

II

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof, wherein

q is 0, 1, or 2;

X^6, X^7, and X^8 are each N or CH;

X^9 is N;

R^1 is H or C_1-C_6 alkyl optionally substituted with halo, hydroxy, or cyano;

Y^2 is -O- or -$C(R^6)_2$-;

R^5 is H or optionally substituted C_1-C_6 alkyl;

each R^6 is independently H, halo, or optionally substituted C_1-C_6 alkyl, or two R^6 together with the carbon atom to which they are attached form a C_1-C_6 alken-1-yl, optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

R^3 and R^4 are independently H, halo, or optionally substituted C_1-C_6 alkyl, or R^3 and R^6 together with the carbon atoms to which they are attached form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring, or R^3 and R^4 together with the carbon atoms to which they are attached, form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

A is an optionally substituted heteroaryl ring, optionally substituted cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl;

L is -$C(R^8)_2$-, or is absent, -O-, -S-, -S(O)-, -$S(O)_2$-, or -NR^7-;

R^7 is H or optionally substituted C_1-C_6 alkyl;

each R^8 is independently H, halo, or optionally substituted C_1-C_6 alkyl, or two R^8 together with the carbon atom to which they are attached form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

R^9 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted heterocyclyl; and

each R^{10} is independently cyano, halo, or optionally substituted alkyl;

and

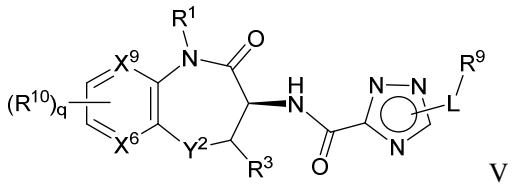
further wherein:

each cycloalkyl is independently a saturated or partially unsaturated cyclic alkyl group of from 3 to 20 ring carbon atoms having a single ring or multiple rings, wherein the cycloalkyl may be fused, bridged, or spiro;

each heterocyclyl is independently a saturated or unsaturated cyclic alkyl group of from 2 to 20 ring carbon atoms with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur, and may comprise one or more oxo (C=O) or N-oxide (N-O-) moieties and/or a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro; and

each heteroaryl is independently an aromatic group having 1 to 20 ring carbon atoms, a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0005b]In one aspect, the present disclosure refers to a compound of Formula V:



V

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof, wherein

q is 0, 1, or 2;

X^6 is N or CR^{14};

X^9 is N;

R^1 is H or optionally substituted C_1-C_6 alkyl;

Y^2 is -O- or $-C(R^6)_2-$;

each R^6 is independently H, halo, optionally substituted C_1-C_6 alkyl;

R^3 is H, halo, optionally substituted C_1-C_6 alkyl, or R^3 and R^6 together with the carbon atoms to which they are attached, form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

L is $-C(R^8)_2-$;

each R^8 is independently H, halo, optionally substituted C_1-C_6 alkyl, or two R^8 together with the carbon atom to which they are attached form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

R^9 is optionally substituted aryl or optionally substituted heteroaryl;

each R^{10} is independently cyano, halo, optionally substituted C_1-C_6 alkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, optionally substituted C_1-C_6 alkoxy, or $-S(O)_2$-C_1-C_6 alkyl;

each R^{14} is independently hydrogen, cyano, halo, C_1-C_3 alkyl optionally substituted with halo, or C_1-C_3 alkoxy optionally substituted with halo; and

wherein each optionally substituted pyridyl, optionally substituted C_1-C_6 alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl ring is independently optionally substituted by one or more substituents, provided that the designated atom's normal valence is not exceeded, selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, acyl, amido, amino, amidino, aryl, aralkyl, azido, carbamoyl, cyano, cycloalkyl, cycloalkylalkyl, guanadino, halo, haloalkyl, haloalkoxy, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydrazine, hydrazone, imino, imido, hydroxy, oxo,

oxime, nitro, sulfonyl, sulfinyl, alkylsulfonyl, alkylsulfinyl, thiocyanate, sulfinic acid, sulfonic acid, sulfonamido, -SH, thioxo, N-oxide, $-Si(R^{100})_3$ wherein each R^{100} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl,-OC(O)R, and -C(O)OR, wherein R is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; and

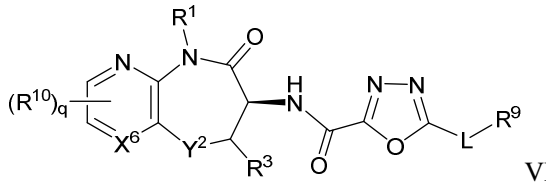
further wherein:

each cycloalkyl is independently a saturated or partially unsaturated cyclic alkyl group of from 3 to 20 ring carbon atoms having a single ring or multiple rings, wherein the cycloalkyl may be fused, bridged, or spiro;

each heterocyclyl is independently a saturated or unsaturated cyclic alkyl group of from 2 to 20 ring carbon atoms with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur, and may comprise one or more oxo (C=O) or N-oxide (N-O-) moieties and/or a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro; and

each heteroaryl is independently an aromatic group having 1 to 20 ring carbon atoms, a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0005c] In one aspect, the present disclosure refers to a compound of Formula VI:



VI

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof, wherein

q is 0, 1, or 2;

X^6 is N or CR^{14};

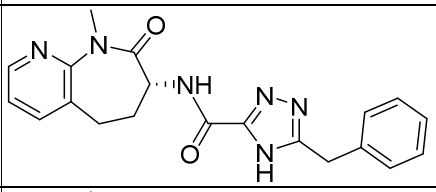
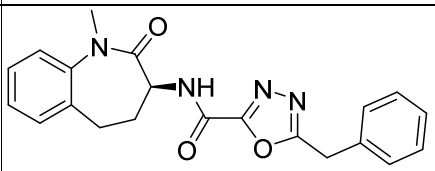
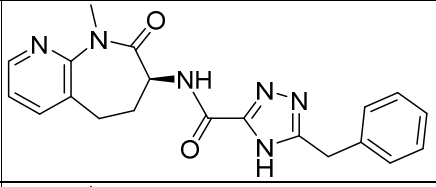
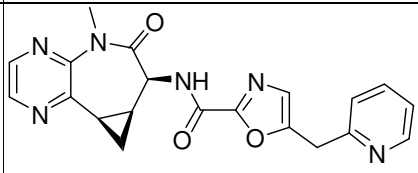
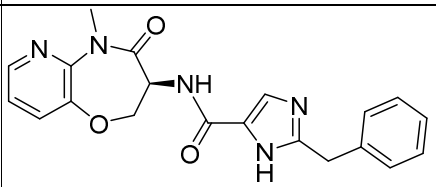
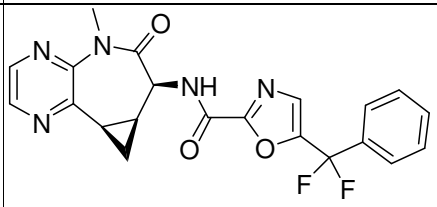
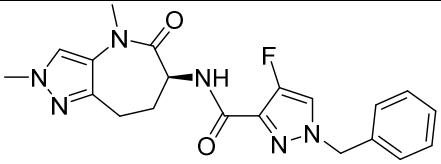
R^1 is H or optionally substituted C_1-C_6 alkyl;

Y^2 is -O- or $-C(R^6)_2-$;

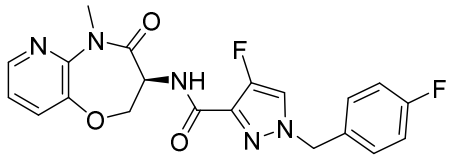
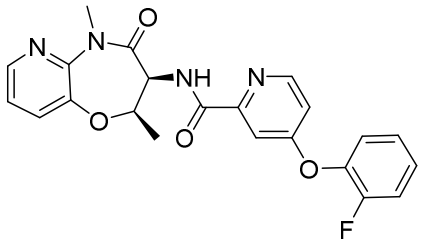
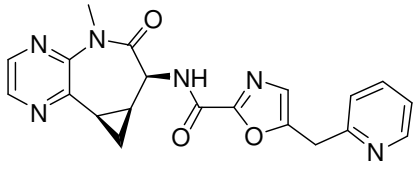
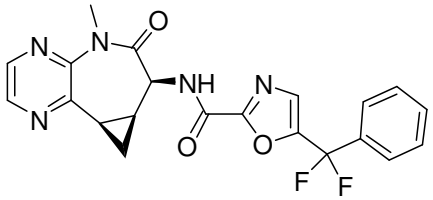
each R^6 is independently H, halo, optionally substituted C_1-C_6 alkyl;

R^3 is H, halo, optionally substituted C_1-C_6 alkyl, or R^3 and R^6 together with the carbon atoms to which they are attached, form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

L is $-C(R^8)_2-$;

No.	Structure	No.	Structure
107A		225	
107B		226	
108		227	 or
109A			

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof.




or


or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof.

[0005f] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound, or a stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, as disclosed herein and an excipient.

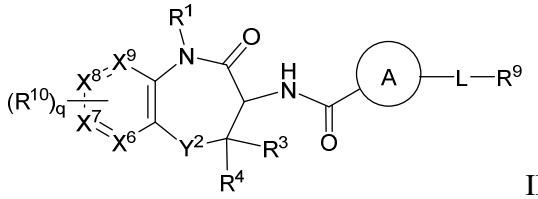
[0005g] In one aspect, the present disclosure refers to a use of any one of the compounds as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of a receptor-interacting protein kinase 1-mediated disease or disorder, wherein the disease or disorder is an inflammatory disease or disorder, a necrotic cell disease, a neurodegenerative disease, a central nervous system disease, an ocular disease, a malignancy, an immune-mediated disease, an allergic disease, an autoimmune disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis, atopic dermatitis, rheumatoid arthritis, spondyloarthritis, gout, SoJIA, systemic lupus erythematosus, Sjogren's syndrome, systemic scleroderma, anti-phospholipid syndrome, vasculitis, osteoarthritis, non-alcohol steatohepatitis, alcohol steatohepatitis, autoimmune hepatitis, autoimmune hepatobiliary diseases, primary sclerosing cholangitis, nephritis, Celiac disease, autoimmune ITP, transplant rejection, ischemia reperfusion injury of solid organs, sepsis, systemic inflammatory response syndrome, cerebrovascular accident, myocardial or cardiac infarction, Huntington's disease, Alzheimer's disease, Parkinson's disease, asthma, multiple sclerosis, type I diabetes, Wegener's granulomatosis, pulmonary sarcoidosis, Behçet's disease, interleukin-1 converting enzyme associated fever syndrome, chronic obstructive pulmonary disease, tumor necrosis factor receptor-associated periodic syndrome, periodontitis, trauma, ischemia, stroke, cardiac infarction, infection, lysosomal storage disease, Gaucher's disease, Krabbe disease, Niemann-Pick disease, amyotrophic lateral sclerosis (ALS/Lou Gehrig's Disease), HIV-associated dementia, retinal degenerative disease, glaucoma, age-related macular degeneration, psoriasis, psoriatic arthritis, brain injury, spinal cord injury, dementia, Huntington's disease, diabetic neuropathy, polyglutamine (polyQ) diseases, Fahr disease, Menke's disease, Wilson's disease, cerebral ischemia, Friedreich's ataxia, Lewy body disease, or a prion disorder.

DESCRIPTION

[0006] Provided herein are compounds that are useful as inhibitors of receptor-interacting protein kinase 1. The disclosure also provides compositions, including pharmaceutical compositions, kits that include the compounds, and methods of using (or administering) and making the compounds. The disclosure further provides compounds or compositions thereof for use in a method of treating a disease,

CLAIMS:

1. A compound of Formula II:



II

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof, wherein

q is 0, 1, or 2;

X^6, X^7, and X^8 are each N or CH;

X^9 is N;

R^1 is H or C_1-C_6 alkyl optionally substituted with halo, hydroxy, or cyano;

Y^2 is -O- or -$C(R^6)_2$-;

R^5 is H or optionally substituted C_1-C_6 alkyl;

each R^6 is independently H, halo, or optionally substituted C_1-C_6 alkyl, or two R^6 together with the carbon atom to which they are attached form a C_1-C_6 alken-1-yl, optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

R^3 and R^4 are independently H, halo, or optionally substituted C_1-C_6 alkyl, or R^3 and R^6 together with the carbon atoms to which they are attached form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring, or R^3 and R^4 together with the carbon atoms to which they are attached, form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

A is an optionally substituted heteroaryl ring, optionally substituted cycloalkyl, optionally substituted heterocyclyl, or optionally substituted aryl;

L is -$C(R^8)_2$-, or is absent, -O-, -S-, -S(O)-, -$S(O)_2$-, or -NR^7-;

R^7 is H or optionally substituted C_1-C_6 alkyl;

each R^8 is independently H, halo, or optionally substituted C_1-C_6 alkyl, or two R^8 together with the carbon atom to which they are attached form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

R^9 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted heterocyclyl; and

each R^{10} is independently cyano, halo, or optionally substituted alkyl;

and

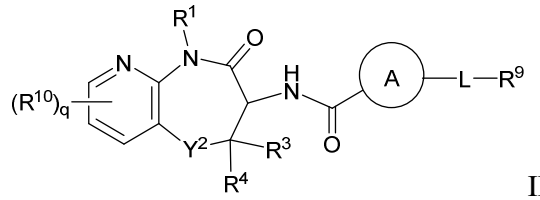
further wherein:

each cycloalkyl is independently a saturated or partially unsaturated cyclic alkyl group of from 3 to 20 ring carbon atoms having a single ring or multiple rings, wherein the cycloalkyl may be fused, bridged, or spiro;

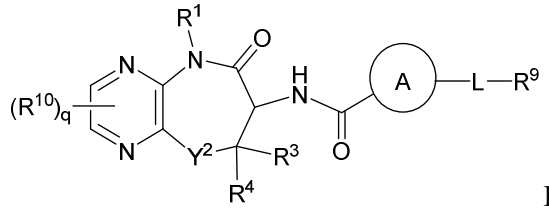
each heterocyclyl is independently a saturated or unsaturated cyclic alkyl group of from 2 to 20 ring carbon atoms with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur, and may comprise one or more oxo (C=O) or N-oxide (N-O-) moieties and/or a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro; and

each heteroaryl is independently an aromatic group having 1 to 20 ring carbon atoms, a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur.

2. The compound of claim 1, wherein the compound is of Formula (IIe) or (IIf):



IIe



IIf

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof;

wherein

q is 0, 1 or 2;

R^1 is H or C_1-C_6 alkyl optionally substituted with halo, hydroxy or cyano;

Y^2 is -O- or -$C(R^6)_2$-;

R^5 is H or optionally substituted C_1-C_6 alkyl;

each R^6 is independently H, halo, or optionally substituted C_1-C_6 alkyl, or two R^6 together with the carbon atom to which they are attached form a C_1-C_6 alken-1-yl, optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

R^3 and R^4 are independently H, halo, or optionally substituted C_1-C_6 alkyl, or R^3 and R^4 together with the carbon atoms to which they are attached, form an optionally substituted cycloalkyl or heterocyclyl ring, or R^3 and R^6 together with the carbon atoms to which they are attached, form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

A is an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl or optionally substituted heteroaryl ring;

L is $-C(R^8)_2-$ or is absent, -O-, -S-, -S(O)-, $-S(O)_2-$, or $-NR^7-$;

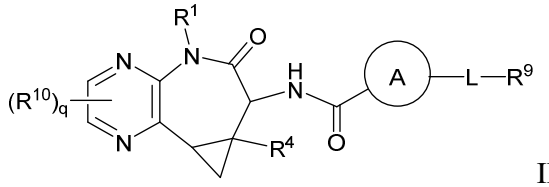
R^7 is H or optionally substituted C_1-C_6 alkyl;

each R^8 is independently H, halo, or optionally substituted C_1-C_6 alkyl, or two R^8 together with the carbon atom to which they are attached form an optionally substituted cycloalkyl or heterocyclyl ring;

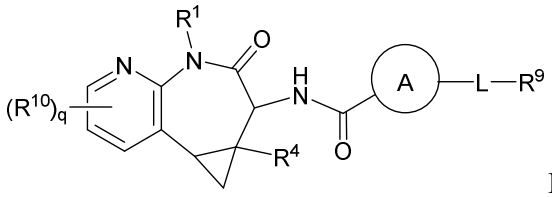
R^9 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted heterocyclyl; and

each R^{10} is independently cyano, halo, or optionally substituted alkyl.

3. The compound of claim 2, wherein the compound is of Formula IIf-1 or IIe-1:



IIf-1



IIe-1

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof;

wherein

q is 0, 1 or 2;

R^1 is H or C_1-C_6 alkyl optionally substituted with halo, hydroxy, or cyano;

R^4 is H, halo, or optionally substituted C_1-C_6 alkyl;

A is an optionally substituted heteroaryl ring, optionally substituted aryl, optionally substituted cycloalkyl, or optionally substituted heterocyclyl;

L is $-C(R^8)_2-$ or is absent, -O-, -S-, -S(O)-, $-S(O)_2-$, or $-NR^7-$;

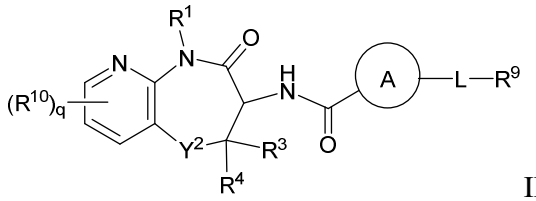
R^7 is H or optionally substituted C_1-C_6 alkyl;

each R^8 is independently H, halo, or optionally substituted C_1-C_6 alkyl, or two R^8 together with the carbon atom to which they are attached form an optionally substituted cycloalkyl or heterocyclyl ring;

R^9 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted heterocyclyl; and

each R^{10} is independently cyano, halo, or optionally substituted alkyl.

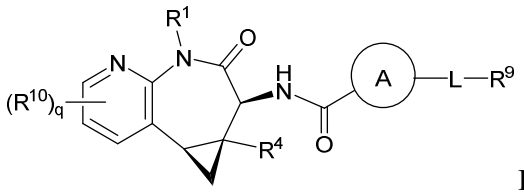
4. The compound of claim 2, wherein the compound is of Formula (IIe):



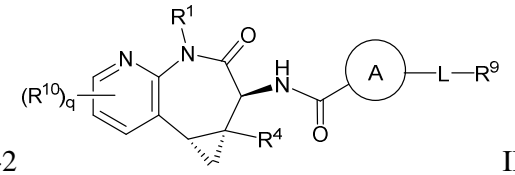
IIe

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof.

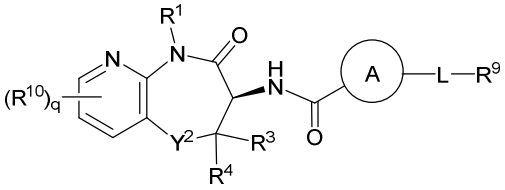
5. The compound of claim 4, wherein the compound is of Formula IIe-2, Formula IIe-3, Formula IIe-4, Formula IIe-5, or Formula IIe-6:



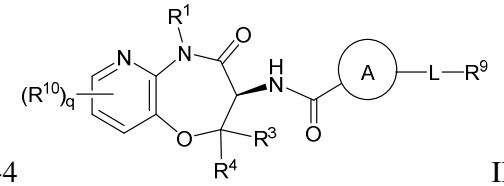
IIe-2



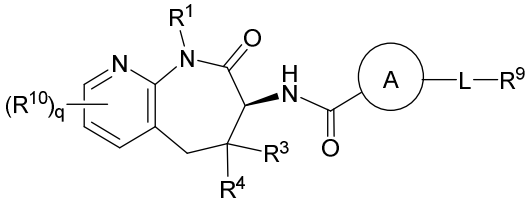
IIe-3



IIe-4



IIe-5



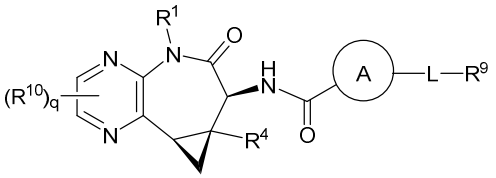
IIe-6

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof.

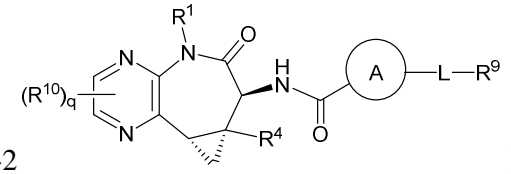
6. The compound of claim 5, wherein the compound is of Formula IIe-2 or IIe-4, or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof.

7. The compound of claim 2, wherein the compound is of Formula IIf, or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof.

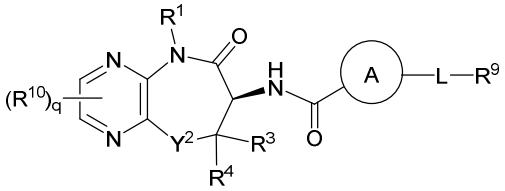
8. The compound of claim 7, wherein the compound is of Formula IIf-2, Formula IIf-3, Formula IIf-4, Formula IIf-5, or Formula IIf-6:



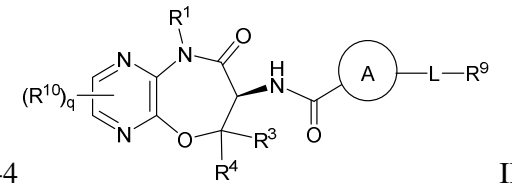
IIf-2



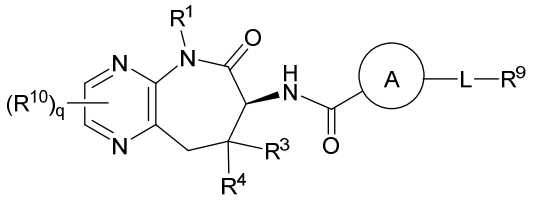
IIf-3



IIf-4



IIf-5



IIf-6

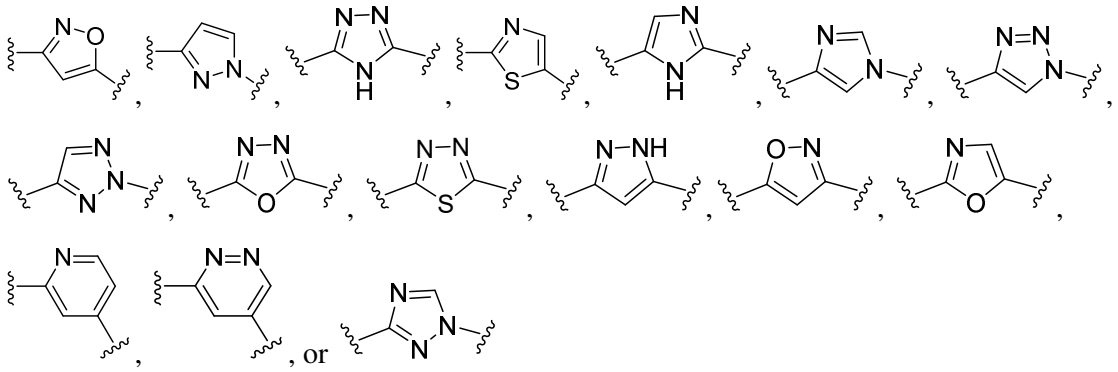
or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof.

