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. 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 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 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 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 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").

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").

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).

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.

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.

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 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 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 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 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 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 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 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 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 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 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 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

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-.

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.

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

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.

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 C_1-C_6 straight chained or branched alkyl group is also referred to as a "lower alkyl" group.

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 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 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

silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CF_3, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CF_3, -CN, and the like.

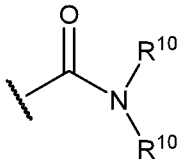
The term "C_{x-y}" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term "C_{x-y}alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-tirfluoroethyl, etc. C_0 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.

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-.

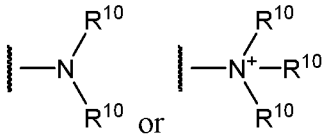
The term "alkynyl", as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the 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 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 R^{10} independently represent a hydrogen or hydrocarbyl group, or two R^{10} 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 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



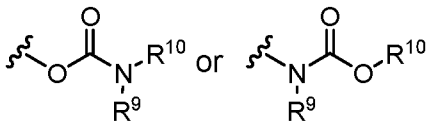
wherein each R^{10} independently represents a hydrogen or a hydrocarbyl group, or two R^{10} are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

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 R^9 and R^{10} independently represent hydrogen or a hydrocarbyl group, such as an alkyl group, or R^9 and R^{10} 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 susbstituted 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 "carbocyclylalkyl", as used herein, refers to an alkyl group substituted with a carbocycle group.

The term "carbonate" is art-recognized and refers to a group $-OCO_2-R^{10}$, wherein R^{10} represents a hydrocarbyl group.

The term "carboxy", as used herein, refers to a group represented by the formula $-CO_2H$.

The term "ester", as used herein, refers to a group $-C(O)OR^{10}$ 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.

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 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 "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 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 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, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

The term "heterocyclylalkyl", 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, heterocyclyl, 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 "polycyclyl", "polycycle", and "polycyclic" refer to two or more rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) 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.

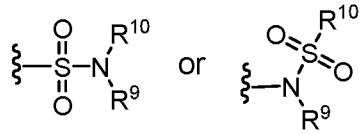
The term "silyl" refers to a silicon moiety with three hydrocarbyl moieties attached thereto.

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. 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 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 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 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 $-OSO_3H$, or a pharmaceutically acceptable salt thereof.

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



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

The term "sulfoxide" is art-recognized and refers to the group $-S(O)-R^{10}$, wherein R^{10} represents a hydrocarbyl.

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

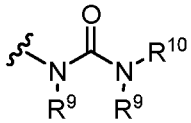
The term "sulfone" is art-recognized and refers to the group $-S(O)_2-R^{10}$, wherein R^{10} represents a hydrocarbyl.

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 $-C(O)SR^{10}$ or $-SC(O)R^{10}$ wherein R^{10} represents a hydrocarbyl.

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

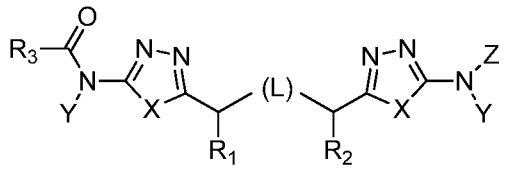


wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl, such as alkyl, or either occurrence of R^9 taken together with R^{10} and the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

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 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 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,



(I),

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 , 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, $CH_2CH_2CH_2$ or CH_2 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 $CH_2O(CO)R_7$;

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

Z represents H or $R_3(CO)$;

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

R_3, independently for each occurrence, represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroaryloxyalkyl or $C(R_8)(R_9)(R_{10})$, $N(R_4)(R_5)$ or OR_6, wherein any free hydroxyl group may be acylated to form $C(O)R_7$;

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, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form $C(O)R_7$;

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 $C(O)R_7$; and

R_8, R_9 and R_{10} 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, or R_8 and R_9 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 $C(O)R_7$;

preferably wherein the compound is administered with a meal.

In some embodiments, at least two of R_8, R_9 and R_{10} 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, 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.*, $C(O)CF_3$)), carbonylalkyl (such as carboxyalkyl, alkoxycarbonylalkyl, formylalkyl, or acylalkyl, including perfluoroacylalkyl (*e.g.*, -alkyl$C(O)CF_3$)), 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, $CH_2CH_2CH_2$, 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, $CH_2CH_2CH_2$ 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 CH=CH. In certain embodiments, one or both X represents CH=CH. In certain embodiments, each X represents S. In certain embodiments, one X represents S and the other X represents CH=CH.

In certain embodiments, Z represents $R_3(CO)$. In certain embodiments wherein Z is $R_3(CO)$, 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 $C(R_8)(R_9)(R_{10})$, 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 $R_3(CO)$, 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 $R_3(CO)$, R_1 and R_2 each represent H, and each R_3 represents $C(R_8)(R_9)(R_{10})$, 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 CH=CH, Z represents $R_3(CO)$, 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 R_3 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 R_3 are not identical.

In certain embodiments, L represents CH_2CH_2, Y represents H, X represents S, Z represents $R_3(CO)$, R_1 and R_2 each represent H, and each R_3 represents $C(R_8)(R_9)(R_{10})$, wherein R_8 represents aryl, arylalkyl or heteroaryl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl or alkoxy. In certain such embodiments, R_8 represents aryl and R_{10} represents hydroxyalkyl. In certain such embodiments, each occurrence of R_3 is identical.

In certain embodiments wherein L represents CH_2, $CH_2CH_2CH_2$ or CH_2CH_2, X represents O, and Z represents $R_3(CO)$, both R_3 groups are not alkyl, such as methyl, or $C(R_8)(R_9)(R_{10})$, wherein R_8, R_9 and R_{10} are each independently hydrogen or alkyl.

In certain embodiments wherein L represents CH_2CH_2, X represents S, and Z represents $R_3(CO)$, both R_3 groups are not phenyl or heteroaryl, such as 2-furyl.

In certain embodiments wherein L represents CH_2CH_2, X represents O, and Z represents $R_3(CO)$, both R_3 groups are not $N(R_4)(R_5)$ wherein R_4 is aryl, such as phenyl, and R_5 is H.

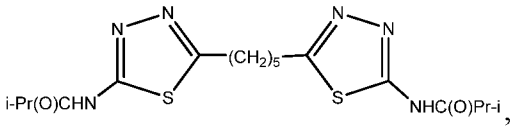
In certain embodiments wherein L represents CH_2SCH_2, X represents S, and Z represents $R_3(CO)$, both R_3 groups are not aryl, such as optionally substituted phenyl, aralkyl, such as benzyl, heteroaryl, such as 2-furyl, 2-thienyl or 1,2,4-trizole, substituted or unsubstituted alkyl, such as methyl, 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 CH_2SCH_2, X represents S, and Z represents $R_3(CO)$, both R_3 groups are not optionally substituted phenyl, aralkyl, heteroaryl, substituted or unsubstituted alkyl, or alkoxy.

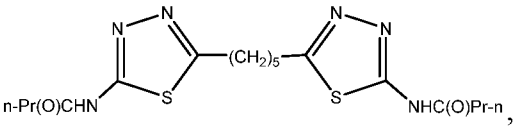
In certain embodiments wherein L represents CH_2SCH_2, X represents S, and Z represents $R_3(CO)$, both R_3 groups are not $N(R_4)(R_5)$ wherein R_4 is aryl, such as substituted or unsubstituted phenyl (*e.g.*, phenyl, 3-tolyl, 4-tolyl, 4-bromophenyl or 4-nitrophenyl), and R_5 is H.

In certain embodiments wherein L represents $CH_2CH_2CH_2$, X represents S, and Z represents $R_3(CO)$, both R_3 groups are not alkyl, such as methyl, ethyl, or propyl, cycloalkyl, such as cyclohexyl, or $C(R_8)(R_9)(R_{10})$, wherein any of R_8, R_9 and R_{10} together with the C to which they are attached, form any of the foregoing.

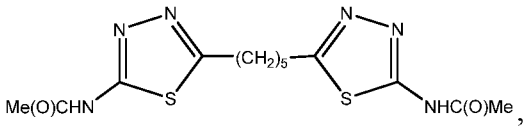
In certain embodiments, the compound is not one of the following:



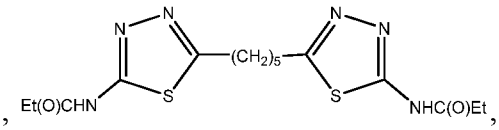
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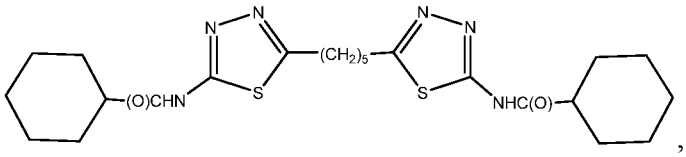
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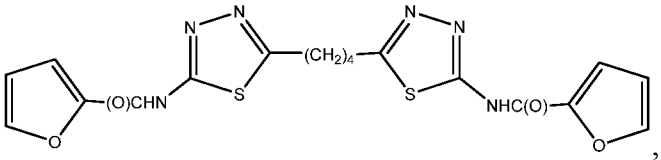
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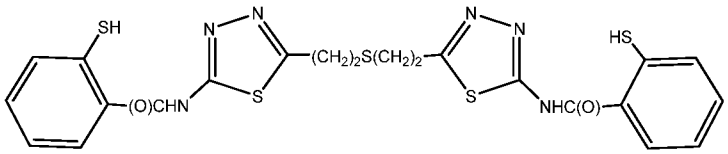
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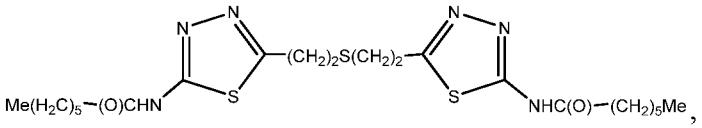
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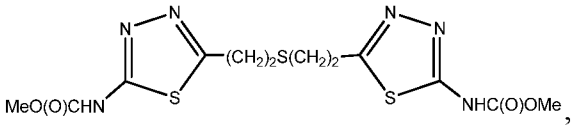
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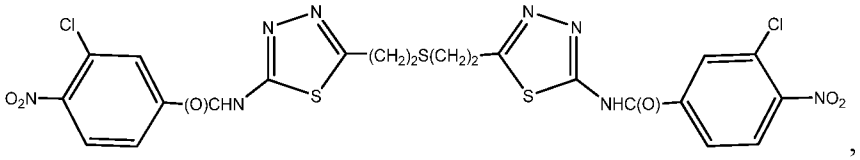
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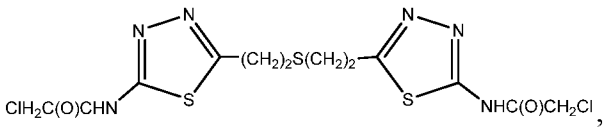
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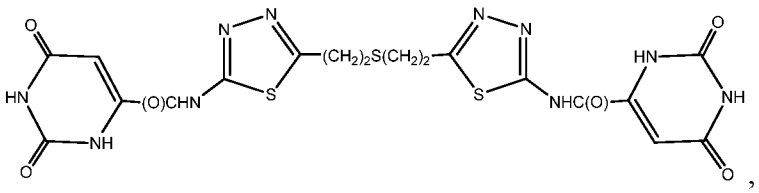
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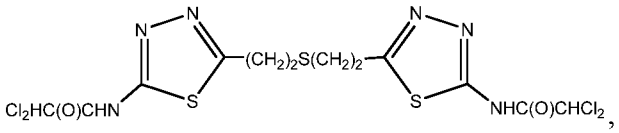


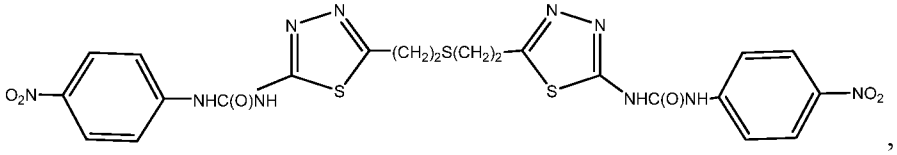
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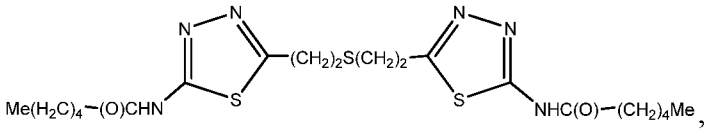


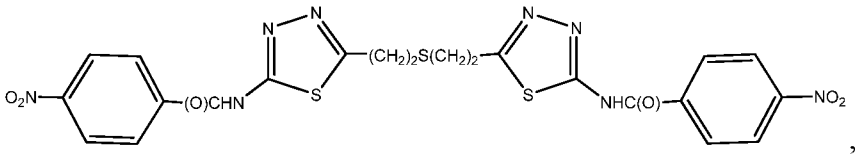
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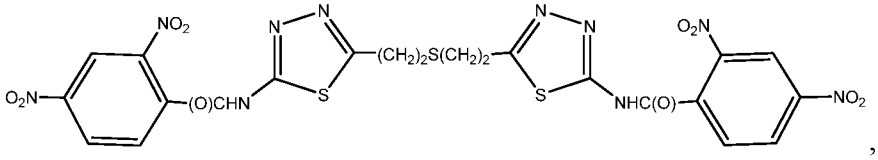


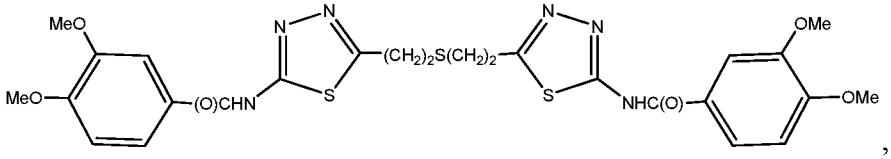


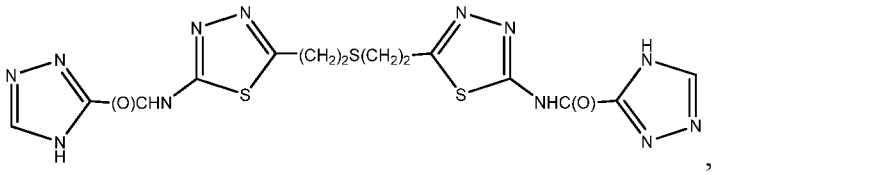


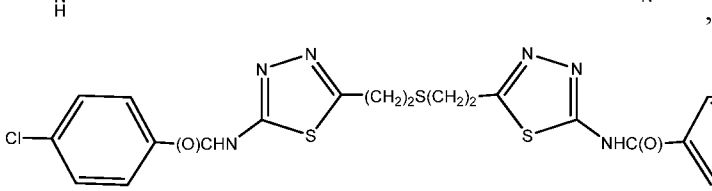


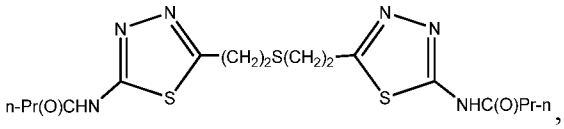


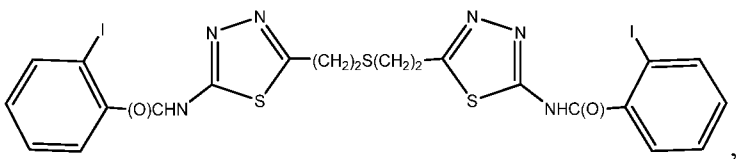


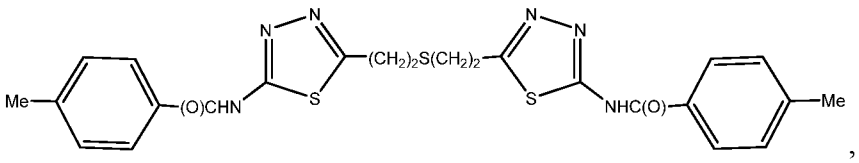


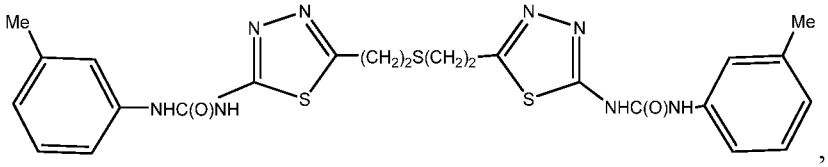


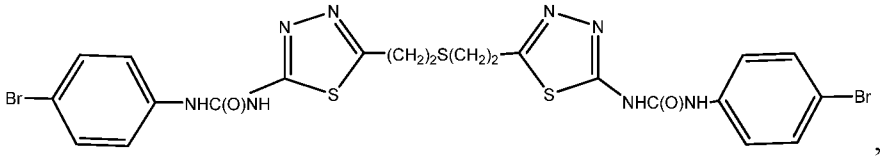


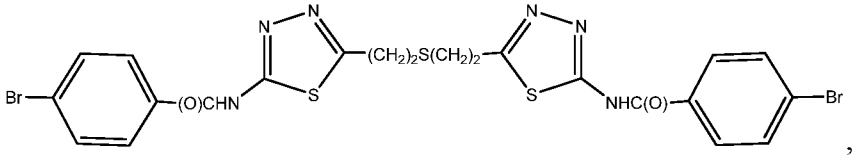


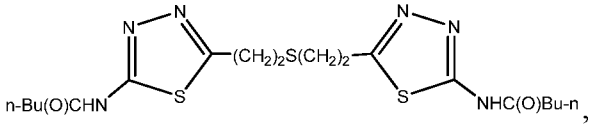


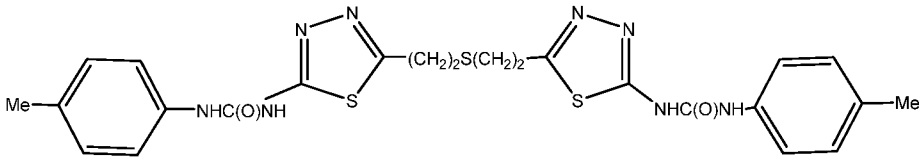

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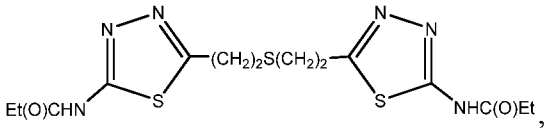

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NHC(O)NH
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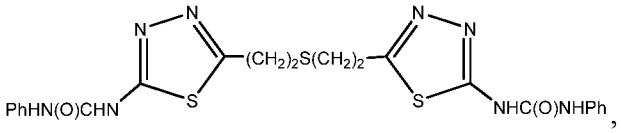

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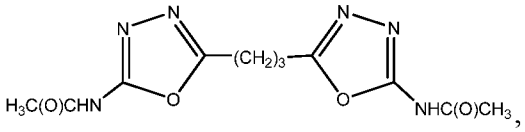

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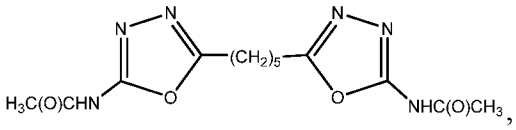

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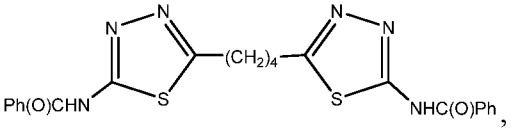

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NHC(O)NH
Me
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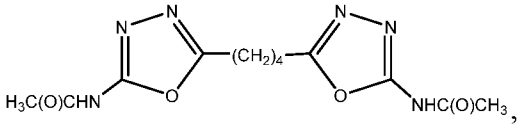

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NHC(O)Et
,

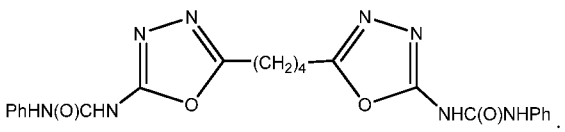

PhHN(O)CHN
(CH2)2S(CH2)2
NHC(O)NHPh
,


H3C(O)CHN
(CH2)3
NHC(O)CH3
,

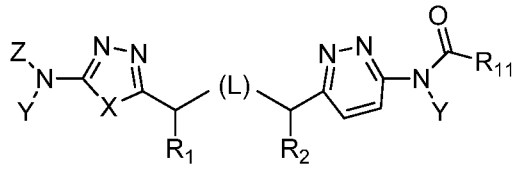

H3C(O)CHN
(CH2)5
NHC(O)CH3
,


Ph(O)CHN
(CH2)4
NHC(O)Ph
,


H3C(O)CHN
(CH2)4
NHC(O)CH3
, or


PhHN(O)CHN
(CH2)4
NHC(O)NHPh
.

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,



(Ia),

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 , 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, $CH_2CH_2CH_2$ or CH_2 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;

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 $R_3(CO)$;

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, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroaryloxyalkyl or $C(R_8)(R_9)(R_{10})$, $N(R_4)(R_5)$ or OR_6, wherein any free hydroxyl group may be acylated to form $C(O)R_7$;

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, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form $C(O)R_7$;

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 $C(O)R_7$; and

R_8, R_9 and R_{10} 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, or R_8 and R_9 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 $C(O)R_7$, and wherein at least two of R_8, R_9 and R_{10} are not H;

R_{11} represents substituted or unsubstituted aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, or $C(R_{12})(R_{13})(R_{14})$, $N(R_4)(R_{14})$ or OR_{14}, wherein any free hydroxyl group may be acylated to form $C(O)R_7$;

R_{12} and R_{13} each independently respresent 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; and

R_{14} represents substituted or unsubstituted aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl;

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 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.*, $C(O)CF_3$)), carbonylalkyl (such as carboxyalkyl, alkoxycarbonylalkyl, formylalkyl, or acylalkyl, including perfluoroacylalkyl (*e.g.*, -alkyl$C(O)CF_3$)), 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, R_{11} represents substituted or unsubstituted arylalkyl, such as substituted or unsubstituted benzyl.

In certain embodiments, L represents CH_2SCH_2, CH_2CH_2, $CH_2CH_2CH_2$, 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, $CH_2CH_2CH_2$ or CH_2 may be replaced by hydroxyl. In certain embodiments, L represents CH_2SCH_2, CH_2CH_2, CH_2S or SCH_2, preferably CH_2CH_2. In certain embodiments, L is not CH_2SCH_2.

In certain embodiments, each Y represents H. In other embodiments, at least one Y is $CH_2O(CO)R_7$.

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

In certain embodiments, R_1 and R_2 each represent H.

In certain embodiments, Z represents $R_3(CO)$. In certain embodiments wherein Z is $R_3(CO)$, R_3 and R_{11} are not identical (*e.g.*, the compound of formula I is not symmetrical).

In certain embodiments, Z represents $R_3(CO)$ and R_3 represents arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl. In certain embodiments, Z represents $R_3(CO)$ and R_3 represents $C(R_8)(R_9)(R_{10})$, 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, Z represents $R_3(CO)$ and R_3 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 $R_3(CO)$, 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.

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 $R_3(CO)$, R_1 and R_2 each represent H, and each R_3 represents $C(R_8)(R_9)(R_{10})$, 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. In certain such embodiments, R_8 represents heteroaryl.

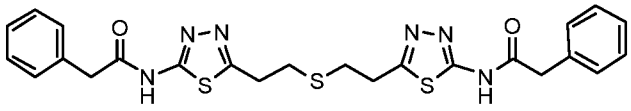
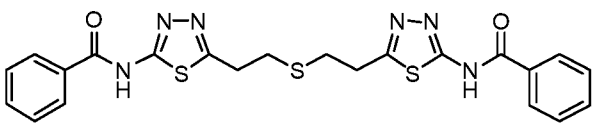
In certain embodiments, L represents CH_2CH_2, Y represents H, X represents S or CH=CH, such as S, Z represents $R_3(CO)$, R_1 and R_2 each represent H, R_3 represents substituted or unsubstituted arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl, and R_{11} represents arylalkyl. In certain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

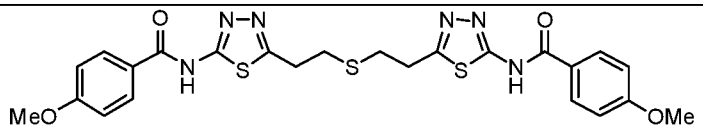
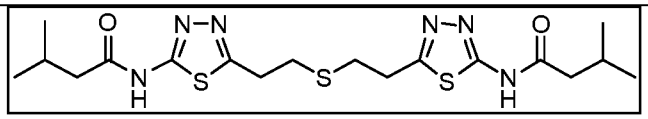
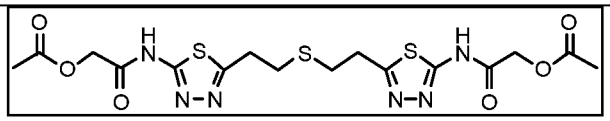
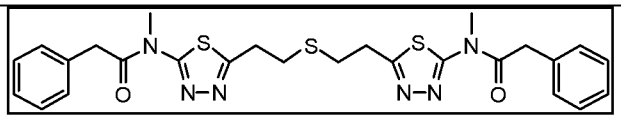
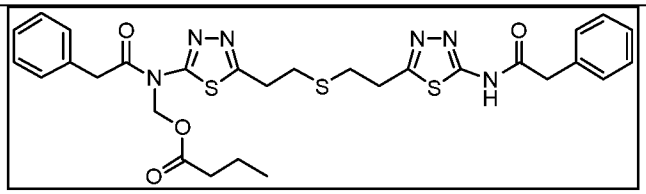
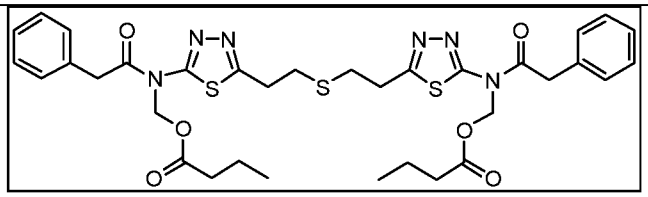
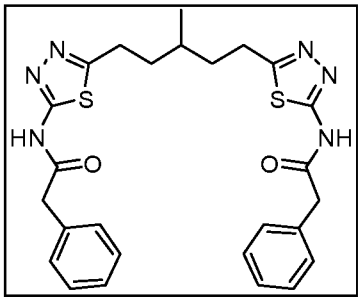
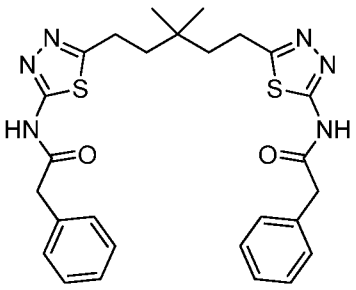
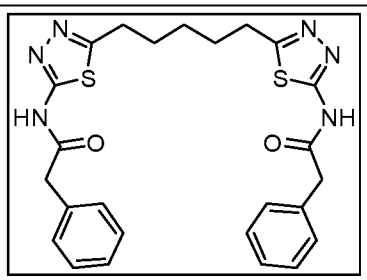
In certain embodiments, L represents CH_2CH_2, Y represents H, X represents S, Z represents $R_3(CO)$, R_1 and R_2 each represent H, R_3 represents $C(R_8)(R_9)(R_{10})$, wherein R_8 represents aryl, arylalkyl or heteroaryl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl or alkoxy, and 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.

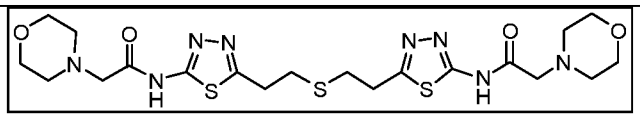
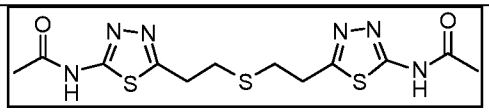
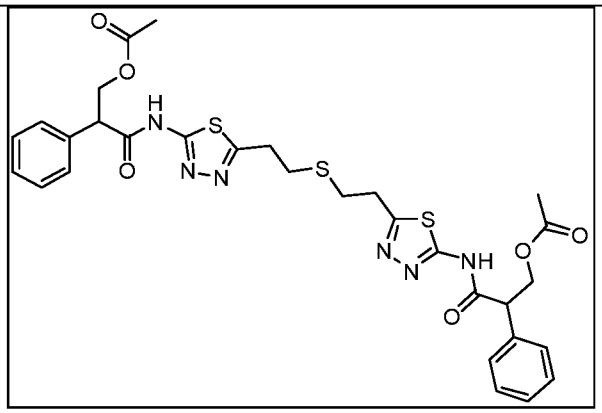
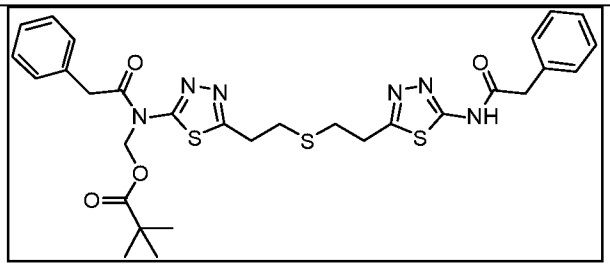
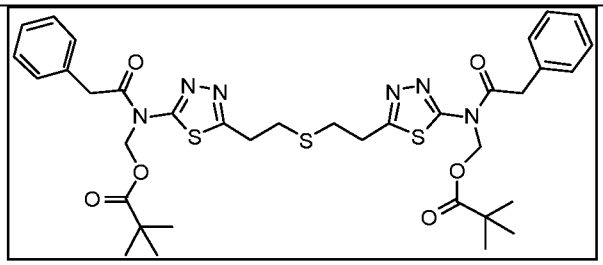
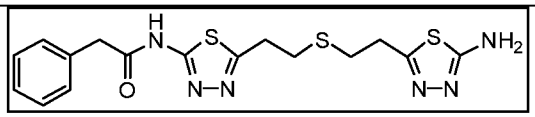
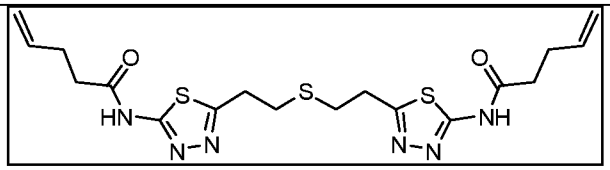
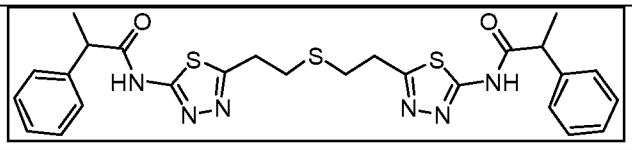
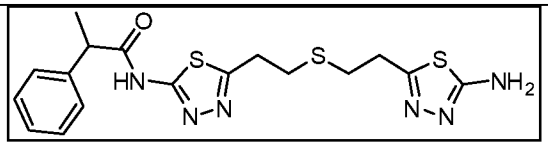
In certain embodiments, the compound is selected from any one of the compounds disclosed in Table 1. Preferably, the compound is selected from compound 1, 2, 6, 7, 8, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 36, 38, 39, 40, 41, 43, 44, 47, 48, 50, 51, 52, 54, 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,

