COMPOUNDS AND THEIR METHODS OF USE

CLAIM OF PRIORITY

This application claims priority from International Application No. PCT/CN2012/085023, filed November 22, 2012, and International Application No. PCT/CN2013/000294, filed March 15, 2013, each of which is incorporated herein by reference in its entirety.

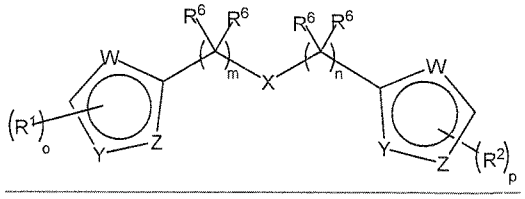
BACKGROUND OF INVENTION

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 generate 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 ~~OF INVENTION~~

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 of the present disclosure, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof:



Formula (I),

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.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a use of a compound or a composition as disclosed herein in the manufacture of a medicament for treating cancer, wherein the cancer is selected from: lung cancer, breast cancer, hepatocellular carcinoma, osteosarcoma, chondrosarcoma, and mesothelioma.

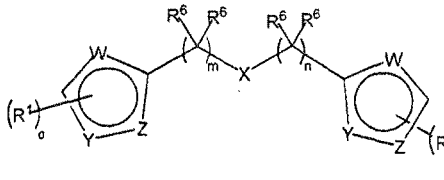
In yet another aspect of the present disclosure there is provided a compound or a composition as disclosed herein for use in treating cancer.

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

CLAIMS

What is claimed is:

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



Formula (I),

wherein

X is an optionally substituted C_3-C_7 cycloalkylene;

each W, Y and Z is independently –S-, -CH=, -O-, -N=, or –NH-, provided that for each ring 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, -O-heterocyclyl,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, -O-heterocyclyl, 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 $-NH_2$ or -NH-C(O)-phenyl; (2) X is other than substituted cyclobutyl or substituted cyclopentyl; and (3) when X is unsubstituted cyclopropyl, and m and n are both 1, then R^1 and R^2 are not both -NH-C(O)-benzyl.

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 o is 1 and p is 1.

4. The compound of claim 1, wherein m is 0 and n is 0.

5. The compound of claim 1, wherein n is 1 and m is 1.

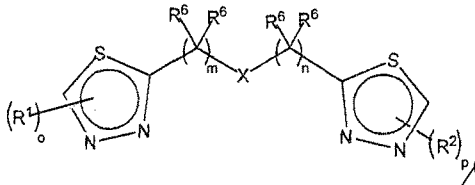
6. The compound of claim 5, wherein each R^6 is hydrogen.

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

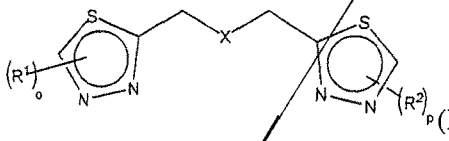
8. The compound of claim 1, wherein R^1 and R^2 are different.

9. The compound of claim 1, wherein R^1 and R^2 are each $-N(R^3)-C(O)-R^4$ 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.

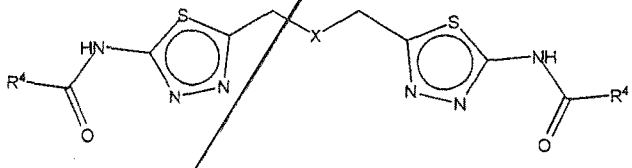
10. The compound of claim 1, wherein the compound is a compound of Formula (II):


(II).

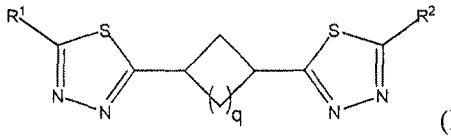
11. The compound of claim 10, wherein the compound is a compound of Formula (IIa):


(IIa).

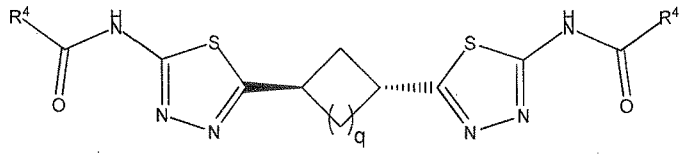
12. The compound of claim 1, wherein the compound is a compound of Formula (III):


(III).

13. The compound of claim 1, wherein the compound is a compound of Formula (IV) and q is 0, 1, 2, 3, or 4:

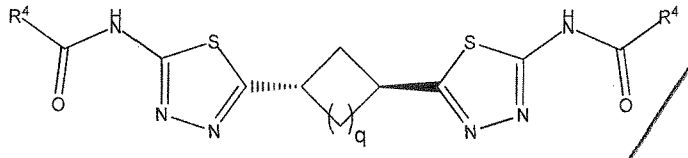

(IV).

14. The compound of claim 1, wherein the compound is a compound of Formula (IVa) and q is 0, 1, 2, 3, or 4:



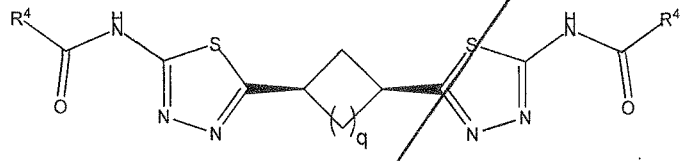
(IVa).

15. The compound of claim 1, wherein the compound is a compound of Formula (IVb) and q is 0, 1, 2, 3, or 4:



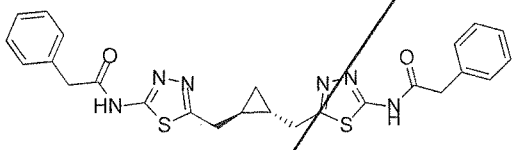
(IVb).

16. The compound of claim 1, wherein the compound is a compound of Formula (IVc) and q is 0, 1, 2, 3, or 4:

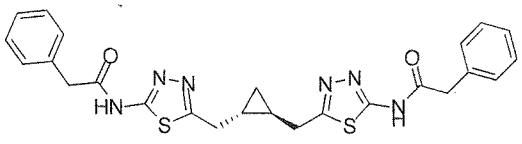


(IVc).

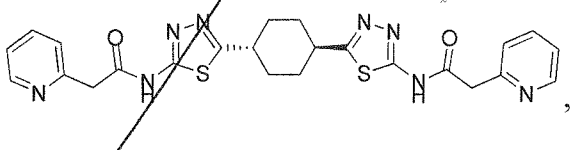
17. The compound of claim 1, which is selected from the group consisting of:



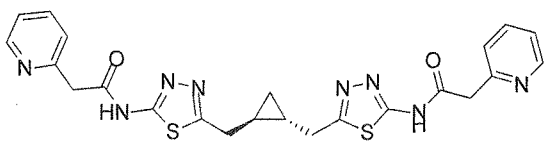
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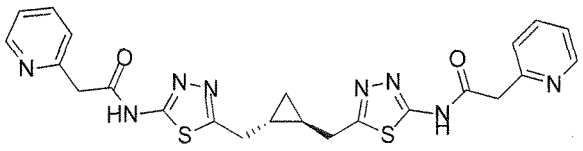
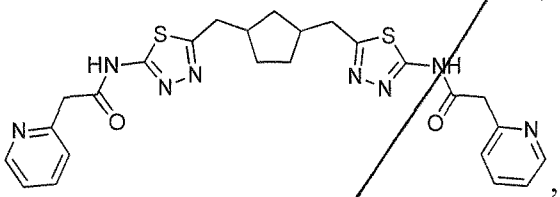
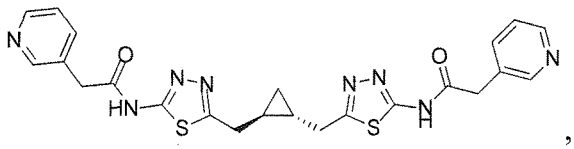
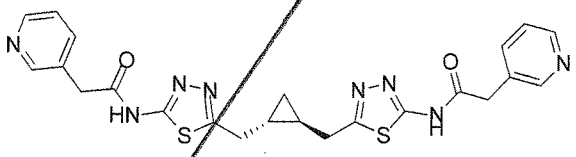
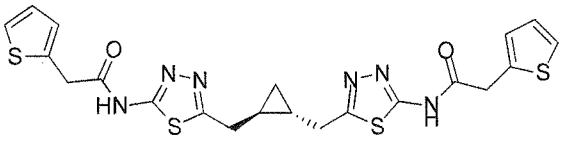
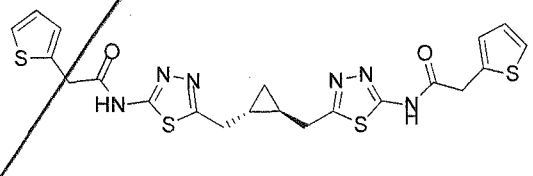
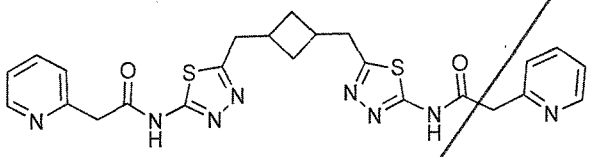
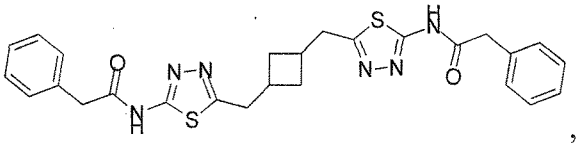
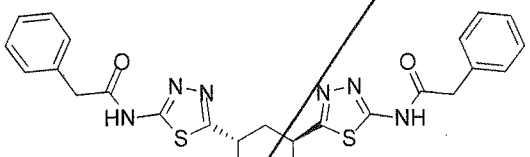
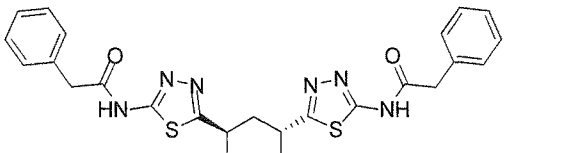
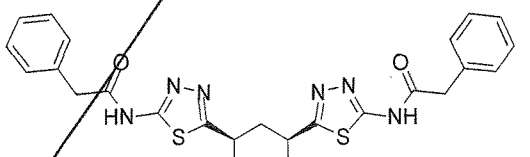
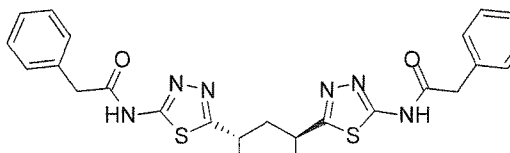
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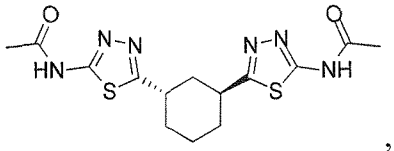
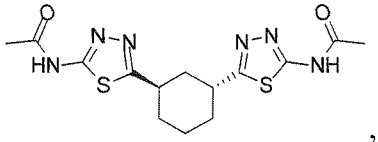
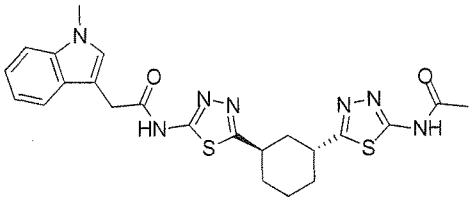
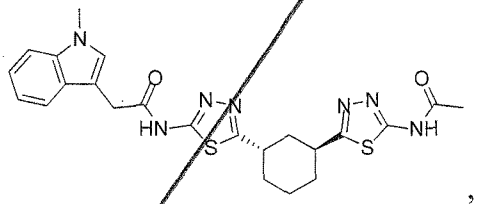
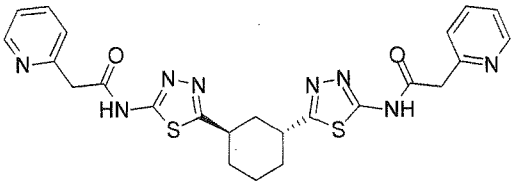
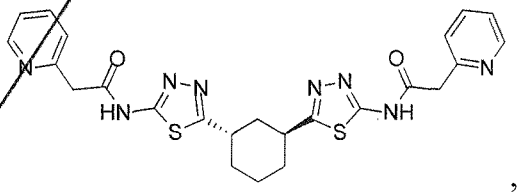
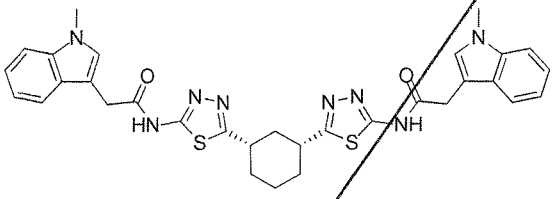
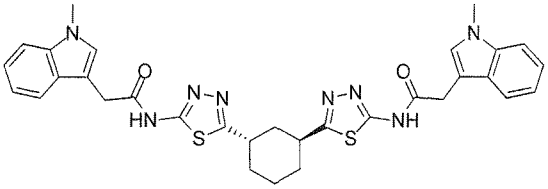
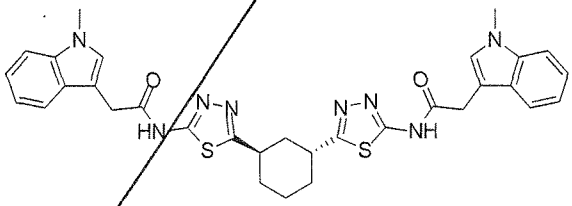
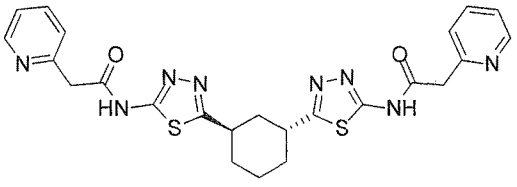
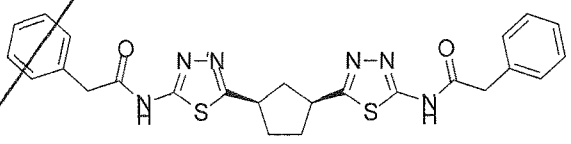
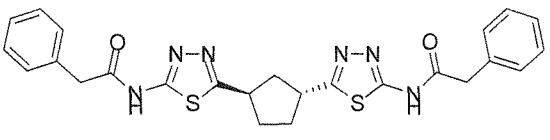


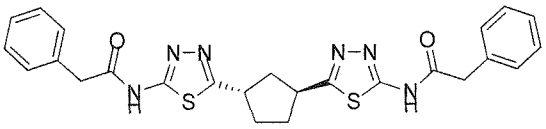
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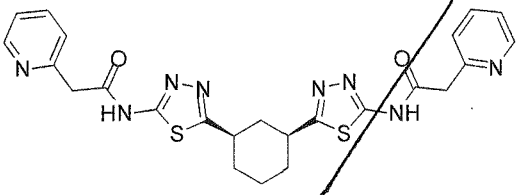
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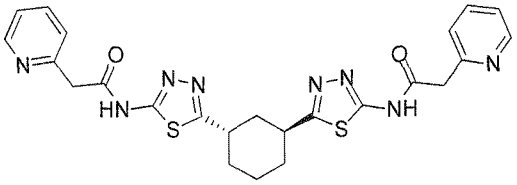