9. The compound of any one of claims 1-8, wherein the A ring is an optionally substituted heteroaryl ring.

10. The compound of claim 9, wherein the A ring is an optionally substituted 5-membered heteroaryl ring.

11. The compound any one of claims 1-8, wherein A is phenyl.

12. The compound of any one of claims 1-8, wherein the A ring is:



wherein each ring is optionally substituted with one or more halo, cyano or C_1-C_6 alkyl.

13. The compound of any one of claims 1-8, wherein A is phenyl, phenylbenzo[d]thiazolyl, isoxazolyl, oxazolyl, pyrazolyl, triazolyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, pyrrolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, cyclobutyl, cyclopropyl, or azetidinyl.

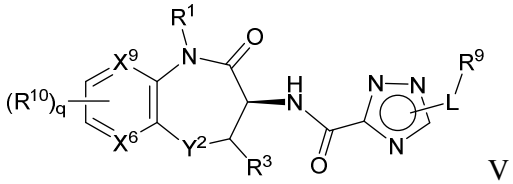
14. The compound of claim 13, wherein A is pyrazolyl, isoxazolyl, oxadiazolyl or triazolyl.

15. The compound of claim 13, wherein A is oxadiazolyl.

16. The compound of claim 13, wherein A is triazolyl.

17. The compound of any one of claims 1-16, wherein L is $-C(R^8)_2-$.

18. A compound of Formula V:



V

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof, wherein

q is 0, 1, or 2;

X^6 is N or CR^{14};

X^9 is N;

R^1 is H or optionally substituted C_1-C_6 alkyl;

Y^2 is -O- or $-C(R^6)_2-$;

each R^6 is independently H, halo, optionally substituted C_1-C_6 alkyl;

R^3 is H, halo, optionally substituted C_1-C_6 alkyl, or R^3 and R^6 together with the carbon atoms to which they are attached, form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

L is $-C(R^8)_2-$;

each R^8 is independently H, halo, optionally substituted C_1-C_6 alkyl, or two R^8 together with the carbon atom to which they are attached form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

R^9 is optionally substituted aryl or optionally substituted heteroaryl;

each R^{10} is independently cyano, halo, optionally substituted C_1-C_6 alkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, optionally substituted C_1-C_6 alkoxy, or -$S(O)_2$-C_1-C_6 alkyl;

each R^{14} is independently hydrogen, cyano, halo, C_1-C_3 alkyl optionally substituted with halo, or C_1-C_3 alkoxy optionally substituted with halo; and

wherein each optionally substituted pyridyl, optionally substituted C_1-C_6 alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl ring is independently optionally substituted by one or more substituents, provided that the designated atom's normal valence is not exceeded, selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, acyl, amido, amino, amidino, aryl, aralkyl, azido, carbamoyl, cyano, cycloalkyl, cycloalkylalkyl, guanadino, halo, haloalkyl, haloalkoxy, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydrazine, hydrazone, imino, imido, hydroxy, oxo, oxime, nitro, sulfonyl, sulfinyl, alkylsulfonyl, alkylsulfinyl, thiocyanate, sulfinic acid, sulfonic acid, sulfonamido, -SH, thioxo, N-oxide, -$Si(R^{100})_3$ wherein each R^{100} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl,-OC(O)R, and -C(O)OR, wherein R is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; and

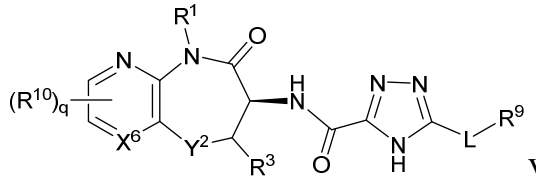
further wherein:

each cycloalkyl is independently a saturated or partially unsaturated cyclic alkyl group of from 3 to 20 ring carbon atoms having a single ring or multiple rings, wherein the cycloalkyl may be fused, bridged, or spiro;

each heterocyclyl is independently a saturated or unsaturated cyclic alkyl group of from 2 to 20 ring carbon atoms with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur, and may comprise one or more oxo (C=O) or N-oxide (N-O-) moieties and/or a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro; and

each heteroaryl is independently an aromatic group having 1 to 20 ring carbon atoms, a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur.

19. The compound of claim 18, wherein the compound of Formula V is represented by Formula Va:

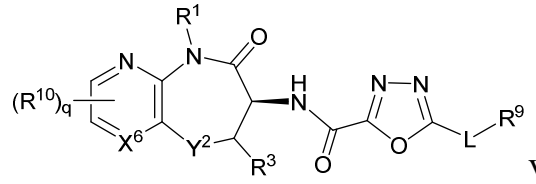


Va

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof.

20. The compound of claim 18 or claim 19, wherein R^{14} is hydrogen, cyano, halo or methyl optionally substituted with 1-3 fluoro or oxo.

21. A compound of Formula VI:



VI

or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof, wherein

q is 0, 1, or 2;

X^6 is N or CR^{14};

R^1 is H or optionally substituted C_1-C_6 alkyl;

Y^2 is -O- or -$C(R^6)_2$-;

each R^6 is independently H, halo, optionally substituted C_1-C_6 alkyl;

R^3 is H, halo, optionally substituted C_1-C_6 alkyl, or R^3 and R^6 together with the carbon atoms to which they are attached, form an optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

L is -$C(R^8)_2$-;

each R^8 is independently H, halo, optionally substituted C_1-C_6 alkyl, or two R^8 together with the carbon atom to which they are attached form a optionally substituted cycloalkyl or optionally substituted heterocyclyl ring;

R^9 is optionally substituted aryl;

each R^{10} is independently halo, optionally substituted C_1-C_6 alkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted cycloalkyl, or optionally substituted C_1-C_6 alkoxy; and

R^{14} is hydrogen, cyano, halo, C_1-C_3 alkyl optionally substituted with halo or oxo, or C_1-C_3 alkoxy optionally substituted with halo or oxo; and

wherein each optionally substituted pyridyl, optionally substituted C_1-C_6 alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl ring is independently optionally substituted by one or more substituents, provided that the designated atom's normal valence is not exceeded, selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, acyl, amido, amino, amidino, aryl, aralkyl, azido, carbamoyl, cyano, cycloalkyl, cycloalkylalkyl, guanadino, halo, haloalkyl, haloalkoxy, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydrazine, hydrazone, imino, imido, hydroxy, oxo, oxime, nitro, sulfonyl, sulfinyl, alkylsulfonyl, alkylsulfinyl, thiocyanate, sulfinic acid, sulfonic acid, sulfonamido, -SH, thioxo, N-oxide, -$Si(R^{100})_3$ wherein each R^{100} is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl,-OC(O)R, and -C(O)OR, wherein R is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; and

further wherein:

each cycloalkyl is independently a saturated or partially unsaturated cyclic alkyl group of from 3 to 20 ring carbon atoms having a single ring or multiple rings, wherein the cycloalkyl may be fused, bridged, or spiro;

each heterocyclyl is independently a saturated or unsaturated cyclic alkyl group of from 2 to 20 ring carbon atoms with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur, and may comprise one or more oxo (C=O) or N-oxide (N-O-) moieties and/or a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro; and

each heteroaryl is independently an aromatic group having 1 to 20 ring carbon atoms, a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur.

22. The compound of any one of claims 19-21, wherein X^6 is CR^{14}.

23. The compound of any one of claims 19-21, wherein X^6 is N.

24. The compound of any one of claims 21-23, wherein R^{14} is hydrogen.

25. The compound of any preceding claim, wherein R^1 is C_1-C_6 alkyl.

26. The compound of claim 25, wherein R^1 is methyl.

27. The compound of any one of claims 1-2 and 4-26, wherein Y^2 is O.

28. The compound of any one of claims 1-2 and 4-26, wherein R^3 is hydrogen or fluoro.

29. The compound of claim 28, wherein R^3 is H.

30. The compound of any one of claims 1-2 and 4-26, wherein R^3 and R^6 together with the carbon atoms to which they are attached form an optionally substituted cycloalkyl.

31. The compound of claim 30, wherein R^3 and R^6 together with the carbon atoms to which they are attached form an optionally substituted cyclopropyl ring.

32. The compound of any preceding claim, wherein R^4 is optionally substituted C_1-C_6 alkyl.

33. The compound of claim 32, wherein R^4 is methyl.

34. The compound of claim 32, wherein R^4 is H.

35. The compound of any preceding claim, wherein L is $-C(R^8)_2-$ and each R^8 is independently H, or two R^8 together with the carbon atom to which they are attached form an optionally substituted cycloalkyl.

36. The compound of claim 35, wherein L is $-C(R^8)_2-$ and two R^8 together with the carbon atom to which they are attached, form a cycloalkyl ring.

37. The compound of claim 36, wherein L is -C(R^8)$_2$- and two R^8 are taken together with the carbon atom to which they are attached to form cyclopropyl.

38. The compound of any one of claims 1-37, wherein L is CH_2.

39. The compound of any one of claims 1-38, wherein R^9 is optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted cycloalkyl.

40. The compound of claim 39, wherein R^9 is phenyl, dihydroindenyl, pyridyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 3-cyano-4-fluorophenyl, or 5-fluoropyridin-3-yl.

41. The compound of claim 39, wherein R^9 is optionally substituted aryl.

42. The compound of claim 39, wherein R^9 is phenyl optionally substituted with one or more halo, cyano, or C_1-C_6 alkyl optionally substituted with halo.

43. The compound of claim 42, wherein R^9 is phenyl substituted by one to two halo.

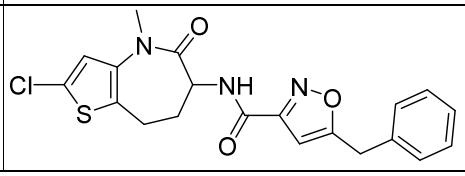
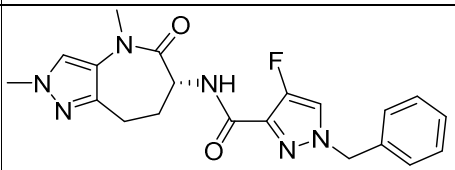
44. The compound of any one of claims 1-39, wherein R^9 is optionally substituted pyridyl, phenyl or 2,3-dihydro-1H-indenyl.

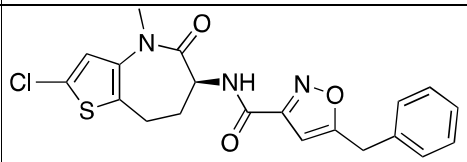
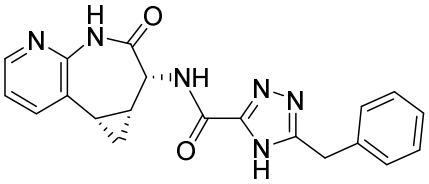
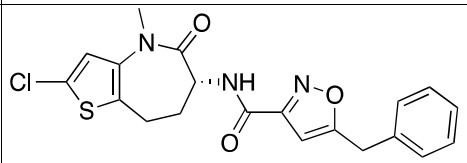
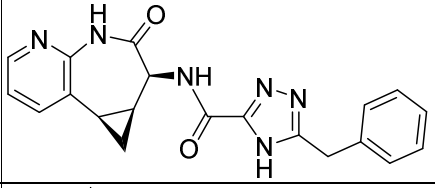
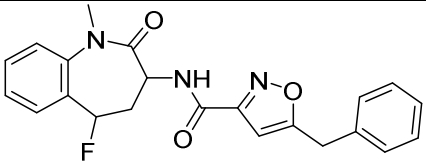
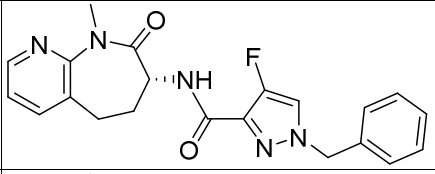
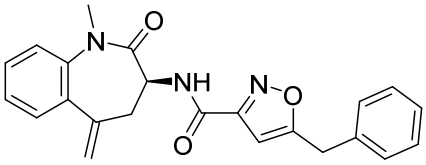
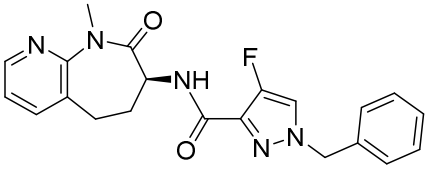
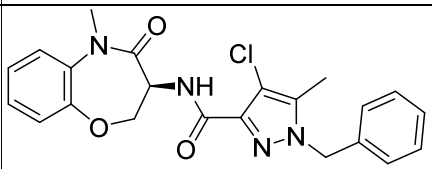
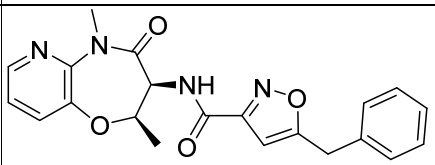
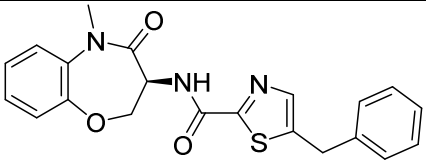
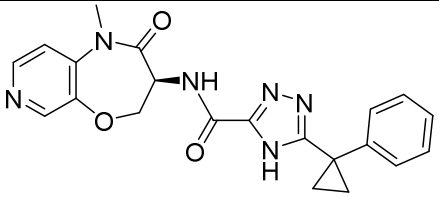
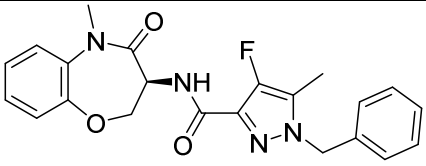
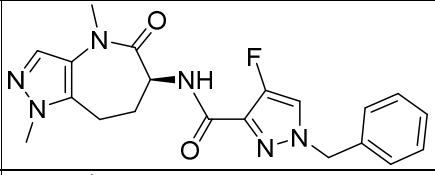
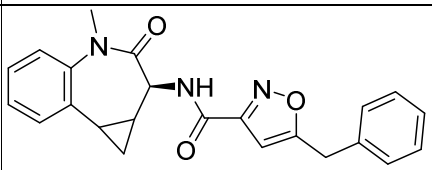
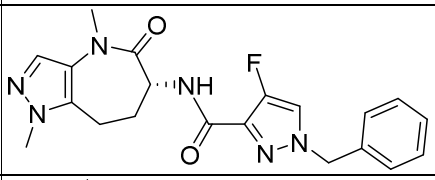
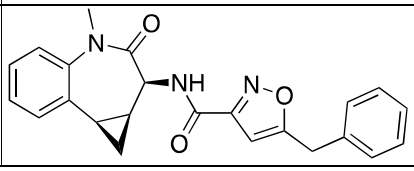
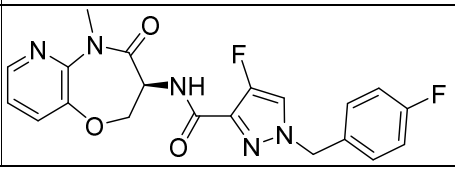
45. The compound of any preceding claim, wherein each R^{10} is independently halo.

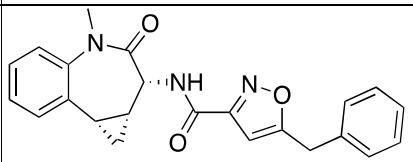
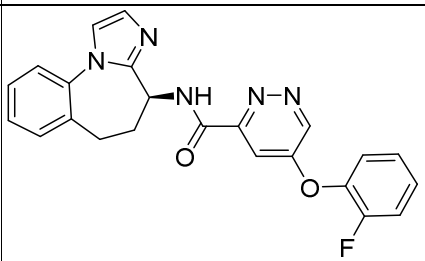
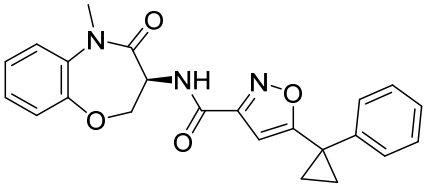
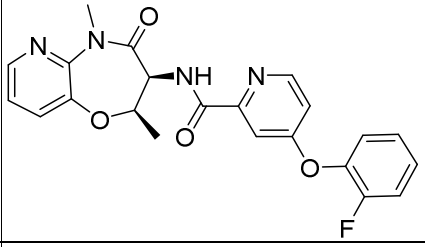
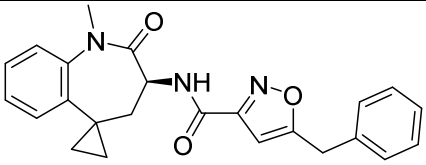
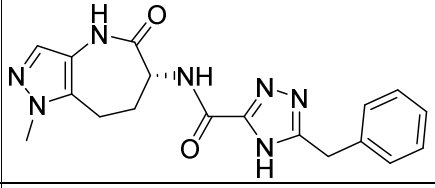
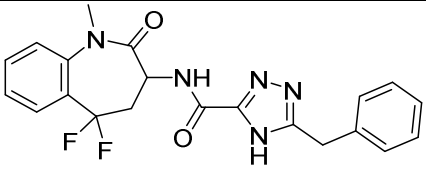
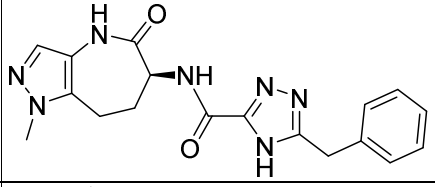
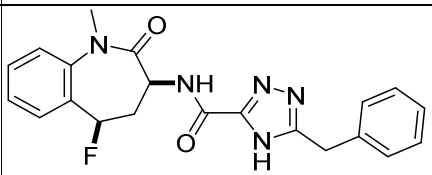
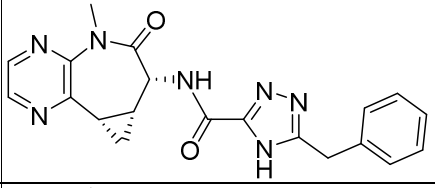
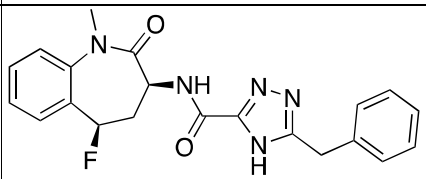
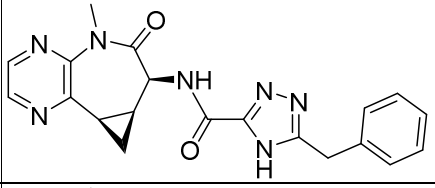
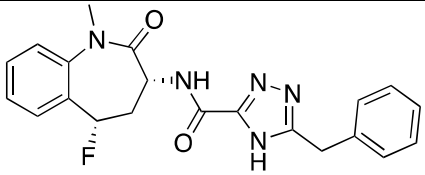
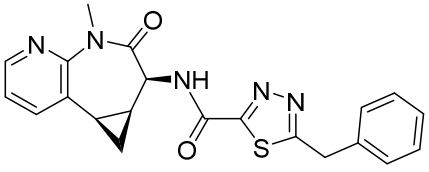
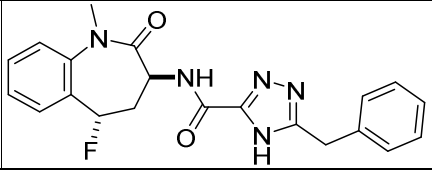
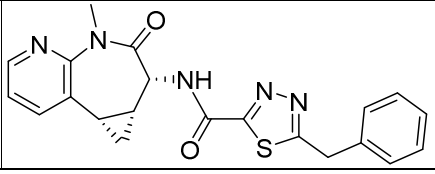
46. The compound of claim 45, wherein each R^{10} is independently fluoro.

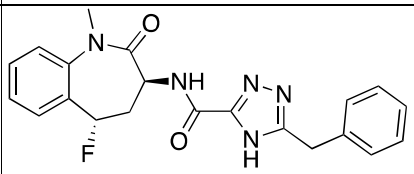
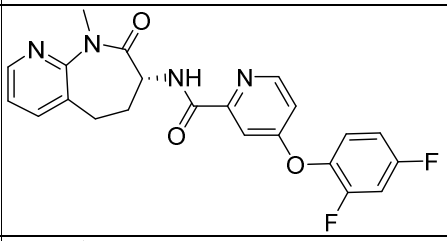
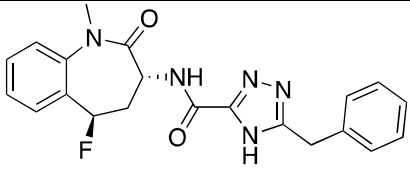
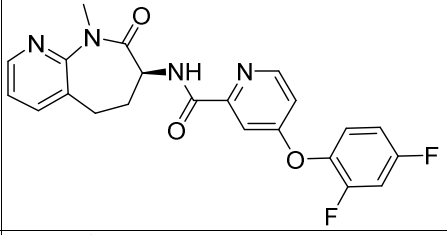
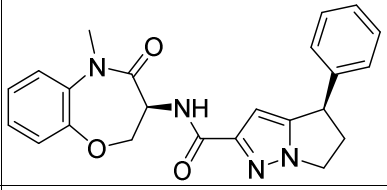
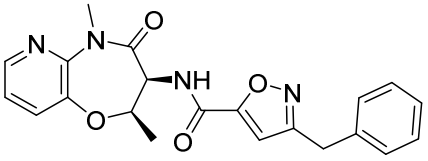
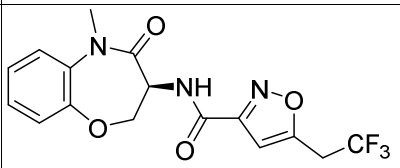
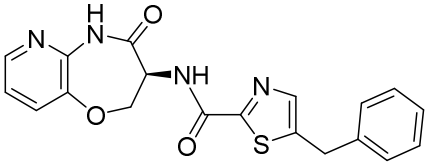
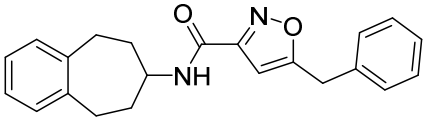
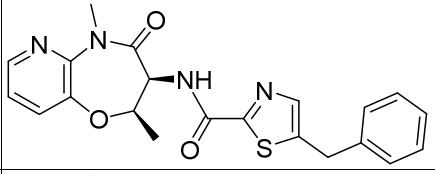
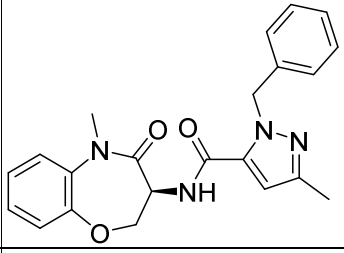
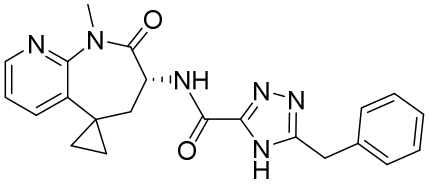
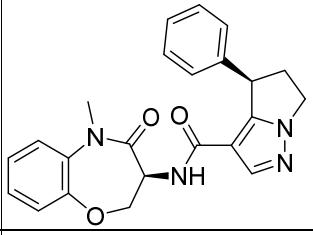
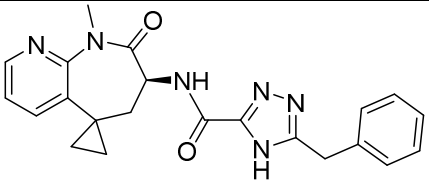
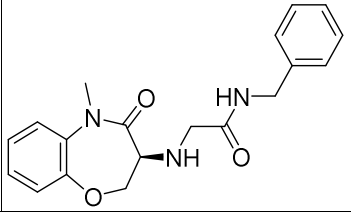
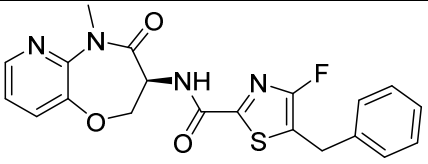
47. The compound of any one of claims 1-46, wherein q is 2.

