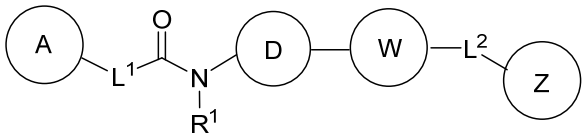
5233). The exchange of GDP with GTP in eIF2 is catalyzed by its dedicated guanine nucleotide exchange factor (GEF) eIF2B. eIF2B exists as a decamer ($B1_2\,B2_2\,B3_2\,B4_2\,B5_2$) or dimer of two pentamers in cells (Gordiyenko, Y. et al, Nat Commun (2014) 5:3902; Wortham, N.C. et al, *FASEB J* (2014) 28:2225-2237). Molecules such as ISRIB interact with and stabilize the eIF2B dimer conformation, thereby enhancing intrinsic GEF activity and making cells less sensitive to the cellular effects of phosphorylation of eIF2α (Sidrauski, C. et al, *eLife* (2015) e07314; Sekine, Y. et al, *Science* (2015) 348:1027-1030). As such, small molecule therapeutics that can modulate eIF2B activity may have the potential to attenuate the PERK branch of the UPR and the overall ISR, and therefore may be used in the prevention and/or treatment of various diseases, such as a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, or a metabolic disease.

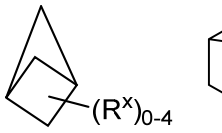
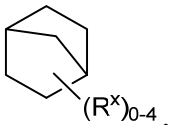
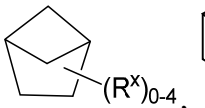
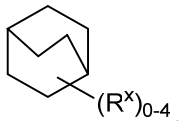
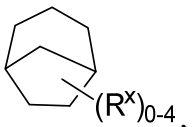
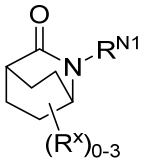
SUMMARY

In one aspect of the present disclosure, there is provided a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

D is selected from the group consisting of:  ,  ,  ,  ,  , and  ;

L^1 is a bond, CH_2O–*, CH_2CH_2O–* OCH_2–* or CH_2OCH_2–*; and L^2 is selected from a bond, CH_2O–*, –OCH_2–*, –CH_2–, –NH–, –NCH_3–, or –O–, wherein "–*" indicates the attachment point to A or Z, respectively;

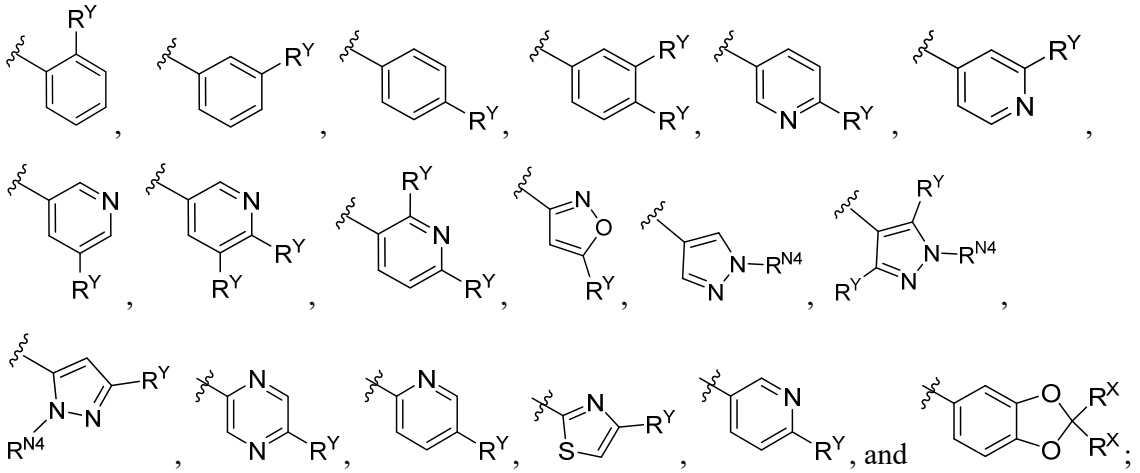
R^1 is hydrogen or C_1-C_6 alkyl;

W is pyrrolidinone, imidazolidinone, dihydroimidazolidinone, oxazolidinone, oxazolidinedione, oxazolone, dihydropyrrolone, piperazine, piperazinone, oxazinanone, or

dihydrooxazole moiety, each of which is optionally substituted with 1-4 R^W groups; and wherein the imidazolidinone may be optionally substituted on an available nitrogen with hydrogen or $–CH_3$;

A is phenyl or pyridyl, each of which is optionally substituted with 1-2 R^Y;

Z is selected from the group consisting of:



each R^W is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

each R^X is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

each R^Y is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $-OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, $–S(O)_2R^D$, and G^1; or

2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl each of which is optionally substituted with 1-5 R^X;

each G^1 is independently 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl is optionally substituted with 1-3 R^Z;

each R^Z is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^A is, at each occurrence, independently hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, $–C(O)NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with 1-3 R^Z;

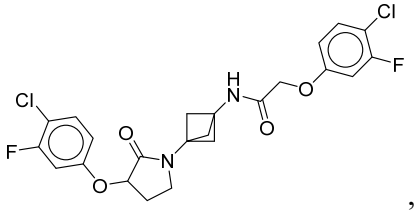
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

each R^E is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

each R^F is independently hydrogen, C_1-C_6 alkyl, or halo; and

m is 1 when R^F is hydrogen or C_1-C_6 alkyl, 3 when R^F is C_1-C_6 alkyl, or 5 when R^F is halo.

In another aspect of the present disclosure, there is provided a compound, wherein the compound is selected from:



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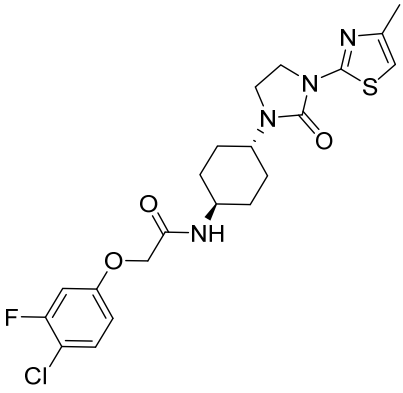

