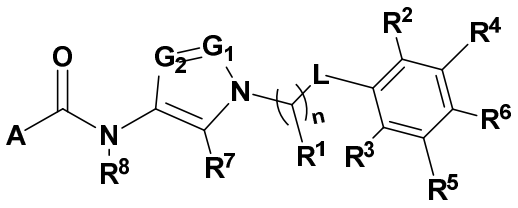
(Grp78), CHOP or XBP-1, that enhance the capacity of the endoplasmic reticulum to fold proteins or mediate quality control. ATF6 works in partnership with IRE1, as one of the target genes of ATF6 is XBP1, the key substrate of IRE1 (Yoshida, H., et al., Cell, 2001, 107(7): 881-891). PERK performs several other roles including pausing the production of new proteins to temporarily lower the protein-folding burden.

[0007] ATF6 is a type-II transmembrane protein localized in the ER that functions as an ER stress sensor and transcription factor (Adachi, Y., et al., Cell Struct Funct, 2008, 33(1): 75-89; Wu, J., et al., Dev Cell, 2007, 13(3): 351-64). When demand exceeds the folding capacity of the ER, ATF6 is transported from the ER to the Golgi apparatus, where sequential cleavage by two Golgi-resident proteases, site-1 and site-2 proteases (S1P and S2P), releases its N-terminal domain (ATF6N) from the Golgi membrane to be imported into the nucleus where it activates transcription of its target genes (Ye, J., et al., Mol Cell, 2000, 6(6): 1355-64). This activation involves binding of ATF6 to a consensus sequence called the ER- stress responsive element (ERSE). The consensus sequence of ERSE is CCAATCGGCGGCGGCCACG (SEQ ID NO. 1).

[0008] ATF6−activated transcription targets play a role in the pathogenesis and development of various diseases, including viral infection, cancer, neurodegeneration, Alzheimer's disease, cerebral ischemia, hereditary cerebellar atrophy and ataxia, type 2 diabetes mellitus, and diabetic nephropathy, as well as cardiovascular diseases, such as myocardial atrophy, heart failure, ischemic heart disease and atherosclerosis (Chu, W.S., et al., Diabetes, 2007, 56(3): 856-62; Vekich, J.A., et al., J Mol Cell Cardiol, 2012, 53(2): 259-67, Liu, C.L., et al., Int J Mol Med, 2016, 37(2): 407-14). Therefore, inhibition of ATF6-mediated transcription may provide a therapeutic strategy for these and other diseases in which modulation of ATF6 is implicated.

SUMMARY

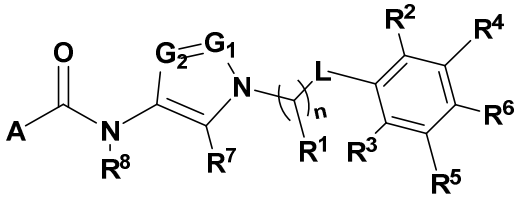
[0009] In one example, provided is a compound of the Formula (A):



(A)

or a pharmaceutically acceptable salt thereof, wherein A, R^1, n, L, R^2, R^3, R^4, R^5, R^6, R^7, R^8, G_1, and G_2 are as detailed herein.

[0009a] In one aspect, the present disclosure refers to a compound of Formula (A):


(A),

or a pharmaceutically acceptable salt thereof, wherein:

one of G_1 and G_2 is N and one of G_1 and G_2 is CR^d,

wherein R^d is H or C_1-C_6alkyl;

R^1 is H, C_1-C_6alkyl, or C_3-C_8cycloalkyl; or R^1 is H, C_1-C_6alkyl, C_3-C_8cycloalkyl, or C_1-C_6 haloalkyl;

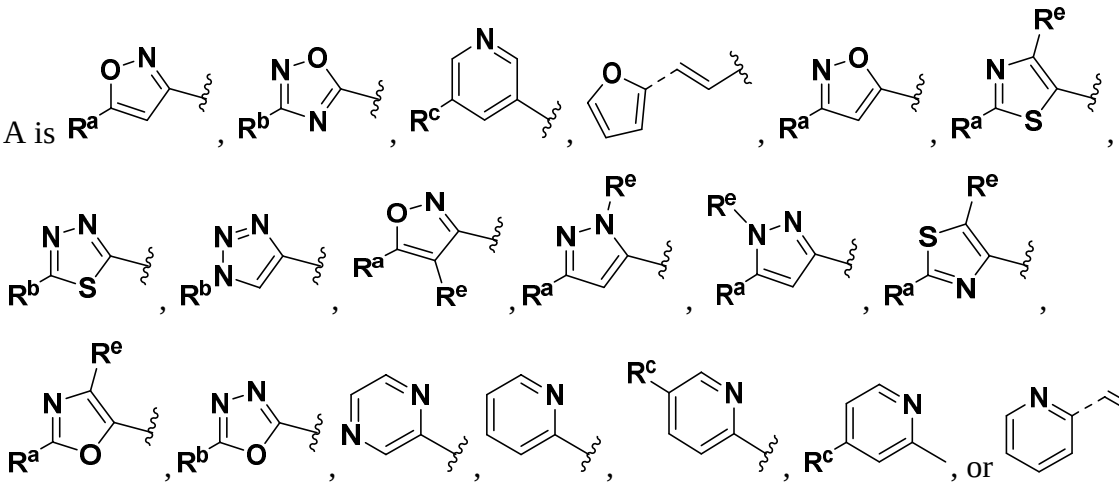
R^8 is H or C_1-C_6alkyl,

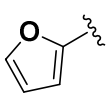
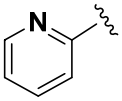
n is 0 or 1;

L is $–CH_2$- or is absent;

R^2, R^3, R^4, R^5, and R^6 are each independently H, halo, CN, C_1-C_6alkyl, or C_1-C_6haloalkyl, provided that either at least two of R^2, R^3, R^4, R^5, and R^6 are other than H, or that one of R^2, R^3, R^4, R^5, and R^6 is cyano;

or R^2, R^4, R^5, and R^6 are each independently H, halo, CN, C_1-C_6alkyl, or C_1-C_6haloalkyl and R^3 is taken together with an R^1 and the atoms to which they are attached to form a 5- or 6-membered ring, wherein the 5- or 6-membered ring is unsubstituted or substituted with one to three groups selected from the group consisting of halo, CN, OH, C_1-C_6alkyl, and C_1-C_6haloalkyl;

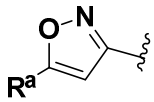
A is ;

wherein --- indicates that  or  is attached in either an E or Z configuration;

R^a and R^b are each independently H, C_1-C_6alkyl, C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^a and R^b is unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, and C_1-C_6alkyl, or is unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy;

R^c is C_1-C_6alkyl, C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^c is unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, and C_1-C_6alkyl;

R^e is H, or C_1-C_6alkyl;

provided that when A is  and R^a is H, methyl, ethyl, n-Pr, i-Pr, i-Bu, 2-thiofuryl, 2-furyl, unsubstituted phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3,4-dimethoxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-fluorophenyl, or 2,4-dichlorophenyl, at least one of (*i.*)-(*ix.*) applies:

(*i.*) G_2 is N;

(*ii.*) n is 1, L is absent, and R^1 is C_1-C_6alkyl;

(*iii.*) n is 0, L is absent, and at least one of R^2, R^3, R^4, R^5, and R^6 is halo, CN, or C_1-C_6haloalkyl;

(*iv.*) n is 1, and R^3 is taken together with R^1 and the atoms to which they are attached to form a 5- or 6-membered ring;

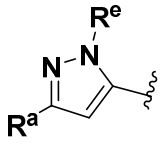
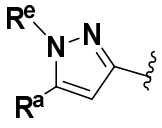
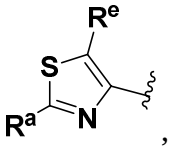
(*v.*) one of R^2, R^3, R^4, R^5, and R^6 is CN;

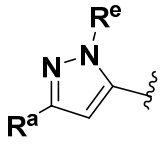
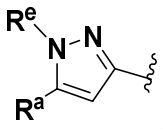
(*vi.*) R^4 and R^5 are each independently Cl, Br, I, CN, C_1-C_6alkyl, or C_1-C_6haloalkyl;

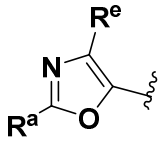
(*vii.*) one of R^d and R^7 is C_1-C_6alkyl;

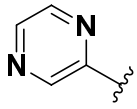
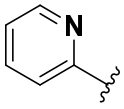
(*viii.*) R^2 and R^3 are each Cl; and

(*ix.*) at least one of R^2, R^3, R^4, R^5, and R^6 is F, Br, I, CN, or C_1-C_6haloalkyl and R^a is H or 2-thiofuryl;

provided that when A is , , or , and n is 1, then R^1 is other than H;

provided that when A is , or , n is 0 and L is absent, then R^a is other than H;

provided that when A is , and R^e is methyl, then R^a is other than unsubstituted phenyl;

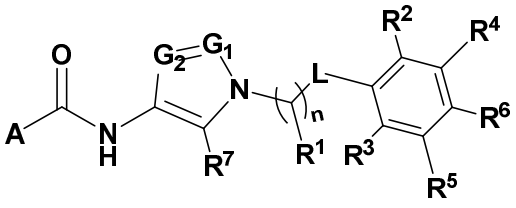
provided that when A is ,or , n is 1 and L is absent, then R^1 is other than H;

and

R^7 is H, C_1-C_6alkyl or C_1-C_6haloalkyl,

provided that when R^d is C_1-C_6alkyl, R^7 is H, and when R^7 is C_1-C_6alkyl, R^d is H.

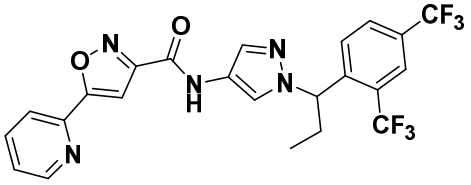
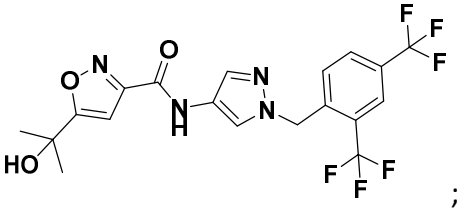
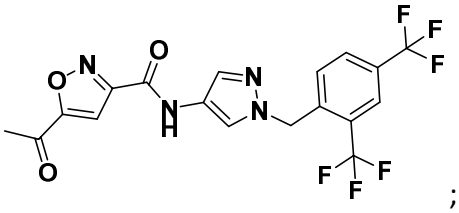
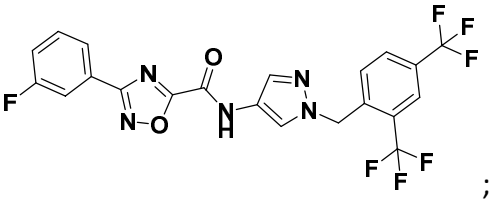
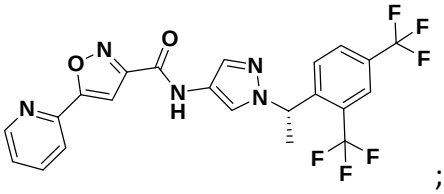
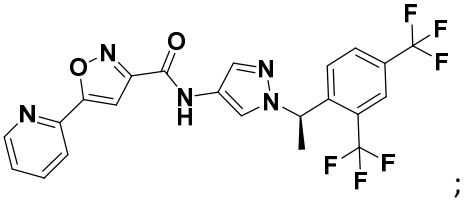
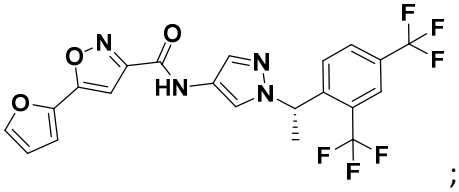
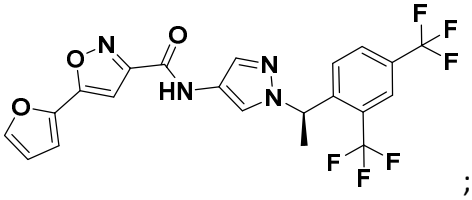
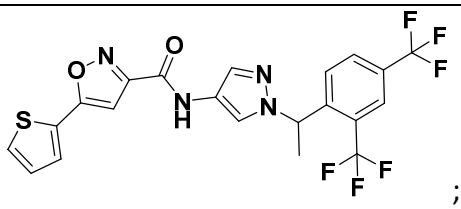
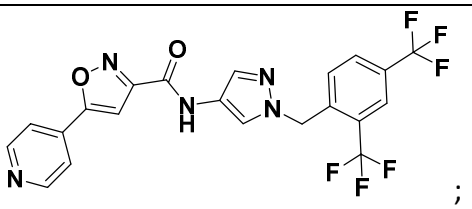
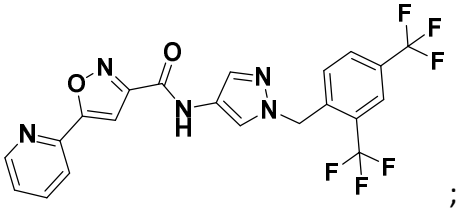
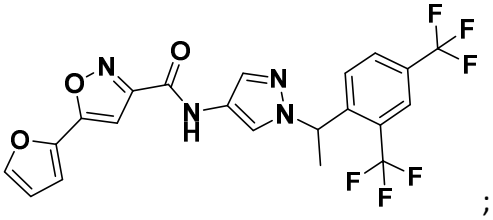
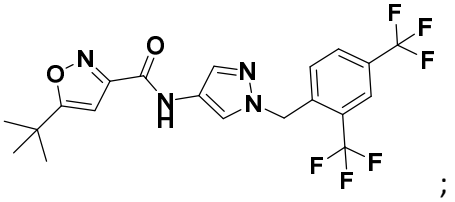
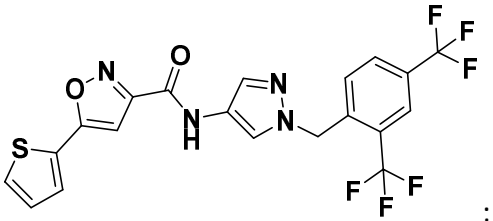
[0010] In some examples, provided is a compound of the formula (I):

