GLUTAMINASE INHIBITORS AND METHOD OF USE

CLAIM OF PRIORITY

This application claims priority from U.S.S.N. 61/729,321, filed November 21, 2012, which is incorporated herein by reference in its entirety.

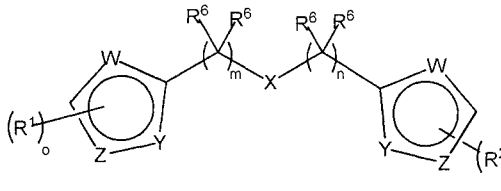
BACKGROUND OF INVENTION

Cancer cells rely primarily on glycolysis to generate cellular energy and biochemical intermediates for biosynthesis of lipids and nucleotides, while the majority of "normal" cells in adult tissues utilize aerobic respiration. This fundamental difference in cellular metabolism between cancer cells and normal cells is termed the Warburg Effect. As a result of this difference, pyruvate generated via the glycolytic pathway is converted to lactic acid, rather than being used to acetyl-CoA and eventually, the citrate utilized in a normal citric acid cycle. To compensate for these energetic changes and to maintain a citric acid cycle, cancer cells rely on glutamine metabolism which is achieved through an elevation of glutaminase activity. Exploitation of this phenomenon can be achieved by inhibition of this elevated glutaminase activity.

SUMMARY

Described herein are heterocyclic containing, pharmaceutically acceptable salts, solvates, and hydrates thereof. The compounds can be used to treat a disorder described herein, for example, by inhibiting glutaminase in a patient. Also provided are compositions (e.g., pharmaceutical compositions) comprising a compound provided herewith and the use of such compositions in methods of treating diseases and conditions, for example, that are associated with the aberrant function of glutaminase or elevated activity of glutaminase, including, e.g., cancer.

In one aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein:


Formula (I),

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_{1-6} alkylene-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_{1-6} alkylene-C(O)-R^4, -$N(R^3)$-C(O)-C_{1-6} 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_{1-6} 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, 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(O)-6-pyrimidine-2,4(1*H*,3*H*)-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;

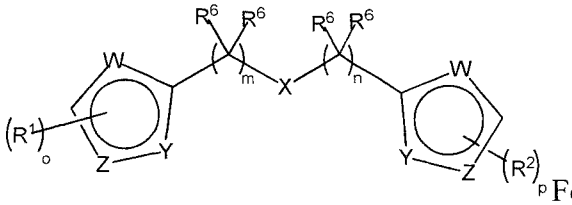
(3) when X is a bond, the sum of m and n is 3, each R^6 is H, then R^1 and R^2 are not both NHC(O)-phenyl;

(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.

In another aspect, there is provided a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein:



Formula (I),

X is -S(O)- or -SO_2-;

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_{1-6} alkylene-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_{1-6} alkylene-C(O)-R^4, -$N(R^3)$-C(O)-C_{1-6} 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_{1-6} 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;

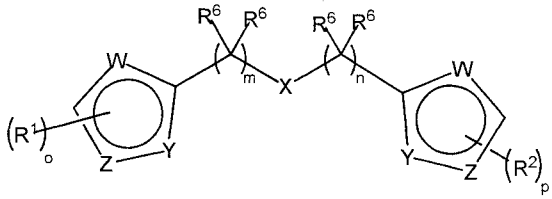
n is 1, 2 or 3; provided that when X is -S(O)- or -SO_2-, the sum of m and n is from 2 to 4;

o is 1, 2 or 3; and

p is 1, 2 or 3.

In yet another aspect, there is provided a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or adjuvant.

In one example, provided is a compound of formula (I) or a pharmaceutically acceptable salt thereof:


Formula (I),

wherein

X is a bond, -S-, -S(O)-, -SO_2-, -CH=CH-, -NH-, or –C(O)-;

each W, Y and Z is independently –S-, -CH=, -CH=CH-, -CH=CR^1-, -CR^1=CR^1-, -O-, -N=, or –NH-, provided that (1) for each ring 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_{1-6} 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_{1-6} alkylene-C(O)-R^4, -N(R^3)-C(O)-C_{1-6} 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_{1-6} 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, a monocyclic ring, monocyclic aralkyl, monocyclic heterocyclylalkyl, 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(O)-6-pyrimidine-2,4(1*H*,3*H*)-dionyl, -N(ethyl)C(O)-benzyl, 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 or –NHC(O)-benzyl;

(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)-R^4, wherein R^4 is monocyclic aryl or monocyclic aralkyl or methyl, and each member of R^4 is optionally substituted with 0-3 occurrences of R^5;

(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, -NHC(O)-NH-phenyl, -NHC(O)-NH-benzyl, or -NH-phenyl wherein said phenyl of the -NH-phenyl moiety is substituted with 0-3 occurrences of R^5;

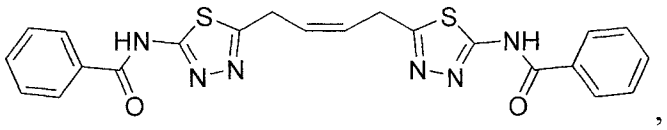
(5) when X is a bond, the sum of m and n is 5, each R^6 is H, then R^1 and R^2 are not both -NHC(O)-C_{1-6} alkyl, -NHC(O)-cyclohexyl, or -NH-phenyl wherein said phenyl of the -NH-phenyl moiety is optionally substituted with methyl; and

(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;

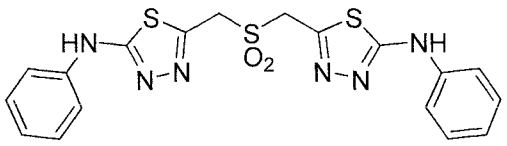
(7) when X is a bond, m and n are both 2, and one of W, Y or Z is -CH=CH- or -CH=CR^1 -, then R^1 and R^2 are not both –NHC(O)C(R*)$_2$-phenyl wherein the phenyl is unsubstituted or substituted with 0-3 occurrences of R^5 and R* is H, -OH, -C$_{1-2}$ alkyl-OH, -C$_{1-2}$ alkyl-OCH$_3$, or -CH$_3$;

(8) when X is a bond, m and n are both 2, one of W, Y or Z is -CH=CH- or -CH=CR^1 -, and one of R^1 and R^2 is -NHC(O)CH$_2$-R^, wherein R^ is hydrogen, –NH$_2$, heteroaryl, or a fused ring, wherein the heteroaryl is unsubstituted or substituted with 0-3 occurrences of R^5; –NHC(O)NH-benzyl; or –NHCO$_2$-benzyl; then the other of R^1 and R^2 is not –NHC(O)C(R*)$_2$-phenyl, wherein the phenyl is unsubstituted or substituted with 0-3 occurrences of R^5, and R* is H, -OH, -C$_{1-2}$ alkyl-OH, -C$_{1-2}$ alkyl-OCH$_3$, or methyl;

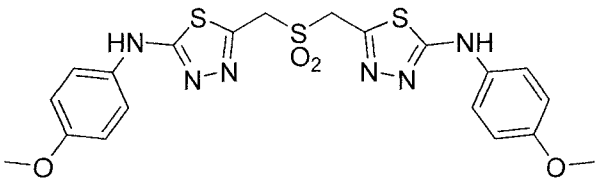
(9) the compound of formula (I) is not:



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, or



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In another example, provided is a composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof. In some examples, the composition is a pharmaceutical composition.

In another example, provided herein is a method for treating or preventing a disease, condition or disorder as described (e.g., treating) herein comprising administering a compound described herein, a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising a compound described herein or a pharmaceutically acceptable salt thereof.

In another example, provided herein is a method of inhibiting glutaminase, e.g, in a patient in need thereof. In some examples, provided here is reducing the level of the product of glutaminase in a subject, e.g., a patient in need thereof. The methods include administering an effective amount of a compound described herein or a pharmacetucally acceptable salt thereof to a subject in need thereof, thereby inhibiting the level of glutaminase in the subject.

In another example, provided herein is a method of treating a subject suffering from or susceptible to a disease or disorder associated with the aberrant function of glutaminase or elevated activity of glutaminase in a subject in need thereof. The method comprises the step of administering an effective amount of a compound described herein to the subject in need thereof, thereby treating, preventing or ameliorating the disease or disorder in the subject. In certain examples, the compound is provided in a pharmaceutical composition. In certain examples, the method includes identifying or selecting a subject who would benefit from inhibiting glutaminase or decreasing the level of glutaminase. E.g., the subject can be identified on the basis of the level of glutaminase activity in a cell or tissue sample of the subject for treatment of cancer associated with aberrant glutaminase function or activity. In another example, the selected subject is a patient suffering from or susceptible to a disorder or disease identified herein, e.g., a disorder characterized by unwanted cell growth or proliferation, e.g., cancer or other neoplastic disorders.

In another example, provided herein is a method for treating cancer in a subject, the method comprising: optionally, acquiring a subject sample; acquiring an evaluation of or evaluating the subject sample, wherein the subject sample is characterized by i) a low level of E-cadherin expression compared to a reference standard, ii) a high level of vimentin expression compared to a reference standard, or iii) a low or decreased level of pyruvate carboxylase expression; and administering to the subject in need thereof a therapeutically effective amount of a compound described here. In some embodiments, the subject sample is characterized by i) a low level of E-cadherin

expression compared to a reference standard and ii) a high level of vimentin expression compared to a reference standard. In some examples, the subject sample is characterized or further characterized by low or decreased levels of pyruvate carboxylase expression compared to a reference standard.

In another example, provided herein is a method for treating cancer in a subject characterized by i) a low level of E-cadherin expression compared to a reference standard, ii) a high level of vimentin expression compared to a reference standard, or iii) a low or decreased level of pyruvate carboxylase expression; comprising administering to the subject in need thereof a therapeutically effective amount of a compound described here. In some examples, the subject is characterized by i) a low level of E-cadherin expression compared to a reference standard and ii) a high level of vimentin expression compared to a reference standard. In some examples, the subject is characterized or further characterized by low or decreased levels of pyruvate carboxylase expression compared to a reference standard.

DETAILED DESCRIPTION

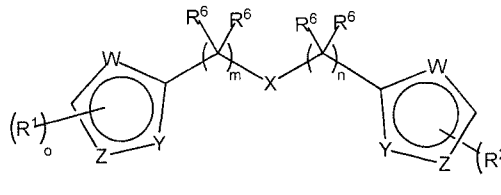
The details of construction and the arrangement of components set forth in the following description or illustrated in the drawings are not meant to be limiting. Embodiments can be practiced or carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing", "involving", and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

Compounds

Described herein are compounds and compositions that inhibit glutaminase. Compounds that inhibit glutaminase, can be used to treat disorders such as neoplastic disorders (e.g., cancer).

What is claimed is:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein:



Formula (I),

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_{1-6} alkylene-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_{1-6} alkylene-C(O)-R^4, -$N(R^3)$-C(O)-C_{1-6} 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_{1-6} 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, 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(O)-6-pyrimidine-2,4(1*H*,3*H*)-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.

2. The compound of claim 1, wherein each W is –S-, each Y is –N= and each Z is –N=.

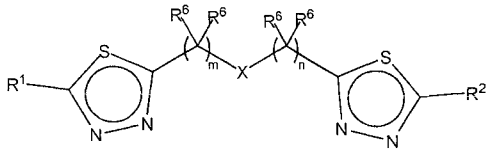
3. The compound of claim 1, wherein each W is –CH=, each Z is –O- and each Y is –N=.