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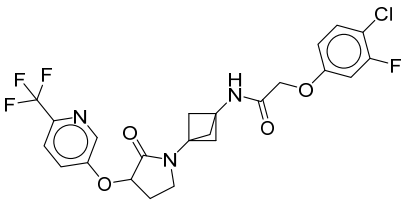
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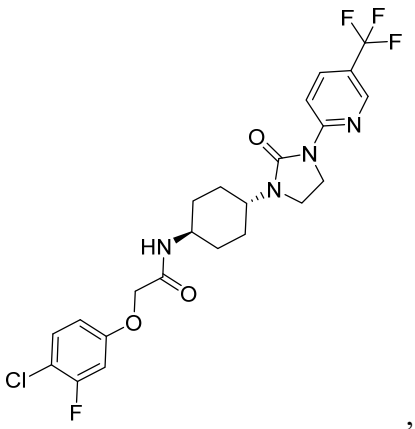
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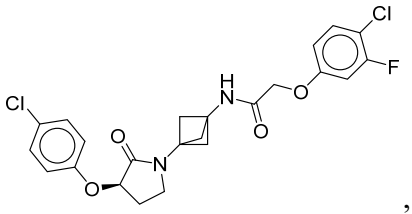
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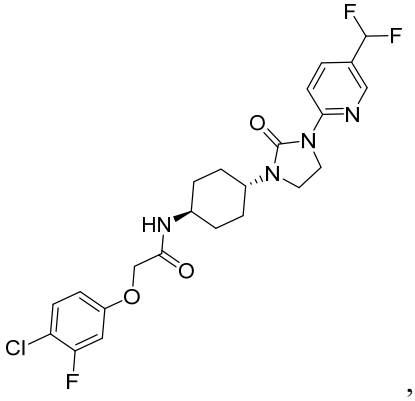
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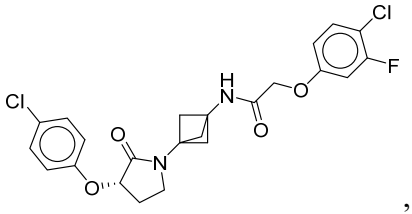
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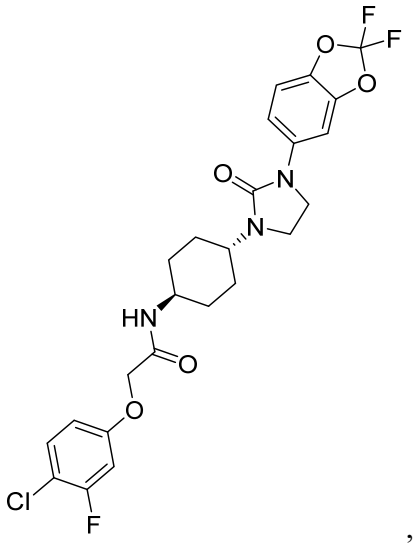
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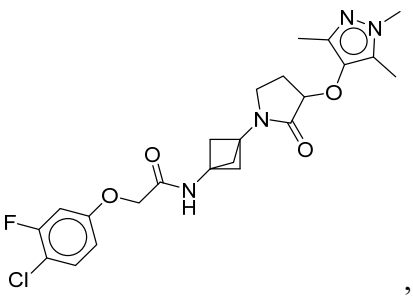
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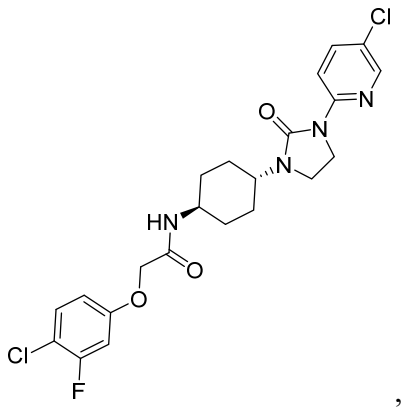
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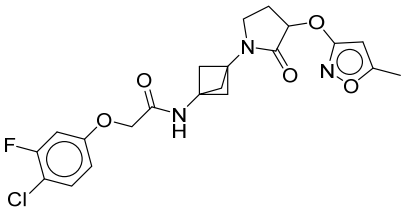
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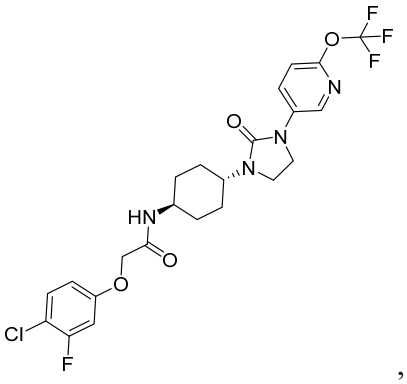
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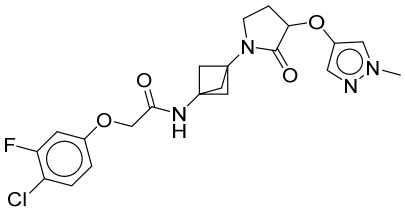
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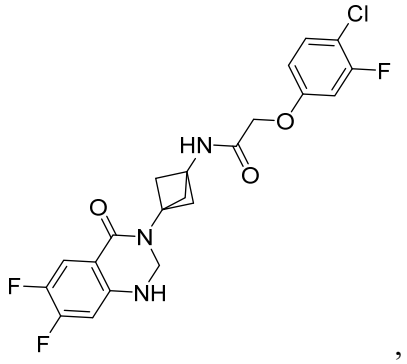
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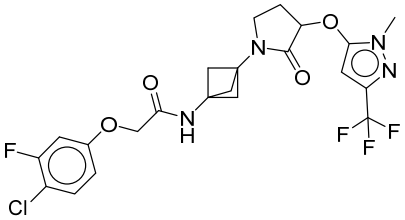
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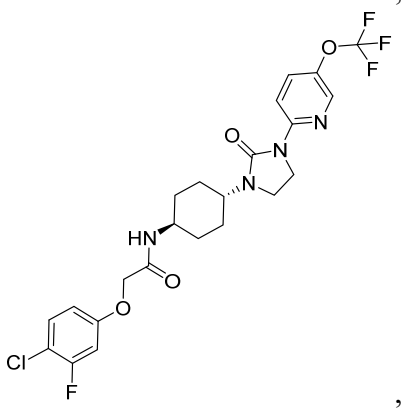
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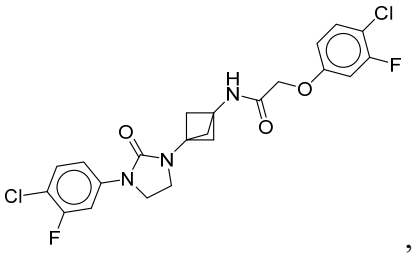
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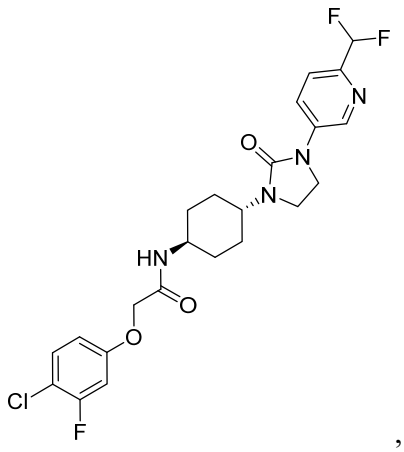
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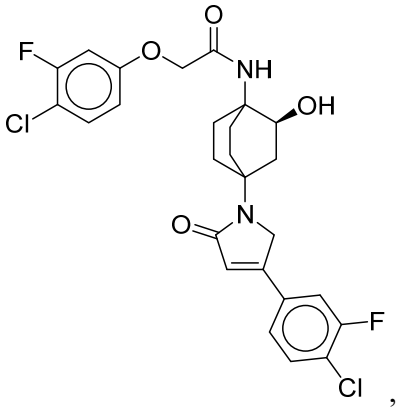
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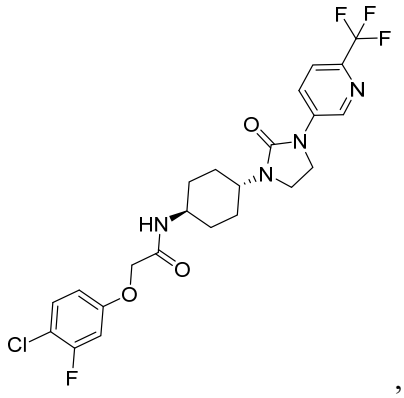
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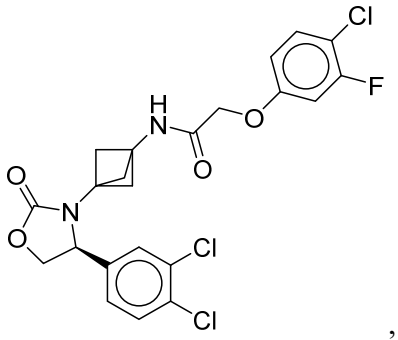
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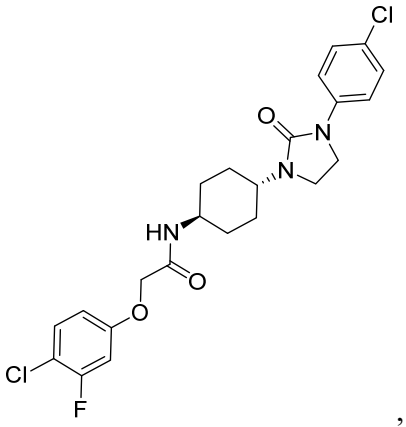
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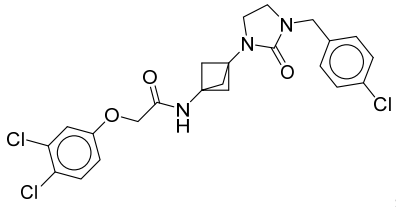
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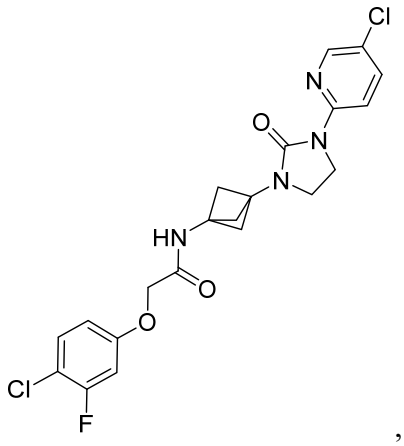
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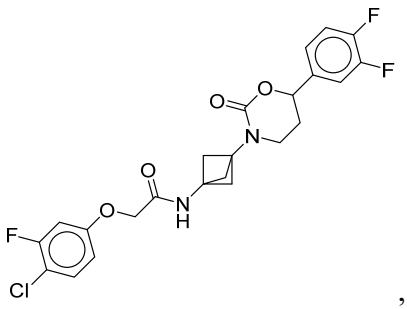
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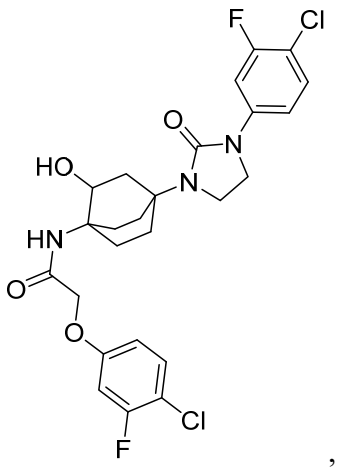
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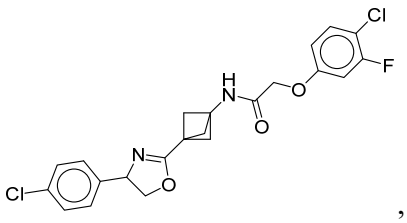
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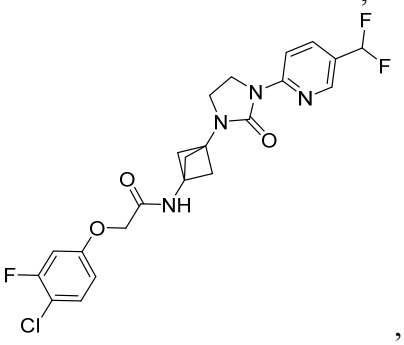
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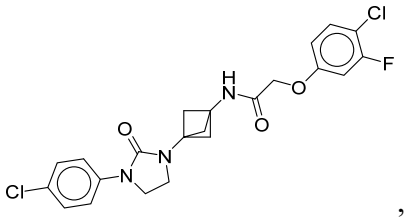
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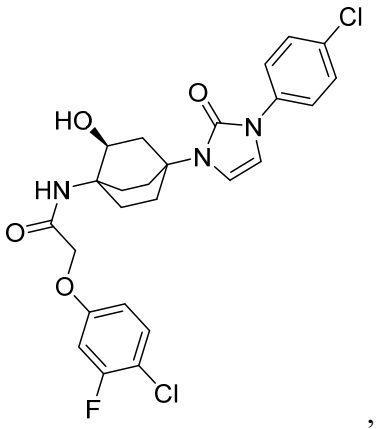
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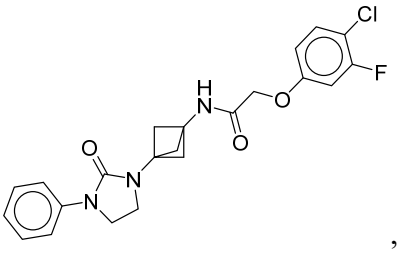
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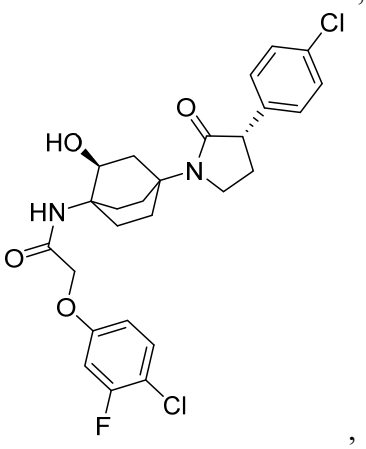