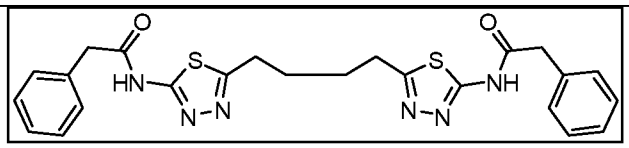
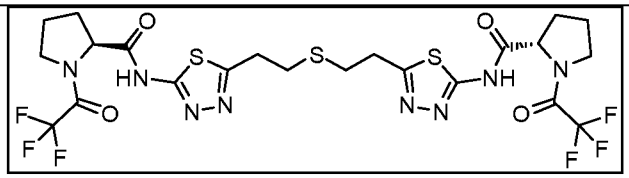
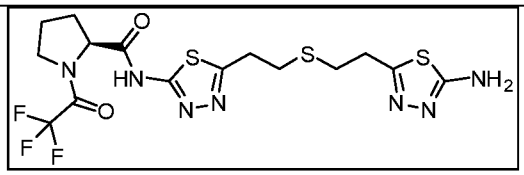
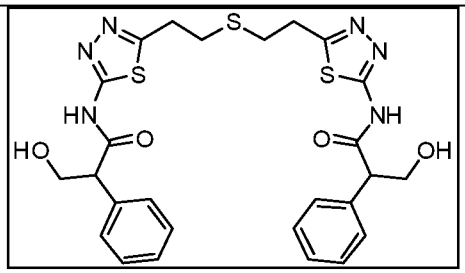
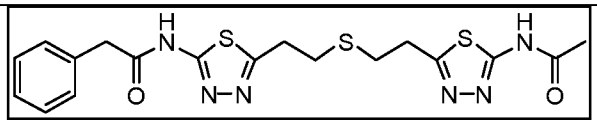
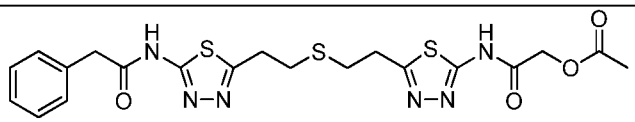
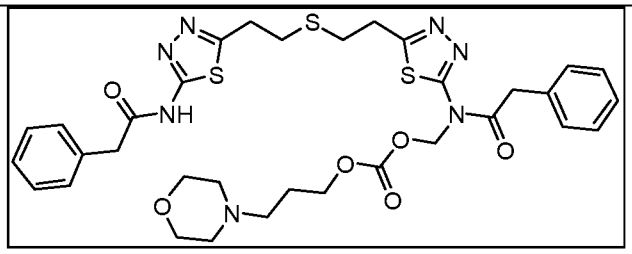
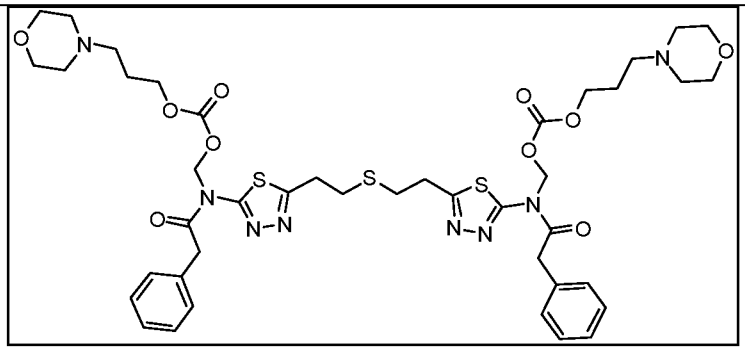
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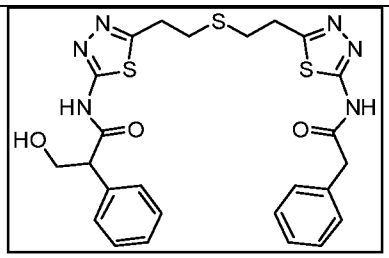
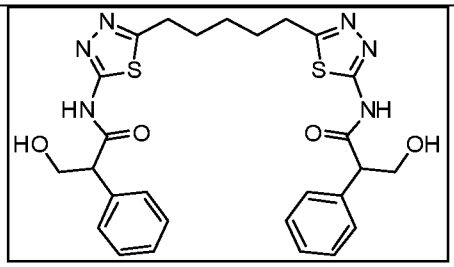
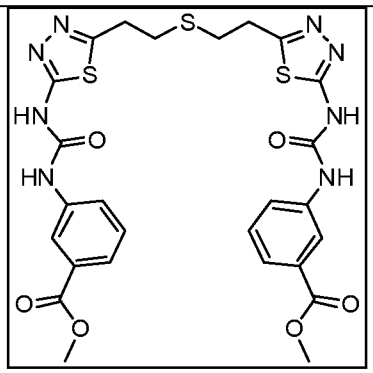
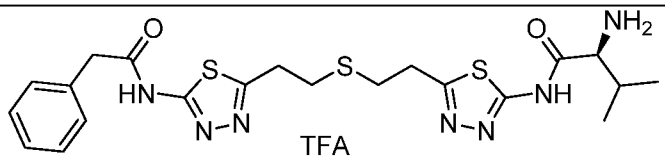
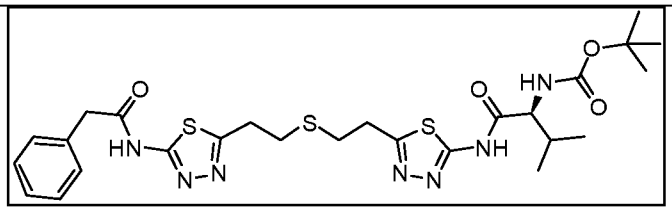
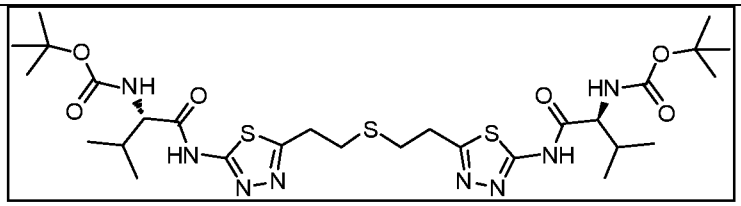
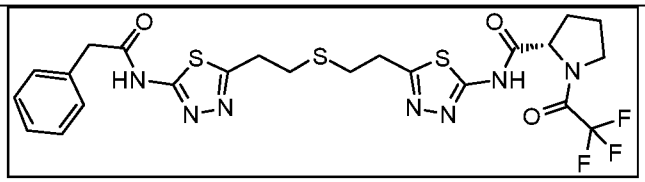
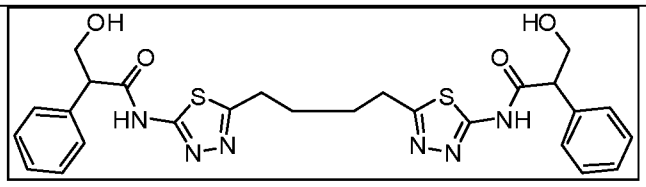
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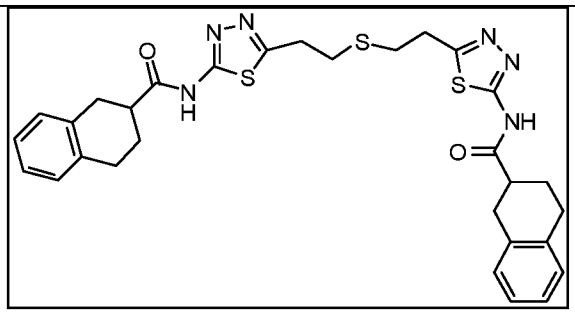
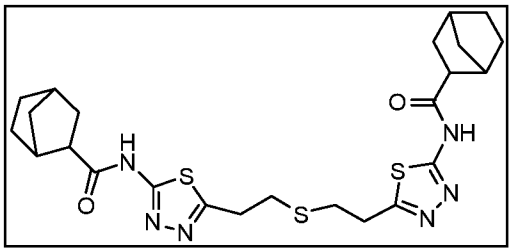
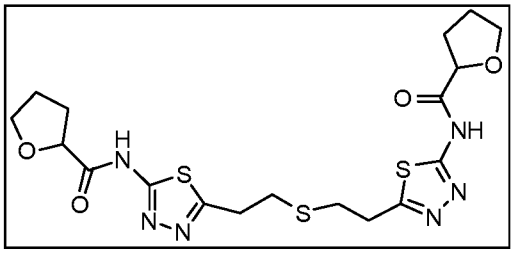
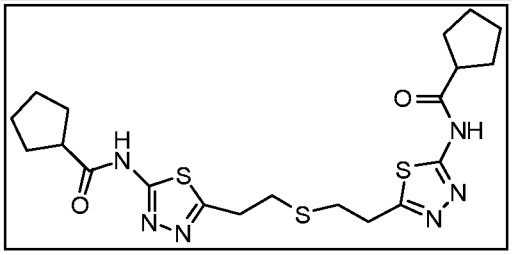
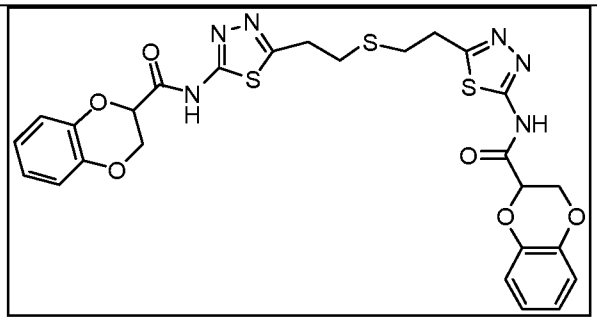
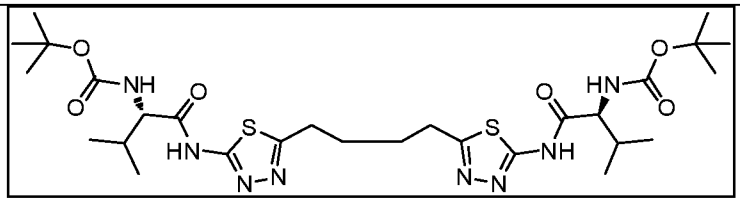
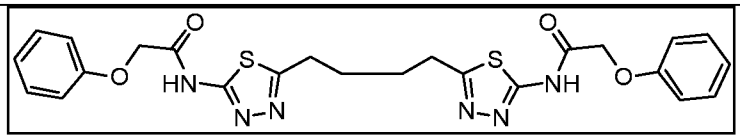
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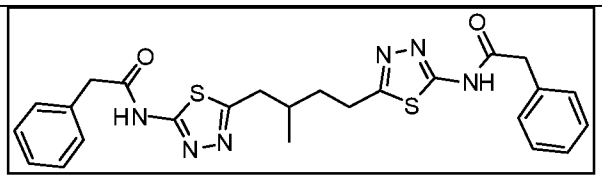
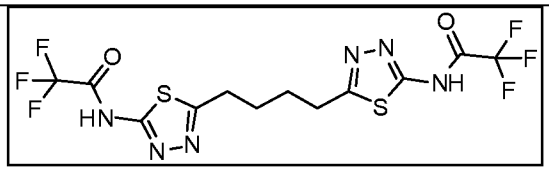
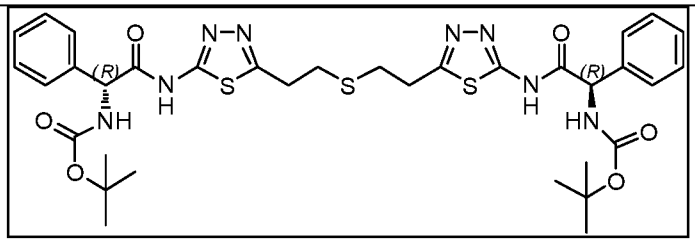
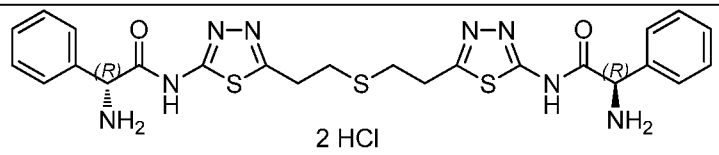
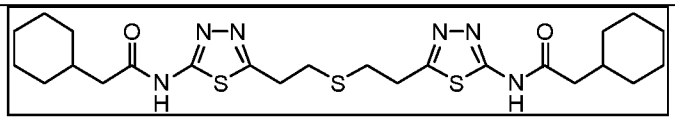
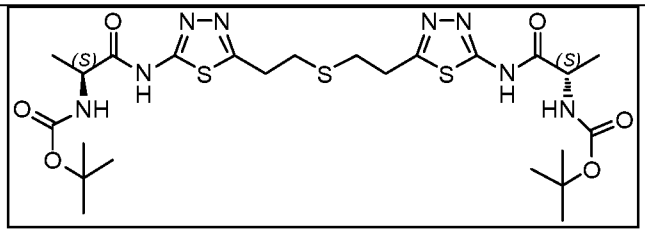
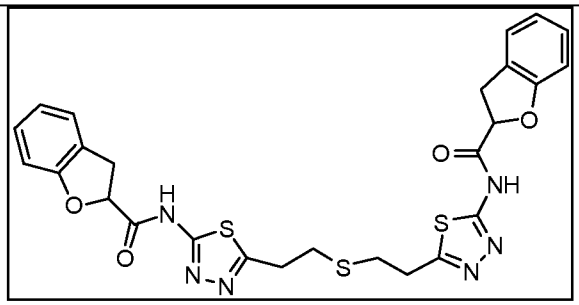
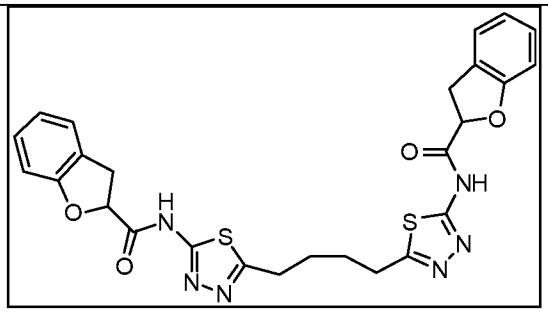
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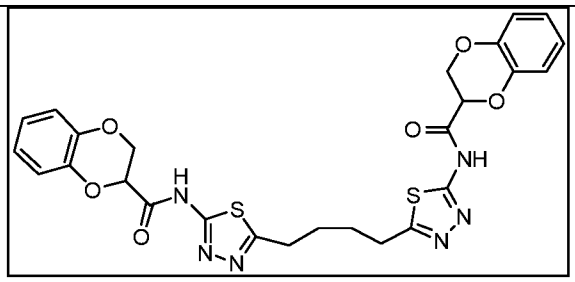
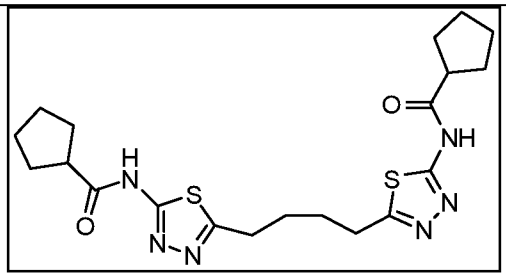
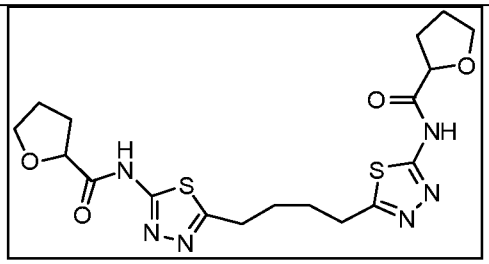
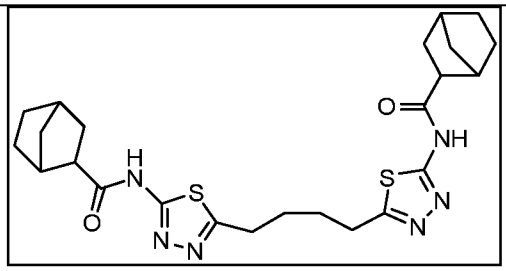
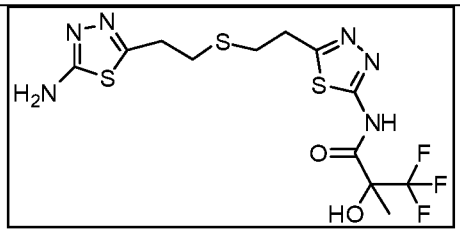
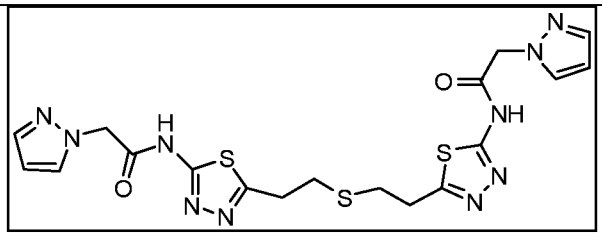
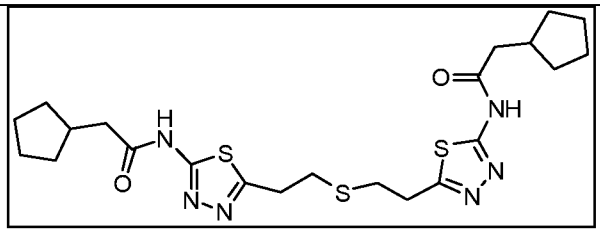
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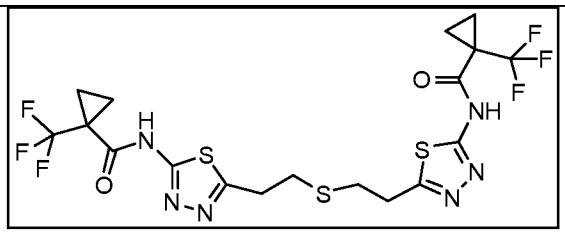
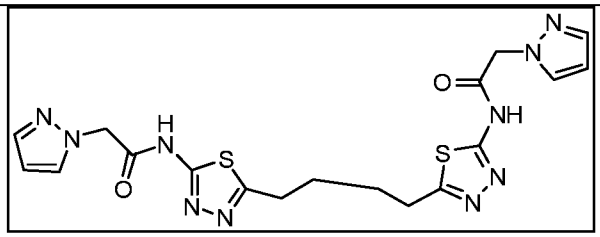
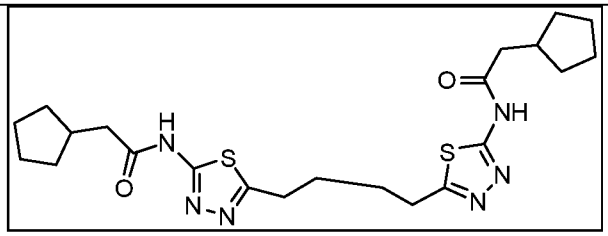
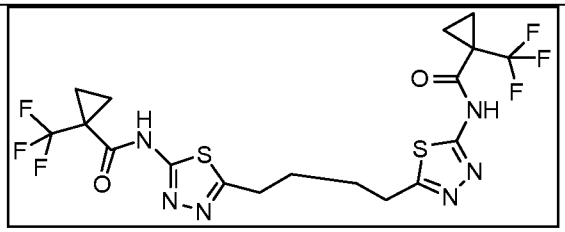
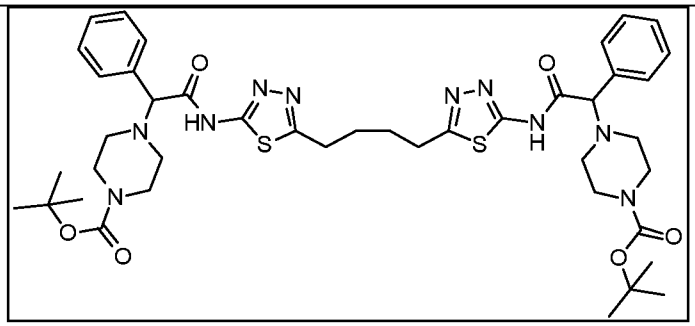
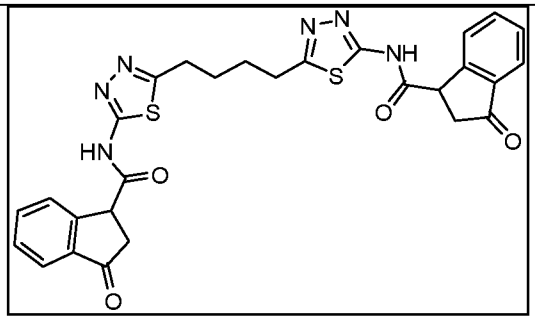
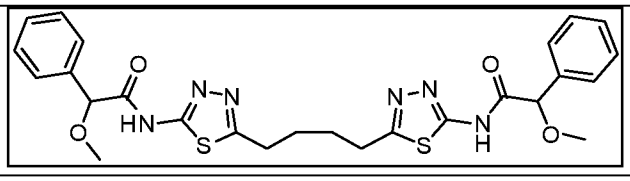
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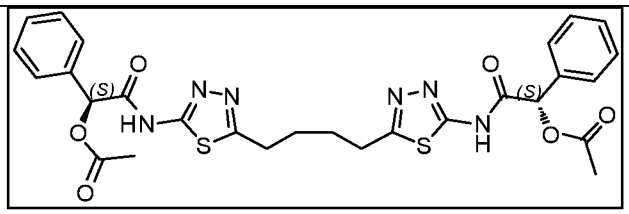
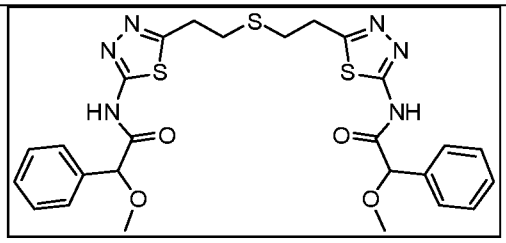
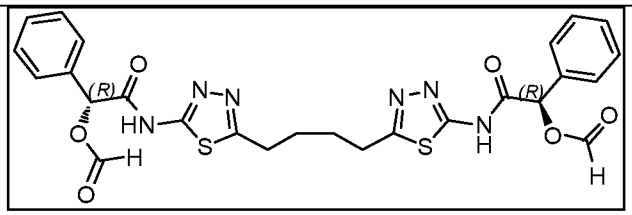
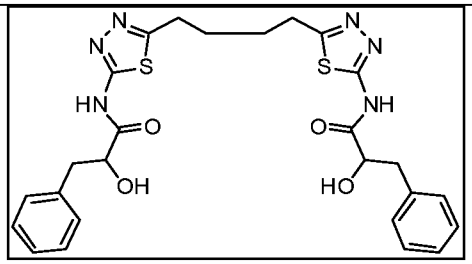
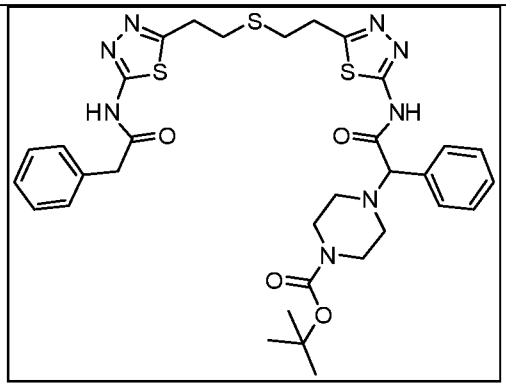
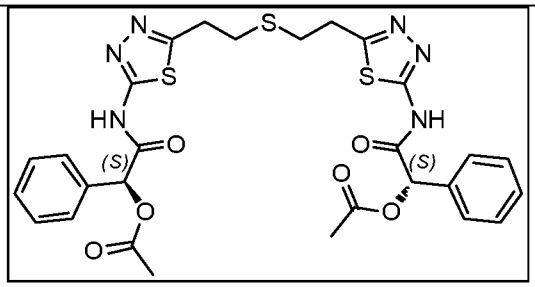
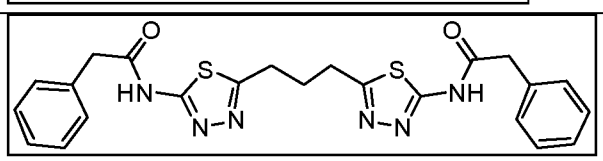
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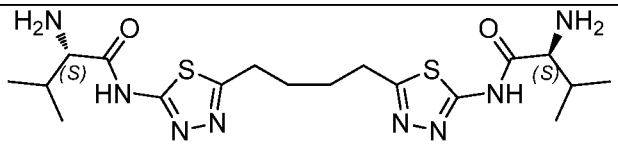
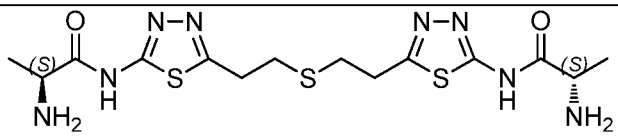
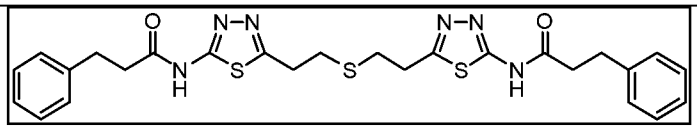
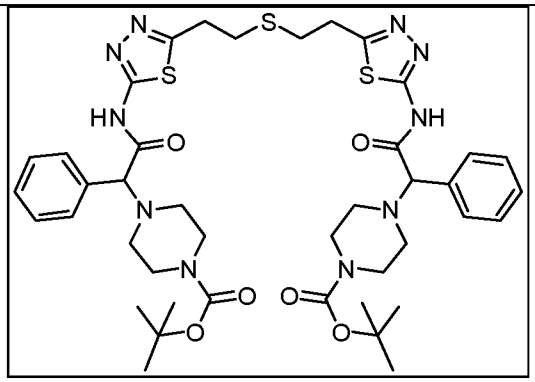
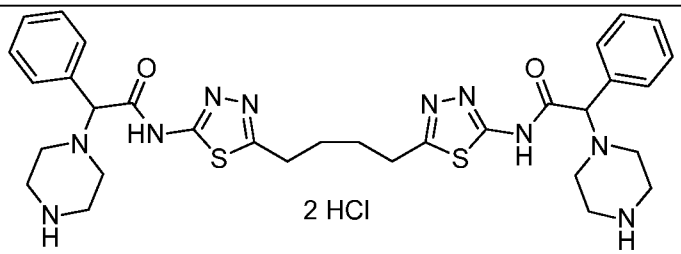
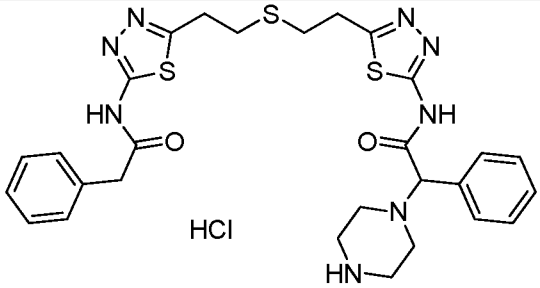
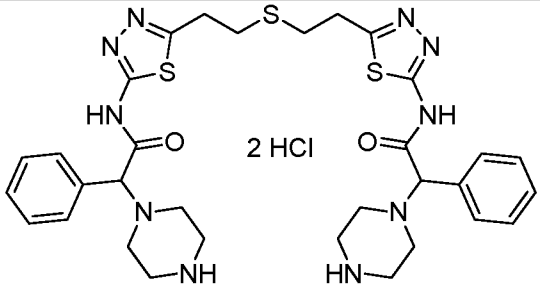
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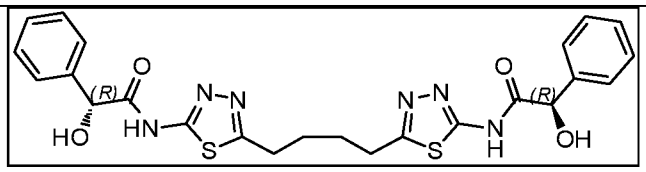
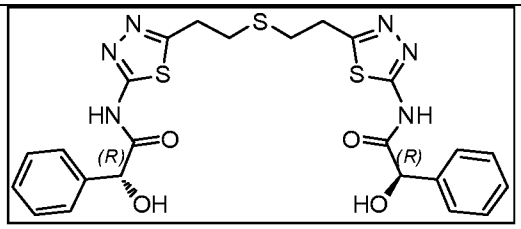
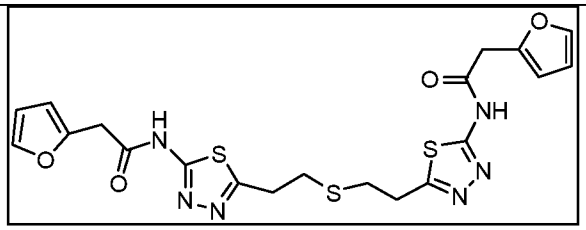
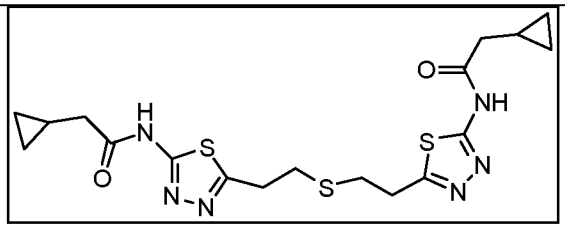
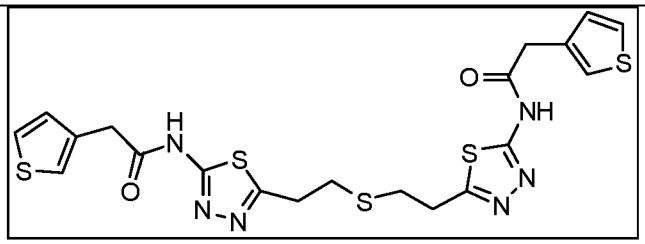
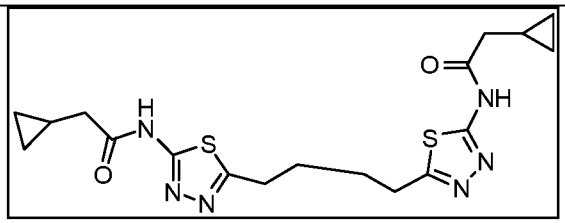
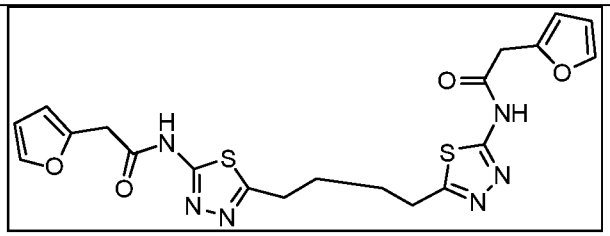
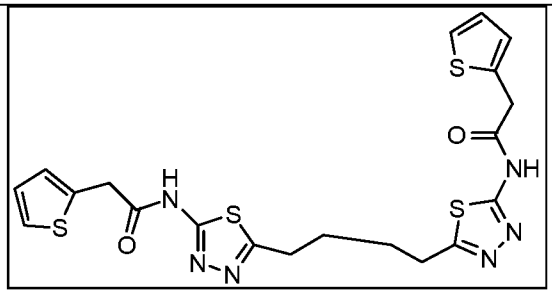
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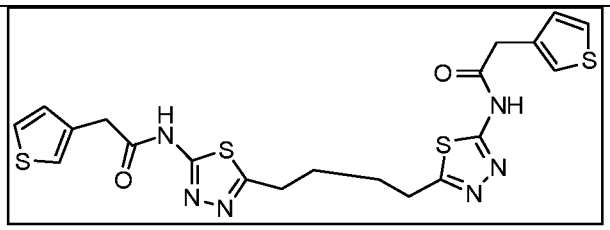
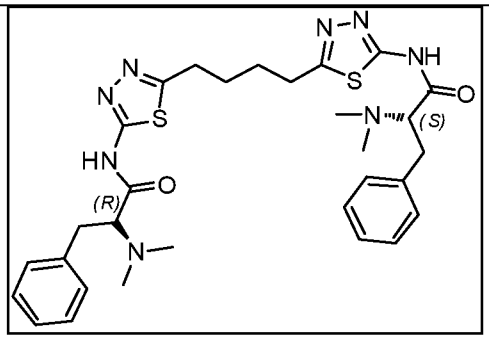
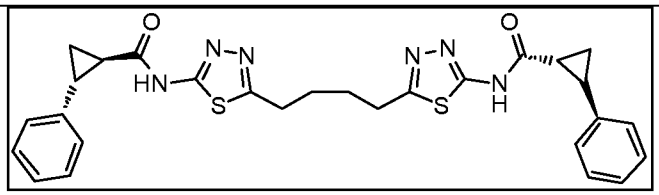
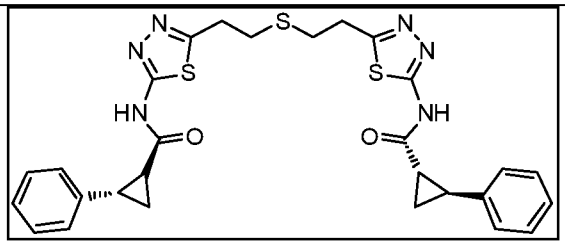
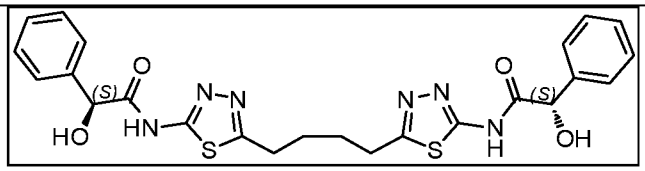
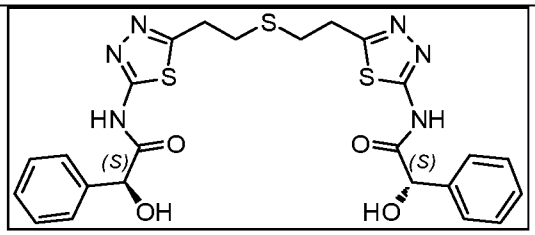
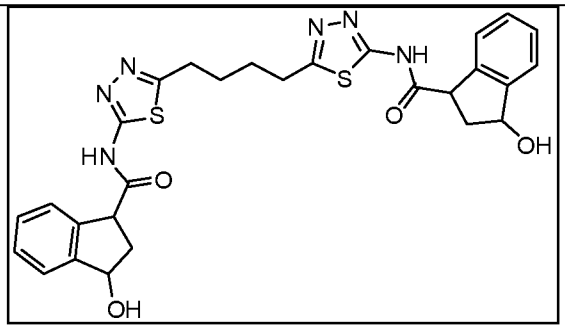
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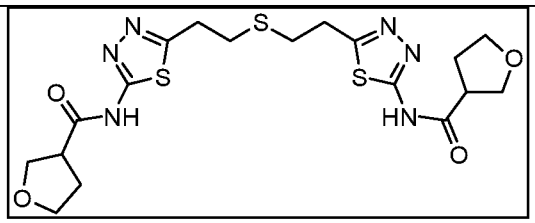
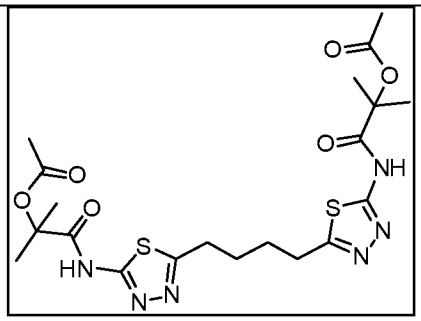
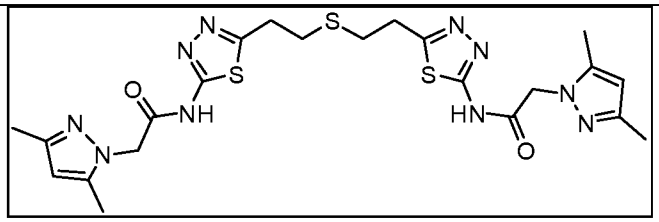
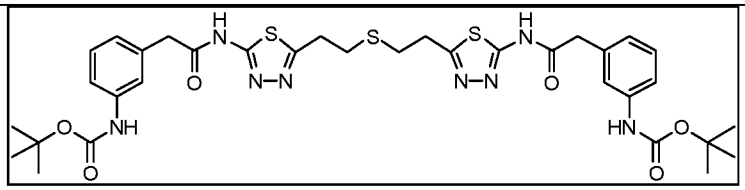
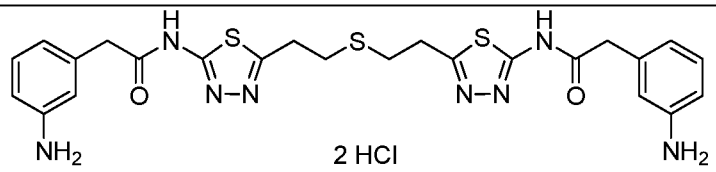
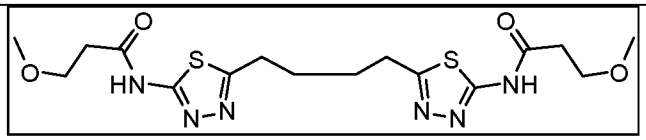
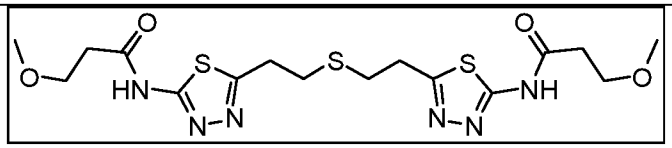
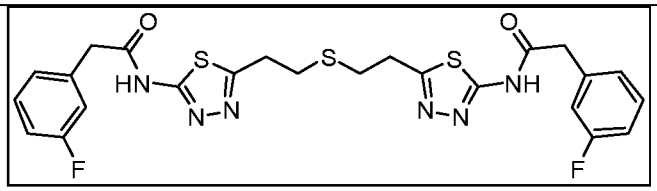
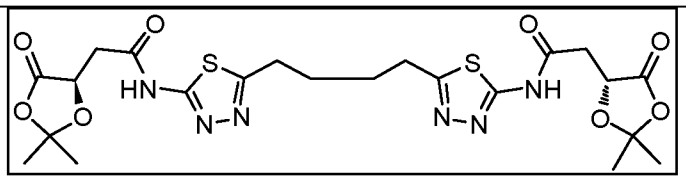
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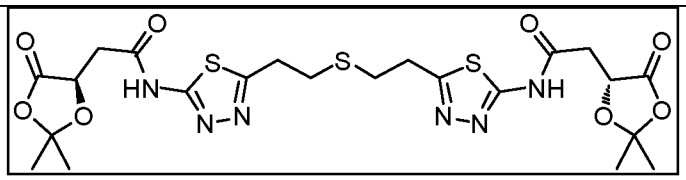
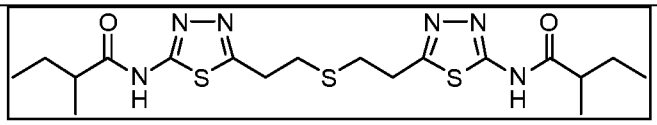
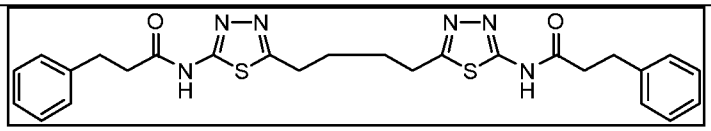
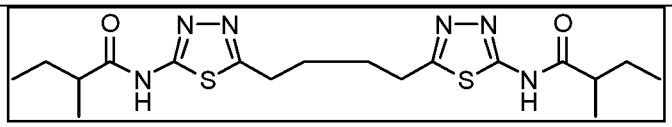
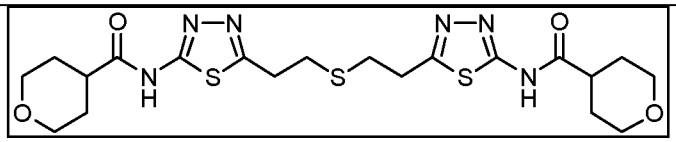
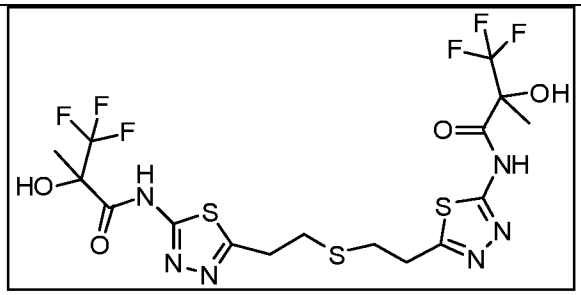
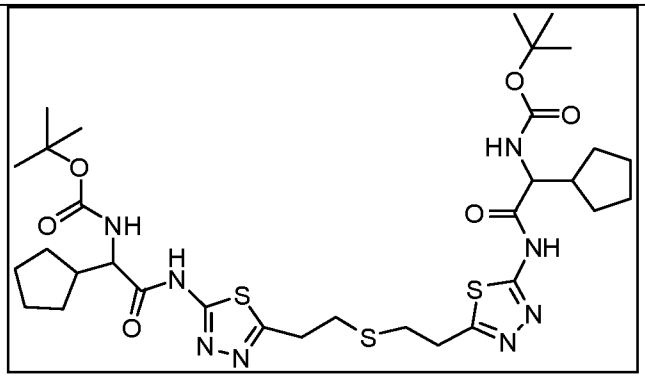
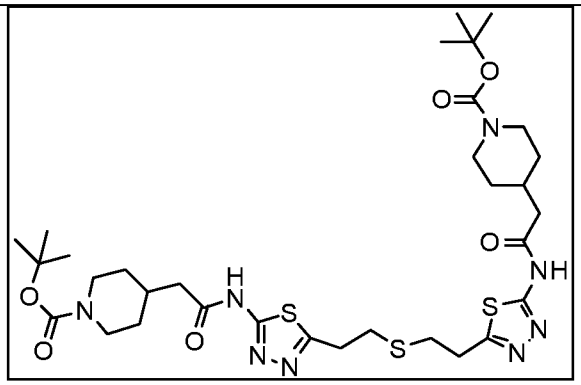
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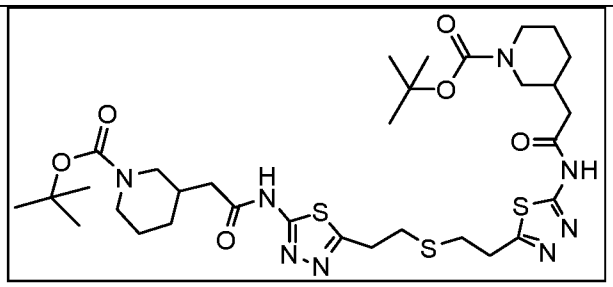
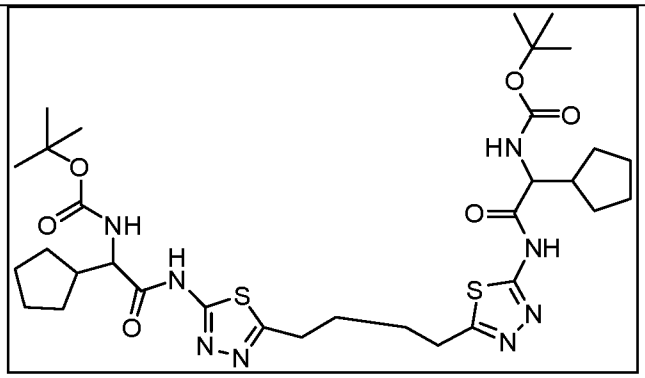
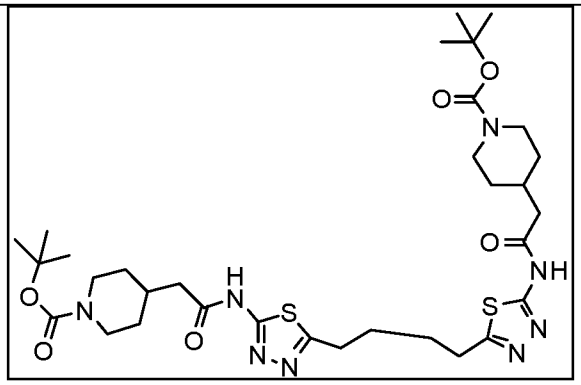
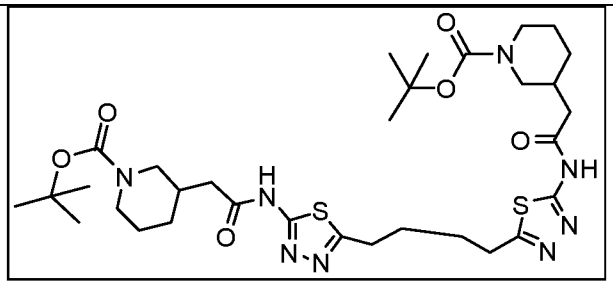
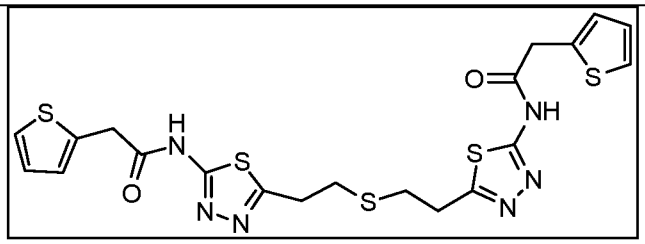
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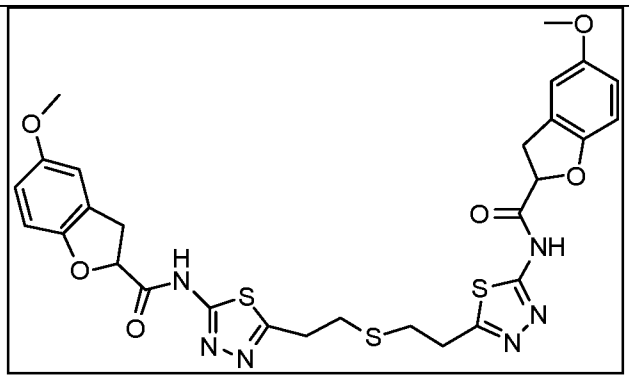
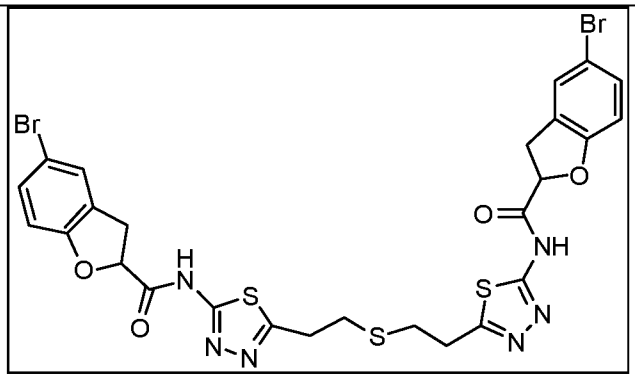
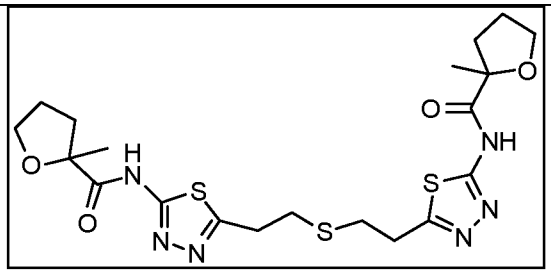
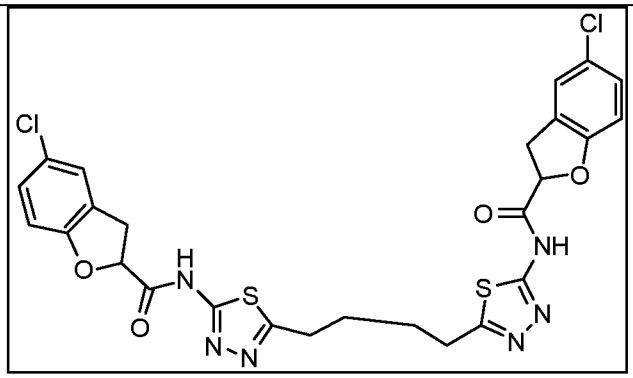
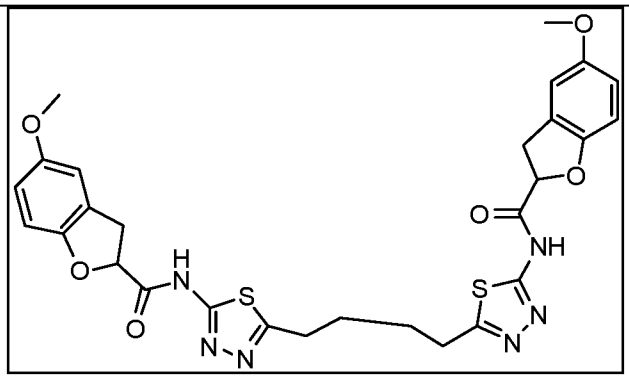
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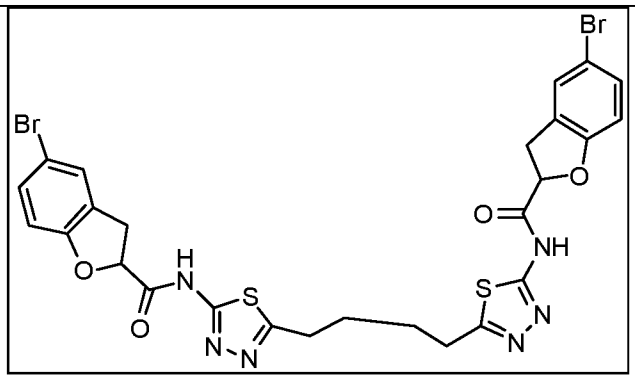
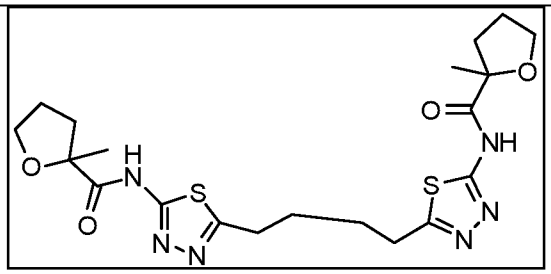
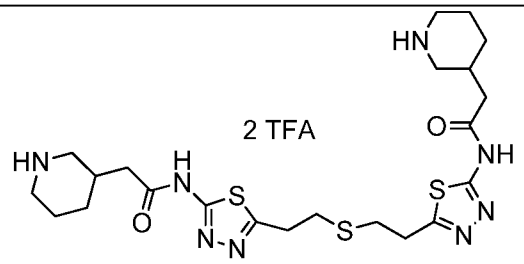
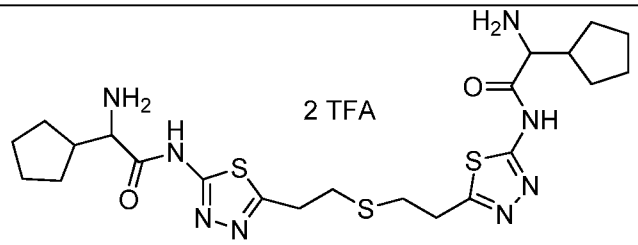
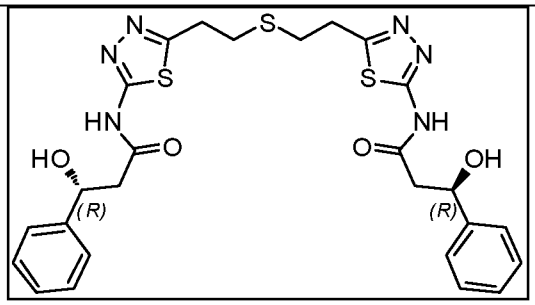
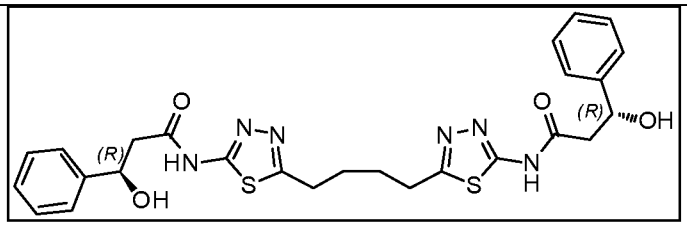
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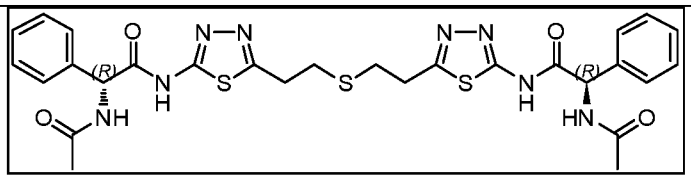
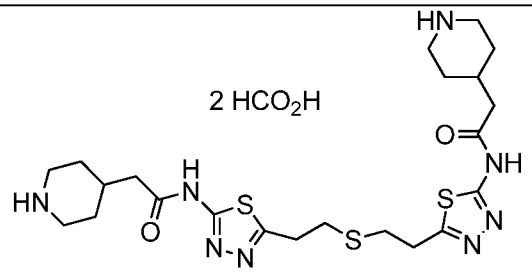
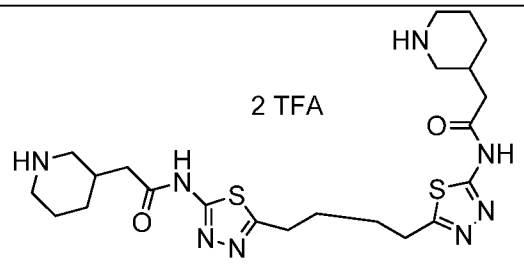
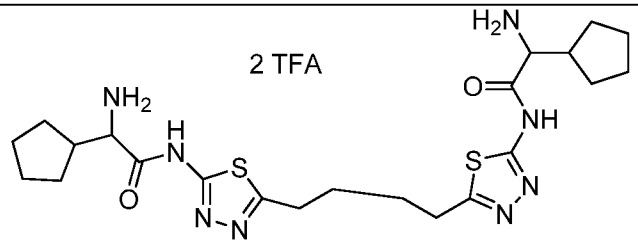
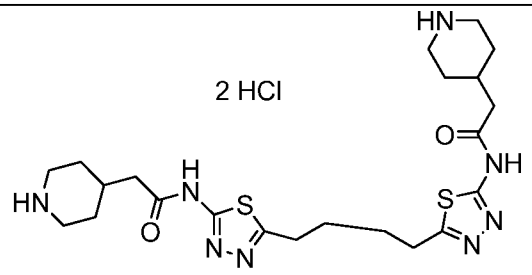
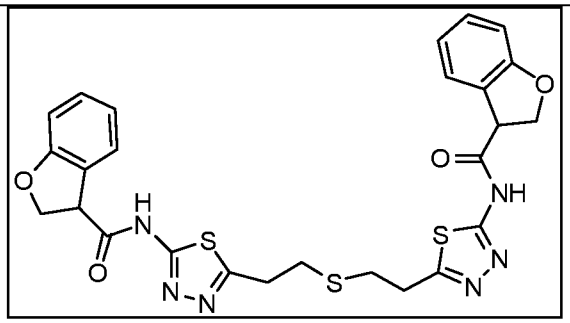
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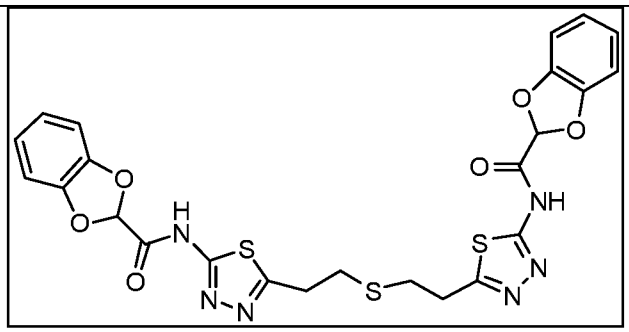
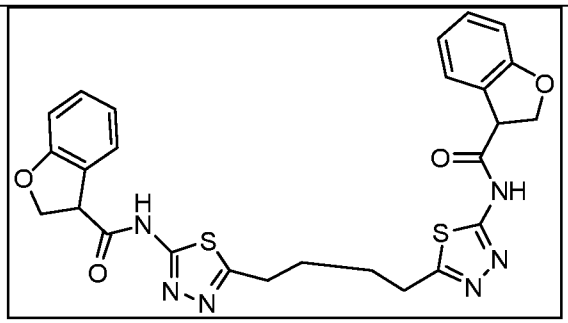
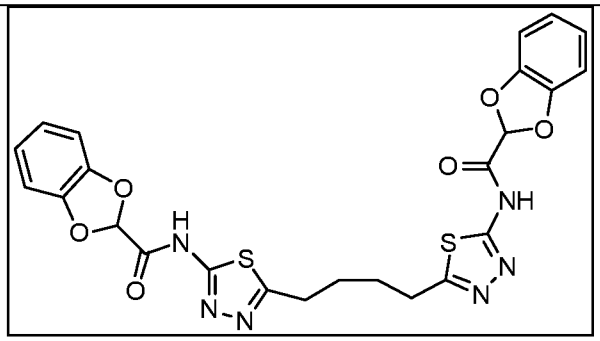
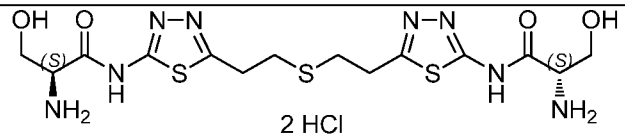
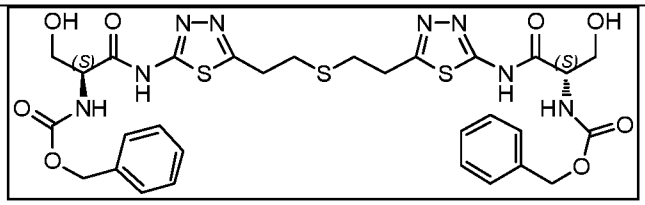
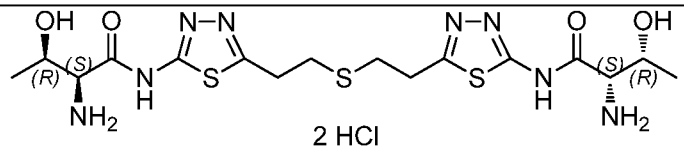