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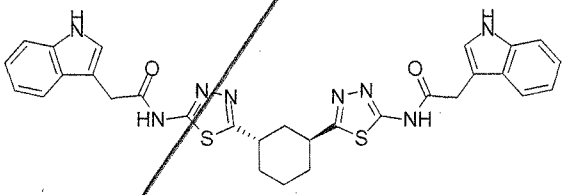
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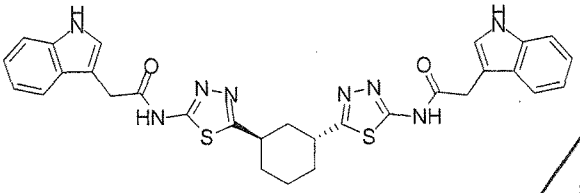
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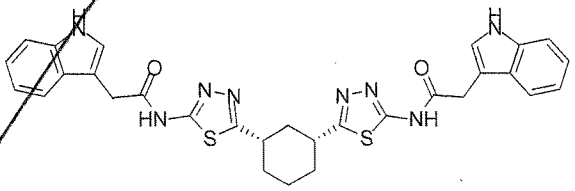
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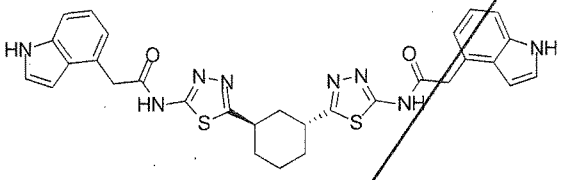
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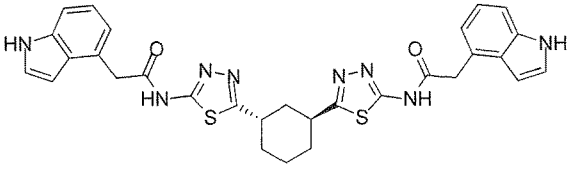
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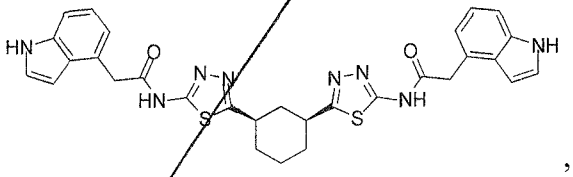
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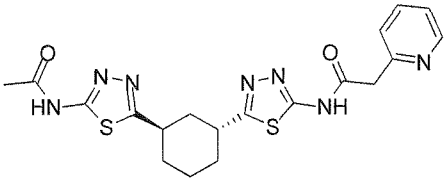
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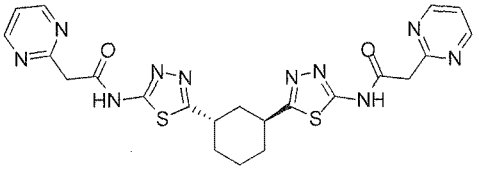
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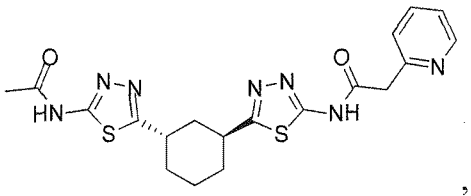
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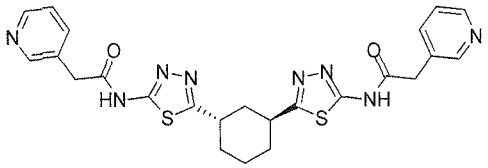
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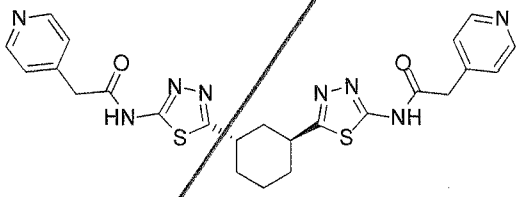
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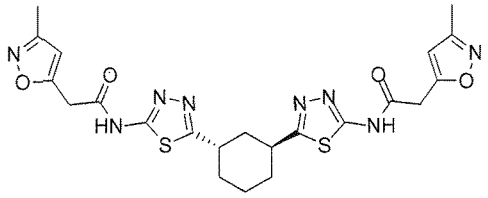
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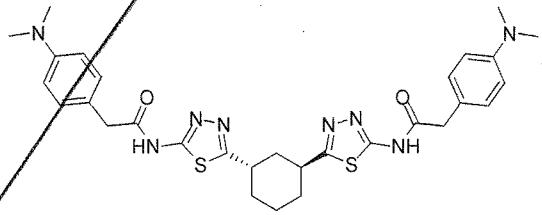
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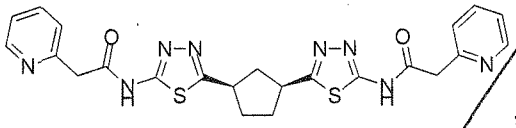
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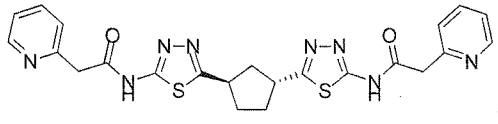
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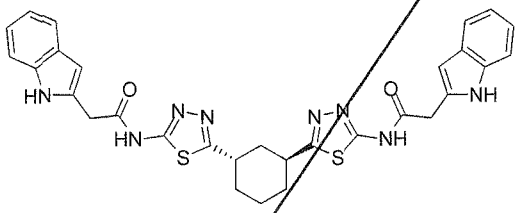
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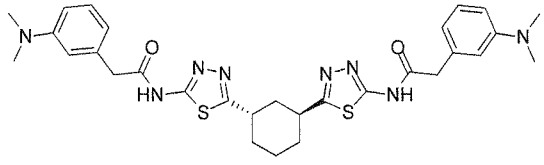
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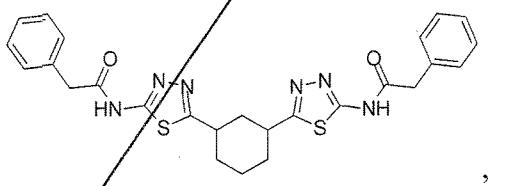
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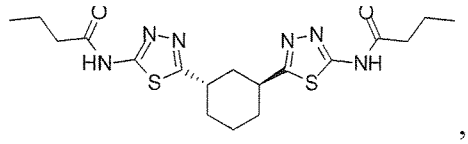
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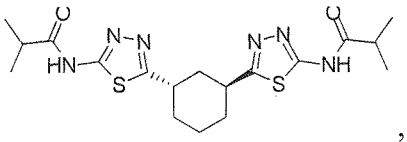
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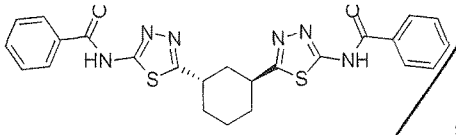
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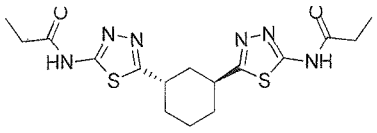
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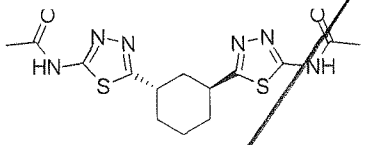
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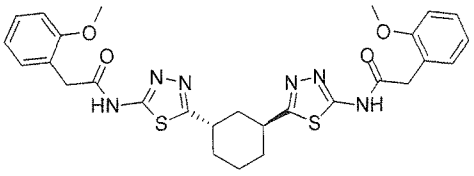
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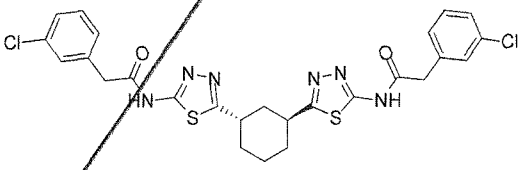
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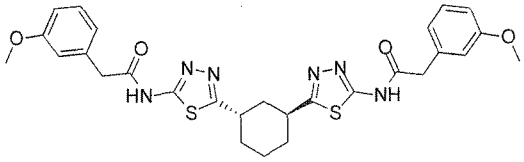
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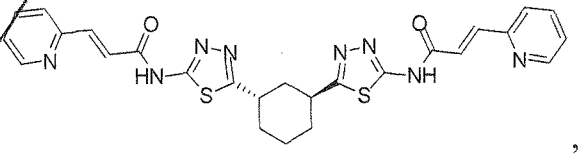
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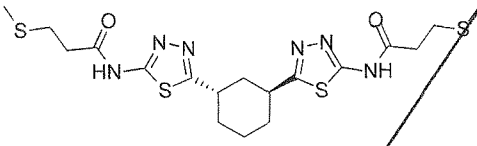
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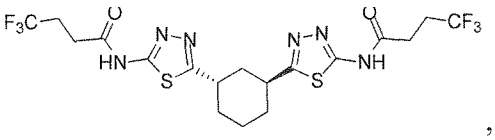
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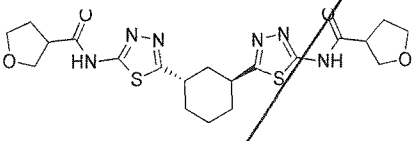
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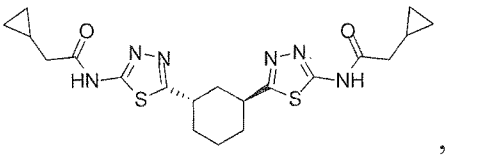
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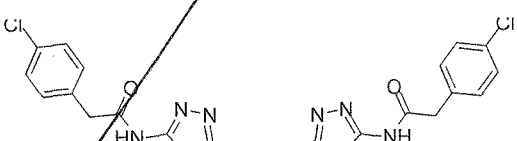
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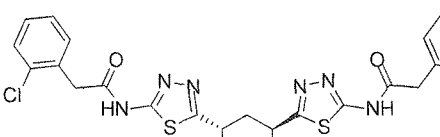
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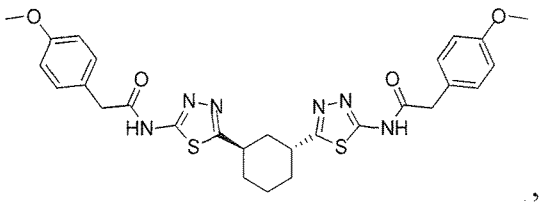


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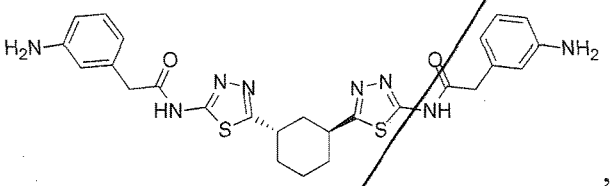


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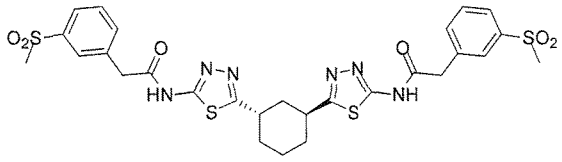
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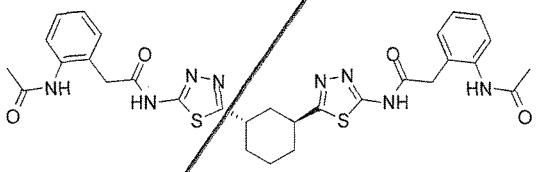
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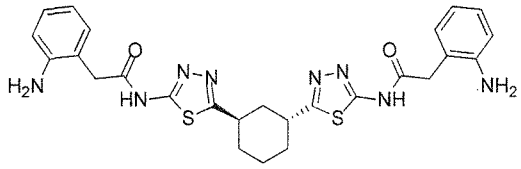
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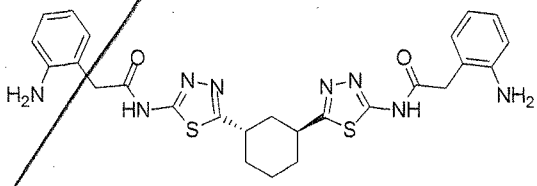
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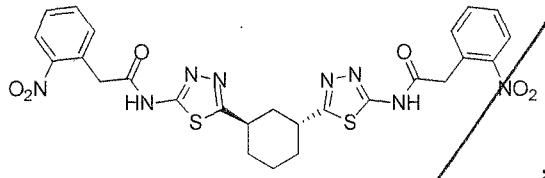
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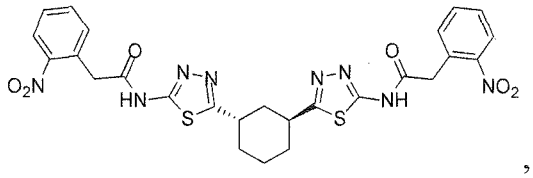
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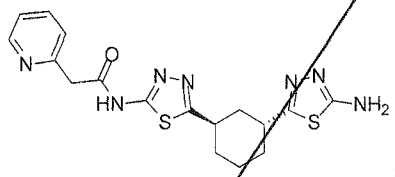
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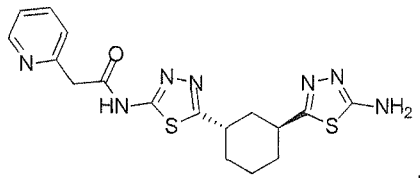
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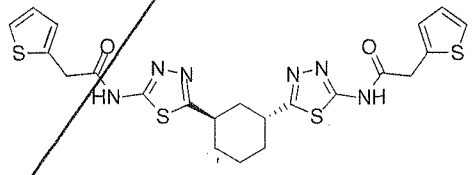
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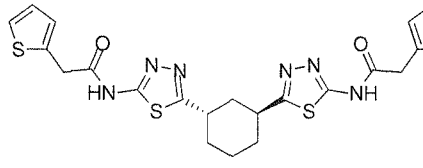
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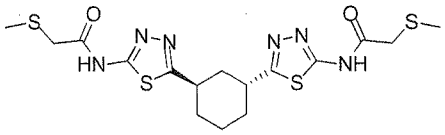
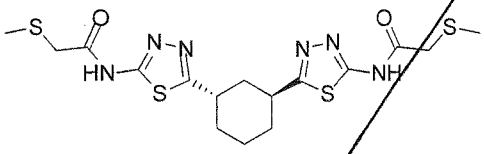
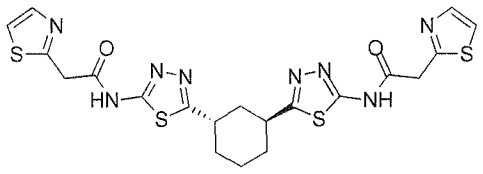
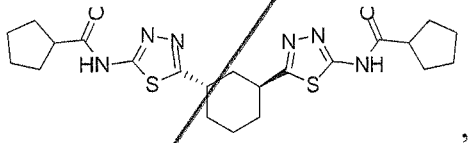
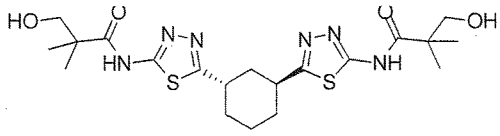
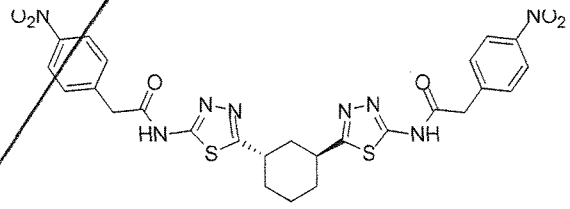
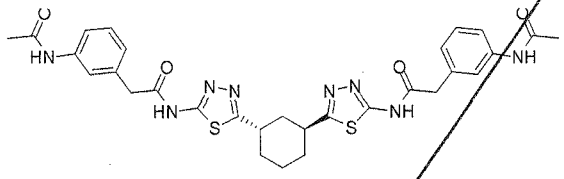
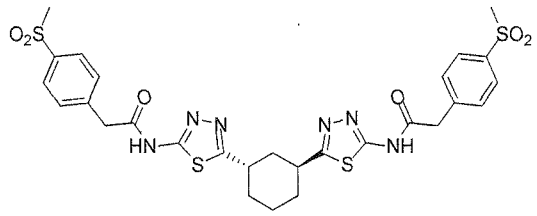
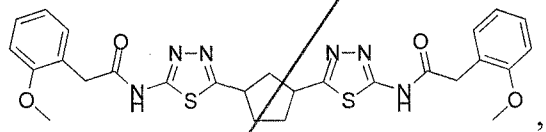
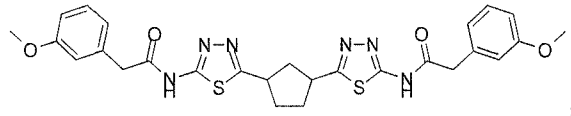
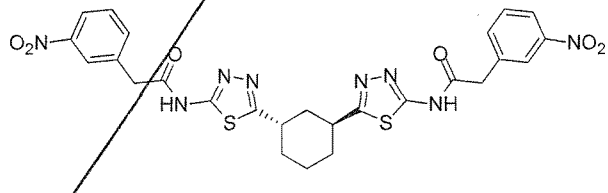
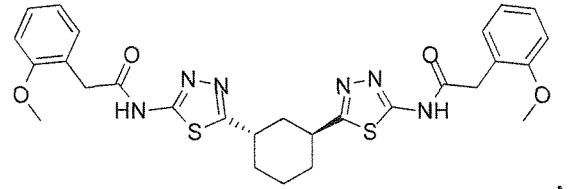
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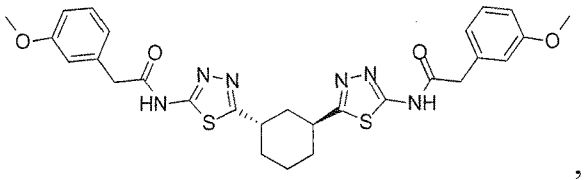
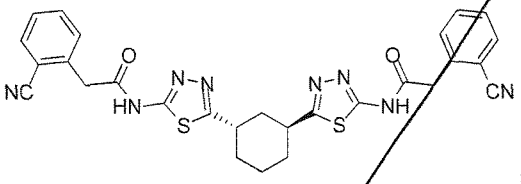
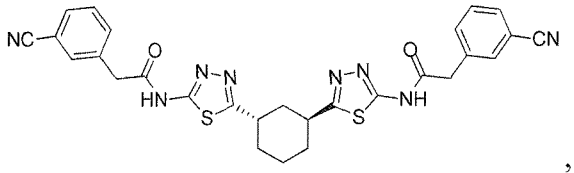
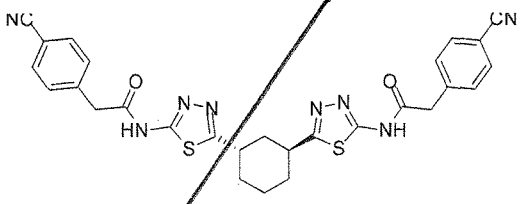
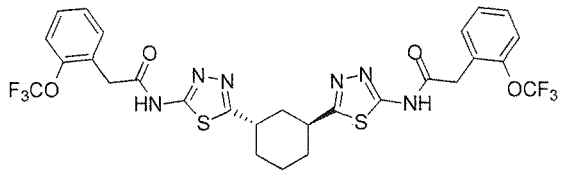
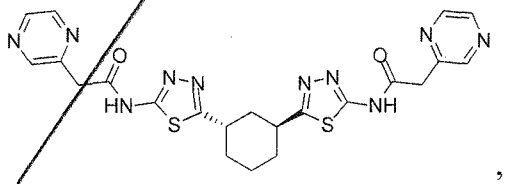
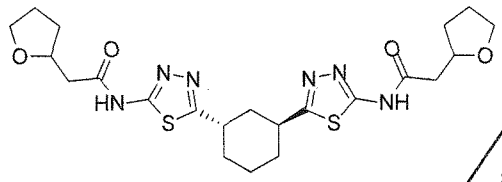
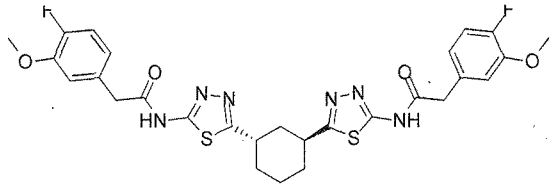
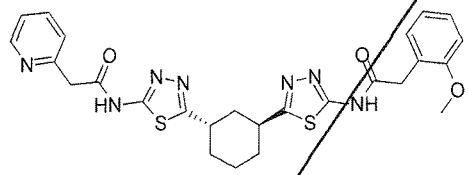
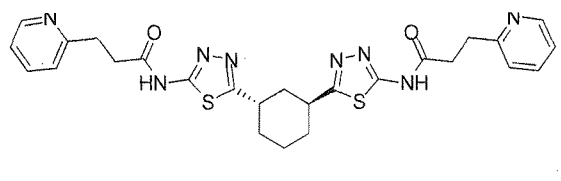
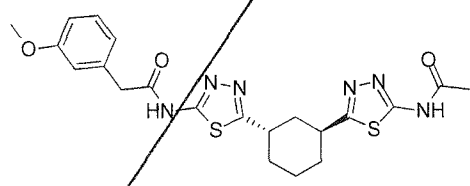
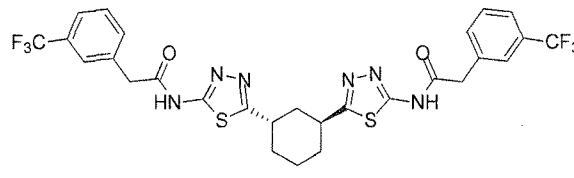


