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(54) Title: METHODS OF ADMINISTERING GLUTAMINASE INHIBITORS

(57) Abstract: In some aspects, the invention relates to a method of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection, comprising orally administering a compound of formula I, formula II, formula III, formula IV, formula V, and/or formula VI, wherein the compound is administered with a meal (e.g., with food as defined herein) or in fed mode.



WO 2016/160980 A1

METHODS OF ADMINISTERING GLUTAMINASE INHIBITORS**Related Applications**

This application claims the benefit of priority to U.S. Provisional Patent Application No. 62/139,928, filed March 30, 2015 and U.S. Provisional Patent Application No.

5 62/168,112, filed May 29, 2015, which applications are hereby incorporated by reference in their entirety.

Background

Glutamine supports cell survival, growth and proliferation through metabolic and non-metabolic mechanisms. In actively proliferating cells, the metabolism of glutamine to
10 lactate, also referred to as “glutaminolysis” is a major source of energy in the form of NADPH. The first step in glutaminolysis is the deamination of glutamine to form glutamate and ammonia, which is catalyzed by the glutaminase enzyme. Thus, deamination via glutaminase is a control point for glutamine metabolism.

Ever since the observation that ascites tumor cells exhibited high rates of glucose
15 consumption and lactate secretion in the presence of oxygen, researchers have been exploring how cancer cells utilize metabolic pathways to be able to continue actively proliferating. Subsequent research has demonstrated how glutamine metabolism supports macromolecular synthesis necessary for cells to replicate.

Thus, glutaminase has been theorized to be a potential therapeutic target for the
20 treatment of diseases characterized by actively proliferating cells, such as cancer. Therefore, compositions and methods for administering glutaminase inhibitors to prevent or treat disease are desirable.

Summary

In some aspects, the invention relates to a method of treating cancer, a
25 myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection, comprising orally administering a compound of formula I, formula II, formula III, formula IV, formula V, and/or formula VI, wherein the compound is administered with a meal (*e.g.*, with food as defined herein) or in fed mode.

Brief Description of the Drawings

Figure 1 shows steady-state pharmacokinetics results for human clinical trials with various oral doses of the compound of formula III, either administered two times per day (“BID”) or three times per day (“TID”).

5 **Figure 2** shows pharmacokinetics results for human clinical trials with various oral doses of the compound of formula III administered three times per day either with meals (“fed”) or in a fasted state (“fasted”).

10 **Figure 3** shows pharmacokinetics profiles for human clinical trials with 600 mg doses of the compound of formula III administered two times per day (“BID”; 2 doses of 600 mg each) or three times per day (“TID”; 3 doses of 600 mg each).

Figure 4 shows pharmacokinetics profiles for human clinical trials with 600 mg doses of the compound of formula III administered two times per day (Squares; 2 doses of 600 mg each) or three times per day (Circles; 3 doses of 600 mg each).

15 **Figure 5** shows pharmacokinetics profiles for human clinical trials with 600 mg doses of the compound of formula III administered two times per day (Squares; 2 doses of 600 mg each) or three times per day (Circles; 3 doses of 600 mg each).

Figure 6 is a table that describes the dosing regimen for CB-839. The findings suggest that the BID Fed dosing regimen provides consistent exposure to CB-839.

20 **Figure 7** shows pharmacokinetics profiles for human clinical trials with 600 mg doses of the compound of formula III administered two times per day (“BID”; 2 doses of 600 mg each) or three times per day (“TID”; 3 doses of 600 mg each).

Figure 8 are graphs plotting the dosage level of the compound of formula III against PK parameters AUC, C_{max} , and C_{min} when the compound of formula III was administered two times per day (triangles) or three times per day (circles) in human subjects.

25 **Detailed Description**

Definitions

As used herein, the phrase “conjoint administration” refers to any form of administration of two or more different therapeutic compounds such that the second compound is administered while the previously administered therapeutic compound is still
30 effective in the body (*e.g.*, the two compounds are simultaneously effective in the patient, which may include synergistic effects of the two compounds). For example, the different

therapeutic compounds can be administered either in the same formulation or in a separate formulation, either concomitantly or sequentially. In certain embodiments, the different therapeutic compounds can be administered within one hour, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, or a week of one another. Thus, an individual who receives such
5 treatment can benefit from a combined effect of different therapeutic compounds.

The term "fed mode," as used herein, refers to a state which is induced by the presence of food in the stomach. In the normal digestive process, the passage of matter through the stomach is delayed by the physiological condition referred to as the fed mode herein. Between fed modes, the stomach is in the interdigestive or "fasting" mode. The fed
10 mode is typically initiated by nutritive materials entering the stomach upon the ingestion of food, and it persists for approximately 4 to 6 hours. The fed mode can also be induced pharmacologically by the administration of a pharmacological agent that has an effect that is the same or similar to that of a meal. These fed-mode inducing agents may be administered separately or they may be included in the dosage form as an ingredient
15 dispersed in the dosage form or in an outer release coating. Examples of pharmacological fed-mode inducing agents are disclosed in U.S. Pat. No. 7,405,238, hereby incorporated by reference.

The term "healthcare providers" refers to individuals or organizations that provide healthcare services to a person, community, etc. Examples of "healthcare providers" include
20 doctors, hospitals, continuing care retirement communities, skilled nursing facilities, subacute care facilities, clinics, multispecialty clinics, freestanding ambulatory centers, home health agencies, and HMO's.

As used herein, a therapeutic that "prevents" a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition
25 in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of
30 sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

The term "prodrug" is intended to encompass compounds which, under physiologic conditions, are converted into the therapeutically active agents of the present invention (*e.g.*, a compound of formulas I-VI). A common method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal. For example, esters or carbonates (*e.g.*, esters or carbonates of alcohols or carboxylic acids) are preferred prodrugs of the present invention. In certain embodiments, some or all of the compounds of formulas I-VI in a formulation can be replaced with the corresponding suitable prodrug, *e.g.*, wherein a hydroxyl in the parent compound is presented as an ester or a carbonate or carboxylic acid present in the parent compound is presented as an ester.

The term "therapeutically effective amount" relates to the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of the patient. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of

therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher *et al.* (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by
5 reference).

The term "treating" includes prophylactic and/or therapeutic treatments. The term "prophylactic or therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (*e.g.*, disease or other unwanted state of the host
10 animal) then the treatment is prophylactic (*i.e.*, it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (*i.e.*, it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The terms "with food", "with a meal", "with meals", "during a meal", "after a meal" refers to the administration of a compound in temporal proximity to (*e.g.*, before, during, or
15 after) the ingestion of food (*e.g.*, a meal), and more particularly refers to the administration of a compound within 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 minutes before ingesting food, during a meal, or within 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 45, 60, or 90 minutes after ingesting food. In preferred embodiments, the terms "with food" and "with a meal" refer to the
20 administration of a compound with a meal, before the meal (*e.g.*, 30 minutes before ingesting the food or meal), and after the meal (*e.g.*, 90 minutes after ingesting the food or meal).

Definitions of Functional Groups

25 The term "acyl" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term "acylamino" is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH-.

30 The term "acyloxy" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O-, preferably alkylC(O)O-.

The term "alkoxy" refers to an alkyl group, preferably a lower alkyl group, having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

5 The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

10 The term "alkenyl", as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

15 An "alkyl" group or "alkane" is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10 unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C₁-C₆ straight chained or branched alkyl group is also referred to as a "lower alkyl" group.

20 Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and

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silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CF₃, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CF₃, -CN, and the like.

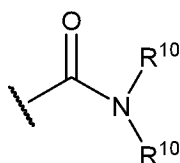
5 The term “C_{x-y}” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term “C_{x-y}alkyl” refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups
10 such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. C₀ alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. The terms “C_{2-y}alkenyl” and “C_{2-y}alkynyl” refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

15 The term “alkylamino”, as used herein, refers to an amino group substituted with at least one alkyl group.

 The term “alkylthio”, as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS-.

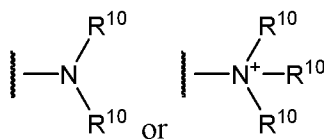
 The term “alkynyl”, as used herein, refers to an aliphatic group containing at least
20 one triple bond and is intended to include both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed
25 above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

 The term “amide”, as used herein, refers to a group



 wherein each R¹⁰ independently represent a hydrogen or hydrocarbonyl group, or two R¹⁰ are
30 taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms “amine” and “amino” are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, *e.g.*, a moiety that can be represented by



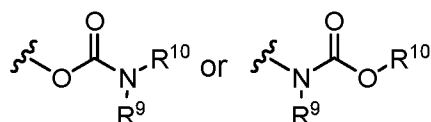
wherein each R¹⁰ independently represents a hydrogen or a hydrocarbyl group, or two R¹⁰ are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term “aminoalkyl”, as used herein, refers to an alkyl group substituted with an amino group.

The term “aralkyl”, as used herein, refers to an alkyl group substituted with an aryl group.

The term “aryl” as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

The term “carbamate” is art-recognized and refers to a group



wherein R⁹ and R¹⁰ independently represent hydrogen or a hydrocarbyl group, such as an alkyl group, or R⁹ and R¹⁰ taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms “carbocycle”, and “carbocyclic”, as used herein, refers to a saturated or unsaturated ring in which each atom of the ring is carbon. The term carbocycle includes both aromatic carbocycles and non-aromatic carbocycles. Non-aromatic carbocycles include both cycloalkane rings, in which all carbon atoms are saturated, and cycloalkene rings, which contain at least one double bond. “Carbocycle” includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic

molecules in which one, two or three or more atoms are shared between the two rings. The term “fused carbocycle” refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, *e.g.*, phenyl, may be fused to a saturated or unsaturated ring, *e.g.*, cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary “carbocycles” include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. “Carbocycles” may be substituted at any one or more positions capable of bearing a hydrogen atom.

A “cycloalkyl” group is a cyclic hydrocarbon which is completely saturated. “Cycloalkyl” includes monocyclic and bicyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms unless otherwise defined. The second ring of a bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. Cycloalkyl includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused cycloalkyl” refers to a bicyclic cycloalkyl in which each of the rings shares two adjacent atoms with the other ring. The second ring of a fused bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. A “cycloalkenyl” group is a cyclic hydrocarbon containing one or more double bonds.

The term “carbocyclalkyl”, as used herein, refers to an alkyl group substituted with a carbocycle group.

The term “carbonate” is art-recognized and refers to a group $-\text{OCO}_2\text{-R}^{10}$, wherein R^{10} represents a hydrocarbyl group.

The term “carboxy”, as used herein, refers to a group represented by the formula $-\text{CO}_2\text{H}$.

The term “ester”, as used herein, refers to a group $-\text{C}(\text{O})\text{OR}^{10}$ wherein R^{10} represents a hydrocarbyl group.

The term “ether”, as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl

group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include "alkoxyalkyl" groups, which may be represented by the general formula alkyl-O-alkyl.

5 The terms "halo" and "halogen" as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

 The terms "hetaralkyl" and "heteroaralkyl", as used herein, refers to an alkyl group substituted with a hetaryl group.

 The term "heteroalkyl", as used herein, refers to a saturated or unsaturated chain of
10 carbon atoms and at least one heteroatom, wherein no two heteroatoms are adjacent.

 The terms "heteroaryl" and "hetaryl" include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heteroaryl" and
15 "hetaryl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and
20 pyrimidine, and the like.

 The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

 The terms "heterocyclyl", "heterocycle", and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more
25 preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, *e.g.*, the other cyclic rings can be cycloalkyls,
30 cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

The term “heterocyclalkyl”, as used herein, refers to an alkyl group substituted with a heterocycle group.

The term “hydrocarbyl”, as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocyclalkyl, alkyl, alkenyl, alkynyl, and combinations thereof.

The term “hydroxyalkyl”, as used herein, refers to an alkyl group substituted with a hydroxy group.

The term “lower” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer non-hydrogen atoms in the substituent, preferably six or fewer. A “lower alkyl”, for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

The terms “polycyclalkyl”, “polycycle”, and “polycyclic” refer to two or more rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclalkyls) in which two or more atoms are common to two adjoining rings, *e.g.*, the rings are “fused rings”. Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

The term “silyl” refers to a silicon moiety with three hydrocarbyl moieties attached thereto.

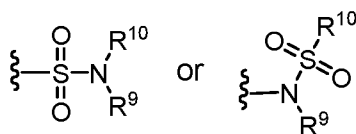
The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with

permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds.

- 5 In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible
- 10 substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an
- 15 imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as “unsubstituted,” references to chemical moieties herein are understood to include substituted variants. For
- 20 example, reference to an “aryl” group or moiety implicitly includes both substituted and unsubstituted variants.

The term “sulfate” is art-recognized and refers to the group -OSO₃H, or a pharmaceutically acceptable salt thereof.

- 25 The term “sulfonamide” is art-recognized and refers to the group represented by the general formulae



wherein R⁹ and R¹⁰ independently represents hydrogen or hydrocarbyl, such as alkyl, or R⁹ and R¹⁰ taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

- 30 The term “sulfoxide” is art-recognized and refers to the group -S(O)-R¹⁰, wherein R¹⁰ represents a hydrocarbyl.

The term “sulfonate” is art-recognized and refers to the group SO_3H , or a pharmaceutically acceptable salt thereof.

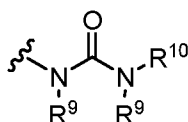
The term “sulfone” is art-recognized and refers to the group $-\text{S}(\text{O})_2-\text{R}^{10}$, wherein R^{10} represents a hydrocarbyl.

5 The term “thioalkyl”, as used herein, refers to an alkyl group substituted with a thiol group.

The term “thioester”, as used herein, refers to a group $-\text{C}(\text{O})\text{SR}^{10}$ or $-\text{SC}(\text{O})\text{R}^{10}$ wherein R^{10} represents a hydrocarbyl.

10 The term “thioether”, as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

The term “urea” is art-recognized and may be represented by the general formula

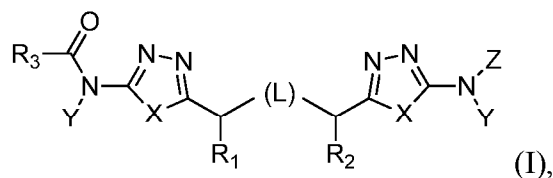


15 wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl, such as alkyl, or either occurrence of R^9 taken together with R^{10} and the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

20 The term “protecting group” refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry*, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative nitrogen protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (“CBZ”), tert-butoxycarbonyl (“Boc”), trimethylsilyl (“TMS”), 2-trimethylsilyl-ethanesulfonyl (“TES”), trityl and
25 substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (“Fmoc”), nitro-veratryloxycarbonyl (“NVOC”) and the like. Representative hydroxylprotecting groups include, but are not limited to, those where the hydroxyl group is either acylated (esterified) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPS groups), glycol ethers, such
30 as ethylene glycol and propylene glycol derivatives and allyl ethers.

I. COMPOUNDS

The present invention relates to methods of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection comprising orally administering a compound of formula I,



or a pharmaceutically acceptable salt thereof, wherein:

L represents CH₂SCH₂, CH₂CH₂, CH₂CH₂CH₂, CH₂, CH₂S, SCH₂, CH₂NHCH₂, CH=CH,

or , preferably CH₂CH₂, wherein any hydrogen atom of a CH or CH₂ unit may be replaced by alkyl or alkoxy, any hydrogen of an NH unit may be replaced by alkyl, and any hydrogen atom of a CH₂ unit of CH₂CH₂, CH₂CH₂CH₂ or CH₂ may be replaced by hydroxy;

X, independently for each occurrence, represents S, O or CH=CH, preferably S or CH=CH, wherein any hydrogen atom of a CH unit may be replaced by alkyl;

Y, independently for each occurrence, represents H or CH₂O(CO)R₇;

15 R₇, independently for each occurrence, represents H or substituted or unsubstituted alkyl, alkoxy, aminoalkyl, alkylaminoalkyl, heterocyclalkyl, arylalkyl, or heterocyclalkoxy;

Z represents H or R₃(CO);

R₁ and R₂ each independently represent H, alkyl, alkoxy or hydroxy;

20 R₃, independently for each occurrence, represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroaryloxyalkyl or C(R₈)(R₉)(R₁₀), N(R₄)(R₅) or OR₆, wherein any free hydroxyl group may be acylated to form C(O)R₇;

25 R₄ and R₅ each independently represent H or substituted or unsubstituted alkyl, hydroxyalkyl, acyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, 30 wherein any free hydroxyl group may be acylated to form C(O)R₇;

R₆, independently for each occurrence, represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form C(O)R₇; and

R₈, R₉ and R₁₀ each independently represent H or substituted or unsubstituted alkyl, hydroxy, hydroxyalkyl, amino, acylamino, aminoalkyl, acylaminoalkyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, or R₈ and R₉ together with the carbon to which they are attached, form a carbocyclic or heterocyclic ring system, wherein any free hydroxyl group may be acylated to form C(O)R₇;

preferably wherein the compound is administered with a meal.

In some embodiments, at least two of R₈, R₉ and R₁₀ are not H.

In certain embodiments wherein alkyl, hydroxyalkyl, amino, acylamino, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl are substituted, they are substituted with one or more substituents selected from substituted or unsubstituted alkyl, such as perfluoroalkyl (*e.g.*, trifluoromethyl), alkenyl, alkoxy, alkoxyalkyl, aryl, aralkyl, arylalkoxy, aryloxy, aryloxyalkyl, hydroxyl, halo, alkoxy, such as perfluoroalkoxy (*e.g.*, trifluoromethoxy), alkoxyalkoxy, hydroxyalkyl, hydroxyalkylamino, hydroxyalkoxy, amino, aminoalkyl, alkylamino, aminoalkylalkoxy, aminoalkoxy, acylamino, acylaminoalkyl, such as perfluoro acylaminoalkyl (*e.g.*, trifluoromethylacylaminoalkyl), acyloxy, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxy, heterocyclylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, heteroaryloxy, heteroaryloxyalkyl, heterocyclylaminoalkyl, heterocyclylaminoalkoxy, amido, amidoalkyl, amidine, imine, oxo, carbonyl (such as carboxyl, alkoxy, carbonyl, formyl, or acyl, including perfluoroacyl (*e.g.*, C(O)CF₃)), carbonylalkyl (such as carboxyalkyl, alkoxy, carbonylalkyl, formylalkyl, or acylalkyl, including perfluoroacylalkyl (*e.g.*, -alkylC(O)CF₃)), carbamate, carbamatealkyl, urea, ureaalkyl, sulfate, sulfonate, sulfamoyl, sulfone, sulfonamide, sulfonamidealkyl, cyano, nitro, azido, sulfhydryl,

alkylthio, thiocarbonyl (such as thioester, thioacetate, or thioformate), phosphoryl, phosphate, phosphonate or phosphinate.

In certain embodiments, L represents CH_2SCH_2 , CH_2CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2 , CH_2S , SCH_2 , or CH_2NHCH_2 , wherein any hydrogen atom of a CH_2 unit may be replaced by alkyl or alkoxy, and any hydrogen atom of a CH_2 unit of CH_2CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$ or CH_2 may be replaced by hydroxyl. In certain embodiments, L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 . In certain embodiments, L represents CH_2CH_2 . In certain embodiments, L is not CH_2SCH_2 .

In certain embodiments, Y represents H.

In certain embodiments, X represents S or $\text{CH}=\text{CH}$. In certain embodiments, one or both X represents $\text{CH}=\text{CH}$. In certain embodiments, each X represents S. In certain embodiments, one X represents S and the other X represents $\text{CH}=\text{CH}$.

In certain embodiments, Z represents $\text{R}_3(\text{CO})$. In certain embodiments wherein Z is $\text{R}_3(\text{CO})$, each occurrence of R_3 is not identical (*e.g.*, the compound of formula I is not symmetrical).

In certain embodiments, R_1 and R_2 each represent H.

In certain embodiments, R_3 represents arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl. In certain embodiments, R_3 represents $\text{C}(\text{R}_8)(\text{R}_9)(\text{R}_{10})$, wherein R_8 represents aryl, arylalkyl, heteroaryl or heteroaralkyl, such as aryl, arylalkyl or heteroaryl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl, alkoxy or alkoxyalkyl, such as hydroxy, hydroxyalkyl or alkoxy.

In certain embodiments, L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 , such as CH_2CH_2 , CH_2S or SCH_2 , Y represents H, X represents S, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, and each R_3 represents arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl. In certain such embodiments, each occurrence of R_3 is identical.

In certain embodiments, L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 , Y represents H, X represents S, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, and each R_3 represents $\text{C}(\text{R}_8)(\text{R}_9)(\text{R}_{10})$, wherein R_8 represents aryl, arylalkyl, heteroaryl or heteroaralkyl, such as aryl, arylalkyl or heteroaryl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl, alkoxy or alkoxyalkyl, such as hydroxy, hydroxyalkyl or alkoxy. In certain such embodiments, each occurrence of R_3 is identical.

In certain embodiments, L represents CH_2CH_2 , Y represents H, X represents S or $\text{CH}=\text{CH}$, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, and each R_3 represents

substituted or unsubstituted arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl. In certain such embodiments, each X represents S. In other embodiments, one or both occurrences of X represents CH=CH, such as one occurrence of X represents S and the other occurrence of X represents CH=CH. In certain embodiments of the foregoing, each occurrence of R₃ is identical. In other embodiments of the foregoing wherein one occurrence of X represents S and the other occurrence of X represents CH=CH, the two occurrences of R₃ are not identical.

In certain embodiments, L represents CH₂CH₂, Y represents H, X represents S, Z represents R₃(CO), R₁ and R₂ each represent H, and each R₃ represents C(R₈)(R₉)(R₁₀), wherein R₈ represents aryl, arylalkyl or heteroaryl, R₉ represents H, and R₁₀ represents hydroxy, hydroxyalkyl or alkoxy. In certain such embodiments, R₈ represents aryl and R₁₀ represents hydroxyalkyl. In certain such embodiments, each occurrence of R₃ is identical.

In certain embodiments wherein L represents CH₂, CH₂CH₂CH₂ or CH₂CH₂, X represents O, and Z represents R₃(CO), both R₃ groups are not alkyl, such as methyl, or C(R₈)(R₉)(R₁₀), wherein R₈, R₉ and R₁₀ are each independently hydrogen or alkyl.

In certain embodiments wherein L represents CH₂CH₂, X represents S, and Z represents R₃(CO), both R₃ groups are not phenyl or heteroaryl, such as 2-furyl.

In certain embodiments wherein L represents CH₂CH₂, X represents O, and Z represents R₃(CO), both R₃ groups are not N(R₄)(R₅) wherein R₄ is aryl, such as phenyl, and R₅ is H.

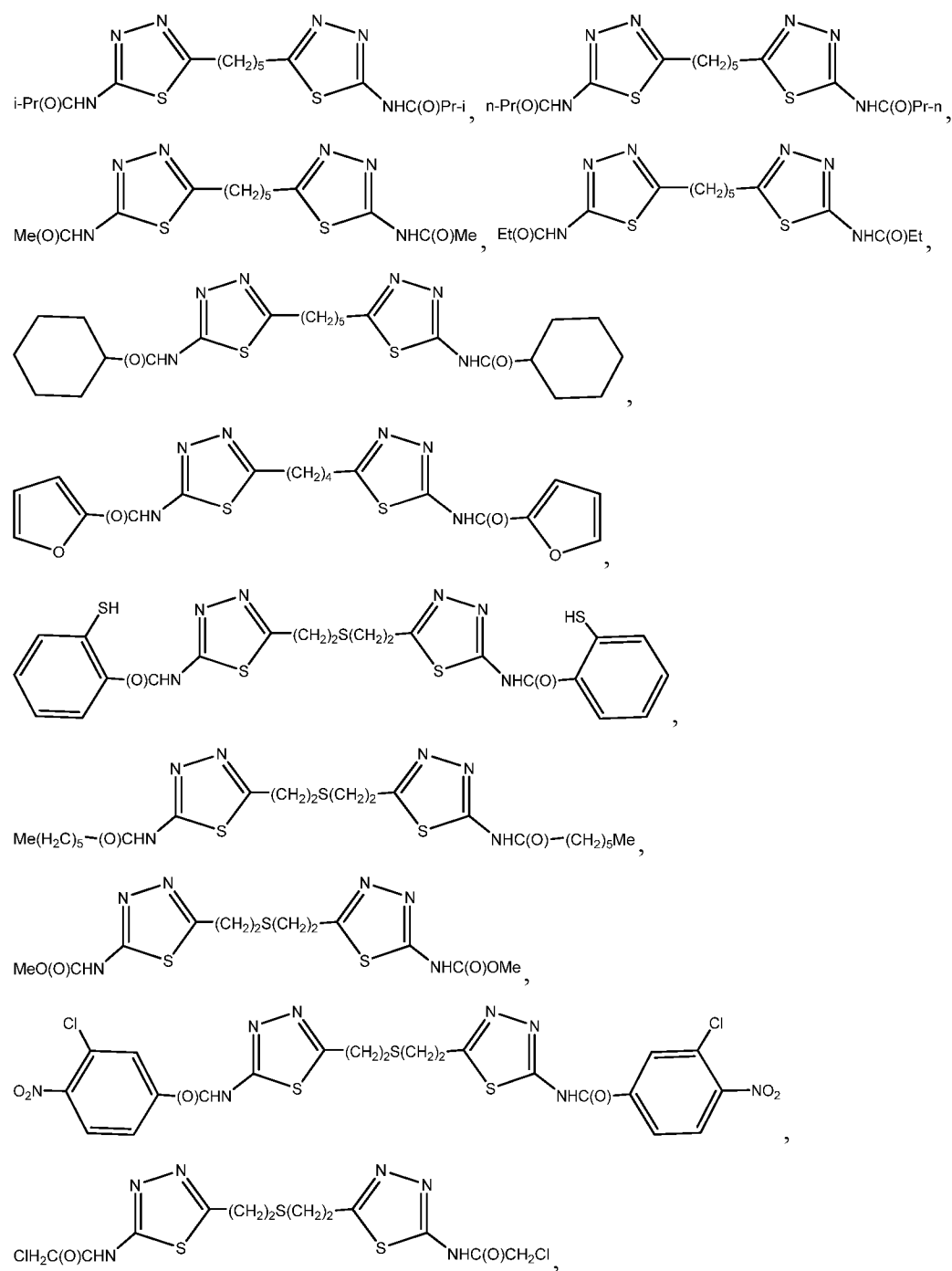
In certain embodiments wherein L represents CH₂SCH₂, X represents S, and Z represents R₃(CO), both R₃ groups are not aryl, such as optionally substituted phenyl, aralkyl, such as benzyl, heteroaryl, such as 2-furyl, 2-thienyl or 1,2,4-triazole, substituted or unsubstituted alkyl, such as methyl, chloromethyl, dichloromethyl, n-propyl, n-butyl, t-butyl or hexyl, heterocyclyl, such as pyrimidine-2,4(1H,3H)-dione, or alkoxy, such as methoxy, pentyloxy or ethoxy.

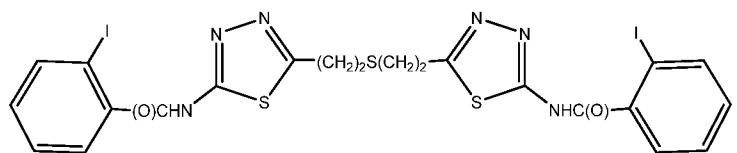
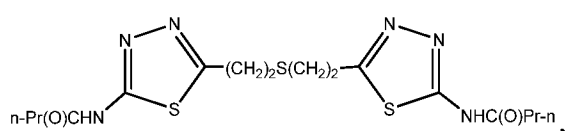
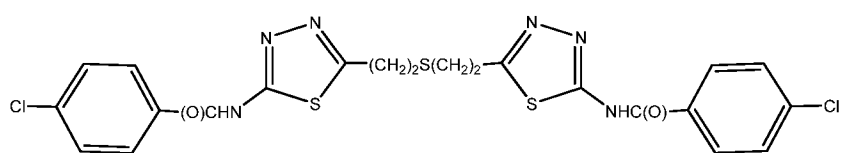
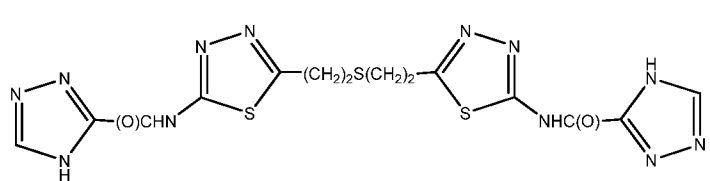
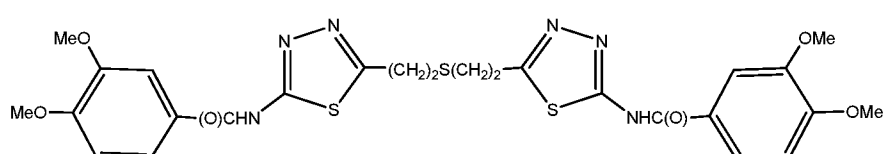
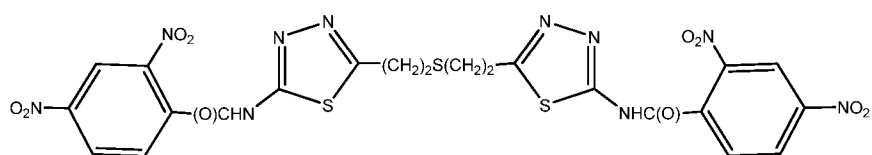
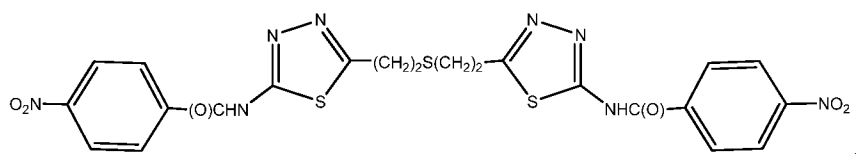
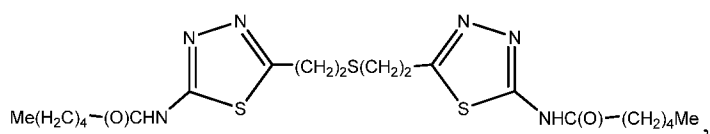
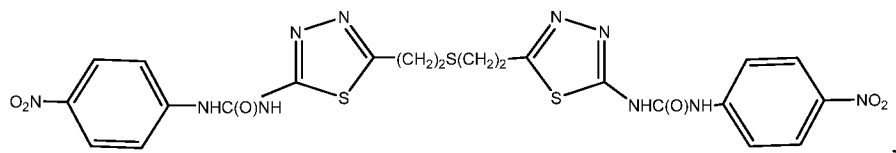
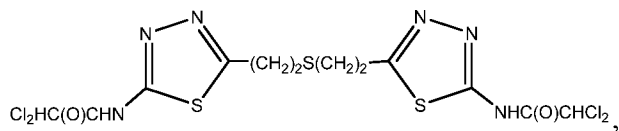
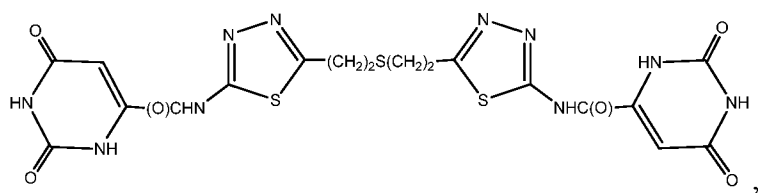
In certain embodiments wherein L represents CH₂SCH₂, X represents S, and Z represents R₃(CO), both R₃ groups are not optionally substituted phenyl, aralkyl, heteroaryl, substituted or unsubstituted alkyl, or alkoxy.

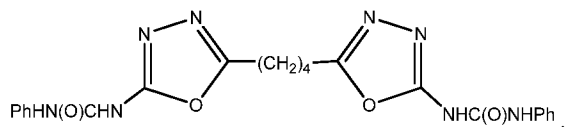
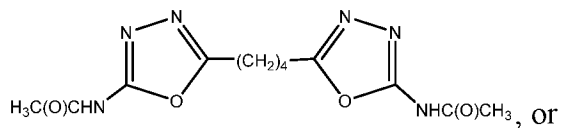
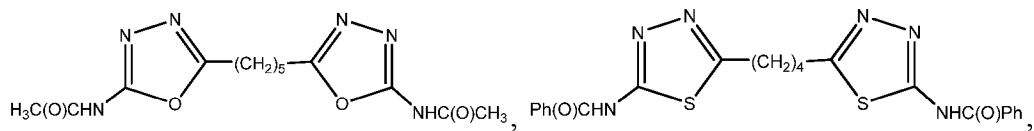
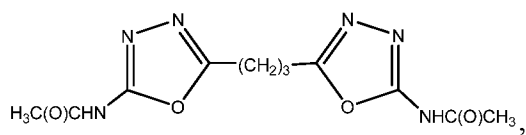
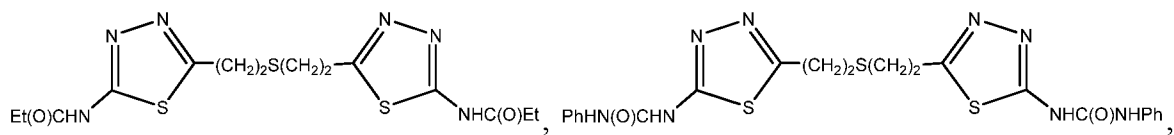
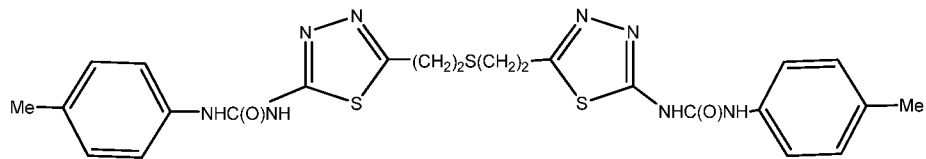
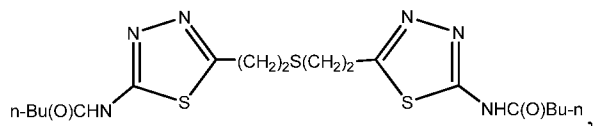
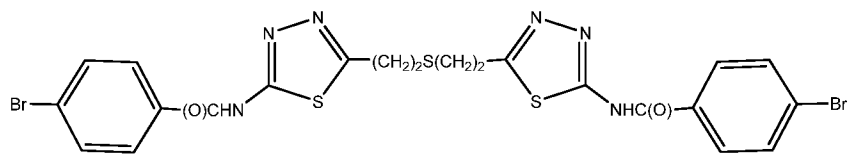
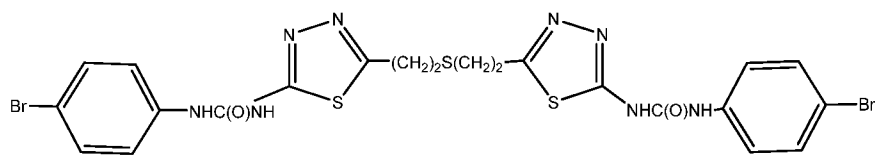
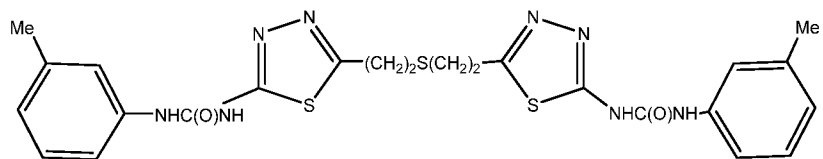
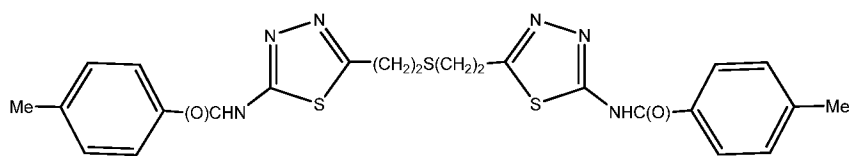
In certain embodiments wherein L represents CH₂SCH₂, X represents S, and Z represents R₃(CO), both R₃ groups are not N(R₄)(R₅) wherein R₄ is aryl, such as substituted or unsubstituted phenyl (*e.g.*, phenyl, 3-tolyl, 4-tolyl, 4-bromophenyl or 4-nitrophenyl), and R₅ is H.

In certain embodiments wherein L represents $\text{CH}_2\text{CH}_2\text{CH}_2$, X represents S, and Z represents $\text{R}_3(\text{CO})$, both R_3 groups are not alkyl, such as methyl, ethyl, or propyl, cycloalkyl, such as cyclohexyl, or $\text{C}(\text{R}_8)(\text{R}_9)(\text{R}_{10})$, wherein any of R_8 , R_9 and R_{10} together with the C to which they are attached, form any of the foregoing.

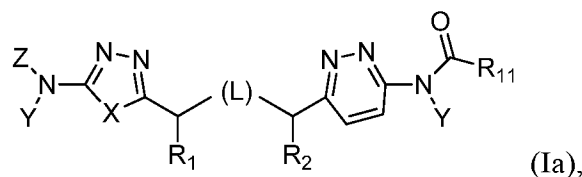
5 In certain embodiments, the compound is not one of the following:







The present invention further provides methods of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection comprising orally administering a compound of formula Ia,



5 or a pharmaceutically acceptable salt thereof, wherein:

L represents CH_2SCH_2 , CH_2CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2 , CH_2S , SCH_2 , CH_2NHCH_2 , $\text{CH}=\text{CH}$,

or , preferably CH_2CH_2 , wherein any hydrogen atom of a CH or CH_2 unit may be replaced by alkyl or alkoxy, any hydrogen of an NH unit may be replaced by alkyl, and any hydrogen atom of a CH_2 unit of CH_2CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$ or CH_2 may be replaced by hydroxy;

X represents S, O or $\text{CH}=\text{CH}$, preferably S or $\text{CH}=\text{CH}$, wherein any hydrogen atom of a CH unit may be replaced by alkyl;

Y, independently for each occurrence, represents H or $\text{CH}_2\text{O}(\text{CO})\text{R}_7$;

R_7 , independently for each occurrence, represents H or substituted or unsubstituted alkyl, alkoxy, aminoalkyl, alkylaminoalkyl, heterocyclalkyl, arylalkyl, or heterocyclalkoxy;

Z represents H or $\text{R}_3(\text{CO})$;

R_1 and R_2 each independently represent H, alkyl, alkoxy or hydroxy, preferably H;

R_3 represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroaryloxyalkyl or $\text{C}(\text{R}_8)(\text{R}_9)(\text{R}_{10})$, $\text{N}(\text{R}_4)(\text{R}_5)$ or OR_6 , wherein any free hydroxyl group may be acylated to form $\text{C}(\text{O})\text{R}_7$;

R_4 and R_5 each independently represent H or substituted or unsubstituted alkyl, hydroxyalkyl, acyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form $\text{C}(\text{O})\text{R}_7$;

R_6 , independently for each occurrence, represents substituted or unsubstituted alkyl,

hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl,

aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form C(O)R₇; and

R₈, R₉ and R₁₀ each independently represent H or substituted or unsubstituted alkyl,

5 hydroxy, hydroxyalkyl, amino, acylamino, aminoalkyl, acylaminoalkyl, alkoxycarbonyl, alkoxycarbonylamino, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, or R₈ and R₉ together with the carbon to which they are attached, form a carbocyclic or
10 heterocyclic ring system, wherein any free hydroxyl group may be acylated to form C(O)R₇, and wherein at least two of R₈, R₉ and R₁₀ are not H;

R₁₁ represents substituted or unsubstituted aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, or C(R₁₂)(R₁₃)(R₁₄),
N(R₄)(R₁₄) or OR₁₄, wherein any free hydroxyl group may be acylated to form
15 C(O)R₇;

R₁₂ and R₁₃ each independently represent H or substituted or unsubstituted alkyl, hydroxy, hydroxyalkyl, amino, acylamino, aminoalkyl, acylaminoalkyl, alkoxycarbonyl, alkoxycarbonylamino, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl,
20 heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form C(O)R₇, and wherein both of R₁₂ and R₁₃ are not H; and

R₁₄ represents substituted or unsubstituted aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl;

25 preferably wherein the compound is administered with a meal.

In certain embodiments wherein alkyl, hydroxyalkyl, amino, acylamino, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl are substituted, they are substituted
30 with one or more substituents selected from substituted or unsubstituted alkyl, such as perfluoroalkyl (*e.g.*, trifluoromethyl), alkenyl, alkoxy, alkoxyalkyl, aryl, aralkyl, arylalkoxy, aryloxy, aryloxyalkyl, hydroxyl, halo, alkoxy, such as perfluoroalkoxy (*e.g.*, trifluoromethylalkoxy), alkoxyalkoxy, hydroxyalkyl, hydroxyalkylamino, hydroxyalkoxy,

amino, aminoalkyl, alkylamino, aminoalkylalkoxy, aminoalkoxy, acylamino, acylaminoalkyl, such as perfluoro acylaminoalkyl (*e.g.*, trifluoromethylacylaminoalkyl), acyloxy, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, heterocyclylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, heteroaryloxy, heteroaryloxyalkyl, heterocyclylaminoalkyl, heterocyclylaminoalkoxy, amido, amidoalkyl, amidine, imine, oxo, carbonyl (such as carboxyl, alkoxycarbonyl, formyl, or acyl, including perfluoroacyl (*e.g.*, C(O)CF₃)), carbonylalkyl (such as carboxyalkyl, alkoxycarbonylalkyl, formylalkyl, or acylalkyl, including perfluoroacylalkyl (*e.g.*, -alkylC(O)CF₃)), carbamate, carbamatealkyl, urea, ureaalkyl, sulfate, sulfonate, sulfamoyl, sulfone, sulfonamide, sulfonamidealkyl, cyano, nitro, azido, sulfhydryl, alkylthio, thiocarbonyl (such as thioester, thioacetate, or thioformate), phosphoryl, phosphate, phosphonate or phosphinate.

In certain embodiments, R₁₁ represents substituted or unsubstituted arylalkyl, such as substituted or unsubstituted benzyl.

In certain embodiments, L represents CH₂SCH₂, CH₂CH₂, CH₂CH₂CH₂, CH₂, CH₂S, SCH₂, or CH₂NHCH₂, wherein any hydrogen atom of a CH₂ unit may be replaced by alkyl or alkoxy, and any hydrogen atom of a CH₂ unit of CH₂CH₂, CH₂CH₂CH₂ or CH₂ may be replaced by hydroxyl. In certain embodiments, L represents CH₂SCH₂, CH₂CH₂, CH₂S or SCH₂, preferably CH₂CH₂. In certain embodiments, L is not CH₂SCH₂.

In certain embodiments, each Y represents H. In other embodiments, at least one Y is CH₂O(CO)R₇.

In certain embodiments, X represents S or CH=CH. In certain embodiments, X represents S.

In certain embodiments, R₁ and R₂ each represent H.

In certain embodiments, Z represents R₃(CO). In certain embodiments wherein Z is R₃(CO), R₃ and R₁₁ are not identical (*e.g.*, the compound of formula I is not symmetrical).

In certain embodiments, Z represents R₃(CO) and R₃ represents arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl. In certain embodiments, Z represents R₃(CO) and R₃ represents C(R₈)(R₉)(R₁₀), wherein R₈ represents aryl, arylalkyl, heteroaryl or heteroaralkyl, such as aryl, arylalkyl or heteroaryl, R₉ represents H, and R₁₀ represents hydroxy, hydroxyalkyl, alkoxy or alkoxyalkyl, such as hydroxy, hydroxyalkyl or alkoxy. In certain embodiments, Z represents R₃(CO) and R₃ represents heteroarylalkyl.

In certain embodiments, L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 , such as CH_2CH_2 , Y represents H, X represents S, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, R_3 represents arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl, and R_{11} represents arylalkyl. In certain such embodiments, R_3 represents heteroarylalkyl.

5 In certain embodiments, L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 , such as CH_2CH_2 , Y represents H, X represents S, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, and each R_3 represents $\text{C}(\text{R}_8)(\text{R}_9)(\text{R}_{10})$, wherein R_8 represents aryl, arylalkyl, heteroaryl or heteroarylalkyl, such as aryl, arylalkyl or heteroaryl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl, alkoxy or alkoxyalkyl, such as hydroxy, hydroxyalkyl or alkoxy, and R_{11} represents arylalkyl. In certain such embodiments, R_8 represents heteroaryl.

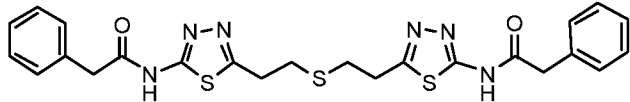
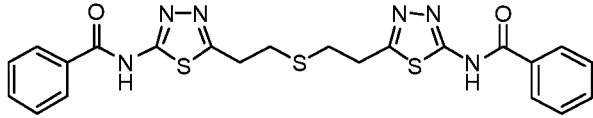
In certain embodiments, L represents CH_2CH_2 , Y represents H, X represents S or $\text{CH}=\text{CH}$, such as S, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, R_3 represents substituted or unsubstituted arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl, and R_{11} represents arylalkyl. In certain such embodiments, R_3 represents heteroarylalkyl.

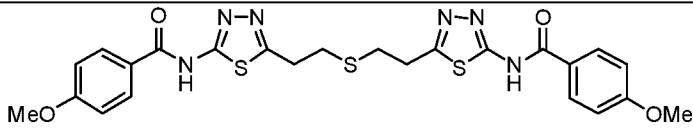
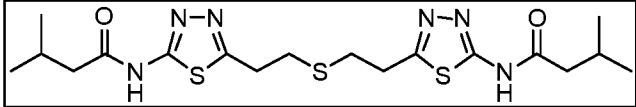
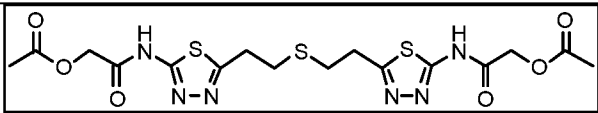
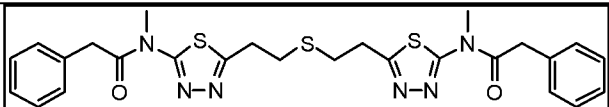
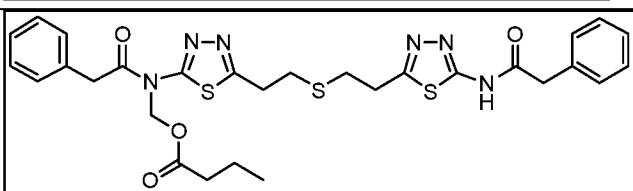
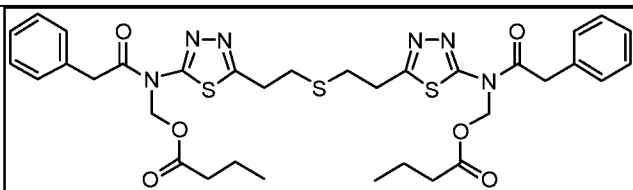
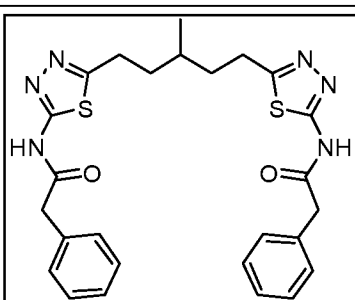
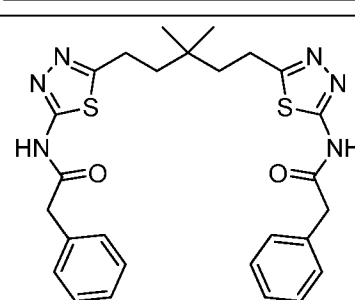
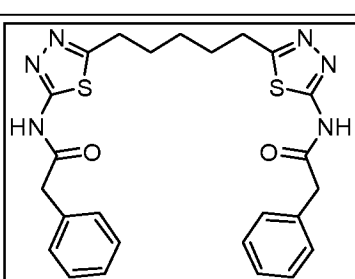
15 In certain embodiments, L represents CH_2CH_2 , Y represents H, X represents S, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, R_3 represents $\text{C}(\text{R}_8)(\text{R}_9)(\text{R}_{10})$, wherein R_8 represents aryl, arylalkyl or heteroaryl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl or alkoxy, and R_{11} represents arylalkyl. In certain such embodiments, R_8 represents aryl and R_{10} represents hydroxyalkyl. In certain other embodiments, R_8 represents heteroaryl.

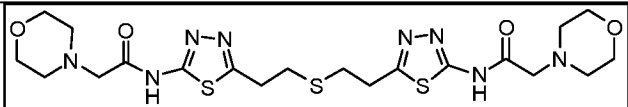
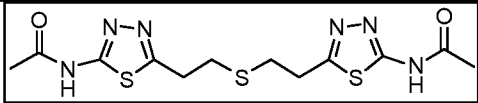
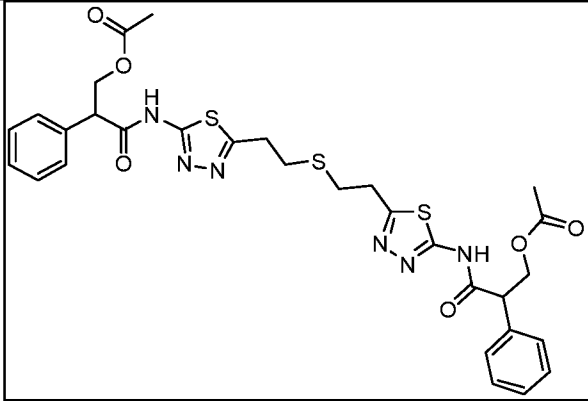
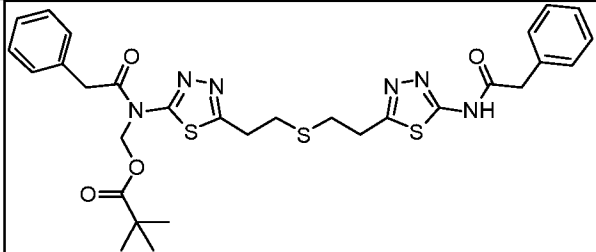
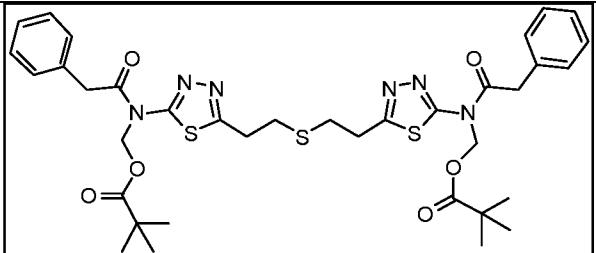
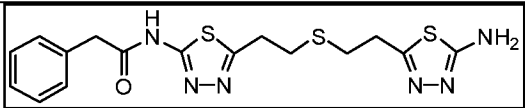
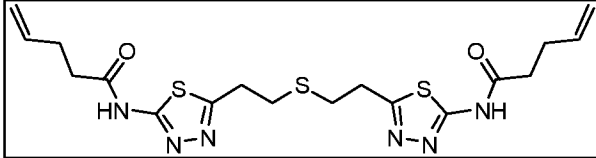
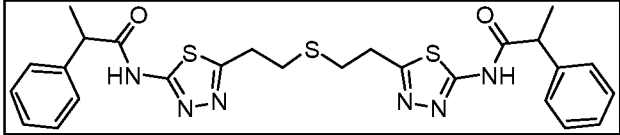
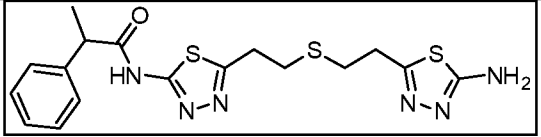
In certain embodiments, the compound is selected from any one of the compounds disclosed in Table 1. Preferably, the compound is selected from compound 1, 2, 6, 7, 8, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 36, 38, 39, 40, 41, 43, 44, 47, 48, 50, 51, 52, 54, 55, 58, 63, 64, 65, 67, 68, 69, 70, 71, 72, 73, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 92, 93, 94, 95, 97, 99, 100, 102, 105, 107, 111, 112, 114, 115, 116, 117, 118, 120, 121, 122, 123, 126, 127, 133, 135, 136, 138, 140, 141, 143, 146, 147, 148, 152, 153, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 168, 169, 170, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 185, 186, 187, 188, 189, 190, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 208, 210, 211, 213, 214, 216, 217, 219, 220, 226, 227, 228, 229, 231, 232, 234, 235, 236, 237, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 273, 274, 275, 276, 278, 279, 280, 281, 282, 283, 285, 286, 287, 288, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 302, 304,

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Table 1. Selected Compounds of Formula I

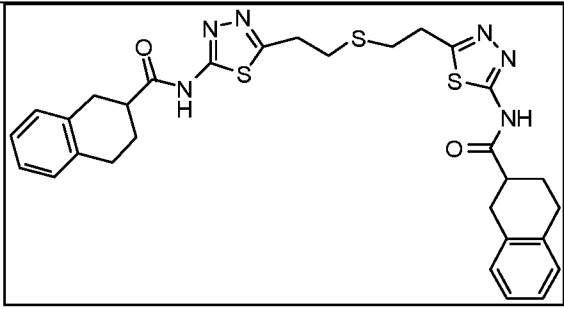
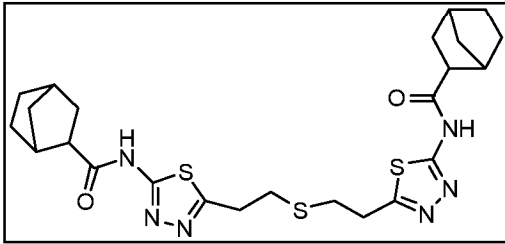
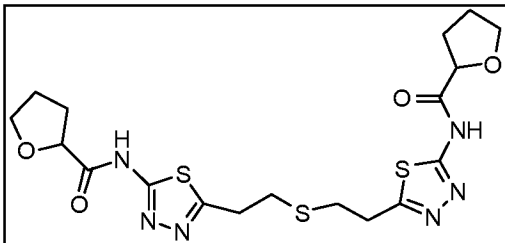
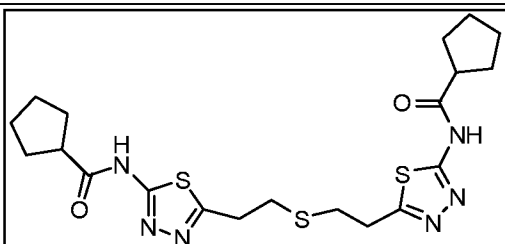
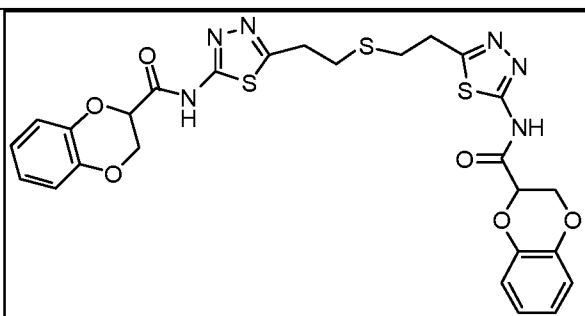
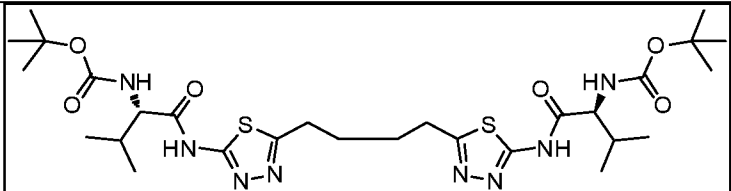
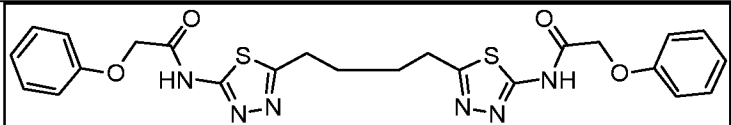
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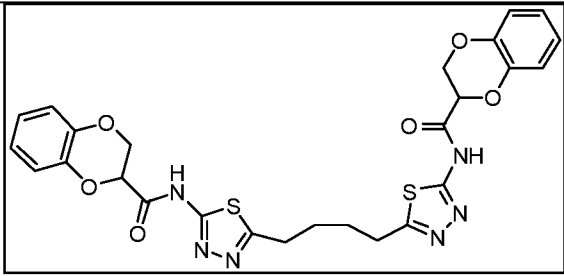
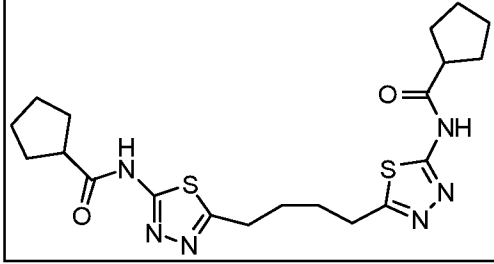
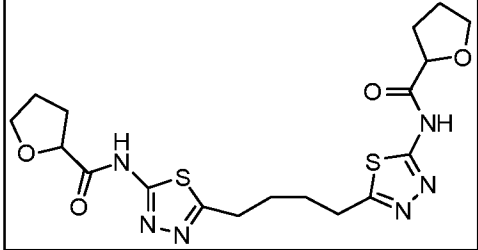
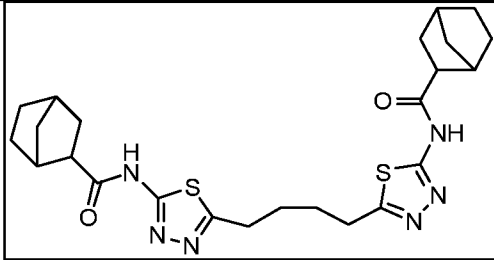
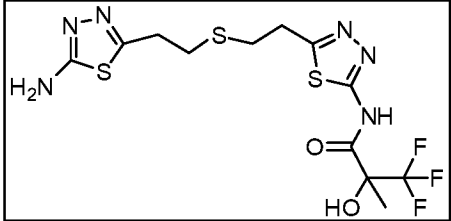
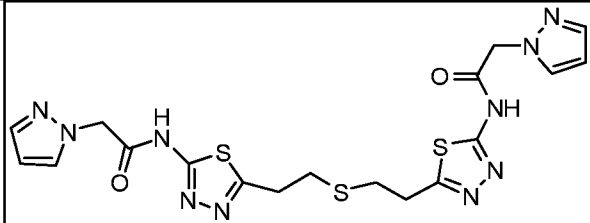
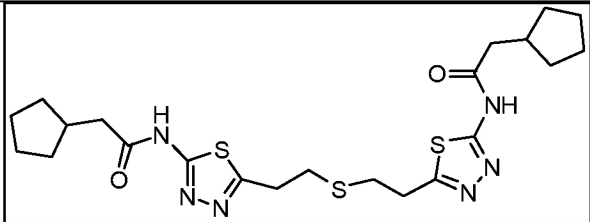
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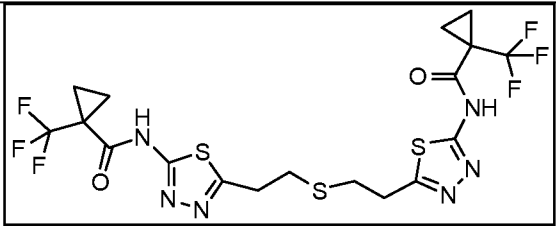
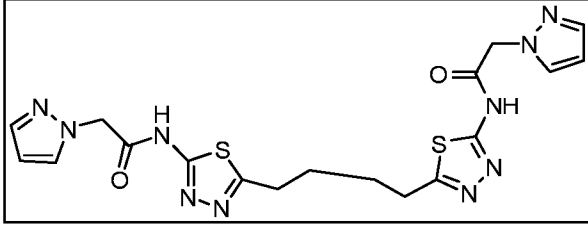
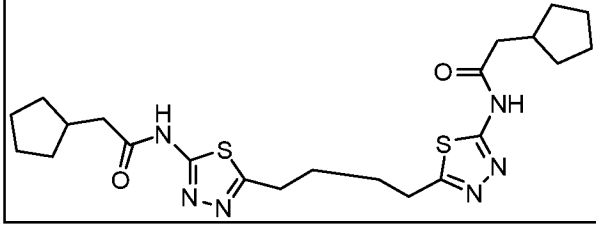
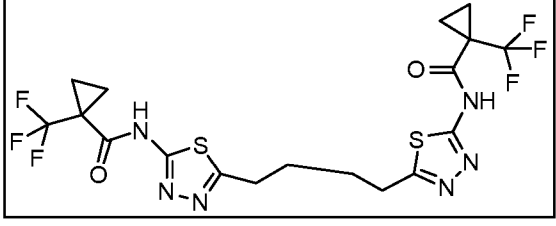
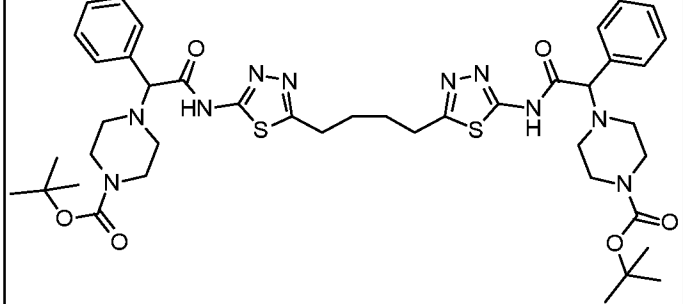
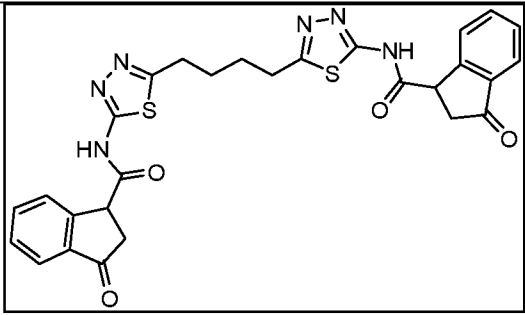
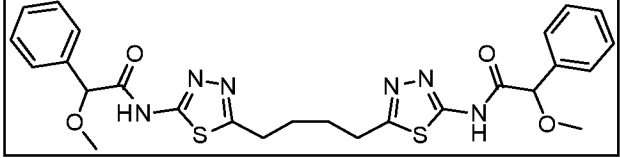
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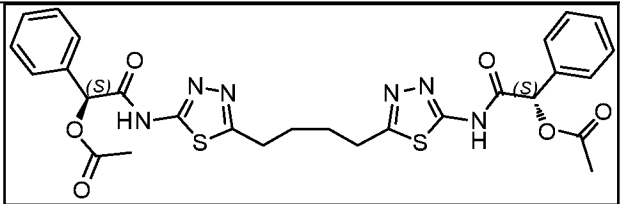
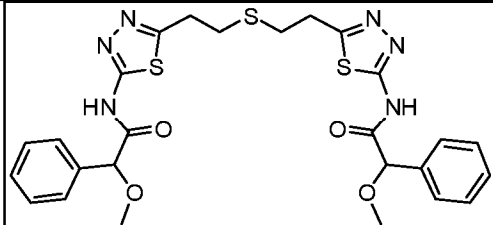
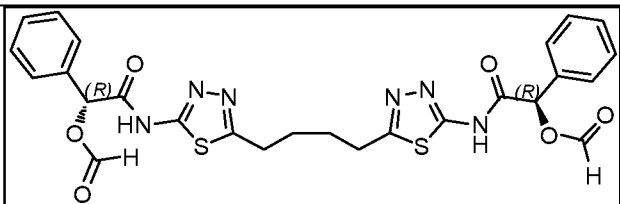
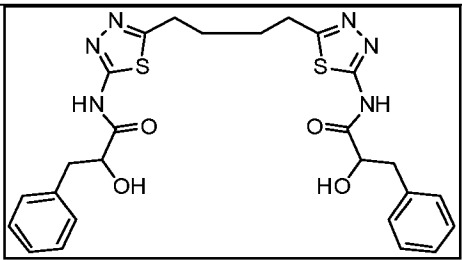
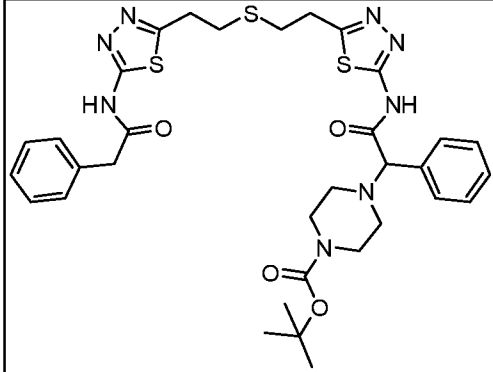
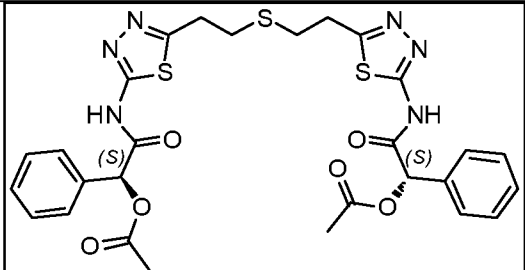
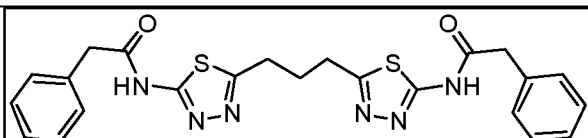
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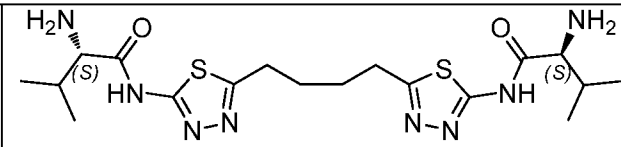
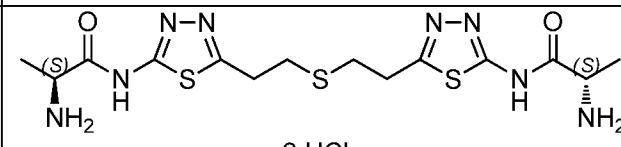
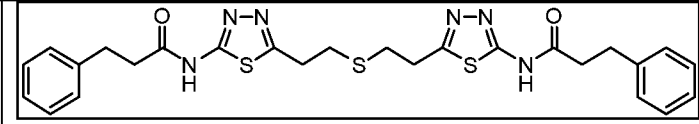
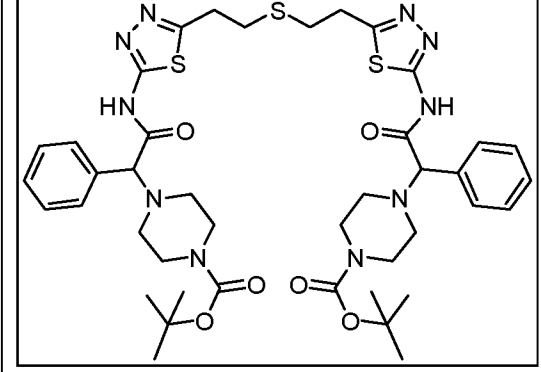
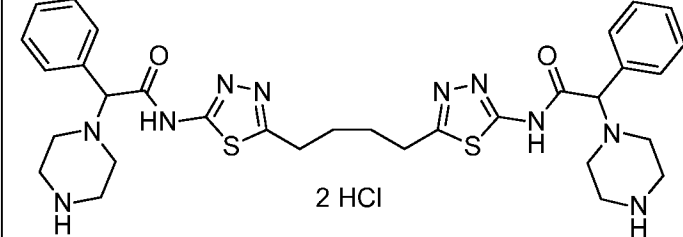
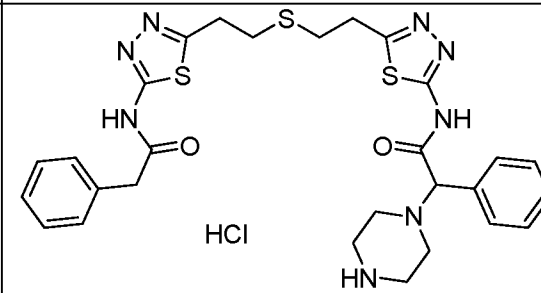
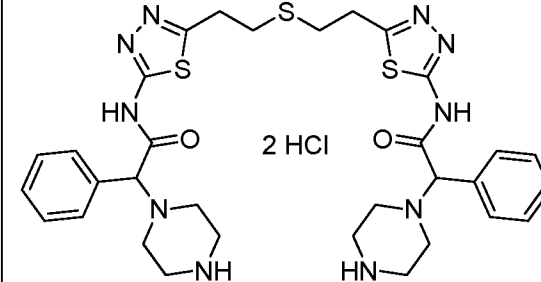
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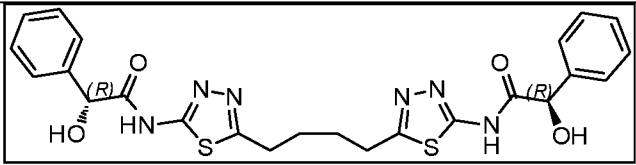
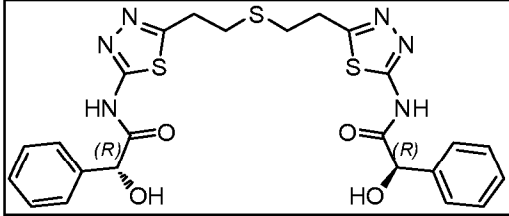
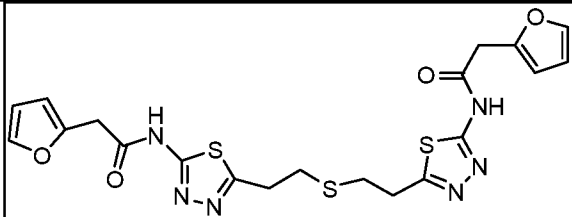
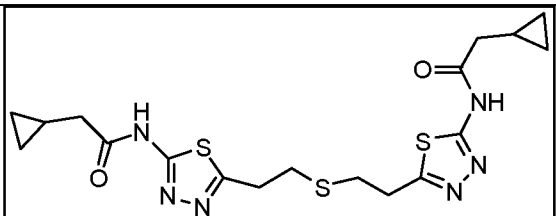
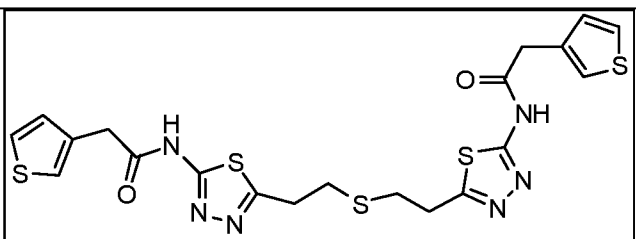
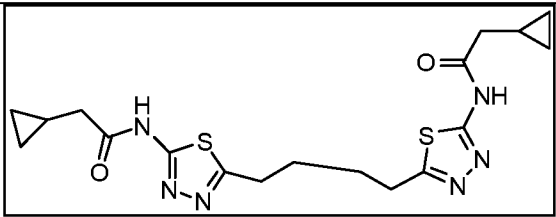
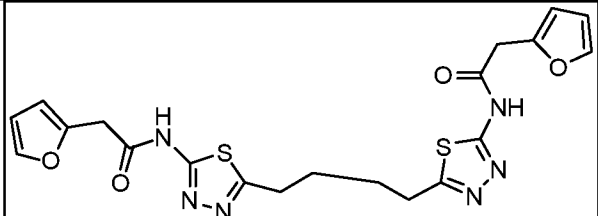
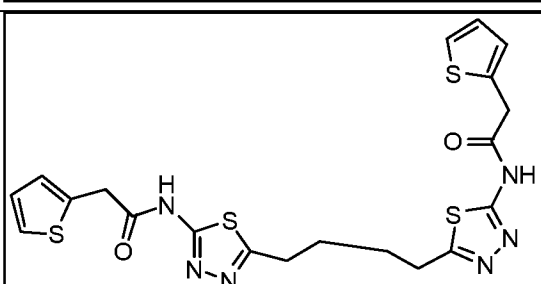
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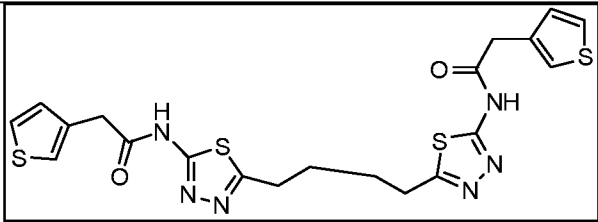
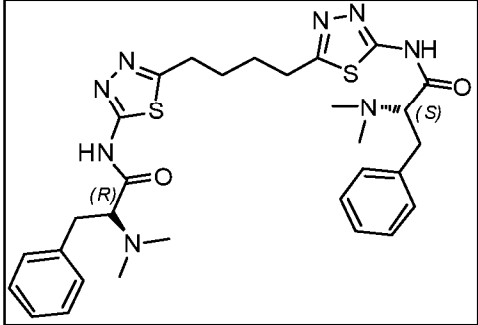
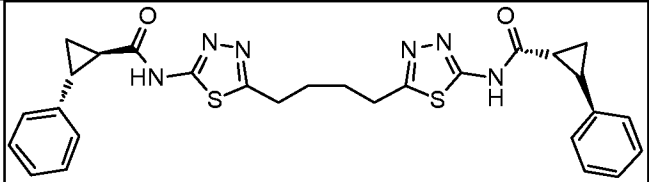
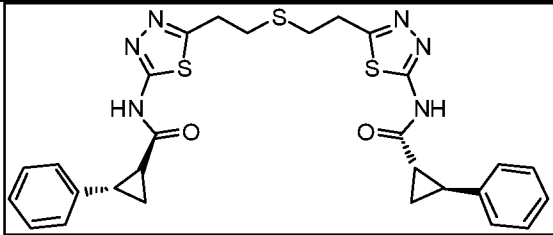
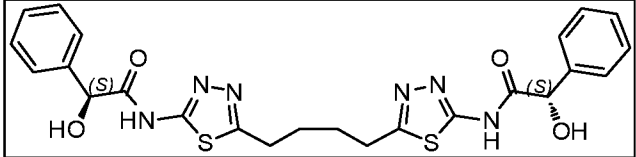
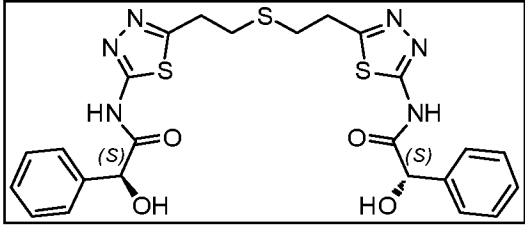
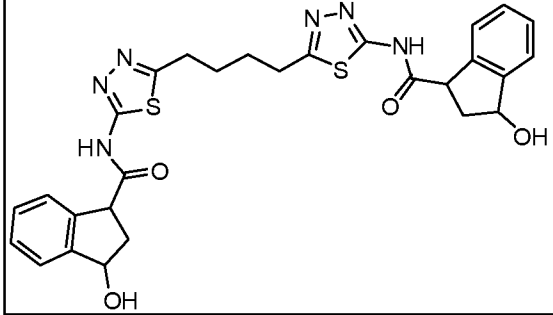
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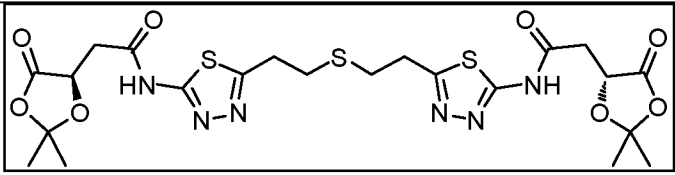
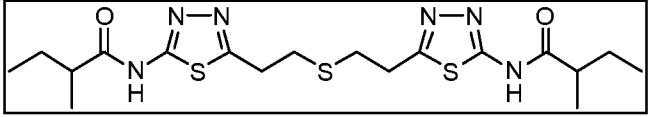
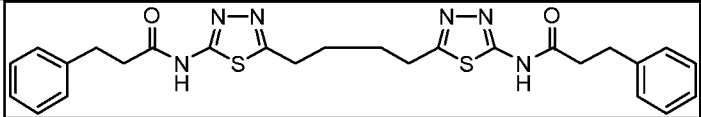
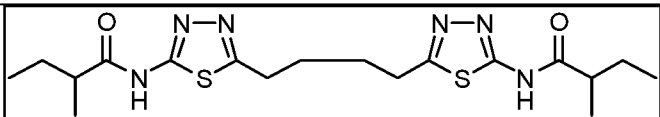
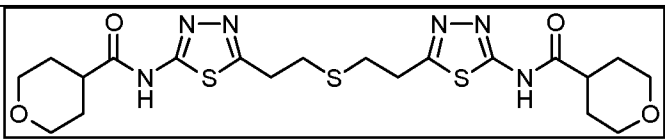
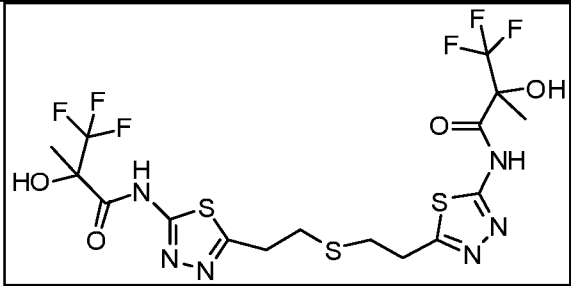
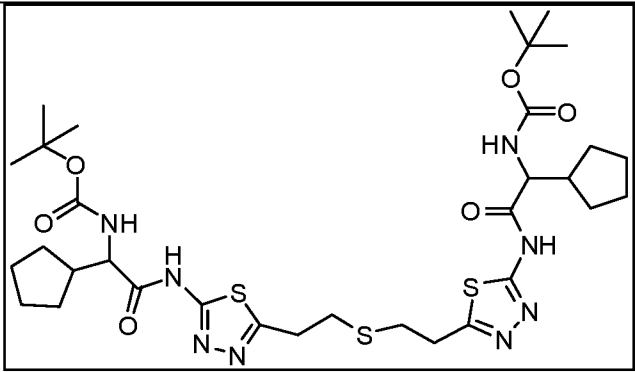
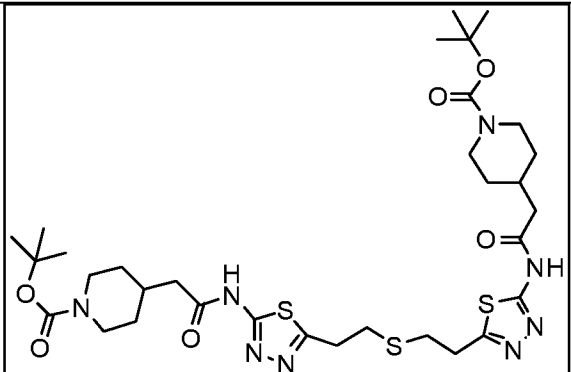
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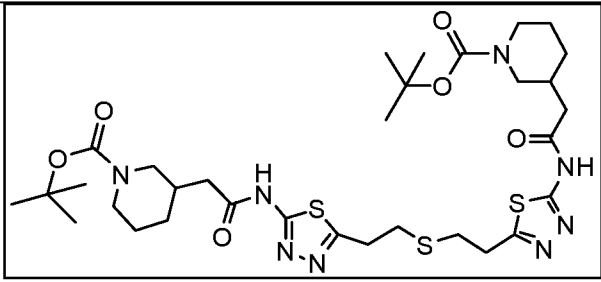
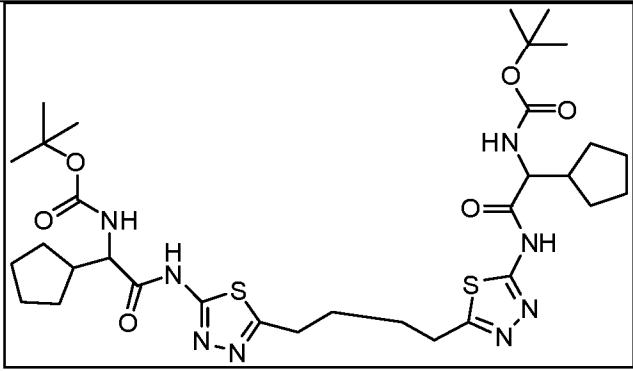
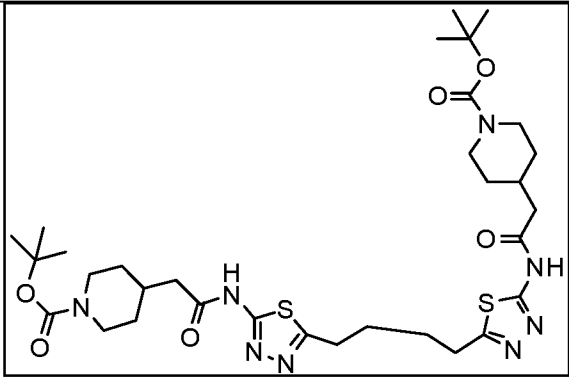
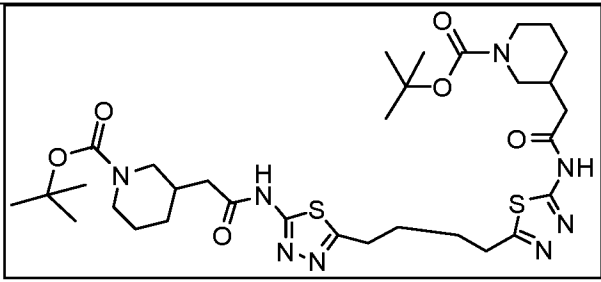
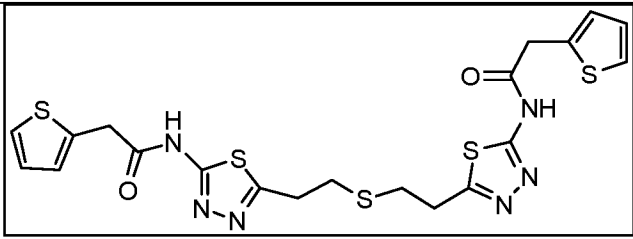
73	 2 TFA
74	 2 HCl
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77	 2 HCl
78	 HCl
79	 2 HCl

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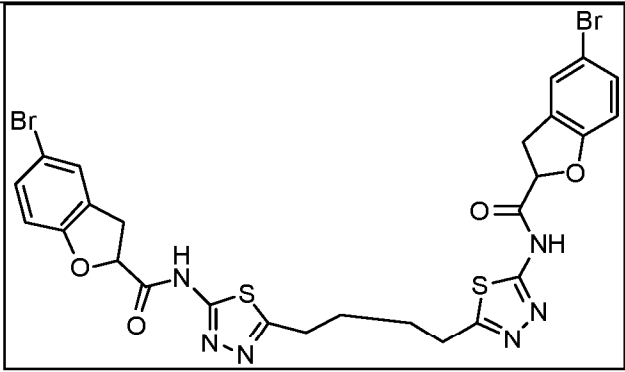
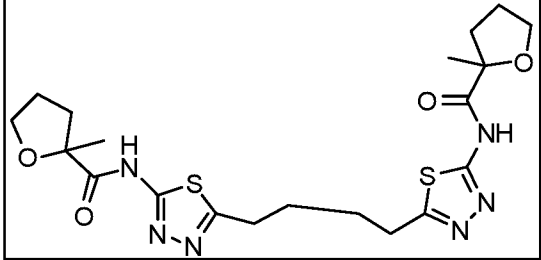
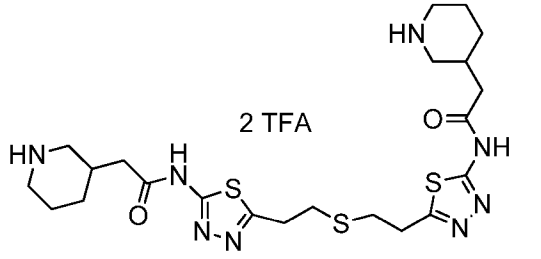
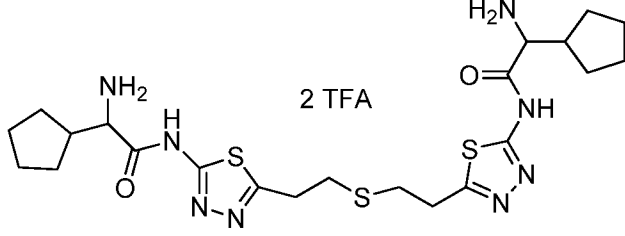
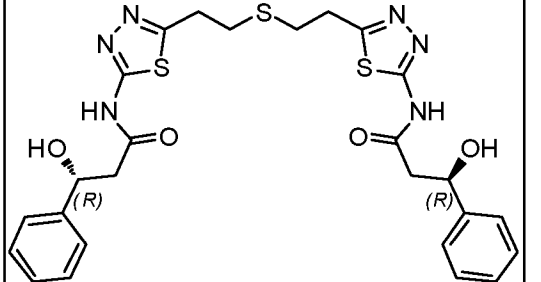
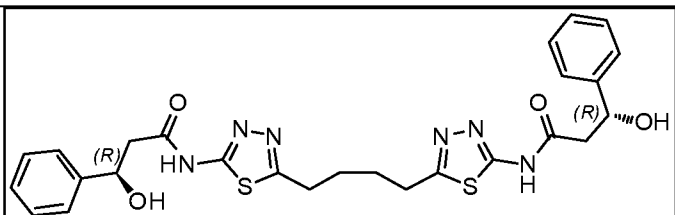
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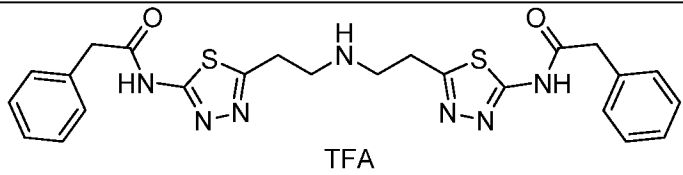
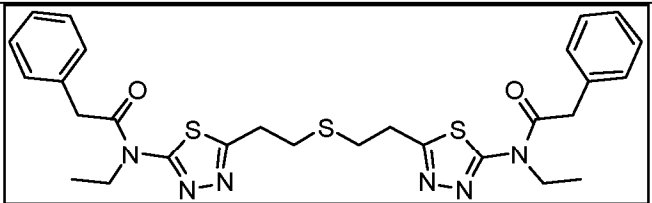
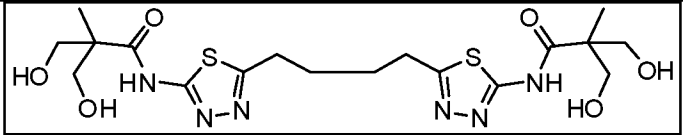
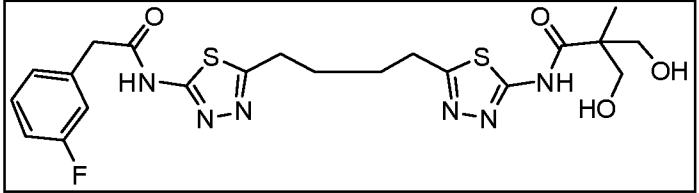
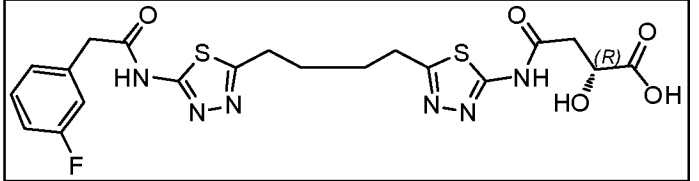
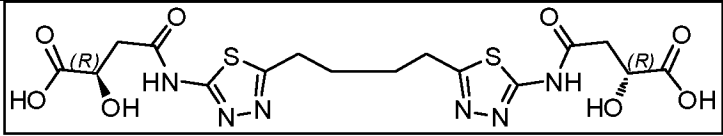
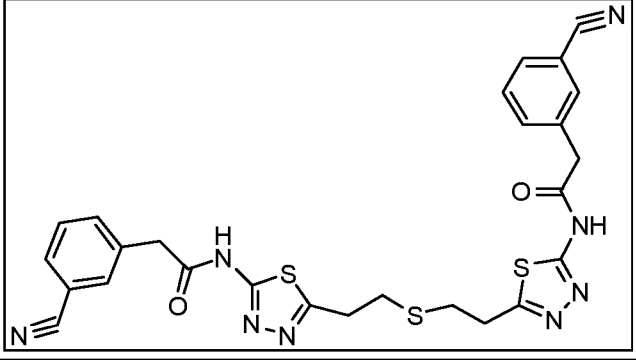
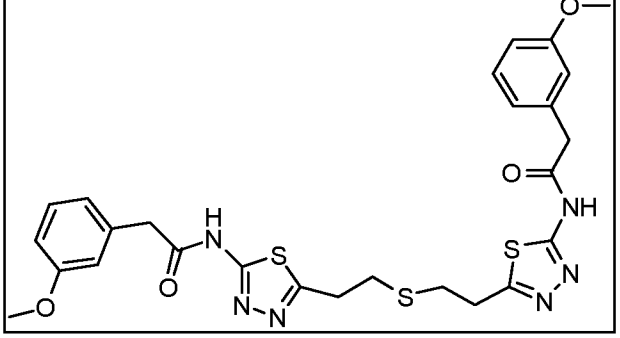
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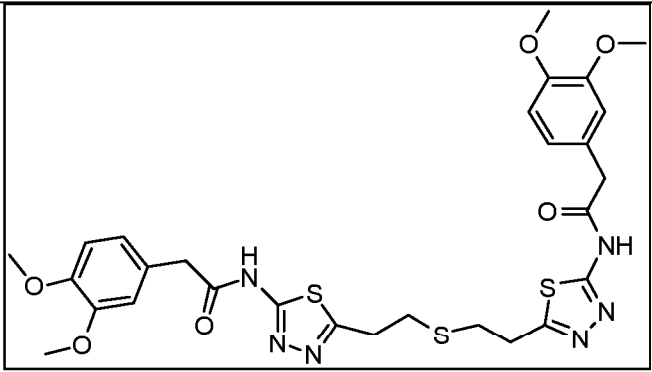
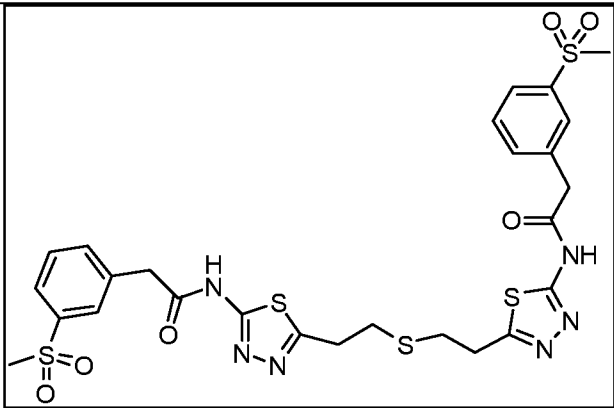
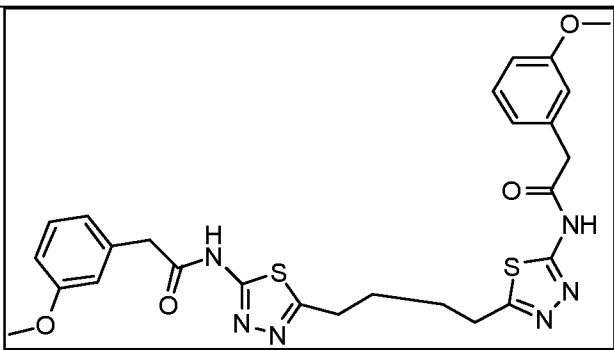
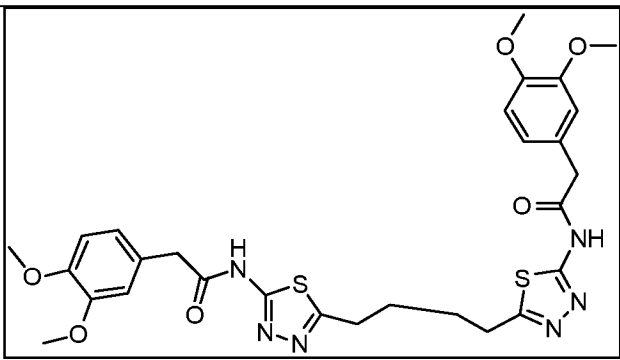
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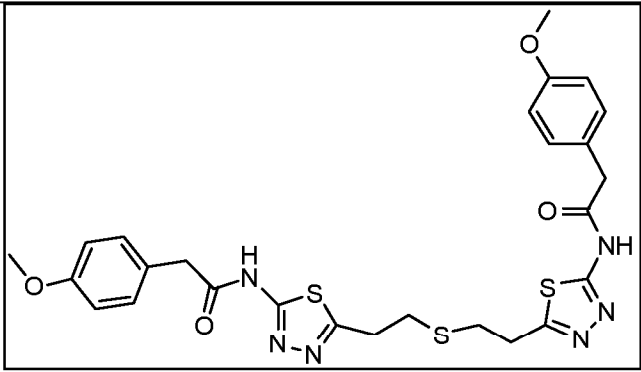
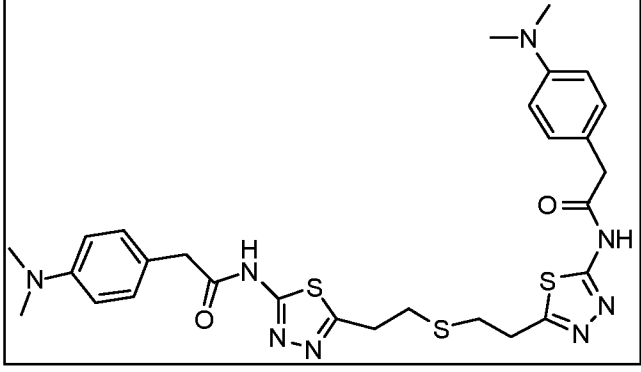
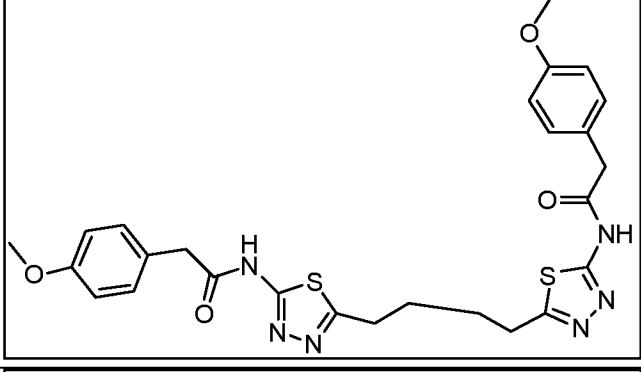
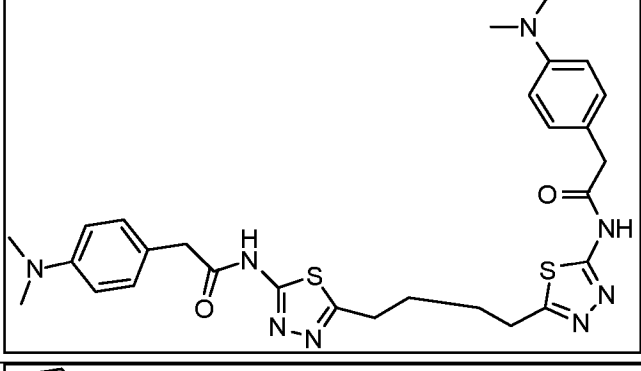
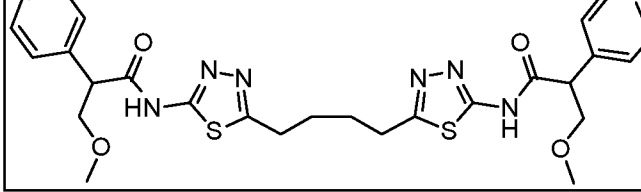
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139	 2 HCl
140	 2 HCl