4. The compound of claim 1, wherein o is 1 and p is 1.

5. The compound of claim 1, wherein R^1 and R^2 are each –N(R^3)-C(O)-O-R^4, wherein R^3 is hydrogen.

6. The compound of claim 5, wherein R^1 and R^2 are the same.

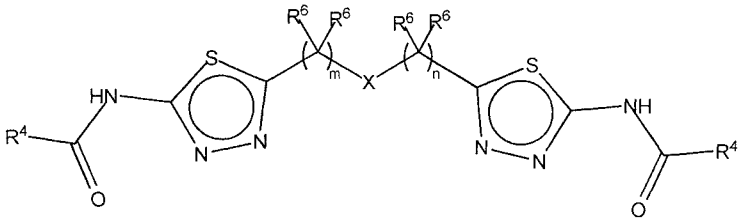
7. The compound of claim 1, wherein the compound is a compound of Formula (II):



(II).

8. The compound of claim 6, wherein R^1 and R^2 are the same.

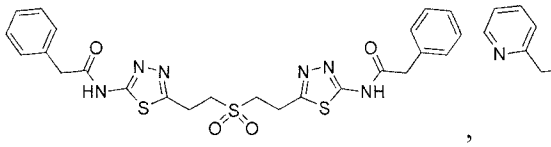
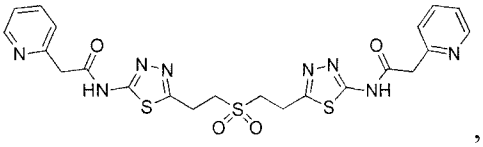
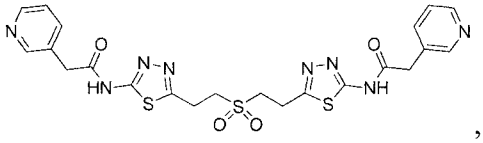
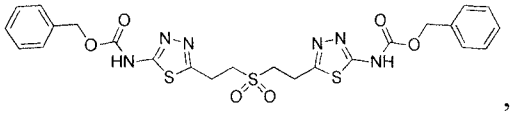
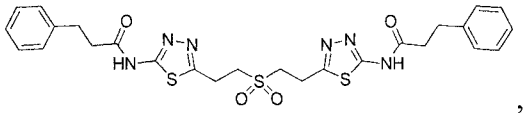
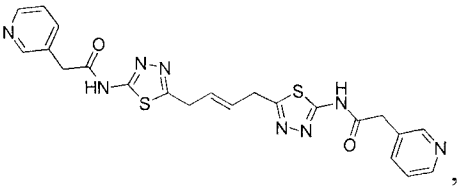
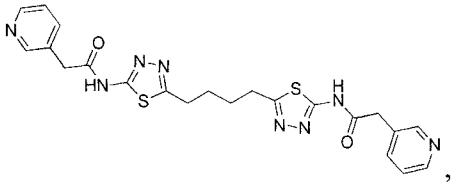
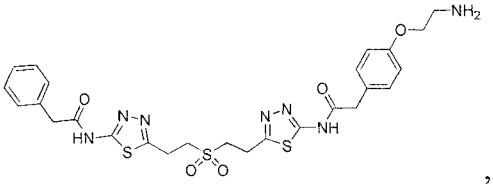
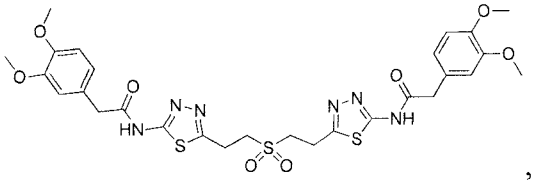
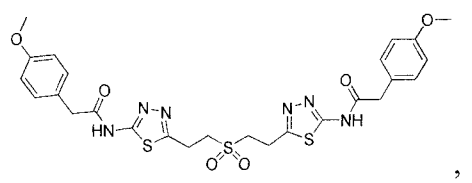
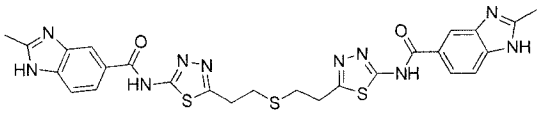
9. The compound of claim 1, wherein the compound is a compound of Formula (III):



(III).

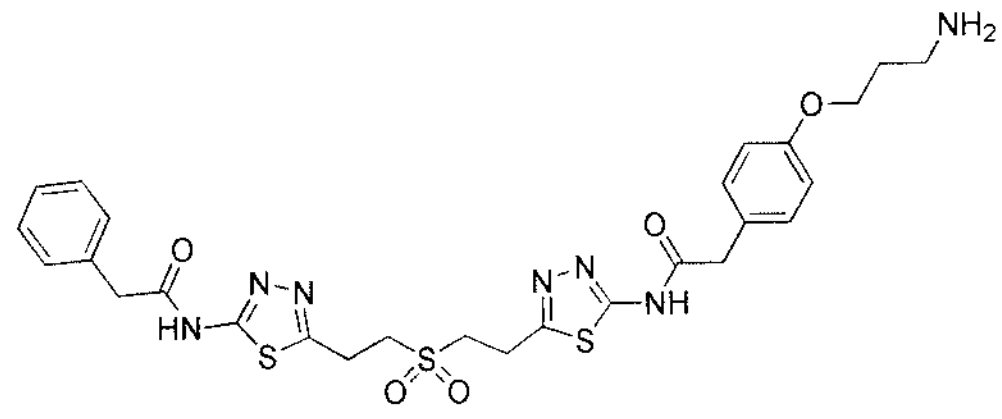
10. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or adjuvant.

