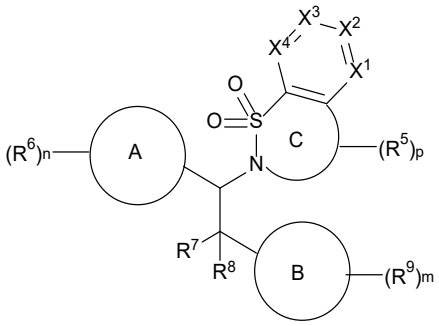
CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof:



Formula (I),

wherein:

X^1 is N or CR^1;

X^2 is N or CR^2;

X^3 is N or CR^3;

X^4 is N or CR^4;

R^1, R^2, R^3, and R^4 are independently hydrogen, deuterium, halogen, -CN, -NO_2, -OH, -OR^a, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -SH, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -NR^cR^d, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$NR^bS(=O)_2R^a$, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring C is a 4- to 8-membered heterocycloalkyl optionally comprising 1 or 2 additional heteroatoms selected from the group consisting of O, S, and N;

each R^5 is independently deuterium, halogen, -CN, -NO_2, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

or 2 R^5 on the same carbon are taken together to form an oxo;

p is 0-4;

Ring A is a 5-membered ring comprising 1-4 heteroatoms selected from the group consisting of O, S, and N;

each R^6 is independently deuterium, halogen, -CN, -NO_2, -OH, -OR^a, -NR^cR^d, -$C(=O)R^a$, -$C(=O)OR^b$, -$C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^6 on the same atom are taken together to form an oxo;

n is 0-3;

R^7 is hydrogen, deuterium, halogen, -CN, -NO_2, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^8 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^9 is independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{9a};

or two R^9 on the same atom are taken together to form an oxo;

each R^{9a} is independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more of deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

or two R^{9a} on the same atom are taken together to form an oxo;

m is 0-5;

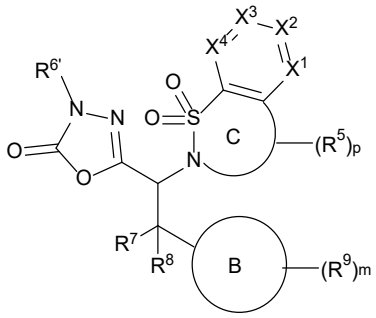
each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more substituents that is oxo, halogen, -CN, -OH, $-OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, -C(=O)OH, $-C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more substituents that is oxo, halogen, -CN, -OH, $-OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, -C(=O)OH, $-C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl; and

each R^c and R^d are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more substituents that is oxo, halogen, -CN, -OH, $-OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, -C(=O)OH, $-C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more substituents that is oxo, halogen, -CN, -OH, $-OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, -C(=O)OH, $-C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl.

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



Formula (Ia);

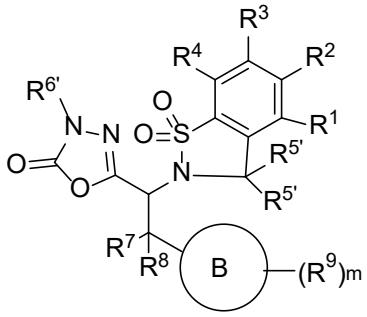
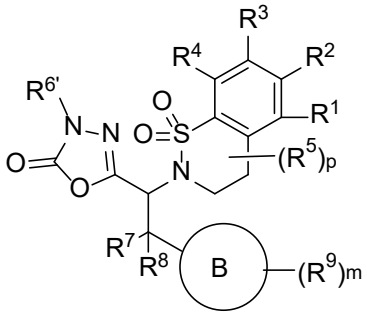
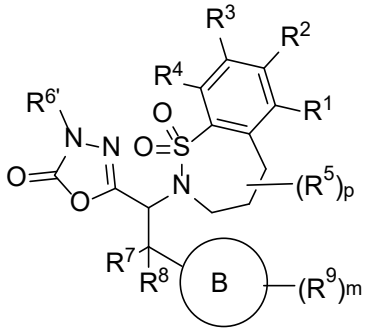
wherein

$R^{6'}$ is hydrogen or C_1-C_6alkyl.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

Ring C is a 5- to 7-membered heterocycloalkyl optionally comprising 1 or 2 additional heteroatoms selected from the group consisting of O, S, and N.

4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein the compound of Formula (I) or (Ia) is of Formula (Ib), (Ic), or (Id):

 Formula (Ib);	 Formula (Ic);
 Formula (Id);	

wherein

$R^{6'}$ is hydrogen or C_1-C_6alkyl; and

each $R^{5'}$ is independently hydrogen or R^5.