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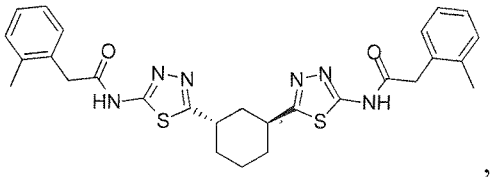
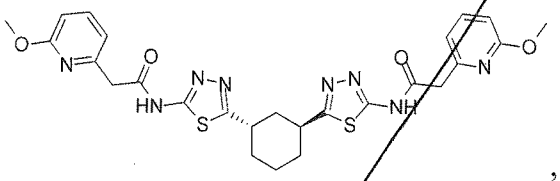
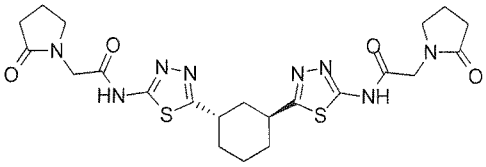
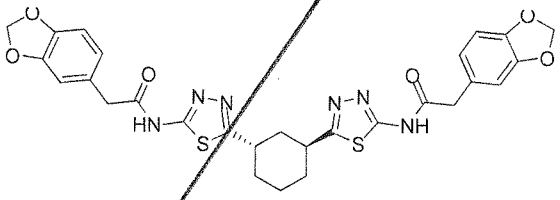
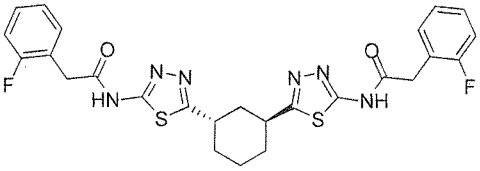
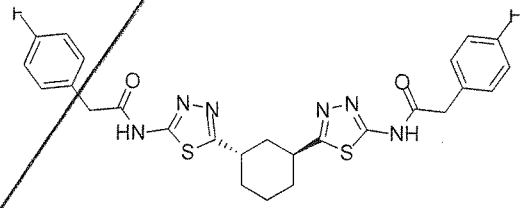
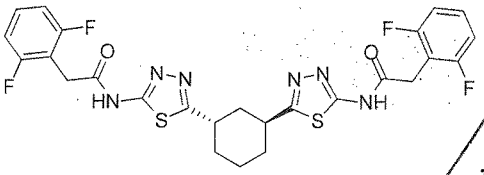
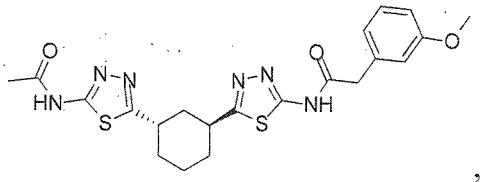
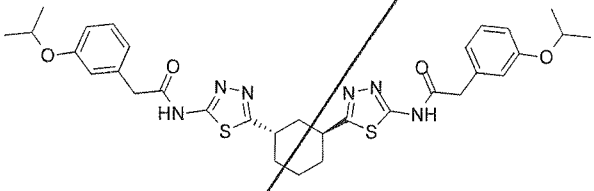
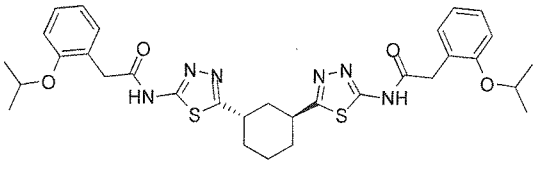
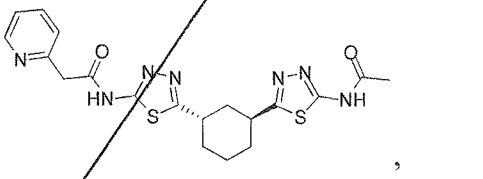
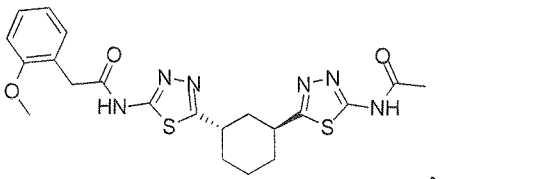
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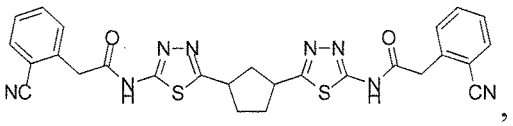
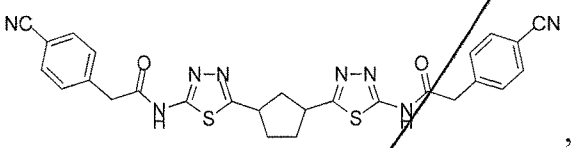
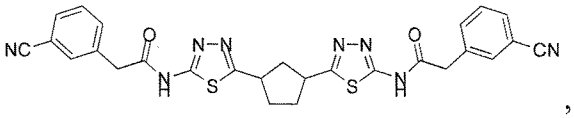
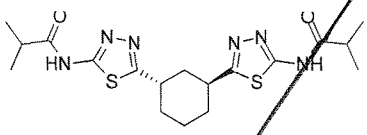
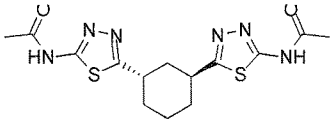
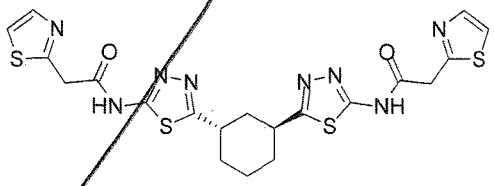
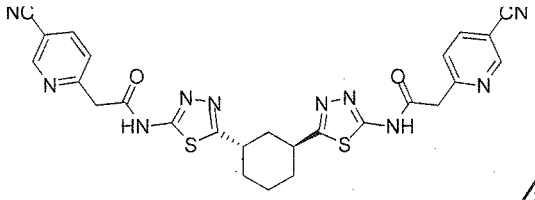
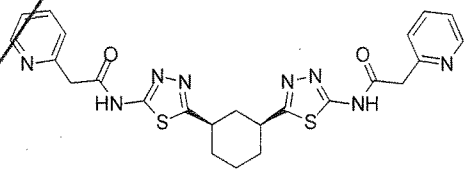
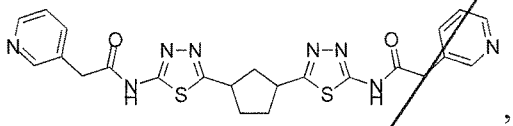
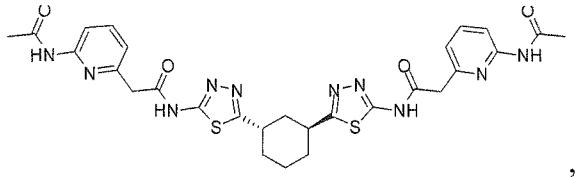
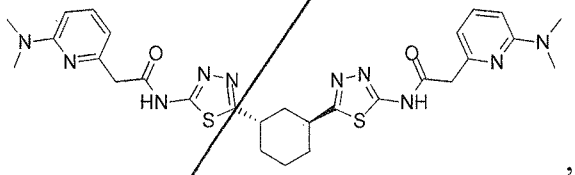
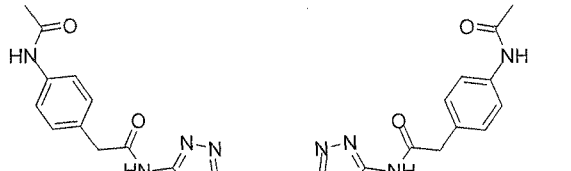
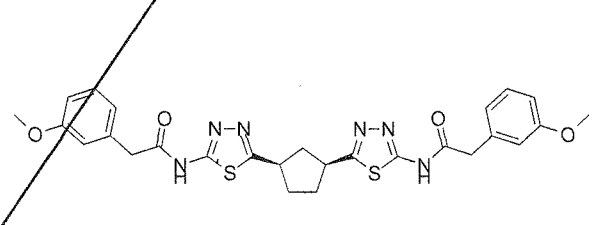
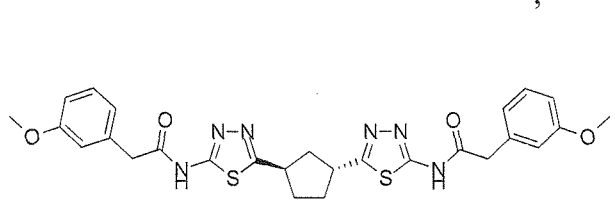
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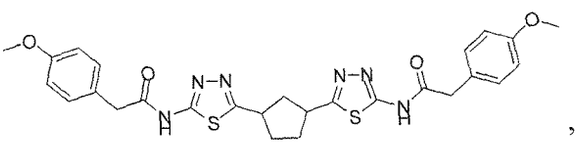
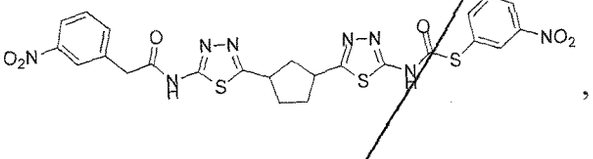
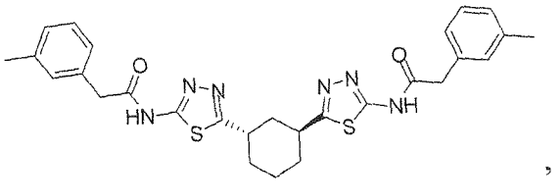
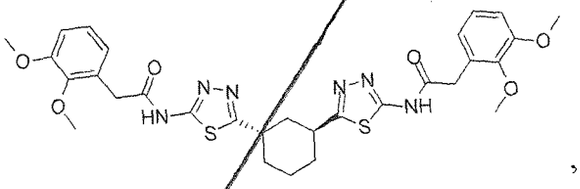
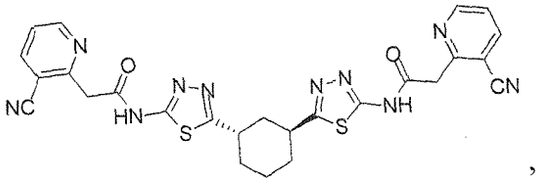
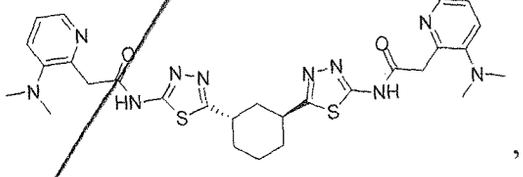
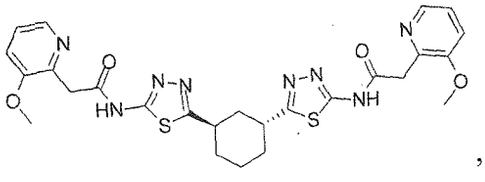
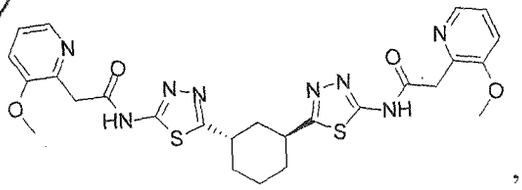
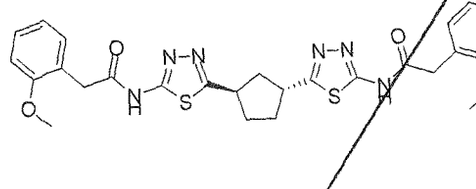
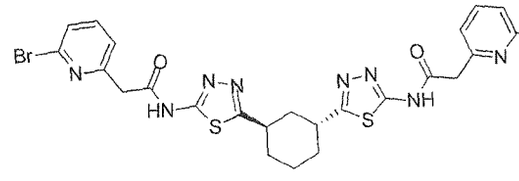
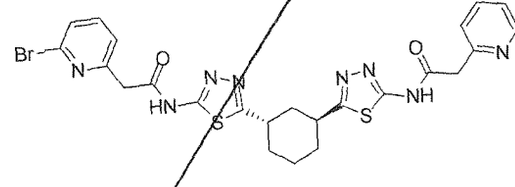
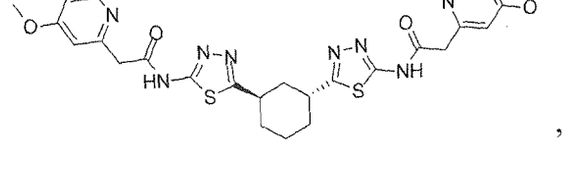
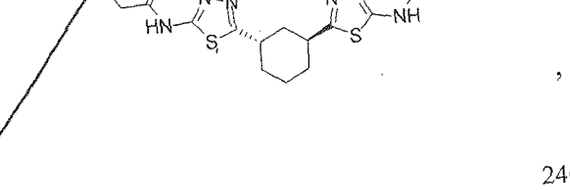
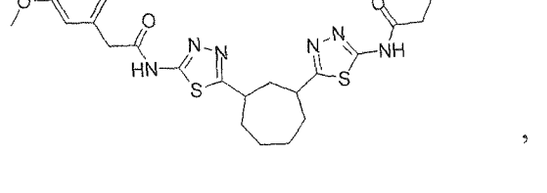
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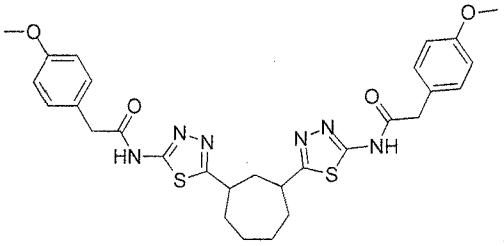
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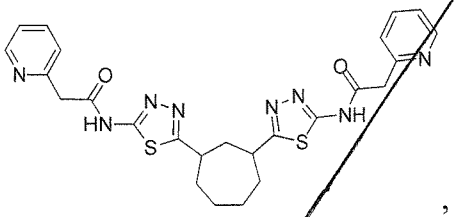

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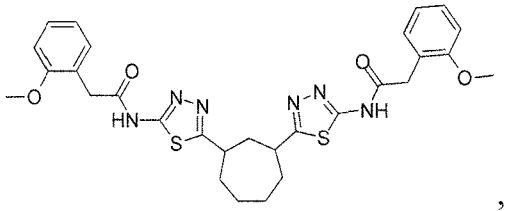
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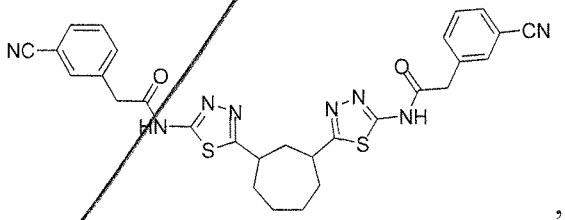
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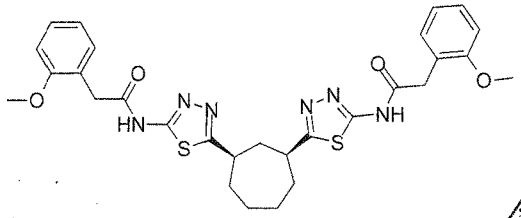
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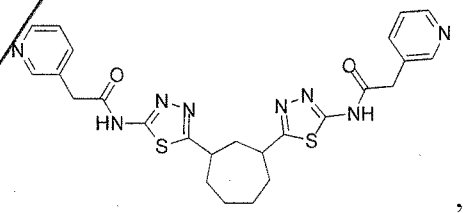
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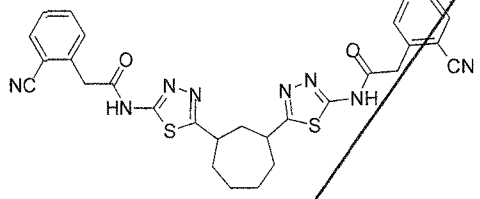
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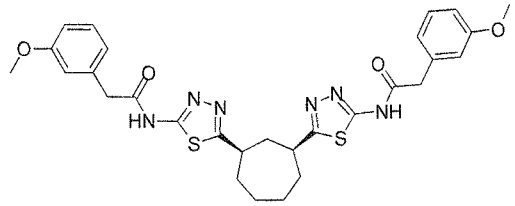
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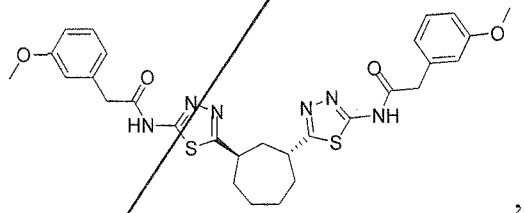
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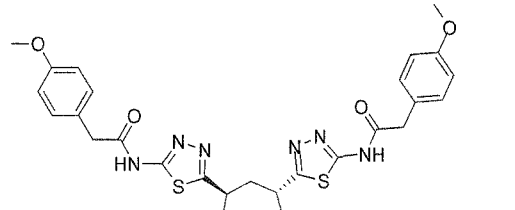


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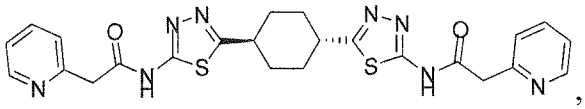
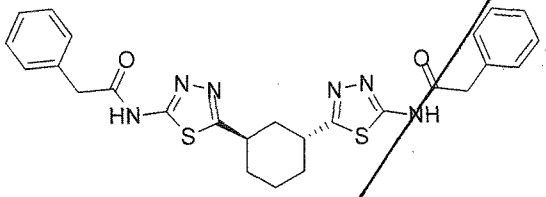
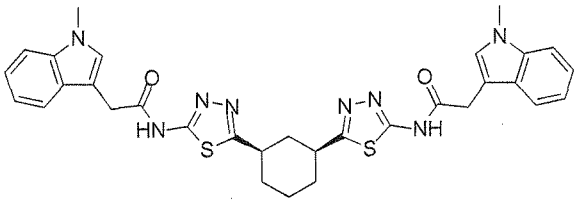


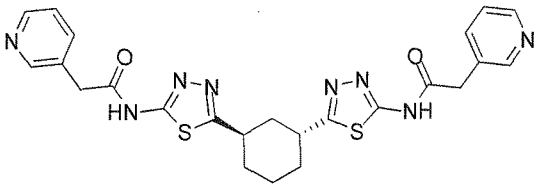
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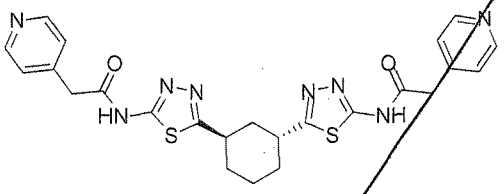
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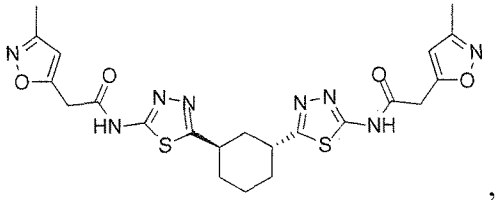