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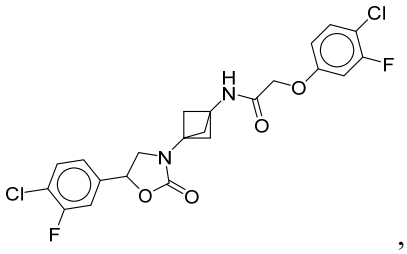
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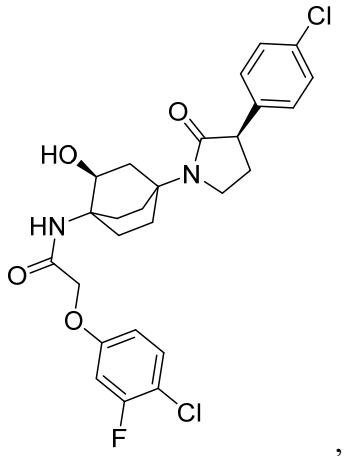
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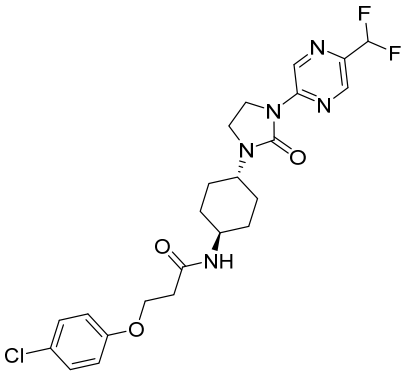
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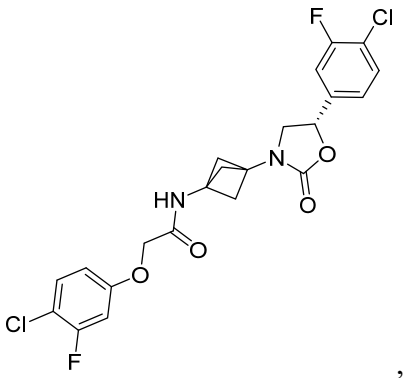
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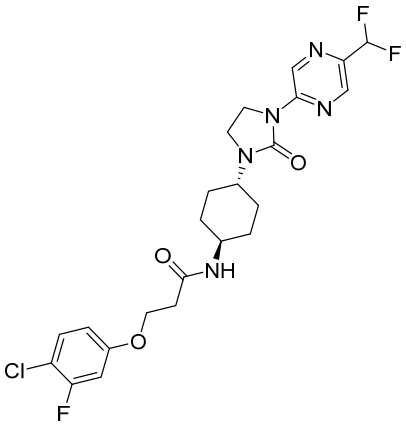
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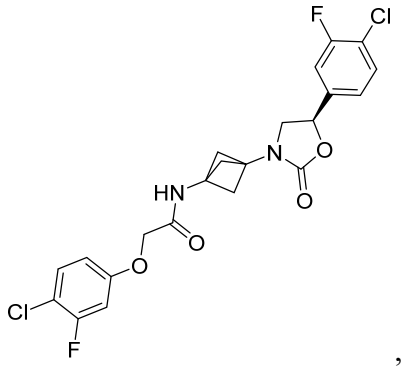
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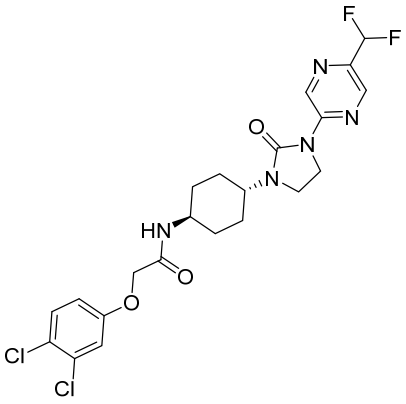
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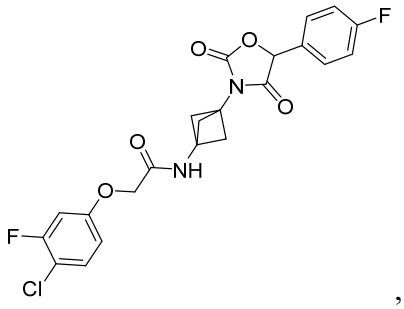
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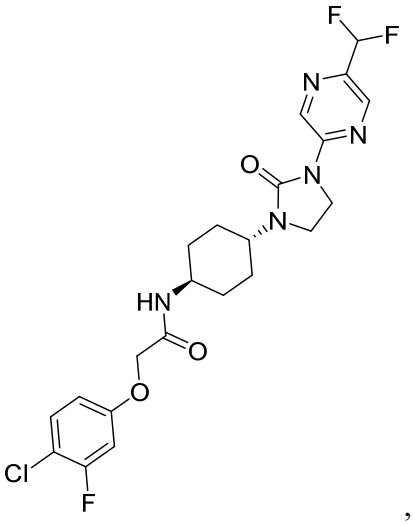
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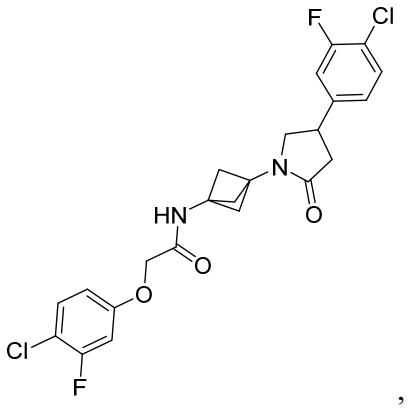
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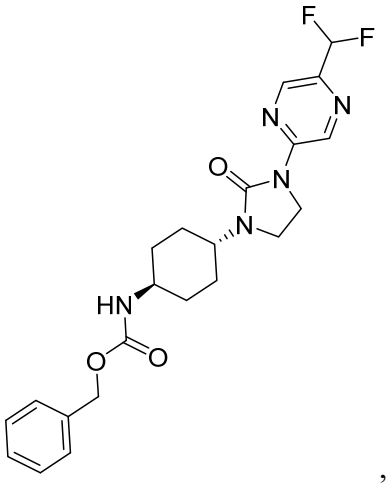
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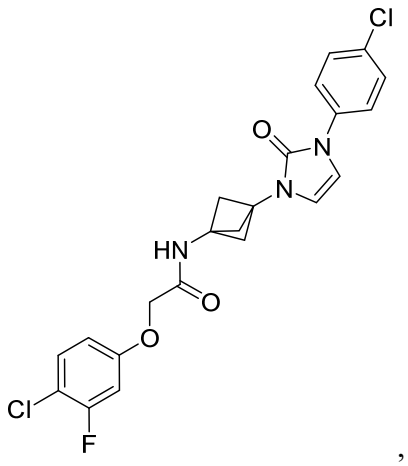
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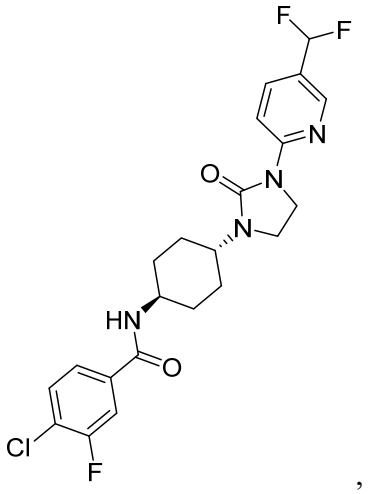
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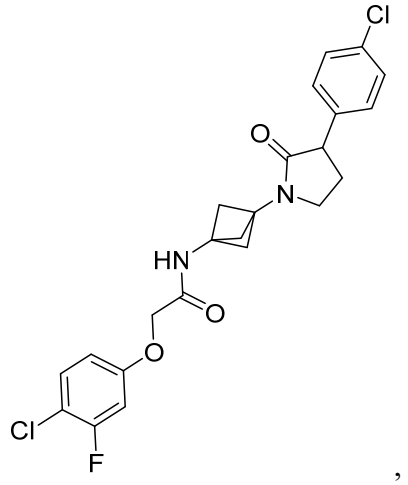
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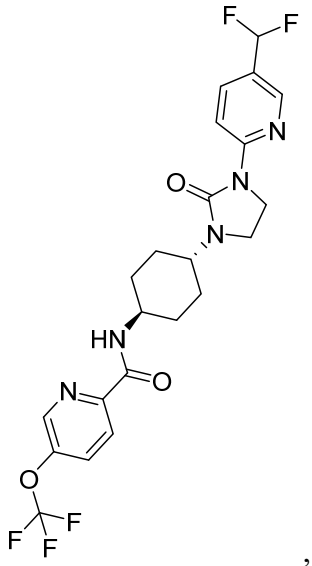
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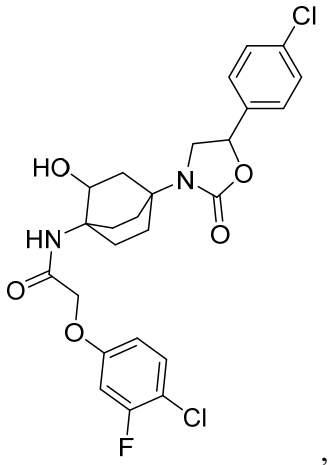
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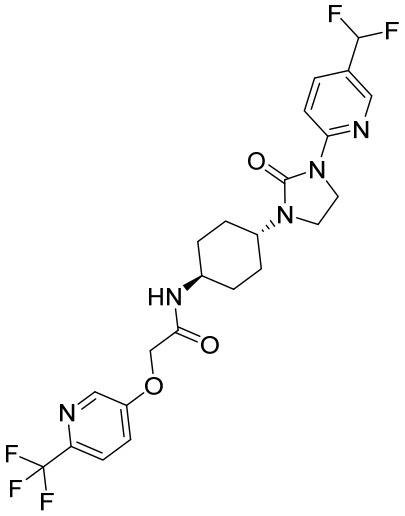
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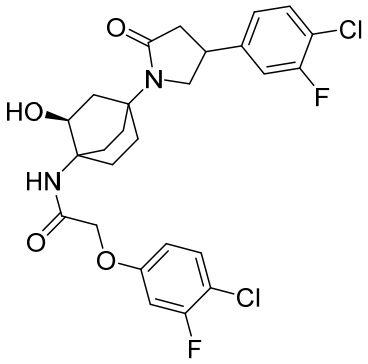
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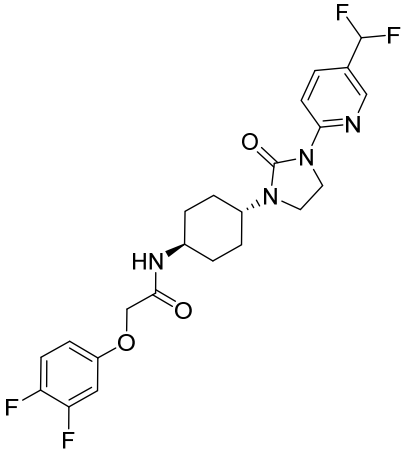
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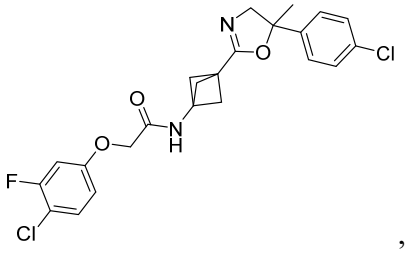
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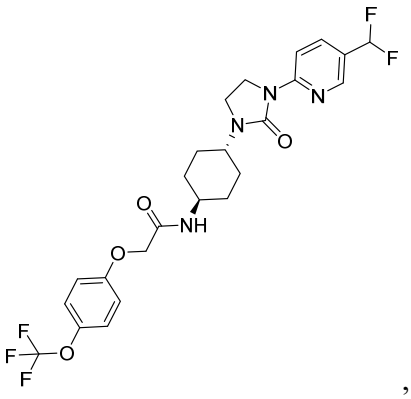
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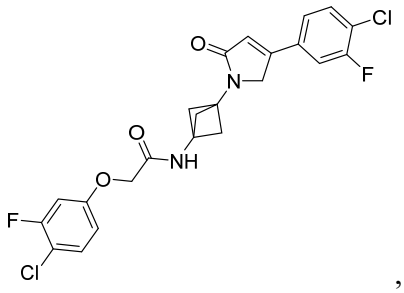
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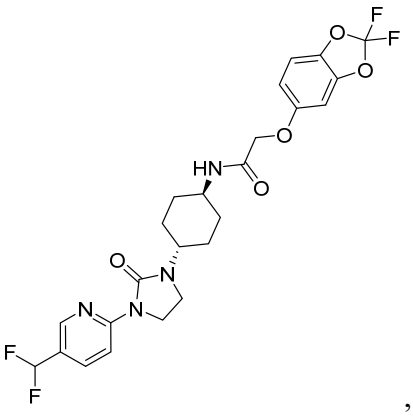
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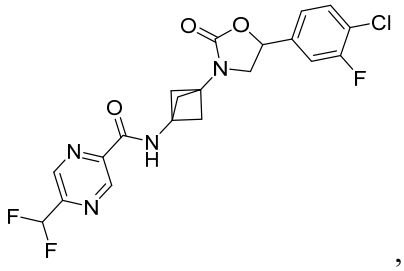
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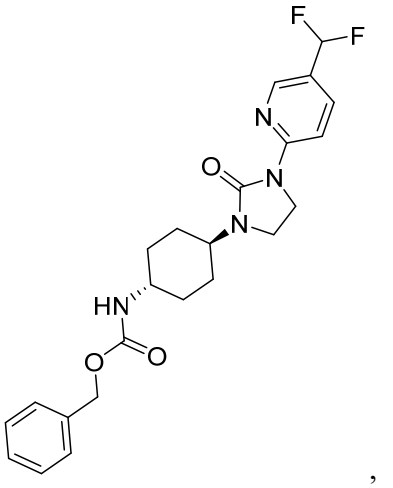
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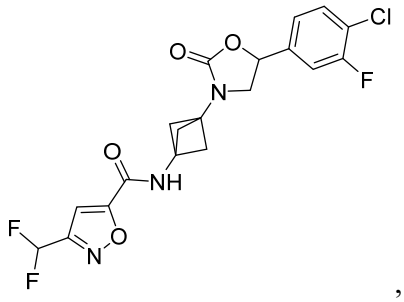
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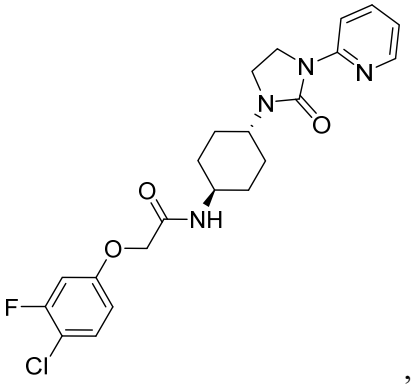
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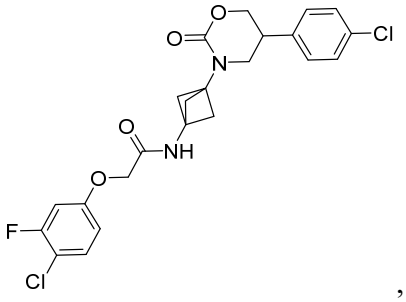
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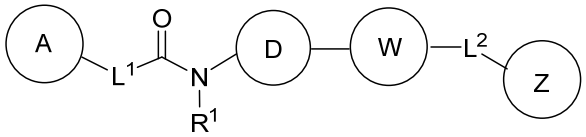
or a pharmaceutically acceptable salt thereof.