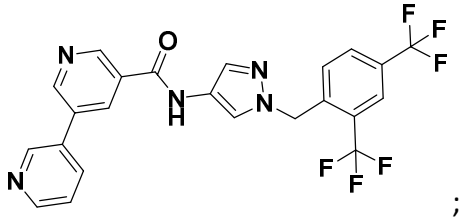
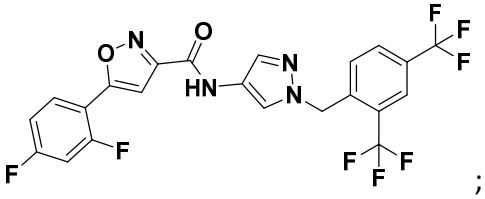
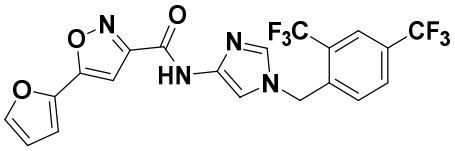
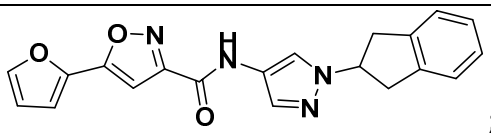
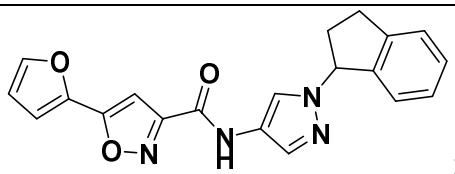
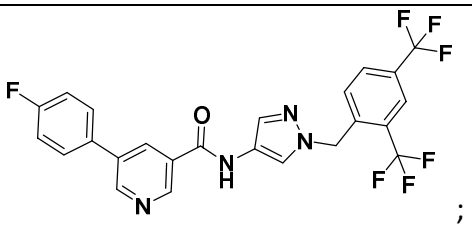
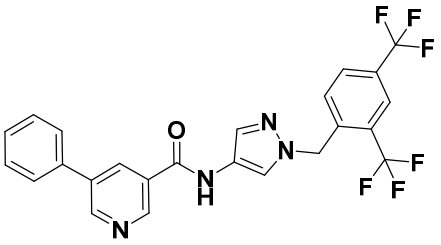
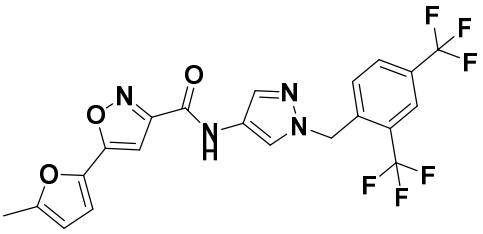
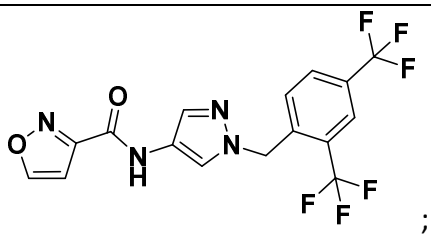
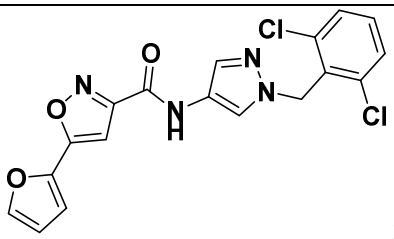
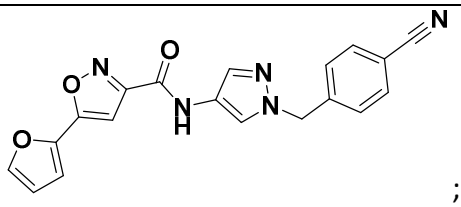
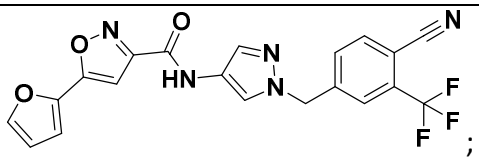
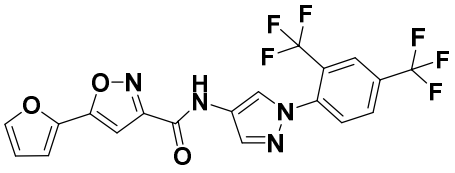
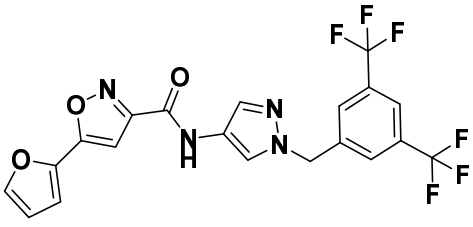

(I)

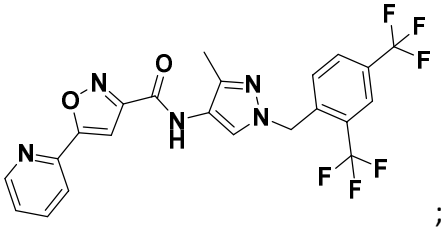
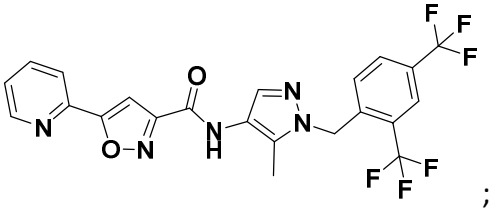
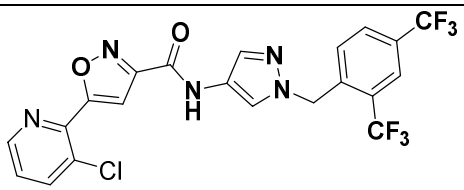
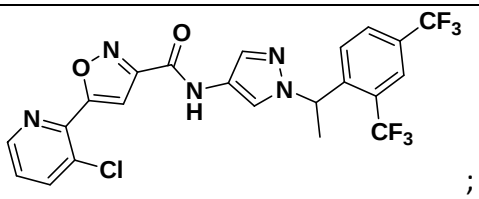
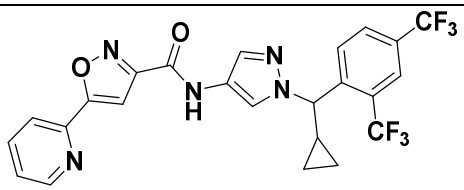
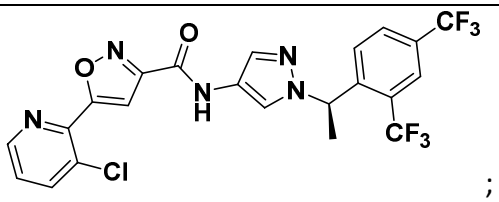
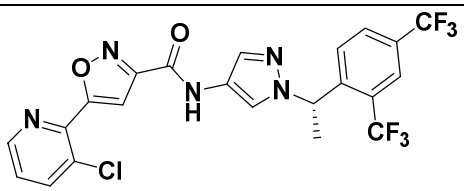
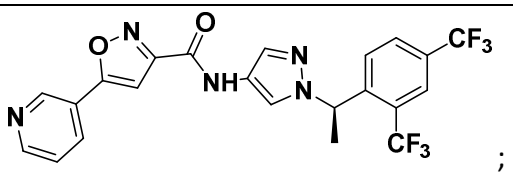
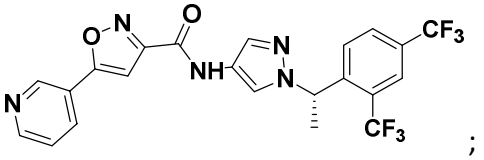
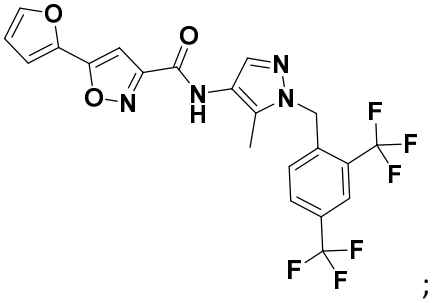
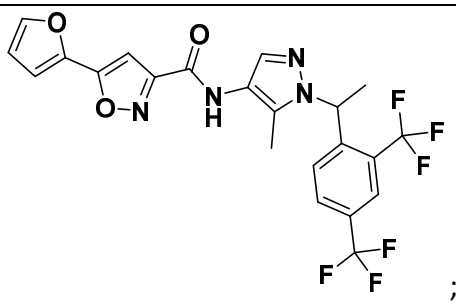
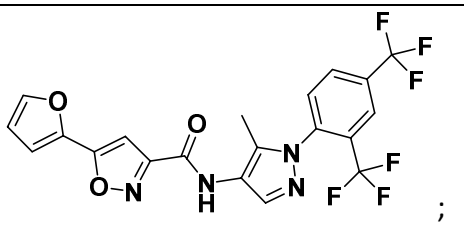
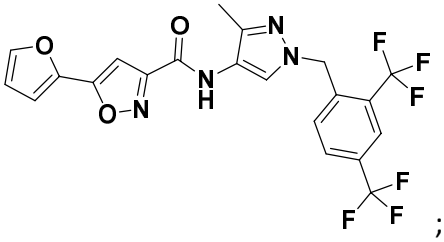
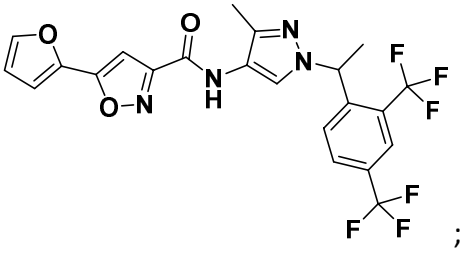
or a pharmaceutically acceptable salt thereof, wherein A, R^1, n, L, R^2, R^3, R^4, R^5, R^6, R^7, G_1, and G_2 are as detailed herein.

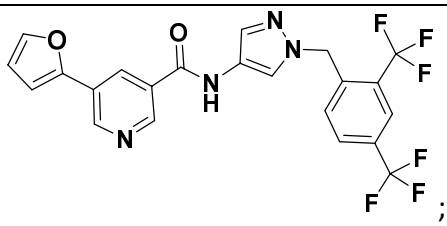
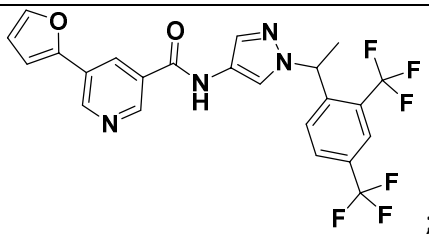
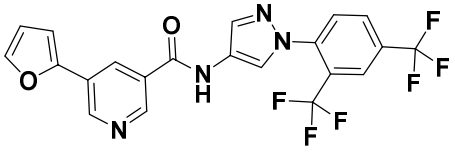
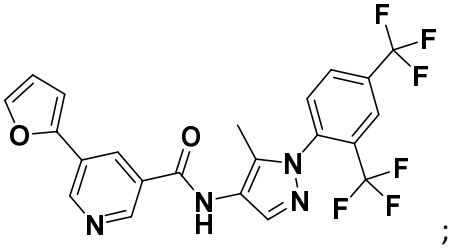
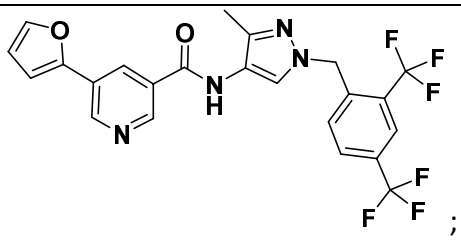
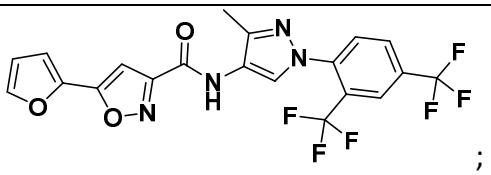
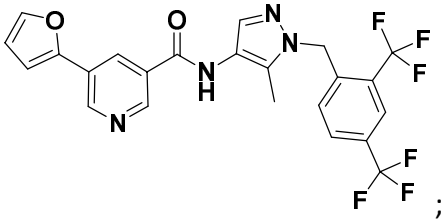
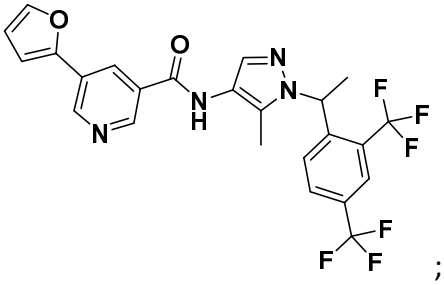
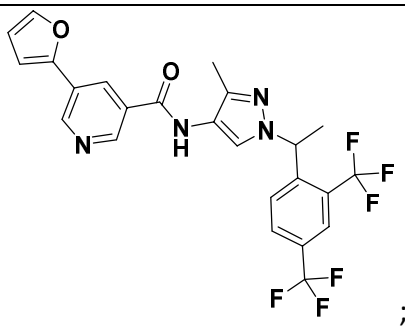
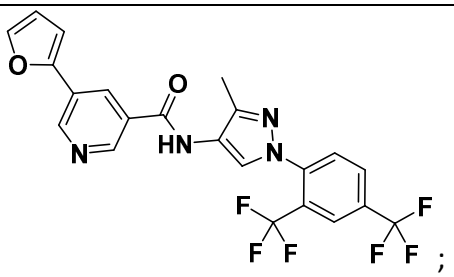
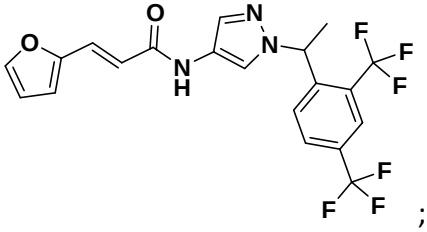
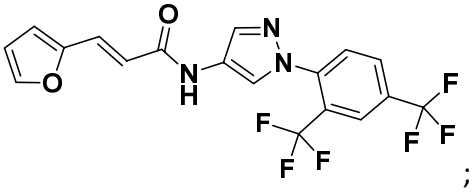
[0011] In some examples, the compound of Formula (A), (I), or a pharmaceutically acceptable salt thereof, is of the Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), or (Ik), as detailed herein.

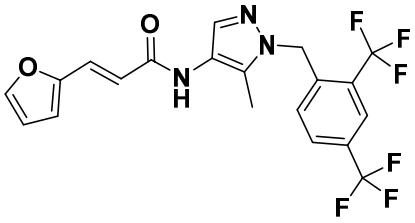
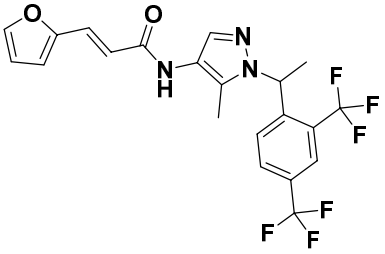
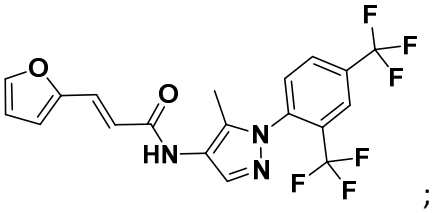
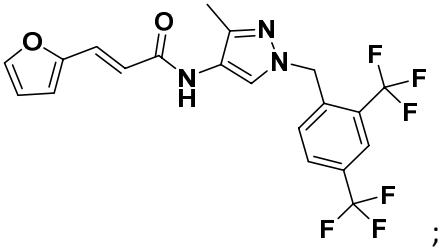
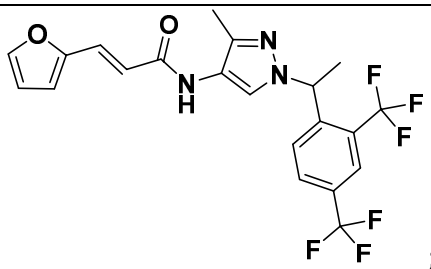
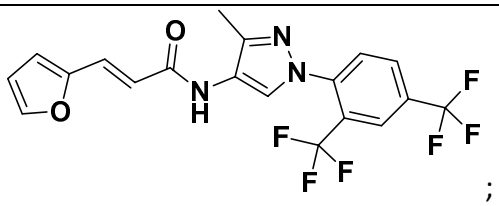
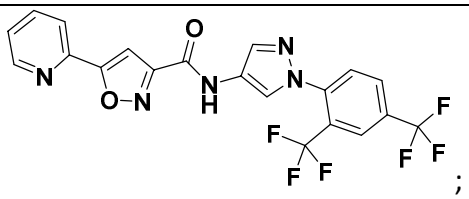
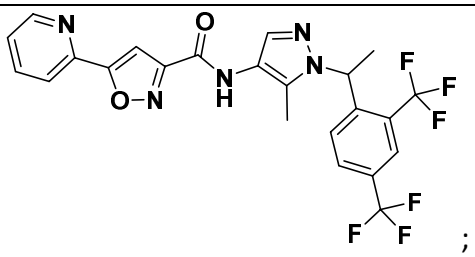
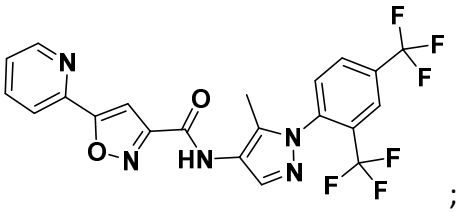
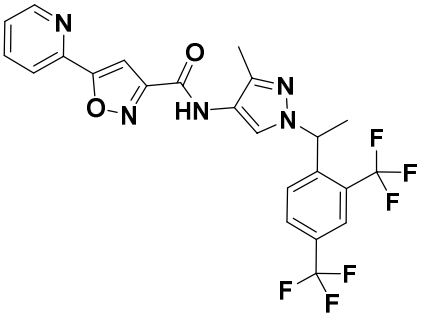
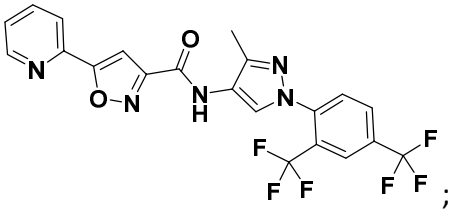
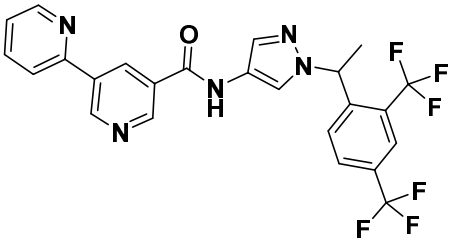
[0011a] In one aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