11. The compound of claim 1, wherein the compound is selected from the group consisting of:

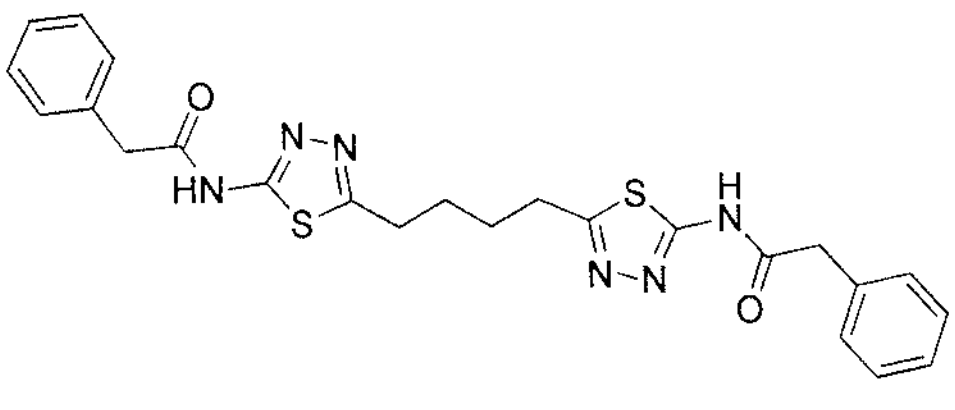

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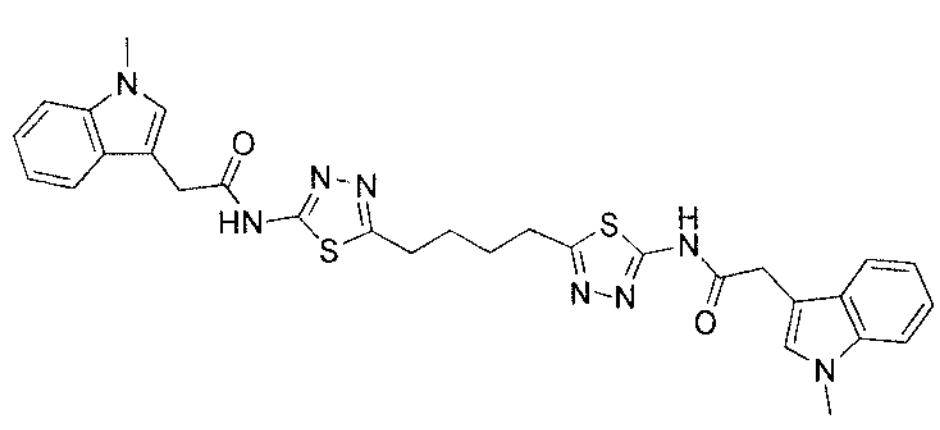
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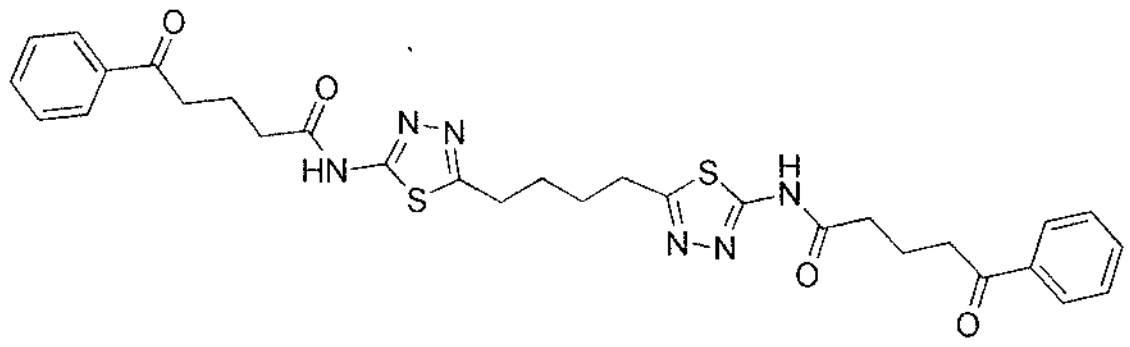
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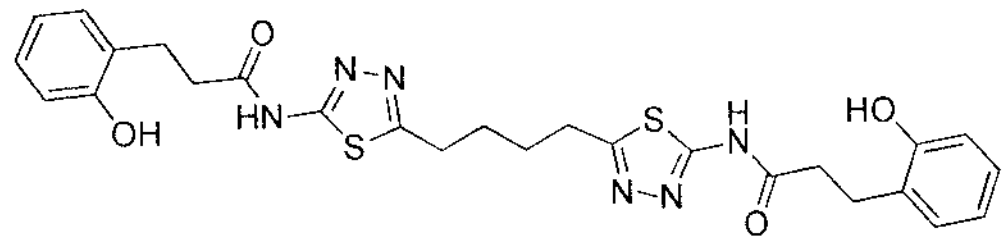
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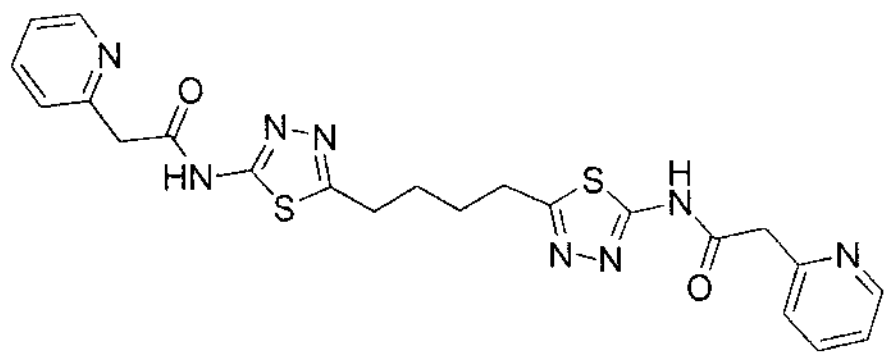
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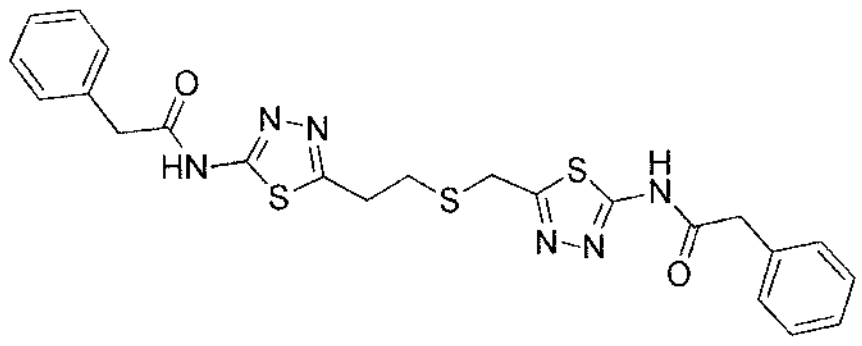
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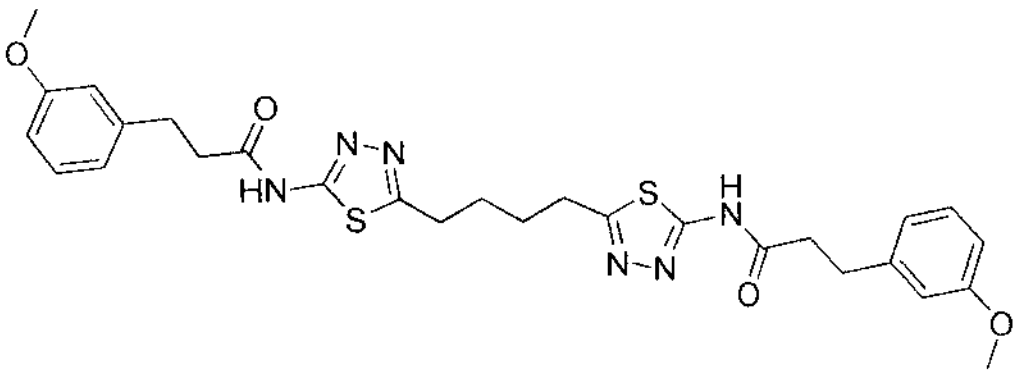
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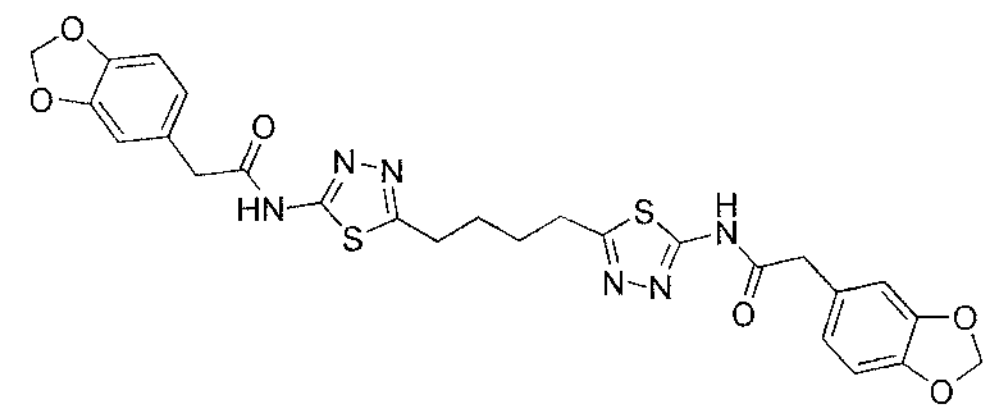
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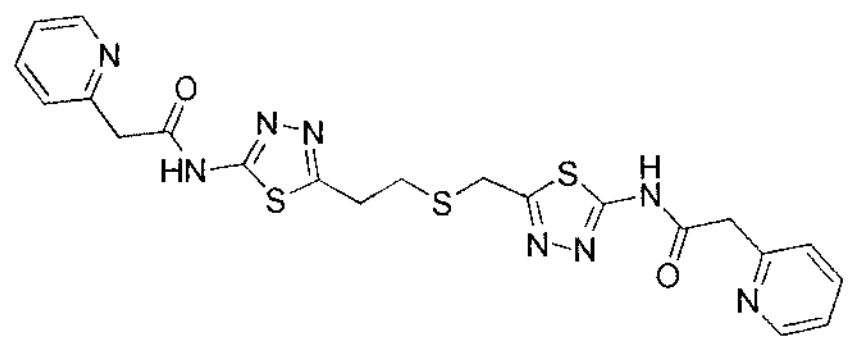
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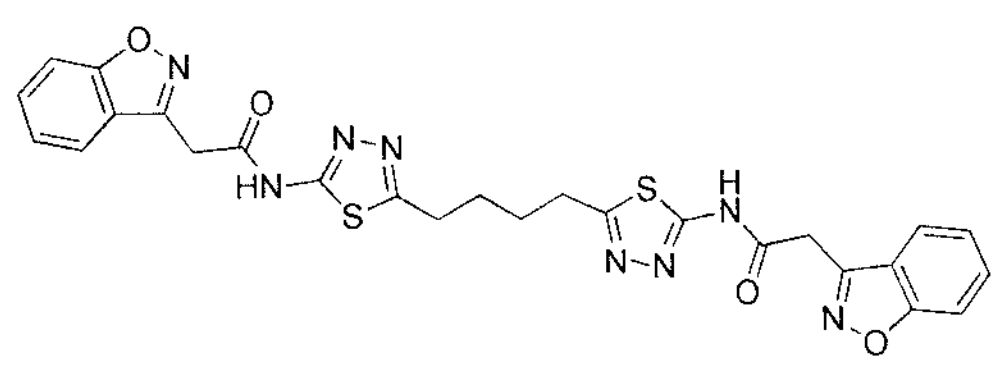
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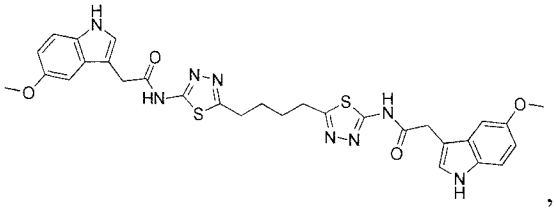
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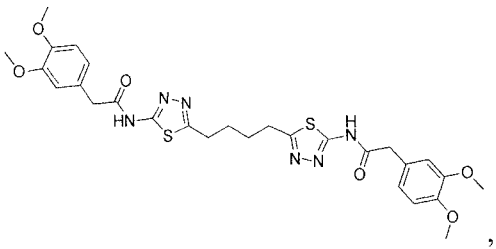

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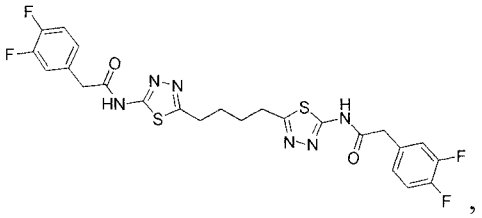
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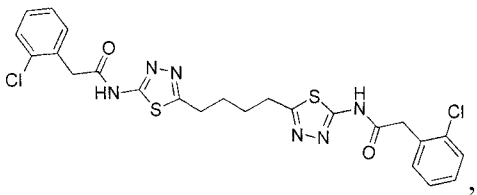

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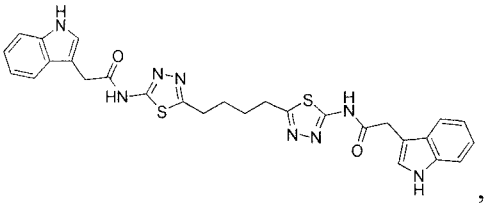
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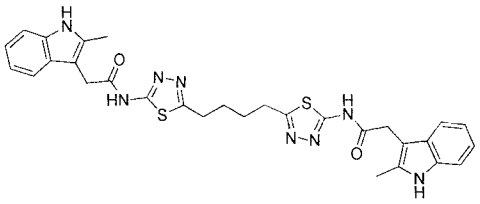

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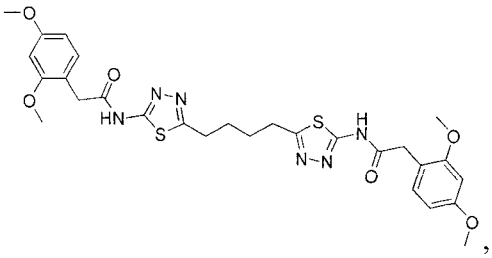

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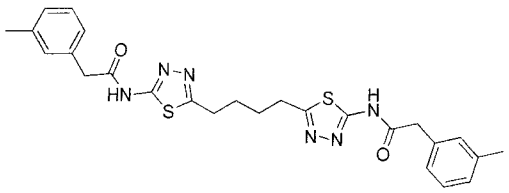

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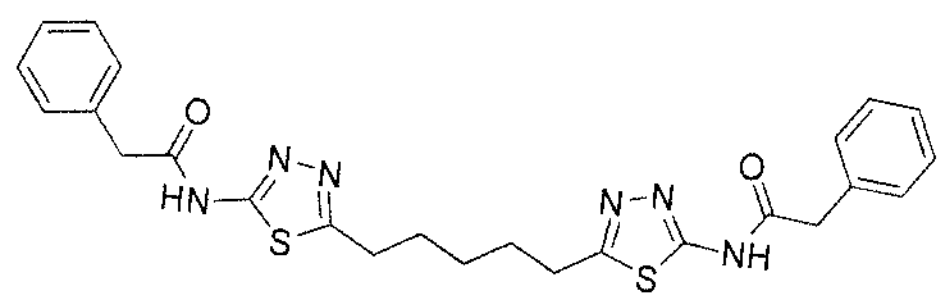

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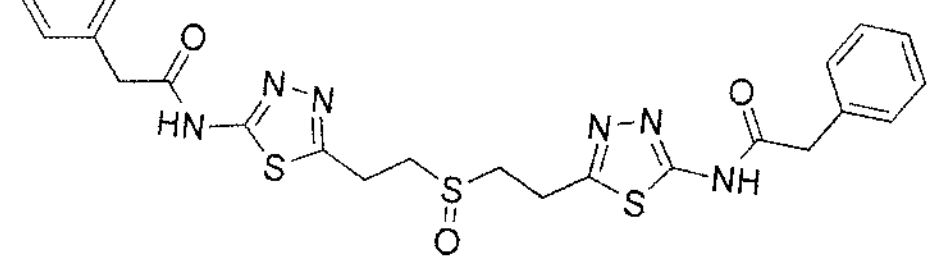

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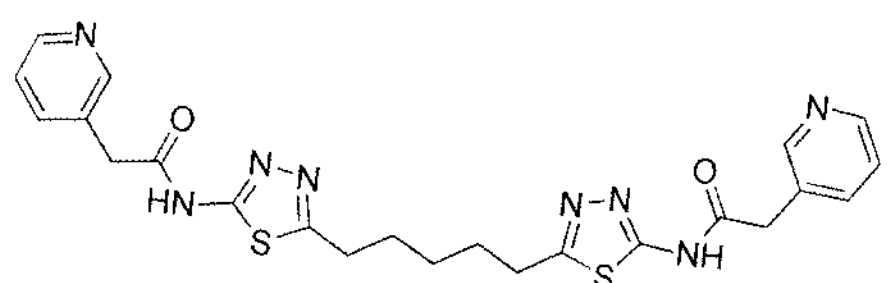

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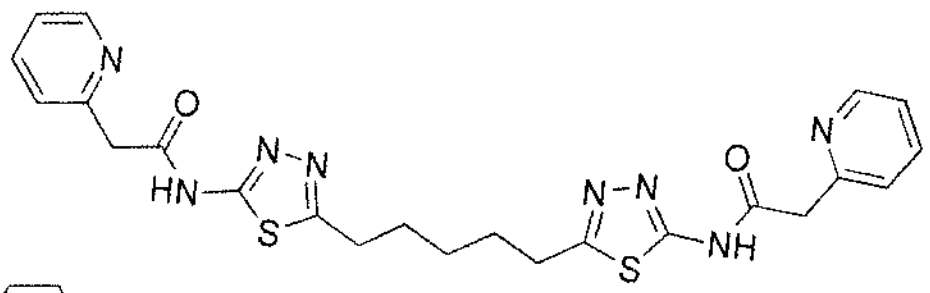