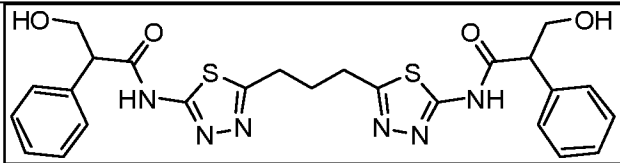
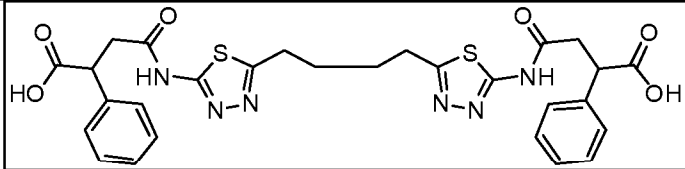
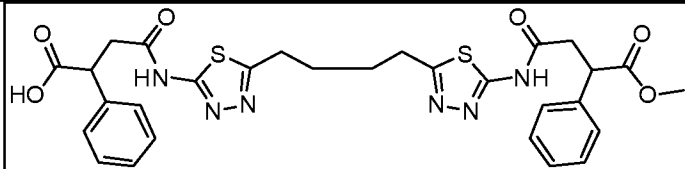
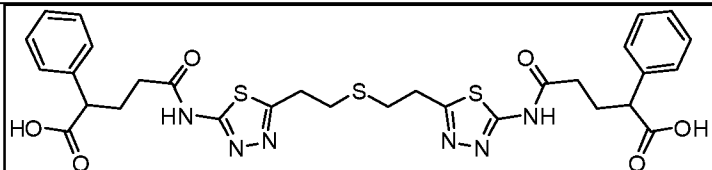
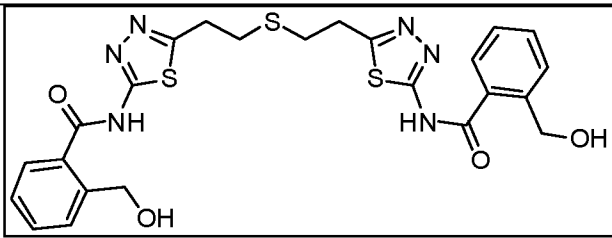
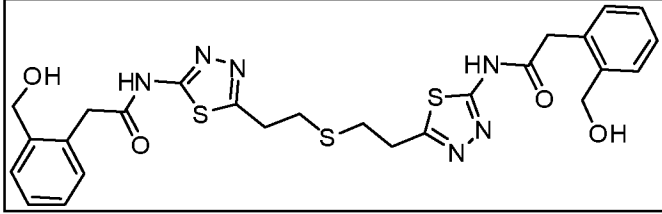
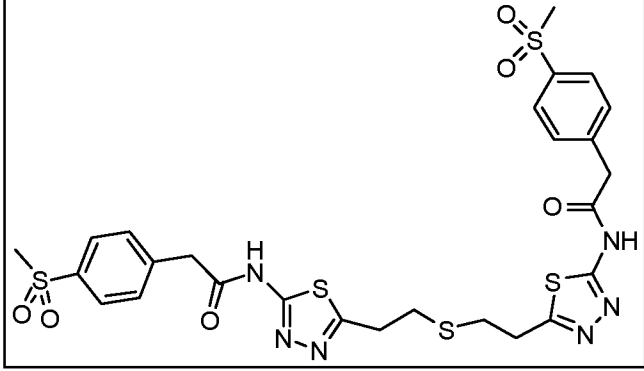
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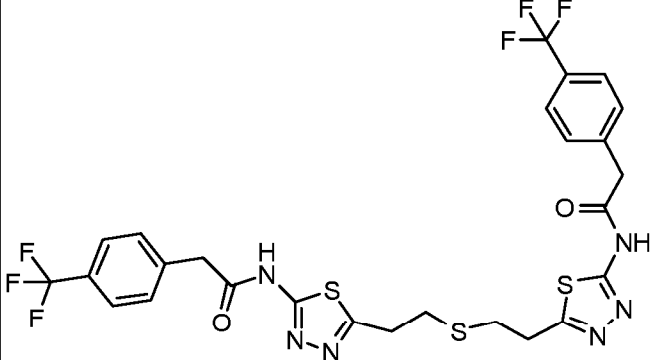
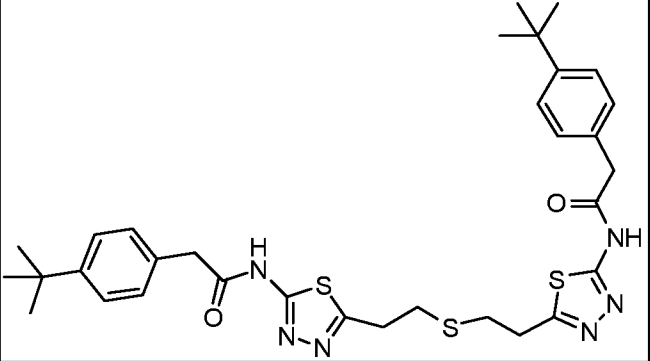
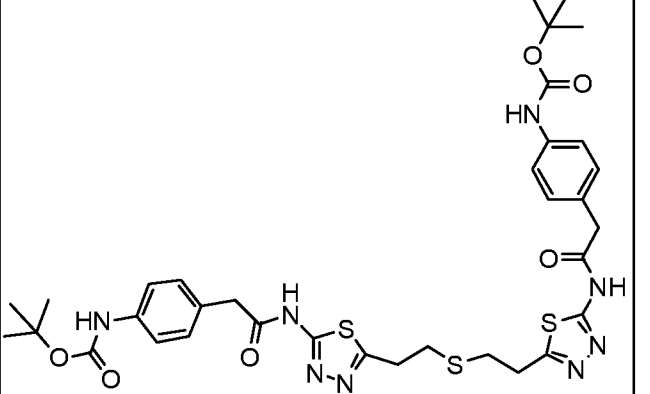
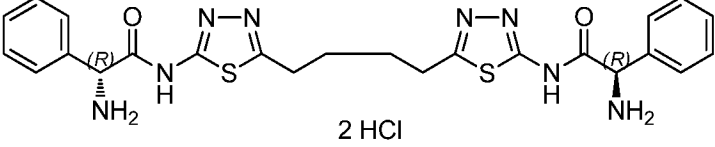
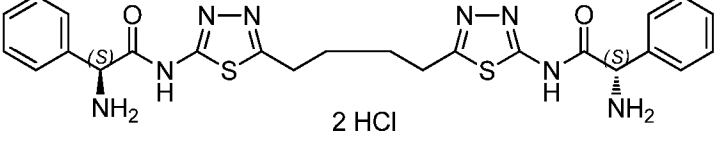
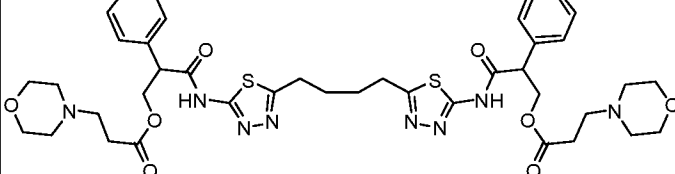
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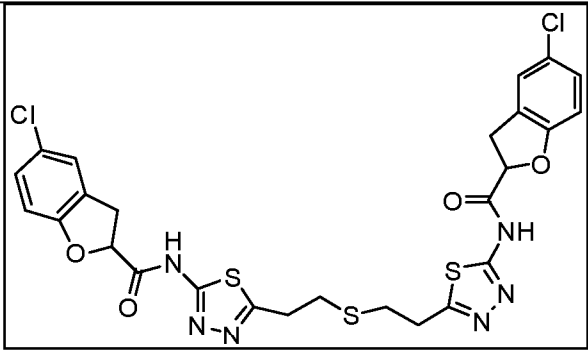
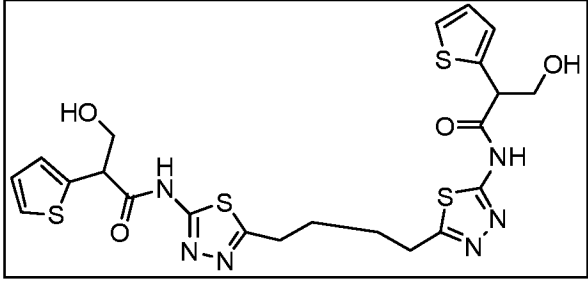
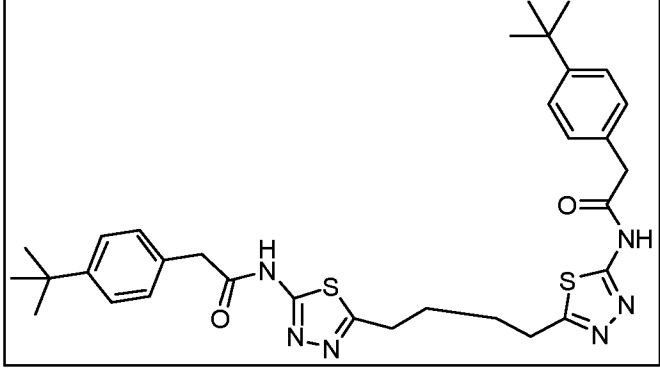
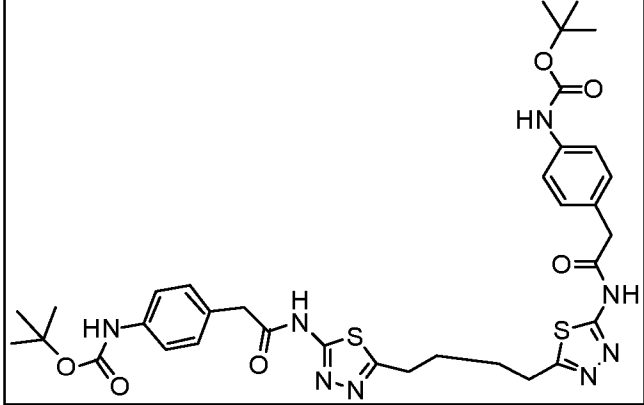
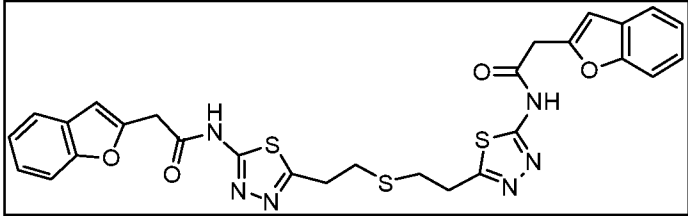
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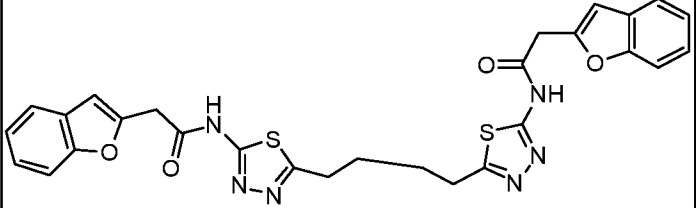
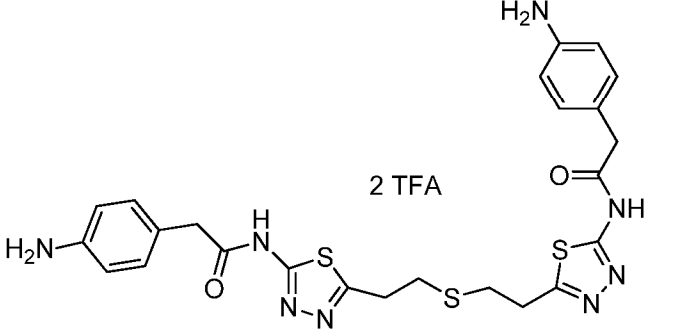
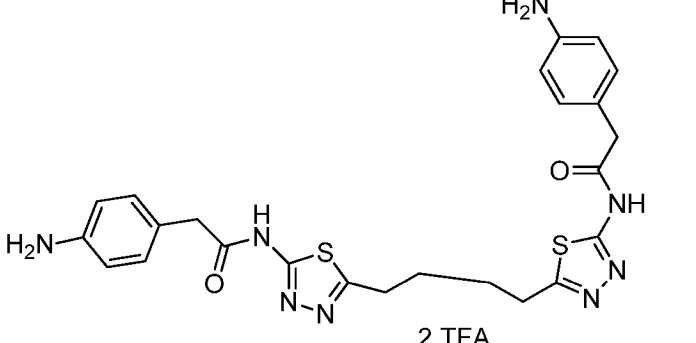
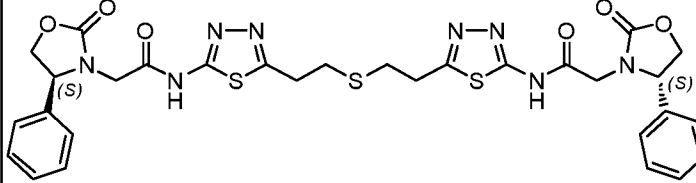
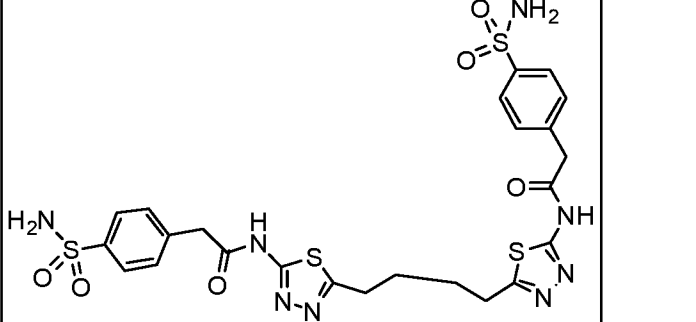
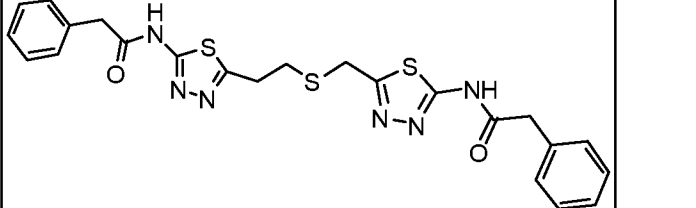
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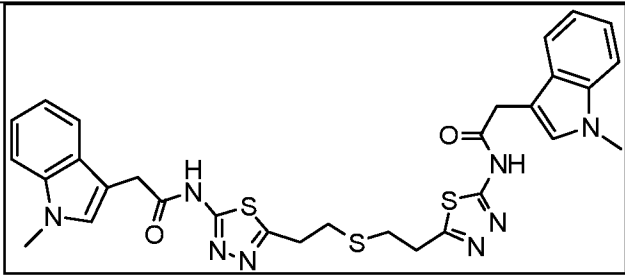
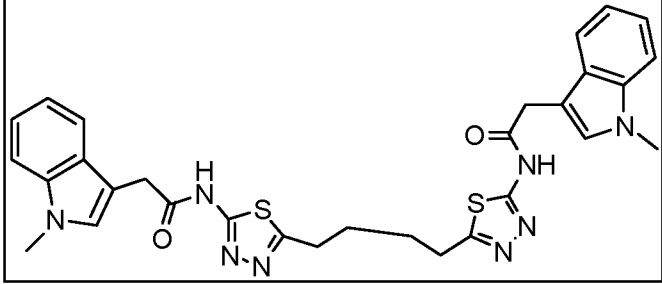
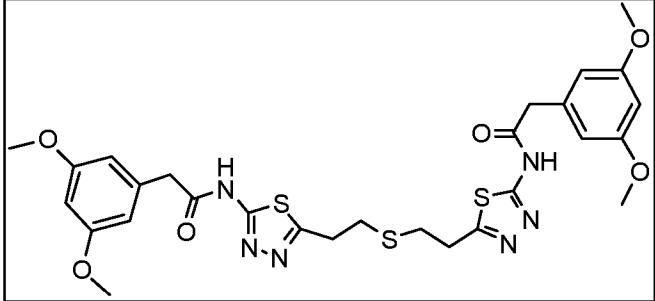
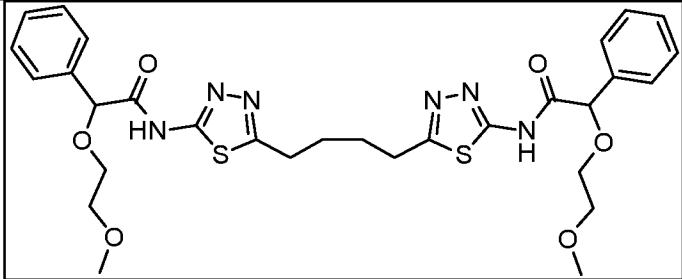
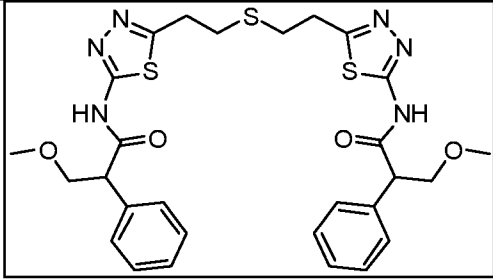
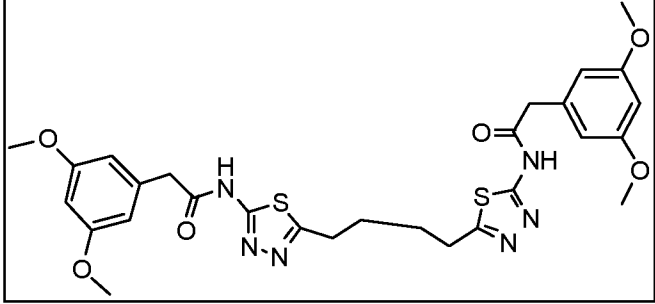
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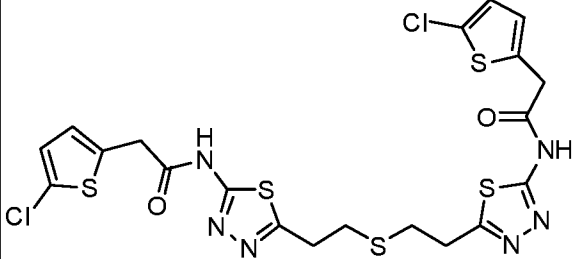
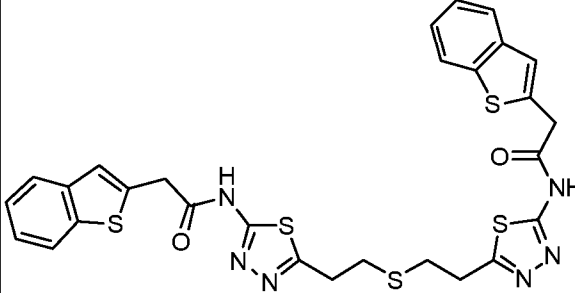
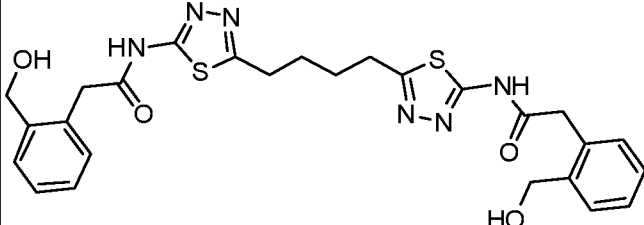
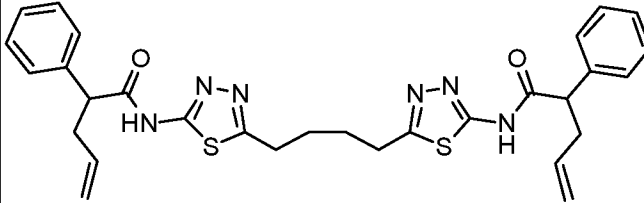
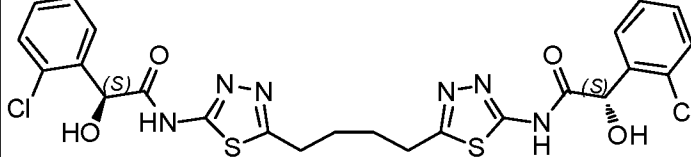
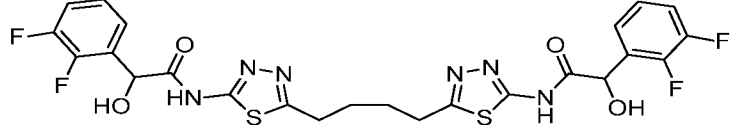
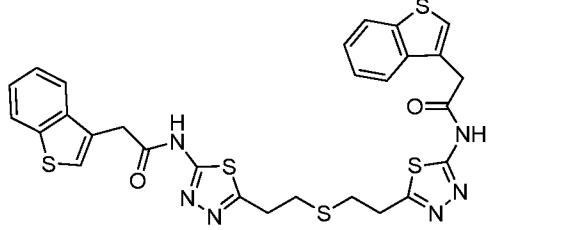
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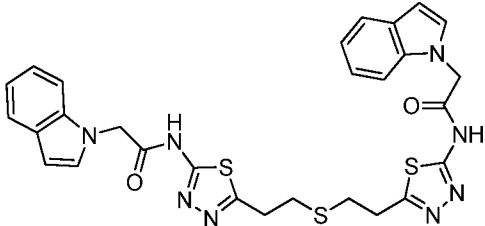
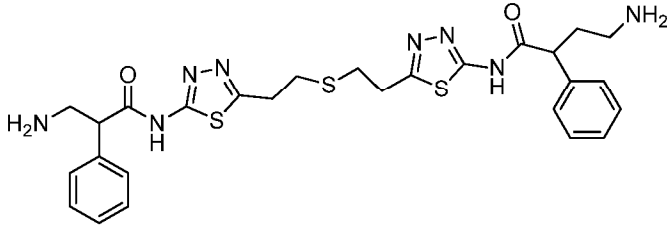
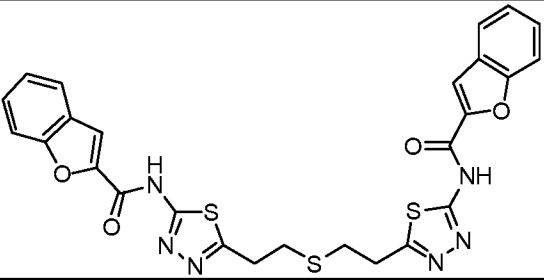
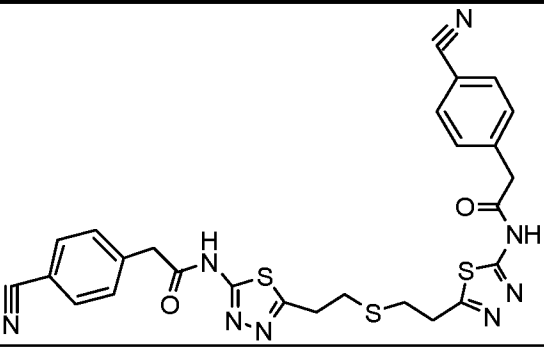
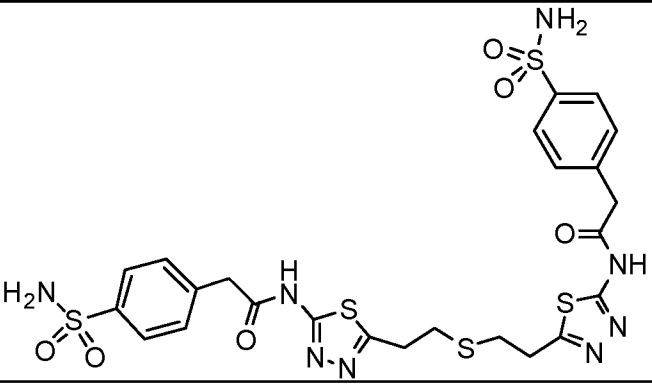
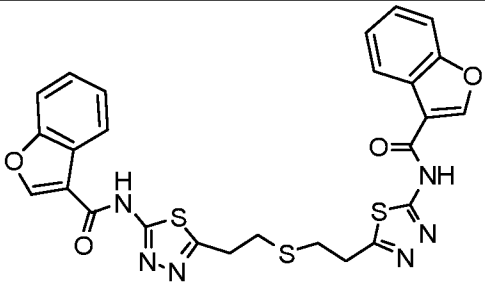
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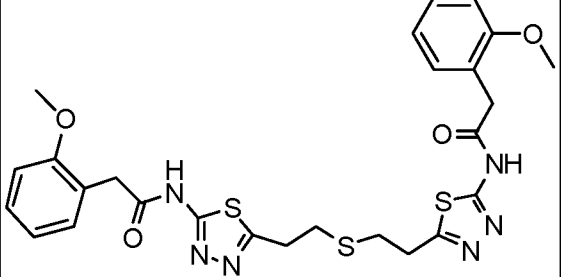
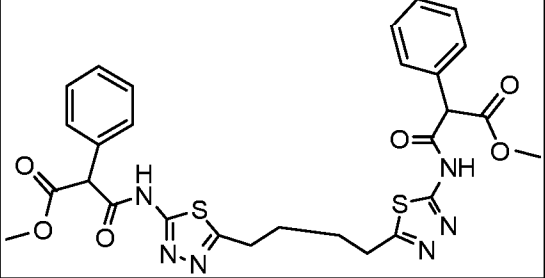
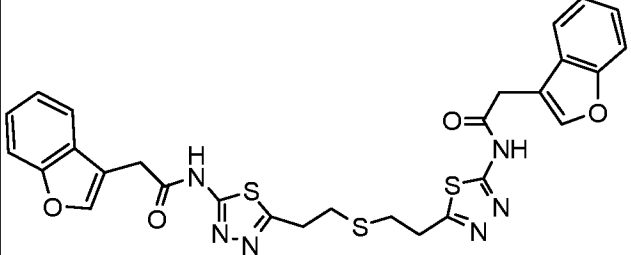
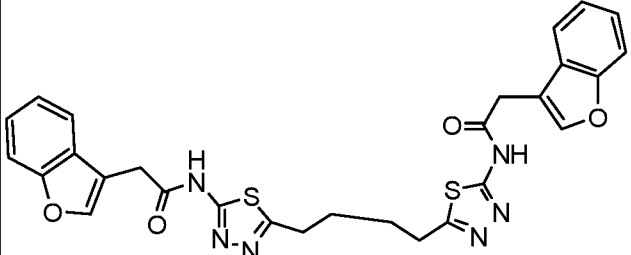
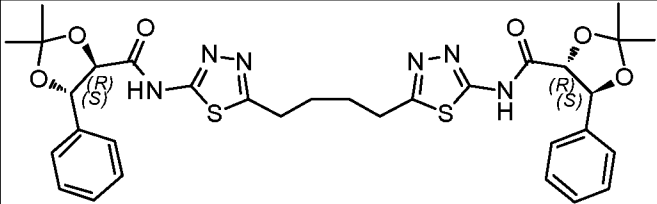
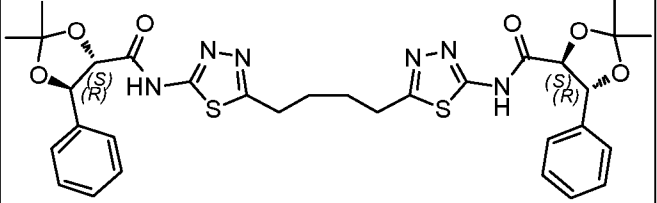
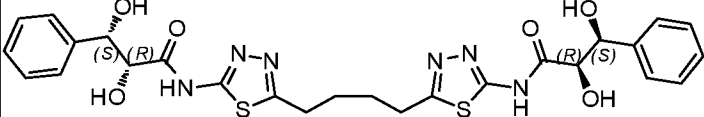
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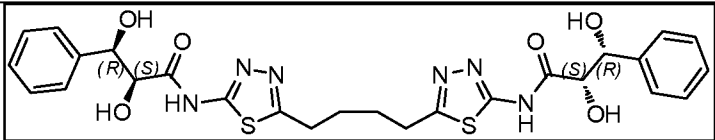
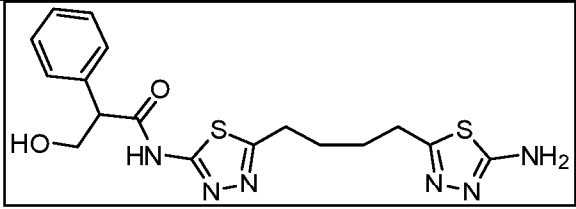
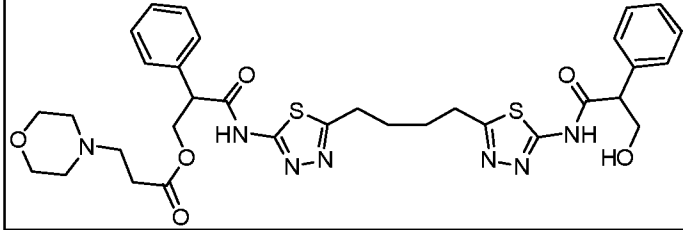
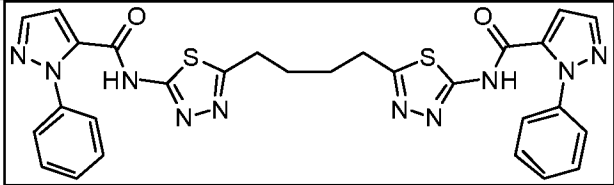
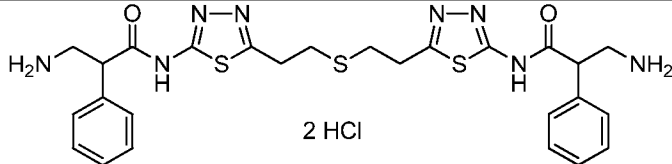
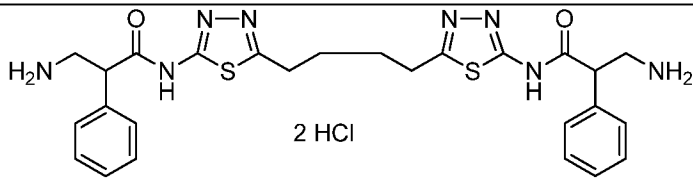
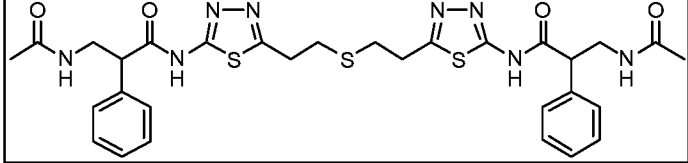
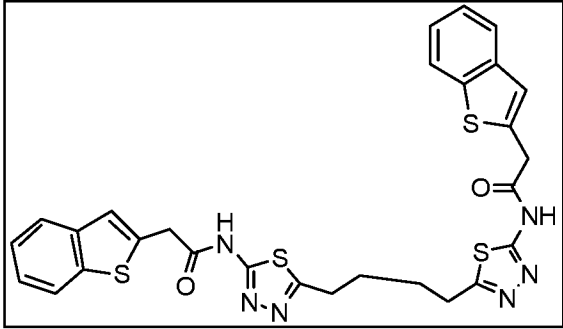
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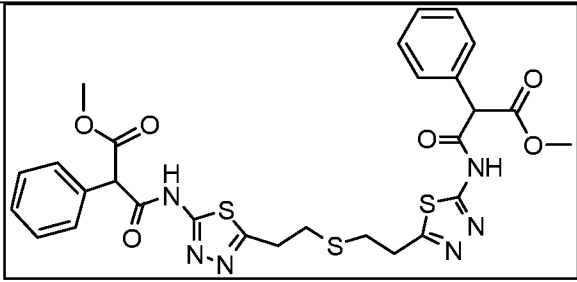
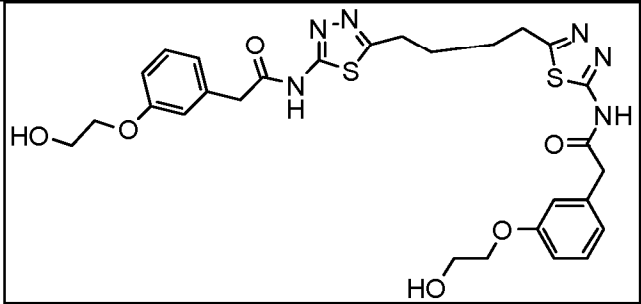
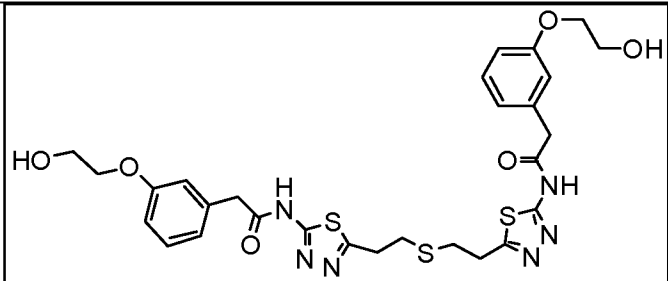
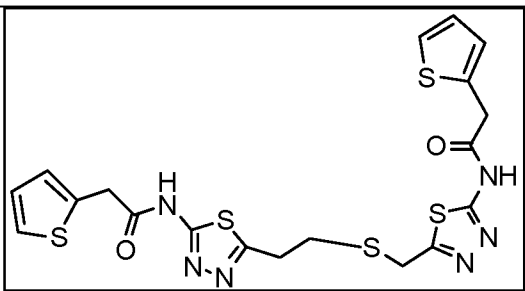
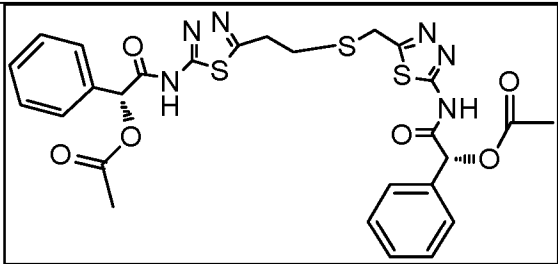
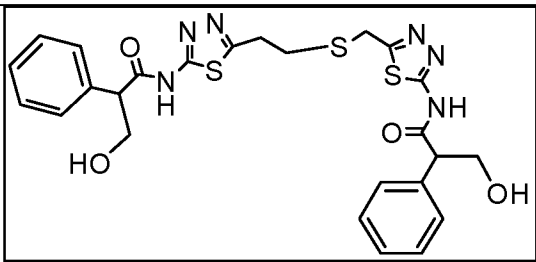
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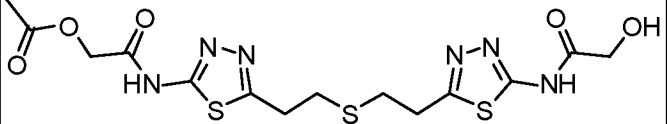
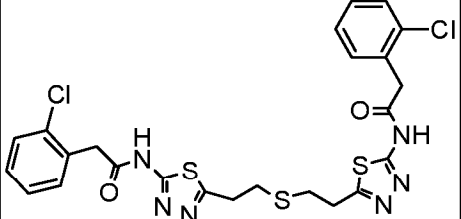
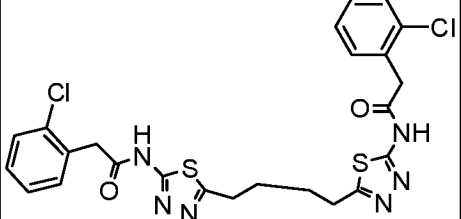
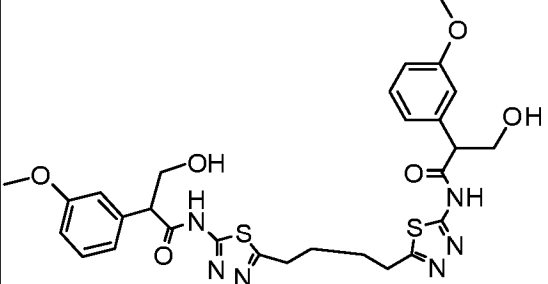
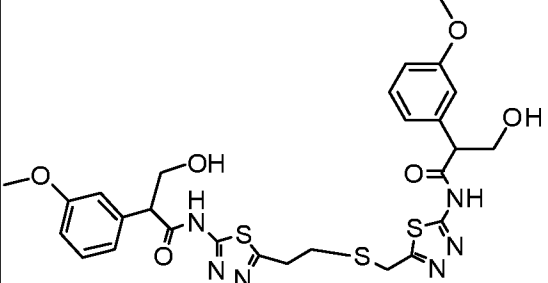
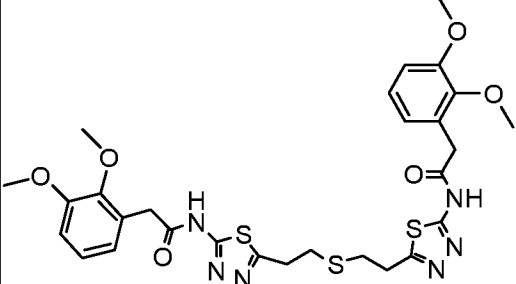
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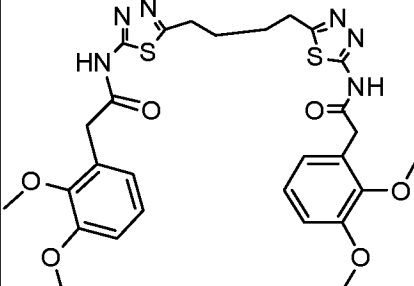
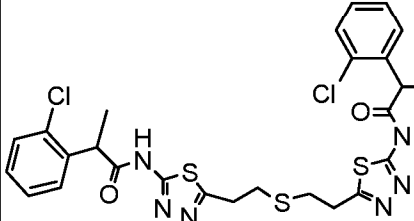
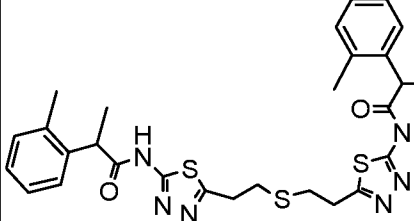
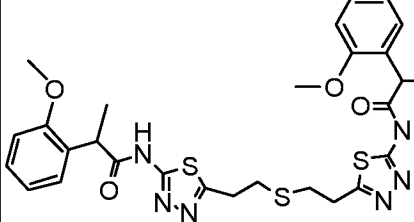
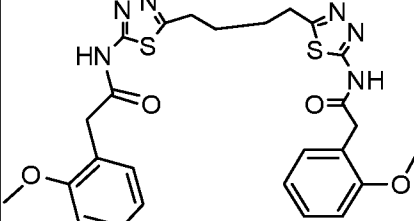
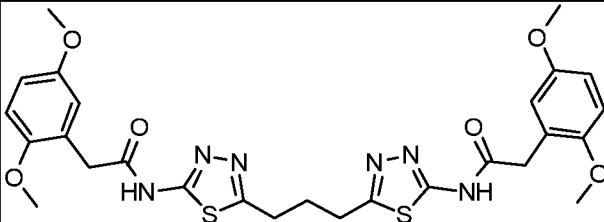
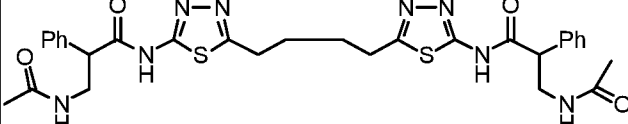
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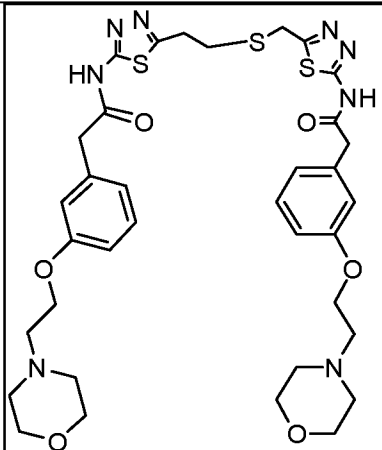
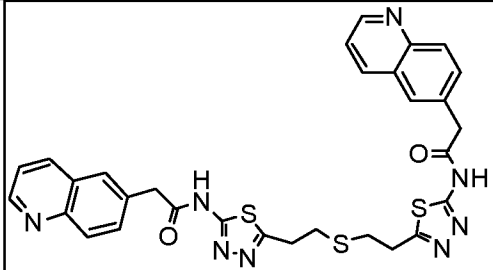
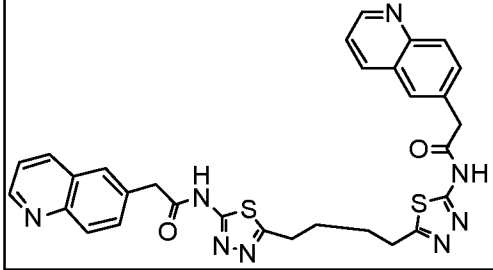
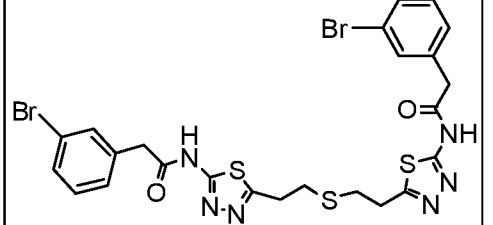
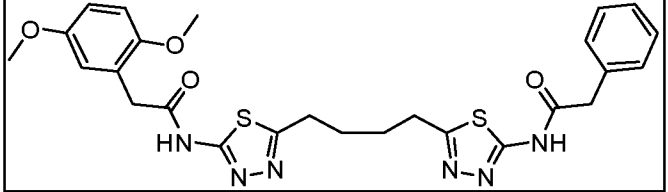
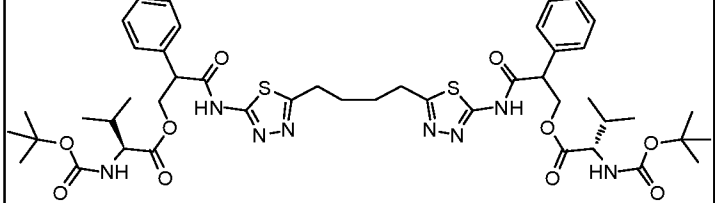
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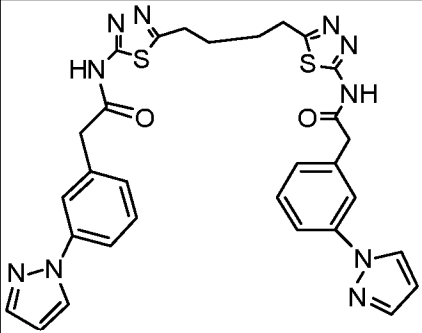
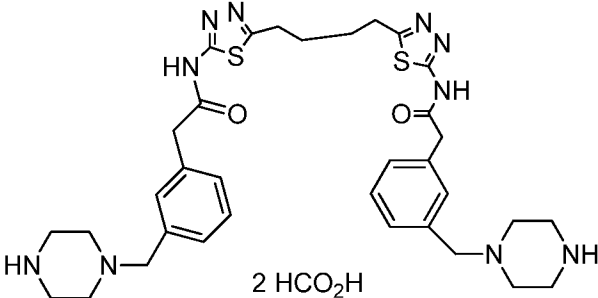
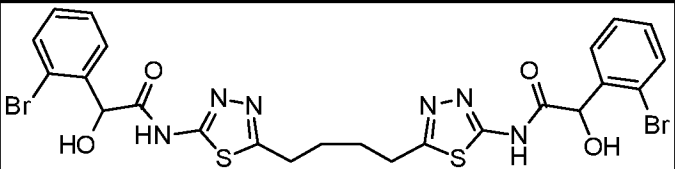
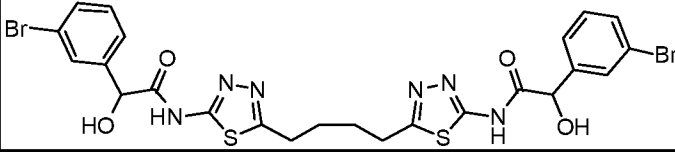
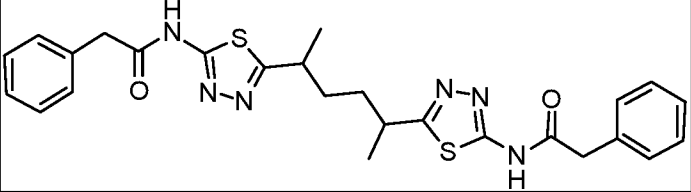
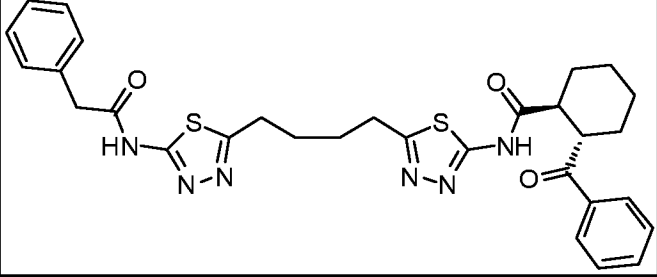
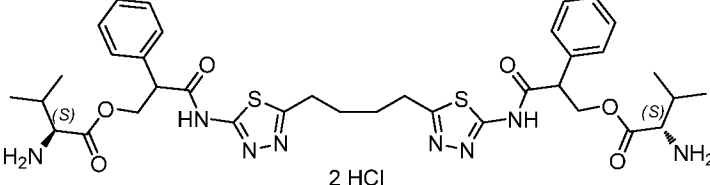
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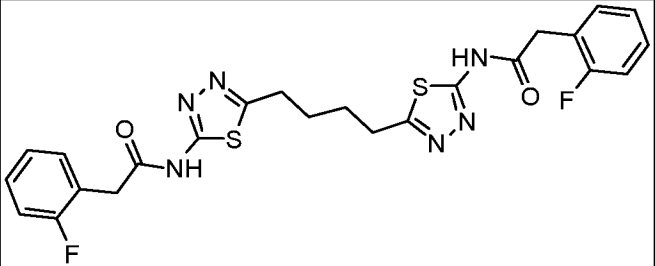
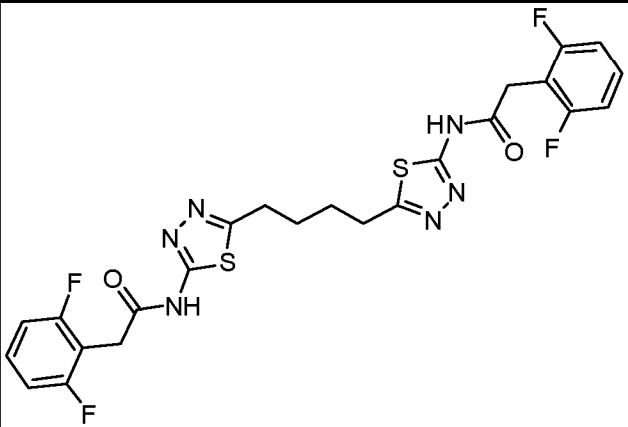
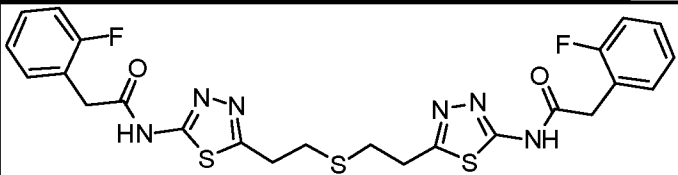
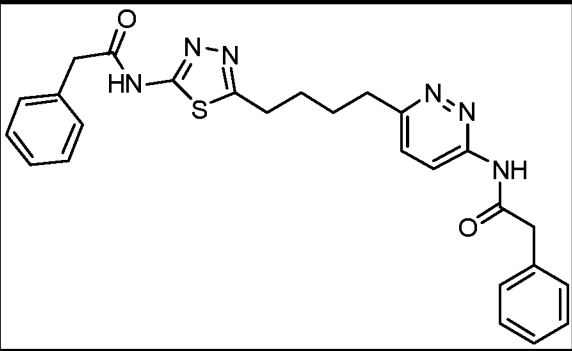
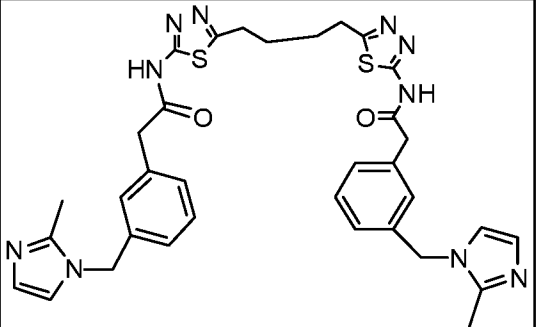
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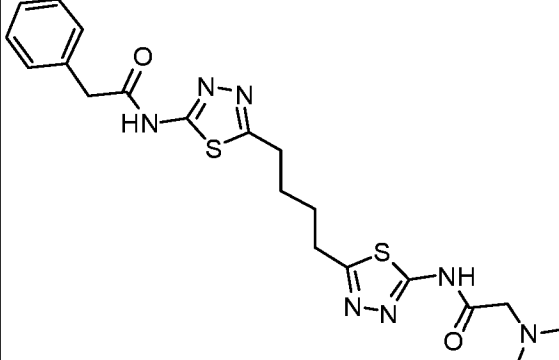
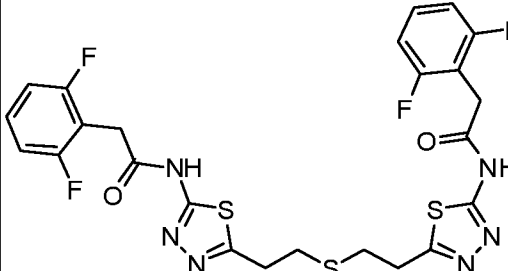
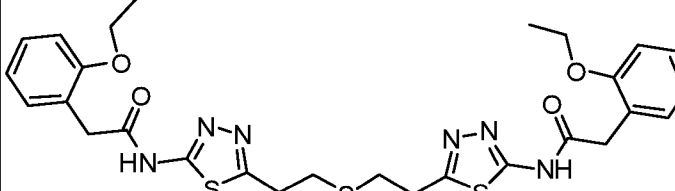
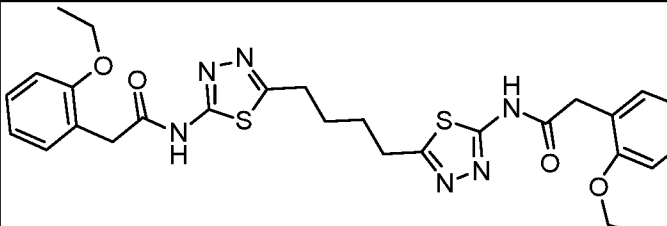
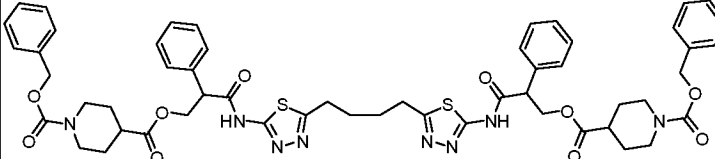
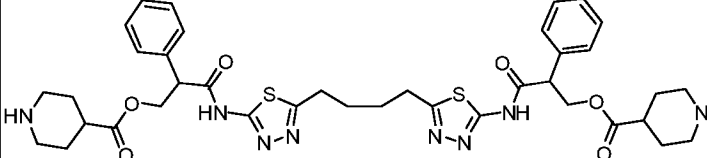
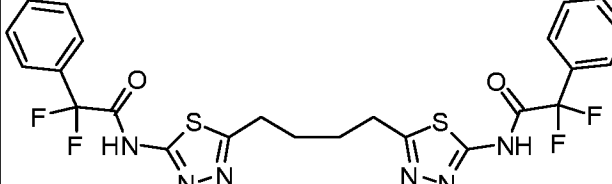
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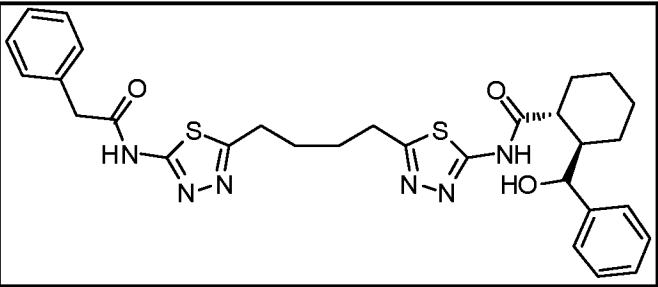
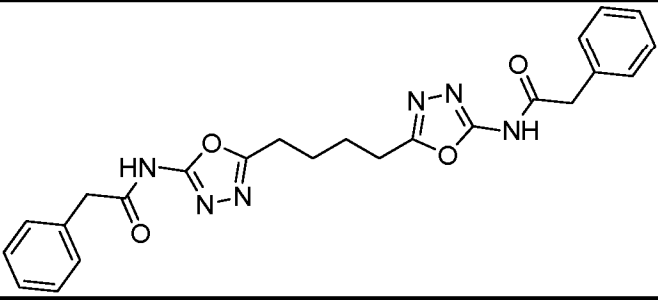
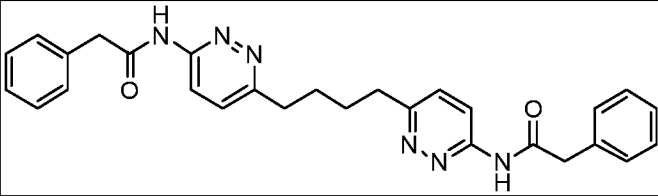
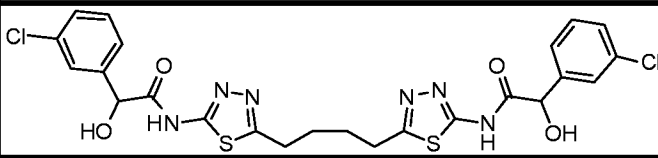
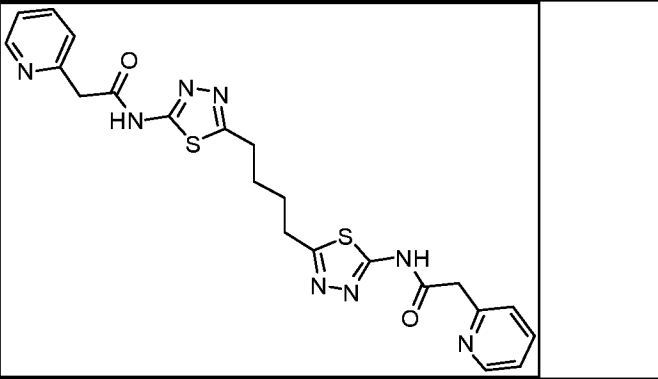
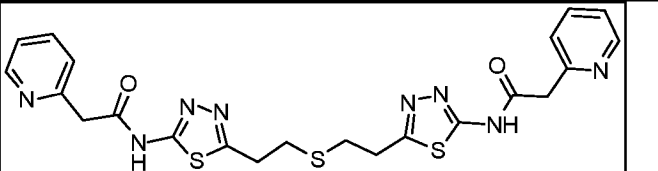
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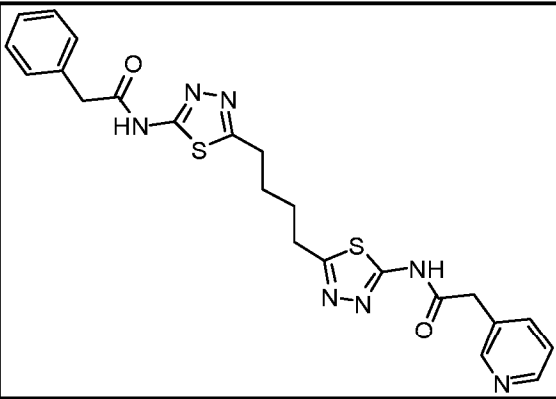
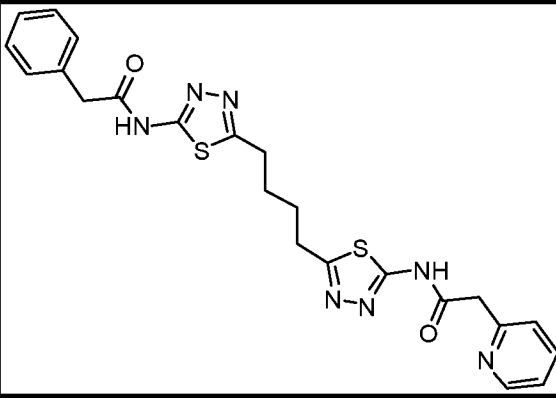
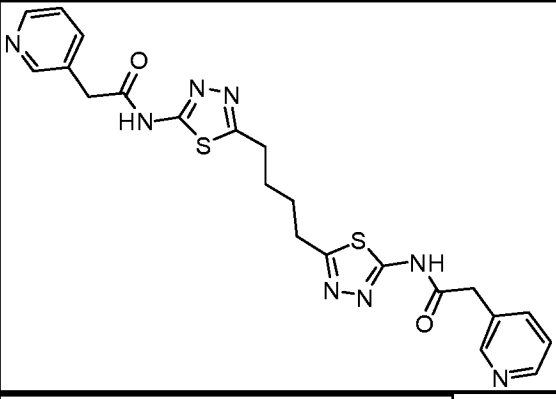
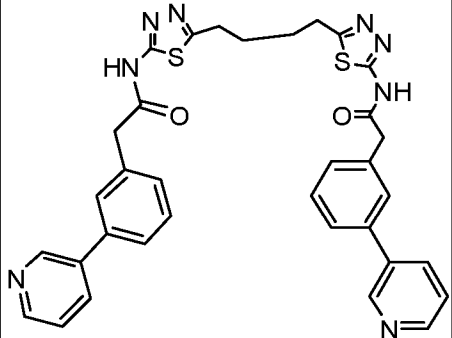
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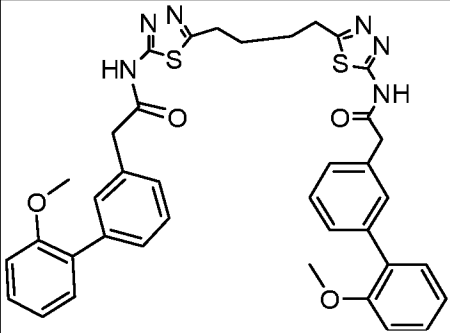
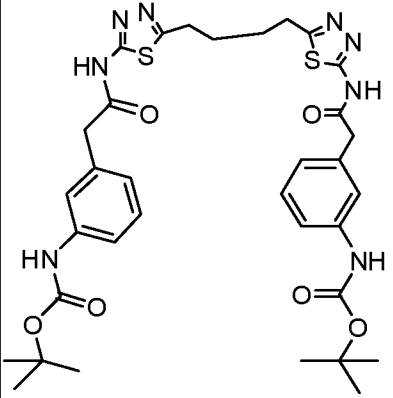
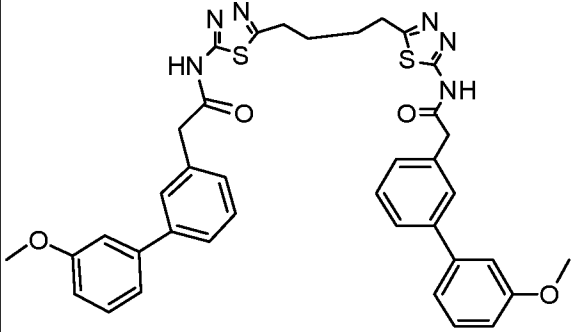
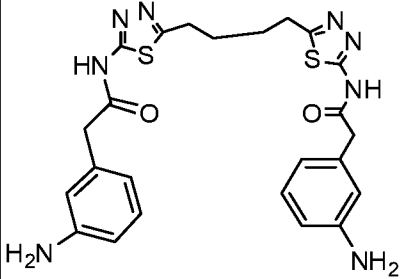
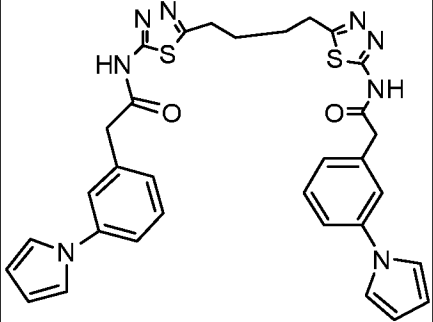
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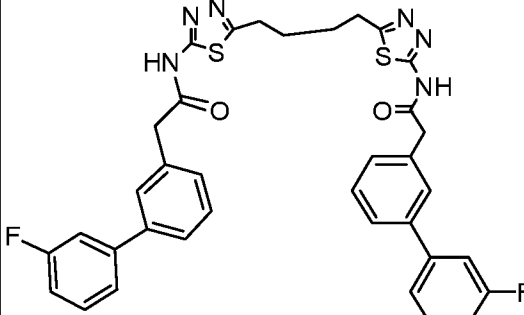
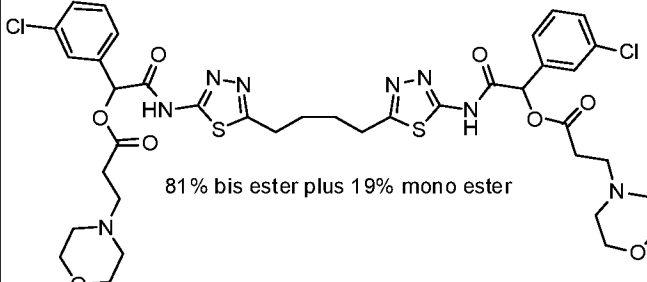
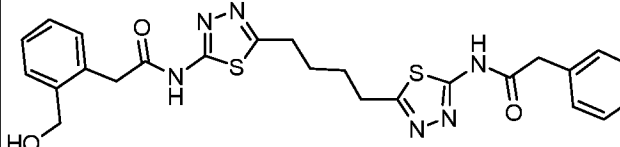
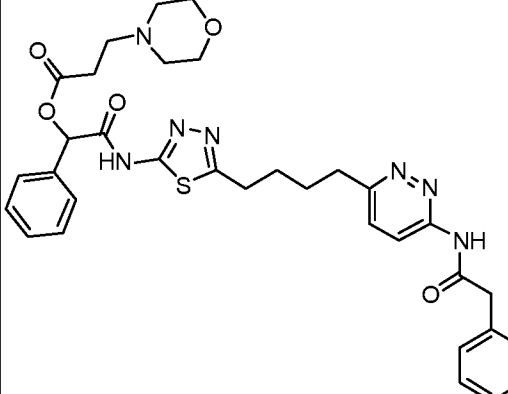
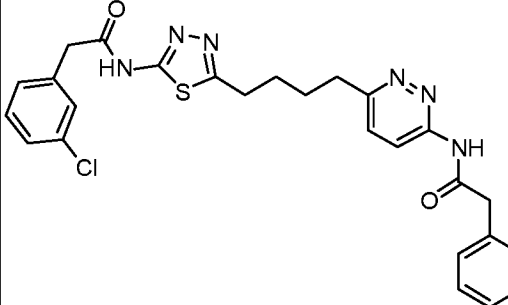
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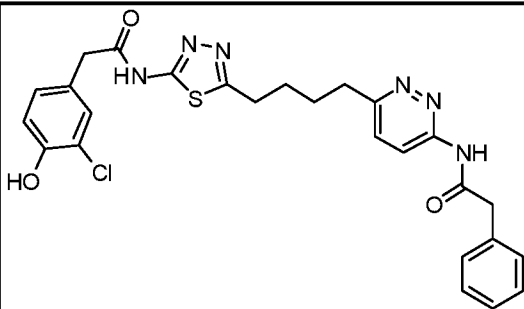
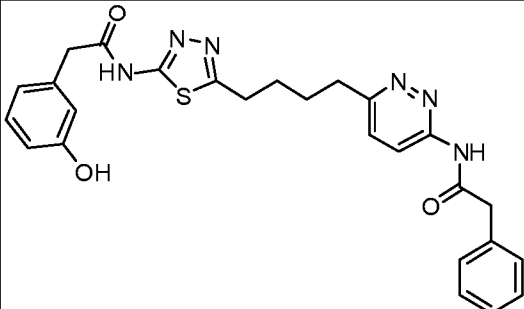
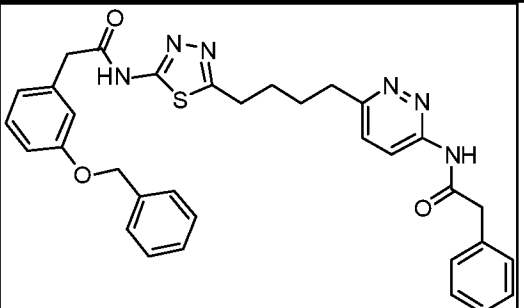
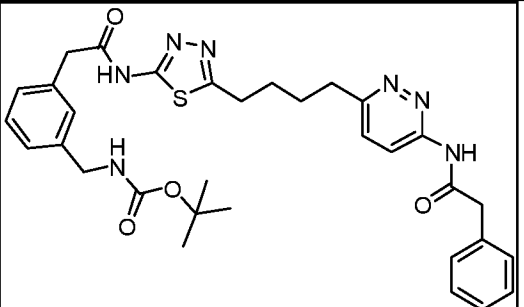
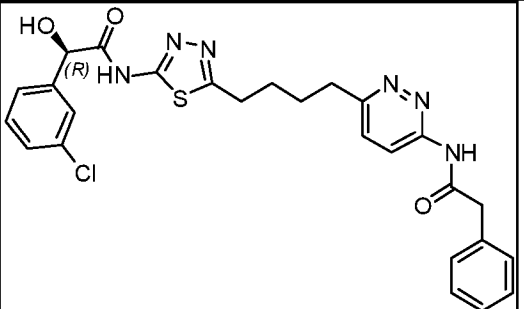
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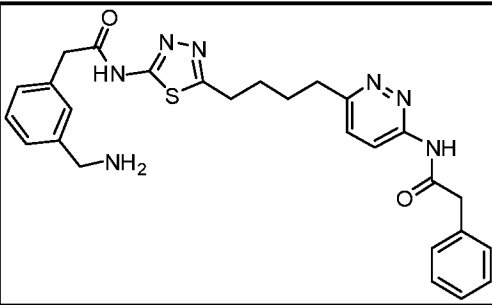
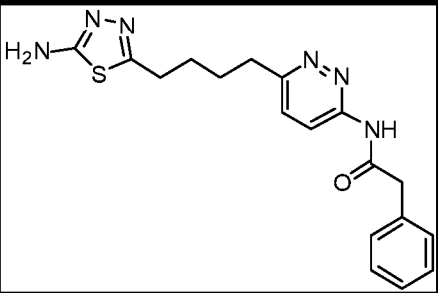
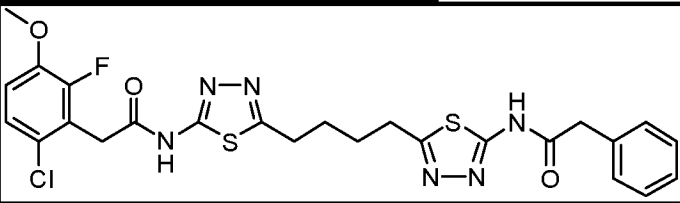
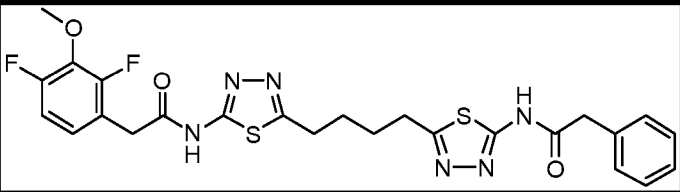
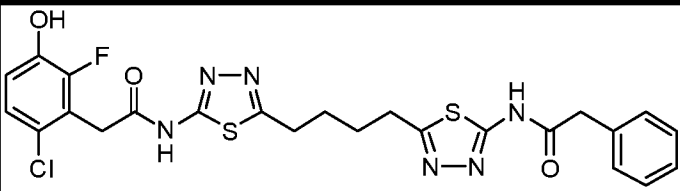
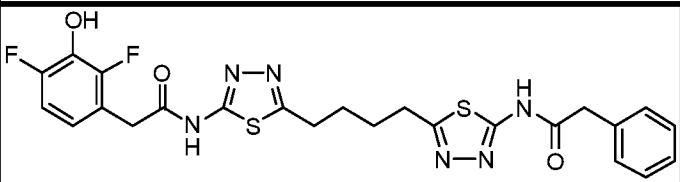
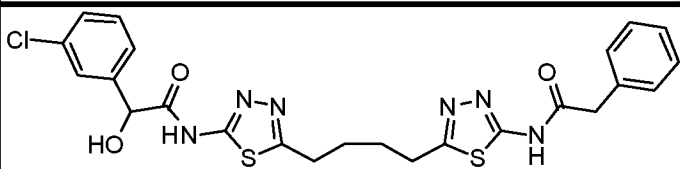
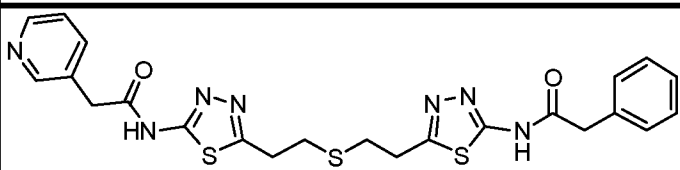
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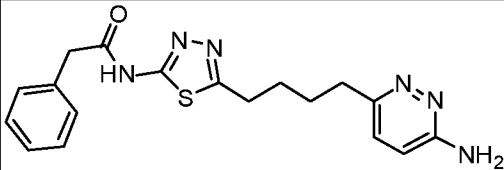
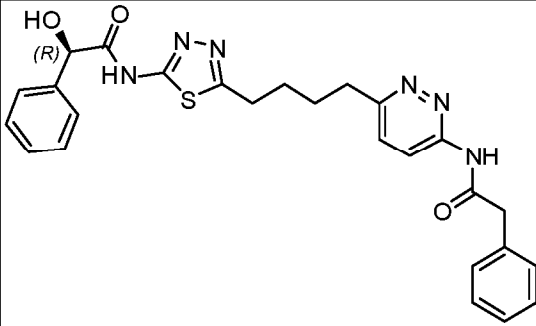
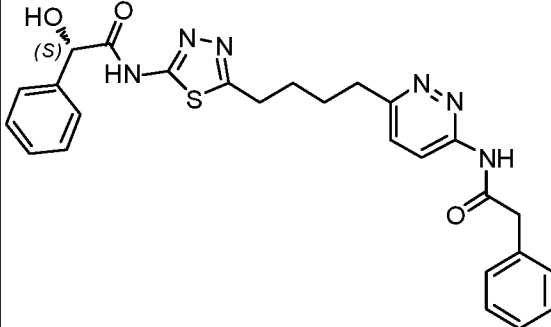
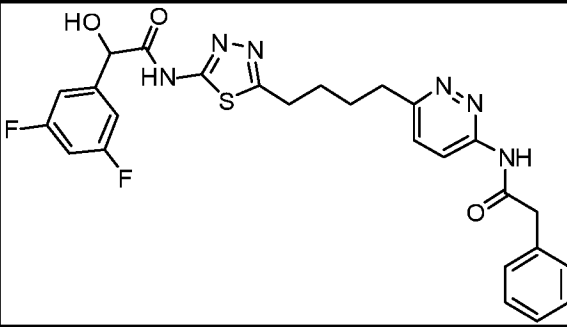
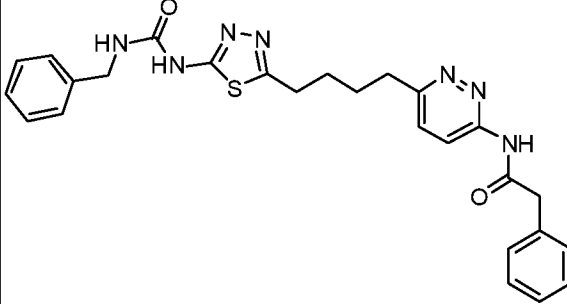
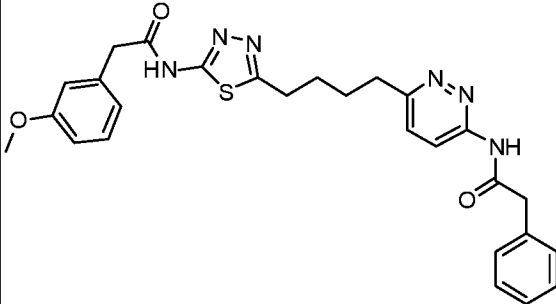
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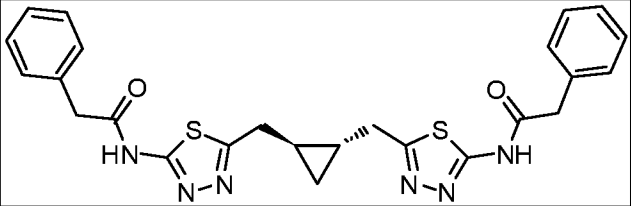
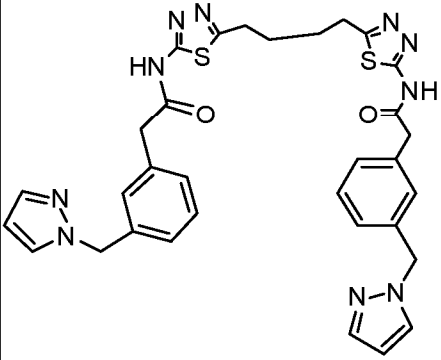
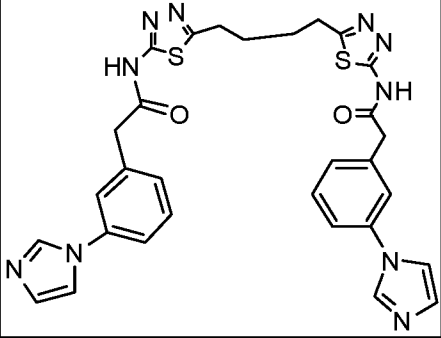
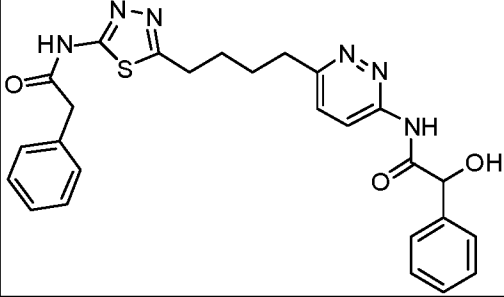
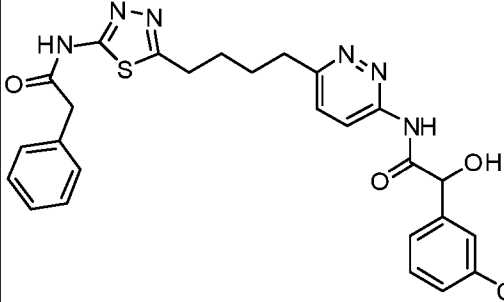
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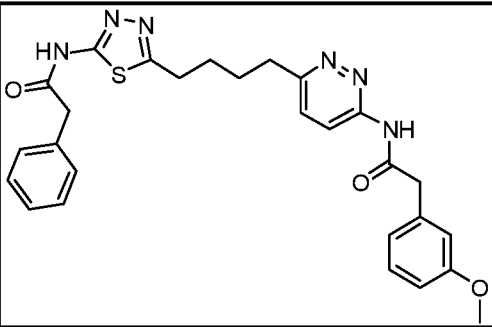
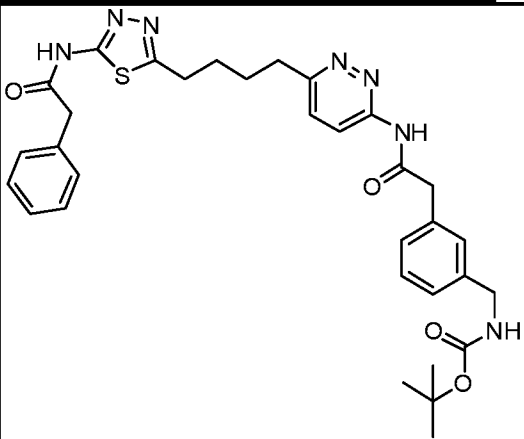
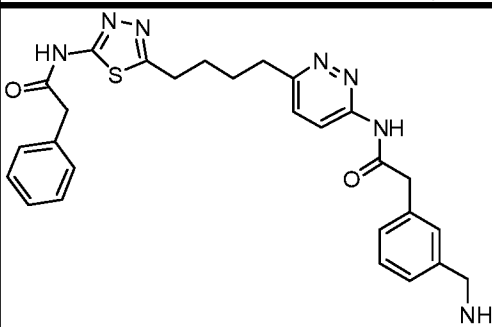
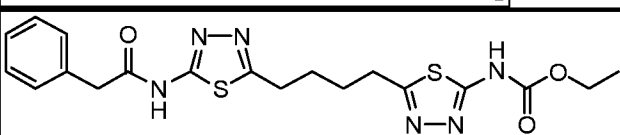
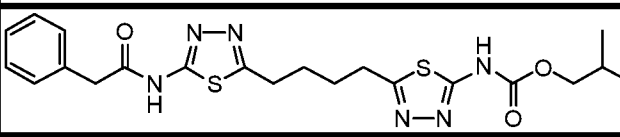
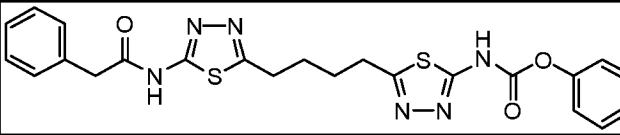
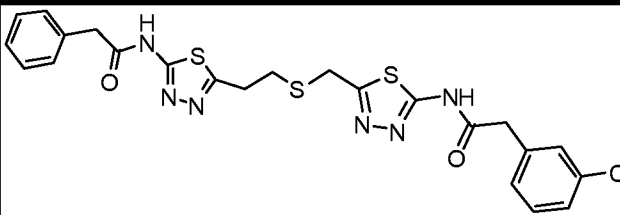
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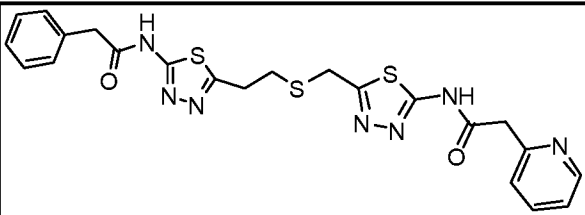
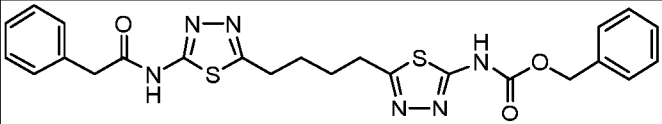
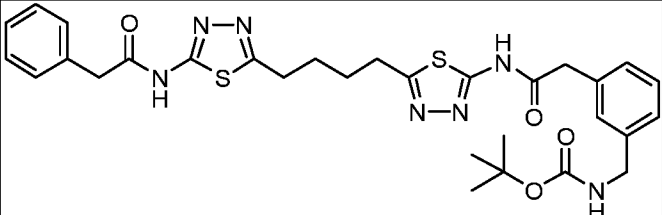
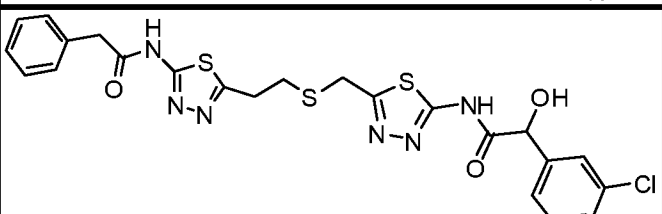
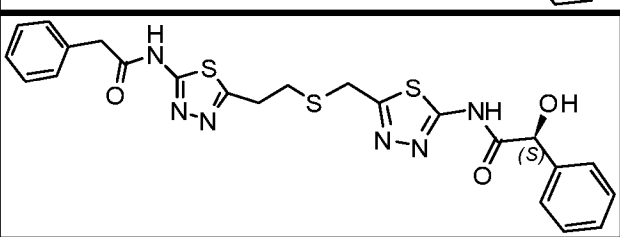
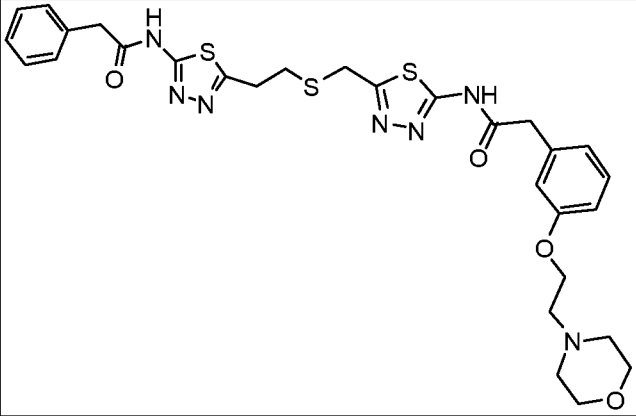
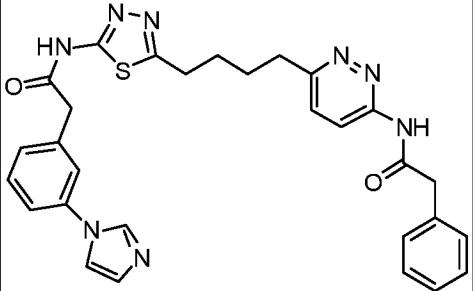
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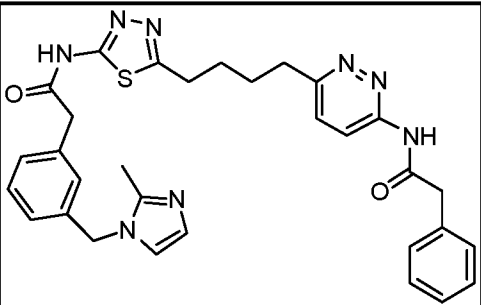
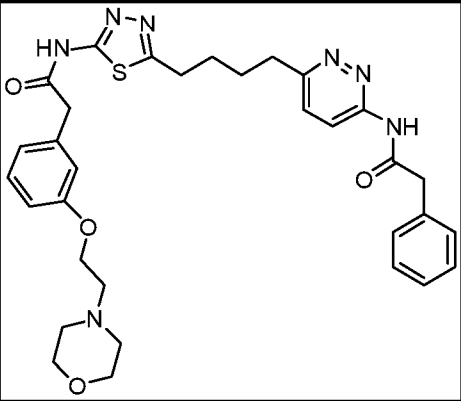
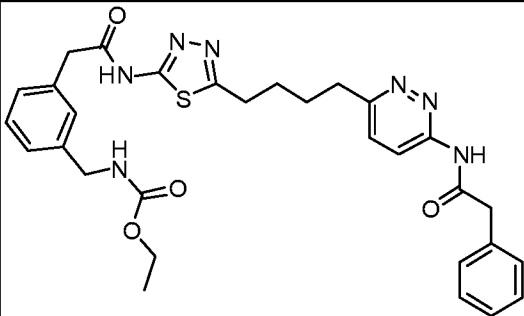
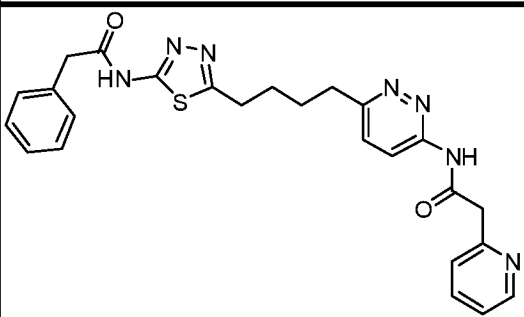
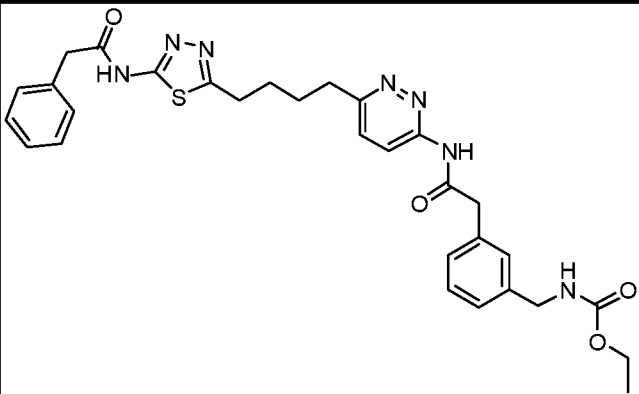
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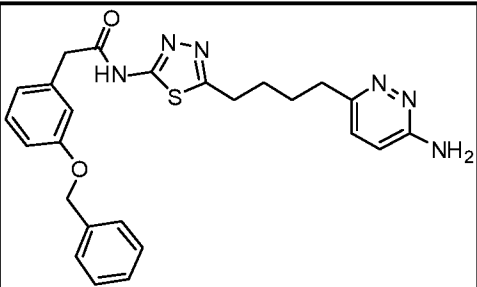
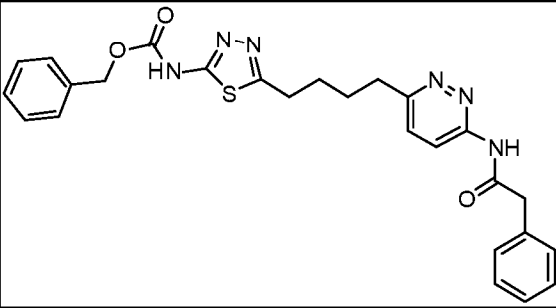
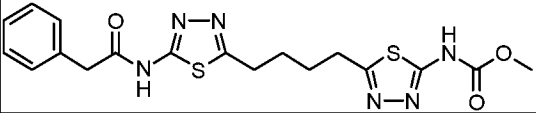
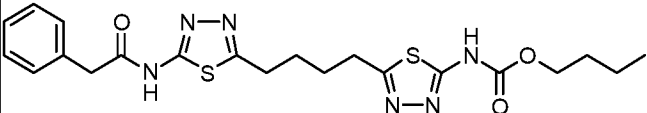
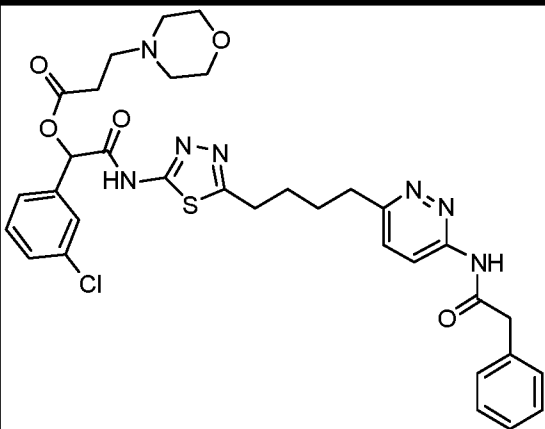
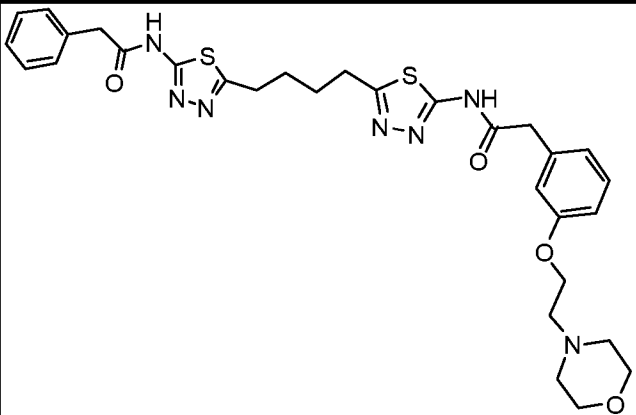
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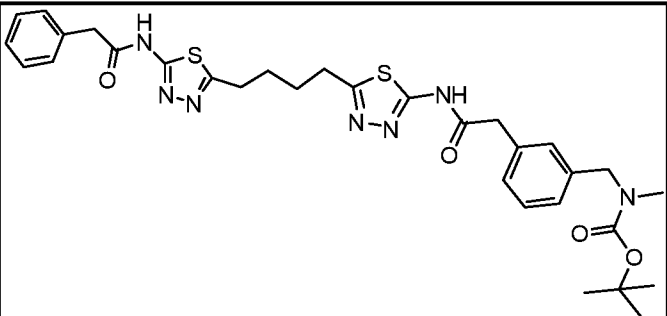
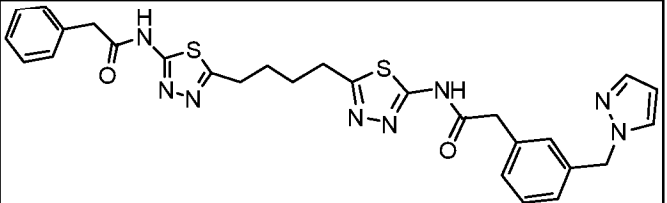
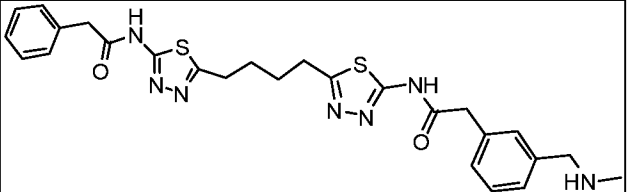
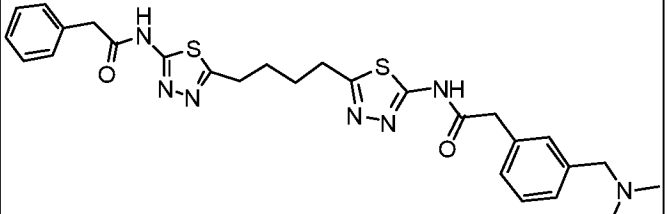
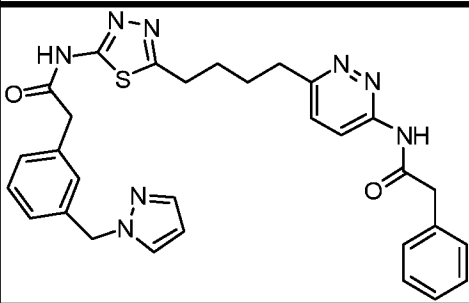
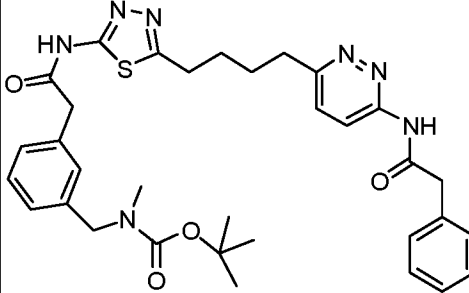
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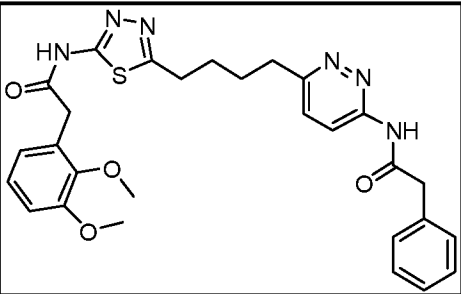
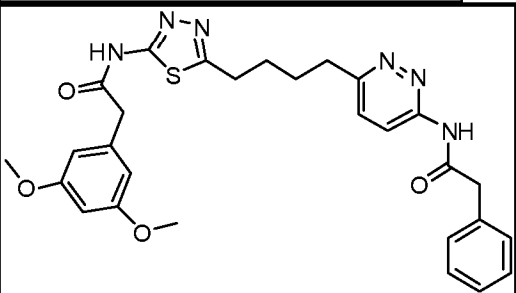
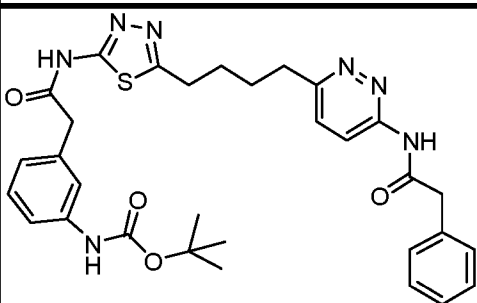
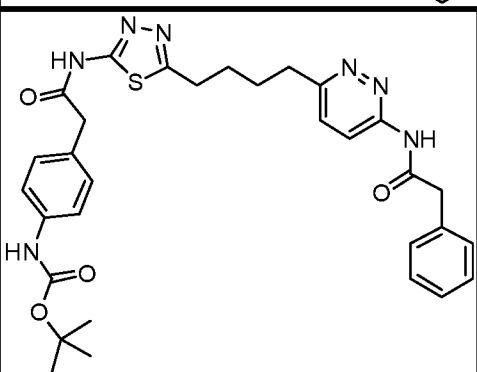
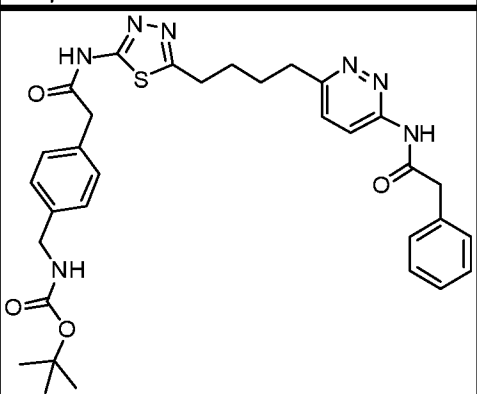
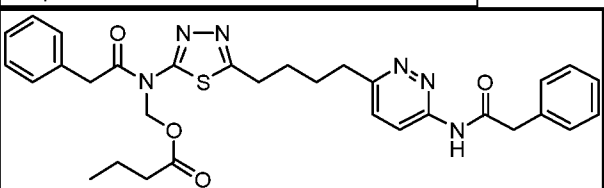
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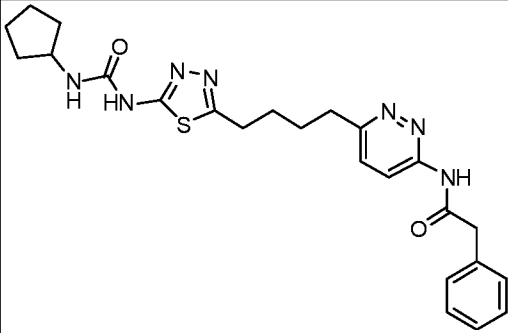
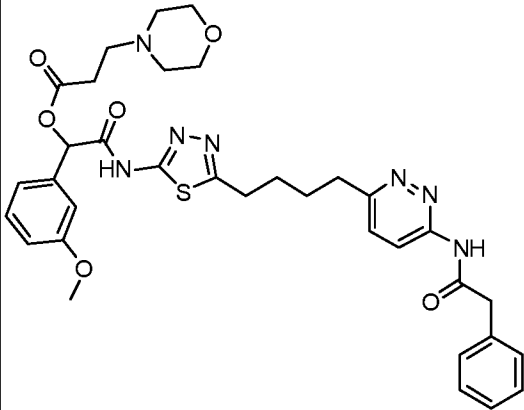
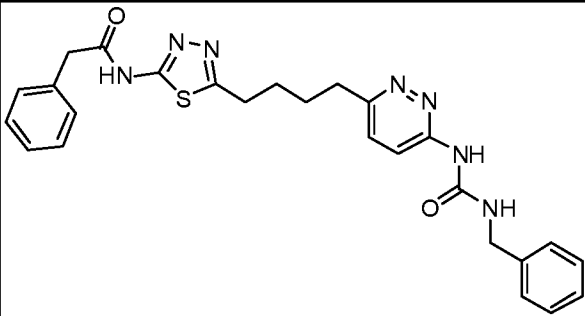
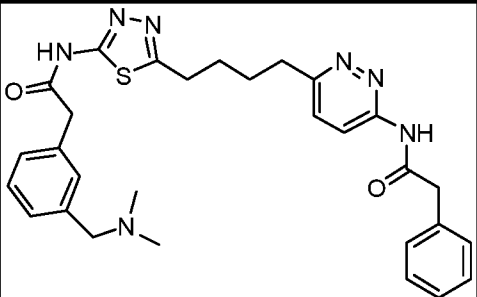
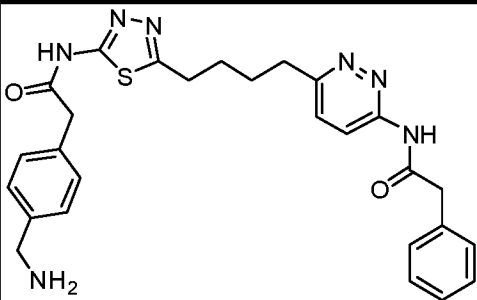
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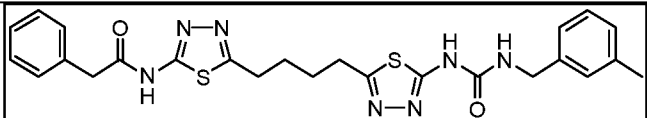
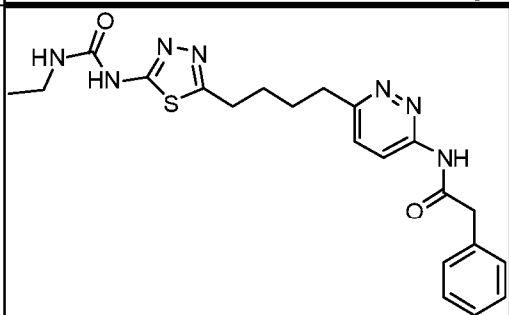
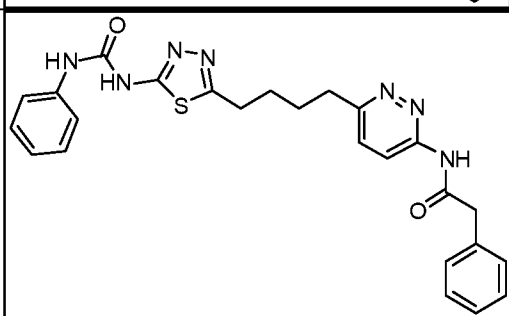
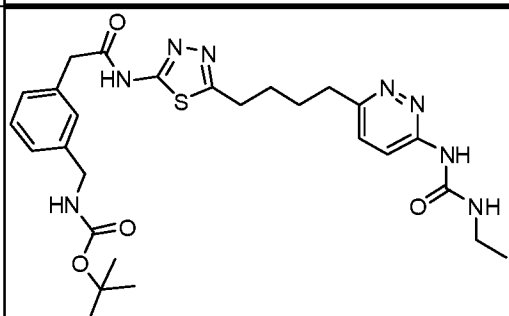
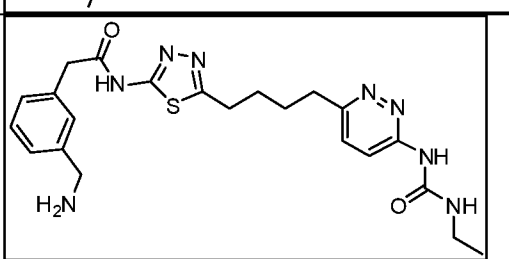
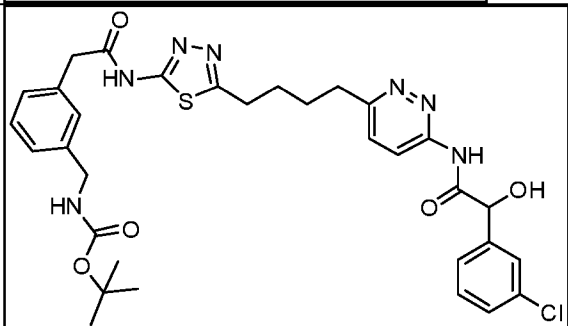
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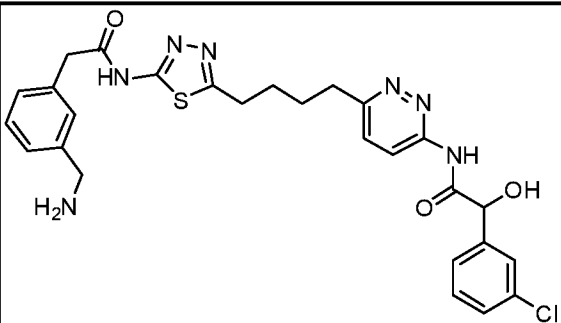
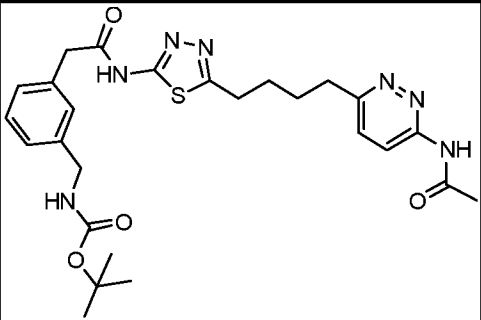
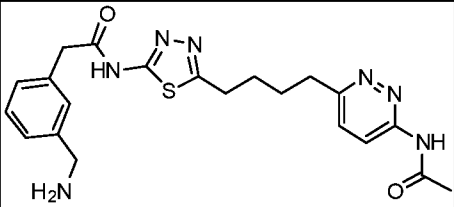
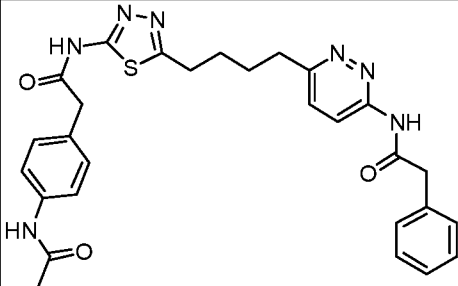
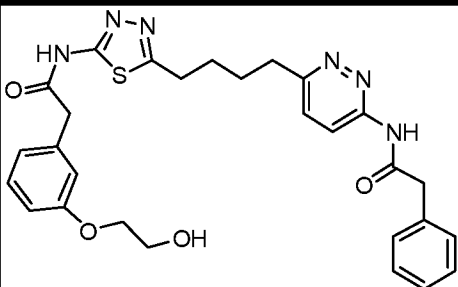
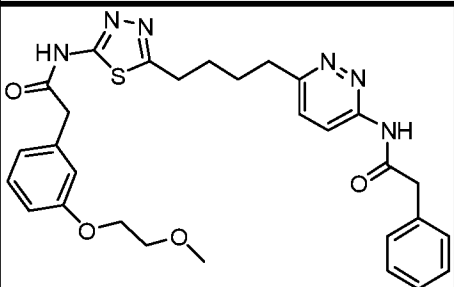
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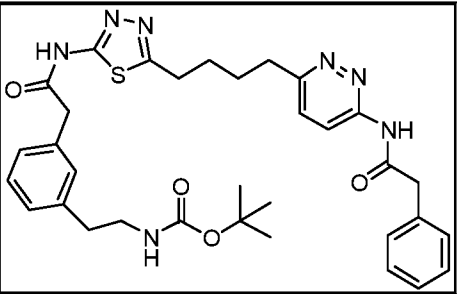
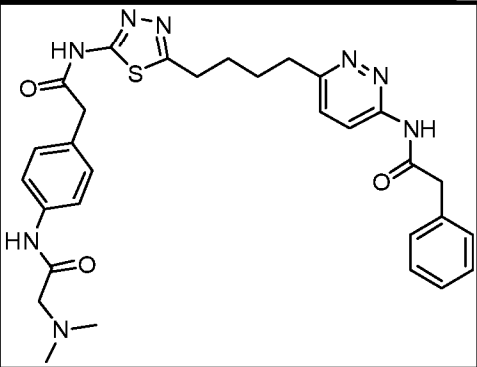
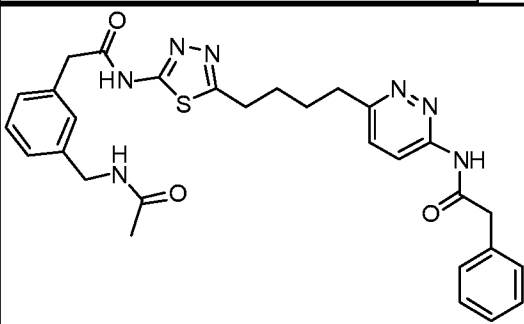
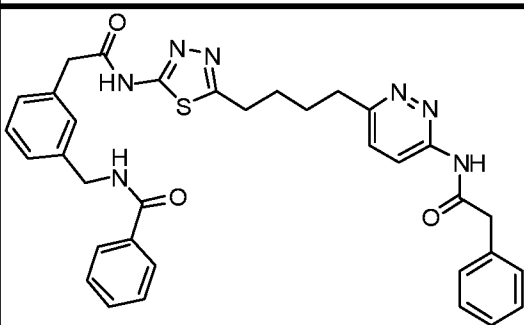
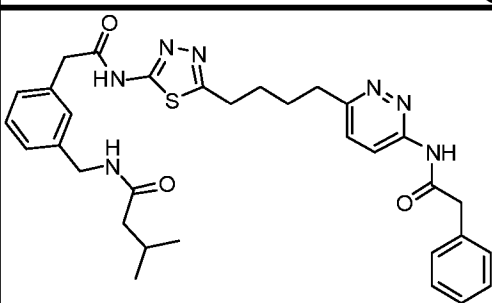
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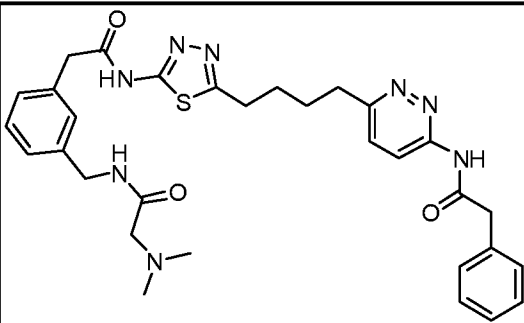
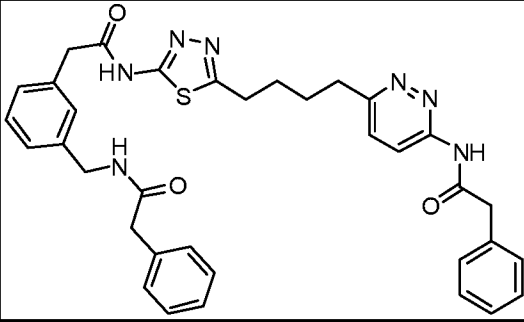
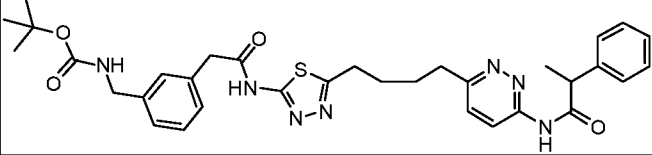
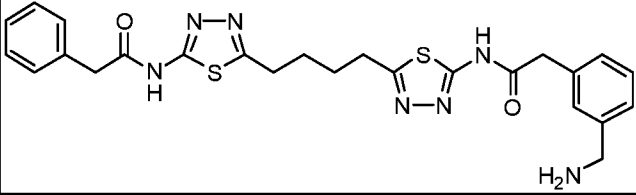
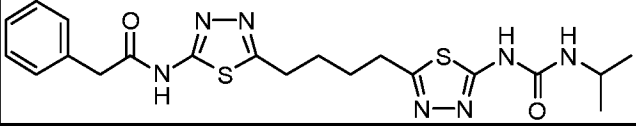
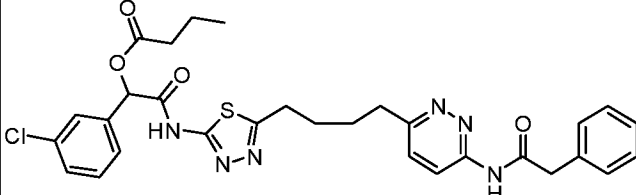
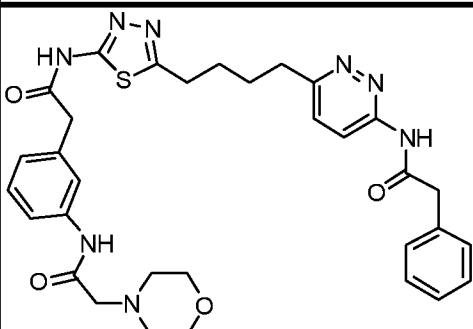
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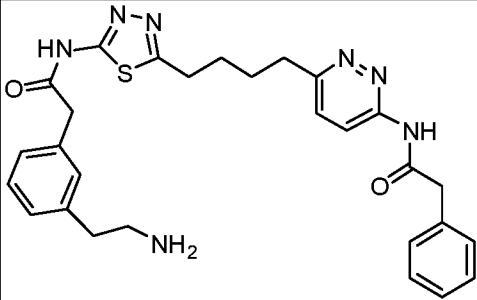
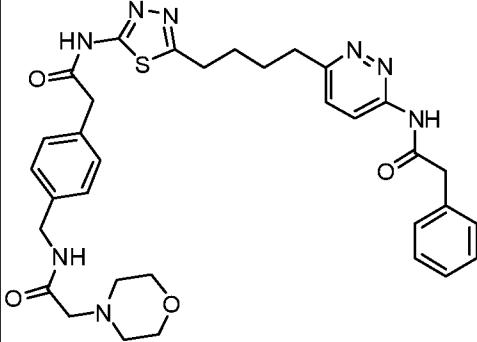
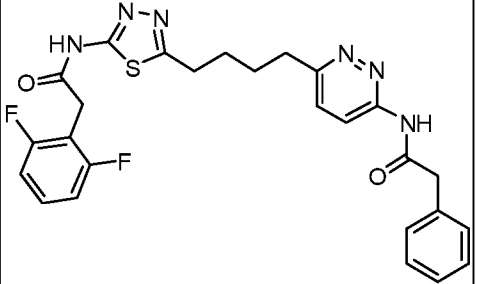
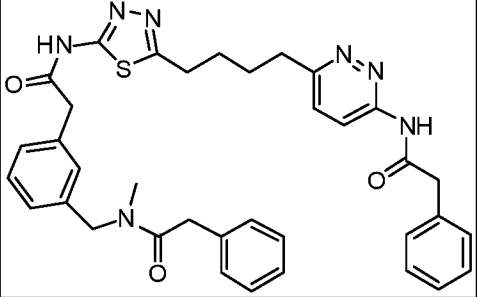
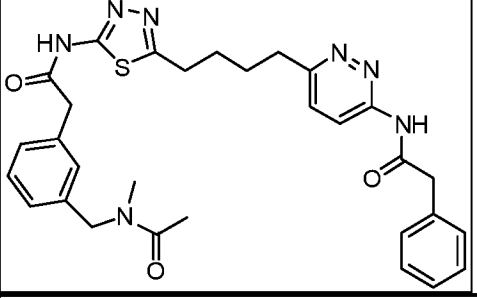
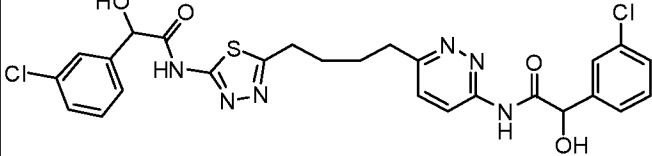
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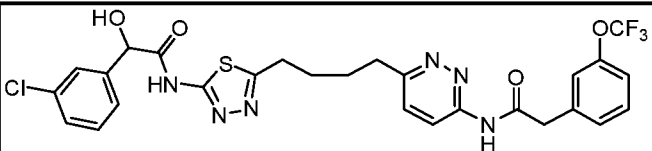
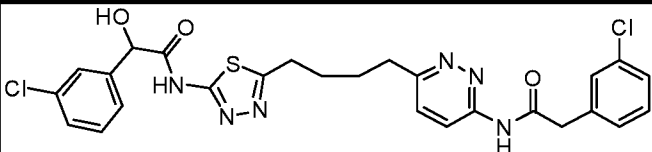
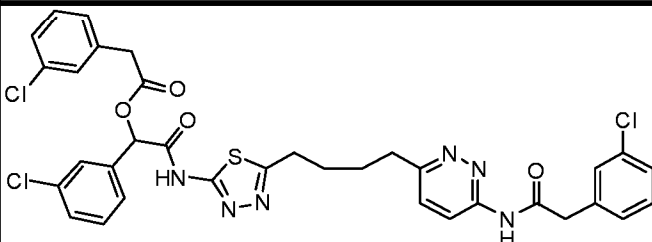
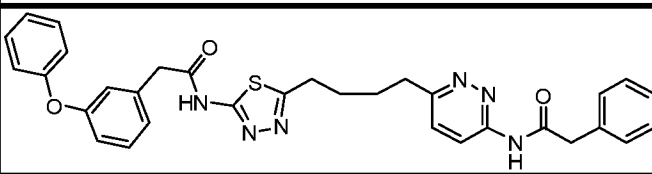
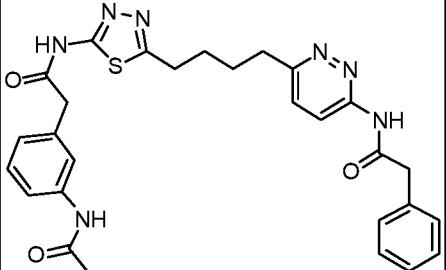
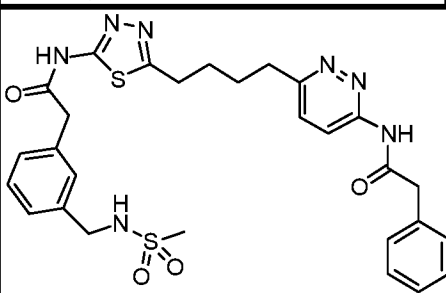
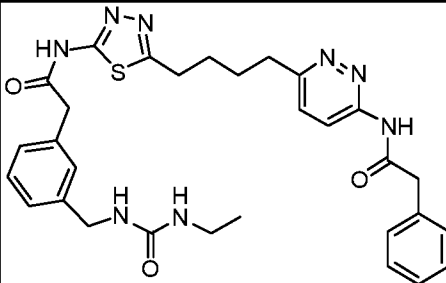
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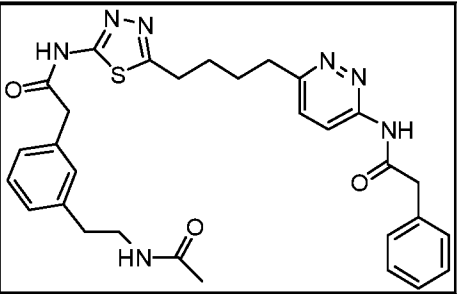
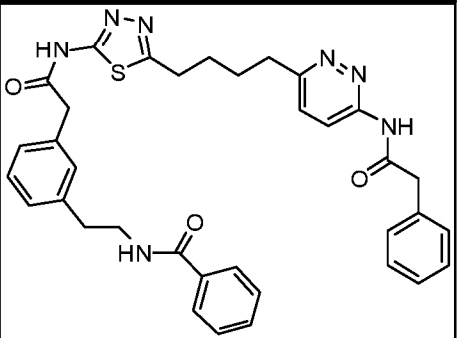
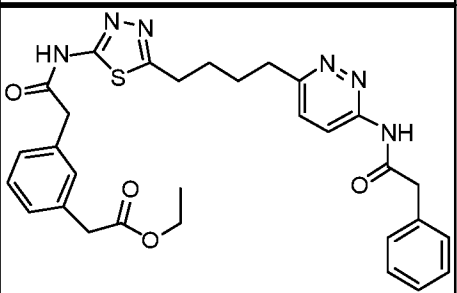
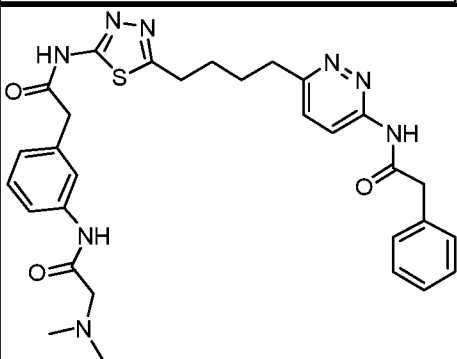
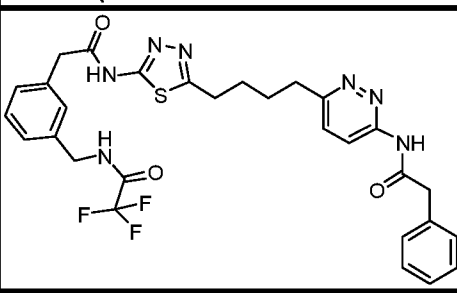
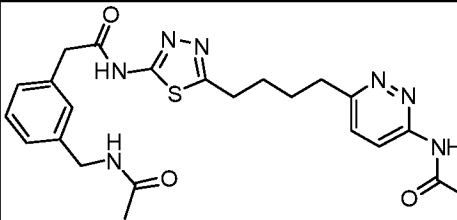
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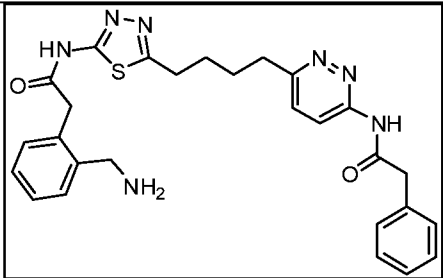
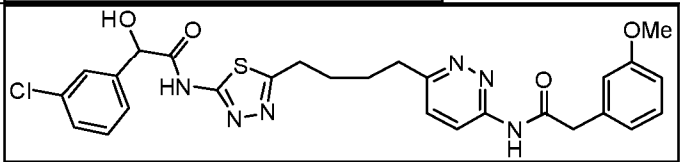
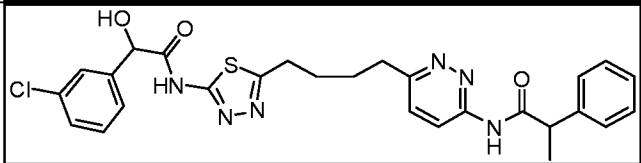
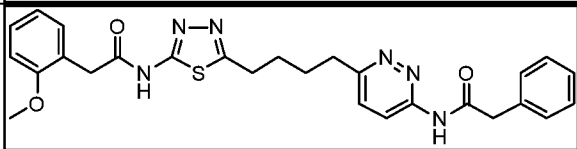
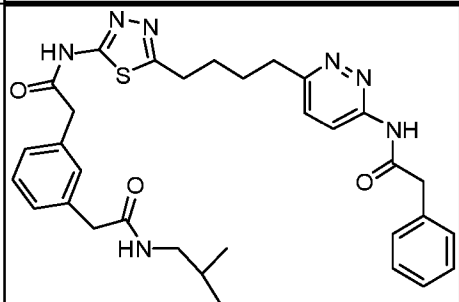
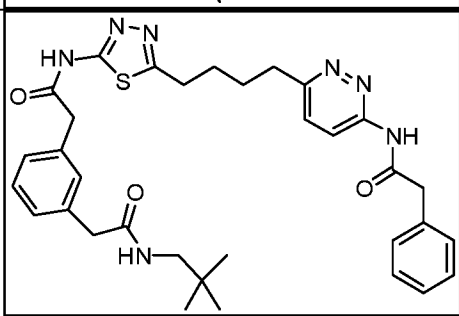
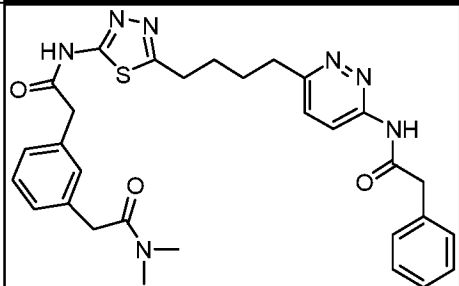
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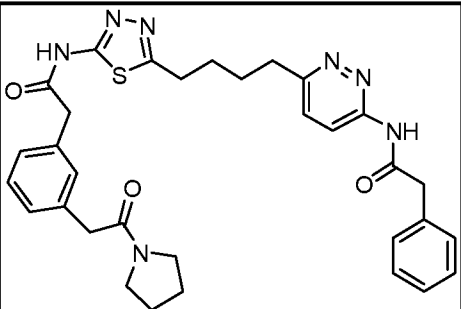
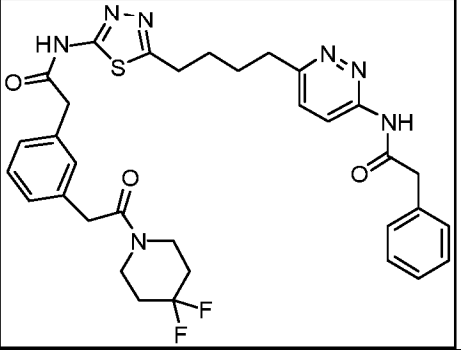
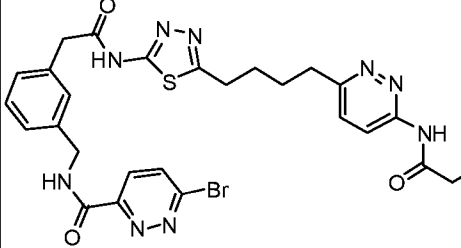
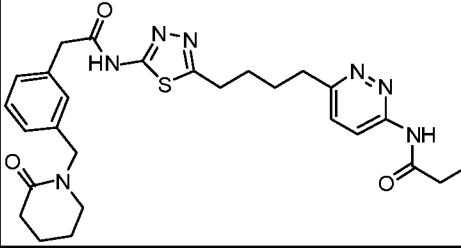
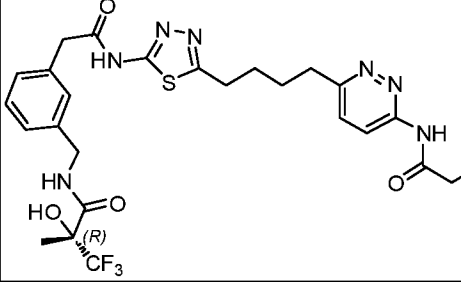
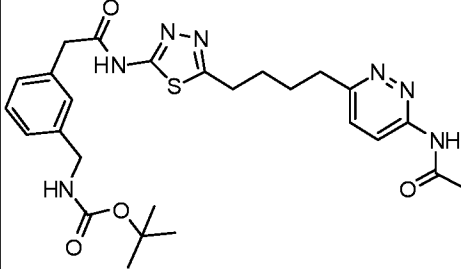
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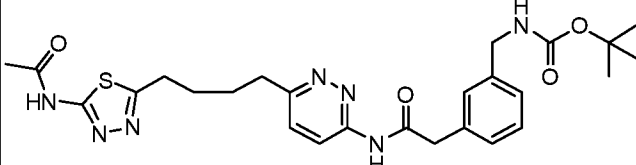
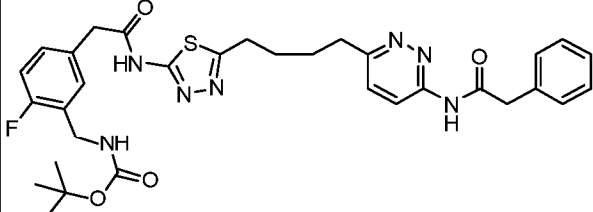
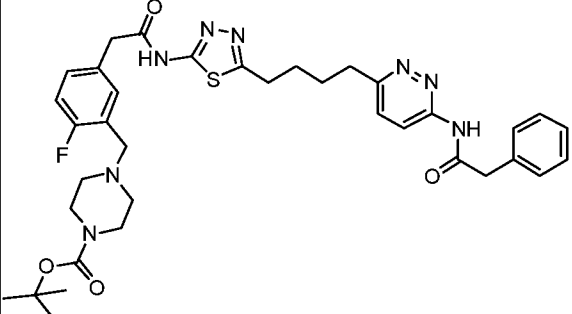
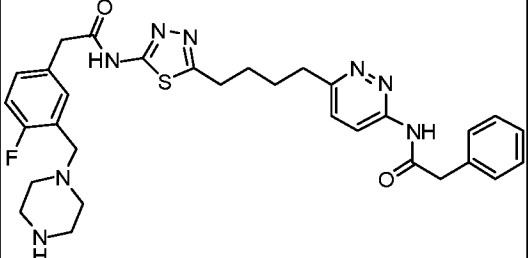
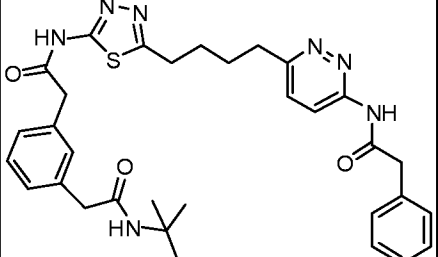
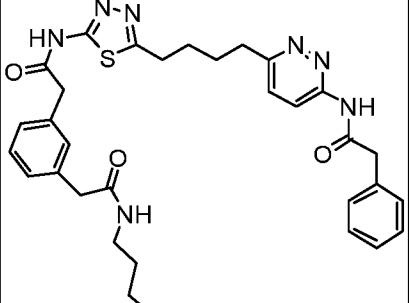
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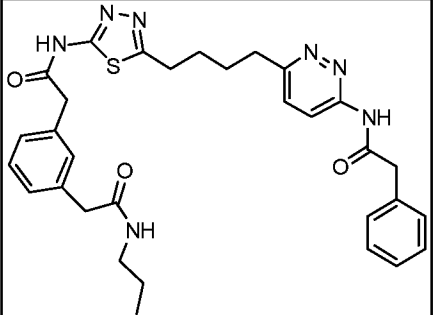
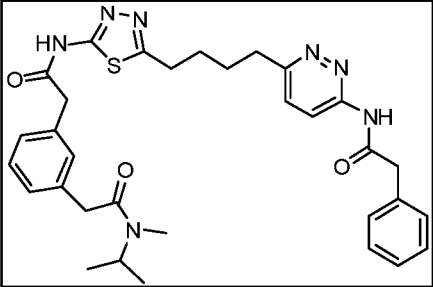
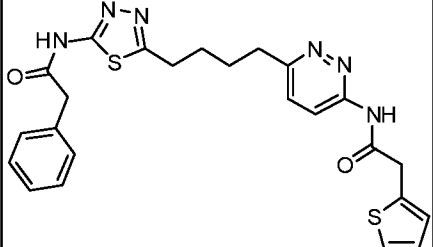
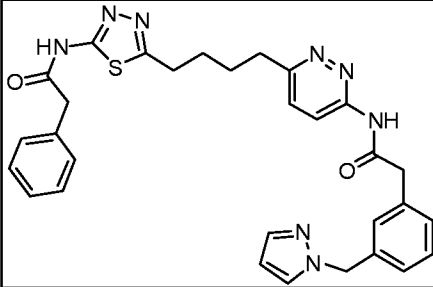
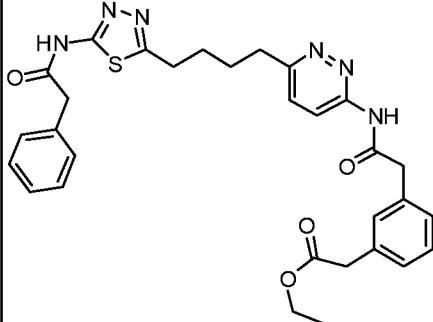
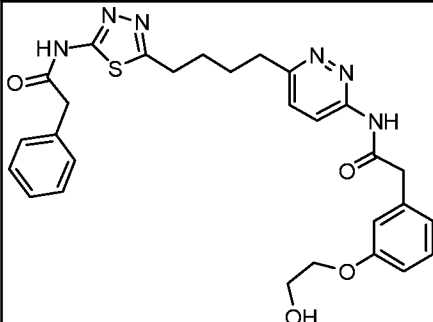
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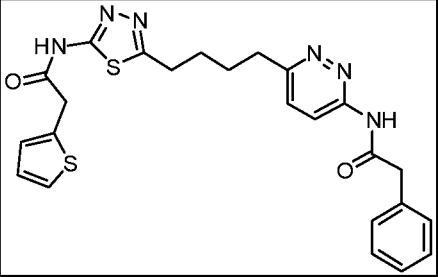
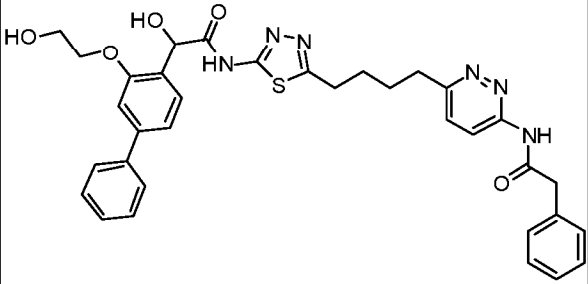
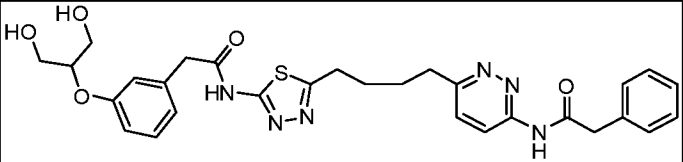
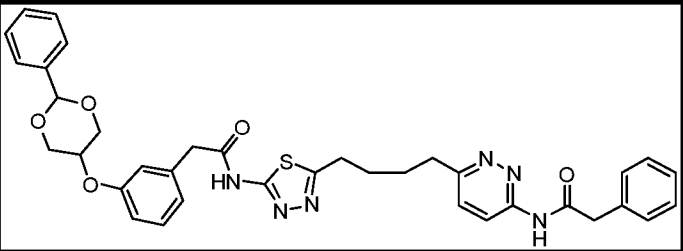
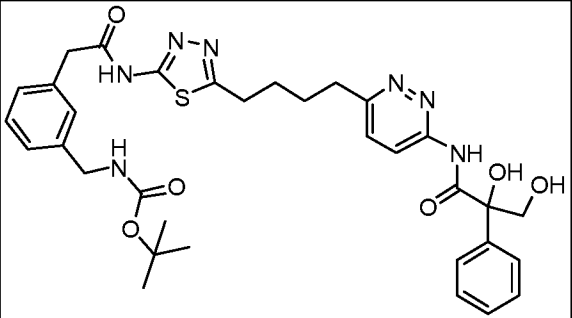
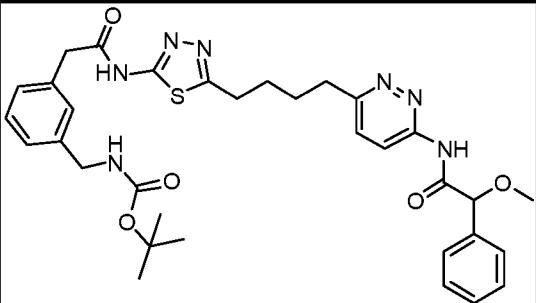
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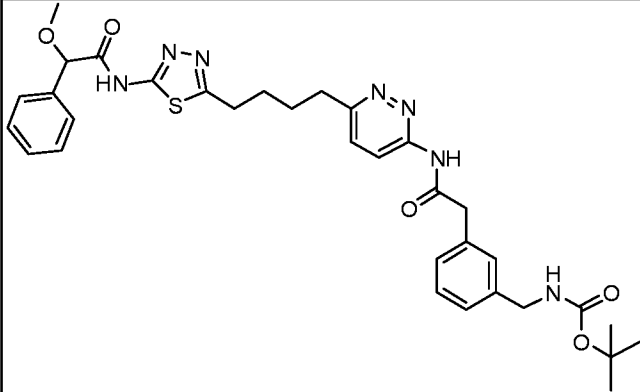
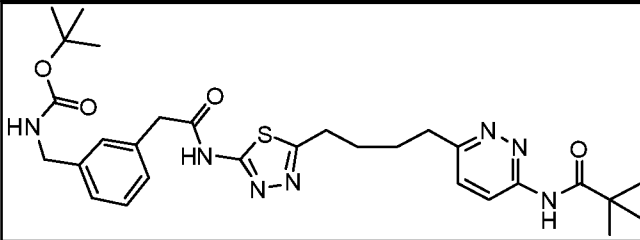
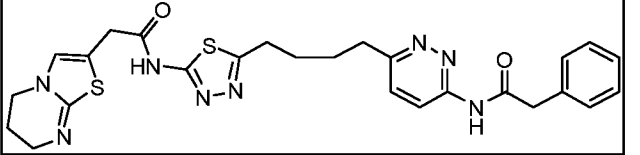
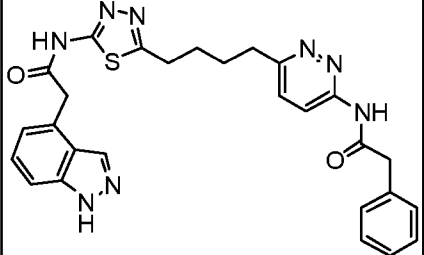
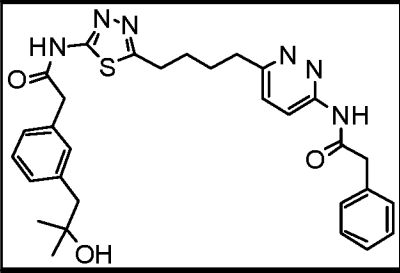
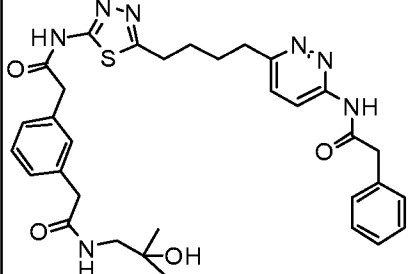
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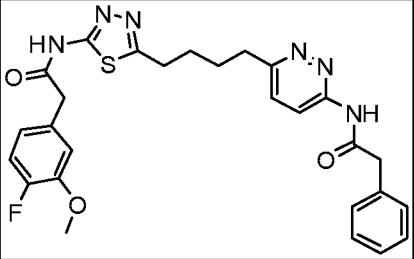
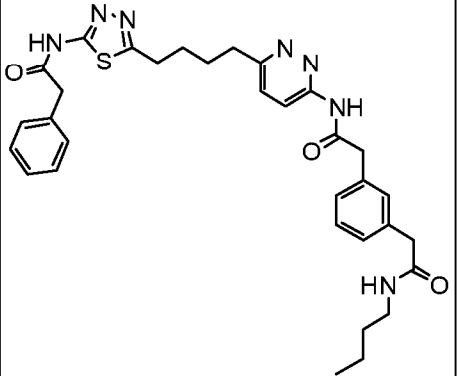
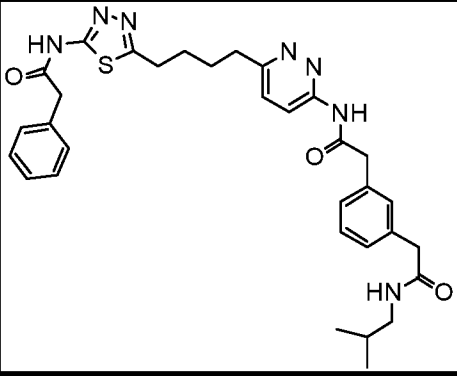
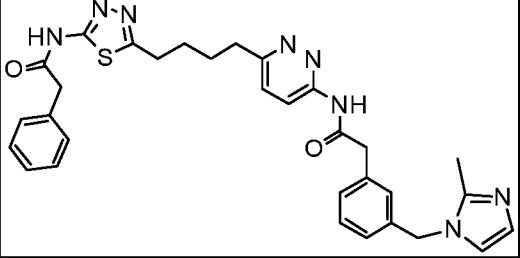
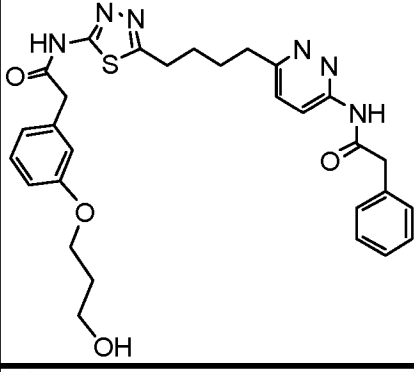
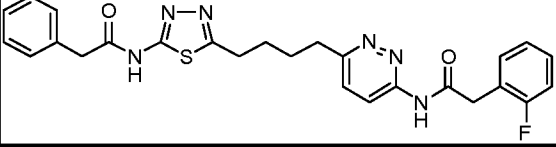
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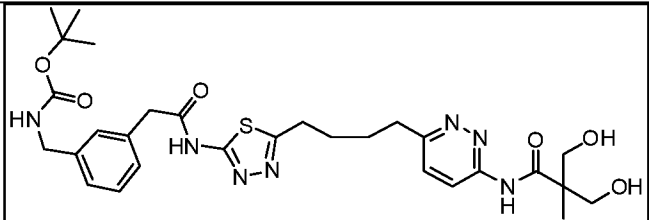
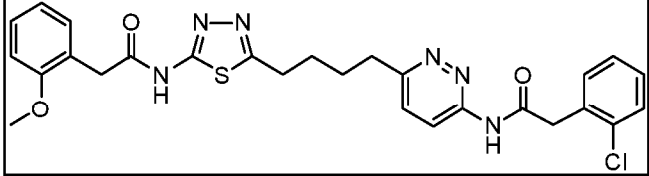
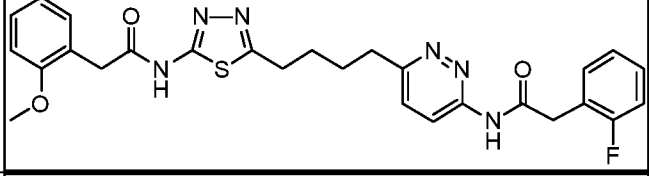
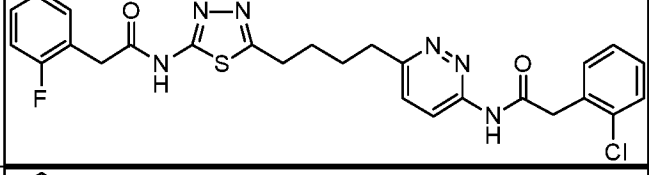
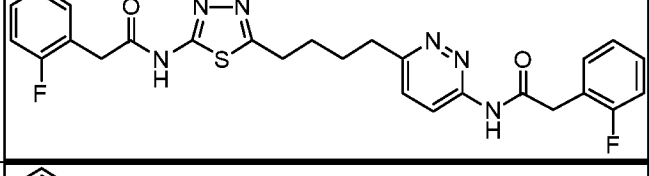
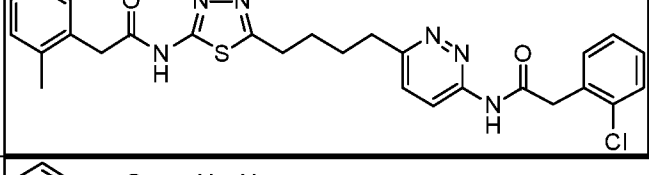
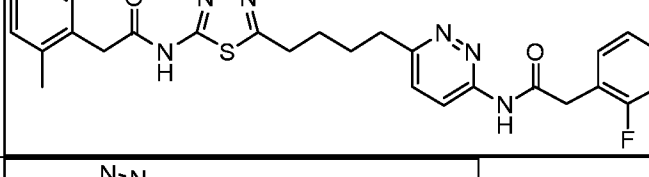
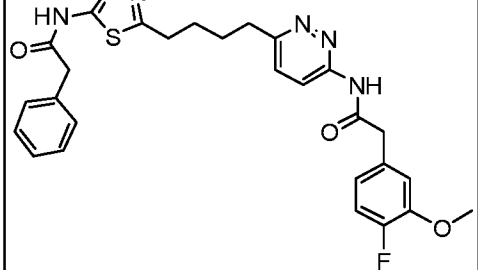
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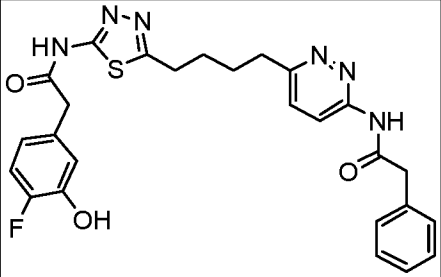
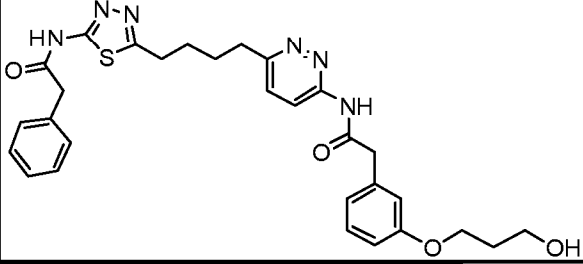
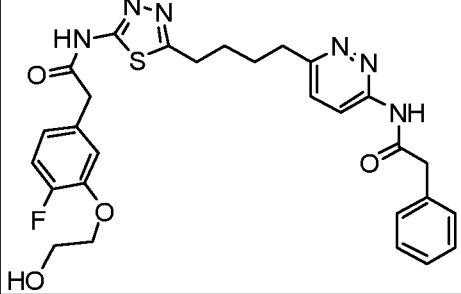
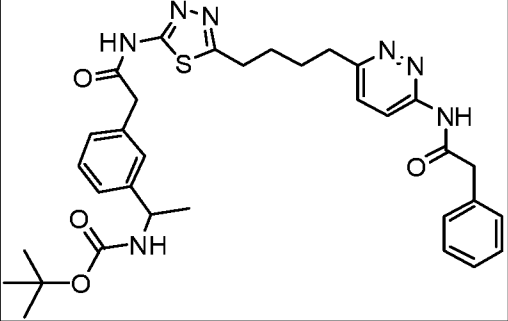
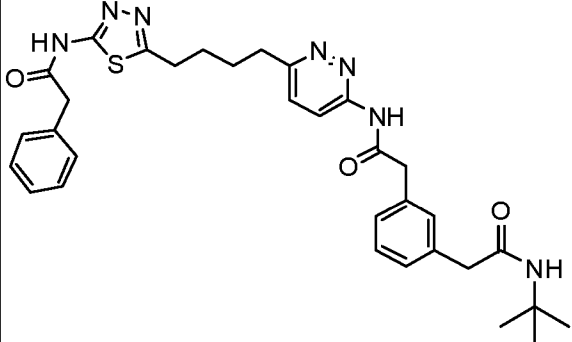
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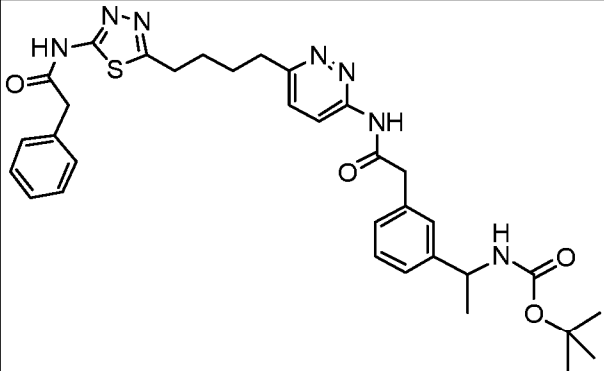
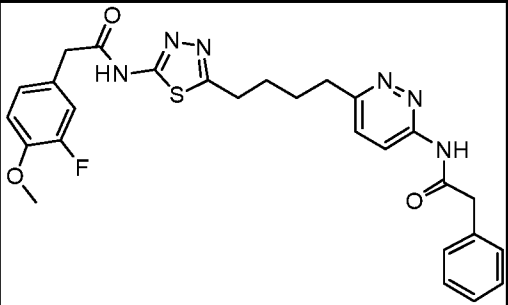
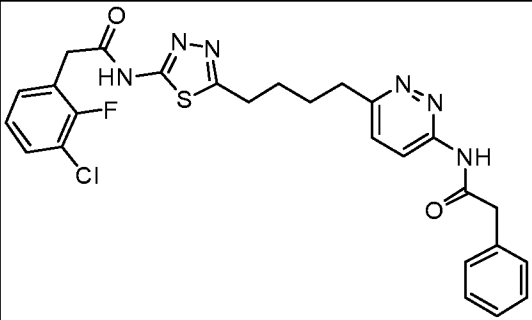
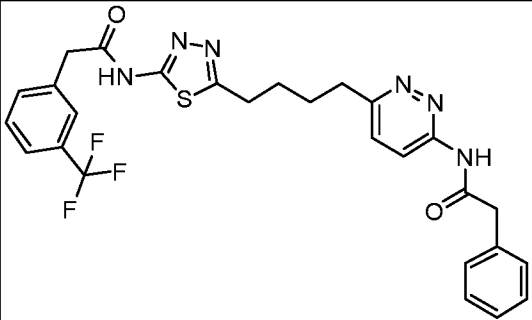
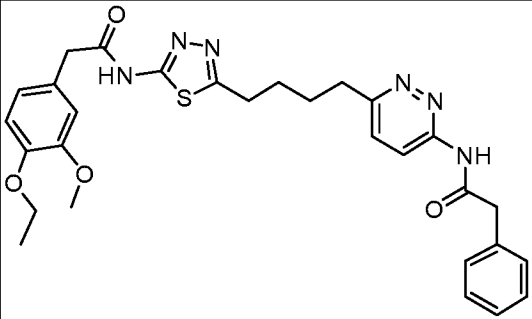
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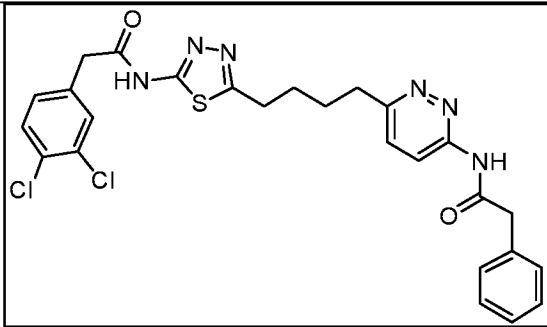
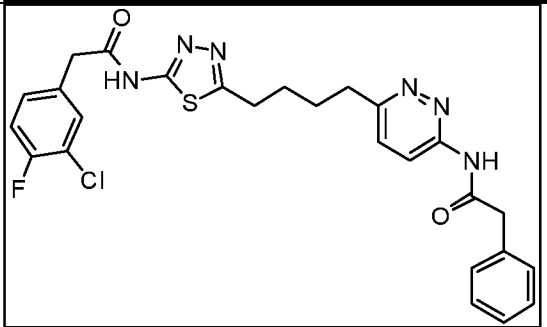
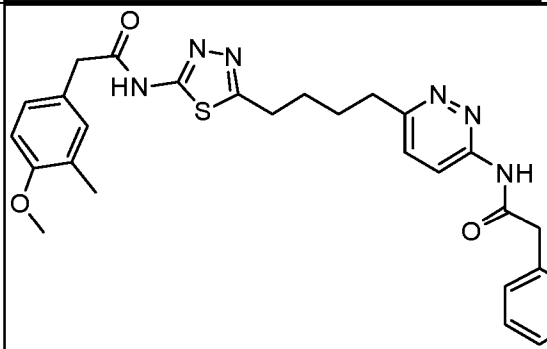
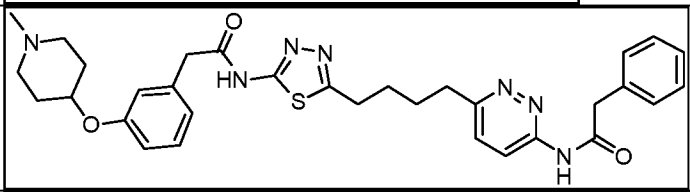
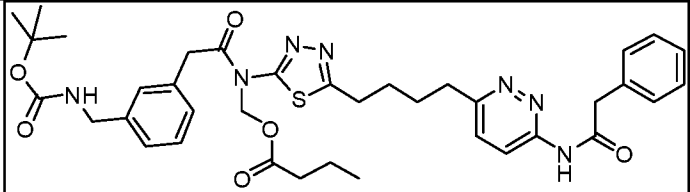
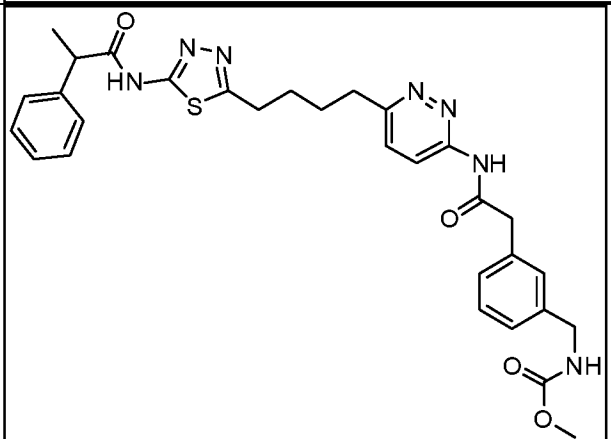
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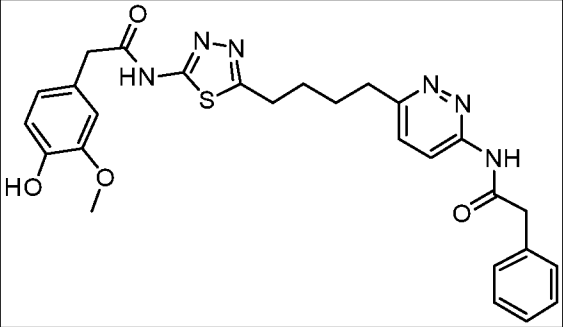
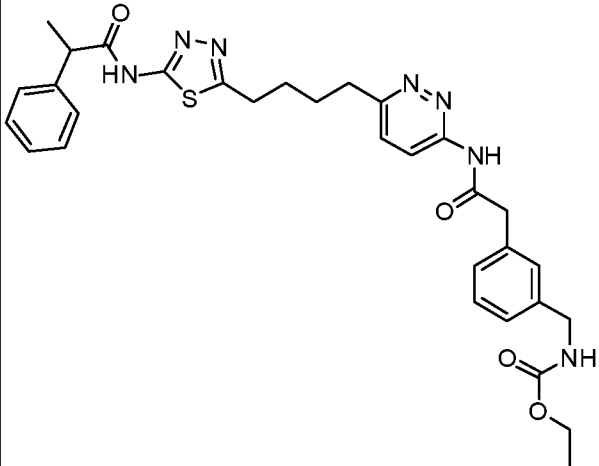
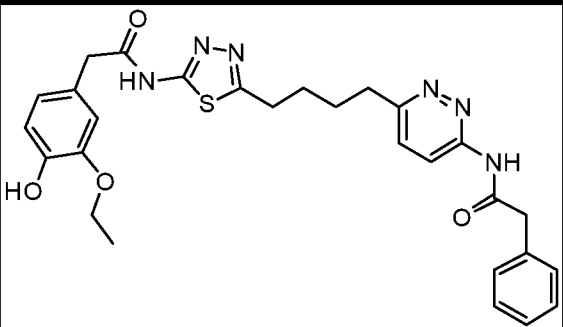
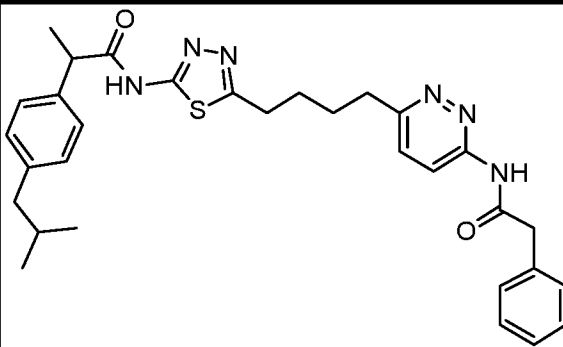
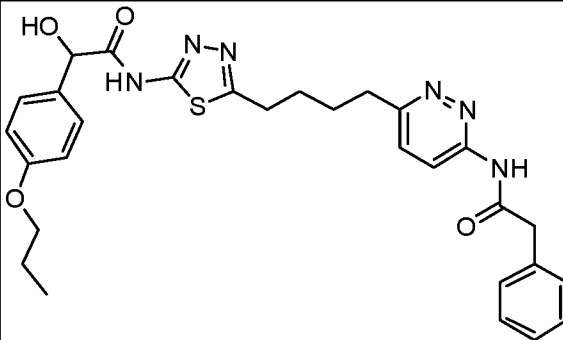
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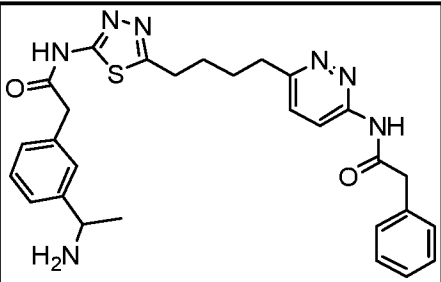
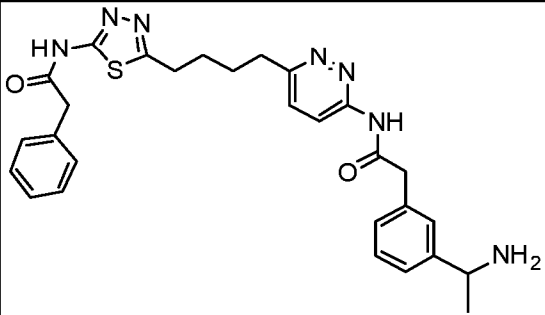
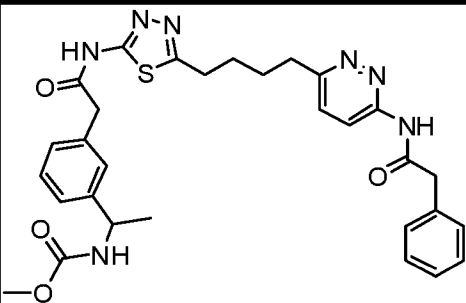
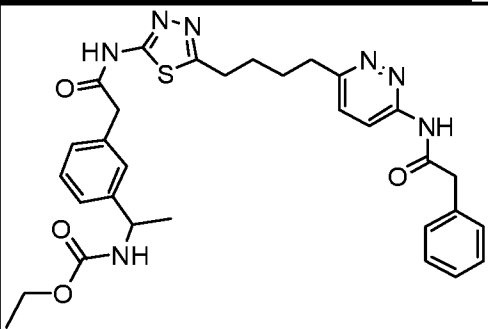
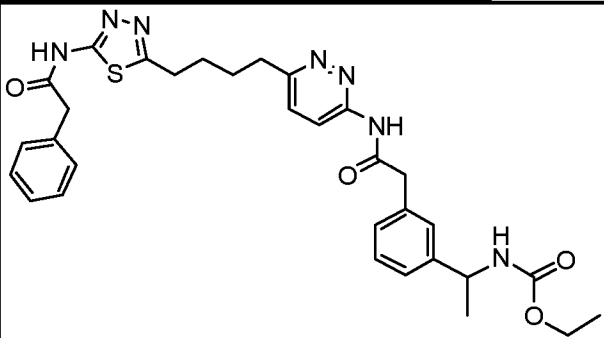
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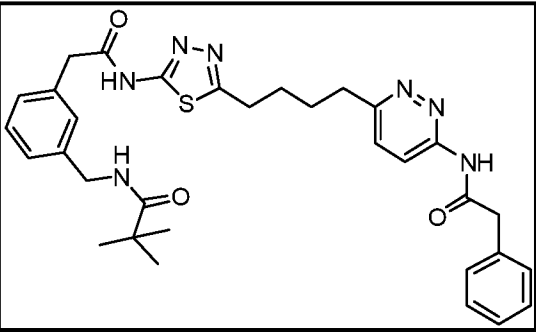
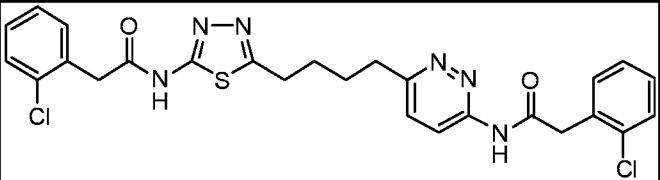
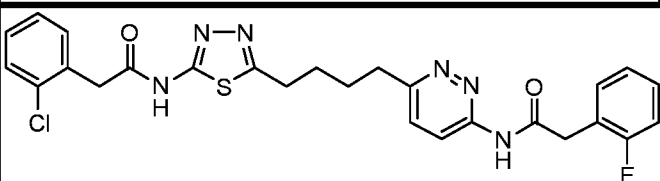
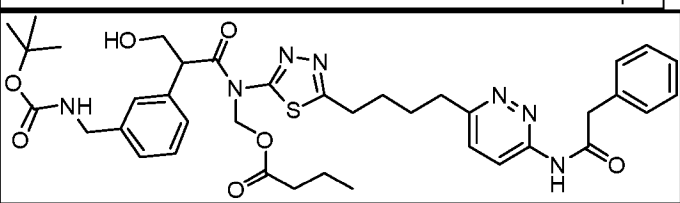
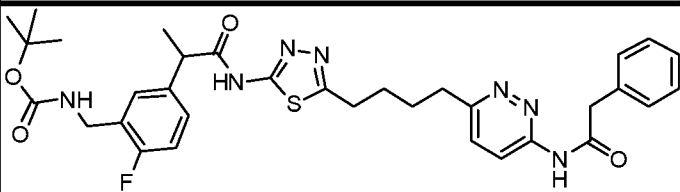
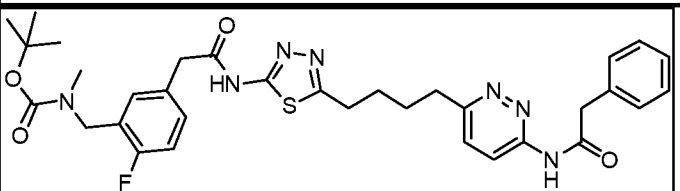
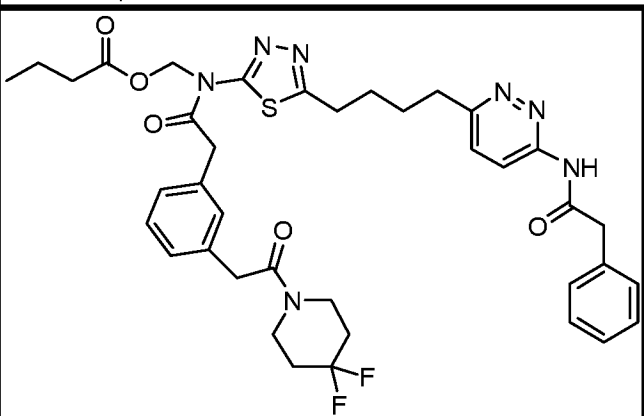
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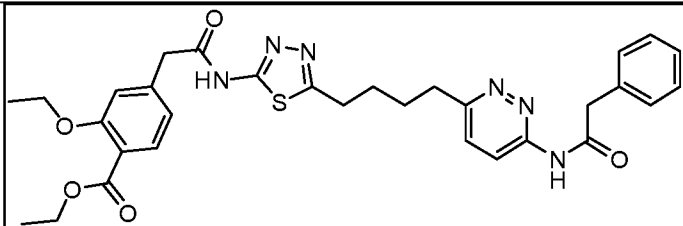
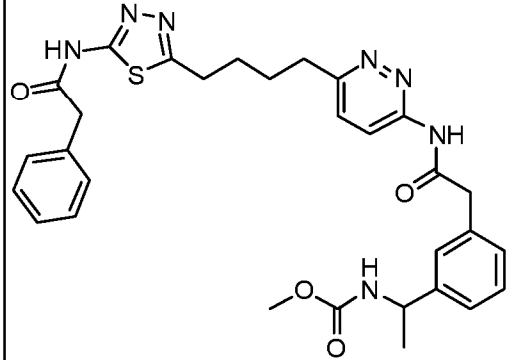
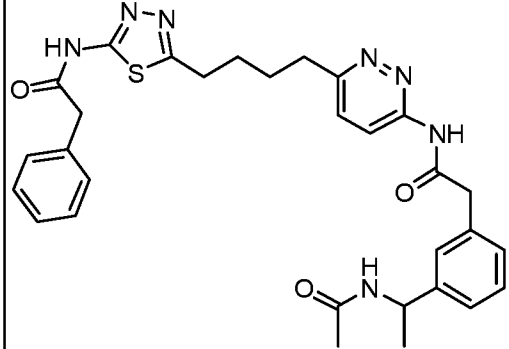
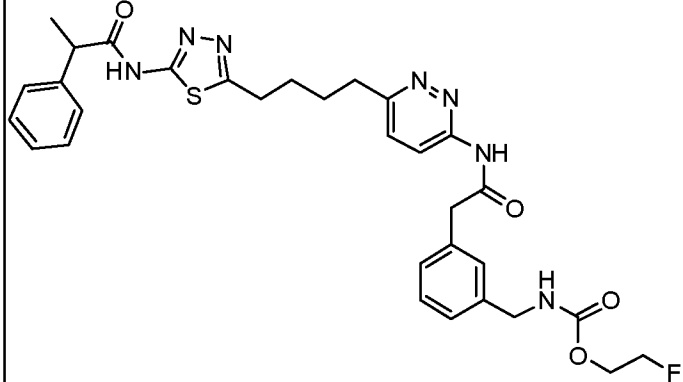
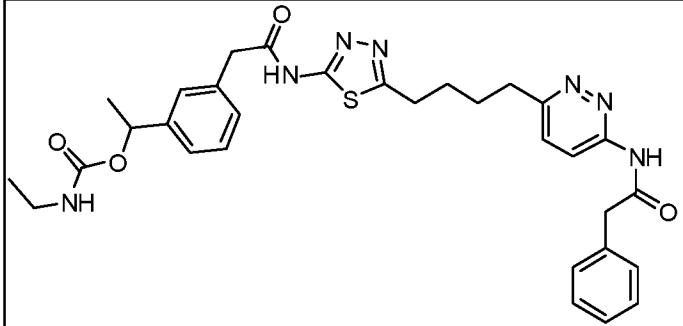
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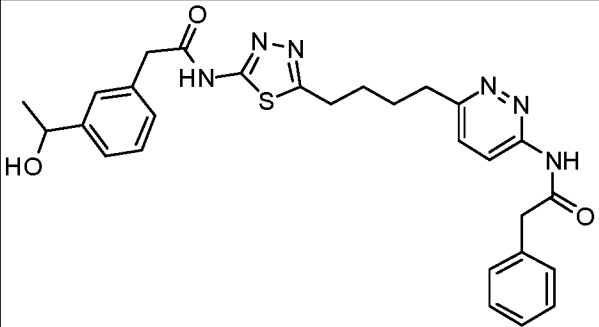
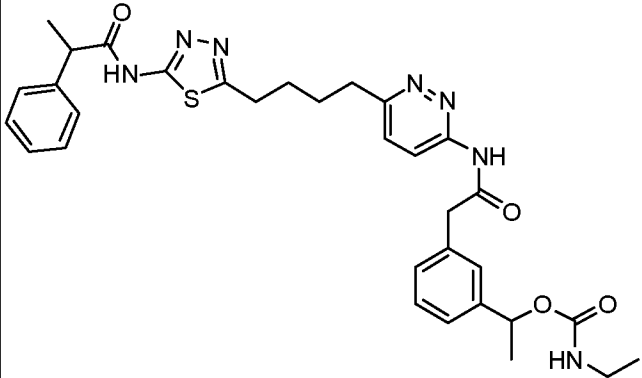
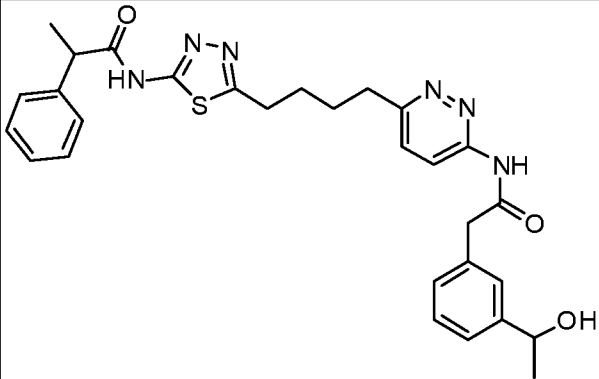
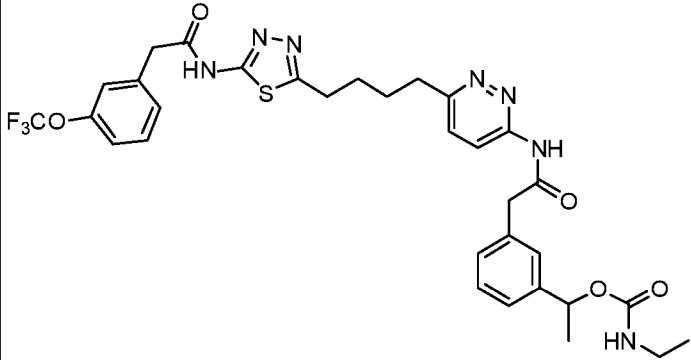
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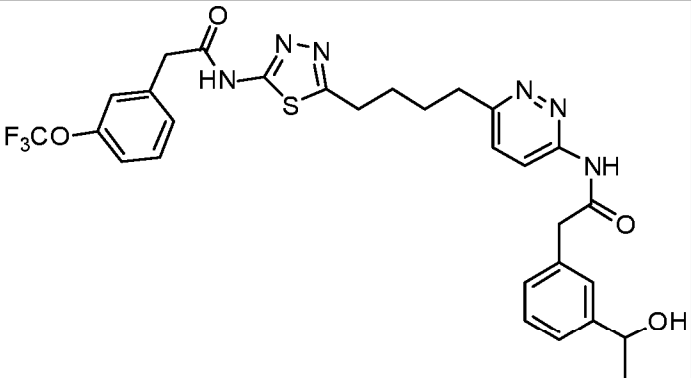
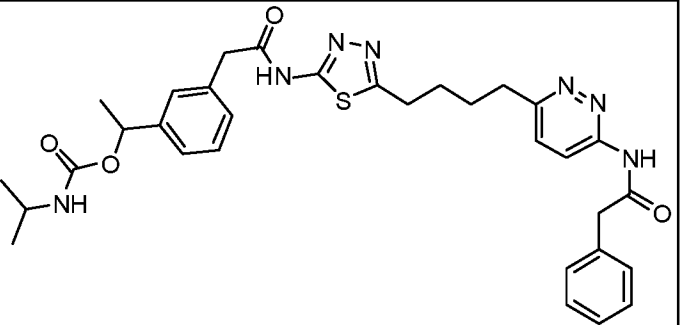
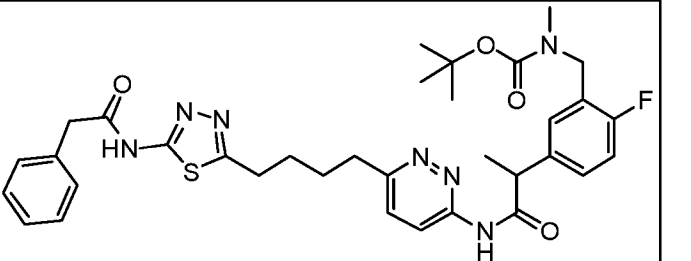
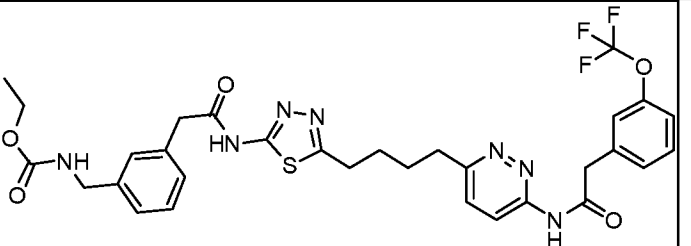
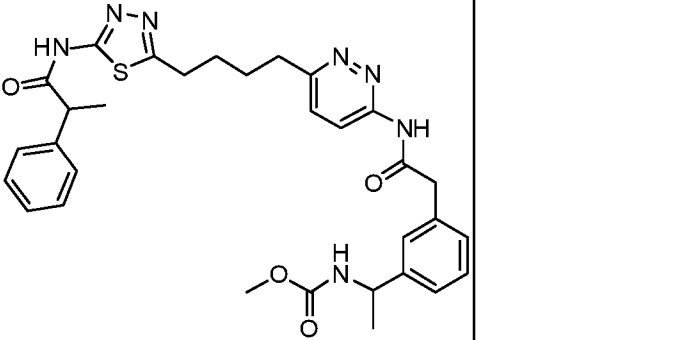
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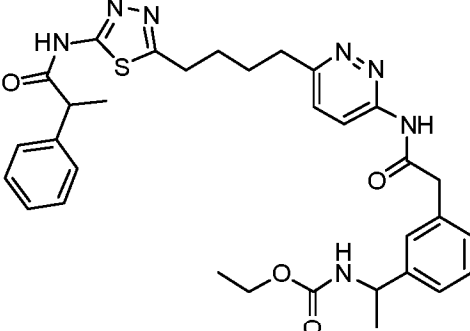
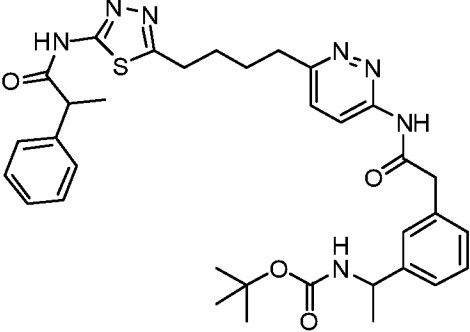
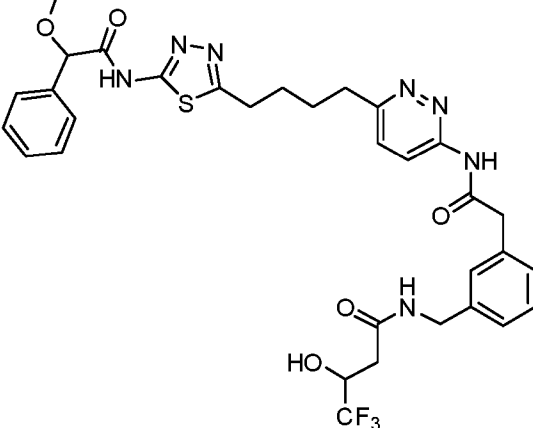
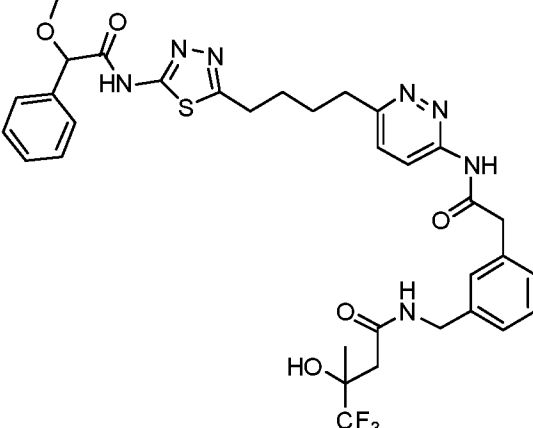
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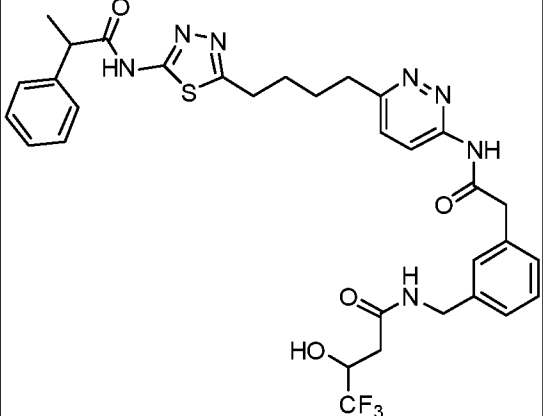
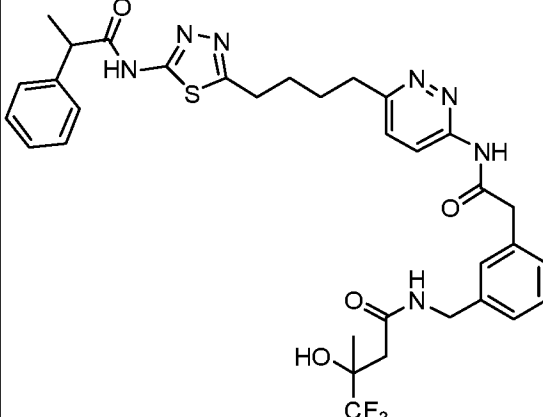
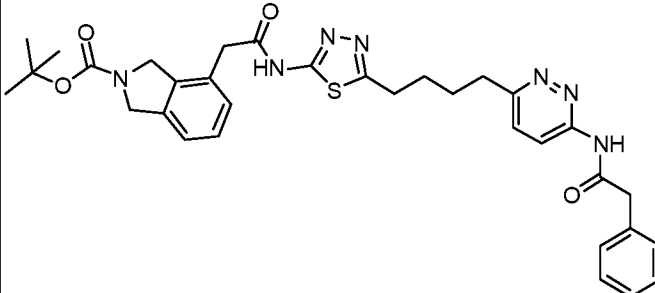
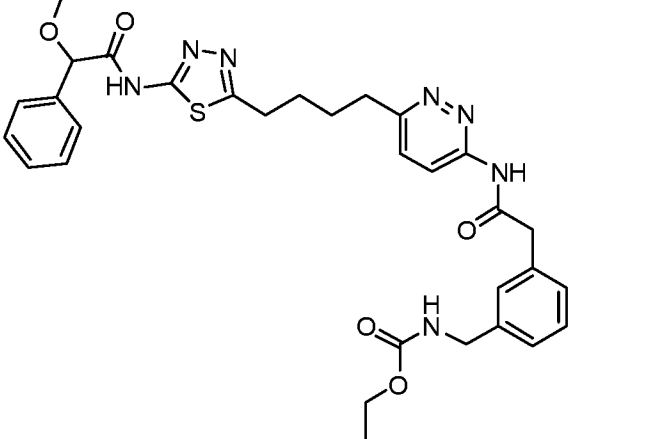
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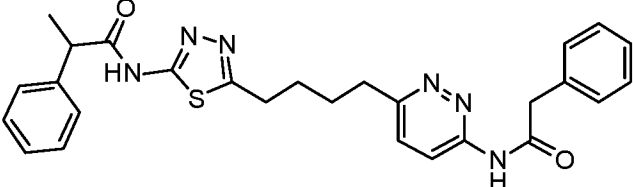
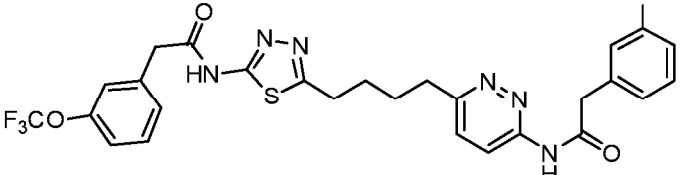
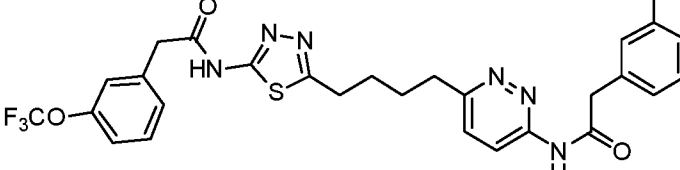
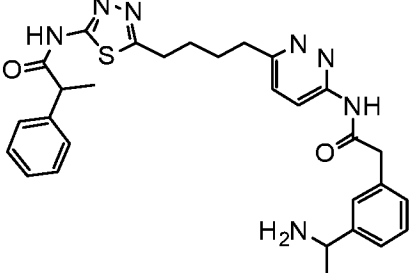
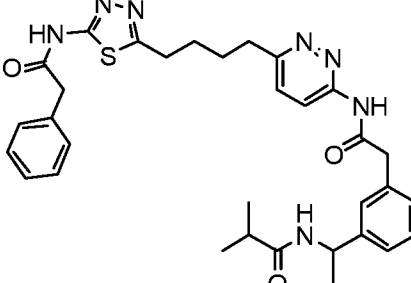
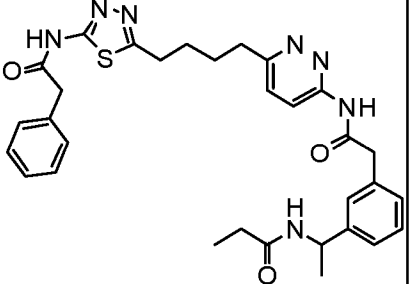
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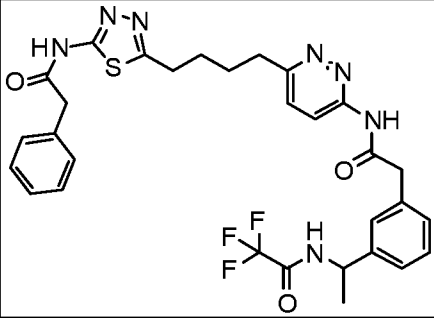
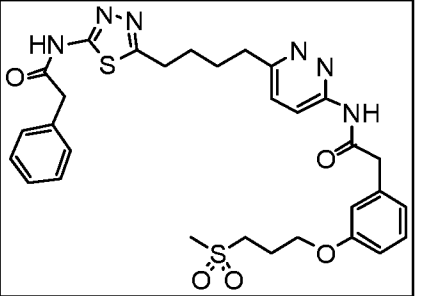
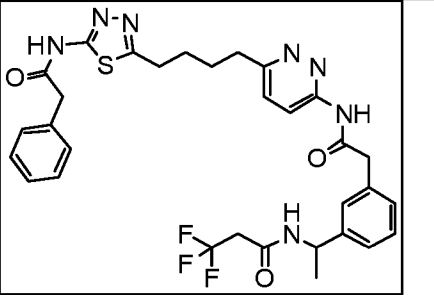
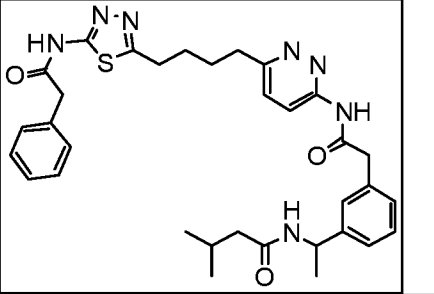
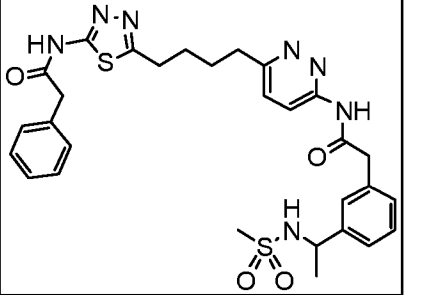
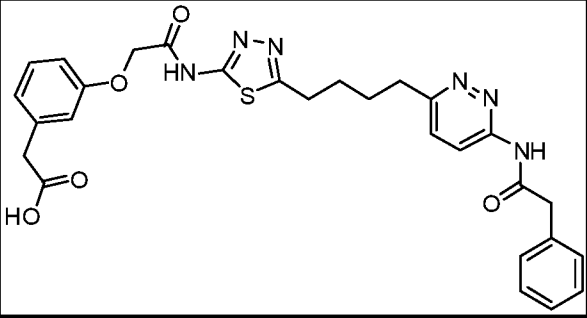
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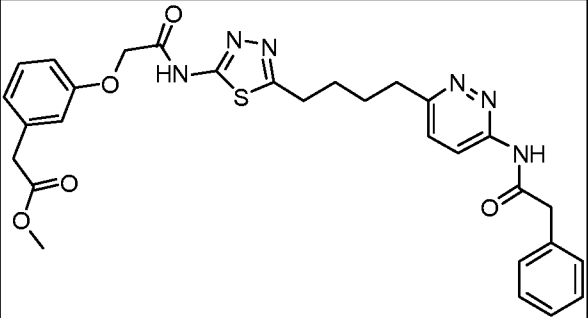
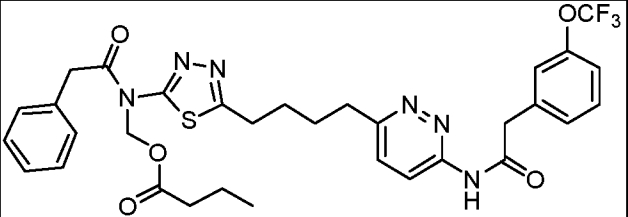
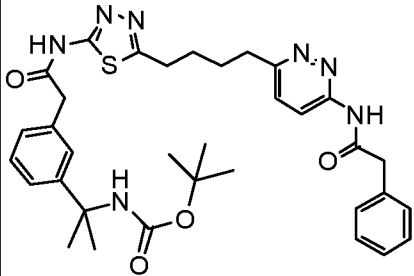
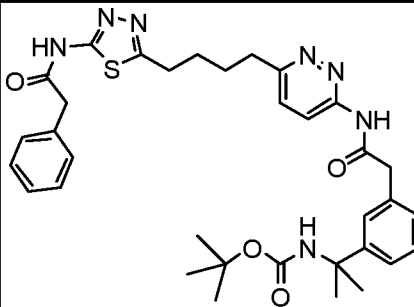
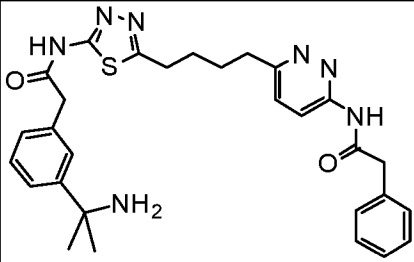
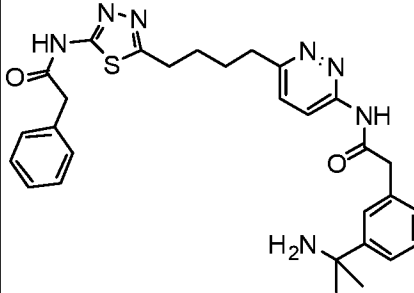
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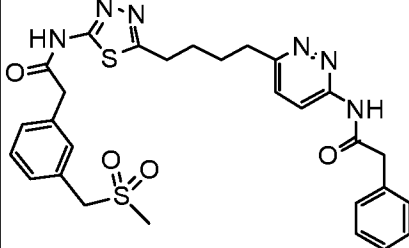
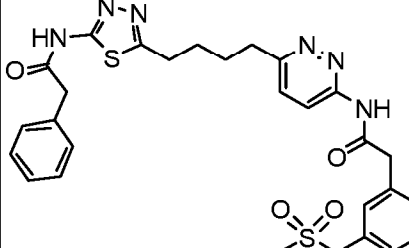
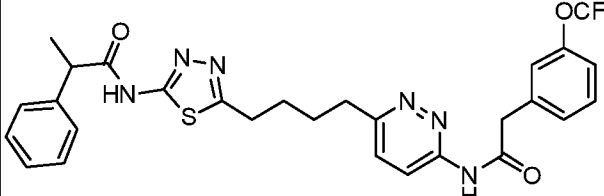
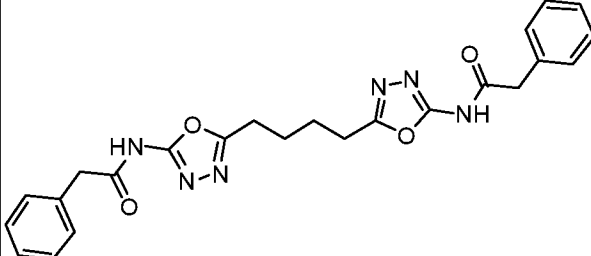
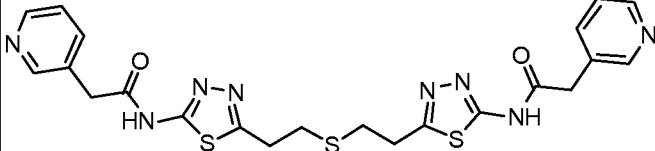
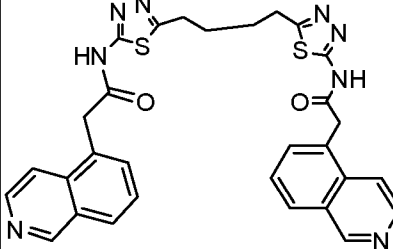
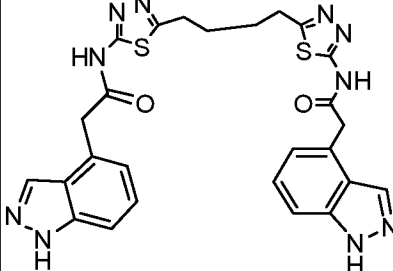
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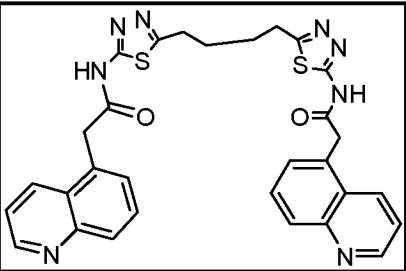
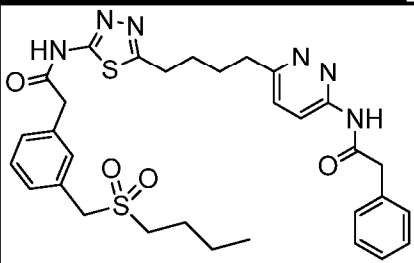
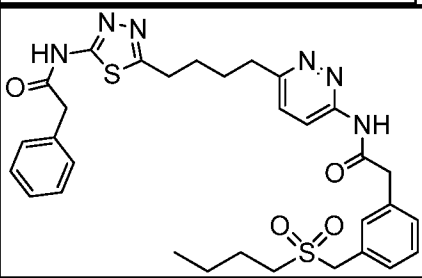
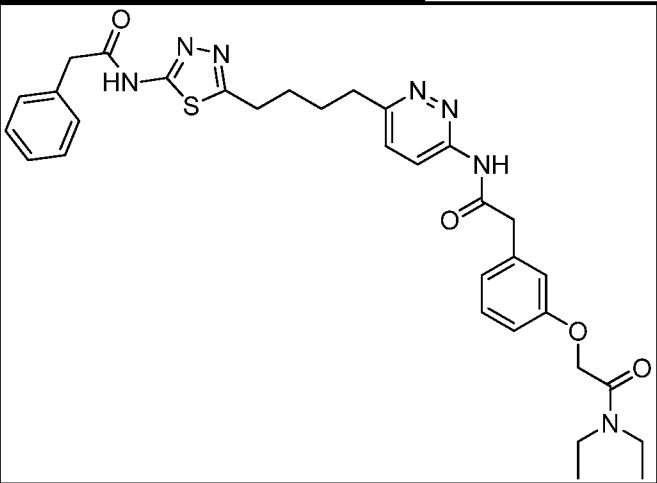
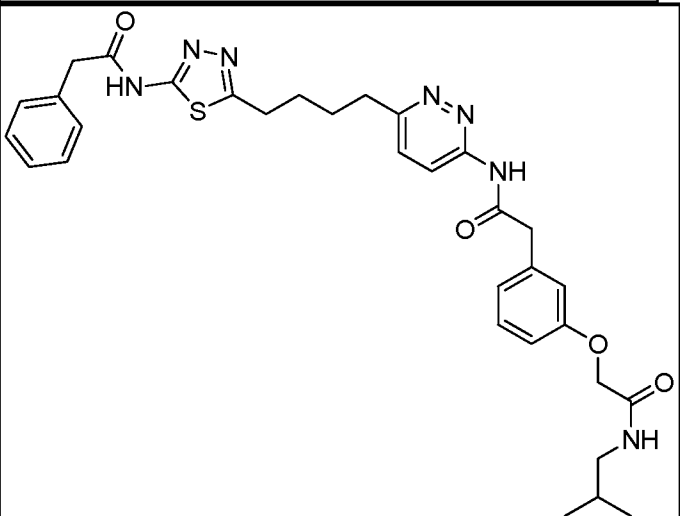
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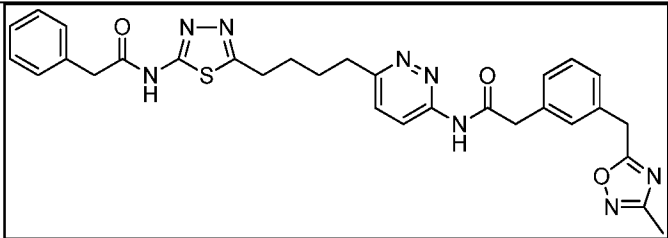
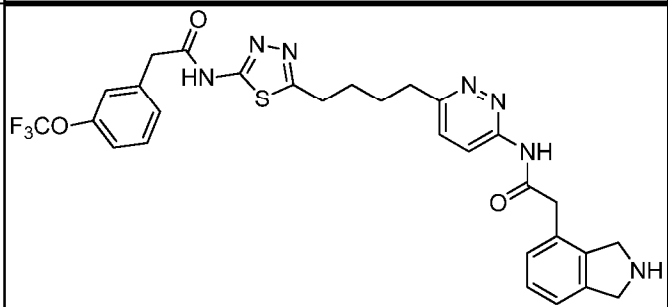
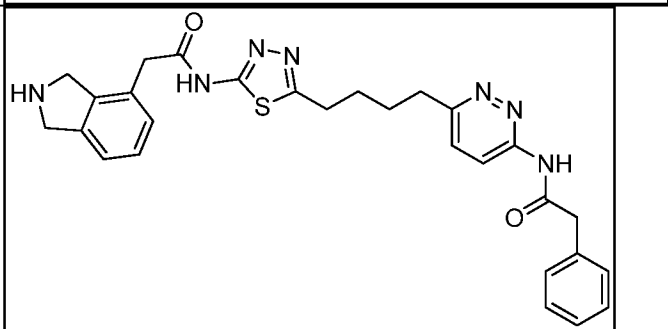
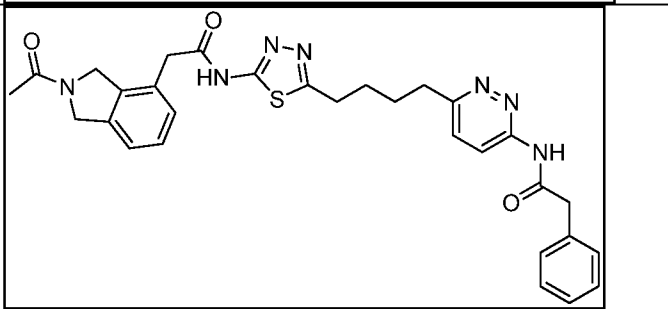
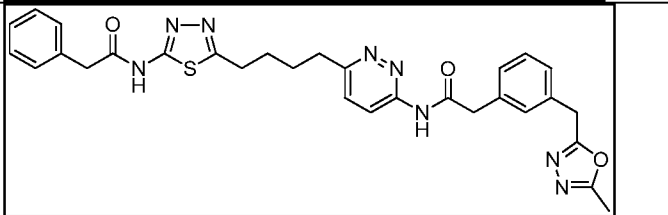
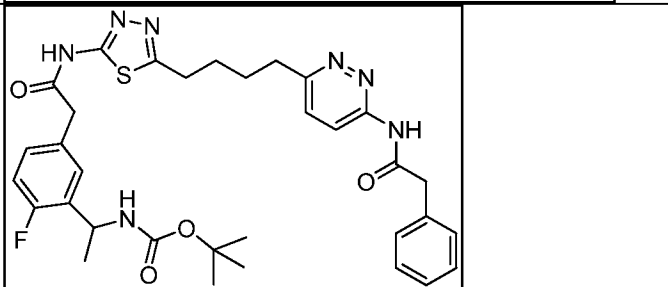
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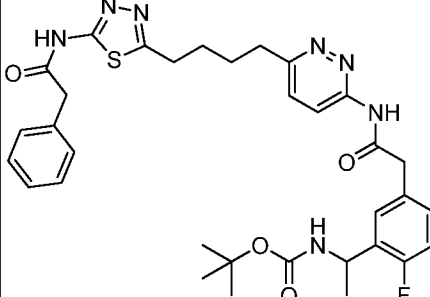
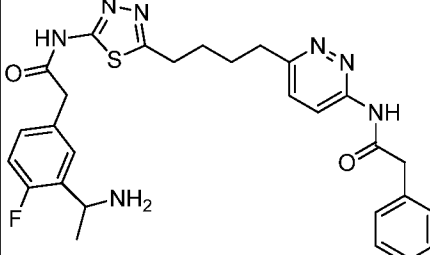
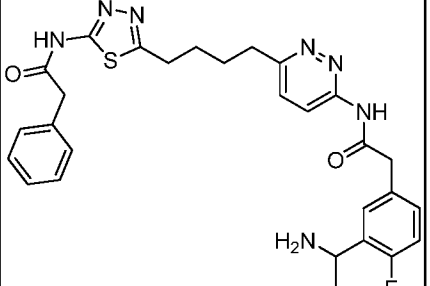
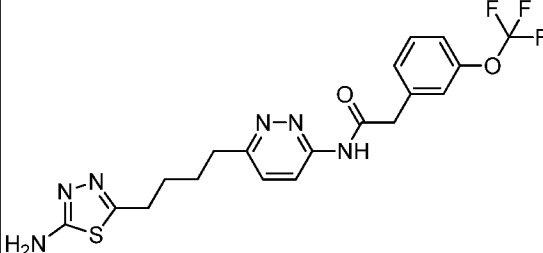
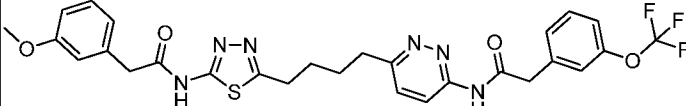
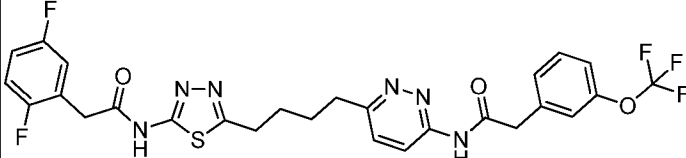
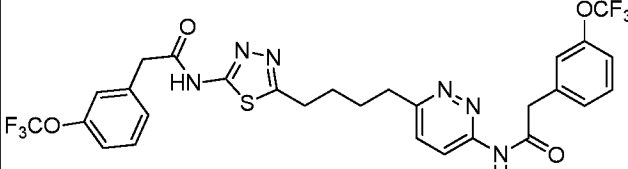
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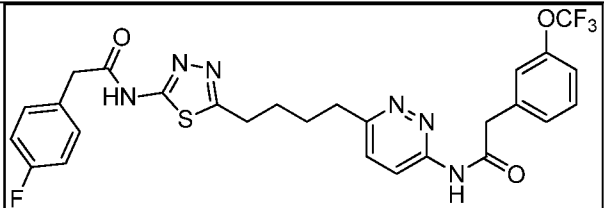
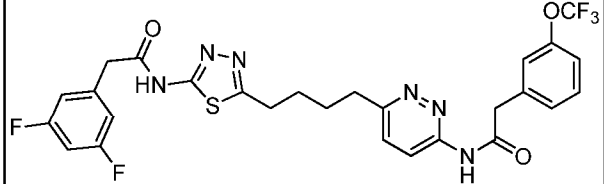
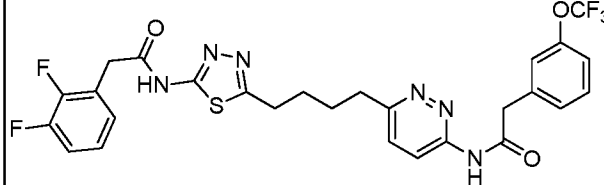
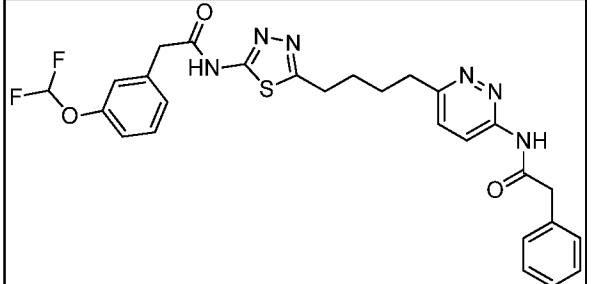
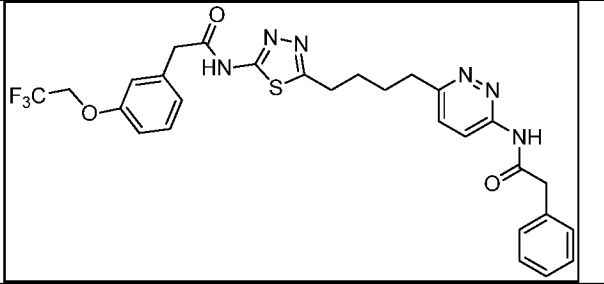
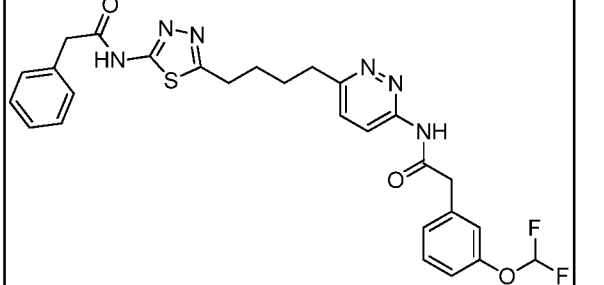
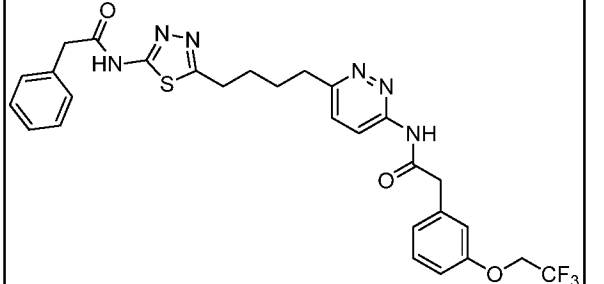
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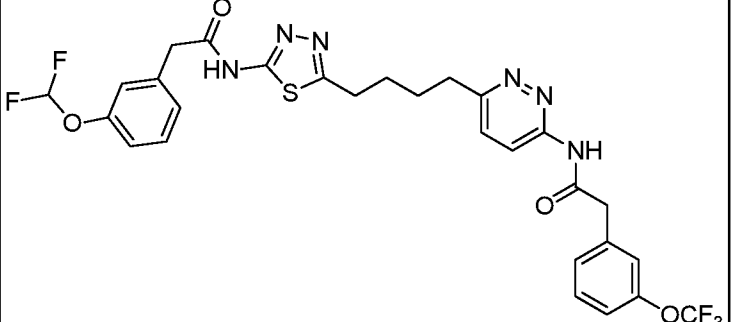
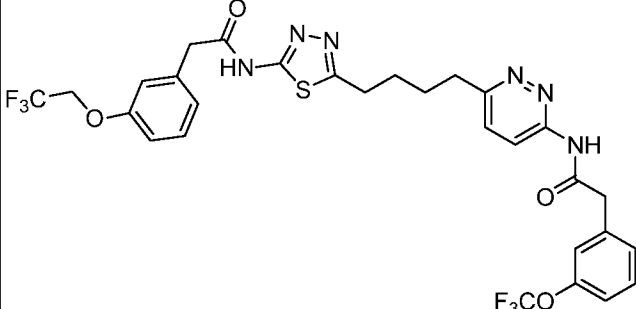
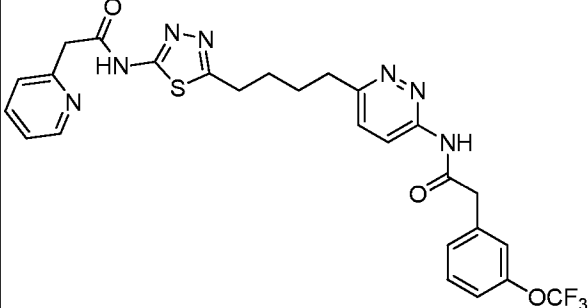
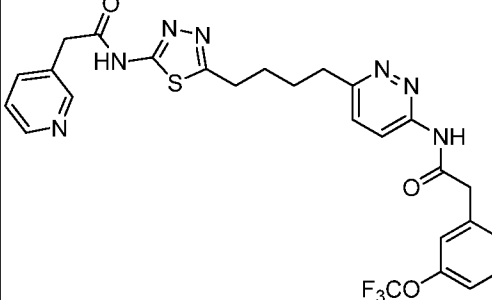
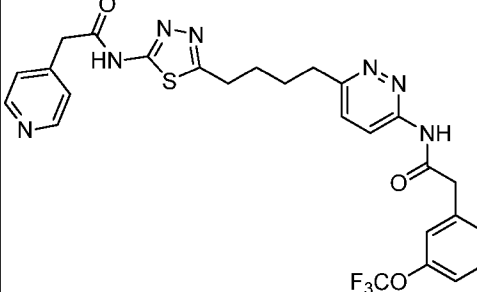
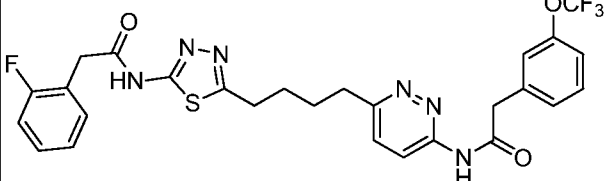
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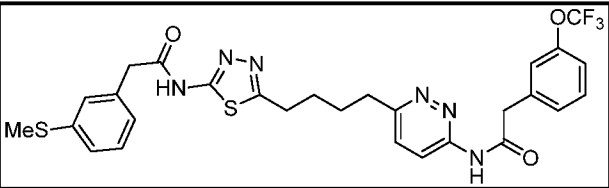
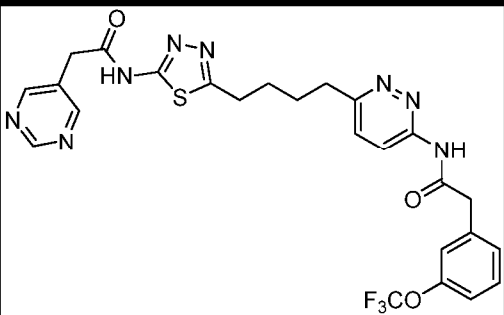
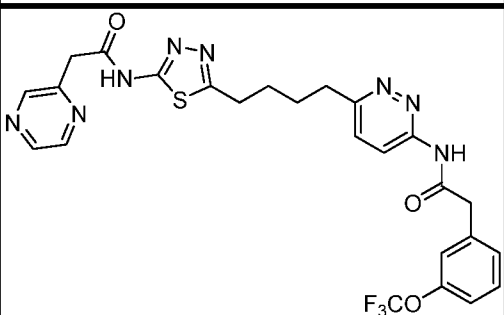
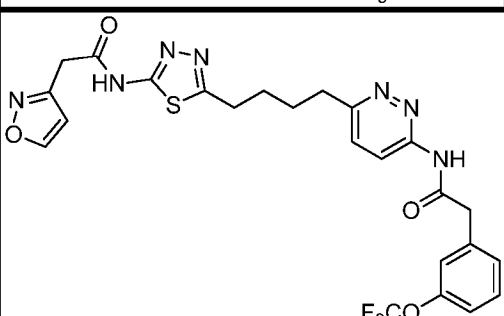
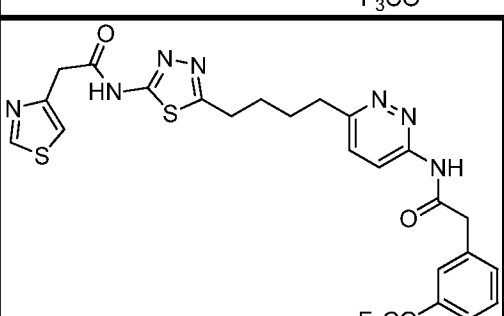
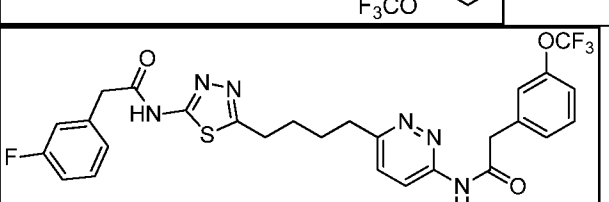
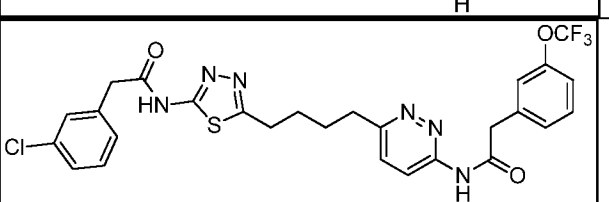
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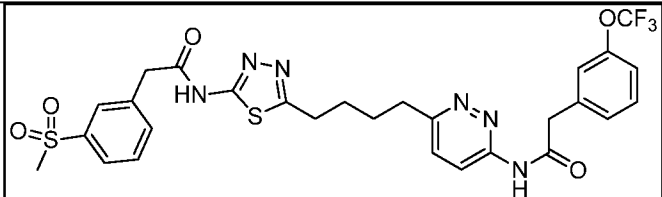
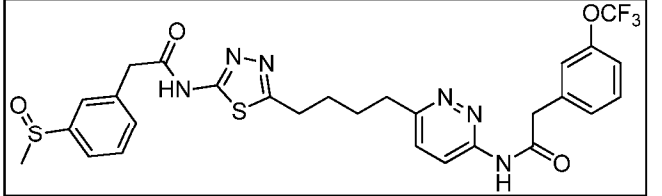
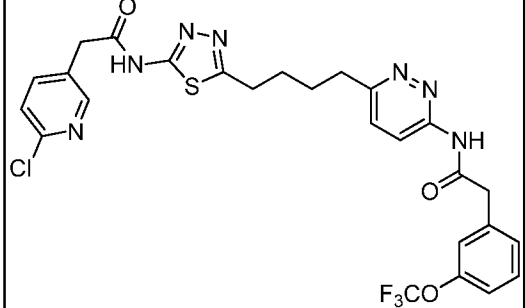
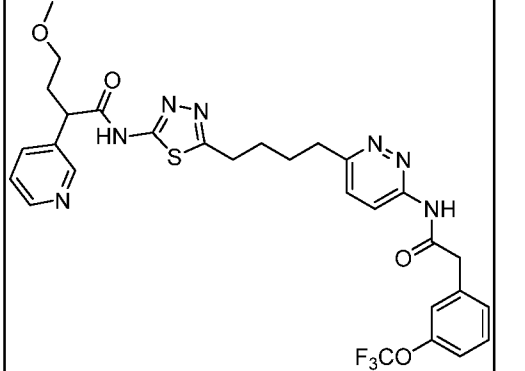
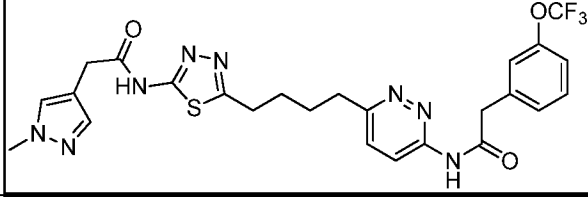
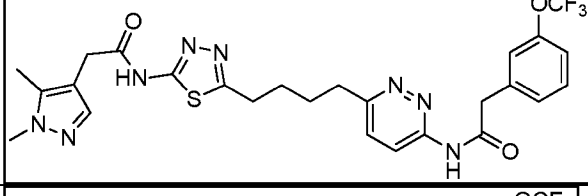
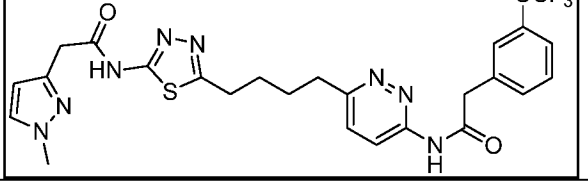
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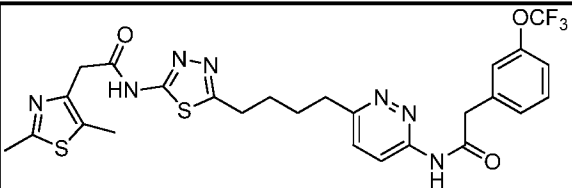
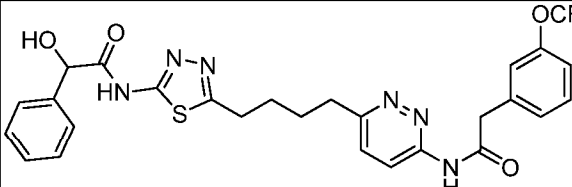
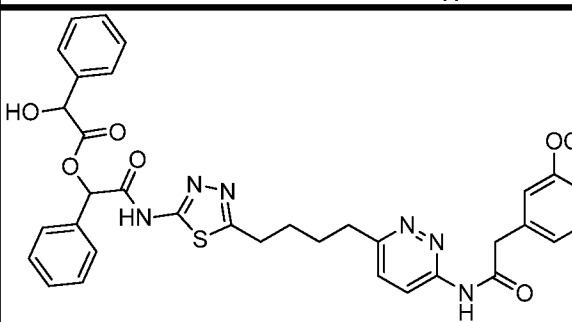
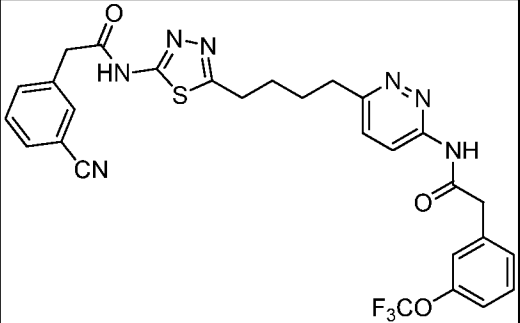
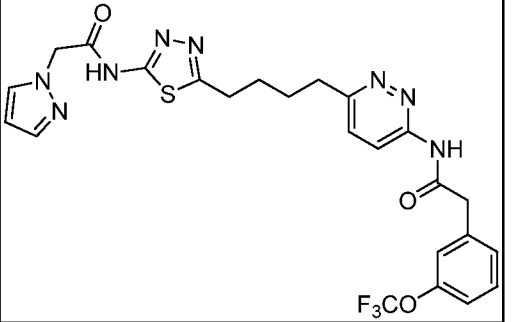
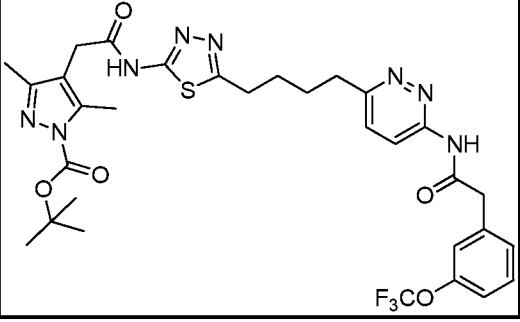
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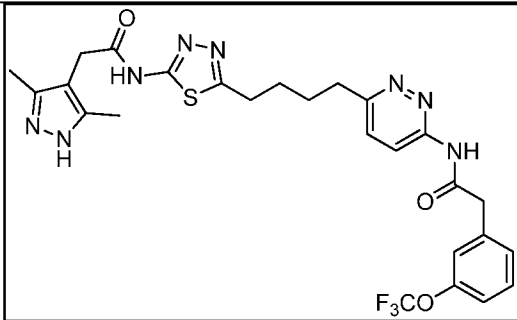
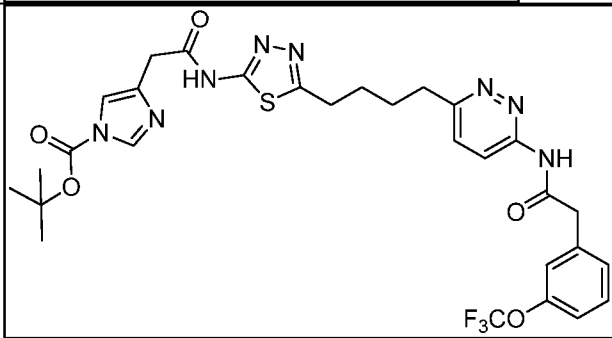
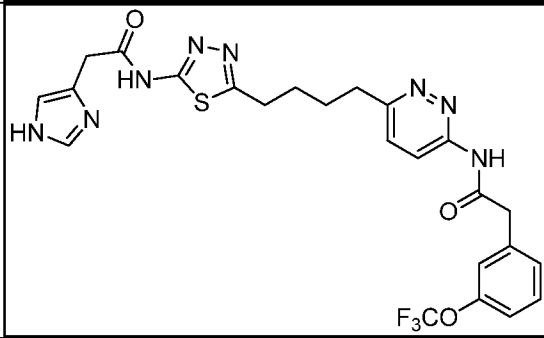
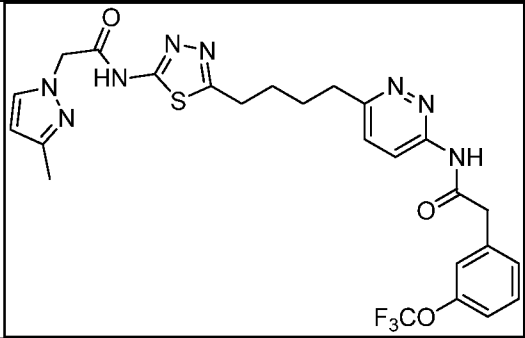
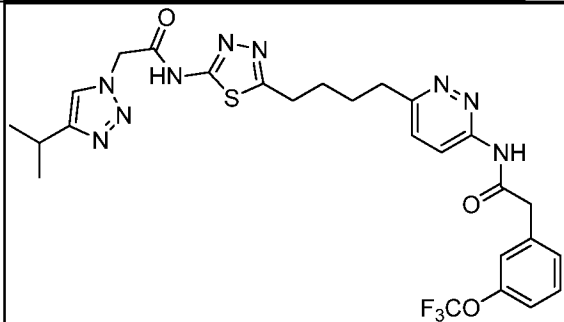
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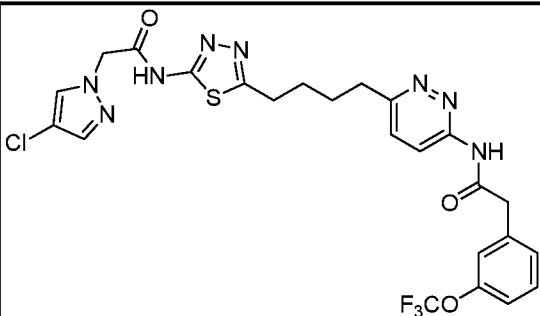
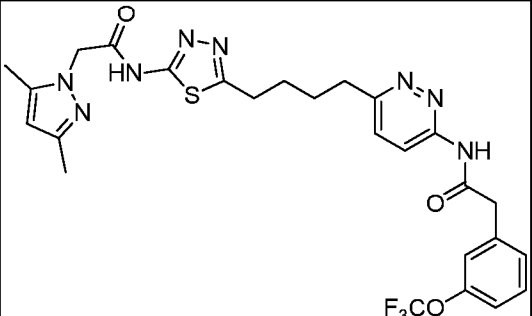
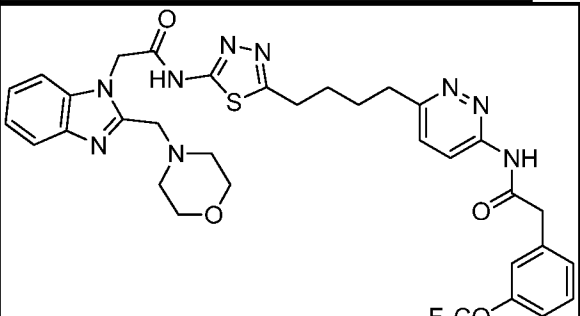
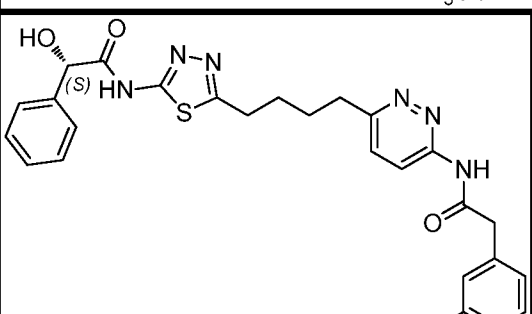
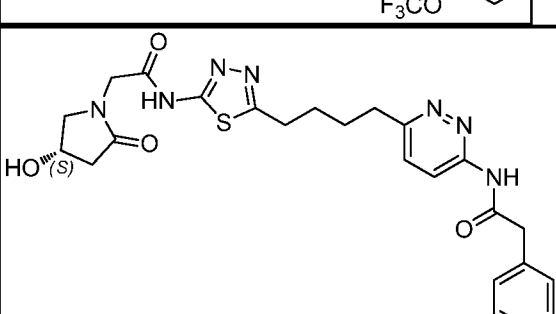
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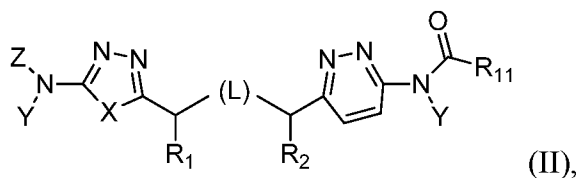
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The present invention further provides methods of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection comprising orally administering a compound of formula II,