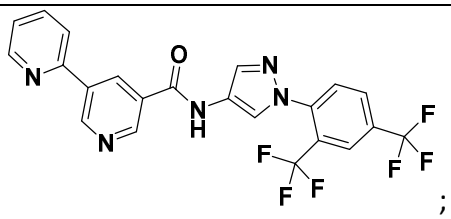
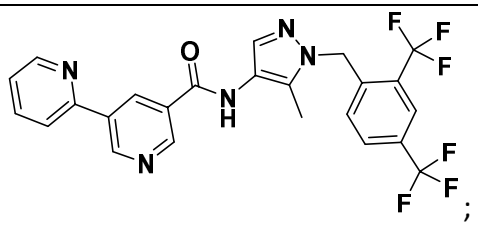
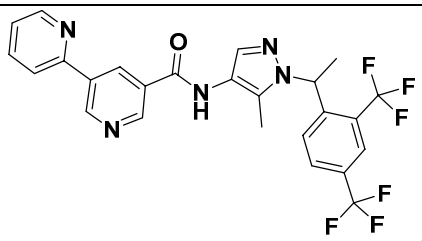
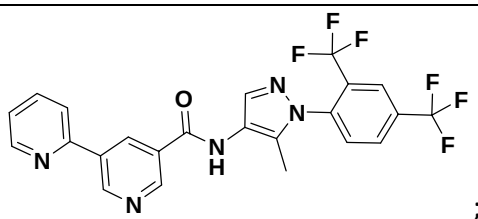
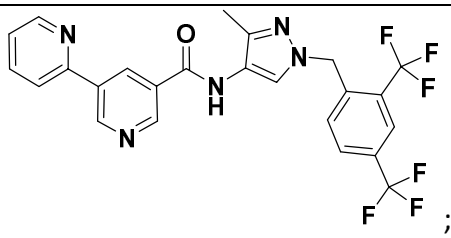
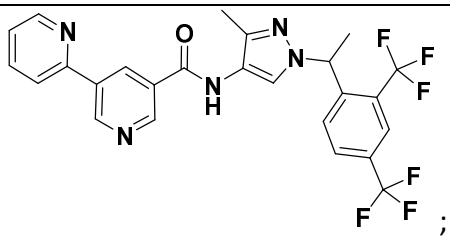
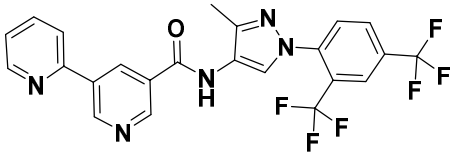
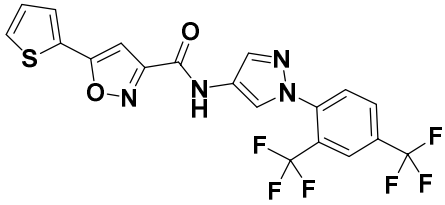
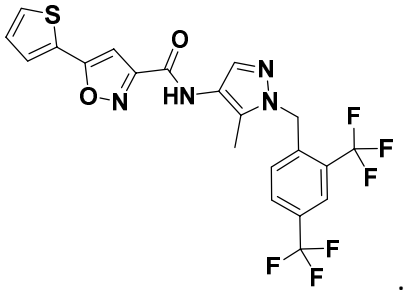
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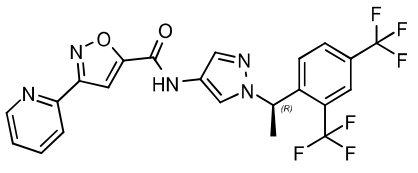
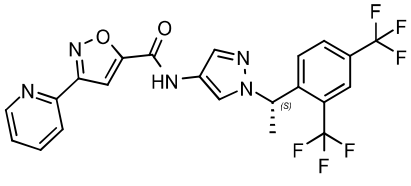
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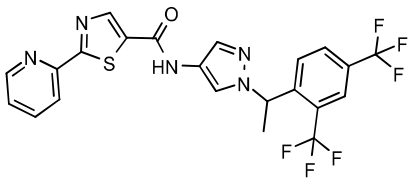
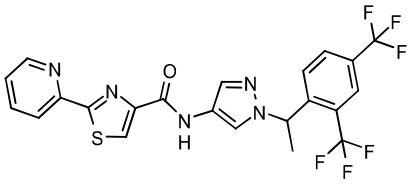
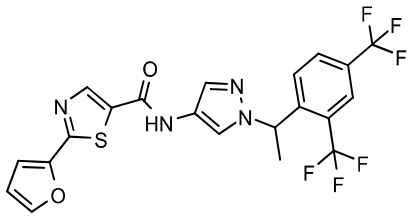
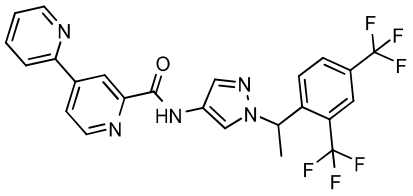
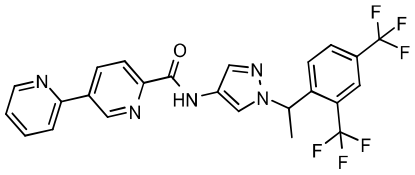
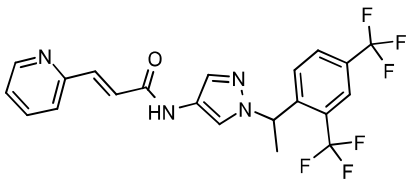
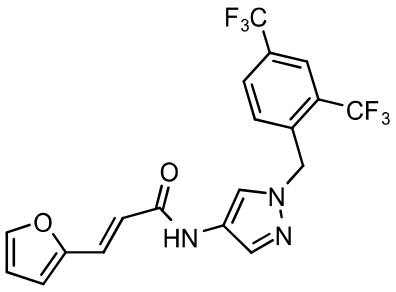
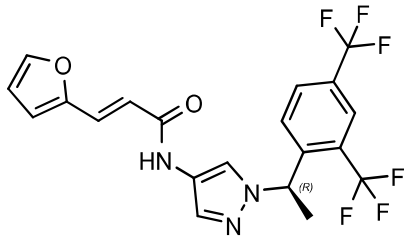
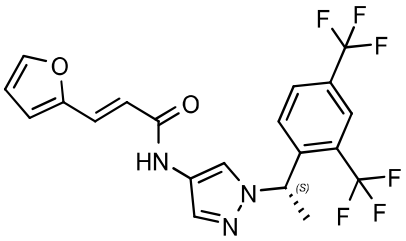
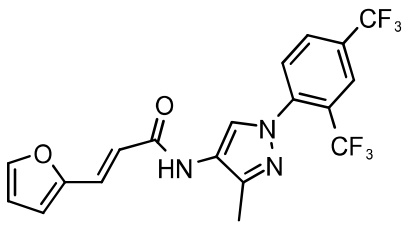
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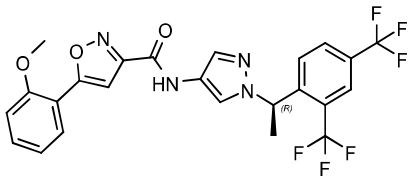
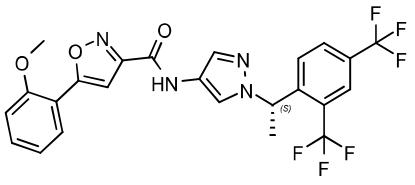
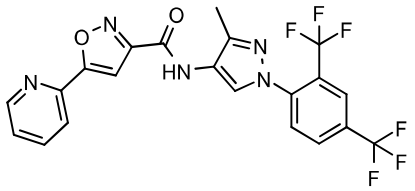
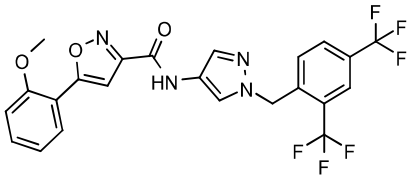
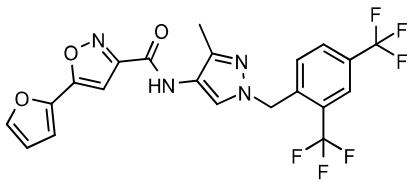
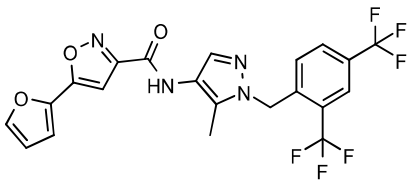
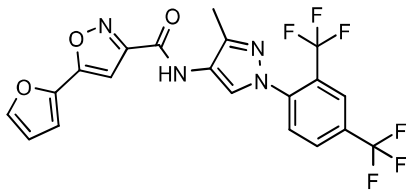
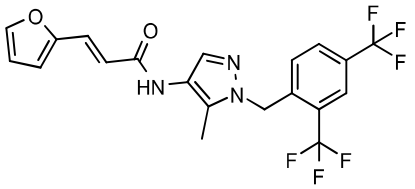
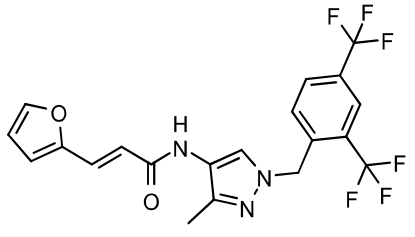
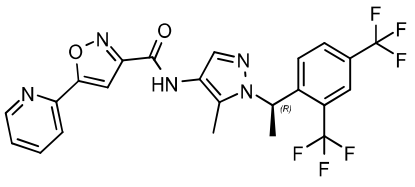
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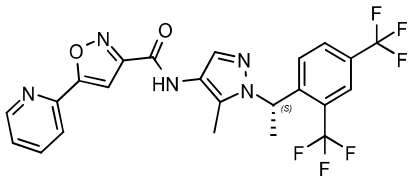
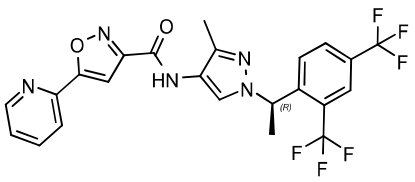
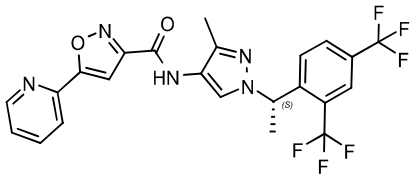
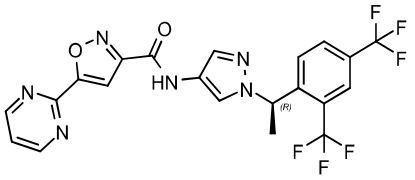
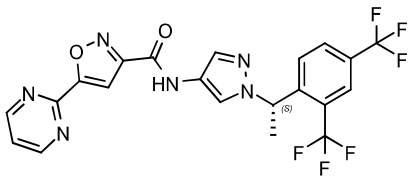
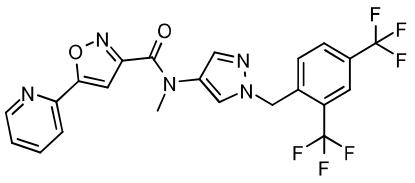
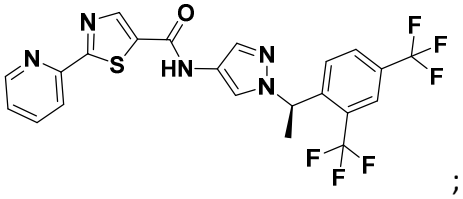
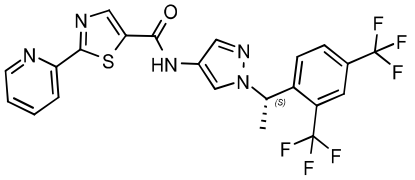
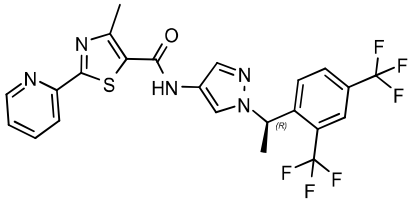
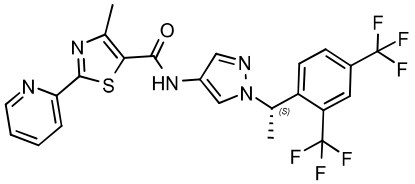
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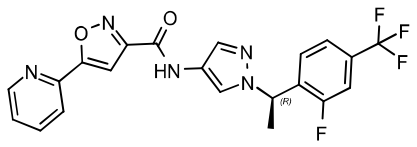
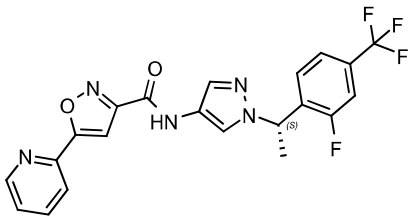
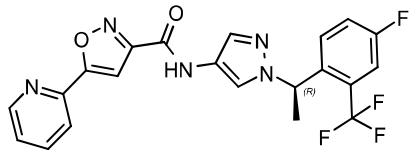
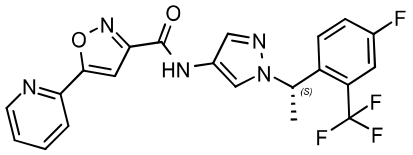
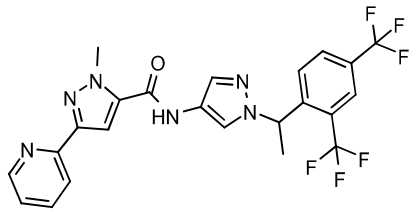
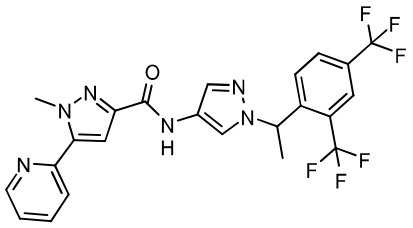
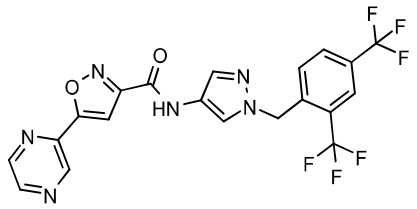
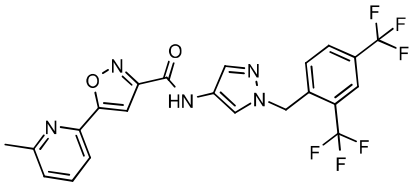
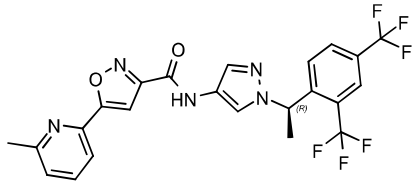
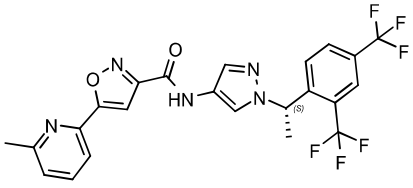
[0011b] In one aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