5. The compound of claim 4, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

$R^{6'}$ is hydrogen.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

each R^5 is independently deuterium, halogen, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, or C_1-C_6haloalkyl; or

2 R^5 on the same carbon are taken together to form an oxo.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

p is 0.

8. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

p is 1 or 2.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

R^1 is hydrogen, halogen, -OH, -OR^a, C_1-C_6alkyl, or C_1-C_6haloalkyl.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

R^2 is hydrogen, halogen, -OH, -OR^a, C_1-C_6alkyl, or C_1-C_6haloalkyl.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

R^3 is hydrogen, halogen, -OH, -OR^a, C_1-C_6alkyl, or C_1-C_6haloalkyl.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

R^4 is hydrogen, halogen, -OH, -OR^a, C_1-C_6alkyl, or C_1-C_6haloalkyl.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

R^7 is C_1-C_6alkyl and R^8 is hydrogen.

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

Ring B is phenyl.

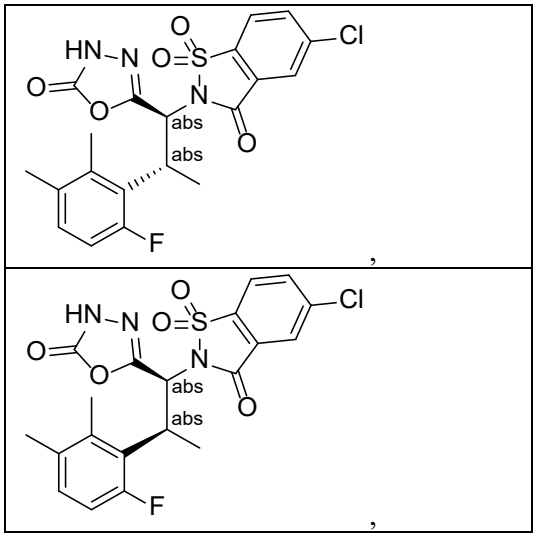
15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

each R^9 is independently halogen or C_1-C_6alkyl.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, wherein:

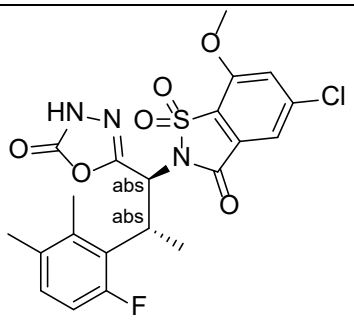
m is 1-3.

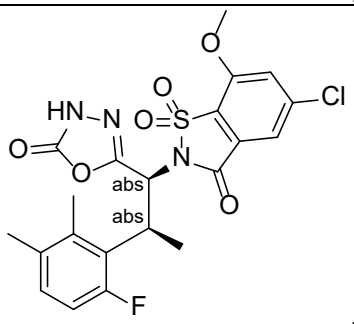
17. The compound of claim 1 selected from the group consisting of:

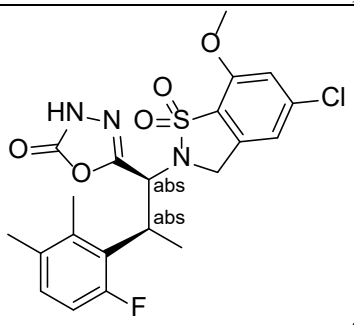


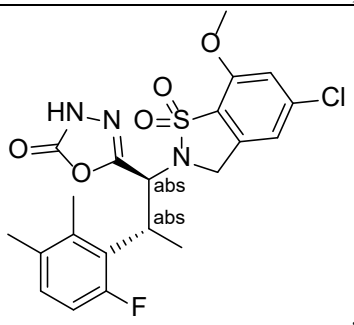
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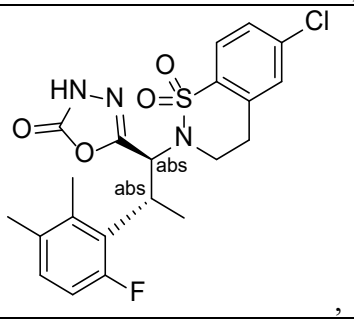
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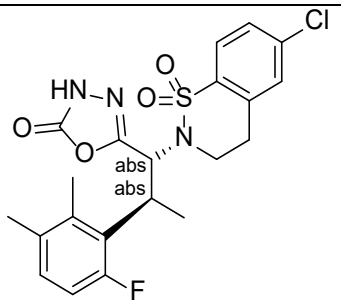

