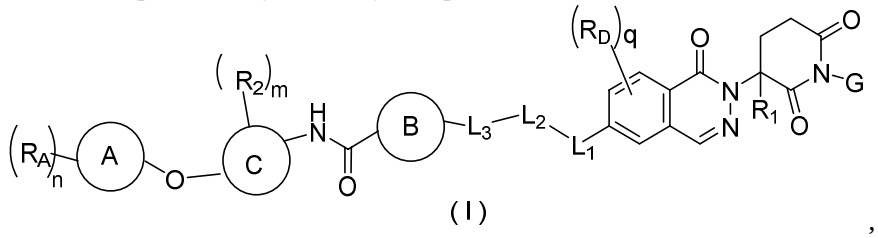
In a first aspect of the present disclosure, there is provided a compound as represented by formula (I), an optical isomer thereof, or a pharmacodynamically acceptable salt thereof,



(I)

,

wherein

R_1 is H;

G is H;

ring B is selected from phenyl and 6-membered heteroaryl, and the phenyl or 6-membered heteroaryl is optionally substituted with 1, 2 or 3 R;

ring C is C_{4-6} cycloalkyl;

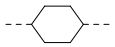
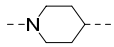
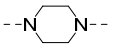
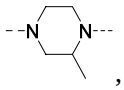
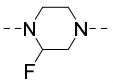
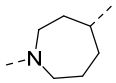
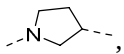
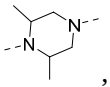
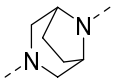
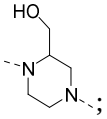
each R_2 is independently selected from H and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with 1, 2 or 3 R;

ring A is 6- to 12-membered aryl;

each R_A is independently selected from H, halogen, and CN;

each R_D is independently selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl and 3- to 6-membered heterocycloalkyl, and the C_{1-6} alkyl, or C_{1-6} alkoxy, C_{3-6} cycloalkyl or 3- to 6-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R;

each R is independently selected from H, F, Cl, Br, I, OH, NH_2 and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with 1, 2 or 3 R';

L_1 and L_3 are each independently selected from , , , , , , , , ,  and ;

L_2 is selected from CH_2 and ;

each R' is independently selected from H, halogen, C_{1-6} alkyl, OH, NH_2, , , CH_2F, CHF_2 and CF_3;

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

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

q is 1, 2, 3 or 4; and

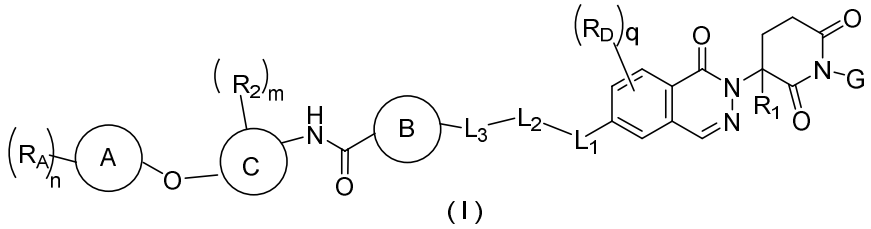
the 6-membered heteroaryl comprises 1, 2 or 3 heteroatoms or heteroatom groups independently selected from NH and N.

In another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

In yet another aspect of the present disclosure, there is provided a use of the compound as disclosed herein, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, in the manufacture of a medicament for prophylaxis and/or treatment of Kennedy's disease.

In a further aspect of the present disclosure, there is provided the compound as disclosed herein, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, for use in therapy.

In an example of the present disclosure, the present disclosure proposes a compound as represented by formula (I), an optical isomer thereof and a pharmacodynamically acceptable salt thereof,



(I)

,

wherein R_1 is selected from H, F, Cl, Br, I and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with 1, 2 or 3 R;

G is selected from H, F, Cl, Br, I and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with 1, 2 or 3 R;

ring B is selected from phenyl and 5- to 6-membered heteroaryl, and the phenyl or 5- to 6-membered heteroaryl is optionally substituted with 1, 2 or 3 R;

ring C is selected from C_{4-6} cycloalkyl;

R_2 is selected from H and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with 1, 2 or 3 R;

ring A is selected from 6- to 12-membered aryl and 5- to 12-membered heteroaryl;

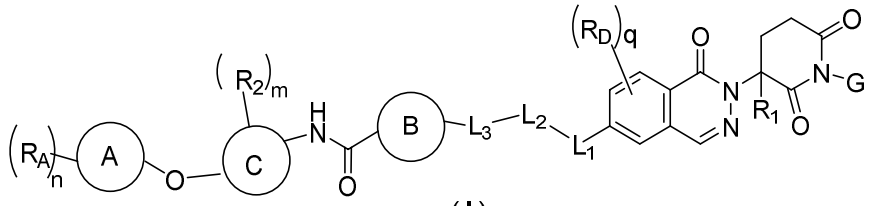
R_A is selected from H, NO_2, halogen, NH_2, CN, C_{1-6} alkyl and C_{1-6} alkoxy, and the C_{1-6} alkyl or C_{1-6} alkoxy is optionally substituted with 1, 2 or 3 R;

R_D is selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl and 3- to 6-membered heterocycloalkyl, and the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl or 3- to 6-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R;

R is independently selected from H, F, Cl, Br, I, OH, NH_2 and C_{1-6} alkyl respectively, and the C_{1-6} alkyl is optionally substituted with 1, 2 or 3 R';

CLAIMS

1. A compound as represented by formula (I), an optical isomer thereof, or a pharmacodynamically acceptable salt thereof,



(I)

,

wherein

R_1 is H;

G is H;

ring B is selected from phenyl and 6-membered heteroaryl, and the phenyl or 6-membered heteroaryl is optionally substituted with 1, 2 or 3 R;

ring C is C_{4-6} cycloalkyl;

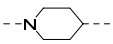
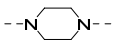
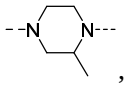
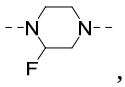
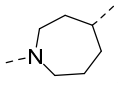
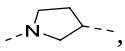
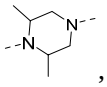
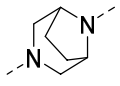
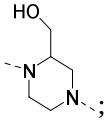
each R_2 is independently selected from H and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with 1, 2 or 3 R;

ring A is 6- to 12-membered aryl;

each R_A is independently selected from H, halogen, and CN;

each R_D is independently selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl and 3- to 6-membered heterocycloalkyl, and the C_{1-6} alkyl, or C_{1-6} alkoxy, C_{3-6} cycloalkyl or 3- to 6-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R;

each R is independently selected from H, F, Cl, Br, I, OH, NH_2 and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with 1, 2 or 3 R';

L_1 and L_3 are each independently selected from , , , , , , , , ,  and ;

L_2 is selected from CH_2 and ;

each R' is independently selected from H, halogen, C_{1-6} alkyl, OH, NH_2, , , CH_2F, CHF_2 and CF_3;

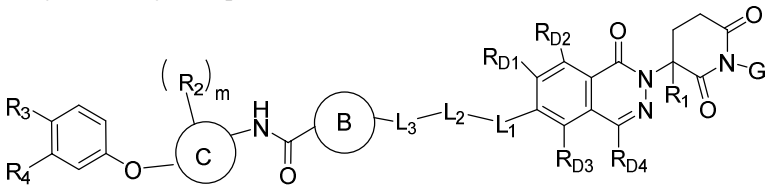
n is 0, 1, 2, 3 or 4;

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

q is 1, 2, 3 or 4; and

the 6-membered heteroaryl comprises 1, 2 or 3 heteroatoms or heteroatom groups independently selected from NH and N.

