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.

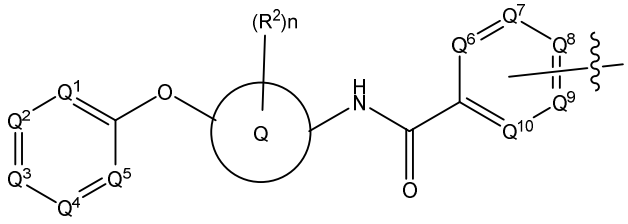
[0010a] In an aspect of the present disclosure, there is provided a bifunctional compound having the structure:

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;

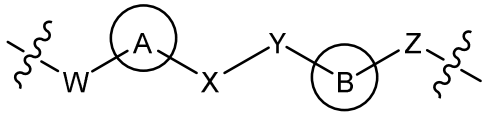
Each R^1 is independently selected from the group consisting of H, optionally substituted linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo;

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 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; and

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

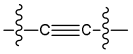
(b) L is a chemical linking moiety having the structure:



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

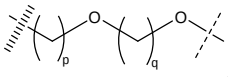
X is $-CH_2-$ or absent;

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



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

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

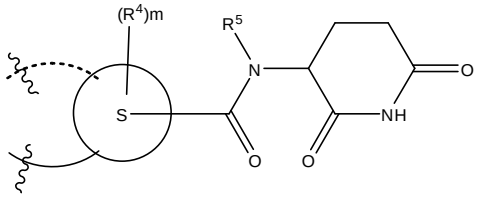
R^6 is H, linear or branched C_{1-6} alkyl, linear or branched C_{1-6} alkoxy-C_{1-6} alkyl, or , wherein  indicates a bond to Y, and  indicates a bond to ;

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; and

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



Wherein:

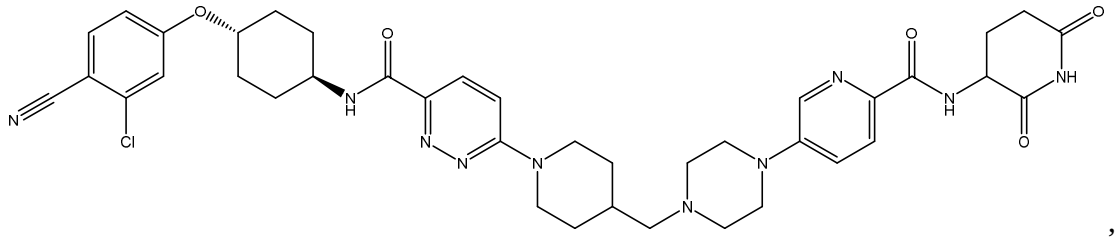
 is phenyl, pyridazinyl, pyrimidinyl, or pyrazinyl;

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

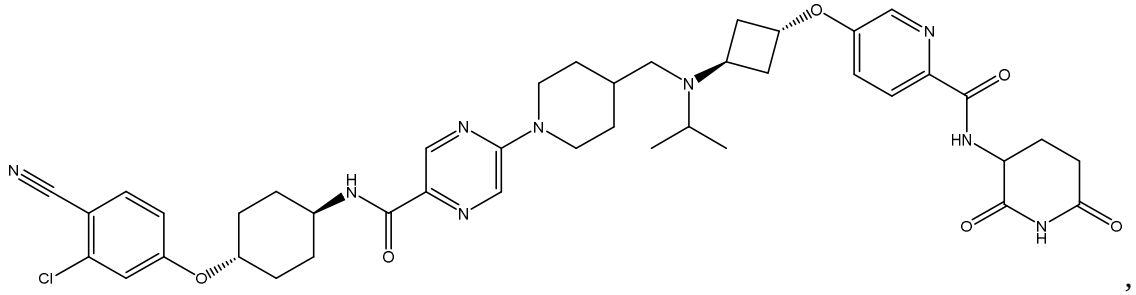
Each R^4 is independently selected from the group consisting of optionally substituted linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo;

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

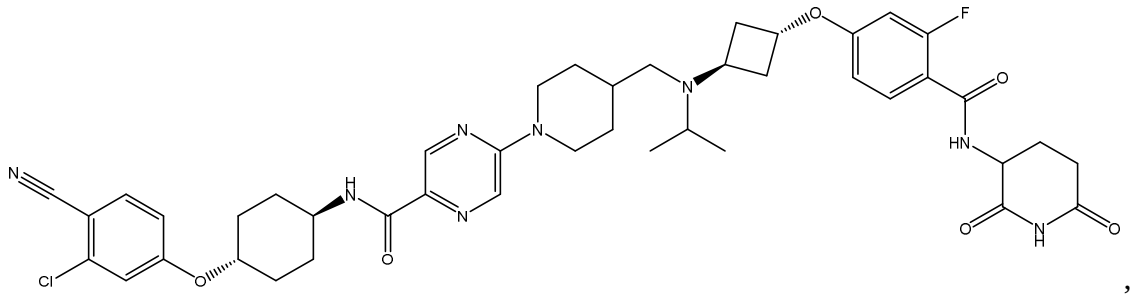
m is 0, 1, 2, 3, or 4;



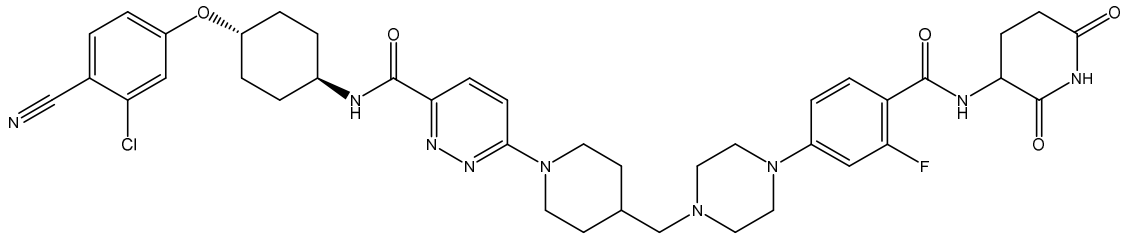
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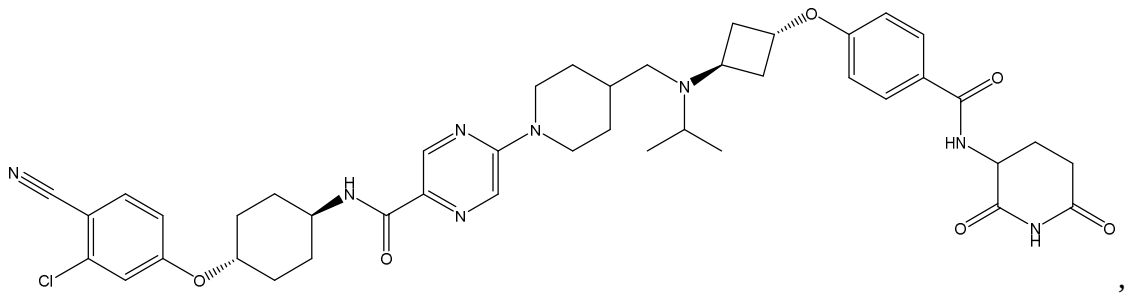
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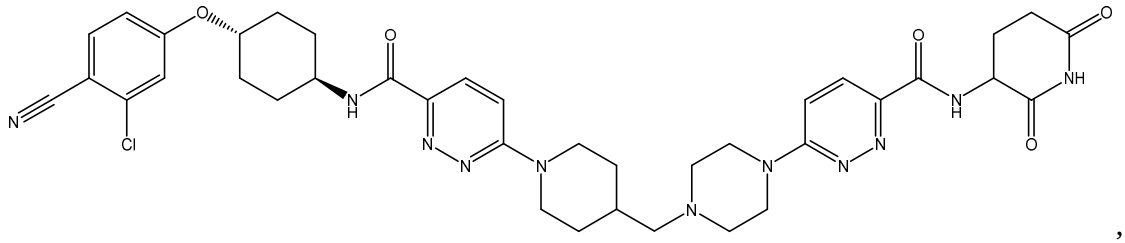
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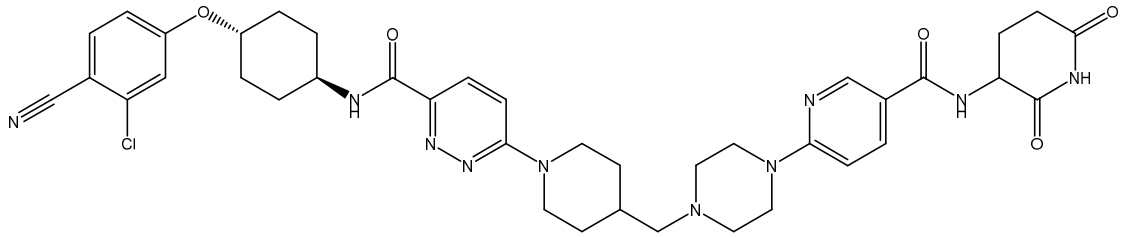
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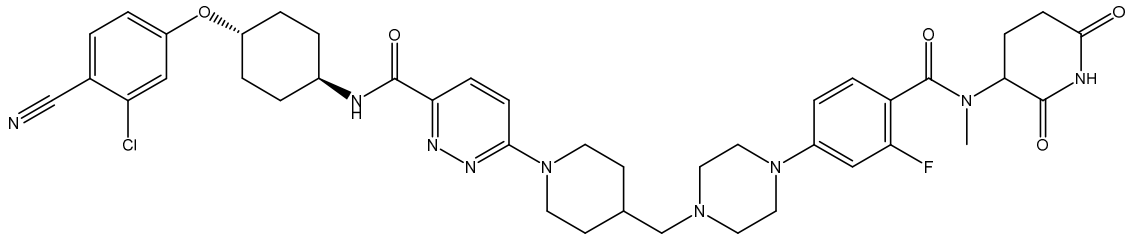
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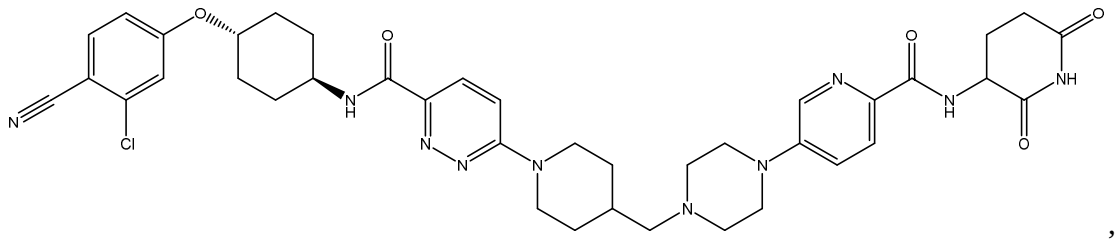
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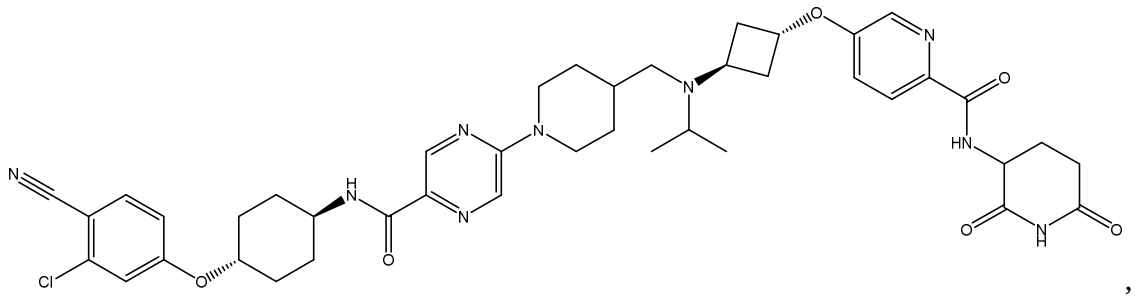
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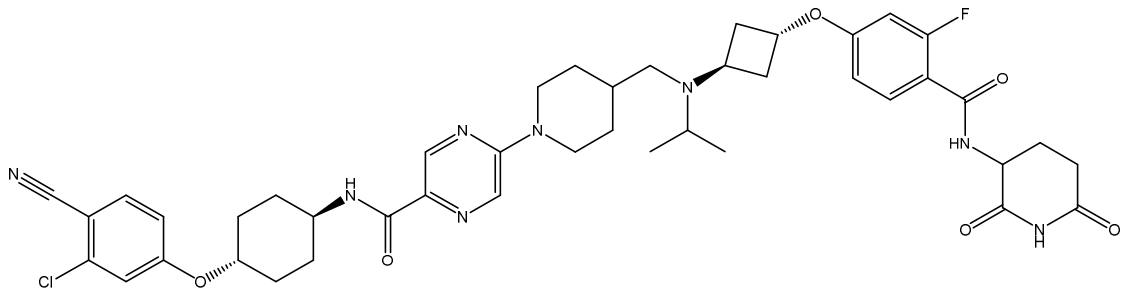
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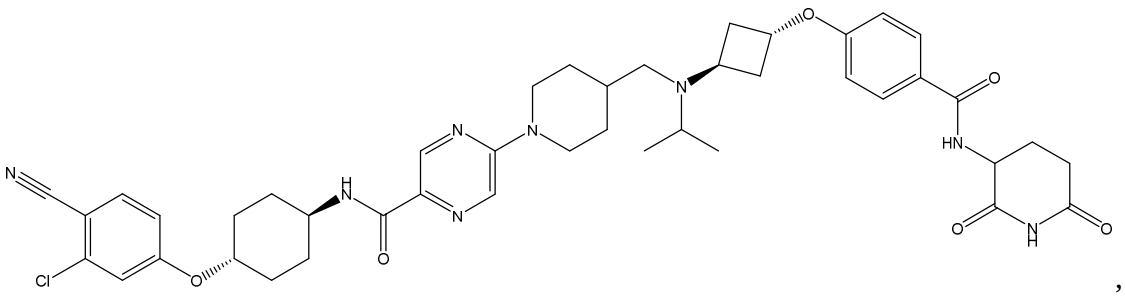
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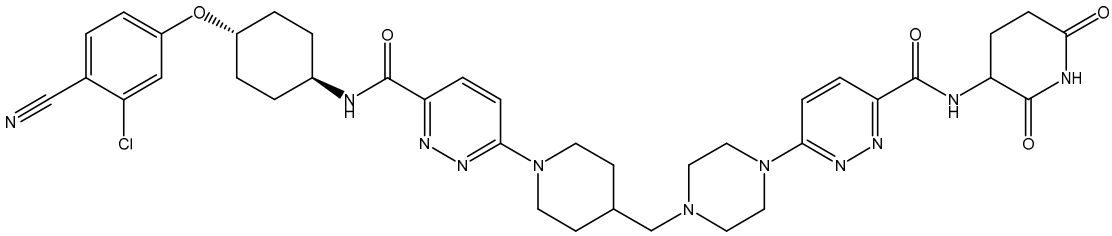
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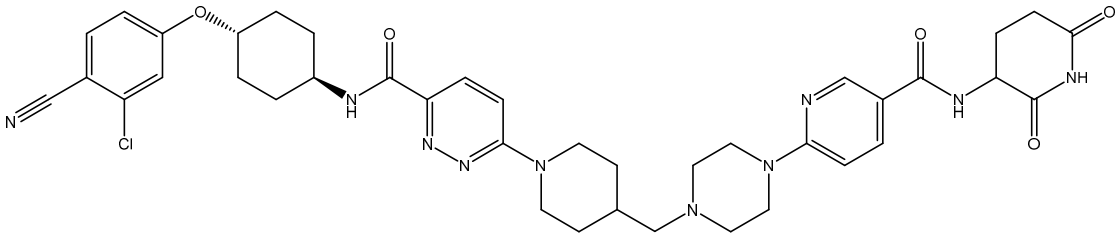
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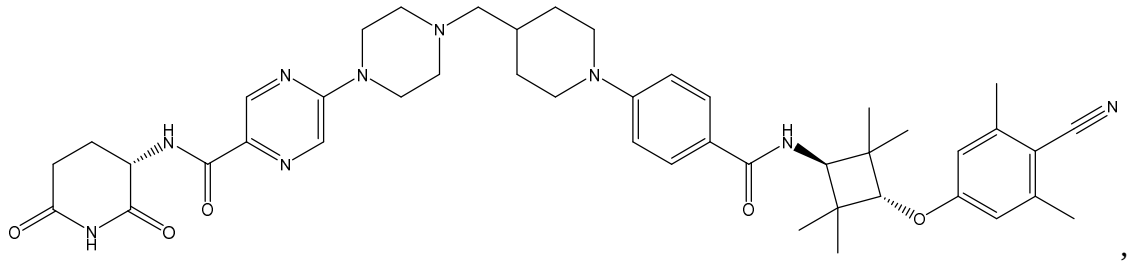
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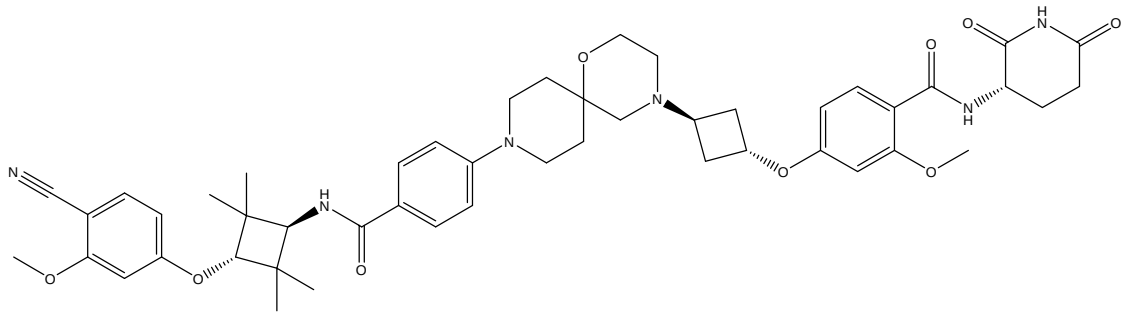
, or

a pharmaceutically acceptable salt thereof.

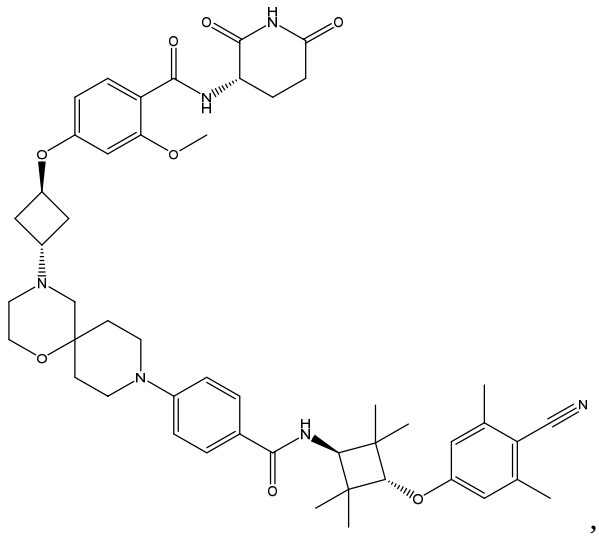
[0010d] In another aspect of the present disclosure, there is provided a bifunctional compound, wherein the compound is:



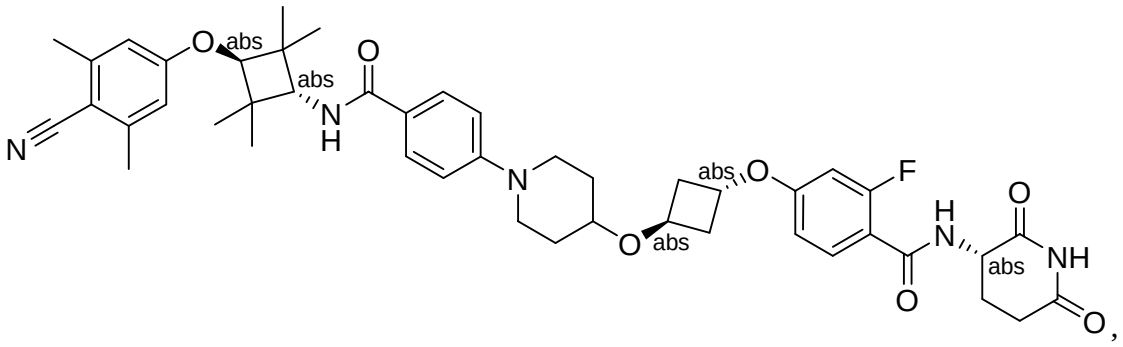
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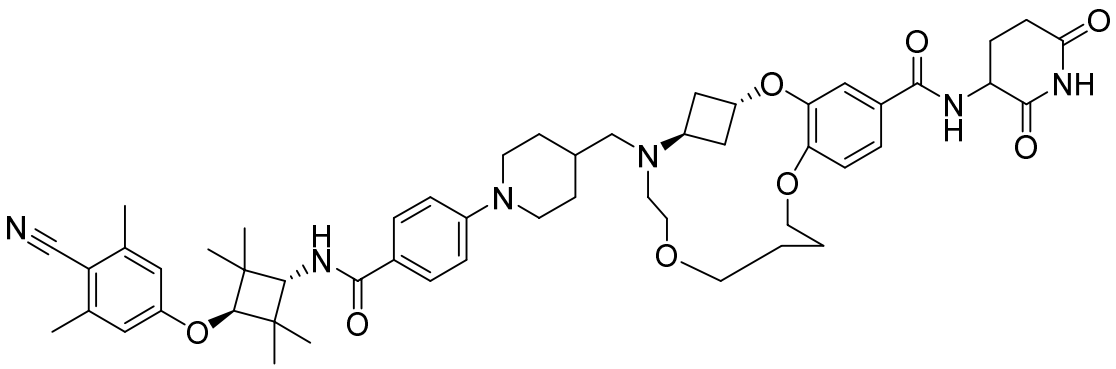
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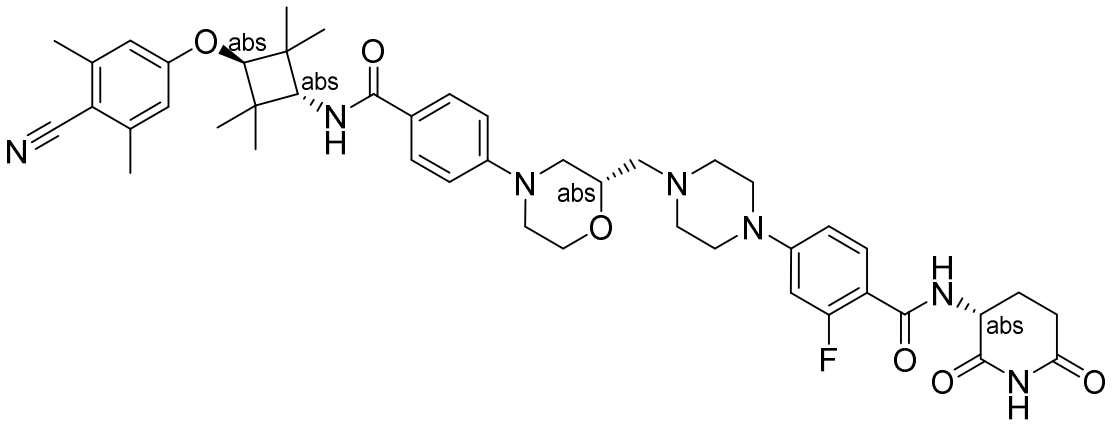
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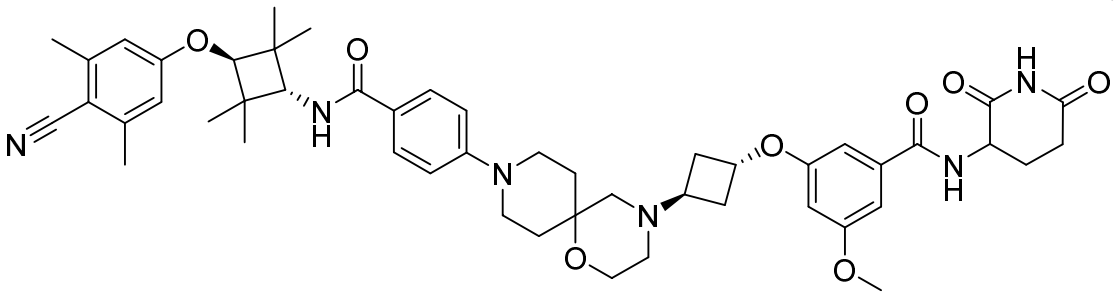
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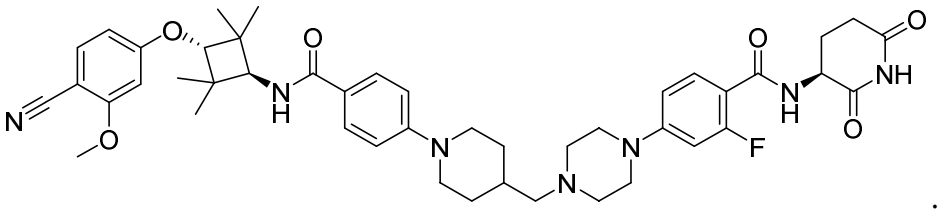
, or



, or

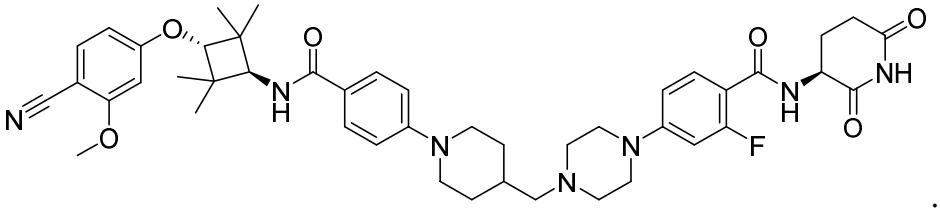
a pharmaceutically acceptable salt thereof.

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



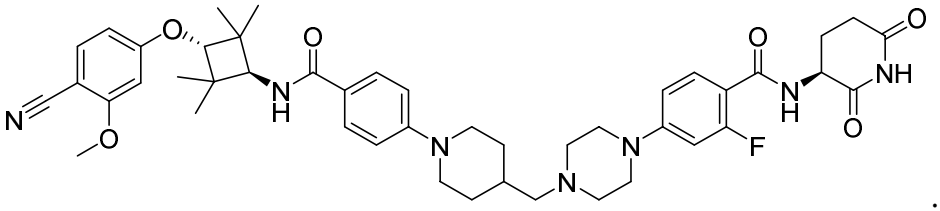
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[0010g] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable salt of a bifunctional compound, wherein the compound is:



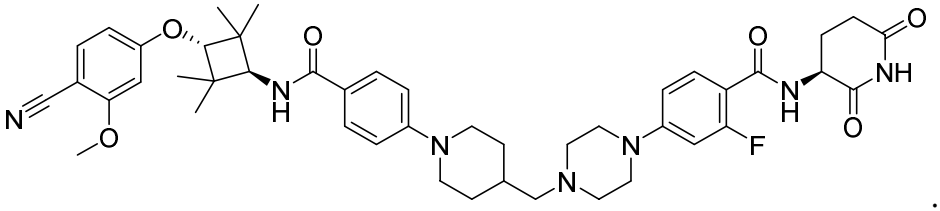
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[0010h] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a bifunctional compound and one or more pharmaceutically acceptable excipients, wherein the compound is:



.

[0010i] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable salt of a bifunctional compound and one or more pharmaceutically acceptable excipients, wherein the compound is:



.

[0010j] 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.

