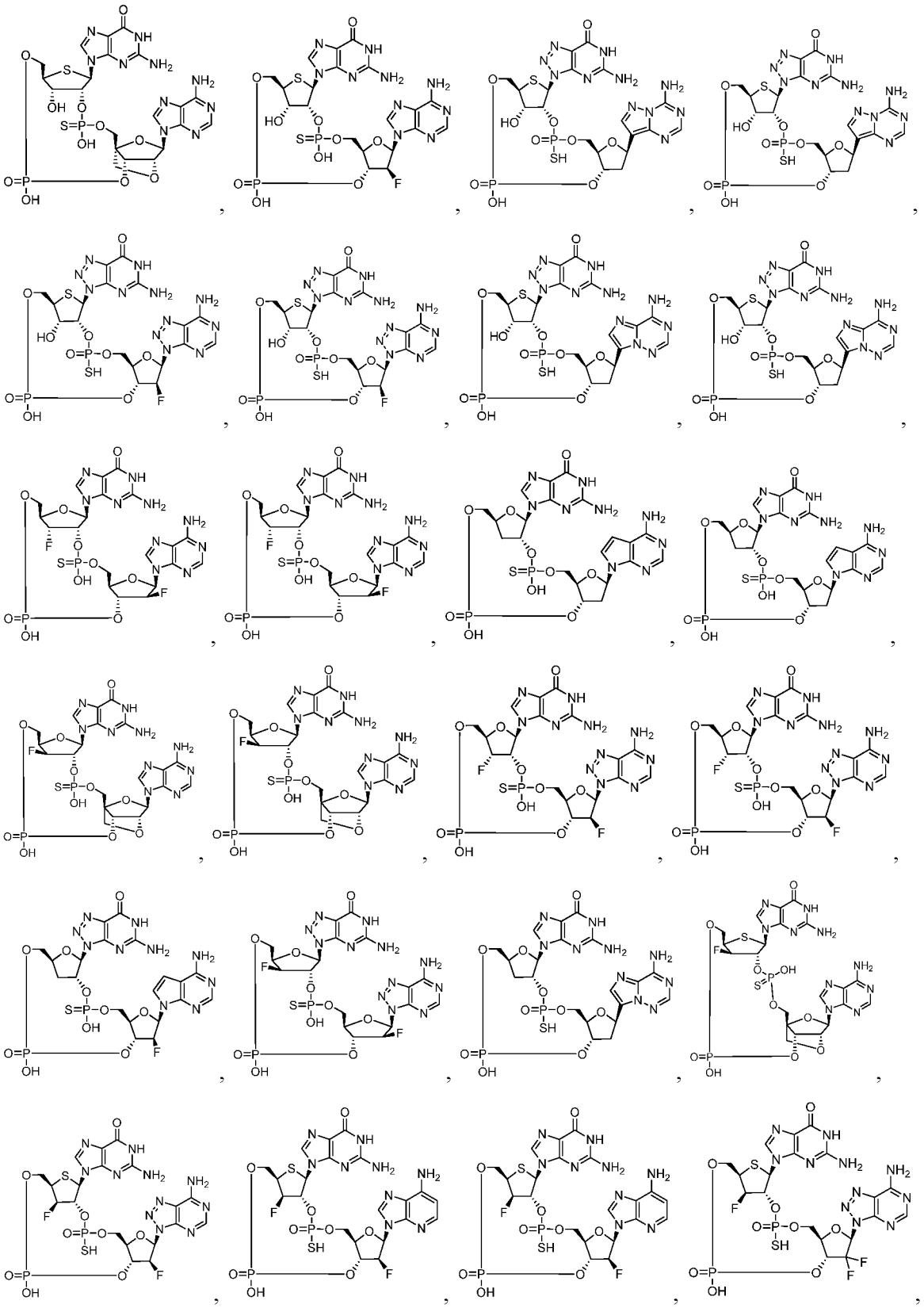


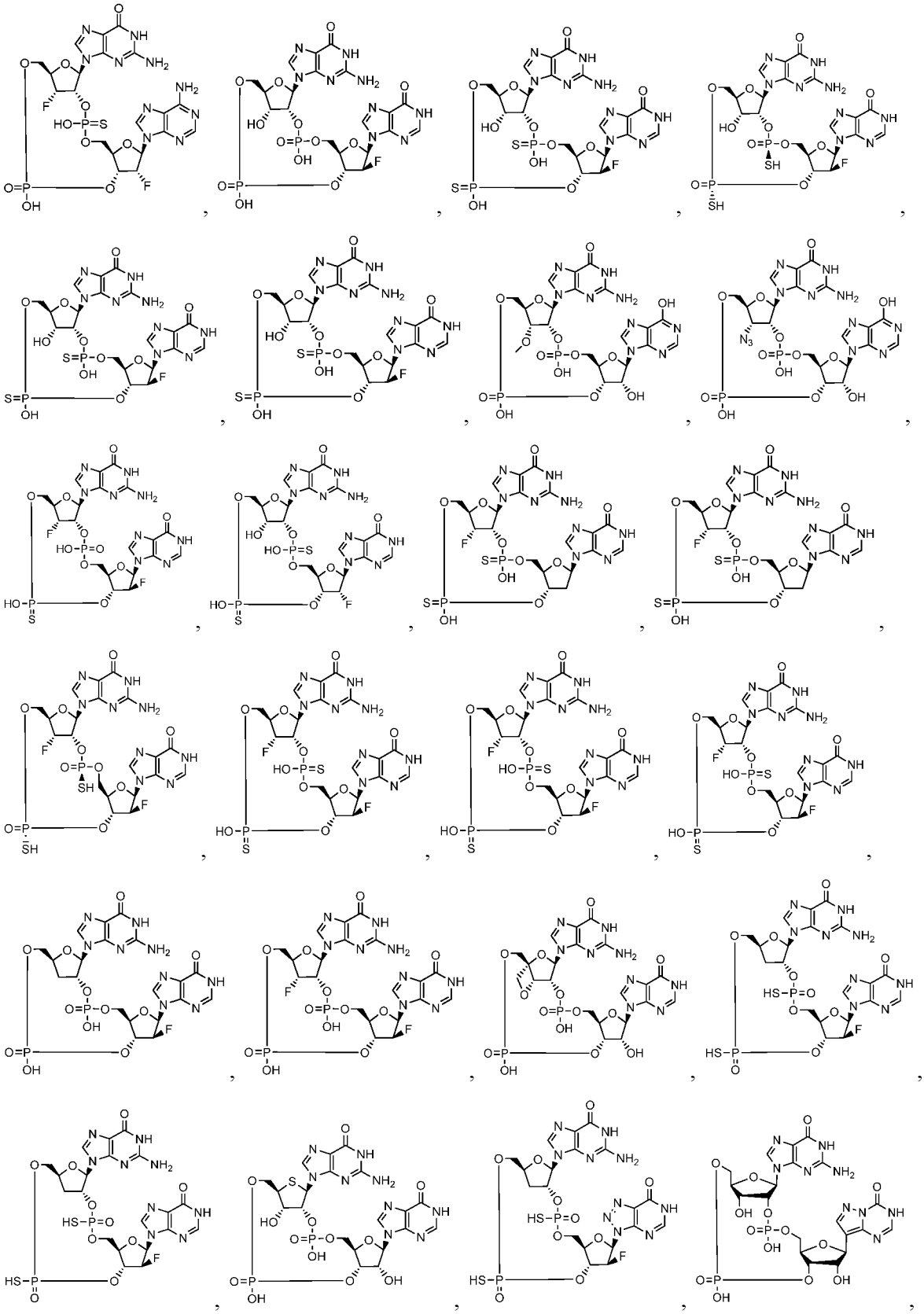


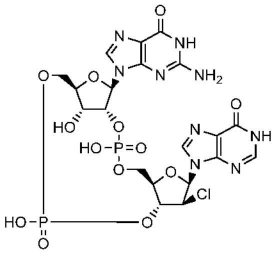
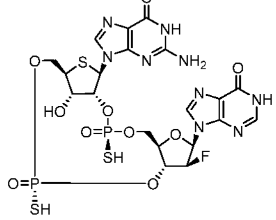
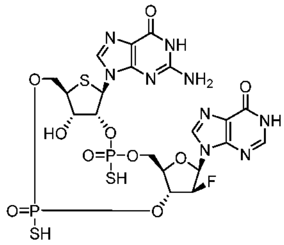
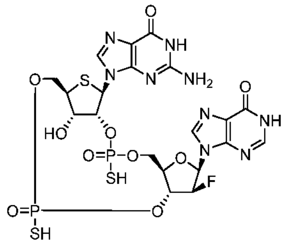


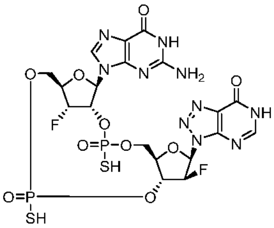
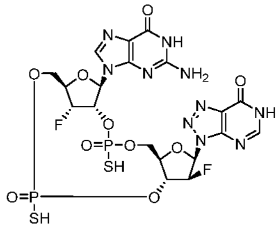
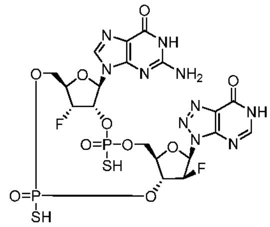
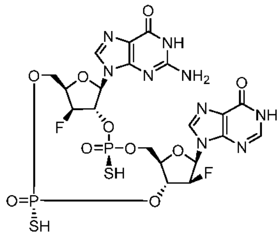


