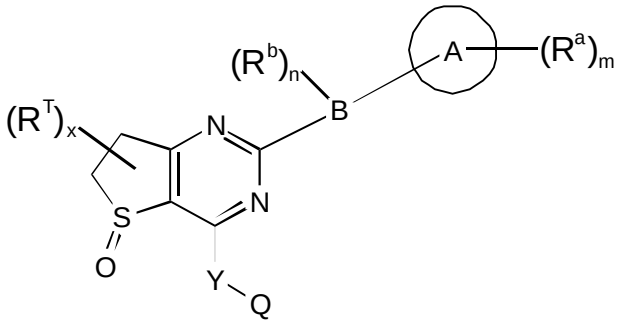
CLAIMS

What is claimed is:

1. A compound represented by Formula I, or a tautomer, stereoisomer, hydrate, solvate, pharmaceutically acceptable salt or prodrug thereof:



I , wherein:

ring A is a 5- to 10-membered aromatic ring or a 5- to 10-membered heteroaromatic ring;

each R^T is independently H, halogen, hydroxyl, deuterium, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, deuterated C_{3-6} cycloalkyl, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy, wherein the C_{1-6} alkyl, the C_{1-6} alkoxy, the C_{3-6} cycloalkyl, the deuterated C_{3-6} cycloalkyl, the deuterated C_{1-6} alkyl, and the deuterated C_{1-6} alkoxy are optionally substituted with one or more substituents of halogen, hydroxyl, amino, nitro, cyano, or carbonyl, and wherein when a plurality of substituents are present, the plurality of substituents are identical or different;

B is 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, or 3- to 10-membered cycloalkyl;

R^a and R^b are each independently H, deuterium, halogen, hydroxyl, amino, nitro, cyano, carbonyl, oxo, carboxyl, C_{1-6} alkyl, C_{3-8} cycloalkyl, deuterated C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, deuterated C_{1-6} alkoxy, or 3- to 10-membered heterocycloalkyl, wherein the C_{1-6} alkyl, the C_{3-8} cycloalkyl, the deuterated C_{1-6} alkyl, the C_{2-6} alkenyl, the C_{2-6} alkynyl, the C_{1-6} haloalkyl, the C_{3-8} halocycloalkyl,

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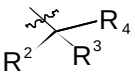
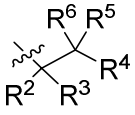
the C_{1-6} hydroxyalkyl, the C_{1-6} alkylcarbonyl, the C_{1-6} alkoxy, and the C_{1-6} haloalkoxy are optionally substituted with one or more R^c, wherein the one or more R^c are each deuterium, halogen, hydroxyl, amino, nitro, cyano, carbonyl, oxo, carboxyl, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy, and wherein when a plurality of substituents R^c are present, the plurality of substituents R^c are identical or different;

Y is NR^1, O, S, or $C(R^1)_2$;

each R^1 is independently H, deuterium, C_{1-10} alkyl, or C_{2-6} alkenyl, wherein the C_{1-10} alkyl and the C_{2-6} alkenyl are optionally substituted with one or more R^d, wherein the one or more R^d are each deuterium, halogen, C_{1-3} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -COO-C_{1-6} alkyl, $-C(O)NR^fR^f$, 5- to 8-membered aromatic ring, -het^1, or monocyclic- or bicyclic- C_{5-8}-cycloalkyl, wherein each R^f is hydrogen or C_{1-6} alkyl, and wherein het^1 represents a 5- to 8-membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring comprising one, two, three, or four heteroatoms independently selected from N, S, and O;

Q is  or  , wherein:

R^2 and R^3 as a pair as well as R^5 and R^6 as a pair each independently forms, together with a carbon atom attached thereto, a saturated or partially saturated 3-, 4-, 5-, or 6-membered monocyclic ring, wherein the 3-, 4-, 5-, or 6-membered monocyclic ring comprises zero, one, two, or three heteroatoms selected from N, O, or S, and wherein the 3-, 4-, 5-, or 6-membered monocyclic ring is further substituted with g R^{23}, wherein the g R^{23} are at least one of H, deuterium, halogen, hydroxyl, amino, cyano, carbonyl, oxo, carboxyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, deuterated C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, deuterated C_{1-6} alkoxy, C_{1-6} haloalkoxy, -COO-C_{1-6} alkyl, or $-C(O)NR^fR^f$, wherein R^f is hydrogen or C_{1-6} alkyl; or

R^5 and R^6 are each independently H, deuterium, halogen, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, or deuterated C_{1-6} alkoxy, wherein the C_{1-6} alkyl, the deuterated C_{1-6} alkyl, the C_{2-6} alkenyl, the C_{1-6} alkoxy, and the deuterated C_{1-6} alkoxy

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are optionally substituted with one or more R^d, wherein the one or more R^d are each deuterium, halogen, C_{1-3} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -COO-C_{1-6} alkyl, -$C(O)NR^fR^f$, -$OC(O)NR^fR^f$, 5- to 8-membered aromatic ring, -het^2, or monocyclic- or bicyclic-C_{5-8}-cycloalkyl, wherein R^f is hydrogen or C_{1-6} alkyl, and wherein het^2 represents a 5- to 8-membered monocyclic or bicyclic, saturated or unsaturated heterocyclic ring comprising one, two, three, or four heteroatoms independently selected from N, S and O; and

R^4 is H, deuterium, halogen, hydroxyl, amino, nitro, cyano, carbonyl, oxo, carboxyl, C_{1-6} alkyl, C_{3-8} cycloalkyl, deuterated C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, deuterated C_{1-6} alkoxy, 3- to 10-membered heterocycloalkyl, wherein the C_{1-6} alkyl, the C_{3-8} cycloalkyl, the deuterated C_{1-6} alkyl, the C_{2-6} alkenyl, the C_{2-6} alkynyl, the C_{1-6} haloalkyl, the C_{3-8} halocycloalkyl, the C_{1-6} hydroxyalkyl, the C_{1-6} alkylcarbonyl, the C_{1-6} alkoxy, the deuterated C_{1-6} alkoxy, the C_{1-6} haloalkoxy, and the 3- to 10-membered heterocycloalkyl are optionally substituted with one or more R^g, wherein the one or more R^g are at least one of deuterium, halogen, hydroxyl, amino, nitro, cyano, carbonyl, oxo, carboxyl, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy, and wherein when a plurality of substituents R^g are present, the plurality of substituents R^g are identical or different;

x is 1, 2, 3, or 4;

m and n are each independently 1, 2, 3, 4, 5, 6, 7, or 8;

g is 1, 2, 3, 4, 5, 6, 7, or 8, and

wherein the compound represented by Formula I satisfies the following condition:

at least one of R^T, R^a, R^b, R^1, R^2, R^3, R^{23}, R^4, R^5, or R^6 is deuterium, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy.

2. The compound according to claim 1, wherein the compound satisfies at least one of the following conditions:

1) the ring A is selected from a 5- to 9-membered heteroaromatic ring;

2) the heteroaromatic ring comprises one or two heteroatoms;

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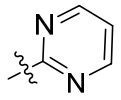
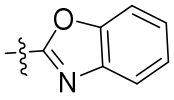
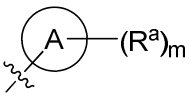
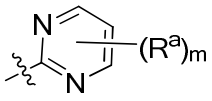
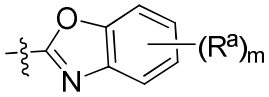
3) the heteroatom is selected from N or O;

4) the ring A is a pyridine ring, a pyrimidine ring, a pyrazine ring, a pyridazine ring, or benzoxazolyl;

5) the ring A is  or  ;

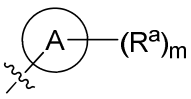
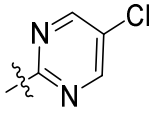
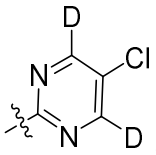
6) the structural unit  is  or  ;

7) R^a is H, deuterium, F, Cl, C_{1-3} alkyl, deuterated C_{1-3} alkyl, or C_{1-3} haloalkyl;

8) R^a is H, deuterium, F, Cl, CH_3, CD_3, or halogen-substituted CH_3;

9) R^a is H, deuterium, F, Cl, CH_3, CD_3, or F-substituted CH_3;

10) R^a is H, deuterium, CD_3, F, Cl, or CHF_2;

11) the structural unit  is  or  ;

12) when Y is NR^1 or CHR^1, R^1 is selected from H, deuterium, or C_{1-6} alkyl; or

13) Y is -NH-.