2. The compound of claim 1, wherein the compound is represented by formula (I-A), an optical isomer thereof, or a pharmacodynamically acceptable salt thereof,



(I-A) ,

wherein

R_1 is H;

G is H;

ring B is selected from phenyl and 6-membered heteroaryl, and the phenyl or 6-membered heteroaryl is optionally substituted with 1, 2 or 3 R;

ring C is selected from C_{4-6} cycloalkyl;

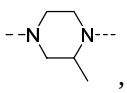
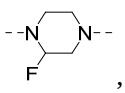
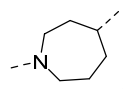
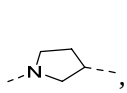
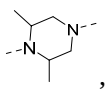
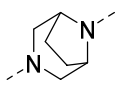
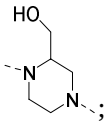
each R_2 is independently selected from H and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with 1, 2 or 3 R;

R_3 and R_4 are each independently selected from H, halogen, and CN;

R_{D1}, R_{D2} and R_{D3} are each independently selected from H, CN, halogen, C_{1-6} alkyl and C_{1-6} alkoxy, and the C_{1-6} alkyl or C_{1-6} alkoxy is optionally substituted with 1, 2 or 3 R;

R_{D4} is independently selected from H, CN, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl and 3- to 6-membered heterocycloalkyl, and the C_{1-6} alkyl, C_{3-6} cycloalkyl or 3- to 6-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R;

each R is independently selected from H, F, Cl, Br, I, OH, NH_2 and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with 1, 2 or 3 R';

L_1 and L_3 are each independently selected from , , , , , , , , ,  and ;

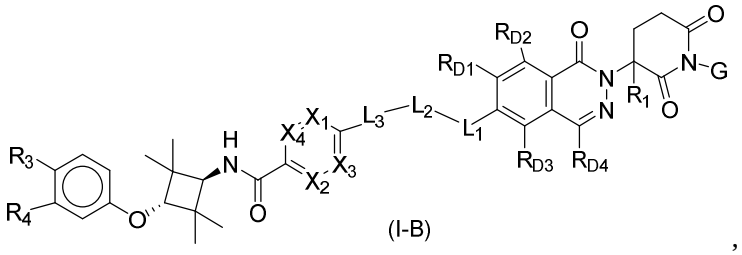
L_2 is selected from CH_2 and ;

each R' is independently selected from H, halogen, C_{1-6} alkyl, OH, NH_2, , , CH_2F, CHF_2 and CF_3;

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

the 6-membered heteroaryl comprises 1, 2 or 3 heteroatoms or heteroatom groups independently selected from NH and N.

3. The compound of claim 2, wherein the compound is represented by formula (I-B), an optical isomer thereof, or a pharmacodynamically acceptable salt thereof,



,

wherein

R_1 is H;

G is H;

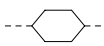
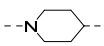
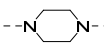
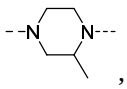
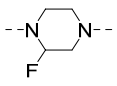
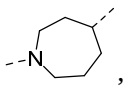
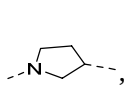
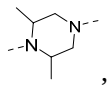
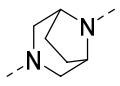
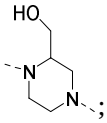
R_3 and R_4 are each independently selected from H halogen, and CN;

X_1, X_2, X_3 and X_4 are each independently selected from C(R) and N;

R_{D1}, R_{D2} and R_{D3} are each independently selected from H, CN, halogen, C_{1-6} alkyl and C_{1-6} alkoxy, and the C_{1-6} alkyl or C_{1-6} alkoxy is optionally substituted with 1, 2 or 3 R;

R_{D4} is independently selected from H, CN, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy, C_{3-6} cycloalkyl and 3- to 6-membered heterocycloalkyl, and the C_{1-6} alkyl, C_{3-6} cycloalkyl or 3- to 6-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R;

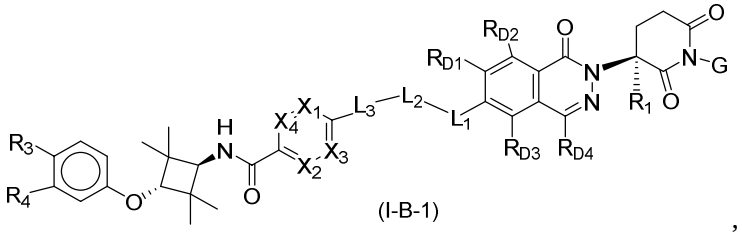
each R is independently selected from H, F, Cl, Br, I, OH, NH_2 and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with 1, 2 or 3 R';

L_1 and L_3 are each independently selected from , , , , , , , , ,  and ;

L_2 is selected from CH_2 and ;

each R' is independently selected from H, halogen, C_{1-6} alkyl, OH, NH_2, , , CH_2F, CHF_2 and CF_3.

4. The compound of claim 3, wherein the compound is represented by formula (I-B-1) or formula (I-B-2), an optical isomer thereof, or a pharmacodynamically acceptable salt thereof,



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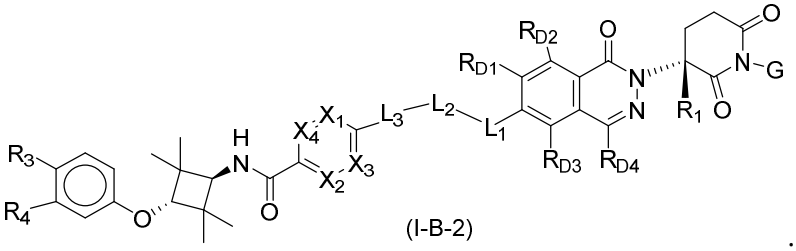


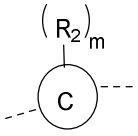
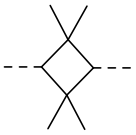
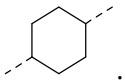
.

5. The compound according to claim 1, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, wherein ring A is phenyl.

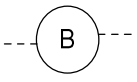
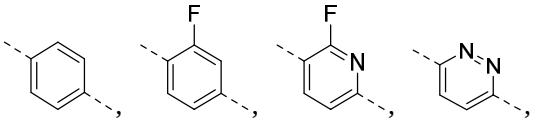
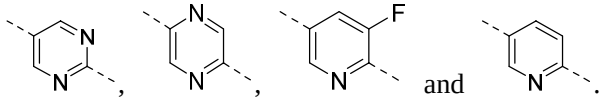
6. The compound according to claim 2, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, wherein each R_3 and R_4 is independently selected from H, F, Cl, Br, I, and CN.

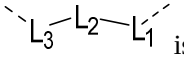
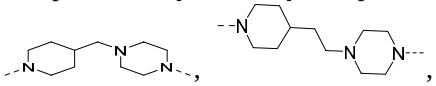
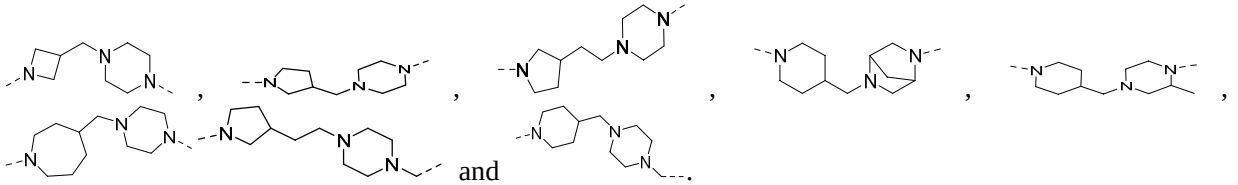
7. The compound according to claim 1, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, wherein each R_2 is independently selected from H, methyl, and ethyl.

8. The compound according to claim 1, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, wherein ring C is selected from cyclobutyl and cyclohexanyl.

9. The compound according to claim 1, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, wherein  is selected from  and .

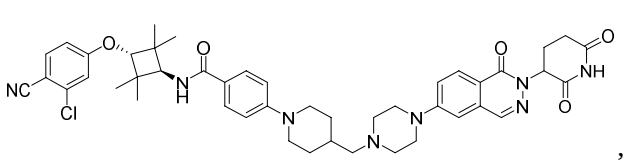
10. The compound according to claim 1, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, wherein ring B is selected from phenyl, pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl, and the phenyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl is optionally substituted with 1, 2 or 3 R.

11. The compound according to claim 1, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, wherein  is selected from   and .

12. The compound according to claim 1, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, wherein the structural unit  is selected from   and .

13. The compound according to claim 2, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, wherein R_{D4} is independently selected from H, CN, F, Cl, Br, I, CF_3, CH_3, CH_2CH_3 and cyclopropyl.