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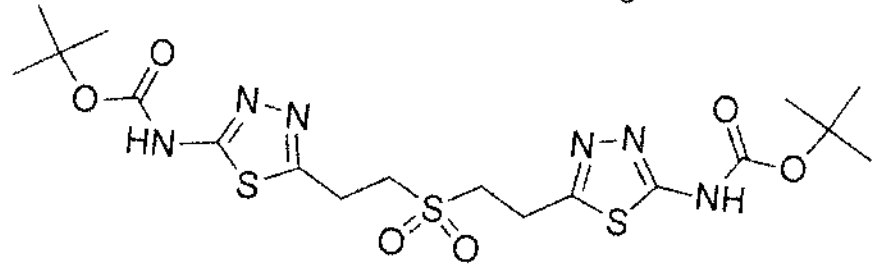
12. The compound of claim 1, wherein the compound is selected from the group consisting of:

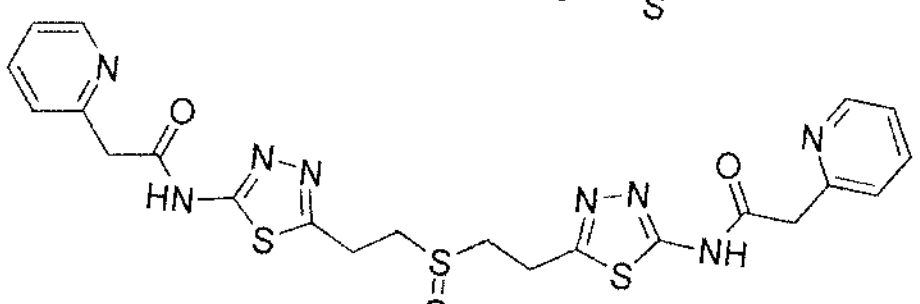

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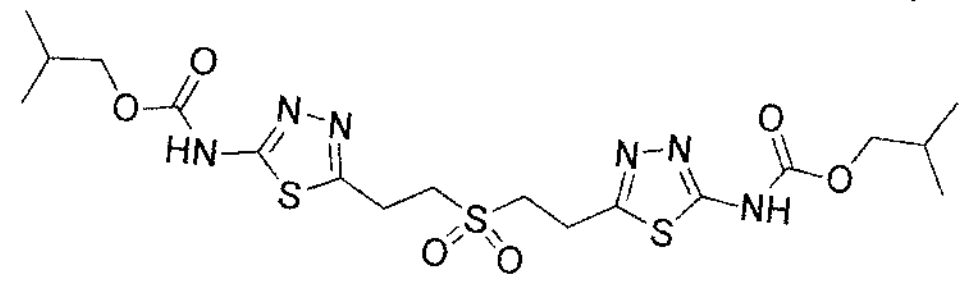

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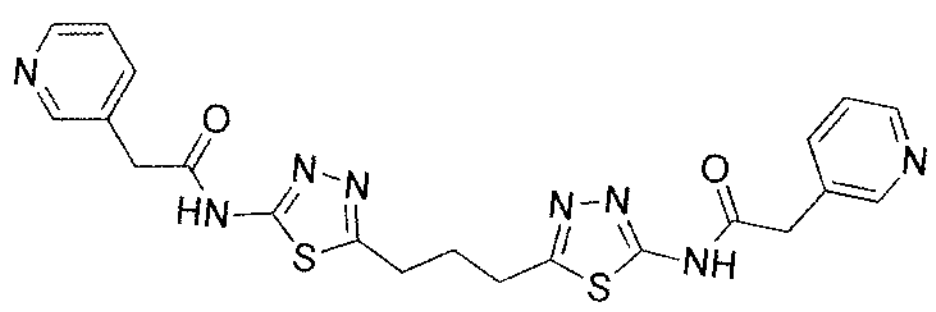

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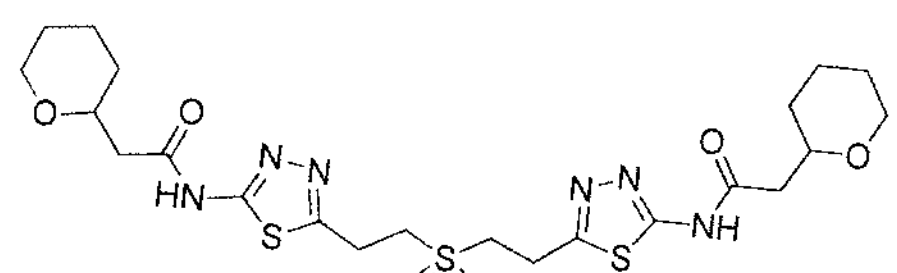

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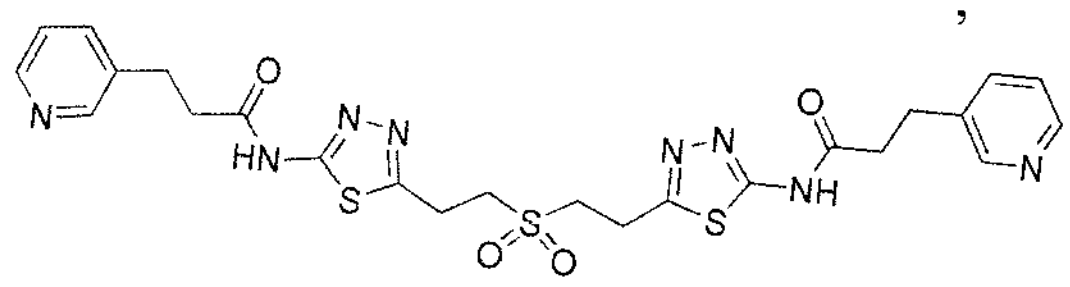

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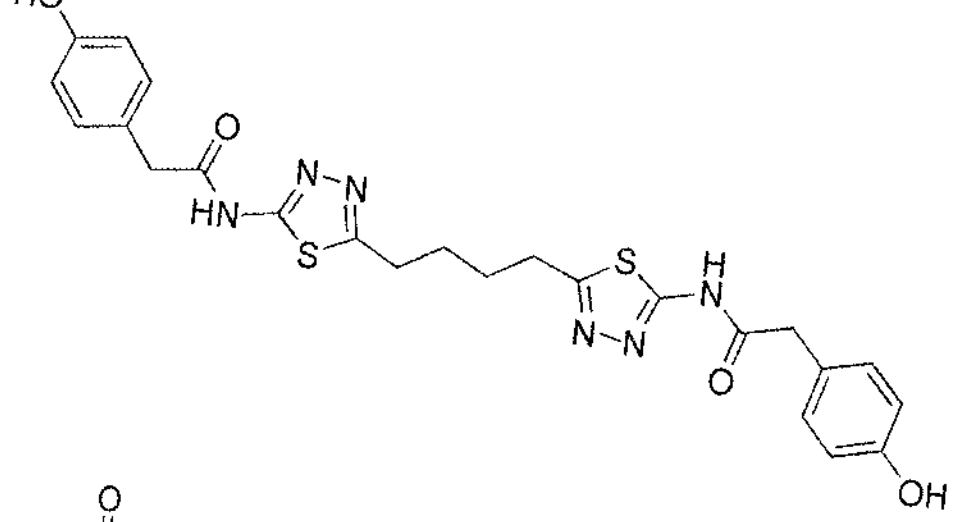

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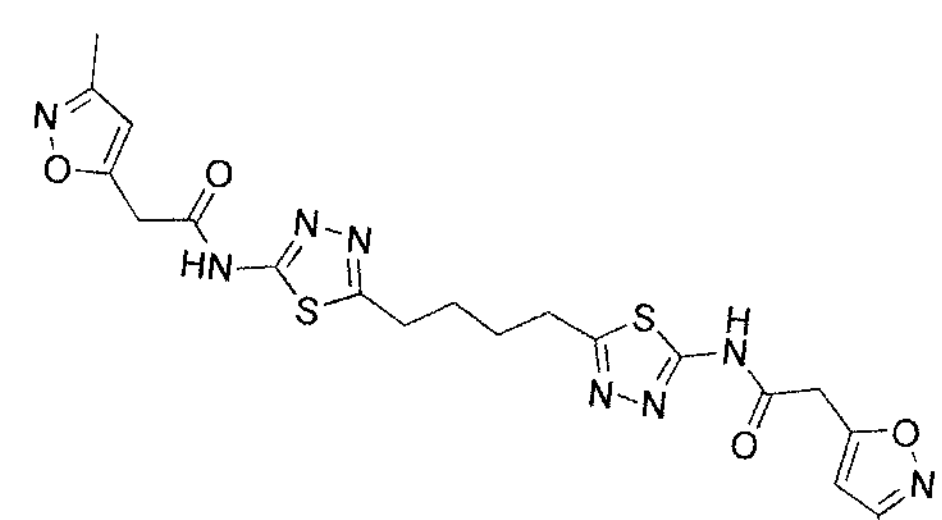

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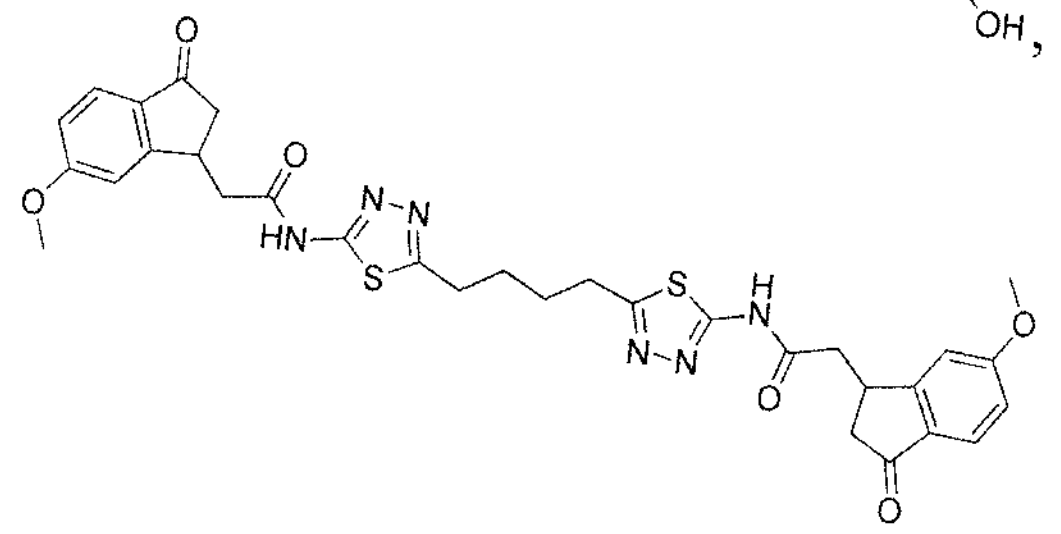