[0010k] 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.

[0010l] 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.

[0010m] 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.

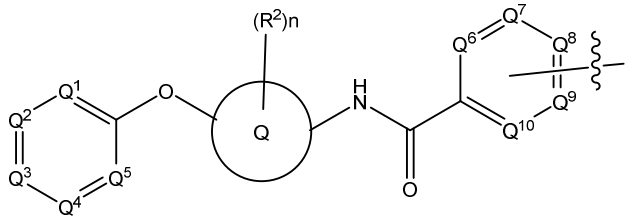
[0011] In one example, the present application provides bifunctional compound having the structure:

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;

CLAIMS

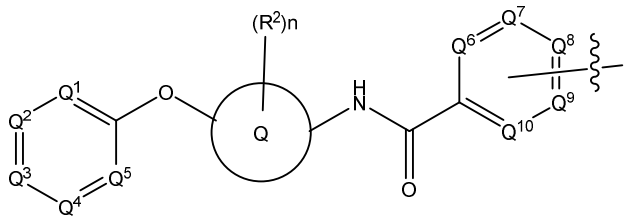
1. A bifunctional compound having the structure:

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;

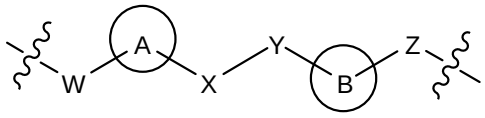
Each R^1 is independently selected from the group consisting of H, optionally substituted linear or branched C_1-C_6 alkyl, cyano, halogen, and optionally substituted linear or branched C_1-C_6 alkoxy, wherein the alkyl or alkoxy group is optionally substituted with one or more halo;

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 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; and

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

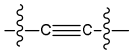
(b) L is a chemical linking moiety having the structure:



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

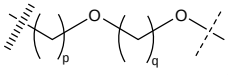
X is $-CH_2-$ or absent;

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



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

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 

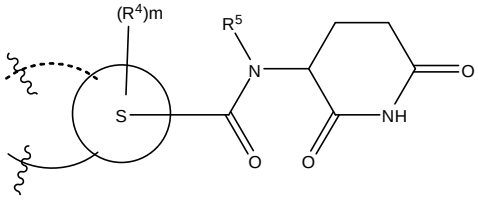
;

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; and

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



Wherein:



is phenyl, pyridazinyl, pyrimidinyl, or pyrazinyl;


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;

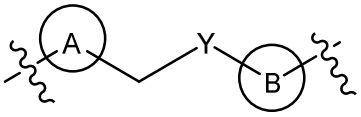
provided that when 

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 L is



wherein:



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

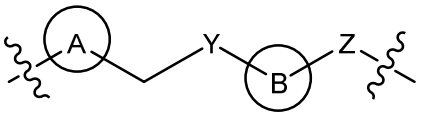
Y is -NR^6-, -O-, or absent;

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



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

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

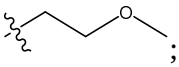


Wherein:



is piperidinyl or morpholinyl;

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

R^6 is  or 

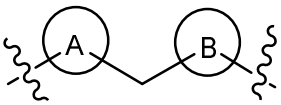
;



is cyclobutyl; and

Z is -O-.

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



Wherein:



is piperidinyl or morpholinyl; and

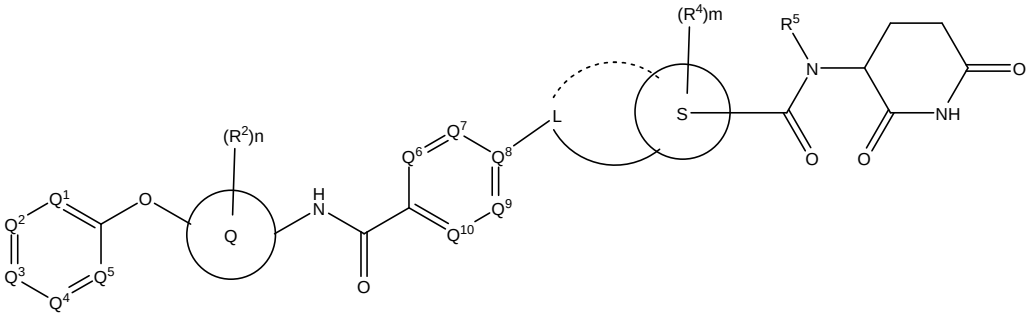


is piperazinyl.

5. The bifunctional compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein 

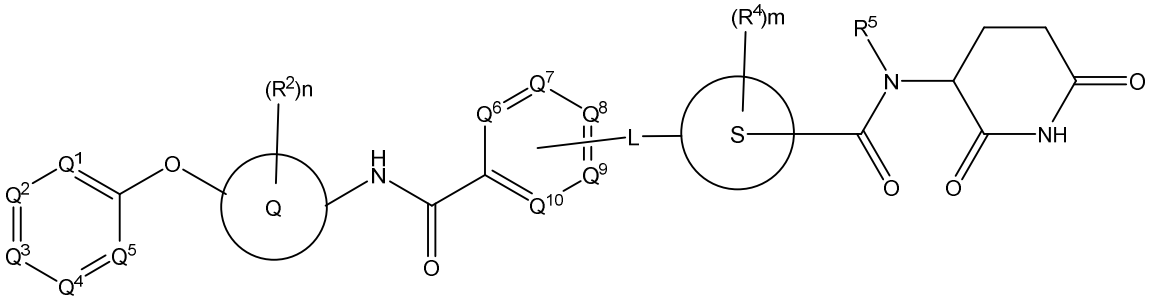
is piperidinyl.

6. The bifunctional compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula (Ib):



(Ib).

7. The bifunctional compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula (Ic):



(Ic).

8. The bifunctional compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein Q^1-Q^5 are each CR^1.

9. The bifunctional compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein exactly 1 of Q^1-Q^5 is N.

10. The bifunctional compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein exactly 2 of Q^1-Q^5 are N.

11. The bifunctional compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein exactly 3 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 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.

13. The bifunctional compound of any one of claims 1-8, 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.

14. The bifunctional compound of any one of claims 1-8, 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.

15. The bifunctional compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein 

is 4-6 membered cycloalkyl.

16. The bifunctional compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein 

is cyclobutyl or cyclohexyl.

17. The bifunctional compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein 

is cyclobutyl.

18. The bifunctional compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein n is 4.

19. The bifunctional compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R^2 is linear or branched C_1-C_6 alkyl.

20. The bifunctional compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein each R^2 is methyl.