14. The compound according to claim 1, or the pharmacodynamically acceptable salt thereof, having the formula: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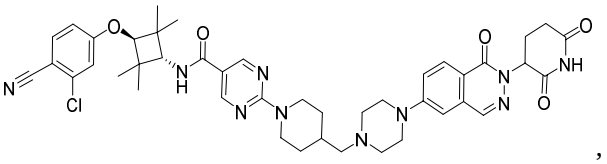
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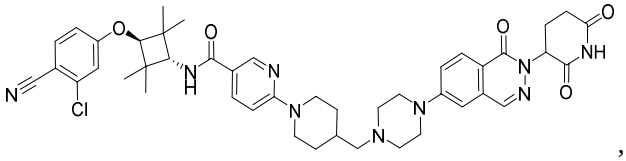
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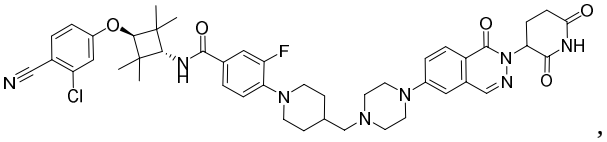
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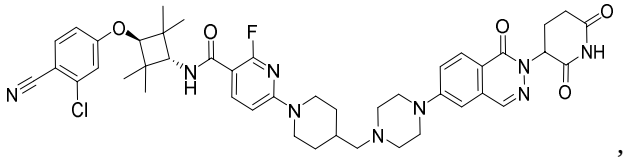
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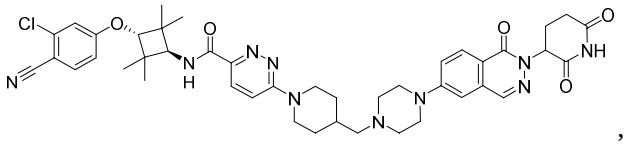
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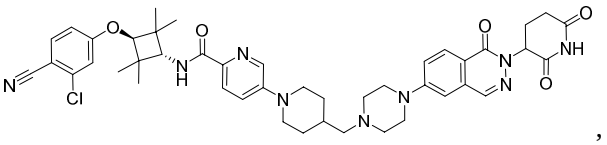
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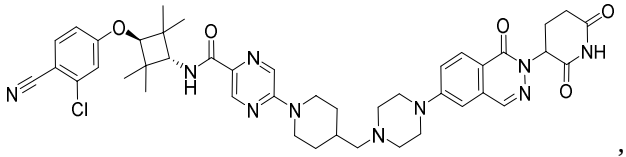
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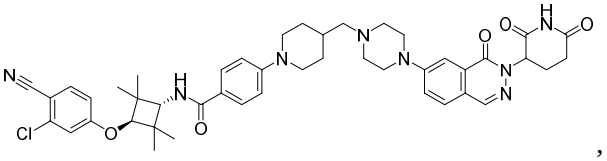
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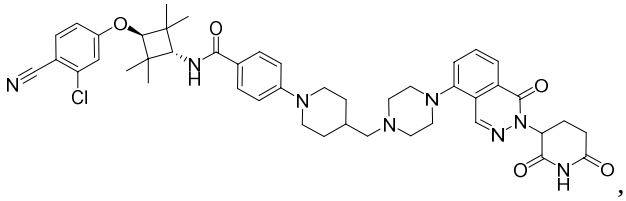
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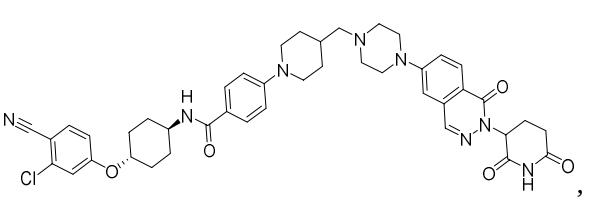
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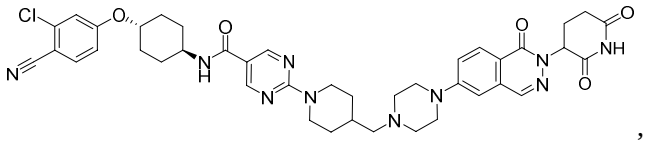
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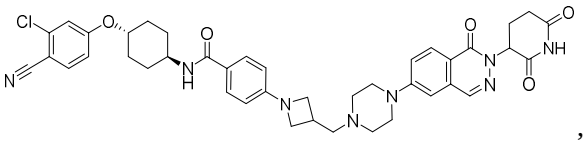
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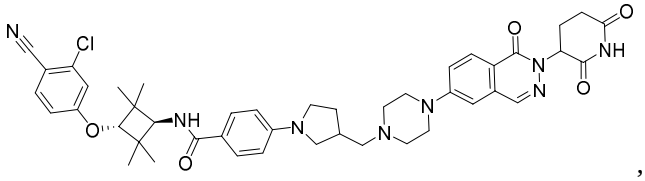
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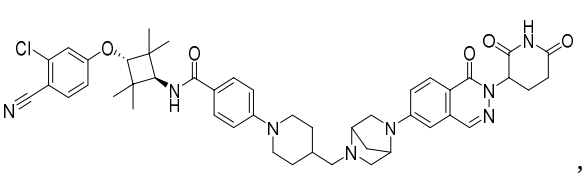
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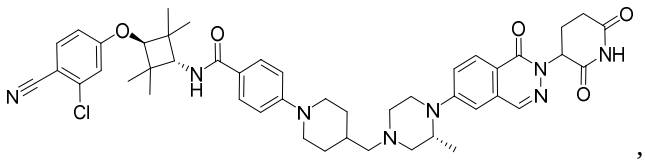
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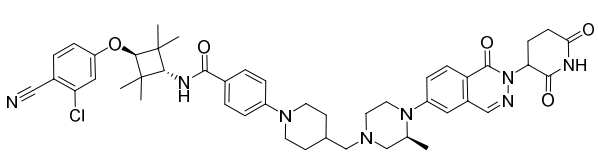
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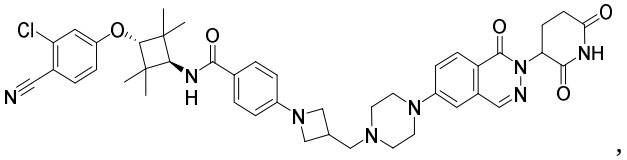
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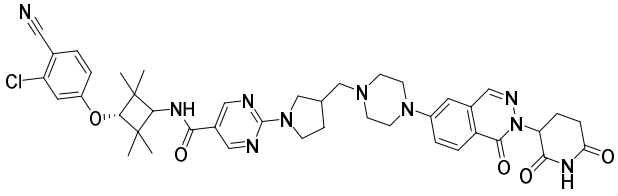
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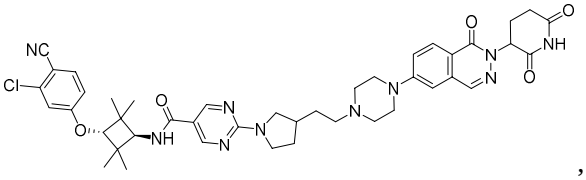
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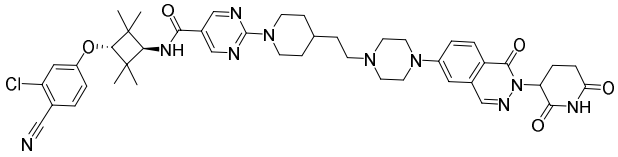
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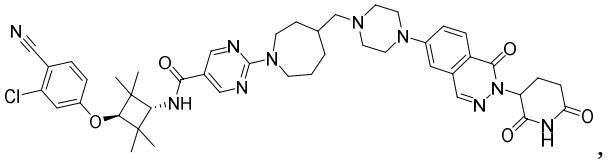
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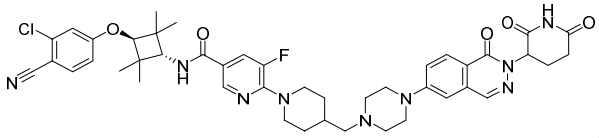
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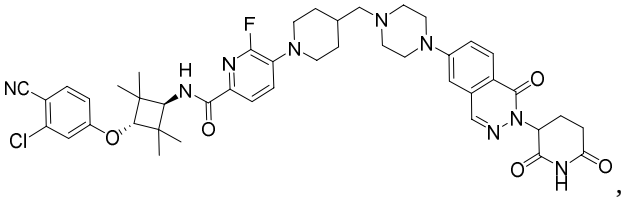
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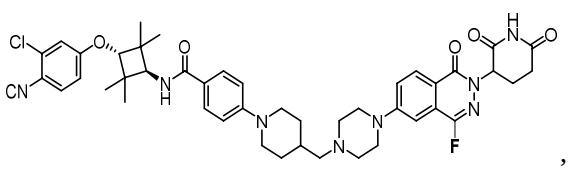
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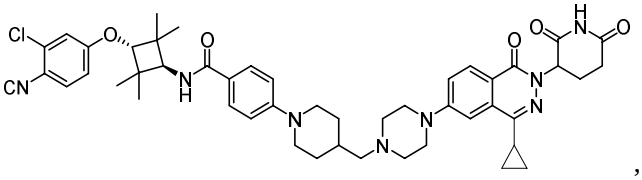
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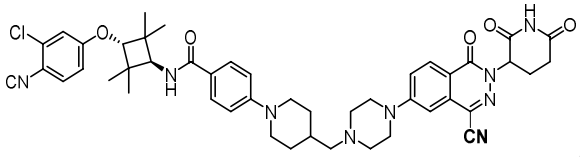
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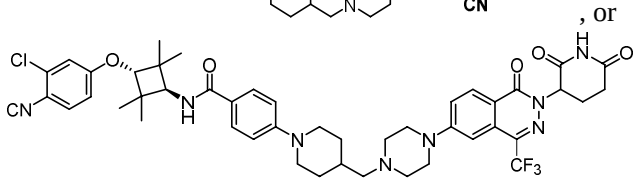
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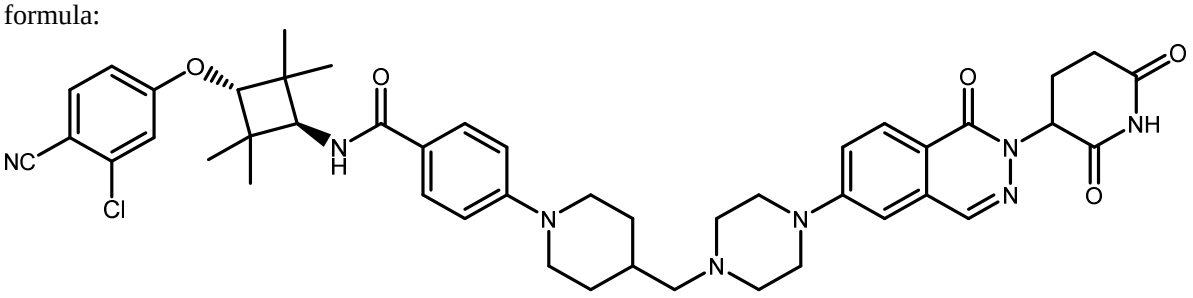
15. The compound according to claim 14, or the pharmacodynamically acceptable salt thereof, having the formula: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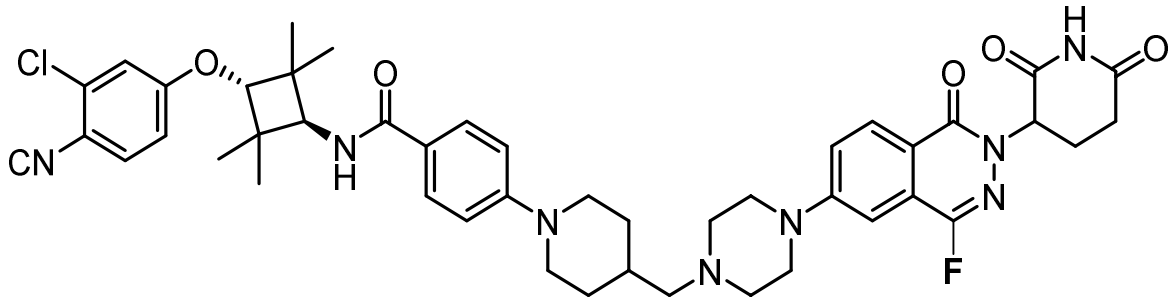
16. The compound according to claim 14, or the pharmacodynamically acceptable salt thereof, having the formula:



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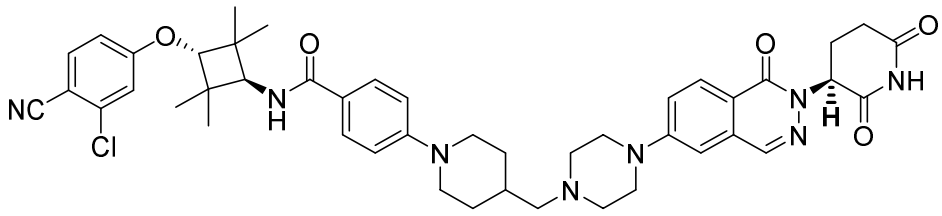
17. The compound according to claim 1, or the pharmacodynamically acceptable salt thereof, having the formula:



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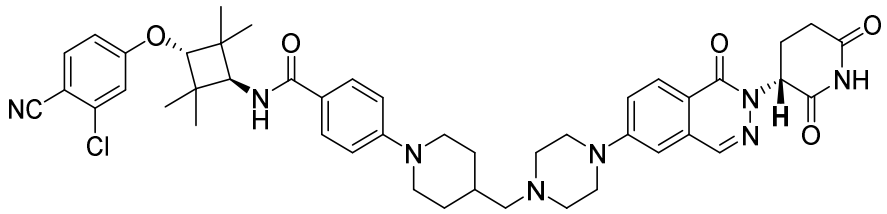

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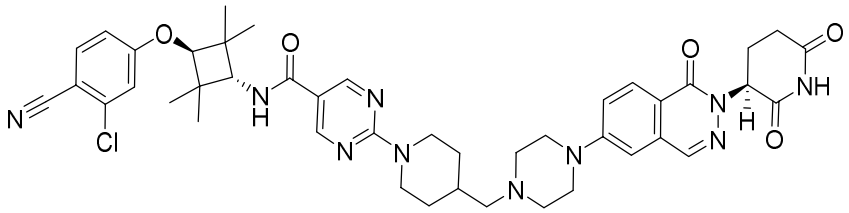

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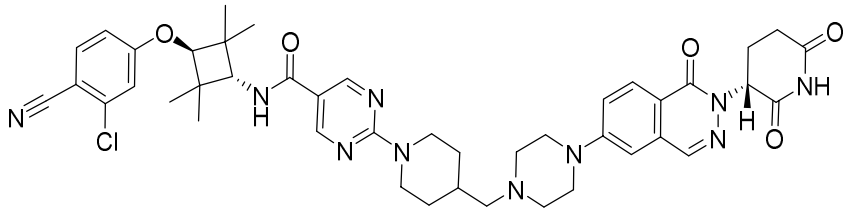

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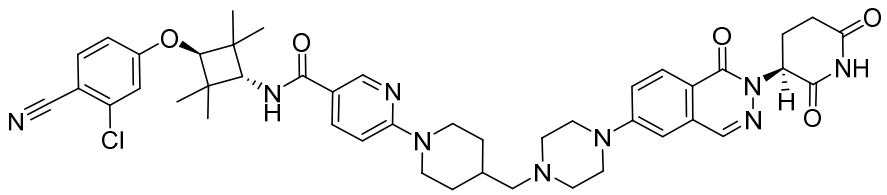

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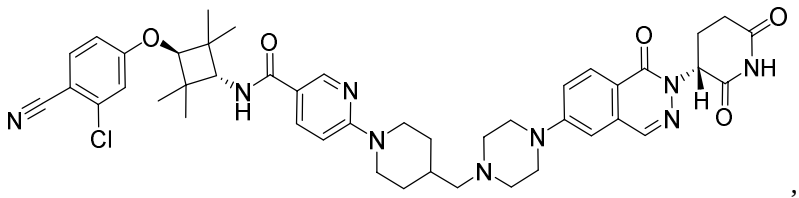

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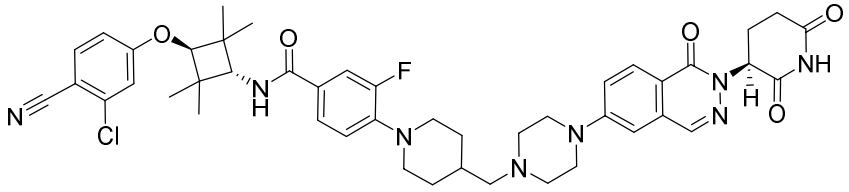

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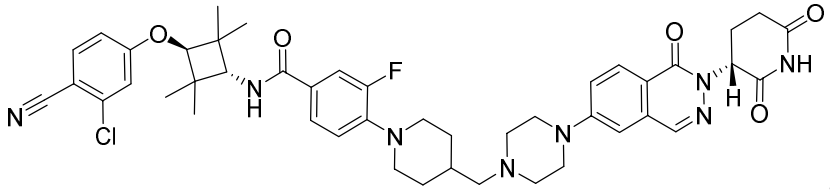

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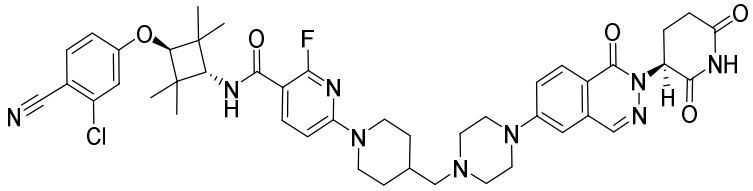