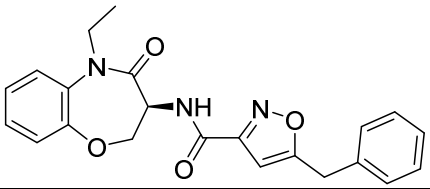
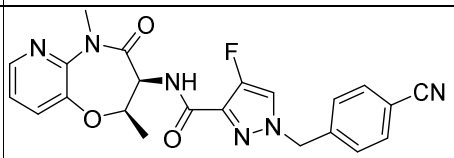
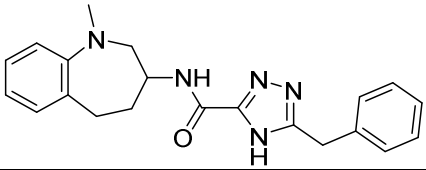
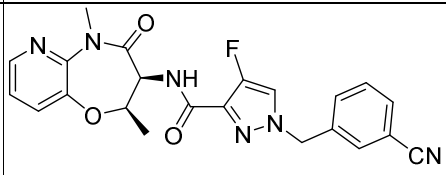
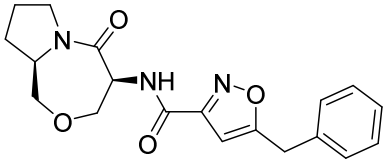
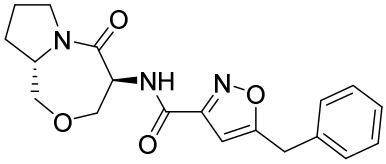
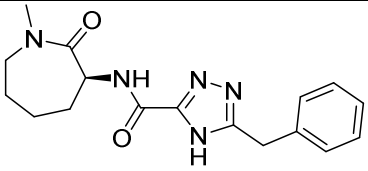
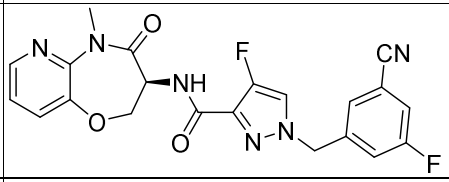
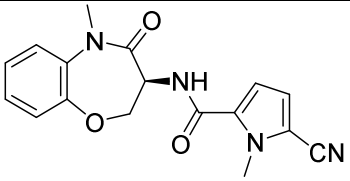
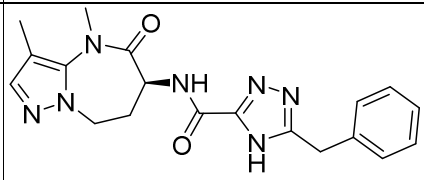
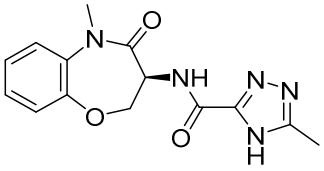
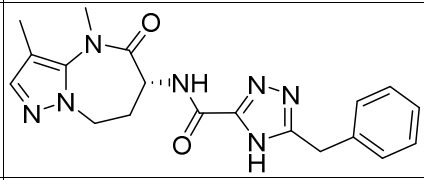
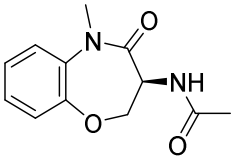
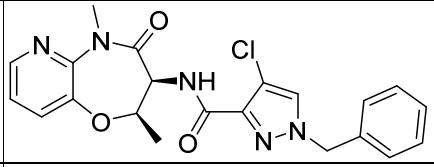
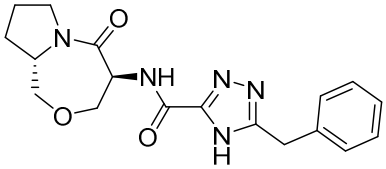
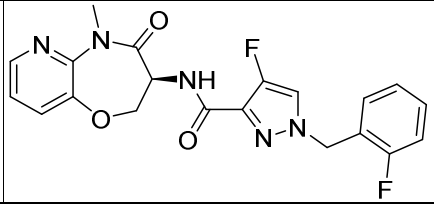
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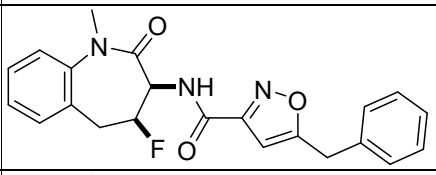
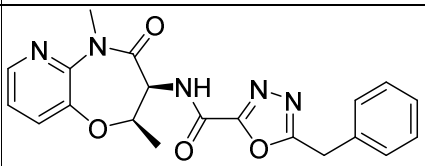
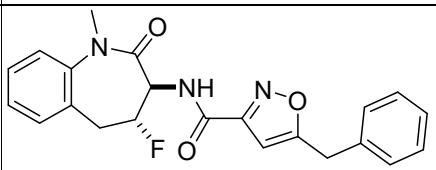
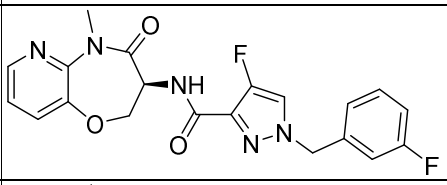
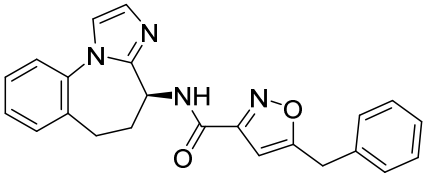
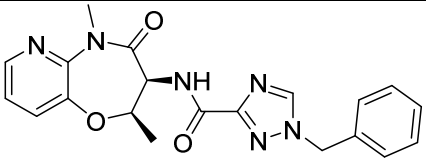
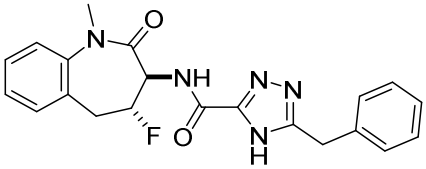
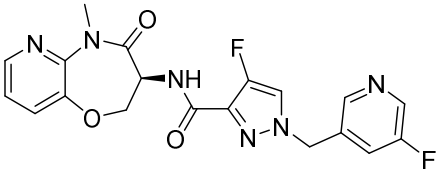
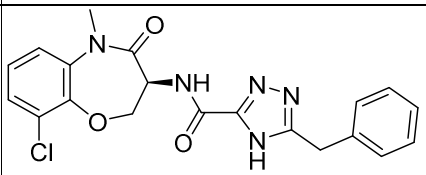
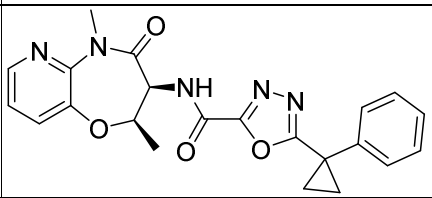
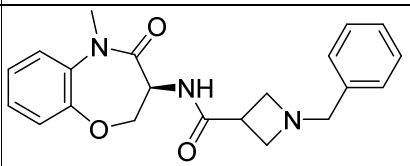
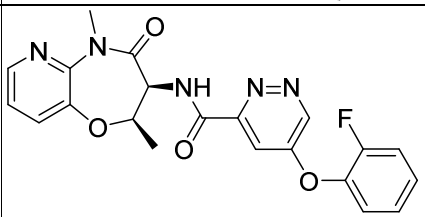
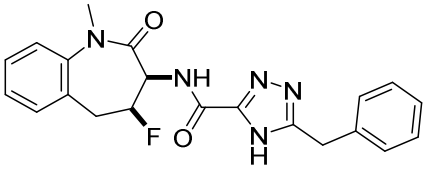
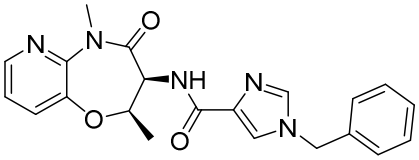
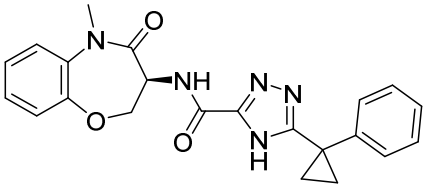
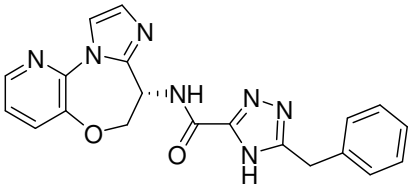
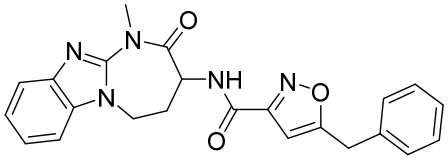
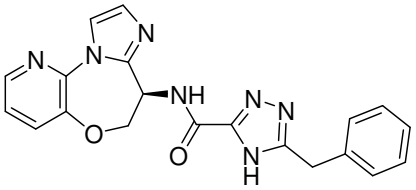
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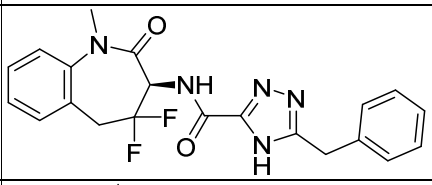
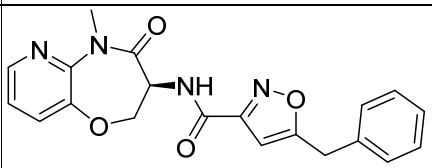
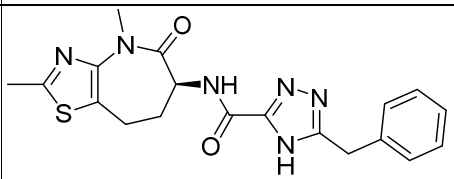
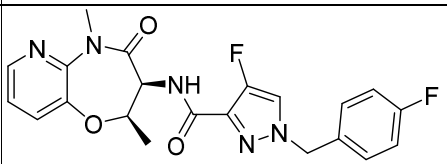
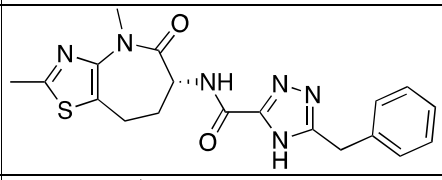
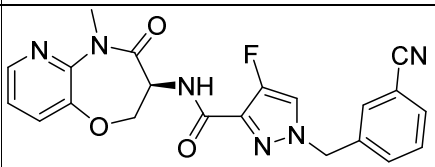
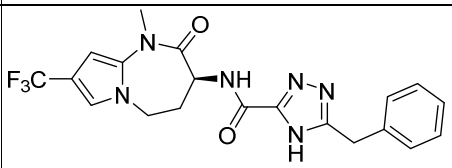
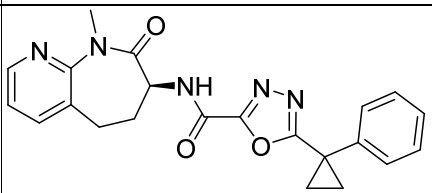
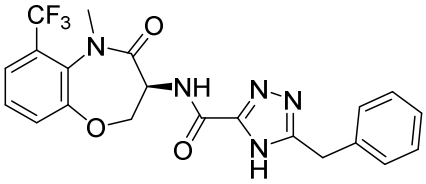
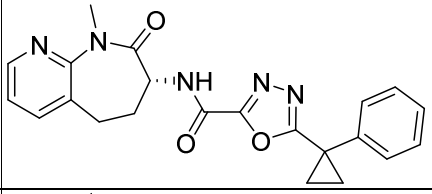
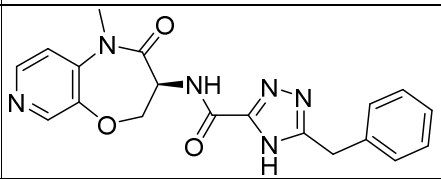
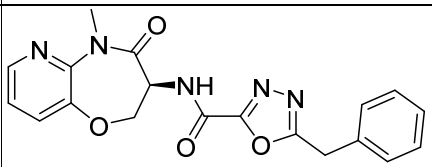
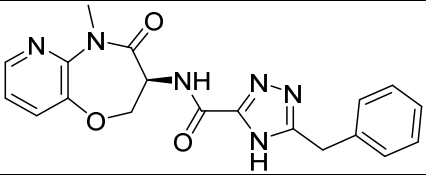
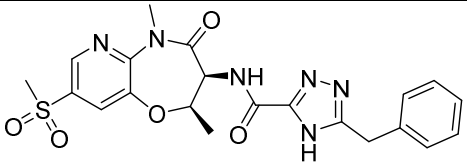
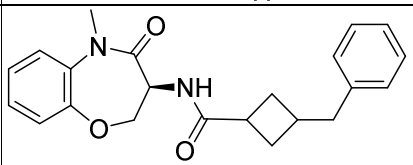
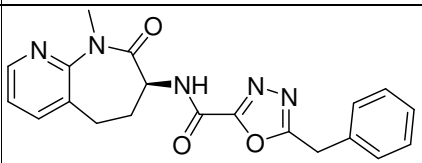
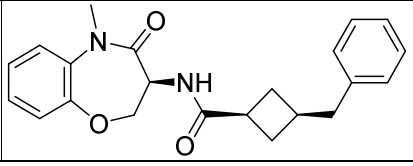
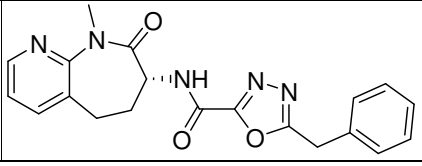
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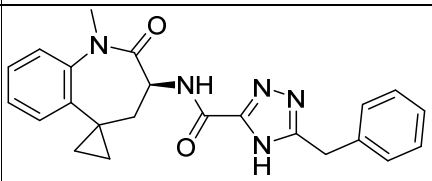
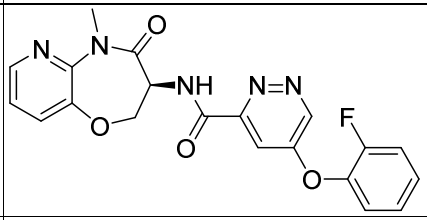
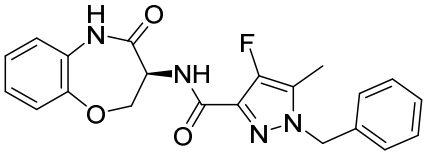
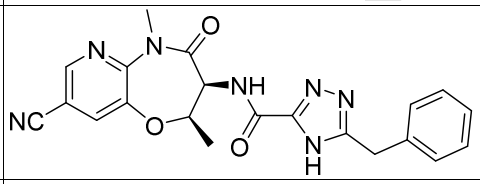
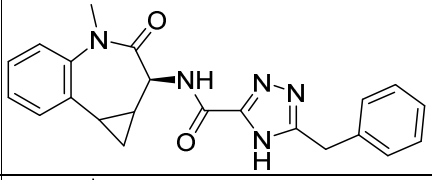
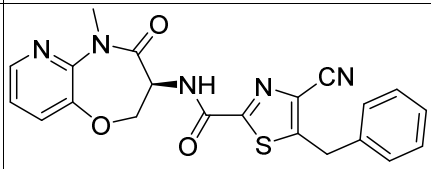
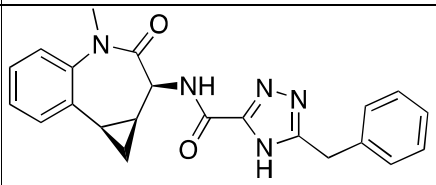
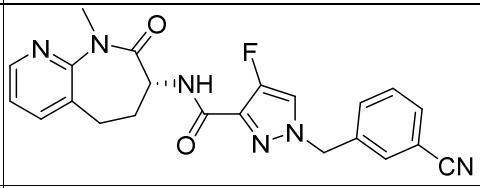
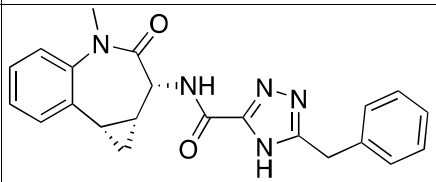
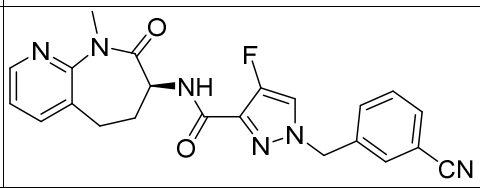
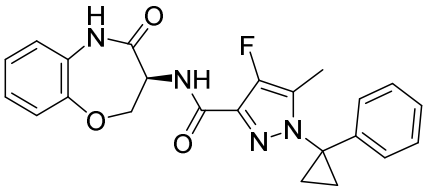
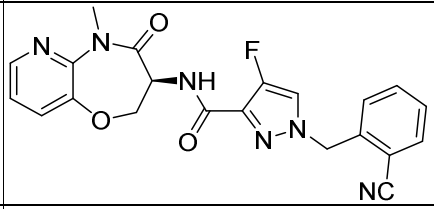
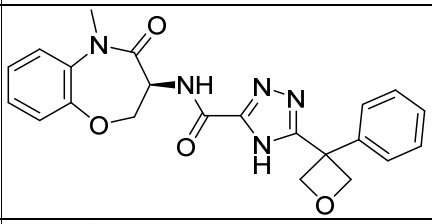
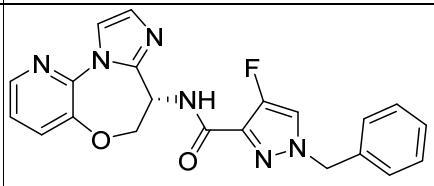
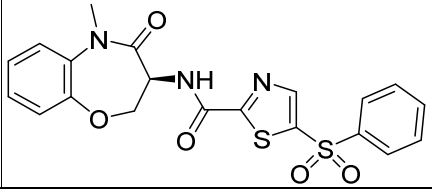
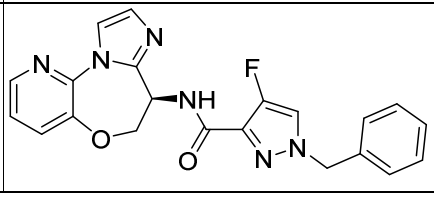
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9		118A	
10		118B	
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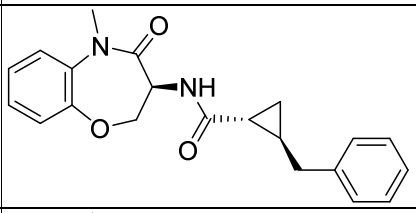
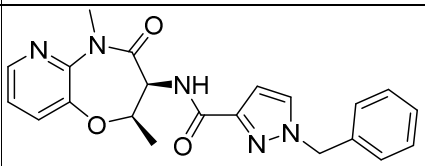
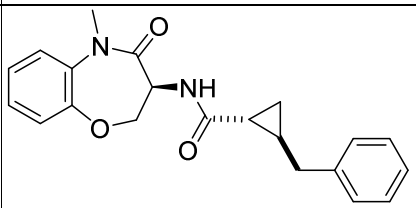
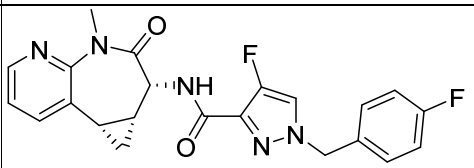
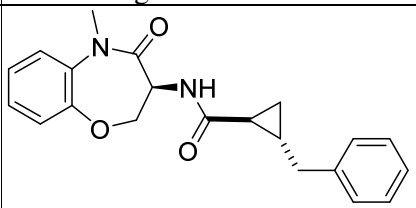
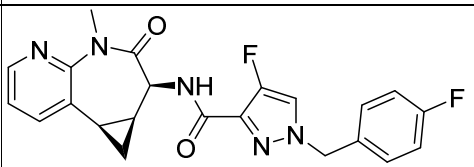
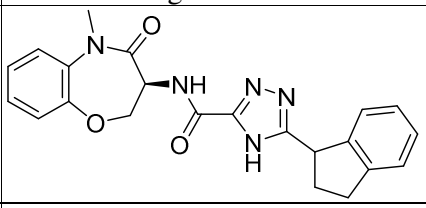
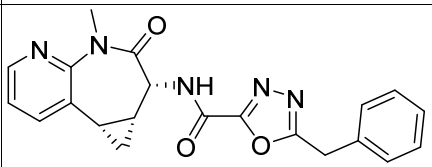
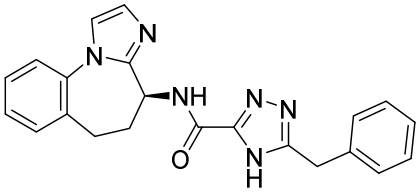
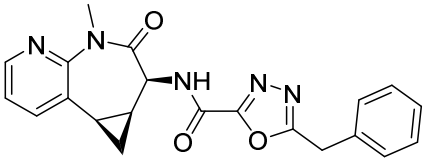
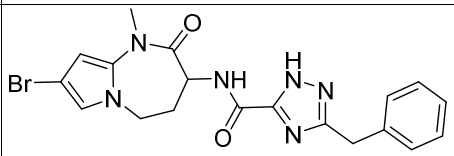
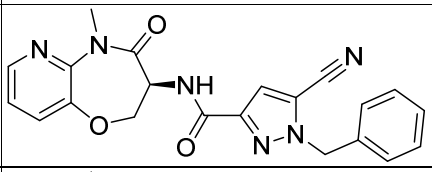
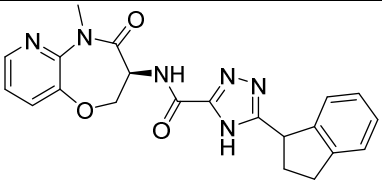
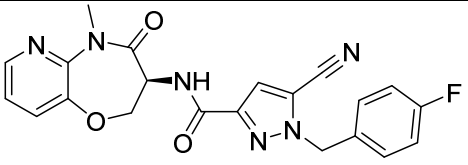
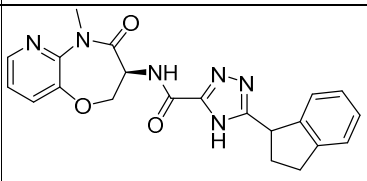
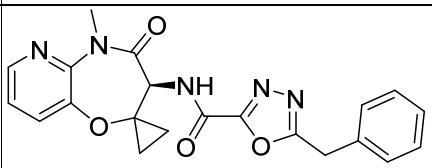
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14		123	
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16		125A	
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18		126	