3. The compound according to claim 1, wherein the compound satisfies at least one of the following conditions:

1a) B is selected from 3- to 10-membered heterocycloalkyl or 3- to 10-membered heterocycloalkenyl;

2a) the 3- to 10-membered heterocycloalkyl is monocyclic, fused bicyclic, bridged bicyclic, or spiro bicyclic;

3a) the 3- to 10-membered heterocycloalkyl further comprises one to three heteroatoms selected from N, O, and S;

4a) the 3- to 10-membered heterocycloalkenyl is monocyclic or fused bicyclic;

5a) the 3- to 10-membered heterocycloalkenyl further comprises one to three heteroatoms selected from N, O, and S;

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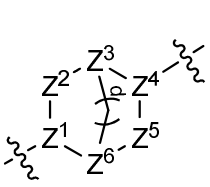
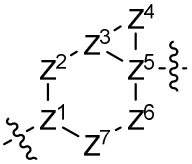
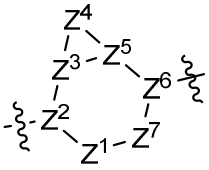
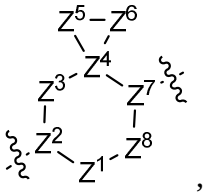
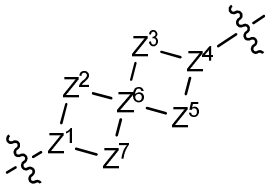
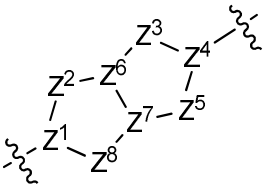
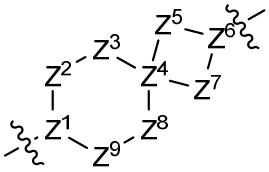
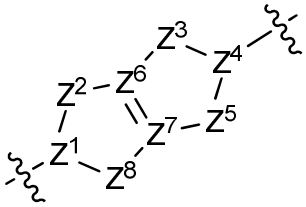
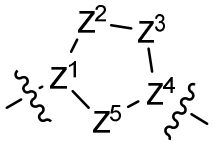
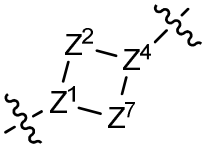
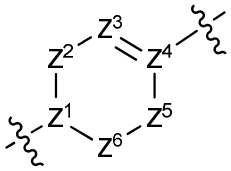
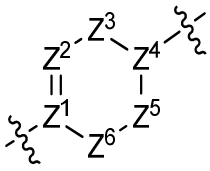
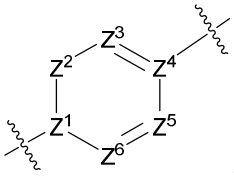
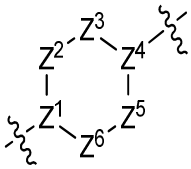
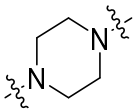
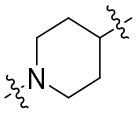
6a) B is  ,  ,  ,  ,

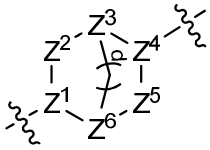
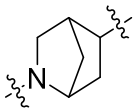
 ,  ,  ,

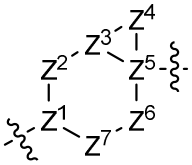
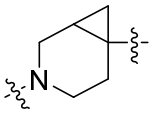
 ,  ,  ,  ,

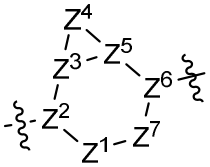
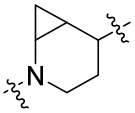
 , or  , where:

Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, and Z^9 are each independently N, NH, CH_2, CH, C, -NH-CH_2-, or -CH_2-CH_2-, and p is 0, 1, or 2;

7a)  is  or  ;

8a)  is  ;

9a)  is  ;

10a)  is  ;

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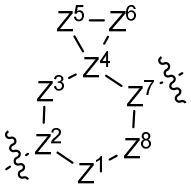
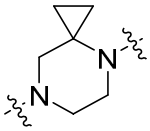
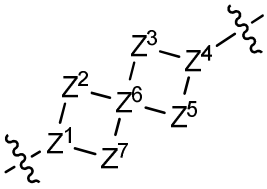
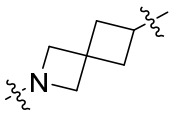
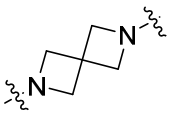
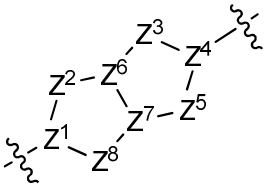
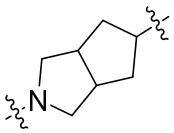
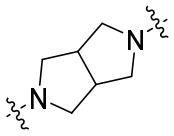
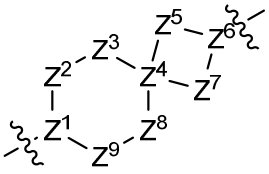
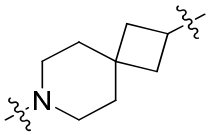
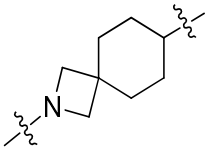
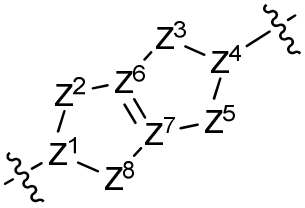
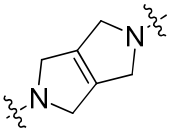
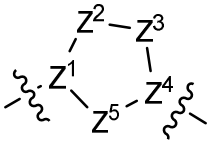
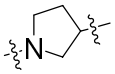
11a)  is  ;

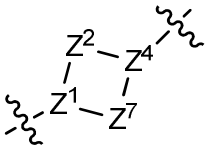
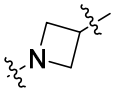
12a)  is  or  ;

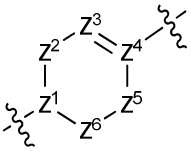
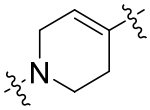
13a)  is  or  ;

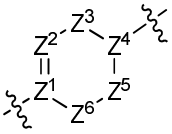
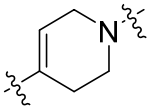
14a)  is  or  ;

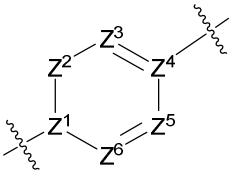
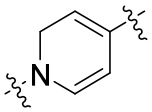
15a)  is  ;

16a)  is  ;

17a)  is  ;

18a)  is  ;

19a)  is  ;

20a)  is  ;

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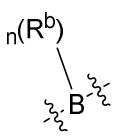
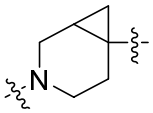
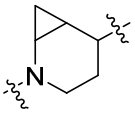
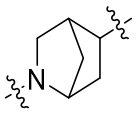
21a) moiety  is  ,  ,  ,

7b) each R^c is independently deuterium, halogen, oxo, deuterated C_{1-3} alkyl, C_{1-3} alkyl, or C_{1-3} haloalkyl;

8b) the number of R^g is 0, 1, 2, or 3;

9b) each R^g is independently deuterium, halogen, hydroxyl, cyano, deuterated C_{1-6} alkyl, C_{1-6} alkyl, or C_{1-6} haloalkyl; or

10b) each R^g is independently deuterium, halogen, oxo, deuterated C_{1-3} alkyl, C_{1-3} alkyl, or C_{1-3} haloalkyl.