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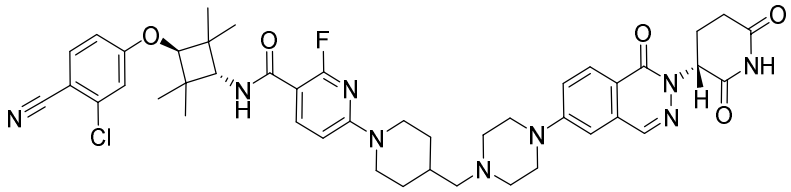

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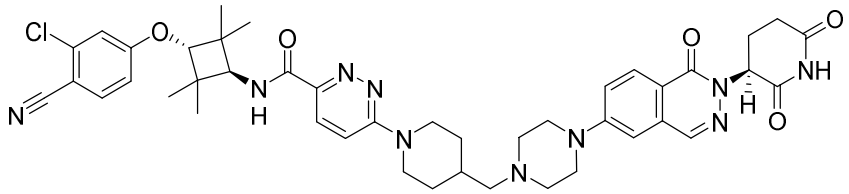

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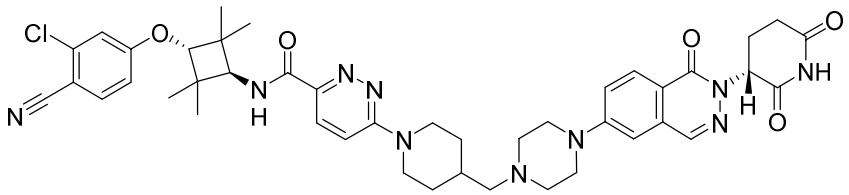

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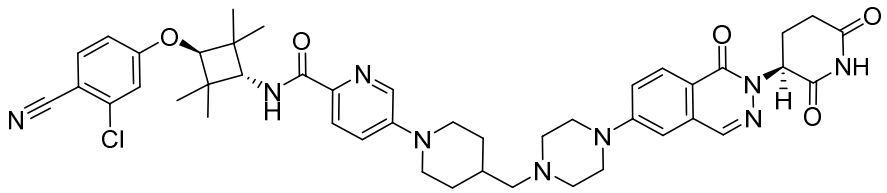

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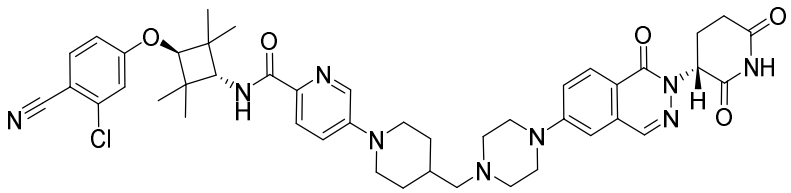

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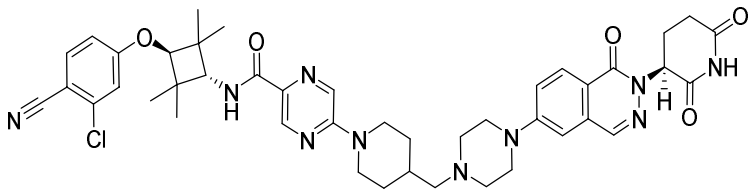

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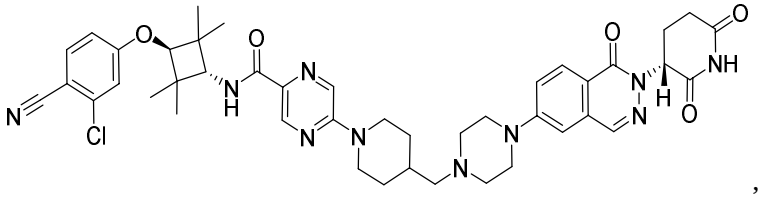

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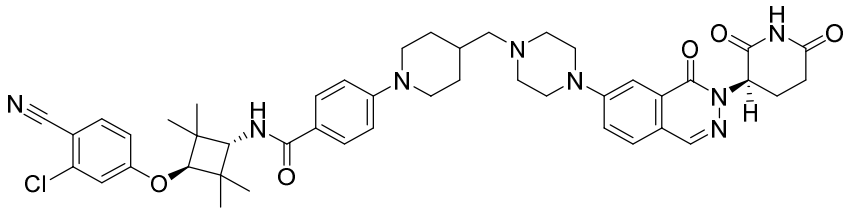

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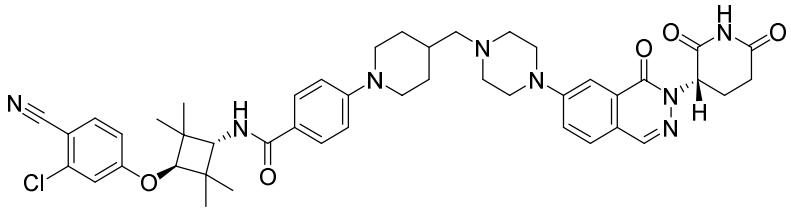

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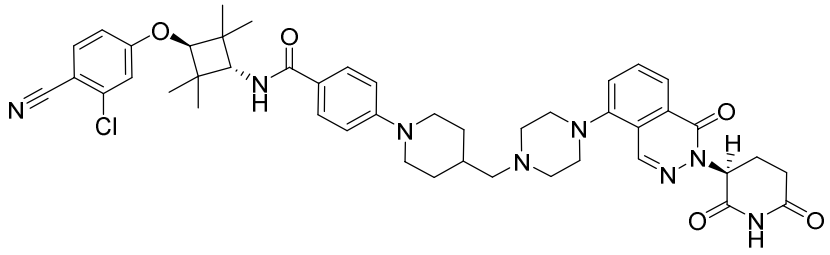

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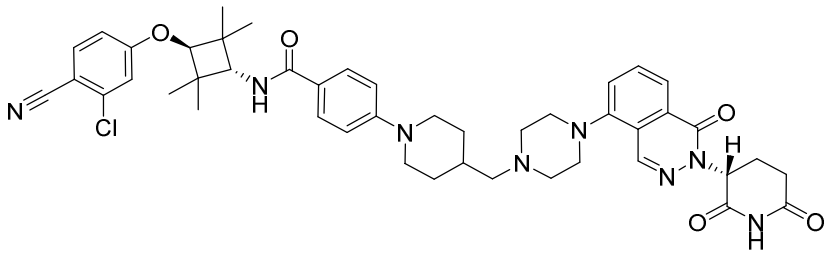

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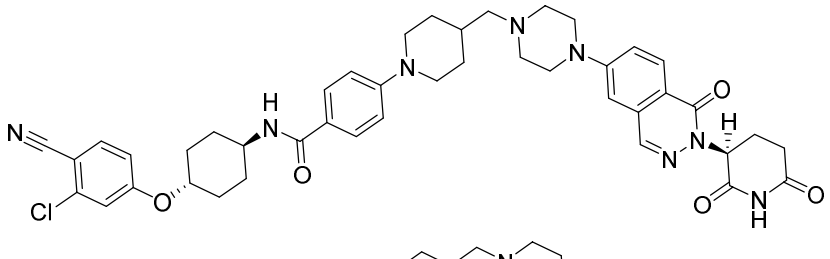

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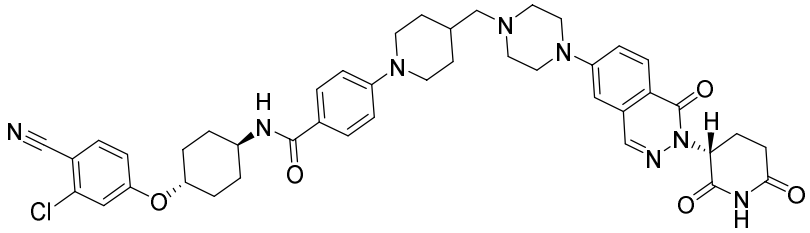

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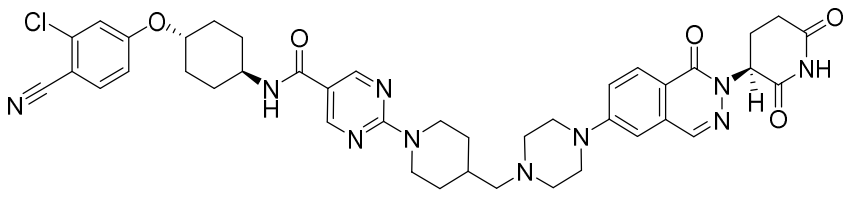

