SUMMARY

[0010] The present disclosure describes bifunctional compounds which function to recruit endogenous proteins to an E3 Ubiquitin Ligase for degradation, and methods of using the same. In particular, the present disclosure provides bifunctional or proteolysis targeting chimeric compounds, which find utility as modulators of targeted ubiquitination of a variety of polypeptides and other proteins, which are then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. An advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of targeted polypeptides from virtually any protein class or family. In addition, the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of a disease condition, such as cancer, e.g., multiple myeloma or prostate cancer.

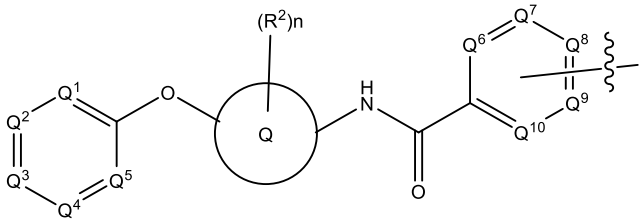
[0010a] In an aspect of the present disclosure, there is provided a bifunctional compound having the structure:

ABM-L-CLM,

or a pharmaceutically acceptable salt thereof,

wherein:

(a) ABM is an androgen receptor (AR) binding moiety having the structure:



wherein:

Q^1, Q^2, Q^3, Q^4, and Q^5 are each independently CR^1, or N;



is 4-6 membered cycloalkyl, C_6-C_{10} aryl, 4-6 membered heterocycloalkyl, or 4-6 membered heteroaryl, wherein the heterocycloalkyl or heteroaryl comprises 0-4 heteroatoms;

Q^6, Q^7, Q^8, Q^9, and Q^{10} are each independently CR^3, or N;

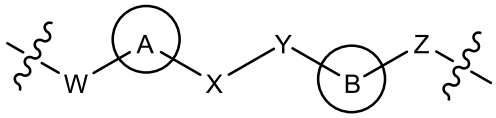
Each R^1 is independently selected from the group consisting of H, optionally substituted linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo;

Each R^2 is independently selected from the group consisting of optionally substituted linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo;

Each R^3 is independently selected from the group consisting of optionally substituted H, linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo; and

n is 0, 1, 2, 3, or 4;

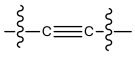
(b) L is a chemical linking moiety having the structure:



wherein:

the ABM is linked to W, and the CLM is linked to Z or

the ABM is linked to Z, and the CLM is linked to W;

W is absent or 



is 4-7 membered cycloalkyl, 4-7 membered heterocycle, or spiro-bicyclic heterocycloalkyl, where each ring in the spiro-bicycle is 4-7 membered;

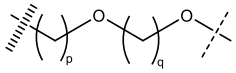
X is $-CH_2-$ or absent;

Y is $-NR^6-$, -O-, or absent;



is 4-7 membered cycloalkyl or 4-7 membered heterocycle;

Z is $-C(R^7)_2-$, $-NR^7-$, -O-, or absent;

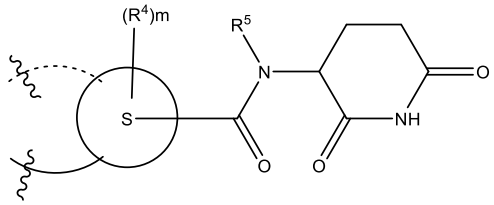
R^6 is H, linear or branched C_{1-6} alkyl, linear or branched C_{1-6} alkoxy-C_{1-6} alkyl, or , wherein  indicates a bond to Y, and  indicates a bond to ;

each R^7 is independently selected from the group consisting of H, linear or branched C_{1-6} alkyl, and linear or branched C_{1-6} alkoxy;

p is 1, 2, 3, or 4; and

q is 1, 2, 3, 4, or 5;

(c) CLM is cereblon E3 ubiquitin ligase binding moiety having the structure:



Wherein:

 is C_6-C_{10} aryl, 4-7 membered heteroaryl, or bridged bicyclic cycloalkyl;

 indicates that linking moiety L is connected to ring S by one or two covalent bonds;

Each R^4 is independently selected from the group consisting of optionally substituted linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo;

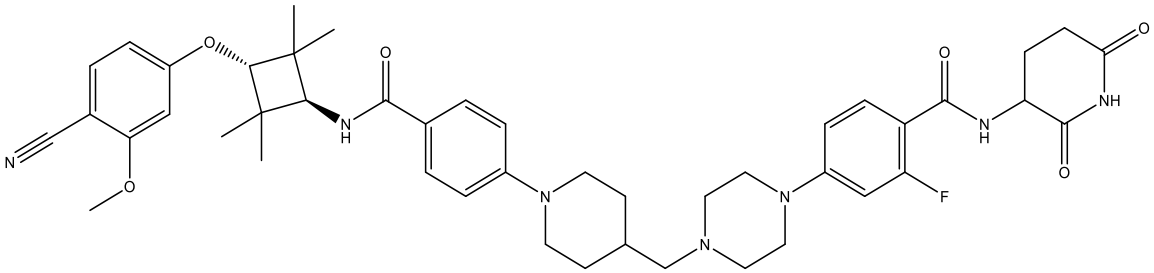
R^5 is H, optionally substituted linear or branched C_1-C_6 alkyl, or optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo; and

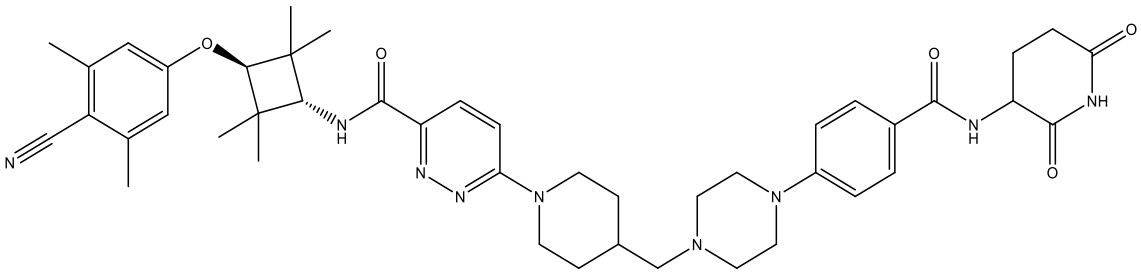
m is 0, 1, 2, 3, or 4;

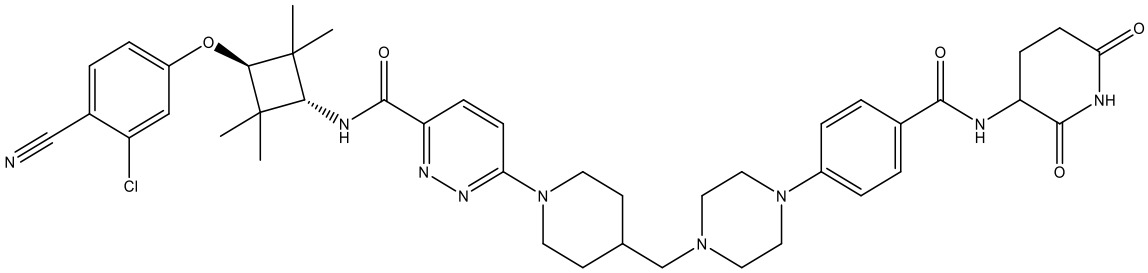
provided that when  is pyridyl,  is tetramethylcyclobutyl, Q^2 is CR^1, and Q^4 is CR^1; that R^1 is not chloro; and

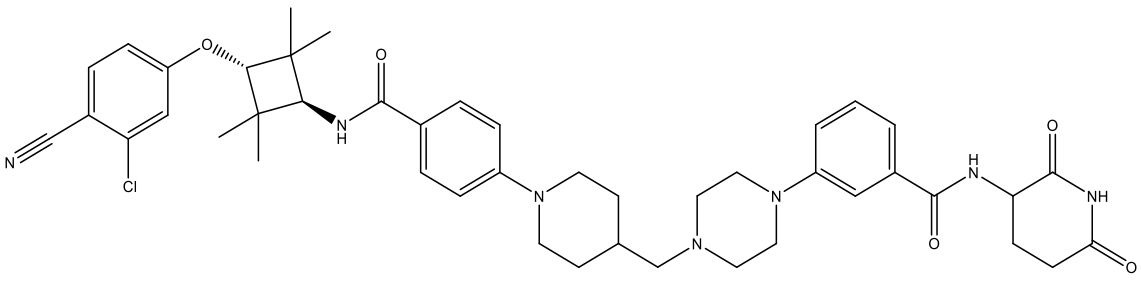
further provided that the compound is not N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-((4-(4-((2,6-dioxopiperidin-3-yl)carbamoyl)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)pyridazine-3-carboxamide.

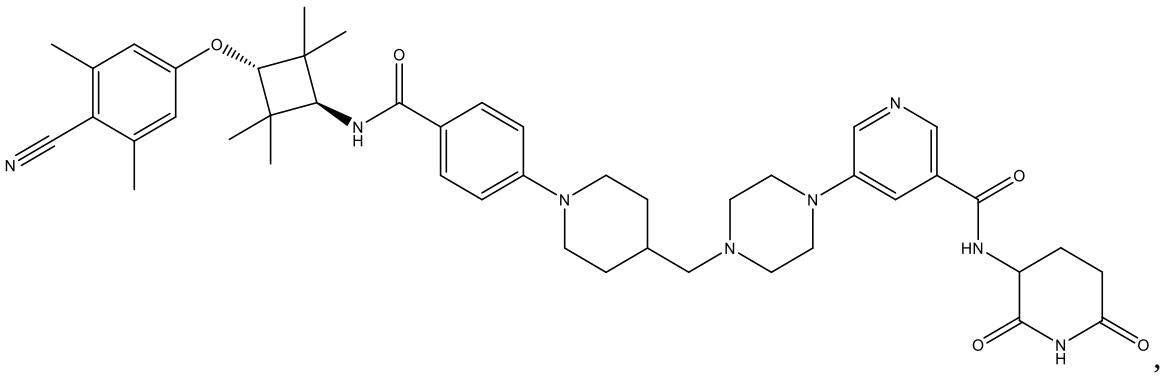
[0010b] In another aspect of the present disclosure, there is provided a bifunctional compound, wherein the compound is:


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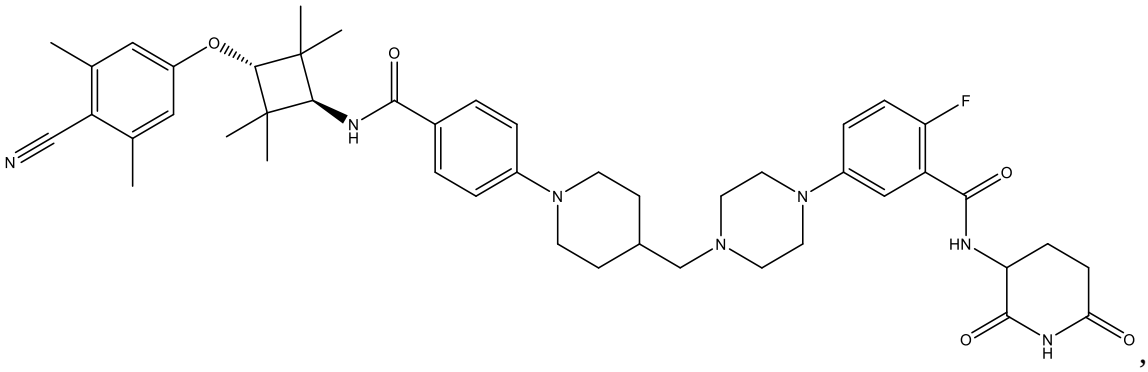

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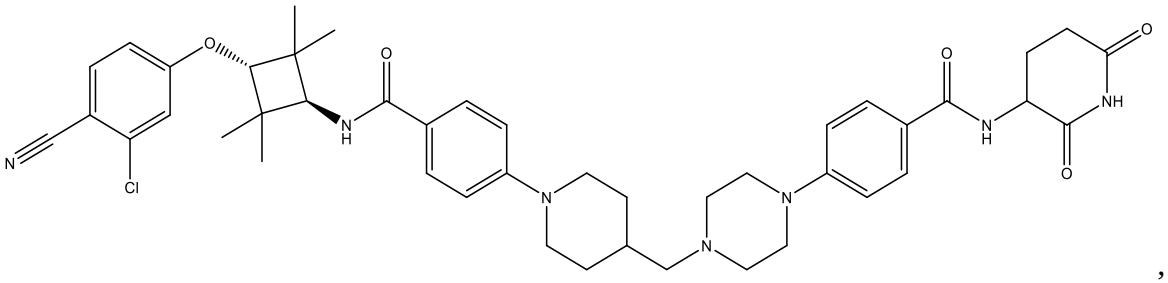

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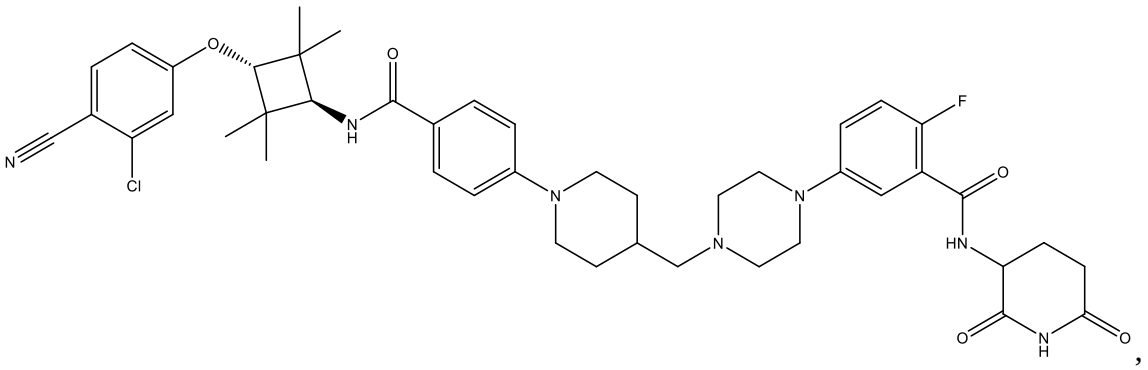
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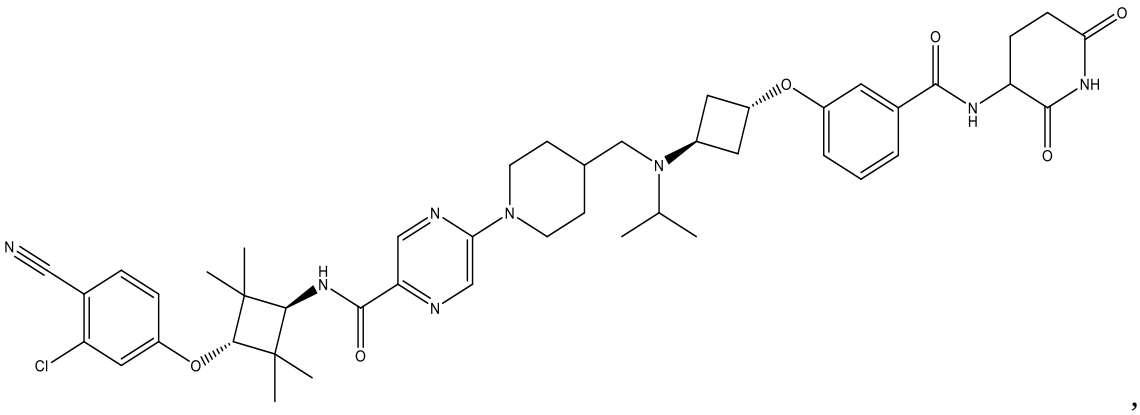
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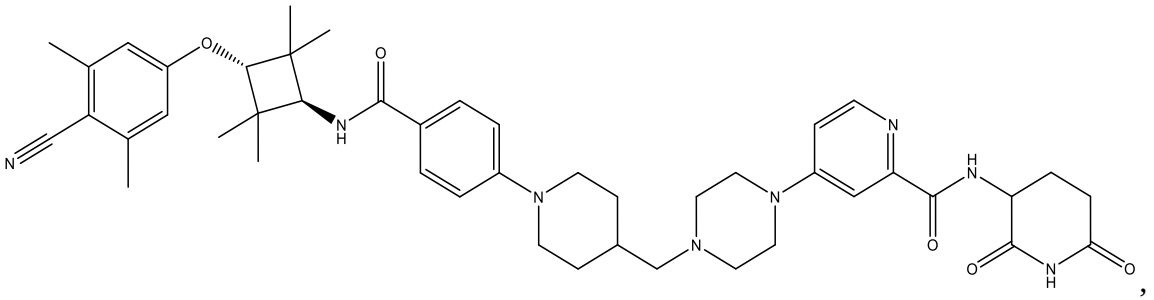
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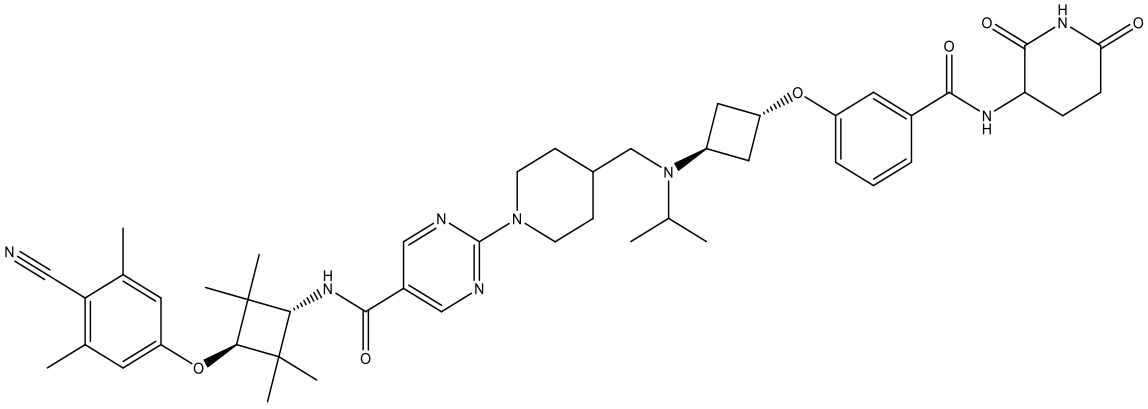
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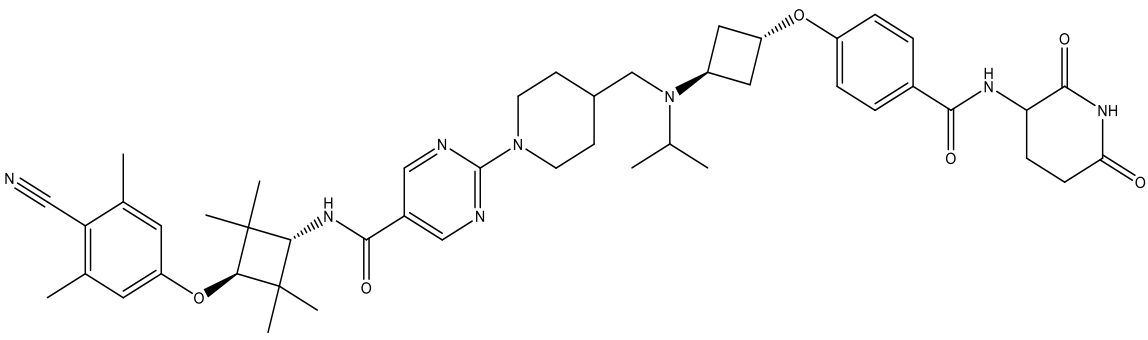
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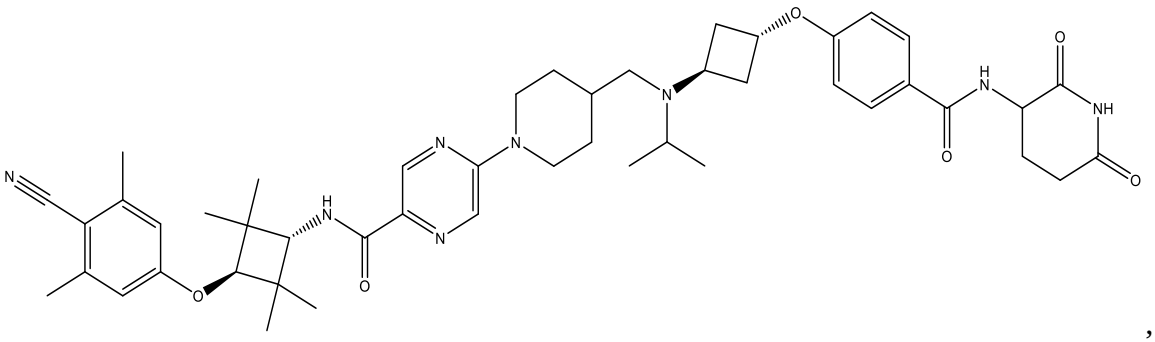
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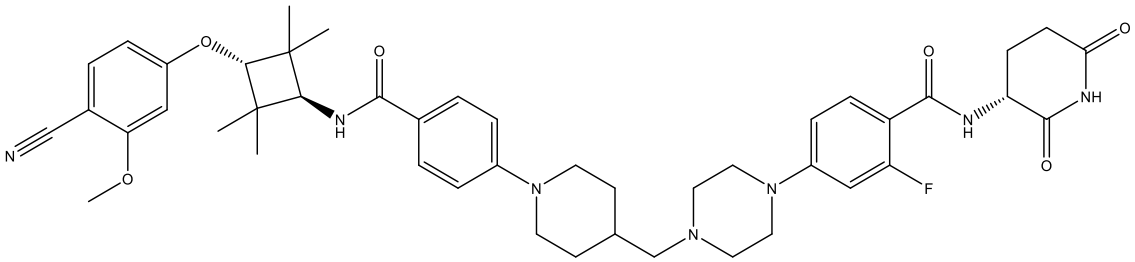
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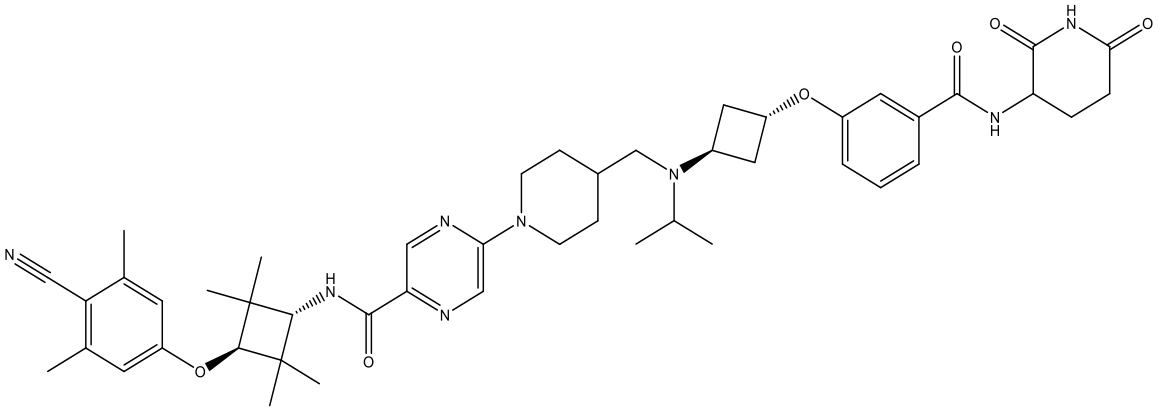
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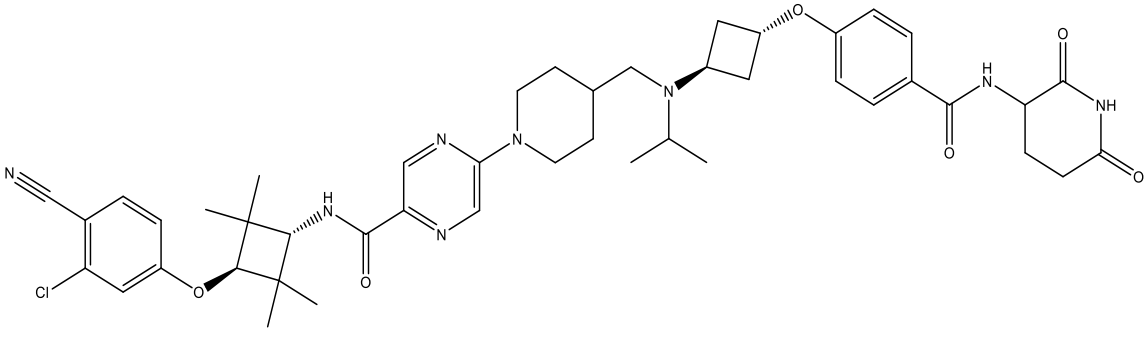
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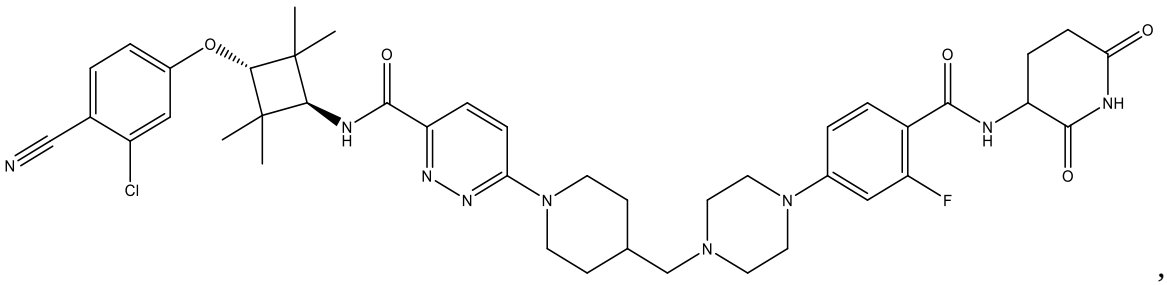
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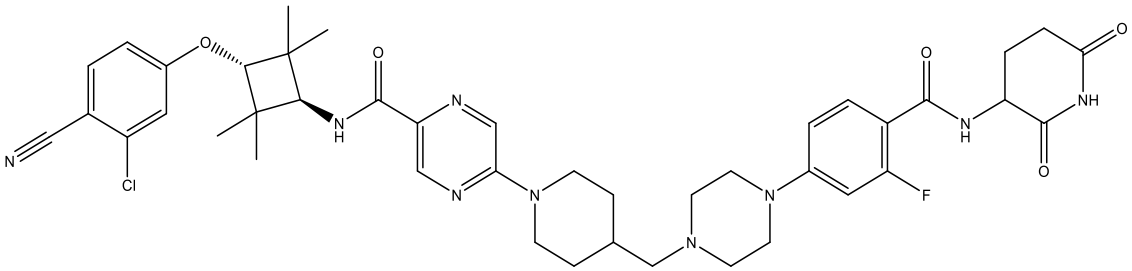
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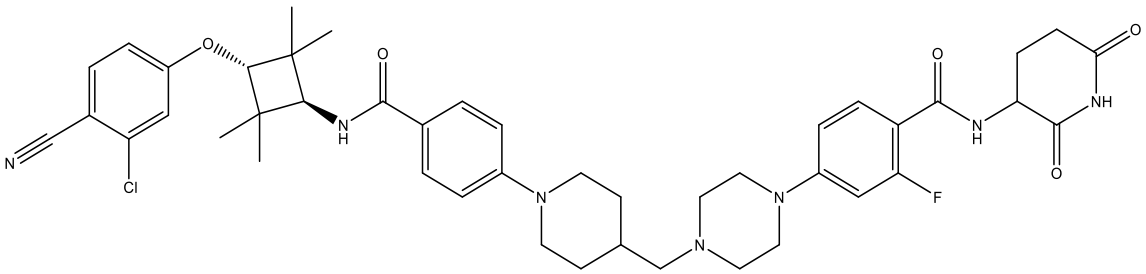
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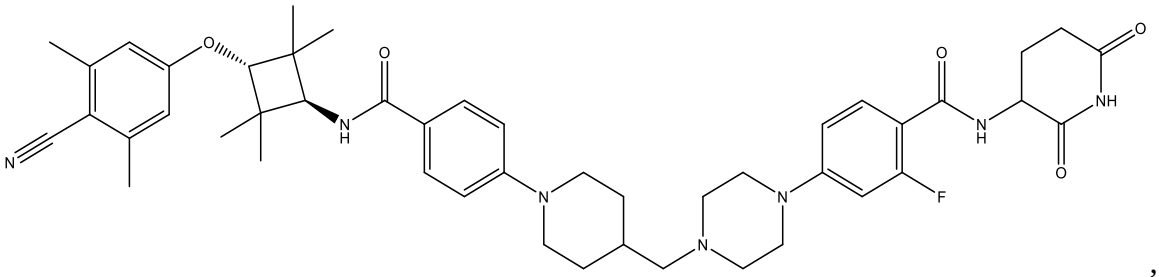
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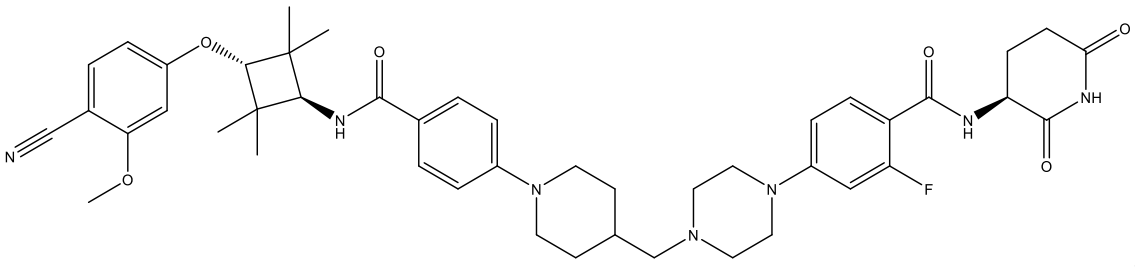
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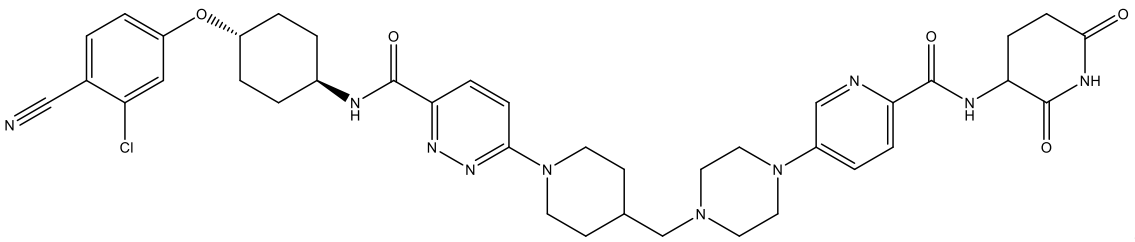
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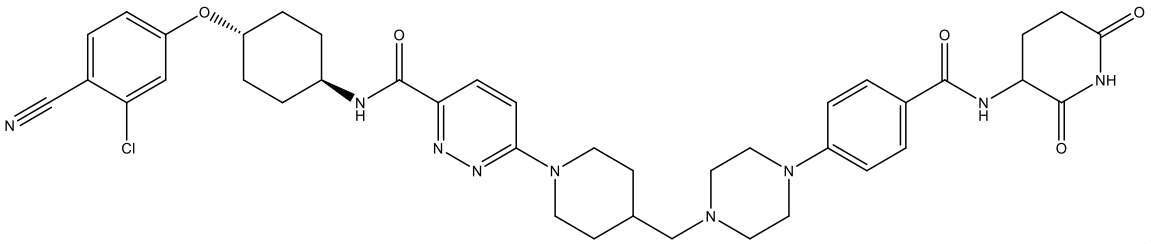
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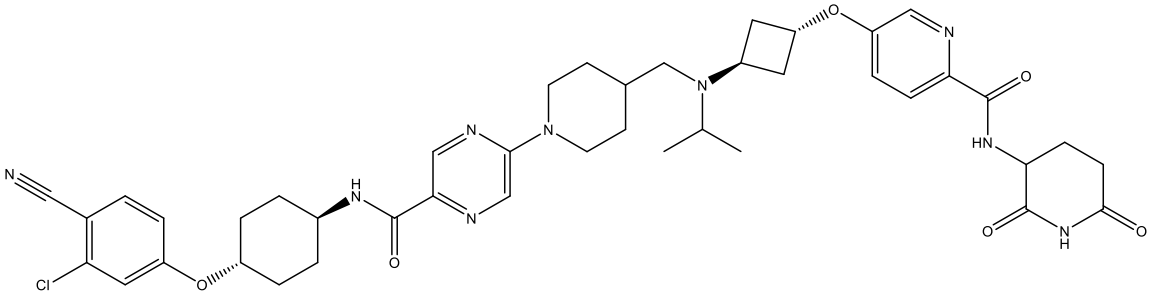
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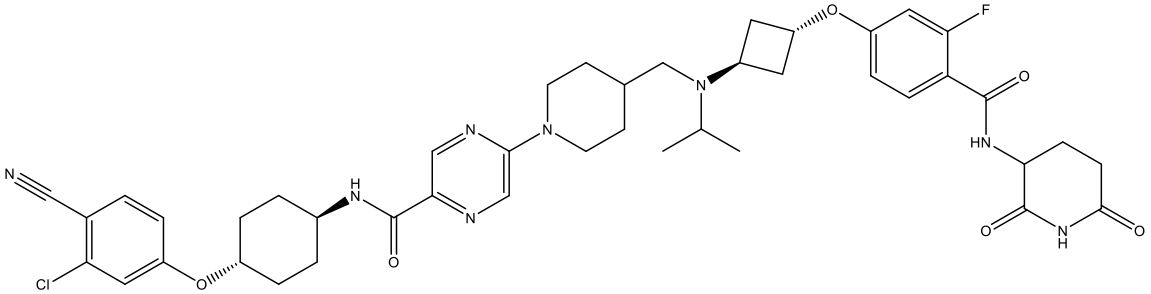
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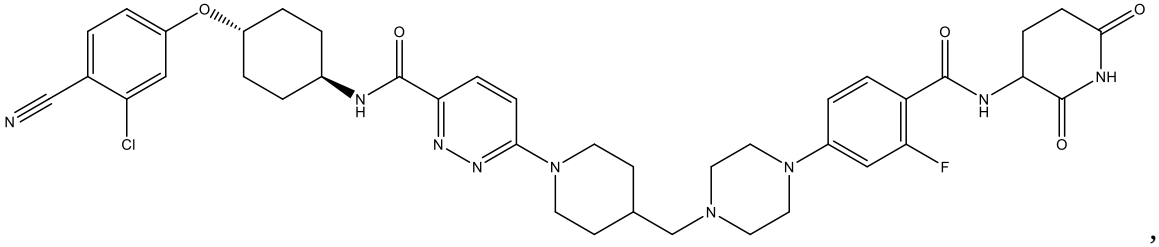
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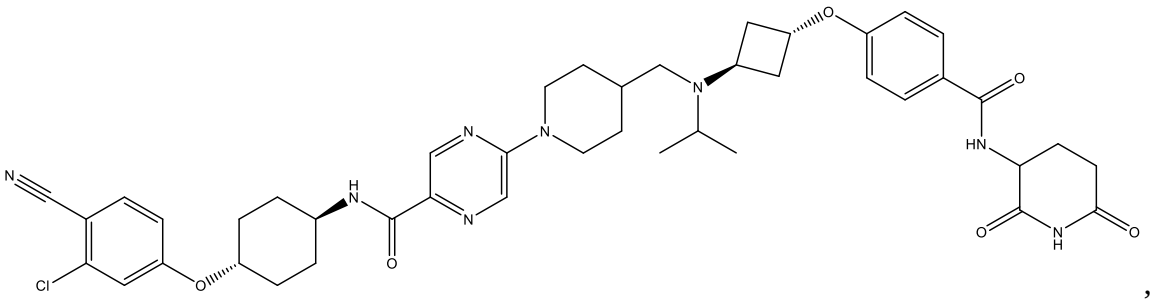


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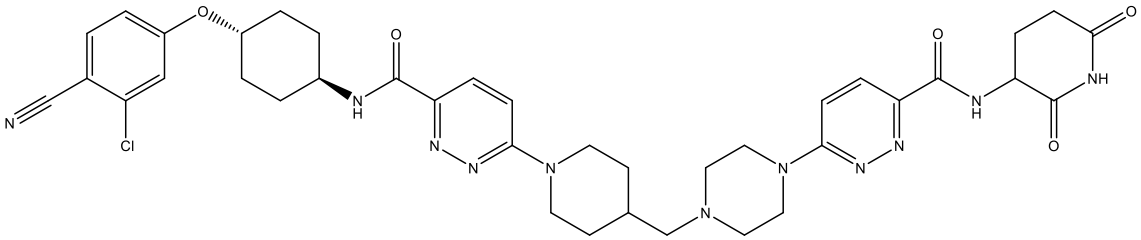


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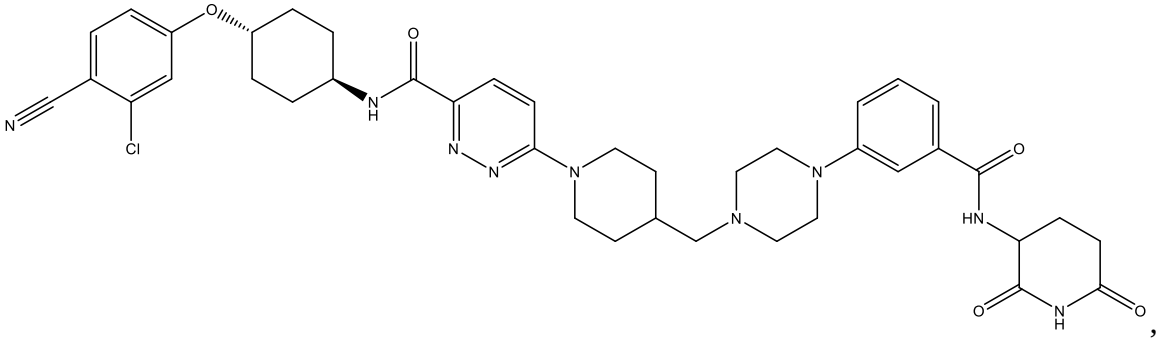
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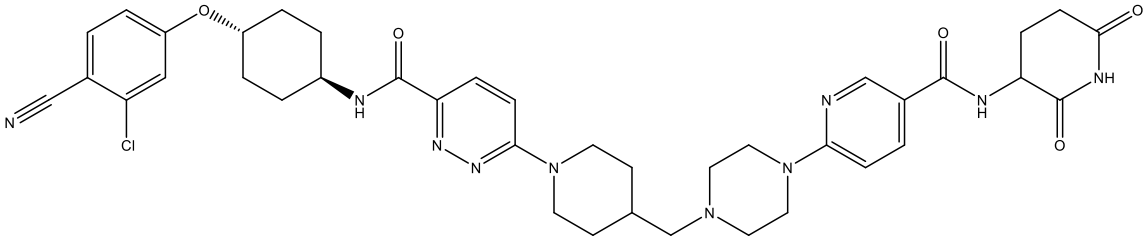
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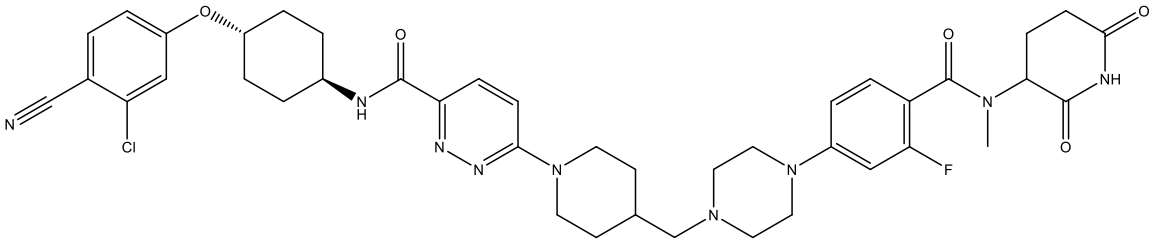
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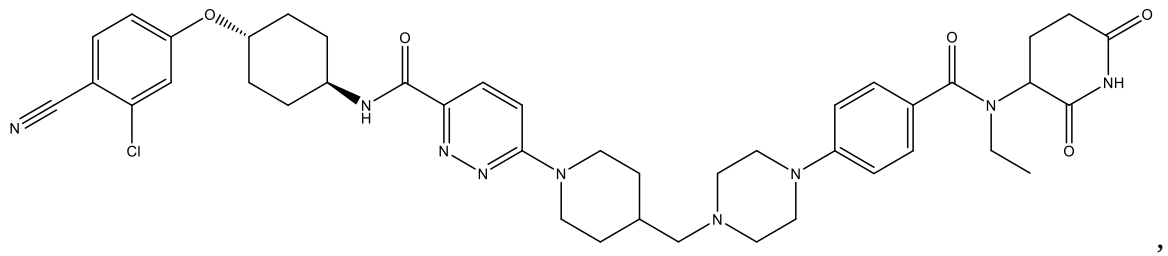
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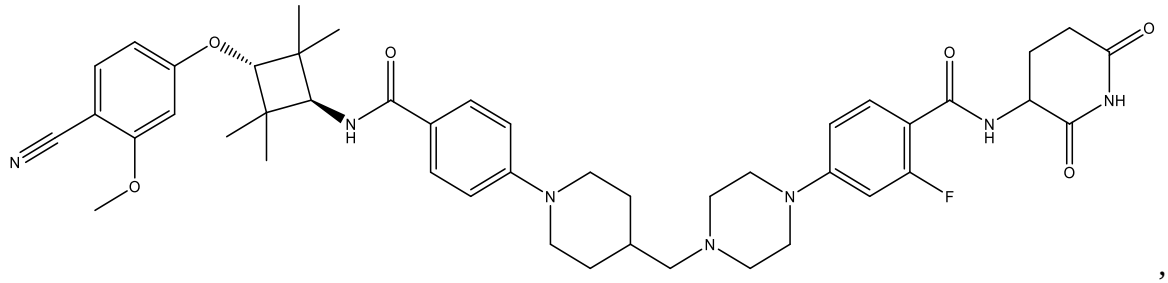
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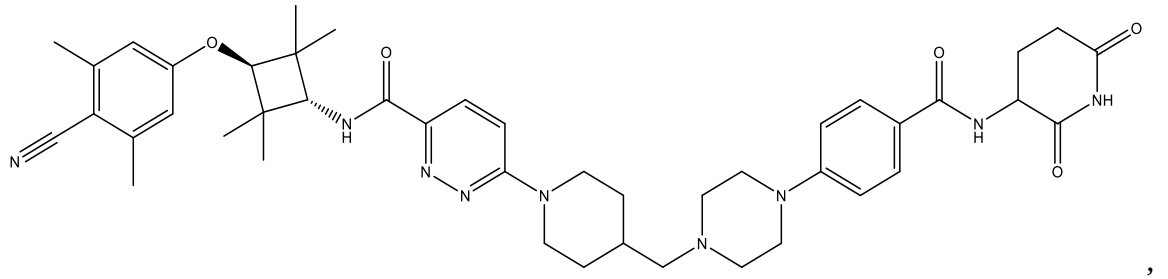
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or a pharmaceutically acceptable salt thereof.

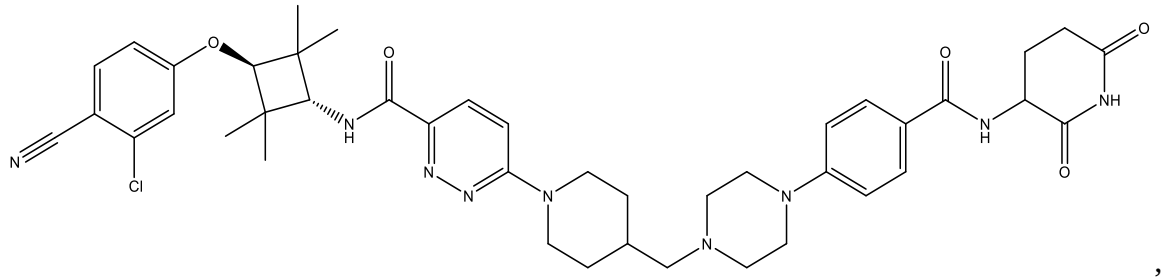
[0010c] In a further aspect of the present disclosure, there is provided a bifunctional compound, wherein the compound is:



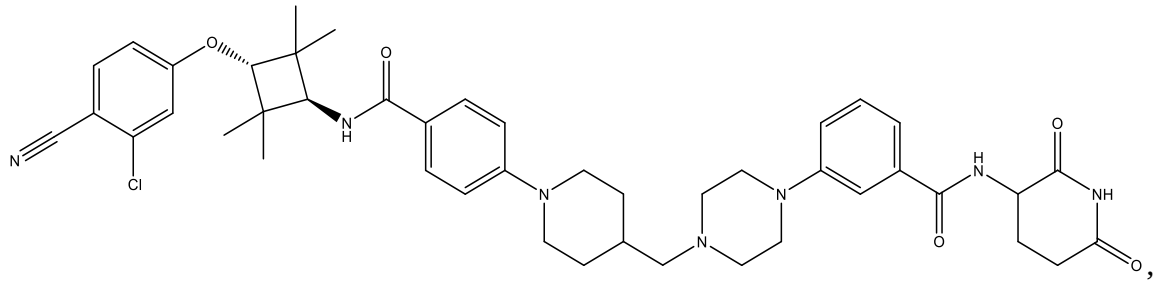
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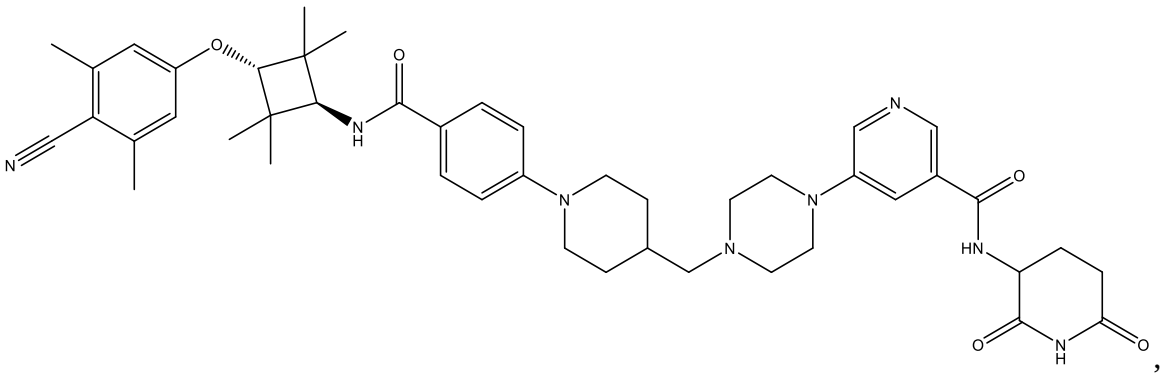
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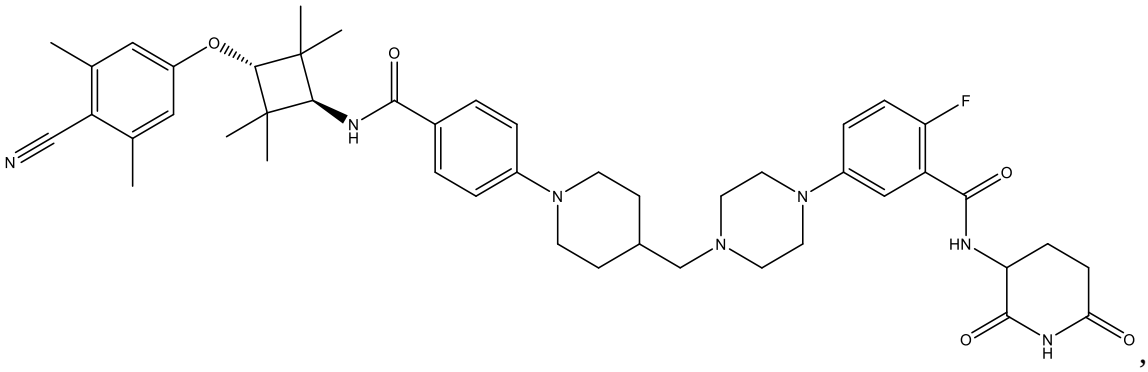


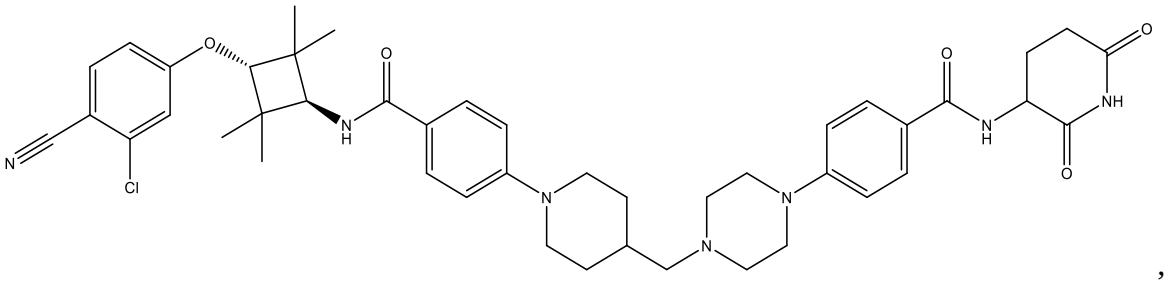
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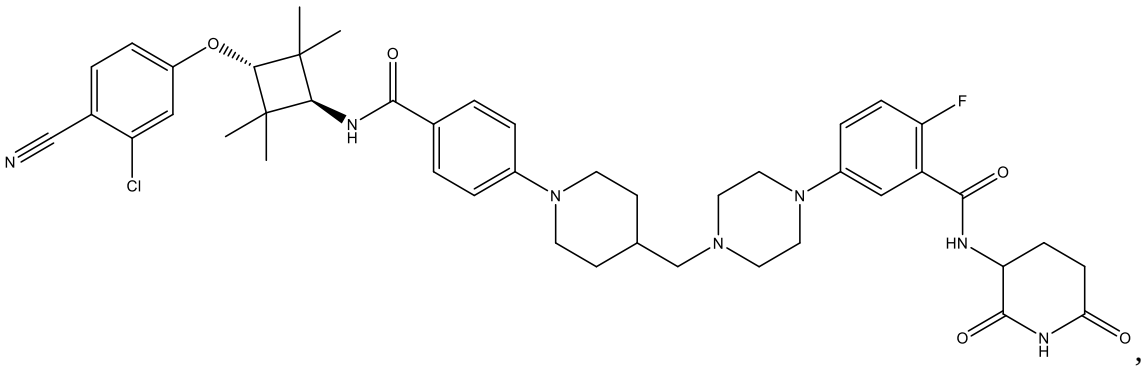


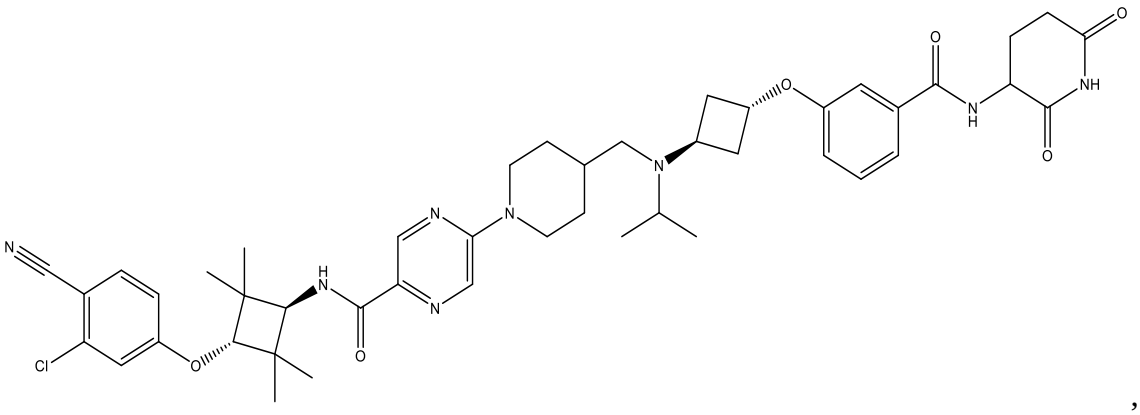
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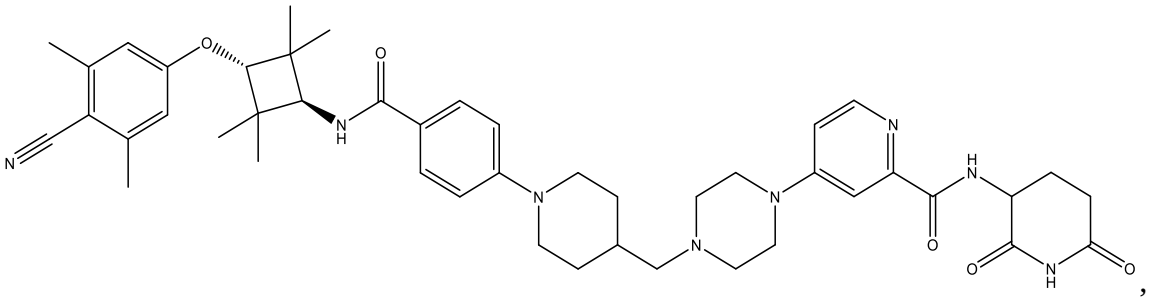