The present disclosure is directed, at least in part, to compounds, compositions, and methods for the modulation of eIF2B (e.g., activation of eIF2B) and the attenuation of the ISR signaling pathway. In some examples, disclosed herein is an eIF2B modulator (e.g., an eIF2B activator) comprising a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, N-oxide, or stereoisomer thereof. In other examples, disclosed herein are methods of using a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, N-oxide, or stereoisomer thereof for the treatment of a disease or disorder, e.g., a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or a disease or disorder associated with impaired function of eIF2B or components in the ISR pathway (e.g., eIF2 pathway).

For example, disclosed herein is a compound of Formula (I):



Formula (I)

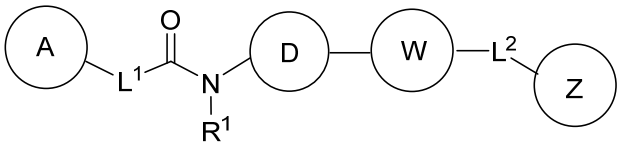
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, *N*-oxide, or stereoisomer thereof, wherein:

D is a bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, cubanyl, cyclohexyl, cyclobutyl, or tetrahydropyranyl wherein each bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, cubanyl, cyclohexyl, cyclobutyl, or tetrahydropyranyl is optionally substituted on

CLAIMS

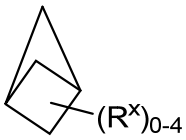
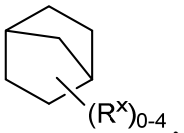
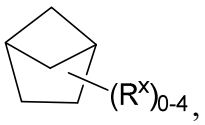
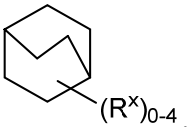
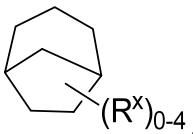
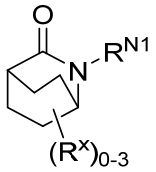
We claim:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

D is selected from the group consisting of:  ,  ,  ,  ,  , and  ;

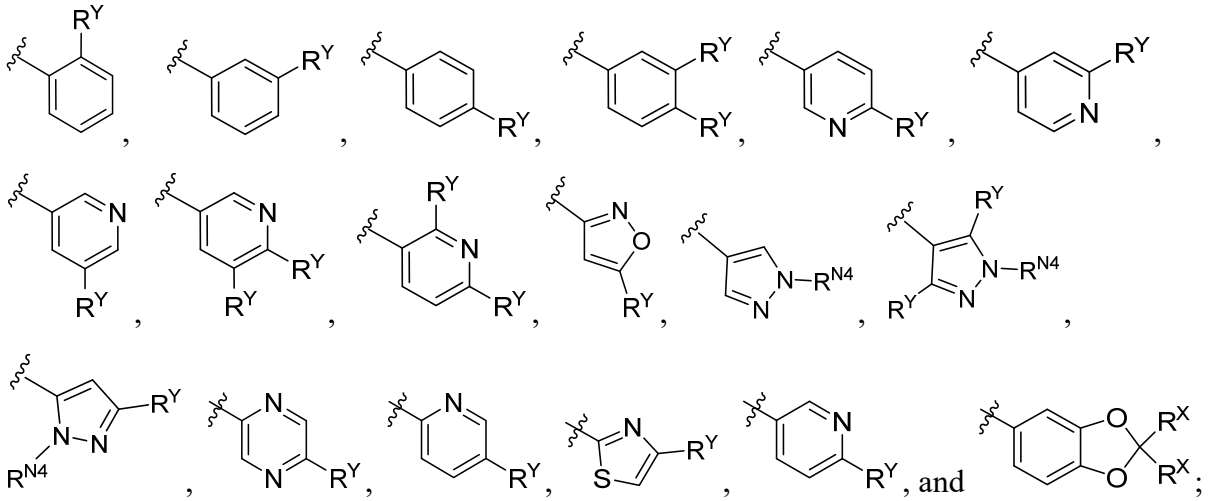
L^1 is a bond, CH_2O–*, CH_2CH_2O–* OCH_2–* or CH_2OCH_2–*; and L^2 is selected from a bond, CH_2O–*, –OCH_2–*, –CH_2–, –NH–, –NCH_3–, or –O–, wherein "–*" indicates the attachment point to A or Z, respectively;

R^1 is hydrogen or C_1-C_6 alkyl;

W is pyrrolidinone, imidazolidinone, dihydroimidazolidinone, oxazolidinone, oxazolidinedione, oxazolone, dihydropyrrolone, piperazine, piperazinone, oxazinanone, or dihydrooxazole moiety, each of which is optionally substituted with 1-4 R^W groups; and wherein the imidazolidinone may be optionally substituted on an available nitrogen with hydrogen or –CH_3;

A is phenyl or pyridyl, each of which is optionally substituted with 1-2 R^Y;

Z is selected from the group consisting of:



each R^W is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

each R^X is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, oxo, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

each R^Y is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, amino-C_1-C_6 alkyl, cyano-C_1-C_6 alkyl, halo, cyano, $-OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, $–S(O)_2R^D$, and G^1; or

2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a 3-7-membered fused cycloalkyl, 3-7-membered fused heterocyclyl, fused aryl, or 5-6 membered fused heteroaryl each of which is optionally substituted with 1-5 R^X;

each G^1 is independently 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each 3-7-membered cycloalkyl, 3-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl is optionally substituted with 1-3 R^Z;

each R^Z is independently selected from the group consisting of C_1-C_6 alkyl, hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, and $–S(O)_2R^D$;

R^A is, at each occurrence, independently hydrogen, C_1-C_6 alkyl, halo-C_1-C_6 alkyl, $–C(O)NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl; or

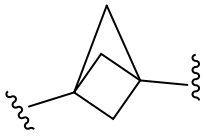
R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with 1-3 R^Z;

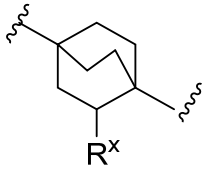
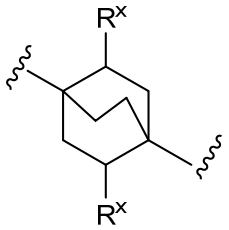
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

each R^E is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

each R^F is independently hydrogen, C_1-C_6 alkyl, or halo; and

m is 1 when R^F is hydrogen or C_1-C_6 alkyl, 3 when R^F is C_1-C_6 alkyl, or 5 when R^F is halo.

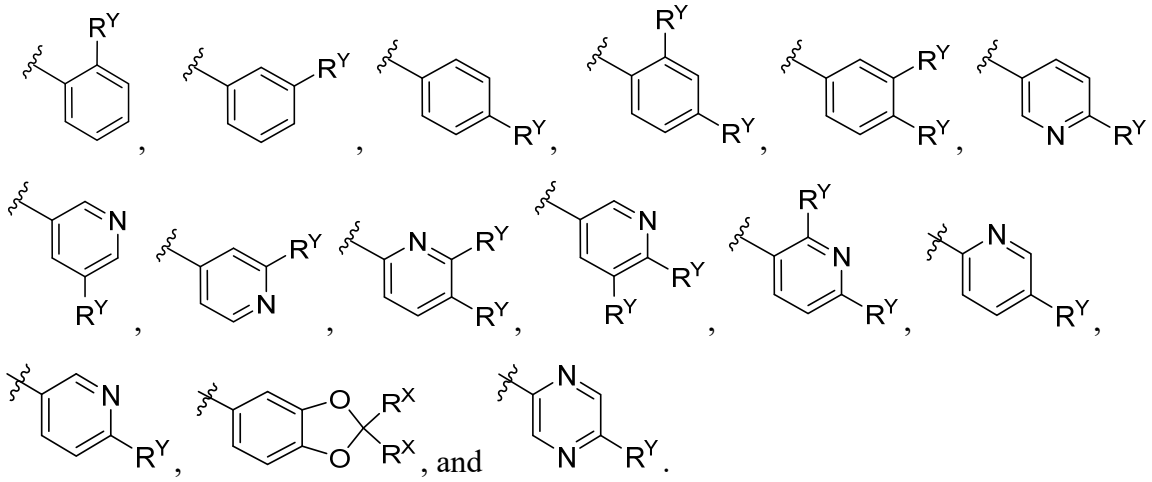
2. The compound of claim 1, wherein D is  .

3. The compound of claim 1, wherein D is  or  .

4. The compound of claim 3, wherein each R^X is independently selected from the group consisting of oxo, $–OR^A$, –C(O)OH, $–C(O)OR^D$, halo, and hydroxy-C_1-C_6 alkyl.

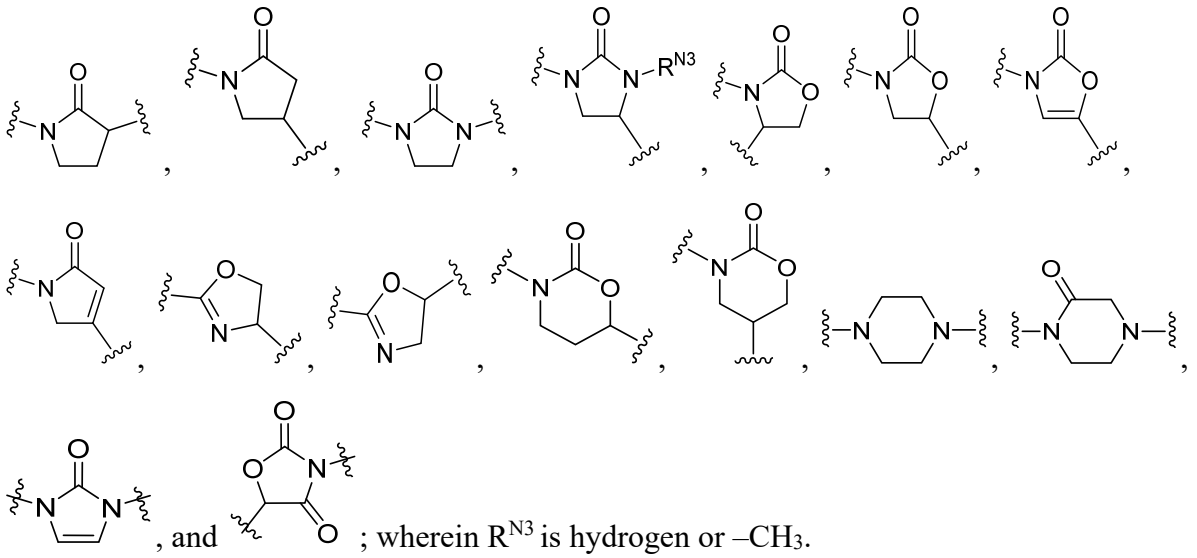
5. The compound of any one of claims 1-3, wherein R^1 is hydrogen or $–CH_3$.

6. The compound of any one of claims 1-4, wherein A is selected from the group consisting of:



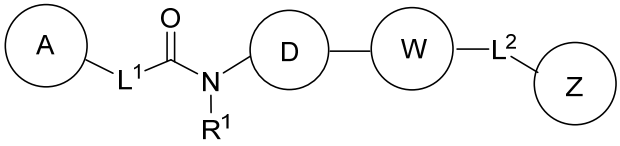
7. The compound of any one of claims 1-5, wherein each R^Y is independently hydrogen, chloro, fluoro, $–CF_3$, $–CHF_2$, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCF_3$, $–OCH(CH_3)_2$, or –CN.

8. The compound of any one of claims 1-6, wherein W is selected from the group consisting of:



; wherein R^{N3} is hydrogen or $–CH_3$.

9. A compound of Formula (I-a):



Formula (I-a)

or a pharmaceutically acceptable salt thereof, wherein:

D is bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, cyclohexyl, cyclobutyl or tetrahydropyranyl, each of which is optionally substituted with 1-4 R^X groups;

L^1 is CH_2O–* or CH_2OCH_2–*, wherein "–*" indicates the attachment point to A;

L^2 is selected from a bond, CH_2O–*, –OCH_2–*, –CH_2–, –NH–, –NCH_3–, or –O–, wherein "–*" indicates the attachment point to Z;

W is a pyrrolidinone, imidazolidinone, dihydroimidazolidinone, oxazolidinone, oxazolidinedione, oxazolone, dihydropyrrolone, piperazine, piperazinone, oxazinanone, or dihydrooxazole moiety, each of which is optionally substituted with 1-4 R^W groups; and wherein the imidazolidinone may be optionally substituted on an available nitrogen with hydrogen or –CH_3;

A is phenyl or pyridyl, each of which is optionally substituted with 1-5 R^Y groups;

Z is phenyl, pyridyl, isoxazolyl, thiazolyl, pyrazinyl or pyrazolyl, each of which is optionally substituted on one or more available carbons with 1-5 R^Y groups; and wherein pyrazolyl may be optionally substituted on an available nitrogen with hydrogen or –CH_3;

each R^W is independently fluoro, chloro, oxo, –OH, –OCH_3, –CHF_2, –OCF_3, –CF_3, –CH_3, –CH_2CH_3, or –$CH(CH_3)_2$;

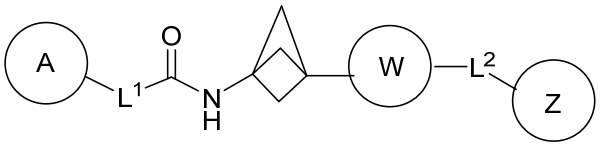
each R^X is independently fluoro, oxo, –OH, –OCH_3, –C(O)OH, or –$C(O)OCH_3$;

each R^Y is independently chloro, fluoro, –CF_3, –CH_3, –CH_2CH_3, –$CH(CH_3)_2$, –OCH_3, –$OCH(CH_3)_2$, or –CN; or

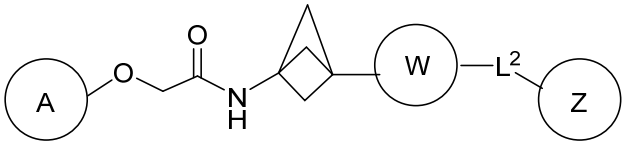
2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a furanyl, pyrrolyl, or dioxolanyl ring, each of which is optionally substituted with 1-2 R^X; and

R^1 is hydrogen.