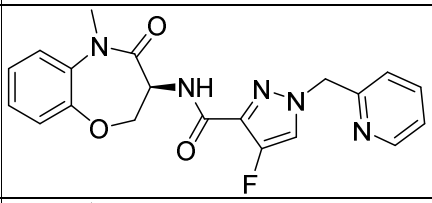
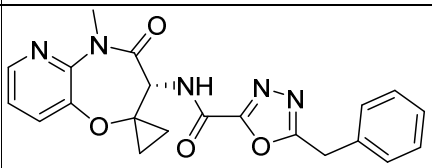
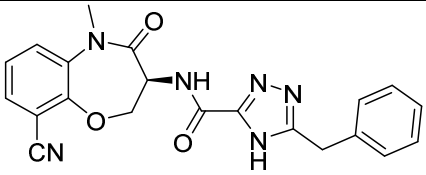
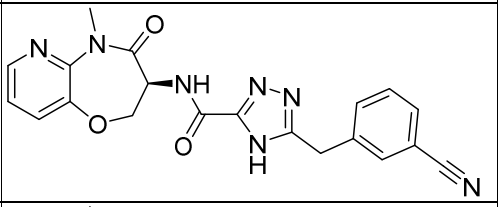
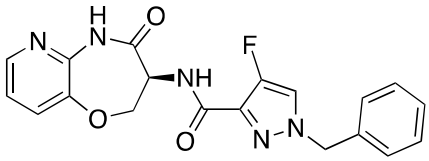
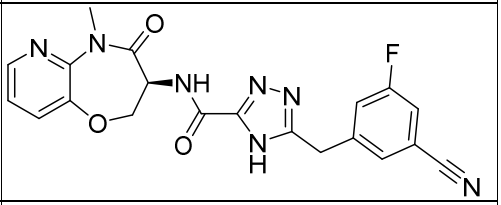
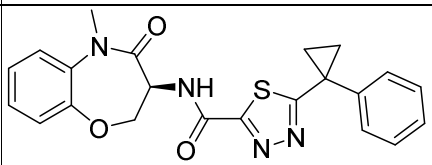
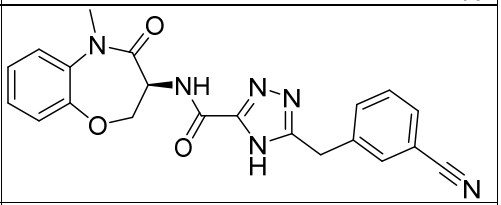
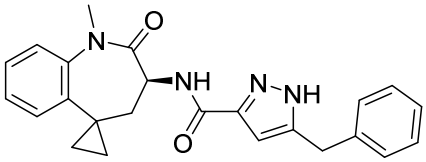
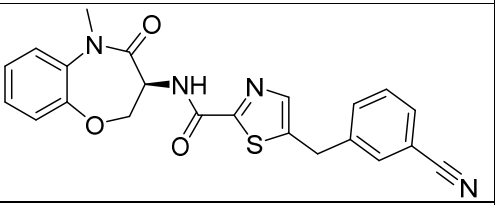
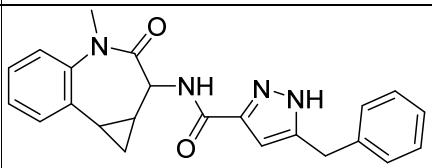
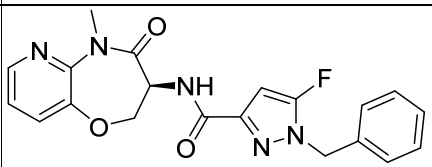
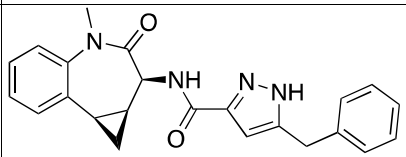
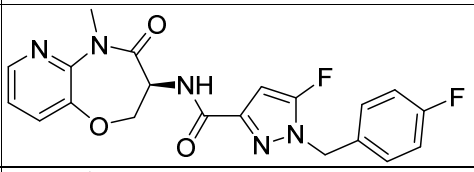
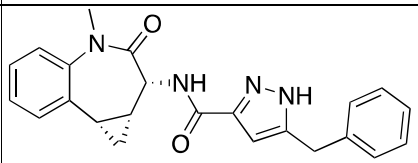
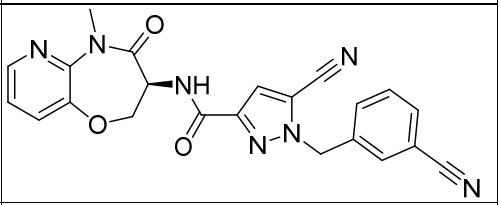
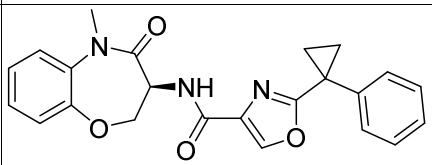
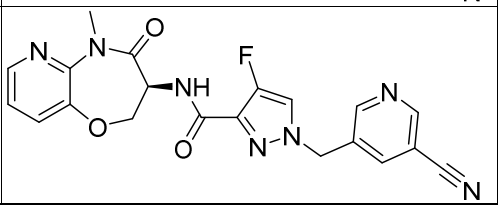
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22			
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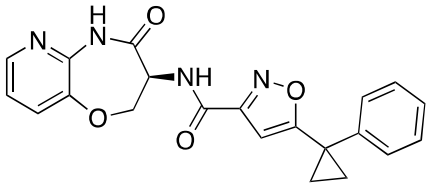
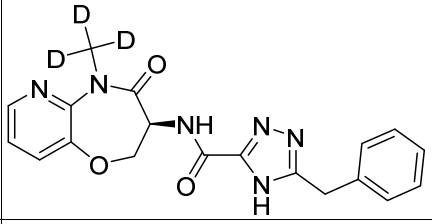
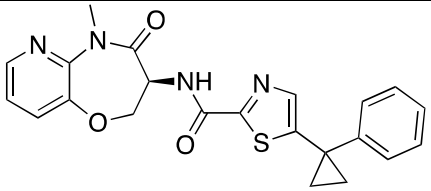
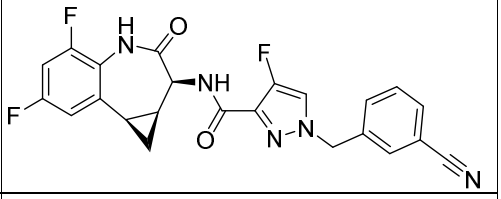
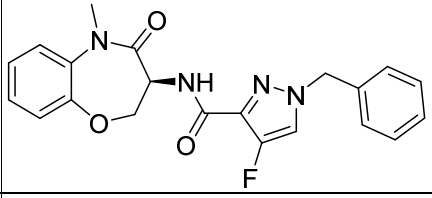
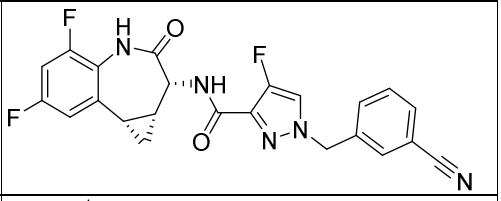
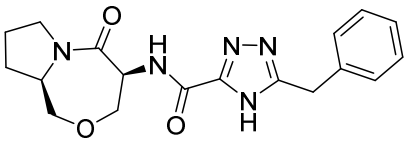
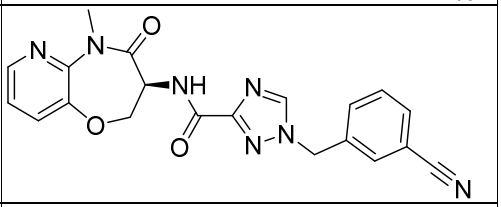
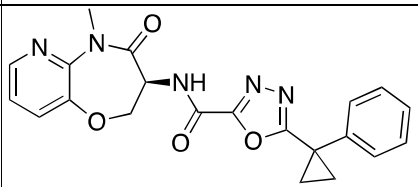
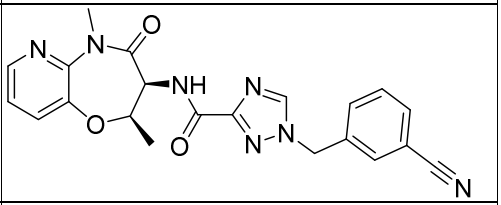
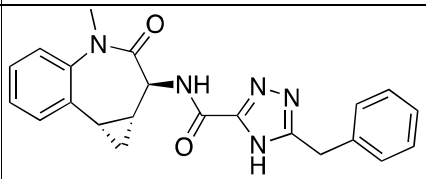
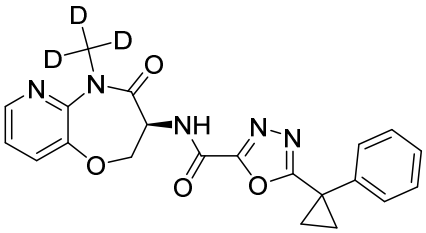
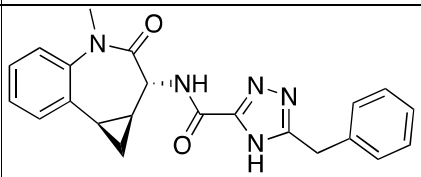
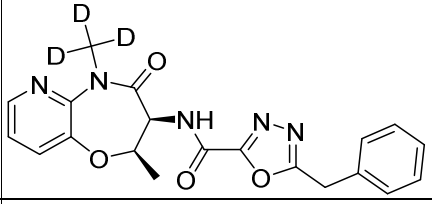
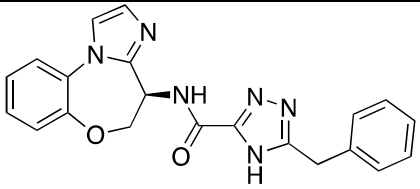
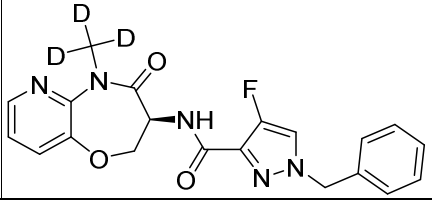
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36		141B	

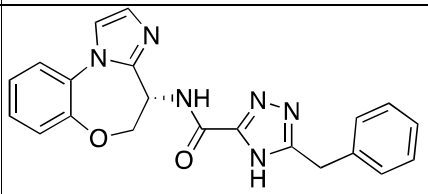
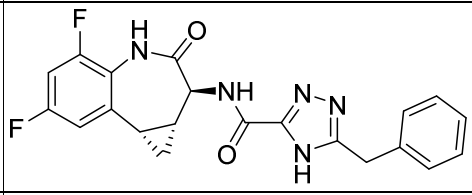
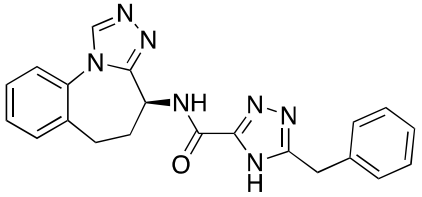
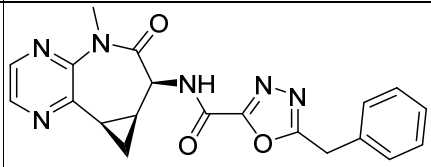
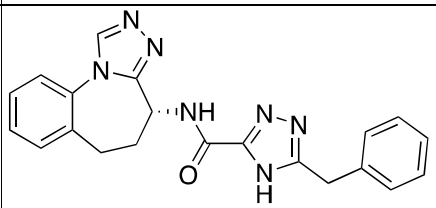
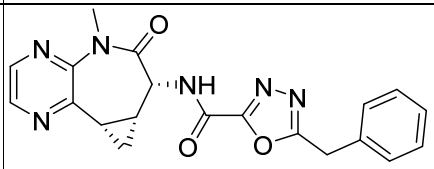
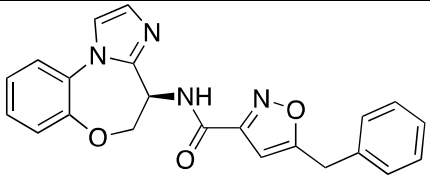
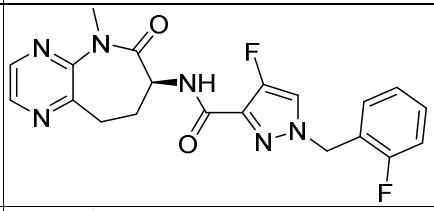
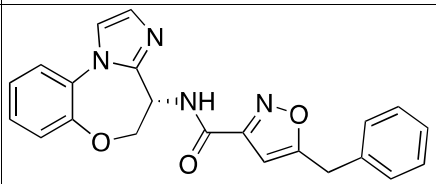
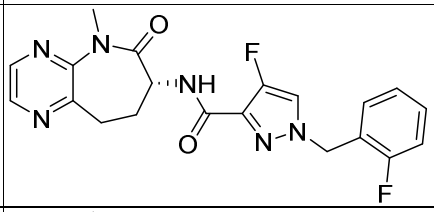
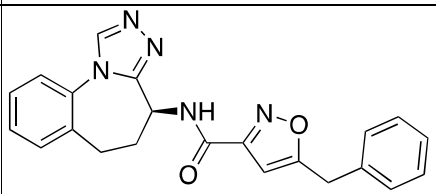
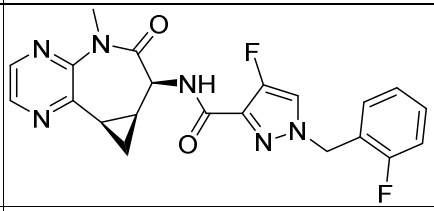
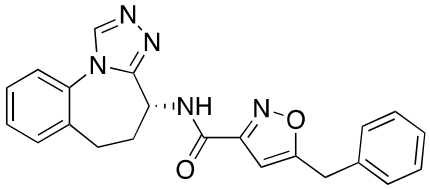
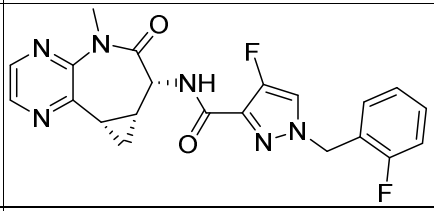
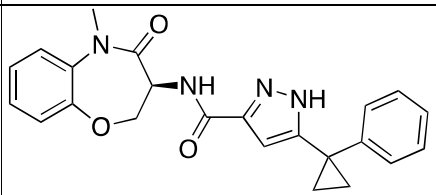
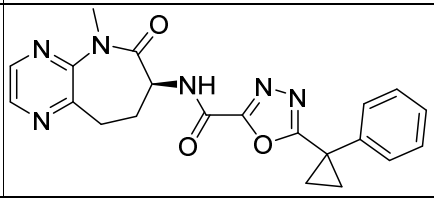
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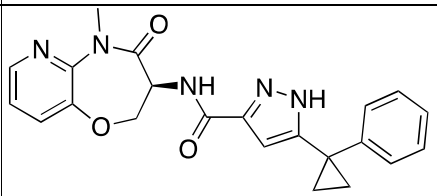
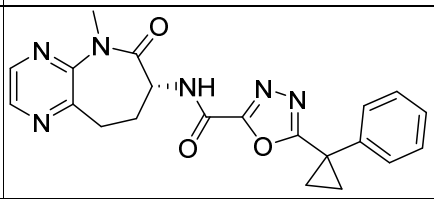
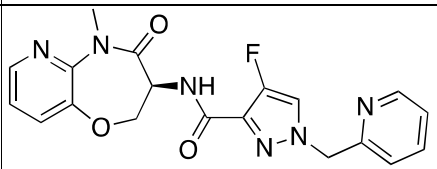
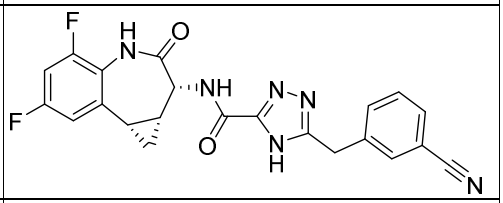
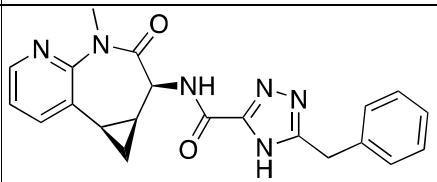
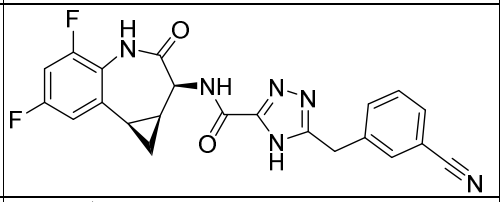
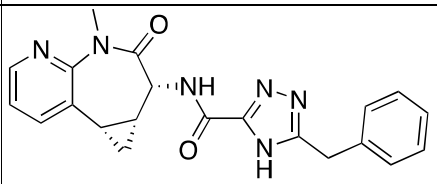
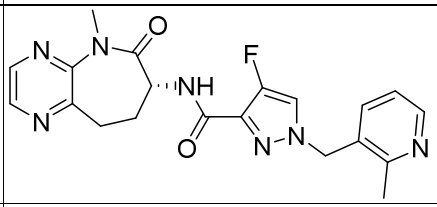
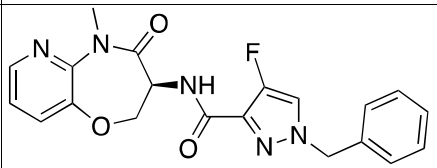
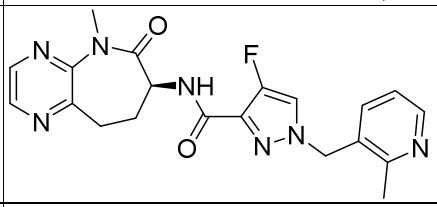
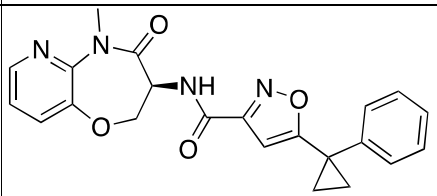
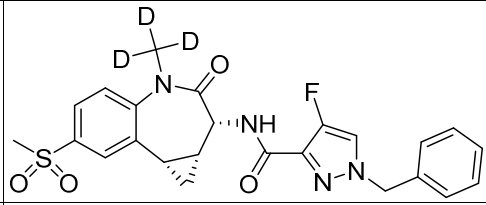
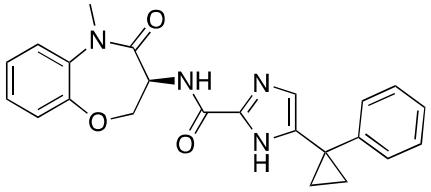
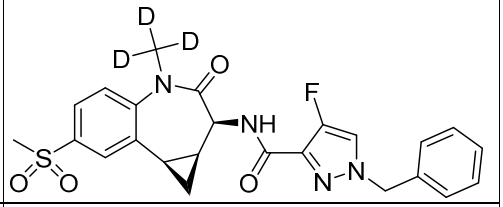
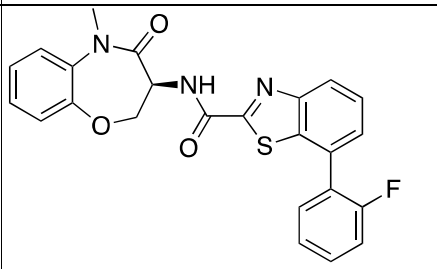
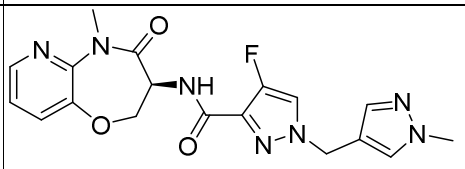
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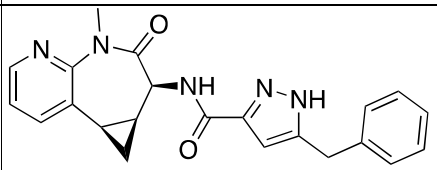
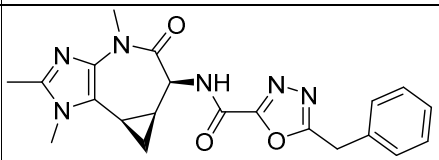
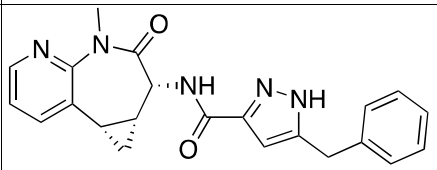
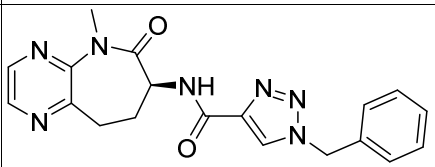
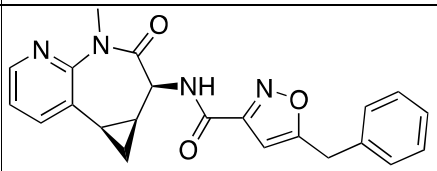
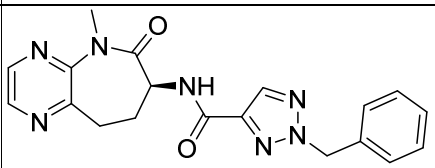
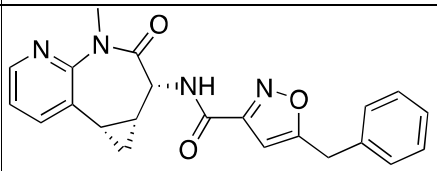
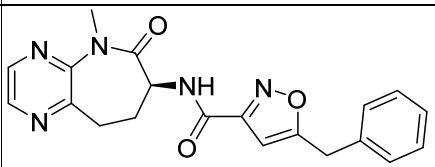
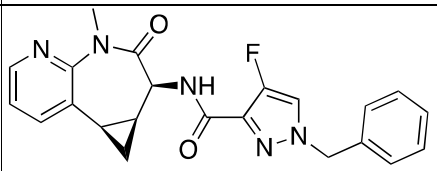
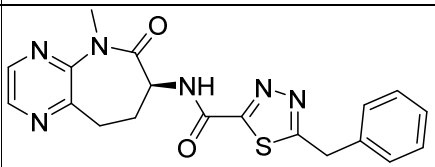
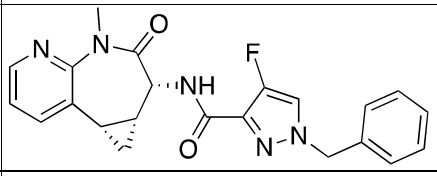
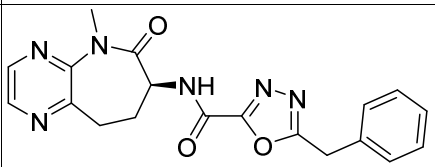
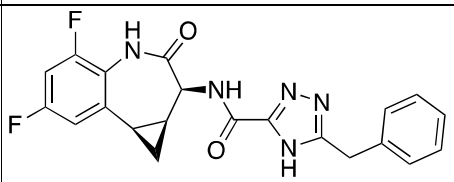
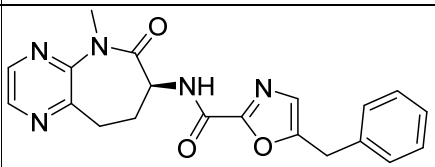
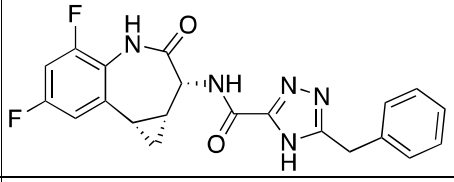
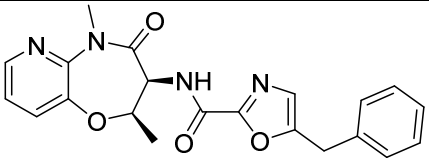
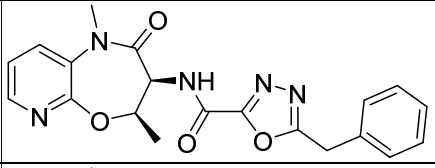
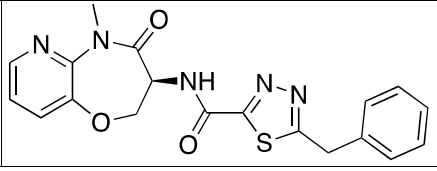
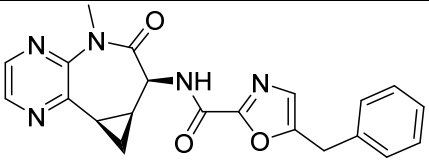
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50B	 Second eluting isomer	156B	
51		157A	
52		157B	
53		158	
54A	 Diastereomer 1	159	
54B	 Diastereomer 2	160A	