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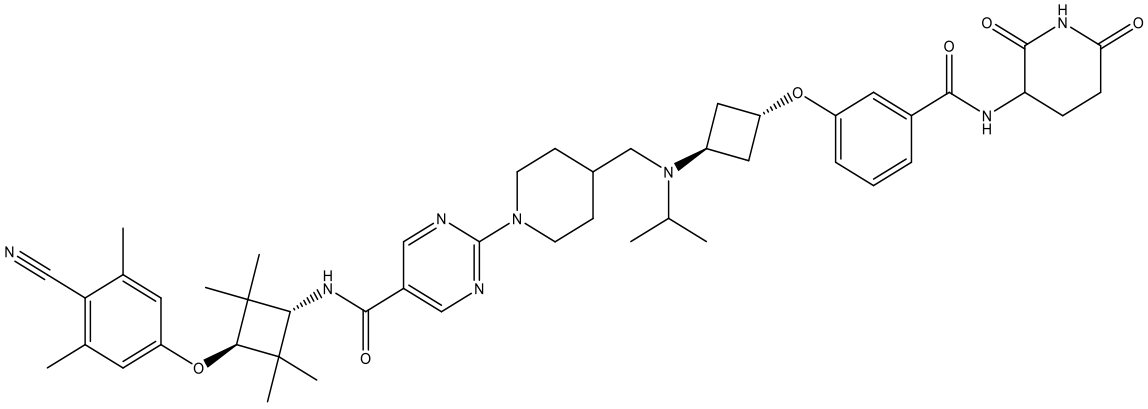

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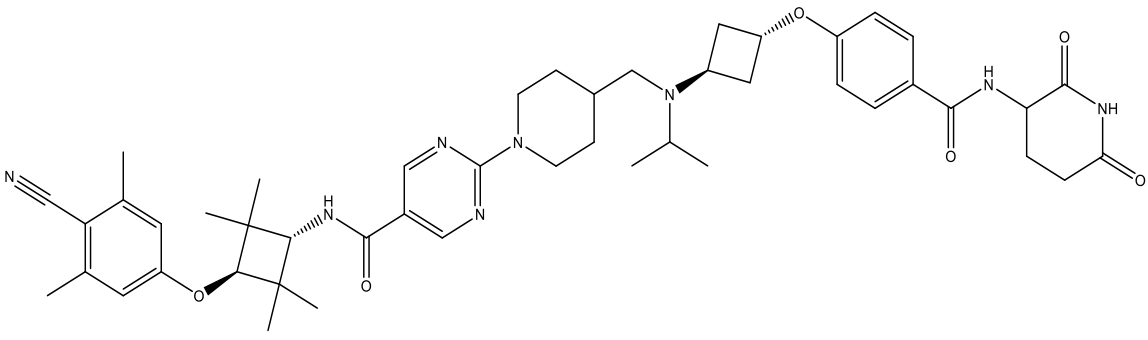
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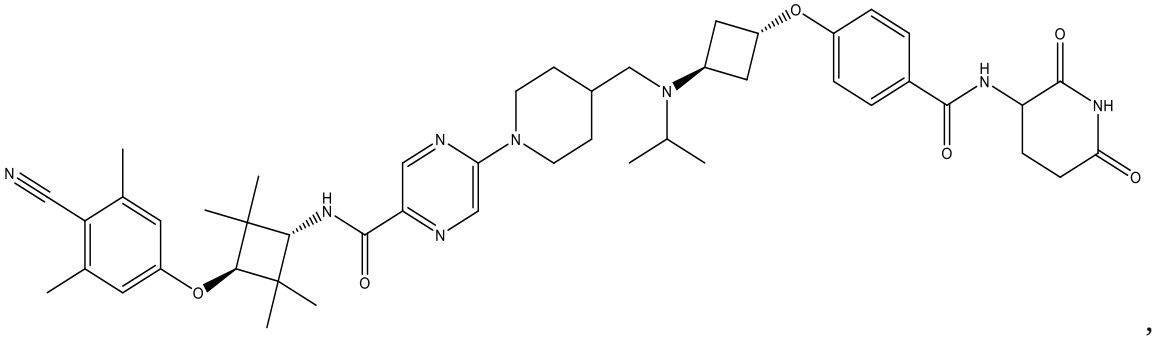
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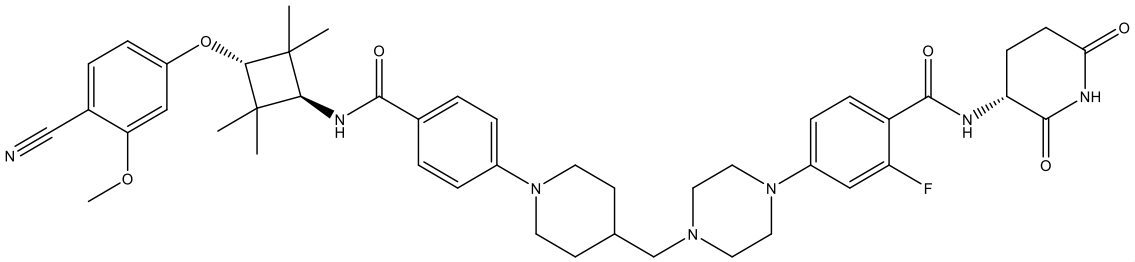
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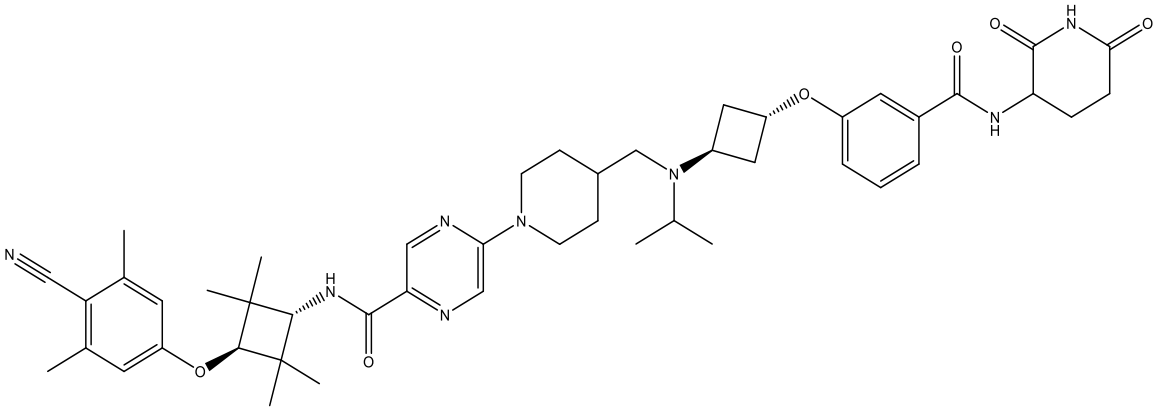
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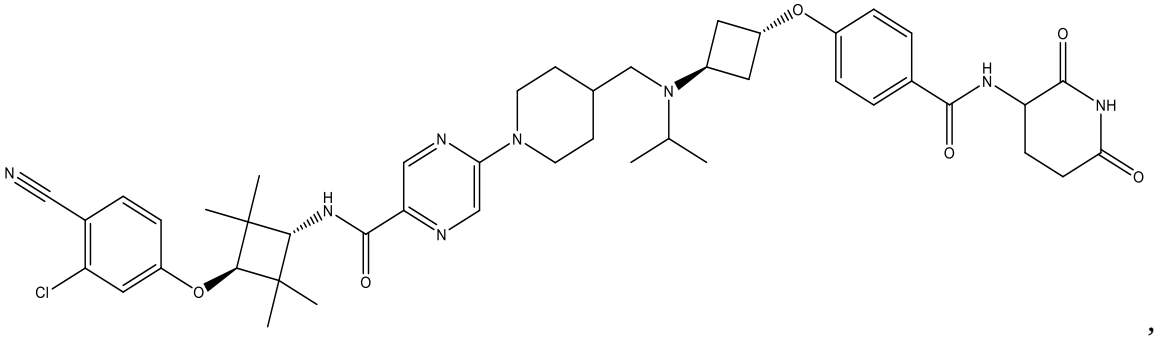
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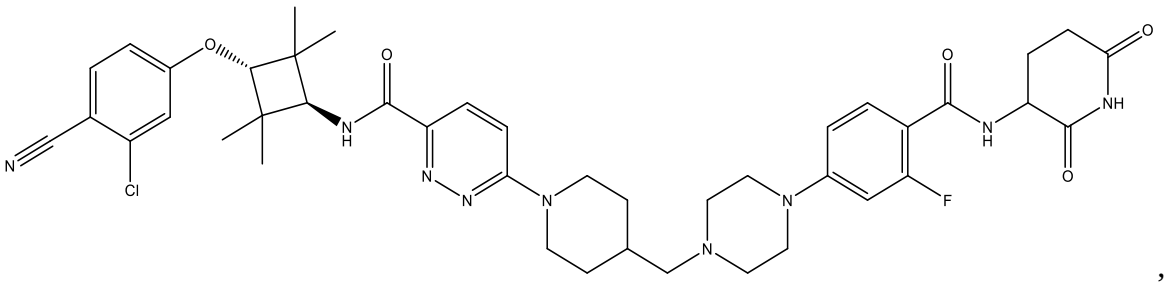
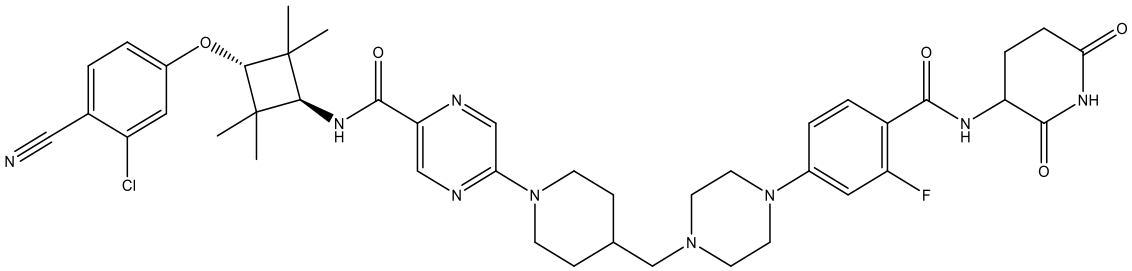
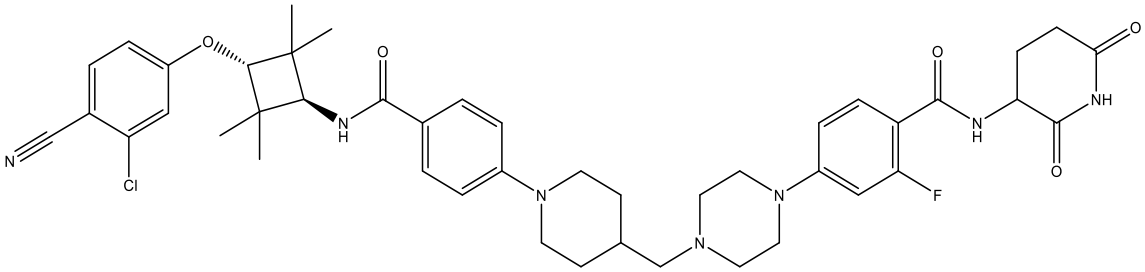
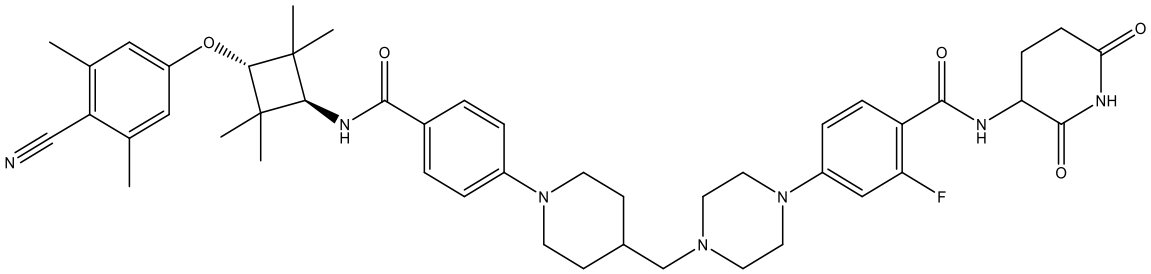
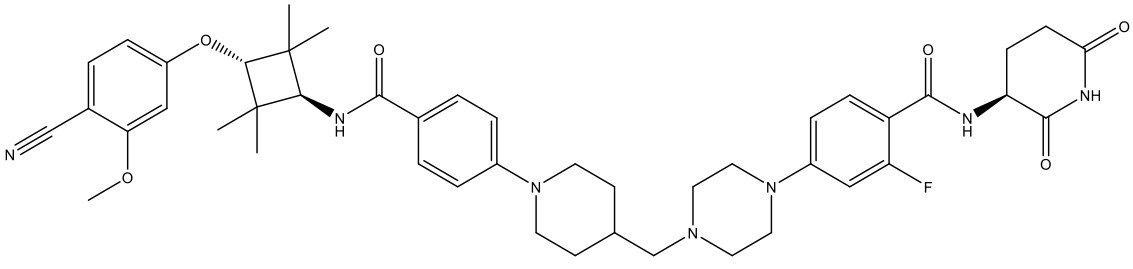
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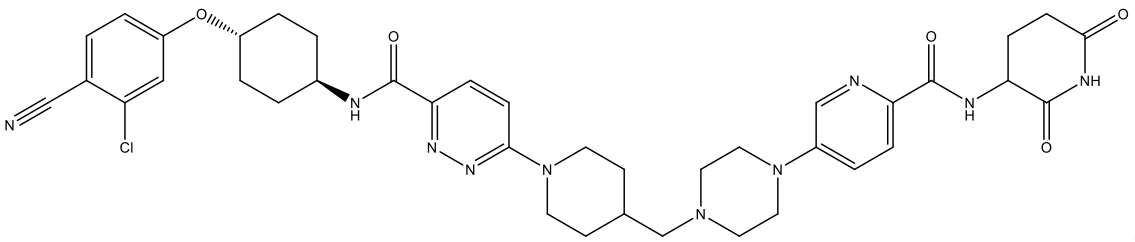


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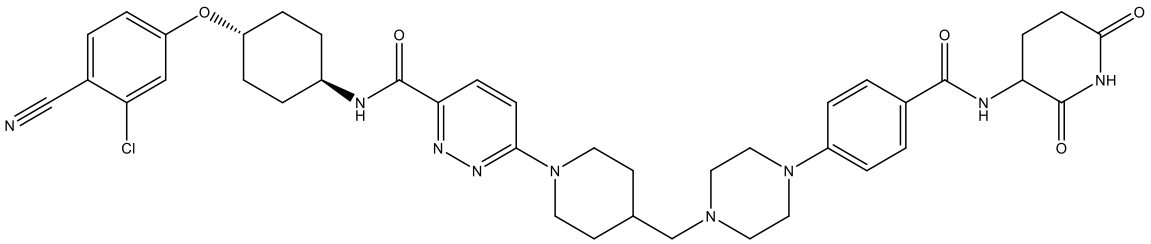


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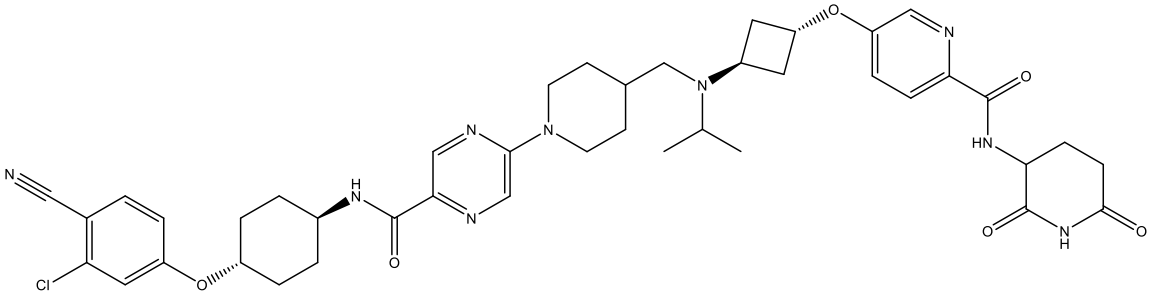

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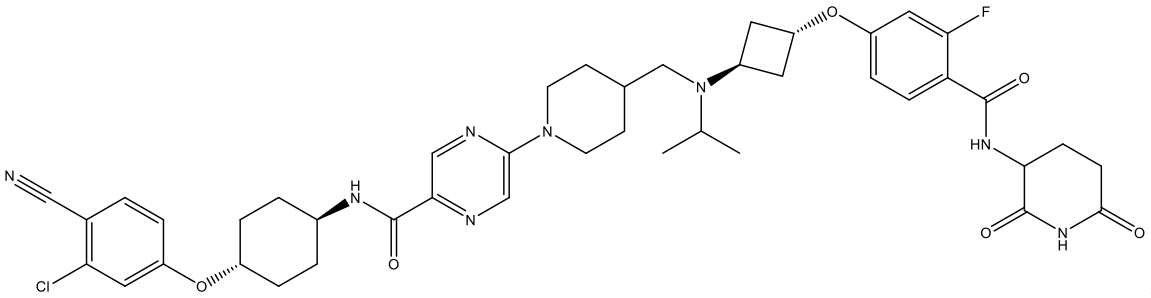
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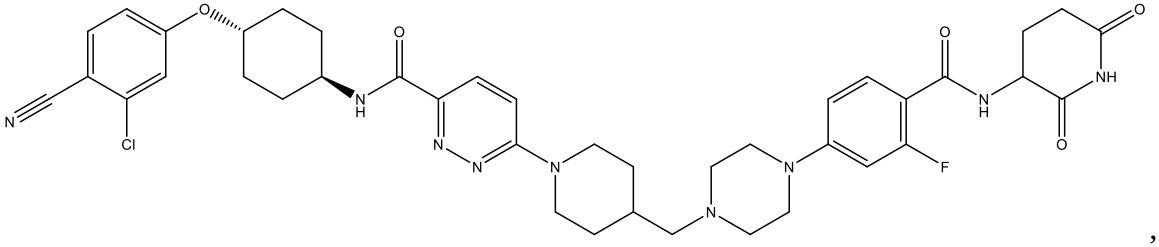
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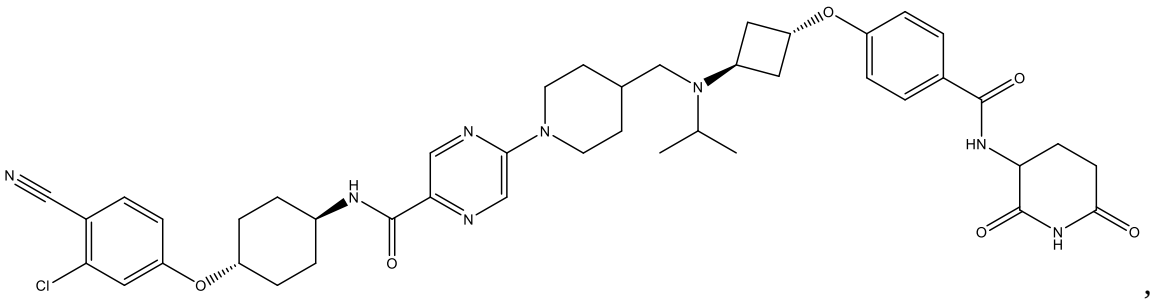
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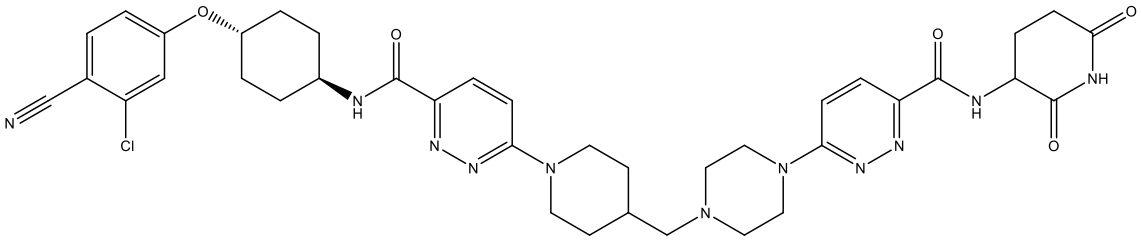


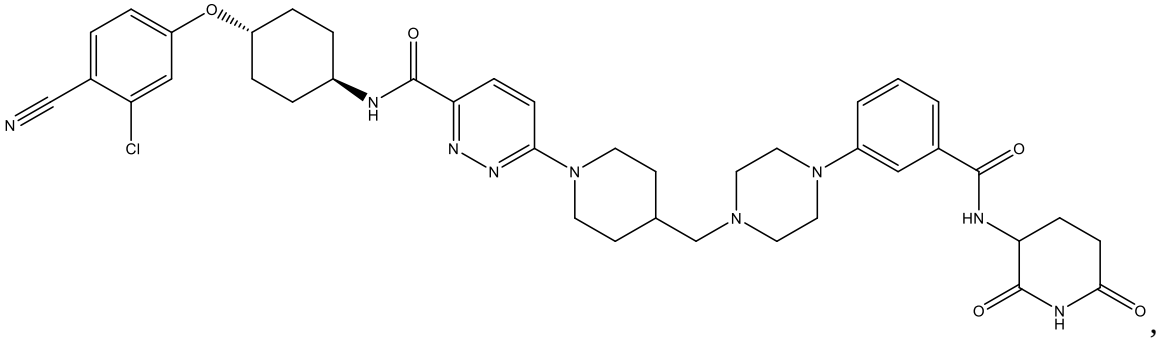
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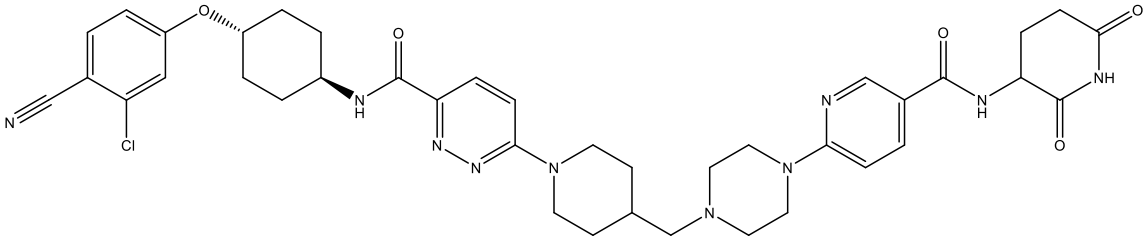


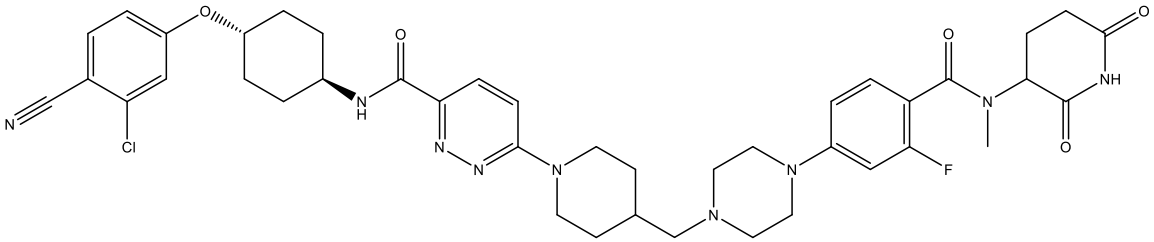
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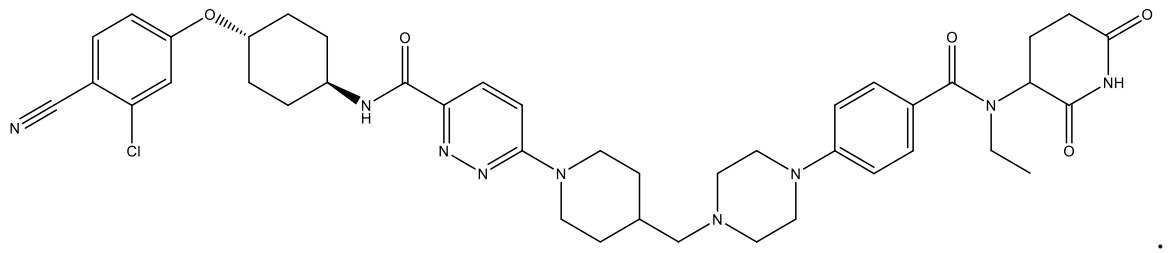

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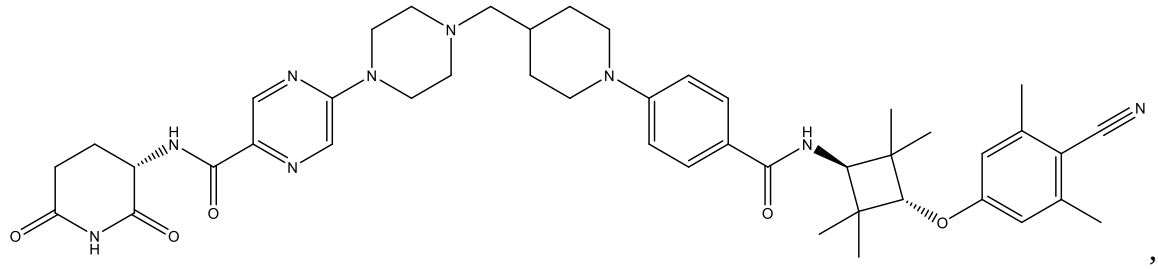

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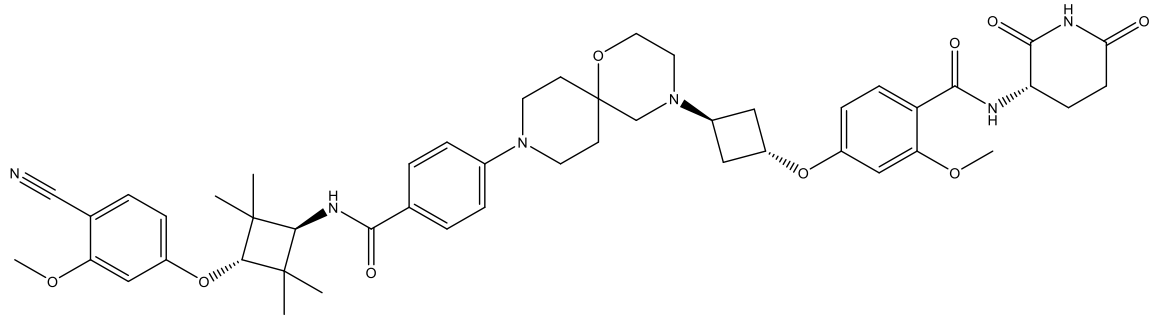


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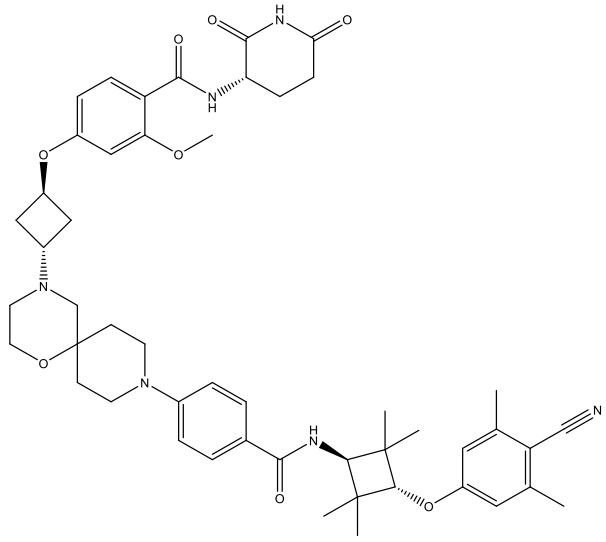
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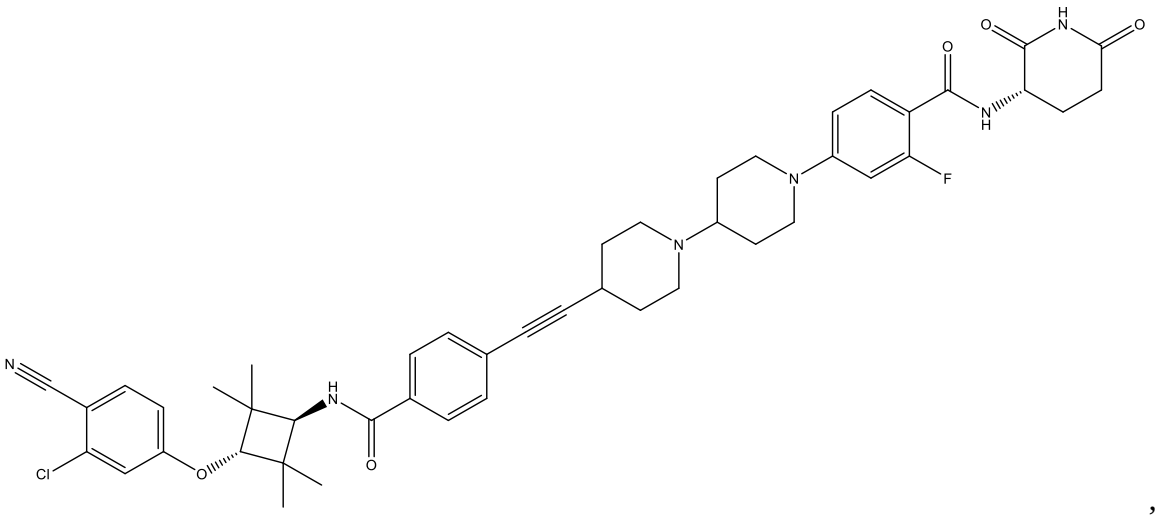
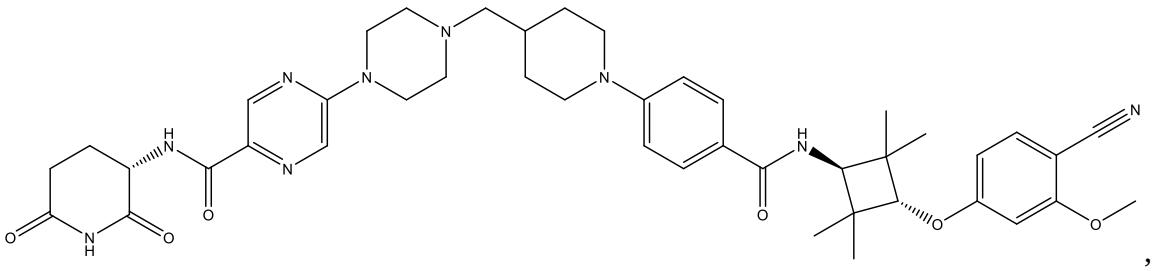
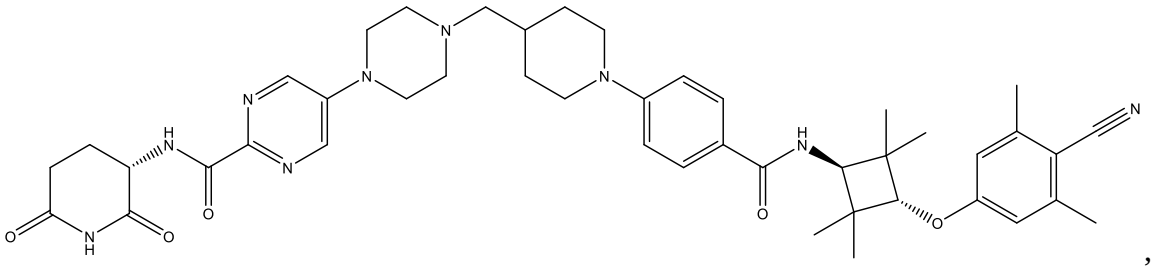
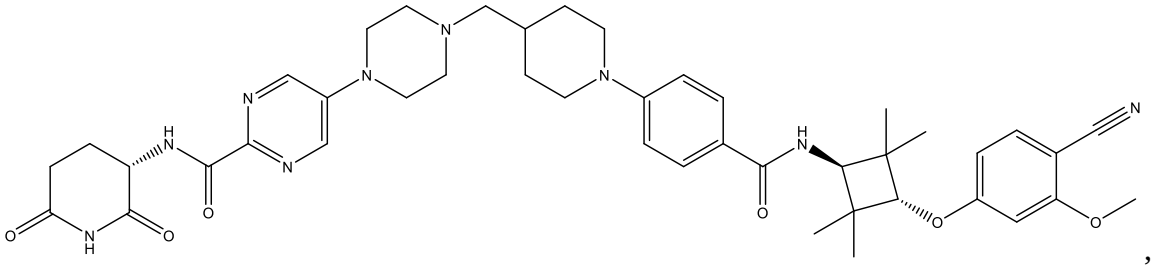
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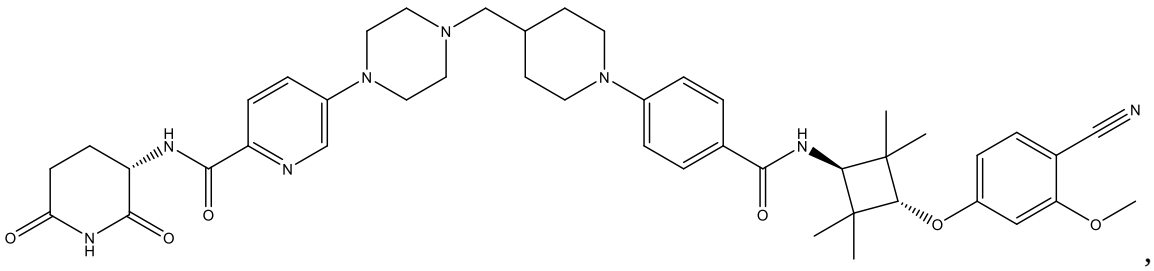


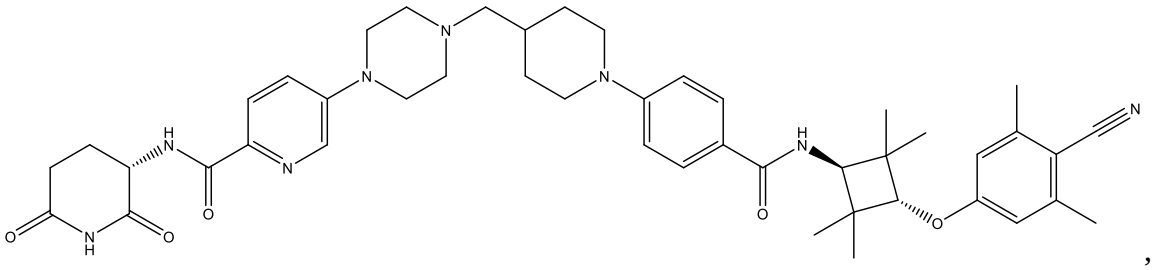
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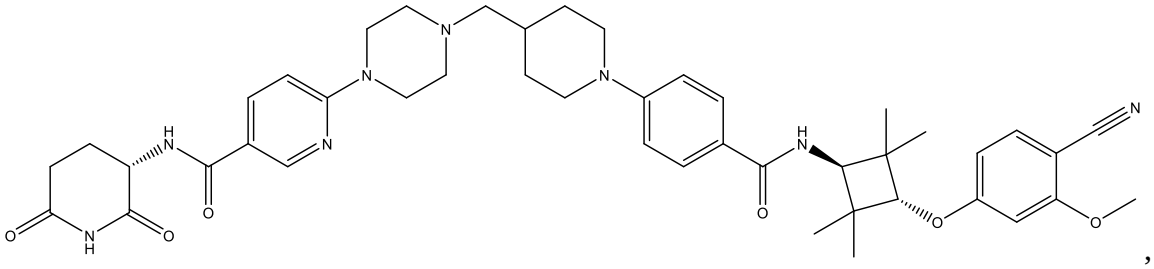


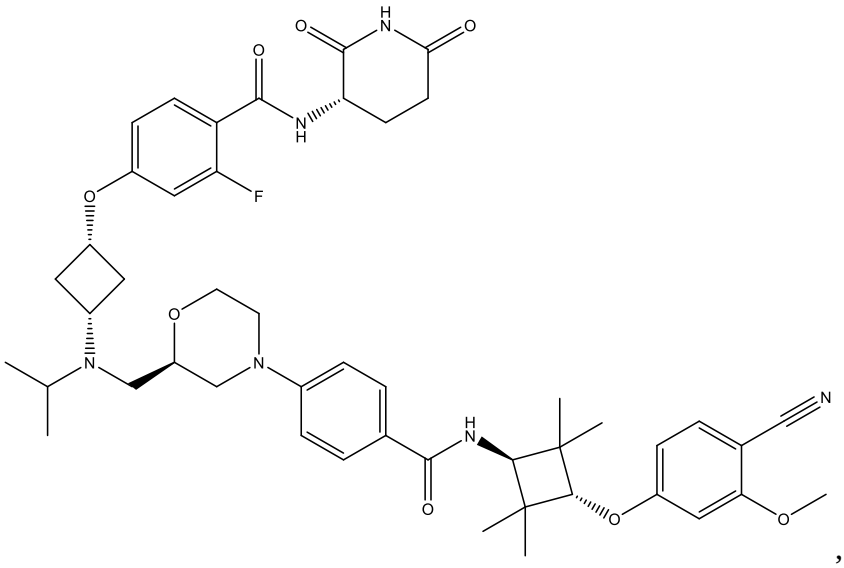
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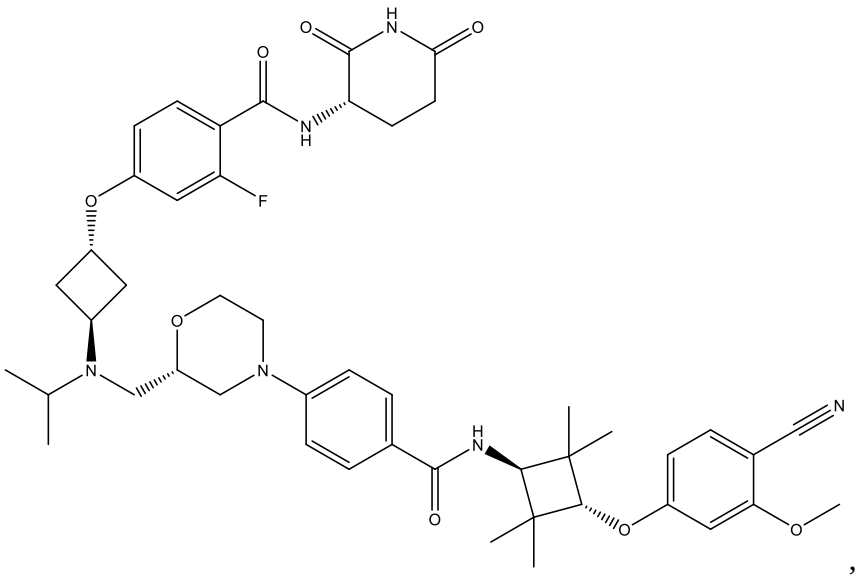

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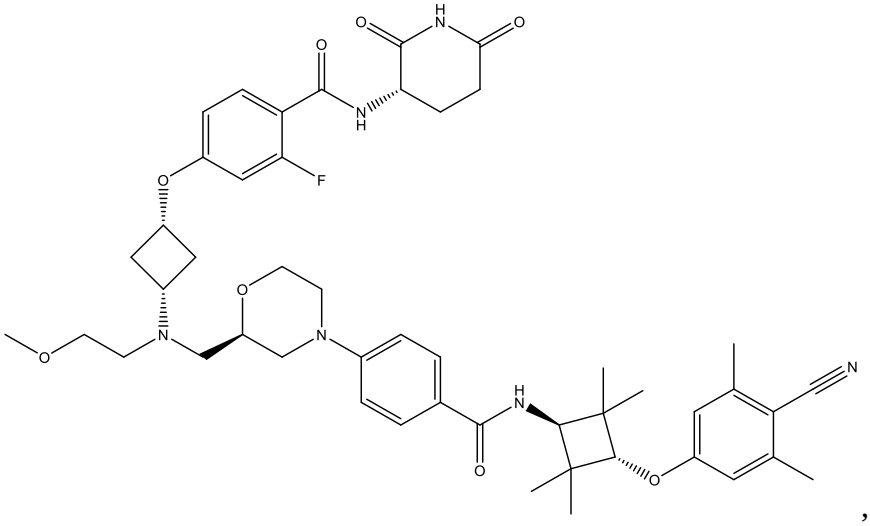

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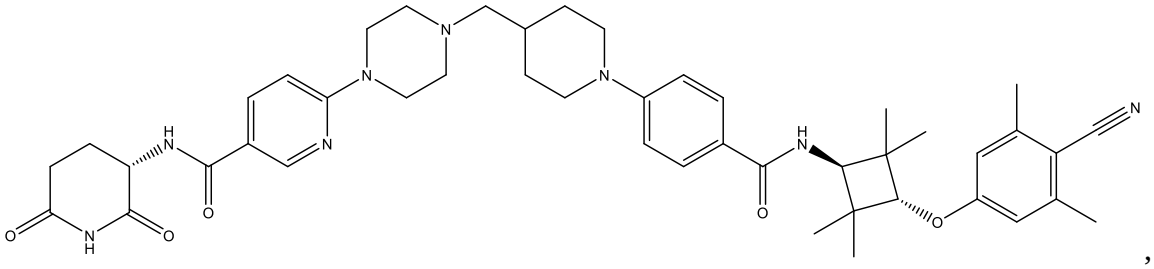

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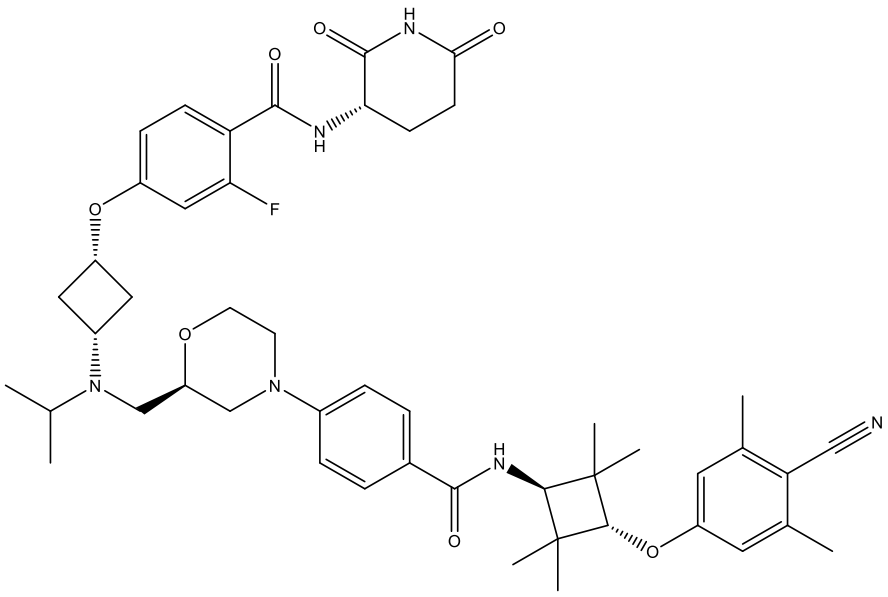
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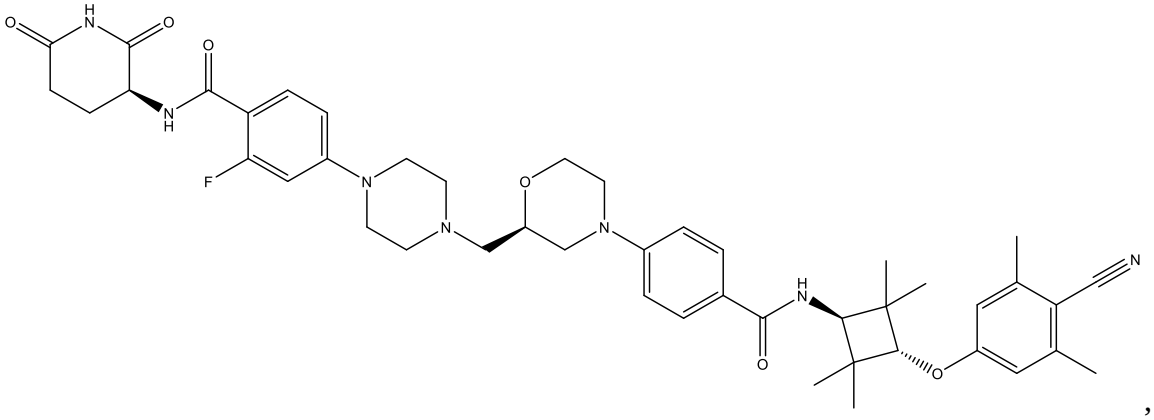
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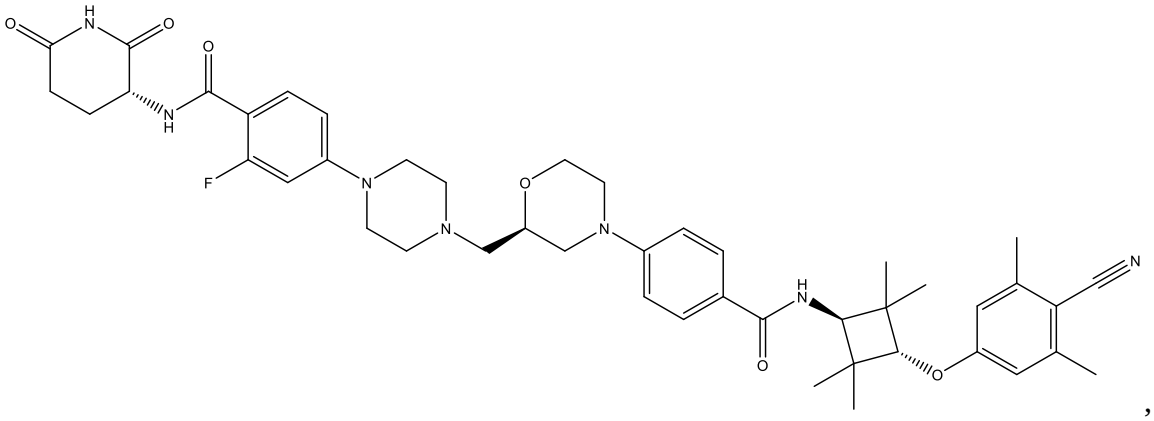
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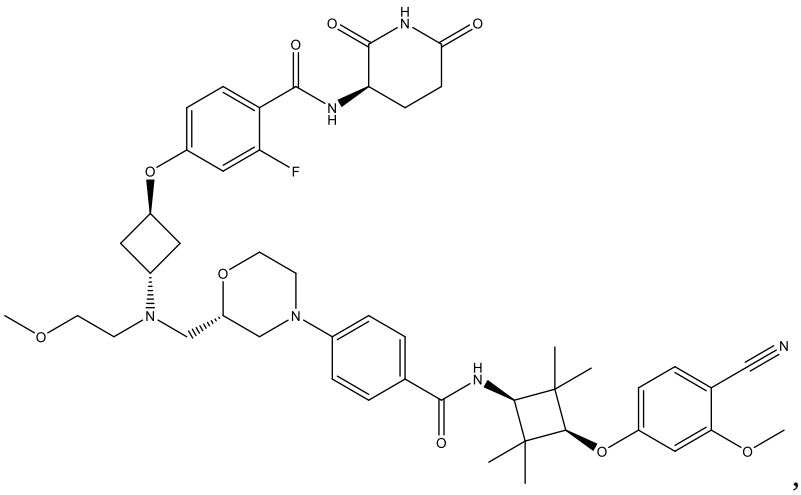
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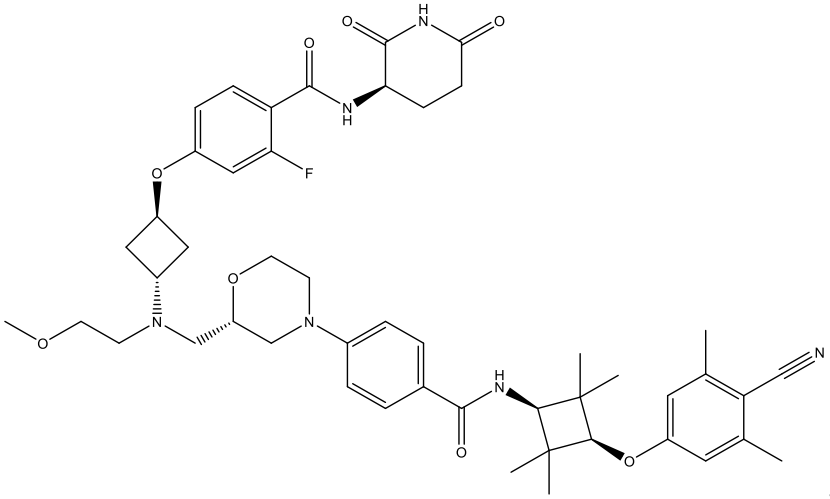
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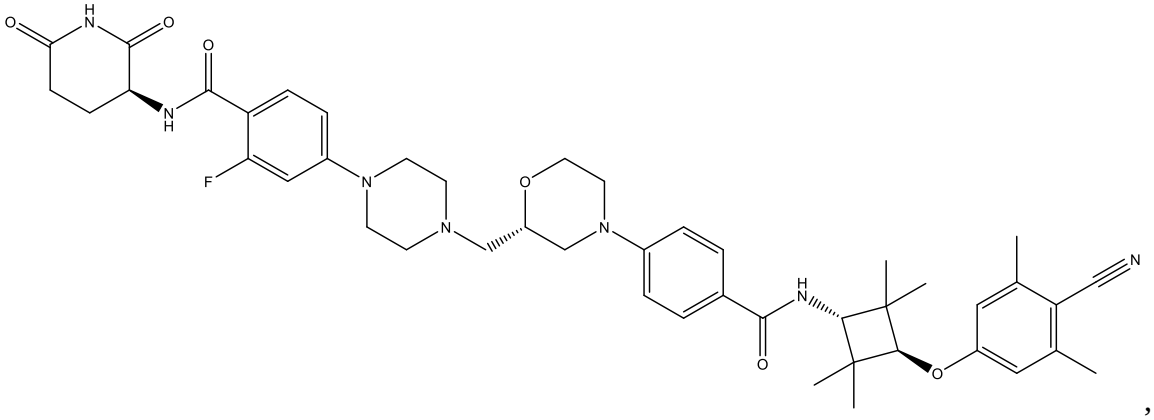
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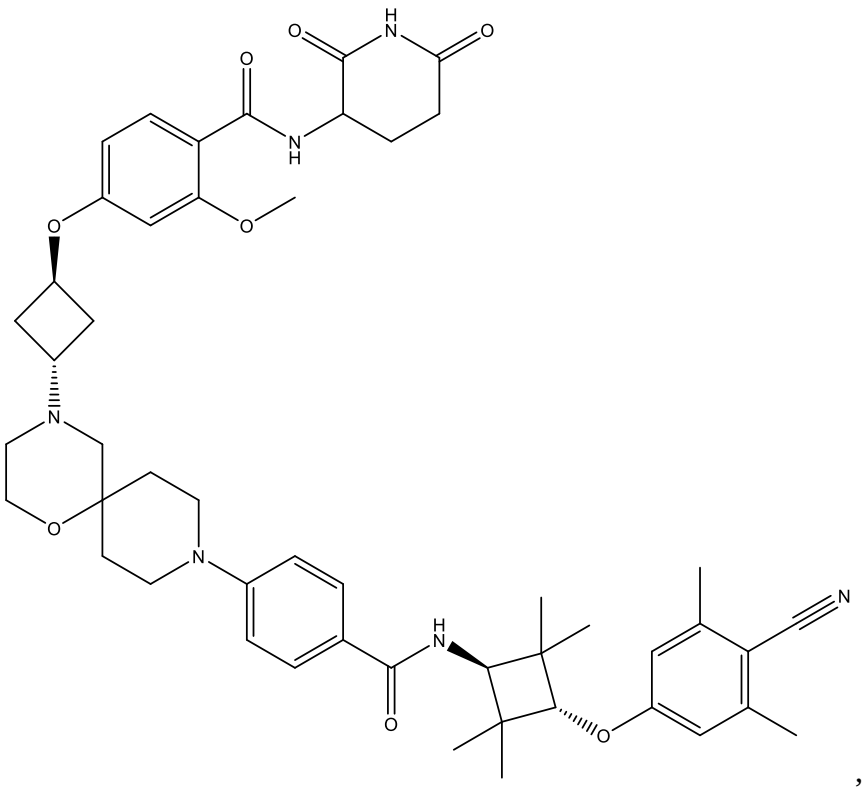
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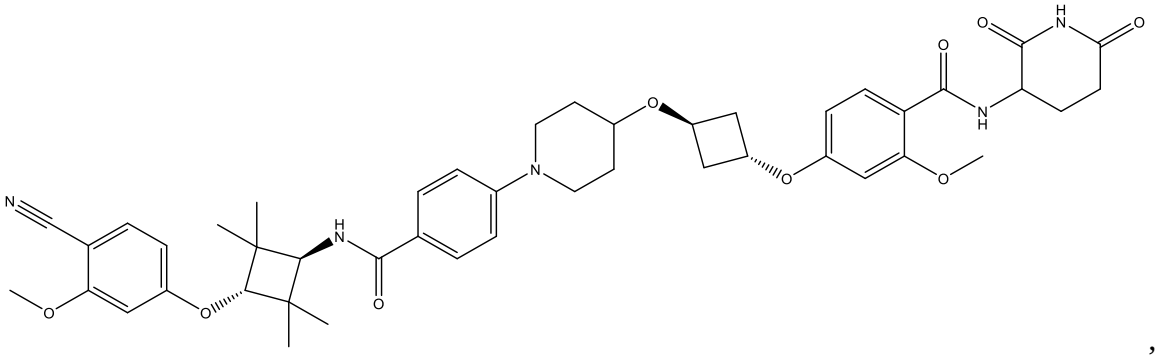
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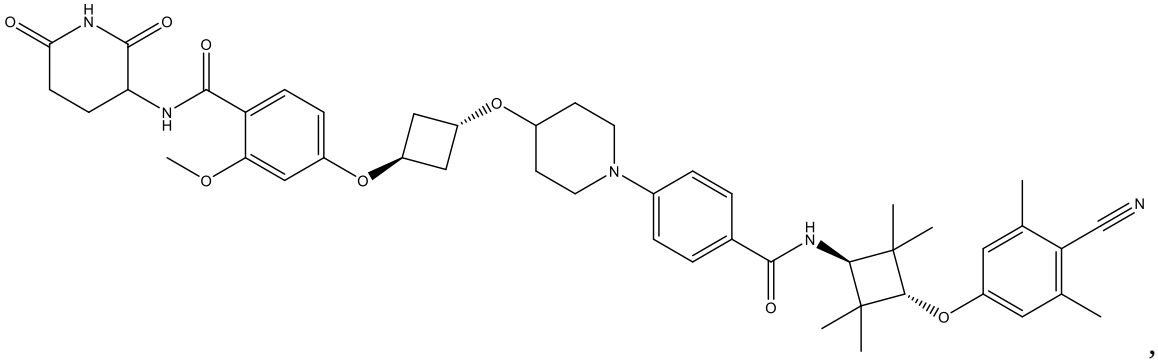
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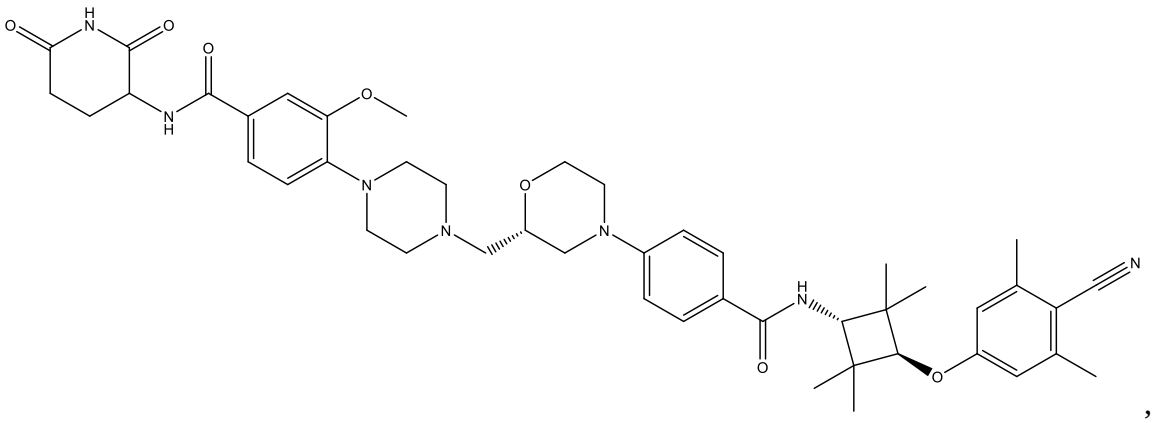
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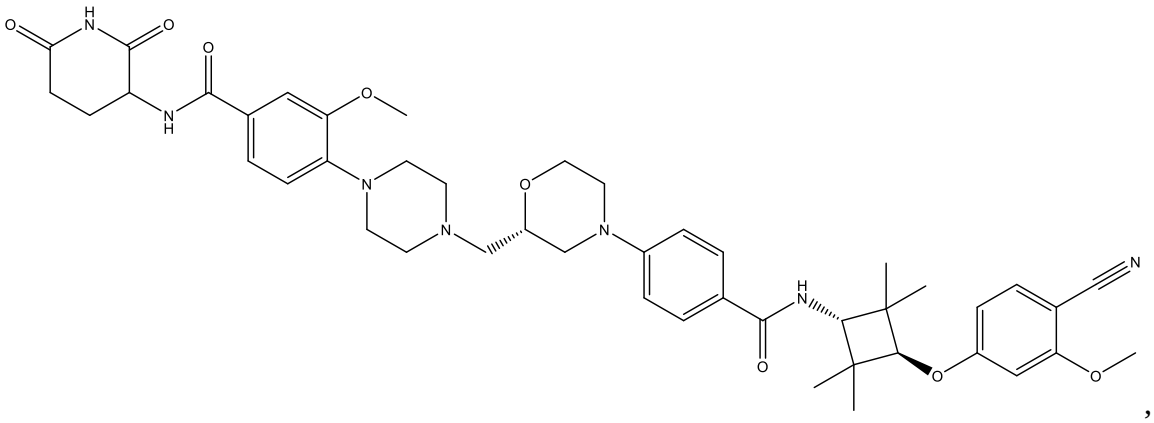