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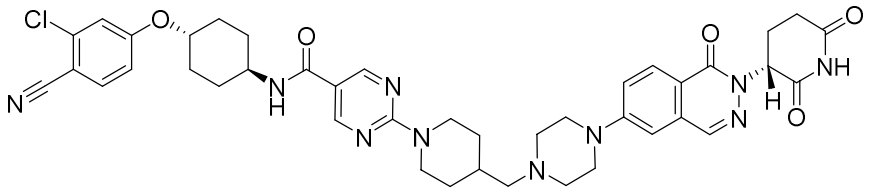
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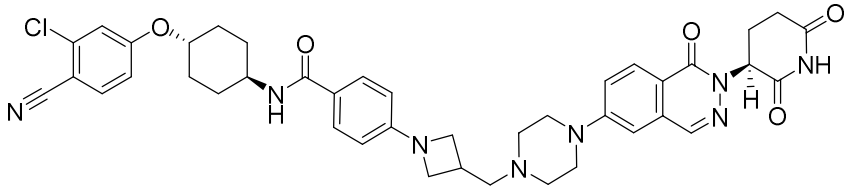
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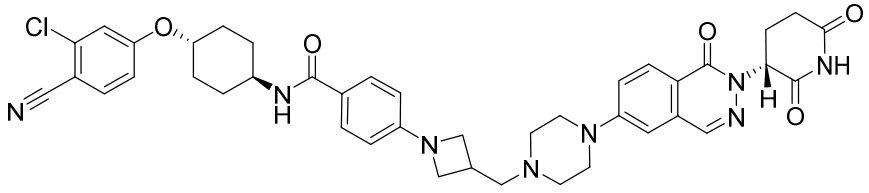
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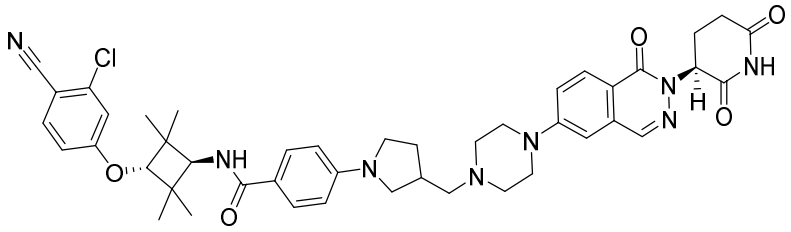
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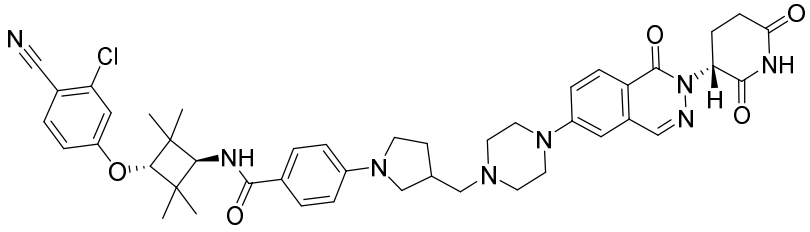
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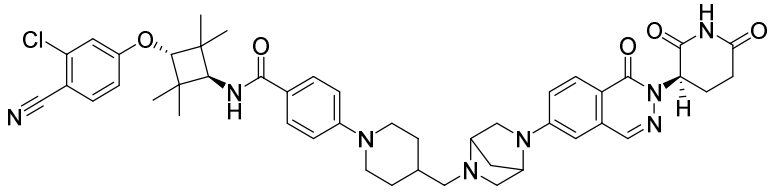
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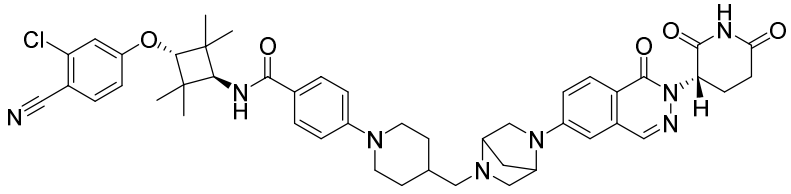
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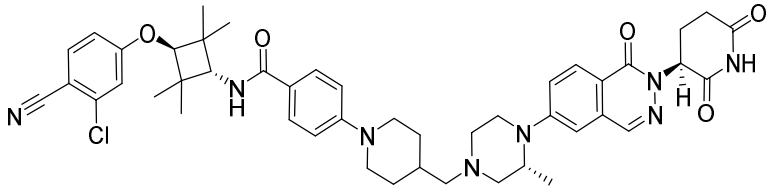
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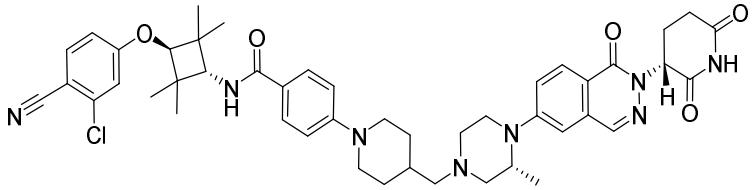
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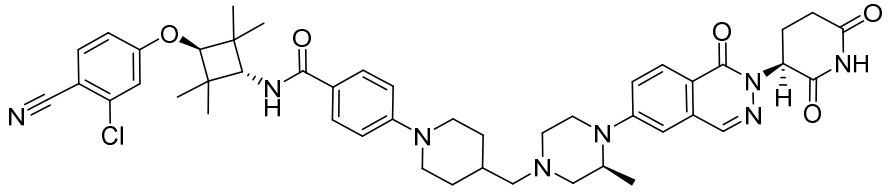
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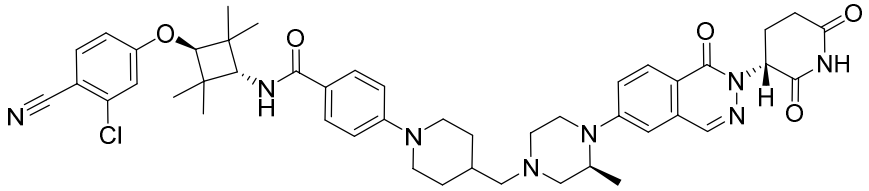
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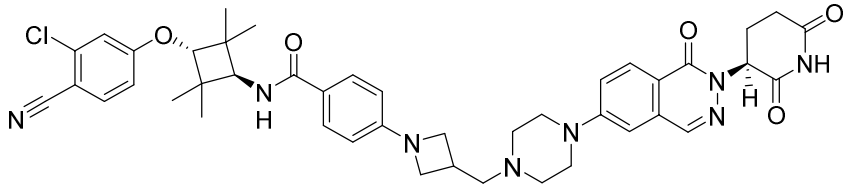
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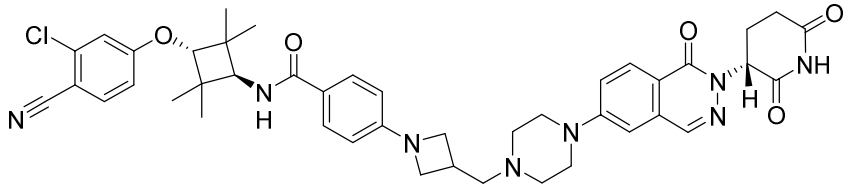
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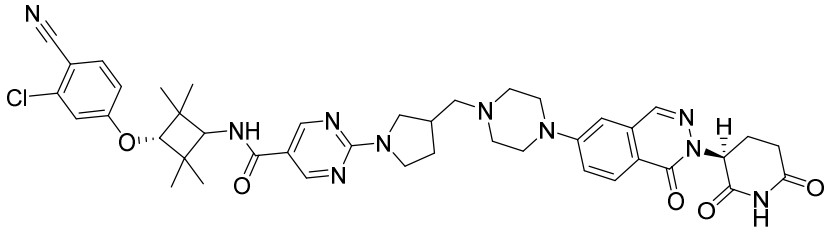
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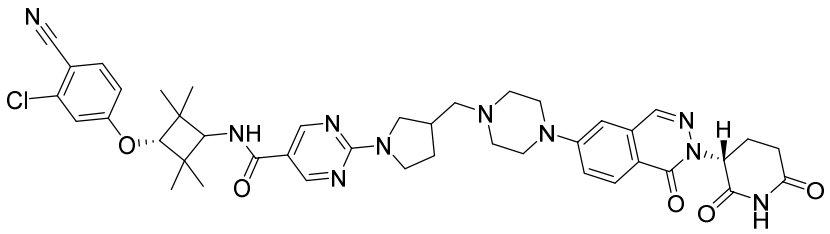
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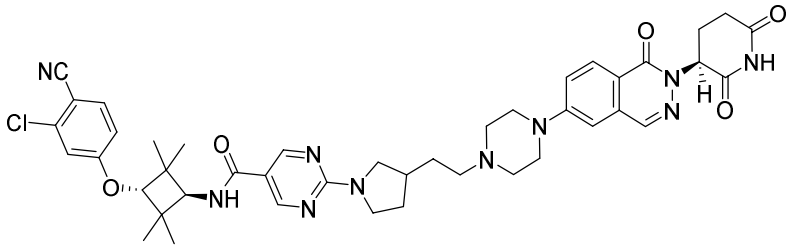
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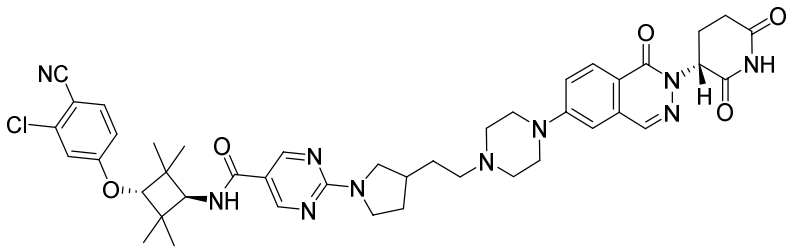
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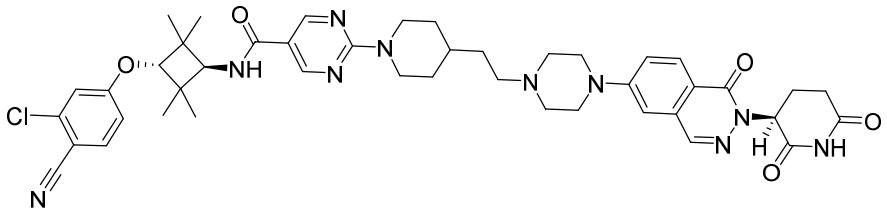