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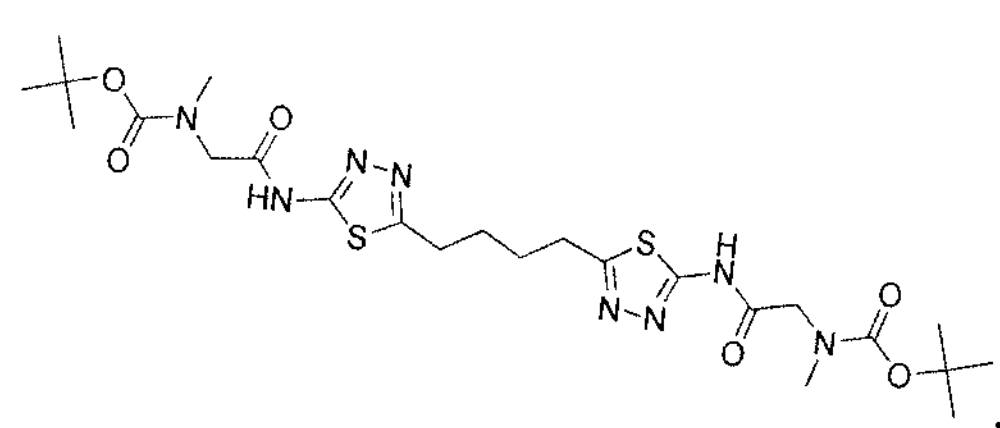

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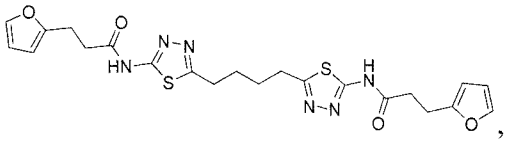
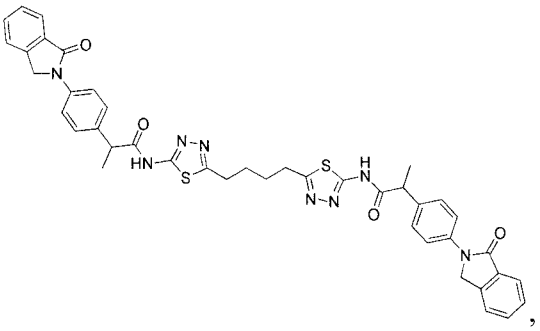
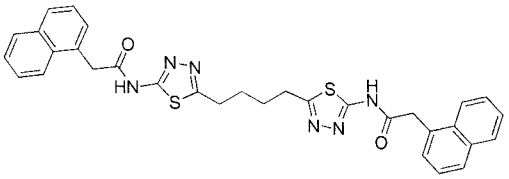
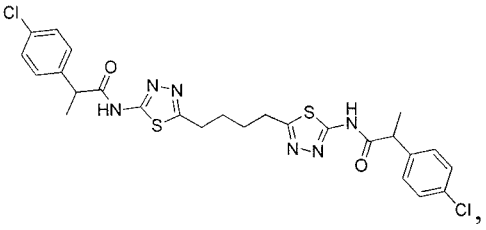
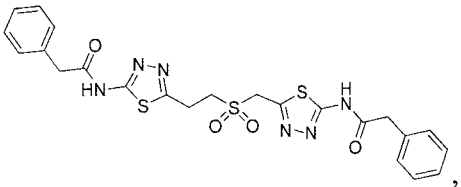
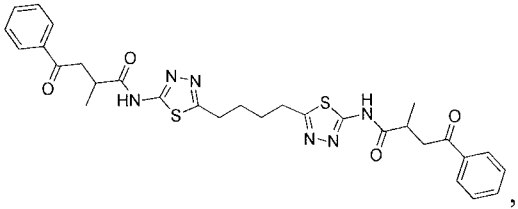
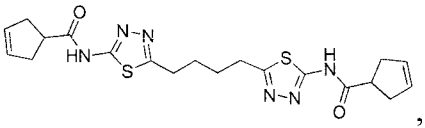
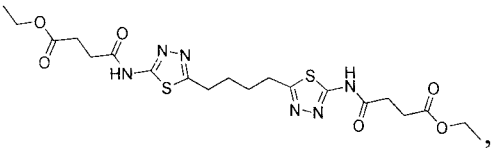
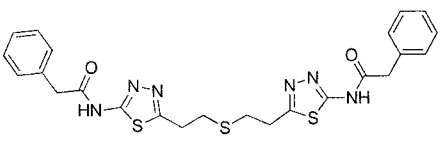
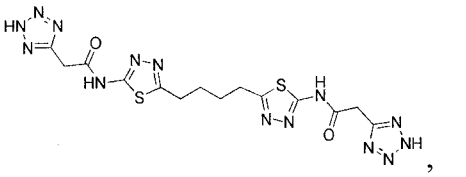

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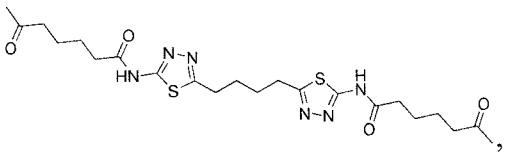
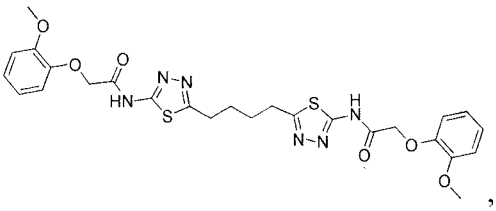

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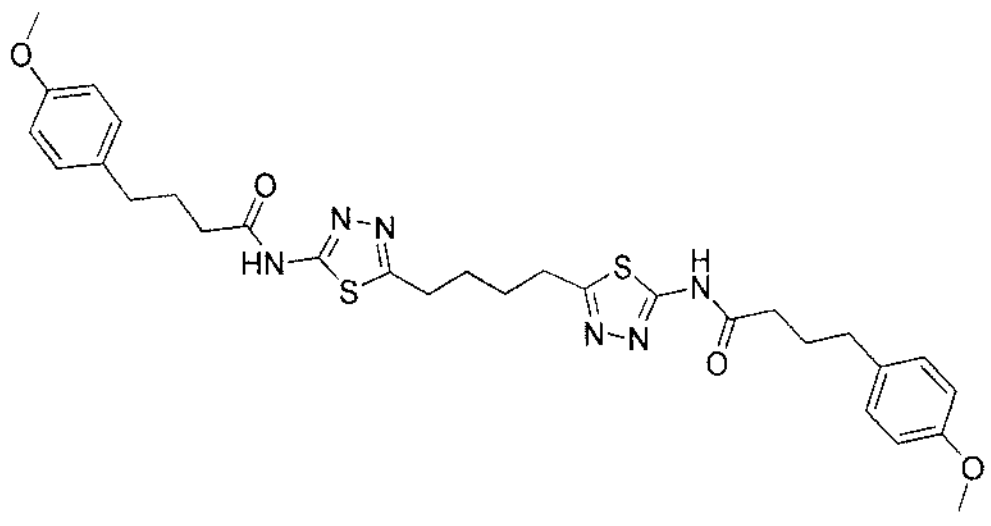

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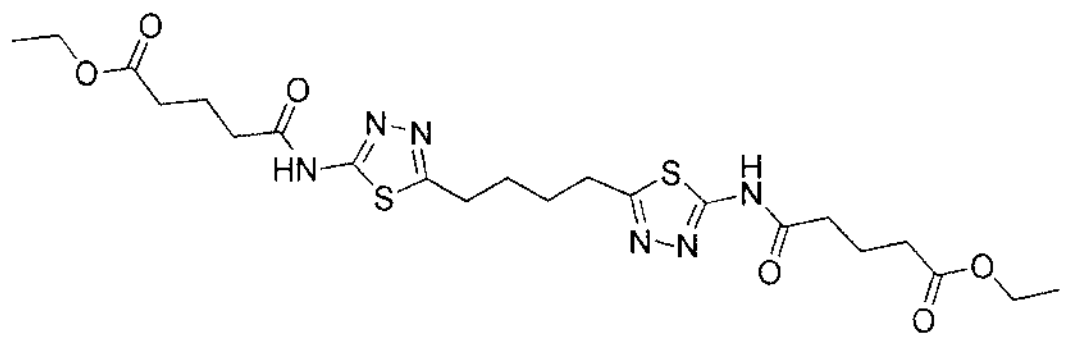

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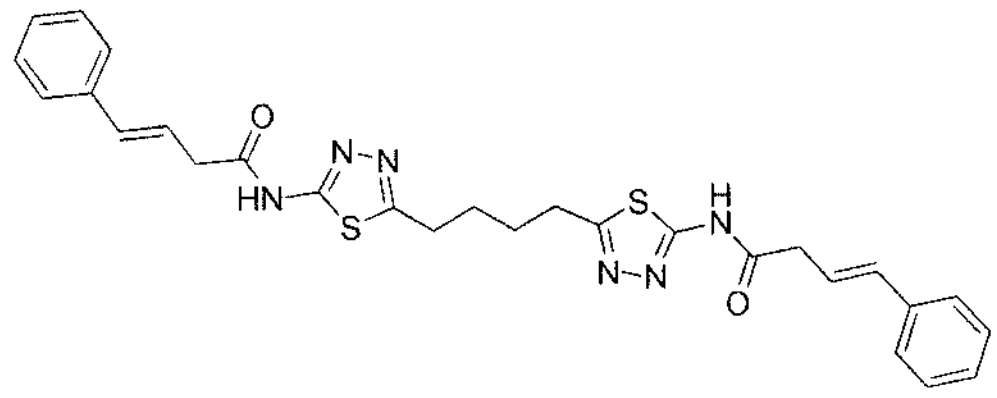