21. The bifunctional compound of any one of claims 1-16 and 18-20, or a pharmaceutically acceptable salt thereof, wherein 

is cyclohexyl.

22. The bifunctional compound of any one of claims 1-17 and 21, or a pharmaceutically acceptable salt thereof, wherein n is 0.

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

is phenyl.

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

is pyridazinyl.

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

is pyrimidinyl.

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

is pyrazinyl.

27. The bifunctional compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein each R^4 is independently selected from the group consisting of F, methoxy, ethoxy, methyl, and ethyl.

28. The bifunctional compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein each R^4 is independently selected from the group consisting of F, methoxy, and methyl.

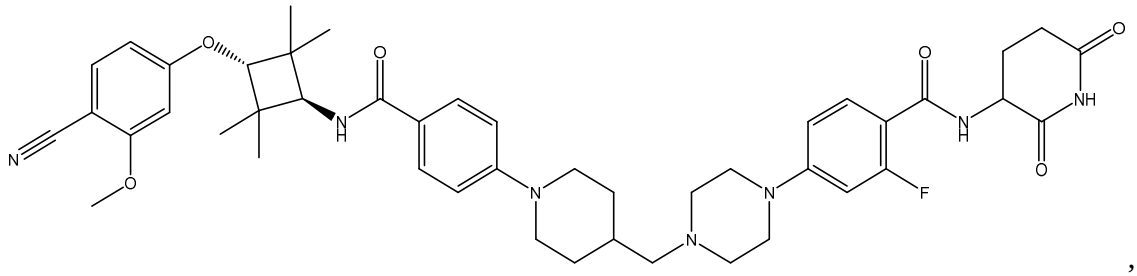
29. The bifunctional compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, or 2.

30. The bifunctional compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, wherein m is 0.

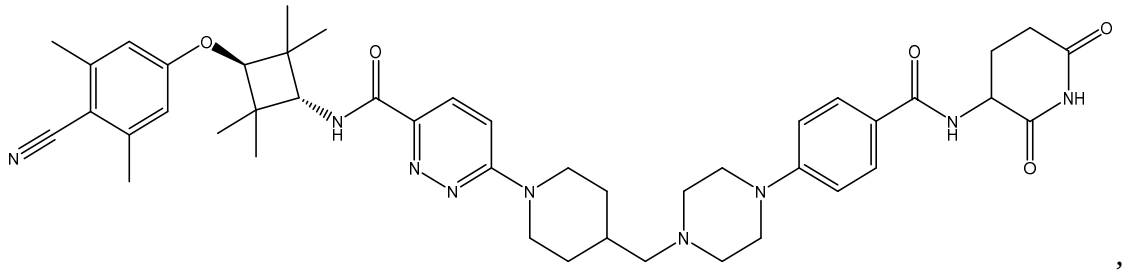
31. The bifunctional compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, wherein m is 1.

32. The bifunctional compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, wherein m is 2.

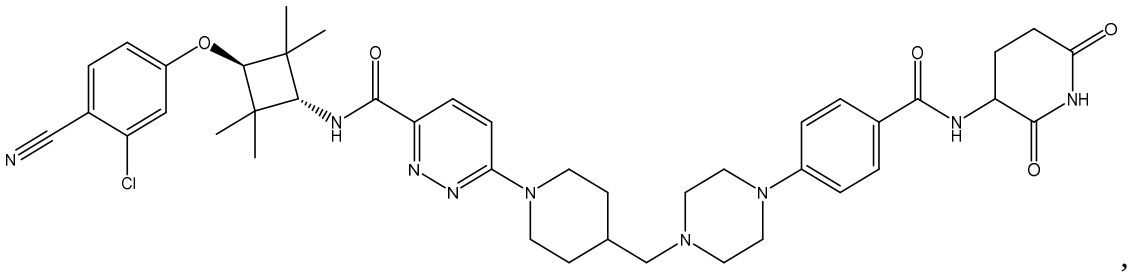
33. A bifunctional compound, wherein the compound is:



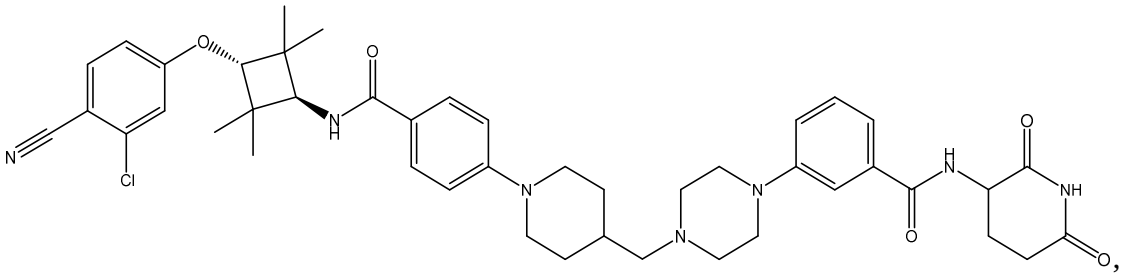
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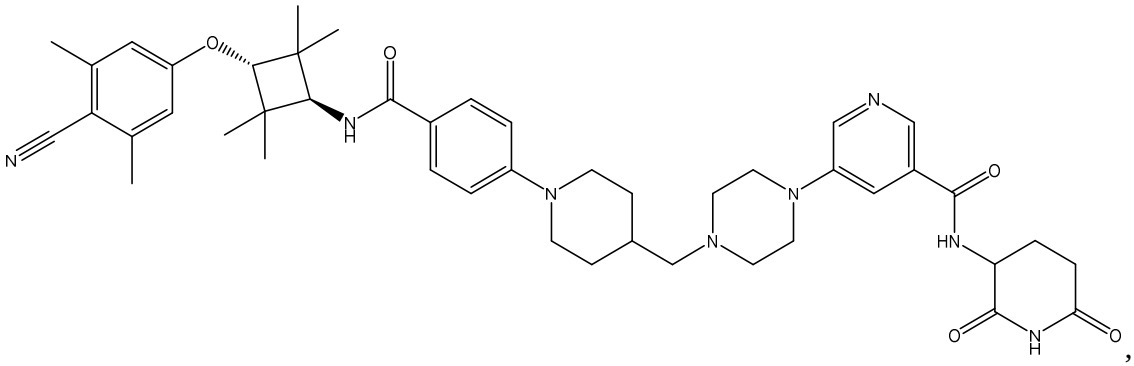
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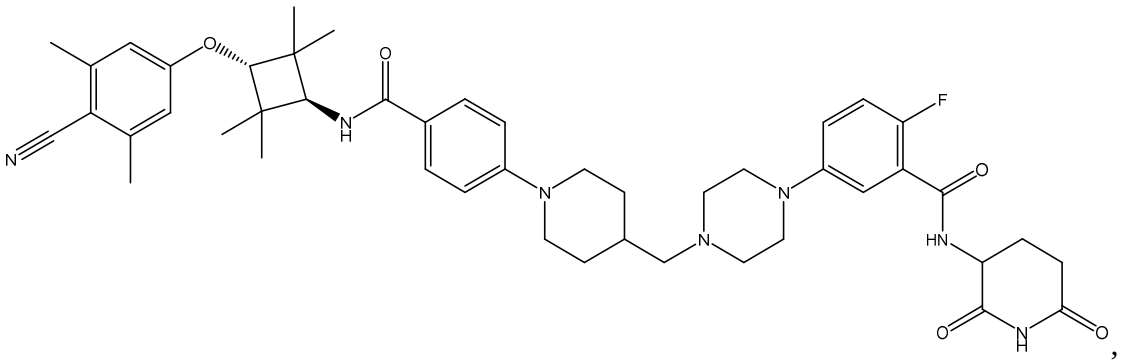
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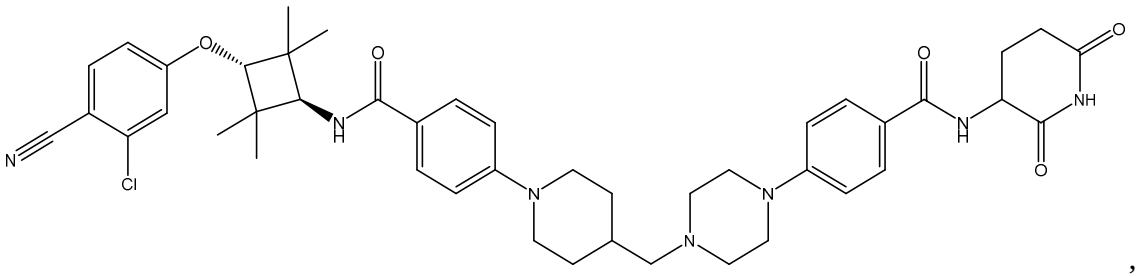
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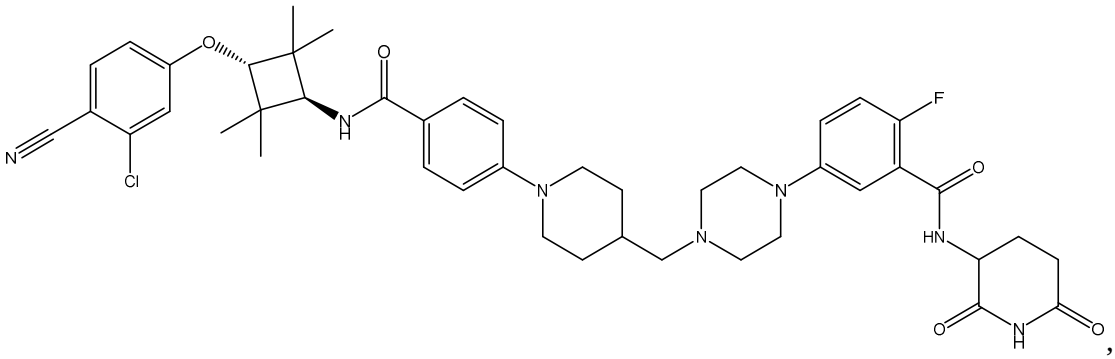
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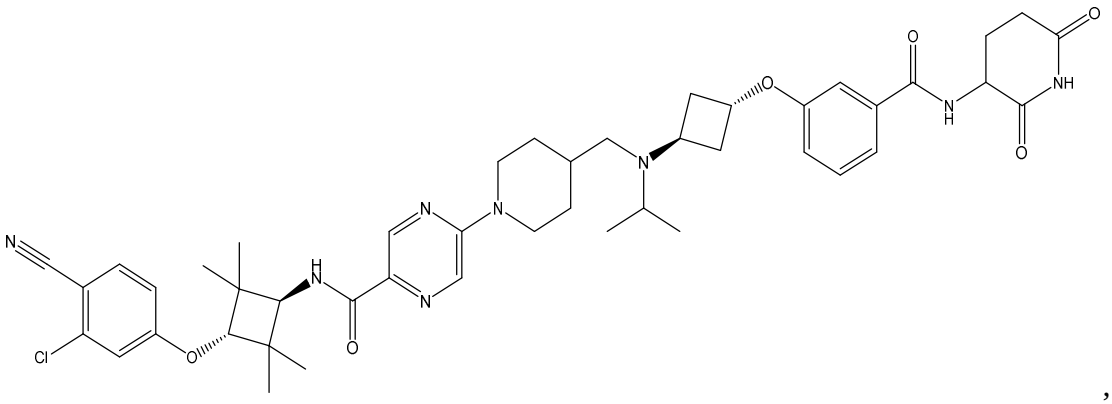
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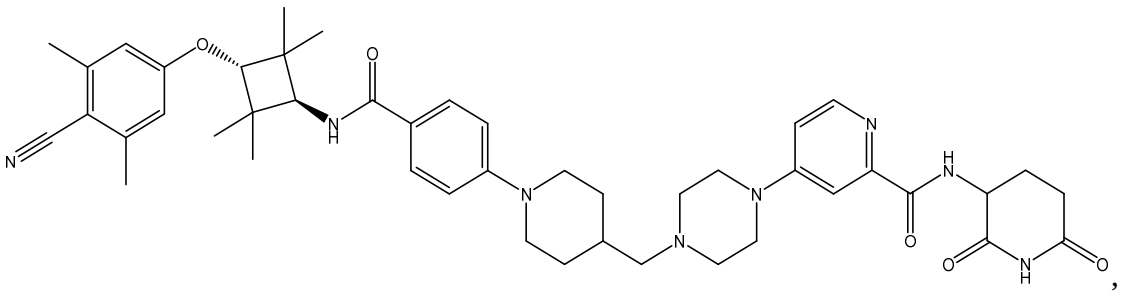
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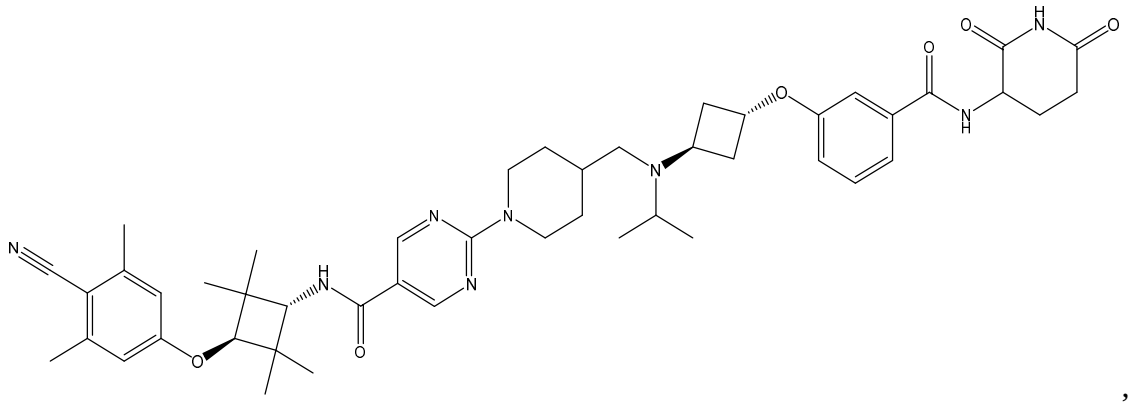
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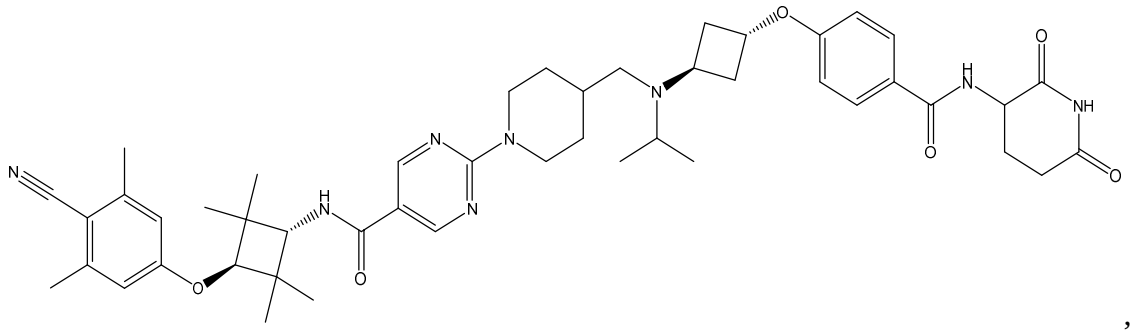
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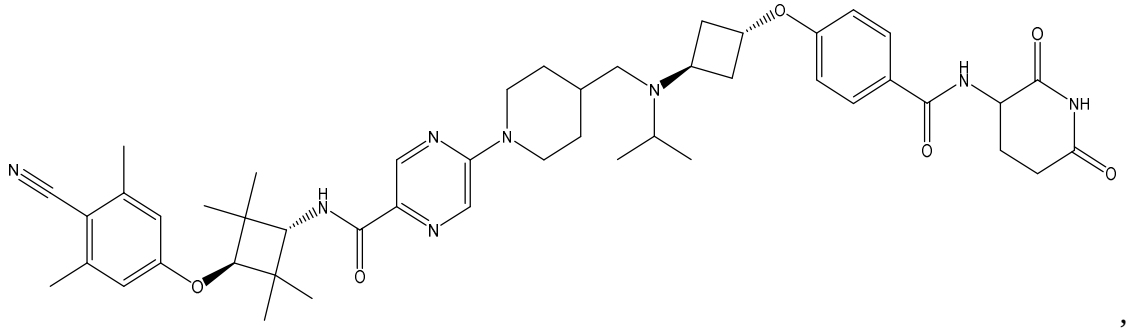
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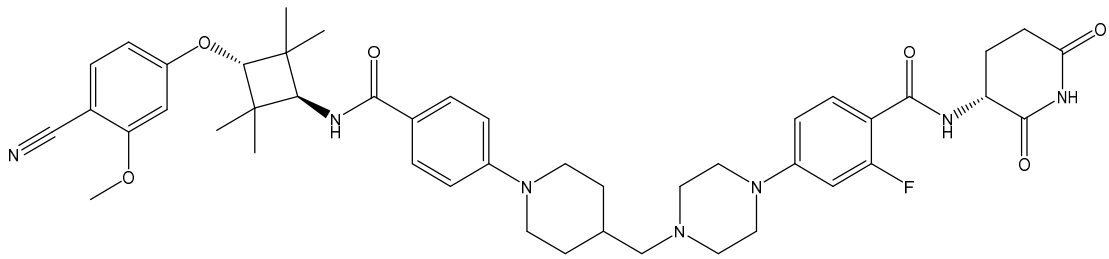
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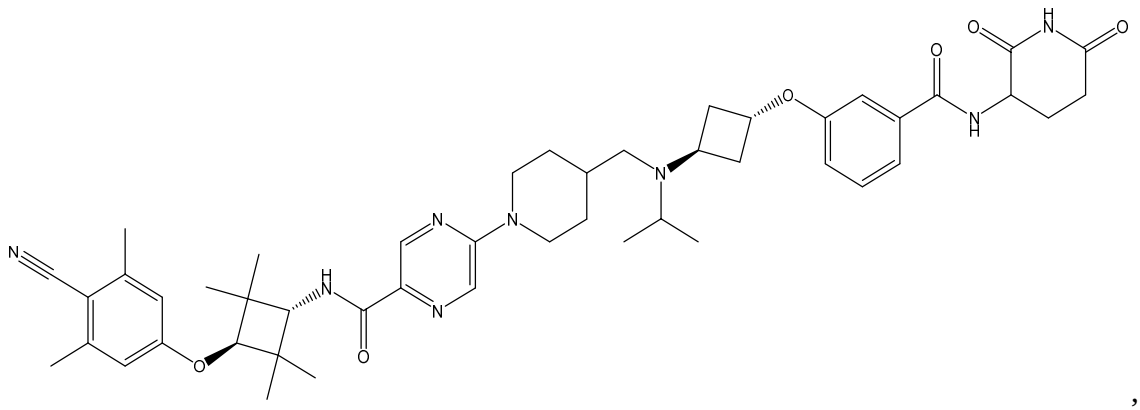
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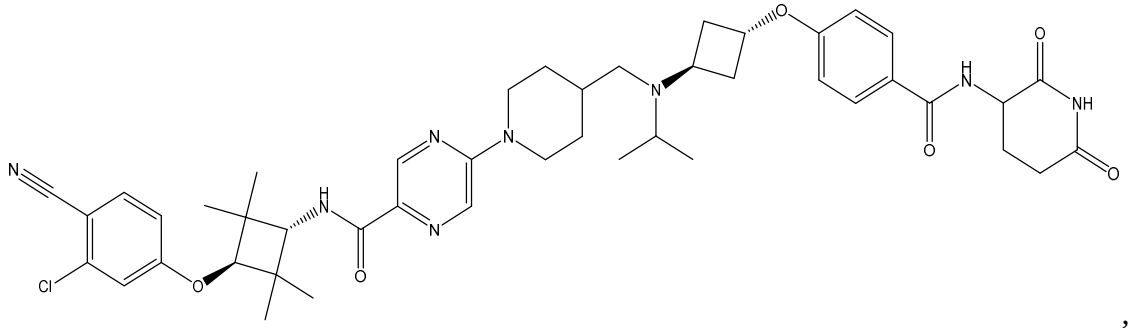
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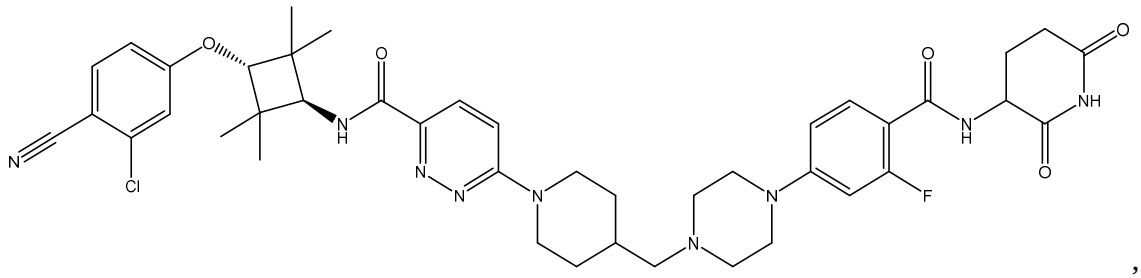
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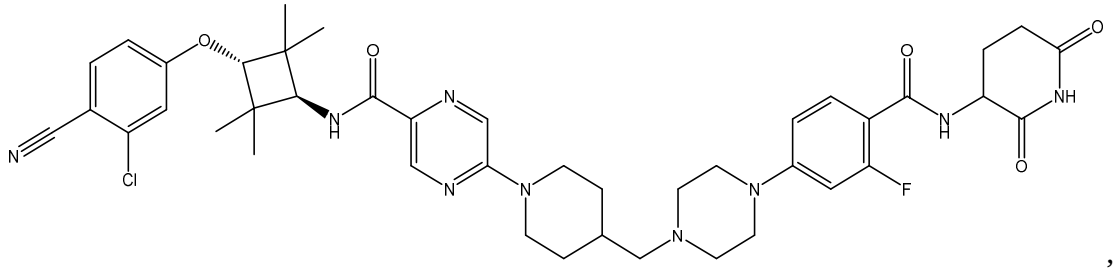
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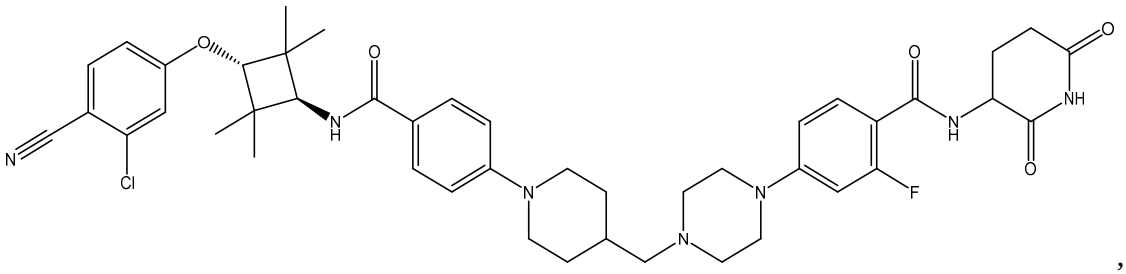
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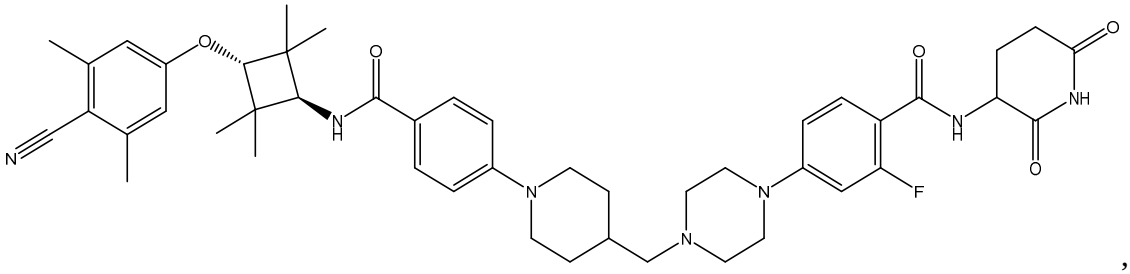
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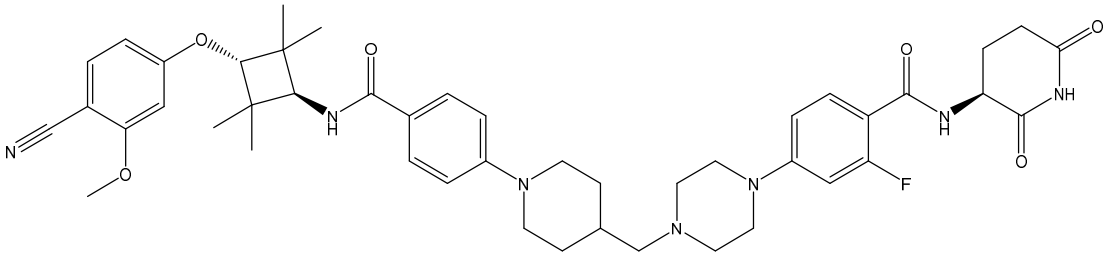
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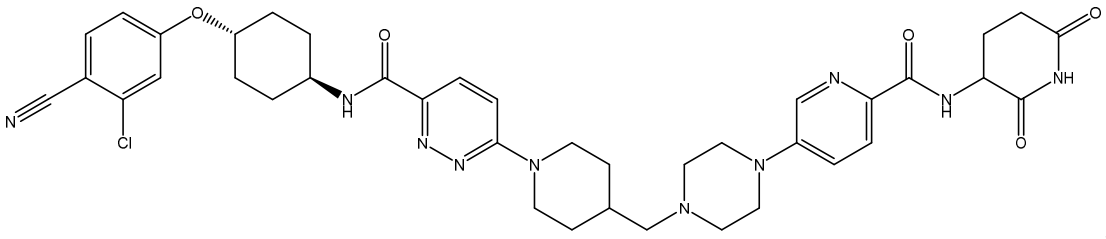
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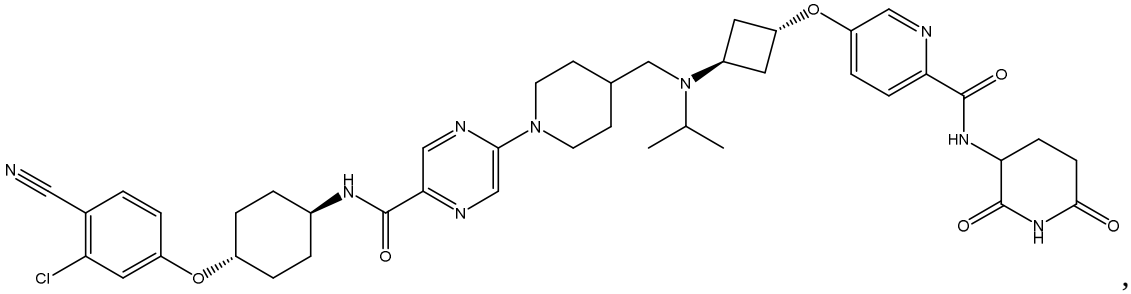
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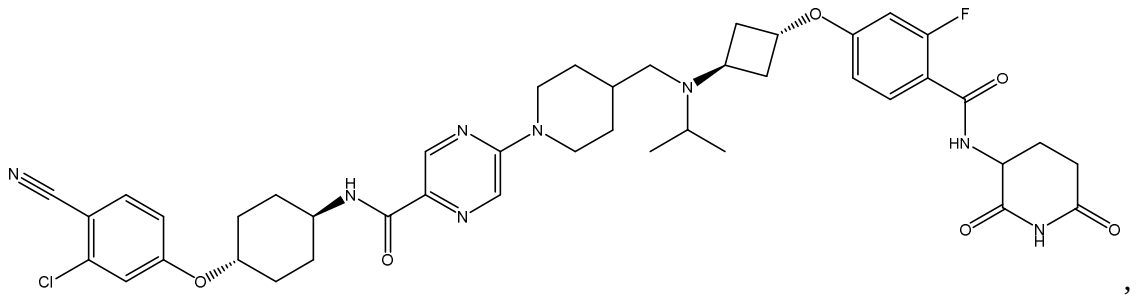
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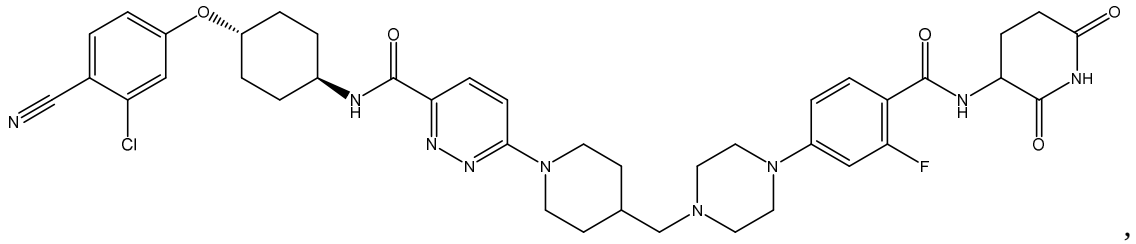
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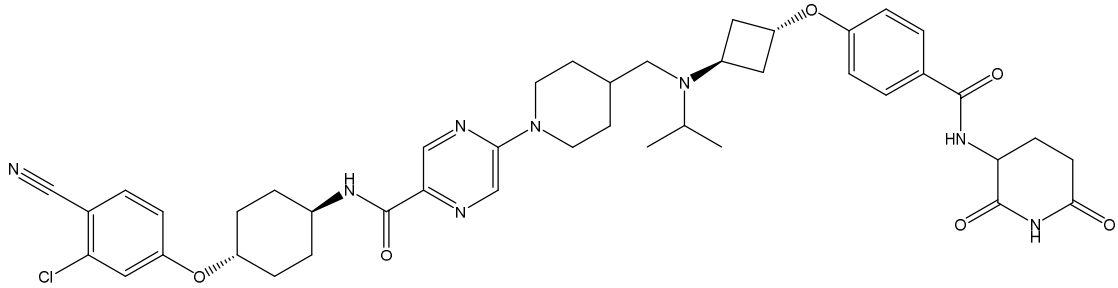
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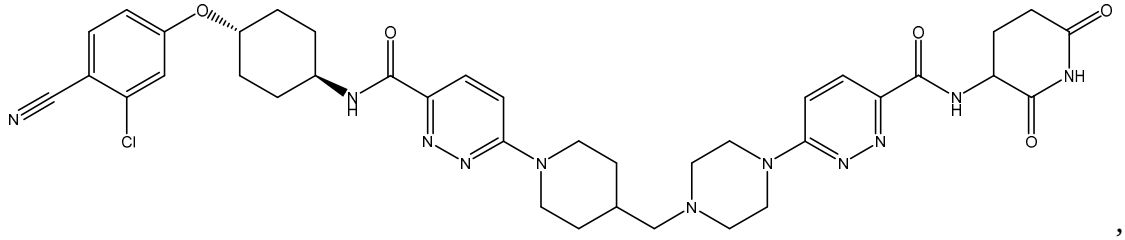
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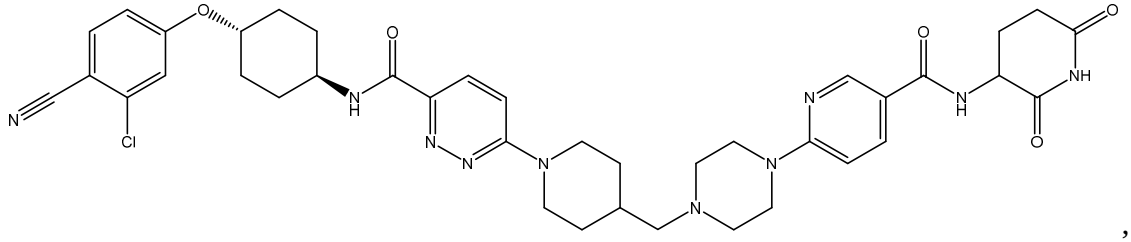
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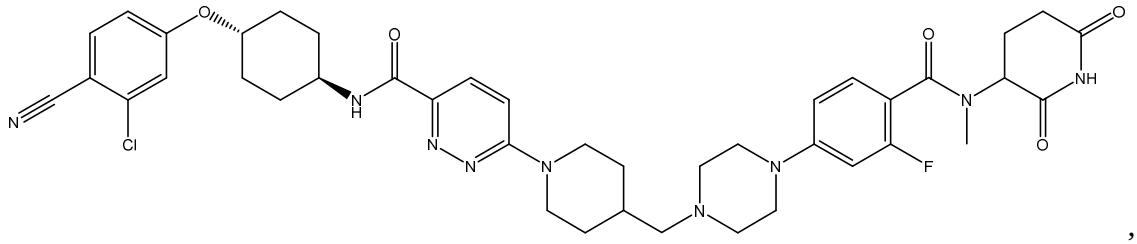
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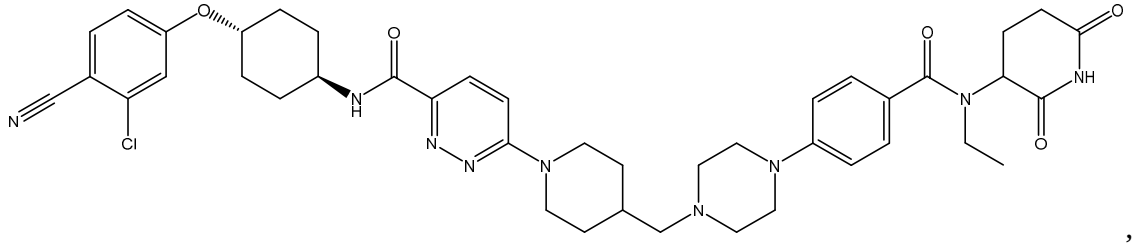
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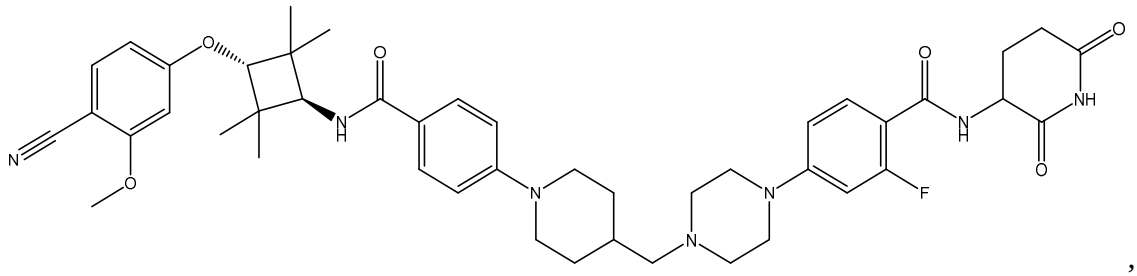
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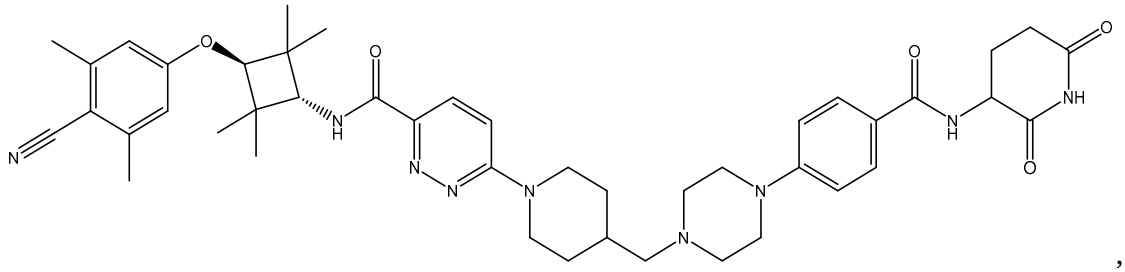
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or a pharmaceutically acceptable salt thereof.