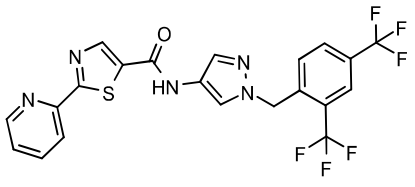
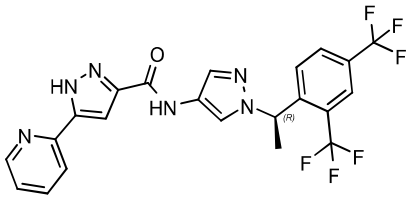
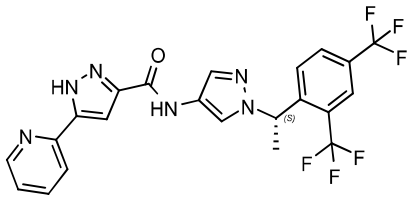
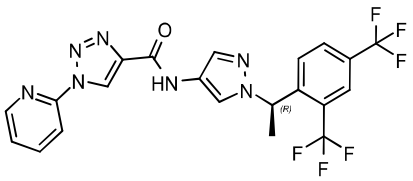
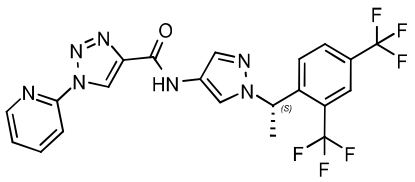
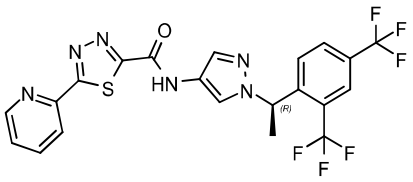
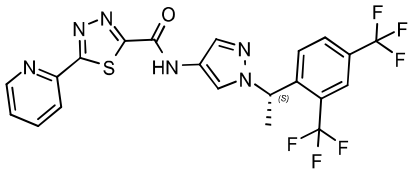
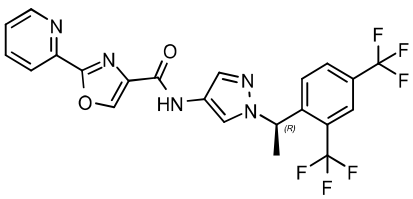
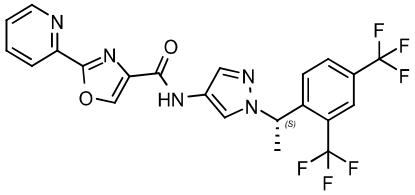
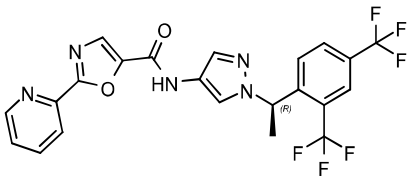
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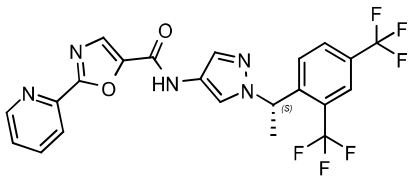
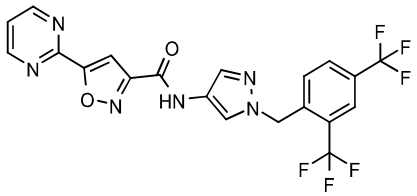
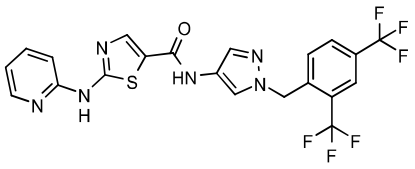
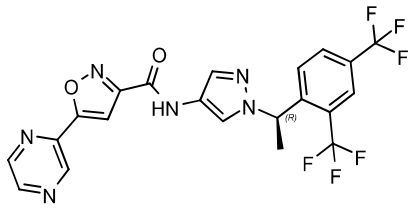
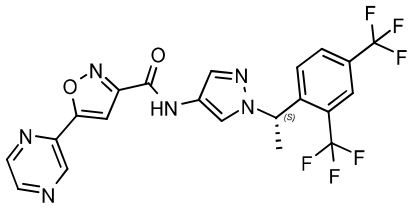
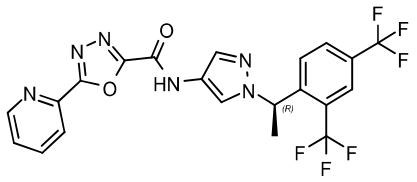
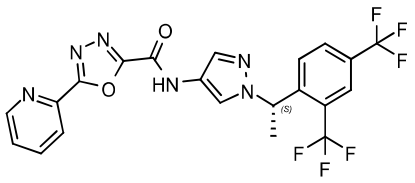
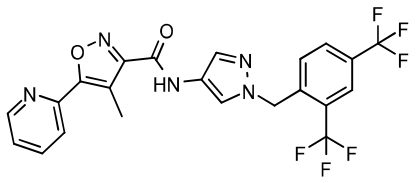
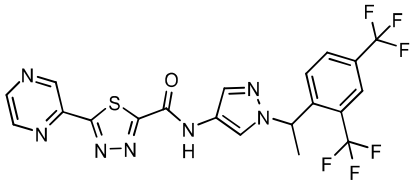
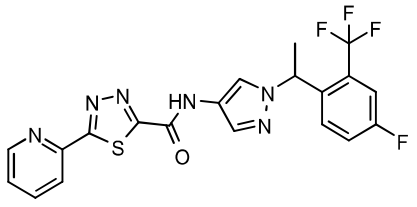
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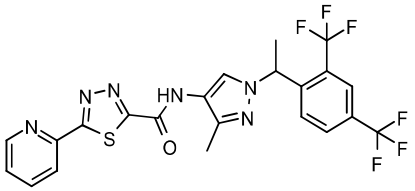
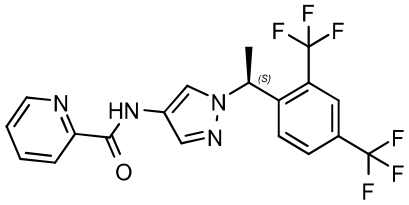
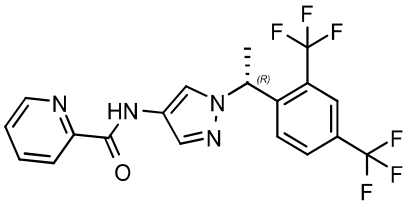
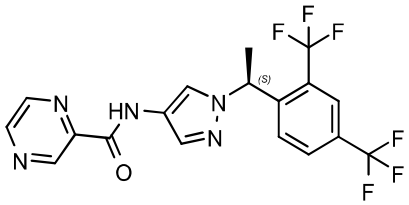
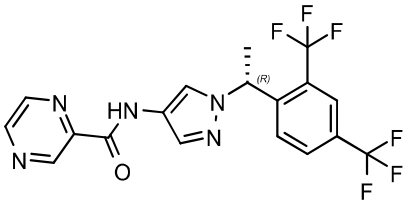
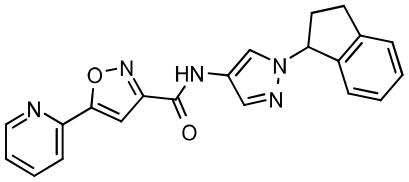
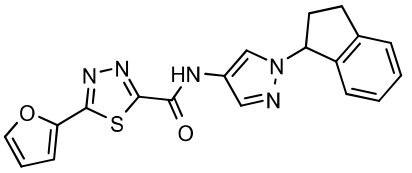
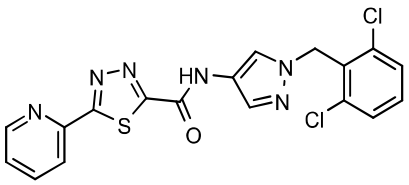
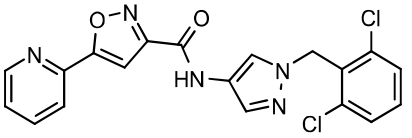
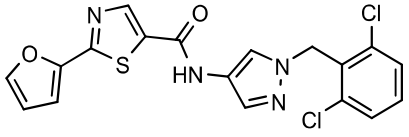
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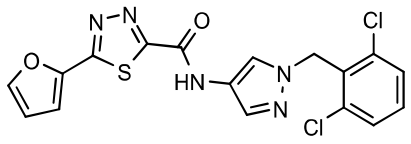
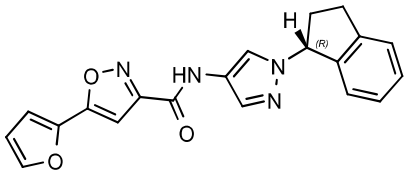
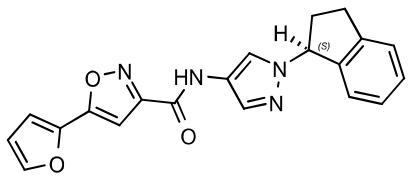
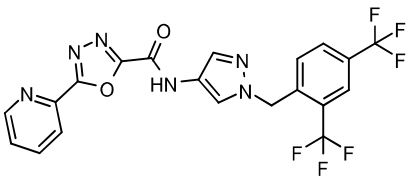
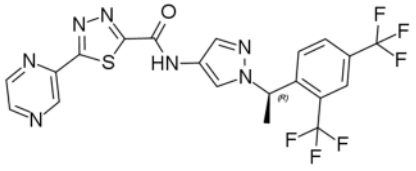
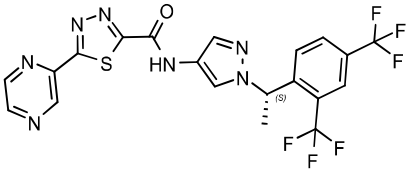
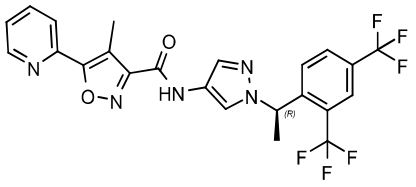
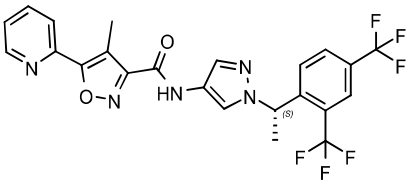
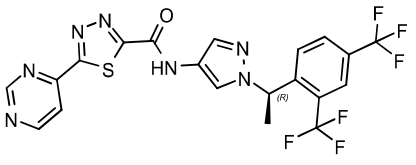
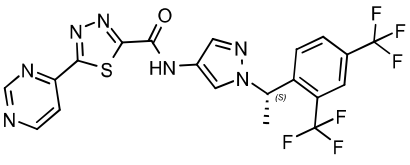
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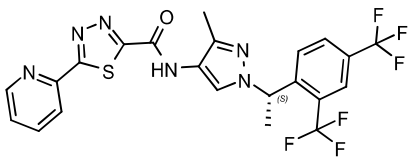
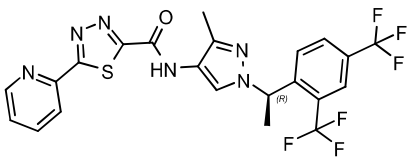
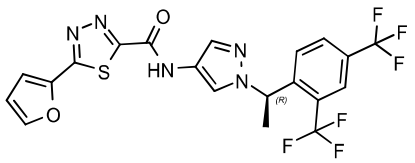
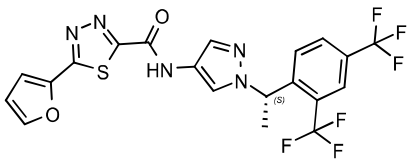
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[0012] In another example, provided is a method of treating a disease or disorder mediated by activating transcription factor 6 (ATF6) in an individual in need thereof, wherein the method comprises administering to the individual an effective amount of a compound of Formula (A), (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound. In a further example of the methods, the compound of Formula (A), (I) or a salt thereof is a compound of the Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), or (Ik), or a pharmaceutically acceptable salt of any of the foregoing or a pharmaceutical composition comprising the compound. In some examples, the disease or disorder mediated by activating transcription factor 6 (ATF6) is viral infection, cancer, a neurodegenerative disease, or a vascular disease. In certain examples, the disease or disorder is viral infection, hereditary cerebellar atrophy and ataxia, Alzheimer's disease, type 2 diabetes mellitus, diabetic nephropathy, myocardial atrophy, heart failure, atherosclerosis, ischemia, ischemic heart disease, or cerebral ischemia. In some examples, the disease or disorder characterized by activating transcription factor 6 (ATF6) is cancer. In some examples, ATF6 is ATF6α. In one aspect, the present disclosure refers to use of a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder mediated by activating transcription factor 6 (ATF6) in an individual in need thereof, wherein the disease or disorder is cancer selected from the group consisting of breast cancer, colorectal cancer (CRC), ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone sarcoma, connective tissue sarcoma, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, leukemia, skin cancer, soft tissue cancer, liver cancer, gastrointestinal carcinoma, and adenocarcinoma.

[0013] In another example, provided is a method of treating a disease or disorder characterized by activating transcription factor 6 (ATF6) in an individual in need thereof, wherein the method comprises administering to the individual an effective amount of a compound of Formula (A), (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound. In a further example of the methods,

the compound of Formula (A), (I) or a salt thereof is a compound of the Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), or (Ik), or a pharmaceutically acceptable salt of any of the foregoing or a pharmaceutical composition comprising the compound. In some examples, the disease or disorder characterized by activation of ATF6 is viral infection, cancer, a neurodegenerative disease, or a vascular disease. In certain examples, the disease or disorder is viral infection, hereditary cerebellar atrophy and ataxia, Alzheimer's disease, type 2 diabetes mellitus, diabetic nephropathy, myocardial atrophy, heart failure, atherosclerosis, ischemia, ischemic heart disease, or cerebral ischemia. In some examples, the disease or disorder characterized by activating transcription factor 6 (ATF6) is cancer. In some examples, ATF6 is ATF6α.

[0014] In another example, provided is a method of treating cancer in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of a compound of Formula (A), (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound. In a further example of the methods, the compound of Formula (A), (I) or a salt thereof is a compound of the Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), or (Ik), or a pharmaceutically acceptable salt of any of the foregoing or a pharmaceutical composition comprising the compound.

[0015] In some examples, the cancer is breast cancer, colorectal cancer, ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone sarcoma, connective tissue sarcoma, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, leukemia, skin cancer, soft tissue cancer, liver cancer, gastrointestinal carcinoma, or adenocarcinoma. In some examples, one or more cancer cells in the individual are dormant cancer cells.

[0016] In some examples, the individual has had a prior treatment. In some examples, the cancer is resistant or refractory to the prior treatment. In some examples, the cancer is resistant to treatment with a ubiquitin-proteasome pathway inhibitor, a taxane, a Cox-2 inhibitor, a platinum-based antineoplastic drug, an anthracycline, a pyrimidine analog, a topoisomerase inhibitor, an mTOR inhibitor, an immune-check point inhibitor, or an agent that is used in immune oncology.

[0017] In some examples, the method further comprises administering radiation. In some examples, the method further comprises administering a second anticancer agent. In some examples, the second anticancer agent targets an immune checkpoint protein.

[0018] In another example, provided is a method of treating a disease or disorder associated with angiogenesis in an individual in need thereof, wherein the method comprises administering to the individual an effective amount of a compound of Formula (A), (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound. In a further example of the methods, the compound of Formula (I) or a salt thereof is a compound of the Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), or (Ik), or a pharmaceutically acceptable salt of any of the foregoing or a pharmaceutical composition comprising the compound. In some examples, the method further comprises administering a second anti-angiogenesis agent.

[0019] In some examples of the methods disclosed herein, the method further comprises administering a second agent that modulates the Unfolded Protein Response or the Integrated Stress Response. In some examples, the second agent inhibits the IRE1/XBP1 pathway.

[0020] In another example, provided is a method of inhibiting ATF6 in an individual comprising administering to the individual a compound of Formula (A), (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound. In a further example of the methods, the compound of Formula (A), (I) or a salt thereof is a compound of the Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), or (Ik), or a pharmaceutically acceptable salt of any of the foregoing or a pharmaceutical composition comprising the compound. In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting ATF6 in an individual.

[0021] In another example, provided is a method of inhibiting ATF6 in a cell comprising delivering to the cell a compound of Formula (A), (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the compound. In a further example of the methods, the compound of Formula (A), (I) or a salt thereof is a compound of the Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), or (Ik), or a pharmaceutically acceptable salt of any of the foregoing or a pharmaceutical composition comprising the compound. In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting ATF6 in a cell.

[0022] Also provided are pharmaceutical compositions comprising: (A) a compound detailed herein, such as a compound of Formula (A), (I) or a pharmaceutically acceptable salt thereof, or a compound of Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), or (Ik) or a pharmaceutically acceptable salt thereof; and (B) a pharmaceutically acceptable carrier or excipient. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. Kits comprising a compound detailed herein or a salt thereof and optionally instructions for use are also provided. Compounds as detailed herein or a pharmaceutically

acceptable salt thereof are also provided for the manufacture of a medicament for the treatment of a disease or disorder characterized by activation of ATF6. In some examples, the disease or disorder is cancer, a neurodegenerative disease, or a vascular disease. In certain examples, the disease or disorder is viral infection, hereditary cerebellar atrophy and ataxia, Alzheimer's disease, type 2 diabetes mellitus, diabetic nephropathy, myocardial atrophy, heart failure, atherosclerosis, ischemia, ischemic heart disease, or cerebral ischemia.

BRIEF DESCRIPTION OF THE FIGURES

[0023] FIG. **1** depitcs modulation of ATF6-dependent molecular machinery from endoplasmic reticulum (ER) proteostasis network in multiple myeloma (MM) cell lines.

[0024] FIGS. **2A, 2B** and **2C** illustrate how modulation of ER proteostasis network using three exemplary compounds affects cell viability of MM cell lines.

DETAILED DESCRIPTION

Definitions

[0025] For use herein, unless clearly indicated otherwise, use of the terms "a", "an" and the like refers to one or more.

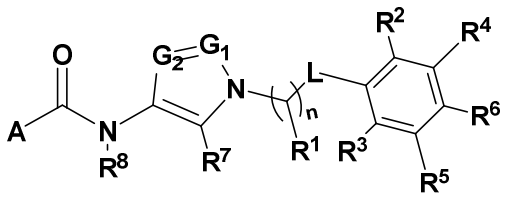
[0026] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".