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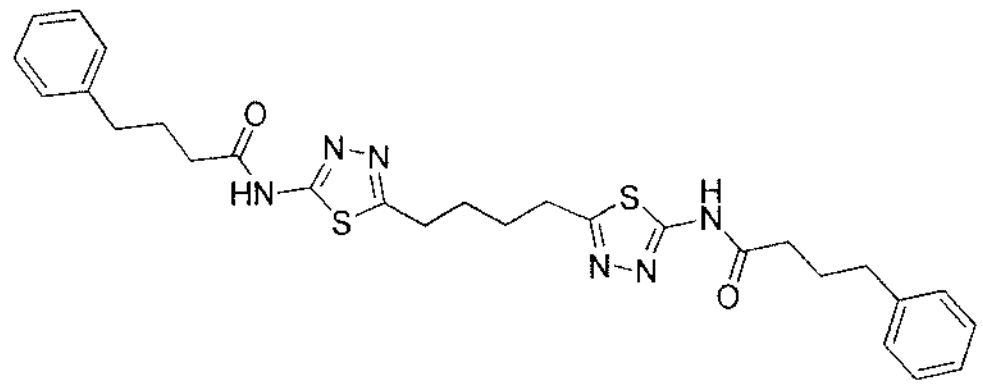
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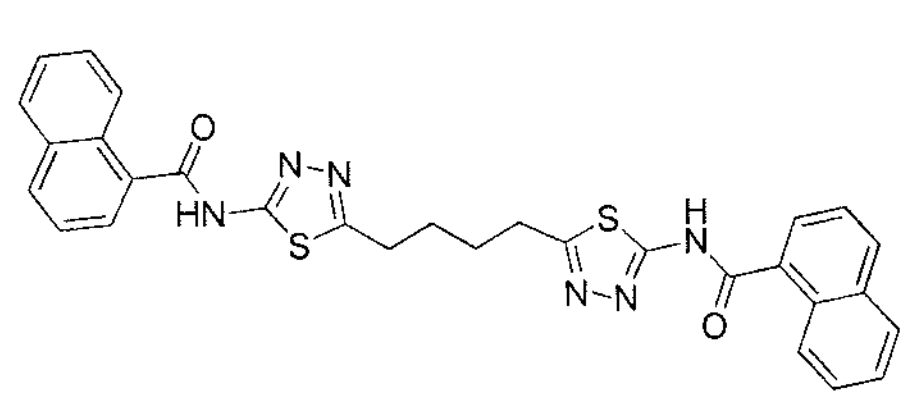
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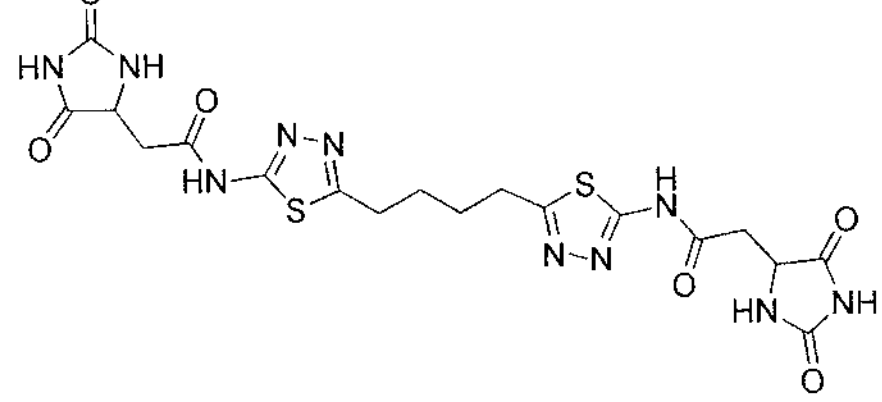
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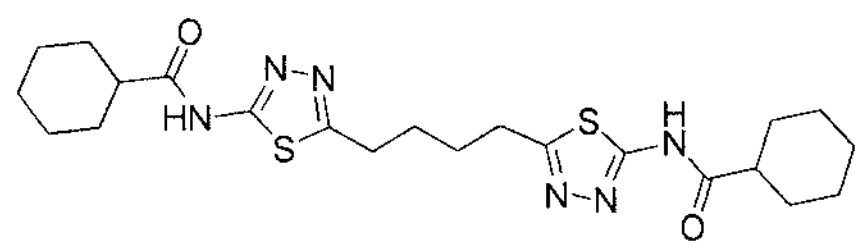
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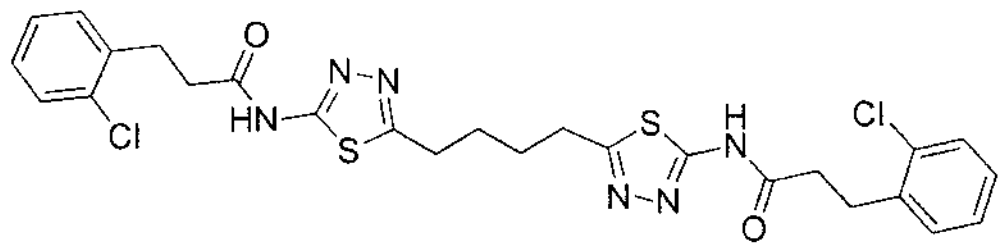
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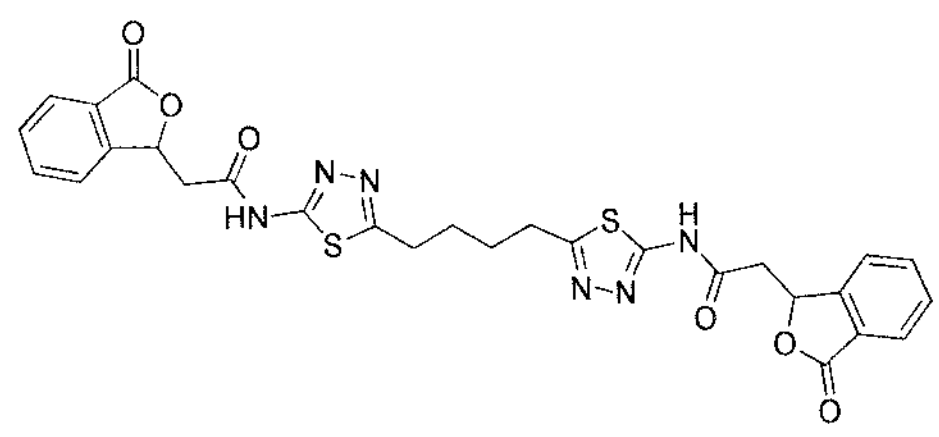
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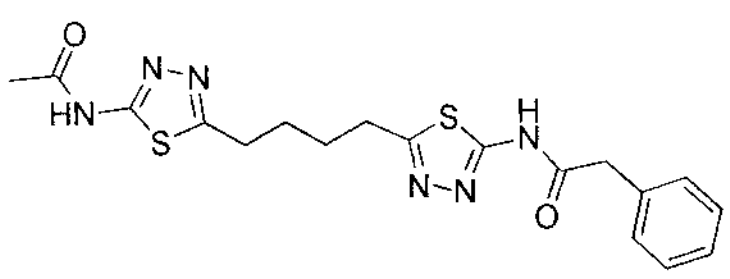
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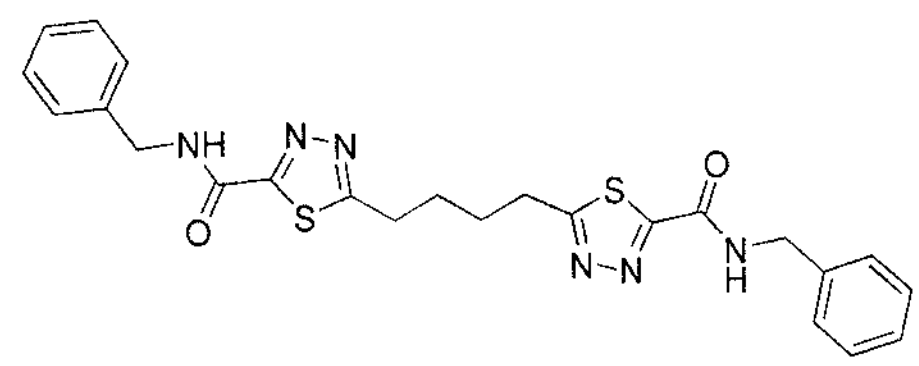
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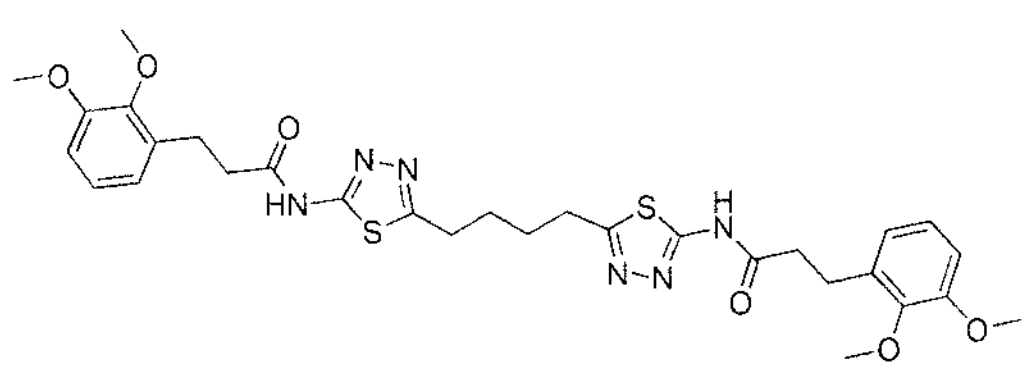
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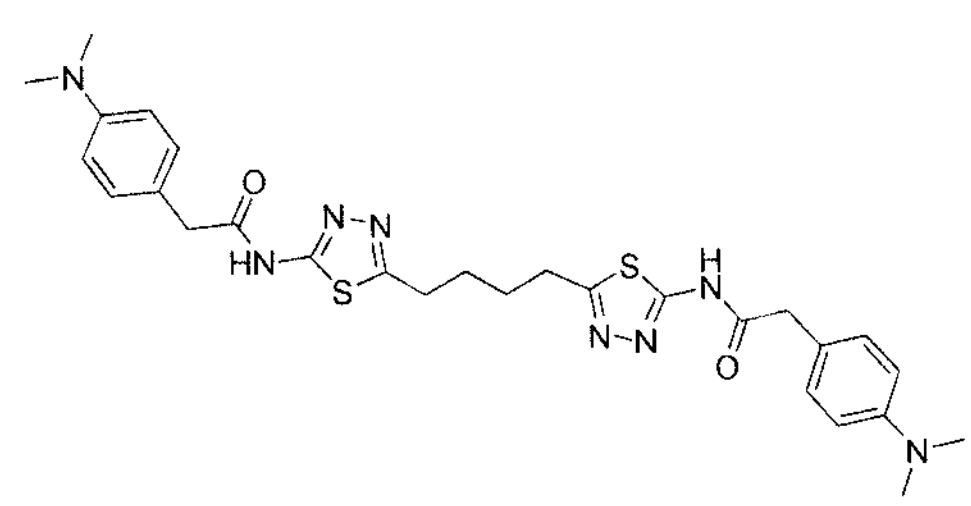
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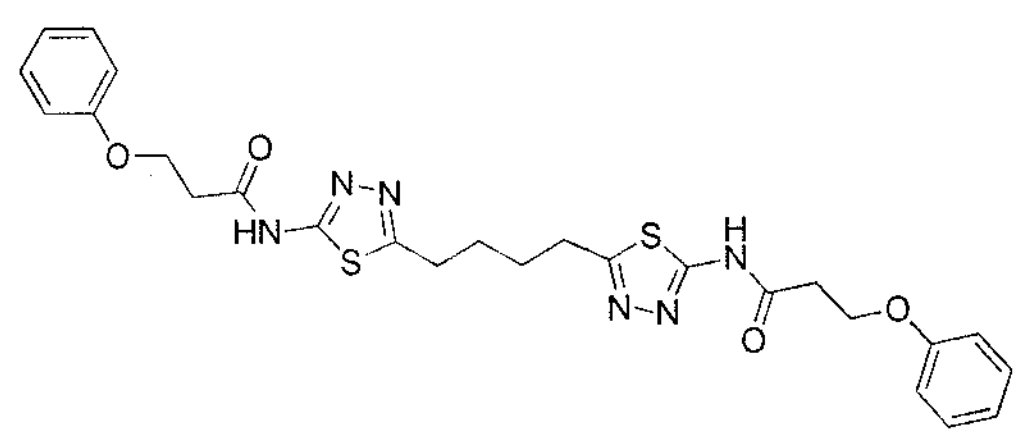
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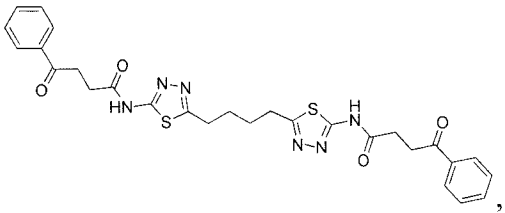
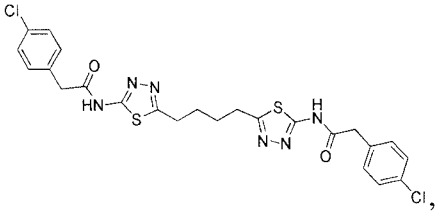
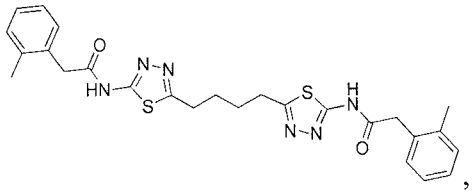
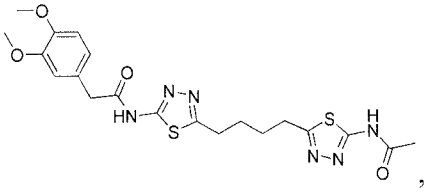
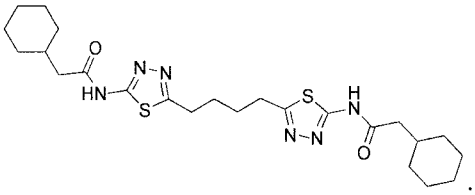
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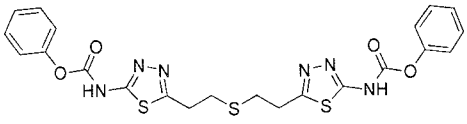
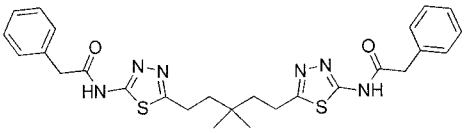
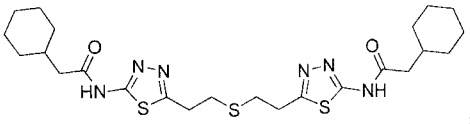
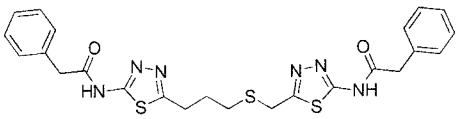
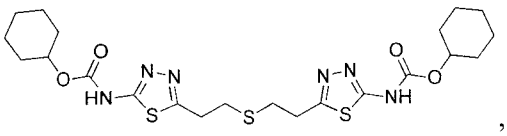
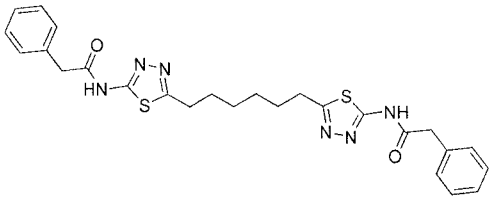
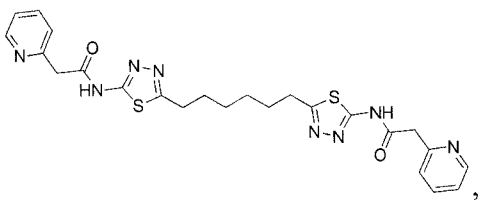
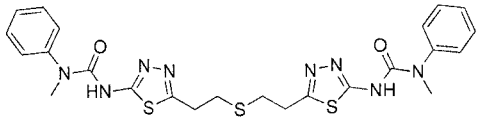
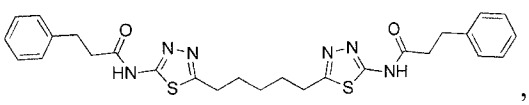
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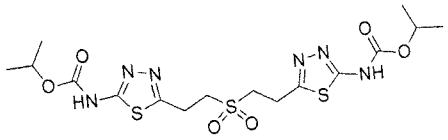
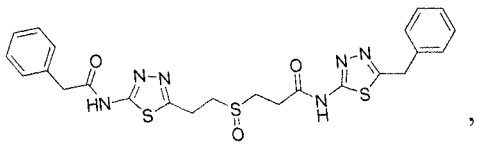
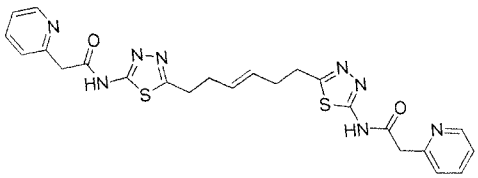
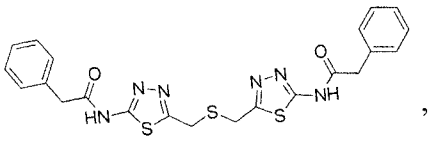
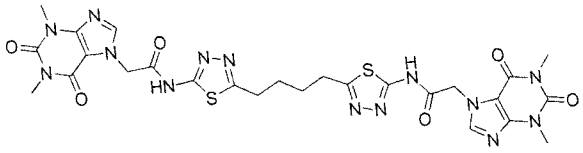
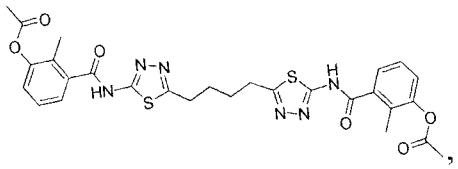
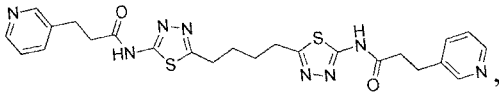
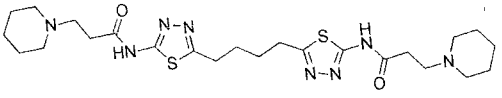
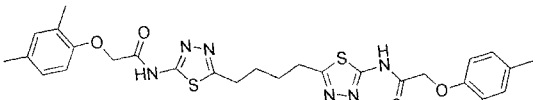
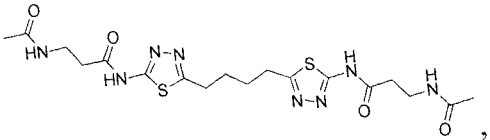
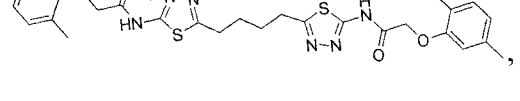
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13. The compound of claim 1, wherein the compound is selected from the group consisting of:

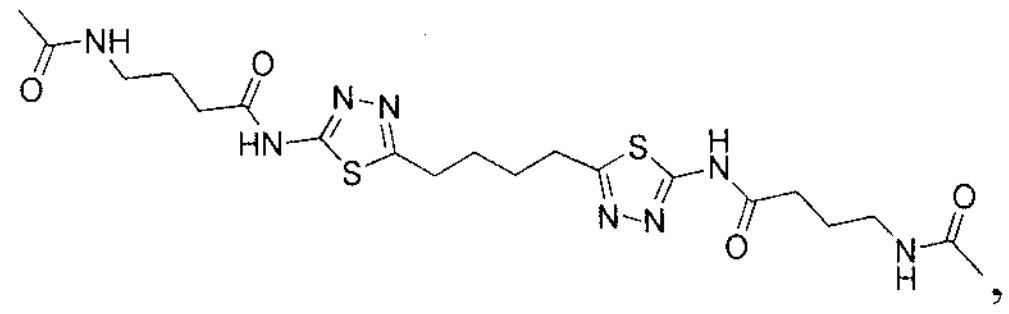

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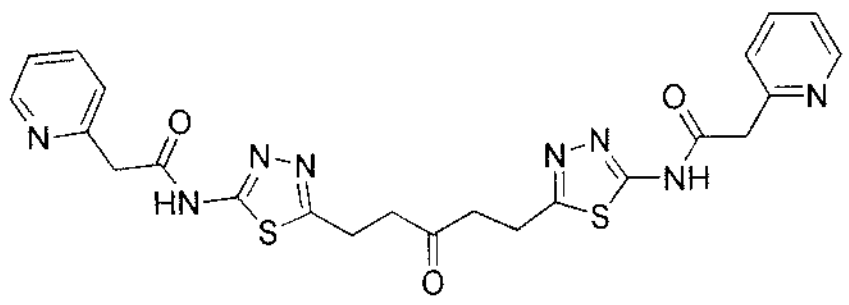