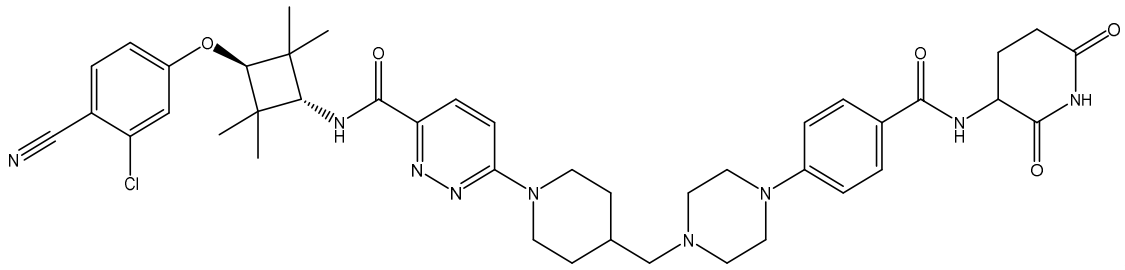
34. A bifunctional compound, wherein the compound is:



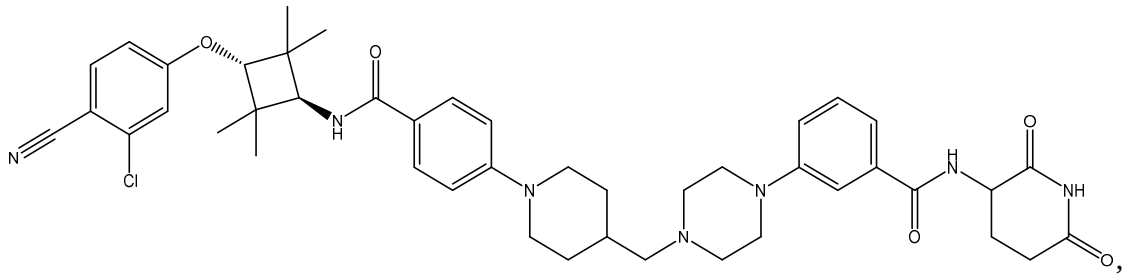
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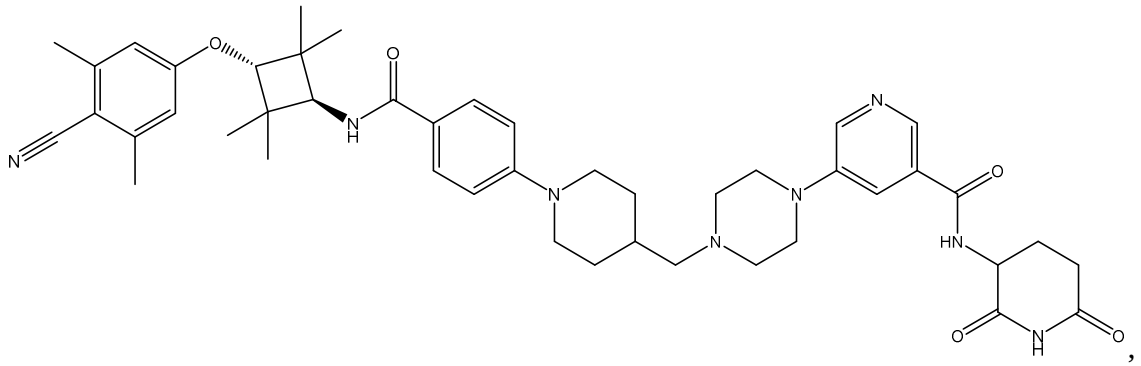
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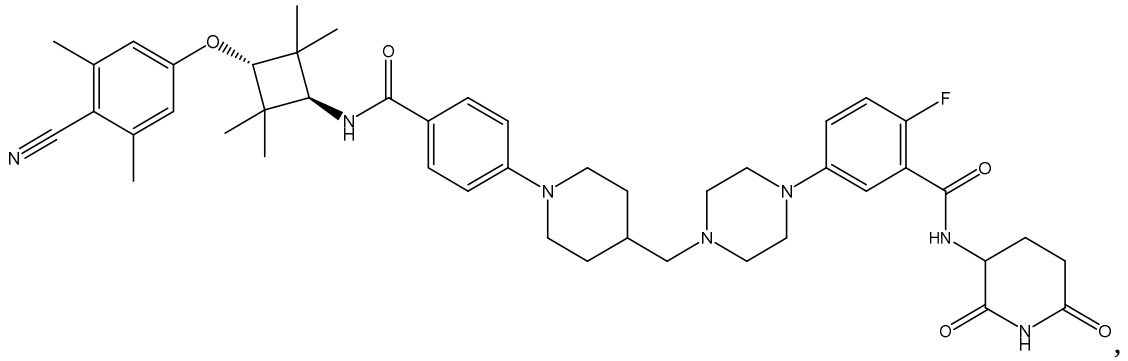
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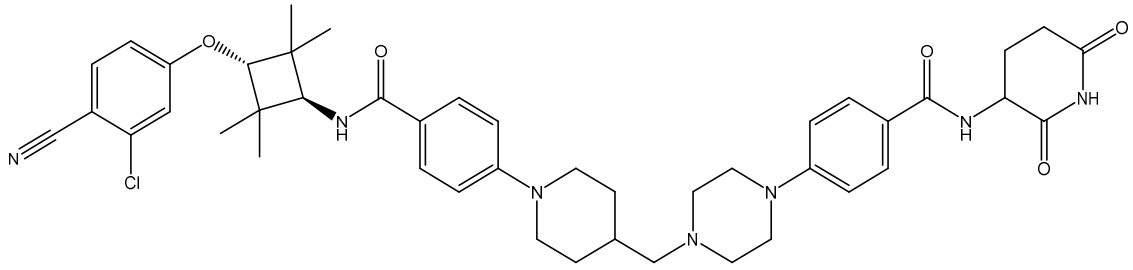
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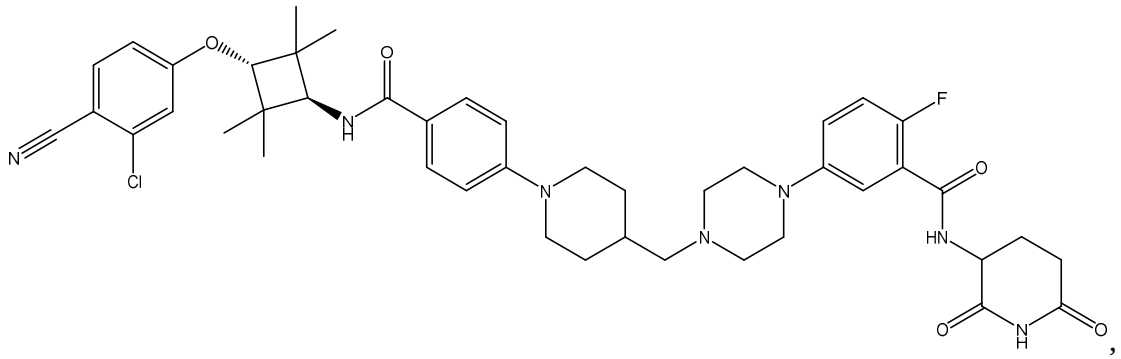
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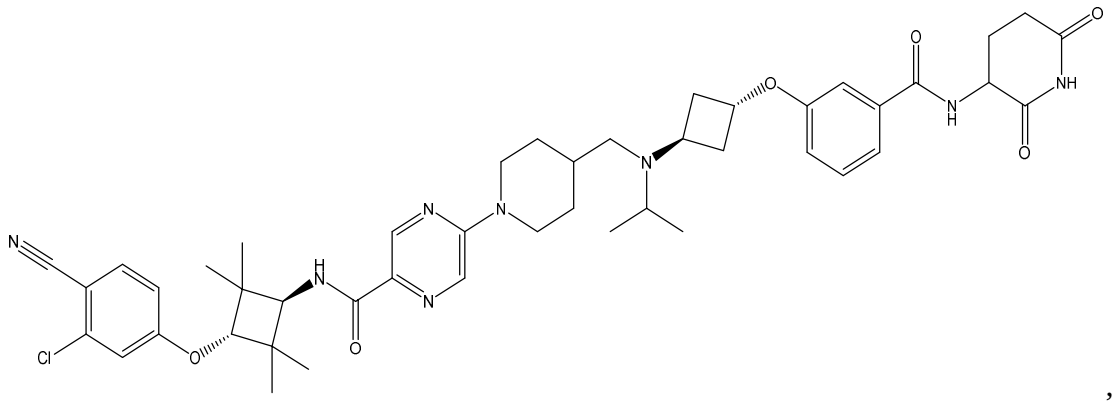
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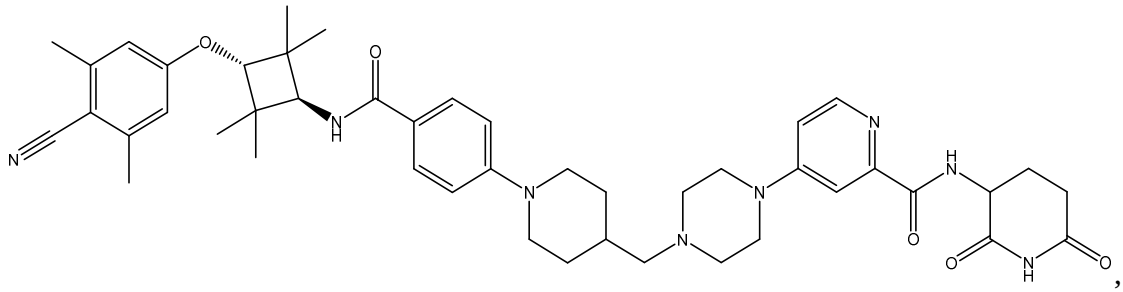
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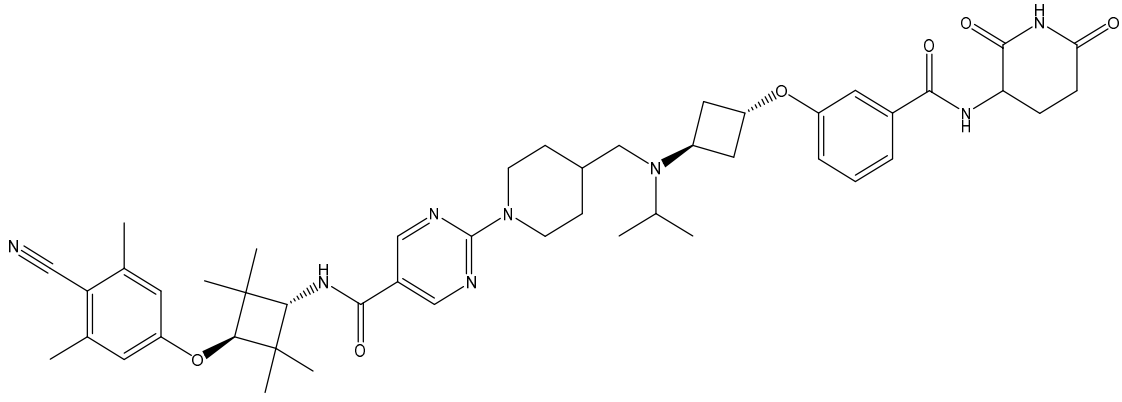
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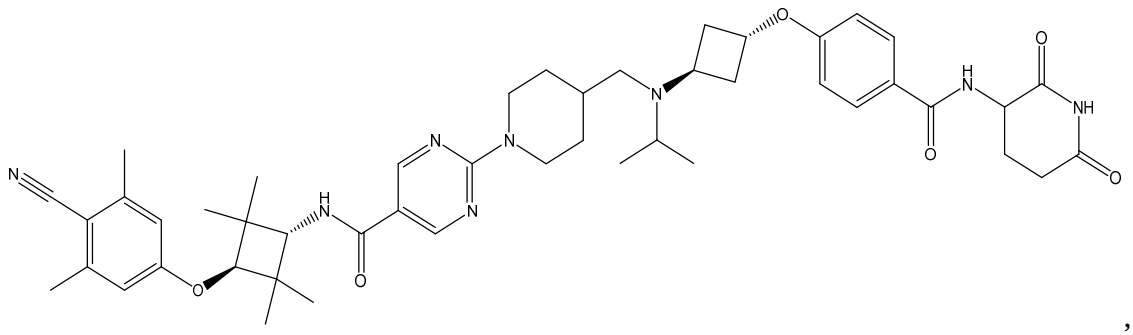
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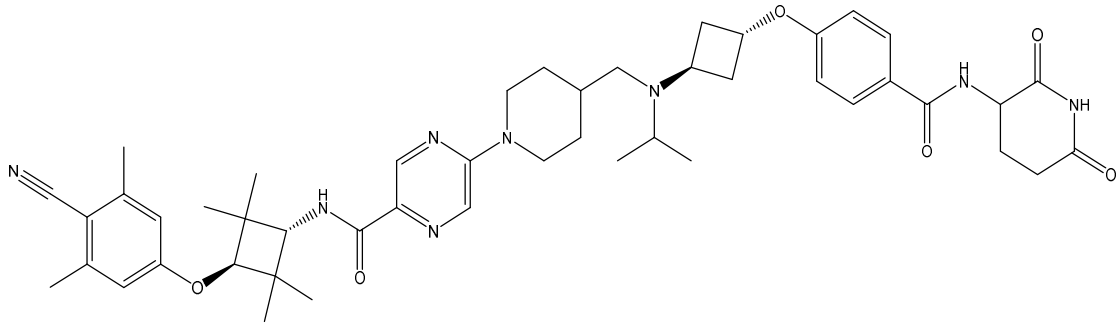
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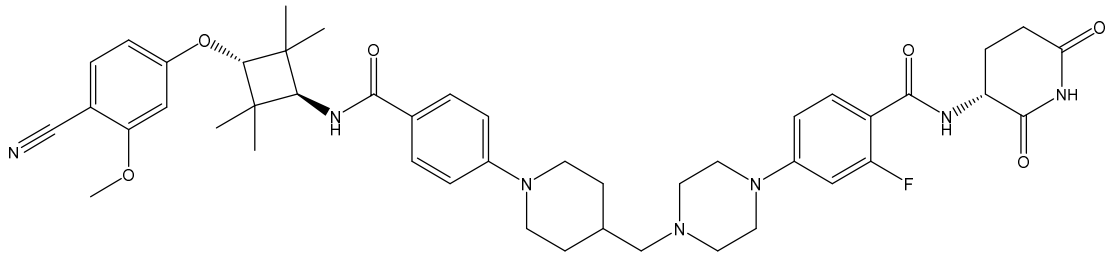
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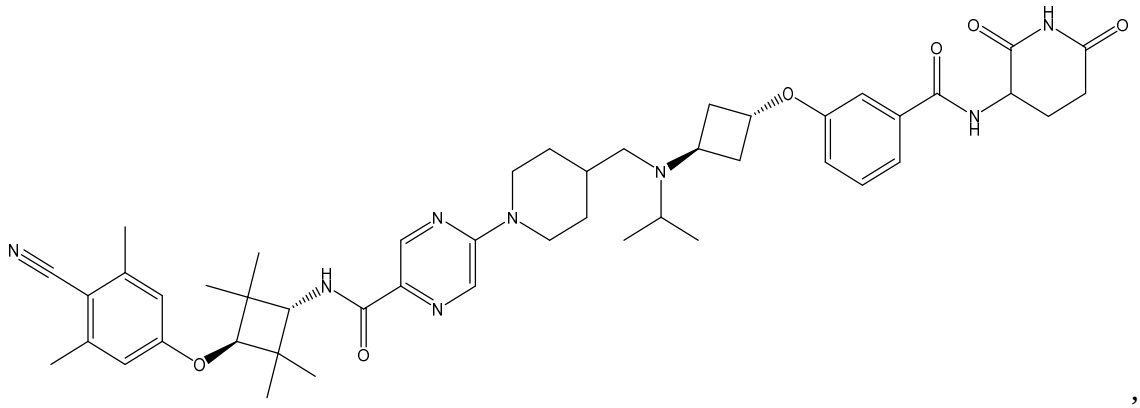
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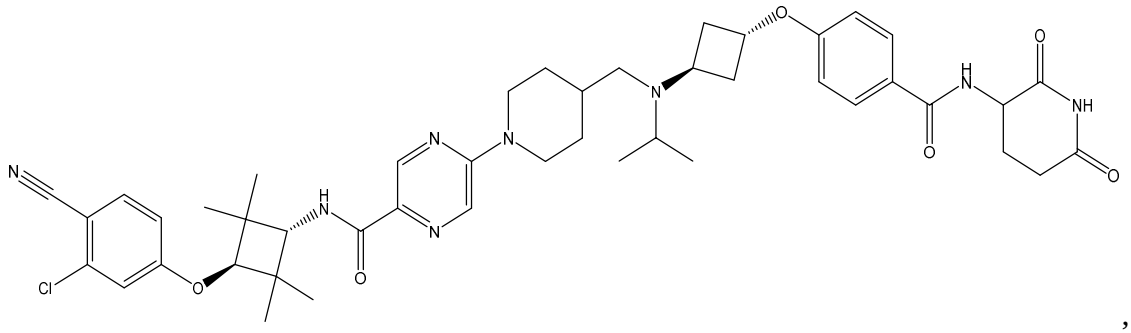
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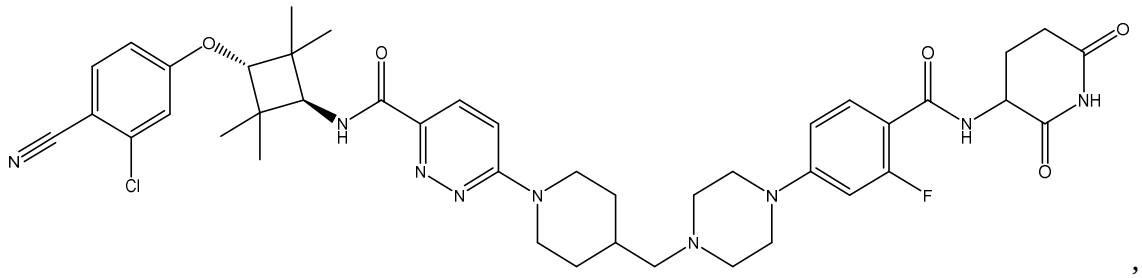
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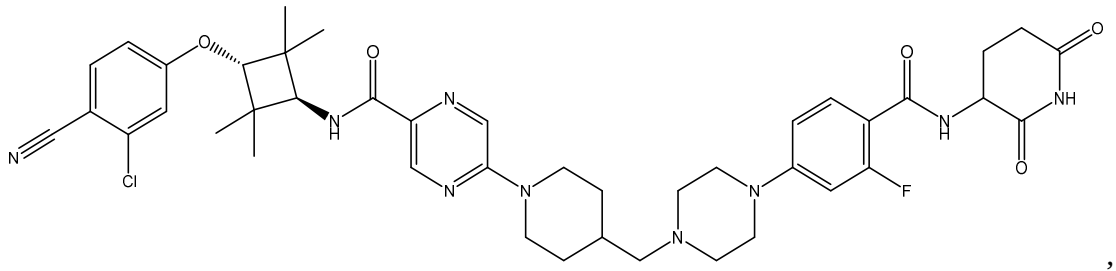
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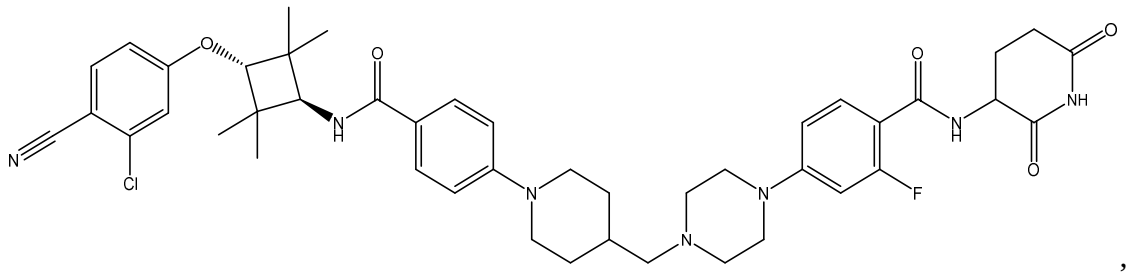
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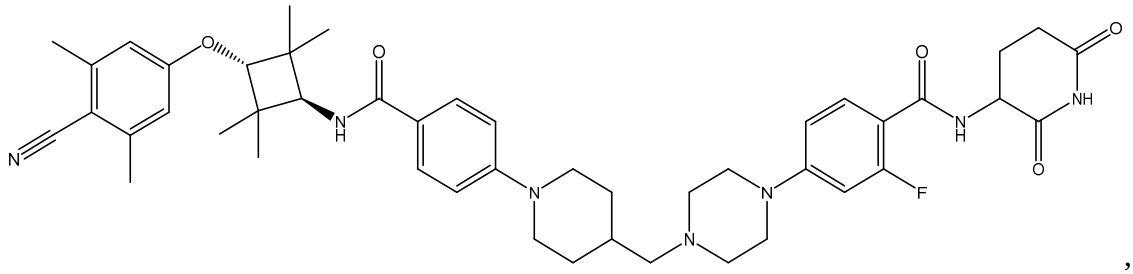
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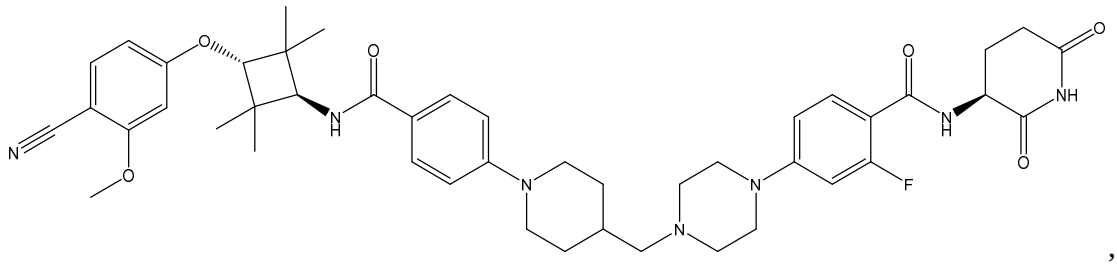
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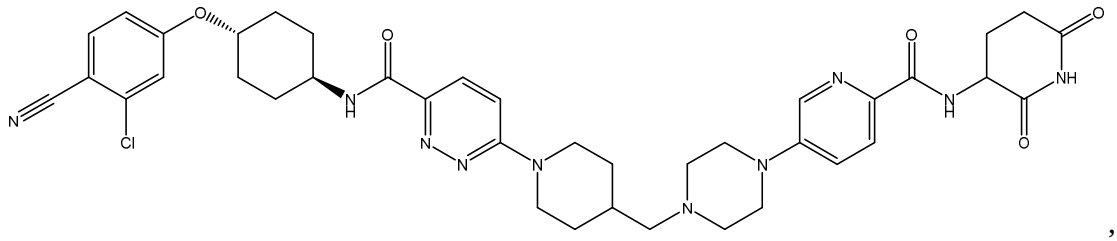
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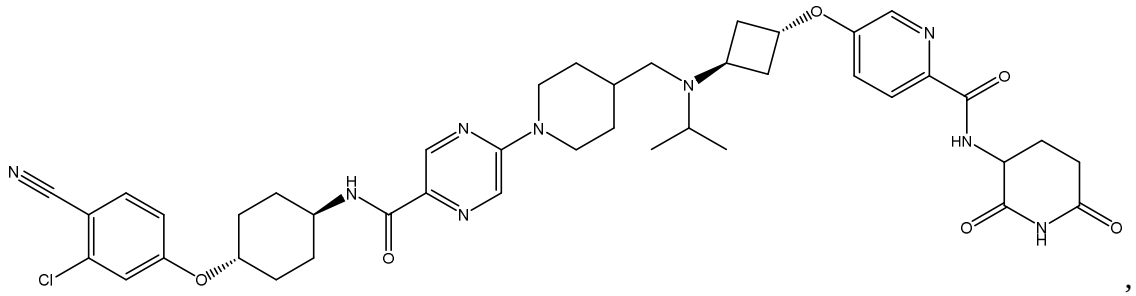
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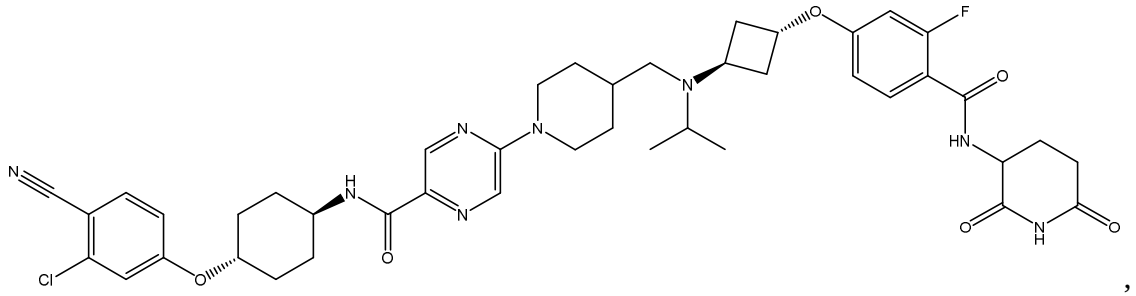
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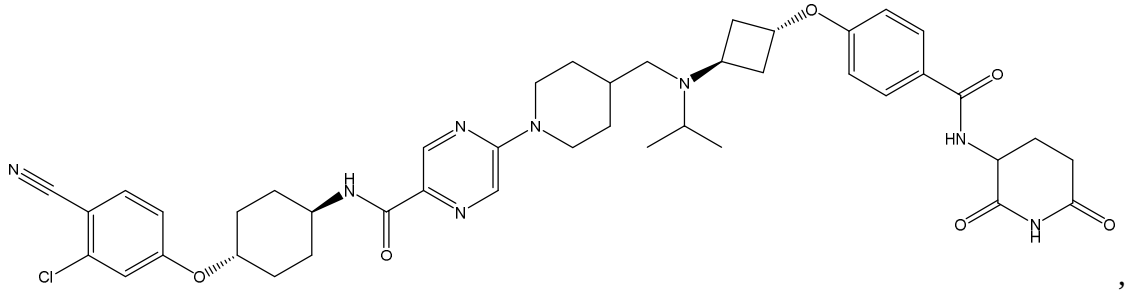
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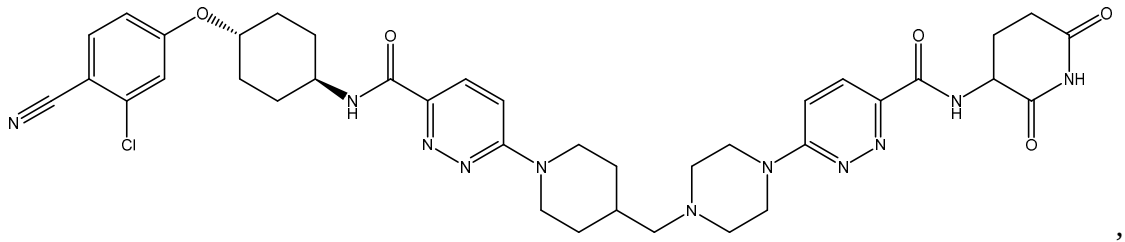
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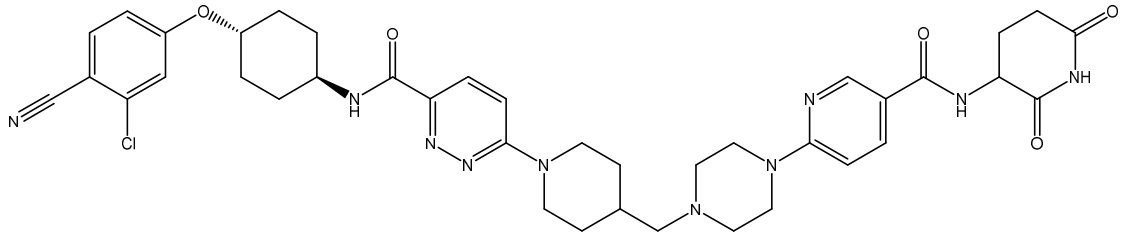
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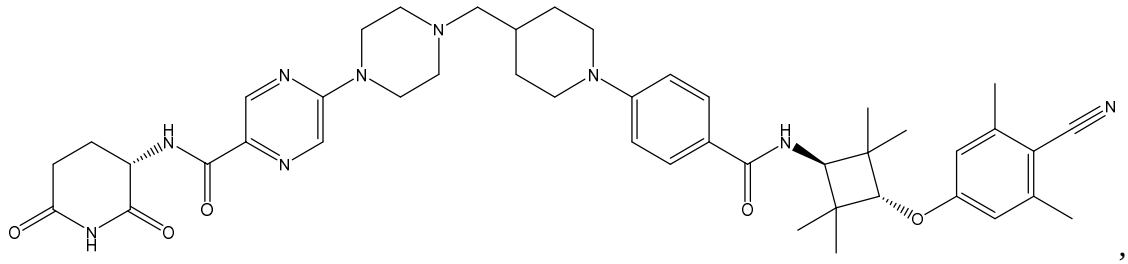
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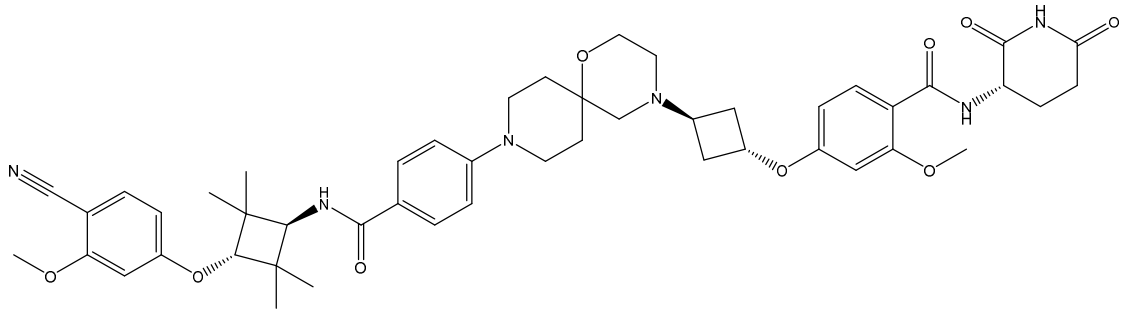
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a pharmaceutically acceptable salt thereof.

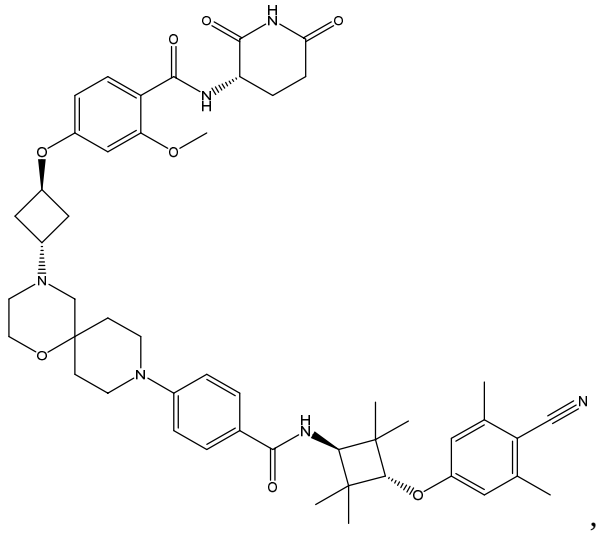
35. A bifunctional compound, wherein the compound is:



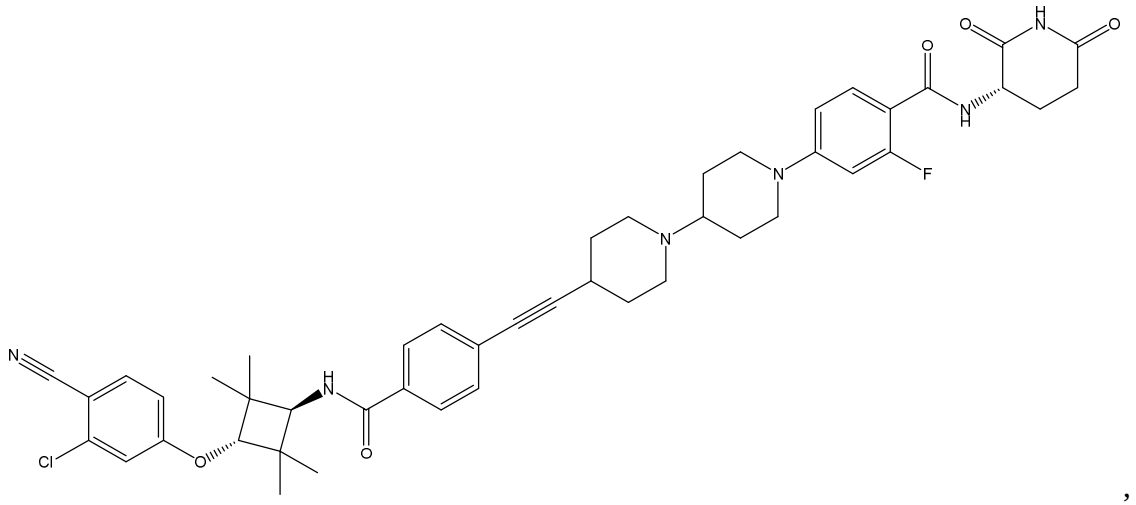
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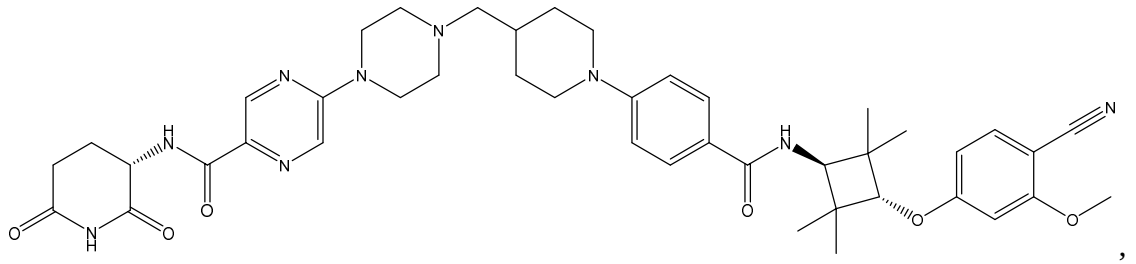
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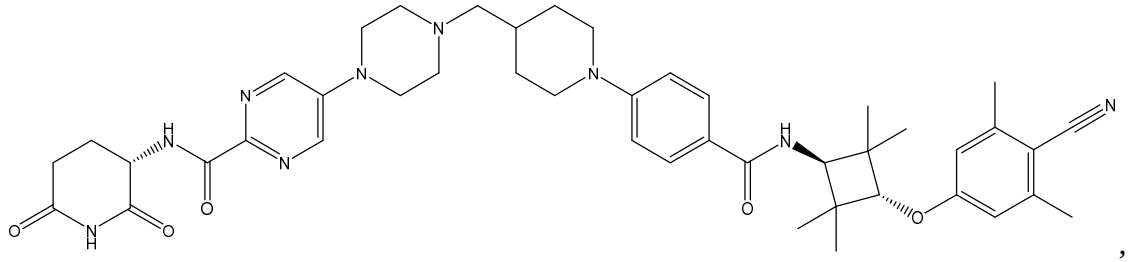
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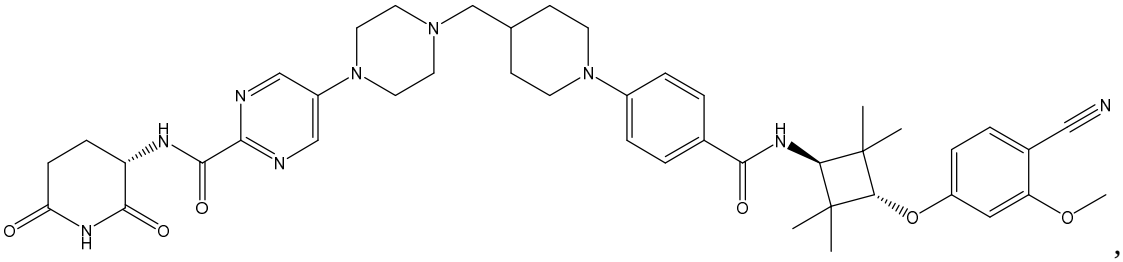
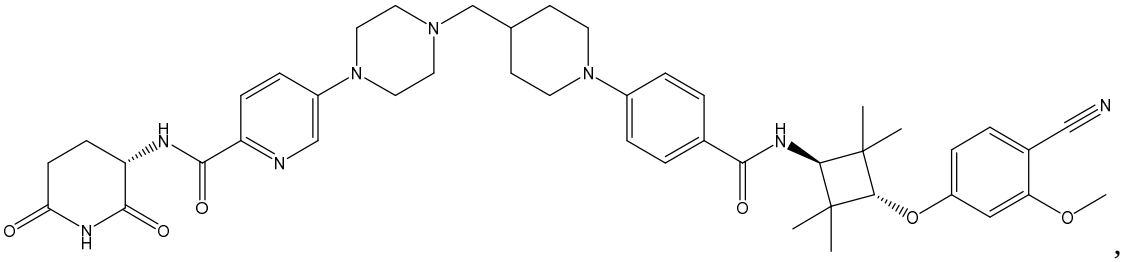
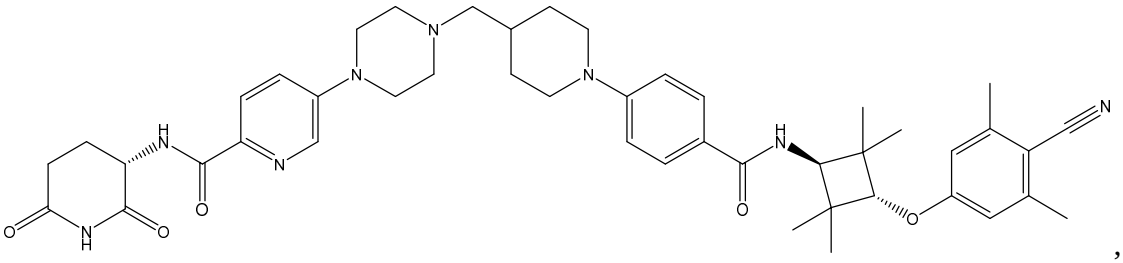
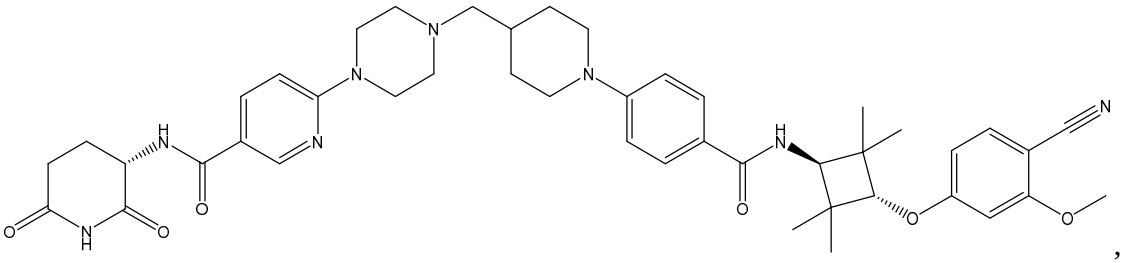
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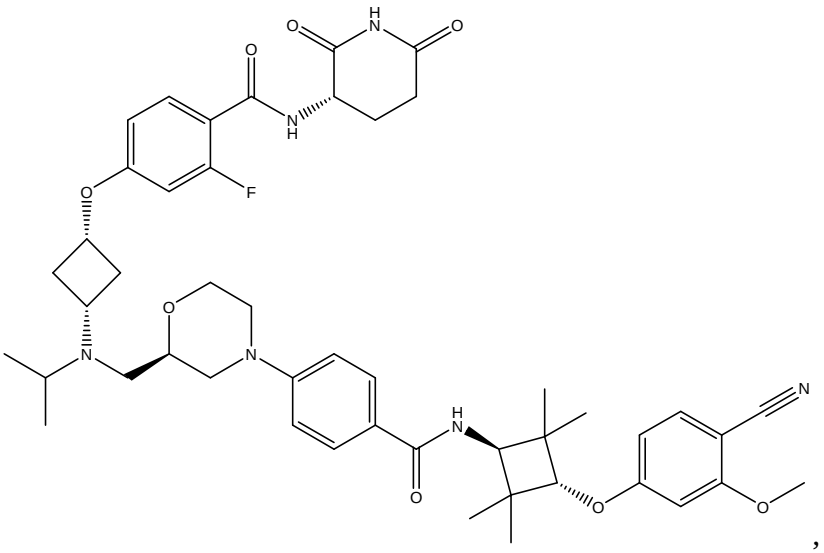