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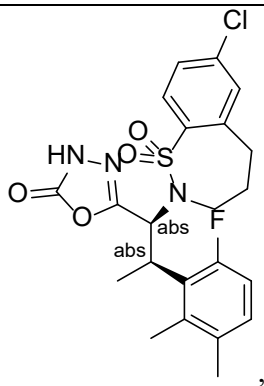

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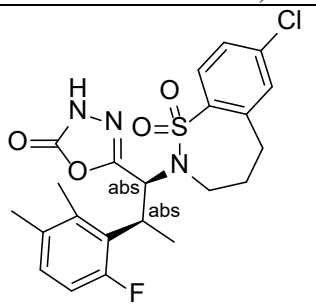

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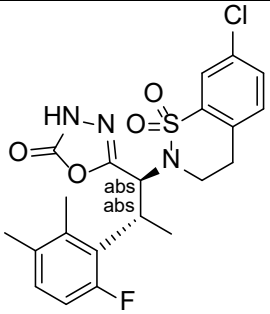

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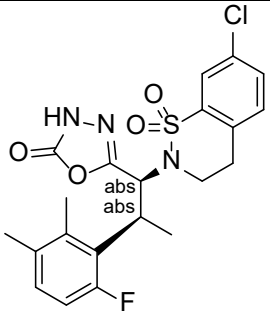

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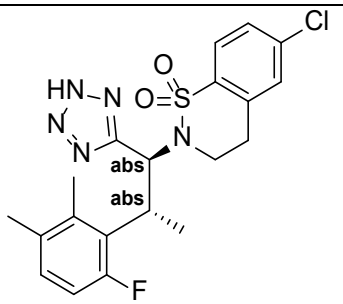

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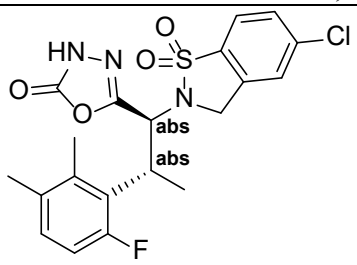

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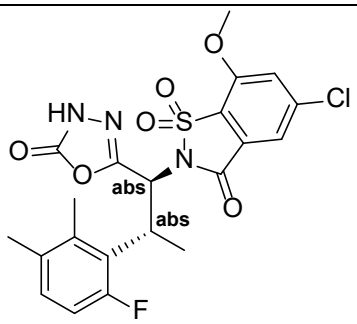

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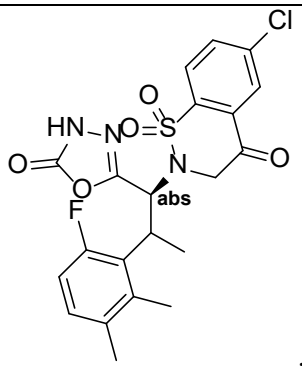

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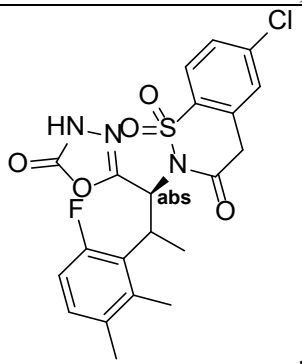

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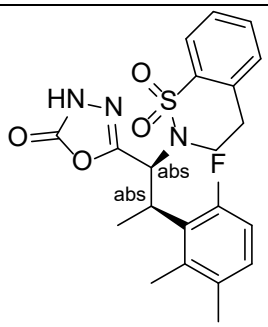

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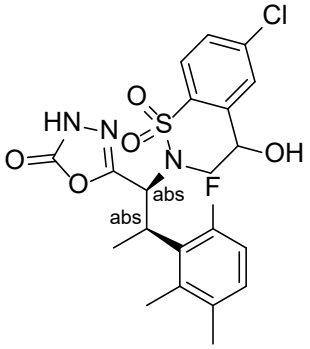

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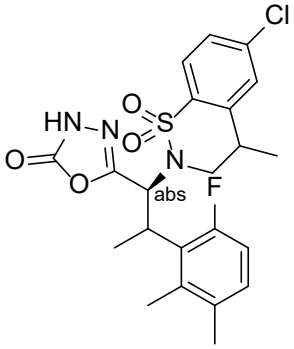

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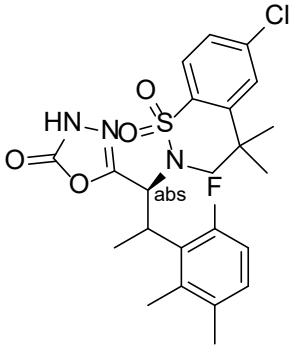