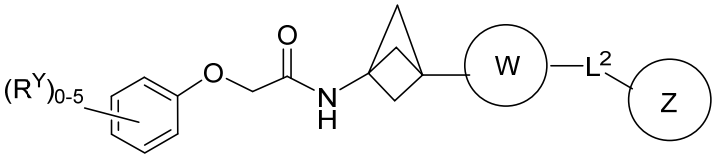
10. The compound of any one of claims 1-8, wherein the compound of Formula (I) is a compound of Formula (I-b), Formula (I-c), or Formula (I-d):



Formula (I-b)



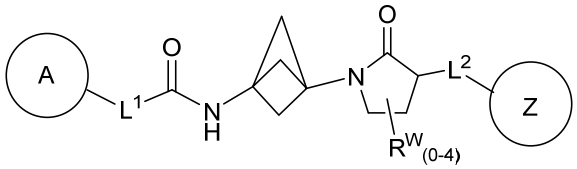
Formula (I-c)



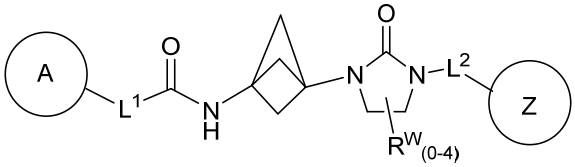
Formula (I-d)

or a pharmaceutically acceptable salt thereof.

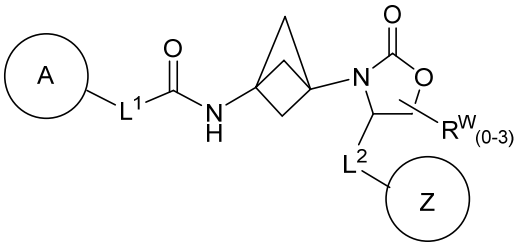
11. The compound of any one of claims 1-9, wherein the compound of Formula (I) is a compound of Formula (I-e-1), Formula (I-e-2), Formula (I-e-3), Formula (I-e-4), Formula (I-e-5), Formula (I-e-6), Formula (I-e-7), Formula (I-e-8), Formula (I-e-9), Formula (I-e-10), Formula (I-e-11), Formula (I-e-12), Formula (I-e-13), Formula (I-e-14), or Formula (I-e-15):



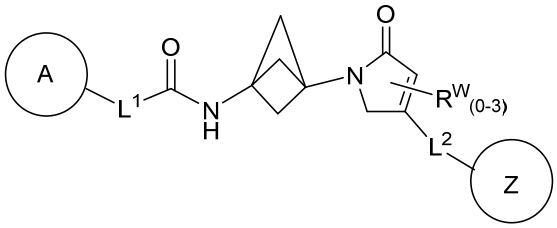
Formula (I-e-1)



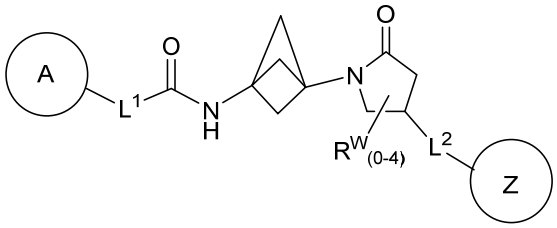
Formula (I-e-2)



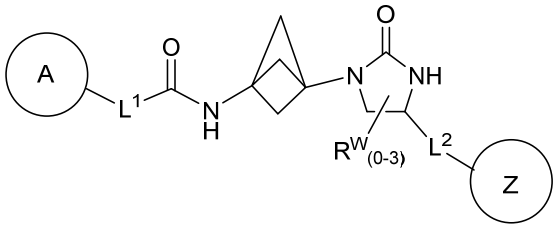
Formula (I-e-3)



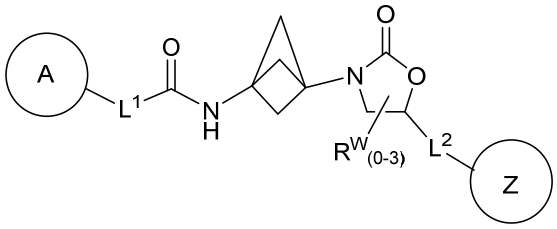
Formula (I-e-4)



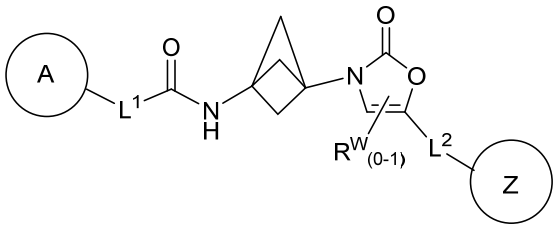
Formula (I-e-5)



Formula (I-e-6)



Formula (I-e-7)



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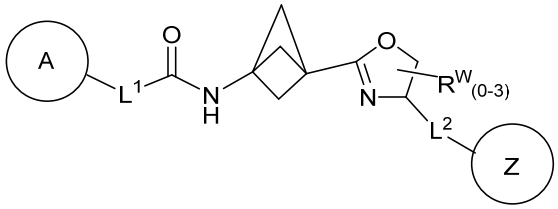
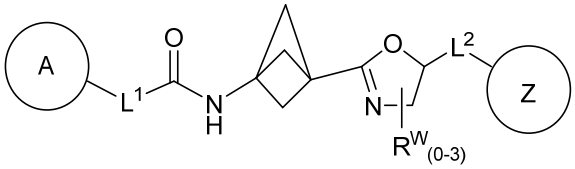
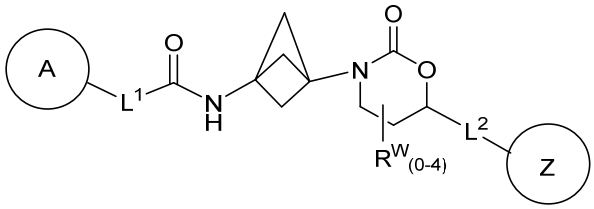


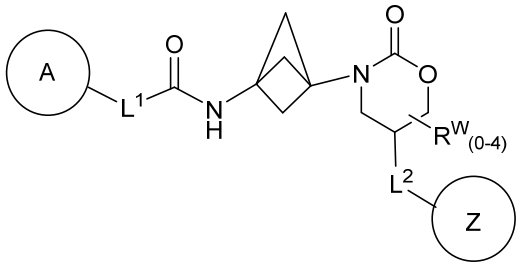
Formula (I-e-9)



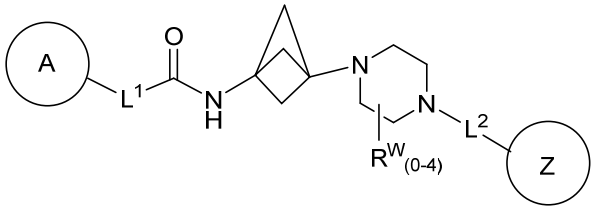
Formula (I-e-10)



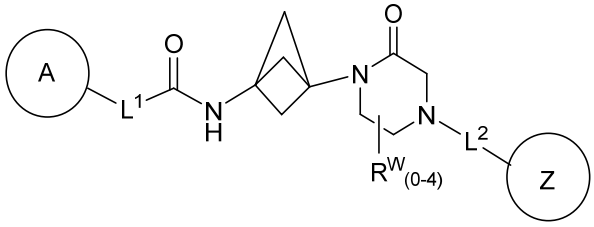
Formula (I-e-11)



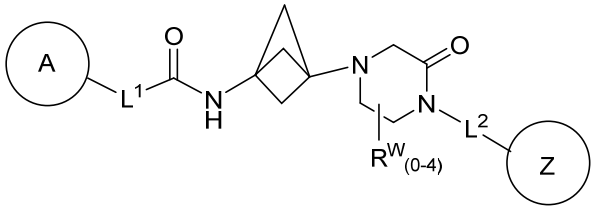
Formula (I-e-12)



Formula (I-e-13)



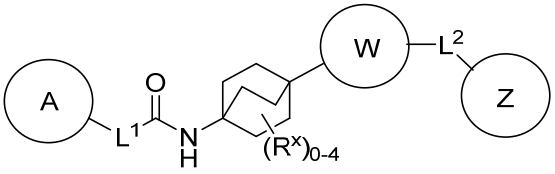
Formula (I-e-14)



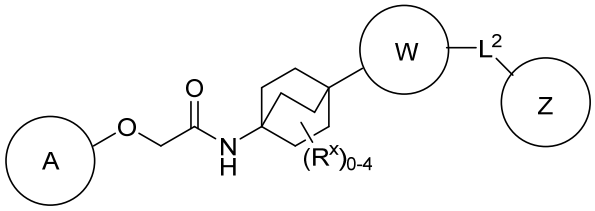
Formula (I-e-15)

or a pharmaceutically acceptable salt thereof.

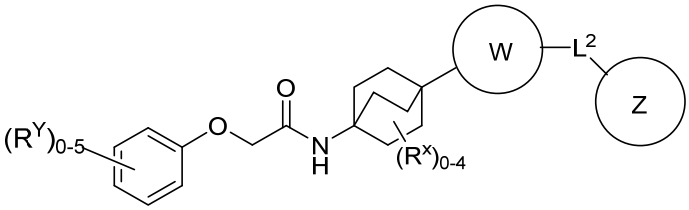
12. The compound of any one of claims 1-8, wherein the compound of Formula (I) is a compound of Formula (I-f), Formula (I-g), or Formula (I-h):



Formula (I-f)



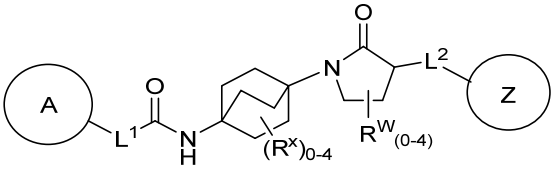
Formula (I-g)



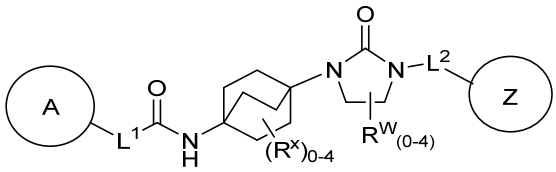
Formula (I-h)

or a pharmaceutically acceptable salt thereof.

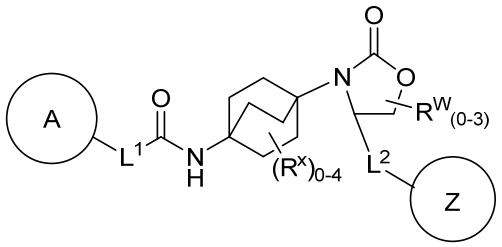
13. The compound of any one of claims 1-8 and 11, wherein the compound of Formula (I) is a compound of Formula (I-i-1), Formula (I-i-2), Formula (I-i-3), Formula (I-i-4), Formula (I-i-5), Formula (I-i-6), Formula (I-i-7), Formula (I-i-8), Formula (I-i-9), Formula (I-i-10), Formula (I-i-11), Formula (I-i-12), Formula (I-i-13), Formula (I-i-14), or Formula (I-i-15):



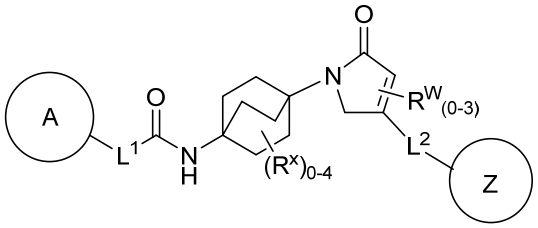
Formula (I-i-1)



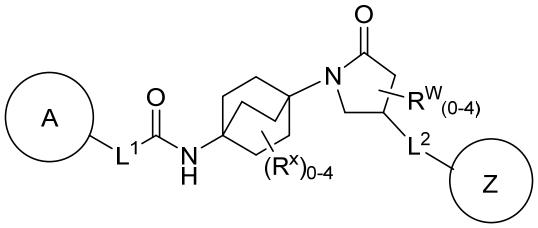
Formula (I-i-2)



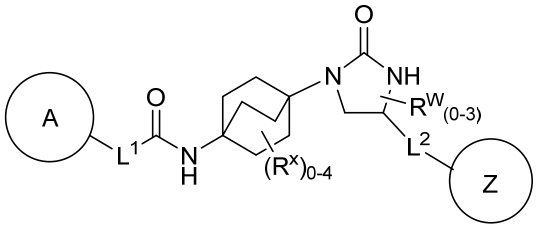
Formula (I-i-3)