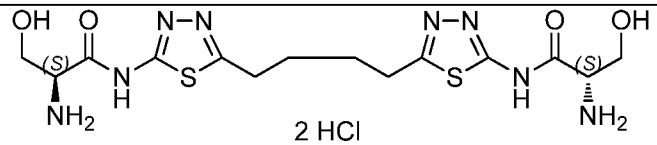
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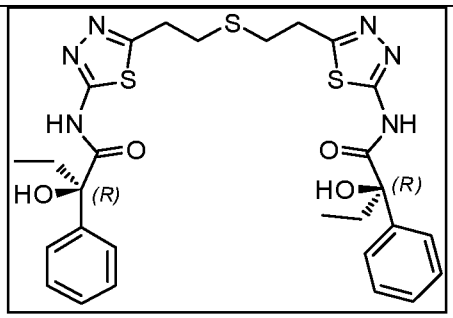
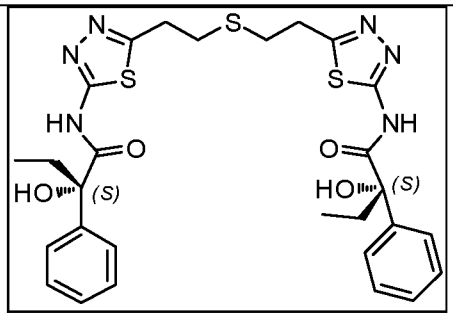
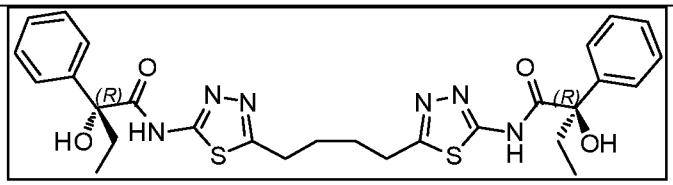
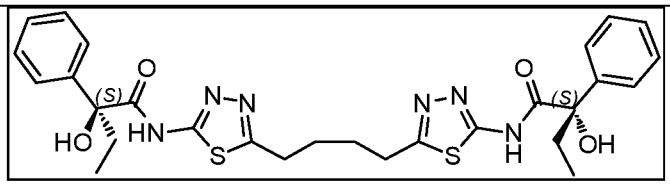
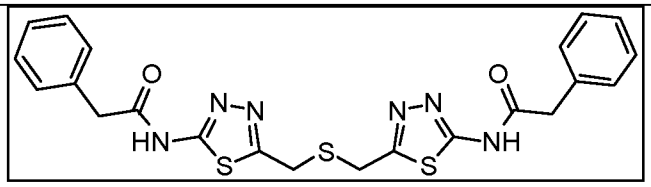
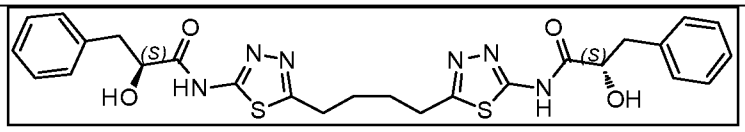
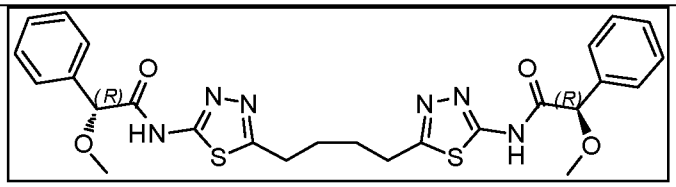
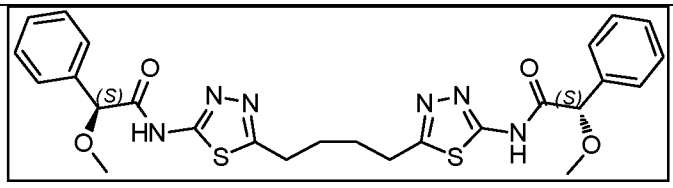
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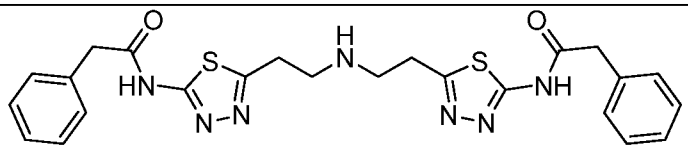
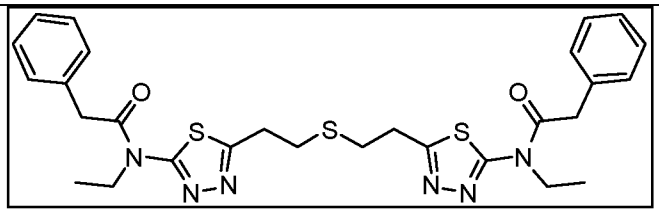
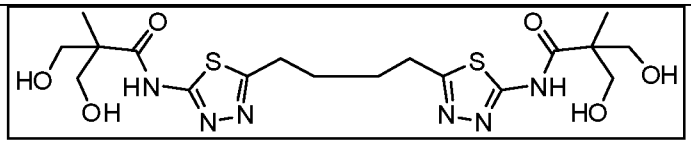
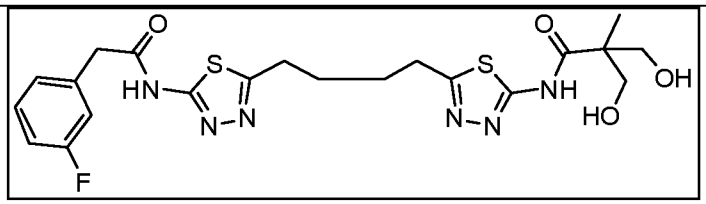
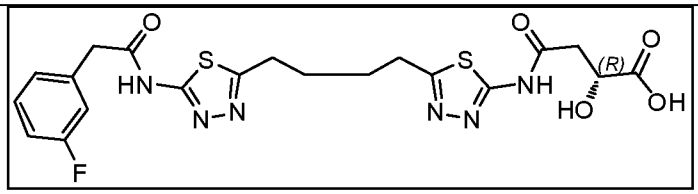
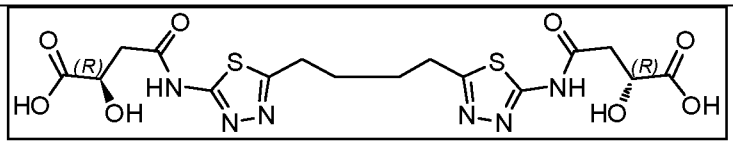
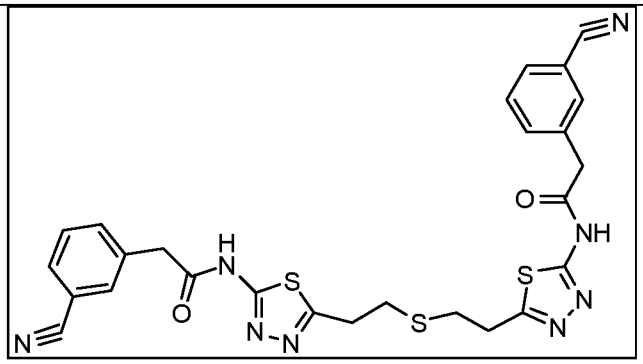
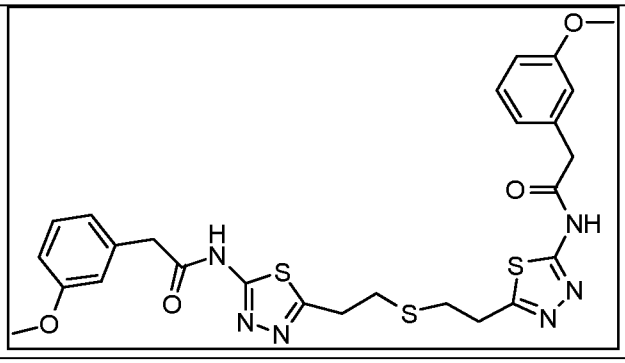
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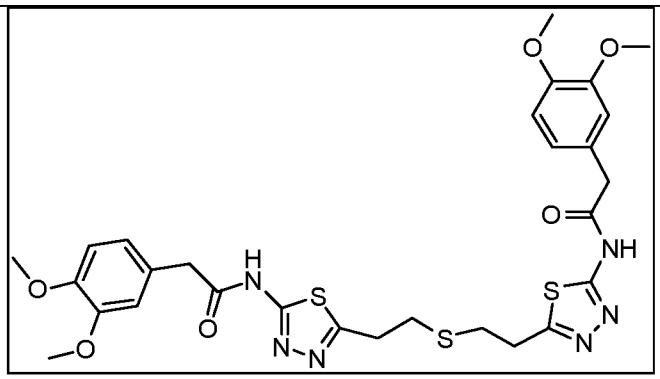
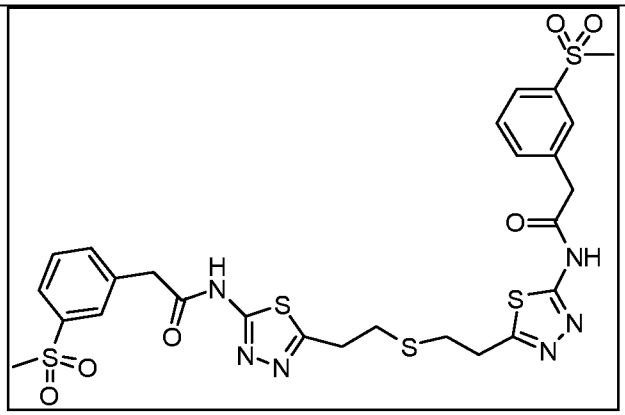
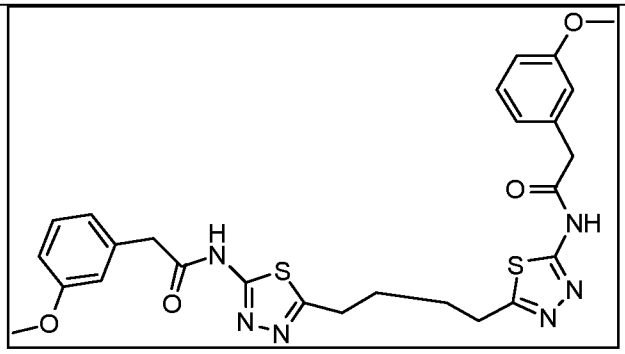
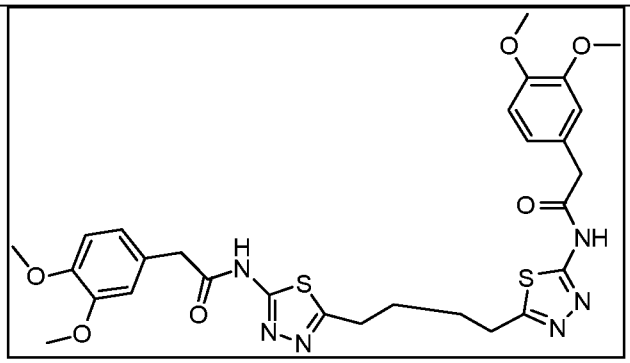
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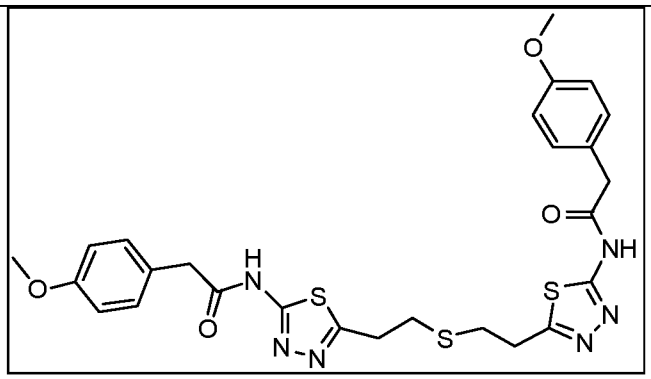
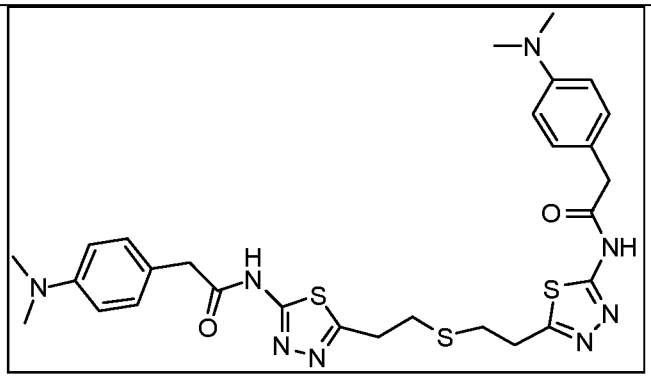
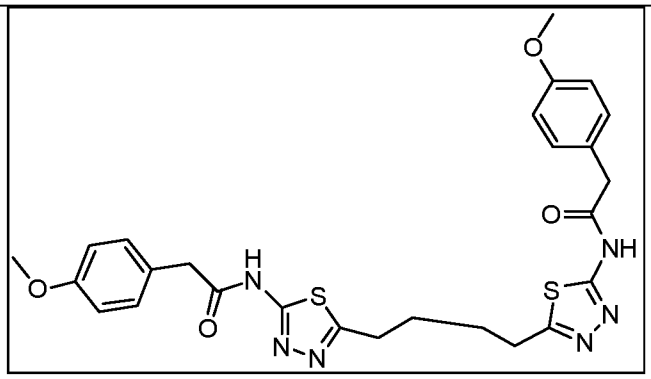
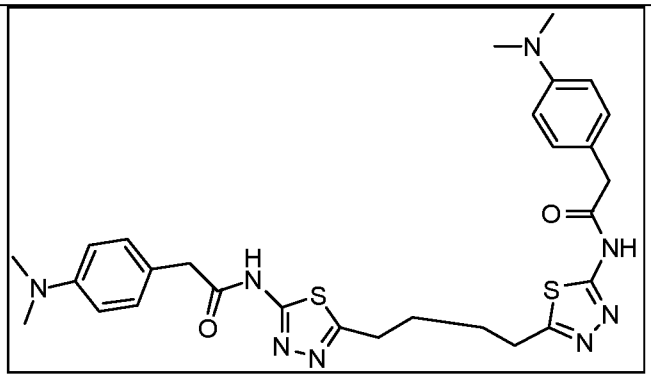
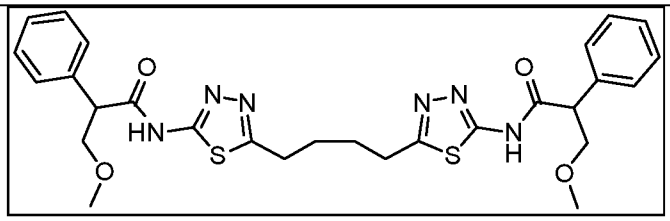
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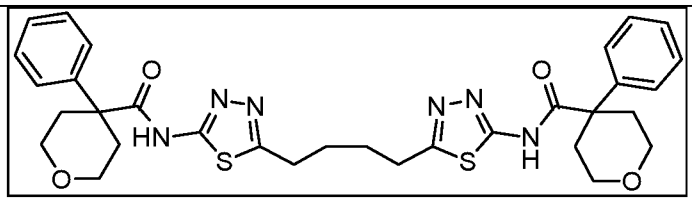
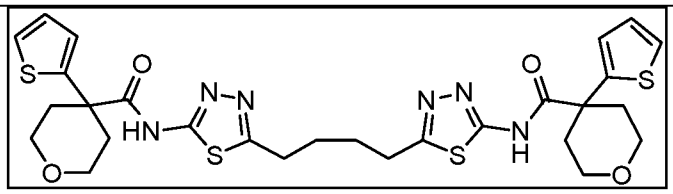
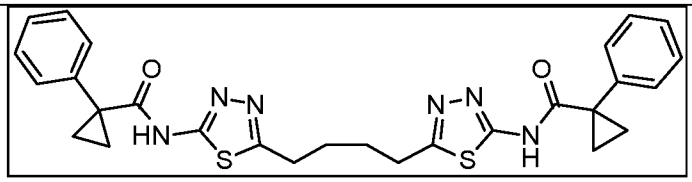
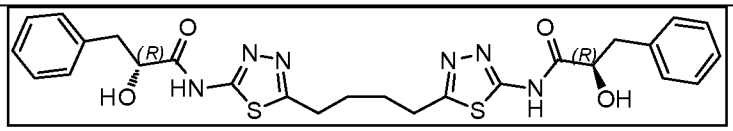
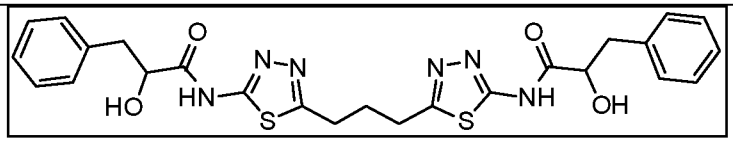
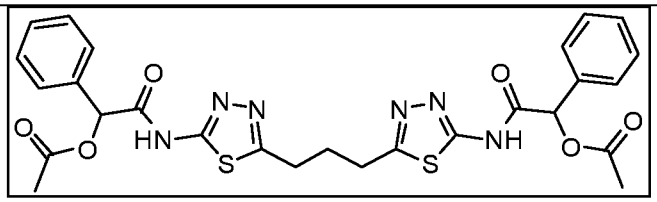
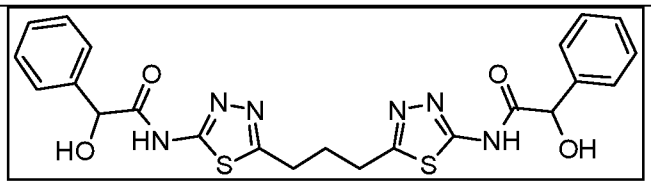
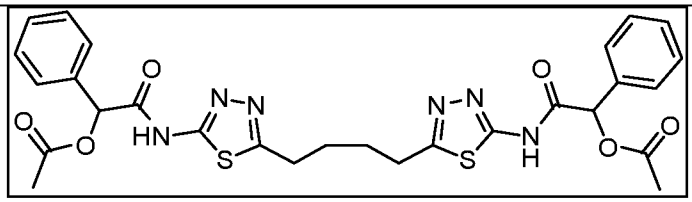
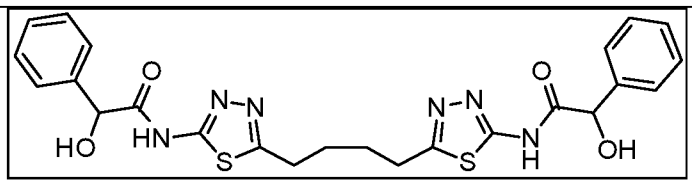
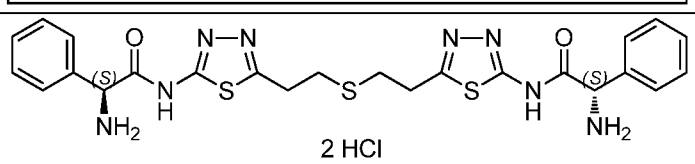
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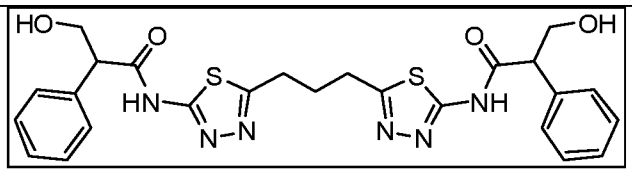
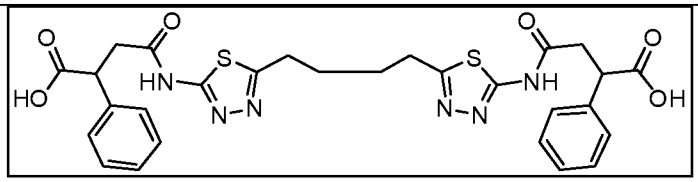
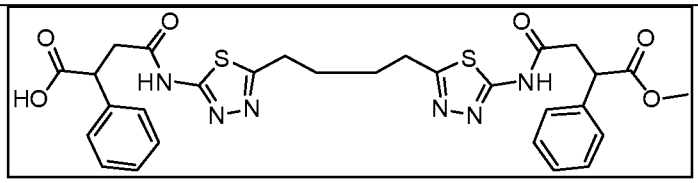
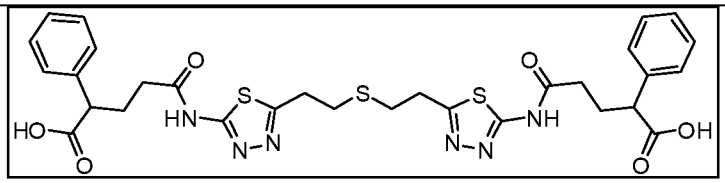
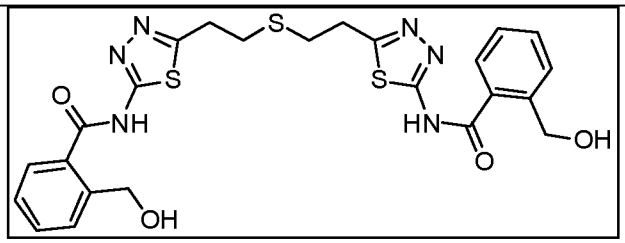
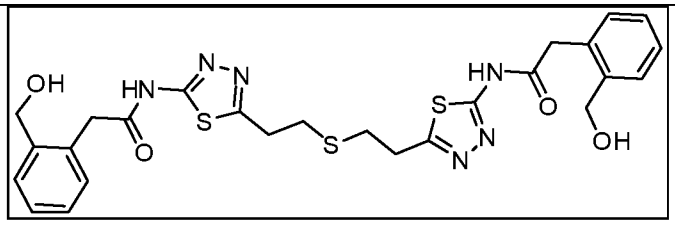
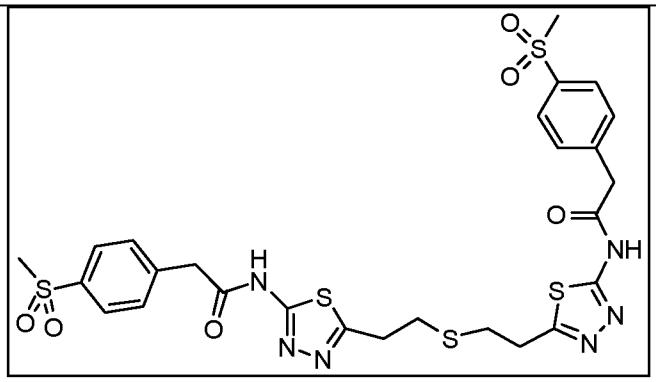
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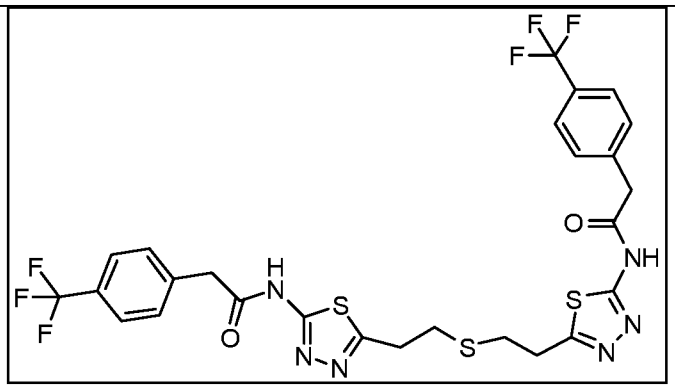
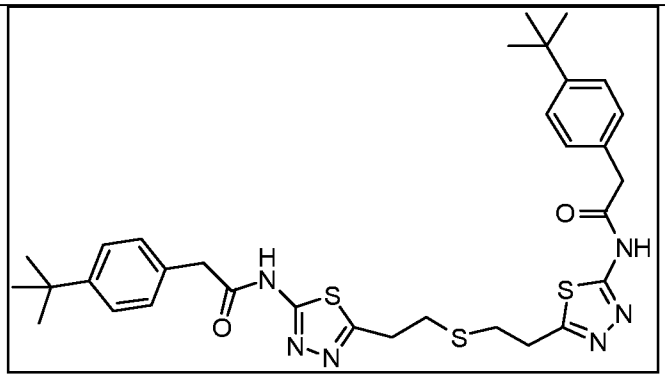
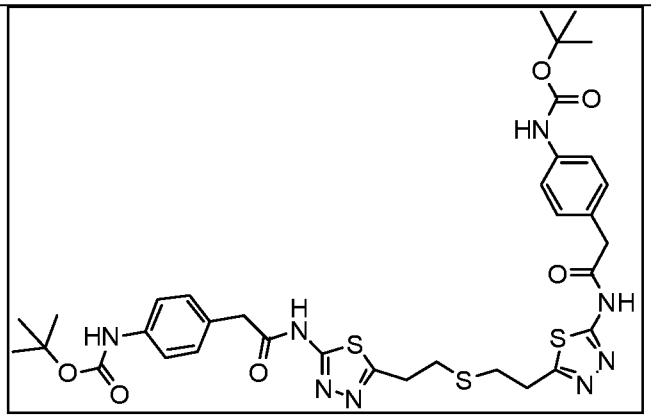
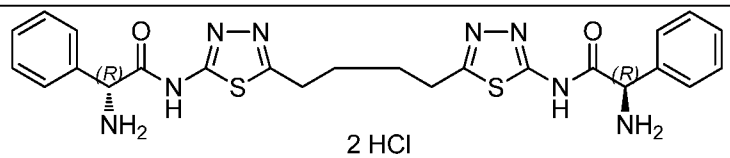
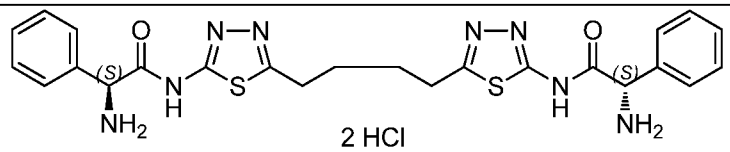
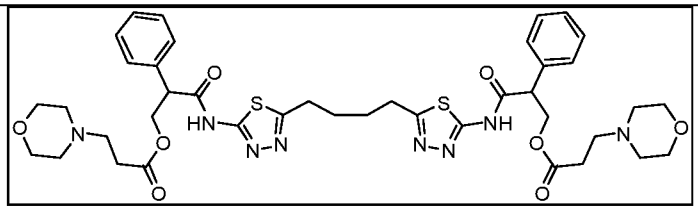
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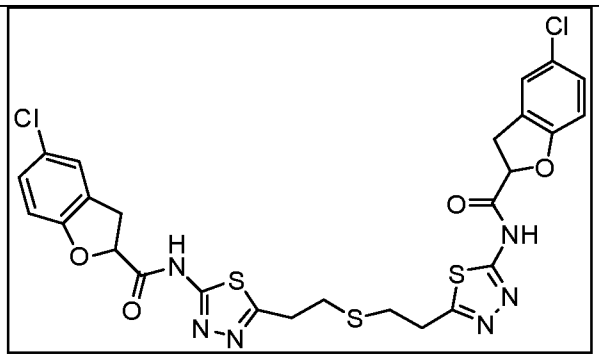
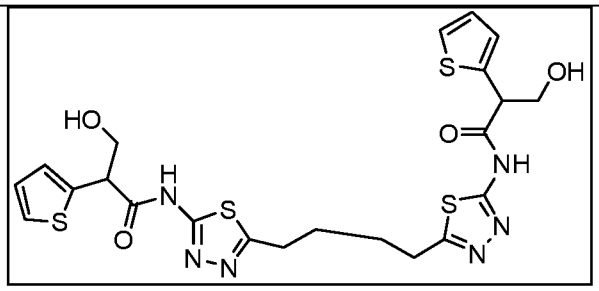
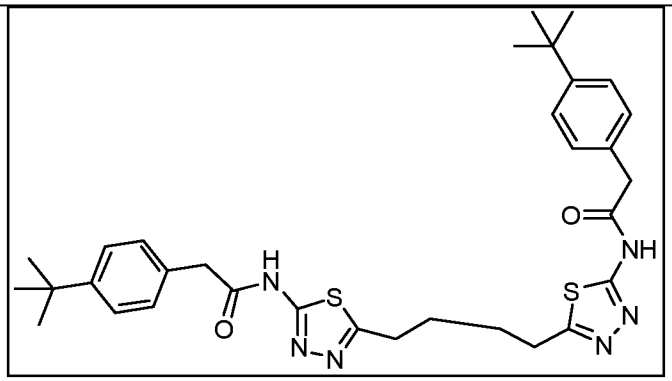
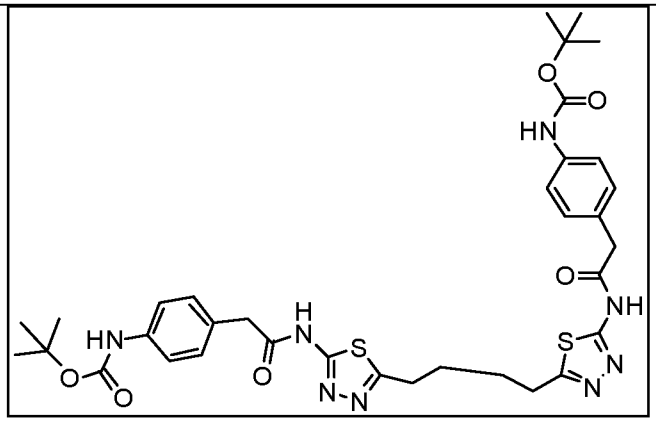
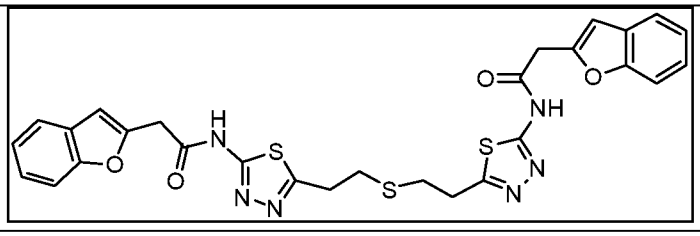
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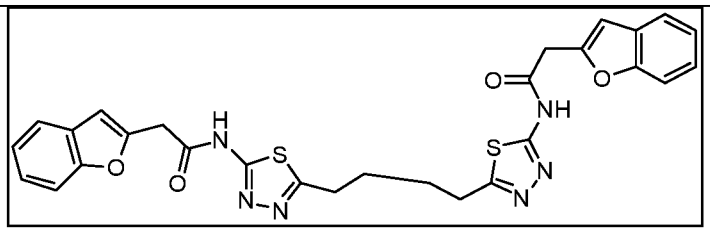
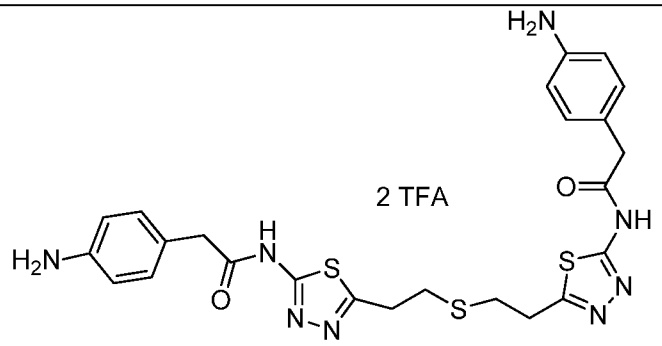
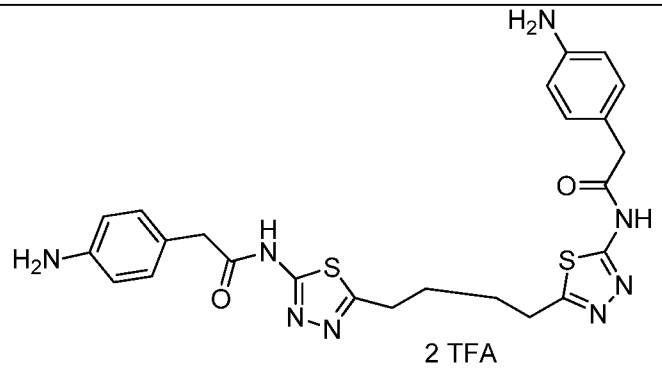
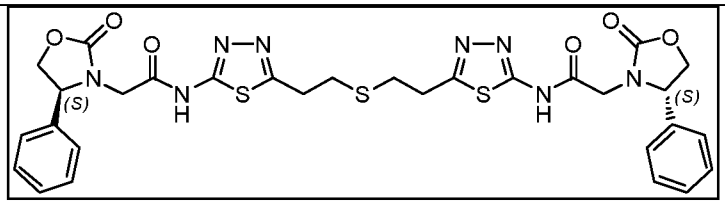
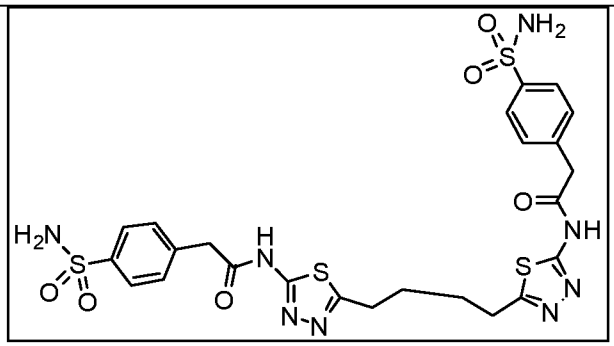
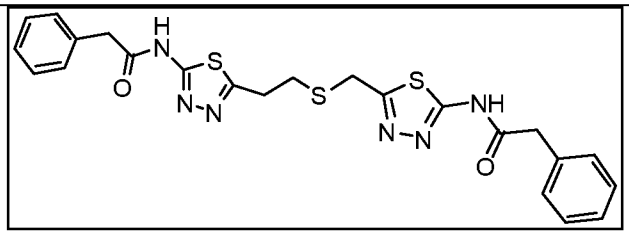
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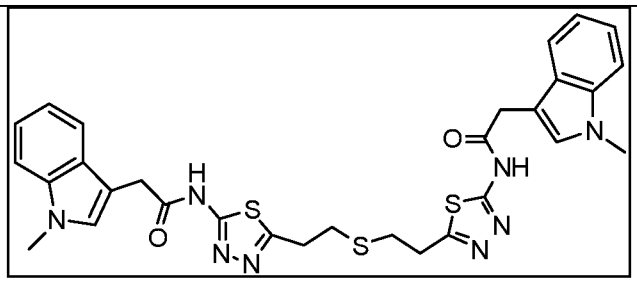
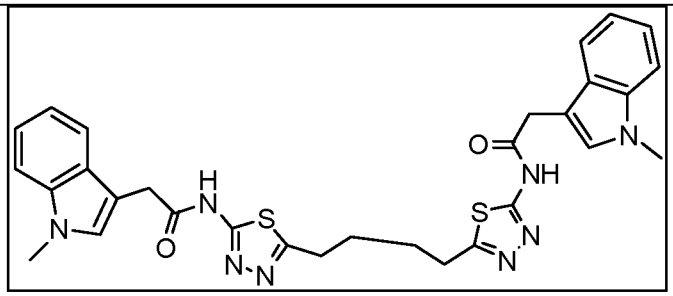
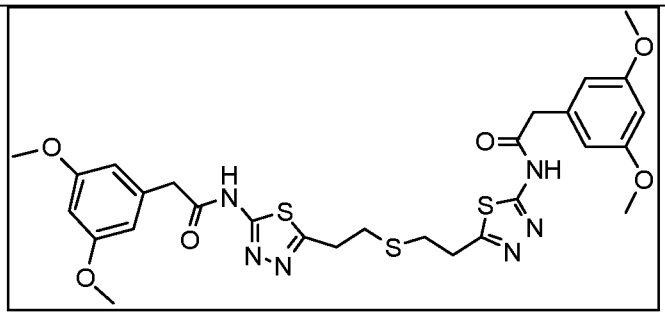
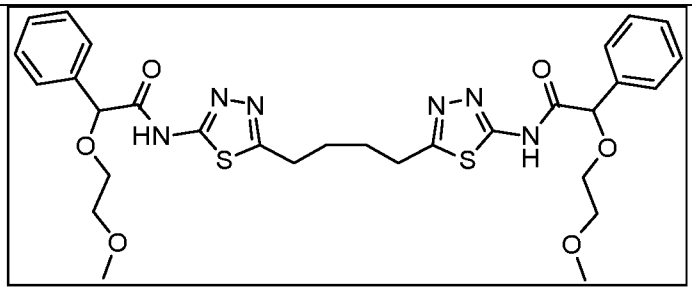
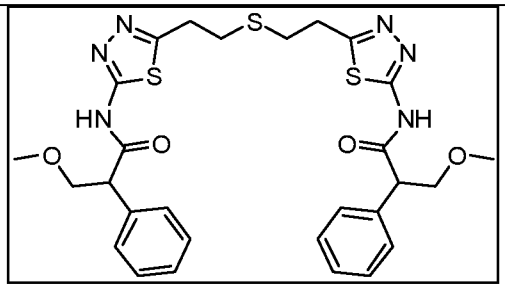
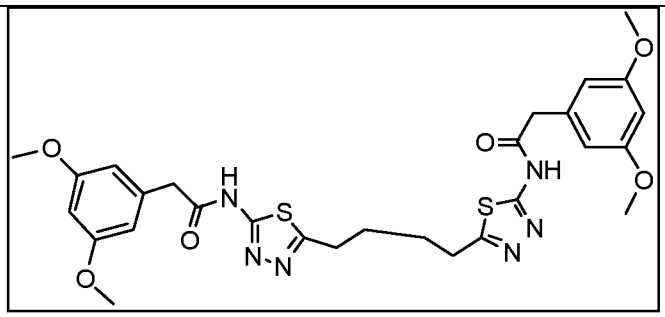
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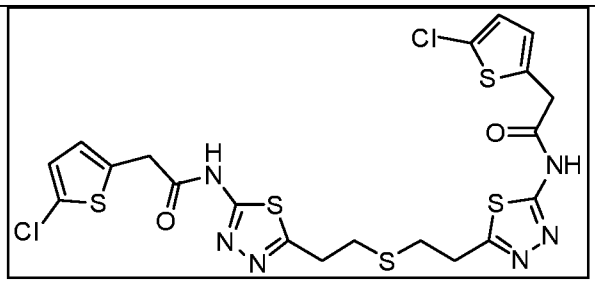
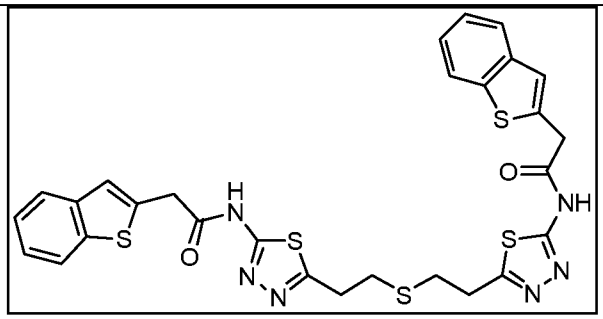
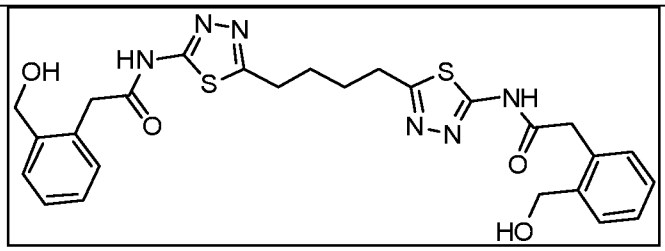
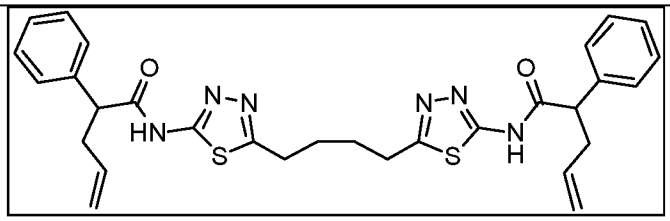
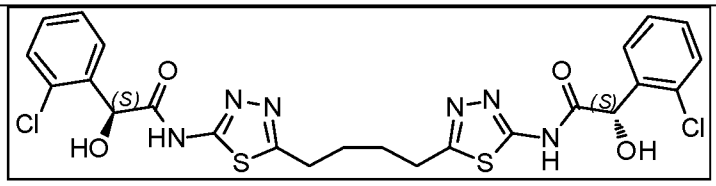
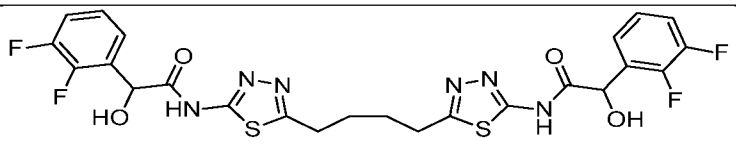
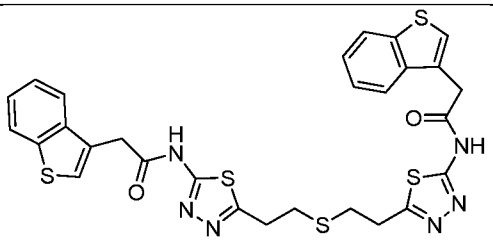
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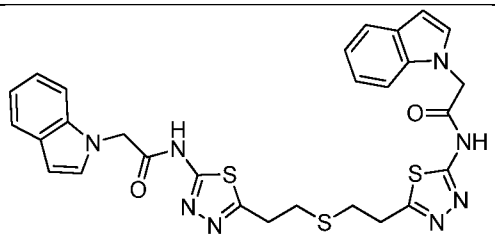
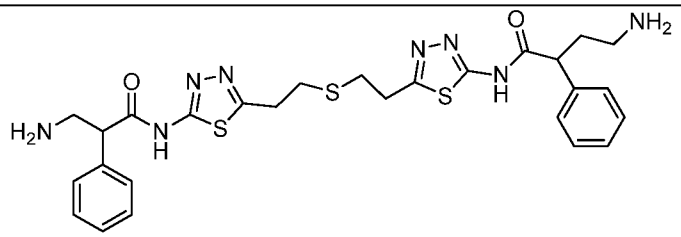
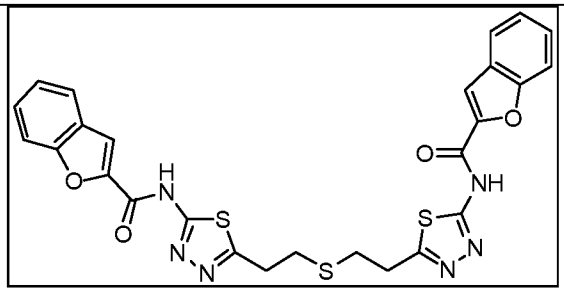
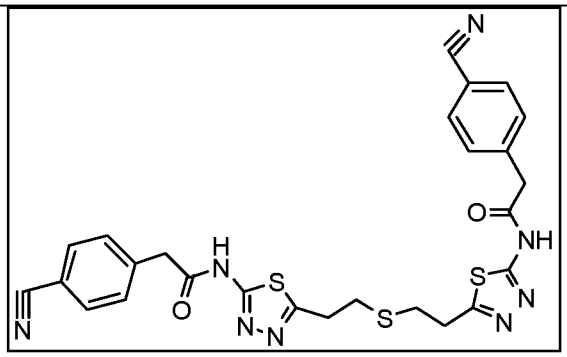
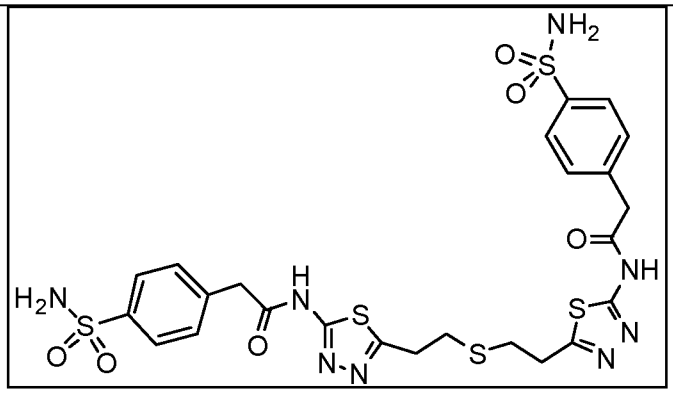
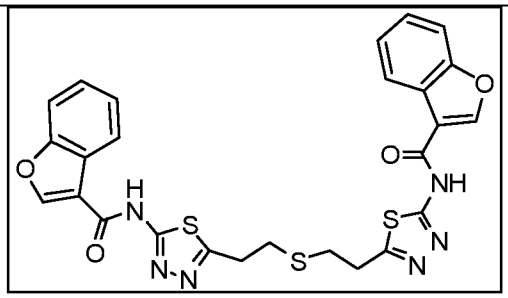
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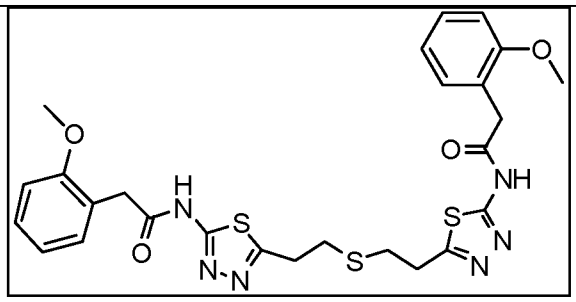
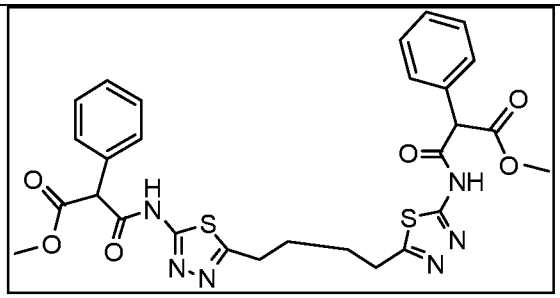
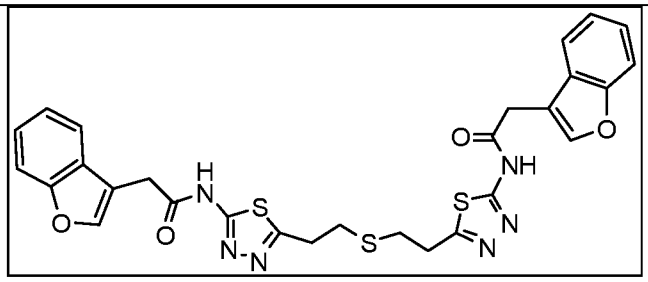
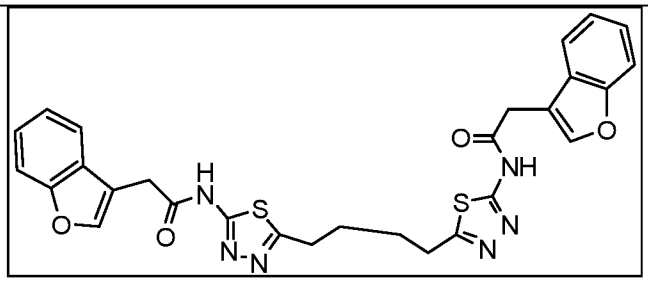
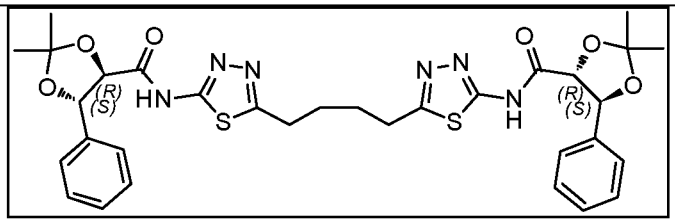
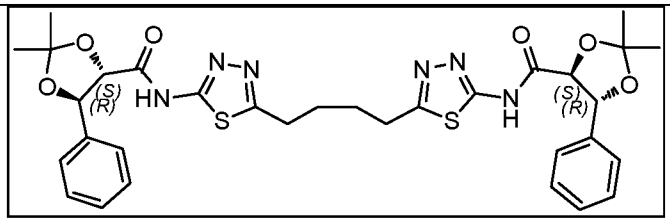
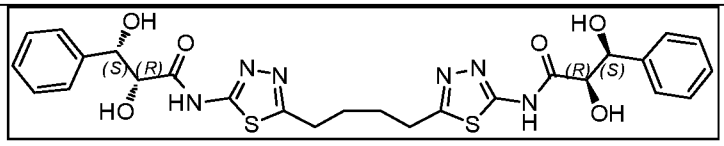
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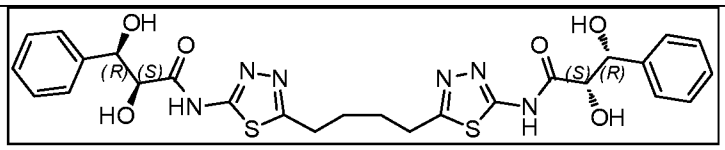
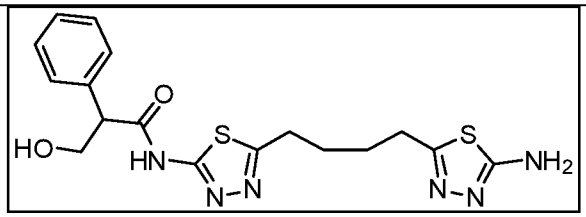
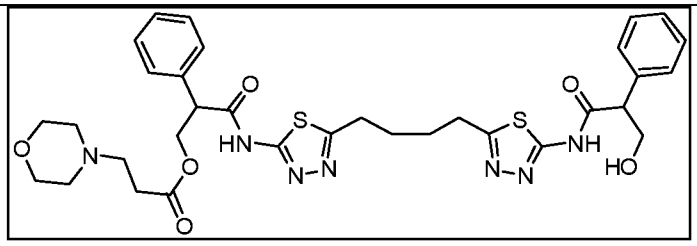
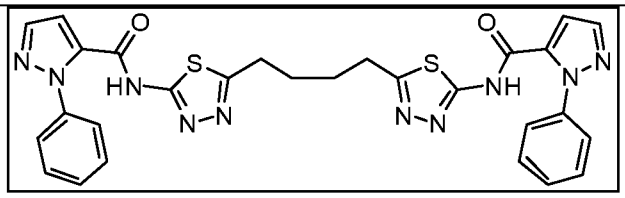
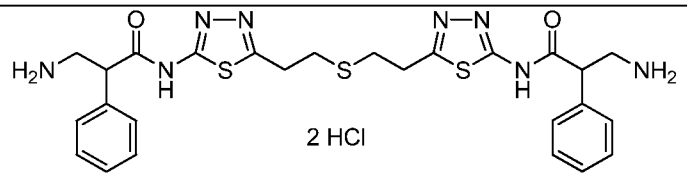
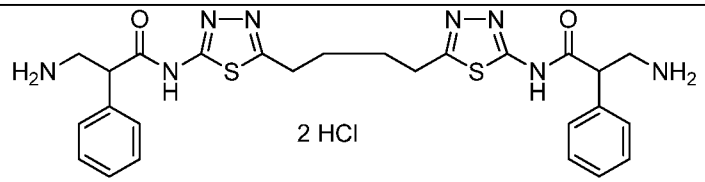
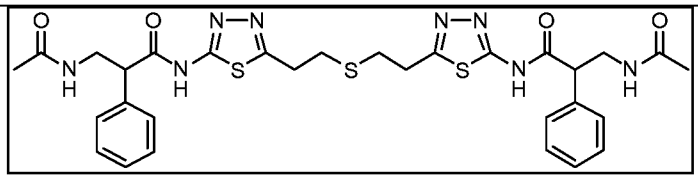
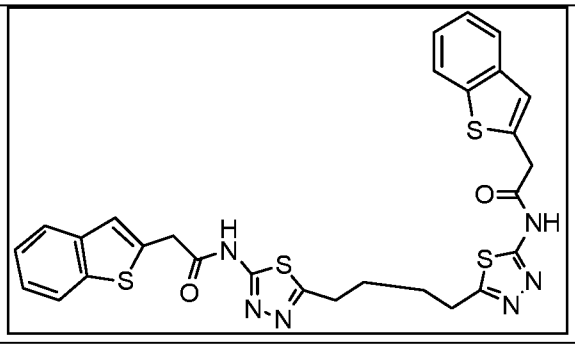
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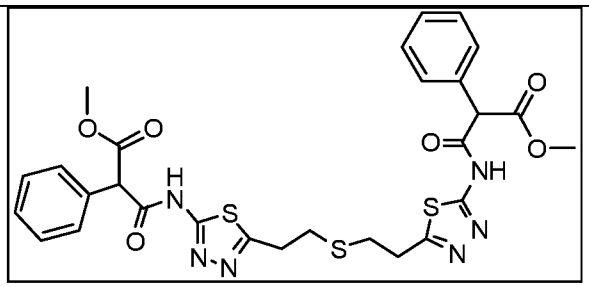
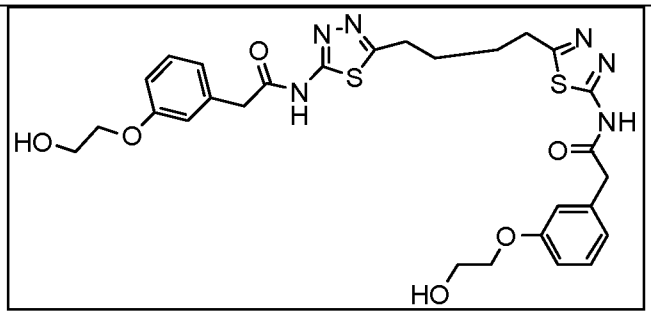
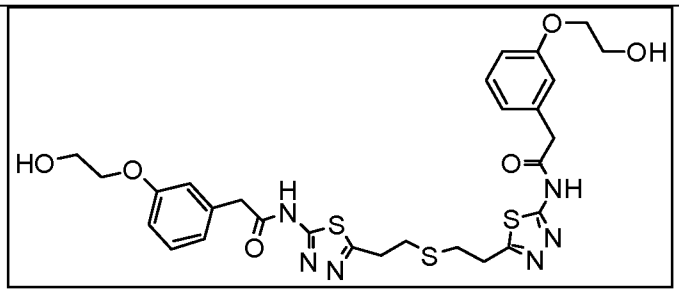
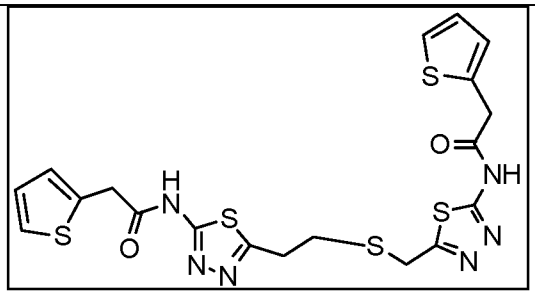
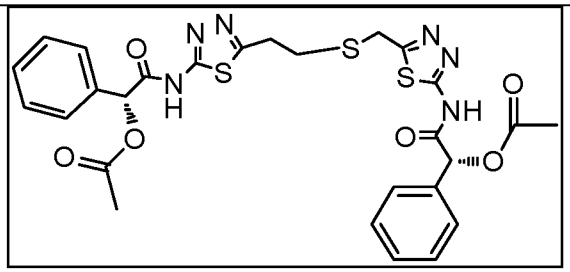
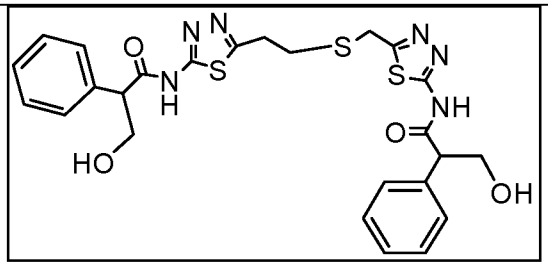
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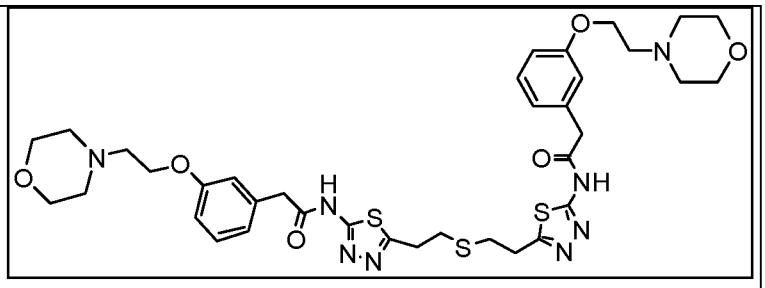
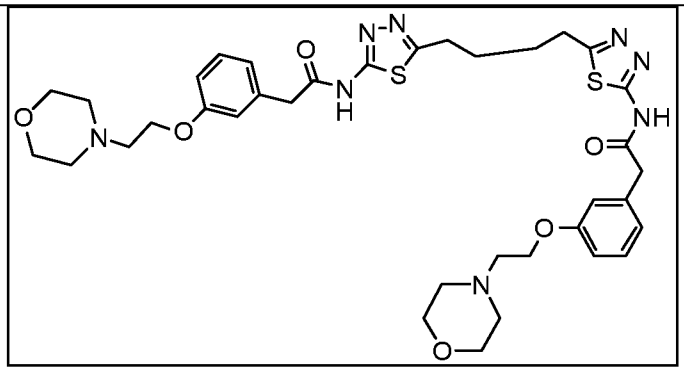
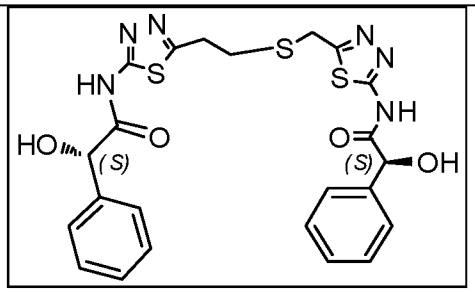
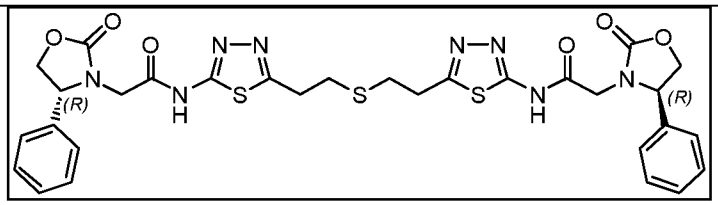
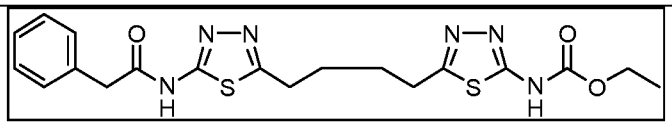
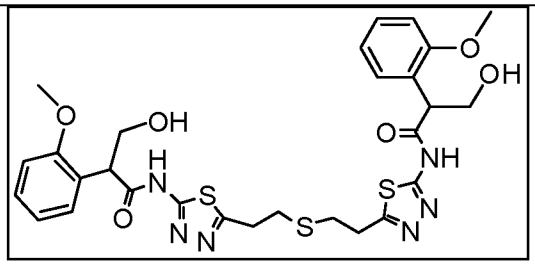
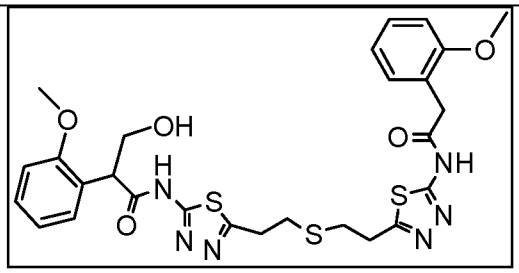
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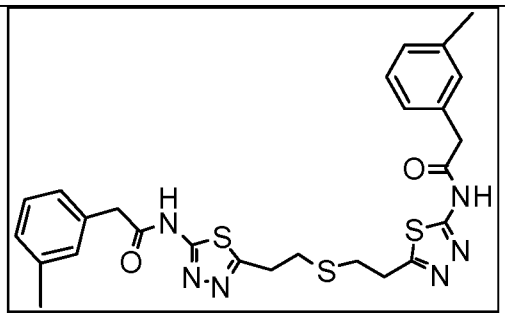
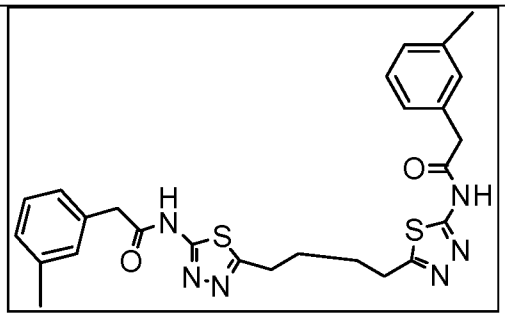
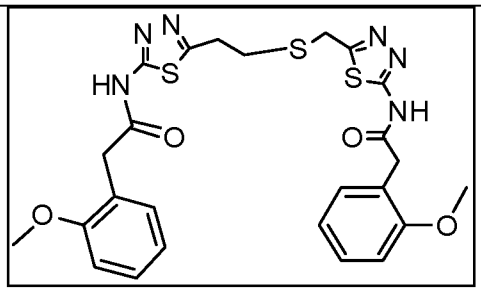
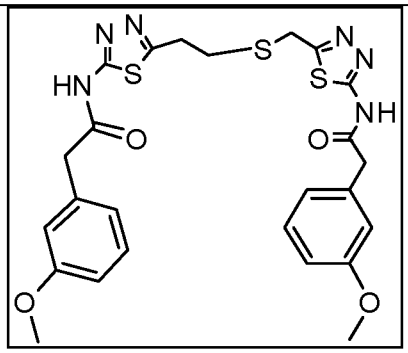
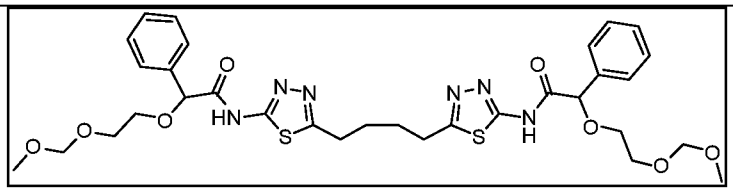
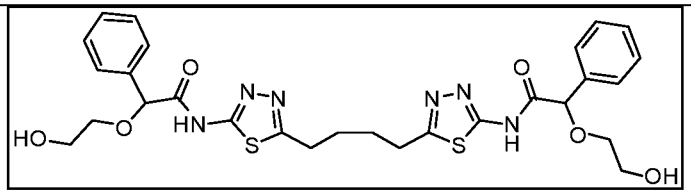
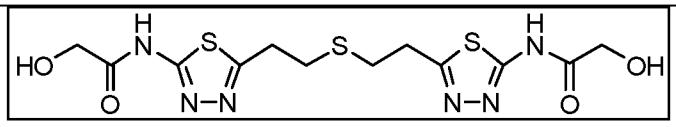
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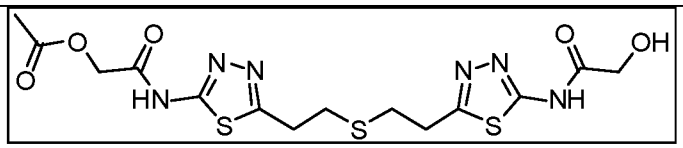
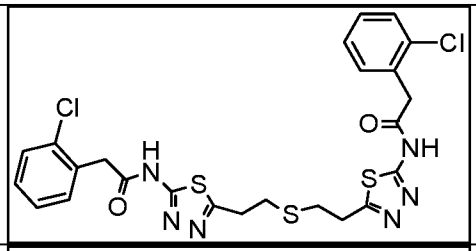