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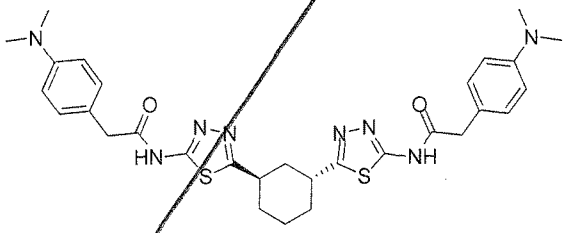
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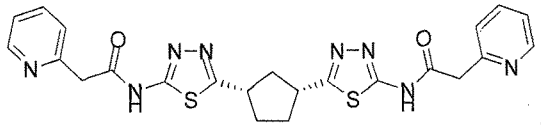
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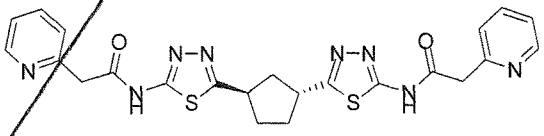
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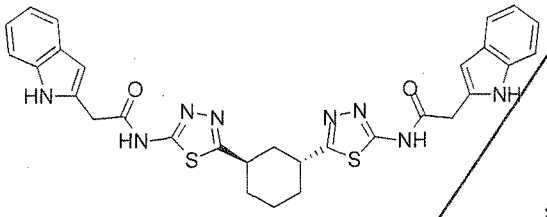
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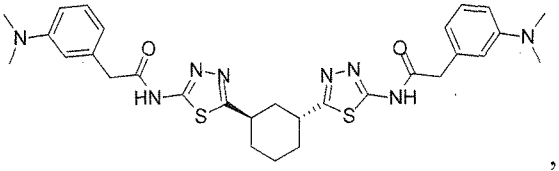
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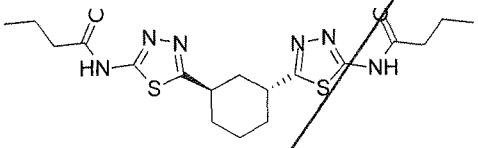
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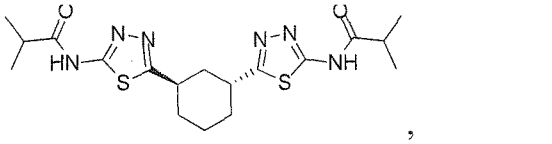
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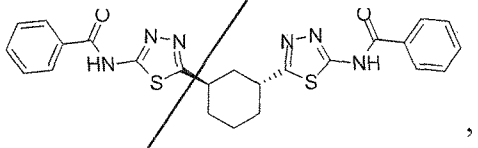
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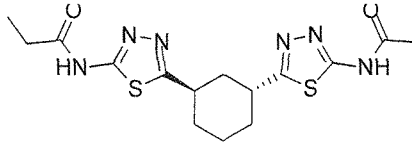
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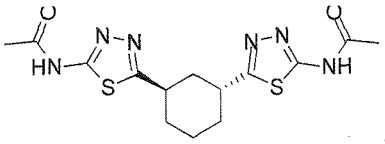
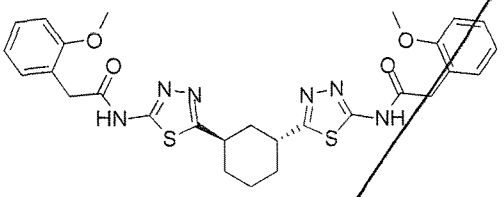
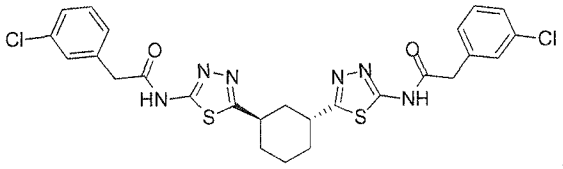
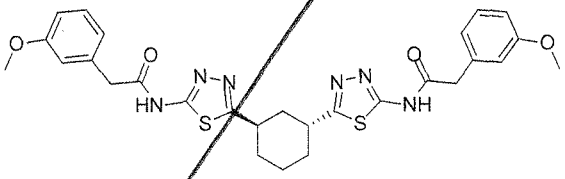
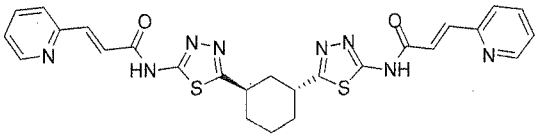
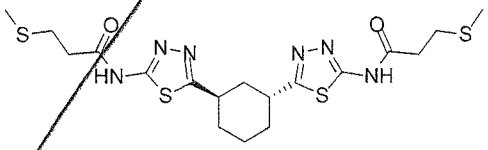
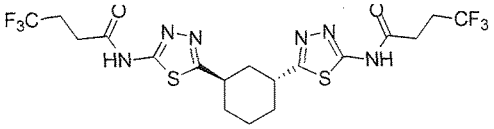
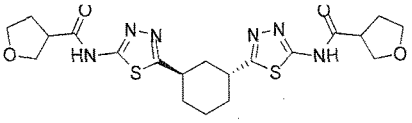
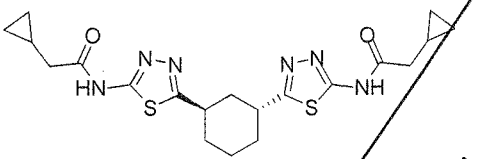
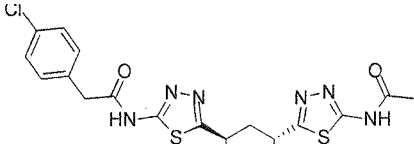


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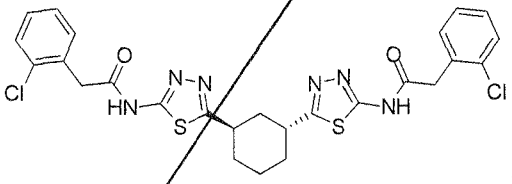
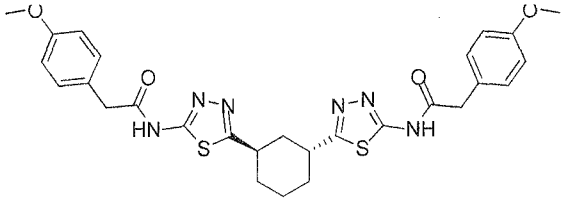
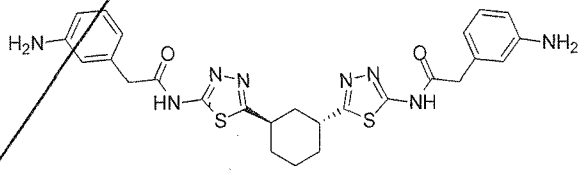
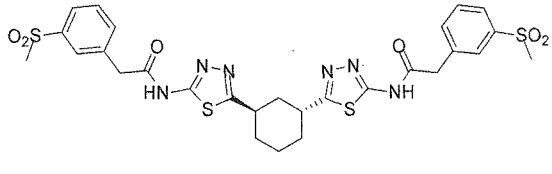


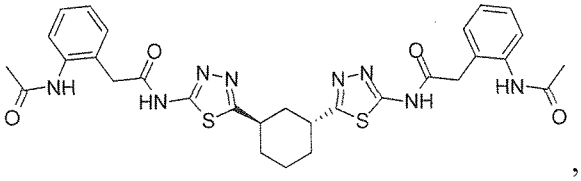
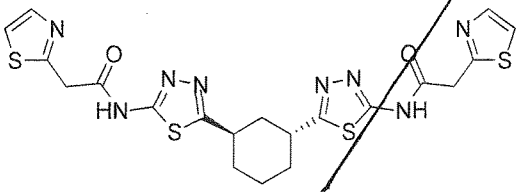
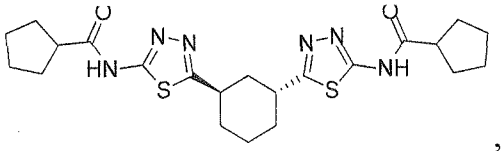
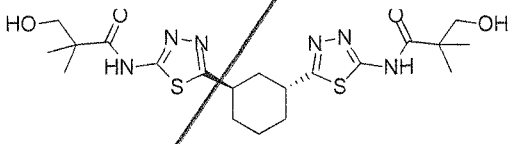
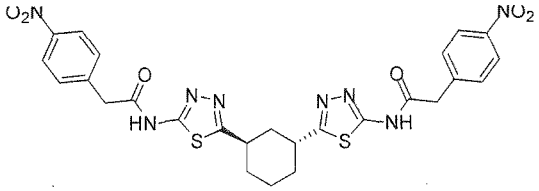
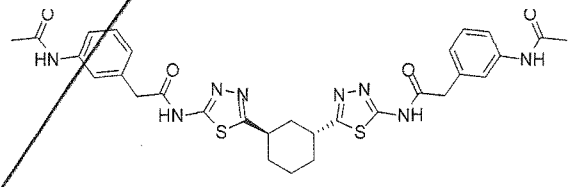
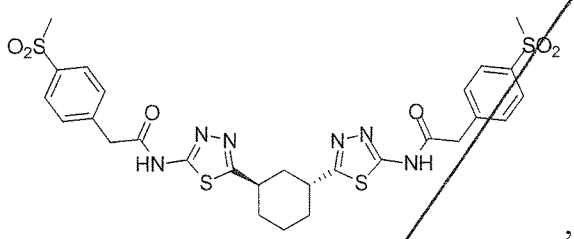
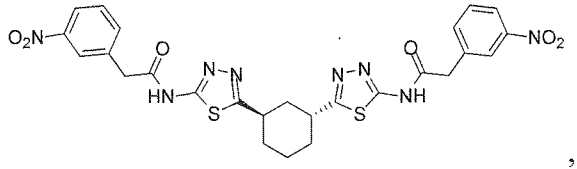
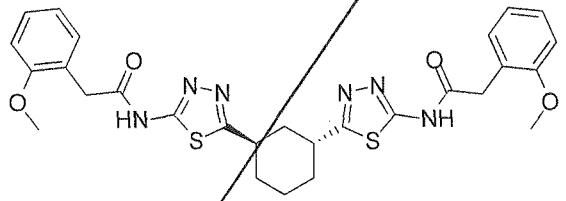
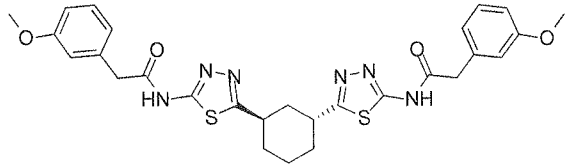
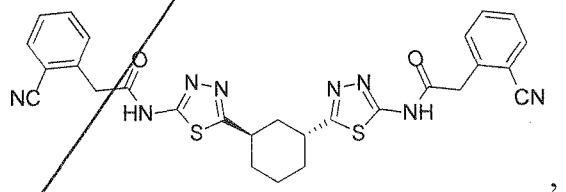
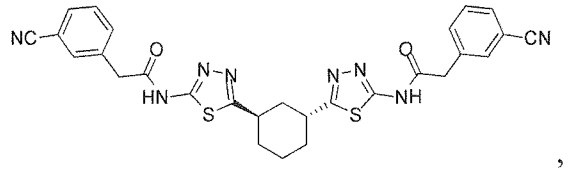
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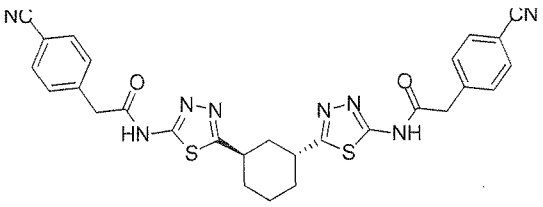
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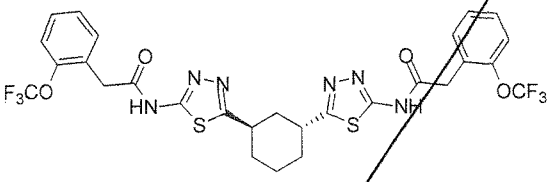

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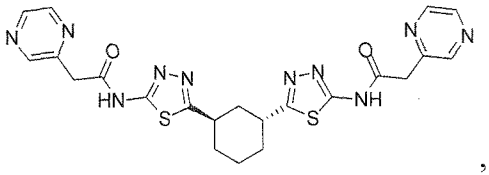
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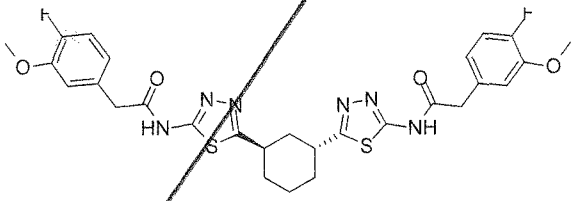
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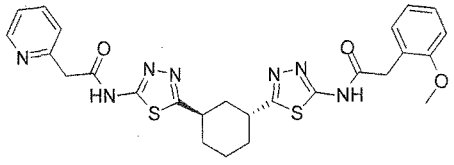
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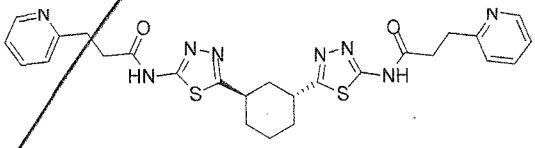
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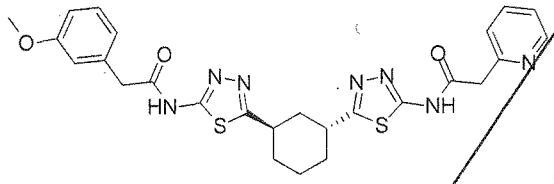
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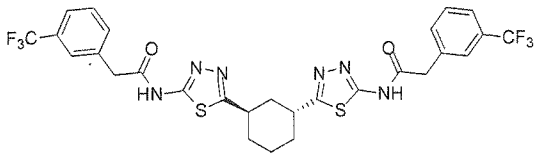
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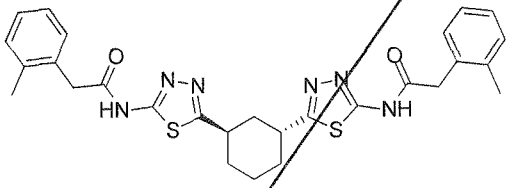
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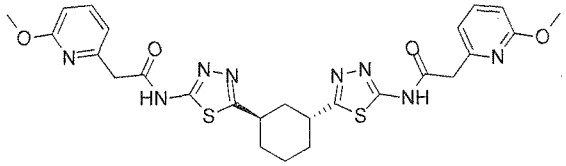
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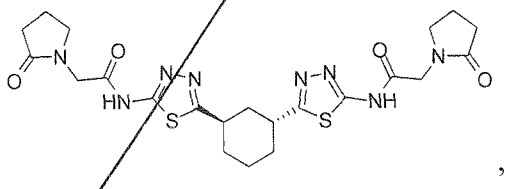
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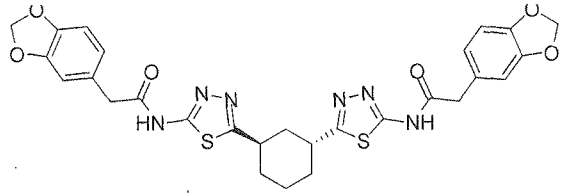
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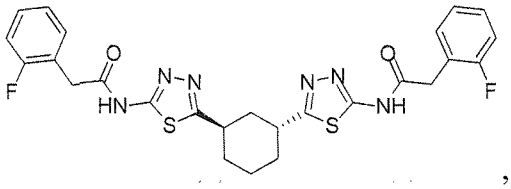
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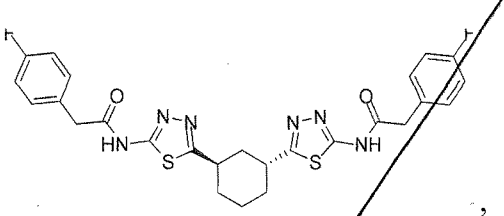
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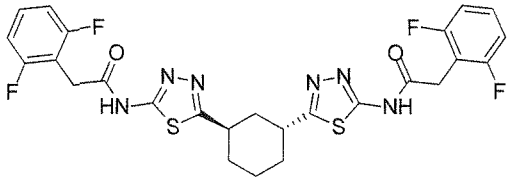
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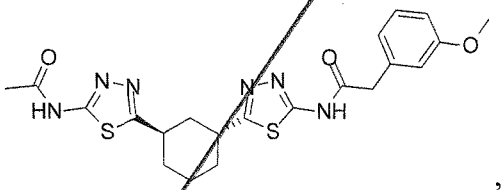
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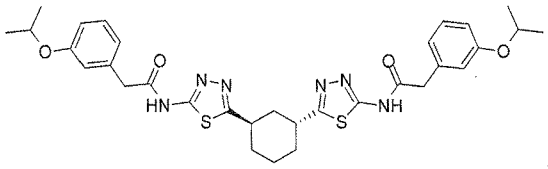
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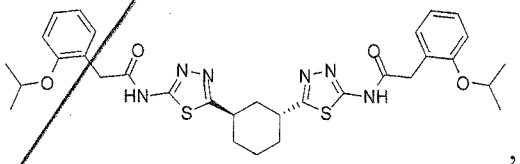
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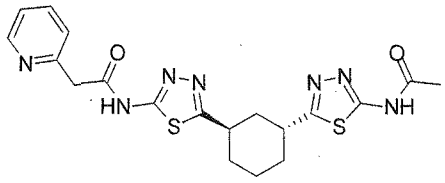
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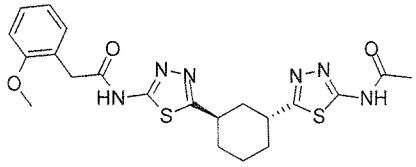
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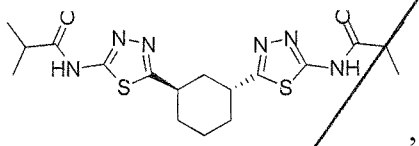
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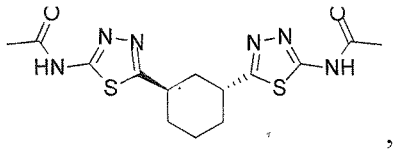
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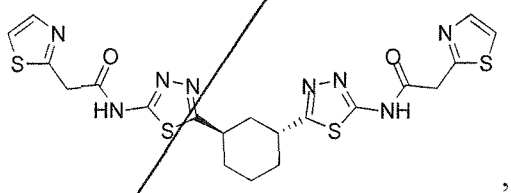
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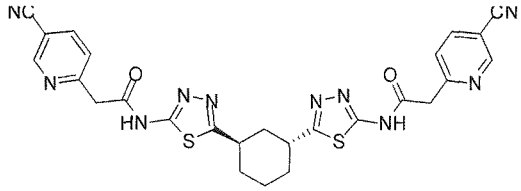
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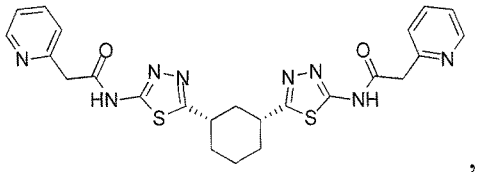
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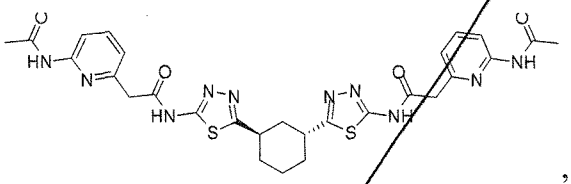
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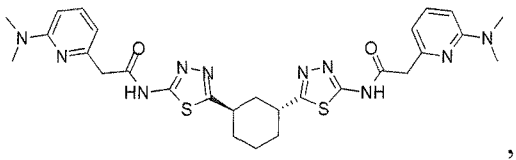
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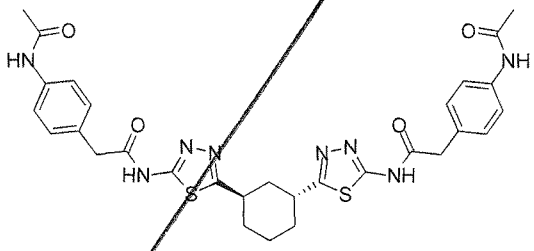
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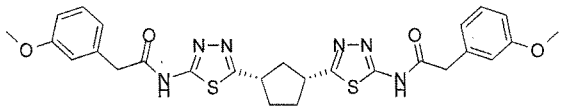
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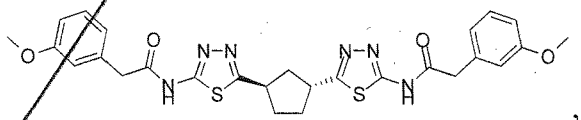
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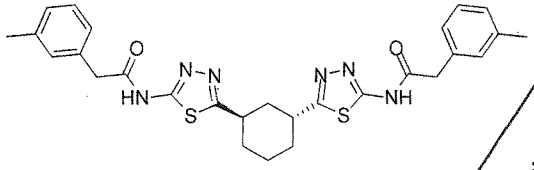
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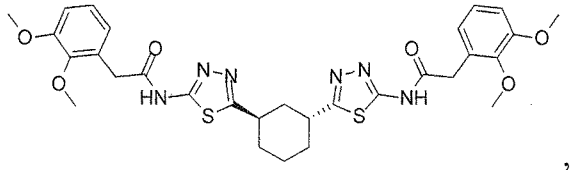
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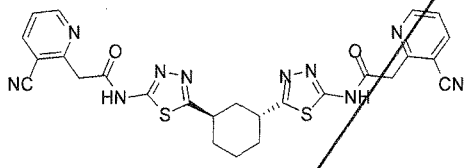
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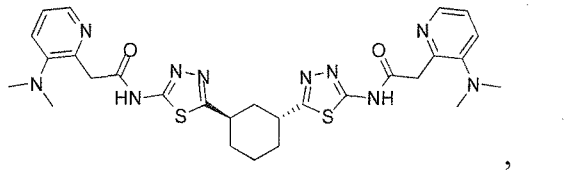
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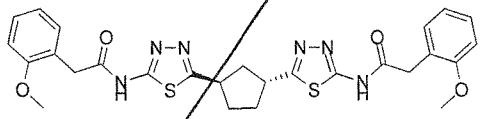
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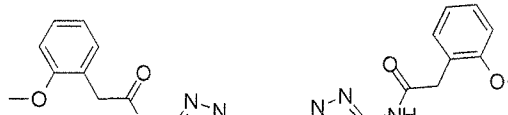
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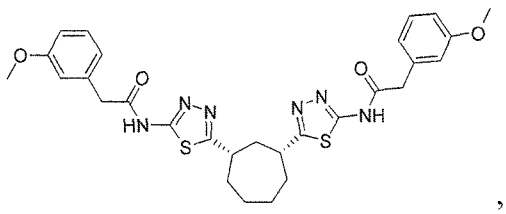
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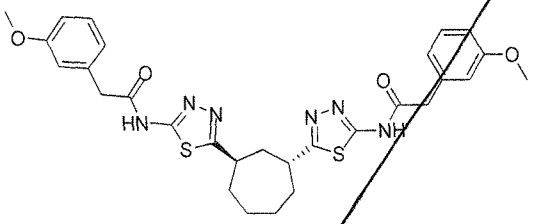
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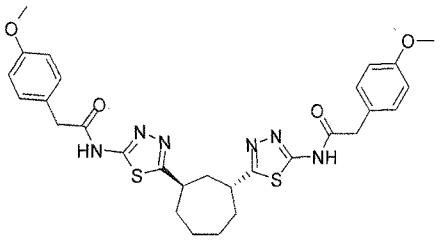
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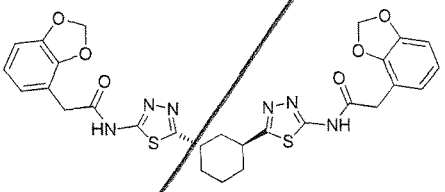
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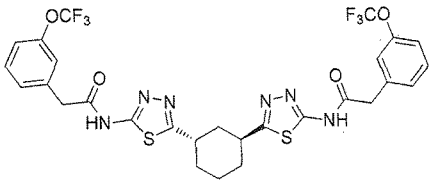
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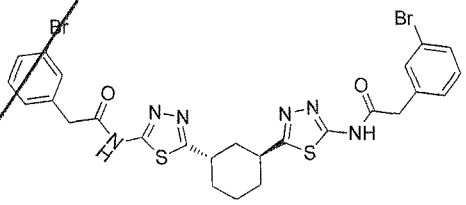