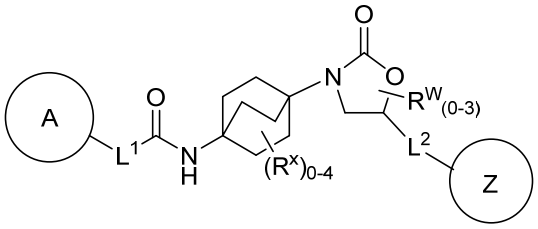
Formula (I-i-4)



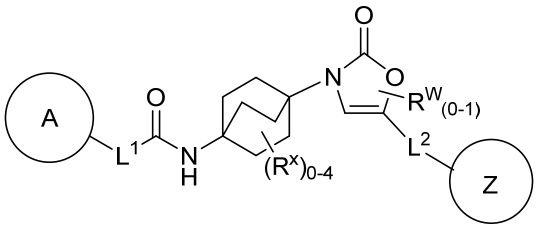
Formula (I-i-5)



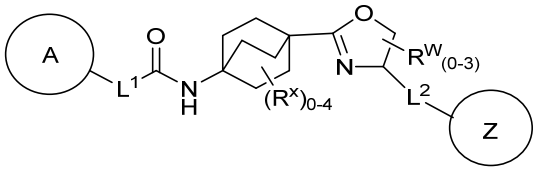
Formula (I-i-6)



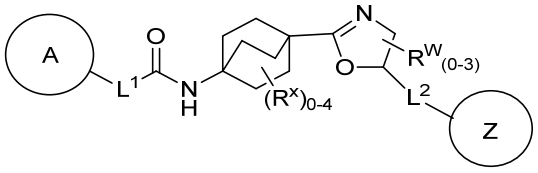
Formula (I-i-7)



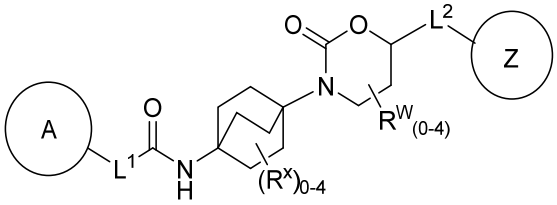
Formula (I-i-8)



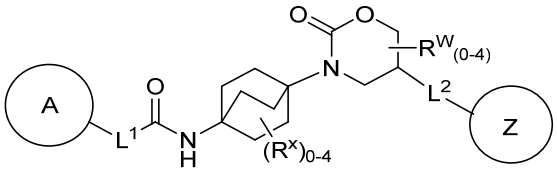
Formula (I-i-9)



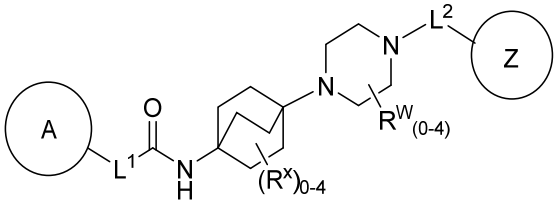
Formula (I-i-10)



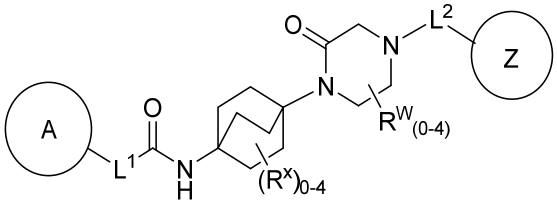
Formula (I-i-11)



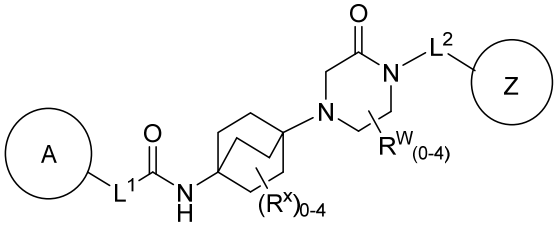
Formula (I-i-12)



Formula (I-i-13)



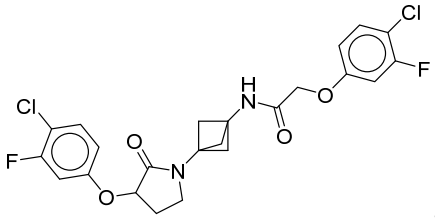
Formula (I-i-14)



Formula (I-i-15)

or a pharmaceutically acceptable salt thereof.

14. A compound, wherein the compound is selected from:



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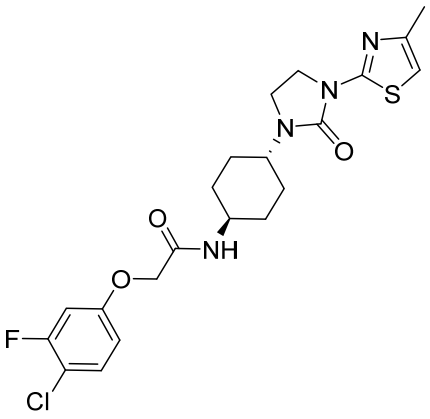