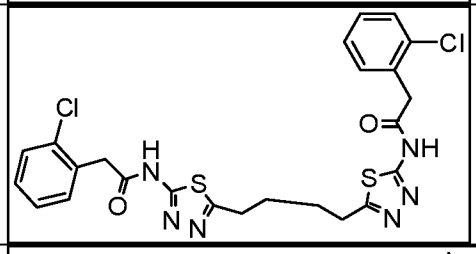
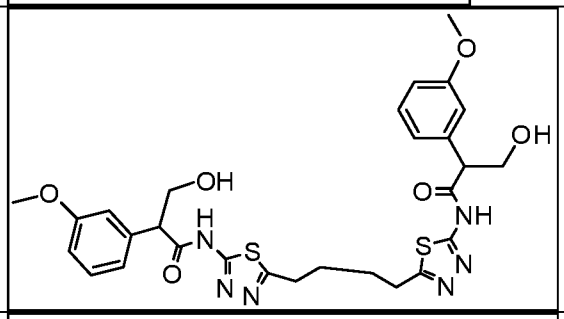
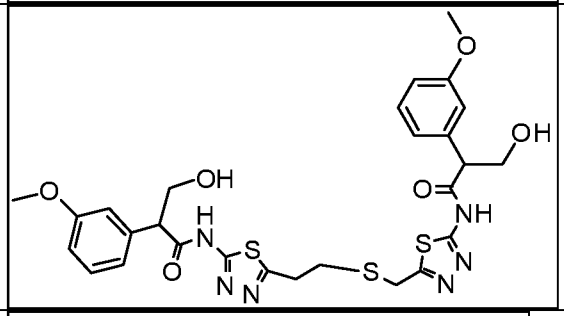
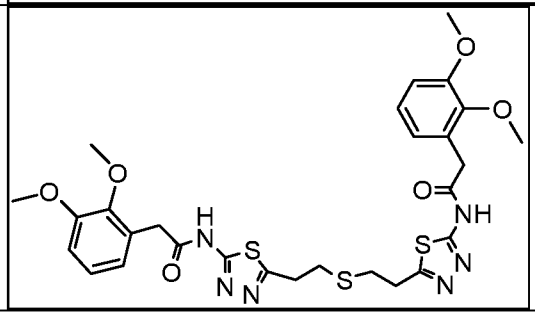
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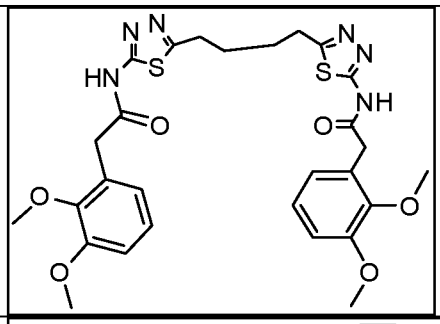
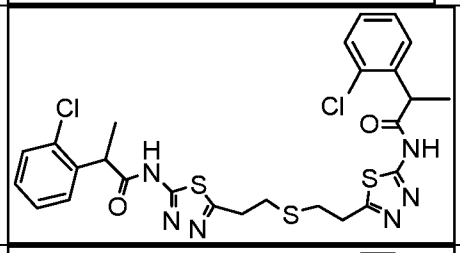
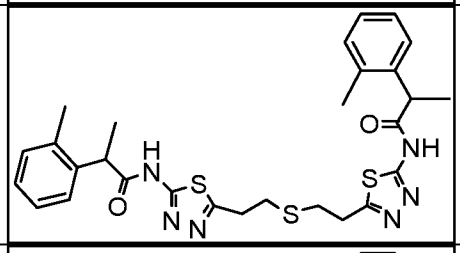
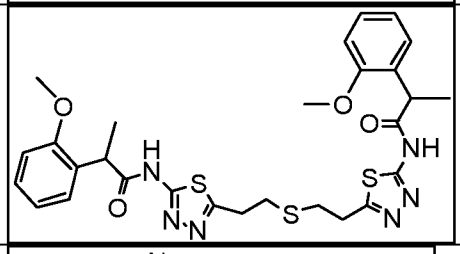
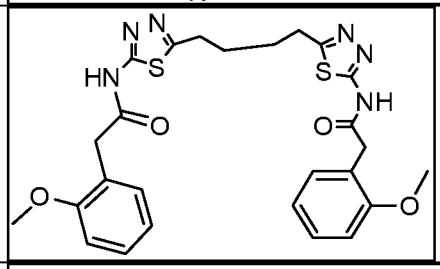
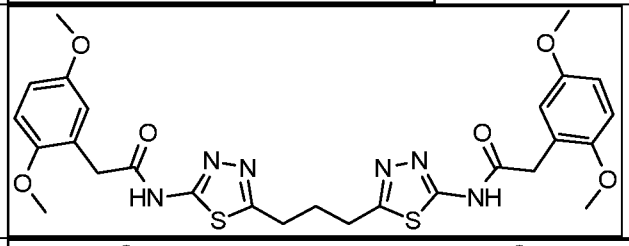
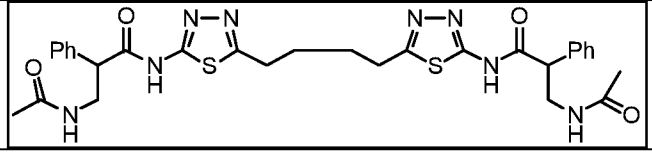
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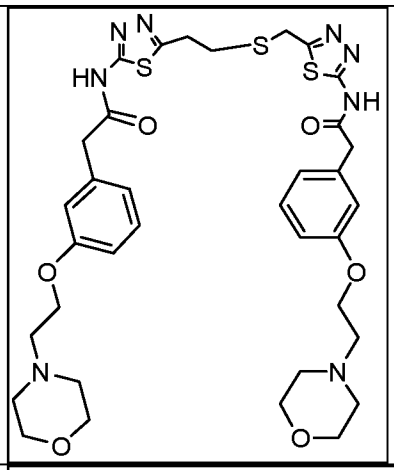
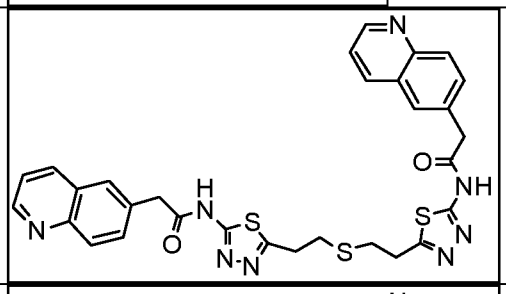
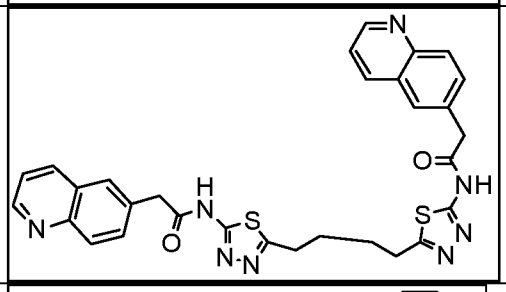
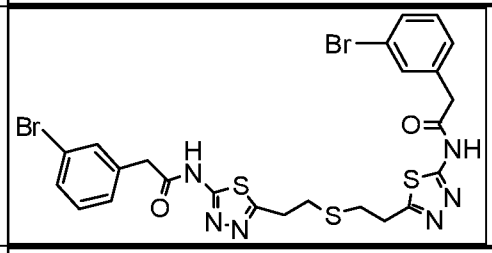
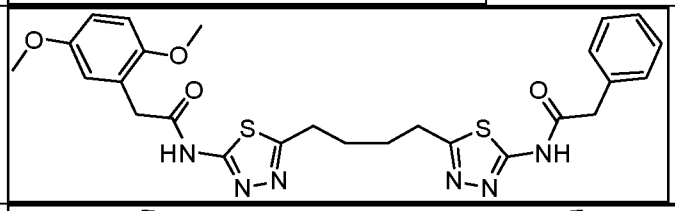
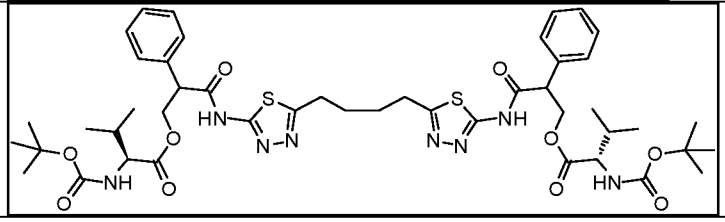
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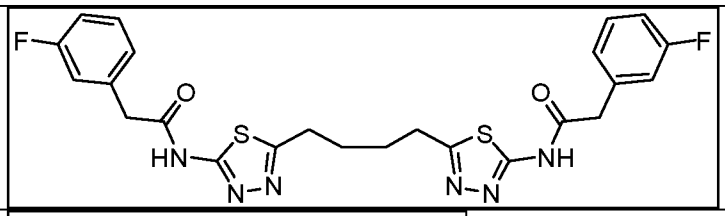
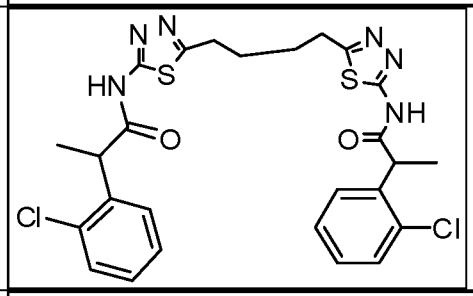
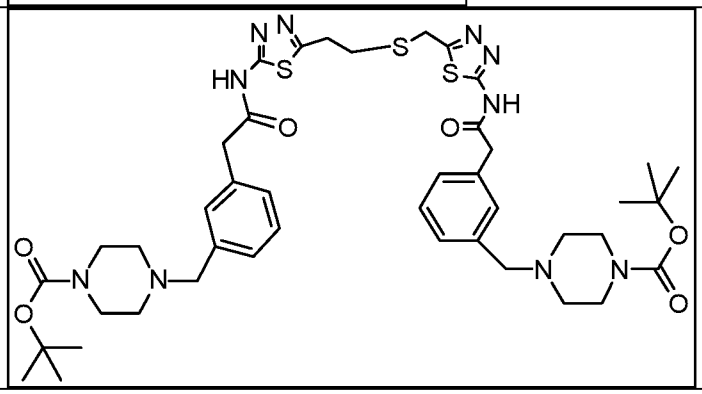
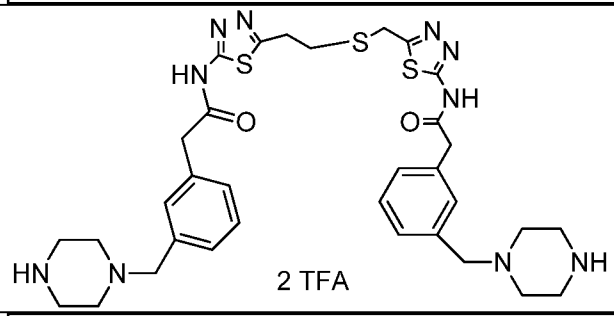
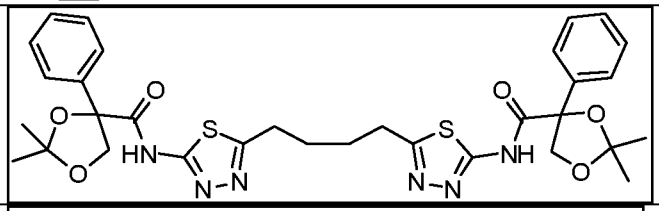
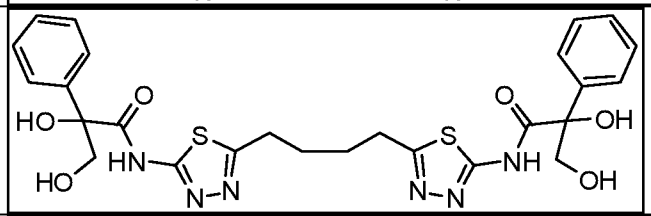
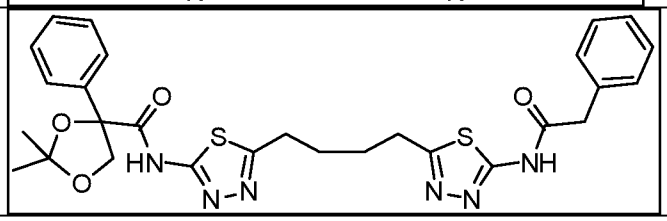
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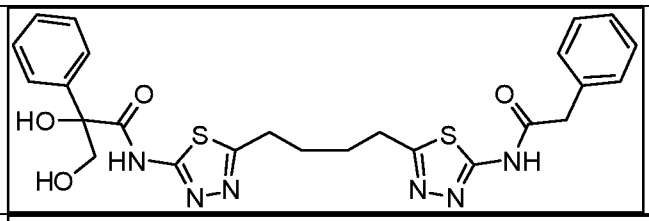
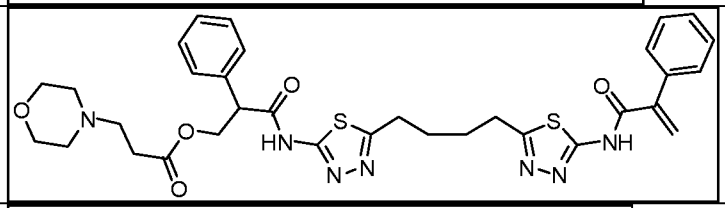
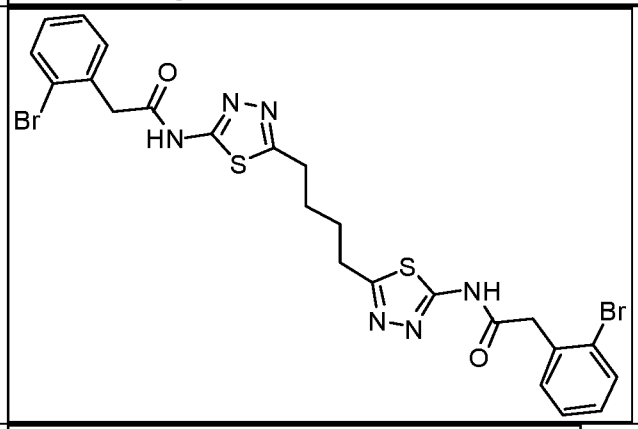
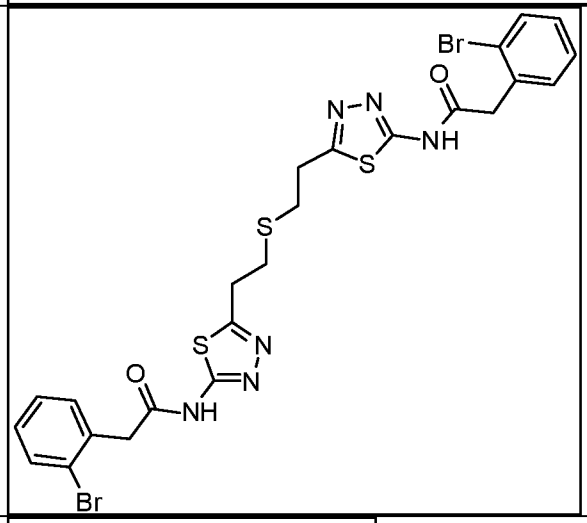
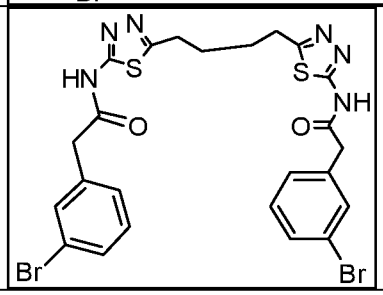
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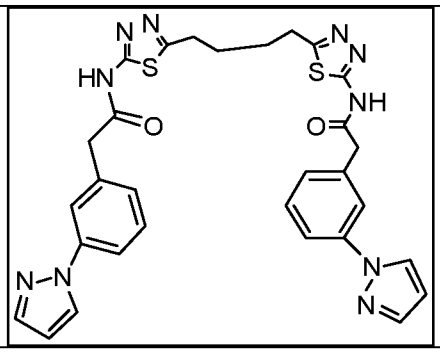
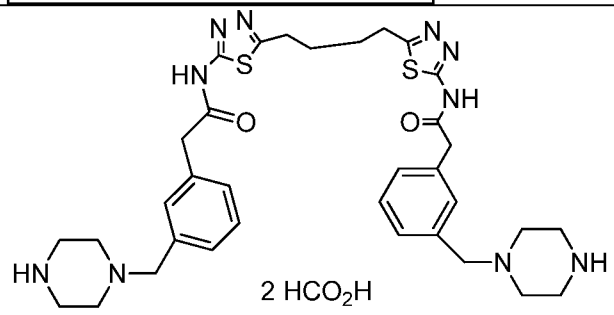
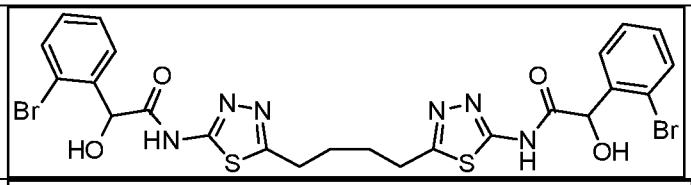
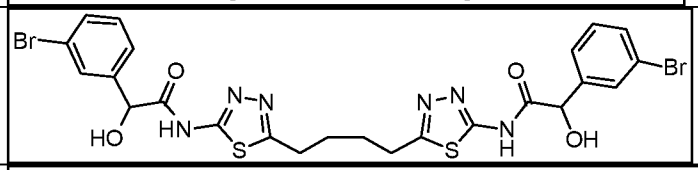
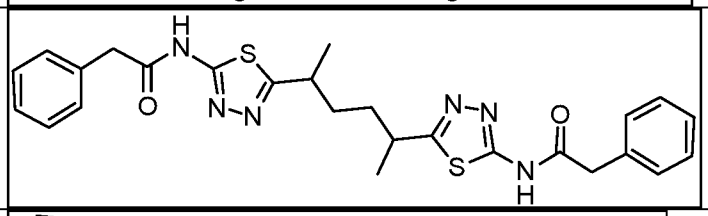
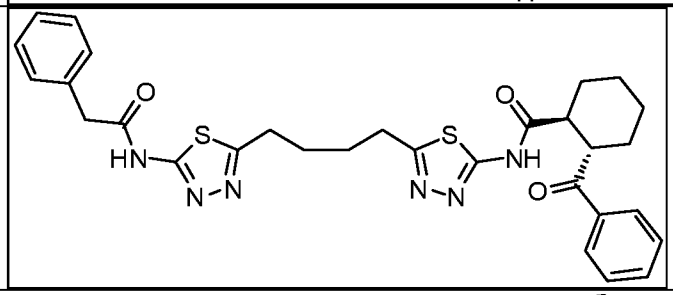
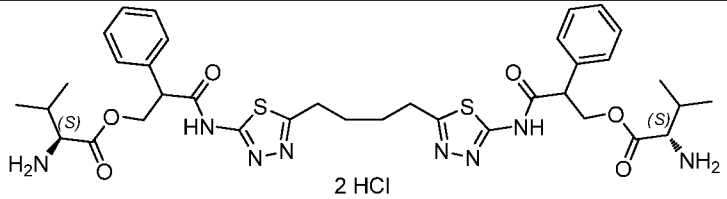
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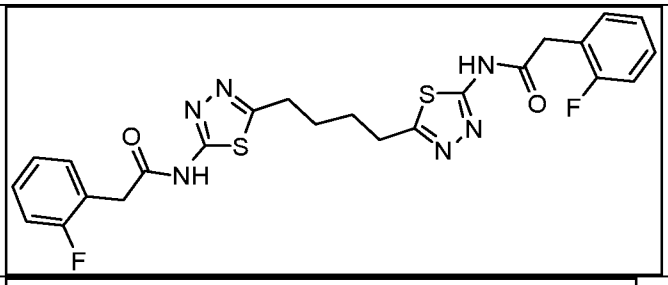
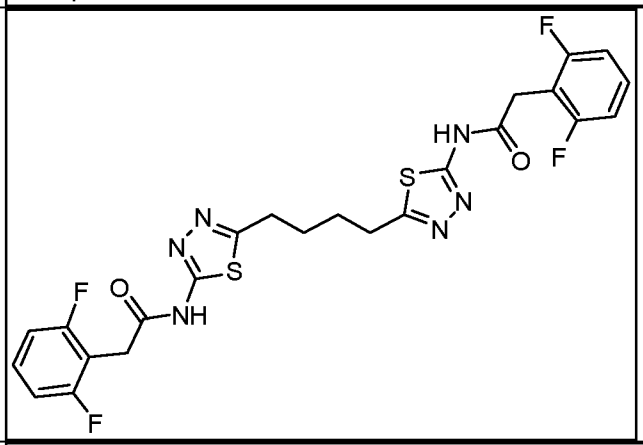
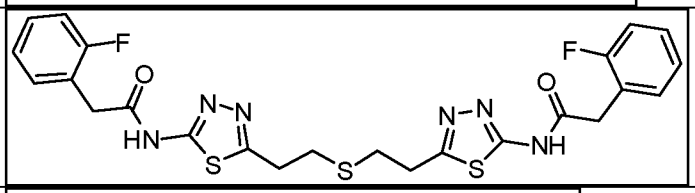
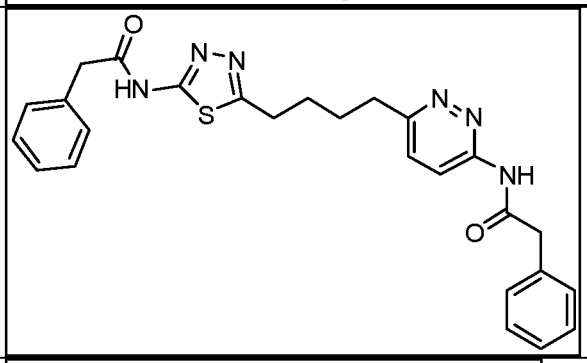
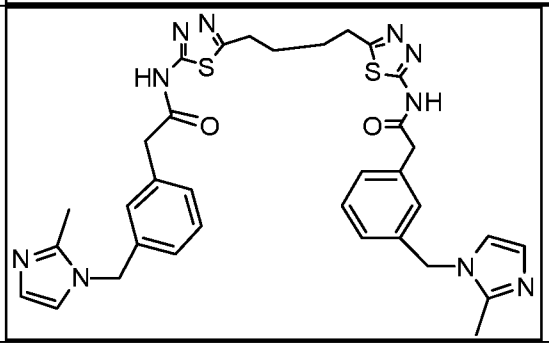
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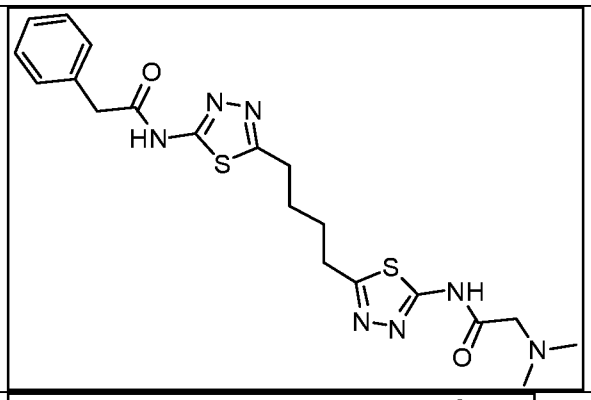
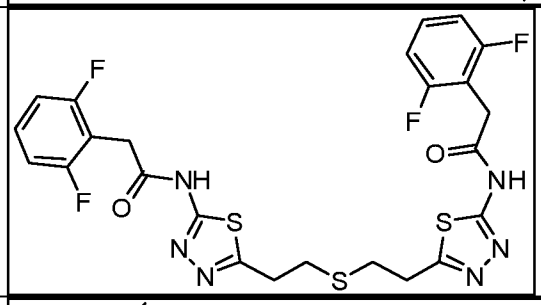
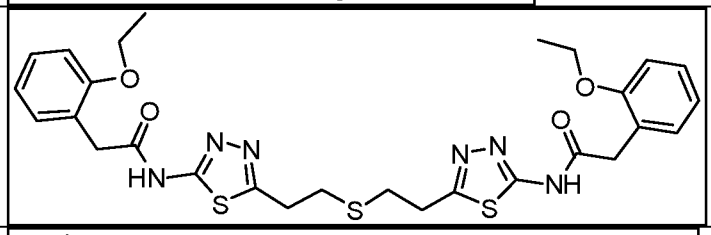
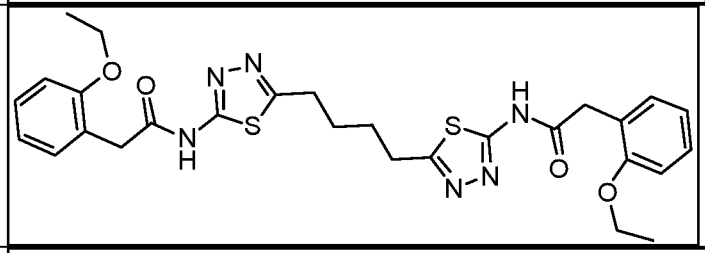
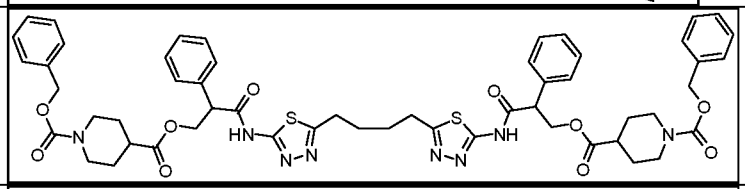
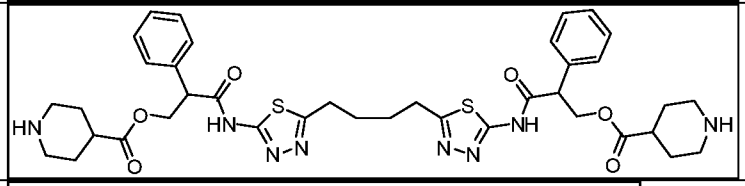
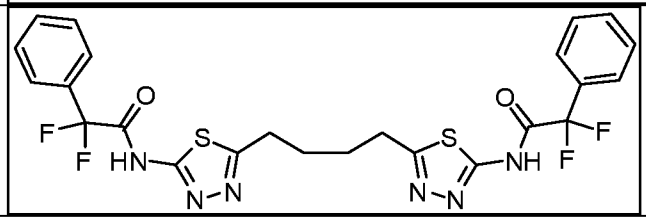
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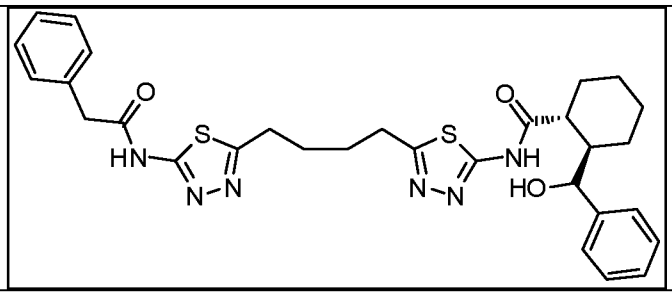
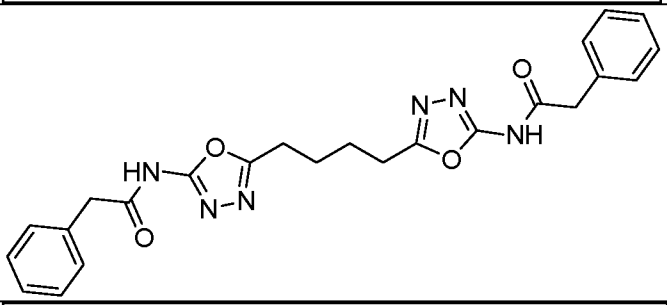
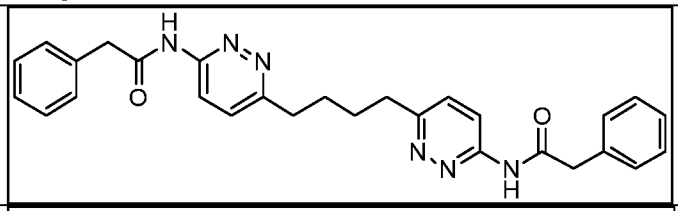
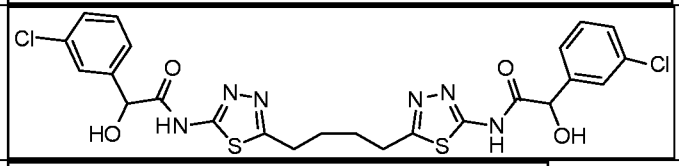
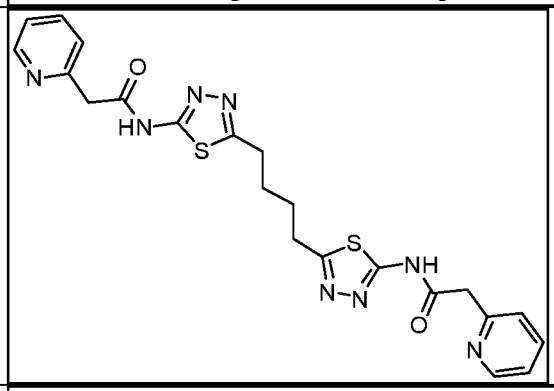
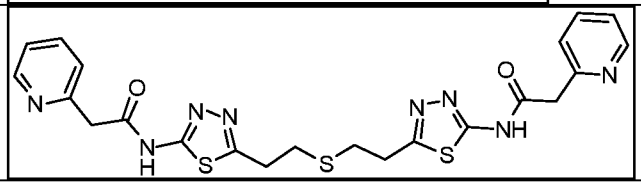
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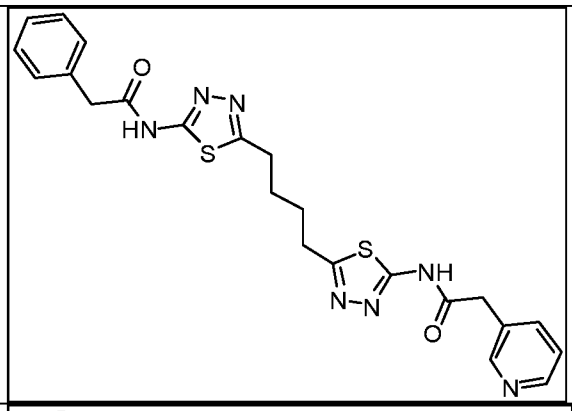
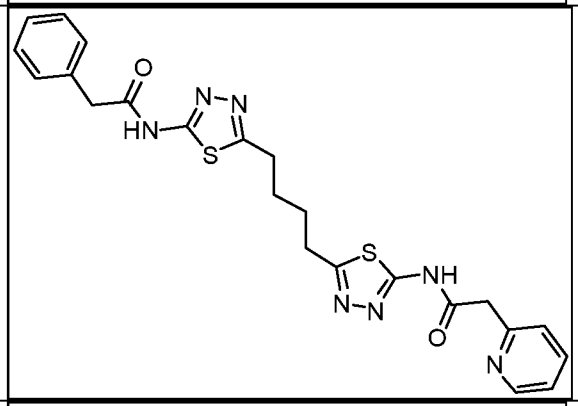
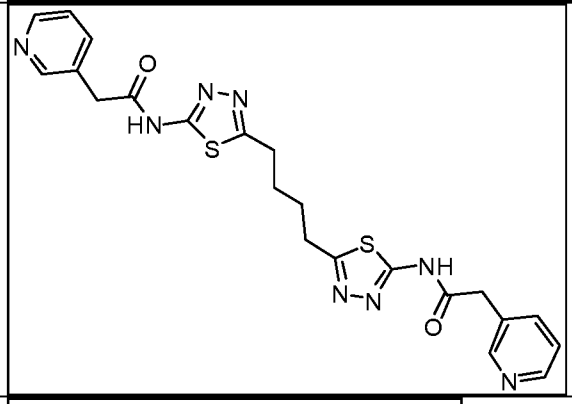
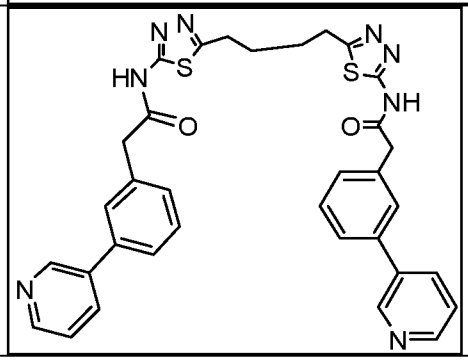
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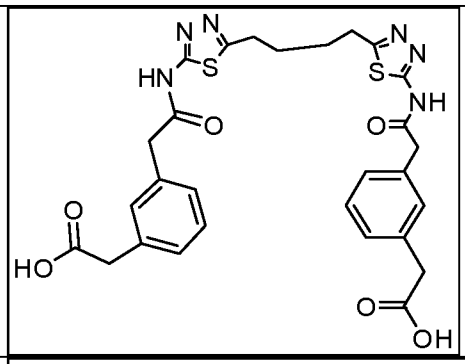
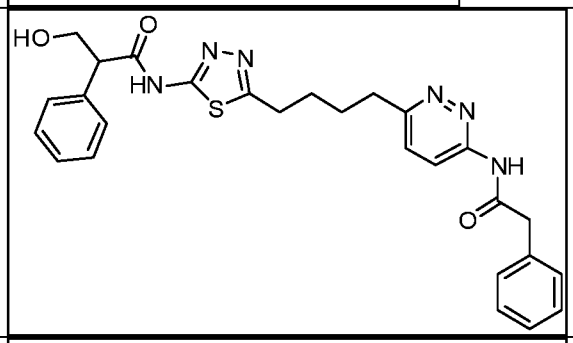
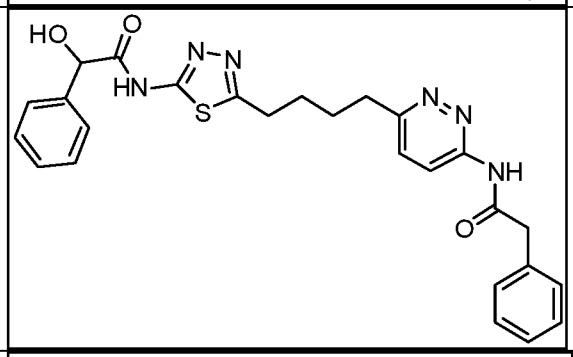
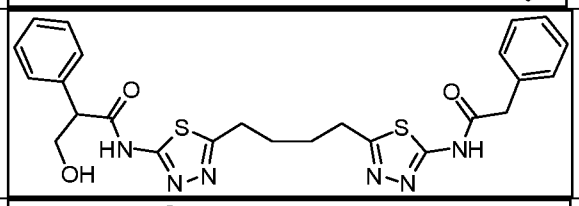
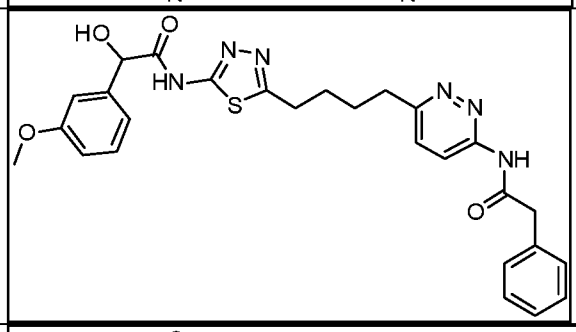
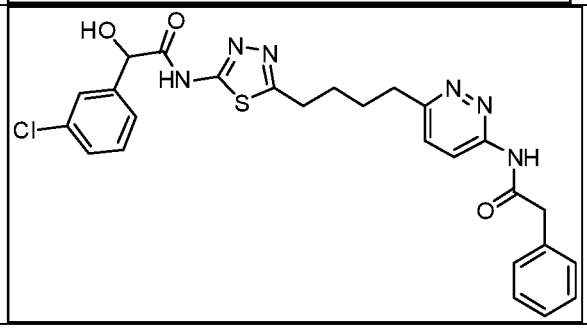
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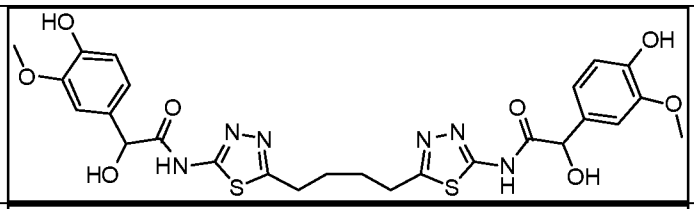
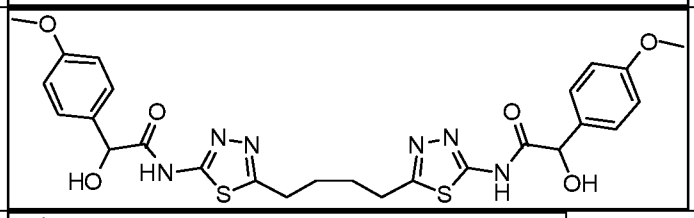
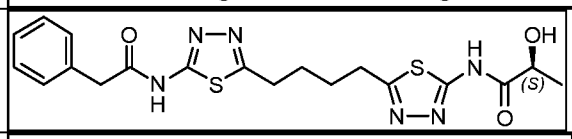
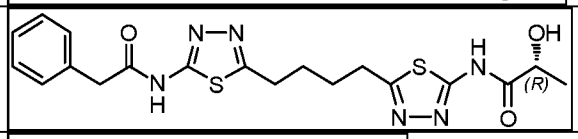
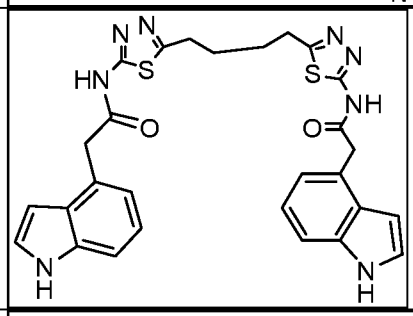
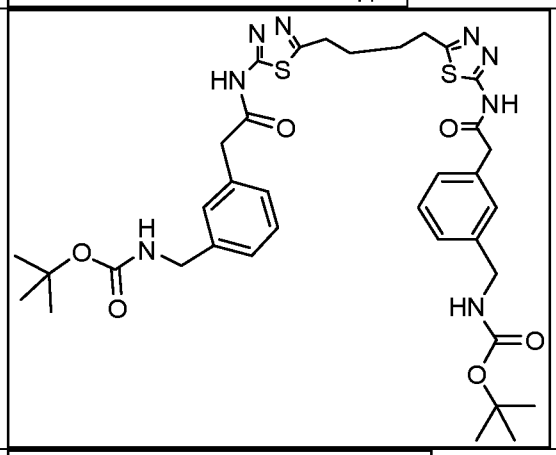
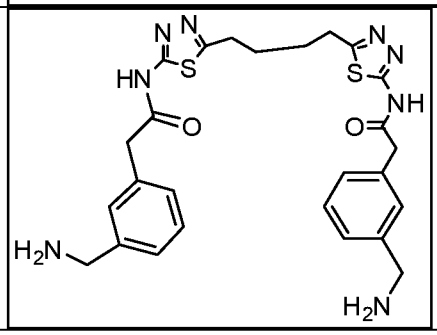
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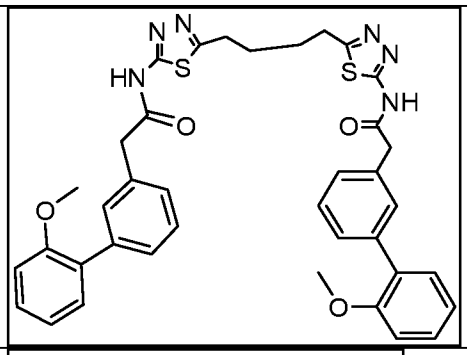
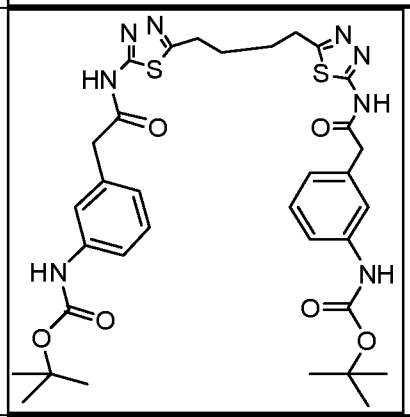
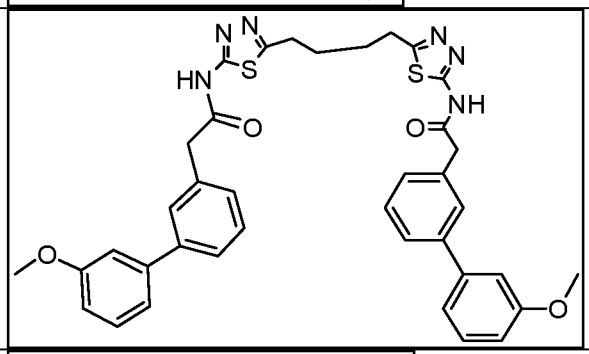
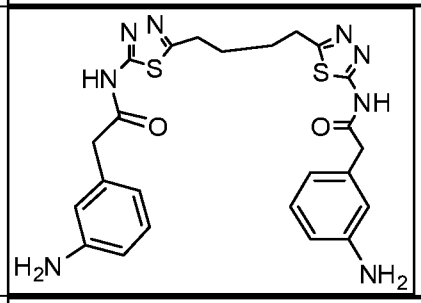
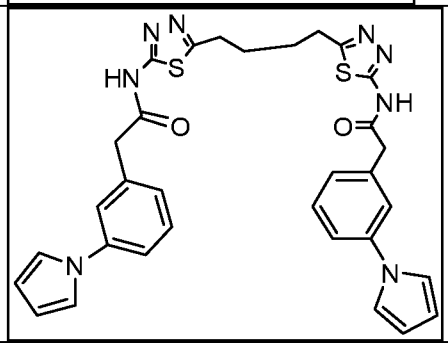
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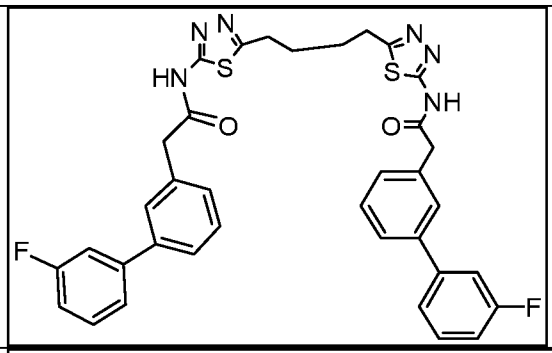
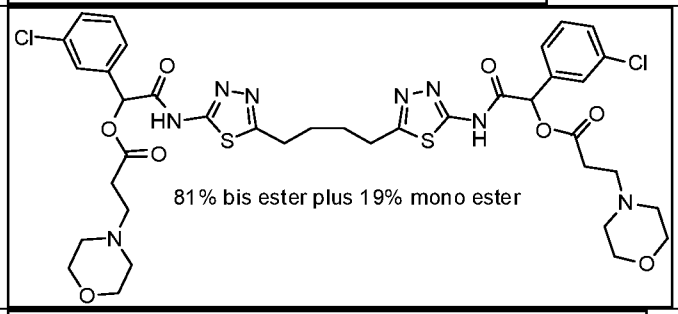
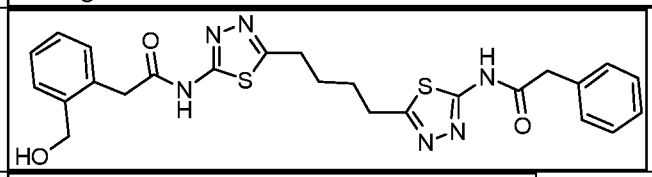
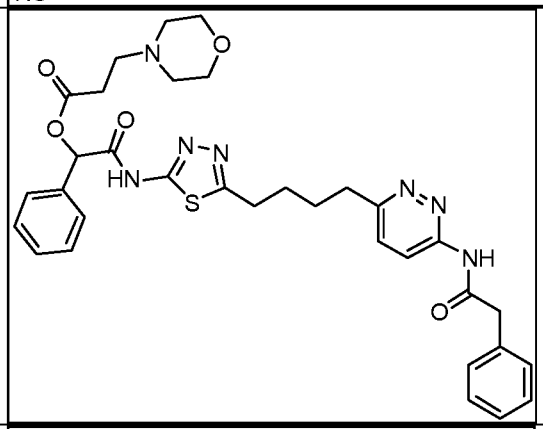
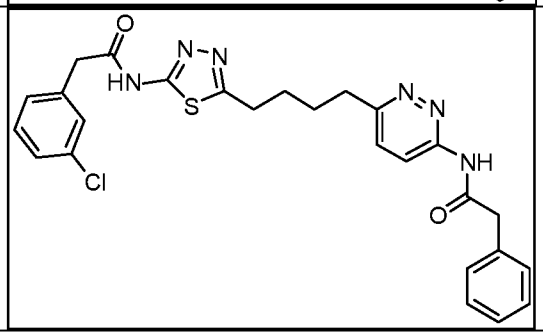
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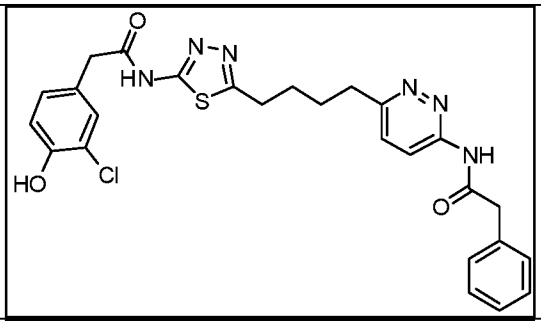
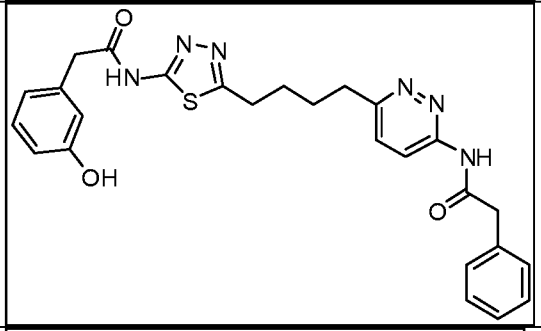
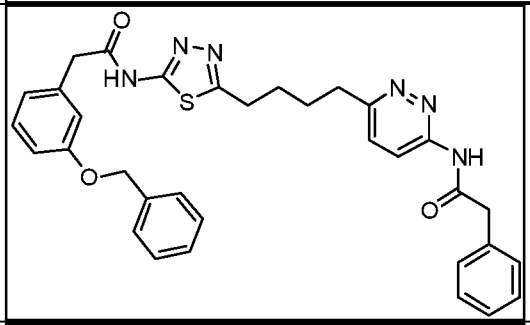
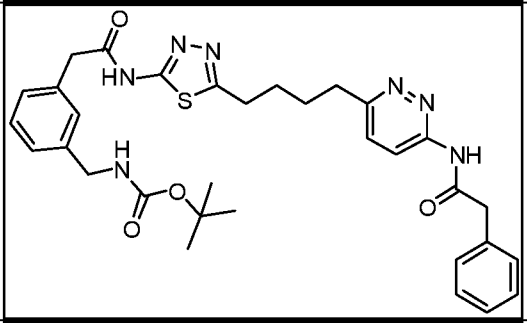
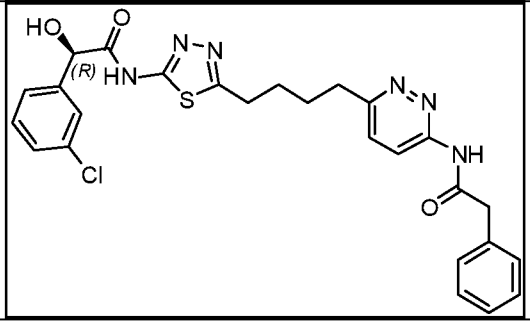
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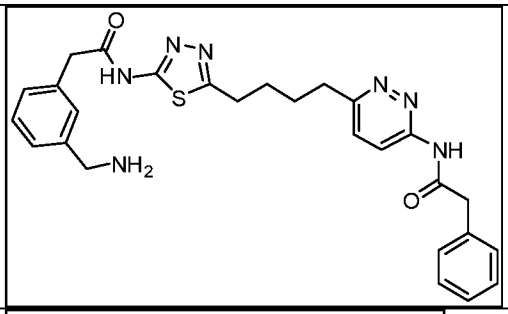
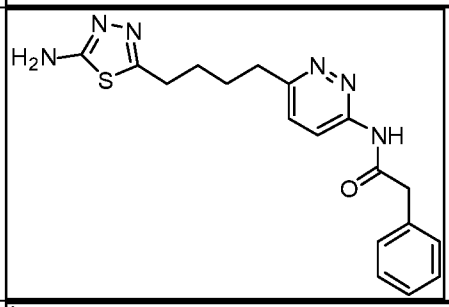
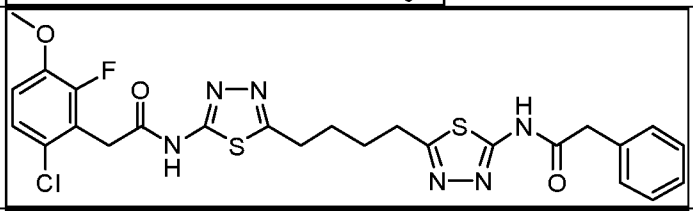
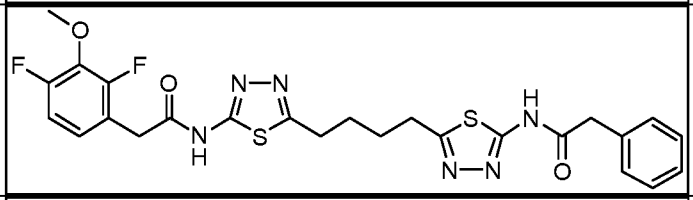
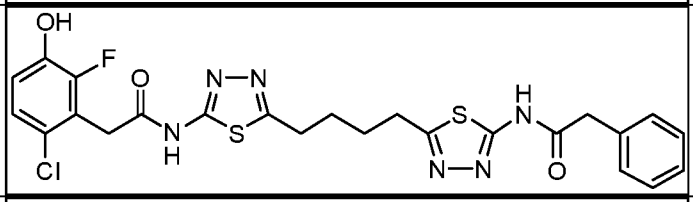
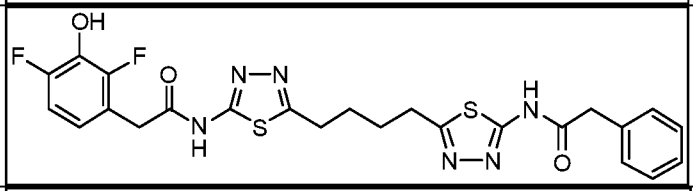
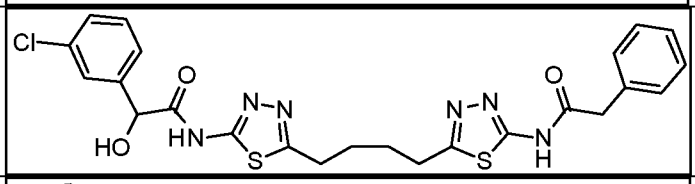
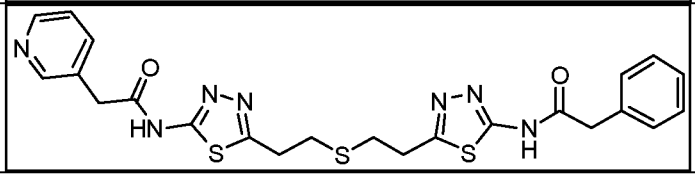
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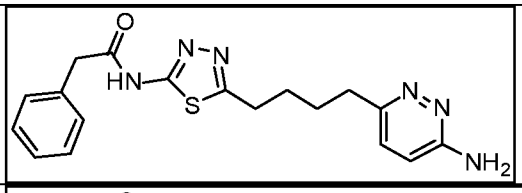
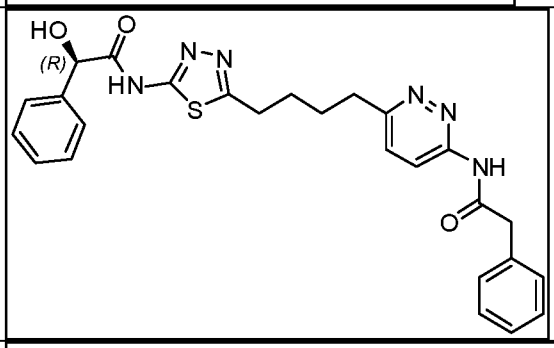
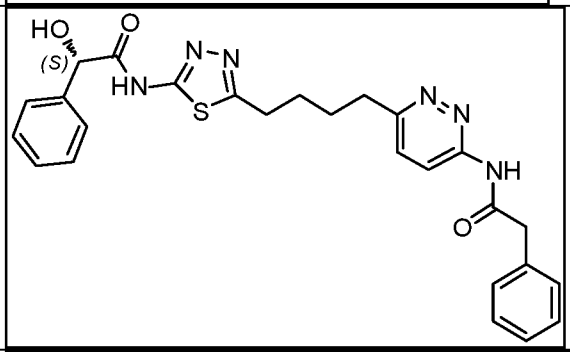
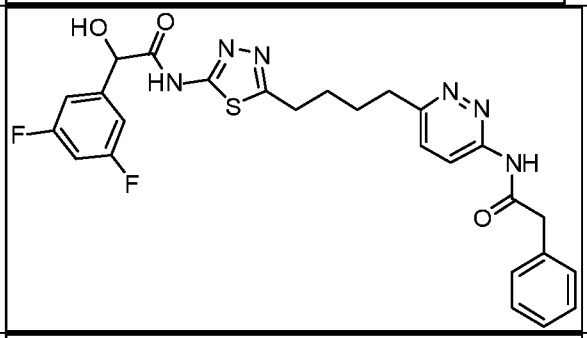
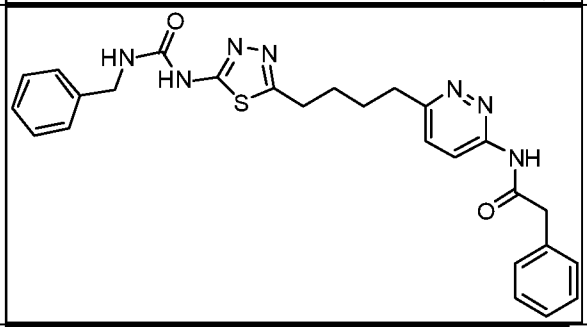
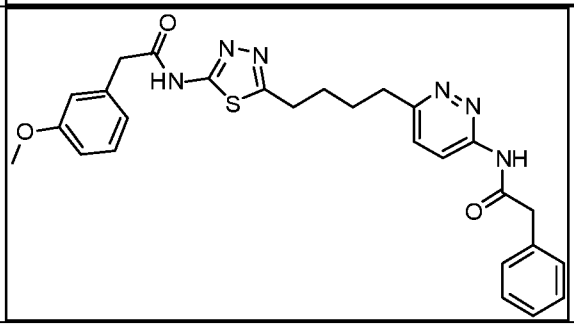
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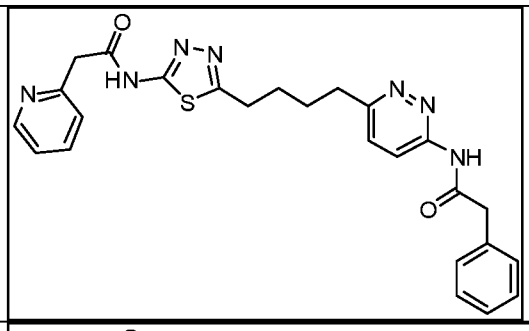
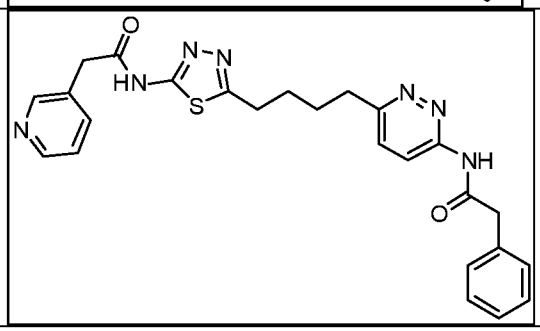
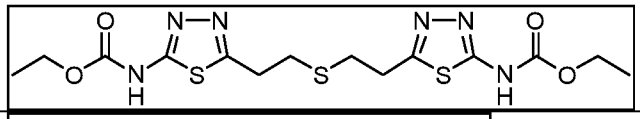
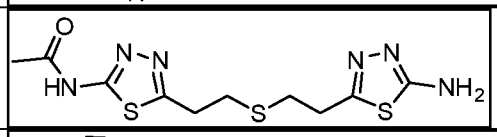
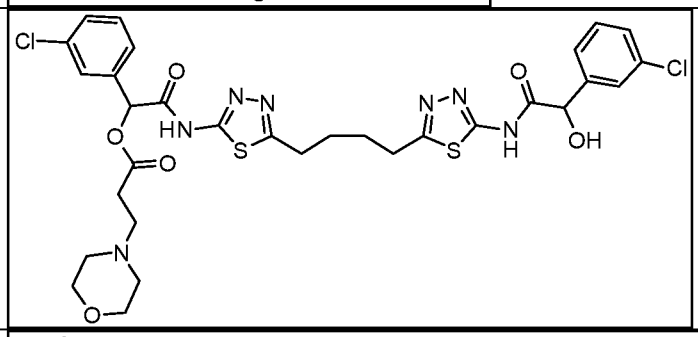
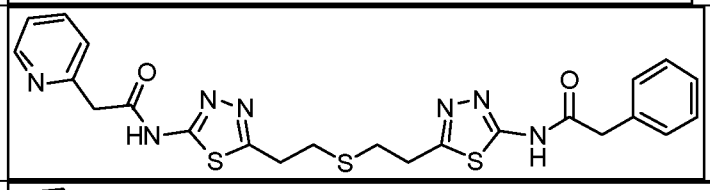
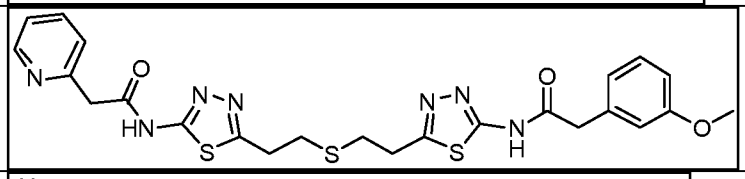
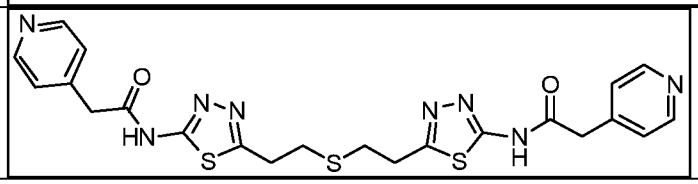
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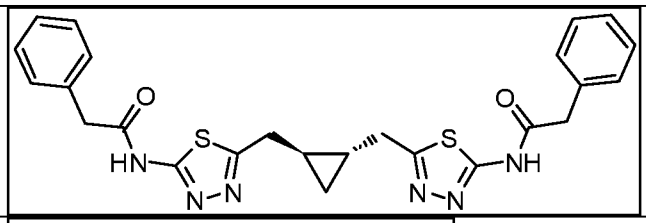
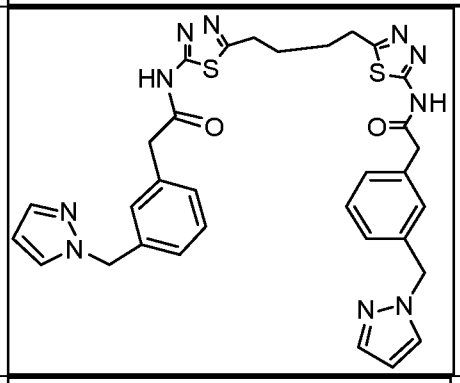
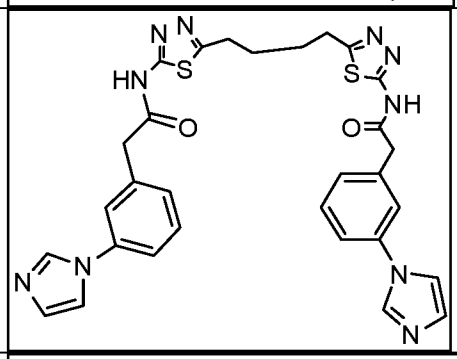
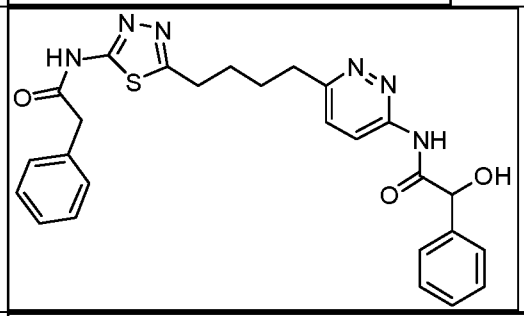
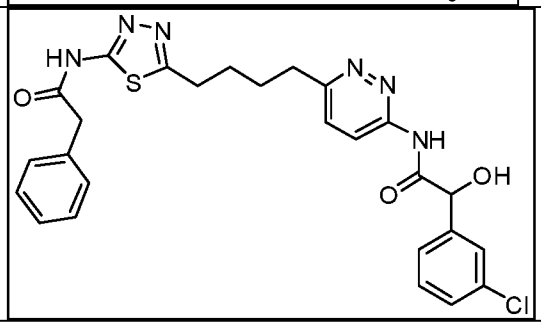
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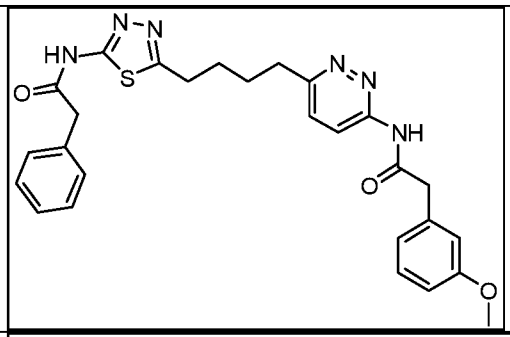
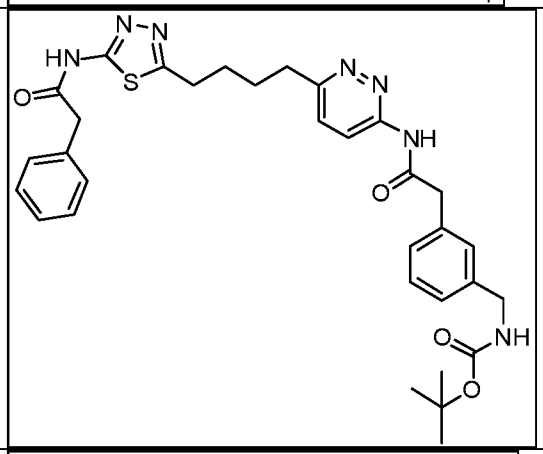
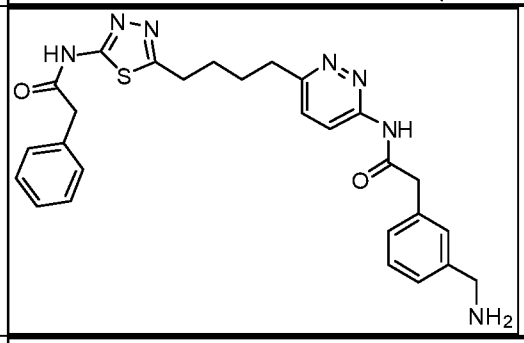