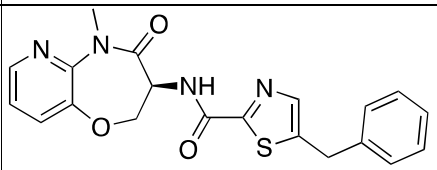
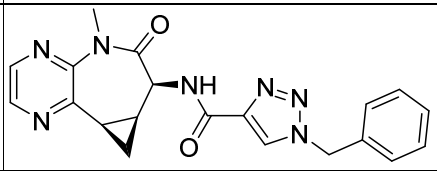
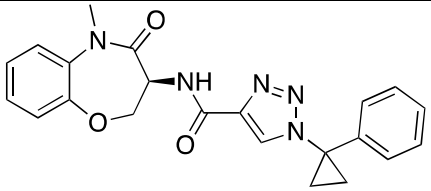
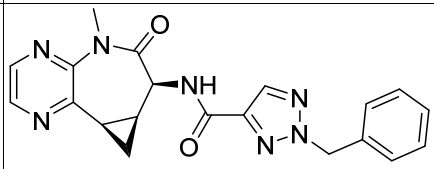
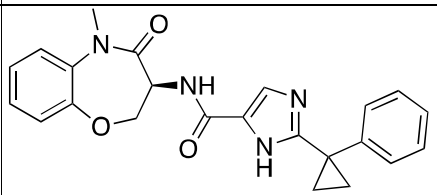
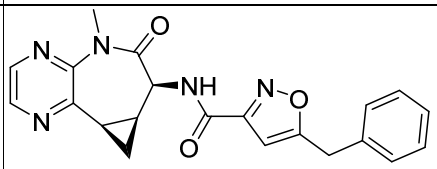
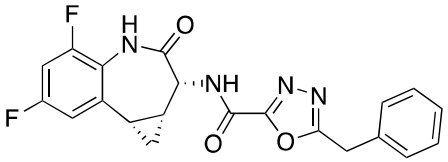
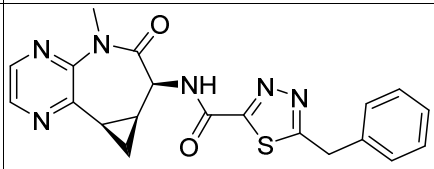
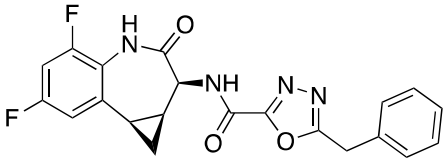
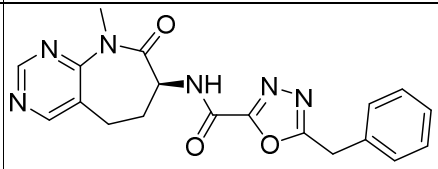
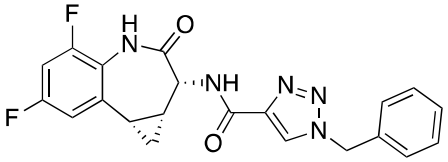
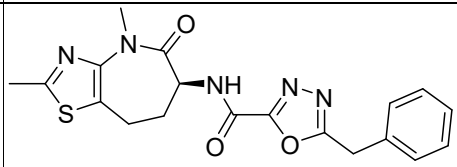
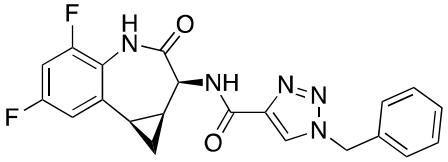
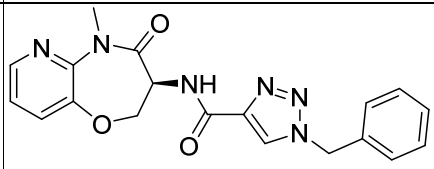
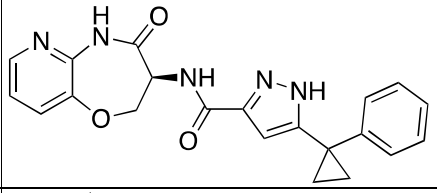
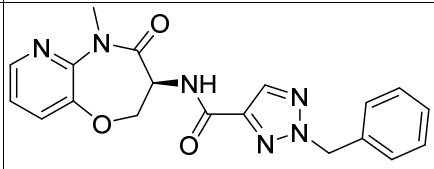
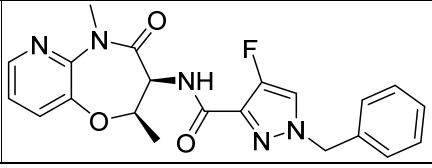
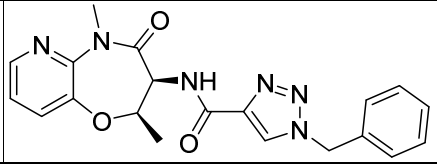
No.	Structure	No.	Structure
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57		162	
58		163	
59		164	
60		165	
60A		166	
60B		167	
61		168	

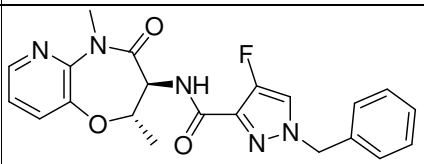
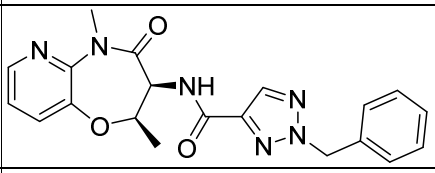
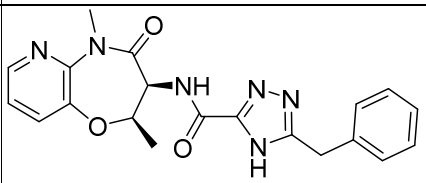
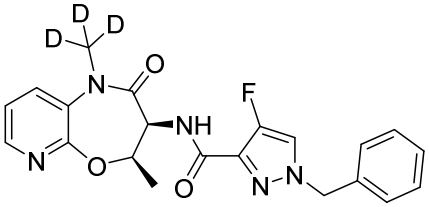
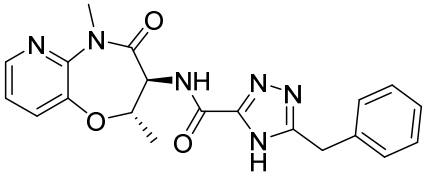
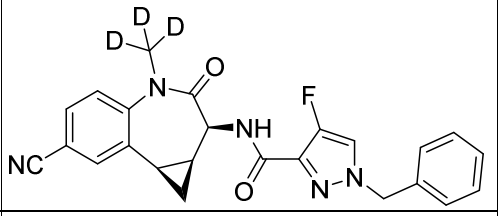
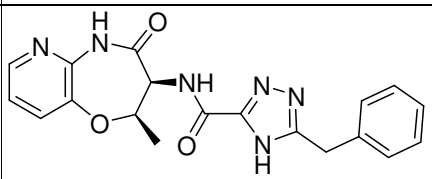
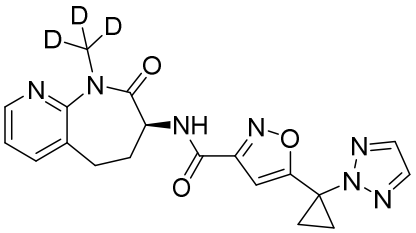
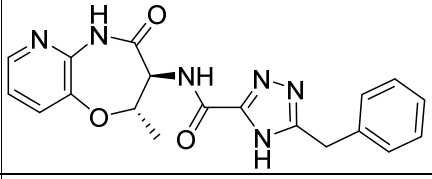
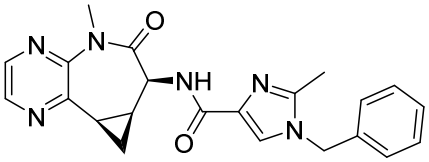
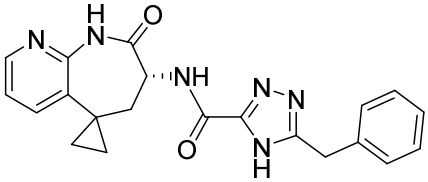
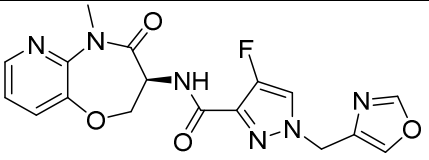
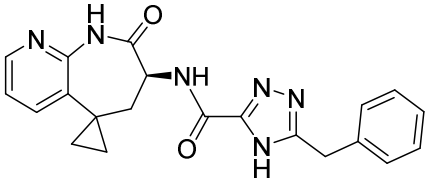
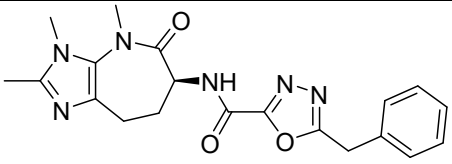
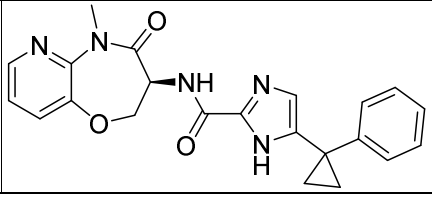
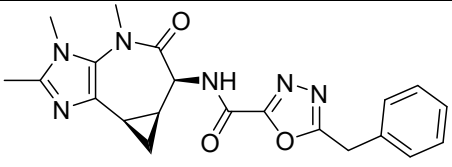
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64		170B	
65		171	
66		172	
67A		173	
67B		174	
68A		175	

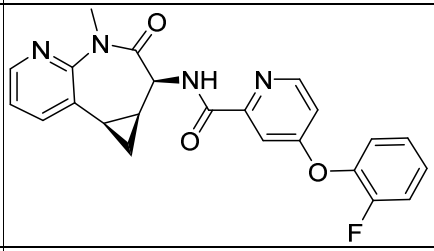
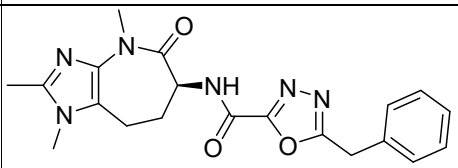
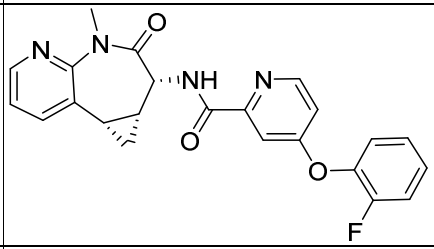
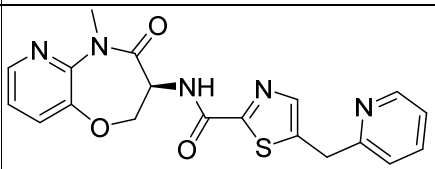
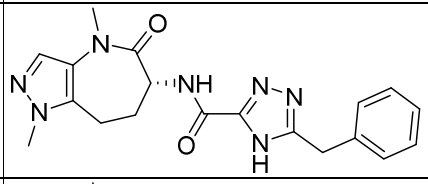
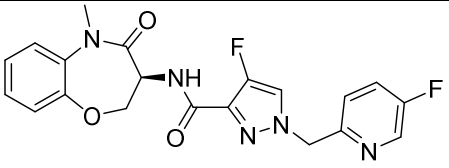
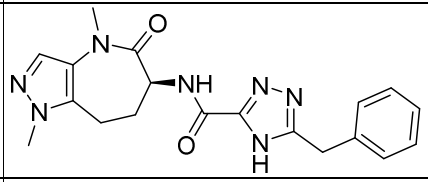
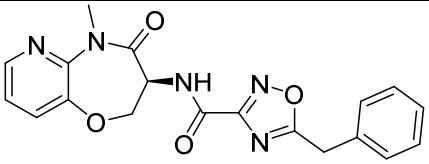
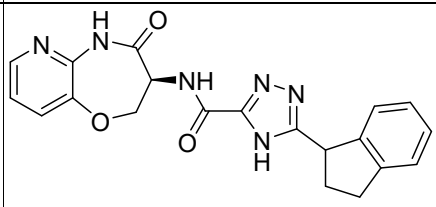
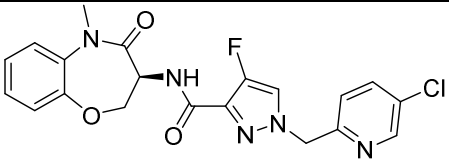
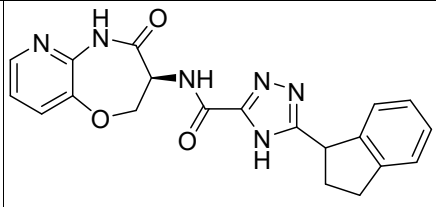
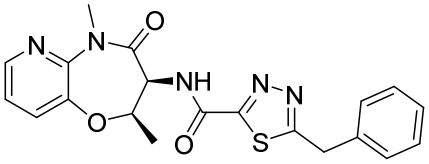
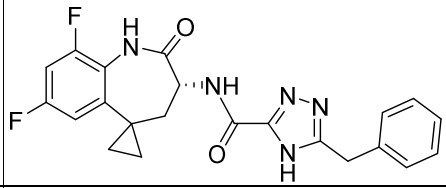
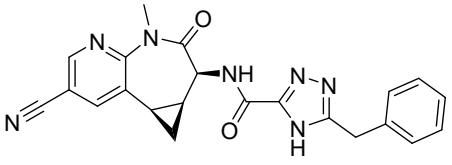
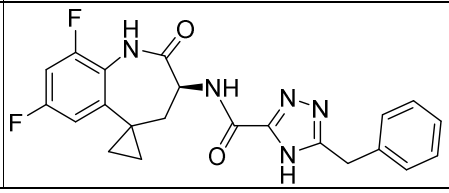
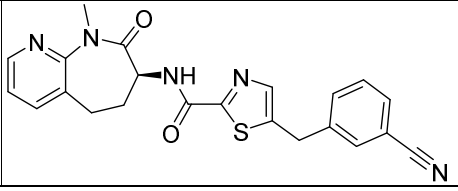
No.	Structure	No.	Structure
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72		180A	

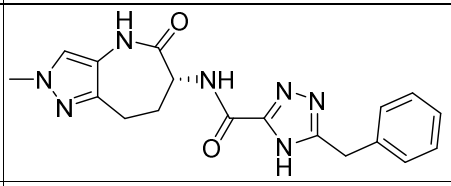
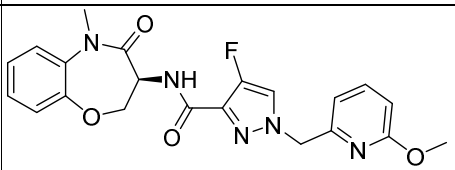
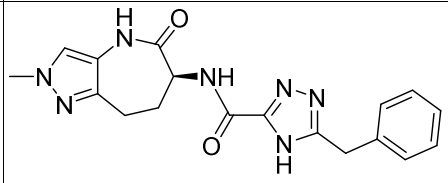
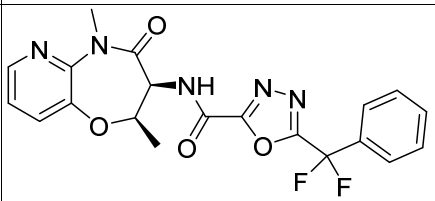
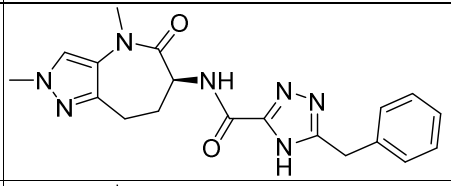
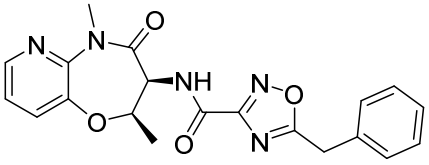
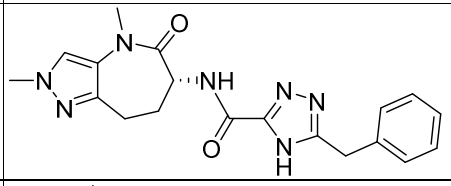
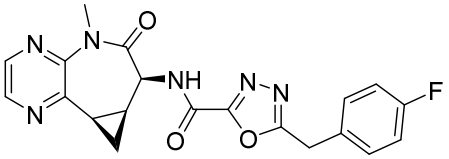
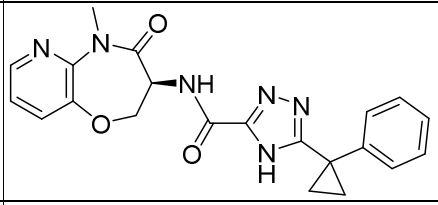
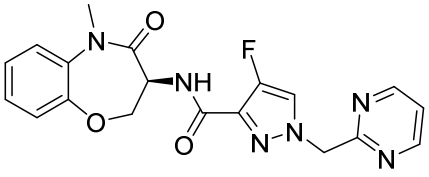
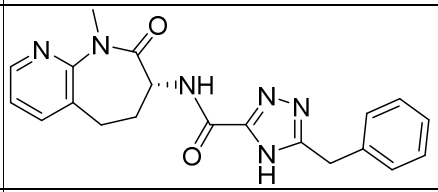
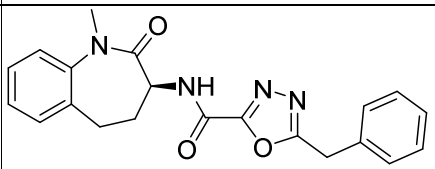
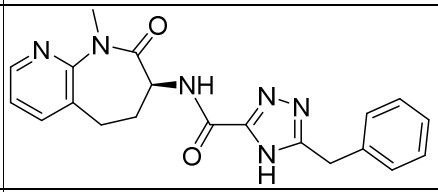
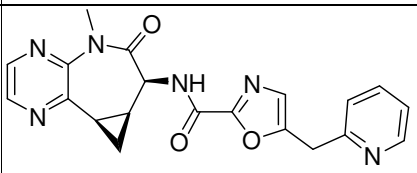
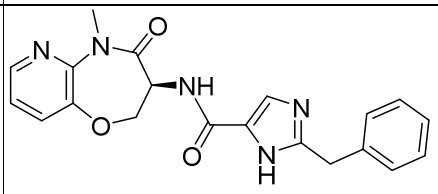
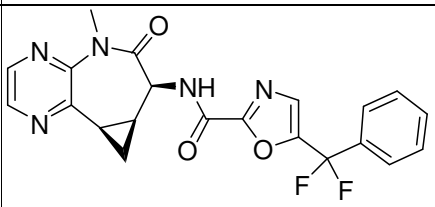
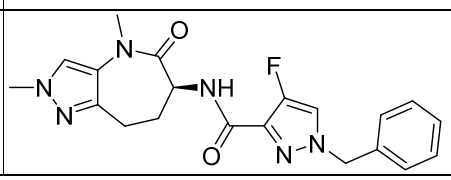
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73		180B	
74		181A	
75A		181B	
75B		182A	
76		182B	
77		183A	
78		183B	
79		184	

No.	Structure	No.	Structure
80A		185	
80B		186	
81A		187	
81B		188	
82A		189	
82B		190	
83A		191	
83B		192	
		193	
85		194	

No.	Structure	No.	Structure
86		195	
87		196	
88		197	
89A		198	
89B		199	
90A		200	
90B		201	
91		202	
92		203	