5. The compound according to claim 1, wherein the compound satisfies at least one of the following conditions:

1c) each R^T is independently H, deuterium, deuterated C_{1-3} alkyl, or deuterated C_{1-3} alkoxy;

2c) each R^T is independently H or deuterium;

3c) each R^4 is independently H, deuterium, halogen, hydroxyl, amino, nitro, cyano, carboxyl, C_{1-6} alkyl, C_{3-8} cycloalkyl, deuterated C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, deuterated C_{1-6} alkoxy, or 3- to 10-membered heterocycloalkyl, wherein the C_{1-6} alkyl, the C_{3-8} cycloalkyl, the deuterated C_{1-6} alkyl, the C_{1-6} haloalkyl, the C_{3-8} halocycloalkyl, the C_{1-6} hydroxyalkyl, the C_{1-6} alkylcarbonyl, the C_{1-6} alkoxy, the C_{1-6} haloalkoxy, the deuterated C_{1-6} alkoxy, and the 3- to 10-membered heterocycloalkyl are optionally substituted with one or more R^g, wherein the one or more R^g are at least one of deuterium, halogen, hydroxyl, amino, nitro, cyano, carbonyl, oxo, carboxyl, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy, and wherein when a plurality of substituents R^g are present, the plurality of substituents R^g are identical or different;

4c) each R^4 is independently H, deuterium, hydroxyl, C_{1-6} alkyl, C_{3-8} cycloalkyl, deuterated C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} halocycloalkyl, or C_{1-6} hydroxyalkyl;

5c) each R^4 is independently H, deuterium, or hydroxyl;

6c) R^5 and R^6 are each independently H, deuterium, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, or deuterated C_{1-6} alkoxy, wherein the C_{1-6} alkyl and the C_{2-6} alkenyl are optionally substituted with one or more R^d, wherein the one or more

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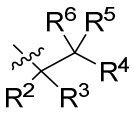
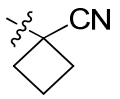
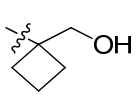
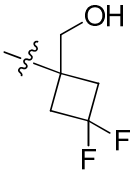
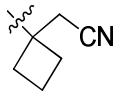
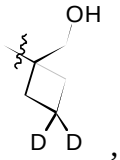
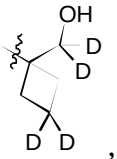
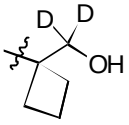
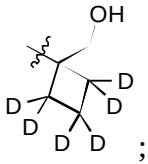
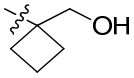
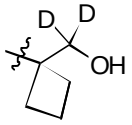
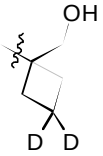
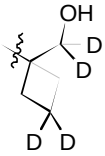
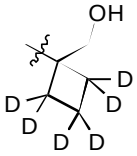
R^d are each deuterium, halogen, C_{1-3} fluoroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or -COO-C_{1-6} alkyl;

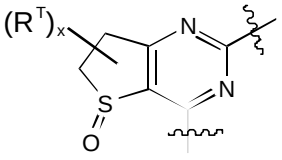
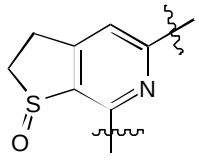
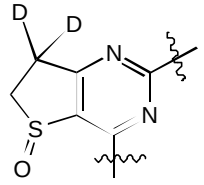
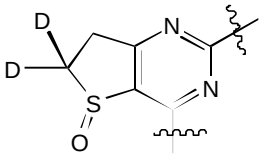
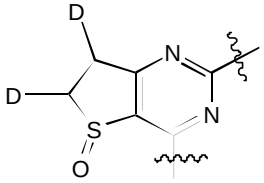
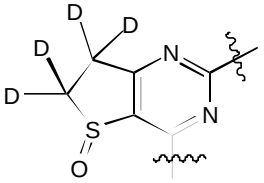
7c) R^5 and R^6 are each independently H, deuterium, C_{1-6} alkyl, deuterated C_{1-6} alkyl;

8c) R^5 and R^6 are each independently H or deuterium;

9c) Q is  , and R^4 is hydroxyl;

10c) Q is  ,  ,  ,  ,  ,  ,  , or  ;

11c) Q is  ,  ,  ,  , or  ; or

12c) is  ,  ,  ,  ,  , or  .

6. The compound according to claim 1, wherein the compound has a structure represented by Formula I-A or Formula I-B:

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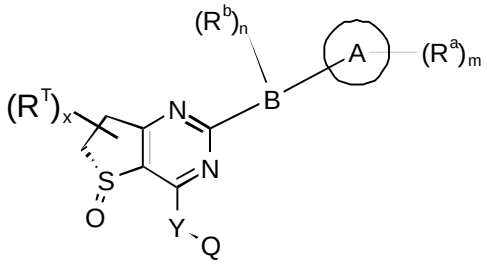
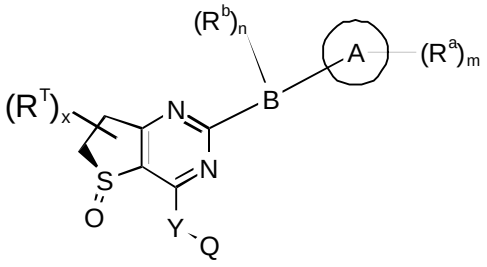
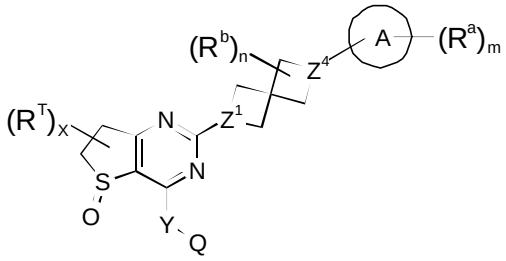


I-A or  I-B ,

wherein:

ring A, B, R^a, R^b, R^T, Y, Q, m, n, and x are as defined in claim 1.

7. The compound according to claim 1, wherein the compound has a structure represented by Formula I-1:

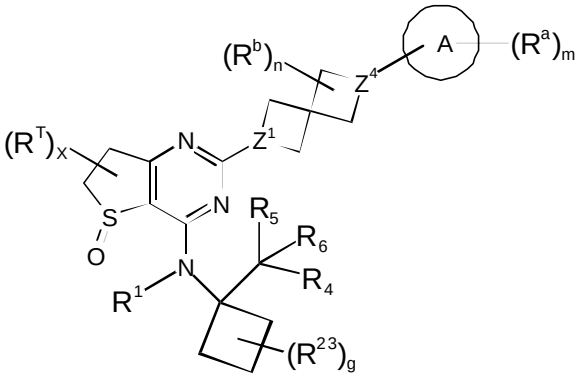


I-1 , wherein:

Z^1 and Z^4 are independently CH or N; and

ring A, R^a, R^b, R^T, Y, Q, m, n, and x are as defined in claim 1.