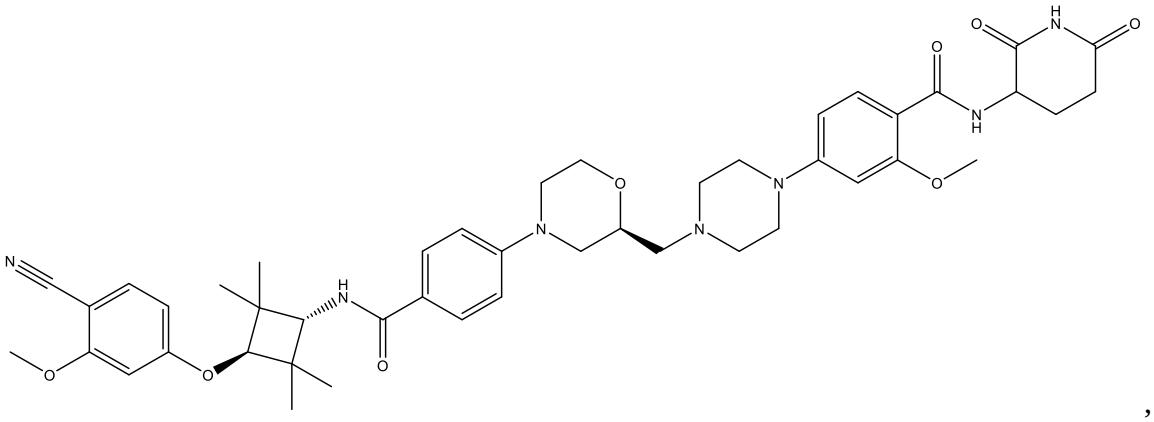
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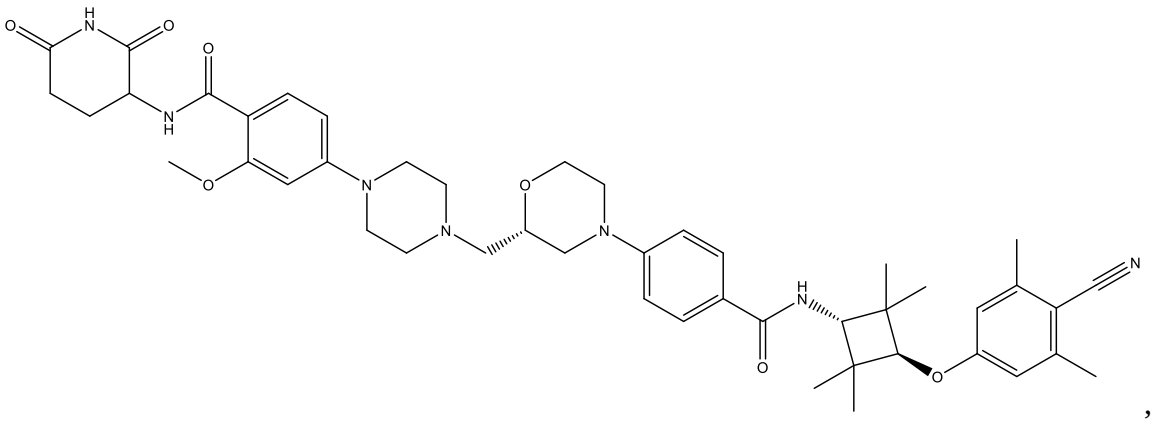


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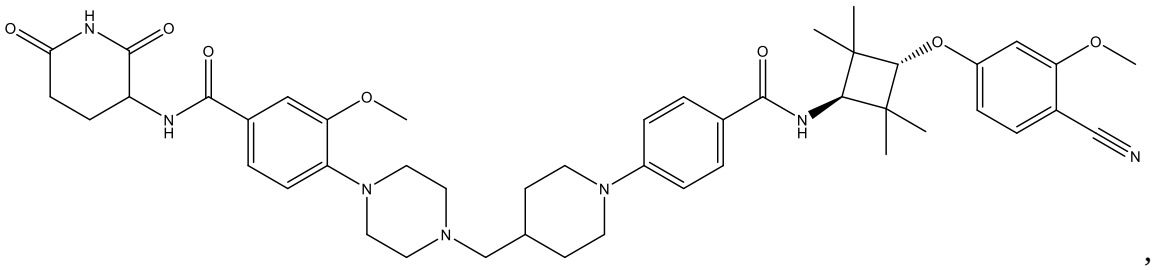

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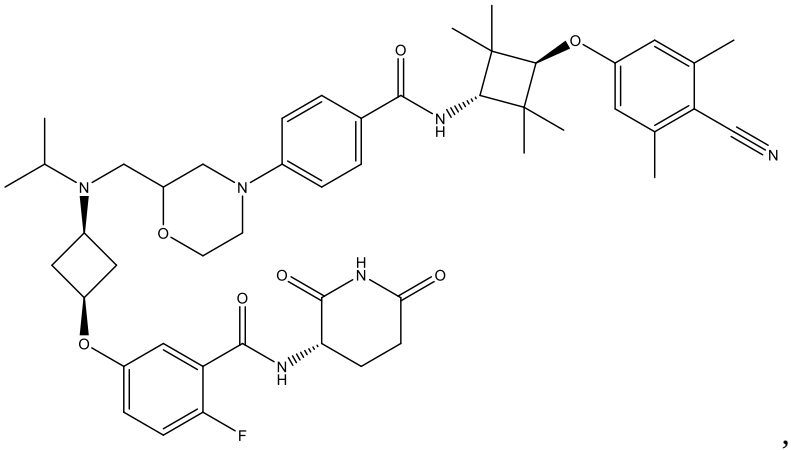

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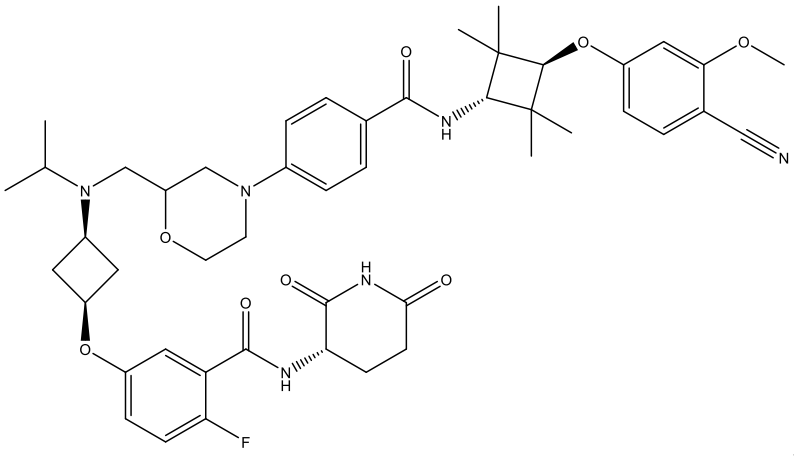
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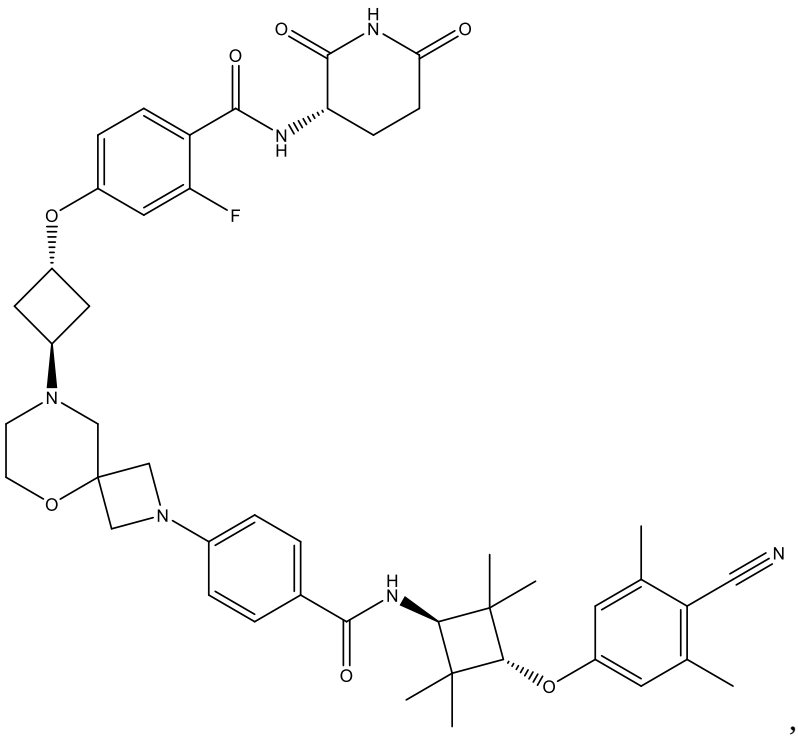
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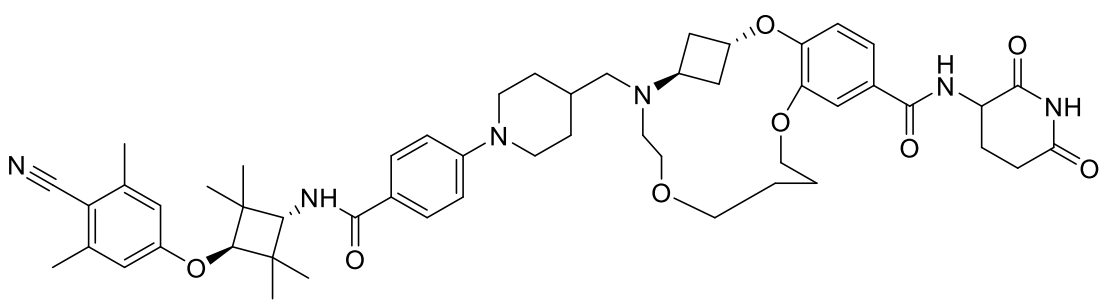
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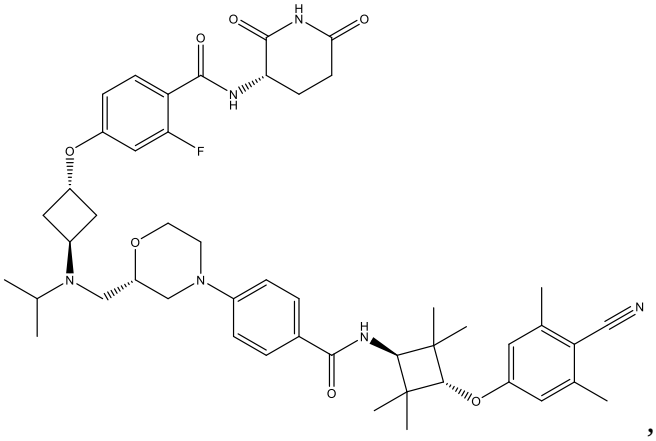
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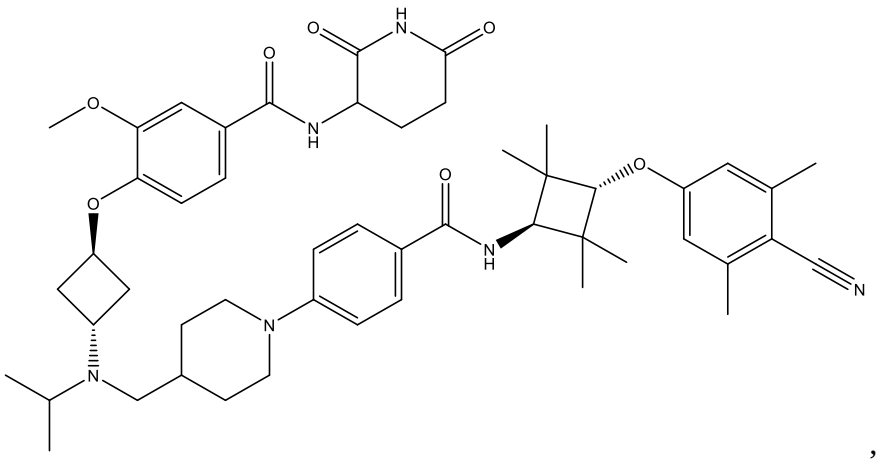
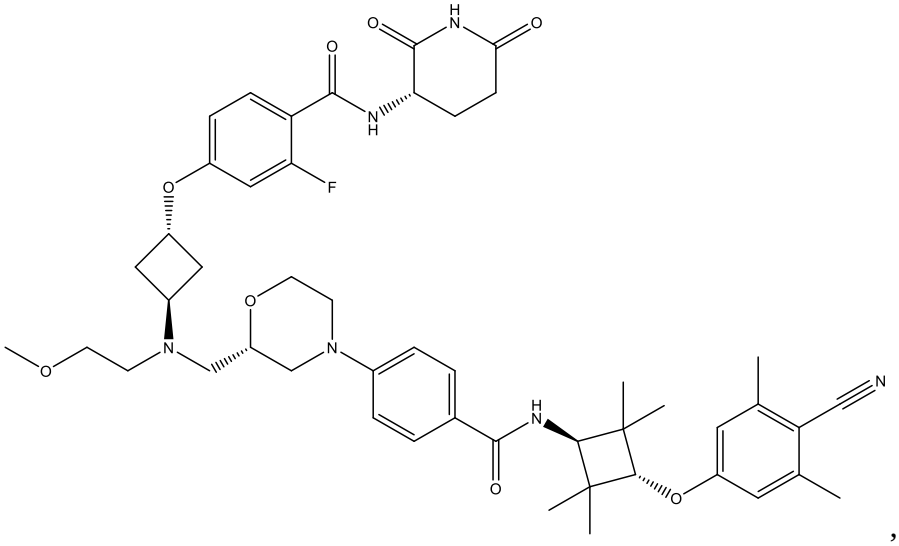
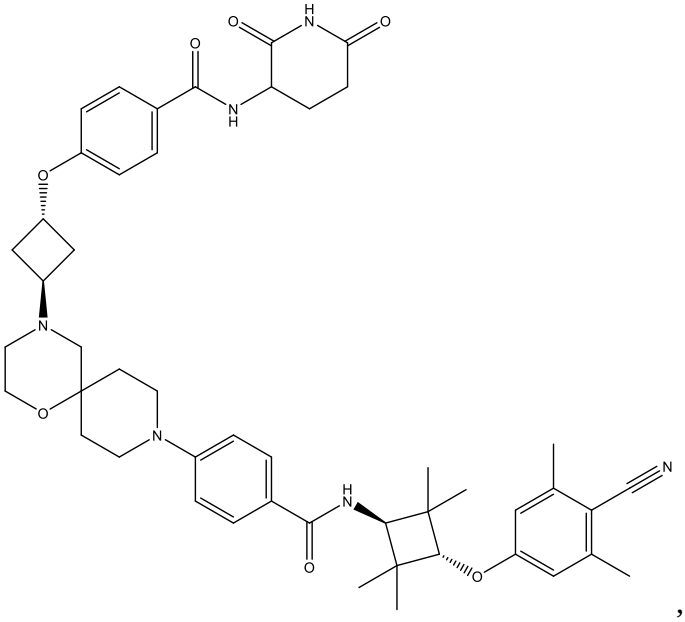
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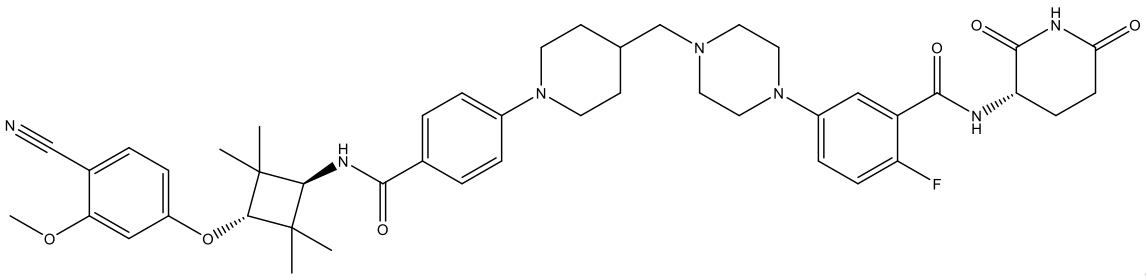


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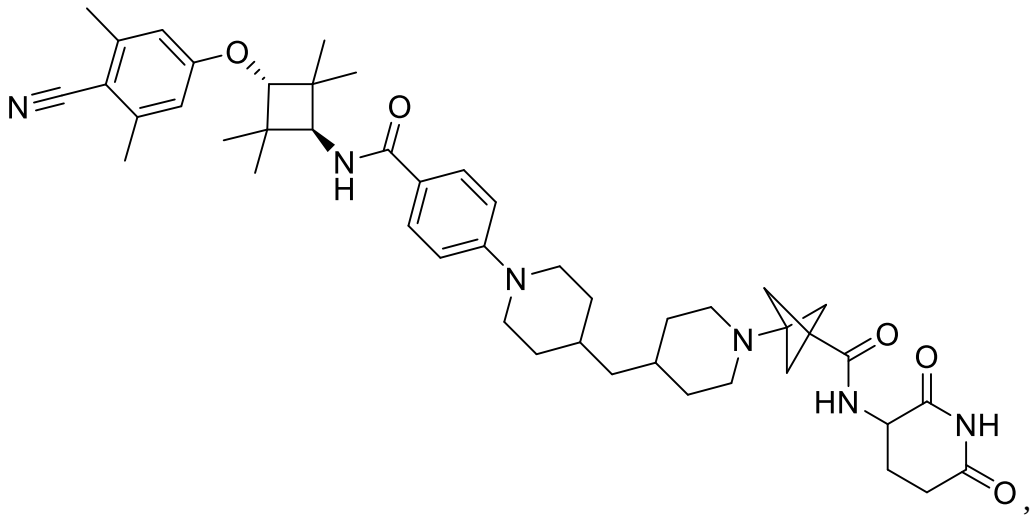


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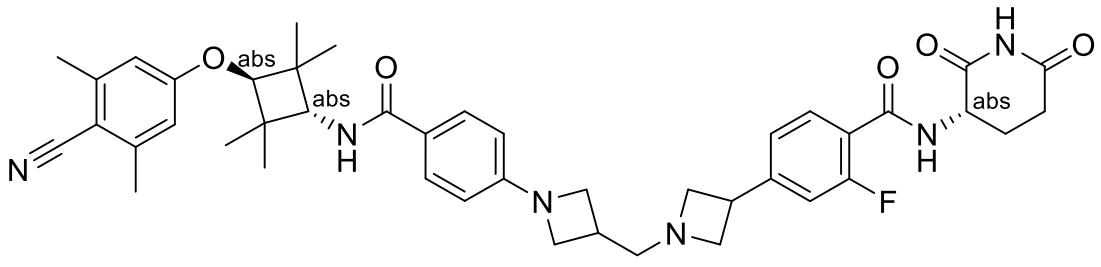

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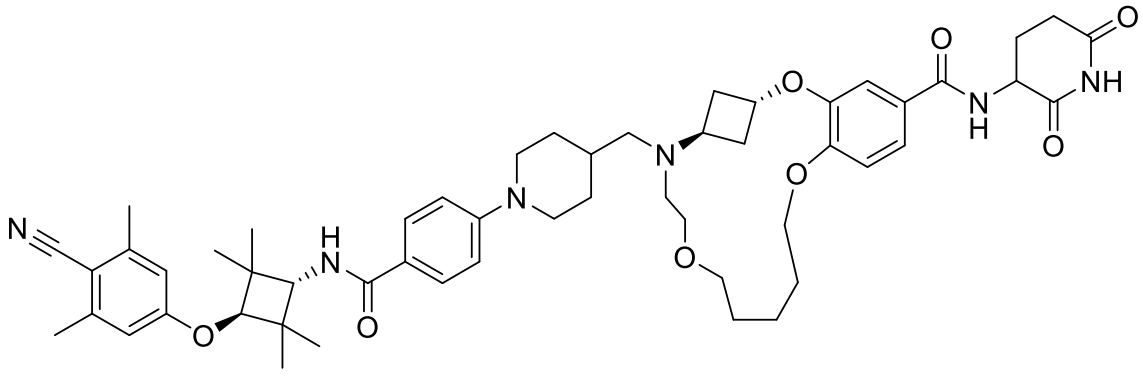
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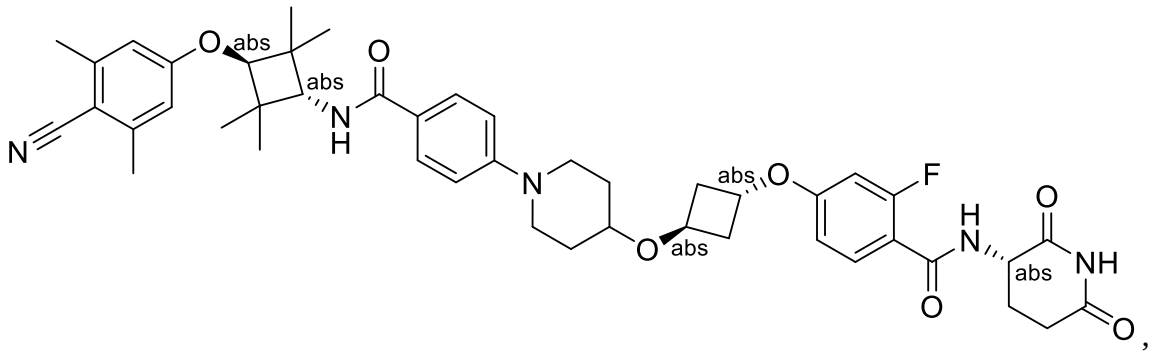
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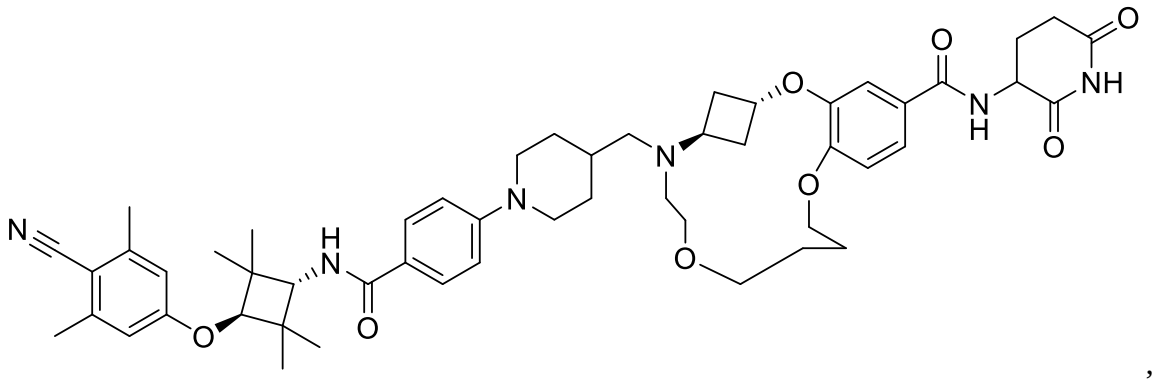
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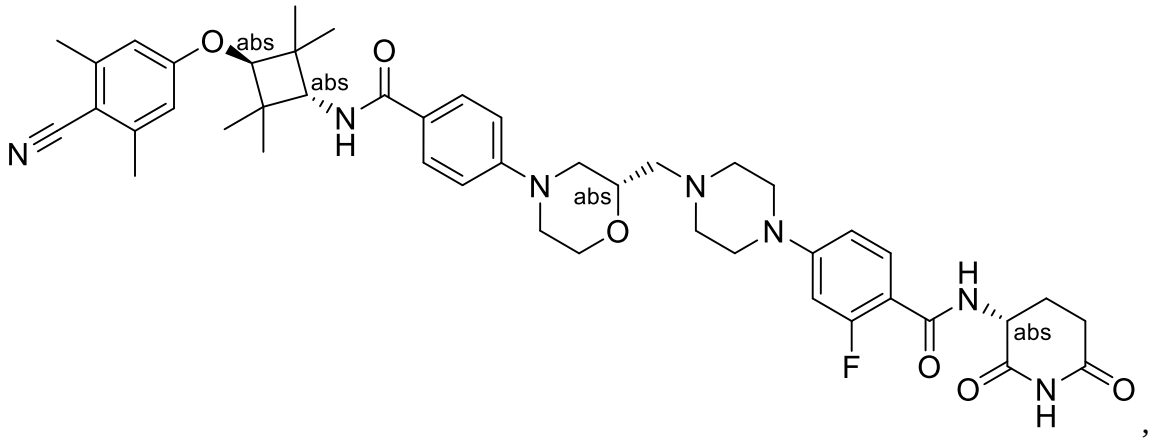
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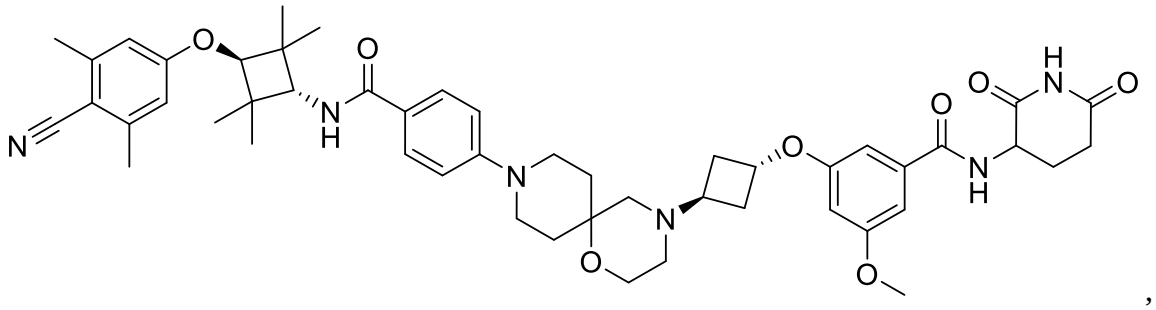
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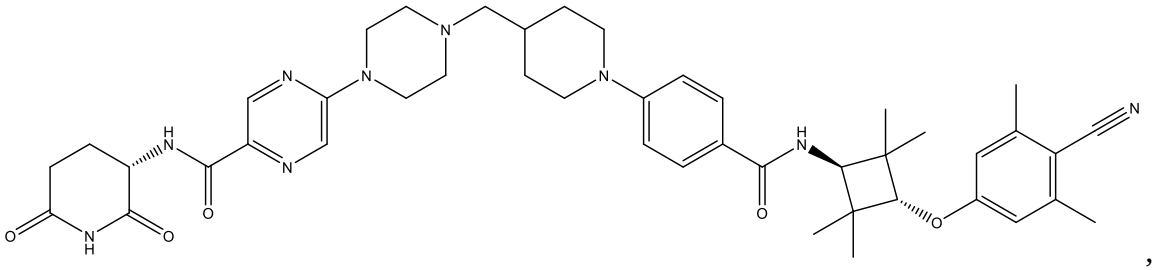
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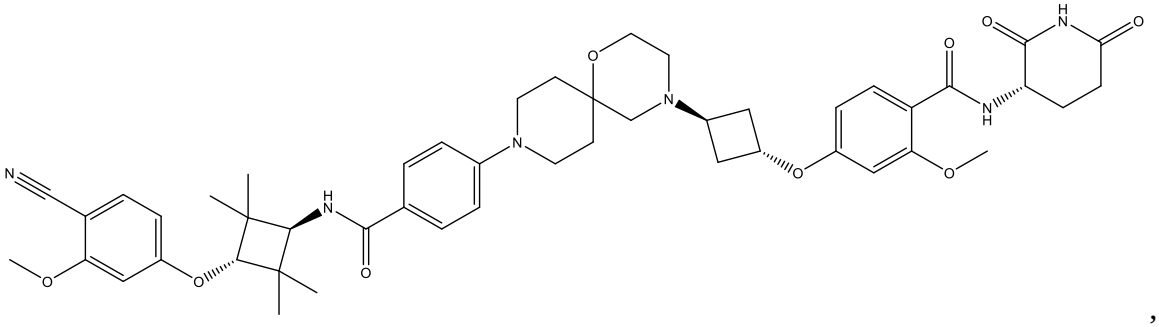


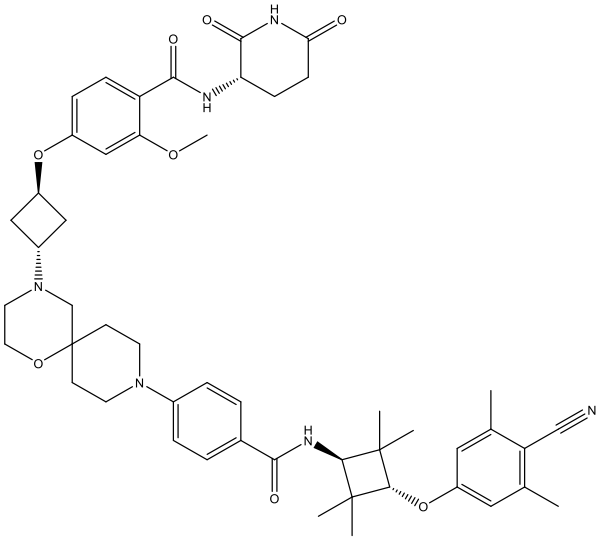
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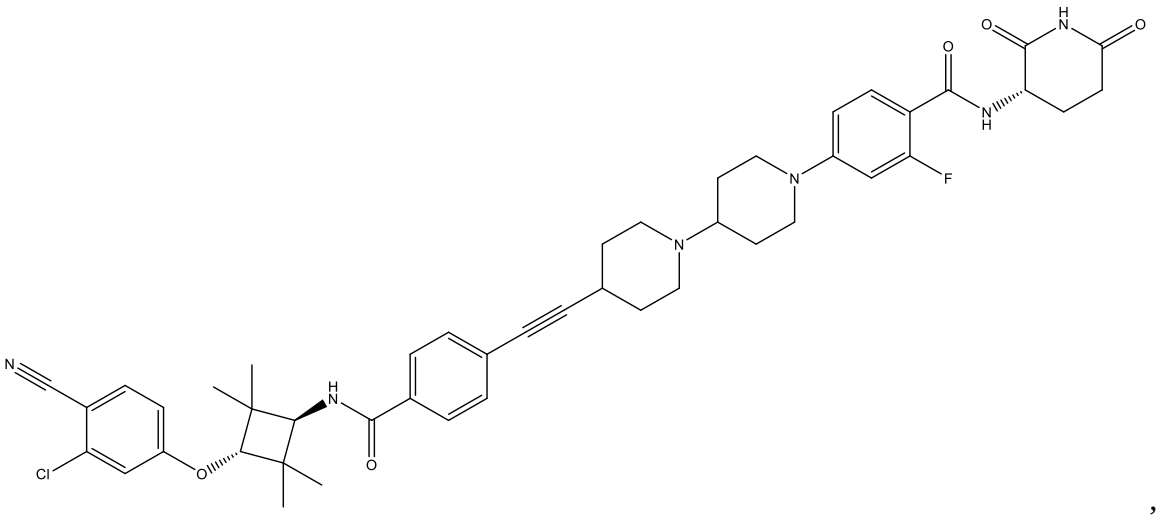
or a pharmaceutically acceptable salt thereof.

[0010e] In a further aspect of the present disclosure, there is provided a bifunctional compound, wherein the compound is:

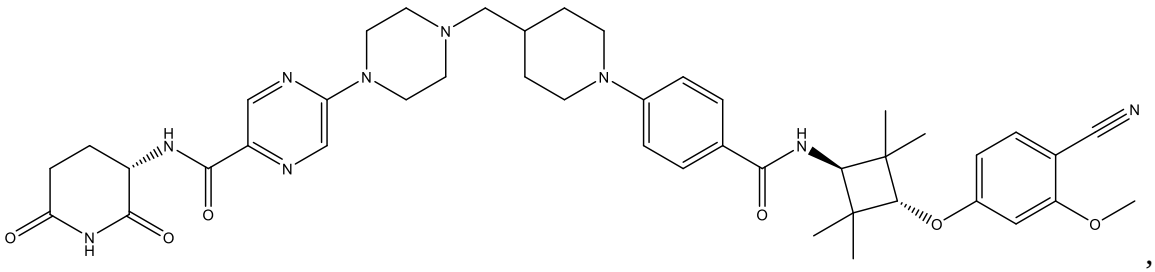

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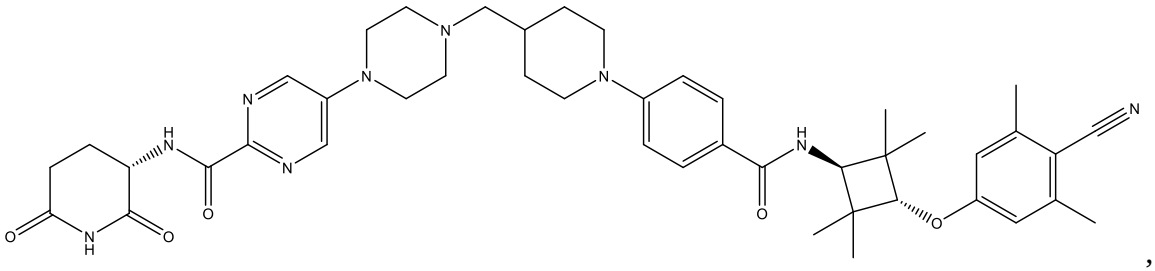

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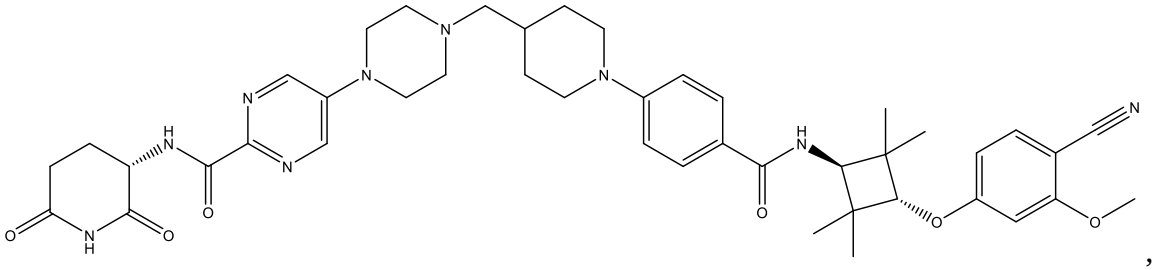
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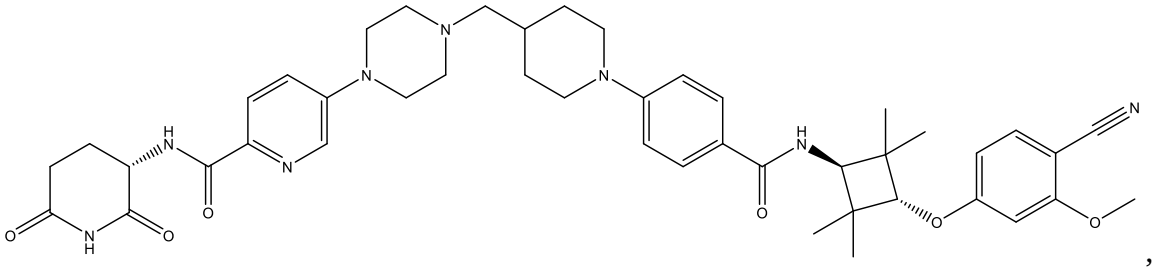
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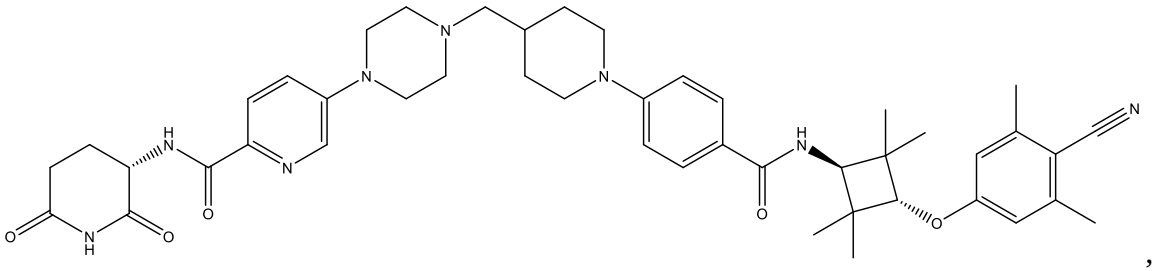


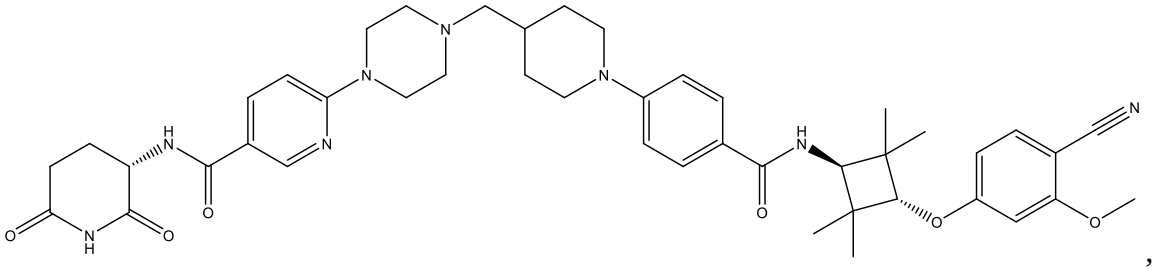
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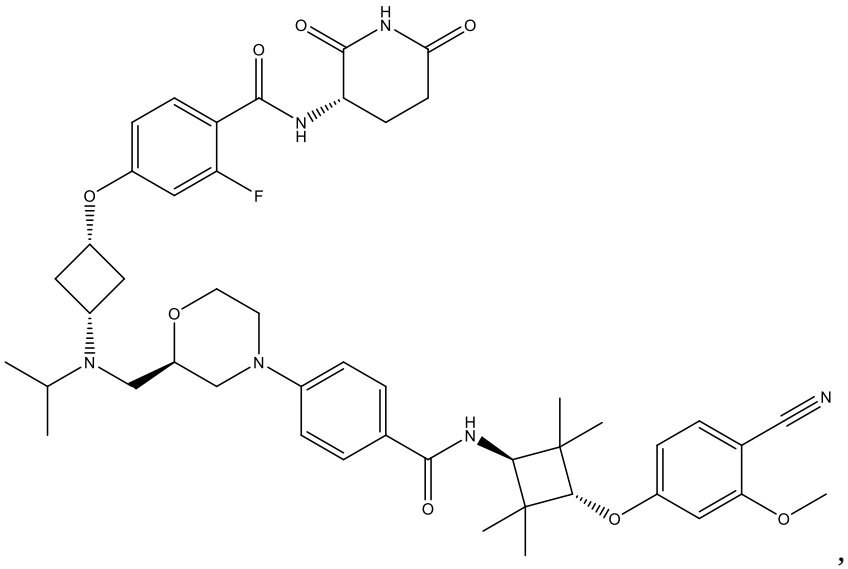


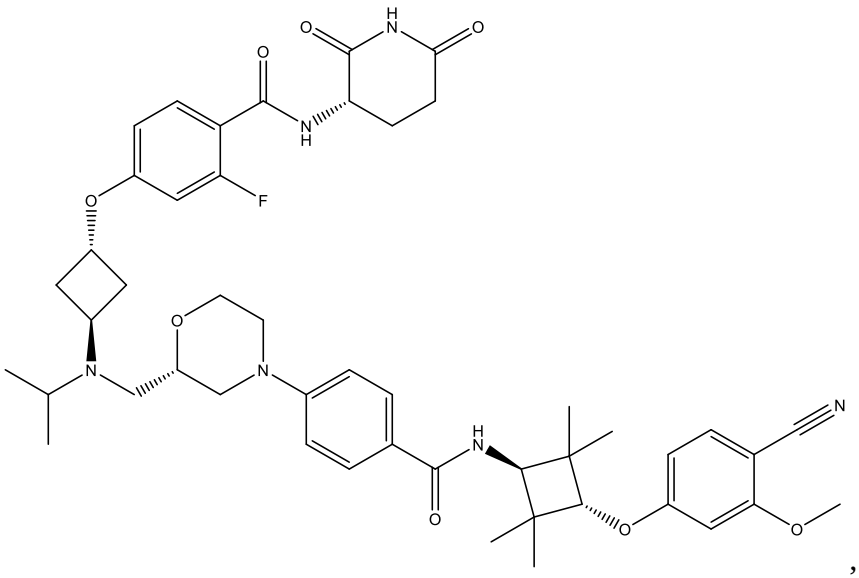
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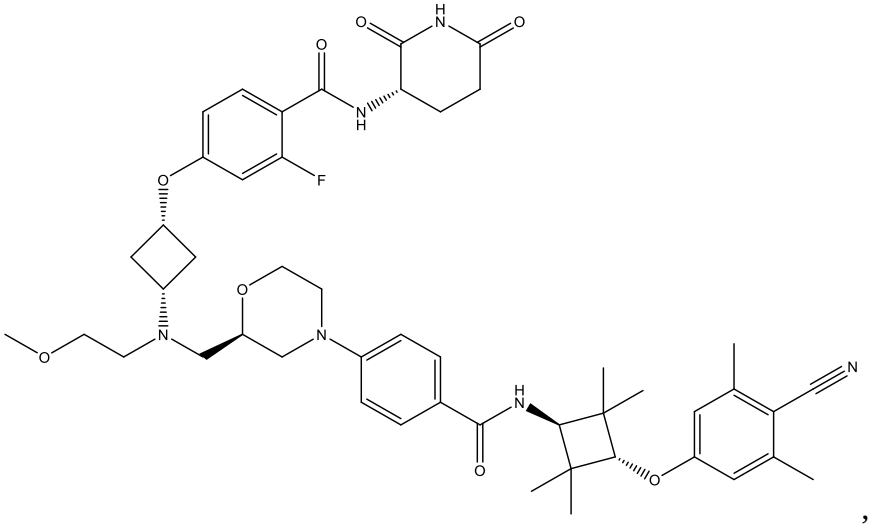

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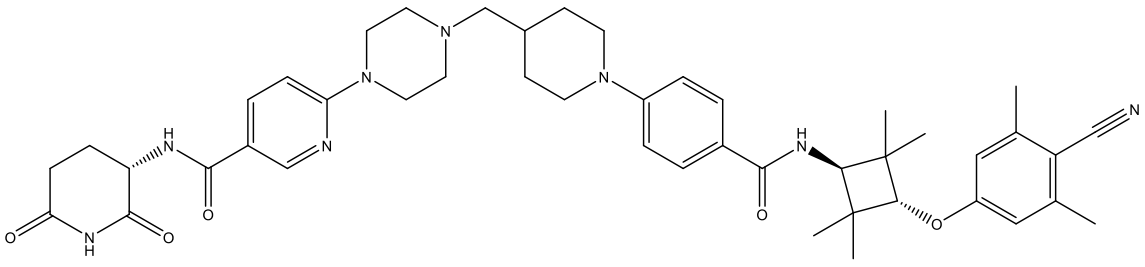