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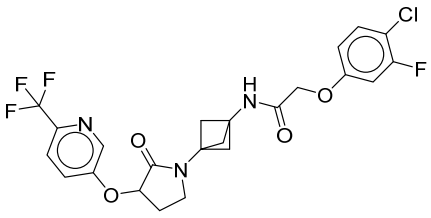
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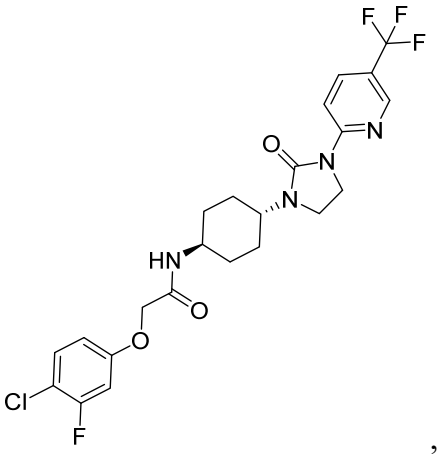
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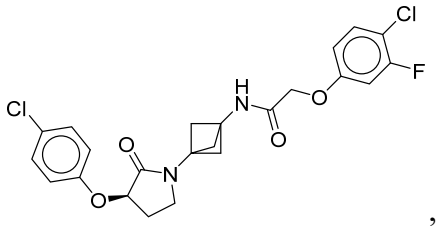
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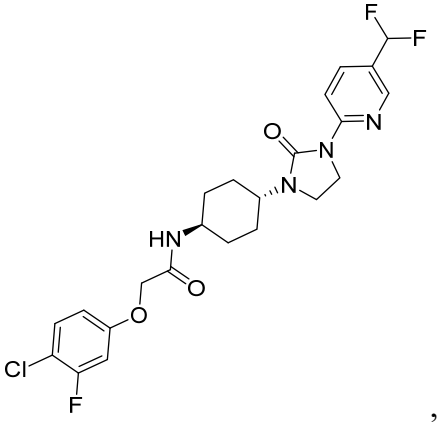
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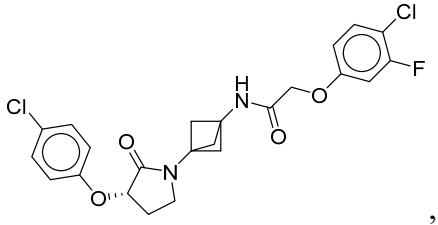
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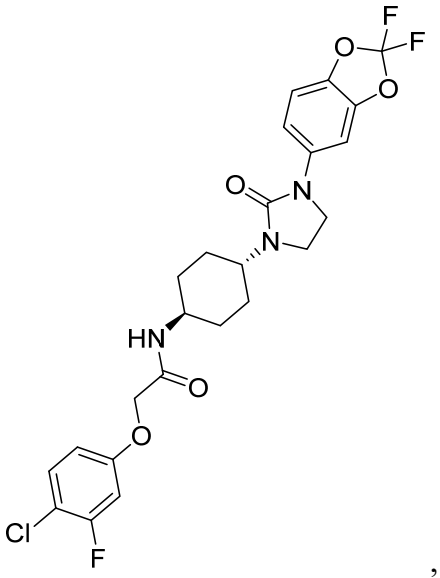
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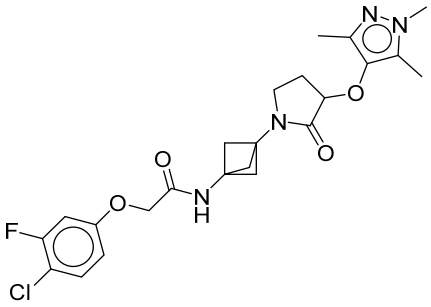
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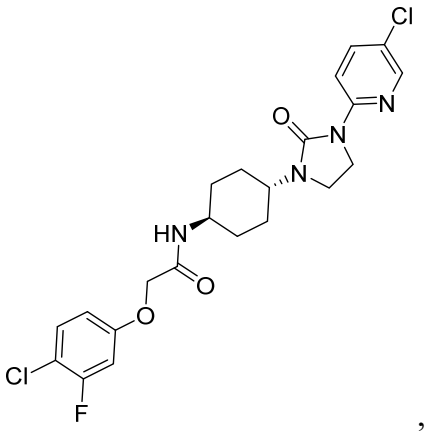
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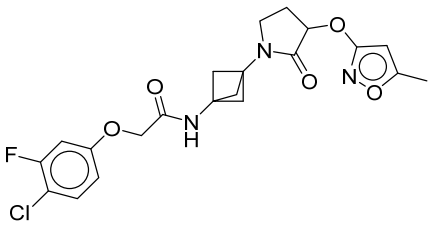
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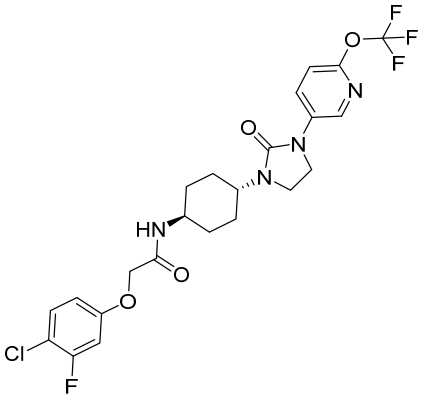
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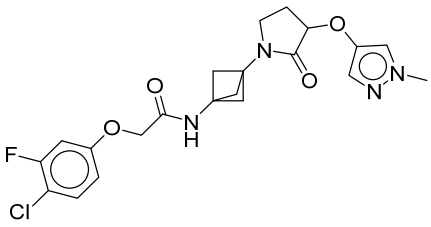
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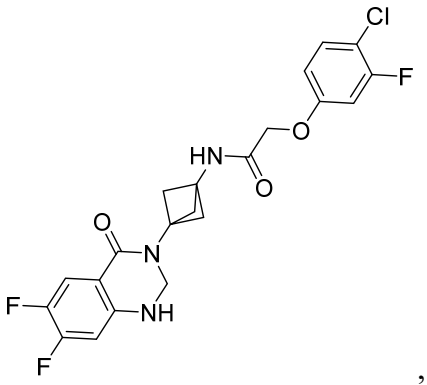
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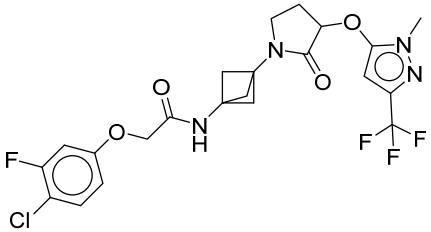
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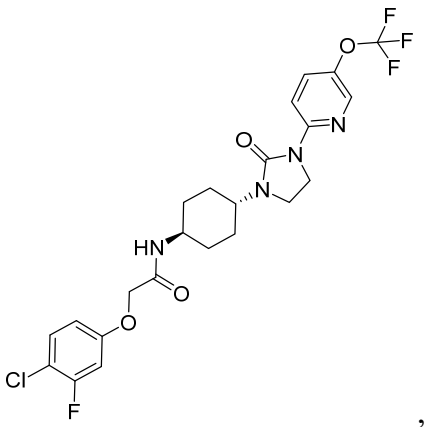
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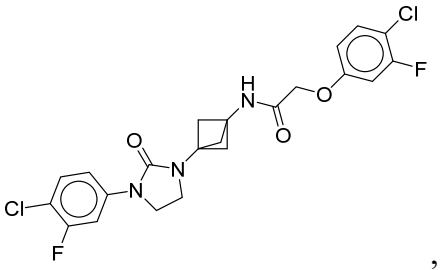
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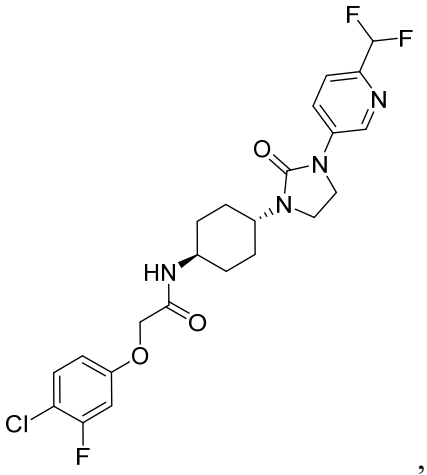
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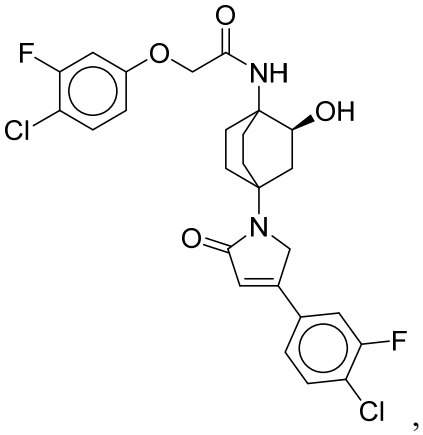
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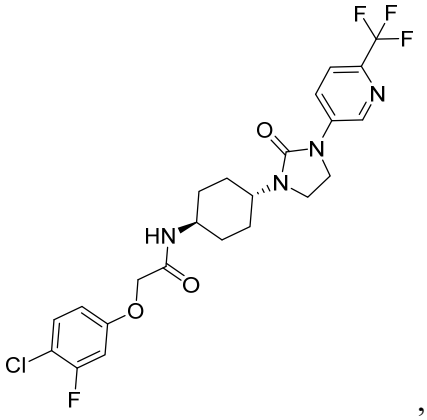
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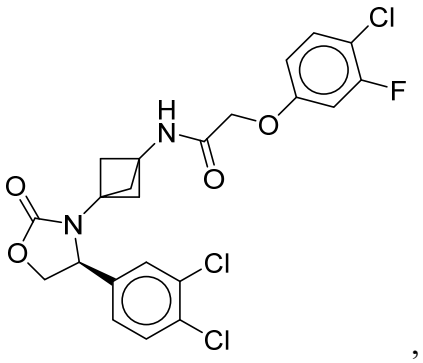
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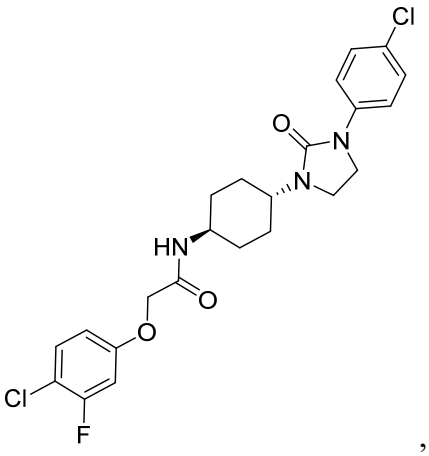
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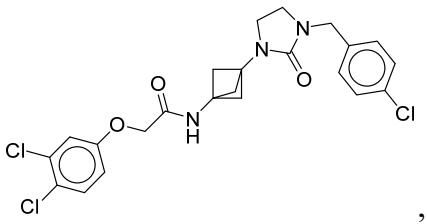
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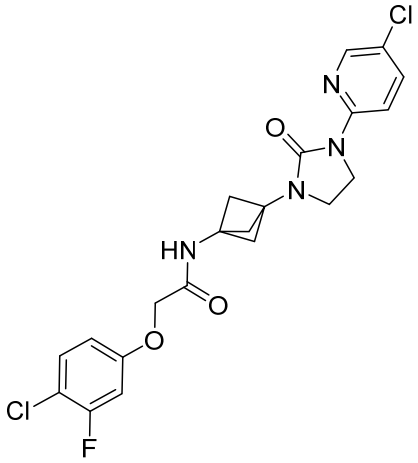
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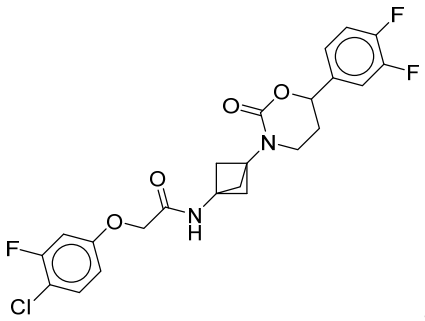
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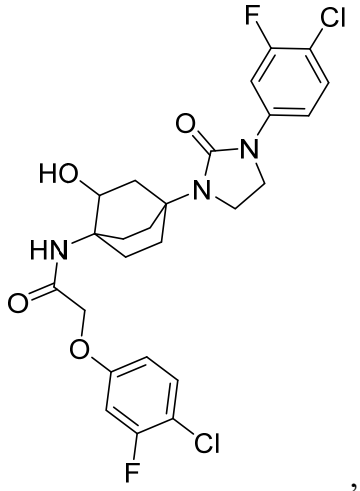
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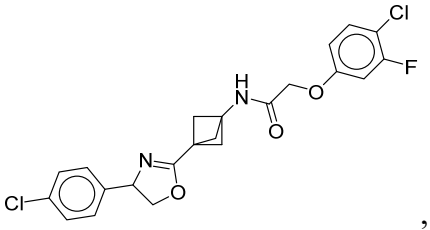
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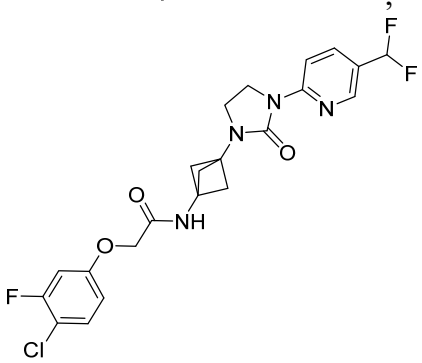
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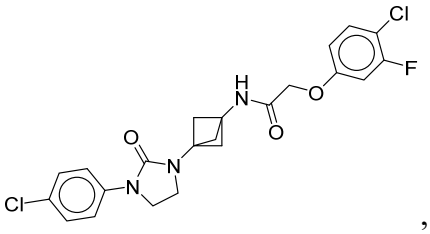
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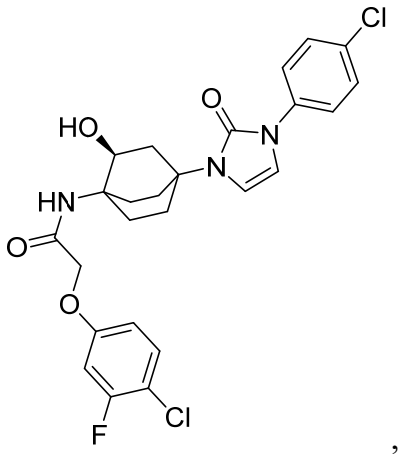
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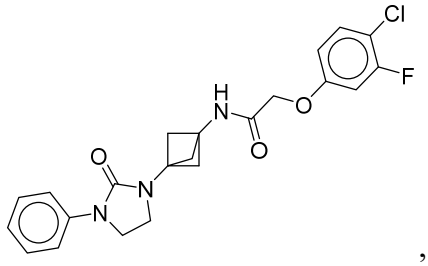
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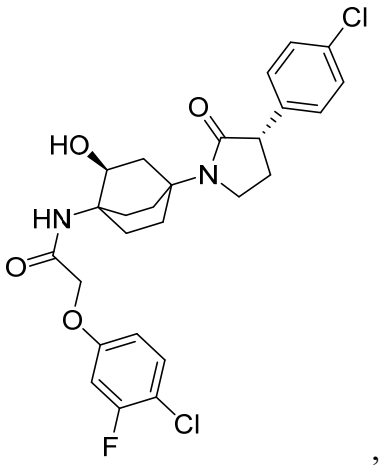
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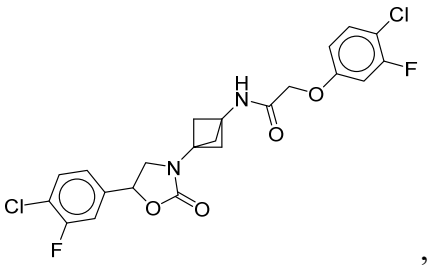
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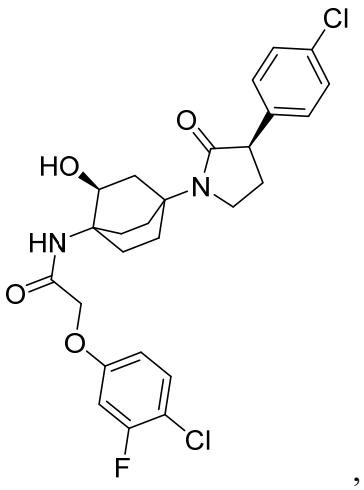
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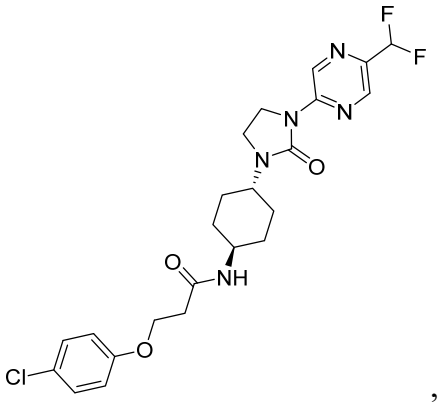
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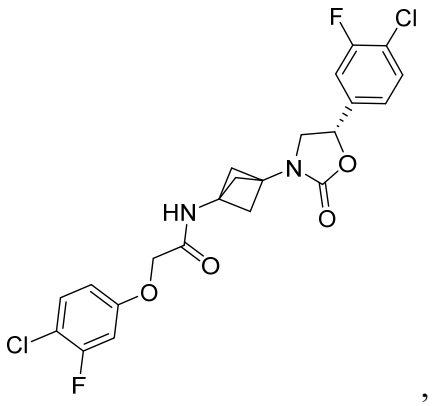
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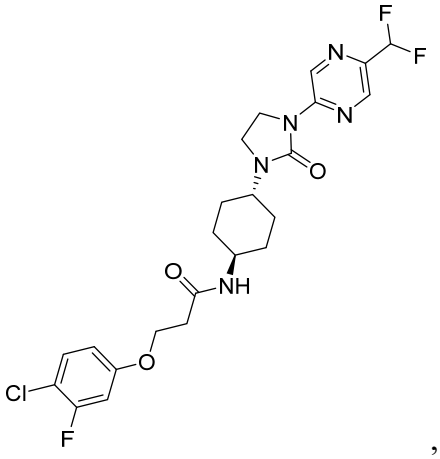
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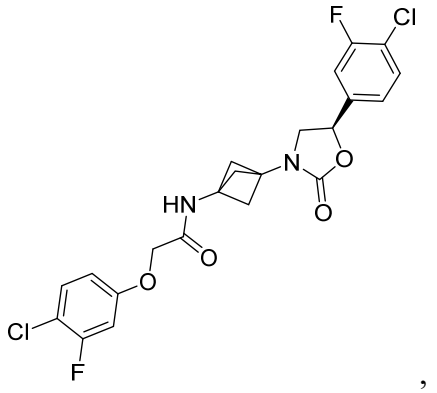
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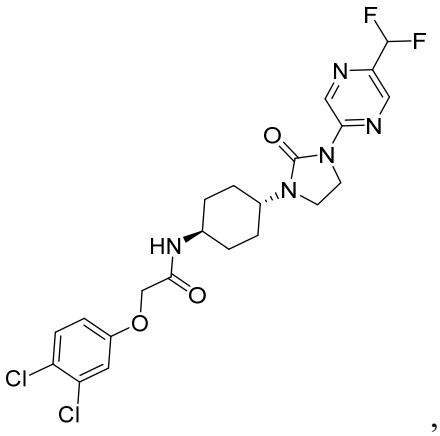
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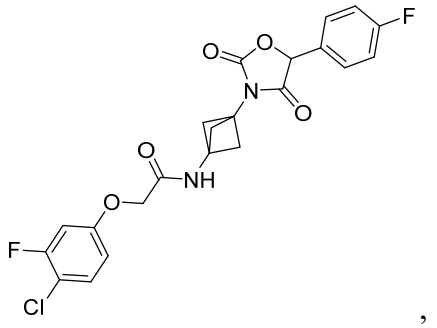
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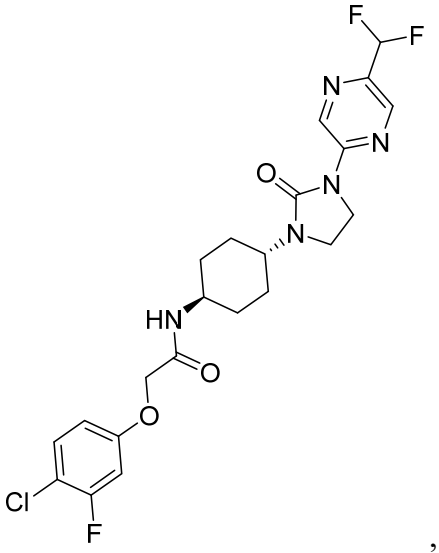