8. The compound according to claim 1, wherein the compound has a structure represented by Formula I-1A:



I-1A , wherein:

Z^1 and Z^2 are independently CH or N; and

ring A, R^a, R^b, R^T, R^1, R^{23}, R^4, R^5, R^6, m, n, and x are as defined in claim 1.

9. The compound according to claim 1, wherein the compound has a structure

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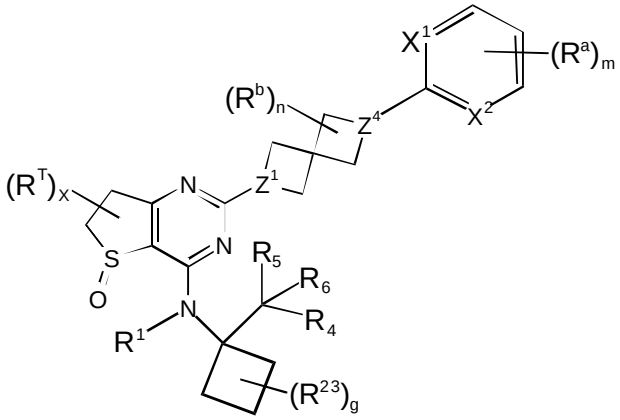
represented by Formula I-1B:



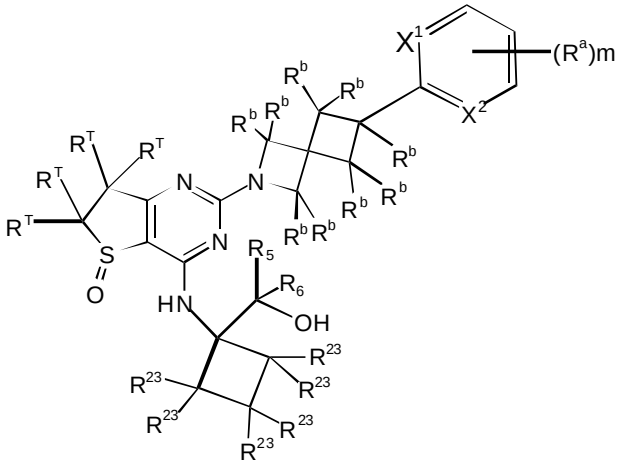
I-1B , wherein:

X^1 and X^2 are each independently CH or N;

Z^1 and Z^4 are each independently N or CH; and

R^a, R^b, R^T, R^1, R^{23}, R^4, R^5, R^6, m, n, g, and x are as defined in claim 1.

10. The compound according to claim 1, wherein the compound has a structure represented by Formula I-1B1, Formula I-1B2, or Formula I-1B3:



I-1B1 ,

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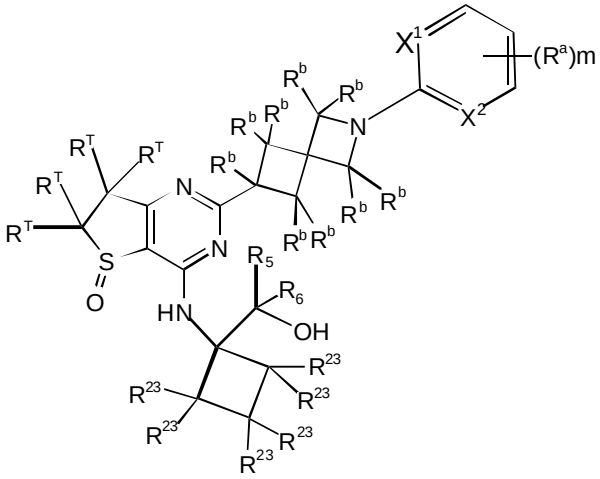
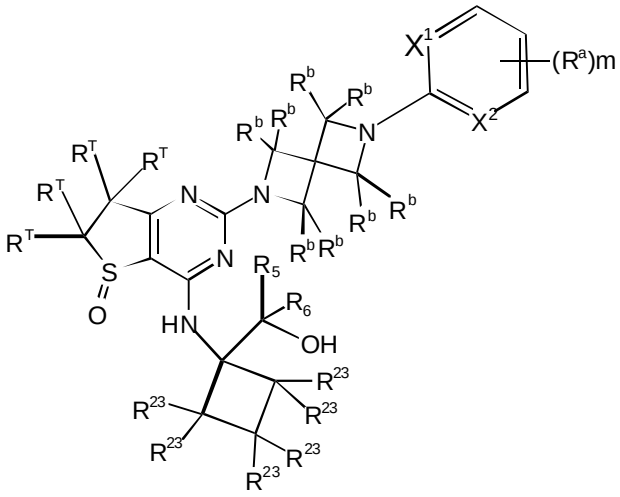


I-1B2 , or



I-1B3 , wherein:

X^1 and X^2 are each independently CH or N;

each R^a is independently H, halogen, hydroxyl, deuterium, C_{1-6} alkyl, C_{1-6} alkoxy, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy;

each R^T is independently H, halogen, hydroxyl, deuterium, C_{1-6} alkyl, C_{1-6} alkoxy, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy;

each R^{23} is independently H, halogen, hydroxyl, deuterium, C_{1-6} alkyl, C_{1-6} alkoxy, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy;

R^5 and R^6 are each independently H, deuterium, halogen, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{1-6} alkoxy, or deuterated C_{1-6} alkoxy; and

each R^b is independently H, halogen, hydroxyl, deuterium, C_{1-6} alkyl, C_{1-6} alkoxy, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy,

wherein at least one of R^T, R^a, R^b, R^{23}, R^5, or R^6 is deuterium, deuterated C_{1-6} alkyl,

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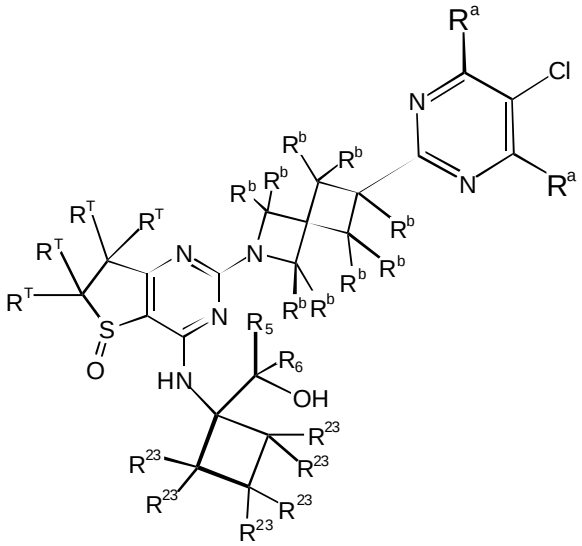
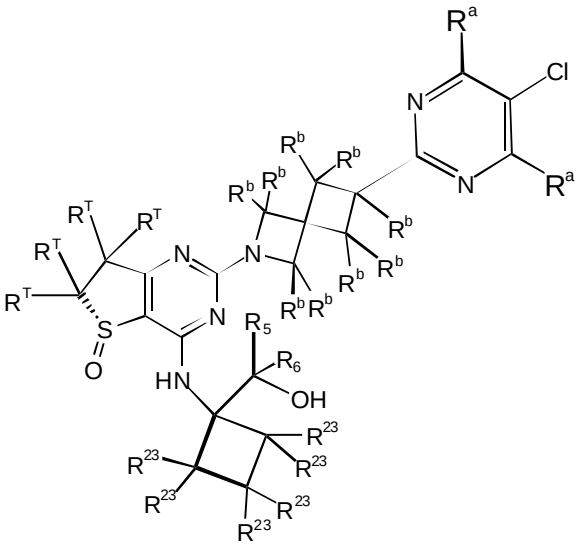
or deuterated C_{1-6} alkoxy.