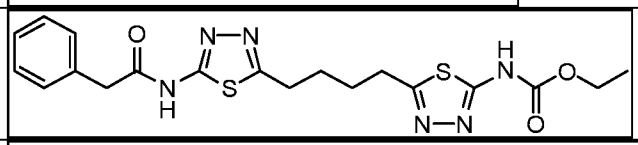
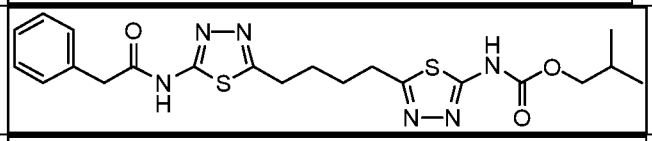
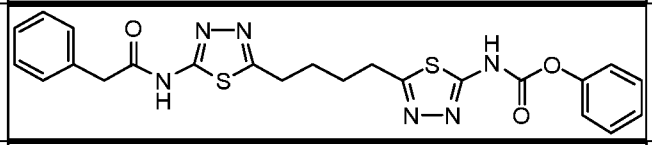
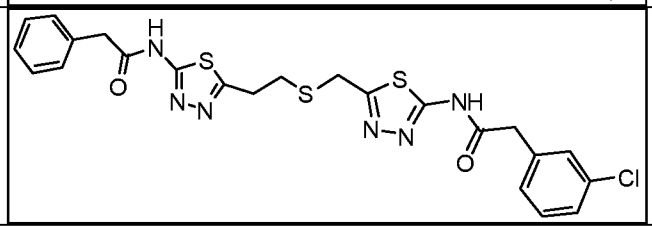
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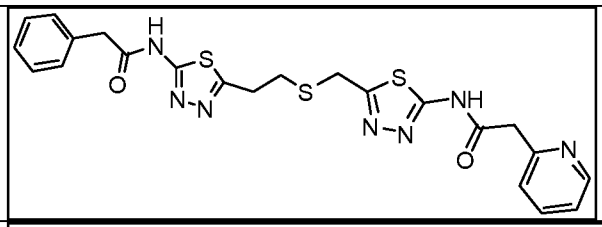
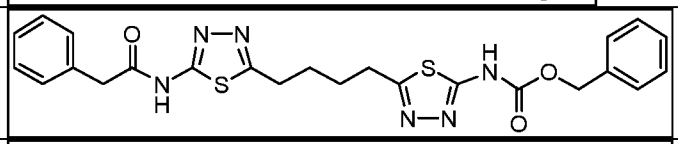
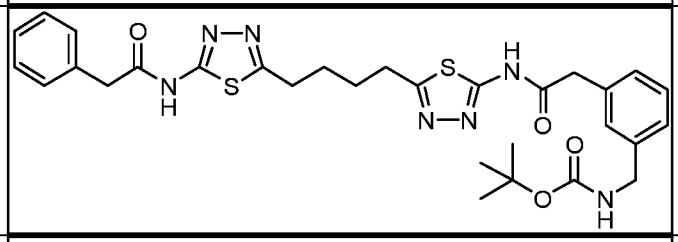
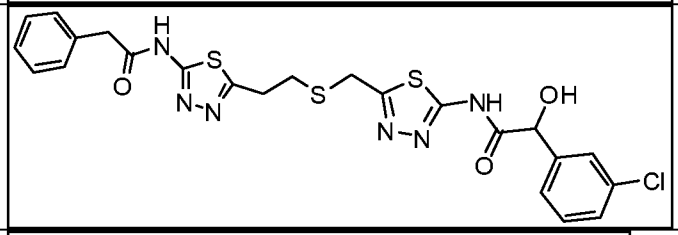
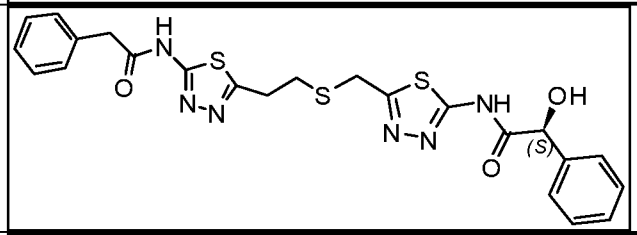
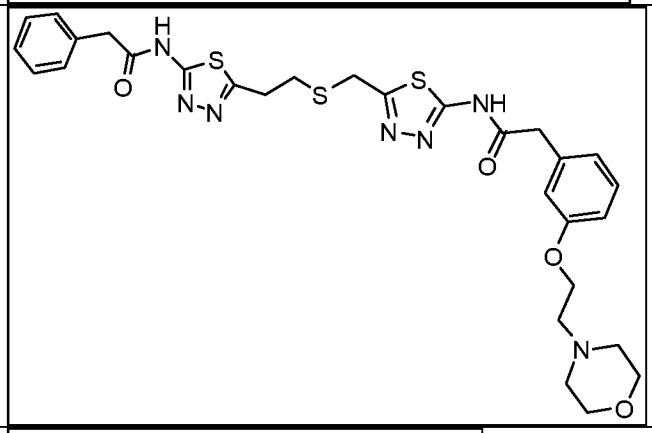
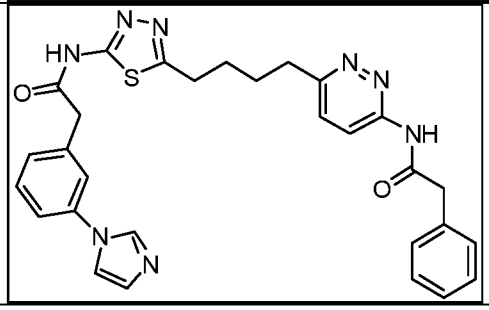
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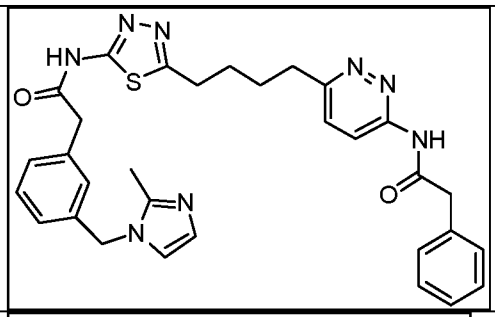
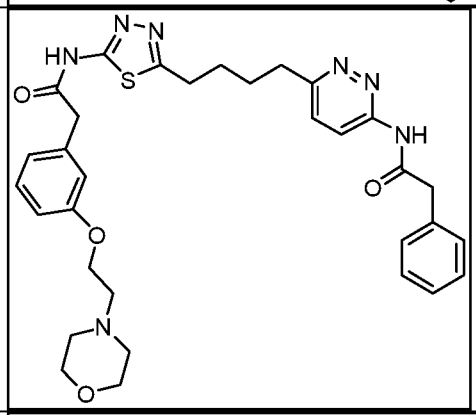
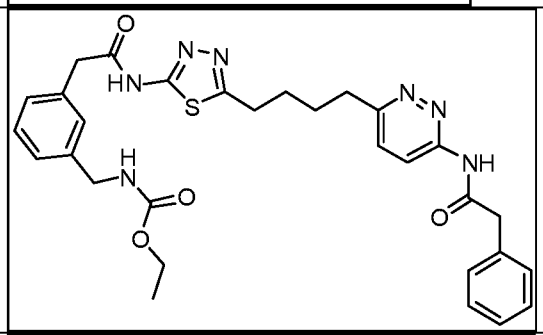
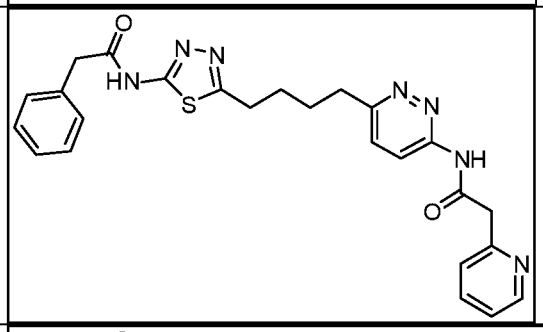
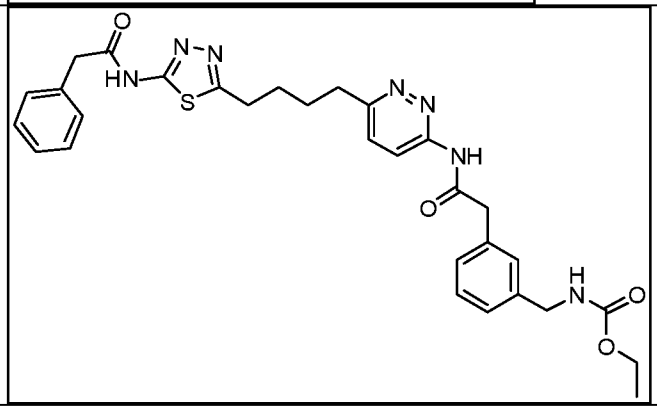
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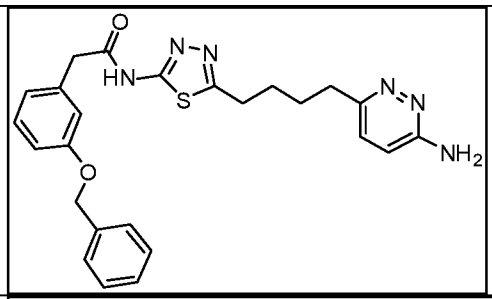
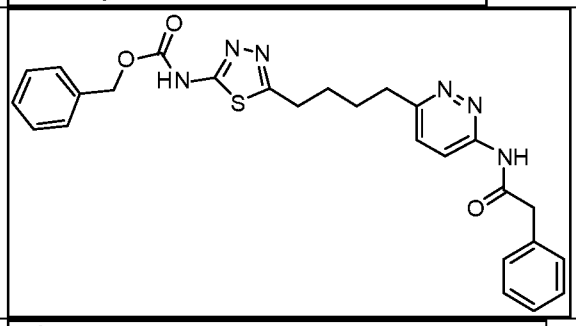
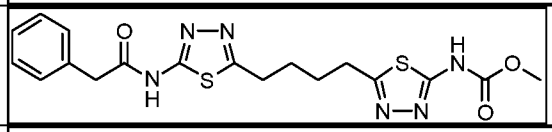
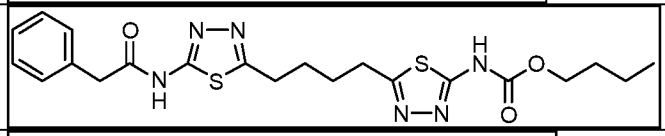
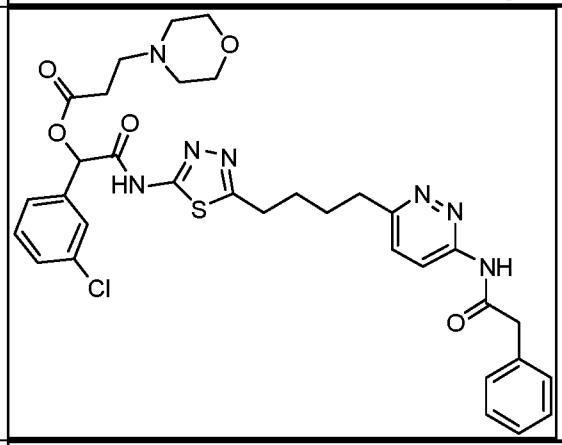
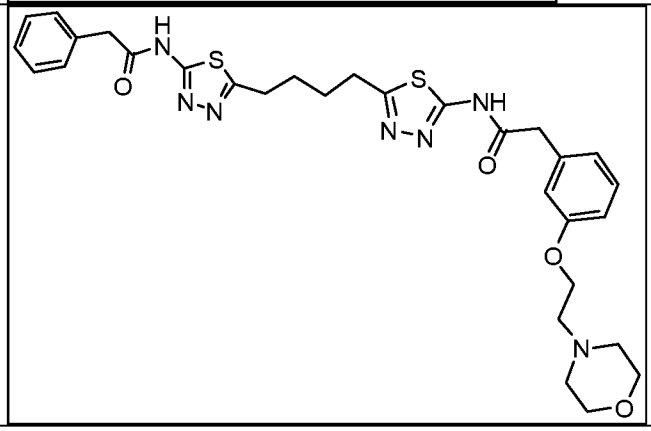
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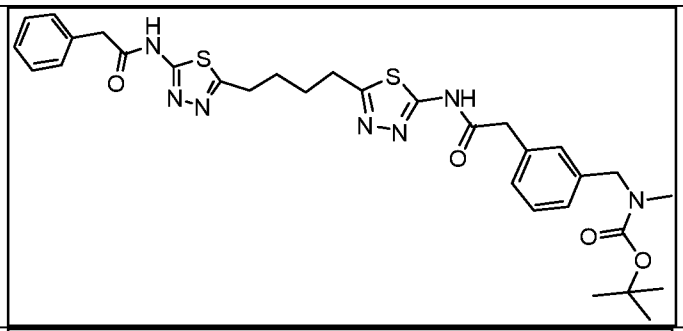
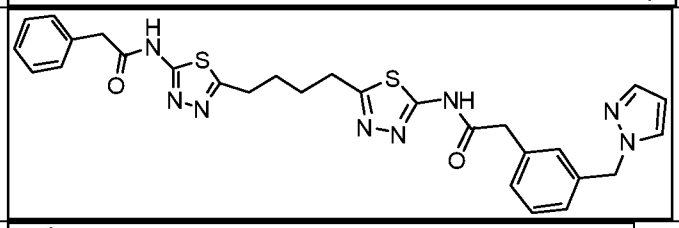
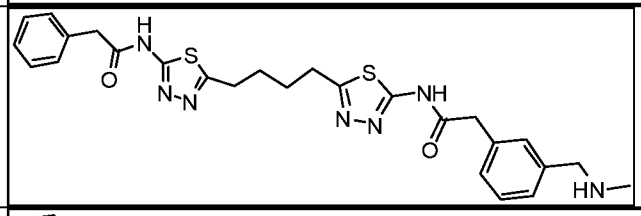
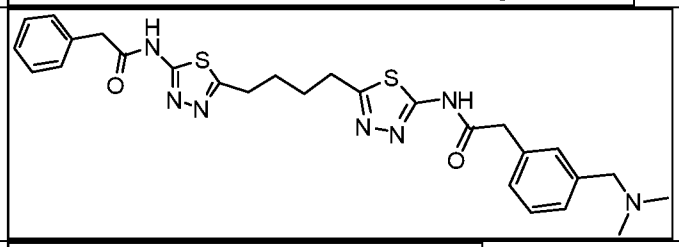
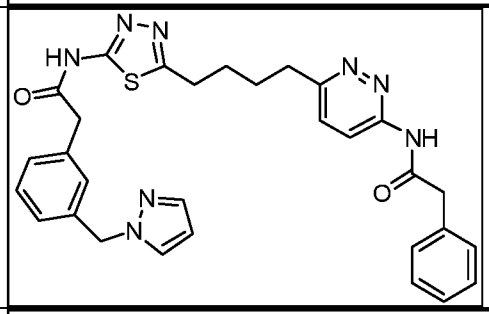
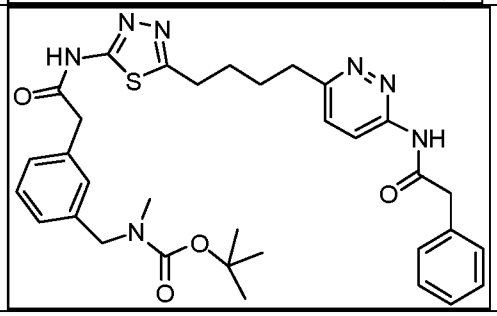
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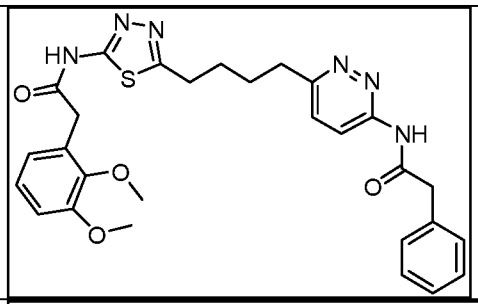
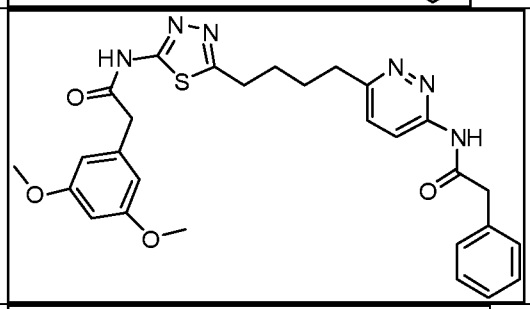
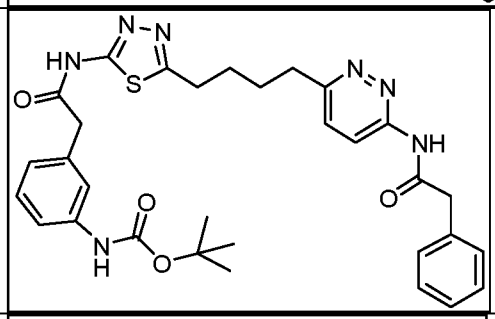
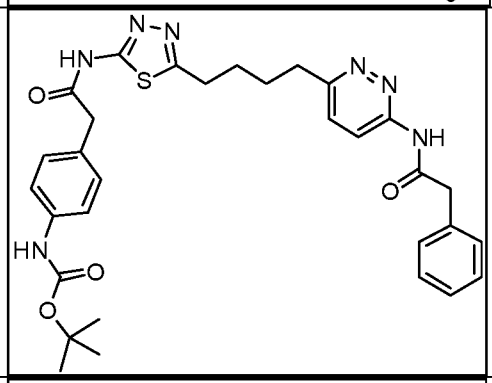
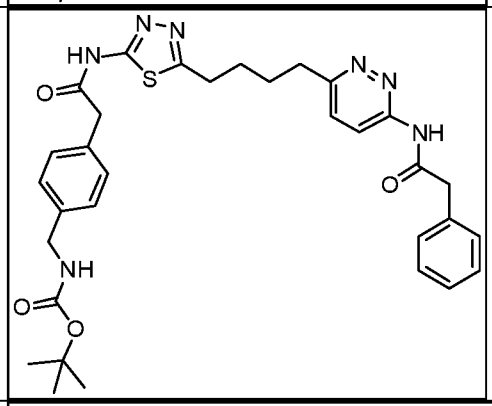
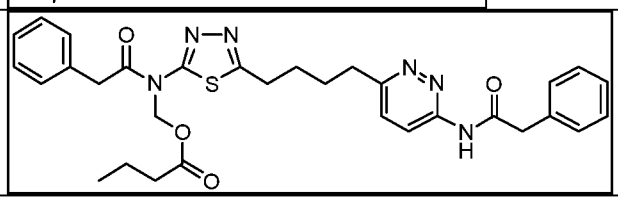
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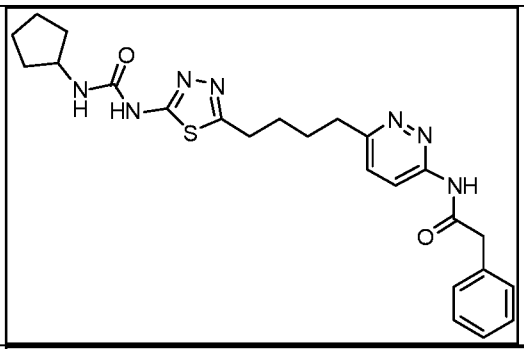
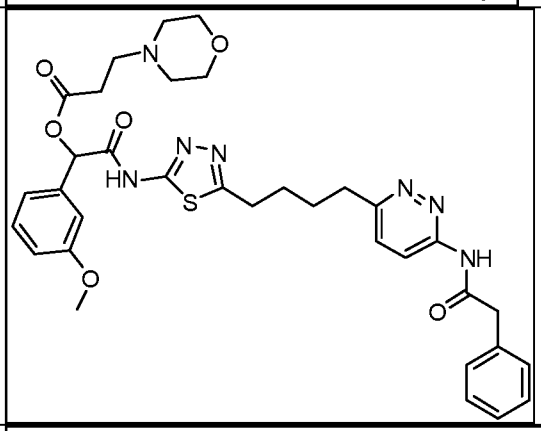
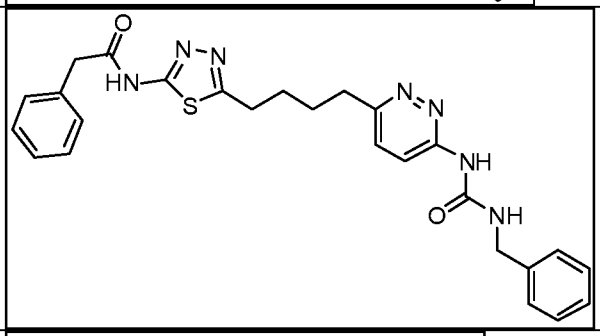
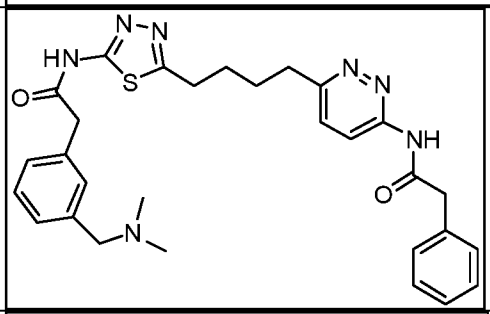
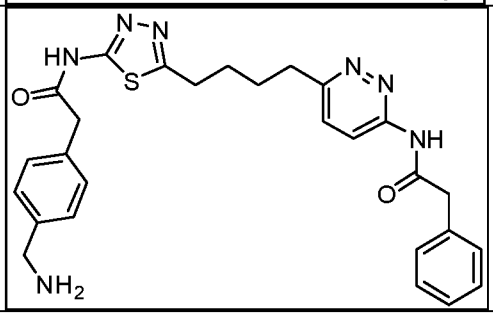
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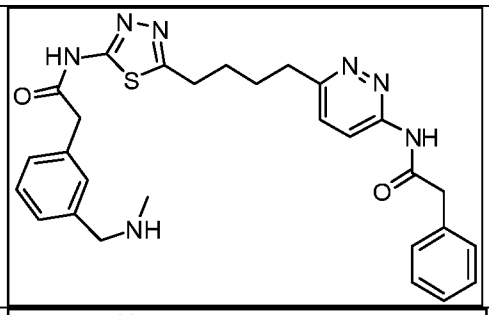
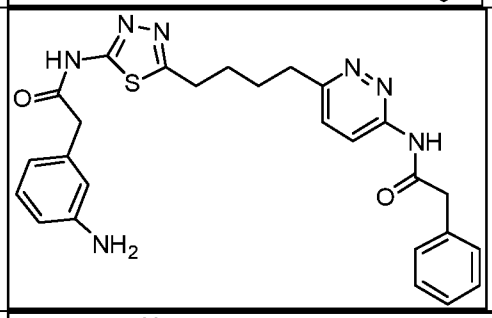
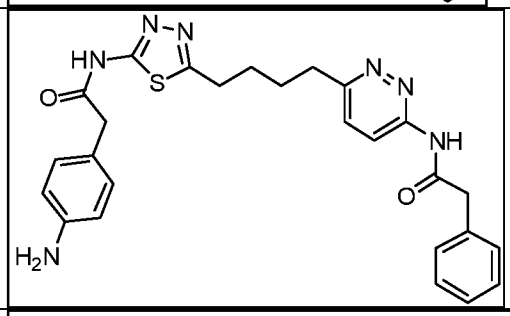
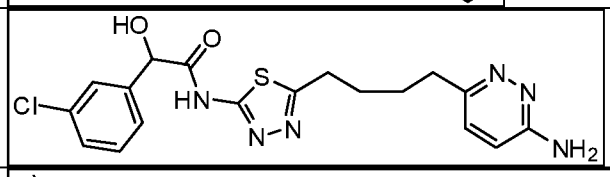
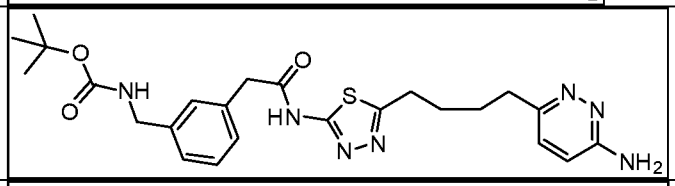
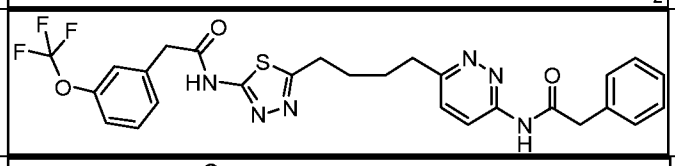
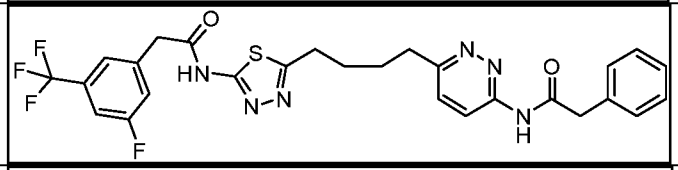
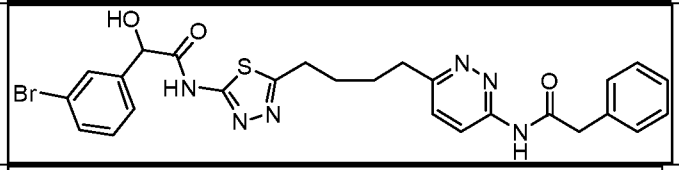
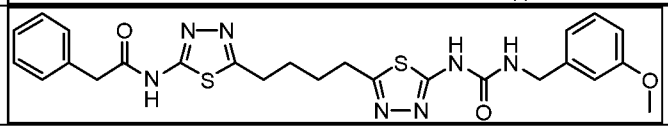
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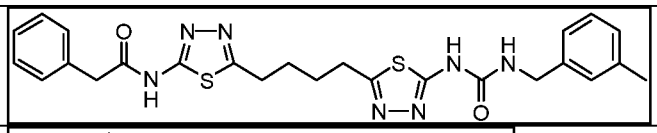
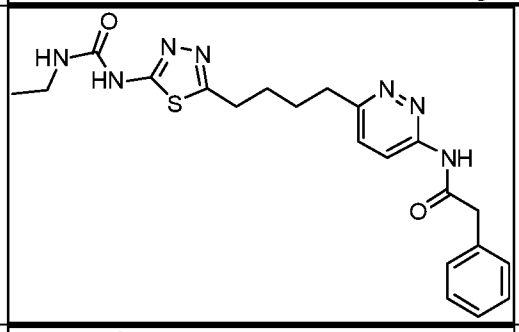
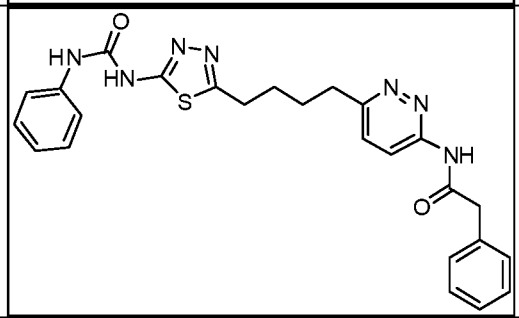
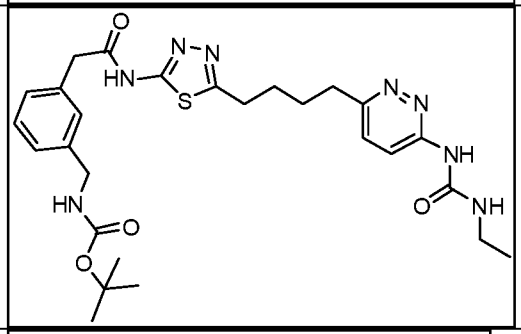
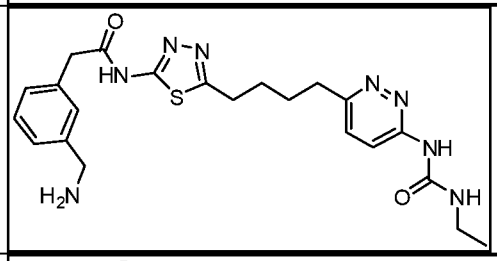
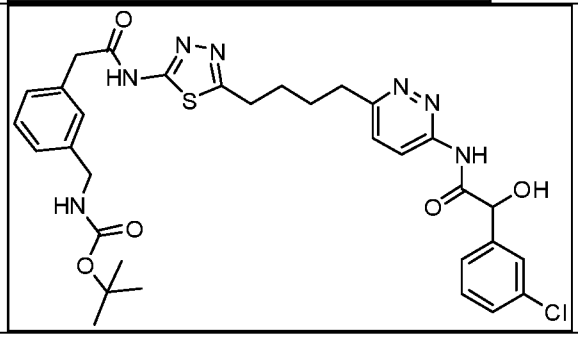
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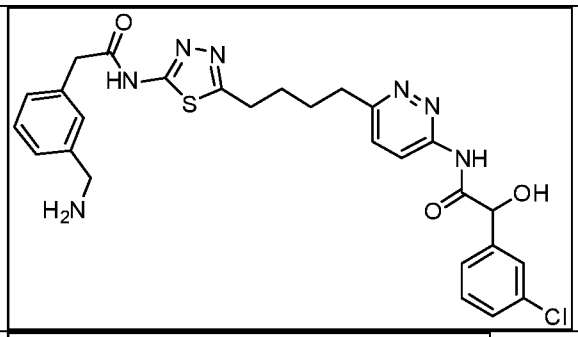
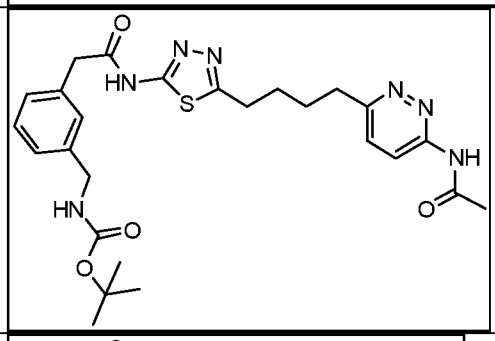
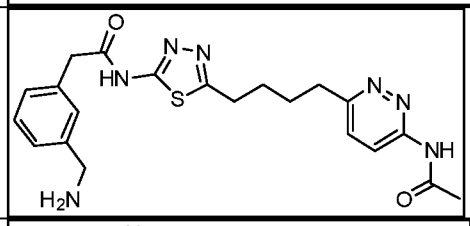
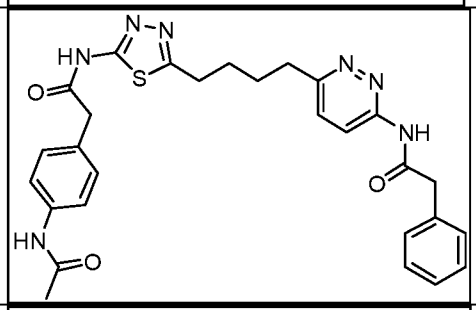
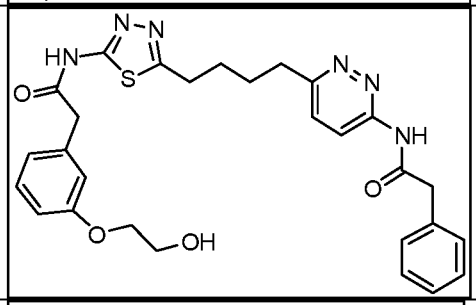
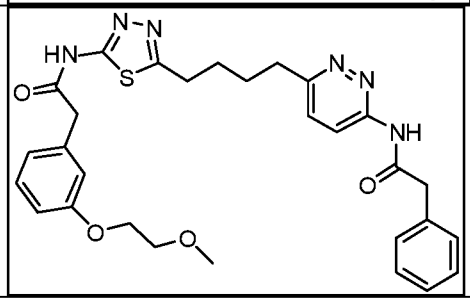
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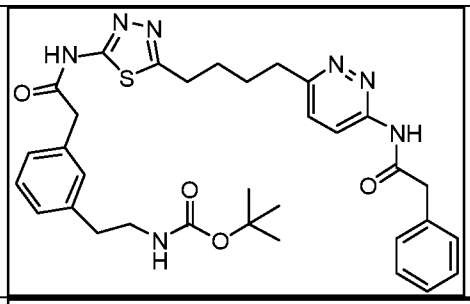
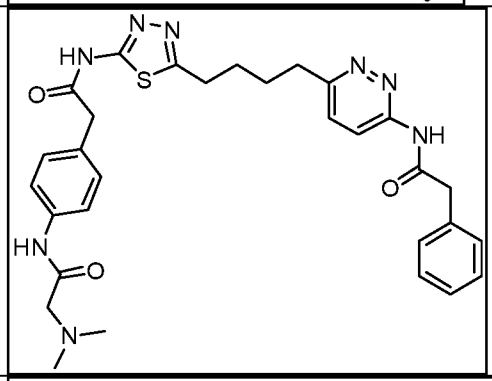
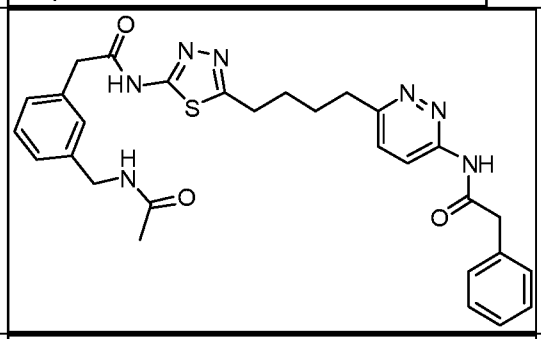
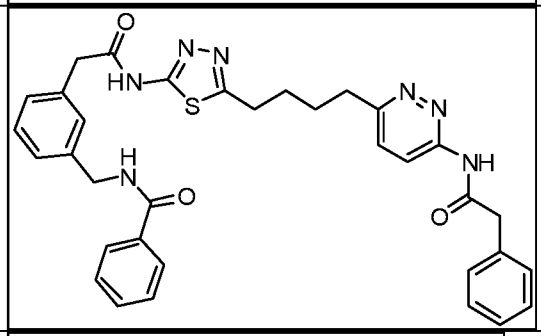
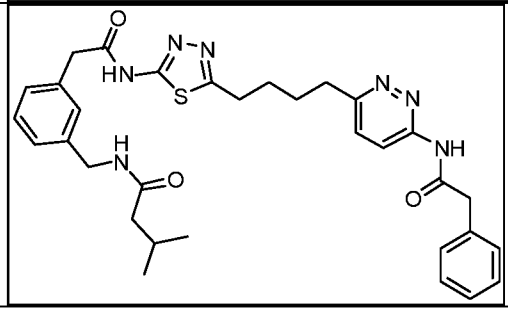
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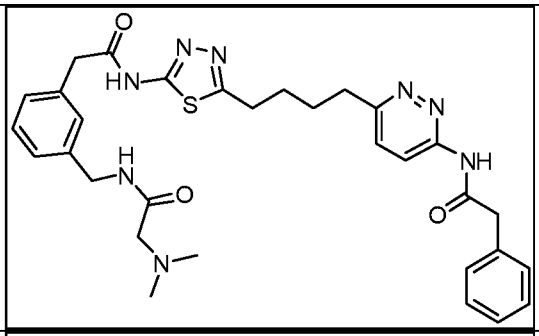
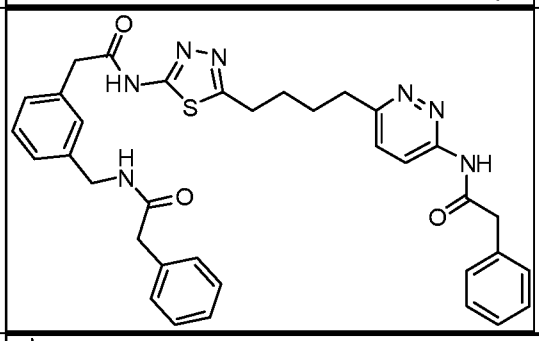
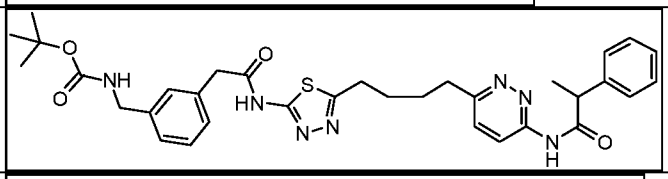
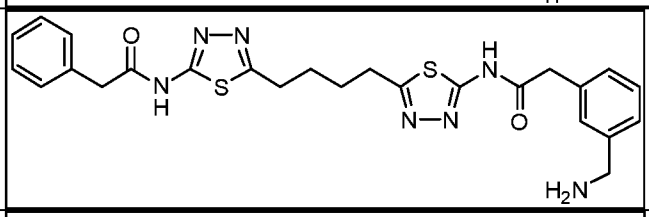
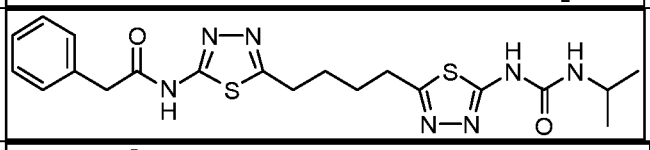
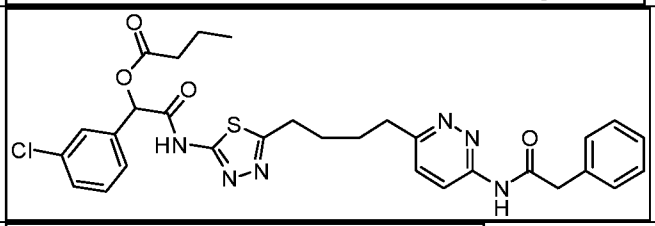
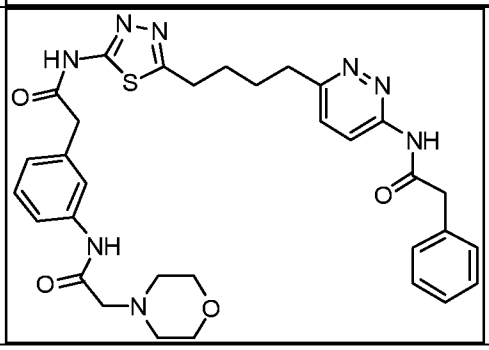
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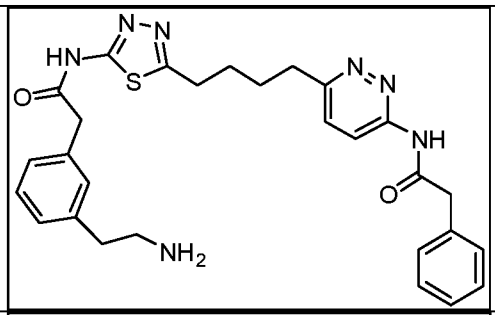
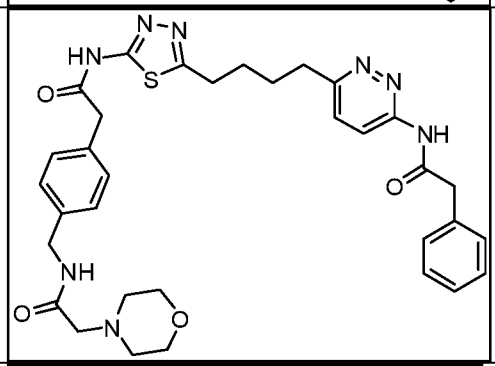
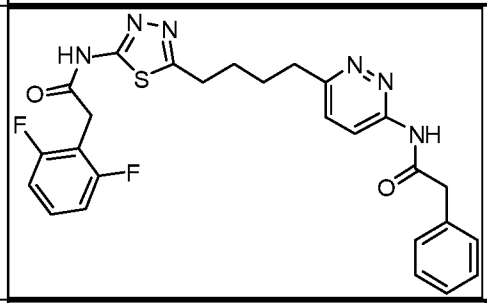
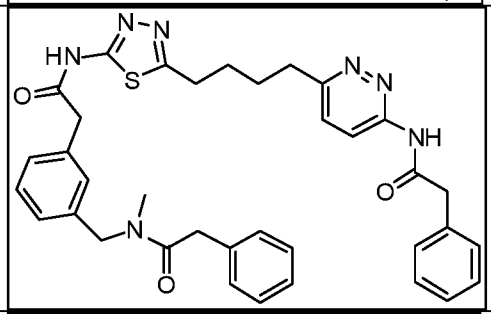
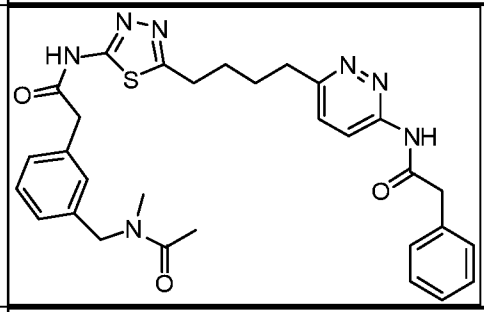
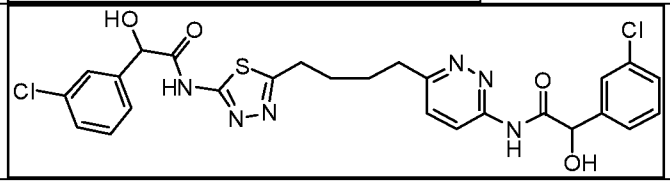
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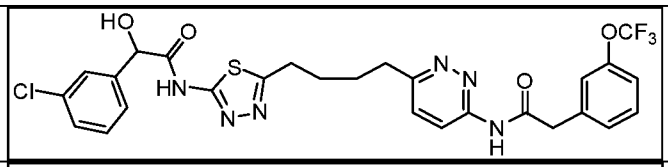
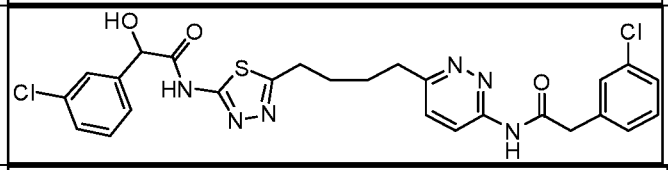
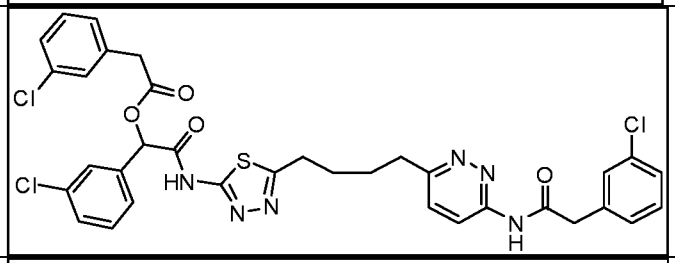
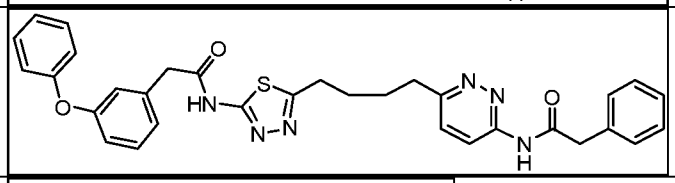
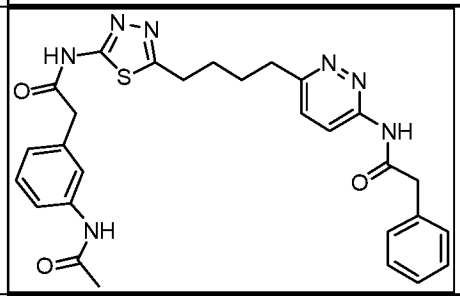
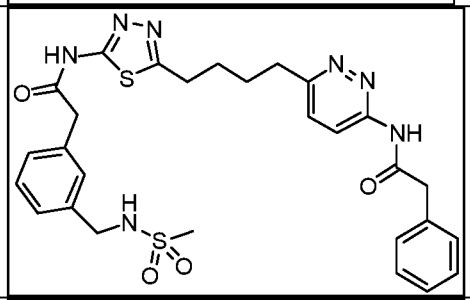
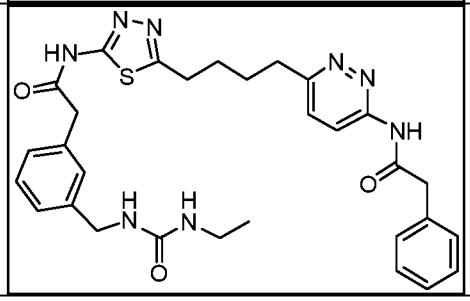
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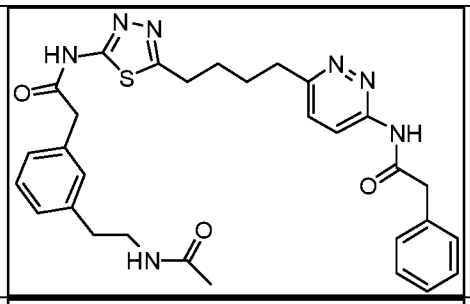
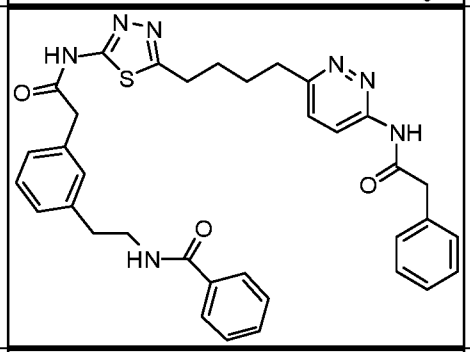
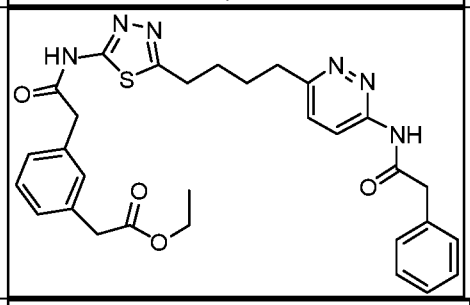
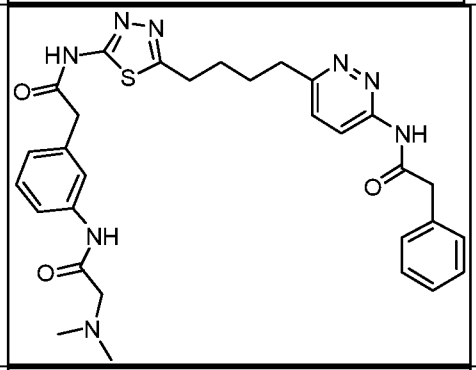
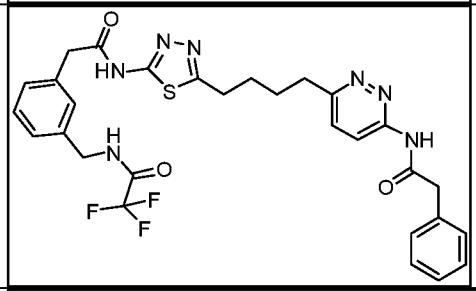
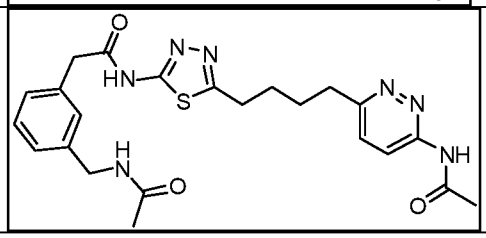
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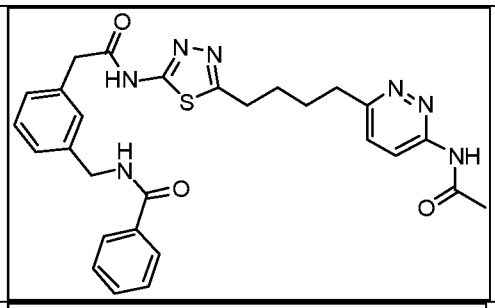
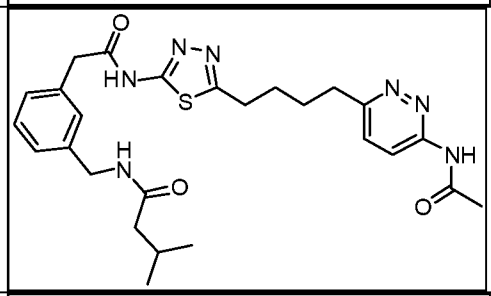
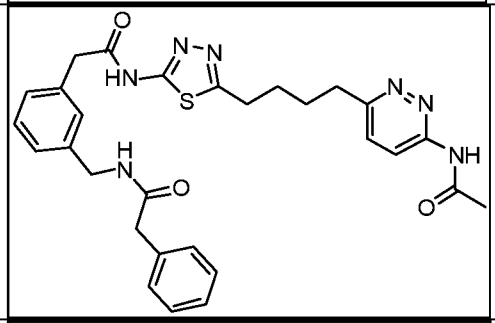
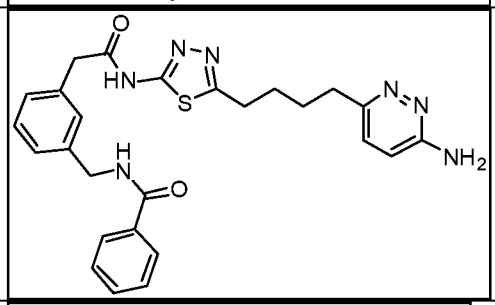
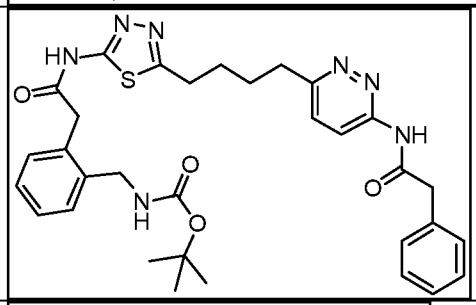
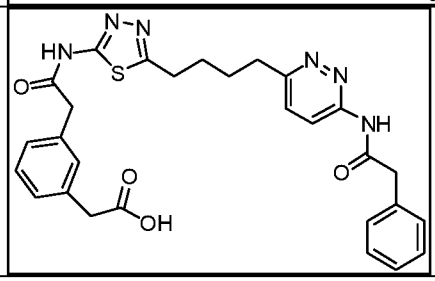
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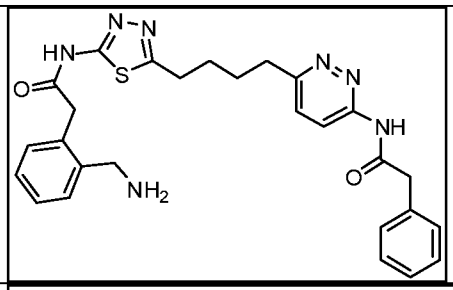
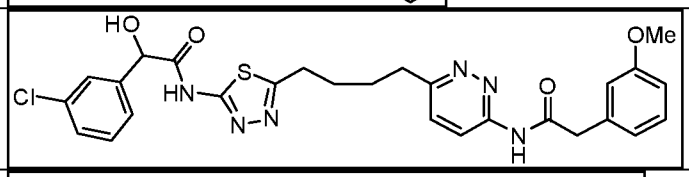
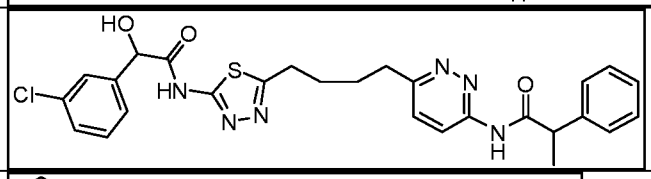
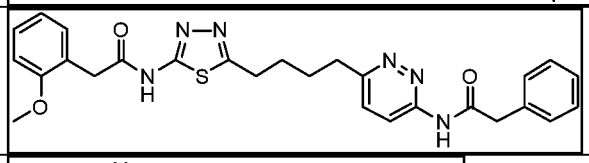
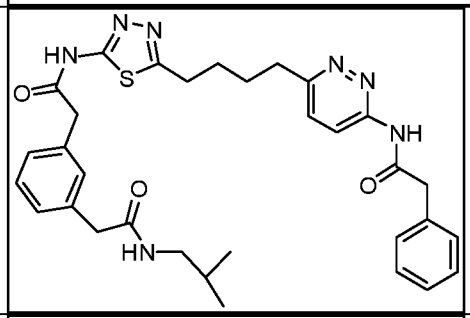
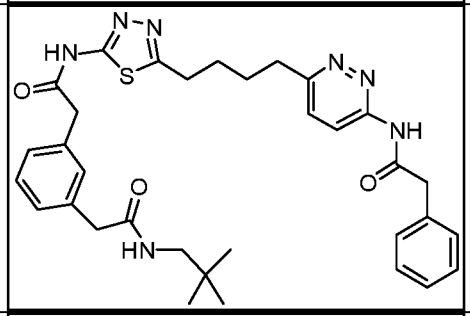
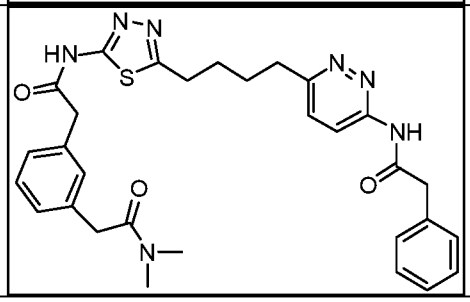
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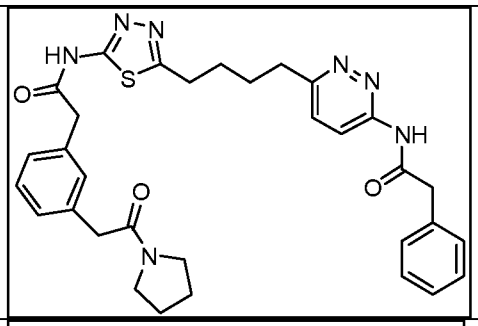
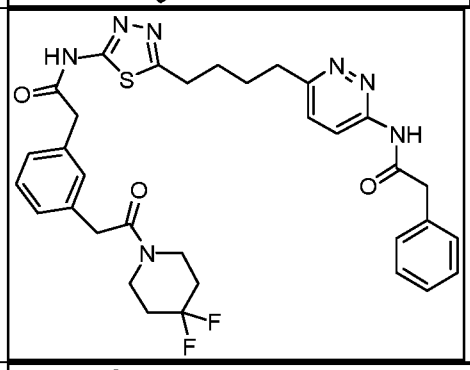
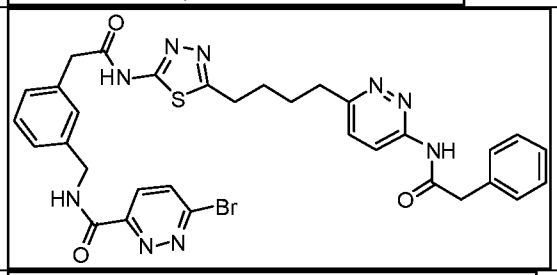
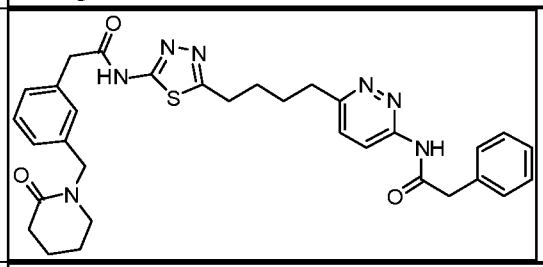
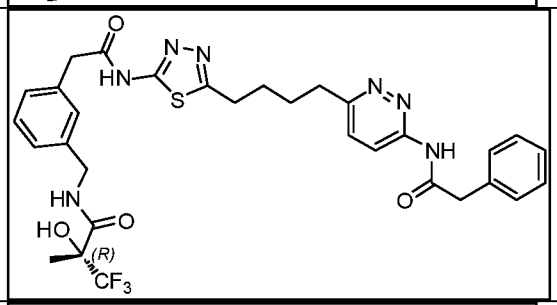
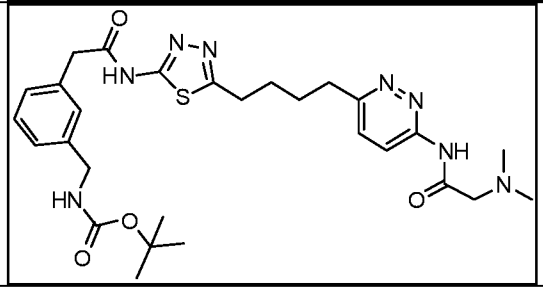
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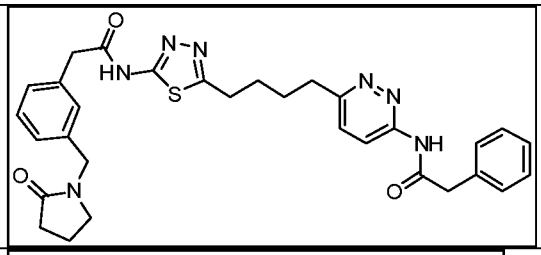
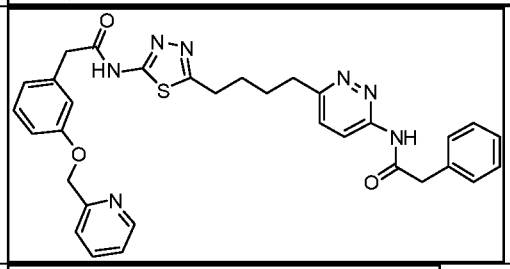
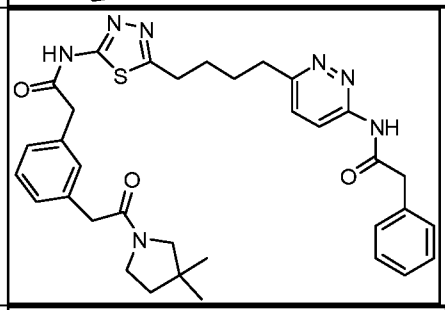
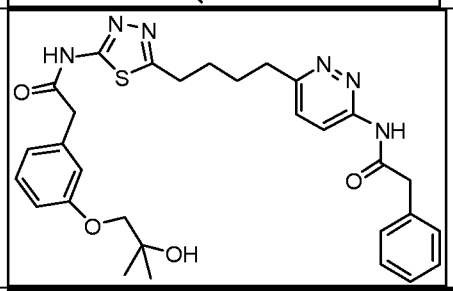
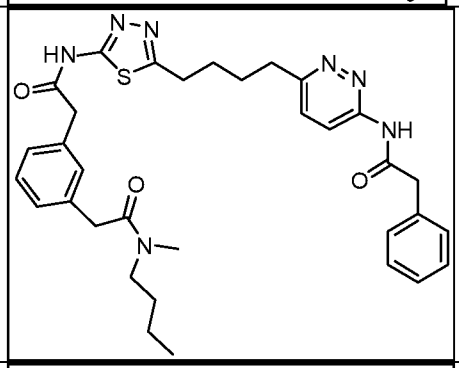
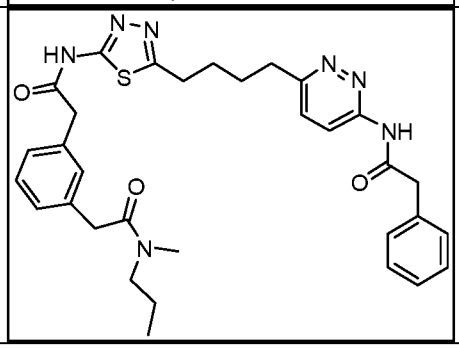