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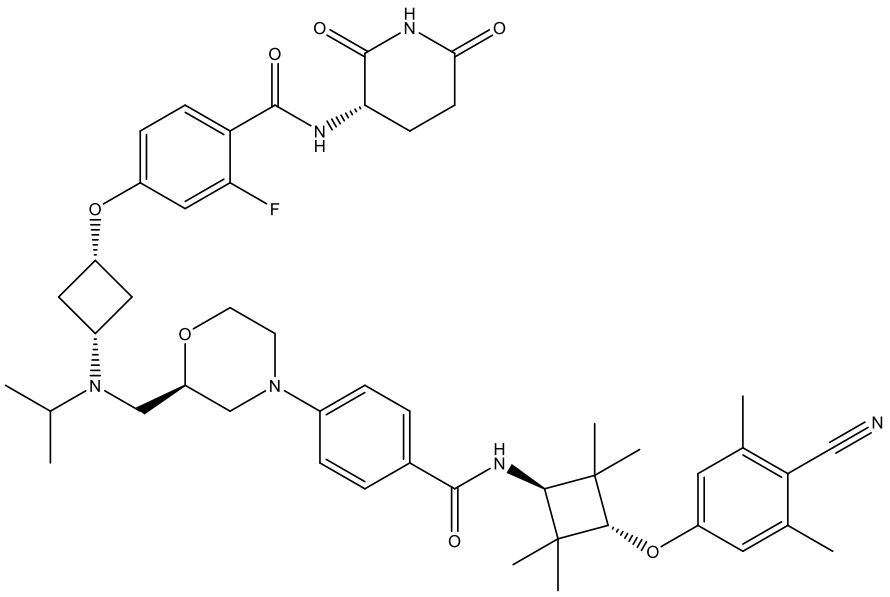
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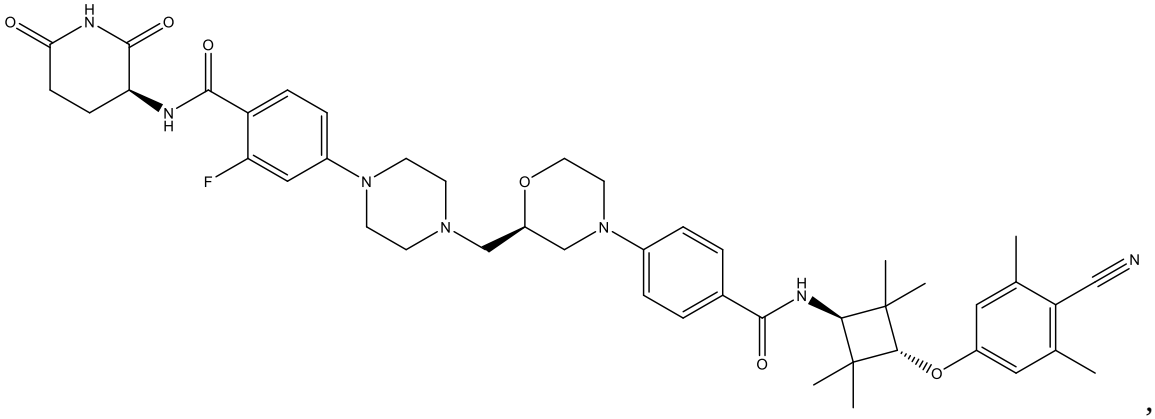
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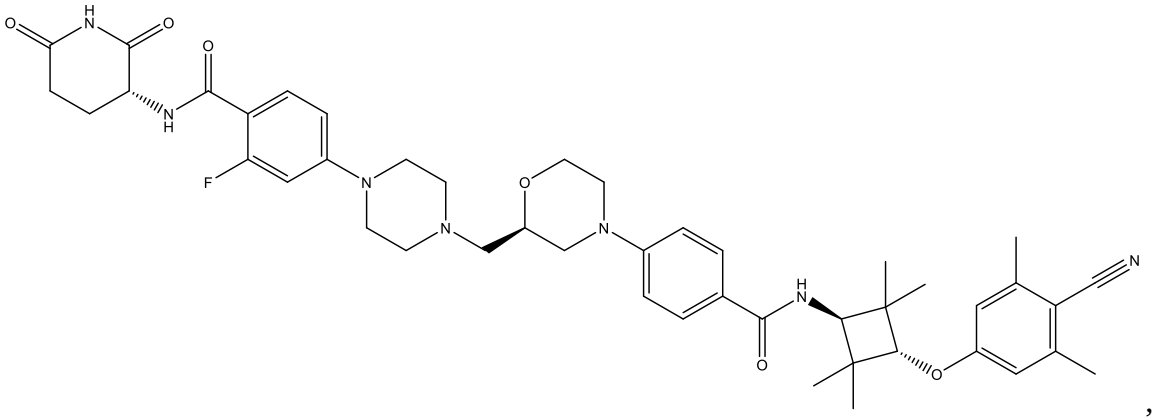
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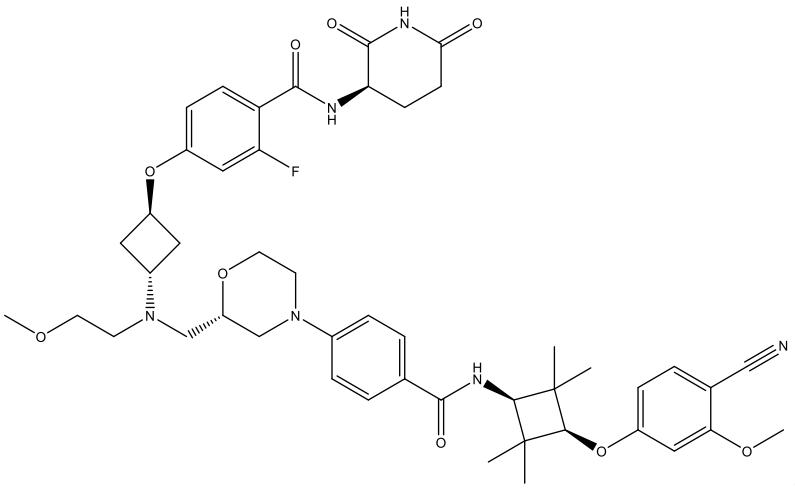
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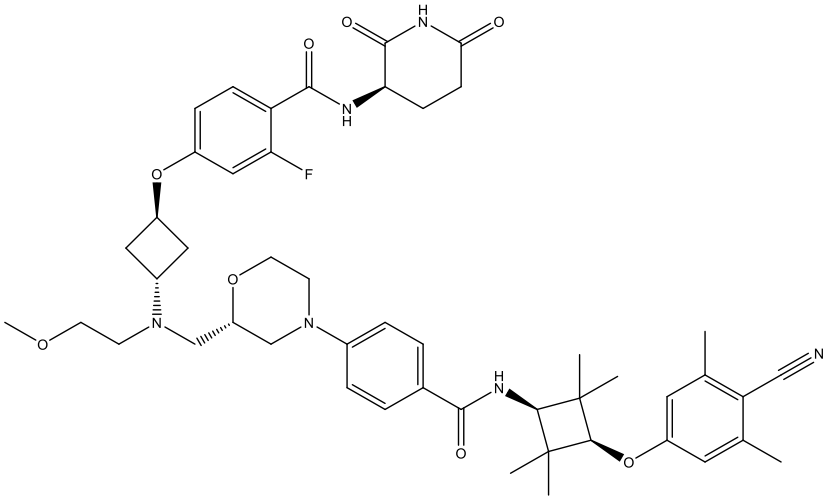
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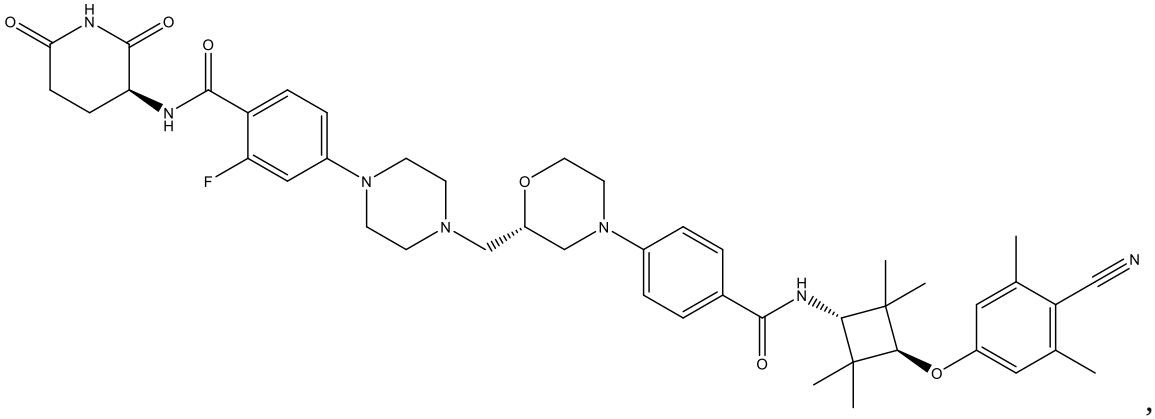
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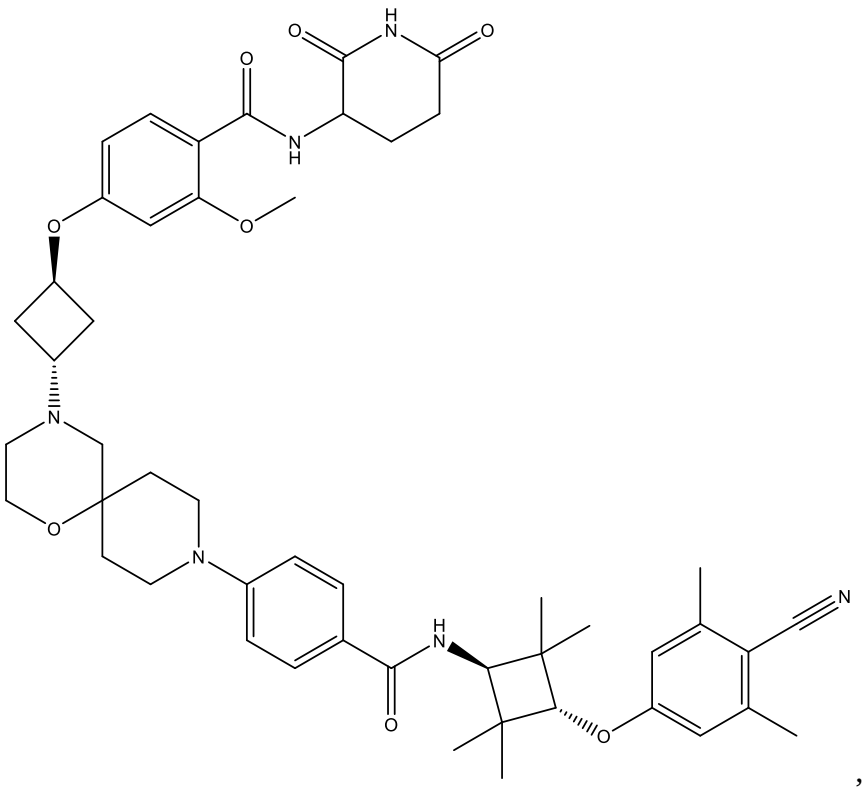
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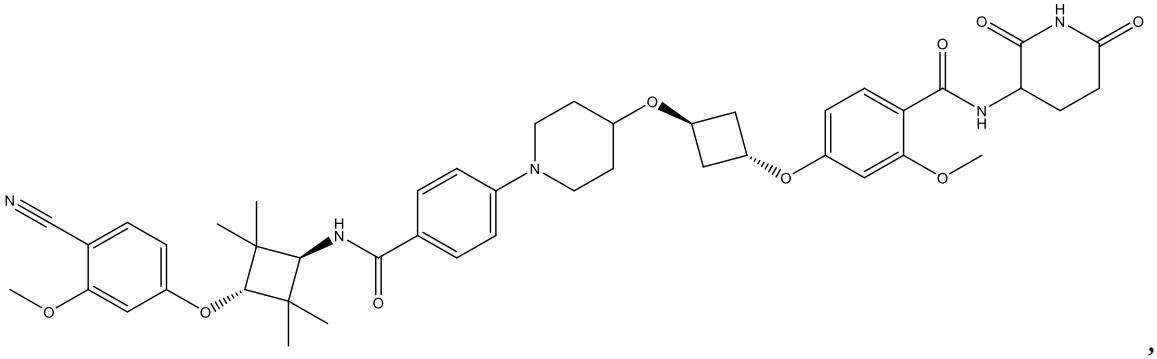
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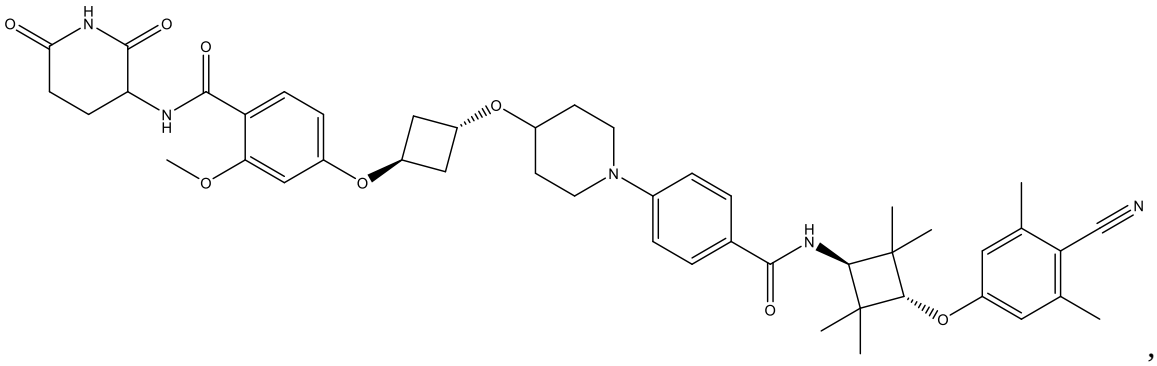
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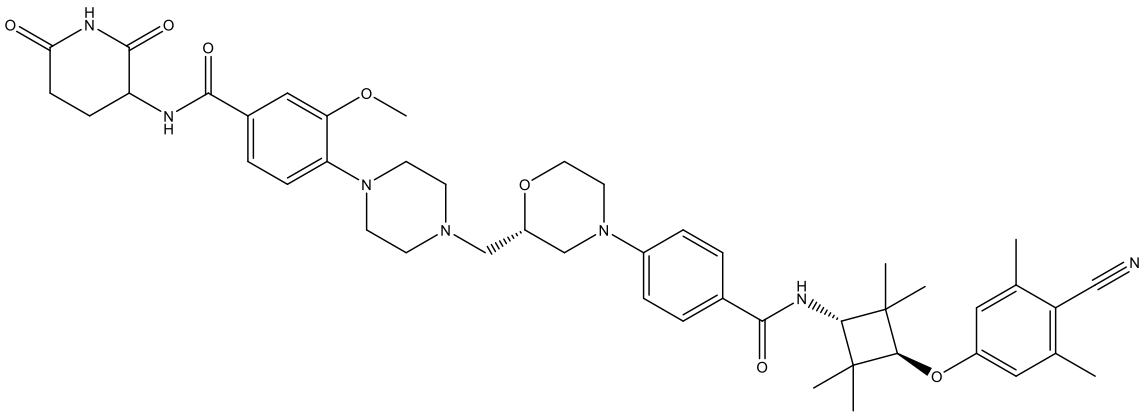
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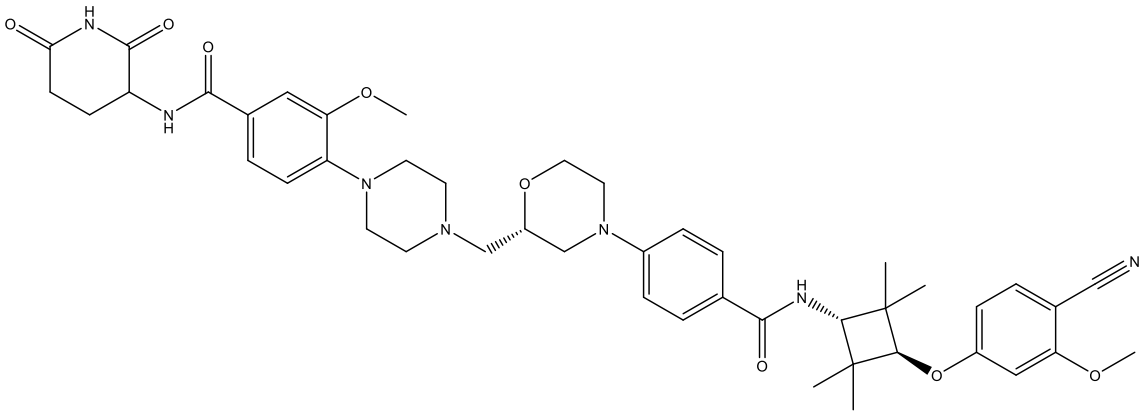
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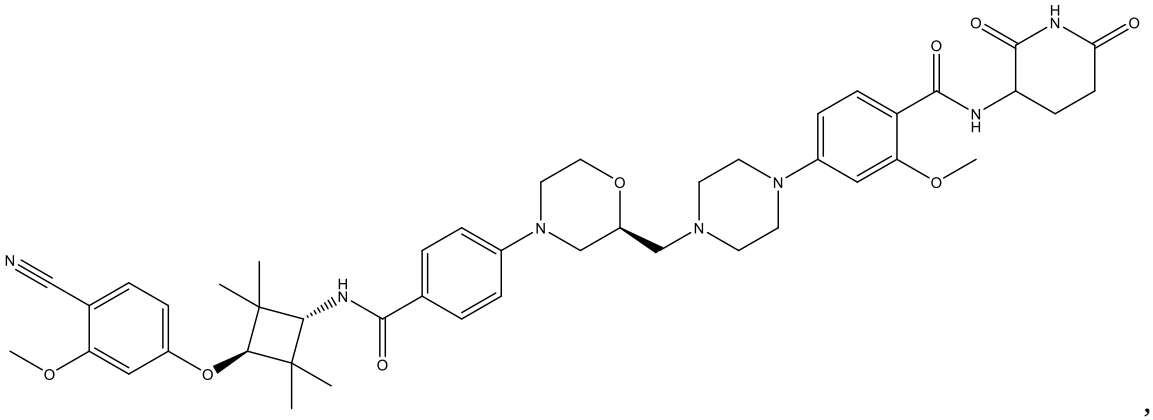
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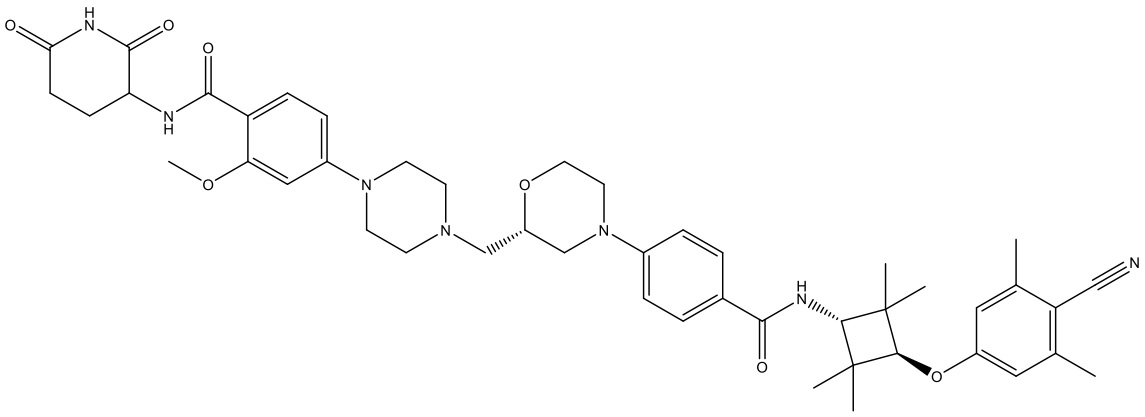
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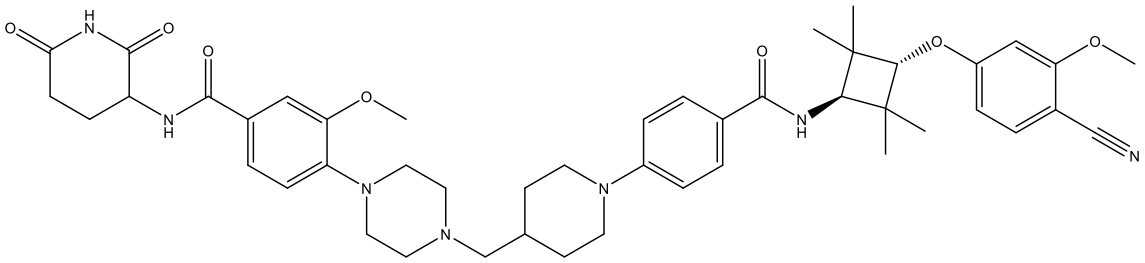
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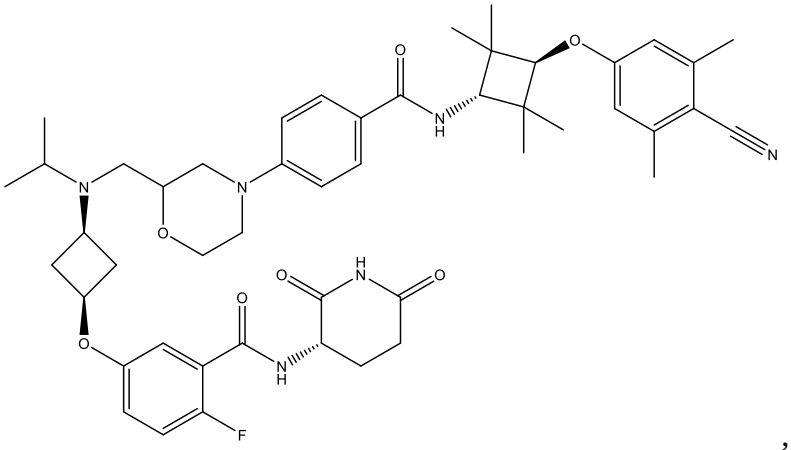
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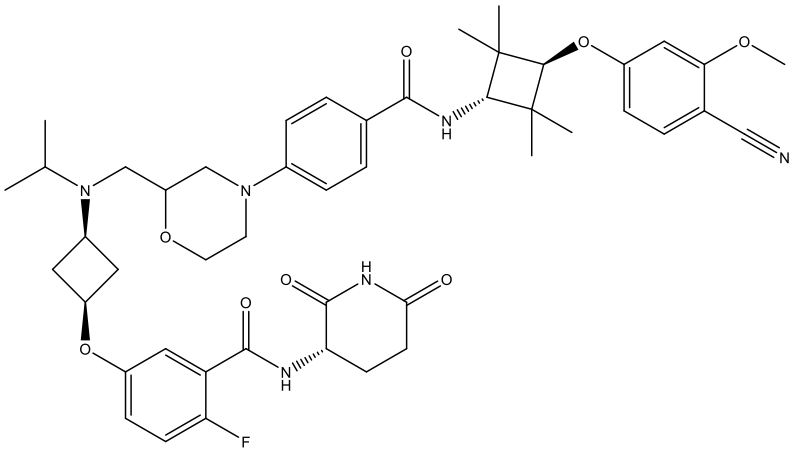
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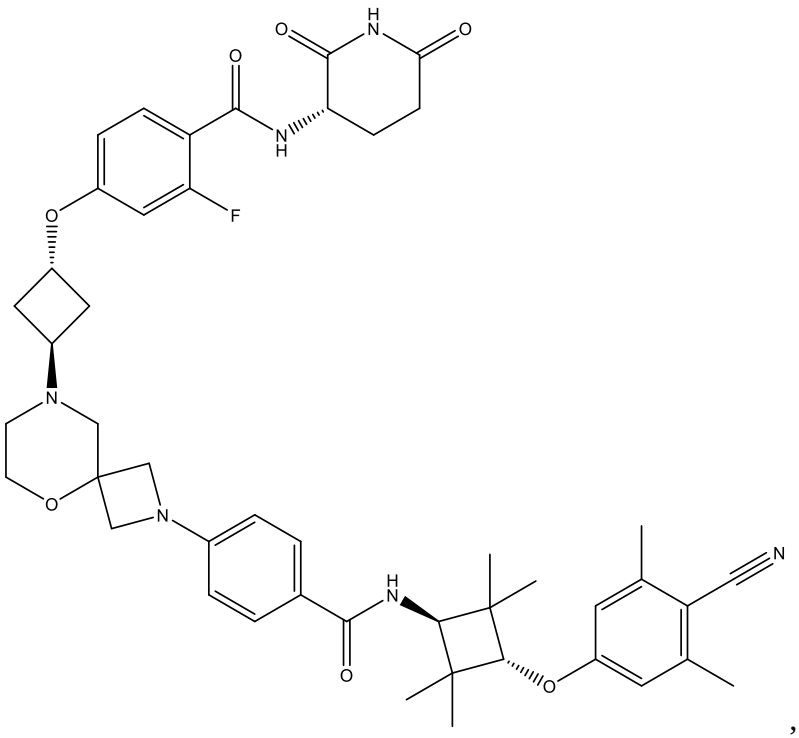
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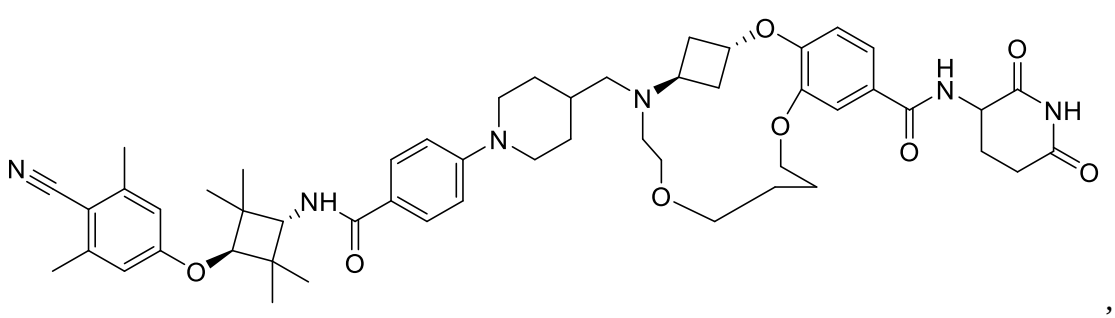
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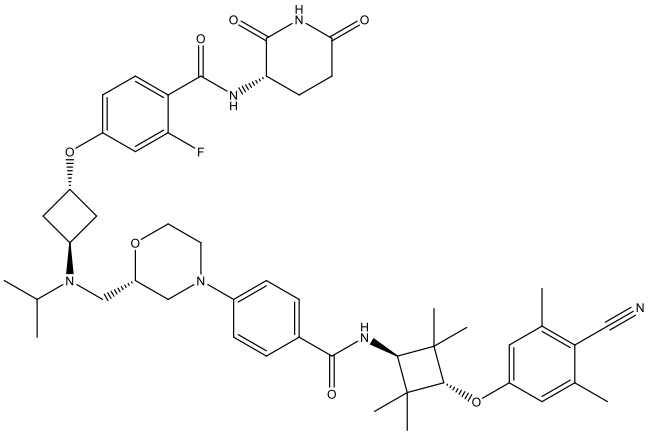
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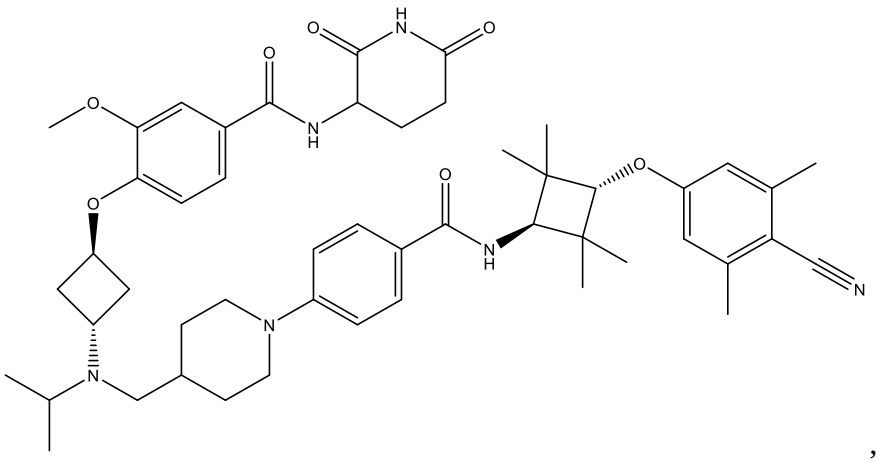
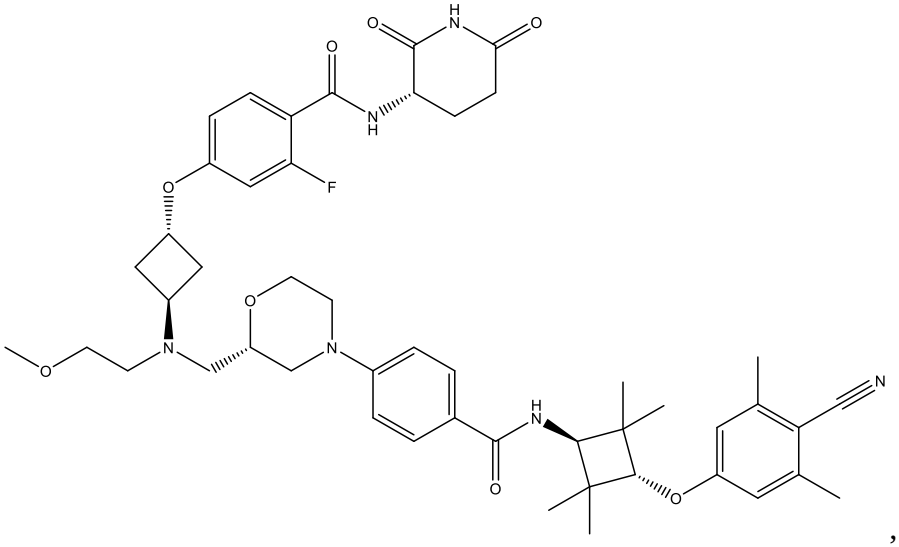
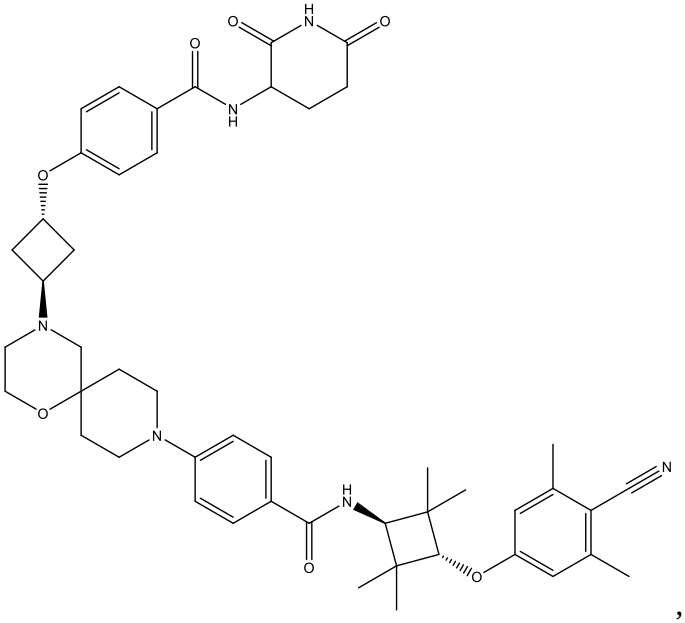
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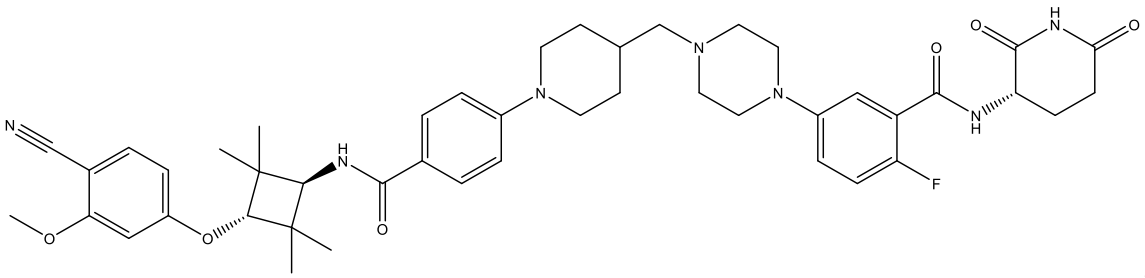


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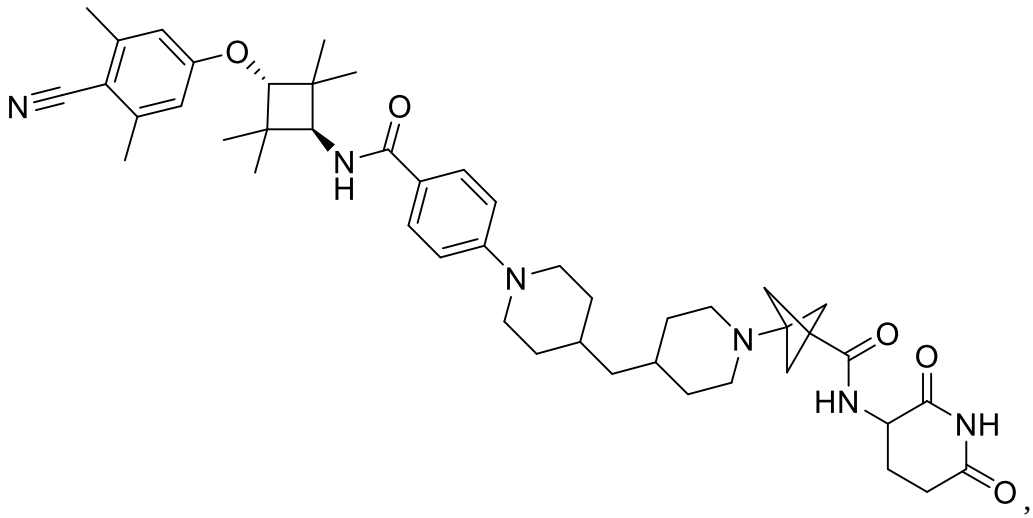


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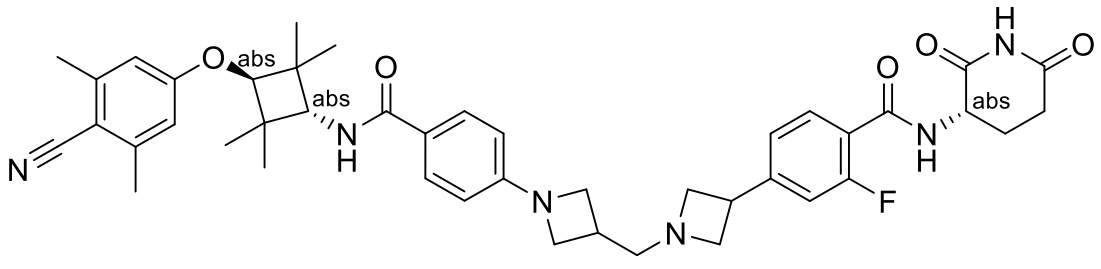

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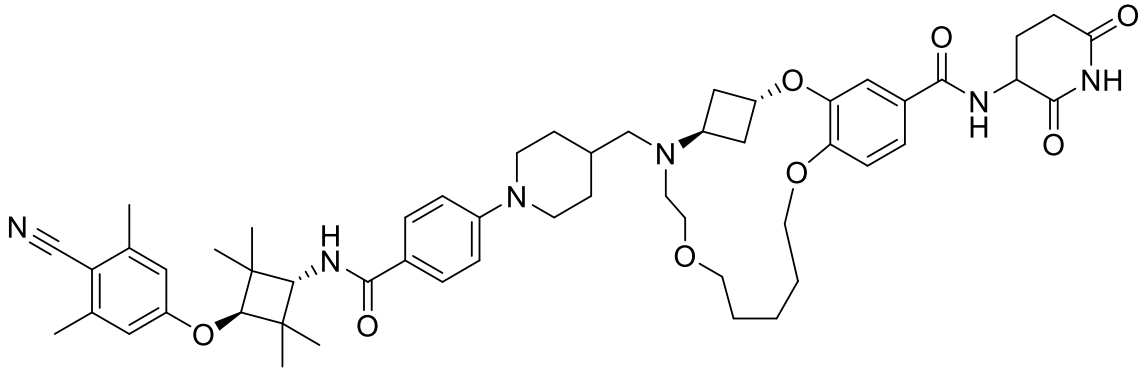
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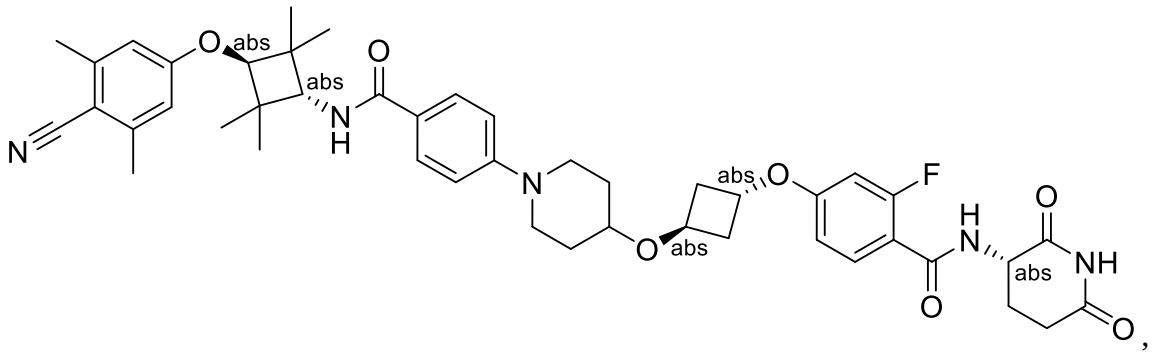
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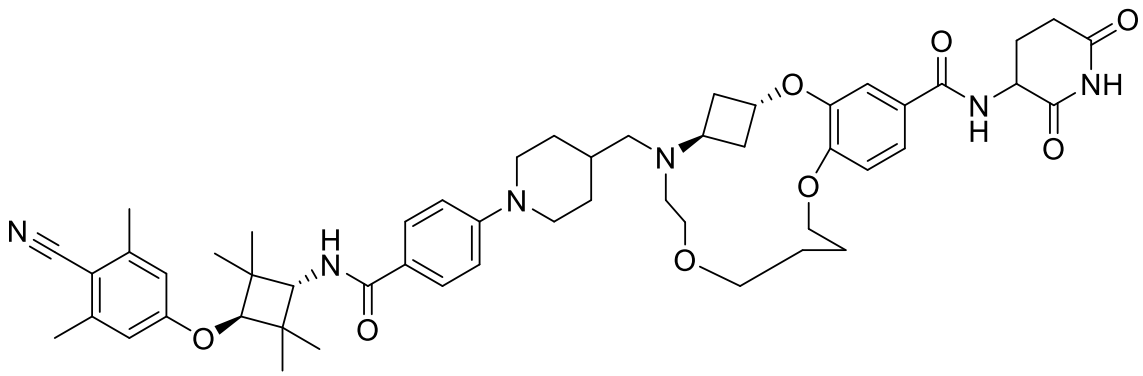
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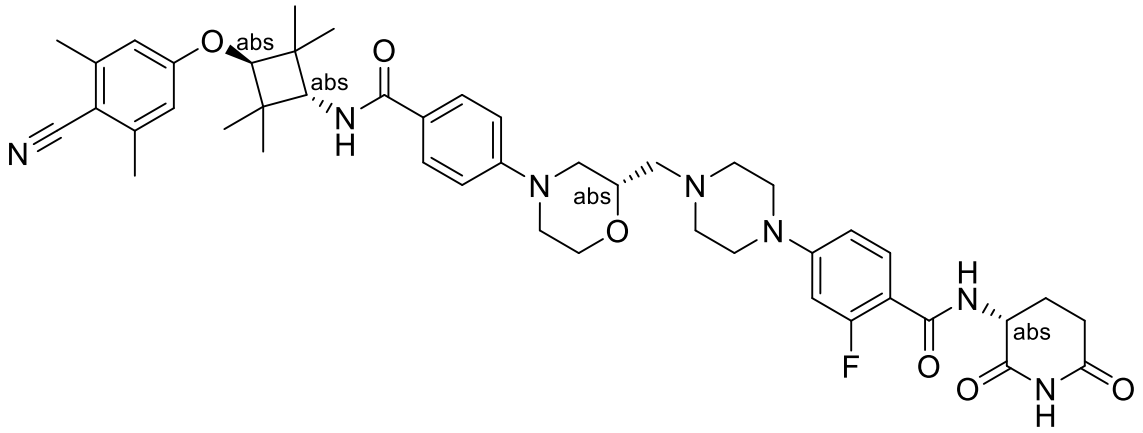
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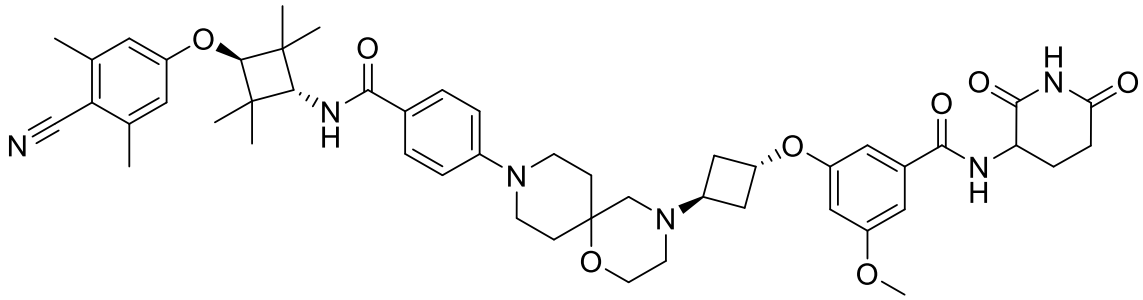
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[0010f] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the bifunctional compound disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0010g] In a further aspect of the present disclosure, there is provided a use of a bifunctional compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating prostate cancer in a subject.

[0010h] In another aspect of the present disclosure, there is provided a use of a bifunctional compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating prostate cancer in a subpopulation of prostate cancer subjects,

wherein a prostate cancer subject is selected for treatment based on the subject's somatic AR tumor biomarker status.

[0010i] In a further aspect of the present disclosure, there is provided a bifunctional compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in therapy.

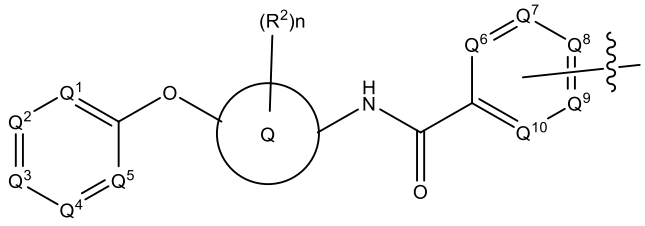
[0011] In one example, the present application provides bifunctional compound having the structure:

ABM-L-CLM,

or a pharmaceutically acceptable salt, solvate, enantiomer, stereoisomer, or isotopic derivative thereof,

wherein:

(a) ABM is an androgen receptor (AR) binding moiety having the structure:



wherein:

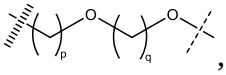
Q^1, Q^2, Q^3, Q^4, and Q^5 are each independently CR^1, or N;



is 4-6 membered cycloalkyl, C_6-C_{10} aryl, 4-6 membered heterocycloalkyl, or 4-6 membered heteroaryl, wherein the heterocycloalkyl or heteroaryl comprises 0-4 heteroatoms;

Q^6, Q^7, Q^8, Q^9, and Q^{10} are each independently CR^3, or N;

Z is -C(R^7)$_2$-, -NR^7-, -O-, or absent;

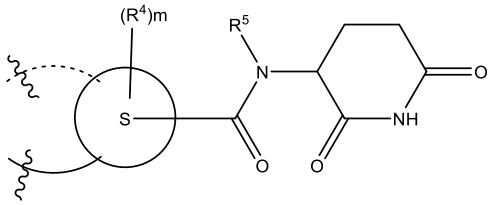
R^6 is H, linear or branched C_{1-6} alkyl, linear or branched C_{1-6} alkoxy-C_{1-6} alkyl, or , wherein  indicates a bond to Y, and  indicates a bond to ;

each R^7 is independently selected from the group consisting of H, linear or branched C_{1-6} alkyl, and linear or branched C_{1-6} alkoxy;

p is 1, 2, 3, or 4; and

q is 1, 2, 3, 4, or 5;

(c) CLM is cereblon E3 ubiquitin ligase binding moiety having the structure:



wherein:

 is C_6-C_{10} aryl, 4-7 membered heteroaryl, or bridged bicyclic cycloalkyl;



 indicates that linking moiety L is connected to ring S by one or two covalent bonds;

Each R^4 is independently selected from the group consisting of optionally substituted linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo;

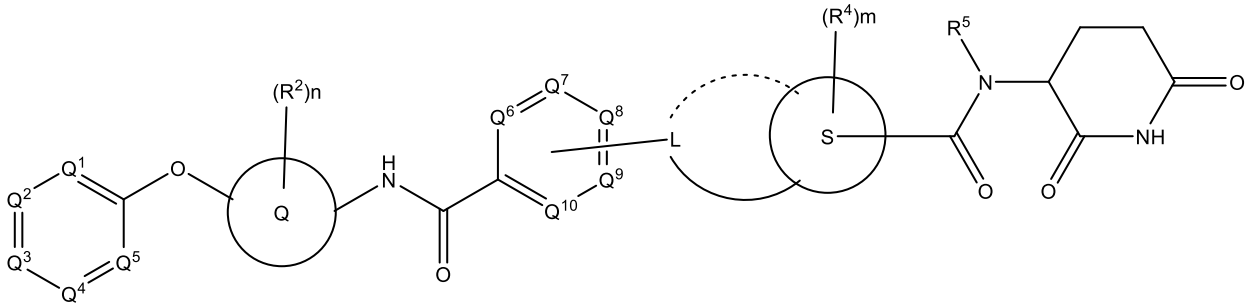
R^5 is H, optionally substituted linear or branched C_1-C_6 alkyl, or optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo; and

m is 0, 1, 2, 3, or 4.

[0012] In some examples, when  is pyridyl,  is tetramethylcyclobutyl, Q2 is CR1, and Q4 is CR1; that R1 is not chloro.

[0013] In some examples, further provided that the compound is not N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-((4-(4-((2,6-dioxopiperidin-3-yl)carbamoyl)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)pyridazine-3-carboxamide.

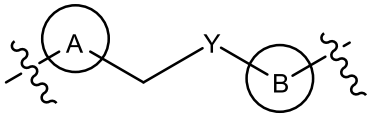
[0014] In another example, this application provides a bifunctional compound disclosed herein, wherein the compound is a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, solvate, enantiomer, stereoisomer, or isotopic derivative thereof.

[0015] In some examples, L is



wherein:

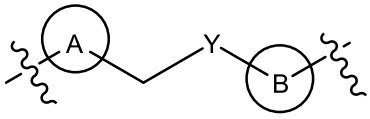
A is 4-7 membered cycloalkyl or 4-7 membered heterocycle;

Y is $-NR^6-$, -O-, or absent;

R^6 is H, linear or branched C_{1-6} alkyl, or linear or branched C_{1-6} alkoxy; and

B is 4-7 membered cycloalkyl or 4-7 membered heterocycle.

[0016] In some examples, L is



wherein:



is 4-7 membered cycloalkyl or 4-7 membered heterocycle;

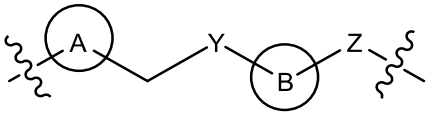
Y is $-NR^6-$ or -O-;

R^6 is H, linear or branched C_{1-6} alkyl, or linear or branched C_{1-6} alkoxy; and



is 4-7 membered cycloalkyl or 4-7 membered heterocycle.

[0017] In some examples, L is

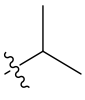
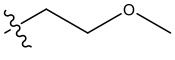


Wherein:



is piperidinyl or morpholinyl;

Y is $-NR^6-$ or -O-;

R^6 is  or 

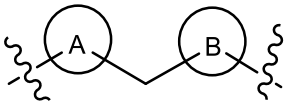
;



is cyclobutyl; and

Z is -O-.

[0018] In some examples, L is



Wherein:



is piperidinyl or morpholinyl; and

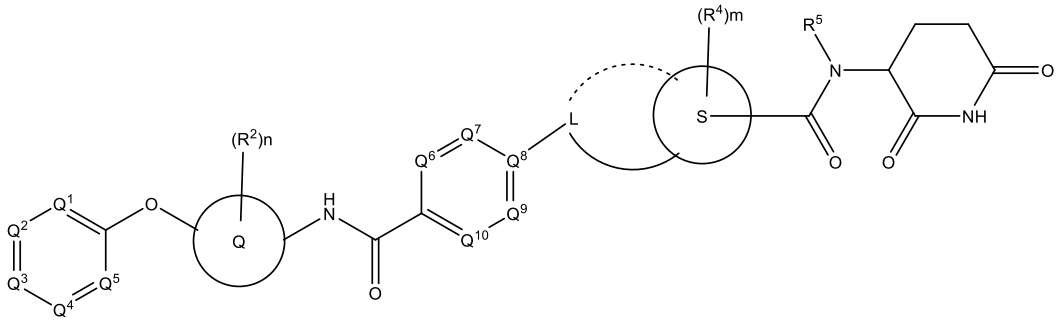


is piperazinyl.

[0019] In some examples, 

is piperidinyl.

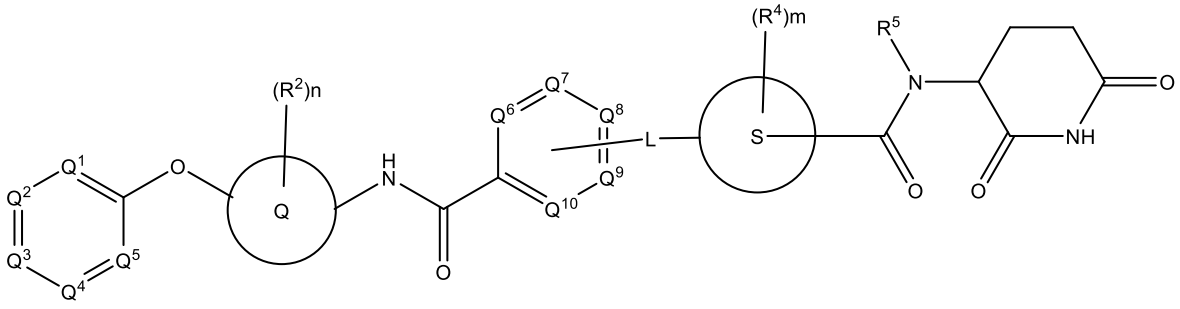
[0020] In some examples, the compound is a compound of Formula (Ib):



(Ib)

or a pharmaceutically acceptable salt, solvate, enantiomer, stereoisomer, or isotopic derivative thereof.

[0021] In some examples, the compound is a compound of Formula (Ic):



(Ic)

or a pharmaceutically acceptable salt, solvate, enantiomer, stereoisomer, or isotopic derivative thereof.

[0022] In some examples, Q^1-Q^5 are each CR^1.

[0023] In some examples, exactly 1 of Q^1-Q^5 is N.

[0024] In some examples, exactly 2 of Q^1-Q^5 are N

[0025] In some examples, exactly 3 of Q^1-Q^5 are N.

[0026] In some examples, Q^6-Q^{10} are each CR^3.

[0027] In some examples, exactly 1 of Q^6-Q^{10} is N.

[0028] In some examples, exactly 2 of Q^6-Q^{10} are N.

[0029] In some examples, exactly 3 of Q^6-Q^{10} are N.

[0030] In some examples, Q^1 is CH, Q^2 is $C(CH_3)$, Q^3 is C(CN), Q^4 is $C(CH_3)$, and Q^5 is CH.

[0031] In some examples, Q^1 is CH, Q^2 is $C(OCH_3)$, Q^3 is C(CN), Q^4 is CH, and Q^5 is CH.

[0032] In some examples, Q^1 is CH, Q^2 is C(Cl), Q^3 is C(CN), Q^4 is CH, and Q^5 is CH.

[0033] In some examples, 

is 4-6 membered cycloalkyl.

[0034] In some examples, 

is cyclobutyl or cyclohexyl.

[0035] In some examples, 

is cyclobutyl.

[0036] In some examples, n is 4.

[0037] In some examples, each R^2 is methyl.

[0038] In some examples, Q is cyclohexyl.

[0039] In some examples, n is 0.

[0040] In some examples, R^2 is linear or branched C_1-C_6 alkyl.

[0041] In some examples, 

is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl.

[0042] In some examples, 

is phenyl.

[0043] In some examples, 

is pyridinyl.

[0044] In some examples, 

is pyridazinyl.

[0045] In some examples, 

is pyrimidinyl.

[0046] In some examples, 

is pyrazinyl.

[0047] In some examples, each R^4 is independently selected from the group consisting of F, methoxy, ethoxy, methyl, and ethyl.

[0048] In some examples, each R^4 is independently selected from the group consisting of F, methoxy, and methyl.

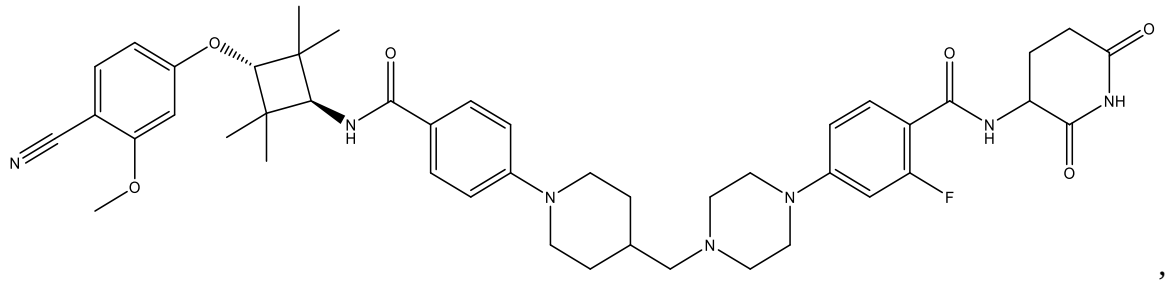
[0049] In some examples, m is 0,1, or 2.

[0050] In some examples, m is 0.

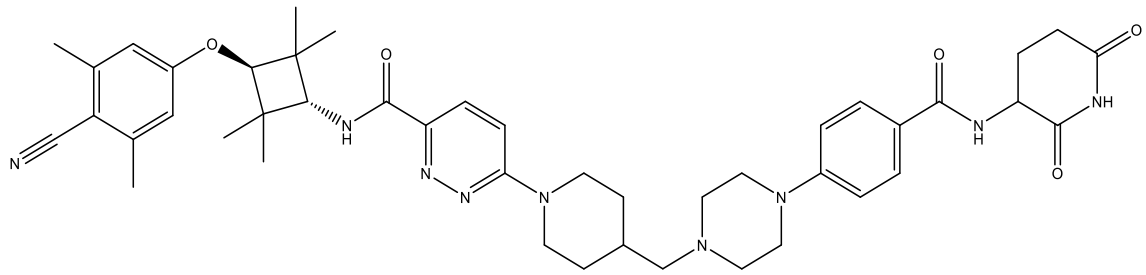
[0051] In some examples, m is 1.

[0052] In some examples, m is 2.

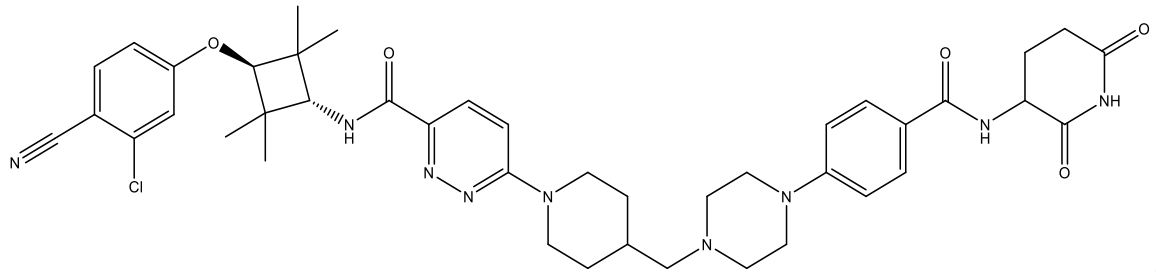
[0053] In one example, the application provides a bifunctional compound, wherein the compound is:



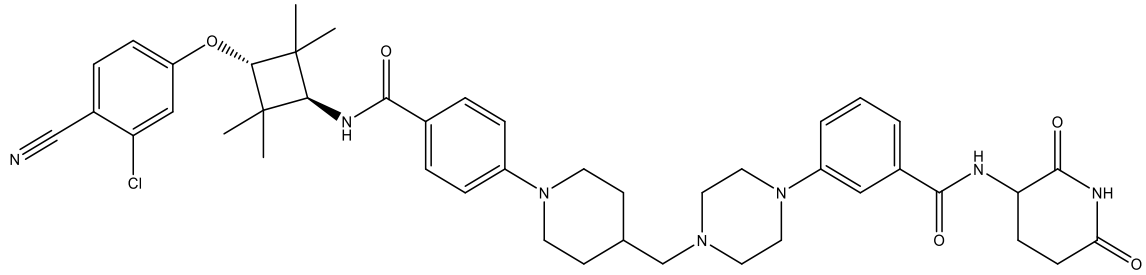
,



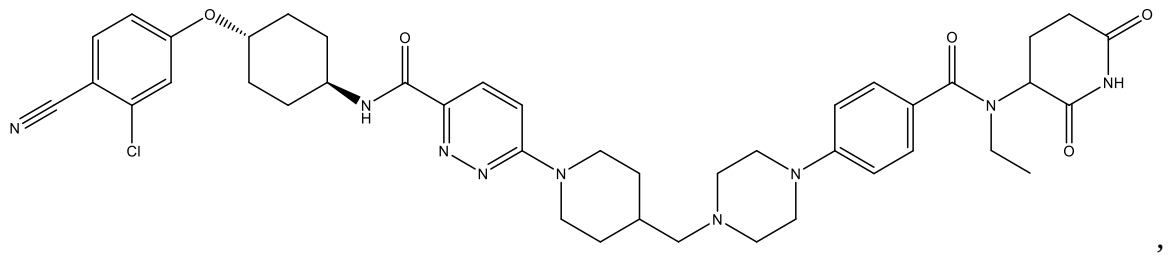
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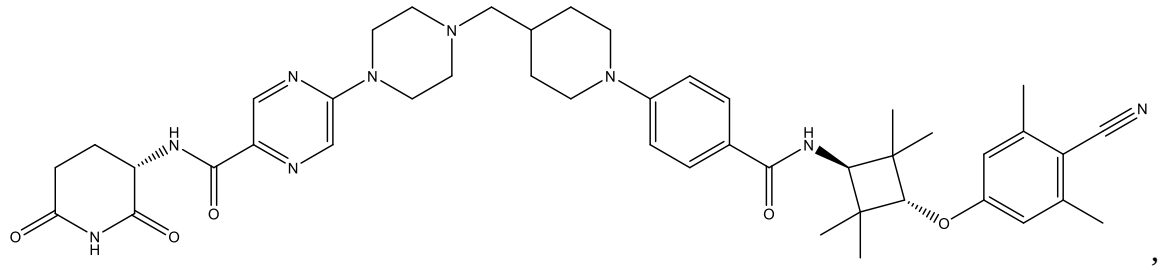


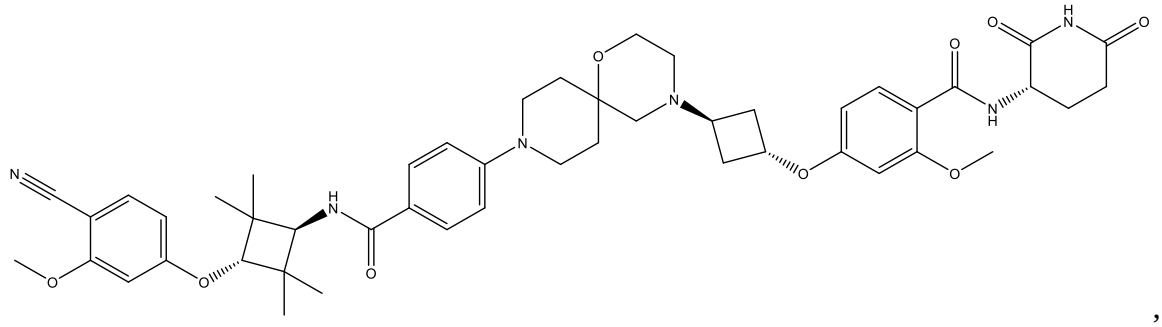
,



or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or isotopic derivative of any of the foregoing.