11. The compound according to claim 10, wherein the compound has a structure represented by Formula I-1B4' or I-1B5':



I-1B4' or



I-1B5' , wherein:

each R^a is independently H, halogen, hydroxyl, deuterium, C_{1-6} alkyl, C_{1-6} alkoxy, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy;

each R^T is independently H, halogen, hydroxyl, deuterium, C_{1-6} alkyl, C_{1-6} alkoxy, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy;

each R^{23} is independently H, halogen, hydroxyl, deuterium, C_{1-6} alkyl, C_{1-6} alkoxy, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy;

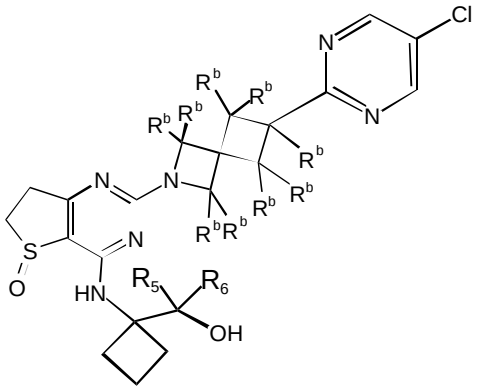
R^5 and R^6 are each independently H, deuterium, halogen, C_{1-6} alkyl, deuterated C_{1-6} alkoxy

$_{6}$ alkyl, C_{1-6} alkoxy, deuterated C_{1-6} alkoxy; and

each R^b is independently H, halogen, hydroxyl, deuterium, C_{1-6} alkyl, C_{1-6} alkoxy, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy,

wherein at least one of R^T, R^a, R^b, R^{23}, R^5, or R^6 is deuterium, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy.

12. The compound according to claim 11, wherein the compound has a structure represented by Formula I-1B4 or I-1B5:



I-1B4

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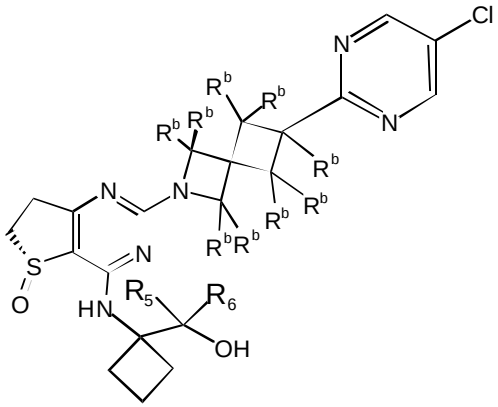

I-1B5

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wherein:

R^5 and R^6 are each independently H, deuterium, halogen, C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{1-6} alkoxy, or deuterated C_{1-6} alkoxy; and

each R^b is independently H, halogen, hydroxyl, deuterium, C_{1-6} alkyl, C_{1-6} alkoxy, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy,

wherein at least one of R^b, R^5, and R^6 is deuterium, deuterated C_{1-6} alkyl, or deuterated C_{1-6} alkoxy.

13. The compound according to claim 10, wherein the compound satisfies at least one of the following conditions:

1d) each R^T is independently H or deuterium;

2d) at least one of R^T substituents is deuterium, and the remaining of R^T substituents are each H;

3d) each R^{23} is independently H or deuterium;

4d) at least one of R^{23} substituents is deuterium, and the remaining of R^{23} substituents are each H;

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5d) R^5 and R^6 are independently H or deuterium;

6d) at least one of R^5 and R^6 is deuterium, and the other one of R^5 and R^6 is H or deuterium;

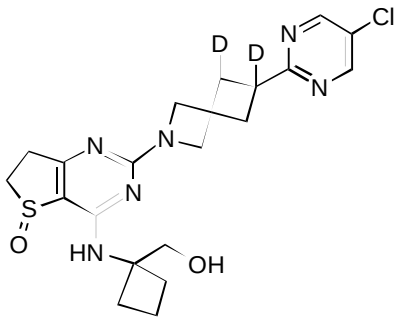
7d) each R^b is independently H or deuterium;

8d) at least one of R^b is deuterium, and the remainder of R^b are each H;

9d) each R^a is independently H, deuterium, Cl or F; or

10d) at least one of R^a is deuterium, and the remainder of R^a are each H, Cl, or F.

14. The compound according to claim 1, wherein the compound has any one of the following structures:



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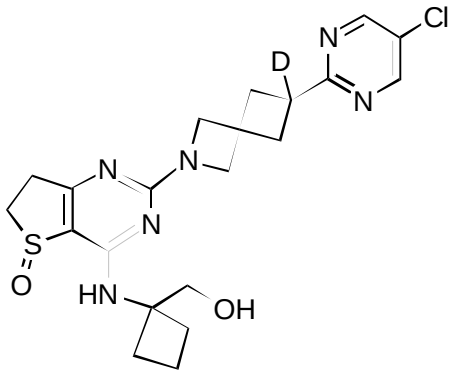

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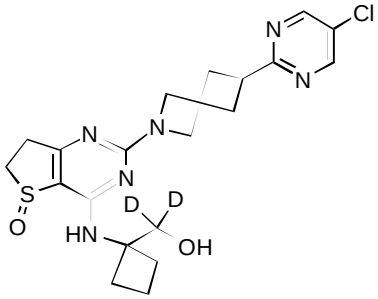

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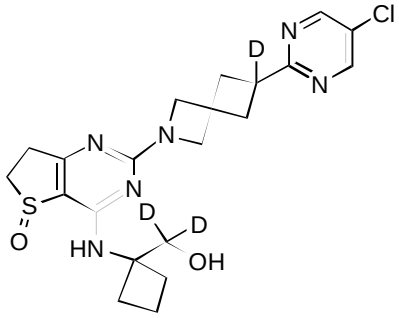

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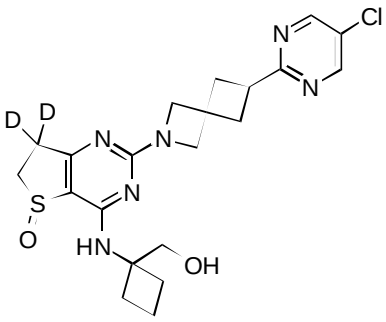

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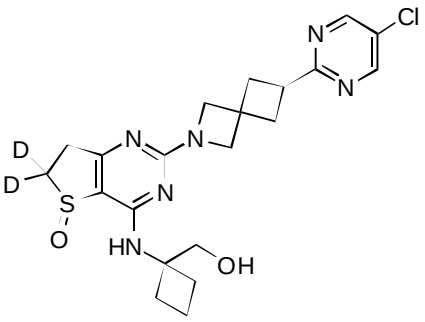