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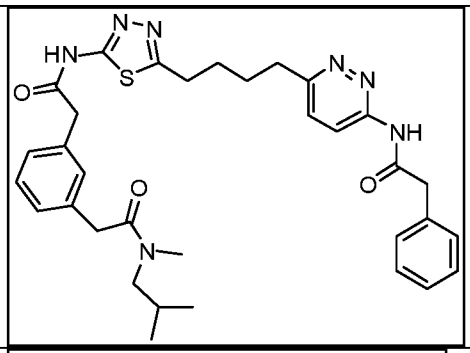
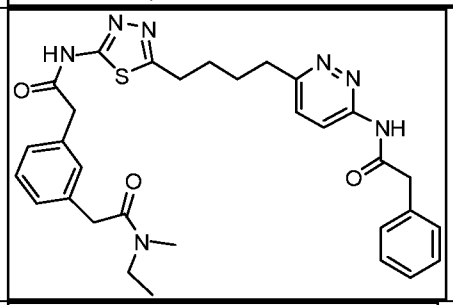
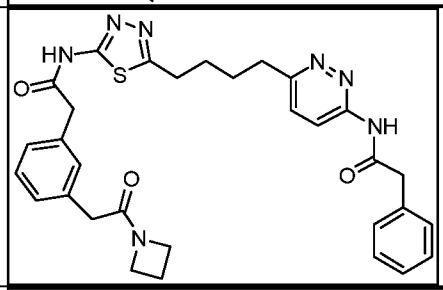
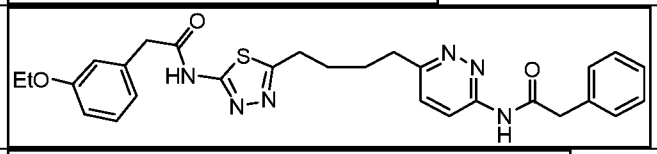
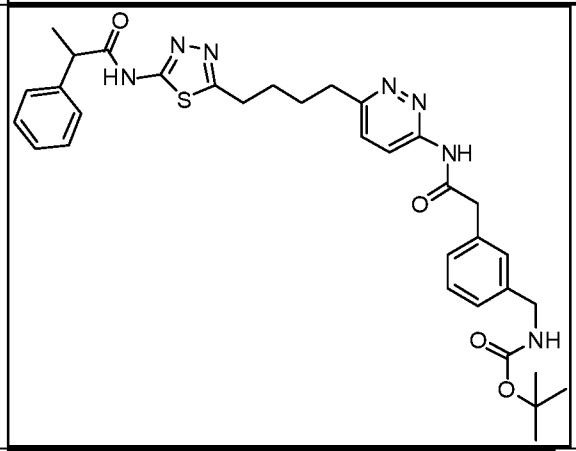
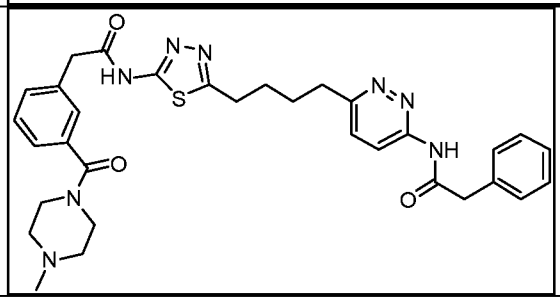
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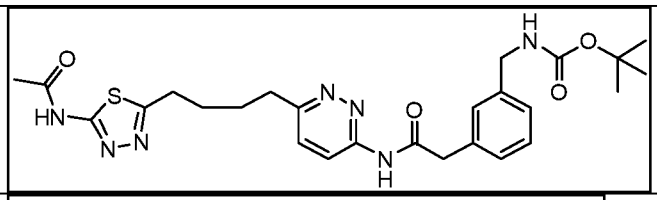
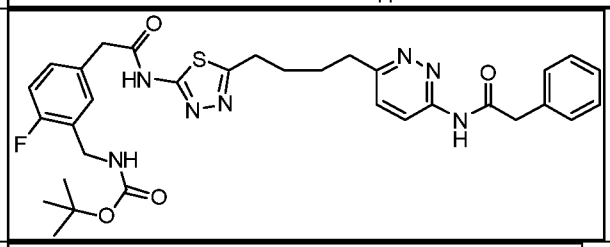
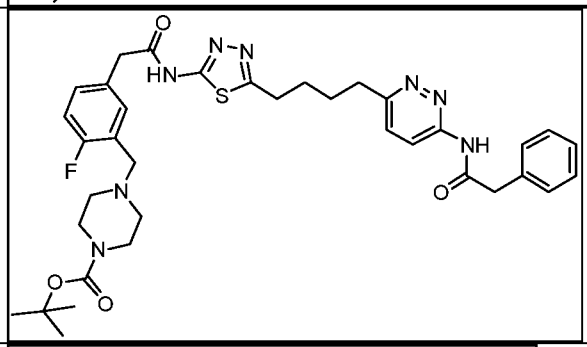
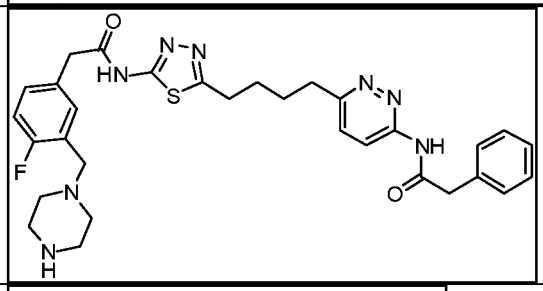
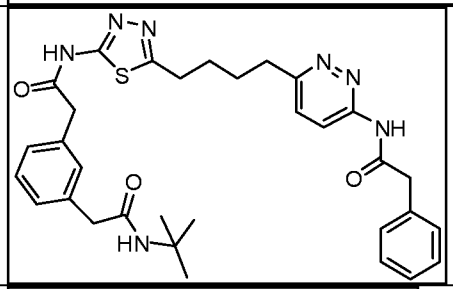
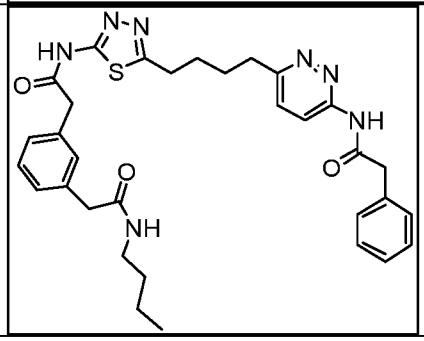
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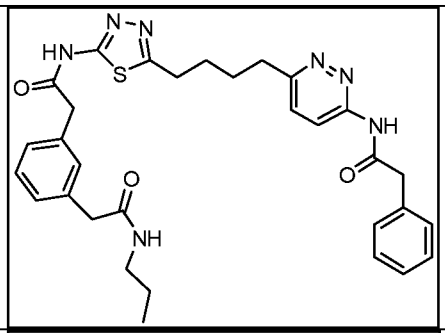
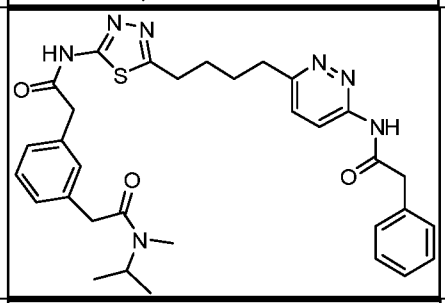
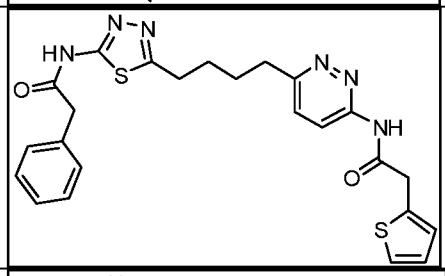
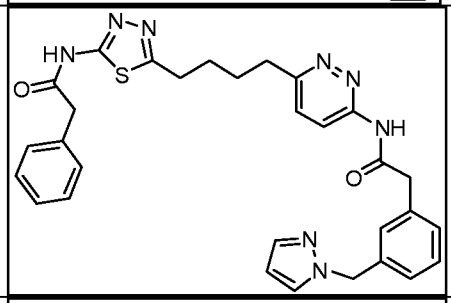
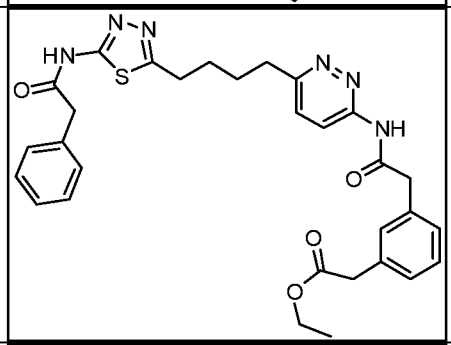
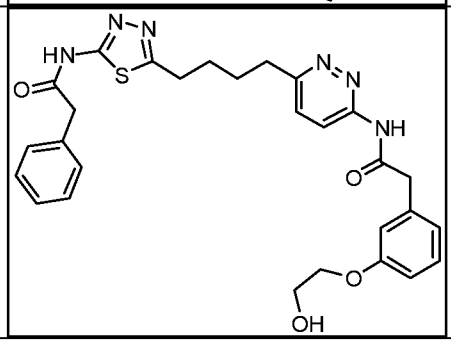
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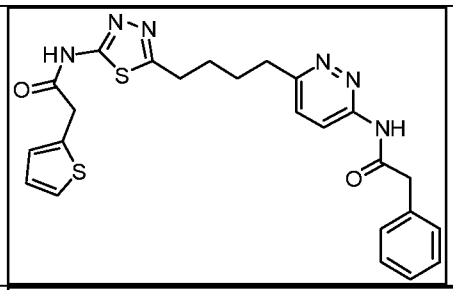
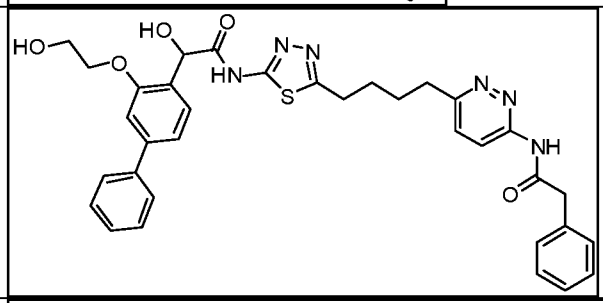
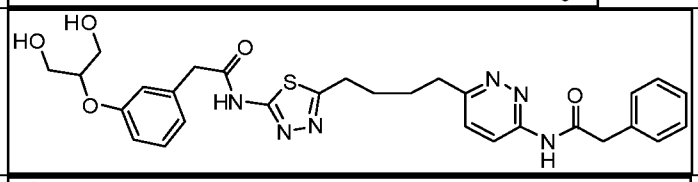
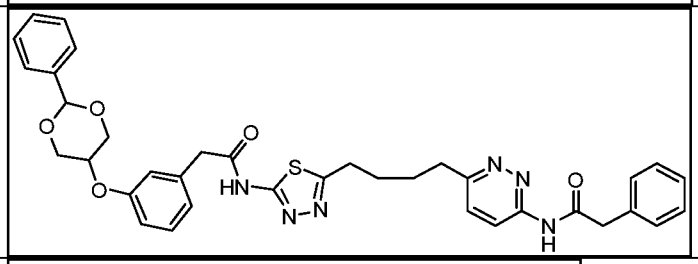
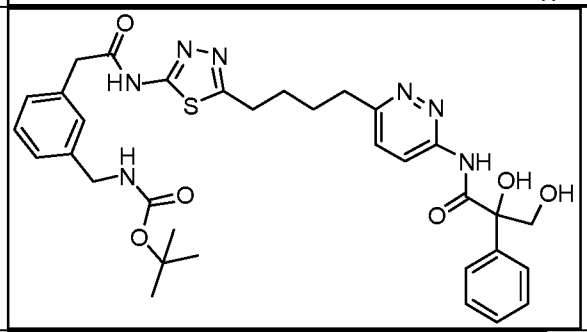
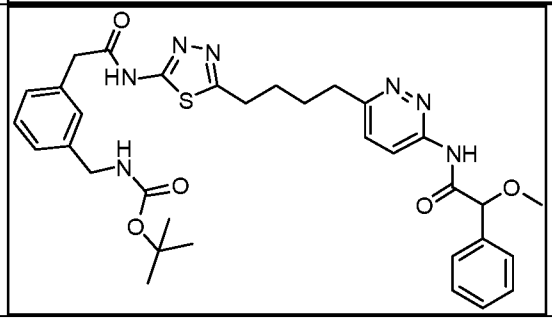
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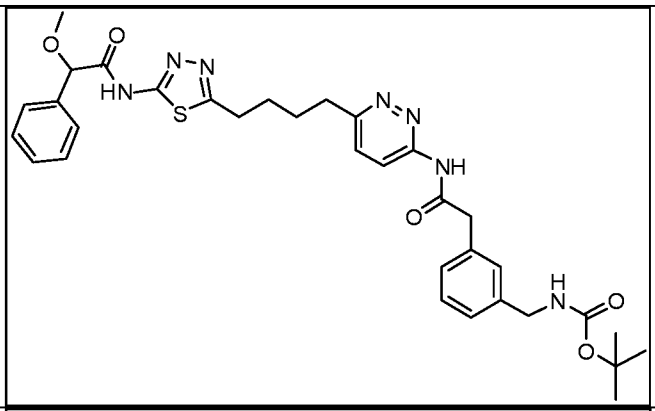
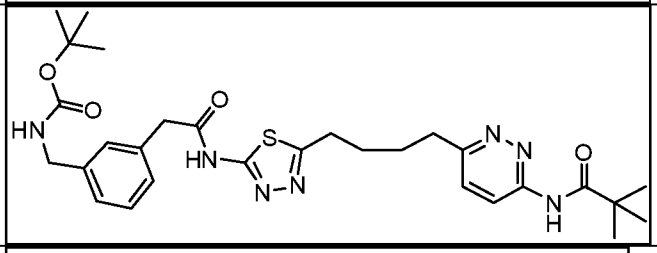
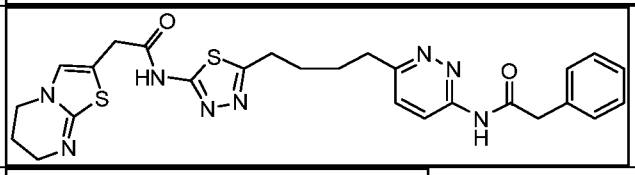
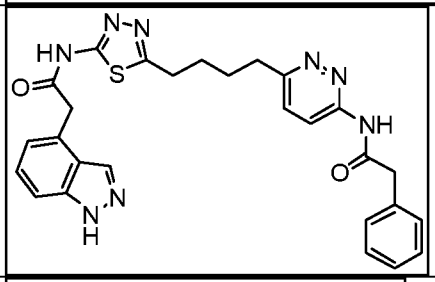
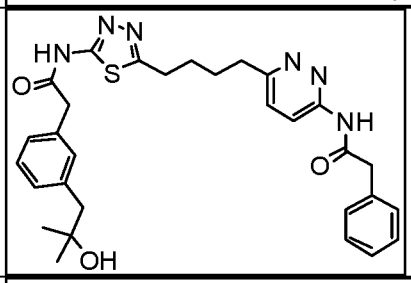
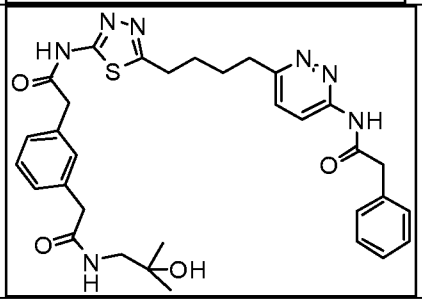
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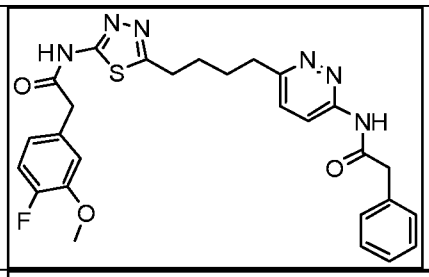
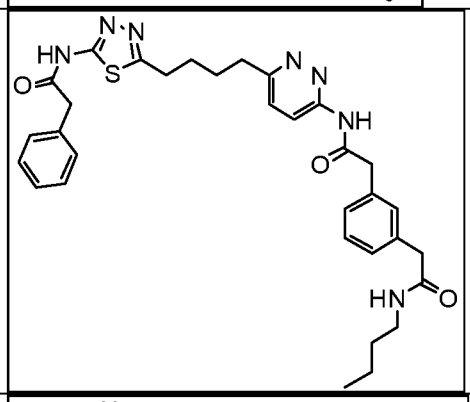
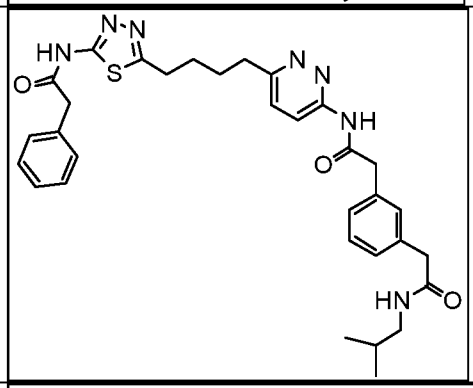
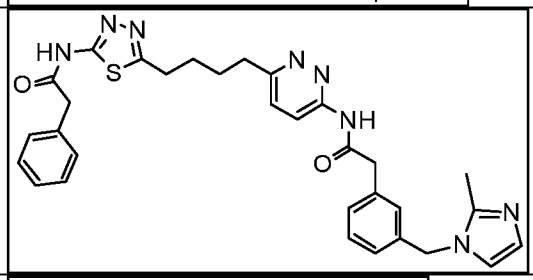
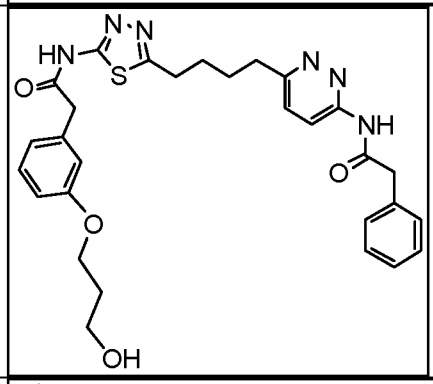
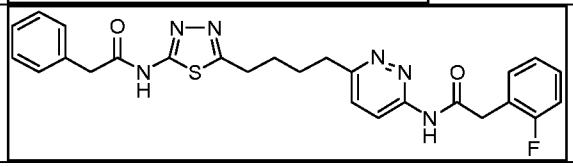
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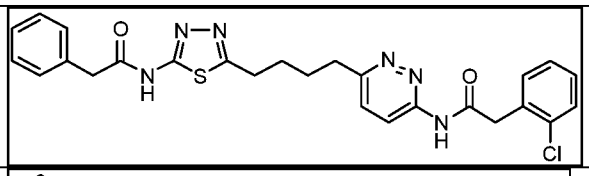
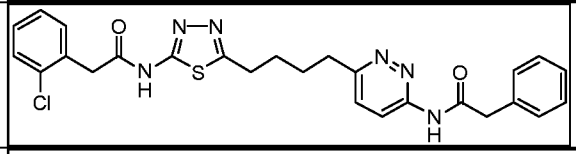
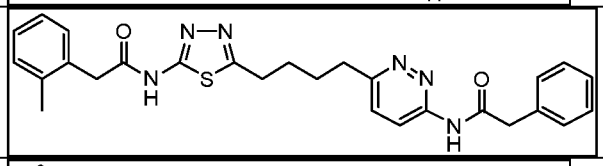
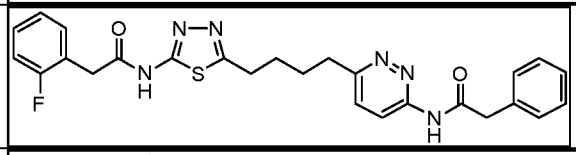
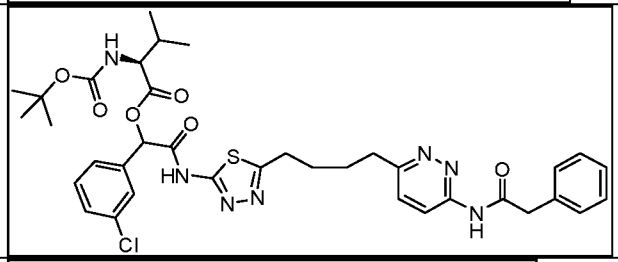
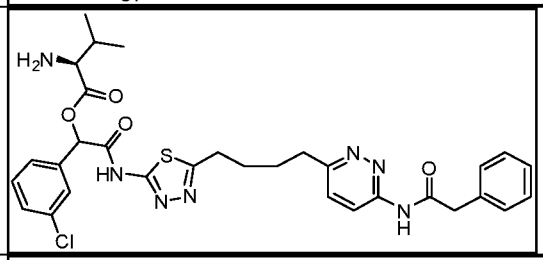
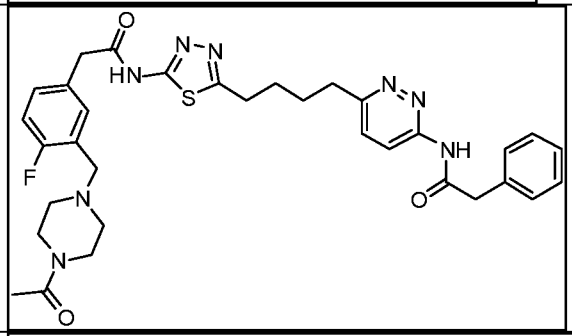
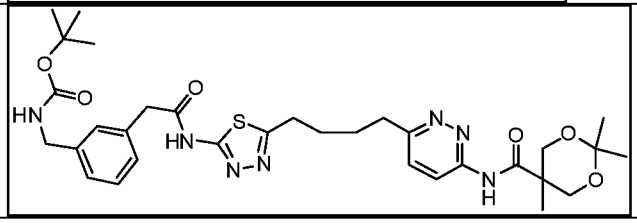
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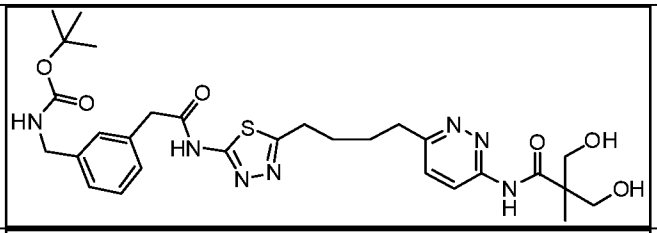
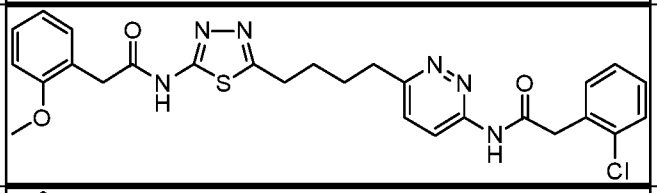
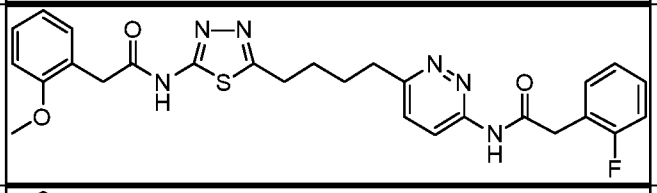
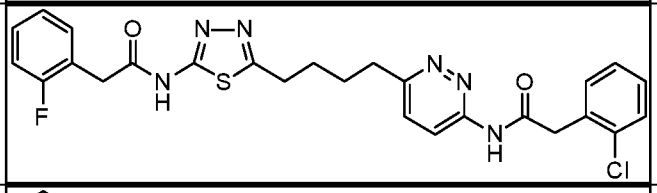
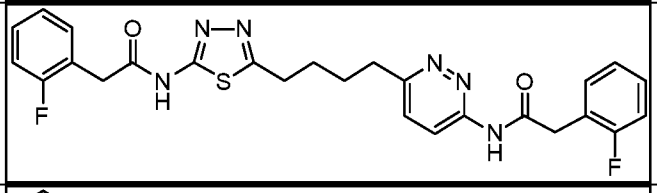
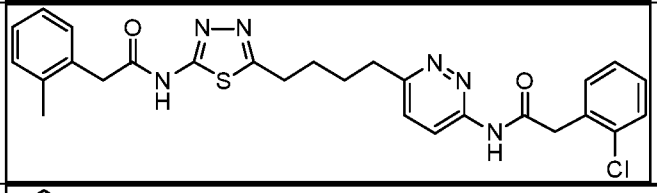
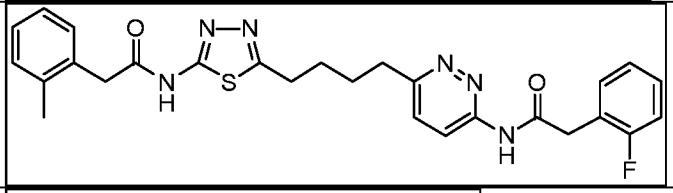
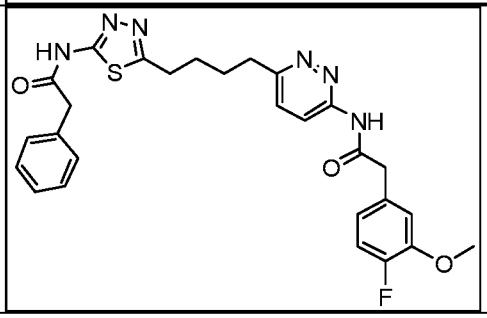
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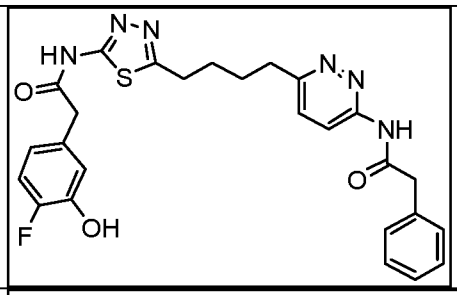
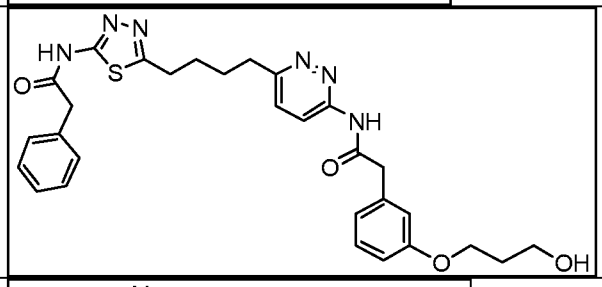
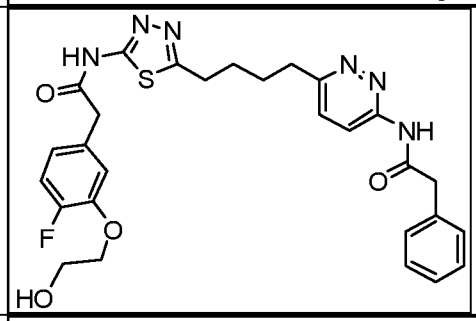
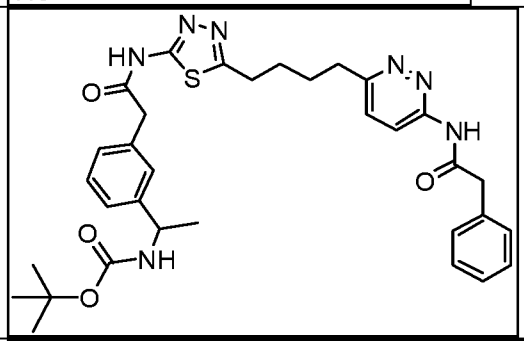
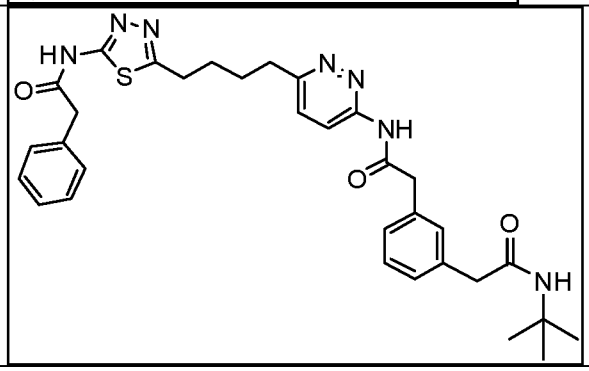
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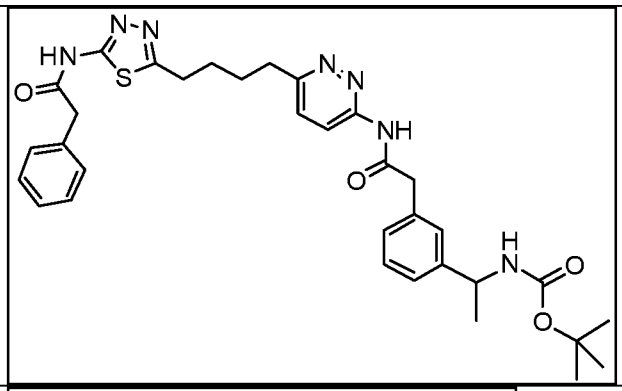
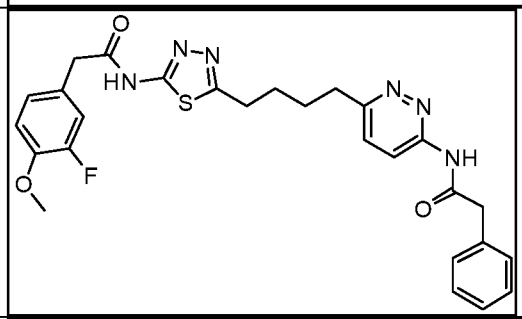
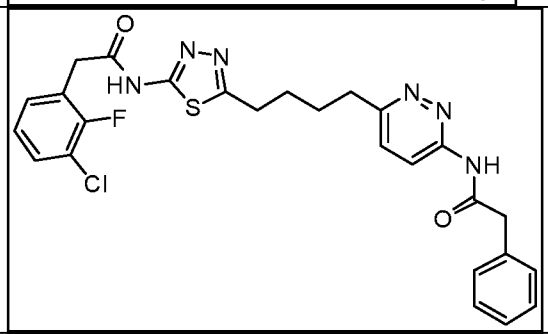
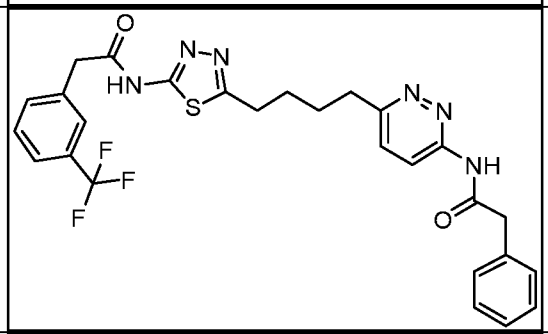
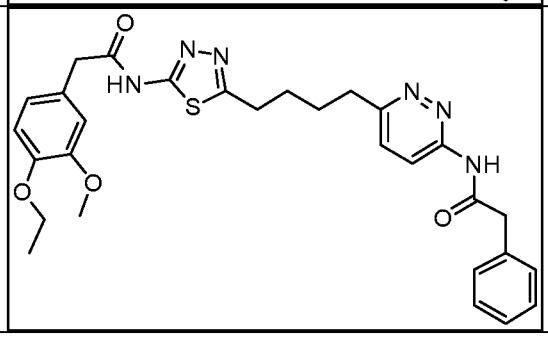
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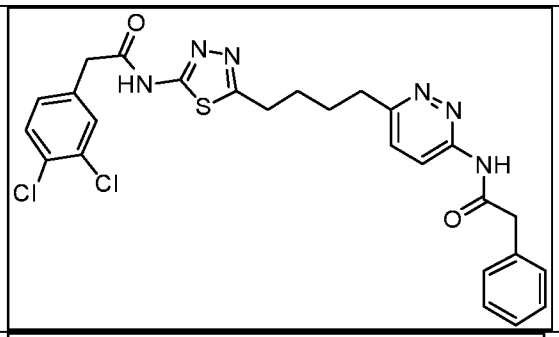
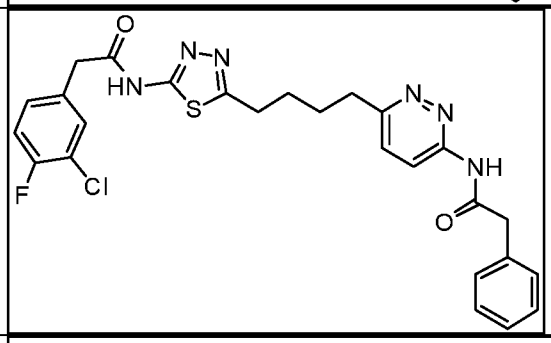
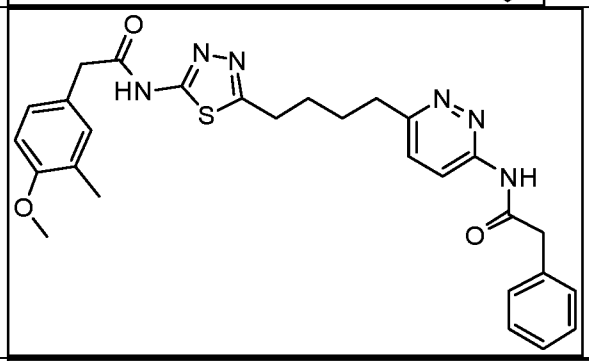
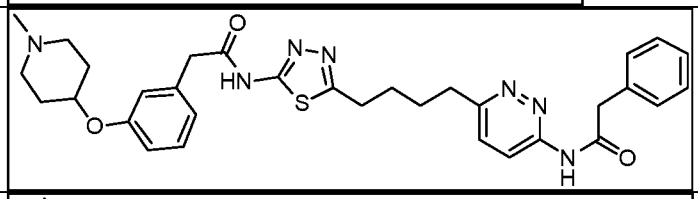
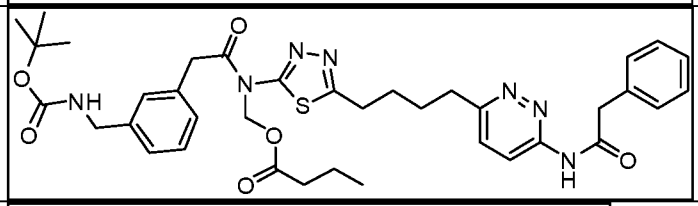
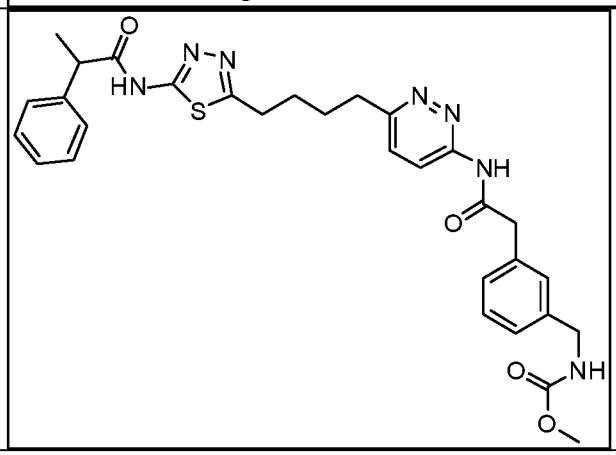
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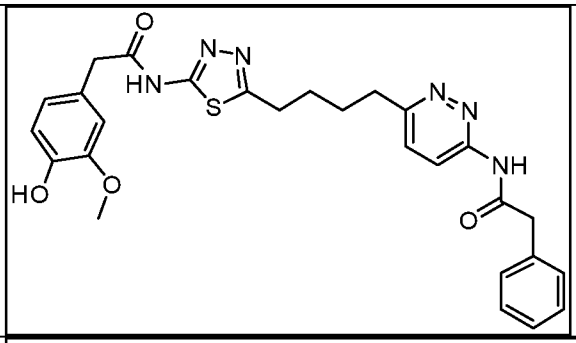
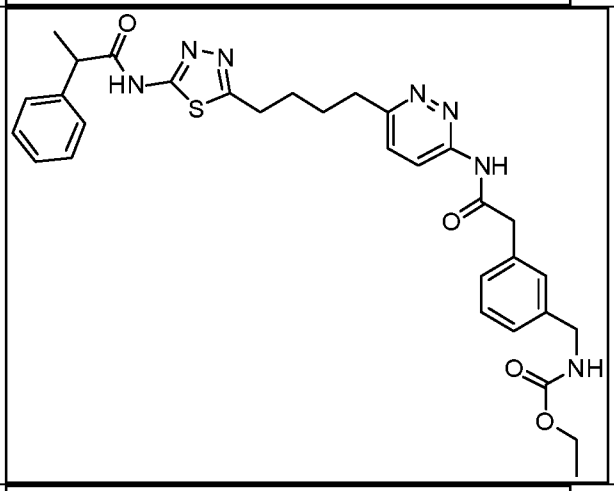
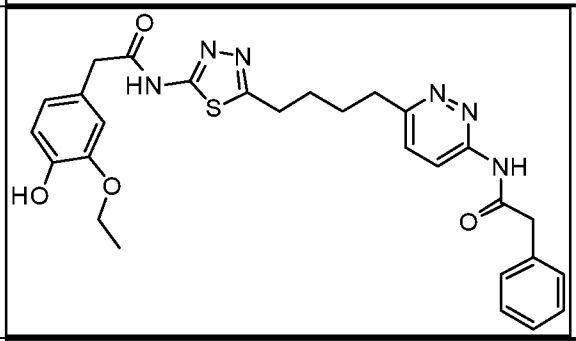
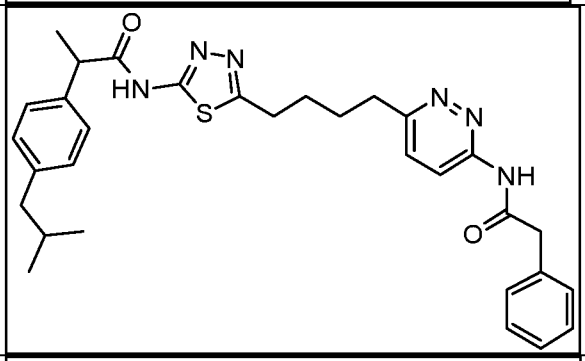
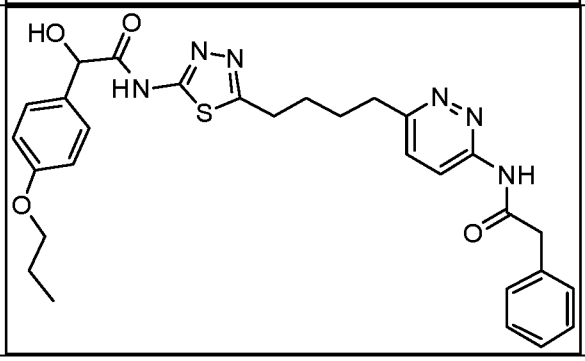
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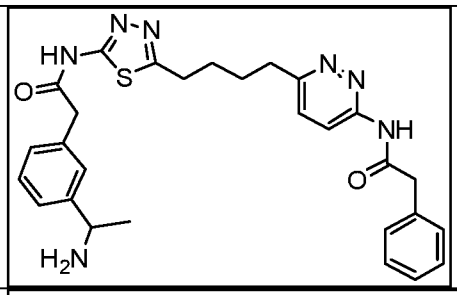
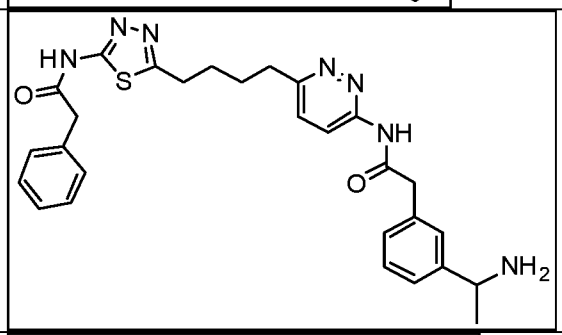
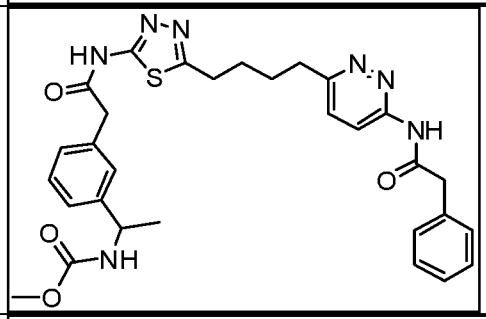
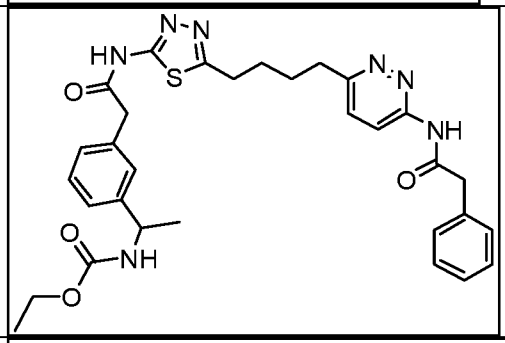
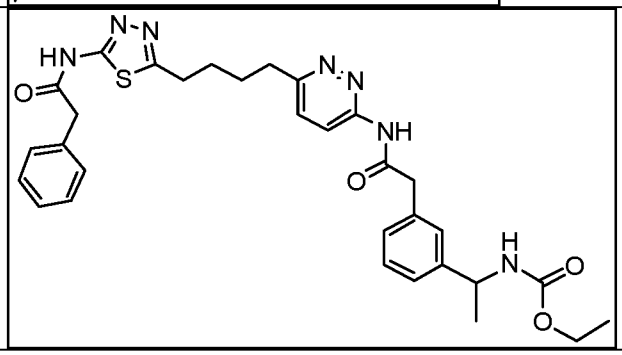
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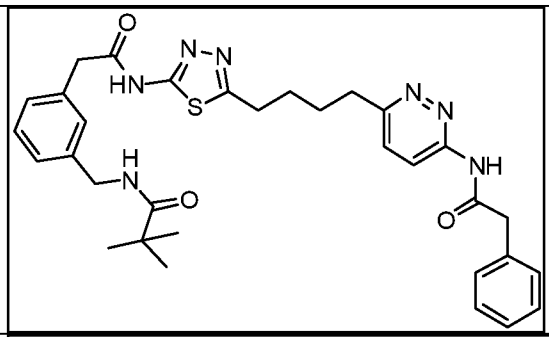
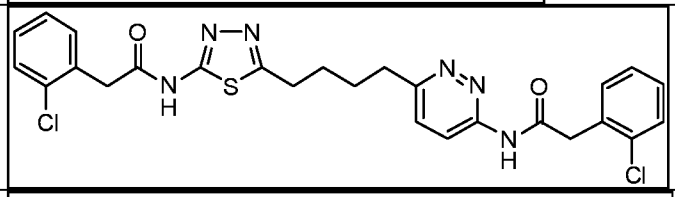
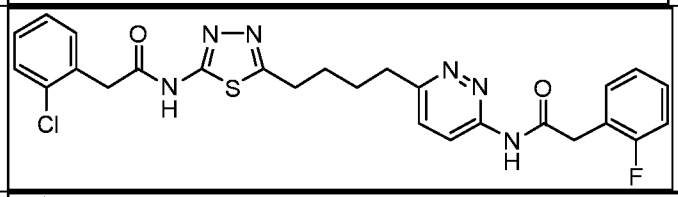
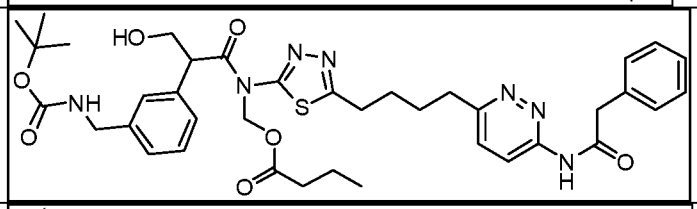
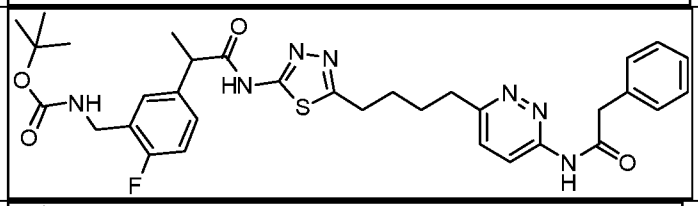
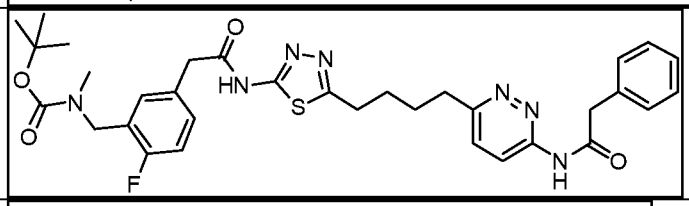
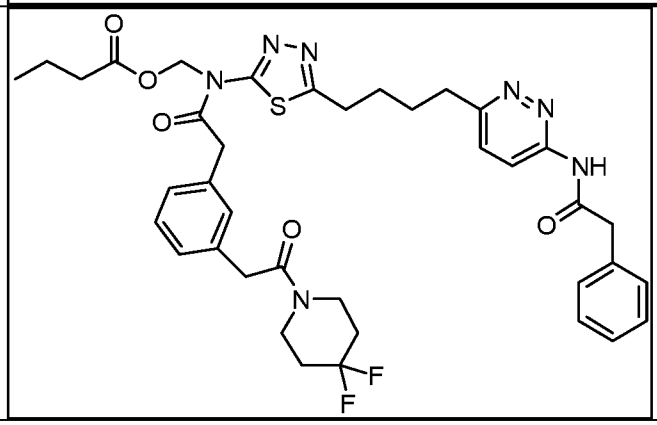
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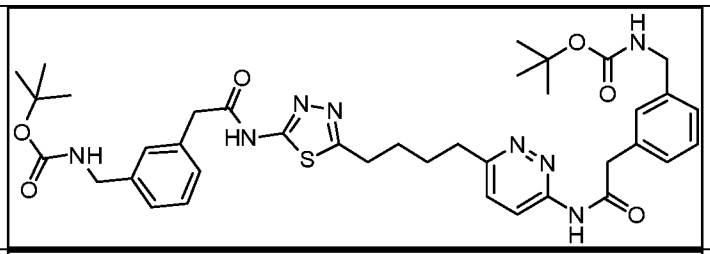
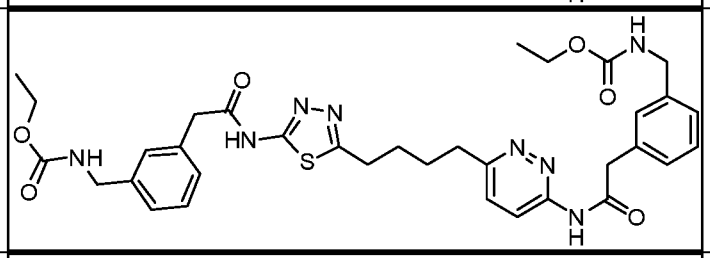
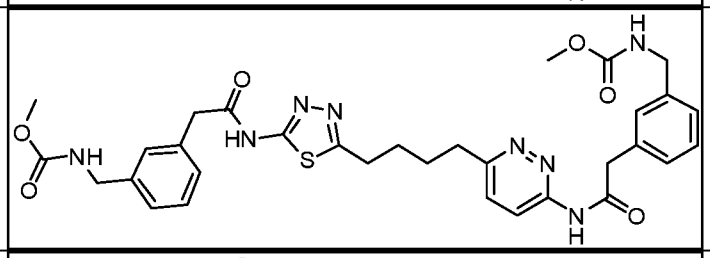
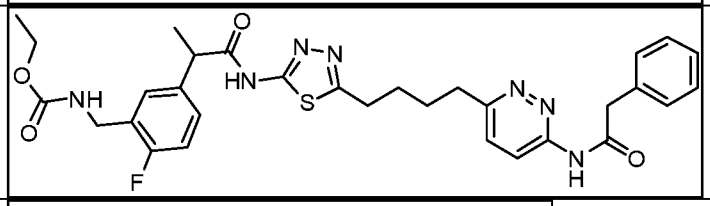
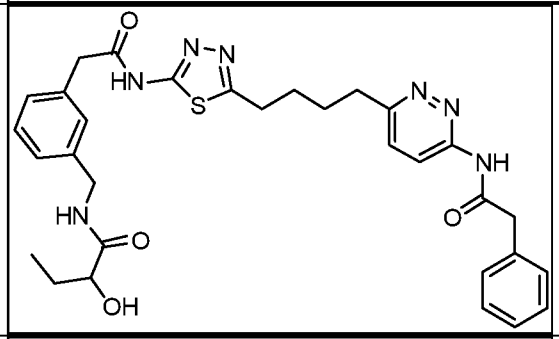
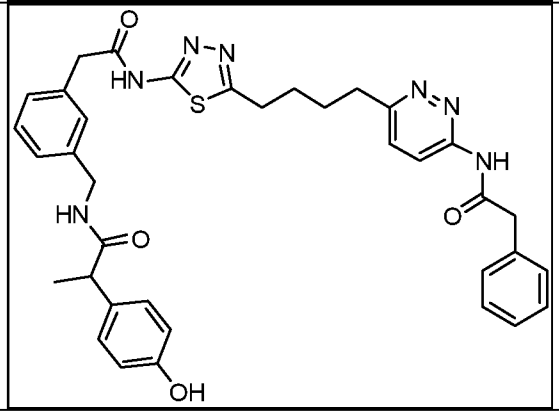
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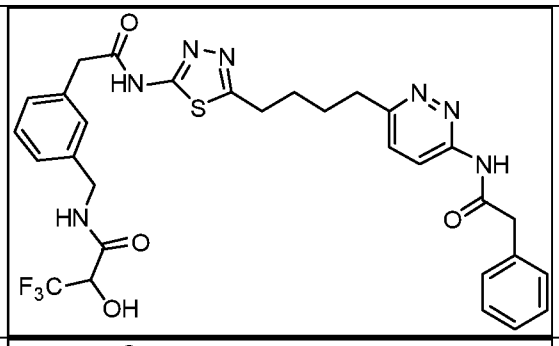
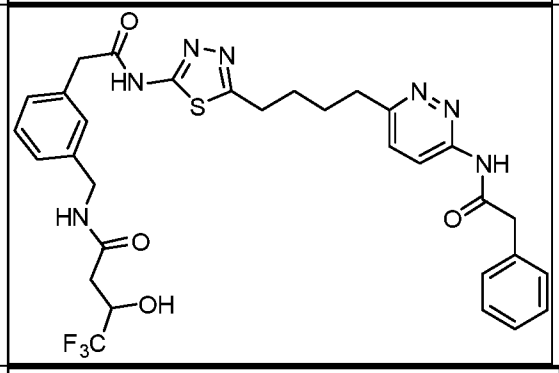
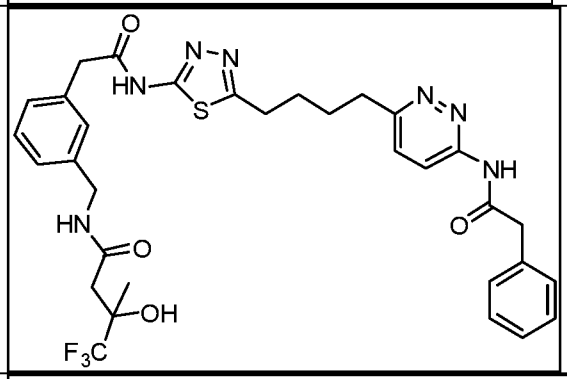
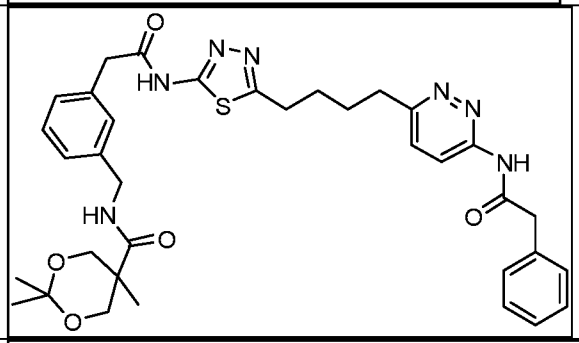
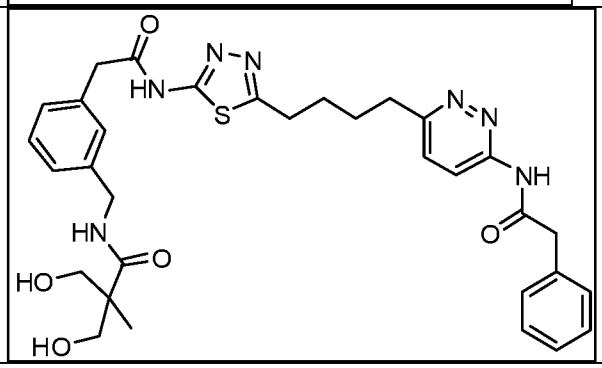
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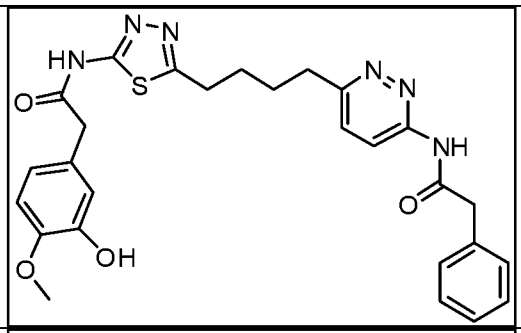
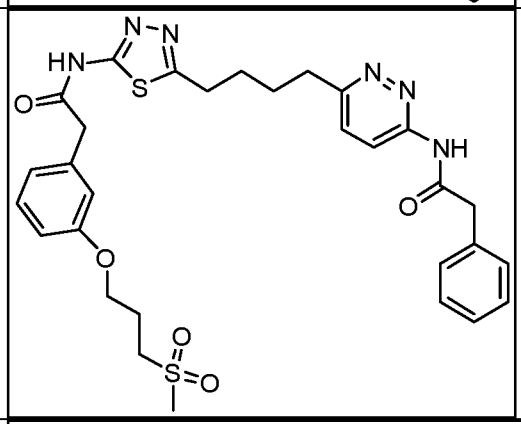
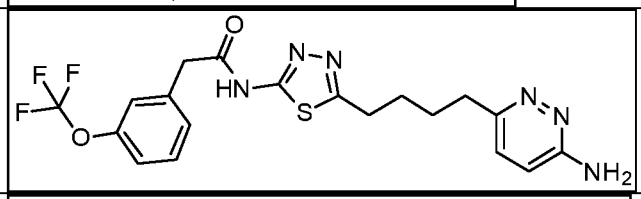
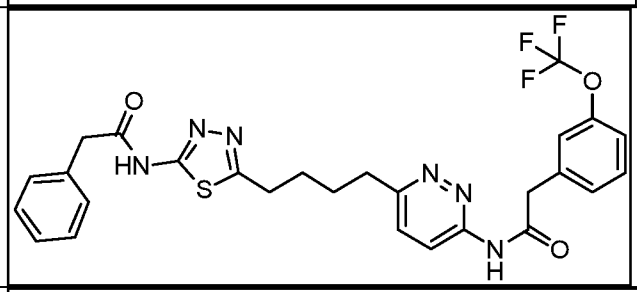
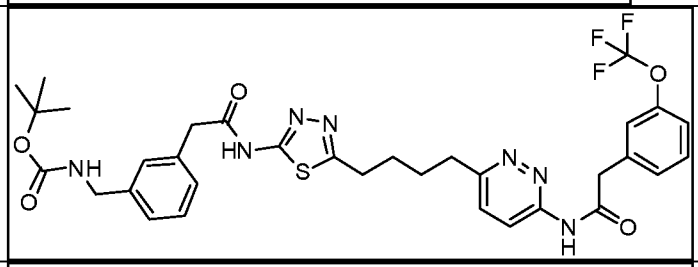
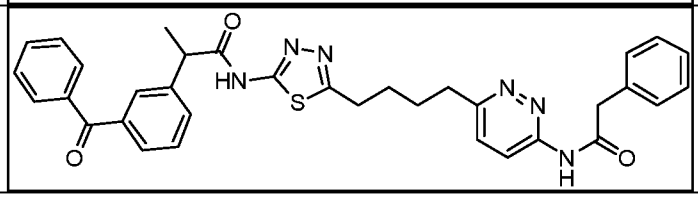
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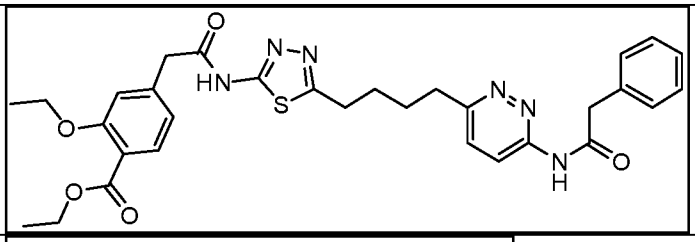
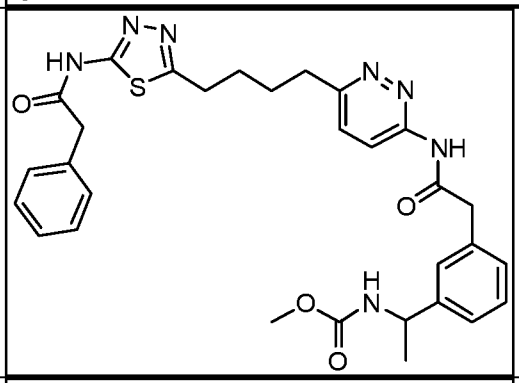
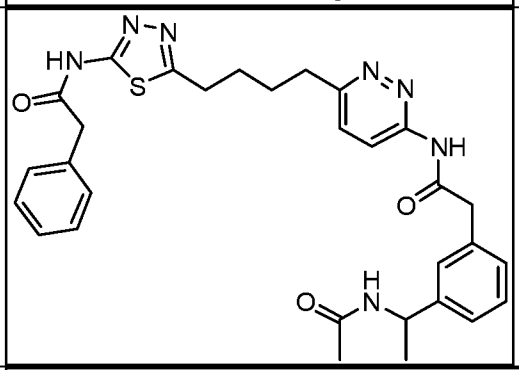
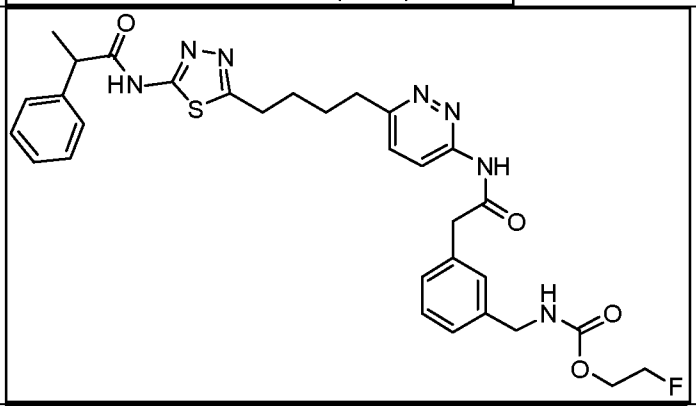
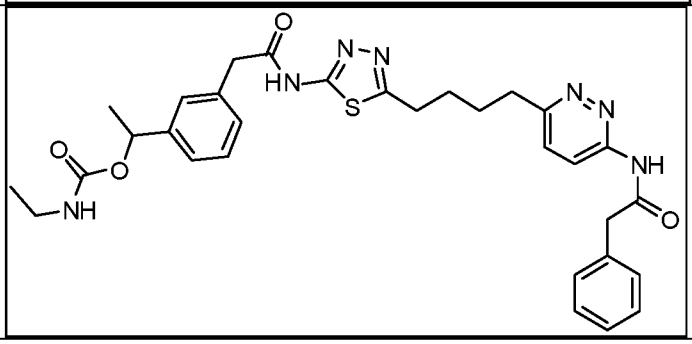
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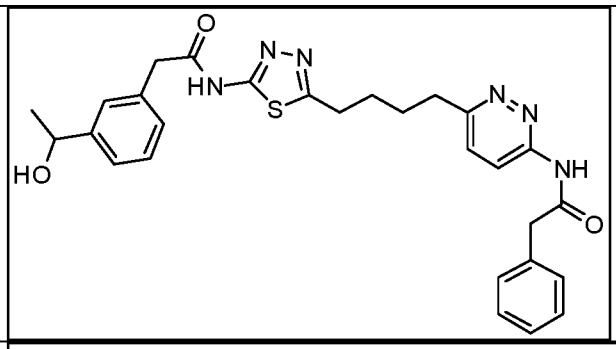
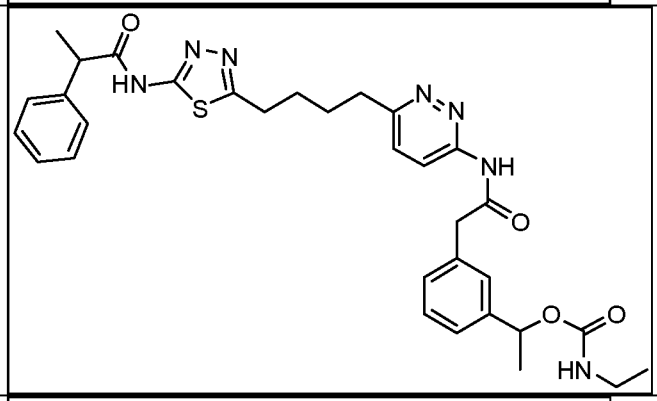
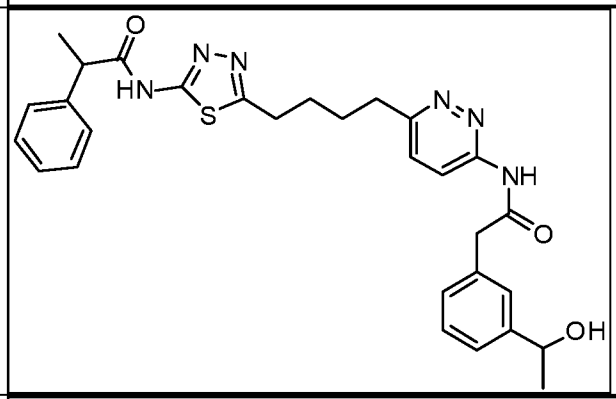
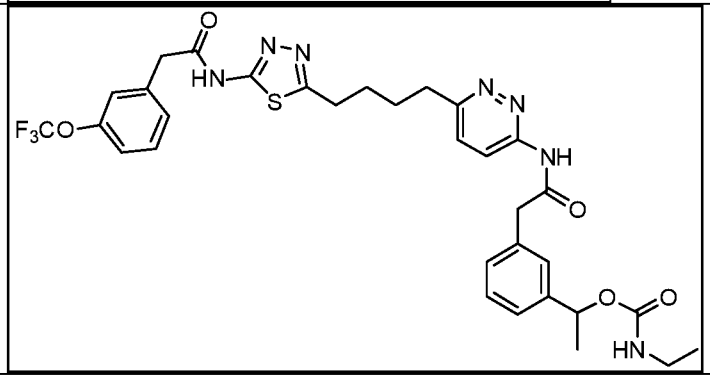
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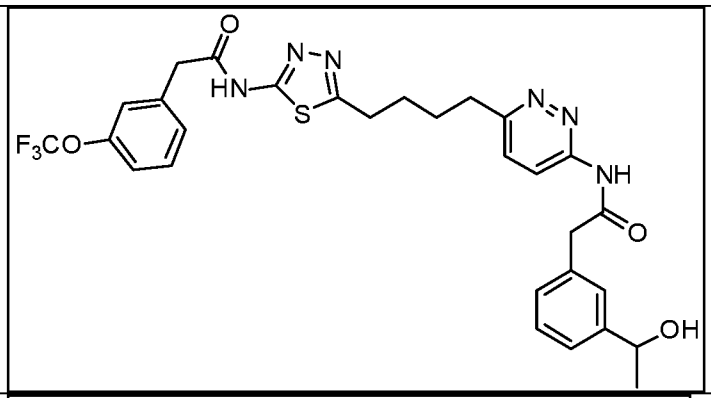
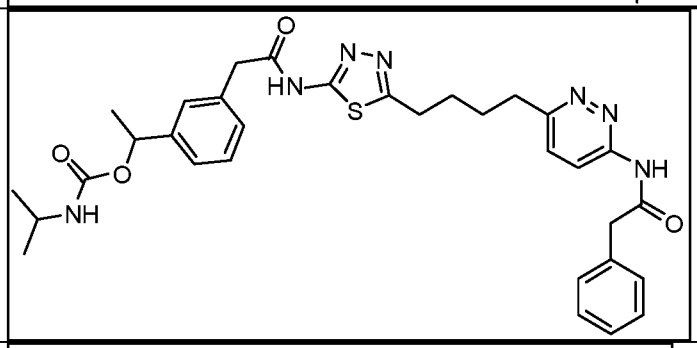
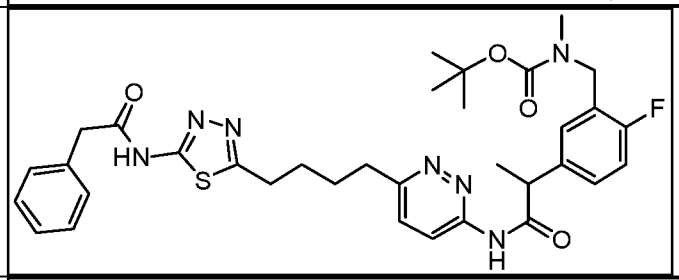