[0054] In one example, the application provides bifunctional compound, wherein the compound is:





[0055] In one example, the application provides a pharmaceutical composition comprising a bifunctional compound described herein and one or more pharmaceutically acceptable excipients.

[0056] In one example, the composition is formulated as a tablet, and comprises one or more of the following: emulsifier; surfactant; binder; disintegrant; glidant; and lubricant.

[0057] In one example, the composition further comprises an effective amount of at least one additional anti-cancer agent.

[0058] In one example, the anti-cancer agent is estramustine, docetaxel, ketoconazole, goserelin, histrelin, triptorelin, buserelin, cyproterone, flutamide, bicalutamide, nilutamide, pamidronate, or zolendronate.

[0059] In one example, the application provides a method of treating prostate cancer in a subject comprising administering to a subject in need thereof a therapeutically effective amount of a bifunctional compound described herein or a therapeutically effective amount of a pharmaceutical composition described herein.

[0060] In one example, the therapeutically effective amount of the bifunctional compound is administered orally to the subject.

[0061] In one example, the therapeutically effective amount of the bifunctional compound is administered to the subject once a day, twice a day, three times a day, or four times a day.

[0062] In one example, the therapeutically effective amount of the bifunctional compound is administered to the subject once a day.

[0063] In one example, the therapeutically effective amount of the bifunctional compound is administered to the subject all at once or is administered in two, three, or four divided doses.

[0064] In one example, the therapeutically effective amount of the bifunctional compound is about 1 mg to about 1000 mg.

[0065] In one example, the therapeutically effective amount of the bifunctional compound is about 5 mg to about 750 mg.

[0066] In one example, the therapeutically effective amount of the bifunctional compound is about 10 mg to about 500 mg.

[0067] In one example, the therapeutically effective amount of the bifunctional compound is about 20 mg to about 250 mg.

[0068] In one example, the subject is in a fed state at the time of administration.

[0069] In one example, the subject is in a fasted state at the time of administration.

[0070] In one example, the method further comprises administering an effective amount of at least one additional anti-cancer agent to the subject in need thereof.

[0071] In one example, the anti-cancer agent is abiraterone, estramustine, docetaxel, ketoconazole, goserelin, histrelin, triptorelin, buserelin, cyproterone, flutamide, bicalutamide, nilutamide, pamidronate, or zolendronate.

[0072] In one example, the subject with prostate cancer comprises at least one somatic AR tumor mutation.

[0073] In one example, the prostate cancer is castrate-resistant prostate cancer.

[0074] In one example, the prostate cancer is metastatic prostate cancer.

[0075] In one example, the application provides a method of treating prostate cancer in a subpopulation of prostate cancer subjects, comprising:

selecting a prostate cancer subject for treatment based on the subject's somatic AR tumor biomarker status; and

administering a therapeutically effective amount of a bifunctional compound of Formula (I), or a pharmaceutical composition comprising an effective amount of a bifunctional compound of Formula (I).

[0076] In one example, the subject's somatic AR tumor biomarker status comprises at least one somatic AR tumor mutation.

[0077] In one example, the AR biomarker status of the subject is determined by ctDNA analysis, fluorescent in situ hybridization, immunohistochemistry, PCR analysis, or sequencing.

[0078] In one example, the AR biomarker status of the subject is determined in a blood sample derived from the subject.

[0079] In one example, the AR biomarker status of the subject is determined in a solid biopsy derived from the tumor of the subject.

[0080] In one example, the prostate cancer is castrate-resistant prostate cancer.

[0081] In one example, the prostate cancer is metastatic prostate cancer.

[0082] In one example, the at least one somatic AR tumor mutation is selected from the group consisting of L702H, M895V, M896V, T878A, F877L, and H875Y.

BRIEF DESCRIPTION OF THE DRAWINGS

[0083] The accompanying drawings, which are incorporated into and form a part of the specification, illustrate several embodiments of the present disclosure and, together with the description, serve to explain the principles of the disclosure. The drawings are only for the purpose of illustrating an embodiment of the disclosure and are not to be construed as limiting the disclosure. Further objects, features and advantages of the disclosure will become apparent from the following detailed description taken in conjunction with the accompanying figures showing illustrative embodiments of the disclosure, in which:

[0084] FIGs.1A and 1B are illustrations of the general principle for the function of proteolysis targeting chimeric compounds. FIG. 1A represents exemplary proteolysis targeting chimeric compounds comprise a protein targeting moiety (PTM; *darkly shaded rectangle*), a cereblon ubiquitin ligase binding moiety (CLM; *unshaded triangle*), and a linker moiety (*black line*) coupling or tethering the PTM to the CLM. FIG. 1B illustrates the functional use of the proteolysis targeting chimeric compounds as described herein. Briefly, the CLM recognizes and binds to cereblon, an E3 Ubiquitin Ligase, and the PTM binds and recruits an intracellular target protein bringing it into close proximity to the cereblon E3 Ubiquitin Ligase. Typically, the cereblon E3 Ubiquitin Ligase is complexed with an E2 ubiquitin-conjugating protein, and either alone or via the E2 protein catalyzes attachment of ubiquitin (*dark circles*) to a lysine on the target protein via an isopeptide bond. The poly-ubiquitinated protein (*far right*) is then targeted for degradation by the proteosomal machinery of the cell.

[0085] FIG. 2 is a scheme showing the synthesis of Compound No. 4.

[0086] FIG. 3 is a scheme showing the synthesis of Compound No. 9.

[0087] FIG. 4 is a scheme showing the synthesis of Compound No. 17.

DETAILED DESCRIPTION

DEFINITIONS

[0088] All references to amino acid mutations in the Androgen Receptor are numbered relative to SEQ ID NO: 1, which is provided herewith.

CLAIMS

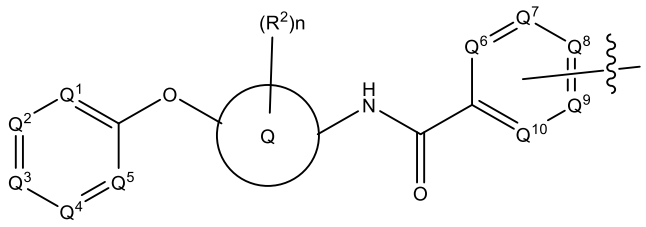
1. A bifunctional compound having the structure:

ABM-L-CLM,

or a pharmaceutically acceptable salt thereof,

wherein:

(a) ABM is an androgen receptor (AR) binding moiety having the structure:



wherein:

Q^1, Q^2, Q^3, Q^4, and Q^5 are each independently CR^1, or N;



is 4-6 membered cycloalkyl, C_6-C_{10} aryl, 4-6 membered heterocycloalkyl, or 4-6 membered heteroaryl, wherein the heterocycloalkyl or heteroaryl comprises 0-4 heteroatoms;

Q^6, Q^7, Q^8, Q^9, and Q^{10} are each independently CR^3, or N;

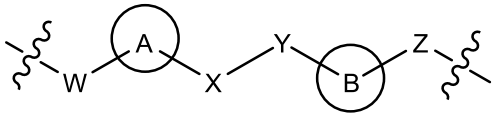
Each R^1 is independently selected from the group consisting of H, optionally substituted linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo;

Each R^2 is independently selected from the group consisting of optionally substituted linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo;

Each R^3 is independently selected from the group consisting of optionally substituted H, linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo; and

n is 0, 1, 2, 3, or 4;

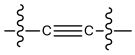
(b) L is a chemical linking moiety having the structure:



wherein:

the ABM is linked to W, and the CLM is linked to Z or

the ABM is linked to Z, and the CLM is linked to W;

W is absent or 



is 4-7 membered cycloalkyl, 4-7 membered heterocycle, or spiro-bicyclic heterocycloalkyl, where each ring in the spiro-bicycle is 4-7 membered;

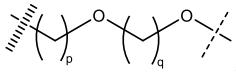
X is $-CH_2-$ or absent;

Y is $-NR^6-$, -O-, or absent;



is 4-7 membered cycloalkyl or 4-7 membered heterocycle;

Z is $-C(R^7)_2-$, $-NR^7-$, -O-, or absent;

R^6 is H, linear or branched C_{1-6} alkyl, linear or branched C_{1-6} alkoxy-C_{1-6} alkyl, or 

, wherein  indicates a bond to Y, and  indicates a bond to 

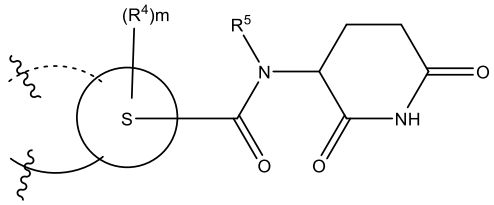
;

each R^7 is independently selected from the group consisting of H, linear or branched C_{1-6} alkyl, and linear or branched C_{1-6} alkoxy;

p is 1, 2, 3, or 4; and

q is 1, 2, 3, 4, or 5;

(c) CLM is cereblon E3 ubiquitin ligase binding moiety having the structure:



Wherein:


is C_6-C_{10} aryl, 4-7 membered heteroaryl, or bridged bicyclic cycloalkyl;


indicates that linking moiety L is connected to ring S by one or two covalent bonds;

Each R^4 is independently selected from the group consisting of optionally substituted linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo;

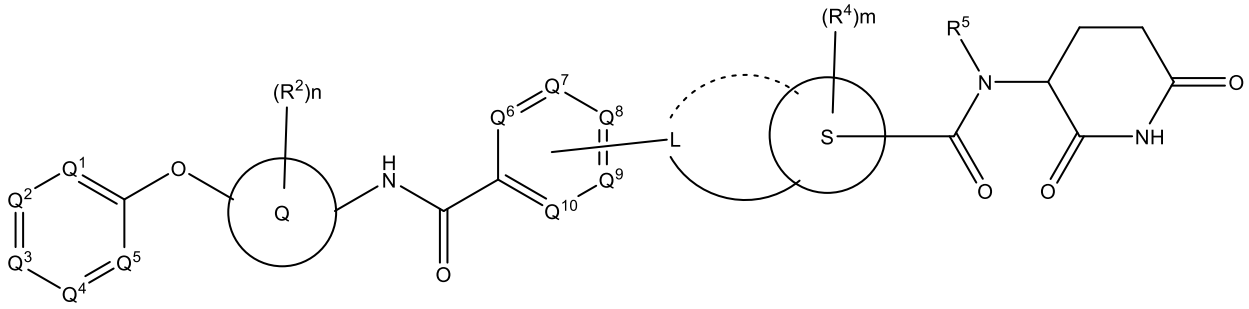
R^5 is H, optionally substituted linear or branched C_1-C_6 alkyl, or optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo; and

m is 0, 1, 2, 3, or 4;

provided that when  is pyridyl,  is tetramethylcyclobutyl, Q^2 is CR^1, and Q^4 is CR^1; that R^1 is not chloro; and

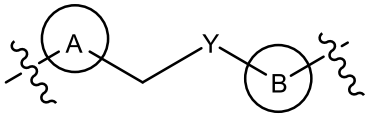
further provided that the compound is not N-(4-(3-chloro-4-cyanophenoxy)cyclohexyl)-6-(4-((4-(4-((2,6-dioxopiperidin-3-yl)carbamoyl)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)pyridazine-3-carboxamide.

2. The bifunctional compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula (I):



(I).

3. The bifunctional compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein L is



wherein:

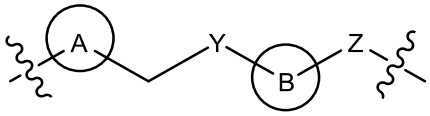
A is 4-7 membered cycloalkyl or 4-7 membered heterocycle;

Y is -NR^6-, -O-, or absent;

R^6 is H, linear or branched C_{1-6} alkyl, or linear or branched C_{1-6} alkoxy; and

B is 4-7 membered cycloalkyl or 4-7 membered heterocycle.

4. The bifunctional compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein L is



Wherein:

A is piperidinyl or morpholinyl;

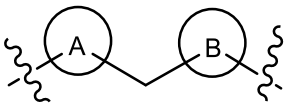
Y is -NR^6- or -O-;

R^6 is  or ;

B is cyclobutyl; and

Z is -O-.

5. The bifunctional compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein L is



Wherein:



is piperidinyl or morpholinyl; and

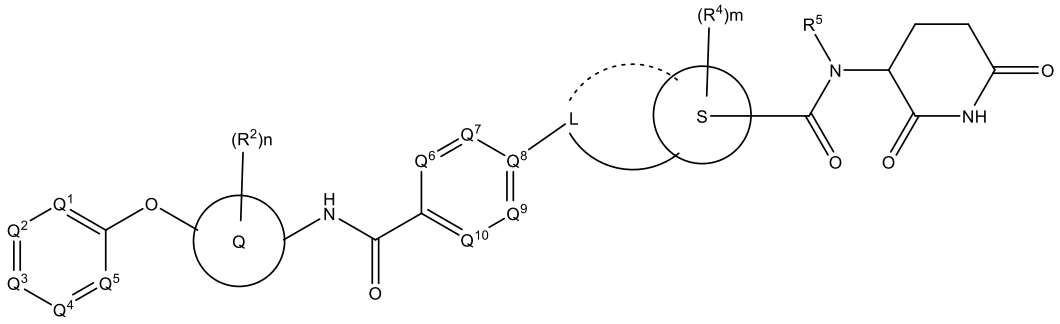


is piperazinyl.

6. The bifunctional compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein 

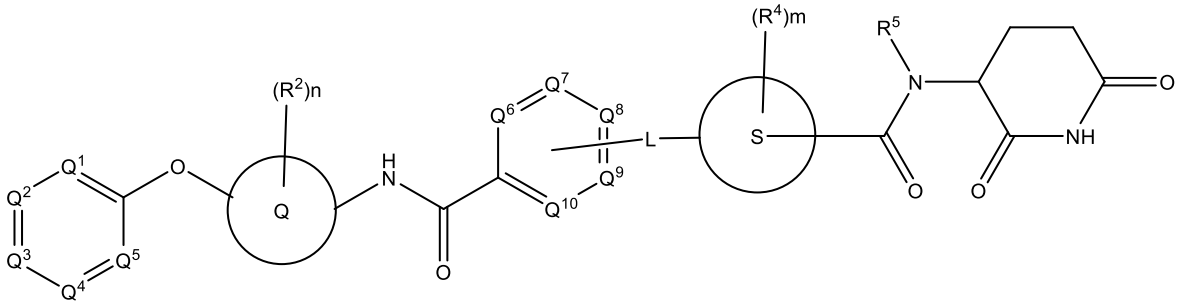
is piperidinyl.

7. The bifunctional compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula (Ib):



(Ib).

8. The bifunctional compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula (Ic):



(Ic).

9. The bifunctional compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein Q^1-Q^5 are each CR^1.

10. The bifunctional compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein exactly 1 of Q^1-Q^5 is N.

11. The bifunctional compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein exactly 2 of Q^1-Q^5 are N.

12. The bifunctional compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein exactly 3 of Q^1-Q^5 are N.

13. The bifunctional compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein Q^6-Q^{10} are each CR^3.

14. The bifunctional compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein exactly 1 of Q^6-Q^{10} is N.

15. The bifunctional compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein exactly 2 of Q^6-Q^{10} are N.

16. The bifunctional compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein exactly 3 of Q^6-Q^{10} are N.

17. The bifunctional compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein Q^1 is CH, Q^2 is $C(CH_3)$, Q^3 is C(CN), Q^4 is $C(CH_3)$, and Q^5 is CH.

18. The bifunctional compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein Q^1 is CH, Q^2 is $C(OCH_3)$, Q^3 is C(CN), Q^4 is CH, and Q^5 is CH.

19. The bifunctional compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein Q^1 is CH, Q^2 is C(Cl), Q^3 is C(CN), Q^4 is CH, and Q^5 is CH.

20. The bifunctional compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein 

is 4-6 membered cycloalkyl.

21. The bifunctional compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein 

is cyclobutyl or cyclohexyl.

22. The bifunctional compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein 

is cyclobutyl.

23. The bifunctional compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein n is 4.

24. The bifunctional compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein each R^2 is methyl.

25. The bifunctional compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein Q is cyclohexyl.

26. The bifunctional compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein n is 0.

27. The bifunctional compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein R^2 is linear or branched C_1-C_6 alkyl.

28. The bifunctional compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein  is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl.

29. The bifunctional compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein  is phenyl.

30. The bifunctional compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein  is pyridinyl.

31. The bifunctional compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein  is pyridazinyl.

32. The bifunctional compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein  is pyrimidinyl.

33. The bifunctional compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein  is pyrazinyl.

34. The bifunctional compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein each R^4 is independently selected from the group consisting of F, methoxy, ethoxy, methyl, and ethyl.

35. The bifunctional compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein each R^4 is independently selected from the group consisting of F, methoxy, and methyl.

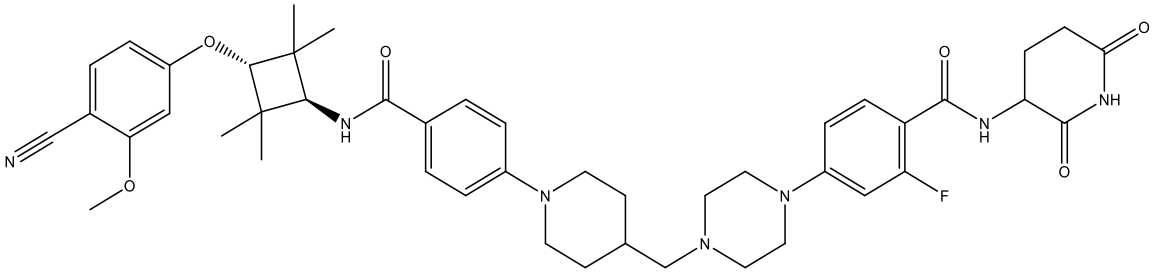
36. The bifunctional compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, or 2.

37. The bifunctional compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, wherein m is 0.

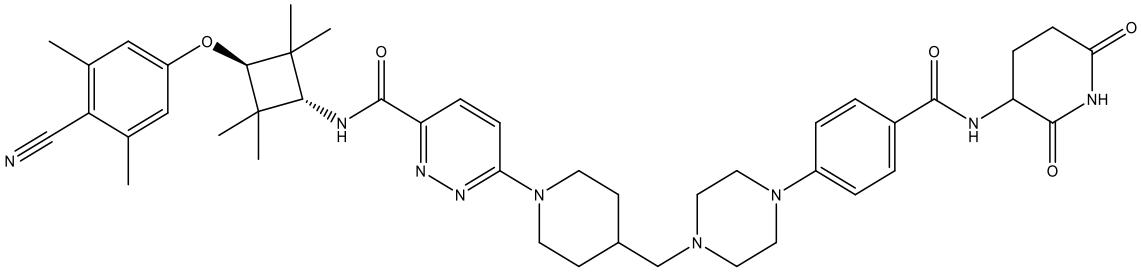
38. The bifunctional compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, wherein m is 1.

39. The bifunctional compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, wherein m is 2.

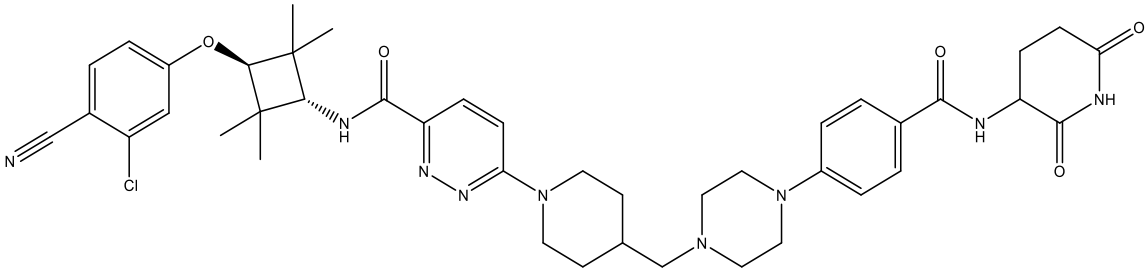
40. A bifunctional compound, wherein the compound is:



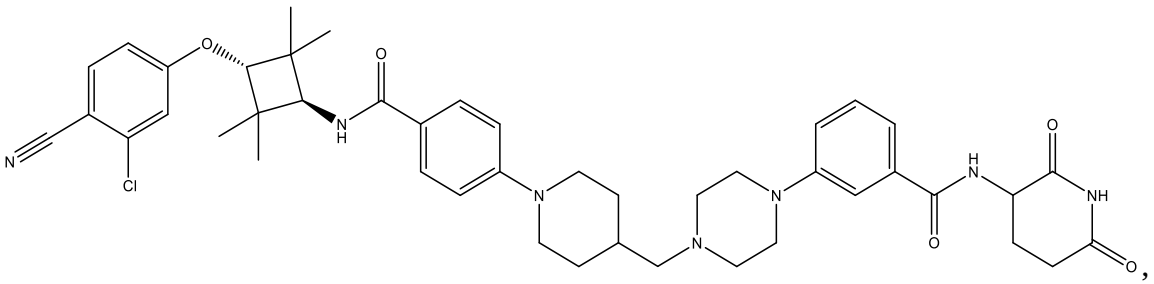
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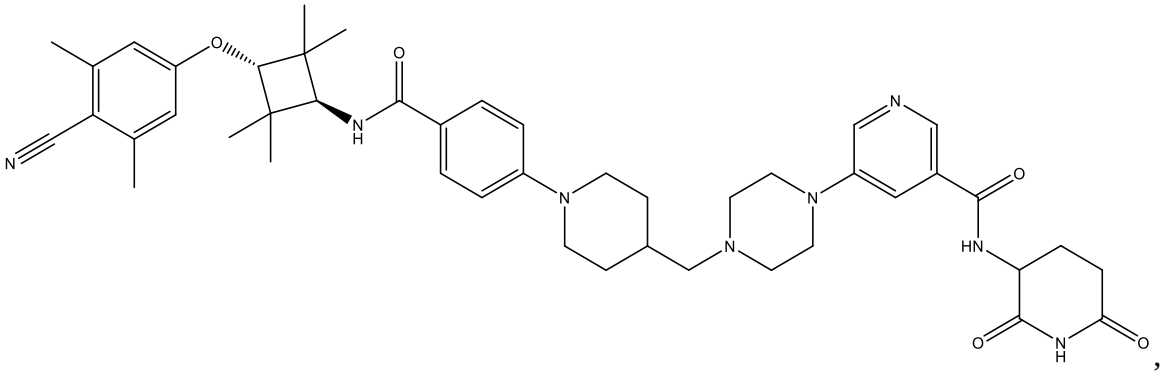
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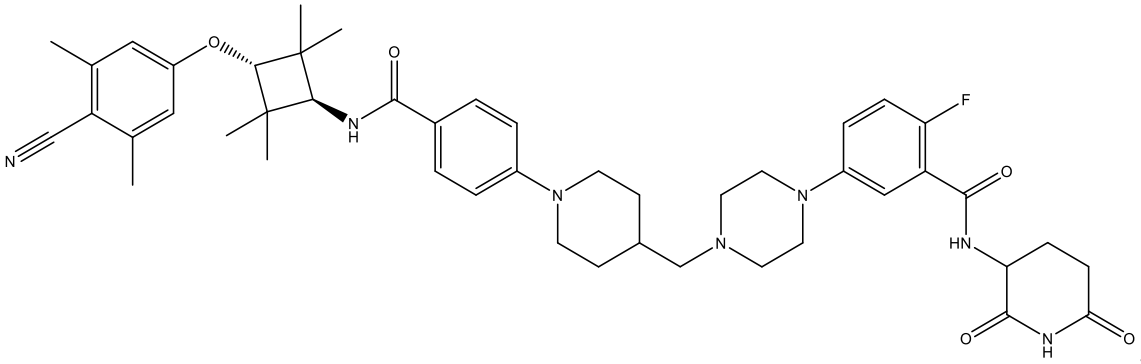
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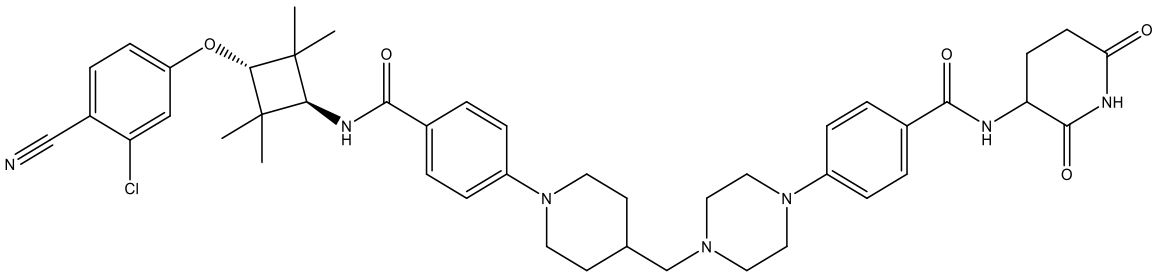
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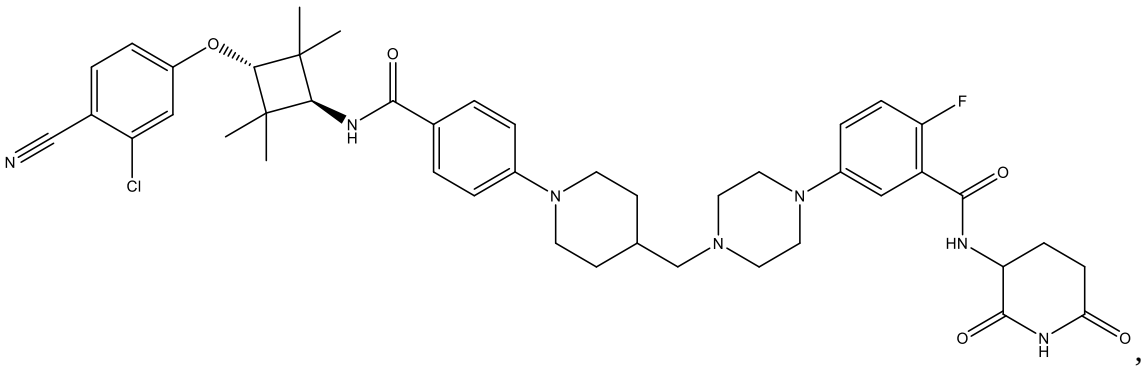
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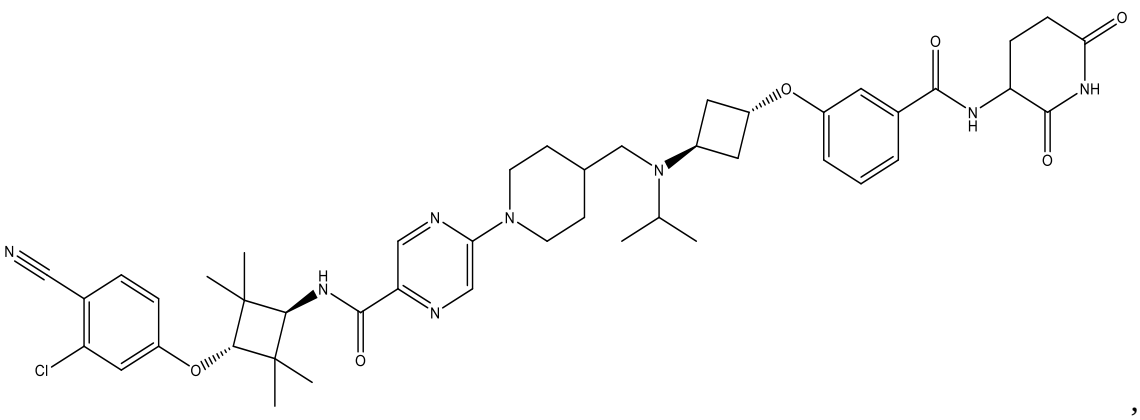
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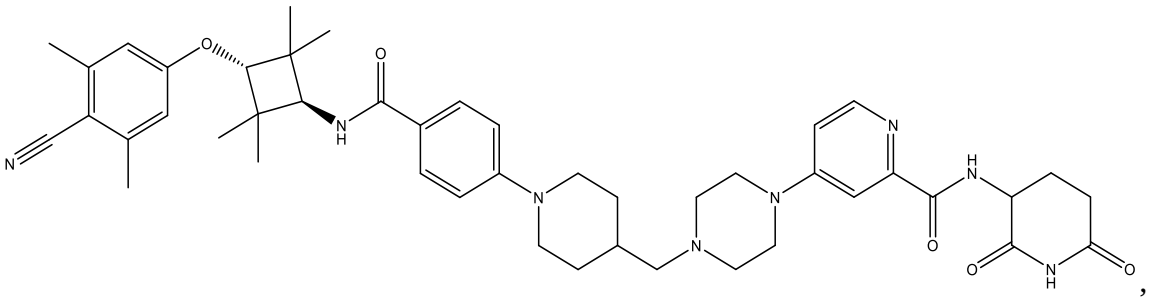
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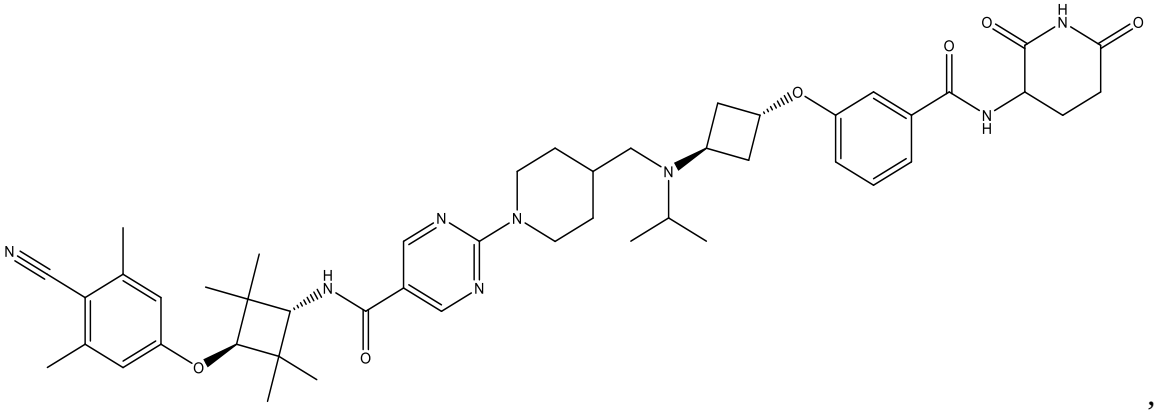
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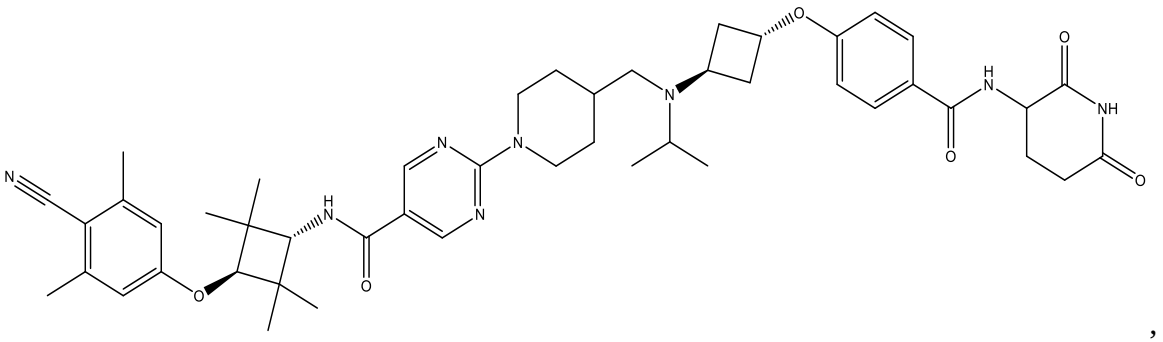
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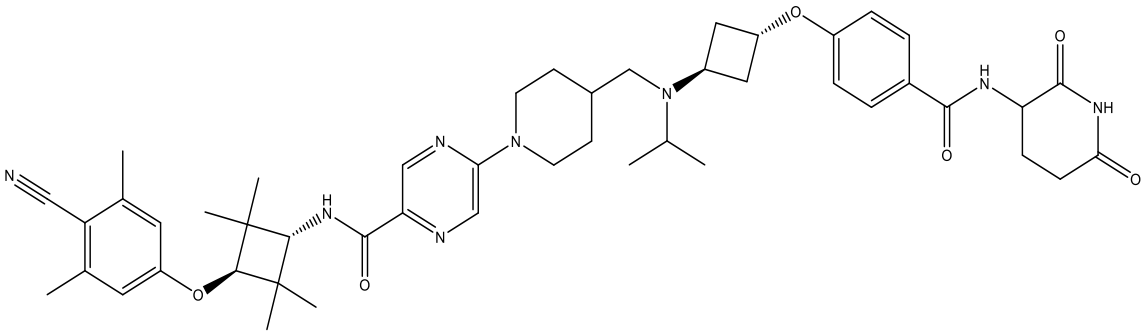
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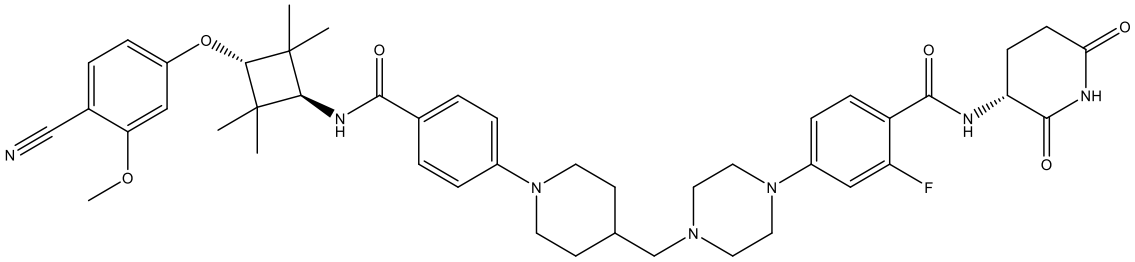
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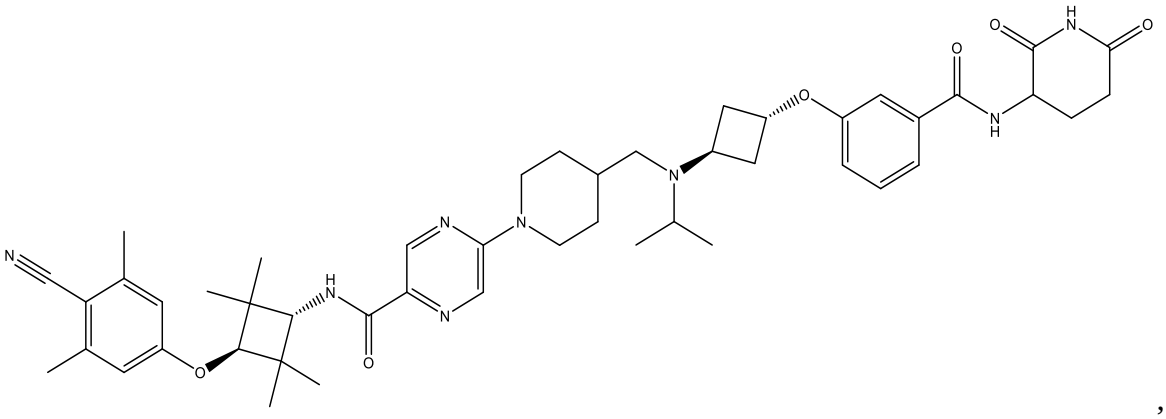
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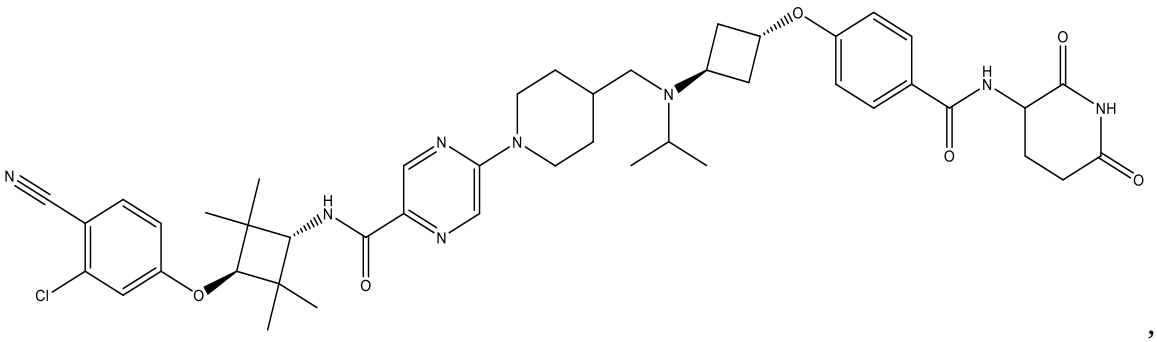
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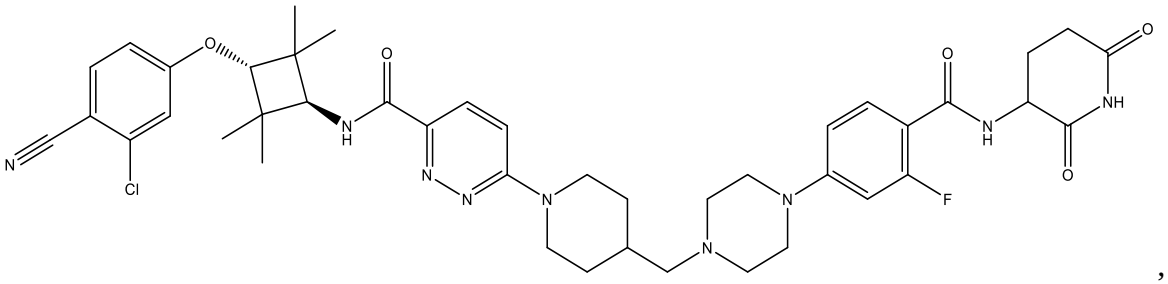
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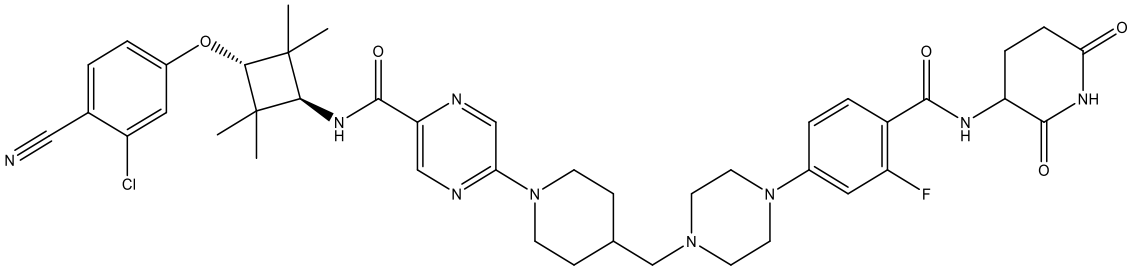
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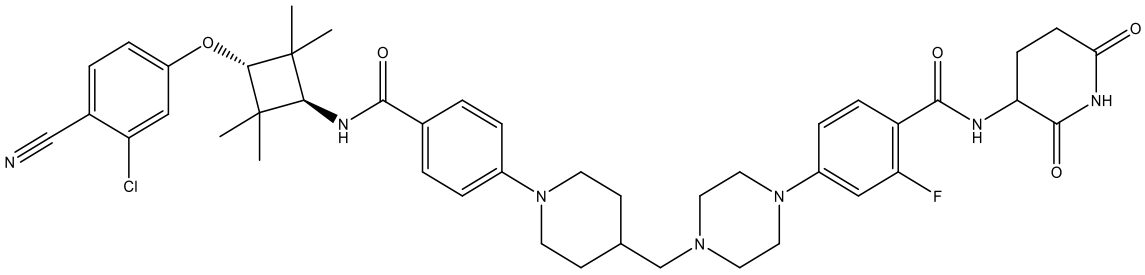
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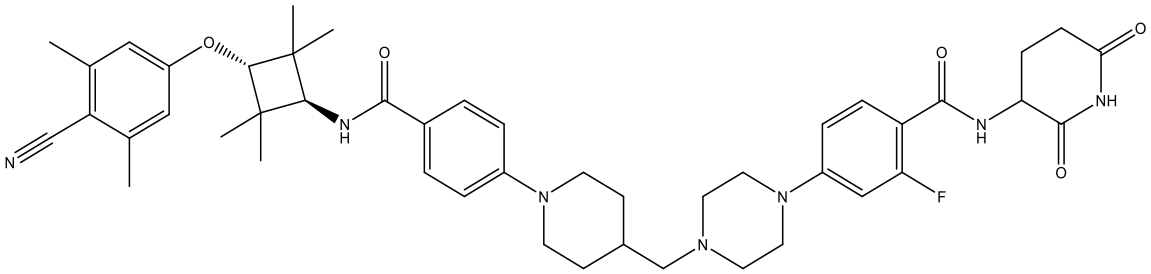
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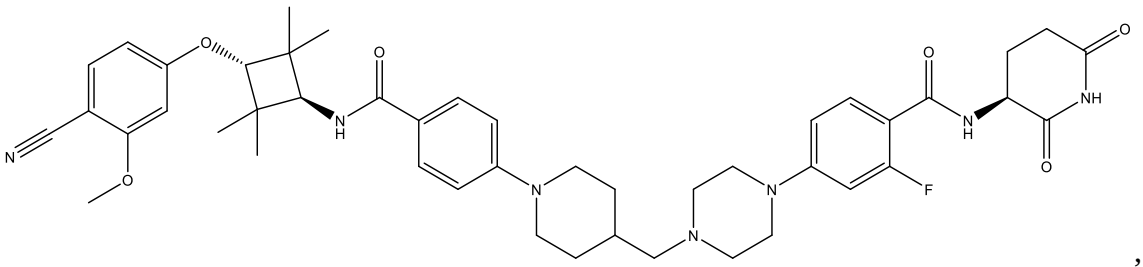
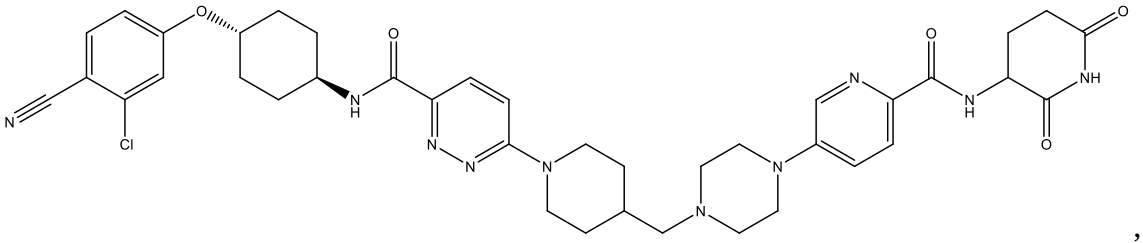
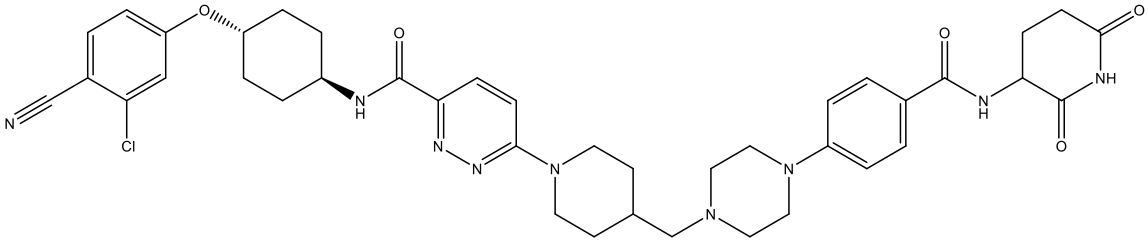
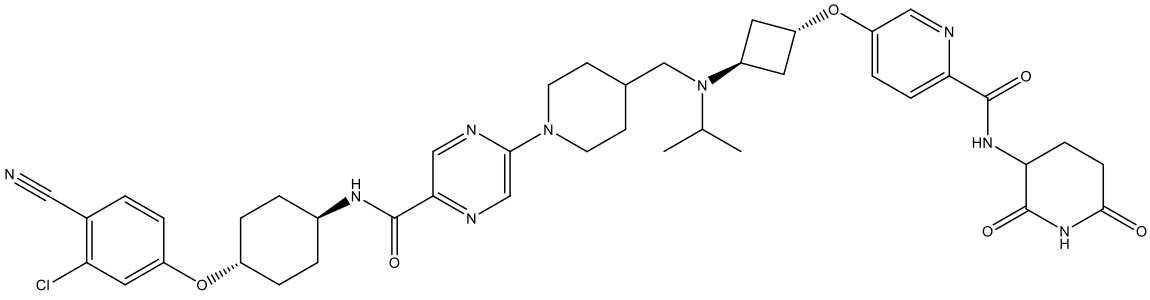
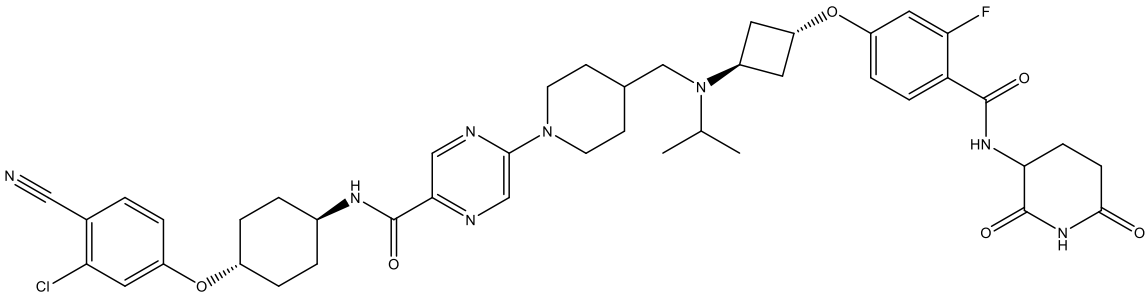
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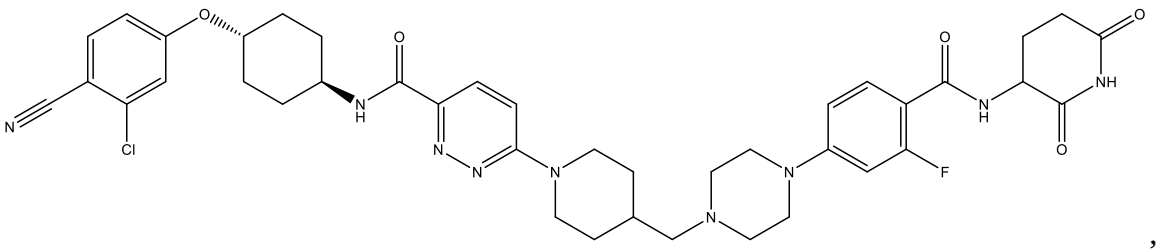


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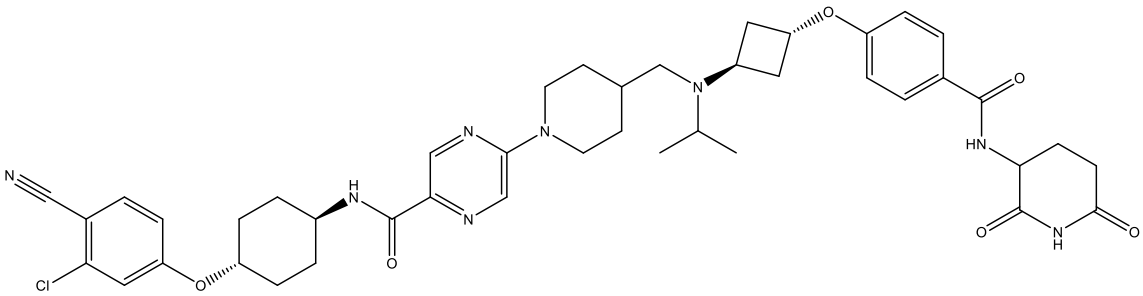


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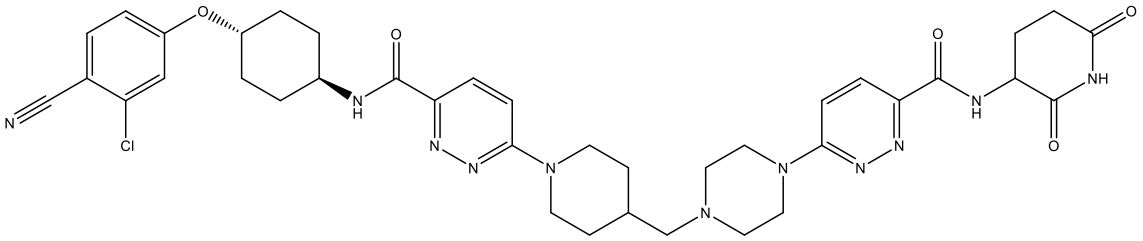

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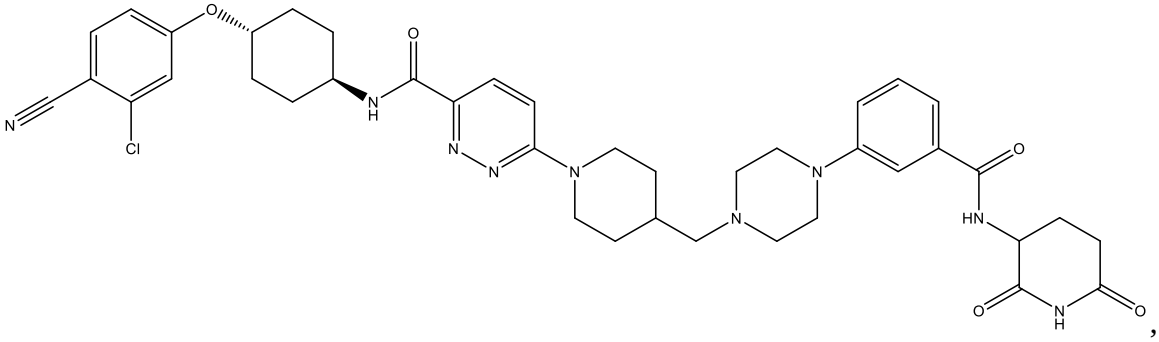
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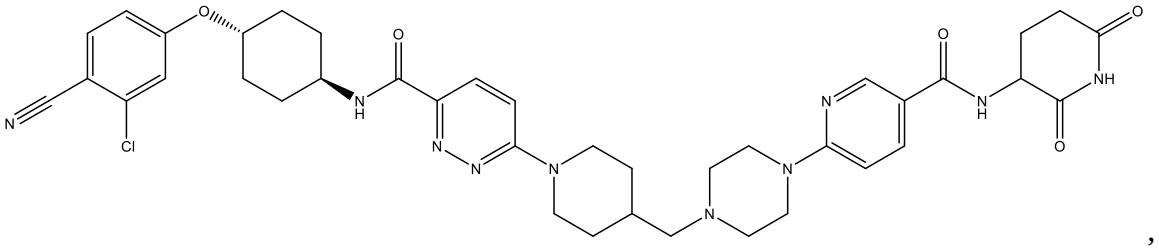
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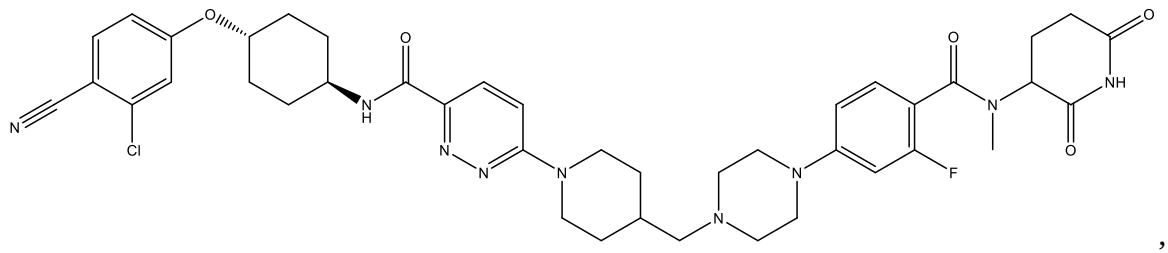
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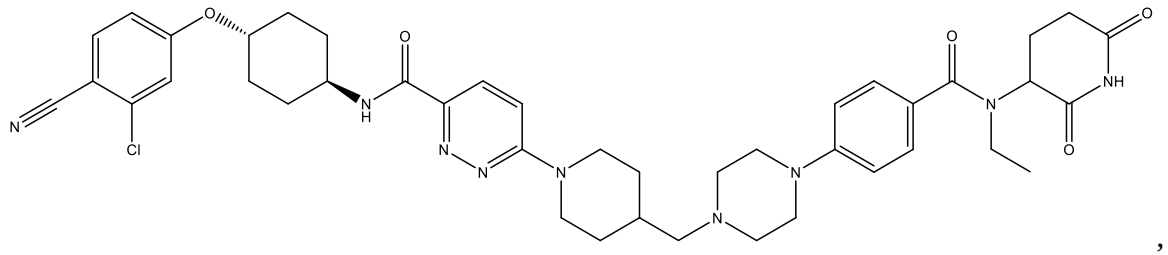
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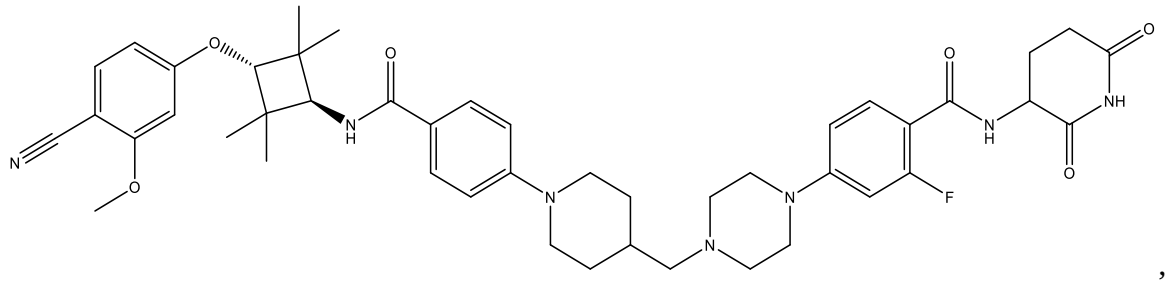
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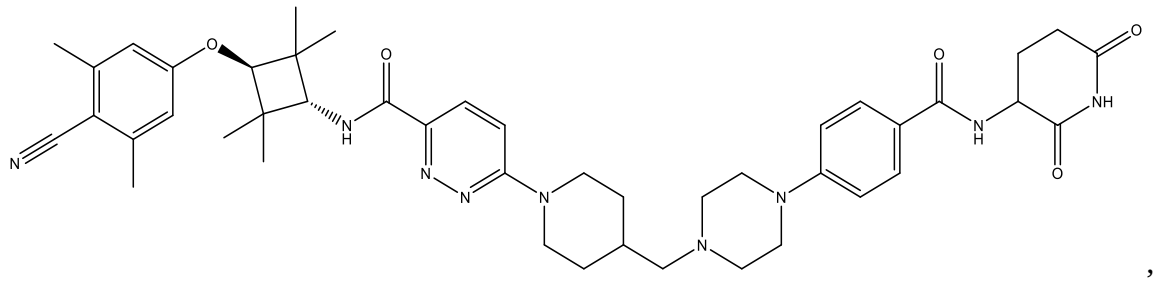
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or a pharmaceutically acceptable salt thereof.