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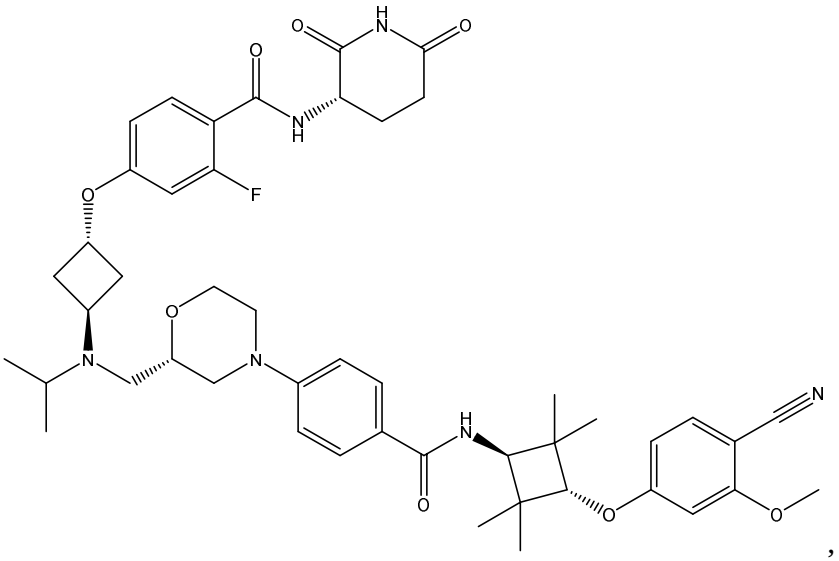


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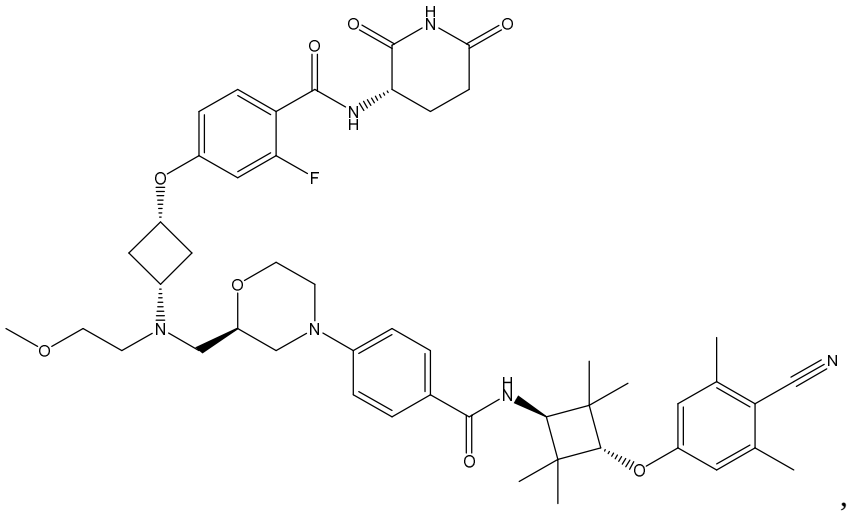

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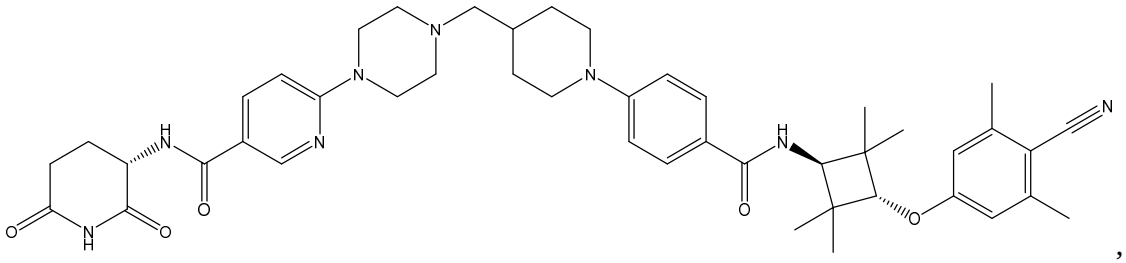
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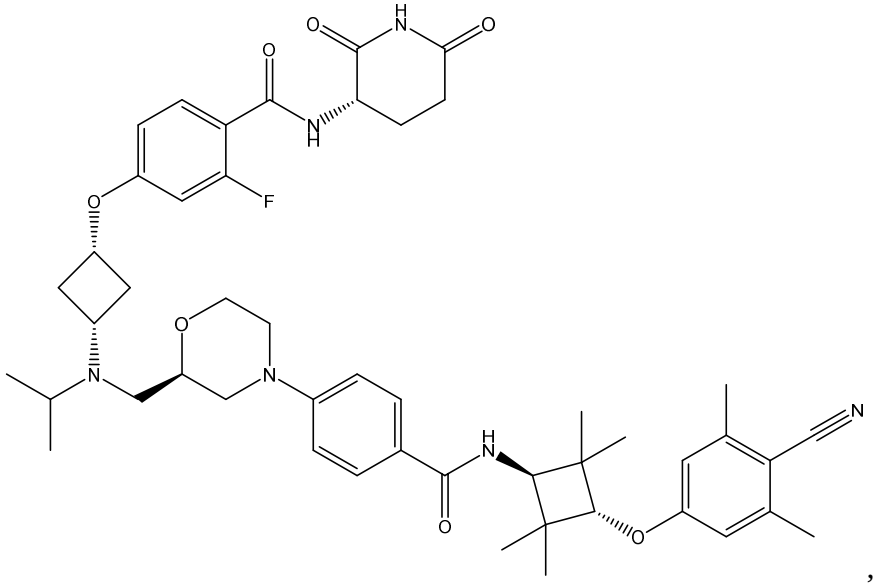
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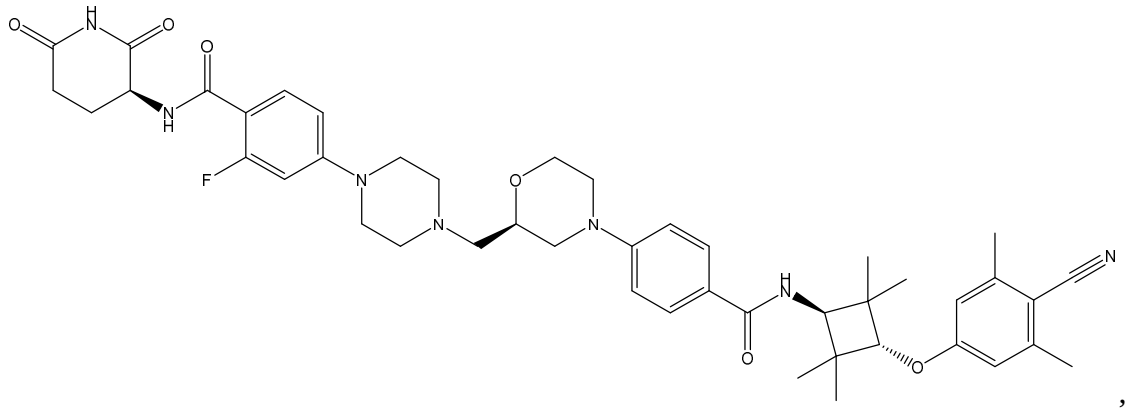
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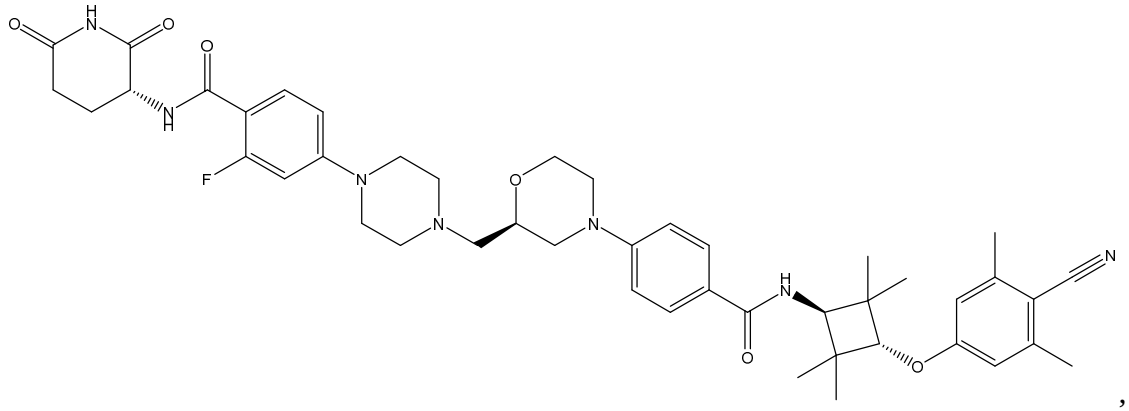
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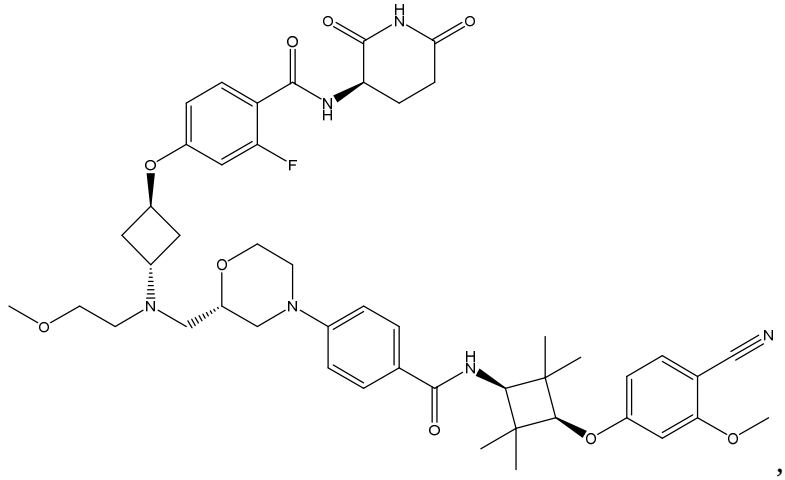
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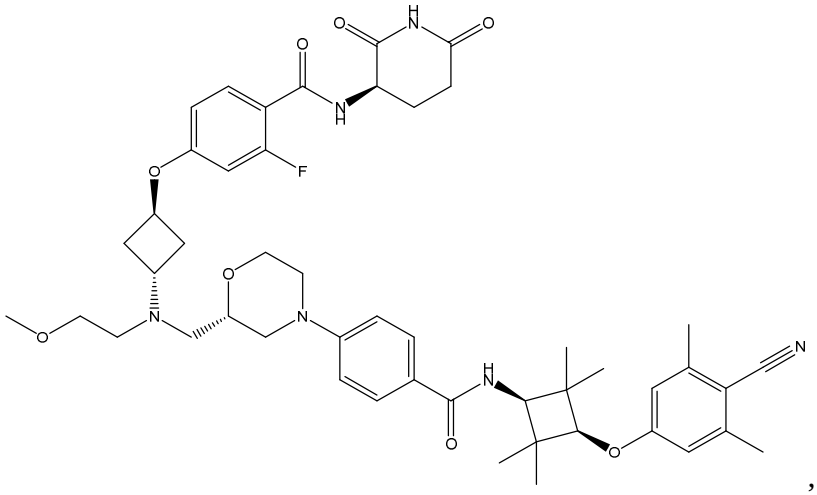
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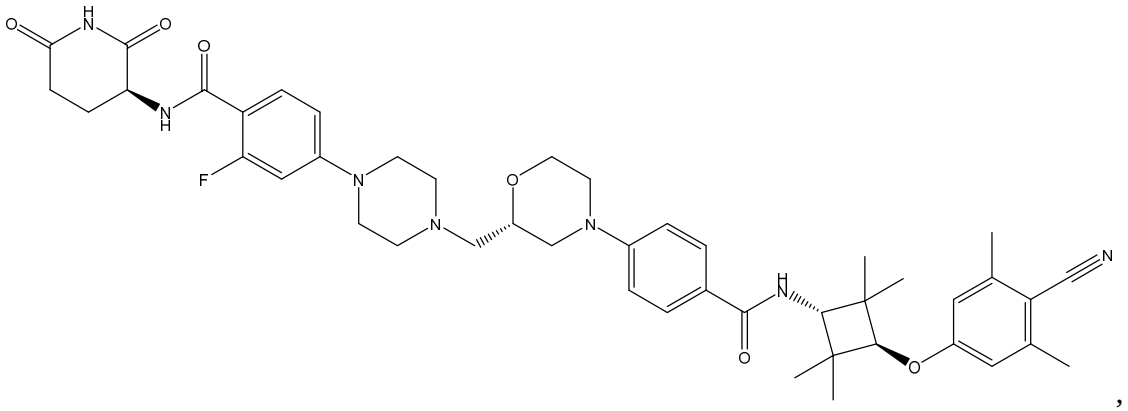
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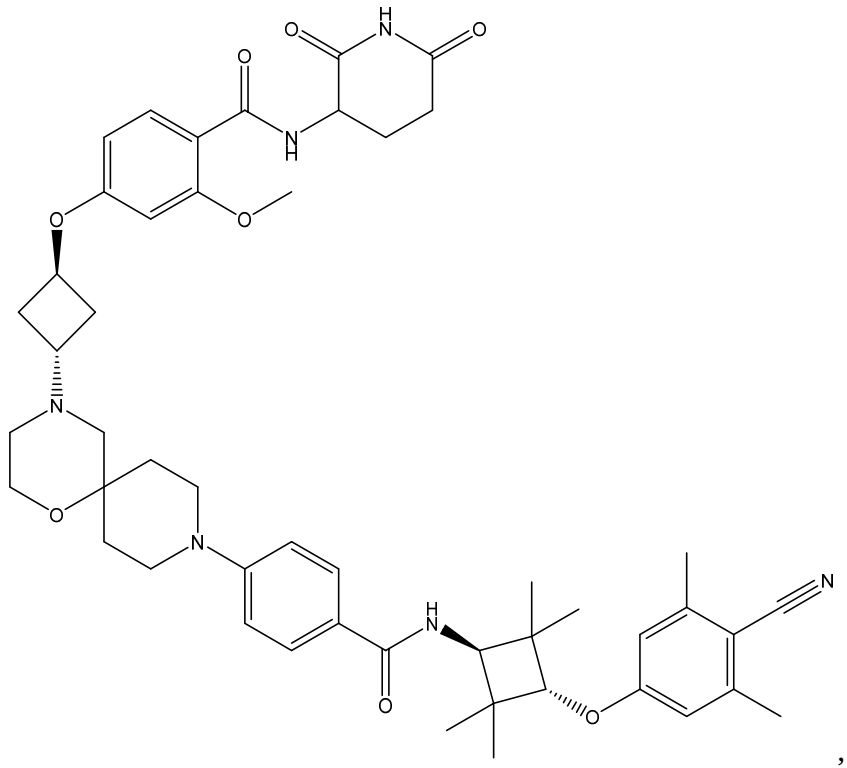
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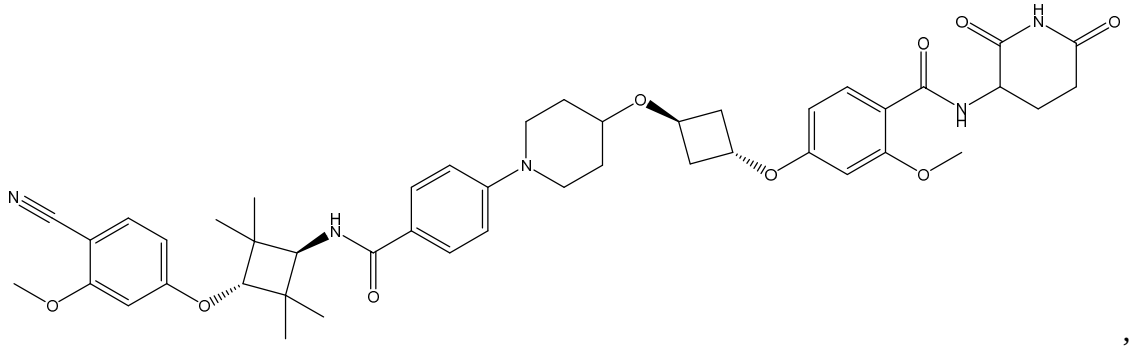
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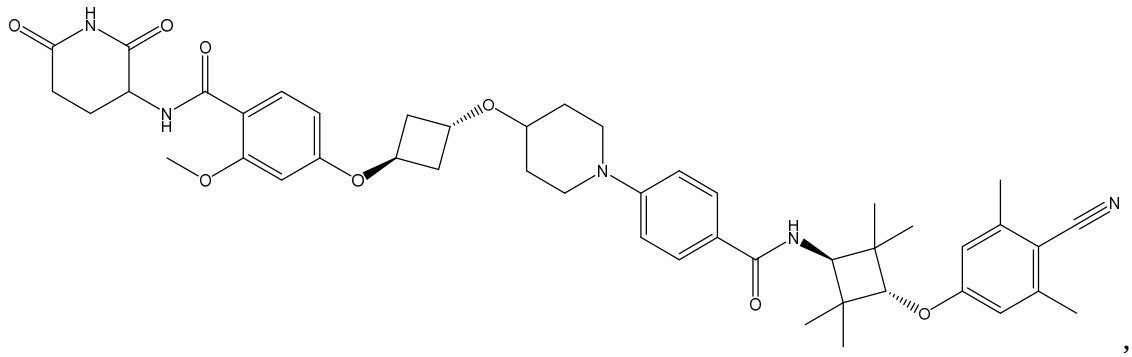
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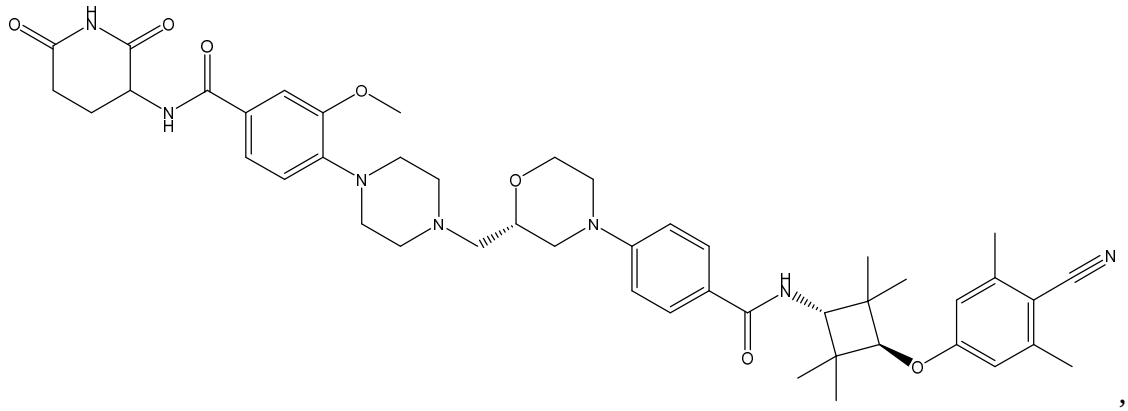
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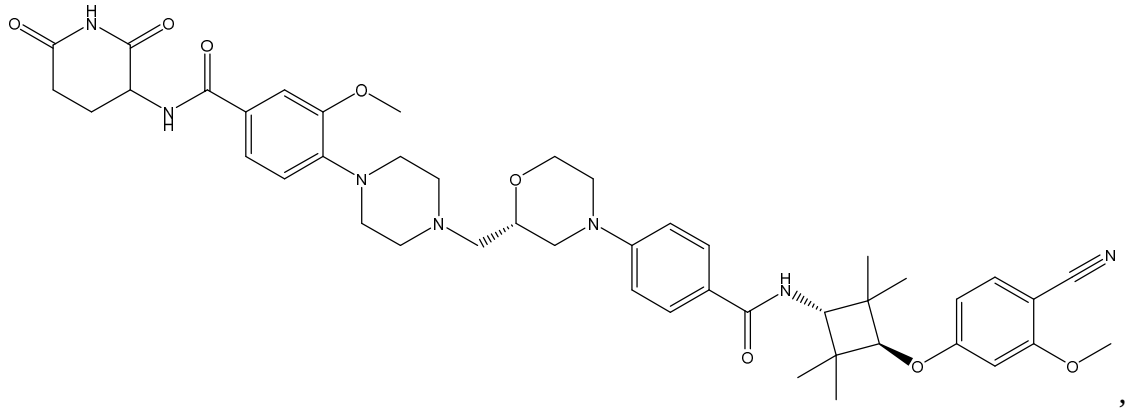
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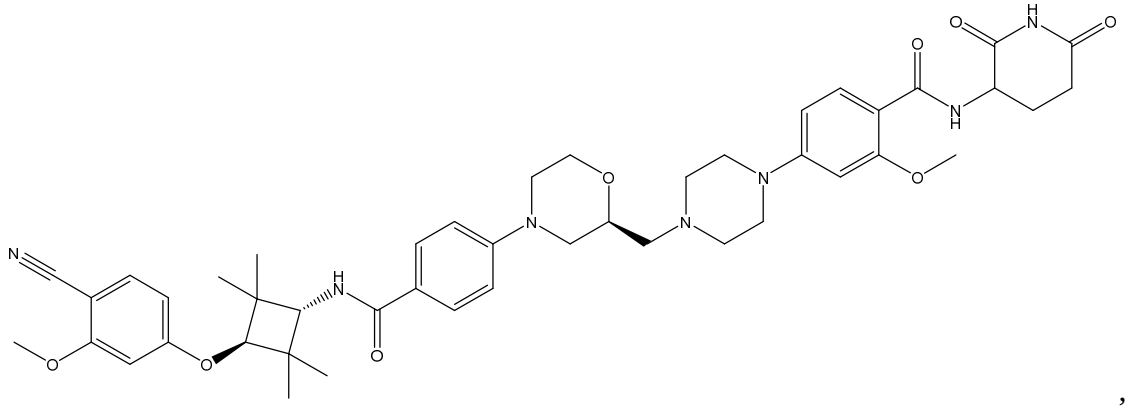
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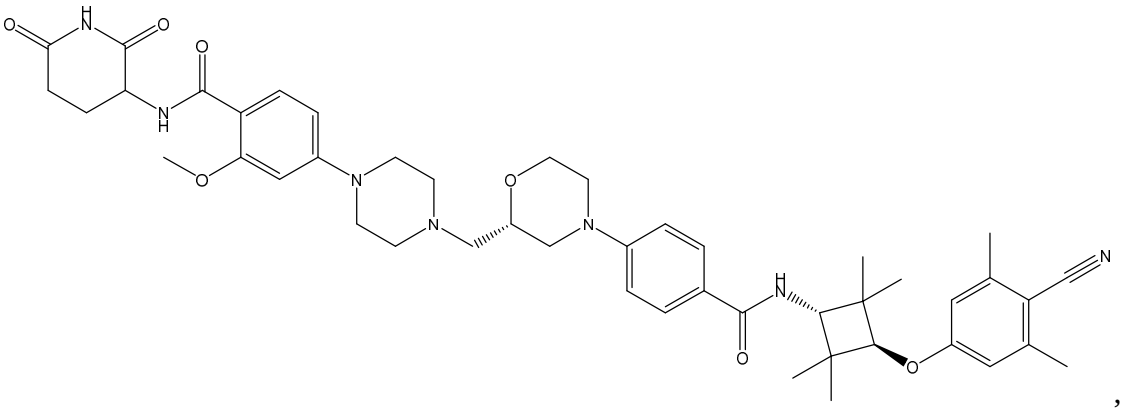
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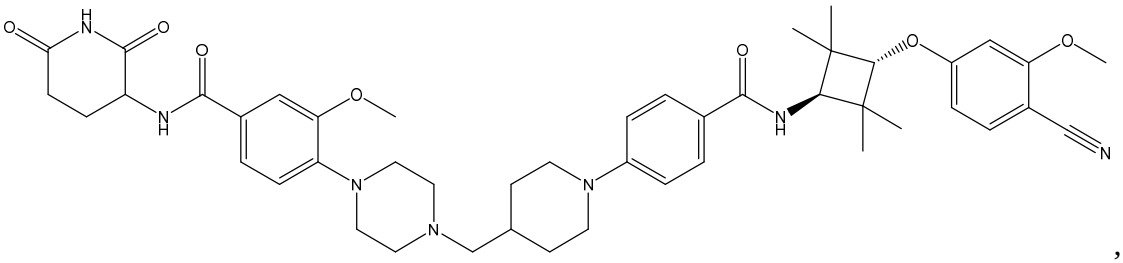