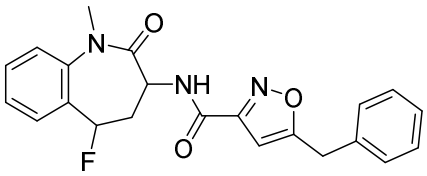
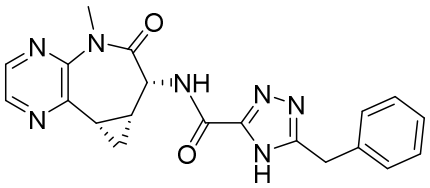
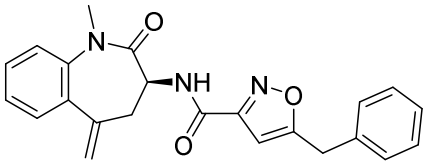
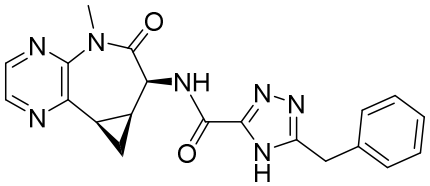
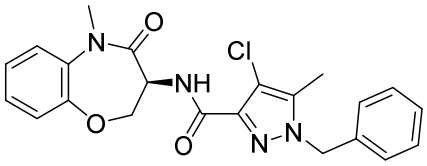
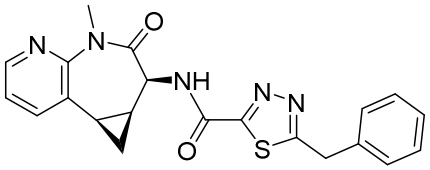
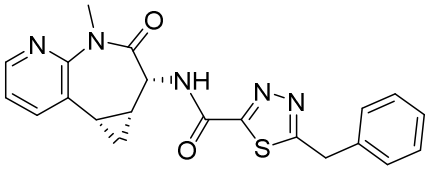
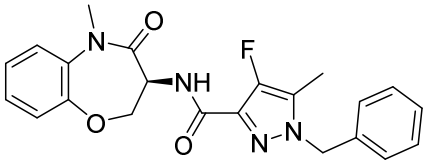
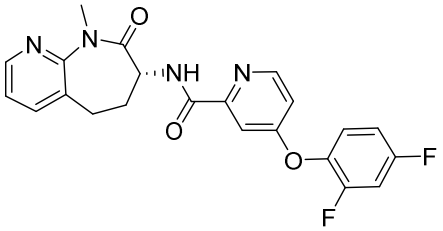
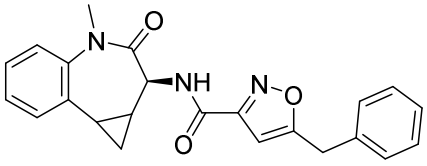
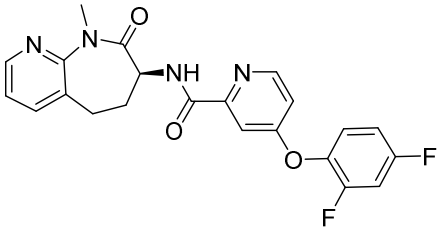
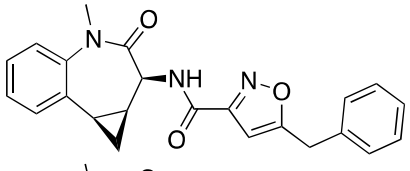
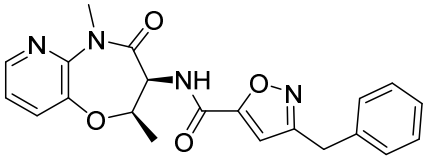
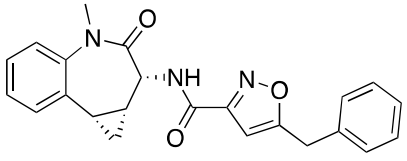
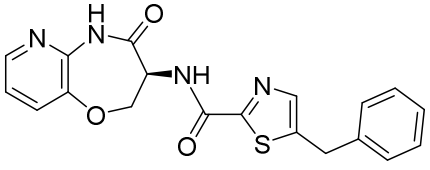
No.	Structure	No.	Structure
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94		205	
95		206	
96		207	
97		208	
98A		209	
98B		210	
99		211	

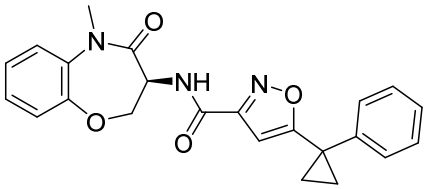
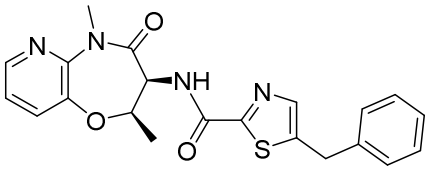
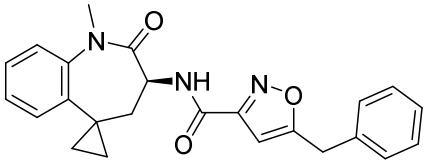
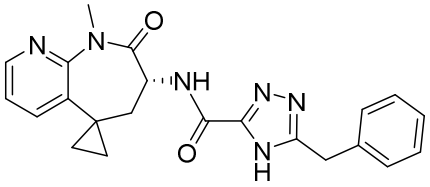
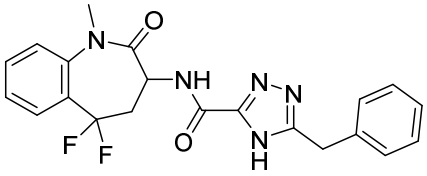
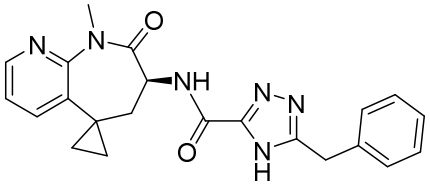
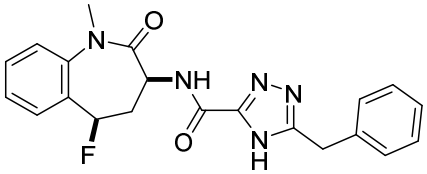
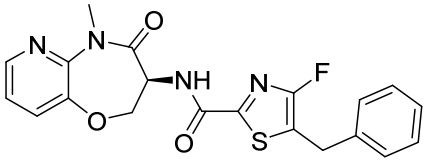
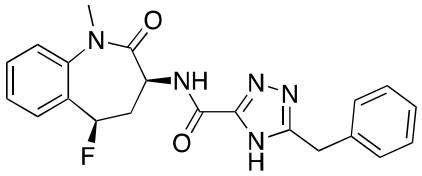
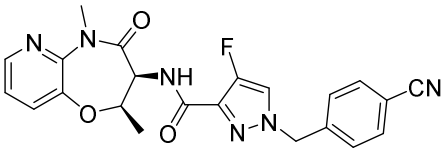
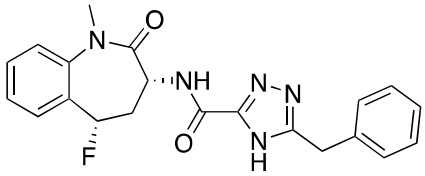
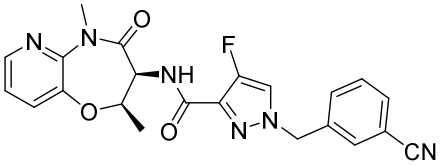
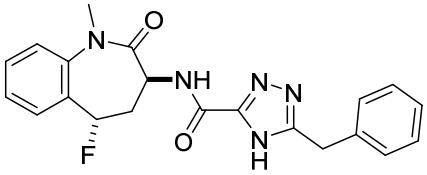
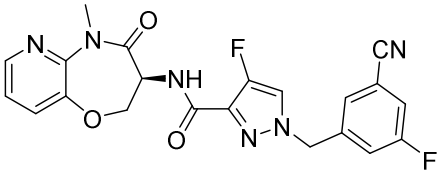
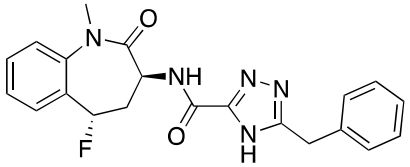
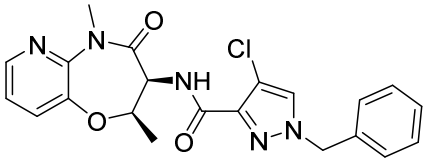
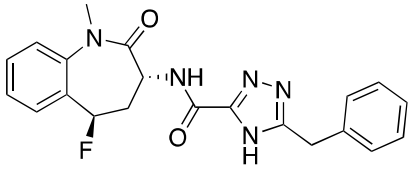
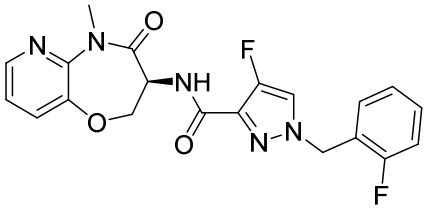
No.	Structure	No.	Structure
100A		212	
100B		213	
101A		214	
101B		215	
102A	 First eluting isomer	216	
102B	 Second eluting isomer	217	
103A		218	
103B		219	

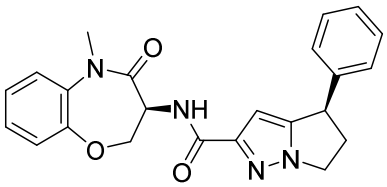
No.	Structure	No.	Structure
104A		220	
104B		221	
105A		222	
105B		223	
106		224	
107A		225	
107B		226	
108		227	 or
109A			

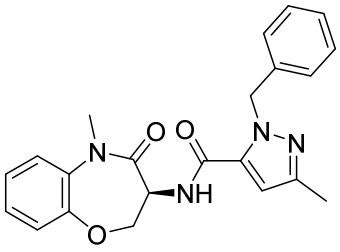
or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof.

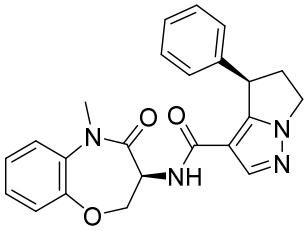
49. A compound that is selected from:

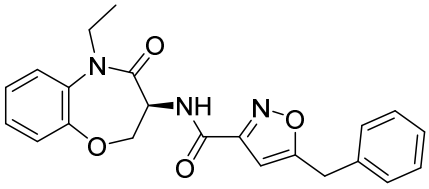
















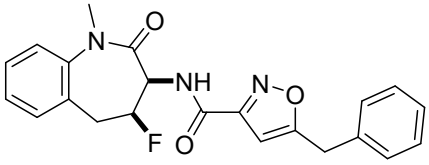



















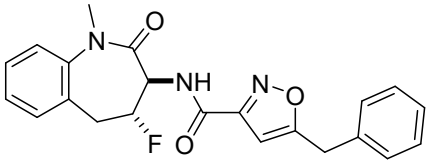


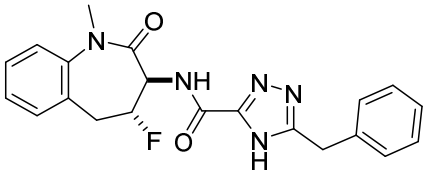


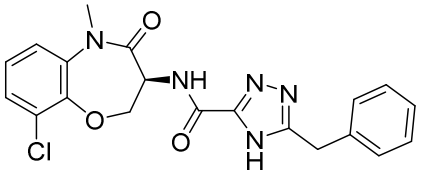


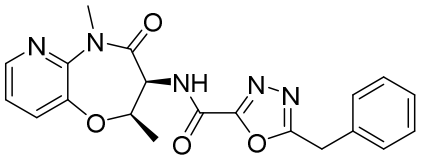


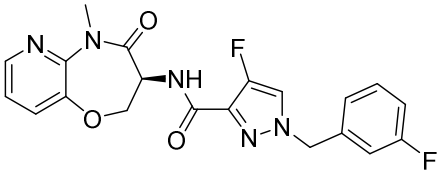


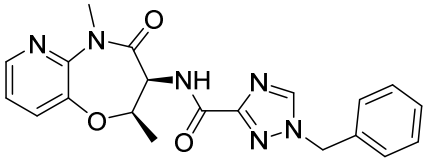


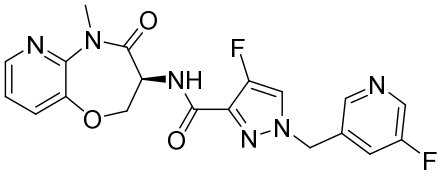


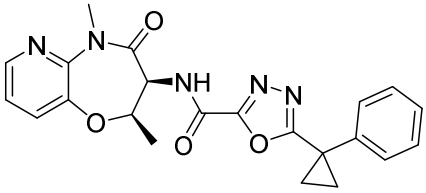


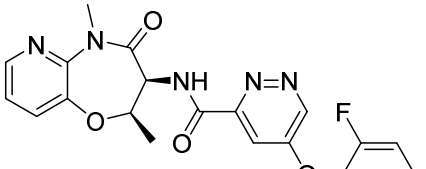


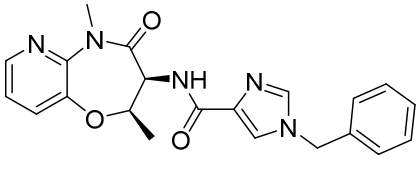


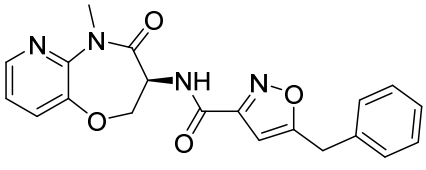


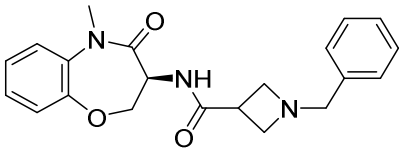


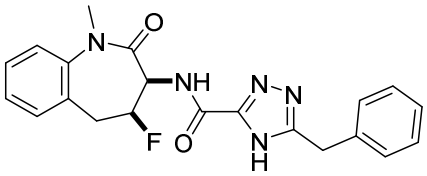


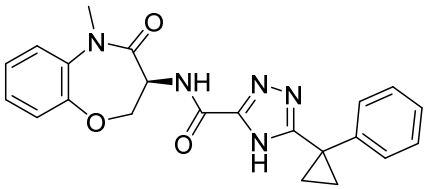


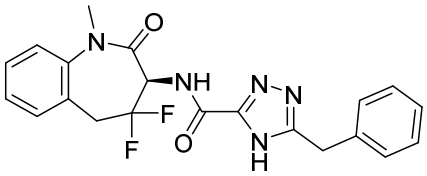


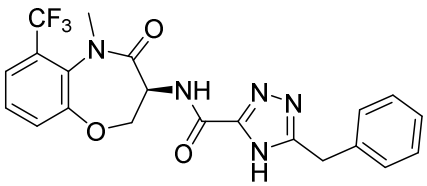


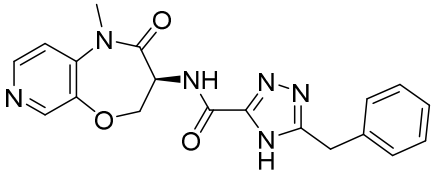


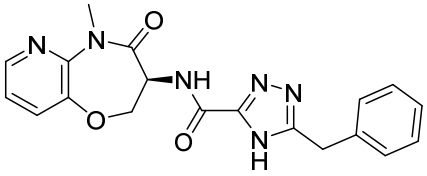


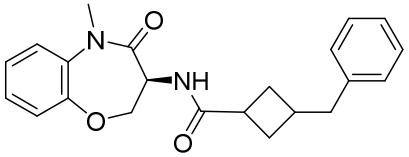


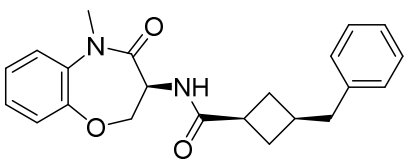


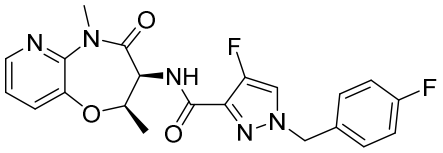


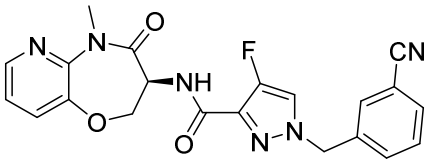


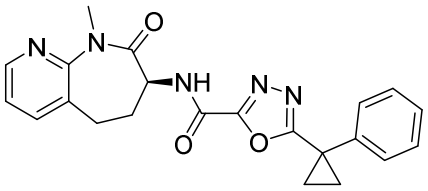


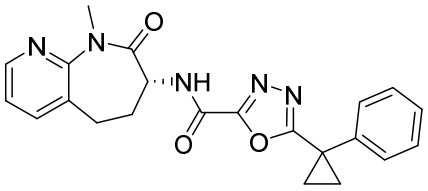


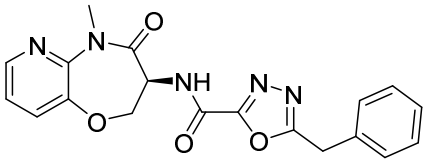


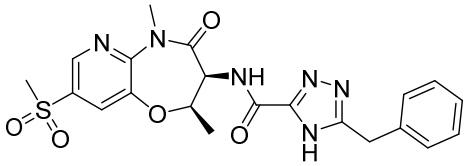


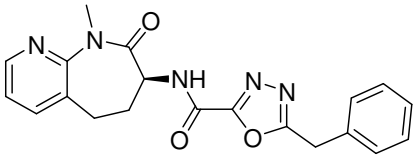


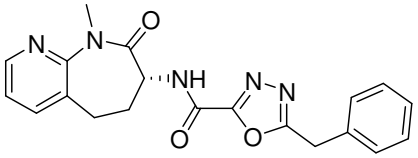


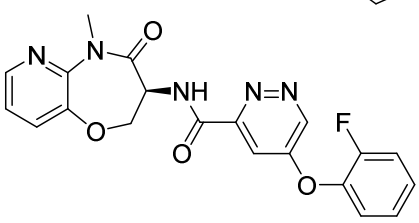


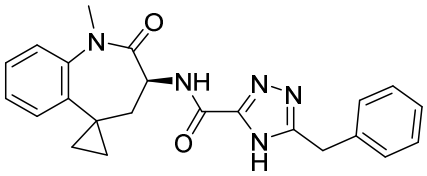


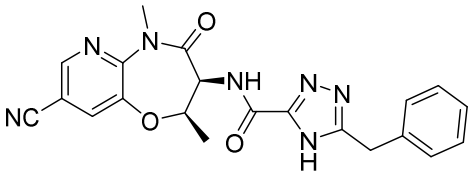


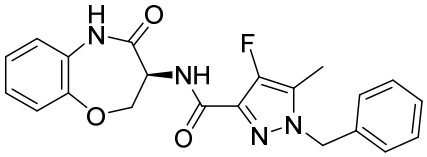


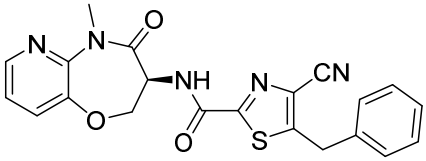


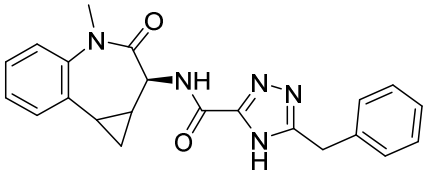


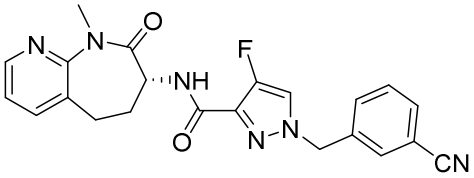


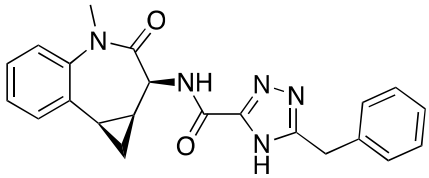


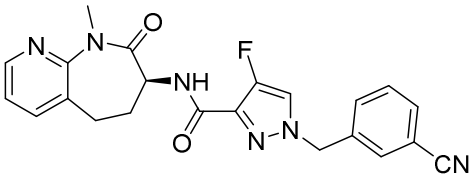


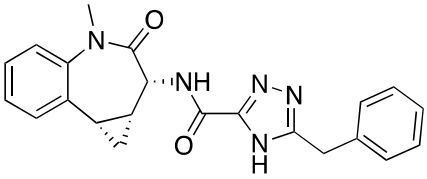


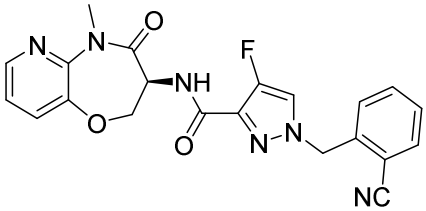


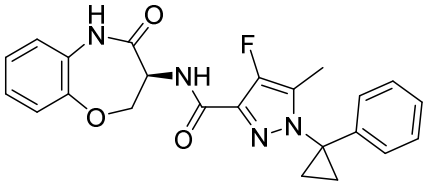


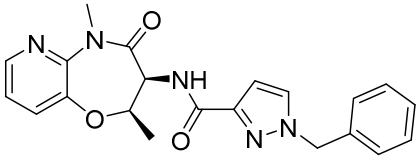


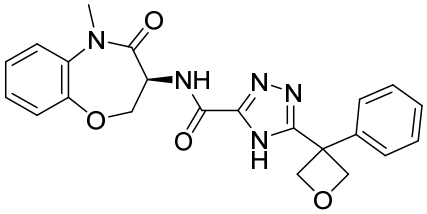


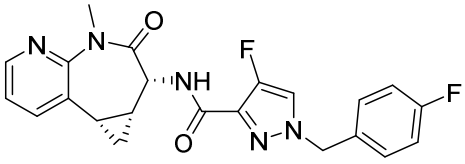


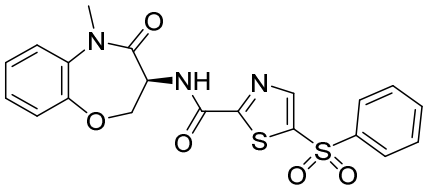


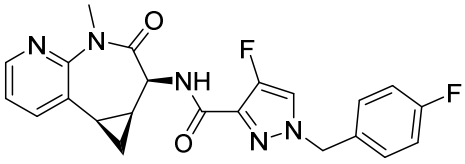


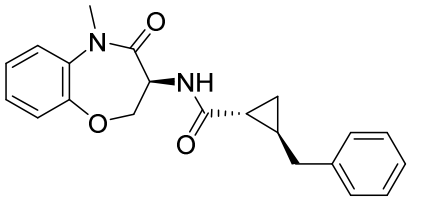


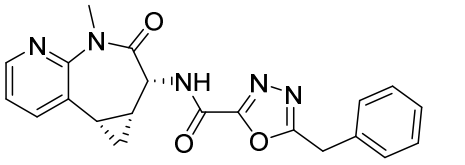




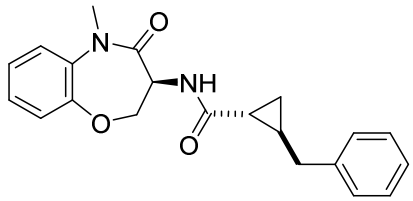


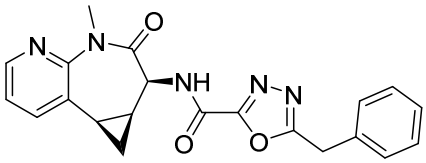




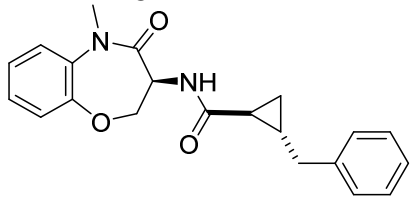


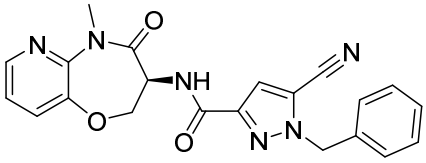




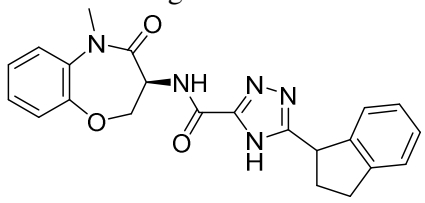


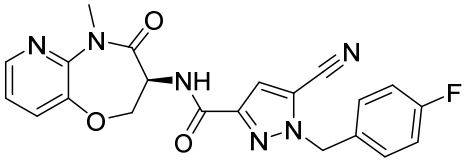
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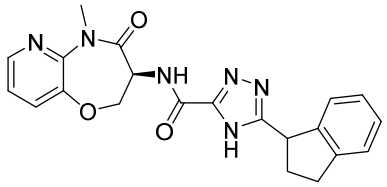