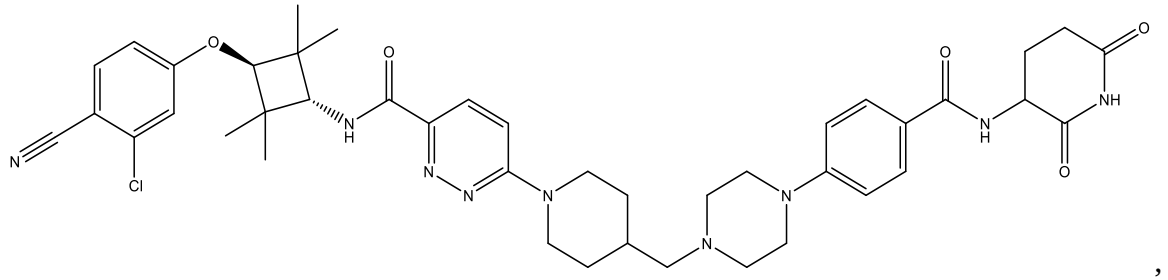
41. A bifunctional compound, wherein the compound is:



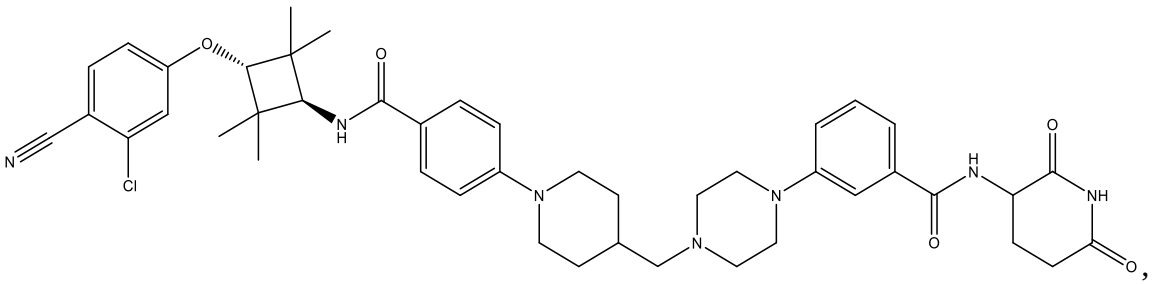
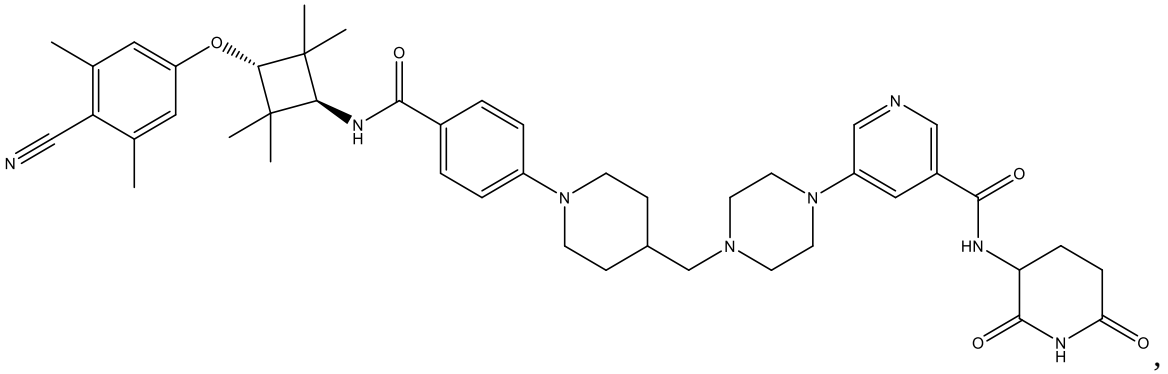
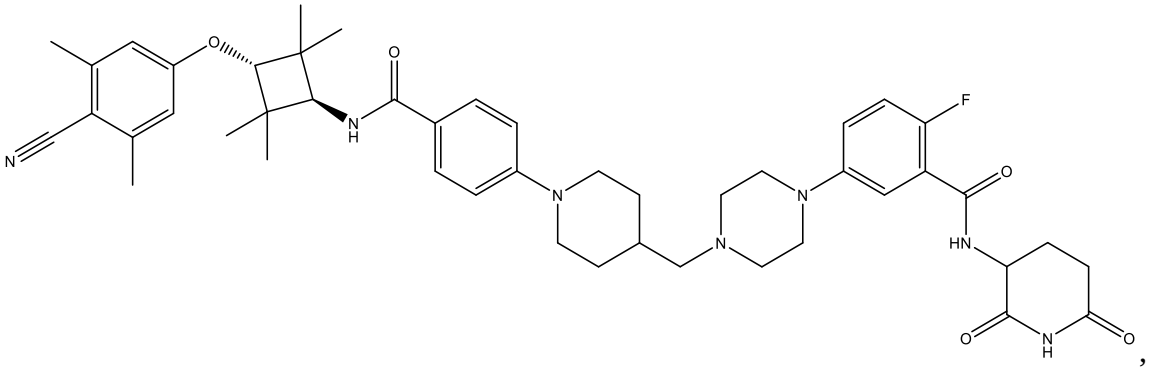
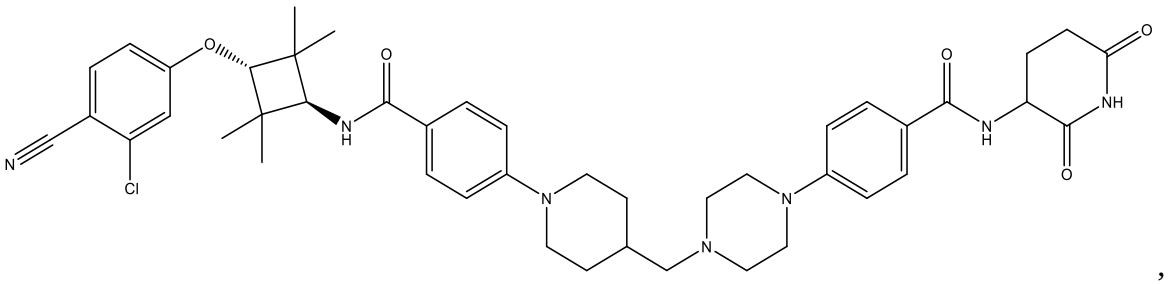
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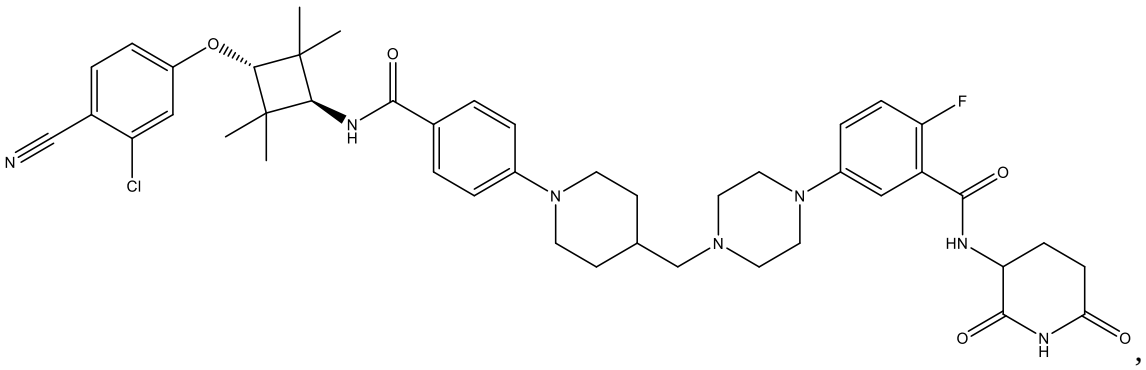


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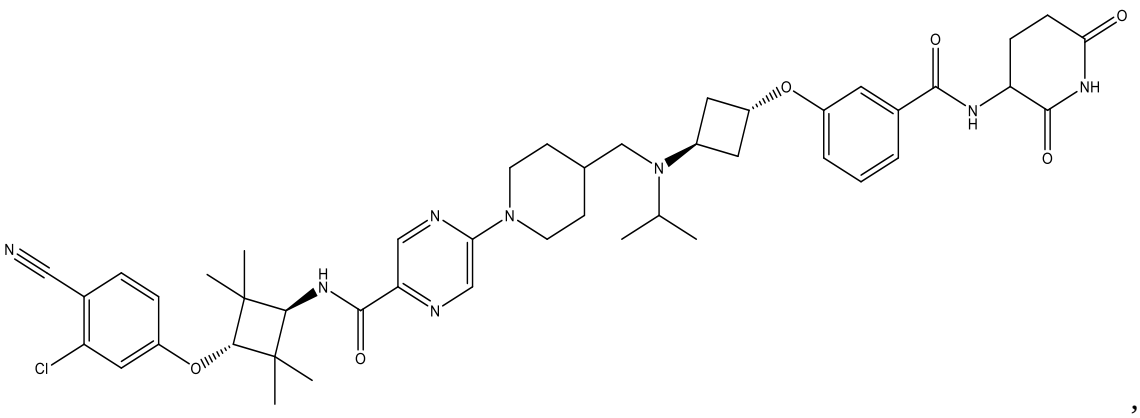


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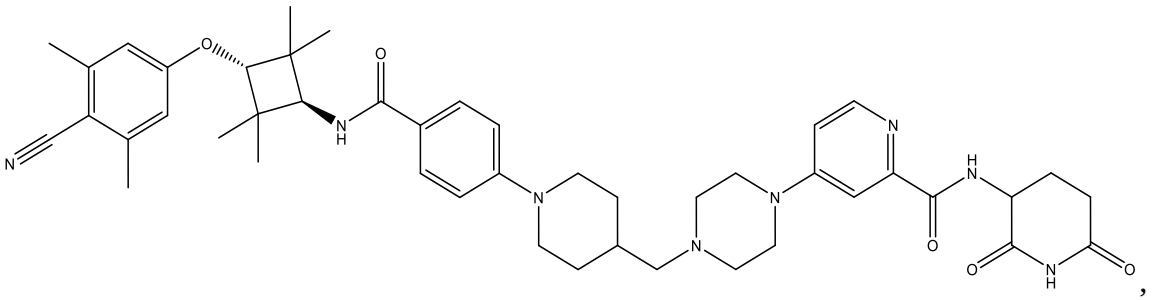

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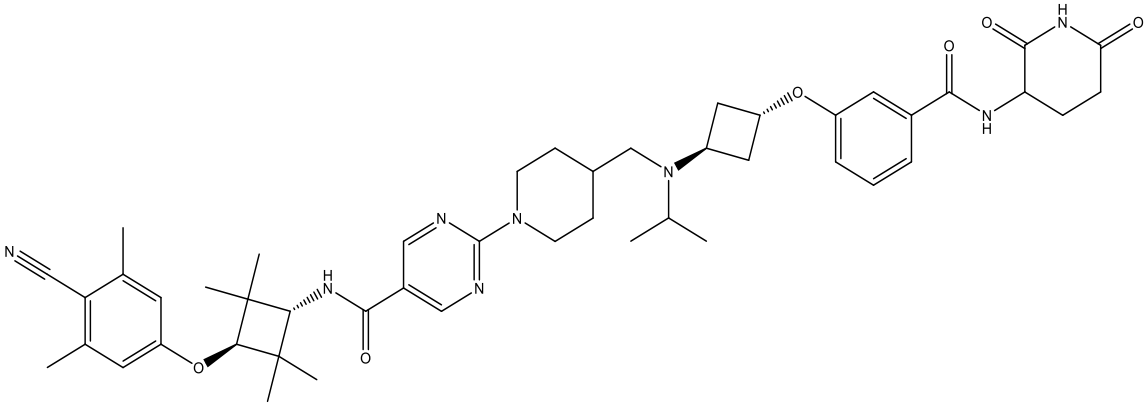
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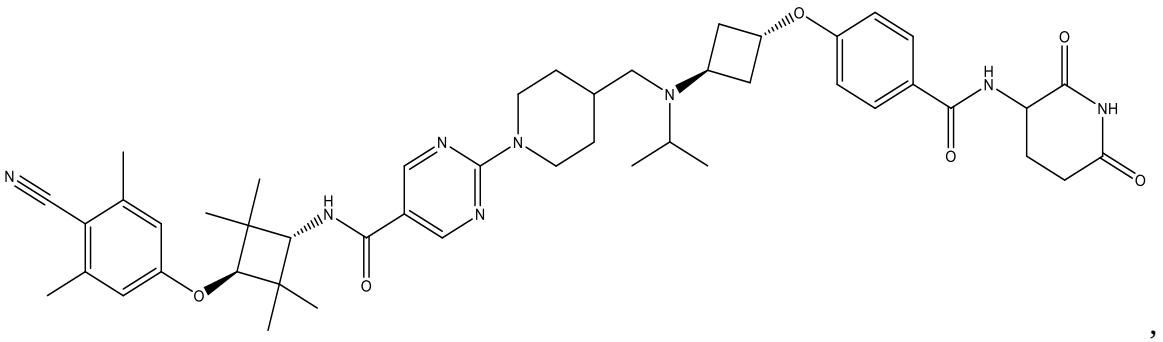
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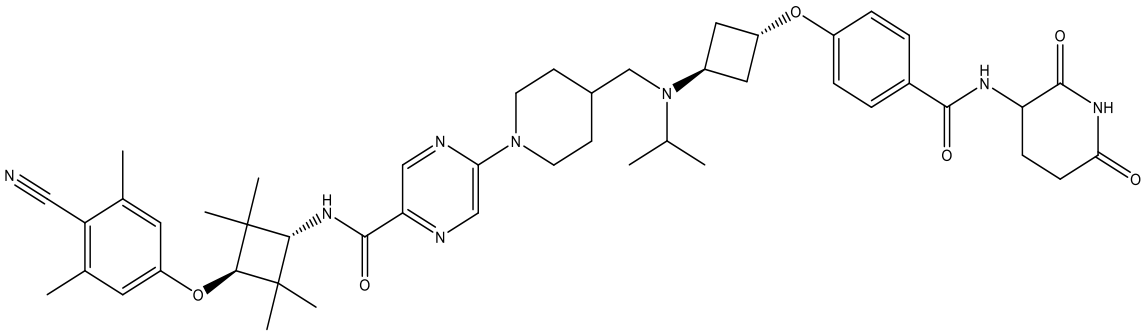
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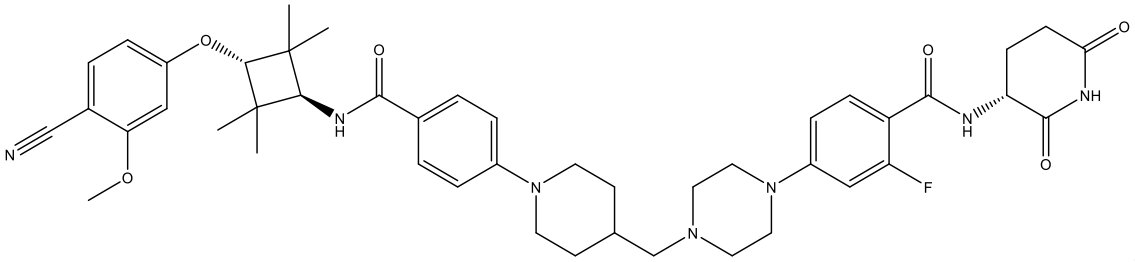
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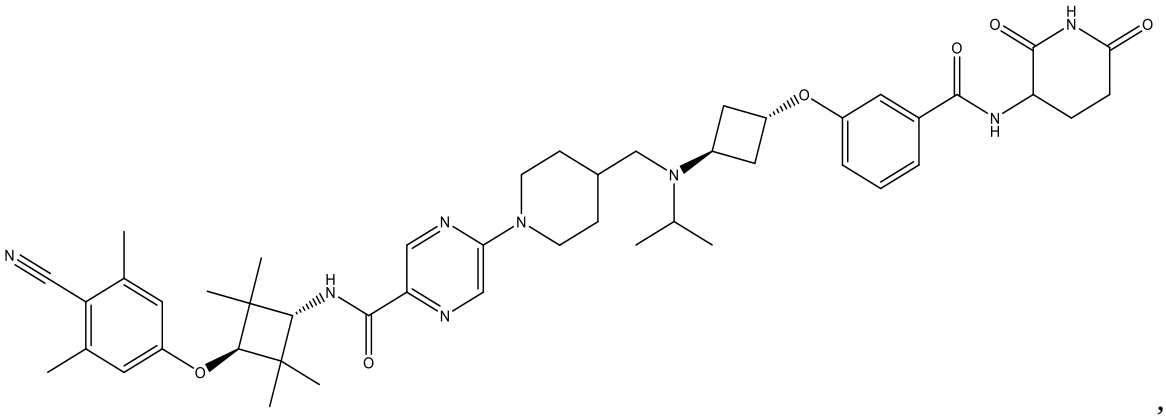
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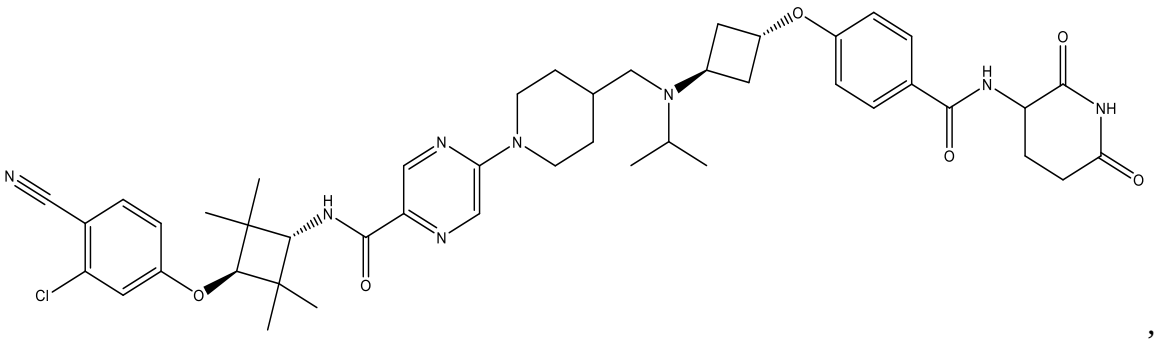
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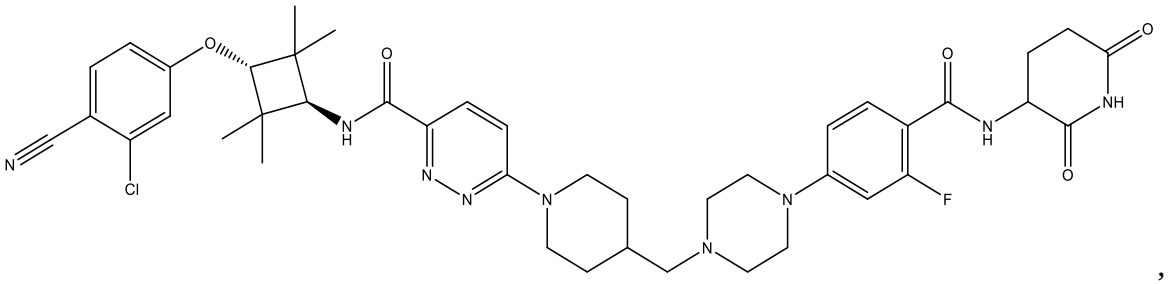
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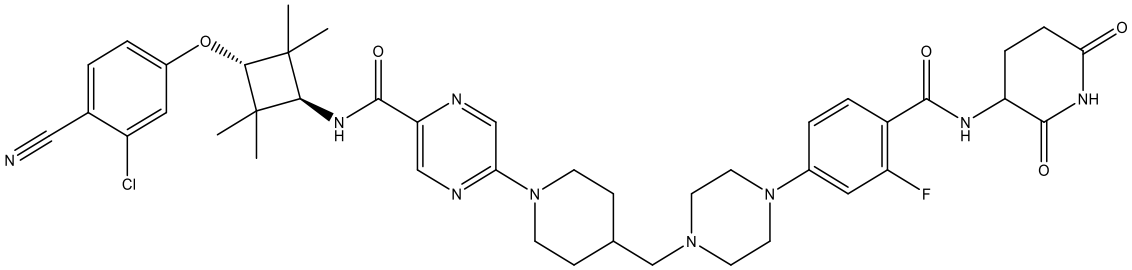
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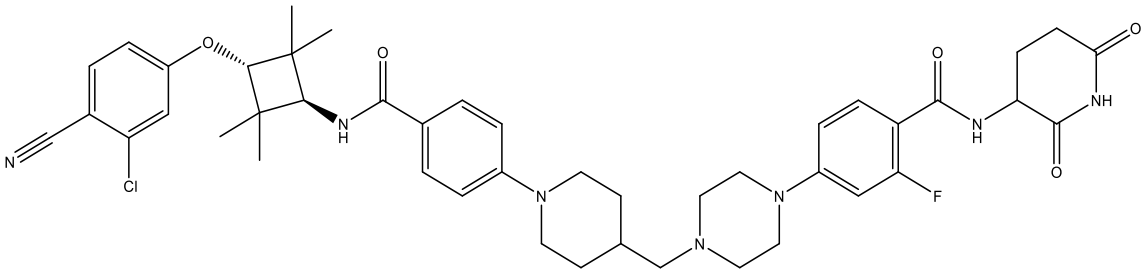
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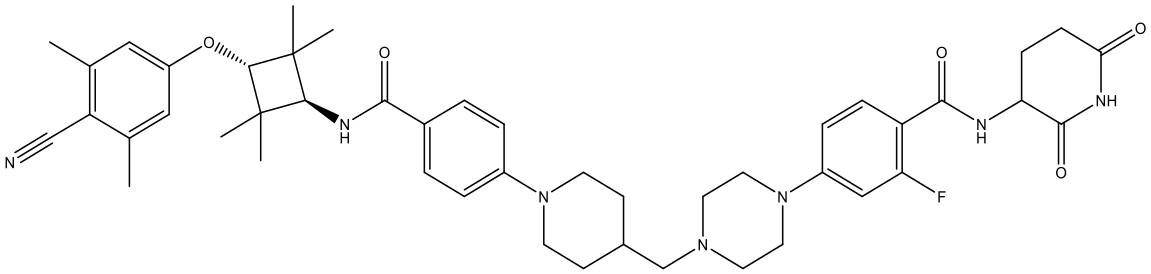
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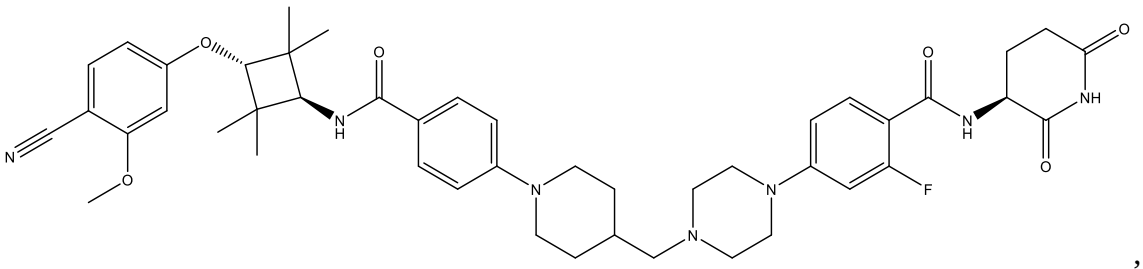
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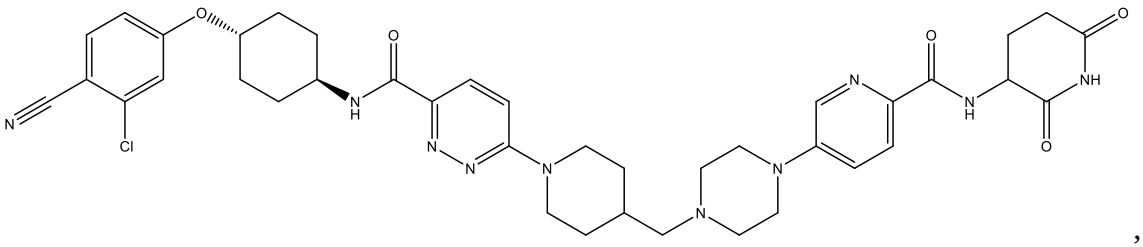
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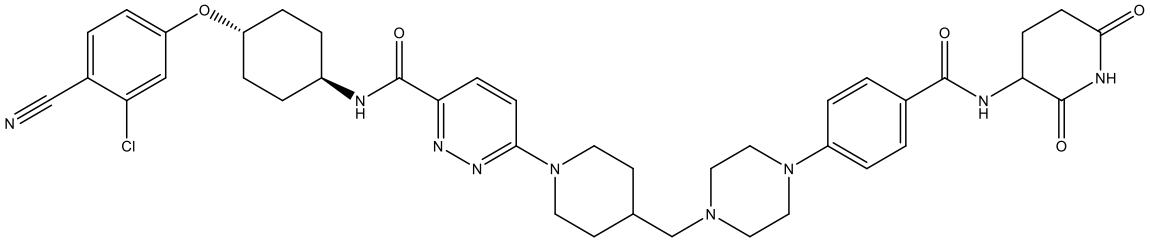
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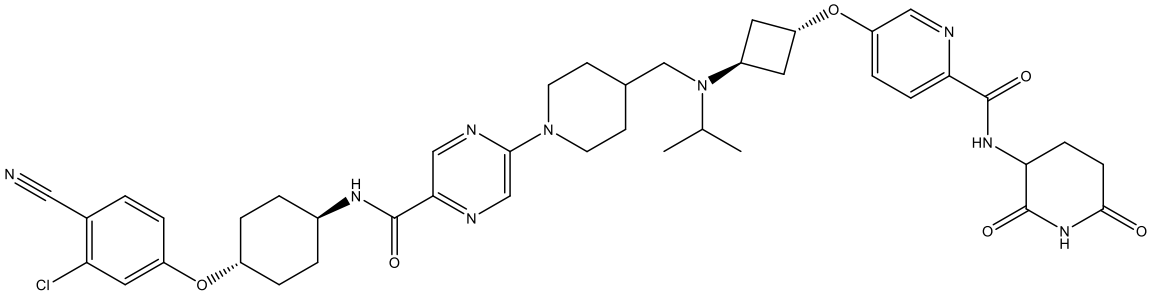
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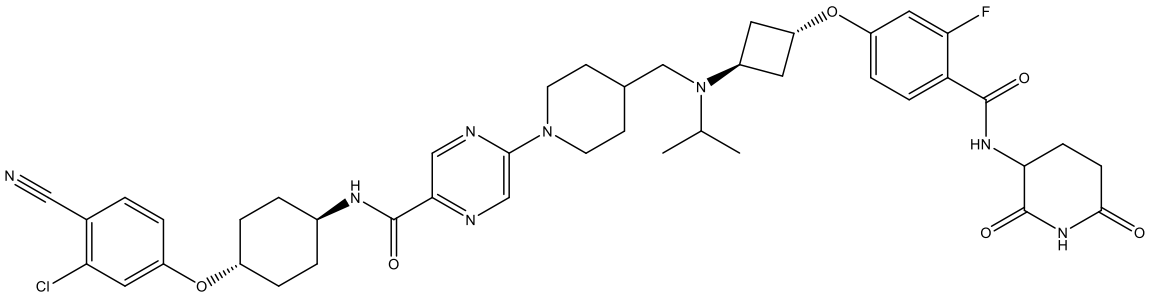
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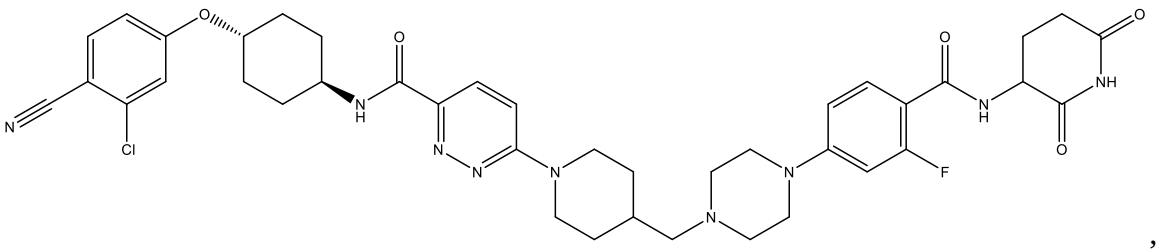
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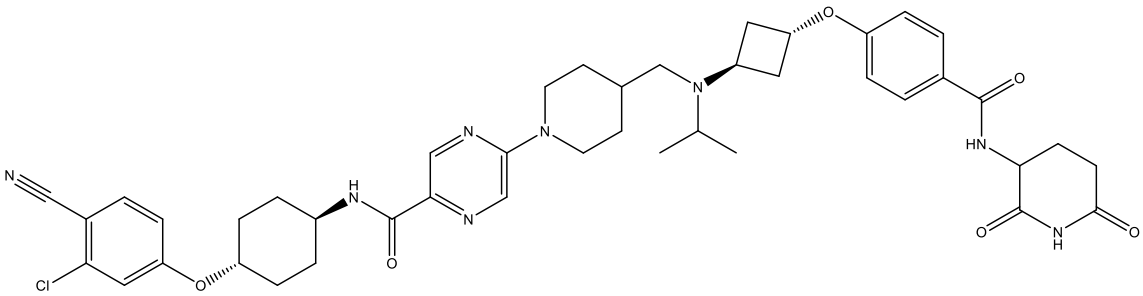
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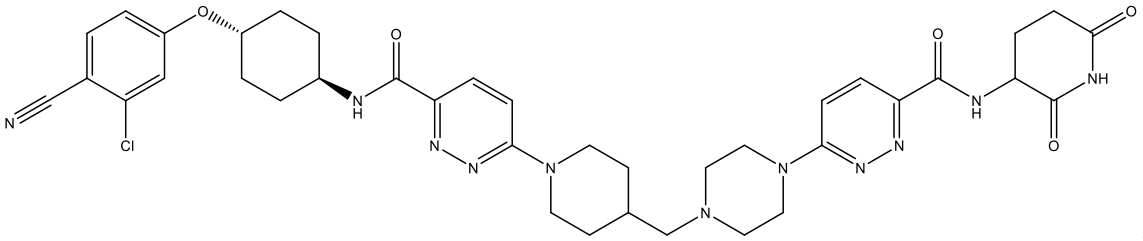
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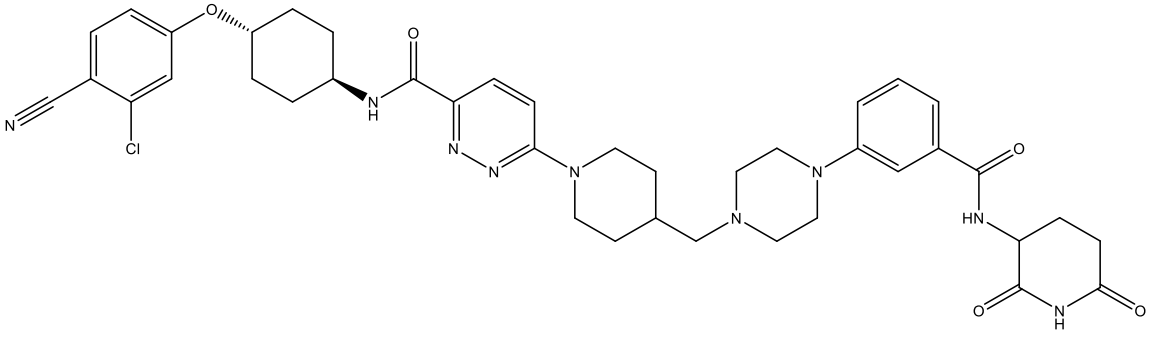
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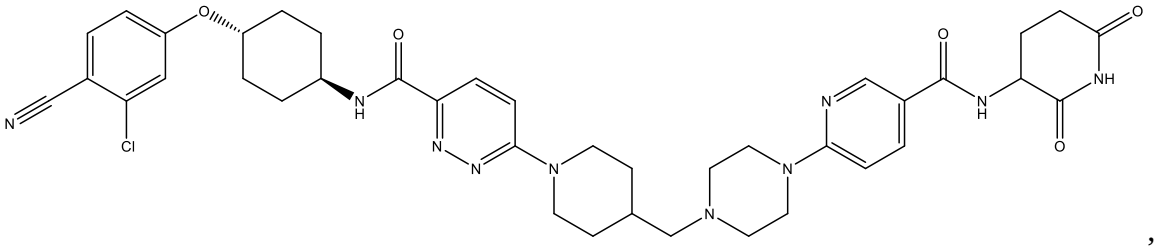
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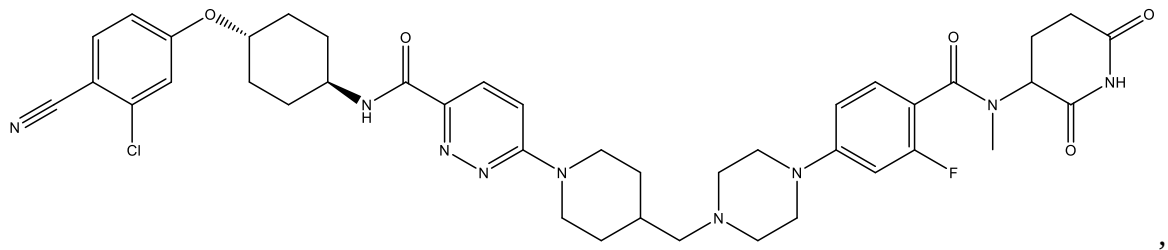
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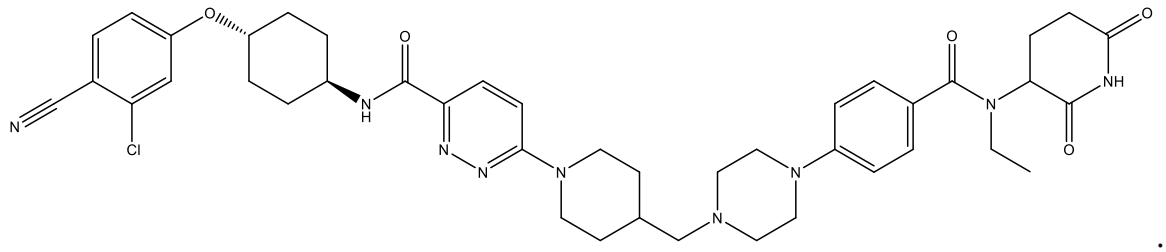
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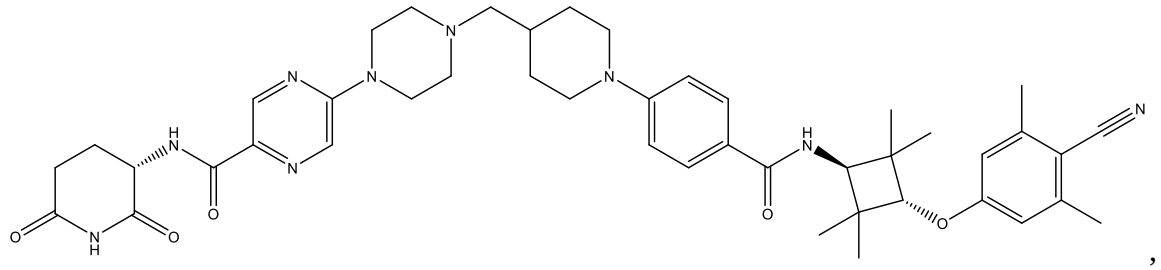


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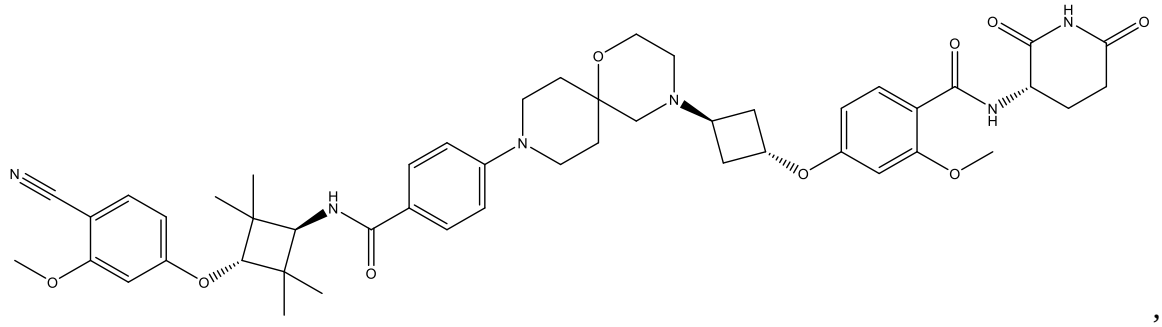


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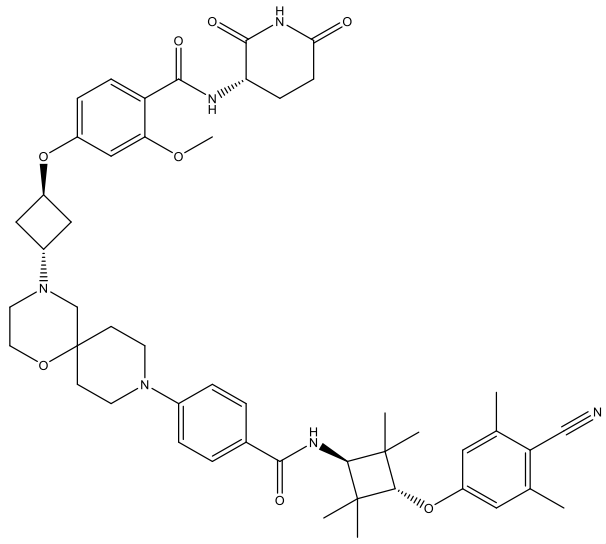
42. A bifunctional compound, wherein the compound is:



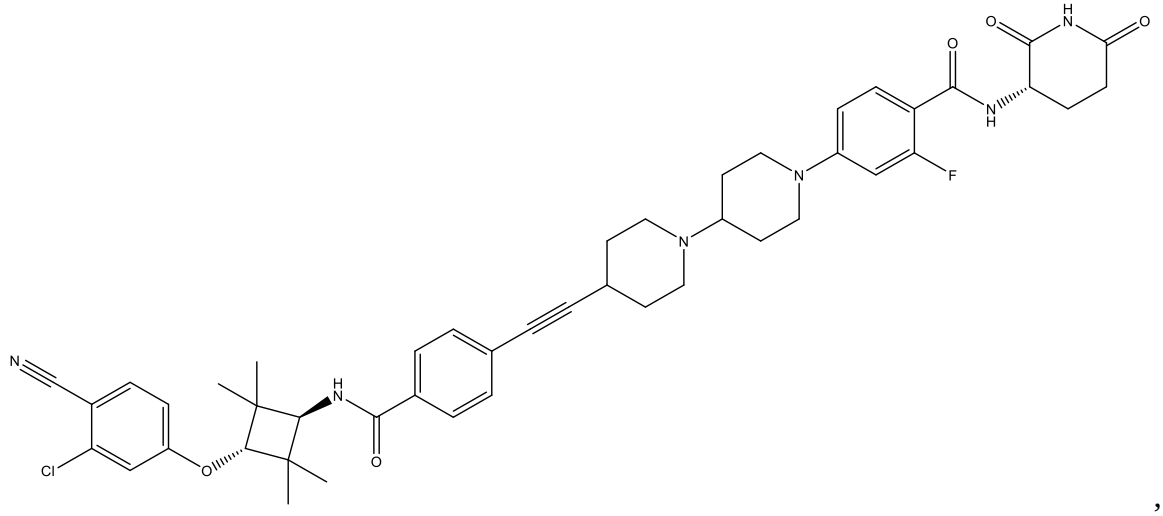
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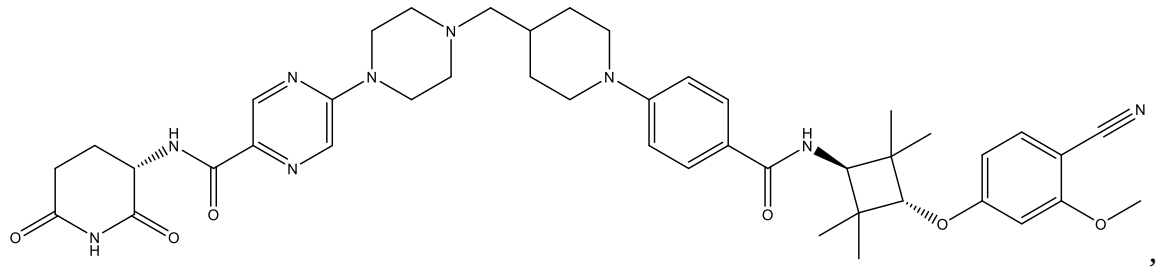
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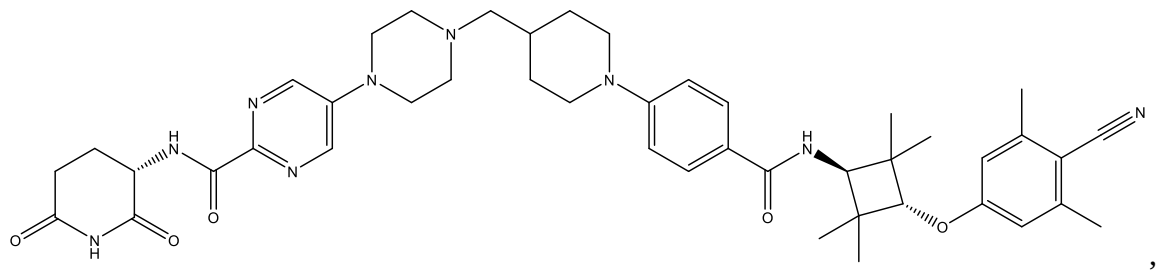
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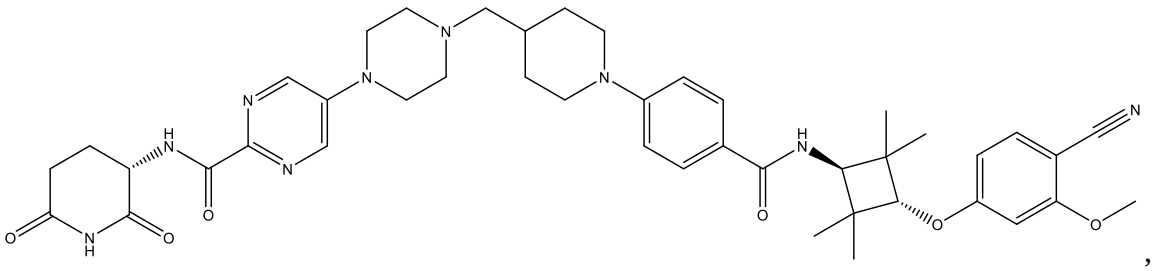
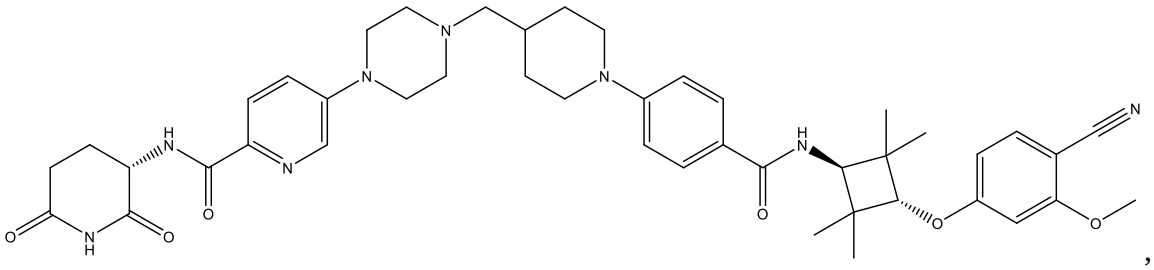
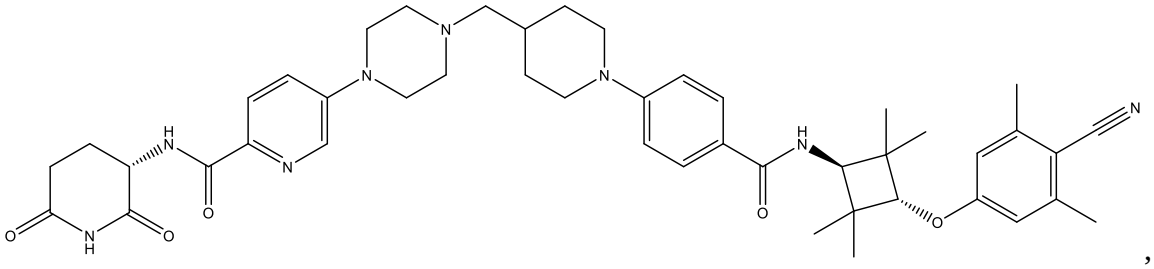
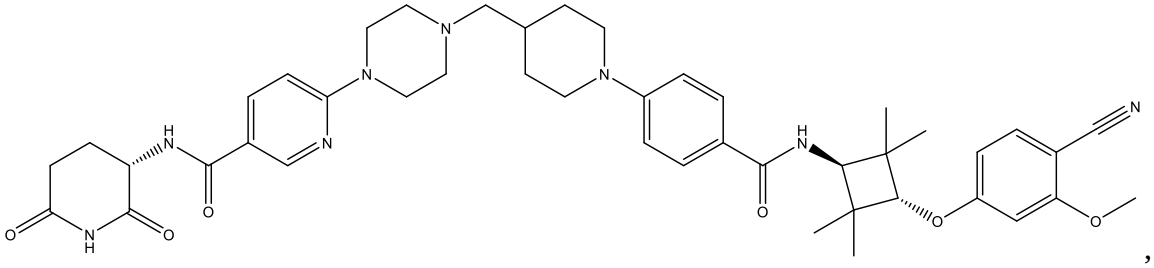
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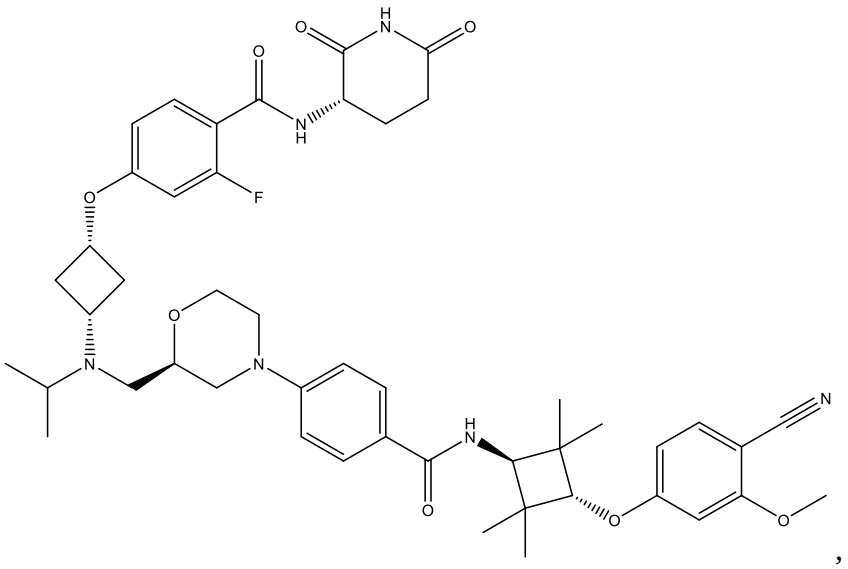


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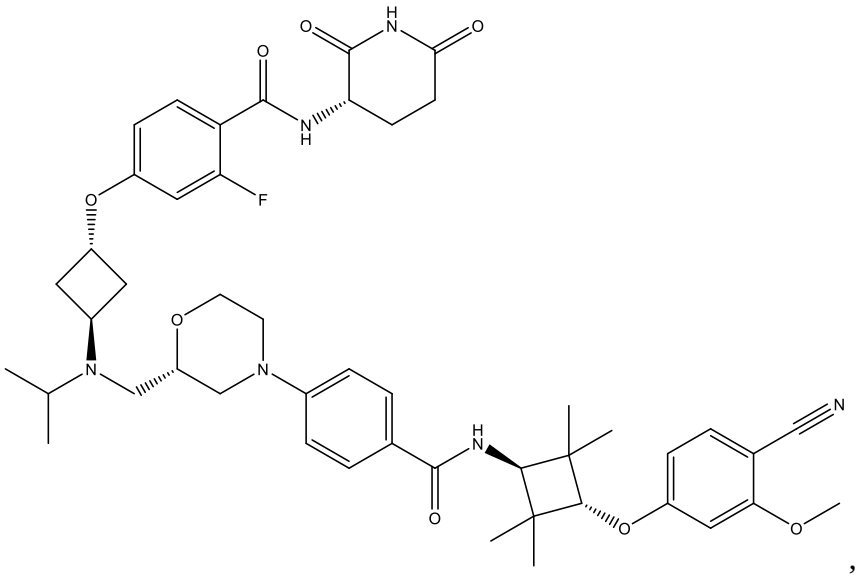


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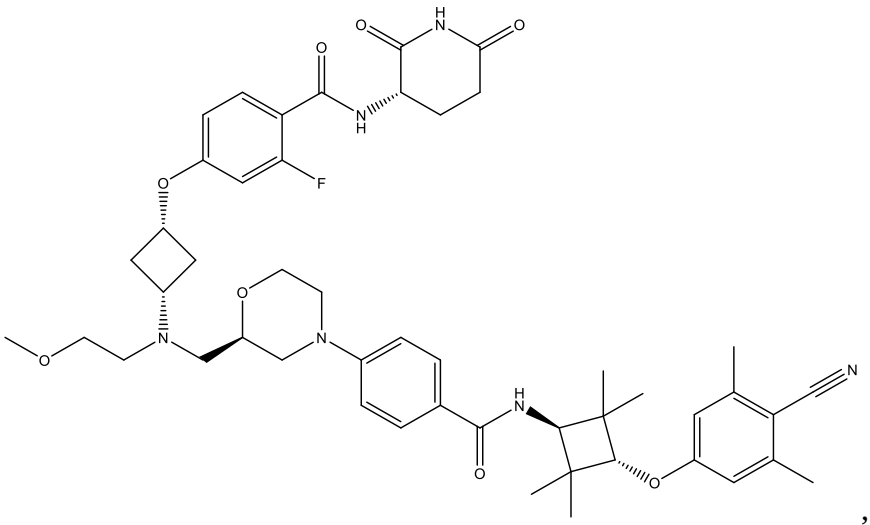