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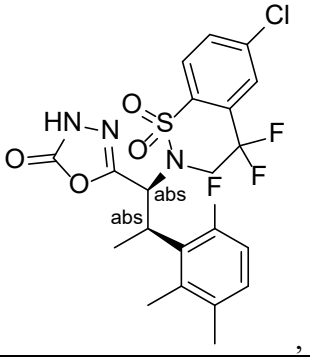

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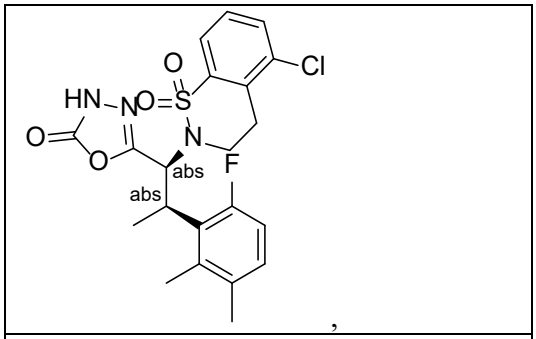

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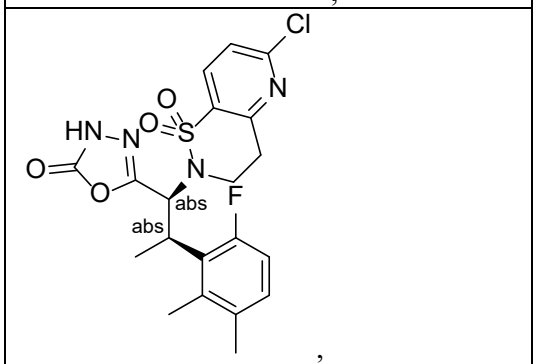

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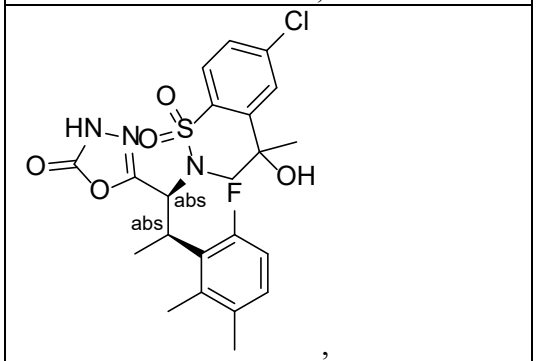

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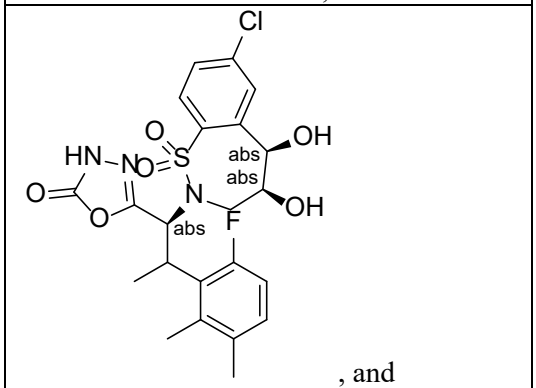

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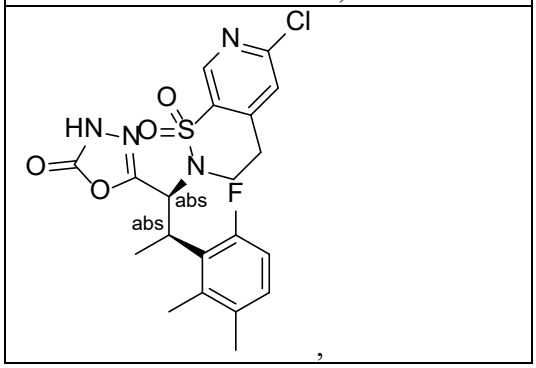

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or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof.

18. A pharmaceutical composition comprising a compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

19. Use of a compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, or a pharmaceutical composition of claim 18, in the manufacture of a medicament for treating cancer in a subject, wherein the compound, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof is to be administered to the subject.

20. Use of a compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, in the manufacture of a medicament for treating a tumor or tumor cells in a subject, wherein the compound, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof is to be administered in an amount sufficient to induce replication stress in the tumor or tumor cells; wherein a cancer-targeted therapeutic agent is to be administered; wherein the tumor or tumor cells have an ecDNA signature; and wherein growth or size of the tumor or growth or number of tumor cells is reduced.

21. A compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt, solvate, tautomer, or stereoisomer thereof, for use as a medicament.