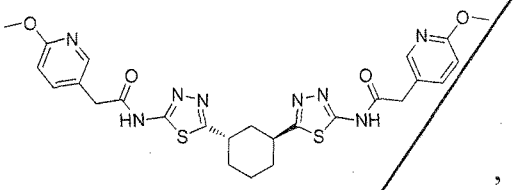


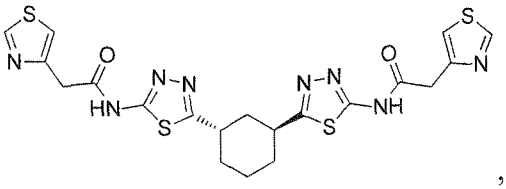


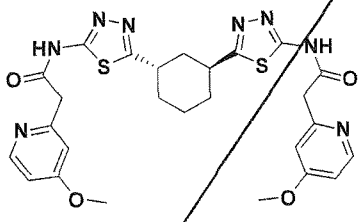


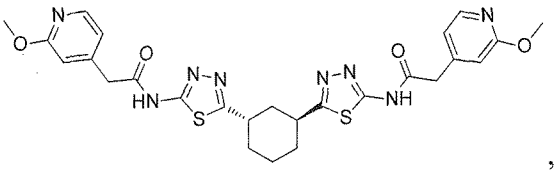


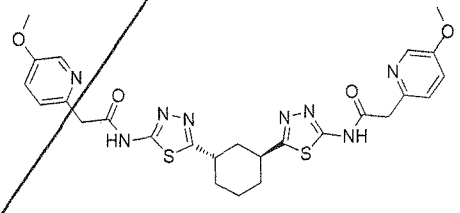


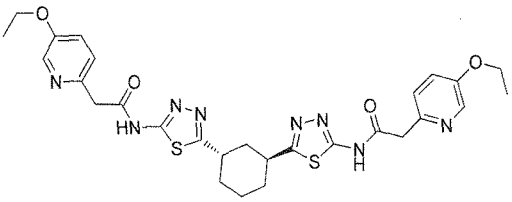


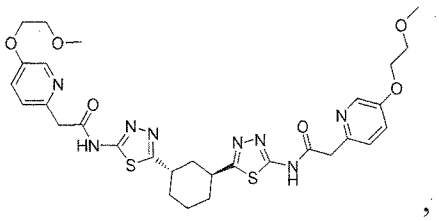




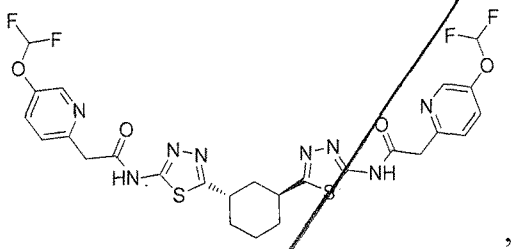




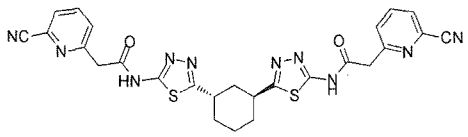




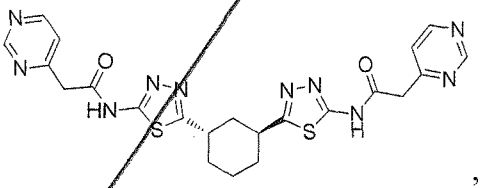
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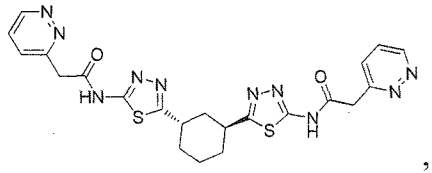
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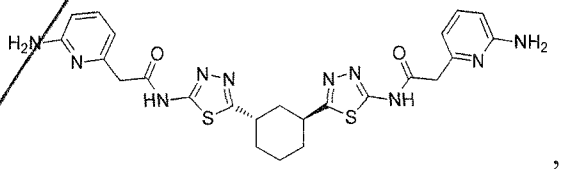
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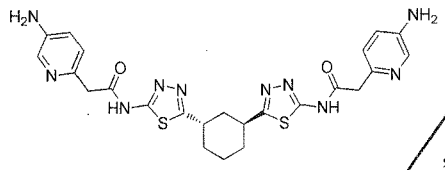
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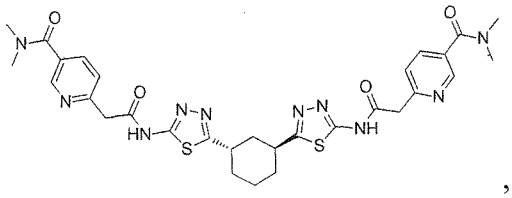
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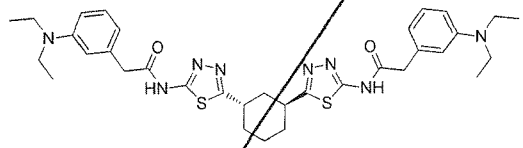
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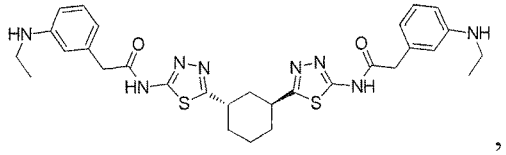
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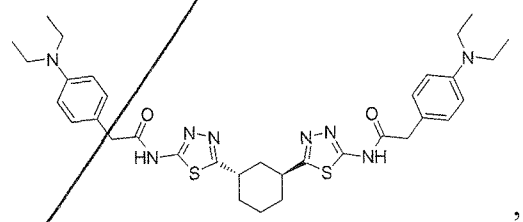
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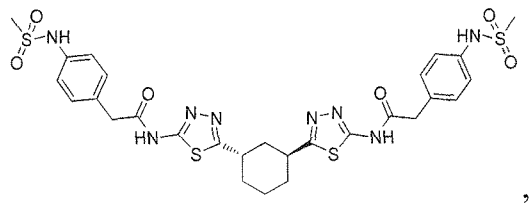
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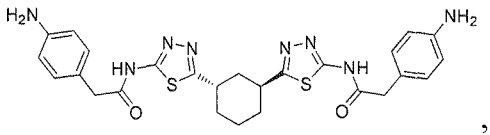
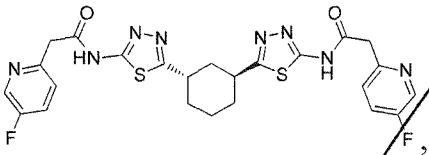
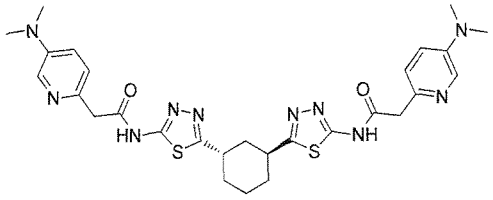
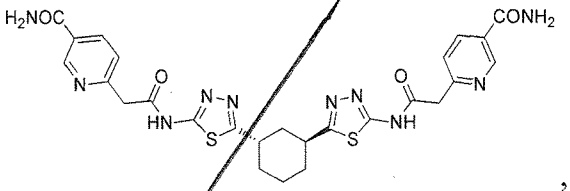
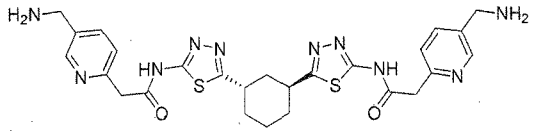
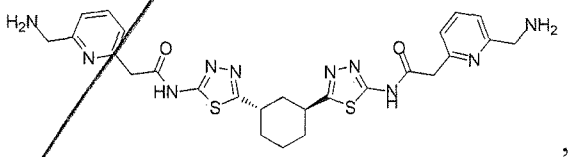
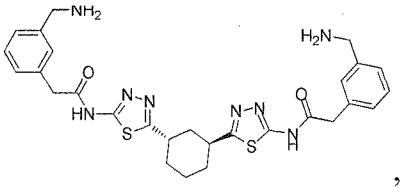
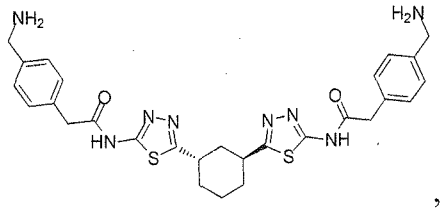
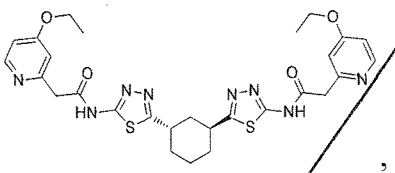
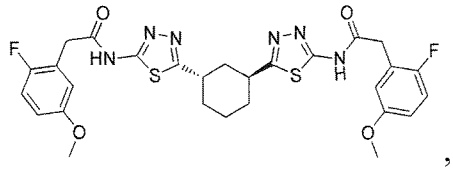
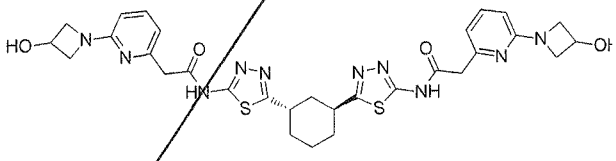
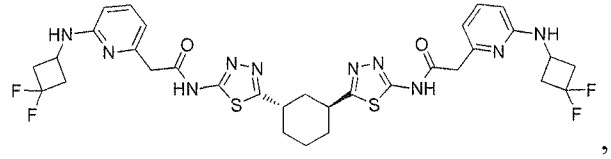
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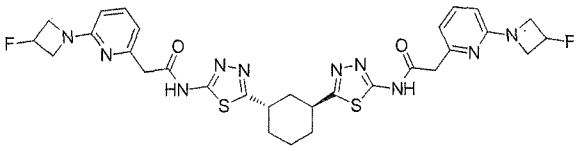


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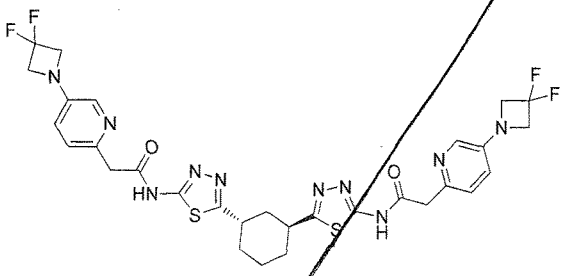


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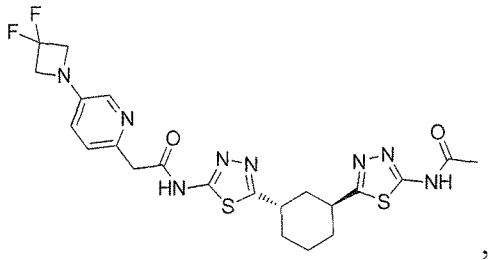

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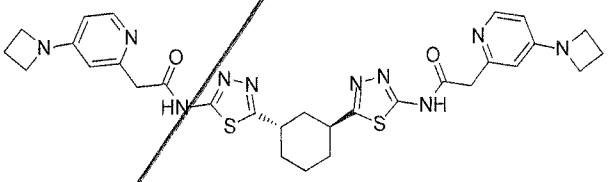
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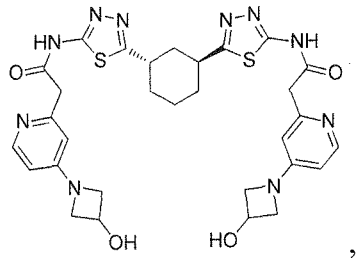
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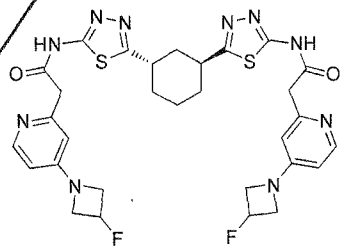
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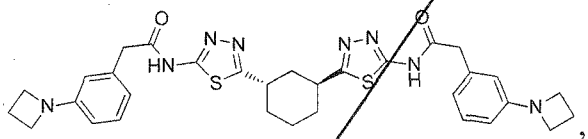
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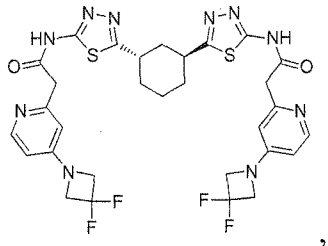
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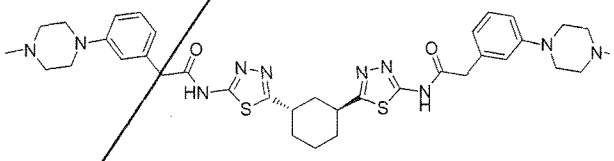
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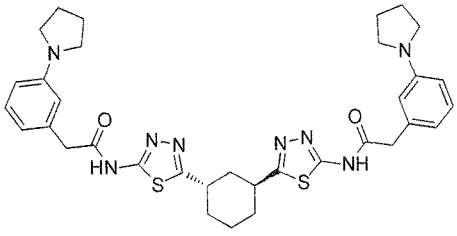
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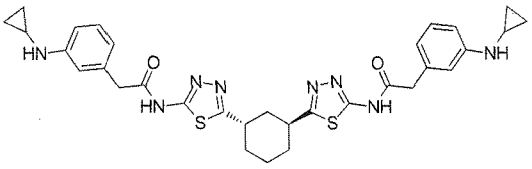
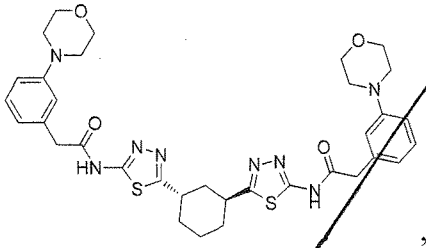
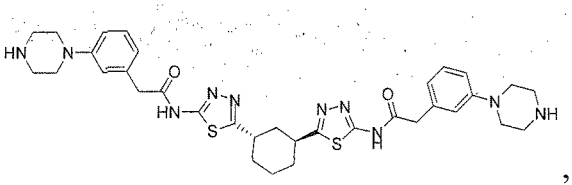
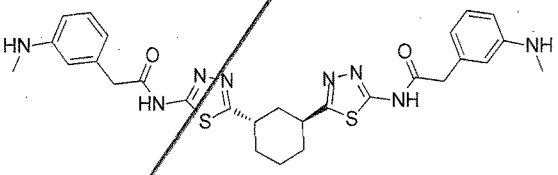
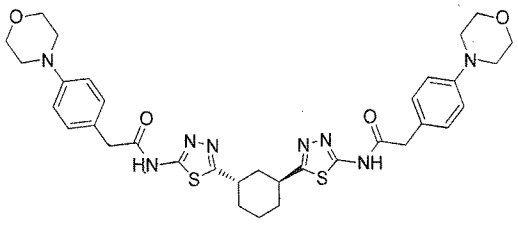
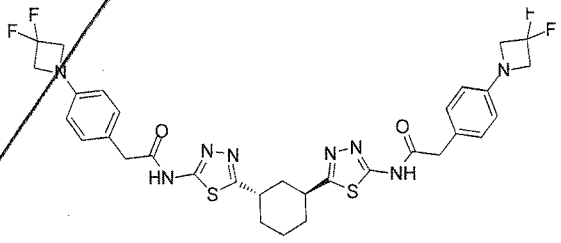
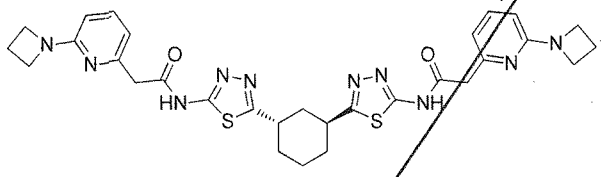
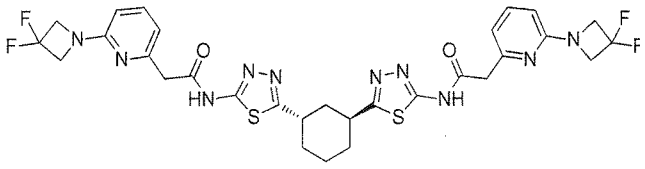
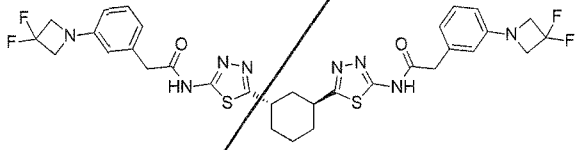
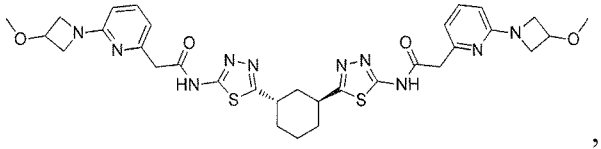
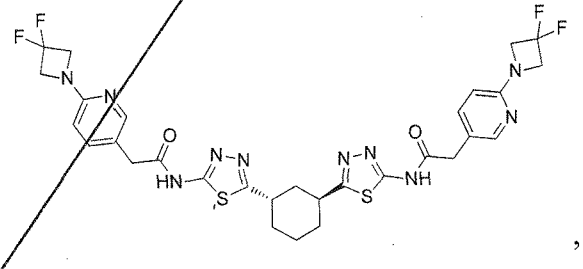
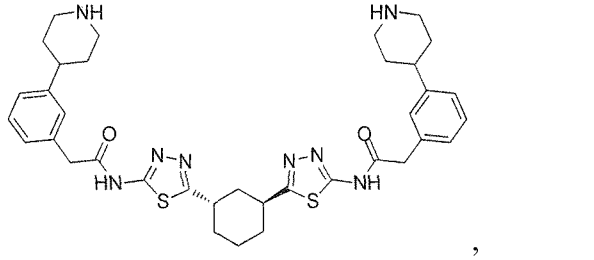
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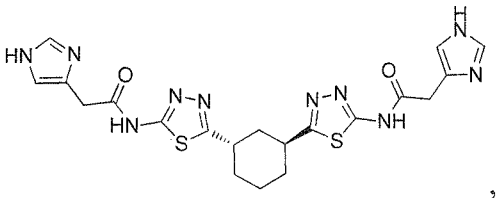