or a pharmaceutically acceptable salt thereof, wherein:

L represents CH_2SCH_2 , CH_2CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2 , CH_2S , SCH_2 , CH_2NHCH_2 ,

$\text{CH}=\text{CH}$, or , preferably CH_2CH_2 , wherein any hydrogen atom of a CH or CH_2 unit may be replaced by alkyl or alkoxy, any hydrogen of an NH unit may be replaced by

alkyl, and any hydrogen atom of a CH₂ unit of CH₂CH₂, CH₂CH₂CH₂ or CH₂ may be replaced by hydroxy;

X represents S, O or CH=CH, preferably S or CH=CH, wherein any hydrogen atom of a CH unit may be replaced by alkyl;

5 Y, independently for each occurrence, represents H or CH₂O(CO)R₇;

R₇, independently for each occurrence, represents H or substituted or unsubstituted alkyl, alkoxy, aminoalkyl, alkylaminoalkyl, heterocyclalkyl, arylalkyl, or heterocyclalkoxy;

Z represents H or R₃(CO);

10 R₁ and R₂ each independently represent H, alkyl, alkoxy or hydroxy;

R₃ represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroaryloxyalkyl or C(R₈)(R₉)(R₁₀), N(R₄)(R₅) or OR₆, wherein any free hydroxyl group may be acylated to form C(O)R₇;

R₄ and R₅ each independently for each occurrence represent H or substituted or unsubstituted alkyl, hydroxyalkyl, acyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form C(O)R₇;

R₆ represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form C(O)R₇;

25 R₈, R₉ and R₁₀ each independently for each occurrence represent H or substituted or unsubstituted alkyl, hydroxy, hydroxyalkyl, amino, acylamino, aminoalkyl, acylaminoalkyl, alkoxycarbonyl, alkoxycarbonylamino, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, or R₈ and R₉ together with the carbon to which they are attached, form a carbocyclic or heterocyclic ring system, wherein any free hydroxyl group may be acylated to form C(O)R₇, and wherein at least two of R₈, R₉ and R₁₀ are not H;

R₁₁ represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, or R₁₁ represents C(R₁₂)(R₁₃)(R₁₄), N(R₄)(R₁₄) or OR₁₄, wherein any free hydroxyl group may be acylated to form C(O)R₇;

R₁₂ and R₁₃ each independently represent H or substituted or unsubstituted alkyl, hydroxy, hydroxyalkyl, amino, acylamino, aminoalkyl, acylaminoalkyl, alkoxycarbonyl, alkoxycarbonylamino, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form C(O)R₇, and wherein both of R₁₂ and R₁₃ are not H; and

R₁₄ represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl;

preferably wherein the compound is administered with a meal.

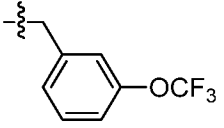
In some embodiments, R₁₁ represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein the aryl or heteroaryl ring is substituted with either -OCHF₂ or -OCF₃ and is optionally further substituted.

In some embodiments, R₁₄ represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein the aryl or heteroaryl ring is substituted with either -OCHF₂ or -OCF₃ and is optionally further substituted.

In certain embodiments wherein alkyl, hydroxyalkyl, amino, acylamino, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl are substituted, they are substituted with one or more substituents selected from substituted or unsubstituted alkyl, such as perfluoroalkyl (*e.g.*, trifluoromethyl), alkenyl, alkoxy, alkoxyalkyl, aryl, aralkyl, arylalkoxy, aryloxy, aryloxyalkyl, hydroxyl, halo, alkoxy, such as perfluoroalkoxy (*e.g.*, trifluoromethoxy), alkoxyalkoxy, hydroxyalkyl, hydroxyalkylamino, hydroxyalkoxy, amino, aminoalkyl, alkylamino, aminoalkylalkoxy, aminoalkoxy, acylamino, acylaminoalkyl, such as perfluoro acylaminoalkyl (*e.g.*, trifluoromethylacylaminoalkyl), acyloxy, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxy, heterocyclylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, heteroaryloxy, heteroaryloxyalkyl, heterocyclylaminoalkyl, heterocyclylaminoalkoxy,

amido, amidoalkyl, amidine, imine, oxo, carbonyl (such as carboxyl, alkoxycarbonyl, formyl, or acyl, including perfluoroacyl (*e.g.*, C(O)CF₃)), carbonylalkyl (such as carboxyalkyl, alkoxycarbonylalkyl, formylalkyl, or acylalkyl, including perfluoroacylalkyl (*e.g.*, -alkylC(O)CF₃)), carbamate, carbamatealkyl, urea, ureaalkyl, sulfate, sulfonate, 5 sulfamoyl, sulfone, sulfonamide, sulfonamidealkyl, cyano, nitro, azido, sulfhydryl, alkylthio, thiocarbonyl (such as thioester, thioacetate, or thioformate), phosphoryl, phosphate, phosphonate or phosphinate.

In certain embodiments, R₁₁ represents arylalkyl, such as benzyl, wherein the aryl group is substituted with -OCF₃, such as meta-substituted with -OCF₃. In certain such 10 embodiments, the aryl ring is not further substituted. In certain embodiments, R₁₁

represents trifluoromethoxybenzyl, such as .

In certain embodiments, L represents CH₂SCH₂, CH₂CH₂, CH₂CH₂CH₂, CH₂, CH₂S, SCH₂, or CH₂NHCH₂, wherein any hydrogen atom of a CH₂ unit may be replaced by alkyl or alkoxy, and any hydrogen atom of a CH₂ unit of CH₂CH₂, CH₂CH₂CH₂ or CH₂ 15 may be replaced by hydroxyl. In certain embodiments, L represents CH₂SCH₂, CH₂CH₂, CH₂S or SCH₂. In certain embodiments, L represents CH₂CH₂. In certain embodiments, L is not CH₂SCH₂.

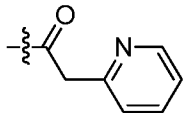
In certain embodiments, Y represents H.

In certain embodiments, X represents S or CH=CH. In certain embodiments, X 20 represents S.

In certain embodiments, Z represents R₃(CO). In certain embodiments wherein Z is R₃(CO), R₃ and R₁₁ are not identical (*e.g.*, the compound of formula II is not symmetrical).

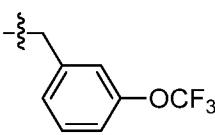
In certain embodiments, R₁ and R₂ each represent H.

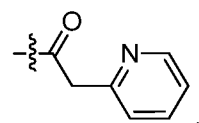
In certain embodiments, Z represents R₃(CO) and R₃ represents arylalkyl, 25 heteroarylalkyl, cycloalkyl or heterocycloalkyl. In certain embodiments, Z represents R₃(CO) and R₃ represents heteroarylalkyl, such as pyridylalkyl (*e.g.*, pyridylmethyl). In

certain such embodiments, Z represents . In certain embodiments, Z represents R₃(CO) and R₃ represents C(R₈)(R₉)(R₁₀), wherein R₈ represents aryl, arylalkyl, heteroaryl or heteroarylalkyl, such as aryl, arylalkyl or heteroaryl, R₉ represents H, and R₁₀

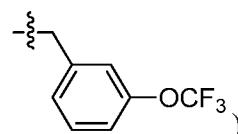
represents hydroxy, hydroxyalkyl, alkoxy or alkoxyalkyl, such as hydroxy, hydroxyalkyl or alkoxy.

- In certain embodiments, L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 , such as CH_2CH_2 , Y represents H, X represents S, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, R_3 represents arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl, such as heteroarylalkyl (*e.g.*, pyridylalkyl), and R_{11} represents arylalkyl, such

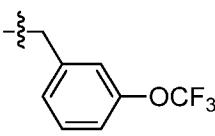
trifluoromethoxybenzyl (*e.g.*, ) . In certain such embodiments, Z represents $\text{R}_3(\text{CO})$ and R_3 represents pyridylmethyl, such as wherein Z represents

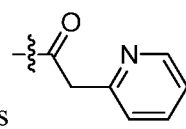


- In certain embodiments, L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 , such as CH_2CH_2 , Y represents H, X represents S, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, and each R_3 represents $\text{C}(\text{R}_8)(\text{R}_9)(\text{R}_{10})$, wherein R_8 represents aryl, arylalkyl, heteroaryl or heteroaralkyl, such as aryl, arylalkyl or heteroaryl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl, alkoxy or alkoxyalkyl, such as hydroxy, hydroxyalkyl or alkoxy,

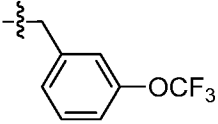
- and R_{11} represents arylalkyl, such trifluoromethoxybenzyl (*e.g.*, ) .

In certain embodiments, L represents CH_2CH_2 , Y represents H, X represents S or $\text{CH}=\text{CH}$, such as S, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, R_3 represents substituted or unsubstituted arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl, such as heteroarylalkyl (*e.g.*, pyridylalkyl), and R_{11} represents arylalkyl, such

- trifluoromethoxybenzyl (*e.g.*, ) . In certain such embodiments, Z represents

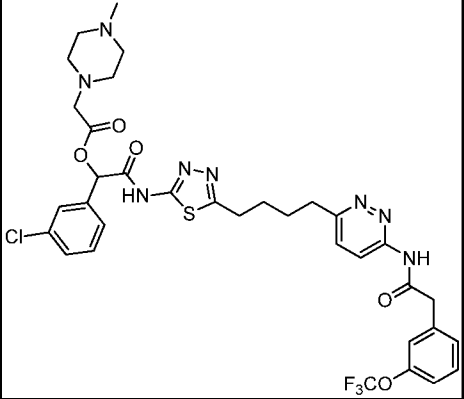
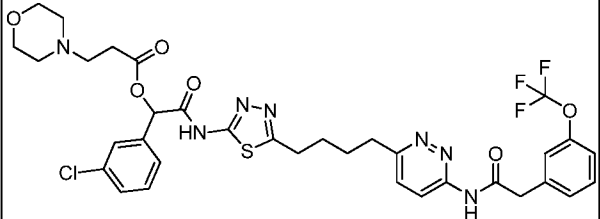
$\text{R}_3(\text{CO})$ and R_3 represents pyridylmethyl, such as wherein Z represents  .

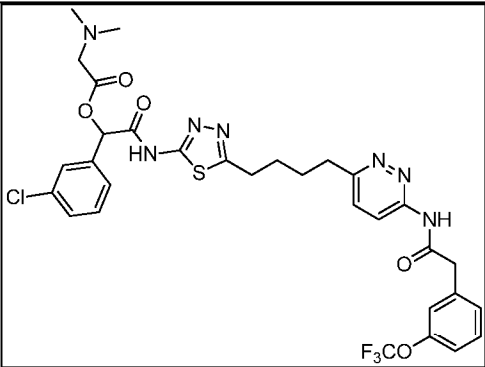
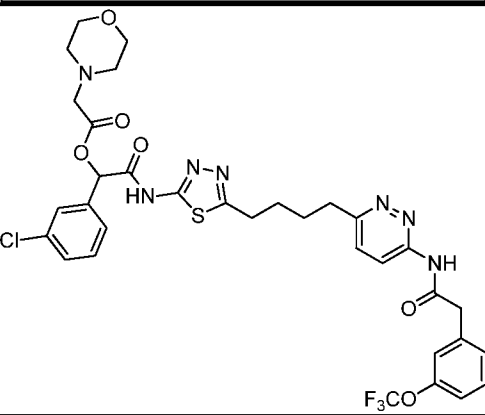
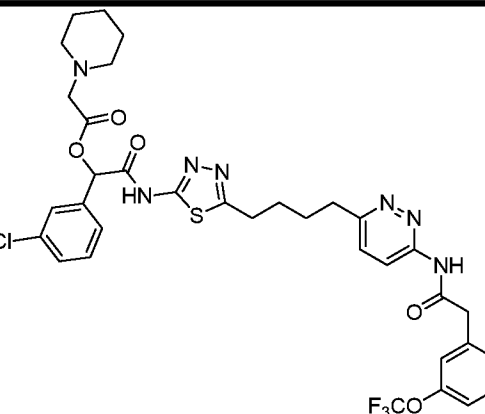
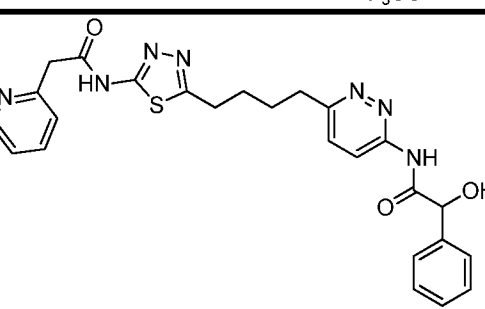
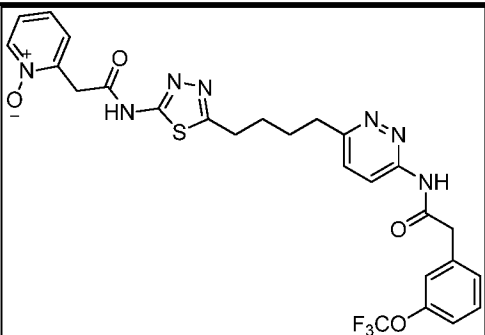
- In certain embodiments, L represents CH_2CH_2 , Y represents H, X represents S, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, R_3 represents $\text{C}(\text{R}_8)(\text{R}_9)(\text{R}_{10})$, wherein R_8 represents aryl, arylalkyl or heteroaryl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl or alkoxy, and R_{11} represents arylalkyl, such trifluoromethoxybenzyl (*e.g.*,

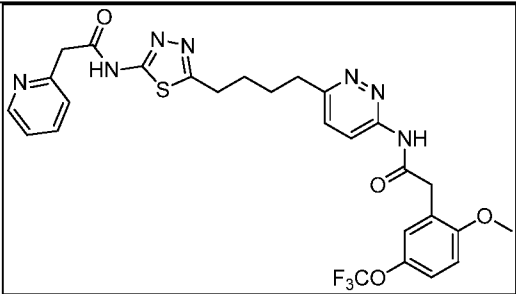
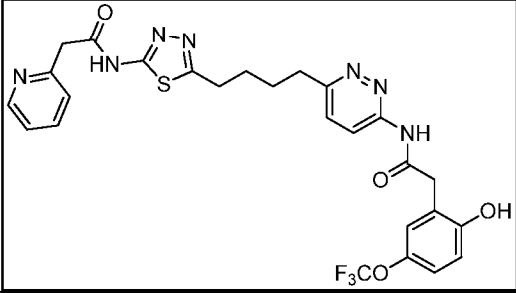
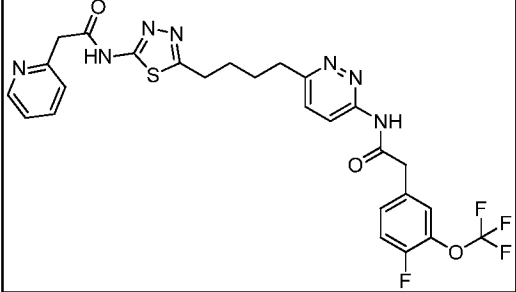
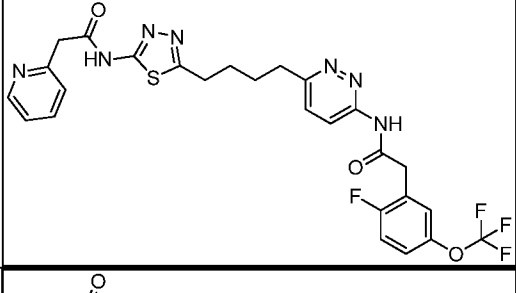
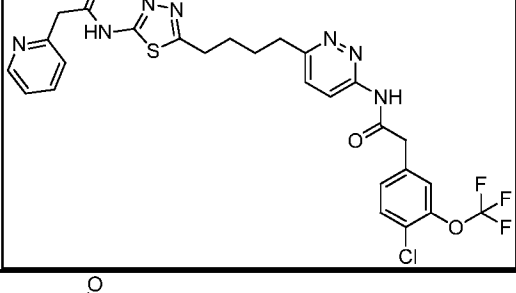
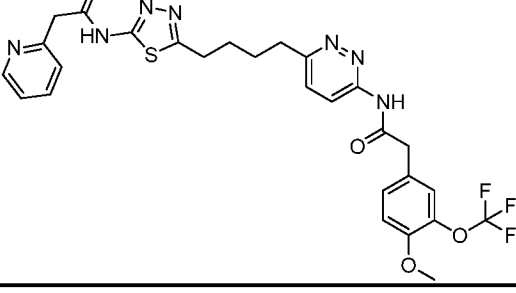

). In certain such embodiments, R_8 represents aryl and R_{10} represents hydroxyalkyl.

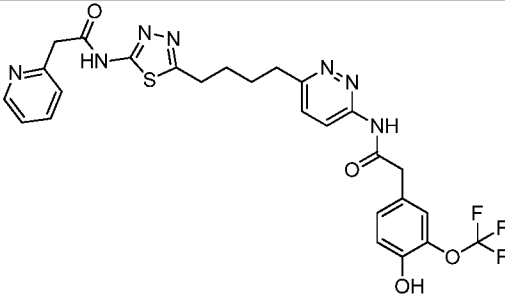
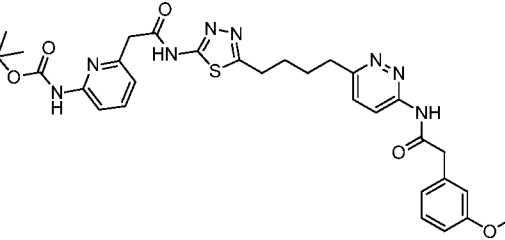
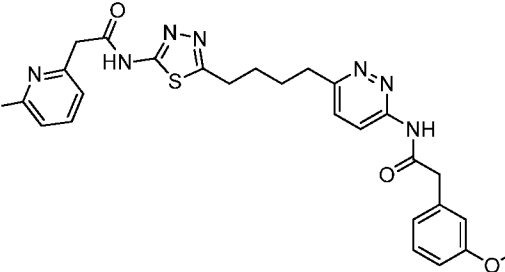
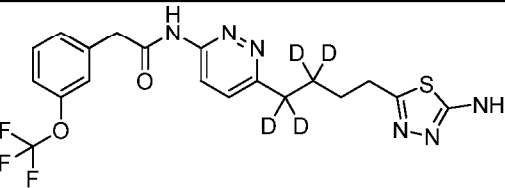
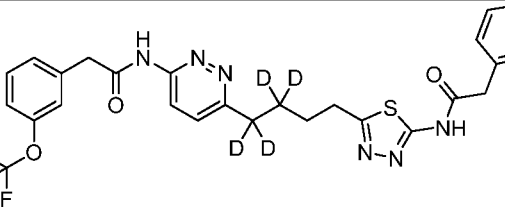
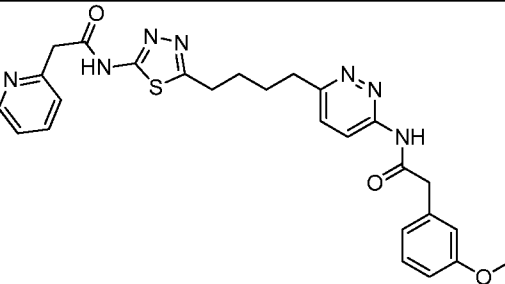
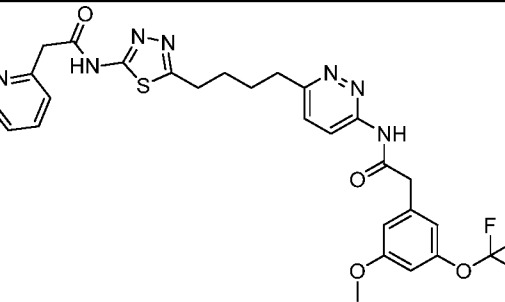
In certain embodiments, the compound is selected from any one of the compounds disclosed in Tables 1 and 2. In certain embodiments, the compound is selected from compound 447, 585, 586, 600, 614, 615, 629, 636, 657, 658, 659, 660, 661, 662, 663, 666, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, or 730. In certain embodiments, the compound is selected from compound 657, 658, 659, 660, 661, 662, 663, 666, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, or 730.

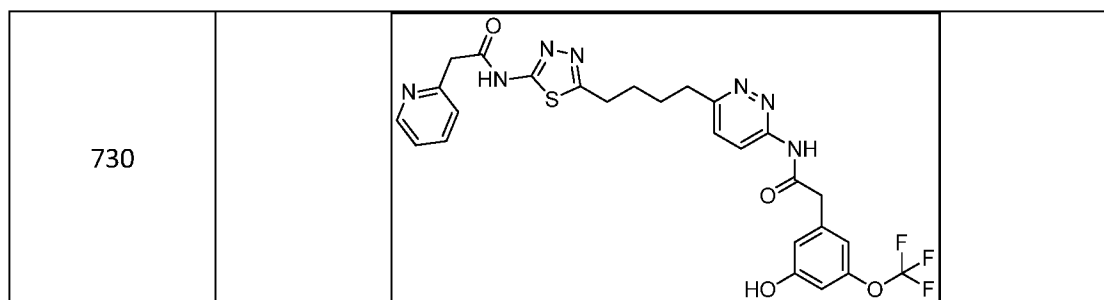
Table 2. Selected Compounds of Formula II

Compound ID	Structure
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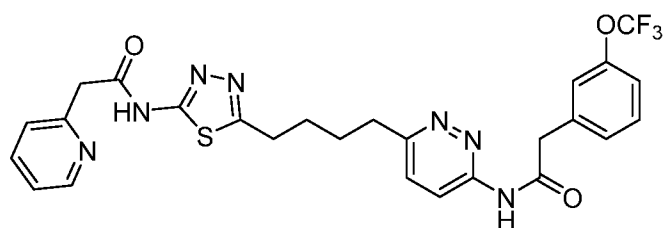
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In certain embodiments of the methods described herein, the compound used in the methods of the invention is a compound having the structure of Formula (III):

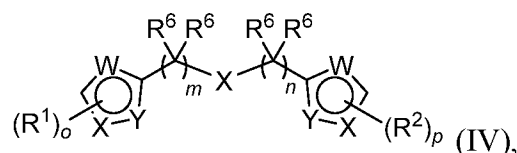


(III), or a pharmaceutically

5 acceptable salt thereof.

Compounds of any of Formulae (I), (Ia), (II), or (III) are alternatively referred to herein as “glutaminase inhibitors.”

In certain embodiments, the invention relates to methods of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection, comprising orally administering a compound having the structure of Formula (IV):



or a pharmaceutically acceptable salt thereof, wherein:

X is a bond, —S—, —S(O)—, —SO₂—, —CH=CH—, or —C(O)—;

15 each W, Y and Z is independently —S—, —CH=, —O—, —N=, or —NH—, provided that (1) at least one of W, Y and Z is not —CH= and (2) when one of W is —S— and the Y in the same ring is N, then the Z in the same ring is not —CH=;

each R¹ and R² is independently C₁₋₆ alkylene-R⁴, —N(R³)—R⁴, —N(R³)—C(O)—R⁴, —C(O)—N(R³)—R⁴, —N(R³)—C(O)—O—R⁴, —N(R³)—C(O)—N(R³)—R⁴, —O—C(O)—N(R³)—R⁴, —N(R³)—C(O)—C₁₋₆ alkylene—C(O)—R⁴, —N(R³)—C(O)—C₁₋₆ alkylene—N(R³)—C(O)—R⁴ or —N(R^{3a})—C(O)—CH₂—N(R³)—C(O)—R⁴;

each R³ is independently hydrogen, C₁₋₆ alkyl or aryl;

each R^4 is independently C_{1-6} alkyl, C_{1-6} alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclalkyl, heterocycl, cycloalkyl or cycloalkylalkyl, each of which is substituted with 0-3 occurrences of R^5 , or two adjacent R^5 moieties, taken together with the atoms to which they are attached form a heterocycl, heteroaryl, cycloalkyl or aryl;

each R^5 is independently oxo ($=O$), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, cyano, halo, $-OH$, $-SH$, $-OCF_3$, $-SO_2-C_{1-6}$ alkyl, $-NO_2$, $-N(R^7)-C(O)-C_{1-6}$ alkyl, $-N(R^6)_2$, $-O-C(O)-C_{1-6}$ alkyl, C_{3-7} cycloalkyl, $(C_{3-7}cycloalkyl)alkyl$, aryl, aryloxy, $-C(O)-aryl$, heteroaryl, aralkyl, heteroaralkyl, heterocyclalkyl or heterocycl, wherein each aryl, heteroaryl or heterocycl is further substituted with 0-3 occurrences of R^7 ;

each R^6 is independently hydrogen, fluoro, OH or C_{1-6} alkyl;

each R^7 is independently hydrogen, C_{1-6} alkyl, $-OH$, $-SH$, cyano, halo, $-CF_3$, $-OCF_3$, $-SO_2-C_{1-6}$ alkyl, $-NO_2$, $-N(R^7)-C(O)-C_{1-6}$ alkyl, $-N(R^6)_2$ or C_{1-6} alkoxy;

m is 1, 2 or 3;

n is 1, 2 or 3; provided that when X is bond, the sum of m and n is from 3 to 6 and when X is $-S-$, $-S(O)-$, $-SO_2-$, $-CH=CH-$, or $-C(O)-$, the sum of m and n is from 2 to 4;

o is 1, 2 or 3; and

p is 1, 2 or 3;

with the proviso that: (1) when X is $-S-$, m and n are both 2, each R^6 is H , then (i) R^1 and R^2 are not both $-NHC(O)-R^4$, wherein R^4 is C_{1-6} alkyl, monocyclic aryl, monocyclic heteroaryl, monocyclic aralkyl, monocyclic heteroaralkyl and each member of R^4 is substituted with 0-3 occurrences of R^5 ; and (ii) R^1 and R^2 are not both $-NHC(O)O$ -methyl, $-NHC(O)O$ -ethyl, $-NHC(\pm)$ -6-pyrimidine-2,4(1H,3H)-dionyl, or $-NHC(O)NH$ -phenyl wherein said phenyl of the $-NHC(O)NH$ -phenyl moiety is optionally substituted with 1 or 2 groups selected from methyl, nitro, and halo;

(2) when X is $-S-$, m and n are both 1, each R^6 is H , then (i) R^1 and R^2 are not both $-NH$ -phenyl or $-NH$ -4-methoxy-phenyl;

(3) when X is a bond, the sum of m and n is 3, each R^6 is H , then R^1 and R^2 are not both $NHC(O)$ -phenyl;

(4) when X is a bond, m and n are both 2, each R⁶ is H, then R¹ and R² are not both —NHC(O)-furanyl, —NHC(O)-phenyl, —NHC(O)-o-methoxy-phenyl, —NHC(O)—C₁₋₆ alkyl, —NH-benzyl, or —NH-phenyl wherein said phenyl of the —NH-phenyl moiety is substituted with 0-3 occurrences of R⁵;

5 (5) when X is a bond, the sum of m and n is 5, each R⁶ is H, then R¹ and R² are not both —NHC(O)—C₁₋₆ alkyl, —NHC(O)-cyclohexyl, or —NH-phenyl wherein said phenyl of the —NH-phenyl moiety is optionally substituted with methyl; and

(6) when X is a bond, m and n are both 3, each R⁶ is H, then R¹ and R² are not both NH-phenyl;

10 preferably wherein the compound of formula (IV) is administered with a meal.

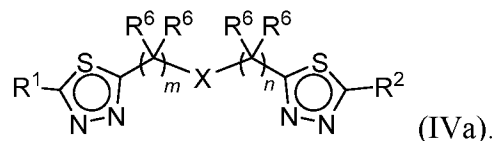
In certain embodiments, W is —S—, each Y is —N=, and each Z is —N=.

In certain embodiments, W is —CH=, each Z is —O—, and each Y is —N=.

In certain embodiments, o is 1 and p is 1.

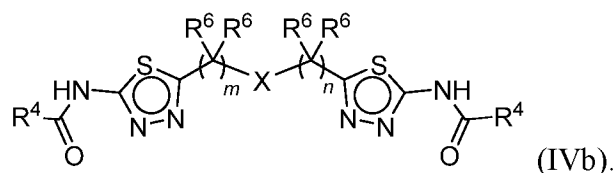
In certain embodiments, R¹ and R² are each —N(R³)—C(O)—O—R⁴.

15 In certain embodiments, the compound having the structure of Formula (IV) has the structure of Formula (IVa):

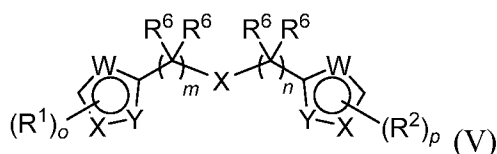


In certain embodiments, R¹ and R² are the same.

20 In certain embodiments, the compound having the structure of Formula (IV) is a compound having the structure of Formula (IVb):



In certain embodiments, the invention relates to methods of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection, comprising orally administering a compound having the structure of Formula (V):



25

wherein:

X is C₃-C₇ cycloalkylene;

each W, Y and Z is independently —S—, —CH=, —O—, —N=, or —NH—, provided that at least one of W, Y and Z is not —CH=;

5 each R¹ and R² is independently —NH₂, —N(R³)—C(O)—R⁴, —C(O)—N(R³)—R⁴, —N(R³)—C(O)—O—R⁴, —N(R³)—C(O)—N(R³)—R⁴ or —N(R³)—C(O)—SR⁴;

each R³ is independently hydrogen, C₁₋₆ alkyl or aryl;

each R⁴ is independently C₁₋₆ alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocyclalkyl, or heterocycl, each of which is substituted with
10 0-3 occurrences of R⁵;

each R⁵ is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, —O—C₁₋₆ alkyleneC₁₋₆ alkoxy, C₁₋₆ thioalkoxy, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclalkyl, heterocycl, cyano, halo, oxo, —OH, —OCF₃, —OCHF₂, —SO₂—C₁₋₆ alkyl, —NO₂, —N(R⁷)—C(O)—C₁₋₆ alkyl, —C(O)N(R⁷)₂, —N(R⁷)S(O)₁₋₂—C₁₋₆ alkyl, —S(O)₂N(R⁷)₂, —N(R⁷)₂, —C₁₋₆ alkylene-N(R⁷)₂, wherein said alkyl, C₁₋₆ alkoxy, —O—C₁₋₆ alkyleneC₁₋₆ alkoxy, C₁₋₆ thioalkoxy, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclalkyl, heterocycl, —SO₂—C₁₋₆ alkyl, —NO₂, —N(R⁷)—C(O)—C₁₋₆ alkyl, —C(O)N(R⁷)₂, —N(R⁷)S(O)₁₋₂—C₁₋₆ alkyl, —S(O)₂N(R⁷)₂, —N(R⁷)₂, or —C₁₋₆ alkylene-N(R⁷)₂ is optionally substituted with 0-3
15 20 occurrences of R⁸; or two adjacent R⁵ moieties, taken together with the atoms to which they are attached form a cycloalkyl or heterocycl;

each R⁶ is independently hydrogen, fluoro, C₁₋₆ alkyl, —OH, —NH₂, —NH(CH₃), —N(CH₃)₂, or C₁₋₆ alkoxy;

25 each R⁷ is independently hydrogen or C₁₋₆ alkyl;

each R⁸ is independently halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, —OH, —N(R⁷)₂, or C₁₋₆ alkoxy, —O—C₁₋₆ alkyleneC₁₋₆ alkoxy, CN, NO₂, —N(R⁷)—C(O)—C₁₋₆ alkyl, —C(O)N(R⁷)₂, —N(R⁷)S(O)₁₋₂C₁₋₆ alkyl, or —S(O)₂N(R⁷)₂;

m is 0, 1, or 2;

30 n is 0, 1, or 2;

o is 1, 2 or 3; and

p is 1, 2 or 3; provided that (1) when X is unsubstituted cyclopropyl, R¹ and R² are not both NH-phenyl; and (2) X is other than substituted cyclobutyl or substituted cyclopentyl;

preferably wherein the compound of formula (V) is administered with a meal.

5 In certain embodiments, W is —S—, each Y is —N=, and each Z is —N=.

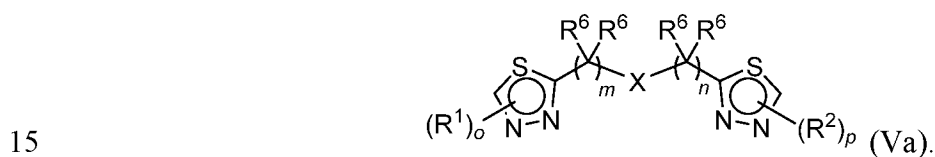
In certain embodiments, o is 1 and p is 1.

In certain embodiments, m is 0 and n is 0. Alternatively, m and n can each be 1.

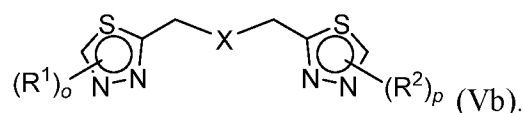
In certain embodiments, R¹ and R² are different. Alternatively, R¹ and R² can be the same.

10 In certain embodiments, R¹ and R² are each —N(R³)—C(O)—O—R⁴, wherein each R³ is hydrogen and each R⁴ is aralkyl or heteroaralkyl, each of which is substituted with 0-3 occurrences of R⁵.

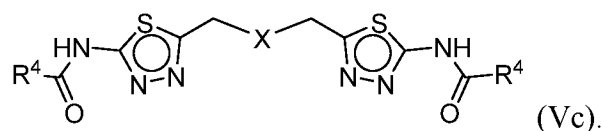
In certain embodiments, the compound having the structure of Formula (V) is a compound having the structure of Formula (Va):



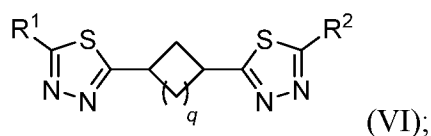
In certain embodiments, the compound having the structure of Formula (V) is a compound having the structure of Formula (Vb):



20 In certain embodiments, the compound having the structure of Formula (V) has the structure of formula (Vc):

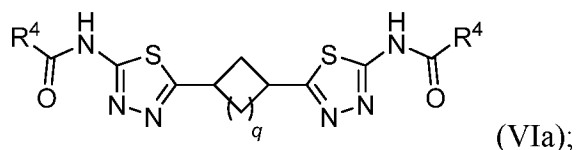


In certain embodiments, the compound of formula (V) is a compound of formula (VI):



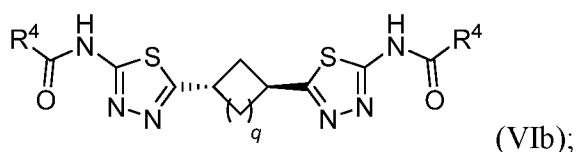
25 wherein q is 0, 1, 2, 3, or 4.

In certain embodiments, the compound of formula (V) has the structure of formula (VIa):



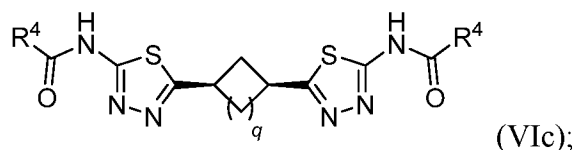
wherein q is 0, 1, 2, 3, or 4.

5 In certain embodiments, the compound of formula (V) has the structure of formula (VIb):



wherein q is 0, 1, 2, 3, or 4.

10 In certain embodiments, the compound of formula (V) has the structure of formula (VIc):



wherein q is 0, 1, 2, 3, or 4.

Compounds of formulas IV to VI are shown in Appendix A. In certain embodiments, the compound is selected from any one of the compounds disclosed in Appendix A. Compounds of any of Formulae IV to VI are alternatively referred to herein as “glutaminase inhibitors.”

20 In certain embodiments, compounds of the invention may be prodrugs of the compounds of formulas I-VI, *e.g.*, wherein a hydroxyl in the parent compound is presented as an ester or a carbonate, or carboxylic acid present in the parent compound is presented as an ester. In certain such embodiments, the prodrug is metabolized to the active parent compound in vivo (*e.g.*, the ester is hydrolyzed to the corresponding hydroxyl, or carboxylic acid).

25 In certain embodiments, compounds of the invention may be racemic. In certain embodiments, compounds of the invention may be enriched in one enantiomer. For example, a compound of the invention may have greater than 30% ee, 40% ee, 50% ee, 60% ee, 70% ee, 80% ee, 90% ee, or even 95% or greater ee. In certain embodiments, compounds of the invention may have more than one stereocenter. In certain such

embodiments, compounds of the invention may be enriched in one or more diastereomer. For example, a compound of the invention may have greater than 30% de, 40% de, 50% de, 60% de, 70% de, 80% de, 90% de, or even 95% or greater de.

In certain embodiments, the present invention relates to methods of treatment with a compound of formulas I-III, or a pharmaceutically acceptable salt thereof. In certain
5 embodiments, the present invention relates to methods of treatment with a compound of formulas IV-VI (e.g., a compound of any of formulas (IV), (IVa), (IVb), (V), (Va), (Vb), (Vc), (VI), (VIa), (VIb), or (VIc)), or a pharmaceutically acceptable salt thereof. In certain
10 embodiments, the therapeutic preparation may be enriched to provide predominantly one enantiomer of a compound (e.g., of formulas I-III, or of formulas IV-VI). An enantiomerically enriched mixture may comprise, for example, at least 60 mol percent of one enantiomer, or more preferably at least 75, 90, 95, or even 99 mol percent. In certain
15 embodiments, the compound enriched in one enantiomer is substantially free of the other enantiomer, wherein substantially free means that the substance in question makes up less than 10%, or less than 5%, or less than 4%, or less than 3%, or less than 2%, or less than
20 1% as compared to the amount of the other enantiomer, e.g., in the composition or compound mixture. For example, if a composition or compound mixture contains 98 grams of a first enantiomer and 2 grams of a second enantiomer, it would be said to contain 98 mol percent of the first enantiomer and only 2% of the second enantiomer.

20 In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one diastereomer of a compound (e.g., of formulas I-III, or of formulas IV-VI). A diastereomerically enriched mixture may comprise, for example, at least 60 mol percent of one diastereomer, or more preferably at least 75, 90, 95, or even 99 mol percent.

25 In certain embodiments, the present invention provides a pharmaceutical preparation suitable for oral administration to a human patient, comprising any of the compounds shown above (e.g., a glutaminase inhibitor, such as a compound of formulas I-III, or a compound of any of formulas IV-VI), and one or more pharmaceutically acceptable excipients.

30 Compounds of any of the above structures may be used in the manufacture of medicaments for the treatment of any diseases or conditions disclosed herein.

II. USE OF COMPOUNDS

Glutamine plays an important role as a carrier of nitrogen, carbon, and energy. It is used for hepatic urea synthesis, for renal ammoniagenesis, for gluconeogenesis, and as respiratory fuel for many cells. The conversion of glutamine into glutamate is initiated by the mitochondrial enzyme, glutaminase (“GLS”). There are two major forms of the enzyme, K-type and L-type, which are distinguished by their K_m values for glutamine and response to glutamate, wherein the K_m value, or Michaelis constant, is the concentration of substrate required to reach half the maximal velocity. The L-type, also known as “liver-type” or GLS2, has a high K_m for glutamine and is glutamate resistant. The K-type, also known as “kidney-type or GLS1, has a low K_m for glutamine and is inhibited by glutamate. An alternative splice form of GLS1, referred to as glutaminase C or “GAC”, has been identified recently and has similar activity characteristics of GLS1. In certain embodiments, the compounds may selectively inhibit GLS1, GLS2 and GAC. In certain preferred embodiments, the compounds selectively inhibit GLS1 and GAC.

In addition to serving as the basic building blocks of protein synthesis, amino acids have been shown to contribute to many processes critical for growing and dividing cells, and this is particularly true for cancer cells. Nearly all definitions of cancer include reference to dysregulated proliferation. Numerous studies on glutamine metabolism in cancer indicate that many tumors are avid glutamine consumers. Accordingly, in certain embodiments, the invention provides methods for treating or preventing cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection comprising orally administering a glutaminase inhibitor (*e.g.*, a compound of any of formulas I-III or formulas IV-VI (*e.g.*, a compound of any of formulas (IV), (IVa), (IVb), (V), (Va), (Vb), (Vc), (VI), (VIa), (VIb), or (VIc)), or a pharmaceutically acceptable salt thereof), preferably wherein the compound is administered with a meal.

In certain embodiments, the cancer may be one or a variant of Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Adrenocortical Carcinoma, AIDS-Related Cancers (Kaposi Sarcoma and Lymphoma), Anal Cancer, Appendix Cancer, Atypical Teratoid/Rhabdoid Tumor, Basal Cell Carcinoma, Bile Duct Cancer (including Extrahepatic), Bladder Cancer, Bone Cancer (including Osteosarcoma and Malignant Fibrous Histiocytoma), Brain Tumor (such as Astrocytomas, Brain and Spinal Cord Tumors, Brain Stem Glioma, Central Nervous System Atypical Teratoid/Rhabdoid Tumor, Central Nervous System Embryonal Tumors, Craniopharyngioma, Ependymoblastoma,

Ependymoma, Medulloblastoma, Medulloepithelioma, Pineal Parenchymal Tumors of Intermediate Differentiation, Supratentorial Primitive Neuroectodermal Tumors and Pineoblastoma), Breast Cancer, Bronchial Tumors, Burkitt Lymphoma, Basal Cell Carcinoma, Bile Duct Cancer (including Extrahepatic), Bladder Cancer, Bone Cancer (including Osteosarcoma and Malignant Fibrous Histiocytoma), Carcinoid Tumor, Carcinoma of Unknown Primary, Central Nervous System (such as Atypical Teratoid/Rhabdoid Tumor, Embryonal Tumors and Lymphoma), Cervical Cancer, Childhood Cancers, Chordoma, Chronic Lymphocytic Leukemia (CLL), Chronic Myelogenous Leukemia (CML), Chronic Myeloproliferative Disorders, Colon Cancer, Colorectal Cancer, Craniopharyngioma, Cutaneous T-Cell Lymphoma (Mycosis Fungoides and Sézary Syndrome), Duct, Bile (Extrahepatic), Ductal Carcinoma In Situ (DCIS), Embryonal Tumors (Central Nervous System), Endometrial Cancer, Ependymoblastoma, Ependymoma, Esophageal Cancer, Esthesioneuroblastoma, Ewing Sarcoma Family of Tumors, Extracranial Germ Cell Tumor, Extragenadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer (like Intraocular Melanoma, Retinoblastoma), Fibrous Histiocytoma of Bone (including Malignant and Osteosarcoma) Gallbladder Cancer, Gastric (Stomach) Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Stromal Tumors (GIST), Germ Cell Tumor (Extracranial, Extragenadal, Ovarian), Gestational Trophoblastic Tumor, Glioma, Hairy Cell Leukemia, Head and Neck Cancer, Heart Cancer, Hepatocellular (Liver) Cancer, Histiocytosis, Langerhans Cell, Hodgkin Lymphoma, Hypopharyngeal Cancer, Intraocular Melanoma, Islet Cell Tumors (Endocrine, Pancreas), Kaposi Sarcoma, Kidney (including Renal Cell), Langerhans Cell Histiocytosis, Laryngeal Cancer, Leukemia (including Acute Lymphoblastic (ALL), Acute Myeloid (AML), Chronic Lymphocytic (CLL), Chronic Myelogenous (CML), Hairy Cell), Lip and Oral Cavity Cancer, Liver Cancer (Primary), Lobular Carcinoma In Situ (LCIS), Lung Cancer (Non-Small Cell and Small Cell), Lymphoma (AIDS-Related, Burkitt, Cutaneous T-Cell (Mycosis Fungoides and Sézary Syndrome), Hodgkin, Non-Hodgkin, Primary Central Nervous System (CNS), Macroglobulinemia, Waldenström, Male Breast Cancer, Malignant Fibrous Histiocytoma of Bone and Osteosarcoma, Medulloblastoma, Medulloepithelioma, Melanoma (including Intraocular (Eye)), Merkel Cell Carcinoma, Mesothelioma (Malignant), Metastatic Squamous Neck Cancer with Occult Primary, Midline Tract Carcinoma Involving *NUT* Gene, Mouth Cancer, Multiple Endocrine Neoplasia Syndromes, Multiple Myeloma/Plasma Cell Neoplasm, Mycosis Fungoides, Myelodysplastic

Syndromes, Myelodysplastic/Myeloproliferative Neoplasms, Myelogenous Leukemia, Chronic (CML), Myeloid Leukemia, Acute (AML), Myeloma and Multiple Myeloma, Myeloproliferative Disorders (Chronic), Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin Lymphoma, Non-Small Cell Lung
 5 Cancer, Oral Cancer, Oral Cavity Cancer, Lip and, Oropharyngeal Cancer, Osteosarcoma and Malignant Fibrous Histiocytoma of Bone, Ovarian Cancer (such as Epithelial, Germ Cell Tumor, and Low Malignant Potential Tumor), Pancreatic Cancer (including Islet Cell Tumors), Papillomatosis, Paraganglioma, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, Penile Cancer, Pharyngeal Cancer, Pheochromocytoma, Pineal
 10 Parenchymal Tumors of Intermediate Differentiation, Pineoblastoma and Supratentorial Primitive Neuroectodermal Tumors, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Pleuropulmonary Blastoma, Pregnancy and Breast Cancer, Primary Central Nervous System (CNS) Lymphoma, Prostate Cancer, Rectal Cancer, Renal Cell (Kidney) Cancer, Renal Pelvis and Ureter, Transitional Cell Cancer, Retinoblastoma,
 15 Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoma (like Ewing Sarcoma Family of Tumors, Kaposi, Soft Tissue, Uterine), Sézary Syndrome, Skin Cancer (such as Melanoma, Merkel Cell Carcinoma, Nonmelanoma), Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Cell Carcinoma, Squamous Neck Cancer with Occult Primary, Metastatic, Stomach (Gastric) Cancer, Supratentorial Primitive Neuroectodermal
 20 Tumors, T-Cell Lymphoma (Cutaneous, Mycosis Fungoides and Sézary Syndrome), Testicular Cancer, Throat Cancer, Thymoma and Thymic Carcinoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Trophoblastic Tumor (Gestational), Unknown Primary, Unusual Cancers of Childhood, Ureter and Renal Pelvis, Transitional Cell Cancer, Urethral Cancer, Uterine Cancer, Endometrial, Uterine Sarcoma,
 25 Waldenström Macroglobulinemia and Wilms Tumor.

In some instances, oncogenic mutations promote glutamine metabolism. Cells expressing oncogenic K-Ras exhibit increased utilization of glutamine. In certain embodiments, the cancer cells have a mutated K-Ras gene. In certain embodiments, the cancer is associated with tissue of the bladder, bone marrow, breast, colon, kidney, liver,
 30 lung, ovary, pancreas, prostate, skin or thyroid. The c-Myc gene is known to be altered in numerous cancers. Increased Myc protein expression has been correlated with increased expression of glutaminase, leading to up-regulation of glutamine metabolism. In certain embodiments, the cancer cells have an oncogenic c-Myc gene or elevated Myc protein

expression. In some embodiments, the cancer is associated with tissue of the bladder, bone, bowel, breast, central nervous system (like brain), colon, gastric system (such as stomach and intestine), liver, lung, ovary, prostate, muscle, and skin.

For example, the most common type of renal cell carcinoma (RCC), clear cell type (ccRCC), is closely associated with von Hippel-Lindau (VHL) gene mutations. VHL-deficient cell lines have been shown to have an increased requirement for glutamine due to a loss of ability to make fatty acids from glucose (Metallo et al, Nature 2013). This dependency on glutamine makes the cells susceptible to glutaminase inhibitors (Gameiro et al., Cell Metab. 2013). Certain embodiments of the invention relate to the use of the compounds described herein for the treatment of VHL-deficient carcinomas. In certain embodiments the cancer is RCC. In certain embodiments the cancer is ccRCC.

EGFR (Epidermal growth factor receptor) is the cell-surface receptor for members of the epidermal growth factor (EGF) family of extracellular protein ligands. Mutations associated with EGFR overexpression have been associated with certain cancers, including lung cancers. Approximately 10% of non-small cell lung cancer patients in the United States, and approximately 35% of nsclc patients in East Asia have tumors associated with an EGFR mutation. Typically the EGFR mutation occurs in a region of the gene that encodes a portion of the EGFR kinase domain. Usually, such mutations result in gene amplification, increased kinase activity of EGFR, and hyperactivation of downstream pro-survival signaling pathways. See A. Kuykendall, et al. ("Advanced EGFR Mutation-Positive Non-Small Cell Lung Cancer: Case Report, Literature Review, and Treatment Recommendations" Cancer Control, 2014, V. 21, No. 1, 67-73) for a review about NSCLC and EGFR mutations.

Glutaminase inhibition may also be effective in certain rare cancers that have mutations or deletions of the TCA cycle enzymes including fumarate hydratase (FH), succinate dehydrogenase (SDH), and isocitrate dehydrogenase (IDH). Glutamate feeds into the TCA cycle upstream of where these mutations or deletions occur. Published studies indicate that glutamine metabolism is important in the synthesis of fumarate and succinate. In addition to FH and SDH, there is evidence that glutamine contributes to the production of 2-hydroxyglutamate, another driver of tumor formation that accumulates in patients with tumors harboring mutations in the enzyme isocitrate dehydrogenase. Thus, inhibitors of glutaminase may block the effect of these mutations or deletions by limiting the availability of upstream starting materials. Rare mutations in FH lead to the development of hereditary

leiomyomatosis and renal cell cancer (HLRCC), where patients can develop tumors of the skin, uterus and kidneys. Some gastrointestinal stromal tumors (GIST), arise from the lack of expression of SDH, and are often hereditary. Other SDH-loss-of-function mutations are found in patients exhibiting a rare head and neck cancer known as paraganglioma, and a
5 rare adrenal or extra-adrenal cancer known as pheochromocytoma, and a rare subset clear cell RCC. Some patients with glioma, a form of brain cancer, chondrosarcoma, a rare bone cancer, cholangiocarcinoma, a rare bile duct tumor, AML, or high risk myelodysplasia/myeloproliferative disorders, a group of blood disorders, have IDH1 or IDH2 driver mutations.

10 In certain embodiments of the invention, compounds described herein can be used for the treatment of disease identified with a FH, SDH or IDH (1 and 2) mutation. For example, in certain embodiments, the disease is an isocitrate dehydrogenase (IDH)-mutant solid tumor. In certain embodiments the disease is hereditary leiomyomatosis or renal cell cancer (HLRCC). In certain embodiments the disease is GIST (e.g., SDH-deficient GIST),
15 paraganglioma, pheochromocytoma, or clear cell RCC. In certain embodiments, the disease is glioma, chondrosarcoma, cholangiocarcinoma, acute myeloid leukemia (AML), or myelodysplasia/myeloproliferative disorder. In certain embodiments, the disease is mesothelioma. In certain embodiments, the disease is multiple myeloma.

In certain embodiments, the cancer is a non-small cell lung cancer having a KRAS
20 or EGFR mutation.

While many cancer cells depend on exogenous glutamine for survival, the degree of glutamine dependence among tumor cell subtypes may make a population of cells more susceptible to the reduction of glutamine. As an example, gene expression analysis of breast cancers has identified five intrinsic subtypes (luminal A, luminal B, basal, HER2+,
25 and normal-like). Although glutamine deprivation has an impact on cell growth and viability, basal-like cells appear to be more sensitive to the reduction of exogenous glutamine. This supports the concept that glutamine is a very important energy source in basal-like breast cancer cell lines, and suggests that inhibition of the glutaminase enzyme would be beneficial in the treatment of breast cancers comprised of basal-like cells. Triple-
30 negative breast cancer (TNBC) is characterized by a lack of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 expression. It has a higher rate of relapse following chemotherapy, and a poorer prognosis than with the other breast cancer subtypes. Interestingly, there appears to be significant similarities in metabolic profiling

between TNBC cells and basal-like breast cancer cells. Therefore, an embodiment of the invention is the use of the compounds described herein for the treatment of TNBC, basal-type breast cancers, or claudin-low breast cancers.

5 In certain embodiments, the invention provides methods for treating colorectal cancer. In certain embodiments, the invention provides methods for treating endocrine cancer, such as adrenal cortex adenoma, adrenal cortex carcinoma, adrenal gland pheochromocytoma, and parathyroid gland adenoma.

In certain embodiments, the cancer is melanoma.

10 Cachexia, the massive loss of muscle mass, is often associated with poor performance status and high mortality rate of cancer patients. A theory behind this process is that tumors require more glutamine than is normally supplied by diet, so muscle, a major source of glutamine, starts to breakdown in order to supply enough nutrient to the tumor. Thus, inhibition of glutaminase may reduce the need to breakdown muscle. An embodiment of the invention is the use of the present compounds to prevent, inhibit or
15 reduce cachexia.

The most common neurotransmitter is glutamate, derived from the enzymatic conversion of glutamine via glutaminase. High levels of glutamate have been shown to be neurotoxic. Following traumatic insult to neuronal cells, there occurs a rise in neurotransmitter release, particularly glutamate. Accordingly, inhibition of glutaminase has
20 been hypothesized as a means of treatment following an ischemic insult, such as stroke (PCT Publication No. WO 99/09825). Huntington's disease is a progressive, fatal neurological condition. In genetic mouse models of Huntington's disease, it was observed that the early manifestation of the disease correlated with dysregulated glutamate release. In HIV-associated dementia, HIV infected macrophages exhibit upregulated glutaminase
25 activity and increased glutamate release, leading to neuronal damage. Similarly, in another neurological disease, the activated microglia in Rett Syndrome release glutamate causing neuronal damage. The release of excess glutamate has been associated with the up-regulation of glutaminase. In mice bred to have reduced glutaminase levels, sensitivity to psychotic-stimulating drugs, such as amphetamines, was dramatically reduced, thus
30 suggesting that glutaminase inhibition may be beneficial in the treatment of schizophrenia. Bipolar disorder is a devastating illness that is marked by recurrent episodes of mania and depression. This disease is treated with mood stabilizers such as lithium and valproate; however, chronic use of these drugs appears to increase the abundance of glutamate

receptors, which may lead to a decrease in the drug's effectiveness over time. Thus, an alternative treatment may be to reduce the amount of glutamate by inhibiting glutaminase. This may or may not be in conjunction with the mood stabilizers. Memantine, a partial antagonist of N-methyl-D-aspartate receptor (NMDAR), is an approved therapeutic in the treatment of Alzheimer's disease. Currently, research is being conducted looking at memantine as a means of treating vascular dementia and Parkinson's disease. Since memantine has been shown to partially block the NMDA glutamate receptor also, it is not unreasonable to speculate that decreasing glutamate levels by inhibiting glutaminase could also treat Alzheimer's disease, vascular dementia and Parkinson's disease. Alzheimer's disease, bipolar disorder, HIV-associated dementia, Huntington's disease, ischemic insult, Parkinson's disease, schizophrenia, stroke, traumatic insult and vascular dementia are but a few of the neurological diseases that have been correlated to increased levels of glutamate. Thus, inhibiting glutaminase with a compound described herein can reduce or prevent neurological diseases. Therefore, in certain embodiments, the compounds may be used for the treatment or prevention of neurological diseases.

Activation of T lymphocytes induces cell growth, proliferation, and cytokine production, thereby placing energetic and biosynthetic demands on the cell. Glutamine serves as an amine group donor for nucleotide synthesis, and glutamate, the first component in glutamine metabolism, plays a direct role in amino acid and glutathione synthesis, as well as being able to enter the Krebs cycle for energy production. Mitogen-induced T cell proliferation and cytokine production require high levels of glutamine metabolism, thus inhibiting glutaminase may serve as a means of immune modulation. In multiple sclerosis, an inflammatory autoimmune disease, the activated microglia exhibit up-regulated glutaminase and release increased levels of extracellular glutamate. Glutamine levels are lowered by sepsis, injury, burns, surgery and endurance exercise. These situations put the individual at risk of immunosuppression. In fact, in general, glutaminase gene expression and enzyme activity are both increased during T cell activity. Patients given glutamine following bone marrow transplantation resulted in a lower level of infection and reduced graft versus host disease. T cell proliferation and activation is involved in many immunological diseases, such as inflammatory bowel disease, Crohn's disease, sepsis, psoriasis, arthritis (including rheumatoid arthritis), multiple sclerosis, graft versus host disease, infections, lupus and diabetes. In an embodiment of the invention, the compounds described herein can be used to treat or prevent immunological diseases.

Hepatic encephalopathy (HE) represents a series of transient and reversible neurologic and psychiatric dysfunction in patients with liver disease or portosystemic shunting. HE is not a single clinical entity and may reflect reversible metabolic encephalopathy, brain atrophy, brain edema, or a combination of these factors; however, the current hypothesis is that the accumulation of ammonia, mostly derived from the intestine, plays a key role in the pathophysiology. The deamination of glutamine in small intestine, renal and muscle synthesis all contribute to ammonia production. Impaired hepatic clearance caused by hepatocellular clearance or portosystemic shunting causes increased accumulation of ammonia. Ammonia toxicity affects astrocytes in the brain via glutamine synthetase, which metabolizes the ammonia to produce increased glutamine. Glutamine, in turn, attracts water into the astrocytes, leading to swelling and oxidative dysfunction of the mitochondria. The resulting cerebral edema is thought to contribute to neurologic dysfunction seen in HE. In an embodiment of the invention, the compounds described herein can be used to treat or prevent HE.

Primary sensory neurons in the dorsal root ganglion have been shown to elevate their glutaminase enzyme activity following inflammation. It is believed that the resulting increased glutamate production contributes to both central and peripheral sensitization, identified as pain. An aspect of the invention is the use of the present compounds herein for the treatment or diminishment of pain. In certain embodiments, the pain can be neuropathic pain, chemotherapy-induced pain or inflammatory pain.

High blood glucose levels, high insulin levels, and insulin resistance are risk factors for developing diabetes mellitus. Similarly, high blood pressure is a risk factor for developing cardiovascular disease. In a recent report from a large human cohort study, these four risk factors were inversely correlated with glutamine-to-glutamate ratios in the blood stream. Furthermore, plasma glutamine-to-glutamate ratios were inversely correlated with the eventual incidence of diabetes mellitus over 12 years. Experiments with animal models were consistent with these findings. Mice fed glutamine-rich diets exhibited lower blood glucose levels in a glucose tolerance test after 6 hours of fasting, and intraperitoneal injection of glutamine into mice rapidly decreased their blood pressure. Therefore, it is plausible that glutaminase inhibitors, which cause increased glutamine levels and decrease glutamate levels, would decrease the incidence of diabetes mellitus and cardiovascular disease. In particular, the liver and small intestine are major sites of glutamine utilization in diabetic animals, and glutaminase activity is higher than normal in these organs in

streptozotocin-induced diabetic rats. In an embodiment of the invention, the compounds described herein can be used to treat diabetes. In another embodiment of the invention, the present compounds can be used to reduce high blood pressure.

- In certain embodiments, the method of treating or preventing cancer, a
- 5 myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection may comprise orally administering a compound of the invention, *e.g.*, a compound of any of formulas I-III or formulas IV-VI (*e.g.*, a glutaminase inhibitor of any of formulas (IV), (IVa), (IVb), (V), (Va), (Vb), (Vc), (VI), (VIa), (VIb), or (VIc)), or a pharmaceutically acceptable salt thereof, *e.g.*, with a meal, conjointly with a chemotherapeutic agent.
- 10 Chemotherapeutic agents that may be conjointly administered with compounds of the invention include: ABT-263, aminoglutethimide, amsacrine, anastrozole, asparaginase, azacitidine, AZD5363, Bacillus Calmette–Guérin vaccine (bcg), bicalutamide, bleomycin, bortezomib, buserelin, busulfan, campothecin, capecitabine, carboplatin, carfilzomib, carmustine, chlorambucil, chloroquine, cisplatin, cladribine, clodronate, cobimetinib,
- 15 colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, demethoxyviridin, dexamethasone, dichloroacetate, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil (*e.g.*, 5-fluorouracil), fluoxymesterone, flutamide, gemcitabine, genistein,
- 20 goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ixabepilone, lenalidomide, letrozole, leucovorin, leuprolide, levamisole, lomustine, lonidamine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, metformin, methotrexate, miltefosine, mitomycin, mitotane, mitoxantrone, MK-2206, nilutamide, nocodazole, octreotide, oxaliplatin, olaparib, paclitaxel, pamidronate,
- 25 pazopanib, pentostatin, perifosine, PF-04691502, plicamycin, pomalidomide, porfimer, procarbazine, raltitrexed, rituximab, romidepsin, rucaparib, selumetinib, sorafenib, streptozocin, sunitinib, suramin, talazoparib, tamoxifen, temozolomide, temsirolimus, teniposide, testosterone, thioguanine, thalidomide, thiotepa, titanocene dichloride, topotecan, trametinib, trastuzumab, tretinoin, veliparib, vinblastine, vincristine, vindesine,
- 30 vinorelbine and vorinostat (SAHA).

In certain embodiments, the one or more additional chemotherapeutic agents are selected from azacitidine, bortezomib, capecitabine, carboplatin, carfilzomib, cyclophosphamide, daunorubicin, dexamethasone, docetaxel, doxorubicin, epirubicin,

eribulin, erlotinib, everolimus, fluorouracil, gemcitabine, ixabepilone, lenalidomide, methotrexate, mitoxantrone, mutamycin, paclitaxel, pomalidomide, rituximab, thiotepa, vincristine, and vinorelbine.

In certain embodiments, the one or more additional chemotherapeutic agents are selected from azacitidine, dexamethasone, docetaxel, erlotinib, everolimus, paclitaxel and pomalidomide.

Many combination therapies have been developed for the treatment of cancer. In certain embodiments, compounds of the invention may be conjointly administered with a combination therapy. Examples of combination therapies with which compounds of the invention may be conjointly administered are included in Table 3.

Table 3: Exemplary combinatorial therapies for the treatment of cancer.

Name	Therapeutic agents
ABV	Doxorubicin, Bleomycin, Vinblastine
ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
AC (Breast)	Doxorubicin, Cyclophosphamide
AC (Sarcoma)	Doxorubicin, Cisplatin
AC (Neuroblastoma)	Cyclophosphamide, Doxorubicin
ACE	Cyclophosphamide, Doxorubicin, Etoposide
ACe	Cyclophosphamide, Doxorubicin
AD	Doxorubicin, Dacarbazine
AP	Doxorubicin, Cisplatin
ARAC-DNR	Cytarabine, Daunorubicin
B-CAVe	Bleomycin, Lomustine, Doxorubicin, Vinblastine
BCVPP	Carmustine, Cyclophosphamide, Vinblastine, Procarbazine, Prednisone
BEACOPP	Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone, Filgrastim
BEP	Bleomycin, Etoposide, Cisplatin
BIP	Bleomycin, Cisplatin, Ifosfamide, Mesna
BOMP	Bleomycin, Vincristine, Cisplatin, Mitomycin
CA	Cytarabine, Asparaginase
CABO	Cisplatin, Methotrexate, Bleomycin, Vincristine

Name	Therapeutic agents
CAF	Cyclophosphamide, Doxorubicin, Fluorouracil
CAL-G	Cyclophosphamide, Daunorubicin, Vincristine, Prednisone, Asparaginase
CAMP	Cyclophosphamide, Doxorubicin, Methotrexate, Procarbazine
CAP	Cyclophosphamide, Doxorubicin, Cisplatin
CaT	Carboplatin, Paclitaxel
CAV	Cyclophosphamide, Doxorubicin, Vincristine
CAVE ADD	CAV and Etoposide
CA-VP16	Cyclophosphamide, Doxorubicin, Etoposide
CC	Cyclophosphamide, Carboplatin
CDDP/VP-16	Cisplatin, Etoposide
CEF	Cyclophosphamide, Epirubicin, Fluorouracil
CEPP(B)	Cyclophosphamide, Etoposide, Prednisone, with or without/ Bleomycin
CEV	Cyclophosphamide, Etoposide, Vincristine
CF	Cisplatin, Fluorouracil or Carboplatin Fluorouracil
CHAP	Cyclophosphamide or Cyclophosphamide, Altretamine, Doxorubicin, Cisplatin
ChlVPP	Chlorambucil, Vinblastine, Procarbazine, Prednisone
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CHOP-BLEO	Add Bleomycin to CHOP
CISCA	Cyclophosphamide, Doxorubicin, Cisplatin
CLD-BOMP	Bleomycin, Cisplatin, Vincristine, Mitomycin
CMF	Methotrexate, Fluorouracil, Cyclophosphamide
CMFP	Cyclophosphamide, Methotrexate, Fluorouracil, Prednisone
CMFVP	Cyclophosphamide, Methotrexate, Fluorouracil, Vincristine, Prednisone
CMV	Cisplatin, Methotrexate, Vinblastine
CNF	Cyclophosphamide, Mitoxantrone, Fluorouracil

Name	Therapeutic agents
CNOP	Cyclophosphamide, Mitoxantrone, Vincristine, Prednisone
COB	Cisplatin, Vincristine, Bleomycin
CODE	Cisplatin, Vincristine, Doxorubicin, Etoposide
COMLA	Cyclophosphamide, Vincristine, Methotrexate, Leucovorin, Cytarabine
COMP	Cyclophosphamide, Vincristine, Methotrexate, Prednisone
Cooper Regimen	Cyclophosphamide, Methotrexate, Fluorouracil, Vincristine, Prednisone
COP	Cyclophosphamide, Vincristine, Prednisone
COPE	Cyclophosphamide, Vincristine, Cisplatin, Etoposide
COPP	Cyclophosphamide, Vincristine, Procarbazine, Prednisone
CP(Chronic lymphocytic leukemia)	Chlorambucil, Prednisone
CP (Ovarian Cancer)	Cyclophosphamide, Cisplatin
CT	Cisplatin, Paclitaxel
CVD	Cisplatin, Vinblastine, Dacarbazine
CVI	Carboplatin, Etoposide, Ifosfamide, Mesna
CVP	Cyclophosphamide, Vincristine, Prednisone
CVPP	Lomustine, Procarbazine, Prednisone
CYVADIC	Cyclophosphamide, Vincristine, Doxorubicin, Dacarbazine
DA	Daunorubicin, Cytarabine
DAT	Daunorubicin, Cytarabine, Thioguanine
DAV	Daunorubicin, Cytarabine, Etoposide
DCT	Daunorubicin, Cytarabine, Thioguanine
DHAP	Cisplatin, Cytarabine, Dexamethasone
DI	Doxorubicin, Ifosfamide
DTIC/Tamoxifen	Dacarbazine, Tamoxifen
DVP	Daunorubicin, Vincristine, Prednisone
EAP	Etoposide, Doxorubicin, Cisplatin
EC	Etoposide, Carboplatin

Name	Therapeutic agents
EFP	Etoposide, Fluorouracil, Cisplatin
ELF	Etoposide, Leucovorin, Fluorouracil
EMA 86	Mitoxantrone, Etoposide, Cytarabine
EP	Etoposide, Cisplatin
EVA	Etoposide, Vinblastine
FAC	Fluorouracil, Doxorubicin, Cyclophosphamide
FAM	Fluorouracil, Doxorubicin, Mitomycin
FAMTX	Methotrexate, Leucovorin, Doxorubicin
FAP	Fluorouracil, Doxorubicin, Cisplatin
F-CL	Fluorouracil, Leucovorin
FEC	Fluorouracil, Cyclophosphamide, Epirubicin
FED	Fluorouracil, Etoposide, Cisplatin
FL	Flutamide, Leuprolide
FZ	Flutamide, Goserelin acetate implant
HDMTX	Methotrexate, Leucovorin
Hexa-CAF	Altretamine, Cyclophosphamide, Methotrexate, Fluorouracil
ICE-T	Ifosfamide, Carboplatin, Etoposide, Paclitaxel, Mesna
IDMTX/6-MP	Methotrexate, Mercaptopurine, Leucovorin
IE	Ifosfamide, Etoposide, Mesna
IfoVP	Ifosfamide, Etoposide, Mesna
IPA	Ifosfamide, Cisplatin, Doxorubicin
M-2	Vincristine, Carmustine, Cyclophosphamide, Prednisone, Melphalan
MAC-III	Methotrexate, Leucovorin, Dactinomycin, Cyclophosphamide
MACC	Methotrexate, Doxorubicin, Cyclophosphamide, Lomustine
MACOP-B	Methotrexate, Leucovorin, Doxorubicin, Cyclophosphamide, Vincristine, Bleomycin, Prednisone
MAID	Mesna, Doxorubicin, Ifosfamide, Dacarbazine

Name	Therapeutic agents
m-BACOD	Bleomycin, Doxorubicin, Cyclophosphamide, Vincristine, Dexamethasone, Methotrexate, Leucovorin
MBC	Methotrexate, Bleomycin, Cisplatin
MC	Mitoxantrone, Cytarabine
MF	Methotrexate, Fluorouracil, Leucovorin
MICE	Ifosfamide, Carboplatin, Etoposide, Mesna
MINE	Mesna, Ifosfamide, Mitoxantrone, Etoposide
mini-BEAM	Carmustine, Etoposide, Cytarabine, Melphalan
MOBP	Bleomycin, Vincristine, Cisplatin, Mitomycin
MOP	Mechlorethamine, Vincristine, Procarbazine
MOPP	Mechlorethamine, Vincristine, Procarbazine, Prednisone
MOPP/ABV	Mechlorethamine, Vincristine, Procarbazine, Prednisone, Doxorubicin, Bleomycin, Vinblastine
MP (multiple myeloma)	Melphalan, Prednisone
MP (prostate cancer)	Mitoxantrone, Prednisone
MTX/6-MO	Methotrexate, Mercaptopurine
MTX/6-MP/VP	Methotrexate, Mercaptopurine, Vincristine, Prednisone
MTX-CDDPAdr	Methotrexate, Leucovorin, Cisplatin, Doxorubicin
MV (breast cancer)	Mitomycin, Vinblastine
MV (acute myelocytic leukemia)	Mitoxantrone, Etoposide
M-VAC Methotrexate	Vinblastine, Doxorubicin, Cisplatin
MVP Mitomycin	Vinblastine, Cisplatin
MVPP	Mechlorethamine, Vinblastine, Procarbazine, Prednisone
NFL	Mitoxantrone, Fluorouracil, Leucovorin
NOVP	Mitoxantrone, Vinblastine, Vincristine
OPA	Vincristine, Prednisone, Doxorubicin
OPPA	Add Procarbazine to OPA.
PAC	Cisplatin, Doxorubicin
PAC-I	Cisplatin, Doxorubicin, Cyclophosphamide

Name	Therapeutic agents
PA-CI	Cisplatin, Doxorubicin
PC	Paclitaxel, Carboplatin or Paclitaxel, Cisplatin
PCV	Lomustine, Procarbazine, Vincristine
PE	Paclitaxel, Estramustine
PFL	Cisplatin, Fluorouracil, Leucovorin
POC	Prednisone, Vincristine, Lomustine
ProMACE	Prednisone, Methotrexate, Leucovorin, Doxorubicin, Cyclophosphamide, Etoposide
ProMACE/cytaBOM	Prednisone, Doxorubicin, Cyclophosphamide, Etoposide, Cytarabine, Bleomycin, Vincristine, Methotrexate, Leucovorin, Cotrimoxazole
PRoMACE/MOPP	Prednisone, Doxorubicin, Cyclophosphamide, Etoposide, Mechlorethamine, Vincristine, Procarbazine, Methotrexate, Leucovorin
Pt/VM	Cisplatin, Teniposide
PVA	Prednisone, Vincristine, Asparaginase
PVB	Cisplatin, Vinblastine, Bleomycin
PVDA	Prednisone, Vincristine, Daunorubicin, Asparaginase
SMF	Streptozocin, Mitomycin, Fluorouracil
TAD	Mechlorethamine, Doxorubicin, Vinblastine, Vincristine, Bleomycin, Etoposide, Prednisone
TCF	Paclitaxel, Cisplatin, Fluorouracil
TIP	Paclitaxel, Ifosfamide, Mesna, Cisplatin
TTT	Methotrexate, Cytarabine, Hydrocortisone
Topo/CTX	Cyclophosphamide, Topotecan, Mesna
VAB-6	Cyclophosphamide, Dactinomycin, Vinblastine, Cisplatin, Bleomycin
VAC	Vincristine, Dactinomycin, Cyclophosphamide
VACAdr	Vincristine, Cyclophosphamide, Doxorubicin, Dactinomycin, Vincristine
VAD	Vincristine, Doxorubicin, Dexamethasone

Name	Therapeutic agents
VATH	Vinblastine, Doxorubicin, Thiotepa, Flouxymesterone
VBAP	Vincristine, Carmustine, Doxorubicin, Prednisone
VBCMP	Vincristine, Carmustine, Melphalan, Cyclophosphamide, Prednisone
VC	Vinorelbine, Cisplatin
VCAP	Vincristine, Cyclophosphamide, Doxorubicin, Prednisone
VD	Vinorelbine, Doxorubicin
VelP	Vinblastine, Cisplatin, Ifosfamide, Mesna
VIP	Etoposide, Cisplatin, Ifosfamide, Mesna
VM	Mitomycin, Vinblastine
VMCP	Vincristine, Melphalan, Cyclophosphamide, Prednisone
VP	Etoposide, Cisplatin
V-TAD	Etoposide, Thioguanine, Daunorubicin, Cytarabine
5 + 2	Cytarabine, Daunorubicin, Mitoxantrone
7 + 3	Cytarabine with/, Daunorubicin or Idarubicin or Mitoxantrone
"8 in 1"	Methylprednisolone, Vincristine, Lomustine, Procarbazine, Hydroxyurea, Cisplatin, Cytarabine, Dacarbazine

In certain embodiments, the compounds of the invention may be conjointly administered with an immunomodulatory agent. Examples of immunomodulatory agents with which the compounds of the invention may be administered in a combination therapy include granulocyte colony-stimulating factor (G-CSF), interferons, imiquimod, IL-2, IL-7, IL-12, various chemokines, synthetic cytosine phosphate-guanosine (CpG) oligodeoxynucleotides, glucans, and synthetic small molecules such as apremilast, CC-122, CC-11006, CC-10015, lenalidomide, pomalidomide, and thalidomide. In certain embodiments, the immunomodulatory agent is a thalidomide analog, such as those disclosed in WO 1999/46258, WO 2008/033567, WO 2010/093434, WO 2010/093605, WO 2011/100380, and WO 2012/097116.

In certain embodiments, the compounds of the invention may be conjointly administered with an anticancer agent selected from an enzyme inhibitor (such as a kinase inhibitor), a mitotic inhibitor, a DNA-modifying agent, and a cytidine analog. Examples of

anticancer agents with which the compounds of the invention may be administered in a combination therapy include microtubule assembly inhibitors, AKT inhibitors, mTOR inhibitors, MEK inhibitors, RTK inhibitors, ATM inhibitors, ATR inhibitors, PI3K inhibitors, EGFR inhibitors, B-Raf inhibitors, C-kit inhibitors, DNA cross-linking agents, DNA intercalating agents, and cytidine analogs. In certain embodiments, the anticancer agent vincristine, carboplatin, cisplatin, gemcitabine, MK2206, everolimus, trametinib, sunitinib, sorafenib, BEZ235, paclitaxel, docetaxel, erlotinib, selumetinib, sirolimus, trametinib, temsirolimus, pazopanib, or GSK1120212.

The proliferation of cancer cells requires lipid synthesis. Normally, acetyl-coA used for lipid synthesis is formed from a mitochondrial pool of pyruvate that is derived from glycolysis. Yet under hypoxic conditions, such as those normally found in a tumor environment, the conversion of pyruvate to acetyl-coA within the mitochondria is downregulated. Recent studies revealed that under such hypoxic conditions, cells instead largely switch to using a pathway involving the reductive carboxylation of alpha-ketoglutarate to make acetyl-coA for lipid synthesis. The first step in this pathway involves converting glutamine to glutamate via glutaminase enzymes. Subsequently, glutamate is converting to alpha-ketoglutarate, and the resulting alpha-ketoglutarate is converted to isocitrate in a reductive carboxylation step mediated by the isocitrate dehydrogenase enzymes. A switch to this reductive carboxylation pathway also occurs in some renal carcinoma cell lines that contain either impaired mitochondria or an impaired signal for induction of the enzyme responsible for converting glycolytic pyruvate to acetyl-coA. A similar switch occurs in cells exposed to mitochondrial respiratory chain inhibitors such as metformin, rotenone, and antimycin. Therefore, in some embodiments of this invention, we propose using combinations of mitochondrial respiratory chain inhibitors and glutaminase inhibitors to simultaneously increase cancer cells' dependence on glutaminase-dependent pathways for lipid synthesis while inhibiting those very pathways.

The increased dependence on glycolysis in tumor cells is likely because the hypoxic tumor environment impairs mitochondrial respiration. Furthermore, depletion of glucose induces apoptosis in cells transformed with the MYC oncogene. These findings suggest that inhibiting glycolysis would have a therapeutic value in preventing cancer cell proliferation. There are currently many documented glycolytic inhibitors. However, available glycolytic inhibitors are generally not very potent, and thus, high doses are required, which may cause high levels of systemic toxicity. Since cancer cells typically use

both glucose and glutamine at higher levels than normal cells, impairing utilization of each of those metabolites will likely have a synergistic effect. Therefore, in some embodiments of this invention, we propose using combinations of glycolytic pathway inhibitors and glutaminase inhibitors. Such glycolytic inhibitors include 2-deoxyglucose, lonidamine, 3-bromopyruvate, imatinib, oxythiamine, rapamycin, and their pharmacological equivalents. Glycolysis can be inhibited indirectly by depleting NAD⁺ via DNA damage induced by DNA alkylating agents through a pathway activated by poly(ADP-ribose) polymerase. Therefore, in one embodiment of this invention, we propose using a combination of DNA alkylating agents and glutaminase inhibitors. Cancer cells use the pentose phosphate pathway along with the glycolytic pathway to create metabolic intermediates derived from glucose. Therefore, in another embodiment of this invention, we propose using a combination of pentose phosphate inhibitors such as 6-aminonicotinamide along with glutaminase inhibitors.

In certain embodiments, a compound of the invention may be conjointly administered (*e.g.*, orally administered, with a meal) with non-chemical methods of cancer treatment. In certain embodiments, a compound of the invention may be conjointly administered with radiation therapy. In certain embodiments, a compound of the invention may be conjointly administered with surgery, with thermoablation, with focused ultrasound therapy, with cryotherapy, or with any combination of these.

In certain embodiments, different compounds of the invention may be conjointly administered with one or more other compounds of the invention. Moreover, such combinations may be conjointly administered with other therapeutic agents, such as other agents suitable for the treatment of cancer, immunological or neurological diseases, such as the agents identified above.

In certain embodiments, the method of treating or preventing cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection may comprise orally administering a compound of the invention, *e.g.*, a glutaminase inhibitor of any of formulas I-III or formulas IV-VI (*e.g.*, a compound of any of formulas (IV), (IVa), (IVb), (V), (Va), (Vb), (Vc), (VI), (VIa), (VIb), or (VIc)), or a pharmaceutically acceptable salt thereof, *e.g.*, with a meal, conjointly with an immunomodulatory agent.

In certain embodiments, conjointly administering the immunomodulatory agent and a compound of the invention (*i.e.*, a glutaminase inhibitor) provides improved efficacy

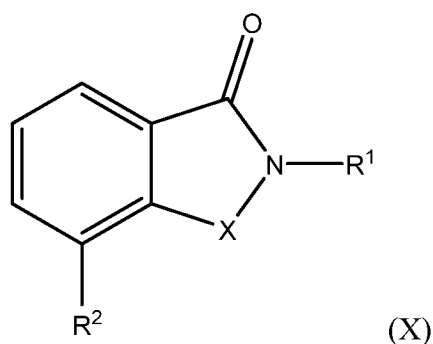
relative to individual administration of the immunomodulatory agent or glutaminase inhibitor as a single agent.

In certain embodiments, the conjoint administration of the immunomodulatory agent and glutaminase inhibitor provides an additive effect.

- 5 In certain embodiments, the conjoint administration of the immunomodulatory agent and glutaminase inhibitor provides a synergistic effect.

In certain embodiments of the invention, the immunomodulatory agent is administered simultaneously with the glutaminase inhibitor. In certain embodiments the immunomodulatory agent is administered within about 5 minutes to within about 168 hours
10 prior or after of the glutaminase inhibitor.

In certain embodiments, the immunomodulatory agent has a structure of Formula X:

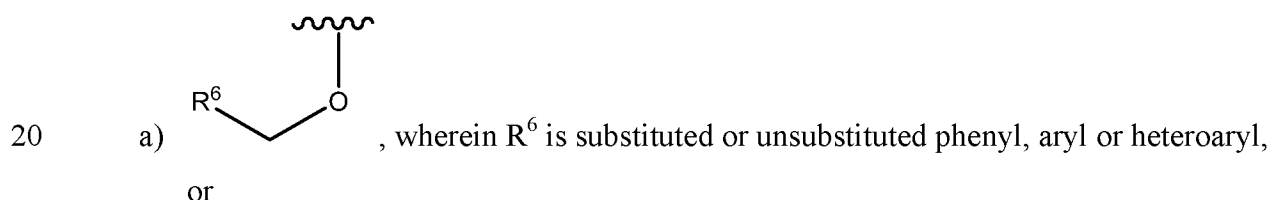


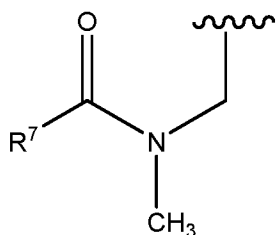
or a pharmaceutically acceptable salt, prodrug, and/or stereoisomer thereof, wherein:

X is C=O or CH₂;

- 15 R¹ is heterocyclyl, such as 2,6-dioxopiperidin-3-yl, or aralkyl, such as a sulfonyl-substituted aralkyl, and

R² is independently a hydrogen, an amino group, an acylamino group, an alkylamino group, or is one of the following moieties:





b) , wherein R⁷ is C₁-C₆ alkyl, cycloalkyl, NH-Ar, where Ar is phenyl or substituted phenyl, or NR⁸R⁹, where R⁸ and R⁹ may be independently H or C₁-C₆-alkyl.

In certain embodiments, the immunomodulatory agent is apremilast, lenalidomide,
5 pomalidomide, thalidomide, CC-11006, or CC-10015.

In certain embodiments, the cancer being treated by the methods of the invention is resistant to an immunodulatory agent. In certain embodiments, the cancer is resistant to a compound having the structure of formula (X). In certain embodiments, the cancer is resistant to apremilast, lenalidomide, pomalidomide, thalidomide, CC-11006, or CC-10015.

10 In certain embodiments, the invention provides methods for treating a myeloproliferative disease, comprising orally administering to a subject a glutaminase inhibitor with a meal, wherein the glutaminase inhibitors are described above.

In certain embodiments, the myeloproliferative disease is selected from chronic eosinophilic leukemia, chronic myelogenous leukemia (CML), chronic neutrophilic
15 leukemia, essential thrombocythemia, polycythemia vera, and myelofibrosis.

In certain embodiments, the myeloproliferative disease being treated by the methods of the invention is resistant to an immunodulatory agent. In certain embodiments, the myeloproliferative disease is resistant to a compound having the structure of formula (X). In certain embodiments, the myeloproliferative disease is resistant to apremilast,
20 lenalidomide, pomalidomide, thalidomide, CC-11006, or CC-10015.

In certain embodiments, the invention provides methods for treating or preventing an immune-related disease, comprising orally administering to a subject a glutaminase inhibitor with a meal, wherein the glutaminase inhibitors are described above.

In certain embodiments, the immune-related disease is selected from ankylosing
25 spondylitis, Crohn's disease, erythema nodosum leprosum (ENL), graft versus host disease (GVHD), HIV-associated wasting syndrome, lupus erythematosus, post-polycythemia, psoriasis, psoriatic arthritis, recurrent aphthous ulcers, rheumatoid arthritis (RA), severe recurrent aphthous stomatitis, and systemic sclerosis.

In certain embodiments, the immune-related disease being treated by the methods of the invention is resistant to an immunomodulatory agent. In certain embodiments, the immune-related disease is resistant to a compound having the structure of formula (X). In certain embodiments, the immune-related disease is resistant to apremilast, lenalidomide, pomalidomide, thalidomide, CC-11006, or CC-10015.

The methods of treating or preventing cancer, a myeloproliferative disease, or an immune-related disease can further comprise administration of one or more additional chemotherapeutic agents, described above.

In certain preferred embodiments, the additional chemotherapeutic agent is dexamethasone.

In certain embodiments, the invention provides methods for treating a viral infection with a glutaminase inhibitor, wherein the virus is smallpox, the common cold, measles, chickenpox, hepatitis, influenza, human papilloma virus, shingles, herpes, polio, rabies, ebola, hanta fever, HIV, cold sores, SARS (Severe acute respiratory syndrome), dengue, Epstein-Barr virus, adenovirus, Avian influenza, Influenza virus type A, Influenza virus type B, Measles, Parainfluenza virus, Respiratory syncytial virus (RSV), Rhinoviruses, SARS-CoV, Cocksackie virus, Enterovirus, Poliovirus, Rotavirus, Hepatitis B virus, Hepatitis C virus, bovine viral diarrhea virus (surrogate), herpes simplex 1, herpes simplex 2, human cytomegalovirus, varicella zoster virus, HIV 1, HIV 2, simian immunodeficiency virus, simian human immunodeficiency virus, Avian influenza, Dengue virus, Hantavirus, Hemorrhagic fever virus, Lymphocytic choromeningitis virus, Smallpox virus surrogates (cowpox, monkeypox, rabbitpox), Vaccinia virus, Venezuelan equine encephalomyelitis virus (VEE), West Nile virus, or Yellow fever virus.

III. KITS

In certain embodiments, the present invention provides a kit comprising: a) one or more single dosage forms of a compound of the invention; b) one or more single dosage forms of a chemotherapeutic agent as mentioned above; and c) instructions for the administration of the compound of the invention and the chemotherapeutic agent. The instructions may state that the compound be taken with food. For example, the instructions may state that the compound should be taken after a meal. The instructions may state that the compound should be taken once, twice, or three times a day, *e.g.*, with meals or after meals.

The present invention provides a kit comprising:

- a) a pharmaceutical formulation (*e.g.*, one or more single dosage forms) comprising a compound of the invention; and
- b) instructions for the administration of the pharmaceutical formulation, *e.g.*, for treating or preventing any of the conditions discussed above, wherein the instructions state that the compound should be taken with food or after a meal.

In certain embodiments, the kit further comprises instructions for the administration of the pharmaceutical formulation comprising a compound of the invention conjointly with a chemotherapeutic agent as mentioned above. In certain embodiments, the kit further comprises a second pharmaceutical formulation (*e.g.*, as one or more single dosage forms) comprising a chemotherapeutic agent as mentioned above.

IV. PHARMACEUTICAL COMPOSITIONS

The compositions and methods of the present invention may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or organic esters. The excipients can be chosen, for example, to effect delayed release of an agent. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, or the like.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients.

A pharmaceutical composition (preparation) may be administered to a patient orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets,

capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes). In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein (hereby incorporated by reference).

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the invention, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as

sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition

that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the
5 above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other
10 solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

15 Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan
20 esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof,
25 vegetable oils, such as olive oil, and organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting
30 agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the

compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

For use in the methods of this invention, active compounds can be given per se or as
5 a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of
10 administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment,
15 other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition
20 required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of an active compound used in the compositions and methods of the invention will be that amount of the compound that is the lowest dose
25 effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of
30 the present invention, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general.

In certain embodiments, compounds of the invention may be used alone or
5 conjointly administered with another type of therapeutic agent.

This invention includes the use of pharmaceutically acceptable salts of compounds of the invention in the compositions and methods of the present invention. In certain embodiments, contemplated salts of the invention include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts
10 of the invention include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc
15 salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent
20 of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the
25 compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin,
30 propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

V. METHODS

In some aspects, the invention relates to a method of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection, comprising orally administering a compound of formula I, formula II, formula III, formula IV, formula V, and/or formula VI, wherein the compound is administered with a meal. The compound may be, for example, any one of the compounds listed in tables 1 or 2, or in Appendix A.

In some aspects, the invention relates to a method of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection, comprising orally administering a compound of formula I, formula II, formula III, formula IV, formula V, and/or formula VI, wherein the compound is administered with food. The compound may be, for example, any one of the compounds listed in tables 1 or 2, or in Appendix A.

In some embodiments, the invention relates to a method of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection, comprising orally administering a compound of formula I, formula II, formula III, formula IV, formula V, and/or formula VI, wherein the compound is administered to a subject in fed mode. The compound may be, for example, any one of the compounds listed in tables 1 or 2, or in Appendix A.

In certain embodiments, the subject is a mammal. In certain preferred embodiments, the subject is a human.

In some embodiments, the compound is administered orally between 30 minutes prior to the subject (e.g., a human) ingesting food to 6 hours after ingesting food, such as between 30 minutes prior to ingesting food to 5 hours after ingesting food, between 30 minutes prior to ingesting food to 4 hours after ingesting food, between 30 minutes prior to ingesting food to 3 hours after ingesting food, between 30 minutes prior to ingesting food to 2 hours after ingesting food, or between 30 minutes prior to ingesting food to 1 hours after ingesting food. Preferably, the compound is administered between 30 minutes prior to the subject ingesting food to 90 minutes after ingesting food, such as between 20 minutes prior to ingesting food to 90 minutes after ingesting food, between 20 minutes prior to ingesting food to 60 minutes after ingesting food, between 10 minutes prior to ingesting food to 60 minutes after ingesting food, between 5 minutes prior to ingesting food to 60 minutes after

ingesting food, or between 5 minutes prior to ingesting food to 30 minutes after ingesting food.

In some embodiments, the method comprises orally administering a glutaminase inhibitor (e.g., preferably a compound of formula III) to a subject (e.g., a human),
5 preferably in the fed mode, wherein between 100 mg and 10 g of the compound is administered orally per day. For example, the daily oral dose of the compound may be from 100 mg to 5000 mg, e.g., 200 mg to 4000 mg, 300 mg to 3000 mg, 600 mg to 2400 mg, 800 mg to 2200 mg, 1000 mg to 2000 mg, or 1200 mg to 1800 mg, or about 1600 mg.

In some embodiments, the method comprises orally administering the compound of
10 formula III, and 100 mg to 10 g of the compound is administered orally per day. For example, 100 mg to 5000 mg of the compound may be administered orally per day, such as 200 mg to 4000 mg, 300 mg to 3000 mg, 600 mg to 2400 mg, 800 mg to 2200 mg, 1000 mg to 2000 mg, 1200 mg to 1800 mg, or about 1600 mg.

In some embodiments, an aggregate dose equivalent to between 100 mg and 10 g of
15 the compound of formula III is administered orally per day. The term “aggregate dose” refers to the total amount of the compound administered, e.g., per day. For example, if a 600 mg dose of the compound is administered two times per day, then the aggregate dose is 1200 mg per day. The term “equivalent to an amount of the compound of formula III” refers to the administration of an amount of a compound that has the same efficacy as an
20 amount of the compound of formula III. For example, if a first compound, such as a compound of formula I, II, IV, V, or VI, has the same efficacy as the compound of formula III, then an equivalent of the first compound is equal to the same amount of the compound of formula III, e.g., 600 mg of the first compound is equivalent to 600 mg of the compound of formula III. Similarly, if a second compound has, for example, twice the efficacy of the
25 compound of formula III, then an equivalent of the second compound is equal to half the amount of the compound of formula III, e.g., 300 mg of the second compound is equivalent to 600 mg of the compound of formula III.

Preferably, the glutaminase inhibitor is administered to the subject with a meal (i.e., the subject is in the fed mode).

30 In some embodiments, an aggregate dose equivalent to between about 100 mg and about 5000 mg of a glutaminase inhibitor (e.g., preferably a compound of formula III) is administered to a subject (e.g., a human) orally per day. In exemplary embodiments, an aggregate dose is equivalent to between about 200 mg and about 4000 mg, about 300 mg

and about 3000 mg, about 400 mg and about 2800 mg, about 600 mg and about 2400 mg, about 800 mg and about 2200 mg, about 1000 mg and about 2000 mg, about 1000 mg and about 1800 mg, about 1200 mg and about 1800 mg, about 1200 mg and about 1600 mg. In certain preferred embodiments, a compound of formula III is delivered orally to a human
5 subject twice daily for an aggregate dose of 1600 mg. Preferably, the human subject is in the fed mode. In certain preferred embodiments, the compound is administered with a meal.

In some embodiments, an aggregate dose equivalent to between about 100 mg and about 5000 mg of the compound of formula III is administered to a subject (e.g., a human)
10 orally per day. In exemplary embodiments, an aggregate dose is equivalent to between about 200 mg and about 4000 mg, about 300 mg and about 3000 mg, about 400 mg and about 2800 mg, about 600 mg and about 2400 mg, about 800 mg and about 2200 mg, about 1000 mg and about 2000 mg, about 1000 mg and about 1800 mg, about 1200 mg and about 1800 mg, about 1200 mg and about 1600 mg. In certain preferred embodiments, a
15 compound of formula III is delivered orally to a human subject twice daily for an aggregate dose of 1600 mg. Preferably, the human subject is in the fed mode, e.g., the compound is administered with a meal.

In some embodiments, between 100 mg and 10 g of the compound is administered daily. For example, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450
20 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1350 mg, 1400 mg, 1500 mg, 1600 mg, 1650 mg, 1700 mg, 1800 mg, 1900 mg, 1950 mg, 2000 mg, 2100 mg, 2200 mg, 2250 mg, 2300 mg, 2400 mg, 2500 mg, 2550 mg, 2600 mg, 2700 mg, 2800 mg, 2850 mg, 2900 mg, 3000 mg, 4000 mg, 5000 mg, 6000 mg, 7000 mg, 8000 mg, 9000 mg, or 10,000 mg may be
25 administered daily. In certain preferred embodiments, 1200 mg of the compound is administered per day, e.g., with two doses of 600 mg each. In some embodiments, 1800 mg of the compound is administered per day, e.g., with three doses of 600 mg each. In other preferred embodiments, 1600 mg of the compound is administered to a subject (e.g., a human) per day, e.g., with two doses of 800 mg each. Preferably, each administration
30 includes a meal.

In some embodiments, the compound is administered once per day, two times per day, three times per day, or four times per day. In preferred embodiments, the compound is administered two times per day or three times per day, e.g., each time with food. In more

preferred embodiments, the compound is administered two times per day, *e.g.*, each time with food.