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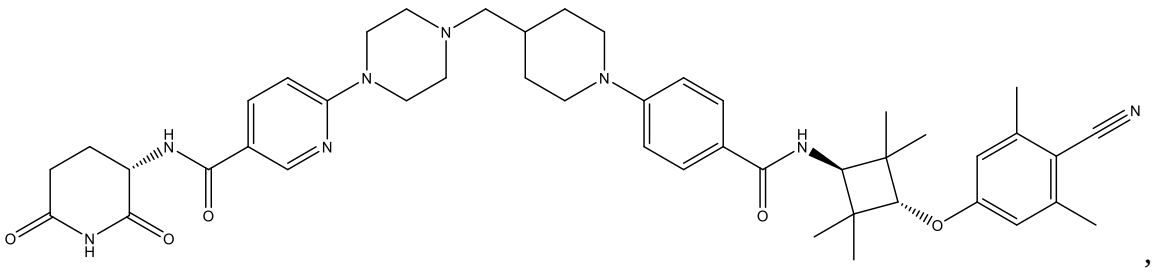
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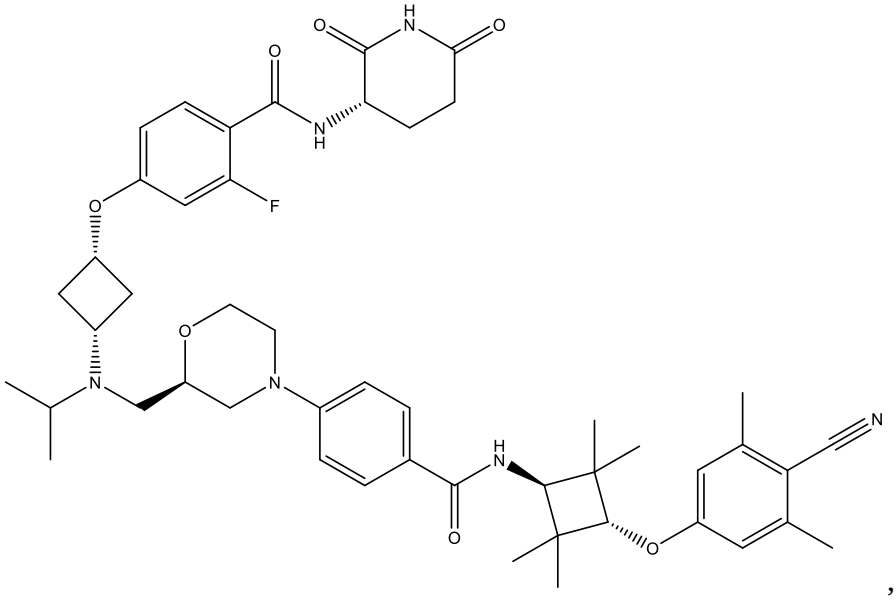
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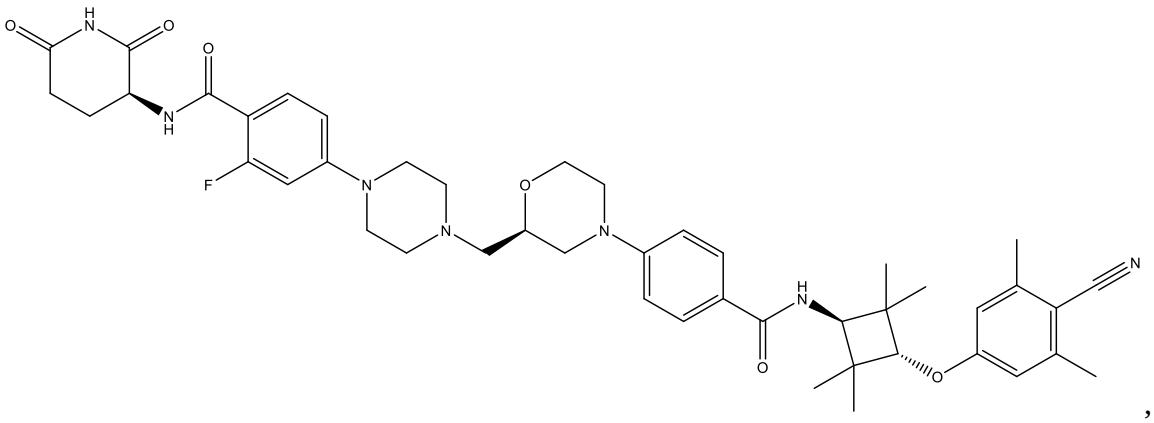
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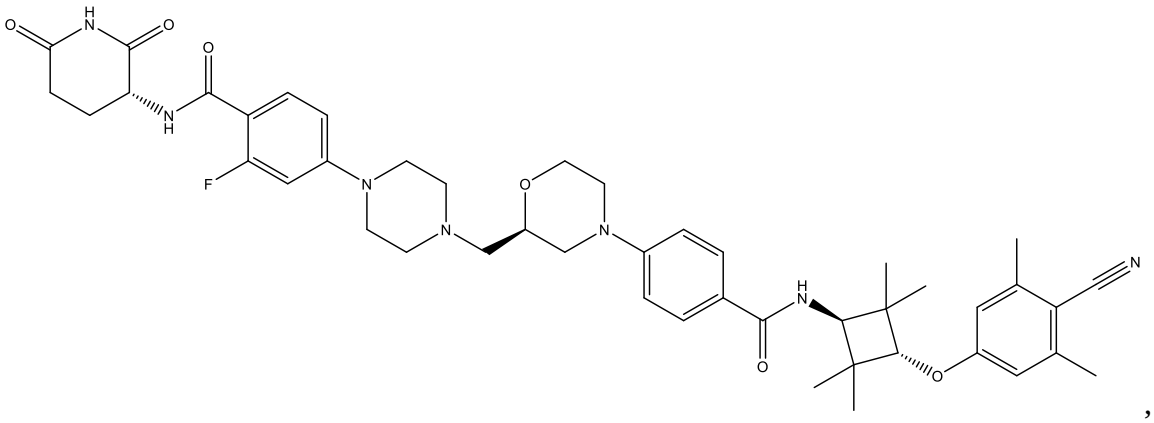


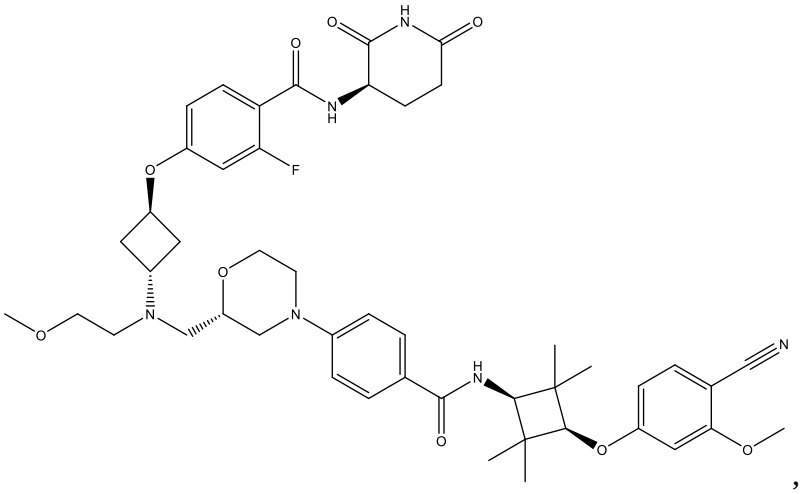
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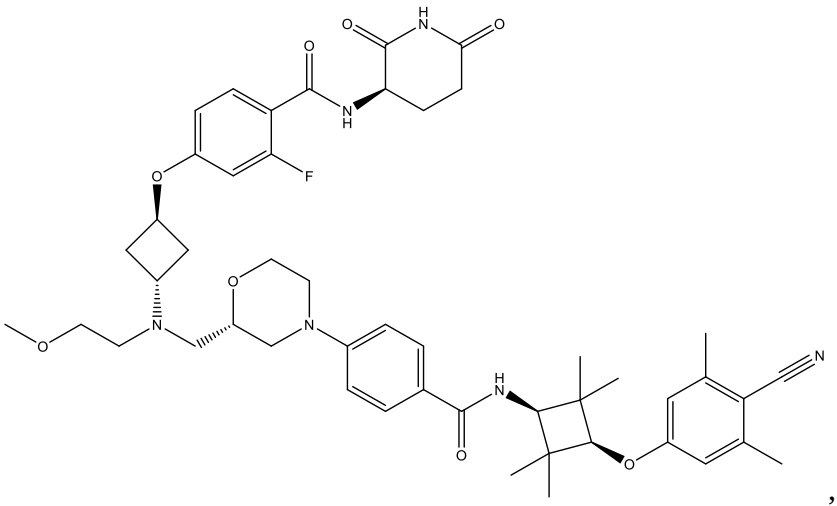


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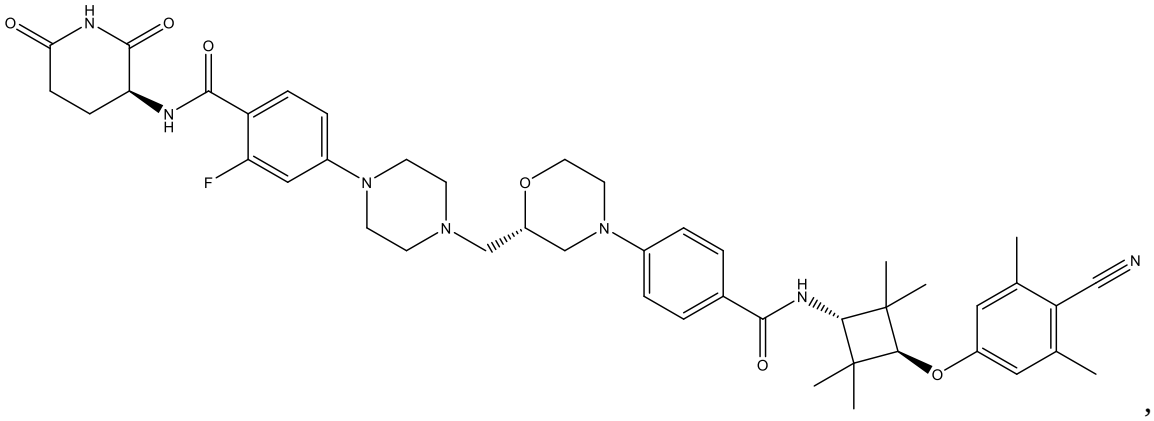

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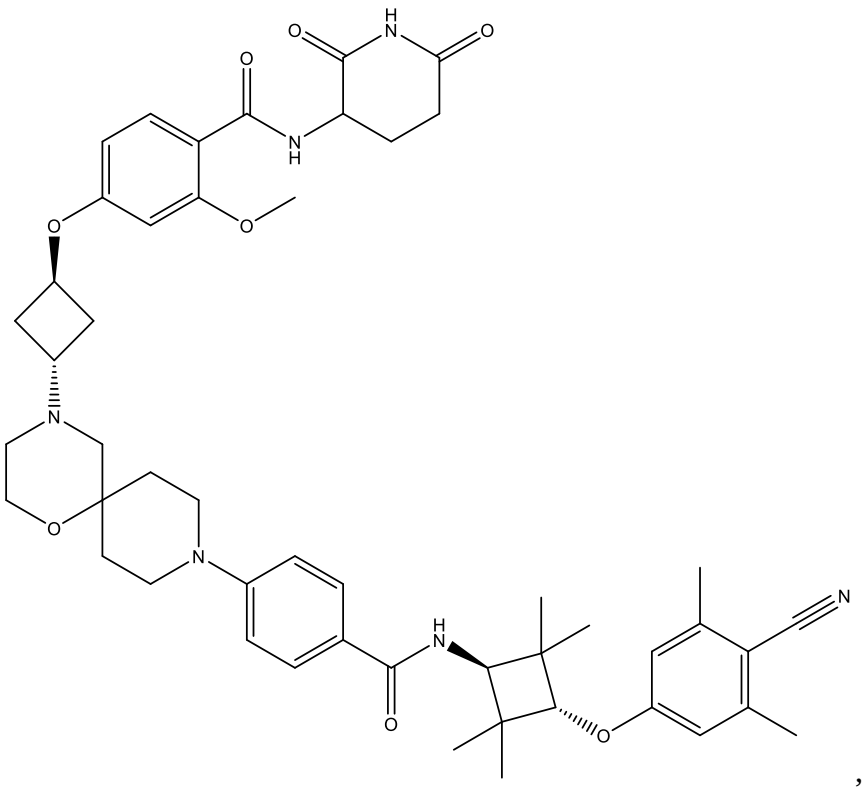

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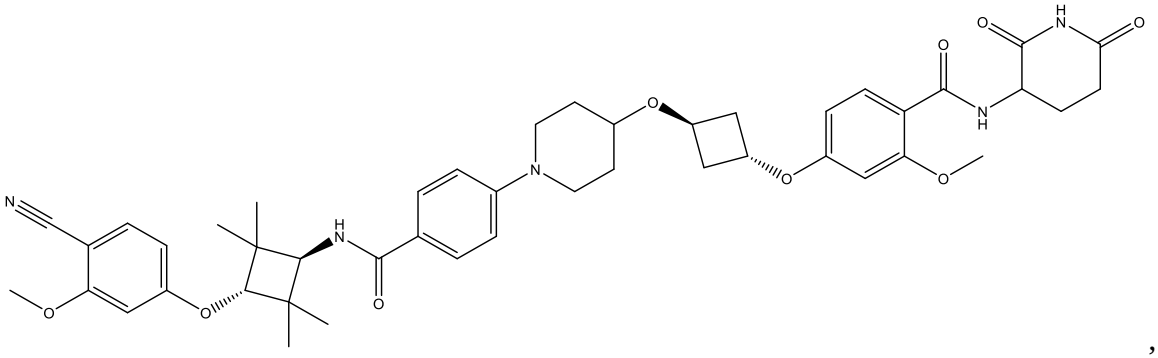
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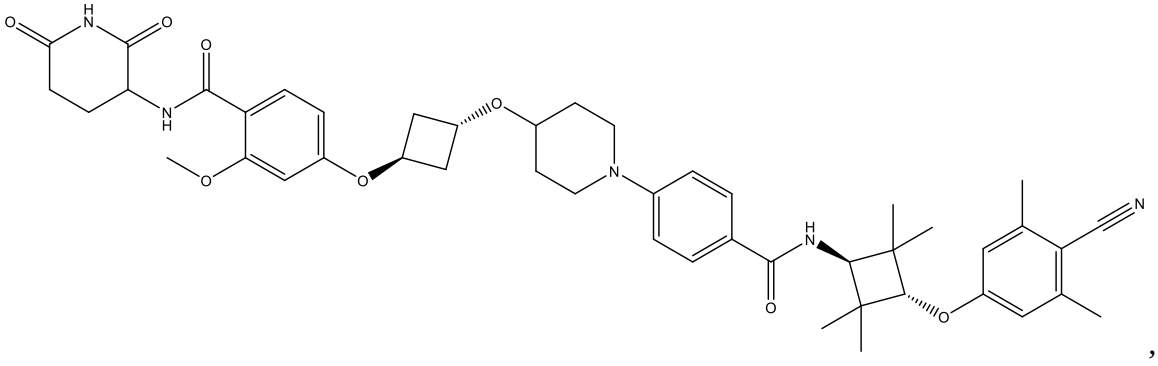
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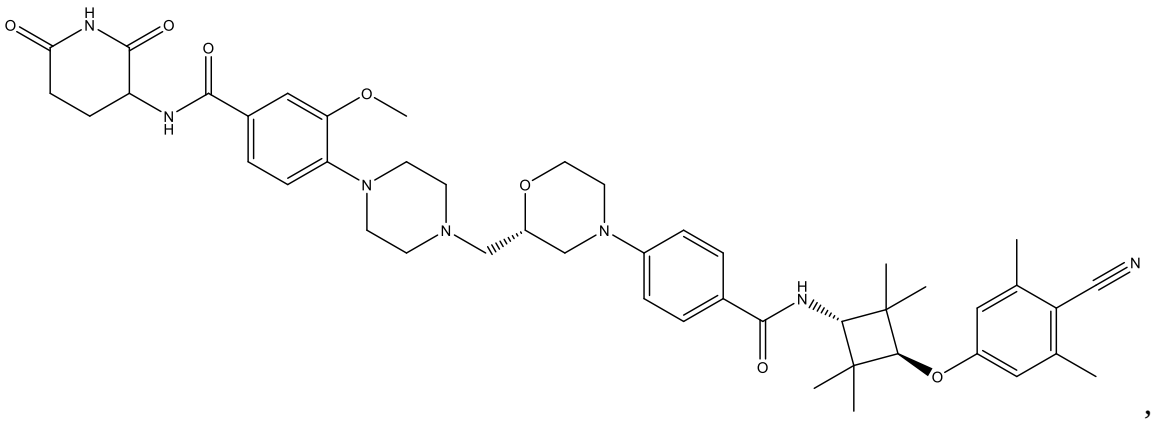
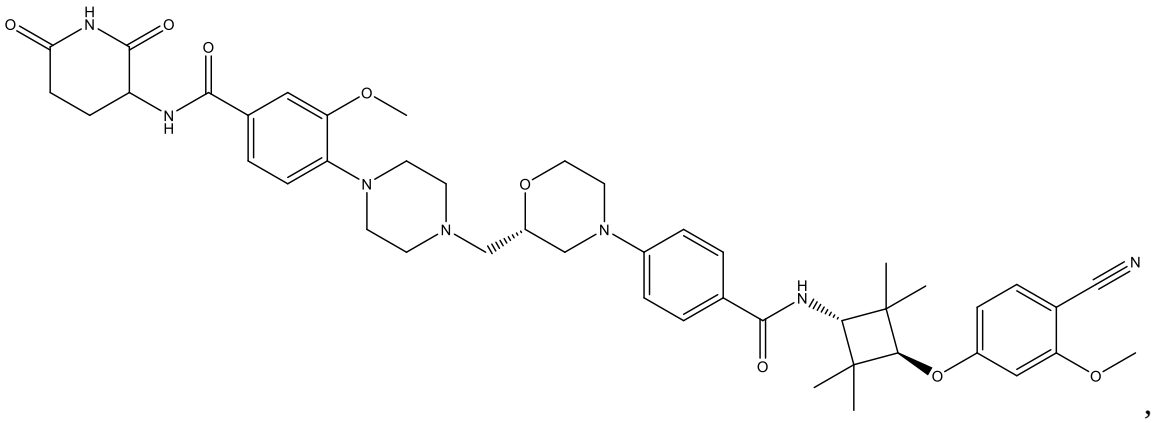
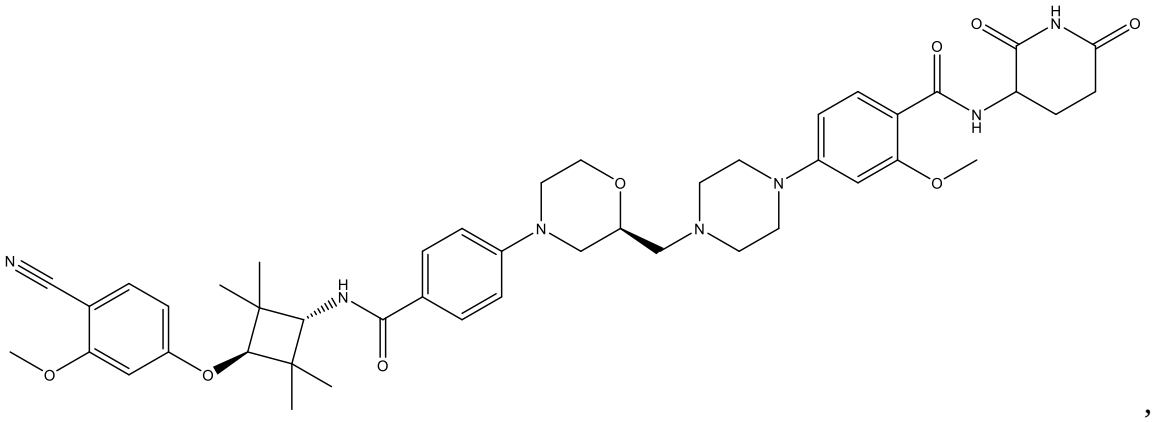
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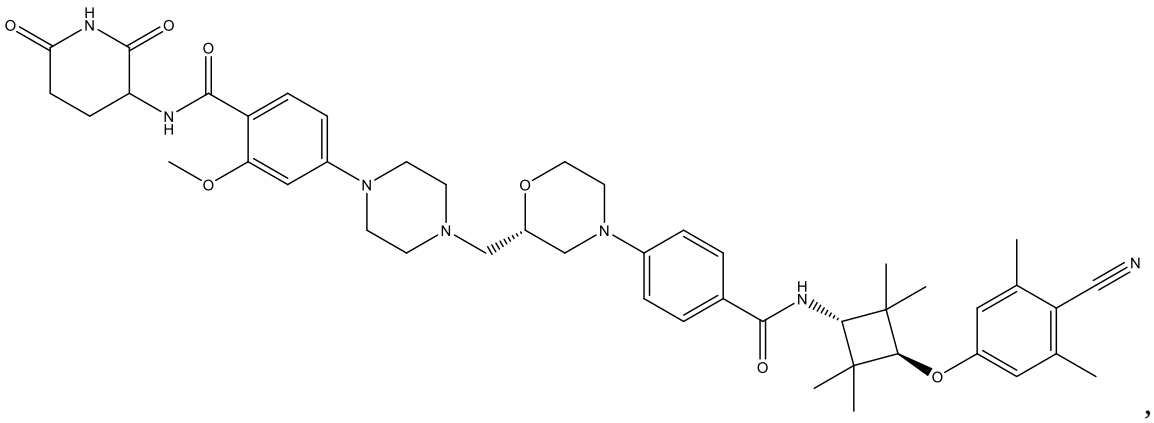


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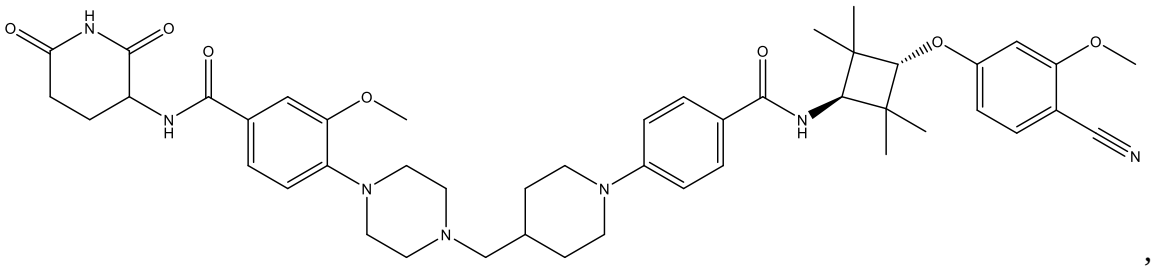


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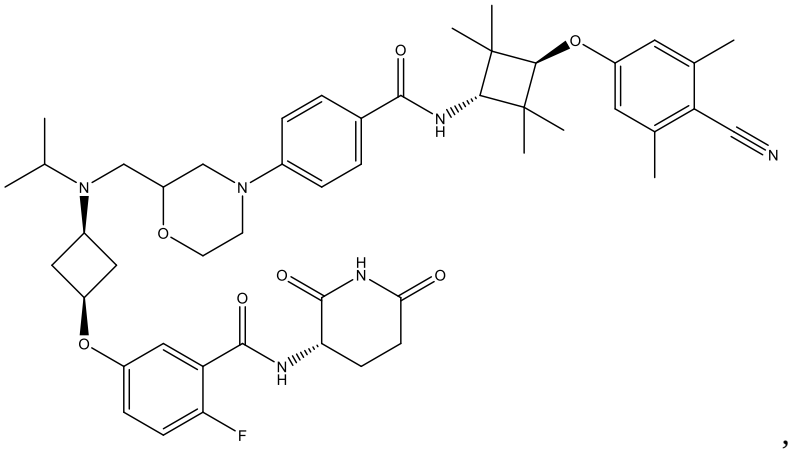

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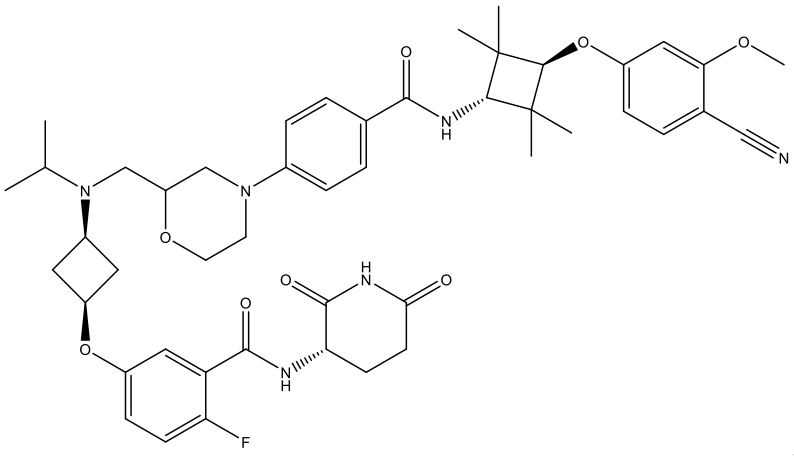
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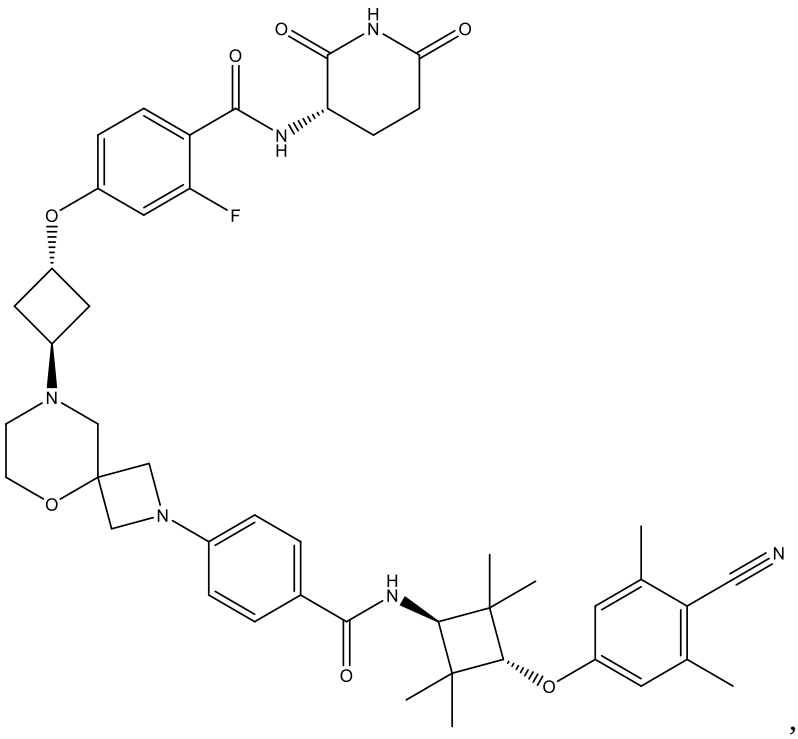
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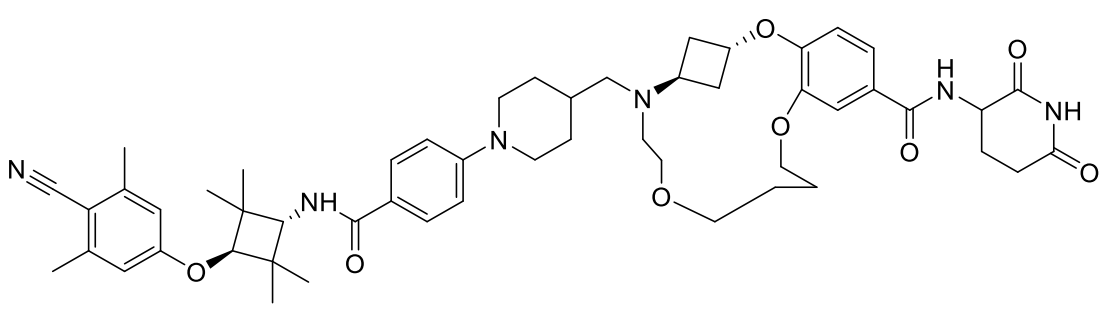
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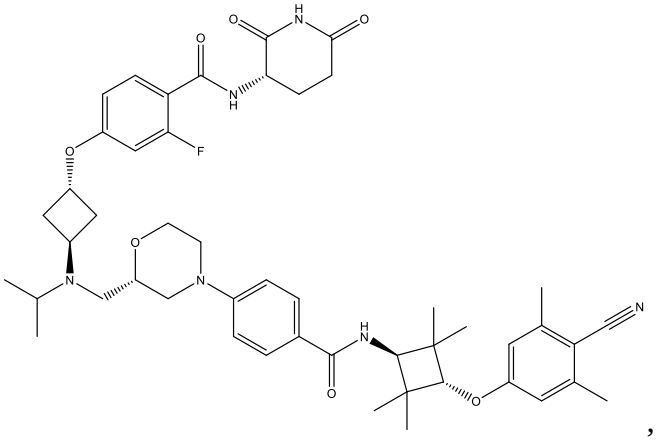
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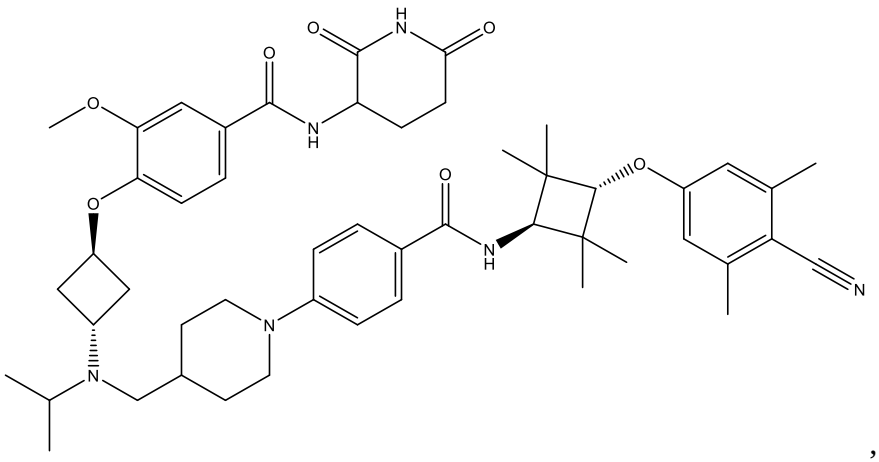
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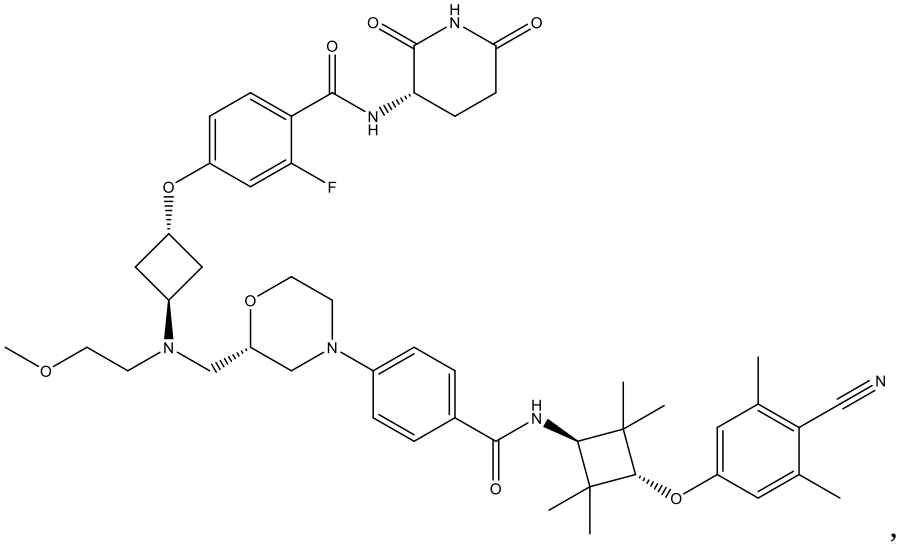
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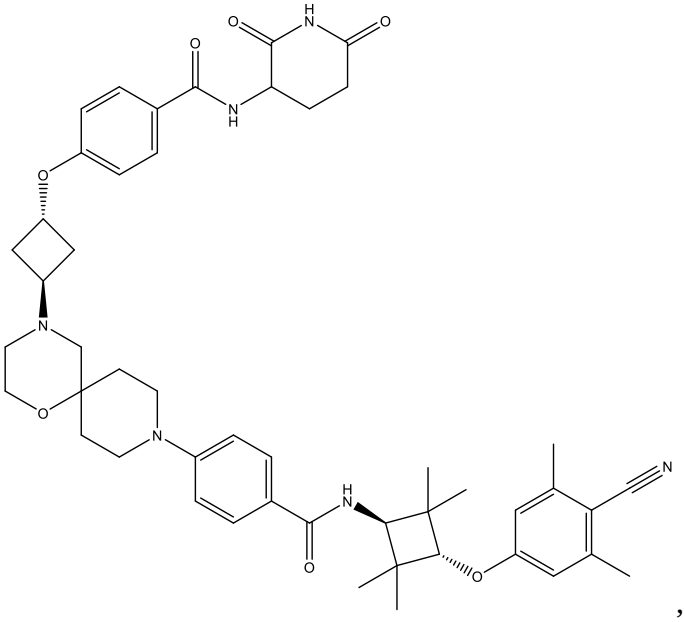
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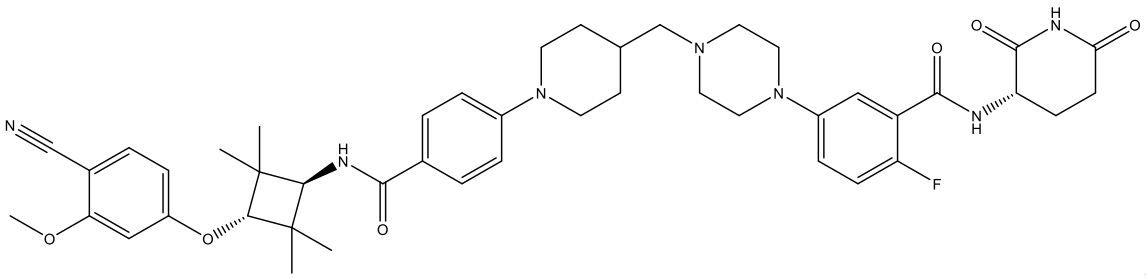
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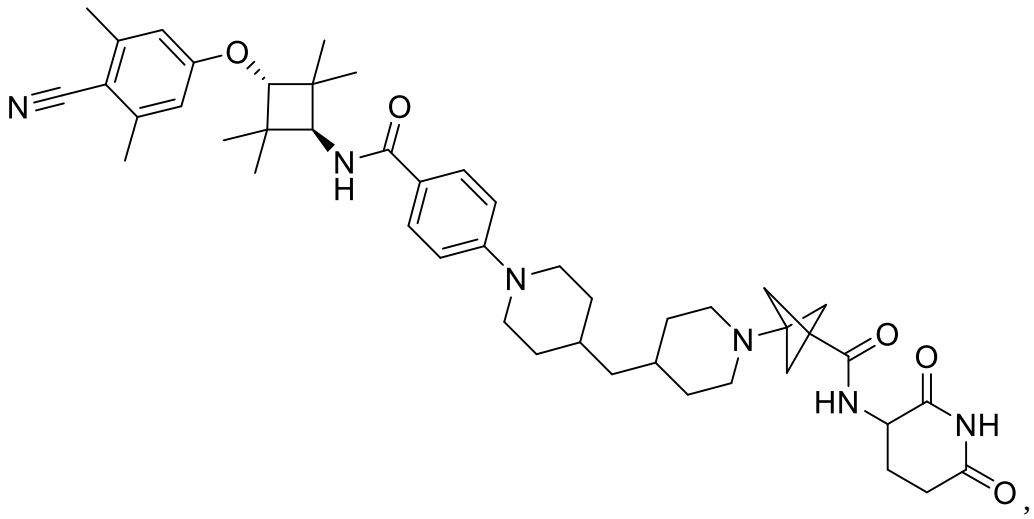
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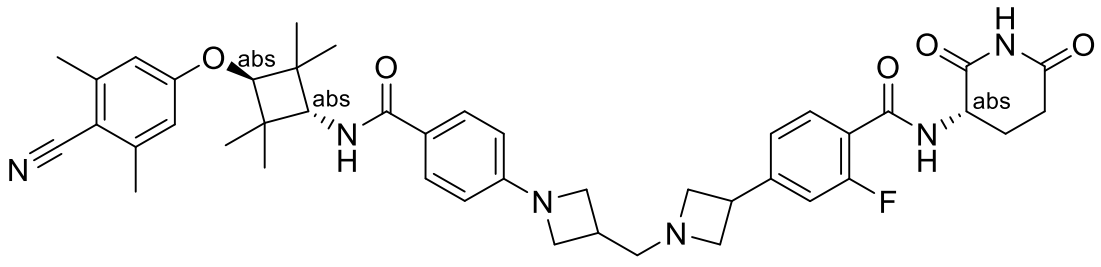
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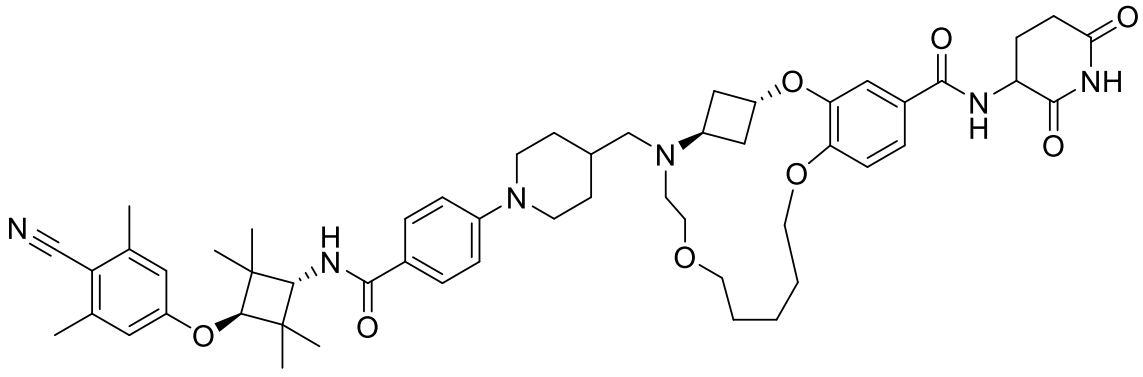
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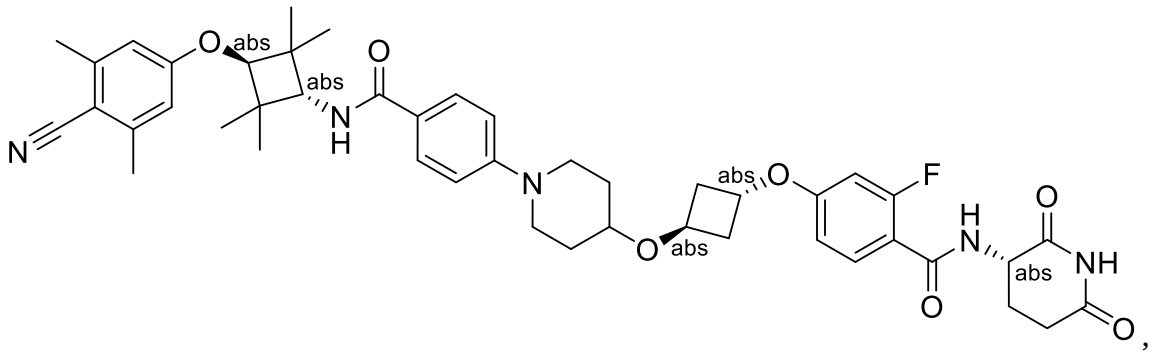
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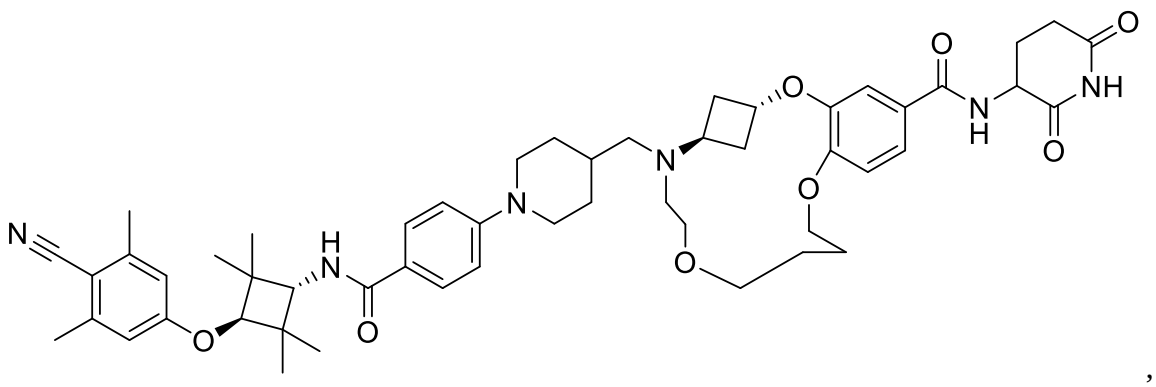


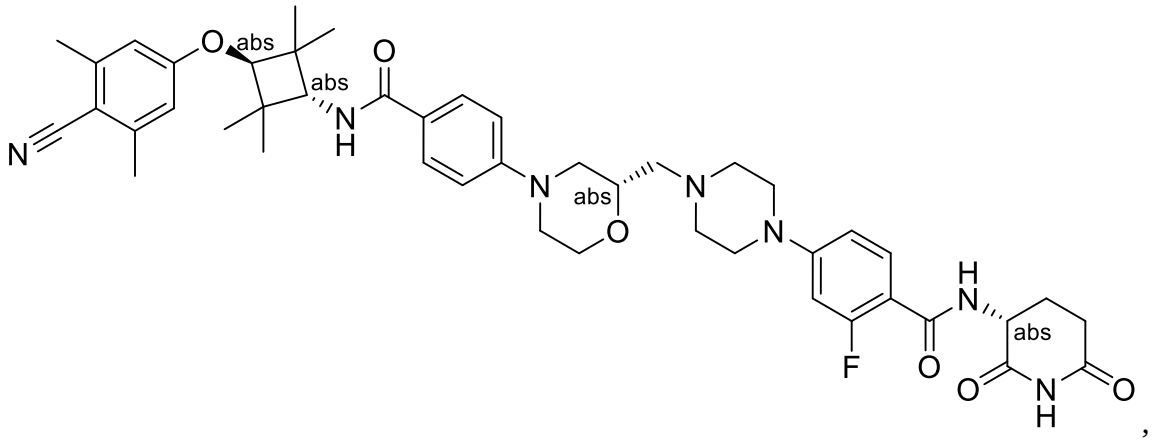
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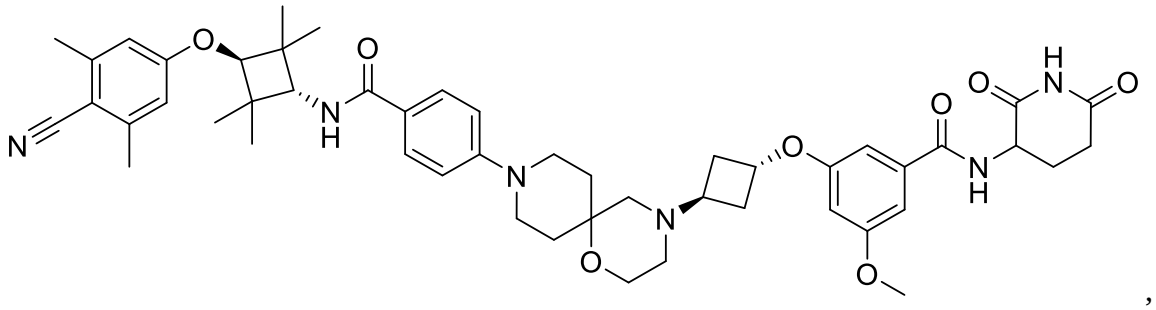


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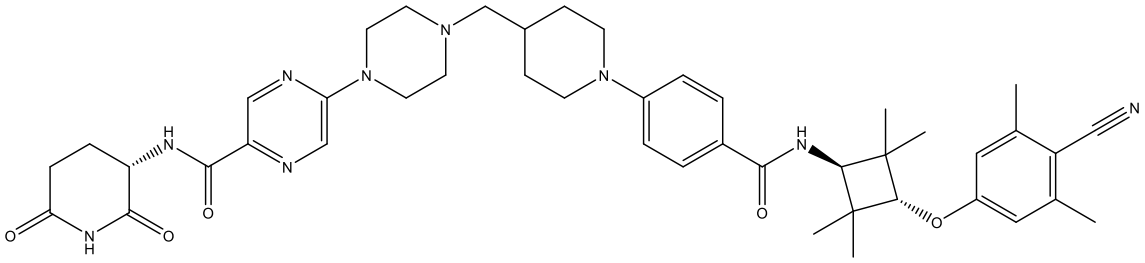

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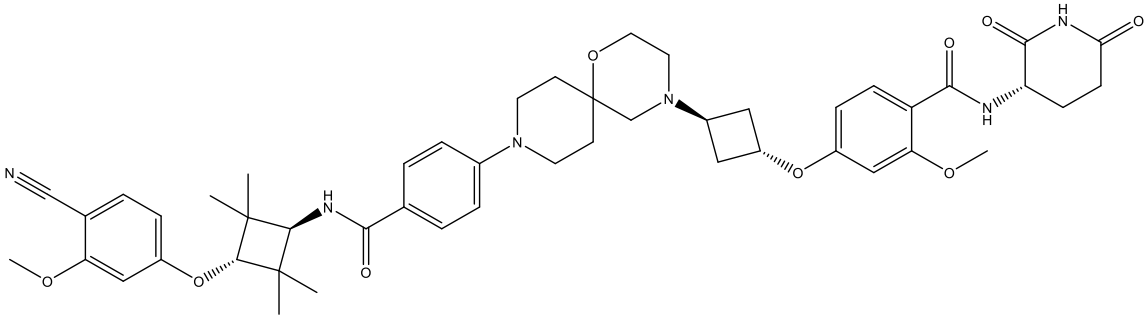

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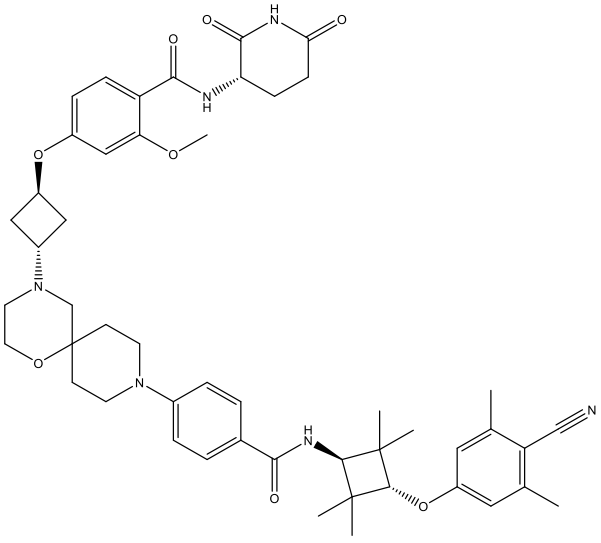

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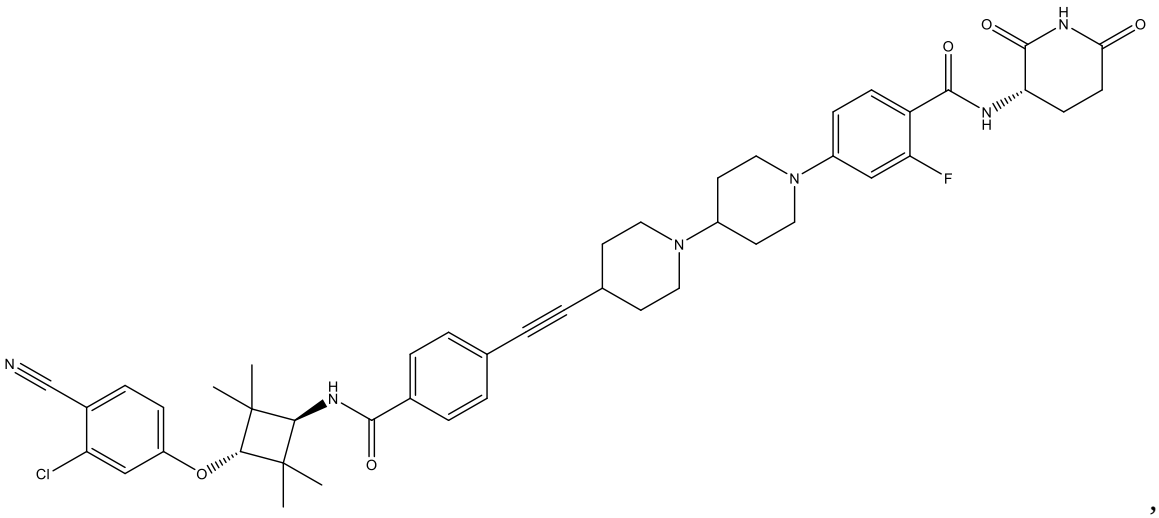
or a pharmaceutically acceptable salt thereof.