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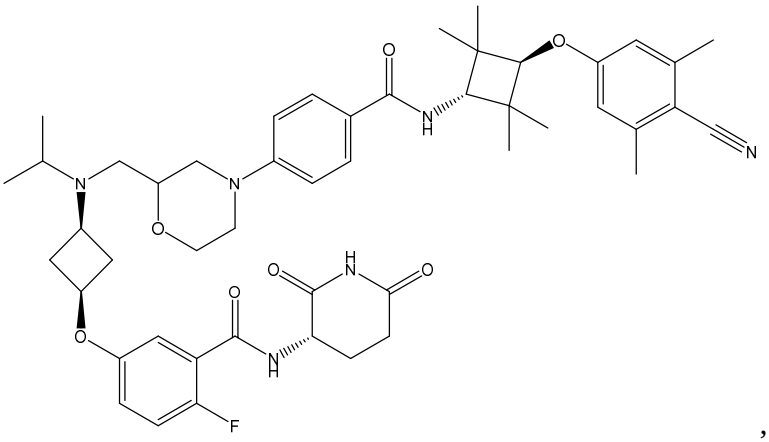
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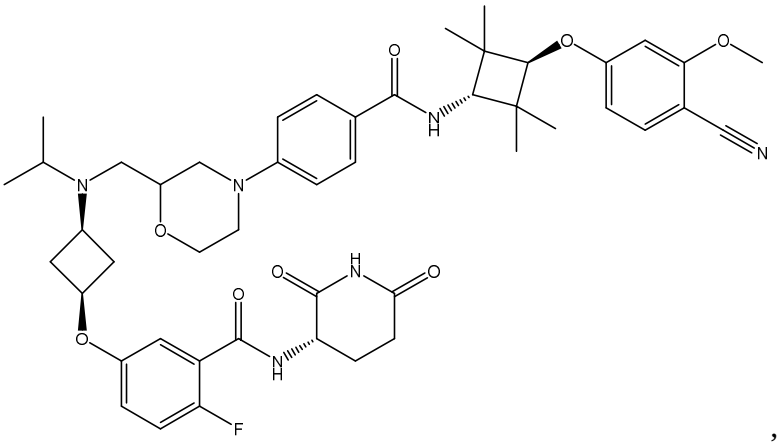
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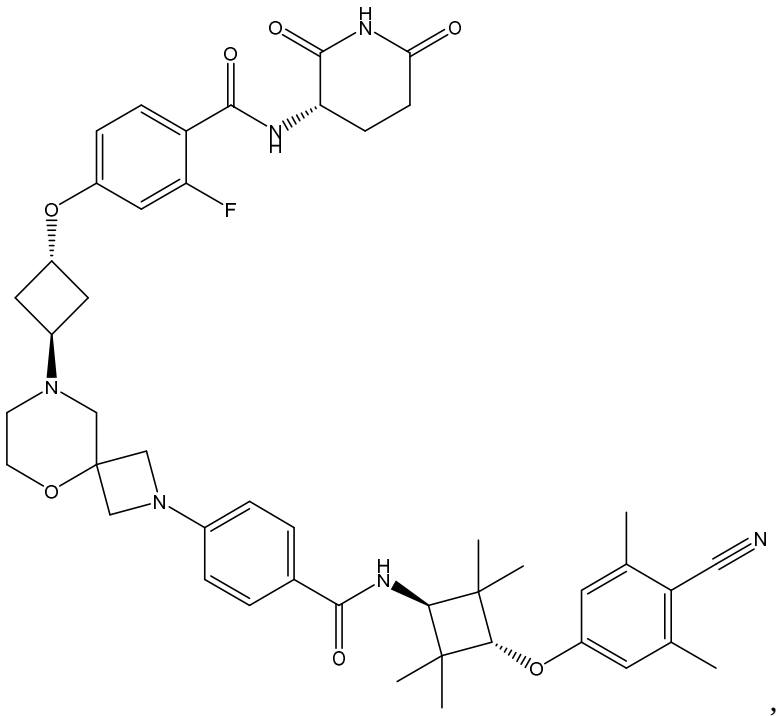
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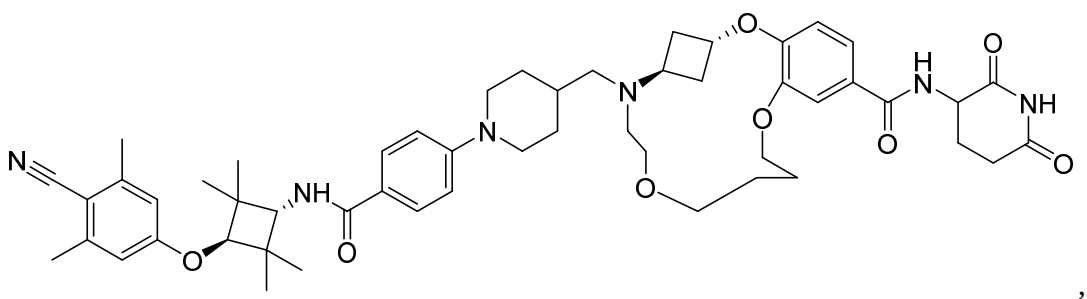
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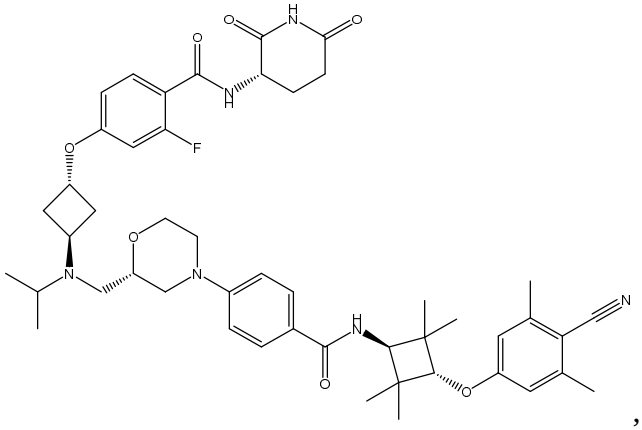
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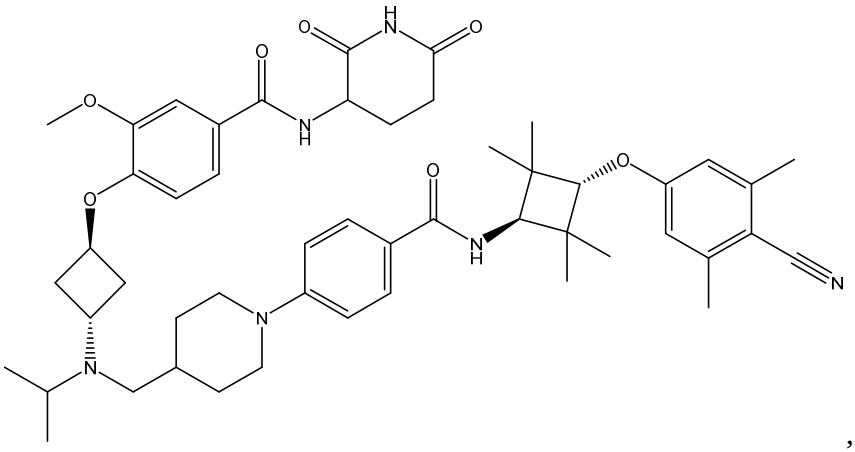
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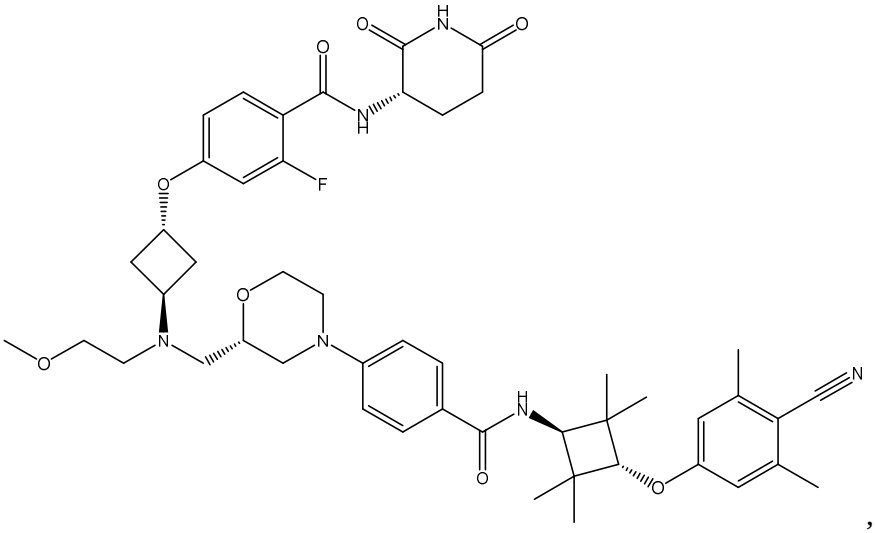
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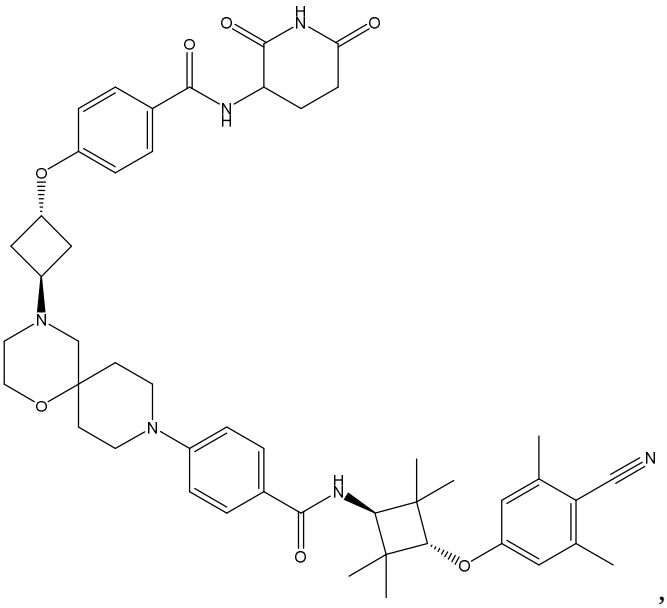
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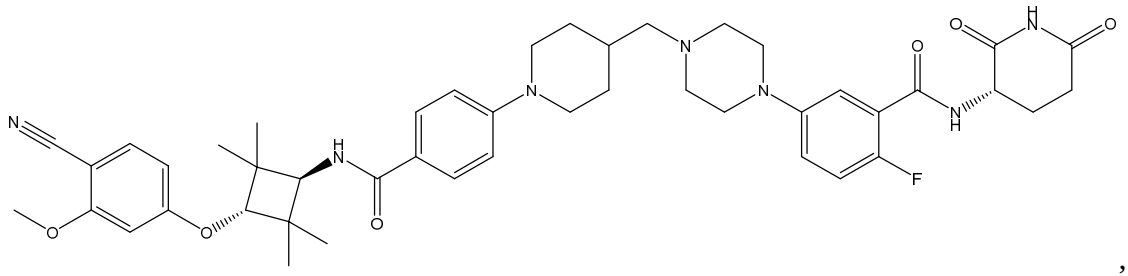
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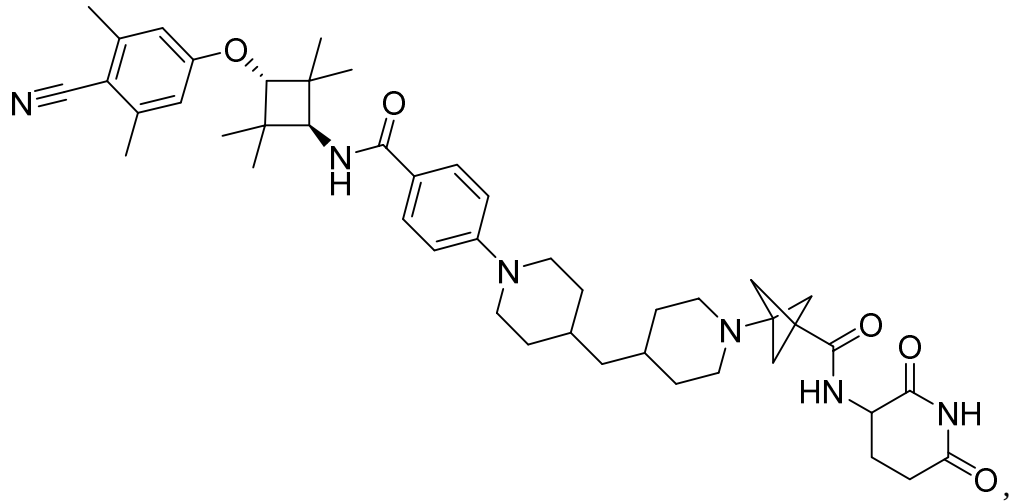
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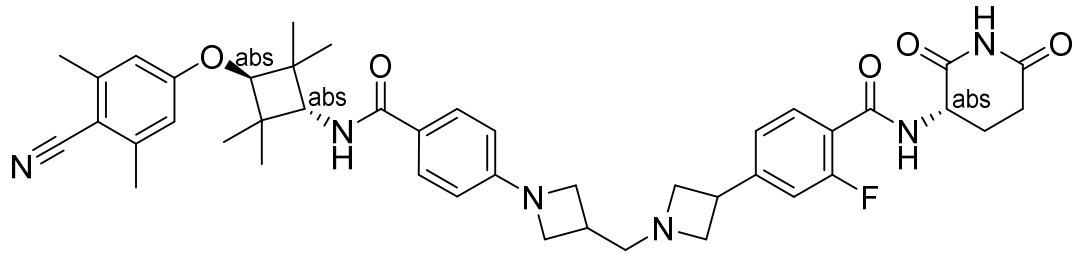
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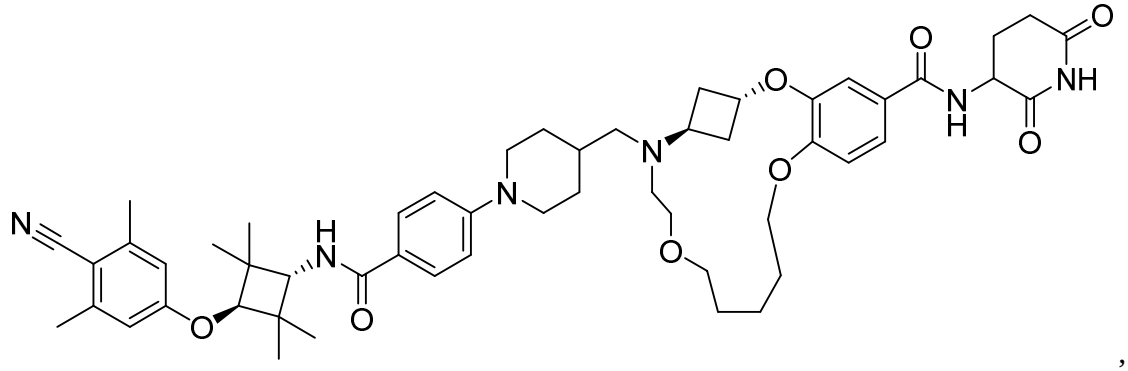
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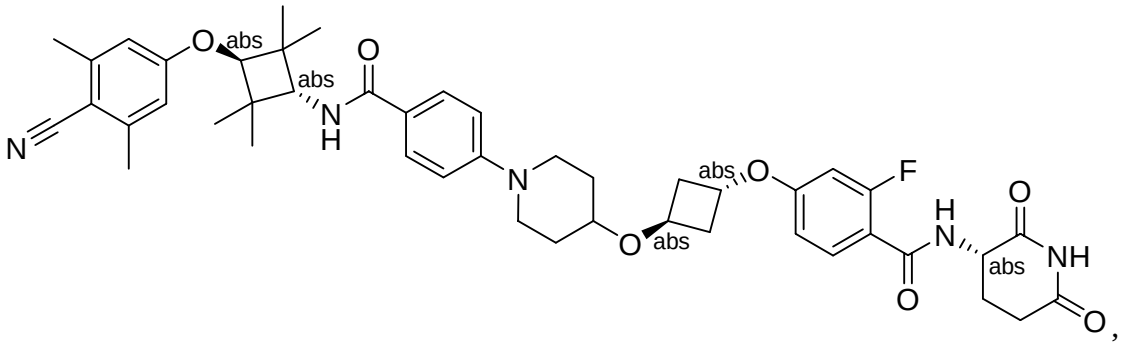
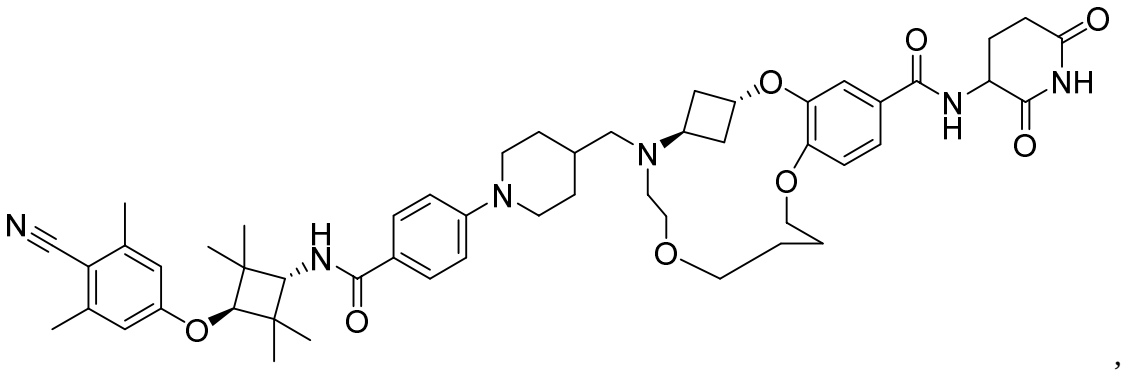
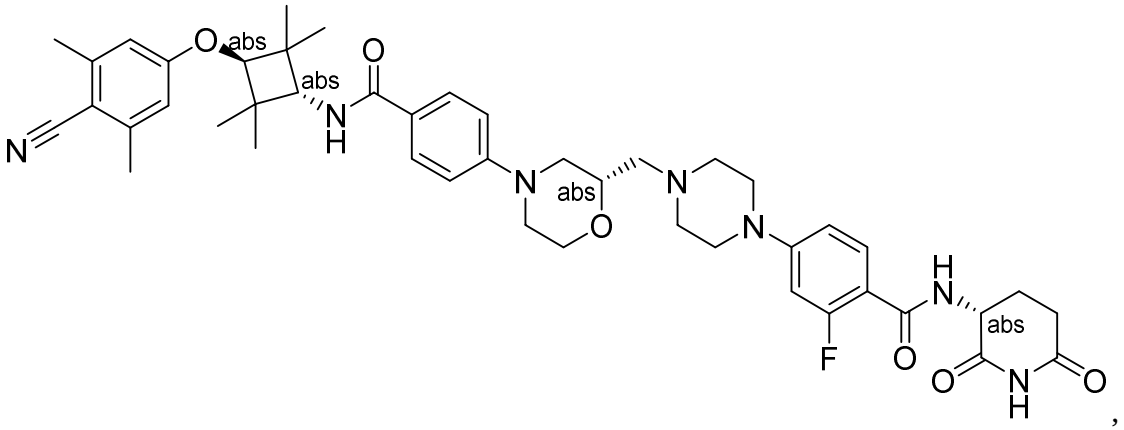
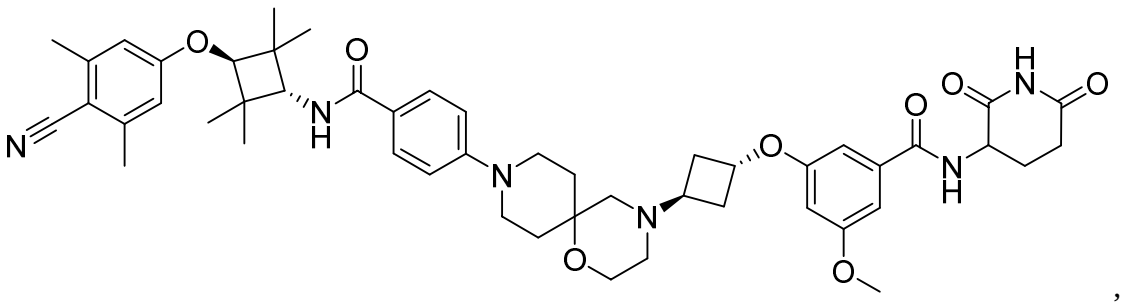
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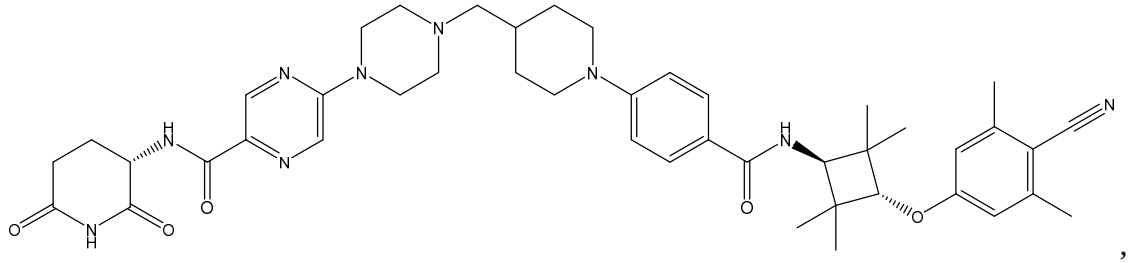
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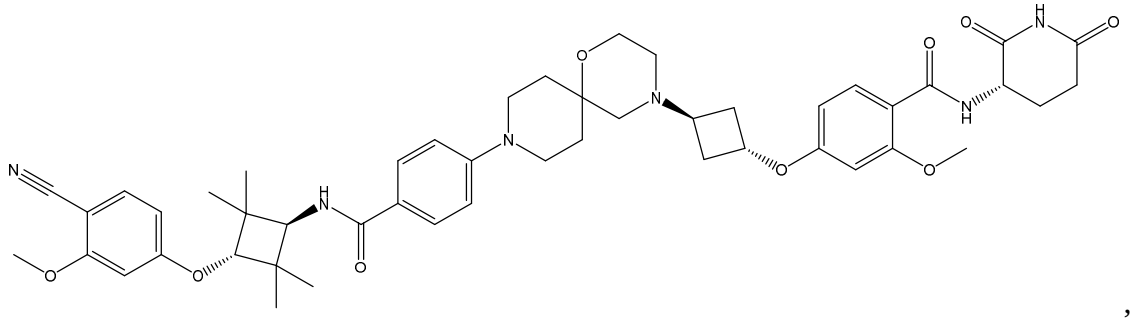
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or a pharmaceutically acceptable salt thereof.