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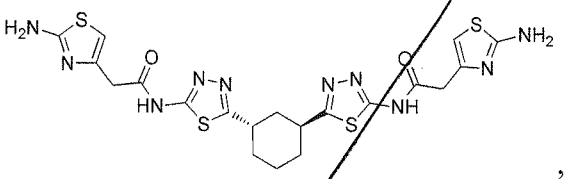


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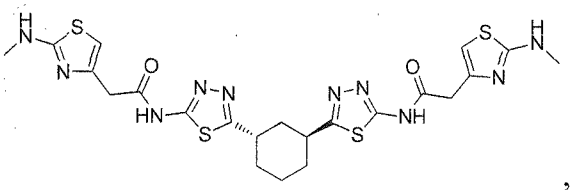

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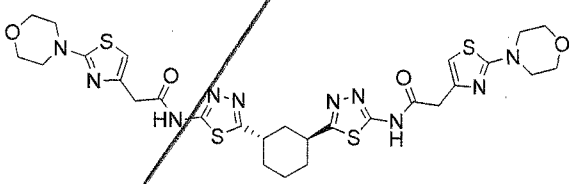
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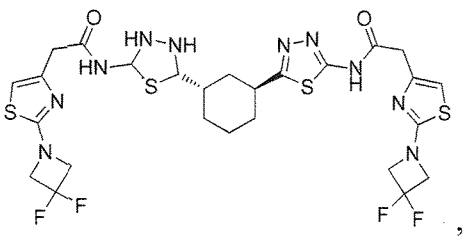
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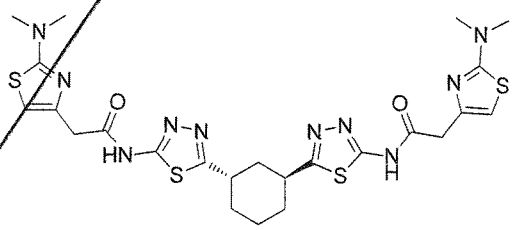
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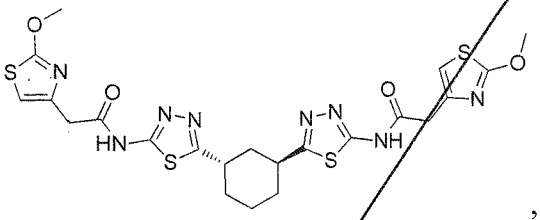
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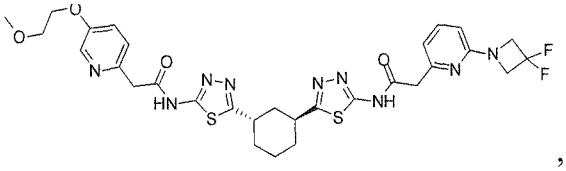
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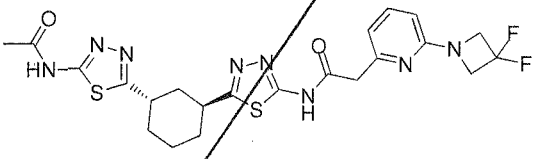
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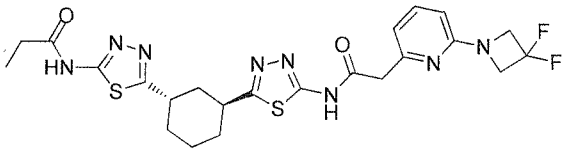
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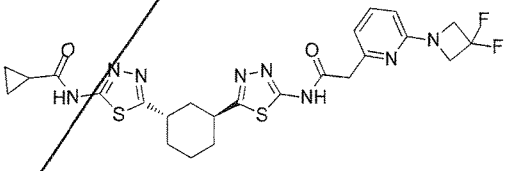
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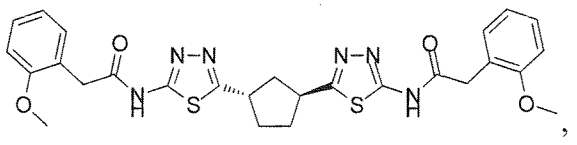
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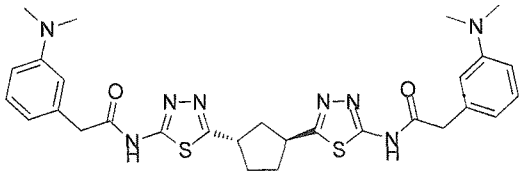
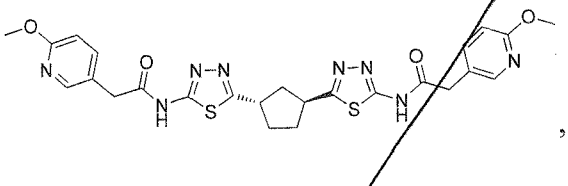
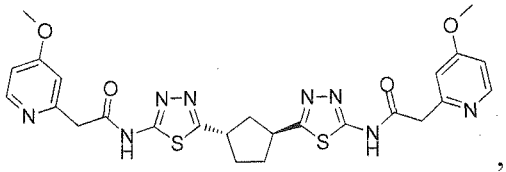
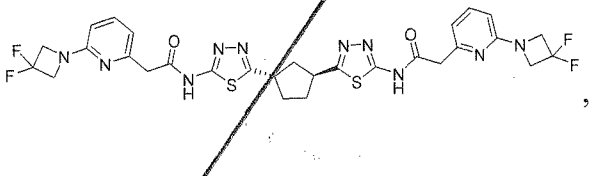
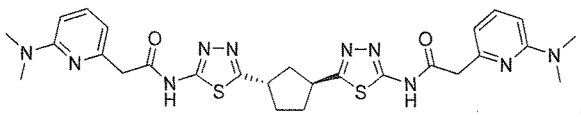
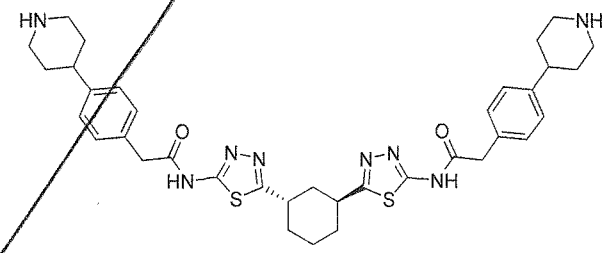
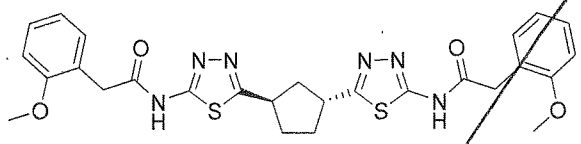
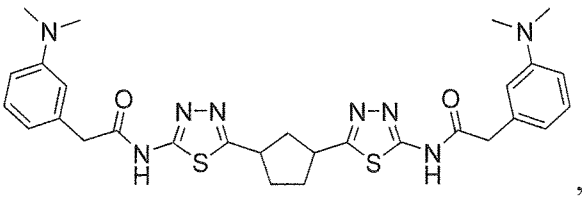
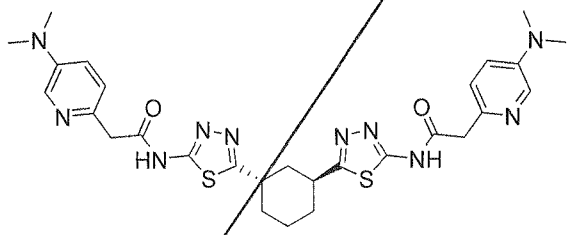
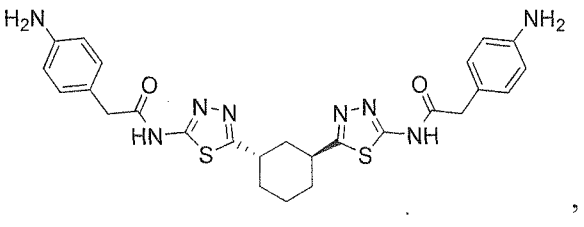
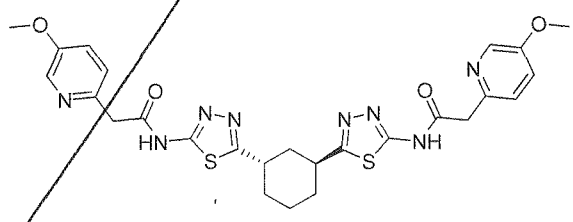
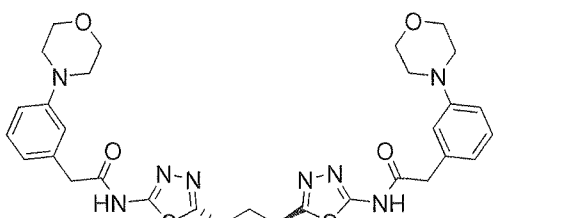
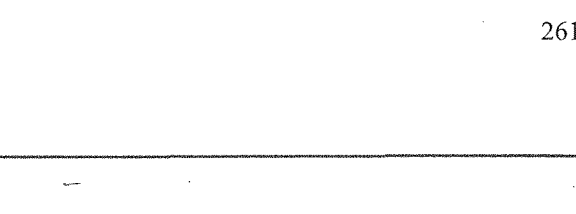
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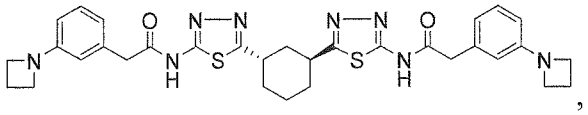
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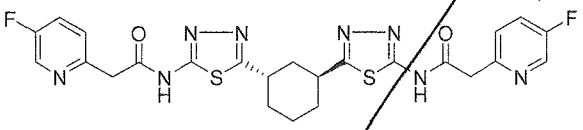
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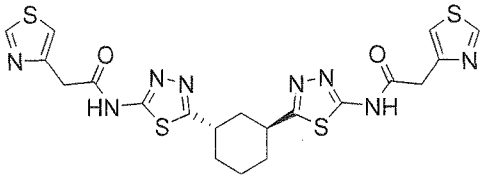
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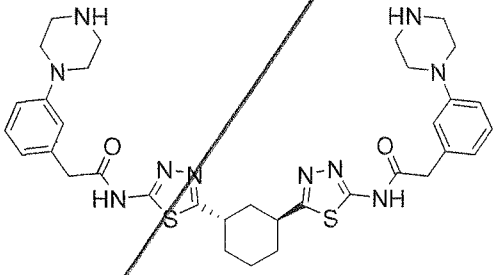
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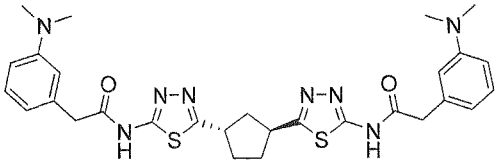
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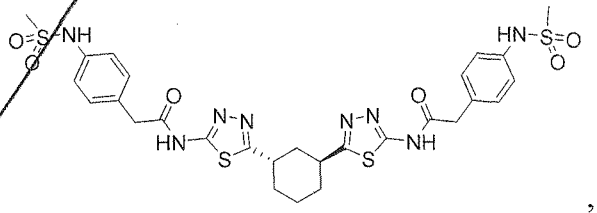
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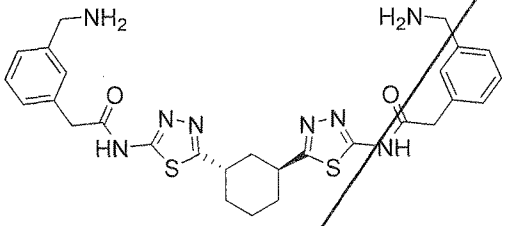
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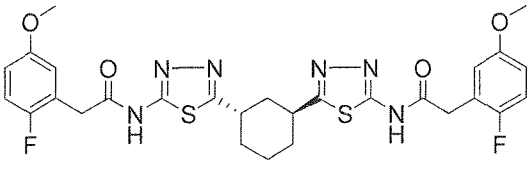
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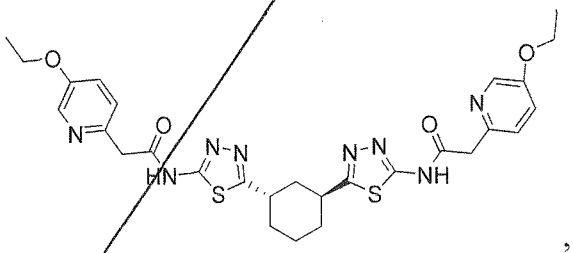
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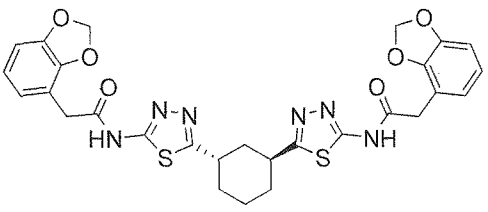
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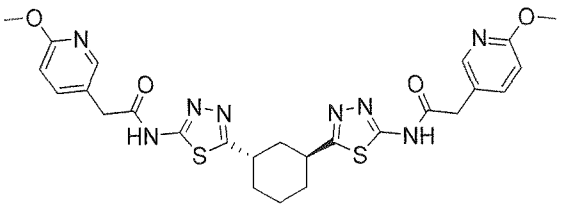
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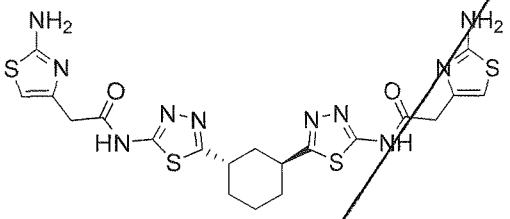
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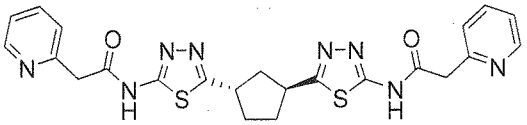
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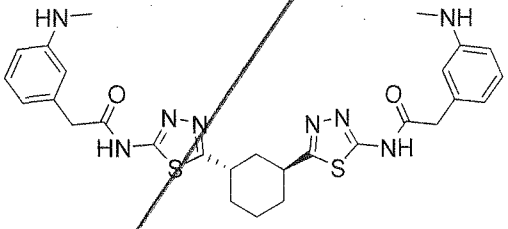
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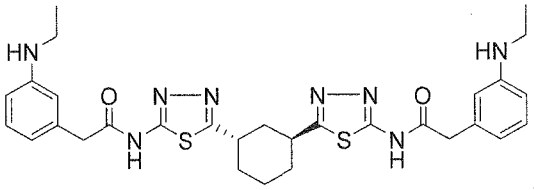
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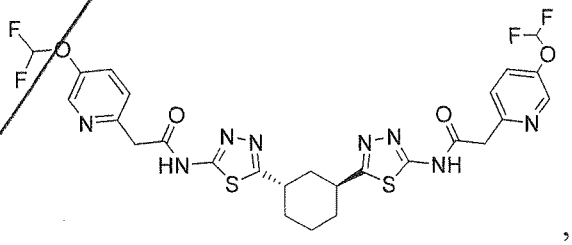
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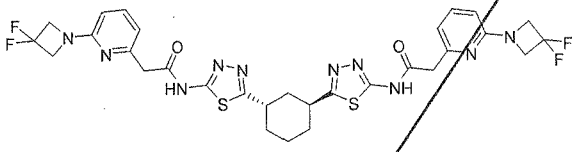
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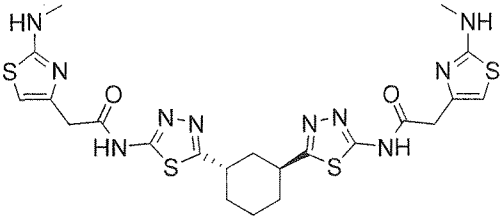
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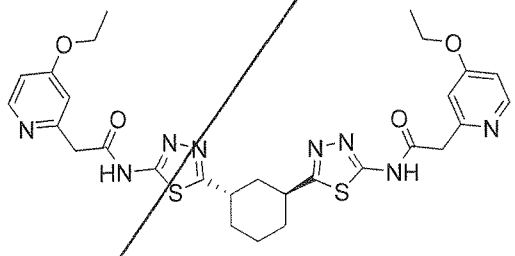
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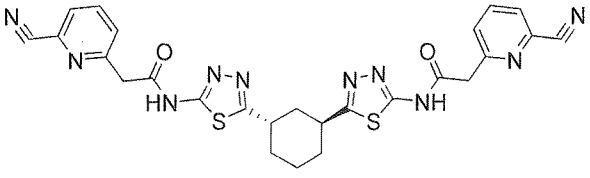
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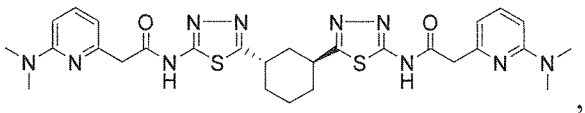
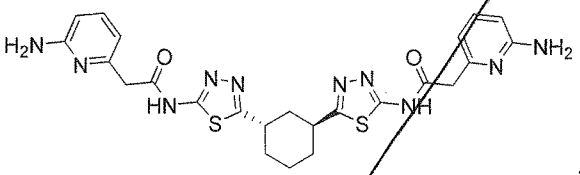
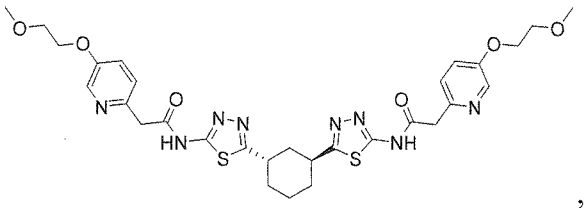
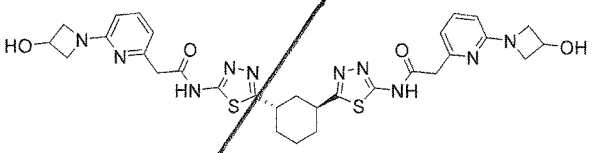
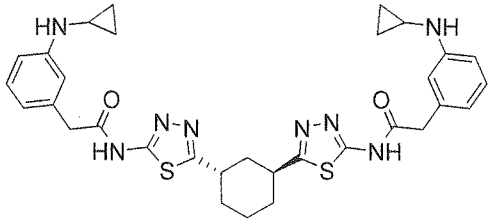
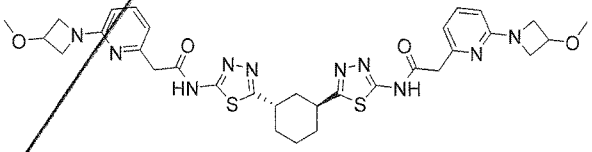
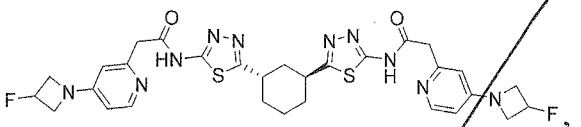
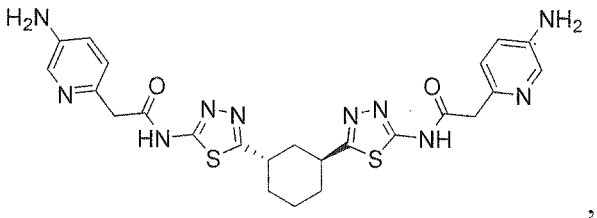
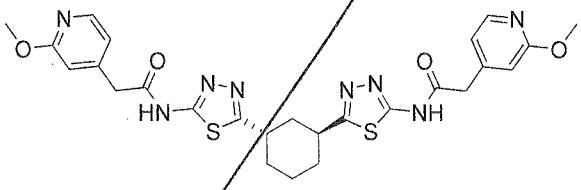
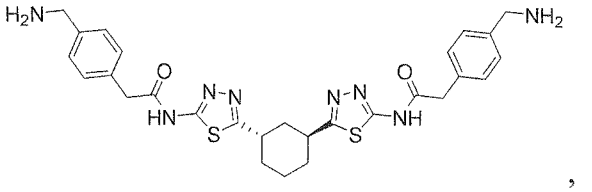
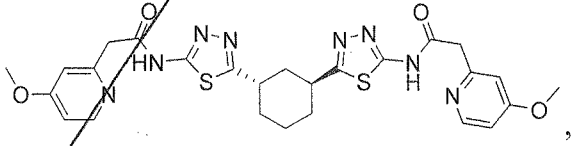
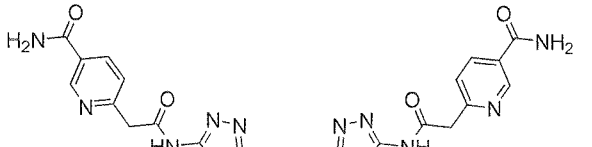
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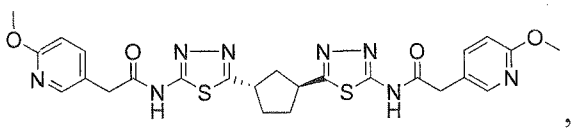