43. A bifunctional compound, wherein the compound is:

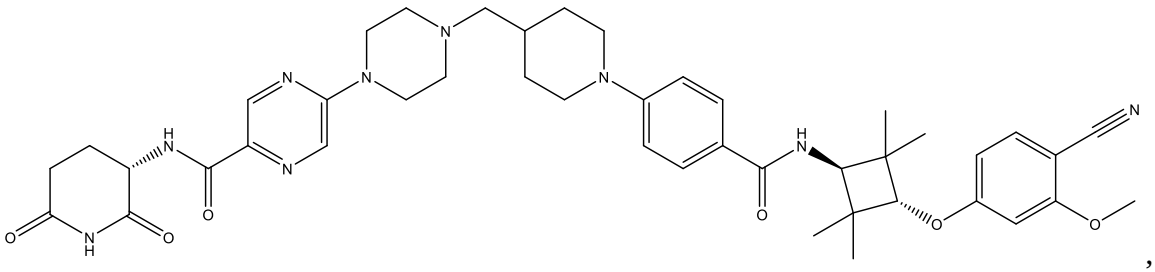

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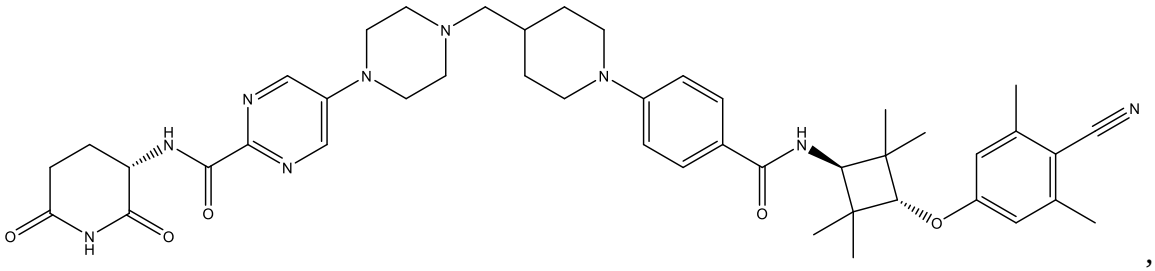

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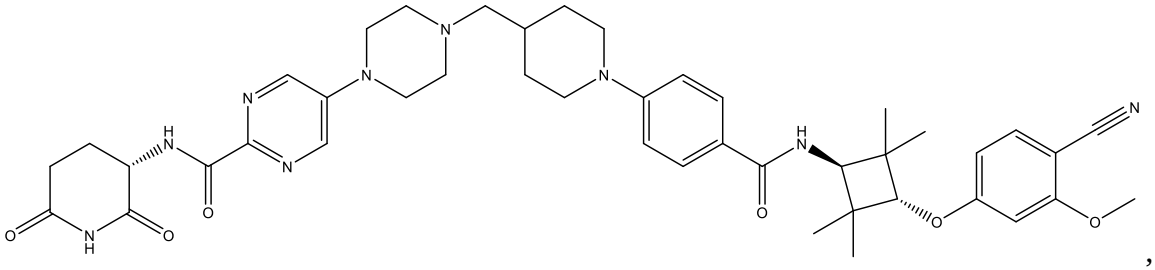
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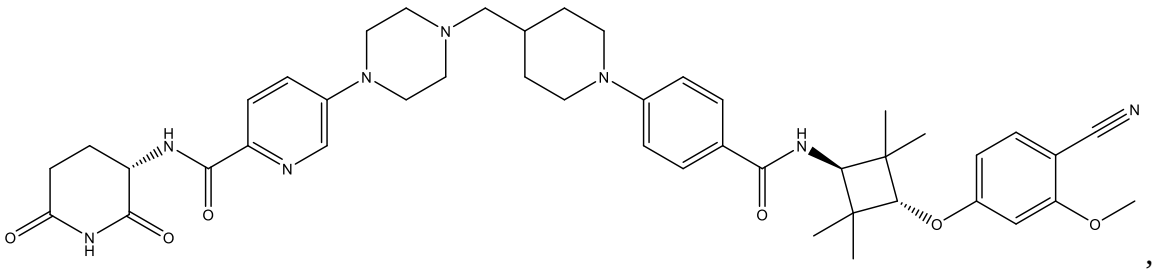
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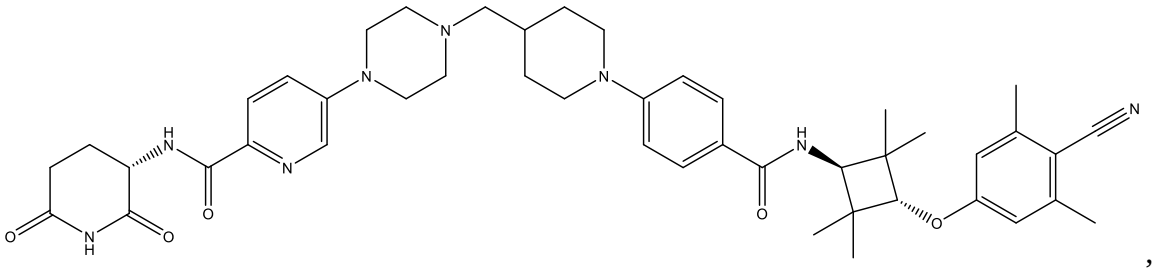


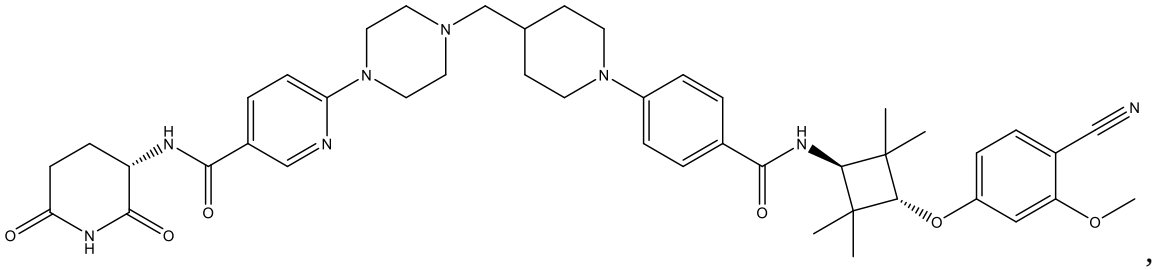
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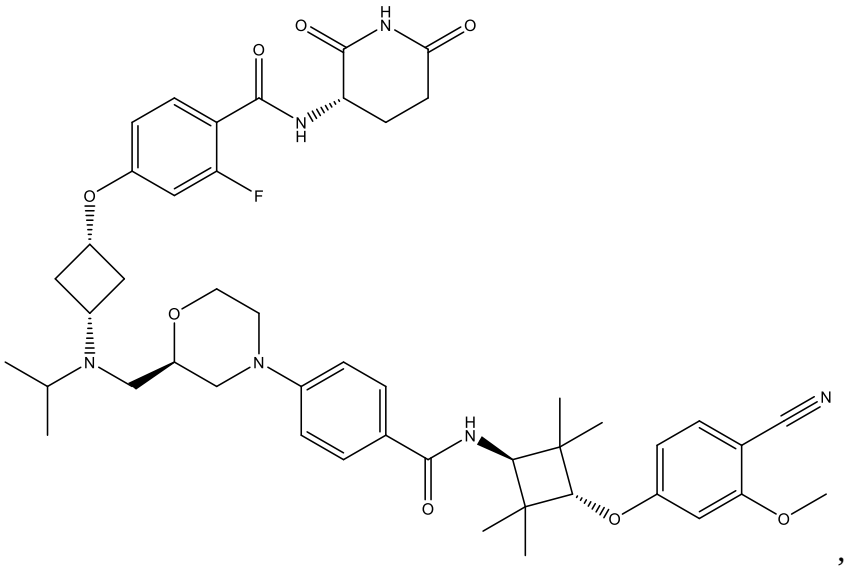


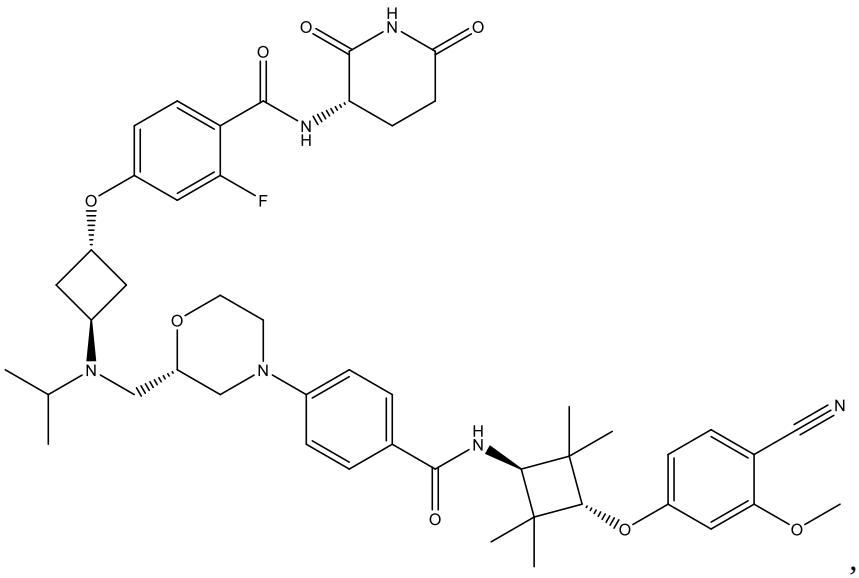
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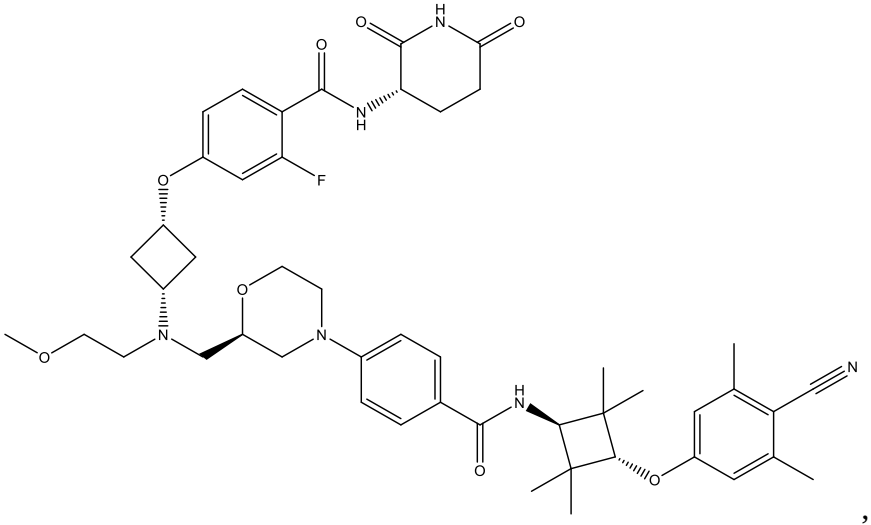

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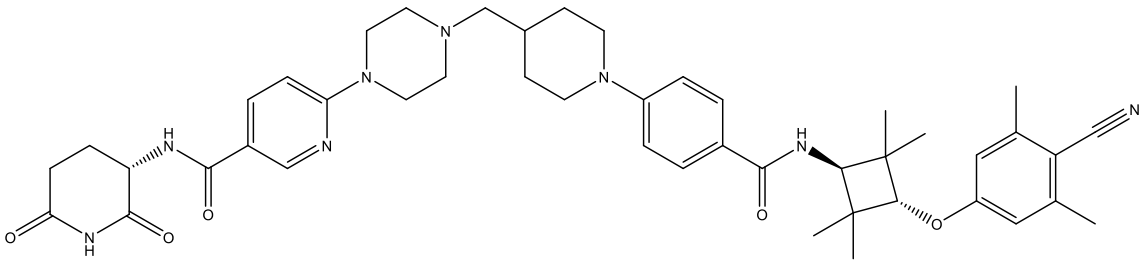

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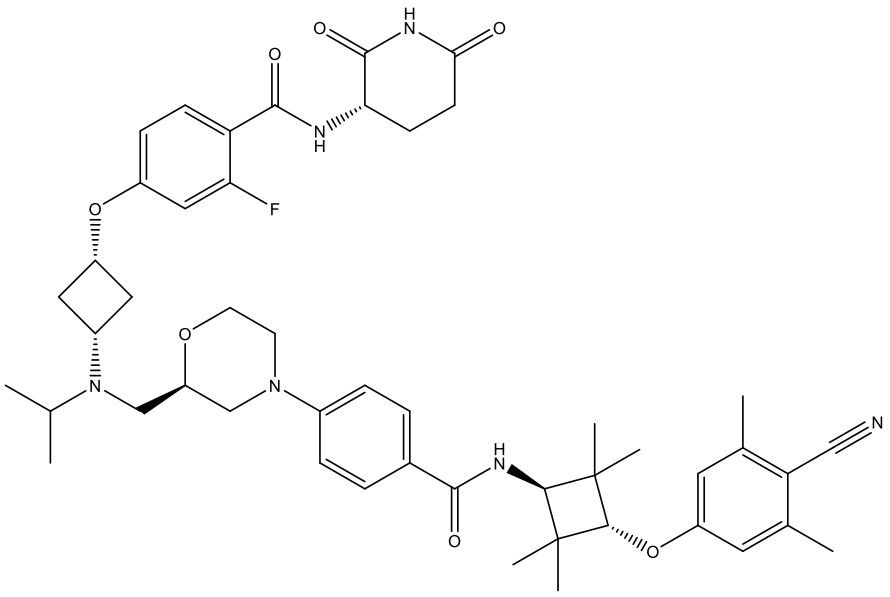
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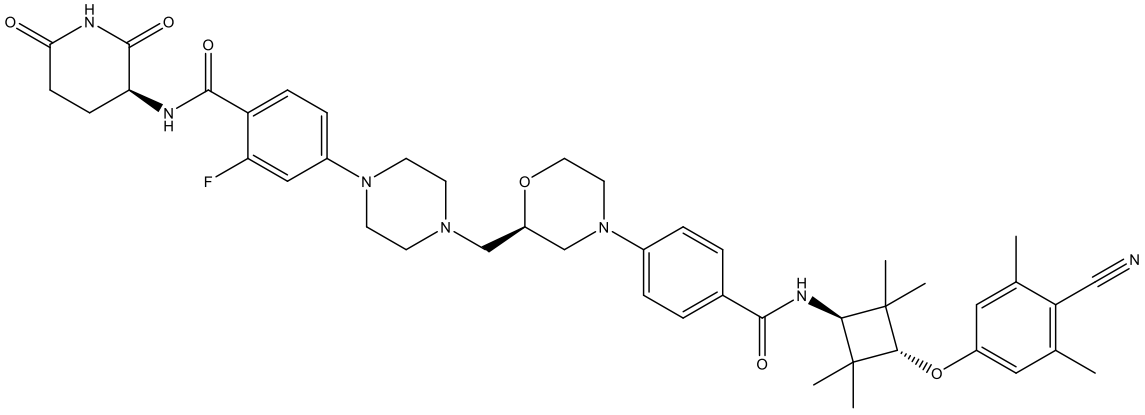
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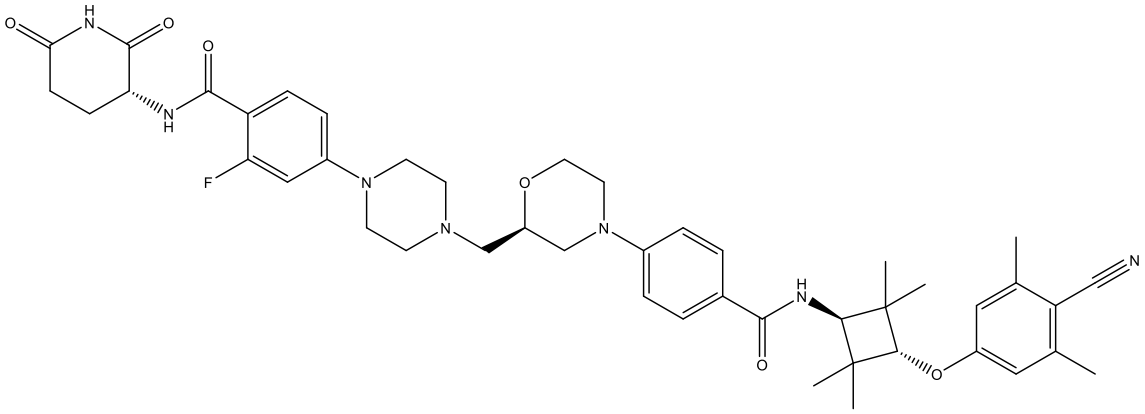
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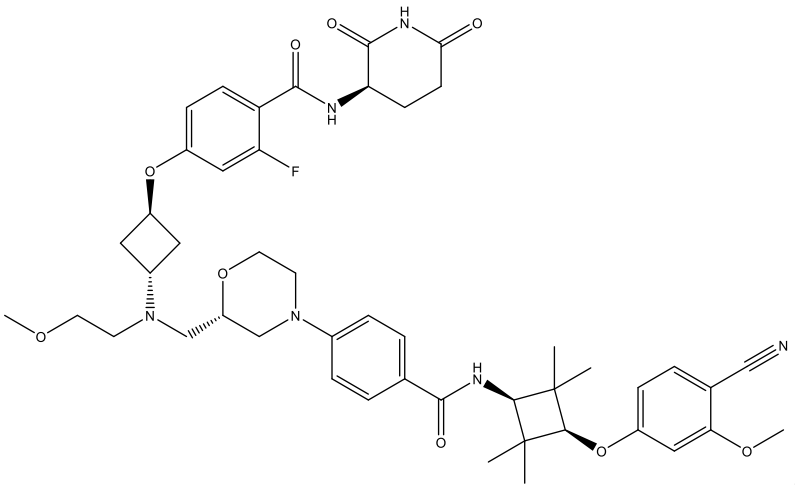
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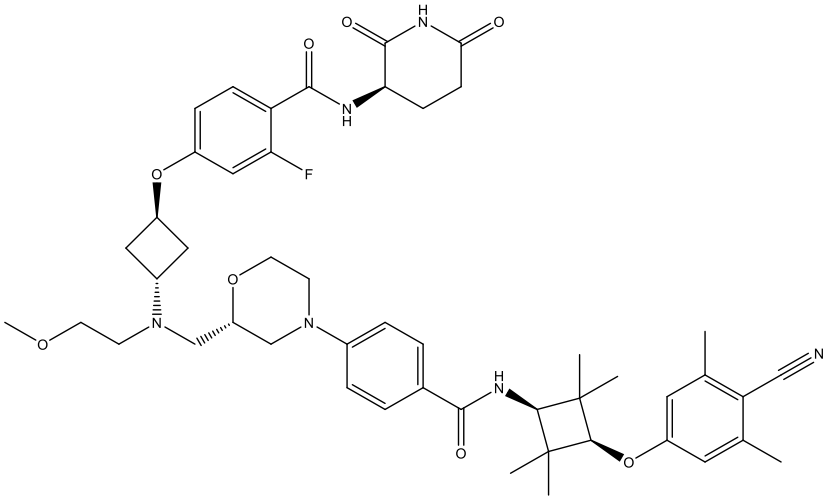
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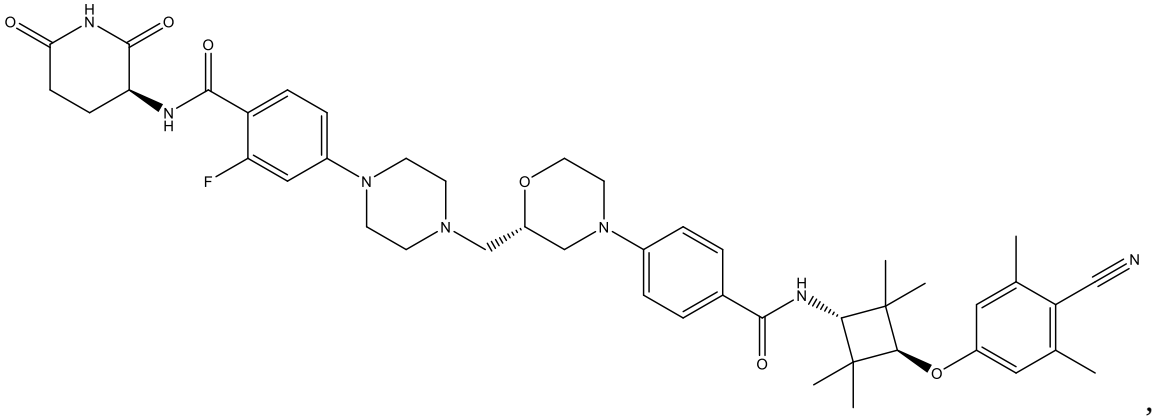
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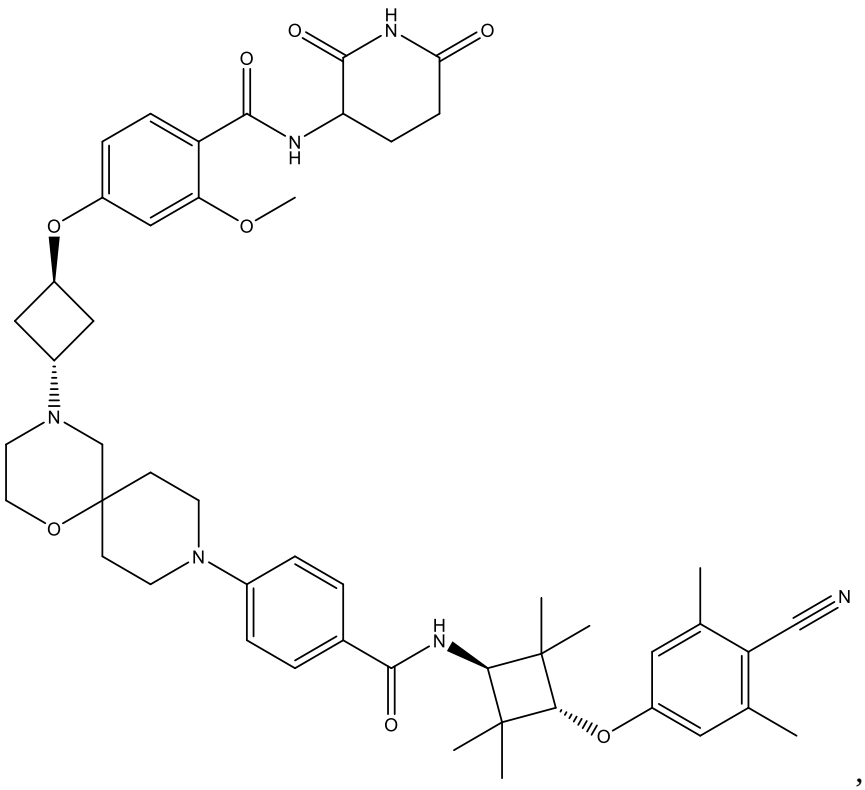
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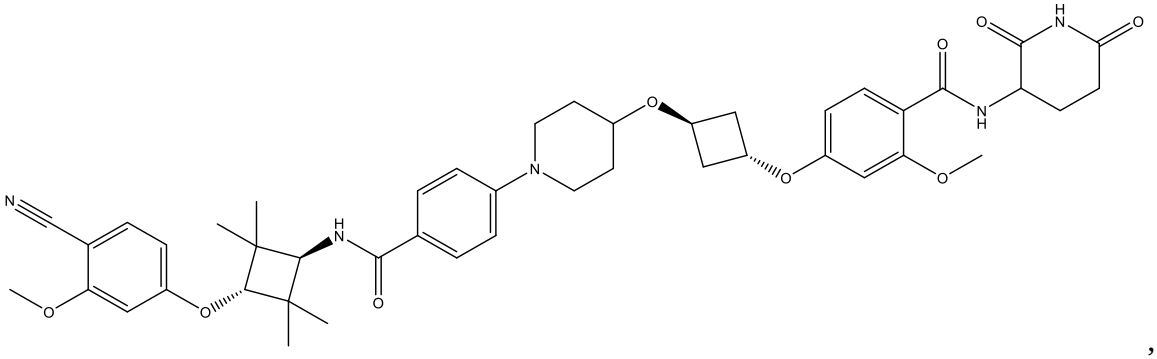
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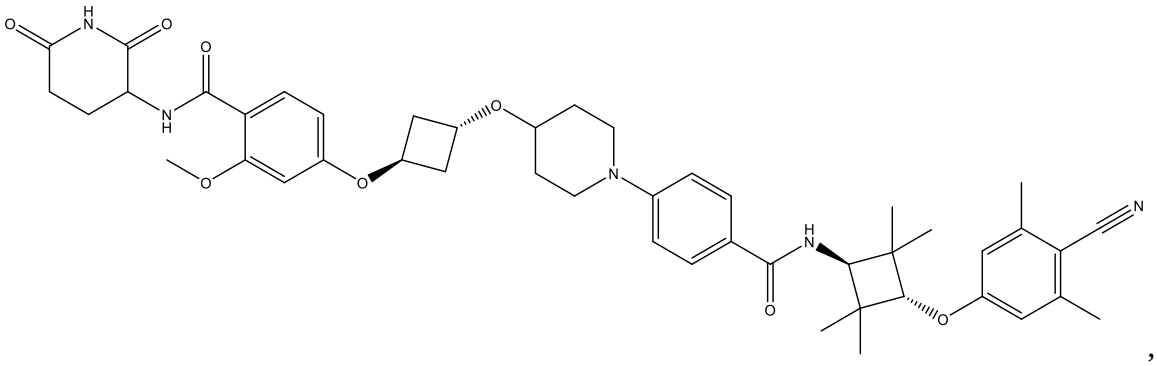
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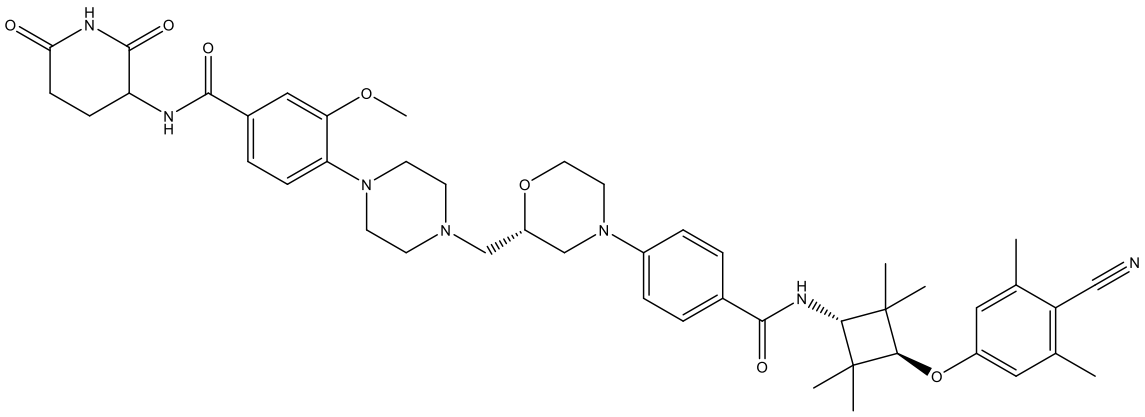
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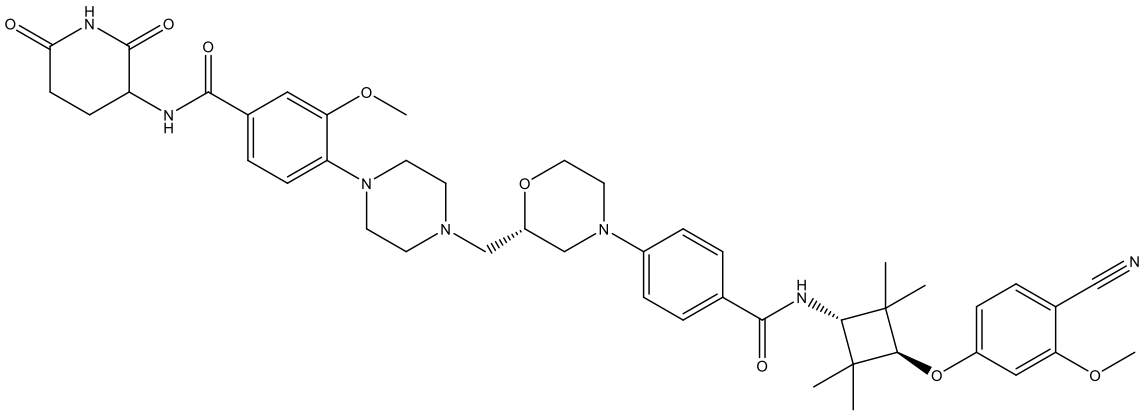


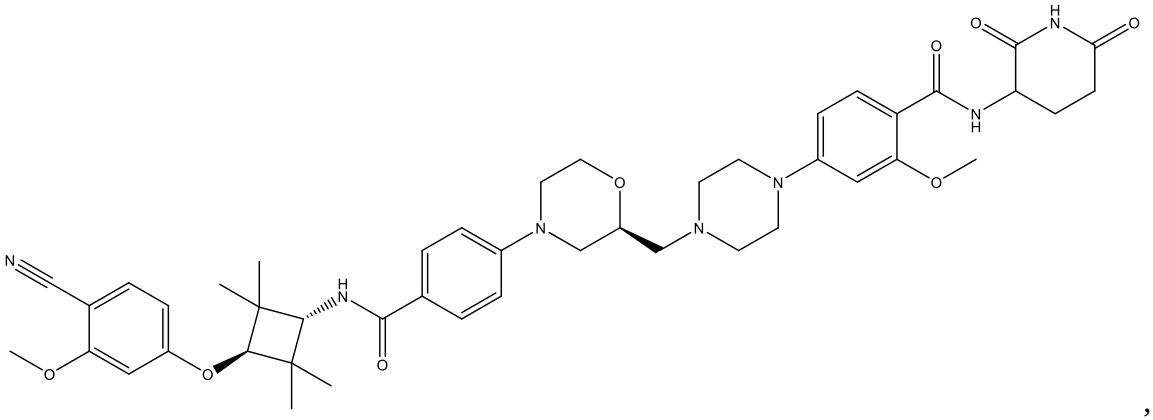
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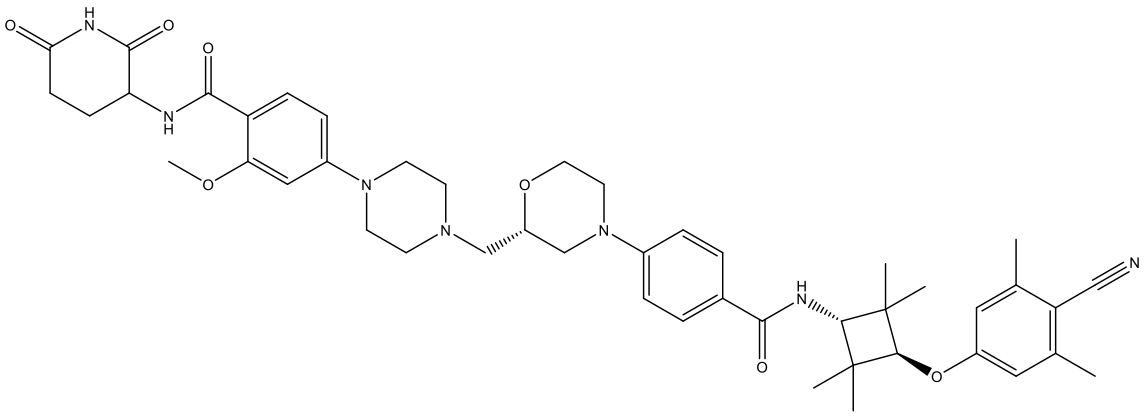


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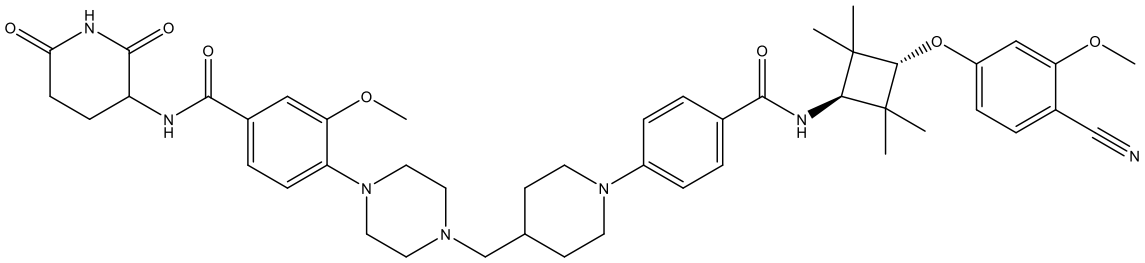

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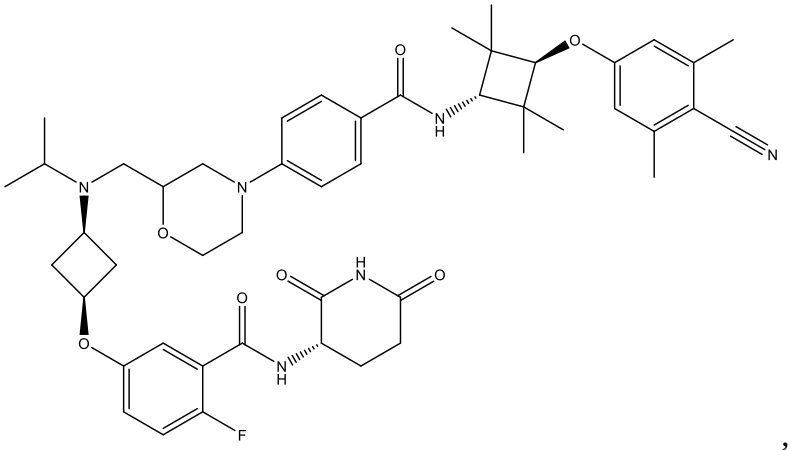

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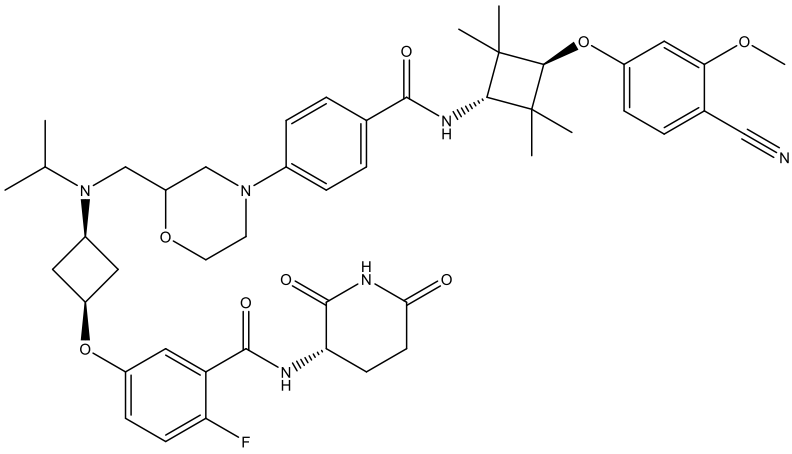
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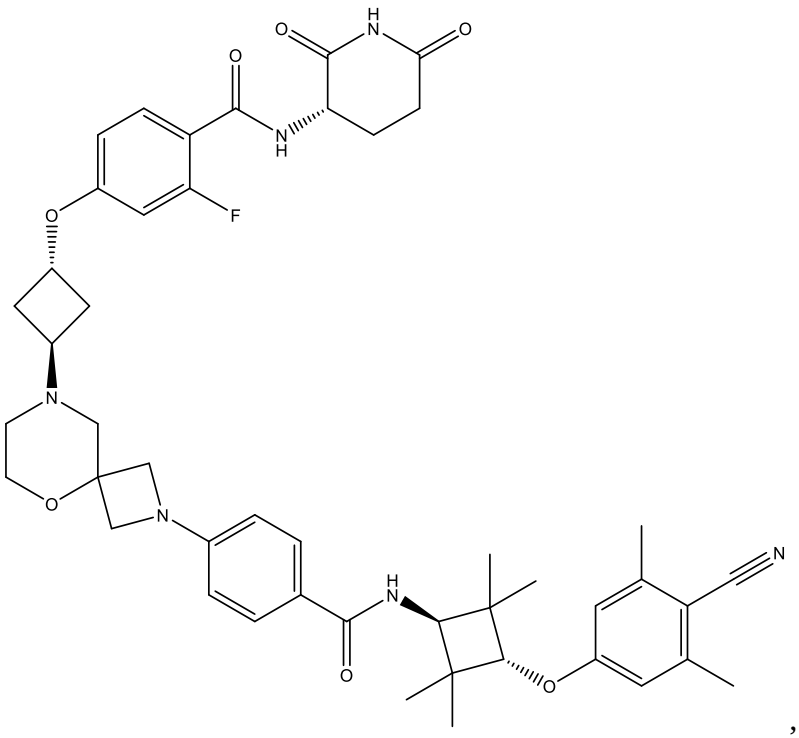
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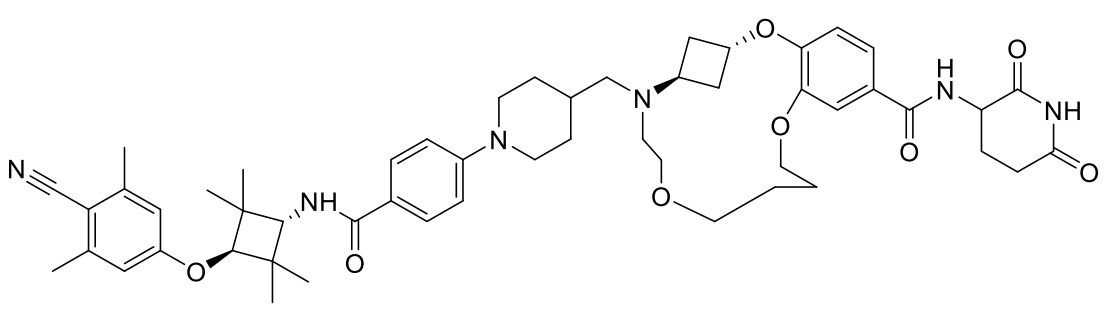
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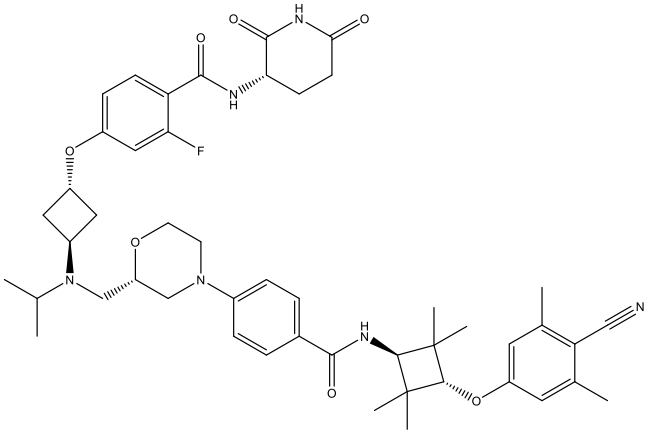
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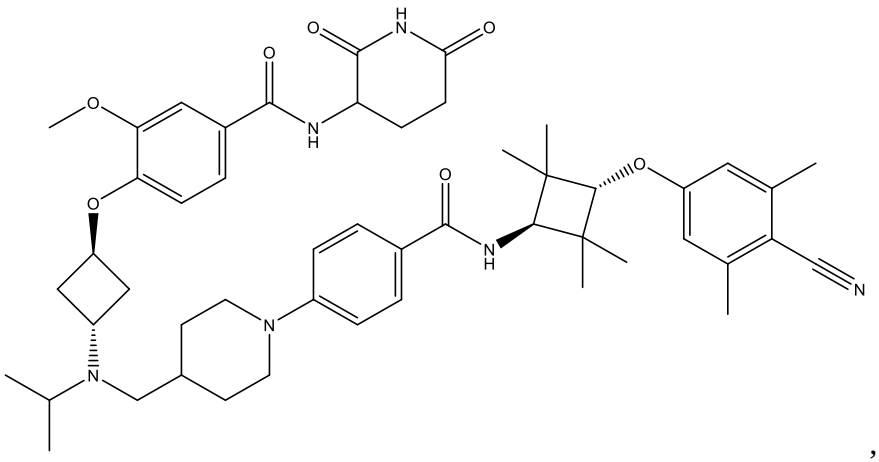
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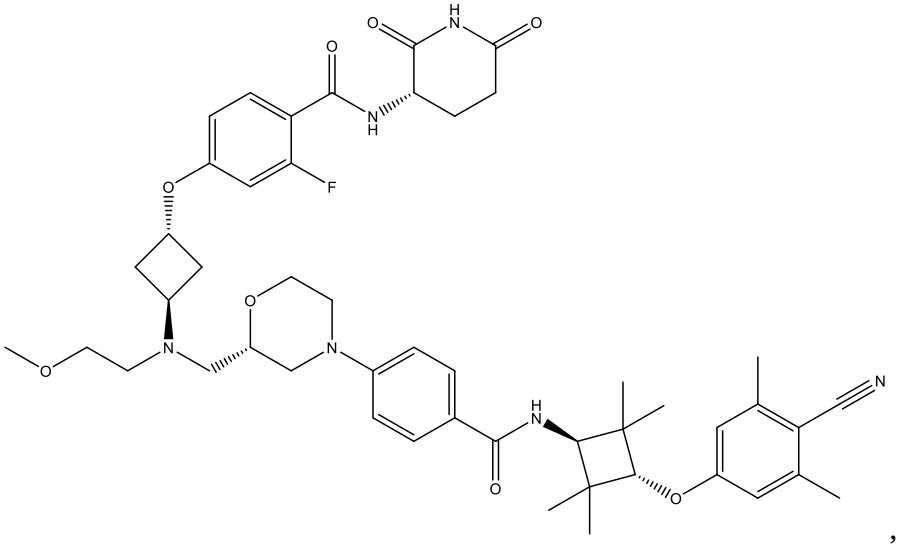
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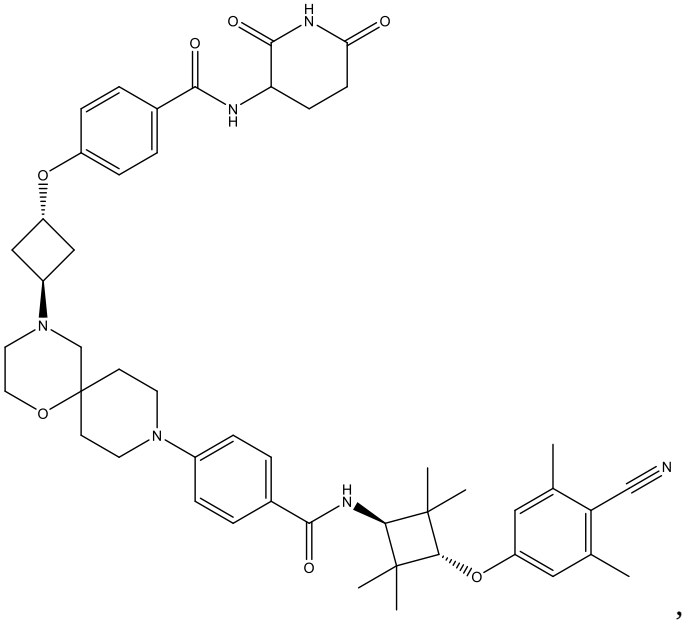
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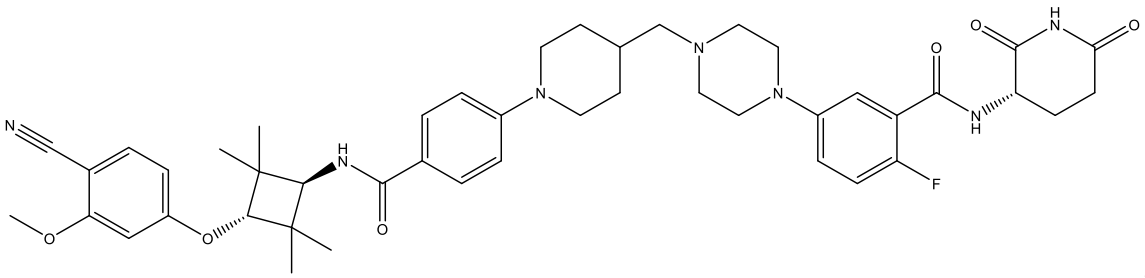
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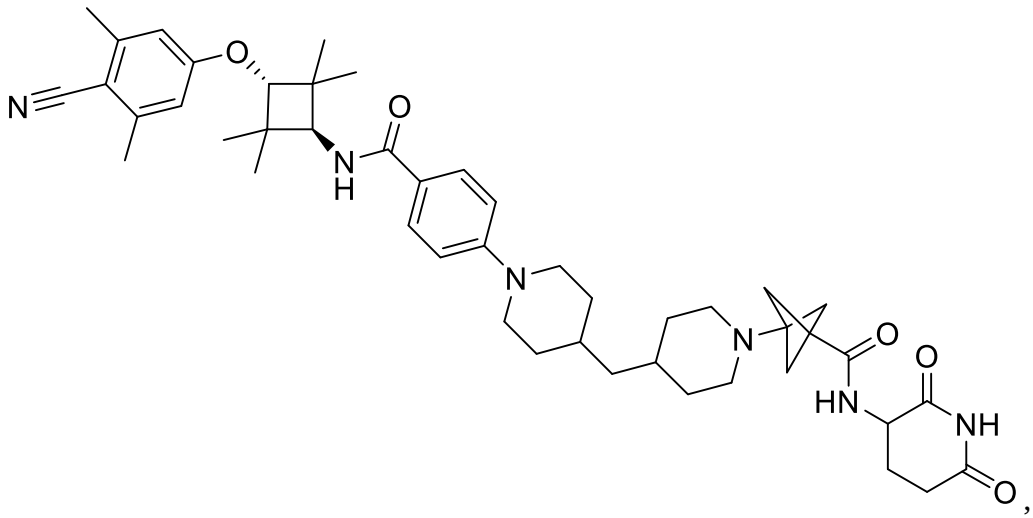
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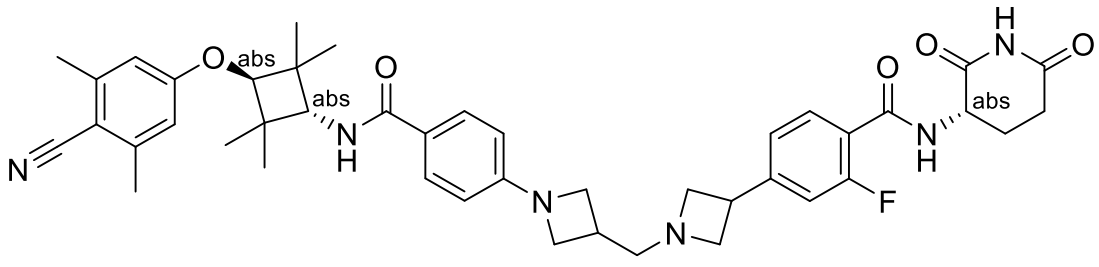
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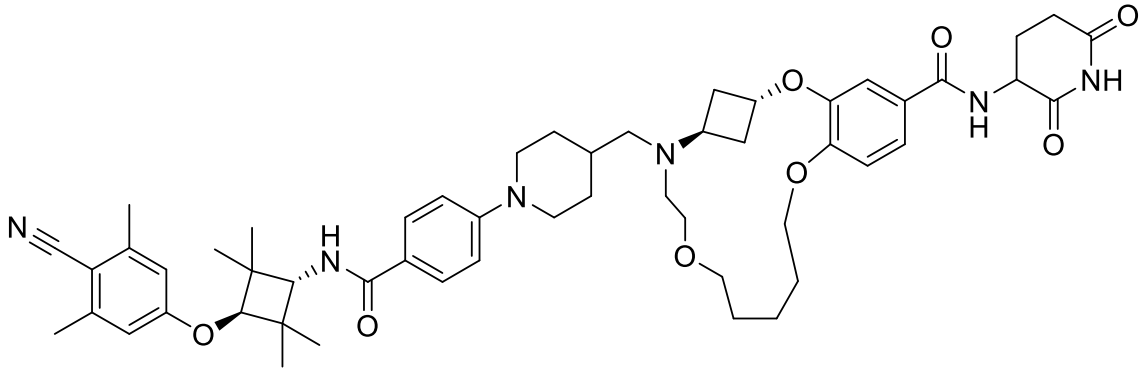
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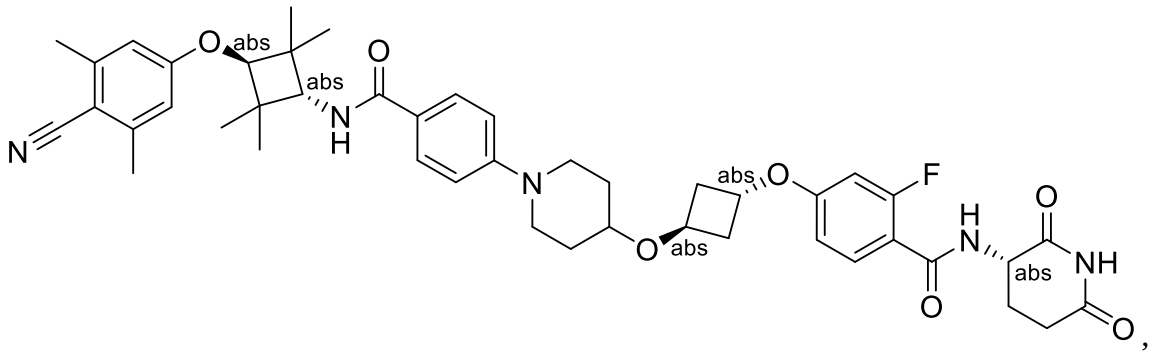
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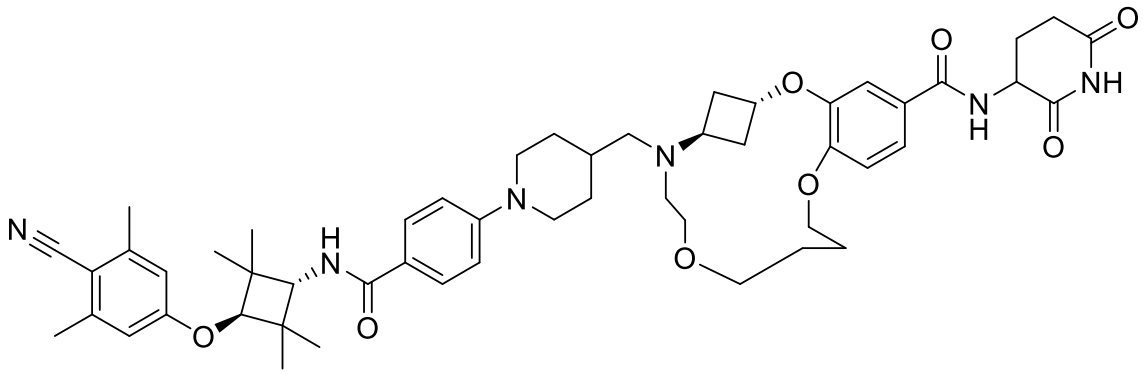
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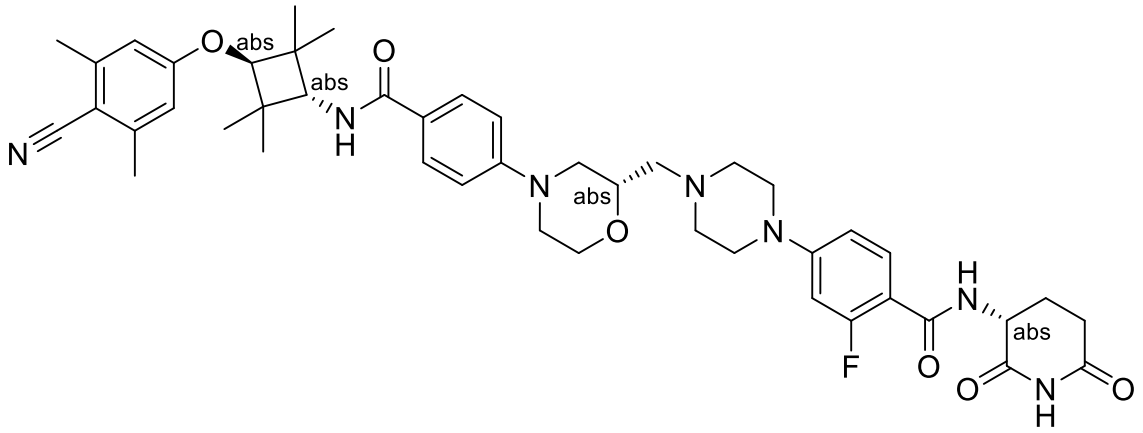
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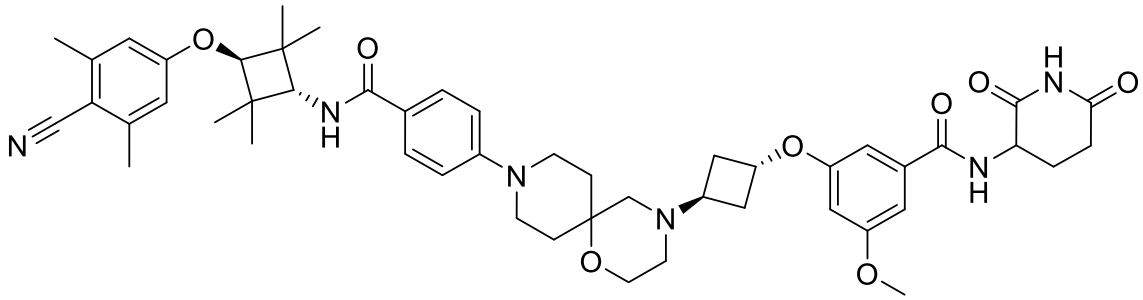
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44. A pharmaceutical composition comprising the bifunctional compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

45. The pharmaceutical composition of claim 44, wherein the composition is formulated as a tablet, and comprises one or more of the following: emulsifier; surfactant; binder; disintegrant; glidant; and lubricant.

46. The pharmaceutical composition of claim 44 or 45, wherein the composition further comprises an effective amount of at least one additional anti-cancer agent.

47. The pharmaceutical composition of claim 46, wherein the additional anti-cancer agent is estramustine, docetaxel, ketoconazole, goserelin, histrelin, triptorelin, buserelin, cyproterone, flutamide, bicalutamide, nilutamide, pamidronate, or zolendronate.

48. Use of a bifunctional compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 44-47, in the manufacture of a medicament for treating prostate cancer in a subject.

49. The use of claim 48, wherein a therapeutically effective amount of the bifunctional compound, or a pharmaceutically acceptable salt thereof, is to be administered orally to the subject.

50. The use of claim 48 or 49, wherein a therapeutically effective amount of the bifunctional compound, or a pharmaceutically acceptable salt thereof, is to be administered to the subject once a day, twice a day, three times a day, or four times a day.

51. The use of any one of claims 48-50, wherein a therapeutically effective amount of the bifunctional compound, or a pharmaceutically acceptable salt thereof, is to be administered to the subject once a day.

52. The use of any one of claims 48-51, wherein a therapeutically effective amount of the bifunctional compound, or a pharmaceutically acceptable salt thereof, is to be administered to the subject all at once or is to be administered in two, three, or four divided doses.

53. The use of any one of claims 48-52, wherein a therapeutically effective amount of the bifunctional compound is to be administered to the subject, wherein the therapeutically effective amount of the bifunctional compound, or a pharmaceutically acceptable salt thereof, is about 1 mg to about 1000 mg.

54. The use of any one of claims 48-53, wherein a therapeutically effective amount of the bifunctional compound is to be administered to the subject, wherein the therapeutically effective amount of the bifunctional compound, or a pharmaceutically acceptable salt thereof, is about 5 mg to about 750 mg.

55. The use of any one of claims 48-54, wherein a therapeutically effective amount of the bifunctional compound is to be administered to the subject, wherein the therapeutically effective amount of the bifunctional compound, or a pharmaceutically acceptable salt thereof, is about 10 mg to about 500 mg.

56. The use of any one of claims 48-55, wherein a therapeutically effective amount of the bifunctional compound is to be administered to the subject, wherein the therapeutically effective amount of the bifunctional compound, or a pharmaceutically acceptable salt thereof, is about 20 mg to about 250 mg.

57. The use of any one of claims 48-56, wherein the bifunctional compound, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition is to be administered to the subject, and the subject is in a fed state at the time of administration.

58. The use of any one of claims 48-56, wherein the bifunctional compound, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition is to be administered to the subject, and the subject is in a fasted state at the time of administration.

59. The use of any one of claims 48-58, wherein the bifunctional compound, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition is to be administered to the subject, and an effective amount of at least one additional anti-cancer agent is to be further administered to the subject in need thereof.

60. The use of claim 59, wherein the additional anti-cancer agent is abiraterone, estramustine, docetaxel, ketoconazole, goserelin, histrelin, triptorelin, buserelin, cyproterone, flutamide, bicalutamide, nilutamide, pamidronate, or zolendronate.

61. The use of any one of claims 48-60, where the subject with prostate cancer comprises at least one somatic AR tumor mutation.

62. The use of claim 61, wherein the at least one somatic AR tumor mutation is selected from the group consisting of L702H, M895V, M896V, T878A, F877L, and H875Y.

63. The use of any one of claims 48-62, wherein the prostate cancer is castrate-resistant prostate cancer.

64. The use of any one of claims 48-63, wherein the prostate cancer is metastatic castrate-resistant prostate cancer.

65. Use of a bifunctional compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 44-47, in the manufacture of a medicament for treating prostate cancer in a subpopulation of prostate cancer subjects,

wherein a prostate cancer subject is selected for treatment based on the subject's somatic AR tumor biomarker status.

66. The use of claim 65, where the subject's somatic AR tumor biomarker status comprises at least one somatic AR tumor mutation.

67. The use of claim 65, wherein the AR biomarker status of the subject is determined by ctDNA analysis, fluorescent in situ hybridization, immunohistochemistry, PCR analysis, or sequencing.

68. The use of claim 65, wherein the AR biomarker status of the subject is determined in a blood sample derived from the subject.

69. The use of claim 65, wherein the AR biomarker status of the subject is determined in a solid biopsy derived from the tumor of the subject.

70. The use of any one of claims 65-69, wherein the prostate cancer is castrate-resistant prostate cancer.

71. The use of any one of claims 65-70, wherein the prostate cancer is metastatic castrate-resistant prostate cancer.

72. The use of claim 66, wherein the at least one somatic AR tumor mutation is selected from the group consisting of L702H, M895V, M896V, T878A, F877L, and H875Y.

73. A bifunctional compound of any one of claims 1-43, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 44-47, for use in therapy.