Examples

5 Example 1: Comparison of various dose sizes

The compound of formula III (CB-839) was administered, orally, to fifteen human subjects with acute leukemia for 22 days. The compound was administered three times per day (“TID”) at doses ranging from 100 mg per dose to 1000 mg per dose (*i.e.*, 300 mg to 3000 mg total compound per day). Plasma levels of the compound were monitored on days 10 1, 15, and 22. Subjects received the compound in a fasted state on days 1 and 15 (*e.g.*, without a meal as defined herein) and in a fed state on day 22 (*e.g.*, with a meal as defined herein). Administration of the compound in a fasted state consisted of oral administration of a first dose 1 hour before breakfast, oral administration of a second dose at 3 PM, and oral administration of a third dose prior to bedtime. An increase in exposure was 15 demonstrated with increasing dose (Figures 1 & 2). The steady state plasma concentration of CB-839 on Day 15 was found to be above 250 nM, continuously, in most patients receiving doses of 600 mg three times per day and higher (Figure 2), which is a plasma concentration that has previously been shown to be therapeutically effective. Peripheral blood mononuclear cells (PBMCs) from three patients treated with doses of 600, 800, and 20 1000 mg three times per day were found to have between 10 and 58% leukemic blast counts and showed >94% inhibition of glutaminase activity. When CB-839 was administered at 600 mg twice a day with food, the C_{max} was reached in 2-6 hours, and plasma levels of the compound exceeded 450 nM in all subjects, suggesting that the fed state resulted in increased drug exposure (Figure 2).

25 Example 2: Comparison of administration in fed and fasted states

Each subject from Example 1 who remained enrolled in the trial were administered 600 mg of the compound of formula III orally, twice a day (“BID”), with food, each day after day 22 of the trial (*i.e.*, 1200 mg of the compound per day). Plasma levels of the compound were monitored on days 1, 15, and 22 of the BID dosing regimen for 30 comparison with the results of Example 1. Pharmacokinetics data was compared for subjects receiving 600 mg of the compound three times per day in a fasted state (*i.e.*, 1800 mg of the compound per day, without meals as defined herein) and subjects receiving 600

mg of the compound two times per day in a fed state (*i.e.*, 1200 mg of the compound per day, with meals as defined herein). This data suggested that each group had the same amount of drug exposure despite the fed group receiving less compound per day than the fasted group (Figures 4 & 5).

5 Example 3: Outcomes

No dose-limiting toxicity was identified in Examples 1 and 2, and treatment-related adverse events that occurred in greater than 10% of the subjects consisted of increased transaminase levels (in 4 subjects) and increased bilirubin levels (in 2 subjects). No grade 3 or higher adverse events were considered treatment-related in more than 10% of the
10 subjects. Stable disease for 4-10 cycles was observed in 5 (33%) of 15 efficacy-evaluable subjects across all dose levels, with subjects remaining on the study drug for an average of 134 days (*i.e.*, greater than 6 cycles; 1 cycle = 21 days). One subject achieved a complete response in the bone marrow with incomplete recovery of peripheral counts after 6 cycles of dosing. All subjects with stable disease or better were older than 65 years of age and
15 ineligible for high-dose therapy.

Example 4: Pharmacokinetics

CB-839 was administered to cancer patients according to the dosing schedule in Figure 6. The half-life of CB-839 is approximately 4 hours. Exposure generally increases with dose.

20 As shown in Figure 6-8, target CB-839 concentrations are maintained with PK variability is reduced with BID Fed dosing regimen.

Incorporation by Reference

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually
25 indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

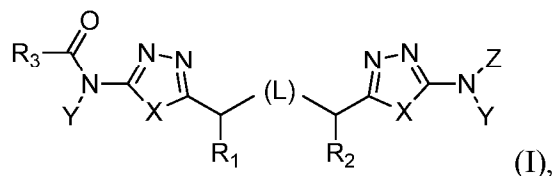
In particular, suitable compounds for practicing the invention, and methods for synthesizing said compounds, are described in U.S. Patent No. 8,604,016, U.S. Patent Application Publication No. 2014/0194421, and U.S. Application Publication Nos.
30 2015/0004134, 2014/0142081, and 2014/0142146, which are hereby incorporated by reference in their entirety.

Equivalents

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims
5 below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

Claims:

1. A method of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection, comprising orally administering a compound of formula I,



or a pharmaceutically acceptable salt thereof, wherein:

L represents CH₂SCH₂, CH₂CH₂, CH₂CH₂CH₂, CH₂, CH₂S, SCH₂, CH₂NHCH₂, CH=CH,

or , wherein any hydrogen atom of a CH or CH₂ unit may be replaced by alkyl or alkoxy, any hydrogen of an NH unit may be replaced by alkyl, and any hydrogen atom of a CH₂ unit of CH₂CH₂, CH₂CH₂CH₂ or CH₂ may be replaced by hydroxy;

X, independently for each occurrence, represents S, O or CH=CH, wherein any hydrogen atom of a CH unit may be replaced by alkyl;

Y, independently for each occurrence, represents H or CH₂O(CO)R₇;

R₇, independently for each occurrence, represents H or substituted or unsubstituted alkyl, alkoxy, aminoalkyl, alkylaminoalkyl, heterocyclalkyl, or heterocyclalkoxy;

Z represents H or R₃(CO);

R₁ and R₂ each independently represent H, alkyl, alkoxy or hydroxy;

R₃, independently for each occurrence, represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroaryloxyalkyl or C(R₈)(R₉)(R₁₀), N(R₄)(R₅) or OR₆, wherein any free hydroxyl group may be acylated to form C(O)R₇;

R₄ and R₅ each independently represent H or substituted or unsubstituted alkyl, hydroxyalkyl, acyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form C(O)R₇;

R₆, independently for each occurrence, represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form C(O)R₇;

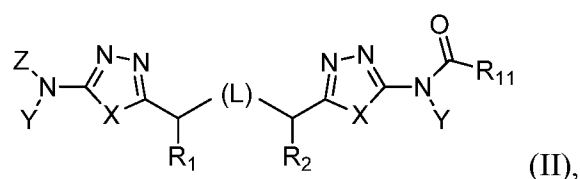
R₈, R₉ and R₁₀ each independently represent H or substituted or unsubstituted alkyl, hydroxy, hydroxyalkyl, amino, acylamino, aminoalkyl, acylaminoalkyl, alkoxycarbonyl, alkoxycarbonylamino, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, or R₈ and R₉ together with the carbon to which they are attached, form a carbocyclic or heterocyclic ring system, wherein any free hydroxyl group may be acylated to form C(O)R₇; and

the compound is preferably administered with a meal.

2. The method of claim 1, wherein L represents CH₂SCH₂, CH₂CH₂, CH₂S or SCH₂.
3. The method of claim 1, wherein L represents CH₂CH₂.
4. The method of any one of the preceding claims, wherein Y represents H.
5. The method of any one of the preceding claims, wherein X, independently for each occurrence, represents S or CH=CH, wherein any hydrogen atom of a CH unit may be replaced by alkyl.
6. The method of any one of the preceding claims, wherein Z represents R₃(CO).
7. The method of claim 6, wherein each occurrence of R₃ is not identical.
8. The method of any one of the preceding claims, wherein R₁ and R₂ each represent H.

9. The method of any one of the preceding claims, wherein R_3 , independently for each occurrence, represents substituted or unsubstituted arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl.
10. The method of any one of the preceding claims, wherein R_3 , independently for each occurrence, represents $C(R_8)(R_9)(R_{10})$, wherein R_8 represents substituted or unsubstituted aryl, arylalkyl, heteroaryl or heteroaralkyl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl, alkoxy or alkoxyalkyl.
11. The method of claim 10, wherein R_8 represents substituted or unsubstituted aryl, arylalkyl, or heteroaryl.
12. The method of claim 10 or 11, wherein R_{10} represents hydroxy, hydroxyalkyl, or alkoxy.
13. The method of claim 1, wherein L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 , Y represents H, X represents S, Z represents $R_3(CO)$, R_1 and R_2 each represent H, and R_3 , independently for each occurrence, represents substituted or unsubstituted arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl.
14. The method of claim 13, wherein each occurrence of R_3 is identical.
15. The method of claim 1, wherein L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 , Y represents H, X represents S, Z represents $R_3(CO)$, R_1 and R_2 each represent H, and R_3 , independently for each occurrence, represents $C(R_8)(R_9)(R_{10})$, wherein R_8 represents substituted or unsubstituted aryl, arylalkyl, heteroaryl or heteroaralkyl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl, alkoxy or alkoxyalkyl.
16. The method of claim 15, wherein L represents CH_2CH_2 .
17. The method of claim 15 or 16, wherein R_8 represents substituted or unsubstituted aryl, arylalkyl or heteroaryl.
18. The method of claim 17, wherein R_8 represents substituted or unsubstituted aryl.

19. The method of any one of claims 15-18, wherein R_{10} represents hydroxy, hydroxyalkyl or alkoxy.
20. The method of claim 19, wherein R_{10} represents hydroxyalkyl.
21. The method of any one of claims 15-20, wherein each occurrence of R_3 is identical.
22. The method of claim 1, wherein L represents CH_2CH_2 , Y represents H, X, independently for each occurrence, represents S or $CH=CH$, Z represents $R_3(CO)$, R_1 and R_2 each represent H, and R_3 , independently for each occurrence, represents arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl.
23. The method of claim 22, wherein each occurrence of R_3 is identical.
24. A method of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection, comprising orally administering a compound of formula II,



or a pharmaceutically acceptable salt thereof, wherein:

L represents CH_2SCH_2 , CH_2CH_2 , $CH_2CH_2CH_2$, CH_2 , CH_2S , SCH_2 , CH_2NHCH_2 , $CH=CH$,

or , wherein any hydrogen atom of a CH or CH_2 unit may be replaced by alkyl or alkoxy, any hydrogen of an NH unit may be replaced by alkyl, and any hydrogen atom of a CH_2 unit of CH_2CH_2 , $CH_2CH_2CH_2$ or CH_2 may be replaced by hydroxy;

X, independently for each occurrence, represents S, O or $CH=CH$, wherein any hydrogen atom of a CH unit may be replaced by alkyl;

Y, independently for each occurrence, represents H or $CH_2O(CO)R_7$;

R_7 , independently for each occurrence, represents H or substituted or unsubstituted alkyl, alkoxy, aminoalkyl, alkylaminoalkyl, heterocyclylalkyl, arylalkyl, or heterocyclylalkoxy;

Z represents H or $R_3(CO)$;

R₁ and R₂ each independently represent H, alkyl, alkoxy or hydroxy;

R₃ represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroaryloxyalkyl or C(R₈)(R₉)(R₁₀), N(R₄)(R₅) or OR₆, wherein any free hydroxyl group may be acylated to form C(O)R₇;

R₄ and R₅ each independently for each occurrence represent H or substituted or unsubstituted alkyl, hydroxyalkyl, acyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form C(O)R₇;

R₆ represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form C(O)R₇;

R₈, R₉ and R₁₀ each independently for each occurrence represent H or substituted or unsubstituted alkyl, hydroxy, hydroxyalkyl, amino, acylamino, aminoalkyl, acylaminoalkyl, alkoxycarbonyl, alkoxycarbonylamino, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, or R₈ and R₉ together with the carbon to which they are attached, form a carbocyclic or heterocyclic ring system, wherein any free hydroxyl group may be acylated to form C(O)R₇, and wherein at least two of R₈, R₉ and R₁₀ are not H;

R₁₁ represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl or R₁₁ represents C(R₁₂)(R₁₃)(R₁₄), N(R₄)(R₁₄) or OR₁₄, wherein any free hydroxyl group may be acylated to form C(O)R₇;

R₁₂ and R₁₃ each independently represent H or substituted or unsubstituted alkyl, hydroxy, hydroxyalkyl, amino, acylamino, aminoalkyl, acylaminoalkyl, alkoxycarbonyl, alkoxycarbonylamino, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl,

heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form $C(O)R_7$, and wherein both of R_{12} and R_{13} are not H;

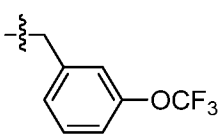
R_{14} represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl; and
the compound is preferably administered with a meal.

25. The method of claim 24, wherein R_{11} represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, and the aryl or heteroaryl ring is substituted with either $-OCHF_2$ or $-OCF_3$ and is optionally further substituted.

26. The method of claim 24 or 25, wherein R_{14} represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, and the aryl or heteroaryl ring is substituted with either $-OCHF_2$ or $-OCF_3$ and is optionally further substituted.

27. The method of claim 25 or 26, wherein R_{11} represents arylalkyl, wherein the aryl ring is substituted with $-OCF_3$.

28. The method of claim 27, wherein R_{11} represents trifluoromethoxybenzyl.

29. The method of claim 28, wherein R_{11} represents .

30. The method of any one of claims 24-29, wherein L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 .

31. The method of any one of claims 24-30, wherein L represents CH_2CH_2 .

32. The method of any one of claims 24-31, wherein each Y represents H.

33. The method of any one of claims 24-32, wherein X represents S or $CH=CH$, wherein any hydrogen atom of a CH unit may be replaced by alkyl.

34. The method of any one of claims 24-33, wherein Z represents $R_3(CO)$.
35. The method of claim 34, wherein R_3 and R_{11} are not identical.
36. The method of any one of claims 24-35, wherein R_1 and R_2 each represent H.
37. The method of any one of claims 24-36, wherein Z represents $R_3(CO)$ and R_3 represents substituted or unsubstituted arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl.
38. The method of claim 37, wherein Z represents $R_3(CO)$ and R_3 represents substituted or unsubstituted heteroarylalkyl.
39. The method of claim 38, wherein Z represents $R_3(CO)$ and R_3 represents substituted or unsubstituted pyridylalkyl.
40. The method of any one of claims 24-36, wherein Z represents $R_3(CO)$ and R_3 represents $C(R_8)(R_9)(R_{10})$, wherein R_8 represents substituted or unsubstituted aryl, arylalkyl, heteroaryl or heteroaralkyl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl, alkoxy or alkoxyalkyl.
41. The method of claim 40, wherein R_8 represents substituted or unsubstituted aryl, arylalkyl, or heteroaryl.
42. The method of claim 40 or 41, wherein R_{10} represents hydroxy, hydroxyalkyl, or alkoxy.
43. The method of any of of claims 24-29, wherein L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 , each Y represents H, X represents S, Z represents $R_3(CO)$, R_1 and R_2 each represent H, and R_3 represents substituted or unsubstituted arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl.
44. The method of any one of claims 24-29, wherein L represents CH_2SCH_2 , CH_2CH_2 , CH_2S or SCH_2 , each Y represents H, X represents S, Z represents $R_3(CO)$, R_1 and R_2 each represent H, and R_3 represents $C(R_8)(R_9)(R_{10})$, wherein R_8 represents substituted or

unsubstituted aryl, arylalkyl, heteroaryl or heteroaralkyl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl, alkoxy or alkoxyalkyl.

45. The method of claim 44, wherein L represents CH_2CH_2 .

46. The method of claim 44 or 45, wherein R_8 represents substituted or unsubstituted aryl, arylalkyl or heteroaryl.

47. The method of claim 46, wherein R_8 represents substituted or unsubstituted aryl.

48. The method of any one of claims 44-47, wherein R_{10} represents hydroxy, hydroxyalkyl or alkoxy.

49. The method of claim 48, wherein R_{10} represents hydroxyalkyl.

50. The method of any one of claims 25-29, wherein L represents CH_2CH_2 , each Y represents H, X represents S, Z represents $\text{R}_3(\text{CO})$, R_1 and R_2 each represent H, and R_3 represents arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl.

51. The method of claim 50, wherein R_3 represents heteroarylalkyl.

52. The method of any one of the preceding claims, further comprising conjointly administering an immunomodulatory agent.

53. The method of claim 52, wherein conjointly administering the immunomodulatory agent and compound provides improved efficacy relative to individual administration of the immunomodulatory agent or compound as a single agent.

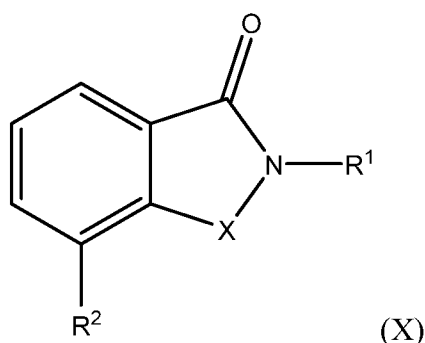
54. The method of claim 53, wherein conjointly administering the immunomodulatory agent and compound provides an additive effect.

55. The method of claim 53, wherein conjointly administering the immunomodulatory agent and compound provides a synergistic effect.

56. The method of any one of claims 52-55, wherein the immunomodulatory agent and compound are administered simultaneously.

57. The method of any one of claims 52-55, wherein the immunomodulatory agent is administered within about 5 minutes to within about 168 hours prior or after of the compound.

58. The method of any one of claims 52 to 57, wherein the immunomodulatory agent has a structure of formula X:

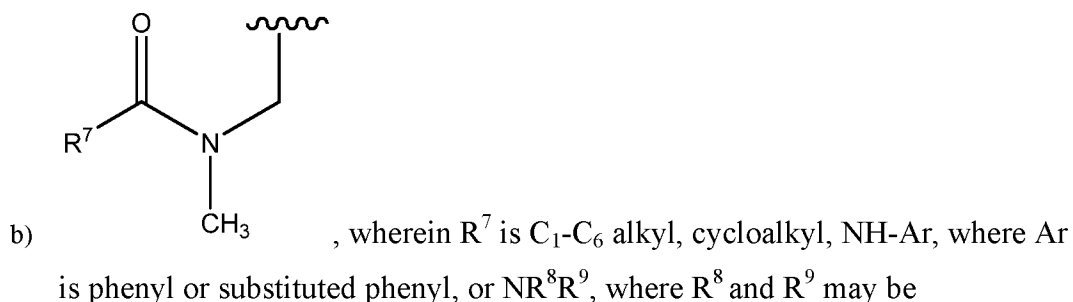
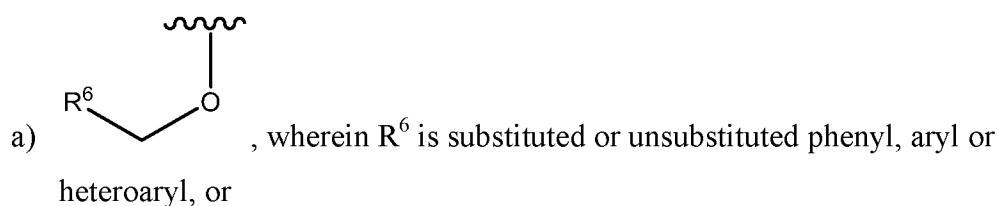


or a pharmaceutically acceptable salt, prodrug, and/or stereoisomer thereof, wherein:

X is C=O or CH₂;

R¹ is heterocyclyl, such as 2,6-dioxopiperidin-3-yl, or aralkyl, such as a sulfonyl-substituted aralkyl, and

R² is independently a hydrogen, an amino group, an acylamino group, an alkylamino group, or is one of the following moieties:



independently H or C₁-C₆-alkyl.

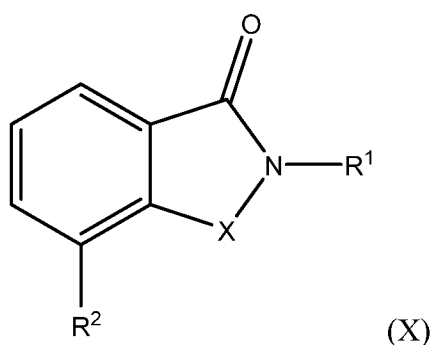
59. The method of any one of claims 52-58, wherein the immunomodulatory agent is selected from apremilast (CC-10004), lenalidomide (CC-5013), pomalidomide (CC-4047), thalidomide, CC-11006, and CC-10015.

60. The method of any one of the preceding claims, for treating cancer, wherein the cancer is selected from acute myeloid leukemia (AML), brain malignancy, chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, Hodgkin's lymphoma, Kaposi's sarcoma, MALT lymphoma, mantle cell lymphoma (MCL), multiple myeloma (MM), myelodysplastic syndromes (MDS), non-Hodgkin lymphoma (NHL), and Waldenstrom macroglobulinemia (WM).

61. The method of claim 60, wherein the cancer is multiple myeloma.

62. The method of claim 60 or 61, wherein the cancer is resistant to an immunomodulatory agent.

63. The method of claim 62, wherein the cancer is resistant to a molecule having a structure of formula X:

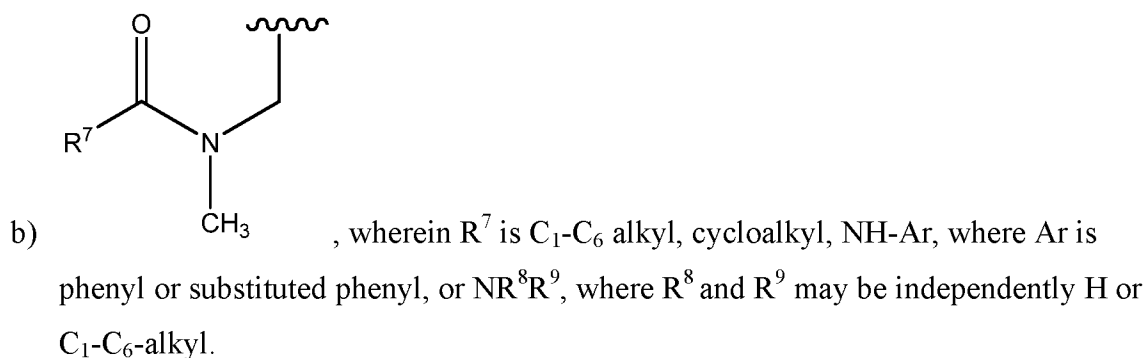
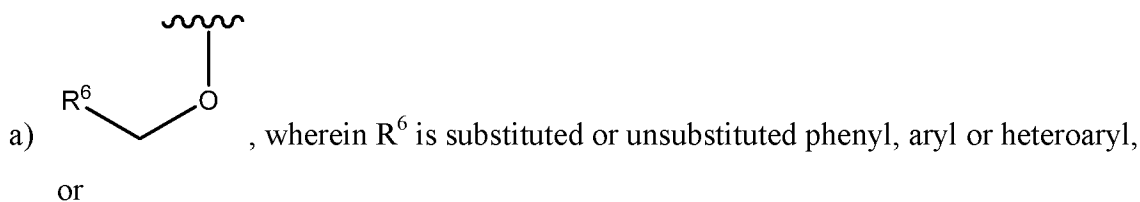


or a pharmaceutically acceptable salt, prodrug, and/or stereoisomer thereof, wherein:

X is C=O or CH₂;

R¹ is heterocyclyl, such as 2,6-dioxopiperidin-3-yl, or aralkyl, such as a sulfonyl-substituted aralkyl, and

R² is independently a hydrogen, an amino group, an acylamino group, an alkylamino group, or is one of the following moieties:



64. The method of any one of claims 60-63, wherein the immunomodulatory agent is apremilast, lenalidomide, pomalidomide, thalidomide, CC-11006, or CC-10015.

65. The method of any one of claims 1 to 59, for treating cancer, wherein the cancer is selected from breast cancer, colorectal cancer, endocrine cancer, lung cancer, melanoma, mesothelioma, renal cancer, and a B cell malignancy.

66. The method of claim 65, wherein the cancer is breast cancer.

67. The method of claim 66, wherein the breast cancer comprises basal-type breast cancer cells, triple-negative breast cancer cells or claudin-low breast cancer cells.

68. The method of claim 67, wherein the breast cancer comprises basal-type breast cancer cells.

69. The method of claim 67, wherein the breast cancer comprises triple-negative breast cancer cells.

70. The method of claim 67, wherein the breast cancer comprises claudin-low breast cancer cells.

71. The method of claim 65, wherein the cancer is colorectal cancer.

72. The method of claim 65, wherein the cancer is endocrine cancer.
73. The method of claim 72, wherein the endocrine cancer is selected from adrenal cortex adenoma, adrenal cortex carcinoma, adrenal gland pheochromocytoma, and parathyroid gland adenoma.
74. The method of claim 65, wherein the cancer is melanoma.
75. The method of claim 65, wherein the cancer is renal cancer.
76. The method of claim 65, wherein the cancer is a B cell malignancy.
77. The method of claim 76, wherein the B cell malignancy is selected from multiple myeloma, leukemia, and lymphoma.
78. The method of claim 77, wherein the B cell malignancy is multiple myeloma.
79. The method of claim 77, wherein the B cell malignancy is leukemia.
80. The method of claim 79, wherein the leukemia is selected from acute lymphoblastic leukemia, and chronic lymphoblastic leukemia.
81. The method of claim 77, wherein the B cell malignancy is lymphoma.
82. The method of claim 81, wherein the lymphoma is selected from Burkitt's lymphoma, Diffuse large B cell lymphoma, follicular lymphoma, and Hodgkin's lymphoma.
83. The method of any one of the preceding claims, further comprising conjointly administering one or more additional chemotherapeutic agents.
84. The method of claim 83, wherein conjointly administering one or more additional chemotherapeutic agents provides improved efficacy relative to each individual administration of the compound or the one or more additional chemotherapeutic agent.

85. The method of claim 84, wherein conjointly administering one or more additional chemotherapeutic agents provides a synergistic effect.
86. The method of claim 84, wherein conjointly administering one or more additional chemotherapeutic agents provides an additive effect.
87. The method of any one of claims 83 to 86, wherein the compound and the one or more additional chemotherapeutic agents are administered simultaneously.
88. The method of any one of claims 83 to 86, wherein the one or more additional chemotherapeutic agents are administered within about 5 minutes to within about 168 hours prior to or after the administration of the compound.
89. The method of any one of claims 83 to 88, wherein the one or more additional chemotherapeutic agents are selected from ABT-263, aminoglutethimide, amsacrine, anastrozole, asparaginase, azacitidine, AZD5363, Bacillus Calmette–Guérin vaccine (bcg), bicalutamide, bleomycin, bortezomib, buserelin, busulfan, camptothecin, capecitabine, carboplatin, carfilzomib, carmustine, chlorambucil, chloroquine, cisplatin, cladribine, clodronate, cobimetinib, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, demethoxyviridin, dexamethasone, dichloroacetate, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil (e.g., 5-fluorouracil), fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ixabepilone, lenalidomide, letrozole, leucovorin, leuprolide, levamisole, lomustine, lonidamine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, metformin, methotrexate, miltefosine, mitomycin, mitotane, mitoxantrone, mutamycin, MK-2206, nilutamide, nocodazole, octreotide, oxaliplatin, olaparib, paclitaxel, pamidronate, pazopanib, pentostatin, perifosine, PF-04691502, plicamycin, pomalidomide, porfimer, procarbazine, raltitrexed, rituximab, romidepsin, rucaparib, selumetinib, sorafenib, streptozocin, sunitinib, suramin, talazoparib, tamoxifen, temozolomide, temsirolimus, teniposide, testosterone, thalidomide, thioguanine, thiotepa, titanocene dichloride, topotecan, trametinib, trastuzumab, tretinoin, veliparib, vinblastine, vincristine, vindesine, vinorelbine, and vorinostat (SAHA).

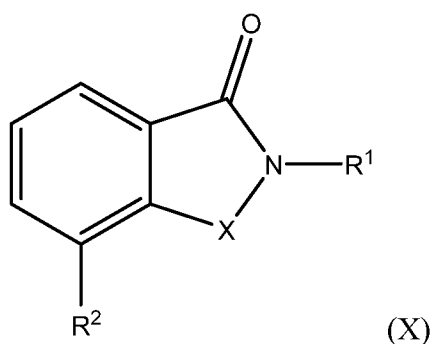
90. The method of claim 89, wherein the one or more additional chemotherapeutic agents are selected from azacitidine, bortezomib, capecitabine, carboplatin, carfilzomib, cyclophosphamide, daunorubicin, dexamethasone, docetaxel, doxorubicin, epirubicin, eribulin, erlotinib, everolimus, fluorouracil, gemcitabine, ixabepilone, lenalidomide, methotrexate, mitoxantrone, mutamycin, paclitaxel, pomalidomide, rituximab, thiotepa, vincristine, and vinorelbine.

91. The method of claim 90, wherein the one or more additional chemotherapeutic agents are selected from azacitidine, dexamethasone, docetaxel, erlotinib, everolimus, paclitaxel and pomalidomide.

92. The method of any one of claims 1 to 59, for treating a myeloproliferative disease, wherein the myeloproliferative disease is selected from chronic eosinophilic leukemia, chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, essential thrombocythemia, polycythemia vera, and myelofibrosis.

93. The method of claim 92, wherein the myeloproliferative disease is resistant to an immunomodulatory agent.

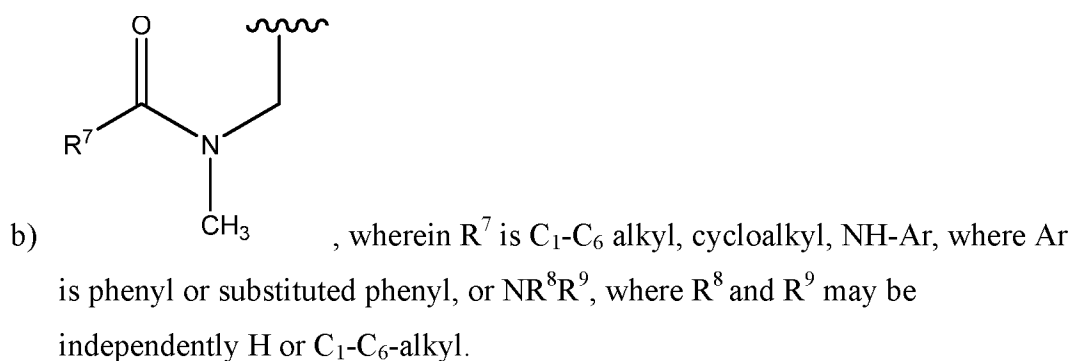
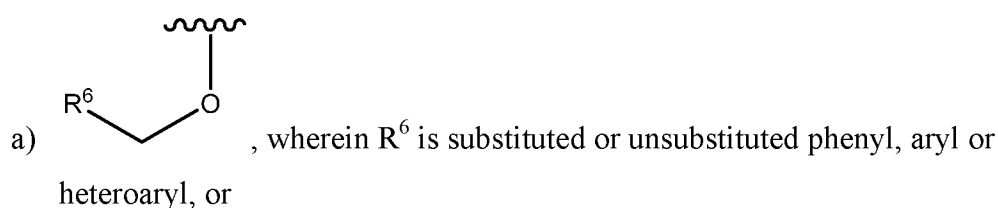
94. The method of claim 93, wherein the immunomodulatory agent has a structure of formula X:



or a pharmaceutically acceptable salt, prodrug, and/or stereoisomer thereof, wherein:
X is C=O or CH₂;

R¹ is heterocyclyl, such as 2,6-dioxopiperidin-3-yl, or aralkyl, such as a sulfonyl-substituted aralkyl, and

R² is independently a hydrogen, an amino group, an acylamino group, an alkylamino group, or is one of the following moieties:

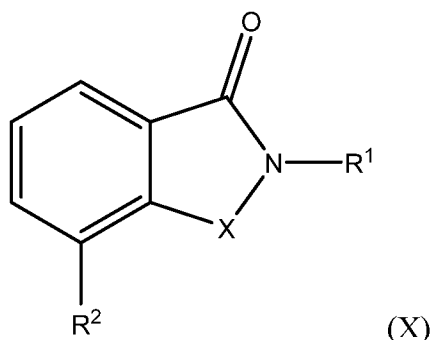


95. The method of any one of claims 92 to 94, wherein the immunomodulatory agent is apremilast, lenalidomide, pomalidomide, thalidomide, CC-11006, or CC-10015.

96. The method of any one of claims 1 to 59, for treating or preventing an immune-related disease, wherein the immune-related disease is selected from ankylosing spondylitis, Crohn's disease, erythema nodosum leprosum (ENL), graft versus host disease (GVHD), HIV-associated wasting syndrome, lupus erythematosus, post-polycythemia, psoriasis, psoriatic arthritis, recurrent aphthous ulcers, rheumatoid arthritis (RA), severe recurrent aphthous stomatitis, and systemic sclerosis.

97. The method of claim 96, wherein the immune-related disease is resistant to an immunomodulatory agent.

98. The method of claim 97, wherein the immunomodulatory agent has a structure of formula X:

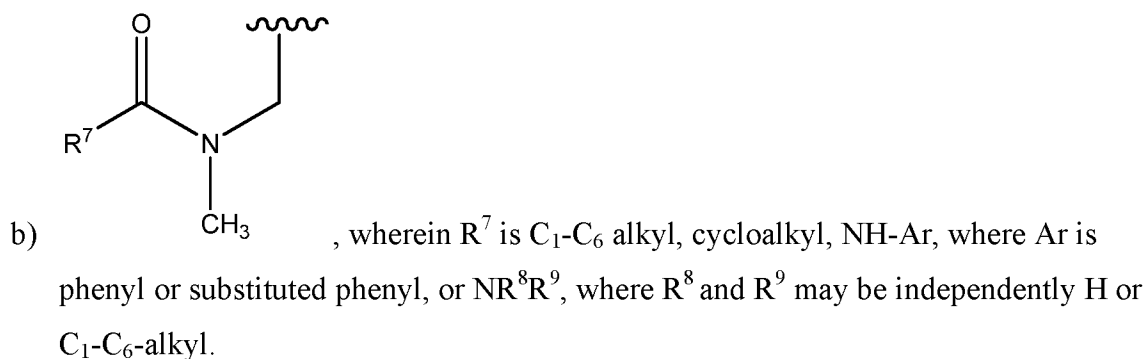
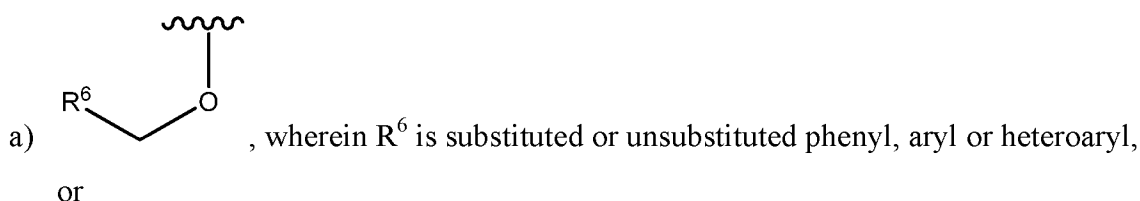


or a pharmaceutically acceptable salt, prodrug, and/or stereoisomer thereof, wherein:

X is C=O or CH₂;

R¹ is heterocyclyl, such as 2,6-dioxopiperidin-3-yl, or aralkyl, such as a sulfonyl-substituted aralkyl, and

R² is independently a hydrogen, an amino group, an acylamino group, an alkylamino group, or is one of the following moieties:



99. The method of any one of claims 96 to 98, wherein the immunomodulatory agent is apremilast, lenalidomide, pomalidomide, thalidomide, CC-11006, or CC-10015.

100. The method of any one of the preceding claims, further comprising conjointly administering one or more additional chemotherapeutic agents.

101. The method of claim 100, wherein the one or more additional chemotherapeutic agents includes ABT-263, aminoglutethimide, amsacrine, anastrozole, asparaginase,

azacitidine, AZD5363, Bacillus Calmette–Guérin vaccine (bcg), bicalutamide, bleomycin, bortezomib, buserelin, busulfan, campothecin, capecitabine, carboplatin, carfilzomib, carmustine, chlorambucil, chloroquine, cisplatin, cladribine, clodronate, cobimetinib, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, demethoxyviridin, dexamethasone, dichloroacetate, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil (e.g., 5-fluorouracil), fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ixabepilone, lenalidomide, letrozole, leucovorin, leuprolide, levamisole, lomustine, lonidamine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, metformin, methotrexate, miltefosine, mitomycin, mitotane, mitoxantrone, mutamycin, MK-2206, nilutamide, nocodazole, octreotide, oxaliplatin, olaparib, paclitaxel, pamidronate, pazopanib, pentostatin, perifosine, PF-04691502, plicamycin, pomalidomide, porfimer, procarbazine, raltitrexed, rituximab, romidepsin, rucaparib, selumetinib, sorafenib, streptozocin, sunitinib, suramin, talazoparib, tamoxifen, temozolomide, temsirolimus, teniposide, testosterone, thalidomide, thioguanine, thiotepa, titanocene dichloride, topotecan, trametinib, trastuzumab, tretinoin, veliparib, vinblastine, vincristine, vindesine, vinorelbine, and vorinostat (SAHA).

102. The method of claim 101, wherein the one or more additional chemotherapeutic agent is dexamethasone.

103. The method of any one of claims 1 to 51, for treating a viral infection, wherein the virus is smallpox, the common cold, measles, chickenpox, hepatitis, influenza, human papilloma virus, shingles, herpes, polio, rabies, ebola, hanta fever, HIV, cold sores, SARS (Severe acute respiratory syndrome), dengue, Epstein-Barr virus, adenovirus, Avian influenza, Influenza virus type A, Influenza virus type B, Measles, Parainfluenza virus, Respiratory syncytial virus (RSV), Rhinoviruses, SARS-CoV, Coxsackie virus, Enterovirus, Poliovirus, Rotavirus, Hepatitis B virus, Hepatitis C virus, bovine viral diarrhea virus (surrogate), herpes simplex 1, herpes simplex 2, human cytomegalovirus, varicella zoster virus, HIV 1, HIV 2, simian immunodeficiency virus, simian human immunodeficiency virus, Avian influenza, Dengue virus, Hantavirus, Hemorrhagic fever virus, Lymphocytic choriomeningitis virus, Smallpox virus surrogates (cowpox,

monkeypox, rabbitpox), Vaccinia virus, Venezuelan equine encephalomyelitis virus (VEE), West Nile virus, or Yellow fever virus.

104. The method of claim 103, further comprising conjointly administering one or more additional antiviral therapeutic agents.

105. The method of claim 104, wherein conjointly administering one or more additional antiviral therapeutic agents provides improved efficacy relative to each individual administration of the compound or the one or more additional antiviral therapeutic agents.

106. The method of claim 105, wherein conjointly administering one or more additional antiviral therapeutic agents provides a synergistic effect.

107. The method of claim 105, wherein conjointly administering one or more additional antiviral therapeutic agents provides an additive effect.

108. The method of any one of claims 104 to 107, wherein the compound and the one or more additional antiviral therapeutic agents are administered simultaneously.

109. The method of any one of claims 104 to 107, wherein the one or more additional antiviral therapeutic agents are administered within about 5 minutes to within about 168 hours prior to or after administration of the compound.

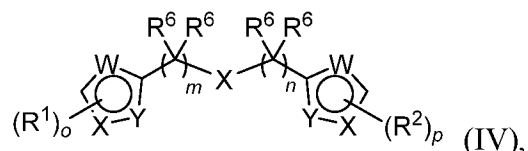
110. The method of any one of the preceding claims, wherein the compound is the compound of formula III and 300 mg to 3000 mg of the compound is administered per day.

111. The method of claim 110, wherein 600 mg to 2400 mg of the compound is administered per day.

112. The method of claim 111, wherein 1000 mg to 2000 mg of the compound is administered per day.

113. The method of claim 112, wherein 1200 mg or 1800 mg of the compound is administered per day.

114. The method of any one of claims 1 to 110, wherein an aggregate dose equivalent to between 300 mg and 3000 mg of the compound of formula III is administered per day.
115. The method of claim 114, wherein an aggregate dose equivalent to between 600 mg to 2400 mg of the compound of formula III is administered per day.
116. The method of claim 115, wherein an aggregate dose equivalent to between 1000 mg to 2000 mg of the compound of formula III is administered per day.
117. The method of claim 116, wherein an aggregate dose equivalent to 1200 mg or 1800 mg of the compound of formula III is administered per day.
118. The method of claim 117, wherein a dose equivalent to 600 mg of the compound of formula III is administered twice a day.
119. The method of claim 117, wherein a dose equivalent to 600 mg of the compound of formula III is administered three times a day.
120. The method of claim 116, wherein an aggregate dose equivalent to 1600 mg of the compound of formula III is administered per day.
121. The method of claim 120, wherein a dose equivalent to 800 mg of the compound of formula III is administered twice a day.
122. The method of any one of the preceding claims, wherein the compound is administered two times per day.
123. The method of any one of claims 1 to 121, wherein the compound is administered three times per day.
124. The method of any preceding claim, wherein compound is administered to a human.
125. A method of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection, comprising orally administering a compound of formula (IV),



or a pharmaceutically acceptable salt thereof, wherein:

X is a bond, —S—, —S(O)—, —SO₂—, —CH=CH—, or —C(O)—;

each W, Y and Z is independently —S—, —CH=, —O—, —N=, or —NH—, provided that (1) at least one of W, Y and Z is not —CH= and (2) when one of W is —S— and the Y in the same ring is N, then the Z in the same ring is not —CH=;

each R¹ and R² is independently C₁₋₆ alkylene-R⁴, —N(R³)—R⁴, —N(R³)—C(O)—R⁴, —C(O)—N(R³)—R⁴, —N(R³)—C(O)—O—R⁴, —N(R³)—C(O)—N(R³)—R⁴, —O—C(O)—N(R³)—R⁴, —N(R³)—C(O)—C₁₋₆ alkylene-C(O)—R⁴, —N(R³)—C(O)—C₁₋₆ alkylene-N(R³)—C(O)—R⁴ or —N(R^{3a})—C(O)—CH₂—N(R³)—C(O)—R⁴;

each R³ is independently hydrogen, C₁₋₆ alkyl or aryl;

each R⁴ is independently C₁₋₆ alkyl, C₁₋₆ alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclalkyl, heterocycl, cycloalkyl or cycloalkylalkyl, each of which is substituted with 0-3 occurrences of R⁵, or two adjacent R⁵ moieties, taken together with the atoms to which they are attached form a heterocycl, heteroaryl, cycloalkyl or aryl;

each R⁵ is independently oxo (=O), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, cyano, halo, —OH, —SH, —OCF₃, —SO₂—C₁₋₆ alkyl, —NO₂, —N(R⁷)—C(O)—C₁₋₆ alkyl, —N(R⁶)₂, —O—C(O)—C₁₋₆ alkyl, C₃₋₇ cycloalkyl, (C₃₋₇cycloalkyl)alkyl, aryl, aryloxy, —C(O)—aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclalkyl or heterocycl, wherein each aryl, heteroaryl or heterocycl is further substituted with 0-3 occurrences of R⁷;

each R⁶ is independently hydrogen, fluoro, OH or C₁₋₆ alkyl;

each R⁷ is independently hydrogen, C₁₋₆ alkyl, —OH, —SH, cyano, halo, —CF₃, —OCF₃, —SO₂—C₁₋₆ alkyl, —NO₂, —N(R⁷)—C(O)—C₁₋₆ alkyl, —N(R⁶)₂ or C₁₋₆ alkoxy;

m is 1, 2 or 3;

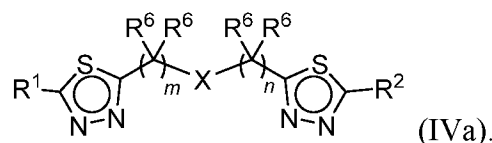
n is 1, 2 or 3; provided that when X is bond, the sum of m and n is from 3 to 6 and when X is —S—, —S(O)—, —SO₂—, —CH=CH—, or —C(O)—, the sum of m and n is from 2 to 4;

o is 1, 2 or 3; and

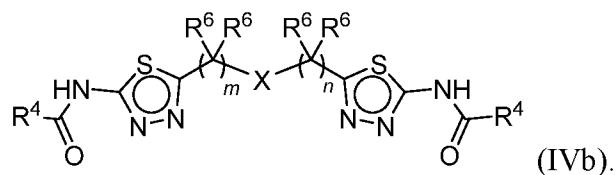
p is 1, 2 or 3;

- with the proviso that: (1) when X is —S—, m and n are both 2, each R⁶ is H, then (i) R¹ and R² are not both —NHC(O)—R⁴, wherein R⁴ is C₁₋₆ alkyl, monocyclic aryl, monocyclic heteroaryl, monocyclic aralkyl, monocyclic heteroaralkyl and each member of R⁴ is substituted with 0-3 occurrences of R⁵; and (ii) R¹ and R² are not both —NHC(O)O-methyl, —NHC(O)O-ethyl, —NHC(±)-6-pyrimidine-2,4(1H,3H)-dionyl, or —NHC(O)NH-phenyl wherein said phenyl of the —NHC(O)NH-phenyl moiety is optionally substituted with 1 or 2 groups selected from methyl, nitro, and halo;
- (2) when X is —S—, m and n are both 1, each R⁶ is H, then (i) R¹ and R² are not both —NH-phenyl or —NH-4-methoxy-phenyl;
- (3) when X is a bond, the sum of m and n is 3, each R⁶ is H, then R¹ and R² are not both NHC(O)-phenyl;
- (4) when X is a bond, m and n are both 2, each R⁶ is H, then R¹ and R² are not both —NHC(O)-furanyl, —NHC(O)-phenyl, —NHC(O)-o-methoxy-phenyl, —NHC(O)—C₁₋₆ alkyl, —NH-benzyl, or —NH-phenyl wherein said phenyl of the —NH-phenyl moiety is substituted with 0-3 occurrences of R⁵;
- (5) when X is a bond, the sum of m and n is 5, each R⁶ is H, then R¹ and R² are not both —NHC(O)—C₁₋₆ alkyl, —NHC(O)-cyclohexyl, or —NH-phenyl wherein said phenyl of the —NH-phenyl moiety is optionally substituted with methyl;
- (6) when X is a bond, m and n are both 3, each R⁶ is H, then R¹ and R² are not both NH-phenyl; and
- the compound is preferably administered with a meal.

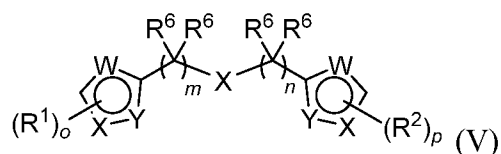
126. The method of claim 125, wherein the compound of formula (IV) has the structure of formula (IVa):



127. The method of claim 125, wherein the compound of formula (IV) has the structure of formula (IVb):



128. A method of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection, comprising orally administering a compound of formula (V),



wherein:

X is C₃-C₇ cycloalkylene;

each W, Y and Z is independently —S—, —CH=, —O—, —N=, or —NH—, provided that at least one of W, Y and Z is not —CH=;

each R¹ and R² is independently —NH₂, —N(R³)—C(O)—R⁴, —C(O)—N(R³)—R⁴, —N(R³)—C(O)—O—R⁴, —N(R³)—C(O)—N(R³)—R⁴ or —N(R³)—C(O)—SR⁴;

each R³ is independently hydrogen, C₁₋₆ alkyl or aryl;

each R⁴ is independently C₁₋₆ alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocyclalkyl, or heterocycl, each of which is substituted with 0-3 occurrences of R⁵;

each R⁵ is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, —O—C₁₋₆ alkyleneC₁₋₆ alkoxy, C₁₋₆ thioalkoxy, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclalkyl, heterocycl, cyano, halo, oxo, —OH, —OCF₃, —OCHF₂, —SO₂—C₁₋₆ alkyl, —NO₂, —N(R⁷)—C(O)—C₁₋₆ alkyl, —C(O)N(R⁷)₂, —N(R⁷)S(O)₁₋₂—C₁₋₆ alkyl, —S(O)₂N(R⁷)₂, —N(R⁷)₂, —C₁₋₆ alkylene-N(R⁷)₂, wherein said alkyl, C₁₋₆ alkoxy, —O—C₁₋₆ alkyleneC₁₋₆ alkoxy, C₁₋₆ thioalkoxy, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclalkyl, heterocycl, —SO₂—C₁₋₆ alkyl, —NO₂, —N(R⁷)—C(O)—C₁₋₆ alkyl, —C(O)N(R⁷)₂, —N(R⁷)S(O)₁₋₂—C₁₋₆ alkyl, —S(O)₂N(R⁷)₂, —N(R⁷)₂, or —C₁₋₆ alkylene-N(R⁷)₂ is optionally substituted with 0-3 occurrences of R⁸; or two adjacent R⁵ moieties, taken together with the atoms to which they are attached form a cycloalkyl or heterocycl;

each R^6 is independently hydrogen, fluoro, C_{1-6} alkyl, $-OH$, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, or C_{1-6} alkoxy;

each R^7 is independently hydrogen or C_{1-6} alkyl;

each R^8 is independently halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OH$, $-N(R^7)_2$, or C_{1-6} alkoxy, $-O-C_{1-6}$ alkylene C_{1-6} alkoxy, CN , NO_2 , $-N(R^7)-C(O)-C_{1-6}$ alkyl, $-C(O)N(R^7)_2$, $-N(R^7)S(O)_{1-2}C_{1-6}$ alkyl, or $-S(O)_2N(R^7)_2$;

m is 0, 1, or 2;

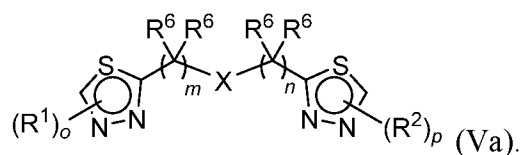
n is 0, 1, or 2;

o is 1, 2 or 3;

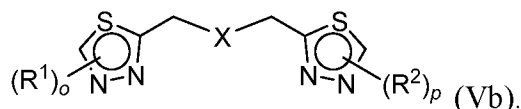
p is 1, 2 or 3; provided that (1) when X is unsubstituted cyclopropyl, R^1 and R^2 are not both NH -phenyl; and (2) X is other than substituted cyclobutyl or substituted cyclopentyl; and

the compound is preferably administered with a meal.

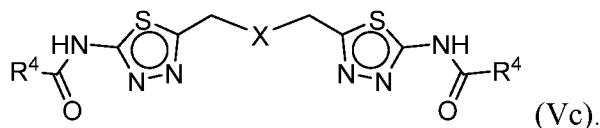
129. The method of claim 128, wherein the compound of formula (V) has the structure of formula (Va):



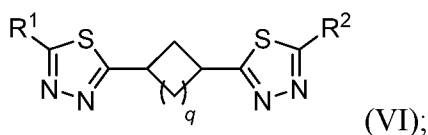
130. The method of claim 128, wherein the compound of formula (V) has the structure of formula (Vb):



131. The method of claim 128, wherein the compound of formula (V) has the structure of formula (Vc):

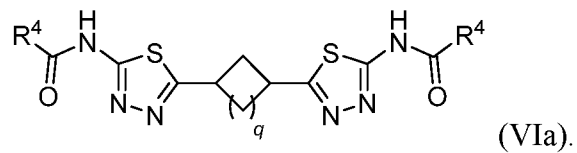


132. The method of claim 128, wherein the compound of formula (V) has the structure of formula (VI):

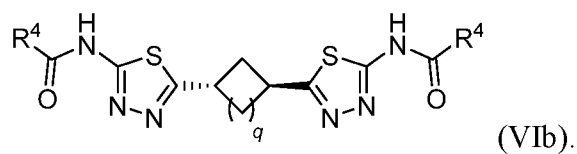


wherein q is 0, 1, 2, 3, or 4.

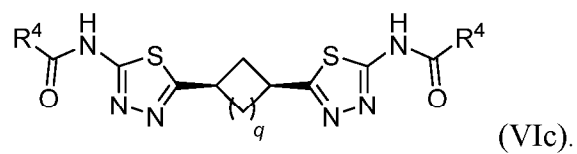
133. The method of claim 128, wherein the compound of formula (V) has the structure of formula (VIa):



134. The method of claim 128, wherein the compound of formula (V) has the structure of formula (VIb):



135. The method of claim 128, wherein the compound of formula (V) has the structure of formula (VIc):



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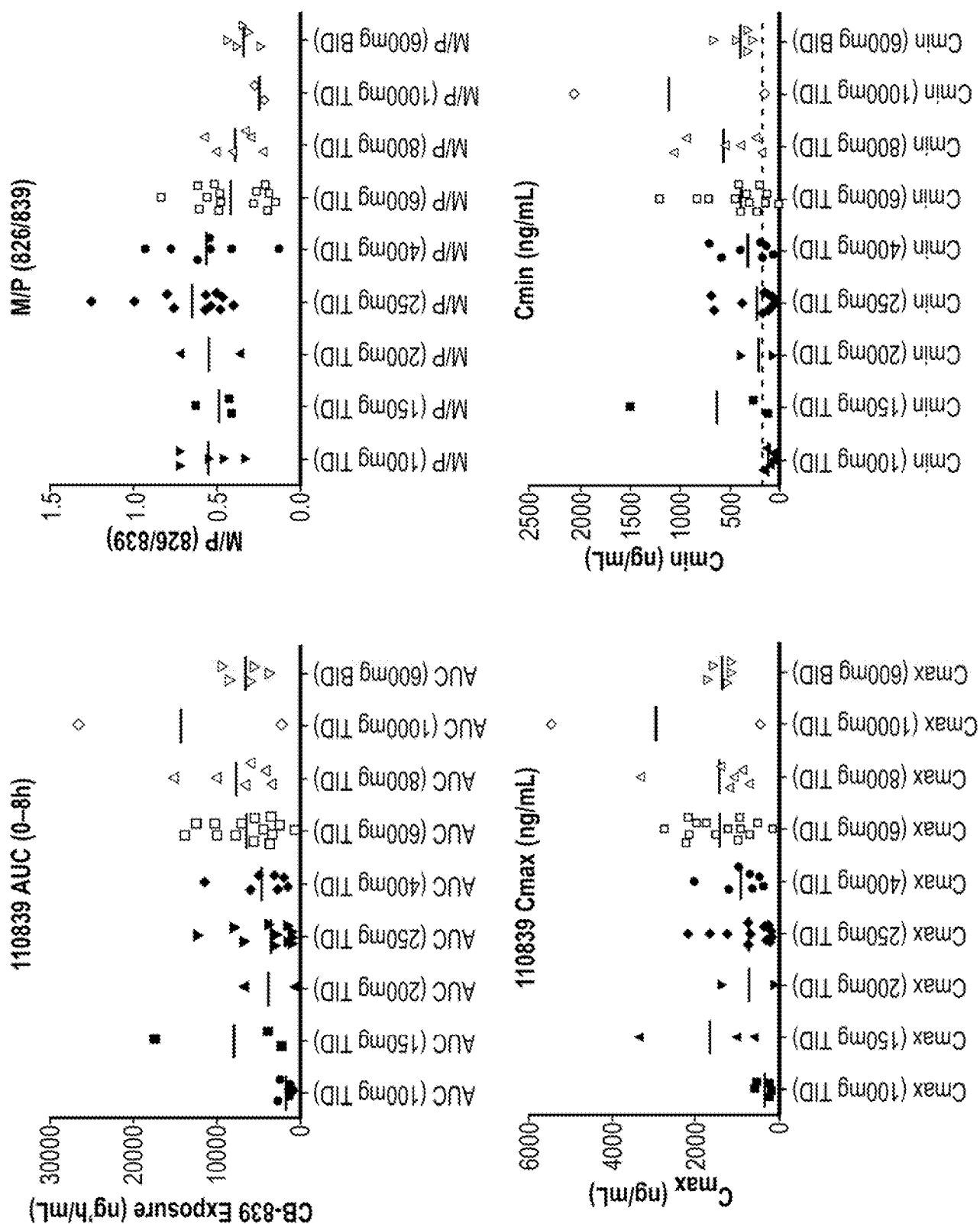


Figure 1

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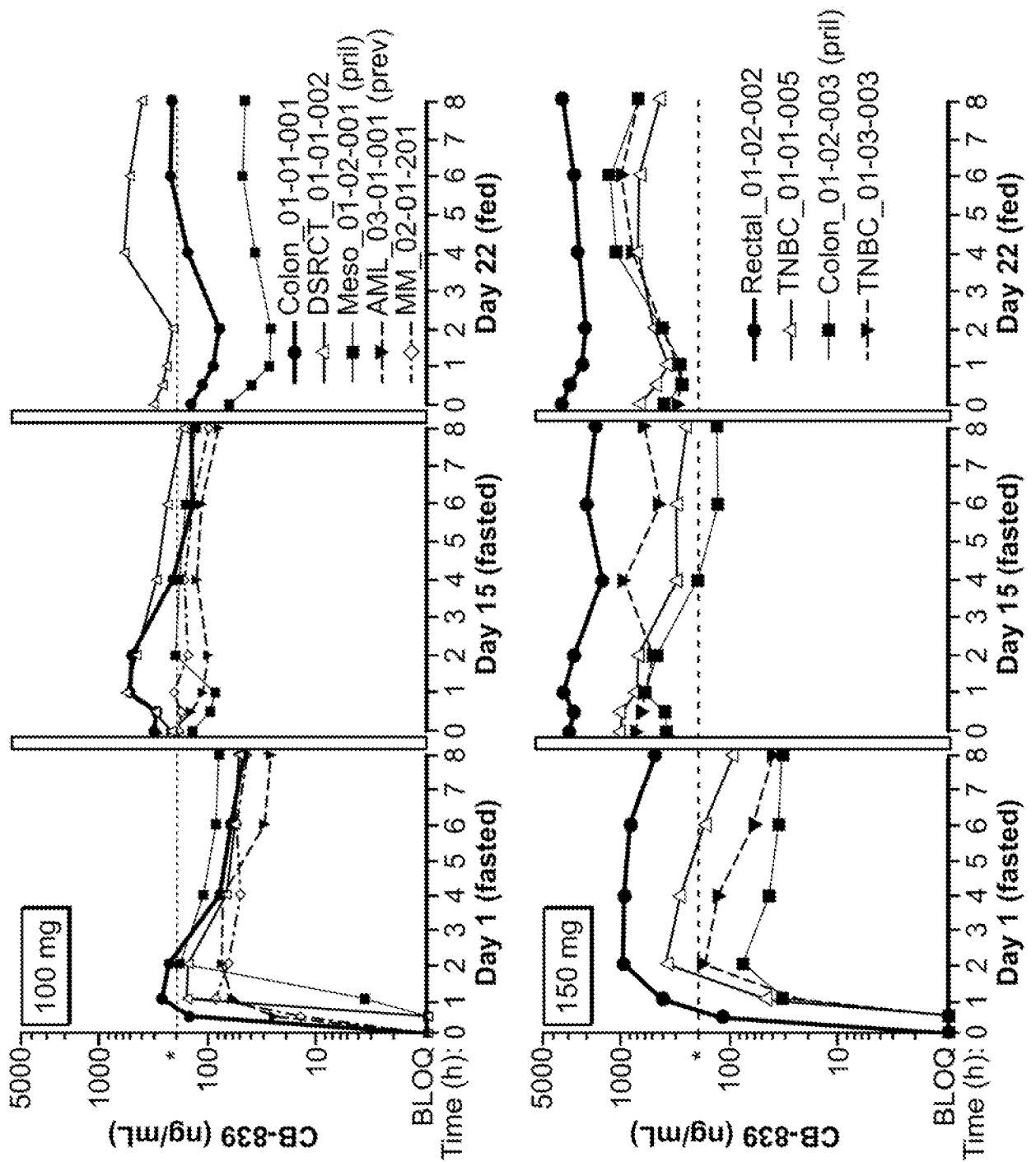
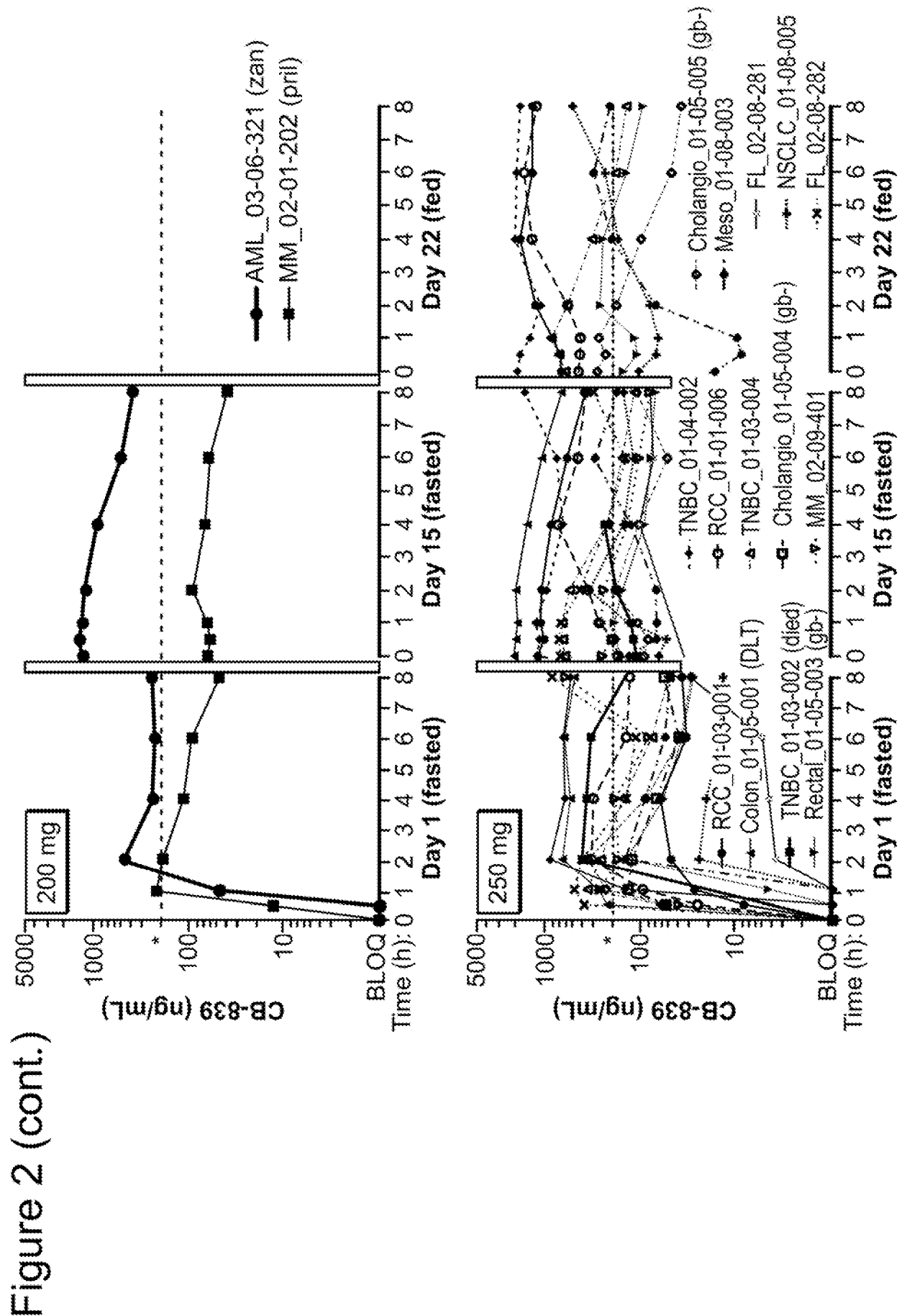
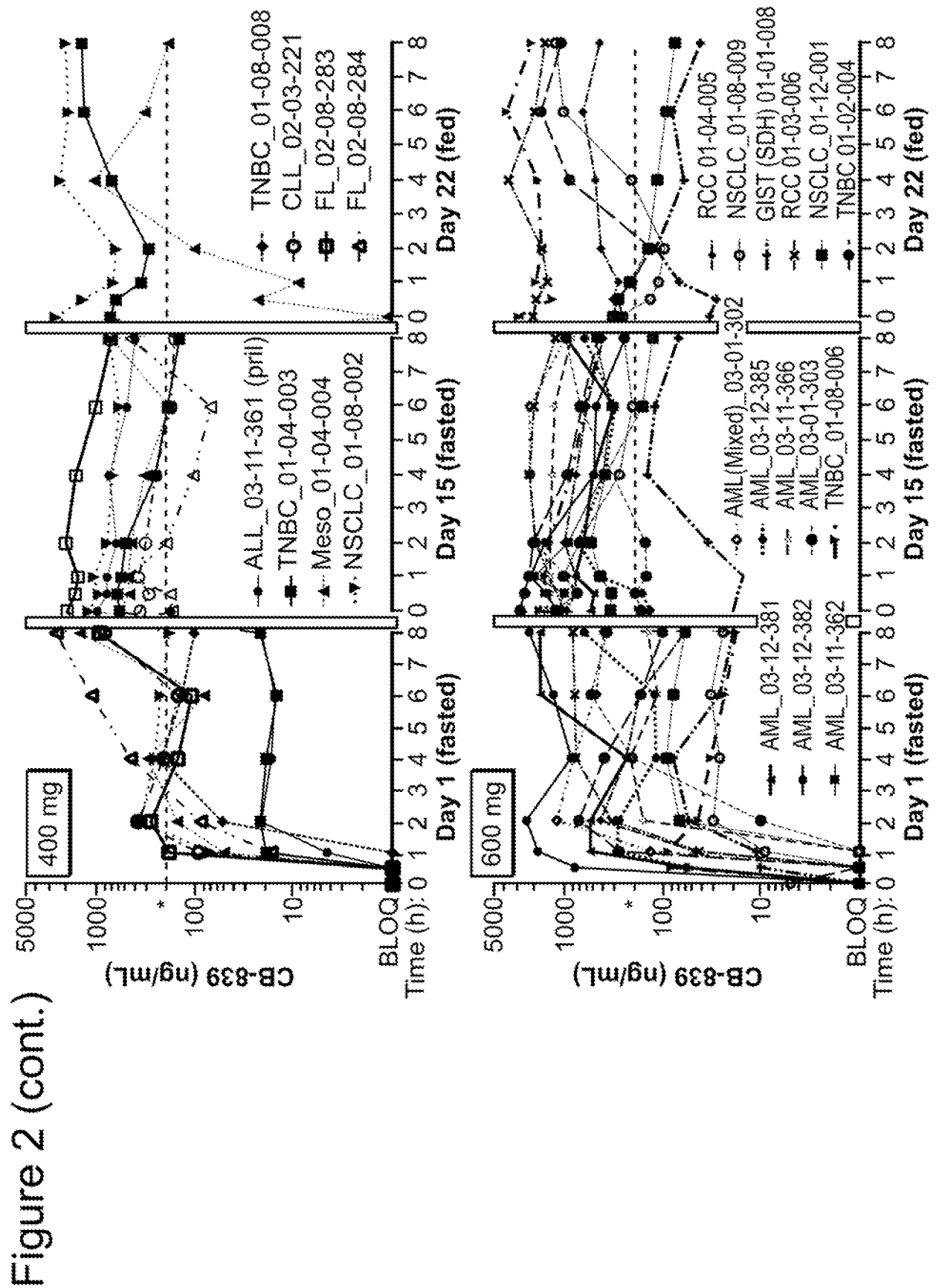


Figure 2

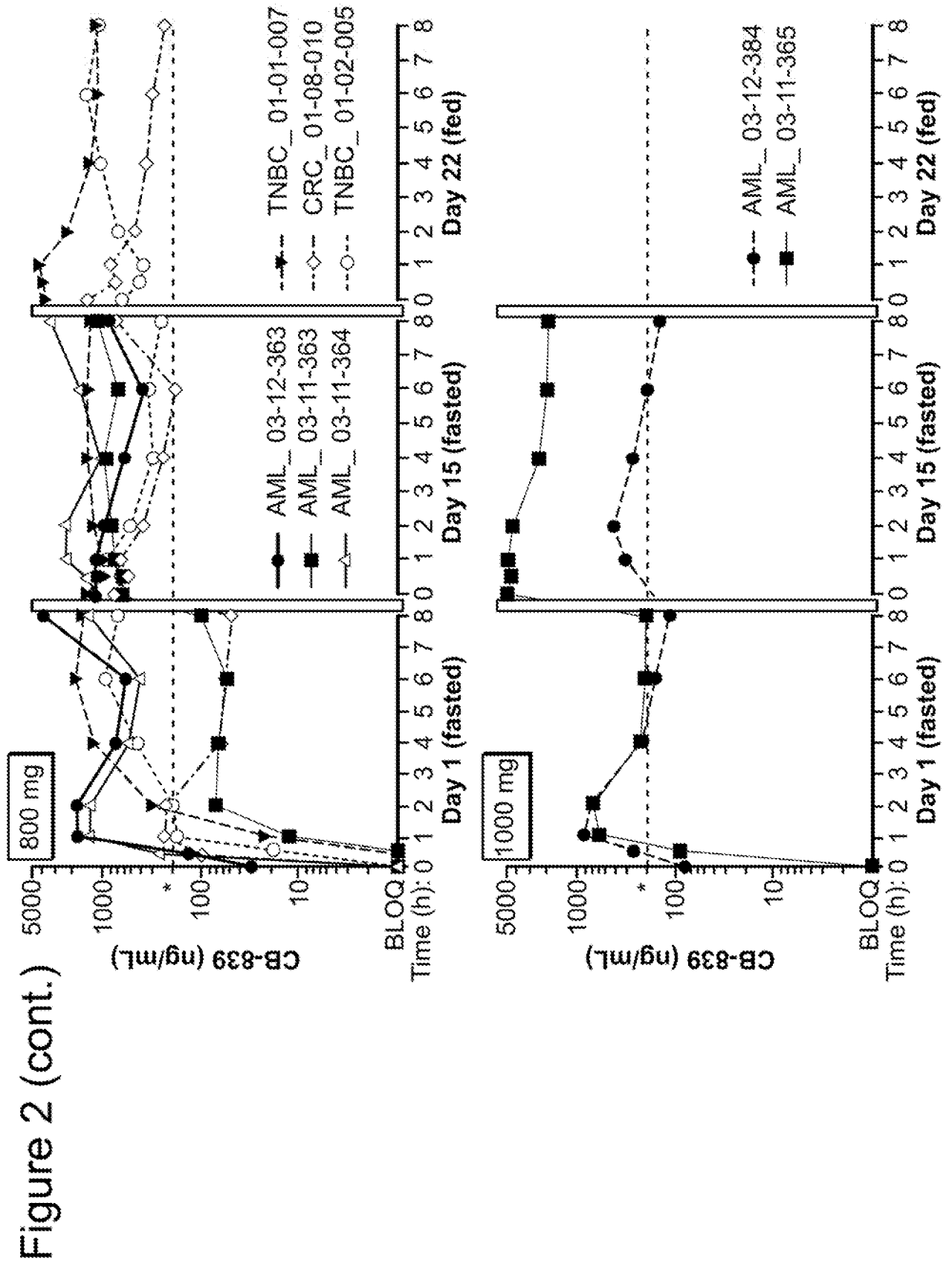
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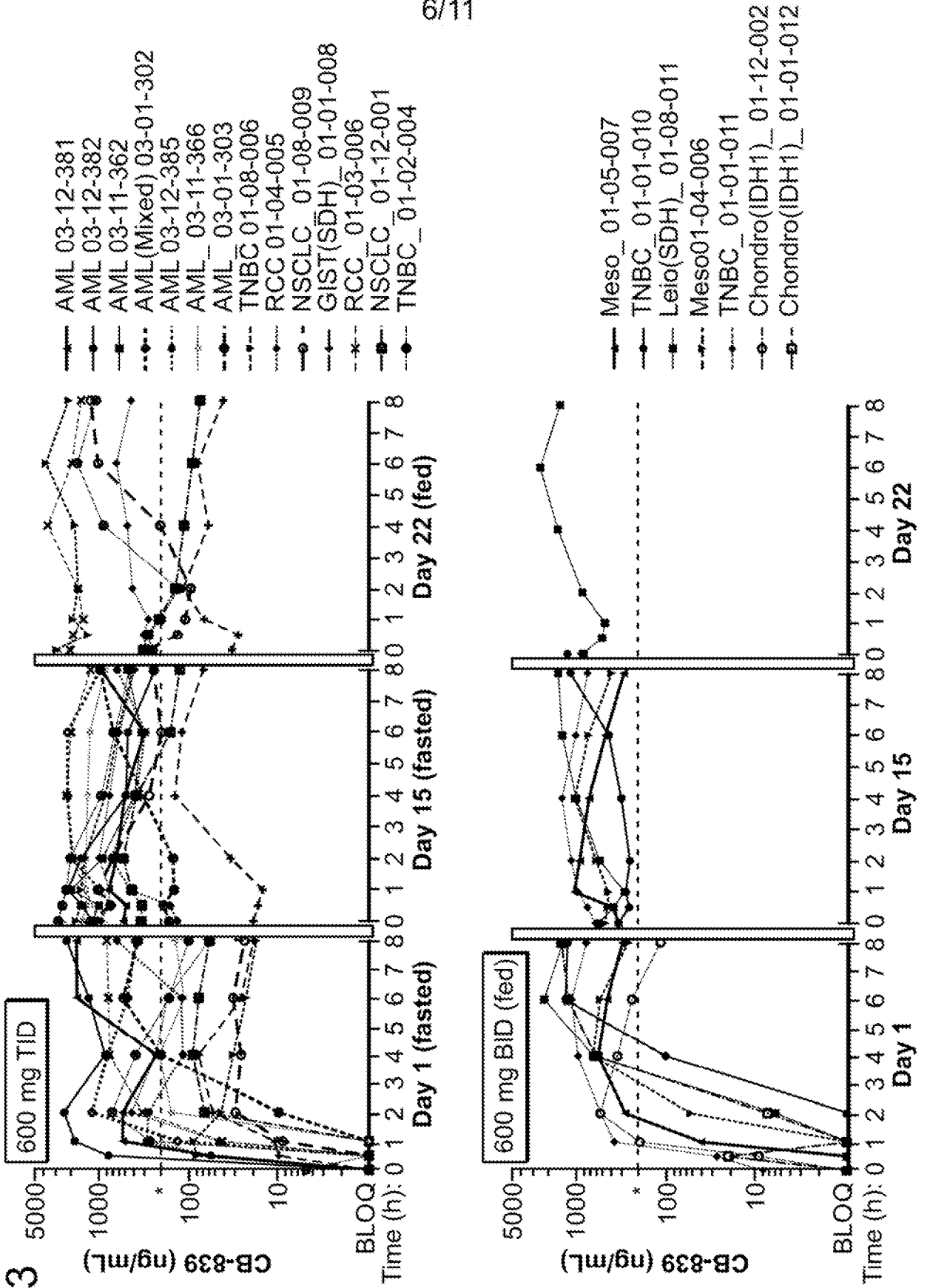


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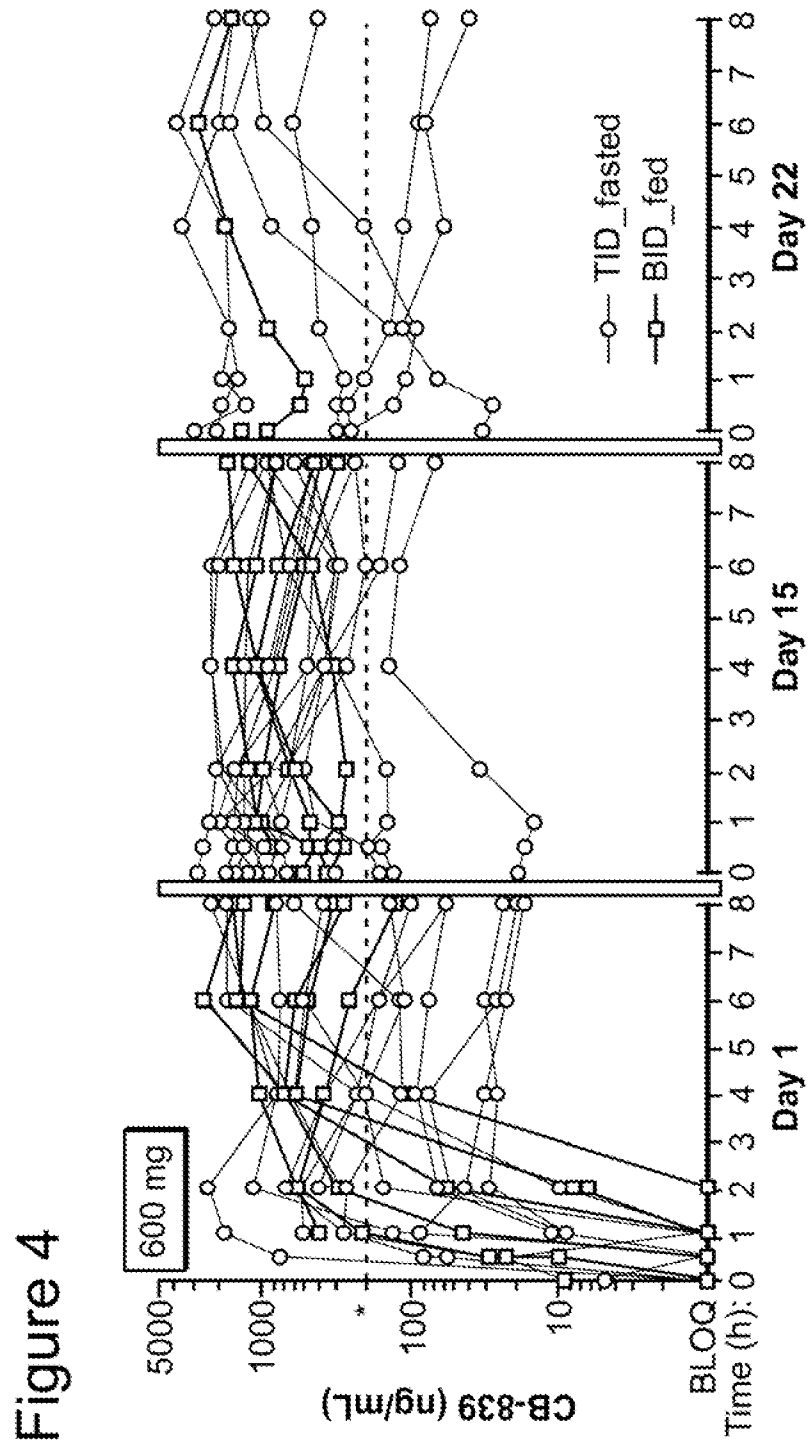


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Figure 3



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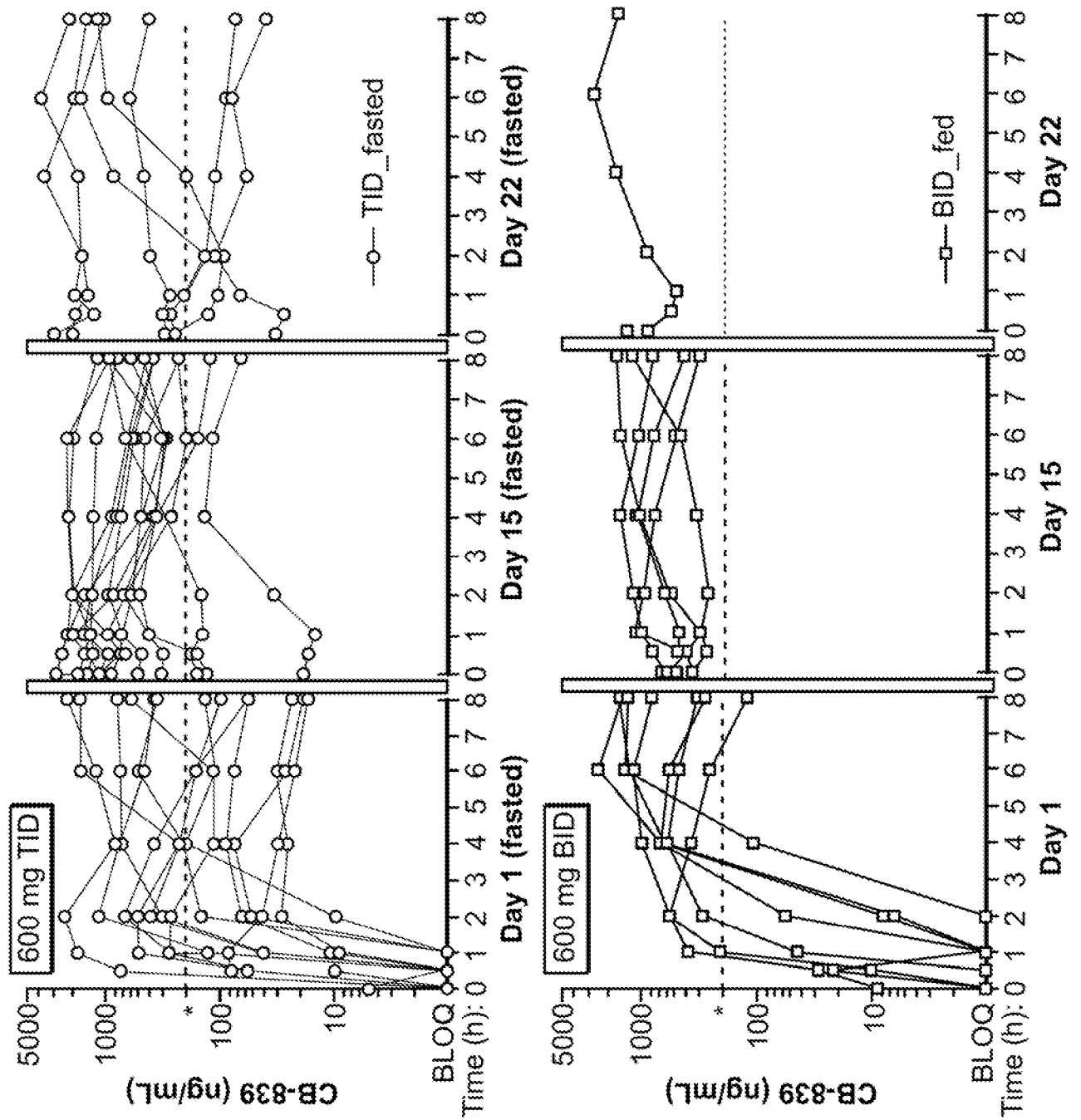


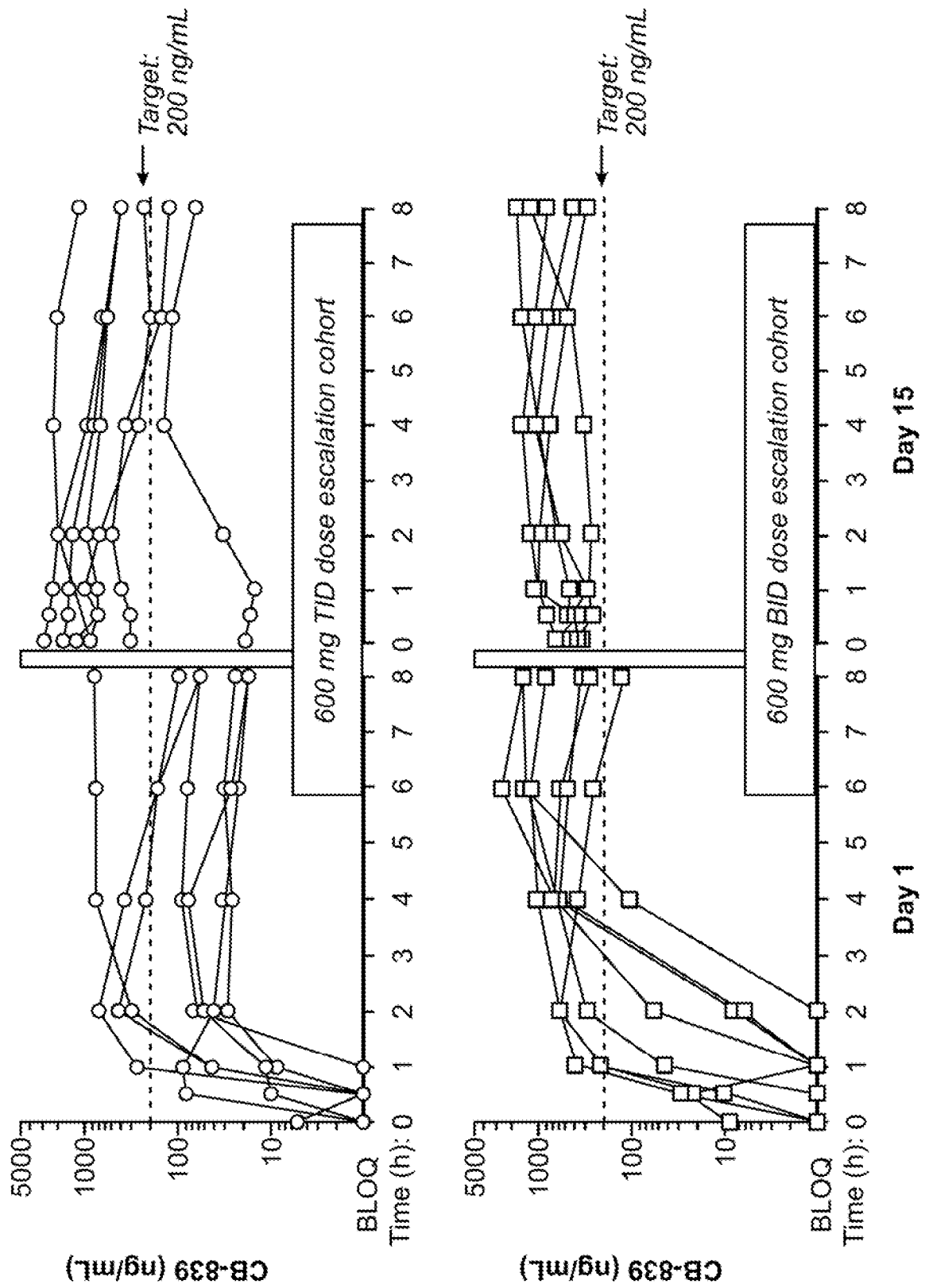
Figure 5

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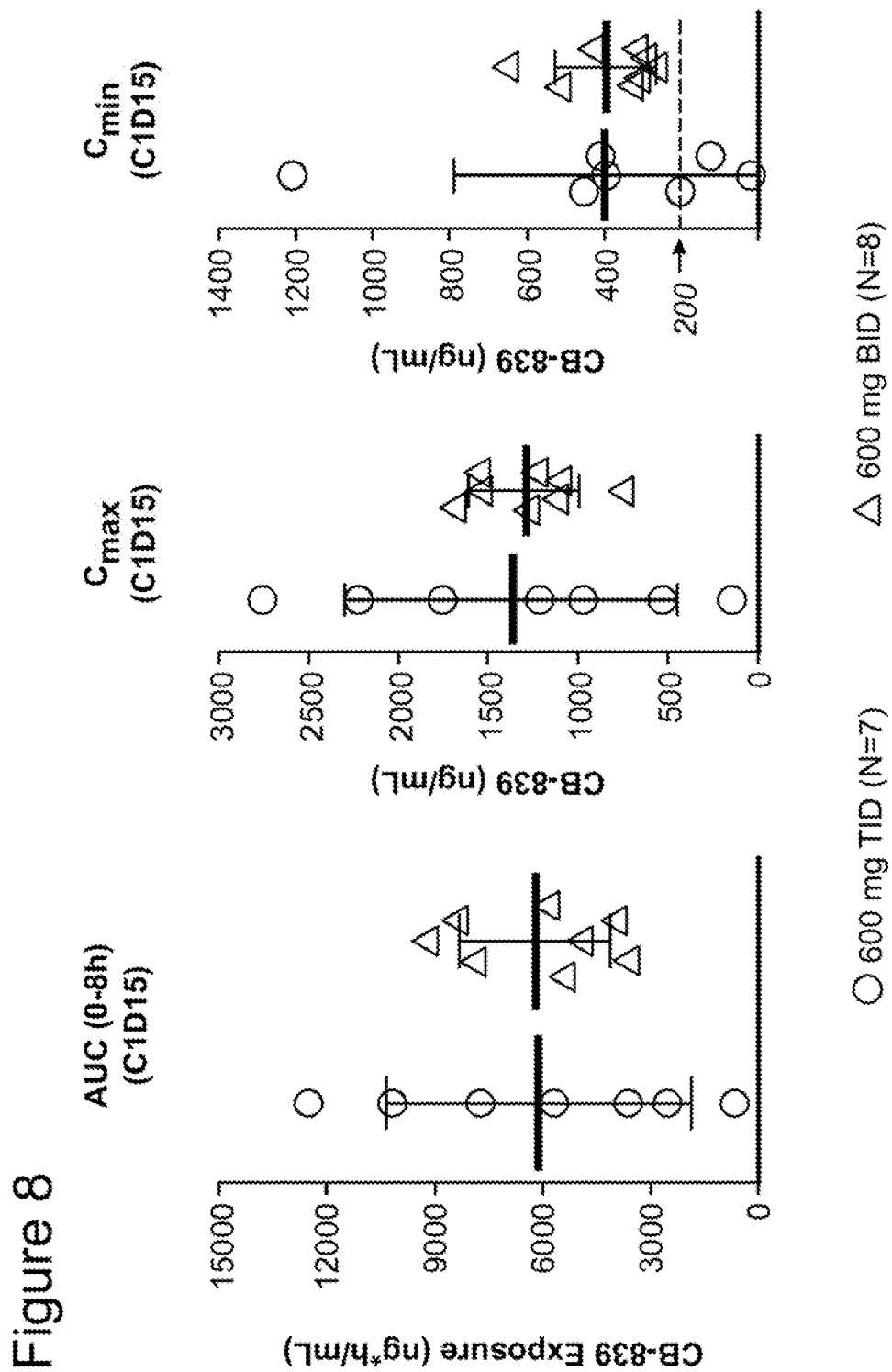
Figure 6	AUC (0-8h) (ng*hr/mL)							
	Dose (mg)	100	150	250	400	600	800	600
	Schedule	TID	TID	TID	TID	TID	TID	BID
	N	3	4	10	3	7	3	8
C_{max} (ng/mL)	Average	1980	7167	3852	3959	6125	5575	6201
	Variation (%CV)	33%	98%	101%	46%	70%	72%	34%
	Average	432	1467	778	846	1366	1019	1291
	Variation (%CV)	46%	87%	89%	38%	68%	35%	23%
C_{min} (ng/mL)	Average	134	585	241	306	400	457	366
	Variation (%CV)	32%	108%	105%	80%	98%	92%	35%

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Figure 7



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/024998

A. CLASSIFICATION OF SUBJECT MATTER IPC (2016.01) A61K 31/433, A61K 31/501, A61K 31/424500, A61P 25/00, A61P 31/12, A61P 35/00, A61P 37/00 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) IPC (2016.01) A61K 31/433, A61K 31/501, A61K 31/424500 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Databases consulted: THOMSON INNOVATION, Google Patents, CAPLUS, REGISTRY, Google Scholar Search terms used: glutaminase, inhibit, cancer, immun. , neuro. , proliferative, viral , infection, oral, administ., dosing regimen, dosage, thiazidazol, pyridazin, meal, food.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Gross, M. I. et al, Antitumor Activity of the Glutaminase Inhibitor CB-839 in Triple-Negative Breast Cancer, Molecular Cancer Therapeutics, Published online 12.4.2014, 13(4) April 2014 pages 890-901. Retrieved from the Internet: <http://mct.aacrjournals.org/content/13/4/890.full>. 12 Apr 2014 (2014/04/12) The whole document	1-9,13,22,24-39,43, 50,51,65-67,69,75-77, 81,83-85,87-91,100, 101,118,121,122
Y	The whole document	1-135
X	Bromley-Dulfano, S. Antitumor Activity Of The Glutaminase Inhibitor CB-839 In Hematological Malignances, Blood, (5 Dec 2013), Vol. 122, No. 21, page: 4226. 05 Dec 2013 (2013/12/05) The whole document	1-9,13,22,24-39,43, 50,51,60,61,76-82,118, 121,122
Y	The whole document	1-135
X	US 2014194421 A1 (CALITHERA BIOSCIENCES, INC.) 10 Jul 2014 (2014/07/10) The whole document	1-124
☒ 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 "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 28 Jun 2016		Date of mailing of the international search report 28 Jun 2016
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616		Authorized officer BARASH SHIFTAN Noga Telephone No. 972-2-5651672

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International application No.

PCT/US2016/024998

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	The whole document	1-135
X	US 2014142146 A1 (LEMIEUX RENE M) 22 May 2014 (2014/05/22) The whole document	125-127
Y	The whole document	1-135
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P,X	Jacque, N. et al. Targeting glutaminolysis has antileukemic activity in acute myeloid leukemia and synergizes with BCL-2 inhibition, Blood (20150910), Vol. 126, No. 11, pages: 1346-1356. 17 July 2015. 17 Jul 2015 (2015/07/17)	1-135
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/024998

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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权利要求书15页 说明书180页 附图11页

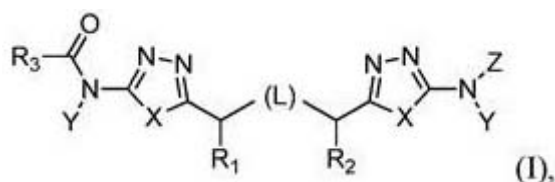
(54)发明名称

给予谷氨酰胺酶抑制剂的方法

(57)摘要

在一些方面,本发明涉及治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法,所述方法包括口服给予式I、式II、式III、式IV、式V和/或式VI的化合物,其中所述化合物与膳食(例如,如本文所定义的食物)一起或以进食模式给药。

1. 一种治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法,所述方法包括口服给予式I化合物或其药学上可接受的盐,



其中:

L表示 CH_2SCH_2 、 CH_2CH_2 、 $\text{CH}_2\text{CH}_2\text{CH}_2$ 、 CH_2 、 CH_2S 、 SCH_2 、 CH_2NHCH_2 、 $\text{CH}=\text{CH}$ 或, 其中CH或 CH_2 单元的任何氢原子可被烷基或烷氧基替代,NH单元的任何氢原子可被烷基替代,且 CH_2CH_2 、 $\text{CH}_2\text{CH}_2\text{CH}_2$ 或 CH_2 的 CH_2 单元的任何氢原子可被羟基替代;

X在每次出现时独立地表示S、O或 $\text{CH}=\text{CH}$,其中CH单元的任何氢原子可被烷基替代;

Y在每次出现时独立地表示H或 CH_2O (CO) R_7 ;

R_7 在每次出现时独立地表示H或取代的或未取代的烷基、烷氧基、氨基烷基、烷基氨基烷基、杂环基烷基或杂环基烷氧基;

Z表示H或 R_3 (CO) ;

R_1 和 R_2 各自独立地表示氢、烷基、烷氧基或羟基;

R_3 在每次出现时独立地表示取代的或未取代的烷基、羟烷基、氨基烷基、酰基氨基烷基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基、杂芳基氧基烷基或C (R_8) (R_9) (R_{10})、N (R_4) (R_5) 或 OR_6 ,其中任何游离的羟基可酰化以形成C (O) R_7 ;

R_4 和 R_5 各自独立地表示H或取代的或未取代的烷基、羟烷基、酰基、氨基烷基、酰基氨基烷基、烯基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,其中任何游离的羟基可酰化以形成C (O) R_7 ;

R_6 在每次出现时独立地表示取代的或未取代的烷基、羟烷基、氨基烷基、酰基氨基烷基、烯基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,其中任何游离的羟基可酰化以形成C (O) R_7 ;且

R_8 、 R_9 和 R_{10} 各自独立地表示H或取代的或未取代的烷基、羟基、羟烷基、氨基、酰基氨基、氨基烷基、酰基氨基烷基、烷氧基羰基、烷氧基羰基氨基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,或 R_8 和 R_9 与它们连接的碳一起形成碳环或杂环系统,其中任何游离的羟基可酰化以形成C (O) R_7 ;并且

所述化合物优选与膳食一起给予。

2. 权利要求1的方法,其中L表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 。

3. 权利要求1的方法,其中L表示 CH_2CH_2 。

4. 前述权利要求中任一项的方法,其中Y表示H。

5. 前述权利要求中任一项的方法,其中X在每次出现时独立地表示S或 $\text{CH}=\text{CH}$,其中CH单

元的任何氢原子可被烷基替代。

6. 前述权利要求中任一项的方法, 其中Z表示 $R_3(CO)$ 。

7. 权利要求6的方法, 其中每次出现的 R_3 不相同。

8. 前述权利要求中任一项的方法, 其中 R_1 和 R_2 各自表示H。

9. 前述权利要求中任一项的方法, 其中 R_3 每次出现时独立地表示取代或未取代的芳基烷基、杂芳基烷基、环烷基或杂环烷基。

10. 前述权利要求中任一项的方法, 其中 R_3 每次出现时独立地表示 $C(R_8)(R_9)(R_{10})$, 其中 R_8 表示取代或未取代的芳基、芳基烷基、杂芳基或杂芳烷基, R_9 表示H, 且 R_{10} 表示羟基、羟烷基、烷氧基或烷氧基烷基。

11. 权利要求10的方法, 其中 R_8 表示取代或未取代的芳基、芳基烷基或杂芳基。

12. 权利要求10或11的方法, 其中 R_{10} 表示羟基、羟烷基或烷氧基。

13. 权利要求1的方法, 其中L表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 , Y表示H, X表示S, Z表示 $R_3(CO)$, R_1 和 R_2 各自表示H, 并且 R_3 每次出现时独立地表示取代或未取代的芳基烷基、杂芳基烷基、环烷基或杂环烷基。

14. 权利要求13的方法, 其中每次出现的 R_3 是相同的。

15. 权利要求1的方法, 其中L表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 , Y表示H, X表示S, Z表示 $R_3(CO)$, R_1 和 R_2 各自表示H, 并且 R_3 每次出现时独立地表示 $C(R_8)(R_9)(R_{10})$, 其中 R_8 表示取代或未取代的芳基、芳基烷基、杂芳基或杂芳烷基, R_9 表示H, 并且 R_{10} 表示羟基、羟烷基、烷氧基或烷氧基烷基。

16. 权利要求15的方法, 其中L表示 CH_2CH_2 。

17. 权利要求15或16的方法, 其中 R_8 表示取代或未取代的芳基、芳基烷基或杂芳基。

18. 权利要求17的方法, 其中 R_8 表示取代或未取代的芳基。

19. 权利要求15-18中任一项的方法, 其中 R_{10} 表示羟基、羟烷基或烷氧基。

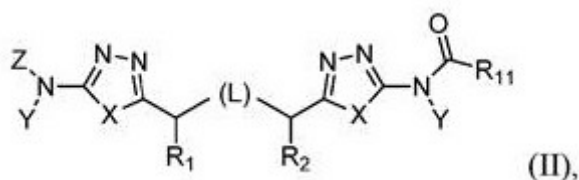
20. 权利要求19的方法, 其中 R_{10} 表示羟烷基。

21. 权利要求15-20中任一项的方法, 其中每次出现的 R_3 是相同的。

22. 权利要求1的方法, 其中L表示 CH_2CH_2 , Y表示H, X每次出现时独立地表示S或 $CH=CH$, Z表示 $R_3(CO)$, R_1 和 R_2 各自表示H, 且 R_3 每次出现时独立地表示芳烷基、杂芳烷基、环烷基或杂环烷基。

23. 权利要求22的方法, 其中每次出现的 R_3 是相同的。

24. 一种治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法, 所述方法包括口服给予式II化合物或其药学上可接受的盐,



其中:

L表示 CH_2SCH_2 、 CH_2CH_2 、 $CH_2CH_2CH_2$ 、 CH_2 、 CH_2S 、 SCH_2 、 CH_2NHCH_2 、 $CH=CH$ 或, 其中CH或 CH_2 单元的任何氢原子可被烷基或烷氧基替代, NH单元的任何氢原子可被烷基替代, 且

CH₂CH₂、CH₂CH₂CH₂或CH₂的CH₂单元的任何氢原子可被羟基替代；

X在每次出现时独立地表示S、O或CH=CH，其中CH单元的任何氢原子可被烷基替代；

Y在每次出现时独立地表示H或CH₂O (CO) R₇；

R₇在每次出现时独立地表示H或取代的或未取代的烷基、烷氧基、氨基烷基、烷基氨基烷基、杂环基烷基、芳基烷基或杂环基烷氧基；

Z表示H或R₃ (CO) ；

R₁和R₂各自独立地表示氢、烷基、烷氧基或羟基；

R₃表示取代的或未取代的烷基、羟烷基、氨基烷基、酰基氨基烷基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基、杂芳基氧基烷基或C (R₈) (R₉) (R₁₀)、N (R₄) (R₅) 或OR₆，其中任何游离的羟基可酰化以形成C (O) R₇；

R₄和R₅每次出现时各自独立地表示H或取代的或未取代的烷基、羟烷基、酰基、氨基烷基、酰基氨基烷基、烯基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基，其中任何游离的羟基可酰化以形成C (O) R₇；

R₆表示取代的或未取代的烷基、羟烷基、氨基烷基、酰基氨基烷基、烯基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基，其中任何游离的羟基可酰化以形成C (O) R₇；

R₈、R₉和R₁₀每次出现时各自独立地表示H或取代的或未取代的烷基、羟基、羟烷基、氨基、酰基氨基、氨基烷基、酰基氨基烷基、烷氧基羰基、烷氧基羰基氨基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基，或R₈和R₉与它们连接的碳一起形成碳环或杂环系统，其中任何游离的羟基可酰化以形成C (O) R₇；且其中R₈、R₉和R₁₀中的至少两个不为氢；

R₁₁表示芳基、芳基烷基、芳基氧基、芳基氧基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基，或R₁₁表示C (R₁₂) (R₁₃) (R₁₄)、N (R₄) (R₁₄) 或OR₁₄，其中任何游离的羟基可酰化以形成C (O) R₇；

R₁₂和R₁₃各自独立地表示H或取代的或未取代的烷基、羟基、羟烷基、氨基、酰基氨基、氨基烷基、酰基氨基烷基、烷氧基羰基、烷氧基羰基氨基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基，其中任何游离的羟基可酰化以形成C (O) R₇，且其中R₁₂和R₁₃二者不都为氢；

R₁₄表示芳基、芳基烷基、芳基氧基、芳基氧基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基；且

所述化合物优选与膳食一起给予。

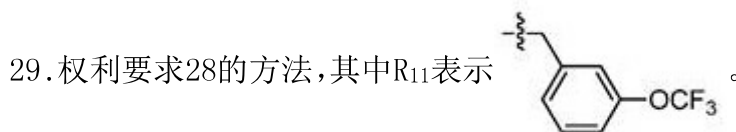
25. 权利要求24的方法，其中R₁₁表示芳基、芳基烷基、芳基氧基、芳基氧基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基，并且所述芳基或杂芳基环被-OCHF₂或-OCF₃取代并任选被进一步取代。

26. 权利要求24或25的方法，其中R₁₄表示芳基、芳基烷基、芳基氧基、芳基氧基烷基、杂

芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,并且所述芳基或杂芳基环被 $-OCHF_2$ 或 $-OCF_3$ 取代并任选被进一步取代。

27. 权利要求25或26的方法,其中 R_{11} 表示芳基烷基,其中所述芳环被 $-OCF_3$ 取代。

28. 权利要求27的方法,其中 R_{11} 表示三氟甲氧基苄基。



30. 权利要求24-29中任一项的方法,其中L表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 。

31. 权利要求24-30中任一项的方法,其中L表示 CH_2CH_2 。

32. 权利要求24-31中任一项的方法,其中每个Y表示H。

33. 权利要求24-32中任一项的方法,其中X表示S或 $CH=CH$,其中CH单元的任何氢原子可被烷基替代。

34. 权利要求24-33中任一项的方法,其中Z表示 $R_3(CO)$ 。

35. 权利要求34的方法,其中 R_3 和 R_{11} 不相同。

36. 权利要求24-35中任一项的方法,其中 R_1 和 R_2 各自表示H。

37. 权利要求24至36中任一项的方法,其中Z表示 $R_3(CO)$ 且 R_3 表示取代或未取代的芳基烷基、杂芳基烷基、环烷基或杂环烷基。

38. 权利要求37的方法,其中Z表示 $R_3(CO)$ 且 R_3 表示取代或未取代的杂芳基烷基。

39. 权利要求38的方法,其中Z表示 $R_3(CO)$ 且 R_3 表示取代或未取代的吡啶基烷基。

40. 权利要求24-36中任一项的方法,其中Z表示 $R_3(CO)$ 且 R_3 表示 $C(R_8)(R_9)(R_{10})$,其中 R_8 表示取代或未取代的芳基、芳基烷基、杂芳基或杂芳烷基, R_9 表示H,且 R_{10} 表示羟基、羟烷基、烷氧基或烷氧基烷基。

41. 权利要求40的方法,其中 R_8 表示取代或未取代的芳基、芳基烷基或杂芳基。

42. 权利要求40或41的方法,其中 R_{10} 表示羟基、羟烷基或烷氧基。

43. 权利要求24-29中任一项的方法,其中L表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 ,每个Y表示H,X表示S,Z表示 $R_3(CO)$, R_1 和 R_2 各自表示H,且 R_3 表示取代或未取代的芳基烷基、杂芳基烷基、环烷基或杂环烷基。

44. 权利要求24-29中任一项的方法,其中L表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 ,每个Y表示H,X表示S,Z表示 $R_3(CO)$, R_1 和 R_2 各自表示H,且 R_3 表示 $C(R_8)(R_9)(R_{10})$,其中 R_8 表示取代或未取代的芳基、芳基烷基、杂芳基或杂芳烷基, R_9 表示H,并且 R_{10} 表示羟基、羟烷基、烷氧基或烷氧基烷基。

45. 权利要求44的方法,其中L表示 CH_2CH_2 。

46. 权利要求44或45的方法,其中 R_8 表示取代或未取代的芳基、芳基烷基或杂芳基。

47. 权利要求46的方法,其中 R_8 表示取代或未取代的芳基。

48. 权利要求44-47中任一项的方法,其中 R_{10} 表示羟基、羟烷基或烷氧基。

49. 权利要求48的方法,其中 R_{10} 表示羟烷基。

50. 权利要求25-29中任一项的方法,其中L表示 CH_2CH_2 ,每个Y表示H,X表示S,Z表示 $R_3(CO)$, R_1 和 R_2 各自表示H,且 R_3 表示芳基烷基、杂芳基烷基、环烷基或杂环烷基。

51. 权利要求50的方法, 其中 R_3 表示杂芳基烷基。

52. 前述权利要求中任一项的方法, 所述方法还包括联合给予免疫调节剂。

53. 权利要求52的方法, 其中相对于作为单一药剂的所述免疫调节剂或化合物的单个给予, 联合给予所述免疫调节剂和化合物提供了改善的功效。

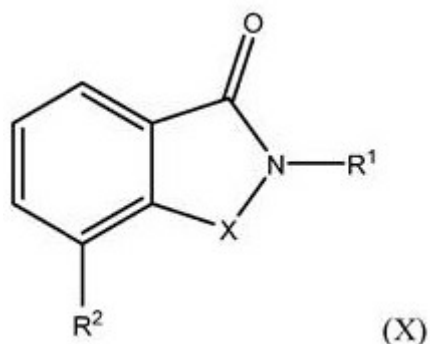
54. 权利要求53的方法, 其中联合给予所述免疫调节剂和化合物提供了累加效应。

55. 权利要求53的方法, 其中联合给予所述免疫调节剂和化合物提供了协同效应。

56. 权利要求52-55中任一项的方法, 其中所述免疫调节剂和化合物同时给予。

57. 权利要求52-55中任一项的方法, 其中所述免疫调节剂在所述化合物之前或之后约5分钟内至约168小时内给予。

58. 权利要求52至57中任一项的方法, 其中所述免疫调节剂具有式X的结构或其药学上可接受的盐、前药和/或立体异构体:

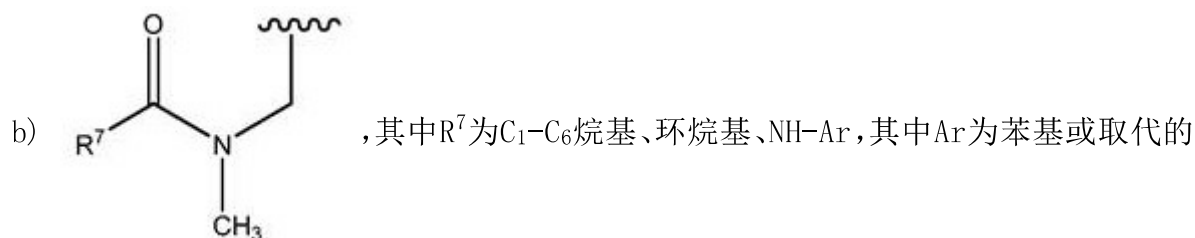
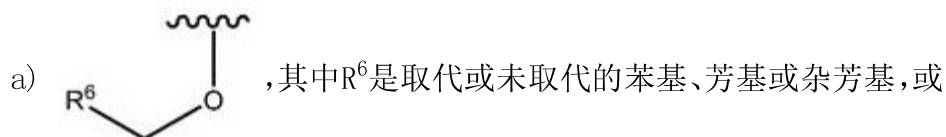


其中:

X是C=O或CH₂;

R¹是杂环基, 诸如2,6-二氧代哌啶-3-基, 或芳烷基, 诸如磺酰基取代的芳烷基, 和

R²独立地为氢、氨基、酰基氨基、烷基氨基, 或者是以下部分之一:



苯基, 或NR⁸R⁹, 其中R⁸和R⁹可独立地为H或C₁-C₆-烷基。

59. 权利要求52-58中任一项的方法, 其中所述免疫调节剂选自阿普斯特 (apremilast) (CC-10004)、来那度胺 (lenalidomide) (CC-5013)、泊马度胺 (pomalidomide) (CC-4047)、沙利度胺 (thalidomide)、CC-11006和CC-10015。

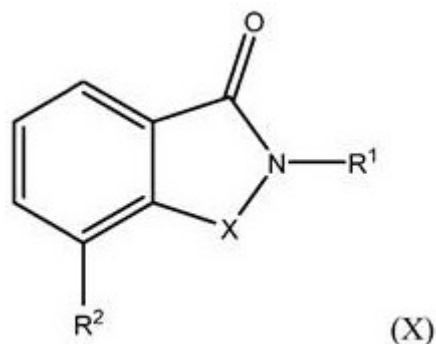
60. 前述权利要求中任一项的方法, 所述方法用于治疗癌症, 其中所述癌症选自急性骨髓性白血病 (AML)、脑恶性肿瘤、慢性淋巴细胞性白血病 (CLL)、弥漫性大B细胞淋巴瘤 (DLBCL)、滤泡淋巴瘤、霍奇金淋巴瘤 (Hodgkin's lymphoma)、卡波西氏肉瘤 (Kaposi's

sarcoma)、MALT淋巴瘤、套细胞淋巴瘤(MCL)、多发性骨髓瘤(MM)、骨髓增生异常综合征(MDS)、非霍奇金淋巴瘤(NHL)和瓦尔登斯特伦巨球蛋白血症(WM)。

61. 权利要求60的方法,其中所述癌症是多发性骨髓瘤。

62. 权利要求60或61的方法,其中所述癌症对免疫调节剂具有抗性。

63. 权利要求62的方法,其中所述癌症对具有式X结构的分子或其药学上可接受的盐、前药和/或立体异构体具有抗性:

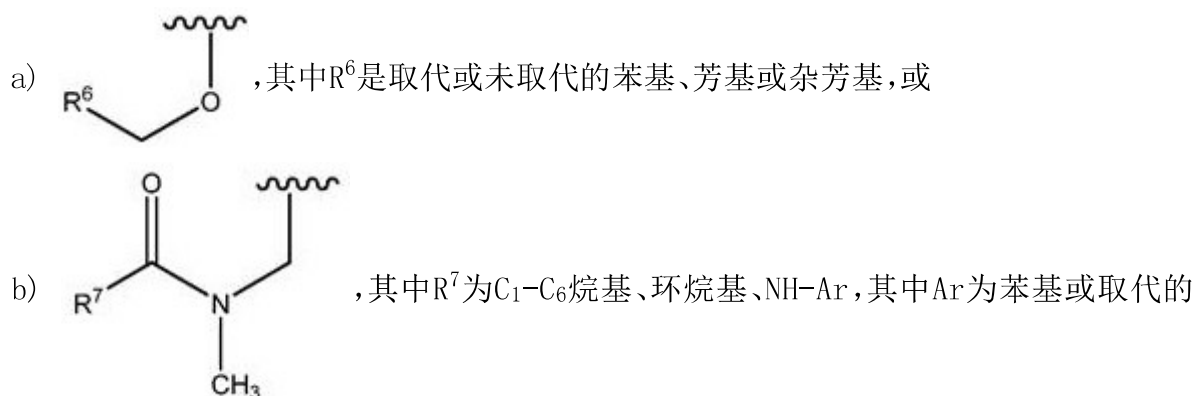


其中:

X是C=O或CH₂;

R¹是杂环基,诸如2,6-二氧代哌啶-3-基,或芳烷基,诸如磺酰基取代的芳烷基,和

R²独立地为氢、氨基、酰基氨基、烷基氨基,或为以下部分之一:



苯基,或NR⁸R⁹,其中R⁸和R⁹可独立地为H或C₁-C₆-烷基。

64. 权利要求60-63中任一项的方法,其中所述免疫调节剂是阿普斯特(apremilast)、来那度胺(lenalidomide)、泊马度胺(pomalidomide)、沙利度胺(thalidomide、CC-11006或CC-10015)。

65. 权利要求1-59中任一项的方法,所述方法用于治疗癌症,其中所述癌症选自乳腺癌、结直肠癌、内分泌癌、肺癌、黑素瘤、间皮瘤、肾癌和B细胞恶性肿瘤。

66. 权利要求65的方法,其中所述癌症是乳腺癌。

67. 权利要求66的方法,其中所述乳腺癌包括基底样乳腺癌细胞、三阴乳腺癌细胞或claudin-low型乳腺癌细胞。

68. 权利要求67的方法,其中所述乳腺癌包括基底样乳腺癌细胞。

69. 权利要求67的方法,其中所述乳腺癌包括三阴乳腺癌细胞。

70. 权利要求67的方法,其中所述乳腺癌包括claudin-low型乳腺癌细胞。

71. 权利要求65的方法,其中所述癌症是结肠直肠癌。
72. 权利要求65的方法,其中所述癌症是内分泌癌。
73. 权利要求72的方法,其中所述内分泌癌选自肾上腺皮质腺瘤、肾上腺皮质瘤、肾上腺嗜铬细胞瘤和甲状旁腺腺瘤。
74. 权利要求65的方法,其中所述癌症是黑素瘤。
75. 权利要求65的方法,其中所述癌症是肾癌。
76. 权利要求65的方法,其中所述癌症是B细胞恶性肿瘤。
77. 权利要求76的方法,其中所述B细胞恶性肿瘤选自多发性骨髓瘤、白血病和淋巴瘤。
78. 权利要求77的方法,其中所述B细胞恶性肿瘤是多发性骨髓瘤。
79. 权利要求77的方法,其中所述B细胞恶性肿瘤是白血病。
80. 权利要求79的方法,其中所述白血病选自急性成淋巴细胞性白血病和慢性成淋巴细胞性白血病。
81. 权利要求77的方法,其中所述B细胞恶性肿瘤是淋巴瘤。
82. 权利要求81的方法,其中所述淋巴瘤选自伯基特氏淋巴瘤 (Burkitt's lymphoma)、弥漫性大B细胞淋巴瘤、滤泡性淋巴瘤和霍奇金淋巴瘤。
83. 前述权利要求中任一项的方法,所述方法还包括联合给予一种或多种另外的化学治疗剂。
84. 权利要求83的方法,其中相对于所述化合物或所述一种或多种另外的化学治疗剂的每次单个给予,联合给予一种或多种另外的化学治疗剂提供了改善的功效。
85. 权利要求84的方法,其中联合给予一种或多种另外的化学治疗剂提供了协同效应。
86. 权利要求84的方法,其中联合给予一种或多种另外的化学治疗剂提供了累加效应。
87. 权利要求83至86中任一项的方法,其中所述化合物和所述一种或多种另外的化学治疗剂同时给予。
88. 权利要求83至86中任一项的方法,其中所述一种或多种另外的化学治疗剂在给予所述化合物之前或之后约5分钟内至约168小时内给予。
89. 权利要求83至88中的任一项,其中所述一种或多种另外的化学治疗剂选自ABT-263、氨鲁米特 (aminoglutethimide)、安吡啶 (amsacrine)、阿那曲唑 (anastrozole)、天冬酰胺酶 (asparaginase)、阿扎胞苷 (azacitidine)、AZD5363、卡介苗 (bcg) (Bacillus Calmette-Guérin vaccine (bcg))、比卡鲁胺 (bicalutamide)、博来霉素 (bleomycin)、硼替佐米 (bortezomib)、布塞瑞林 (buserelin)、白消安 (busulfan)、喜树碱 (camptothecin)、卡培他滨 (capecitabine)、卡铂 (carboplatin)、卡非佐米 (carfilzomib)、卡莫司汀 (carmustine)、苯丁酸氮芥 (chlorambucil)、氯喹 (chloroquine)、顺铂 (cisplatin)、克拉屈滨 (cladribine)、氯膦酸盐 (clodronate)、考比替尼 (cobimetinib)、秋水仙碱 (colchicine)、环磷酰胺 (cyclophosphamide)、环丙孕酮 (cyproterone)、阿糖胞苷 (cytarabine)、达卡巴嗪 (dacarbazine)、更生霉素 (dactinomycin)、柔红霉素 (daunorubicin)、脱甲绿胶酶素 (demethoxyviridin)、地塞米松 (dexamethasone)、二氯乙酸酯 (dichloroacetate)、双烯雌酚 (dienestrol)、己烯雌酚 (diethylstilbestrol)、多西他赛 (docetaxel)、阿霉素 (doxorubicin)、表柔比星 (epirubicin)、艾日布林 (eribulin)、厄洛替尼 (erlotinib)、雌二醇 (estradiol)、雌莫司汀 (estramustine)、依托泊苷

(etoposide)、依维莫司(everolimus)、依西美坦(exemestane)、非格司亭(filgrastim)、氟达拉滨(fludarabine)、氟氢可的松(fludrocortisone)、氟尿嘧啶(flurouracil(例如5-氟尿嘧啶))、氟甲睾酮(flouxymesterone)、氟他米特(flutamide)、吉西他滨(gemcitabine)、染料木黄酮(genistein)、戈舍瑞林(goserelin)、羟基脲(hydroxyurea)、伊达比星(idarubicin)、异环磷酰胺(ifosfamide)、伊马替尼(imatinib)、干扰素(interferon)、伊立替康(irinotecan)、伊沙匹隆(ixabepilone)、来那度胺(lenalidomide)、来曲唑(letrozole)、亚叶酸(leucovorin)、亮丙瑞林(leuprolide)、左旋咪唑(levamisole)、洛莫司汀(lomustine)、氯尼达明(lonidamine)、氮芥(mechlorethamine)、甲羟孕酮(medroxyprogesterone)、甲地孕酮(megestrol)、美法仑(melphalan)、巯基嘌呤(mercaptopurine)、美司钠(mesna)、二甲双胍(metformin)、甲氨蝶呤(methotrexate)、米替福新(miltefosine)、丝裂霉素(mitomycin)、米托坦(mitotane)、米托蒽醌(mitoxantrone)、自力霉素(mutamycin)、MK-2206、尼鲁米特(nilutamide)、诺考达唑(nocodazole)、奥曲肽(octreotide)、奥沙利铂(oxaliplatin)、奥拉帕尼(olaparib)、紫杉醇(paclitaxel)、帕米膦酸盐(pamidronate)、帕唑帕尼(pazopanib)、喷司他丁(pentostatin)、哌立福辛(perifosine)、PF-04691502、普卡霉素(plicamycin)、泊马度胺(pomalidomide)、吡吩姆(porfimer)、丙卡巴肼(procarbazine)、雷替曲塞(raltitrexed)、利妥昔单抗(rituximab)、罗米地新(romidepsin)、rucaparib、司美替尼(selumetinib)、索拉非尼(sorafenib)、链佐星(streptozocin)、舒尼替尼(sunitinib)、苏拉明(suramin)、talazoparib、他莫昔芬(tamoxifen)、替莫唑胺(temozolomide)、坦罗莫司(temsirolimus)、替尼泊苷(teniposide)、睾酮(testosterone)、沙利度胺(thalidomide)、硫鸟嘌呤(thioguanine)、塞替派(thiotepa)、二氯环戊二烯钛(titanocene dichloride)、拓扑替康(topotecan)、曲美替尼(trametinib)、曲妥珠单抗(trastuzumab)、维甲酸(tretinoin)、艾伯维(veliparib)、长春碱(vinblastine)、长春新碱(vincristine)、长春地辛(vindesine)、长春瑞滨(vinorelbine)和伏立诺他(vorinostat)(SAHA)。

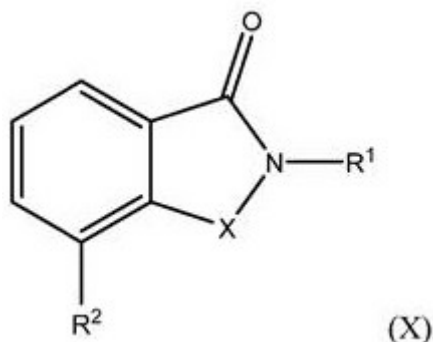
90. 权利要求89的方法, 其中所述一种或多种另外的化疗剂选自阿扎胞苷(azacitidine)、硼替佐米(bortezomib)、卡培他滨(capecitabine)、卡铂(carboplatin)、卡非佐米(carfilzomib)、环磷酰胺(cyclophosphamide)、柔红霉素(daunorubicin)、地塞米松(dexamethasone)、多西他赛(docetaxel)、阿霉素(doxorubicin)、表柔比星(epirubicin)、艾日布林(eribulin)、厄洛替尼(erlotinib)、依维莫司(everolimus)、氟尿嘧啶(flurouracil)、吉西他滨(gemcitabine)、伊沙匹隆(ixabepilone)、来那度胺(lenalidomide)、甲氨蝶呤(methotrexate)、米托蒽醌(mitoxantrone)、自力霉素(mutamycin)、紫杉醇(paclitaxel)、泊马度胺(pomalidomide)、利妥昔单抗(rituximab)、塞替派(thiotepa)、长春新碱(vincristine)和长春瑞滨(vinorelbine)。

91. 权利要求90的方法, 其中所述一种或多种另外的化学治疗剂选自阿扎胞苷(azacitidine)、地塞米松(dexamethasone)、多西他赛(docetaxel)、厄洛替尼(erlotinib)、依维莫司(everolimus)、紫杉醇(paclitaxel)和泊马度胺(pomalidomide)。

92. 权利要求1至59中任一项的方法, 所述方法用于治疗骨髓增殖性疾病, 其中所述骨髓增殖性疾病选自慢性嗜酸性粒细胞白血病、慢性髓细胞白血病(CML)、慢性中性粒细胞白血病、原发性血小板增多症、真性红细胞增多症和骨髓纤维化。

93. 权利要求92的方法, 其中所述骨髓增殖性疾病对免疫调节剂具有抗性。

94. 权利要求93的方法, 其中所述免疫调节剂具有式X的结构或其药学上可接受的盐、前药和/或立体异构体:

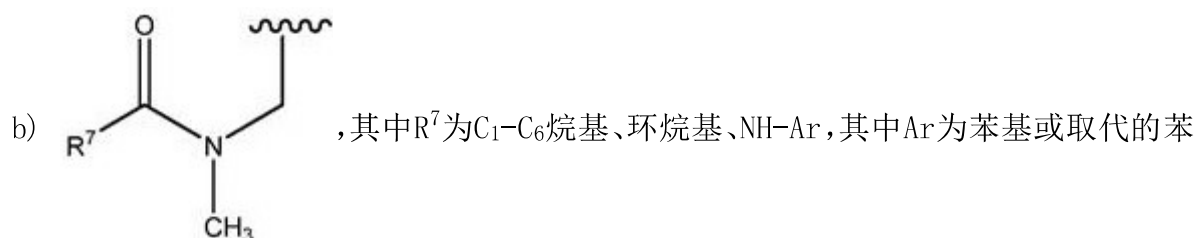
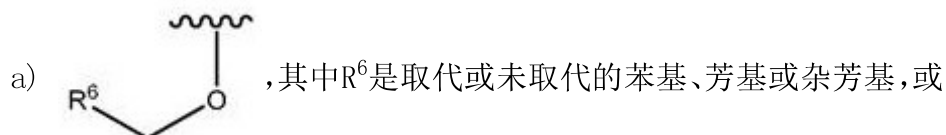


其中:

X是C=O或CH₂;

R¹是杂环基, 诸如2,6-二氧代哌啶-3-基, 或芳烷基, 诸如磺酰基取代的芳烷基, 且

R²独立地为氢、氨基、酰氨基、烷氨基, 或者是以下部分之一:

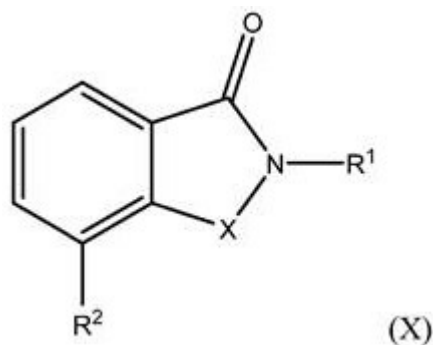


95. 权利要求92至94中任一项的方法, 其中所述免疫调节剂是来普斯特 (apremilast)、来那度胺 (lenalidomide)、泊马度胺 (pomalidomide)、沙利度胺 (thalidomide)、CC-11006 或CC-10015。

96. 权利要求1至59中任一项的方法, 所述方法用于治疗或预防免疫相关疾病, 其中所述免疫相关疾病选自强直性脊柱炎、克罗恩病、麻风结节性红斑 (ENL)、移植物抗宿主病 (GVHD)、HIV相关性消耗综合征、红斑狼疮、红细胞增多症、牛皮癣、牛皮癣性关节炎、复发性口腔溃疡、类风湿性关节炎 (RA)、严重复发性阿弗他性口炎和系统性硬化症。

97. 权利要求96的方法, 其中所述免疫相关疾病对免疫调节剂具有抗性。

98. 权利要求97的方法, 其中所述免疫调节剂具有式X的结构或其药学上可接受的盐、前药和/或立体异构体:

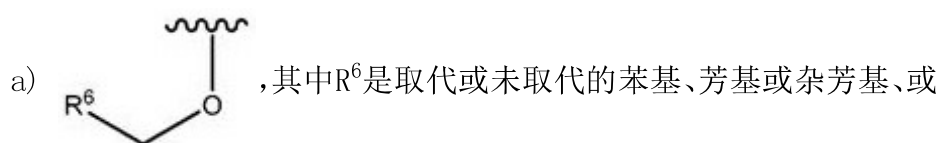


其中：

X是C=O或CH₂；

R¹是杂环基，诸如2,6-二氧代哌啶-3-基，或芳烷基，诸如磺酰基取代的芳烷基，和

R²独立地为氢、氨基、酰氨基、烷氨基，或者是以下部分之一：



基，或NR⁸R⁹，其中R⁸和R⁹可以独立地为H或C₁-C₆-烷基。

99. 权利要求96至98中任一项的方法，其中所述免疫调节剂是来普斯特 (apremilast)、来那度胺 (lenalidomide)、泊马度胺 (pomalidomide)、沙利度胺 (thalidomide)、CC-11006 或CC-10015。

100. 前述权利要求中任一项的方法，所述方法还包括联合给予一种或多种另外的化学治疗剂。

101. 权利要求100的方法，其中所述一种或多种另外的化学治疗剂包括ABT-263、氨鲁米特 (aminoglutethimide)、安吖啶 (amsacrine)、阿那曲唑 (anastrozole)、天冬酰胺酶 (asparaginase)、阿扎胞苷 (azacitidine)、AZD5363、卡介苗 (bcg) (Bacillus Calmette-Guérin vaccine (bcg))、比卡鲁胺 (bicalutamide)、博来霉素 (bleomycin)、硼替佐米 (bortezomib)、布塞瑞林 (buserelin)、白消安 (busulfan)、喜树碱 (camptothecin)、卡培他滨 (capecitabine)、卡铂 (carboplatin)、卡非佐米 (carfilzomib)、卡莫司汀 (carmustine)、苯丁酸氮芥 (chlorambucil)、氯喹 (chloroquine)、顺铂 (cisplatin)、克拉屈滨 (cladribine)、氯膦酸盐 (clodronate)、考比替尼 (cobimetinib)、秋水仙碱 (colchicine)、环磷酰胺 (cyclophosphamide)、环丙孕酮 (cyproterone)、阿糖胞苷 (cytarabine)、达卡巴嗪 (dacarbazine)、更生霉素 (dactinomycin)、柔红霉素 (daunorubicin)、脱甲绿胶酶素 (demethoxyviridin)、地塞米松 (dexamethasone)、二氯乙酸酯 (dichloroacetate)、双烯雌酚 (dienestrol)、己烯雌酚 (diethylstilbestrol)、多西

他赛(docetaxel)、阿霉素(doxorubicin)、表柔比星(epirubicin)、艾日布林(eribulin)、厄洛替尼(erlotinib)、雌二醇(estradiol)、雌莫司汀(estramustine)、依托泊苷(etoposide)、依维莫司(everolimus)、依西美坦(exemestane)、非格司亭(filgrastim)、氟达拉滨(fludarabine)、氟氢可的松(fludrocortisone)、氟尿嘧啶(flurouracil(例如5-氟尿嘧啶))、氟甲睾酮(fluxymesterone)、氟他米特(flutamide)、吉西他滨(gemcitabine)、染料木黄酮(genistein)、戈舍瑞林(goserelin)、羟基脲(hydroxyurea)、伊达比星(idarubicin)、异环磷酰胺(ifosfamide)、伊马替尼(imatinib)、干扰素(interferon)、伊立替康(irinotecan)、伊沙匹隆(ixabepilone)、来那度胺(lenalidomide)、来曲唑(letrozole)、亚叶酸(leucovorin)、亮丙瑞林(leuprolide)、左旋咪唑(levamisole)、洛莫司汀(lomustine)、氯尼达明(lonidamine)、氮芥(mechlorethamine)、甲羟孕酮(medroxyprogesterone)、甲地孕酮(megestrol)、美法仑(melphalan)、巯基嘌呤(mercaptopurine)、美司钠(mesna)、二甲双胍(metformin)、甲氨蝶呤(methotrexate)、米替福新(miltefosine)、丝裂霉素(mitomycin)、米托坦(mitotane)、米托蒽醌(mitoxantrone)、自力霉素(mutamycin)、MK-2206、尼鲁米特(nilutamide)、诺考达唑(nocodazole)、奥曲肽(octreotide)、奥沙利铂(oxaliplatin)、奥拉帕尼(olaparib)、紫杉醇(paclitaxel)、帕米膦酸盐(pamidronate)、帕唑帕尼(pazopanib)、喷司他丁(pentostatin)、哌立福辛(perifosine)、PF-04691502、普卡霉素(plicamycin)、泊马度胺(pomalidomide)、吡吩姆(porfimer)、丙卡巴肼(procarbazine)、雷替曲塞(raltitrexed)、利妥昔单抗(rituximab)、罗米地新(romidepsin)、rucaparib、司美替尼(selumetinib)、索拉非尼(sorafenib)、链佐星(streptozocin)、舒尼替尼(sunitinib)、苏拉明(suramin)、talazoparib、他莫昔芬(tamoxifen)、替莫唑胺(temozolomide)、坦罗莫司(temsirrolimus)、替尼泊苷(teniposide)、睾酮(testosterone)、沙利度胺(thalidomide)、硫鸟嘌呤(thioguanine)、塞替派(thiotepa)、二氯环戊二烯钛(titanocene dichloride)、拓扑替康(topotecan)、曲美替尼(trametinib)、曲妥珠单抗(trastuzumab)、维甲酸(tretinoin)、艾伯维(veliparib)、长春碱(vinblastine)、长春新碱(vincristine)、长春地辛(vindesine)、长春瑞滨(vinorelbine)和伏立诺他(vorinostat)(SAHA)。

102. 权利要求101的方法,其中所述一种或多种另外的化学治疗剂是地塞米松(dexamethasone)。

103. 权利要求1至51中任一项的方法,所述方法用于治疗病毒感染,其中所述病毒是天花、普通感冒、麻疹、水痘、肝炎、流感、人乳头瘤病毒、带状疱疹、疱疹、脊髓灰质炎、狂犬病、埃博拉病毒、汉他热、HIV、感冒疮、SARS(严重急性呼吸系统综合症)、登革热、爱泼斯坦-巴尔病毒、腺病毒、禽流感、A型流感病毒、B型流感病毒、麻疹、副流感病毒、呼吸道合胞病毒(RSV)、鼻病毒、SARS-CoV、柯萨奇病毒、肠病毒、脊髓灰质炎病毒、轮状病毒、乙型肝炎病毒、丙型肝炎病毒、牛病毒性腹泻病毒(替代物)、单纯疱疹1、单纯疱疹2、人巨细胞病毒、水痘带状疱疹病毒、HIV1、HIV2、猿免疫缺陷病毒、猿人免疫缺陷病毒、禽流感、登革热病毒、汉坦病毒、出血热病毒、淋巴细胞性脉络丛脑膜炎病毒、天花病毒替代物(牛痘、猴痘、兔痘)、牛痘病毒、委内瑞拉马脑脊髓炎病毒(VEE)、西尼罗河病毒或黄热病病毒。

104. 权利要求103的方法,所述方法还包括联合给予一种或多种另外的抗病毒治疗剂。

105. 权利要求104的方法,其中相对于所述化合物或所述一种或多种另外的抗病毒治

疗剂的每个单个给予,联合给予一种或多种另外的抗病毒治疗剂提供了改善的功效。

106. 权利要求105的方法,其中联合给予一种或多种另外的抗病毒治疗剂提供了协同效应。

107. 权利要求105的方法,其中联合给予一种或多种另外的抗病毒治疗剂提供了累加效应。

108. 权利要求104至107中任一项的方法,其中所述化合物和所述一种或多种另外的抗病毒治疗剂同时给予。

109. 权利要求104至107中任一项的方法,其中所述一种或多种另外的抗病毒治疗剂在给予所述化合物之前或之后约5分钟内至约168小时内给予。

110. 根据前述权利要求中任一项的方法,其中所述化合物是式III化合物并且每天给予300mg至3000mg的所述化合物。

111. 权利要求110的方法,其中每天给予600mg至2400mg的所述化合物。

112. 权利要求111的方法,其中每天给予1000mg至2000mg的所述化合物。

113. 权利要求112的方法,其中每天给予1200mg或1800mg的所述化合物。

114. 权利要求1至110中任一项的方法,其中每天给予相当于300mg至3000mg式III化合物的总剂量。

115. 权利要求114的方法,其中每天给予相当于600mg至2400mg式III化合物的总剂量。

116. 权利要求115的方法,其中每天给予相当于1000mg至2000mg式III化合物的总剂量。

117. 权利要求116的方法,其中每天给予相当于1200mg或1800mg式III化合物的总剂量。

118. 权利要求117的方法,其中每天两次给予相当于600mg式III化合物的剂量。

119. 权利要求117的方法,其中每天三次给予相当于600mg式III化合物的剂量。

120. 权利要求116的方法,其中每天给予相当于1600mg式III化合物的总剂量。

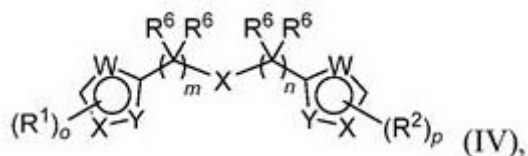
121. 权利要求120的方法,其中每天两次给予相当于800mg式III化合物的剂量。

122. 根据前述权利要求中任一项的方法,其中所述化合物每天给予两次。

123. 权利要求1至121中任一项的方法,其中所述化合物每天给予三次。

124. 根据前述权利要求中任一项的方法,其中将所述化合物给予于人。

125. 一种治疗癌症、骨髓增殖性疾病、免疫学疾病、神经疾病或病毒感染的方法,所述方法包括口服给予式(IV)的化合物或其药学上可接受的盐,



其中:

X为键、-S-、-S(O)-、-SO₂-、-CH=CH-或-C(O)-;

每个W、Y和Z独立地为-S-、-CH-、-O-、-N-或-NH-,条件是:(1)W、Y和Z中的至少一个不为-CH-;和(2)当W之一为-S-且同一环中的Y为N时,则同一环中的Z不为-CH-;

每个R¹和R²独立地为C₁₋₆亚烷基-R⁴、-N(R³)-R⁴、-N(R³)-C(O)-R⁴、-C(O)-N(R³)-R⁴、-N

$(R^3)-C(O)-O-R^4$ 、 $-N(R^3)-C(O)-N(R^3)-R^4$ 、 $-O-C(O)-N(R^3)-R^4$ 、 $-N(R^3)-C(O)-C_{1-6}$ 亚烷基- $C(O)-R^4$ 、 $-N(R^3)-C(O)-C_{1-6}$ 亚烷基- $N(R^3)-C(O)-R^4$ 或 $-N(R^{3a})-C(O)-CH_2-N(R^3)-C(O)-R^4$;

每个 R^3 独立地为氢、 C_{1-6} 烷基或芳基;

每个 R^4 独立地为 C_{1-6} 烷基、 C_{1-6} 烯基、芳基、杂芳基、芳烷基、杂芳烷基、杂环基烷基、杂环基、环烷基或环烷基烷基,其中各基团被 R^5 取代0-3次,或两个相邻的 R^5 部分与它们连接的原子一起形成杂环基、杂芳基、环烷基或芳基;

每个 R^5 独立地为氧代($-O$)、 C_{1-6} 烷基、 C_{1-6} 卤代烷基、 C_{1-6} 烷氧基、氰基、卤素、 $-OH$ 、 $-SH$ 、 $-OCF_3$ 、 $-SO_2-C_{1-6}$ 烷基、 $-NO_2$ 、 $-N(R^7)-C(O)-C_{1-6}$ 烷基、 $-N(R^6)_2$ 、 $-O-C(O)-C_{1-6}$ 烷基、 C_{3-7} 环烷基、 $(C_{3-7}$ 环烷基)烷基、芳基、芳基氧基、 $-C(O)-$ 芳基、杂芳基、芳烷基、杂芳烷基、杂环基烷基或杂环基,其中每个芳基、杂芳基或杂环基进一步被 R^7 取代0-3次;

每个 R^6 独立地为氢、氟、 OH 或 C_{1-6} 烷基;

每个 R^7 独立地为氢、 C_{1-6} 烷基、 $-OH$ 、 $-SH$ 、氰基、卤素、 $-CF_3$ 、 $-OCF_3$ 、 $-SO_2-C_{1-6}$ 烷基、 $-NO_2$ 、 $-N(R^7)-C(O)-C_{1-6}$ 烷基、 $-N(R^6)_2$ 或 C_{1-6} 烷氧基;

m 为1、2或3;

n 为1、2或3;条件是,当 X 为键时, m 和 n 的总和为3-6,且当 X 为 $-S-$ 、 $-S(O)-$ 、 $-SO_2-$ 、 $-CH-CH-$ 或 $-C(O)-$ 时, m 和 n 的总和为2-4;

o 为1、2或3;且

p 为1、2或3;

条件是:

(1) 当 X 为 $-S-$, m 和 n 均为2,每个 R^6 为 H 时,则(i) R^1 和 R^2 不都是 $-NHC(O)-R^4$,其中 R^4 为 C_{1-6} 烷基、单环芳基、单环杂芳基、单环芳烷基、单环杂芳烷基且 R^4 的每个成员被 R^5 取代0-3次;和(ii) R^1 和 R^2 不都是 $-NHC(O)O$ -甲基、 $-NHC(O)O$ -乙基、 $-NHC(\pm)-6$ -嘧啶-2,4(1H,3H)-二酮基或 $-NHC(O)NH$ -苯基,其中 $-NHC(O)NH$ -苯基部分的所述苯基任选地被1或2个选自甲基、硝基和卤素的基团取代;

(2) 当 X 为 $-S-$, m 和 n 均为1,每个 R^6 为 H 时,则(i) R^1 和 R^2 不都是 $-NH$ -苯基或 $-NH$ -4-甲氧基-苯基;

(3) 当 X 为键, m 和 n 之和为3,每个 R^6 为 H 时,则 R^1 和 R^2 不都是 $NHC(O)-$ 苯基;

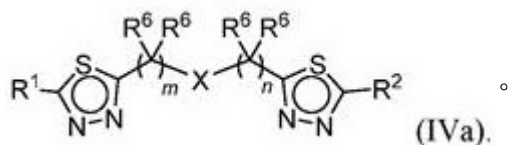
(4) 当 X 为键, m 和 n 均为2,每个 R^6 为 H 时,则 R^1 和 R^2 不都是 $-NHC(O)-$ 呋喃基、 $-NHC(O)-$ 苯基、 $-NHC(O)-$ 邻甲氧基-苯基、 $-NHC(O)-C_{1-6}$ 烷基、 $-NH$ -苄基或 $-NH$ -苯基,其中 $-NH$ -苯基部分的所述苯基被 R^5 取代0-3次;

(5) 当 X 为键, m 和 n 之和为5,每个 R^6 为 H 时,则 R^1 和 R^2 不都是 $-NHC(O)-C_{1-6}$ 烷基、 $-NHC(O)-$ 环己基或 $-NH$ -苯基,其中 $-NH$ -苯基部分的所述苯基任选地被甲基取代;

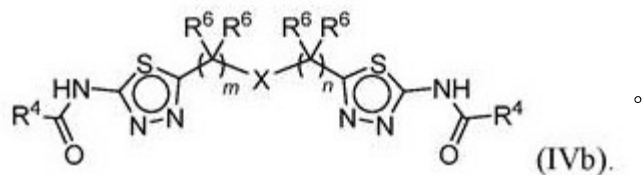
(6) 当 X 为键, m 和 n 均为3,每个 R^6 为 H 时,则 R^1 和 R^2 不都是 NH -苯基;且

所述化合物优选与膳食一起给予。

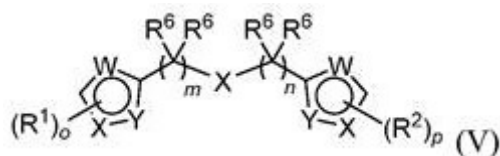
126. 权利要求125的方法,其中所述式(IV)的化合物具有式(IVa)的结构:



127. 权利要求125的方法, 其中所述式 (IV) 的化合物具有式 (IVb) 的结构:



128. 一种治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法, 所述方法包括口服给予式 (V) 的化合物,



其中

X为C₃-C₇亚环烷基;

每个W、Y和Z独立地为-S-、-CH=、-O-、-N=或-NH-, 条件是W、Y和Z中的至少一个不为-CH-;

每个R¹和R²独立地为-NH₂、-N(R³)-C(O)-R⁴、-C(O)-N(R³)-R⁴、-N(R³)-C(O)-O-R⁴、-N(R³)-C(O)-N(R³)-R⁴或-N(R³)-C(O)-SR⁴;

每个R³独立地为氢、C₁₋₆烷基或芳基;

每个R⁴独立地为C₁₋₆烷基、芳基、杂芳基、芳烷基、杂芳烷基、环烷基、环烷基烷基、杂环基烷基或杂环基, 其中各基团被R⁵取代0-3次;

每个R⁵独立地为C₁₋₆烷基、C₁₋₆烷氧基、-O-C₁₋₆亚烷基C₁₋₆烷氧基、C₁₋₆硫代烷氧基、C₁₋₆卤代烷基、C₃₋₇环烷基、C₃₋₇环烷基烷基、芳基、杂芳基、芳烷基、杂芳烷基、杂环基烷基、杂环基、氰基、卤素、氧代、-OH、-OCF₃、-OCHF₂、-SO₂-C₁₋₆烷基、-NO₂、-N(R⁷)-C(O)-C₁₋₆烷基、-C(O)-N(R⁷)₂、-N(R⁷)S(O)₁₋₂-C₁₋₆烷基、-S(O)₂N(R⁷)₂、-N(R⁷)₂-C₁₋₆亚烷基-N(R⁷)₂, 其中所述烷基、C₁₋₆烷氧基、-O-C₁₋₆亚烷基C₁₋₆烷氧基、C₁₋₆硫代烷氧基、C₁₋₆卤代烷基、C₃₋₇环烷基、C₃₋₇环烷基烷基、芳基、杂芳基、芳烷基、杂芳烷基、杂环基烷基、杂环基、-SO₂-C₁₋₆烷基、-NO₂、-N(R⁷)-C(O)-C₁₋₆烷基、-C(O)-N(R⁷)₂、-N(R⁷)S(O)₁₋₂-C₁₋₆烷基、-S(O)₂N(R⁷)₂、-N(R⁷)₂或-C₁₋₆亚烷基-N(R⁷)₂任选地被R⁸取代0-3次; 或两个相邻的R⁵部分与它们连接的原子一起形成环烷基或杂环基;

每个R⁶独立地为氢、氟、C₁₋₆烷基、-OH、-NH₂、-NH(CH₃)、-N(CH₃)₂或C₁₋₆烷氧基;

每个R⁷独立地为氢或C₁₋₆烷基;

每个R⁸独立地为卤素、C₁₋₆烷基、C₁₋₆卤代烷基、-OH、-N(R⁷)₂, 或C₁₋₆烷氧基、-O-C₁₋₆亚烷基C₁₋₆烷氧基、CN、NO₂、-N(R⁷)-C(O)-C₁₋₆烷基、-C(O)-N(R⁷)₂、-N(R⁷)S(O)₁₋₂-C₁₋₆烷基或-S(O)₂N(R⁷)₂;

m为0、1或2;

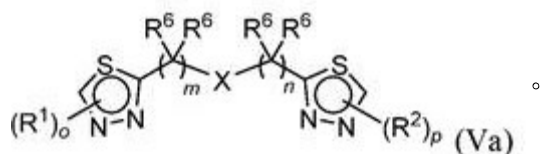
n为0、1或2;

o为1、2或3;

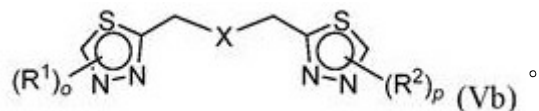
p为1、2或3; 条件是: (1) 当X为不饱和环丙基时, R¹和R²不都是NH-苯基; 且 (2) X不是取代的环丁基或取代的环戊基; 且

所述化合物优选与膳食一起给予。

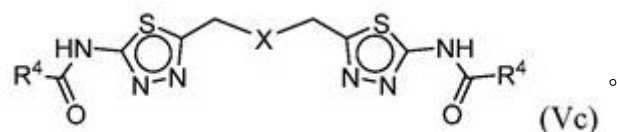
129. 权利要求128的方法, 其中所述式(V)的化合物具有式(Va)的结构:



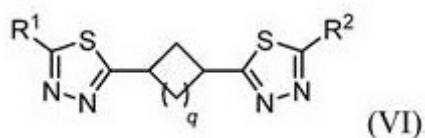
130. 权利要求128的方法, 其中所述式(V)的化合物具有式(Vb)的结构:



131. 权利要求128的方法, 其中所述式(V)的化合物具有式(Vc)的结构:

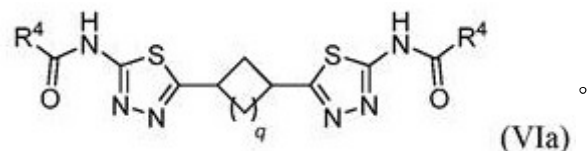


132. 权利要求128的方法, 其中所述式(V)的化合物具有式(VI)的结构:

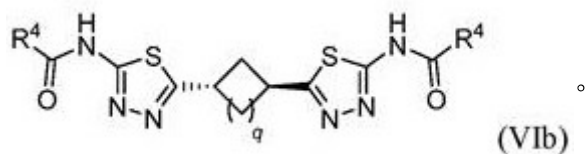


其中q是0、1、2、3或4。

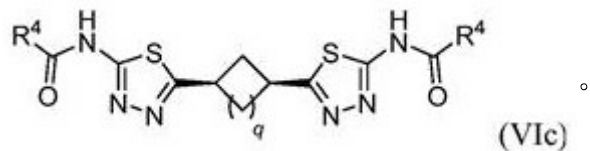
133. 权利要求128的方法, 其中所述式(V)的化合物具有式(VIa)的结构:



134. 权利要求128的方法, 其中所述式(V)的化合物具有式(VIb)的结构:



135. 权利要求128的方法, 其中所述式(V)的化合物具有式(VIc)的结构:



给予谷氨酰胺酶抑制剂的方法

[0001] 相关申请

[0002] 本申请要求2015年3月30日提交的美国临时专利申请No.62/139928和2015年5月29日提交的美国临时专利申请No.62/168112的优先权,其全部内容通过引用结合于此。

背景技术

[0003] 谷氨酰胺通过代谢和非代谢机制支持细胞存活、生长和增殖。在活性增殖细胞中,谷氨酰胺向乳酸的代谢,也称为“谷氨酰胺酵解(glutaminolysis)”,是NADPH形式的能量的主要来源。谷氨酰胺酵解中的第一步是谷氨酰胺的脱氨作用而形成谷氨酸和氨,其经谷氨酰胺酶催化。因此,经由谷氨酰胺酶的脱氨作用是对谷氨酰胺代谢的控制点。

[0004] 自从观察到腹水肿瘤细胞在氧的存在下显示出高的葡萄糖消耗和乳酸分泌速率以来,研究人员一直在探索癌症细胞如何利用代谢途径以便能够继续活性增殖。随后的研究已经证实谷氨酰胺代谢如何支持细胞复制必需的大分子合成。

[0005] 因此,已有理论认为谷氨酰胺酶为治疗以活性增殖细胞为特征的疾病诸如癌症的潜在性治疗靶标。因此,用于给予谷氨酰胺酶抑制剂以预防或治疗疾病的组合物的组合物和方法是期望的。

发明内容

[0006] 在一些方面,本发明涉及治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法,所述方法包括口服给予式I、式II、式III、式IV、式V和/或式VI化合物,其中所述化合物与膳食(例如,与如本文所定义的食物)一起给予或以进食模式给予。

附图说明

[0007] 图1显示了用各种口服剂量的式III化合物每天两次(“BID”)或每天三次(“TID”)给药进行人临床试验的稳态药代动力学结果。

[0008] 图2显示了用各种口服剂量的式III化合物每天三次与膳食一起(“进食”)或禁食状态(“禁食”)给药进行人临床试验的药代动力学结果。

[0009] 图3显示了用600mg剂量的式III化合物每天两次(“BID”;两个剂量,每次600mg)或每天三次(“TID”;三个剂量,每次600mg)给药进行人临床试验的药代动力学曲线。

[0010] 图4显示了用600mg剂量的式III化合物每天两次(“方形”;两个剂量,每次600mg)或每天三次(“圆形”;三个剂量,每次600mg)给药进行人临床试验的药代动力学曲线。

[0011] 图5显示了用600mg剂量的式III化合物每天两次(“方形”;两个剂量,每次600mg)或每天三次(“圆形”;三个剂量,每次600mg)给药进行人临床试验的药代动力学曲线。

[0012] 图6是描述CB-839的给药方案的表格。结果表明,BID进食给药方案提供了对CB-839的一致暴露。

[0013] 图7显示了用600mg剂量的式III化合物每天两次(“BID”;两个剂量,每次600mg)或每天三次(“TID”;三个剂量,每次600mg)给药进行人临床试验的药代动力学曲线。

[0014] 图8是当式III化合物在人受试者中每天两次(三角形)或每天三次(圆形)给予时绘制式III化合物的剂量水平相对于PK参数AUC、 $C_{\max}$ 和 $C_{\min}$ 的图。

具体实施方式

[0015] 定义

[0016] 如本文所用,短语“联合给予”是指两种或更多种不同的治疗化合物的任何给药形式,以便在先前给予的治疗化合物在体内仍然有效时给予第二化合物(例如,两种化合物在患者中同时有效,这可包括两种化合物的协同作用)。例如,不同的治疗化合物可以同一制剂或者以分开的制剂同时地或者顺序地给予。在某些实施方案中,不同的治疗化合物可彼此在1小时、12小时、24小时、36小时、48小时、72小时或1周内给予。因此,接受这样治疗的个体可得益于不同的治疗化合物的联合作用。

[0017] 如本文所用,术语“进食模式”是指由于胃中存在食物而引起的状态。在正常的消化过程中,物质通过胃的过程被本文中称为进食模式的生理状况延迟。在进食模式之间,胃处于消化歇息或“禁食”模式。进食模式通常由摄取食物时进入胃中的营养物质引发,并持续约4至6小时。进食模式也可以通过给予具有与膳食相同或相似效果的药理学试剂以药理学方式引发。这些进食模式引发剂可以分开给予,或者它们可以作为分散在剂型中的成分包括在剂型中或包括在外部释放包衣中。药理学进食模式引发剂的实例公开于US专利No.7,405,238中,该专利通过引用结合到本文中。

[0018] 术语“卫生保健提供者”是指提供卫生保健服务给人、社会团体等的个人或组织。“卫生保健提供者”的实例包括医师、医院、持续护理退休社区、专业护理设施、亚急性护理设施、诊所、多专科诊所、独立式门诊中心(freestanding ambulatory centers)、家庭保健服务机构和HMO。

[0019] 如本文所用的,“预防”疾病或病况的治疗剂指在统计样本中,在治疗的样本相对于未治疗的对照样本中减少疾病或病况的发生,或相对于未治疗的对照样本中延迟疾病或病况的一种或多种症状的发作或减轻其严重性的化合物。

[0020] 本文使用短语“药学上可接受的”是指在合理的医学判断范围内适合用于与人和动物的组织接触,而无过度的毒性、刺激性、过敏反应,或其它问题或并发症,与合理的利益/风险比相称的那些化合物、材料、组合物和/或剂型。

[0021] 本文所用的短语“药学上可接受的载体”意指药学上可接受的材料、组合物或溶媒,例如液体或固体填充剂、稀释剂、赋形剂、溶剂或包封材料。每种载体在与制剂的其它成分适配和对患者无害的意义上,必须是“可接受的”。可用作药学上可接受的载体的材料的一些实例包括:(1)糖,例如乳糖、葡萄糖和蔗糖;(2)淀粉,例如玉米淀粉和马铃薯淀粉;(3)纤维素及其衍生物,例如羧甲基纤维素钠、乙基纤维素和醋酸纤维素;(4)粉末化黄蓍胶;(5)麦芽;(6)明胶;(7)滑石;(8)赋形剂,例如可可脂和栓剂蜡;(9)油,例如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和豆油;(10)二醇,例如丙二醇;(11)多元醇,例如甘油、山梨醇、甘露醇和聚乙二醇;(12)酯,例如油酸乙酯和月桂酸乙酯;(13)琼脂;(14)缓冲剂,例如氢氧化镁和氢氧化铝;(15)藻酸;(16)无热原水;(17)等渗盐水;(18)林格氏溶液;(19)乙醇;(20)磷酸盐缓冲溶液;和(21)其它用于药物制剂中的无毒适配物质。

[0022] 术语“前药”旨在涵盖在生理条件下转化为本发明的治疗活性剂(例如式I-VI化合

物)的化合物。制备前药的常用方法是包括在生理条件下水解的一个或多个选择的部分以展露出所需的分子。在其他实施方案中,前药通过宿主动物的酶活性转化。例如,酯或碳酸酯(例如,醇或羧酸的酯或碳酸酯)是优选的本发明的前药。在某些实施方案中,在制剂中的某些或所有的式I-VI化合物可用相应的合适的前药替代,例如,其中母体化合物中的羟基作为酯或碳酸酯存在,或者存在于母体化合物中的羧酸作为酯存在。

[0023] 术语“治疗有效量”是指足以引起所需治疗效果的化合物浓度。一般认为化合物的有效量将根据患者的体重、性别、年龄及病史而变化。影响有效量的其它因素可包括但不限于患者状况的严重性、所治疗的疾病、化合物的稳定性,以及如果需要,与本发明化合物一起给予的另一种类型的治疗剂。较大的总剂量可通过多次给予药物而递送。确定功效和剂量的方法是本领域技术人员已知的(Isselbacher等(1996)哈里森内科原理(Harrison's Principles of Internal Medicine)第13版,1814-1882,通过引用结合到本文中)。

[0024] 术语“治疗”包括预防性治疗和/或治疗性治疗。术语“预防性或治疗性”治疗为本领域公知的并包括给予宿主一种或多种主题组合物。如果在临床表现不需要的状况(例如,宿主动物的疾病或其它不需要的状态)之前给药,那么治疗是预防性的(即,它保护宿主免于出现不需要的状况),而如果在表现不需要的状况之后给药,则治疗就是治疗性的(即,它意欲减轻、缓解或稳定已存在的不需要的状况或其副作用)。

[0025] 术语“与食物一起”、“与膳食一起”、“餐前”、“餐后”是指在时间上接近(例如,之前、期间或之后)摄取食物(例如膳食)给予化合物,更具体地说,是指在摄取食物前1、2、3、4、5、10、15、20、25或30分钟内,在进餐期间,或摄取食物后1、2、3、4、5、10、15、20、25、30、45、60或90分钟内给予化合物。在优选的实施方案中,术语“与食物一起”和“与膳食一起”是指与膳食一起、餐前(例如在摄取食物或膳食之前30分钟)、餐后(例如在摄取食物或餐之后90分钟)给予化合物。

[0026] 官能团的定义

[0027] 术语“酰基”为本领域公知的且指由通式烃基C(O)-,优选烷基C(O)-表示的基团。

[0028] 术语“酰基氨基”为本领域公知的且指用酰基取代的氨基并可例如由式烃基C(O)NH-表示。

[0029] 术语“酰基氧基”为本领域公知的且指由通式烃基C(O)O-,优选烷基C(O)O-表示的基团。

[0030] 术语“烷氧基”指其上连接有氧的烷基,优选低级烷基。代表性的烷氧基包括甲氧基、乙氧基、丙氧基、叔丁氧基等。

[0031] 术语“烷氧基烷基”指用烷氧基取代的烷基并可由通式烷基-O-烷基表示。

[0032] 本文使用的术语“烯基”指含有至少一个双键的脂族基团并意欲包括“未取代的烯基”和“取代的烯基”二者,其后者指具有替代烯基的一个或多个碳上的氢的取代基的烯基部分。这样的取代基可出现在包括或不包括在一个或多个双键中的一个或多个碳上。而且,这样的取代基包括考虑如下讨论的用于烷基的全部取代基,其中稳定性受到抑制的除外。例如,考虑被一个或多个烷基、碳环基、芳基、杂环基或杂芳基取代的烯基。

[0033] “烷基”基团或“烷烃”是完全饱和的直链或分支的非芳族烃。典型地,直链或分支的烷基具有1至约20个碳原子,优选地1至约10个碳原子,除非另外限定。直链和分支的烷基的实例包括甲基、乙基、正丙基、异丙基、正丁基、仲丁基、叔丁基、戊基、己基、戊基和辛基。

C₁-C₆直链或分支的烷基也称为“低级烷基”基团。

[0034] 而且,如在说明书、实施例和权利要求书通篇中使用的术语“烷基”(或“低级烷基”)意欲包括“未取代的烷基”和“取代的烷基”二者,其后者指具有替代烃骨架的一个或多个碳上的氢的取代基的烷基部分。这样的取代基,如果没有另外指明,可包括,例如卤素、羟基、羰基(例如羧基、烷氧基羰基、甲酰基或酰基)、硫代羰基(例如硫代酯、硫代乙酸酯或硫代甲酸酯)、烷氧基、磷酰基、磷酸酯、膦酸酯、亚膦酸酯、氨基、酰氨基、脒、亚胺、氰基、硝基、叠氮基、巯基、烷硫基、硫酸酯、磺酸酯、氨磺酰基、磺酰氨基(sulfonamido)、磺酰基、杂环基、芳烷基,或芳族或杂芳族部分。本领域技术人员应该理解,如果适宜,在烃链上取代的部分本身可被取代。例如,取代的烷基的取代基可包括取代的和未取代形式的氨基、叠氮基、亚氨基、酰氨基、磷酰基(包括膦酸酯和亚膦酸酯)、磺酰基(包括硫酸酯、磺酰氨基、氨磺酰基和磺酸酯),和甲硅烷基,以及醚、烷硫基、羰基(包括酮、醛、羧酸酯,和酯)、-CF₃、-CN等。示例性的取代的烷基在下文描述。环烷基可用烷基、烯基、烷氧基、烷硫基、氨基烷基、羰基-取代的烷基、-CF₃、-CN等进一步取代。

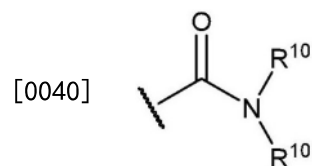
[0035] 术语“C_{x-y}”当与化学部分,例如酰基、酰基氧基、烷基、烯基、炔基或烷氧基结合使用时,意欲包括链中含有从x至y个碳的基团。例如,术语“C_{x-y}烷基”指取代的或未取代的饱和烃基,包括链中含有从x至y个碳的直链烷基和支链烷基,包括卤代烷基,例如三氟甲基和2,2,2-三氟乙基等。C₀烷基指氢,其中所述基团在末端位置,如果在内部位置的话则为键。术语“C_{2-y}烯基”和“C_{2-y}炔基”指在长度和可能的取代上类似于上述烷基,但是分别含有至少一个双键或三键的取代的或未取代的不饱和脂族基团。

[0036] 本文使用的术语“烷基氨基”指用至少一个烷基取代的氨基。

[0037] 本文使用的术语“烷硫基”指用烷基取代的硫醇基并可以由通式烷基S-表示。

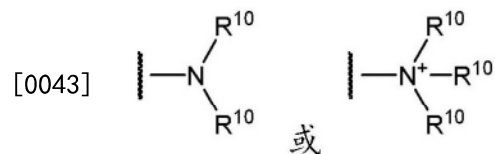
[0038] 本文使用的术语“炔基”指含有至少一个三键的脂族基团并意欲包括“未取代的炔基”和“取代的炔基”二者,其后者指具有替代炔基的一个或多个碳上的氢的取代基的炔基部分。这样的取代基可出现在包括或不包括在一个或多个三键中的一个或多个碳上。而且,这样的取代基包括考虑用于如上讨论的烷基的全部取代基,其中稳定性受到抑制的除外。例如,考虑了被一个或多个烷基、碳环基、芳基、杂环基或杂芳基取代的炔基。

[0039] 本文使用的术语“酰胺”指基团:



[0041] 其中各个R¹⁰独立地表示氢或烃基,或两个R¹⁰与它们连接的N原子一起完成在环结构中含有4-8个原子的杂环。

[0042] 术语“胺”和“氨基”是本领域公知的并且指未取代的和取代的胺二者及其盐,例如可由下式表示的部分:



[0044] 其中各个R¹⁰独立地表示氢或烃基,或两个R¹⁰与它们连接的N原子一起完成在环结

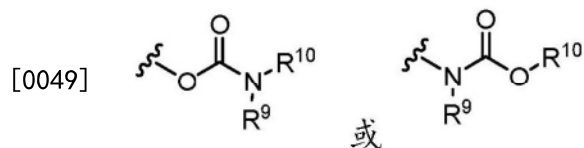
构中含有4-8个原子的杂环。

[0045] 本文使用的术语“氨基烷基”指用氨基取代的烷基。

[0046] 本文使用的术语“芳烷基”指用芳基取代的烷基。

[0047] 本文使用的术语“芳基”包括取代的或未取代的单环芳族基团,其中环上的各个原子是碳。优选所述环是5-至7-元环,更优选6-元环。术语“芳基”也包括具有两个或更多个环的多环系统,其中两个或更多个碳为两个相邻环所共有,其中至少一个环是芳族的,例如其它的环可以是环烷基、环烯基、环炔基、芳基、杂芳基和/或杂环基。芳基包括苯、萘、菲、酚、苯胺等。

[0048] 术语“氨基甲酸酯”为本领域公知的且指以下基团:



[0050] 其中 R^9 和 R^{10} 独立地表示氢或烃基,例如烷基,或 R^9 和 R^{10} 与插入的原子一起完成在环结构中含有4-8个原子的杂环。

[0051] 本文使用的术语“碳环”和“碳环的”指饱和的或不饱和的环,其中环中的各个原子是碳。术语碳环包括芳族碳环和非芳族碳环二者。非芳族碳环包括环烷烃环(其中所有的碳原子都是饱和的)和环烯烃环(其含有至少一个双键)二者。“碳环”包括5-7元单环和8-12元双环。双环碳环的每一个环可以选自饱和的、不饱和的和芳族环。碳环包括双环分子,其中一个、两个或三个或更多个原子是在两个环之间共享的。术语“稠合的碳环”指双环碳环,其中每个环与另一个环共享两个相邻的原子。稠合碳环的每个环可以选自饱和的、不饱和的和芳族环。在一个示例性实施方案中,芳族环,例如苯基,可以稠合于饱和的或不饱和环,例如环己烷、环戊烷或环己烯。饱和的、不饱和的和芳族双环的任何组合,在化学价允许时,包括在碳环的定义中。示例性“碳环”包括环戊烷、环己烷、二环[2.2.1]庚烷、1,5-环辛二烯、1,2,3,4-四氢化萘、二环[4.2.0]辛-3-烯、萘和金刚烷。示例性的稠合碳环包括十氢化萘、萘、1,2,3,4-四氢化萘、二环[4.2.0]辛烷、4,5,6,7-四氢-1H-茚和二环[4.1.0]庚-3-烯。“碳环”可以在能够携带氢原子的任何一个或多个位置上被取代。

[0052] “环烷基”基团是完全饱和的环烃。“环烷基”包括单环和双环。典型地,单环环烷基具有3至约10个碳原子,更优选3至8个碳原子,除非另外限定。双环环烷基的第二个环可选自饱和的、不饱和的和芳族环。环烷基包括双环分子,其中一个、两个或三个或更多个原子是在两个环之间共享的。术语“稠合的环烷基”指双环环烷基,其中所述环的每一个与其它环共享两个相邻的原子。稠合双环环烷基的第二个环可选自饱和的、不饱和的和芳族环。“环烯基”基团是含有一个或多个双键的环烃。

[0053] 本文使用的术语“碳环基烷基”指用碳环基取代的烷基。

[0054] 术语“碳酸酯”为本领域公知的且指基团 $-OC(=O)R^{10}$,其中 R^{10} 表示烃基。

[0055] 本文使用的术语“羧基”指由式 CO_2H 表示的基团。

[0056] 本文使用的术语“酯”指基团 $-C(=O)OR^{10}$,其中 R^{10} 表示烃基。

[0057] 本文使用的术语“醚”指通过氧连接于另一个烃基的烃基。因此,烃基的醚取代基可以是烃基- O -。醚可以是对称的或不对称的。醚的实例包括,但不限于杂环- O -杂环和芳基- O -杂环。醚包括“烷氧基烷基”,其可以通式烷基- O -烷基表示。

[0058] 本文使用的术语“卤代”和“卤素”意指卤素并包括氯、氟、溴和碘。

[0059] 本文使用的术语“杂芳烷基”和“杂芳基烷基”指用杂芳基取代的烷基。

[0060] 本文使用的术语“杂烷基”指碳原子和至少一个杂原子的饱和或不饱和链,其中没有两个杂原子是相邻的。

[0061] 术语“杂芳基(heteroaryl)”和“杂芳基(hetaryl)”包括取代的或未取代的芳族单环结构,优选5-至7-元环,更优选5-至6-元环,其环结构包括至少一个杂原子,优选1至4个杂原子,更优选地一个或两个杂原子。术语“杂芳基”和“杂芳基”也包括具有两个或更多个环的多环系统,其中两个或更多个碳为两个相邻的环所共享,其中至少一个环是杂芳族的,例如,另一个环可以是环烷基、环烯基、环炔基、芳基、杂芳基和/或杂环基。杂芳基包括,例如,吡咯、呋喃、噻吩、咪唑、噁唑、噻唑、吡唑、吡啶、吡嗪、哒嗪和嘧啶等。

[0062] 本文使用的术语“杂原子”意指不是碳或氢的任何元素的原子。优选的杂原子是氮、氧和硫。

[0063] 术语“杂环基”、“杂环”和“杂环的”指取代的或未取代的非芳族环结构,优选3-至10-元环,更优选3-至7-元环,其环结构包括至少一个杂原子,优选1至4个杂原子,更优选地一个或两个杂原子。术语“杂环基”和“杂环的”也包括具有两个或更多个环的多环系统,其中两个或更多个碳是两个相邻的环所共享的,其中至少一个环是杂环,例如,其它的环状环可以是环烷基、环烯基、环炔基、芳基、杂芳基和/或杂环基。杂环基包括,例如,哌啶、哌嗪、吡咯烷、吗啉、内酯、内酰胺等。

[0064] 本文使用的术语“杂环基烷基”指用杂环基取代的烷基。

[0065] 本文使用的术语“烃基”指通过碳原子连接的基团,其不具有=O或=S取代基,且典型地具有至少一个碳-氢键和主要为碳的骨架,但是可任选地包括杂原子。因此,基团像甲基、乙氧基乙基、2-吡啶基和三氟甲基被认为是用于本申请目的的烃基,但取代基例如乙酰基(其在连接碳上具有=O取代基)和乙氧基(其通过氧而不是碳连接)则不是。烃基包括,但不限于芳基、杂芳基、碳环、杂环基、烷基、烯基、炔基及其组合。

[0066] 本文使用的术语“羟烷基”指用羟基取代的烷基。

[0067] 术语“低级”当与化学部分例如酰基、酰基氧基、烷基、烯基、炔基或烷氧基联用时,意在包括其中取代基中有10个或更少,优选6个或更少的非氢原子的基团。“低级烷基”,例如,指含有10个或更少,优选6个或更少的碳原子的烷基。在某些实施方案中,本文限定的酰基、酰基氧基、烷基、烯基、炔基或烷氧基取代基分别是低级酰基、低级酰基氧基、低级烷基、低级烯基、低级炔基或低级烷氧基,无论它们是单独出现或与其它取代基组合出现,例如在描述羟烷基和芳烷基中(在这样的情况中,例如,当计数烷基取代基中的碳原子时,不计数芳基中的原子)。

[0068] 术语“多环基”、“多环”和“多环的”指两个或更多个环(如,环烷基、环烯基、环炔基、芳基、杂芳基和/或杂环基),其中两个或更多个原子为两个相邻的环所共享,例如,所述环是“稠合的环”。多环的各个环可以是取代的或未取代的。在某些实施方案中,多环的各个环在环中含有3至10个原子,优选5至7个原子。

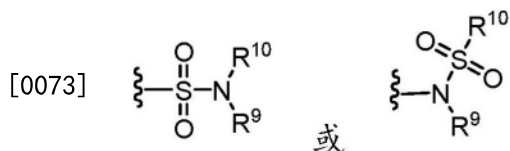
[0069] 术语“甲硅烷基”指其上连接有三个烃基部分的硅部分。

[0070] 术语“取代的”指具有替代在骨架的一个或多个碳上的氢的取代基的部分。应该理解“取代”或“用…取代”包括这样的隐含条件,即这样的取代符合取代的原子和取代基的允

许化学价,以及所述取代产生稳定的化合物,例如,其不会自发地经历转化例如通过重排、环化、消去等。如本文所用的术语“取代的”预期包括有机化合物的所有允许的取代基。在一个广泛的方面,可允许的取代基包括有机化合物的无环的和环状的、分支的和未分支的、碳环的和杂环的、芳族和非芳族取代基。对于适宜的有机化合物,可允许的取代基可以是一个或多个、相同的或不同的。为了本发明的目的,杂原子例如氮可具有氢取代基和/或本文所述的有机化合物的任何可允许的取代基,其满足杂原子的化学价。取代基可包括本文所述的任何取代基,例如,卤素、羟基、羰基(例如羧基、烷氧基羰基、甲酰基或酰基)、硫代羰基(例如硫代酯、硫代乙酸酯或硫代甲酸酯)、烷氧基、磷酰基、磷酸酯、膦酸酯、亚膦酸酯、氨基、酰氨基、脒、亚胺、氰基、硝基、叠氮基、巯基、烷硫基、硫酸酯、磺酸酯、氨磺酰基、磺酰氨基、磺酰基、杂环基、芳烷基,或芳族或杂芳族部分。本领域技术人员应该理解,如果合适,取代基本身可被取代。除非特别地陈述为“未取代的”,否则提及本文的化学部分时应理解为包括取代的变体。例如,提及“芳基”基团或部分隐含地包括取代的和未取代的变体。

[0071] 术语“硫酸酯(sulfate)”为本领域公知的且指基团 $-\text{OSO}_3\text{H}$,或其药学上可接受的盐。

[0072] 术语“磺酰胺(sulfonamide)”为本领域公知的且指由以下通式表示的基团:



[0074] 其中 R^9 和 R^{10} 独立地表示氢或烃基,例如烷基,或 R^9 和 R^{10} 与插入的原子一起完成在环结构中含有4-8个原子的杂环。

[0075] 术语“亚磺”为本领域公知的且指基团 $\text{S}(\text{O})-\text{R}^{10}$,其中 R^{10} 表示烃基。

[0076] 术语“磺酸酯(sulfonate)”为本领域公知的且指基团 SO_3H ,或其药学上可接受的盐。

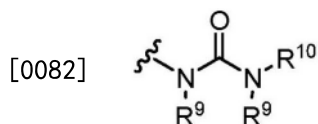
[0077] 术语“磺”为本领域公知的且指基团 $\text{S}(\text{O})_2-\text{R}^{10}$,其中 R^{10} 表示烃基。

[0078] 本文使用的术语“硫代烷基(thioalkyl)”指用硫醇基取代的烷基。

[0079] 本文使用的术语“硫代酯”指基团 $-\text{C}(\text{O})\text{SR}^{10}$ 或 $\text{SC}(\text{O})\text{R}^{10}$,其中 R^{10} 表示烃基。

[0080] 本文使用的术语“硫醚”是醚的等价物,其中氧被硫替代。

[0081] 术语“脲”为本领域公知的并可通过以下通式表示:



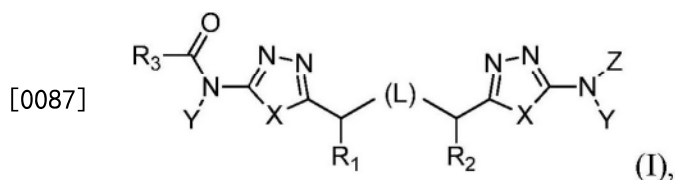
[0083] 其中 R^9 和 R^{10} 独立地表示氢或烃基,例如烷基,或任何存在的 R^9 与 R^{10} 和插入原子一起完成在环结构中含有4-8个原子的杂环。

[0084] 术语“保护基团”指一组原子,当连接于分子中反应性官能团时,遮蔽、减少或防止官能团的反应性。典型地,保护基团可以在合成的过程中根据需要被选择性地除去。保护基团的实例可参见Greene和Wuts,有机化学中的保护基团(Protective Groups in Organic Chemistry),第3版1999,John Wiley&Sons,NY和Harrison等,合成有机方法大全(Compendium of Synthetic Organic Methods),Vols.1-8,1971-1996,John Wiley&Sons,NY。代表性的氮保护基团包括但不限于甲酰基、乙酰基、三氟乙酰基、苄基、苄氧基羰基

(“CBZ”)、叔丁氧基羰基(“Boc”)、三甲基甲硅烷基(“TMS”)、2-三甲基甲硅烷基-乙磺酰基(“TES”)、三苯甲基和取代的三苯甲基、烯丙氧基羰基、9-芴基甲氧基羰基(“Fmoc”)、硝基-藜芦基氧基羰基(“NVOC”)等。代表性的羟基保护基团包括但不限于其中羟基是酰化的(酯化的)或者烷基化的那些,例如苄基和三苯甲基醚,以及烷基醚、四氢吡喃醚、三烷基甲硅烷基醚(例如,TMS或TIPS基团)、二醇醚,例如乙二醇和丙二醇衍生物和烯丙基醚。

[0085] I. 化合物

[0086] 本发明涉及治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法,所述方法包括口服给予式I化合物或其药学上可接受的盐,



[0088] 其中:

[0089] L表示 CH_2SCH_2 、 CH_2CH_2 、 $\text{CH}_2\text{CH}_2\text{CH}_2$ 、 CH_2 、 CH_2S 、 SCH_2 、 CH_2NHCH_2 、 $\text{CH}=\text{CH}$ 或, 优

选 CH_2CH_2 , 其中CH或 CH_2 单元的任何氢原子可被烷基或烷氧基替代,NH单元的任何氢原子可被烷基替代,且 CH_2CH_2 、 $\text{CH}_2\text{CH}_2\text{CH}_2$ 或 CH_2 的 CH_2 单元的任何氢原子可被羟基替代;

[0090] X在每次出现时独立地表示S、O或 $\text{CH}=\text{CH}$,优选S或 $\text{CH}=\text{CH}$,其中CH单元的任何氢原子可被烷基替代;

[0091] Y在每次出现时独立地表示H或 $\text{CH}_2\text{O}(\text{C}(\text{O})\text{R}_7)$;

[0092] R_7 在每次出现时独立地表示H或取代的或未取代的烷基、烷氧基、氨基烷基、烷基氨基烷基、杂环基烷基、芳基烷基或杂环基烷氧基;

[0093] Z表示H或 $\text{R}_3(\text{C}(\text{O})\text{R}_7)$;

[0094] R_1 和 R_2 各自独立地表示氢、烷基、烷氧基或羟基;

[0095] R_3 在每次出现时独立地表示取代的或未取代的烷基、羟烷基、氨基烷基、酰基氨基烷基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基、杂芳基氧基烷基或 $\text{C}(\text{R}_8)(\text{R}_9)(\text{R}_{10})$ 、 $\text{N}(\text{R}_4)(\text{R}_5)$ 或 $\text{O}(\text{R}_6)$,其中任何游离的羟基可酰化以形成 $\text{C}(\text{O})\text{R}_7$;

[0096] R_4 和 R_5 各自独立地表示H或取代的或未取代的烷基、羟烷基、酰基、氨基烷基、酰基氨基烷基、烯基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,其中任何游离的羟基可酰化以形成 $\text{C}(\text{O})\text{R}_7$;

[0097] R_6 在每次出现时独立地表示取代的或未取代的烷基、羟烷基、氨基烷基、酰基氨基烷基、烯基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,其中任何游离的羟基可酰化以形成 $\text{C}(\text{O})\text{R}_7$;且

[0098] R_8 、 R_9 和 R_{10} 各自独立地表示H或取代的或未取代的烷基、羟基、羟烷基、氨基、酰基氨基、氨基烷基、酰基氨基烷基、烷氧基羰基、烷氧基羰基氨基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳

基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,或 R_8 和 R_9 与它们连接的碳一起形成碳环或杂环系统,其中任何游离的羟基可酰化以形成 $C(O)R_7$;

[0099] 优选其中所述化合物与膳食一起给予。

[0100] 在某些实施方案中, R_8 、 R_9 和 R_{10} 中的至少两个不为氢。

[0101] 在其中烷基、羟烷基、氨基、酰基氨基、氨基烷基、酰基氨基烷基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基被取代的某些实施方案中,它们可被一个或多个选自以下的取代基取代:取代的或未取代的烷基诸如全氟烷基(例如,三氟甲基)、烯基、烷氧基、烷氧基烷基、芳基、芳烷基、芳基烷氧基、芳基氧基、芳基氧基烷基、羟基、卤素、烷氧基诸如全氟烷氧基(例如,三氟甲氧基)、烷氧基烷氧基、羟烷基、羟烷基氨基、羟基烷氧基、氨基、氨基烷基、烷基氨基、氨基烷基烷氧基、氨基烷氧基、酰基氨基、酰基氨基烷基诸如全氟酰基氨基烷基(例如,三氟甲基酰基氨基烷基)、酰基氧基、环烷基、环烷基烷基、环烷基烷氧基、杂环基、杂环基烷基、杂环基氧基、杂环基烷氧基、杂芳基、杂芳基烷基、杂芳基烷氧基、杂芳基氧基、杂芳基氧基烷基、杂环基氨基烷基、杂环基氨基烷氧基、酰氨基、酰氨基烷基、脒、亚胺、氧代、羰基(诸如羧基、烷氧基羰基、甲酰基或酰基包括全氟酰基(例如, $C(O)CF_3$))、羰基烷基(诸如羧基烷基、烷氧基羰基烷基、甲酰基烷基或酰基烷基包括全氟酰基烷基(例如, $-烷基C(O)CF_3$))、氨基甲酸酯(carbamate)、氨基甲酸酯烷基(carbamatealkyl)、脲、脲烷基、硫酸酯、磺酸酯、氨磺酰基、砒、磺酰胺、磺酰胺烷基、氰基、硝基、叠氮基、巯基、烷硫基、硫代羰基(诸如硫代酯、硫代乙酸酯或硫代甲酸酯)、磷酰基、磷酸酯、膦酸酯或亚膦酸酯。

[0102] 在某些实施方案中,L表示 CH_2SCH_2 、 CH_2CH_2 、 $CH_2CH_2CH_2$ 、 CH_2 、 CH_2S 、 SCH_2 或 CH_2NHCH_2 ,其中 CH_2 单元的任何氢原子可被烷基或烷氧基替代, CH_2CH_2 、 $CH_2CH_2CH_2$ 或 CH_2 的 CH_2 单元的任何氢原子可被羟基替代。在某些实施方案中,L表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 。在某些实施方案中,L表示 CH_2CH_2 。在某些实施方案中,L不为 CH_2SCH_2 。

[0103] 在某些实施方案中,Y表示H。

[0104] 在某些实施方案中,X表示S或 $CH=CH$ 。在某些实施方案中,一个或两个X表示 $CH=CH$ 。在某些实施方案中,每个X表示S。在某些实施方案中,一个X表示S且另一个X表示 $CH=CH$ 。

[0105] 在某些实施方案中,Z表示 $R_3(CO)$ 。在某些实施方案中,其中Z是 $R_3(CO)$, R_3 的每次出现不相同(例如,式I化合物不是对称的)。

[0106] 在某些实施方案中, R_1 和 R_2 各自表示H。

[0107] 在某些实施方案中, R_3 表示芳基烷基、杂芳基烷基、环烷基或杂环烷基。在某些实施方案中, R_3 表示 $C(R_8)(R_9)(R_{10})$,其中 R_8 表示芳基、芳基烷基、杂芳基或杂芳烷基,诸如芳基、芳基烷基或杂芳基, R_9 表示H,且 R_{10} 表示羟基、羟烷基、烷氧基或烷氧基烷基,诸如羟基、羟烷基或烷氧基。

[0108] 在某些实施方案中,L表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 ,诸如 CH_2CH_2 、 CH_2S 或 SCH_2 ,Y表示H,X表示S,Z表示 $R_3(CO)$, R_1 和 R_2 各自表示H,并且每个 R_3 表示芳基烷基、杂芳基烷基、环烷基或杂环烷基。在一些这样的实施方案中,每次出现的 R_3 是相同的。

[0109] 在某些实施方案中,L表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 ,Y表示H,X表示S,Z表示 R_3

(CO), R_1 和 R_2 各自表示H,并且每个 R_3 表示C(R_8)(R_9)(R_{10}),其中 R_8 表示芳基、芳基烷基、杂芳基或杂芳烷基,诸如芳基、芳基烷基或杂芳基, R_9 表示H,且 R_{10} 表示羟基、羟烷基、烷氧基或烷氧基烷基,诸如羟基、羟烷基或烷氧基。在一些这样的实施方案中,每次出现的 R_3 是相同的。

[0110] 在某些实施方案中,L表示 CH_2CH_2 ,Y表示H,X表示S或 $\text{CH}=\text{CH}$,Z表示 R_3 (CO), R_1 和 R_2 各自表示H,并且每个 R_3 表示取代的或未取代的芳基烷基、杂芳基烷基、环烷基或杂环烷基。在一些这样的实施方案中,每个X表示S。在其他实施方案中,X的一次或两次出现表示 $\text{CH}=\text{CH}$,诸如X的一次出现表示S且X的另一次出现表示 $\text{CH}=\text{CH}$ 。在上述的某些实施方案中,每次出现的 R_3 是相同的。在上述的其他实施方案中,其中X的一次出现表示S且X的另一次出现表示 $\text{CH}=\text{CH}$, R_3 的两次出现不相同。

[0111] 在某些实施方案中,L表示 CH_2CH_2 ,Y表示H,X表示S,Z表示 R_3 (CO), R_1 和 R_2 各自表示H,并且每个 R_3 表示C(R_8)(R_9)(R_{10}),其中 R_8 表示芳基、芳基烷基或杂芳基, R_9 表示H,且 R_{10} 表示羟基、羟烷基或烷氧基。在一些这样的实施方案中, R_8 表示芳基和 R_{10} 表示羟烷基。在一些这样的实施方案中,每次出现的 R_3 是相同的。

[0112] 在某些实施方案中,其中L表示 CH_2 、 $\text{CH}_2\text{CH}_2\text{CH}_2$ 或 CH_2CH_2 ,X表示O,且Z表示 R_3 (CO),两个 R_3 基团不为烷基,诸如甲基,或C(R_8)(R_9)(R_{10}),其中 R_8 、 R_9 和 R_{10} 各自独立地为氢或烷基。

[0113] 在某些实施方案中,其中L表示 CH_2CH_2 ,X表示S,且Z表示 R_3 (CO),两个 R_3 基团不为苯基或杂芳基,诸如2-呋喃基。

[0114] 在某些实施方案中,其中L表示 CH_2CH_2 ,X表示O,且Z表示 R_3 (CO),两个 R_3 基团不为N(R_4)(R_5),其中 R_4 为芳基,诸如苯基,且 R_5 为H。

[0115] 在某些实施方案中,其中L表示 CH_2SCH_2 ,X表示S,且Z表示 R_3 (CO),两个 R_3 基团不为芳基(诸如任选取代的苯基)、芳烷基(诸如苄基)、杂芳基(诸如2-呋喃基、2-噻吩基或1,2,4-三唑)、取代的或未取代的烷基(诸如甲基、氯甲基、二氯甲基、正丙基、正丁基、叔丁基或己基)、杂环基(诸如嘧啶-2,4(1H,3H)-二酮)或烷氧基(诸如甲氧基、戊氧基或乙氧基)。

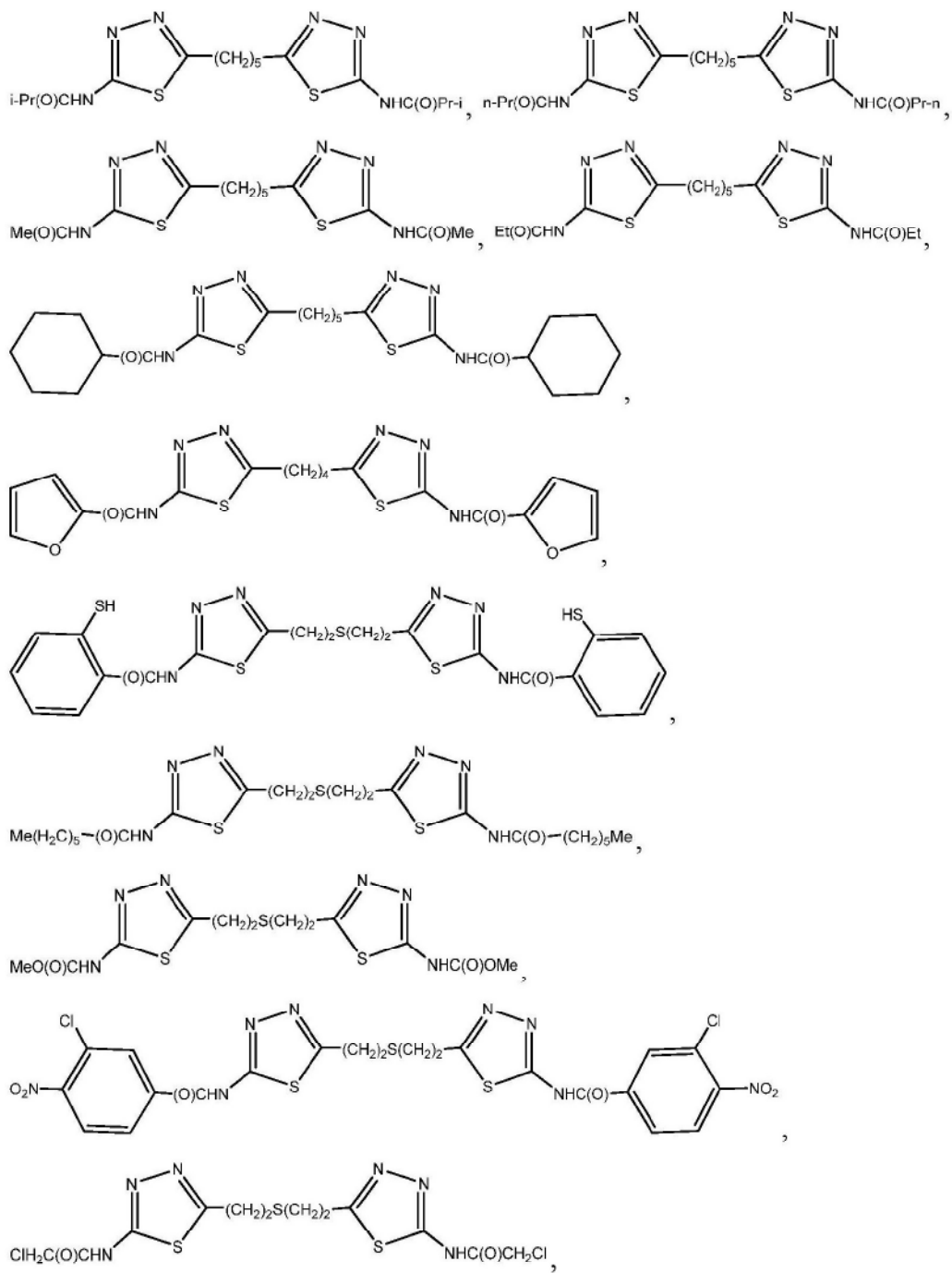
[0116] 在某些实施方案中,其中L表示 CH_2SCH_2 ,X表示S,且Z表示 R_3 (CO),两个 R_3 基团不为任选取代的苯基、芳烷基、杂芳基、取代的或未取代的烷基或烷氧基。

[0117] 在某些实施方案中,其中L表示 CH_2SCH_2 ,X表示S,且Z表示 R_3 (CO),两个 R_3 基团不为N(R_4)(R_5),其中 R_4 为芳基诸如取代的或未取代的苯基(例如苯基、3-甲基苯基、4-甲基苯基、4-溴苯基或4-硝基苯基)且 R_5 为H。

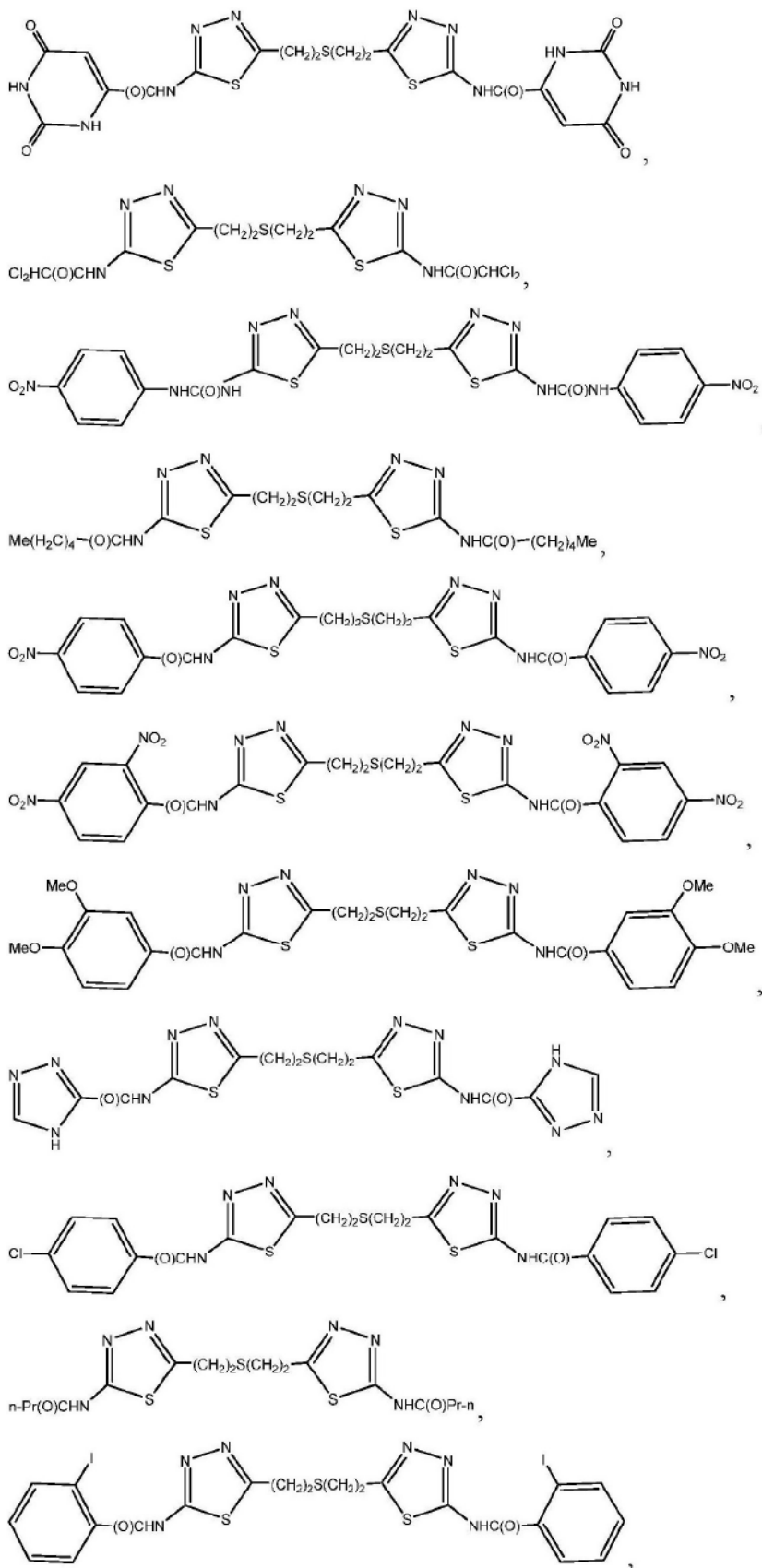
[0118] 在某些实施方案中,其中L表示 $\text{CH}_2\text{CH}_2\text{CH}_2$,X表示S,且Z表示 R_3 (CO),两个 R_3 基团不为烷基(诸如甲基、乙基或丙基)、环烷基(诸如环己基)或C(R_8)(R_9)(R_{10}),其中 R_8 、 R_9 和 R_{10} 中的任一个与它们连接的碳一起形成以上中的任一个。

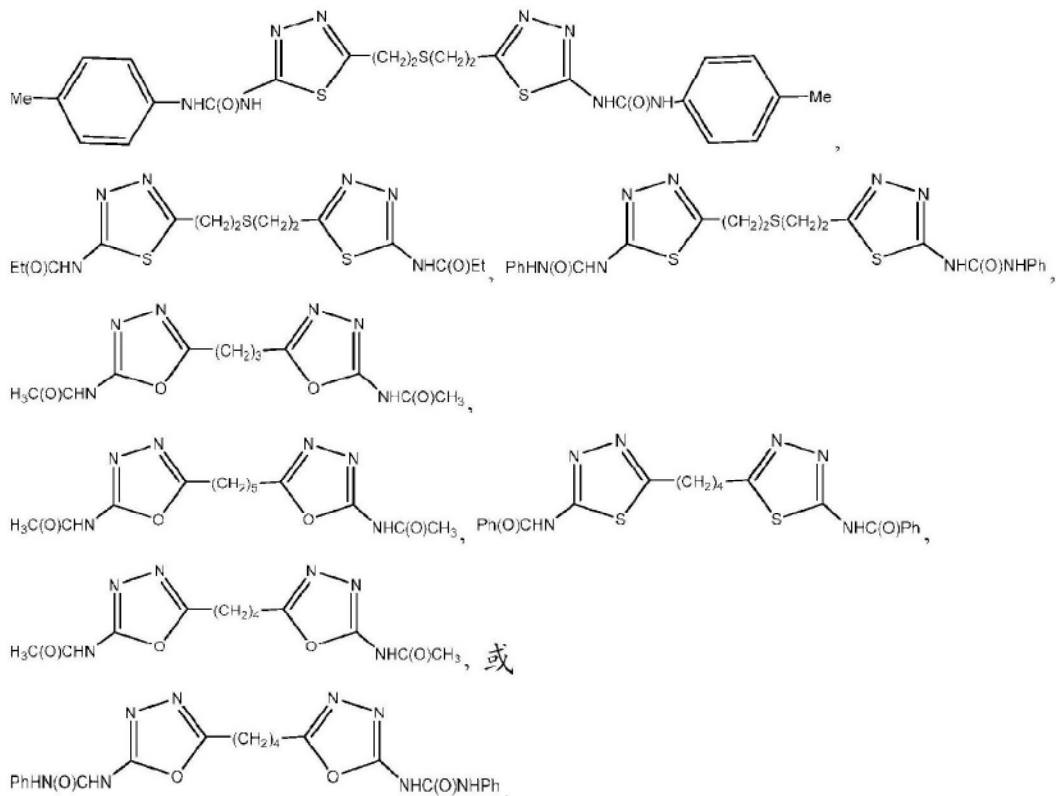
[0119] 在某些实施方案中,所述化合物不是以下之一:

[0120]



[0121]





[0124]



[0125] 其中：

[0126] L表示 CH_2SCH_2 、 CH_2CH_2 、 $\text{CH}_2\text{CH}_2\text{CH}_2$ 、 CH_2 、 CH_2S 、 SCH_2 、 CH_2NHCH_2 、 $\text{CH}=\text{CH}$ 或，

优选 CH_2CH_2 ，其中CH或 CH_2 单元的任何氢原子可被烷基或烷氧基替代，NH单元的任何氢原子可被烷基替代，且 CH_2CH_2 、 $\text{CH}_2\text{CH}_2\text{CH}_2$ 或 CH_2 的 CH_2 单元的任何氢原子可被羟基替代；

[0127] X表示S、O或 $\text{CH}=\text{CH}$ ，优选S或 $\text{CH}=\text{CH}$ ，其中CH单元的任何氢原子可被烷基替代；

[0128] Y在每次出现时独立地表示H或 CH_2O (CO) R_7 ；

[0129] R_7 在每次出现时独立地表示H或取代的或未取代的烷基、烷氧基、氨基烷基、烷基氨基烷基、杂环基烷基、芳基烷基或杂环基烷氧基；

[0130] Z表示H或 R_3 (CO) ；

[0131] R_1 和 R_2 各自独立地表示氢、烷基、烷氧基或羟基，优选H；

[0132] R_3 表示取代的或未取代的烷基、羟烷基、氨基烷基、酰基氨基烷基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基、杂芳基氧基烷基或 $\text{C}(\text{R}_8)(\text{R}_9)(\text{R}_{10})$ 、 $\text{N}(\text{R}_4)(\text{R}_5)$ 或 OR_6 ，其中任何游离的羟基可酰化以形成 $\text{C}(\text{O})\text{R}_7$ ；

[0133] R_4 和 R_5 各自独立地表示H或取代的或未取代的烷基、羟烷基、酰基、氨基烷基、酰基氨基烷基、烯基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基，其中任何游离的羟基可酰化以形成 $\text{C}(\text{O})\text{R}_7$ ；

[0134] R_6 在每次出现时独立地表示取代的或未取代的烷基、羟烷基、氨基烷基、酰基氨基烷基、烯基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基，其中任何游离的羟基可酰化以形成 $\text{C}(\text{O})\text{R}_7$ ；且

[0135] R_8 、 R_9 和 R_{10} 各自独立地表示H或取代的或未取代的烷基、羟基、羟烷基、氨基、酰基氨基、氨基烷基、酰基氨基烷基、烷氧基羰基、烷氧基羰基氨基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基，或 R_8 和 R_9 与它们连接的碳一起形成碳环或杂环系统，其中任何游离的羟基可酰化以形成 $\text{C}(\text{O})\text{R}_7$ ；且其中 R_8 、 R_9 和 R_{10} 中的至少两个不为氢；

[0136] R_{11} 表示取代的或未取代的芳基、芳基烷基、芳基氧基、芳基氧基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基或 $\text{C}(\text{R}_{12})(\text{R}_{13})(\text{R}_{14})$ 、 $\text{N}(\text{R}_4)(\text{R}_{14})$ 或 OR_{14} ，其中任何游离的羟基可酰化以形成 $\text{C}(\text{O})\text{R}_7$ ；

[0137] R_{12} 和 R_{13} 各自独立地表示H或取代的或未取代的烷基、羟基、羟烷基、氨基、酰基氨基、氨基烷基、酰基氨基烷基、烷氧基羰基、烷氧基羰基氨基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基，其中任何游离的羟基可酰化以形成 $\text{C}(\text{O})\text{R}_7$ ，且其中 R_{12} 和 R_{13} 二者不都为氢；且

[0138] R_{14} 表示取代的或未取代的芳基、芳基烷基、芳基氧基、芳基氧基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基；

[0139] 优选其中所述化合物与膳食一起给予。

[0140] 在其中烷基、羟烷基、氨基、酰基氨基、氨基烷基、酰基氨基烷基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基被取代的某些实施方案中，它们可被一个或多个选自以下的取代基取代：取代的或未取代的烷基诸如全氟烷基（例如，三氟甲基）、烯基、烷氧基、烷氧基烷基、芳基、芳烷基、芳基烷氧基、芳基氧基、芳基氧基烷基、羟基、卤素、烷氧基诸如全氟烷氧基（例如，三氟甲氧基）、烷氧基烷氧基、羟烷基、羟烷基氨基、羟基烷氧基、氨基、氨基烷基、烷基氨基、氨基烷基烷氧基、氨基烷氧基、酰基氨基、酰基氨基烷基诸如全氟酰基氨基烷基（例如，三氟甲基酰基氨基烷基）、酰基氧基、环烷基、环烷基烷基、环烷基烷氧基、杂环基、杂环基烷基、杂环基氧基、杂环基烷氧基、杂芳基、杂芳基烷基、杂芳基烷氧基、杂芳基氧基、杂芳基氧基烷基、杂环基氨基烷基、杂环基氨基烷氧基、酰氨基、酰氨基烷基、脒、亚胺、氧代、羰基（诸如羧基、烷氧基羰基、甲酰基或酰基包括全氟酰基（例如， $C(O)CF_3$ ））、羰基烷基（诸如羧基烷基、烷氧基羰基烷基、甲酰基烷基或酰基烷基包括全氟酰基烷基（例如，-烷基 $C(O)CF_3$ ））、氨基甲酸酯（carbamate）、氨基甲酸酯烷基（carbamatealkyl）、脲、脲烷基、硫酸酯、磺酸酯、氨磺酰基、砒、磺酰胺、磺酰胺烷基、氰基、硝基、叠氮基、巯基、烷硫基、硫代羰基（诸如硫代酯、硫代乙酸酯或硫代甲酸酯）、磷酰基、磷酸酯、膦酸酯或亚膦酸酯。

[0141] 在某些实施方案中， R_{11} 表示取代的或未取代的芳基烷基，诸如取代的或未取代的苄基。

[0142] 在某些实施方案中， L 表示 CH_2SCH_2 、 CH_2CH_2 、 $CH_2CH_2CH_2$ 、 CH_2 、 CH_2S 、 SCH_2 或 CH_2NHCH_2 ，其中 CH_2 单元的任何氢原子可被烷基或烷氧基替代，且 CH_2CH_2 、 $CH_2CH_2CH_2$ 或 CH_2 的 CH_2 单元的任何氢原子可被羟基替代。在某些实施方案中， L 表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 ，优选 CH_2CH_2 。在某些实施方案中， L 不为 CH_2SCH_2 。

[0143] 在某些实施方案中，每个 Y 表示 H 。在其他实施方案中，至少一个 Y 为 $CH_2O(CO)R_7$ 。

[0144] 在某些实施方案中， X 表示 S 或 $CH=CH$ 。在某些实施方案中， X 表示 S 。

[0145] 在某些实施方案中， R_1 和 R_2 各自表示 H 。

[0146] 在某些实施方案中， Z 表示 $R_3(CO)$ 。在某些实施方案中，其中 Z 为 $R_3(CO)$ ， R_3 和 R_{11} 不是相同的（例如，式I化合物不是对称的）。

[0147] 在某些实施方案中， Z 表示 $R_3(CO)$ 且 R_3 表示芳基烷基、杂芳基烷基、环烷基或杂环烷基。在某些实施方案中， Z 表示 $R_3(CO)$ 且 R_3 表示 $C(R_8)(R_9)(R_{10})$ ，其中 R_8 表示芳基、芳基烷基、杂芳基或杂芳烷基，诸如芳基、芳基烷基或杂芳基， R_9 表示 H ，且 R_{10} 表示羟基、羟烷基、烷氧基或烷氧基烷基，诸如羟基、羟烷基或烷氧基。在某些实施方案中， Z 表示 $R_3(CO)$ 且 R_3 表示杂芳基烷基。

[0148] 在某些实施方案中， L 表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 ，诸如 CH_2CH_2 ， Y 表示 H ， X 表示 S ， Z 表示 $R_3(CO)$ ， R_1 和 R_2 各自表示 H ， R_3 表示芳基烷基、杂芳基烷基、环烷基或杂环烷基，且 R_{11} 表示芳基烷基。在一些这样的实施方案中， R_3 表示杂芳基烷基。

[0149] 在某些实施方案中， L 表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 ，诸如 CH_2CH_2 ， Y 表示 H ， X 表示 S ， Z 表示 $R_3(CO)$ ， R_1 和 R_2 各自表示 H ，并且每个 R_3 表示 $C(R_8)(R_9)(R_{10})$ ，其中 R_8 表示芳基、芳基烷基、杂芳基或杂芳烷基，诸如芳基、芳基烷基或杂芳基， R_9 表示 H ，且 R_{10} 表示羟基、羟烷基、烷

氧基或烷氧基烷基,诸如羟基、羟烷基或烷氧基,且 R_{11} 表示芳基烷基。在一些这样的实施方案中, R_8 表示杂芳基。

[0150] 在某些实施方案中, L 表示 CH_2CH_2 , Y 表示 H , X 表示 S 或 $CH=CH$,诸如 S , Z 表示 $R_3(CO)$, R_1 和 R_2 各自表示 H , R_3 表示取代的或未取代的芳基烷基、杂芳基烷基、环烷基或杂环烷基,且 R_{11} 表示芳基烷基。在一些这样的实施方案中, R_3 表示杂芳基烷基。

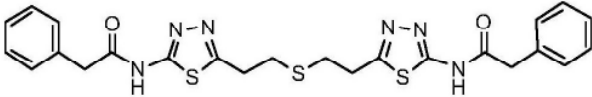
[0151] 在某些实施方案中, L 表示 CH_2CH_2 , Y 表示 H , X 表示 S , Z 表示 $R_3(CO)$, R_1 和 R_2 各自表示 H , R_3 表示 $C(R_8)(R_9)(R_{10})$,其中 R_8 表示芳基、芳基烷基或杂芳基, R_9 表示 H ,且 R_{10} 表示羟基、羟烷基或烷氧基,且 R_{11} 表示芳基烷基。在一些这样的实施方案中, R_8 表示芳基且 R_{10} 表示羟烷基。在一些其他的实施方案中, R_8 表示杂芳基。

[0152] 在某些实施方案中,所述化合物选自表1中公开的任一种化合物。优选地,所述化合物选自化合物1、2、6、7、8、11、13、14、15、16、17、18、19、20、21、24、25、26、27、28、29、30、31、32、33、35、36、38、39、40、41、43、44、47、48、50、51、52、54、55、58、63、64、65、67、68、69、70、71、72、73、77、78、79、80、81、82、83、84、85、86、87、88、92、93、94、95、97、99、100、102、105、107、111、112、114、115、116、117、118、120、121、122、123、126、127、133、135、136、138、140、141、143、146、147、148、152、153、155、156、157、158、159、160、161、162、163、164、165、166、168、169、170、172、173、174、175、176、177、178、179、180、181、182、185、186、187、188、189、190、193、194、195、196、197、198、199、200、201、202、203、204、205、208、210、211、213、214、216、217、219、220、226、227、228、229、231、232、234、235、236、237、239、240、241、242、243、244、245、246、247、248、249、250、251、252、255、256、257、258、259、260、261、262、263、264、265、266、267、268、269、270、271、273、274、275、276、278、279、280、281、282、283、285、286、287、288、290、291、292、293、294、295、296、297、298、299、300、302、304、1038、306、307、308、309、310、311、313、314、315、316、317、318、319、320、321、322、323、324、325、327、329、332、333、334、335、336、337、338、339、340、341、342、343、344、345、346、527、347、348、349、350、351、352、353、354、355、358、359、360、361、362、363、364、365、366、367、368、369、370、371、372、373、374、375、376、377、378、379、380、381、382、383、384、385、386、387、388、389、390、391、392、393、394、395、396、397、398、399、400、401、402、403、404、405、406、407、408、409、410、411、412、413、414、415、416、417、418、419、420、421、422、423、424、425、426、427、428、429、430、431、432、433、434、435、436、437、438、439、440、441、442、443、444、445、446、447、448、449、450、451、452、453、454、455、456、457、458、459、460、461、462、463、464、465、466、467、468、469、470、471、472、473、474、475、476、477、478、479、480、481、482、483、484、485、486、487、488、489、490、491、492、493、494、495、496、497、498、499、500、501、502、503、504、505、506、507、508、509、510、511、512、513、514、515、516、517、518、519、520、521、522、523、528、529、530、531、532、533、534、535、536、537、538、539、540、541、542、543、544、545、546、547、548、549、550、551、552、553、554、555、556、557、558、559、560、561、562、563、564、565、566、567、568、569、570、571、572、573、574、575、576、577、578、579、580、581、582、583、584、585、586、587、588、589、590、591、592、593、594、595、596、597、598、599、600、601、602、603、604、605、606、607、608、609、610、611、612、613、614、615、616、617、618、619、620、621、622、623、624、625、626、627、628、629、630、631、632、633、634、635、636、638、639、640、641、644、645、646、647、648、649、650、651、652、653、654、655、656、657、658、659、660、661、662、

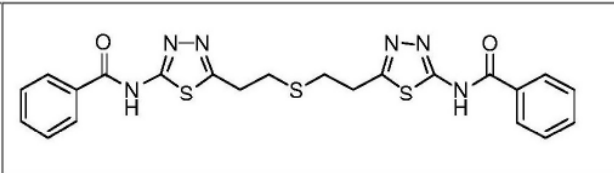
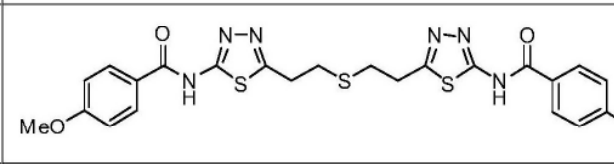
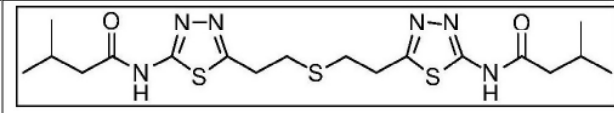
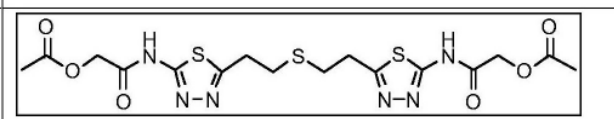
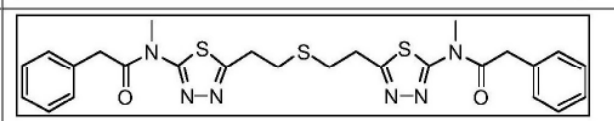
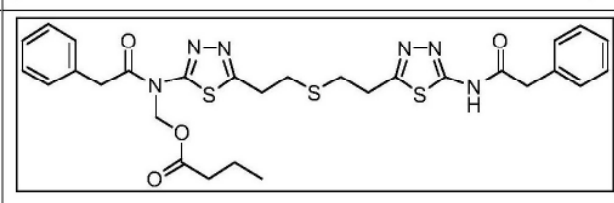
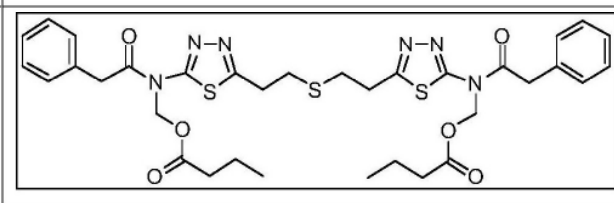
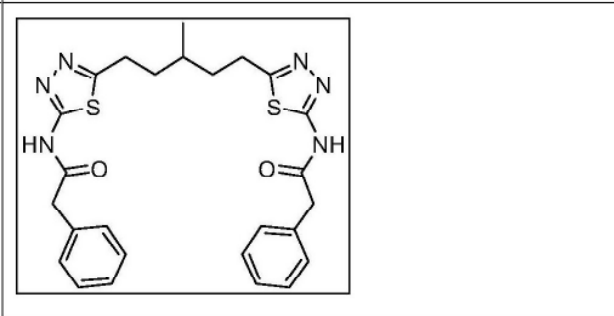
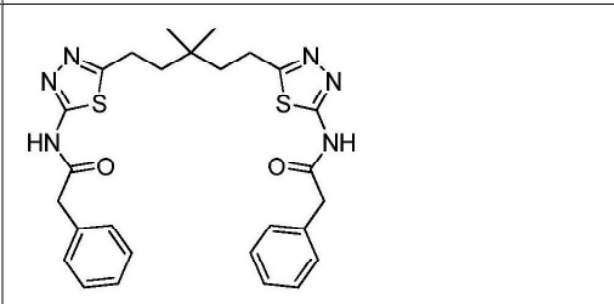
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[0153] 表1. 所选的式I化合物

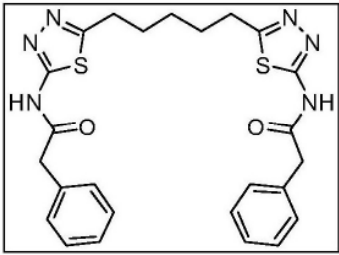
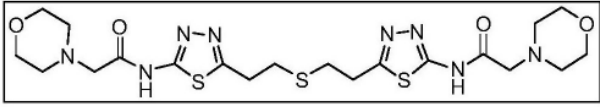
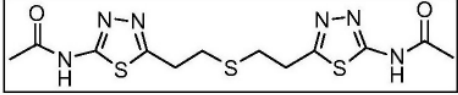
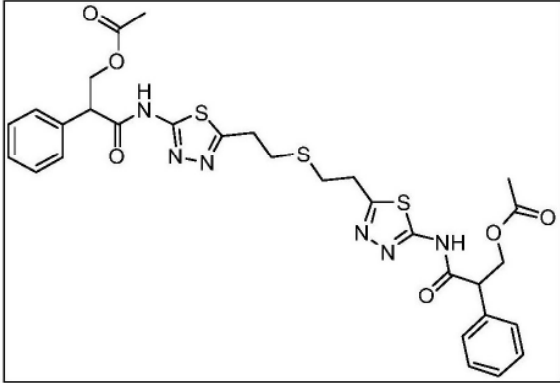
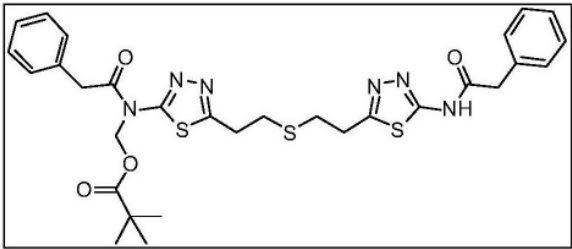
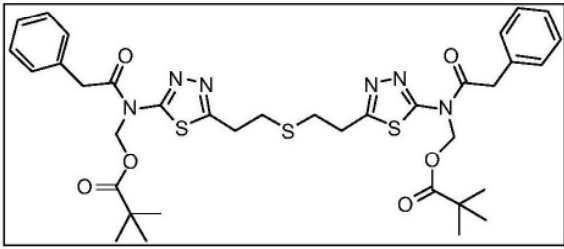
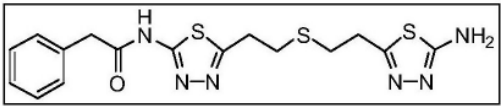
[0154]

化合物 ID	结构
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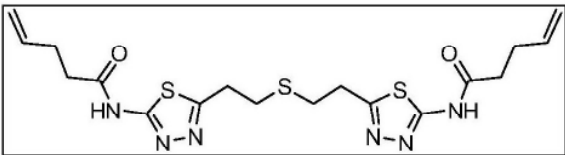
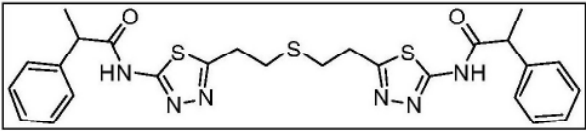
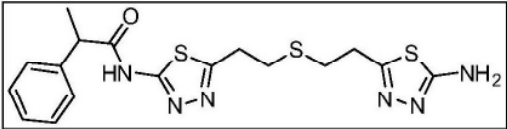
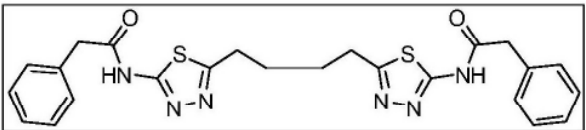
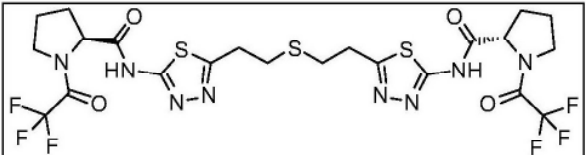
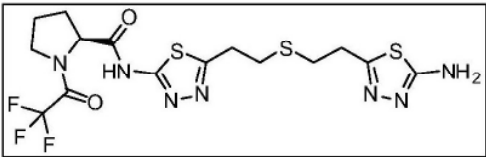
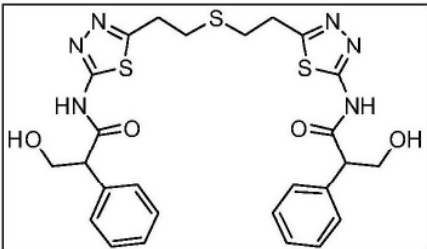
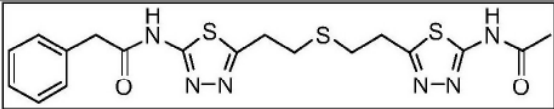
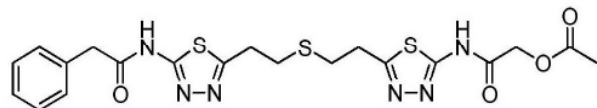
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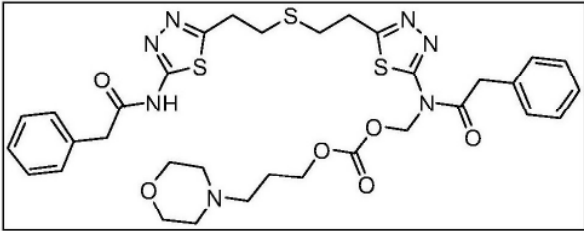
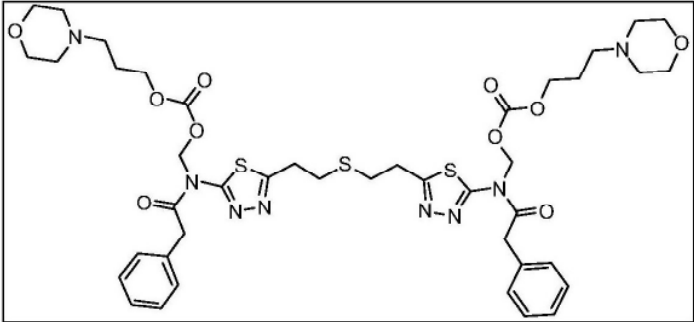
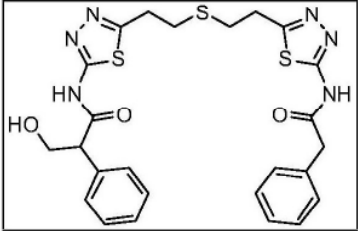
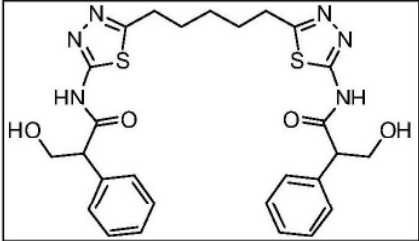
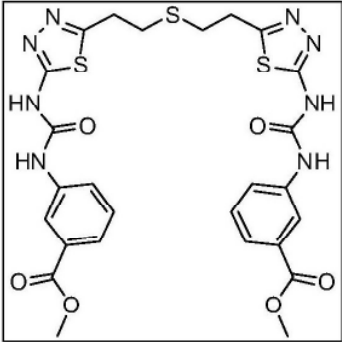
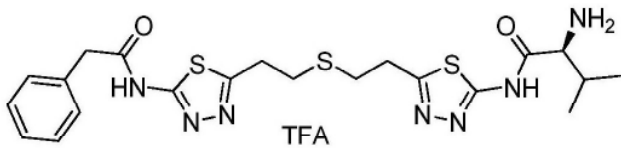
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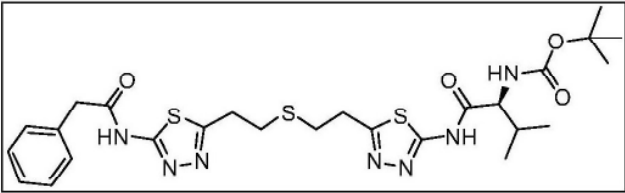
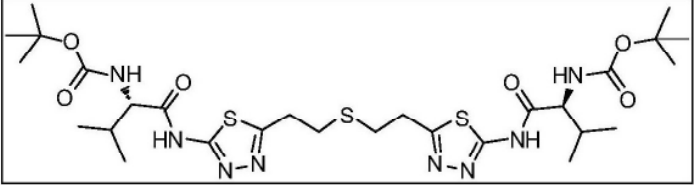
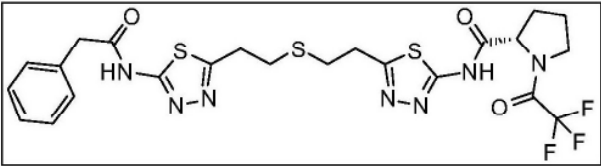
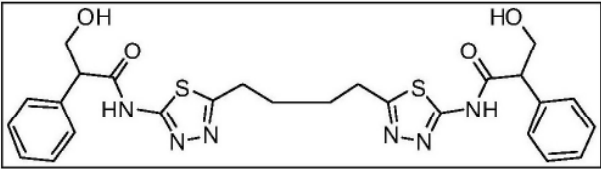
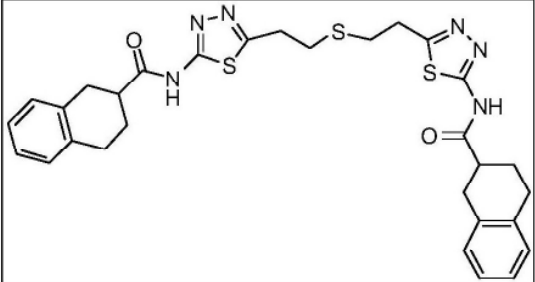
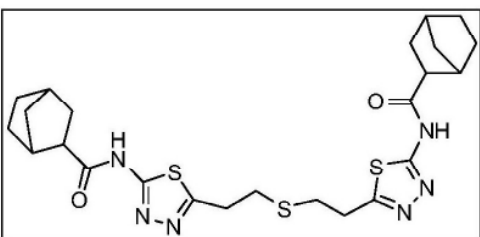
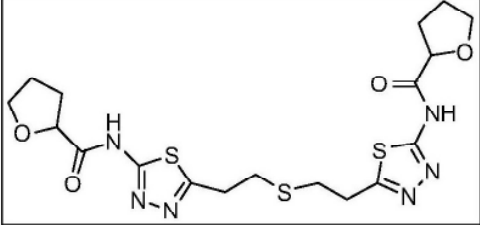
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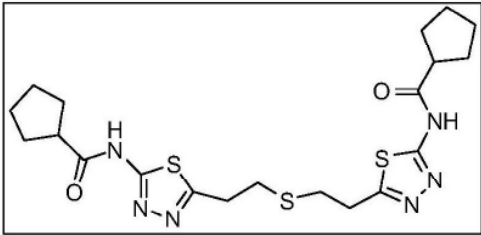
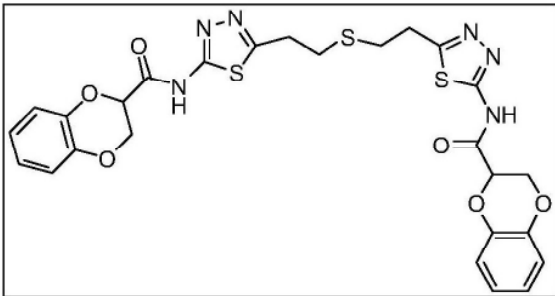
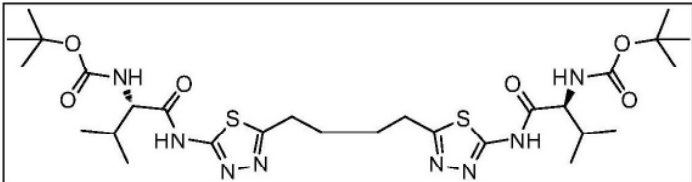
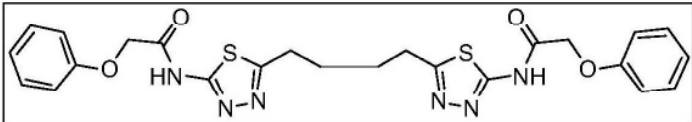
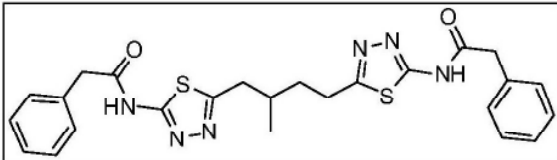
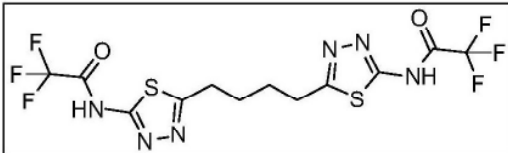
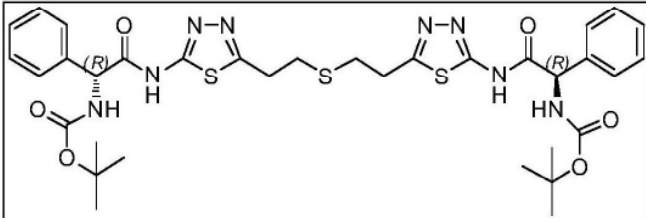
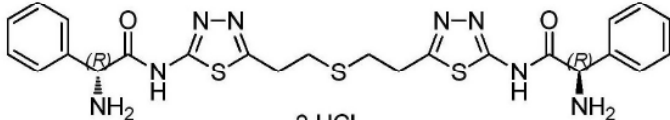
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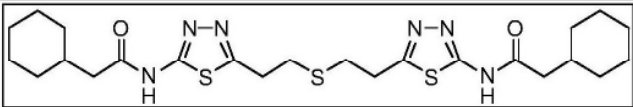
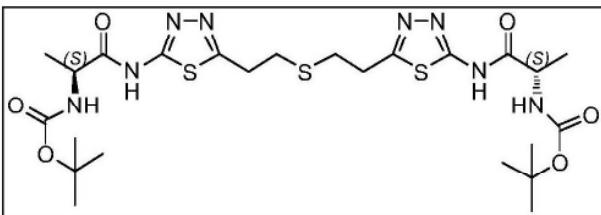
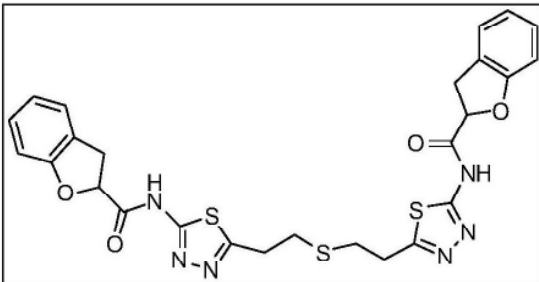
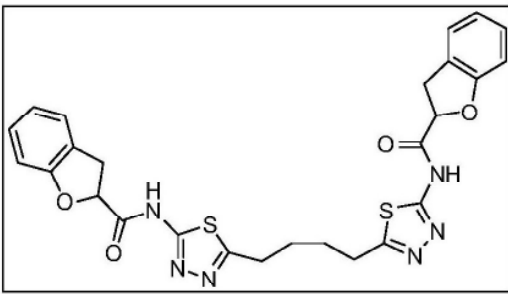
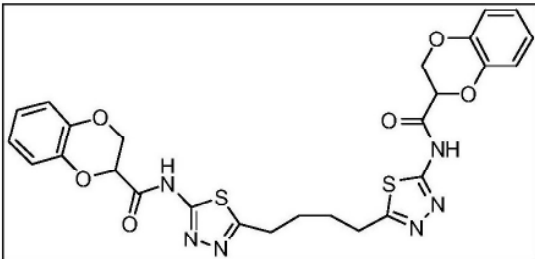
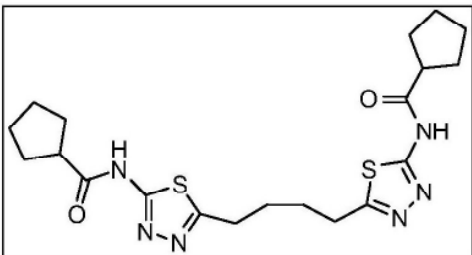
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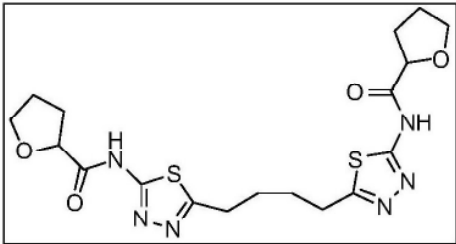
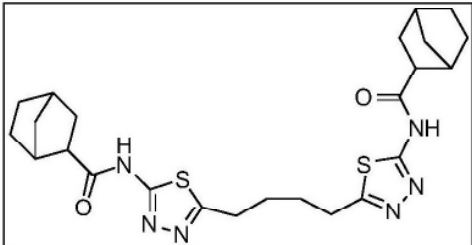
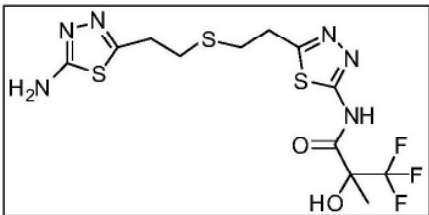
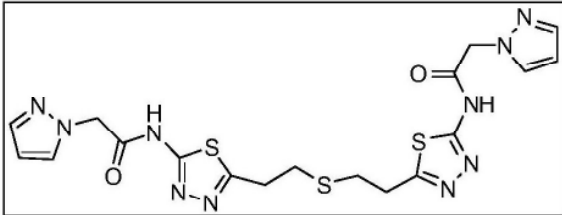
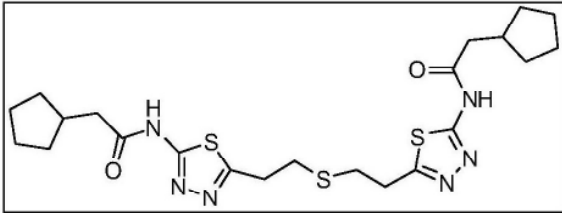
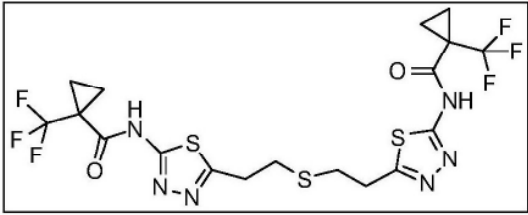
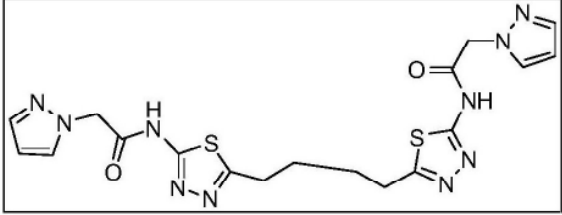
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[0160]

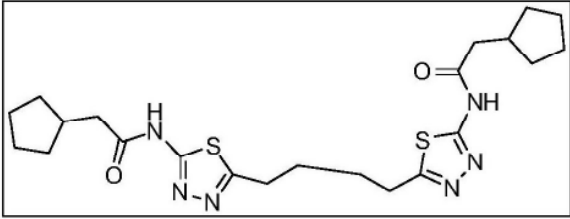
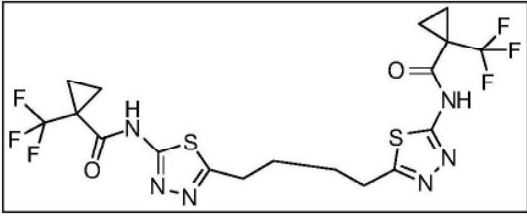
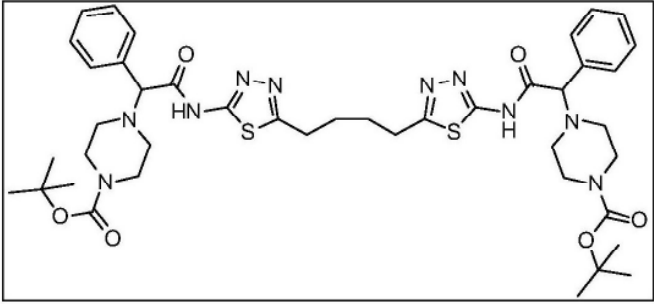
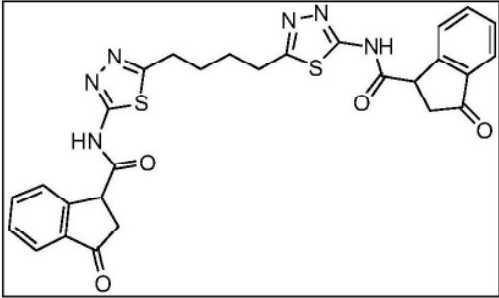
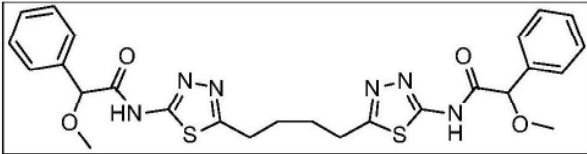
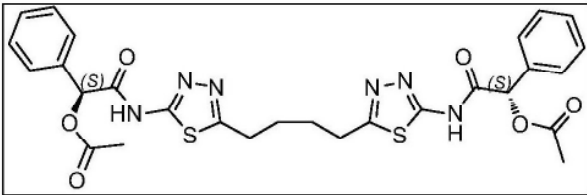
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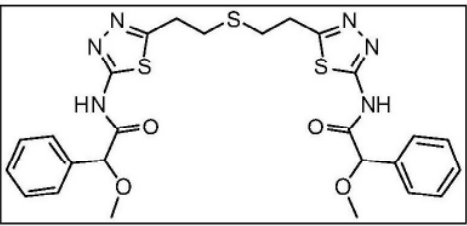
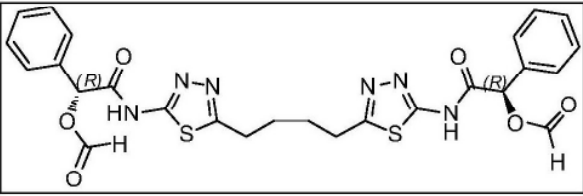
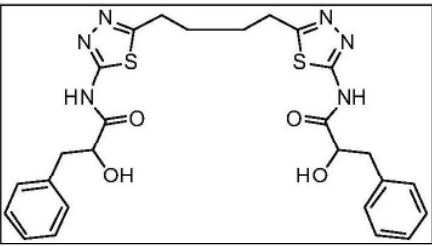
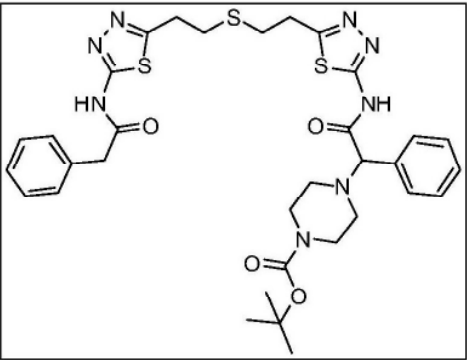
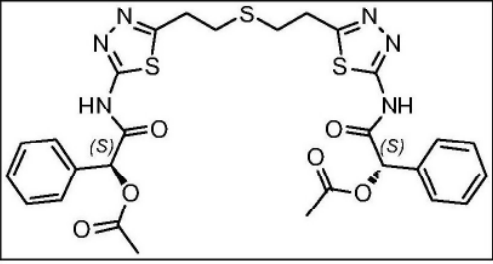
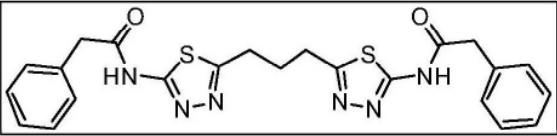
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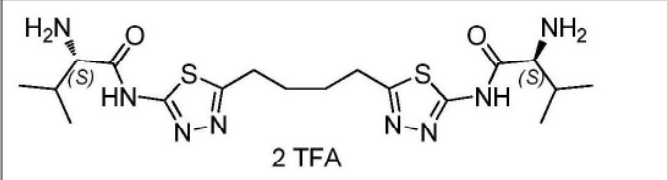
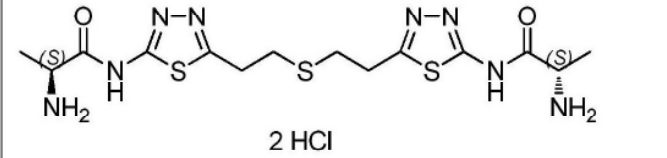
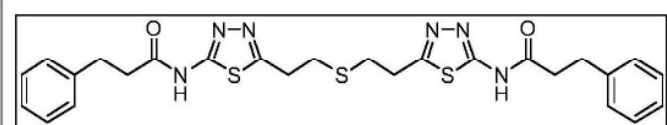
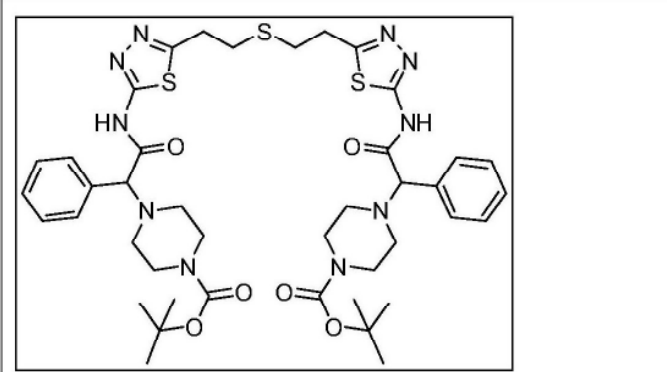
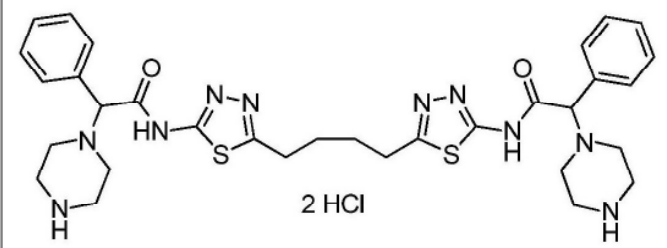
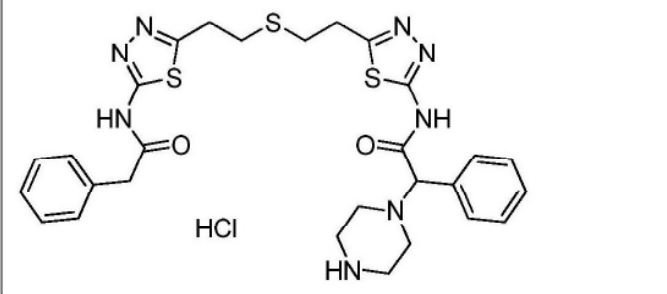
[0162]

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[0163]

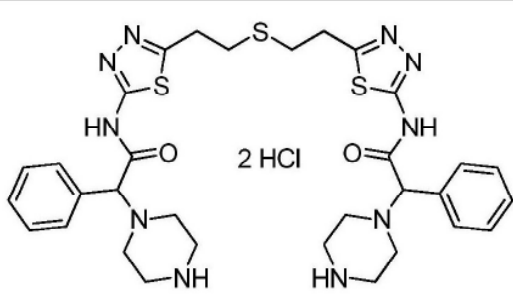
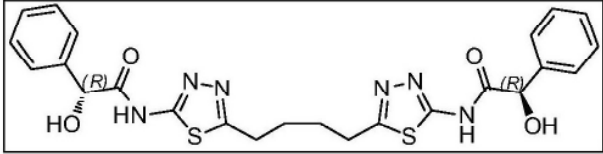
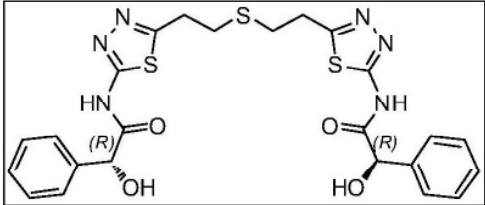
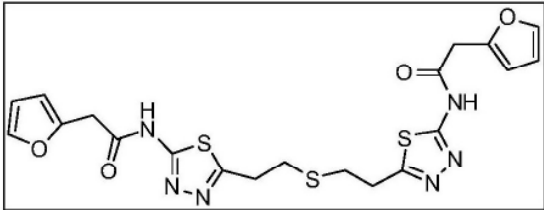
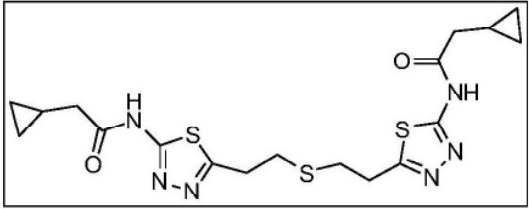
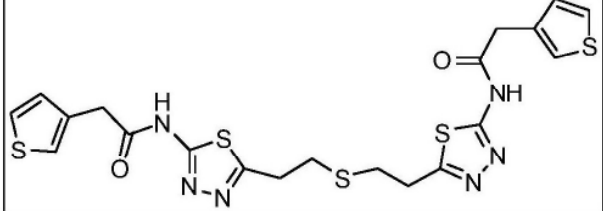
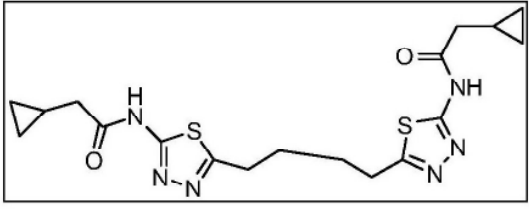
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[0164] 70	
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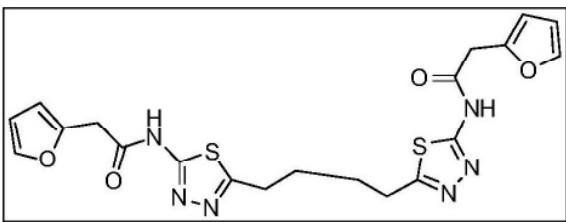
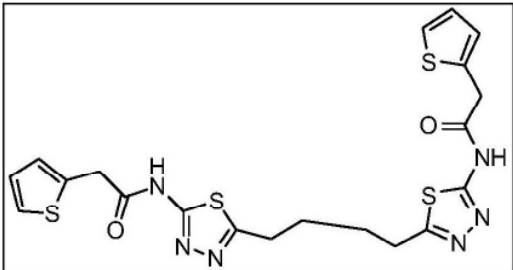
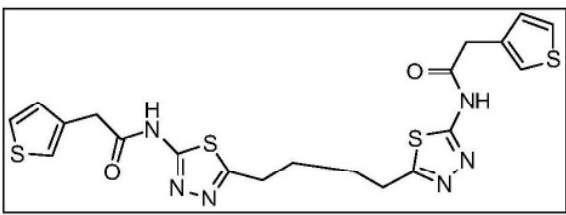
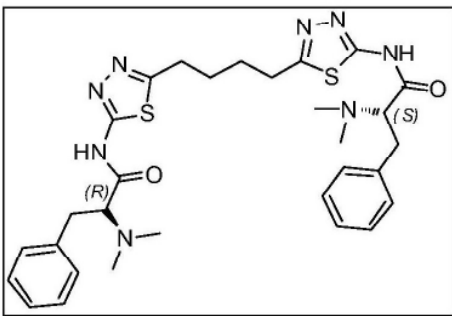
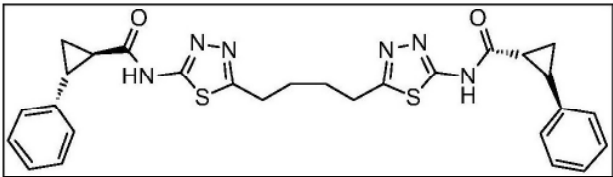
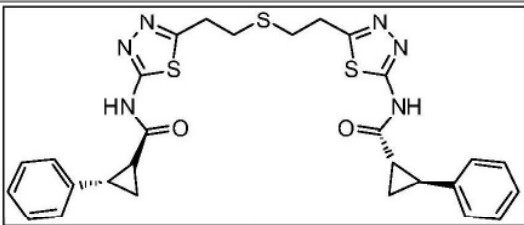
73	 2 TFA
74	 2 HCl
75	
76	
77	 2 HCl
78	 HCl

[0165]

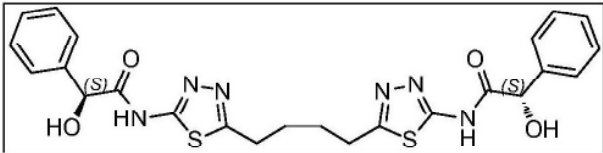
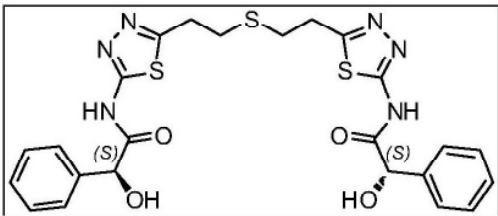
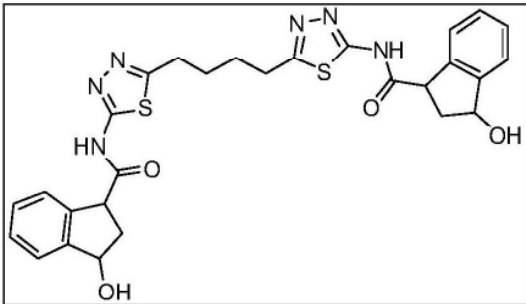
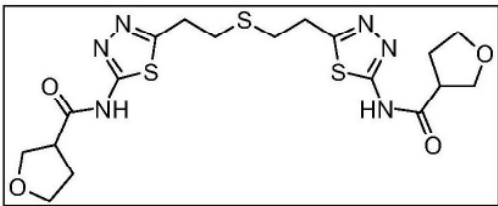
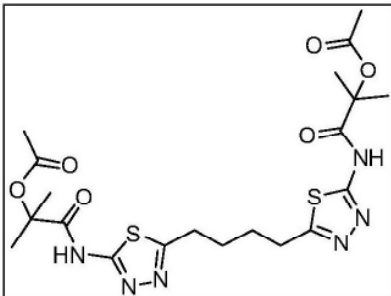
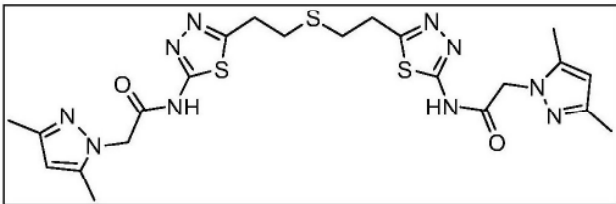
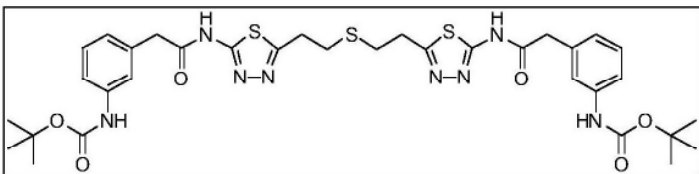
[0166]

79	 <chem>C1CCNCC1C(=O)NC2=NC=CC=C2.SCCS.C1=NC=NC=C1S2=NC=NC=C2N2C(=O)NC3=CC=CC=C3C4CCNCC4.[Cl-].[Cl-]</chem>
80	 <chem>C1=CC=CC=C1[C@H](O)C(=O)NC2=NC=CC=C2S3=NC=NC=C3N3C(=O)NC4=CC=CC=C4[C@H](O)C5=CC=CC=C5SCCSCC6=NC=NC=C6S7=NC=NC=C7N7</chem>
81	 <chem>C1=CC=CC=C1[C@H](O)C(=O)NC2=NC=CC=C2S3=NC=NC=C3N3C(=O)NC4=CC=CC=C4[C@H](O)C5=CC=CC=C5SCCSCC6=NC=NC=C6S7=NC=NC=C7N7</chem>
82	 <chem>C1=CC=C(C=C1)OC(=O)NC2=NC=CC=C2S3=NC=NC=C3N3C(=O)NC4=CC=CC=C4[C@H](O)C5=CC=CC=C5SCCSCC6=NC=NC=C6S7=NC=NC=C7N7</chem>
83	 <chem>C1CC2CC1CC2C(=O)NC3=NC=CC=C3S4=NC=NC=C4N4C(=O)NC5=CC=CC=C5SCCSCC6=NC=NC=C6S7=NC=NC=C7N7</chem>
84	 <chem>C1=CC=C(C=C1)SCC(=O)NC2=NC=CC=C2S3=NC=NC=C3N3C(=O)NC4=CC=CC=C4[C@H](O)C5=CC=CC=C5SCCSCC6=NC=NC=C6S7=NC=NC=C7N7</chem>
85	 <chem>C1CC2CC1CC2C(=O)NC3=NC=CC=C3S4=NC=NC=C4N4C(=O)NC5=CC=CC=C5SCCSCC6=NC=NC=C6S7=NC=NC=C7N7</chem>

[0167]

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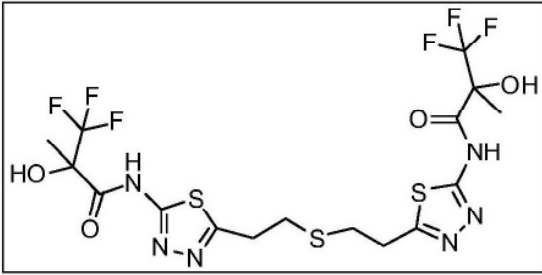
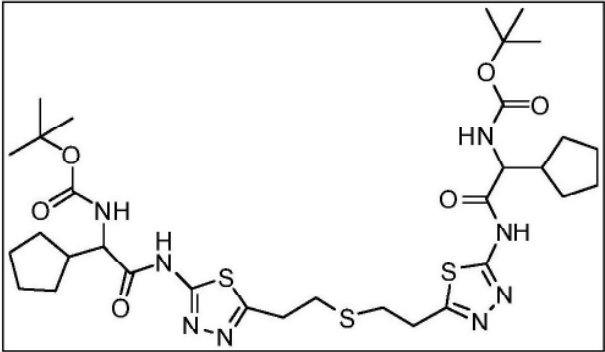
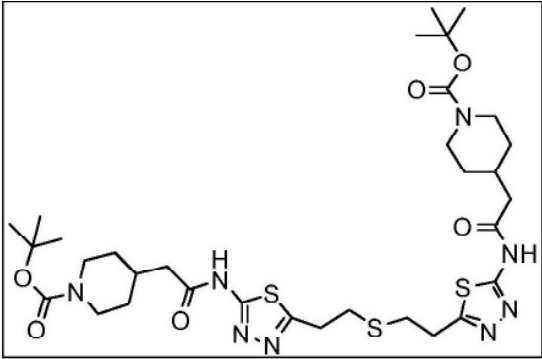
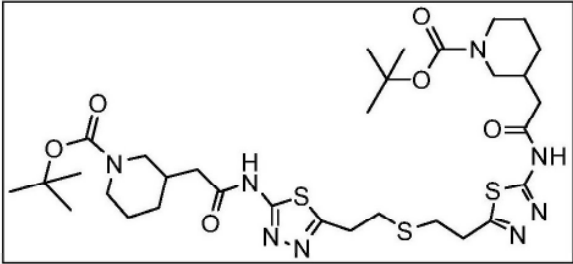
[0168]

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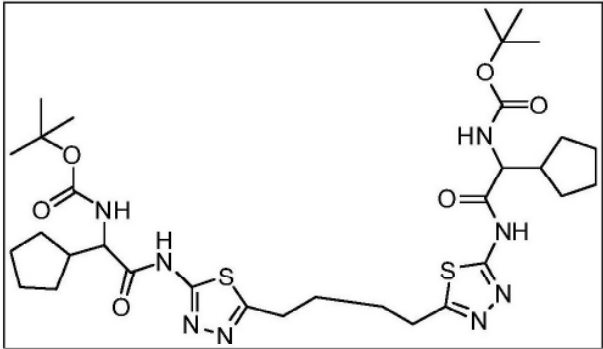
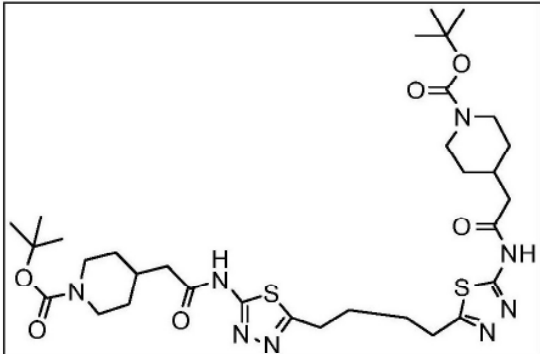
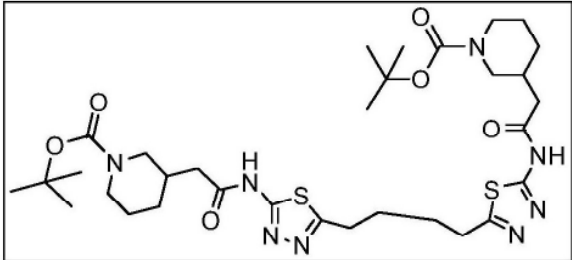
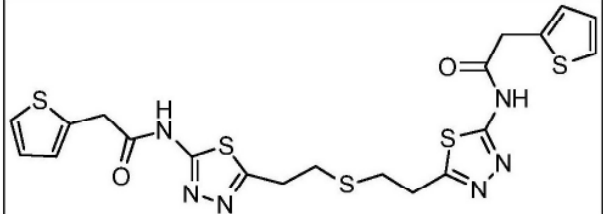
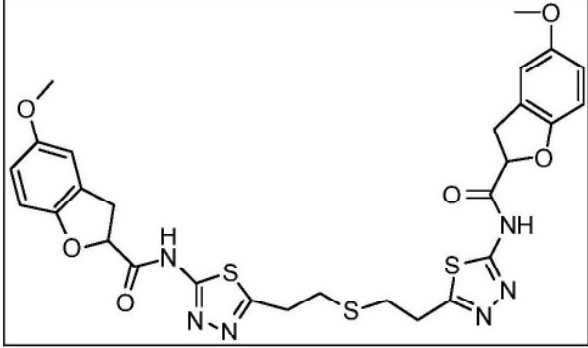
99	 <chem>Nc1ccc(cc1)CC(=O)Nc2ncnc2SCCSCC3N=NC=S3NC(=O)Cc4ccc(N)cc4.[Cl-].[Cl-]</chem>
100	 <chem>COCC(=O)Nc1ncnc1SCCSCC2N=NC=S2NC(=O)CCOC</chem>
101	 <chem>COCC(=O)Nc1ncnc1SCCSCC2N=NC=S2NC(=O)CCOC</chem>
102	 <chem>Fc1ccc(cc1)CC(=O)Nc2ncnc2SCCSCC3N=NC=S3NC(=O)Cc4ccc(F)cc4</chem>
103	 <chem>COCC(=O)Nc1ncnc1SCCSCC2N=NC=S2NC(=O)CCOC</chem>
104	 <chem>COCC(=O)Nc1ncnc1SCCSCC2N=NC=S2NC(=O)CCOC</chem>
105	 <chem>COCC(=O)Nc1ncnc1SCCSCC2N=NC=S2NC(=O)CCOC</chem>
106	 <chem>COCC(=O)Nc1ncnc1SCCSCC2N=NC=S2NC(=O)CCOC</chem>
107	 <chem>COCC(=O)Nc1ncnc1SCCSCC2N=NC=S2NC(=O)CCOC</chem>
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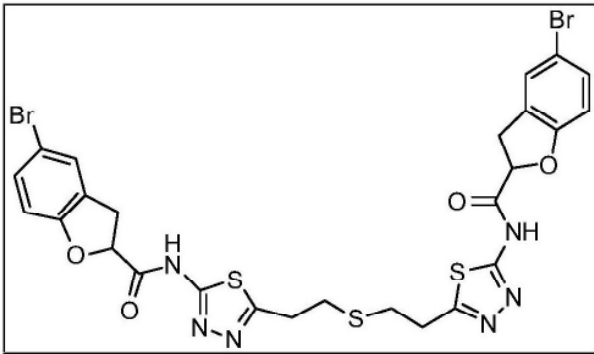
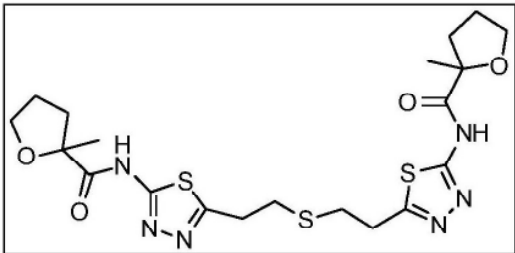
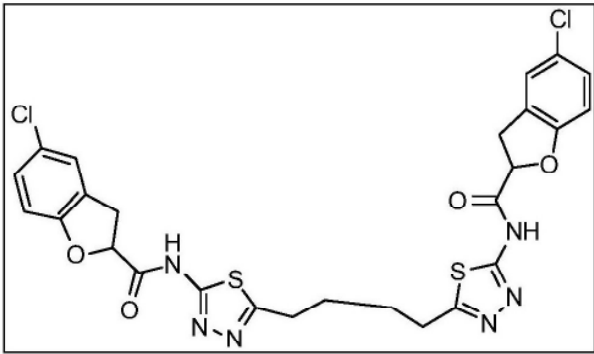
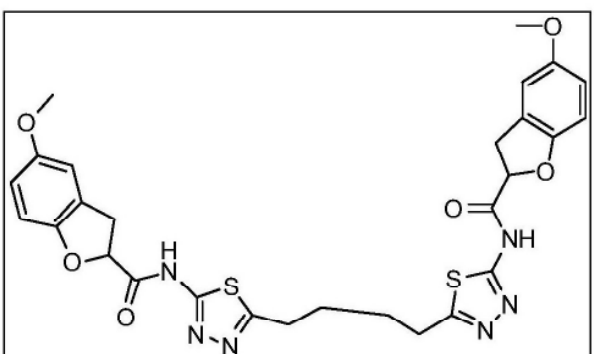
[0169]

[0170]

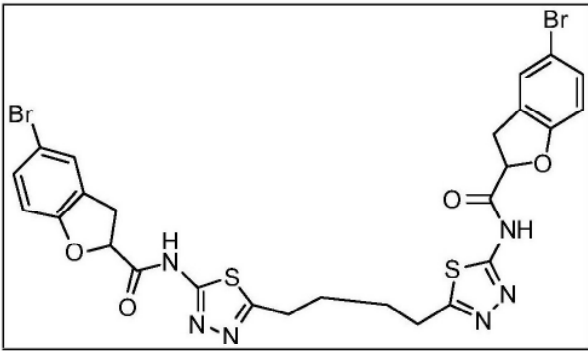
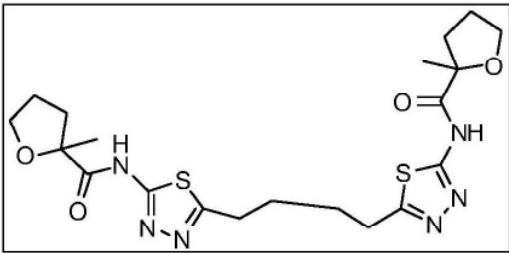
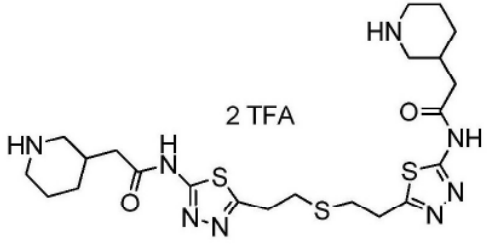
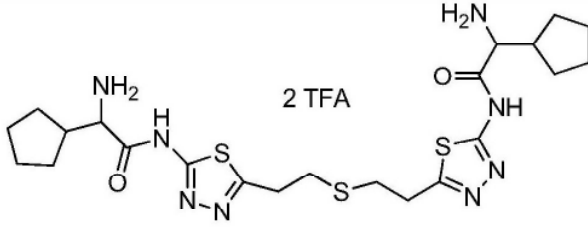
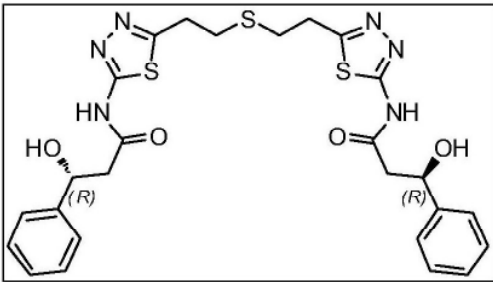
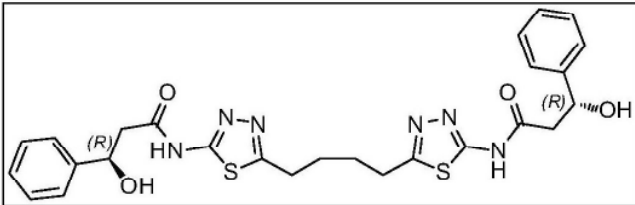
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[0171]

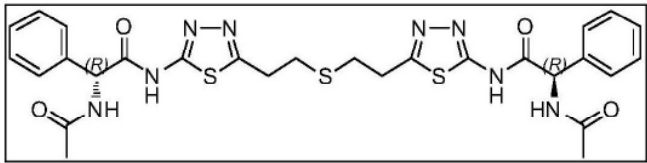
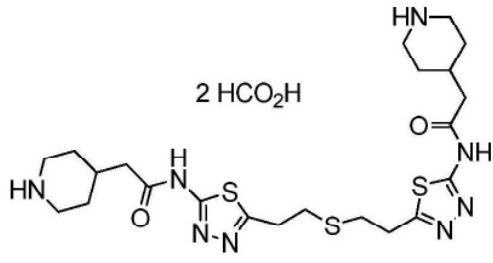
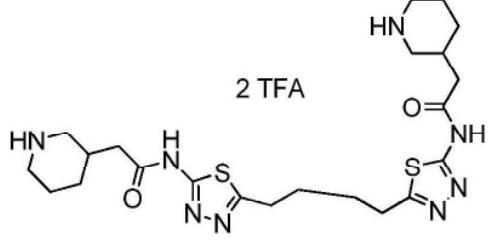
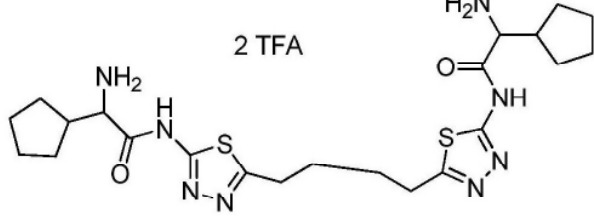
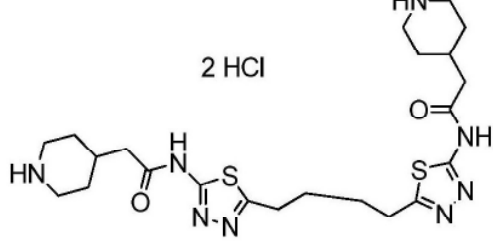
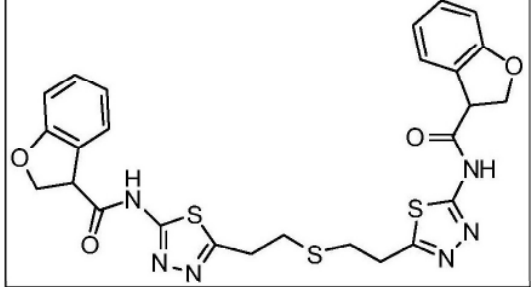
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[0172] 120	
121	

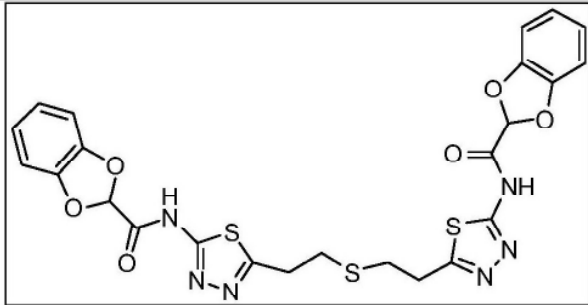
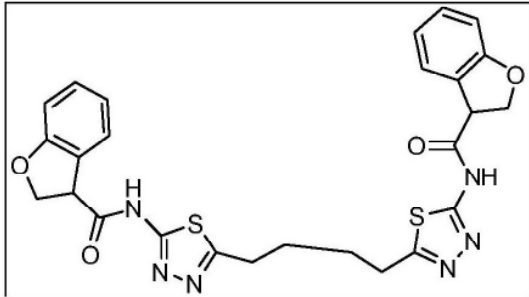
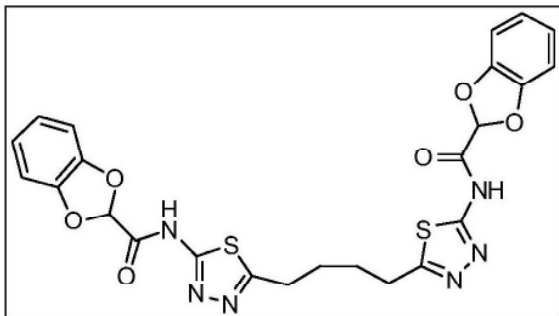
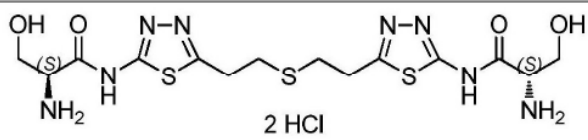
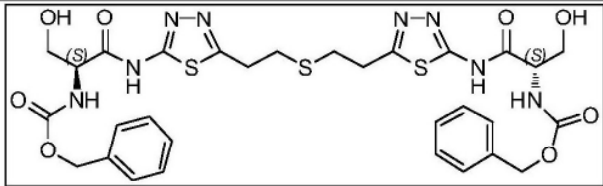
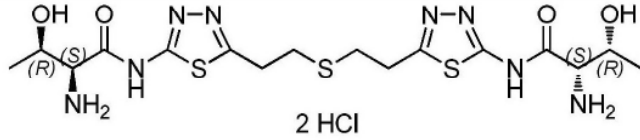
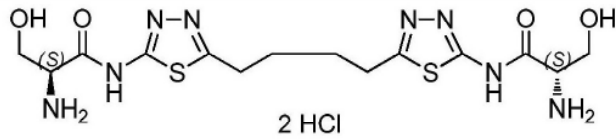
[0173]