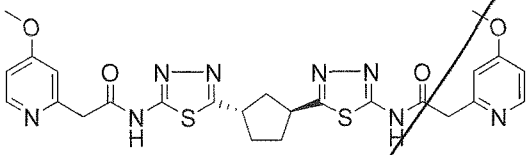
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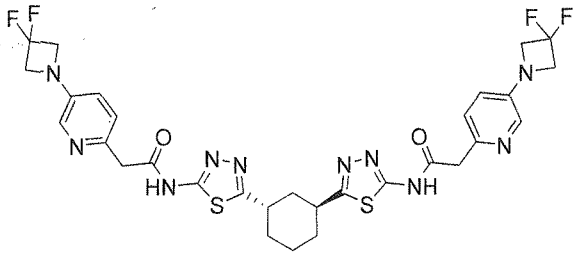

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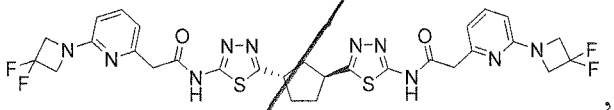
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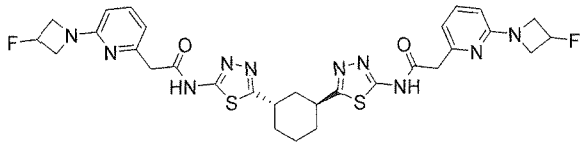
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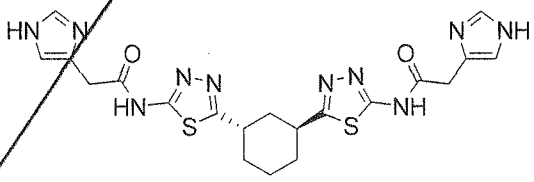


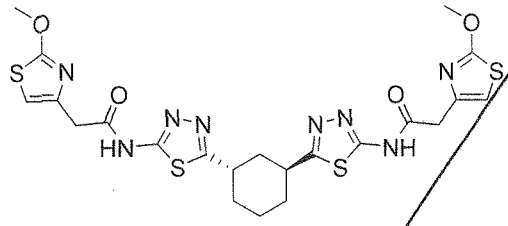


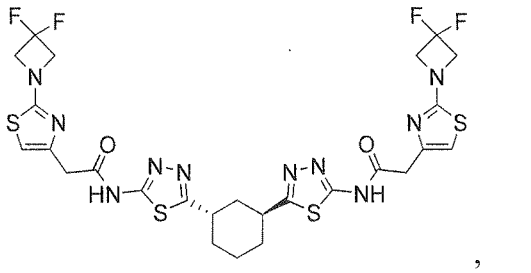


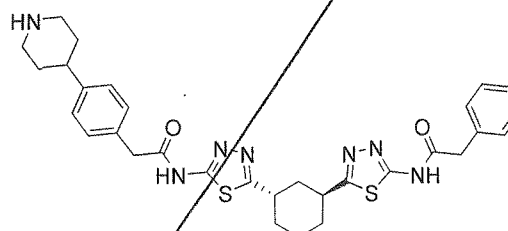


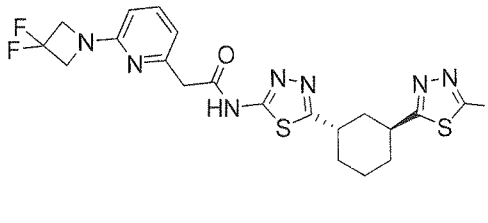


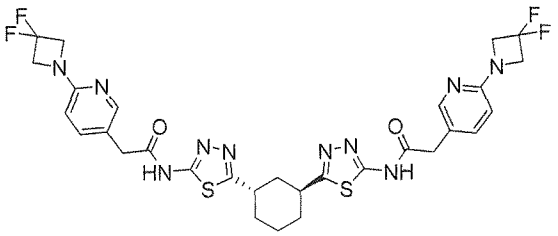
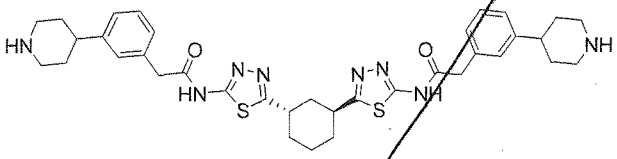
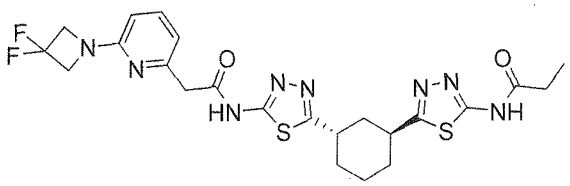
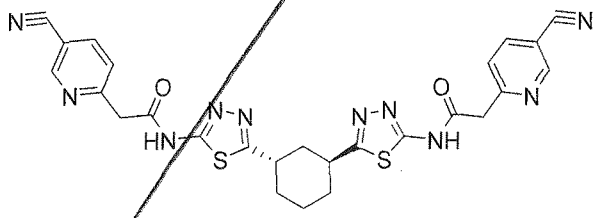
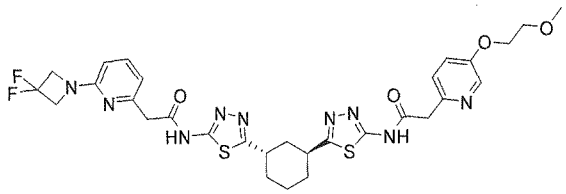
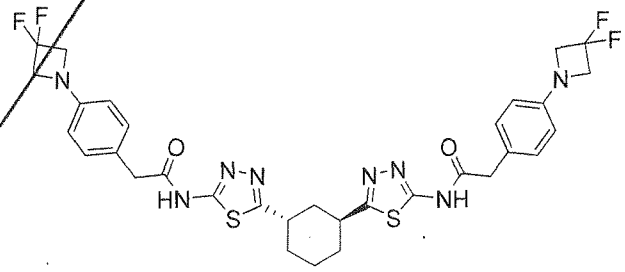
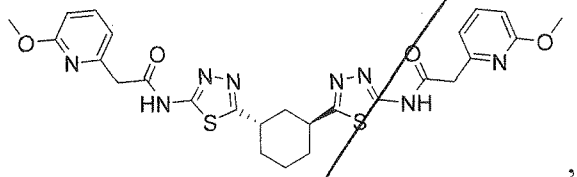
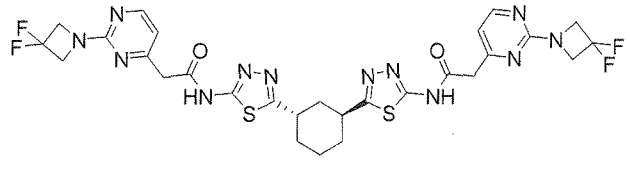
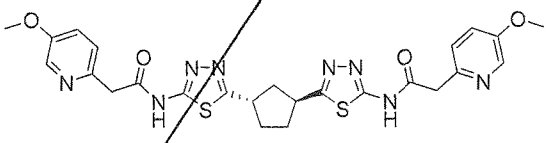
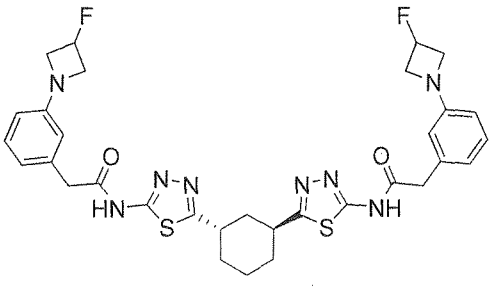