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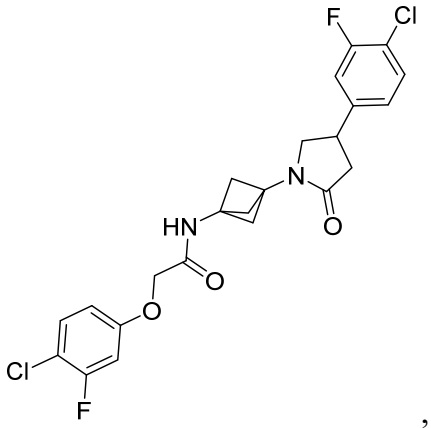

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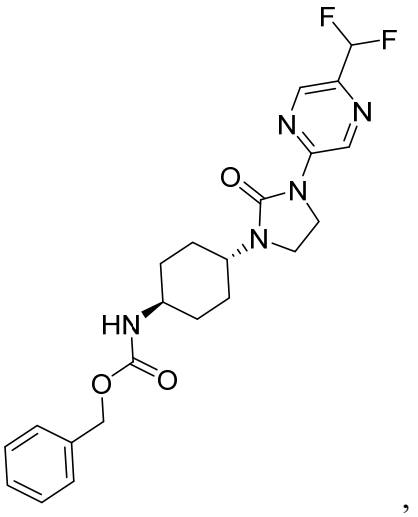

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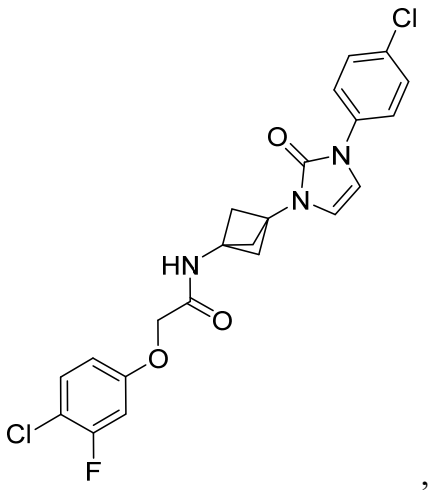

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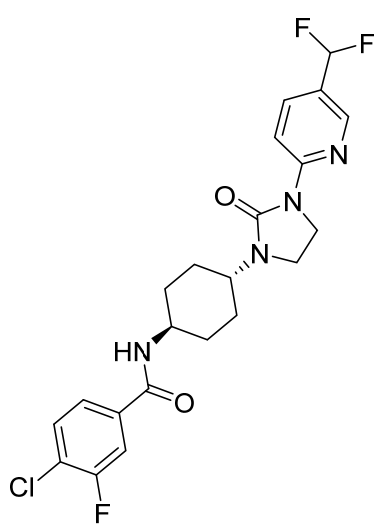

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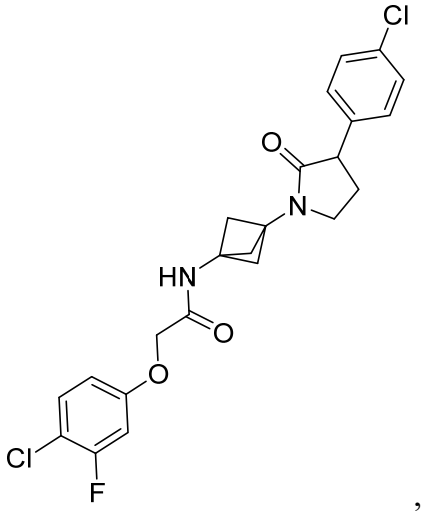

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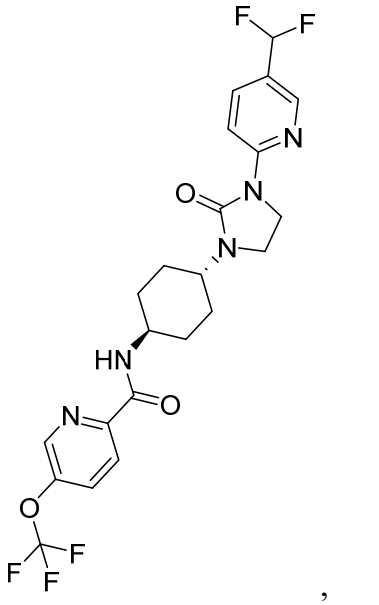

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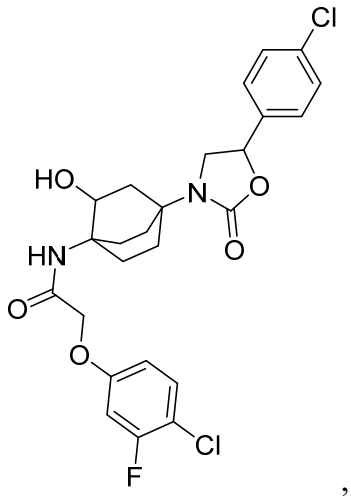

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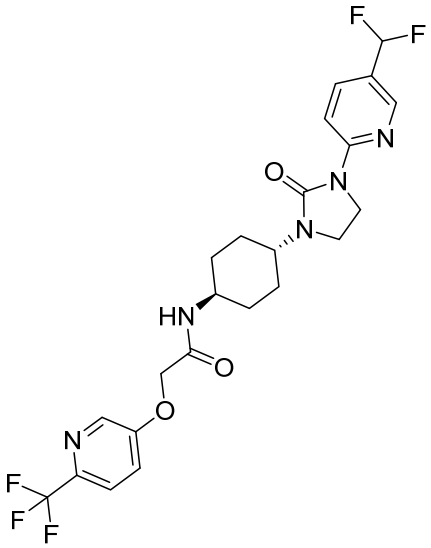

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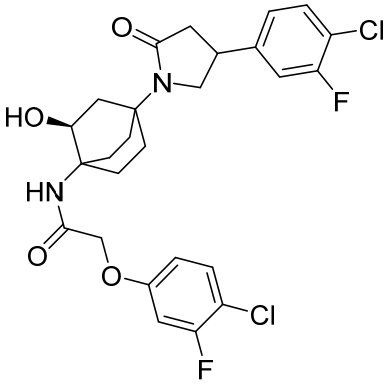

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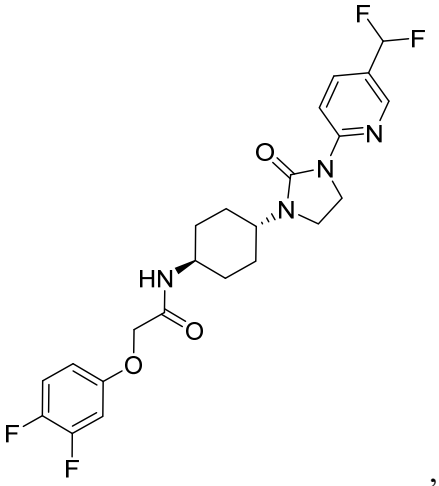

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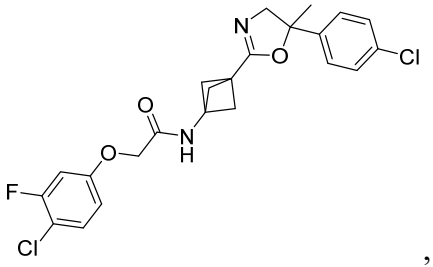

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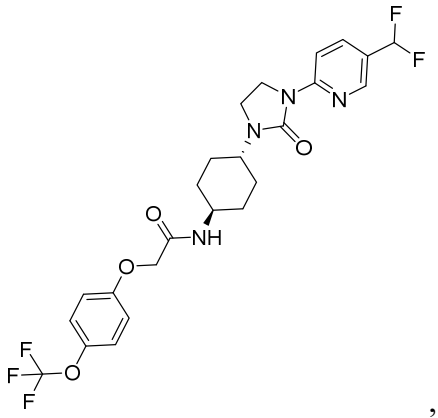
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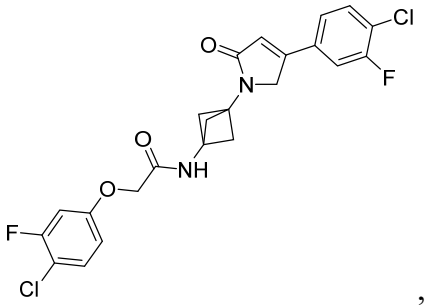
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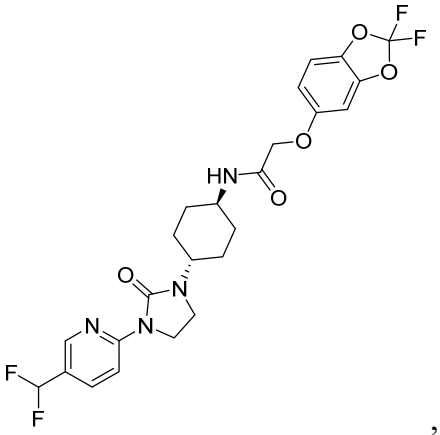
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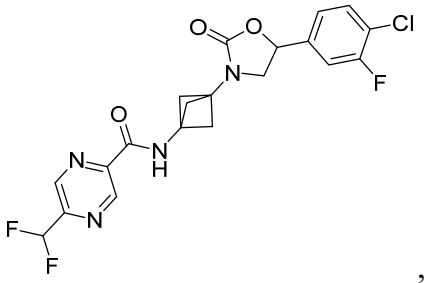
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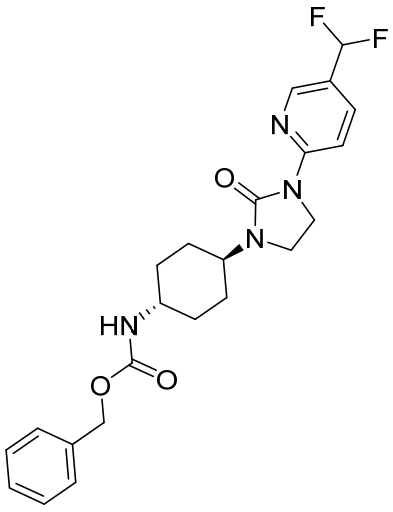
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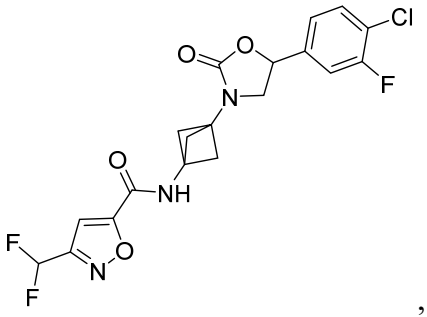
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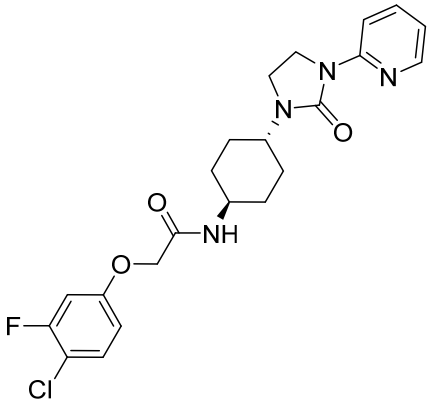

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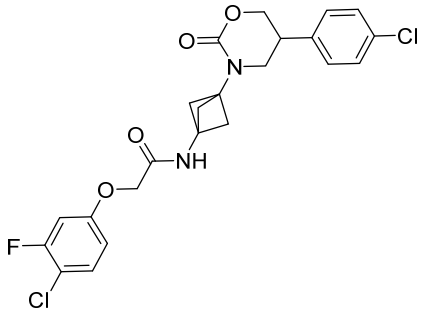

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or a pharmaceutically acceptable salt thereof.