[0027] "Alkyl" as used herein refers to and includes, unless otherwise stated, a saturated linear (*i.e.*, unbranched) or branched univalent hydrocarbon chain or combination thereof, having the number of carbon atoms designated (*i.e.*, C_1-C_{10} means one to ten carbon atoms). Particular alkyl groups are those having 1 to 20 carbon atoms (a "C_1-C_{20} alkyl"), having 1 to 10 carbon atoms (a "C_1-C_{10} alkyl"), having 6 to 10 carbon atoms (a "C_6-C_{10} alkyl"), having 1 to 6 carbon atoms (a "C_1-C_6 alkyl"), having 2 to 6 carbon atoms (a "C_2-C_6 alkyl"), or having 1 to 4 carbon atoms (a "C_1-C_4 alkyl"). Examples of alkyl groups include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, and the like.

CLAIMS

What is claimed is:

1. A compound of Formula (A):



(A),

or a pharmaceutically acceptable salt thereof, wherein:

one of G_1 and G_2 is N and one of G_1 and G_2 is CR^d,

wherein R^d is H or C_1-C_6alkyl;

R^1 is H, C_1-C_6alkyl, or C_3-C_8cycloalkyl; or R^1 is H, C_1-C_6alkyl, C_3-C_8cycloalkyl, or C_1-C_6 haloalkyl;

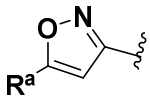
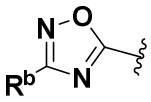
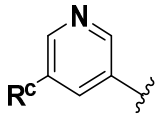
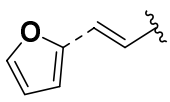
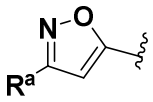
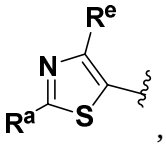
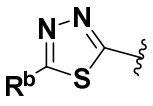
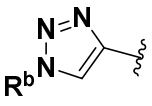
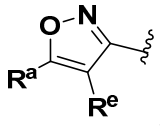
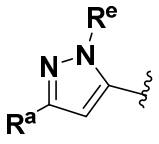
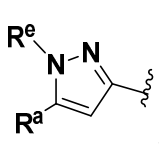
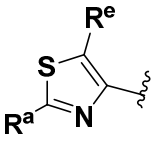
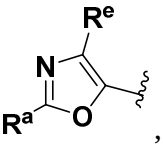
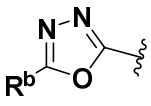
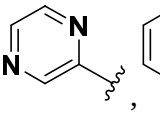
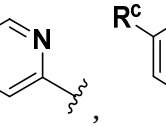
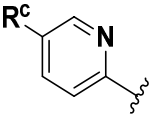
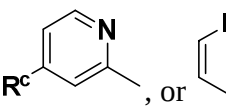
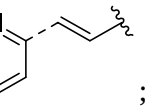
R^8 is H or C_1-C_6alkyl,

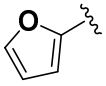
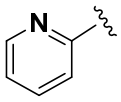
n is 0 or 1;

L is $–CH_2$- or is absent;

R^2, R^3, R^4, R^5, and R^6 are each independently H, halo, CN, C_1-C_6alkyl, or C_1-C_6haloalkyl, provided that either at least two of R^2, R^3, R^4, R^5, and R^6 are other than H, or that one of R^2, R^3, R^4, R^5, and R^6 is cyano;

or R^2, R^4, R^5, and R^6 are each independently H, halo, CN, C_1-C_6alkyl, or C_1-C_6haloalkyl and R^3 is taken together with an R^1 and the atoms to which they are attached to form a 5- or 6-membered ring, wherein the 5- or 6-membered ring is unsubstituted or substituted with one to three groups selected from the group consisting of halo, CN, OH, C_1-C_6alkyl, and C_1-C_6haloalkyl;

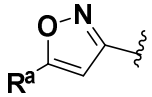
A is , , , , , , , , , , , , , , , , , , , , , , , , , or ;

wherein --- indicates that  or  is attached in either an E or Z configuration;

R^a and R^b are each independently H, C_1-C_6alkyl, C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^a and R^b is unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, and C_1-C_6alkyl, or is unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy;

R^c is C_1-C_6alkyl, C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^c is unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, and C_1-C_6alkyl;

R^e is H, or C_1-C_6alkyl;

provided that when A is  and R^a is H, methyl, ethyl, n-Pr, i-Pr, i-Bu, 2-thiofuryl, 2-furyl, unsubstituted phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 3,4-dimethoxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-fluorophenyl, or 2,4-dichlorophenyl, at least one of (*i.*)-(*ix.*) applies:

(*i.*) G_2 is N;

(*ii.*) n is 1, L is absent, and R^1 is C_1-C_6alkyl;

(*iii.*) n is 0, L is absent, and at least one of R^2, R^3, R^4, R^5, and R^6 is halo, CN, or C_1-C_6haloalkyl;

(*iv.*) n is 1, and R^3 is taken together with R^1 and the atoms to which they are attached to form a 5- or 6-membered ring;

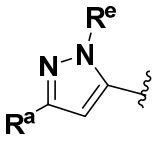
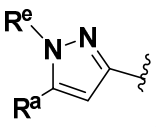
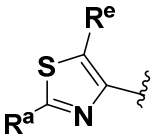
(*v.*) one of R^2, R^3, R^4, R^5, and R^6 is CN;

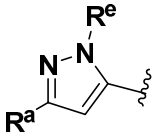
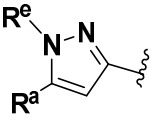
(*vi.*) R^4 and R^5 are each independently Cl, Br, I, CN, C_1-C_6alkyl, or C_1-C_6haloalkyl;

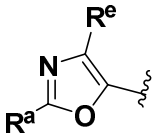
(*vii.*) one of R^d and R^7 is C_1-C_6alkyl;

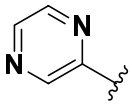
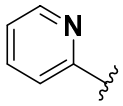
(*viii.*) R^2 and R^3 are each Cl; and

(*ix.*) at least one of R^2, R^3, R^4, R^5, and R^6 is F, Br, I, CN, or C_1-C_6haloalkyl and R^a is H or 2-thiofuryl;

provided that when A is , , or , and n is 1, then R^1 is other than H;

provided that when A is , or , n is 0 and L is absent, then R^a is other than H;

provided that when A is , and R^e is methyl, then R^a is other than unsubstituted phenyl;

provided that when A is ,or , n is 1 and L is absent, then R^1 is other than H;

and

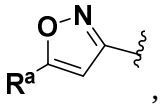
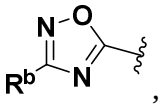
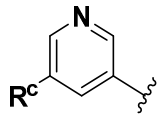
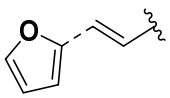
R^7 is H, C_1-C_6alkyl or C_1-C_6haloalkyl,

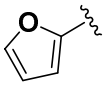
provided that when R^d is C_1-C_6alkyl, R^7 is H, and when R^7 is C_1-C_6alkyl, R^d is H.

2. The compound of claim 1, wherein:

R^1 is H, C_1-C_6alkyl, or C_3-C_8cycloalkyl;

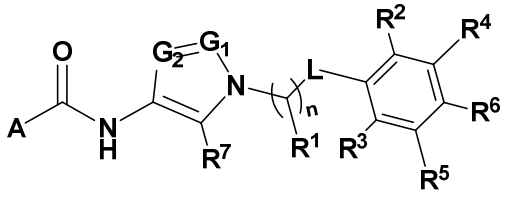
R^8 is H;

A is , , , or ;

wherein --- indicates that  is attached in either an E or Z configuration;

R^a and R^b are each independently H, C_1-C_6alkyl, C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^a and R^b is unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, and C_1-C_6alkyl;

and the compound is represented by Formula (I):

 (I).

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein G_1 is N and G_2 is CR^d.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein G_1 is CR^d and G_2 is N.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^d is H.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^d is C_1-C_6alkyl.

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein n is 1.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is H.

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_1-C_6alkyl.

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl or ethyl.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_3-C_8cycloalkyl.

12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_1-C_6haloalkyl.

13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is taken together with R^1 and the atoms to which they are attached to form a 5- or 6-membered ring.

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein R^3 is taken together with R^1 and the atoms to which they are attached to form a 5-membered carbocyclic ring.

15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein n is 0.

16. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is absent.

17. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L is –CH_2-.

18. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^4, R^5, and R^6 are each independently H, halo, CN, C_1-C_6alkyl, or C_1-C_6haloalkyl.

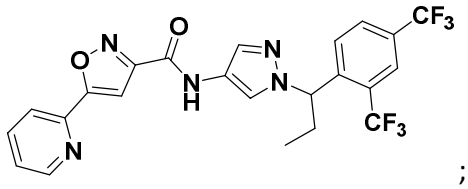
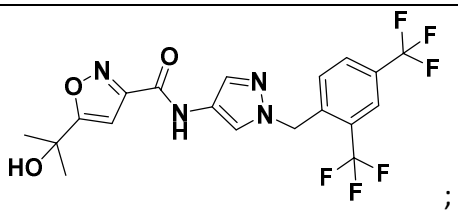
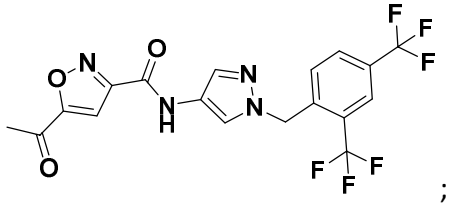
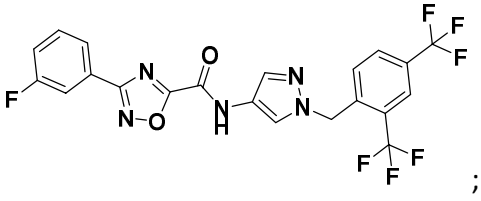
19. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^4, R^5, and R^6 are each independently H, Cl, CN, or CF_3.

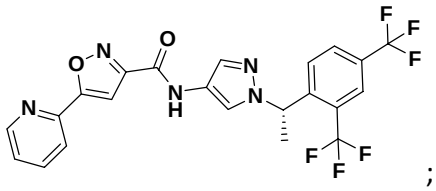
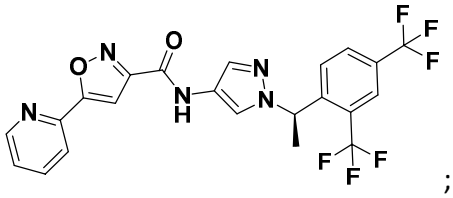
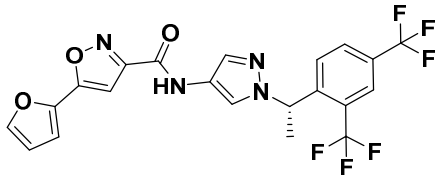
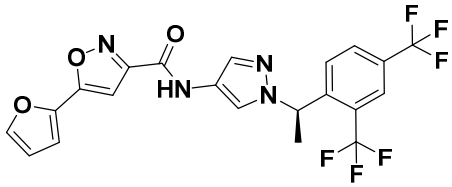
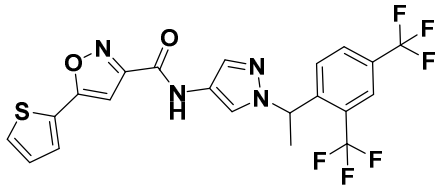
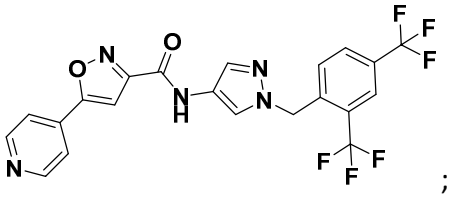
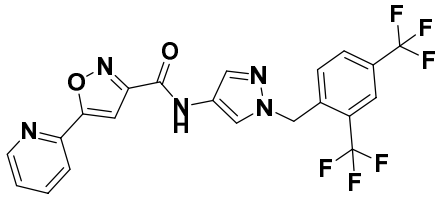
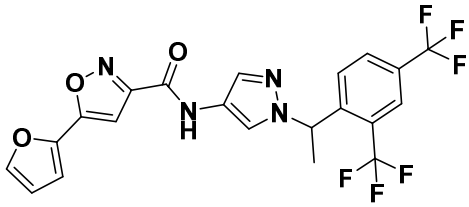
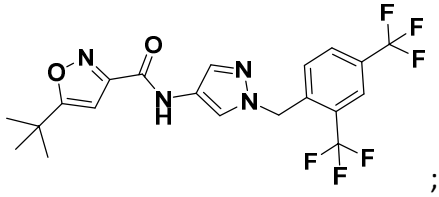
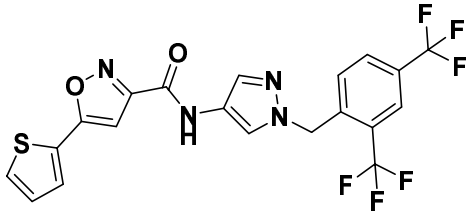
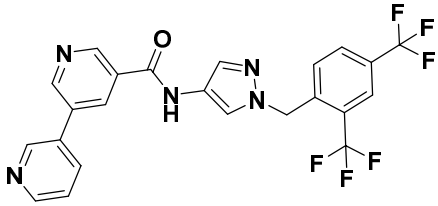
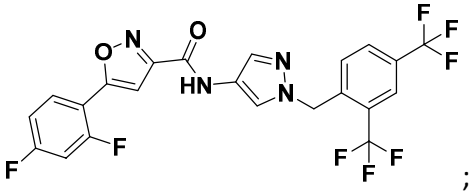
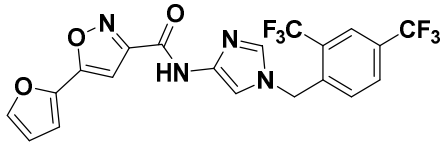
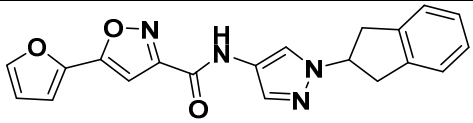
20. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5 are each independently Cl, Br, I, CN, C_1-C_6alkyl, or C_1-C_6haloalkyl.

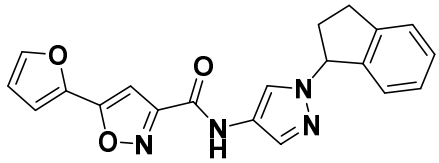
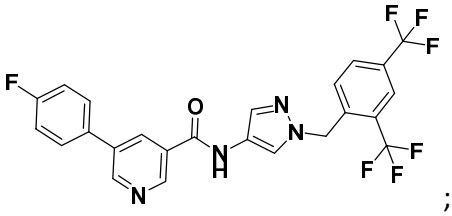
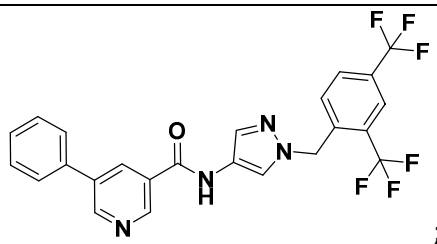
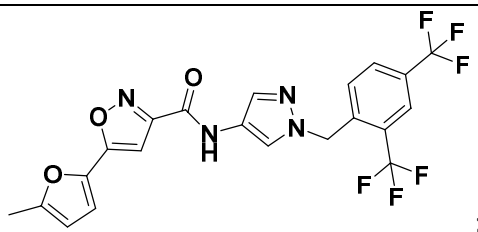
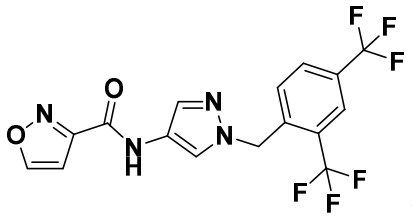
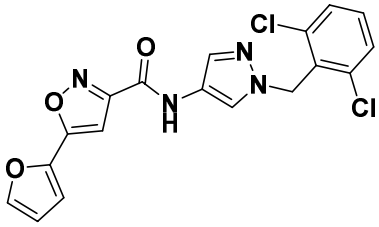
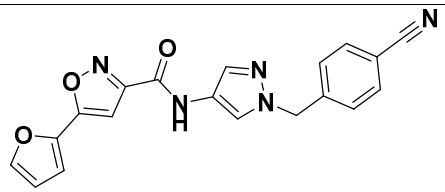
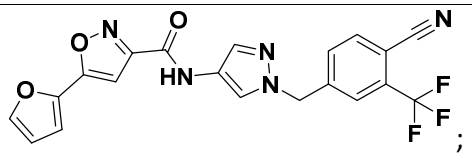
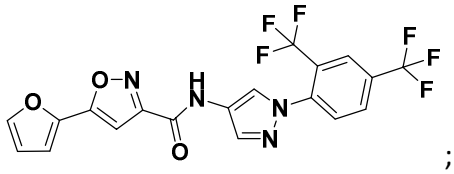
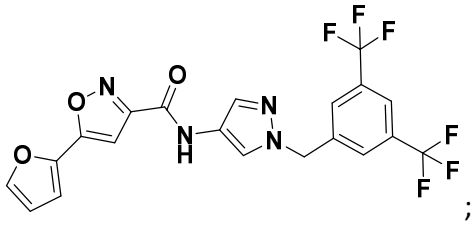
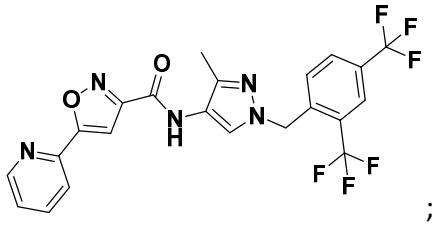
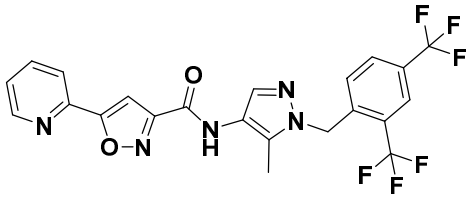
21. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^7 is H.