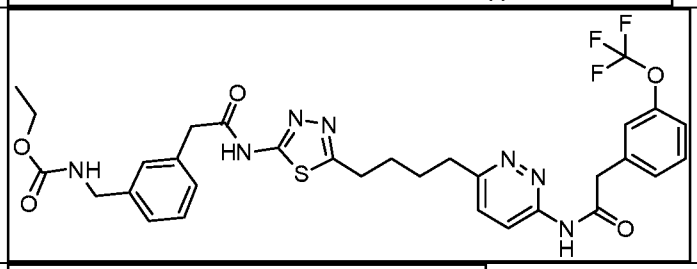
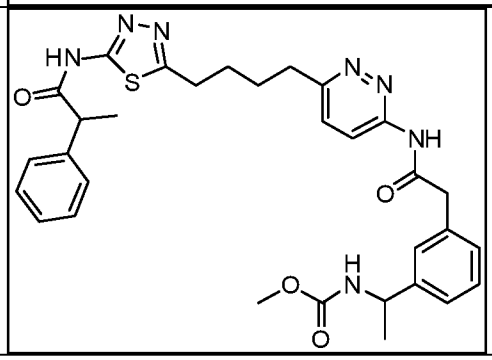
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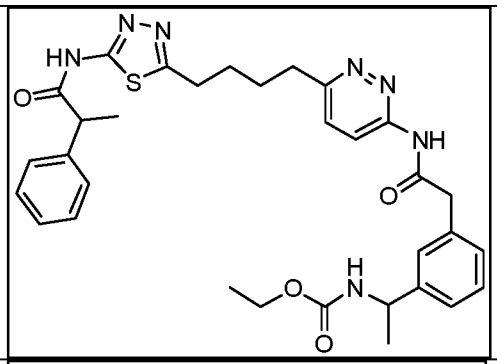
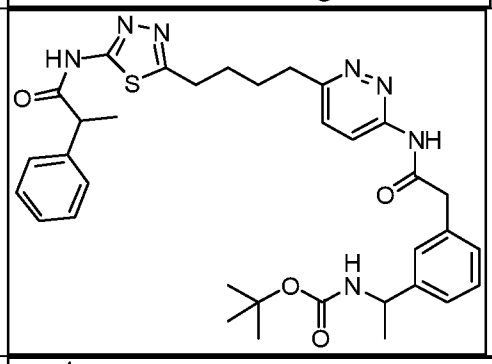
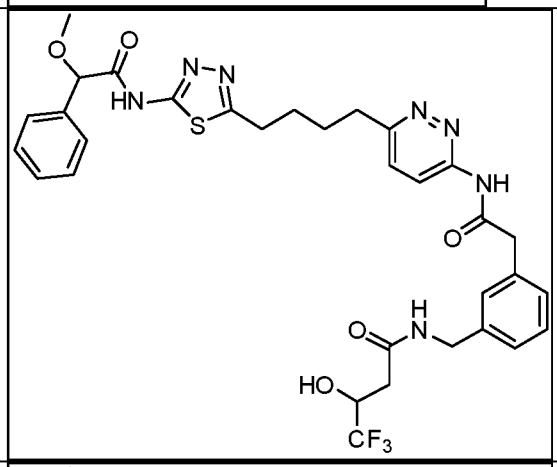
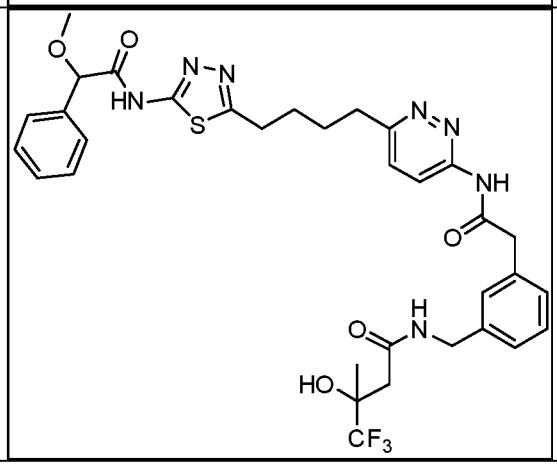
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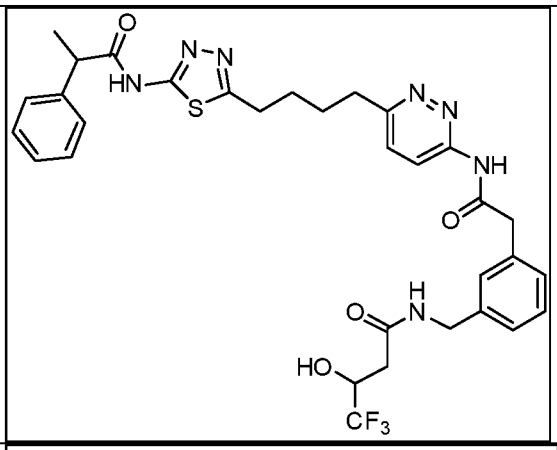
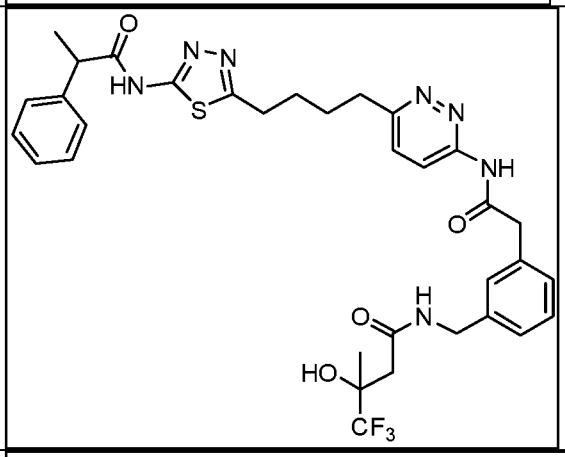
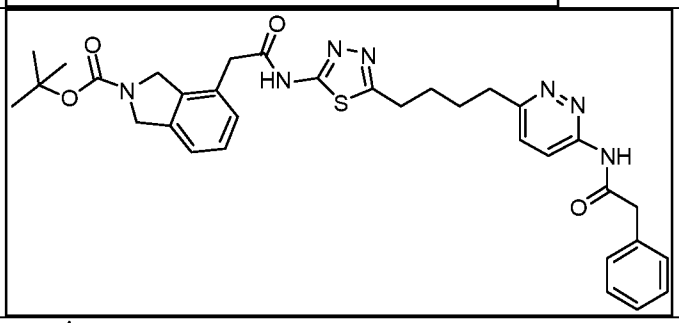
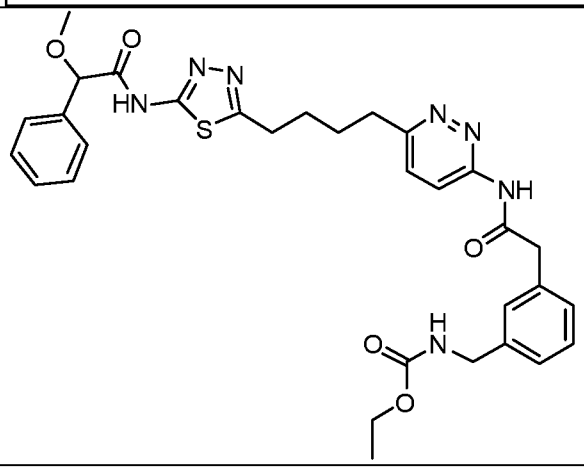
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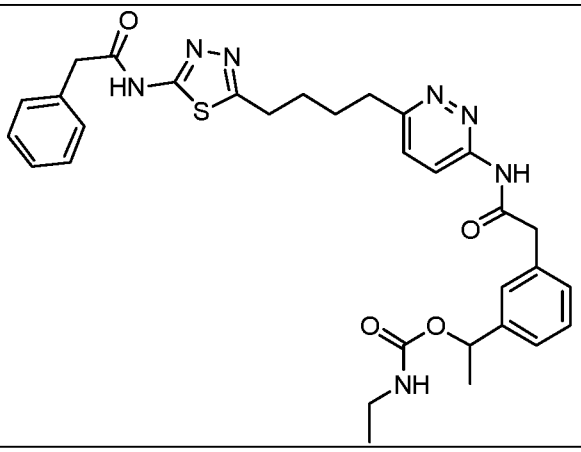
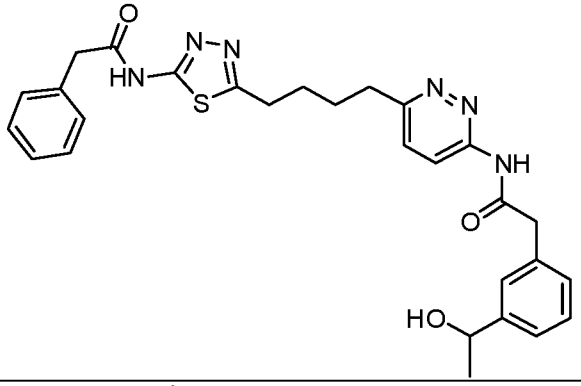
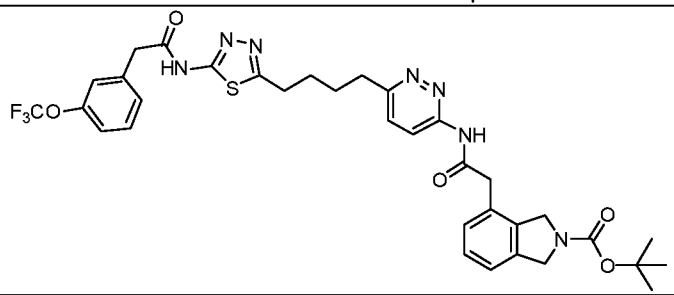
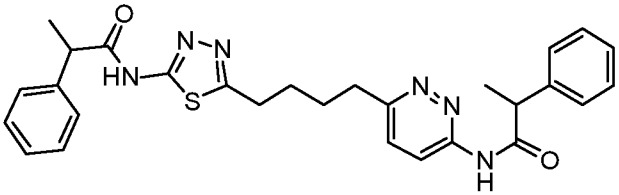
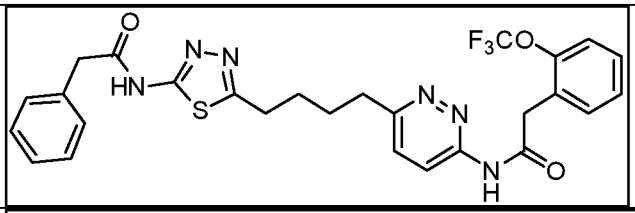
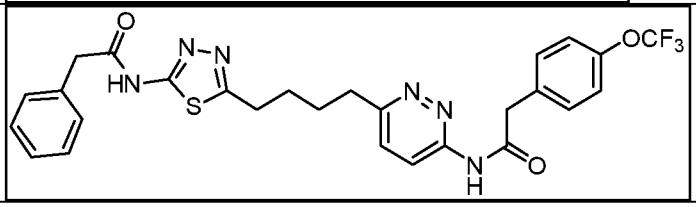
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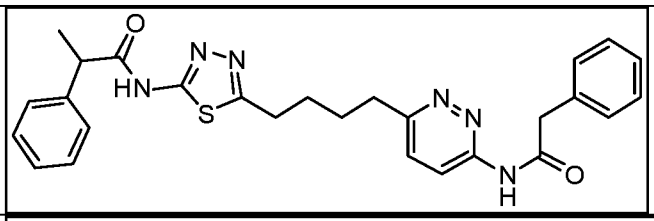
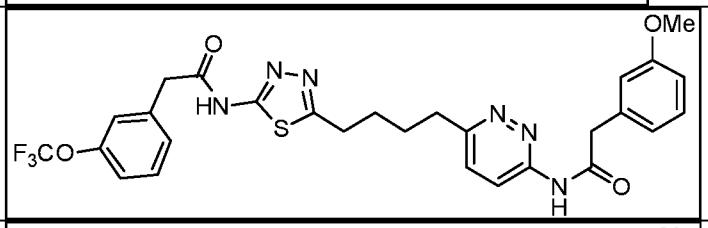
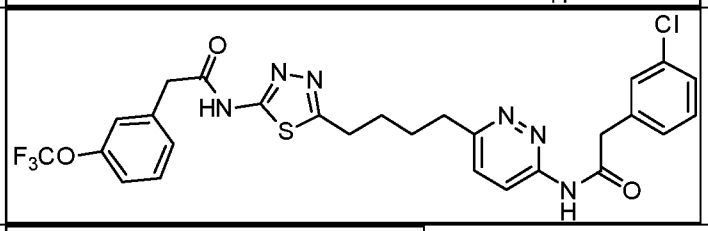
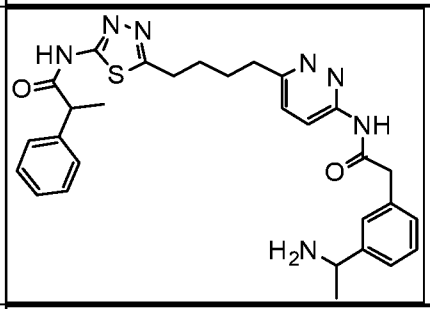
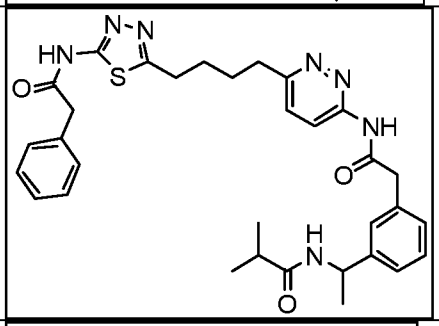
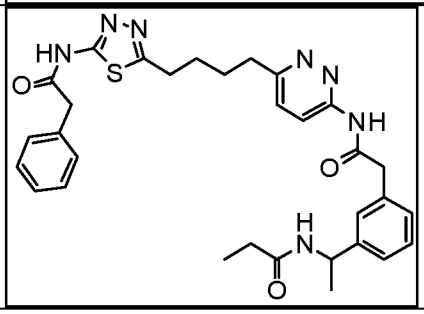
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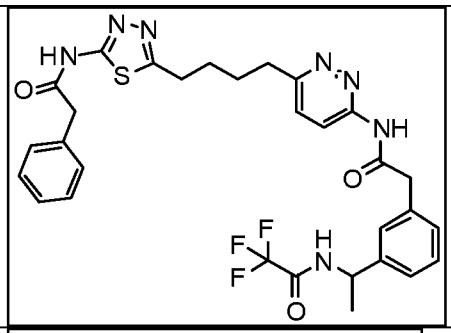
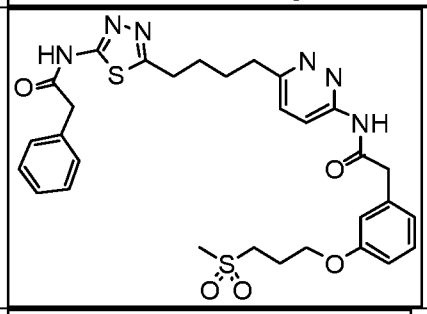
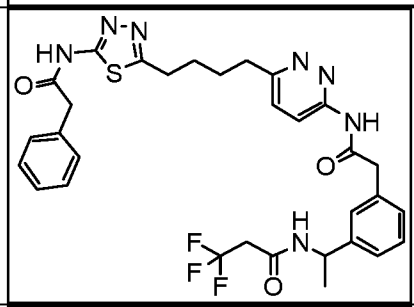
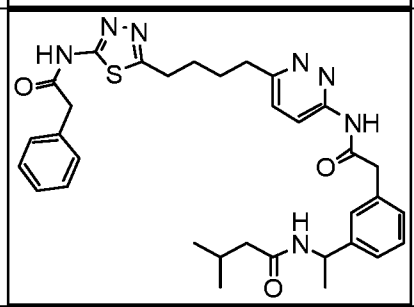
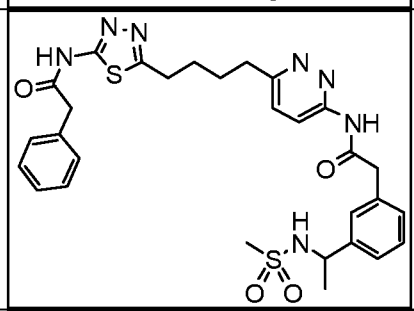
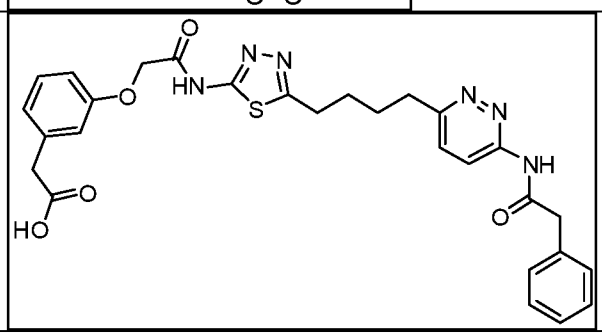
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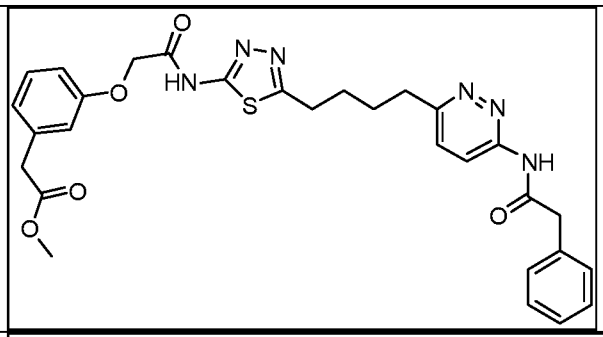
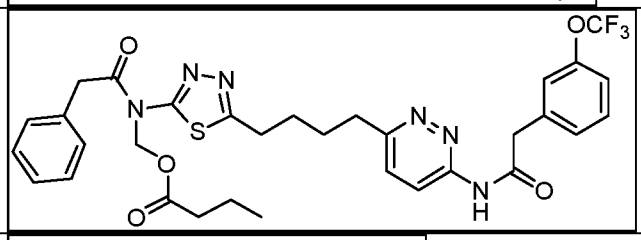
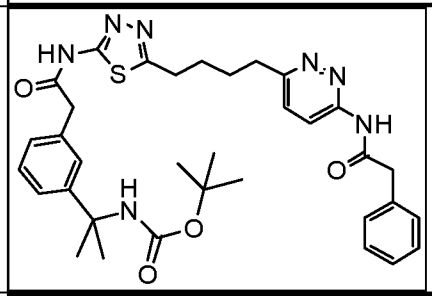
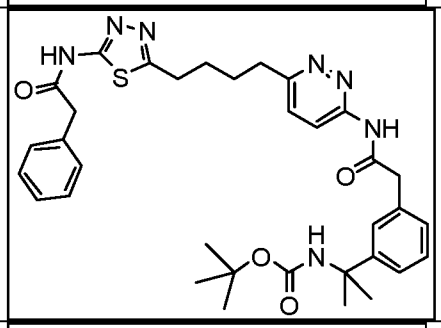
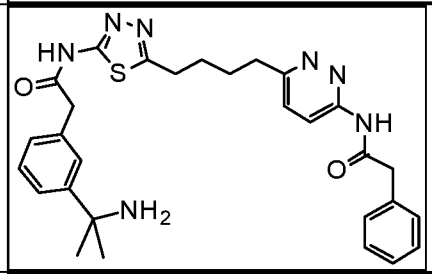
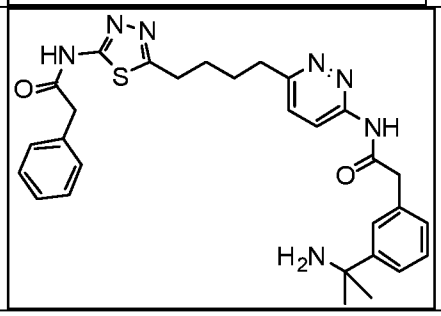
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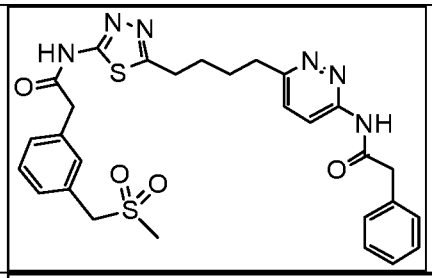
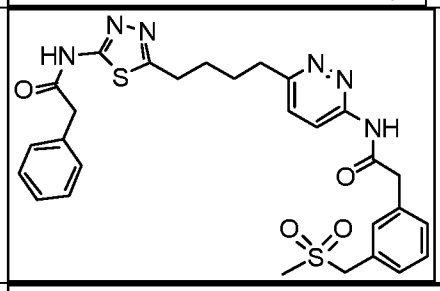
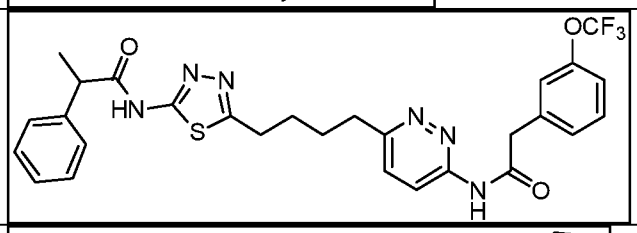
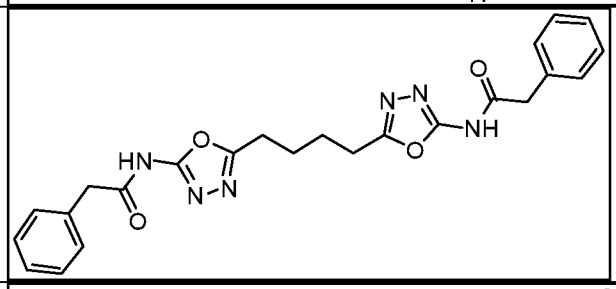
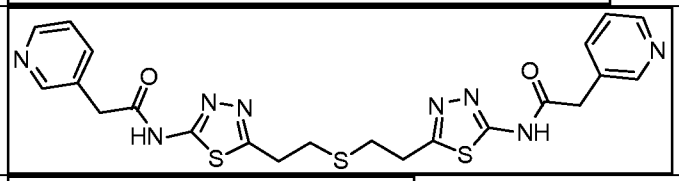
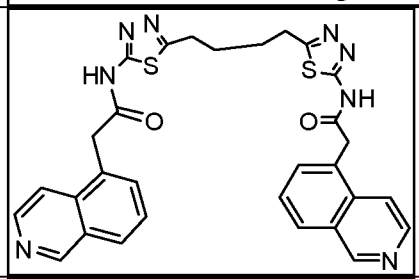
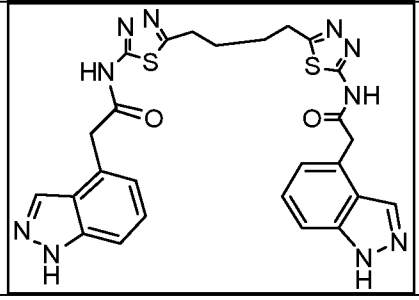
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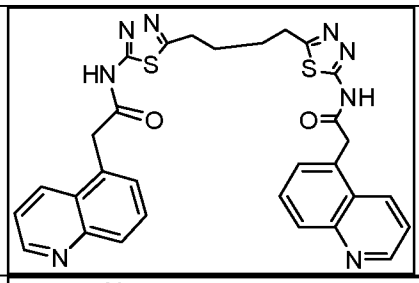
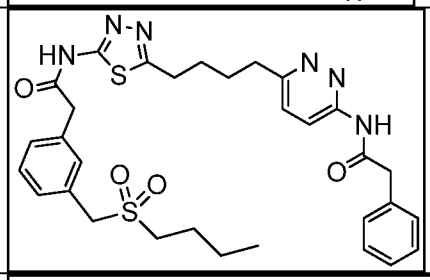
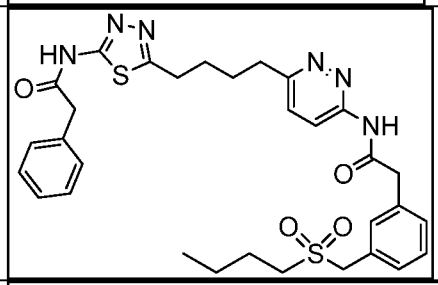
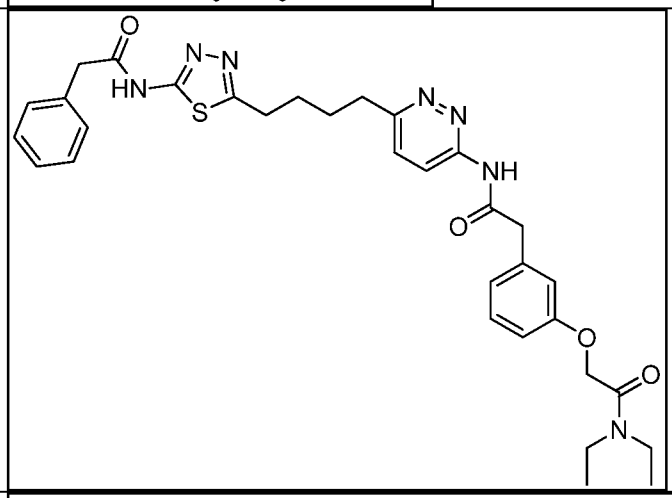
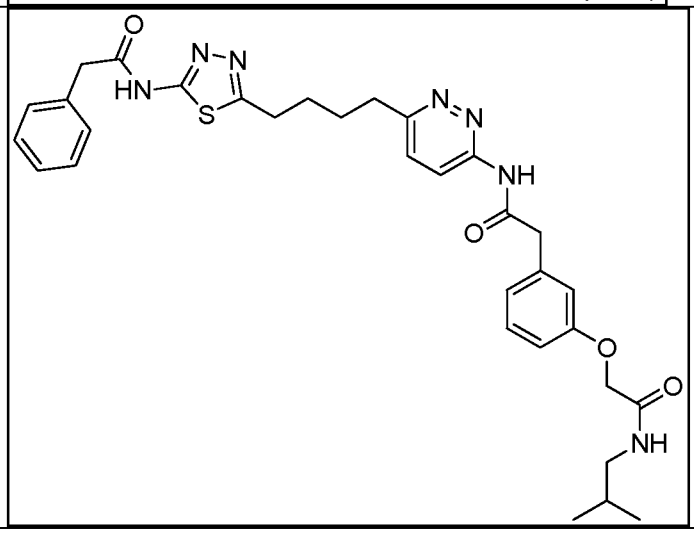
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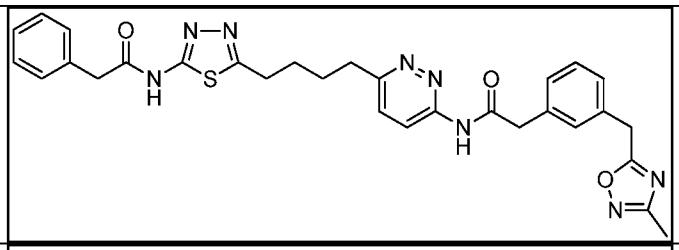
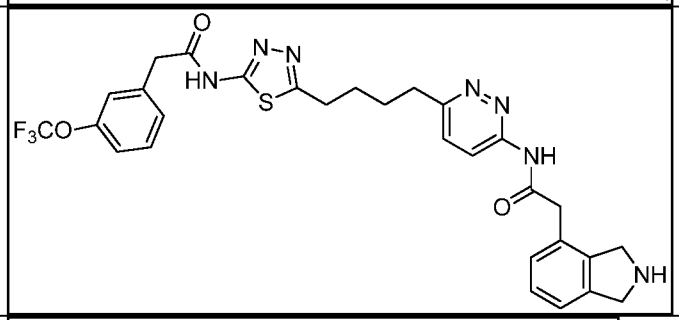
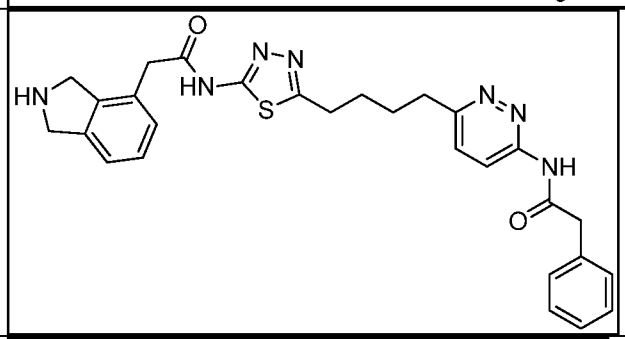
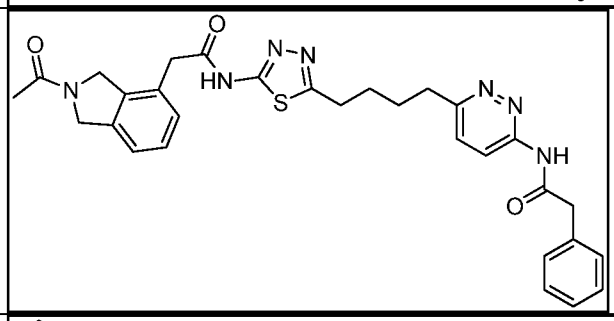
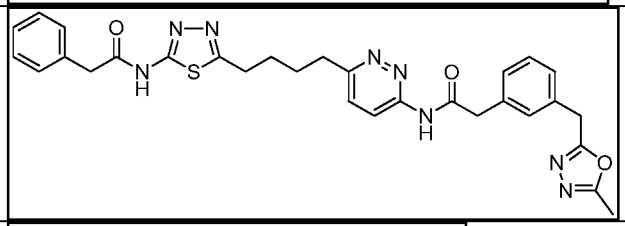
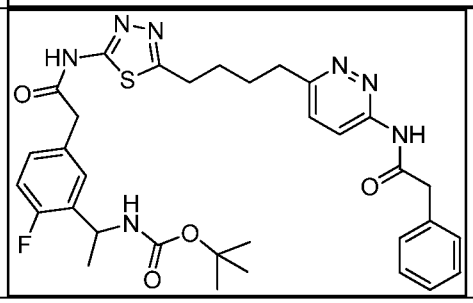
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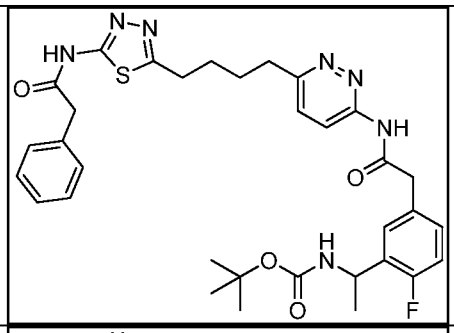
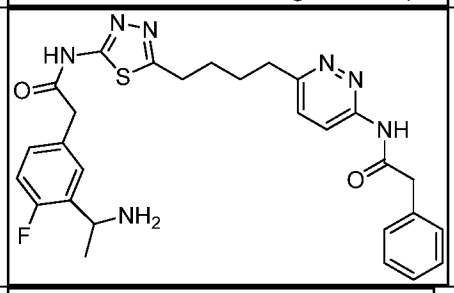
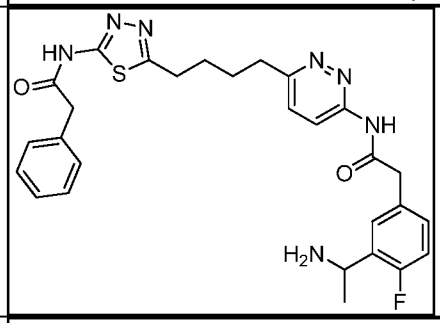
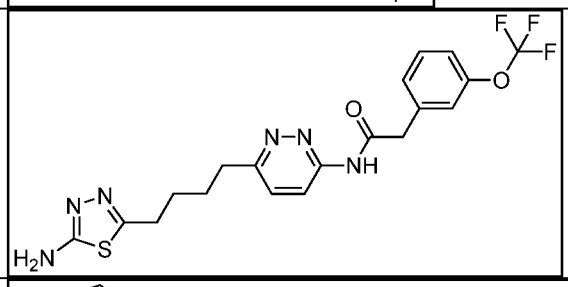
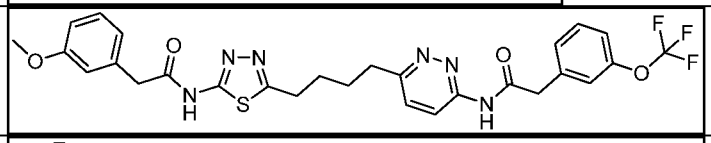
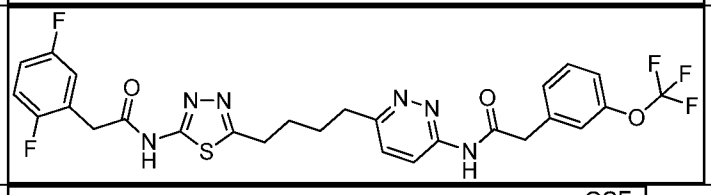
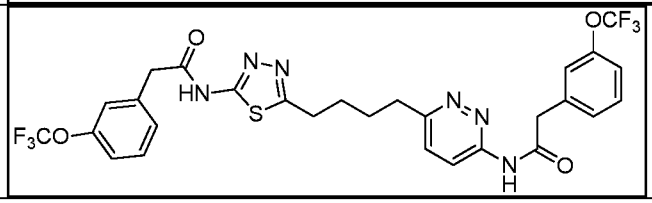
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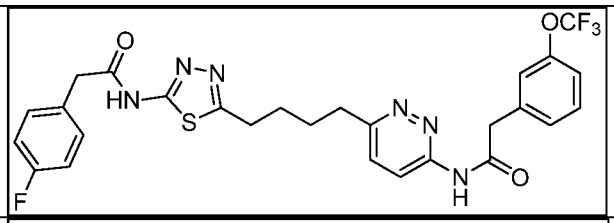
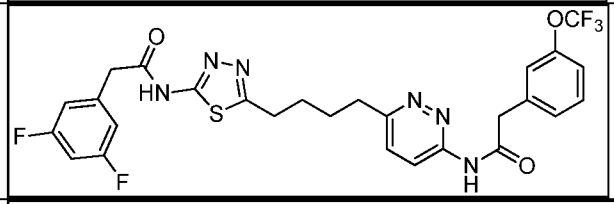
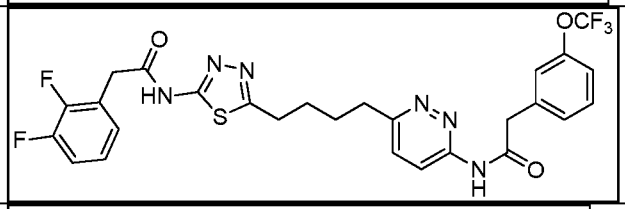
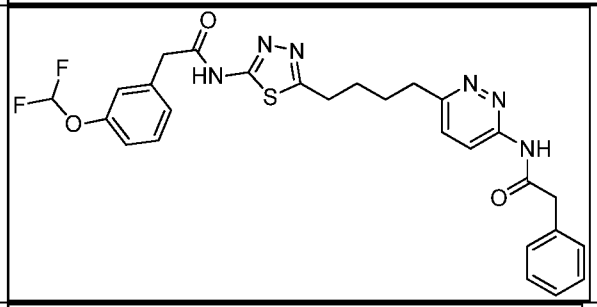
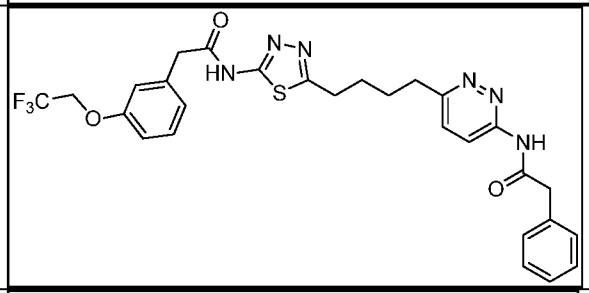
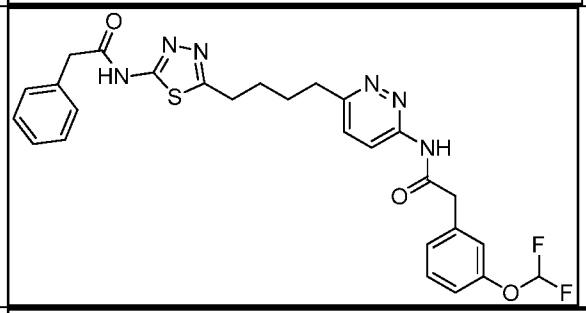
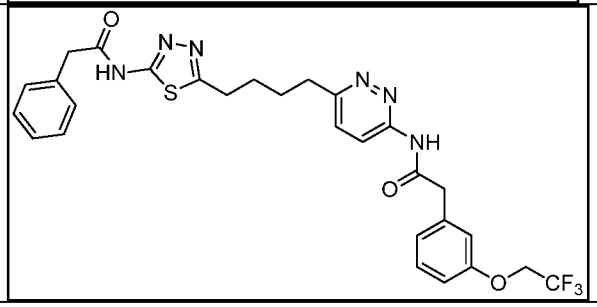
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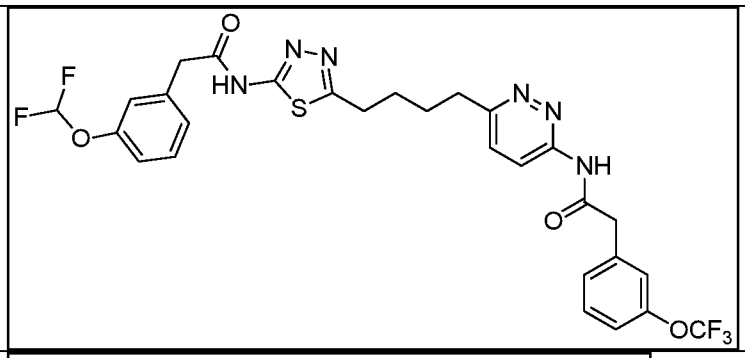
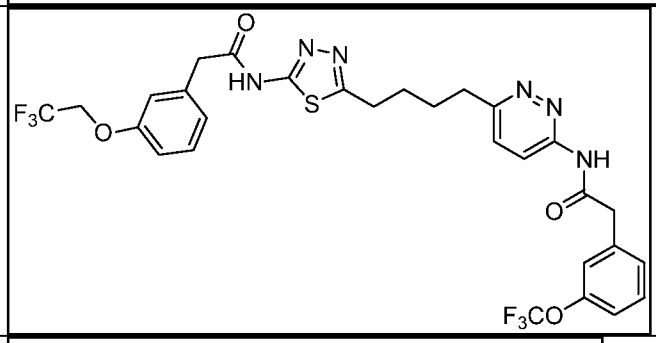
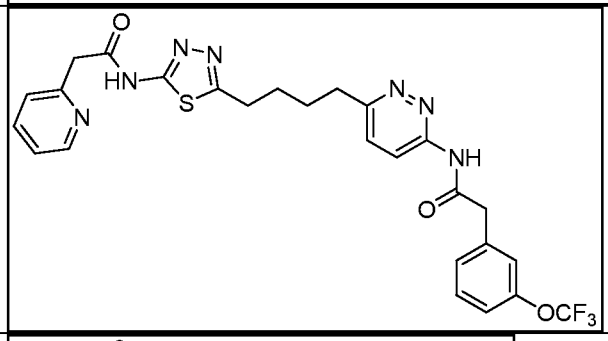
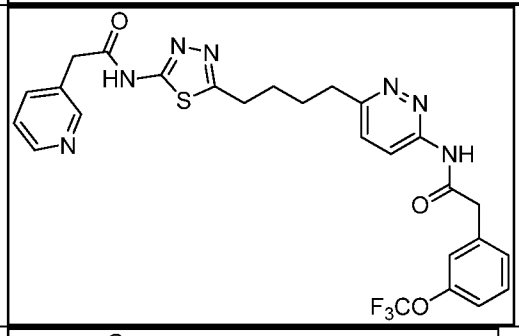
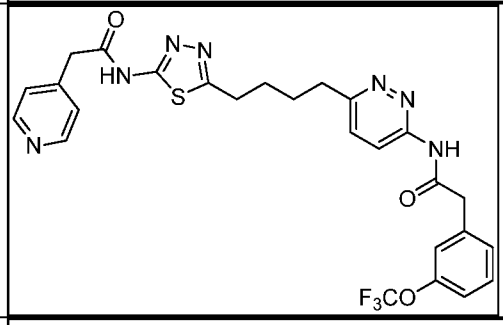
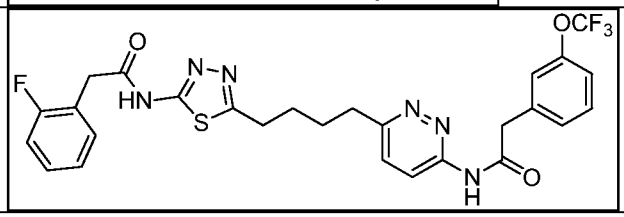
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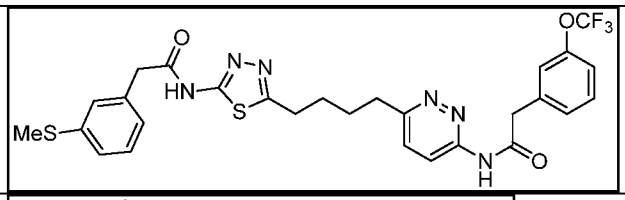
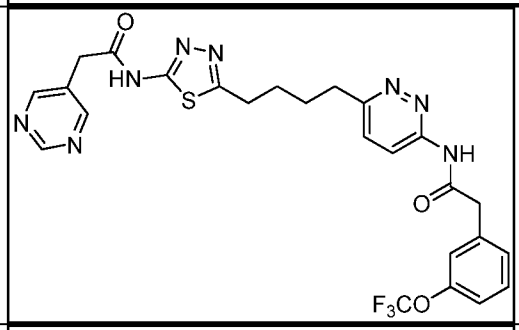
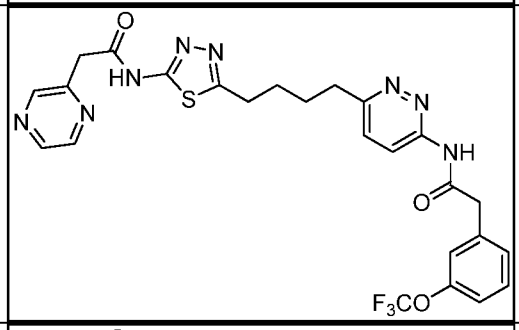
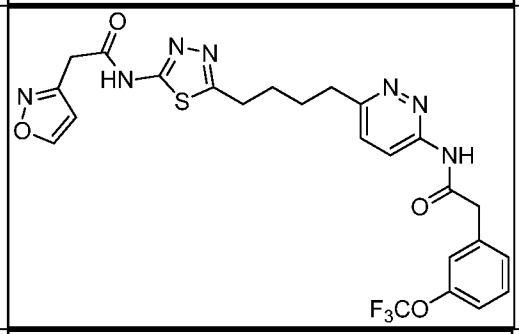
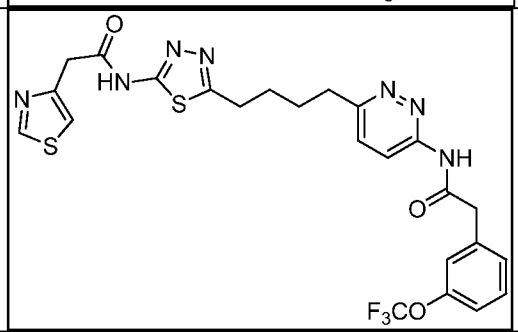
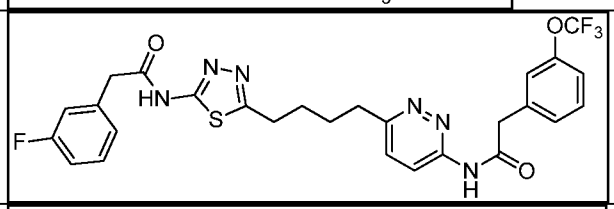
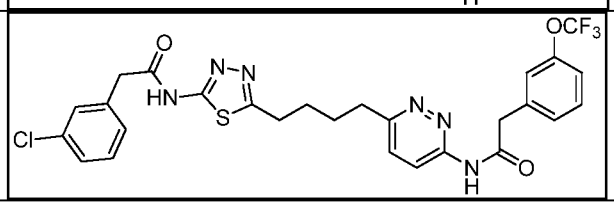
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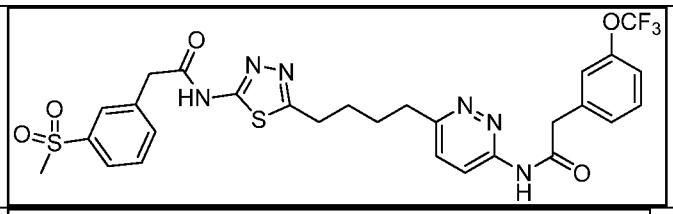
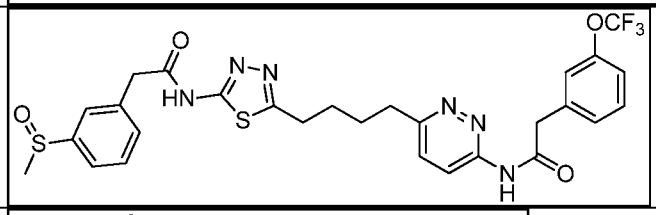
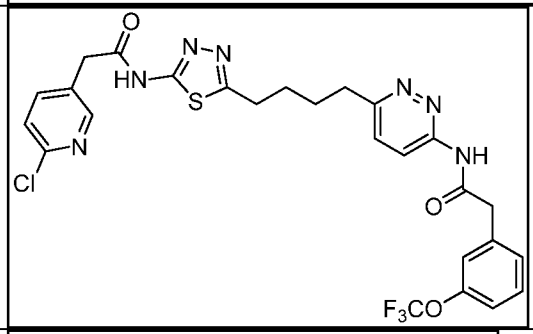
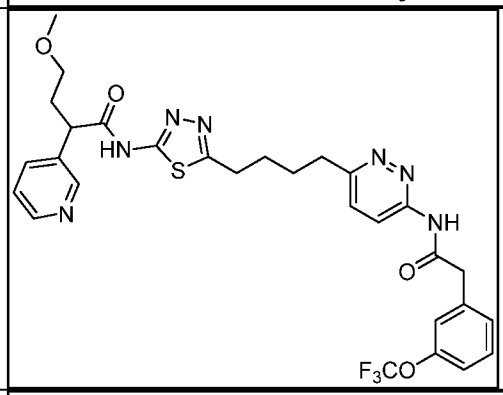
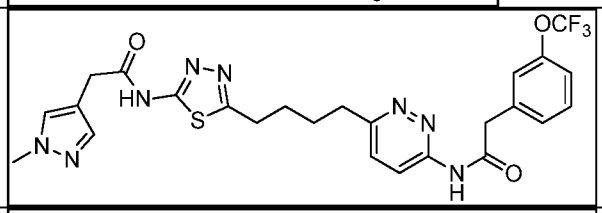
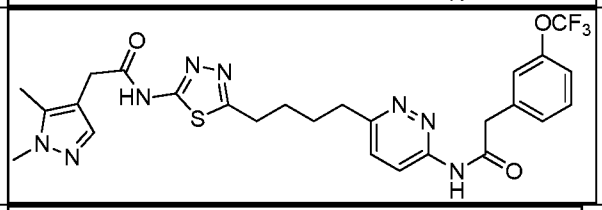
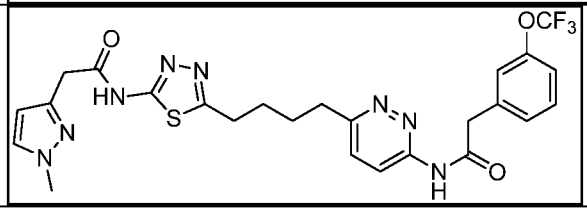
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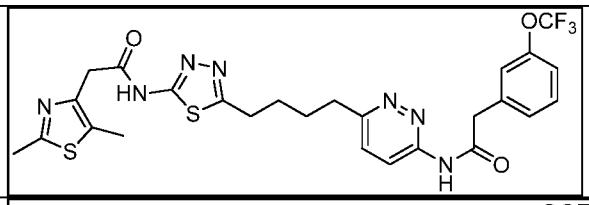
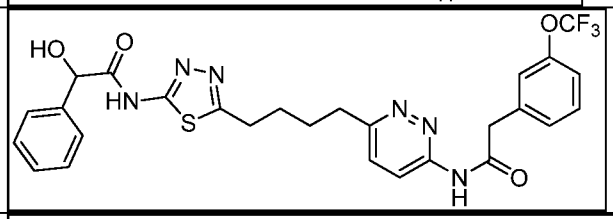
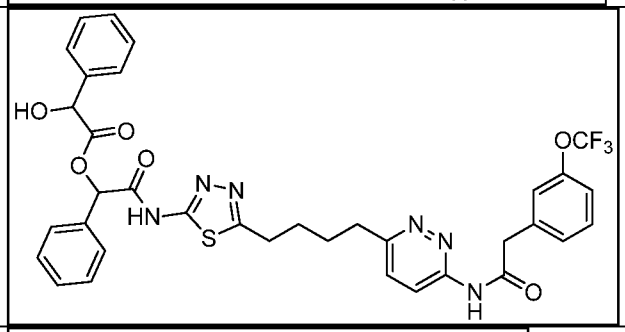
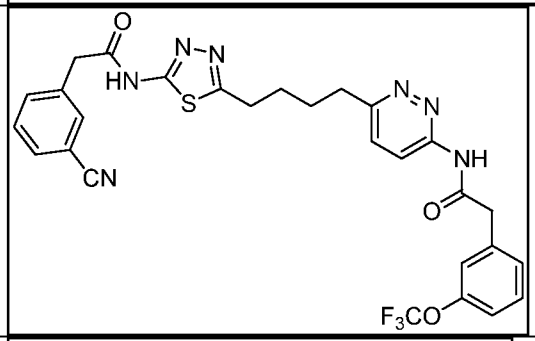
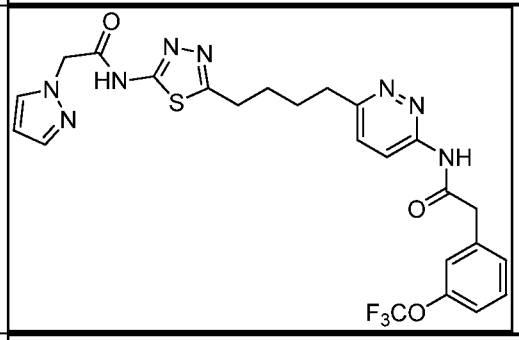
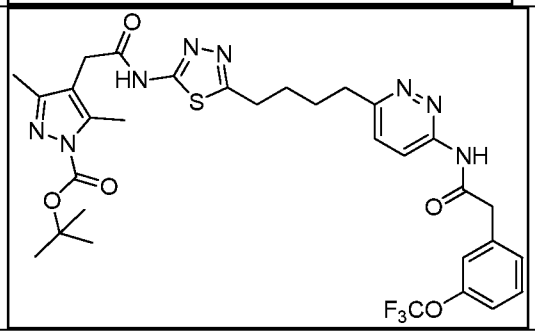
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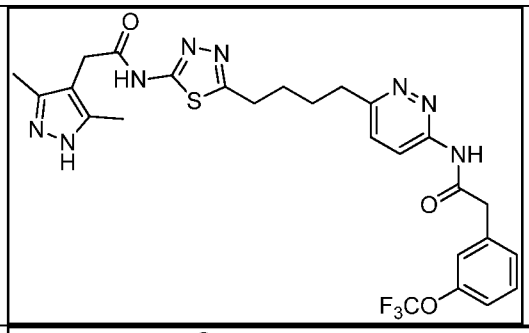
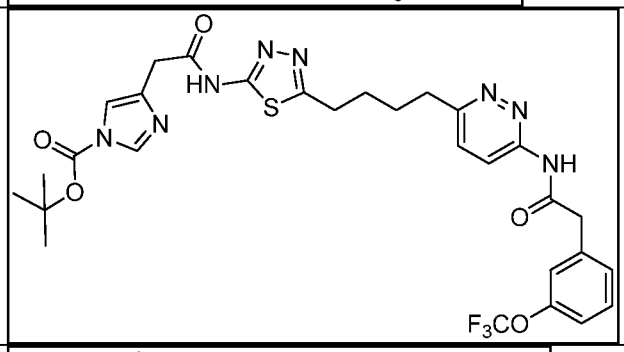
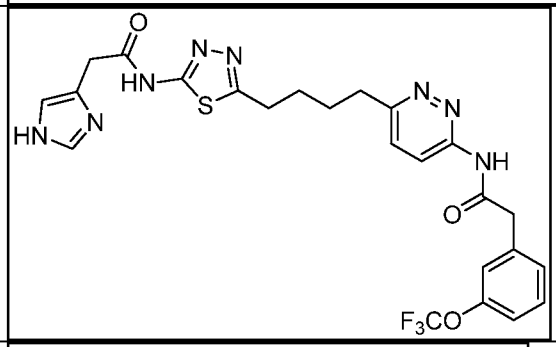
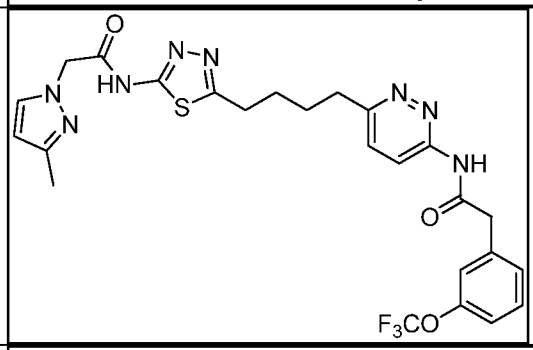
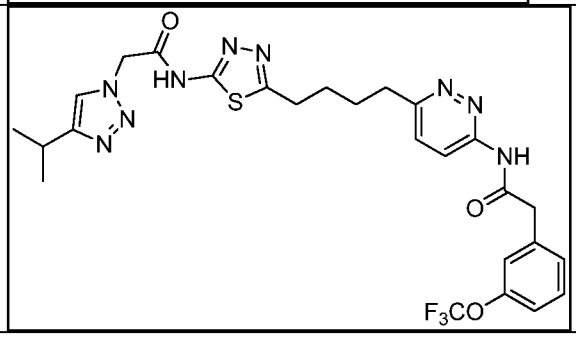
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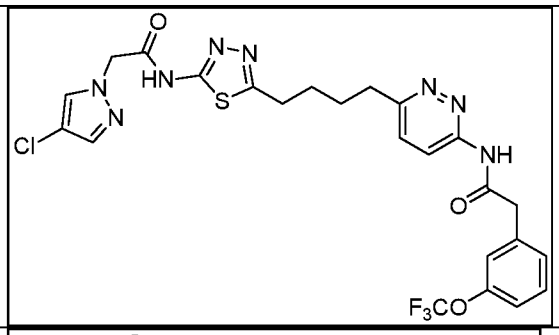
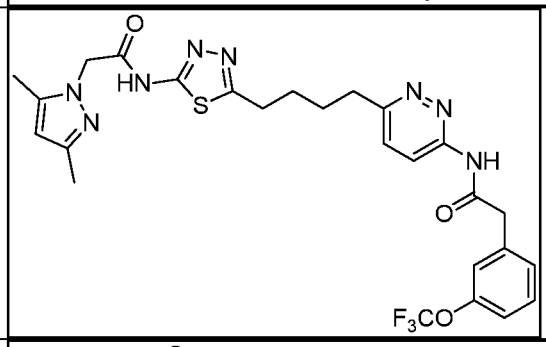
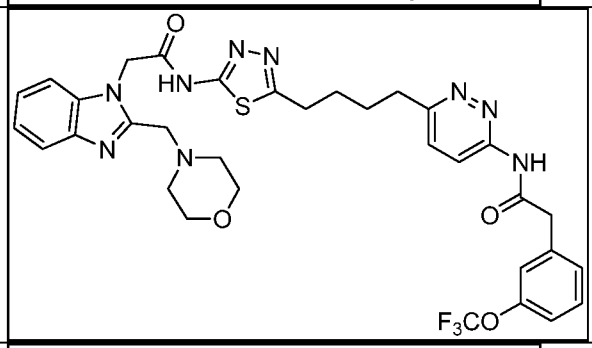
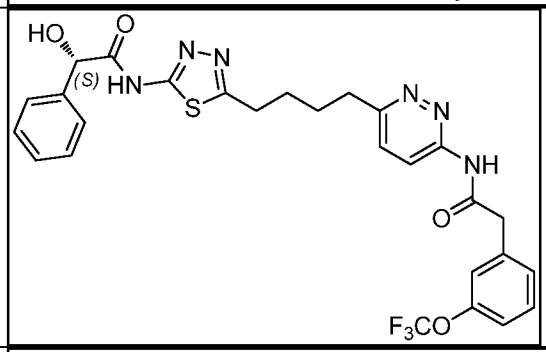
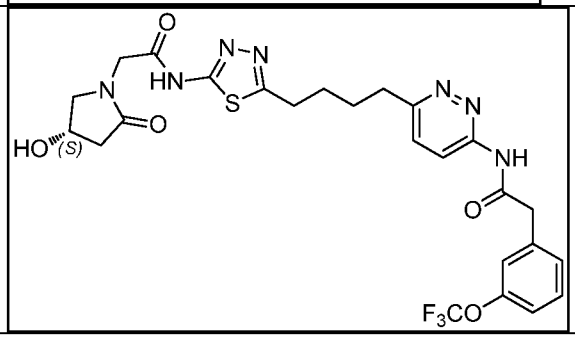
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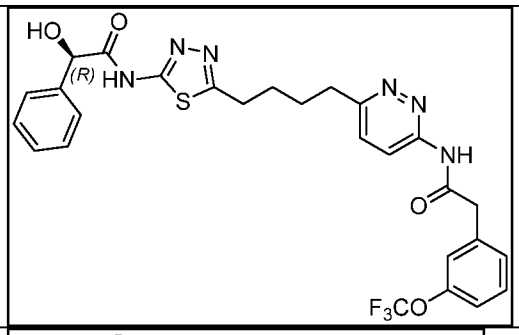
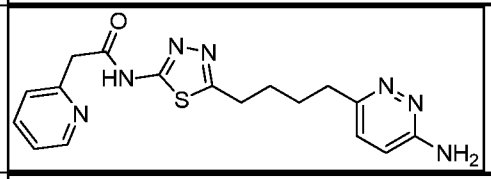
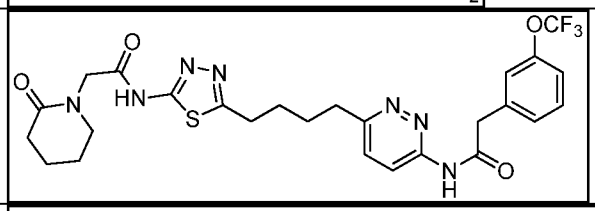
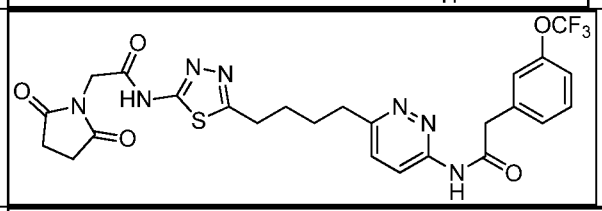
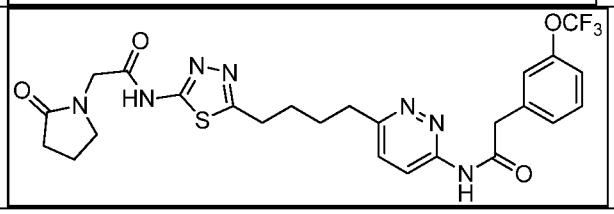
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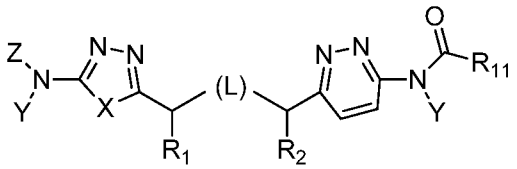
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The present invention further provides methods of treating cancer, a myeloproliferative disease, an immunological disease, a neurological disease, or a viral infection comprising orally administering a compound of formula II,