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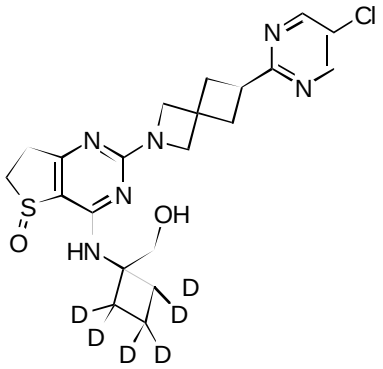
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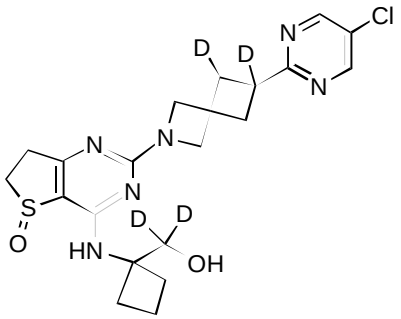
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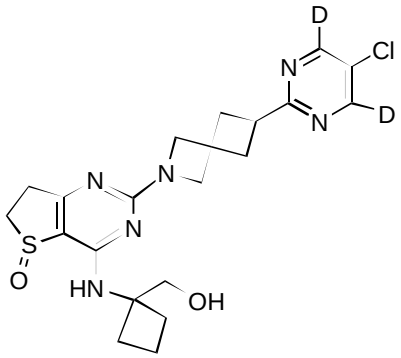
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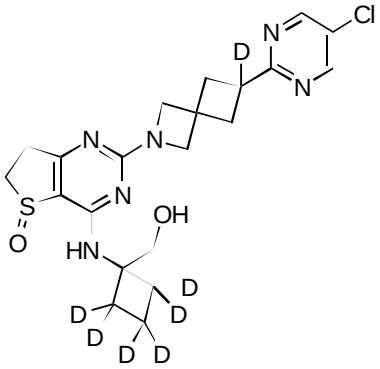
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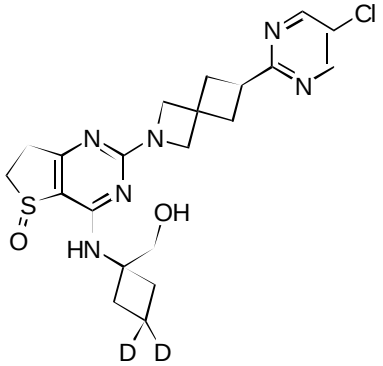
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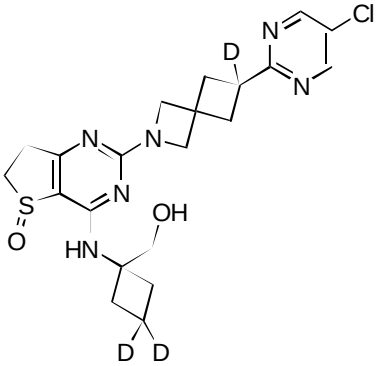
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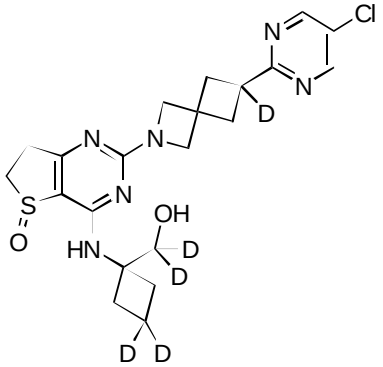
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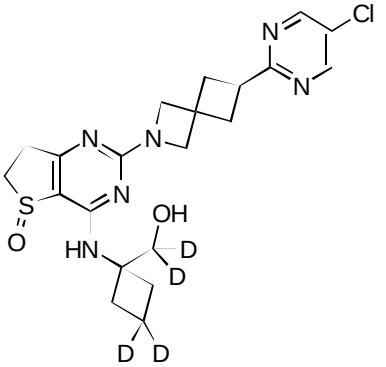
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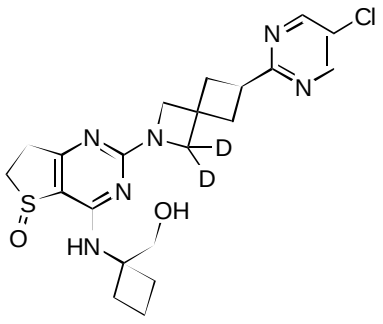
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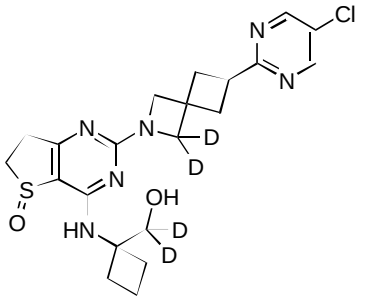
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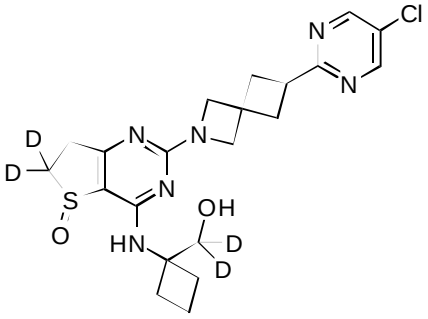
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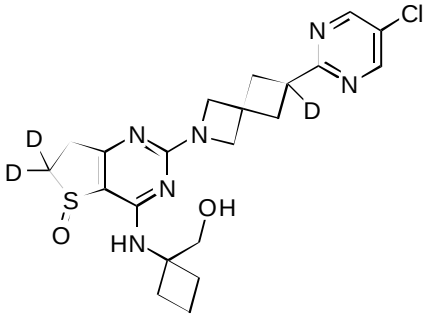
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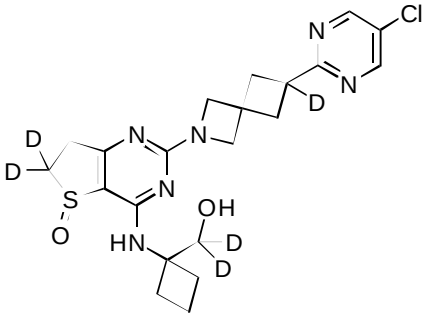
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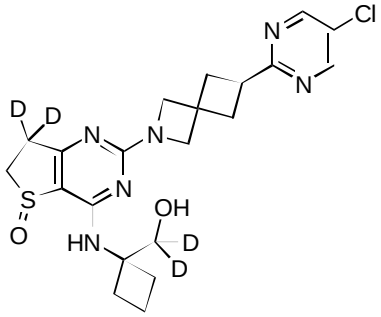
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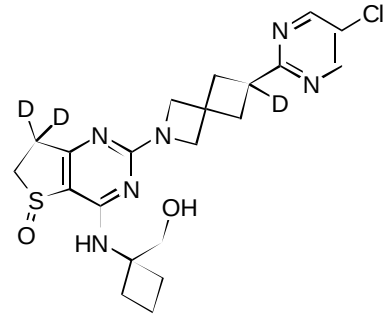
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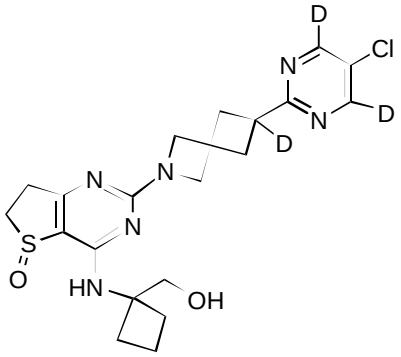
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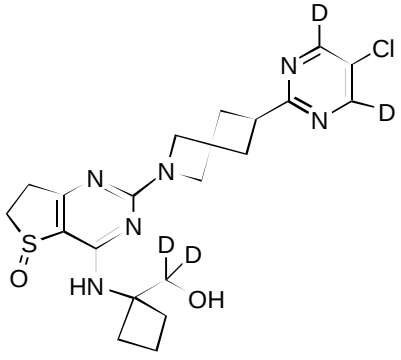
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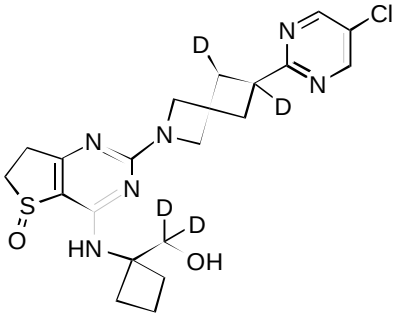
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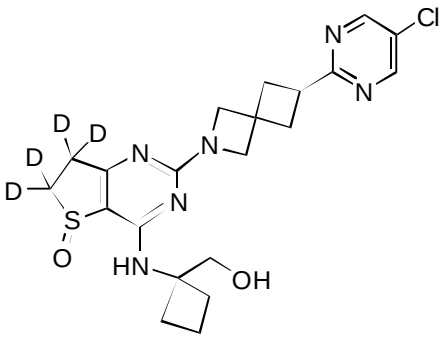
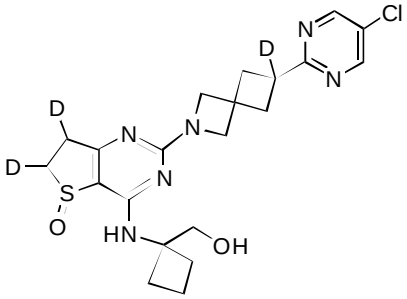