122	
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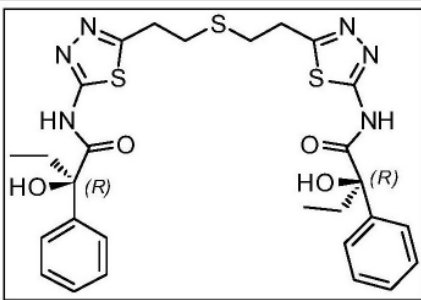
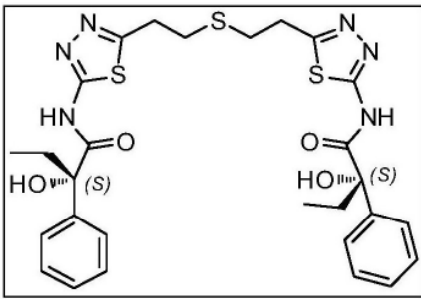
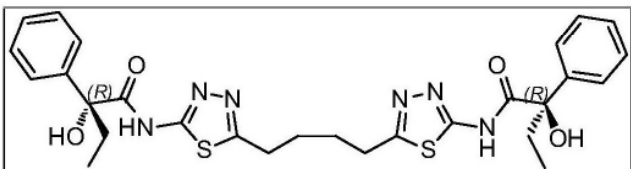
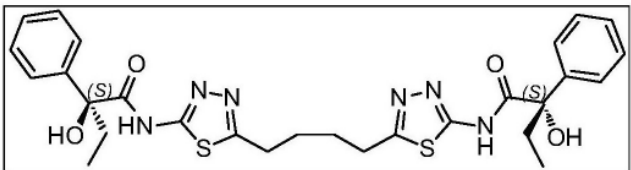
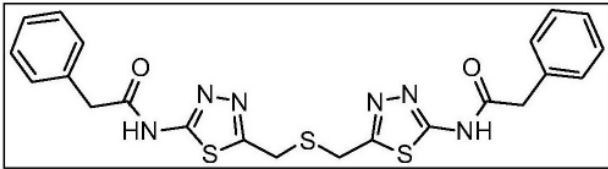
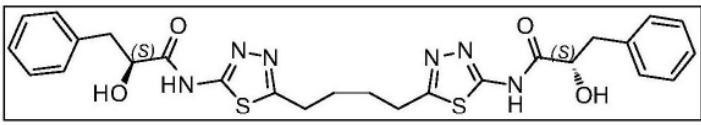
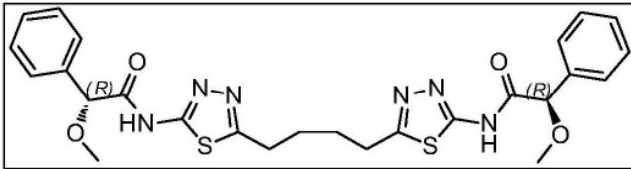
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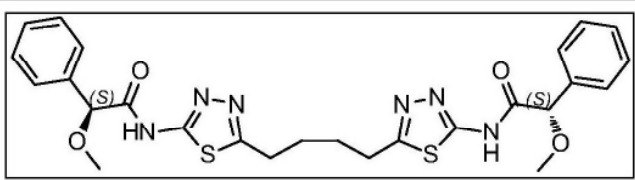
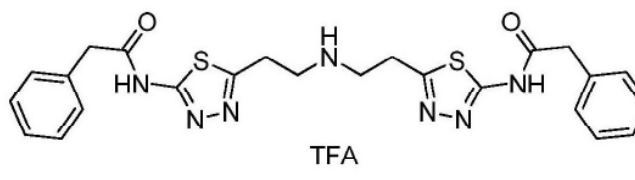
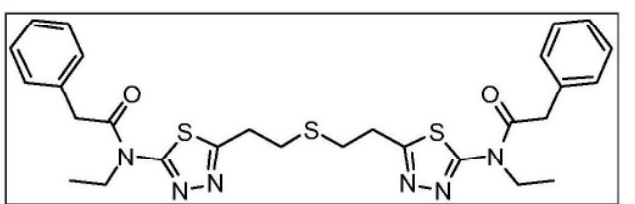
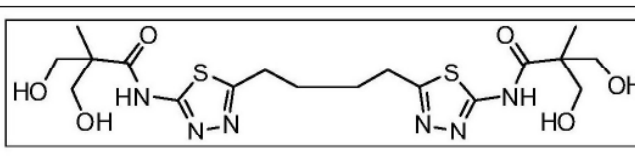
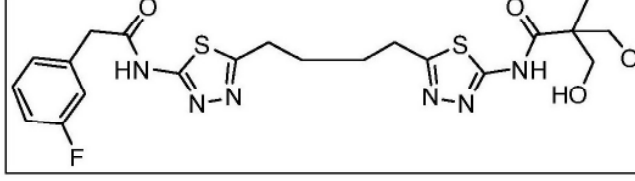
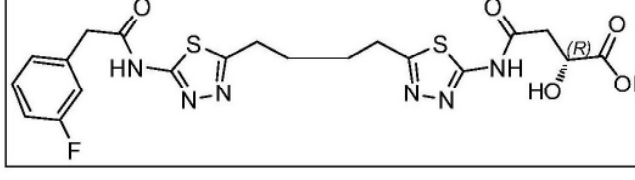
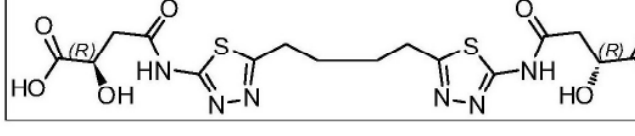
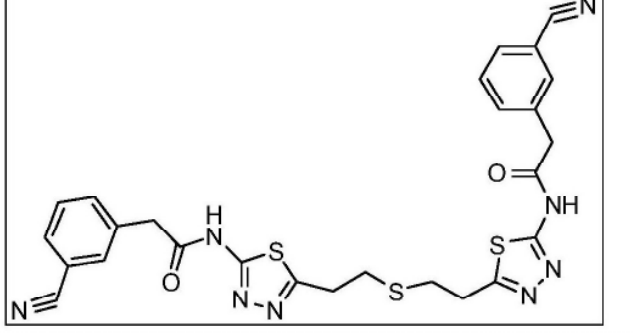
128	
129	2 HCO₂H 
130	2 TFA 
131	2 TFA 
132	2 HCl 
133	

[0175]

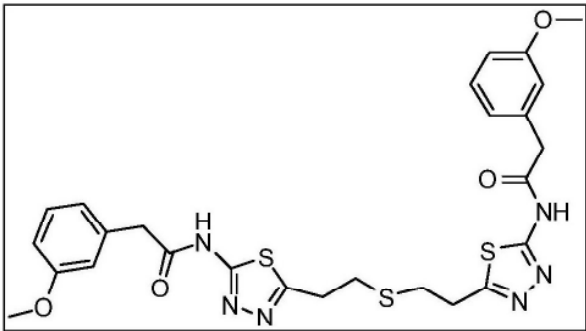
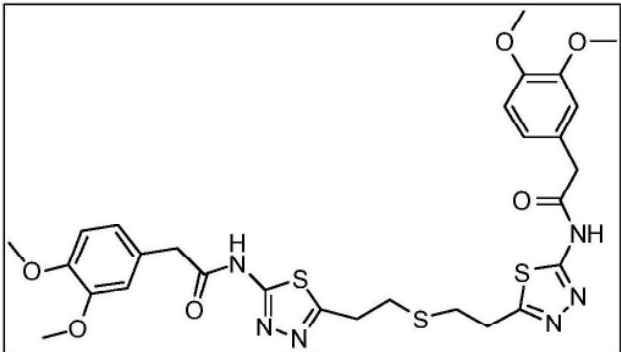
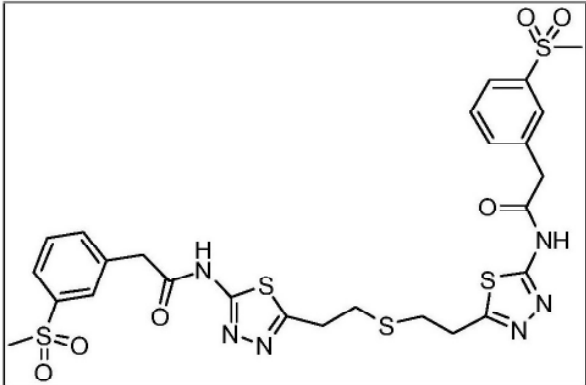
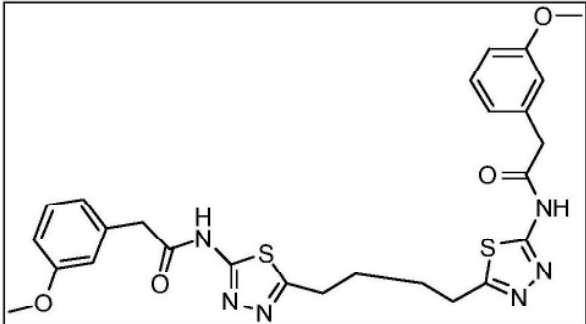
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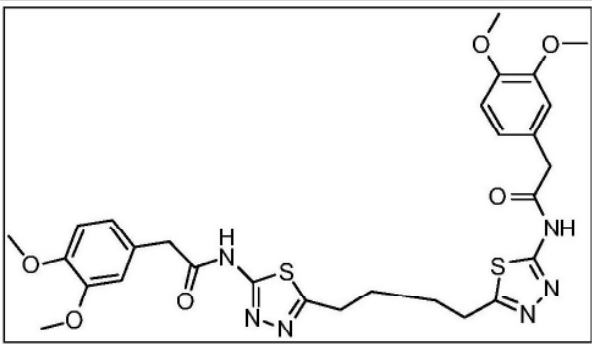
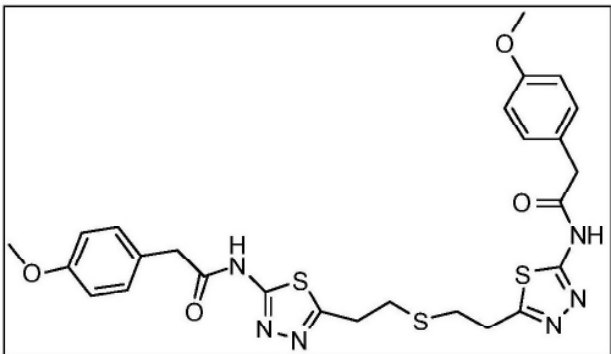
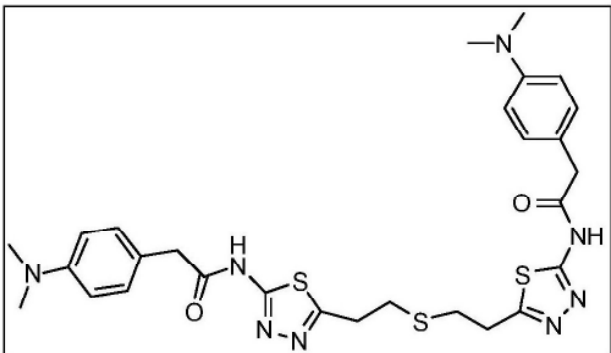
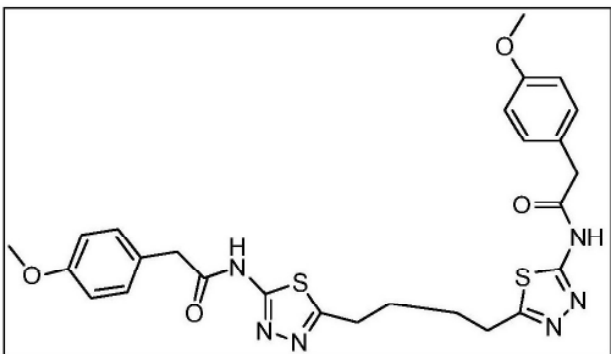
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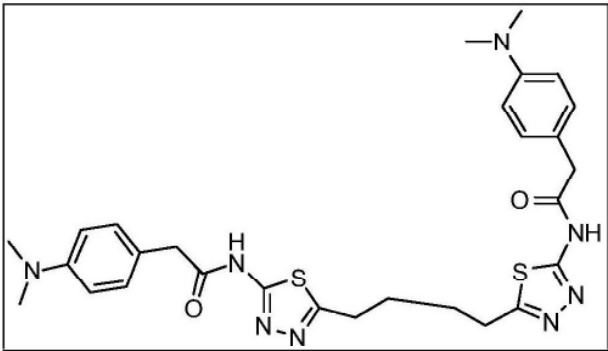
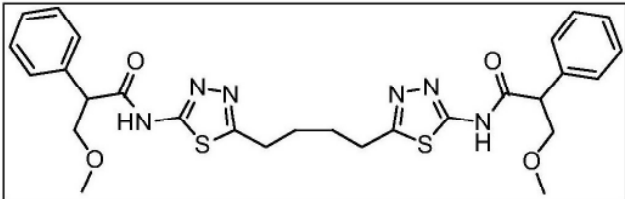
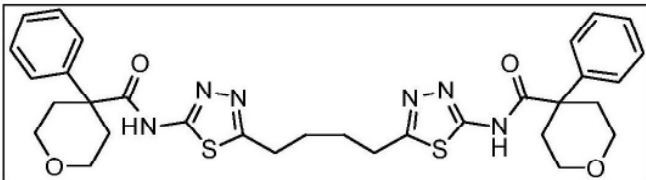
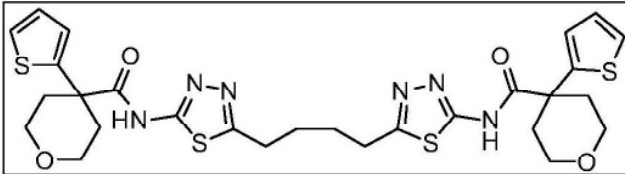
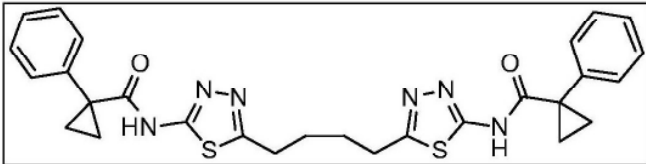
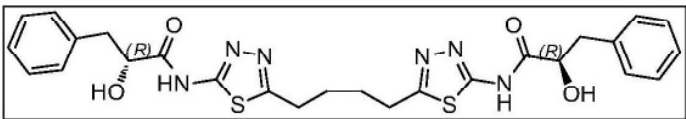
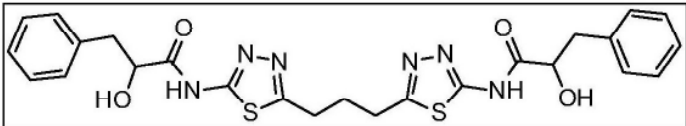
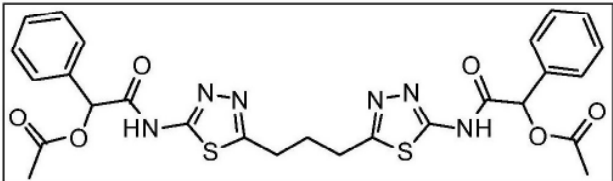
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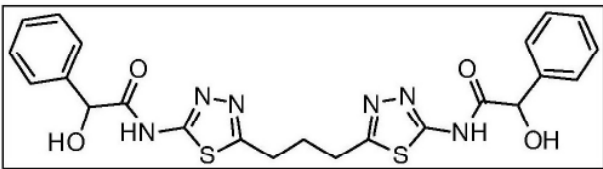
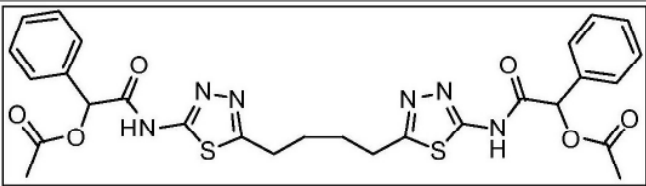
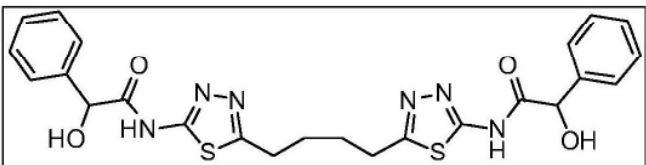
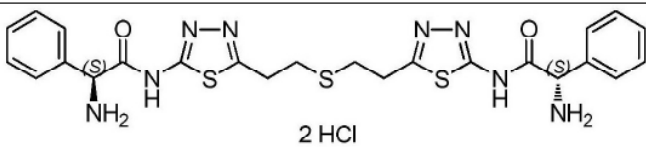
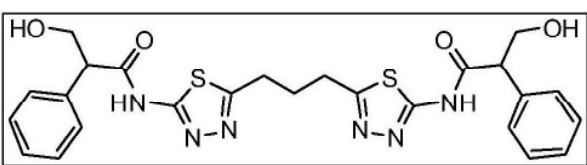
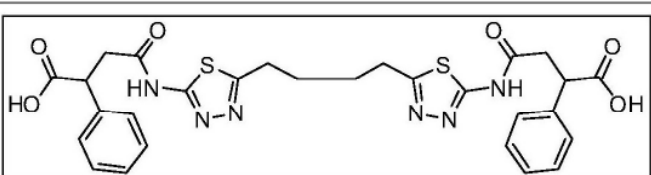
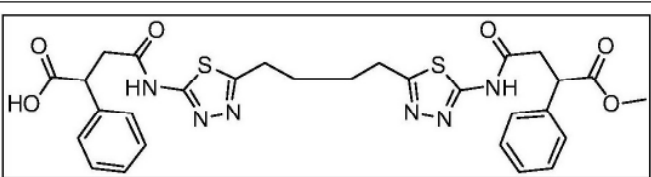
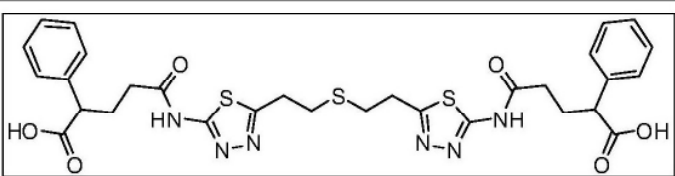
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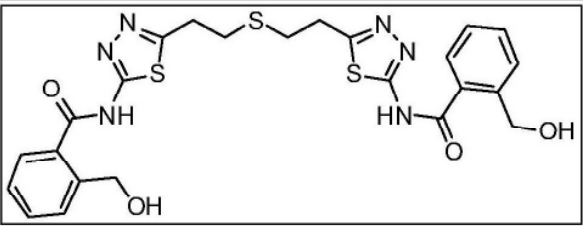
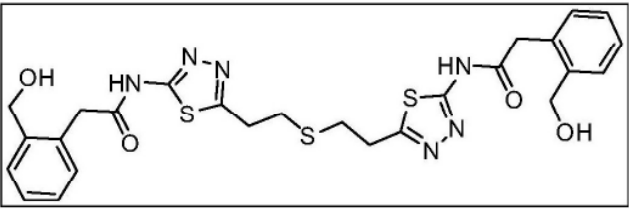
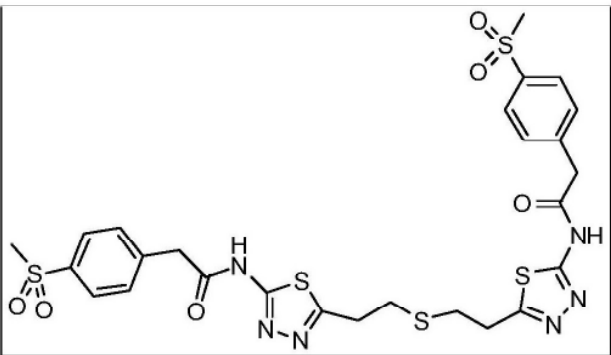
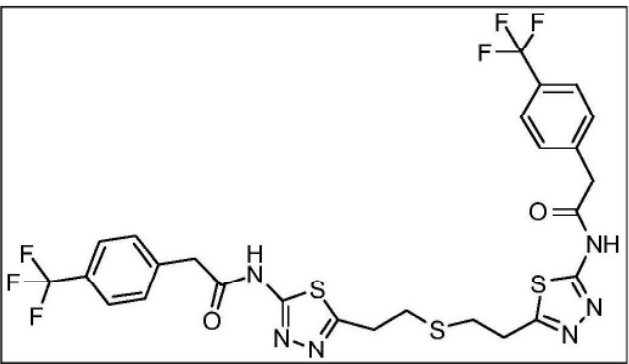
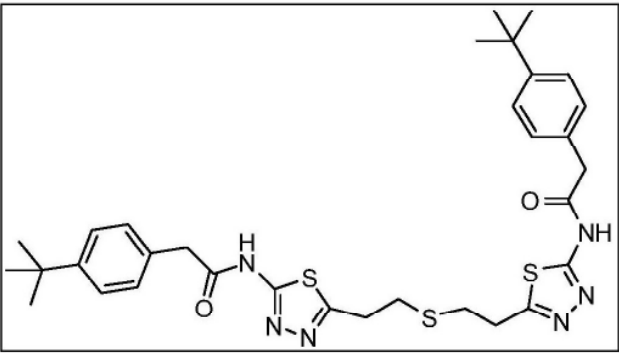
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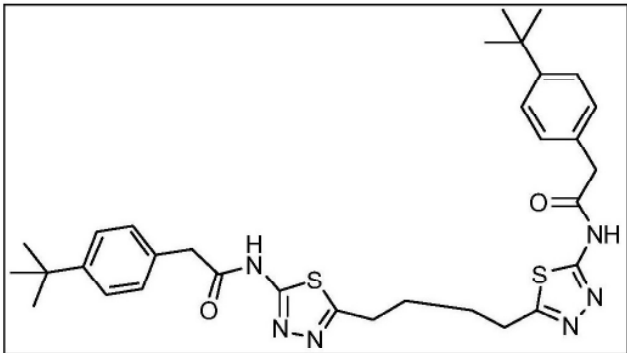
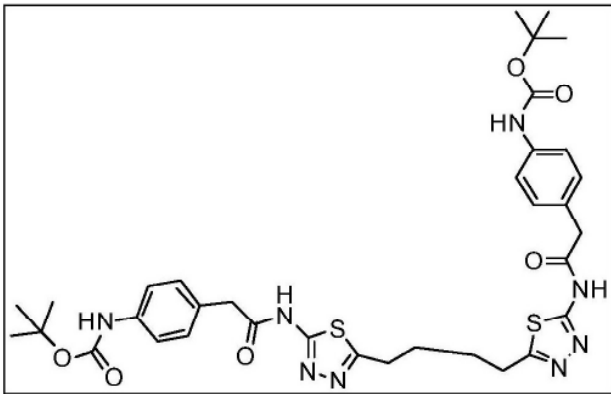
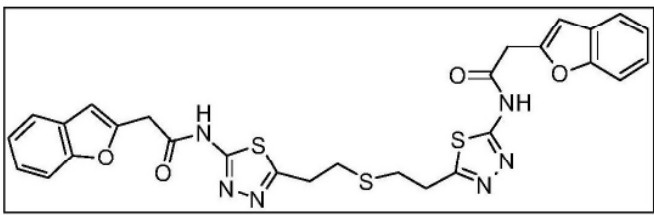
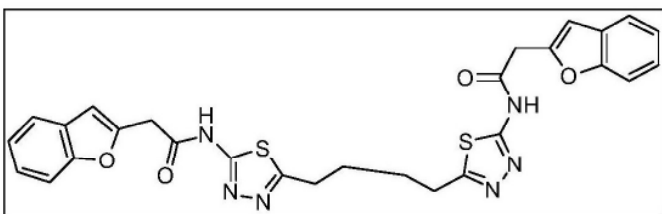
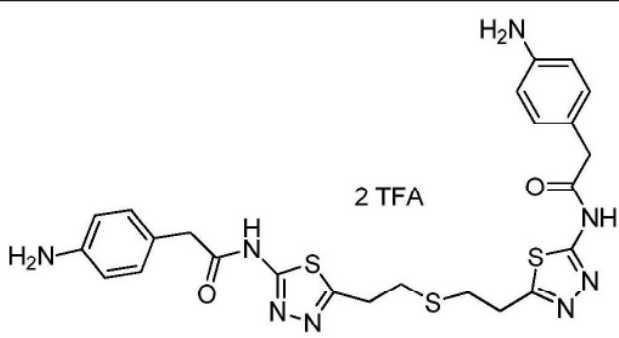
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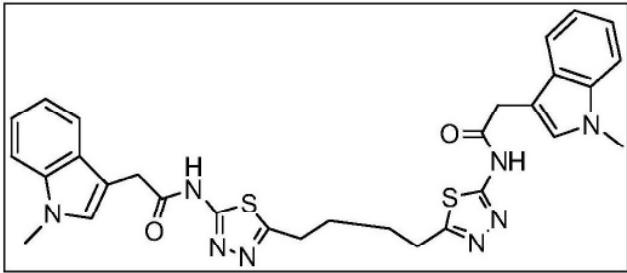
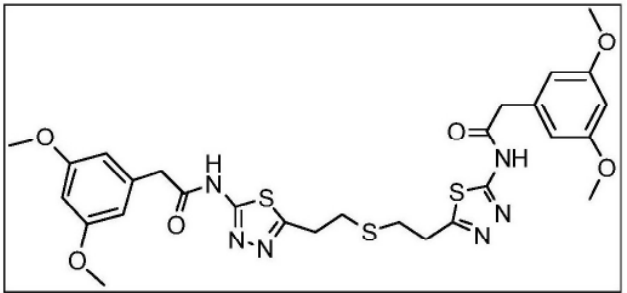
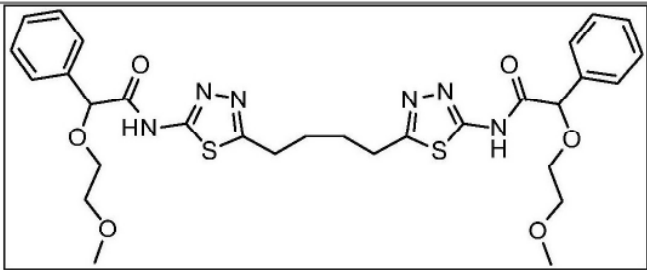
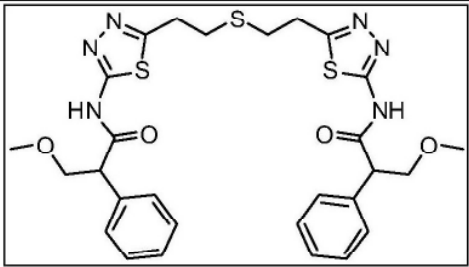
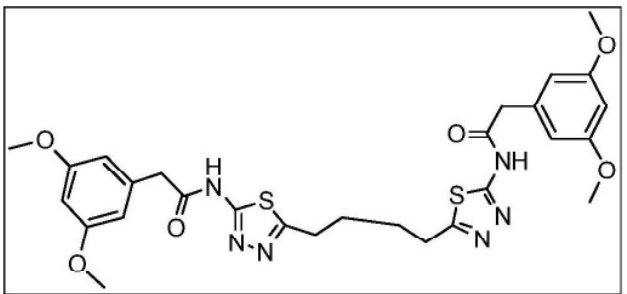
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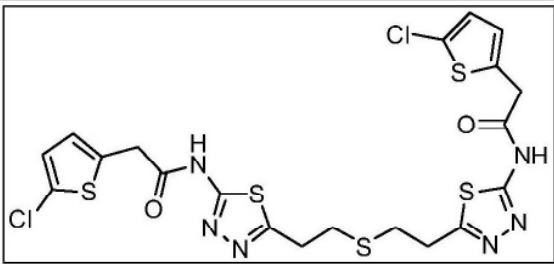
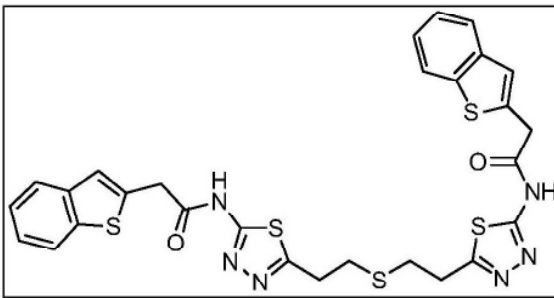
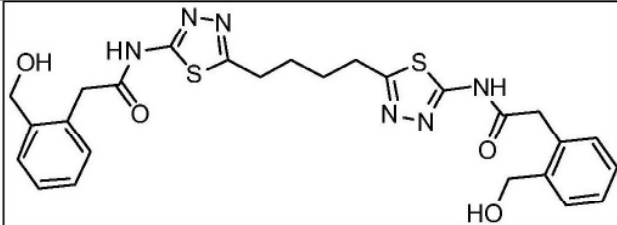
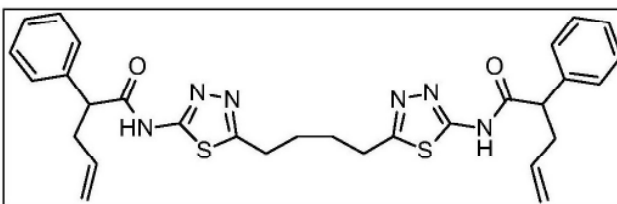
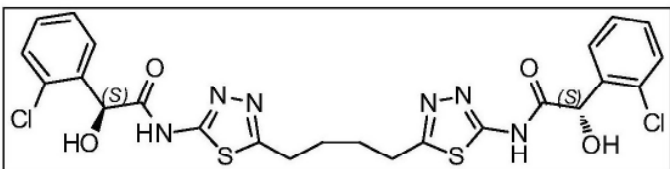
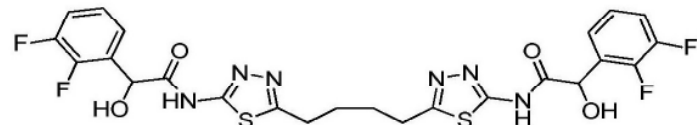
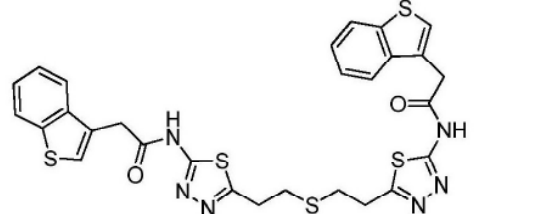
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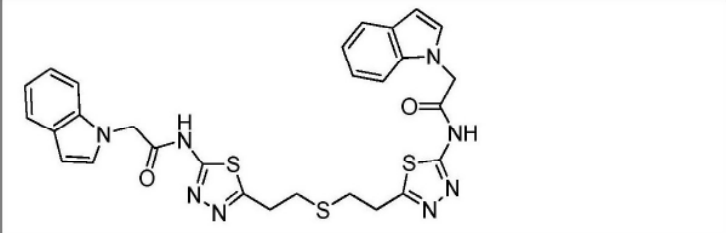
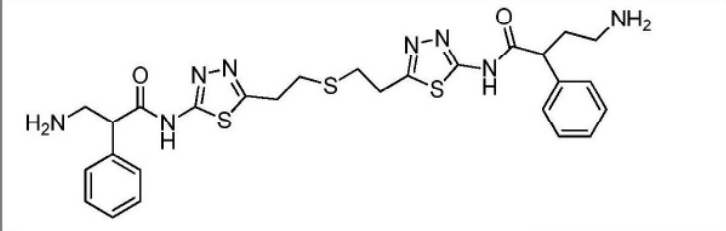
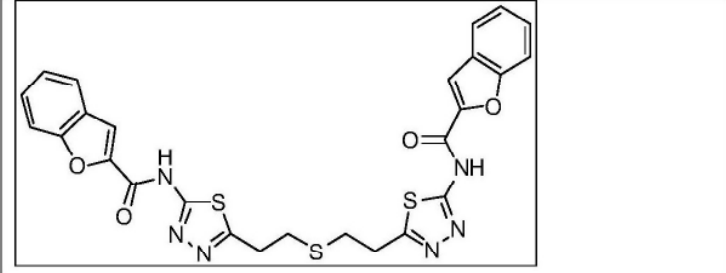
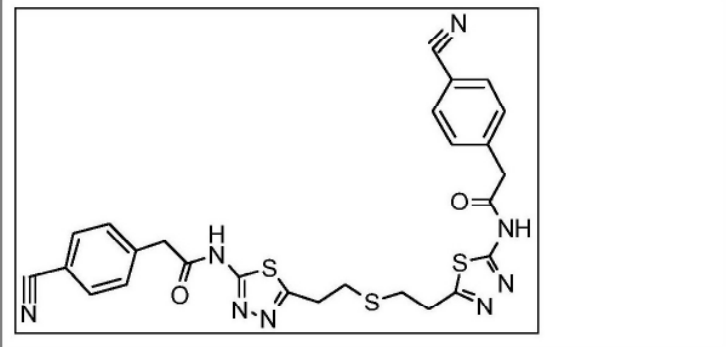
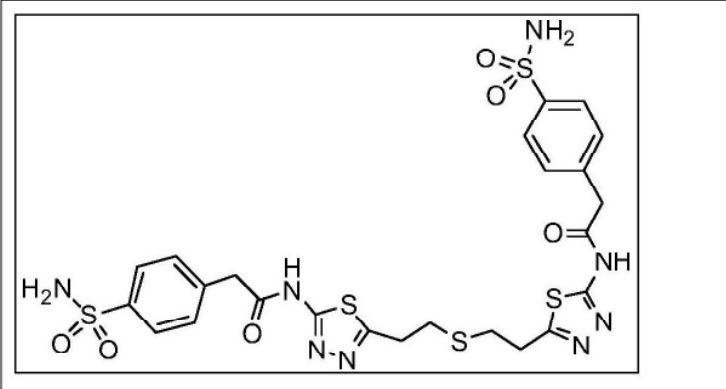
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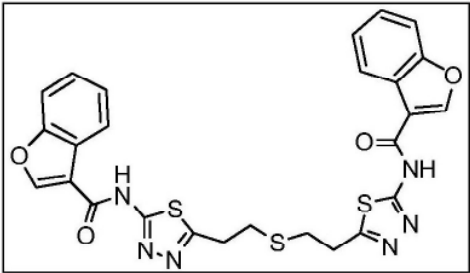
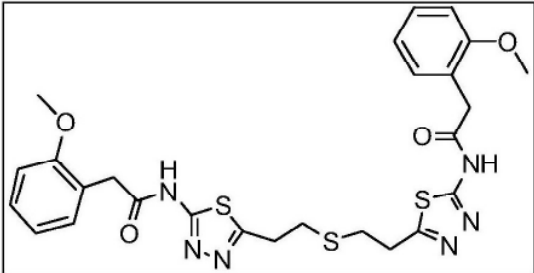
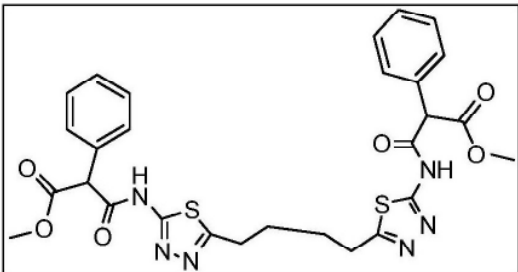
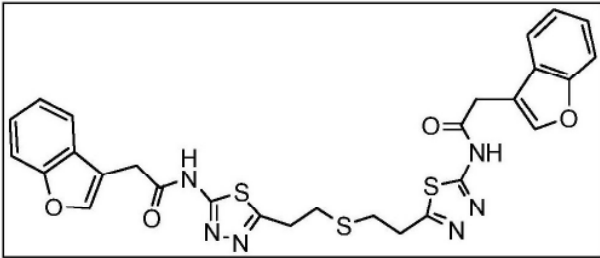
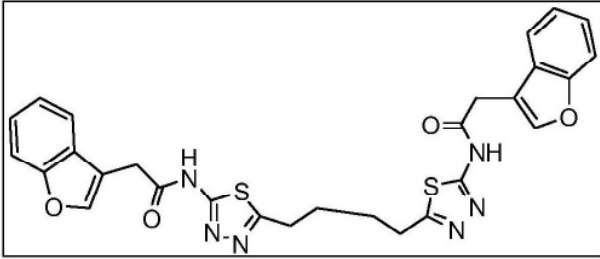
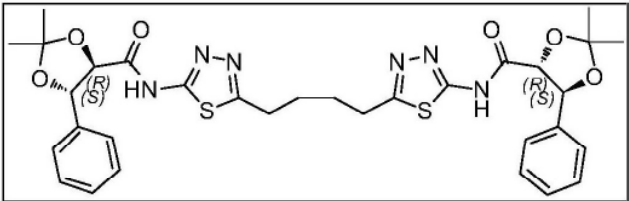
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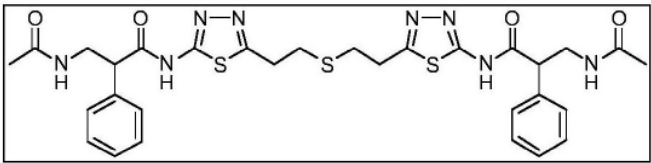
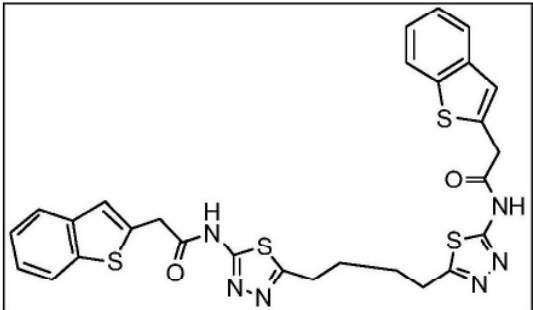
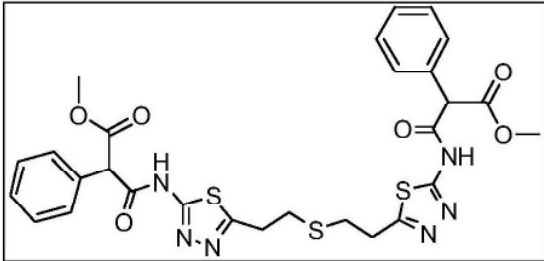
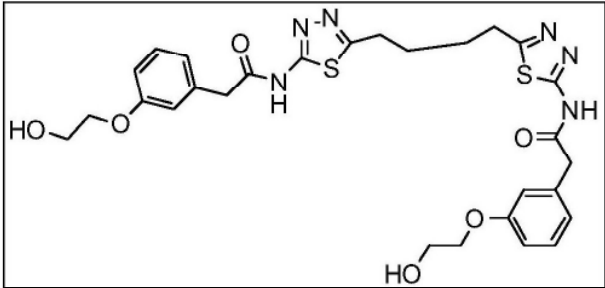
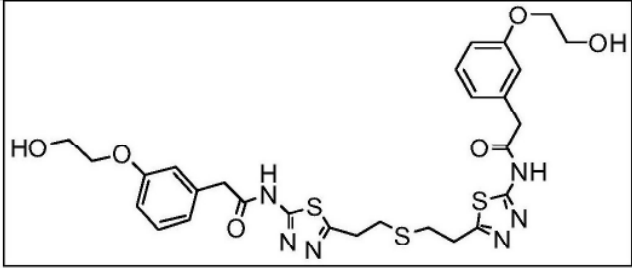
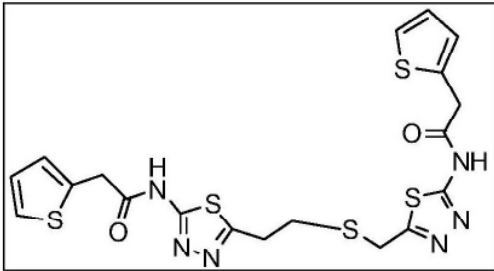
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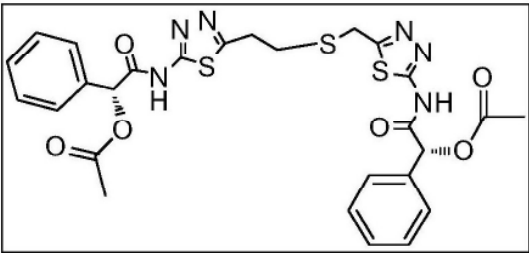
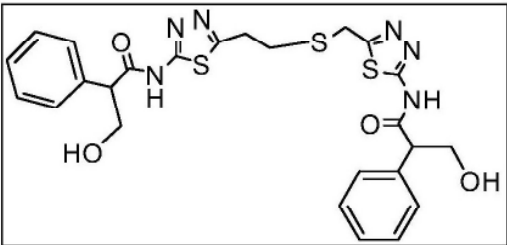
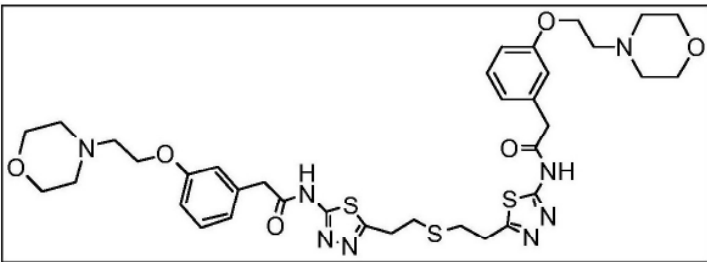
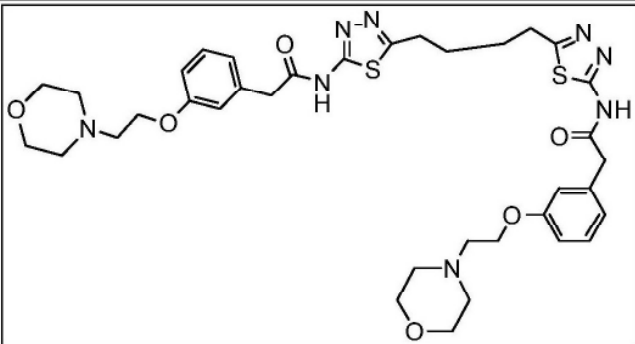
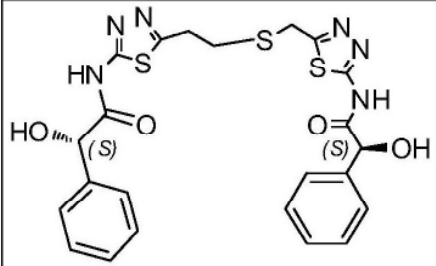
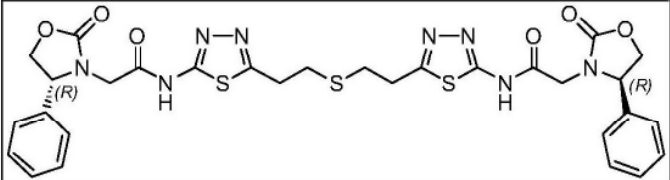
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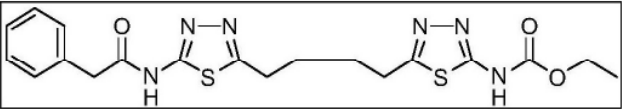
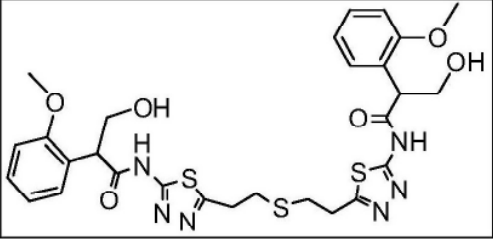
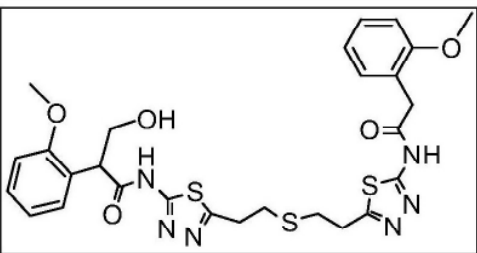
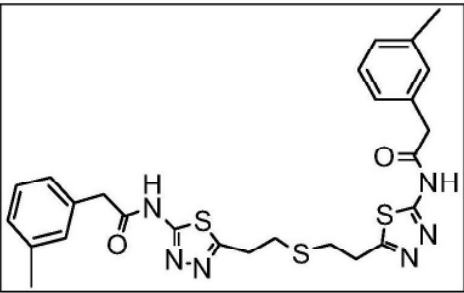
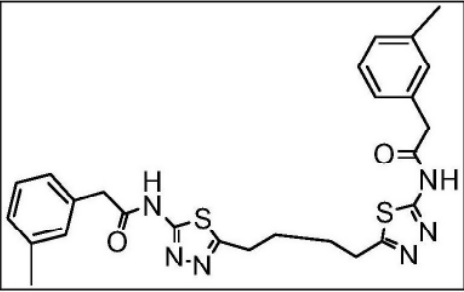
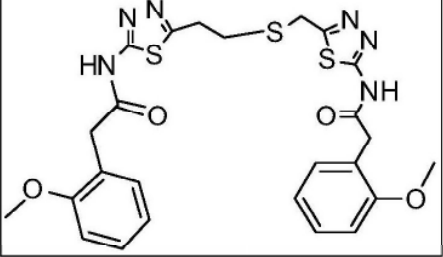
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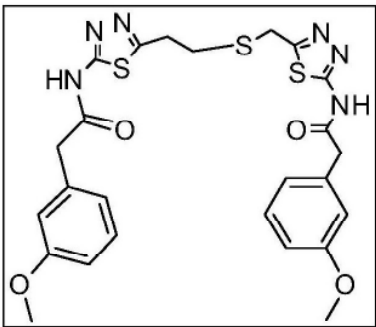
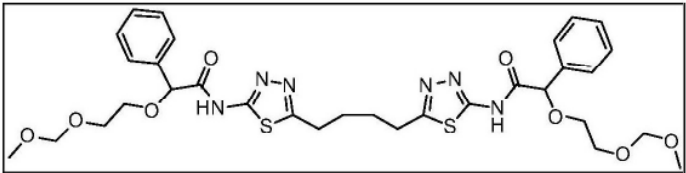
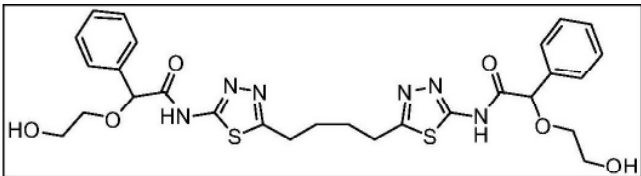
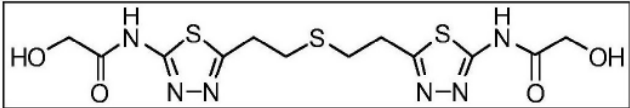
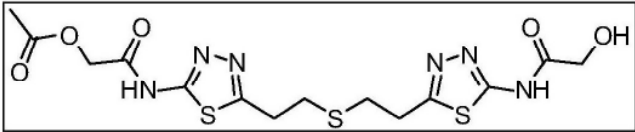
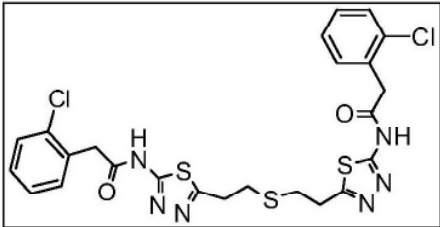
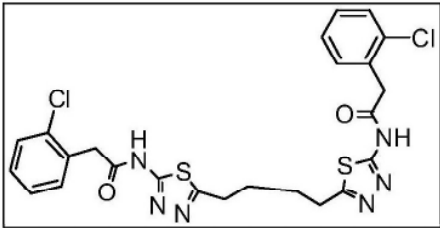
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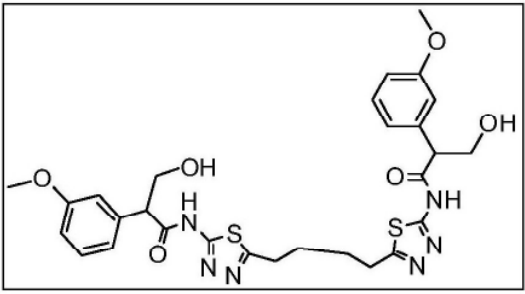
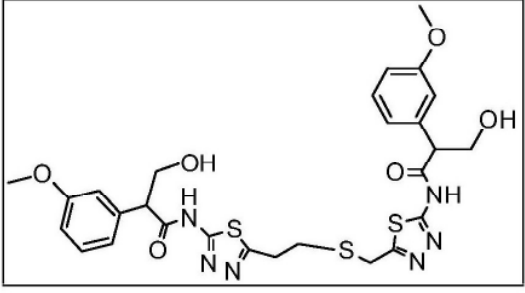
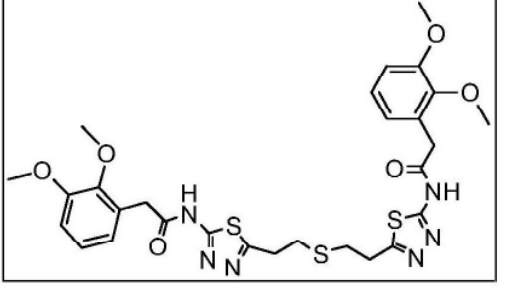
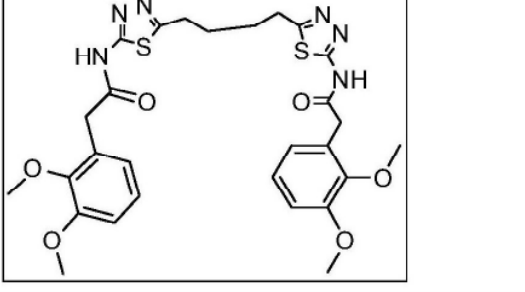
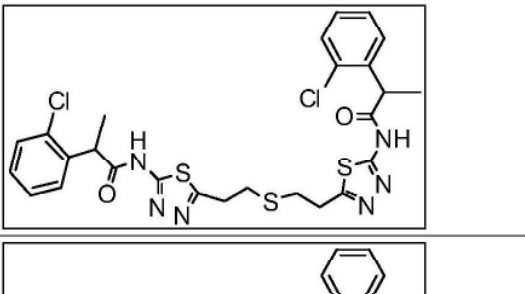
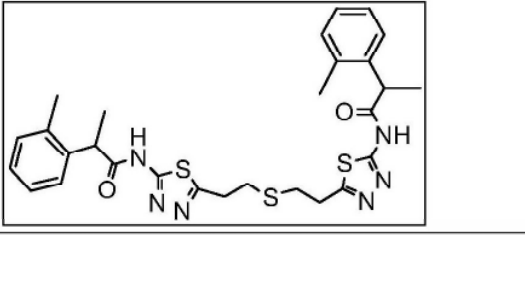
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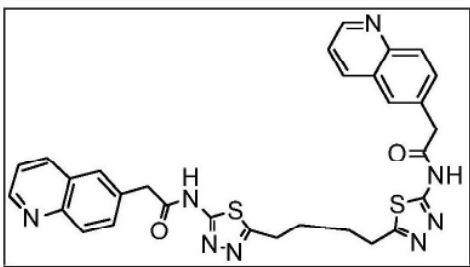
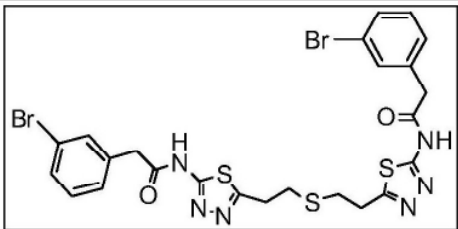
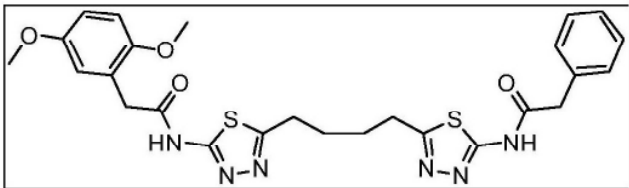
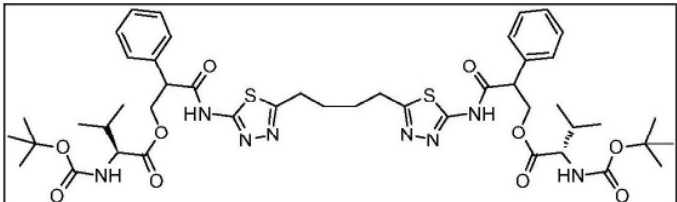
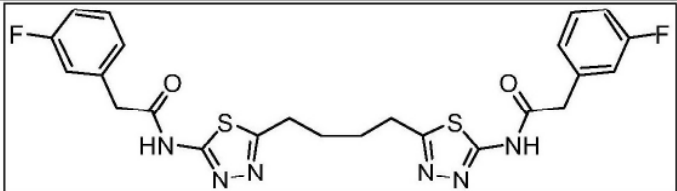
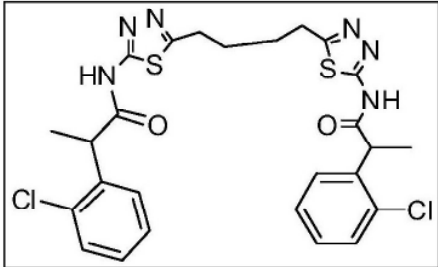
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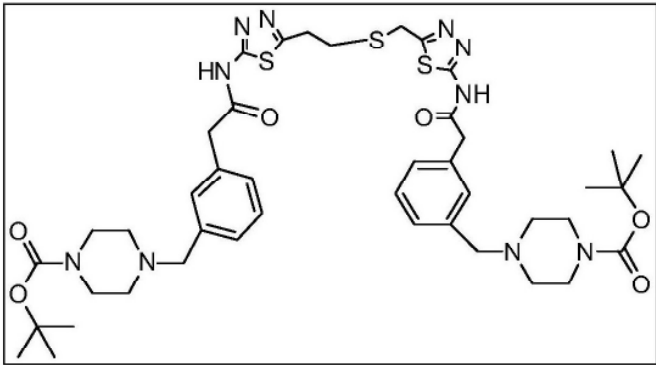
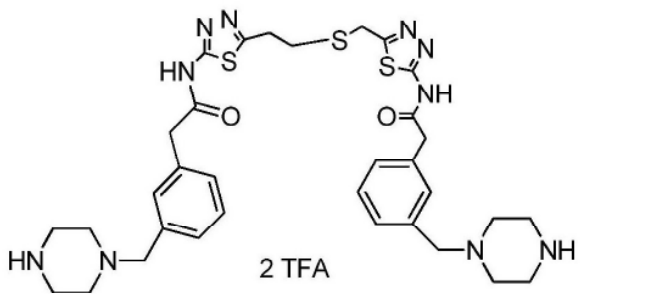
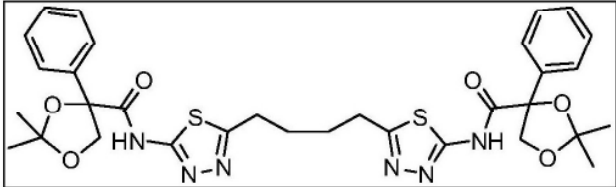
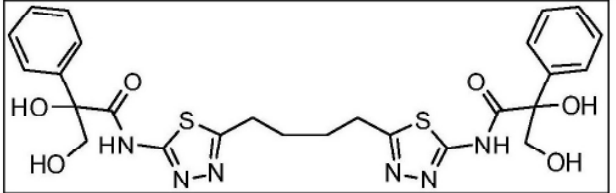
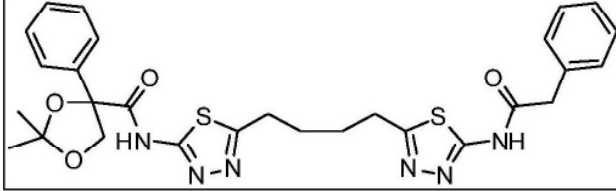
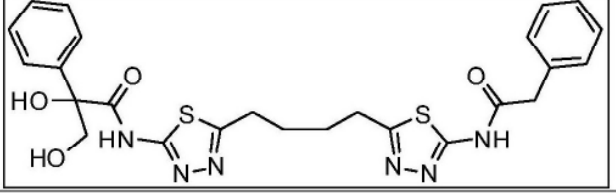
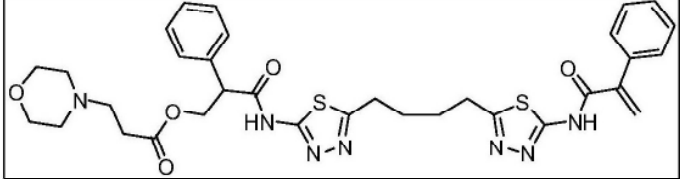
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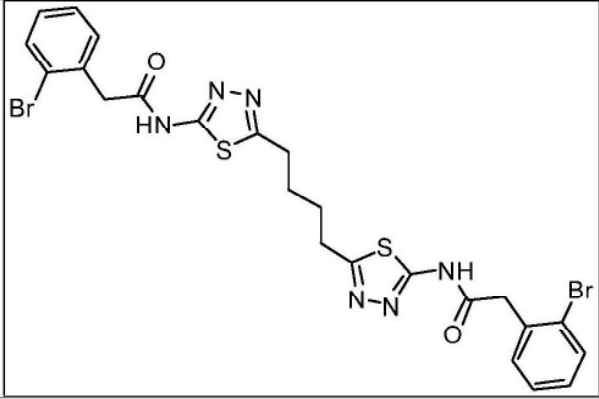
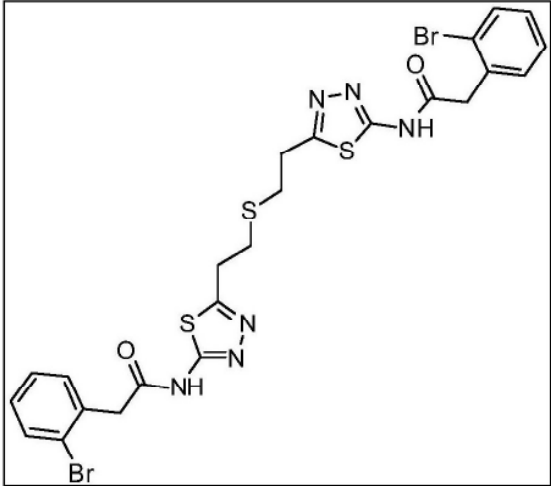
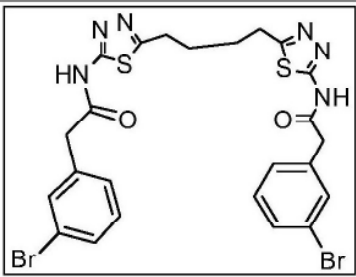
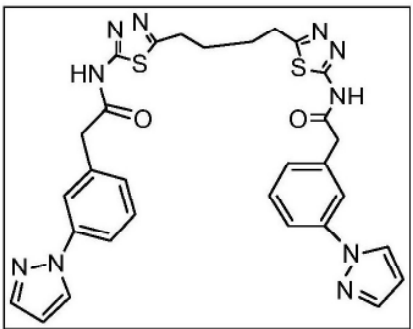
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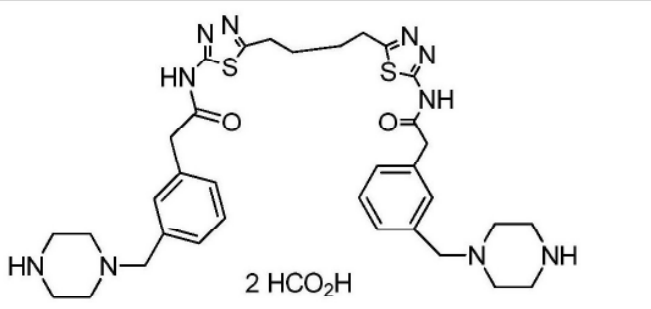
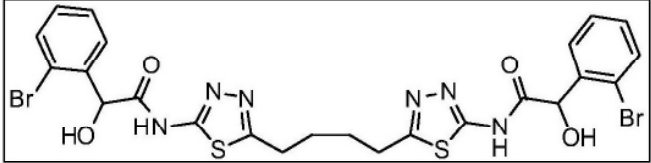
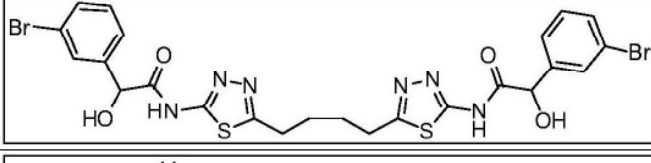
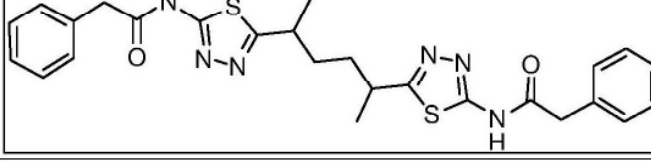
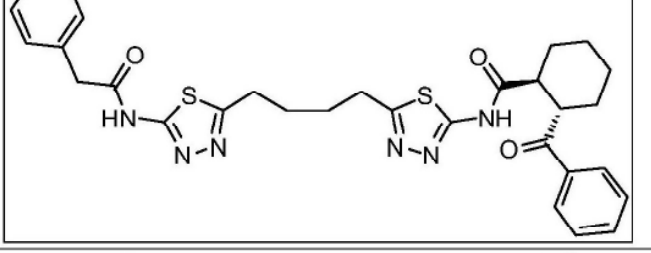
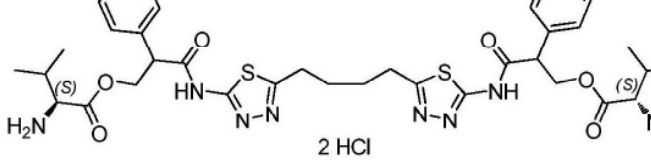
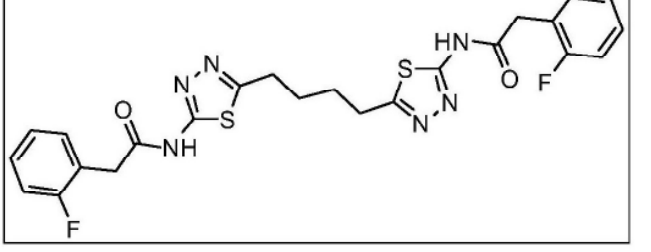
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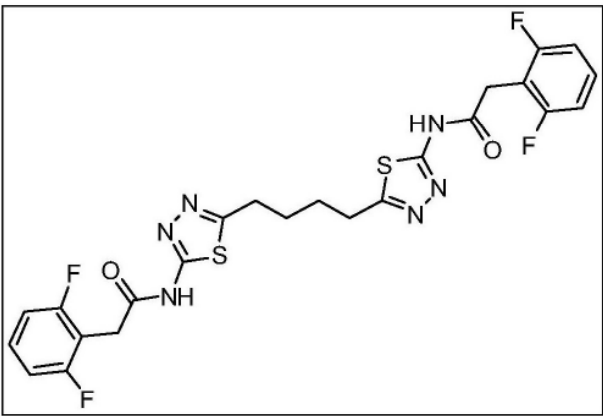
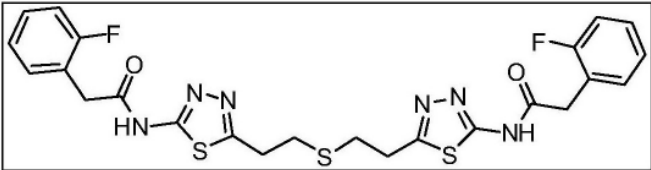
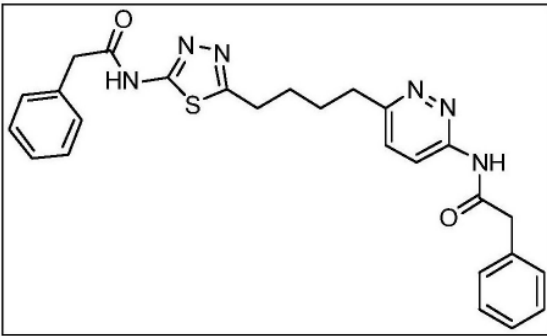
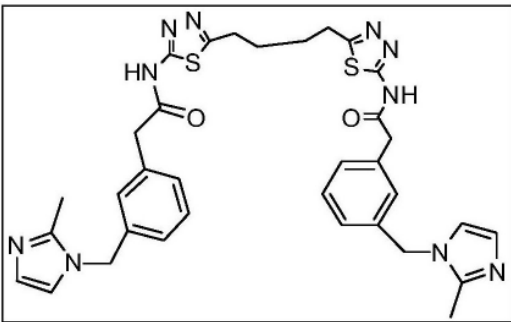
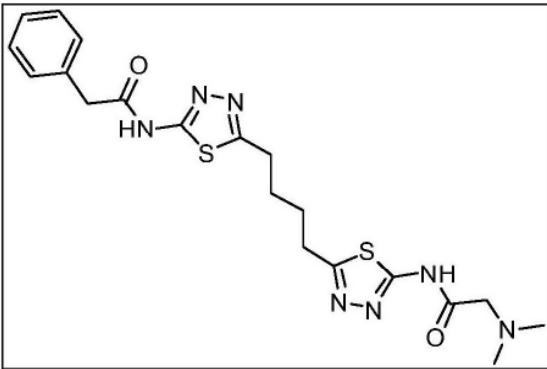
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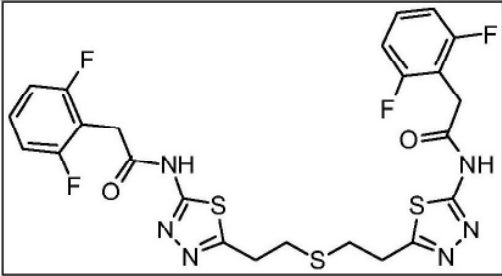
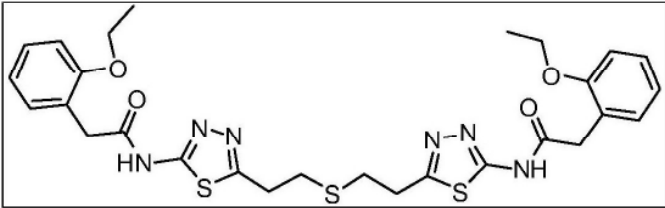
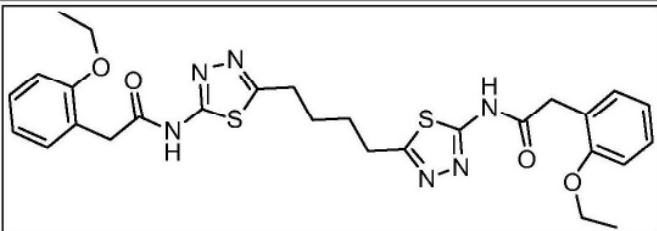
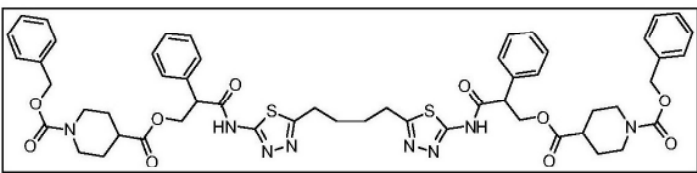
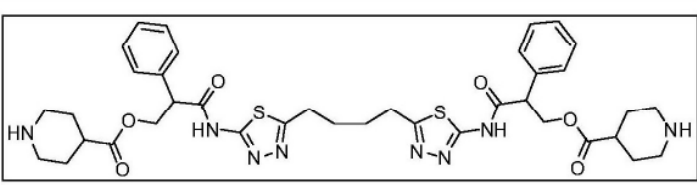
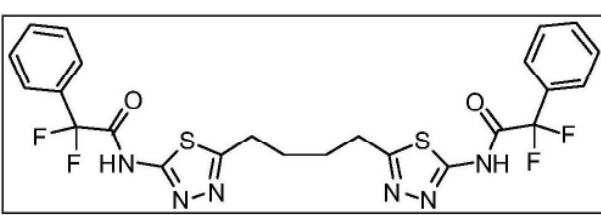
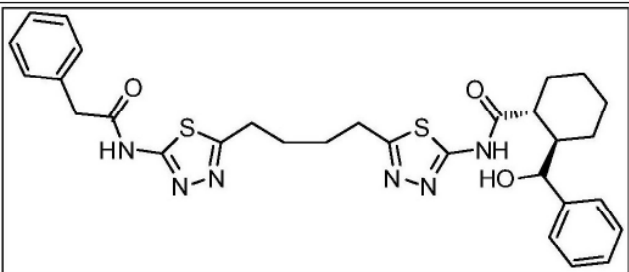
[0200]

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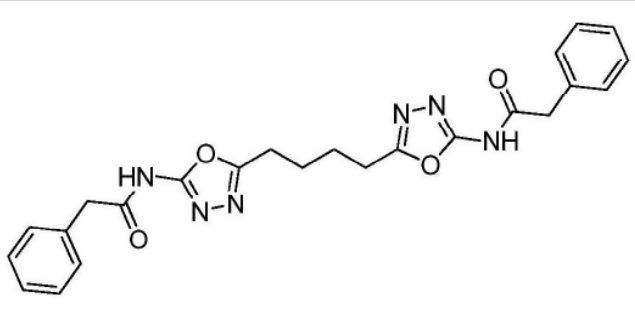
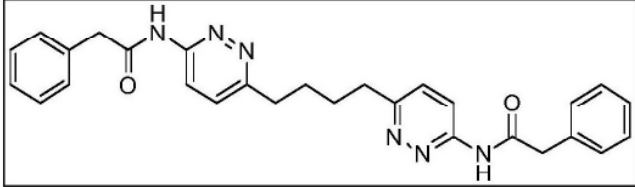
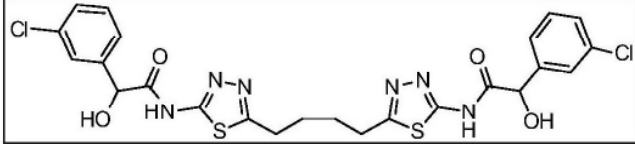
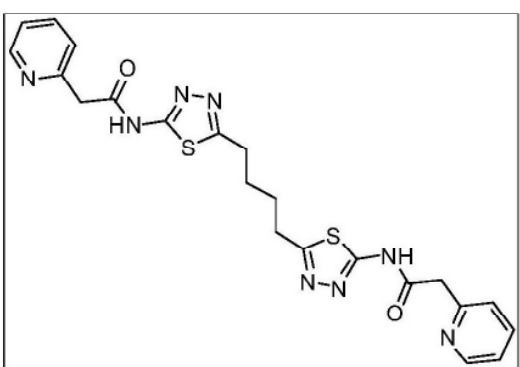
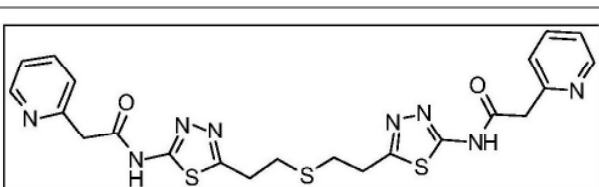
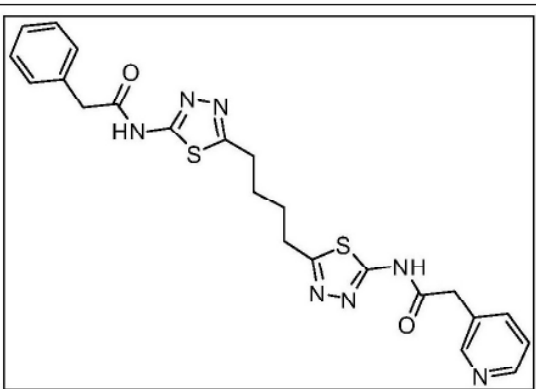
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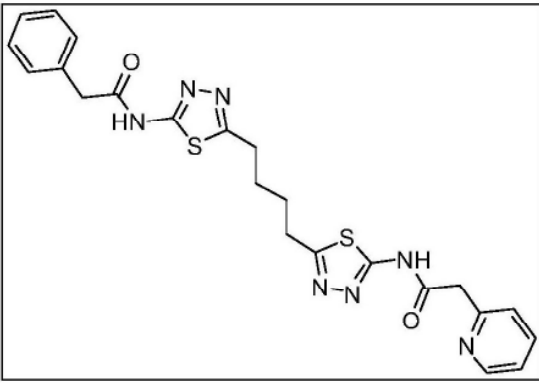
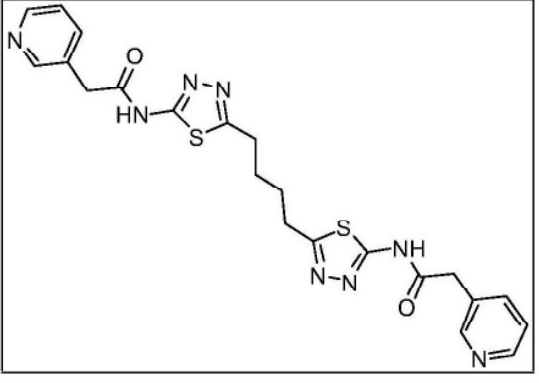
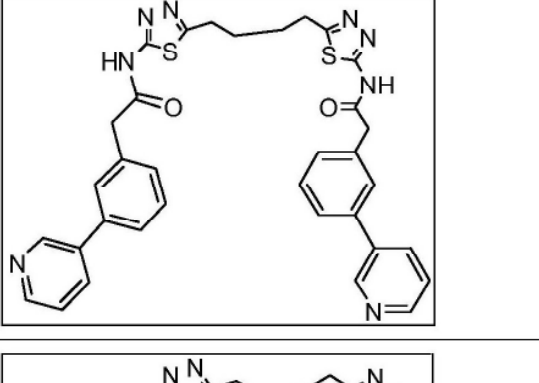
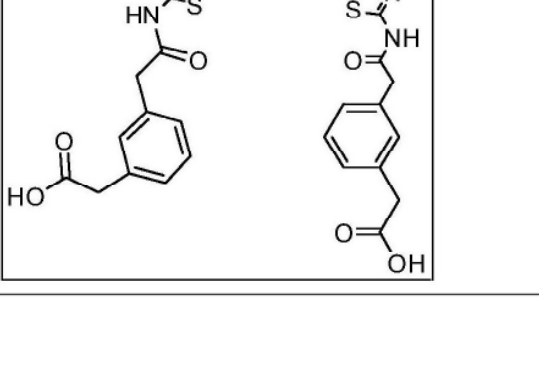
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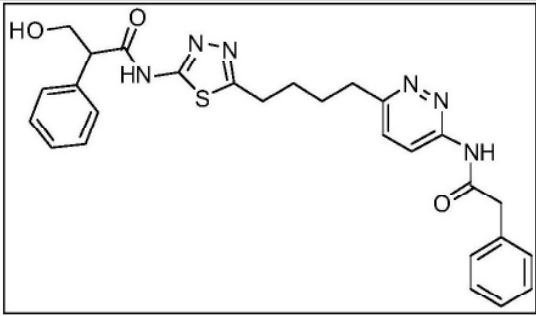
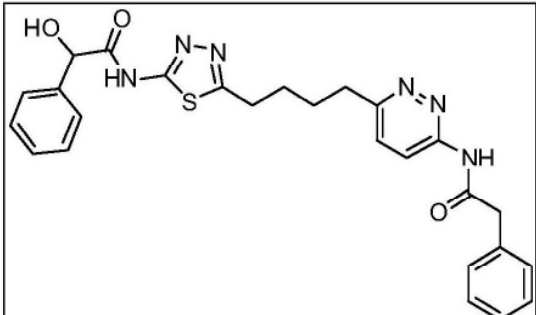
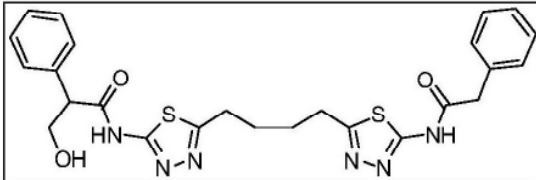
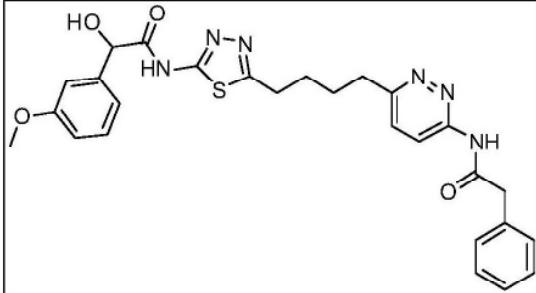
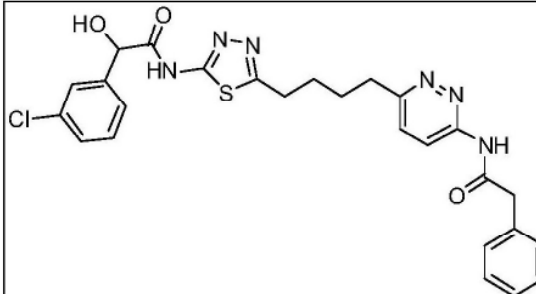
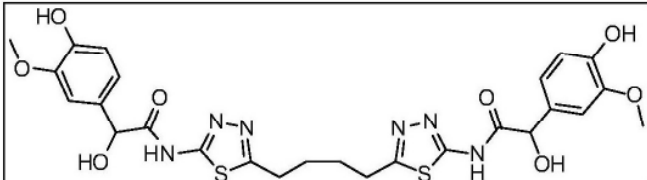
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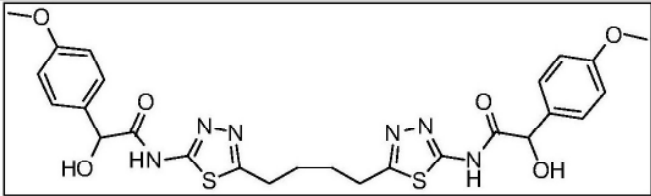
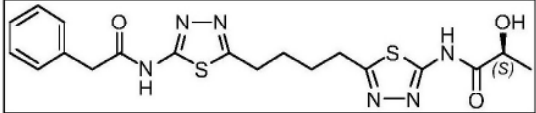
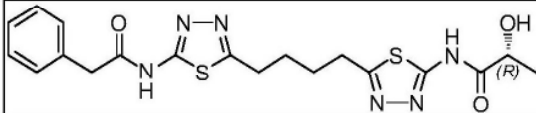
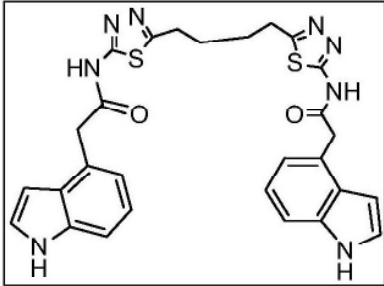
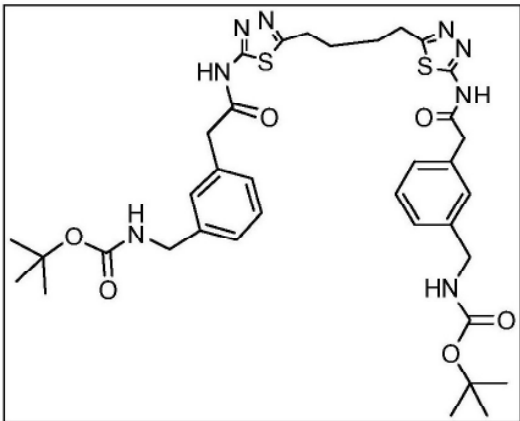
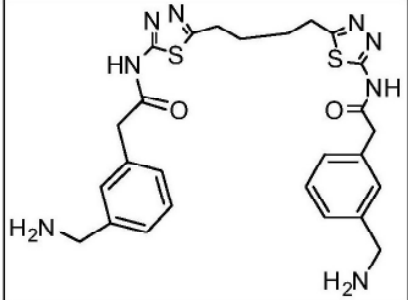
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[0204]

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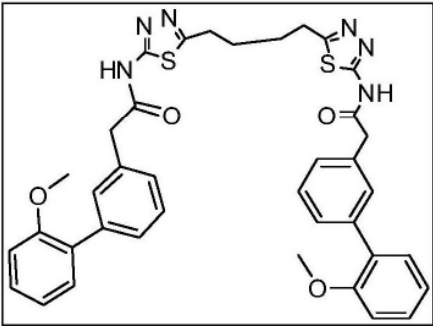
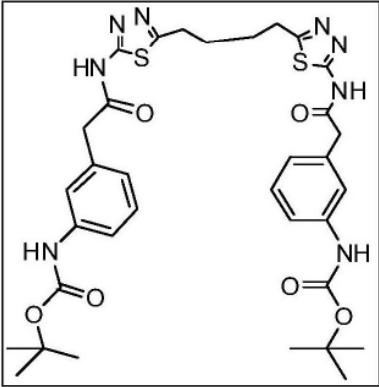
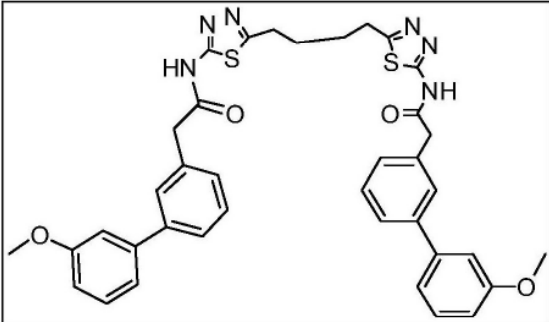
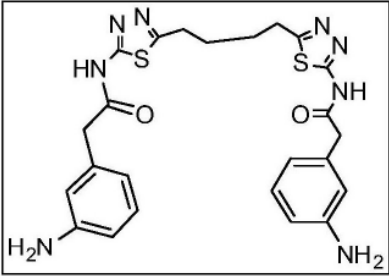
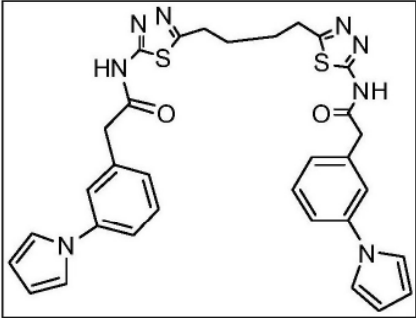
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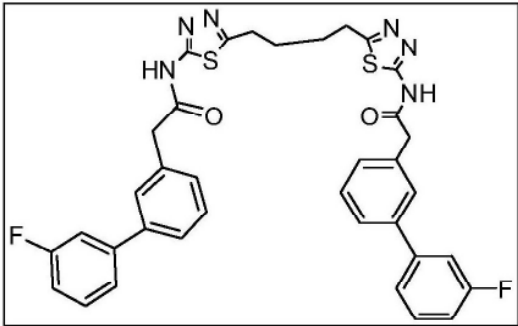
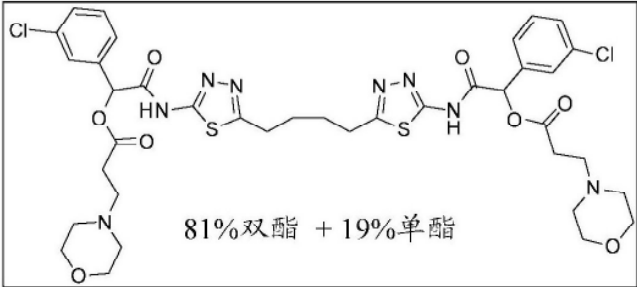
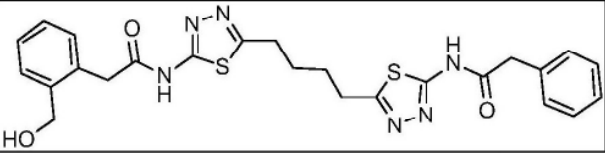
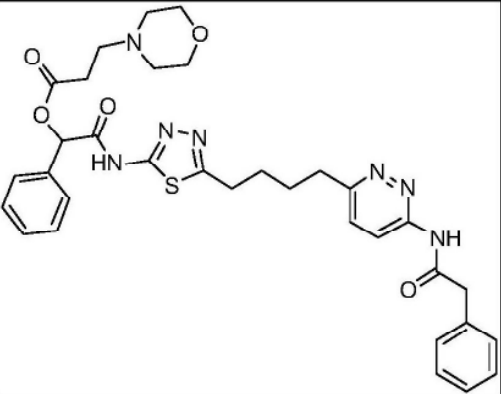
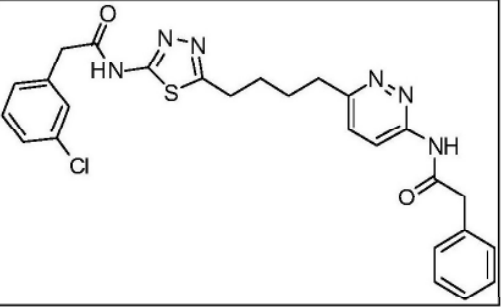
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[0206]

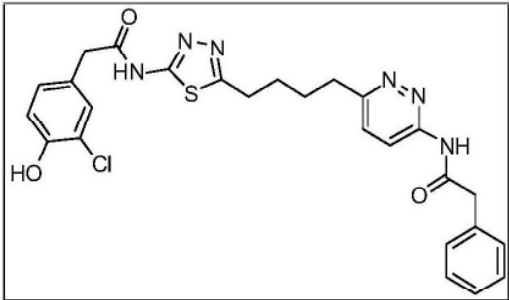
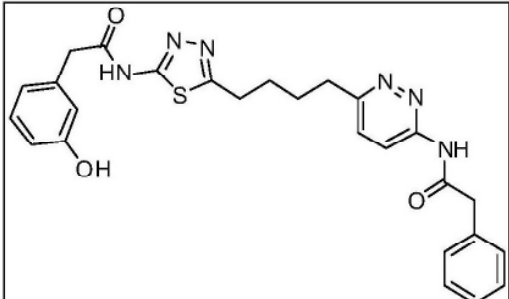
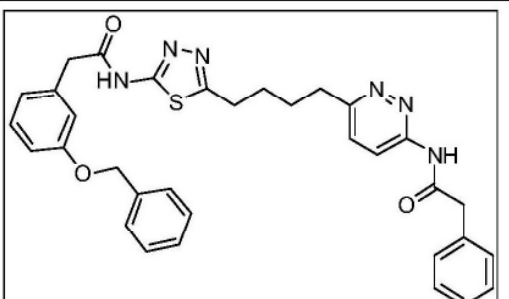
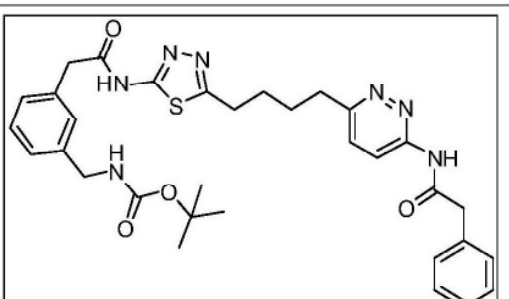
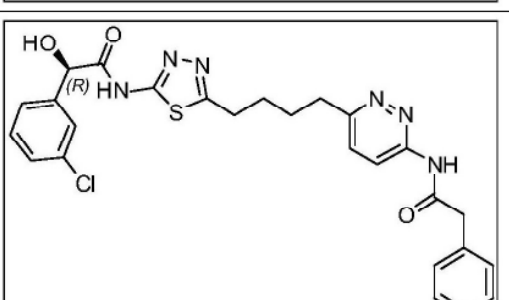
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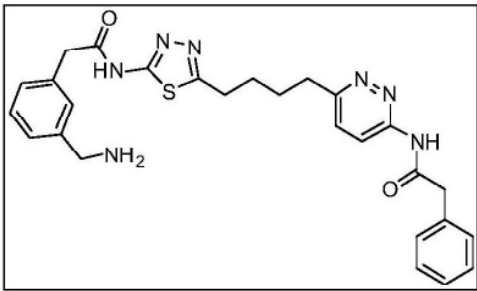
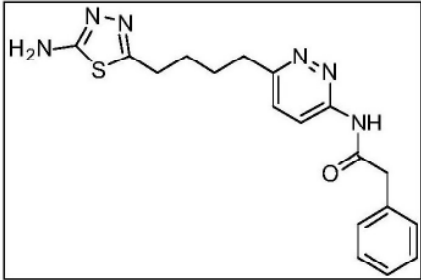
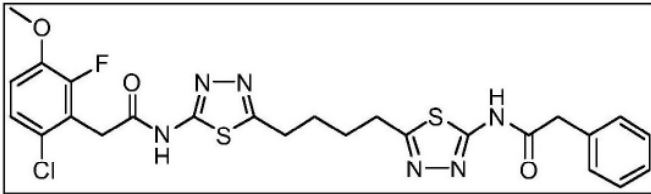
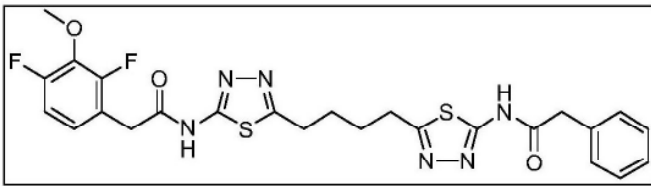
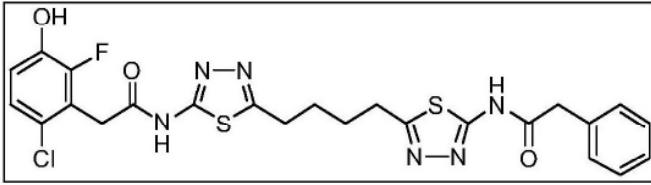
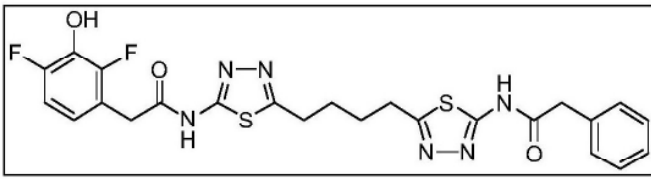
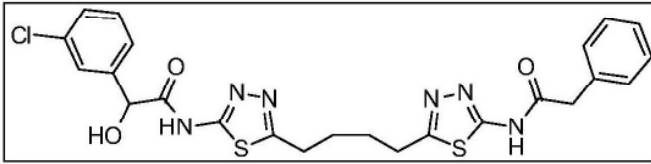
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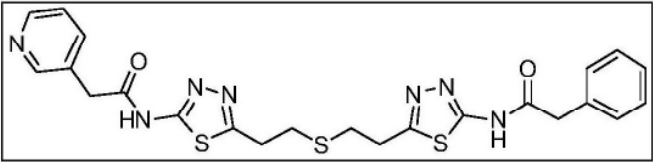
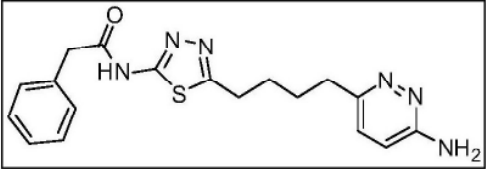
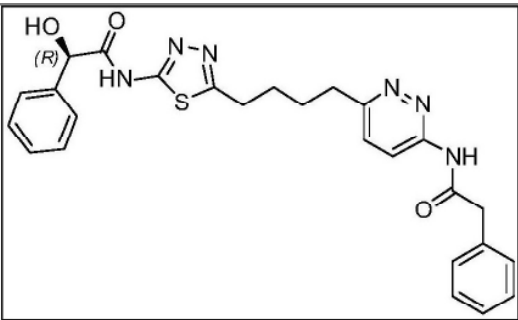
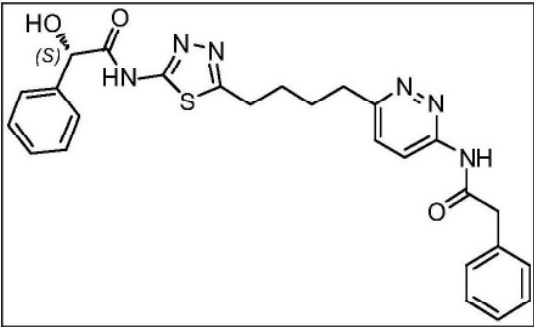
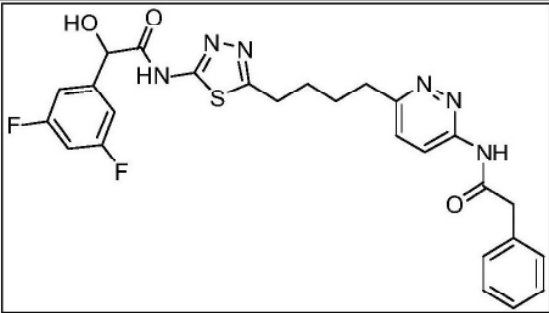
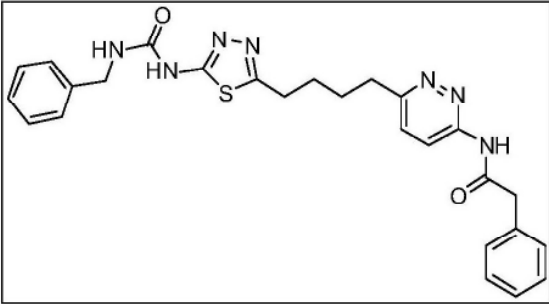
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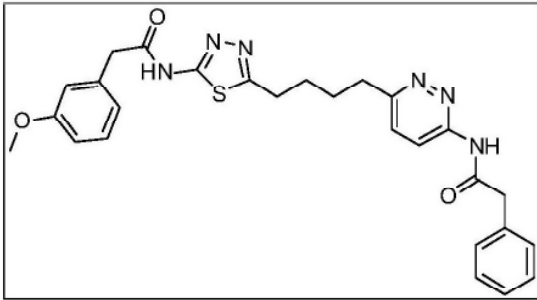
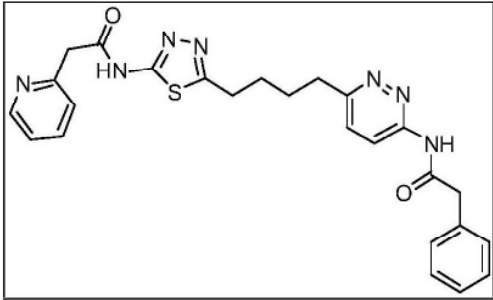
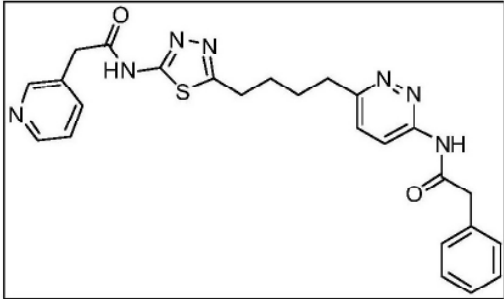
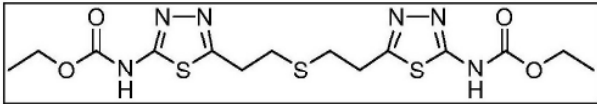
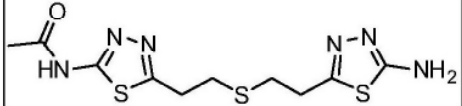
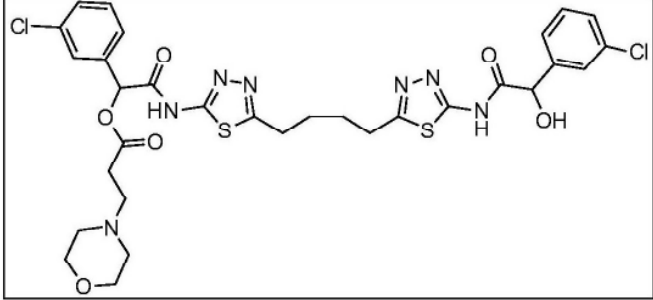
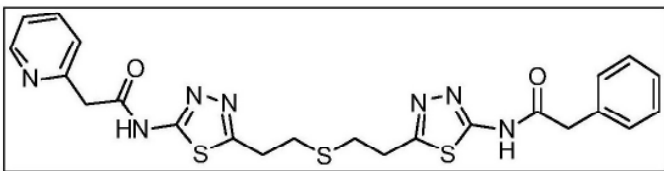
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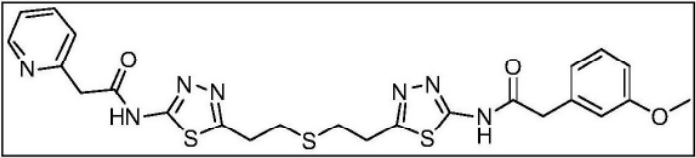
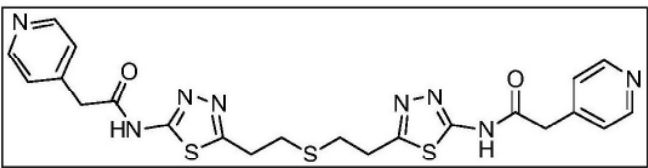
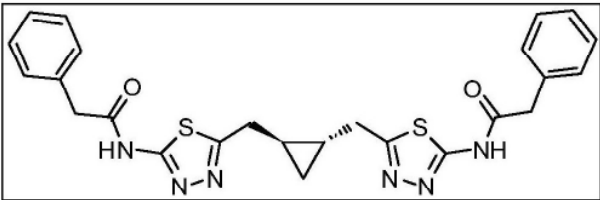
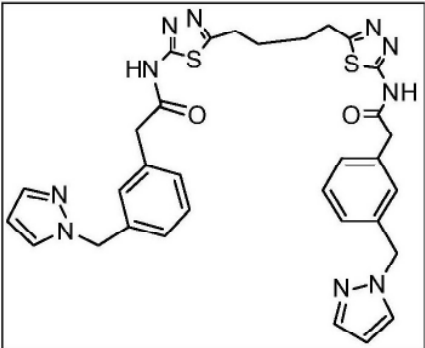
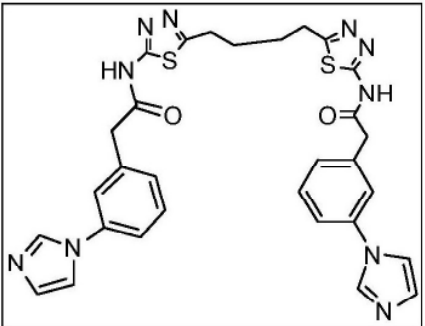
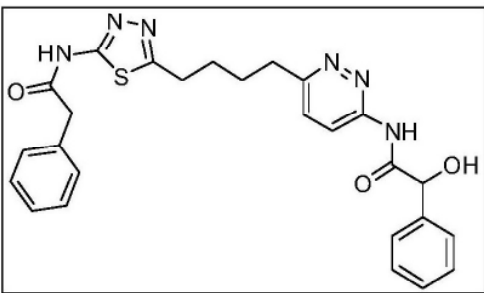
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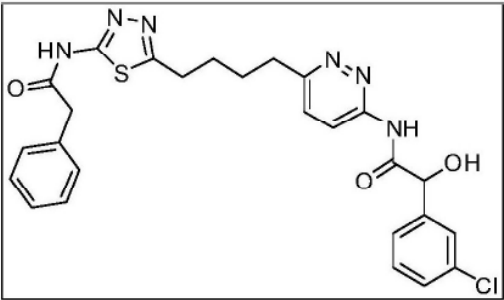
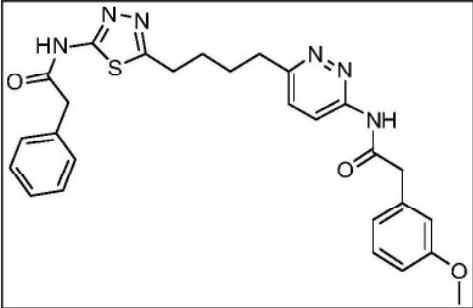
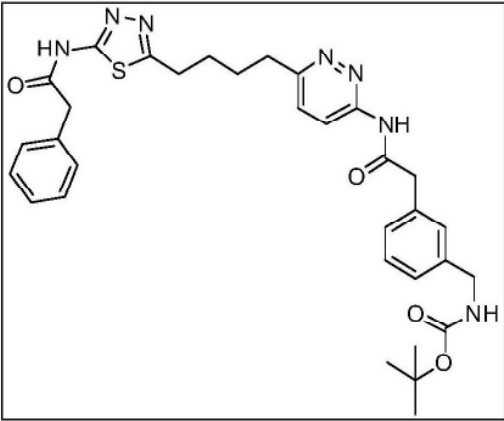
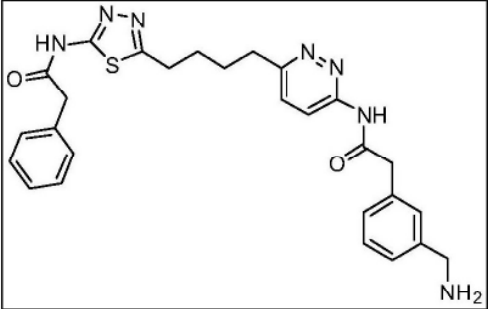
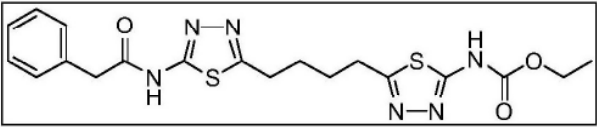
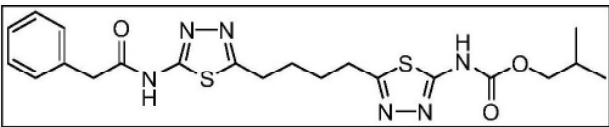
[0212]

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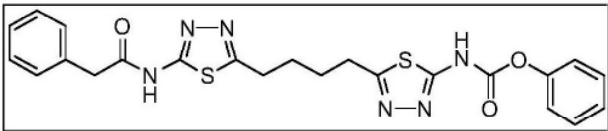
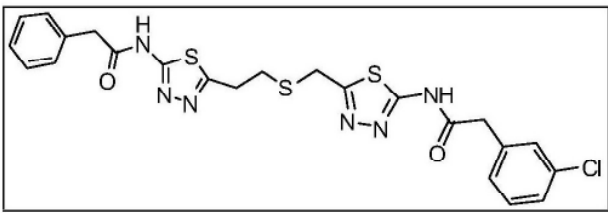
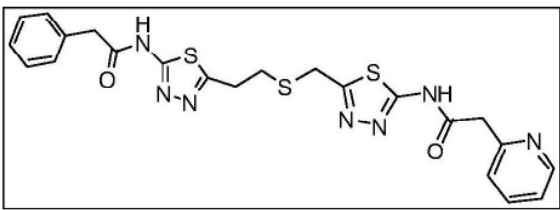
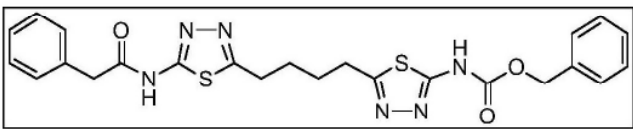
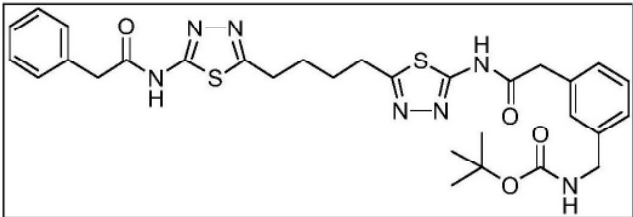
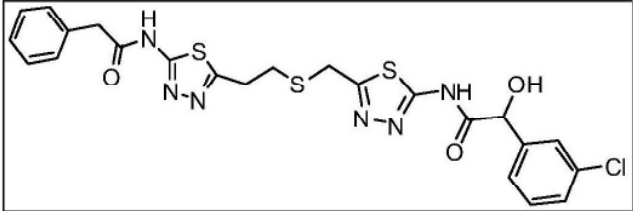
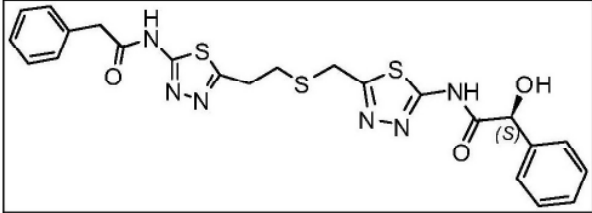
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[0213]

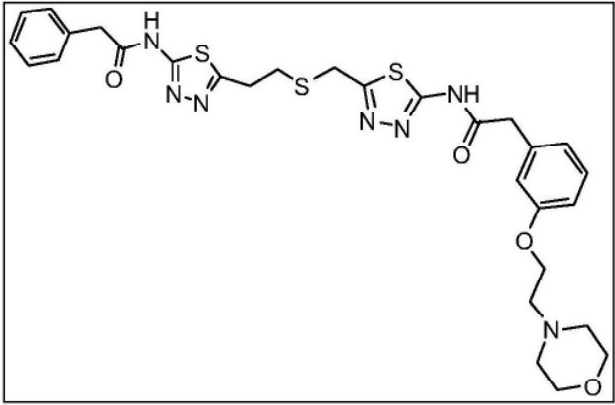
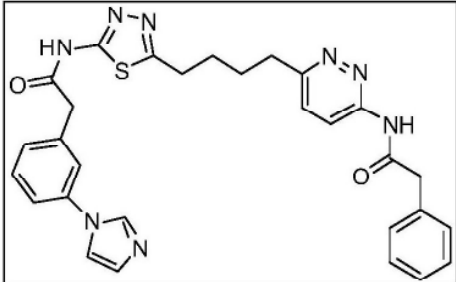
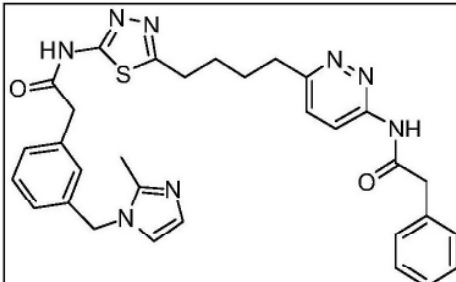
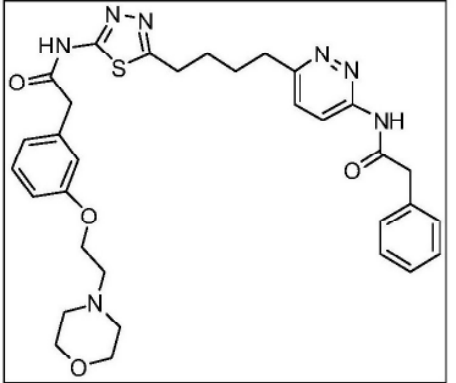
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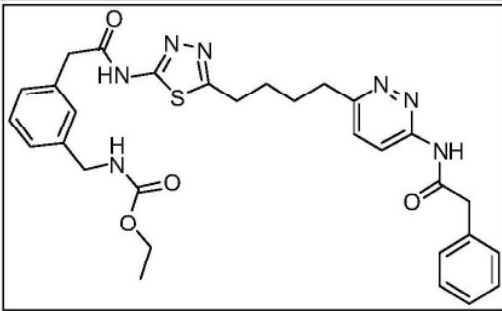
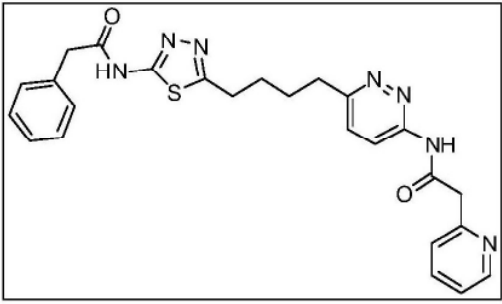
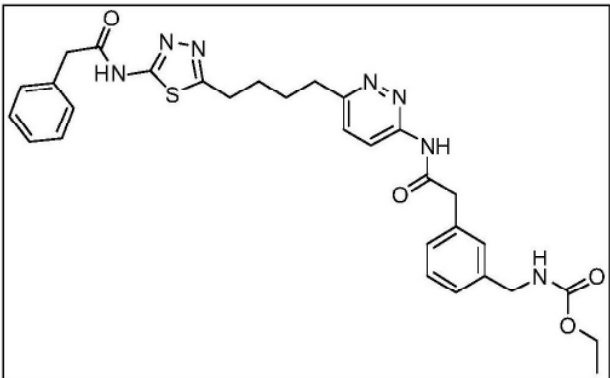
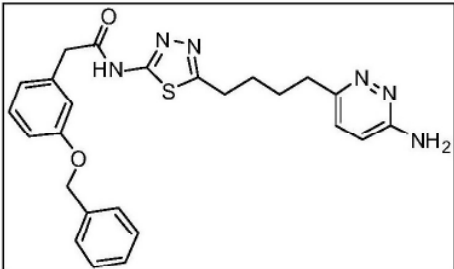
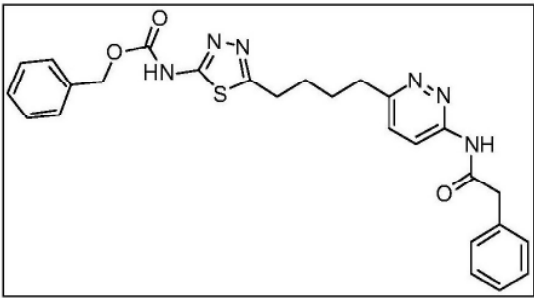
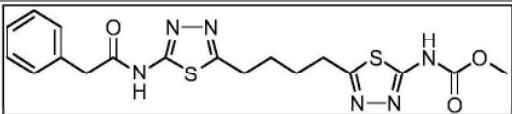
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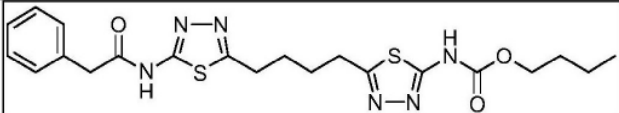
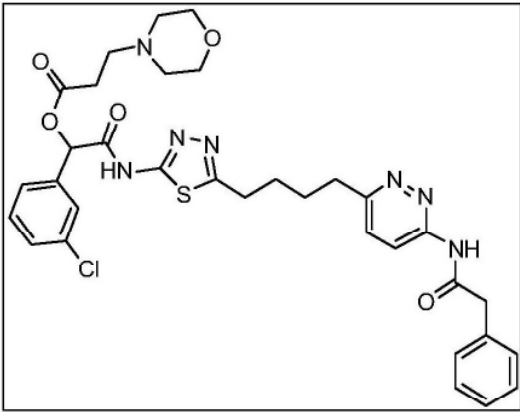
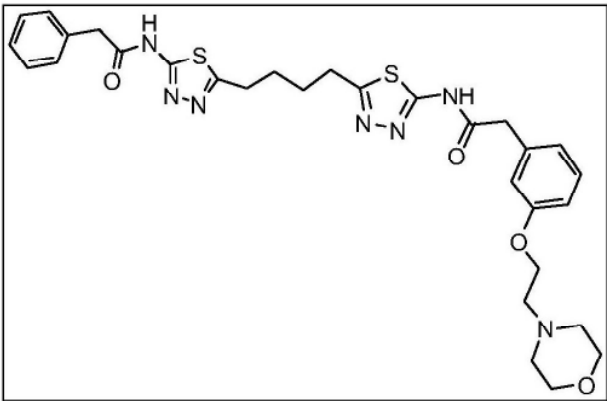
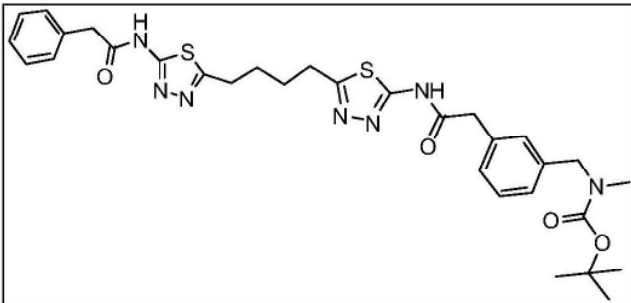
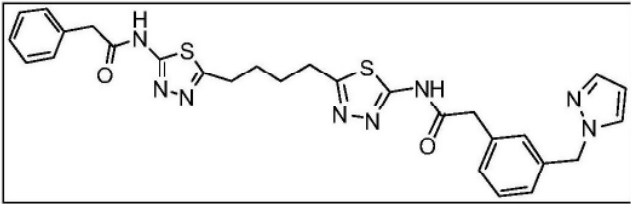
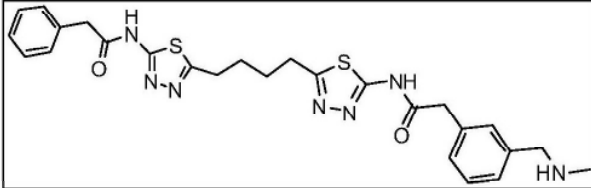
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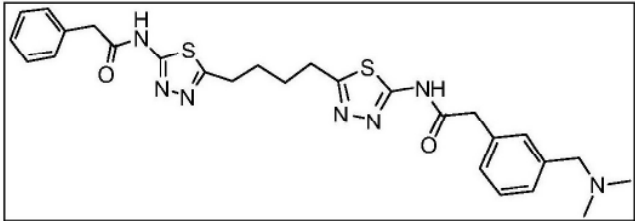
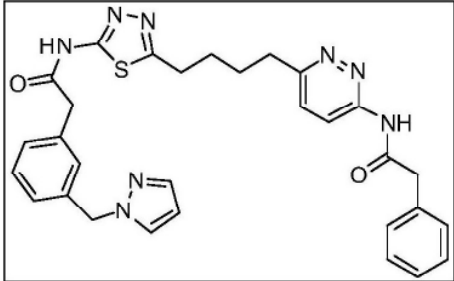
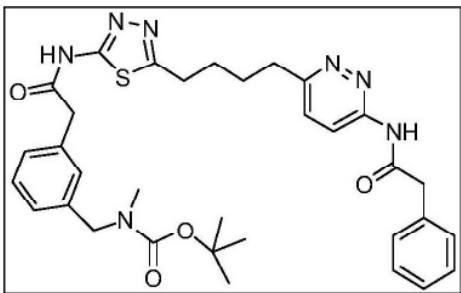
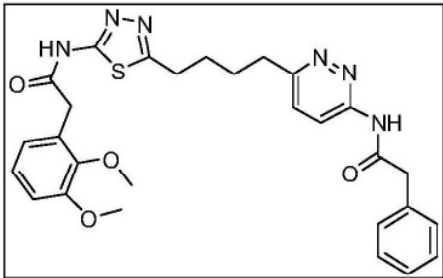
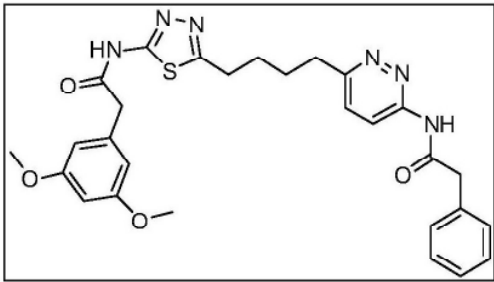
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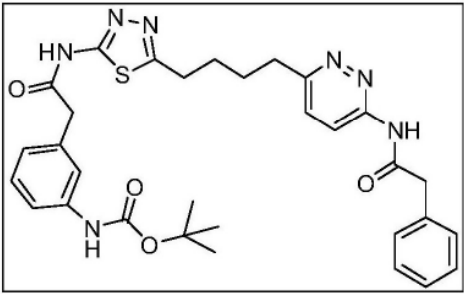
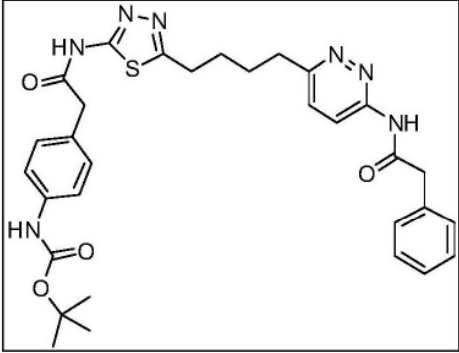
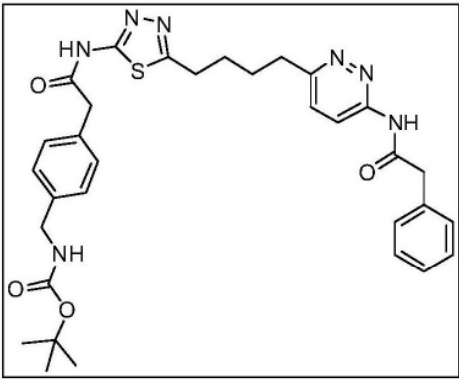
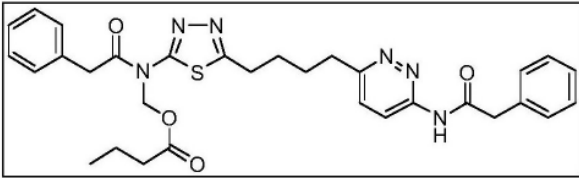
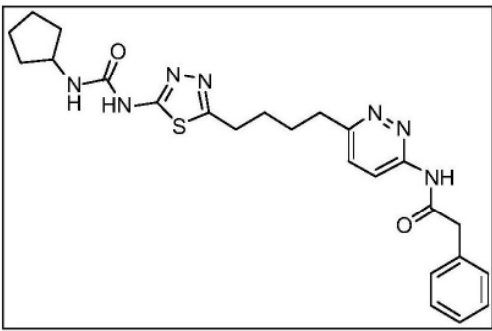
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[0219]

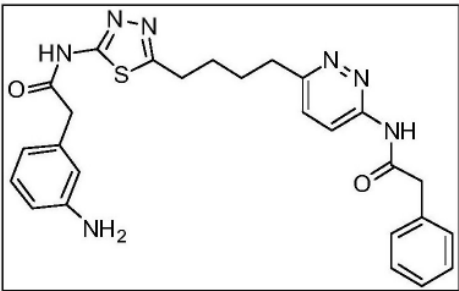
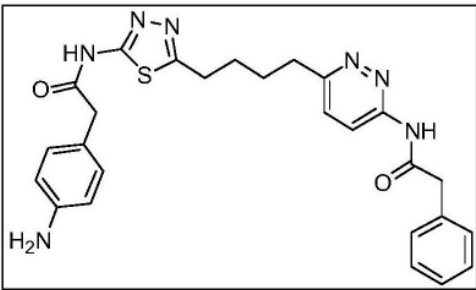
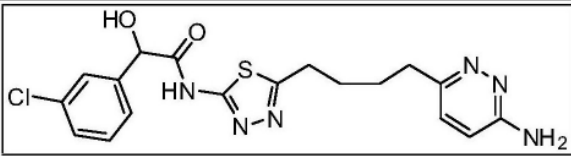
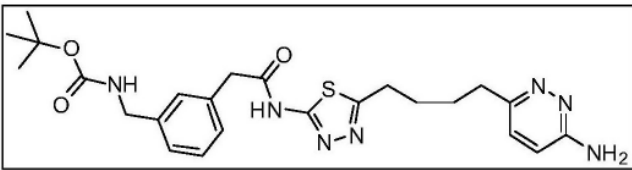
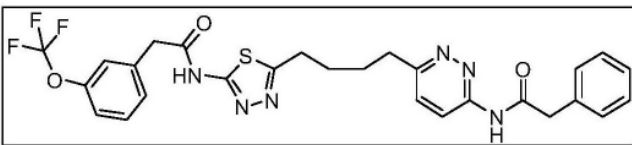
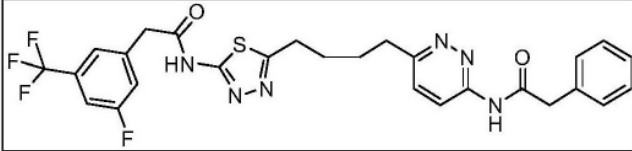
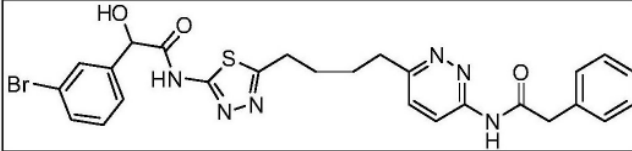
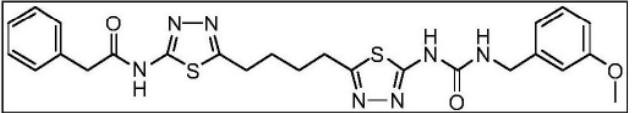
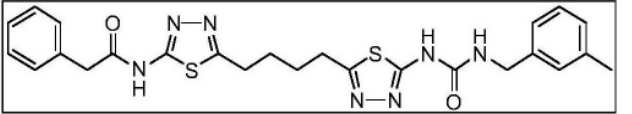
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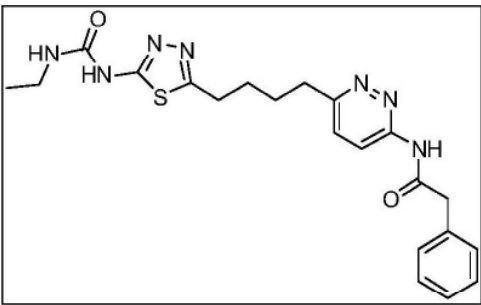
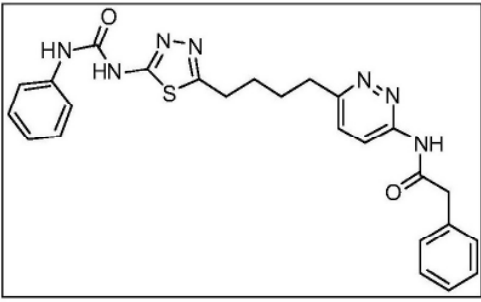
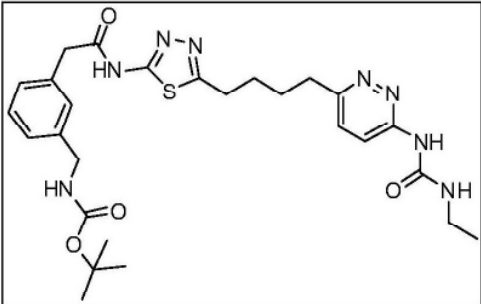
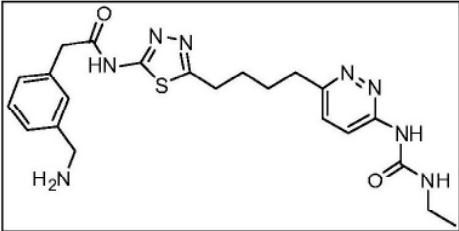
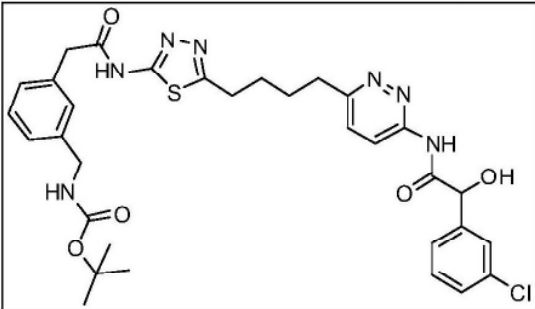
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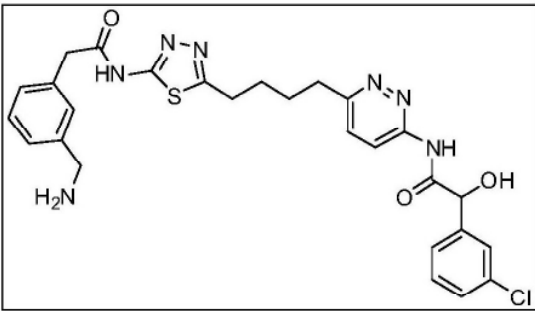
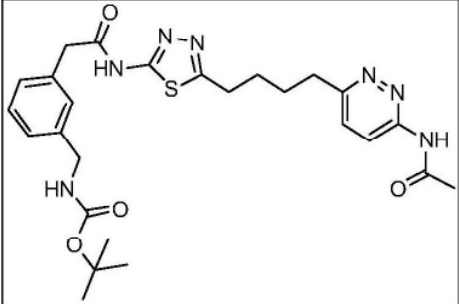
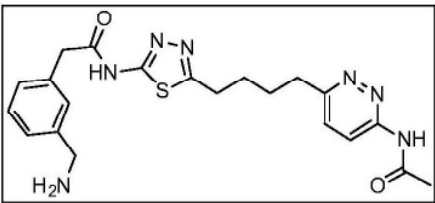
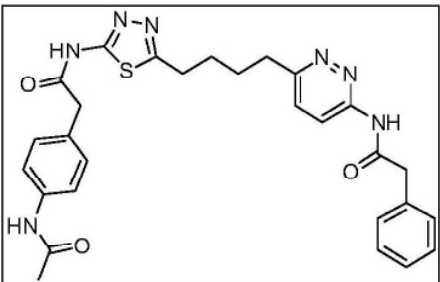
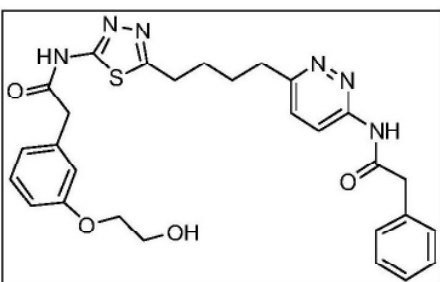
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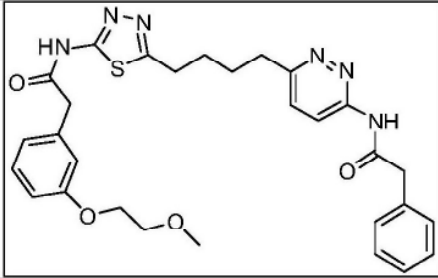
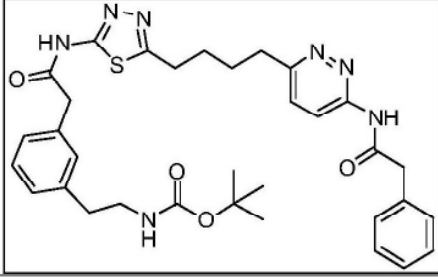
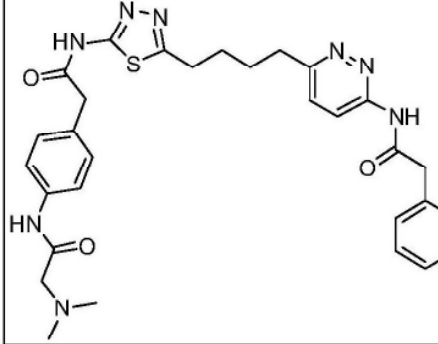
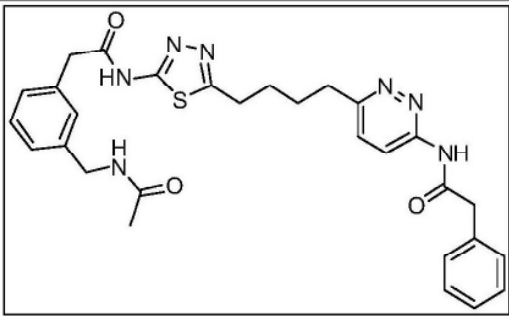
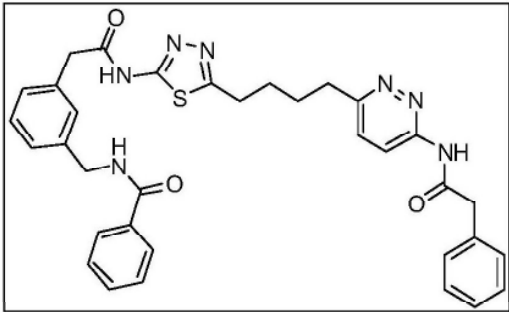
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[0225]