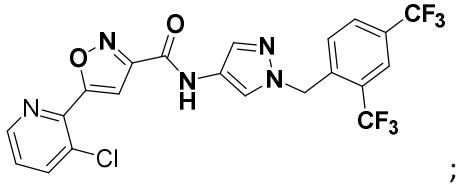
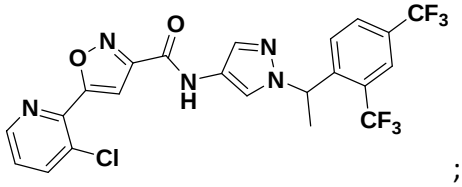
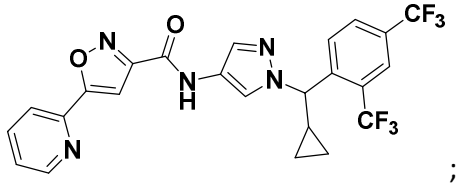
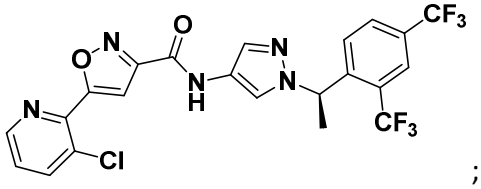
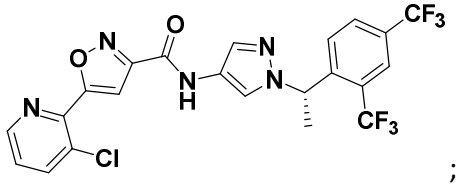
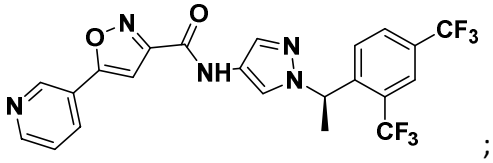
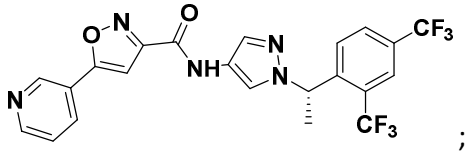
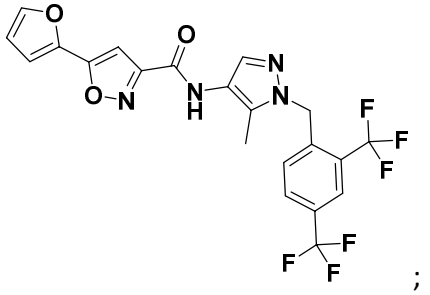
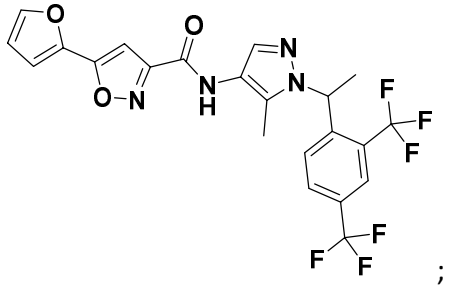
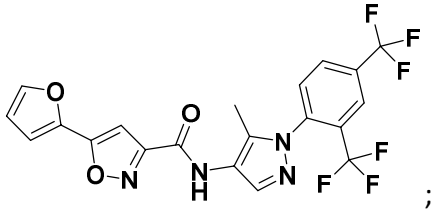
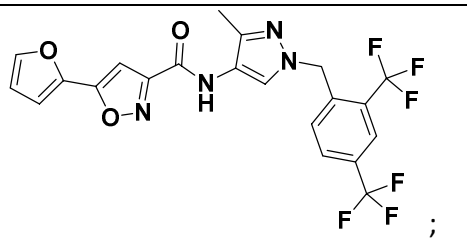
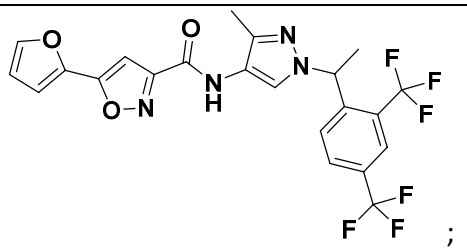
22. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1-C_6alkyl.

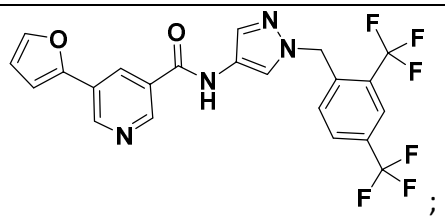
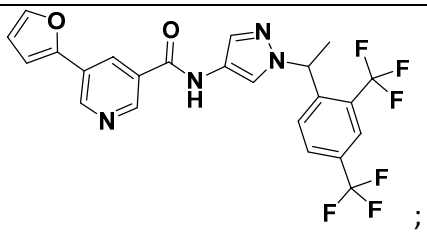
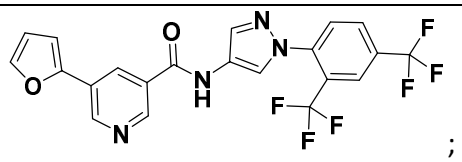
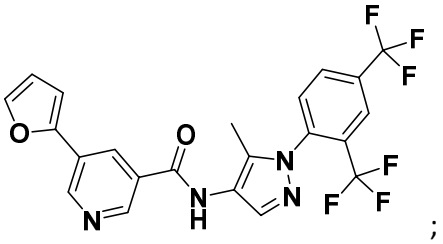
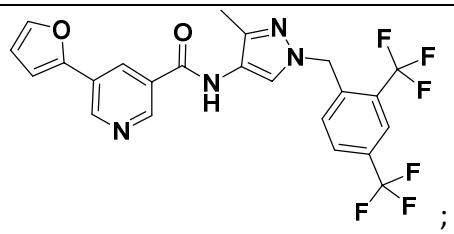
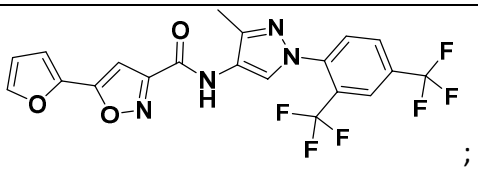
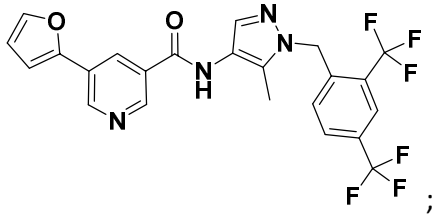
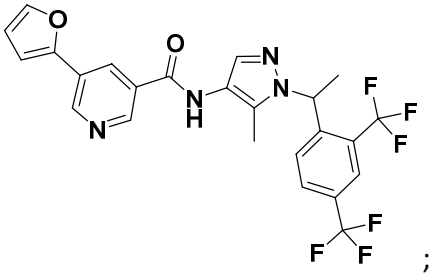
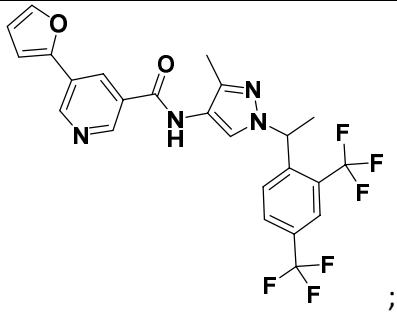
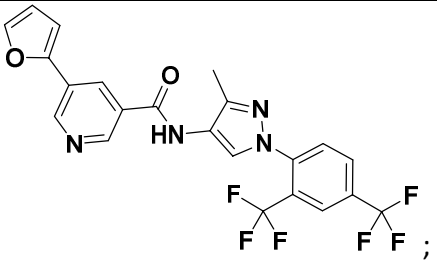
23. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