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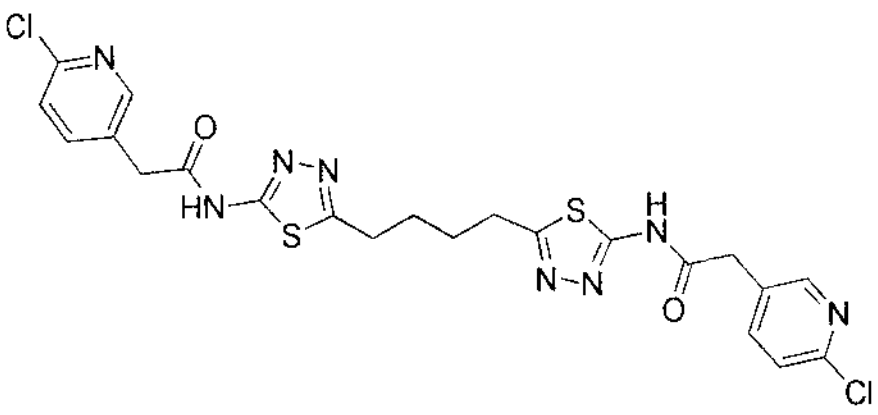
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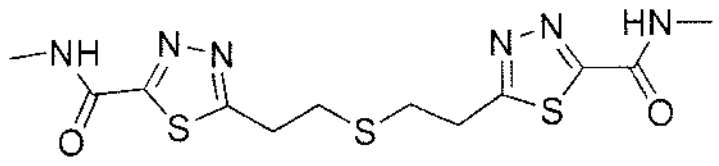
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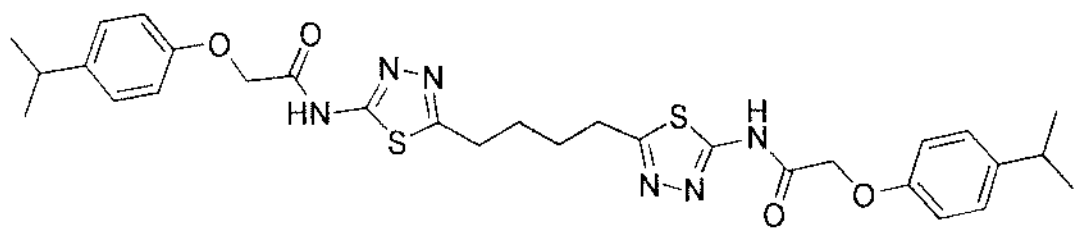
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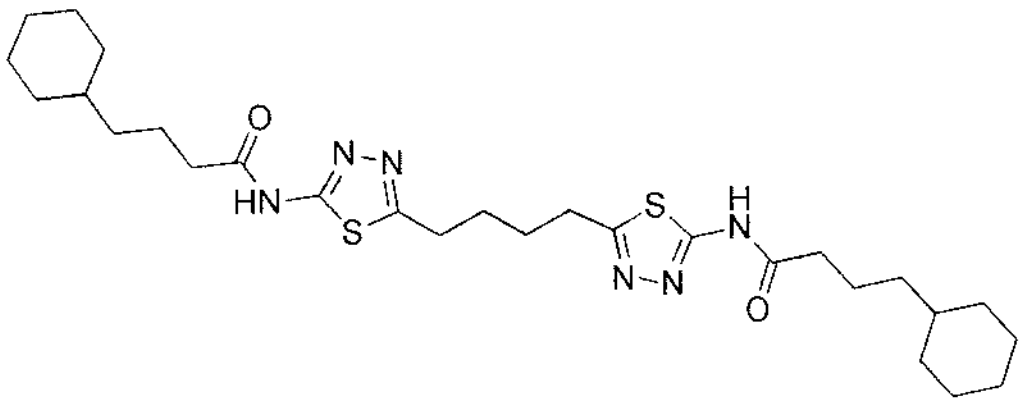
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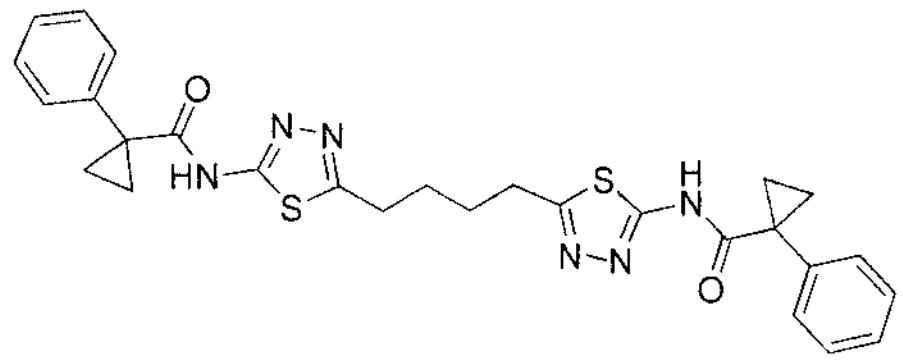
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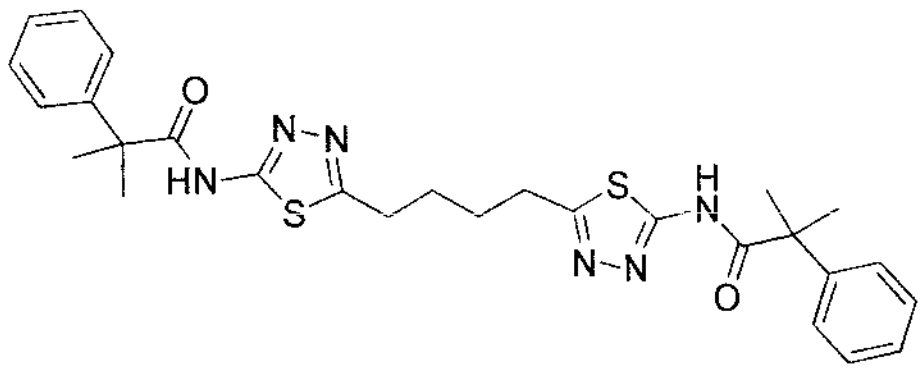
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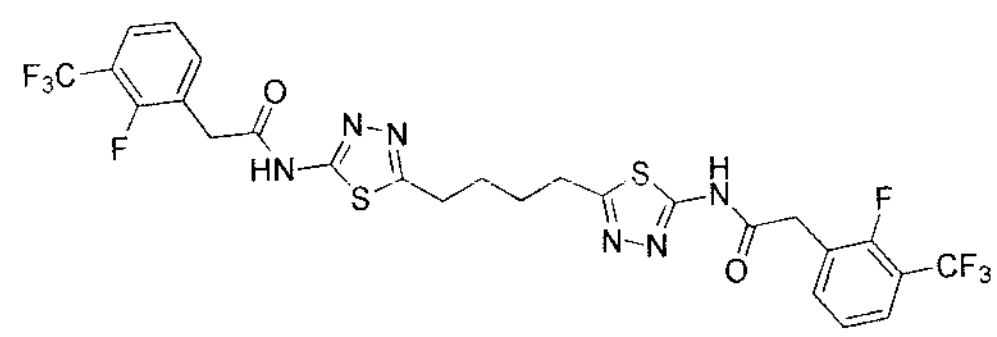
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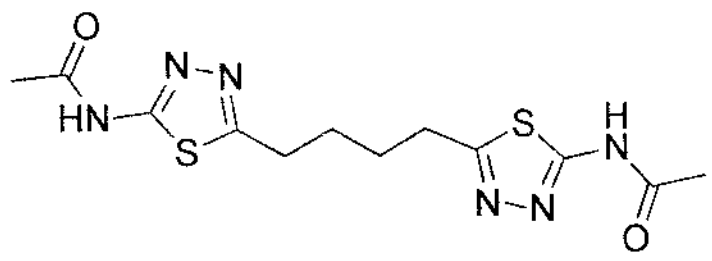
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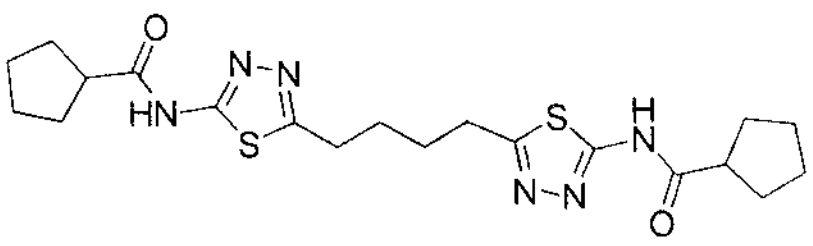
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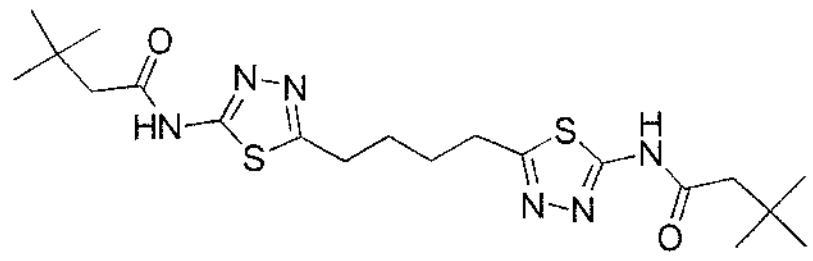
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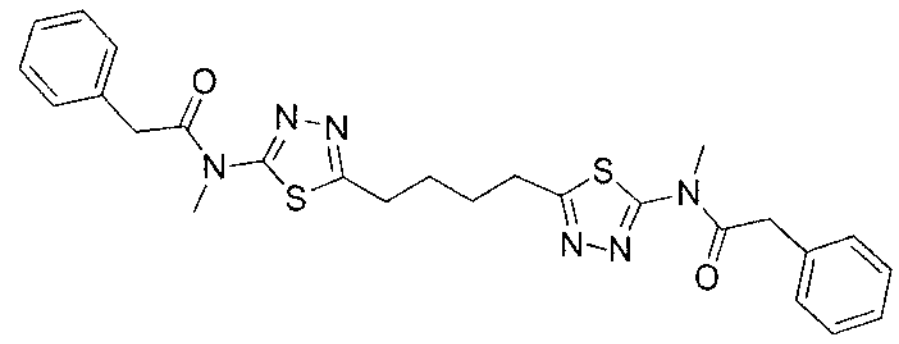
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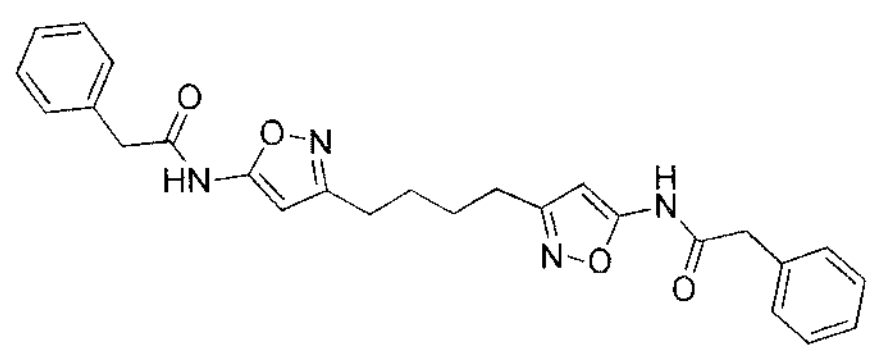
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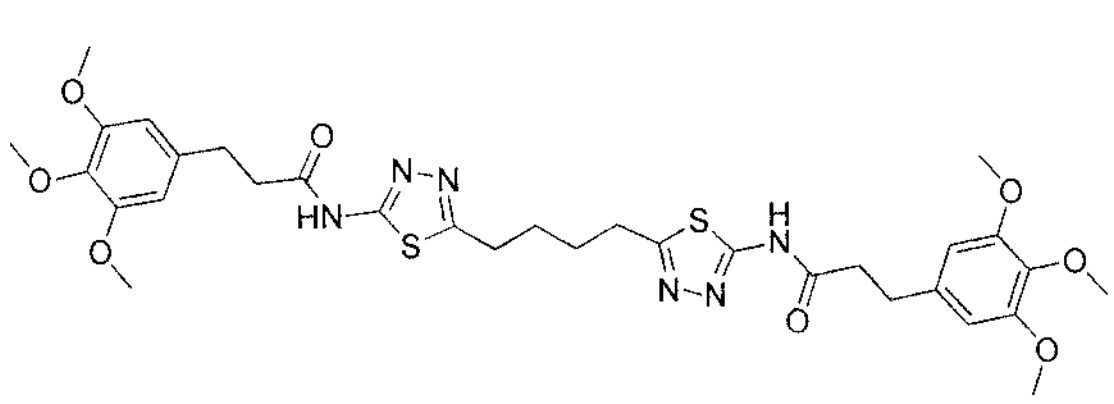
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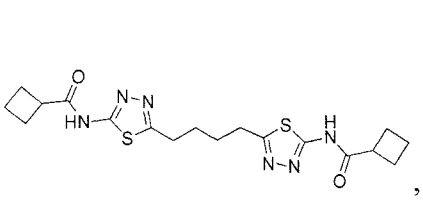
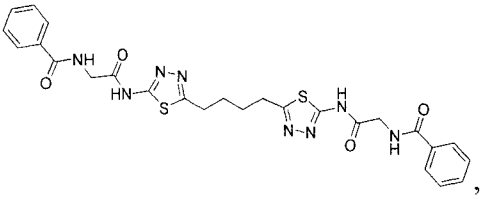
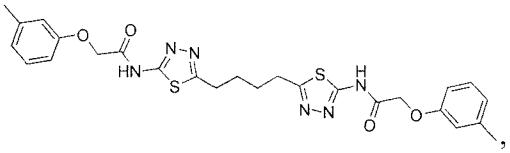
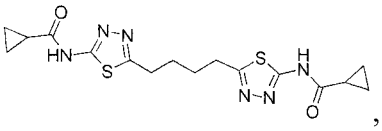
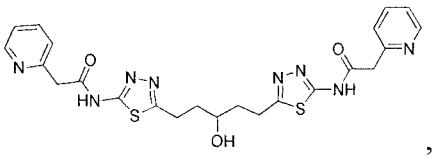
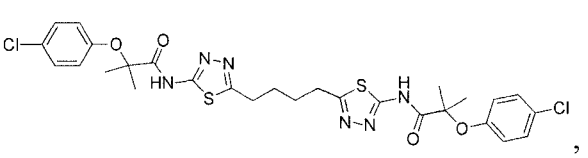
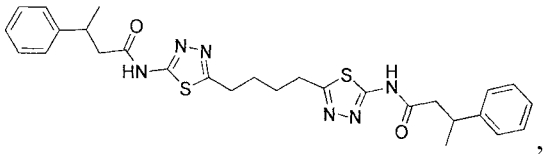
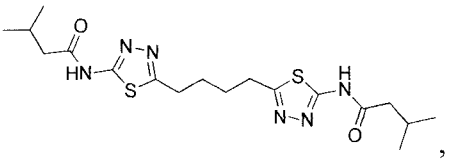
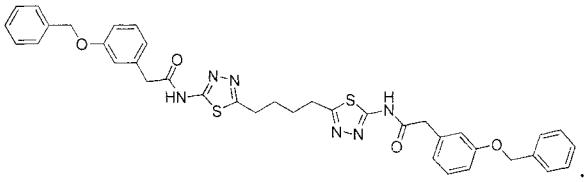
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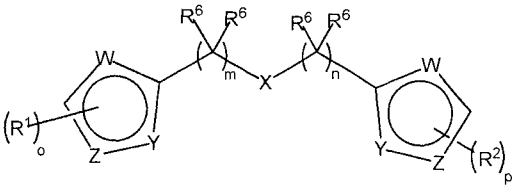
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14. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein:


Formula (I),

X is -S(O)- or -SO_2-;

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_{1-6} alkylene-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_{1-6} alkylene-C(O)-R^4, -$N(R^3)$-C(O)-C_{1-6} 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_{1-6} 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 -S(O)- or -SO_2-, the sum of m and n is from 2 to 4;

o is 1, 2 or 3; and

p is 1, 2 or 3.

15. A pharmaceutical composition comprising a compound of claim 14 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or adjuvant.