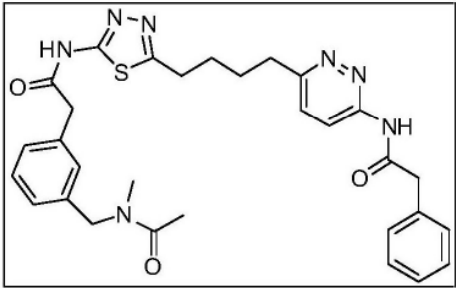
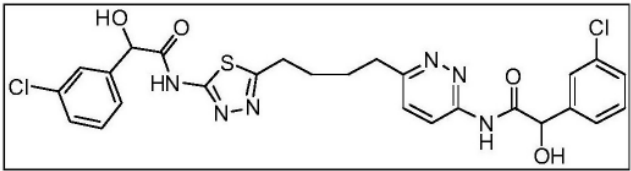
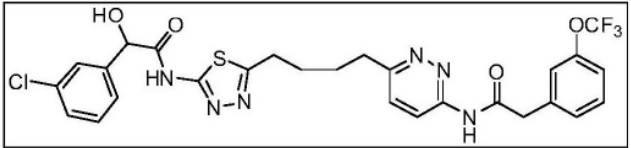
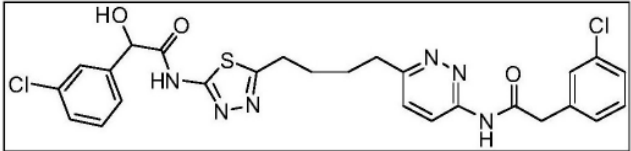
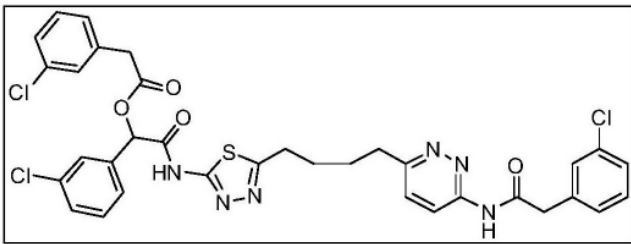
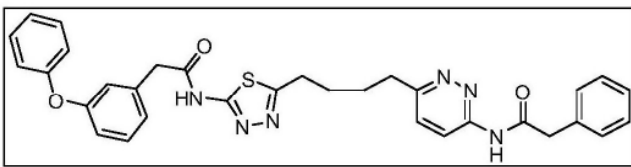
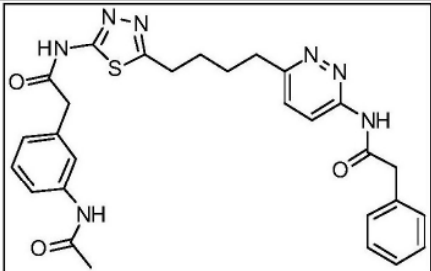
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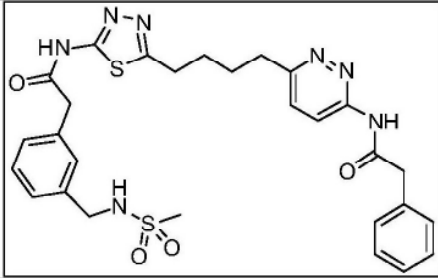
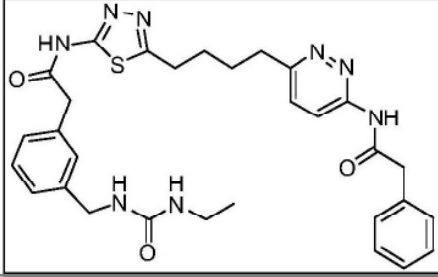
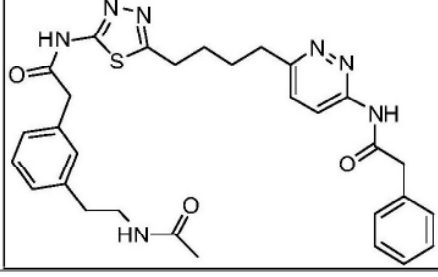
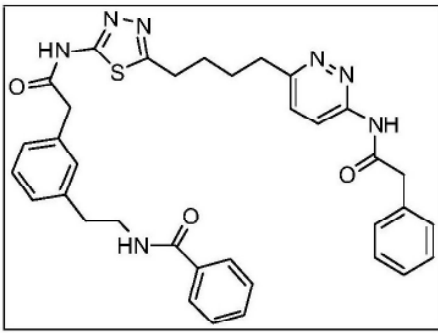
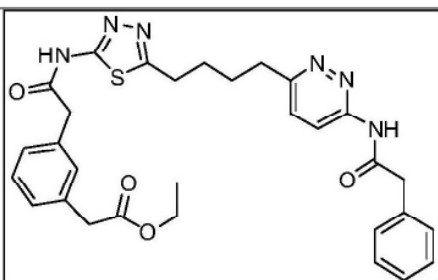
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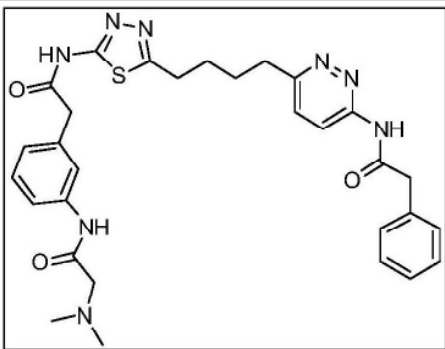
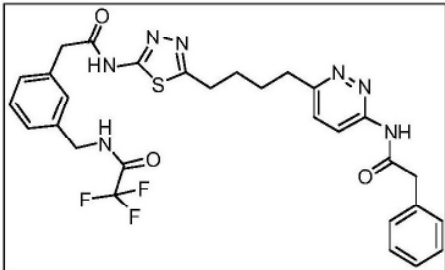
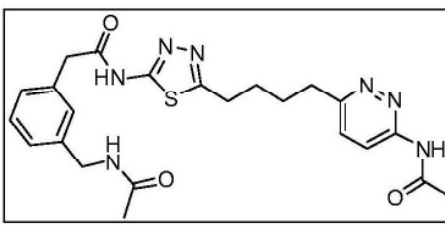
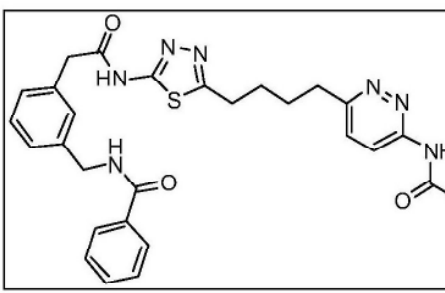
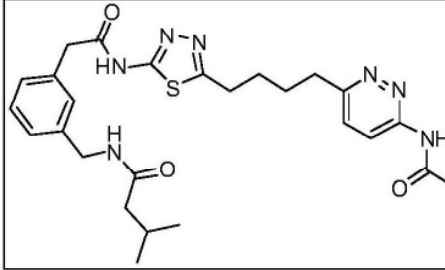
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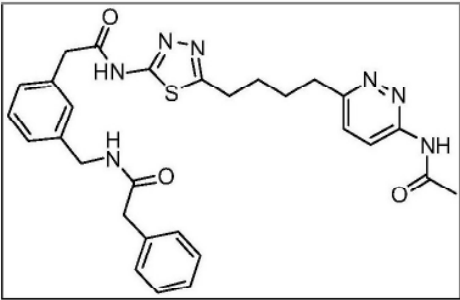
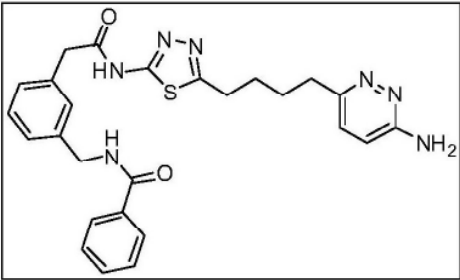
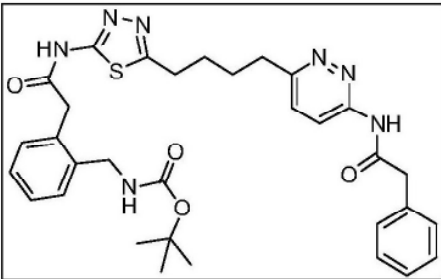
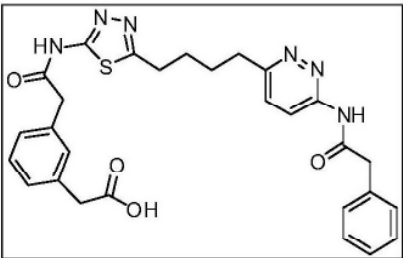
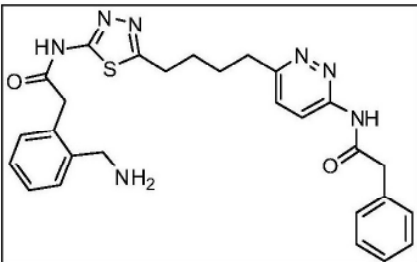
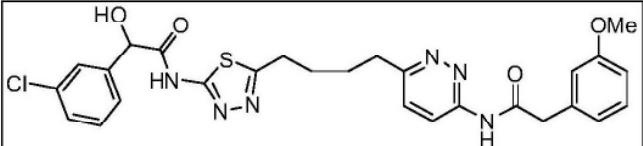
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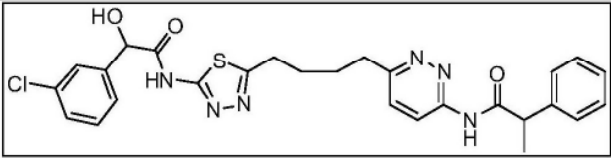
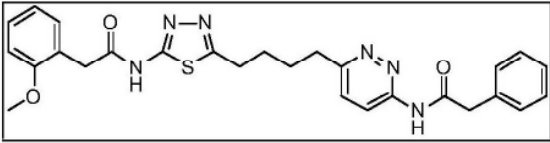
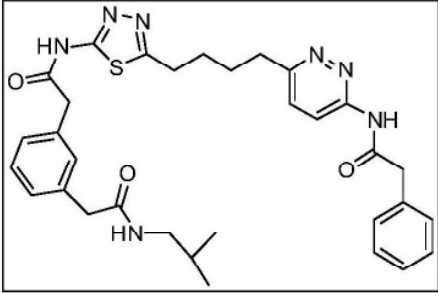
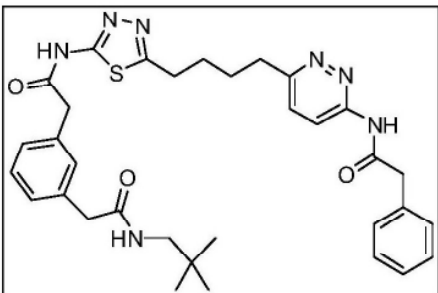
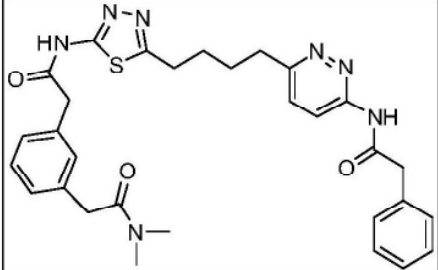
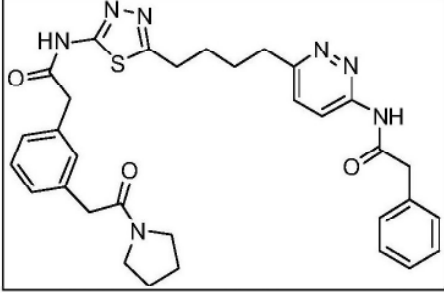
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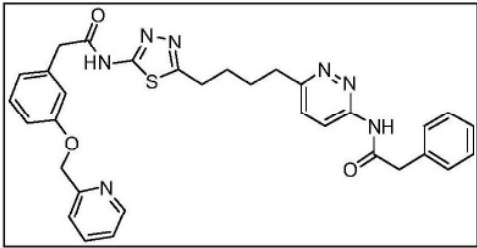
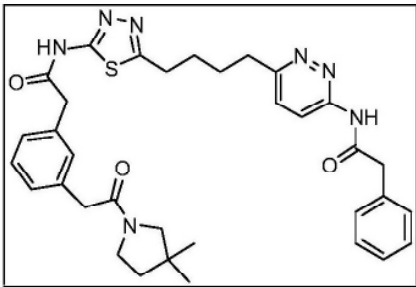
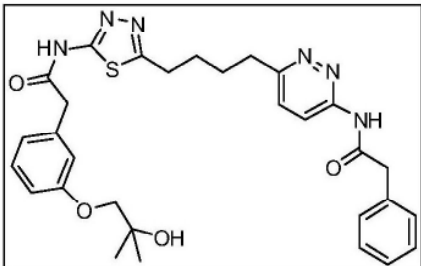
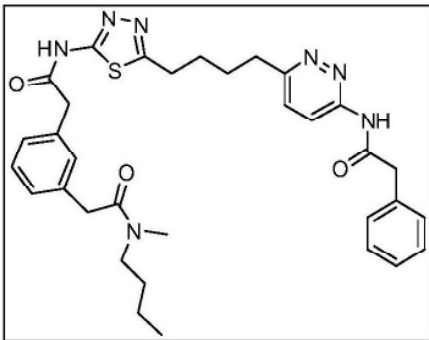
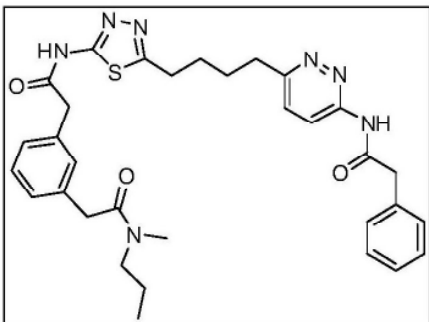
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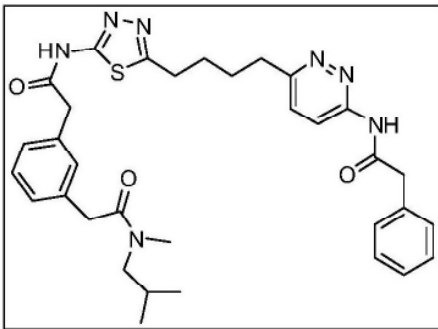
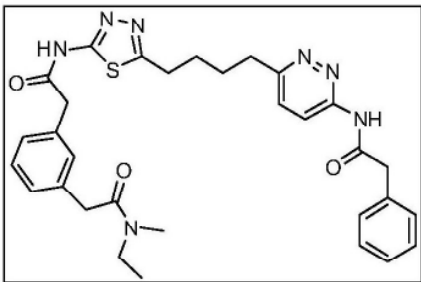
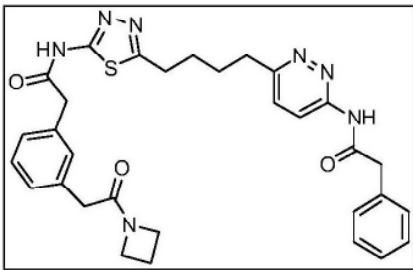
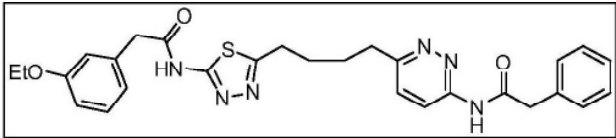
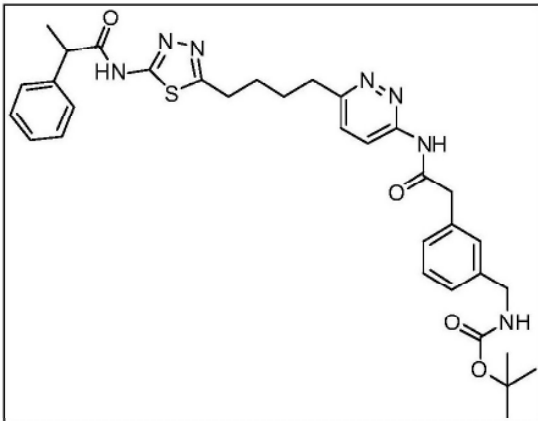
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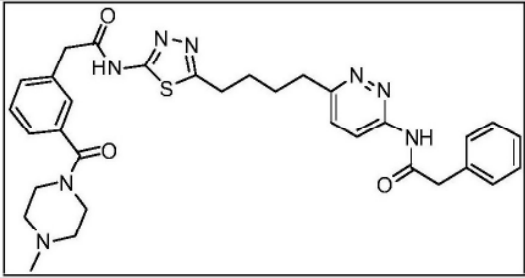
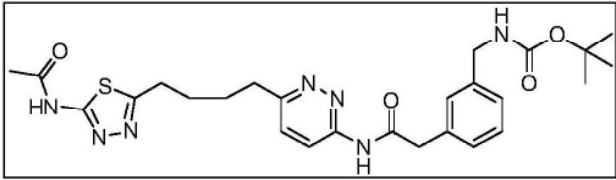
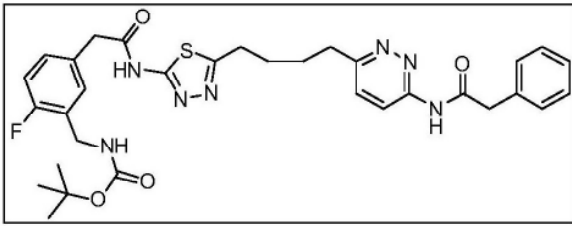
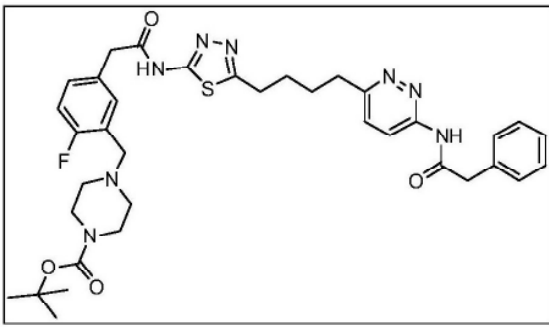
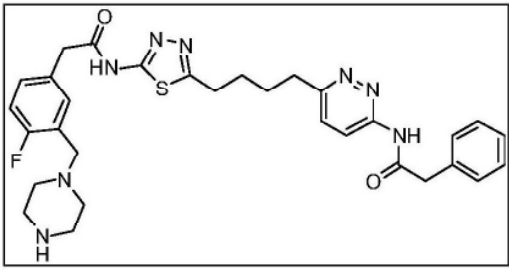
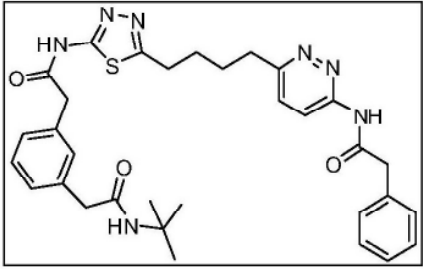
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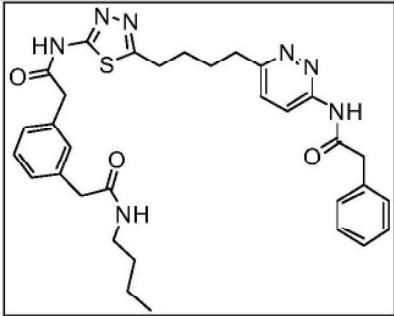
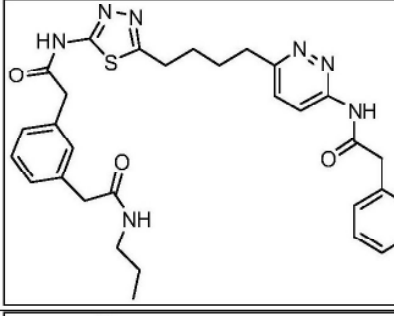
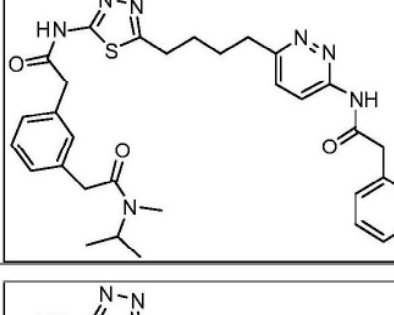
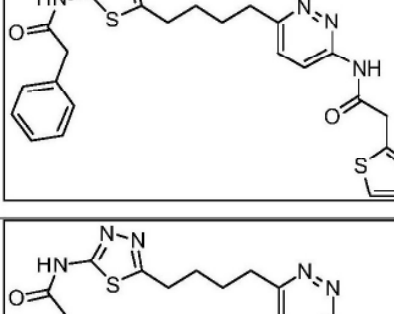
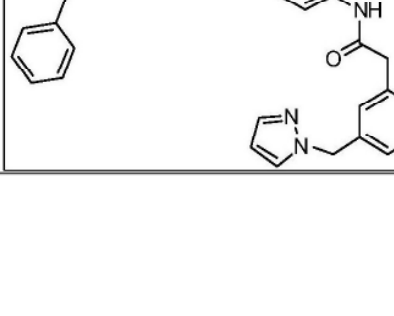
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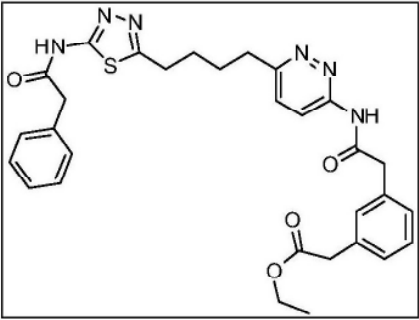
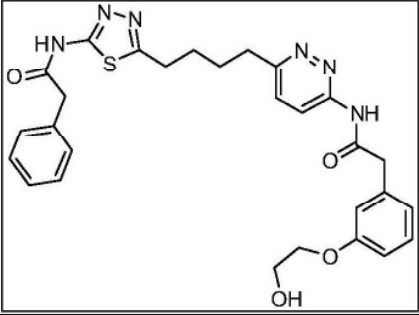
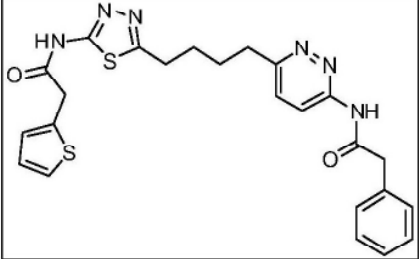
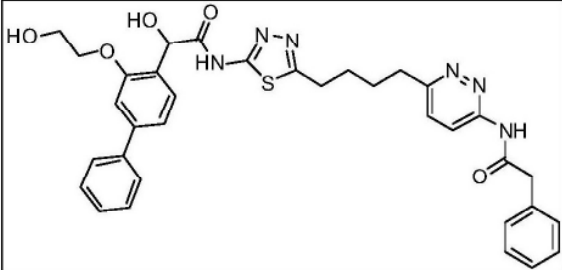
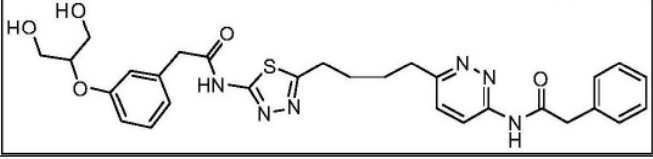
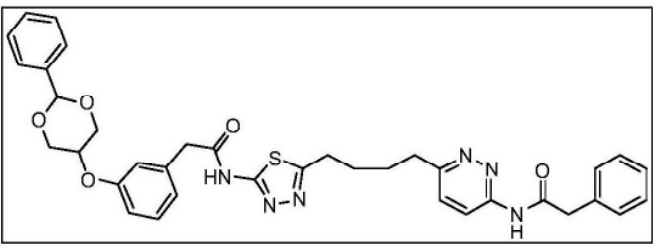
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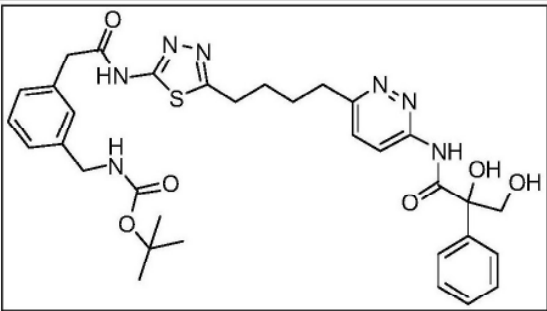
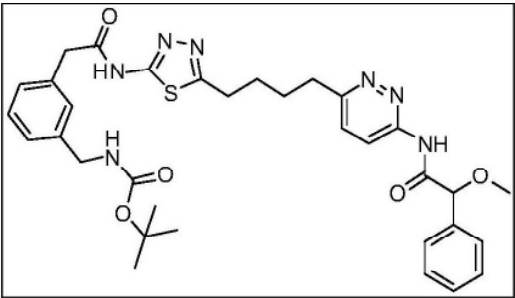
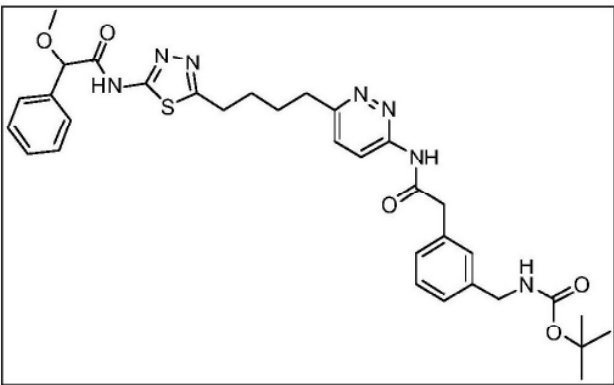
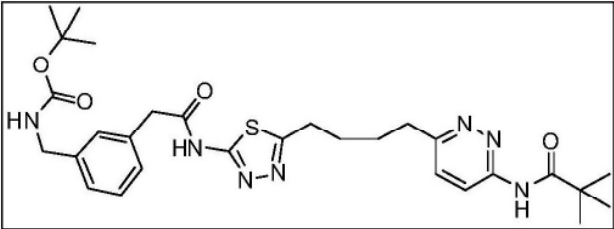
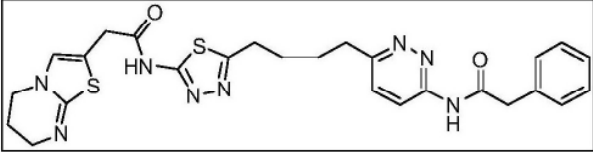
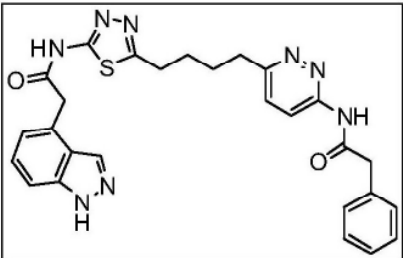
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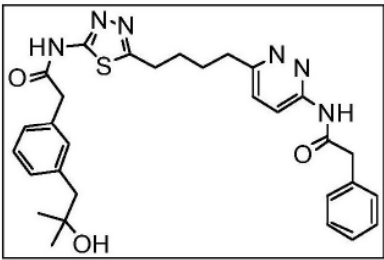
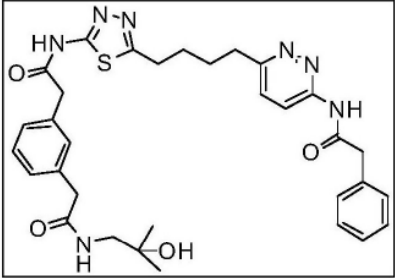
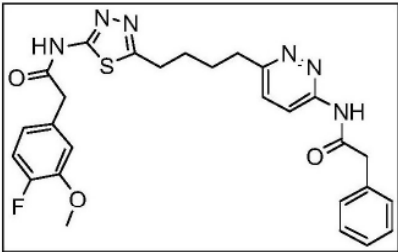
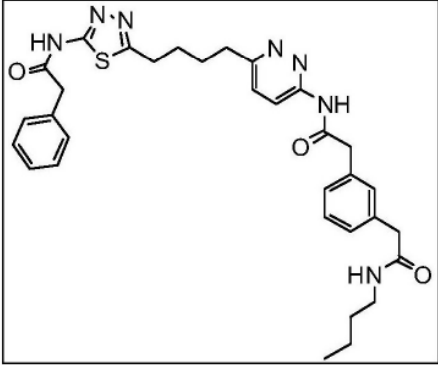
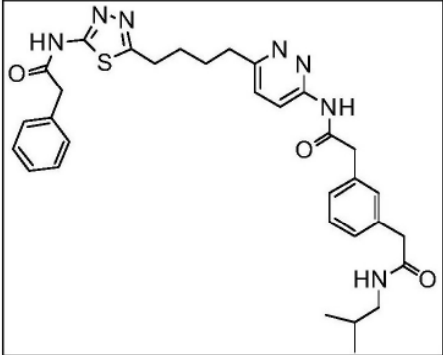
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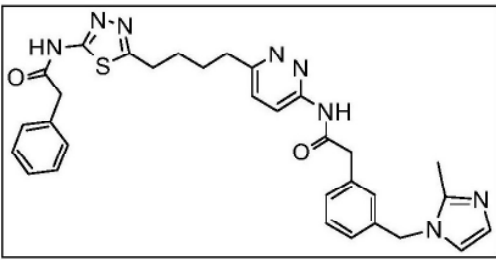
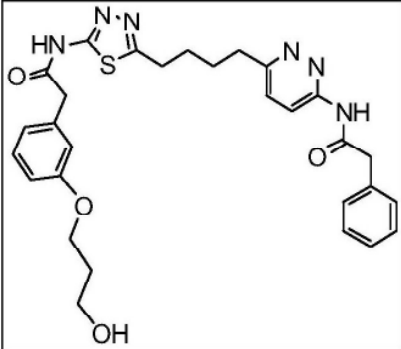
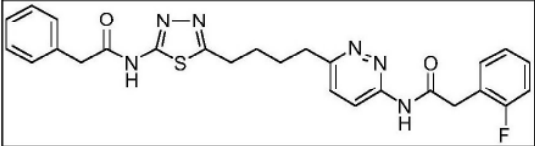
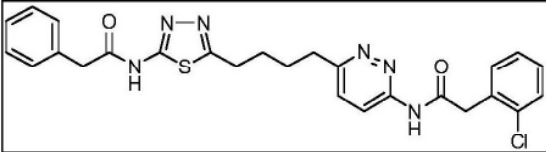
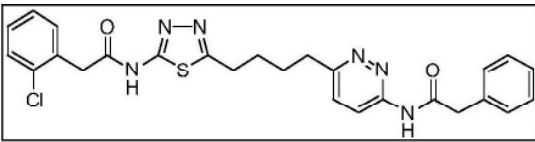
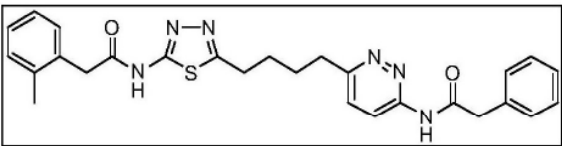
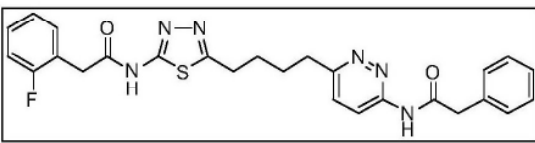
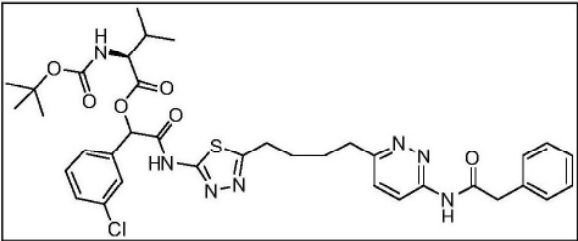
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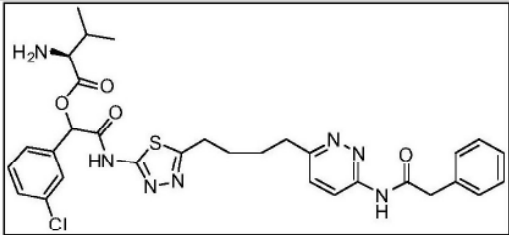
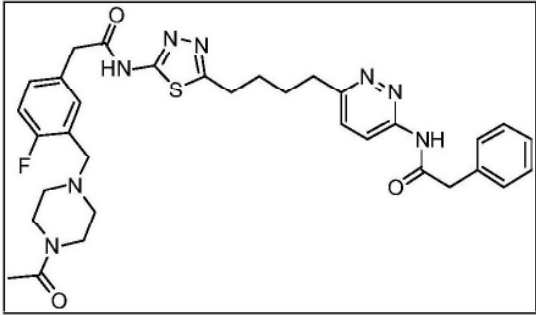
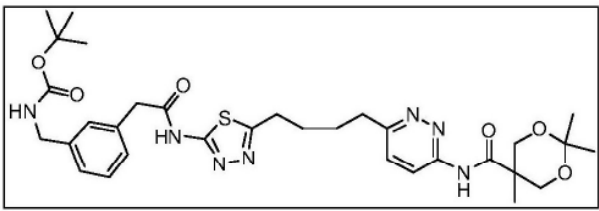
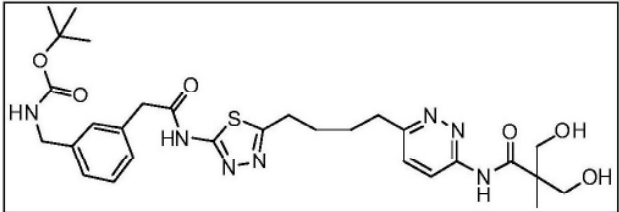
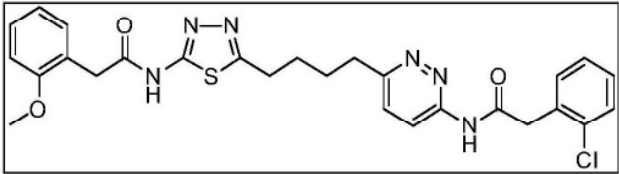
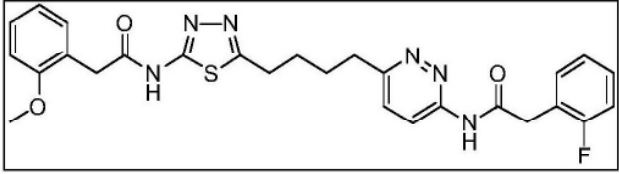
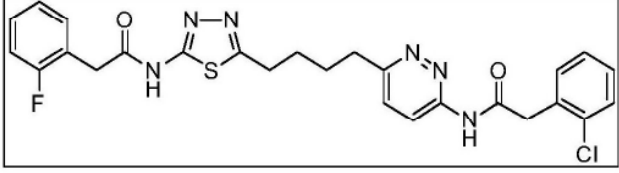
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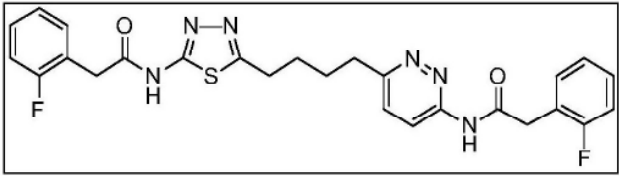
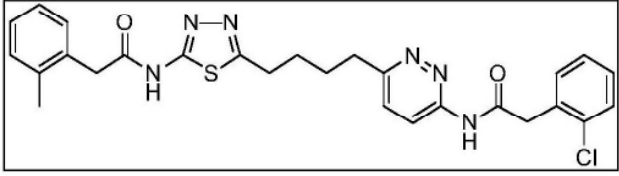
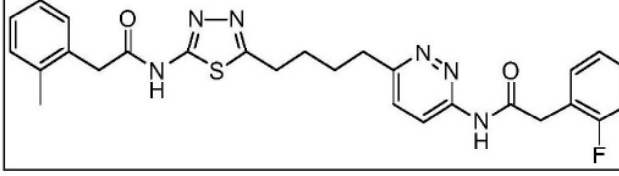
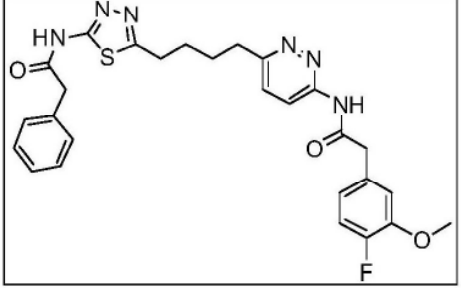
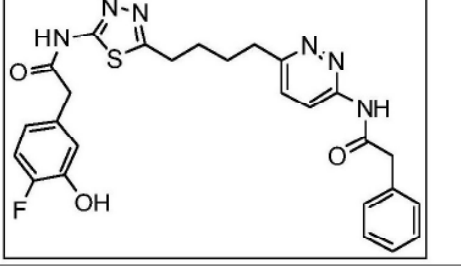
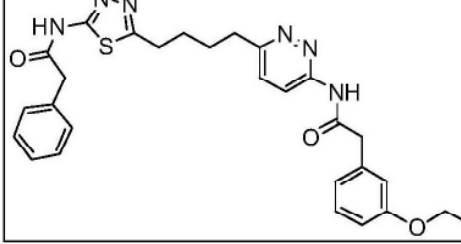
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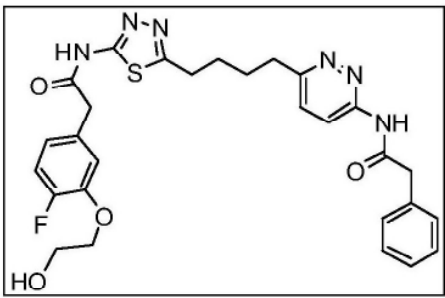
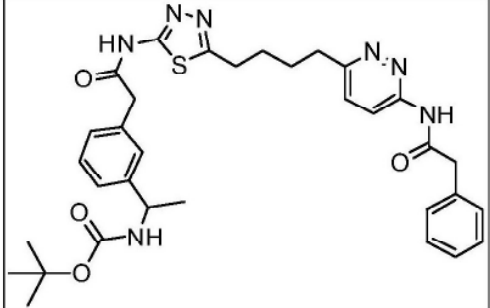
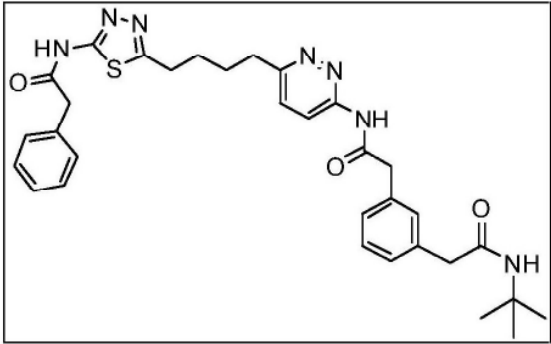
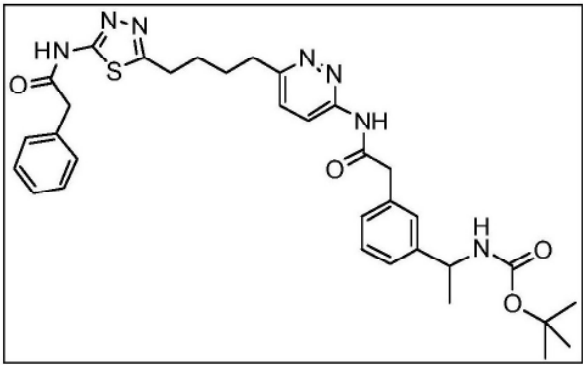
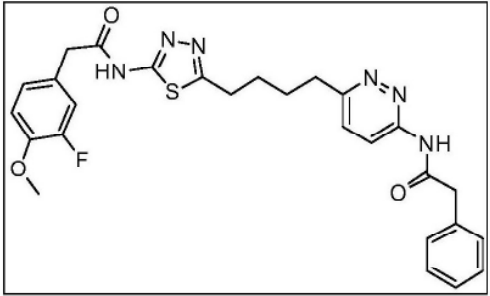
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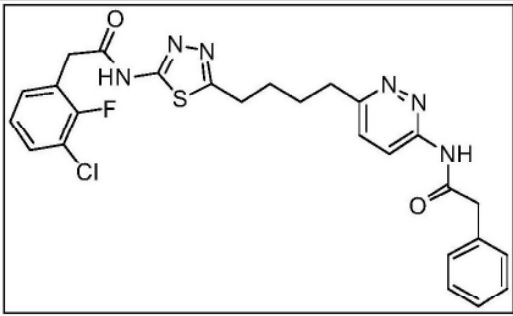
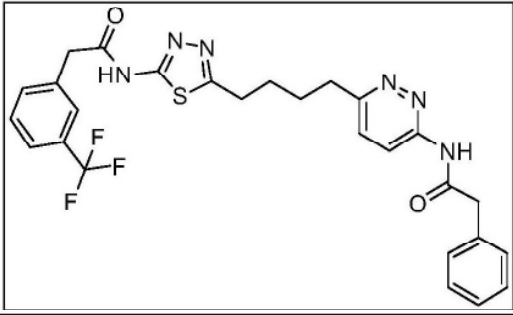
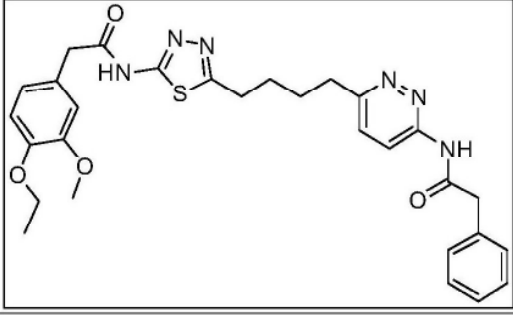
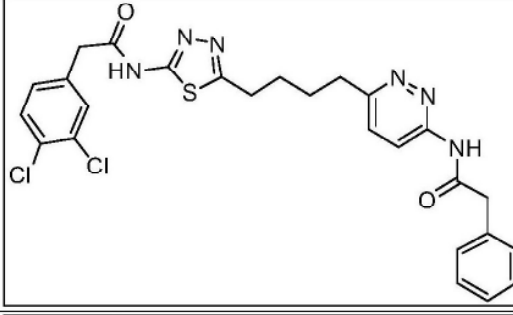
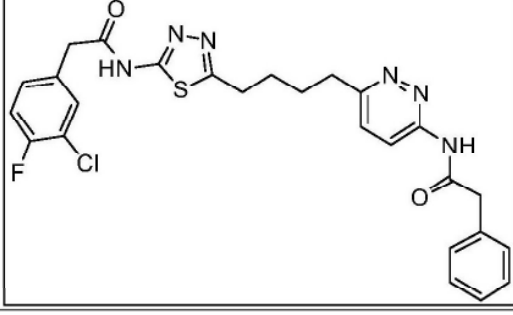
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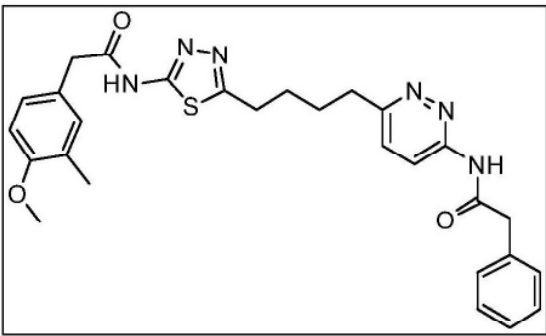
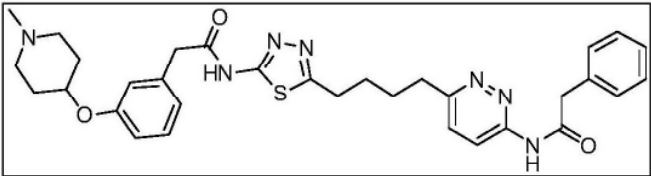
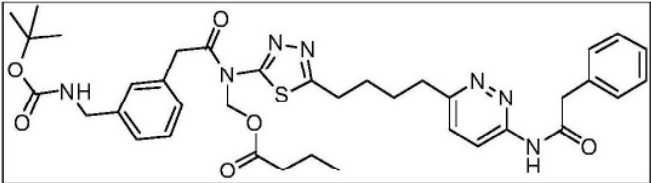
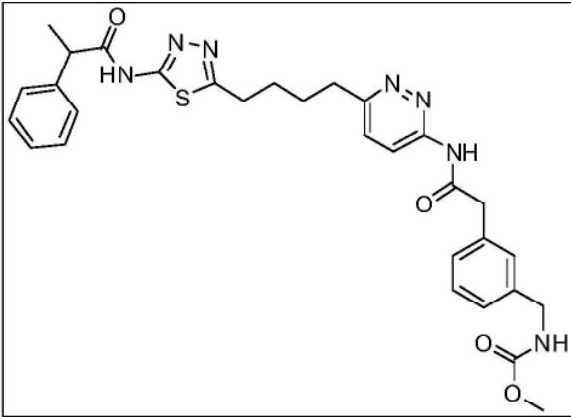
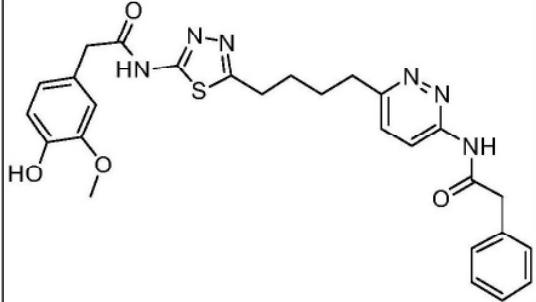
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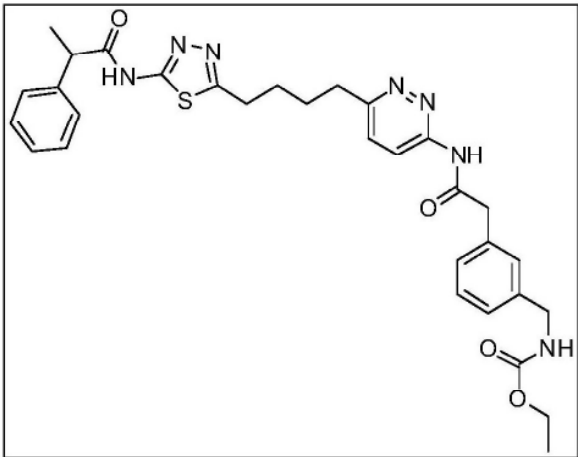
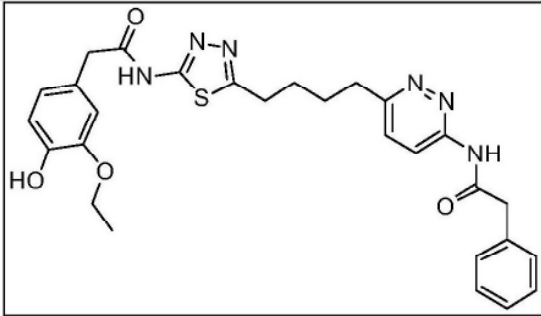
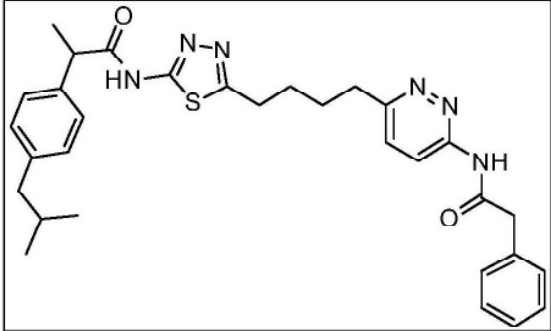
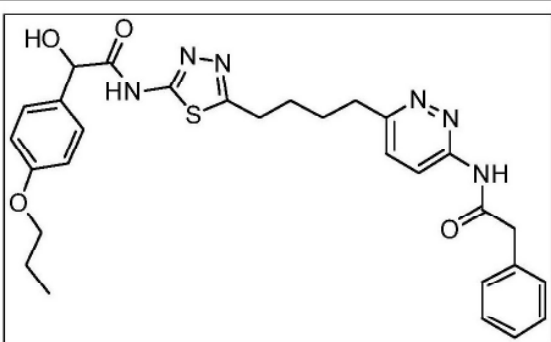
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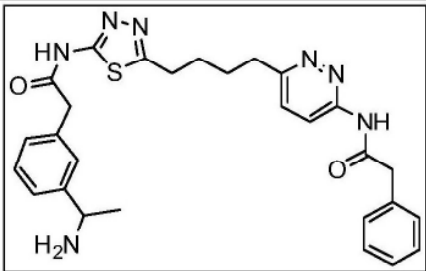
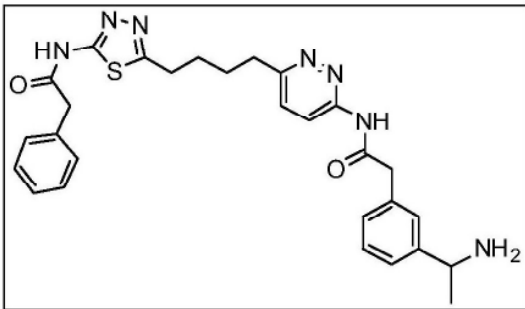
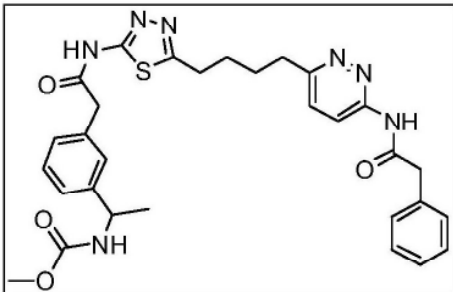
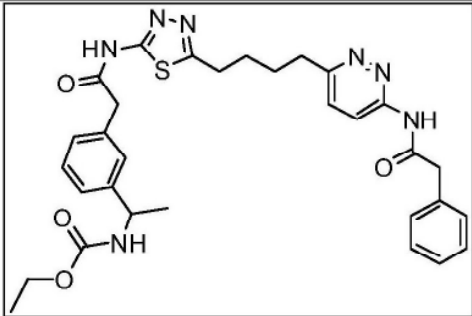
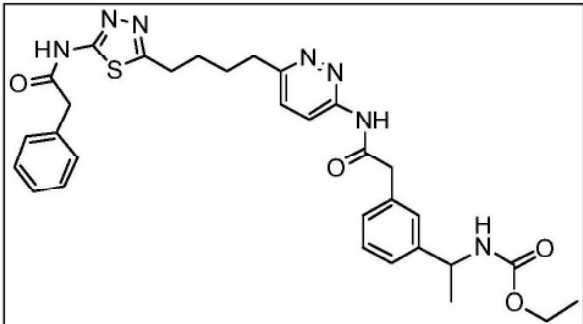
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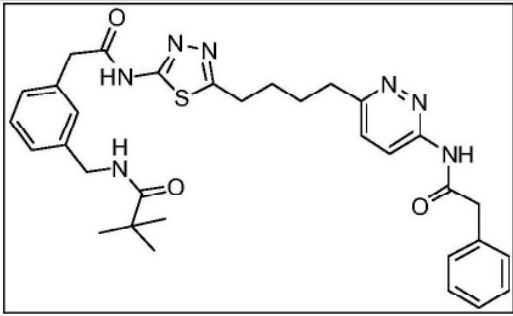
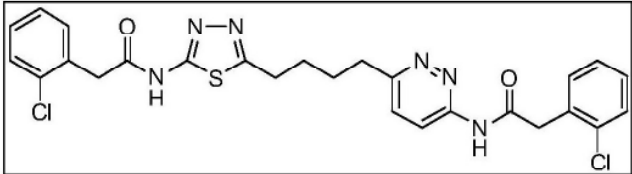
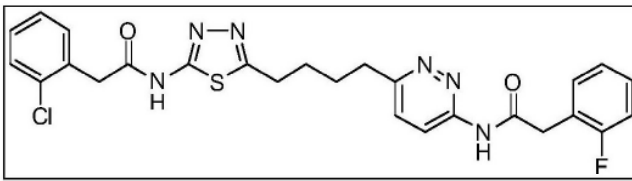
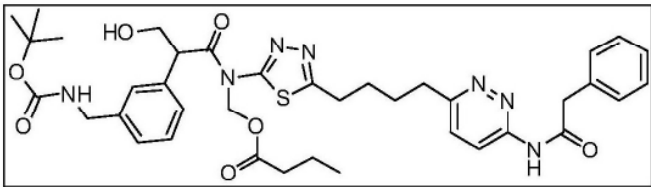
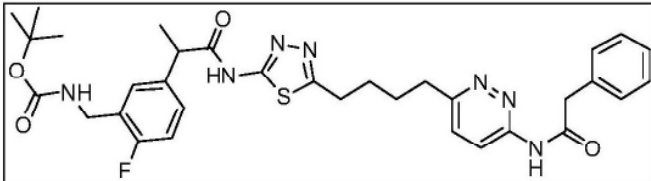
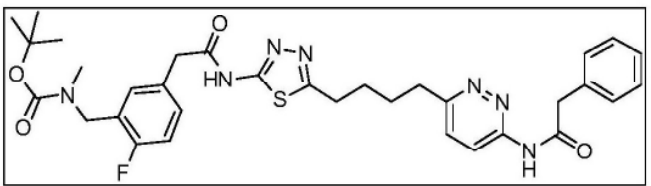
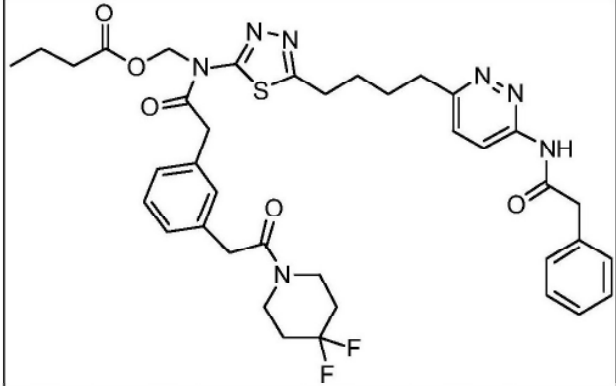
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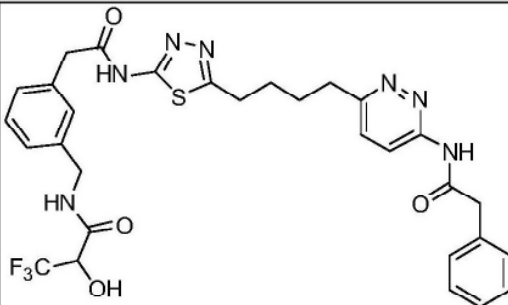
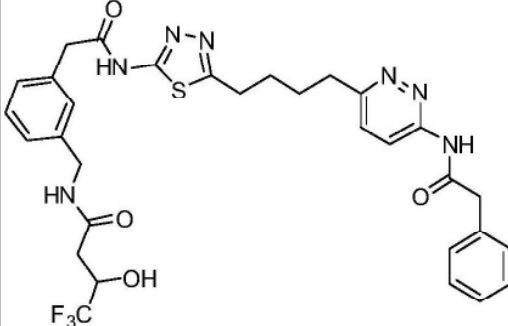
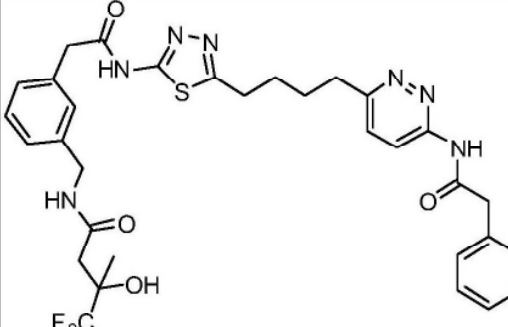
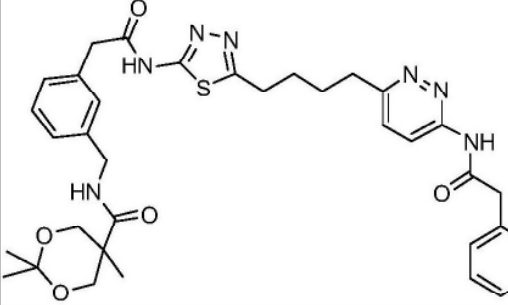
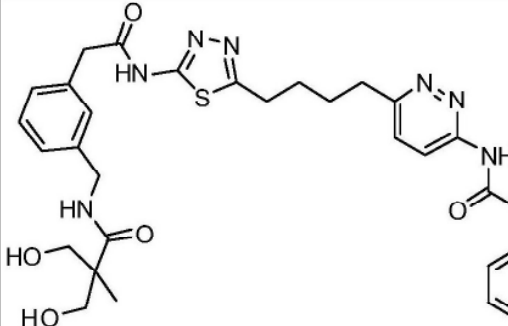
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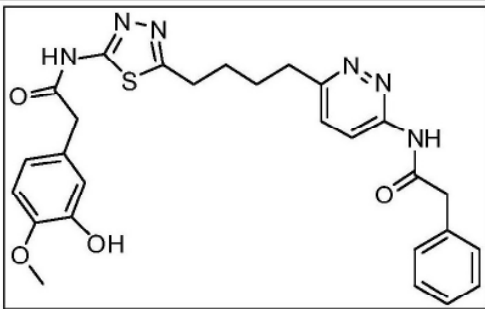
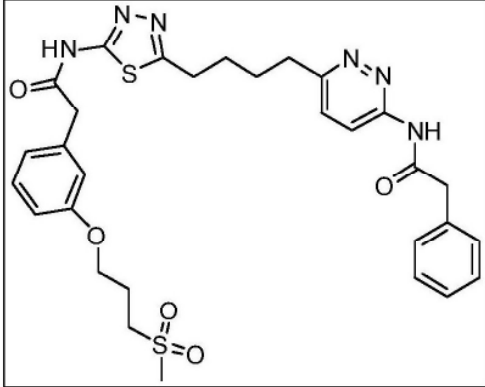
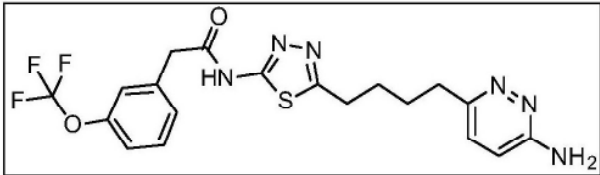
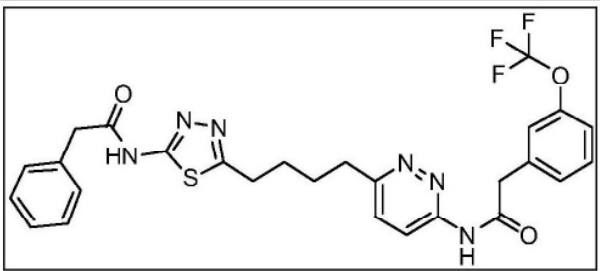
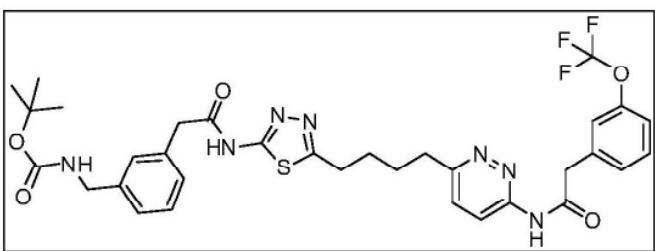
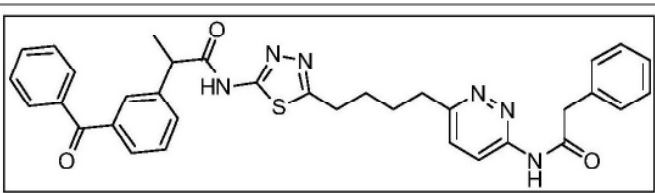
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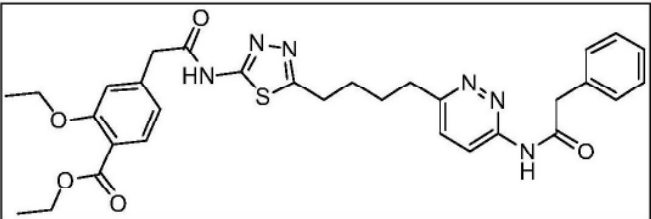
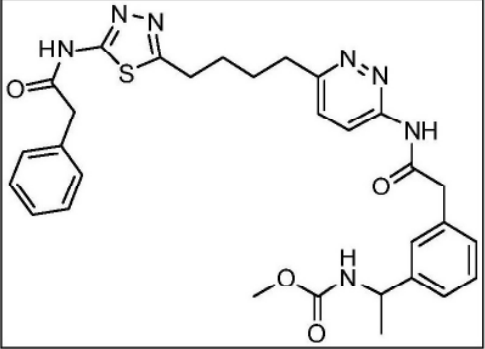
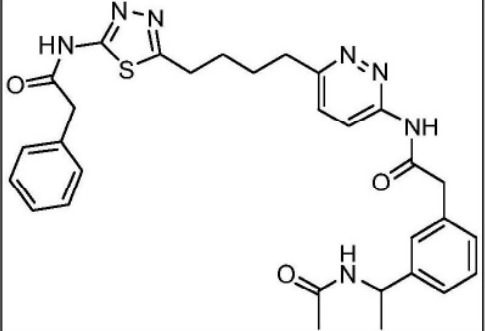
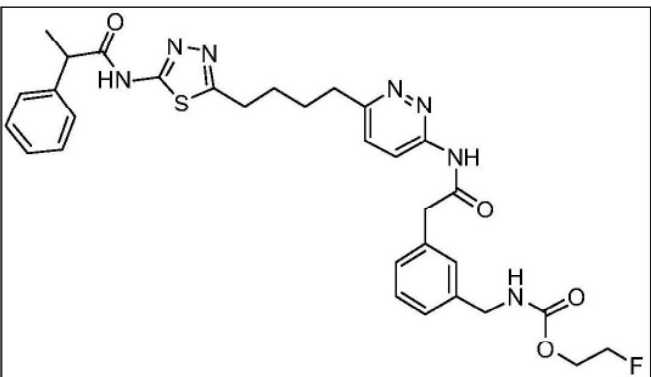
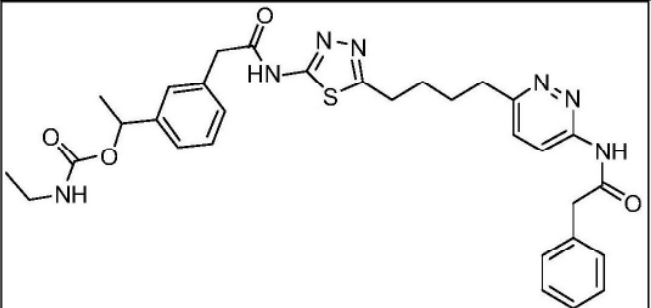
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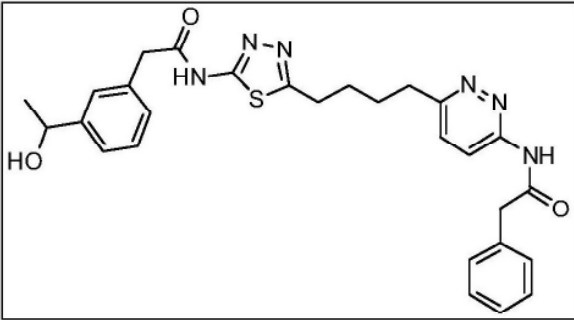
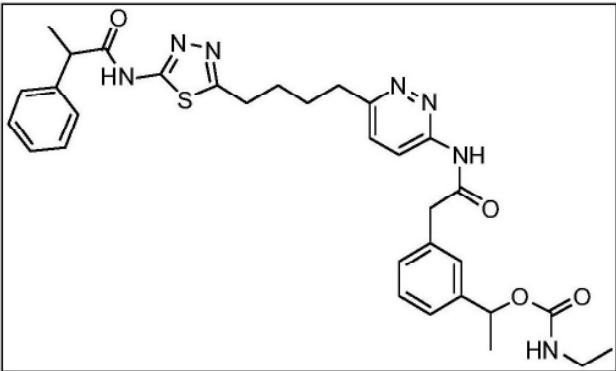
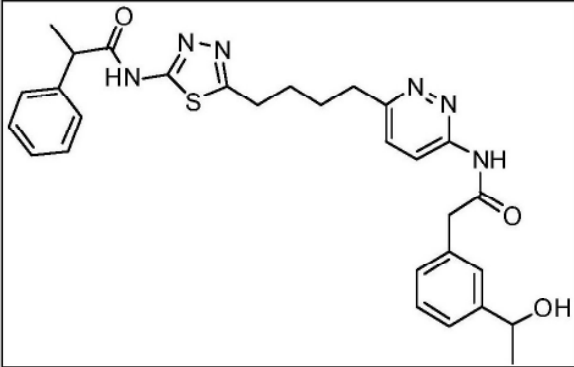
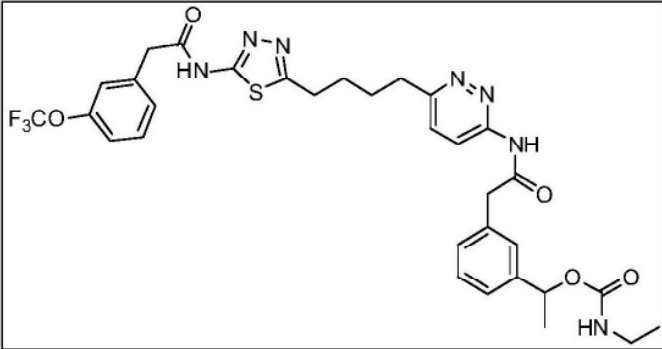
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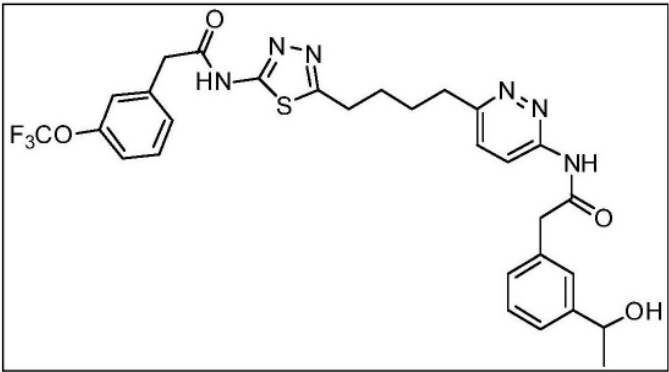
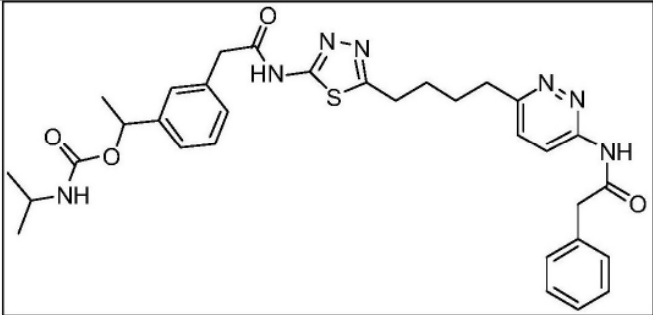
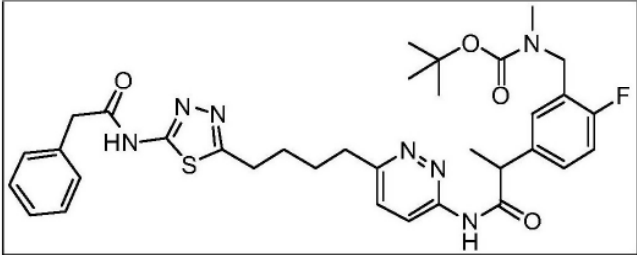
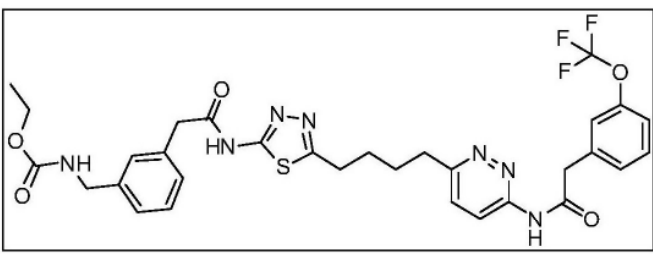
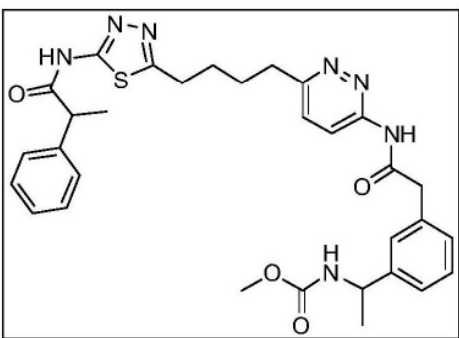
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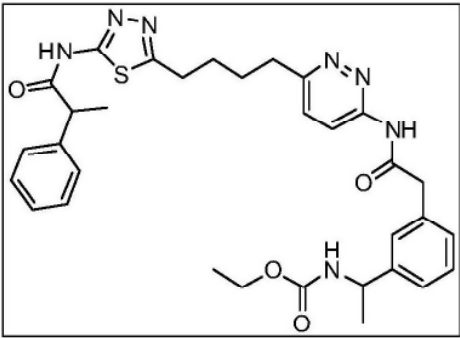
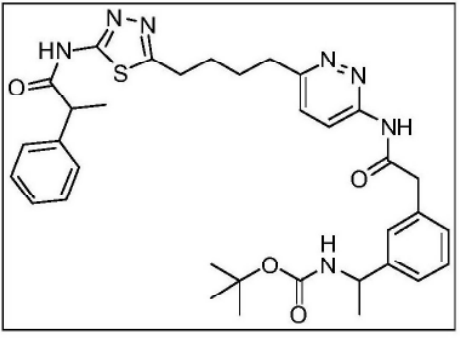
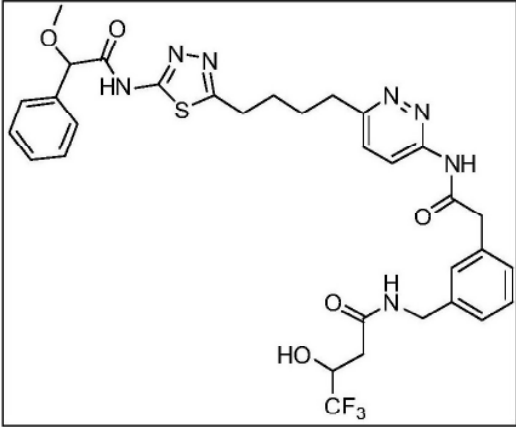
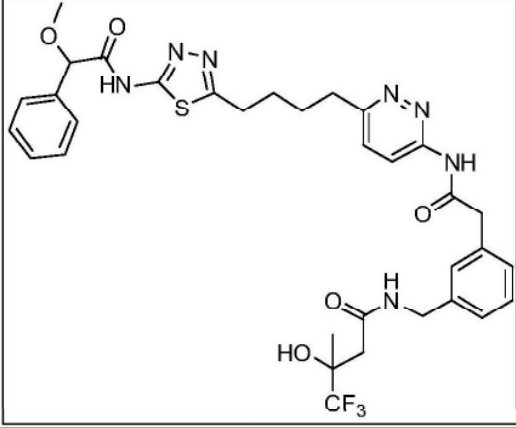
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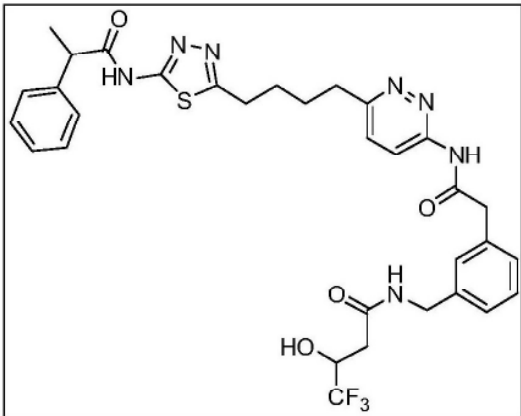
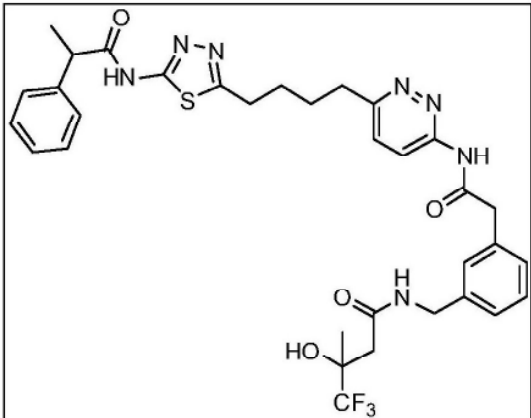
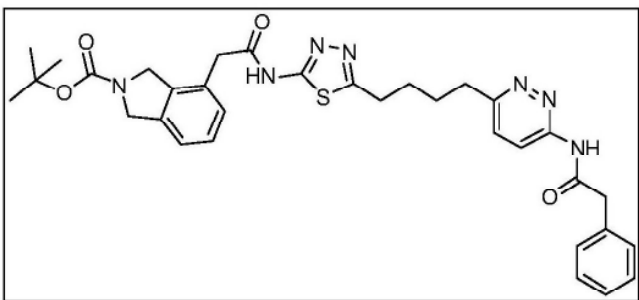
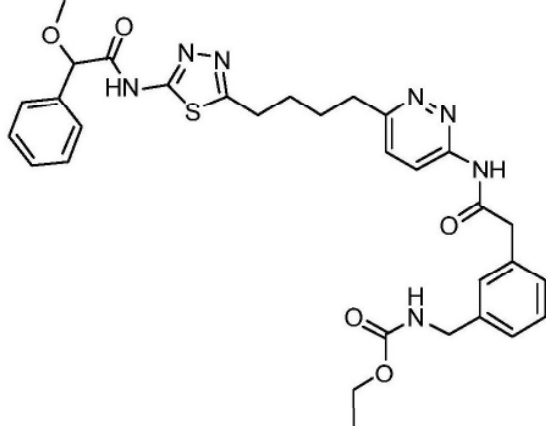
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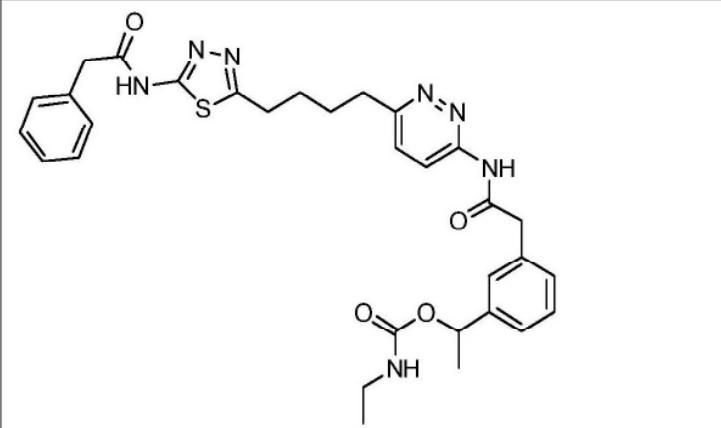
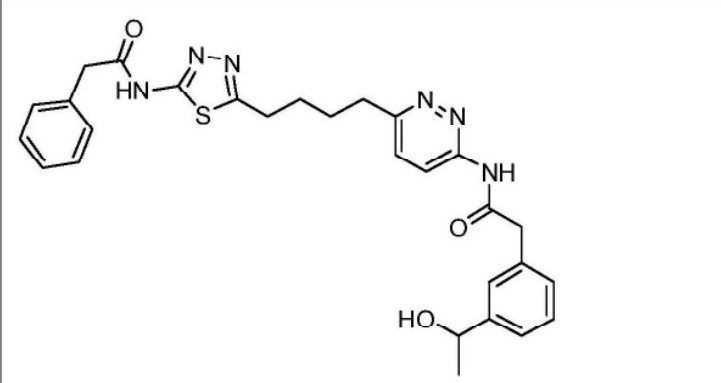
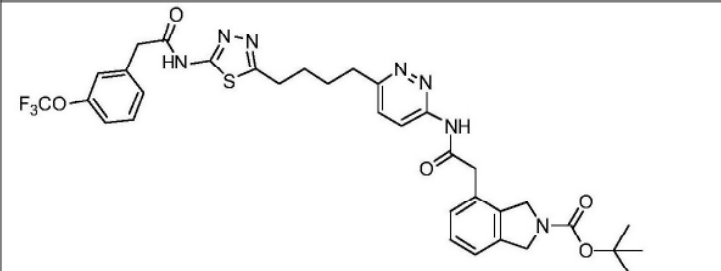
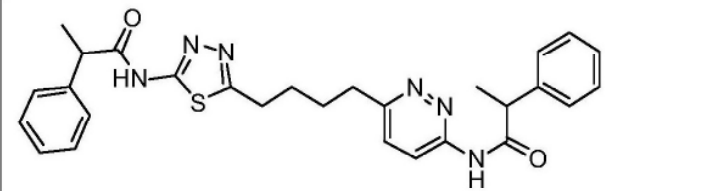
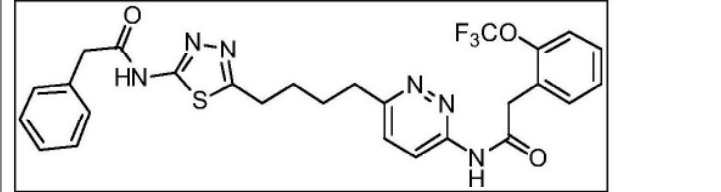
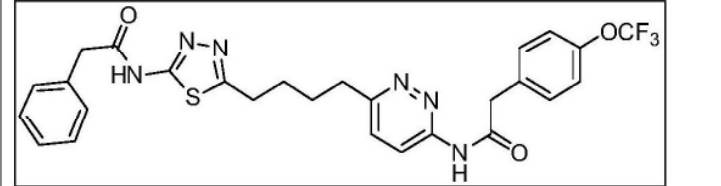
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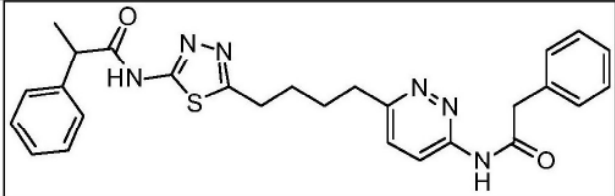
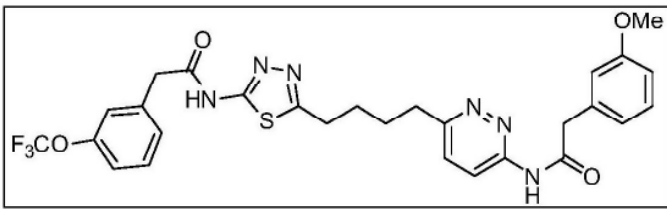
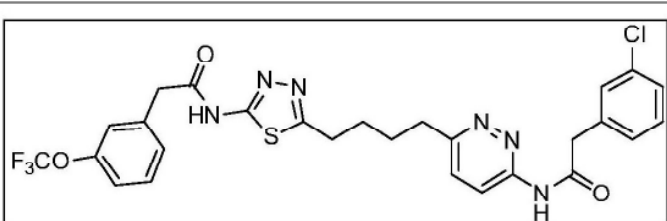
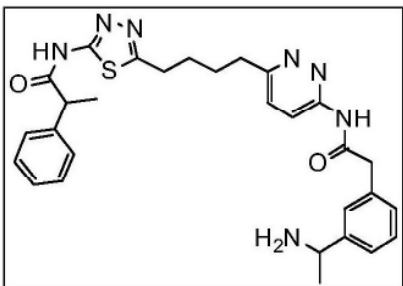
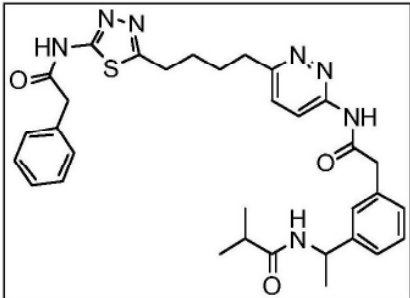
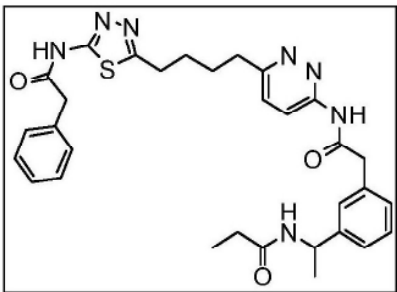
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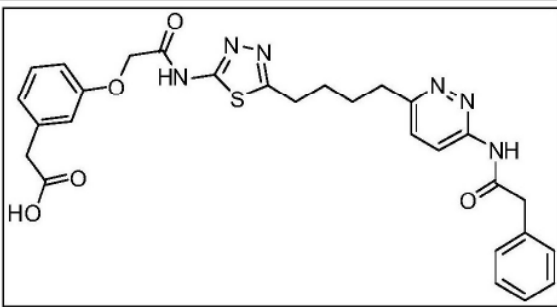
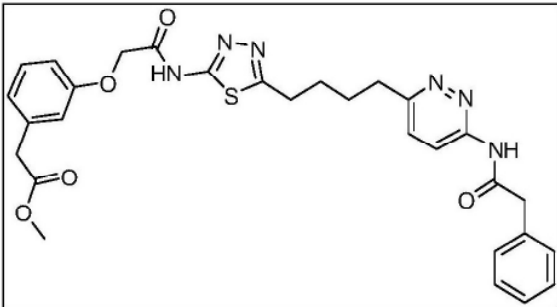
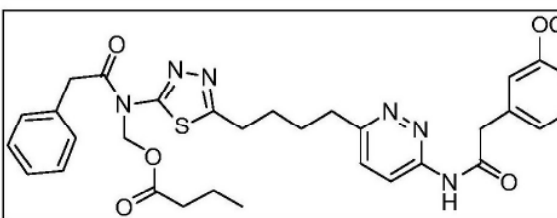
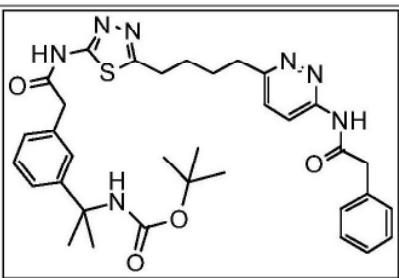
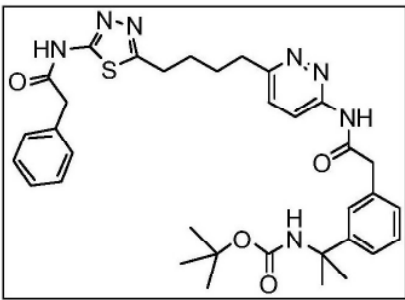
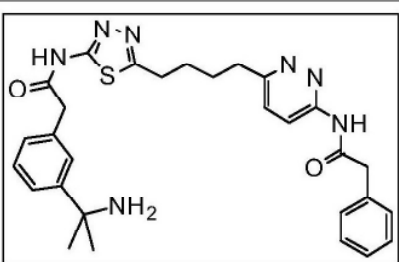
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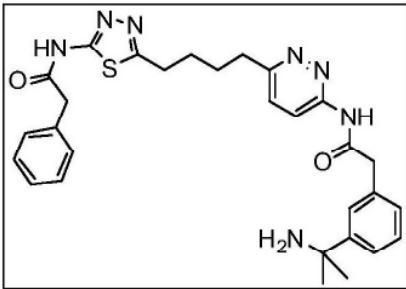
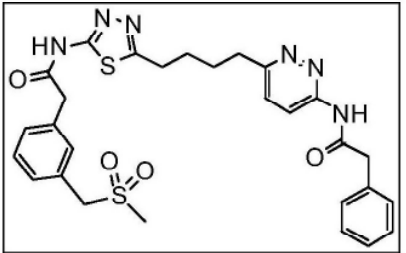
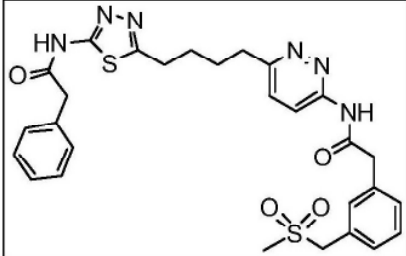
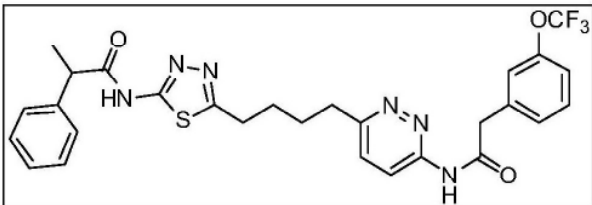
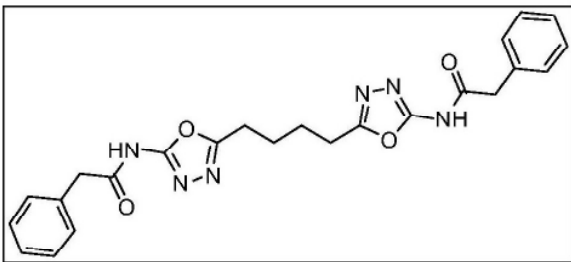
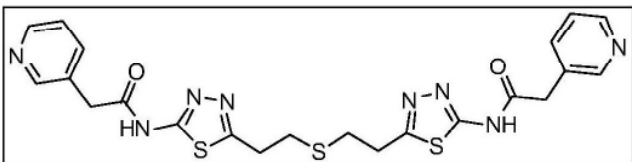
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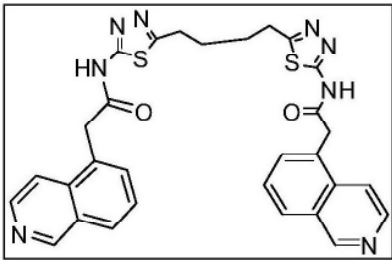
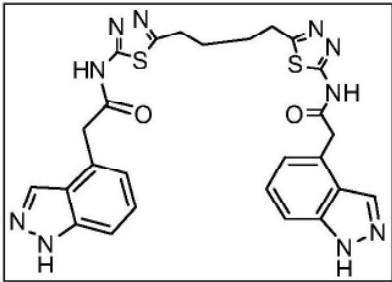
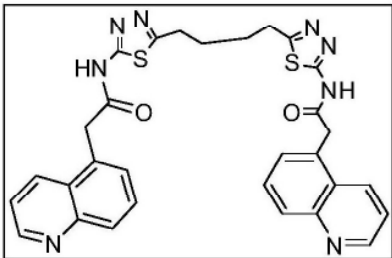
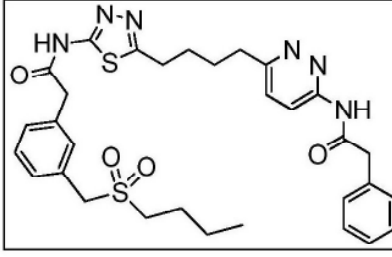
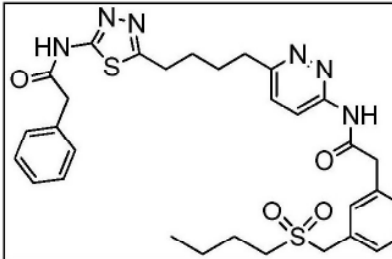
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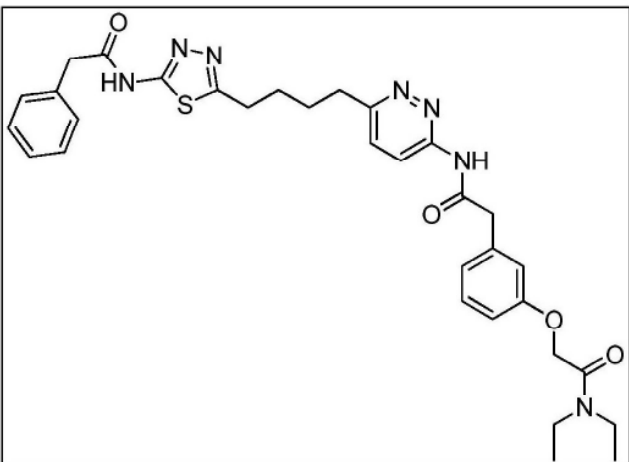
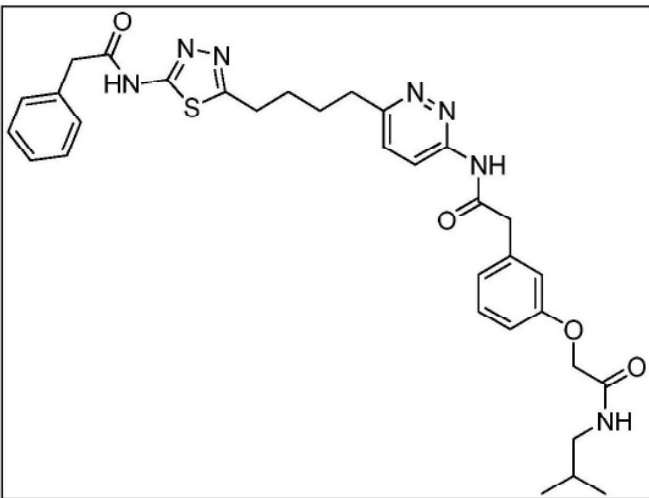
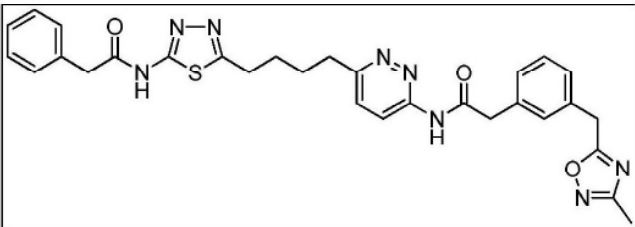
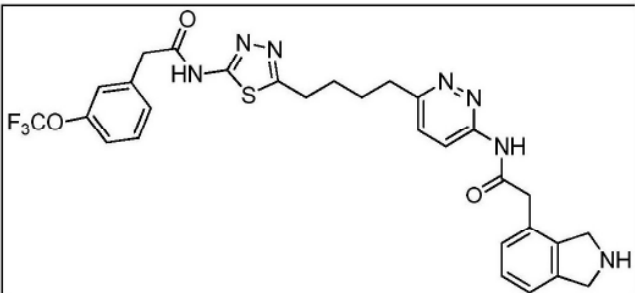
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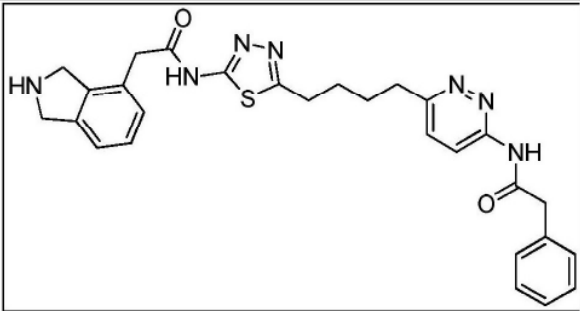
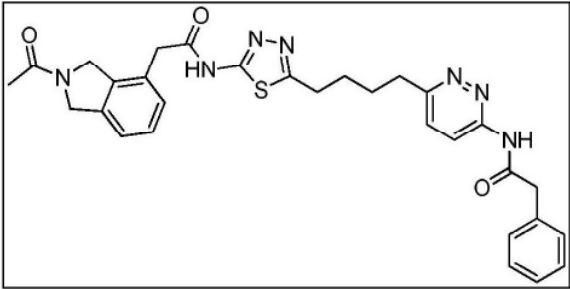
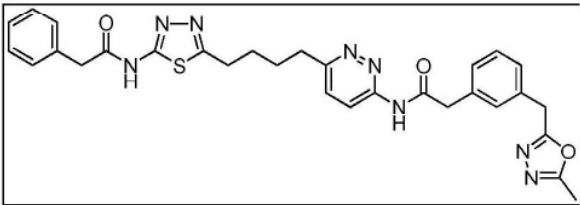
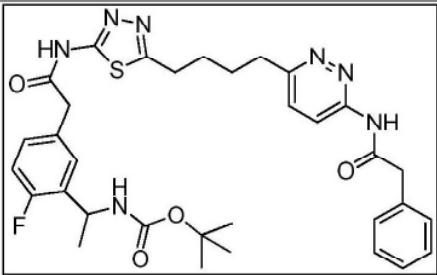
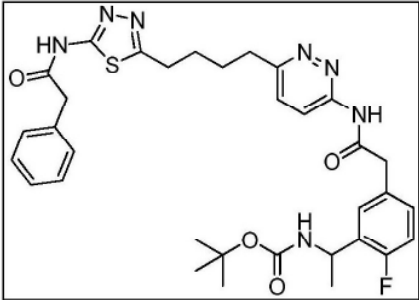
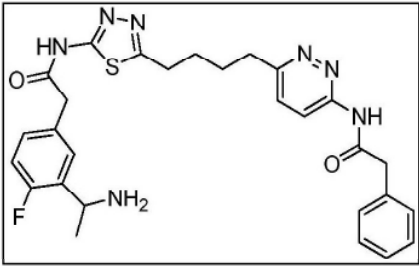
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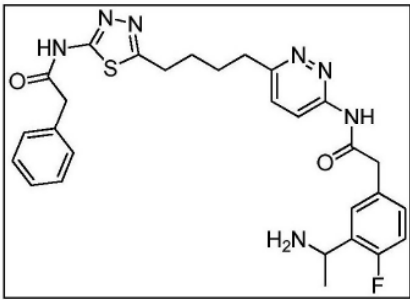
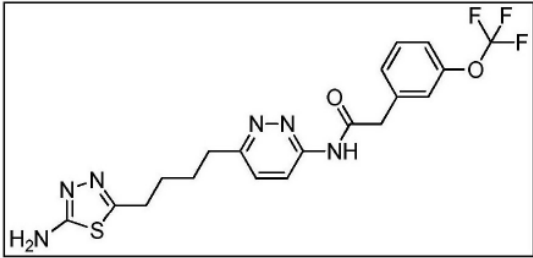
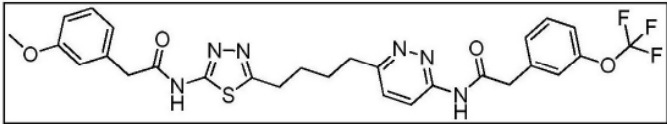
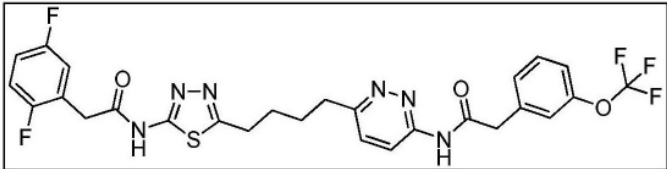
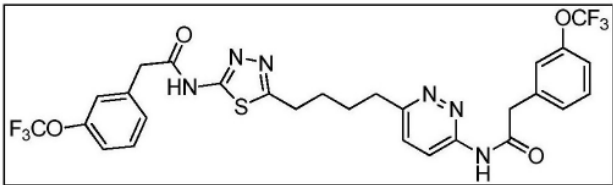
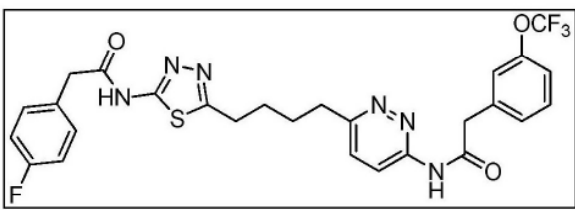
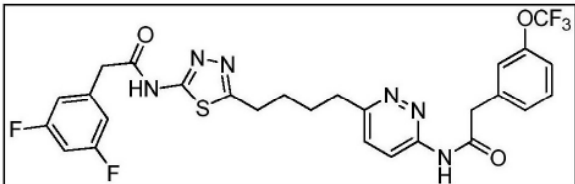
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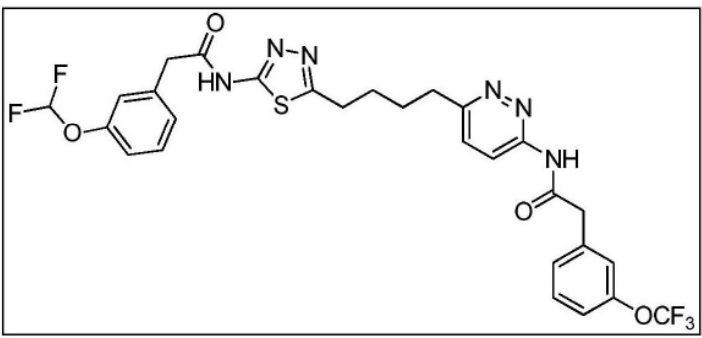
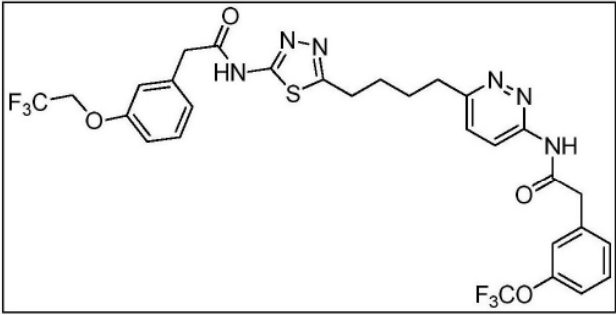
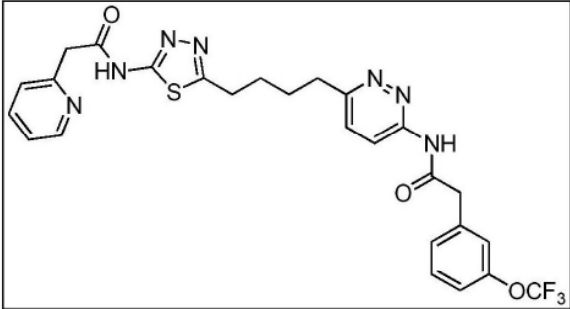
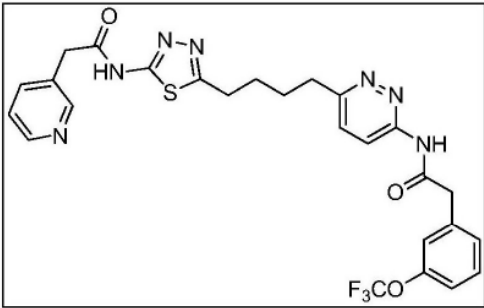
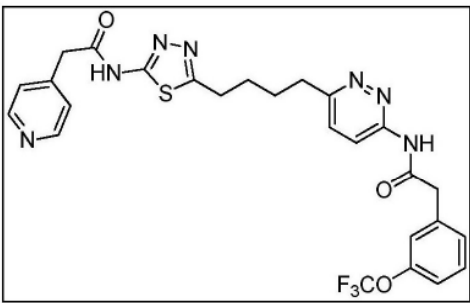
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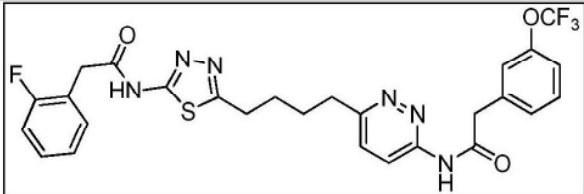
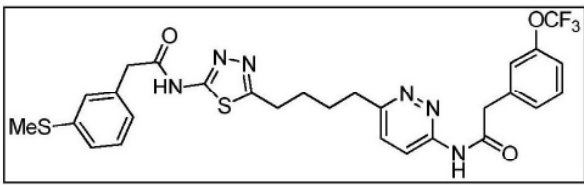
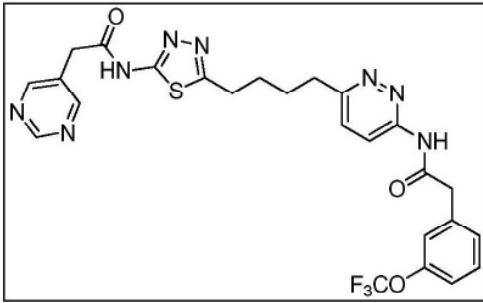
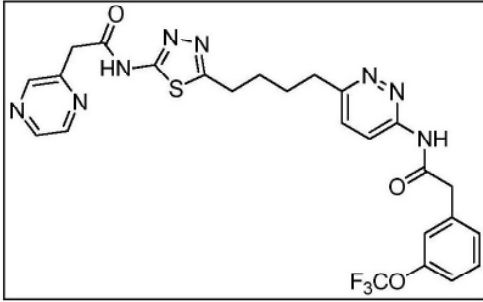
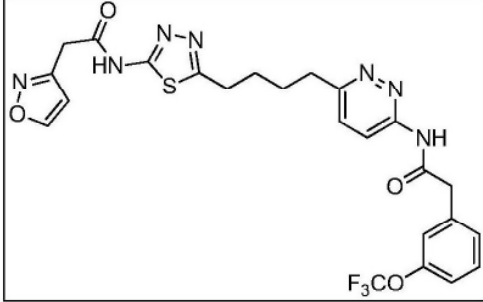
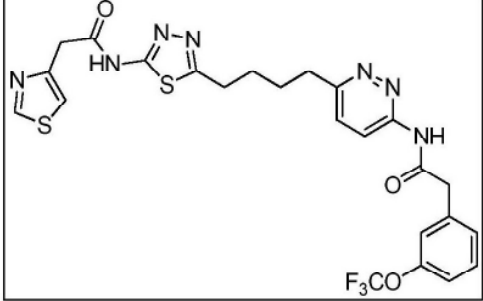
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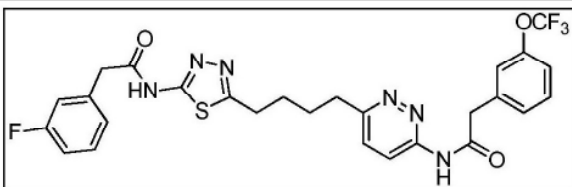
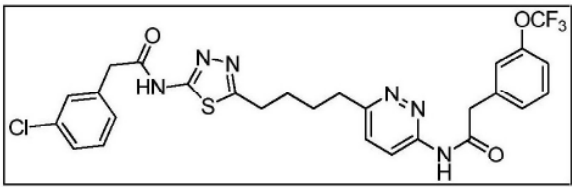
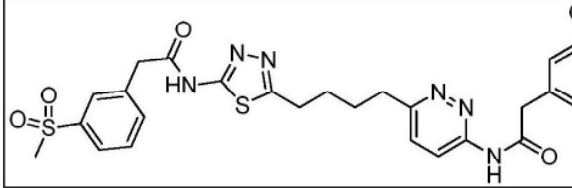
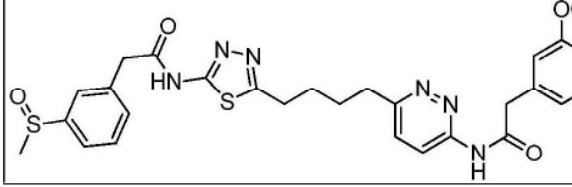
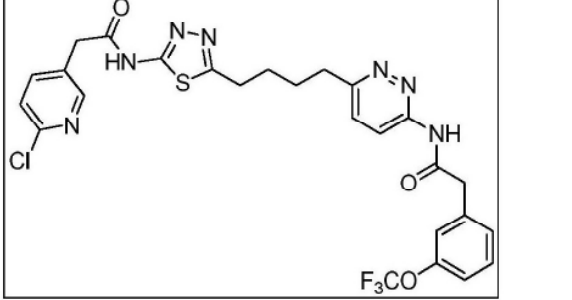
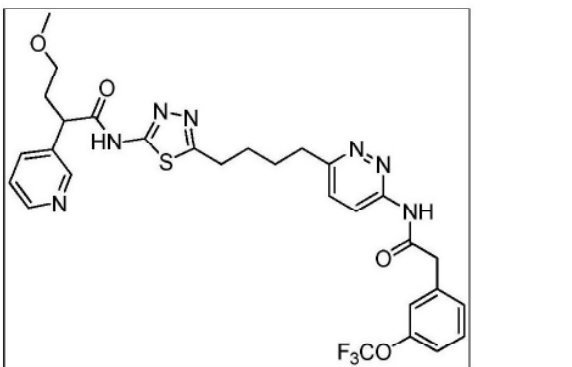
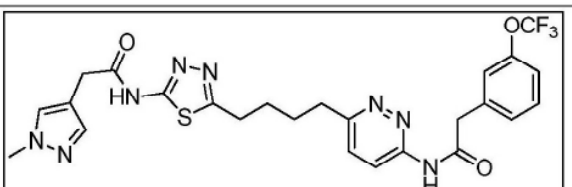
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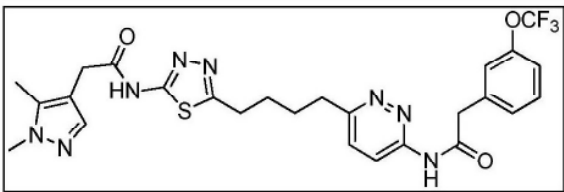
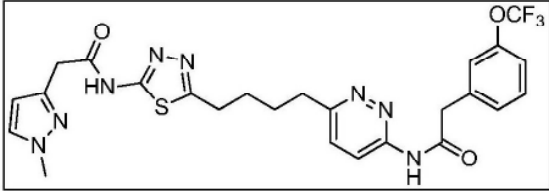
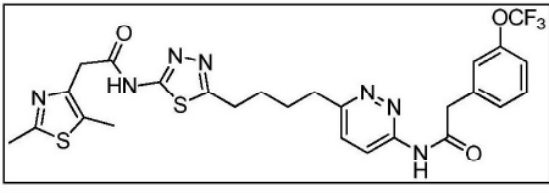
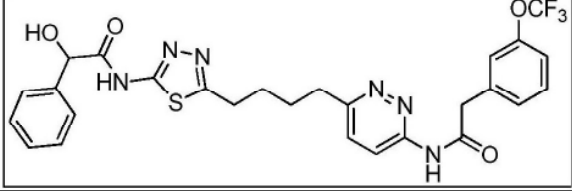
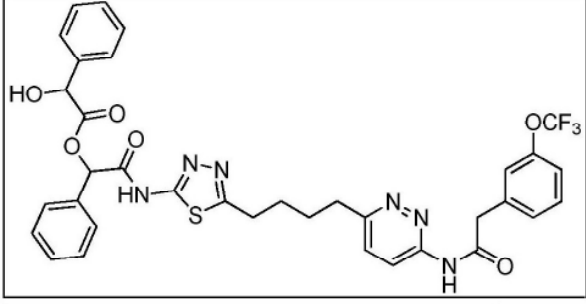
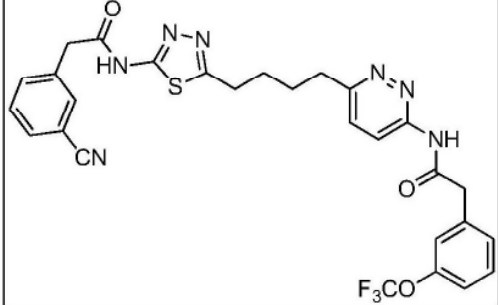
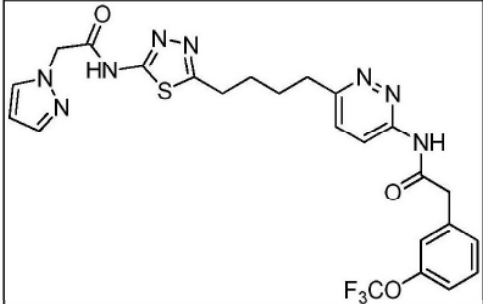
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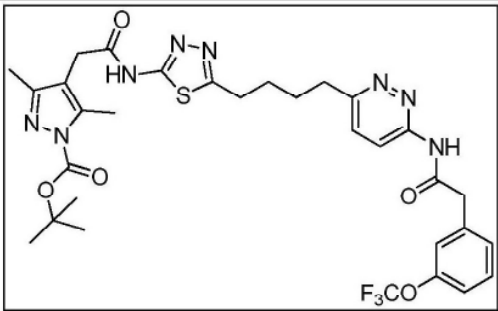
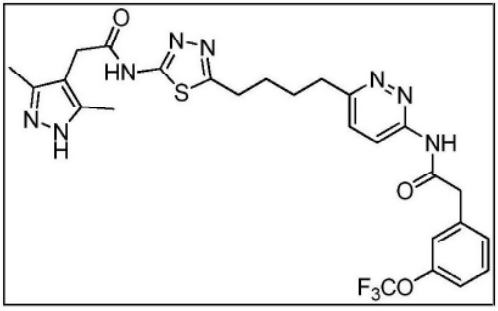
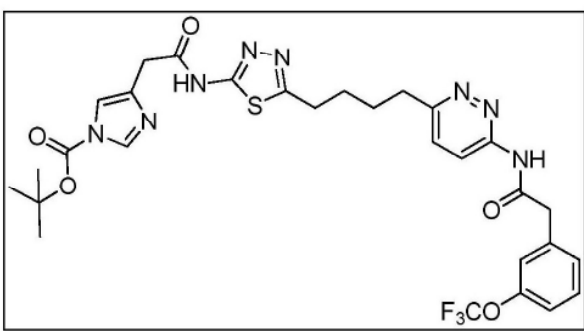
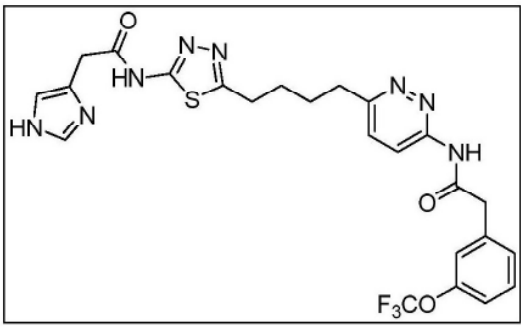
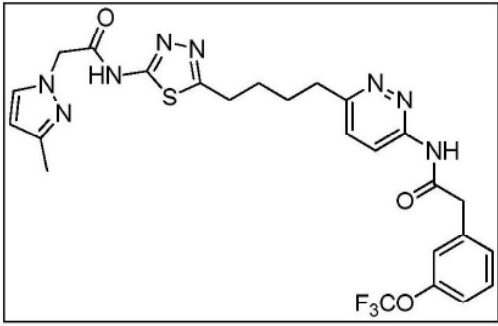
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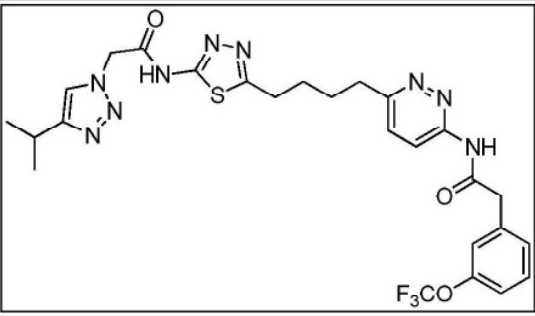
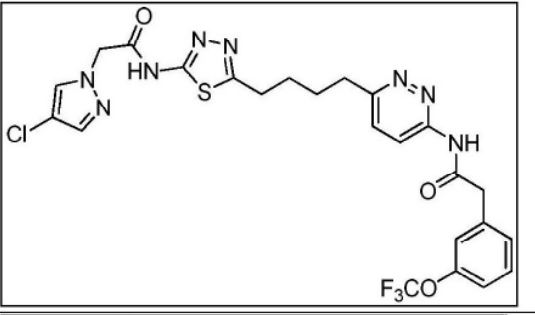
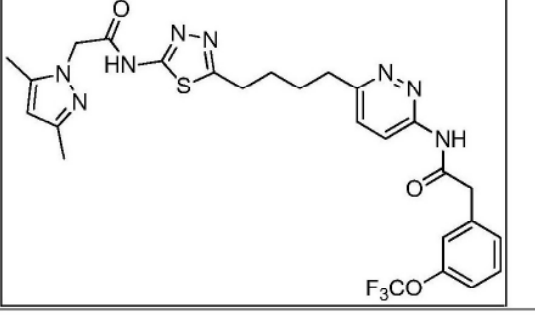
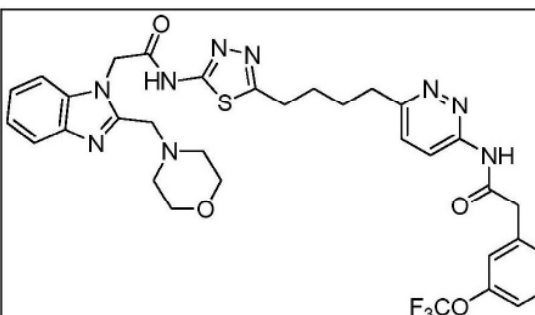
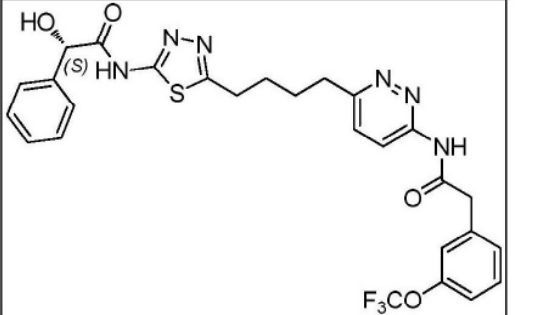
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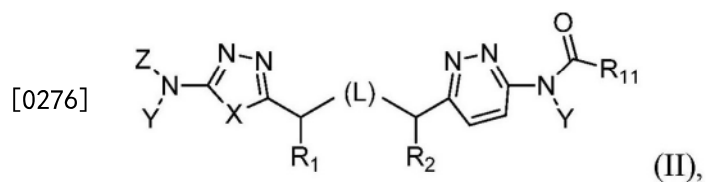
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[0275] 本发明进一步提供了治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法,所述方法包括口服给予式II化合物或其药学上可接受的盐,



[0277] 其中:

[0278] L表示CH₂SCH₂、CH₂CH₂、CH₂CH₂CH₂、CH₂、CH₂S、SCH₂、CH₂NHCH₂、CH=CH或, 优

选CH₂CH₂,其中CH或CH₂单元的任何氢原子可被烷基或烷氧基替代,NH单元的任何氢原子可被烷基替代,且CH₂CH₂、CH₂CH₂CH₂或CH₂的CH₂单元的任何氢原子可被羟基替代;

[0279] X表示S、O或CH=CH,优选S或CH=CH,其中CH单元的任何氢原子可被烷基替代;

[0280] Y在每次出现时独立地表示H或CH₂O(CO)R₇;

[0281] R₇在每次出现时独立地表示H或取代的或未取代的烷基、烷氧基、氨基烷基、烷基氨基烷基、杂环基烷基、芳基烷基或杂环基烷氧基;

[0282] Z表示H或R₃(CO);

[0283] R₁和R₂各自独立地表示氢、烷基、烷氧基或羟基;

[0284] R₃表示取代的或未取代的烷基、羟烷基、氨基烷基、酰基氨基烷基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基、杂芳基氧基烷基或C(R₈)(R₉)(R₁₀)、N(R₄)(R₅)或OR₆,其中任何游离的羟基可酰化以形成C(O)R₇;

[0285] R₄和R₅每次出现时各自独立地表示H或取代的或未取代的烷基、羟烷基、酰基、氨基烷基、酰基氨基烷基、烯基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,其中任何游离的羟基可酰化以形成C(O)R₇;

[0286] R₆表示取代的或未取代的烷基、羟烷基、氨基烷基、酰基氨基烷基、烯基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,其中任何游离的羟基可酰化以形成C(O)R₇;

[0287] R₈、R₉和R₁₀每次出现时各自独立地表示H或取代的或未取代的烷基、羟基、羟烷基、氨基、酰基氨基、氨基烷基、酰基氨基烷基、烷氧基羰基、烷氧基羰基氨基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,或R₈和R₉与它们连接的碳一起形成碳环或杂环系统,其中任何游离的羟基可酰化以形成C(O)R₇;且其中R₈、R₉和R₁₀中的至少两个不为氢;

[0288] R₁₁表示芳基、芳基烷基、芳基氧基、芳基氧基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,或R₁₁表示C(R₁₂)(R₁₃)(R₁₄)、N(R₄)(R₁₄)或OR₁₄,其中任何游离的羟基可酰化以形成C(O)R₇;

[0289] R₁₂和R₁₃各自独立地表示H或取代的或未取代的烷基、羟基、羟烷基、氨基、酰基氨基、氨基烷基、酰基氨基烷基、烷氧基羰基、烷氧基羰基氨基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,其中任何游离的羟基可酰化以形成C(O)R₇,且其中R₁₂和R₁₃二者不都为氢;且

[0290] R₁₄表示芳基、芳基烷基、芳基氧基、芳基氧基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基;

[0291] 优选其中所述化合物与膳食一起给予。

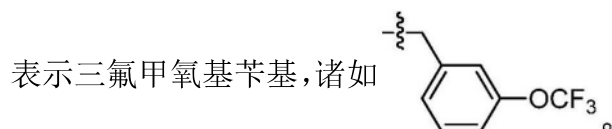
[0292] 在某些实施方案中,R₁₁表示芳基、芳基烷基、芳基氧基、芳基氧基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基,其中芳基或杂芳基环被-OCHF₂或-OCF₃取代且任

选地被进一步取代。

[0293] 在某些实施方案中, R_{14} 表示芳基、芳基烷基、芳基氧基、芳基氧基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基, 其中芳基或杂芳基环被 $-OCHF_2$ 或 $-OCF_3$ 取代且任选地被进一步取代。

[0294] 在其中烷基、羟烷基、氨基、酰基氨基、氨基烷基、酰基氨基烷基、烯基、烷氧基、烷氧基烷基、芳基、芳基烷基、芳基氧基、芳基氧基烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳基烷基、杂芳基氧基或杂芳基氧基烷基被取代的某些实施方案中, 它们被一个或多个选自以下的取代基取代: 取代的或未取代的烷基, 诸如全氟烷基 (例如, 三氟甲基)、烯基、烷氧基、烷氧基烷基、芳基、芳烷基、芳基烷氧基、芳基氧基、芳基氧基烷基、羟基、卤素、烷氧基诸如全氟烷氧基 (例如, 三氟甲氧基)、烷氧基烷氧基、羟烷基、羟烷基氨基、羟烷基烷氧基、氨基、氨基烷基、烷基氨基、氨基烷基烷氧基、氨基烷氧基、酰基氨基、酰基氨基烷基诸如全氟酰基氨基烷基 (例如, 三氟甲基酰基氨基烷基)、酰基氧基、环烷基、环烷基烷基、环烷基烷氧基、杂环基、杂环基烷基、杂环基氧基、杂环基烷氧基、杂芳基、杂芳基烷基、杂芳基烷氧基、杂芳基氧基、杂芳基氧基烷基、杂环基氨基烷基、杂环基氨基烷氧基、酰氨基、酰氨基烷基、脒、亚胺、氧代、羰基 (诸如羧基、烷氧基羰基、甲酰基或酰基包括全氟酰基 (例如, $C(O)CF_3$))、羰基烷基 (诸如羧基烷基、烷氧基羰基烷基、甲酰基烷基或酰基烷基包括全氟酰基烷基 (例如, $-烷基C(O)CF_3$))、氨基甲酸酯、氨基甲酸酯烷基、脲、脲烷基、硫酸酯、磺酸酯、氨磺酰基、砒、磺酰胺、磺酰胺烷基、氰基、硝基、叠氮基、巯基、烷硫基、硫代羰基 (诸如硫代酯、硫代乙酸酯或硫代甲酸酯)、磷酰基、磷酸酯、膦酸酯或亚膦酸酯。

[0295] 在某些实施方案中, R_{11} 表示芳基烷基诸如苄基, 其中芳基被 $-OCF_3$ 取代, 诸如被 $-OCF_3$ 间位取代。在一些这样的实施方案中, 芳基环不被进一步取代。在某些实施方案中, R_{11}



[0296] 在某些实施方案中, L 表示 CH_2SCH_2 、 CH_2CH_2 、 $CH_2CH_2CH_2$ 、 CH_2 、 CH_2S 、 SCH_2 或 CH_2NHCH_2 , 其中 CH_2 单元的任何氢原子可被烷基或烷氧基替代, 且 CH_2CH_2 、 $CH_2CH_2CH_2$ 或 CH_2 的 CH_2 单元的任何氢原子可被羟基替代。在某些实施方案中, L 表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 。在某些实施方案中, L 表示 CH_2CH_2 。在某些实施方案中, L 不为 CH_2SCH_2 。

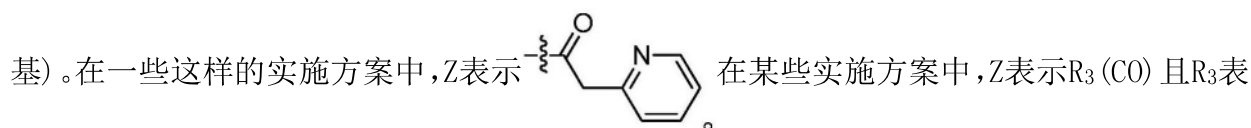
[0297] 在某些实施方案中, Y 表示H。

[0298] 在某些实施方案中, X 表示S或 $CH=CH$ 。在某些实施方案中, X 表示S。

[0299] 在某些实施方案中, Z 表示 $R_3(CO)$ 。在某些实施方案中, 其中 Z 为 $R_3(CO)$, R_3 和 R_{11} 不相同 (例如, 式II化合物不是对称的)。

[0300] 在某些实施方案中, R_1 和 R_2 各自表示H。

[0301] 在某些实施方案中, Z 表示 $R_3(CO)$ 且 R_3 表示芳基烷基、杂芳基烷基、环烷基或杂环烷基。在某些实施方案中, Z 表示 $R_3(CO)$ 且 R_3 表示杂芳基烷基, 诸如吡啶基烷基 (例如, 吡啶基甲

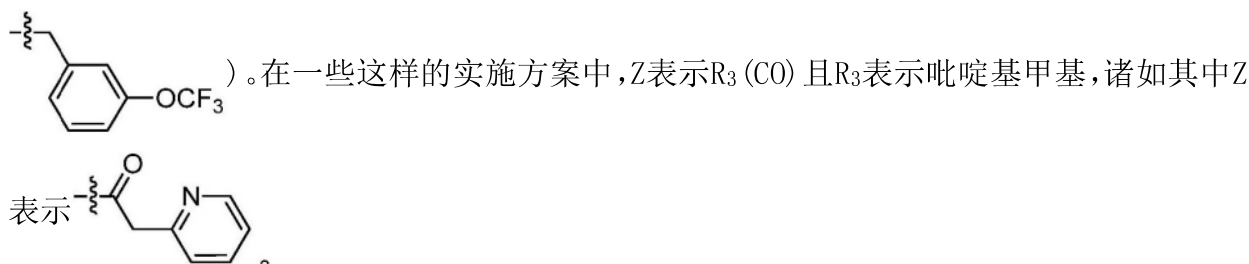


基)。在某些实施方案中, Z 表示 $R_3(CO)$ 且 R_3 表示

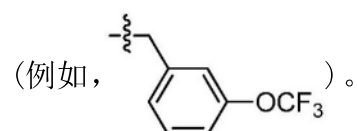
示 $C(R_8)(R_9)(R_{10})$, 其中 R_8 表示芳基、芳基烷基、杂芳基或杂芳烷基, 诸如芳基、芳基烷基或杂

芳基, R_9 表示H, 且 R_{10} 表示羟基、羟烷基、烷氧基或烷氧基烷基, 诸如羟基、羟烷基或烷氧基。

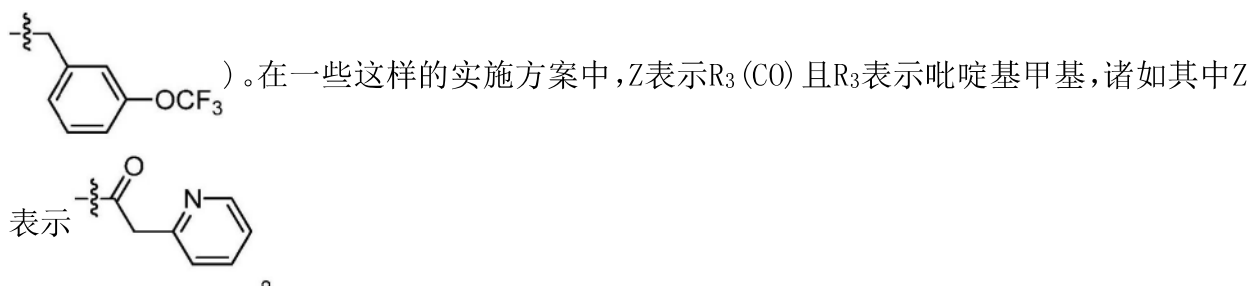
[0302] 在某些实施方案中, L表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 , 诸如 CH_2CH_2 , Y表示H, X表示S, Z表示 $R_3(\text{CO})$, R_1 和 R_2 各自表示H, R_3 表示芳基烷基、杂芳基烷基、环烷基或杂环烷基, 诸如杂芳基烷基(例如, 吡啶基烷基), 且 R_{11} 表示芳基烷基诸如三氟甲氧基苄基(例如,



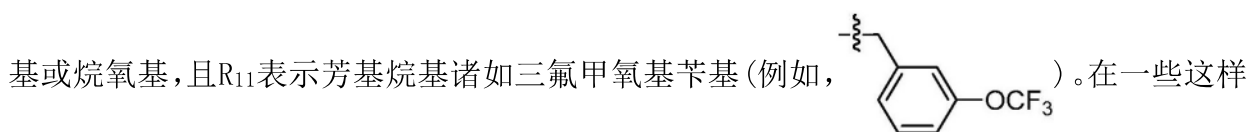
[0303] 在某些实施方案中, L表示 CH_2SCH_2 、 CH_2CH_2 、 CH_2S 或 SCH_2 , 诸如 CH_2CH_2 , Y表示H, X表示S, Z表示 $R_3(\text{CO})$, R_1 和 R_2 各自表示H, 并且每个 R_3 表示C(R_8)(R_9)(R_{10}), 其中 R_8 表示芳基、芳基烷基、杂芳基或杂芳烷基, 诸如芳基、芳基烷基或杂芳基, R_9 表示H, 且 R_{10} 表示羟基、羟烷基、烷氧基或烷氧基烷基, 诸如羟基、羟烷基或烷氧基, 且 R_{11} 表示芳基烷基诸如三氟甲氧基苄基



[0304] 在某些实施方案中, L表示 CH_2CH_2 , Y表示H, X表示S或 $\text{CH}=\text{CH}$, 诸如S, Z表示 $R_3(\text{CO})$, R_1 和 R_2 各自表示H, R_3 表示取代的或未取代的芳基烷基、杂芳基烷基、环烷基或杂环烷基, 诸如杂芳基烷基(例如, 吡啶基烷基), 且 R_{11} 表示芳基烷基诸如三氟甲氧基苄基(例如,



[0305] 在某些实施方案中, L表示 CH_2CH_2 , Y表示H, X表示S, Z表示 $R_3(\text{CO})$, R_1 和 R_2 各自表示H, R_3 表示C(R_8)(R_9)(R_{10}), 其中 R_8 表示芳基、芳基烷基或杂芳基, R_9 表示H, 且 R_{10} 表示羟基、羟烷基或烷氧基, 且 R_{11} 表示芳基烷基诸如三氟甲氧基苄基(例如,

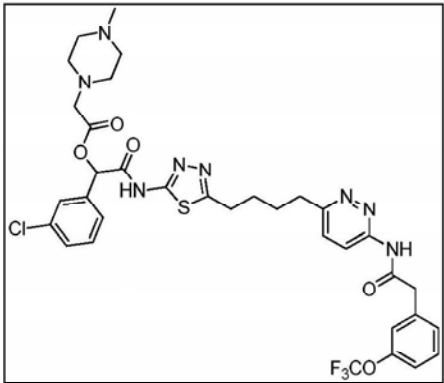
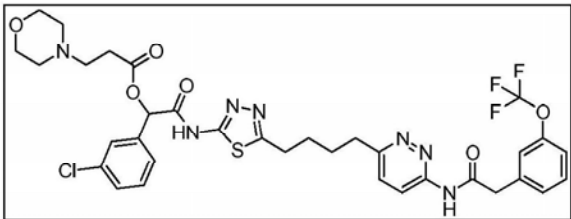
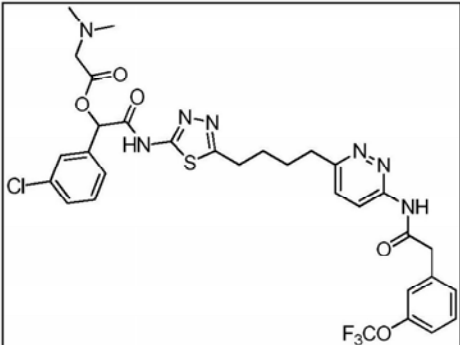
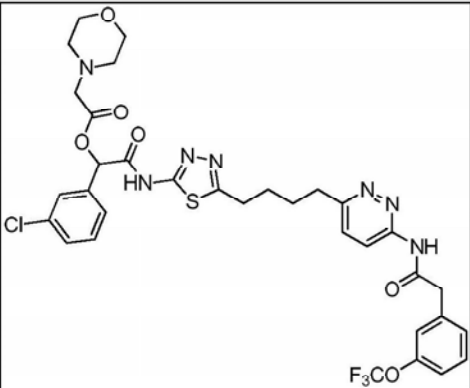


的实施方案中, R_8 表示芳基且 R_{10} 表示羟烷基。

[0306] 在某些实施方案中, 所述化合物选自表1和表2中公开的任一化合物。在某些实施方案中, 所述化合物选自化合物447、585、586、600、614、615、629、636、657、658、659、660、661、662、663、666、668、669、670、671、672、673、674、675、676、677、678、679、680、681、682、683、684、685、686、687、688、689、690、692、693、694、695、696、697、698、699、700、701、702、703、704、705、706、707、708、709、715、716、717、718、719、720、721、722、723、724、725、726、727、728、729或730。在某些实施方案中, 所述化合物选自化合物657、658、659、660、661、662、663、666、668、669、670、671、672、673、674、675、676、677、678、679、680、681、682、683、

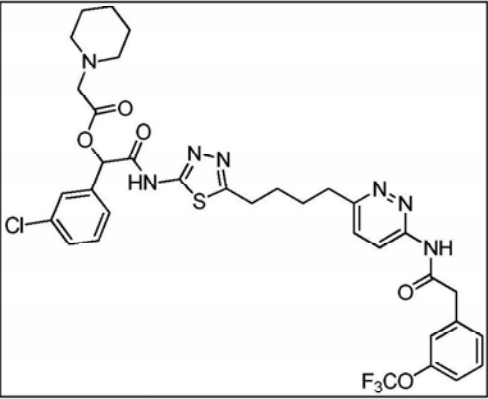
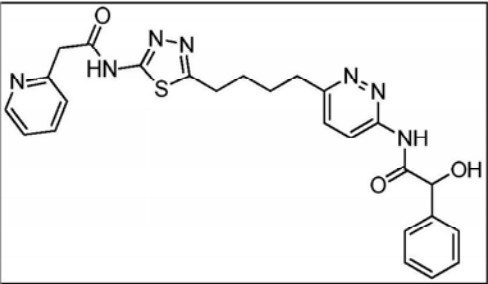
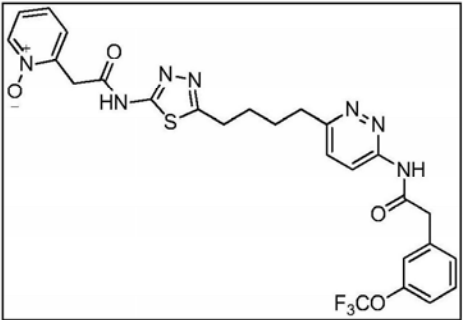
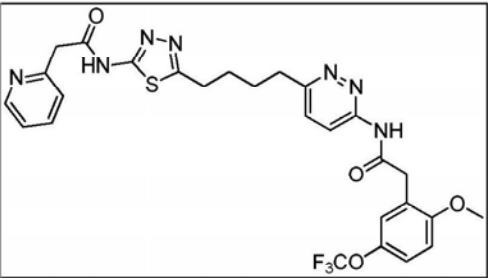
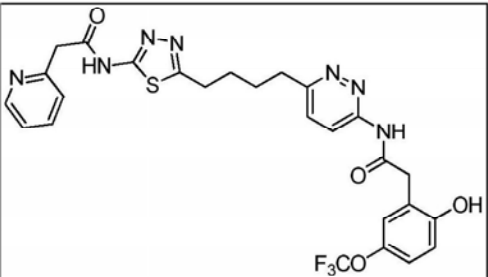
684、685、686、687、688、689、690、692、693、694、695、696、697、698、699、700、701、702、703、704、705、706、707、708、709、715、716、717、718、719、720、721、722、723、724、725、726、727、728、729或730。

[0307] 表2.所选的式II化合物

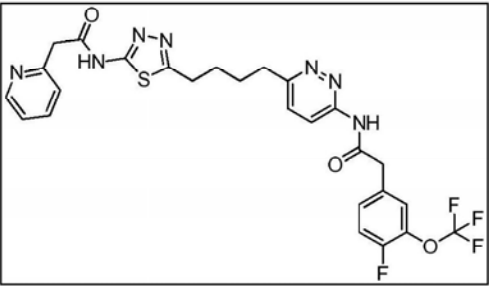
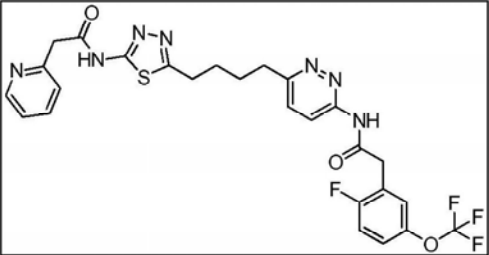
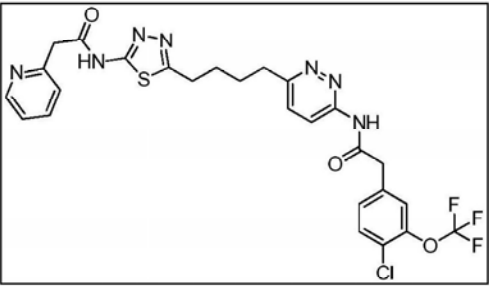
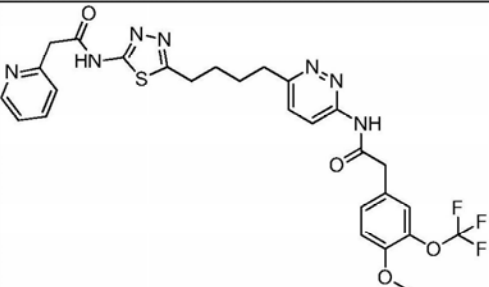
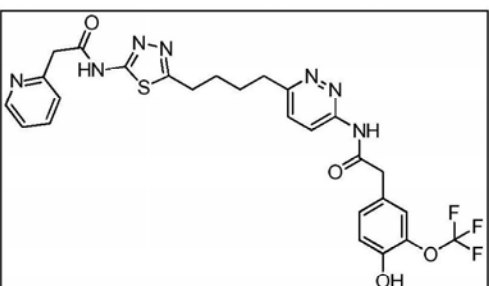
化合物 ID	结构
710	
711	
712	
713	

[0308]

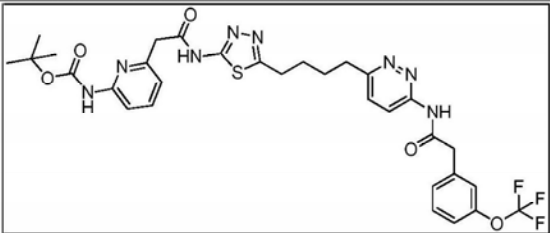
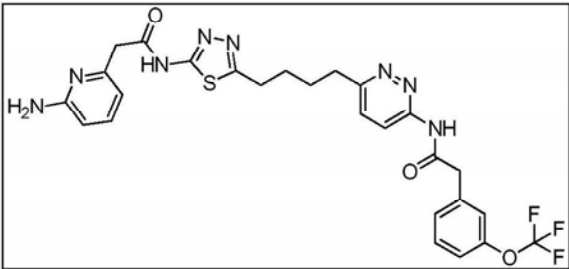
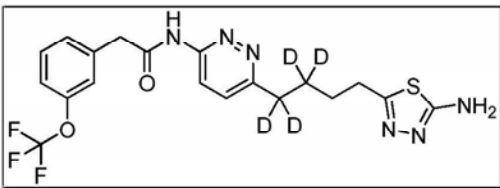
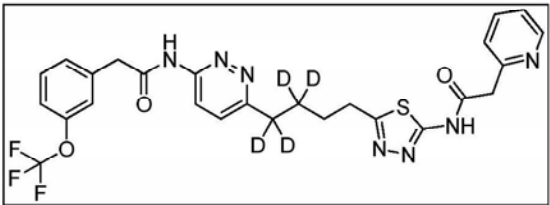
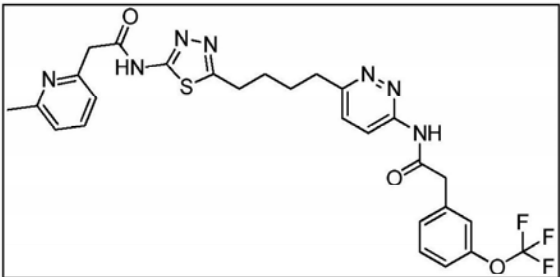
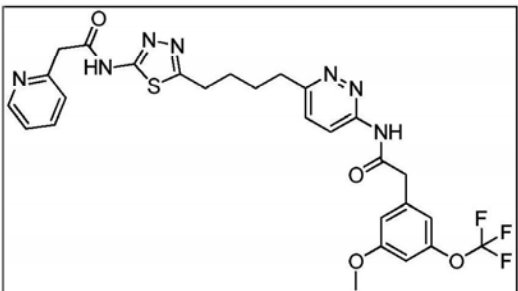
[0309]

714	
715	
716	
717	
718	

[0310]

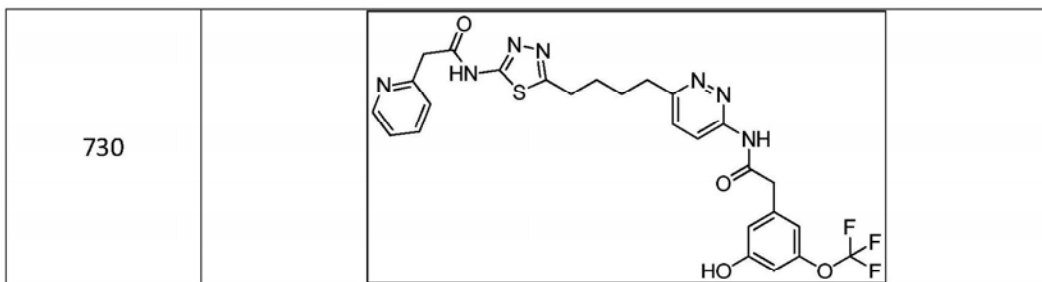
719	
720	
721	
722	
723	

[0311]

724	
725	
726	
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728	
729	

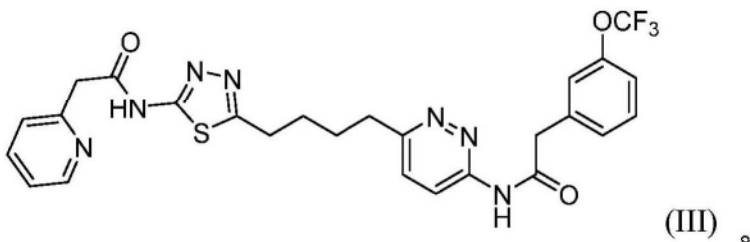
[0312]

730



[0313] 在本文所述方法的某些实施方案中,用于本发明的方法中的化合物为具有式(III)结构的化合物或其药学上可接受的盐:

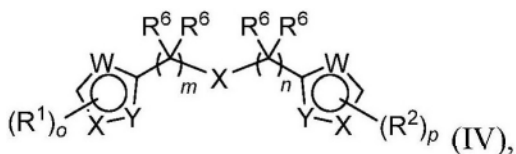
[0314]



[0315] 任一式(I)、(Ia)、(II)或(III)的化合物或者在本文中称作“谷氨酰胺酶抑制剂”。

[0316] 在某些实施方案中,本发明涉及治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法,所述方法包括口服给予具有式(IV)的结构化合物或其药学上可接受的盐,

[0317]



[0318] 其中:

[0319] X为键、-S-、-S(O)-、-SO₂-、-CH=CH-或-C(O)-;

[0320] 每个W、Y和Z独立地为-S-、-CH-、-O-、-N-或-NH-,条件是:(1)W、Y和Z中的至少一个不为-CH-;和(2)当W之一为-S-且同一环中的Y为N时,则同一环中的Z不为-CH-;

[0321] 每个R¹和R²独立地为C₁₋₆亚烷基-R⁴、-N(R³)-R⁴、-N(R³)-C(O)-R⁴、-C(O)-N(R³)-R⁴、-N(R³)-C(O)-O-R⁴、-N(R³)-C(O)-N(R³)-R⁴、-O-C(O)-N(R³)-R⁴、-N(R³)-C(O)-C₁₋₆亚烷基-C(O)-R⁴、-N(R³)-C(O)-C₁₋₆亚烷基-N(R³)-C(O)-R⁴或-N(R^{3a})-C(O)-CH₂-N(R³)-C(O)-R⁴;

[0322] 每个R³独立地为氢、C₁₋₆烷基或芳基;

[0323] 每个R⁴独立地为C₁₋₆烷基、C₁₋₆烯基、芳基、杂芳基、芳烷基、杂芳烷基、杂环基烷基、杂环基、环烷基或环烷基烷基,其中各基团被R⁵取代0-3次,或两个相邻的R⁵部分与它们连接的原子一起形成杂环基、杂芳基、环烷基或芳基;

[0324] 每个R⁵独立地为氧代(-O)、C₁₋₆烷基、C₁₋₆卤代烷基、C₁₋₆烷氧基、氰基、卤素、-OH、-SH、-OCF₃、-SO₂-C₁₋₆烷基、-NO₂、-N(R⁷)-C(O)-C₁₋₆烷基、-N(R⁶)₂、-O-C(O)-C₁₋₆烷基、C₃₋₇环烷基、(C₃₋₇环烷基)烷基、芳基、芳基氧基、-C(O)-芳基、杂芳基、芳烷基、杂芳烷基、杂环基烷基或杂环基,其中每个芳基、杂芳基或杂环基进一步被R⁷取代0-3次;

[0325] 每个R⁶独立地为氢、氟、OH或C₁₋₆烷基;

[0326] 每个R⁷独立地为氢、C₁₋₆烷基、-OH、-SH、氰基、卤素、-CF₃、-OCF₃、-SO₂-C₁₋₆烷基、-NO₂、-N(R⁷)-C(O)-C₁₋₆烷基、-N(R⁶)₂或C₁₋₆烷氧基;

[0327] m为1、2或3；

[0328] n为1、2或3；条件是，当X为键时，m和n的总和为3-6，且当X为-S-、-S(O)-、-SO₂-、-CH=CH-或-C(O)-时，m和n的总和为2-4；

[0329] o为1、2或3；且

[0330] p为1、2或3；

[0331] 条件是：

[0332] (1) 当X为-S-，m和n均为2，每个R⁶为H时，则(i) R¹和R²不都是-NHC(O)-R⁴，其中R⁴为C₁₋₆烷基、单环芳基、单环杂芳基、单环芳烷基、单环杂芳烷基且R⁴的每个成员被R⁵取代0-3次；和(ii) R¹和R²不都是-NHC(O)O-甲基、-NHC(O)O-乙基、-NHC(±)-6-嘧啶-2,4(1H,3H)-二酮基或-NHC(O)NH-苯基，其中-NHC(O)NH-苯基部分的所述苯基任选地被1或2个选自甲基、硝基和卤素的基团取代；

[0333] (2) 当X为-S-，m和n均为1，每个R⁶为H时，则(i) R¹和R²不都是-NH-苯基或-NH-4-甲氧基-苯基；

[0334] (3) 当X为键，m和n之和为3，每个R⁶为H时，则R¹和R²不都是NHC(O)-苯基；

[0335] (4) 当X为键，m和n均为2，每个R⁶为H时，则R¹和R²不都是-NHC(O)-呋喃基、-NHC(O)-苯基、-NHC(O)-邻甲氧基-苯基、-NHC(O)-C₁₋₆烷基、-NH-苄基或-NH-苯基，其中-NH-苯基部分的所述苯基被R⁵取代0-3次；

[0336] (5) 当X为键，m和n之和为5，每个R⁶为H时，则R¹和R²不都是-NHC(O)-C₁₋₆烷基、-NHC(O)-环己基或-NH-苯基，其中-NH-苯基部分的所述苯基被甲基任选取代；且

[0337] (6) 当X为键，m和n均为3，每个R⁶为H时，则R¹和R²不都是NH-苯基；

[0338] 优选其中式(IV)化合物与膳食一起给予。

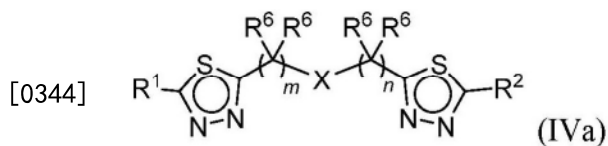
[0339] 在某些实施方案中，W为-S-，每个Y为-N-，且每个Z为-N-。

[0340] 在某些实施方案中，W为-CH-，每个Z为-O-，且每个Y为-N-。

[0341] 在某些实施方案中，o为1且p为1。

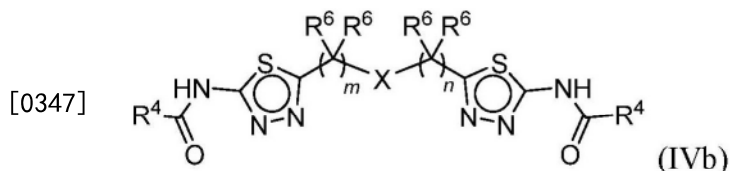
[0342] 在某些实施方案中，R¹和R²各自为-N(R³)-C(O)-O-R⁴。

[0343] 在某些实施方案中，具有式(IV)结构的化合物具有式(IVa)结构：

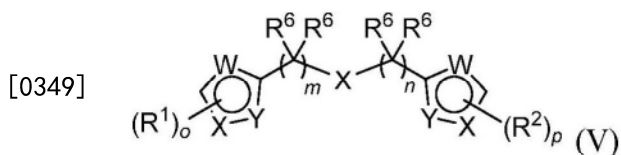


[0345] 在某些实施方案中，R¹和R²相同。

[0346] 在某些实施方案中，具有式(IV)结构的化合物具有式(IVb)结构：



[0348] 在某些实施方案中，本发明涉及治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法，所述方法包括口服给予具有式(V)的结构的化合物或其药学上可接受的盐，