, and 

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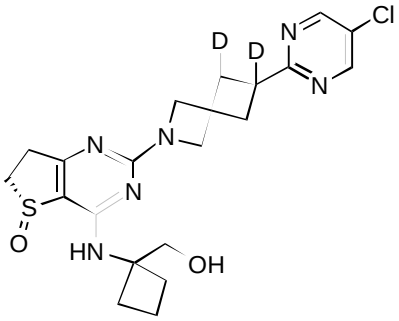
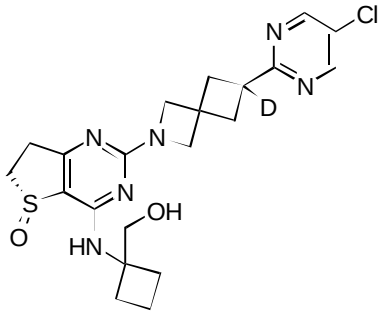
preferably, the compound has any one of the following structures:



1 , 

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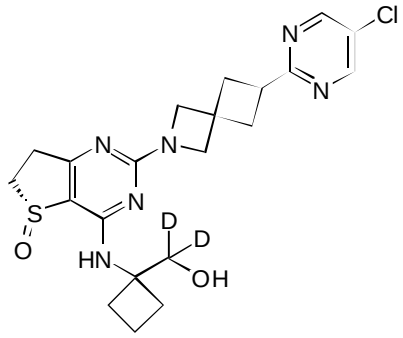
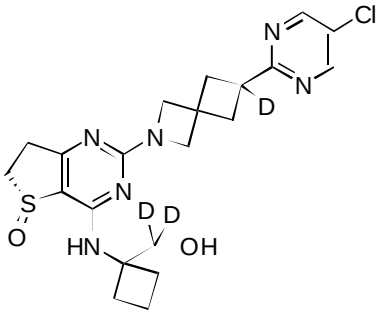


3 , 

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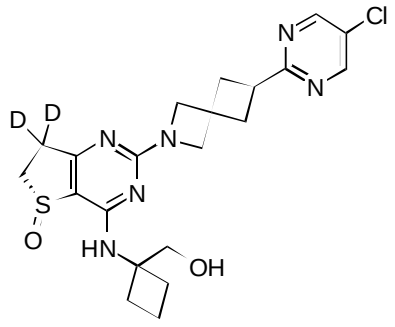
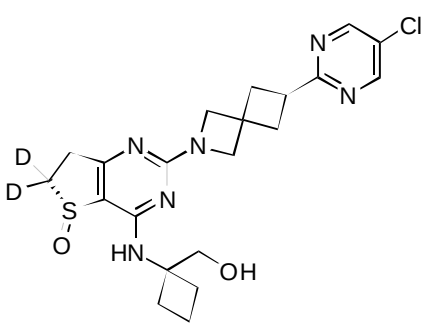


5 , 

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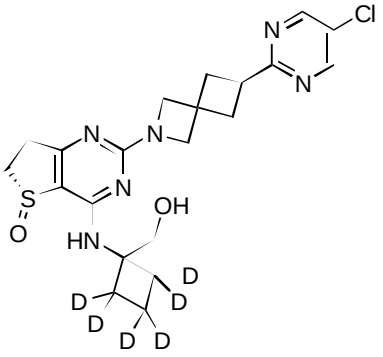

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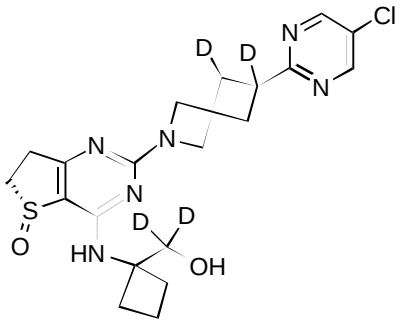

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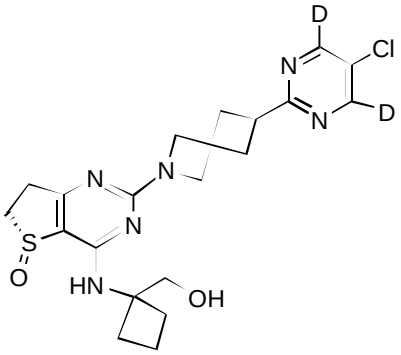

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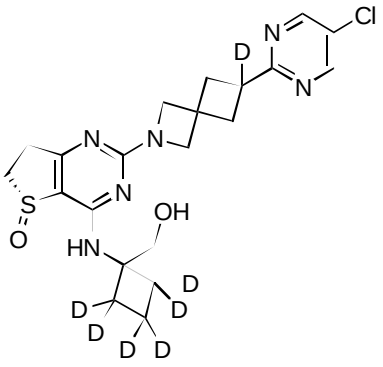

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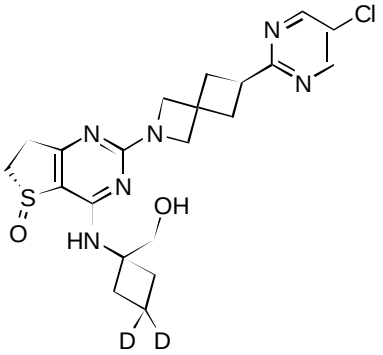

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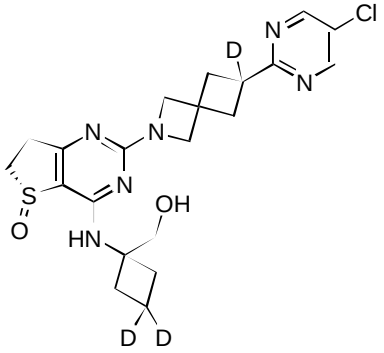

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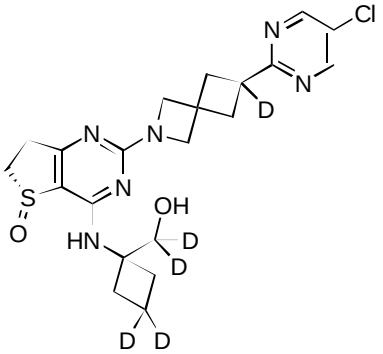

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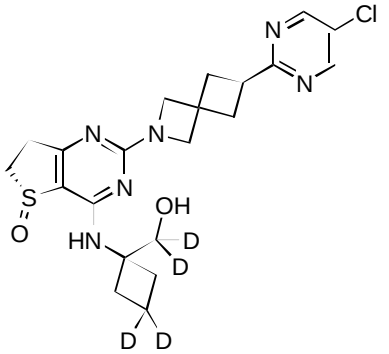

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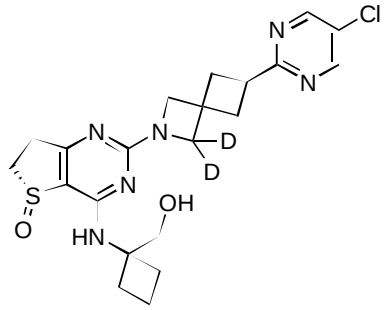