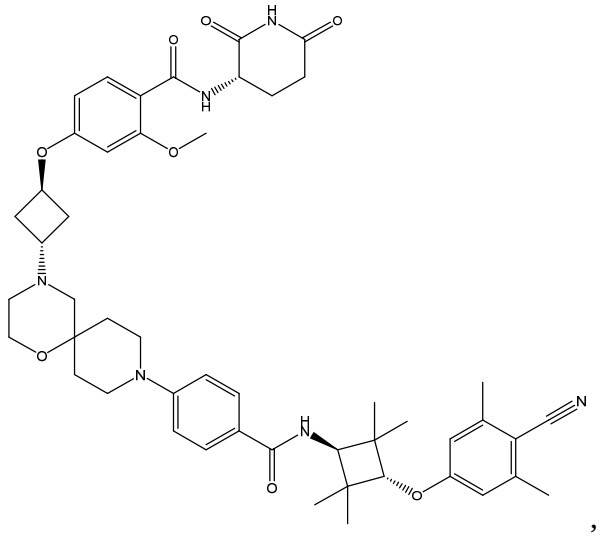
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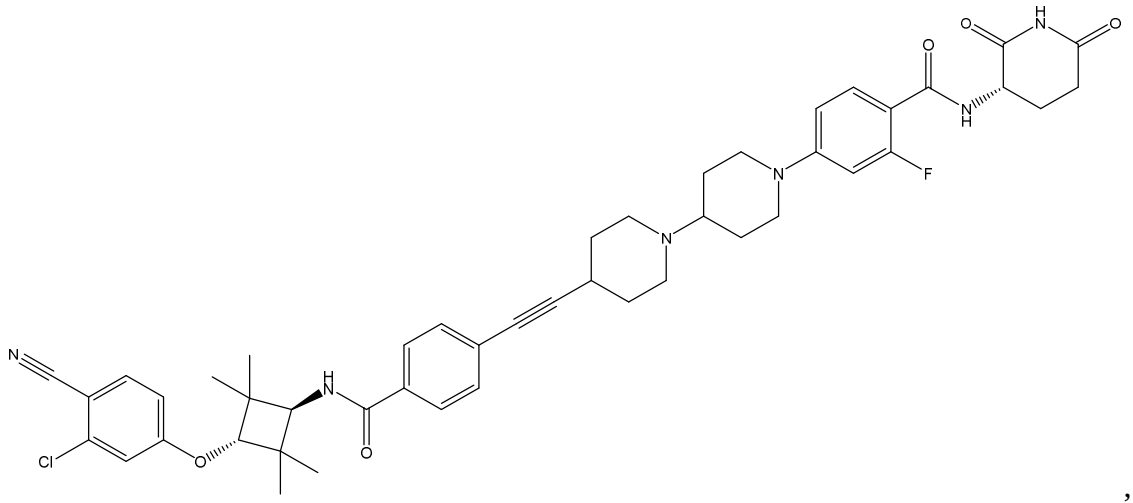
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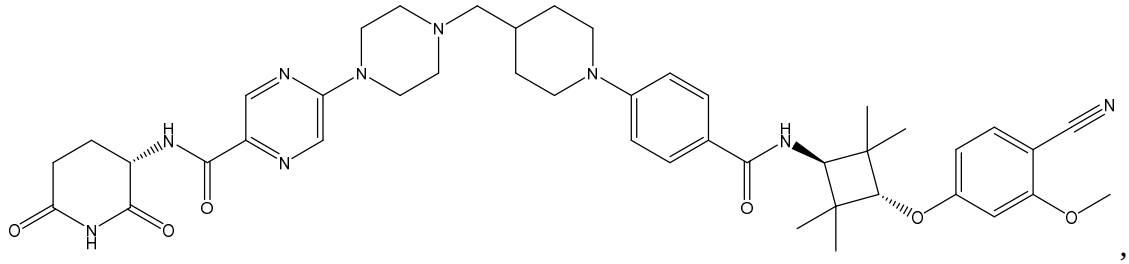
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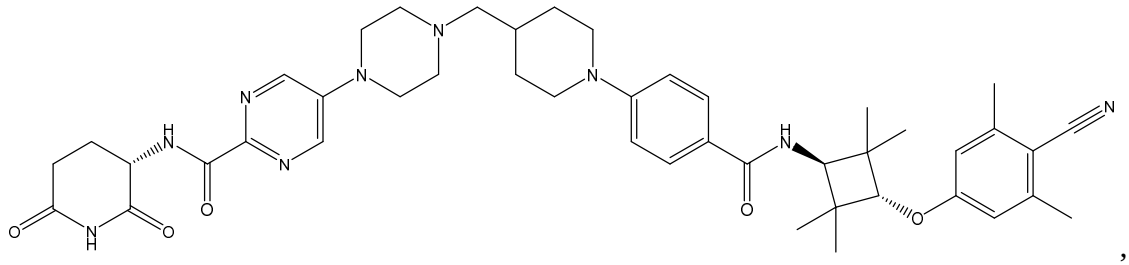
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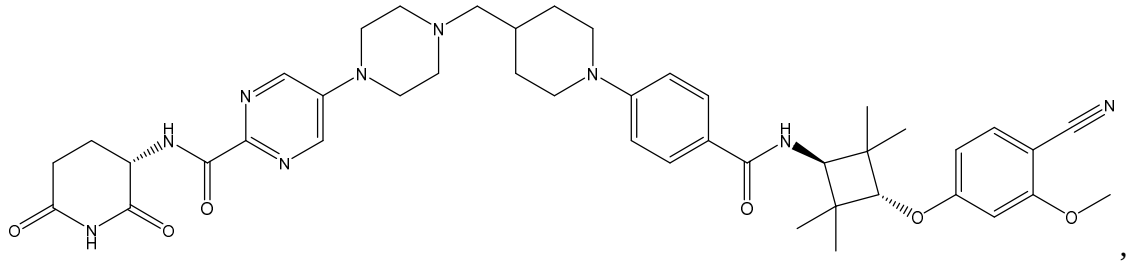
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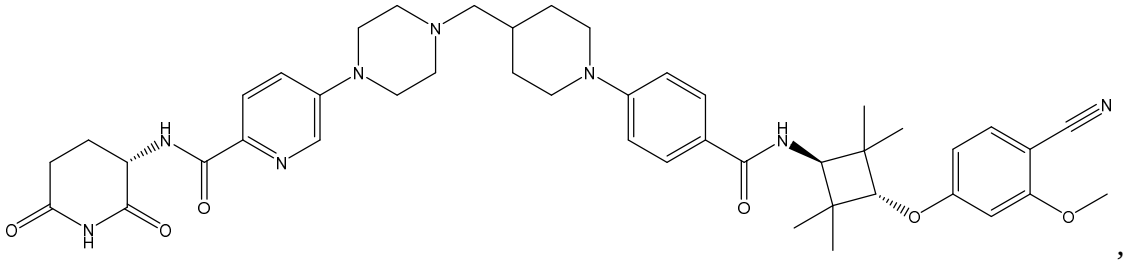
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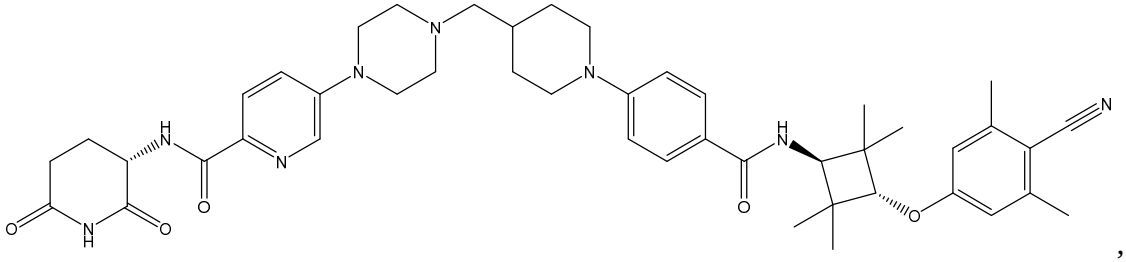
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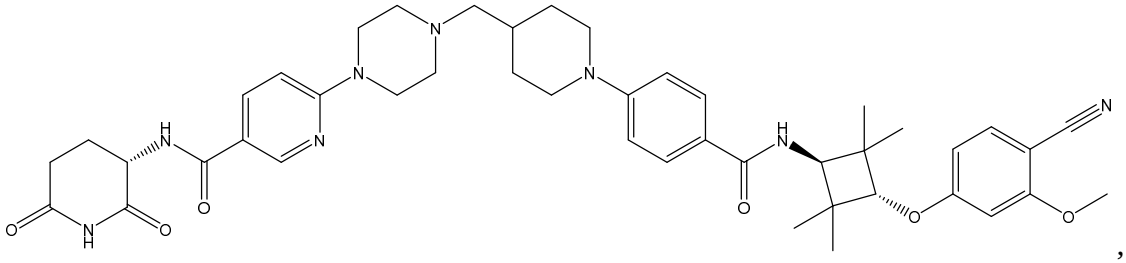
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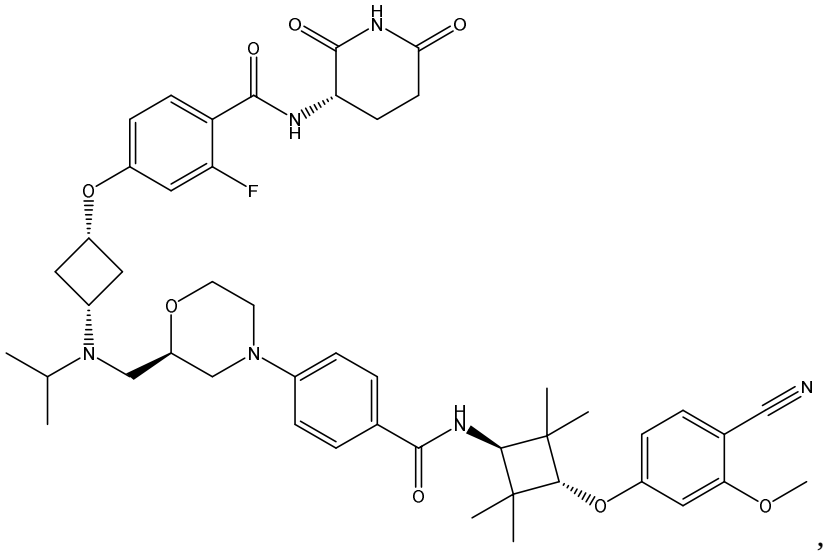
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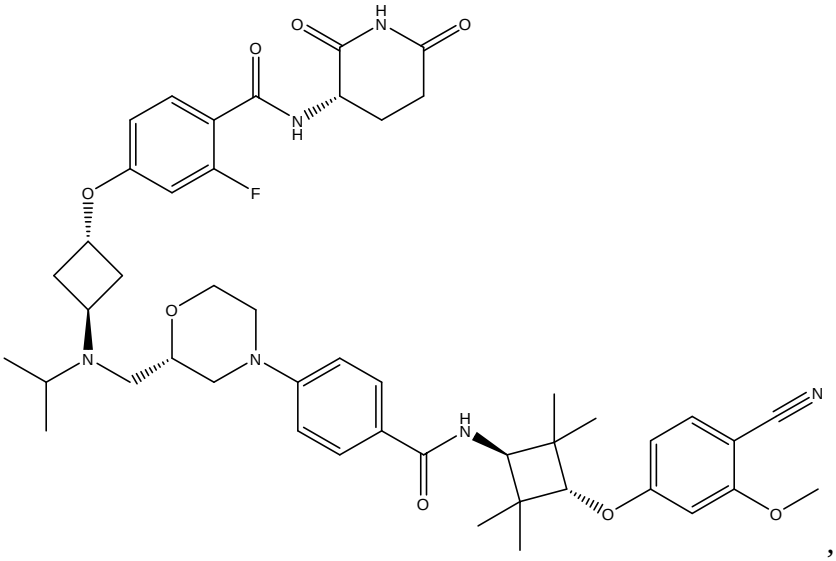
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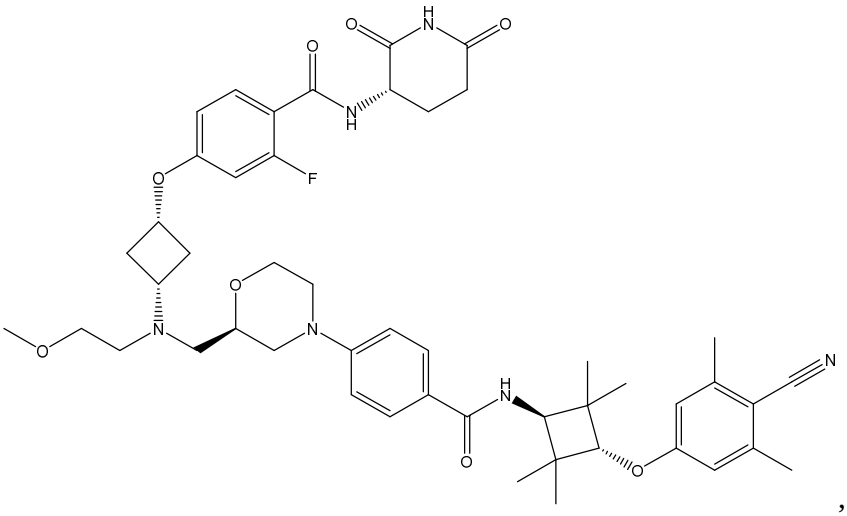
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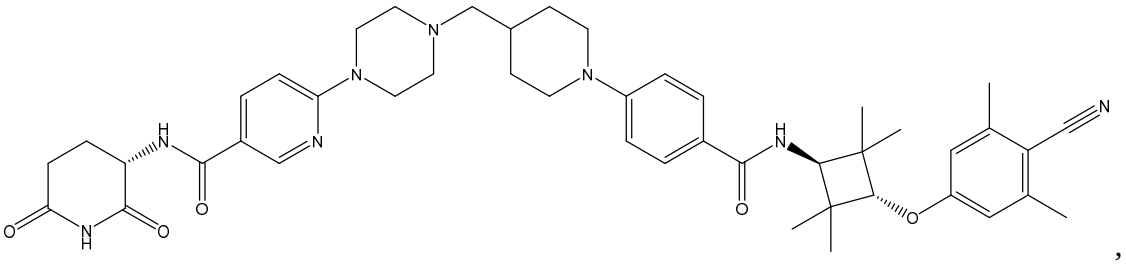
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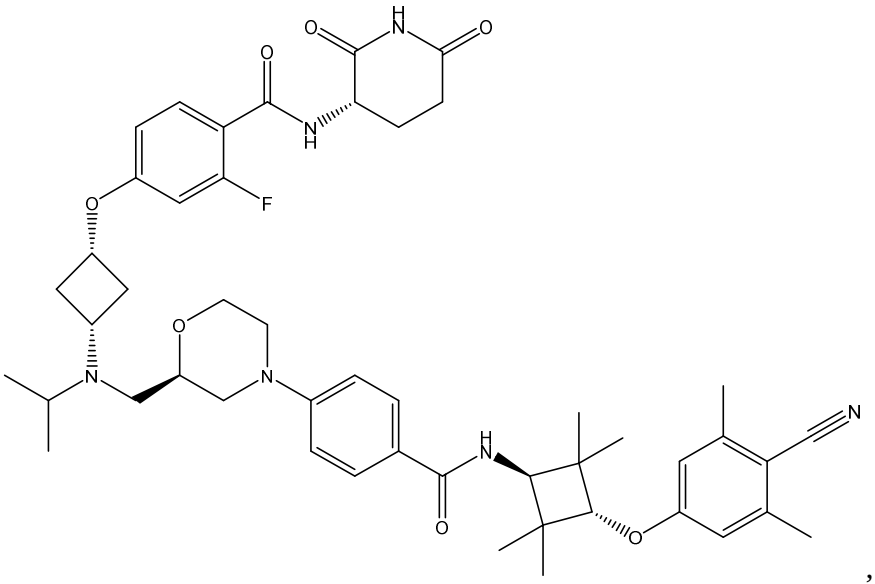
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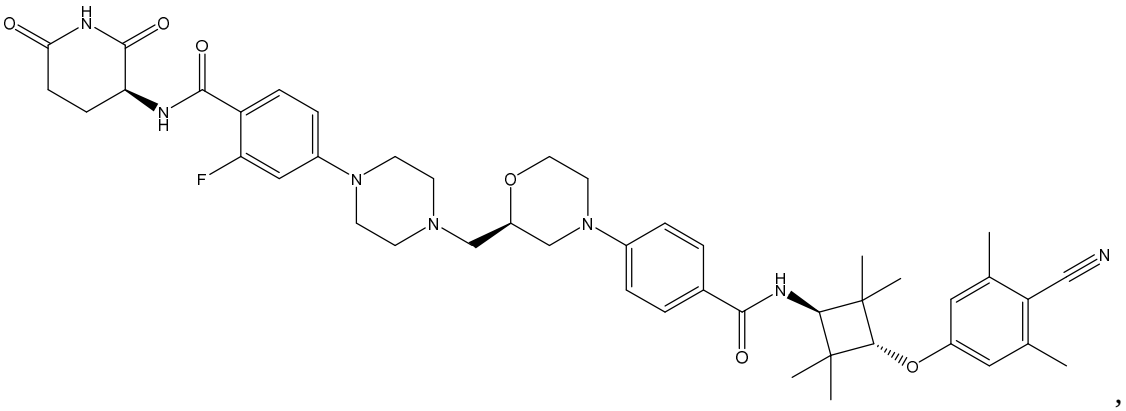
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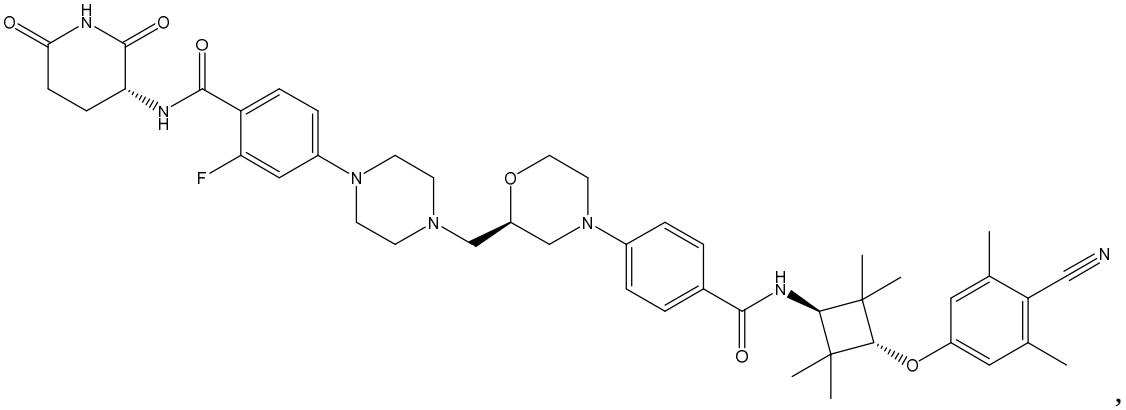
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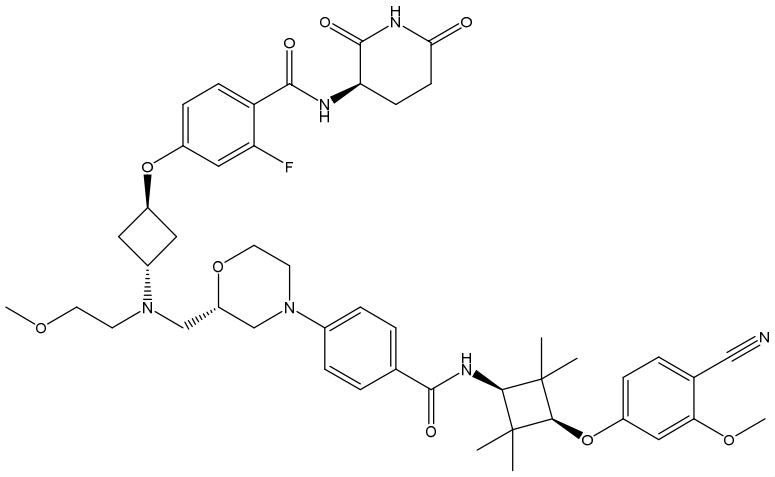
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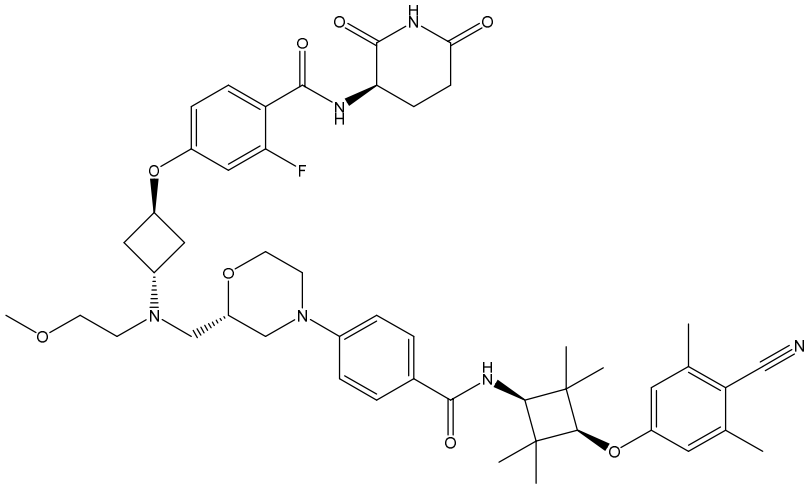
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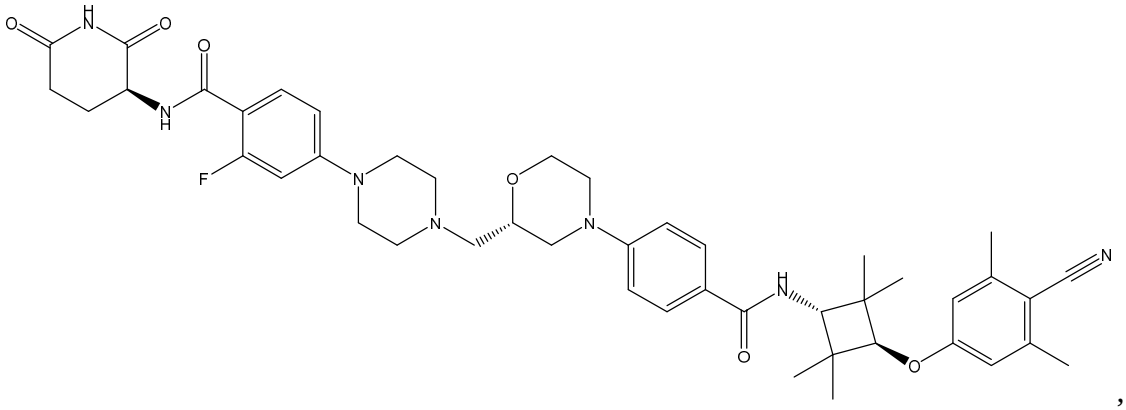
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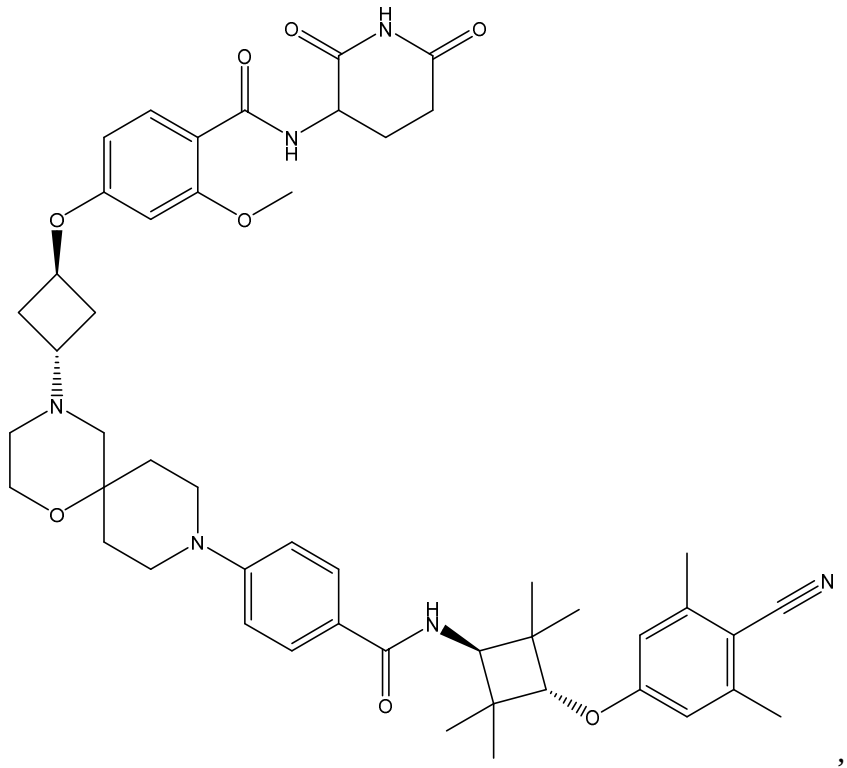
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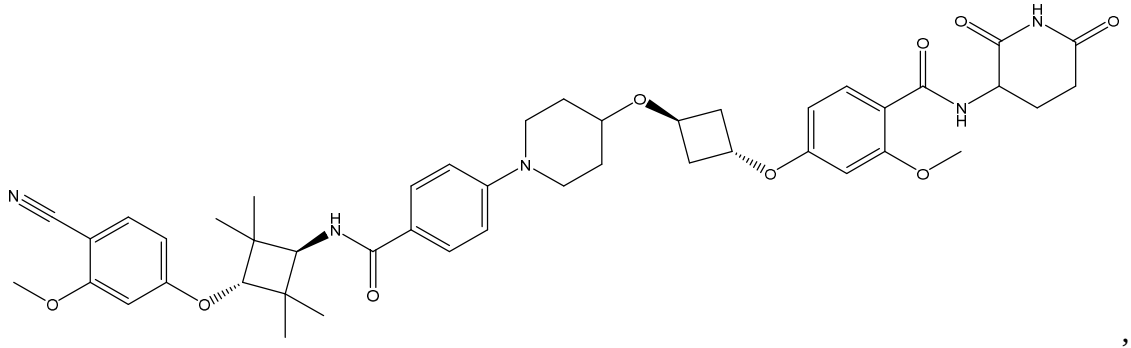
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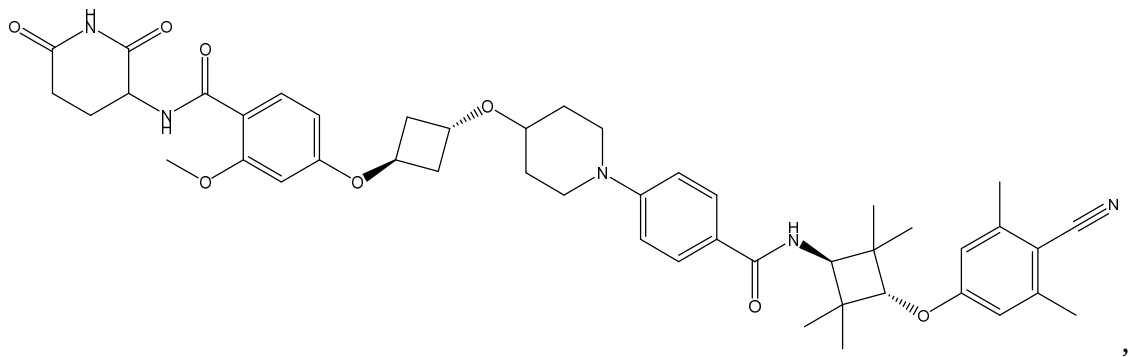
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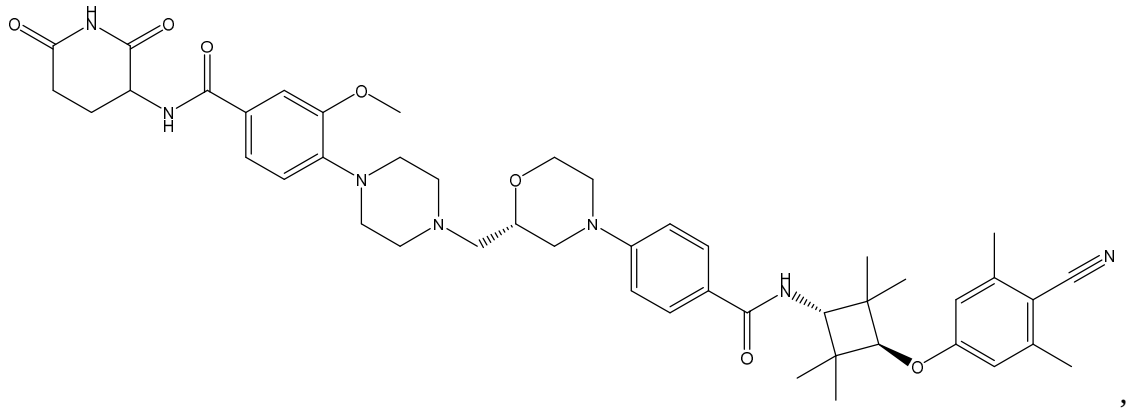
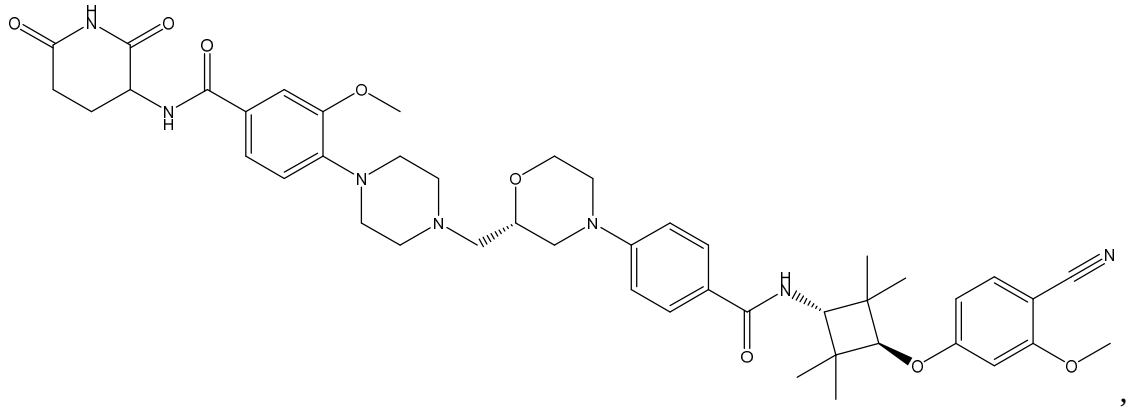
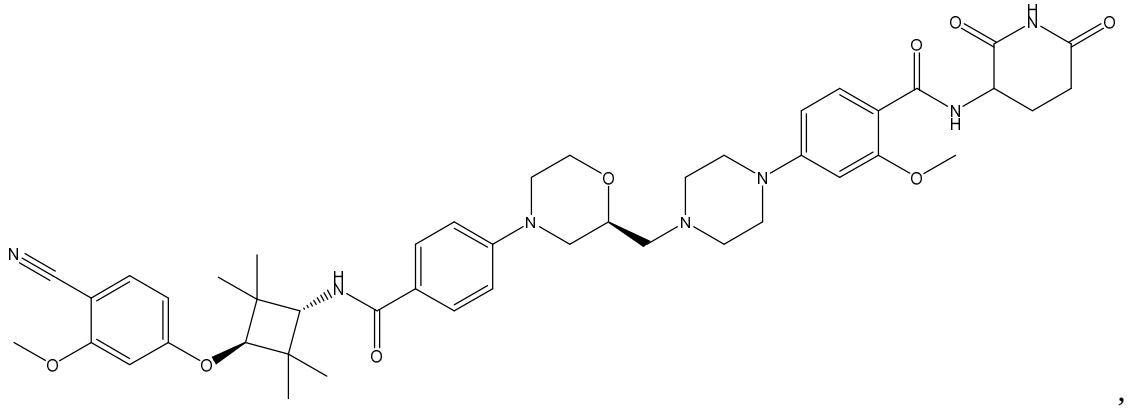
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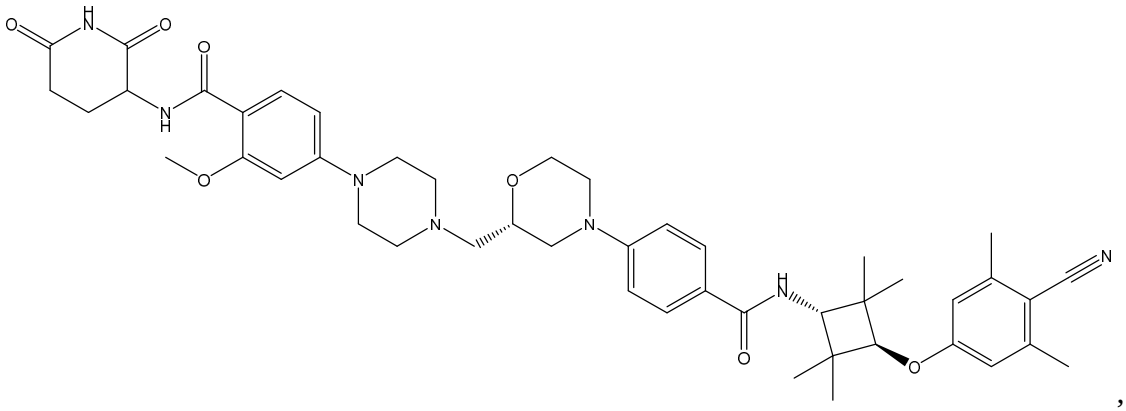