[0350] 其中

[0351] X为C₃-C₇亚环烷基；

[0352] 每个W、Y和Z独立地为-S-、-CH-、-O-、-N-或-NH-，条件是W、Y和Z中的至少一个不为-CH-；

[0353] 每个R¹和R²独立地为-NH₂、-N(R³)-C(O)-R⁴、-C(O)-N(R³)-R⁴、-N(R³)-C(O)-O-R⁴、-N(R³)-C(O)-N(R³)-R⁴或-N(R³)-C(O)-SR⁴；

[0354] 每个R³独立地为氢、C₁₋₆烷基或芳基；

[0355] 每个R⁴独立地为C₁₋₆烷基、芳基、杂芳基、芳烷基、杂芳烷基、环烷基、环烷基烷基、杂环基烷基或杂环基，其中每个被R⁵取代0-3次；

[0356] 每个R⁵独立地为C₁₋₆烷基、C₁₋₆烷氧基、-O-C₁₋₆亚烷基C₁₋₆烷氧基、C₁₋₆硫代烷氧基、C₁₋₆卤代烷基、C₃₋₇环烷基、C₃₋₇环烷基烷基、芳基、杂芳基、芳烷基、杂芳烷基、杂环基烷基、杂环基、氰基、卤素、氧代、-OH、-OCF₃、-OCHF₂、-SO₂-C₁₋₆烷基、-NO₂、-N(R⁷)-C(O)-C₁₋₆烷基、-C(O)N(R⁷)₂、-N(R⁷)S(O)₁₋₂-C₁₋₆烷基、-S(O)₂N(R⁷)₂、-N(R⁷)₂、-C₁₋₆亚烷基-N(R⁷)₂，其中所述烷基、C₁₋₆烷氧基、-O-C₁₋₆亚烷基C₁₋₆烷氧基、C₁₋₆硫代烷氧基、C₁₋₆卤代烷基、C₃₋₇环烷基、C₃₋₇环烷基烷基、芳基、杂芳基、芳烷基、杂芳烷基、杂环基烷基、杂环基、-SO₂-C₁₋₆烷基、-NO₂、-N(R⁷)-C(O)-C₁₋₆烷基、-C(O)N(R⁷)₂、-N(R⁷)S(O)₁₋₂-C₁₋₆烷基、-S(O)₂N(R⁷)₂、-N(R⁷)₂或-C₁₋₆亚烷基-N(R⁷)₂任选地被R⁸取代0-3次；或两个相邻的R⁵部分与它们连接的原子一起形成环烷基或杂环基；

[0357] 每个R⁶独立地为氢、氟、C₁₋₆烷基、-OH、-NH₂、-NH(CH₃)、-N(CH₃)₂或C₁₋₆烷氧基；

[0358] 每个R⁷独立地为氢或C₁₋₆烷基；

[0359] 每个R⁸独立地为卤素、C₁₋₆烷基、C₁₋₆卤代烷基、-OH、-N(R⁷)₂，或C₁₋₆烷氧基、-O-C₁₋₆亚烷基C₁₋₆烷氧基、CN、NO₂、-N(R⁷)-C(O)-C₁₋₆烷基、-C(O)N(R⁷)₂、-N(R⁷)S(O)₁₋₂-C₁₋₆烷基或-S(O)₂N(R⁷)₂；

[0360] m为0、1或2；

[0361] n为0、1或2；

[0362] o为1、2或3；且

[0363] p为1、2或3；条件是：(1) 当X为不饱和环丙基时，R¹和R²不都是NH-苯基；且(2) X不是取代的环丁基或取代的环戊基；

[0364] 优选其中式(V)化合物与膳食一起给予。

[0365] 在某些实施方案中，W为-S-，每个Y为-N-，且每个Z为-N-。

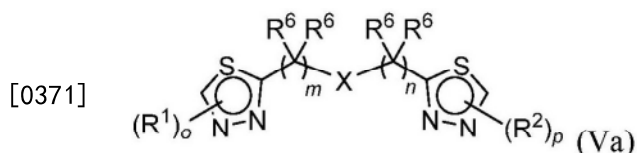
[0366] 在某些实施方案中，o为1且p为1。

[0367] 在某些实施方案中，m为0且n为0。或者，m和n可各自为1。

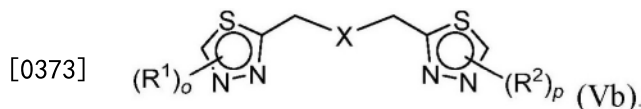
[0368] 在某些实施方案中，R¹和R²不同。或者，R¹和R²可相同。

[0369] 在某些实施方案中，R¹和R²各自为-N(R³)-C(O)-O-R⁴，其中每个R³为氢且每个R⁴为芳烷基或杂芳烷基，其中每个被R⁵取代0-3次。

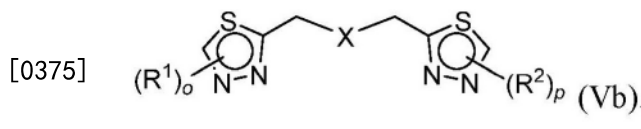
[0370] 在某些实施方案中,具有式(V)结构的化合物为具有式(Va)结构的化合物:



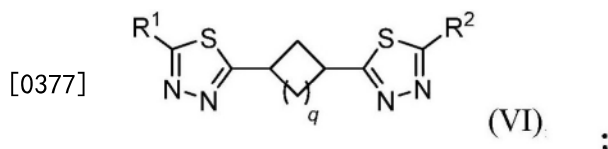
[0372] 在某些实施方案中,具有式(V)结构的化合物为具有式(Vb)结构的化合物:



[0374] 在某些实施方案中,具有式(V)结构的化合物具有式(Vc)结构:

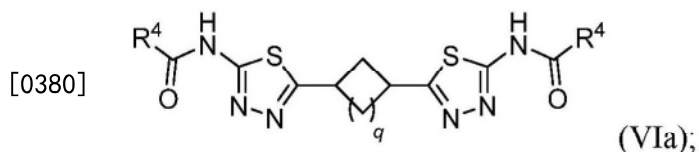


[0376] 在某些实施方案中,式(V)化合物为式(VI)化合物:



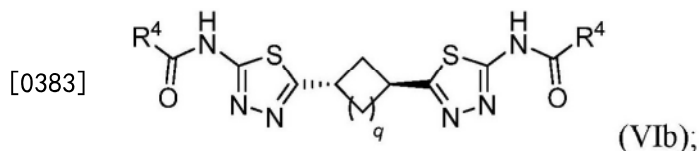
[0378] 其中q为0、1、2、3或4。

[0379] 在某些实施方案中,式(V)化合物具有式(VIa)结构:



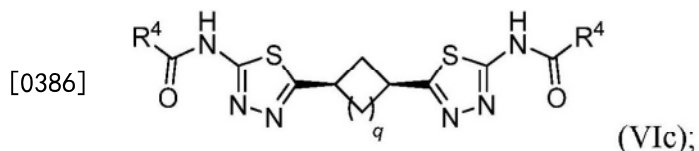
[0381] 其中q为0、1、2、3或4。

[0382] 在某些实施方案中,式(V)化合物具有式(VIb)结构:



[0384] 其中q为0、1、2、3或4。

[0385] 在某些实施方案中,式(V)化合物具有式(VIc)结构:



[0387] 其中q为0、1、2、3或4。

[0388] 式IV至VI化合物显示于附录A。在某些实施方案中,所述化合物选自附录A中公开的任何一种化合物。式IV至VI中任一个化合物在本文中或者称为“谷氨酰胺酶抑制剂”。

[0389] 在某些实施方案中,本发明的化合物可以是式I-VI化合物的前药,例如,其中母体化合物中的羟基以酯或碳酸酯形式存在,或存在于母体化合物中的羧酸以酯形式存在。在

某些这样的实施方案中,前体药物在体内代谢为活性母体化合物(例如酯水解成相应的羟基,或羧酸)。

[0390] 在某些实施方案中,本发明的化合物可以是外消旋的。在某些实施方案中,本发明的化合物可以富含一种对映异构体。例如,本发明的化合物可具有大于30%ee、40%ee、50%ee、60%ee、70%ee、80%ee、90%ee或甚至95%或更大的ee。在某些实施方案中,本发明的化合物可以具有多于一个立构中心。在某些这样的实施方案中,本发明的化合物可以富含一种或多种非对映异构体。例如,本发明的化合物可以具有大于30%de、40%de、50%de、60%de、70%de、80%de、90%de或甚至95%或更大de。

[0391] 在某些实施方案中,本发明涉及用式I-III化合物或其药学上可接受的盐治疗的方法。在某些实施方案中,本发明涉及用式IV-VI化合物(例如式(IV)、(IVa)、(IVb)、(V)、(Va)、(Vb)、(Vc)、(VI)、(VIa)、(VIb)或(VIc)中任一化合物)或其药学上可接受的盐治疗的方法。在某些实施方案中,治疗制剂可以富集以主要提供化合物(例如式I-III或式IV-VI化合物)的一种对映体。对映体富集的混合物可以包含例如至少60摩尔%的一种对映体,或者更优选至少75、90、95或甚至99摩尔%。在某些实施方案中,富含一种对映异构体的化合物基本上不含其他对映异构体,其中“基本上不含”意指所述物质,与例如在组合物或化合物混合物中的其它对映体的量比较,构成少于10%,或少于5%,或少于4%,或少于3%,或少于2%,或少于1%。例如,如果组合物或化合物混合物含有98克的第二种对映体和2克的第二种对映体,则可以说是含有98mol%的第一种对映体和仅含有2%的第二种对映体。

[0392] 在某些实施方案中,治疗制剂可以富集以主要提供化合物(例如式I-III或式IV-VI的化合物)的一种非对映体。非对映异构体富集的混合物可以包含例如至少60摩尔%的一种非对映异构体,或者更优选至少75、90、95或者甚至99摩尔%。

[0393] 在某些实施方案中,本发明提供了适合于口服给予人患者的药物制剂,其包含任何上述化合物(例如谷氨酰胺酶抑制剂,如式I-III化合物或式IV-VI中的任一化合物)和一种或多种药学上可接受的赋形剂。

[0394] 以上结构的任何一种的化合物可以用于制备治疗本文公开的任何疾病或病况的药物。

[0395] II. 化合物的用途

[0396] 谷氨酰胺作为氮、碳和能量的载体起着重要的作用。其用于肝脉合成、用于肾脏产氨作用(ammoniogenesis)、用于糖异生,和作为许多细胞的呼吸燃料。谷氨酰胺转化为谷氨酸通过线粒体酶谷氨酰胺酶(“GLS”)启动。有两种主要形式的酶,K-型和L-型,它们通过其对谷氨酰胺的Km值和对谷氨酸的反应来区别,其中Km值或米氏常数(Michaelis constant),是达到最大速率一半所需的底物浓度。L-型,也称为“肝-型”或GLS2,具有对谷氨酰胺的高Km并且为谷氨酸抗性的。K-型,也称为“肾-型”或GLS1,具有对谷氨酰胺的低Km并且受谷氨酸的抑制。GLS1的备选剪接形式,也称为谷氨酰胺酶C或“GAC”,最近已被鉴定并具有类似的GLS1活性特征。在某些实施方案中,所述化合物可选择性地抑制GLS1、GLS2和GAC。在某些优选的实施方案中,所述化合物选择性地抑制GLS1和GAC。

[0397] 除了用作蛋白合成的基本结构单元,还已经显示氨基酸对生长和分裂细胞至关重要的许多过程有贡献,并且这对于癌细胞尤其如此。几乎所有的癌症定义包括涉及失调的增殖。对癌症中的谷氨酰胺代谢的大量研究表明许多肿瘤是谷氨酰胺的饥渴消费者。因此,

在某些实施方案中,本发明提供了治疗或预防癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法,所述方法包括口服给予谷氨酰胺酶抑制剂(例如式I-III或式IV-VI的任一化合物(例如式(IV)、(IVa)、(IVb)、(V)、(Va)、(Vb)、(Vc)、(VI)、(VIa)、(VIb)或(VIc)的任一化合物)或其药学上可接受的盐),优选其中所述化合物与膳食一起给予。

[0398] 在某些实施方案中,癌症可以是以下的一种或其变体:急性淋巴母细胞性白血病(ALL)、急性骨髓性白血病(AML)、肾上腺皮质癌、AIDF-相关癌症(卡波济氏肉瘤和淋巴瘤)、肛门癌、阑尾癌、非典型畸胎样瘤/横纹肌样瘤(Atypical Teratoid/Rhabdoid Tumor)、基底细胞癌、胆管癌(包括肝外的)、膀胱癌、骨癌(包括骨肉瘤和恶性纤维组织细胞癌)、脑瘤(例如星形细胞瘤、脑和脊髓瘤、脑干胶质瘤、中枢神经系统非典型畸胎样瘤/横纹肌样瘤、中枢神经系统胚胎瘤、颅咽管瘤、成室管膜细胞瘤、室管膜瘤、成神经管细胞瘤、髓上皮瘤(Medulloepithelioma)、中分化松果体实质瘤(Pineal Parenchymal Tumors of Intermediate Differentiation)、幕上原始神经外胚层肿瘤(Supratentorial Primitive Neuroectodermal Tumors)和松果体母细胞瘤)、乳癌、支气管肿瘤、伯基特淋巴瘤、基底细胞癌、胆管癌(包括肝外的)、膀胱癌、骨癌(包括骨肉瘤和恶性纤维组织细胞癌)、类癌瘤、未知原发性癌、中枢神经系统(例如非典型畸胎样瘤/横纹肌样瘤、胚胎瘤和淋巴瘤)、子宫颈癌、儿童癌症、脊索瘤、慢性淋巴细胞白血病(CLL)、慢性粒细胞性白血病(CML)、慢性骨髓增殖性疾病、结肠癌、结肠直肠癌、颅咽管瘤、皮肤T-细胞淋巴瘤(蕈样肉芽肿(Mycosis Fungoides)和Sézary综合征)、胆管癌(Duct,Bile)(肝外的)、导管原位癌(Ductal Cancer In Situ(DCIS))、胚胎瘤(中枢神经系统)、子宫内膜癌、成室管膜细胞瘤、室管膜瘤、食管癌、嗅神经母细胞瘤(Esthesioneuroblastoma)、尤因肉瘤家族肿瘤、颅外胚细胞瘤(Extracranial Germ Cell Tumor)、性腺外生殖细胞瘤、肝外胆管癌、眼癌(像眼内黑色素瘤、视网膜母细胞瘤)、骨纤维组织细胞瘤(包括恶性和骨肉瘤)胆囊癌、胃(Gastric)(胃部(Stomach))癌症、胃肠道类癌瘤、胃肠道间质瘤(GIST)、胚细胞瘤(颅外胚细胞瘤、性腺外生殖细胞瘤、卵巢瘤)、妊娠滋养细胞肿瘤(Gestational Trophoblastic Tumor)、神经胶质瘤、毛细胞白血病、头颈癌、心脏癌症、肝细胞(肝)癌症、组织细胞增多症、郎格罕氏细胞、何杰金氏淋巴瘤、下咽癌、眼内黑色素瘤、胰岛细胞瘤(内分泌、胰腺)、卡波济氏肉瘤、肾(包括肾细胞)、郎格罕氏细胞组织细胞增多症、喉癌、白血病(包括急性成淋巴细胞白血病(ALL)、急性骨髓性白血病(AML)、慢性淋巴细胞白血病(CLL)、慢性骨髓性白血病(CML)、毛细胞白血病)、唇和口腔癌、肝癌(原发性)、原位小叶癌(LCIS)、肺癌(非小细胞和小细胞)、淋巴瘤(AIDS-相关的、伯基特淋巴瘤、皮肤T-细胞淋巴瘤(蕈样肉芽肿和Sézary综合征)、何杰金、非-何杰金、原发性中枢神经系统(CNS)、巨球蛋白血症(Macroglobulinemia)、瓦尔登斯特伦血症(Waldenström)、雄性乳腺癌、骨的恶性纤维组织细胞癌和骨肉瘤、成神经管细胞瘤、髓上皮瘤、黑色素瘤(包括眼内(眼))、梅克尔细胞癌(Merkel Cell Carcinoma)、间皮瘤(恶性)、隐匿性原发性转移鳞状颈癌(Metastatic Squamous Neck Cancer with Occult Primary)、涉及NUT基因的中线癌(Midline Tract Cancer Involving NUT Gene)、口腔癌、多发性内分泌瘤综合征、多发性骨髓瘤/浆细胞瘤、蕈样肉芽肿、骨髓增生异常综合征、骨髓增生异常/骨髓增生性肿瘤、慢性骨髓性白血病(CML)、急性骨髓性白血病(AML)、骨髓瘤和多发性骨髓瘤、骨髓增殖性病症(慢性)、鼻腔和副鼻窦癌症、鼻咽癌、成神经细胞瘤、非何杰金淋巴瘤、非小细胞肺癌、口癌、口腔癌、唇癌和口咽癌、骨肉瘤和骨的恶性纤维组织细胞

癌、卵巢癌(例如上皮、生殖细胞癌和低恶性潜在性肿瘤)、胰腺癌(包括胰岛细胞瘤)、乳头瘤病、副神经节瘤、副鼻窦和鼻腔癌症、副甲状腺癌、阴茎癌、咽癌、嗜铬细胞瘤、中分化松果体实质细胞肿瘤、松果体母细胞瘤和颅内幕上原始神经外胚层肿瘤、垂体瘤、浆细胞瘤/多发性骨髓瘤、胸膜肺母细胞瘤、妊娠与乳腺癌、原发性中枢神经系统(CNS)淋巴瘤、前列腺癌、直肠癌、肾细胞(肾)癌症、肾骨盆和输尿管、过渡细胞癌、视网膜母细胞瘤、横纹肌肉瘤、唾液腺癌、肉瘤(像肿瘤的尤因肉瘤家族肿瘤、卡波济氏肉瘤、软组织肉瘤、子宫肉瘤)、Sézary综合征、皮肤癌(例如黑色素瘤、梅克尔细胞癌、非黑色素瘤)、小细胞肺癌、小肠癌、软组织肉瘤、鳞状细胞癌、隐匿性原发性转移鳞状颈癌、转移性、胃(胃部)癌症、幕上原始神经外胚层肿瘤、T-细胞淋巴瘤(皮肤、蕈样肉芽肿和Sézary综合征)、睾丸癌、喉癌、胸腺瘤和胸腺癌、甲状腺癌、肾骨盆和输尿管的过渡细胞癌、滋养层肿瘤(妊娠)、未知的原发性的,儿童不寻常癌症、输尿管和肾骨盆的,过渡细胞癌、尿道癌、子宫癌、子宫内膜、子宫肉瘤、瓦尔登斯特伦巨球蛋白血症和维尔姆斯肿瘤。

[0399] 在某些情况下,致瘤突变促进谷氨酰胺代谢。表达致瘤K-Ras的细胞显示出谷氨酰胺利用的增加。在某些实施方案中,癌症细胞具有变异的K-Ras基因。在某些实施方案中,癌症与膀胱、骨髓、乳腺、结肠、肾、肝、肺、卵巢、胰腺、前列腺、皮肤或甲状腺的组织有关。已知c-Myc基因在许多癌症中有改变。增加的Myc蛋白表达与增加的谷氨酰胺酶的表达相关,导致谷氨酰胺代谢的上调。在某些实施方案中,癌症细胞具有致瘤c-Myc基因或升高的Myc蛋白表达。在某些实施方案中,癌症与膀胱、骨、肠、乳腺、中枢神经系统(像脑)、结肠、胃系统(例如胃和肠)、肝、肺、卵巢、前列腺、肌肉和皮肤的组织相关。

[0400] 例如,最常见类型的肾细胞癌(RCC)、透明细胞型(ccRCC)与von Hippel-Lindau(VHL)基因突变密切相关。由于缺乏从葡萄糖制造脂肪酸的能力,已经显示VHL缺陷型细胞系对谷氨酰胺的需求增加(Metallo等,Nature 2013)。这种对谷氨酰胺的依赖性使细胞对谷氨酰胺酶抑制剂敏感(Gameiro等,Cell Metab.2013)。本发明的某些实施方案涉及本文描述的化合物用于治疗VHL缺陷型癌症的用途。在某些实施方案中,癌症是RCC。在某些实施方案中,癌症是ccRCC。

[0401] EGFR(表皮生长因子受体)是细胞外蛋白质配体的表皮生长因子(EGF)家族成员的细胞表面受体。与EGFR过表达相关的突变已经与某些癌症相关,包括肺癌。美国大约10%的非小细胞肺癌患者和东亚约35%的nscLc患者患有与EGFR突变相关的肿瘤。通常,EGFR突变发生在编码一部分EGFR激酶结构域的基因区域中。通常,这样的突变导致基因扩增、增加的EGFR激酶活性和下游促生存信号传导途径的过度活化。参见A.Kuykendall等人(“Advanced EGFR Mutation-Positive Non-Small Cell Lung Cancer:Case Report,Literature Review,and Treatment Recommendations”Cancer Control,2014,V.21,No.1,67-73)关于NSCLC和EGFR突变的综述。

[0402] 谷氨酰胺酶抑制在某些具有TCA循环酶(包括延胡索酸水合酶(FH)、琥珀酸脱氢酶(SDH)和异柠檬酸脱氢酶(IDH))突变或缺失的罕见癌症中也可能是有效的。谷氨酸在这些突变或缺失发生的上游进入TCA循环。已发表的研究表明,谷氨酰胺代谢在富马酸盐和琥珀酸盐的合成中是重要的。除了FH和SDH之外,有证据表明谷氨酰胺有助于产生2-羟基戊二酸盐,另一个肿瘤形成的驱动因素是在患有携带异柠檬酸脱氢酶突变的肿瘤的患者中的累积。因此,谷氨酰胺酶抑制剂可通过限制上游起始材料的可得性来阻断这些突变或缺失的

作用。FH的罕见突变导致遗传性平滑肌瘤病和肾细胞癌(HLRCC)的发展,其中患者可以发展皮肤、子宫和肾脏的肿瘤。由于缺乏SDH表达而引起一些胃肠道间质瘤(GIST),并且通常是遗传性的。其他SDH功能丧失性突变发生在表现出称为副神经节瘤(paranglioma)的罕见头颈部癌以及称为嗜铬细胞瘤(pheochromocytoma)的罕见肾上腺或肾上腺外肾癌和罕见的罕见亚组透明细胞RCC的患者中。一些患有神经胶质瘤(一种类型的脑癌)、软骨肉瘤、罕见骨癌、胆管细胞癌、罕见胆管瘤、AML或高风险的骨髓增生异常/骨髓增殖性疾病(一类血液病)的患者具有IDH1或IDH2驱动突变。

[0403] 在本发明的某些实施方案中,本文所述的化合物可用于治疗鉴定具有FH、SDH或IDH(1和2)突变的疾病。例如,在某些实施方案中,所述疾病是异柠檬酸脱氢酶(IDH)-突变型实体瘤。在某些实施方案中,所述疾病是遗传性平滑肌瘤病或肾细胞癌(HLRCC)。在某些实施方案中,所述疾病是GIST(例如,SDH缺陷型GIST)、副神经节瘤、嗜铬细胞瘤或透明细胞RCC。在某些实施方案中,所述疾病是神经胶质瘤、软骨肉瘤、胆管细胞癌、急性骨髓性白血病(AML)或骨髓增生异常/骨髓增殖性疾病。在某些实施方案中,所述疾病是间皮瘤。在某些实施方案中,所述疾病是多发性骨髓瘤。

[0404] 在某些实施方案中,所述癌症是具有KRAS或EGFR突变的非小细胞肺癌。

[0405] 虽然许多癌症细胞的存活取决于外源性谷氨酰胺,但谷氨酰胺在肿瘤细胞亚型中的依赖程度可使得细胞群更容易受谷氨酰胺的减少的影响。作为一个例子,乳腺癌的基因表达分析已鉴定5个内在亚型(腔(luminal)A、腔B、基底的(basal)、HER2+和正常-样)。虽然谷氨酰胺缺乏对细胞生长和生存力具有影响,基底样细胞似乎对外源性谷氨酰胺的减少更加敏感。这支持了谷氨酰胺是基底样乳腺癌细胞系中的非常重要的能量来源的概念,并表明谷氨酰胺酶的抑制作用在治疗包含基底样细胞的乳腺癌中将是有利的。三阴乳腺癌(TNBC)的特征在于缺乏雌激素受体、孕酮受体和人上皮生长因子受体2表达。这种癌症在化学疗法后具有较高的复发率,以及与其它乳腺癌亚型相比的较差预后。有趣的是,在TNBC细胞和基底样乳腺癌细胞之间的代谢概况中似乎有着明显的相似性。因此,本发明的一个实施方案为本文所述的化合物用于治疗TNBC、基底-型乳腺癌或claudin-low型乳腺癌的用途。

[0406] 在某些实施方案中,本发明提供了治疗结肠直肠癌的方法。在某些实施方案中,本发明提供了治疗内分泌癌症的方法,所述内分泌癌症例如肾上腺皮质腺瘤、肾上腺皮质癌、肾上腺嗜铬细胞瘤和甲状旁腺腺瘤。

[0407] 在某些实施方案中,所述癌症是黑素瘤。

[0408] 恶病质即肌肉质量的大量丧失常常与癌症患者的差的功能状态和高的死亡率有关。这种过程背后的理论是肿瘤需要比由膳食正常供应的更多的谷氨酰胺,所以肌肉,谷氨酰胺的主要来源,开始分解以向肿瘤供应足够的营养素。因此,抑制谷氨酰胺酶可以减少对分解肌肉的需要。本发明的一个实施方案为本化合物预防、抑制或减轻恶病质的用途。

[0409] 最常见的神经递质是谷氨酸,其衍生自谷氨酰胺经由谷氨酰胺酶的酶促转化。已显示高水平的谷氨酸是神经毒性的。在对神经元细胞的创伤损害后,出现神经递质释放的升高,特别是谷氨酸。因此,谷氨酰胺酶的抑制作用已被假设为缺血性损害,例如中风后的治疗的一种手段(PCT公开号WO 99/09825)。亨廷顿氏病(Huntington's disease)是一种进行性、致命性神经性疾病。在亨廷顿氏病的遗传小鼠模型中,观察到该病的早期表现与失调

的谷氨酸释放相关。在HIV-相关痴呆中,HIV感染的巨噬细胞表现出谷氨酰胺酶活性上调和谷氨酸释放增加,导致神经元损伤。类似地,在另一种神经性疾病中,在雷特综合征(Rett Syndrome)中的激活的小胶质细胞释放谷氨酸,引起神经元损害。过量的谷氨酸释放已与谷氨酰胺酶的上调相关。在经繁殖而减少谷氨酰胺酶水平的小鼠中,对精神病刺激性药物,例如安非他明的敏感性被极大地降低,因此表明谷氨酰胺酶抑制作用在治疗精神分裂症中可为有益的。双相型障碍是一种破坏性疾病,其以狂躁和抑郁的反复发作为标志。这种疾病用情绪稳定剂例如锂和丙戊酸盐治疗;然而,这些药物的长期使用似乎增加谷氨酸受体的丰度,其可导致药物的有效性随时间的推移而降低。因此,可供选择的治疗可以通过抑制谷氨酰胺酶而减少谷氨酸的量。这可以与或不与情绪稳定剂联合使用。美金刚,一种N-甲基-D-天冬氨酸受体(NMDAR)的部分拮抗剂,是经批准治疗阿尔茨海默氏病的治疗剂。当前,正在进行将美金刚视为治疗血管性痴呆和帕金森氏病的手段的研究。因为已显示美金刚也部分地阻断NMDA谷氨酸受体,有理由推测通过抑制谷氨酰胺酶来降低谷氨酸水平也可治疗阿尔茨海默氏病、血管性痴呆和帕金森氏病。阿尔茨海默氏病、双相型障碍、HIV-相关痴呆、亨廷顿氏病、缺血性损害、帕金森氏病、精神分裂症、中风、创伤性损害和血管性痴呆仅仅是几种与增加的谷氨酸水平相关的神经性疾病。因此,用本文描述的化合物抑制谷氨酰胺酶可减轻或预防神经性疾病。因此,在某些实施方案中,所述化合物可以用于治疗或预防神经性疾病。

[0410] T淋巴细胞的激活诱导细胞生长、增殖和细胞因子产生,从而使细胞具有能量和生物合成需求。谷氨酰胺用作核苷酸合成的胺供体,而谷氨酸,谷氨酰胺代谢中的第一个成分,在氨基酸和谷胱甘肽合成中起直接的作用,以及能够进入用于能量产生的三羧酸循环。有丝分裂原-诱导的T细胞增殖和细胞因子产生需要高水平的谷氨酰胺代谢,因此抑制谷氨酰胺酶可用作免疫调节的手段。在多发性硬化,即一种炎性自身免疫性疾病中,激活的小胶质细胞显示出上调的谷氨酰胺酶和释放增加的细胞外谷氨酸水平。谷氨酰胺水平经脓毒症、损伤、烧伤、手术和耐力训练而降低。这些情形将个体置于免疫抑制的危险中。事实上,一般来说,谷氨酰胺酶基因表达和酶活性两者在T细胞活动期间均增加。骨髓移植后给予谷氨酰胺的患者导致较低水平的感染和减少的移植物抗宿主疾病。T细胞增殖和激活涉及许多免疫性疾病,例如炎性肠病、克罗恩病、脓毒症、牛皮癣、关节炎(包括类风湿性关节炎)、多发性硬化、移植物抗宿主疾病、感染、狼疮和糖尿病。在本发明的一个实施方案中,本文所述的化合物可用于治疗或预防免疫性疾病。

[0411] 肝性脑病(HE)表示肝病患者或门体分流术后患者中的一系列短暂性和可逆性神经和精神病功能障碍。HE不是一种单一的临床实体并可反映可逆性代谢性脑病、脑萎缩、脑水肿,或这些因素的组合;然而,目前的假设是大部分来自肠的氨的积聚在病理生理学方面起关键作用。谷氨酰胺在小肠、肾和肌肉合成中的脱氨作用都有利于氨的产生。由肝细胞清除或门体分流术造成的受损肝清除引起氨的积聚增加。氨毒性经由谷氨酰胺合成酶而影响脑中的星形胶质细胞,所述谷氨酰胺合成酶使氨代谢以产生增加的谷氨酰胺。谷氨酰胺继而将水吸收进星形胶质细胞,导致线粒体肿胀和氧化性功能障碍。所产生的脑水肿被认为引起在HE中观察到的神经功能障碍。在本发明的一个实施方案中,本文所述的化合物可用于治疗或预防HE。

[0412] 已显示出背根神经节中的初级感觉神经元在炎症后升高其谷氨酰胺酶活性。认为

作为结果的增加的谷氨酸产生促使中枢和外周二者敏感化,确定为疼痛。本发明的一个方面为本文的化合物用于治疗或减轻疼痛的用途。在某些实施方案中,疼痛可以是神经性疼痛、化学疗法-诱导的疼痛或炎性疼痛。

[0413] 高血糖水平、高胰岛素水平和胰岛素抵抗是发展糖尿病的危险因素。类似地,高血压是发生心血管疾病的危险因素。在最近得自大规模的人群组(cohort)研究的报告中,这四种危险因素与血流中的谷氨酰胺-对-谷氨酸的比率呈负相关性。此外,血浆谷氨酰胺-对-谷氨酸的比率与糖尿病在12年中的最终发病率呈负相关性。采用动物模型的实验与这些结果一致。喂给富含谷氨酰胺饮食的小鼠在空腹6小时后的葡萄糖耐受试验中表现出较低的血糖水平,和将谷氨酰胺腹膜内注射进入小鼠快速地降低其血压。因此,似乎合理的是谷氨酰胺酶抑制剂,其引起谷氨酰胺水平增加并降低谷氨酸水平,将降低糖尿病和心血管性疾病的发病率。特别是,肝和小肠是患糖尿病动物的谷氨酰胺利用的主要场所,而谷氨酰胺酶活性在链脲霉素(streptozotocin)-诱导的糖尿病大鼠的这些器官中高于正常。在本发明的一个实施方案中,本文所述的化合物可用于治疗糖尿病。在本发明的另一个实施方案中,本化合物可用于降低高血压。

[0414] 在某些实施方案中,所述治疗或预防癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法可以包括口服给予本发明的化合物,例如式I-III或式IV-VI中任一种的化合物(例如式(IV)、(IVa)、(IVb)、(V)、(Va)、(Vb)、(Vc)、(VI)、(VIa)、(VIb)或(VIc)化合物中任一种的谷氨酰胺酶)或其药学上可接受的盐,例如与膳食一起,与化学治疗剂联合。可与本发明化合物联合给予的化学治疗剂包括:ABT-263、氨鲁米特(aminoglutethimide)、安吡啶(amsacrine)、阿那曲唑(anastrozole)、天冬酰胺酶(asparaginase)、阿扎胞苷(azacitidine)、AZD5363、卡介苗(bcg)(Bacillus Calmette-Guérin vaccine(bcg))、比卡鲁胺(bicalutamide)、博来霉素(bleomycin)、硼替佐米(bortezomib)、布塞瑞林(buserelin)、白消安(busulfan)、喜树碱(camptothecin)、卡培他滨(capecitabine)、卡铂(carboplatin)、卡非佐米(carfilzomib)、卡莫司汀(carmustine)、苯丁酸氮芥(chlorambucil)、氯喹(chloroquine)、顺铂(cisplatin)、克拉屈滨(cladribine)、氯膦酸盐(clodronate)、考比替尼(cobimetinib)、秋水仙碱(colchicine)、环磷酰胺(cyclophosphamide)、环丙孕酮(cyproterone)、阿糖胞苷(cytarabine)、达卡巴嗪(dacarbazine)、更生霉素(dactinomycin)、柔红霉素(daunorubicin)、脱甲绿胶酶素(demethoxyviridin)、地塞米松(dexamethasone)、二氯乙酸酯(dichloroacetate)、双烯雌酚(dienestrol)、己烯雌酚(diethylstilbestrol)、多西他赛(docetaxel)、阿霉素(doxorubicin)、表柔比星(epirubicin)、艾日布林(eribulin)、厄洛替尼(erlotinib)、雌二醇(estradiol)、雌莫司汀(estramustine)、依托泊苷(etoposide)、依维莫司(everolimus)、依西美坦(exemestane)、非格司亭(filgrastim)、氟达拉滨(fludarabine)、氟氢可的松(fludrocortisone)、氟尿嘧啶(flurouracil(例如5-氟尿嘧啶))、氟甲睾酮(flouxymesterone)、氟他胺(flutamide)、吉西他滨(gemcitabine)、染料木黄酮(genistein)、戈舍瑞林(goserelin)、羟基脲(hydroxyurea)、伊达比星(idarubicin)、异环磷酰胺(ifosfamide)、伊马替尼(imatinib)、干扰素(interferon)、伊立替康(irinotecan)、伊沙匹隆(ixabepilone)、来那度胺(lenalidomide)、来曲唑(letrozole)、亚叶酸(leucovorin)、亮丙瑞林(leuprolide)、左旋咪唑(levamisole)、洛莫

司汀 (lomustine)、氯尼达明 (lonidamine)、氮芥 (mechlorethamine)、甲羟孕酮 (medroxyprogesterone)、甲地孕酮 (megestrol)、美法仑 (melphalan)、巯基嘌呤 (mercaptopurine)、美司钠 (mesna)、二甲双胍 (metformin)、甲氨蝶呤 (methotrexate)、米替福新 (miltefosine)、丝裂霉素 (mitomycin)、米托坦 (mitotane)、米托蒽醌 (mitoxantrone)、MK-2206、尼鲁米特 (nilutamide)、诺考达唑 (nocodazole)、奥曲肽 (octreotide)、奥沙利铂 (oxaliplatin)、奥拉帕尼 (olaparib)、紫杉醇 (paclitaxel)、帕米膦酸盐 (pamidronate)、帕唑帕尼 (pazopanib)、喷司他丁 (pentostatin)、哌立福辛 (perifosine)、PF-04691502、普卡霉素 (plicamycin)、泊马度胺 (pomalidomide)、吡吩姆 (porfimer)、丙卡巴肼 (procarbazine)、雷替曲塞 (raltitrexed)、利妥昔单抗 (rituximab)、罗米地新 (romidepsin)、rucaparib、司美替尼 (selumetinib)、索拉非尼 (sorafenib)、链佐星 (streptozocin)、舒尼替尼 (sunitinib)、苏拉明 (suramin)、talazoparib、他莫昔芬 (tamoxifen)、替莫唑胺 (temozolomide)、坦罗莫司 (temsirrolimus)、替尼泊苷 (teniposide)、睾酮 (testosterone)、硫鸟嘌呤 (thioguanine)、沙利度胺 (thalidomide)、塞替派 (thiotepa)、二氯环戊二烯钛 (titanocene dichloride)、拓扑替康 (topotecan)、曲美替尼 (trametinib)、曲妥珠单抗 (trastuzumab)、维甲酸 (tretinoin)、艾伯维 (veliparib)、长春碱 (vinblastine)、长春新碱 (vincristine)、长春地辛 (vindesine)、长春瑞滨 (vinorelbine) 和伏立诺他 (vorinostat) (SAHA)。

[0415] 在某些实施方案中,所述一种或多种另外的化学治疗剂选自:阿扎胞苷 (azacitidine)、硼替佐米 (bortezomib)、卡培他滨 (capecitabine)、卡铂 (carboplatin)、卡非佐米 (carfilzomib)、环磷酰胺 (cyclophosphamide)、柔红霉素 (daunorubicin)、地塞米松 (dexamethasone)、多西他赛 (docetaxel)、阿霉素 (doxorubicin)、表柔比星 (epirubicin)、艾日布林 (eribulin)、厄洛替尼 (erlotinib)、依维莫司 (everolimus)、氟尿嘧啶 (fluorouracil)、吉西他滨 (gemcitabine)、伊沙匹隆 (ixabepilone)、来那度胺 (lenalidomide)、甲氨蝶呤 (methotrexate)、米托蒽醌 (mitoxantrone)、自力霉素 (mutamycin)、紫杉醇 (paclitaxel)、泊马度胺 (pomalidomide)、利妥昔单抗 (rituximab)、塞替派 (thiotepa)、长春新碱 (vincristine) 和长春瑞滨 (vinorelbine)。

[0416] 在某些实施方案中,所述一种或多种另外的化学治疗剂选自阿扎胞苷 (azacitidine)、地塞米松 (dexamethasone)、多西他赛 (docetaxel)、厄洛替尼 (erlotinib)、依维莫司 (everolimus)、紫杉醇 (paclitaxel) 和泊马度胺 (pomalidomide)。

[0417] 已经开发了许多用于治疗癌症的联合疗法。在某些实施方案中,本发明的化合物可以联合疗法联合给予。表3中包括了本发明化合物可与之联合给予的联合疗法的实例。

[0418] 表3:用于治疗癌症的示例性联合疗法。

[0419]

名称	治疗剂
ABV	阿霉素(Doxorubicin)，博来霉素(Bleomycin)，长春碱(Vinblastine)
ABVD	阿霉素(Doxorubicin)，博来霉素(Bleomycin)，长春碱(Vinblastine)，达卡巴嗪(Dacarbazine)
AC (乳腺)	阿霉素(Doxorubicin)，环磷酰胺(Cyclophosphamide)
AC (肉瘤)	阿霉素(Doxorubicin)，顺铂(Cisplatin)

[0420]

名称	治疗剂
AC (成神经细胞瘤)	环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin)
ACE	环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin), 依托泊苷(Etoposide)
ACe	环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin)
AD	阿霉素(Doxorubicin), 达卡巴嗪(Dacarbazine)
AP	阿霉素(Doxorubicin), 顺铂(Cisplatin)
ARAC-DNR	阿糖胞苷(Cytarabine), 柔红霉素(Daunorubicin)
B-CAVe	博来霉素(Bleomycin), 洛莫司汀(Lomustine), 阿霉素 (Doxorubicin), 长春碱(Vinblastine)
BCVPP	卡莫司汀(Carmustine), 环磷酰胺(Cyclophosphamide), 长春碱(Vinblastine), 丙卡巴肼(Procarbazine), 泼尼松 (Prednisone)
BEACOPP	博来霉素(Bleomycin), 依托泊苷(Etoposide), 阿霉素 (Doxorubicin), 环磷酰胺(Cyclophosphamide), 长春新碱 (Vincristine), 丙卡巴肼(Procarbazine), 泼尼松 (Prednisone), 非格司亭(Filgrastim)
BEP	博来霉素(Bleomycin), 依托泊苷(Etoposide), 顺铂 (Cisplatin)
BIP	博来霉素(Bleomycin), 顺铂(Cisplatin), 异环磷酰胺 (Ifosfamide), 美司钠(Mesna)
BOMP	博来霉素(Bleomycin), 长春新碱(Vincristine), 顺铂

[0421]

名称	治疗剂
	(Cisplatin), 丝裂霉素(Mitomycin)
CA	阿糖胞苷(Cytarabine), 天冬酰胺酶(Asparaginase)
CABO	顺铂(Cisplatin), 甲氨蝶呤(Methotrexate), 博来霉素(Bleomycin), 长春新碱(Vincristine)
CAF	环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin), 氟尿嘧啶(Fluorouracil)
CAL-G	环磷酰胺(Cyclophosphamide), 柔红霉素(Daunorubicin), 长春新碱(Vincristine), 泼尼松(Prednisone), 天冬酰胺酶(Asparaginase)
CAMP	环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin), 甲氨蝶呤(Methotrexate), 丙卡巴肼(Procarbazine)
CAP	环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin), 顺铂(Cisplatin)
CaT	卡铂(Carboplatin), 紫杉醇(Paclitaxel)
CAV	环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin), 长春新碱(Vincristine)
CAVE ADD	CAV 和依托泊苷(Etoposide)
CA-VP16	环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin), 依托泊苷(Etoposide)
CC	环磷酰胺(Cyclophosphamide), 卡铂(Carboplatin)
CDDP/VP-16	顺铂(Cisplatin), 依托泊苷(Etoposide)

[0422]

名称	治疗剂
CEF	环磷酰胺(Cyclophosphamide), 表柔比星(Epirubicin), 氟尿嘧啶(Fluorouracil)
CEPP(B)	环磷酰胺(Cyclophosphamide), 依托泊苷(Etoposide), 泼尼松(Prednisone), 与或不与博来霉素(Bleomycin) 一起
CEV	环磷酰胺(Cyclophosphamide), 依托泊苷(Etoposide), 长春新碱(Vincristine)
CF	顺铂 (Cisplatin) , 氟尿嘧啶 (Fluorouracil) 或卡铂 (Carboplatin), 氟尿嘧啶(Fluorouracil)
CHAP	环磷酰胺 (Cyclophosphamide) 或 环磷酰胺 (Cyclophosphamide), 三乙蜜胺(Altretamine), 阿霉素 (Doxorubicin), 顺铂(Cisplatin)
ChIVPP	苯丁酸氮芥(Chlorambucil), 长春碱(Vinblastine), 丙卡巴肼(Procarbazine), 泼尼松(Prednisone)
CHOP	环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin), 长春新碱(Vincristine), 泼尼松(Prednisone)
CHOP-BLEO	将博来霉素(Bleomycin) 加入 CHOP
CISCA	环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin), 顺铂(Cisplatin)
CLD-BOMP	博来霉素(Bleomycin) , 顺铂(Cisplatin) , 长春新碱 (Vincristine), 丝裂霉素(Mitomycin)

[0423]

名称	治疗剂
CMF	甲氨蝶呤(Methotrexate), 氟尿嘧啶(Fluorouracil), 环磷酰胺(Cyclophosphamide)
CMFP	环磷酰胺 (Cyclophosphamide) , 甲氨蝶呤 (Methotrexate) , 氟尿嘧啶 (Fluorouracil) , 泼尼松 (Prednisone)
CMFVP	环磷酰胺 (Cyclophosphamide) , 甲氨蝶呤 (Methotrexate) , 氟尿嘧啶 (Fluorouracil) , 长春新碱 (Vincristine), 泼尼松(Prednisone)
CMV	顺铂(Cisplatin) , 甲氨蝶呤(Methotrexate) , 长春碱 (Vinblastine)
CNF	环磷酰胺 (Cyclophosphamide) , 米托蒽醌 (Mitoxantrone), 氟尿嘧啶(Fluorouracil)
CNOP	环磷酰胺 (Cyclophosphamide) , 米托蒽醌 (Mitoxantrone) , 长春新碱 (Vincristine) , 泼尼松 (Prednisone)
COB	顺铂(Cisplatin) , 长春新碱(Vincristine) , 博来霉素 (Bleomycin)
CODE	顺铂(Cisplatin) , 长春新碱 (Vincristine) , 阿霉素 (Doxorubicin), 依托泊苷(Etoposide)
COMLA	环磷酰胺(Cyclophosphamide), 长春新碱(Vincristine), 甲氨蝶呤(Methotrexate), 亚叶酸(Leucovorin), 阿糖胞苷 (Cytarabine)

[0424]

名称	治疗剂
COMP	环磷酰胺(Cyclophosphamide), 长春新碱(Vincristine), 甲氨蝶呤(Methotrexate), 泼尼松(Prednisone)
Cooper Regimen	环磷酰胺 (Cyclophosphamide) , 甲氨蝶呤 (Methotrexate), 氟尿嘧啶(Fluorouracil), 长春新碱 (Vincristine), 泼尼松(Prednisone)
COP	环磷酰胺(Cyclophosphamide), 长春新碱(Vincristine), 泼尼松(Prednisone)
COPE	环磷酰胺(Cyclophosphamide), 长春新碱(Vincristine), 顺铂(Cisplatin), 依托泊苷(Etoposide)
COPP	环磷酰胺(Cyclophosphamide), 长春新碱(Vincristine), 丙卡巴肼(Procarbazine), 泼尼松(Prednisone)
CP(慢性淋巴细胞性白血 病)	苯丁酸氮芥(Chlorambucil), 泼尼松(Prednisone)
CP (卵巢癌)	环磷酰胺(Cyclophosphamide), 顺铂(Cisplatin)
CT	顺铂(Cisplatin), 紫杉醇(Paclitaxel)
CVD	顺铂 (Cisplatin) , 长春碱 (Vinblastine) , 达卡巴嗪 (Dacarbazine)
CVI	卡铂(Carboplatin), 依托泊苷(Etoposide), 异环磷酰胺 (Ifosfamide), 美司钠(Mesna)
CVP	环磷酰胺(Cyclophosphamide), 长春新碱(Vincristine), 泼尼松(Prednisone)

[0425]

名称	治疗剂
CVPP	洛莫司汀(Lomustine), 丙卡巴肼(Procarbazine), 泼尼松(Prednisone)
CYVADIC	环磷酰胺(Cyclophosphamide), 长春新碱(Vincristine), 阿霉素(Doxorubicin), 达卡巴嗪(Dacarbazine)
DA	柔红霉素(Daunorubicin), 阿糖胞苷(Cytarabine)
DAT	柔红霉素(Daunorubicin), 阿糖胞苷(Cytarabine), 硫鸟嘌呤(Thioguanine)
DAV	柔红霉素(Daunorubicin), 阿糖胞苷(Cytarabine), 依托泊苷(Etoposide)
DCT	柔红霉素(Daunorubicin), 阿糖胞苷(Cytarabine), 硫鸟嘌呤(Thioguanine)
DHAP	顺铂(Cisplatin), 阿糖胞苷(Cytarabine), 地塞米松(Dexamethasone)
DI	阿霉素(Doxorubicin), 异环磷酰胺(Ifosfamide)
DTIC/ 他莫昔芬 (Tamoxifen)	达卡巴嗪(Dacarbazine), 他莫昔芬(Tamoxifen)
DVP	柔红霉素(Daunorubicin), 长春新碱(Vincristine), 泼尼松(Prednisone)
EAP	依托泊苷(Etoposide), 阿霉素(Doxorubicin), 顺铂(Cisplatin)
EC	依托泊苷(Etoposide), 卡铂(Carboplatin)
EFP	依托泊苷(Etoposide), 氟尿嘧啶(Fluorouracil), 顺铂

[0426]

名称	治疗剂
	(Cisplatin)
ELF	依托泊苷(Etoposide), 亚叶酸(Leucovorin), 氟尿嘧啶(Fluorouracil)
EMA 86	米托蒽醌(Mitoxantrone), 依托泊苷(Etoposide), 阿糖胞苷(Cytarabine)
EP	依托泊苷(Etoposide), 顺铂(Cisplatin)
EVA	依托泊苷(Etoposide), 长春碱(Vinblastine)
FAC	氟尿嘧啶(Fluorouracil), 阿霉素(Doxorubicin), 环磷酰胺(Cyclophosphamide)
FAM	氟尿嘧啶(Fluorouracil), 阿霉素(Doxorubicin), 丝裂霉素(Mitomycin)
FAMTX	甲氨蝶呤(Methotrexate), 亚叶酸(Leucovorin), 阿霉素(Doxorubicin)
FAP	氟尿嘧啶(Fluorouracil), 阿霉素(Doxorubicin), 顺铂(Cisplatin)
F-CL	氟尿嘧啶(Fluorouracil), 亚叶酸(Leucovorin)
FEC	氟尿嘧啶(Fluorouracil), 环磷酰胺(Cyclophosphamide), 表柔比星(Epirubicin)
FED	氟尿嘧啶(Fluorouracil), 依托泊苷(Etoposide), 顺铂(Cisplatin)
FL	氟他米特(Flutamide), 亮丙瑞林(Leuprolide)
FZ	氟他米特(Flutamide), 乙酸戈舍瑞林(Goserelin acetate)

[0427]

名称	治疗剂
	植入物
HDMTX	甲氨蝶呤(Methotrexate), 亚叶酸(Leucovorin)
Hexa-CAF	三乙蜜胺(Altretamine), 环磷酰胺(Cyclophosphamide), 甲氨蝶呤(Methotrexate), 氟尿嘧啶(Fluorouracil)
ICE-T	异环磷酰胺>Ifosfamide), 卡铂(Carboplatin), 依托泊苷 (Etoposide), 紫杉醇(Paclitaxel), 美司钠(Mesna)
IDMTX/6-MP	甲氨蝶呤(Methotrexate), 巯基嘌呤(Mercaptopurine), 亚叶酸(Leucovorin)
IE	异环磷酰胺>Ifosfamide), 依托泊苷(Etoposide), 美司钠 (Mesna)
IfoVP	异环磷酰胺>Ifosfamide), 依托泊苷(Etoposide), 美司钠 (Mesna)
IPA	异环磷酰胺>Ifosfamide), 顺铂(Cisplatin), 阿霉素 (Doxorubicin)
M-2	长春新碱(Vincristine), 卡莫司汀(Carmustine), 环磷酰 胺(Cyclophosphamide), 泼尼松(Prednisone), 美法仑 (Melfalan)
MAC-III	甲氨蝶呤(Methotrexate), 亚叶酸(Leucovorin), 更生霉 素(Dactinomycin), 环磷酰胺(Cyclophosphamide)
MACC	甲氨蝶呤(Methotrexate), 阿霉素(Doxorubicin), 环磷酰 胺(Cyclophosphamide), 洛莫司汀(Lomustine)

[0428]

名称	治疗剂
MACOP-B	甲氨蝶呤(Methotrexate), 亚叶酸(Leucovorin), 阿霉素(Doxorubicin), 环磷酰胺(Cyclophosphamide), 长春新碱(Vincristine), 博来霉素(Bleomycin), 泼尼松(Prednisone)
MAID	美司钠(Mesna), 阿霉素(Doxorubicin), 异环磷酰胺(Ifosfamide), 达卡巴嗪(Dacarbazine)
m-BACOD	博来霉素(Bleomycin), 阿霉素(Doxorubicin), 环磷酰胺(Cyclophosphamide), 长春新碱(Vincristine), 地塞米松(Dexamethasone), 甲氨蝶呤(Methotrexate), 亚叶酸(Leucovorin)
MBC	甲氨蝶呤(Methotrexate), 博来霉素(Bleomycin), 顺铂(Cisplatin)
MC	米托蒽醌(Mitoxantrone), 阿糖胞苷(Cytarabine)
MF	甲氨蝶呤(Methotrexate), 氟尿嘧啶(Fluorouracil), 亚叶酸(Leucovorin)
MICE	异环磷酰胺(Ifosfamide), 卡铂(Carboplatin), 依托泊苷(Etoposide), 美司钠(Mesna)
MINE	美司钠(Mesna), 异环磷酰胺(Ifosfamide), 米托蒽醌(Mitoxantrone), 依托泊苷(Etoposide)
mini-BEAM	卡莫司汀(Carmustine), 依托泊苷(Etoposide), 阿糖胞苷(Cytarabine), 美法仑(Melphalan)
MOBP	博来霉素(Bleomycin), 长春新碱(Vincristine), 顺铂

[0429]

名称	治疗剂
	(Cisplatin), 丝裂霉素(Mitomycin)
MOP	氮芥(Mechlorethamine), 长春新碱(Vincristine), 丙卡巴肼(Procarbazine)
MOPP	氮芥(Mechlorethamine), 长春新碱(Vincristine), 丙卡巴肼(Procarbazine), 泼尼松(Prednisone)
MOPP/ABV	氮芥(Mechlorethamine), 长春新碱(Vincristine), 丙卡巴肼(Procarbazine), 泼尼松(Prednisone), 阿霉素(Doxorubicin), 博来霉素(Bleomycin), 长春碱(Vinblastine)
MP (多发性骨髓瘤)	美法仑(Melphalan), 泼尼松(Prednisone)
MP (前列腺癌)	米托蒽醌(Mitoxantrone), 泼尼松(Prednisone)
MTX/6-MO	甲氨蝶呤(Methotrexate), 巯基嘌呤(Mercaptopurine)
MTX/6-MP/VP	甲氨蝶呤(Methotrexate), 巯基嘌呤(Mercaptopurine), 长春新碱(Vincristine), 泼尼松(Prednisone)
MTX-CDDPAdr	甲氨蝶呤(Methotrexate), 亚叶酸(Leucovorin), 顺铂(Cisplatin), 阿霉素(Doxorubicin)
MV (乳腺癌)	丝裂霉素(Mitomycin), 长春碱(Vinblastine)
MV (急性髓细胞白血病)	米托蒽醌(Mitoxantrone), 依托泊苷(Etoposide)
M-VAC 甲氨蝶呤(Methotrexate)	长春碱(Vinblastine), 阿霉素(Doxorubicin), 顺铂(Cisplatin)

[0430]

名称	治疗剂
MVP 丝裂霉素 (Mitomycin)	长春碱(Vinblastine), 顺铂(Cisplatin)
MVPP	氮芥(Mechlorethamine), 长春碱(Vinblastine), 丙卡巴 肼(Procarbazine), 泼尼松(Prednisone)
NFL	米托蒽醌(Mitoxantrone), 氟尿嘧啶(Fluorouracil), 亚叶 酸(Leucovorin)
NOVP	米托蒽醌(Mitoxantrone), 长春碱(Vinblastine), 长春新 碱(Vincristine)
OPA	长春新碱(Vincristine), 泼尼松(Prednisone), 阿霉素 (Doxorubicin)
OPPA	将丙卡巴肼(Procarbazine)加入 OPA.
PAC	顺铂(Cisplatin), 阿霉素(Doxorubicin)
PAC-I	顺铂(Cisplatin), 阿霉素(Doxorubicin), 环磷酰胺 (Cyclophosphamide)
PA-CI	顺铂(Cisplatin), 阿霉素(Doxorubicin)
PC	紫杉醇(Paclitaxel), 卡铂(Carboplatin) 或 紫杉醇 (Paclitaxel), 顺铂(Cisplatin)
PCV	洛莫司汀(Lomustine), 丙卡巴肼(Procarbazine), 长春新 碱(Vincristine)
PE	紫杉醇(Paclitaxel), 雌氮芥(Estramustine)
PFL	顺铂(Cisplatin), 氟尿嘧啶(Fluorouracil), 亚叶酸 (Leucovorin)

[0431]

名称	治疗剂
POC	泼尼松(Prednisone), 长春新碱(Vincristine), 洛莫司汀(Lomustine)
ProMACE	泼尼松(Prednisone), 甲氨蝶呤(Methotrexate), 亚叶酸(Leucovorin), 阿霉素(Doxorubicin), 环磷酰胺(Cyclophosphamide), 依托泊苷(Etoposide)
ProMACE/cytaBOM	泼尼松(Prednisone), 阿霉素(Doxorubicin), 环磷酰胺(Cyclophosphamide), 依托泊苷(Etoposide), 阿糖胞苷(Cytarabine), 博来霉素(Bleomycin), 长春新碱(Vincristine), 甲氨蝶呤(Methotrexate), 亚叶酸(Leucovorin), 复方新诺明(Cotrimoxazole)
PRoMACE/MOPP	泼尼松(Prednisone), 阿霉素(Doxorubicin), 环磷酰胺(Cyclophosphamide), 依托泊苷(Etoposide), 氮芥(Mechlorethamine), 长春新碱(Vincristine), 丙卡巴肼(Procarbazine), 甲氨蝶呤(Methotrexate), 亚叶酸(Leucovorin)
Pt/VM	顺铂(Cisplatin), 替尼泊苷(Teniposide)
PVA	泼尼松(Prednisone), 长春新碱(Vincristine), 天冬酰胺酶(Asparaginase)
PVB	顺铂(Cisplatin), 长春碱(Vinblastine), 博来霉素(Bleomycin)
PVDA	泼尼松(Prednisone), 长春新碱(Vincristine), 柔红霉素

[0432]

名称	治疗剂
	(Daunorubicin), 天冬酰胺酶(Asparaginase)
SMF	链佐星(Streptozocin), 丝裂霉素(Mitomycin), 氟尿嘧啶(Fluorouracil)
TAD	氮芥(Mechlorethamine), 阿霉素(Doxorubicin), 长春碱(Vinblastine), 长春新碱(Vincristine), 博来霉素(Bleomycin), 依托泊苷(Etoposide), 泼尼松(Prednisone)
TCF	紫杉醇(Paclitaxel), 顺铂(Cisplatin), 氟尿嘧啶(Fluorouracil)
TIP	紫杉醇(Paclitaxel), 异环磷酰胺(Ifosfamide), 美司钠(Mesna), 顺铂(Cisplatin)
TTT	甲氨蝶呤(Methotrexate), 阿糖胞苷(Cytarabine), 氢化可的松(Hydrocortisone)
Topo/CTX	环磷酰胺(Cyclophosphamide), 托泊替康(Topotecan), 美司钠(Mesna)
VAB-6	环磷酰胺(Cyclophosphamide), 更生霉素(Dactinomycin), 长春碱(Vinblastine), 顺铂(Cisplatin), 博来霉素(Bleomycin)
VAC	长春新碱(Vincristine), 更生霉素(Dactinomycin), 环磷酰胺(Cyclophosphamide)
VACAdr	长春新碱(Vincristine), 环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin), 更生霉素(Dactinomycin), 长春新

[0433]

名称	治疗剂
	碱(Vincristine)
VAD	长春新碱(Vincristine), 阿霉素(Doxorubicin), 地塞米松(Dexamethasone)
VATH	长春碱(Vinblastine), 阿霉素(Doxorubicin), 塞替派(Thiotepa), Flouxymesterone
VBAP	长春新碱(Vincristine), 卡莫司汀(Carmustine), 阿霉素(Doxorubicin), 泼尼松(Prednisone)
VBCMP	长春新碱(Vincristine), 卡莫司汀(Carmustine), 美法仑(Melphalan), 环磷酰胺(Cyclophosphamide), 泼尼松(Prednisone)
VC	长春瑞滨(Vinorelbine), 顺铂(Cisplatin)
VCAP	长春新碱(Vincristine), 环磷酰胺(Cyclophosphamide), 阿霉素(Doxorubicin), 泼尼松(Prednisone)
VD	长春瑞滨(Vinorelbine), 阿霉素(Doxorubicin)
VelP	长春碱(Vinblastine), 顺铂(Cisplatin), 异环磷酰胺(Ifosfamide), 美司钠(Mesna)
VIP	依托泊苷(Etoposide), 顺铂(Cisplatin), 异环磷酰胺(Ifosfamide), 美司钠(Mesna)
VM	丝裂霉素(Mitomycin), 长春碱(Vinblastine)
VMCP	长春新碱(Vincristine), 美法仑(Melphalan), 环磷酰胺(Cyclophosphamide), 泼尼松(Prednisone)

[0434]

名称	治疗剂
VP	依托泊苷(Etoposide), 顺铂(Cisplatin)
V-TAD	依托泊苷(Etoposide), 硫鸟嘌呤(Thioguanine), 柔红霉素(Daunorubicin), 阿糖胞苷(Cytarabine)
5 + 2	阿糖胞苷(Cytarabine), 柔红霉素(Daunorubicin), 米托蒽醌(Mitoxantrone)
7 + 3	阿糖胞苷(Cytarabine) 与 柔红霉素(Daunorubicin) 或 Idarubicin 或米托蒽醌(Mitoxantrone)
"8 合 1"	甲泼尼龙(Methylprednisolone), 长春新碱(Vincristine), 洛莫司汀(Lomustine), 丙卡巴肼(Procarbazine), 羟基脲(Hydroxyurea), 顺铂(Cisplatin), 阿糖胞苷(Cytarabine), 达卡巴嗪(Dacarbazine)

[0435] 在某些实施方案中, 本发明的化合物可以与免疫调节剂联合给予。本发明化合物可与之在联合疗法中给予的免疫调节剂的实例包括粒细胞集落刺激因子(G-CSF)、干扰素、咪喹莫特(imiquimod)、IL-2、IL-7、IL-12、各种趋化因子、合成的胞嘧啶磷酸鸟苷(CpG)寡脱氧核苷酸、葡聚糖和合成的小分子例如阿普斯特(apremilast)、CC-122、CC-11006、CC-10015、来那度胺(lenalidomide)、泊马度胺(pomalidomide)和沙利度胺(thalidomide)。在某些实施方案中, 免疫调节剂是沙利度胺类似物, 例如在W01999/46258、W02008/033567、W02010/093434、W02010/93305、W02011/100380和W02012/097116中公开的那些。

[0436] 在某些实施方案中, 本发明化合物可以与选自酶抑制剂(例如激酶抑制剂)、有丝分裂抑制剂、DNA修饰剂和胞苷类似物的抗癌剂联合给予。本发明化合物可与之在联合疗法中给予的抗癌剂的实例包括微管组装抑制剂、AKT抑制剂、mTOR抑制剂、MEK抑制剂、RTK抑制剂、ATM抑制剂、ATR抑制剂、PI3K抑制剂、EGFR抑制剂、B-Raf抑制剂、C-kit抑制剂、DNA交联剂、DNA插入剂和胞苷类似物。在某些实施方案中, 抗癌剂长春新碱(vincristine)、卡铂(carboplatin)、顺铂(cisplatin)、吉西他滨(gemcitabine)、MK2206、依维莫司(everolimus)、曲美替尼(trametinib)、舒尼替尼(sunitinib)、索拉非尼(sorafenib)、BEZ235、紫杉醇(paclitaxel)、多西他赛(docetaxel)、厄洛替尼(erlotinib)、司美替尼(selumetinib)、西罗莫司(sirolimus)、曲美替尼(trametinib)、坦罗莫司(temsirolimus)、帕唑帕尼(pazopanib)或GSK1120212。

[0437] 癌细胞的增殖需要脂质合成。正常地, 用于脂质合成的乙酰基辅酶A由丙酮酸的线

粒体库形成,丙酮酸衍生自糖酵解。然而在低氧条件下,例如通常在肿瘤环境中发现的那些低氧条件下,在线粒体内丙酮酸向乙酰基辅酶A的转化被下调。最近研究揭示在这样的低氧条件下,细胞取而代之地主要转变成使用这样的途径,所述途径涉及 α -酮戊二酸的还原性羧化作用以生产用于脂质合成的乙酰基辅酶A。在这个途径中的第一个步骤涉及经由谷氨酰胺酶将谷氨酰胺转化为谷氨酸。随后,谷氨酸被转化为 α -酮戊二酸,而生成的 α -酮戊二酸在由异柠檬酸脱氢酶介导的还原性羧化步骤中被转化为异柠檬酸。转换到还原性羧化作用途径也发生在某些肾癌细胞系中,所述肾癌细胞系含有或者受损的线粒体或者减弱的信号,供诱导负责将糖酵解丙酮酸转化为乙酰基辅酶A的酶。一种类似的转换发生在暴露于线粒体呼吸链抑制剂例如二甲双胍、鱼藤酮和抗霉素的细胞中。因此,在本发明的某些实施方案中,我们提议使用线粒体呼吸链抑制剂和谷氨酰胺酶抑制剂的组合以同时地增加癌细胞对用于脂质合成的谷氨酰胺酶-依赖性途径的依赖性,同时恰好抑制这些途径。

[0438] 对肿瘤细胞中糖酵解的依赖性增加很可能是由于低氧的肿瘤环境削弱了线粒体呼吸。此外,葡萄糖的耗尽诱导用MYC致癌基因转化的细胞的细胞凋亡。这些结果提示抑制糖酵解将具有预防癌细胞增殖的治疗价值。目前存在许多文献记载的糖酵解抑制剂。然而,可获得的糖酵解抑制剂通常不是很有效的,因此需要高剂量,而高剂量可引起高水平的系统毒性。因为癌细胞典型地以比正常细胞更高的水平利用葡萄糖和谷氨酰胺二者,那些代谢物的每一种的弱化的利用将可能具有协同作用。因此,在本发明的某些实施方案中,我们提议使用糖酵解途径抑制剂和谷氨酰胺酶抑制剂的组合。这样的糖酵解抑制剂包括2-脱氧葡萄糖、氯尼达明、3-溴代丙酮酸、伊马替尼(imatinib)、羟基硫胺素、雷帕霉素及其药理学等价物。糖酵解可通过耗尽NAD⁺,经由通过聚(ADP-核糖)聚合酶激活的途径的DNA烷基化剂而诱导的DNA损害被间接地抑制。因此,在本发明的一个实施方案中,我们提议使用DNA烷基化剂和谷氨酰胺酶抑制剂的组合。癌细胞利用磷酸戊糖途径连同糖酵解途径一起,以产生衍生自葡萄糖的代谢中间体。因此,在本发明的另一个实施方案中,我们提议使用磷酸戊糖抑制剂例如6-氨基烟酰胺连同谷氨酰胺酶抑制剂的组合。

[0439] 在某些实施方案中,本发明的化合物可以与癌症治疗的非化学方法联合给予(例如,口服给予,与膳食一起)。在某些实施方案中,本发明的化合物可以与放射疗法联合给予。在某些实施方案中,本发明的化合物可以与手术、热消融、聚焦超声疗法、冷冻疗法或与这些疗法的任何组合联合给予。

[0440] 在某些实施方案中,不同的本发明的化合物可以与一种或多种本发明的其它化合物联合给予。而且,这样的组合可以与其它治疗剂,例如其它适合用于治疗癌症、免疫性疾病或神经性疾病的药物,例如上文指定的药物联合给予。

[0441] 在某些实施方案中,所述治疗或预防癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法可包括口服给予本发明化合物,例如具有式I-III或式IV-VI中任一个的谷氨酰胺酶抑制剂(例如式(IV)、(IVa)、(IVb)、(V)、(Va)、(Vb)、(Vc)、(VI)、(VIa)、(VIb)或(VIc)中任一个的化合物)或其药学上可接受的盐,例如与膳食一起,与免疫调节剂联合。

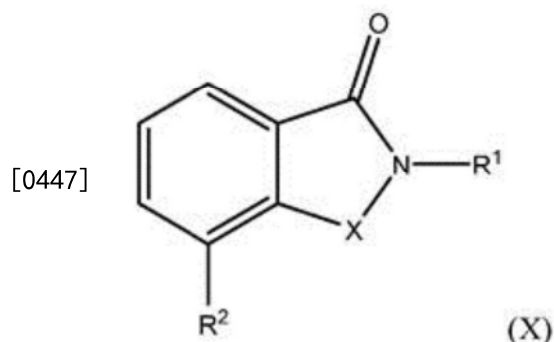
[0442] 在某些实施方案中,相对于作为单一药剂的免疫调节剂或谷氨酰胺酶抑制剂的单个给予,联合给予免疫调节剂和本发明化合物(即谷氨酰胺酶抑制剂)提供改善的功效。

[0443] 在某些实施方案中,联合给予免疫调节剂和谷氨酰胺酶抑制剂提供了累加效应。

[0444] 在某些实施方案中,联合给予免疫调节剂和谷氨酰胺酶抑制剂提供了协同效应。

[0445] 在本发明的某些实施方案中,免疫调节剂与谷氨酰胺酶抑制剂同时给予。在某些实施方案中,免疫调节剂在谷氨酰胺酶抑制剂之前或之后约5分钟内至约168小时内给予。

[0446] 在某些实施方案中,所述免疫调节剂具有式X的结构或其药学上可接受的盐、前药和/或立体异构体:

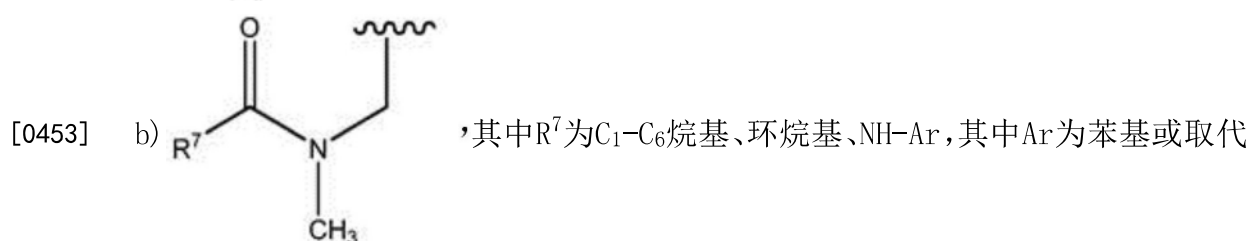
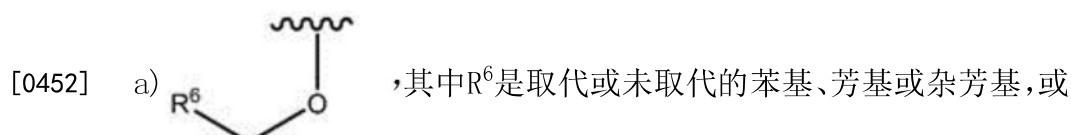


[0448] 其中:

[0449] X是C=O或CH₂;

[0450] R¹是杂环基,诸如2,6-二氧化哌啶-3-基,或芳烷基,诸如磺酰基取代的芳烷基,和

[0451] R²独立地为氢、氨基、酰基氨基、烷基氨基,或者是以下部分之一:



的苯基,或NR⁸R⁹,其中R⁸和R⁹可独立地为H或C₁-C₆-烷基。

[0454] 在某些实施方案中,所述免疫调节剂是阿普斯特(apremilast)、来那度胺(lenalidomide)、泊马度胺(pomalidomide)、沙利度胺(thalidomide)、CC-11006或CC-10015。

[0455] 在某些实施方案中,通过本发明的方法治疗的癌症对免疫调节剂具有抗性。在某些实施方案中,所述癌症对具有式(X)结构的化合物具有抗性。在某些实施方案中,所述癌症对阿普斯特(apremilast)、来那度胺(lenalidomide)、泊马度胺(pomalidomide)、沙利度胺(thalidomide)、CC-11006或CC-10015具有抗性。

[0456] 在某些实施方案中,本发明提供了用于治疗骨髓增殖性疾病的方法,所述方法包括与膳食一起口服给予受试者谷氨酰胺酶抑制剂,其中所述谷氨酰胺酶抑制剂如上所述。

[0457] 在某些实施方案中,所述骨髓增殖性疾病选自慢性嗜酸性粒细胞白血病、慢性髓细胞白血病(CML)、慢性中性粒细胞白血病、原发性血小板增多症、真性红细胞增多症和骨髓纤维化。

[0458] 在某些实施方案中,通过本发明的方法治疗的骨髓增殖性疾病对免疫调节剂具有

抗性。在某些实施方案中,所述骨髓增殖性疾病对具有式(X)结构的化合物具有抗性。在某些实施方案中,所述骨髓增殖性疾病对阿普斯特(apremilast)、来那度胺(lenalidomide)、泊马度胺(pomalidomide)、沙利度胺(thalidomide)、CC-11006和CC-10015具有抗性。

[0459] 在某些实施方案中,本发明提供了用于治疗或预防免疫相关疾病的方法,所述方法包括将谷氨酰胺酶抑制剂与膳食一起口服给予受试者,其中谷氨酰胺酶抑制剂如上所述。

[0460] 在某些实施方案中,所述免疫相关疾病选自强直性脊柱炎、克罗恩病、麻风结节性红斑(ENL)、移植物抗宿主病(GVHD)、HIV相关性消耗综合征、红斑狼疮、红细胞增多症、牛皮癣、牛皮癣性关节炎、复发性口腔溃疡、类风湿性关节炎(RA)、严重复发性阿弗他性口炎和系统性硬化症。

[0461] 在某些实施方案中,通过本发明的方法治疗的免疫相关疾病对免疫调节剂具有抗性。在某些实施方案中,所述免疫相关疾病对具有式(X)结构的化合物具有抗性。在某些实施方案中,免疫相关疾病对阿普斯特(apremilast)、来那度胺(lenalidomide)、泊马度胺(pomalidomide)、沙利度胺(thalidomide)、CC-11006或CC-10015具有抗性。

[0462] 所述治疗或预防癌症、骨髓增殖性疾病或免疫相关疾病的方法可以进一步包括给予一种或多种如上所述的另外的化学治疗剂。

[0463] 在某些优选的实施方案中,所述另外的化学治疗剂是地塞米松(dexamethasone)。

[0464] 在某些实施方案中,本发明提供了用谷氨酰胺酶抑制剂治疗病毒感染的方法,其中病毒是天花、普通感冒、麻疹、水痘、肝炎、流感、人乳头瘤病毒、带状疱疹、疱疹、脊髓灰质炎、狂犬病、埃博拉病毒、汉他热、HIV、感冒疮、SARS(严重急性呼吸系统综合症)、登革热、爱泼斯坦-巴尔病毒、腺病毒、禽流感、A型流感病毒、B型流感病毒、麻疹、副流感病毒、呼吸道合胞病毒(RSV)、鼻病毒、SARS-CoV、柯萨奇病毒、肠病毒、脊髓灰质炎病毒、轮状病毒、乙型肝炎病毒、丙型肝炎病毒、牛病毒性腹泻病毒(替代物)、单纯疱疹1、单纯疱疹2、人巨细胞病毒、水痘带状疱疹病毒、HIV1、HIV2、猿免疫缺陷病毒、猿人免疫缺陷病毒、禽流感、登革热病毒、汉坦病毒、出血热病毒、淋巴细胞性脉络丛脑膜炎病毒、天花病毒替代物(牛痘、猴痘、兔痘)、牛痘病毒、委内瑞拉马脑脊髓炎病毒(VEE)、西尼罗河病毒或黄热病病毒。

[0465] III. 药盒

[0466] 在某些实施方案中,本发明提供了药盒,其包含:a)一种或多种单一剂型的本发明化合物;b)一种或多种单一剂型的如上所述的化学治疗剂;和c)给予本发明化合物和化学治疗剂的说明书。说明书可能会说明该化合物是与食物一起服用的。例如,说明书可能会陈述该化合物应在膳食后服用。说明书可能会陈述化合物应该每天服用一次、两次或三次,例如与膳食一起或膳食后服用。

[0467] 本发明提供一种药盒,其包含:

[0468] a) 包含本发明化合物的药物制剂(例如一种或多种单一剂型);和

[0469] b) 给予所述药物制剂的说明书,例如用于治疗或预防上述任何疾病的说明书,其中所述说明书指出化合物应与食物一起或膳食后服用。

[0470] 在某些实施方案中,所述药盒还包括用于联合给予包含本发明化合物的药物制剂与如上所述的化学治疗剂的说明书。在某些实施方案中,药盒还包括第二种药物制剂(例如,作为一个或多个单一剂型),其包含如上所述的化学治疗剂。

[0471] IV. 药物组合物

[0472] 本发明的组合物和方法可用于治疗有需要的个体。在某些实施方案中,所述个体是哺乳动物,例如人或非人哺乳动物。当给予于动物例如人时,组合物或化合物优选作为药物组合物给予,所述药物组合物包含例如本发明的化合物和药学上可接受的载体。药学上可接受的载体在本领域是公知的,并且包括例如水溶液如水或生理缓冲盐水或其它溶剂或溶媒如二醇、甘油、油如橄榄油或有机酯。例如,可以选择赋形剂以实现药物的延迟释放。药物组合物可以是单位剂量形式,如片剂、胶囊(包括粉末胶囊和明胶胶囊)、颗粒剂、重组冻干剂、粉剂、溶液剂、糖浆剂等。

[0473] 药学上可接受的载体可以包含生理学上可接受的试剂,其例如用于稳定、增加化合物如本发明化合物的溶解度或增加其吸收。这样的生理学上可接受的试剂包括例如糖类(如葡萄糖、蔗糖或葡聚糖)、抗氧化剂(如抗坏血酸或谷胱甘肽)、螯合剂、低分子量蛋白或其它稳定剂或赋形剂。

[0474] 药物组合物(制剂)可以口服给予患者(例如,以水性或非水性溶液或混悬液的浸湿形式(drench)、片剂、胶囊剂(包括粉末胶囊和明胶胶囊)、大丸剂(boluses)、粉剂、颗粒剂、糊剂)。在某些实施方案中,化合物可以简单地溶解或悬浮在无菌水中。合适的给药途径和适用于其的组合物的细节可以在例如美国专利Nos.6,110,973、5,763,493、5,731,000、5,541,231、5,427,798、5,358,970和4,172,896中以及在其中引用的专利(在此引入作为参考)找到。

[0475] 制剂可以方便地以单位剂量形式存在,并且可以通过制药领域中公知的任何方法制备。可以与载体材料组合以产生单一剂型的活性成分的量将取决于要治疗的宿主、特定的给药模式而变化。可以与载体材料组合以产生单一剂型的活性成分的量通常是产生治疗效果的化合物的量。通常,按照百分比计,该量范围为约1%至约99%活性成分,优选约5%至约70%,最优选约10%至约30%。

[0476] 制备这些制剂或组合物的方法包括使活性化合物如本发明化合物与载体以及任选的一种或多种辅助成分结合的步骤。通常,通过将本发明的化合物与液体载体或细分散的固体载体或两者均匀且充分地混合,然后如果需要,使产物成形来制备制剂。

[0477] 适合于口服给药的本发明制剂可以是胶囊(包括粉末胶囊和明胶胶囊)、扁囊剂、丸剂、片剂、锭剂(使用调味基质,通常为蔗糖和阿拉伯胶或黄蓍胶)、冻干粉剂、粉剂、颗粒剂的形式,或作为水性或非水性液体中的溶液或混悬剂,或作为水包油或油包水液体乳液,或作为酏剂或糖浆,或作为软锭剂(使用惰性基质,如明胶和甘油,或蔗糖和阿拉伯胶)和/或作为漱口水等,各自包含预定量的作为活性成分的本发明化合物。组合物或化合物也可以作为大丸剂、药糖剂或糊剂给予。

[0478] 为制备口服给药的固体剂型(胶囊(包括粉末胶囊和明胶胶囊)、片剂、丸剂、糖衣丸、粉剂、颗粒剂等),将活性成分与一种或多种药学上可接受的载体混合,例如柠檬酸钠或磷酸二钙,和/或以下任一种:(1)填充剂或增量剂,例如淀粉、乳糖、蔗糖、葡萄糖、甘露醇和/或硅酸;(2)粘合剂,例如,羧甲基纤维素、藻酸盐、明胶、聚乙烯吡咯烷酮、蔗糖和/或阿拉伯胶;(3)湿润剂,例如甘油;(4)崩解剂,例如琼脂、碳酸钙、马铃薯或木薯淀粉、藻酸、某些硅酸盐和碳酸钠;(5)溶液阻滞剂,例如石蜡;(6)吸收促进剂,例如季胺化合物;(7)湿润剂,例如,鲸蜡醇和单硬脂酸甘油酯;(8)吸收剂,例如高岭土和膨润土;(9)润滑剂,例如滑

石粉、硬脂酸钙、硬脂酸镁、固体聚乙二醇、十二烷基硫酸钠,及其混合物;(10)络合剂(complexing agents),例如,改性和未改性的环糊精;和(11)着色剂。在胶囊(包括粉末胶囊和明胶胶囊)、片剂和丸剂的情况下,药物组合物也可包含缓冲剂。也可使用类似类型的固体组合物,使用这样的赋形剂如乳糖(lactose)或乳糖(milk sugars)以及高分子量聚乙二醇等作为在软和硬-填充明胶胶囊中的填充剂。

[0479] 片剂可以通过压制或模制,任选地用一种或多种辅助成分制得。压制片剂可以使用粘合剂(例如,明胶或羟丙基甲基纤维素)、润滑剂、惰性稀释剂、防腐剂、崩解剂(例如,羧基乙酸淀粉钠或交联的羧甲基纤维素钠)、表面活性剂或分散剂制备。模制片剂可以通过在合适的机器中将经惰性液体稀释剂湿润的粉末化合物混合物的混合物模压成形而制得。

[0480] 药物组合物的片剂和其它固体剂型,例如糖锭剂、胶囊(包括粉末胶囊和明胶胶囊)、丸剂和颗粒剂,可任选划痕或用包衣和壳制备,例如肠溶包衣和制药领域熟知的其它包衣。它们也可使用例如各种比例的羟丙基甲基纤维素(以提供所需的释放曲线)、其它聚合物基质、脂质体和/或微球体来配制,以提供缓慢释放或控制释放其中的活性成分。它们可以例如,通过细菌截留滤器而过滤,或通过包括可溶于无菌水的无菌固体组合物形式的灭菌剂,或通过临用前包括某些其它无菌可注射的介质来灭菌。这些组合物也可任选地含有遮光剂并且可以具有仅释放活性成分的组分,或优先地在胃肠道的某些部分,任选地,以延迟方式释放。可以使用的包埋组合物的实例包括聚合物物质和蜡。活性成分也可以微囊形式存在,如果合适的话,与一种或多种上述赋形剂一起。

[0481] 可用于口服给药的液体剂型包括药学上可接受的乳剂、用于重构的冻干制剂、微乳剂、溶液剂、悬浮液、糖浆剂和酏剂。除了活性成分,液体剂型还可含有本领域常用的惰性稀释剂,例如,水或其它溶剂、环糊精及其衍生物、增溶剂和乳化剂,例如乙醇、异丙醇、碳酸乙酯、乙酸乙酯、苧醇、苯甲酸苧酯、丙二醇、1,3-丁二醇、油(特别是棉籽油、花生油、玉米油、胚芽油、橄榄油、蓖麻油和芝麻油)、甘油、四氢呋喃醇、聚乙二醇和脱水山梨醇脂肪酸酯,及其混合物。

[0482] 除了惰性稀释剂,口服组合物还可包括辅助剂例如湿润剂、乳化剂和助悬剂、甜味剂、矫味剂、着色剂、香料和防腐剂。

[0483] 除了活性化合物以外,悬浮液还可以包含悬浮剂,例如乙氧基化异硬脂醇、聚氧乙烷山梨醇和脱水山梨醇酯、微晶纤维素、偏氢氧化铝、膨润土、琼脂和黄耆胶及其混合物。

[0484] 可用于本发明药物组合物的合适的水性和非水性载体的实例包括水、乙醇、多元醇(例如甘油、丙二醇、聚乙二醇等)及其合适的混合物、植物油、如橄榄油和有机酯如油酸乙酯。例如,通过使用诸如卵磷脂的包衣材料,通过在分散体的情况下维持所需的粒度,并且通过使用表面活性剂,可以保持适当的流动性。

[0485] 这些组合物还可以包含佐剂,如防腐剂、润湿剂、乳化剂和分散剂。通过包含各种抗菌剂和抗真菌剂,例如对羟基苯甲酸酯、氯丁醇、苯酚山梨酸等可以确保防止微生物的作用。将等渗剂如糖、氯化钠等包括在组合物中也是可合乎需要的。另外,可通过包含延迟吸收的试剂例如单硬脂酸铝和明胶来延长可注射药物形式的吸收。

[0486] 为了用于本发明的方法,活性化合物可以其本身或作为包含例如0.1-99.5%(更优选0.5-90%)的活性成分与药学上可接受载体组合的药物组合物给予。

[0487] 药物组合物中活性成分的实际剂量水平可以变化,以获得有效达到对特定患者的

所需治疗反应的一定量的活性成分、组合物,和给药方式,而对患者没有毒性。

[0488] 选择的剂量水平将取决于多种因素,包括具体化合物或所用化合物或其酯、盐或酰胺的组合物活性、给药途径、给药时间、所用具体化合物的排泄速率、治疗持续时间、与所用具体化合物组合使用的其它药物、化合物和/或物质、所治疗患者的年龄、性别、体重、状况、一般健康和先前病史以及医学领域熟知的因素。

[0489] 具有本领域普通技术的医生或兽医可以容易地确定和开出所需药物组合物的治疗有效量。例如,医师或兽医可以从低于达到所需治疗效果所需要水平的药物组合物或化合物的剂量开始并逐渐增加剂量直至达到所需效果。

[0490] 一般来说,用于本发明的组合物和方法的活性化合物的合适日剂量将是有效产生治疗效果的最低剂量的化合物的量。这样的有效剂量通常将取决于上述因素。

[0491] 如果需要,活性化合物的有效日剂量可作为1、2、3、4、5、6或更多个亚剂量给予,其在整天以合适间隔、任选地以单位剂型分开给予。在本发明的某些实施方案中,活性化合物可以每日给予2或3次。在优选的实施方案中,活性化合物将每日给予1次。

[0492] 接受这种治疗的患者是有需要的任何动物,包括灵长类动物,特别是人,和其它哺乳动物例如马、牛、猪和绵羊;以及一般家禽和宠物。

[0493] 在某些实施方案中,本发明的化合物可以单独使用或与另一种类型的治疗剂联合给予。

[0494] 本发明包括本发明化合物的药学上可接受的盐在本发明的组合物和方法中的用途。在某些实施方案中,本发明考虑的盐包括,但不限于烷基、二烷基、三烷基或四烷基铵盐。在某些实施方案中,本发明考虑的盐包括,但不限于L-精氨酸、苄乙苄胺(benenthamine)、苄星、甜菜碱、氢氧化钙、胆碱、地阿诺、二乙醇胺、二乙胺、2-(二乙基氨基)乙醇、乙醇胺、乙二胺、N-甲基葡萄糖胺、海巴明(hydrabamine)、1H-咪唑、锂、L-赖氨酸、镁、4-(2-羟乙基)吗啉、哌嗪、钾、1-(2-羟乙基)吡咯烷、钠、三乙醇胺、氨丁三醇和锌盐。在某些实施方案中,本发明考虑的盐包括,但不限于Na、Ca、K、Mg、Zn或其它金属盐。

[0495] 药学上可接受的酸加成盐也可作为各种溶剂合物,例如与水、甲醇、乙醇、二甲基甲酰胺等的溶剂合物存在。也可制备这样的溶剂合物的混合物。这样的溶剂合物的来源可来自结晶的溶剂,在制剂或结晶的溶剂中固有的,或对于所述溶剂为外来的。

[0496] 润湿剂、乳化剂和润滑剂,例如十二烷基硫酸钠和硬脂酸镁,以及着色剂、释放剂、包衣剂、甜味剂、矫味剂和芳香剂、防腐剂和抗氧化剂也可存在于组合物中。

[0497] 药学上可接受的抗氧化剂的实例包括:(1)水溶性抗氧化剂,例如抗坏血酸、半胱氨酸盐酸盐、硫酸氢钠、偏亚硫酸氢钠、亚硫酸钠等;(2)油溶性抗氧化剂,例如抗坏血酸棕榈酸酯、丁羟基茴香醚(BHA)、丁羟基甲苯(BHT)、卵磷脂、没食子酸丙酯、 α -生育酚等;和(3)金属螯合剂,例如柠檬酸、乙二胺四乙酸(EDTA)、山梨醇、酒石酸、磷酸等。

[0498] V. 方法

[0499] 在一些方面,本发明涉及治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法,所述方法包括口服给予式I、式II、式III、式IV、式V和/或式VI化合物,其中所述化合物与膳食一起给予。所述化合物可以是例如表1或2或附录A中列出的任何一种化合物。

[0500] 在一些方面,本发明涉及治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或

病毒感染的方法,所述方法包括口服给予式I、式II、式III、式IV、式V和/或式VI化合物,其中所述化合物与食物一起给予。所述化合物可以是例如表1或2或附录A中列出的任何一种化合物。

[0501] 在某些实施方案中,本发明涉及治疗癌症、骨髓增殖性疾病、免疫性疾病、神经性疾病或病毒感染的方法,所述方法包括口服给予式I、式II、式III、式IV、式V和/或式VI的化合物,其中所述化合物以进食模式给予受试者。所述化合物可以是例如表1或2或附录A中列出的任何一种化合物。

[0502] 在某些实施方案中,受试者是哺乳动物。在某些优选的实施方案中,受试者是人。

[0503] 在某些实施方案中,所述化合物在受试者(例如人)摄取食物前30分钟至摄取食物后6小时之间口服给予,例如在摄取食物前30分钟至摄取食物后5小时之间,在摄取食物前30分钟至摄取食物后4小时之间,在摄取食物前30分钟至摄取食物后3小时之间,在摄取食物前30分钟至摄取食物后2小时之间,在摄取食物前30分钟至摄取食物后1小时之间。优选地,所述化合物在受试者摄取食物前30分钟至摄取食物后90分钟之间给予,例如在摄取食物前20分钟至摄取食物后90分钟之间,在摄取食物前20分钟至摄取食物后60分钟之间,在摄取食物前10分钟至摄取食物后60分钟之间,在摄取食物前5分钟至摄取食物后60分钟之间,或在摄取食物前5分钟至摄取食物后30分钟之间。

[0504] 在某些实施方案中,所述方法包括向受试者(例如人)口服给予谷氨酰胺酶抑制剂(例如,优选式III化合物),优选以进食模式,其中每天口服给予100mg至10g所述化合物。例如,化合物的每日口服剂量可以是100mg至5000mg,例如200mg至4000mg,300mg至3000mg,600mg至2400mg,800mg至2200mg,1000mg至2000mg,或1200mg至1800mg,或约1600mg。

[0505] 在某些实施方案中,所述方法包括口服给予式III化合物,并且每天口服给予100mg至10g所述化合物。例如,可以每天口服给予100mg至5000mg所述化合物,例如200mg至4000mg,300mg至3000mg,600mg至2400mg,800mg至2200mg,1000mg至2000mg,1200mg至1800mg,或约1600mg。

[0506] 在某些实施方案中,每天口服给予相当于100mg至10g式III化合物的总剂量。术语“总剂量”是指例如每天给予的化合物的总量。例如,如果600mg剂量的化合物每天给药两次,则总剂量是每天1200mg。术语“相当于式III化合物的量”是指给予化合物的量与式III化合物的量具有相同功效。例如,如果第一化合物如式I、II、IV、V或VI的化合物具有与式III化合物相同的功效,则第一化合物的当量等于相同量的式III化合物,例如600mg第一化合物相当于600mg式III化合物。类似地,如果第二化合物具有例如式III化合物的效力的两倍,则第二化合物的当量等于式III的化合物的一半,例如300mg第二化合物相当于600mg式III化合物。

[0507] 优选地,将谷氨酰胺酶抑制剂与膳食一起给予受试者(即,受试者处于进食模式)。

[0508] 在某些实施方案中,每天口服给予受试者(例如人)相当于约100mg至约5000mg谷氨酰胺酶抑制剂(例如优选式III化合物)的总剂量。在示例性实施方案中,总剂量相当于约200mg至约4000mg,约300mg至约3000mg,约400mg至约2800mg,约600mg至约2400mg,约800mg至约2200mg,约1000mg至约2000mg,约1000mg至约1800mg,约1200mg至约1800mg,约1200mg至约1600mg。在某些优选的实施方案中,式III化合物每天两次口服给予人类受试者,总剂量为1600mg。优选地,人类受试者处于进食模式。在某些优选的实施方案中,所述化合物与

膳食一起给予。

[0509] 在某些实施方案中,每天口服给予受试者(例如人)相当于约100mg至约5000mg式III化合物的总剂量。在示例性实施方案中,总剂量相当于约200mg至约4000mg,约300mg至约3000mg,约400mg至约2800mg,约600mg至约2400mg,约800mg至约2200mg,约1000mg至约2000mg,约1000mg至约1800mg,约1200mg至约1800mg,约1200mg至约1600mg。在某些优选的实施方案中,式III化合物每天两次口服给予人类受试者,总剂量为1600mg。优选地,人类受试者处于进食模式,例如,所述化合物与膳食一起给予。

[0510] 在某些实施方案中,每天给予100mg至10g的所述化合物。例如,可以每天给予100mg、150mg、200mg、250mg、300mg、350mg、400mg、450mg、500mg、550mg、600mg、650mg、700mg、750mg、800mg、850mg、900mg、950mg、1000mg、1100mg、1200mg、1300mg、1350mg、1400mg、1500mg、1600mg、1650mg、1700mg、1800mg、1900mg、1950mg、2000mg、2100mg、2200mg、2250mg、2300mg、2400mg、2500mg、2550mg、2600mg、2700mg、2800mg、2850mg、2900mg、3000mg、4000mg、5000mg、6000mg、7000mg、8000mg、9000mg或10000mg。在某些优选的实施方案中,每天给予1200mg化合物,例如以两个剂量,各600mg。在某些实施方案中,每天给予1800mg化合物,例如以三个剂量,各600mg。在其它优选的实施方案中,每天将1600mg化合物给予受试者(例如人),例如以两次剂量,各800mg。优选地,每次给药包括膳食。

[0511] 在某些实施方案中,所述化合物每天一次、每天两次、每天三次或每天四次给予。在优选的实施方案中,所述化合物每天给予两次或每天三次,例如每次与食物一起。在更优选的实施方案中,所述化合物每天给予两次,例如每次与食物一起。

[0512] 实施例

[0513] 实施例1:各种剂量大小的比较

[0514] 历时22天,将式III化合物(CB-839)口服给予15名患有急性白血病的人类受试者。该化合物以每剂100mg至每剂1000mg的剂量每天给药三次(“TID”) (即,每天300mg至3000mg总化合物)。在第1天、第15天和第22天监测化合物的血浆水平。接受化合物的受试者在第1天和第15天处于禁食状态(没有如本文所定义的与膳食一起)并且在第22天处于进食状态(如本文所定义的与膳食一起)。禁食状态下的化合物的给予由早餐前1小时口服第一剂、在下午3点口服第二剂和睡前口服第三剂组成。随着剂量的增加,暴露增加(图1和2)。在大多数接受每天三次600mg和更高剂量的患者中发现第15天CB-839的稳态血浆浓度持续大于250nM(图2),该血浆浓度是先前已经发现显示出治疗有效的血浆浓度。发现来自三名治疗患者(剂量600mg、800mg和1000mg,每天三次)的外周血单核细胞(PBMCs)具有10至58%的白血病性母细胞计数,并显示>94%的谷氨酰胺酶活性抑制。当CB-839以600mg每日两次与食物一起给予时,在2-6小时内达到C_{max},并且在所有受试者中所述化合物的血浆水平超过450nM,这表明进食状态导致药物暴露增加(图2)。

[0515] 实施例2:进食和禁食状态下的给药比较

[0516] 仍然参加试验的来自实施例1的每个受试者在试验第22天后每天口服给予600mg式III化合物,每天两次(“BID”),与食物一起(即每天1200mg化合物)。在BID给药方案的第1天、第15天和第22天监测化合物的血浆水平,以与实施例1的结果进行比较。比较在禁食状态下每天三次接受600mg化合物(即每天1800mg的化合物,本文所定义的不与膳食一起)的受试者和在进食状态下每天两次接受600mg化合物(即每天1200mg的化合物,本文所定义的

与膳食一起)的受试者的药代动力学数据。该数据表明,尽管进食组每天比禁食组接受更少化合物,但是每个组有相同的药物暴露(图4和5)。

[0517] 实施例3:结果

[0518] 在实施例1和2中没有确定剂量限制性毒性,并且在超过10%的受试者中发生的与治疗有关的不良事件由增加的转氨酶水平(4名受试者)和增加的胆红素水平(2名受试者)构成。在超过10%的受试者中没有3级或更高的不良事件被认为与治疗有关。在所有剂量水平的15个功效可评估受试者中的5个(33%)中观察到稳定的疾病4-10个周期,其中受试者保持该研究药物平均134天(即,大于6个周期;1个周期=21天)。一个受试者在6个周期的给药后在骨髓中获得了完全的反应,外周计数不完全恢复。具有稳定疾病或更好的所有受试者年龄大于65岁,不适合高剂量治疗。

[0519] 实施例4:药代动力学

[0520] CB-839根据图6中的给药方案给予癌症患者。CB-839的半衰期约为4小时。暴露一般随剂量而增加。

[0521] 如图6-8所示,采用BID进食给药方案靶标CB-839的浓度得以维持,而PK变异性减少。

[0522] 通过引用并入

[0523] 本文提及的所有出版物和专利都通过引用整体并入本文,如同每个单独的出版物或专利被具体地且单独地指出通过引用并入。在冲突的情况下,以本申请(包括本文中的任何定义)为准。

[0524] 特别地,用于实施本发明的合适的化合物和用于合成所述化合物的方法描述于美国专利号8,604,016、美国专利申请公开号2014/0194421和美国申请公开号2015/0004134、2014/0142081和2014/0142146,其全部内容通过引用结合于此。

[0525] 等同物

[0526] 虽然已经讨论了本发明的具体实施方案,但是上述说明是说明性的而不是限制性的。在阅读本说明书和下面的权利要求后,本发明的许多变体对于本领域技术人员将变得显而易见。本发明的全部范围应该通过参考权利要求以及它们的等同物的全部范围和说明书以及这样的变体来确定。

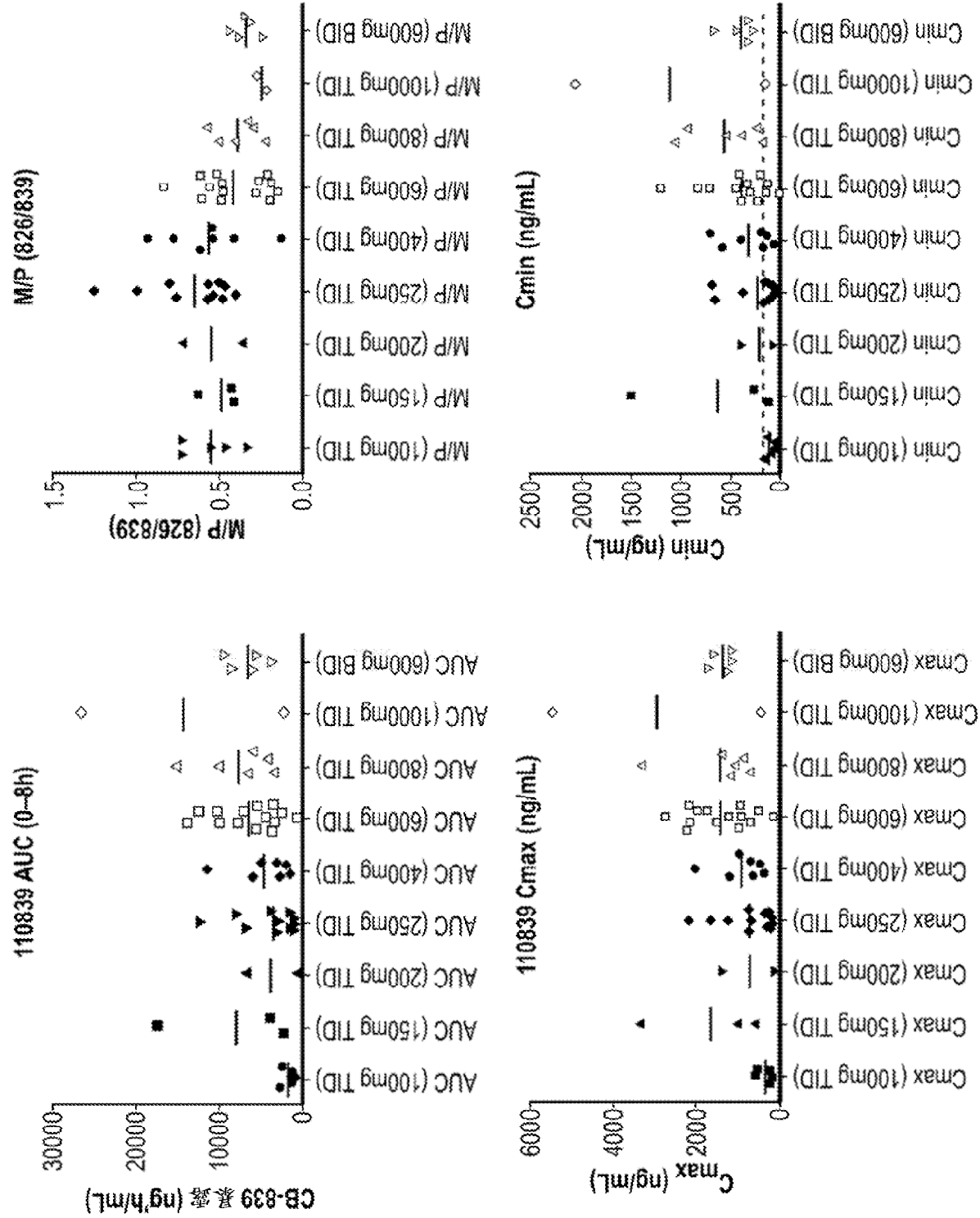


图 1

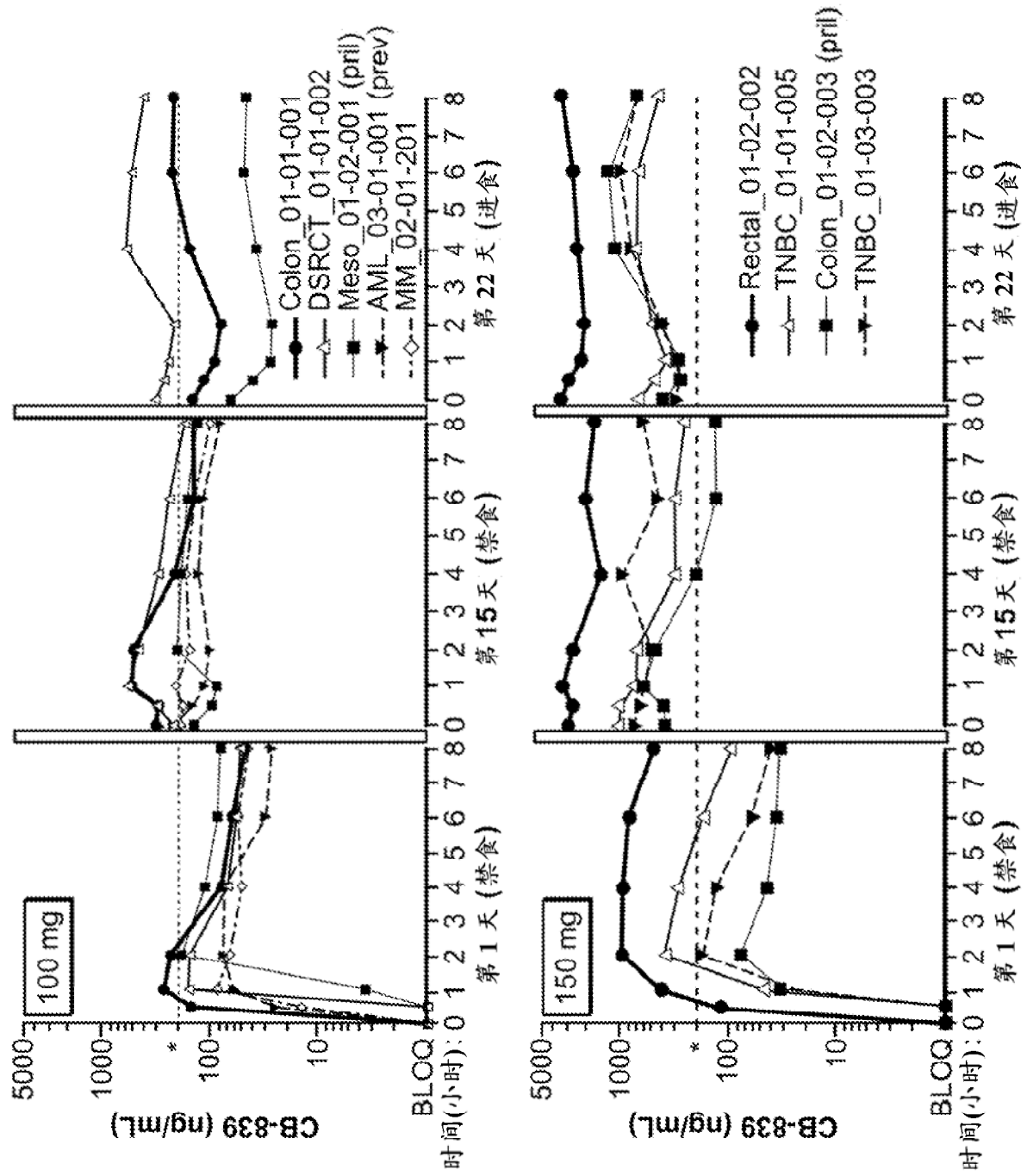


图 2

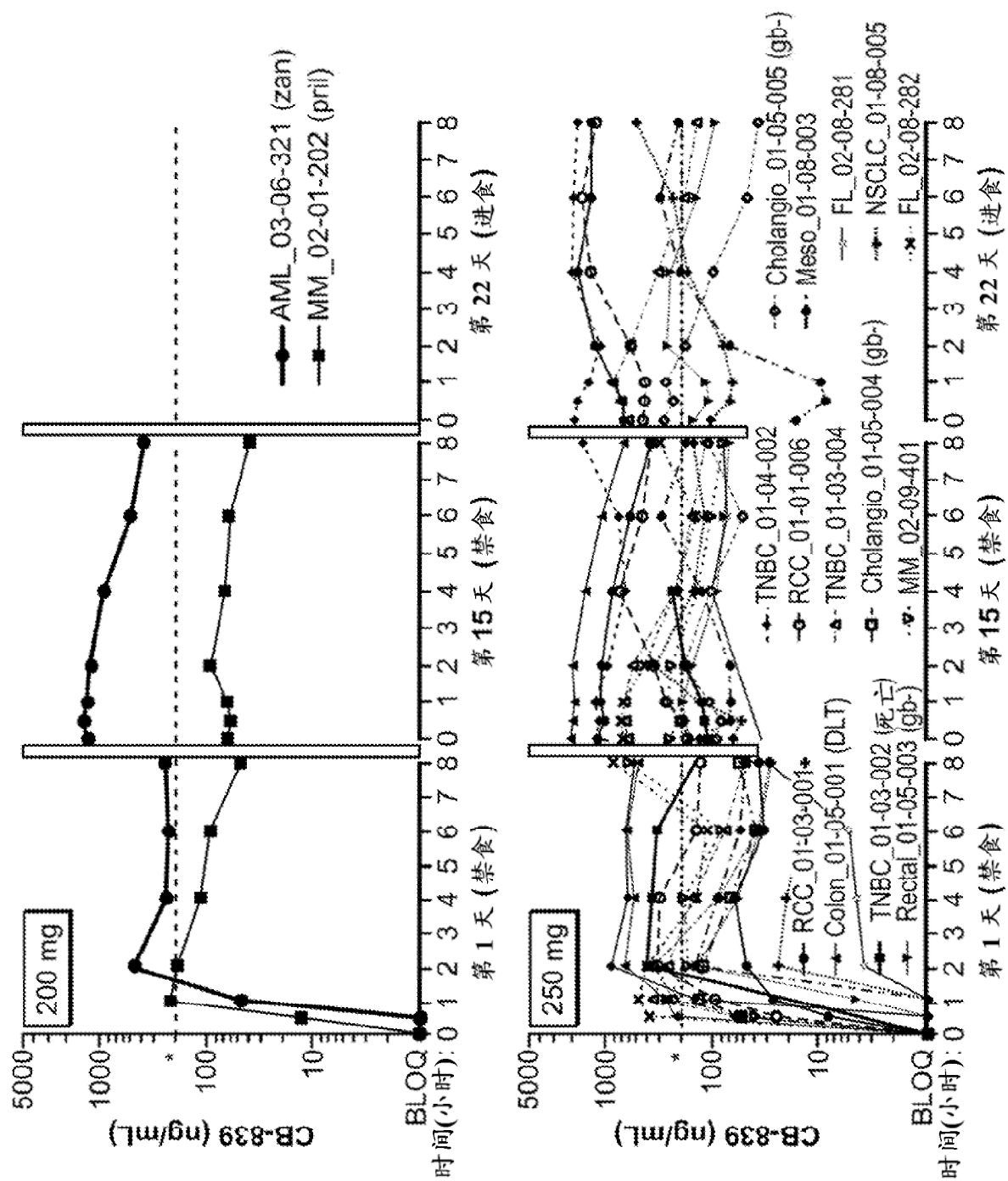


图 2(续)

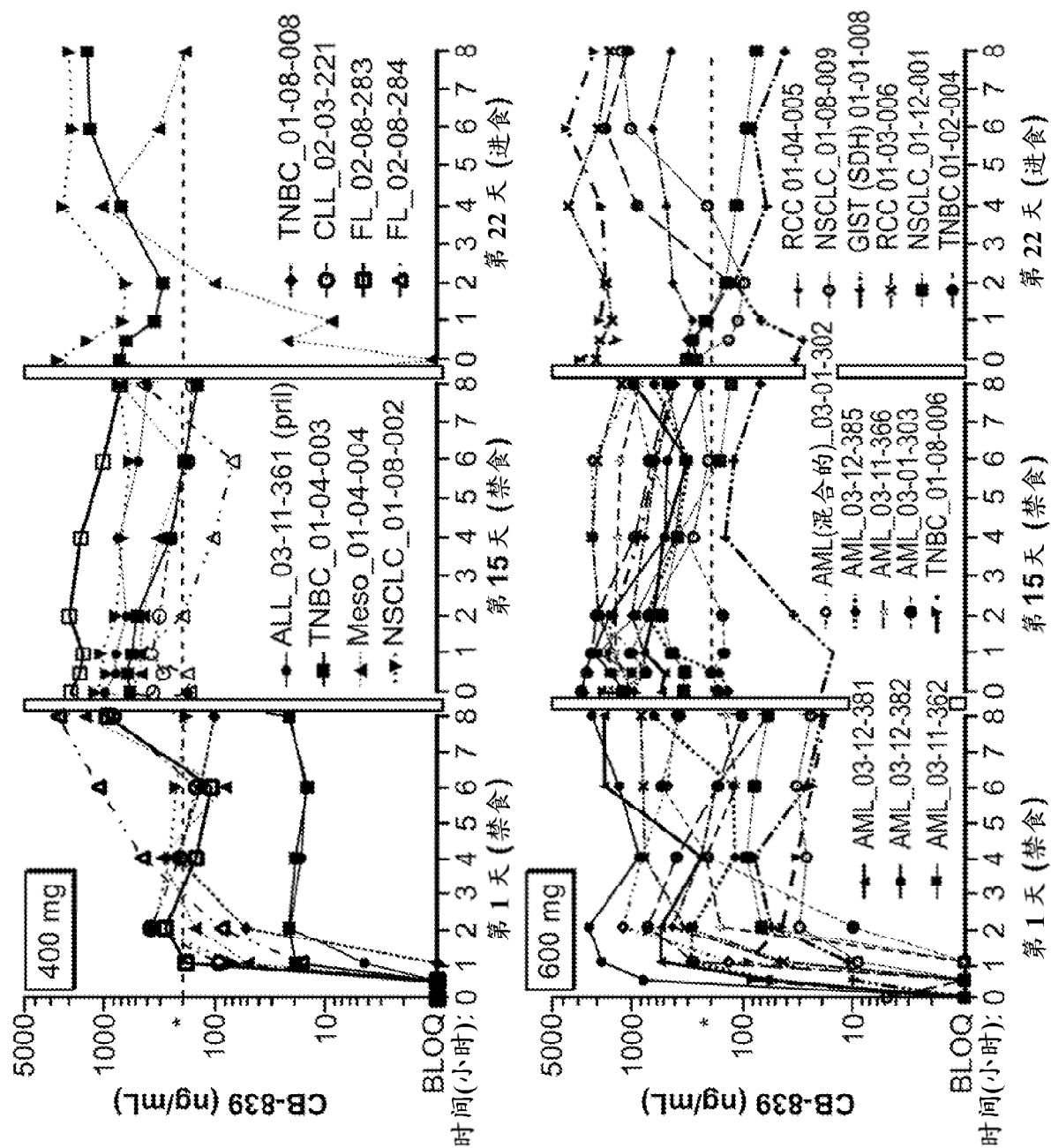


图 2(续)

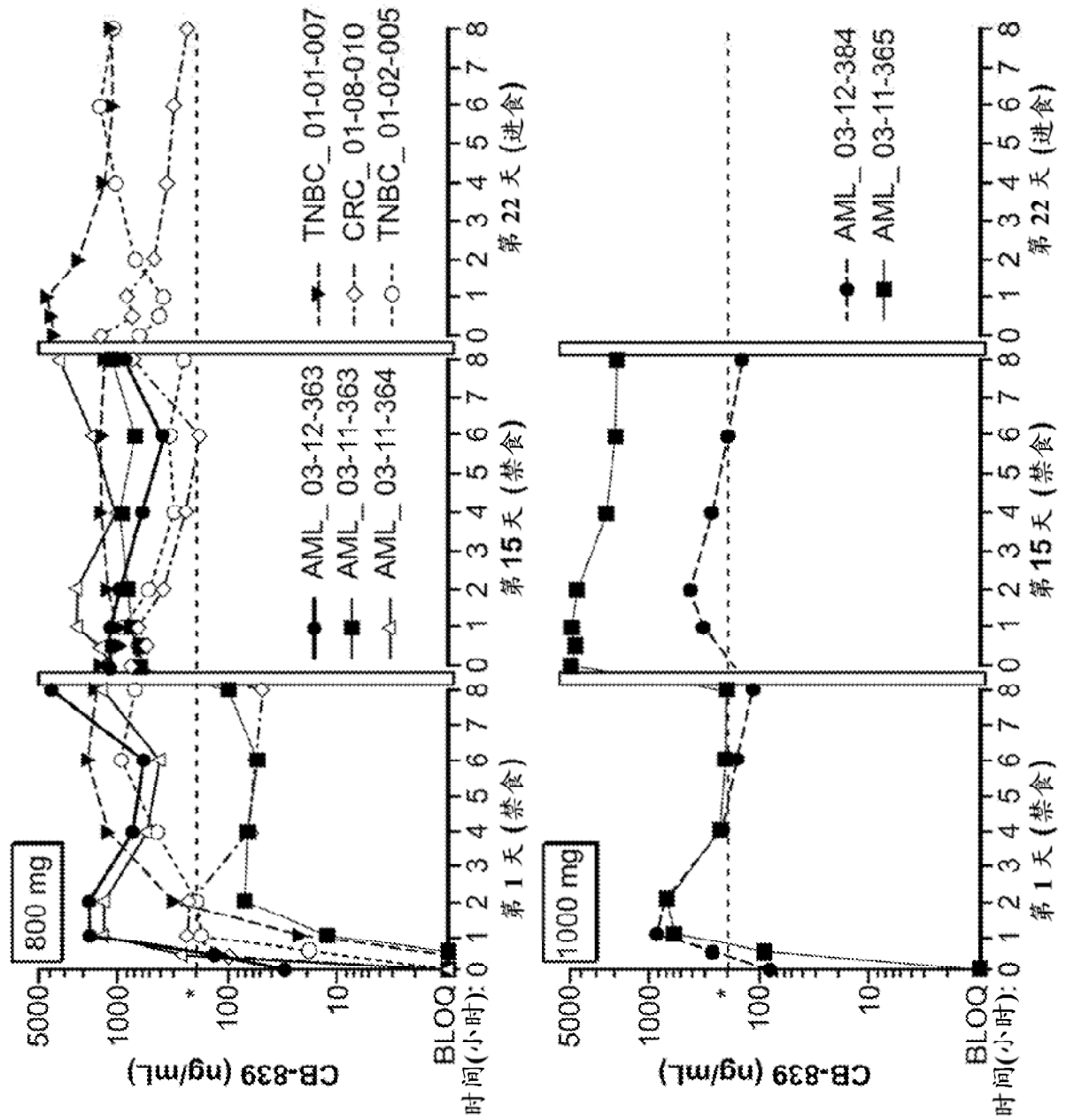


图 2(续)

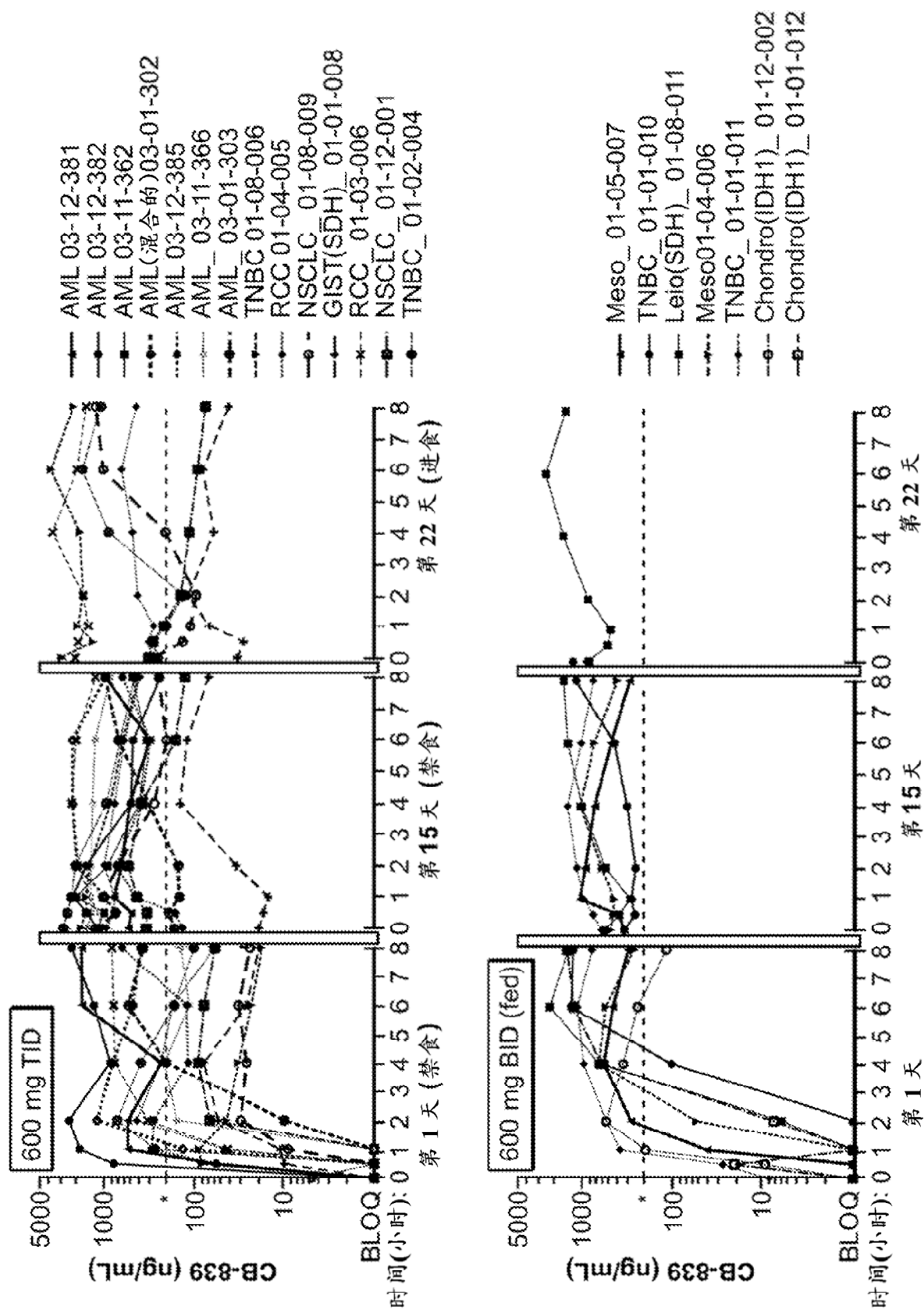


图 3

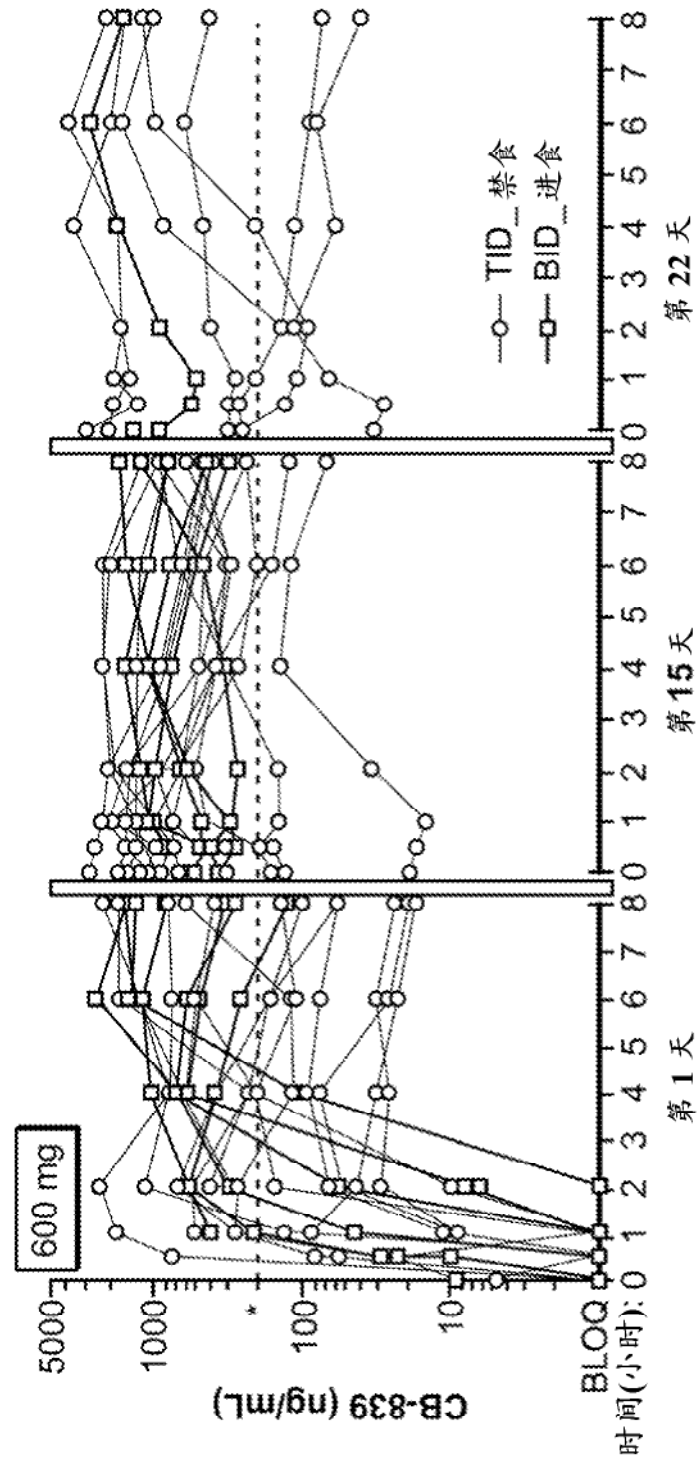


图 4

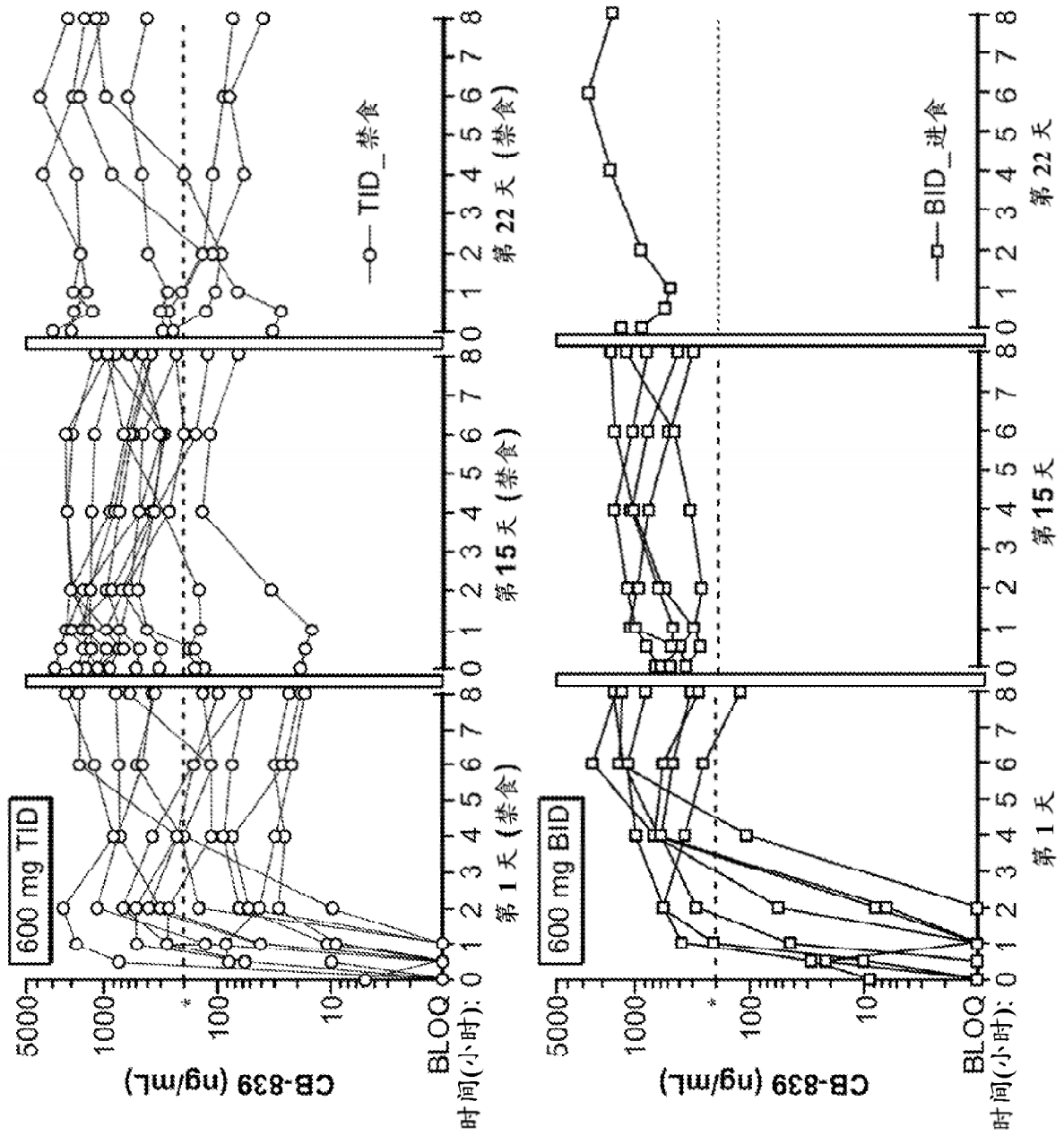


图 5

剂量 (mg)	100	150	250	400	600	800	600
方案	TID	TID	TID	TID	TID	TID	BID
N	3	4	10	3	7	3	8
AUC (0-8h) (ng*hr/mL)	1980	7167	3852	3959	6125	5575	6201
偏差 (%CV)	33%	98%	101%	46%	70%	72%	34%
C _{max} (ng/mL)	432	1467	778	846	1366	1019	1291
偏差 (%CV)	46%	87%	89%	38%	68%	35%	23%
C _{min} (ng/mL)	134	585	241	306	400	457	366
偏差 (%CV)	32%	108%	105%	80%	98%	92%	35%

图 6

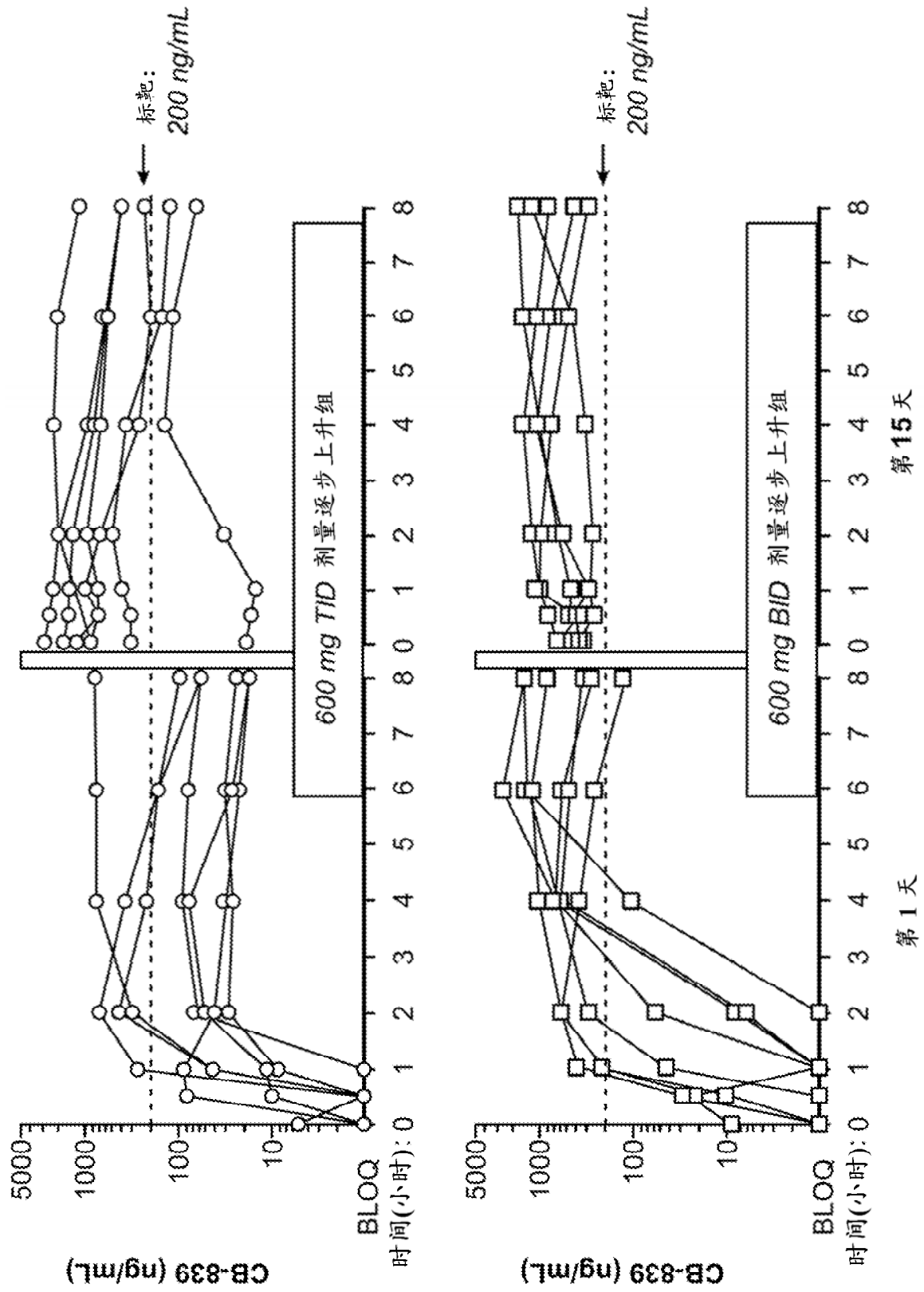


图 7

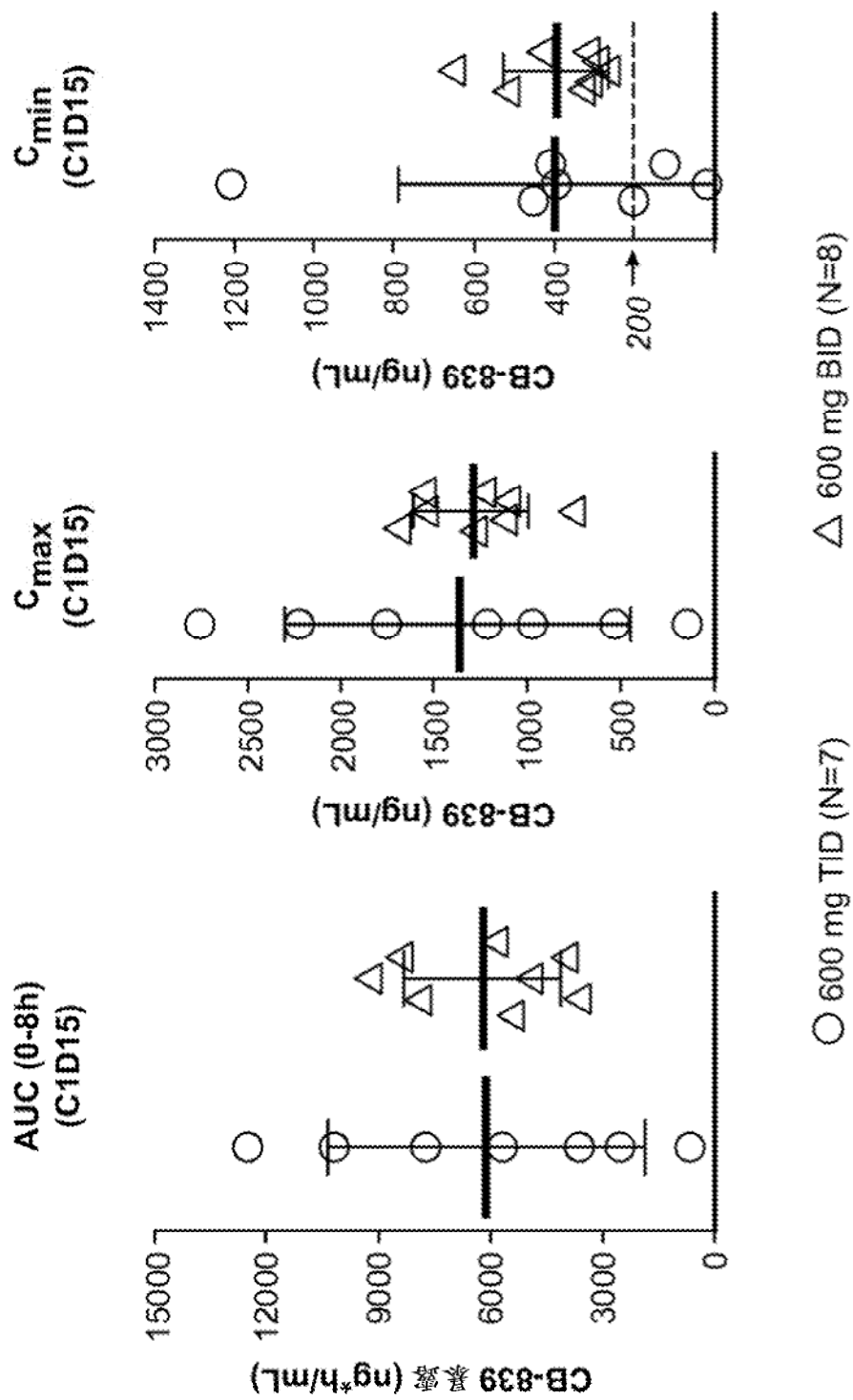


图 8