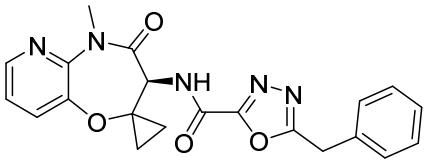


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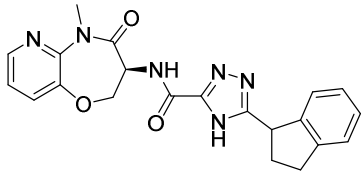


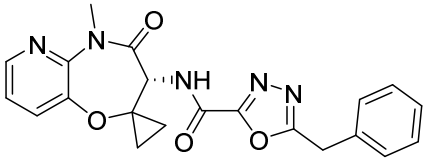




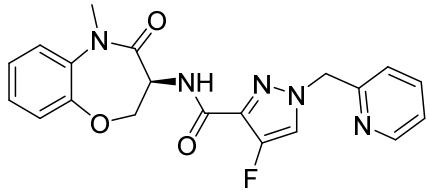


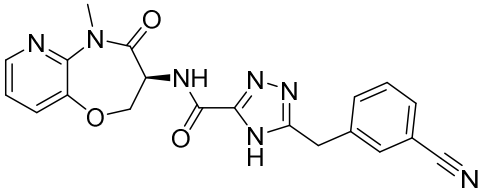
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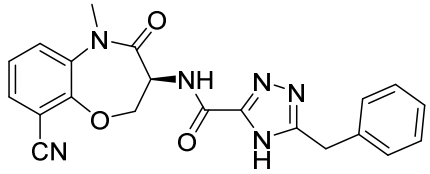


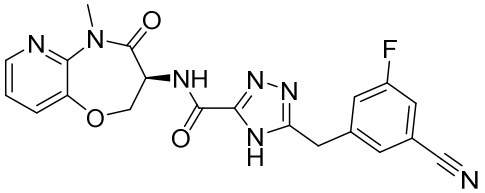


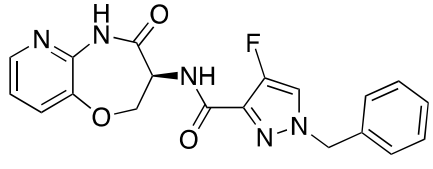
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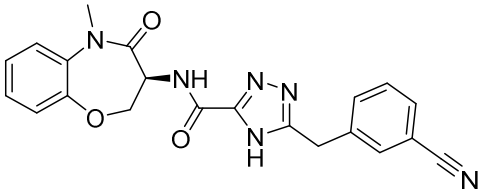


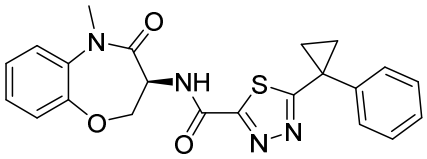
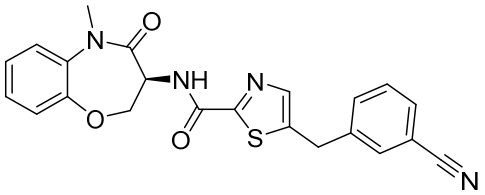
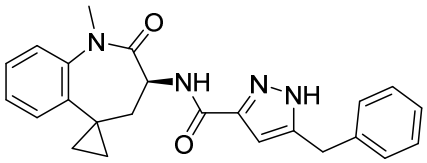
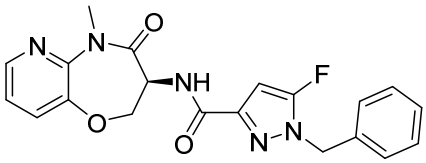
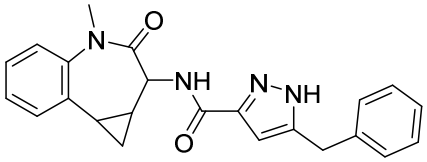
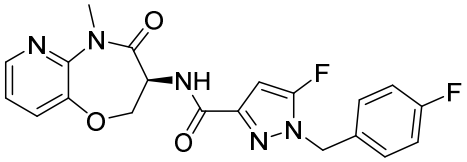
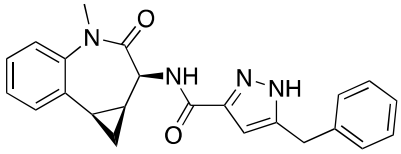
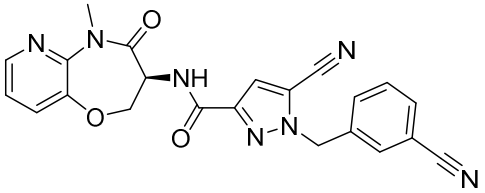
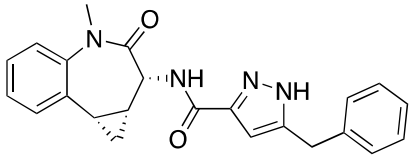
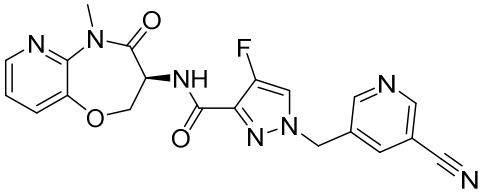
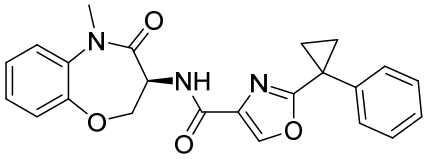
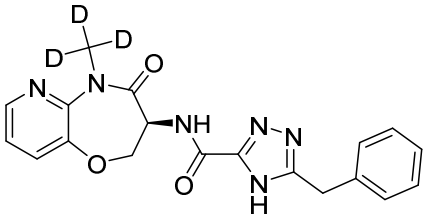
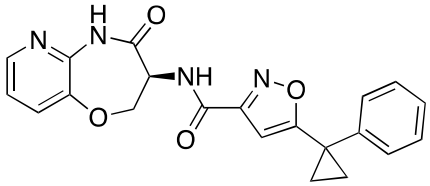
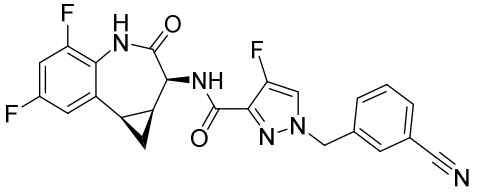
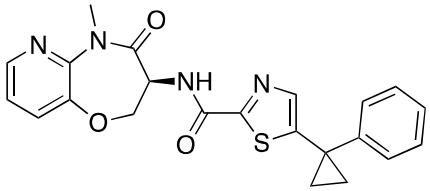
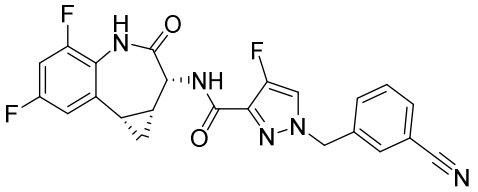
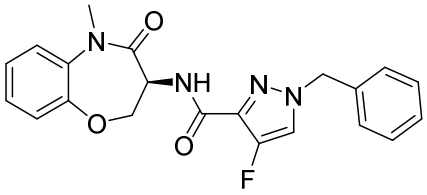
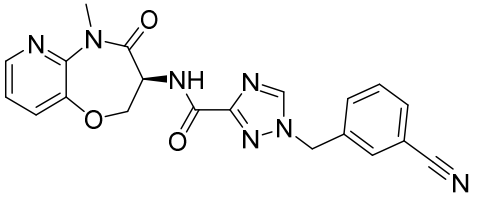