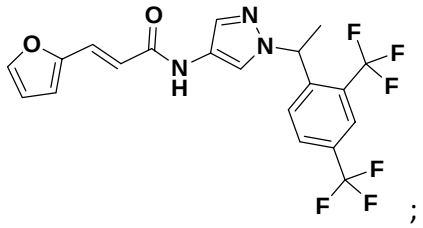
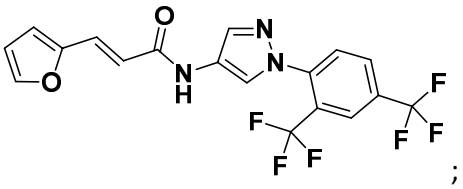
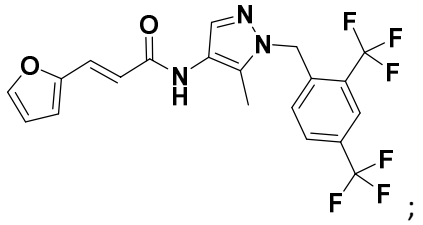
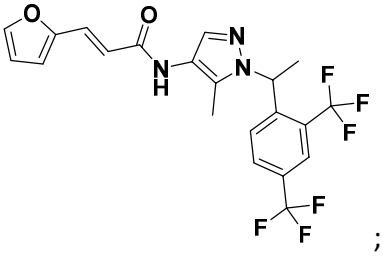
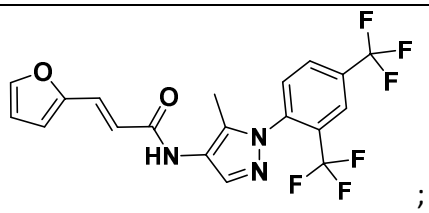
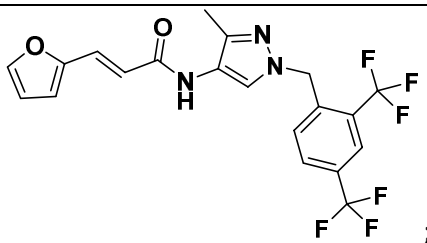
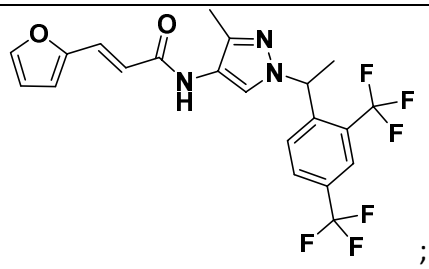
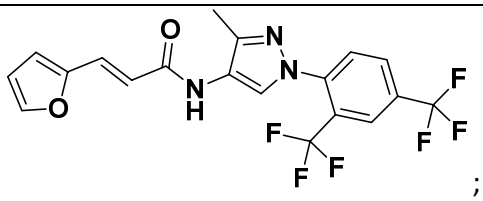
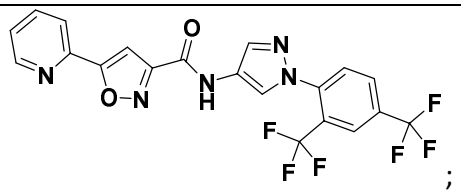
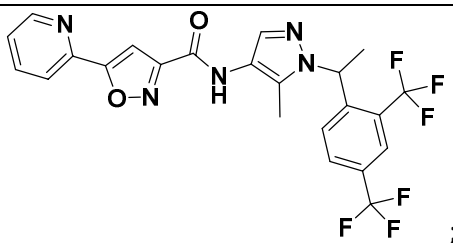
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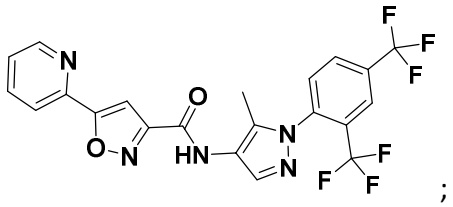
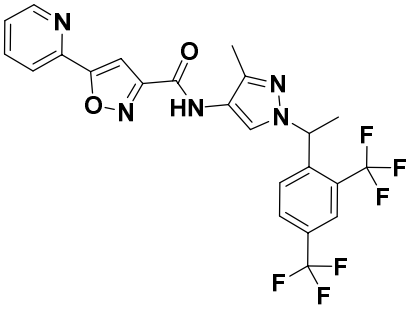
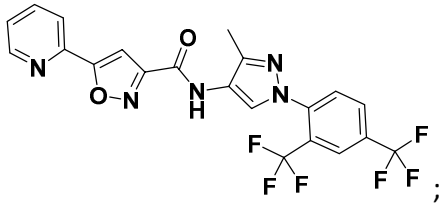
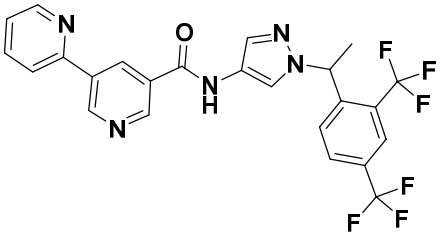
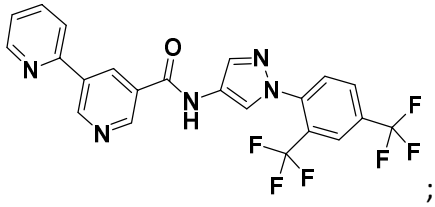
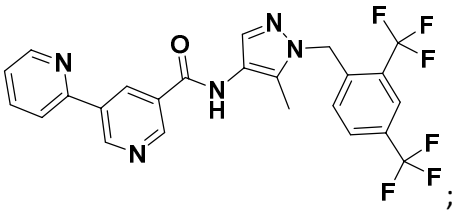
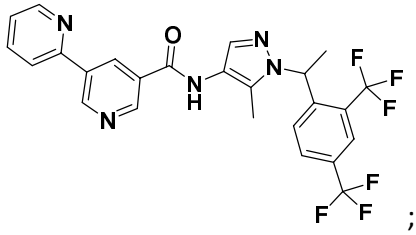
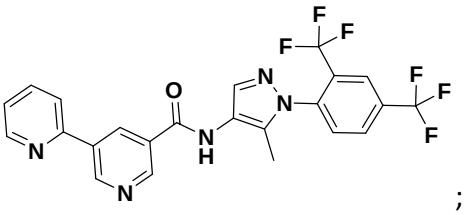
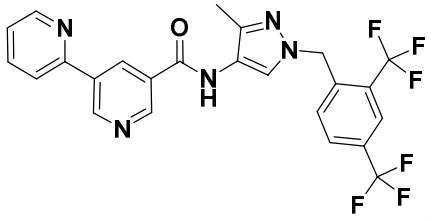
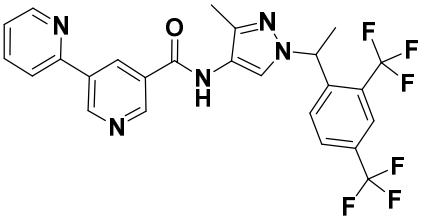
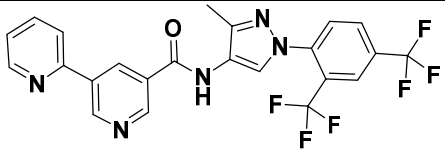
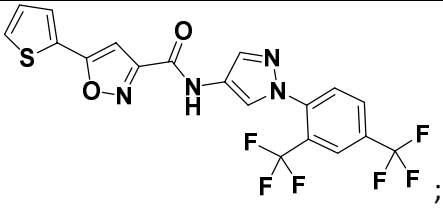
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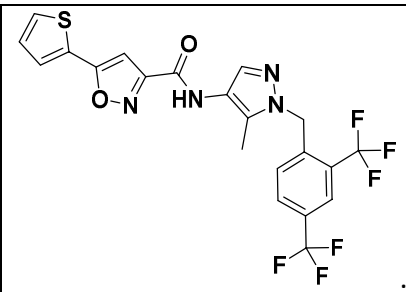
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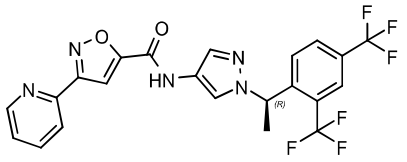
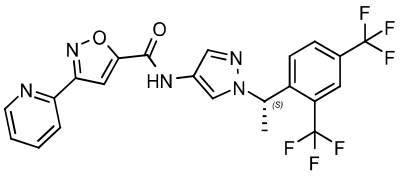
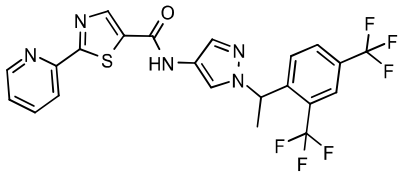
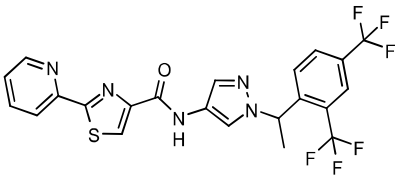
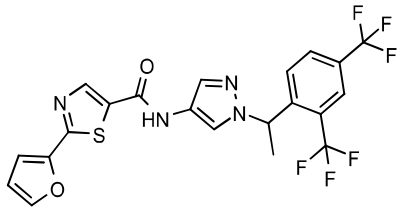
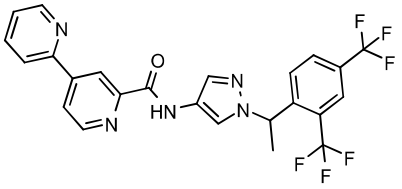
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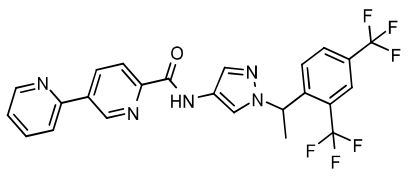
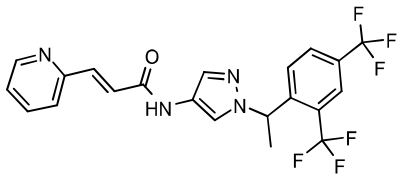
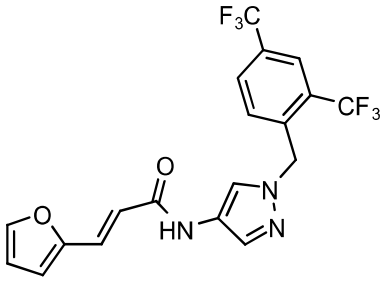
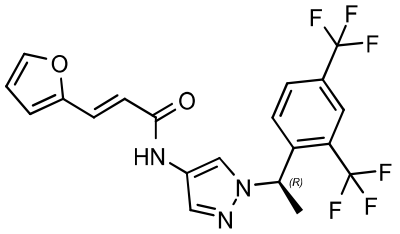
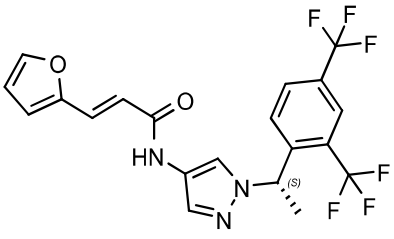
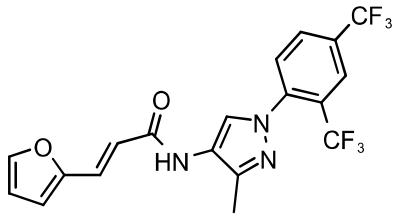
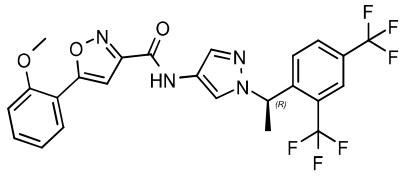
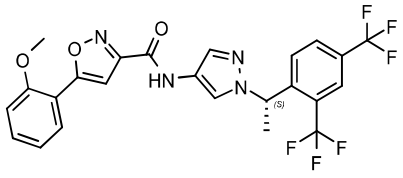
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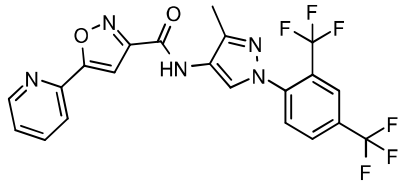
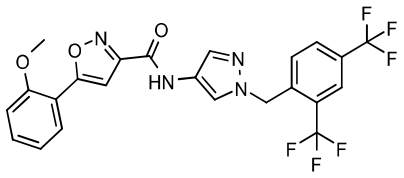
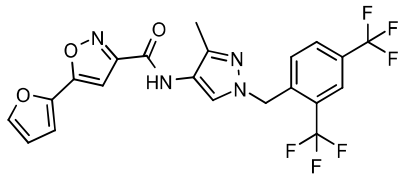
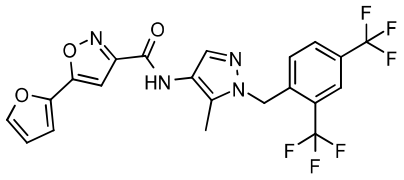
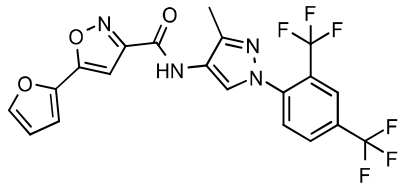
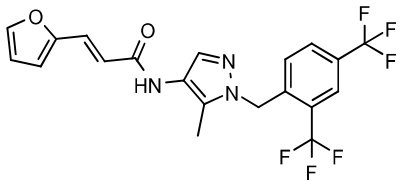
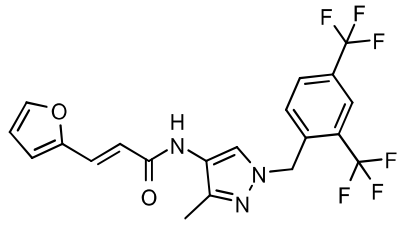
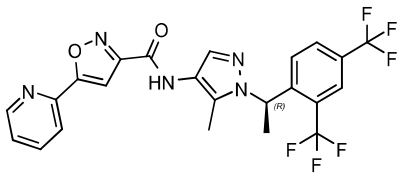
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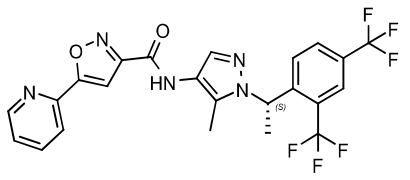
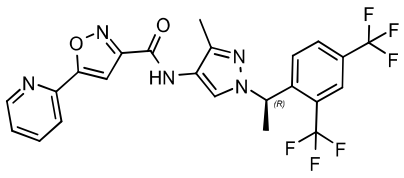
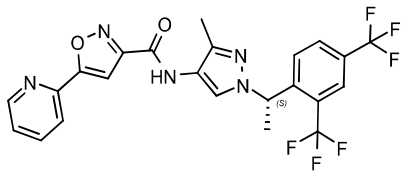
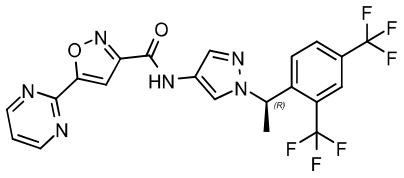
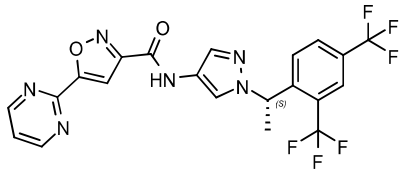
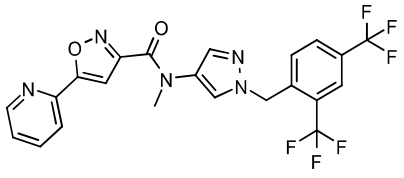
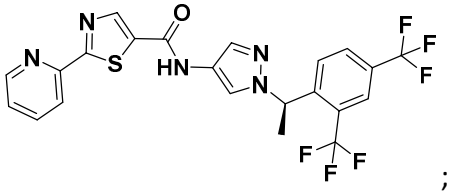
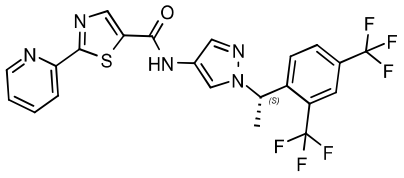
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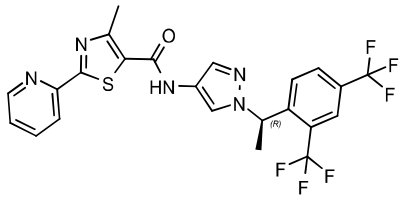
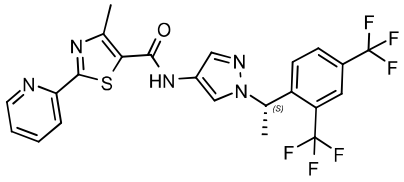
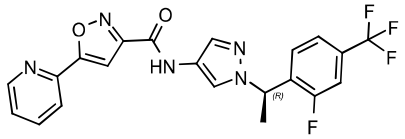
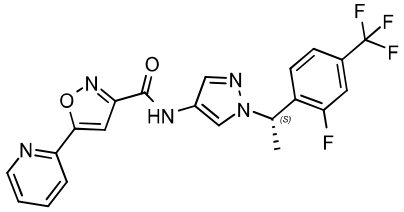
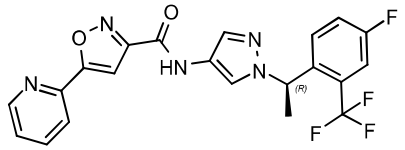
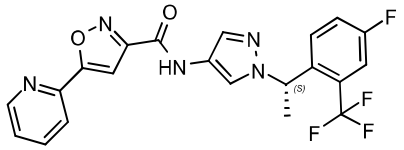
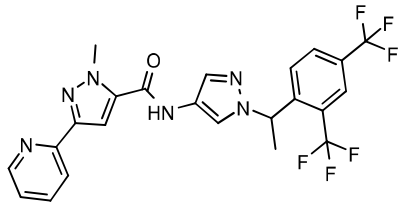
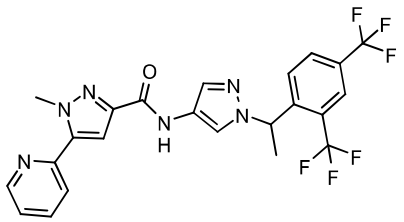
24. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