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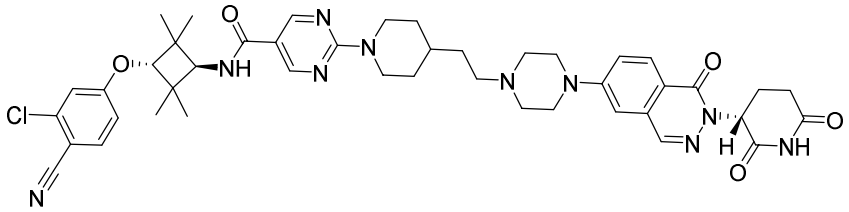
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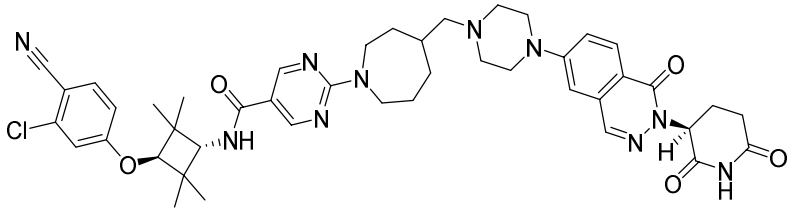
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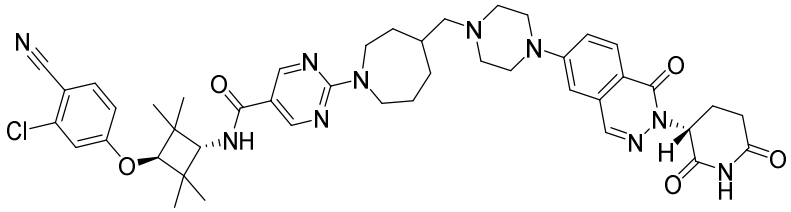
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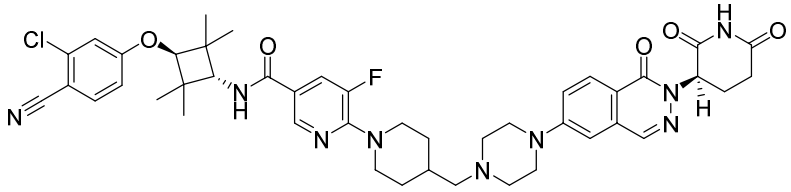
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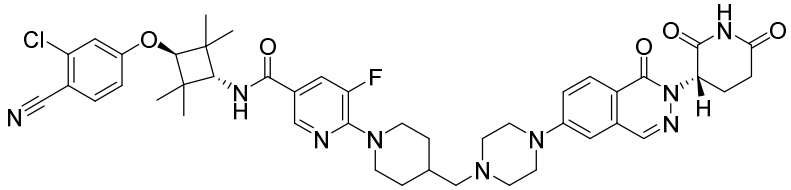
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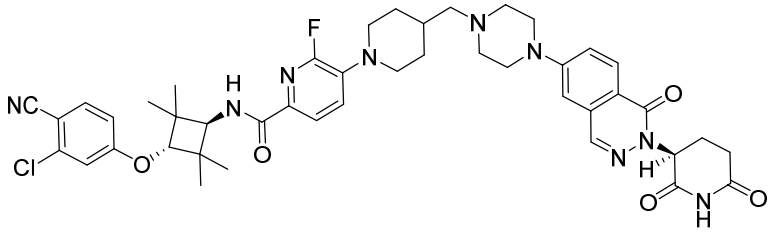
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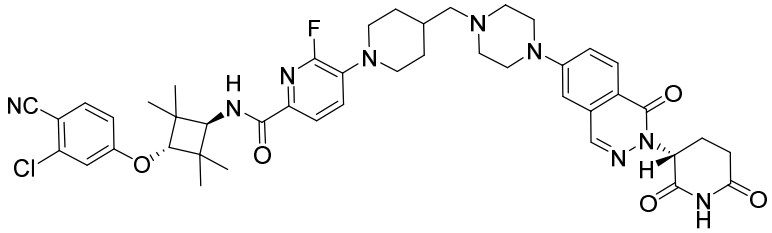
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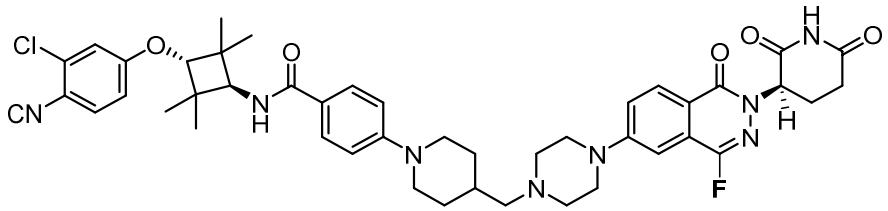
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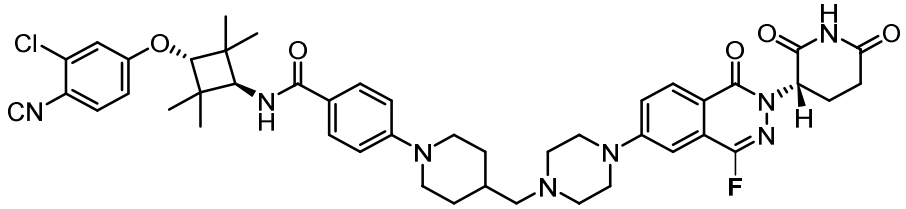
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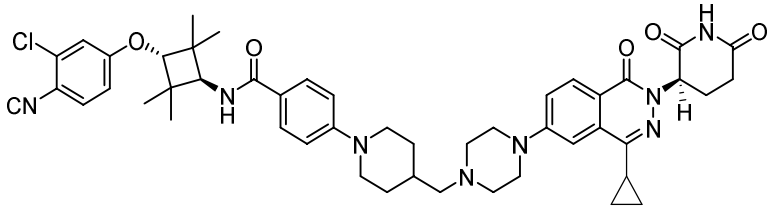
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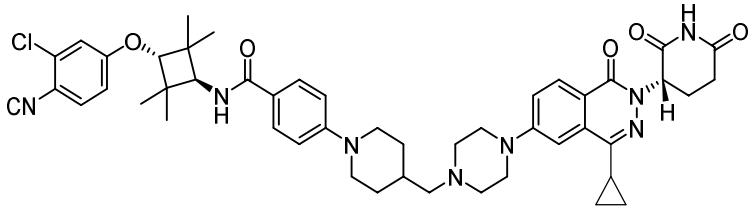
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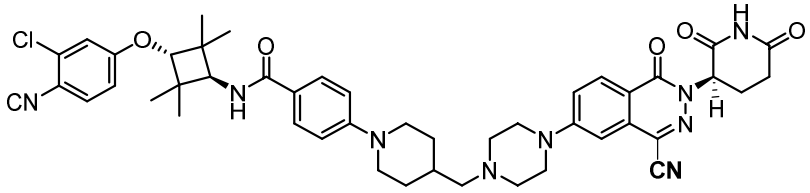
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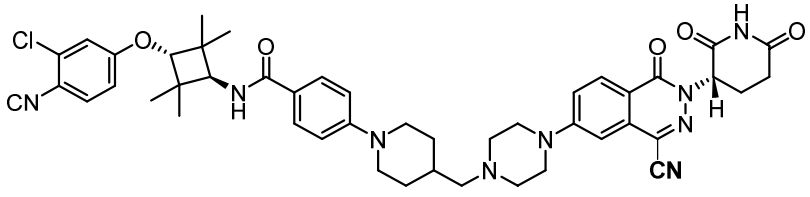
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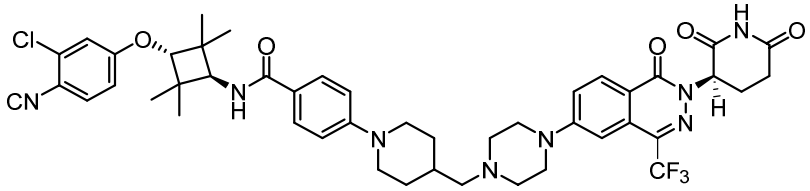
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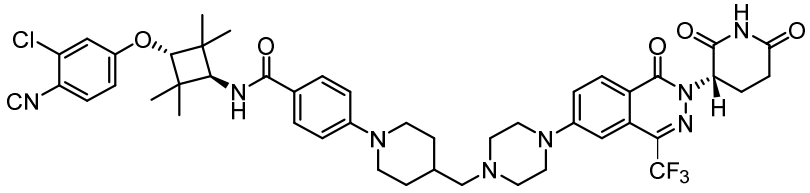
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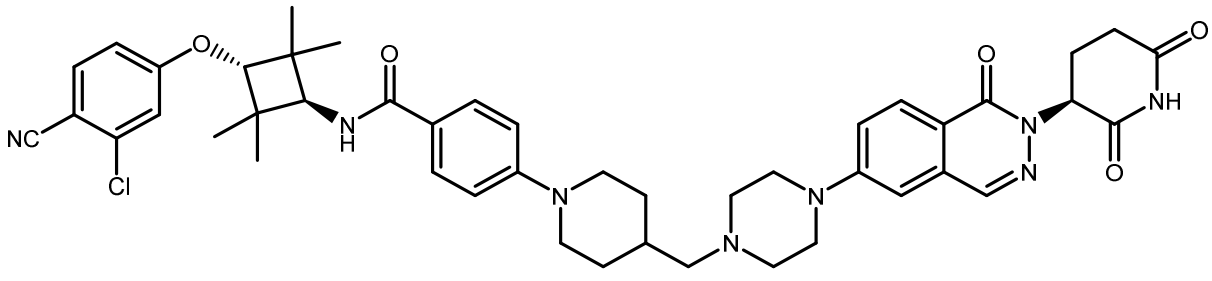
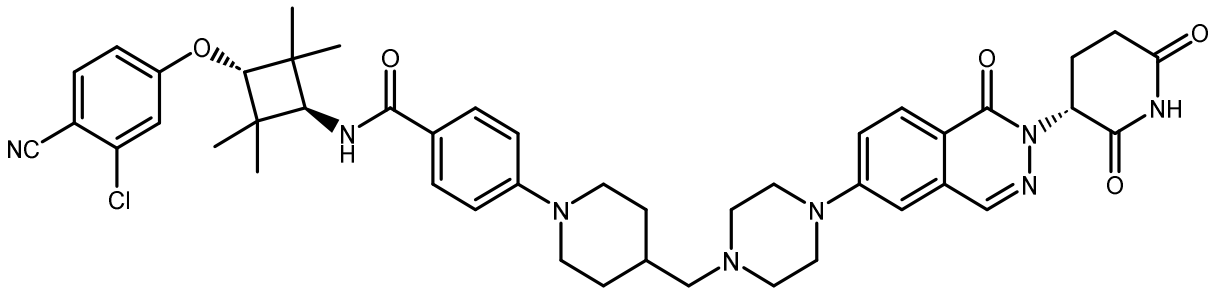
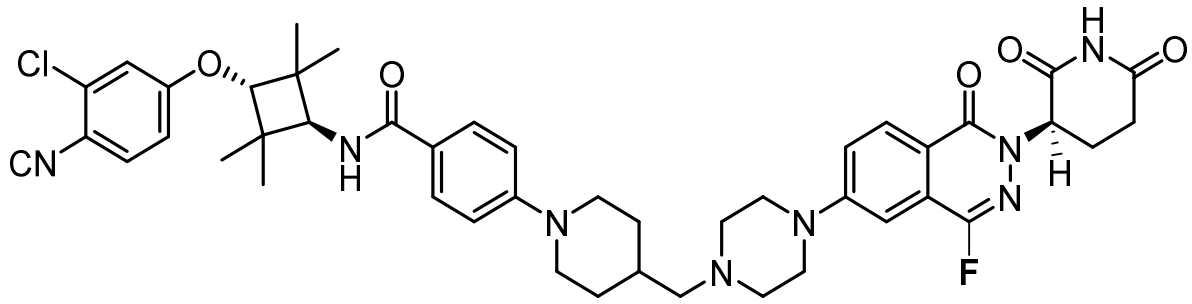
18. The compound according to claim 17, or the pharmacodynamically acceptable salt thereof, having the formula:



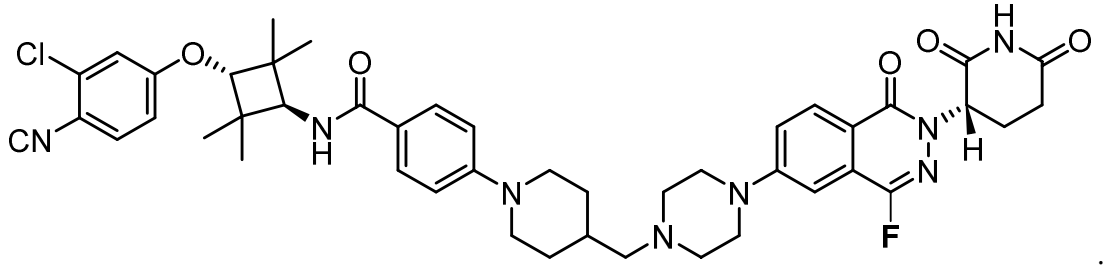
19. The compound according to claim 17, or the pharmacodynamically acceptable salt thereof, having the formula:



20. The compound according to claim 17, or the pharmacodynamically acceptable salt thereof, having the formula:



21. The compound according to claim 17, or the pharmacodynamically acceptable salt thereof, having the formula:



22. Use of the compound of any one of claims 1–21, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

23. The use according to claim 22, wherein the cancer is prostate cancer.

24. The use according to claim 22, wherein the cancer is breast cancer.

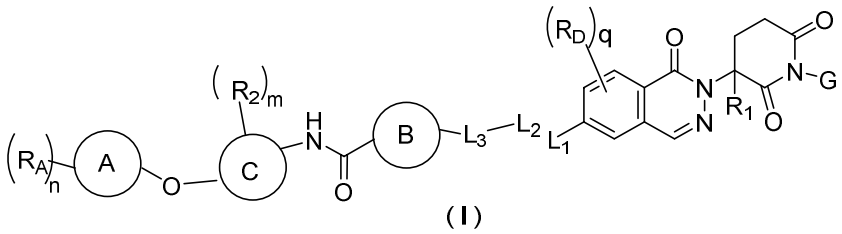
25. Use of the compound of any one of claims 1–21, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, in the manufacture of a medicament for prophylaxis and/or treatment of Kennedy's disease.

26. The compound of any one of claims 1 to 21, the optical isomer thereof, or the pharmacodynamically acceptable salt thereof, for use in therapy.

PHTHALAZINONE COMPOUND, AND PREPARATION METHOD THEREFOR AND MEDICAL USE THEREOF

Abstract

Disclosed are a phthalazinone compound, and a preparation method therefor and the medical use thereof. In particular, disclosed are a compound as represented by formula (I), and a pharmacodynamically acceptable salt, and the use of the compound as an androgen receptor (AR) for degradation.



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