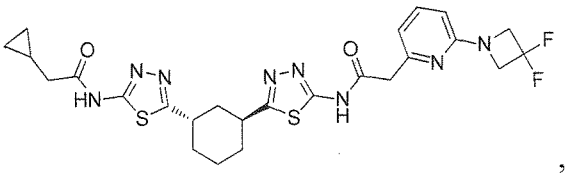




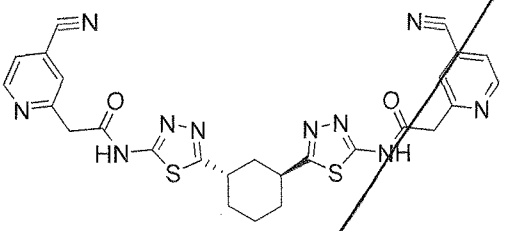




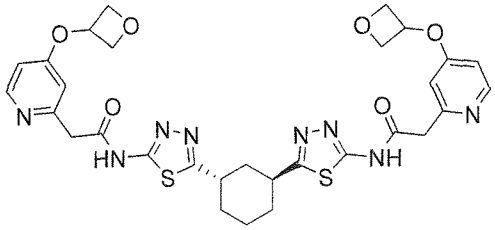

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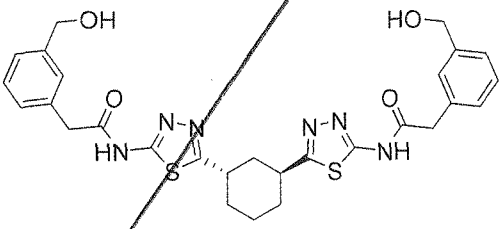
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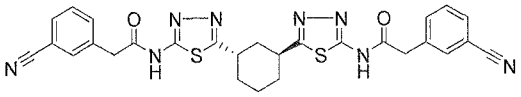
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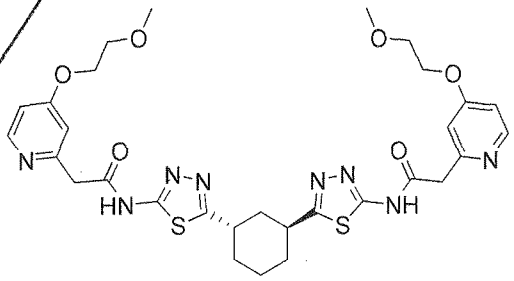
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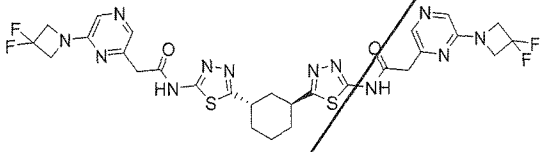
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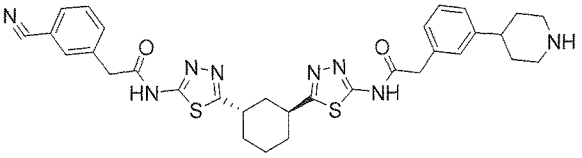
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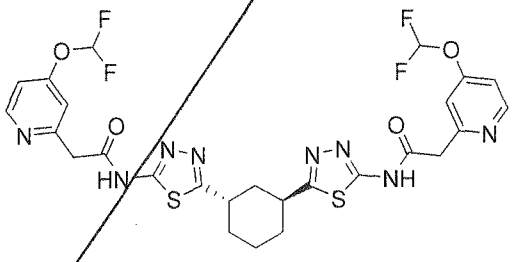
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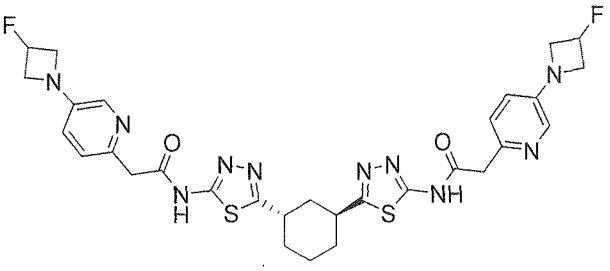
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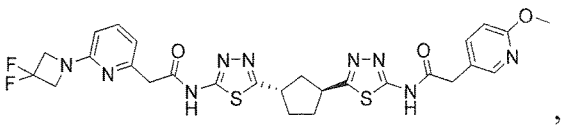
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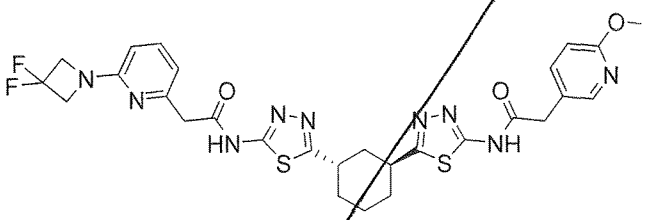
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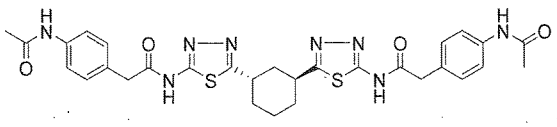
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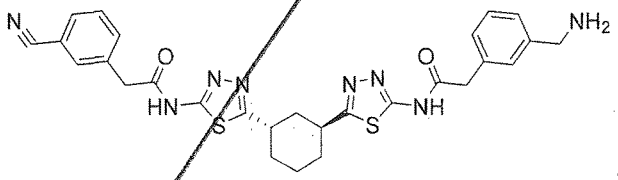
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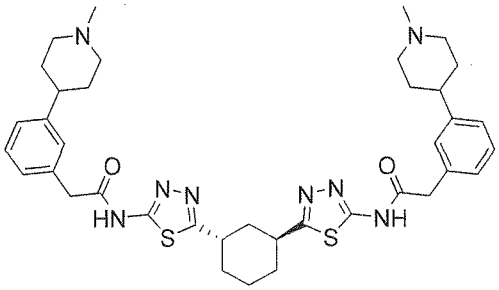
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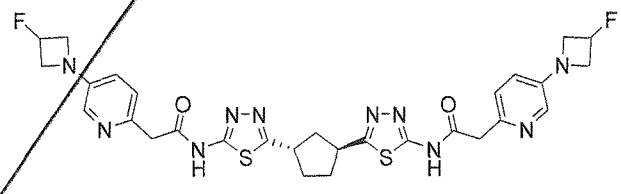
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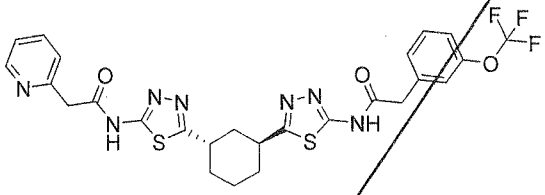
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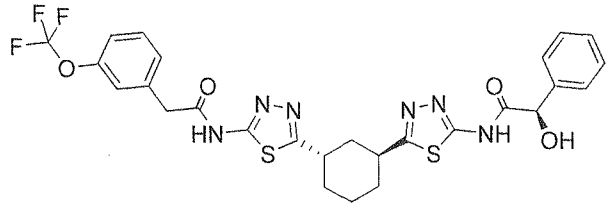
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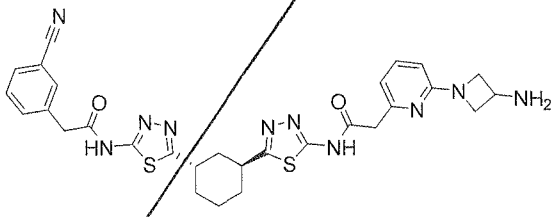
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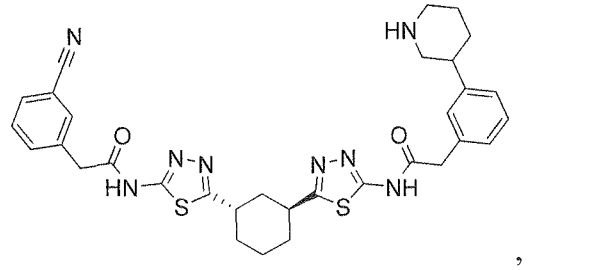
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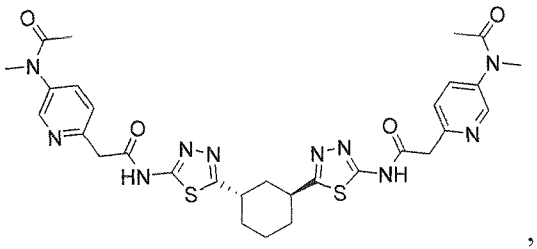
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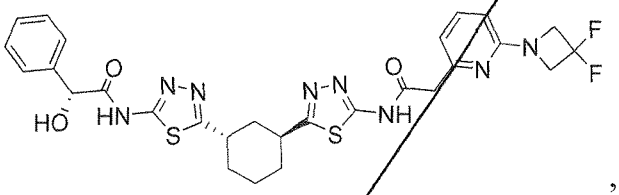
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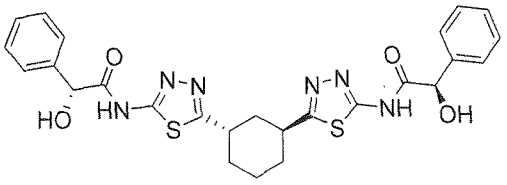
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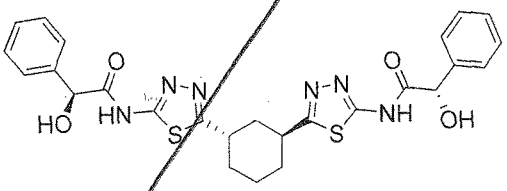
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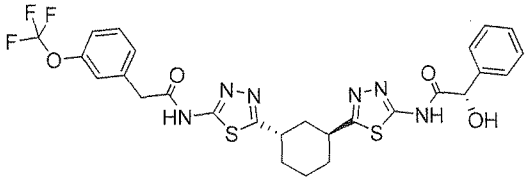
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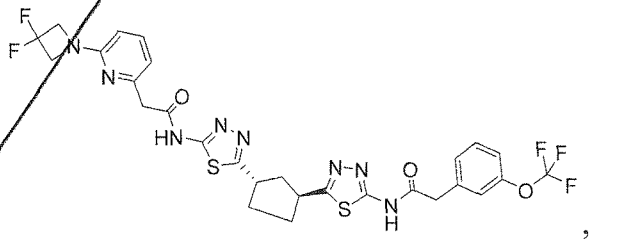
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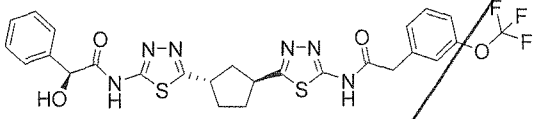
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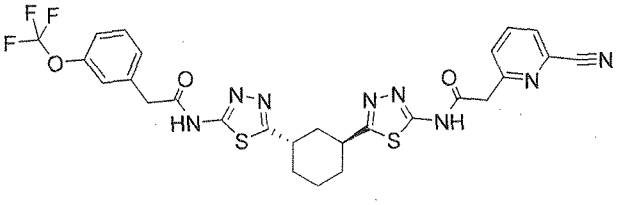
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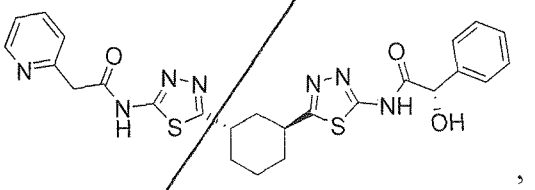
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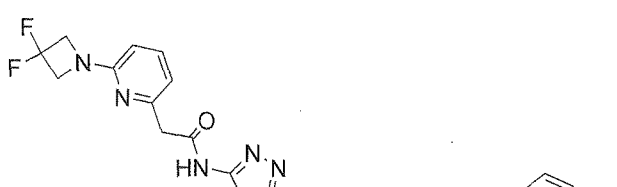
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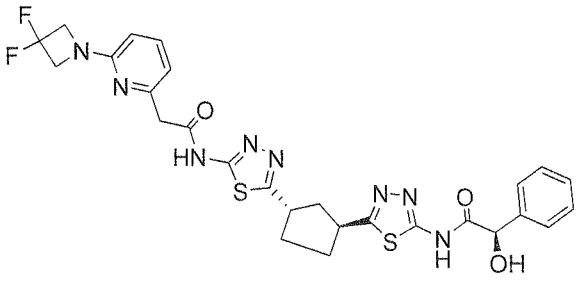
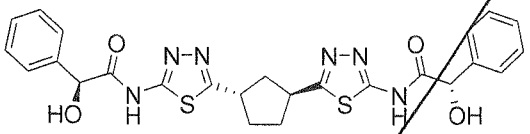
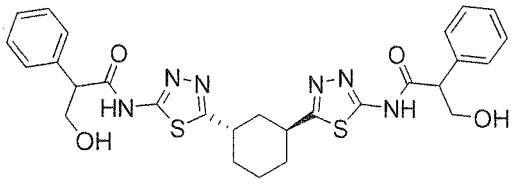
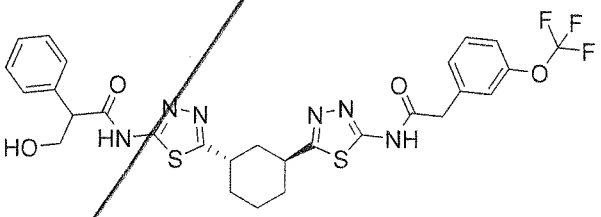
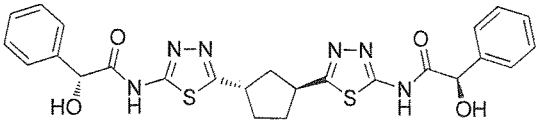
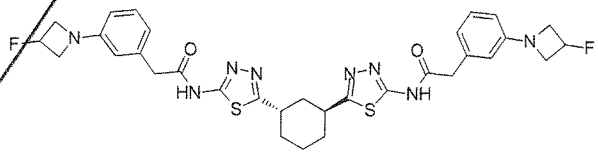
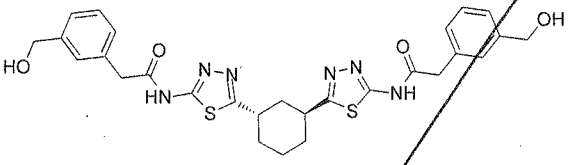
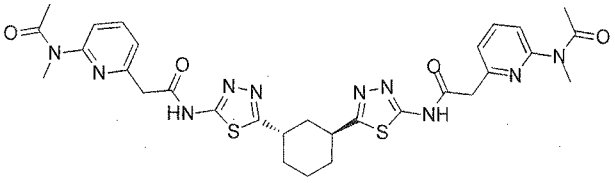
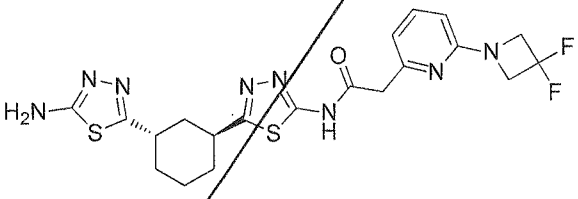
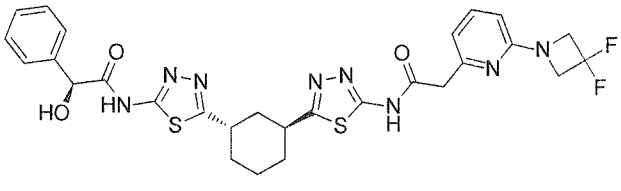
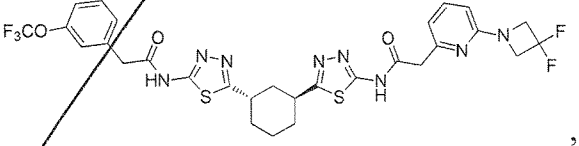
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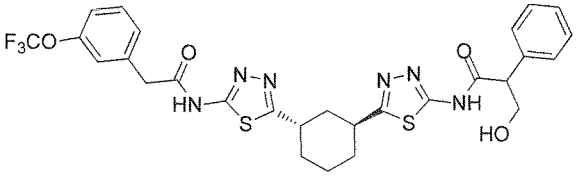


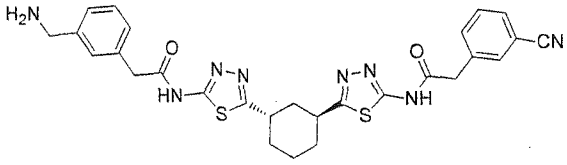
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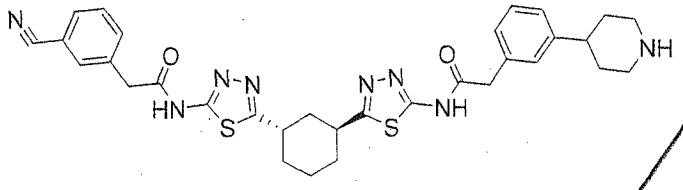
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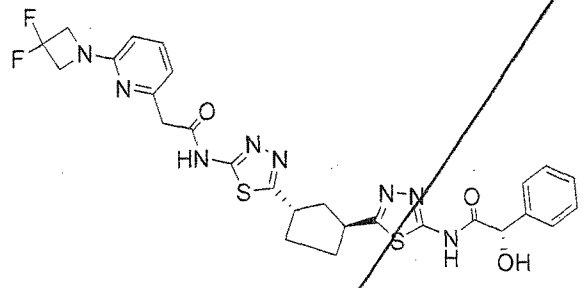
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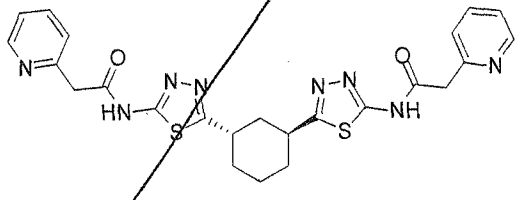
18. The compound of claim 1, which is



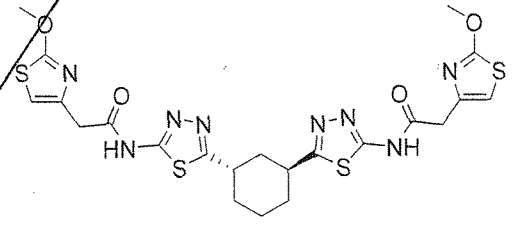
19. The compound of claim 1, which is



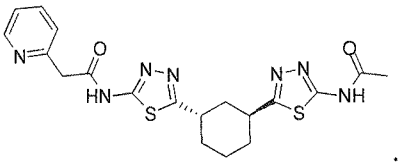
20. The compound of claim 1, which is



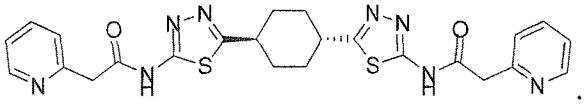
21. The compound of claim 1, which is



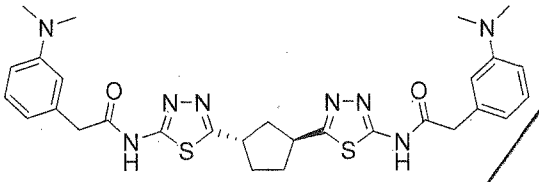
22. The compound of claim 1, which is



23. The compound of claim 1, which is



24. The compound of claim 1, which is



25. A pharmaceutical composition comprising a compound of Formula (I) according to any one of claims 1 to 24 and a pharmaceutically acceptable carrier.

26. Use of a compound of any one of claims 1 to 24 in the manufacture of a medicament for treating cancer in a subject in need thereof.

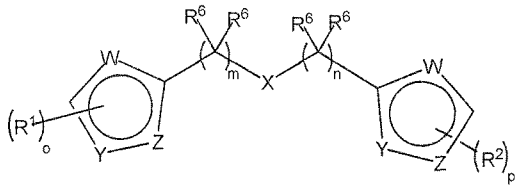
27. The use of claim 26, wherein the cancer is selected from a cancer characterized by i) a low level of E-cadherin expression compared to a reference standard, ii) a high level of vimentin expression compared to a reference standard, or iii) a low or decreased level of pyruvate carboxylase expression.

28. The use of claim 26 or 27, wherein said cancer is selected from non-small cell lung cancer, breast cancer, hepatocellular carcinoma, osteosarcoma, lipomas, chondrosarcoma, mesothelioma, colon cancer, renal cell carcinoma, acute myeloid leukemia (AML), melanoma and multiple myeloma.

CLAIMS

What is claimed is:

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



Formula (I),

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.

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

3. The compound of any one of the preceding claims, wherein o is 1 and p is 1.

4. The compound of any one of the preceding claims, wherein m is 0 and n is 0.

5. The compound of any one of the preceding claims, wherein n is 1 and m is 1.

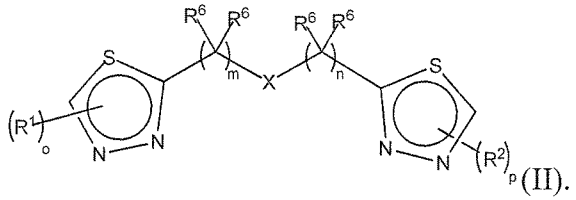
6. The compound any one of the preceding claims, wherein each R^6 is hydrogen.

7. The compound of any one of the preceding claims, wherein R^1 and R^2 are the same.

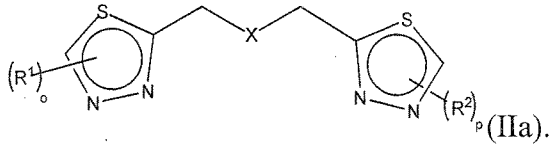
8. The compound of any one of the preceding claims, wherein R^1 and R^2 are different.

9. The compound of any one of the preceding claims, wherein R^1 and R^2 are each $-N(R^3)-C(O)-R^4$ 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.

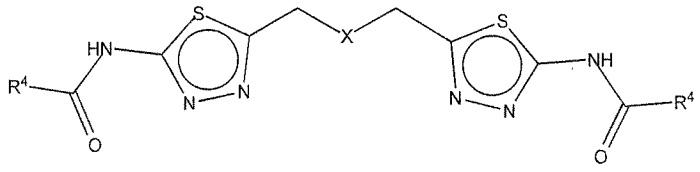
10. The compound of any one of claims 1 to 9, wherein the compound is a compound of Formula (II):


(II).

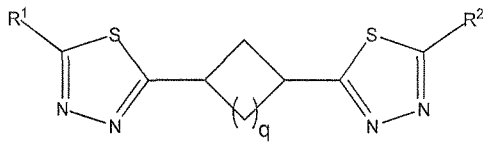
11. The compound of any one of claims 1 to 10, wherein the compound is a compound of Formula (IIa):


(IIa).

12. The compound of any one of claims 1 to 11, wherein the compound is a compound of Formula (III):

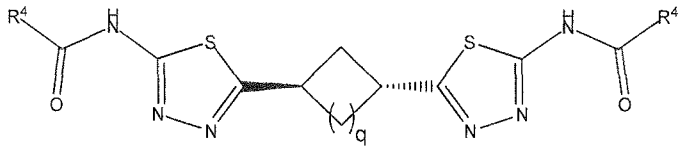

(III).

13. The compound of any one of claims 1 to 9, wherein the compound is a compound of Formula (IV) and q is 0, 1, 2, 3, or 4:



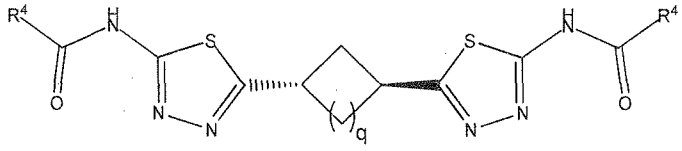
(IV).

14. The compound of any one of claims 1 to 9, wherein the compound is a compound of Formula (IVa) and q is 0, 1, 2, 3, or 4:



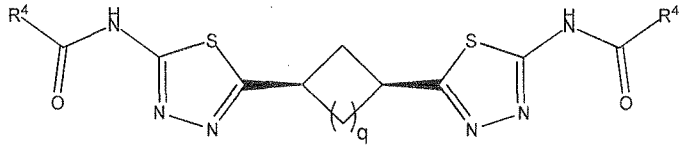
(IVa).

15. The compound of any one of claims 1 to 9, wherein the compound is a compound of Formula (IVb) and q is 0, 1, 2, 3, or 4:



(IVb).

16. The compound of any one of claims 1 to 9, wherein the compound is a compound of Formula (IVc) and q is 0, 1, 2, 3, or 4:



(IVc).

17. A pharmaceutical composition comprising a compound of any one of the preceding claims or a pharmaceutically acceptable salt thereof.

18. Use of a compound of any one of claims 1 to 16 or a composition of claim 17 in the manufacture of a medicament for treating cancer, wherein the cancer is selected from: lung cancer, breast cancer, hepatocellular carcinoma, osteosarcoma, chondrosarcoma, and mesothelioma.

19. The use of claim 18, wherein the cancer is lung cancer.

20. The use of claim 19, wherein the lung cancer is non-small cell lung cancer.

21. The compound of any one of claims 1 to 16 or a composition of claim 17 for use in treating cancer.