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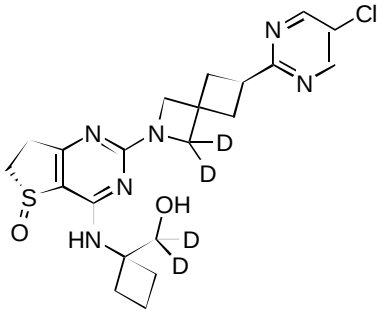

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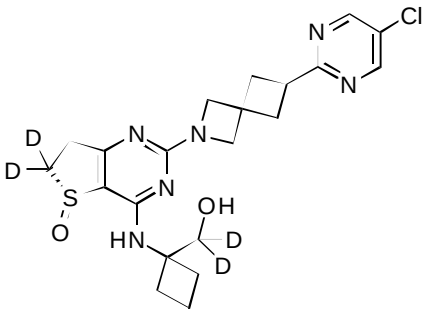

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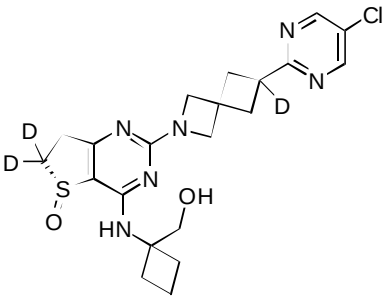

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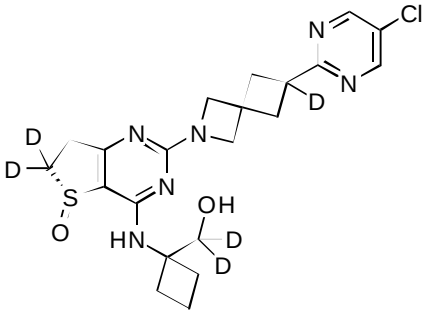

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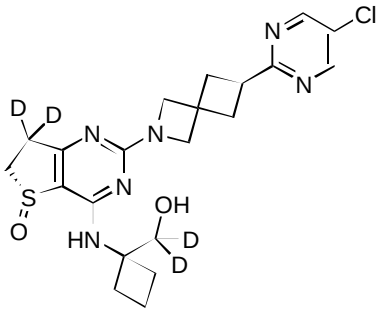

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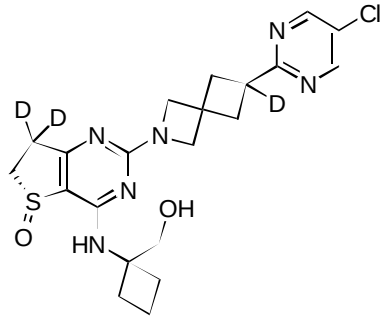

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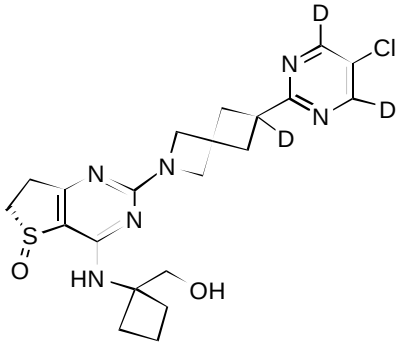

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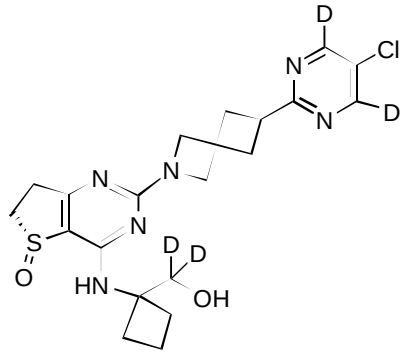

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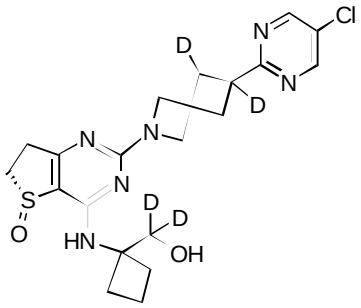

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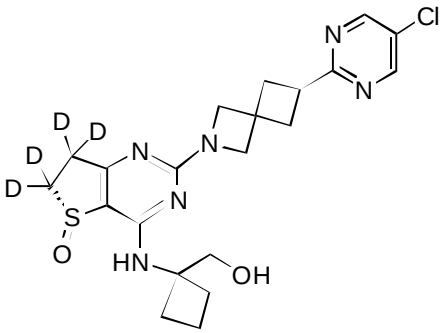

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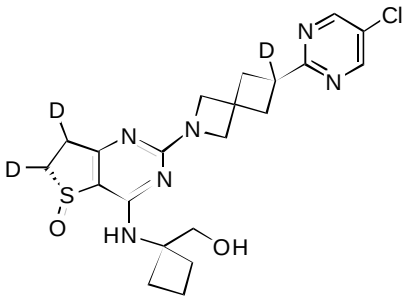

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15. A pharmaceutical composition, comprising:

the compound, or the tautomer, stereoisomer, hydrate, solvate, pharmaceutically acceptable salt or prodrug thereof according to any one of claims 1 to 14; and/or

a pharmaceutically acceptable carrier or excipient.

16. Use of the compound, or the tautomer, stereoisomer, hydrate, solvate, pharmaceutically acceptable salt or prodrug thereof according to any one of claims 1 to 14, or the pharmaceutical composition according to claim 15 in the preparation of a medicament or a formulation for:

inhibiting PDE4B; and/or

preventing and/or treating a PDE4B-related disease; and/or

avoiding or reducing a gastrointestinal side effect in the treatment of a PDE4B-related disease;

preferably, the PDE4B-related disease comprises a respiratory disease, a gastrointestinal disease, an inflammatory disease of joints, skin, or eyes, a cancer, a peripheral or central nervous system disease, an autoimmune disease, a transplant rejection, or a disease related to smooth muscle contractility,

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optionally, the respiratory disease is a respiratory or pulmonary disease accompanied by increased mucus production, airway inflammation, and/or obstructive disease;

optionally, the respiratory disease is COPD, idiopathic pulmonary fibrosis, interstitial lung disease, α1-antitrypsin deficiency, chronic sinusitis, asthma, or chronic bronchitis;

optionally, the autoimmune disease is a diffuse connective tissue disease such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, dermatomyositis, polymyositis, vasculitis, or Sjögren's syndrome;

optionally, the gastrointestinal disease is regional ileitis, ulcerative colitis, or Crohn's disease;

optionally, the inflammatory disease of the joints, skin, or eyes is rheumatoid arthritis, sarcoidosis, dry eye syndrome, or glaucoma;

optionally, the cancer is mesothelioma, neuroblastoma, rectal cancer, colon cancer, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, esophageal cancer, lip cancer, laryngeal cancer, hypopharyngeal cancer, tongue cancer, salivary gland cancer, gastric cancer, adenocarcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, renal cancer, renal parenchymal cancer, ovarian cancer, cervical cancer, uterine cancer, endometrial cancer, choriocarcinoma, pancreatic cancer, prostate cancer, bladder cancer, testicular cancer, breast cancer, urological cancer, melanoma, brain tumor, lymphoma, head-and-neck cancer, acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, hepatocellular carcinoma, gallbladder cancer, bronchial carcinoma, small cell lung cancer, non-small cell lung cancer, multiple myeloma, basal sarcoma, teratoma, retinoblastoma, choroidal melanoma, seminoma, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, myoma, liposarcoma, fibrosarcoma, Ewing's sarcoma, and plasmacytoma; and

optionally, the peripheral or central nervous system disease is depression, bipolar depression or manic depression, acute and chronic anxiety states, schizophrenia, Alzheimer's disease, Parkinson's disease, acute and chronic multiple sclerosis or acute

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and chronic pain, and brain damage caused by stroke, hypoxia, or cranio-cerebral trauma.

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