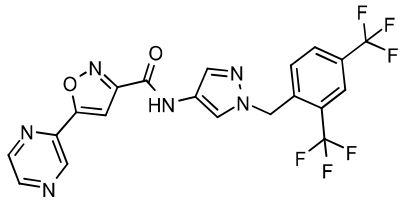
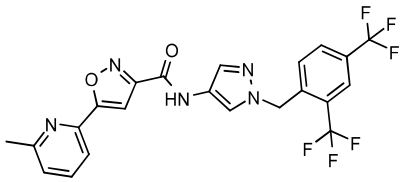
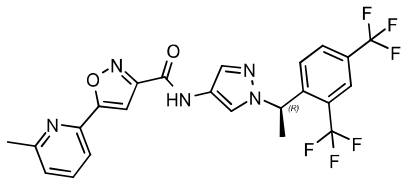
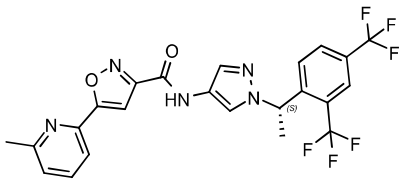
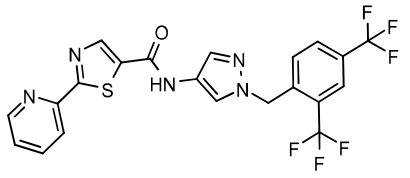
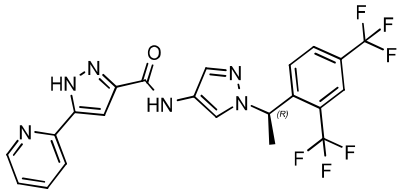
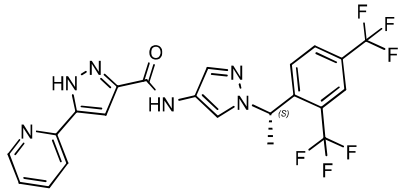
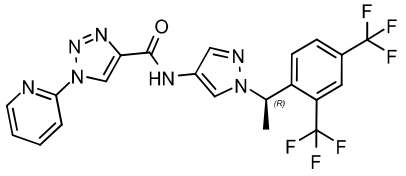
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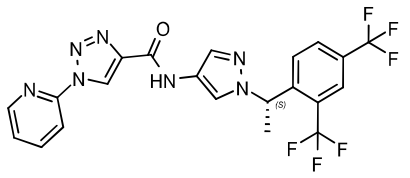
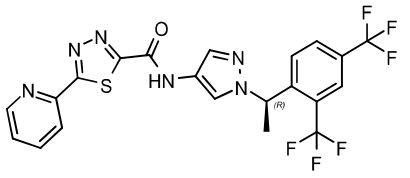
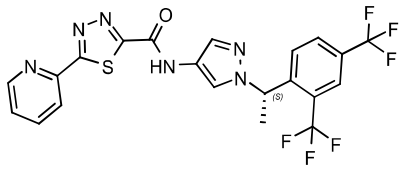
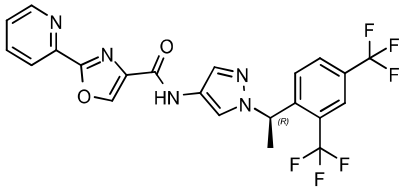
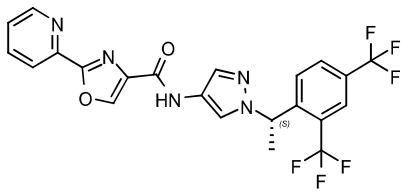
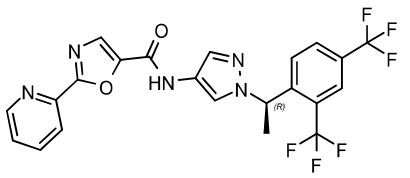
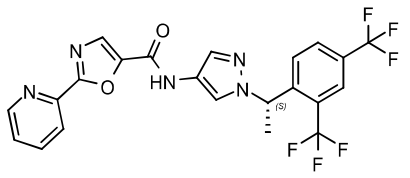
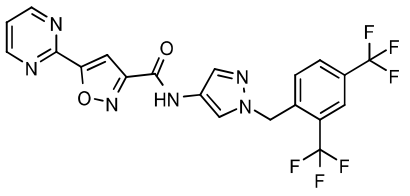
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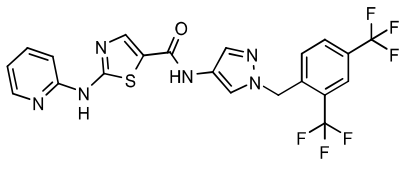
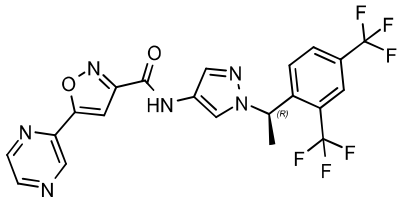
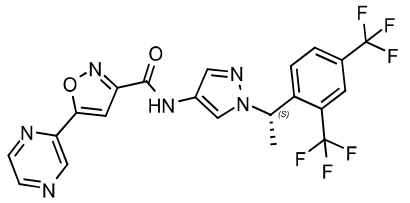
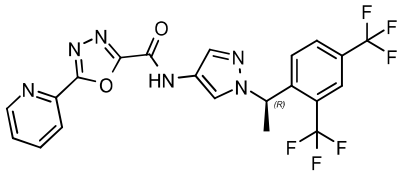
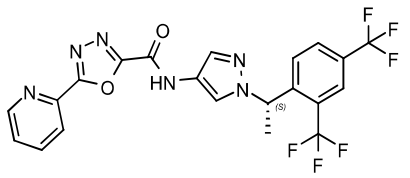
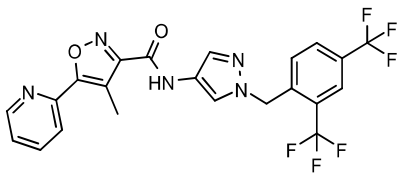
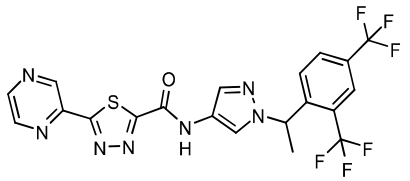
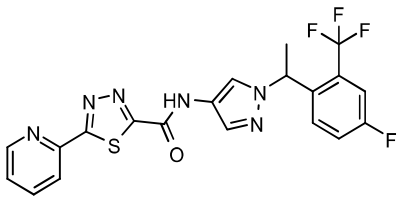
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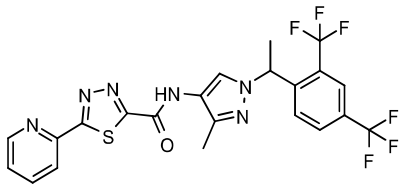
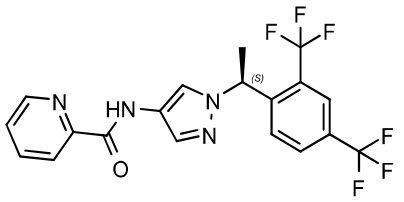
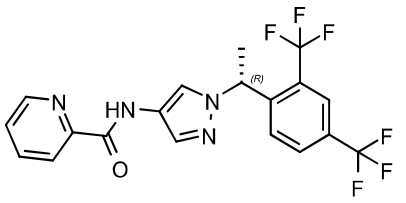
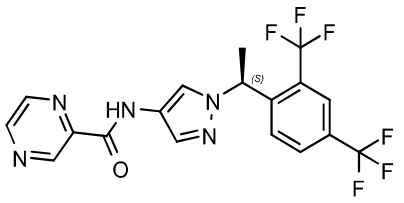
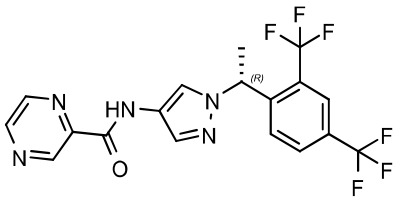
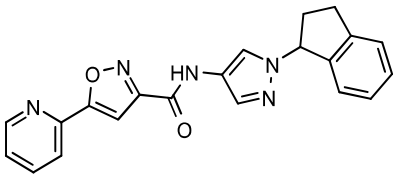
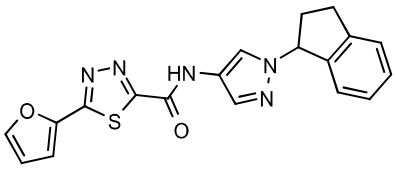
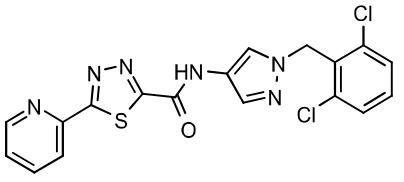
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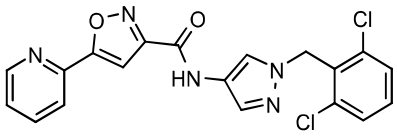
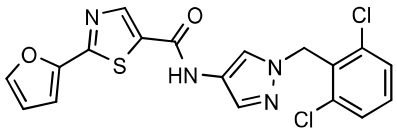
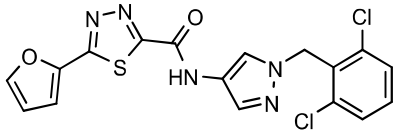
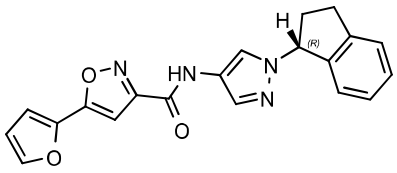
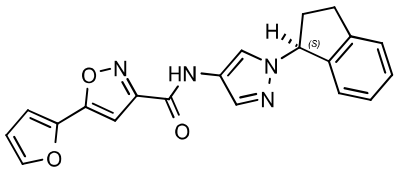
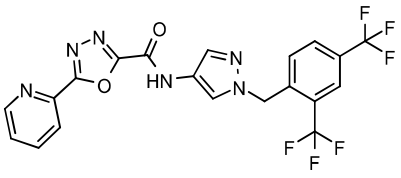
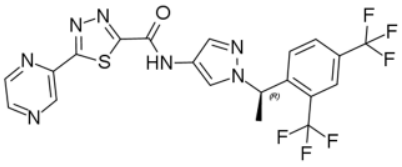
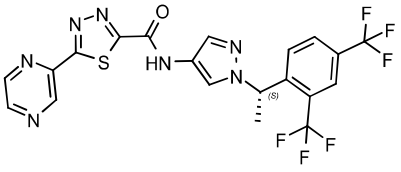
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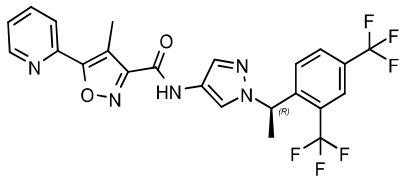
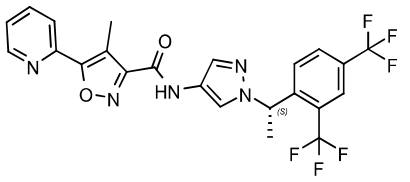
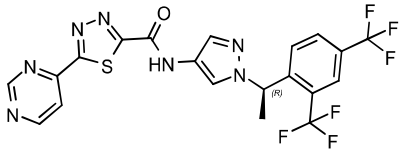
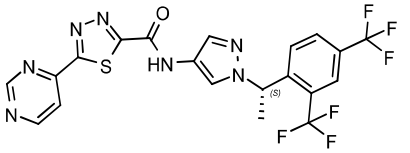
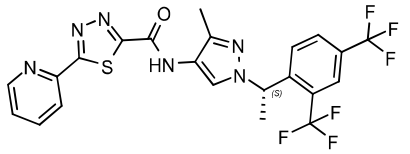
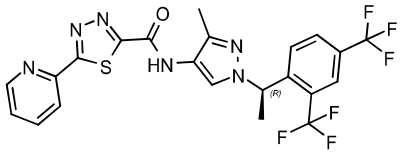
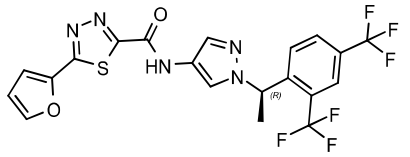
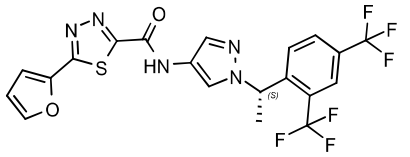
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160	 ; and	161	 .

25. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

26. Use of a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease or disorder mediated by activating transcription factor 6 (ATF6) in an individual in need thereof, wherein the disease or disorder is cancer selected from the group consisting of breast cancer, colorectal cancer (CRC), ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone sarcoma, connective tissue sarcoma, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, leukemia, skin cancer, soft tissue cancer, liver cancer, gastrointestinal carcinoma, and adenocarcinoma.

27. The use of claim 26, wherein ATF6 is ATF6α.

28. The use of claim 26, wherein the cancer is colorectal cancer (CRC).

29. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting ATF6 in an individual.

30. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting ATF6 in a cell.

31. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein two of R^2, R^3, R^4, R^5, and R^6 are other than H.

32. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein one of R^2, R^3, R^4, R^5, and R^6 is CF_3.

33. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein two of R^2, R^3, R^4, R^5, and R^6 are CF_3.

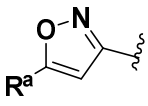
34. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:
R^2 and R^6 are each CF_3, or

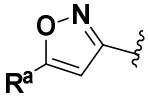
R^4 and R^5 are each CF_3, or

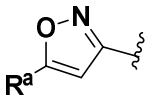
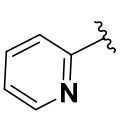
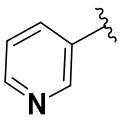
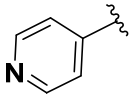
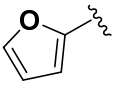
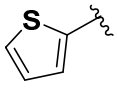
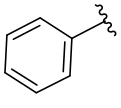
R^3 and R^6 are each CF_3.

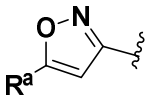
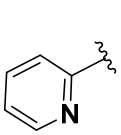
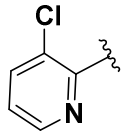
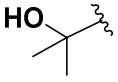
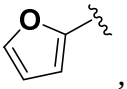
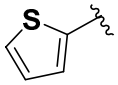
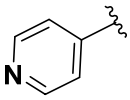
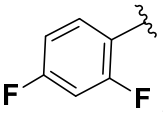
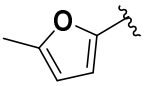
35. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein one or two of R^2, R^3, R^4, R^5, and R^6 is Cl.

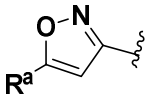
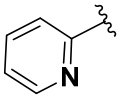
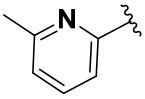
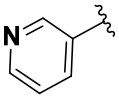
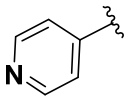
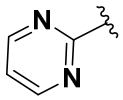
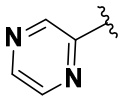
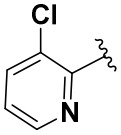
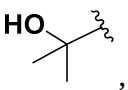
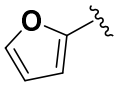
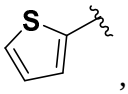
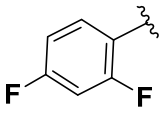
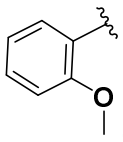
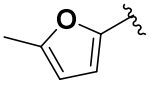
36. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5 are each Cl.

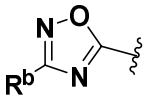
37. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^a is selected from the group consisting of H, C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, and 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^a are unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

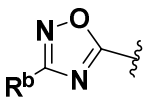
38. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^a is a 5- or 6-membered heteroaryl that is unsubstituted or is substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

39. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^a is selected from the group consisting of C_1-C_6alkyl, , , , , , and , each of which is unsubstituted or is substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

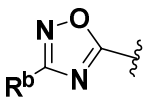
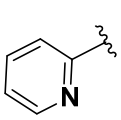
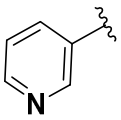
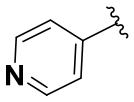
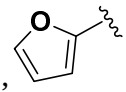
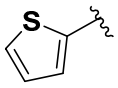
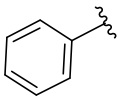
40. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^a is selected from the group consisting of H, , , , , , , , , , and .

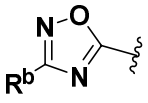
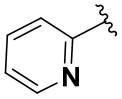
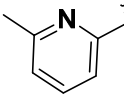
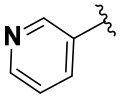
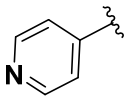
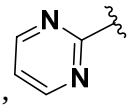
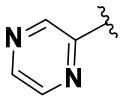
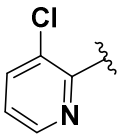
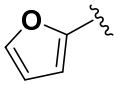
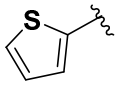
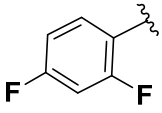
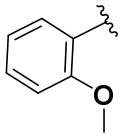
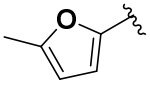
41. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^a is selected from the group consisting of H, , , , , , , , , , , , , , , and .

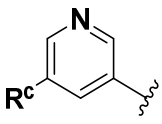
42. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^b is selected from the group consisting of H, C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, and 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^b is unsubstituted or is substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

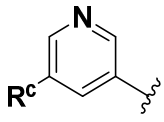
43. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^b is selected from the group consisting of 6-membered aryl and 5- or 6-

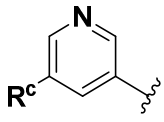
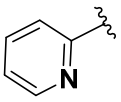
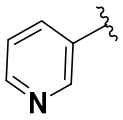
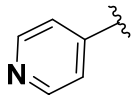
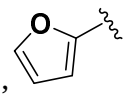
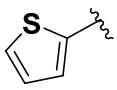
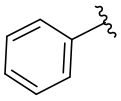
membered heteroaryl, wherein each 6-membered aryl and 5- or 6-membered heteroaryl of R^b is unsubstituted or is substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

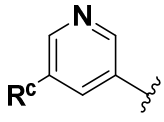
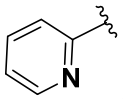
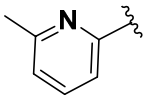
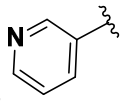
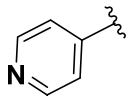
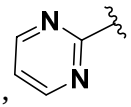
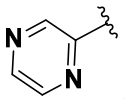
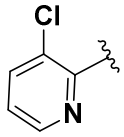
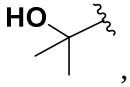
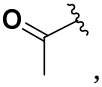
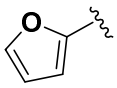
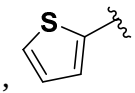
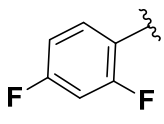
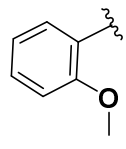
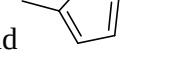
44. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^b is selected from the group consisting of C_1-C_6alkyl, , , , , , and , each of which is unsubstituted or is substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

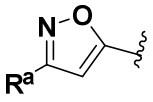
45. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^b is selected from the group consisting of H, , , , , , , , , , , , , , , and .

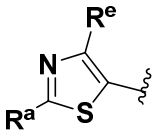
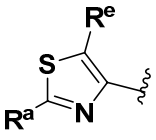
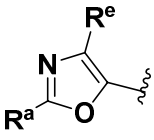
46. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^c is selected from the group consisting of C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^c is unsubstituted or is substituted with one to four groups selected from the group consisting of OH, halo, and C_1-C_6alkyl.

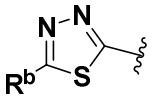
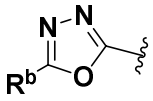
47. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^c is selected from the group consisting of 6-membered aryl and 5- or 6-membered heteroaryl, wherein the 6-membered aryl and 5- or 6-membered heteroaryl of R^c are unsubstituted or are substituted with one to four groups selected from the group consisting of OH, halo, and C_1-C_6alkyl.

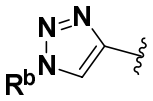
48. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^c is selected from the group consisting of C_1-C_6alkyl, , , , , , and , each of which is unsubstituted or is substituted with one to four groups selected from the group consisting of OH, halo, and C_1-C_6alkyl.

49. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^b is selected from the group consisting of H, , , , , , , , , , , , , , , and .

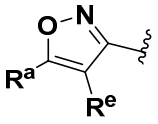
50. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^a is selected from the group consisting of H, C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, and 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^a are unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

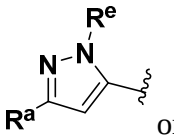
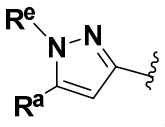
51. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is , , or , and R^a is selected from the group consisting of H, C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, and 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^a are unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

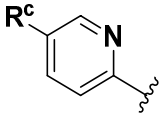
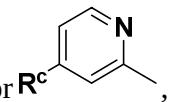
52. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  or , and R^b is selected from the group consisting of H, C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, and 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^a are unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

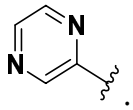
53. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^b is selected from the group consisting of H, C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, and 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-

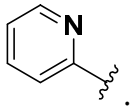
membered aryl, or 5- or 6-membered heteroaryl of R^a are unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

54. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  and R^a is selected from the group consisting of H, C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, and 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^a are unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

55. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  or , and R^a is selected from the group consisting of H, C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, and 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^a are unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

56. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is  or , and R^c is selected from the group consisting of H, C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, and 5- or 6-membered heteroaryl, wherein each C_1-C_6alkyl, -C(O)C_1-C_6alkyl, 6-membered aryl, or 5- or 6-membered heteroaryl of R^a are unsubstituted or substituted with one to four groups selected from the group consisting of OH, halo, C_1-C_6alkyl and C_1-C_6alkoxy.

57. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is .

58. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is .

59. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^8 is H.

60. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^8 is C_1-C_6alkyl.