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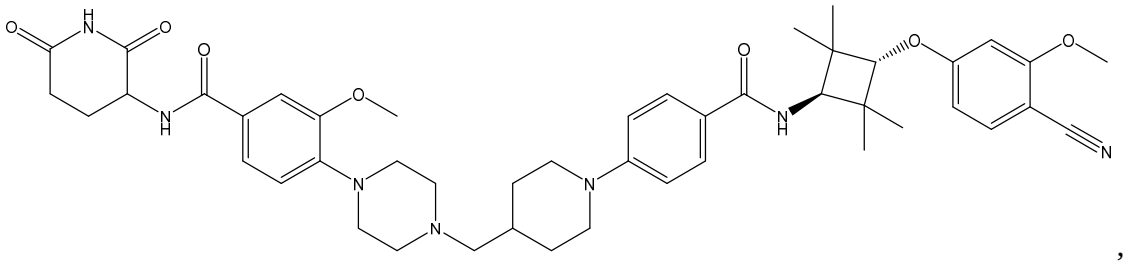


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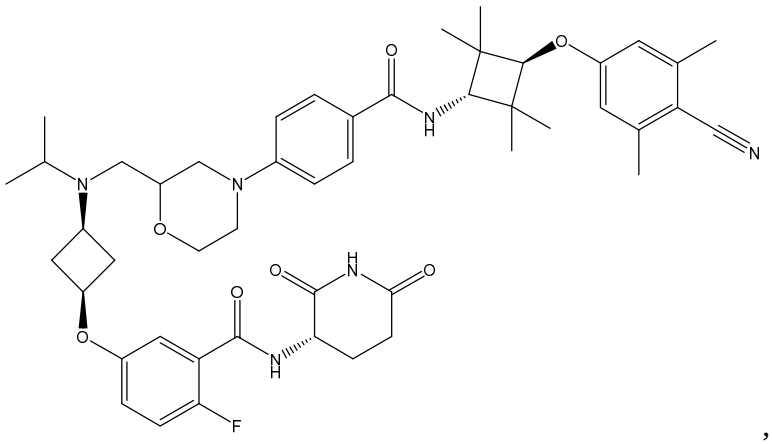

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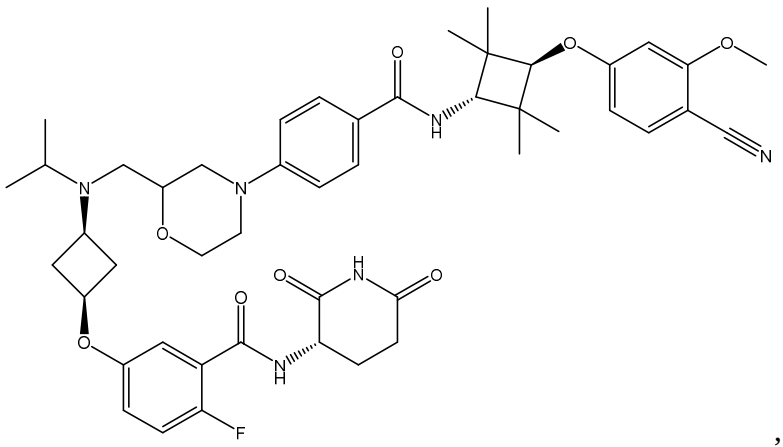
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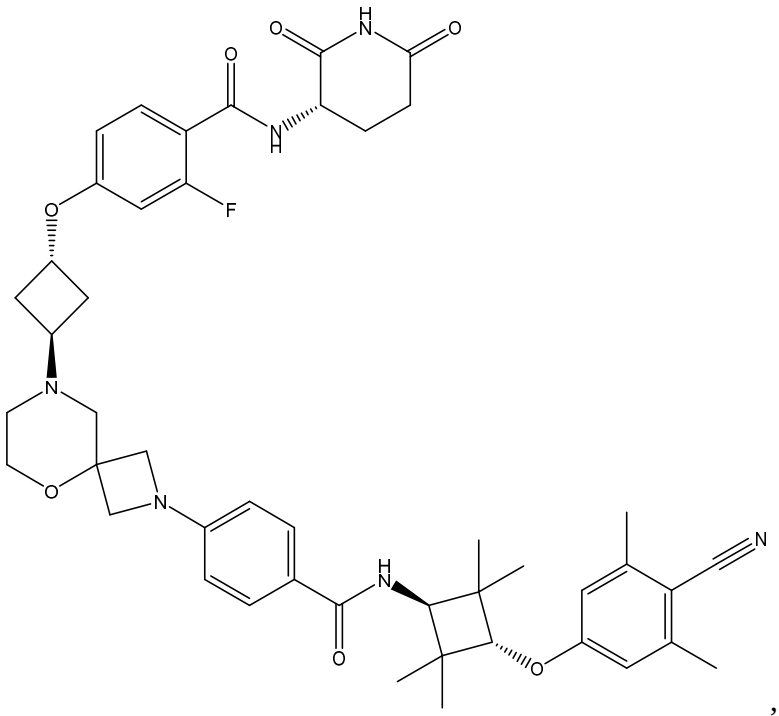
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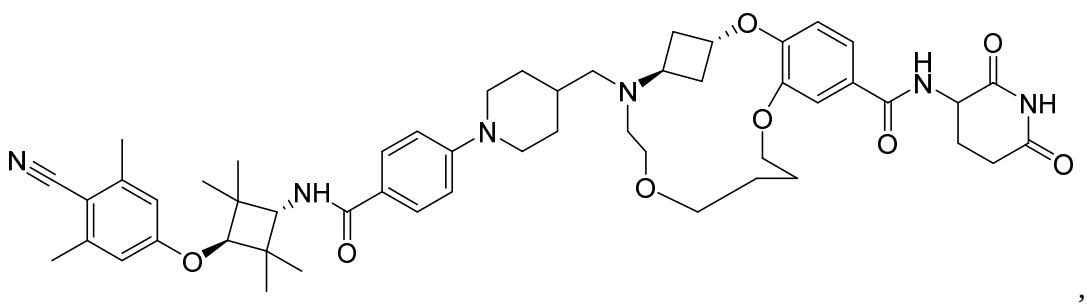
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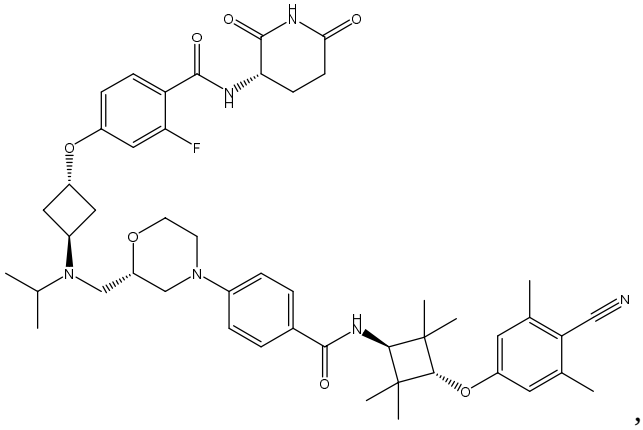
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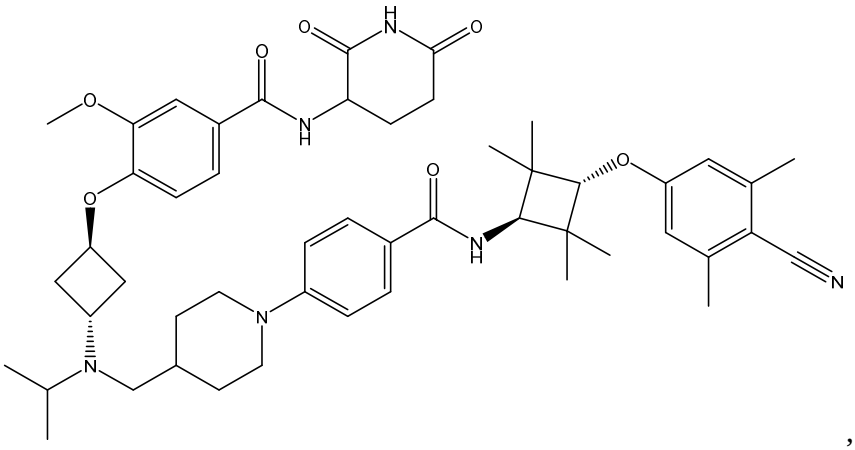
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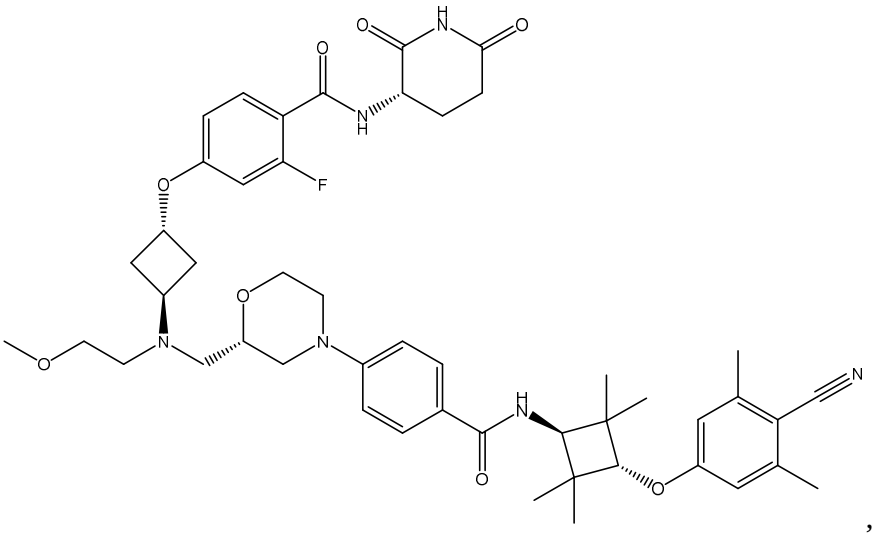
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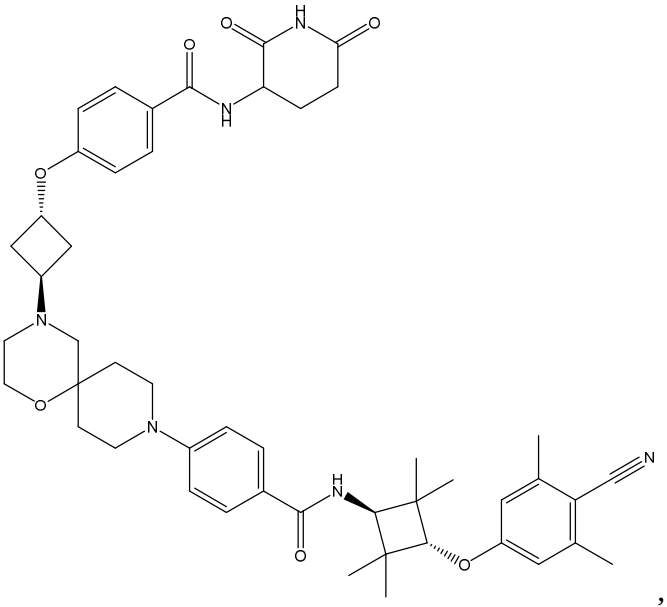
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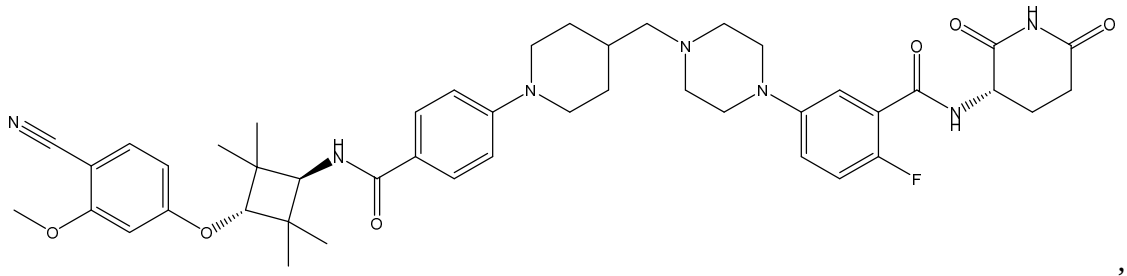
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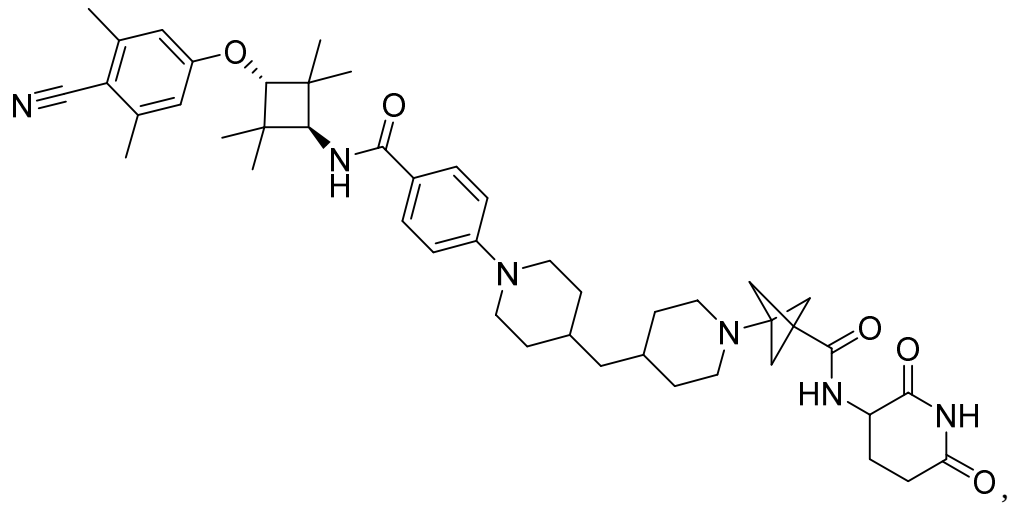
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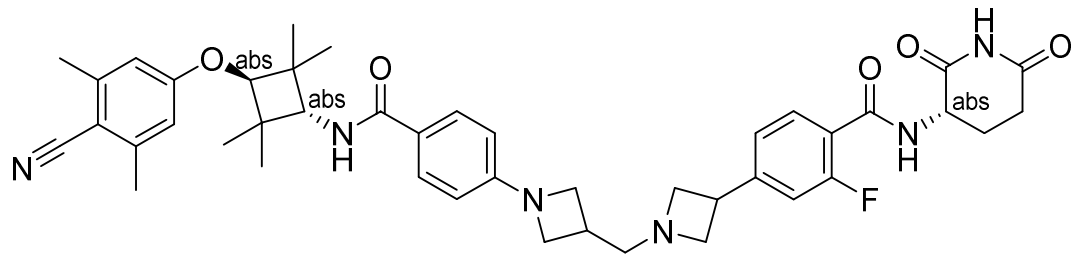
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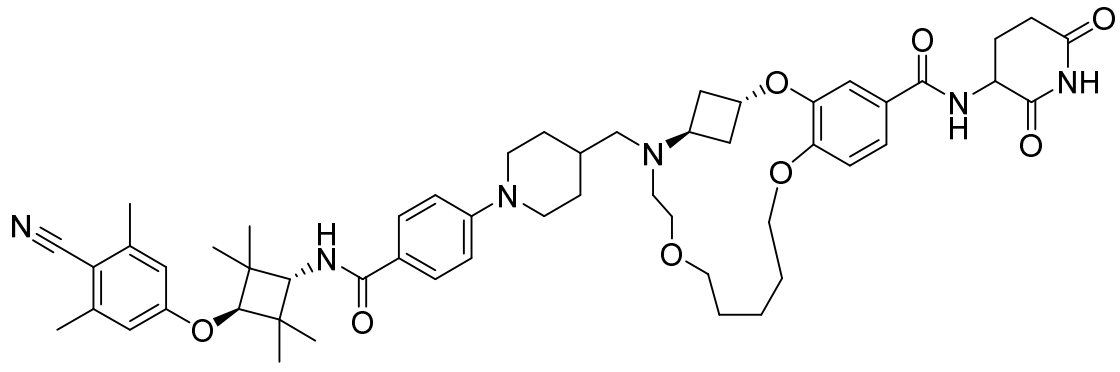
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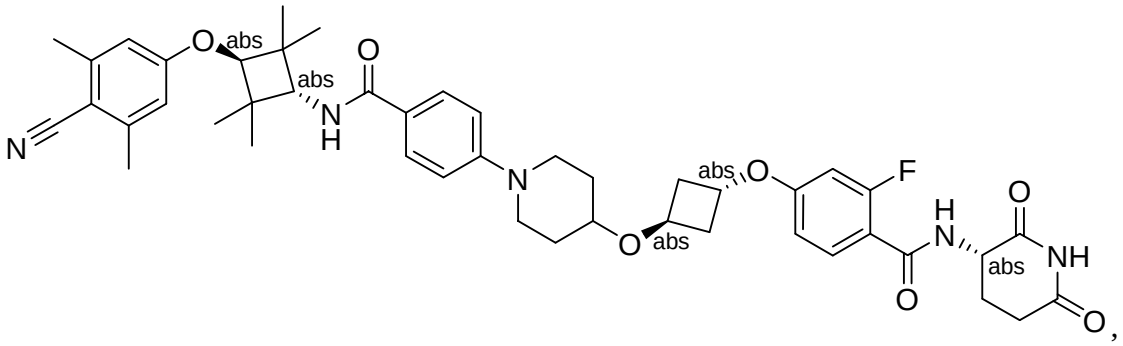
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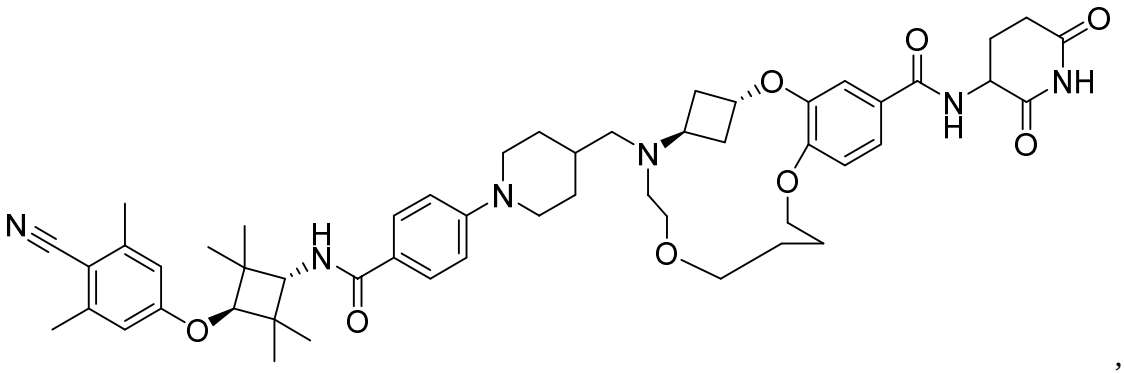
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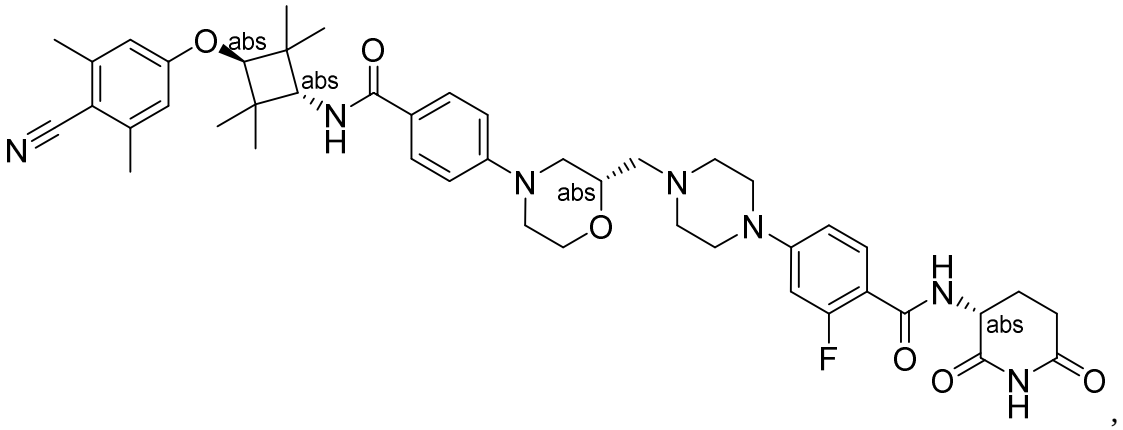
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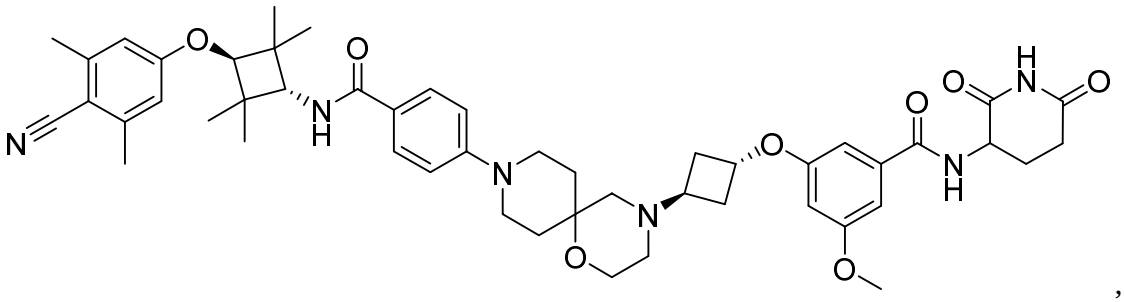
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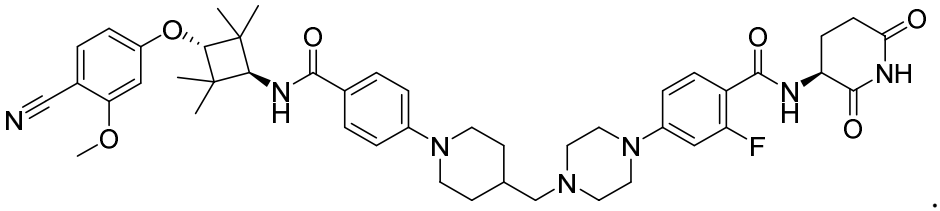


, or

a pharmaceutically acceptable salt thereof.

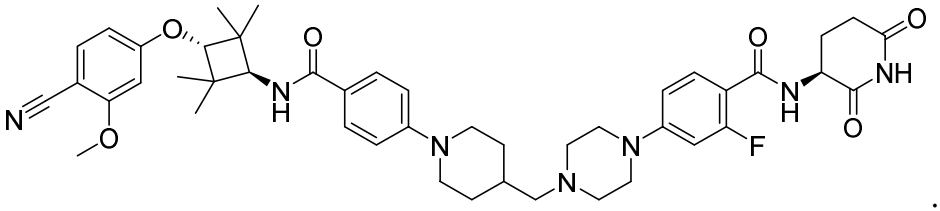
37. A pharmaceutical composition comprising the bifunctional compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

38. A bifunctional compound, wherein the compound is:



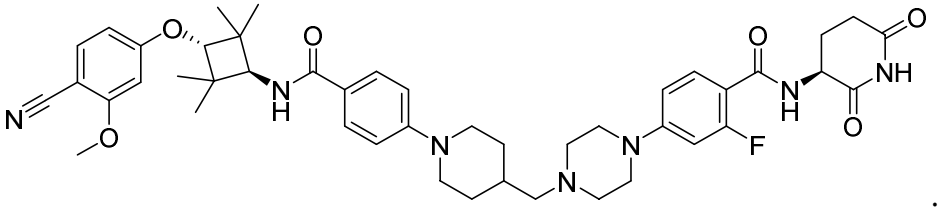
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39. A pharmaceutically acceptable salt of a bifunctional compound, wherein the compound is:



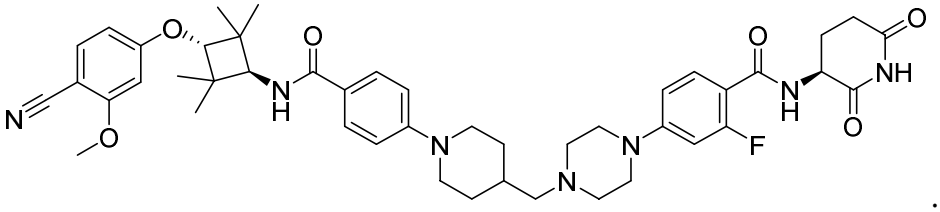
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40. A pharmaceutical composition comprising a bifunctional compound and one or more pharmaceutically acceptable excipients, wherein the compound is:



.

41. A pharmaceutical composition comprising a pharmaceutically acceptable salt of a bifunctional compound and one or more pharmaceutically acceptable excipients, wherein the compound is:



.

42. The pharmaceutical composition of any one of claims 37 and 40-41, wherein the composition is formulated as a tablet, and comprises one or more of the following: emulsifier; surfactant; binder; disintegrant; glidant; and lubricant.

43. The pharmaceutical composition of any one of claims 37 and 40-42, wherein the composition further comprises an effective amount of at least one additional anti-cancer agent.

44. The pharmaceutical composition of claim 43, wherein the additional anti-cancer agent is estramustine, docetaxel, ketoconazole, goserelin, histrelin, triptorelin, buserelin, cyproterone, flutamide, bicalutamide, nilutamide, pamidronate, or zolendronate.

45. The pharmaceutical composition of claim 43, wherein the additional anti-cancer agent is abiraterone acetate.

46. Use of a bifunctional compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 37 and 40-45, in the manufacture of a medicament for treating prostate cancer in a subject.

47. The use of claim 46, wherein a therapeutically effective amount of the bifunctional compound, or a pharmaceutically acceptable salt thereof, is to be administered orally to the subject.

48. The use of claim 46 or 47, 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.

49. The use of any one of claims 46-48, 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.

50. The use of any one of claims 46-49, 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.

51. The use of any one of claims 46-50, 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 1 mg to 1000 mg.

52. The use of any one of claims 46-51, 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 5 mg to 750 mg.

53. The use of any one of claims 46-52, 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 10 mg to 500 mg.

54. The use of any one of claims 46-53, 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 20 mg to 250 mg.

55. The use of any one of claims 46-54, 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.

56. The use of any one of claims 46-54, 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.

57. The use of any one of claims 46-56, 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.

58. The use of claim 57, wherein the additional anti-cancer agent is abiraterone, estramustine, docetaxel, ketoconazole, goserelin, histrelin, triptorelin, buserelin, cyproterone, flutamide, bicalutamide, nilutamide, pamidronate, or zolendronate.

59. The use of claim 57, wherein the additional anti-cancer agent is abiraterone acetate.

60. The use of any one of claims 46-59, where the subject with prostate cancer comprises at least one somatic AR tumor mutation.

61. The use of claim 60, wherein the at least one somatic AR tumor mutation is selected from the group consisting of L702H, M895V, M896V, T878A, F877L, and H875Y.

62. The use of any one of claims 46-61, wherein the prostate cancer is castrate-resistant prostate cancer.

63. The use of any one of claims 46-62, wherein the prostate cancer is metastatic castrate-resistant prostate cancer.

64. Use of a bifunctional compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 37 and 40-45, 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.

65. The use of claim 64, where the subject’s somatic AR tumor biomarker status comprises at least one somatic AR tumor mutation.

66. The use of claim 64, wherein the AR biomarker status of the subject is determined by ctDNA analysis, fluorescent in situ hybridization, immunohistochemistry, PCR analysis, or sequencing.

67. The use of claim 64, wherein the AR biomarker status of the subject is determined in a blood sample derived from the subject.

68. The use of claim 64, wherein the AR biomarker status of the subject is determined in a solid biopsy derived from the tumor of the subject.

69. The use of any one of claims 64-68, wherein the prostate cancer is castrate-resistant prostate cancer.

70. The use of any one of claims 64-69, wherein the prostate cancer is metastatic castrate-resistant prostate cancer.

71. The use of claim 65, wherein the at least one somatic AR tumor mutation is selected from the group consisting of L702H, M895V, M896V, T878A, F877L, and H875Y.

72. A bifunctional compound of any one of claims 1-36, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 37 and 40-45, for use in therapy.