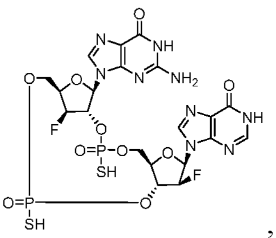
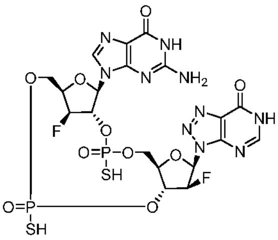
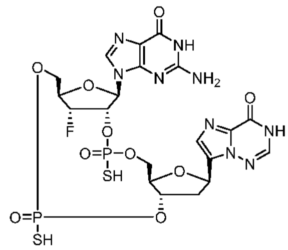
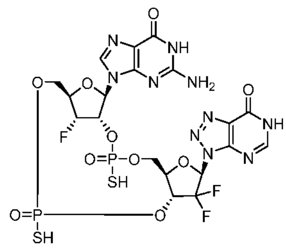


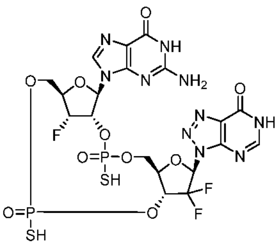
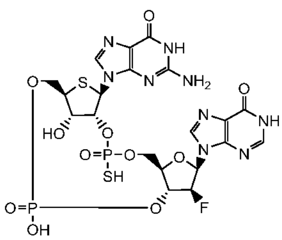
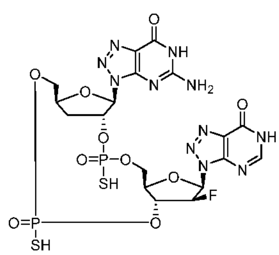
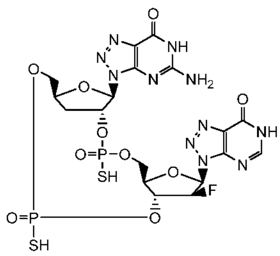


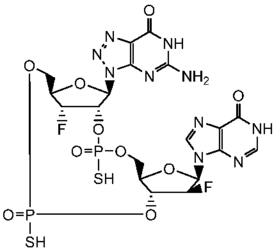
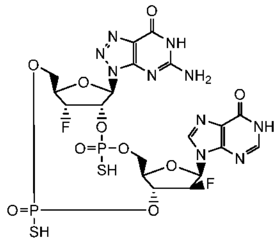
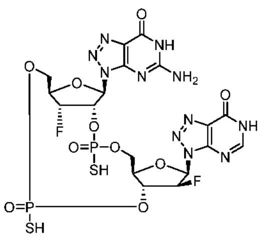
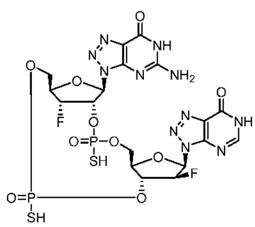


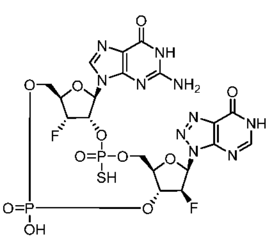
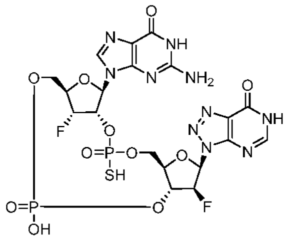
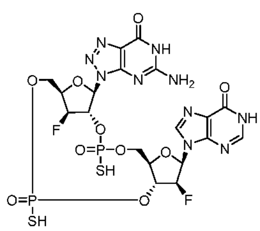
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  , and  , and pharmaceutically acceptable salts thereof.

10. The method according to claim 9, wherein the cyclic dinucleotide STING agonist is administered orally, by intravenous infusion, by intratumoral injection, or by subcutaneous injection.

5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/66557

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/7084, A61P 35/00, C07H 21/00 (2018.01)
CPC - A61K3 9/39, C07H 19/20, C07H 19/23

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)
See Search History Document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/0056224 A1 (DUBENSKY et al.), 26 February 2015 (26.02.2015) entire document, especially: para [0021]; para [0052]; para [0069]; para [0078]; para [0126]; para [0160]; para [0175]; para [0178]; para [0180]; Figure 5, first formula; Figure 6, first formula; FIG. 19A.	1-10
A	DUBENSKY et al. "Rationale, progress and development of vaccines utilizing STING-activating cyclic dinucleotide adjuvants", Ther Adv Vaccines. 2013. Vol. 1(4), pp 131-143, entire document.	1-10
A	WO 2015/077354 A1 (UNIVERSITY OF CHICAGO), 28 May 2015 (28.05.2015), entire document.	1-10
A	LEMOS et al. "Activation of the Stimulator of Interferon Genes (STING) adaptor attenuates experimental autoimmune encephalitis, entire document", J Immunol. 2014. Vol. 192(12), pp 5571-5578, entire document.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 February 2018	27 MAR 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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