(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 , 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, $CH_2CH_2CH_2$ or CH_2 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;

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 $R_3(CO)$;

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

R_3 represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroaryloxyalkyl or $C(R_8)(R_9)(R_{10})$, $N(R_4)(R_5)$ or OR_6, wherein any free hydroxyl group may be acylated to form $C(O)R_7$;

R_4 and R_5 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 $C(O)R_7$;

R_6 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 $C(O)R_7$;

R_8, R_9 and R_{10} 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 R_8 and R_9 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 $C(O)R_7$, and wherein at least two of R_8, R_9 and R_{10} are not H;

R_{11} represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, or R_{11} represents $C(R_{12})(R_{13})(R_{14})$, $N(R_4)(R_{14})$ or OR_{14}, wherein any free hydroxyl group may be acylated to form $C(O)R_7$;

R_{12} and R_{13} each independently respresent 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; and

R_{14} represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl;

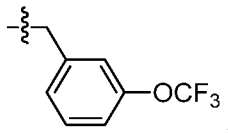
preferably wherein the compound is administered with a meal.

In some embodiments, R_{11} represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein the aryl or heteroaryl ring is substituted with either $-OCHF_2$ or $-OCF_3$ and is optionally further substituted.

In some embodiments, R_{14} represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein the aryl or heteroaryl ring is substituted with either $-OCHF_2$ or $-OCF_3$ 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, 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.*, $C(O)CF_3$)), carbonylalkyl (such as carboxyalkyl, alkoxycarbonylalkyl, formylalkyl, or acylalkyl, including perfluoroacylalkyl (*e.g.*, -alkyl$C(O)CF_3$)), 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, R_{11} represents arylalkyl, such as benzyl, wherein the aryl group is substituted with $-OCF_3$, such as meta-substituted with $-OCF_3$. In certain such embodiments, the aryl ring is not further substituted. In certain embodiments, R_{11} represents trifluoromethoxybenzyl, such as .

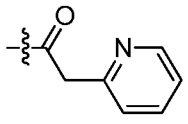
In certain embodiments, L represents CH_2SCH_2, CH_2CH_2, $CH_2CH_2CH_2$, CH_2, CH_2S, SCH_2, or CH_2NHCH_2, wherein any hydrogen atom of a CH_2 unit may be replaced by alkyl or alkoxy, and any hydrogen atom of a CH_2 unit of CH_2CH_2, $CH_2CH_2CH_2$ or CH_2 may be replaced by hydroxyl. In certain embodiments, 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.

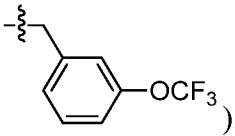
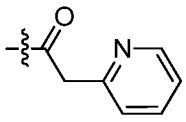
In certain embodiments, X represents S or CH=CH. In certain embodiments, X represents S.

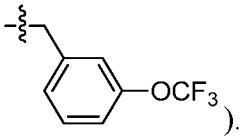
In certain embodiments, Z represents $R_3(CO)$. In certain embodiments wherein Z is $R_3(CO)$, R_3 and R_{11} are not identical (*e.g.*, the compound of formula II is not symmetrical).

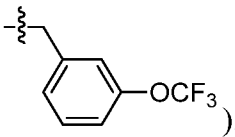
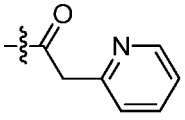
In certain embodiments, R_1 and R_2 each represent H.

In certain embodiments, Z represents $R_3(CO)$ and R_3 represents arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl. In certain embodiments, Z represents $R_3(CO)$ and R_3 represents heteroarylalkyl, such as pyridylalkyl (*e.g.*, pyridylmethyl). In certain such embodiments, Z represents . In certain embodiments, Z represents $R_3(CO)$ and R_3 represents $C(R_8)(R_9)(R_{10})$, wherein R_8 represents aryl, arylalkyl, heteroaryl or heteroaralkyl, such as aryl, arylalkyl or heteroaryl, R_9 represents H, and R_{10}

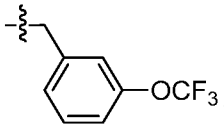
represents hydroxy, hydroxyalkyl, alkoxy or alkoxyalkyl, such as hydroxy, hydroxyalkyl or alkoxy.

In certain embodiments, L represents CH_2SCH_2, CH_2CH_2, CH_2S or SCH_2, such as CH_2CH_2, Y represents H, X represents S, Z represents $R_3(CO)$, 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 $R_3(CO)$ 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 $R_3(CO)$, R_1 and R_2 each represent H, and each R_3 represents $C(R_8)(R_9)(R_{10})$, 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.*, ).

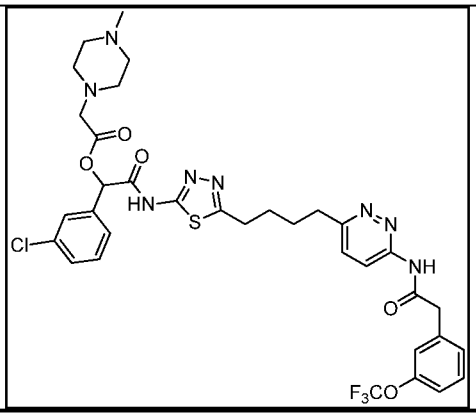
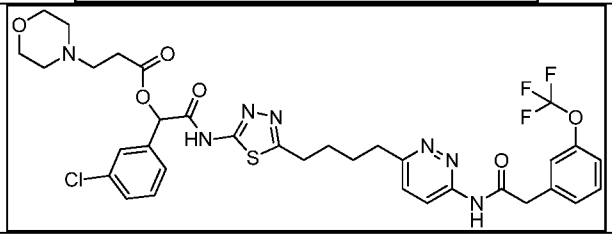
In certain embodiments, L represents CH_2CH_2, Y represents H, X represents S or CH=CH, such as S, Z represents $R_3(CO)$, R_1 and R_2 each represent H, R_3 represents substituted or unsubstituted arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl, such as heteroarylalkyl (*e.g.*, pyridylalkyl),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

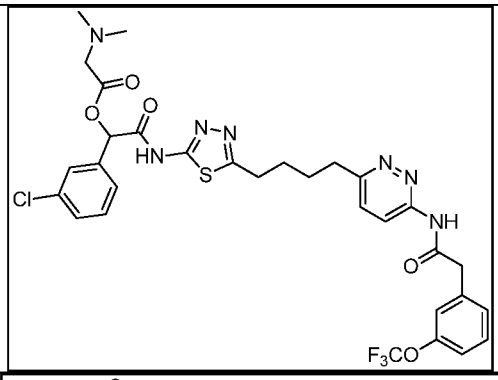
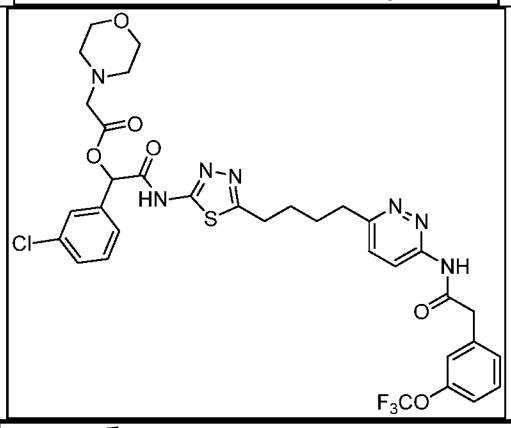
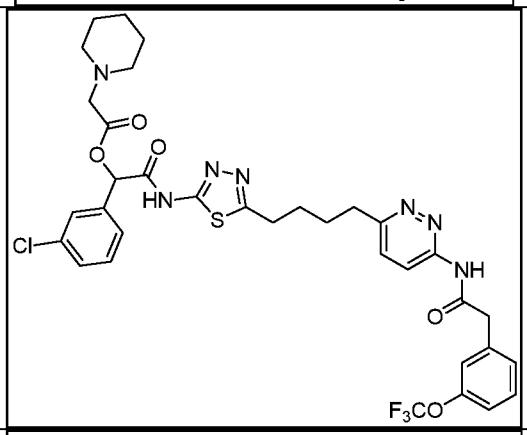
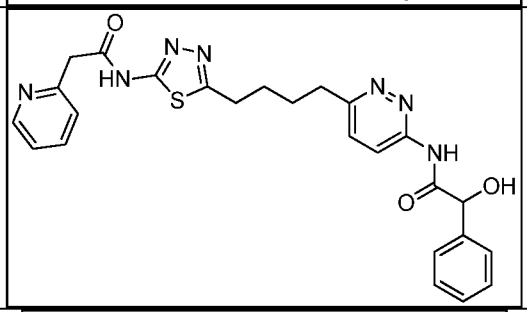
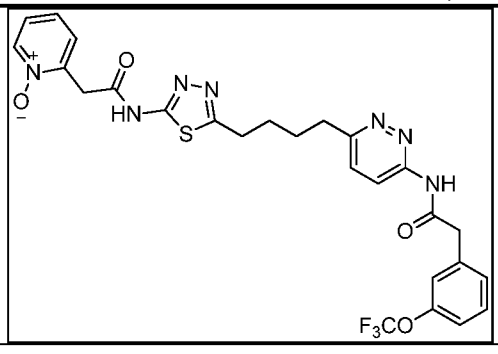
In certain embodiments, L represents CH_2CH_2, Y represents H, X represents S, Z represents $R_3(CO)$, R_1 and R_2 each represent H, h R_3 represents $C(R_8)(R_9)(R_{10})$, wherein R_8 represents aryl, arylalkyl or heteroaryl, R_9 represents H, and R_{10} represents hydroxy, hydroxyalkyl or alkoxy, and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

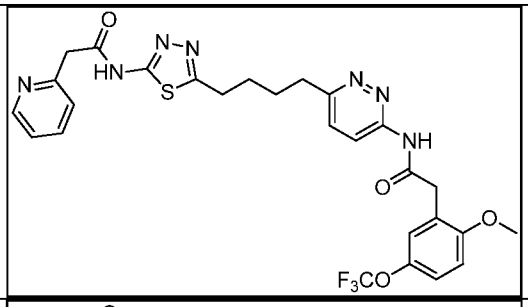
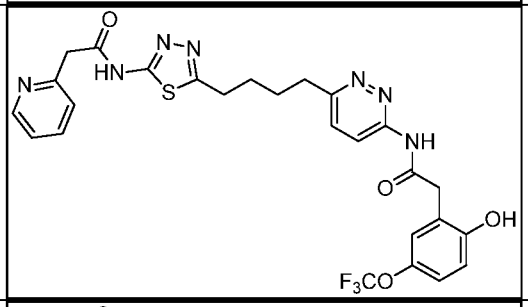
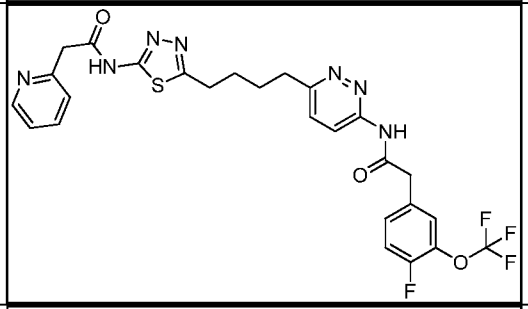
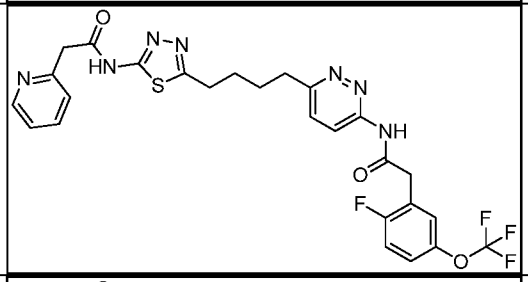
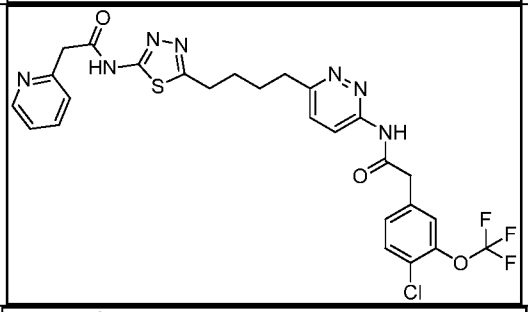
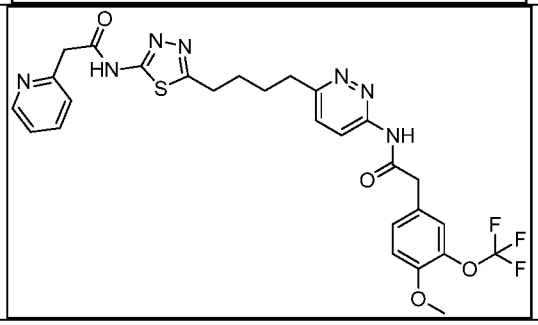

). In certain such embodiments, R_8 represents aryl and R_{10} represents hydroxyalkyl.

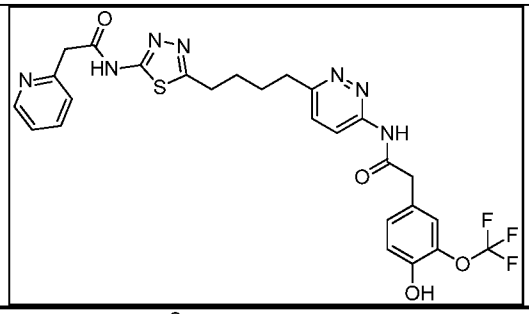
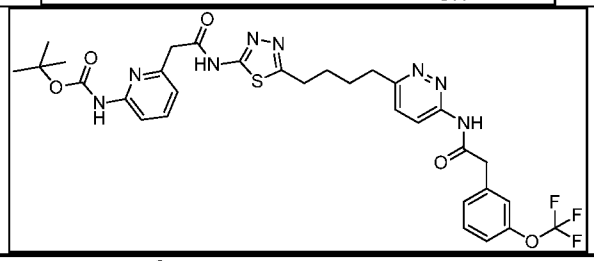
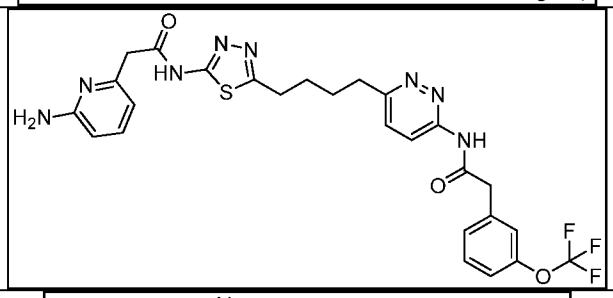
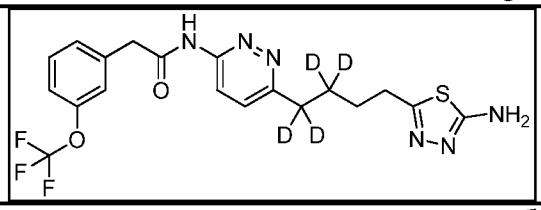
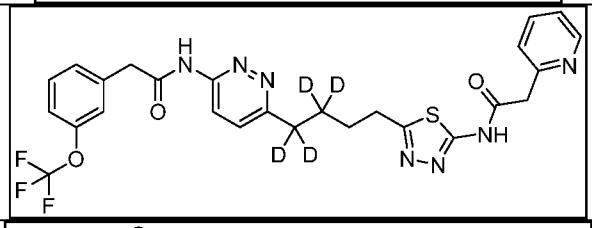
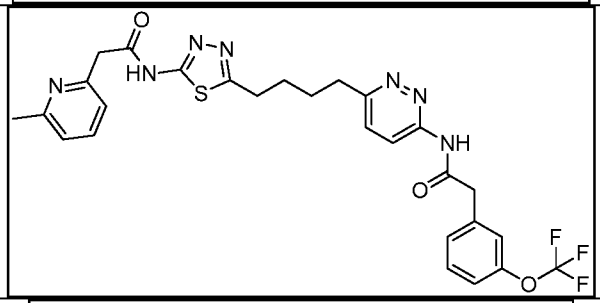
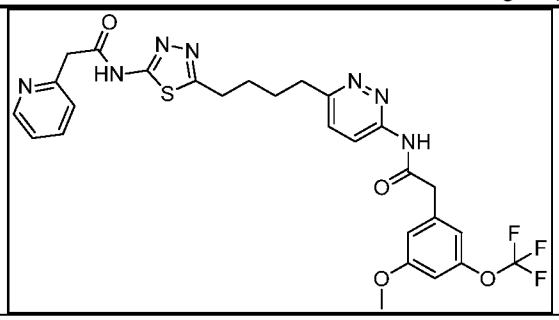
In certain embodiments, the compound is selected from any one of the compounds disclosed in Tables 1 and 2. In certain embodiments, the compound is selected from compound 447, 585, 586, 600, 614, 615, 629, 636, 657, 658, 659, 660, 661, 662, 663, 666, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 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.

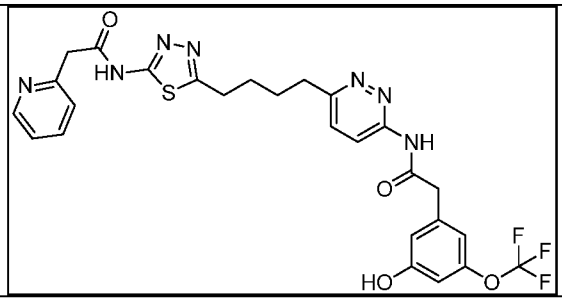
Table 2. Selected Compounds of Formula II

Compound ID	Structure
710	
711	

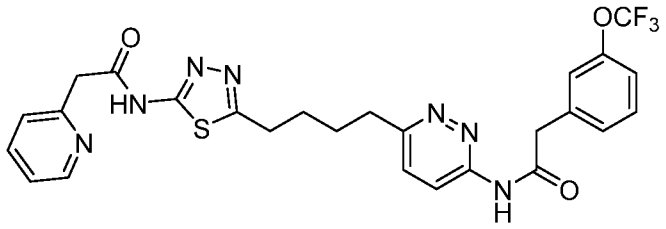
712			
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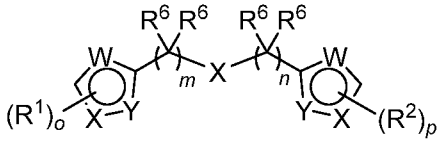
In certain embodiments of the methods described herein, the compound used in the methods of the invention is a compound having the structure of Formula (III):



(III), or a pharmaceutically 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):



(IV),

or a pharmaceutically acceptable salt thereof, wherein:

X is a bond, —S—, —S(O)—, —SO_2—, —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 R^1 and R^2 is independently $C_{1\text{-}6}$ alkylene-R^4, —$N(R^3)$—R^4, —$N(R^3)$—C(O)—R^4, —C(O)—$N(R^3)$—R^4, —$N(R^3)$—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)—$C_{1\text{-}6}$ alkylene-C(O)—R^4, —$N(R^3)$—C(O)—$C_{1\text{-}6}$ alkylene-$N(R^3)$—C(O)—R^4 or —$N(R^{3a})$—C(O)—CH_2—$N(R^3)$—C(O)—R^4;

each R^3 is independently hydrogen, $C_{1\text{-}6}$ alkyl or aryl;

each R^4 is independently C_{1-6} alkyl, C_{1-6} alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclylalkyl, heterocyclyl, 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 heterocyclyl, 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, heterocyclylalkyl or heterocyclyl, wherein each aryl, heteroaryl or heterocyclyl 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(±)-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 R^6 is H, then R^1 and R^2 are not both —NHC(O)-furanyl, —NHC(O)-phenyl, —NHC(O)-o-methoxy-phenyl, —NHC(O)—C_{1-6} alkyl, —NH-benzyl, or —NH-phenyl wherein said phenyl of the —NH-phenyl moiety is substituted with 0-3 occurrences of R^5;

(5) when X is a bond, the sum of m and n is 5, each R^6 is H, then R^1 and R^2 are not both —NHC(O)—C_{1-6} 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 R^6 is H, then R^1 and R^2 are not both NH-phenyl;

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

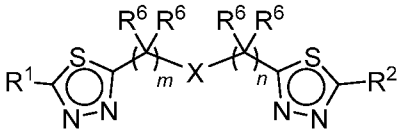
In certain embodiments, W is —S—, each Y is —N=, and each Z is —N=.

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, R^1 and R^2 are each —N(R^3)—C(O)—O—R^4.

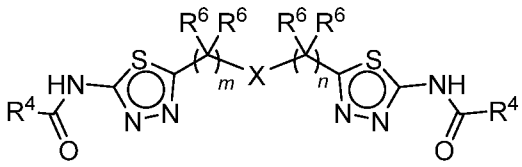
In certain embodiments, the compound having the structure of Formula (IV) has the structure of Formula (IVa):



(IVa).

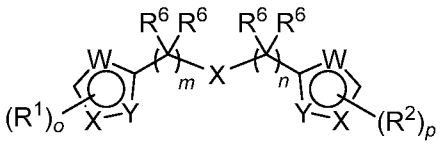
In certain embodiments, R^1 and R^2 are the same.

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



(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):



(V)

wherein:

X is C_3-C_7 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 R^1 and R^2 is independently $—NH_2$, $—N(R^3)—C(O)—R^4$, $—C(O)—N(R^3)—R^4$, $—N(R^3)—C(O)—O—R^4$, $—N(R^3)—C(O)—N(R^3)—R^4$ or $—N(R^3)—C(O)—SR^4$;

each R^3 is independently hydrogen, C_{1-6} alkyl or aryl;

each R^4 is independently C_{1-6} alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocyclylalkyl, or heterocyclyl, each of which is substituted with 0-3 occurrences of R^5;

each R^5 is independently C_{1-6} alkyl, C_{1-6} alkoxy, $—O—C_{1-6}$ alkyleneC_{1-6} alkoxy, C_{1-6} thioalkoxy, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclylalkyl, heterocyclyl, cyano, halo, oxo, —OH, $—OCF_3$, $—OCHF_2$, $—SO_2—C_{1-6}$ alkyl, $—NO_2$, $—N(R^7)—C(O)—C_{1-6}$ alkyl, $—C(O)N(R^7)_2$, $—N(R^7)S(O)_{1-2}—C_{1-6}$ alkyl, $—S(O)_2N(R^7)_2$, $—N(R^7)_2$, $—C_{1-6}$ alkylene-$N(R^7)_2$, wherein said alkyl, C_{1-6} alkoxy, $—O—C_{1-6}$ alkyleneC_{1-6}alkoxy, C_{1-6} thioalkoxy, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclylalkyl, heterocyclyl, $—SO_2—C_{1-6}$alkyl, $—NO_2$, $—N(R^7)—C(O)—C_{1-6}$ alkyl, $—C(O)N(R^7)_2$, $—N(R^7)S(O)_{1-2}—C_{1-6}$alkyl, $—S(O)_2N(R^7)_2$, $—N(R^7)_2$, or $—C_{1-6}$ alkylene-$N(R^7)_2$ is optionally substituted with 0-3 occurrences of R^8; or two adjacent R^5 moieties, taken together with the atoms to which they are attached form a cycloalkyl or heterocyclyl;

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, $—O—C_{1-6}$ alkyleneC_{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; and

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;

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

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

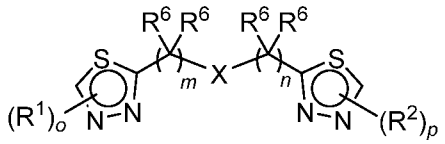
In certain embodiments, o is 1 and p is 1.

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

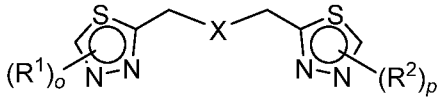
In certain embodiments, R^1 and R^2 are different. Alternatively, R^1 and R^2 can be the same.

In certain embodiments, R^1 and R^2 are each —N(R^3)—C(O)—O—R^4, wherein each R^3 is hydrogen and each R^4 is aralkyl or heteroaralkyl, each of which is substituted with 0-3 occurrences of R^5.

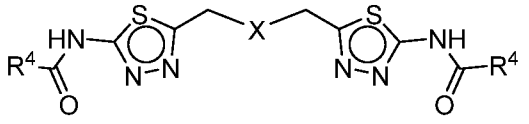
In certain embodiments, the compound having the structure of Formula (V) is a compound having the structure of Formula (Va):


(Va).

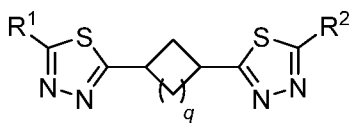
In certain embodiments, the compound having the structure of Formula (V) is a compound having the structure of Formula (Vb):


(Vb).

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

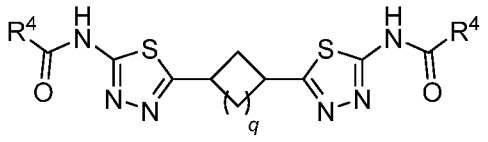

(Vc).

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


(VI);

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

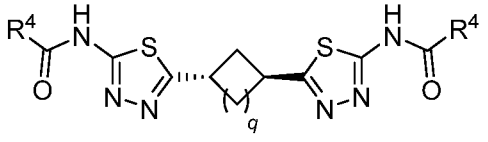
In certain embodiments, the compound of formula (V) has the structure of formula (VIa):



(VIa);

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

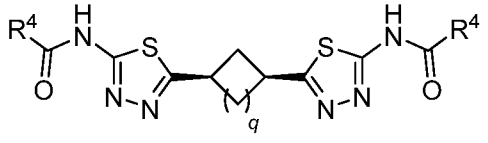
In certain embodiments, the compound of formula (V) has the structure of formula (VIb):



(VIb);

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

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



(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."

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).

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 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 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 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 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.

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.

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.

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 initated by the mitochondrial enzyme, glutaminase ("GLS"). There are two major forms of the enzyme, K-type and L-type, which are distinguished by their Km values for glutamine and response to glutamate, wherein the Km 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 Km for glutamine and is glutamate resistant. The K-type, also known as "kidney-type or GLS1, has a low Km for glutamine and is inhibited by glutamate. An alternative splice form of GLS1, referred to as glutmainase 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, Extragonadal 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, Extragonadal, 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 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 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, 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 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, 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, 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-hydroxyglutatrate, 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 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 myeldysplasia/myeloproliferative disorders, a group of blood disorders, have IDH1 or IDH2 driver mutations.

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), 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 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+, 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-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.

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.

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 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 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 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 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 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. 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, 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, 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, thioguanine, thalidomide, thiotepa, titanocene dichloride, topotecan, trametinib, trastuzumab, tretinoin, veliparib, vinblastine, vincristine, vindesine, 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, Prednisome
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	Etoposie, 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, Etoposie, 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

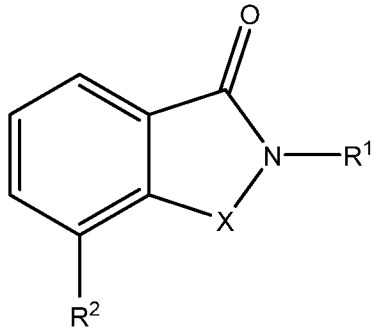
relative to individual administration of the immunomodulatory agent or glutaminase inhibitor as a single agent.

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

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 prior or after of the glutaminase inhibitor.

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



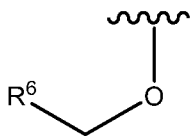
(X)

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

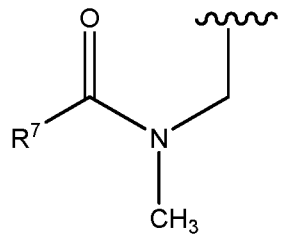
X is C=O or CH_2;

R^1 is heterocyclyl, such as 2,6-dioxopiperidin-3-yl, or aralkyl, such as a sulfonyl-substituted aralkyl, and

R^2 is independently a hydrogen, an amino group, an acylamino group, an alkylamino group, or is one of the following moieties:

a) 

, wherein R^6 is substituted or unsubstituted phenyl, aryl or heteroaryl, or

b) 

, wherein R^7 is C_1-C_6 alkyl, cycloalkyl, NH-Ar, where Ar is phenyl or substituted phenyl, or NR^8R^9, where R^8 and R^9 may be independently H or C_1-C_6-alkyl.

In certain embodiments, the immunomodulatory agent is apremilast, lenalidomide, 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.

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 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, 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 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 immunodulatory 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, 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 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 a 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 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 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.

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 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, 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 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 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 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, 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 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 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 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 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 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 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 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 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, 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), 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 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 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 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 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).

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 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) 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 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, mg, 400 mg, 450 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 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 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

Example 1: Comparision 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 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 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 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 Cmax 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).

Example 2: Comparision 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 comparision 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).

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 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 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.

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 indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

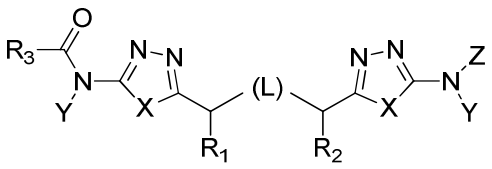
In particular, suitable compounds for practicing the invention, and methods for synthesizing said compounds, are described in U.S. Patent No. 8,604,016, U.S. Patent Application Publication No. 2014/0194421, and U.S. Application Publication Nos. 2015/0004134, 2014/0142081, and 2014/0142146, which are 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 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. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer,


(I),

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, or heterocyclylalkoxy;

Z represents H or $R_3(CO)$;

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

R_3, independently for each occurrence, represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroaryloxyalkyl or $C(R_8)(R_9)(R_{10})$, $N(R_4)(R_5)$ or OR_6, wherein any free hydroxyl group may be acylated to form $C(O)R_7$;

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, heterocyclyl,

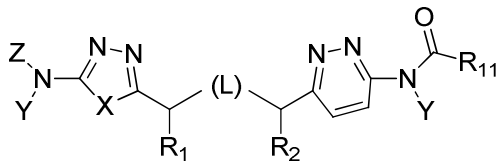
heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl, wherein any free hydroxyl group may be acylated to form $C(O)R_7$;

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 $C(O)R_7$;

R_8, R_9 and R_{10} 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, or R_8 and R_9 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 $C(O)R_7$; and

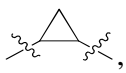
wherein the medicament is to be orally administered with a meal.

2. Use of a compound of formula (II), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer,



(II),

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 $R_3(CO)$;

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

R_3 represents substituted or unsubstituted alkyl, hydroxyalkyl, aminoalkyl, acylaminoalkyl, alkenyl, alkoxy, alkoxyalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroaryloxyalkyl or $C(R_8)(R_9)(R_{10})$, $N(R_4)(R_5)$ or OR_6, wherein any free hydroxyl group may be acylated to form $C(O)R_7$;

R_4 and R_5 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 $C(O)R_7$;

R_6 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 $C(O)R_7$;

R_8, R_9 and R_{10} 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 R_8 and R_9 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 $C(O)R_7$, and wherein at least two of R_8, R_9 and R_{10} are not H;

R_{11} represents aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl or R_{11} represents $C(R_{12})(R_{13})(R_{14})$, $N(R_4)(R_{14})$ or OR_{14}, wherein any free hydroxyl group may be acylated to form $C(O)R_7$;

R_{12} and R_{13} 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 substituted or unsubstituted aryl, arylalkyl, aryloxy, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, or heteroaryloxyalkyl; and

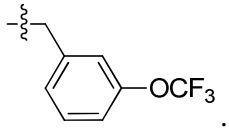
wherein the medicament is to be orally administered with a meal.

3. The use of claim 2, 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.

4. The use of claim 2 or 3, 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.

5. The use of claim 3 or 4, wherein R_{11} represents arylalkyl, wherein the aryl ring is substituted with $–OCF_3$.

6. The use of claim 5, wherein R_{11} represents trifluoromethoxybenzyl.

7. The use of claim 6, wherein R_{11} represents 

.

8. The use of any one of claims 2-7, wherein one or more of (a) – (e) applies:

(a) L represents CH_2SCH_2, CH_2CH_2, CH_2S or SCH_2, preferably CH_2CH_2;

(b) Y represents H;

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

(d) Z represents $R_3(CO)$; or

(e) R_1 and R_2 each represent H.

9. The use of claim 8, wherein R_3 and R_{11} are not identical.

10. The use of any one of claims 2-9, wherein Z represents $R_3(CO)$ and R_3 represents substituted or unsubstituted arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl.

11. The use of claim 10, wherein Z represents $R_3(CO)$ and R_3 represents substituted or unsubstituted heteroarylalkyl.

12. The use of claim 11, wherein Z represents $R_3(CO)$ and R_3 represents substituted or unsubstituted pyridylalkyl.

13. The use of any one of claims 2-7, 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.

14. The use of any one of claims 3-7, wherein L represents CH_2CH_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 arylalkyl, heteroarylalkyl, cycloalkyl or heterocycloalkyl.

15. The use of claim 14, wherein R_3 represents heteroarylalkyl.

16. The use of any one of claims 1 to 15, wherein the cancer is selected from breast cancer, colorectal cancer, endocrine cancer, lung cancer, melanoma, mesothelioma, renal cancer, and a B cell malignancy.

17. The use of claim 16, wherein the cancer is breast cancer.

18. The use of claim 17, wherein the breast cancer comprises basal-type breast cancer cells, triple-negative breast cancer cells or claudin-low breast cancer cells.

19. The use of claim 16, wherein the cancer is colorectal cancer.

20. The use of claim 16, wherein the cancer is endocrine cancer.

21. The use of claim 20, wherein the endocrine cancer is selected from adrenal cortex adenoma, adrenal cortex carcinoma, adrenal gland pheochromocytoma, and parathyroid gland adenoma.

22. The use of claim 16, wherein the cancer is melanoma.

23. The use of claim 16, wherein the cancer is renal cancer.

24. The use of claim 16, wherein the cancer is a B cell malignancy.

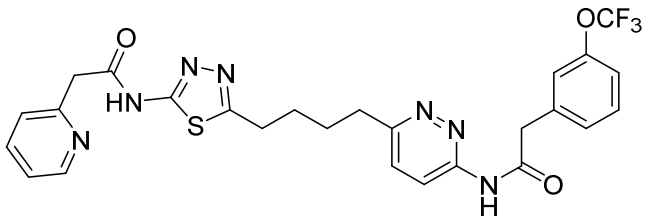
25. The use of claim 24, wherein the B cell malignancy is selected from multiple myeloma, leukemia, and lymphoma.

26. The use of claim 25, wherein the B cell malignancy is leukemia, such as acute lymphoblastic leukemia, or chronic lymphoblastic leukemia.

27. The use of claim 25, wherein the B cell malignancy is lymphoma, such as Burkitt's lymphoma, Diffuse large B cell lymphoma, follicular lymphoma, or Hodgkin's lymphoma.

28. The use of any one of the preceding claims, wherein the compound is the compound of formula III or a pharmaceutically acceptable salt thereof and 300 mg to 3000 mg of the compound is to be administered per day;

wherein formula III has the following structure:



(III).

29. The use of any one of the preceding claims, wherein the medicament is to be administered two times per day.

30. The use of any one of claims 1-28, wherein the medicament is to be administered three times per day.

31. The use of any one of the preceding claims, wherein the medicament is to be administered to a human.

32. The use of any one of the preceding claims, wherein the medicament is to be administered with one or more additional chemotherapeutic agents.

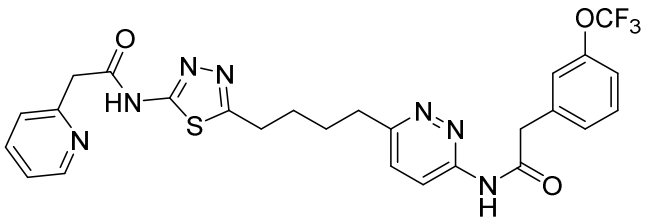
33. The use of claim 32, wherein the one or more additional chemotherapeutic agents are selected from ABT-263, aminoglutethimide, amsacrine, anastrozole, asparaginase, azacitidine, AZD5363, Bacillus Calmette–Guérin vaccine (bcg), bicalutamide, bleomycin, bortezomib, buserelin, busulfan, campothecin, 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, lenalidomaide, 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).

34. The use of claim 33, 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.

35. The use of claim 34, wherein the one or more additional chemotherapeutic agents are selected from azacitidine, dexamethasone, docetaxel, erlotinib, everolimus, paclitaxel and pomalidomide.

36. Use of a compound of formula (III), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer,



(III),

wherein the medicament is to be orally administered with a meal.