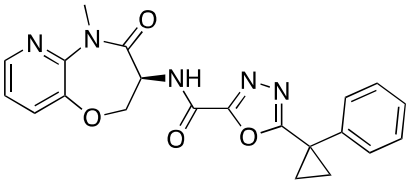


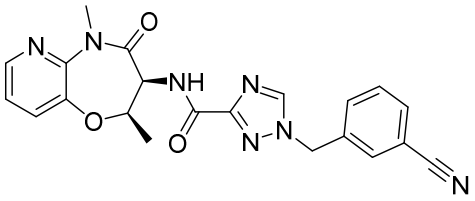


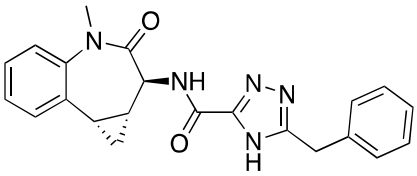


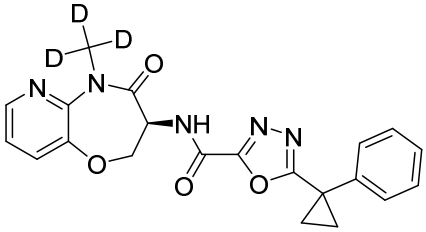


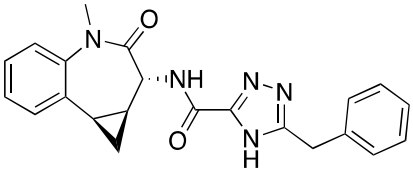



















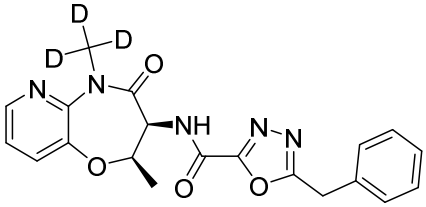


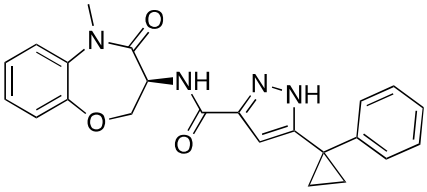


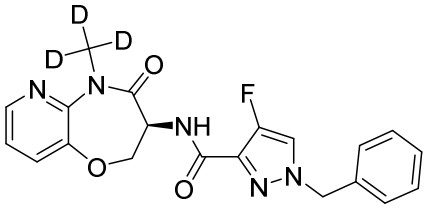


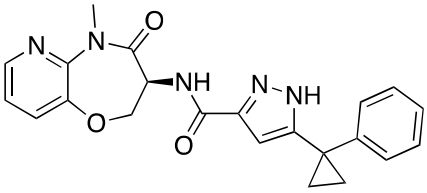


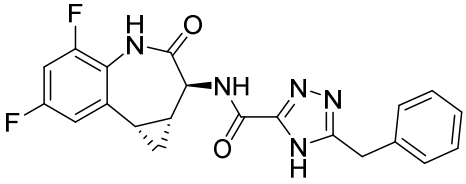


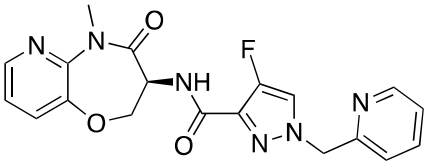


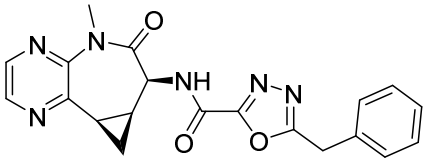


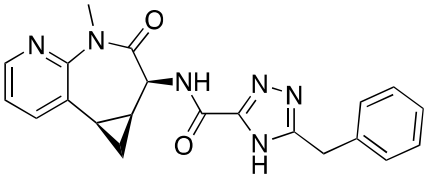


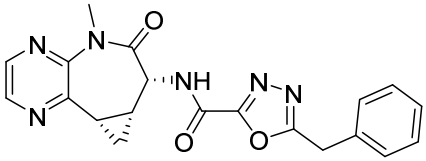


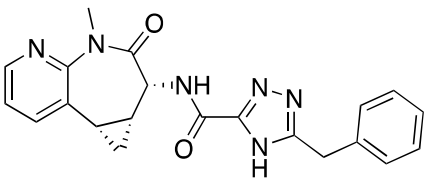


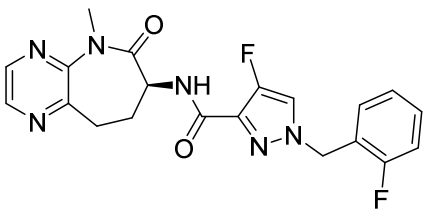


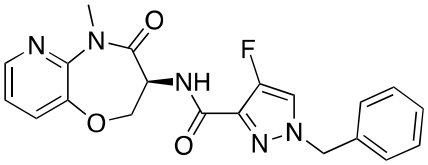


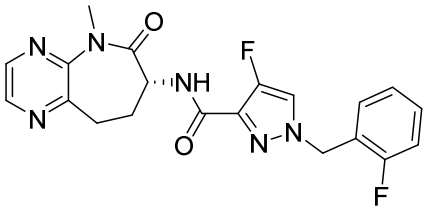


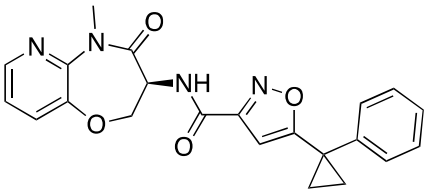


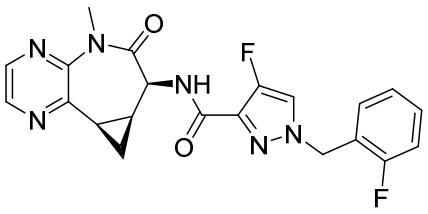


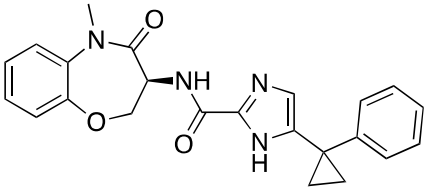


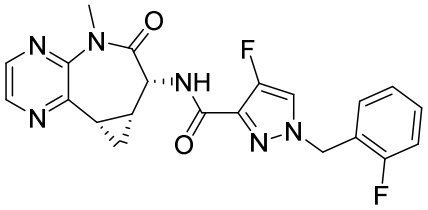


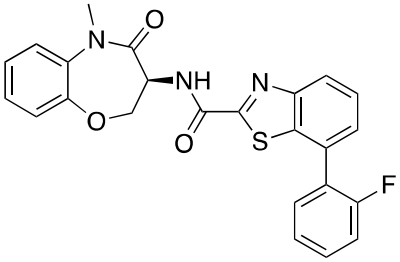


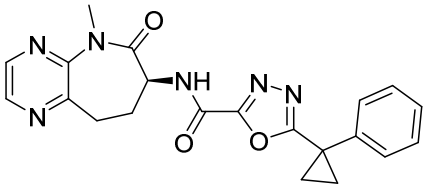


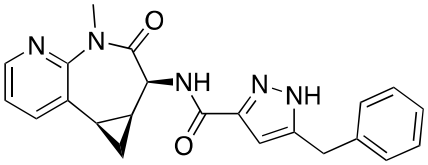


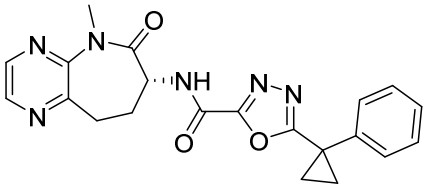


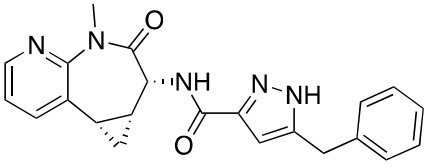


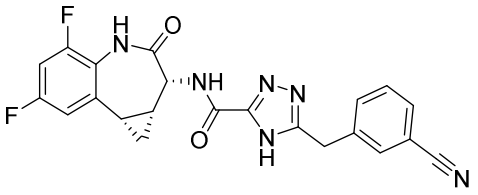


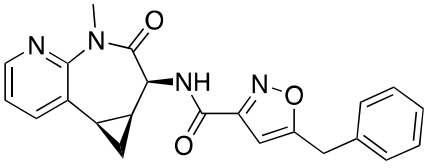


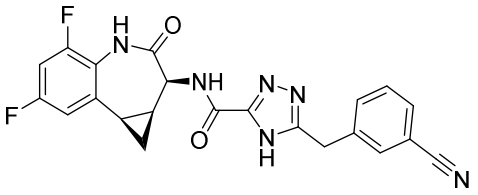


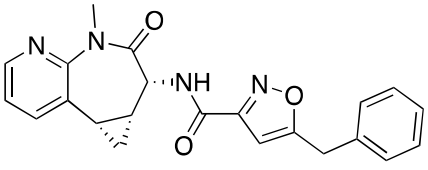


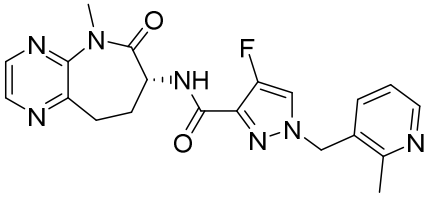


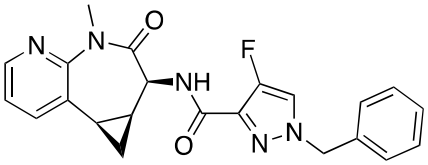


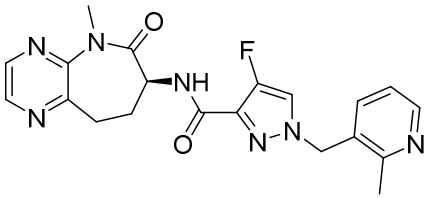


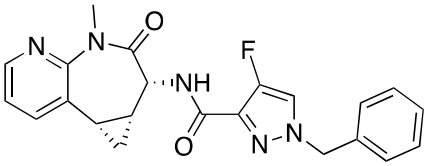


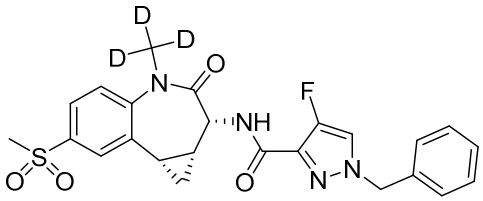


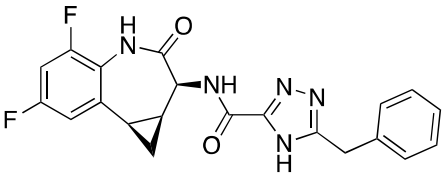


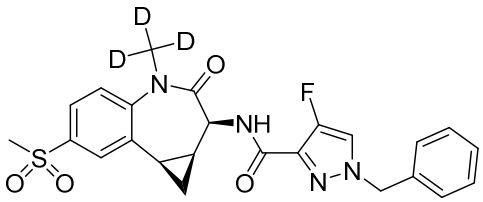


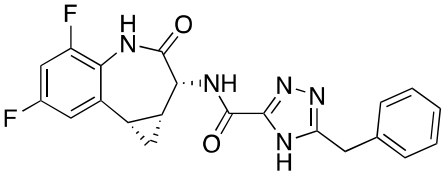


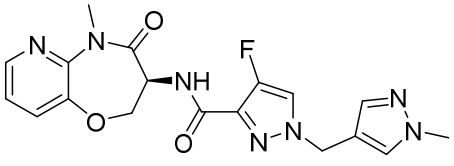


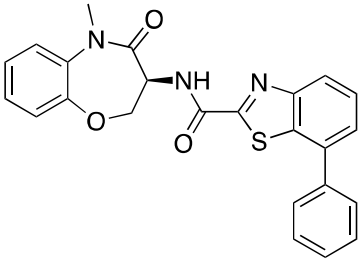


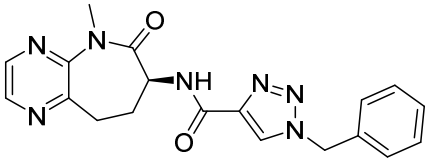


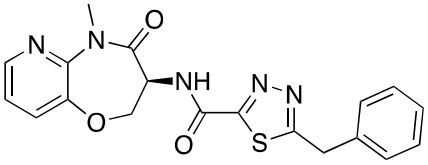


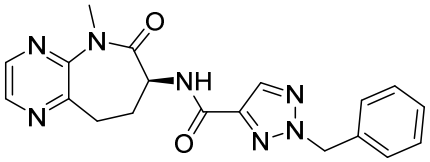


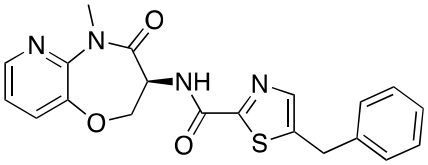


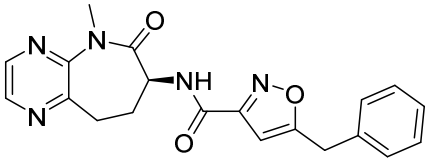


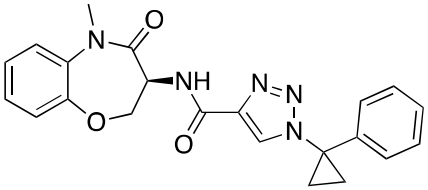


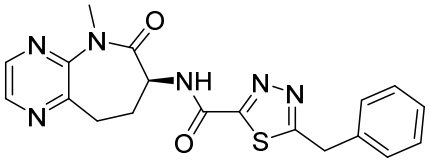


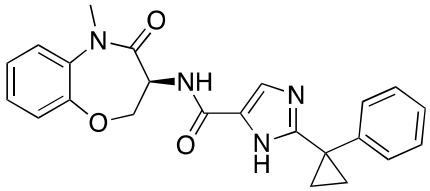
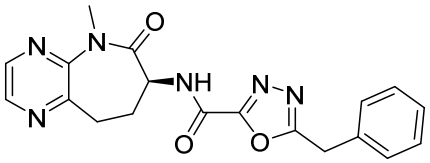
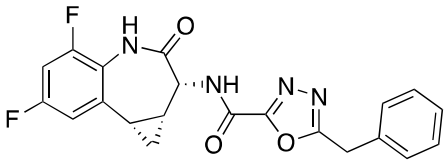
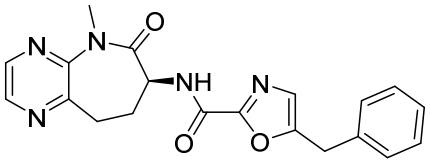
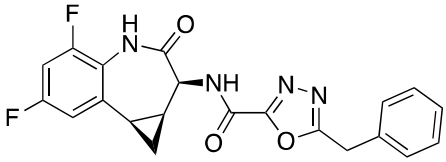
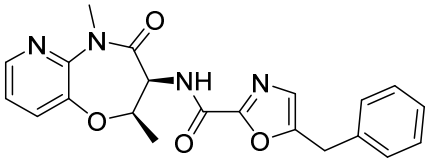
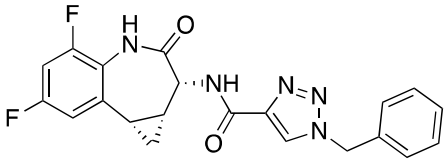
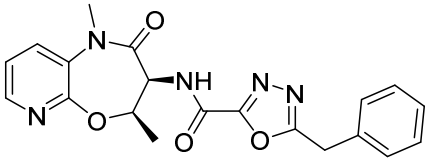
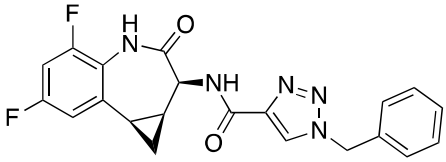
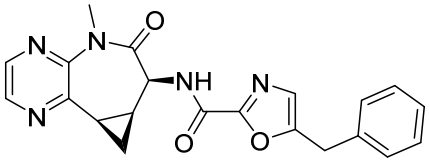
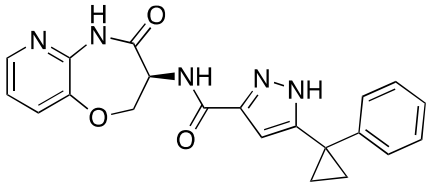
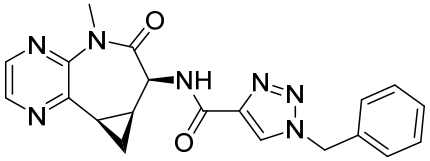
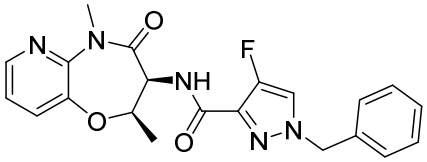
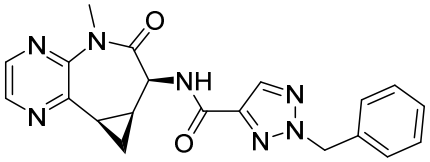
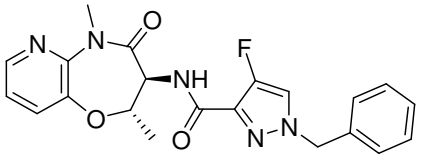
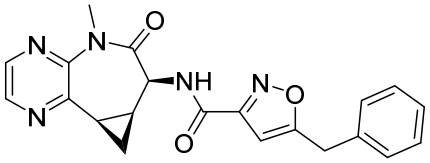
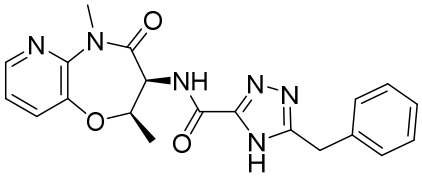
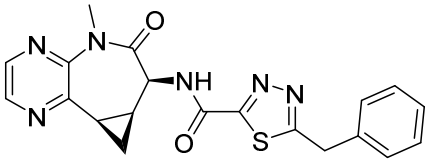
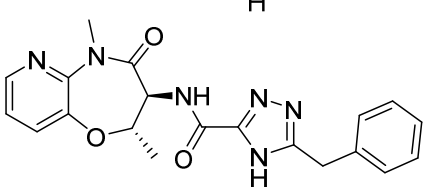
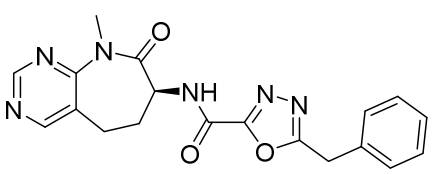


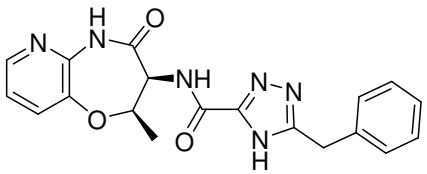
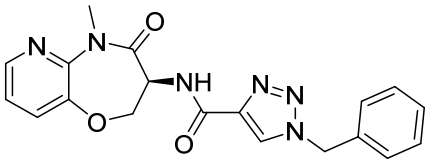
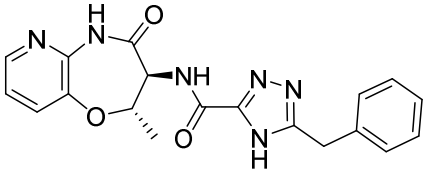
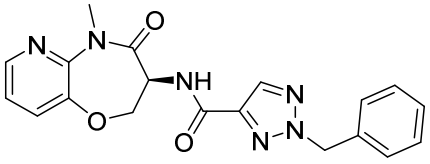
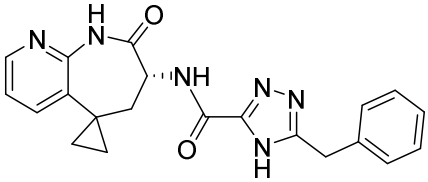
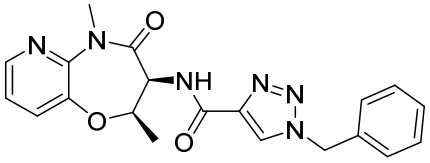
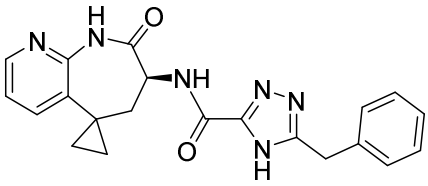
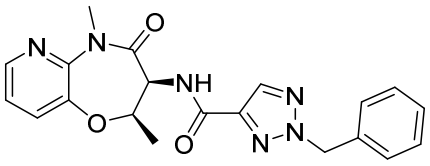
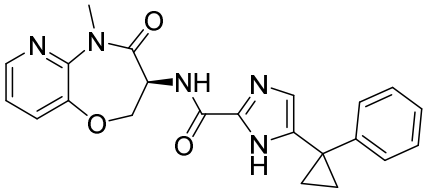
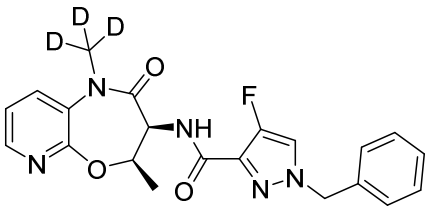
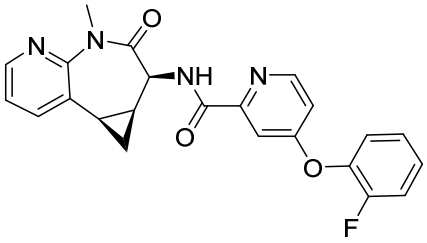
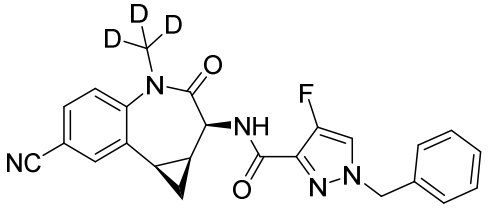
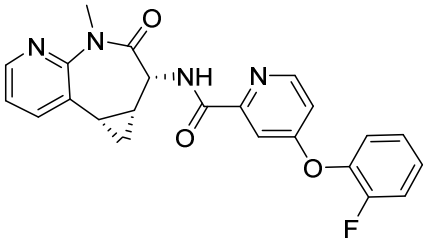
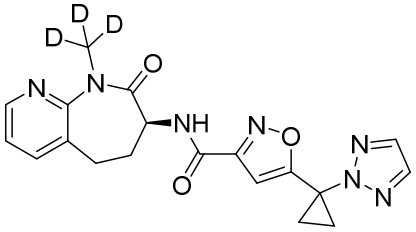
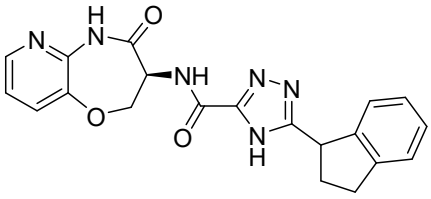
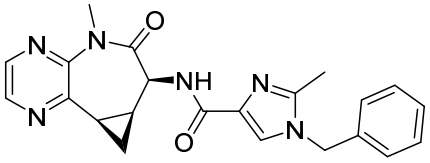




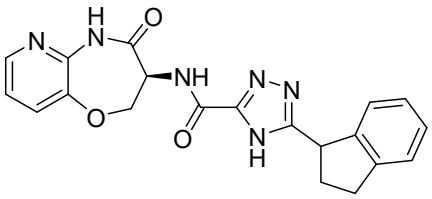


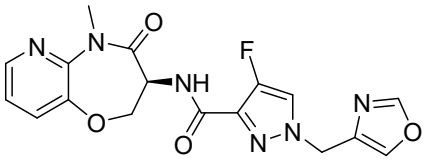


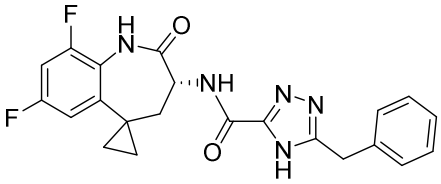

















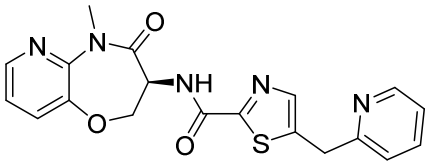
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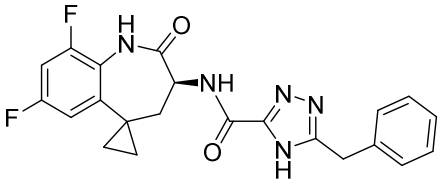


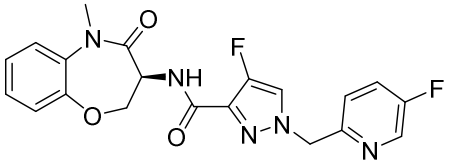


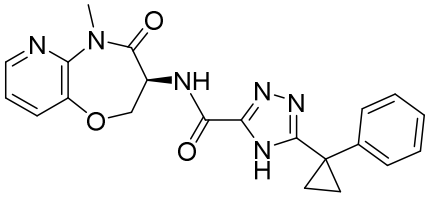
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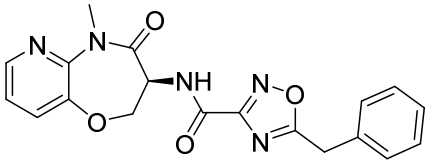


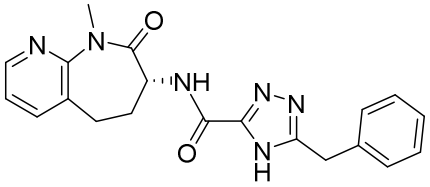


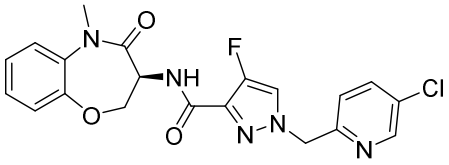


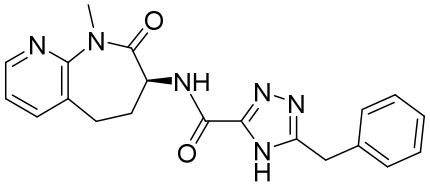


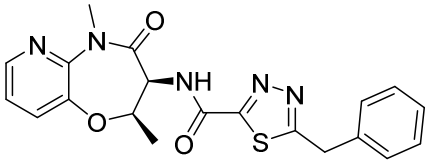


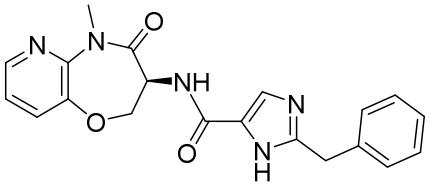


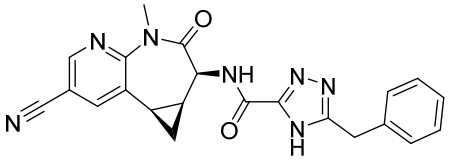


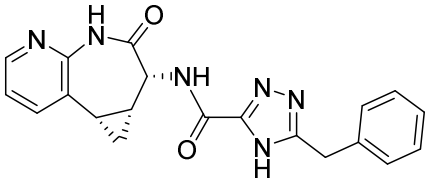


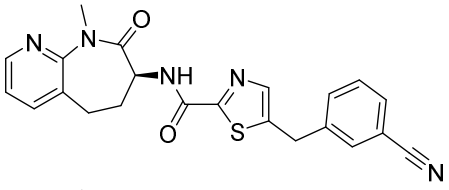


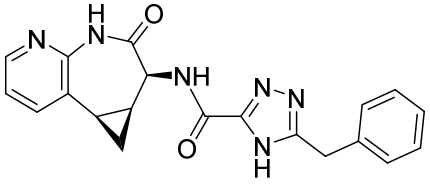


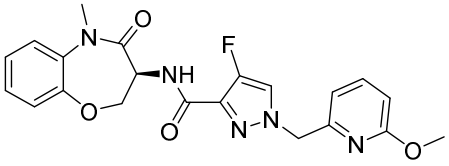


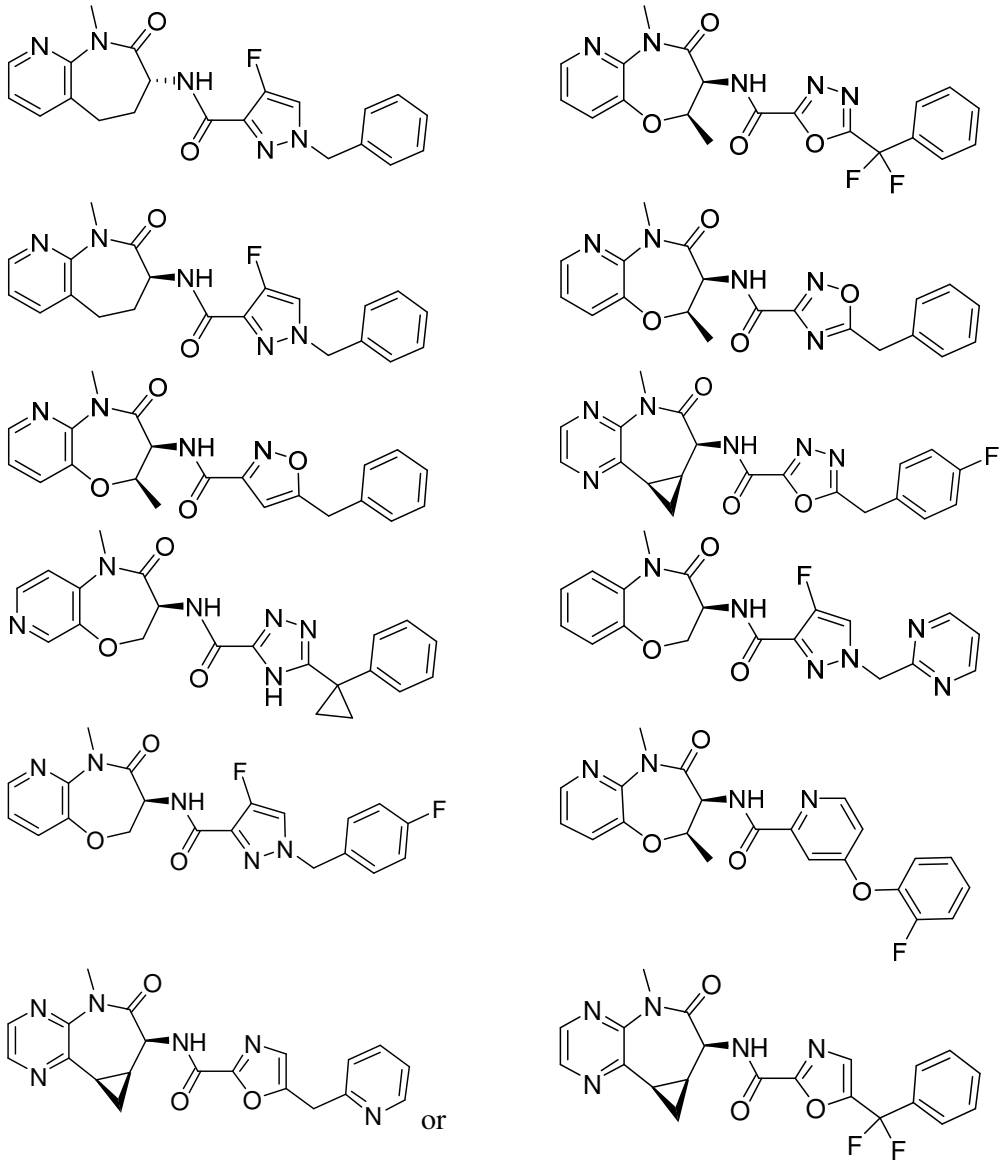






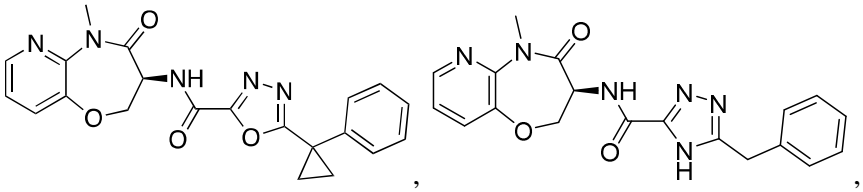


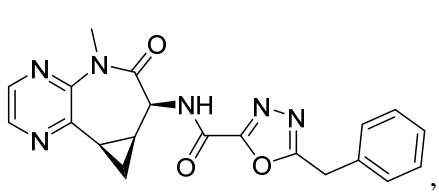
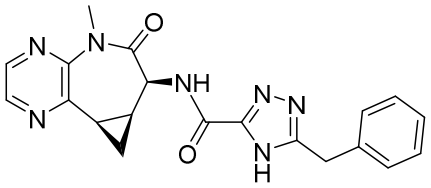
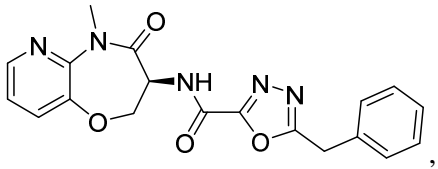
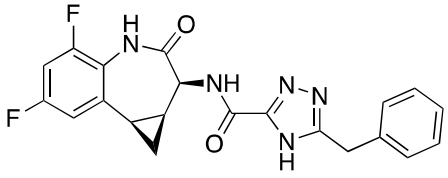




or a pharmaceutically acceptable salt, tautomer, stereoisomer or mixture of stereoisomers thereof.

50. The compound of claim 49, wherein the compound is:




,

,

, or


or a stereoisomer or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

51. A pharmaceutical composition comprising a compound, or a stereoisomer or a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, from any preceding claim and an excipient.

52. Use of the compound according to any one of claims 1-50 or the pharmaceutical composition of claim 51 in the manufacture of a medicament for the treatment of a receptor-interacting protein kinase 1-mediated disease or disorder, wherein the disease or disorder is an inflammatory disease or disorder, a necrotic cell disease, a neurodegenerative disease, a central nervous system disease, an ocular disease, a malignancy, an immune-mediated disease, an allergic disease, an autoimmune disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis, atopic dermatitis, rheumatoid arthritis, spondyloarthritis, gout, SoJIA, systemic lupus erythematosus, Sjogren's syndrome, systemic scleroderma, anti-phospholipid syndrome, vasculitis, osteoarthritis, non-alcohol steatohepatitis, alcohol steatohepatitis, autoimmune hepatitis, autoimmune hepatobiliary diseases, primary sclerosing cholangitis, nephritis, Celiac disease, autoimmune ITP, transplant rejection, ischemia reperfusion injury of solid organs, sepsis, systemic inflammatory response syndrome, cerebrovascular accident, myocardial or cardiac infarction, Huntington's disease, Alzheimer's disease, Parkinson's disease, asthma, multiple sclerosis, type I diabetes, Wegener's granulomatosis, pulmonary sarcoidosis, Behçet's disease, interleukin-1 converting enzyme associated fever syndrome, chronic obstructive pulmonary disease, tumor necrosis factor receptor-associated periodic syndrome, periodontitis, trauma, ischemia, stroke, cardiac infarction, infection, lysosomal storage disease, Gaucher's

disease, Krabbe disease, Niemann-Pick disease, amyotrophic lateral sclerosis (ALS/Lou Gehrig's Disease), HIV-associated dementia, retinal degenerative disease, glaucoma, age-related macular degeneration, psoriasis, psoriatic arthritis, brain injury, spinal cord injury, dementia, Huntington's disease, diabetic neuropathy, polyglutamine (polyQ) diseases, Fahr disease, Menke's disease, Wilson's disease, cerebral ischemia, Friedreich's ataxia, Lewy body disease, or a prion disorder.

53. The use of claim 52, wherein the disease or disorder is multiple sclerosis, amyotrophic lateral sclerosis (ALS/Lou Gehrig's Disease), Alzheimer's disease, rheumatoid arthritis, or psoriasis.